

Single Technology Appraisal

**Daratumumab with bortezomib,
lenalidomide and dexamethasone for
untreated multiple myeloma when a
stem cell transplant is unsuitable
[ID3843]**

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable
[ID3843]

Contents:

The following documents are made available to stakeholders:

The [final scope and final stakeholder list](#) are available on the NICE website.

1. [Company submission](#) from Johnson & Johnson
2. [Company summary of information for patients \(SIP\)](#) from Johnson & Johnson
3. [Clarification questions and company responses](#)
4. [Patient group, professional group and NHS organisation submissions](#) from:
 - [Myeloma UK](#)
5. [Expert personal perspectives](#) from:
 - [Dr David Owen – patient expert, nominated by Myeloma UK](#)
6. [External Assessment Report](#) prepared by Southampton Health Technology Assessments Centre (SHTAC)
7. [External Assessment Report – factual accuracy check](#)
8. [Addendum to Company Submission](#)
 - a. [Company addendum \(DBLd versus IsaBLd\)](#)
 - b. [EAG critique of company addendum](#)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Company evidence submission

16th July 2025

File name	Version	Contains confidential information	Date
ID3843_Daratumumab_NICE_Company Evidence Submission [noCON]	V1.0	Yes	16 th July 2025

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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Abbreviations

Acronym	Definition
AE	Adverse event
AIC	Akaike information criterion
AKI	Acute kidney injury
ASCT	Autologous stem cell transplant
ATC	Average treatment effect for the control
ATE	Average treatment effect
ATT	Average effect of the treatment
BCd = VCd	Bortezomib, cyclophosphamide and dexamethasone
BCP	Bortezomib, cyclophosphamide and prednisone
Bd	Bortezomib and dexamethasone
BeBd	Belantamab mafodotin, bortezomib and dexamethasone
BePomd	Belantamab mafodotin, pomalidomide and dexamethasone
BIC	Bayesian information criterion
BLd = VRd	Bortezomib, lenalidomide and dexamethasone
BMI	Body mass index
BMP = VMP	Bortezomib, melphalan and prednisone
BNF	British National Formulary
BP	Bortezomib and prednisone
BPI	Brief pain inventory
BSA	Body surface area
BSH	British Society for Haematology
CAA	Commercial access agreement
Cd	Carfilzomib and dexamethasone
CDF	Cancer drug fund
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CLd	Carfilzomib, lenalidomide and dexamethasone
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRAB	Calcium levels (hypercalcemia), renal impairment, anaemia and bone disease
CRF	Case report form
CrI	Credible interval
CRUK	Cancer Research UK
CSR	Clinical study report
CUA	Cost-utility analysis
DBd	Daratumumab, bortezomib and dexamethasone
DBLd = DVRd	Daratumumab, bortezomib, lenalidomide and dexamethasone
DBMP=DVMP	Daratumumab, bortezomib, melphalan and prednisone
DBTd	Daratumumab, bortezomib, thalidomide and dexamethasone
DCO	Data cut-off
DIC	Deviance Information Criterion
DLd = DRd	Daratumumab, lenalidomide and dexamethasone
DNA	Deoxyribonucleic acid
DOR	Duration of response
DPomd	Daratumumab, pomalidomide and dexamethasone
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
EC	European Commission

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Acronym	Definition
ECOG	Eastern Cooperative Oncology Group
EEPRU	Economic Methods of Evaluation of Health and Care Interventions Policy Research Unit
EMA	European Medicines Agency
EMD	Extramedullary plasmacytoma;
EMN	European Myeloma Network
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment report
ESMO	European Society of Medical Oncology
ESS	Effective sample size
FDA	Food and Drug Administration
FE	Fixed effects
FISH	Fluorescence in situ hybridisation
FLC	Free light chain
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GPM	General population mortality
HDT	High dose chemotherapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
Ig	Immunoglobulin
ILd	Ixazomib, lenalidomide and dexamethasone
iMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group;
INHB	Incremental net health benefit
IPD	Individual patient data
IPTW	Inverse probability of treatment weighting
IRC	Independent Review Committee
IRP	International Reliance Procedure
IRR	Injection related reactions
IsaBLd = IsaVRd	Isatuximab, bortezomib, lenalidomide and dexamethasone
IsaPomd	Isatuximab, pomalidomide and dexamethasone
ISS	International staging system
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system
KM	Kaplan-Meier
Ld = Rd	Lenalidomide and dexamethasone
LDH	Lactate dehydrogenase
LY	Life year
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
mAB	Monoclonal antibody
MGUS	Monoclonal gammopathy of undetermined significance
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MM	Multiple myeloma
MP	Melphalan and prednisone
MPT	Melphalan, prednisone and thalidomide
MRD	Minimal residual disease

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Acronym	Definition
MyPOS	Myeloma Patient Outcome Scale
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service
NDMM	Newly diagnosed multiple myeloma
NE	Not evaluable
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ONS	Office for National Statistics
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PaBd	Panobinostat, bortezomib and dexamethasone
PAR	Public assessment report
PAS	Patient access scheme
PD	Progressive disease
PF	Progression-free
PFS	Progression-free survival
PFS2	Progression-free survival on the next line of therapy
PI	Proteasome inhibitor
PK	Pharmacokinetics
Pomd	Pomalidomide and dexamethasone
PRISMA	Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses
PR	Partial response
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSM	Partitional survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QLQ	Quality of life questionnaire
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random effects
RoB	Risk of bias
RRMM	Relapsed/refractory multiple myeloma
RWE	Real-world evidence
SAE	Serious adverse event
SBd	Selinexor, bortezomib and dexamethasone
SC	Subcutaneous
sCR	Stringent complete response
Sd	Selinexor and dexamethasone
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SmPC	Summary of Product Characteristics
SoC	Standard of care
TA	Technology appraisal
TD	Transplant deferred
TEAE	Treatment emergent adverse event

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Acronym	Definition
TEM	Treatment effect modifier
TFI	Treatment-free interval
TIE	Transplant ineligible
ToT	Time on treatment
TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTP	Time to progression
UK	United Kingdom
USA	United States of America
VAT	Value added tax
VGPR	Very good partial response
WHO	World Health Organisation
WTP	Willingness to pay

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

1.1 *Decision problem*

The anticipated marketing authorisation extension for daratumumab (Darzalex®) in combination with bortezomib, lenalidomide and dexamethasone (DBLd) for the indication under consideration is: [REDACTED]

This submission covers the use of DBLd for a patient population that is narrower than its full anticipated marketing authorisation. Specifically, the target population addressed by this submission is adult patients with NDMM who are ineligible for autologous stem cell transplant (ASCT). DBLd for the treatment of adult patients with NDMM who are eligible for ASCT is covered as part of a separate, ongoing submission [ID6249].²

The decision problem addressed within this submission is broadly consistent with the National Institute of Health and Care Excellence (NICE) final scope for this appraisal. An overview of the decision problem addressed in this submission compared to the final scope issued by NICE, is summarised in Table 1. Any differences between the decision problem addressed and the NICE final scope are also outlined in Table 1 below.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated multiple myeloma when a stem cell transplant is unsuitable	[REDACTED]	The population addressed in the company submission is line with the NICE final scope. However, to align with the anticipated wording for the indication of interest in the draft daratumumab summary of product characteristics (SmPC), the target population is described as [REDACTED] throughout the submission.
Intervention	DBLd		N/A – in line with the NICE final scope.
Comparator(s)	• Daratumumab with lenalidomide and dexamethasone (DLd) • Lenalidomide with dexamethasone (Ld) • Bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone) • Isatuximab with bortezomib, lenalidomide and dexamethasone (IsaBLd; subject to NICE evaluation)	• Daratumumab with lenalidomide and dexamethasone (DLd) • Lenalidomide with dexamethasone (Ld) • Bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone)	DBLd is positioned as a treatment option for adult patients with NDMM who are ineligible for ASCT. DLd represents the current National Health Service (NHS) standard of care (SoC) which was confirmed by a UK Advisory Board meeting in May 2025 when clinical experts estimated that DLd accounts for 82.5% (range: 70–90%) of the treatment share for ASCT-ineligible NDMM patients.³ [REDACTED] As such, DLd is considered the main comparator in this submission. Following the NICE recommendation for DLd in 2023 (TA917), J&J understand the doublet regimen, Ld, is now mainly reserved for patients who are not considered fit enough to receive a triplet regimen, or who live far from a hospital and prefer the convenience of an all oral option.⁵

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			Similarly, these patients would not be considered suitable for a quadruplet regimen such as DBLd, so Ld is not considered a relevant comparator in this submission. This was confirmed by clinical experts consulted during the May 2025 UK Advisory Board meeting and as part of an ongoing appraisal for IsaBLd in this indication.³ Bortezomib combination therapies are typically only used in a small proportion of patients with renal impairment. This was supported by clinical experts at the May 2025 UK Advisory Board who estimated that bortezomib-based treatments are only used in ~5% of patients.³ Therefore, J&J do not consider bortezomib combination therapies to be a relevant comparator to DBLd in this indication, considering their minimal usage in UK clinical practice. However, for completeness, and in line with the final scope, analyses versus Ld and bortezomib-based therapies are presented within this submission.⁵ At the time of this submission, the NICE appraisal for IsaBLd is ongoing and IsaBLd has not received a positive recommendation in this indication.⁶ As such, IsaBLd cannot be considered to represent routine clinical practice for ASCT-ineligible NDMM patients and therefore does not represent a relevant comparator for DBLd.
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates • Time to treatment discontinuation (TTD)		N/A – in line with the NICE final scope.

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	- Minimal residual disease (MRD) negativity - Adverse effects (AEs) of treatment - Health-related quality of life (HRQoL)	
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 - If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out - 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 (PSS) perspective - The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	The economic analysis aligns with that described in the NICE decision problem N/A
Subgroups to be considered	N/A	N/A – No subgroups have been identified for which DBLd is expected to be more clinically effective and cost effective. J&J do not consider there are any other groups that should be examined separately.

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Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HRQoL: health-related quality of life; Ld: lenalidomide and dexamethasone; NDMM: newly diagnosed multiple myeloma; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; OS: overall survival; PFS: progression-free survival; PSS: Personal Social Services.

1.2 Description of the technology being evaluated

A description of the technology being appraised, DBLd, is presented in Table 2.

The draft SmPC and European public assessment report (PAR) for DBLd in the indication of relevance to this submission are provided in the reference pack accompanying this submission (see Appendix A).^{1, 7}

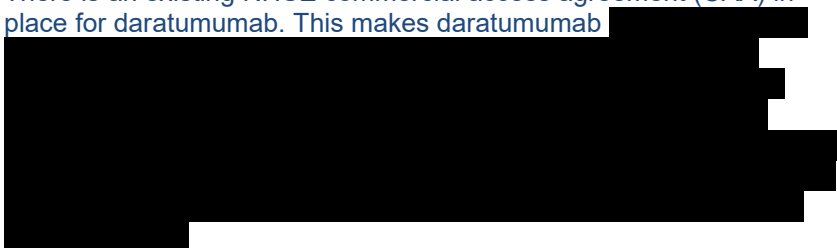
Table 2: Technology being evaluated

UK approved name and brand name	Daratumumab (Darzalex®) in combination with bortezomib, lenalidomide and dexamethasone.
Mechanism of action	Daratumumab is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds to the CD38 glycoprotein, expressed at high levels on the surface of multiple myeloma (MM) tumour cells, in addition to other cell types at various levels.^{8, 9} Pre-clinical data suggest that daratumumab has a distinct mechanism of action driving both direct and indirect antitumor activities. Direct activities include induction of apoptosis and immune-mediated actions such as complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis.¹⁰ Indirect activities of daratumumab include immunomodulatory functions, which involve off tumour, on target depletion of tumour promoting CD38-positive immunosuppressive cells (Figure 1). In patients with a response, this additional mechanism contributes to augmentation of anti-tumour immune responses to recognise and drive further the elimination of tumour cells.^{10, 11} Figure 1: Mechanism of action of daratumumab The diagram illustrates the mechanism of action of daratumumab. A central 'Myeloma cell' is shown with various immune-mediated actions around it. On the left, 'DIRECT ON-TUMOR actions' include CDC, ADCC, ADCP, and Apoptosis, leading to 'MYELOMA CELL DEATH'. On the right, 'IMMUNOMODULATORY actions' include 'Modulation of tumor microenvironment', 'Clonal expansion of cytotoxic T cells', 'Increase in helper T cells', 'Increase in CD8+ granzyme B+ cells', and 'Depletion of CD38+ immunosuppressive cells', which also contribute to 'MYELOMA CELL DEATH'. Bortezomib is a proteasome inhibitor (PI) used in the treatment of MM as either a single-agent and in combination therapies. Preclinical studies propose that bortezomib controls cell cycle progression and induces cancer cell death through a number of mechanisms. These include upregulation of proapoptotic proteins, inhibition of nuclear factor kappa B and its anti-apoptotic target genes, suppression of several anti-apoptotic proteins, down-regulation of expression of several proteins involved in DNA repair pathways, and induction of

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	endoplasmic reticulum stress and pro-apoptotic Unfolded Protein Response.¹² Studies have found that combination therapies containing bortezomib demonstrate significant improvements in clinical outcomes compared to those without.¹³ Lenalidomide is an immunomodulatory drug (iMiD) which targets MM by enhancing the activity of T-cells and natural killer cells, both of which are involved in anti-tumour immunity, and directly inhibiting the proliferation of MM cells. Additionally, lenalidomide blocks the formation of new blood vessels, which are required for tumour growth.^{14, 15}
Marketing authorisation/CE mark status	UK marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) is expected for daratumumab (in combination with lenalidomide, bortezomib and dexamethasone) in the indication of relevance to this submission in [REDACTED], via the International Reliance Procedure (IRP) based on European Commission (EC) approval.¹
Indications and any restriction(s) as described in the draft SmPC	The anticipated licenced indication for daratumumab of relevance to this submission is: [REDACTED]¹ Other licenced indications for daratumumab in MM are:¹ • In combination with lenalidomide and dexamethasone (DLd) or with bortezomib, melphalan and prednisone (DBMP) for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant • In combination with bortezomib, thalidomide and dexamethasone (DBTd) for the treatment of adult patients with NDMM who are eligible for ASCT. • In combination with lenalidomide and dexamethasone (DLd), or bortezomib and dexamethasone (DBd), for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. • In combination with pomalidomide and dexamethasone (DPd) for the treatment of adult patients with MM who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy [daratumumab subcutaneous (SC) formulation only]. • As monotherapy for the treatment of adult patients with relapsed and refractory MM, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy Licensed indications for daratumumab in light chain amyloidosis are: • In combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain amyloidosis [daratumumab SC formulation only].
Method of administration and dosage	• Daratumumab 1,800 mg solution for SC injection is available as a fixed dose with each 15 mL vial • The dosing schedule for <i>daratumumab</i> in combination with bortezomib, lenalidomide and dexamethasone (3-week cycle

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	regimens) for treatment of newly diagnosed patients who are <u>ineligible</u> for ASCT is as follows: ○ Weeks 1–6: Administered weekly for a total of 6 doses ○ Weeks 7–24: Administered every three weeks for a total of 6 doses ○ Weeks 25 onwards until disease progression: Administered every four weeks Drug administration should be performed by a healthcare professional over approximately 3–5 minutes, and the first dose should be administered in an environment where resuscitation facilities are available • The dosing schedule for <i>bortezomib</i> is: ○ Weeks 1-24: 1.3 mg/m² bortezomib twice weekly on Days 1, 4, 8, and 11 of each 21-day cycle and then stopped^a • The dosing schedule for <i>lenalidomide</i> is: ○ Weeks 1-24: 25 mg once daily on Days 1-14 of each 21-day cycle for patients with CrCl ≥60 mL/min ○ Weeks 25 onwards until disease progression: 25 mg once daily on days 1-21 of each 28-day cycle • The dosing schedule for <i>dexamethasone</i> is: ○ Weeks 1-24: 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for Cycles 1-8. For patients older than 75 years or underweight (body mass index [BMI] <18.5), the dexamethasone dose administered at a dose of 20 mg on days 1, 4, 8, and 11. ○ Weeks 25 onwards until disease progression: 40 mg orally at a total dose of 40 mg on Days 1, 8, 15, 22 of each 28-day cycle. For patients older than 75 years or underweight (BMI <18.5), the dexamethasone dose administered at a dose of 20 mg weekly.
Additional tests or investigations	A one-off blood sample to type and screen patients' serum is required prior to starting daratumumab. ¹⁶
List price and average cost of a course of treatment	• List Price 1,800 mg (fixed-dose vial; SC injection) = £4,320.00 (excl. VAT).¹⁷
Patient access scheme/commercial arrangement (if applicable)	There is an existing NHSE commercial access agreement (CAA) in place for daratumumab. This makes daratumumab 

Footnotes: ^a In UK clinical practice, the full bortezomib dose is given once weekly as advised in the November 2024 and May 2025 UK Advisory Boards.

Abbreviations: ASCT: autologous stem cell transplant; CD38: cluster of differentiation-38; CHMP: Committee for Medicinal Products for Human Use; DBd: daratumumab, bortezomib and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBMP: daratumumab, bortezomib, melphalan and prednisone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DLBd: daratumumab, bortezomib, lenalidomide and dexamethasone; EMA: European Medicines Agency; IgG1κ: human immunoglobulin G1 kappa; IMWG: International Myeloma Working Group; IV: intravenous; mAb: monoclonal antibody; MHRA: Medicines and Healthcare Products Regulatory Agency; MM: multiple myeloma; SC: subcutaneous; SmPC: Summary of Product Characteristics; VAT: value added tax.

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

MM is a rare, incurable cancer associated with a high clinical and patient burden

- MM is a rare and incurable type of haematological cancer accounting for 2% of all new cancer cases in England.¹⁸
- MM is associated with a high clinical burden with patients often presenting with fatigue, unremitting bone pain, poor mobility, recurrent or persistent infection and hyperviscosity.¹⁹⁻²²
- Compared to the general population, patients with MM face a significant disease burden and substantially shorter life expectancy.^{23, 24} ASCT-ineligible patients experience particularly poor outcomes, despite the recent advancements in the availability of therapies for these patients.
- The clonal and heterogeneous nature of MM presents a particular challenge, requiring treatment options that can effectively target all malignant plasma cells. Many MM patients relapse because of the presence of resistant plasma cells in the bone marrow in the form of MRD. With each relapse, prognosis worsens as it becomes more difficult to induce deep and durable responses to treatment due to the presence of additional clones.²⁵⁻²⁹
- As only ~60% of patients are able to receive second-line therapy, it is vital to prioritise the most effective treatments in the first-line, as many patients may not survive or remain fit enough to receive subsequent treatment lines.^{25, 30}

An unmet need exists in newly diagnosed, ASCT-ineligible MM patients for alternative, effective treatments that drive deeper, more durable responses, in turn offering improved OS whilst maintaining tolerability and quality of life

- In UK clinical practice, patients with newly diagnosed MM are initially assessed for suitability for ASCT.³¹
- For patients who are ineligible to receive ASCT (estimated to be around 70% of MM patients in England),³² DLd represents the current first-line SoC.^{3, 5}
- Whilst the recent introduction of the triplet regimen DLd has led to substantial therapeutic advancements in the treatment of ASCT-ineligible NDMM, survival outcomes for ASCT-ineligible patients remain considerably below the age-matched general population, and lower compared to ASCT-eligible patients³³
 - Crucially, despite an overall response rate [ORR] of over 90% among ASCT-ineligible patients treated with DLd, and a 45% reduction in the risk of disease progression or death (95% confidence interval [CI]: 0.45, 0.67) for DLd over Ld, only around one third of ASCT-ineligible patients (32.1%) on DLd achieve MRD negativity.⁵
- Achieving MRD negativity and a sustained MRD negative response is a critical goal of first-line treatment, given MRD negative status is associated with substantial improvements in PFS and OS and thus is an important prognostic factor in patients with MM.³⁴⁻⁴⁰
- There is a wealth of evidence that supports a correlation between MRD negativity and improved survival in patients with NDMM and, more recently, a meta-analysis establishing a correlation between a treatment effect on MRD negativity and a treatment effect on PFS/OS. Indeed, this evidence supported MRD negativity being recently accepted as an accelerated approval endpoint of new treatments for MM by the FDA.³⁴⁻⁴⁰
 - This suggests the criteria for Level 1 evidence, referenced in the NICE report of surrogate endpoints in HTA, is clearly met.
- An unmet need exists in ASCT-ineligible NDMM for new, effective combination therapies which achieve greater rates of MRD negativity and sustained MRD negative response, in turn helping to delay disease progression and ultimately improve OS, whilst maintaining tolerability and HRQoL.
- The lack of a highly efficacious quadruplet regimen for patients with ASCT-ineligible NDMM also reflects a considerable disparity in the treatment options available for ASCT-ineligible NDMM versus ASCT-eligible NDMM patients.

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Daratumumab, as part of a quadruplet regimen with bortezomib, lenalidomide and dexamethasone would provide newly diagnosed, ASCT-ineligible MM patients with an alternative, more effective treatment option that drives deeper responses versus the current SoC

- Studies have found that the introduction of bortezomib in combination with other agents prolongs survival in both relapsed and NDMM patients.¹³ As such, the introduction of DBLd into the treatment pathway at first line has the potential to address the existing unmet need in ASCT-ineligible NDMM patients.
- DBLd would represent a new, effective quadruplet combination therapy which tackles further aspects of the clonal heterogeneity of MM, thus achieving higher rates of MRD negativity and sustained MRD negativity which is correlated with improvements in long term outcomes and therefore providing the prospect of achieving a functional cure for the best responders.

1.3.1 Disease overview

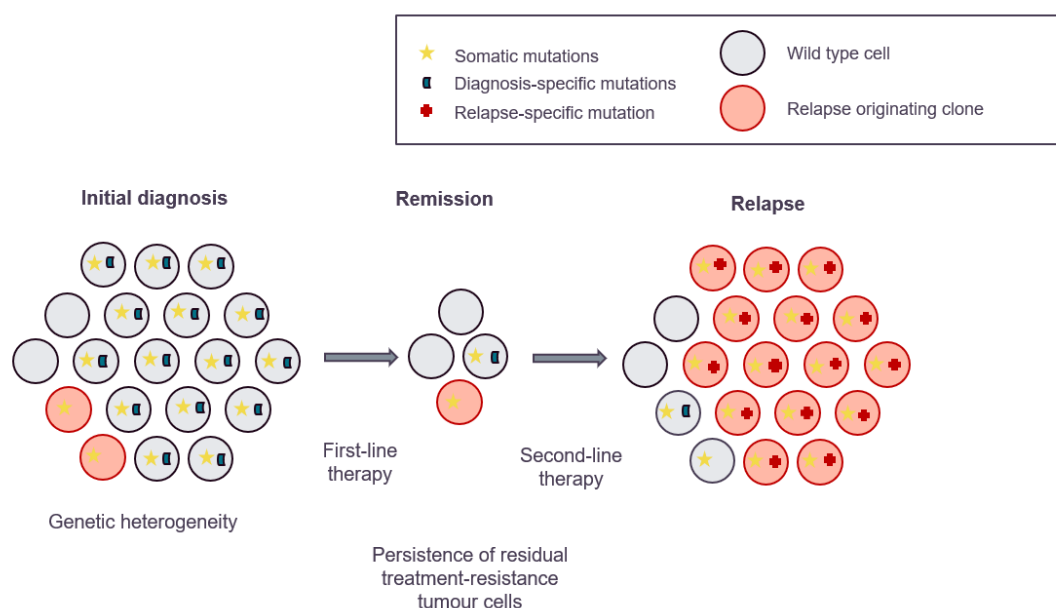
MM is a rare and predominantly incurable type of haematological cancer characterised by uncontrolled proliferation of malignant plasma cells in the bone marrow. This uncontrolled proliferation results in the over-production of an abnormal monoclonal immunoglobulin called M-protein. Over time, this protein accumulates in the bones, blood and multiple organs throughout the body. This leads to progressive morbidity and eventual mortality by impairing the body's ability to fight infection and causing serious complications which require immediate medical treatment, including elevated calcium levels (hypercalcemia), renal impairment, anaemia and bone disease (CRAB) and other types of end stage organ failure.^{19, 41} Additional presenting features include fatigue, unremitting bone pain, recurrent or persistent infection and hyperviscosity (i.e. increased blood viscosity).^{19, 20, 42}

MM is a highly heterogeneous disease with a variable clinical course, and as such, prognosis varies greatly from patient to patient depending on several factors. At a genetic level, heterogeneity exists in the form of mutations and genetic translocations, which increases challenges in terms of treatment options that effectively target and eliminate all malignant plasma cells.⁴³ Additionally, clinical outcomes including PFS and OS, vary depending on a number of prognostic factors, such as age, International Staging System (ISS) stage and whether the patient is considered high-risk, amongst other determinants.^{44, 45}

Central to the evolution of MM is the acquisition and accumulation of secondary genetic events, such as additional chromosomal translocations, copy-number variations, epigenetic modifications, and single-nucleotide somatic mutations.⁴⁶⁻⁴⁸ As depicted in Figure 2, treatment-resistant subclones that have obtained resistance mutations via clonal evolution initially exist at low frequencies, but persist residually, therefore giving rise to relapsing disease. Under the selective pressure of antitumour therapies, these treatment-resistant clones eventually predominate, giving rise to the development of drug resistance.⁴⁹

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Figure 2: Genetic heterogeneity and clonal evolution cause drug resistance in MM



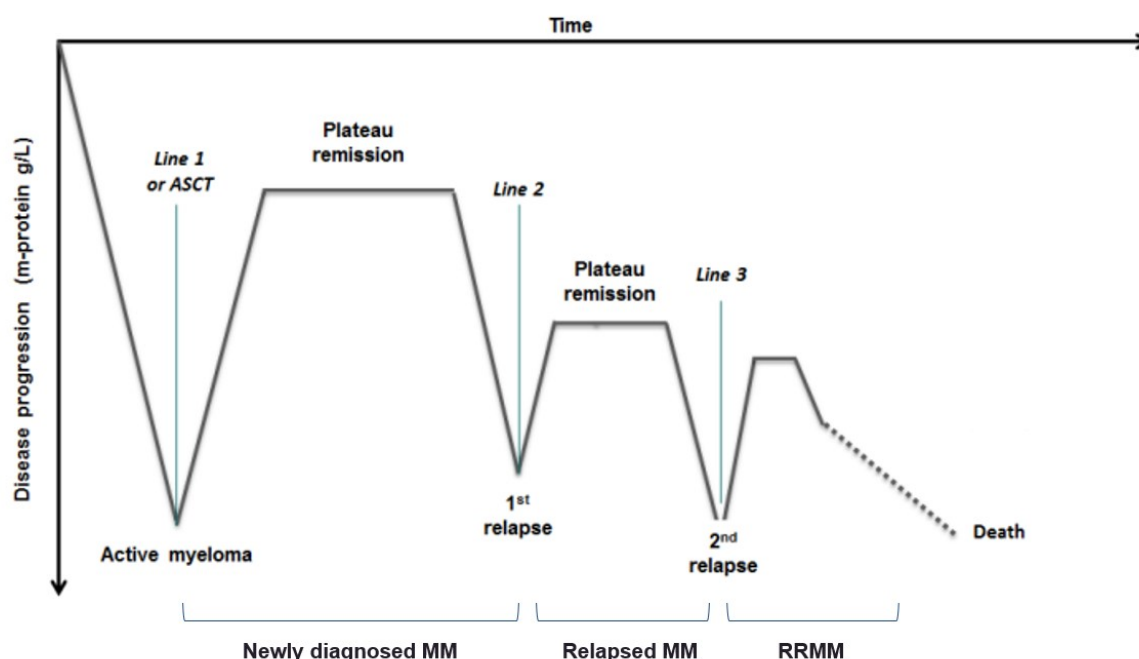
Abbreviations: MM: multiple myeloma.

Source: Adapted from Vosberg and Greif (2019).⁴⁹

Patients experience remission periods before ultimately becoming refractory to a class of drugs and relapsing with each line of therapy – this progression repeats itself in ongoing cycles of relapse and remission (Figure 3).⁵⁰ Each subsequent relapse carries a cumulative risk of additional clones, which arise due to genetic mutations in myeloma cells.⁵¹ Furthermore, with each relapse prognosis worsens as it becomes more difficult to induce deep and durable responses to treatment and attrition rates increase.²⁵⁻²⁹ As such, the prognosis of patients with relapsed/refractory disease is poorer than those with NDMM. A key challenge of treatment is finding options which effectively target and eliminate all clonal and subclonal mutations, as clones that remain following treatment will re-populate the disease via clonal expansion and evolution. The concept of clonal heterogeneity contributing to disease progress in MM led to the strategy of adopting combination therapies to eradicate both dominant and minor clones.³¹

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Figure 3: Clinical model of disease progression in MM



Abbreviations: ACST: autologous stem cell transplant; MM: multiple myeloma; RRMM: relapsed/refractory multiple myeloma.

Source: Adapted from TA763.⁵²

The emergence of novel therapeutic agents and combination regimens has significantly enhanced both survival rates and HRQoL for patients with MM. Despite these advances, MM remains an incurable malignancy, with nearly all patients eventually experiencing a relapse or failing to respond to treatment, in turn becoming refractory to at least one class of drugs commonly used to treat MM.^{53, 54} Due to the refractory nature of the disease, the use of optimal first-line therapies is therefore critical to induce the deepest level of response and stabilise the disease for as long as possible in order to maximise OS, particularly as patients may not survive or be fit enough to receive treatment at later lines. A more effective first-line treatment can extend the first remission, and therefore positively shift the subsequent outcomes of surviving patients. Understanding the genetic complexity of MM is critical for tailoring effective therapies and improving outcomes for MM patients.

Depth of response and minimal residual disease

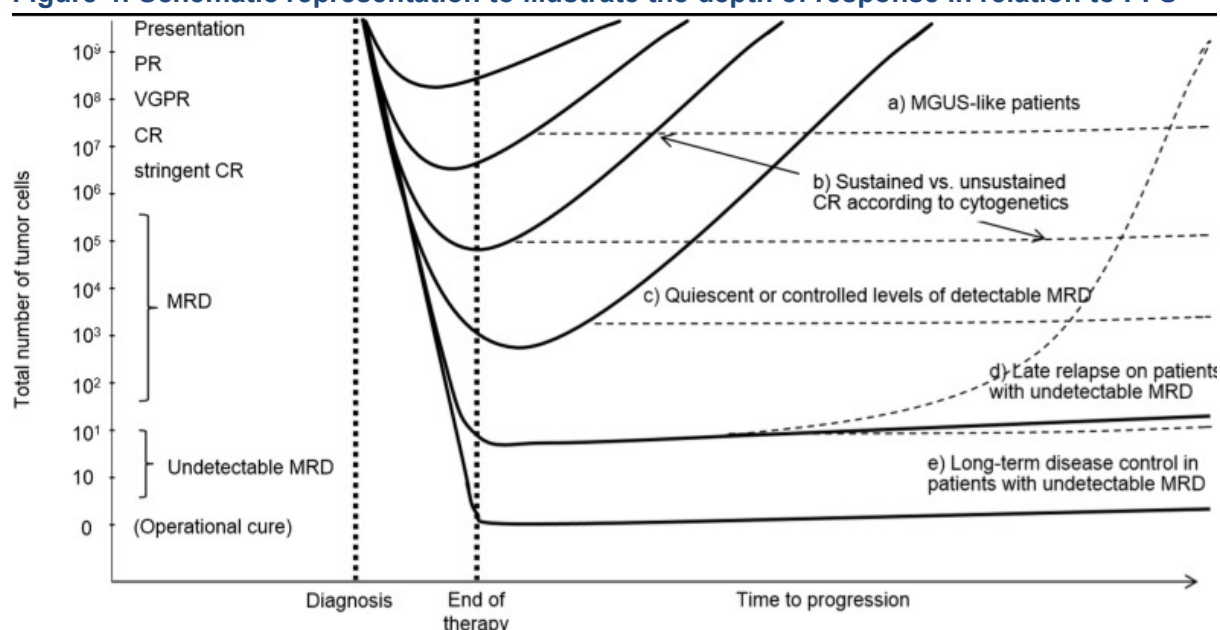
Many patients relapse because of the continued presence of resistant plasma cells in the bone marrow in the form of MRD. MRD refers to a small number of myeloma cells that remain in the bone marrow after treatment and achieving a complete response (CR), which can increase the risk of relapse for patients who are MRD positive compared to those that are MRD negative.⁵⁵ It is therefore critical that measures of response are able to identify these small but clinically relevant populations of myeloma cells that persist in MM patients, despite achieving a CR. MRD is the most sensitive measure of response currently available and is recommended in the International Myeloma Working Group (IMWG) response assessment criteria.⁵⁶

High sensitivity assays are needed for the detection of MRD in patients with MM. Nearly all MM patients will eventually experience relapse, therefore MRD diagnostics are important to assessing treatment effectiveness.

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Figure 4 provides a representative comparison of time to progression based on traditional measures of response and MRD.

Figure 4: Schematic representation to illustrate the depth of response in relation to PFS



Abbreviations: CR: complete response; MGUS: monoclonal gammopathy of undetermined significance; MRD: minimal residual disease; PR: partial response; VGPR: very good partial response.

Source: Paiva *et al.* (2015).³⁴

As such, in the context of NDMM where it can often take many years to demonstrate a statistical survival advantage, the efficacy of treatments is assessed beyond conventional endpoints such as PFS and OS. There is a growing body of evidence which indicates that achieving a deep, sustained response to therapy is prognostic for improved survival outcomes, and that MRD negative status is associated with substantial improvements in PFS and OS:

- A meta-analysis evaluating the prognostic value of MRD for PFS and OS within a large cohort of patients with MM determined that MRD negativity is associated with significantly improved survival outcomes across various disease settings (i.e., NDMM, RRMM, ASCT-eligible and ASCT-ineligible patients). Specifically, among ASCT-ineligible NDMM patients, patients who achieved MRD-negative status had statistically significant PFS and OS improvements compared to those who were MRD positive (PFS; hazard ratio [HR]: 0.32 [95% CI: 0.27, 0.39], $p < 0.001$; OS; HR: 0.40 [95% CI: 0.31, 0.51], $p < 0.001$).³⁵
- A further meta-analysis of 4,907 NDMM patients (which was designed based on the Food and Drug Administration [FDA] guidance for considerations for a meta-analysis of MRD as a clinical end point and potential basis for accelerated approval) also demonstrated strong individual-level associations between 12-month MRD negativity and PFS, and OS among NDMM patients (PFS, odds ratio [OR]: 4.72 [95% CI: 3.53, 5.90]; OS, OR: 4.02 [95% CI: 2.57, 5.46]).³⁸ The identified individual-level associations were particularly strong within the ASCT-ineligible population (PFS, OR: 6.15 [95% CI: 4.27, 8.03]; OS, OR: 4.08 [95% CI: 2.44, 5.72]).³⁸
 - Correlations between the treatment effect on MRD negativity and the treatment effect on PFS and OS at the trial level were also strong (PFS: R^2 of 0.67 [95% CI: 0.43, 0.91] for the NDMM population and 0.83 [95% CI: 0.71, 0.96] for the ASCT-ineligible

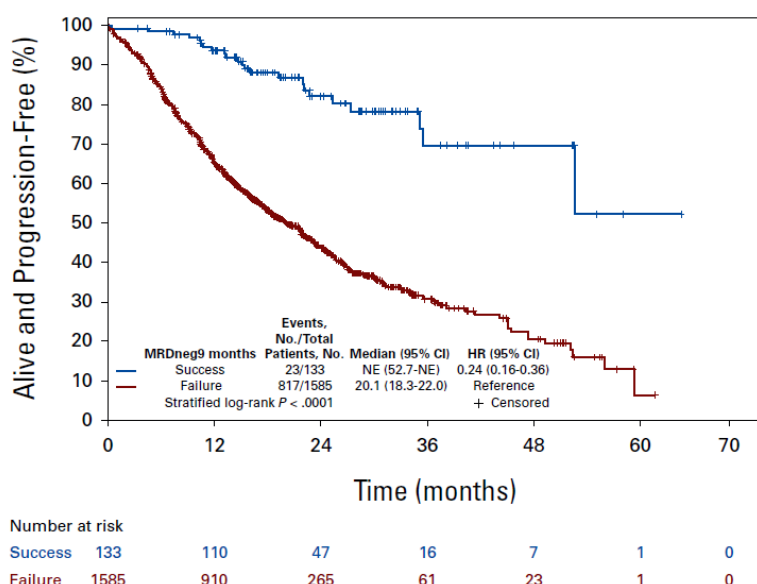
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subgroup; OS: R^2 of 0.21 [95% CI: <0.01 to 0.53] for the NDMM population and 0.79 [95% CI: 0.63, 0.95] for the ASCT-ineligible subgroup).³⁸

- These findings led to the FDA supporting MRD-negative complete response as an early endpoint reasonably likely to predict clinical benefit in multiple myeloma.
- A pooled analysis of individual patient data (IPD) from 11 RCTs of patients with MM further demonstrated that both MRD-CR at 9 months and MRD-CR at 12 months is strongly correlated with PFS among patients with NDMM, and also identified that the patient-level correlation was strongest among ASCT-ineligible patients.³⁹ Among ASCT-ineligible patients, the global OR for the patient-level correlation between 9-month MRD-CR and PFS was 9.8 (95% CI: 5.1, 14.5), while the correlation between 12-month MRD-CR and PFS was 12.0 (95% CI: 7.3, 16.6). Of note, consistent results were observed for the correlation between MRD-CR and OS. Landmark Kaplan-Meier estimates of PFS and OS for ASCT-ineligible patients achieving MRD-CR at 9 months compared with those who did not are presented in Figure 5.³⁹

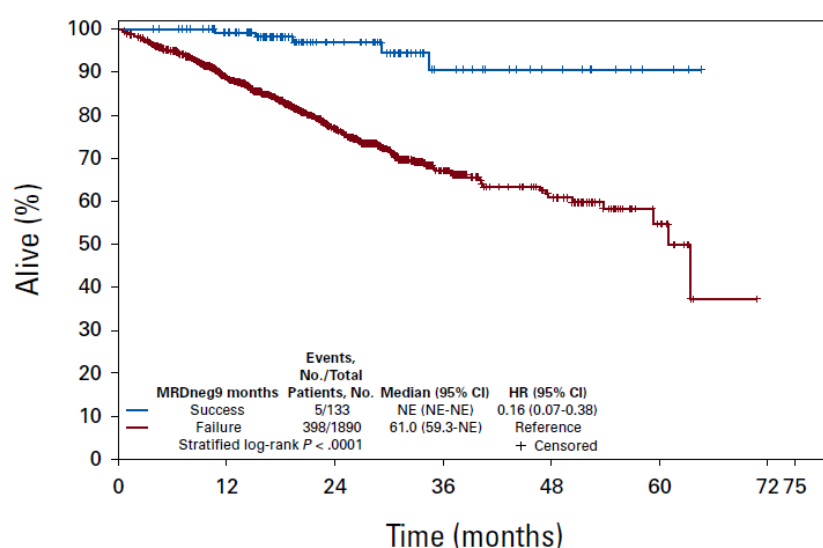
Figure 5: Landmark analyses assessing prognostic values of 9-month MRD-CR status regarding PFS and OS in ASCT-ineligible MM patients

A – 9-month MRD-CR status regarding PFS



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B – 9-month MRD-CR status regarding OS



Abbreviations: CI: confidence interval; HR: hazard ratio; MRD-CR: minimal residual disease- complete response; NE: not estimable; OS: overall survival; PFS: progression-free survival.

Source: Shi *et al.* (2025)³⁹

- The results of a systematic literature review (SLR), including 41 studies, indicated that deeper treatment responses are also associated with improvements in HRQoL in MM patients.⁵⁷

These studies, along with the FDA's acceptance of MRD as an intermediate endpoint for progression-free and overall survival in multiple myeloma, collectively demonstrate the importance of response-based outcomes in MM, especially in ASCT-ineligible NDMM, and suggest that MRD-negativity may be an objective measure of anti-myeloma clinical activity that is highly prognostic of long-term outcomes and thus is a suitable surrogate endpoint for longer-term outcomes (such as OS and PFS).

There is clear evidence based on multiple randomised trials to demonstrate the relationship between the treatment effect in the surrogate endpoint (i.e., MRD negativity) and the effect on the final outcome measure (i.e., long-term survival), and that changes in the surrogate can predict commensurate changes in the final outcomes. This was specifically investigated in the meta-analysis by Landgren *et al.* (2024), which demonstrated a strong observed correlation between treatment effect on MRD negativity and treatment effect on long-term survival outcomes, particularly for ASCT-ineligible patients (see details above).³⁸ The criteria for Level 1 evidence outlined by Ciani *et al.* (2017),⁵⁸ which is referenced in the NICE report of surrogate endpoints in health technology assessment (HTA),⁵⁹ is therefore clearly met. Level 1 evidence represents the highest possible strength of evidence as per the Ciani *et al.* (2017) criteria.⁵⁸

Aligned to guidance provided in the NICE report of surrogate endpoints in HTA, clinical expert opinion was also sought on the appropriateness of MRD negativity as a surrogate endpoint for long-term survival outcomes.⁵⁹ At the May 2025 UK Advisory Board, clinical experts confirmed that they would expect MRD negativity to translate to improvements in PFS and OS in NDMM patients given sufficient follow-up. In summary, there is a wealth of evidence to demonstrate that MRD negativity is a powerful independent predictor of long-term survival in MM. Additionally,

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response-based outcomes are increasingly being used as a proxy for long-term survival in UK clinical practice.

1.3.2 *Epidemiology*

Approximately 6,200 new MM cases were recorded in the UK from 2017–2019, accounting for just 2% of all new cancer cases.¹⁸ Owing to its rarity, NDMM has been granted an orphan disease designation both in the USA and Europe.^{60, 61} However, data from 2017–2019 showed that over the prior decade, MM incidence rates had increased by approximately 10% in the UK and are projected to rise a further 11% between 2014 and 2035; this increase is largely a reflection of the changing prevalence of risk factors and improvements in diagnosis.¹⁸ Specifically, projections indicate that, on average, there will be approximately 8,300 new cases of myeloma annually in the UK by 2038–2040.¹⁸

An increased risk of developing MM has been associated with the following factors:

- Age: MM most commonly affects individuals over the age of 65.⁶²
- Race: Individuals with African heritage experience MM at twice the frequency of Caucasian people, although the reason for this disparity remains unclear.⁶³
- Family history: Family clusters of MM have been observed, though the underlying predisposing genetic mutations are yet unclear. Retrospective results from the Multiple Myeloma Consortium found that individuals with first-degree relatives with MM had an almost twice as high odds of being diagnosed with MM versus individuals without first-degree relatives with MM. This finding was statistically significant (OR: 1.90 [95% CI: 1.26–2.87]).⁶³
- Exposure to radiation or chemicals: Some studies have demonstrated that individuals exposed to radiation or certain chemicals (such as asbestos, benzene and pesticides) face an elevated risk of developing MM.⁶⁴
- Sex: MM is more prevalent in men (men are associated with a 1.5 times greater risk of being diagnosed compared with women), with suggested underlying factors including health-risk behaviours such as smoking, alcohol consumption and higher obesity rates.⁶³ In England, between 2017–2019, incidence rates were 62% higher in males versus females.¹⁸

High-dose therapy (HDT) followed by an ASCT is an intensive treatment option and involves giving high doses of chemotherapy (typically melphalan) to kill myeloma cells and then infusing stem cells back into the patient, allowing the bone marrow to recover. The interplay between disease- and patient-specific factors such as age, fitness, performance status and comorbidities are ultimately used to determine a patient's eligibility for ASCT.^{31, 65-67} Notably however, the majority of patients in the UK with MM are diagnosed at a later stage of life (74% diagnosed aged ≥65 years), and so may not be fit enough to receive HDT with ASCT.¹⁸ As a result, ASCT-ineligible patients account for approximately 70% of all NDMM patients in England.^{32, 68} This was supported by estimates provided by UK clinical experts as part of the May 2025 UK Advisory Board.³

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1.3.3 *Effect of MM on patients and carers*

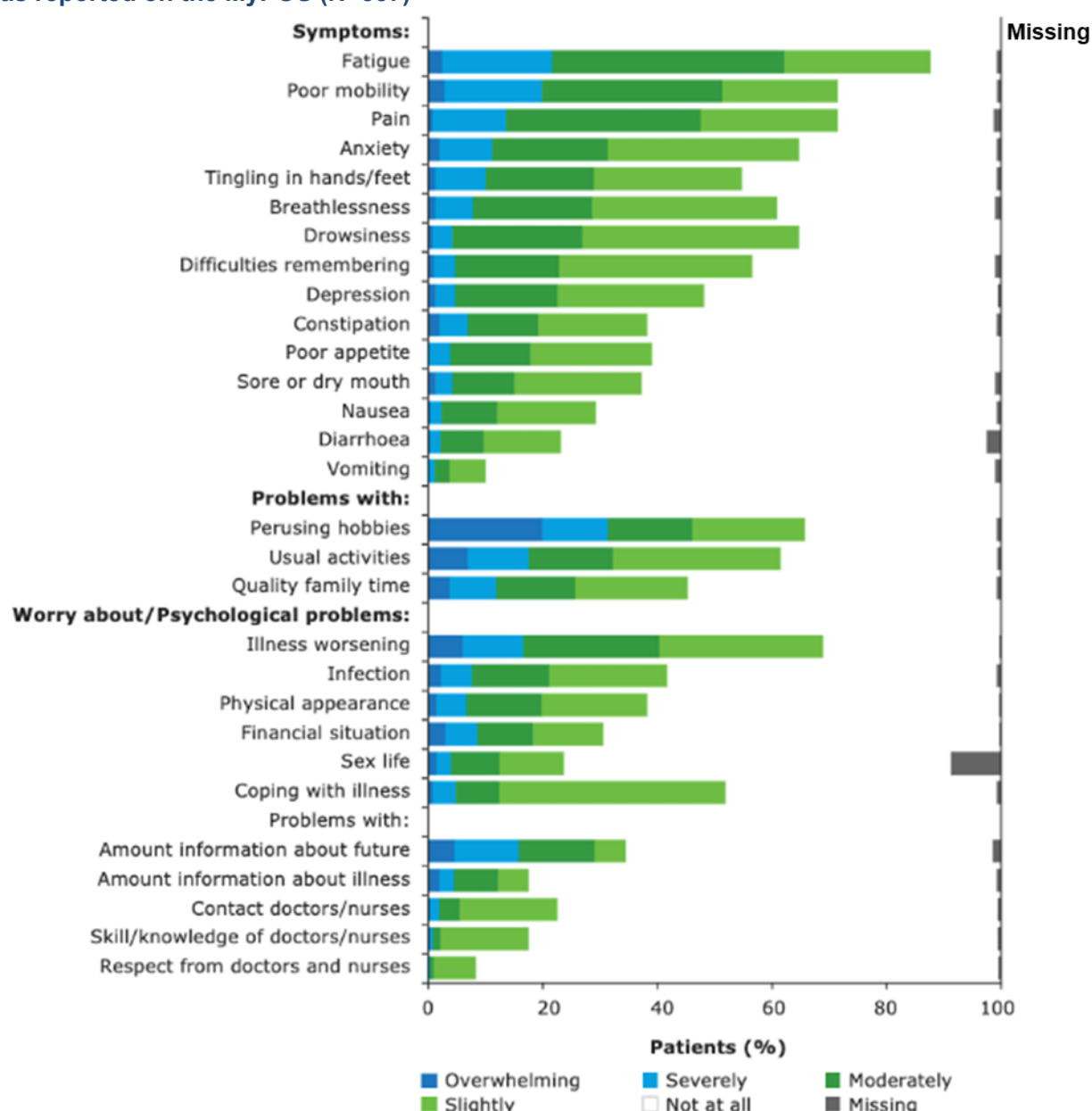
Symptom burden

A diagnosis of MM has a profound impact on patients and their carers. Indeed, there is evidence that patients with MM report worse symptoms and HRQoL than those with other haematological cancers, including lymphoma or leukaemia.⁶⁹ Patients with MM experience a particularly high clinical burden, and often present with recurring or persistent infection, fatigue and unremitting bone pain.^{25, 70} Furthermore, the disruption of the normal balance between osteoclast and osteoblast activity in MM can cause an increase in the rate of bone tissue reabsorption.⁷¹ This in turn can lead to complications such as osteopenia (increased risk of bone fractures) and the development of osteolytic bone disease (bone damage resulting from the build-up of cancerous plasma cells).⁷¹ Additionally, around 25% of patients report unexplained weight loss, with many also experiencing impaired renal function, and more than two thirds experiencing anaemia due to disease-related complications.^{72, 73}

A 2016 cross-sectional study used the Myeloma Patient Outcome Scale (MyPOS) score to assess the prevalence and severity of individual symptoms in 557 patients with MM across 18 centres in the UK. The most prevalent and severe symptoms were fatigue (experienced by 87.6% of patients), followed by poor mobility (71.5%) and pain (71.5%), as shown in Figure 6.²² A 2019 prospective, longitudinal cohort study of patients with MM in England (N=238) reported similar findings. Over half of patients reported fatigue (52.1%) and 40.3% reported moderate to overwhelming pain.²¹ These symptoms have a significant impact on patients' ability to carry out daily activities, contributing to reduced independence (Figure 6).^{22, 74} A recent Canadian cohort study evaluating the symptom burden among ASCT-ineligible patients with NDMM (N=4,610) further corroborates these findings.⁷⁵ Specifically, in the first month after diagnosis, tiredness (64%) and impaired wellbeing (60%) were the most prevalent symptoms among the cohort of ASCT-ineligible NDMM patients; the substantial burden of symptoms was reported to remain over time, with over 25% of the cohort reporting moderate to severe levels of each of the following symptoms at one year post-diagnosis: tiredness, impaired well-being, pain, drowsiness and loss of appetite.⁷⁵

The progression of MM to relapsed/refractory disease intensifies the burden of disease on patients, with relapsed/progressive MM patients reporting more severe and numerous symptoms than those with newly diagnosed or stable MM.²² This highlights the importance of patients in the newly diagnosed setting receiving effective treatments that achieve deep and durable responses, translating to delayed disease progression and ultimately prolonged survival.

Figure 6: Prevalence and severity of symptoms and other problems in patients with MM, as reported on the MyPOS (N=557)^a



Footnotes: ^a Outcomes with missing data for >2% of patients included diarrhoea (2.5%) and worries about sex life (8.8%)

Abbreviations: MM: multiple myeloma; MyPOS: Myeloma Patient Outcome Scale.

Source: Ramsenthaler *et al.* (2016).²²

Impact on health-related quality of life

In addition to the physical symptoms of the disease, MM significantly impacts the mental and emotional wellbeing of patients, resulting in significant detriments to patient HRQoL. Particularly noteworthy, MM is associated with the lowest patient quality of life among all haematological cancers.^{69, 76}

A diagnosis of MM substantially impacts patients psychological wellbeing – patients experience fear as a direct result of their diagnosis and its uncertainty, with some describing a MM diagnosis as a ‘time bomb’, living in fear of a relapse.⁷⁷ Initial disease relapse is associated with a period of

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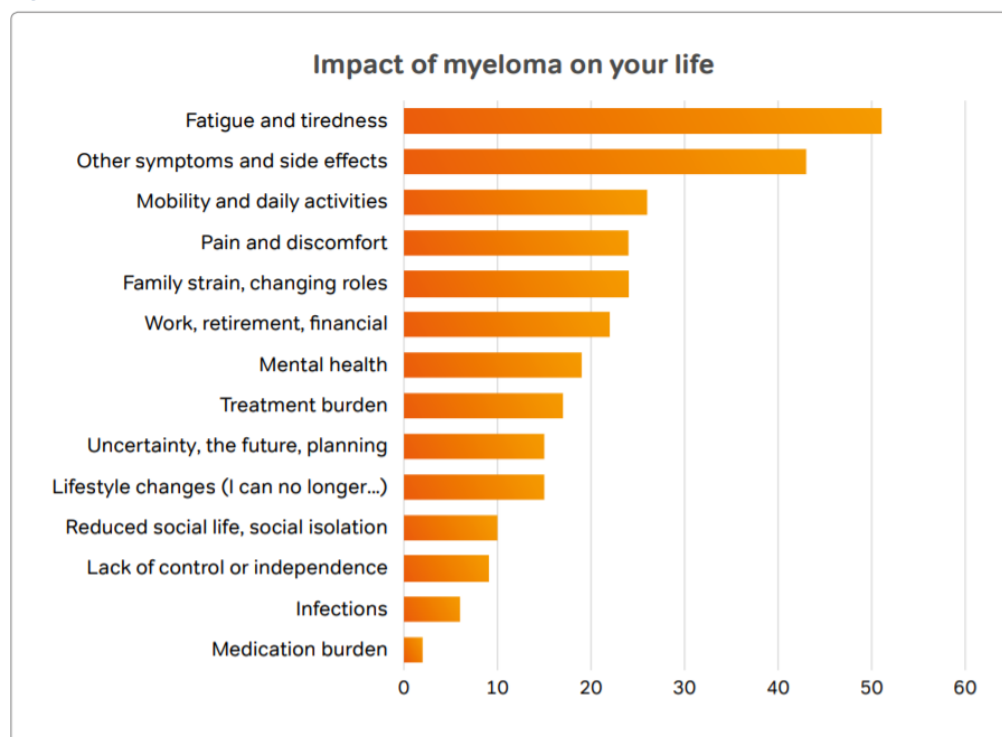
negative emotions, including hopelessness and a general sense of resignation.⁷⁸ Subsequent relapses are linked to increasing distress and pessimism.⁷⁸ As a result, HRQoL significantly deteriorates with each relapse and subsequent line of treatment. Observational data from a Germany-based cross-sectional study, which included responses from 490 MM patients, demonstrated that patient HRQoL decreases with subsequent lines of treatment ($p < 0.001$), with the largest HRQoL reduction occurring when patients switched from active treatment to best supportive care.⁷⁹ This study also demonstrated that patients in a treatment-free interval (TFI) had better HRQoL than patients undergoing treatment, irrespective of lines of treatment.⁷⁹ A further study by Myeloma UK identified that HRQoL among MM patients reduced following progression from their first TFI to second-line treatment and subsequent lines of therapy, and showed that a longer TFI was significantly associated with improved patient HRQoL.⁸⁰ These results highlight the value of effective first-line therapies, which are able to induce deep responses and therefore extend the TFI in patients.⁸⁰

Uncertainty about the future causes ongoing anxiety and often affects patients' relationships with family and friends who may act as informal caregivers.⁷⁸ The psychological distress caused by the disease is evidenced by the fact that one in four patients with MM have anxiety and/or depression which can in turn result in increased social isolation.^{5, 74} Furthermore, an SLR and meta-analysis including 36 studies of symptoms associated with MM found that an alarming 98.9% of patients experienced a decline in physical functioning, as measured by European Organisation for Research and Treatment of Cancer (EORTC), while 80.2% of patients exhibited decreased cognitive functioning. These findings underscore the significant impact MM has on the HRQoL of patients.⁸¹

Patient preferences

Treatments that achieve lasting remission, optimise life expectancy and deliver early and sustained improvement in HRQoL are highly valued by patients. In 2019, NICE embarked on a research project funded by Myeloma UK to explore the quantitative methodology for eliciting patient preferences and how it could be applied in HTA.⁸² The study employed robust research methodology, including a nested survey and a focus group involving 97 MM patients. The goal was to gain deeper insights into the patient experience and the types of preferences that matter most to them. Respondents in the study reported that 'fatigue and tiredness' impacted their lives most (Figure 7 below). Additionally, patients highlighted that MM affected their personal lives by reducing their sense of control/independence, altering their lifestyles, and causing financial strain. It is worth mentioning, these experiences might not be effectively captured in traditional HRQoL instruments.⁸²

Figure 7: Impact of MM on lives of patients



Abbreviations: MM: multiple myeloma.

Source: Myeloma UK (2019).⁸²

Furthermore, a 2020 US-based cross-sectional study of 180 patients undergoing treatment for MM (of which 60 patients had NDMM) concluded that the primary goal of treatment for both patients and oncologists was to extend life for as long as possible.⁸³ This was also supported by a recent study conducted in Europe which explored patient perceptions on key efficacy and safety outcomes of MM treatment (n=30). The mean age of the patients was 60.3 years, and the study included 10 ASCT-ineligible NDMM patients.⁸⁴ The qualitative interviews highlighted that increased life expectancy (reported by 87% of respondents), achieving remission or response (80%), and reduced fatigue (80%) were the most critical treatment preferences for patients.⁸⁴ Fatigue and bone pain symptoms were frequently discussed as symptoms that patients would most like to avoid, while cognitive impairment emerged as the most commonly mentioned side-effect among patients with NDMM (94%).⁸⁴ As well as avoiding burdensome side-effects, 83% of NDMM respondents indicated that a prolonged period of treatment-free remission would be highly valued.⁸⁴ These findings are broadly consistent with results from the NICE and Myeloma UK's patient survey, in which MM patients reported returning to normal activities, work and social life and longer remission/treatment-free periods as the most highly ranked attributes.⁸² These studies indicate that an effective first-line therapy that achieves a deep response and prolonged TFI, with an improved tolerability profile, would be of value to patients and would help alleviate the clinical, symptomatic and emotional burden of MM.

Caregiver burden

Beyond the direct impact of the disease on patients, MM also has a detrimental impact on patients' carers. Caregivers may perform complicated technical procedures (e.g. dressing changes, intravenous line care and injections), assist the patient with daily living, attend appointments and take in complex information.⁸⁵ Of note, most of the clinical management of MM is provided in the outpatient setting, with the bulk of care provided by informal caregivers, Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

typically comprising patients' family and friends.⁸⁵ Therefore, the detrimental effects of MM on working life are not only experienced by patients, but also their carers.⁷⁴ A 2016 study carried out by Myeloma UK surveyed 374 carers of patients with MM and found that 71% were caring for a spouse or partner and 23% were caring for a parent.^{85, 86} Almost half (49%) of the partners of patients with MM reported symptoms of anxiety and 14% reported symptoms of depression.⁷⁴ Similarly, a recent Western Europe-based qualitative cross-sectional study of NDMM patients (N=164) and their caregivers (N=131) reported that caregivers' self-rated caring burden increased within the first year following diagnosis, with a peak in the burden reported after three months post-diagnosis. Of note, the study identified that caregivers of ASCT-ineligible patients consistently felt more burdened than those caring for ASCT-eligible patients. By month 12, half of the participating caregivers had developed stress, anxiety or depression, further highlighting that NDMM is burdensome for caregivers, as well as patients, even within the first year post-diagnosis.⁸⁷

Family members can neglect their own needs while providing practical and emotional support to patients. Thus, the emotional impact experienced by carers of patients with MM further hinders their ability to work, leading to loss of productivity and missed work days which contribute to the overall economic impact of MM. Caregivers can suffer financial difficulties as a result of a relative being diagnosed with MM; they may suffer from loss of wages, difficulty in paying bills, lack of sick leave and premature use of retirement funds.⁸⁵ In addition, MM causes productivity losses, on average carers lost 104.5 working hours per year due to providing informal care.⁸⁸

A targeted literature review carried out by J&J in 2023 to capture the quantitative impact of caregiving on the HRQoL of carers of patients with MM, reported that MM carers often experience reduced HRQoL due to increased stress levels, reduced productivity and financial strain.⁸⁶ The unmet need in supportive care is considerable and carers have specifically reported a need for help to manage the side effects and complications experienced by patients due to treatment for MM.⁷⁴

Disease burden

Patients diagnosed with MM still experience reduced life expectancy compared to the general population, particularly in patients who are ASCT-ineligible, as highlighted by the CASSIOPIEA (ASCT-eligible patients) and MAIA (ASCT-ineligible patients) trials.^{23, 24} The ASCT-ineligible population lacks access to the same range of treatments and consequently has poorer outcomes compared to ASCT-eligible patients. Despite advancements in therapies such as DLd for the ASCT-ineligible population, the disparity in life expectancy still exists. The US-based cross-sectional study of MM patients undergoing treatment indicated improving life expectancy is the primary goal of treatment, and most important to patients.⁸³ For the 70% of patients who are transplant-ineligible, there is a need for improvements in life expectancy, to bring treatment options and therefore survival in line with patients who are transplant-eligible.

1.3.4 Clinical management of MM and place of daratumumab in the treatment pathway

Treatment guidelines for the management of MM are available from the British Society for Haematology (BSH), European Society of Medical Oncology (ESMO), European Myeloma Network (EMN), National Comprehensive Cancer Network (NCCN) and NICE (NG35).^{31, 33, 89-91} NCCN and EMN guidelines have recently been updated to include DBLd as a treatment option in

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newly diagnosed transplant-ineligible patients.^{91, 92} The guidelines most relevant to the management of MM in UK clinical practice, and therefore informing the treatment pathway below (Figure 8), are the NICE NG35 guidelines as well as any technology recommendations published by NICE since the latest guideline update.³¹ Various regimens have been recommended by NICE for the treatment of MM, however several of these regimens are reserved for later treatment lines (see Figure 8).³¹

In the current NICE treatment guidelines (NG35), patients with newly diagnosed MM are initially assessed for suitability for intensive treatment, HDT followed by ASCT, according to factors such as age, frailty and performance status.^{31, 52} 'Fitter' patients typically receive an induction/consolidation regimen followed by treatment with high-dose chemotherapy and ASCT. However, many patients may not be fit enough to receive HDT-ASCT, given that the majority of patients in the UK with MM are diagnosed at a later age.¹⁸ The population of relevance to this submission is patients who are ineligible for ASCT and therefore the treatment pathway for ASCT-ineligible patients is discussed in more detail below.

Among patients who are ineligible for ASCT, NICE recommends the following treatments as first-line therapy options:

- Daratumumab in combination with lenalidomide and dexamethasone (DLd) (TA917)
- Lenalidomide in combination with dexamethasone (Ld) (TA587)
- Bortezomib in combination with an alkylating agent and a corticosteroid if the patient is unable to tolerate or has contraindications to thalidomide (TA228)
- Thalidomide in combination with an alkylating agent and a corticosteroid (TA228)

UK clinical experts at the UK Advisory Board held in May 2025 stated that DLd represents the current NHS SoC in the NDMM ASCT-ineligible population (with the treatment share for DLd as of May 2025 estimated to be 82.5% [range: 70–90%]), with very few patients receiving the other available treatment options such as Ld and bortezomib-based treatments.³ [REDACTED]

[REDACTED] It is J&J's understanding that the doublet regimen, Ld, is mainly reserved for patients who are not considered fit enough to receive a triplet regimen, or who live far from a hospital and prefer the convenience of an all oral option,⁵ and so would therefore also not receive a quadruplet therapy. Bortezomib combination therapies are typically only used in a very small proportion of patients with renal impairment (~5%). Additionally, results from the MAIA study (comparing DLd to Ld) and the indirect treatment comparison (ITC) comparing DLd to BMP in TA917 indicate that DLd is associated with significant improvement in survival gains compared with both Ld and BMP.^{5, 23} As such, DLd represents the first-line SoC in patients with NDMM who are ASCT-ineligible.⁵

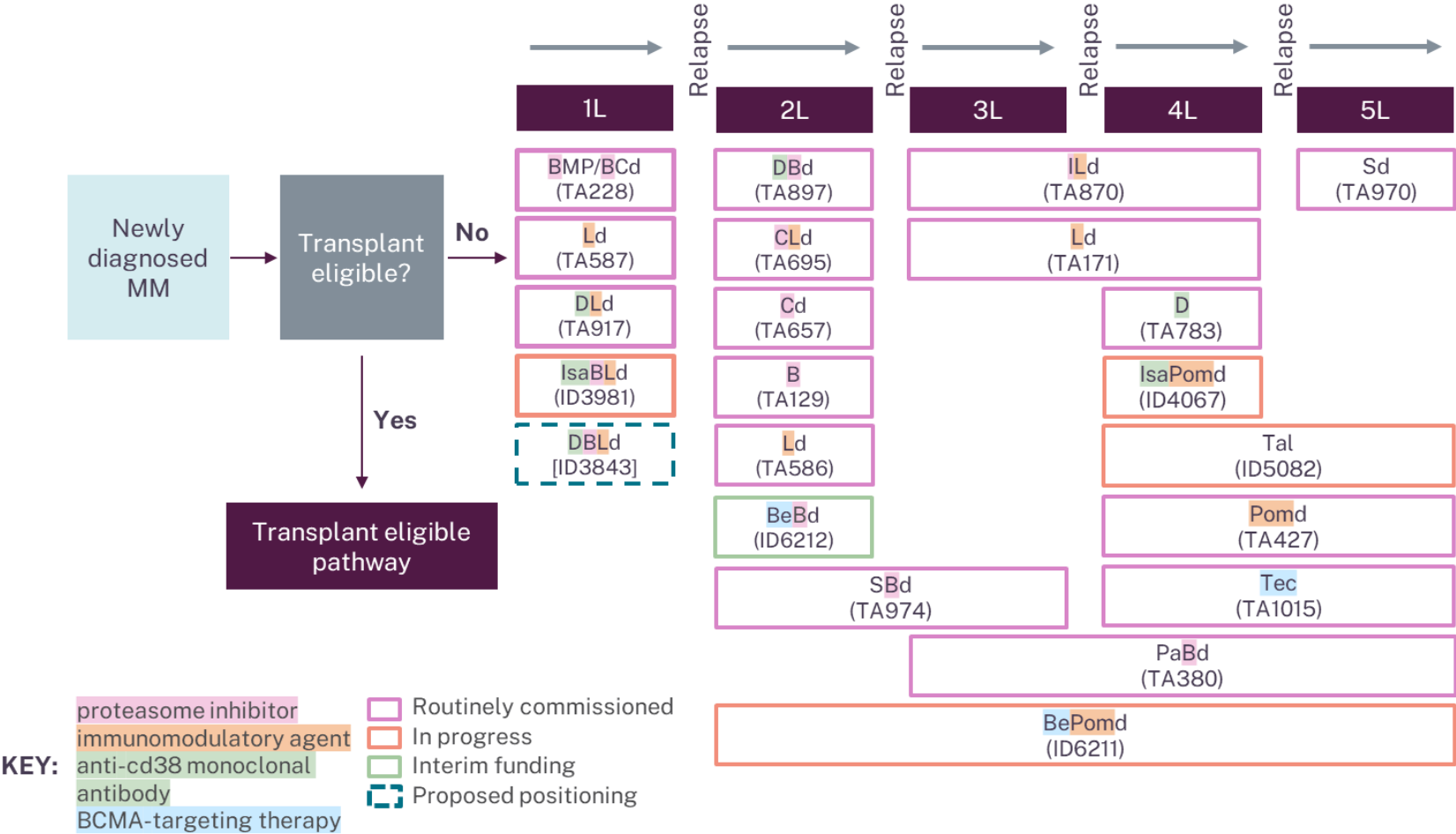
Thalidomide based treatments are no longer used in this patient population. This was agreed upon by clinical experts in the May 2025 UK Advisory Board who cited no thalidomide usage, as well as in the NICE final scope for ID3981 (in the same ASCT-ineligible NDMM population) and for this present submission (Table 1) where thalidomide treatments were not listed as relevant comparators.

However, most MM patients eventually require multiple lines of treatment due to the relapsing and remitting nature of the disease. The subsequent lines of treatment are highly individualised

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and dependent on response to previous therapies. Despite recent therapeutic advancements in the treatment of MM, almost all surviving patients eventually become refractory to existing treatment options, making MM progressively more difficult with each relapse.⁹³ Each additional line of therapy is associated with shorter remission periods, lower rates of deep response, and increased rates of toxicities and comorbidities.^{25, 94} Furthermore, patients ineligible for ASCT may not respond to salvage therapy at first relapse, or survive long enough to benefit from subsequent treatment lines.⁶⁷ It is therefore crucial that the most effective treatment regimens are used in the first-line in order to maximise OS by inducing the deepest levels of response and stabilising the disease for as long as possible whilst maintaining HRQoL. The available treatment options in UK clinical practice in the first-line setting and beyond are summarised in Figure 8 below for completeness.

Figure 8: Current treatment pathway for MM in England



Footnotes: This figure excludes Cancer drug fund (CDF)-approved treatments.

Abbreviations: 1/2/3/4L/5L: 1st/2nd/3rd/4th/5th line; BCd: bortezomib, cyclophosphamide and dexamethasone; BeBd: Belantamab mafodotin, bortezomib and dexamethasone; BePomd: belantamab mafodotin, pomalidomide and dexamethasone; BMP: bortezomib, melphalan and prednisolone/prednisone; Cd: carfilzomib and dexamethasone; CLd: carfilzomib, lenalidomide and dexamethasone; CD38: cluster of differentiation 38; D: daratumumab; DBd: daratumumab, bortezomib and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HDT: high dose therapy; ILd: ixazomib, lenalidomide and dexamethasone; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; IsaPomd: isatuximab, pomalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; MM: Multiple Myeloma; NHS: National Health Service; PaBd: panobinostat, bortezomib and dexamethasone; Pomd: pomalidomide and dexamethasone; RRMM: relapsed/refractory multiple myeloma; SBd: selinexor, bortezomib and dexamethasone; Sd: selinexor and dexamethasone; TA: technical appraisal; Tal: talquetamab; Tec: teclistamab.

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Unmet need

Treatment options that induce deep and durable responses are required to delay relapse and ultimately prolong survival

MM incidence rates in the UK have increased by approximately 10% over the past ten years and are projected to rise further.¹⁸ As detailed throughout Section 1.3, whilst treatable, MM remains an incurable disease. Surviving patients will inevitably relapse and progress on each line of therapy, as clones that remain following treatment will re-populate the disease via clonal expansion and evolution.^{8, 9} As such, combination treatment strategies that aim to tackle clonal heterogeneity and deliver higher rates of deep and sustained response are now recommended for routine clinical practice by the IMWG,⁵⁶ and have been demonstrated to be superior over single- or double-agent combinations in treating MM.^{95, 96} In fact, long-term disease control and ultimately, functional cure – where a patient's disease is kept under control for long enough so that they die of other causes, rather than myeloma – is emerging as a distinct possibility among patients who experience deep and durable responses over a prolonged period of time.⁹⁷

The daratumumab-based triplet therapy DLd was recommended by NICE in 2023 for the treatment of newly diagnosed adult patients with MM who are ineligible for ASCT (TA917).⁵ Findings from the MAIA trial (the pivotal trial for DLd in this indication) demonstrated statistically significant and clinically meaningful improvements in PFS (the primary endpoint of the MAIA trial) and OS in patients who received DLd compared with the doublet therapy Ld.²³ As such, DLd represents the current NHS SoC for ASCT-ineligible NDMM patients, as confirmed by clinical experts during Advisory boards held in November 2024 and May 2025.^{3, 98}

However, whilst the introduction of DLd has drastically improved clinical outcomes for ASCT-ineligible NDMM patients, only approximately a third of patients (32.1%) achieve MRD negativity and less than one fifth (18.8%) achieved durable MRD (defined as having MRD negativity for at least 12 months, also known as sustained MRD).⁵ As detailed in Section 1.3.1, MRD negativity is highly prognostic of long-term outcomes in MM, and given the genetically complex nature of MM and the need to limit re-population of the disease via clonal expansion and evolution, one of the primary aims of treatment in the first-line setting is to achieve deep and durable responses by eliminating as many clonal types as possible. There therefore exists an unmet need for a more effective first-line treatment option that achieves higher rates of MRD negativity and sustained MRD negative response which is expected to translate into improved PFS/OS and the prospect of achieving a functional cure for the best responders.

Positioning of DBLd in the UK MM treatment pathway

DBLd is being positioned as a first-line treatment for adult patients with NDMM who are ineligible for ASCT (Figure 8). As DLd represents the predominantly used treatment in this setting with current patient share of over 80%, DLd is considered the main relevant comparator.⁵

The proposed positioning of DBLd and identification of DLd as the most relevant comparator in this setting was supported by feedback received from UK clinical experts consulted as part of the May 2025 UK Advisory Board. Specifically, the clinicians noted that, given DBLd comprises the same treatments as DLd with the addition of bortezomib, it is anticipated that DBLd will displace DLd among patients who are able to tolerate the quadruplet regimen.³ Of note, DBLd is not expected to displace Ld, given patients who are unable to tolerate DLd (and therefore remain on treatment with Ld) would also be unable to tolerate the quadruplet regimen of DBLd.

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Bortezomib is a PI that induces cancer cell apoptosis.¹² Bortezomib has been extensively studied either alone or in combination with other agents for the treatment of MM.⁹⁹ The introduction of bortezomib in combination with other agents has been shown to prolong survival in both relapsed and NDMM patients.¹³ Additionally, comparisons of the efficacy of DBLd (in the CEPHEUS trial) compared to DLd (in the MAIA trial) indicate that DBLd offers significantly improved rates of MRD negativity which are sustained over time, translating into improvements in long-term PFS and OS when compared to DLd (see Section 2.10.2).

Additionally, at present, there is a considerable disparity in the range of treatment options available to NDMM patients. Among ASCT-eligible NDMM patients, the recent introduction of the quadruplet regimen DBTd to the treatment pathway as induction/consolidation therapy has provided a step-change in efficacy with substantially improved outcomes.⁵² However, no quadruplet therapies are currently available for patients with NDMM who are ineligible for ASCT. As a key goal of treatment is to effectively target and eliminate all clonal and subclonal mutations (see Section 1.3.1), it is paramount that ASCT-ineligible patients are also afforded access to a quadruplet regimen. Specifically, the DBLd combination therapy (comprising an anti-CD38 mAB [daratumumab], a PI [bortezomib], an iMiD [lenalidomide] and a glucocorticoid [dexamethasone]) exhibits synergistic effects through targeting multiple biological pathways, thereby maximising cytotoxicity and inducing deeper and more durable responses compared to agents targeting fewer pathways. The introduction of DBLd as the first quadruplet combination therapy in this population therefore presents an opportunity to reduce disparities in available treatment options (and ultimately outcomes) across patients with NDMM.

In summary, access to DBLd in the first-line ASCT-ineligible setting is important to optimise long-term clinical outcomes, minimise disparities in available treatment options between ASCT-eligible and ASCT-ineligible patients, and is imperative to build upon the improvements in prognosis initiated with DLd.

1.4 *Equality considerations*

No equality considerations related to the use of DBLd for the treatment of ASCT-ineligible NDMM patients have been identified.

2 Clinical effectiveness

The CEPHEUS trial compared DBLd versus BLd in patients with NDMM ineligible for ASCT

- An SLR identified the CEPHEUS trial as the only viable source of efficacy and safety data for DBLd in this indication. The CEPHEUS trial is an ongoing, randomised, open-label, multicentre, Phase III trial comparing DBLd versus BLd in patients with NDMM for whom hematopoietic stem cell transplant is not planned as initial therapy
- The CEPHEUS trial population is slightly broader than the NICE scope. CEPHEUS includes both ASCT-ineligible patients and those who are eligible for and have refused treatment with ASCT. To align with the target population of this submission, and what is recognised in UK clinical practice, the focus of this section is on the population of patients in CEPHEUS who are specifically ASCT-ineligible
- UK clinical experts confirmed the ASCT-ineligible subgroup is the most relevant population for this submission, and that these patients are broadly generalisable to UK clinical practice
- The CEPHEUS trial was conducted at the height of the COVID-19 pandemic. Overall, █% of study participants in the ASCT-ineligible population died due to COVID-19, with an █ in COVID-19 deaths between the DBLd (n=█) and BLd (n=█) arms. To account for this, additional analyses were conducted adjusting for COVID-19 deaths

DBLd demonstrated statistically significant and clinical meaningful improvement across the primary and secondary endpoints compared to BLd

- The primary endpoint of overall MRD negativity was met in the ASCT-ineligible subgroup of CEPHEUS, with DBLd resulting in a statistically significant and clinically meaningful improvement in overall MRD negativity rate (at 10^{-5}) compared with BLd (DBLd: 60.4%; BLd: 39.3%; OR: 2.365 (1.471; 3.802); 2-sided nominal $p=0.0004$)
- In the ASCT-ineligible population, treatment with DBLd also demonstrated a statistically significant and clinically meaningful improvement in response rates (sCR, ORR, $\geq$ VGPR and $\geq$ CR) compared to BLd. These improvements translated to a significant improvement in PFS (HR: 0.51 (95% CI: 0.35, 0.74; 2-sided nominal $p=0.0003$)
- Median OS was not reached in either arm for the ASCT-ineligible subgroup, although CEPHEUS demonstrated a positive trend towards OS benefit in favour of the DBLd arm versus BLd (0.66 (95% CI: 0.42, 1.03; $p=0.0682$) which was statistically significant when adjusting for COVID-19 deaths (HR: 0.55 [95% CI: 0.34, 0.90]; p -value=0.0159)

Improvements in HRQoL and physical functioning were observed in both DBLd and BLd treatment arms

- Improvement in HRQoL and physical functioning, as well as reductions in symptoms (pain, fatigue, overall disease symptoms) as measured by EORTC QLQ-C30 and EORTC QLQ-MY20 scale scores and EQ-5D-5L, were observed in both DBLd and BLd arms.
- Data were similar across treatment arms supporting no detriment of HRQoL, symptoms or functioning with the addition of daratumumab to BLd

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DBLd was well tolerated with clinically manageable side effects

- DBLd was well tolerated, with clinically manageable side effects and safety data consistent with the known safety profiles of daratumumab and BLd
- All patients experienced treatment-emergent AEs. Although a slightly higher proportion of patients in the DBLd arm experienced a serious TEAE (DBLd: 72.2%; BLd: 69.7%), fewer patients on DBLd discontinued treatment due to TEAEs (DBLd: █%; BLd: █%)

An ITC using IPD from the CEPHEUS and MAIA trials utilising an IPTW approach was used to compare DBLd to the current UK SoC, DLd, in ASCT-ineligible NDMM patients

- Eleven key prognostic variables were adjusted for in the base case ITC analysis using an ATE approach. Following adjustment, the two trial arms (DBLd from CEPHEUS and DLd from MAIA) were highly matched with respect to all prognostic variables.

COVID-19 disproportionately impacted CEPHEUS compared to MAIA. To avoid any risk of bias, the base case ITCs censored all patients who died due to COVID-19 in both trials

- Unlike MAIA, the CEPHEUS trial began during the height of the pandemic, with █% of all deaths among patients treated with DBLd in CEPHEUS due to COVID-19, compared to █% of all deaths among patients treated with DLd in MAIA.
- The disproportionate impact of COVID-19 can be explained by the timing of study enrolment with patients in MAIA in (long-term) remission when the pandemic first started, compared to CEPHEUS, where patients were first presenting with MM and were therefore much more clinically vulnerable.
- To avoid any risk of bias in the base case ITCs, all deaths due to COVID-19 were censored in both the CEPHEUS and MAIA trial populations in analyses of PFS, OS and TTD

Patients receiving DBLd were over three times more likely to achieve ≥CR and MRD-negativity versus DLd, which translated into statistically significant PFS and OS benefits

- The addition of bortezomib to DLd resulted in clinically meaningful improvements in all outcomes (PFS, PFS2, ORR, ≥VGPR, ≥CR, MRD negative CR rate and OS); all of the base case ITC results were statistically significant in favour of DBLd
 - Patients receiving DBLd were more than three times more likely to achieve ≥CR and MRD negativity compared to DLd (≥CR OR: 3.58 [95% CI: 2.21, 5.79]; MRD-negativity OR: 3.04 [95% CI: 2.01, 4.61])
 - DBLd significantly extended both PFS and OS versus DLd. In the base case ITCs, DBLd reduced the risk of disease progression or death by 45% versus DLd (HR: 0.55 [95% CI: 0.38, 0.79]), and the risk of death by 37% (HR: 0.63 95% CI: 0.41, 0.98)
- The base case results were consistent across a range of sensitivity analyses that explored additional covariates, the impact of COVID-19 adjustment and alternative ITC methodologies, as well as a supplementary NMA, supporting the robustness of the base case ITC

DBLd resulted in statistically significant and clinically meaningful improvements in PFS and OS versus other treatments listed in the NICE final scope

- While DLd represents the key comparator in this submission, supportive ITCs (including COVID-19 adjustment) also explored the relative efficacy of DBLd versus Ld, BMP and BCd
- Compared to Ld (in MAIA), DBLd resulted in statistically significant improvements in OS (HR: 0.43 [95% CI: 0.28, 0.66]; $p < 0.0001$), PFS (HR: 0.30 [95% CI: 0.21, 0.43]; $p < 0.001$) and TTD (HR: 0.41 [95% CI: 0.31, 0.54]; $p < 0.0001$)
- DBLd also results in a greater OS benefit (HR: 0.36 [95% CI 0.23, 0.57]) and improved PFS (HR: 0.16 [95% CI: 0.10, 0.25]) when compared to BMP (in the ALCYONE trial)
- No clinical trial evidence was available for BCd. UK clinical experts supported an assumption of equal efficacy between BMP and BCd and is also supported by a naïve comparison of UK Real World Evidence (RWE), meaning the ITC results versus BMP can also be considered a proxy for ITC results between DBLd and BCd

DBLd represents a further step-change in the treatment pathway for ASCT-ineligible patients, bridging the gap in treatments available, and expected outcomes, for NDMM regardless of transplant eligibility

- The high proportion of patients experiencing MRD negativity with DBLd, compared to DLd, indicates that the quadruplet combination therapy tackles further aspects of the clonal heterogeneity of MM. Achieving higher rates of MRD negativity is expected to translate to OS improvements and the prospect of a functional cure among ASCT-ineligible patients
- As a result, the introduction of DBLd has the potential to provide ASCT-ineligible MM patients with an effective treatment option with the potential to deliver similar rates of response and MRD-negativity to the current SoC for ASCT-eligible patients (daratumumab, bortezomib, thalidomide and dexamethasone [DBTd] in combination with ASCT)

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was initially conducted in November 2020, and subsequently updated in August 2024, to identify any published evidence on the clinical efficacy/effectiveness and safety of treatments used in patients with NDMM who are ASCT-ineligible. A further update was conducted in April 2025, to identify clinical efficacy/effectiveness and safety data for daratumumab and relevant comparators in patients with NDMM for the purposes of the current submission. The SLRs adhered to established methods for conducting SLRs and were reported in accordance with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) statement.¹⁰⁰

Following prioritisation of studies reporting on relevant comparators for the purposes of the current submission (DBLd, DLd, BMP, Ld and BCd), 13 publications reporting on 9 unique studies were extracted. From the previous SLRs, 77 publications reporting on 24 unique studies reported data for relevant comparators for the purposes of the current submission, resulting in a total of 90 prioritised publications reporting on 27 unique studies. Of these, only one study reported on DBLd as a treatment for patients with NDMM who are ASCT-ineligible – the CEPHEUS trial.

Full details of the SLR search strategies, study selection processes and results are presented in Appendix B.

2.2 List of relevant clinical effectiveness evidence

CEPHEUS (NCT03652064) is an ongoing, randomised, open-label, multicentre, Phase III trial conducted across 98 centres that enrolled participants in Brazil, Canada, Czech Republic, France, Germany, Israel, Japan, Netherlands, Poland, Spain, Turkey, United Kingdom, and United States. CEPHEUS forms the principal clinical evidence base for DBLd in the treatment of NDMM in ASCT-ineligible patients comparing DBLd to BLd. An overview of the CEPHEUS trial is provided below in Table 3.

As described in Table 3, the population of patients enrolled in CEPHEUS was slightly broader than the population of relevance to this submission. The patient population in CEPHEUS was patients with NDMM for whom hematopoietic stem cell transplant is not planned as initial therapy. This population of patients comprised:

- Patients aged <70 years and ineligible for ASCT
- Patients aged <70 years and refused transplant
- Patients aged ≥70 years

However, the patient population of relevance to this submission as outlined in Section 1.1, is adult patients with NDMM who are ineligible for ASCT, and therefore patients aged <70 years and refused transplant in CEPHEUS do not fall within the remit of this target population. Feedback from UK clinical experts confirmed this “transplant-deferred/refused transplant” group of patients is not recognised as a distinct clinical subgroup for treatment in UK clinical practice and so is not relevant for the purposes of this submission. As such, the evidence included in this submission focuses on the ASCT-ineligible population of CEPHEUS, which comprises the subgroups of patients aged <70 years and ineligible for ASCT, and aged ≥70 years.

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Table 3: Clinical effectiveness evidence

Study	CEPHEUS (NCT03652064)
Study design	Ongoing, randomised, open-label, multicentre, Phase III trial assessing the efficacy and safety of DBLd versus BLd
Population	- As of 7th May 2024 (data cut-off [DCO] for the final PFS analysis), 395 patients had been randomised in CEPHEUS (intent-to-treat [ITT] analysis set: DBLd: 197; BLd: 198) and 392 (197 for DBLd and 195 for BLd) had received ≥ 1 dose of the assigned treatment (safety analysis set). - For the ASCT-ineligible population, as of 7th May 2024, 289 patients had been randomised (ASCT-ineligible ITT analysis set; DBLd: 144; BLd: 145), and 286 had received ≥ 1 dose of the assigned treatment (ASCT-ineligible safety analysis set; DBLd: 144; BLd: 142).
Intervention(s)	DBLd in the following dosing: Subcutaneous daratumumab: 1,800 mg per week during Cycles 1 and 2 (21-day cycles); 1,800 mg every 3 weeks during Cycles 3–8 (21-day cycles); 1,800 mg every 4 weeks during Cycle 9 and beyond (28-day cycles) until the participant had disease progression or experienced an unacceptable toxicity Subcutaneous bortezomib: 1.3 mg/m² bortezomib as a subcutaneous injection twice weekly on Days 1, 4, 8, and 11 of each 21-day cycle for Cycles 1–8^a Oral lenalidomide: 25 mg orally each day on Days 1 through 14 of each 21-day cycle for patients with CrCl ≥ 60 mL/min. During Cycles 9 and beyond, lenalidomide 25 mg administered daily on Days 1–21 of each 28-day cycle. Lenalidomide continued until disease progression or unacceptable toxicity whichever occurs first Oral or intravenous dexamethasone: 20 mg self-administered orally on Days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for Cycles 1–8. For patients older than 75 years or underweight (body mass index [BMI] < 18.5), the dexamethasone dose administered at a dose of 20 mg on days 1, 4, 8, and 11. In Cycle 9 and beyond, dexamethasone self-administered orally at a total dose of 40 mg on Days 1, 8, 15, 22 of each 28-day cycle. For patients older than 75 years or underweight (BMI < 18.5), the dexamethasone dose administered at a dose of 20 mg weekly. The dexamethasone 20 mg oral or IV dose administered as a pre-injection medication on daratumumab injection days, replaced the oral dexamethasone dose for that day
Comparator(s)	BLd in the following dosing: Subcutaneous bortezomib:^b 1.3 mg/m² bortezomib as a subcutaneous injection twice weekly on Days 1, 4, 8, and 11 of each 21-day cycle for Cycles 1–8 Oral lenalidomide: 25 mg orally each day on Days 1 through 14 of each 21-day cycle for patients with CrCl ≥ 60 mL/min. During Cycles 9 and beyond, lenalidomide 25 mg administered daily on Days 1–21 of each 28-day cycle. Lenalidomide continued until disease progression or unacceptable toxicity whichever occurs first Oral or intravenous dexamethasone: 20 mg self-administered orally on Days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for Cycles 1–8. For patients older than 75 years or underweight (BMI < 18.5), the

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Study	CEPHEUS (NCT03652064)
	dexamethasone dose administered at a dose of 20 mg on days 1, 4, 8, and 11. In Cycle 9 and beyond, dexamethasone self-administered orally at a total dose of 40 mg on Days 1, 8, 15, 22 of each 28-day cycle. For patients older than 75 years or underweight (BMI <18.5), the dexamethasone dose administered at a dose of 20 mg weekly
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	N/A
Reported outcomes specified in the decision problem	Primary endpoint: - Overall MRD negativity rate (10⁻⁵)^c Secondary endpoints: - OS - PFS - Response rates ≥CR - ORR ≥VGPR - Time to response - DOR - Time to treatment discontinuation (TTD) - Minimal residual disease (MRD) negativity^c - Sustained MRD negativity - Landmark MRD negativity rate at 1 year - AEs - HRQoL outcomes: - EORTC QLQ-C30 scores - EORTC QLQ-MY20 scores - EQ-5D-5L scores
All other reported outcomes presented in the submission	PFS2

Footnotes: ^aIn UK clinical practice, the full bortezomib dose is given once weekly as advised in the November 2024 and May 2025 UK Advisory Boards. ^b For patients who experienced injection-site reactions at the subcutaneous administration site, bortezomib was able to be administered by IV injection ^cAssessed for patients that achieved a ≥CR.

Abbreviations: AEs: adverse events; ASCT: autologous stem cell transplantation; BLd: bortezomib, lenalidomide and dexamethasone; BMI: body mass index; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; EORTC: European organisation for Research and Treatment of Cancer; EQ-5D-5L: European Quality of Life Five Dimension Five Level Questionnaire; HDT: high-dose therapy; HRQoL: health-related quality of life; ITT: intent-to-treat; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival; rHuPH20: recombinant human PH20 hyaluronidase.

Source: J&J Data on File (CEPHEUS Clinical Study Report);¹⁰¹ J&J Data on File (CEPHEUS Clinical Protocol)¹⁰²

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

2.3.1 *Trial design*

CEPHEUS was designed to compare the efficacy of DBLd with that of BLd in patients with untreated MM for whom ASCT is not planned as initial therapy. Patients eligible for inclusion in the study were aged 18 years or older, had NDMM, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, and were not considered a candidate for high-dose chemotherapy with SCT. Patients were not considered eligible for ASCT if they were ≥65 years of age or if they were 18–65 years of age with comorbid conditions that would have a negative impact on tolerability to HDT with ASCT or who refuse HDT with ASCT as initial treatment. As mentioned above, the CEPHEUS population of relevance to this submission is the ASCT-ineligible population (i.e., excluding the population of patients refusing ASCT).

An overview of the CEPHEUS trial design is provided in Figure 9. Patients were randomly allocated to either Arm A (BLd) or Arm B (DBLd). Specifically, eligible patients were stratified by ISS (Stage I, II, or III, based on β -2 microglobulin and albumin by central laboratory), and age/transplant eligibility (<70 years ineligible, or age <70 years and refused transplant, or age ≥70 years), and then assigned randomly to 1 of 2 treatment arms in a 1:1 ratio based on an algorithm implemented in the interactive web response system (IWRS) before the study.

The study consisted of 3 phases: a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase was up to 28 days before randomisation. Participants received either DBLd or BLd for 8 cycles (of 21 days), following which no patient was to receive bortezomib after completion of the first 8 cycles of BLd.

During the Treatment Phase, participants were to receive treatment for 8 cycles with either:

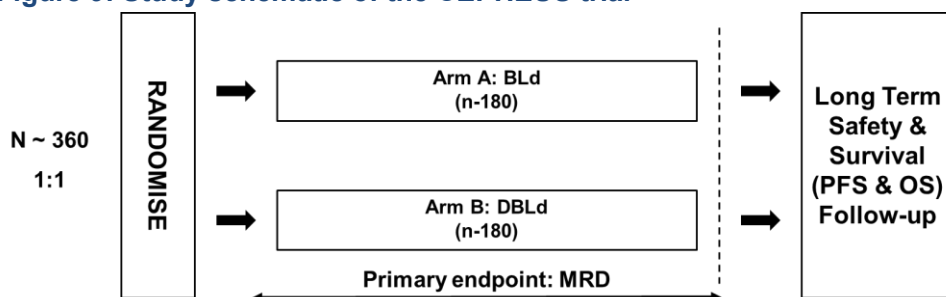
- **Arm A:** BLd alone for eight cycles followed by Ld alone until disease progression or unacceptable toxicity
- **Arm B:** DBLd for eight cycles followed by DLd therapy until disease progression or unacceptable toxicity

Participants who discontinued treatment with any component of study treatment (bortezomib, lenalidomide, dexamethasone, or daratumumab) could continue to receive treatment with the other components of study treatment, as assigned.

Participants were to enter the Follow-up Phase once they had documented disease progression or an unacceptable toxicity and all treatment was discontinued. Participants who discontinued before disease progression were to continue to have disease evaluations confirmed disease progression, death, withdrawal of consent, loss to follow-up, or the end of data collection. After disease progression was documented, follow-up evaluations were to continue at least every 16 weeks until the final PFS analysis. Subsequent anticancer treatment, PFS2 (per investigator judgement), second primary malignancies, and survival were to be recorded.

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Figure 9: Study schematic of the CEPHEUS trial



Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; MRD; minimal residual disease; OS: overall survival; PFS: progression-free survival

Source: J&J Data on File (CEPHEUS Clinical Study Report: Figure 1);¹⁰¹ J&J Data on File (CEPHEUS Clinical Protocol)¹⁰²

2.3.2 Trial methodology

A summary of the methodology and trial design of CEPHEUS is presented in Table 4.

Table 4: Summary of CEPHEUS trial methodology

Trial name	CEPHEUS
Location	114 centres across Brazil (N=10), Canada (N=9), Czechia (N=5), France (N=8), Germany (N=7), Israel (N=8), Japan (N=13), Netherlands (N=3), Poland (N=10), Spain (N=6), Turkey (N=7), United Kingdom (N=9), and United States (N=19)
Trial design	An ongoing, randomised, open-label, multicentre, Phase III trial that evaluates DBLd versus BLd in participants with NDMM for whom an ASCT was not planned as initial therapy.
Eligibility criteria for patients	Key inclusion criteria: - Newly diagnosed patients and not considered a suitable candidate for high-dose chemotherapy with stem cell transplant (SCT) due to: - being age ≥ 65 years or - age 18-65 years with presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with SCT or who refuse high-dose chemotherapy with SCT as initial treatment - Diagnosis of multiple myeloma as documented per IMWG criteria: monoclonal plasma cells in the bone marrow $\geq 10\%$ or the presence of a biopsy proven plasmacytoma and documented MM satisfying at least one of the CRAB criteria or biomarkers of malignancy criteria - ECOG performance status score of 0, 1, or 2 - Have measurable disease defined by any of the following: - Immunoglobulin G (IgG), IgA, IgM, IgD, or IgE MM: serum M-protein level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours, or - Light chain MM without measurable disease in serum or urine: serum Ig free light chain (FLC) ≥ 10 mg/dL and abnormal serum Ig kappa lambda FLC ratio Key exclusion criteria: - Frailty index of ≥ 2 according to Myeloma Geriatric Assessment score - Prior therapy for multiple myeloma other than a short course of corticosteroids - Prior or concurrent invasive malignancy (other than multiple myeloma) within 5 years of date of randomisation - Peripheral neuropathy or neuropathic pain Grade 2 or higher - Focal radiation therapy within 14 days of randomisation with the exception of palliative radiotherapy for symptomatic pain

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	management • Plasmapheresis within 28 days of randomization. • Clinical signs of meningeal involvement of multiple myeloma • Chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted • Moderate or severe persistent asthma within the past 2 years, uncontrolled asthma of any classification. • Seropositive for human immunodeficiency virus (HIV) or hepatitis B or C • Concurrent medical or psychiatric condition or disease • Has clinically significant cardiac disease • Received a strong CYP3A4 inducer within 5 half-lives prior to randomisation • Allergy, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients or sensitivity to mammalian-derived products or lenalidomide
Method of study drug administration	See Table 3.
Permitted and disallowed concomitant medication	Permitted: • Colony stimulating factors, erythropoietin, and transfusion of platelets and red cells • Loperamide recommended for the treatment of diarrhoea, starting at the time of the first watery stool • Prevention of constipation • Adequate hydration recommended for prevention of myeloma-related kidney disease • Prophylactic antiemetics, except for corticosteroids • An emergency short course of corticosteroid (equivalent of dexamethasone 40 mg/day for a maximum 4 days) permitted before treatment • G-CSF/plerixafor for mobilisation of stem cells • Single dose of cyclophosphamide for mobilisation of stem cells • Vaccination recommended per local guidelines Prohibited: • Concomitant administration of strong CYP3A4 inducers prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) should be avoided and not recommended in patients receiving bortezomib • Other agents that target CD38 • Medications used for other indications that have anti-myeloma properties

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	• Approved or investigational treatments for multiple myeloma (including but not limited to conventional chemotherapies, IMiDs, or PIs) • Concomitant administration of investigational agents prohibited, including administration of commercially available agents with activity against or under investigation for multiple myeloma • Systemic corticosteroids (>10 mg dexamethasone per day or equivalent, or a total maximum dose of 140 mg dexamethasone or equivalent in 14 days) other than those given for injection related reactions (IRRs) • Non-steroidal anti-inflammatory agents should be avoided as they may exacerbate myeloma-related kidney disease
Primary outcome	Overall MRD negativity rate, defined as the proportion of patients who have achieved MRD negative status (at 10^{-5}) by bone marrow aspirate after randomisation and prior to progressive disease (PD) or subsequent anti-myeloma therapy
Other secondary outcomes	• See Table 3.
Pre-planned subgroups	• Sex (male versus female) • Age (<70 versus ≥ 70) • Region (Europe versus North America versus Other) • Weight (≤ 65 kg versus >65–≤ 85 kg versus >85 kg) • IWRS ISS Stage (Stage I versus Stage II versus Stage III) • Cytogenic risk (standard versus high) • ECOG performance score at baseline (0 versus ≥ 1)
Duration of study and follow-up	The first patient in the study was screened on 15 th November 2018 and at the latest data cut (final PFS analysis; May 2024), the median duration of follow-up was 58.7 months (range: 0.1–64.7 months) for the ITT analysis set.

Footnotes: ^a For patients who experienced injection-site reactions at the subcutaneous administration site, bortezomib was able to be administered by IV injection.

Abbreviations: ASCT: autologous stem cell transplantation; COPD: Chronic obstructive pulmonary disease; CR: complete response; CRAB: hypercalcemia, renal dysfunction, anaemia, bone pain; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; EORTC: European organisation for Research and Treatment of Cancer; EQ-5D-5L: European Quality of Life Five Dimension Five Level Questionnaire; FEV1: forced expiratory volume in 1 second; G-CSF: Granulocyte colony-stimulating factor; HDT: high-dose therapy; HIV: human immunodeficiency virus; Ig: immunoglobulin; IMiD: immunomodulatory drug; IRR: injection related reactions; MRD: minimal residual disease; NDMM: newly diagnosed multiple myeloma; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PI: proteasome inhibitors; rHuPH20: recombinant human PH20 hyaluronidase; VGPR: very good partial response.

Source: J&J Data on File (CEPHEUS Clinical Study Report);¹⁰¹ J&J Data on File (CEPHEUS Clinical Protocol)¹⁰² Usmani *et al.* (2025)¹⁰³

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2.3.3 Demographic and baseline disease characteristics

ITT analysis set

The population of relevance to this submission is the ASCT-ineligible subgroup of CEPHEUS. However, for completeness, a summary of patient demographics and other baseline characteristics for the 395 patients in the ITT analysis set of the CEPHEUS trial, including both patients with NDMM who are ineligible for ASCT and patients who refused ASCT, is provided below. Demographic and baseline disease characteristics were generally balanced between the two treatment arms.

Table 5: Summary of baseline demographic and disease characteristics (ITT analysis set)

Characteristics	ITT analysis set		
	BLd N=198	DBLd N=197	Total N=395
Age, years			
Mean (SD)	██████	██████	██████
Median (range)	70 (31, 80)	70 (42, 79)	70 (31, 80)
Overall age group, n (%)			
<65	35 (17.7%)	36 (18.3%)	71 (18.0%)
≥65 and <70	53 (26.8%)	52 (26.4%)	105 (26.6%)
≥70	110 (55.6%)	109 (55.3%)	219 (55.4%)
Sex, n (%)			
Male	111 (56.1%)	87 (44.2%)	198 (50.1%)
Female	87 (43.9%)	110 (55.8%)	197 (49.9%)
Race, n (%)			
White	156 (78.8%)	162 (82.2%)	318 (80.5%)
Black or African American	9 (4.5%)	10 (5.1%)	19 (4.8%)
Asian	14 (7.1%)	11 (5.6%)	25 (6.3%)
Native Hawaiian or other Pacific Islander	1 (0.5%)	0	1 (0.3%)
Other	2 (1.0%)	1 (0.5%)	3 (0.8%)
Not reported	16 (8.1%)	13 (6.6%)	29 (7.3%)
Ethnicity, n (%)			
Hispanic or Latino	██████	██████	██████
Not Hispanic or Latino	██████	██████	██████
Not reported	██████	██████	██████
Body weight, kg			
Category, n (%)			
≤65	63 (31.8%)	58 (29.4%)	121 (30.6%)
>65 and ≤ 85	88 (44.4%)	101 (51.3%)	189 (47.8%)
>85	47 (23.7%)	38 (19.3%)	85 (21.5%)

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Mean (SD)			
Median (range)			
Height, cm			
Mean (SD)			
Median (range)			
Body surface area (BSA), m²			
Mean (SD)			
Median (range)			
Baseline ECOG, n (%)			
0	84 (42.4%)	71 (36.0%)	155 (39.2%)
1	100 (50.5%)	103 (52.3%)	203 (51.4%)
2	14 (7.1%)	23 (11.7%)	37 (9.4%)
Total Additive (Frailty) Score			
Fit (score=0)	132 (66.7%)	124 (62.9%)	256 (64.8%)
Intermediate-fitness (score=1)	66 (33.3%)	73 (37.1%)	139 (35.2%)
Type of myeloma by immunofixation or serum FLC assay, n (%)			
IgG			
IgA			
IgM			
IgD			
IgE			
Light chain			
Kappa			
Lambda			
FLC-Kappa ^a			
FLC-Lambda ^b			
Biclonal			
Negative Immunofixation			
Unknown			
Type of measurable disease, n (%)^c			
Serum	108 (54.5%)	120 (60.9%)	228 (57.7%)
IgG	76 (38.4%)	89 (45.2%)	165 (41.8%)
IgA	31 (15.7%)	27 (13.7%)	58 (14.7%)
Other ^d	1 (0.5%)	4 (2.0%)	5 (1.3%)
Serum and urine	45 (22.7%)	41 (20.8%)	86 (21.8%)
Urine only	24 (12.1%)	20 (10.2%)	44 (11.1%)
Serum FLC	21 (10.6%)	16 (8.1%)	37 (9.4%)
ISS Staging, n (%)^e			

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Stage I	68 (34.3%)	68 (34.5%)	136 (34.4%)
Stage II	75 (37.9%)	73 (37.1%)	148 (37.5%)
Stage III	55 (27.8%)	56 (28.4%)	111 (28.1%)
Time since initial MM diagnosis, months			
Mean (SD)	██████	██████	██████
Median (range)	██████	██████	██████
Number of lytic bone lesions, n (%)			
None	██████	██████	██████
1-3	██████	██████	██████
4-10	██████	██████	██████
>10	██████	██████	██████
Presence of extramedullary plasmacytomas, n (%)			
Yes	██████	██████	██████
No	██████	██████	██████
Presence of evaluable bone marrow assessment, n (%)			
Yes	██████	██████	██████
No	I	██████	██████
% Plasma cells, bone marrow biopsy/aspirate			
<10	██████	██████	██████
10-30	██████	██████	██████
30-60	██████	██████	██████
>60	██████	██████	██████
% Plasma cells, bone marrow biopsy			
<10	██████	██████	██████
10-30	██████	██████	██████
>30-60	██████	██████	██████
>60	██████	██████	██████
% Plasma cells, bone marrow aspirate			
<10	██████	██████	██████
10-30	██████	██████	██████
>30-60	██████	██████	██████
>60	██████	██████	██████
Bone marrow cellularity by biopsy, n (%)			
Hypercellular	██████	██████	██████
Normocellular	██████	██████	██████
Hypocellular	██████	██████	██████
Indeterminate	██████	██████	██████
Bone marrow cellularity by aspirate, n (%)			
Hypercellular	██████	██████	██████
Normocellular	██████	██████	██████

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Hypocellular			
Indeterminate			
Cytogenetic risk, n (%)			
Standard risk ^f	149 (75.3)	149 (75.6)	298 (75.4%)
High risk ^f	27 (13.6)	25 (12.7)	52 (13.2%)
del(17p)			
t(4;14)			
t(14;16)			
Un-evaluable or missing	22 (11.1)	23 (11.7)	45 (11.4%)

Footnotes: ^a Includes participants without a positive immunofixation but with evidence of free light chain kappa by FLC testing.

^b Includes participants without a positive immunofixation but with evidence of free light chain lambda by FLC testing.

^c Includes participants without measurable disease in serum and urine.

^d Includes IgD, IgM, IgE and biclonal.

^e ISS staging is derived based on the combination of serum β 2-microglobulin and albumin.

^f Standard risk includes participants who are negative for del17p, t(14;16), or t(4;14) by FISH. High risk includes the participants who are positive for any of del17p, t(14;16), or t(4;14) by FISH.

Percentages calculated with the number of participants in each dose level with available data as denominator

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; BSA: body surface area; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ECOG: Eastern Cooperative Oncology Group; FLC: free light chain; Ig: immunoglobulin; ISS: International Staging System; ITT: intent-to-treat; SD: standard deviation.

Source: J&J Data on File (CEPHEUS Clinical Study Report May 2024 DCO: Tables 4-5);¹⁰¹ J&J Data on File (CEPHEUS Clinical Protocol);¹⁰² Usmani *et al.* (2025).¹⁰³

ASCT-ineligible ITT analysis set

A summary of patient demographics and other baseline disease characteristics for the 289 patients in the ASCT-ineligible ITT analysis set is provided in Table 6 below. Demographic and baseline disease characteristics were generally balanced between the two treatment arms. At the May 2025 UK Advisory Board, clinical experts confirmed that the baseline characteristics of ASCT-ineligible patients in the CEPHEUS trial are broadly generalisable to patients in UK clinical practice.³

Table 6: Summary of baseline demographic and disease characteristics (ASCT-ineligible ITT analysis set)

Characteristics	ASCT-ineligible ITT analysis set		
	BLd (N=145)	DBLd (N=144)	Total (N=289)
Age, years			
Mean (SD)			
Median (range)	72.0 (51, 80)	72.0 (58, 79)	72.0 (51, 80)
Overall age group, n (%)			
<65			
≥65 to <70			
≥70			
Stratification factor age/transplant			
<70 ineligible	35 (24.1%)	35 (24.3%)	70 (24.2%)
≥70			

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Sex, n (%)			
Female	63 (43.4%)	79 (54.9%)	142 (49.1%)
Male	82 (56.6%)	65 (45.1%)	147 (50.9%)
Region, n (%)			
Europe			
North America			
Other			
Race, n (%)			
White			
Other			
Missing			
Body weight, kg			
Category, n (%)			
≤65			
>65 and ≤ 85			
>85			
Mean (SD)			
Median (range)			
Baseline ECOG, n (%)			
0	57 (39.3%)	52 (36.1%)	109 (37.7%)
1	78 (53.8%)	75 (52.1%)	153 (52.9%)
2	10 (6.9%)	17 (11.8%)	27 (9.3%)
Total Additive (Frailty) Score, n (%)			
Fit (score=0)	88 (60.7%)	82 (56.9%)	170 (58.8%)
Intermediate-fitness (score=1)	57 (39.3%)	62 (43.1%)	119 (41.2%)
Renal function, n (%)			
<30			
≥30 and <60			
≥60 and <90			
≥90			
Hepatic function, n (%)			
Normal			
Impaired			
Type of myeloma by immunofixation or serum FLC assay, n (%)			
IgG	78 (53.8%)	92 (63.9%)	170 (58.8%)
IgA	42 (29.0%)	26 (18.1%)	68 (23.5%)
IgD	2 (1.4%)	2 (1.4%)	4 (1.4%)
Light chain	3 (2.1%)	4 (2.8%)	7 (2.4%)
Kappa	12 (8.3%)	10 (6.9%)	22 (7.6%)
Lambda	6 (4.1%)	10 (6.9%)	16 (5.5%)
FLC-Lambdaa	1 (0.7%)	0	1 (0.3%)
Biclonal	3 (2.1%)	4 (2.8%)	7 (2.4%)

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Missing	1 (0.7%)	0	1 (0.3%)
Type of measurable disease, n (%)^b			
Serum only	██████	██████	██████
Serum and urine	██████	██████	██████
Urine only	██████	██████	██████
Serum FLC	██████	██████	██████
IWRS ISS Staging, n (%)			
Stage I	██████	██████	██████
Stage II	██████	██████	██████
Stage III	██████	██████	██████
ISS Staging, n (%)^c			
Stage I	48 (33.1%)	50 (34.7%)	98 (33.9%)
Stage II	57 (39.3%)	54 (37.5%)	111 (38.4%)
Stage III	40 (27.6%)	40 (27.8%)	80 (27.7%)
Revised ISS Staging, n (%)			
Stage I	██████	██████	██████
Stage II	██████	██████	██████
Stage III	██████	██████	██████
Missing	██████	1	██████
Number of lytic bone lesions, n (%)			
None	██████	██████	██████
1-3	██████	██████	██████
4-10	██████	██████	██████
>10	██████	██████	██████
Presence of extramedullary plasmacytomas, n (%)			
Yes	12 (8.3%)	9 (6.3%)	21 (7.3%)
No	133 (91.7%)	135 (93.8%)	268 (92.7%)
Cytogenetic risk, n (%)			
Standard risk ^d	111 (76.6%)	105 (72.9%)	216 (74.7%)
High risk ^d	18 (12.4%)	20 (13.9%)	38 (13.1%)
Indeterminate	16 (11%)	19 (13.2%)	35 (12.1%)

Footnotes: ^a Includes participants without a positive immunofixation but with evidence of free light chain lambda by FLC testing.

^b Includes participants without measurable disease in serum and urine.

^c ISS staging is derived based on the combination of serum β 2-microglobulin and albumin.

^d Standard risk includes participants who are negative for del17p, t(14;16), or t(4;14) by FISH. High risk includes the participants who are positive for any of del17p, t(14;16), or t(4;14) by FISH.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; BSA: body surface area; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescence in situ hybridisation; FLC: free light chain; Ig: immunoglobulin; ISS: International Staging System; ITT: intent-to-treat; IWRS: Interactive Web Response System.

Source: J&J Data on File (CEPHEUS Clinical Study Report May 2024 DCO: Tables 4-5);¹⁰¹ J&J Data on File (CEPHEUS Clinical Protocol);¹⁰² Facon *et al.* (2025)¹⁰⁴

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

Study population

The study populations used for the analysis of outcomes from the CEPHEUS trial are presented in Table 7. The key efficacy outcomes presented in this submission are based on all randomised ASCT-ineligible patients, termed the ASCT-ineligible ITT analysis set. For completeness, efficacy outcomes for the ITT analysis set, which includes all randomised participants in the CEPHEUS trial (including patients who refused ASCT) are also presented in this submission (in Section 2.6.1 for the primary endpoint and Appendix L for all other endpoints).

Safety outcomes for the ASCT-ineligible subgroup of the CEPHEUS trial are presented in Section 2.11. Safety outcomes for the all-treated set (safety analysis set) are presented in Appendix L for completeness. PK analyses (not presented; see the CEPHEUS Clinical Study Report [CSR]) were performed on the pharmacokinetic-evaluable population.

Table 7: CEPHEUS analysis set definitions

Analysis set	Analysis set description	Number of patients		
		BLd	DBLd	Total
ASCT-ineligible ITT analysis set	ASCT-ineligible patients who were randomly assigned to either the BLd group or DBLd group	145	144	289
ITT analysis set	Patients who were randomly assigned to either the BLd group or DBLd group	198	197	395
Safety analysis set	All participants who were randomised and received at least 1 administration of any study treatment (partial or complete) in the study	195	197	392
ASCT-ineligible safety analysis set	ASCT-ineligible patients who were randomised and received at least 1 administration of any study treatment (partial or complete) in the study	142	144	286

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intent-to-treat.

Source: J&J Data on File (CEPHEUS Clinical Study Report May 2024 DCO – Table 3),¹⁰¹ J&J Data on File (CEPHEUS Statistical Analysis Plan: Section 2.4)¹⁰⁵ J&J Data on File (CEPHEUS Clinical Protocol).¹⁰²

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2.4.1 Statistical analysis

Details of the statistical methods for the CEPHEUS trial are presented in Table 8.

Table 8: Statistical methods for the primary analysis of CEPHEUS

Trial name	CEPHEUS
Hypothesis objective	The null hypothesis states there is no difference in overall MRD negativity rate between daratumumab in combination with BLd (DBLd) and BLd alone in patients with NDMM who are not intended for initial transplant.
Statistical analysis	The treatment arms were: Arm A: BLd alone for eight 21-day cycles followed by Ld alone until disease progression or unacceptable toxicity Arm B: DBLd for eight 21-day cycles followed by DLd therapy until disease progression or unacceptable toxicity General analysis - Continuous variables were summarised using descriptive statistics such as mean, standard deviation (SD), median and range. Categorical variables were summarised using frequency and percentage. For time-to-event variables, the Kaplan-Meier (KM) method was used for descriptive summaries Primary endpoint - The primary endpoint, overall MRD negativity rate, was compared between the two treatment arms using the stratified Cochran Mantel Haenszel test based on the ITT population (ISS staging and age/transplant eligibility as stratification factors). A Mantel-Haenszel OR, along with its 2-sided 95% CI, was calculated Secondary endpoints - If the primary endpoint of overall MRD negativity rate was statistically significant, the key secondary endpoints (i.e., $\geq$CR rate, PFS, and sustained MRD negativity rate) were sequentially tested, each with an overall two-sided alpha of 0.05, by utilising a hierarchical testing approach as proposed by Tang and Geller (1999) that strongly controls family wise Type I error rate - Time-to-event efficacy endpoints, including PFS, PFS2 and OS were compared between the two treatment arms using a stratified log-rank test. The KM method was used to estimate their distribution in each treatment arm. HR and its 95% CI was estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable - The binary secondary endpoints, including sustained MRD negativity rate, rate of $\geq$CR, rate of $\geq$VGPR and ORR, were analyses similarly to overall MRD negativity rate - The time to response was provided descriptively for each treatment arm without formal statistical comparison Safety analyses: adverse events

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	- The verbatim terms used in the CRF by investigators to identify AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events were AEs with onset during the Treatment Phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs were included in the analysis. For each AE, the percentage of participants who experienced at least 1 occurrence of the given event was summarised by treatment arm. In addition, comparisons between treatment arms were provided if appropriate - Summaries, listings, datasets, or patient narratives were provided, as appropriate, for those participants who die, who discontinue study drug due to an AE, or who experience a severe or a serious AE
Sample size, power calculation	- It was assumed that the addition of daratumumab to BLd would lead to a 15% absolute increase in overall MRD negativity rate (50% DBLd versus 35% BLd alone). A sample size of 360 participants (180 each arm) was needed to achieve a power of 80% to detect such a treatment difference at a 2-sided alpha of 0.05 - This sample size would also provide approximately 80% power to detect a 37% reduction in the risk of progression or death (HR=0.63, translating to an improvement in median PFS from 43 months to 68 months) with a log-rank test at a 2-sided alpha of 0.05
Data management, patient withdrawals	Discontinuation and withdrawal: - A patient was not automatically withdrawn from the study if they discontinued study drug before the end of the treatment regimen. Patients were withdrawn from the study for any of the following reasons: - Lost to follow-up - Withdrawal of consent for study participation - Death - Sponsor terminated the study - When a participant withdrew before completing the study, the reason for withdrawal was documented in the electronic case report form (eCRF) and in the source document - Study drug assigned to the withdrawn participant were not permitted to be assigned to another patient - Patients who withdrew were not replaced - If a patient discontinued study treatment and withdrew from the study before the end of the Treatment Phase, End-of-Treatment assessments were obtained - If the reason for withdrawal from the study was withdrawal of consent, then no additional assessments were allowed

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab and lenalidomide; DLd: daratumumab, lenalidomide and dexamethasone; eCRF: electronic case report form; HR: hazard ratio; IMWG: International Myeloma Working Group; PFS: progression-free survival; SD: standard deviation.

Source: J&J Data on File (CEPHEUS Statistical Analysis plan – Table 2 and Section 1.4),¹⁰⁵ J&J Data on File (CEPHEUS Clinical Protocol: Section 7.3).¹⁰²

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Definitions for outcome measures

As shown in Table 4, a variety of outcomes were employed to explore the efficacy of DBLd versus BLd in CEPHEUS. Full definitions for these outcome measures employed in CEPHEUS are presented in Table 9.

Table 9: Definitions for outcome measures used in CEPHEUS

Outcome measure	Definition
Primary outcome	
Overall MRD negativity rate	The proportion of patients who achieve $\geq$ CR response and have MRD negative status (at 10^{-5}) by bone marrow biopsy/aspirate after randomisation but prior to progressed disease (PD), subsequent anti-myeloma therapy, or both.
Key secondary outcomes	
$\geq$ CR rate	The proportion of patients achieving CR or sCR based on the computerised algorithm, according to IMWG response criteria, during or after the study treatment prior to the start of subsequent antimyeloma therapy.
PFS	The duration from the date of randomisation to either PD or death due to any cause, whichever comes first. Disease progression will be determined according to IMWG criteria.
Sustained MRD negativity rate	The proportion of patients who achieve $\geq$ CR response and have achieved MRD negative status (at 10^{-5}) at two bone marrow biopsy/aspirate examinations that are a minimum of one year apart (and the two examinations should be prior to PD, subsequent anti-myeloma therapy, or both), without any examination showing MRD positive status in between.
Other secondary outcomes	
Landmark MRD negativity rate at one year	The proportion of patients who achieved $\geq$ CR response and MRD negative status (at 10^{-5}) by bone marrow biopsy/aspirate at 12 months after the first dose of study treatment and prior to PD, subsequent anti-myeloma therapy, or both. Patients who have achieved MRD negative status on or after PD or the start of subsequent anti-myeloma therapy, will not be considered as MRD negative.
ORR	The proportion of patients who achieve $\geq$ PR responses (i.e., PR, VGPR, CR, or sCR) based on the computerised algorithm, in accordance with the IMWG criteria, during or after the study treatment but before the start of subsequent antimyeloma therapy.
$\geq$ VGPR rate	The proportion of patients achieving VGPR, CR, and sCR based on the computerised algorithm, in accordance with the IMWG criteria, during or after the study treatment but before the start of subsequent anti-myeloma therapy.
PFS2	The time from randomisation to progression on the next line of treatment or death (due to any cause), whichever comes first.
OS	The time from the date of randomisation to the date of the patients death due to any cause. Patients who are lost to follow-up will be censored at the time of lost to follow-up. Patients who died after consent withdrawal will be considered as having an OS event. If the patient is alive at the cut-off date for the analysis or the survival status is

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Outcome measure	Definition
	unknown, then the patients data will be censored at the date the patient was last known to be alive.
Time to first response	The time between the randomisation and the first efficacy evaluation at which the patient meets all criteria for ≥PR based on the computerised algorithm, according to IMWG response criteria.
DOR	The duration from the date of initial documentation of a response (≥PR) to the date of first documented evidence of PD based on computerised algorithm, according to IMWG response criteria, or death due to PD, whichever occurs first.

Abbreviations: CR: complete response; DOR: duration of response; IMWG: International Myeloma Working Group; ITT: intent-to-treat; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PFS2: Progression-free survival on the next line of therapy; PR: partial response; sCR: stringent complete response; VGPR: very good partial response.

Source: J&J Data on File (CEPHEUS Statistical Analysis plan)¹⁰⁵

Adjustments for COVID-19

The CEPHEUS trial coincided with the COVID-19 pandemic. While the overall impact of the COVID-19 pandemic on this study did not affect the integrity or data quality, █% of study participants in the ITT population, and █ of ASCT-ineligible patients died due to COVID-19. The majority of deaths occurred in █ at the height of the pandemic (see █

Figure 20). There was an imbalance in COVID-19 deaths between the DBLd and BLd trial arms (n=█ and n=█, respectively, for the ITT population, and n=█ and n=█, respectively, for the ASCT-ineligible population), with the higher rate of COVID-19 deaths in the DBLd arm predominantly driven by the majority of deaths in █, a country that was heavily impacted by the COVID-19 pandemic.

The disproportionate impact of COVID-19 on patients receiving DBLd is likely due to the immunosuppressive effects of anti-CD38 monoclonal antibodies. Data suggest that the effect of COVID-19 infection is more severe on patients receiving daratumumab-containing regimens than those not receiving such regimens.

With the introduction of COVID-19 vaccinations, increased availability of targeted COVID-19 treatments, and improved medical understanding of COVID-19 infection management in patients with MM on immunosuppressive therapies, the rate of COVID-19 SAEs and deaths decreased substantially in the last 3 years of the study. As such, the increased risk of COVID-19 is no longer relevant given COVID-19 management post-pandemic. To account for the impact of COVID-19 on the CEPHEUS trial, additional analyses were conducted on the primary and secondary endpoints of the trial, where COVID-19 deaths were censored to understand the impact of the pandemic on the study results. These analyses are presented alongside the adjusted results throughout Section 2.6.

Table 10 presents the baseline disease and clinical characteristics of patients who died from COVID-19 in the DBLd arm compared to the overall DBLd ASCT-ineligible population. When looking at specific characteristics, █ between the two groups. █

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On balance, this suggests that the patients who died from COVID-19 are broadly representative of the trial population (considering the small sample of patients), indicating they would likely not have died if the study had not started recruitment at the peak of the COVID-19 pandemic.

Table 10: Baseline and disease characteristics of patients who died of COVID-19 in the DBLd arm of CEPHEUS

Characteristics		
	COVID-deaths in DBLd arm (N=7)	Total DBLd ASCT-ineligible (N=144)
Age, years		
Mean		
Median		
Overall age group, n (%)		
<70		
70 – 74		
≥75		
Sex, n (%)		
Female		
Male		
Race, n (%)		
White		
Non white/missing		
Baseline ECOG, n (%)		
0		
1		
2		
Total Additive (Frailty) Score, n (%)		
0-1		
>1		
Type of myeloma by immunofixation, n (%)		
IgG		
Other		
ISS Staging, n (%)^a		
Stage I		
Stage II		
Stage III		
Presence of extramedullary plasmacytomas, n (%)		
Yes		
No		
Cytogenetic risk, n (%)		
Standard risk ^b		

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High risk ^b		
Indeterminate		
Renal function, eGFR		
<60		
≥60		
LDH		
≤280		
>280		
Missing		
Haemoglobin		
<100		
≥100		
Calcium		
≤2.75		
> 2.75		

Footnotes: ^a ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

^b Standard risk includes participants who are negative for del17p, t(14;16), or t(4;14) by FISH. High risk includes the participants who are positive for any of del17p, t(14;16), or t(4;14) by FISH.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; Ig: immunoglobulin; ISS: International Staging System.

Of particular note, due to the timing of the trial, COVID-19 disproportionately impacted the CEPHEUS trial compared to other trials of relevance in the NDMM landscape, including MAIA, which is used to inform the efficacy of DLd in the ITCs versus DBLd. This is considered in more detail in Section 2.10.2.

2.4.2 Study population and patient disposition

A CONSORT diagram of the CEPHEUS ASCT-ineligible participant disposition (as of the final PFS analysis) is provided in Figure 10. A CONSORT diagram of the CEPHEUS ITT population participant disposition is presented in Appendix L.

A total of 289 ASCT-ineligible participants were randomised. Of these, 286 were treated, 142 with BLd and 144 with DBLd. Fewer patients discontinued treatment in the DBLd treatment arm (██████) compared with the BLd arm (██████). The most common reasons for treatment discontinuation were PD, death and AEs. More participants in the BLd arm discontinued treatment due to PD (DBLd: ██████; BLd: ██████) and AEs (DBLd: ██████; BLd: ██████); however, more patients in the DBLd arm discontinued treatment due to death (DBLd: ██████; BLd: ██████).

██████ and ██████ participants in the DBLd and BLd arms, respectively, discontinued the study. The most common reason for discontinuation of study was death (DBLd: ██████; BLd: ██████).

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Figure 10: CONSORT diagram for CEPHEUS trial, ASCT-ineligible population



Abbreviations: ASCT: autologous stem cell transplant; DVRd: daratumumab, bortezomib, lenalidomide and dexamethasone; TD: transplant deferred; TIE: transplant ineligible; VRd: bortezomib, lenalidomide and dexamethasone;.

Source: J&J Data on File.

2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

CEPHEUS was assessed for risk of bias using the Cochrane RoB 2.0 Quality Assessment tool 2.0, as recommended by NICE.¹⁰⁶ The quality assessment was based on published sources for the CEPHEUS trial where possible, and supplemented with information provided in the trial protocol. Overall, the trial was associated with a low risk of bias. The results from the quality assessment are presented in Table 11.

Table 11: Quality assessment of CEPHEUS using the Cochrane RoB 2.0 tool

Study Question	Grade (yes/no/unclear)	Justification
Bias arising from the randomisation process		
1.1 Was the allocation sequence random?	Y	Patients were randomly assigned (1:1) to DBLd or BLd by randomly permuted blocks using an IRWS. Randomisation was stratified by ISS disease stage (I, II or III) and age or transplant eligibility (<70 years and transplant ineligible, <70 years and transplant deferred or ≥70 years). There was no selection of patients.

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1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Y	IWRS used for randomisation.
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	The baseline characteristics were similar.
Risk of bias judgement	Low	
Bias due to deviations from intended interventions, effect of assignment to intervention		
2.1. Were participants aware of their assigned intervention during the trial?	Y	Open-label.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	Open-label.
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	N	No evidence of discontinuations or switches due to trial context based on the information provided in the CONSORT diagram.
2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis used
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	NA
Risk of bias judgement	Low	
Bias due to missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcomes were consistently reported for the same number of randomised patients.
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
Risk of bias judgement	Low	
Bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	N	Outcomes and measurement clearly defined.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Objective outcomes (OS) and some subjective but standardised criteria used; although it was unclear if ORR

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		was assessed by investigator or IRC.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y	Open-label.
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	Objective outcomes (OS) and some subjective but standardised criteria used; although it was unclear if ORR was assessed by investigator or IRC.
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
Risk of bias judgement	Low	
Bias in selection of the reported result		
5.1. Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Methods well-reported with outcomes defined.
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Primary outcome had one definition; other analyses clearly and transparently defined.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	
Risk of bias judgement	Low	
Overall Risk of bias judgement	Low	

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IRC: Independent Review Committee; IRWS: interactive web response system; ISS: International Staging System; N: no; NA: not applicable; ORR: onjective response rate; OS: overall survival; RoB: risk of bias; Y: yes.

2.6 Clinical effectiveness results of the relevant studies

Summary of CEPHEUS data cuts

At the time of this submission, three data cuts from the CEPHEUS trial were available:

- **Primary MRD analysis clinical cut-off:** 08 April 2021 (date of the last observation recorded as part of the database for the primary analysis)
- **Interim PFS analysis clinical cut-off:** 08 September 2022 (date of last observation recorded as part of the database for interim analysis)
- **Final PFS analysis clinical cut-off:** 07 May 2024 (date of last observation recorded as part of the database for final PFS analysis)

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Detailed results from the most recent data cut (final PFS analysis, 07 May 2024), representing a median follow-up of 58.71 months, are presented in this section. These data represent the most recent data available from CEPHEUS and inform the cost-effectiveness model for this submission.

A summary of the key clinical efficacy results for the ASCT-ineligible ITT analysis set at the final PFS analysis are presented in Table 12, with full discussion of each endpoint provided in the remainder of this section.

Table 12: Summary of CEPHEUS outcomes at final PFS analysis (ASCT-ineligible ITT analysis set)

Outcome	BLd N=145	DBLd N=144	DBLd versus BLd ^a (95% CI)
Primary endpoint			
MRD negativity rate (10^{-5} , $\geq$ CR), n (%)	57 (39.3%)	87 (60.4%)	2.365 (1.471, 3.802); p=0.0004
Key secondary endpoints			
MRD negativity rate (10^{-6} , $\geq$ CR), n (%)	████████	████████	2.283 (1.397; 3.731); p=0.0009
$\geq$ CR, n (%)	████████	████████	████████
Median PFS, months (unadjusted) ^b	49.61 ██████	████████	0.51 (0.35, 0.74); p=0.0003
Median PFS, months (adjusted for COVID-19)	████████	████████	████████
1-year sustained MRD negativity rate ($\geq$ CR), n (%)	████████	████████	████████
2-year sustained MRD negativity rate ($\geq$ CR), n (%)	████████	████████	████████
3-year sustained MRD negativity rate ($\geq$ CR), n (%)	████████	████████	████████
Other secondary outcomes			
MRD-negativity rates (10^{-5} ; $\geq$ CR) at 12 months, n (%)	████████	████████	NA
ORR, n (%)	████████	████████	████████
$\geq$ VGPR, n (%)	████████	████████	████████
sCR, n (%)	████████	████████	████████
Median time to first response, months	████████	████████	████████
DOR, n events (%)	████████	████████	████████
PFS2, n events (%)	████████	████████	████████
Median OS, months (unadjusted) ^b	████████	████████	0.66 (0.42, 1.03); p=0.0682
Median OS, months (adjusted for COVID-19)	████████	████████	0.55 (0.34, 0.90); p=0.0159

Footnotes: ^a HRs presented for time-to-event outcomes; ORs presented for response outcomes and MRD negativity; absolute difference presented for HRQoL outcomes. ^b Scenario analyses unadjusted for COVID-19 deaths; ^c N=132; ^d N=142.

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Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intention-to-treat; MRD: minimal residual disease; N/A: not applicable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; sCR: stringent complete response; VGPR: very good partial response.
Source: J&J Data on File (CEPHEUS Clinical Study Report May 2024 DCO: Tables 9, 11-13);¹⁰¹ Facon *et al.* (2025)¹⁰⁴

2.6.1 Primary efficacy endpoints

MRD negativity rate

As discussed in Section 1.3.1, MRD negativity is a highly sensitive measure of the depth of response and is a powerful independent predictor of long-term survival outcomes.³⁴⁻⁴⁰ Treatments that achieve deep and sustained MRD negativity have been shown to translate into PFS and OS benefits.⁹⁷ Given the high median age of patients ineligible for ASCT, it is reasonable to expect such improvements to lead to a functional cure for the best responders, where they are likely to die from other age-related factors instead of their myeloma. This was supported by a panel of UK clinical experts at the May 2025 UK Advisory Board.³

ITT analysis set

At the primary MRD analysis cut-off (08 April 2021), with a median follow-up of [REDACTED] months, the addition of daratumumab to BLd resulted in a statistically significant and clinically meaningful improvement in overall MRD negativity rate at 10^{-5} compared with BLd alone, with an absolute increase of [REDACTED]% favouring DBLd (DBLd: [REDACTED]%; BLd: [REDACTED]%; OR: [REDACTED] [95% CI: [REDACTED]; 2-sided p = [REDACTED]; Table 13) in the ITT population.

Treatment effect of DBLd over BLd in overall MRD negativity rate continued to improve at the final PFS analysis (07 May 2024) in the ITT population, with a median follow-up of 58.71 months. Overall MRD negativity was 60.9% in the DBLd arm compared to 39.4% in the BLd arm (DCO: 7 May 2024; OR: 2.37 [95% CI: 1.58, 3.55]; Table 13).

Table 13: Summary of MRD negativity rate at 10^{-5} in bone marrow (ITT analysis set)

	Primary MRD analysis (mFU: 22.31 months)		Final PFS analysis (mFU: 58.71 months)	
	BLd N=198	DBLd N=197	BLd N=198	DBLd N=197
MRD negativity rate (10^{-5}), n (%)	[REDACTED]	[REDACTED]	78 (39.4%)	120 (60.9%)
95% CI ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
OR (95% CI); ^b p-value ^c	[REDACTED]		2.37 (1.58, 3.55); $p < 0.0001$	

Footnotes: ^a Exact 95% CI.

^b Mantel-Haenszel estimate of the common OR for stratified tables is used. The stratification factors are: ISS staging (I, II, III), age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised. An OR >1 indicates an advantage for DBLd.

^c p-value from Fisher's exact test.

MRD negativity rate is defined as the proportion of patients who achieve ≥CR response and have MRD negative status (at 10^{-5}) by bone marrow aspirate after randomisation but prior to PD, subsequent anti-myeloma therapy, or both.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ISS: International Staging System; ITT: intent-to-treat; MRD: minimal residual disease; OR: odds ratio; PD: progressive disease; PFS: progression-free survival.

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ASCT-ineligible ITT analysis set

In the ASCT-ineligible ITT analysis set, at the final PFS analysis (07 May 2024), the addition of daratumumab to BLd resulted in a statistically significant and clinically meaningful improvement in overall MRD negativity rate (10^{-5}) compared with BLd alone, with an absolute increase of 21.1% favouring DBLd (DBLd: 60.4%; BLd: 39.3%; OR: 2.365 [95% CI: 1.471; 3.802; 2-sided $p=0.0004$]; Table 14). Primary endpoint results in the ASCT-ineligible ITT analysis set (Table 14) were highly consistent with those in the ITT population (Table 13). Statistically significant and clinically meaningful improvements in overall MRD negativity rate (10^{-6}) were also observed for DBLd versus BLd at the final PFS analysis (Appendix K).

Table 14: Summary of MRD negativity rate at 10^{-5} in bone marrow (ASCT-ineligible ITT analysis set) – final PFS analysis

	BLd N=145	DBLd N=144
MRD negativity rate (10^{-5}), n (%)	57 (39.3%)	87 (60.4%)
OR (95% CI); p-value	2.365 (1.471; 3.802); $p=0.0004$	

Footnotes: Mantel-Haenszel estimate of the common OR for stratified tables is used. The stratification factors are: ISS staging (I, II, III), age/transplant eligibility (<70 years ineligible, or age <70 years and refusal to transplant, or age ≥70 years) as randomised. An OR >1 indicates an advantage for DBLd. p-value from Fisher's exact test.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intent-to-treat; MRD: minimal residual disease; OR: odds ratio; PFS: progression-free survival.

Source: J&J Data on File; Facon *et al.* (2025)¹⁰⁴

2.6.2 Key secondary efficacy endpoints

In the following sections, data presented are for the ASCT-ineligible ITT analysis set of CEPHEUS only (final PFS analysis). Results for the full ITT analysis set are presented in Appendix L for completeness.

Sustained MRD negativity

As of the final PFS analysis cut-off, among the ASCT-ineligible patients of CEPHEUS, the sustained 1-year MRD negativity rate was █% (n=█) in the DBLd arm versus █% (n=█) in the BLd arm. The common OR from Chi-square estimate was █ (95% CI: █) and the 2-sided nominal p-value=█; Table 15). A consistent treatment effect was observed across both 2- and 3-year sustained MRD negativity (see Appendix K).

The statistically significant improvements in sustained 1-year MRD-negativity rates observed for DBLd over BLd in the ASCT-ineligible population of CEPHEUS are expected to translate into improvements in long-term patient outcomes among patients treated with the quadruplet regimen.

Table 15: Summary of sustained 1-year MRD-negative rate at 10^{-5} in bone marrow (ASCT-ineligible ITT analysis set) – final PFS analysis

MRD negativity	BLd N=145	DBLd N=144

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Sustained 1-year MRD negativity rate (10 ⁻⁵)		
MRD negativity ≥CR rate (10 ⁻⁵), n (%)	██████	██████
OR (95% CI) ^a	████████████████	
p-value ^b	██████	

Footnotes ^a Mantel-Haenszel estimate of the common OR for stratified tables is used. The stratification factors are: ISS staging (I, II, III), age/transplant eligibility (<70 years ineligible, or age<70 years and refusal to transplant, or age ≥70 years) as randomised. An OR > 1 indicates an advantage for DBLd. ^b p-value from Fisher's exact test.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intent-to-treat; MRD: minimal residual disease; OR: odds ratio; PFS: progression-free survival.

Source: J&J Data on File.

MRD-negativity landmark rates over time

The landmark rate of MRD-negativity (at 10⁻⁵) at Month 12 was higher in the DBLd arm compared with the BLd arm (DBLd: █████%; BLd: █████%); with an absolute difference of █████% favouring treatment with DBLd (Table 16). The proportion of patients achieving MRD-negativity (at 10⁻⁵) at different landmark timepoints increased over time, with the MRD-negativity rate at Month 24 being █████ in the DBLd arm compared to █████ in the BLd arm, an absolute difference of █████. This increase in patients achieving MRD-negativity is particularly notable in the DBLd arm, where the proportion of patients achieving MRD negativity █████ between 18 and 24 months. By contrast, the BLd group exhibits a █████ in MRD negativity rates █████. This difference can be linked to the more durable MRD negative responses seen in patients receiving DBLd, and the increased conversion of MRD positive to MRD negative over time suggests patients continue to achieve these deep responses well into treatment.

Table 16: MRD negativity rate at 10⁻⁵ in bone marrow over time (ASCT-ineligible ITT analysis set) – final PFS analysis

MRD negativity	BLd N=145	DBLd N=144
MRD negativity rate		
MRD negativity rate at 12 months, n (%)	██████	██████
MRD negativity rate at 18 months, n (%)	██████	██████
MRD negativity rate at 24 months, n (%)	██████	██████

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; ITT: intent-to-treat; MRD: minimal residual disease; PFS: progression-free survival.

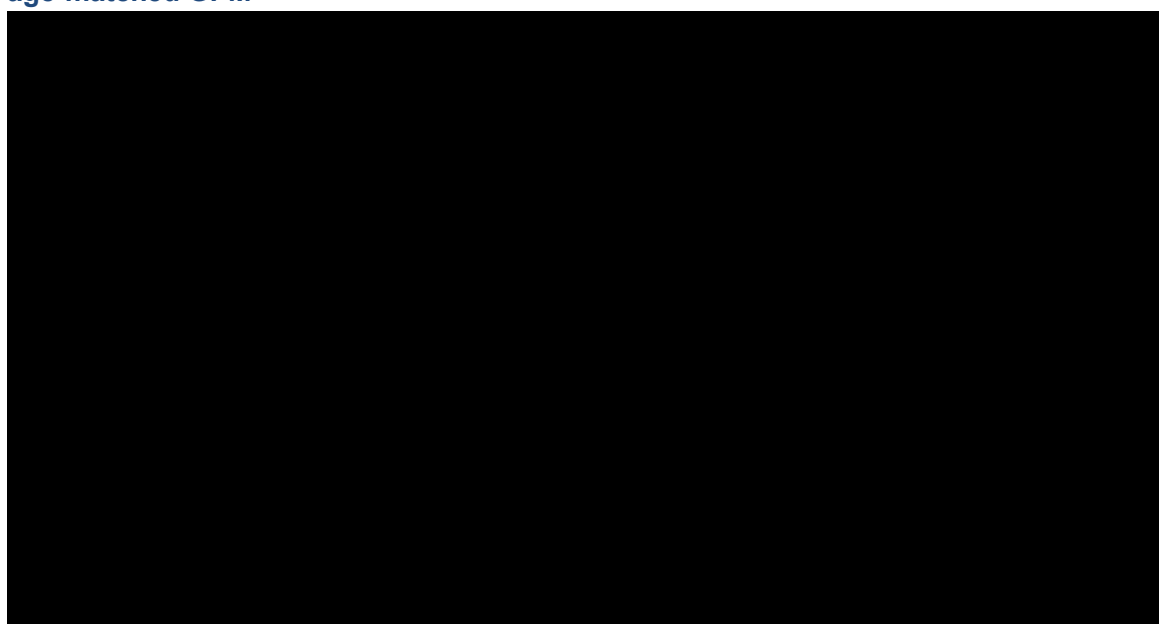
Source: J&J Data on File.

OS for patients who achieve MRD negativity

For patients who achieve MRD negativity following DBLd treatment, the level of depth of response allows for long-term disease control and there is hope for a functional cure, as discussed in Section 1.3.3. In an exploratory analysis, the overall survival (adjusted for COVID-19) for MRD negative patients tracks outcomes resembling that seen in the UK general population (assuming a median age of 72 years) after five years of follow-up, as demonstrated in Figure 11. This shows that for patients on DBLd who achieve MRD negativity, they have the hope for functional cure in achieving outcomes similar to the general population.

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Figure 11: Comparison of OS for DBLd patients who achieved MRD negative status versus age-matched GPM



Abbreviations: ASCT: autologous stem cell transplant; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; GMP: general population mortality; MRD: minimal residual disease OS: overall survival.

Progression-free survival

At the final PFS analysis cut-off date, a total of [REDACTED] PFS events were observed (DBLd: [REDACTED]; BLd: [REDACTED]). The addition of daratumumab to BLd resulted in a statistically significant improvement in PFS with a HR (DBLd versus BLd) of 0.51 (95% CI: 0.35, 0.74; 2-sided nominal $p=0.0003$). The median PFS was not reached in the DBLd arm and was 49.61 months in the BLd arm (Table 17; Figure 12). At 54 months, the PFS rate was considerably higher for DBLd (69.0%) than for BLd (48.0%), and as demonstrated by Figure 12, the KM PFS curves separate early at 12 months and continue to diverge over time with longer follow-up.

The statistically significant decrease in risk of disease progression or death for DBLd over BLd in the ASCT-ineligible population of CEPHEUS is of great importance to patients. As discussed in Section 1.3.3, due to the increased symptom burden experienced by patients as their disease progresses, prolonging the time patients are in a progression-free state is vital in preventing the decrement in HRQoL following disease progression.¹⁰⁷

Table 17: Summary of progression-free survival (ASCT-ineligible ITT analysis set) – final PFS analysis

PFS	BLd N=145	DBLd N=144
Number of events, n (%)	[REDACTED]	[REDACTED]
Number of events censored, n (%)	[REDACTED]	[REDACTED]
Median KM estimate, months		
25% percentile (95% CI)	[REDACTED]	[REDACTED]
Median (95% CI)	49.61 ([REDACTED])	NE [REDACTED]
75% percentile (95% CI)	[REDACTED]	[REDACTED]
p-value ^a	0.0003	

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

HR (95% CI) ^b	0.51 (0.35, 0.74)	
PFS rate (%)		
12-month PFS rate, % (95% CI)	██████████	██████████
18-month PFS rate, % (95% CI)	██████████	██████████
24-month PFS rate, % (95% CI)	██████████	██████████
30-month PFS rate, % (95% CI)	██████████	██████████
36-month PFS rate, % (95% CI)	██████████	██████████
48-month PFS rate, % (95% CI)	██████████	██████████
54-month PFS rate, % (95% CI)	48.0 (38.9, 56.5)	69.0 (60.3, 76.2)

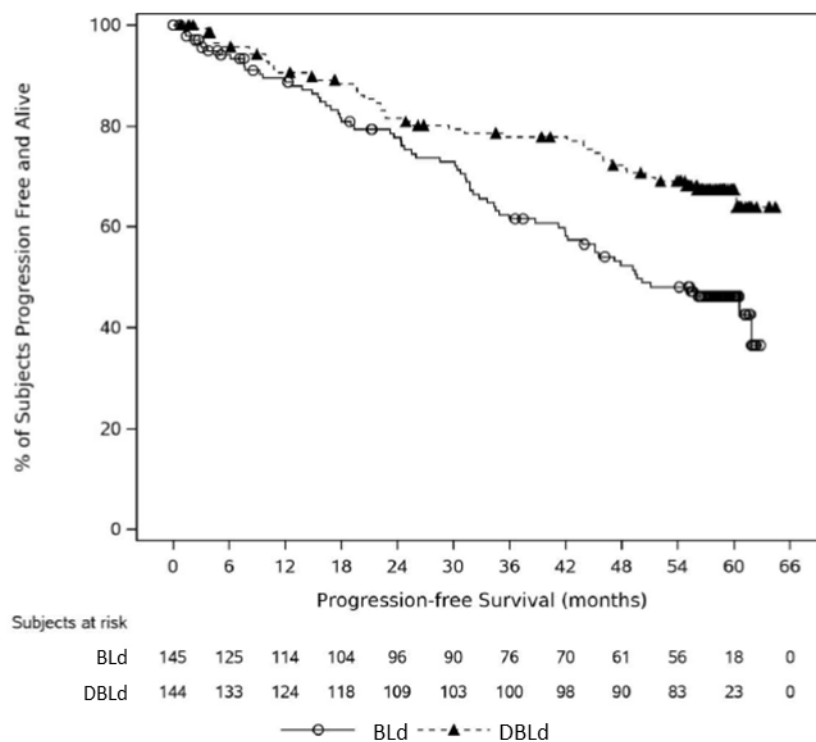
Footnotes: ^a p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised.

^b HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised. A HR<1 indicates an advantage for DBLd.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; ITT: intent-to-treat; PFS: progression-free survival.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

Figure 12: KM plot of PFS (ASCT-ineligible ITT analysis set) – final PFS analysis



Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intent-to-treat; KM: Kaplan-Meier; PFS: progression-free survival.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

PFS- adjusted for COVID-19

An analysis where PFS was adjusted for COVID-19 in the ASCT-ineligible population of CEPHEUS also showed a statistically significant HR and narrower 95% CI, further supporting a positive PFS trend favouring DBLd. As discussed in Section 2.4.1, it is important to account for COVID-19 considering the timing of the pandemic and the impact on the CEPHEUS trial.

Compared to a HR of [REDACTED] (95% CI: [REDACTED]) in the unadjusted analyses, adjusting for COVID-19 resulted in an improved HR of [REDACTED] (95% CI: [REDACTED]; 2-sided nominal p<[REDACTED]; Table 18). The Kaplan-Meier plot for PFS (censored for death due to COVID-19) among the ASCT-ineligible ITT analysis set is presented in Appendix L.

Table 18: Summary of progression-free survival based on computerised algorithm (adjusted for COVID-19; (ASCT-ineligible ITT analysis set) – final PFS analysis

PFS	BLd N=145	DBLd N=144
Number of events, n (%)	[REDACTED]	[REDACTED]
Number of events censored, n (%)	[REDACTED]	[REDACTED]
KM estimate, months		
25% percentile (95% CI)	[REDACTED]	[REDACTED]
Median (95% CI)	[REDACTED]	[REDACTED]
75% percentile (95% CI)	[REDACTED]	[REDACTED]
p-value ^a	[REDACTED]	
HR (95% CI) ^b	[REDACTED]	

Footnotes: ^a p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised.

^b HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised. A HR <1 indicates an advantage for DBLd.

Patients who died due to COVID-19 without PD and subsequent antineoplastic therapies are censored at the last disease assessment before death.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; ISS: International Staging System; PFS: progression-free survival.

Source: J&J Data on File.

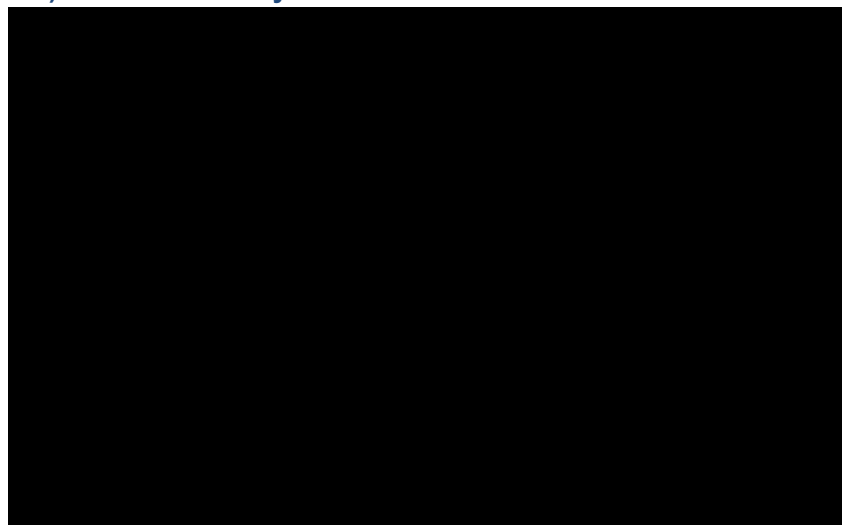
PFS by MRD status

PFS based on MRD negative status is presented in Figure 13. A trend towards a longer PFS was observed for DBLd compared to BLd in both patients achieving MRD negativity (HR: [REDACTED] [95% CI: [REDACTED]]; p=[REDACTED]) and those who remained MRD positive (HR: [REDACTED] [95% CI: [REDACTED]]; p=[REDACTED]). PFS at 54 months was higher for DBLd than BLd among the MRD-positive patients ([REDACTED]% versus [REDACTED]%, respectively). The difference in treatment effect on PFS rates among MRD-positive patients is likely due to more patients in the DBLd arm achieving ≥VGPR/≥CR than patients in the BLd arm (Table 19); the deep responses induced by treatment with DBLd in turn drives improved survival outcomes.

Among patients achieving MRD negativity, the estimated 54-month PFS was also greater for DBLd than for BLd ([REDACTED]% versus [REDACTED]%, respectively). This treatment effect difference can be explained by a higher proportion of patients receiving DBLd achieving MRD negativity at a 10⁻⁶ threshold than patients receiving BLd in CEPHEUS (see Appendix K). The 10⁻⁶ threshold is more sensitive than the IMWG-recommended 10⁻⁵ threshold; as such, higher rates of MRD negativity Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

at a 10^{-6} among patients receiving DBLd suggests deeper response to treatment, which, as discussed in detail in Section 1, is associated with better long-term survival outcomes.

Figure 13: KM plot of PFS based on MRD negative status (ASCT-ineligible ITT analysis set) – final PFS analysis



Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; KM: Kaplan-Meier; MRD: minimal residual disease; PFS: progression-free survival.

Source: J&J Data on File.

Response rates

There is a growing body of evidence which indicates that achieving a deep, sustained response to therapy is prognostic for improved survival outcomes.³⁰ Furthermore, deeper treatment responses are associated with improvements in HRQoL in patients with MM.⁵⁷ Response-based outcomes, along with other key secondary outcomes in the CEPHEUS trial are outlined and defined in Section 2.4.1.

At the final PFS analysis, the addition of daratumumab to BLd resulted in a statistically significant and clinically meaningful improvement in overall $\geq$ CR rate among ASCT-ineligible patients compared with BLd alone. The overall $\geq$ CR rate was █ in DBLd and █ in BLd (OR: █ [95% CI: █; 2-sided nominal p =█]) (Table 19).

Overall, an improvement was observed in the DBLd arm compared with BLd for all response categories including ORR, $\geq$ VGPR, $\geq$ CR rate, and sCR. The absolute difference observed in the DBLd arm compared to the BLd arm was █% for ORR rate (DBLd: █%; BLd: █%; OR: █ [95% CI: █]), █% for $\geq$ VGPR rate (DBLd: █%; BLd: █%; OR: █ [95% CI: █]), █% for $\geq$ CR rate (see above), and █% for sCR rate (DBLd: █%; BLd: █%; OR: █ [95% CI: █]; Table 19).

Table 19: Summary of response rates (ASCT-ineligible ITT analysis set) – final PFS analysis

Response rates	BLd N=145		DBLd N=144		OR (95% CI); ^a p-value ^b
	n (%)	95% CI	n (%)	95% CI	
sCR					
CR					
VGPR					
PR					
SD					
PD	I		I		
NE			I		
ORR (sCR + CR + VGPR + PR)					
≥VGPR (sCR + CR + VGPR)					
≥CR (sCR + CR)					

Footnote: ^a Mantel-Haenszel estimate of the common OR for stratified tables is used. The stratification factors are: ISS staging (I, II, III), age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised. An OR > 1 indicates an advantage for DBLd. ^b p-value from the Cochran Mantel-Haenszel Chi-Squared test. Response was assessed by computerised algorithm, based on International Uniform Response Criteria Consensus Recommendations. Percentages are calculated with the number of participants in each group as denominator.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IMWG: International Myeloma Working Group; NE: not evaluable; OR: odds ratio; ORR: overall response rate; PD: progressive disease; PFS: progression-free survival; PR: partial response; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.

Source: J&J Data on File.

Duration of response

DOR ($\geq$ PR) was calculated from the date of the initial documentation of a response ($\geq$ PR) to the date of the first documented evidence of PD, as defined in the IMWG criteria, or death due to PD, whichever occurred first. As of the final PFS analysis, the median duration of response ($\geq$ PR) was [REDACTED] (Table 20) among ASCT-ineligible patients. The Kaplan-Meier plot for DOR ($\geq$ PR) among the ASCT-ineligible ITT analysis set is presented in Appendix L.

The addition of daratumumab to BLd resulted in a statistically significantly improved DOR ($\geq$ PR), with a HR (DBLd versus BLd) of [REDACTED] (95% CI: [REDACTED]; 2-sided nominal $p < [REDACTED]$).

Table 20: Summary of duration of response based on computerised algorithm (responders $\geq$ PR] in ASCT-ineligible ITT analysis set) – final PFS analysis

Duration of response	BLd [REDACTED]	DBLd [REDACTED]
Number of events, n (%)	[REDACTED]	[REDACTED]
Median KM estimate, months		
25% percentile (95% CI)	[REDACTED]	[REDACTED]
Median (95% CI)	[REDACTED]	[REDACTED]
75% percentile (95% CI)	[REDACTED]	[REDACTED]
p-value ^b	[REDACTED]	
HR (95 % CI) ^a	[REDACTED]	

Footnotes: Number of events refers to number of responders ($\geq$ PR) who developed disease progression or died due to disease progression.

^a p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age $\geq$ 70 years) as randomised.

^b HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age $\geq$ 70 years) as randomised. A HR<1 indicates an advantage for DBLd

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival; PR: partial response; SD: standard deviation.

Source: J&J Data on File.

2.6.3 Other secondary endpoints

Overall survival

At the final PFS analysis, with a median follow-up of 58.7 months, a total of [REDACTED] deaths [DBLd: [REDACTED]; BLd: [REDACTED]] had occurred and the median OS [REDACTED] (Table 21 and Figure 14). The HR (DBLd versus BLd) was 0.66 (95% CI: 0.42, 1.03; $p=0.0682$), demonstrating a positive trend towards OS benefit in favour of the DBLd arm.

Despite the immaturity of the OS data, the rate of $\geq$ VGPR and MRD negativity in patients receiving DBLd showed a statistically significant improvement. These results are highly predictive of superior long-term survival outcomes with DBLd versus BLd once the trial data matures.

Due to the incurable nature of MM, patients place high value on treatments that extend life expectancy.⁸⁴ As such, OS is an important outcome as it reflects the effectiveness of treatments in prolonging life, a primary concern for those affected by MM.

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Table 21: Summary of OS (ASCT-ineligible ITT analysis set) – final PFS analysis

Overall survival	BLd (n=145)	DBLd (n=144)
Number of events (%)	████████	████████
Number of censored (%)	████████	████████
KM estimate (months)		
25% quantile (95% CI)	██████████	██████████
Median (95% CI)	████████	████████
75% quantile (95% CI)	████████	████████
p-value ^s	0.0682	
HR (95% CI) ^b	0.66 (0.42, 1.03)	
OS rate (%)		
12-month survival rate % (95% CI)	██████████	██████████
18-month survival rate % (95% CI)	██████████	██████████
24-month survival rate % (95% CI)	██████████	██████████
30-month survival rate % (95% CI)	██████████	██████████
36-month survival rate % (95% CI)	██████████	██████████
48-month survival rate % (95% CI)	██████████	██████████
54-month survival rate % (95% CI)	██████████	██████████

Footnotes: ^a p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised.

^b HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised. A HR <1 indicates an advantage for DBLd.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; ISS: International Staging System; NE: not estimable; OS: overall survival; PFS: progression-free survival.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

Figure 14: KM plot for OS (ASCT-ineligible ITT analysis set) – final PFS analysis



Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; OS: overall survival; PFS: progression-free survival.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

OS – adjusted for COVID-19

The CEPHEUS study was ongoing during the COVID-19 pandemic. As of the cut-off date of the final PFS analysis, in the ASCT-ineligible population, there were █ COVID-19 deaths (█% of the total deaths), with an imbalance between the DBLd arm (n=█) versus the BLd arm (n=█), and there were █ deaths not due to COVID-19 (DBLd: n=█; BLd: n=█). Most COVID-19 related deaths (█ out of █) occurred during the peak of the COVID-19 pandemic in 2020 and 2021.

As such, as described in Section 2.4.1, an analysis where OS was adjusted for COVID-19 deaths was performed whereby deaths due to COVID-19 were censored. The analysis censoring for COVID-19 deaths demonstrated an improved HR and its 95% CI, resulting in a statistically significant and clinical meaningful improvement in OS for DBLd versus BLd (HR: 0.55 [95% CI: 0.34, 0.90]; p-value=0.0159, Table 22). The Kaplan-Meier plot for OS (censored for death due to COVID-19) among the ASCT-ineligible ITT analysis set is presented in Appendix K.

Table 22: Summary of OS (adjusted for COVID-19; ASCT-ineligible ITT analysis set) – final PFS analysis

Overall survival (censored for death due to COVID-19)	BLd (n=145)	DBLd (n=144)
Number of events (%)	██████	██████
Number of censored (%)	██████	██████
KM estimate (months)		
25% quantile (95% CI)	██████████████	██████████████
Median (95% CI)	██████████	██████████
75% quantile (95% CI)	██████	██████

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

p-value ^a	0.0159
HR (95% CI) ^b	0.55 (0.34, 0.90)

Footnotes: ^a p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised.

^b HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised. A HR <1 indicates an advantage for DBLd.

Patients having COVID-19 death as event were censored at the date of death - 1.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; ISS: International Staging System; NE: not estimable; OS: overall survival; PFS: progression-free survival.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

Progression free survival on the next line of therapy (PFS2)

At the time of the final PFS DCO, the PFS2 data were not yet mature; [REDACTED] participants in the DBLd arm and [REDACTED] in the BLd arm had a PFS2 event (Table 23). The Kaplan-Meier plot for PFS2 among the ASCT-ineligible ITT analysis set is presented in Appendix K.

Analysis of PFS2 demonstrated a [REDACTED] reduction in the risk of progression on the next line of therapy for participants treated with DBLd versus BLd (HR: [REDACTED] [95% CI: [REDACTED]]; 2-sided nominal p=[REDACTED]). These results demonstrate that the PFS benefit of DBLd is maintained into the next line of therapy, providing patients with hope for the future and alleviating the constant fear of relapse often experienced by MM patients. Median PFS2 was reached in the BLd treatment arm ([REDACTED] months (range: [REDACTED])), but was not reached for the DBLd treatment arm.

Table 23: Summary of PFS2 based on investigator assessment (ASCT-ineligible ITT analysis set) – final PFS analysis

Progression free survival on the next line of therapy	BLd (n=145)	DBLd (n=144)
Number of events (%)	[REDACTED]	[REDACTED]
KM estimate (months)		
25% quantile (95% CI)	[REDACTED]	[REDACTED]
Median (95% CI)	[REDACTED]	[REDACTED]
75% quantile (95% CI)	[REDACTED]	[REDACTED]
p-value ^a	[REDACTED]	
HR (95% CI) ^b	[REDACTED]	
PFS2 rate (%)		
6-month PFS2 rate % (95% CI)	[REDACTED]	[REDACTED]
12-month PFS2 rate % (95% CI)	[REDACTED]	[REDACTED]
18-month PFS2 rate % (95% CI)	[REDACTED]	[REDACTED]
24-month PFS2 rate % (95% CI)	[REDACTED]	[REDACTED]
30-month PFS2 rate % (95% CI)	[REDACTED]	[REDACTED]
36-month PFS2 rate % (95% CI)	[REDACTED]	[REDACTED]
48-month PFS2 rate % (95% CI)	[REDACTED]	[REDACTED]
54-month PFS2 rate % (95% CI)	[REDACTED]	[REDACTED]

Footnotes: ^a p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised.

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^b HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised. A HR<1 indicates an advantage for DBLd.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; ISS: International Staging System; NE: not estimable; PFS: progression-free survival; PFS2: progression free survival on the next line of therapy.

Source: J&J Data on File.

PFS2 – adjusted for COVID-19

An analysis where PFS2 was adjusted for COVID-19 in the ASCT-ineligible population of CEPHEUS also showed an improved HR and its 95% CI, with a statistically significant and clinically meaningful improvement in PFS2 for favouring DBLd versus BLd. Compared to a HR of [REDACTED] (95% CI: [REDACTED]) in the unadjusted analyses, adjusting for COVID-19 resulted in an improved HR of [REDACTED] (95% CI: [REDACTED]; 2-sided nominal p=[REDACTED]) (Table 24). The Kaplan-Meier plot for PFS2 (censored for deaths due to COVID-19) among the ASCT-ineligible ITT analysis set is presented in Appendix K.

Table 24: Summary of PFS2 based on computerised algorithm (adjusted for COVID-19; (ASCT-ineligible ITT analysis set) – final PFS analysis

PFS2	BLd N=145	DBLd N=144
Number of events, n (%)	[REDACTED]	[REDACTED]
Number of events censored, n (%)	[REDACTED]	[REDACTED]
KM estimate, months		
Median (95% CI)	[REDACTED]	[REDACTED]
p-value ^a	[REDACTED]	
HR (95% CI) ^b	[REDACTED]	

Footnotes: ^a p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised.

^b HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refused transplant, or age ≥70 years) as randomised. A HR <1 indicates an advantage for DBLd.

Patients who died due to COVID-19 without PD and subsequent antimyeloma therapies are censored at the last disease assessment before death.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; ISS: International Staging System; PFS: progression-free survival.

Source: J&J Data on File.

2.6.4 Patient-reported outcomes

Patients' HRQoL, symptoms, functioning, and general well-being were captured using 3 patient-reported outcome (PRO) measures: EORTC QLQ-C30, EORTC QLQ-MY20 and EQ-5D-5L scale scores. The PRO measures were electronically (ePRO) collected to understand the change in PRO endpoints. The measures were administered according to the Schedule of Activities to understand how participants self-reported health state changed over time and the difference between treatment arms during treatment, maintenance, and post-progression.

The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

recall period for the EORTC QLQ-C30 is 1 week (“past week”) and responses are reported using a verbal rating scale. Item and scale scores are transformed to a 0 to 100 scale. A higher score represents greater HRQoL, better functioning, and more (worse) symptoms. The EORTC QLQ-C30 has been widely used among cancer patients. Reliability, validity, and clinically meaningful change have been demonstrated in multiple myeloma patients.^{108, 109}

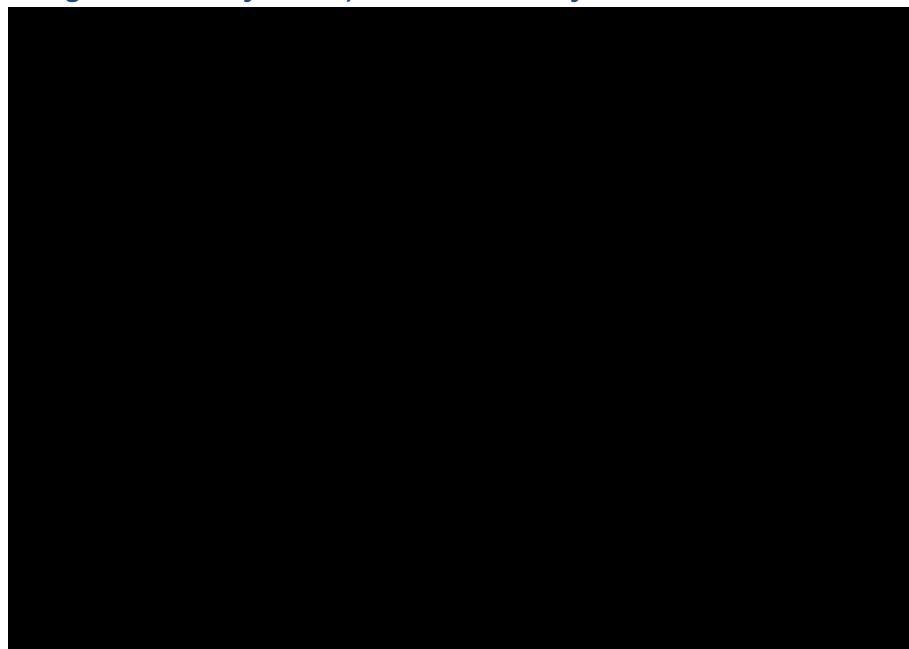
The EORTC QLQ-MY20 has been designed to use alongside the EORTC QLQ-C30 to address issues of more relevance to myeloma patients.¹¹⁰ The 20-items make up 4 scales: disease symptoms, side effects of treatment, future perspective, and body image. Recall, response options, and interpretation is similar to the EORTC QLQ-C30.

The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analogue scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual.

In the ASCT-ineligible population of CEPHEUS, [REDACTED] in HRQoL and physical functioning, as well as [REDACTED] in symptoms (pain, fatigue, overall disease symptoms) as measured by EORTC QLQ-C30 (Figure 15), EORTC QLQ-MY20 (Appendix K) and EQ-5D-5L (Figure 16) scale scores, were observed. Data were [REDACTED] across treatment arms supporting [REDACTED] of HRQoL, symptoms or functioning with the addition of daratumumab to BLd.

EORTC QLQ-C30

Figure 15: Least squares plot of change in C30-Global health status over time (ASCT-ineligible ITT analysis set) – final PFS analysis



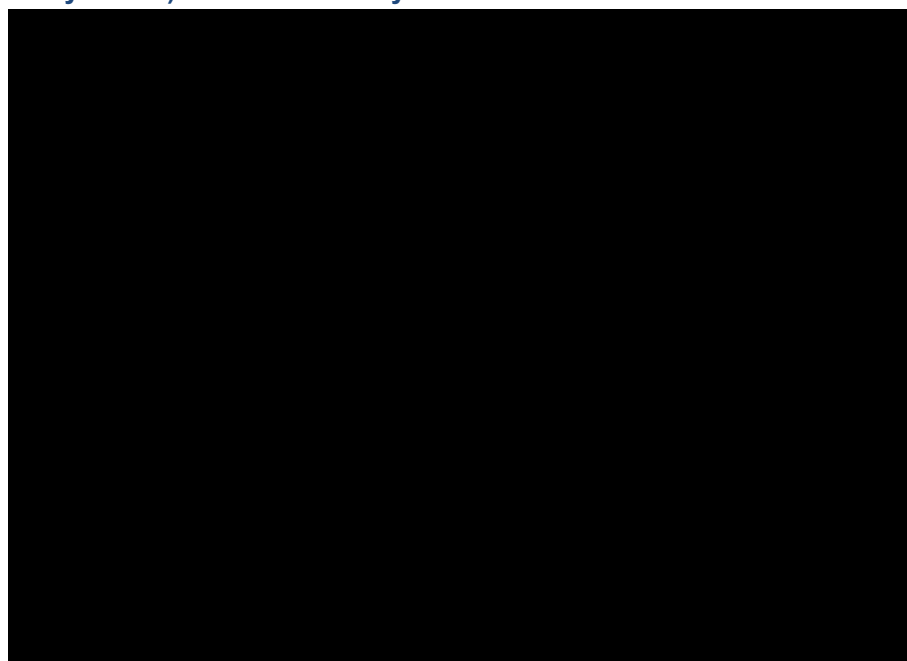
Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CL: confidence level; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; LS: least squares; PFS: progression-free survival; PRO: patient-reported outcomes.

Source: J&J Data on File.

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EQ-5D-5L

Figure 16: Least squares plot of change in EQ-5D utility over time (ASCT-ineligible ITT analysis set) – final PFS analysis



Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CL: confidence level; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; LS: least squares; PFS: progression-free survival; PRO: patient-reported outcomes.

Source: J&J Data on File.

2.7 Subsequent treatments used in the relevant studies

Owing to the effectiveness of both DBLd and BLd as treatment regimens, only a small proportion of patients had received subsequent treatment at the time of the latest DCO in the CEPHEUS trial. Overall, █ patients received at least one subsequent treatment following DBLd, and █ patients received at least one subsequent treatment following BLd.

A summary of the subsequent treatment regimens received by more than one patient in either treatment arm as an initial subsequent treatment is provided in Table 25 below.

Table 25: Subsequent treatment regimens received as a first subsequent treatment following either DBLd or BLd (ASCT-ineligible ITT population) – final PFS analysis

Subsequent treatment, n (%)	BLd █ who received subsequent treatment	DBLd █ who received subsequent treatment
Carfilzomib plus dexamethasone	█	█
Carfilzomib, pomalidomide and dexamethasone	█	█
Daratumumab, bortezomib and dexamethasone	█	█
Daratumumab, carfilzomib and dexamethasone	█	█
Daratumumab, lenalidomide and dexamethasone	█	█
Daratumumab, pomalidomide and dexamethasone	█	█
Investigational drugs	█	█

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Isatuximab, pomalidomide and dexamethasone		
Lenalidomide and dexamethasone		
Pomalidomide and dexamethasone		
Other		

Footnotes: Only subsequent treatment regimens received by more than one patient as a first subsequent therapy in either treatment arm have been included.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intent-to-treat; PFS: progression-free survival.

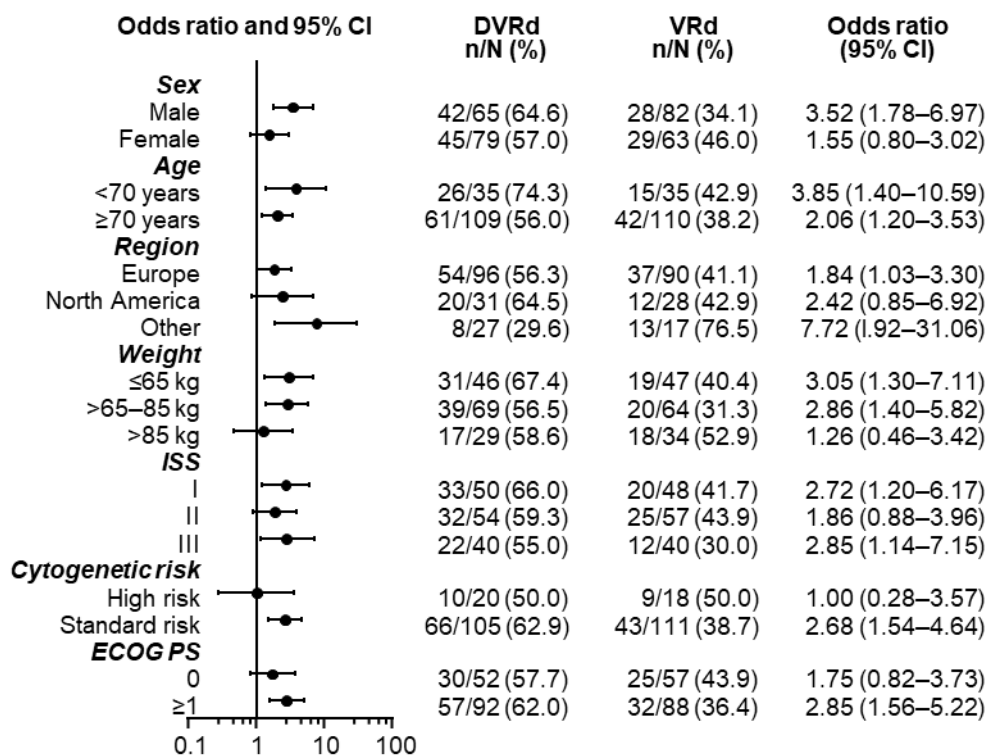
Source: J&J Data on File.

2.8 Subgroup analysis

Subgroup analyses of overall MRD-negativity in the ASCT-ineligible ITT population are summarised for the final PFS analysis in Figure 17. Treatment effect on overall MRD negativity rate (DBLd over BLd) was generally consistent across the pre-specified subgroups. However, the trial was not powered to detect differences in treatment effect between subgroups; the results from the subgroups with small sample sizes are to be interpreted with caution.

Subgroup analyses of overall MRD-negativity in the full ITT population are presented in Appendix L for completeness.

Figure 17: Subgroup analyses on MRD negativity rate at 10⁻⁵ in bone marrow (ASCT-ineligible ITT population) – final PFS analysis



Footnotes: High risk is defined by FISH testing: t (4; 14), t (14; 16), and 17p deletion.

Mantel-Haenszel estimate of the common OR for un-stratified tables is used. An OR >1 indicates an advantage for DBLd.

MRD negativity rate is defined as the proportion of patients who achieve ≥CR response and have MRD negative status (at 10⁻⁵) by bone marrow aspirate after randomisation but prior to PD, subsequent anti-myeloma therapy, or both.

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Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System; ITT: intent-to-treat; PFS: progression-free survival.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

2.9 *Meta-analysis*

The CEPHEUS trial is the only relevant trial for DBLd in this indication. As such, a meta-analysis is not considered applicable for this appraisal.

2.10 Indirect and mixed treatment comparisons

2.10.1 Overview of indirect treatment comparisons

As previously highlighted in Section 1.1, DLd represents the SoC for ASCT-ineligible patients with NDMM in the UK. As such, DLd is the key comparator to DBLd relevant in this submission. Given the absence of direct trial evidence comparing DBLd to DLd (see Section 2.10.2), an ITC was conducted to assess the comparative efficacy of DBLd and DLd for the treatment of ASCT-ineligible NDMM patients. For this comparison, given J&J is sponsor of both the CEPHEUS and MAIA trials, and thus IPD are accessible from CEPHEUS (DBLd versus BLd) and MAIA (DLd versus Ld), an IPTW approach was selected in line with NICE TSD 18.¹¹¹ Details of the IPTW ITC of DBLd versus DLd are presented in Section 2.10.2.

While DLd is the most relevant comparator to DBLd in this indication (Section 1.1), ITCs between DBLd and the other comparators listed in the NICE final scope for this submission were also conducted for completeness:

- **DBLd vs Ld:** IPD from the CEPHEUS (DBLd versus BLd) and MAIA (DLd versus Ld) trials were leveraged to facilitate the comparison of DBLd and Ld via the IPTW approach, in line with NICE TSD 18 guidance for when IPD is available for both the intervention and comparator.¹¹¹ Details of the IPTW ITC of DBLd versus Ld are also presented in Section 2.10.2, with further details provided in Appendix D.
- **DBLd vs BMP:** IPD from the CEPHEUS (DBLd versus BLd) and ALCYONE (DBMP versus BMP) trials were leveraged to facilitate the comparison of DBLd and BMP via the IPTW approach (as both sets of IPD is available for the intervention and comparator). Details of this additional ITC is presented in Section 2.10.3 with further details provided in Appendix D.
- **DBLd vs BCd:** No clinical trial evidence was identified for BCd in the patient population of relevance to this submission, meaning an ITC between DBLd and BCd was not feasible. However, as further detailed in Section 2.10.4, published observational studies between BMP and BCd and naïve comparison of UK RWE, indicate that an assumption of equal efficacy between the two treatments is reasonable – an assumption also supported by clinical expert feedback at a May 2025 UK Advisory Board. As such, the ITCs between DBLd and BMP can also be considered to represent a reasonable proxy for the comparative efficacy for DBLd vs BCd.

Lastly, while the IPTW approach represents the most suitable approach when IPD are available for all relevant studies,¹¹¹ an NMA comparing DBLd with DLd, Ld and BMP was also conducted as a supportive analysis to the IPTW ITCs (it is not possible to connect BCd to the network of evidence). Details of the NMA are presented in Section 2.10.5 and Appendix M.

2.10.2 Indirect treatment comparison (DBLd versus DLd; DBLd versus Ld)

An SLR was conducted in November 2020 and updated in August 2024, and again in April 2025, to identify studies of relevant therapies for patients with ASCT-ineligible NDMM.

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The review did not identify any clinical studies directly comparing the efficacy of DBLd with DLd. The SLR identified MAIA, a randomised controlled trial (RCT) which evaluated the efficacy and safety of DLd compared with Ld. As such, in the absence of direct evidence comparing the clinical efficacy of DBLd versus DLd, an ITC was conducted leveraging data from CEPHEUS trial (for DBLd) and MAIA trial (for DLd). Given that J&J is the study sponsor for both the CEPHEUS and MAIA trials, and therefore have access to IPD, population adjustment-based methods were explored to conduct an ITC, in line with NICE decision support unit (DSU) TSD 17.¹¹²

For completeness, the same approach was also used to conduct an ITC between DBLd and Ld.

Data sources

CEPHEUS is an ongoing, randomised, multicentre, open-label Phase III trial which investigated the clinical efficacy and safety of DBLd compared with BLd. Full details of the trial methodology are presented in Section 2.3.1. A summary of the MAIA trial (DLd versus Ld) is presented below.

MAIA (NCT02252172) is an ongoing, randomised, open-label, active-controlled, parallel-group, multicentre, Phase III clinical trial which compared DLd with Ld in patients with ASCT-ineligible NDMM. A total of 737 patients across 176 hospitals in 14 countries across North America, Europe, the Middle East, and the Asia-Pacific region were randomised in a 1:1 ratio to Ld or DLd, stratified by ISS (I, II or III), region (North America versus other), and age (<75 versus ≥75 years). During the Treatment Phase, patients in both treatment arms received lenalidomide 25 mg orally on Days 1 through 21 of each 28-day cycle (recommended to be 10 mg every 24 hours for patients with creatinine clearance 30 to 50 mL/min) and dexamethasone 40 mg orally on Days 1, 8, 15 and 22 of each cycle (patients >75 years of age or with BMI <18.5 kg/m² could receive 20 mg weekly). In addition, patients randomised to treatment with DLd received daratumumab 16 mg/kg weekly for eight weeks (Cycles 1 to 2), then every other week for 16 weeks (Cycles 3 to 6), then every four weeks (Cycle 7 and beyond). Patients in both treatment arms continued treatment until disease progression or unacceptable toxicity.

At the time of the final PFS analysis of MAIA, the median follow-up time was 64.5 months; OS data at the time of the final PFS analysis was immature. As the time of the final OS analysis of MAIA, the median follow-up for OS was 89.3 months. These two data cuts were used to inform the ITC of DBLd versus DLd (the final PFS analysis [median follow-up: 64.5 months] for the PFS analyses, the final OS analysis [median follow-up: 89.3 months]) for the OS and TTD analyses.

A summary of the MAIA trial is presented in Table 26. The MAIA trial was estimated to have a low risk of bias when assessed using Cochrane RoB2 (Appendix B).

Table 26: Overview of the MAIA trial

Trial name	MAIA (NCT02252172)
Location	176 hospitals in 14 countries: Austria (4 sites), Australia (9 sites), Belgium (3 sites), Canada (8 sites), Denmark (3 sites), France (45 sites), Germany (14 sites), Ireland (2 sites), Israel (4 sites), Italy (4 sites), Netherlands (3 sites), Sweden (7 sites), United Kingdom (14 sites), United States (56 sites).
Trial design	Randomised, open-label, active controlled, parallel-group, multicentre, Phase III study.
Intervention^a	DLd (N=368)
Comparator^a	Ld (N=369)

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Key inclusion/exclusion criteria	Inclusion criteria: • Diagnosis of NDMM • ASCT-ineligible (due to age ≥ 65 years or coexisting conditions) • Measurable disease • ECOG PS 0–2 Exclusion criteria: • Prior or current systemic therapy or ASCT for MM (except short-course of steroids) • Diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smouldering MM • Diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present • History of malignancy (other than MM) within five years before the date of randomisation (see exceptions in MAIA Protocol, included within the reference pack) • Patient has plasma cell leukaemia (according to World Health Organisation [WHO] criterion) Full inclusion and exclusion criteria can be found in the MAIA Protocol included within the reference pack.
Method of study drug administration	• Daratumumab (16 mg/kg) administered by IV infusion weekly on days 1, 8, 15 and 22 for two 28-day cycles, then every two weeks for the remaining induction and consolidation cycles based on treatment assignment • Lenalidomide 25 mg administered orally on Days 1 through 21 of each 28-day cycle (10 mg every 24 hours for patients with creatinine clearance 30 to 50 mL/min)^a • Dexamethasone 40 mg administered once weekly (patients >75 years of age or with body mass index <18.5 kg/m² could receive 20 mg weekly)
Primary outcome	PFS
Secondary outcomes^a	• TTP • CR rate • MRD negativity rate • PFS2 • OS • sCR rate • Time to next treatment (TTNT) • ORR • $\geq$VGPR • Time to response • DOR • HRQoL • AEs
Pre-specified subgroups	• Sex (male, female) • Race (white, other) • Age (<75 years, ≥ 75 years) • Region (North America, other)

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	• Baseline renal function, CrCl (>60 mL/min, ≤60 mL/min) • Baseline hepatic function (normal, impaired) • ISS staging (I, II, III) • Type of MM (IgG, non-IgG) • Cytogenetic risk at study entry (high risk, standard risk) • ECOG performance score (0, 1, ≥2)
Duration of study and follow-up	At the final PFS analysis, median follow-up time was 64.5 months. At the final OS analysis, median follow-up time was 89.3 months.

Footnotes: ^a Method of lenalidomide administration was taken from the MAIA study protocol since the daratumumab SmPC does not list details of lenalidomide dose modification.

Abbreviations: AE: adverse events; ASCT: autologous stem cell transplant; CR: complete response; DLd: daratumumab, lenalidomide and dexamethasone; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; HRQoL: health-related quality of life; ISS: International Staging System; IV: intravenous; Ld: lenalidomide and dexamethasone; MM: multiple myeloma; MRD: minimal residual disease; NDMM: newly diagnosed multiple myeloma; ORR: overall response rate; OS: overall survival; PFS: progression free survival; PFS2: progression-free survival on next line of therapy; PS: performance status; sCR: stringent complete response; TTP: time to disease progression; VGPR: very good partial response; WHO: World Health Organisation.

Source: J&J Data on File.

Feasibility of an ITC between CEPHEUS and MAIA

When conducting ITCs, there should be no systematic differences between studies other than the interventions being compared, so that any differences in outcomes between the intervention groups may be attributed to the difference in interventions. Accordingly, the suitability of comparing CEPHEUS and MAIA in an ITC was determined by assessing whether they were sufficiently homogeneous, similar and consistent across their populations and outcomes. Based on a comparison of the study designs of CEPHEUS and MAIA, including comparisons of the study treatment, key inclusion and exclusion criteria (see Table 27 for an overview; see Appendix B for a full comparison), enrollment period, median follow up, and key study endpoints, it was determined that the two trials were sufficiently similar in design to be compared via an ITC.

Table 27: Key inclusion criteria for the CEPHEUS and MAIA trials

CEPHEUS	MAIA
• ≥18 years • Not considered a suitable candidate for ASCT (due to eligibility or refusal of ASCT) • Measurable disease • ECOG PS 0–2	• ≥18 years • ASCT-ineligible (due to age ≥65 years or coexisting conditions) • Measurable disease • ECOG PS 0–2

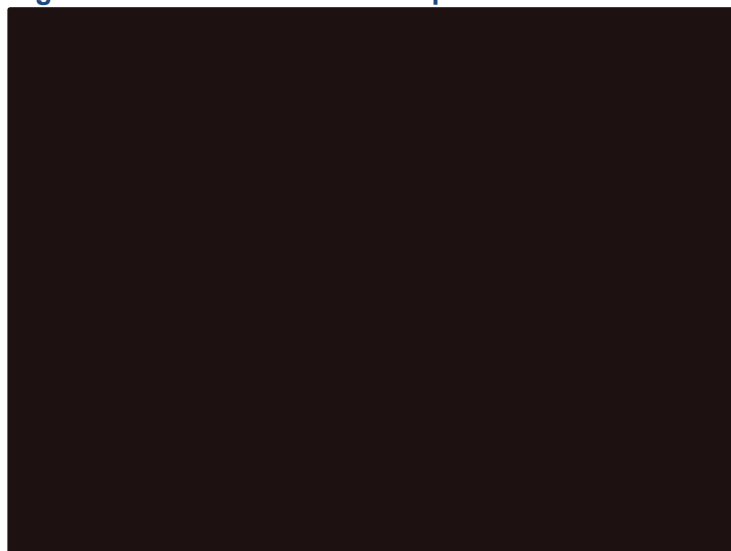
Abbreviations: ASCT: autologous stem cell transplant; ECOG: Eastern Cooperative Oncology Group.

Of note, while most key inclusion/exclusion criteria were aligned across CEPHEUS and MAIA, initial differences in patient population were identified. As highlighted in Section 2.3.1, the CEPHEUS trial population included patients with NDMM for whom ASCT was not planned as initial therapy (i.e. <70 years ineligible, or age <70 years and refused transplant, or age ≥70 years). In contrast, the MAIA trial population was patients who were transplant-ineligible due to age ≥65 years or coexisting conditions (Table 26). As outlined in Section 1.1, the focus of this submission is specifically patients who are ASCT-ineligible. As such, in line with the target population of this submission, the CEPHEUS population informing both the ITCs of DBLd versus DLd, and DBLd versus Ld was restricted to the ASCT-ineligible subgroup (i.e. <70 years ineligible, or age ≥70 years).

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Furthermore, it is important to ensure that the CEPHEUS and MAIA trials had completely overlapping populations as differences in population inclusion criteria could result in overrepresentation of certain baseline characteristics, thus biasing the probability of allocation. Therefore, given the oldest ASCT-ineligible patient enrolled into the CEPHEUS trial was 80 years of age at baseline (see Table 6), the patient population from MAIA was limited to those up to 80 years of age to align with the CEPHEUS trial. Figure 18 depicts the selected patient populations from MAIA and CEPHEUS informing the ITCs of DBLd versus DLd, and DBLd versus Ld.

Figure 18: MAIA and CEPHEUS patient inclusion for the ITCs



Abbreviations: ASCT: autologous stem cell transplant; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone.

Source: J&J Data on File.

Additionally, when conducting an ITC, ensuring consistency in outcome definitions and censoring rules is paramount. Based on the definitions and availability of data for endpoints assessed in CEPHEUS (see Table 4) and MAIA (see Table 26), it was determined that ITCs could be conducted across numerous outcomes, including PFS, PFS2, OS, $\geq$ VGPR, $\geq$ CR, ORR, sCR, MRD negative CR rate and TTD (Table 28).

Table 28: Outcomes compared in the ITCs of DBLd versus DLd, and versus Ld (CEPHEUS versus MAIA)

Outcome	Details
OS	- Defined as time from randomisation to death from any cause - If the patient was alive at the cut-off date for the analysis or the survival status was unknown, the patient was censored at the date the patient was last known to be alive - A sensitivity analysis censoring deaths due to COVID-19 was conducted
PFS	- Defined as time from randomisation to disease progression or death, whichever occurred first - Patients who had no event and were still alive at the cut-off date for analysis would be censored at the last disease assessment
PFS2	Defined as time from randomisation to progression on the next line of treatment or death, whichever came first

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	Patients who were still alive and not yet progressed on the next line of treatment would be censored on the last date of follow-up
TTD	- Defined as time from treatment start date to end of treatment - Patients who were still on treatment would be censored on the last date of follow up
MRD negative CR rate	Proportion of patients achieving MRD negativity (assessed at 10-5 sensitivity by means of NGS) and a $\geq$CR
$\geq$ CR	Proportion of patients achieving a CR or sCR
sCR	CR plus normal FLC ratio, and absence of clonal plasma cells by immunohistochemistry, immunofluorescence, or 2- to 4-color flow cytometry
$\geq$ VGPR	VGPR + CR + sCR
ORR	PR + VGPR + CR + sCR

Abbreviations: CR: complete response; FLC: free light chain; MRD: minimal residual disease; OS: overall survival; PFS: progression free survival; PFS2: progression-free survival on next line of therapy; sCR: stringent CR; TTD: time to treatment discontinuation; VGPR: very good partial response.

Source: J&J Data on File.

Analysis methods

Given J&J is the study sponsor for both CEPHEUS and MAIA, IPD were available from both trials to inform the analyses of DBLd versus DLd and DBLd versus Ld, and therefore population-adjustment methods were considered in line with NICE DSU TSD 17.¹¹² An overview of the population-adjustment methods is presented in the following sections.

Base case approach: inverse probability treatment weighting

Naïve comparisons of non-randomised data are typically biased due to confounding arising from imbalances between study populations for PFs of interest. In these situations, multivariable regression and propensity score analyses – both of which are established methods recognised by NICE¹¹² – are routinely used to estimate relative treatment effects while adjusting for observed differences between populations of interest.

Regression refers to a class of methods in which an endpoint of interest (i.e. dependent variable) is related to a treatment indicator and one or more covariates. In contrast, propensity score-based methods involve weighting, matching or stratifying based on an estimated propensity score. Propensity scores represent the conditional probability that a patient is assigned to an intervention based on their baseline observed covariates.^{113, 114}

Although matching methods (e.g. nearest neighbour matching) are among the most commonly used propensity score methods, weighting (i.e. IPTW) is generally considered more efficient, since it leverages information from all patients rather than a limited subset of patients with available data and similar propensity scores.

In the base case, IPTW was the method used to control for differences in baseline characteristics that could introduce bias between CEPHEUS and MAIA. IPTW utilises the propensity scores to derive weights for each individual so that the baseline patient characteristics in the treated and control groups are balanced after weighting. IPTW aims to address the correlation between baseline characteristics and the probability of being in a treatment arm by using logistic regression and is part of the recommended method from the NICE DSU TSD 18.¹¹¹

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IPTW is particularly useful for this analysis as it maintains the sample size of the study. Furthermore, as IPTW adjusts for a single scalar (i.e. the propensity score), rather than a full set of covariates, propensity score weighting methods are considered appropriate when there are many covariates relative to the sample size and/or the number of events.

Weights are calculated for each patient using the formula “1/propensity score” for the treatment arm (CEPHEUS patients treated with DBLd) and “1/(1 - propensity score)” for the control group (MAIA patients). This means that individuals with a lower probability of exposure to the treatment of interest receive larger weights, thus increasing their relative influence on the comparison. Including these weights in the analysis makes the allocation of patients to each clinical trial independent of the variables included in the propensity score model. Conceptually, the model aims to reweight subpopulations across patient groups to neutralise baseline characteristics and deviations from the average patient profile across all groups.

In this case, patients from CEPHEUS and MAIA were pooled, and their baseline characteristics used to create the propensity score.

Weighting approaches

There are multiple weighting approaches available using IPTW; average treatment effect for the control (ATC), ATE and average effect of the treatment (ATT) are the most commonly used. The ATE, which is typically of interest in NICE appraisals, measures the average differences in outcomes between patients who receive the treatment of interest and those who do not, as if the patients under consideration were randomly allocated to treatment.¹¹² As such, ATE indicates the effect that would be identified by an RCT. ATE is relevant where the treatment is applicable to the entire population represented by the data.¹¹²

It is unclear if either the CEPHEUS or MAIA trial is more generalisable to UK clinical practice, and therefore employing the ATE approach (over other approaches such as ATC or ATT) is appropriate. Using IPTW with ATE weights, each patient's weight is determined by the inverse of their propensity score of belonging to either the treatment or control group.¹¹²

Scenario approaches

To explore the impact of using alternative adjustment methods, multivariate regression and doubly robust analyses, as outlined in NICE DSU TSD 17, were explored in scenario analyses.¹¹²

Identification of covariates

The rationale for conducting population-adjusted indirect comparisons is based on the understanding that there is at least one potential, or known, treatment effect modifier (TEM)/PF, and that these factors are imbalanced between the trials under consideration.

Selection of baseline covariates used for the ITCs was informed by two literature reviews, an empirical assessment of baseline characteristics' role as prognostic variables in CEPHEUS, MAIA, and ALCYONE, and input from clinical experts specialising in MM.

The first literature review, conducted in 2024, identified evidence of TEMs based on RCTs, and reported variables adjusted by population-adjusted indirect comparisons in the public domain. The second literature review identified which covariates were adjusted for in prior ITCs in the ASCT-ineligible NDMM setting. To further explore potential TEMs/PFs, based on the framework

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outlined in NICE DSU TSD 18,¹¹¹ regression analyses assessing baseline covariate's prognostic association with PFS and OS were performed using pooled IPD from CEPHEUS, MAIA, and ALCYONE.

The list of potential covariates for the ITCs was then refined based on discussions with clinical experts on the importance of variables. Modifications to the final list were based on clinical plausibility, missing data and collinearity. The final list of covariates for the ITC was subsequently validated by UK clinical experts during an Advisory Board in May 2025.

In total, 11 covariates were considered priority variables to be adjusted for in the base case (Table 29). Three additional covariates (race, time since initial MM diagnosis and calcium levels) were included in a sensitivity analysis.

Table 29: TEMs and PFs for the ITC

Variable	Base case	Sensitivity analysis (all covariates adjusted)
Age	✓	✓
Sex	✓	✓
Race		✓
ECOG PS	✓	✓
MM stage per ISS	✓	✓
Cytogenetic risk	✓	✓
EMD	✓	✓
Time since initial MM diagnosis		✓
Frailty (based on simplified IMWG frailty score)	✓	✓
Type of MM (IgG versus other)	✓	✓
Anaemia, haemoglobin (< versus ≥ 100mg/L)	✓	✓
Creatinine clearance (≥ versus < 60mL/min/1.73 m ²)	✓	✓
LDH (> versus ≤ 280 U/L)	✓	✓
Calcium levels (> versus ≤ 2.75 mmol/L)		✓

Abbreviations: BPI: brief pain inventory; ECOG PS: Eastern Cooperative Oncology Group performance score; EMD: extramedullary plasmacytoma; GFR: estimated glomerular filtration rate; IMWG: International Myeloma Working Group; IPTW: inverse probability of treatment weighting; ISS: International Staging System; ITC: indirect treatment comparison; L: litre; LDH: lactate dehydrogenase; MM: multiple myeloma; PF: prognostic factor; TEM: treatment effect modifier.

Source: J&J Data on File.

Assessment of overlap

The extent of overlap between populations with respect to the 14 identified covariates was evaluated before and after adjustment. SMDs were used to evaluate the differences for each variable included in the analysis, with a SMD greater than 0.1 indicating a substantial difference between the populations.

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SMDs calculated before and after adjustment are presented in Table 30. Figure 19 shows the performance of IPTW in the DBLd versus DLd ITC.

Before adjustment

As shown in Table 30 and Figure 19, SMDs in unadjusted comparisons of DBLd and DLd were within a ± 0.2 threshold for all variables in the base case. This indicates a high degree of overlap between the two trials, even prior to adjustment.

After adjustment

Following IPTW, the overlap between the CEPHEUS DBLd and MAIA DLd populations improved following adjustment (Table 30). No variables adjusted for in the base case had SMDs outside a threshold of ± 0.1 , indicating that the two patient populations were well balanced in the base case comparison of DBLd versus DLd.

Table 30: SMD for unadjusted and adjusted baseline characteristics for CEPHEUS (DBLd) and MAIA (DLd)

	Unweighted			Weighted		
Variables	DLd (N=■)	DBLd (N=144)	SMD	DLd (ESS=■)	DBLd (ESS=■)	SMD
ISS (%)						
I	■	50.0 (34.7)	■	■	■	■
II	■	54.0 (37.5)	■	■	■	■
III	■	40.0 (27.8)	■	■	■	■
Baseline cytogenetic profile (%)						
High-risk	■	20.0 (13.9)	■	■	■	■
Not done	■	19.0 (13.2)	■	■	■	■
Standard-risk	■	105.0 (72.9)	■	■	■	■
Age (%)						
≤69	■	35.0 (24.3)	■	■	■	■
70–74	■	68.0 (47.2)	■	■	■	■
>75	■	41.0 (28.5)	■	■	■	■
ECOG PS (%)						
0	■	52.0 (36.1)	■	■	■	■
1	■	75.0 (52.1)	■	■	■	■
2 and above	■	17.0 (11.8)	■	■	■	■
Type of MM at diagnosis: IgG (%)	■	92.0 (63.9)	■	■	■	■
EMD (%)	■	9.0 (6.3)	■	■	■	■
Frail, based on Simplified frailty score (%)	■	48.0 (33.3)	■	■	■	■
Male (%)	■	65.0 (45.1)	■	■	■	■
Estimated GFR <60mL/min/1.73 m² (%)	■	■	■	■	■	■

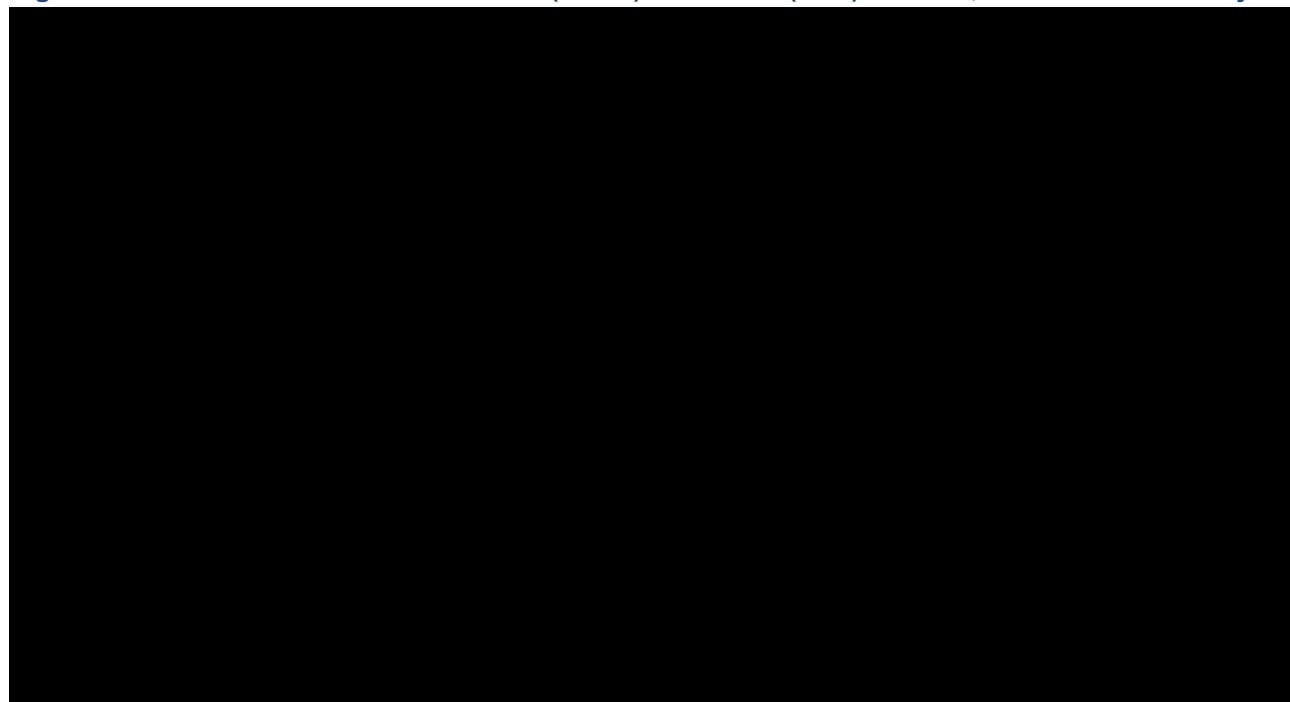
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Anaemia, haemoglobin <100 mg/L (%)	██████	██████	██	██████	██████	██
LDH >280 U/L (%)	██████	██████	██	██████	██████	██
Calcium >2.75 mmol/L (%) (Sensitivity analysis)	██████	██████	██	██████	██████	██
White (%) (Sensitivity analysis)	██████	██████	██	██████	██████	██
Diagnosed ≥1 month (%) (Sensitivity analysis)	██████	██████	██	██████	██████	██

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ECOG PS: Eastern Cooperative Oncology Group performance status; EMD: extramedullary plasmacytoma; ESS: effective sample size; GFR: estimated glomerular filtration rate; IgG: immunoglobulin G; ISS: International Staging System; L: litre; LDH: lactate dehydrogenase; MM: multiple myeloma; PF: prognostic factor; SMD: standardised mean difference.

Source: J&J Data on File. Facon *et al.* (2025)¹⁰⁴

Figure 19: SMDs between the CEPHEUS (DBLd) and MAIA (DLd) cohorts, before and after adjustment (base case ITC)



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Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone
ECOG: Eastern Cooperative Oncology Group performance status; EMD: extramedullary plasmacytoma; GFR: estimated glomerular filtration rate; IgG: immunoglobulin G; ISS: International Staging System; L: litre; LDH: lactate dehydrogenase; MM: multiple myeloma; PF: prognostic factor; SMD: standardised mean difference.

Source: J&J Data on File.

COVID-19 adjustment

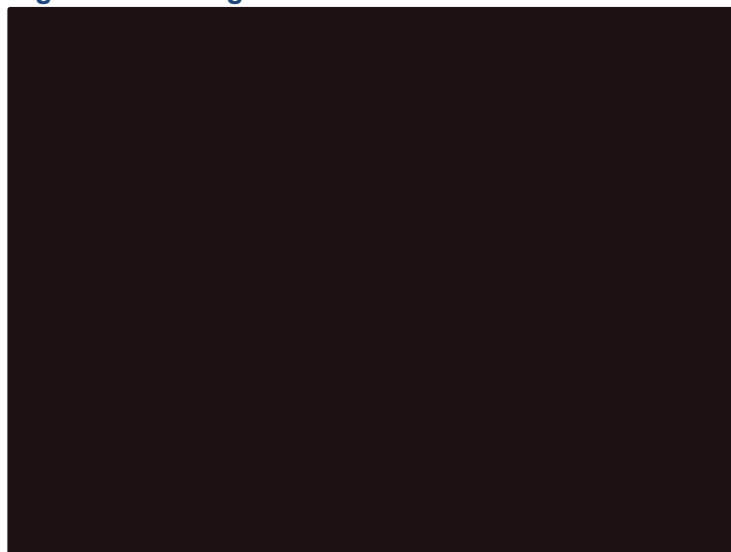
As previously detailed, the CEPHEUS trial was ongoing during the height of the COVID-19 pandemic; in contrast, the MAIA trial was mostly conducted prior to the COVID-19 pandemic, which only impacted the trial towards the end of its follow-up. Additionally, COVID-19 heavily impacted CEPHEUS due to the recruitment of the trial, with many of the patients who died of COVID-19 in the DBLd arm in CEPHEUS from [REDACTED].

UK clinical experts highlighted that this difference in timings is a key consideration.³ They highlighted in MAIA, it is likely that more patients were in (long-term) remission when the pandemic first started, compared to CEPHEUS, where patients were first presenting with MM. Patients are more vulnerable at presentation and early on in their treatment journey, compared to remission, meaning that COVID-19 was likely to have disproportionately impacted CEPHEUS compared to MAIA. Additionally, due to the shorter follow-up of CEPHEUS (compared to MAIA), the COVID-19 deaths represent a higher proportion of total deaths which would have a disproportionate impact on the comparison.

**

Figure 20 provides a visual comparison of the timelines of the pandemic relative to both the CEPHEUS and MAIA trials and the associated COVID-19 mortality rates. It illustrates that patients in the MAIA trial were recruited significantly earlier than those in the CEPHEUS trial. By the time the pandemic began, patients in MAIA had likely achieved long-term remission, remaining progression-free and on treatment for at least three years, as indicated by the mPFS for DLd in MAIA (61.9 months). Conversely, patients in CEPHEUS began treatment closer to the onset of the pandemic, making them more susceptible to catching COVID-19, and therefore accounting for a higher proportion of total deaths. [REDACTED]

Figure 20: Timing of the CEPHEUS and MAIA trials alongside the pandemic



Source: J&J Data on File (CEPHEUS Clinical Study Report May 2024 DCO);¹⁰¹ J&J Data on File (MAIA Clinical Study Report November 2023 DCO).¹¹⁵

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Table 31 summarises deaths due to COVID-19 in both the CEPHEUS and MAIA trials. In CEPHEUS, █ patients in the ASCT-ineligible patient population treated with DBLd died due to COVID-19 – representing █% of all deaths in the DBLd arm. In contrast, █ patients died due to COVID-19 after receiving DLd in MAIA, equating to █% of all deaths on DLd. The higher proportion on COVID-19 deaths in CEPHEUS vs MAIA can be attributed to the timing and recruitment of the trials and where patients were in their disease journey, as illustrated in **

Figure 20.

Table 31: Summary of COVID-19 deaths in CEPHEUS and MAIA

	CEPHEUS		MAIA	
	DBLd	BLd	DLd	Ld
ITT population	197	195	368	369
All deaths	████	████	████	████
COVID-19 deaths	████	████	████	████
ASCT-ineligible population	144	145		
All deaths	████	████		
COVID-19 deaths	████	████		
<80 population			█	█
All deaths			████	████
COVID-19 deaths			████	████

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone.

Source: J&J Data on File (CEPHEUS Clinical Study Report May 2024 DCO);¹⁰¹ J&J Data on File (MAIA Clinical Study Report November 2023 DCO).¹¹⁵

In current clinical practice, with the widespread availability of COVID-19 vaccinations and considering the end of the COVID-19 pandemic, and the baseline characteristics of the patients who died of COVID-19 were generalisable to the overall ASCT-ineligible population (see Table 10, Section 2.4.1), it is likely that most, if not all, of these deaths would have been avoided. As such, given the disproportionate impact of COVID-19 on the CEPHEUS trial due to the timing, any ITCs that did not take into account the impact of COVID-19 would be inherently biased in favour of DLd. As such, for the key endpoints of relevance to the economic model (PFS, OS, TTD), patients who died due to COVID-19 were censored in both the CEPHEUS and MAIA trials in the base case ITC analysis, to provide a more meaningful comparison between DBLd and DLd. For completeness, a sensitivity analysis was conducted where COVID-19 deaths were not censored.

Base case and sensitivity analysis results (DBLd versus DLd)

PFS

The PFS ITC results between DBLd and DLd are presented in Table 32, and the associated KM curves for the base case ITC are presented in Figure 21.

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In the base case analysis of PFS, DBLd statistically significantly reduced the risk of disease progression or death by 45% (HR: 0.55; 95% CI: 0.38, 0.79, p=0.001) when compared to DLd. This is reflected in the PFS KM curves, where clear separation is observed early after treatment initiation, and is sustained across the duration of follow-up.

These results were consistent across sensitivity analyses where all covariates were adjusted, and using the unadjusted COVID -19 analyses, demonstrating the robustness of the base case results.

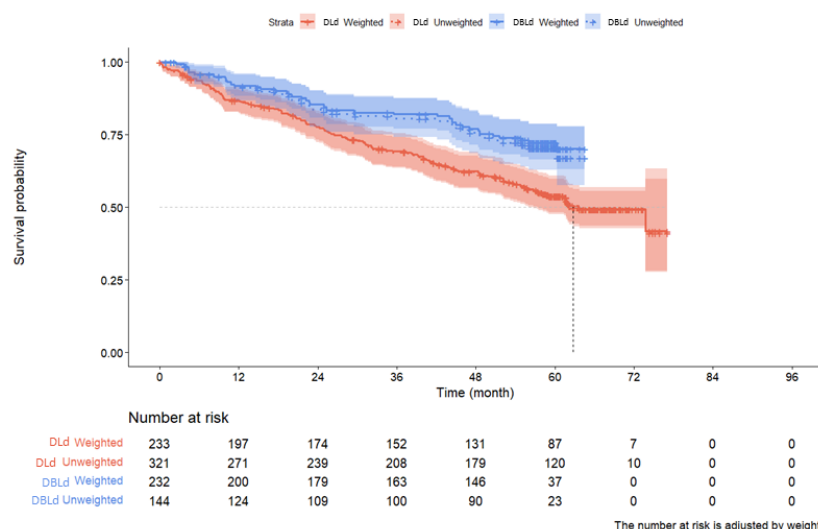
Table 32: PFS results of the ITC (DBLd versus DLd)

Model	Adjusted ITC (IPTW)	
	HR (95% CI)	p-value
Unadjusted (naïve)	0.59 (0.42, 0.85)	p= 0.004
Base case	0.55 (0.38, 0.79)	p=0.001
Sensitivity analysis (all covariates adjusted)	0.54 (0.37, 0.79)	p=0.001
Sensitivity analysis (base case model; unadjusted for COVID-19)	0.62 (0.44, 0.88)	p=0.007

Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; ITC: indirect treatment comparison; IPTW: inverse probability treatment weighting; PFS: progression-free survival.

Source: J&J Data on File.

Figure 21: PFS (censored for COVID-19) KM curves for DBLd and DLd (unadjusted and adjusted; base case model)



Footnotes: ATE weights are applied in this case. Patient volume was reweighted with weighted sum at time zero equals to unweighted sum at time zero.

Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; PFS: progression-free survival.

Source: J&J Data on File.

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OS

The OS ITC results for DBLd versus DLd are presented in Table 33, and associated KM curves for the base in Figure 22.

In the base case analysis of OS censored for COVID-19, compared to DLd, DBLd statistically significantly reduced the risk of death by 37% (HR: 0.63; 95% CI: 0.41, 0.98, $p=0.040$), with sustained separation of the KM curves observed after approximately 24 months.

These results were consistent across sensitivity analyses, all of which demonstrated a substantial OS benefit in favour of DBLd.

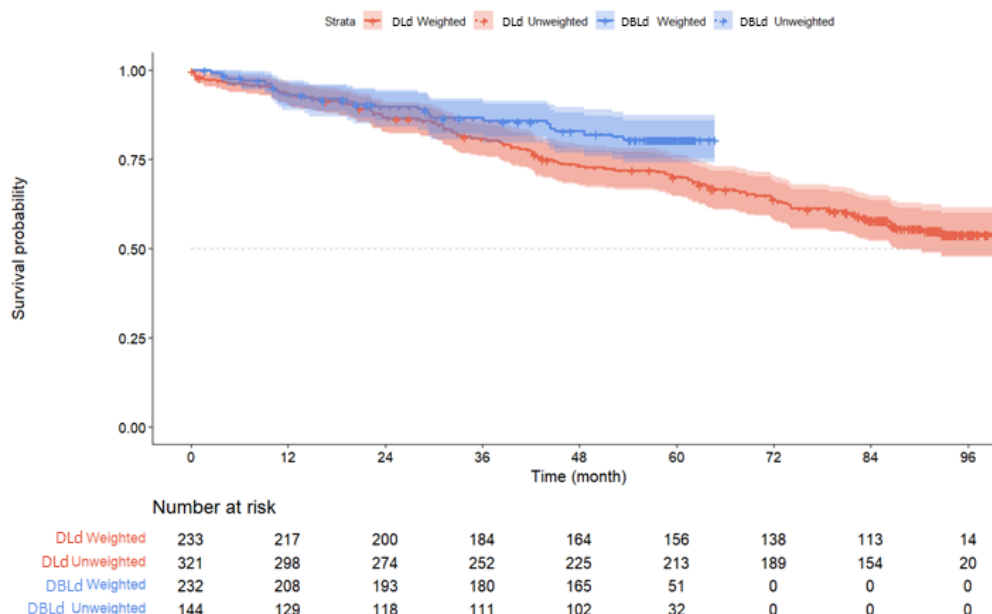
Table 33: OS results of the ITC (DBLd versus DLd)

Model	Adjusted ITC (IPTW)	
	HR (95% CI)	p-value
Unadjusted (naïve)	0.63 (0.41, 0.97)	$p=0.036$
Base case	0.63 (0.41, 0.98)	$p=0.040$
Sensitivity analysis (all covariates adjusted)	0.65 (0.41, 1.02)	$p=0.060$
Sensitivity analysis (base case model; unadjusted for COVID-19)	0.80 (0.53, 1.19)	$p=0.262$

Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; ITC: indirect treatment comparison; IPTW: inverse probability treatment weighting; OS: overall survival.

Source: J&J Data on File.

Figure 22: OS (censored for COVID-19) KM curves for DBLd and DLd (unadjusted and adjusted; base case model)



Footnotes: ATE weights are applied in this case. Patient volume was reweighted with weighted sum at time zero equals to unweighted sum at time zero.

Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; OS: overall survival.

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Source: J&J Data on File.

TTD censored for COVID-19 deaths

TTD (censored for COVID-19 deaths) results for the unadjusted and adjusted base case, and sensitivity analysis (all covariates adjusted), for DBLd versus DLd are presented in Table 34, and associated KM curves for the base case in Figure 23.

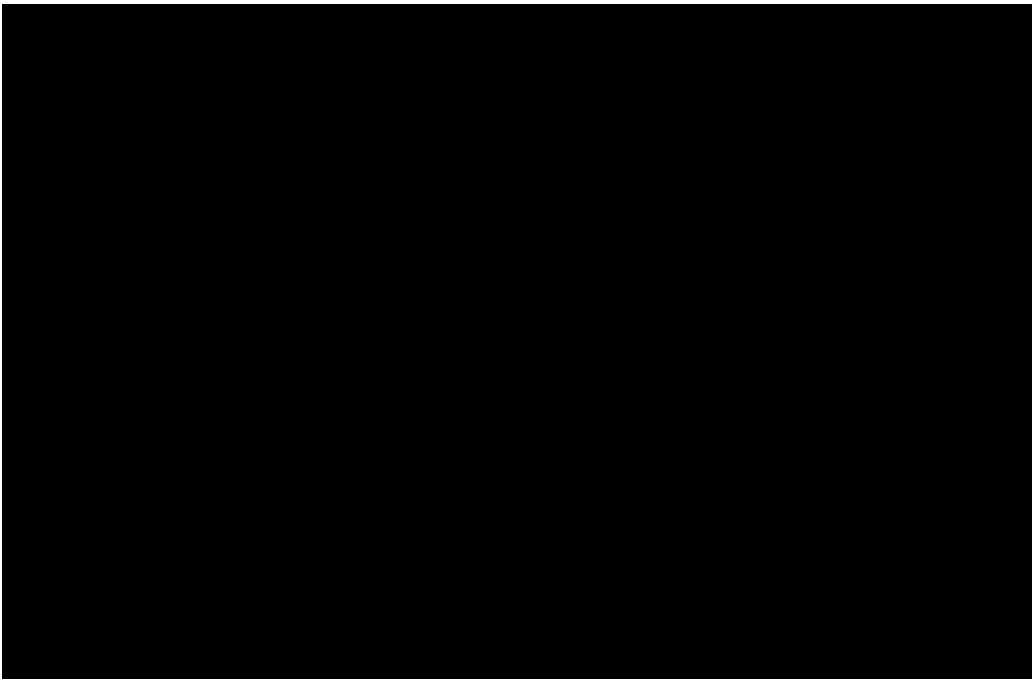
In the base case analysis of TTD censored for COVID-19, compared to DLd, DBLd reduced the risk of discontinuing treatment by █% (HR: █; 95% CI: █).

Table 34: TTD results of the ITC (DBLd versus DLd)

Model	Adjusted ITC (IPTW)	
	HR (95% CI)	p-value
Unadjusted (naïve)	█	█
Base case	█	█
Sensitivity analysis (all covariates adjusted)	█	█
Sensitivity analysis (base case model; unadjusted for COVID-19)	█	█

Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; ITC: indirect treatment comparison; TTD: time to discontinuation.
Source: J&J Data on File.

Figure 23: TTD (censored for COVID-19) KM curves for DBLd and DLd (base case model)



Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; TTD: time to treatment discontinuation.
Source: J&J Data on File.

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PFS2

PFS2 results for the unadjusted and adjusted base case, and sensitivity analysis (all covariates adjusted), for DBLd versus DLd are presented in Table 35, and associated KM curves for the base case in Figure 24.

With or without adjustment, the HR of PFS2 was statistically significant in favour of DBLd. In the base case, compared to DLd, DBLd statistically significantly delayed disease progression or death on the next line of therapy by 33% (HR: 0.67; 95% CI: 0.44, 1.00, p=0.048). The sensitivity analysis (adjusting for all potential PFs) indicated similar results.

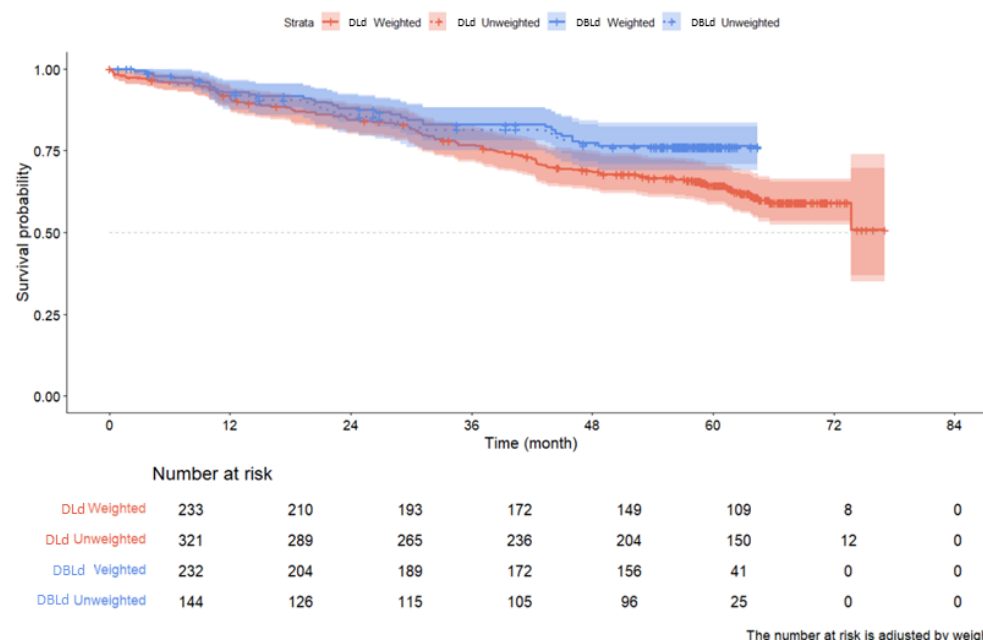
Table 35: PFS2 results of the ITC (DBLd versus DLd)

Model	Adjusted ITC (IPTW)	
	HR (95% CI)	p-value
Unadjusted (naïve)	0.67 (0.45, 0.99)	p=0.044
Base case	0.67 (0.44, 1.00)	p=0.048
Sensitivity analysis (all covariates adjusted)	0.66 (0.44, 1.00)	p=0.047

Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; ITC: indirect treatment comparison; IPTW: inverse probability treatment weighting; PFS2: progression-free survival on next line of therapy.

Source: J&J Data on File.

Figure 24: PFS2 KM curves for DBLd and DLd (unadjusted and adjusted; base case model)



Footnotes: ATE weights are applied in this case. Patient volume was reweighted with weighted sum at time zero equals to unweighted sum at time zero

Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; PFS2: progression-free survival on next line of therapy.

Source: J&J Data on File.

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MRD-negative CR rate

MRD-negative CR rate results for the unadjusted and adjusted base case, and sensitivity analysis (all covariates adjusted), for DBLd versus DLd are presented in Table 36.

With or without adjustment, the MRD-negative CR rate with DBLd was statistically significantly higher than that of DLd. The adjusted OR (DBLd versus DLd) in the base case was 3.04 (95% CI: 2.01, 4.61, $p < 0.001$), reflecting that patients treated with DBLd are over 3 times as likely to achieve a MRD-negative CR as patients treated with DLd. The sensitivity analysis (adjusting for all potential PFs) indicated consistent similar results. MRD negativity has been accepted by the FDA as a predictor for longer term outcomes including PFS and OS for ASCT-ineligible NDMM and can be considered Level 1 evidence (representing the highest possible strength of evidence as a surrogate endpoint). There is a wealth of evidence that supports a correlation between MRD negativity and improved survival in patients with NDMM, demonstrated in Section 1.3.1, and, more recently, a meta-analysis establishing a correlation between a treatment effect on MRD negativity and a treatment effect on PFS/OS. This is supported by the ITC results presented above for OS and PFS.

Table 36: MRD-negative CR rate results of the ITC (DBLd versus DLd)

Model	DLd	DBLd	Adjusted ITC (IPTW)	
	MRD-negative CR rate (%)	MRD-negative CR rate (%)	OR (95% CI)	p-value
Unadjusted (naïve)	34.27	60.42	2.93 (1.95, 4.39)	$p < 0.001$
Base case	34.16	61.22	3.04 (2.01, 4.61)	$p < 0.001$
Sensitivity analysis (all covariates adjusted)	33.64	60.89	3.07 (2.01, 4.69)	$p < 0.001$

Abbreviations: CI: confidence interval; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; IPTW: inverse probability treatment weighting; ITC: indirect treatment comparison; MRD: minimal residual disease; OR: odds ratio.

Source: J&J Data on File.

Response rates

An overview of the results of the response rate ITCs of DBLd versus DLd are presented in Table 37 below. For each response outcome, with or without adjustment, statistically significantly higher responses were achieved with DBLd than with DLd. For each response rate, the sensitivity analyses (adjusting for all potential PFs) indicated similar results.

Similar findings were observed for $\geq$ CR (OR: 3.58; 95% CI: 2.21, 5.79), sCR (OR: 2.91; 95% CI: 1.92, 4.41) and $\geq$ VGPR (OR: 3.09; 95% CI: 1.45, 6.61), reflecting that patients treated with DBLd are around 3 times as likely to achieve $\geq$ CR, sCR and $\geq$ VGPR as patients treated with DLd. Deeper level of responses are associated with improvements in longer term outcomes such as PFS and OS, as detailed in Section 1.3.1.

The adjusted OR (DBLd versus DLd) in the base case for ORR was 5.01 (95% CI: 1.11, 22.71), reflecting that patients treated with DBLd are just over 5 times as likely to achieve overall response as patients treated with DLd.

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Table 37: Summary of the response rate results of the ITC (DBLd versus DLd)

DBLd versus DLd	≥CR	sCR	≥VGPR	ORR
	OR (95% CI); p-value	OR (95% CI); p-value	OR (95% CI); p-value	OR (95% CI); p-value
Unadjusted (naïve)	3.59 (2.25, 5.73); p<0.001	2.70 (1.80, 4.05); p<0.001	2.97 (1.42, 6.19); p=0.004	4.72 (1.09, 20.46); p=0.038
Base case	3.58 (2.21, 5.79); p<0.001	2.91 (1.92, 4.41); p<0.001	3.09 (1.45, 6.61); p=0.004	5.01 (1.11, 22.71); p=0.037
Sensitivity analysis (all covariates adjusted)	3.67 (2.25, 6.01); p<0.001	2.94 (1.93, 4.49); p<0.001	3.32 (1.50, 7.31); p=0.003	6.12 (1.36, 27.51); p=0.018

Abbreviations: CI: confidence interval; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; OR: odds ratio; ORR: overall response rates; sCR: stringent complete response; VGPR: very good partial response.

Source: J&J Data on File.

Scenario analysis results

The results for scenario analyses which explored double robust and multivariate regression as alternative ITC methodologies, are presented in Table 38.

The scenario analyses results were consistent with those obtained via IPTW. The consistency of the results across the base case and scenario analyses demonstrate the robustness of the outcomes, and provide compelling evidence supporting the superior clinical efficacy of DBLd over DLd.

Table 38: Results of ITC scenario analyses (DBLd versus DLd)

Model	IPTW	Doubly robust	Multivariate regression
PFS (adjusted for COVID-19 deaths), HR (95% CI)			
Base case	0.55 (0.38, 0.79)	0.57 (0.39, 0.82)	0.60 (0.42, 0.86)
OS (adjusted for COVID-19 deaths), HR (95% CI)			
Base case	0.63 (0.41, 0.98)	0.65 (0.42, 1.01)	0.66 (0.42, 1.02)
TTD (adjusted for COVID-19 deaths), HR (95% CI)			
Base case	██████████	NA	██████████
PFS2, HR (95% CI)			
Base case	0.67 (0.44, 1.00)	0.70 (0.46, 1.06)	0.71 (0.47, 1.06)
MRD negative CR rate, OR (95% CI)			
Base case	3.04 (2.01, 4.61)	3.17 (2.03, 4.97)	3.11 (2.04, 4.74)
≥CR, OR (95% CI)			
Base case	3.58 (2.21, 5.79)	3.79 (2.26, 6.37)	3.86 (2.37, 6.29)
sCR, OR (95% CI)			
Base case	2.91 (1.92, 4.41)	3.07 (1.96, 4.81)	2.98 (1.95, 4.55)

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≥VGPR, OR (95% CI)			
Base case	3.09 (1.45, 6.61)	3.14 (1.42, 6.96)	3.12 (1.46, 6.65)
ORR, OR (95% CI)			
Base case	5.01 (1.11, 22.71)	7.14 (1.31, 38.95)	5.75 (1.17, 28.39)

Abbreviations: CI: confidence interval; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; IPTW: inverse probability treatment weighting; ITC: indirect treatment comparison; MRD: minimal residual disease; OS: overall survival; OR: odds ratio; ORR: overall response rate; PFS: progression-free survival; PFS2: progression-free survival on next line of therapy; sCR: stringent complete response; TTD: time to treatment discontinuation; VGPR: very good partial response.

Source: J&J Data on File.

Summary

The availability of IPD from both MAIA and CEPHEUS enabled robust IPTW ITCs using the ATE approach. The results of the base case IPTW ITC analyses of DBLd versus DLd demonstrate that DBLd provides statistically significant and clinically meaningful improvements in all evaluated outcomes. The improvement in outcomes with DBLd vs DLd was consistently shown across sensitivity analyses and scenario analyses.

Base case and sensitivity analysis results (DBLd versus Ld)

Although not a relevant comparator for this submission, as detailed in Section 1.1, a summary of the key results of the IPTW ITCs of DBLd versus Ld are presented in Table 39 below. As shown, comparisons on all outcomes were statistically significant in favour of DBLd (over Ld). Results of the sensitivity analyses (adjusting for all potential PFs) were consistent with the base case analyses across all outcomes. A full overview of the DBLd versus Ld ITC results are presented in Appendix B.

Table 39: Summary of results of the IPTW ITC (DBLd versus Ld)

	PFS (COVID-19 adjusted)	PFS	OS (COVID-19 adjusted)	OS	MRD-CR
DBLd versus Ld					
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	OR (95% CI)
Unadjusted (naïve)	0.32 (0.23, 0.45)	0.36 (0.26, 0.50)	0.41 (0.27, 0.64)	0.51 (0.34, 0.75)	11.39 (7.05, 18.38)
Base case	0.30 (0.21, 0.43)	0.36 (0.25, 0.50)	0.43 (0.28, 0.66)	0.54 (0.36, 0.80)	12.08 (7.40, 19.72)
Sensitivity analysis (all covariates adjusted)	0.31 (0.21, 0.45)	0.37 (0.26, 0.52)	0.44 (0.29, 0.69)	0.56 (0.37, 0.84)	12.15 (7.38, 19.99)

Abbreviations: CI: confidence interval; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; IPTW: inverse probability treatment weighting; ITC: indirect treatment comparison; Ld: lenalidomide and dexamethasone; MRD: minimal residual disease; OR: odds ratio; OS: overall survival; PFS: progression-free survival.

Source: J&J Data on File.

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2.10.3 Indirect treatment comparison (DBLd versus BMP)

As discussed in Section 2.10.2, an SLR was conducted in November 2020 and updated in August 2024, and again in April 2025, to identify studies of relevant therapies for patients with ASCT-ineligible NDMM. The review did not identify any clinical studies directly comparing the efficacy of DBLd with BMP. The SLR identified the ALCYONE RCT, which evaluated the efficacy and safety of DBMP compared with BMP. As such, in the absence of direct evidence comparing the clinical efficacy of DBLd versus BMP an ITC was conducted leveraging data from CEPHEUS trial (for DBLd) and ALCYONE trial (for BMP). The ITC used an IPTW approach, in line with the methodology used for the ITCs between DBLd and DLd presented above. Further details on the ALCYONE trial methodology are presented in Appendix B, alongside further details of the ITC methodology.

A summary of the key results of the IPTW ITCs of DBLd versus BMP are presented in Table 40. In the base case ITCs, DBLd significantly extended both COVID-19-adjusted OS (HR: 0.36, 95% CI: 0.23, 0.57) and COVID-19-adjusted PFS (HR: 0.16, 95% CI: 0.10, 0.25) when compared to BMP. A full overview of the DBLd versus BMP ITC results are presented in Appendix B.

Table 40: Summary of results of the IPTW ITC (DBLd versus BMP)

DBLd versus BMP	PFS	PFS censored for COVID-19 deaths	OS	OS censored for COVID-19 deaths
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Unadjusted (naïve)	0.15 (0.11, 0.23)	0.13 (0.09, 0.20)	0.39 (0.27, 0.58)	0.31 (0.20, 0.48)
Base case	0.18 (0.12, 0.27)	0.16 (0.10, 0.25)	0.47 (0.31, 0.71)	0.36 (0.23, 0.57)
Sensitivity analysis (all covariates adjusted)	0.18 (0.12, 0.28)	0.16 (0.10, 0.25)	0.49 (0.32, 0.74)	0.39 (0.24, 0.62)

Abbreviations: BMP: bortezomib, melphalan and prednisone; CI: confidence interval; CR: complete response; HR: hazard ratio; ITC: indirect treatment comparison; IPTW: inverse probability treatment weighting; MRD: minimal residual disease; OS: overall survival; OR: odds ratio; ORR: overall response rate; PFS: progression-free survival; PFS2: progression-free survival on next line of therapy; sCR: stringent complete response; TTD: time to treatment discontinuation; VGPR: very good partial response.

Source: J&J Data on File.

2.10.4 BMP versus BCd

In the clinical SLR (see Appendix B), there was no clinical trial evidence or IPD available for BCd in this population. As such, given the availability of IPD for BMP (see Section 2.10.3), an exploratory matching-adjusted indirect treatment comparison (MAIC) was conducted between BMP and observational studies reporting clinical data for BCd, identified by the clinical SLR. The results of the exploratory MAIC are presented in Table 41 – the adjusted analysis demonstrated no statistically significant differences with respect to either PFS or OS between the two treatments. Further details of the MAIC analysis are presented in Appendix B.

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The results support an assumption of clinical equivalence between BMP and BCd; as such, the ITCs between DBLd and BMP can also be used as a proxy to support the comparative efficacy of DBLd versus BCd. This approach was discussed with UK clinical experts at the May 2025 Advisory Board, who confirmed that an assumption of equal efficacy between BMP and BCd was appropriate.

Table 41: MAIC results

Endpoint	BMP vs BCd	
	Unweighted BMP (all patients)	MAIC adjusting for prognostic variables
OS, HR (95% CI)		
PFS, HR (95% CI)		

Abbreviations: BCd: cyclophosphamide, bortezomib and dexamethasone; BMP: bortezomib, melphalan and prednisone; CI: confidence interval; HR: hazard ratio; MAIC: matching adjusted indirect comparison.

Source: J&J Data on File.

The assumption of equivalent efficacy was further supported by three additional sources of evidence:

1. Sandecká *et al.* (2021) – An observational study conducted in 794 ASCT-ineligible NDMM patients between 2005 and 2017 in the Czech Republic. Of these, 377 (47.5%) and 172 (21.7%) received BCd and BMP, respectively. The data for PFS and OS after 23 months of follow-up are presented in Table 42 below.¹¹⁶ The results show median PFS and OS was lower in patients treated with BCd compared to BMP (PFS: 22.3 versus 18.5; OS: 49.0 versus 41.7 for BMP and BCd, respectively). Probability of survival without progression and probability of survival was also lower in the BCd group compared to the BMP group, at 1, 2 and 5 years.
2. Jimenez-Zepeda *et al.* (2021) – An observational study conducted in 1,156 ASCT-ineligible NDMM patients between 2007 and 2018 in Canada. Of these, 377 (47.5%) and 172 (21.7%) received BCd/or prednisone and BMP, respectively. The KMs for PFS and OS are presented in Figure 25 and Figure 26, respectively. Median PFS was 21.0 and 21.1 months ($p=0.0002$) and median OS was 52.0 and 63.6 months ($p=0.0001$) in the BCd/p and BMP groups, respectively. There was no significant difference in PFS and OS between the two triplet bortezomib regimens (BMP and BCd/p).¹¹⁷
3. A real-world evidence data set from NHS Digital National Cancer Registration and Analysis Service (NCRAS) including patients diagnosed with MM in England between January 2015 and December 2022 inclusive. The data for OS and TTNT for patients who did not receive an ASCT are presented in Table 43. The results of this naïve comparison demonstrate the probability of survival and probability of not receiving a subsequent treatment is similar or slightly lower in the BCd group compared to the BMP group, at 1, 2 and 5 years.

Table 42: PFS and OS data from Sandecká *et al.* (2021)

	BMP (n=172)	BCd (n=377)

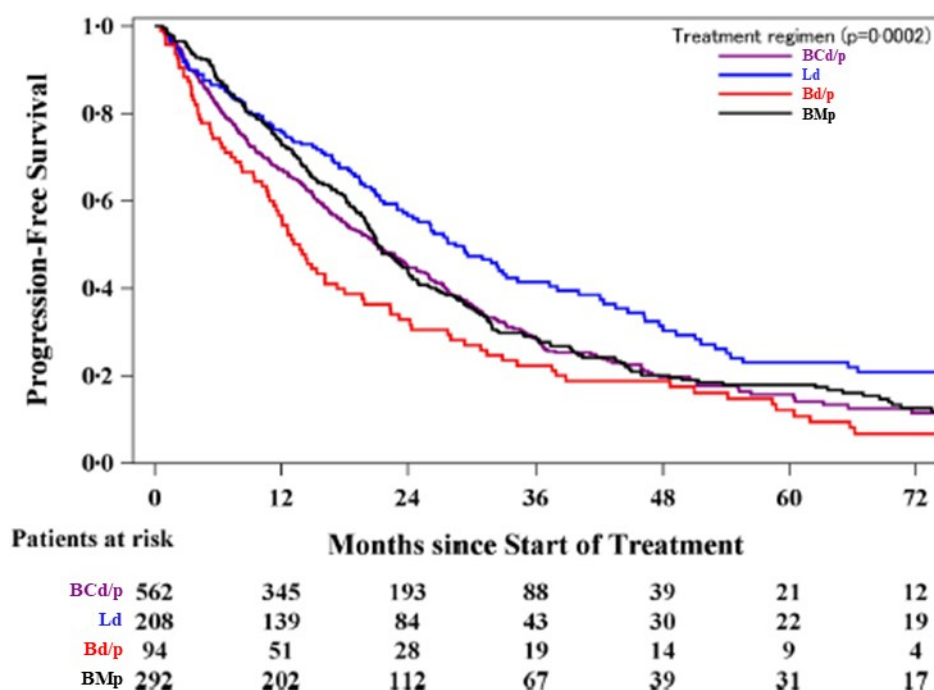
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OS		
Median OS, months (95% CI)	49.0 (38.4, 59.6)	41.7 (33.9, 49.6)
Probability of survival, % (95% CI)		
1 year	92.2 (86.6, 95.5)	84.8 (80.8, 88.1)
2 years	81.1 (72.9, 87.1)	71.8 (66.6, 76.2)
5 years	43.2 (30.6, 55.1)	39.4 (30.4, 48.3)
PFS		
Median PFS, months (95% CI)	22.3 (19.6, 25.1)	18.5 (15.9, 21.2)
Probability of survival without progression or death related to MM, % (95% CI)		
1 year	73.9 (66.1, 80.2)	66.5 (61.2, 71.2)
2 years	42.8 (33.5, 51.9)	38.3 (32.8, 43.8)
5 years	15.7 (7.4, 26.8)	14.4 (8.6, 21.8)

Abbreviations: BCd; bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; CI: confident interval; OS: overall survival; PFS: progression-free survival; MM: multiple myeloma.

Source: Sandecká *et al.* (2021).¹¹⁶

Figure 25: KM estimates of PFS in Jimenez-Zepeda *et al.* (2021)

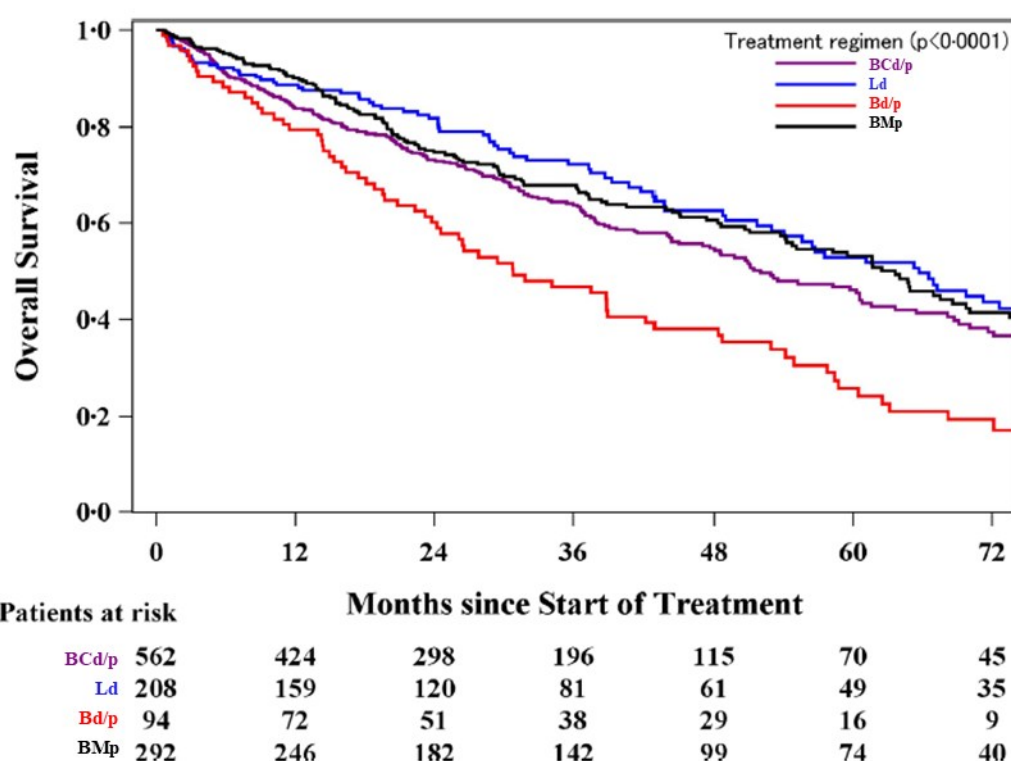


Abbreviations: BCd/p: bortezomib, cyclophosphamide and dexamethasone/or prednisone, Bd/p: bortezomib and dexamethasone or prednisone; BMP: bortezomib, melphalan and prednisone; KM: Kaplan-Meier; Ld: lenalidomide and dexamethasone; PFS: progression-free survival.

Source: Jimenez-Zepeda *et al.* (2021).¹¹⁷

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Figure 26: KM estimates of OS in Jimenez-Zepeda *et al.* (2021)



Abbreviations: BCd/p: bortezomib, cyclophosphamide and dexamethasone/or prednisone, Bd/p: bortezomib and dexamethasone or prednisone; BMP: bortezomib, melphalan and prednisone; KM: Kaplan-Meier; Ld: lenalidomide and dexamethasone; OS: overall survival.

Source: Jimenez-Zepeda *et al.* (2021).¹¹⁷

Table 43: OS and TTNT data from NHS Digital NCRAS for England between January 2015 and December 2022^a

	BMP (n=████)	BCd (n=████)
Proportion of patients alive (%)		
1 year	████	████
2 years	████	████
5 years	████	████
Proportion of patients who have not received a subsequent treatment (%)		
1 year	████	████
2 years	████	████
5 years	████	████

Footnotes: ^a Comparisons presented are considered naïve with no attempt to adjust or match study populations. **Abbreviations:** BCd; bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; NCRAS: National Cancer Registration and Analysis Service; NHS: National Health Service; OS: overall survival; TTNT: time to next treatment.

Source: NHS Digital NCRAS⁶⁸

Overall, the above three sources and the MAIC (see Appendix B) support the similarity of OS and PFS estimates for patients treated with BCd compared to BMP, or BMP efficacy being greater than BCd, suggesting an equivalent efficacy assumption is conservative. Additionally, considering the limited use of bortezomib combination treatments in clinical practice, as advised

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in the May 2025 Advisory Board and supported by J&J UK internal market research, these treatments are not a main comparator for this submission. Therefore, the assumption of equivalent efficacy in the model is informative with respect to the comparison of BCd versus DBLd.

2.10.5 Network meta-analysis

In addition to the ITCs conducted for DBLd versus all comparators listed in the NICE final scope (Sections 2.10.2), for completeness, a NMA was conducted to provide supportive comparative efficacy estimates between DBLd and DLd, Ld and BMP. It was not possible to include BCd as part of a connected network of evidence.

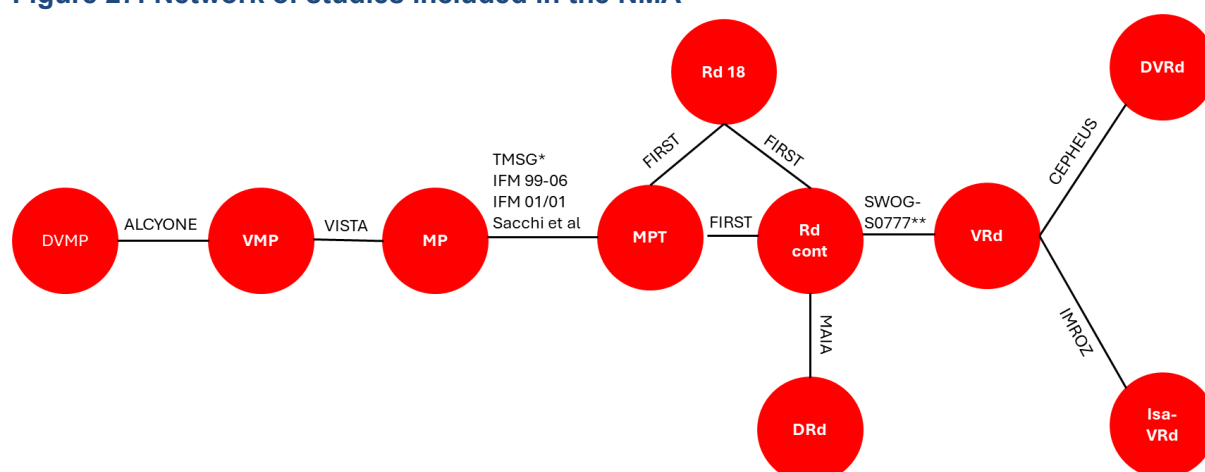
Summary of trials included in the NMA

The following trials were included in the NMA: CEPHEUS (ASCT-ineligible),¹⁰¹ MAIA,²³ ALCYONE,¹¹⁸ FIRST,¹¹⁹ VISTA,¹²⁰ Sacchi 2011,¹²¹ IFM 99-06,¹²² IMROZ,¹²³ and SWOG S0777.¹³ A full summary of the trials included in the NMA is included in Appendix M.

Of note, not all patients in the SWOG S0777 (median age: 63 years) were ASCT-ineligible. SWOG S0777 enrolled patients with NDMM for whom immediate transplant was not intended and included a mix of patients who were ASCT-ineligible as well as patients who were ASCT-eligible but chose to decline or defer transplant. Outcome data was not specifically reported for the ASCT-ineligible subgroup relevant to this decision problem. However, outcome data were reported for a subgroup of patients >65, as well as a subgroup of patients who were not intended for transplant.

Of these, intent to transplant was included as a stratification factor in SWOG S0777, whilst age was not. Therefore, to preserve the randomisation of the SWOG S0777 study, the no-intent to transplant subgroup population was considered the best proxy for the ASCT-ineligible population in this NMA. For completeness, results of the NMA for the >65 years of age subgroup, as well as the ITT population of SWOG S0777, are presented in Appendix M.

Figure 27: Network of studies included in the NMA



*Inputs for PFS not available; **No-intent to transplant subgroup was used as a proxy for the ASCT-ineligible population

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Abbreviations: DRd=DLd: daratumumab, lenalidomide and dexamethasone; DVMP=DBMP: daratumumab, bortezomib, melphalan and prednisone; DVRd=DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaVRd=IsaBLd: isatuxumab, bortezomib, lenalidomide and dexamethasone; MP: melphalan and prednisone; MPT: melphalan, prednisone and thalidomide; Rd=Ld: lenalidomide and dexamethasone; VMP=BMP: bortezomib, melphalan and prednisone; VRd=BLd: bortezomib, lenalidomide and dexamethasone.
Source: J&J Data on File.

Methods of NMA

Both fixed-effects (FE) and random-effects (RE) Bayesian NMAs were performed. Due to the network's sparseness, measures of between-study variation in the RE model were influenced mainly by the prior distribution of the standard deviation parameter. Therefore, FE models were selected as the base case over RE models for all analyses, unless the DIC of the RE model was at least three points lower than that of the FE model.

As previously detailed in Section 2.4.1, COVID-19 disproportionately impacted the CEPHEUS trial, compared to the MAIA trial as well as potentially other trials included in the NMA network. As such, in line with the base case IPTW ITCs, deaths due to COVID-19 were censored in both the CEPHEUS and MAIA trials as part of the NMA. All other trials included in the NMA were unadjusted for COVID-19, this is not expected to impact results due to the trials of interest being conducted prior to the pandemic (ALCYONE, FIRST and VISTA trials). The MAIA population was also restricted to patients <80 to ensure consistency with the population of interest.

Results of the NMA

A FE model was chosen for both endpoints (PFS and OS) due to a smaller DIC score compared to the RE model.

Table 44 and Table 45 below show the relative treatment effects for OS (adjusted for COVID-19) and PFS (adjusted for COVID-19), respectively. The results of the NMA were broadly consistent with those observed in the pairwise ITCs between DLd, Ld and BMP, demonstrated a substantial reduction in the risk of both OS and PFS versus each comparator.

When considering the NMA results versus DLd in particular, the magnitude of the point estimates for both PFS and OS were highly consistent with those observed in the IPTW ITC presented in Section 2.10.2. DBLd reduced the risk of disease progression or death by █ in the IPTW ITC (HR: █, 95% CrI: █, █), which was very similar to the █% reduction based on the NMA (HR: █, 95% CrI: █, █). Similarly, DBLd reduced the risk of death by █% versus DLd in the NMA (HR: █, 95% CrI: █, █) and █% in the IPTW ITC (HR: █, 95% CrI: █, █). As such, the NMA results support the robustness of the base case IPTW ITC results.

Table 44: NMA results for OS (adjusted for COVID-19)

OS HR (95% CrI)	DBLd	DLd	Ld	BMP
DBLd		██████████	██████████	██████████
DLd	██████████		██████████	██████████
Ld	██████████	██████████		██████████
BMP	██████████	██████████	██████████	

Abbreviations: BMP: bortezomib, melphalan and prednisone; CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; OS: overall survival.

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Source: J&J Data on File.

Table 45: NMA results for PFS (adjusted for COVID-19)

PFS HR (95% CrI)	DBLd	DLd	Ld	BMP
DBLd				
DLd				
Ld				
BMP				

Abbreviations: BMP: bortezomib, melphalan and prednisone; CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; PFS: progression-free survival.

Source: J&J Data on File.

Additional details of the NMA results are provided in Appendix M. In summary, the NMA results using different subgroups of SWOG S0777 are consistent with the base case NMA results and closely match the results from the ITC for DBLd versus DLd.

2.10.6 Uncertainties in the indirect and mixed treatment comparisons

OS data

Although there was almost 5 years of follow up for OS in both the DBLd and BLd arms of the CEPHEUS trial (ASCT-ineligible population), the OS event rates of % and % in the DBLd and BLd arms, respectively, and OS rates (censored for COVID-19 deaths) of % and %, respectively, potentially introduces some uncertainty. However, this is an inherent and unavoidable limitation associated with assessing new treatment options for NDMM. DLd is already an effective treatment regimen that has improved long-term survival outcomes for ASCT-ineligible patients. DBLd offers a further step change in efficacy with patients living longer, meaning that substantial follow-up is required for mature OS data to become available.

However, this should not be considered to represent a meaningful source of uncertainty. The base case PFS and OS ITC results are already statistically significant in favour of DBLd compared to DLd (and other comparators included in the NICE scope), and these are underpinned by response rate ITCs which indicate that patients treated with DBLd are more than three times more likely to achieve ≥CR and MRD-negativity compared to DLd. As discussed in Section 1.3.1, there is an extensive body of evidence highlighting the significance of achieving a deep, sustained treatment response, and the prognostic impact on long-term survival outcomes. Studies by Landgren *et al.* (2024) and Shi *et al.* (2025) suggest that a treatment effect on MRD negativity is likely to correspond with a benefit in PFS and OS.^{38, 39} The statistically significant improvement in MRD-negative CR rate with DBLd compared to DLd (OR: 3.04 [95% CI: 2.01, 4.61]; $p < 0.001$) is therefore anticipated to be a strong predictor of the improved clinical benefit of DBLd in the absence of mature OS data. As such, it is highly likely that the magnitude of OS benefit already observed at the time of the latest DCO will continue to improve over time, as those patients achieving the best responses to treatment fully realise the associated long-term survival benefits.

Weighting variables

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It is possible that residual bias remains in the analyses as a result of differences in CEPHEUS and MAIA/ALCYONE trial populations that were unaccounted for. However, the availability of IPD from both the CEPHEUS and MAIA/ALCYONE trials enabled the use of propensity-based ITC methodologies, which allows for a more robust matching process compared to MAICs, which only match to aggregate reported baseline characteristics. The process to identify the most important covariates to include in the analysis and improve matching was extensive and the list of covariates adjusted for was thorough, and therefore the risk of residual bias is minimal.

In the case of the most relevant ITCs between DBLd and DLd, the CEPHEUS and MAIA trials already had a high degree of overlap even prior to adjustment. Following adjustment for all 11 priority variables in the base case analysis, the CEPHEUS DBLd and MAIA DLd patient populations were highly matched on observable characteristics, with all SMDs in the base case <0.1. Nevertheless, it is possible that some residual bias remains in the analyses as a result of population differences that were unaccounted for, although as highlighted the risk is low. While J&J acknowledges the potential for residual confounding, there is no *a priori* reason to expect that this bias would act in favour of DBLd. The results of the NMA were slightly more favourable but generally highly consistent with the base case IPTW ITC results, suggesting the ITC results may be conservative and providing reassurance that any residual confounding remains minimal.

COVID-19

As discussed in Section 2.4.1, the CEPHEUS trial was disproportionately impacted by the COVID-19 pandemic, with ███% of all deaths caused by COVID-19, compared to just ███% in the MAIA trial. UK clinical experts highlighted that this was likely due to the difference in timings between the two trials – COVID-19 coincided with the initial phase of the CEPHEUS trial, where most patients were newly presenting with their disease and much more vulnerable to COVID-19 compared to the patients in long-term remission in the MAIA trial who had completed treatment with DLd. This meant that it was necessary to adjust for COVID-19 in the base case ITCs, to ensure that the results were not inherently biased in favour of DLd. As J&J had access to IPD for both trials, a robust ITC was able to be conducted which allowed adjustment for COVID-19 for both DBLd and DLd ensuring consistency across trials.

The adjusted ITC results best reflect current UK clinical practice, where the COVID-19 pandemic is no longer as prevalent as there is widespread availability of vaccinations, making many of the COVID-19 related deaths in CEPHEUS now preventable. The consistency of the results across a conservative sensitivity analysis, where COVID-19 is not accounted for, further supports the clear clinical benefit of DBLd over DLd in terms of inducing deep and durable responses and prolonging PFS, both of which are critically important to patients.

2.10.7 Conclusions of the indirect treatment comparisons

The MAIA trial was considered to present the most appropriate source of evidence for the key comparator of relevance in this submission, DLd. The availability of IPD to J&J from both MAIA and CEPHEUS facilitated conducting robust IPTW ITCs using the ATE approach. The CEPHEUS and MAIA trial population demonstrated a high level of overlap even prior to adjustment, which was further improved following comprehensive adjustment for 11 identified key prognostic variables.

The results of the base case IPTW ITC analyses of DBLd versus DLd demonstrate that DBLd provides statistically significant and clinically meaningful improvements in all outcomes

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evaluated. Patients treated with DBLd were over three times more likely to experience both a $\geq$ CR and MRD-negativity versus DLd, which translated to a 37% reduction in the risk of death (OS HR: 0.63; 95% CI: 0.41, 0.98) and a 45% reduction in the risk of disease progression or death (PFS HR: 0.55; 95% CI: 0.38, 0.79).

As discussed in Section 1.3.1, MRD negativity has been accepted by the FDA as a predictor for longer term outcomes including PFS and OS for ASCT-ineligible NDMM and can be considered Level 1 evidence (representing the highest possible strength of evidence as a surrogate endpoint). There is a wealth of evidence that supports a correlation between MRD negativity and improved survival in patients with NDMM, demonstrated in Section 1.3.1, and, more recently, a meta-analysis establishing a correlation between a treatment effect on MRD negativity and a treatment effect on PFS/OS. Patients who achieve MRD negativity with DBLd have the opportunity to achieve functional cure, with OS tracking similar to the general population as illustrated in Section 2.6.2.³⁴⁻⁴⁰

The magnitude of these efficacy benefits is particularly notable. In 2022, as part of the NICE submission for DLd, UK clinical experts commented that *'The reported outcomes for DLd in a Phase 3 trial are internationally considered to set a new gold standard for 1st line treatment for newly diagnosed transplant ineligible myeloma'*. Considering this, the incremental benefits of DBLd compared to DLd represent another significant step-forward in the UK myeloma treatment pathway, and an important step towards parity in outcomes for patients regardless of ASCT-eligibility.

The results from the base case ITC of DBLd versus DLd were also consistent across a range of sensitivity analyses exploring alternative prognostic variables, removal of COVID-19 adjustment, ITC methodologies (recommended in NICE DSU TSD 17 (multivariate and double robust regressions) and a supportive NMA.¹¹² Collectively, this provides support for the robustness of the results demonstrating clinically meaningful improvements across all endpoints with DBLd versus DLd.

In addition, while J&J maintains that DLd represents the most relevant comparator in this indication, further ITCs to assess the comparative efficacy of DBLd against Ld and bortezomib-based treatments were conducted for completeness. Across all outcomes and methodologies, DBLd demonstrated statistically significant and clinically meaningful benefit over Ld and BMP. As the ITCs between DBLd and BMP were used as a proxy to support the comparative efficacy of DBLd versus BCd, these results also indicate the significant and clinically meaningful benefit of DBLd over BCd.

2.11 Adverse reactions

As of the final PFS analysis (DCO: 07 May 2024), the safety data for daratumumab given in combination with BLd were consistent with the known safety profiles of daratumumab and BLd. Summaries of AEs and other safety data were based on ASCT-ineligible patients who were randomised and received at least 1 administration of any study treatment (partial or complete) in the study, termed the safety ASCT-ineligible analysis set. Safety data reported for the safety ASCT-ineligible analysis set was broadly reflective of the full ITT safety analysis set, presented in Appendix M.

2.11.1 Treatment duration and dosage

A summary of treatment duration and dose intensity of ASCT-ineligible patients receiving BLd or DBLd in the CEPHEUS trial is provided in Table 46. The median duration of study treatment was longer in the DBLd treatment arm (■■■■ months) compared with the BLd arm (■■■■ months). The median number of treatment cycles was higher in the DBLd arm (■■■■ cycles) compared to the BLd arm (■■■■ cycles).

Table 46: Summary of treatment duration and dose intensity (safety ASCT-ineligible analysis set)

	BLd arm N=142	DBLd arm N=144
Duration of study drug (months)		
Mean (SD)	■■■■	■■■■
Median (range)	■■■■	■■■■
Daratumumab dose intensity (mg/cycle)^a		
Mean (SD)	-	■■■■
Median (range)	-	■■■■
Bortezomib dose intensity (mg/m²/cycle)^b		
Mean (SD)	■■■■	■■■■
Median (range)	■■■■	■■■■
Lenalidomide dose intensity (mg/cycle)^c		
Mean (SD)	■■■■	■■■■
Median (range)	■■■■	■■■■
Dexamethasone dose intensity (mg/cycle)^c		
Mean (SD)	■■■■	■■■■
Median (range)	■■■■	■■■■

Footnotes: ^a Dose intensity (mg/cycle) is calculated as the sum of total doses (mg) received in all cycles divided by the number of treatment cycles on daratumumab.

^b Dose intensity (mg/m²/cycle) is calculated as the sum of total doses (mg/m²) received in all cycles divided by the number of treatment cycles on bortezomib.

^c Dose intensity (mg/cycle) is calculated as the sum of total doses (mg) received in all cycles divided by the number of treatment cycles on lenalidomide and dexamethasone, respectively.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; SD: standard deviation.

Source: J&J Data on File.

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2.11.2 Summary of all adverse events

In the ASCT-ineligible population, all participants in both treatment arms experienced TEAEs (DBLd: 100.0%; BLd: 100.0%;

Table 47). The proportion of participants with TEAEs leading to discontinuation of all study treatment (DBLd: █%; BLd: █%) was █ in the DBLd arm compared with the BLd arm. The overall incidence of Grade 5 TEAEs (DBLd: █%; BLd: █%;

Table 47) was █ in the DBLd arm compared with the BLd arm. Of the Grade 5 TEAEs, Grade 5 COVID-19 TEAEs were reported in 4.2% and 0.7% of participants in the DBLd and BLd arms, respectively. The incidence of COVID-19 TEAEs was █ in the DBLd arm compared with the BLd arm (DBLd: █%; BLd: █%;

Table 47).

Table 47: Overview of TEAEs (safety ASCT-ineligible analysis set) – final PFS analysis

TEAEs	BLd N=142	DBLd N=144
Any TEAE	142 (100.0%)	144 (100.0%)
At least one related ^a	█	█
Maximum toxicity grade		
Grade 1	█	█
Grade 2	█	█
Grade 3	█	█
Grade 4	█	█
Grade 5	13 (9.2%)	19 (13.2%)
Any serious TEAE	99 (69.7%)	104 (72.2%)
At least one related ^a	█	█
TEAE leading to discontinuation of bortezomib	█	█
At least one related to bortezomib	█	█
TEAE leading to discontinuation of lenalidomide	█	█
At least one related to lenalidomide	█	█
TEAE leading to discontinuation of dexamethasone	█	█
At least one related to dexamethasone	█	█
TEAE leading to discontinuation of daratumumab	█	█
At least one related to daratumumab	█	█
TEAE leading to discontinuation of study treatment^b	27 (19.0%)	11 (7.6%)
AE (COVID-19)	█	█
SAE (COVID-19)	█	█
AE leading to death (COVID-19)	1 (0.7%)	6 (4.2%)

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Footnotes: ^a TEAEs related to at least 1 of the 4 components of study treatment: bortezomib, lenalidomide, dexamethasone, daratumumab.

^b Includes those participants indicated as having discontinued treatment due to an AE on the end of treatment CRF page.

Adverse events are reported using MedDRA version 23.0.

Percentages are calculated with the number of participants in each group as denominator.

Abbreviations: AE: adverse event; BLd: bortezomib, lenalidomide and dexamethasone; CRF: case report form; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Source: J&J Data on File; Facon *et al.* (2025)¹⁰⁴

2.11.3 TEAEs

The incidences of adverse events were similar between the full safety analysis set and the ACST-ineligible population (Table 48, Appendix L). All participants in both treatment arms of the ASCT-ineligible population experienced TEAEs (DBLd: 100%; BLd: 100%; Table 48). TEAEs with a frequency $\geq 10\%$ in either treatment arm are presented in Table 48. TEAEs that occurred with a frequency $\geq 30\%$ in either treatment arm were:

- Diarrhoea (DBLd: █%; BLd: █%)
- Peripheral sensory neuropathy (DBLd: 59.7%; BLd: 63.4%)
- Neutropenia (DBLd: █%; BLd: █%)
- Thrombocytopenia (DBLd: █%; BLd: █%)
- Oedema peripheral (DBLd: █%; BLd: █%)
- Constipation (DBLd: █%; BLd: █%)
- Fatigue (DBLd: █%; BLd: █%)
- COVID-19 (DBLd: █%; BLd: █%)
- Anaemia (DBLd: █%; BLd: █%)
- Insomnia (DBLd: █%; BLd: █%)
- Upper respiratory tract infection (DBLd: █%; BLd: █%)
- Hypokalaemia (DBLd: █%; BLd: █%)

Table 48: Most common (at least 10%) TEAEs by MedDRA system organ class and preferred term (safety ASCT-ineligible analysis set) – final PFS analysis

MedDRA system organ class/preferred term	BLd N=142	DBLd N=144
Total number of participants with TEAE	142 (100%)	144 (100%)
Infections and infestations	██████	██████
Upper respiratory tract infection	██████	██████
COVID-19	██████	██████
Pneumonia	██████	██████
Urinary tract infection	██████	██████
Nasopharyngitis	██████	██████
Bronchitis	██████	██████
Influenza	██████	██████

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Blood and lymphatic system disorders		
Neutropenia		
Thrombocytopenia		
Anaemia		
Lymphopenia		
Leukopenia		
Nervous system disorders		
Peripheral sensory neuropathy	90 (63.4%)	86 (59.7%)
Dizziness		
Headache		
Neuralgia		
Paraesthesia		
Tremor		
Dysgeusia		
General disorders and administration site conditions		
Oedema peripheral		
Fatigue		
Asthenia		
Pyrexia		
Injection site erythema		
Influenza like illness		
Malaise		
Gastrointestinal disorders		
Diarrhoea		
Constipation		
Nausea		
Abdominal pain		
Dyspepsia		
Vomiting		
Musculoskeletal and connective tissue disorders		
Back pain		
Arthralgia		
Muscular weakness		
Muscle spasms		
Pain in extremity		
Musculoskeletal pain		
Musculoskeletal chest pain		
Metabolism and nutrition disorders		
Hypokalaemia		
Decreased appetite		
Hypocalcaemia		

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Hyponatraemia		
Skin and subcutaneous tissue disorders		
Rash		
Dry skin		
Pruritus		
Respiratory, thoracic and mediastinal disorders		
Cough		
Dyspnoea		
Eye disorders		
Cataract		
Vision blurred		
Psychiatric disorders		
Insomnia		
Depression		
Vascular disorders		
Hypotension		
Hypertension		
Investigations		
Alanine aminotransferase increased		
Weight decreased		
Renal and urinary disorders		
Dysuria		
Renal impairment		
Injury, poisoning and procedural complications		
Contusion		
Cardiac disorders		
Atrial fibrillation		
Ear and labyrinth disorders		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Hepatobiliary disorders		
Reproductive system and breast disorders		

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival; TEAEs: treatment emergent adverse events.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

2.11.4 Grade 3 or 4 TEAEs

The Grade 3 or 4 TEAEs reported in the ASCT-ineligible population with a frequency $\geq 5\%$ in either treatment arm are presented in Table 49 below.

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The Grade 3 or 4 TEAEs that occurred with a frequency $\geq 10\%$ in either treatment arm were:

- Neutropenia (DBLd: 43.8%; BLd: 31.7%)
- Thrombocytopenia (DBLd: 30.6%; BLd: 23.2%)
- Hypokalaemia (DBLd: █%; BLd: █%)
- Pneumonia (DBLd: 13.9%; BLd: 12.0%)
- Anaemia (DBLd: 12.5%; BLd: 12.7%)
- Diarrhoea (DBLd: 11.8%; BLd: 9.9%)
- Lymphopenia (DBLd: █%; BLd: █%)
- Fatigue (DBLd: 9.0%; BLd: 10.6%)

Table 49: Most common (at least 5%) Grade 3 or 4 TEAEs by MedDRA system organ class, preferred term (safety ASCT-ineligible analysis set) – final PFS analysis

MedDRA system organ class/preferred term	BLd N=142	DBLd N=144
Total number of participants with TEAE	██████	██████
Blood and lymphatic system disorders	██████	██████
Neutropenia	45 (31.7%)	63 (43.8%)
Thrombocytopenia	33 (23.2%)	44 (30.6%)
Anaemia	18 (12.7%)	18 (12.5%)
Lymphopenia	██████	██████
Infections and infestations	██████	██████
Pneumonia	17 (12.0%)	20 (13.9%)
COVID-19	5 (3.5%)	14 (9.7%)
Nervous system disorders	██████	██████
Peripheral sensory neuropathy	12 (8.5%)	14 (9.7%)
Syncope	██████	██████
Metabolism and nutrition disorders	██████	██████
Hypokalaemia	██████	██████
Musculoskeletal and connective tissue disorders	██████	██████
Muscular weakness	██████	██████
Gastrointestinal disorders	██████	██████
Diarrhoea	14 (9.9%)	17 (11.8%)
General disorders and administration site conditions	██████	██████
Fatigue	15 (10.6%)	13 (9.0%)
Vascular disorders	██████	██████
Hypertension	██████	██████
Respiratory, thoracic and mediastinal disorders	██████	██████
Pulmonary embolism	██████	██████
Eye disorders	██████	██████

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Cataract	████	████
Investigations	████	████
Cardiac disorders	████	████
Renal and urinary disorders	████	████
Skin and subcutaneous tissue disorders	████	████
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	████	████
Psychiatric disorders	████	████
Injury, poisoning and procedural complications	████	████

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival; TEAEs: treatment emergent adverse events.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

2.11.5 Serious adverse events

The incidence of treatment-emergent SAEs was numerically higher in the DBLd arm compared with the BLd arm (DBLd: 72.2%; BLd: 69.7%; Table 50). The treatment-emergent SAEs with a frequency $\geq 2\%$ in either treatment arm are presented in Table 50. The treatment-emergent SAEs that occurred with a frequency $\geq 5\%$ in either treatment arm were:

- Pneumonia (DBLd: █████%; BLd: █████%)
- COVID-19 (DBLd: █████%; BLd: █████%)
- Pulmonary embolism (DBLd: █████%; BLd: █████%)
- Diarrhoea (DBLd: █████%; BLd: █████%)

Table 50: Most common (at least 2%) treatment-emergent SAEs by MedDRA system organ class and preferred term (safety ASCT-ineligible population) – final PFS analysis

MedDRA system organ class/preferred term	BLd N=142	DBLd N=144
Total number of participants with serious TEAE	99 (69.7%)	104 (72.2%)
Infections and infestations	████	████
Pneumonia	████	████
COVID-19	████	████
Gastrointestinal disorders	████	████
Diarrhoea	████	████
Cardiac disorders	████	████
General disorders and administration site conditions	████	████
Musculoskeletal and connective tissue disorders	████	████
Metabolism and nutrition disorders	████	████
Nervous system disorders	████	████

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Respiratory, thoracic and mediastinal disorders	██████	██████
Pulmonary embolism	██████	██████
Blood and lymphatic system disorders	██████	██████
Vascular disorders	██████	██████
Neoplasms benign, malignant and unspecified	██████	██████
Renal and urinary disorders	██████	██████
Injury, poisoning and procedural complications	██████	██████

Footnotes: Adverse events are reported using MedDRA version 23.0.

Percentages are calculated with the number of participants in each group as denominator.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

2.11.6 Deaths

Overall summary of deaths

As of the final PFS analysis, 22.9% of participants in the DBLd arm and 32.4% of participants in the BLd arm of the safety analysis set had died (Table 51). The primary causes of death were either AEs (DBLd: ██████; BLd: ██████) or disease progression (DBLd: ██████%; BLd: ██████%). █ of the █ deaths caused by AEs were due to COVID-19 AEs (DBLd: ██████; BLd: ██████ Section 2.4.1).

The proportion of participants who died within 30 days of the last dose of study treatment was ██████ in the DBLd arm compared with the BLd arm (DBLd: ██████%; BLd: ██████%) (Table 51), all with AEs as the primary cause.

█ early deaths (occurring within 60 days of the first study treatment dose) were reported in for the DBLd treatment arm. In the BLd treatment arm, █ [█████%] participants died within 60 days of the first treatment dose. The primary causes of all █ of these early deaths were AEs unrelated to the study treatment.

Table 51: Summary of death and cause of death (safety ASCT-ineligible population) – final PFS analysis

Primary cause of death	BLd N=142	DBLd N=144	Total N=286
Total number of participants who died during study	46 (32.4%)	33 (22.9%)	79 (27.6%)
AE	██████	██████	██████
At least one related ^a	██████	██████	██████
AE(s) unrelated	██████	██████	██████
AE (COVID-19)	1 (0.7%)	6 (4.2%)	7 (2.4%)
PD	██████	██████	██████
Other	██████	██████	██████
COVID-19	██████	██████	██████

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Total number of participants who died within 30 days of last study treatment dose	██████	██████	██████
AE	██████	██████	██████
At least one related ^a	██████	██████	██████
AE(s) unrelated	██████	██████	██████
AE (COVID-19)	██████	██████	██████
Total number of participants who died within 60 days of first study treatment dose	██████	█	██████
AE	██████	█	██████
AE(s) unrelated	██████	█	██████

Footnotes: ^a Includes adverse events that were related to at least 1 of the 4 components of study treatment: bortezomib, lenalidomide, dexamethasone or daratumumab.

Abbreviations: AE: adverse event; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; PD: progressive disease; PFS: progression-free survival.

Source: J&J Data on File; Facon *et al.* (2025).¹⁰⁴

2.12 Ongoing studies

The latest data cut of the CEPHEUS trial, the principal evidence base for patients with NDMM who are ineligible for ASCT, is presented in this submission (07 May 2024). The final data cut for CEPHEUS is expected in ████████. No other studies of DBLd in this indication are ongoing.

2.13 Interpretation of clinical effectiveness and safety evidence

Patients with ASCT-ineligible MM face an unmet need for alternative, effective treatment options that drive deeper responses including MRD-negativity which translate to clinically meaningful improvements in PFS and OS and reduce the disparity in outcomes compared to ASCT-eligible patients

As described in Section 1.3.4, patients with MM require multiple lines of therapy due to the relapsing and remitting nature of the disease, with prognosis worsening with each successive relapse due to the presence of additional clones.²⁵⁻²⁹ The introduction of DLd significantly improved clinical outcomes for patients with ASCT-ineligible NDMM, with almost all patients experiencing a response to treatment, and a median PFS greater than five years (61.9 months).⁵ However, less than one third of DLd patients achieved MRD negativity in MAIA (32.1%), despite a deep and durable response to therapy being a primary aim in the first-line setting. Ultimately this means that the majority of patients will eventually experience relapse.⁵

First remission is widely regarded as the best opportunity to gain the deepest response with the longest period until disease progression. As such, there is a clear unmet need for a more effective first-line treatment option that achieves higher rates of MRD negativity, which would be reasonably expected to translate into improved PFS and OS, with the ultimate aim of keeping patients progression free long enough for them to naturally live out the rest of their lives.³²

The CEPHEUS trial showed DBLd demonstrated statistically significant and clinically meaningful improvements across all of the primary and secondary endpoints versus BLd

For ASCT-ineligible patients in the CEPHEUS trial, treatment with DBLd resulted in a statistically significant and clinically meaningful improvement in overall MRD negativity, response rates and Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

PFS compared to BLd. A positive trend towards OS benefit in favour of the DBLd arm was also observed, which was statistically significant when adjusting for COVID-19 deaths.

An improvement in HRQoL and physical functioning, as well as reduction in symptoms (pain, fatigue, overall disease symptoms) was observed in the DBLd and BLd arms, indicating that the addition of daratumumab to BLd is not to the detriment of patient HRQoL. Results from the CEPHEUS trial also demonstrated that DBLd was well tolerated, with clinically manageable side effects and a safety profile that is consistent with the known safety profiles of daratumumab and BLd.

Patients receiving DBLd were over three times more likely to experience a $\geq$ CR and MRD negativity versus DLd, which translated into statistically significant improvements in both PFS and OS

As described in Section 1.3.4, DLd is considered the most relevant comparator to DBLd in UK clinical practice. In the absence of direct trial evidence comparing the effectiveness of DBLd and DLd, J&J was able to perform a robust ITC leveraging IPD from both the CEPHEUS and MAIA trials. COVID-19 disproportionately impacted CEPHEUS, with [REDACTED] of all deaths due to COVID-19, compared to [REDACTED] in MAIA, due to the timing of the trial. As such, all patients who died due to COVID-19 in both trials were censored, to remove the inherent residual bias in the comparison.

The ITCs demonstrate that addition of bortezomib to DLd resulted in statistically significant clinically meaningful improvements across all outcomes (PFS [adjusted for COVID-19], OS [adjusted for COVID-19], PFS2, ORR, $\geq$ VGPR, $\geq$ CR, MRD negative CR rate). The results from the ITC indicate that DBLd is associated with a 45% reduction in the risk of disease progression or death (HR: 0.55; 95% CI: 0.38, 0.79) and a 37% reduction of the risk of death (HR: 0.63; 95% CI: 0.41, 0.98). The odds of experiencing a $\geq$ CR (OR: 3.58; 95% CI: 2.21, 5.79), or MRD-negativity CR (OR: 3.04; 95% CI: 2.01, 4.61), are at least three times higher for DBLd compared with DLd. There is a wealth of evidence that supports a correlation between MRD negativity and improved survival in patients with NDMM, demonstrated in Section 1.3.1, and, more recently, a meta-analysis establishing a correlation between a treatment effect on MRD negativity and a treatment effect on PFS/OS. The results from the ITC were consistent across scenario and sensitivity analyses, as well as a supportive NMA, providing support for the robustness of these findings of the improvement in outcomes with DBLd versus DLd.³⁴⁻⁴⁰

For completeness, ITCs were also conducted to compare DBLd with other comparators listed in the NICE final scope (Ld and bortezomib-based treatments). Across these ITCs, DBLd demonstrated statistically significant and clinically meaningful results for all evaluated endpoints.

Several unavoidable limitations were considered when conducting the ITCs including immature PFS and OS data, the potential residual bias from unaccounted for differences in trial populations arising from an unanchored ITC, and the effect of COVID-19 on the CEPHEUS trial. However, the availability of IPD data and the highly matched patient populations of the CEPHEUS and MAIA trials facilitated the conduct of methodologically robust ITCs, and the consistent magnitude of benefit across endpoints provides strong evidence to support the additional effectiveness of DBLd when compared to DLd and other comparators for patients with ASCT-ineligible MM.

DBLd would represent a further step-change in the treatment pathway for ASCT-ineligible patients, helping to bridge the gap in treatment options available, and expected outcomes, for NDMM regardless of transplant eligibility

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The introduction of DBLd into the UK NDMM clinical pathway would meet the unmet need for a novel, effective, well-tolerated treatment option for patients with ASCT-ineligible NDMM, for whom MRD-negativity rates remain suboptimal. Despite efficacious treatment options, such as DLd, survival outcomes for ASCT-ineligible patients remain significantly lower than observed in the general age-matched population and in newly diagnosed patients who are ASCT-eligible.³³ The introduction of the DBLd quadruplet regimen has the potential to provide ASCT-ineligible patients with an effective treatment option that can deliver similar rates of MRD negativity to those observed in ASCT-eligible patients receiving DBTd, providing hope of a functional cure for patients achieving the deepest levels of sustained response.⁵²

Achieving remission or response, and optimising life expectancy, are highly valued by patients.⁸⁴ Studies have demonstrated that achieving a deep, sustained response to therapy is prognostic for improved survival and HRQoL outcomes.^{30, 57} MRD negativity is a highly relevant prognostic marker associated with substantial clinical benefit. Treatment effects on MRD negativity have been shown to strongly correlate to treatment effects on both PFS and OS in ASCT-ineligible MM patients, indicating that MRD negativity is a valuable early clinical endpoint that can reasonably predict the clinical benefit of treatment.^{35, 38, 39}

As the ITC approaches supported by sensitivity analyses have shown, DBLd can substantially increase response rates and delay disease progression versus DLd (the current SoC). The higher degree of MRD-negative CR achievement with DBLd indicates that patients receiving this combination are more likely to achieve a deeper response than those receiving the triplet therapy DLd, addressing the existing unmet need in ASCT-ineligible NDMM patients with the expected translation to OS benefits, has the potential for achieving a functional cure. In 2022, DLd was considered to represent a new gold-standard therapy for patients with newly diagnosed MM, and now patients treated with DBLd are three times more likely to experience a $\geq$ CR and MRD-negativity, have a 45% reduced risk of disease progression and a 37% reduction in the risk of death compared to treatment with DLd.

3 Cost effectiveness

A partitioned survival model (PSM) was developed to evaluate the cost-effectiveness of DBLd versus DLd, in line with extensive precedent across past NICE appraisals in MM

- A cost-utility model was developed to estimate the cost-effectiveness of DBLd versus DLd for the treatment of patients with ASCT-ineligible NDMM from a UK NHS and Personal Social Services (PSS) perspective
- Similar to previous NICE evaluations of MM therapies, including the recent NICE appraisal of DLd (TA917) in the same target population,⁵ the model was a PSM consisting of three mutually exclusive health states: (i) progression-free (PF), (ii) progressed disease (PD), and (iii) death
- The baseline characteristics of patients in the model were based on the ASCT-ineligible population of the CEPHEUS trial

Base case extrapolations: OS, PFS and TTD

- Independent extrapolations were fitted to patient-level survival data for each treatment arm. Seven standard parametric distributions were fitted to KM data (exponential, Weibull, log-logistic, log-normal, Gompertz, Gamma and Generalised Gamma).
- For DBLd, COVID-19-adjusted OS, PFS and TTD ATE-weighted Kaplan-Meier data from the ASCT-ineligible population of CEPHEUS were used. For DLd, COVID-19-adjusted OS, PFS and TTD ATE-weighted Kaplan-Meier data from the MAIA trial (<80 years) were used.
- The choice of base case extrapolations were based upon statistical and visual fit and long-term clinical plausibility; of note, clinical expert feedback was the central consideration for the choice of base case curves, ensuring all long-term extrapolations for DBLd and DLd were based on the most clinically plausible curves.
- To ensure clinical plausibility, best statistically fitting DBLd OS and PFS curves were calibrated after Year 5 to align with the clinical expert estimates of survival via attenuation of the survival data.
- For TTD, attenuation resulted in parts of the curve underestimating TTD compared to PFS (i.e. clinically implausible separation between two curves), and as the standard parametric TTD curves predicted the proportion of patients on treatment similar to clinical expert feedback, DBLd TTD was modelled using the Gompertz extrapolation (unattenuated) based on good statistical fit and long-term estimates of TTD that aligned to clinical expert estimates.
- The same approach, whereby the best statistically fitting DLd OS and PFS curves were calibrated to align with the clinical expert estimates of survival for DLd to ensure consistency across the intervention and comparator endpoints, although given the longer follow-up data available for the DLd OS from MAIA, DLd OS was calibrated after Year 7.
- Similar to DBLd, the attenuated DLd TTD curve resulted in a clinically implausible separation between TTD and PFS. Therefore, DLd TTD was modelled using the Weibull extrapolation (unattenuated) as it predicted proportions on treatment closely in line with the clinical expert estimates, had a good statistical fit, and a clinically plausible relationship between DLd PFS and TTD.
- The approach to modelling DBLd and DLd long-term survival considers both the internal and external validity of the curves and reflects a conservative modelling approach, as the unattenuated curves predict higher long-term survival than the clinical experts estimates across both PFS and OS endpoints, particularly for DBLd.

Model inputs were generally sourced from the pivotal CEPHEUS and MAIA trials for DBLd and DLd

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- AEs were modelled based on CEPHEUS (ASCT-ineligible population) for DBLd and MAIA for DLd
- Health state utility values (HSUVs) for both DBLd and DLd were derived from the CEPHEUS trial. In the base case economic analysis, HSUVs were modelled to be time-independent in the PD state and time-dependent in the PF state, based on the observed improvement in HRQoL over time in CEPHEUS
- Cost inputs used in the model (administration, drug acquisition, AEs, monitoring costs, concomitant medication and end-of-life cost) are generally aligned to costs used in prior appraisals in ASCT-ineligible NDMM

Summary of cost-effectiveness results

- Overall, the base case analysis demonstrated that DBLd was associated with positive incremental LYGs (1.15 LYG) and QALYs (■■■■) versus DLd. These results highlight the expected improvements in both quality and length of life with DBLd.
- At list and discounted daratumumab prices, DBLd was dominant compared to DLd.
- As referred to in Section 1, there is an existing NHS England commercial access agreement (CAA) in place for daratumumab. ICERs in this Section are therefore presented considering the ■■■■
■■■■
■■■■
■■■■¹²⁴
- Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess uncertainty in the economic analysis and demonstrated that the base case cost-effectiveness results were robust to an extensive number of sensitivity analyses; at list and discounted daratumumab prices, the probabilistic ICER showed that DBLd was dominant compared to DLd
- Sensitivity and scenario analyses conducted to address sources of uncertainty in the model demonstrated the results of the base case analysis are robust to uncertainties in the model inputs and assumptions, with a number of plausible scenarios, including analyses unadjusted for COVID-19, reducing the ICER compared to the base case.
- Overall, these results demonstrate that DBLd could address a significant unmet need for a novel, effective and well-tolerated treatment option that tackles more aspects of the clonal heterogeneity of MM, in turn inducing enduring sustained responses that translate to an anticipated increase in OS of 1.15 LYs versus DLd.
 - Incremental life years gained of 1.15 for DBLd are intuitive given the almost doubling of the MRD negativity rate per the base-case ITC (DBLd: 61.22% vs DLd: 34.16%), and with outcomes for these patients resembling general population as illustrated in Section 2.6.2.

3.1 Published cost-effectiveness studies

SLRs were conducted in order to identify published economic evaluations of interventions for patients with NDMM who are ineligible for ASCT, evidence relating to the HRQoL and utility (humanistic burden) and cost/resource use (economic burden) that may be of relevance to this submission. Full details of all SLRs (including identified HRQoL and cost/resource studies) are presented in Appendix E, F and G, respectively.

No economic evaluations were identified for DBLd in this indication. An overview of the economic evaluations identified in the SLR is provided in Appendix E.

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3.2 *Economic analysis*

As the economic SLR did not identify any economic evaluations assessing the cost-effectiveness of DBLd versus the relevant comparators in patients with NDMM who are ineligible for ASCT, a *de novo* cost-utility analysis (CUA) has been conducted for the purpose of this evaluation. This model is described in detail below.

The aim of the economic analysis was to determine the cost-effectiveness of DBLd versus relevant comparators (being DLd as the current standard of care) as a treatment for adult patients with ASCT-ineligible NDMM. The analysis has been conducted from the perspective of the NHS and PSS, taking into account direct costs and benefits only.

The economic evaluation was approached as follows, in line with the NICE reference case:¹²⁵

- Health outcomes were measured both in terms of life years gained (LYG) and QALYs gained
- Primary outcome measure for the economic evaluation was the ICER (cost per QALY gained) for the comparison of DBLd versus the relevant comparators
- Clinical effectiveness for DBLd and the comparators was measured through OS and PFS outcomes (see Section 3.3)
- All relevant costs are considered including:
 - Treatment acquisition costs (see Section 3.5.1)
 - Administration costs (see Section 3.5.1)
 - AE costs (see Section 3.4.4)
 - Costs associated with subsequent treatments (see Section 3.5.1)
 - Concomitant medicines (see 3.5.1)
 - Resource use (see Section 3.5.2)
 - End-of-life costs (see Section 3.5.2)
- The model used a lifetime time horizon (equivalent to ■ years; the maximum age that could be reached in the model is 100 years old)
- The discount rate is set to 3.5% for both costs and benefits

3.2.1 *Patient population*

The population of interest is patients with ASCT-ineligible NDMM. This population is in line with the decision problem for this submission, and the ASCT-ineligible population of the CEPHEUS trial (see Section 2.3.3).²

The characteristics of patients entering the model were based on the baseline demographic and disease characteristics of the ASCT-ineligible population in CEPHEUS (Table 52). As discussed in Section 2.3.3, these data are well balanced across treatment arms. Clinical experts consulted as part of the May 2025 UK Advisory Board validated that baseline characteristics of the CEPHEUS ASCT-ineligible population are also considered to be broadly generalisable to clinical practice in England. A real-world evidence data set from NCRAS including patients diagnosed with MM in England between January 2015 and December 2022 inclusive further validates the

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generalisability of the ASCT-ineligible CEPHEUS trial population, with a mean age of [REDACTED] in the NCRAS cohort (compared to [REDACTED] in CEPHEUS [ASCT-ineligible]), and [REDACTED]% males in the NCRAS cohort (compared to [REDACTED] in CEPHEUS [ASCT-ineligible]).⁶⁸

Age and gender are included in the model to determine general population mortality inputs. Baseline mean body weight and body surface area (BSA) are included in the model to inform drug dosages, and therefore drug costs (Section 3.5.1).

Table 52: Summary of baseline characteristics used in the economic analysis

Characteristic	Value	Source
Mean age of patients (years)	[REDACTED]	CEPHEUS trial (ASCT-ineligible population)
Mean weight of patients (kg)	[REDACTED]	CEPHEUS trial (ASCT-ineligible population)
Mean BSA of patients (m ²)	[REDACTED]	CEPHEUS trial (ASCT-ineligible population)
Male (%)	[REDACTED]	CEPHEUS trial (ASCT-ineligible population)

Abbreviations: BSA: body surface area.

Source: J&J Data on File.

3.2.2 *Model structure*

The *de novo* model consisted of three mutually exclusive health states: (i) pre-progression, (ii) post-progression, and (iii) death. The occupancy of health states over time was calculated using PFS and OS survival extrapolations, as described below:

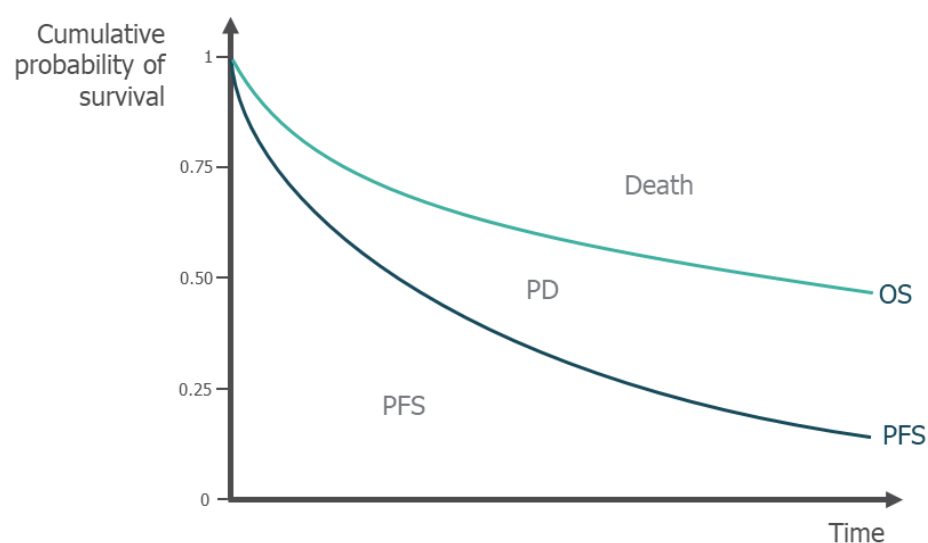
- The proportion of patients occupying the pre-progression state was calculated as the proportion alive and PF (based on PFS extrapolations)
- The proportion of patients occupying the post-progression state was calculated as the proportion alive (based on OS extrapolations) minus the proportion of patients alive and PF (based on PFS extrapolations)
- The proportion of patients occupying the death state was calculated as the proportion who had died (based on OS extrapolations)

Patients may discontinue treatments for reasons other than disease progression. As such, TTD was used to determine the time on treatment (ToT), to account for patients who may have discontinued treatment before progression. This allows for the application of specific health-state costs, such as treatment acquisition, treatment administration and monitoring costs, to be applied only while patients are on or off treatment, while also allowing patients to occupy the PF and PD health-states regardless of whether they are on treatment.

The model uses a cycle duration of four weeks to align with the cycle lengths in the DBLd (after 9 treatment cycles) and DLd regimens. Half-cycle correction was applied in line with modelling best practice, to avoid systemic over or underestimation of costs and outcomes.¹²⁶

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Figure 28: Partitioned survival model structure



Abbreviations: OS: overall survival; PD: progressed disease; PFS: progression-free survival.

Justification for choice of model structure

In line with the NICE appraisals for DLd (TA917) and IsaBLd (ID3981), a PSM was deemed the most appropriate model structure to inform the cost-effectiveness of DBLd, as the modelled health states are considered to accurately reflect the natural disease course for patients with ASCT-ineligible NDMM.^{5, 6}

The key outcomes in this setting, PFS and OS, are time-to-event endpoints. The PSM approach facilitates the direct and intuitive incorporation of observed data from the relevant clinical trials within the economic model, ensuring a precise representation of disease progression and the survival outcomes for patients treated with DBLd or the relevant comparators.

As discussed in Section 2.6, the median follow-up in the ASCT-ineligible cohort of CEPHEUS (final PFS analysis: 07 May 2024) was 58.71 months. The PSM structure allows uncertainty in long-term extrapolations to be explored through scenario analyses (see Section 3.11.3).

In alignment with the model developed during the appraisal of DLd (TA917), the progressive and predominantly incurable nature of NDMM means that there is no requirement for a functionality to move backwards between the health states, thus further supporting the use of a PSM for the cost-effectiveness analysis.⁵ Additionally, the model structure choice aligns with the extensive precedent for using and accepting PSMs in previous NICE appraisals in MM, including NDMM.^{5, 6, 127-134}

A limitation of the PSM is the lack of structural link between PFS and OS because each endpoint is modelled independently. This could lead to incongruent relationships of PFS and OS (e.g. the PFS and OS curves crossing). However, as PFS is capped by OS (which is in turn capped by general population mortality [GPM]) in this model, such logical inconsistencies are prevented. Hence, the PSM is considered appropriate to model the occupancy of the PF, PD and death health states.

The additional features of the economic analysis are outlined and justified in Table 53 below.

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Table 53: Features of the economic analysis

Factor	Previous evaluation	Current evaluation	
	TA917 ⁵	Chosen values	Justification
Model structure	Three-state PSM	Three-state PSM	A PSM accurately reflects disease progression and the observed survival profile of patients with ASCT-ineligible NDMM patients treated with DBLd or relevant comparators, and is in line with extensive precedent in previous NICE appraisals in MM. ^{5, 6, 127-134}
Time horizon	Lifetime (26 years)	Lifetime (■ years)	Sufficiently long to be considered a lifetime horizon based on patient starting age of ■ and sufficient to capture any differences in costs or outcomes between the technologies being compared.
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 <i>et al.</i> 2017. ¹³⁵	Pre- and post-progression utilities derived from CEPHEUS. EQ-5D-5L scores from CEPHEUS were cross walked to 3L using the mapping function developed by Hernández Alava <i>et al.</i> 2017.¹³⁵ In the PF health state, utilities were modelled to be time dependent. For the PD health state, utilities were modelled to be time independent.	For consistency with the patient population and source of efficacy inputs used in the model, pooled utility values were derived from the transplant ineligible population in CEPHEUS. The mapping algorithm used was consistent with the NICE reference case.¹²⁵ The CEPHEUS trial demonstrated that patient utility values after being treated with DBLd improved with increasing time spent in the PF health state, and therefore HSUVs in the PF

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			health state were modelled as time-dependent. As HSUVs were modelled as treatment-independent, time-dependent HSUVs in the PF health state were assumed for both DBLd and DLd.
Source of costs	NHS reference costs, the British National Formulary and pharmaceutical eMIT. Costs included: • Drug acquisition and administration for front line and subsequent therapies • Concomitant medications (e.g. prophylaxis) • Monitoring costs • Management of AEs (Grade 3 and above, with incidence $\geq 5\%$ in any treatment arm) • End-of-life costs	NHS reference costs, the British National Formulary and pharmaceutical eMIT. Costs included: • Drug acquisition and administration for front line and subsequent therapies • Concomitant medications (e.g. prophylaxis) • Monitoring costs • Management of AEs (Grade 3 and above, with incidence $\geq 5\%$ in any treatment arm) • End-of-life costs	Cost inputs used in the model (administration costs, incidence of AEs, monitoring costs, end-of-life cost) have been aligned with previous evaluations in MM, including previous daratumumab evaluations (NICE TA917,⁵ TA897,¹²⁷ TA783¹²⁸ and TA763⁵²).

Abbreviations: AE: adverse events; ASCT: autologous stem cell transplant; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; eMIT: electronic market information tool; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; PSM: partitioned survival model; TA: technology appraisal.

3.2.3 Intervention technology and comparators

Intervention

The intervention included in the cost-effectiveness model was DBLd in patients with NDMM who are ineligible for ASCT. The treatment protocols included in the model for DBLd are consistent with the CEPHEUS trial (refer to Section 3.5.1 for full details), and the draft SmPC-recommended posology for daratumumab.^{1, 102}

The anticipated license for DBLd in this indication states that treatment should be administered until disease progression. As such, treatment costs for DBLd are modelled until the end of the TTD period to align with the recommendations of the draft SmPC.¹

Comparators

As described in Section 1.1, DLd is considered the main comparator of interest for this submission. At the May 2025 UK Advisory Board, clinical experts specialising in MM agreed that DLd was the most common treatment for patients with NDMM who are ineligible for ASCT, representing over 80% of the current treatment share in ASCT-ineligible NDMM.³

As discussed in detail in Section 1.1, bortezomib-based treatments are used in a very small proportion of patients in clinical practice (~5%), and Ld is used for patients who are unable to tolerate a triplet or have a preference for an oral treatment and would therefore not receive DBLd. Therefore, both treatments are not considered relevant comparators to DBLd. However, for completeness, and to adhere to the final NICE scope, a comparison of cost-effectiveness against Ld and BMP/BCd (both representing bortezomib with an alkylating agent and corticosteroid) are provided in Appendix B. BCd was modelled assuming equivalent efficacy to BMP, as detailed in Section 2.10.4.

DLd, Ld and BMP are modelled in line with their respective SmPCs in the indication of interest. Full details are presented in Section 3.5.1.

3.3 Clinical parameters and variables

3.3.1 Survival inputs and assumptions

The economic model is a cohort-based PSM consisting of three mutually exclusive health states: PF, PD and death. The proportion of patients in each health state at each four-weekly model cycle was determined for DBLd and DLd [and for Ld and BMP/BCd] from survival probabilities from PFS and OS extrapolations, while a TTD extrapolation was used to determine the proportion of patients in the model who remained on treatment. The follow-up periods for CEPHEUS and pivotal trials for the comparators were shorter than the model time horizon and extrapolations of the observed OS, PFS and TTD data were required.

Extrapolation of PFS, OS and TTD was performed in accordance with the guidance provided in the NICE DSU TSD 14.¹³⁶ The full range of parametric distributions were explored (exponential, Weibull, loglogistic, lognormal, Gompertz, Gamma and generalised gamma), with each model assessed in terms of goodness-of-fit statistics (Akaike information criterion [AIC] and the Bayesian information criteria [BIC]), visual inspection of the hazard function and survival curves

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to the observed data from the relevant clinical trials, and clinical plausibility of long-term survival predictions.

Proportional hazards

The proportional hazard assumptions were tested for completeness via log cumulative hazard plots, Schoenfeld test plots and cloglog plots. The results of proportional hazards assessments and smoothed hazard plots for DBLd versus DLd for each of the endpoints can be found in Appendix N. The results from the cloglog plot suggests proportional hazards are violated for OS (adjusted for COVID-19) as the curves cross at certain timepoints and this is further supported by the log-cumulative hazard plot where the DBLd and DLd curves cross at certain timepoints and are not parallel, with separation over time. Although the PFS (COVID-19 adjusted) proportional hazards are not violated, to ensure consistency between PFS and OS, independent extrapolation of the ATE-weighted Kaplan-Meier data from the ITCs were fit. This approach was validated by the health economic experts in the May 2025 Advisory Board who considered independent extrapolation most appropriate given the availability of patient-level data from both CEPHEUS and MAIA.

Extrapolation of survival data

As discussed in detail in Section 2, COVID-19 disproportionately impacted CEPHEUS compared to MAIA and therefore to remove bias, the base case ITCs censored all patients who died due to COVID-19 in both trials. As such, the COVID-19-adjusted OS, PFS, and TTD data from the IPTW analysis of DBLd versus DLd informs the cost-effectiveness analysis of DBLd versus DLd in this indication.

Extrapolations of PFS, OS and TTD for DBLd were performed using patient-level data from the ASCT-ineligible ITT population of CEPHEUS, adjusted for population imbalances between CEPHEUS and MAIA via the IPTW method using ATE weights as detailed in Section 2.10.2.

Similarly, for DLd, PFS, OS and TTD extrapolations were performed using patient-level data from the aged <80 years population of MAIA adjusted for population imbalances between CEPHEUS and MAIA via the IPTW method using ATE weights as detailed in Section 2.10.2.

Capping of survival data

Mortality for patients with MM is expected to be higher than the mortality of the general population when matched for age and gender. To ensure that the hazard of death is at least equal to GPM at any timepoint, age- and gender-matched GPM was used in any cycle where the predicted rate of death was lower than GPM. The age- and gender-matched GPM used to cap OS across all interventions and comparators was based on life tables for England from the Office for National Statistics (ONS) 2017–2019. All subsequent available ONS data (i.e. beyond 2019) are impacted by COVID-19 excess mortality and reflect a world in which COVID-19 vaccinations were not widely available, and are therefore not reflective of the general population in current UK clinical practice. As such, it was considered most appropriate to base the GPM cap of OS data on ONS data from 2017–2019. The approach to the GPM cap of OS data aligns with TA917.⁵

Additionally, PFS extrapolations implemented in the model include a cap to ensure that PFS does not exceed OS to ensure clinical plausibility. Likewise, the TTD extrapolations include a cap to ensure that TTD does not exceed the PFS extrapolation at any given point.

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Curve selection

The choice of distribution for the base case for all OS, PFS and TTD curves was initially informed considering:

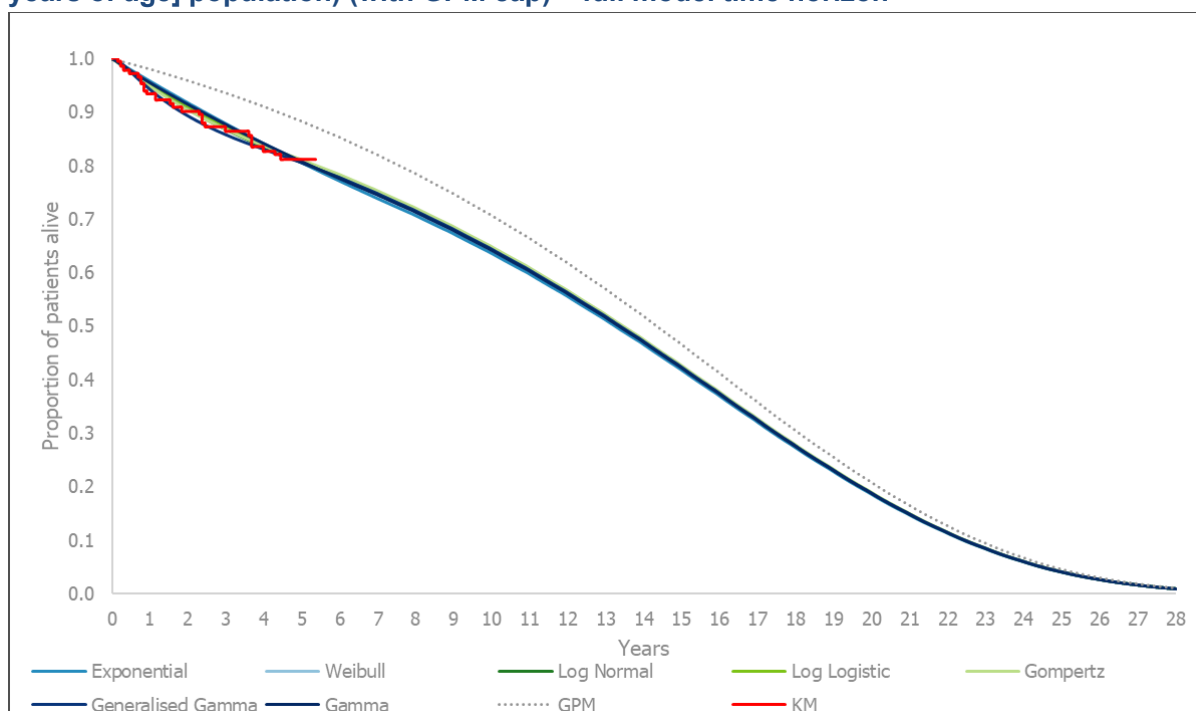
- **Graphical assessment of fit:** visual inspection regarding how well the predicted curve captured the shape of the observed Kaplan-Meier curve
- **Statistical fit:** AIC and BIC statistics were generated for each extrapolation, the best fit to the observed data is the curve with the lowest AIC and BIC
- **Clinical validation of long-term extrapolations for current treatments in clinical practice:** Given clinician experience with currently available treatments, an Advisory Board in May 2025 UK was conducted where clinical experts provided estimates of the proportion of patients in clinical practice expected to be PF, alive and remaining on treatment at timepoints up to 20 years following treatment with DBLd (the intervention) and DLd (the main comparator).

3.3.2 Overall survival

DBLd

To model long-term DBLd OS, extrapolations were fitted to the COVID-19-adjusted DBLd OS data from the ATE-weighted ASCT-ineligible population of CEPHEUS, as previously described in Section 2.10.2. Each of the DBLd OS extrapolations over the full model time horizon, and over the first six years for clarity, are presented in Figure 29 and Figure 30, respectively. As shown, all extrapolations follow similar trajectories across the modelled time horizon given the early influence of the GPM cap. Goodness-of-fit statistics of each of the extrapolations are presented in Table 54. Long-term estimates of DBLd OS for each parametric extrapolation are provided in Table 55. For completeness, the hazard plots are provided in the Appendix N.

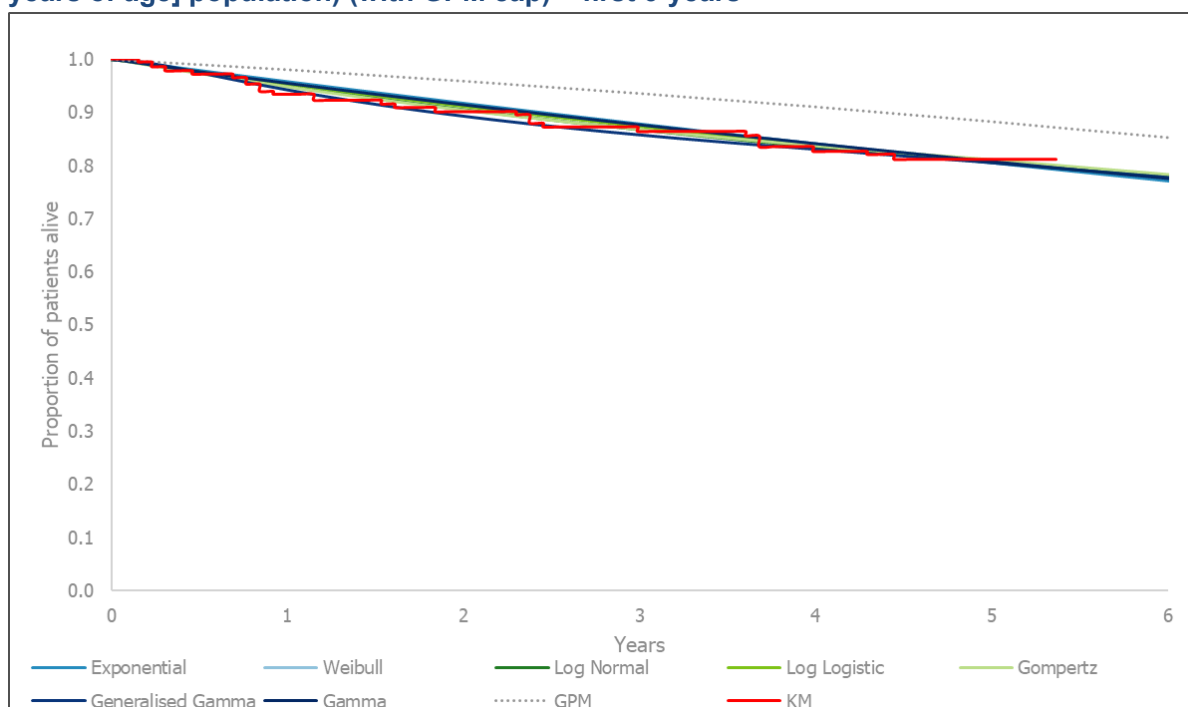
Figure 29: Extrapolation of COVID-19-adjusted OS for DBLd using IPD from the ASCT-ineligible CEPHEUS population (adjusted via IPTW using ATE weights to the MAIA [<80 years of age] population) (with GPM cap) – full model time horizon



Note: Extrapolations shown are with the GPM cap applied

Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; GPM: general population mortality; KM; Kaplan-Meier; OS: overall survival.

Figure 30: Extrapolation of COVID-19-adjusted OS for DBLd using IPD from the ASCT-ineligible CEPHEUS population (adjusted via IPTW using ATE weights to the MAIA [<80 years of age] population) (with GPM cap) – first 6-years



Note: Extrapolations shown are with the GPM cap applied

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Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; GPM: general population mortality; KM; Kaplan-Meier; OS: overall survival.

Table 54: Goodness-of-fit statistics for DBLd OS extrapolations

Survival model	DBLd			
	AIC	BIC	AIC Rank	BIC Rank
Exponential	337.97	340.93	1	1
Weibull	339.80	345.73	6	5
LogLog	339.46	345.39	5	4
LogNormal	338.04	343.97	2	2
Gen Gamma	338.90	347.79	3	7
Gamma	339.85	345.78	7	6
Gompertz	339.05	344.98	4	3

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; OS: overall survival.

Table 55: Comparison of predicted survival rates for DBLd OS extrapolations (with GPM cap)

	OS survival rates (%)		
	DBLd		
	10 years	15 years	20 years
Clinical Expert Estimates			
Clinical expert estimates	50	22.5	10
Extrapolations			
Exponential	63.4	41.7	18.5
Weibull	64.1	42.1	18.7
LogNormal	64.3	42.2	18.8
LogLog	64.2	42.2	18.8
Gompertz	64.6	42.5	18.9
Gen Gamma	64.2	42.2	18.8
Gamma	64.0	42.0	18.7

Abbreviations: NA: not applicable; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; OS: overall survival.

Visual fit of the extrapolations to the observed CEPHEUS data was considered, although as shown in Figure 29, the trajectories of all extrapolations across the modelled time horizon were similar, with very little to distinguish between the curves. Statistical fit to the observed CEPHEUS data was an important determinant of the chosen base case extrapolation. The exponential extrapolation provided the best statistical fit to the observed OS data with respect to both AIC and BIC. However, all of the other extrapolations were at least 2 AIC points within of the exponential and all except the Generalised Gamma were within 5 BIC points of the exponential, indicating that all curves provide a similar fit to the observed data in CEPHEUS.

In line with NICE TSD 14, the external validity of the extrapolations was considered based on long-term predictions of survival provided by UK clinical experts at the May 2025 UK Advisory Board.¹³⁶

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Clinical experts considered this a difficult exercise given the lifetime time horizon of the model and lack of clinical experience with DBLd. Of note, the clinical experts highlighted that the GPM estimates were higher than they had expected given the age of patients diagnosed with NDMM.³ The clinical experts commented that the DBLd OS curves (Figure 29) estimated a high proportion of patients alive beyond a 10 year timepoint and this could be plausible, highlighting that it is reasonable that patients who survive for ~10 years may then be more likely to die of something other than their MM – and hence be ‘functionally cured’. This was particularly relevant given the older population starting age, and the high proportions of patients achieving MRD negativity and sustained MRD negativity in the CEPHEUS trial, and outcomes for these patients resembling general population as illustrated in Section 2.6.2.

Additionally, clinical experts confirmed that they consider there to be a clear OS benefit of DBLd over DLd in the long term (e.g. beyond 10 years). However, given all the extrapolations predicted similar long-term outcomes, no clear consensus was reached on the plausibility of the presented DBLd OS curves. As part of the May 2025 UK Advisory Board, clinical experts estimated that long-term OS for DBLd would be 50% at 10 years, 22.5% at 15 years and 10% at 20 years.

Given there remained some uncertainty among clinical experts regarding the clinical plausibility of the DBLd OS curves in Figure 29, and considering the curves predict higher OS than the clinical experts estimates, a more conservative approach was taken to model OS which ensures the clinical feedback and estimates are the central consideration of decision making for the choice of base case extrapolations.

Specifically, to ensure clinical face validity of the base case curve selection, a calibration approach was taken whereby the curves were attenuated to align extrapolations with the most clinically plausible estimates of long-term survival for DBLd (informed by estimates provided by UK clinical experts as part of the May 2025 UK Advisory Board). This approach was previously used and accepted in TA1015 to align extrapolations with clinically plausible estimates of long-term survival for teclistamab.¹²⁹ In TA1015, the EAG concluded that “the Company approach to modelling OS for patients treated with teclistamab makes the best use of available evidence”.¹²⁹ Of note, the choice of extrapolation has little impact on the long term estimates due to the impact of attenuation, so for a consistent approach across all endpoints, the extrapolation which provided the best statistical fit to the observed data from CEPHEUS was used. For DBLd OS, the best statistically fitting curve was the exponential as detailed above.

Derivation of a calibrated exponential extrapolation for DBLd OS

Initially, it was necessary to consider when to start calibration of the exponential extrapolation. Nearly five years of follow-up data were available from CEPHEUS, with a median follow up of 58.71 months at the time of the latest DCO, suggesting that the extrapolation should not be adjusted any earlier than this. With regard to long-term survival, clinical expert estimates predicted lower OS than the 10-, 15- and 20-year OS estimates for the exponential extrapolation, and therefore it was considered necessary to calibrate the exponential extrapolation after Year 5.

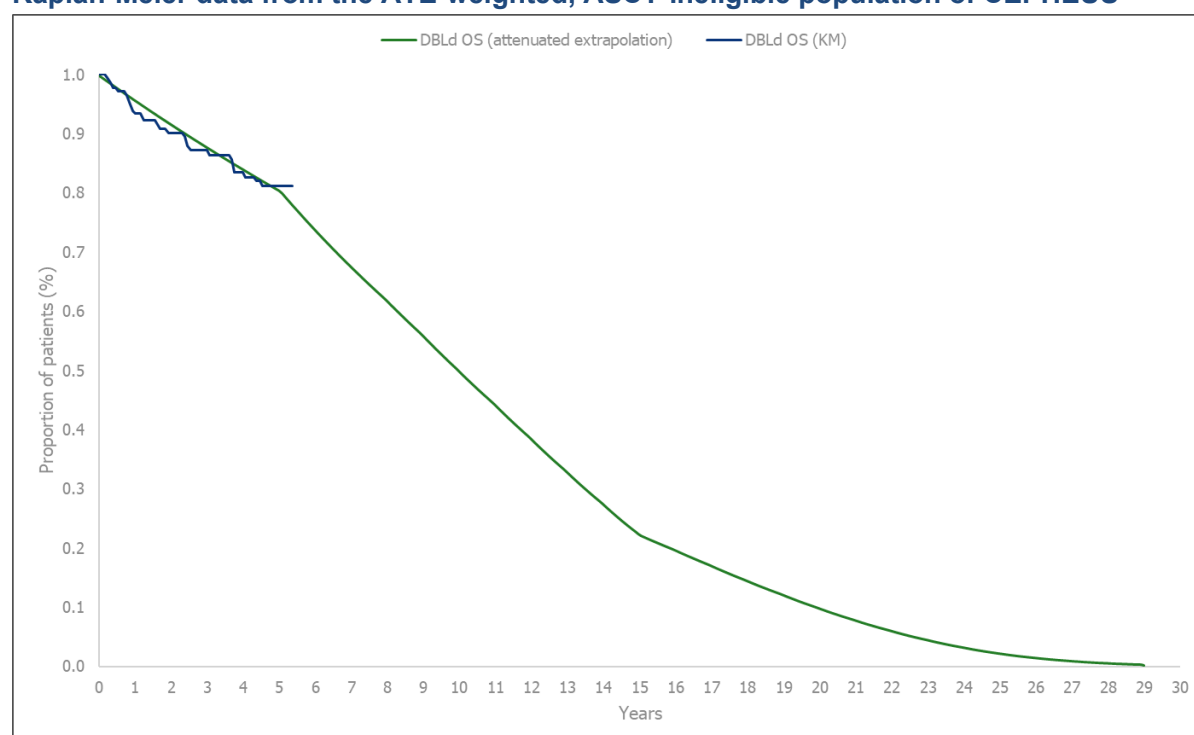
After Year 5, an attenuation factor was derived using a multiplier applied to the general population mortality. The attenuation factor was therefore applied to the extrapolation to increase the hazard of death in each cycle from Year 5 onwards so that the exponential resulted in 10, 15 and 20-year survival of 50%, 22.5% and 10%, respectively – in line with clinical experts’ estimates. The resulting extrapolation presented in Figure 31 thus provides the best fit to the

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observed CEPHEUS OS data whilst also importantly ensuring that the long-term survival extrapolations are clinically plausible and directly in line with clinical expectations.

This approach is considered conservative as the long term OS estimates for DBLd are much lower compared to the unattenuated (standard) extrapolations beyond 10 years, even though there is a high proportion of patients who achieve MRD negativity with DBLd, with their OS tracking similar to the general population as illustrated in Section 2.6.2. The calibration approach has been leveraged across all endpoints (except for TTD, as detailed below) and for both the intervention and comparator (DLd) to ensure a consistent approach.

Figure 31: Attenuated exponential extrapolation fitted to the DBLd COVID-19-adjusted OS Kaplan-Meier data from the ATE-weighted, ASCT-ineligible population of CEPHEUS



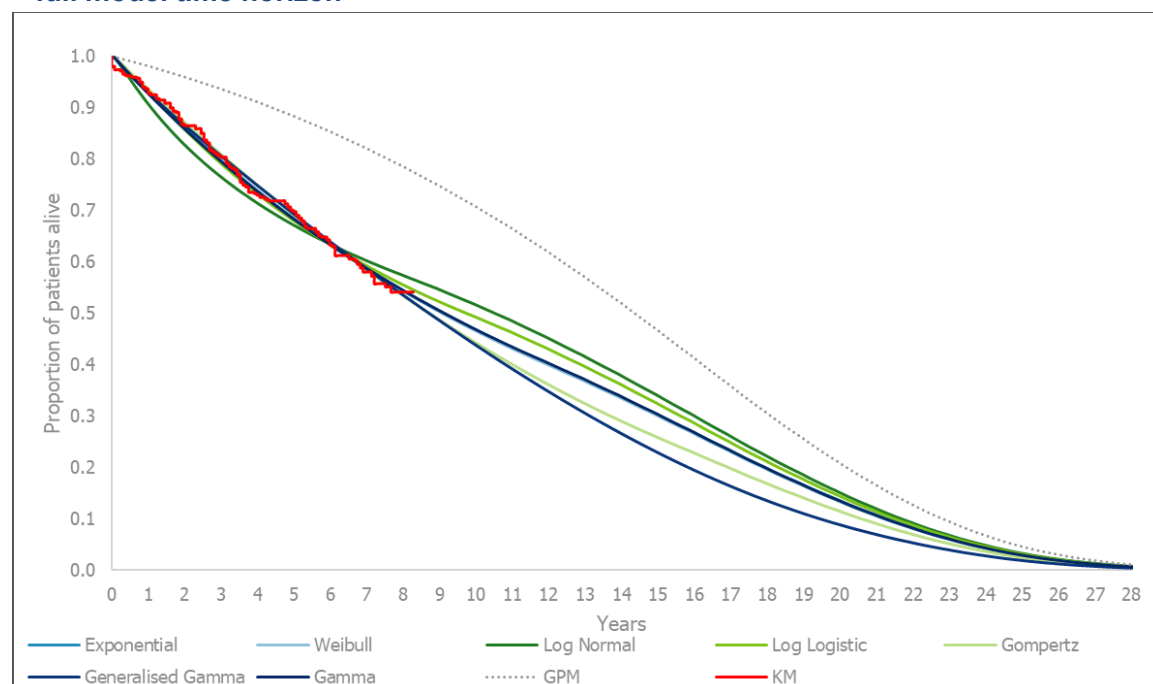
Abbreviations: ATE: average treatment effect; KM: Kaplan-Meier; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; OS: overall survival.

DLd

Similar to the approach for DBLd, extrapolations were fitted to the COVID-19 adjusted OS data for DLd from the ATE-weighted MAIA trial population, as previously described in Section 2.10.2. Each of the DLd OS (adjusted for COVID-19, and capped by GPM) extrapolations over the full model time horizon and over the first nine years for clarity are presented in Figure 32 and Figure 33, respectively. Goodness-of-fit statistics for each of the DLd OS extrapolations are presented in Table 56. Long-term estimates of DLd OS for each parametric extrapolation are provided in Table 57. For completeness, the hazard plots are provided in Appendix N.

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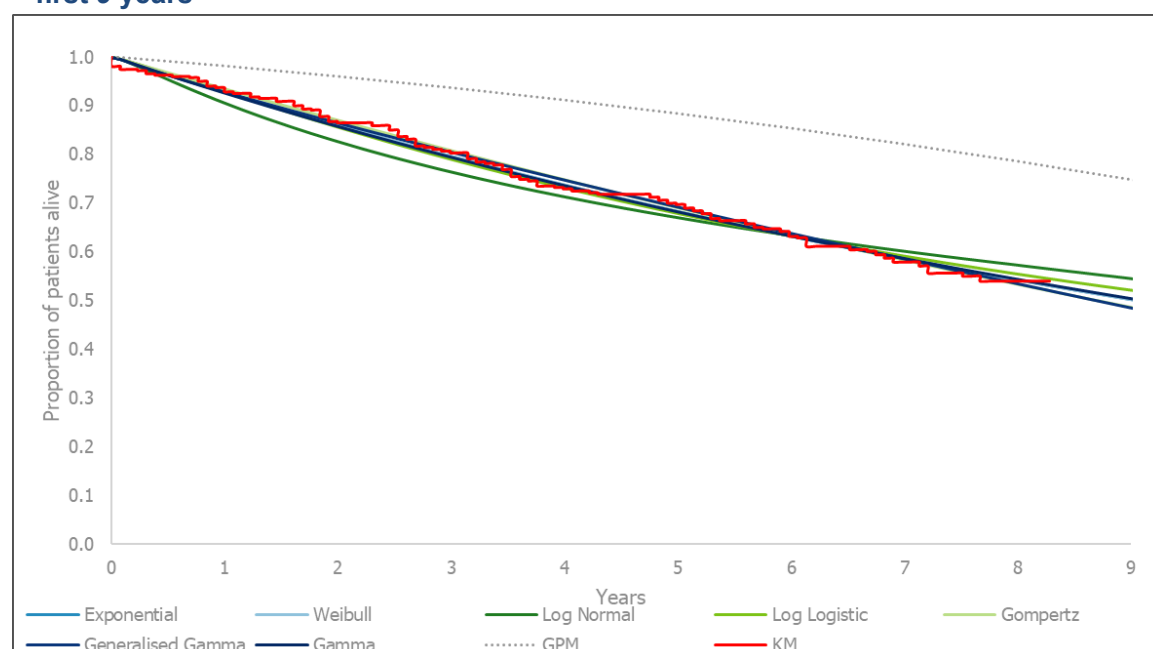
Figure 32: Extrapolation of COVID-19-adjusted OS for DLd using IPD from MAIA (adjusted via IPTW using ATE weights to the ASCT-ineligible CEPHEUS population) (with GPM cap) – full model time horizon



Note: Extrapolations shown are with the GPM cap applied

Abbreviations: ATE: average treatment effect; DLd: daratumumab, lenalidomide, dexamethasone; GPM: general population mortality; KM; Kaplan-Meier; OS: overall survival.

Figure 33: Extrapolation of COVID-19-adjusted OS for DLd using IPD from MAIA (adjusted via IPTW using ATE weights to the ASCT-ineligible CEPHEUS population) (with GPM cap) – first 9 years



Note: Extrapolations shown are with the GPM cap applied

Abbreviations: ATE: average treatment effect; DLd: daratumumab, lenalidomide, dexamethasone; GPM: general population mortality; KM; Kaplan-Meier; OS: overall survival.

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Table 56: Goodness-of-fit statistics for DLd OS extrapolations

Survival model	DLd			
	AIC	BIC	AIC Rank	BIC Rank
Exponential	1,685.73	1,689.50	1	1
Weibull	1,687.73	1,695.27	5	4
LogLog	1,692.20	1,699.74	6	6
LogNormal	1,712.46	1,720.00	7	7
Gen Gamma	1,687.39	1,698.71	3	5
Gamma	1,687.69	1,695.24	4	3
Gompertz	1,686.85	1,694.39	2	2

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DLd: daratumumab, lenalidomide, dexamethasone; OS: overall survival.

Table 57: Comparison of predicted survival rates for DLd OS extrapolations (with GPM cap)

	OS survival rates (%)		
	DLd		
	10 years	15 years	20 years
Clinical Expert Estimates			
Clinical expert estimates	40	20	4.5
Extrapolations			
Exponential	46.4	30.0	13.3
Weibull	46.3	29.9	13.3
LogNormal	51.4	33.8	15.0
LogLog	49.0	32.2	14.3
Gompertz	44.0	25.7	11.4
Gen Gamma	43.5	22.8	8.8
Gamma	46.6	30.2	13.4

Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; OS: overall survival.

The exponential curve provided the best statistical fit to the observed OS data with respect to both AIC and BIC. In terms of visual fit, most curves (excluding the LogNormal) provided similar visual fit to the ~7 years of available OS data from MAIA. Clinical expert estimates for DLd OS at the May 2025 UK Advisory Board were also substantially lower than the OS rates predicted by the extrapolations at all timepoints at 10 years and beyond.

Considering both the internal and external validity of the curves, and considering the curves predict higher OS than the clinical experts estimates, a consistent approach was taken as for DBLd, to ensure clinical face validity with the base case curves. First, the extrapolation which provided the best statistical fit to the observed data from MAIA (the exponential) was taken forward, and aligning with the approach for DBLd, calibrations were then explored in order to align the extrapolation with the most clinically plausible estimates of long-term survival for DLd.

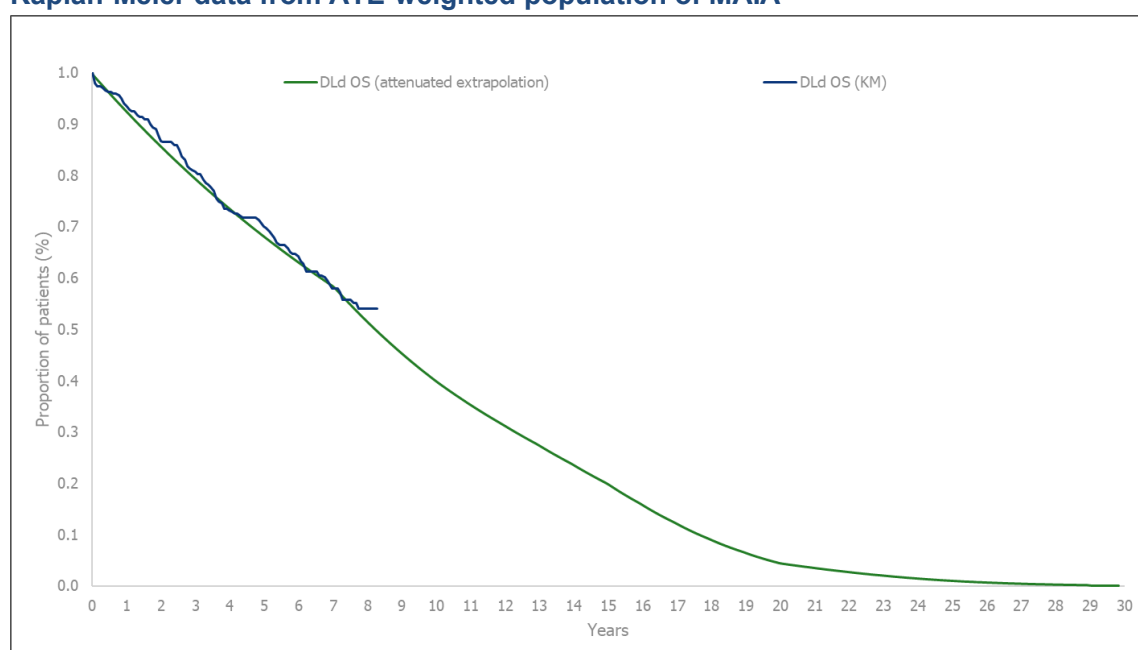
Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Derivation of a calibrated exponential extrapolation for DLd OS

As for DBLd OS, an attenuation factor (derived using a multiplier applied to the general population mortality) was applied to the exponential extrapolation from Year 7 onwards. Attenuation was applied from Year 7 onwards for DLd OS given the median follow up for OS in MAIA is 89.3 months. The attenuated extrapolation resulted in 10, 15 and 20-year survival estimates for DLd that align to the clinical expert estimates at each timepoint (40%, 20% and 4.5%, respectively).

The resulting extrapolation presented in Figure 34 thus provides the best fit to the observed MAIA OS data whilst importantly also ensuring that the long-term survival extrapolations remain fully in line with clinical expectations.

Figure 34: Attenuated exponential extrapolation fitted to the DLd COVID-19-adjusted OS Kaplan-Meier data from ATE-weighted population of MAIA



Abbreviations: ATE: average treatment effect; DLd: daratumumab, lenalidomide, dexamethasone; KM: Kaplan-Meier; OS: overall survival.

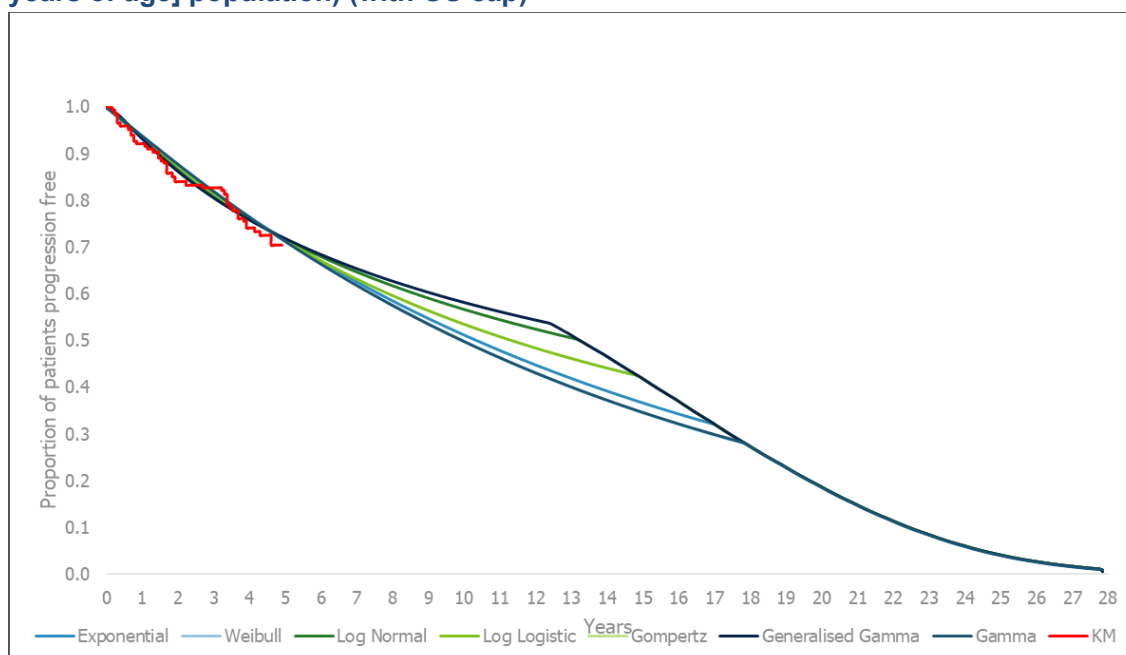
3.3.3 Progression-free survival

DBLd

To model long-term DBLd PFS, extrapolations were fitted to the COVID-19-adjusted DBLd PFS data from the ATE-weighted ASCT-ineligible population of CEPHEUS. Each of the DBLd PFS (capped by OS) extrapolations are presented in Figure 35 below, with goodness-of-fit statistics of each of the extrapolations presented in Table 58. Long-term estimates of DBLd PFS for each parametric extrapolation are provided in Table 59. For completeness, the hazard plots are provided in Appendix N.

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Figure 35: Extrapolation of COVID-19-adjusted PFS for DBLd using IPD from the ASCT-ineligible CEPHEUS population (adjusted via IPTW using ATE weights to the MAIA [<80 years of age] population) (with OS cap)



Footnotes: Extrapolations shown are capped by the DBLd exponential OS extrapolation (prior to attenuation).
Abbreviations: ATE: average treatment effect; GPM: general population mortality; KM: Kaplan-Meier; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; OS: overall survival; PFS: progression-free survival.

Table 58: Goodness-of-fit statistics for DBLd PFS extrapolations

Survival model	DBLd			
	AIC	BIC	AIC Rank	BIC Rank
Exponential	448.086	451.051	1	1
Weibull	450.009	455.939	5	5
LogLog	448.932	454.862	3	3
LogNormal	449.878	455.808	2	2
Gen Gamma	450.863	459.758	7	7
Gamma	449.981	455.912	4	4
Gompertz	450.081	456.012	6	6

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; PFS: progression-free survival.

Table 59: Comparison of predicted survival rates for DBLd PFS extrapolations (with OS cap)

	PFS survival rates (%)		
	DBLd		
	10 years	15 years	20 years
Clinical Expert Estimates			
Clinical expert estimates	40	20	5
Extrapolations			
Exponential	50.9	36.5	18.5

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Weibull	49.6	34.4	18.5
LogNormal	56.5	41.6	18.5
LogLog	53.3	41.6	18.5
Gompertz	50.1	34.8	18.5
Gen Gamma	58.0	41.6	18.5
Gamma	49.6	34.6	18.5

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; OS: overall survival; PFS: progression-free survival.

As for DBLd and DLd OS detailed above, and in line with NICE TSD 14, the selection of the extrapolation for DBLd PFS was based on internal and external validity of the PFS curves, capped by the exponential DBLd OS curve.¹³⁶

The exponential curve provided the best statistical fit to the observed PFS data with respect to both AIC and BIC, although all curves except the Generalised Gamma were within 2 AIC and 5 BIC points of the exponential, indicating most curves provide a similar fit to the observed data. In terms of visual fit, all curves provided similar visual fit to the ~5 years of available data from CEPHEUS.

Considering both the internal and external validity of the curves, and that the unattenuated curves predict higher PFS than the clinical experts estimates, a conservative approach was taken to ensure clinical face validity with the base case curves. To ensure consistency across endpoints, and the intervention and comparator, the extrapolation which provided the best statistical fit to the observed data from CEPHEUS (the exponential) was taken forward, and additional calibrations were explored in order to align the extrapolation with the most clinically plausible estimates of long-term PFS for DBLd.

Derivation of a calibrated exponential extrapolation for DBLd PFS

An attenuation factor (derived using a multiplier applied to the attenuated DBLd PFS curve) was applied to the exponential extrapolation from Year 5 onwards. As such, the attenuated extrapolation resulted in 10- and 15-year PFS estimates for DBLd that align to the clinical expert estimates.

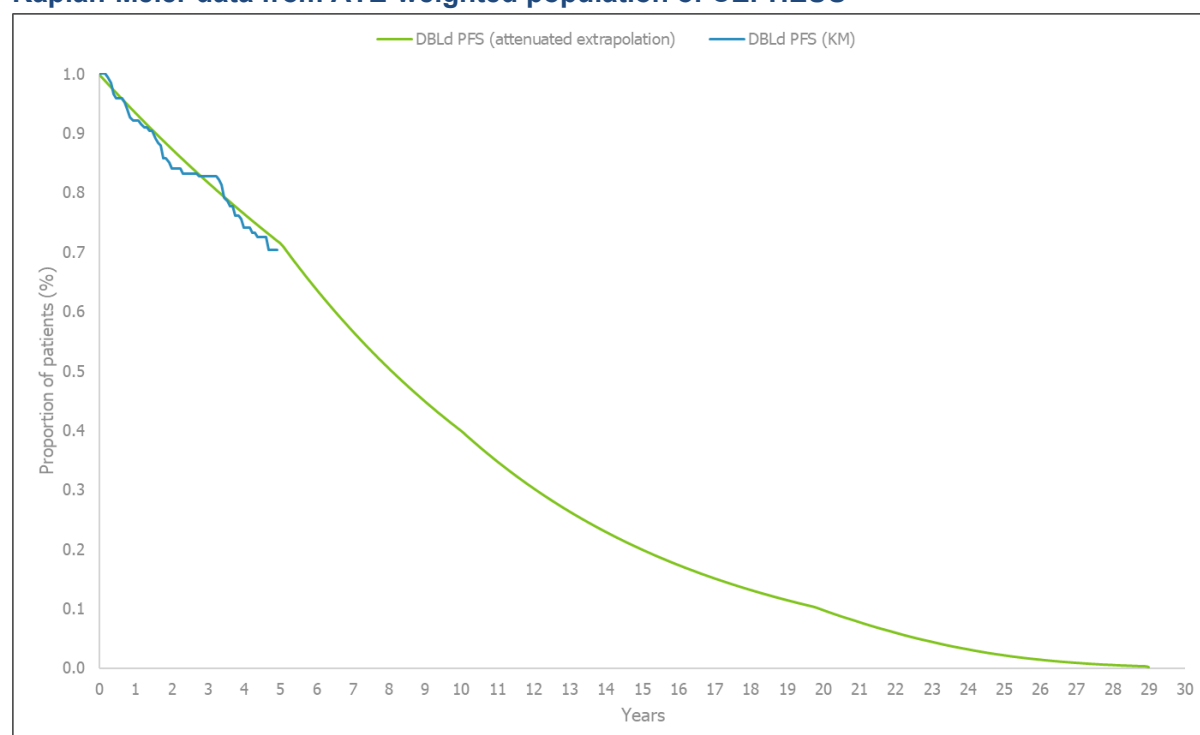
Between Year 15 and Year 20, the attenuated extrapolations predict that a large proportion of patients continue to experience disease progression between Year 15 and Year 20. This resulted in an inflection in the attenuated PFS curve at 15 years and an inconsistent/implausible relationship with the attenuated OS curve. During the May 2025 UK Advisory Board discussion, clinical experts expressed their expectation that some patients would be long-term survivors, largely due to a high proportion of patients achieving and sustaining MRD negativity. It is therefore anticipated that a subset of patients will remain progression-free and alive in the long term, e.g. at the 20-year mark. To incorporate these long-term responders, it is assumed that the 20-year PFS estimate aligns with the higher end of the clinical estimates received, set at 10%. The higher end represents the highest 20 year estimate received from the clinical experts during the May 2025 Advisory Board and ensures a plausible relationship is maintained between attenuated PFS and OS curves beyond 15 years. This 20-year PFS rate is further justified as it closely aligns to the projected 20-year PFS rate of 11.23% from the EAG estimate for IsaBLd in ID3981 (another anti-CD38 based quadruplet therapy being appraised by NICE for ASCT-ineligible NDMM).⁶ Additionally, the PFS attenuated curve predicts a median PFS of 96.59

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months. This is similar to the projected median PFS estimates from long-term modelling for DBLd published at EMN in April 2025 which uses the same baseline age in CEPHEUS and UK general population data and estimated the median PFS in the DBLd ASCT-ineligible population to be between 96 and 118 months.¹³⁷ This suggests the attenuation approach currently used to model DBLd could be conservative as it aligns with the lower bound of the externally published evidence for median PFS projections from long-term modelling.

The resulting extrapolation presented in Figure 36 thus provides the best fit to the observed CEPHEUS PFS data while also ensuring that the long-term PFS extrapolations remain in line with clinical expectations and relevant external data sources.

Figure 36: Attenuated exponential extrapolation fitted to the DBLd COVID-19-adjusted PFS Kaplan-Meier data from ATE-weighted population of CEPHEUS

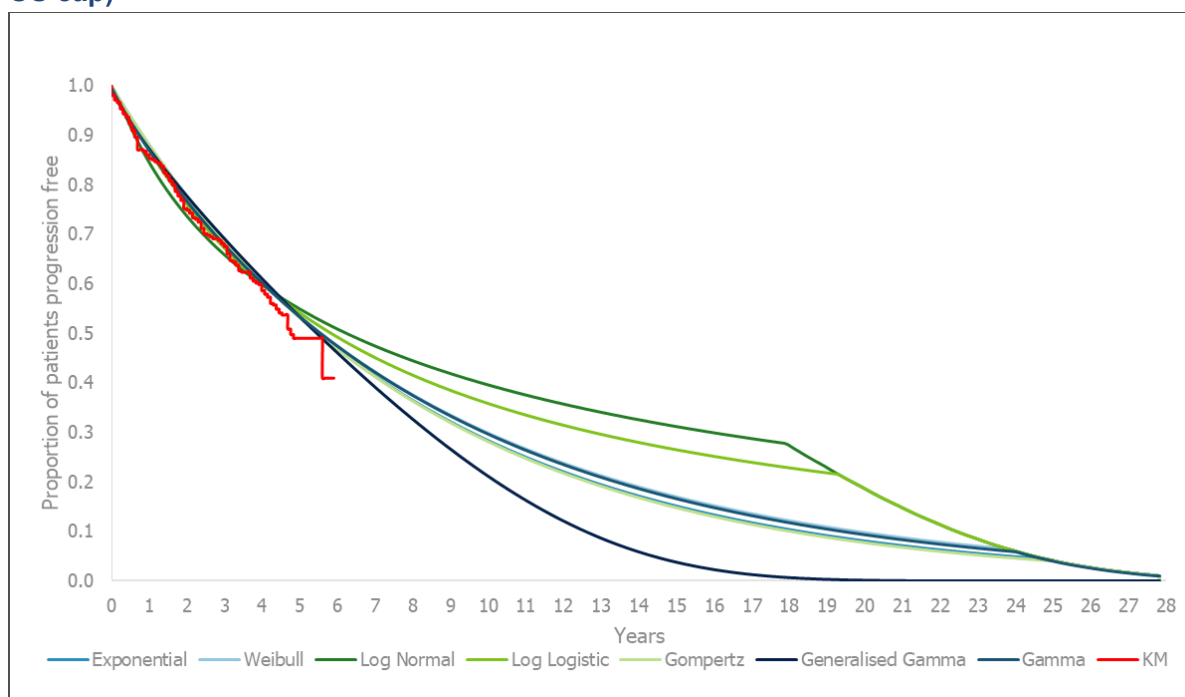


Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone KM: Kaplan-Meier; PFS: progression-free survival.

DLd

Extrapolations were fitted to the COVID-19 adjusted PFS data for DLd from the ATE-weighted MAIA trial population. Each of the DLd PFS (capped by OS) extrapolations are presented in Figure 37, with goodness-of-fit statistics for each of the DLd PFS extrapolations presented in Table 60. Long-term estimates of DLd PFS for each parametric extrapolation are provided in Table 61. For completeness, the hazard plots are provided in the Appendix N.

Figure 37: Extrapolation of COVID-19-adjusted PFS for DLd using IPD from MAIA (adjusted via IPTW using ATE weights to the ASCT-ineligible CEPHEUS population) (with OS cap)



Footnotes: Extrapolations shown are capped by the DLd exponential OS extrapolation (prior to attenuation).

Abbreviations: ATE: average treatment effect; GPM: general population mortality; KM: Kaplan-Meier; DLd: daratumumab, lenalidomide and dexamethasone; OS: overall survival; PFS: progression-free survival.

Table 60: Goodness-of-fit statistics for DLd PFS extrapolations

Survival model	DLd			
	AIC	BIC	AIC Rank	BIC Rank
Exponential	1,687.56	1,691.33	1	1
Weibull	1,689.05	1,696.59	3	3
LogLog	1,693.16	1,700.70	6	5
LogNormal	1,705.38	1,712.92	7	7
Gen Gamma	1,689.68	1,701.00	5	6
Gamma	1,688.86	1,696.41	2	2
Gompertz	1,689.55	1,697.10	4	4

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DLd: daratumumab, lenalidomide, dexamethasone; PFS: progression-free survival.

Table 61: Comparison of predicted survival rates for DLd PFS extrapolations (with OS cap)

	PFS survival rates (%)		
	DLd		
	10 years	15 years	20 years
Clinical Expert Estimates			
Clinical expert estimates	32.5	15	3
Extrapolations			

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Exponential	28.1	15.0	8.0
Weibull	29.6	16.9	9.7
LogNormal	39.4	31.1	18.5
LogLog	35.6	26.4	18.5
Gompertz	27.9	14.6	7.6
Gen Gamma	20.9	3.7	0.1
Gamma	29.5	16.6	9.4

Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; OS: overall survival; PFS: progression-free survival.

The selection of the extrapolation for DLd PFS was based on internal and external validity of the PFS curves, capped by the exponential DLd OS curve.¹³⁶ The exponential curve provided the best statistical fit to the observed PFS data with respect to both AIC and BIC. In terms of visual fit, all curves provided similar visual fit to the ~5 years of available data from MAIA.

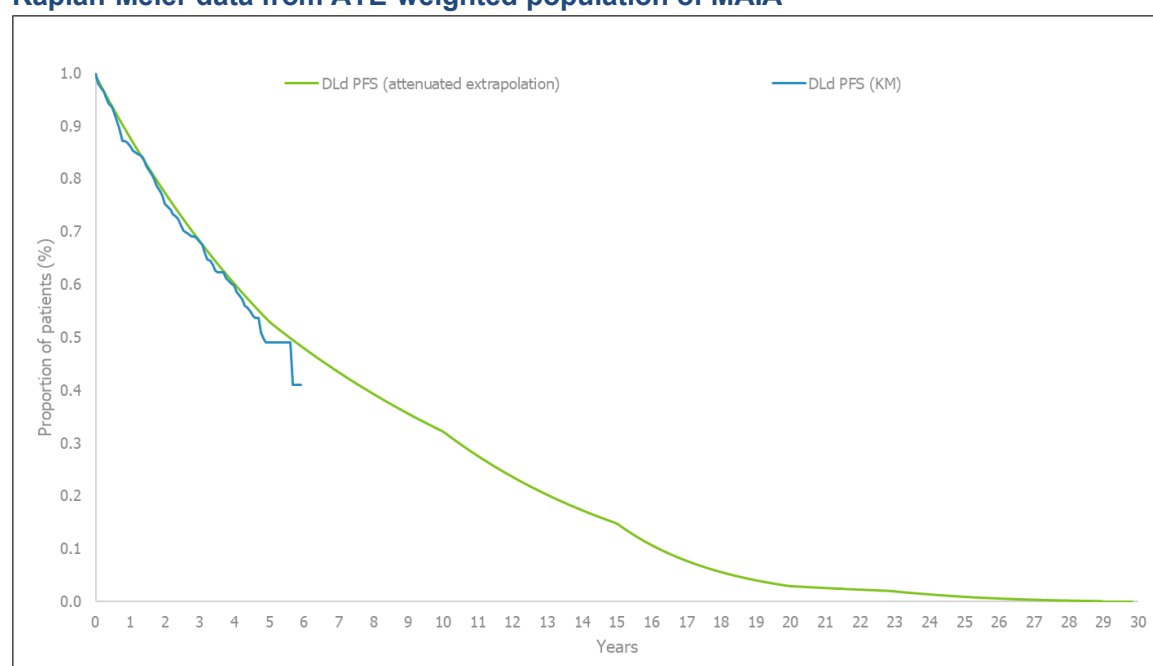
Considering both the internal and external validity of the curves, and that most curves predict higher DLd PFS than the clinical experts' estimates (with the exception of the Gen Gamma which estimated lower PFS across all timepoints), to ensure consistency across the endpoints (as well as the intervention and comparator), the extrapolation which provided the best statistical fit to the observed data from MAIA (the exponential) was taken forward and additional calibrations were explored in order to align the exponential extrapolation with the most clinically plausible estimates of long-term PFS for DLd.

Derivation of a calibrated exponential extrapolation for DLd PFS

As for DBLd PFS, an attenuation factor (derived using a multiplier applied to the attenuated DLd OS curve) was applied to the exponential extrapolation from Year 5 onwards. Of note, while the attenuation for DLd OS was applied from Year 7 onwards (median follow up for OS in MAIA: 89.3 months) the attenuation for DLd PFS is applied from Year 5 onwards, given at the final data cut for PFS in MAIA, median follow-up time for PFS was 64.5 months. The attenuated extrapolation resulted in 10, 15 and 20-year progression-free survival estimates for DLd that align to the clinical expert estimates at each timepoint (32.5%, 15% and 3%, respectively).

The resulting extrapolation presented in Figure 38 thus provides the best fit to the observed MAIA PFS data whilst importantly also ensuring that the long-term survival extrapolations remain in line with clinical expectations.

Figure 38: Attenuated exponential extrapolation fitted to the DLd COVID-19-adjusted PFS Kaplan-Meier data from ATE-weighted population of MAIA



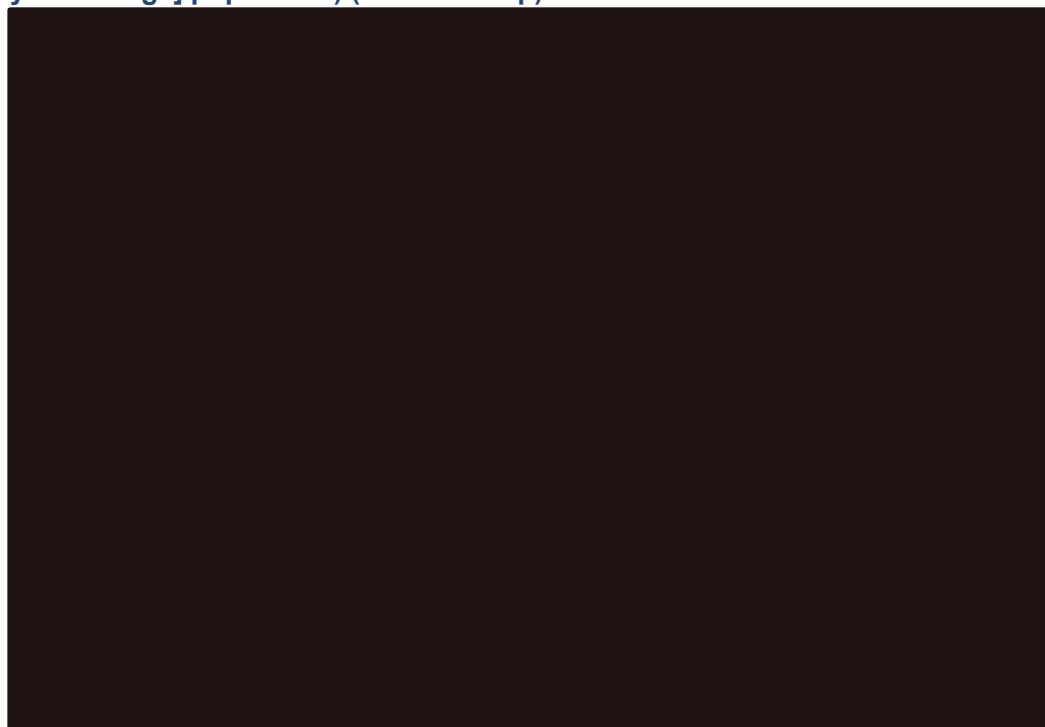
Abbreviations: ATE: average treatment effect; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; PFS: progression-free survival.

3.3.4 Time to treatment discontinuation

DBLd

In order to model treatment duration for DBLd, extrapolations were fitted to COVID-19-adjusted TTD data from the ATE-weighted ASCT-ineligible population of CEPHEUS (capped by PFS), as presented in Figure 39. Goodness-of-fit statistics for each of the DBLd TTD extrapolations are presented in Table 62, and long-term estimates of DBLd TTD (capped by PFS) for each parametric extrapolation are provided in Table 63. For completeness, the hazard plots are provided in Appendix N.

Figure 39: Extrapolation of COVID-19-adjusted TTD for DBLd using IPD from the ASCT-ineligible CEPHEUS population (adjusted via IPTW using ATE weights to the MAIA [<80 years of age] population) (with PFS cap)



Footnote: In the model, TTD is capped by the unattenuated DBLd PFS exponential extrapolation.

Abbreviations: ATE: average treatment effect; KM; Kaplan-Meier; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival; TTD: time to treatment discontinuation.

Table 62: Goodness-of-fit statistics for DBLd TTD extrapolations

Survival model	DBLd			
	AIC	BIC	AIC Rank	BIC Rank
Exponential	752.85	755.81	1	1
Weibull	754.64	760.58	5	4
LogLog	757.67	763.60	6	6
LogNormal	763.51	769.44	7	7
Gen Gamma	754.37	763.27	2	5
Gamma	754.48	760.41	3	2
Gompertz	754.52	760.45	4	3

Footnote: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; TTD: time to discontinuation.

Table 63: Comparison of predicted estimates for DBLd TTD extrapolations (with PFS cap)

	TTD rates (%)		
	DBLd		
	10 years	15 years	20 years
Clinical Expert Estimates			
Clinical expert estimates	■	■	■
Extrapolations			

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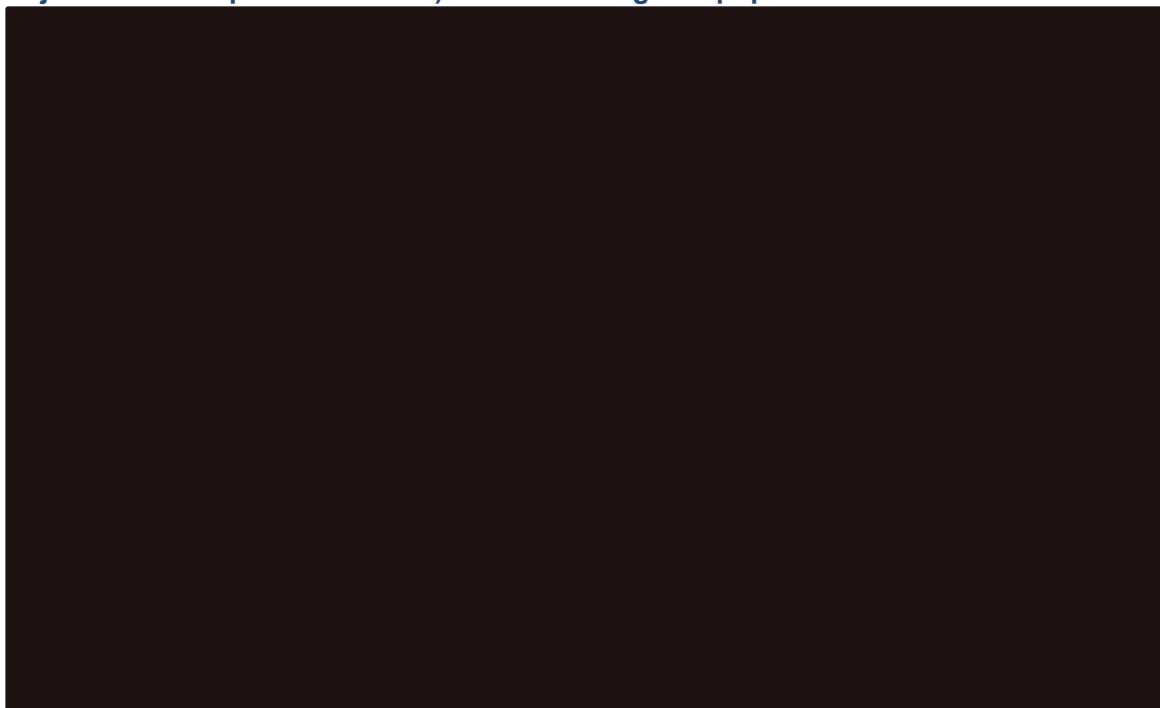
Exponential	■	■	■
Weibull	■	■	■
LogNormal	■	■	■
LogLog	■	■	■
Gompertz	■	■	■
Gen Gamma	■	■	■
Gamma	■	■	■

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; PFS: progression-free survival; TTD: time to treatment discontinuation.

The exponential curve provided the best statistical fit, although the Gamma, Gompertz and Weibull extrapolations all fell within 2 AIC points and 5 BIC points, indicating that they provided comparable statistical fits to the exponential. In terms of visual fit, all curves provided similar visual fit to the ~5 years of available data from CEPHEUS.

Initially, for consistency with the OS and PFS extrapolations, attenuation of the best statistically fitting exponential extrapolation was considered for TTD, to align to long-term estimates of TTD provided by clinicians. However, this attenuation approach for TTD led to an inconsistent relationship with the attenuated PFS curve due to an inflection at Year 10 (Figure 40). This inflection necessitated a different approach for TTD compared to OS and PFS, so exploration of the initial unattenuated extrapolations was considered to assess if any of the curves broadly aligned with clinical expert opinion.

Figure 40: Attenuated exponential extrapolation fitted to the DBLd COVID-19-adjusted TTD Kaplan-Meier data (and attenuated exponential extrapolation fitted to the DBLd COVID-19-adjusted PFS Kaplan-Meier data) from ATE-weighted population of CEPHEUS



Footnotes: In the model, TTD is capped by PFS.

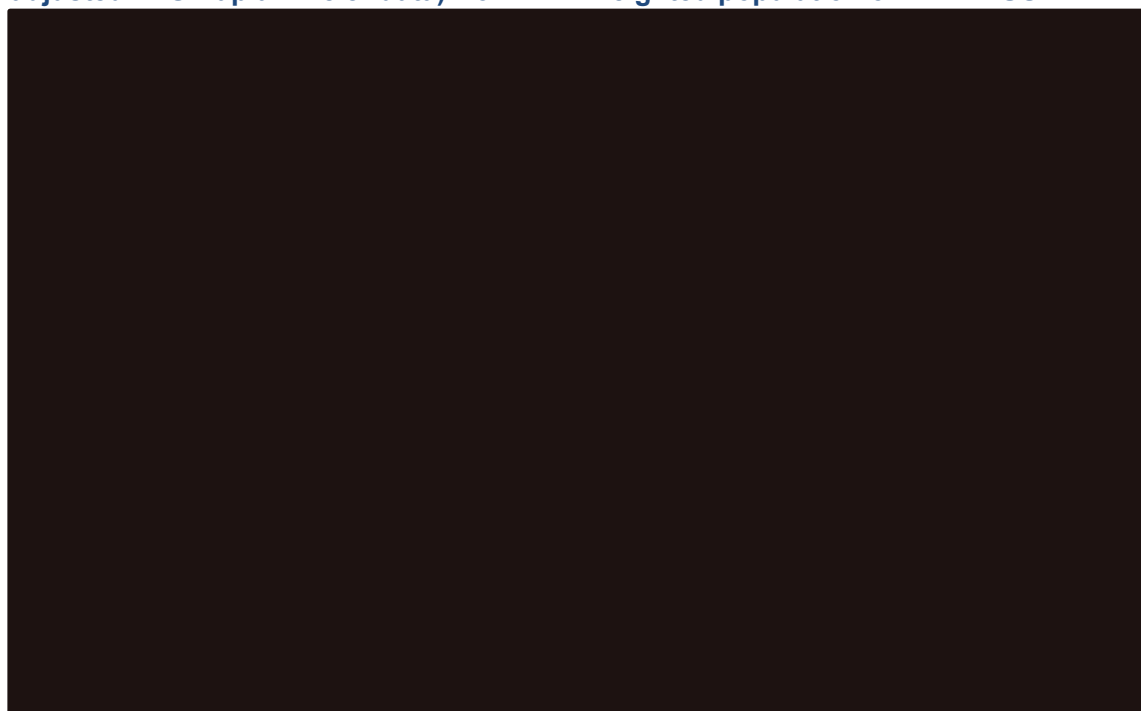
Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; KM: Kaplan-Meier; PFS: progression-free survival; TTD: time to treatment discontinuation.

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Out of all of the extrapolations, the Gompertz broadly aligns with the estimates received from the clinical experts, and slightly overestimates TTD versus the experts at Year 15 (Gompertz: █%; clinical experts: █%) and at Year 20 (Gompertz: █% and clinical experts: █%). The Gompertz also provided a comparable statistical fit to the best fitting exponential extrapolation, falling within 2 AIC and 5 BIC points.

Therefore, the base case DBLd TTD curve uses the Gompertz selection without attenuation (see Figure 41) – this produces a curve with an improved visual fit and more accurately reflects the true treatment duration in relation to PFS.

Figure 41: Gompertz extrapolation fitted to the DBLd COVID-19-adjusted TTD Kaplan-Meier data (and attenuated exponential extrapolation fitted to the DBLd COVID-19-adjusted PFS Kaplan-Meier data) from ATE-weighted population of CEPHEUS



Footnotes: In the model, TTD is capped by PFS.

Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; KM: Kaplan-Meier; PFS: progression-free survival; TTD: time to treatment discontinuation.

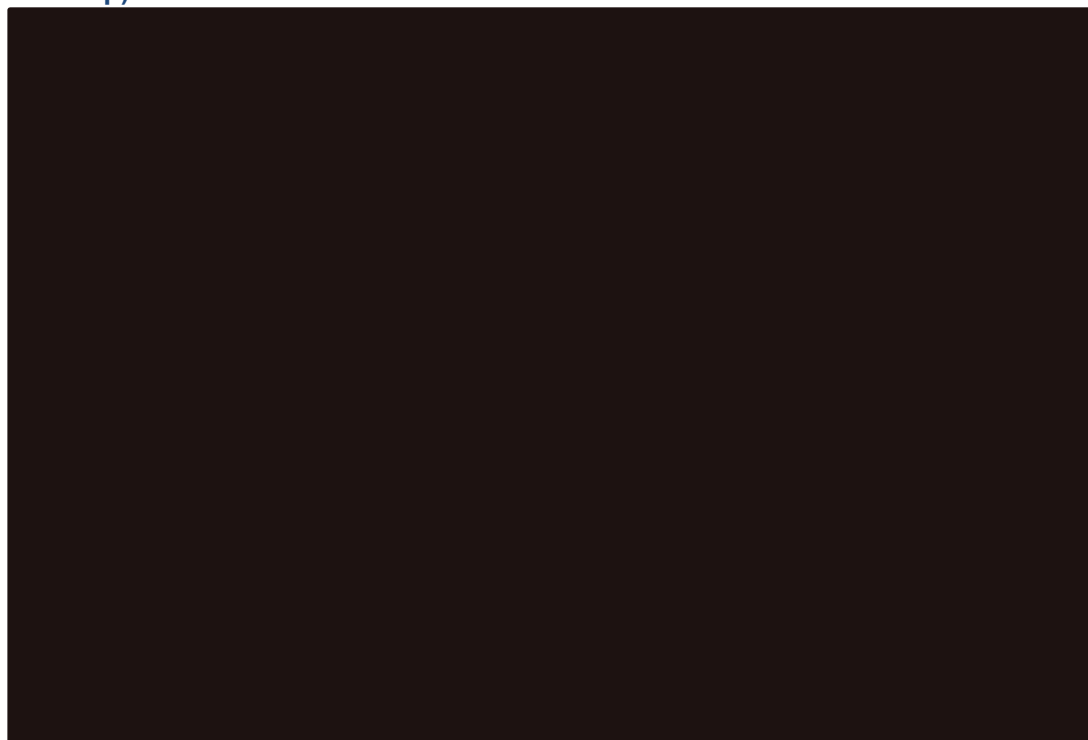
For completeness and to explore a fully consistent approach across all endpoints, a scenario is explored which applies the calibration approach for the DBLd TTD curve to align with the approach to the other endpoints. This has a minimal impact on the ICER (see Section 3.11.3).

DLd

Extrapolations were fitted to the COVID-19 adjusted TTD data for DLd from the ATE-weighted MAIA trial population. Each of the DLd TTD (capped by PFS) extrapolations are presented in Figure 42, with goodness-of-fit statistics for each of the DLd TTD extrapolations presented in Table 64. Long-term estimates of DLd TTD (capped by PFS) for each parametric extrapolation are provided in Table 65. For completeness, the hazard plots are provided in Appendix N.

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Figure 42: Extrapolation of COVID-19-adjusted TTD for DLd using IPD from MAIA (adjusted via IPTW using ATE weights to the ASCT-ineligible CEPHEUS population) (with PFS cap)



Footnote: In the model, TTD is capped by PFS. The model also caps DLd TTD by DBLd TTD.

Abbreviations: ATE: average treatment effect; KM; Kaplan-Meier; DLd: daratumumab, lenalidomide and dexamethasone; PFS: progression-free survival; TTD: time to treatment discontinuation.

Table 64: Goodness-of-fit statistics for DLd TTD extrapolations

Survival model	DLd			
	AIC	BIC	AIC Rank	BIC Rank
Exponential	2569.96	2573.73	3	1
Weibull	2570.23	2577.77	4	3
LogLog	2592.41	2599.96	6	6
LogNormal	2624.60	2632.14	7	7
Gen Gamma	2567.28	2578.60	2	4
Gamma	2571.20	2578.74	5	5
Gompertz	2567.08	2574.63	1	2

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DLd: daratumumab, lenalidomide and dexamethasone; TTD: time to discontinuation.

Table 65: Comparison of predicted survival rates for DLd TTD extrapolations (with PFS cap)

	TTD rates (%)		
	DLd		
	10 years	15 years	20 years
Clinical Expert Estimates			
Clinical expert estimates	■	■	■

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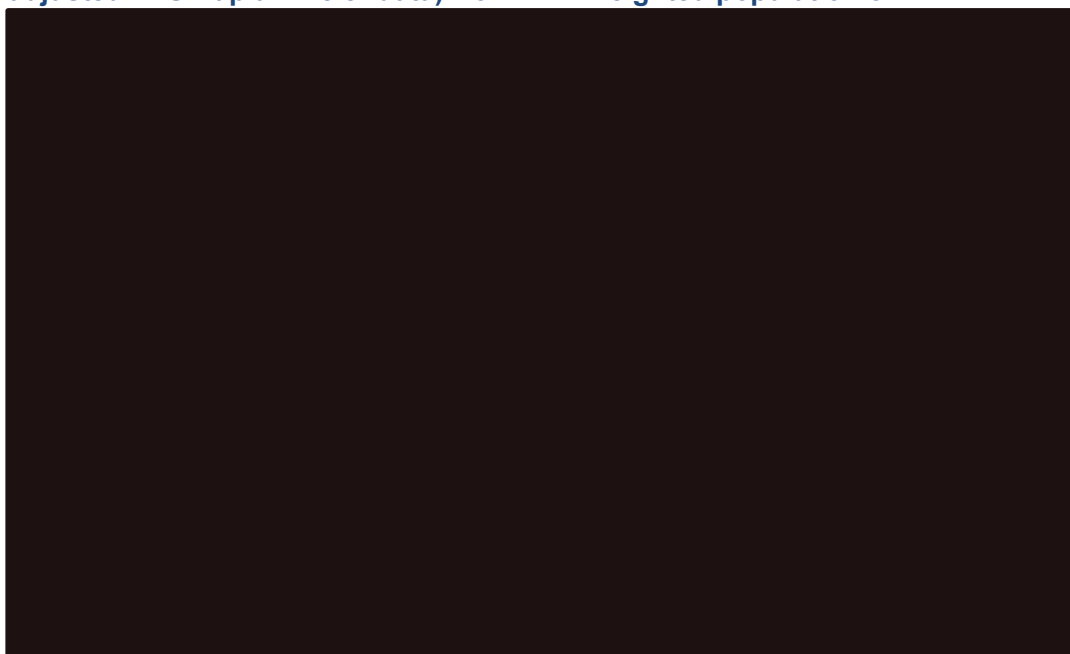
Extrapolations			
Exponential	■	■	■
Weibull	■	■	■
LogNormal	■	■	■
LogLog	■	■	■
Gompertz	■	■	■
Gen Gamma	■	■	■
Gamma	■	■	■

Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; PFS: progression-free survival; TTD: time to treatment discontinuation.

Selection of the extrapolation for DLd TTD was based on internal and external validity of the TTD curves, capped by the exponential DLd PFS curve.¹³⁶ The Gompertz curve provided the best statistical fit to the observed TTD data with respect to AIC, while the exponential provided the best statistical fit with respect to BIC. The Gamma, Generalised Gamma and Weibull extrapolations all fell within 4 AIC points and 5 BIC points, indicating that they provided comparable statistical fits to the best statistical fitting curves. In terms of visual fit, all curves provided similar visual fit to the ~7 years of available data from MAIA.

In line with the other endpoints, an attenuation approach was initially explored, whereby the curve with the best statistical fit for the observed data from MAIA (the Gompertz) was attenuated to align with long-term estimates of TTD for DLd provided by clinical experts. However, the resulting curve produced a clinically implausible increasing separation between PFS and TTD from Year 7 (Figure 43), particularly when considering the broadly parallel relationship observed between PFS and TTD during the initial follow up for DLd.

Figure 43: Attenuated Gompertz extrapolation fitted to the DLd COVID-19-adjusted TTD Kaplan-Meier data (and attenuated exponential extrapolation fitted to the DLd COVID-19-adjusted PFS Kaplan-Meier data) from ATE-weighted population of MAIA



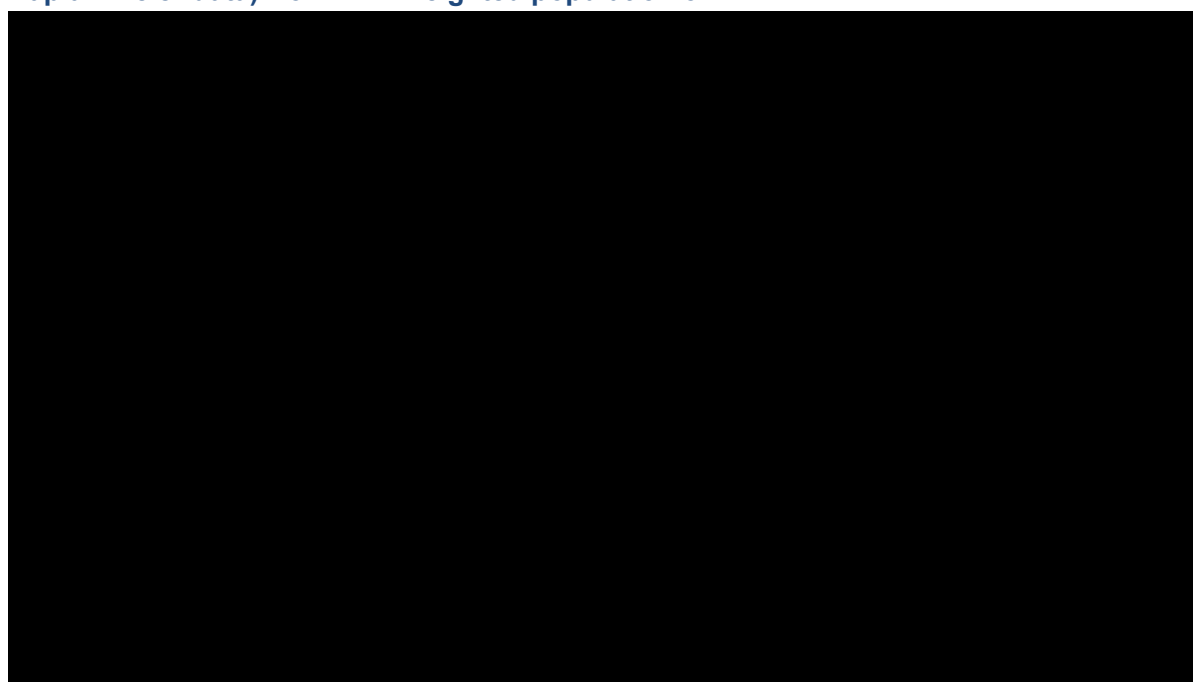
Footnote: In the model, TTD is capped by PFS. The model also caps DLd TTD by DBLd TTD.

Abbreviations: ATE: average treatment effect; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; PFS: progression-free survival; TTD: time to treatment discontinuation.

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Therefore, exploration of the initial unattenuated extrapolations was considered to assess if any of the curves broadly aligned with expert opinion. The estimates from the Weibull extrapolation broadly aligned to the estimates received from the clinical experts (Year 10 – Weibull: █%; clinical experts: █%; Year 15 – Weibull: █%; clinical experts: █%; Year 20 – Weibull: █% and clinical experts: █%). The Weibull also provided comparable statistical fit to the best fitting Gompertz extrapolation, falling within 3.2 AIC and BIC points. Therefore, the base case DLd TTD curve uses the Weibull selection without attenuation (see Figure 44), considering this results in a better visual fit, more accurately reflects the true treatment duration and results in a more clinically plausible relationship between DLd PFS and DLd TTD.

Figure 44: Weibull extrapolation fitted to the DLd COVID-19-adjusted TTD Kaplan-Meier data (and attenuated exponential extrapolation fitted to the DBLd COVID-19-adjusted PFS Kaplan-Meier data) from ATE-weighted population of MAIA



Footnote: In the model, TTD is capped by PFS. The model also caps DLd TTD by DBLd TTD.

Abbreviations: ATE: average treatment effect; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; TTD: time to treatment discontinuation.

For completeness and to explore a fully consistent approach across all endpoints, a scenario is explored which applies the calibration approach for the DLd TTD curve to align with the approach to the other endpoints. This has a minimal impact on the ICER (see Section 3.11.3).

3.3.5 *Adverse events*

AEs considered in the model included treatment-emergent Grade 3 or 4 AEs with an incidence $\geq 5\%$ for any of the comparators of interest. The inclusion rule that events must have occurred in at least 5% of patients in any trial was selected in order to capture AEs that would impact patients consistently enough to have validity in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting.

In the model, a proportion of patients were assumed to experience AEs during treatment, with rates informed by the CEPHEUS trial (ASCT-ineligible population; DBLd), MAIA trial (DLd and Ld) and the ALCYONE trial (BMP). For the analysis versus BCd, AE rates for BCd were

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assumed equal to BMP, based on the assumption of clinical equivalence (see Section 2.10.4). The AE rates are provided in Table 66.

The change in utility and costs associated with each AE are presented in Section 3.4.4 and Section 3.5.3, respectively. In line with approach taken in TA917, the cost and disutility of AEs were applied in the first cycle of the model (i.e. when all patients are still alive).⁵

Table 66: Incidence of AEs included in the model

AE	DBLd	DLd	Ld	BMP and BCd ^a
Neutropenia	■	■	■	■
Lymphopenia	■	■	■	■
Thrombocytopenia	■	■	■	■
Leukopenia	■	■	■	■
Anaemia	■	■	■	■
Pneumonia	■	■	■	■
Hypokalaemia	■	■	■	■
Pulmonary embolism	■	■	■	■
Hyperglycaemia	■	■	■	■
Diarrhoea	■	■	■	■
Fatigue	■	■	■	■
Hypertension	■	■	■	■
Asthenia	■	■	■	■
Acute kidney injury	■	■	■	■
Chronic kidney disease	■	■	■	■
Cataract	■	■	■	■

Footnotes: ^a Incidence of AEs assumed equivalent between BMP and BCd based on the lack of trial evidence for BCd.

Abbreviations: AE: adverse event; CSR: clinical study report; BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone.

3.4 Measurement and valuation of health effects

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

HRQoL was measured as a secondary outcome in the CEPHEUS trial, using EORTC QLQ-C30 and EQ-5D-5L instruments. Both questionnaires were completed at the timepoints outlined in the Schedule of Activities prespecified in the protocol.

EORTC QLQ-C30 and EQ-5D-5L questionnaires were administered on Day 1 of Cycles 1–8 and then every 3rd cycle thereafter until progressed disease. Questionnaires were also administered at Weeks 8 and 16 after disease progression occurred for patients. Following progression, questionnaires were then administered every 16 weeks (EQ-5D-5L only) and at the start of subsequent therapy, and four weeks after the start of subsequent therapy. Of note, compliance with the questionnaire was >■% at baseline and >■% at all subsequent timepoints.

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In summary, improvement in HRQoL and physical functioning, as well as reductions in symptoms (pain, fatigue, overall disease symptoms) as measured by EORTC QLQ-C30 [and EORTC QLQ-MY20 scale scores] and EQ-5D-5L, were observed.

3.4.2 Mapping

HRQoL data were collected in the CEPHEUS trial using the EQ-5D-5L. In accordance with the NICE position statement in the use of EQ-5D-5L to derive utility values, the EQ-5D-5L descriptive scores from CEPHEUS were mapped onto the 3L UK value set using the mapping function developed by Hernández Alava *et al.* (2017) through the NICE DSU, using the EEPRU dataset (Hernández Alava *et al.* 2020).^{135, 138, 139}

3.4.3 Health-related quality-of-life studies

An SLR of humanistic burden was conducted to identify evidence on HRQoL, patient-reported outcomes and utilities in patients with ASCT-ineligible NDMM. In total, 77 publications were identified, with a full list of the results can be found in Appendix F.

Of the identified studies, the pivotal clinical trials for DBLd and DLd (CEPHEUS and MAIA) were considered to represent the most relevant sources of utility data for inclusion in the economic model, as described in Section 3.4.3. The utility values from CEPHEUS were used in the base case economic analysis; the utility values from MAIA were considered in scenario analyses.

3.4.4 Adverse reactions

One-off decrements in utility were applied in the model for the proportion of patients who experienced TEAEs (see Section 3.3.5). The utility decrements used in the model were primarily based on those used in previous UK HTA submissions for daratumumab (TA897 and TA783) and values from the literature, identified using targeted literature searches (Table 67).^{127, 128} Asthenia was assumed equivalent to fatigue as patients experience similar symptoms.

As no disutility value could be found in the literature, the disutility for acute kidney injury (AKI) and chronic kidney disease (CKD) was calculated using utility values reported in Appendix K of the NICE Guidelines for AKI (NG148).¹⁴⁰ The utility values reported for AKI, Stage 3/4 and Stage 5 were converted to yearly values and a disutility was calculated for each stage by subtracting these utility values from the average general population utility value for this population. The average disutility value for Stage 3/4 and Stage 5 was used for CKD.

Of note, the approach to modelling the duration and utility decrements associated with AEs (Table 67) is aligned to the approach accepted in TA917.⁵

Table 67: Duration and utility decrements associated with AEs included in the model

AE	Disutility	Duration (days)	Source
Neutropenia	-0.15	7	Based on TA897/TA783 (Brown 2013/Partial Review TA171) ^{127, 128} Duration of AE assumption, aligning with TA783 ¹²⁷
Lymphopenia	-0.07	16	
Thrombocytopenia	-0.31	7	
Leukopenia	-0.07	15	
Anaemia	-0.31	180	
Pneumonia	-0.19	7	

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Hypokalaemia	-0.07	11	
Pulmonary embolism	-0.31	7	
Hyperglycaemia	-0.15	15	Assumed equivalent to hypertension
Diarrhoea	-0.10	12	Lloyd et al. 2006 ¹⁴¹
Fatigue	-0.12	15	
Hypertension	-0.15	11	Assumed equivalent to hypokalaemia
Asthenia	-0.12	15	Assumed equivalent to fatigue
Acute kidney disease ^a	-0.13	7	Appendix K of the NICE Guidelines for AKI (NG148) ¹⁴⁰
Chronic kidney disease ^a	-0.004	365	Appendix K of the NICE Guidelines for AKI (NG148) ¹⁴⁰
Cataract	-0.01	28	Goodsmith et al., 2019, supplementary data ¹⁴²

Footnotes: ^a Reflect the utility decrements calculated with the base case assumption of time-dependent utility values in the PF health state and time-independent utility values in the PD health state (see Section 3.4.5).

Abbreviations: AE: adverse event; AKI: acute kidney injury; NG: NICE guidelines; NICE: National Institute of Health and Care Excellence; TA: Technology Appraisal.

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

As DBLd and DLd are both daratumumab-based regimens, with very similar treatment regimens with the exception of a short, fixed-duration period of bortezomib, it was deemed appropriate to assume equal utilities (i.e. treatment-independent utilities) for both the intervention (DBLd) and comparator (DLd). AE disutilities were applied to consider the treatment-specific impact of AEs on QoL (see Section 3.4.4). This also follows the approach used in TA917 and ID3981 for the intervention and main comparator.

Utility values for the progression-free (PF) and progressed disease (PD) health states were therefore derived using EQ-5D-5L data in CEPHEUS (ASCT-ineligible population), based on the cross-walk method reported by Hernández Alava *et al.* (2017) to map EQ-5D-5L dimension scores from the CEPHEUS to utilities using the UK EQ-5D-3L value set described in Section 3.4.2. These utility values were deemed to be the most appropriate for use in the cost-effectiveness model, as per the NICE reference case.¹²⁵

PF health state

EQ-5D data collected during the CEPHEUS trial demonstrated that patient utility values improved with increasing time spent in the PF health state, with PF HSUVs in Cycles 9+ (■) notably higher than HSUVs in Cycles 0–8 (■). As such, in the base case analysis, utility values for PFS were modelled to be time-dependent based on PFS HSUVs estimated from Cycles 0–8 and Cycles 9+. This also ensures a plausible difference between the PF and PD HSUV.

The use of time-dependent utilities in the base case analysis was accepted in the recent appraisal of teclistamab in RRMM, where clinical experts consulted noted that time-dependent Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

utility values were most appropriate, given the observed initial decline in quality of life typically experienced by patients initiating treatment, which correlated with active disease. Clinical experts confirmed that over the course of treatment, as patients' disease is controlled, quality of life tends to improve.¹²⁹

This approach also reflects the evolving composition of the overall patient cohorts over time, with patients who fail to respond to treatment progressing more rapidly, while those who remain in a PF health state for extended periods experiencing the deepest and most durable treatment responses. It also accounts for the change in the dosing schedules, with a less intense daratumumab dosing schedule from Cycle 9 onwards (doses reducing from weekly to every four weeks).

PD health state

There was insufficient granularity in the data to inform the use of time-dependent HSUV in the PD health state. As a result, a utility of [REDACTED] was applied uniformly across the PD health state. The decrease in utility for patients with PD embodies the psychological and emotional burden that patients experience when their disease progresses.

The utility values for the PF and PD states used in the base case are presented in Table 68.

Table 68: Utility values derived from CEPHEUS

	PF (Cycles 0–8)	PF (Cycles 9+)	PD
Mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]
95% CI	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: CI: confidence interval; PF: progression-free; PD: progressed disease; SD: standard deviation.
Source: J&J Data on File.

When comparing the base case selected utility to utility values derived from trials among ASCT-ineligible patients, the chosen utility values can be considered conservative, with a [REDACTED] PF utility reported the MAIA trial and used in TA917, and the IMROZ reported PF utility in ID3981 (another anti-CD38 based quadruplet therapy being appraised by NICE for ASCT-ineligible NDMM). Alternative utilities were tested in scenario analyses (see Section 3.11.3).

3.5 Cost and healthcare resource use identification, measurement and valuation

An economic SLR was also conducted to identify cost/resource use studies associated with NDMM in the ASCT-ineligible setting, in the UK. Full details of the SLR can be found in Appendix G.

The health economic analysis was conducted from the perspective of the NHS in England and therefore included only costs that would be incurred by the health system. Appropriate sources of unit costs, such as NHS reference costs 2023–24, British National Formulary (BNF) and drugs and pharmaceutical electronic market information tool (eMIT) were used for cost inputs in the model.

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3.5.1 *Intervention and comparators' costs and resource use*

Dosing regimens

The dosing regimens for front-line treatments included in the model are presented in

Table 69. These were based on the treatment protocols specified in the CEPHEUS trial (DBLd), the MAIA trial (DLd and Ld) and the ALCYONE trial (BMP), which used a reduced bortezomib dose compared to the SmPC.^{16, 143} This BMP reduced dosing regimen was deemed appropriate in TA917.⁵ The dosing regimen included for BCd was based on the dosing regimen outlined in the NHS Chemotherapy Protocol in MM.¹⁴⁴

Drug acquisition costs

The drug acquisition costs of DBLd and all comparators per administration are presented in Table 70 based on their current list prices and licensed doses. For daratumumab, both the drug acquisition costs at list price and incorporating the [REDACTED] are provided.

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 or skipped doses. The model applies RDI to drug acquisition costs in the base case, with the applied RDIs sourced from the ASCT-ineligible cohort in CEPHEUS (for DBLd and for DLd), MAIA (for Ld) and ALCYONE (for BMP and bortezomib as part of BCd). The CEPHEUS trial was considered the most appropriate source of RDIs for daratumumab, [bortezomib], lenalidomide and dexamethasone for both DBLd and DLd combination therapies as it is the most recent trial relevant to the population of interest in this submission, and is therefore likely to best reflect current prescribing trends of daratumumab, lenalidomide and dexamethasone across both regimens. Moreover, the population in MAIA was slightly different due to the inclusion of patients over 80 years old which is likely to impact comparability of RDI.

In UK clinical practice, bortezomib is given once weekly, rather than the twice weekly dosing as per the SmPC.^{16, 143} This was confirmed by clinical experts in both the November 2024 and more recent May 2025 UK Advisory Boards.³ Therefore, in the model, the full bortezomib dose is given once a week, rather than split to be twice weekly, to align with UK clinical practice. A scenario is provided where the bortezomib dosing is given twice weekly as per the SmPCs.^{16, 143} This was applied to all bortezomib treatments in the front-line treatment setting (DBLd, BMP and BCd).

The cost per administration for bortezomib (BSA-based dosing) was calculated using the mean BSA ([REDACTED] m²) of patients included in the CEPHEUS trial. In the base case analysis, it was assumed that there would be no vial sharing (for any treatments for which this is relevant) and so the number of vials required per administration was rounded up to the nearest whole integer. Drug costs were sourced from the BNF and eMIT. The total costs of therapy applied per administration are presented in Table 70.

Table 69: Summary of dosing regimens for front-line treatment included in the model

Treatment	Treatment cycle duration	Dosing regimen	Source/Justification
DBLd	3-week treatment cycle for Cycles 1–8, 4-week treatment cycle for Cycles 9+, until disease progression	Daratumumab – 1,800 mg QW for 2 treatment cycles	CEPHEUS ¹⁰²
		Daratumumab – 1,800 mg Q3W for 6 treatment cycles	
		Daratumumab – 1,800 mg Q4W for Cycles 9+	
		Bortezomib – 1.3 mg/m ² twice a week for 2 weeks, Cycles 1–8*	
		Lenalidomide 25 mg QD for 2 weeks, Cycles 1–8	
		Lenalidomide 25 mg QD for 3 weeks, Cycles 9+	
		Dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12, Cycles 1–8	
		Dexamethasone 40 mg QW, Cycles 9+	
DLd	4-week treatment cycle, until disease progression	Daratumumab – 1,800 mg QW for 2 cycles	Darzalex SmPC ¹⁶
		Daratumumab – 1,800 mg Q2W for 4 cycles	
		Daratumumab – 1,800 mg Q4W, Cycles 7+	
		Lenalidomide 25 mg QD for 3 weeks	
		Dexamethasone 40 mg QW	
Ld	4-week treatment cycle, until disease progression	Lenalidomide 25 mg QD for 3 weeks	Revlimid SmPC ¹⁴⁵
		Dexamethasone 40 mg QW	
BMP	9 treatment cycles of 6 weeks	Bortezomib – 1.3 mg/m ² on days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycle 1* and on days 1, 8, 22, and 29 of Cycles 2–9	ALCYONE ¹⁴⁶
		Melphalan – 9 mg/m ² Day 1 to 4 of bortezomib cycle	
		Prednisone – 60 mg/m ² Day 1 to 4 of bortezomib cycle	
BCd	8 treatment cycles of 3 weeks	Bortezomib – 1.3 mg/m ² twice a week for 2 weeks Cycles 1–8*	Chemotherapy Protocol – NHS VCD (SC-21) ¹⁴⁴
		Cyclophosphamide – 500 mg QW for 2 weeks Cycles 1–8	
		Dexamethasone – 20 mg four times per week for 2 weeks	

Footnotes: *To align with UK clinical practice, bortezomib doses are modelled to be given once weekly as advised in the November 2024 and May 2025 Advisory Boards.

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Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; BW: bi-weekly; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; QD: daily; QW: every week; Q2W: every 2 weeks; Q3W: every 3 weeks; Q4W: every 4 weeks; SmPC: summary of product characteristics.

Table 70: Summary of drug costs for DBLd, and all comparators

Intervention	Drug	Total dose per administration	Vial/unit size (mg)	Price per vial/pack (£)	Price per administration	RDI	Price per administration (RDI)	PAS Discount	Discounted price per administration	Source
DBLd	Daratumumab	1,800 mg	1,800.0	£4,320.00	£4,320.00	████	██████	■	██████	BNF 2025. Price per vial of Darzalex 1,800 mg/15 mL solution for injection.
	Bortezomib	2.38 mg	2.5	£97.54	£97.54	████	████	NA	NA	eMIT 2024. Price per vial of Velcade 2.5 mg powder for solution for injection.
	Lenalidomide	25.00 mg	25.0	£28.27	£1.35	████	████	NA	NA	eMIT 2024. Price per pack of 21 Revlimid 25 mg capsules.
	Dexamethasone	20.00 mg	2.0	£2.38	£0.48	████	████	NA	NA	eMIT 2024. Price per pack of 50 dexamethasone (generic) 2 mg tablets.
	Dexamethasone	40.00 mg	2.0	£2.38	£0.95	████	████	NA	NA	eMIT 2024. Price per pack of 50 dexamethasone (generic) 2 mg tablets.
DLd	Daratumumab	1,800 mg	1,800.0	£4,320.00	£4,320.00	████	██████	■	██████	BNF 2025. Price per vial of Darzalex 1,800 mg/15 mL solution for injection.
	Lenalidomide	25.00 mg	25.0	£28.27	£1.35	████	████	NA	NA	eMIT 2024. Price per pack of 50 dexamethasone (generic) 2 mg tablets
	Dexamethasone	40 mg	2.0	£2.38	£0.95	████	████	NA	NA	eMIT 2024. Price per pack of 50 dexamethasone (generic) 2 mg tablets.
Ld	Lenalidomide	25 mg	25.0	£28.27	£1.35	████	████	NA	NA	eMIT 2024. Price per pack of 50 dexamethasone (generic) 2 mg tablets

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	Dexamethasone	40 mg	2.0	£2.38	£0.95	■	■	NA	NA	eMIT 2024. Price per pack of 50 dexamethasone (generic) 2 mg tablets.
BMP	Bortezomib	2.38 mg	2.5	£97.54	£97.54	■	■	NA	NA	eMIT 2024. Price per vial of Velcade 2.5 mg powder for solution for injection.
	Melphalan	16.47 mg	2.0	£16.48	£5.43	■	■	NA	NA	BNF 2025. Price per pack of 25 melphalan (generic) 2 mg tablets
	Prednisolone	109.80 mg	25.0	£12.78	£1.00	■	■	NA	NA	eMIT 2024. Price per pack of 56 prednisolone (generic) 25 mg tablets
BCd	Bortezomib	2.38 mg	2.5	£97.54	£97.54	■	■	NA	NA	eMIT 2024. Price per vial of Velcade 2.5 mg powder for solution for injection.
	Cyclophosphamide	500.00 mg	50.0	£153.00	£15.30	NA	£15.30	NA	NA	BNF 2025. Price per pack of 100 cyclophosphamide (generic) 50 mg tablets
	Dexamethasone	20.00 mg	2.0	£2.38	£0.48	NA	£0.48	NA	NA	eMIT 2024. Price per pack of 50 dexamethasone (generic) 2 mg tablets.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; BNF: British National Formulary; DBLd; daratumumab, bortezomib, lenalidomide and dexamethasone; DLd; daratumumab, lenalidomide and dexamethasone; eMIT: electronic market information tool; Ld: lenalidomide and dexamethasone; NA: not applicable; PAS: Patient Access Scheme; PomDex: pomalidomide and dexamethasone; RDI: relative dose intensity.

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Subsequent therapies

Subsequent treatment methodology

In the model, which consists of two alive health states (PF and PD), the cost of subsequent therapies across each subsequent line of therapy (second-line, third-line and fourth-line) has been included as a single, per-cycle cost, based on a weighted average, which is applied in all cycles for patients in the PD health state. An advantage of applying a per-cycle cost compared to applying the cost as a single, lump-sum cost is that the impact of annual discounting of costs in the model and the impact of deaths on the number of patients receiving subsequent treatment is captured. Fourth-line treatments were included in the model, given the recent advancements in the 4th line treatment setting, where new, efficacious treatment options including teclistamab are now available.¹²⁹

In order to calculate this total cost per cycle for all subsequent treatments, firstly the total acquisition and administration costs for each subsequent treatment in each line of therapy were calculated, based on the relevant dosing regimens and ToT for each subsequent treatment. A weighted total subsequent acquisition and administration cost for each line of therapy was then calculated using the relevant treatment share estimates. Separately, a weighted average subsequent treatment duration for each line of therapy was calculated by multiplying the ToT for each subsequent treatment in each line of therapy by the relevant treatment share. A cost per cycle for each line of therapy was calculated by dividing the total weighted average subsequent acquisition and administration costs by the weighted average subsequent treatment duration for each line of therapy. A total cost per cycle for all subsequent treatments was calculated using the cost per cycle for each line of therapy and the relevant attrition rates for each subsequent line of therapy. This cost was then applied throughout the time horizon to all patients in the PD health state.

Subsequent treatment inputs

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 1st line and 2nd line (Table 71). For transitions between 2nd line and 3rd line, and between 3rd line and 4th, data from clinical trials were unavailable, so attrition rates were sourced from Yong *et al.* (2016)²⁵ with the same proportions applied irrespective of previous lines of treatment (Table 72). Since the proportion of patients at 3rd line and 4th line depends on the proportion at 2nd line, which varies by comparator, these proportions were converted into rates relative to the previous line (Table 73). The final proportions of patients with treatment at each line were then recalculated and are described in Table 74.

Based on the data from the CEPHEUS and MAIA trials, fewer patients who progress are modelled to receive subsequent treatment following DBLd compared with DLd. This can be explained by the significant PFS benefits associated with DBLd, compared with DLd, with a 45% reduction in the risk of disease progression or death (PFS HR: 0.55) (Section 2.10.2). This means, that on average, patients will be much older following disease progression on DBLd compared to DLd, and therefore less likely to receive further subsequent treatments.

The distribution of patients receiving treatment with each subsequent therapy in the 2nd line, 3rd line and 4th line treatment setting is presented in Table 75. The subsequent treatments for 2nd and 3rd line therapy were based on treatment share estimates provided by the clinical experts in

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attendance at the May 2025 UK Advisory Board.³ As part of the Advisory Board, clinical experts provided estimates for subsequent treatments should belantamab mafodotin with bortezomib (BeBd) and belantamab mafodotin with pomalidomide and dexamethasone (BePomd) receive a positive recommendation from NICE.³ As such, the treatment share estimates account for BeBd as a 2nd line treatment for MM, in light of the recent positive draft guidance from NICE.¹⁴⁷ The proportions of BePomd were reweighted to BeBd considering the negative draft guidance from NICE for BePomd.¹⁴⁸ Of note, in order to ensure subsequent treatment costs were reflective of the UK treatment pathway, where applicable, the clinical experts' estimated subsequent treatment distributions were re-weighted to remove subsequent treatments not routinely available in the UK as well as combinations of treatments which would be unlikely in clinical practice. During the May 2025 UK Advisory Board, clinical experts agreed that it would be reasonable to assume the same the subsequent treatment distributions for DBLd and DLd at 2nd and 3rd line. Fourth-line treatment distributions are modelled in line with those informing the recent NICE appraisal for teclistamab as a 4th line treatment option for RRMM.

Table 71: Proportion of patients with a subsequent treatment among patients with a PFS event by treatment at 1st line

	DBLd	DLd	Ld	BMP	BCd
PFS, n (%)	■ (100)	160 (100)	217 (100)	265 (100)	265 (100)
Progressive disease, n (%)	■ (■)	112 (70)	171 (79)	230 (87)	230 (87)
Progressive disease with subsequent treatment, n (%)	■	91 (81)	145 (85)	177 (77)	177 (77)
Death, n (%)	■	48 (30)	46 (21)	35 (13)	35 (13)
Source	CEPHEUS (ASCT-ineligible)	MAIA	MAIA	ALCYONE	Assumed equal to BMP

Abbreviations: BCd: bortezomib, cyclophosphamide, and dexamethasone; BMP: bortezomib, melphalan, and prednisone; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone DLd: daratumumab, lenalidomide, and dexamethasone; PFS: progression-free survival; Ld: lenalidomide and dexamethasone.

Table 72: Attrition rates described in Yong *et al.* (2016)

	Proportion with a treatment at each LoT (%)	Proportion with a treatment at each LoT, re-based to 100% (%)	Proportion with a treatment at each LoT, relative to the previous line (%)
1 st line	95%	100.00%	100%
2 nd line	61%	64.21%	64.21%
3 rd line	38%	40.00%	62.30%
4 th line	15%	15.79%	39.47%

Abbreviations: LoT: line of therapy.

Source: Yong *et al.* (2016)²⁵

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Table 73: Proportion of patients with treatment estimated from clinical trials and Yong et al. (2016) relative to the previous line of treatment

	DBLd	DLd	Ld	BMP	BCd	Source
1 st line	100%	100%	100.00%	100.00%	100.00%	Assumption
2 nd line		81.25%	84.80%	76.96%	76.96%	Clinical trials - progressive disease with subsequent treatment (Table 71)
3 rd line	62.30%	62.30%	62.30%	62.30%	62.30%	Yong et al. (2016) ²⁵
4 th line	39.47%	39.47%	39.47%	39.47%	39.47%	Yong et al. (2016) ²⁵

Abbreviations: BCd: bortezomib, cyclophosphamide, and dexamethasone; BMP: bortezomib, melphalan, and prednisone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone DLd: daratumumab, lenalidomide, and dexamethasone; Ld: lenalidomide and dexamethasone.

Table 74: Final proportion of patients with treatment applied in the cost-effectiveness model, relative to the 1st line of treatment

	DBLd	DLd	Ld	BMP	BCd	Source
1 st line	100.00%	100.00%	100.00%	100.00%	100.00%	Calculation
2 nd line		81.25%	84.80%	76.96%	76.96%	
3 rd line		50.61%	52.82%	47.94%	47.94%	
4 th line		19.98%	20.85%	18.92%	18.92%	

Abbreviations: BCd: bortezomib, cyclophosphamide, and dexamethasone; BMP: bortezomib, melphalan, and prednisone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone DLd: daratumumab, lenalidomide, and dexamethasone; Ld: lenalidomide and dexamethasone.

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Table 75: Distribution of patients to subsequent therapies (by line of therapy) – clinical expert estimates

Line:	2 nd line (%)						
Subsequent therapy:	Ld	Cd	DBd	B	CLd	SBd	BeBd
DBLd	0.00	9.38	0.00	0.00	0.00	3.13	87.50
DLd	0.00	9.38	0.00	0.00	0.00	3.13	87.50
Ld	■	■	■	■	■	■	■
BMP	10.81	2.70	48.65	2.70	35.14	0.00	0.00
BCd	10.53	0.00	52.63	7.89	28.95	0.00	0.00
Line:	3 rd line (%)						
Subsequent therapy:	Ld	PanoBd	ILd	SBd	Cyclo	CLd	-
DBLd	0.00	17.65	0.00	41.18	41.18	0.00	-
DLd	0.00	17.65	0.00	41.18	41.18	0.00	-
Ld	0.00	18.18	4.55	45.45	31.82	0.00	-
BMP	27.50	6.25	55.00	11.25	0.00	0.00	-
BCd	26.83	8.54	53.66	10.98	0.00	0.00	-
Line:	4 th line (%)						
Subsequent therapy:	PomDex	Teclistamab	-	-	-	-	-
All treatments	■	■	-	-	-	-	-

Abbreviations: B: bortezomib; BCd: bortezomib, cyclophosphamide and dexamethasone; BeBd: belantamab mafodotin with bortezomib; BMP: bortezomib, melphalan and prednisone; Cd: carfilzomib and dexamethasone; CLd: carfilzomib, lenalidomide and dexamethasone; Cyclo: cyclophosphamide; DBd: daratumumab, bortezomib and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ILd: ixazomib, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PanoBd: panobinostat, bortezomib and dexamethasone; PomDex: pomalidomide and dexamethasone; SBd: selinexor, bortezomib and dexamethasone; UK: United Kingdom.

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Concomitant medication

The cost of concomitant medications were included in the cost-effectiveness model. For patients receiving daratumumab, both pre-infusion medications (antipyretics and antihistamine) and post-infusion medications (oral corticosteroids) were included, as per the recommendations for daratumumab as part of a combination therapy. For patients receiving bortezomib, the cost of antiviral treatment for the prevention of herpes zoster reactivation was included in the model based on recommendations from the bortezomib SmPC.¹⁵

The total cost of concomitant medications was applied as a single cost in the first cycle of the model, along with the main treatment costs. Concomitant medications for treatments received at subsequent lines of therapy were not included in the model as a simplification. Concomitant medication costs were sourced from the BNF and the Monthly Index of Medical Specialities (MIMS) websites.

Table 76: Concomitant medication costs

Treatment	Dosing regimen	Unit size	Units per pack	Cost per pack	Cost per unit	Total cost per cycle	Source
Daratumumab concomitant medications							
Antipyretic: oral paracetamol pre-infusion	1,000 mg per administration of daratumumab	500 mg	100	£0.79	£0.01	£1.48	Dosing regimen: Darzalex SmPC Drug costs: Paracetamol: eMIT 2024; Price per pack of 100 500 mg oral tablets (generic) Diphenhydramine: MIMS 2021 Methylprednisone: BNF 2025; Price per pack of 30 Medrone 16 mg tablets.
Antihistamine: oral/IV diphenhydramine pre-infusion	50 mg per administration of daratumumab	25 mg	20	£3.16	£0.16		
Corticosteroid: oral methylprednisolone post infusion	20 mg per administration of daratumumab	16 mg	30	£17.17	£0.57		
Bortezomib concomitant medication							
Antiviral: aciclovir daily	400 mg QD	400 mg	56	£1.91	£0.03	£0.18 (DBLd arm) ^a £0.11 (BMP arm) ^a	Dosing regimen: Velcade SmPC ¹⁴³ Drug costs: eMIT 2024; Price per pack of 56 400 mg dispersible tablets (generic)

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						£0.18 (BCd arm) ^a	

Footnotes: ^a Total cost differs between treatment arms due to the different duration of induction and consolidation therapy in each model cohort

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; IV: intravenous; MIMS: Monthly Index of Medical Specialities; QD: daily; SmPC: Summary of Product Characteristics.

Administration costs

The cost of administration was included for both front-line treatment and subsequent therapies (Table 77). In line with the assumptions accepted in NICE TA917, for oral chemotherapy regimens, a one-off cost was applied on treatment initiation, whereas for therapies administered via SC injection (i.e. daratumumab), a cost was applied for each administration.⁵ The cost of a blood test prior to the first administration of daratumumab was also included in the cost of administration for DBLd and DLd, in line with the respective SmPCs.

Table 77: Administration costs

Drug	Parameter	Cost	Source
Subcutaneous drugs	All administrations	£115.36	National Schedule of NHS Costs 2023/24. Specialist nursing, cancer related, adult, face to face (N10AF)
	Blood test (prior to first administration, daratumumab only)	£2.98	National Schedule of NHS Costs 2023/24. DAPS05 - Haematology
Intravenous drugs	First administration	£554.23	National Schedule of NHS Costs 2023/24. SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance – Weighted average of Day case and Regular Day/Night admissions
	Subsequent administration	£250.77	National Schedule of NHS Costs 2023/24. SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle - Weighted average Outpatient Procedure costs across all services
Oral chemotherapies	First administration only	£247.13	National Schedule of NHS Costs 2023/24. Deliver exclusively oral chemotherapy, Outpatient (SB11Z)

Abbreviations: NHS: National Health Service.

3.5.2 Health-state unit costs and resource use

Monitoring costs

Ongoing monitoring costs were included in the model, with the frequency of monitoring visits and tests dependent on whether patients were receiving active anti-cancer therapy (Table 78), based on ToT. It was assumed that patients would receive ‘on-treatment’ monitoring for as long as a patient is on some form of active treatment (front-line or subsequent), with the ‘off-treatment’ monitoring costs applied when not on active treatment (e.g. pre-progression, but after discontinuing treatment). This is of most relevance to patients treated with BMP, as it has a fixed

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duration and therefore, patients spend longer periods in the 'off treatment' state before progressing.

The type and frequency of monitoring visits and tests were based on those used in prior NICE appraisals include NICE TA897, TA763 and SMC2302.^{52, 127, 149} The approach to modelling costs is fully aligned to the accepted approach in TA917.⁵

Table 78: Monitoring costs

Item	Frequency per cycle		Unit cost	Source
	On-treatment	Off-treatment		
Haematologist visit	0.92	0.32	£192.53	NHS Reference Costs 2023–24. WF01A: Clinical Haematology (303). Non-Admitted Face-to-Face Attendance, Follow-up
Full blood count	0.84	2.56	£2.98	NHS Reference Costs 2023–24. DAPS05: Haematology
Biochemistry	0.76	1.32	£1.53	NHS Reference Costs 2023–24. DAPS04: Clinical Biochemistry
Protein electrophoresis	0.52	0.72	£1.53	
Immunoglobulin	0.48	0.76	£1.53	
Urinary light chain excretion	0.20	0.20	£1.53	

Abbreviations: NHS: National Health Service.

End-of-life cost

A one-off cost representing the cost of terminal care was applied in the model for the proportion of patients that died in each cycle. The cost applied in the model (£13,409.00) was derived from the PSSRU (2024) hospital care and social care cost.

3.5.3 Adverse reaction unit costs and resource use

The cost of managing AEs experienced by patients receiving treatment was included in the model. The unit costs per event were based on NHS reference costs 2023–2024 and are presented in Table 79.

AE unit costs were applied to the proportion of patients experiencing each event in each of the treatment arms in the model and were applied in the first cycle of the model.

Table 79: AE costs

AE	Costs	Source	Details
Neutropenia	£2,058.10	NHS reference costs 2023/24	SA08G-H,J: Weighted Average of Non-Elective Long and Short Stays (Other Haematological or Splenic Disorders)
Lymphopenia	£2,058.10		SA08G-H,J: Weighted Average of Non-Elective Long and Short Stays (Other Haematological or Splenic Disorders)
Thrombocytopenia	£2,515.70		SA12G-H,J-K: Weighted Average of Non-Elective Long and Short Stays (Thrombocytopenia)
Leukopenia	£2,058.10		SA08G-H,J: Weighted Average of Non-Elective Long and Short Stays (Other Haematological or Splenic Disorders)
Anaemia	£1,544.30		SA04G-H,J-L: Weighted Average of Non-Elective Long and Short Stays (Iron Deficiency Anaemia)
Pneumonia	£2,655.47		DZ11K-N,P-V: Weighted Average of Non-Elective Long and Short Stays (Lobar, Atypical or Viral Pneumonia, with Multiple, Single and without Interventions)
Hypokalaemia	£1,982.36		KC05G-H,J-N: Weighted Average of Non-Elective Long and Short Stays (Fluid or Electrolyte Disorders, with & without Interventions)
Pulmonary embolism	£2,106.05		DZ09J-N,P-Q: Weighted Average of Non-Elective Long and Short Stays (Pulmonary Embolus with & without Interventions)
Hyperglycaemia	£1,840.73		KB01C-F & KB02G-H,J-K: Weighted Average of Non-Elective Long and Short Stays (Diabetes with Hypoglycaemic & Hyperglycaemic Disorders)
Diarrhoea	£1,938.73		FD01A-H,J: Weighted Average of Non-Elective Long and Short Stays (Gastrointestinal Infections with Multiple, Single and without Interventions)
Fatigue	£2,057.05		WH17A-C: Weighted Average of Non-Elective Long and Short Stays (Admission Related to Social Factors with and without Interventions)
Hypertension	£774.04		EB04Z: Weighted Average of Non-Elective Long and Short Stays (Hypertension)
Asthenia	£3,514.99		SA03G-H: Weighted Average of Non-Elective Long and Short Stays (Haemolytic Anaemia)
Acute kidney injury	£2,732.43		LA07H,J-N,P: Weighted Average of Non-Elective Long and Short Stays (Acute Kidney Injury with & without Interventions)
Chronic kidney disease	£3,714.60		LA08G-H,J-N,P: Weighted Average of Non-Elective Long and Short Stays (Chronic Kidney Disease with & without Interventions)

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Cataract	£1,579.66		BZ24D-G: Weighted Average of Non-Elective Long and Short Stays (Non-Surgical Ophthalmology with & without Interventions)

Abbreviations: AE: adverse event; NHS: National Health Service.

3.5.4 *Miscellaneous unit costs and resource use*

No additional costs were included in the cost utility analysis.

3.6 *Severity*

No severity modifier is applicable for this appraisal.

3.7 *Uncertainty*

Long-term uncertainty in survival estimates despite use of the latest DCO from the CEPHEUS trial

Long-term extrapolation of the PFS and OS data from the CEPHEUS trial were required, which is inevitably associated with uncertainty. Although data from the latest DCO (07 May 2024) with almost 5 years of follow-up were used, neither median PFS nor median OS were reached in the DBLd arm of CEPHEUS. This is a highly positive result after 5 years of follow up and means the treatment is working and consequently many patients have not progressed or died. It does, however, create some uncertainty when used for the purpose of modelling long term outcomes. Survival modelling uncertainty was mitigated by eliciting survival estimates from UK clinical experts as part of this appraisal, which, in line with NICE TSD 14, were incorporated to inform the modelled long-term extrapolations of survival for ASCT-ineligible patients with NDMM treated with DBLd or DLd (the main comparator). In addition, MRD is considered a Level 1 surrogate endpoint in MM with a wealth of evidence that demonstrates a strong correlation with long-term survival outcomes including progression-free and overall survival.¹³⁶ This provides confidence that the high level of MRD negativity will translate to the longer-term outcomes with further follow-up with the potential of the best responders achieving functional cure (as illustrated by the OS for DBLd patients who achieve MRD negativity tracking similar to the general population in Section 2.6.2). The consistent approach of selection of the DBLd and DLd base case extrapolations for OS and PFS was based on a rigorous process which applied an attenuation effect to ensure that long-term survival estimates were clinically plausible and in line with expert estimates while also maintaining the best statistical fit to the observed data. This approach has been accepted in prior appraisals in MM (TA1015),¹²⁹ and ensured that choice of the most suitable extrapolation considered external validity and clinical plausibility and is potentially conservative - considering the unattenuated curves predict higher survival (OS and PFS) than the clinical expert estimates, particularly for DBLd, and the high rates of MRD negativity achieved for DBLd vs DLd in the base-case ITC with the evidence suggesting there is a strong observed correlation between treatment effect on MRD negativity and treatment effect on long-term survival outcomes for ASCT-ineligible NDMM.³⁴⁻⁴⁰

No direct clinical data for DBLd versus the main comparator, DLd (or versus all other included comparators) are available

No trials were identified reporting on DBLd versus the relevant comparator, DLd in this population. Therefore, ITCs were required to generate comparative efficacy estimates for DBLd versus DLd (and all other comparators). In the base case economic analysis, comparative effectiveness was derived from the IPTW ITC. Whilst there may be potential for the uncertainties in the ITC to influence the economic model, the availability of IPD for both the CEPHEUS and MAIA trials (and ALCYONE trial for BMP) facilitated robust IPTW ITCs to be conducted and

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inform the economic model, representing a key strength of the economic analysis. It should also be noted that the ITC results were highly consistent across all sensitivity analyses considered, and slightly conservative compared to the NMA (see Section 2.10.5). Together, this provides strong evidence for the statistically significant and clinically meaningful benefits of DBLd versus DLd (and versus all comparators). Input from UK clinical experts at the May 2025 UK Advisory Board confirmed that DBLd is expected to result in a clear survival benefit over DLd in UK clinical practice.

COVID-19 disproportionately impacted CEPHEUS compared to MAIA (and ALCYONE)

As detailed extensively in Section 2.4.1, CEPHEUS was conducted at the height of the COVID-19 pandemic, with ███% of all deaths among patients treated with DBLd in CEPHEUS due to COVID-19. CEPHEUS was disproportionately impacted by COVID-19 compared to MAIA (and ALCYONE); in contrast, the MAIA trial was mostly conducted prior to the COVID-19 pandemic, with deaths across both arms only recorded towards the end of the trial follow-up. Additionally, patients in MAIA were much further into their treatment compared to patients in CEPHEUS who were early on in their treatment with DBLd. Clinical advisors suggested this may also be why COVID-19 disproportionately affected patients in CEPHEUS over MAIA, as discussed in Section 2.10.2. Therefore, to mitigate the bias that would arise from conducting naïve comparisons between CEPHEUS and MAIA (and ALCYONE), the data informing the survival estimates in the cost-effectiveness analysis of DBLd versus DLd (and all other comparators) were COVID-19 adjusted, in which all deaths due to COVID-19 were censored. While J&J consider the use of the COVID-19-adjusted data in the base case analyses appropriate, scenario analyses have been conducted to explore the use of the data unadjusted for COVID-19 on the cost-effectiveness results. Of note, the COVID-19-adjusted (base case) and COVID-19-unadjusted (scenario analysis) results are aligned, indicating that the COVID-19 adjustment has negligible impact on the overall cost-effectiveness of DBLd versus DLd, and therefore is a source of minimal uncertainty.

3.8 *Managed access proposal*

This submission does not include a proposal for managed access. Whilst there is the final OS data cut-off planned for the CEPHEUS trial, this is not expected to reduce inherent long-term modelling uncertainty when considering a lifetime model time horizon. This is due to the indication being in the first-line treatment setting where even final OS analyses is not expected to substantively reduce uncertainty around long term survival for newly diagnosed patients. Moreover, as detailed in Section 1.3.1, there is a wealth of evidence to demonstrate that MRD negativity is a powerful independent predictor of long-term survival in MM.³⁴⁻⁴⁰ Patients who achieve deep and durable responses as well as MRD negativity are anticipated to remain disease progression-free for longer, as confirmed by clinical experts at the May 2025 UK Advisory Board. Therefore, there is sufficient evidence on the basis of MRD negativity and robust ITCs versus UK relevant comparators, to demonstrate the long-term benefits of DBLd for ASCT-ineligible NDMM patients.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of the base case inputs for the primary comparison of DBLd versus DLd can be found in Table 80, below.

Table 80: Summary of variables applied in the economic model for the comparison between DBLd and DLd

Variable	Value		Reference to section
Model settings			
Discount rate (costs and benefits)	3.5%		Section 3.2.2, Table 53
Time horizon			
Patient baseline characteristics			
Mean age of patients (years)			Section 3.2.1, Table 52
Mean weight of patients (kg)			
Mean BSA of patients (m²)			
Male (%)			
Survival inputs	DBLd	DLd	
OS extrapolation	Attenuated exponential	Attenuated exponential	Section 3.3
PFS extrapolation	Attenuated exponential	Attenuated exponential	
TTD extrapolation	Gompertz	Weibull	
AEs	DBLd	DLd	
Neutropenia			Section 3.3.5, Table 66
Lymphopenia			
Thrombocytopenia			
Leukopenia			
Anaemia			
Pneumonia			
Hypokalaemia			
Pulmonary embolism			
Hyperglycaemia			
Diarrhoea			
Fatigue			
Hypertension			
Asthenia			
Acute kidney injury			
Chronic kidney disease			
Cataract			
AE disutilities	Disutility	Duration	
Neutropenia	-0.15	7	

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Lymphopenia	-0.07	16	Section 3.4.4, Table 67
Thrombocytopenia	-0.31	7	
Leukopenia	-0.07	15	
Anaemia	-0.31	180	
Pneumonia	-0.19	7	
Hypokalaemia	-0.07	11	
Pulmonary embolism	-0.31	7	
Hyperglycaemia	-0.15	15	
Diarrhoea	-0.10	12	
Fatigue	-0.12	15	
Hypertension	-0.15	11	
Asthenia	-0.12	15	
Acute kidney injury	-0.13	7	
Chronic kidney disease	-0.004	365	
Cataract	-0.01	28	
Resource use	On-treatment	Off-treatment	Section 3.5.2, Table 78
Haematologist visit	0.92	0.32	
Full blood count	0.84	2.56	
Biochemistry	0.76	1.32	
Protein electrophoresis	0.52	0.72	
Immunoglobulin	0.48	0.76	
Urinary light chain excretion	0.20	0.20	
Utility inputs			
Progression-free (Cycles 0-8)	■■■		Section 3.4.5, Table 68
Progression-free (Cycles 9+)	■■■		
Progressed disease	■■■		
Treatment costs	List price	Discounted price	Section 3.5.1, Table 70
Daratumumab SC, cost per vial (1,800 mg) – DBLd	£4,320.00	■■■■■	
Daratumumab SC, cost per vial (1,800 mg) – DLd	£4,320.00	■■■■■	
Bortezomib, cost per vial (2.5 mg)	£97.54	NA	
Lenalidomide, cost per pack	£28.27	NA	
Dexamethasone, cost per pack	£2.38	NA	
Subsequent treatments			
Proportion of progressed patients receiving subsequent treatment, relative to 1L treatment	DBLd	DLd	
2L	■■■	81.25%	
3L	■■■	50.61%	

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4L		19.98%	Section 3.5.1, Table 74
2L subsequent treatment proportions	DBLd	DLd	
Cd	9.38%	9.38%	Section 3.5.1 Table 75
SBd	3.13%	3.13%	
BeBd	87.50%	87.50%	
3L subsequent treatment proportions	DBLd	DLd	
PanoBd	17.65%	17.65%	Section 3.5.1 Table 75
SBd	41.18%	41.18%	
Cyclo	41.18%	41.18%	
4L subsequent treatment proportions	DBLd	DLd	
PomDex			Section 3.5.1, Table 75
Teclistamab			
Administration costs			
Subcutaneous administration (all administrations)	£115.36		Section 3.5.2, Table 77
Blood test (first daratumumab initiation)	£2.98		
First administration (IV)	£554.23		
Subsequent administration (IV)	£250.77		
Oral administration (first only)	£247.13		
Monitoring costs			
Haematologist visit	£192.53		Section 3.5.2, Table 78
Full blood count	£2.98		
Biochemistry	£1.53		
Protein electrophoresis	£1.53		
Immunoglobulin	£1.53		
Urinary light chain excretion	£1.53		
AE costs			
Neutropenia	£2,058.10		Section 3.5.3, Table 79
Lymphopenia	£2,058.10		
Thrombocytopenia	£2,515.70		
Leukopenia	£2,058.10		
Anaemia	£1,544.30		
Pneumonia	£2,655.47		
Hypokalaemia	£1,982.36		
Pulmonary embolism	£2,106.05		
Hyperglycaemia	£1,840.73		

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Diarrhoea	£1,938.73	
Fatigue	£2,057.05	
Hypertension	£774.04	
Asthenia	£3,514.99	
Acute kidney injury	£2,732.43	
Chronic kidney disease	£3,714.60	
Cataract	£1,579.66	
End of life costs		
End of life costs	£13,409.00	Section 3.5.2

Abbreviations: 2L: second-line; 3L; third-line; 4L; fourth-line; AE: adverse event; B: bortezomib; BeBd: belantamab mafodotin, bortezomib and dexamethasone; BSA: body surface area; Cyclo: cyclophosphamide; DBLd; daratumumab, bortezomib, lenalidomide and dexamethasone; DLd; daratumumab, lenalidomide and dexamethasone; IV: intravenous; OS: overall survival; PanoBd; panobinostat, bortezomib and dexamethasone; PFS: progression-free survival; PomDex: pomalidomide and dexamethasone; SBd: selinexor, bortezomib and dexamethasone; SC: subcutaneous; TTD: time to treatment discontinuation.

3.9.2 Assumptions

A summary of the assumptions utilised in the base case economic analysis can be found in Table 81.

Table 81: Summary of assumptions in the economic analysis

Parameter	Assumption	Justification
Survival inputs	In the base case analysis, survival inputs for DBLd and DLd are modelled using individually fitted curves to the ATE-weighted Kaplan-Meier data from the IPTW analyses.	The addition of bortezomib to DLd introduces an additional therapy with a distinct mechanism of action to the those present in the triplet therapy DLd. The DBLd combination therefore exhibits further synergistic effects through targeting multiple biological pathways and induces improvements in MRD-negativity rates and sustained MRD negativity rates compared to DLd. The independent extrapolation of the ATE-weighted Kaplan-Meier data from the ITCs between ASCT-ineligible population of the CEPHEUS and the MAIA trial population represents the most appropriate base case approach, and was confirmed to be the best approach by health economic experts at the May 2025 Advisory Board.
	In the base case analysis, OS and PFS for both DBLd and DLd are modelled using the best statistically fitting curves attenuated to clinical expert estimates.	Attenuating the curves to clinical expert estimates (from experts specialising in MM in England) ensures the clinical face validity of the base case survival curves, and places clinical plausibility as the central consideration of decision making for the choice of base case extrapolations. This approach was previously used and accepted in TA1015 to align extrapolations with clinically plausible estimates of long-term survival for teclistamab.¹²⁹ For a consistent approach across both endpoints and treatments, the extrapolation which provided the best statistical fit to the observed trial was used for both DBLd and DLd. Of note, considering the unattenuated curves predict higher survival (OS and PFS) than the clinical expert estimates, particularly for DBLd, the attenuation approach represents a conservative approach to addressing the decision problem- particularly considering the high rates of MRD negativity achieved for DBLd vs DLd in the base-case ITC, and the wealth of evidence that supports a correlation between MRD negativity and improved survival in patients with NDMM, demonstrated in Section 1.3.1, and, more recently, a meta-analysis establishing a correlation between a treatment effect on MRD negativity and a treatment effect on PFS/OS.
	In the base case analysis, TTD for both DBLd and DLd were modelled using unattenuated curves (Gompertz and Weibull for	The attenuation approach to modelling DBLd and DLd TTD was explored but this approach resulted in treatment duration estimates that were not clinically plausible, considering the large gap between PFS and TTD estimates (Figure 40 and Figure 43). Instead, exploration of the initial unattenuated extrapolations was considered to assess if any of the curves aligned with expert opinion.

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	DBLd and DLd, respectively).	For DBLd TTD, the Gompertz provided good statistical fit to the Kaplan-Meier data from CEPHEUS and broadly aligned to clinical experts' estimates and therefore using the Gompertz extrapolation without attenuation was considered the most appropriate approach to derive clinically plausible estimates of DBLd TTD. For DLd TTD, the Weibull provided good visual fit to the Kaplan-Meier data from MAIA, and broadly aligned to clinical experts' estimates. Additionally, the Weibull curve for DLd TTD resulted in a clinically plausible relationship between DLd TTD and DLd PFS and therefore using the Weibull extrapolation without attenuation was considered the most appropriate approach to derive clinically plausible estimates of DLd TTD.
Utility values	In the base case analysis, health state utility values were assumed to be treatment-independent.	As DBLd and DLd are both daratumumab-based regimens, with very similar treatment regimens with the exception of a short, fixed-duration period of bortezomib, it was deemed appropriate to assume equal utilities (i.e. treatment-independent utilities) for DBLd and DLd.
	In the base case analysis, health state utility values were assumed to be time-dependent in the progression-free health state.	As previously detailed in Section 2.6.4, HRQoL data was collected in the CEPHEUS trial using the EQ-5D-5L, the EORTC-QLQ-C30 and the QLQ-MY20 questionnaires. The PRO results showed that patients experienced improvements in HRQoL and physical functioning over time, as well as reductions in symptoms, including pain, fatigue and overall disease symptoms. As such, the use of time-dependent utility values in the PF health state was considered to represent the most appropriate approach to align with the PRO trends observed in the CEPHEUS trial. The use of time-dependent utilities in the base case analysis is aligned with the recent appraisal of teclistamab in RRMM, where clinical experts consulted noted that time-dependent utility values were most appropriate, given the observed initial decline in quality of life typically experienced by patients initiating treatment, which correlated with active disease.¹²⁹ Clinical experts confirmed that over the course of treatment, as their disease is controlled and symptoms are alleviated, quality of life tends to improve.¹²⁹ This approach also reflects the evolving composition of the overall patient cohorts over time – with patients who fail to respond to treatment progressing more rapidly, while those who remain in a PF health state for extended periods experiencing the deepest and most durable treatment responses. It also accounts for the reduced dosing schedule of daratumumab after the first eight cycles. In the absence of suitably granular data to allow the modelling of time-dependent utilities in the progressed disease health state, a single aggregate utility value was applied for the duration of the progressed disease health state.

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Bortezomib dosing	In the base case analysis, bortezomib as part of DBLd, BMP and BCd was assumed to be given once weekly.	In UK clinical practice, bortezomib is given once weekly, rather than the twice weekly dosing as per the SmPC. ^{16, 143} This was confirmed by clinical experts in both the November 2024 and more recent May 2025 UK Advisory Board. ^{3, 98} A scenario is provided where the bortezomib dosing is given twice weekly as per the SmPCs. ^{16, 143} This was applied to all bortezomib treatments in the front-line treatment setting (DBLd, BMP and BCd).

3.10 Base-case results

Results of the economic analysis of DBLd versus DLd (the main comparator in this submission) are presented in Section 3.10.1 below. Results from the economic analyses of DBLd versus all other comparators (Ld, BMP and BCd) are presented in Appendix O, given they are presented for completeness to align to the NICE final scope, but are not considered relevant comparators. As detailed in Section 1.1, the comparison of DBLd versus Ld is not relevant given patients currently treated with Ld would not be suitable for treatment with DBLd, and therefore DBLd is not anticipated (were it to receive a positive recommendation from NICE) to displace Ld. Bortezomib combination therapies are typically only used in a small proportion of patients with renal impairment and therefore, given their minimal usage in UK clinical practice, do not represent relevant comparators to DBLd in this indication.

3.10.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic cost-effectiveness results for DBLd versus DLd at list price and with the current [REDACTED] applied for daratumumab are presented in Table 82 and Table 83, respectively.

In the deterministic base case analysis at list price, DBLd was associated with [REDACTED] more QALYs and reduced total costs of [REDACTED] in comparison to DLd, resulting in DBLd dominating DLd in this population (Table 82). Incremental life years gained of 1.15 for DBLd are intuitive given the almost doubling of the MRD negativity rate per the base-case ITC (DBLd: 61.22% vs DLd: 34.16%), and with outcomes for these patients resembling general population as illustrated in Section 2.6.2. As discussed in Section 1.3.1, MRD negativity has been accepted by the FDA as a predictor for longer term outcomes including PFS and OS for ASCT-ineligible NDMM and can be considered Level 1 evidence (representing the highest possible strength of evidence as a surrogate endpoint). There is a wealth of evidence that supports a correlation between MRD negativity and improved survival in patients with NDMM, demonstrated in Section 1.3.1, and, more recently, a meta-analysis establishing a correlation between a treatment effect on MRD negativity and a treatment effect on PFS/OS. DBLd also dominated DLd in the deterministic analysis with the discounted prices for daratumumab (as detailed in Section 1.1) applied. Across both analyses (at list price and with discounted daratumumab prices applied), the NHB results at both the £20,000 and £30,000 WTP threshold are positive, indicating that DBLd represents a cost-effective use of NHS resources vs DLd in ASCT-ineligible NDMM patients.

Table 82: Deterministic base-case results (list price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	[REDACTED]	8.59	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
DLd	[REDACTED]	7.44	[REDACTED]	[REDACTED]	1.15	[REDACTED]	Dominant	[REDACTED]	[REDACTED]

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

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Table 83: Deterministic base-case results (discounted daratumumab price)

Intervention	Total Costs	Total LYs	Total QALYs	Inc. Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	■	8.59	■						
DLd	■	7.44	■	■	1.15	■	Dominant	■	■

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

There is an existing CAA in place for daratumumab with NHS England (NHSE). As such, for the analysis with discounted daratumumab prices, [REDACTED]

3.11 Exploring uncertainty

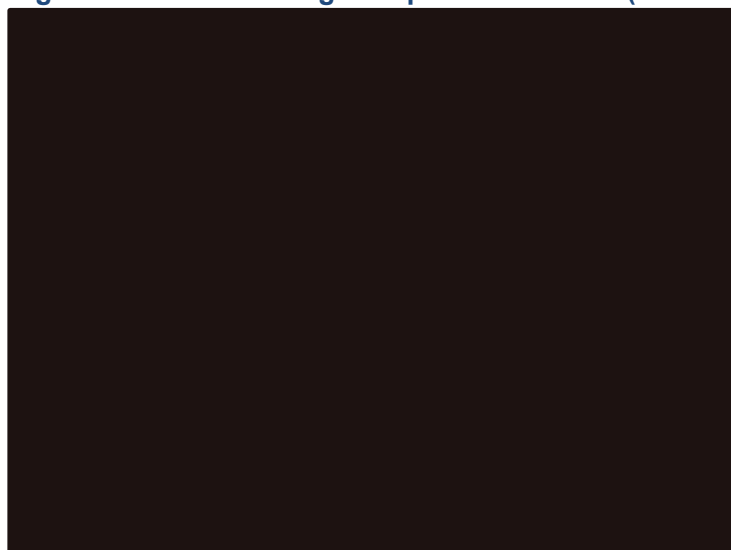
Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses, the results of which are presented in Sections 3.11.1 and 3.11.2, respectively. In addition, key assumptions in the model were explored in several scenario analyses, the results of which are presented in Section 3.11.3. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact of parameter uncertainty on the results of the cost-effectiveness model. The PSA was run for 1,000 iterations and in each iteration model inputs for all parameters were randomly drawn from specified distributions (e.g. gamma for costs; beta for proportions and lognormal for HRs). Where possible the SE or SD associated with the mean value was used to define the distribution, otherwise it was assumed that the standard error would be 10% of the mean value.

An ICER convergence plot for the PSA for the comparison of DBLd versus DLd is presented in Figure 45 below which demonstrates that the cumulative ICER stabilised after approximately 600 iterations.

Figure 45: ICER convergence plot for the PSA (DBLd versus DLd)



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

The base case probabilistic cost-effectiveness results for DBLd versus DLd at list price and with the discounted daratumumab prices are presented in Table 84 and Table 85, respectively.

In the probabilistic base case analysis (list prices), DBLd was associated with [REDACTED] more QALYs and reduced total costs of £[REDACTED] in comparison to DLd, meaning DBLd was dominant compared to DLd (Table 84). DBLd also dominated DLd in the probabilistic analysis with the discounted daratumumab prices applied. These results are broadly consistent with the discounted daratumumab price deterministic cost-effectiveness analysis presented in Section 3.10.1.

Table 84: Probabilistic base-case results – DBLd versus DLd (list price)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
DBLd	[REDACTED]	[REDACTED]			
DLd	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 85: Probabilistic base-case results – DBLd versus DLd (discounted daratumumab price)

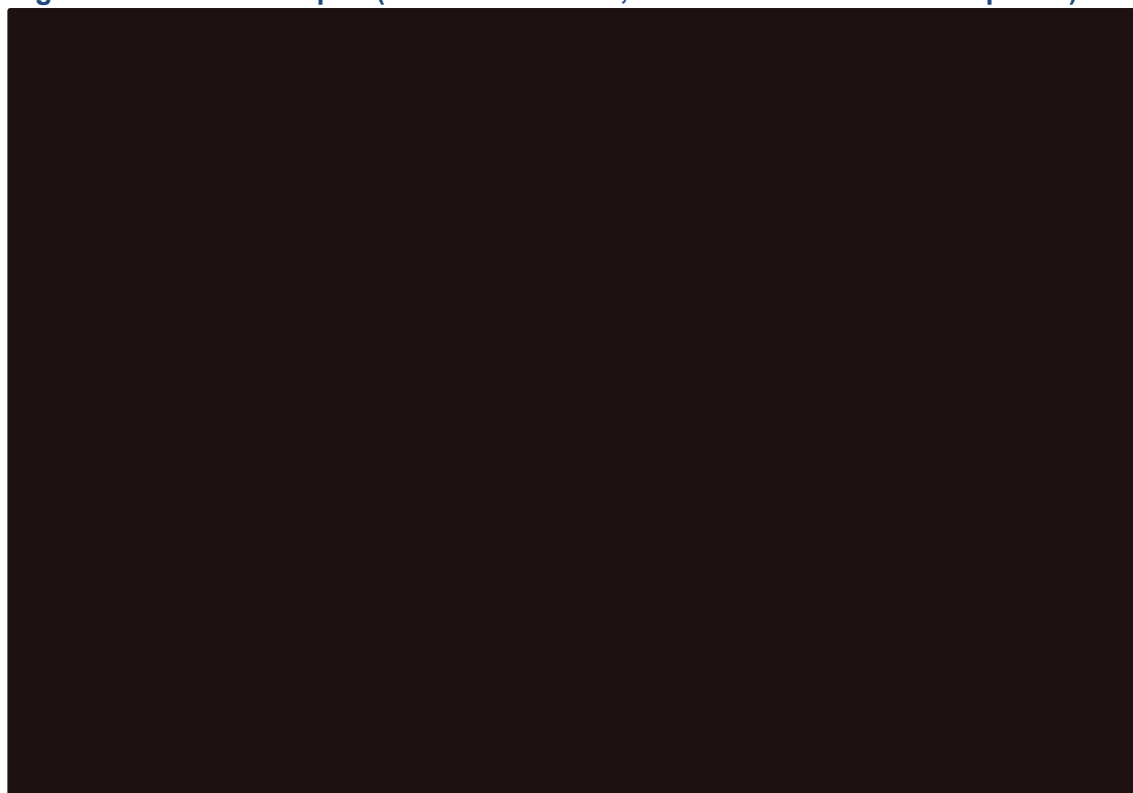
Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
DBLd	[REDACTED]	[REDACTED]			
DLd	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

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A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for DBLd versus DLd is presented in Figure 46, with a cost-effectiveness acceptability curve (CEAC) for DBLd versus DLd presented in Figure 47.

Figure 46: PSA scatter plot (DBLd versus DLd, discounted daratumumab prices)

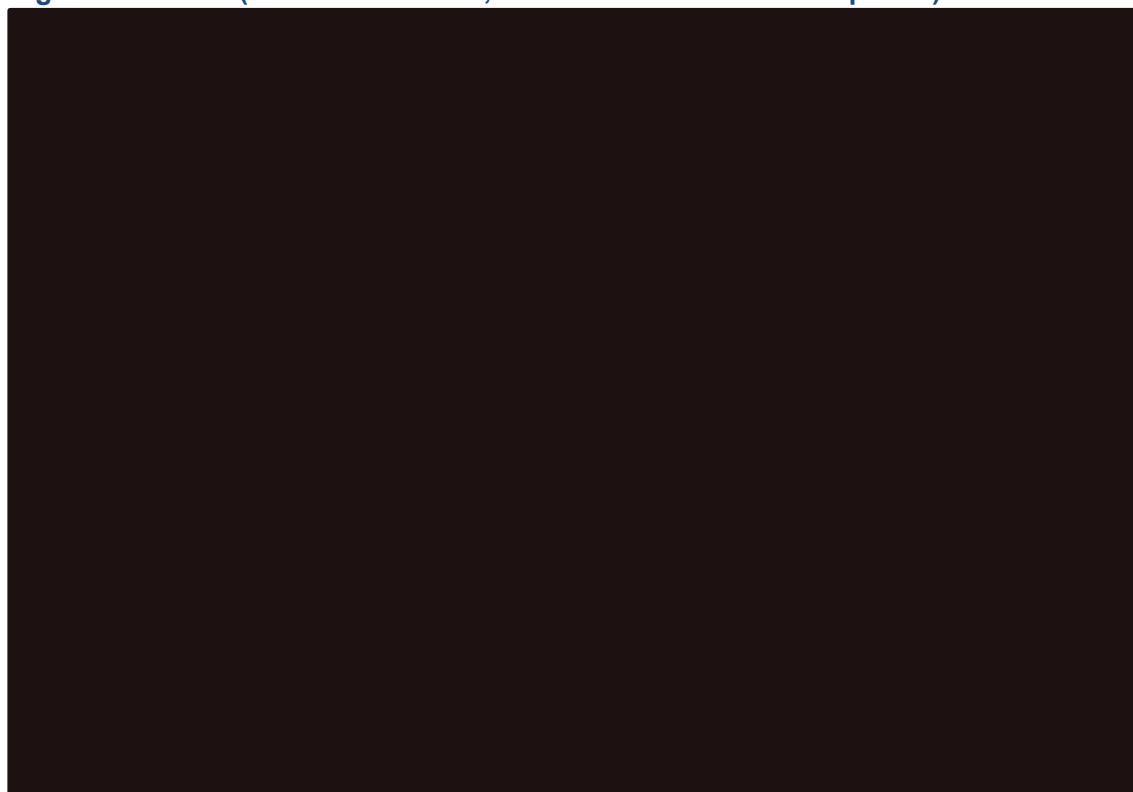


Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Figure 47: CEAC (DBLd versus DLd, discounted daratumumab prices)

Abbreviations: CEAC: cost-effectiveness acceptability curve; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; QALY: quality-adjusted life year; WTP: willingness to pay.

Figure 47: CEAC (DBLd versus DLd, discounted daratumumab prices)



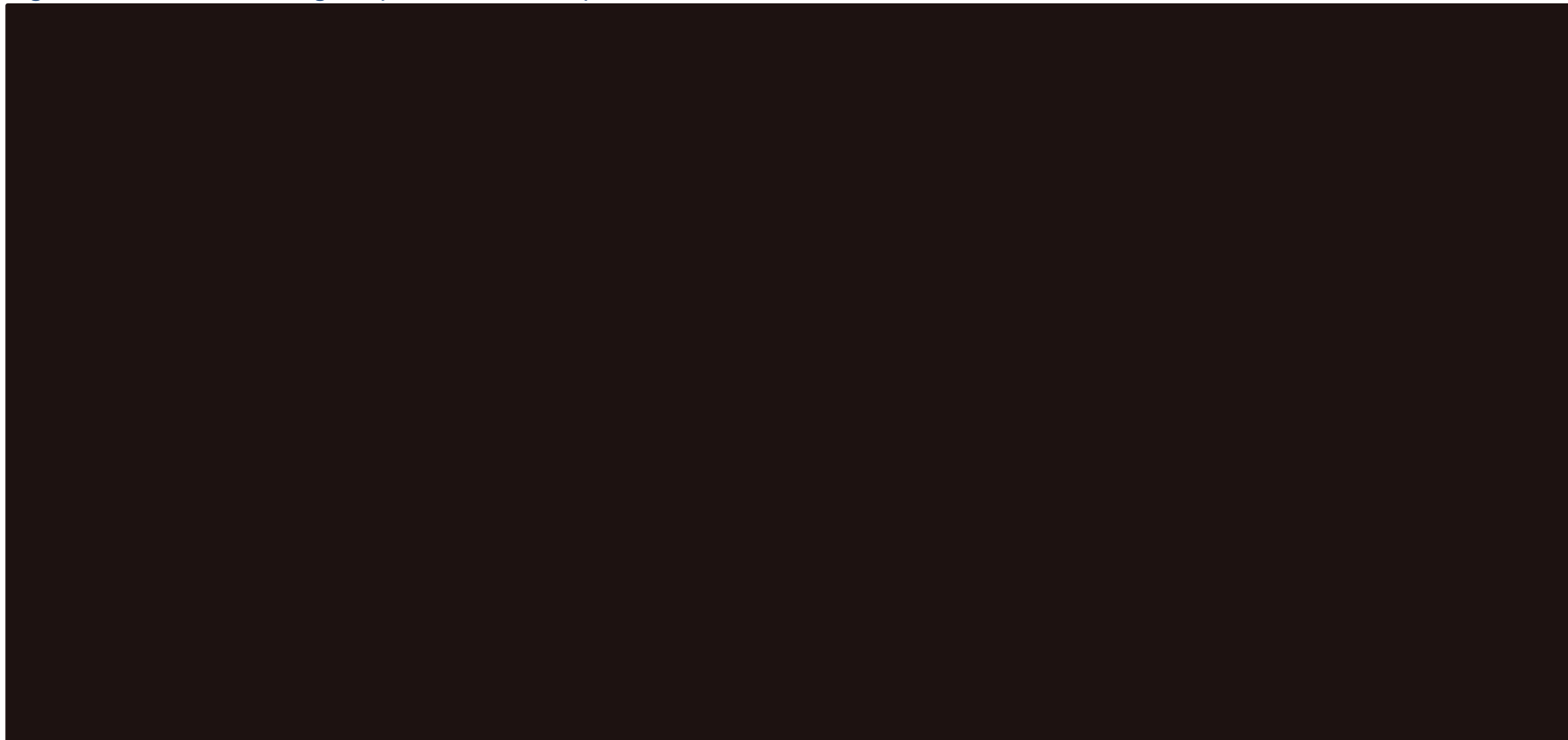
Abbreviations: CEAC: cost-effectiveness acceptability curve; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; QALY: quality-adjusted life year; WTP: willingness to pay.

3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, DSAs were conducted by varying the input for each parameter in the model, whilst keeping all other inputs the same. For certain parameters where SEs of the mean were available, the lower and upper limits were defined by the 95% CI around the mean. In the absence of 95% CI, the inputs were arbitrarily varied by $\pm 10\%$.

The tornado diagram showing the key drivers of the DSA in the base case economic analysis of DBLd versus DLd is presented in Figure 48. The largest model driver was average subsequent treatment acquisition costs per cycle. However, all subsequent treatments in the model are based on their list price; with the applicable PAS's applied, subsequent treatments are likely to be less of a driver than the below DSA depicts. The subsequent treatment distributions were based on feedback from UK clinical experts, providing confidence in the base case inputs.³ Other inputs were shown to have a minimal impact on the base case ICER.

Figure 48: DSA tornado diagram (DBLd versus DLd)



Abbreviations: AE: adverse event; BOR: bortezomib; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LEN: lenalidomide; QALY: quality-adjusted life year

3.11.3 Scenario analysis

For the comparison of DBLd versus DLd, a number of scenario analyses were explored in which model assumptions or parameters were altered to explore the impact of structural assumptions and alternative inputs on the results of the cost-effectiveness model. Details of and justifications for all scenario analyses conducted are provided in

Table 86. The results for all scenario analyses conducted in are presented in Table 87. In conclusion, the results of the scenario analyses demonstrate that the results of the base case analysis are robust to uncertainties in the model inputs and assumptions, with DBLd dominating DLd across all scenarios.

Table 86: Summary of scenario analyses (DBLd versus DLd)

Scenario	Description of scenario analysis	Rationale
1a: Utility source	Utility source: CEPHEUS (EQ-5D-3L cross-walked). Assumption of time-independence.	In the base case analysis, utilities for both DBLd and DLd were modelled as time-dependent to reflect that patient utility values improved with increasing time spent in the PF health state. This approach was accepted as part of TA1015, ¹²⁹ and reflects the evolving composition of the overall patient cohorts over time, with patients who fail to respond to treatment progressing more rapidly, while those who remain in a PF health state for extended periods experiencing the deepest and most durable treatment responses. It also accounts for the reduced dosing schedule of daratumumab after the first eight cycles.
1b: Utility source	Utility source: CEPHEUS (EQ-5D-3L cross-walked). Assumption of time-dependence across both PF and PD health states.	
1c: Utility source	Utility source: MAIA (EQ-5D-3L cross-walked).	However for completeness, scenario analyses were conducted to explore the impact of using time-dependent utilities versus time-independent utilities. One scenario analysis was conducted whereby both the PF and PD health states were modelled using time-independent utilities (with utilities sourced from CEPHEUS), although this is associated with limitations as it does not reflect the change associated with the reduced daratumumab dosing schedule and leads to an implausible small difference between the PF and PD utility. A second scenario analysis was conducted with the assumption of time-dependent utilities in both the PF and PD health states (with utilities sourced from CEPHEUS) although as discussed in Section 3.4.5. A third scenario was conducted using utilities derived from the MAIA trial given the MAIA trial provides an alternative source of utility data from patients with the target indication, and given these data were readily available to J&J.

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2: Bortezomib dosing	Bortezomib dosing: Twice weekly bortezomib dosing to align with the SmPC.	Although clinical experts have stated that bortezomib would be given once weekly in UK clinical practice, a scenario is considered where bortezomib is given twice weekly as per the SmPCs.
3: TTD	DBLd TTD: Attenuated exponential DLd TTD: Attenuated Gompertz	In the base case analysis, the Gompertz (unattenuated) and the Weibull (unattenuated) informed the long-term extrapolation of DBLd TTD data and DLd TTD data, respectively as detailed in Section 3.3.4. For completeness and to explore a fully consistent approach across all endpoints for DBLd (and across DBLd and DLd), a scenario is explored which applies the calibration approach to the DBLd TTD and the DLd TTD curves to align with the approach to the other endpoints. Specifically, in line with the other endpoints, the best statistical fitting curve for DBLd and DLd TTD was attenuated to align to clinical expert estimates at 10-, 15- and 20-years.
4: Discounting	Discounting: 1.5%	As per the NICE reference case, a scenario analysis using a discount rate of 1.5% has been conducted, given that DBLd is associated with long-term health benefits (see Section 2), and the prospect for functional cure. It is anticipated that the health benefits associated with DBLd will be sustained over the modelled time horizon for the best responders (■ years) and therefore it was considered appropriate to explore discounting costs and outcomes at a 1.5% rate. ¹²⁵
5: COVID-19	COVID-19: OS, PFS and TTD estimates for both DBLd and DLd informed by data from CEPHEUS and MAIA, respectively, unadjusted for the impact of COVID-19	As discussed in Section 2.4.1, the CEPHEUS trial was disproportionately impacted by the COVID-19 pandemic. Therefore to mitigate the bias that would arise from conducting naïve comparisons between CEPHEUS and MAIA, the base case (i.e., COVID-19 adjusted) IPTW analysis of DBLd versus DLd informs the base case cost-effectiveness analysis of DBLd versus DLd. This analysis censored all deaths due to COVID-19 (in both CEPHEUS and MAIA). However, it is acknowledged that the impact of the COVID-19 pandemic is an inherent source of uncertainty and therefore scenario analyses have been conducted to explore the use of the data unadjusted for COVID-19 on the cost-effectiveness results.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; RDI: relative dose intensity; TTD: time to treatment discontinuation.

Table 87: Summary of scenario analysis results – DBLd versus DLd (probabilistic; discounted daratumumab prices)

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)

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Base case		████	██	Dominant
1a	Utility source: CEPHEUS (EQ-5D-3L cross-walked). Assumption of time-independence.	████	██	Dominant
1b	Utility source: CEPHEUS (EQ-5D-3L cross-walked). Assumption of time-dependence across both PF and PD health states	████	██	Dominant
1c	Utility source: MAIA (EQ-5D-3L cross-walked)	████	██	Dominant
2	Bortezomib dosing: Twice weekly bortezomib dosing to align with the SmPC.	████	██	Dominant
3	DBLd TTD: Attenuated exponential DLd TTD: Attenuated Gompertz	████	██	Dominant
4	Discounting: 1.5%	████	██	Dominant
5	COVID-19: OS, PFS and TTD estimates for both DBLd and DLd informed by data from CEPHEUS and MAIA, respectively, unadjusted for the impact of COVID-19	████	██	Dominant

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost effectiveness ratio; INHB: incremental net health benefit; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; QALY: quality-adjusted life year; RDI: relative dose intensity.

3.12 Subgroup analysis

No cost-effectiveness analyses were conducted in subgroups.

3.13 Benefits not captured in the QALY calculation

Reduced discrepancies between ASCT-ineligible and ASCT-eligible patients

In the younger, newly diagnosed, ASCT-eligible patient population, patients have the opportunity to receive effective quadruplet treatments, often resulting in prolonged remission, and the consequent potential for improved prognosis.^{52, 150} In contrast, newly diagnosed patients who are classified as ineligible for ASCT currently do not have access to quadruplet therapies and so only 32.1% of patients receiving the SoC for this population (DLd) achieve MRD negativity which is considerably below the rates achieved in the ASCT-eligible population.⁵

The introduction of DBLd into the ASCT-ineligible treatment setting has the potential to bridge the gap in outcomes between ASCT-eligible and ASCT-ineligible patients, given 60.4% of ASCT-ineligible patients achieve MRD negative status on treatment with DBLd, which is much more closely aligned to the proportion of patients achieving MRD negativity in the ASCT-eligible setting.^{52, 150}

Value of hope associated with new treatment achieving deep and durable responses

As detailed extensively in Section 2.6.1, DBLd would offer patients a new, effective treatment option that induces deep and durable responses, with 60.4% of ASCT-ineligible patients treated with DBLd achieving MRD negativity. Given that MRD negativity is highly prognostic of long-term outcomes in MM, long-term disease control and ultimately, functional cure, is emerging as a distinct possibility among patients who experience deep and durable responses over a prolonged period of time. The value of hope for effective therapy, offering prolonged remission and a good quality of life cannot be fully captured in the economic model; the psychological impact of the possibility of functional cure on both patients and caregivers can also not be captured in the QALY calculation.

Value of additional treatment choice

As well as representing an efficacious treatment alternative for ASCT-ineligible NDMM patients, DBLd will provide additional hope to patients by providing them with the treatment choice they currently desire. Providing patients with choice and allowing clinicians to tailor treatment to patients' individual needs is a fundamental aspect of NHS care and service, and is extremely important in giving patients an increased sense of control over their disease.^{151, 152} Patients' increased hope and reductions in anxiety resulting from the availability of DBLd as an additional treatment choice are not captured in the QALY calculation.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

Face validity

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Model validations were performed in alignment with best practices.¹⁵³ At the May 2025 UK Advisory Board, the model structure, source data and statistical analysis design were reviewed by external experts, including health economic and UK clinical experts in MM.³

Internal validity

Quality-control procedures for verification of input data and coding were performed by health economists not involved in the model development and in accordance with a pre-specified test plan. These procedures included verification of all input data with original sources and programming validation. Any discrepancies were discussed, and the model input data was updated where required. Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code.

External validity

Clinical feedback was also used to validate key inputs and assumptions utilised in the model, including subsequent treatment choices. Where possible, UK sources were used for model inputs and similar inputs and approaches to those used in prior appraisals, namely TA917 [DLd], were adopted.⁵

3.15 Interpretation and conclusions of economic evidence

MM is an orphan disease for which there is currently no cure. MM becomes progressively harder to treat at each subsequent relapse, with each additional line of therapy associated with lower rates of response, and increased rates of toxicities and comorbidities. Despite significant advances in the treatment pathway of MM, the current SoC DLd is associated with low rates of MRD negativity – at a position in the treatment pathway where patients have the best chance of experiencing an enduring response. There therefore remains a high unmet need for new effective treatments which can drive deeper and more durable levels of response, in turn prolonging remission and OS, and introducing the prospect of functional cure for the best responders.

The CEPHEUS trial demonstrated the efficacy of DBLd in a population of ASCT-ineligible NDMM who clinical experts confirmed were generalisable to UK clinical practice.^{3, 101} IPTW ITC analyses of DBLd versus DLd subsequently confirmed the clinical superiority of DBLd over DLd in the target indication. Patients receiving DBLd were more than three times more likely to achieve $\geq$ CR and MRD negativity compared to DLd ($\geq$ CR OR: 3.58 [95% CI: 2.21, 5.79]; MRD-negativity OR: 3.04 [95% CI: 2.01, 4.61]). These deep responses observed with DBLd resulted in clinically meaningful and statistically significant improvements in PFS and OS in the base case ITC analyses. This is expected given the wealth of evidence that supports a correlation between MRD negativity and improved survival in patients with NDMM and, more recently, a meta-analysis establishing a correlation between a treatment effect on MRD negativity and a treatment effect on PFS/OS. Indeed, this evidence supported MRD negativity being recently accepted as an accelerated approval endpoint of new treatments for MM by the FDA.³⁴⁻⁴⁰ Specifically, the base case ITCs demonstrated that DBLd was associated with a HR of 0.55 for OS and a HR of 0.63 for PFS; these findings translate to a remarkable 45% reduction in risk of death and a 37% reduction in the risk of progression compared to DLd. For patients who achieve MRD negativity with DBLd, they have the opportunity of functional cure, with OS tracking similar to the general population as illustrated in Section 2.6.2. These compelling efficacy results were reflected in the

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base case deterministic economic analysis, where DBLd was associated with a substantially increased 1.15 LYG and ■■■ QALYs versus DLd. These results underscore the potential for DBLd to improve both the quality and duration of life for ASCT-ineligible patients. The increase in LYs from the model of 1.15 years for DBLd are expected, considering the almost doubling of MRD negativity rate in the base-case ITC with DBLd compared to DLd (DBLd: 61.22% vs DLd: 34.16%). The modelled LYs may also be considered conservative considering all PFS and OS curves have been calibrated to align to the clinical estimates, resulting in lower PFS and OS estimates versus the unattenuated curves, particularly for DBLd, as the OS for DBLd MRD negative patients shows survival tracks close to the general population.

In the base case probabilistic and deterministic analyses, these clinical results translated to DBLd representing a cost-effective treatment option compared to DLd. At both list price and with the discounted prices for daratumumab applied, DBLd was associated with more QALYs and decreased total costs in comparison to DLd (in both the deterministic and probabilistic analyses), resulting in DBLd dominating DLd in ASCT-ineligible NDMM patients. Thus, DBLd can be considered a cost-effective use of NHS resources in patients with ASCT-ineligible NDMM.

Of note, these economic results omit important benefits that cannot be captured in the QALY, including the value of hope and real option value, which both mean that the base case results may represent a conservative estimate of the true cost-effectiveness of DBLd in UK clinical practice. The positive effect that treatment with DBLd could have on informal carers in terms of reduced anxiety/depression and the ability to return to work is also not captured in the economic analysis. Similarly, the psychological impact of achieving sustained remission, in terms of the sense of hope that patients and carers may experience in place of the fear of relapse, is not intrinsically captured as part of the QALY framework.

Scenario analyses conducted to address sources of uncertainty in the model additionally demonstrated that variations in the ICER were minimal across most analyses, including scenario analyses of using COVID-19-unadjusted data from CEPHEUS and MAIA.

Strengths

The economic analysis presented in this submission is robust, makes best use of available data, and captures the treatment effect of DBLd versus relevant comparators, particularly the key comparator in this setting, DLd. The cost-effectiveness of DBLd as a treatment for adult patients with NDMM who are ineligible for ASCT was assessed via cost-effectiveness analysis from the perspective of the NHS in England, and across most inputs, was aligned to previous appraisals in this indication.

Although there was no direct data comparing DBLd to DLd, the unique situation of having patient level data from both the CEPHEUS and MAIA clinical trials allowed a robust ITC to be performed, which was validated as being the appropriate approach by health economic experts in the May 2025 Advisory Board.

A robust clinical validation exercise was conducted by J&J with UK clinical and health economic experts in order to validate key inputs and assumptions, including subsequent treatment options as well as elicit plausible long-term survival estimates.³ Furthermore, the selection of the most suitable extrapolation to estimate long-term survival for both DBLd and DLd was grounded in clinical plausibility. The economic model adopts a calibration approach which was previously

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accepted as part of TA1015,¹²⁹ whereby a consistent approach of the statistically best fitting PFS and OS curves for DBLd and DLd are subsequently attenuated over time to directly align with long-term estimates of survival provided by the clinical experts at the May 2025 UK Advisory Board.³ This approach ensured consistency across the endpoints and intervention and comparator and that survival estimates included in the model were associated with long-term clinical plausibility and conservative compared to the unattenuated extrapolations (specifically for DBLd where OS for MRD negative patients tracks close to GPM and there is the potential for functional cure for the best responders). For estimates of DBLd and DLd treatment duration, where the calibration approach was not considered necessary to derive clinically plausible TTD estimates, extrapolations were selected based on clinical plausibility and statistical fit in consideration of the relationship between PFS and TTD as per the NICE reference case.¹²⁵ The model also aligns to other aspects of the NICE reference case, including adopting an NHS and PSS perspective, utilising a lifetime time horizon to ensure all costs and QALY gains associated with the interventions are fully captured, and discounting costs and benefits at a rate of 3.5% per annum.¹²⁵ The results of the economic analysis are therefore considered highly relevant to decision-making on the introduction of DBLd into NHS clinical practice.

Limitations

A limitation of the evidence base was the lack of direct data comparing DBLd and DLd. To address this limitation, an IPTW ATE-weighted analysis was conducted to obtain a relative efficacy estimate for DBLd versus DLd (as detailed Section 2.10.2). The ITC was conducted in line with the best practices outlined in NICE TSD17 and additionally, was validated by UK health economic experts who stated that the methodology was highly robust, owing to the comparison being trial-versus-trial and additionally because the IPD was available for both trials.³ Any uncertainty surrounding the base case results were explored in multiple sensitivity analyses which found the base case cost-effectiveness conclusions to be robust to uncertainty surrounding key model inputs and assumptions (as presented in Section 3.11.3).

Due to the median follow-up of CEPHEUS and MAIA being shorter than the lifetime model time horizon, long-term extrapolations of OS, PFS and TTD data were required which are commonly associated with uncertainty. However, extrapolation of OS, PFS and TTD data for DBLd and DLd was performed using IPD from the CEPHEUS and MAIA trials respectively, which represent the highest grade of evidence available for assessing the effects of DBLd and DLd. Additionally, as detailed above, the calibration approach leveraged for the long-term survival estimates of DBLd and DLd ensured clinical plausibility at the centre of decision-making, which is a key strength of this cost-effectiveness analysis. The uncertainty around long term estimates is also reduced considering the high levels of MRD negativity achieved with DBLd compared to DLd in the base-case ITC. There is a wealth of evidence that supports a correlation between MRD negativity and improved survival in patients with NDMM, demonstrated in Section 1.3.1, and, more recently, a meta-analysis establishing a correlation between a treatment effect on MRD negativity and a treatment effect on PFS/OS.³⁴⁻⁴⁰ The high levels of MRD negativity and sustained MRD negativity across 1, 2 and 3 years for patients treated with DBLd in CEPHEUS also support the long term sustained treatment benefit.

Conclusion

Overall, a positive recommendation from NICE for DBLd in this patient population would address the current unmet need for a new, safe and cost-effective quadruplet combination therapy which

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can provide deeper, more sustained responses, ultimately leading to improvements in patient HRQoL and prolonging survival. The introduction of DBLd in this indication would increase the likelihood of achieving MRD negativity by more than three times compared to the current SoC DLd, and the prospect of achieving a functional cure for the best responders.

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Company evidence submission template for daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Available at: <https://www.scottishmedicines.org.uk/medicines-advice/daratumumab-darzalex-full-smc2302/> [Last accessed: 05/04/22].

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Appendices

The appendices have been provided in a separate document alongside this submission.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID3843]

Summary of Information for Patients (SIP)

July 2025

File name	Version	Contains confidential information	Date
ID3843_Janssen_Daratumumab_SIP_FINAL	Final	No	16 th July 2025

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):

Generic name: Daratumumab
Brand name: Darzalex®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Daratumumab in combination with bortezomib, lenalidomide and dexamethasone (DBLd, commonly also referred to as DVRd) for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible to receive a stem cell transplant.

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:

Daratumumab (Darzalex®) 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 marketing authorisation was received in April 2025. Marketing authorisation in the UK via the Medicines and Healthcare products Regulatory Agency (MHRA) is expected Q3 2025.¹

Further information is available on the European Medicines Agency (EMA) website:
<https://www.ema.europa.eu/en/medicines/human/EPAR/darzalex>

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:

Johnson & Johnson (J&J) provided the following support to relevant patient groups in the UK in the last 12 months.

As a member of the Association of the British Pharmaceutical Industry, J&J is required to publish information about relationships with patient organisations, annually, known as transfer of value as presented in **Table 1**. Any contributions or fees shall be used exclusively as per the letter of request from the patient organisation or as outlined in the contracted service agreement, and do not obligate

the patient organisation to purchase, use, recommend or arrange for the use of any product of J&J or any of its affiliates.

Table 1: Summary of support provided by J&J to relevant patient groups

Patient group	Engagement/activity	Reason for engagement/activity	Financial support provided
Anthony Nolan	J&J provided Anthony Nolan with a grant of £19,000 to support the implementation of a Cell Therapies Nurse Specialist – Year 2	Grant requested by patient organisation	£19,000
Blood Cancer UK	J&J covered travel costs of £371.50 for Blood Cancer UK's involvement in a J&J Haematology study day	Patient organisation attending J&J event to demonstrate resources available to HCP's and their patients	£371.50
Blood Cancer UK	J&J provided Blood Cancer UK with a grant of £45,910 towards the cost of delivering their National Blood Cancer Action Plan –Year 2	Grant requested by patient organisation	£45,910
Cancer 52	J&J provided sponsorship of £20,000 to Cancer 52 towards their activities to improve the lives of patients with less common cancers through their policy and campaigns work	Grant requested by patient organisation	£20,000
Leukaemia Care	J&J provided Leukaemia Care with a grant of £5000 to support the delivery of their core services including a helpline, support groups and hospital hubs	Grant requested by patient organisation	£5,000
Leukaemia UK	Johnson & Johnson provided Leukaemia UK with a grant of £9,500 to support the development of a report on the analysis of Leukaemia diagnosis, treatment, and economic impact	Grant requested by patient organisation	£9,500
Myeloma UK	J&J provided Myeloma UK with a grant of £19,400 to support the delivery of their core services including costs towards their Myeloma Info line, Ask the Nurse service, patient materials and information days	Grant requested by patient organisation	£19,400
Myeloma UK	J&J covered travel costs of £166.42 for Myeloma UK's involvement in an Access and Reimbursement Policy Roundtable meeting	Invited to attend and contribute due to their expertise in this area	£166.42
Myeloma UK	J&J provided sponsorship of £13,990 to Myeloma UK by paying the entry fee for ten of its' employees to participate in the annual fundraising Ride Myeloma 2024 event	Sponsorship fee to participate in fundraising event	£13,990
Specialised Health Care Alliance	J&J provided the Specialised Healthcare Alliance funding of £14,500, which was paid directly to an agency who provided secretariat support for the Specialised Healthcare Alliance, focused on policies and structures relating to NHS specialised services – 2024 programme of work	Sponsorship requested by patient group	£14,500
Specialised Health Care Alliance	J&J provided the Specialised Healthcare Alliance a corporate sponsorship fee of £14,500 towards 2025 work programme, which includes campaigns on policies aligned to NHS specialised services. Fee paid to agency providing secretariat support	Sponsorship requested by patient group	£14,500

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.

Description of the condition

Multiple myeloma (MM) is a rare and incurable cancer of plasma cells, a type of white blood cell found in the bone marrow. These plasma cells are important because they create antibodies that help the body fight infections. Cancerous plasma cells produce abnormal proteins called M proteins.²

The main health issues related to myeloma happen when these abnormal plasma cells accumulate in the bone marrow. Over time, this can cause problems including a weakened immune system, kidney damage and bone diseases.² People with MM often feel very tired, have bone pain, weakness, weight loss, frequent infections, confusion, trouble moving around and excessive thirst.^{3, 4}

These symptoms, along with other complications like nerve damage and side effects from treatments, can make life feel significantly harder for patients compared to others who are healthy. The term “multiple myeloma” is used because the disease can affect various parts of the body such as the spine, skull, pelvis and ribs.^{2, 5, 6}

Multiple myeloma is characterised as a relapsing-remitting cancer that distinguishes it from various other types of cancer. The term ‘relapsing-remitting’ indicates that there are intervals when the myeloma is active, resulting in complications that require treatment.²

Number of patients affected

Multiple myeloma is the 19th most common cancer in the UK, and mainly affects people above 65 years old; but younger individuals can also get it.⁷⁻⁹ As the majority of patients in the UK with MM are diagnosed at a later stage of life, they may not be fit enough to receive high dose treatment followed by autologous stem cell transplant (ASCT).¹⁰ As a result, ASCT-ineligible patients account for approximately two-thirds of all newly diagnosed multiple myeloma (NDMM) patients in England.¹¹

Between 2017 and 2019, about 6,200 new cases of myeloma annually were reported in the UK which makes nearly 2% of all new cancer cases. Looking ahead, forecasts suggest that by 2038 to 2040, there could be around 8,300 new cases of MM each year in the UK.⁹ Of note, MM occurs 1.5 times more often in men than in women.¹²⁻¹⁴

Life expectancy

In England and Wales, about 55.5% of adults who are newly diagnosed with MM are expected to live for 5 years after their diagnosis and only 29% are expected to survive for 10 years.¹⁵ These survival rates can vary from one patient to another because of several factors. Some of these factors are related to the individual, like their age, or other health conditions they may have and whether they are eligible for a stem cell transplant. Other factors are specific to the cancer itself, such as how advanced it is, how aggressive it is, and how well it responds to therapy.

Once patients stop responding to current treatment (this is called a relapse), their life expectancy tends to be shorter.^{16, 17}

Impact of multiple myeloma on patients' quality of life

Being diagnosed with MM significantly impacts both patients and their carers. Research shows that patients with MM report experiencing worse symptoms and a lower quality of life compared to those with other blood cancers like lymphoma or leukaemia.¹⁸

Patients with MM face a heavy burden of health issues, often dealing with ongoing or repeated infections, tiredness and severe bone pain.^{18, 19} About 25% of these patients also experience unexplained weight loss, and many have kidney problems. More than two thirds suffer from anaemia which is a common issue related to their disease.²⁰

In 2021, an online survey showed that 80% of people with MM felt their mental health had been negatively impacted by their diagnosis, with 30% saying the impact was very severe.^{21, 22} Additionally, 37% of patients expressed worries about their future health, 34% often thought about their disease, and 21% were afraid of dying.²¹ In the UK, 27.4% of MM patients showed signs of anxiety, and 25.2% had symptoms of depression.²³

Impact of multiple myeloma on elderly patients

In the UK, most people diagnosed with MM are over the age of 65.¹⁵ These patients are especially at risk of experiencing side effects from their treatments, which often leads them to choose to stop receiving treatment. Hence, it is important that newly diagnosed patients receive the best possible treatments as early as possible in the treatment pathway. This approach helps to extend the time they remain in remission, and improves the quality of life for both patients and their carers. This is particularly important for older patients, who may not survive long enough to benefit from treatments later down the treatment pathway.²⁴

Impact of multiple myeloma on caregivers

Caring for someone with MM can be very challenging, often causing a negative impact on carers well-being. Caregivers may have to perform complicated tasks like changing dressings, caring for intravenous line care and giving injections. They also help patients everyday activities, accompany them to medical appointments, and manage complex information.²⁵

Most care is provided by family members rather than professional carers, which can lead to increased stress and anxiety for those family members, affecting their health.²⁵ A Myeloma UK study found that 94% of carers felt emotionally impacted, with uncertainty being a major concern. Nearly 84% of caregivers said they always put the patient's needs over their own and 25% of working carers had to stop working or retire early due to their caregiving responsibilities. Carers also reported feeling a loss of control over their lives, changes in household roles, lifestyle changes, and missing important life events.^{25, 26}

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?

Diagnosis of multiple myeloma

MM is a complex cancer, and its diagnosis can involve several different types of tests. It may include the following:²⁷⁻²⁹

- Imaging tests: such as X-rays, computerised tomography scan (CT scan), magnetic resonance imaging (MRI), or positron emission tomography (PET) scans. These tests look for bone damage or find tumour cells in the bone marrow
- Blood tests: to check 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 in urine that may indicate MM
- Bone marrow biopsy: this test involves taking a small sample of bone marrow (usually from the hip bone or another large bone) to look for cancer cells. Unlike the other tests, this is a more invasive procedure

After diagnosis, many of these tests are also used to monitor and track the disease getting worse (disease progression) and response to treatment.

Monoclonal antibodies work by helping the immune system kill cancer cells. As a monoclonal antibody drug, daratumumab requires a blood test before the first injection to check if the treatment is likely to work.

Impact of a multiple myeloma diagnosis on patients

Being diagnosed with MM can make patients feel overwhelmed, fearful and frustrated. For patients with MM in the UK, the average time it takes from the first symptom to receiving a diagnosis is reported to be 163 days, one of the longest for any cancer.^{21, 30} In addition, an estimated 25% of patients wait for more than a year before getting the right diagnoses, and 31% are diagnosed via an emergency route.²¹ Patients who are diagnosed later on in life tend to have a much worse quality of life compared to those who are diagnosed early. About 49% of those with delayed diagnoses experience significant issues, whilst only 30% of those diagnosed on time report the same level of impact.²¹ These patients who receive a late diagnoses are more likely to experience a severe impact on their mobility, ability to socialise, exercise and

work, impacting their finances and mental health.²¹ It is therefore crucial that patients are diagnosed and treated with effective treatments as early as possible in the treatment pathway.

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.

The goal of MM treatment is to stop the disease getting worse, increase survival and to maintain patients' quality of life. All patients with MM will eventually relapse and many patients do not make it to a subsequent line of therapy.³¹ Therefore, it is crucial to receive the most effective treatment as early as possible in the treatment pathway to optimise depth and durability of response which are expected to translate to an improvement in long-term survival outcomes.

As per recommendations made by the National Institute for Health and Care Excellence (NICE), patients who are not eligible for stem cell transplant are able to receive treatments such as daratumumab with lenalidomide and dexamethasone³², lenalidomide plus dexamethasone³³ or bortezomib-based therapies.³⁴

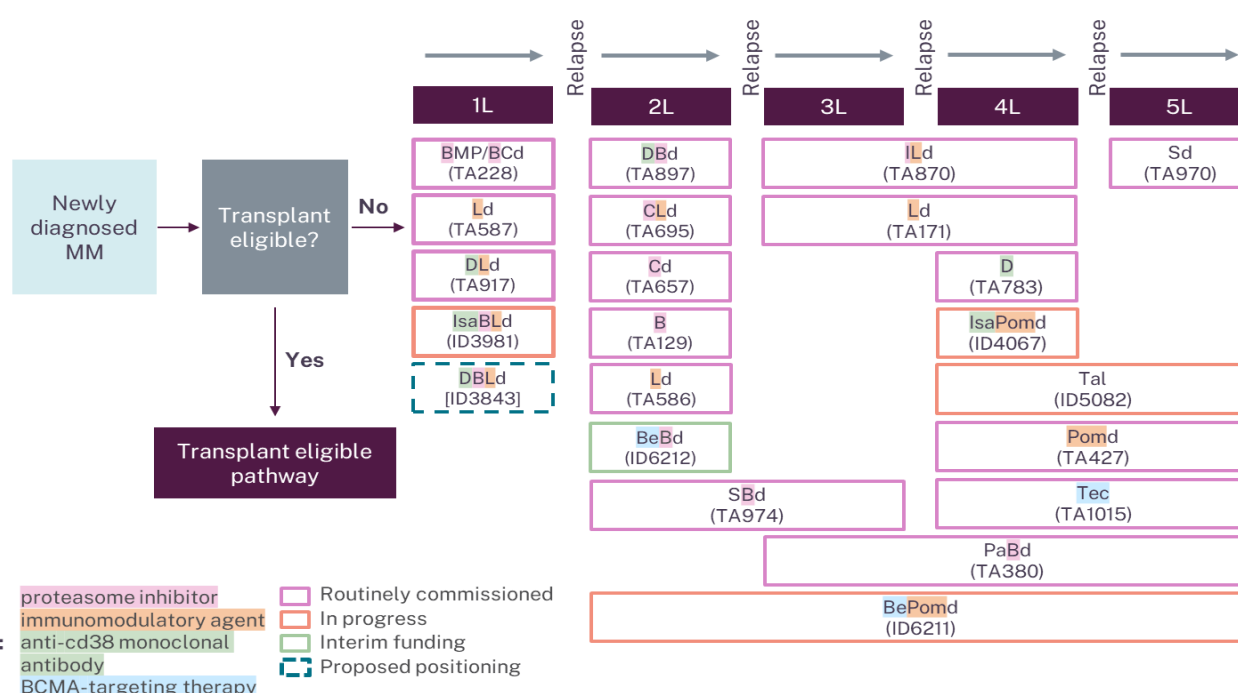
Current treatment pathway

The comparators in the final scope for this appraisal are:³⁵

- Daratumumab, lenalidomide and dexamethasone (DLd, commonly also referred to as DRd)
- Lenalidomide and dexamethasone (Ld, commonly also referred to as Rd)
- Bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone)

The current clinical pathway of the care for patients with NDM in the UK, along with the proposed positioning of DBLd, is provided in Figure 1

Figure 1: Current treatment pathway for MM in the UK including proposed positioning of DBLd



Abbreviations: BCp: bortezomib, cyclophosphamide and prednisolone/prednisone; BeBd: Belantamab mafodotin, bortezomib and dexamethasone; BePd: belantamab mafodotin, pomalidomide and dexamethasone; BelBd: belantamab mafodotin bortezomib and dexamethasone; BMP: bortezomib, melphalan and prednisolone/prednisone; Cd: carfilzomib and dexamethasone; CLd: carfilzomib, lenalidomide and dexamethasone; Dara: daratumumab; DBd: daratumumab, bortezomib and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ILd: ixazomib, lenalidomide and dexamethasone; Elran: elranatamab; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; Len: lenalidomide; PaBd: panobinostat, bortezomib and dexamethasone; Pd: pomalidomide and dexamethasone; SBd: selinexor, bortezomib and dexamethasone; Sd: selinexor and dexamethasone; Tal: talquetamab; Tec: teclistamab

Current standard of care

Daratumumab in combination with lenalidomide and dexamethasone (DLd):

For patients who have just been diagnosed with MM and are not eligible for a transplant, the standard treatment is called DLd. According to clinical experts in a recent advisory board, this treatment is given to over 80% of patients.

Other treatments

Lenalidomide with dexamethasone (Ld)

Ld is given to a small number of patients who either cannot tolerate a combination of three therapies or prefer taking oral treatments (often because it is difficult for them to travel to the hospital). Clinical experts estimated that this group makes up about 12% of patients.

However, patients who can't tolerate the three-drug combination (i.e. DLd) or prefer an oral treatment would not qualify or be suitable for a quadruplet (four drugs) treatment called DBLd. This means that DBLd isn't a relevant option for these particular patients.

Bortezomib combination treatments (BMP/BCd)

For some patients who have kidney problems, a treatment combining bortezomib with melphalan and prednisone (called BMP) or bortezomib with cyclophosphamide and dexamethasone (called BCd) may be used. Clinical experts noted that these bortezomib combination treatments are given to only a small proportion of patients, around 5%. This means that these treatments are not considered one of the main comparators to DBLd.

The use of daratumumab is contraindicated for patients who have a history of severe hypersensitivity reactions to daratumumab itself or any of its formulation component.

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.

Impact of multiple myeloma symptoms on quality of life

The symptoms of MM have a significant impact on patient's quality of life. There have been several studies aiming to understand patient preferences, and most valued treatment benefits.

One recent study included 300 MM patients across France, Germany and the UK suggested that patients with newly diagnosed MM placed the highest value on reducing symptoms such as pain and tiredness, as well as wanting to live longer.³⁶ Within this study, patients from the UK particularly valued reducing the level of pain from extreme pain to no pain. The study also found that a patient's current health condition affects what they want.³⁶

Key findings from European studies on treatment valuation

Another recent European study looking at patients with newly diagnosed multiple myeloma suggested that:³⁷

- 87% of patients said that living longer was the most important feature they looked for in treatment
- 80% valued treatments that showed clear improvements in their condition
- A further 80% of patients valued a treatment that would reduce their symptoms of tiredness
- 94% of patients expressed concern about cognitive impairment as a side-effect of treatment, meaning patients may struggle with their memory, attention or speech, affecting their everyday lives

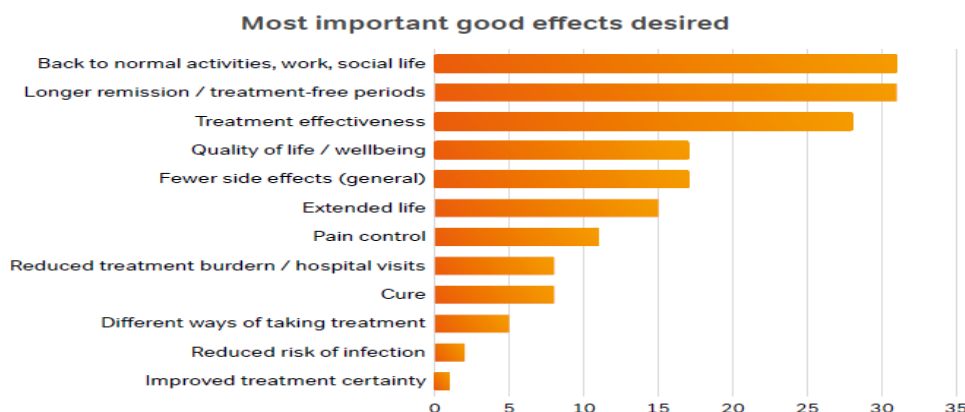
NICE survey insights on patient considerations

A survey carried out by NICE in collaboration with Myeloma UK, suggested that patients with myeloma prioritise several important factors in their treatment and recovery. The main concerns for these patients include (see Figure 2 below):

- Returning to normal activities: they want to get back to their everyday life, work and social interactions
- Longer periods without treatment: patients also value having longer times without needing treatment

The survey highlighted the significant burden of symptoms associated with myeloma. Patients reported that fatigue and tiredness; other symptoms and side effects; difficulties with mobility and daily activities as well as pain and discomfort greatly affect their quality of life.³⁸

Figure 2: Treatment effects most desired by MM patients



Source: Myeloma UK (2019).³⁸

Comparative burden of multiple myeloma on quality of life

A study that looked at how blood cancers affect patient's daily lives found that those with multiple myeloma face a greater burden compared to patients with other blood cancers like lymphoma and leukemia.

In this study, patients filled out a questionnaire called the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30), which helps assess the quality of life for cancer patients. The results showed that multiple myeloma patients experience worse symptoms that affect their physical, emotional and social well-being compared to those with other types of blood cancer.³⁹

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

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.

Daratumumab is a type of treatment known as a monoclonal antibody. It is a specially created immune cell that targets specific proteins on the surface of cells. Daratumumab attaches to a protein called CD38, which is often found on the surface of MM cells. The presence of CD38 can indicate that a cell is not working properly, often producing harmful proteins that cause MM. By binding to CD38, daratumumab helps the body's immune system recognise and attack the harmful MM cells, helping their destruction.²⁷⁻²⁹

In the UK, healthcare professionals are experienced in treating patients with daratumumab due to its widespread use across a number of different indications. In this treatment, daratumumab is given in combination with other medications: bortezomib, lenalidomide and dexamethasone (DBLd). This combination therapy uses multiple drugs that target different pathways in the body, making it an effective and well-tolerated option for treating multiple myeloma. The benefits of this combination treatment include higher rates of response, longer periods before the disease worsens, and better survival rates compared to current standard treatments.⁴⁰⁻⁴⁶

Innovation in patient care

DBLd offers patients who are not eligible for a transplant the chance to receive a novel treatment that combines four different drugs, known as quadruplet therapy. This helps to close the treatment gap between these patients and those who are eligible for a transplant.

Using a combination of multiple drugs that work in different ways is an important strategy in multiple myeloma treatment. Specifically, the four drugs included in DBLd - daratumumab (which targets a specific protein – anti-CD38), bortezomib (a proteasome inhibitor), lenalidomide (an immunomodulatory agent) and dexamethasone (a steroid) – work together to improve patient outcomes, described further in Section 3b.

This combination not only aims to enhance the effectiveness of treatment but also does so while maintaining a safety profile that is manageable for patients compared to current standard treatments.

The summary of product characteristics for the treatment is currently not available. This is because it is pending approval from the Medicines and Healthcare products Regulatory Agency (MHRA).

A patient information leaflet for daratumumab can be found here:

<https://www.medicines.org.uk/emc/files/pil.11488.pdf?view=pil>

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.

Yes, DBLd is meant to be used along with other medicines. Below is a breakdown of each of the drugs involved:

Daratumumab:

As described in Section 3a, daratumumab is a special type of treatment known as a monoclonal antibody. It is designed to target cancer cells directly.²⁷

Bortezomib

Bortezomib helps kill cancer cells in a couple of ways. It acts as a proteasome inhibitor, which means it encourages cancer cells to die by increasing proteins that trigger this process and blocking other proteins that help cancer cells survive.⁴⁷

Lenalidomide

Lenalidomide is a targeted therapy drug that prevents tumours from forming new blood vessels (this process is called angiogenesis). Without blood vessels, cancer cells can't grow and spread.⁴⁸

Dexamethasone

Dexamethasone is a steroid, which helps control the immune response by reducing inflammation and lowering blood pressure, and is commonly used alongside cancer drugs.⁴⁷

By putting these four drugs – daratumumab, bortezomib, lenalidomide and dexamethasone – together, DBLd can more effectively target and destroy harmful cancer cells. This combination allows for a stronger overall treatment without adding serious side effects that might come from each drug individually.⁴⁹

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?

DBLd is given to patients until MM gets worse or the treatment is no longer tolerable. Patients are given daratumumab as an injection by a trained healthcare professional in a hospital. Below is the DBLd dosing schedule. Cycles 1-8 are 21 day cycles with cycle 9 and beyond moving to a 28 day cycle length.⁴⁴

Table 2: Daratumumab dosing schedule in combination with bortezomib, lenalidomide, and dexamethasone

Daratumumab (Injection); • Dosage: 1800mg • Schedule: ○ Cycles 1-2: injected once a week ○ Cycles 3-8: injected every 3 weeks ○ Cycles 9 and beyond: injected every 4 weeks	Bortezomib (injection) • Dosage: 1.3mg/m² (this means the amount depends on the patient's body size) • Schedule: ○ Cycles 1-8: injected twice a week on days 1, 4, 8, and 11, and then stopped
Lenalidomide (tablet) • Dosage: 25mg (1 tablet) • Schedule: ○ Cycles 1-8: taken daily from days 1 through 14 ○ Cycles 9 and beyond: taken daily from days 1 through 21	Dexamethasone (tablet or injection) • Dosage for Cycles 1-8: 20 mg • Dosage for Cycles 9 and beyond: 40 mg • Schedule: ○ Cycles 1-8: Taken on days 1, 2, 4, 5, 8, 9, 11, 12 ▪ If the patient is 75 years or older or underweight, it is given on days 1, 4, 8 and 11 instead ○ Cycles 9 and beyond: Taken on days 1, 8, 15 and 22 ▪ For patients 75 years or older or underweight they receive 20 mg weekly instead during a 28 day cycle • Special Note: On the days when daratumumab is injected, the dexamethasone 20 mg dose can be given either orally or through an IV before the daratumumab injection, replacing the usual oral dexamethasone for that day

Differences in administration vs current SoC and impact on patients and caregivers

Caregivers may need to help patients get to and from the hospital for their daratumumab treatments. The first 8 cycles of DBLd require more trips to the hospital compared to the current standard of care, DLd. This is because of the addition of the fixed duration bortezomib. However, from cycle 9 onwards (about 5 and a half months into treatment), the number of hospital visits for DBLd decreases and it becomes once every 4 weeks. This schedule is the same as what is required for the current standard treatment, DLd.

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.

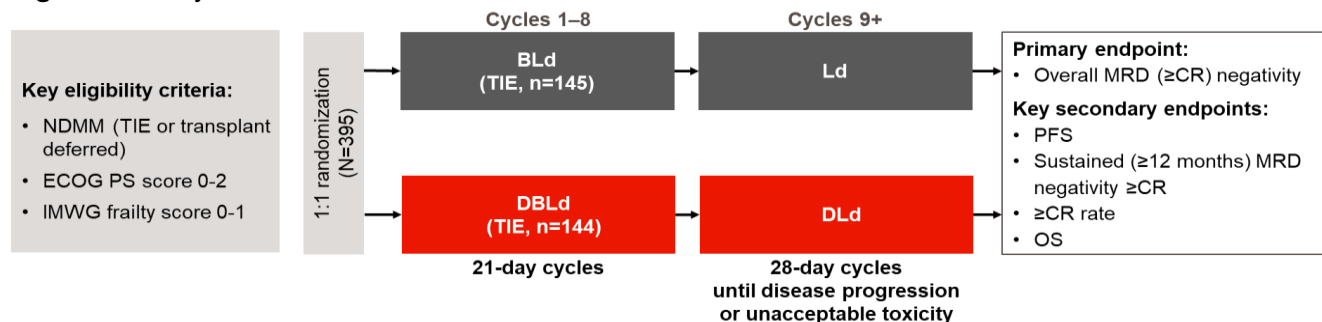
CEPHEUS

The CEPHEUS clinical trial looked at how well daratumumab works and its safety when combined with bortezomib, lenalidomide and dexamethasone (called DBLd) compared to just using bortezomib, lenalidomide and dexamethasone (called BLd) (clinical trial number: NCT03652064). This ongoing international Phase 3 involves patients from various regions, including Europe, North America, Asia, South America and included 14 sites in the UK. ⁴⁴

The CEPHEUS trial includes a broader group than the decision problem specified in the NICE scope, as it also included patients who were eligible for, but have refused transplant (transplant deferred). The group that deferred a transplant isn't typically recognised UK clinical practice. Therefore, the NICE submission focuses mainly on the patients who are not eligible for a transplant, in line with standard treatment approaches in the UK. ⁴⁴

To participate in the trial, patients needed to be aged 18 or older, newly diagnosed MM, have an Eastern Cooperative Oncology Group performance score of 0-2 (indicating their health status), and either be ineligible for a stem cell transplant or have chosen to delay it. One important restriction was that patients could not be over the age of 80. Further details can be found on the clinical trial website (link: <https://clinicaltrials.gov/study/NCT03652064>). ⁴⁴

Figure 3: Study schematic of the CEPHEUS trial



Abbreviations: CR, complete response; DLd, daratumumab, lenalidomide, and dexamethasone; DBLd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; Ld, lenalidomide and dexamethasone; TIE, transplant ineligible; BLd, bortezomib, lenalidomide, and dexamethasone

The main goal of the study was to see how many patients achieved a state called minimal residual disease (MRD) negativity. MRD measures if a patient has any remaining (or residual) multiple myeloma cancer cells in the bone marrow during or after treatment. Participants were MRD negative if no multiple myeloma cells were detected in a sample of 100,000 healthy cells. Achieving MRD negativity is associated with better treatment outcomes.

Other important objectives of the trial included:

- Measuring the of time without disease progression: observing how long patients lived without their multiple myeloma worsening (called PFS) ⁴⁴
- Overall survival (OS) rates: tracking how long patients lived overall during the trial ⁴⁴
- Overall response rate: finding out what percentage of patients showed at least some improvement in their condition during or after treatment ⁴⁴
- Sustained MRD negativity rate: checking how many patients maintained an MRD negative status (no traceable disease) at different timepoints i.e. participant has no sign of MM cells at two back-to-back (at least 12 months apart), with no positive MRD result (presence of multiple myeloma) in between ⁴⁴

Other daratumumab trials:

There were two other trials that investigated daratumumab in patients who are newly diagnosed and not eligible for a transplant.

- MAIA trial: This trial compared the treatment combination of DLd versus Ld. ⁴³ DLd is the current standard treatment used for these patients as described in Section 2b.
- ALCYONE trial: This trial examined the combination of daratumumab with bortezomib, melphalan and prednisone (referred to as DBMP) compared to the combination of bortezomib, melphalan and

prednisone alone (BMP).⁵⁰ However, DBMP is not funded or available for use in the UK for this group of patients.

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.

Efficacy vs. UK Standard of Care

An indirect treatment comparison (ITC) is a statistical approach, used to compare treatments that have not been directly compared in a clinical trial. Results for the indirect treatment comparison of DBLd versus the UK relevant standard of care (DLd) have been explored by making use of data from the CEPHEUS and MAIA trials. After statistical adjustment to enhance the comparability of the data from the studies and for the impact of COVID-19, results show that treatment with DBLd leads to a statistically significant improvement in the MRD-negative complete response or better rate (MRD-negative CR) compared to DLd with an odds ratio of 3.04 [95% CI: 2.01, 4.61]. This indicates patients treated with DBLd are over three times more likely to achieve an MRD-negative CR compared to patients treated with DLd.⁵¹

Deep responses measured by MRD are of paramount importance to patients given the association between MRD-negativity and improved survival outcomes for MM patients.⁵²⁻⁵⁸ Indeed, results from the ITC (that account for the impact of COVID-19) indicate a statistically significant improvement in PFS with a 45% reduction in the risk of disease progression or death [HR=0.55; 95% CI (0.38, 0.79)], as well as statistically significantly improved OS represented by a 37% reduction in the risk of death [HR=0.63; 95% CI (0.41, 0.98)] compared to DLd.⁵¹

Analysis results not adjusting for COVID-19 were broadly in line with this, and supported a numerical trend towards OS improvement [HR=0.80; 95% CI (0.53, 1.19)].⁵¹ Please refer to Section 2 of Company Submission for further details of the ITC versus DLd.

Data from the CEPHEUS study presented below are the latest available published data (07 May 2024 data cut-off) and this is presented in Section 2 of the Company Submission.⁴⁴ No other studies of DBLd in this indication are ongoing. The data presented below is for the transplant ineligible population, comparing versus BLd (trial comparator).

Efficacy demonstrated in clinical trial

Reduction in residual disease

MRD negativity is a significant measure it demonstrates the effectiveness of the treatment and can provide insights into the likelihood of a patient's long-term survival with MM. In the CEPHEUS trial, researchers found that DBLd led to nearly two and a half times more patients achieving an MRD negative status (10^{-5}) compared to those treated BLd [odds ratio [OR], 2.37; 95% CI, 1.47–3.80; $P<0.0001$). Similar results were observed for sustained MRD negativity, at least 12 months apart (OR, 2.28 (95% CI, 1.40–3.72); $P=0.0010$). More information regarding MRD negativity is provided in Section 2 of the Company Submission^{44, 59, 60}

Progression Free Survival

After an average of 58.7 months of median follow-up, the results of the CEPHEUS study showed that DBLd increased the time without their disease worsening compared to BLd. There was a 49% reduction (HR, 0.51; 95% CI, 0.35–0.74; $P=0.0003$) in the risk of disease progression or death for patients who were treated with the DBLd compared to BLd with the median PFS in the BLd arm being reached at 49.6 months but still not yet being reached in the DBLd arm (meaning patients are staying progression free for longer).^{59, 60}

Overall survival

Overall survival favoured DBLd compared to BLd with a 34% reduction in the risk of death (HR:0.66; 95% CI, 0.42–1.03). When censoring for COVID-19 (considering the pandemic negatively impacted DBLd over

BLd due to the timing of the trial), the reduction in the risk of death improved to a 45% reduction in the risk of death with DBLd vs BLd (COVID-19, HR: 0.55; 95% CI, 0.34–0.90).^{59, 60}

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.

Adding daratumumab to bortezomib, lenalidomide and dexamethasone indicated an improvement to the quality of life for patients with multiple myeloma.

Patient reported outcomes were measured as part of the CEPHEUS trial to gather information on any symptoms experienced by patients, their physical and emotional wellbeing and the impact of their disease on social interactions.⁴⁴

Results from the EORTC Quality of Life Questionnaire Core-30 Item (a cancer-specific questionnaire with 30 items), EORTC Myeloma Module Quality of Life Questionnaire scale-20 (a cancer-specific questionnaire with 20 items) and European Quality of Life 5-Dimension 5-Levels (a general health questionnaire with 5 dimensions and 5 levels per Dimension) indicated a greater improvement in HRQoL and physical functioning, as well as reductions in symptoms with DBLd compared BLd.⁴⁴

Overall, the benefit to patients of DBLd, as shown in the CEPHEUS trial include:

- Improvements were observed in HRQoL and physical functioning, as well as reductions in symptoms (pain, fatigue, overall disease symptoms) as measured by EORTC QLQ-C30, EORTC QLQ-MY20 and EQ-5D-5L scale scores.⁴⁴
- Importantly, adding another drug (daratumumab) to three drug combination (BLd) did not worsen overall quality of life⁴⁴

If reimbursed and used in place of DLd, it is anticipated that the introduction of DBLd to UK clinical practice will improve transplant ineligible patients' health-related quality of life by allowing them to spend a longer period of time progression-free in good health prior to their symptoms worsening following relapse of their myeloma.

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.

Each medicine has its own side effects, and the same medicine can produce different reactions in different people. The data presented below is for the transplant ineligible population, comparing versus BLd (CEPHEUS trial comparator).

Overall, the DBLd safety profile was consistent with the safety profile of BLd. DBLd showed no additional safety concerns in older, frailer transplant ineligible patients. In the CEPHEUS trial, treatment with DBLd was well-tolerated, with fewer deaths and less patients stopping treatment as a result of side-effects than in the group treated with BLd alone.⁶⁰

The appearance of more serious (also called “Grade 3 or 4”) adverse events were equal in the DBLd group than the BLd group.⁶⁰ The most common serious adverse events ($\geq 5\%$) grade 3 or 4) are presented in table below.

Table 3: Common ($\geq 5\%$) grade 3 or 4 treatment adverse event

Side effect	Symptoms	Patients who experienced side effects with DBLd (%)
Diarrhoea	Passing of loose or watery stools more than three times a day	11.8
Peripheral sensory neuropathy	Tingling or numbness (often in your hands and feet), burning sensation, sensitivity to touch, weakness, balance problems, pain, temperature sensitivity, reduced reflexes	9.7
Neutropenia (low white blood cells)	Feeling sick, extreme tiredness and getting frequent infections	43.8
Thrombocytopenia	Bruising easily, tiny red spots under the skin and unusual bleeding from the gums or nose	30.6
Fatigue	Feeling extreme tiredness, lethargy or exhaustion, which persists most or all of the time	9.0
Anaemia (low red blood cell count)	Feeling extreme tiredness, weakness, pale skin, cold hands and feet, dizziness and shortness of breath	12.5
Pneumonia	Coughing, fever, chills, shortness of breath, chest pain, fatigue, and loss of appetite	13.9

It is important to note that patients received DBLd for longer compared to patients who received BLd, and the higher rate of Grade 3/4 adverse events did not cause a higher rate of discontinuation of treatment in the DBLd group.⁶⁰ More details regarding side effects are presented in Section 2 of the Company Submission.

All serious side-effects were safely managed by healthcare professionals and did not lead to an increase of patients stopping treatment.⁶⁰

Daratumumab is associated with potential injection site related reactions, which may include symptoms at the site of injection may include redness of the skin, itching, swelling, pain, bruising, rash, bleeding. To make sure that patients do not experience any serious infusion related-reactions, patients should receive daratumumab from a healthcare professional somewhere with access to resuscitation facilities.^{61, 62}

Managing side effects

The side effects of daratumumab can be managed by treatments such as: blood transfusions, antibiotics, and medicines to control the movements of the gut. Patients who have side effects due to the reduction of blood cells are effectively managed by:

- Blood transfusions (the transfer of blood from a donor to the patient), and
- Growth factors (a type of supportive medicine that stimulates the bone marrow to make blood cells).⁶³

Compared with DLd, it is anticipated that there may be additional toxicities associated with DBLd and the addition of a fourth agent, bortezomib, to the current triplet regimen. However, healthcare professionals in the UK are used to managing such side effects. For example, withholding bortezomib until symptoms have resolved or dropping down to a weekly, rather than bi-weekly, dosing schedule.

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

For newly diagnosed transplant ineligible MM patients it is important to manage their disease as early as possible by offering an effective combination treatment option, such as an anti-CD38. This is because each time a patients disease gets worse and they need a subsequent treatment, the treatment options become

less effective, and the chances of a patient surviving reduces. Additionally, many patients don't make it to a second-line therapy. If a patient chooses to stop subsequent treatment, this can lead to worse outcomes and a poorer quality of life for patients.^{24, 31, 64, 65}

It is therefore important to optimise the first line treatment for MM patients. This can help to reduce problems linked to disease coming back (relapse) and lead to better health outcomes.⁶⁶

DBLd is an effective treatment regimen that combines four different types of medicines, including an anti-CD38 (daratumumab) and by combining these treatments, it fights the cancer in various ways, which increases the likelihood of achieving deep and durable responses (i.e. the treatment has successfully suppressed the disease, and this suppression is maintained for a significant period, improving the patient's prognosis and quality of life).

The deep and durable responses achieved with DBLd are expected to translate to good long-term control of the disease. This is supported by the ITC results versus DLd that show a statistically significant improvement in the MRD-negative CR rate, PFS and OS after censoring for COVID-19 deaths. These results were supported by sensitivity analysis that show statistically significant improvement in MRD-negative CR and PFS, with a numerical trend in favour of DBLd for OS versus DLd. Refer to Section 3e above, and Section 2 of the Company Submission for further details.

Lastly, administration of daratumumab is a convenient process designed with patient safety in mind. It is injected under the skin by a qualified healthcare professional that lasts approximately 3 to 5 minutes. After the initial 8 cycles, this represents no change in administration or time in hospital compared to the current standard of care, DLd.⁴⁴

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
- Both daratumumab as part of the DBLd and DLd (the current SoC) combinations are given via subcutaneous injection, however, DBLd requires 8 cycles of bortezomib. This means more visits to hospital to receive the bortezomib in the induction phase. This may place additional burden on patients and carers, however bortezomib is fixed duration, so this will only be for a limited time.
- As with all treatments there can be side-effects. However, clinical trial evidence indicate that DBLd has a manageable safety profile. Refer to Section 3g above and Section 2 of the Company Submission.

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:

Model Structure

- The economic model for this submission assesses the costs and quality of life of patients over a lifetime for those receiving DBLd compared to the current standard of care treatment (SoC) in the UK, DLd (the current SoC)
- The model simulates a patient's treatment journey over a 30-year time horizon through a set of different health states (before disease progression, after disease progression, and death). Each health state is associated with relevant costs and a specific quality-of-life benefit.
- The following health states were used in this cost-effectiveness model:
 - **Progression-free:** This means a patient's disease is stable or responding to treatment and not actively getting worse. Quality of life (QoL) is higher compared to patients with progressed disease but is also affected by adverse events.
 - **Progressed disease:** This means a patient's disease has progressed. QoL is lower compared to patients with progression-free disease.
 - **Death:** This state includes costs associated with palliative care and end-of-life costs. The time spent in each health state is then adjusted by the health-related QoL of a patient in that health state, to estimate the total number of quality-adjusted life years (QALYs) gained by a patient for each treatment. A QALY is therefore a measure of health that combines both the length of life and the quality of life.

Trial endpoints used in the model

- The main trial outcomes that are used in the model are progression-free survival to calculate time spent in the progression free state, overall survival used to calculate time spent in the progressed disease state, treatment duration to calculate treatment costs and safety information to calculate the negative impact on quality of life and costs
- For DBLd, the CEPHEUS trial data is used for approximately 5 years of follow-up (see Section 2 of Company Submission) and then the expected progression free and overall survival estimates are forecasted using standard statistical modelling techniques to predict longer-term outcomes over a patients' lifetime
- For DLd, a similar approach is taken but the data from the MAIA trial is used

Modelling how much a treatment improves quality of life

- Quality of life in the model is based on data from CEPHEUS, collected using the European Quality of Life 5-Dimension 3-Levels questionnaire. Specifically, the model assigns values or 'utilities' between 0 (representing death) and 1 (representing full health), to reflect patients' health-related QoL in the different health states (progression-free and progressed disease)

Modelling how the costs of treatment differ with the new treatment

- The costs in the model include treatment acquisition (drug costs), administration, monitoring, subsequent treatment, adverse events and end-of life costs
- Drug costs for DBLd are estimated using treatment duration data from CEPHEUS. For DLd, treatment duration data from the MAIA trial is used
- The total costs associated with DBLd are higher than for existing treatments; however, this is balanced by the increased benefits (measured by the QALY) of the quadruplet combination

Uncertainty

- There is always some uncertainty in long-term predictions of survival for each treatment as trial data are only available for a certain duration of follow-up and therefore extrapolated data needs to be used. It is possible to gain confidence in these extrapolated estimates considering the high rates of MRD negativity (deep responses) seen in the CEPHEUS trial, and there being a large amount of external evidence supporting a strong correlation between MRD negativity and long-term survival outcomes. The long-term estimates predicted from the model (for PFS and OS) were also aligned to clinical expert long-term estimates, ensuring clinical plausibility in the modelled long-term outcomes.
- In the absence of direct trial evidence comparing the effectiveness of DBLd with DLd in UK clinical practice, ITC's (a statistical method used to compare the effectiveness of two treatments that have not been directly compared in a single trial) were conducted between DBLd vs DLd

- Alternative assumptions have been tested in the model and the impact on the results presented in Section 3 of the Company Submission

Cost effectiveness results

- In line with the ITC results versus DLd, and reflective of the deep, durable responses, the cost-effectiveness model assumes patients treated with DBLd remain progression-free in good health for longer which translates to a long-term OS benefit.
- The cost-effectiveness results for DBLd versus DLd is confidential but can be found in Section 3 of the Company Submission

Additional factors

- Key benefits not captured in the modelling include reduced caregiver burden, potential return to work which alleviates financial worry/stress, and enhanced emotional well-being from the prospect of long-term disease control
- Additionally, there is the value of hope for the future associated with the prospect of achieving a state of no detectable disease

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)

If reimbursed, DBLd will be the first quadruplet therapy for newly diagnosed transplant ineligible patients, adding bortezomib to the current standard of care (DLd). By using multiple drugs with different mechanisms of action, DBLd leverages the synergistic benefit of different classes leading to deeper and more durable responses. This approach is expected to translate into improved long-term survival and, for the best responders, the prospect of dying from other age-related factors rather than their myeloma (often referred to as a functional cure). This represent a step change to current standard of care delivering transformative outcomes that have not previously been seen in the transplant ineligible setting.⁴⁴

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

No equality issues related to the use of daratumumab combination therapy for the treatment of this patient population have been identified.

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.

Further information on daratumumab:

- <https://www.darzalex.com/>
- <https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/daratumumab>

Further information on the CEPHEUS trial and results:

- <https://clinicaltrials.gov/study/NCT03652064>
- <https://www.nature.com/articles/s41591-024-03485-7>

Further information on NICE and the role of patients:

- Public Involvement at NICE <https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement>
- NICE's guides and templates for patient involvement in HTAs <https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/support-for-vcs-organisations/help-us-develop-guidance/guides-to-developing-our-guidance>
- 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>
- 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

Antibody: A protein that plays an important role in the body's immune system. Each antibody is unique and recognises a specific part of a germ or other invader. Antibodies can be custom designed for use as drugs.⁶⁷

Biopsy: A process in which a very small part of tissue in the body is removed to look for signs of disease.⁶⁸

Bone marrow: The spongy material found inside the centre of large bones in the body, where all blood cells are made.²

European Medicines Agency (EMA): The regulatory body that evaluates, approves, and supervises medicines throughout the European Union.⁶⁹

Minimal residual disease: A term used to describe a very small number of cancer cells that remain in the body during or after treatment.⁶⁷

M protein: An antibody found in unusually large amounts in the blood or urine of people with multiple myeloma and other types of plasma cell tumours. Also called monoclonal protein.⁶⁷

Multiple myeloma: A type of cancer that begins in plasma cells.⁶⁷

Plasma cell: A type of white blood cell that makes large amounts of a specific antibody.⁶⁷

Progression: The course of a disease, such as cancer, as it spreads in the body.⁶⁷

Relapse: Return of the signs and symptoms of a disease after a period of improvement.⁶⁷

Quality of life: The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out activities of daily living.⁶⁷

Stem cell transplant: The process of providing a patient with healthy stem cells that can replace diseased cells intentionally destroyed by therapy.⁶⁷

4c) References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Clarification questions

August 2025

File name	Version	Contains confidential information	Date
ID3843_Daratumumab_NICE_Clarification Question Response [NoCON]	V1.0	Yes	22.08.25

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

Search strategy

A1. CS Appendix B states the aim of the clinical SLR was to identify “any published evidence” but the search strings show that only randomised controlled trials (RCTs) were searched for. Please explain how the seven observational studies reported in CS Appendix B.1.5 (page 98) were identified and screened for eligibility.

Identification of Studies:

Although the search strategy primarily targeted randomised controlled trials (RCTs), the search strings were designed to be sensitive enough to also capture non-randomised interventional studies and to minimise the chances of missing any relevant studies. In addition to database searches, we conducted hand-searching of reference lists from relevant published systematic literature reviews (SLRs), which often include a broader range of study designs.

The studies referenced in CS Appendix B.1.5 (page 98) were identified through this process. To clarify, these are not observational studies, but interventional non-randomised clinical trials. They were classified as such because they were either single-arm studies or involved non-randomised treatment allocation.

Screening of Studies:

All identified records were screened using predefined eligibility criteria based on the research question and PICOS framework. These criteria allowed for the inclusion of RCTs, non-RCTs and single-arm studies. Studies were excluded if they met any of the following criteria: SLRs and meta-analyses; observational studies; non-systematic reviews; non-human studies; pharmacodynamic studies; preclinical studies; case reports; commentaries, editorials, and letters; consensus reports.

This structured and rigorous approach ensured that the SLR captured the most relevant and high-quality evidence available, providing reassurance that the evidence base was both comprehensive and fit for purpose.

CEPHEUS trial

A2. CS Table 25 reports the subsequent treatments received by patients in the trial.

- a) Please state the maximum, minimum and average number of lines of subsequent therapy given.

Further detail on the number of subsequent treatments received in patients in the daratumumab, bortezomib, lenalidomide and dexamethasone (DBLd) and bortezomib, lenalidomide and dexamethasone (BLd) arms of the CEPHEUS autologous stem cell transplant (ASCT)-ineligible population are provided in Table 1. In patients receiving subsequent treatment(s), the minimum number received in both the DBLd and BLd arms was ■■■, while the maximum was ■■■ and ■■■, respectively. Following DBLd, ■■■ patients received at least one subsequent treatment; following BLd, ■■■ patients received at least one subsequent treatment. Of the ■■■ patients in the DBLd arm who received subsequent treatment, ■■■ received at least two lines of subsequent treatment, and ■■■ received three lines. Of the ■■■ patients in the BLd arm who received subsequent treatment, ■■■ received at least two lines of subsequent treatment, ■■■ received three lines, ■■■ received four lines and ■■■ received five lines.

Table 1: Subsequent treatment regimens received as a first subsequent treatment following either DBLd or BLd (ASCT-ineligible ITT population) – final PFS analysis

[illegible]

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Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intent to treat; PFS: progression-free survival.

b) Please comment on the extent to which the subsequent treatments reflect those that would commonly be given in clinical practice in the NHS.

As shown in Table 1, and owing to the effectiveness of DBLd, only a small proportion of patients in the DBLd arm (■■■%) had received a subsequent treatment at the time of the latest data cut-off in the CEPHEUS trial. The small patient number receiving subsequent treatment in the DBLd arm suggests that subsequent treatments are unlikely to have a meaningful impact on the observed overall survival (OS) and are therefore a source of negligible uncertainty.

Data relating to subsequent treatments are in line with UK clinical expert feedback received at the May 2025 UK Advisory Board, which indicated that carfilzomib-based therapies would be most commonly used at second-line following first-line treatment with DBLd.¹ This is in line with the subsequent treatments observed in CEPHEUS, where ■■■ patients (■■%) received a ■■■ regimen at second-line after DBLd. The other most common second-line treatment following DBLd in CEPHEUS was ■■■ which also reflects UK clinical practice as ■■■ is reimbursed at second-line in England. ■■■ retreatment is known to be effective at second-line, especially considering ■■■.² As such, the available subsequent treatment data is in line with UK clinical expert feedback and UK clinical practice.

Johnson & Johnson (J&J) acknowledges that subsequent treatments received in CEPHEUS do not include belantamab mafodotin with bortezomib and dexamethasone (BeBd), which recently received a positive draft recommendation from NICE as a treatment option for previously treated multiple myeloma.³ The impact of this on the comparison between DBLd and DLd (the key comparator) is expected to be minimal given BeBd was also not used as a subsequent treatment in the MAIA trial. The subsequent treatment distributions from the MAIA trial are provided in the Committee Papers of TA917 (Appendix B.5).⁴

ITCs

A3. Please supply reference 68, J&J Data on File. NHS Digital NCRAS, England 2015-2022 (page 107 of main CS).

The “J&J Data on File for the NHS Digital NCRAS, England 2015-2022” data referenced in the Company evidence submission has been provided as part of the reference pack accompanying this response (titled: ‘J&J Data on File_NHS Digital NCRAS_England 2015-2022’).

A4. The MAIA Protocol and the ALCYONE Protocol were not provided with the reference pack as indicated in CS Appendix Tables 24 and 25. Please provide both trial protocols.

Both the MAIA and ALCYONE protocols referenced in the Company evidence submission have been provided as part of the reference pack accompanying this response (titled: ‘MAIA protocol’ and ‘ALCYONE protocol’, respectively).

A5. Please provide a summary of the methodology for the multivariate and double robust regressions which were done as sensitivity analyses to the base case ITC (CS page 114).

Alongside the primary inverse probability of treatment weighting (IPTW) analysis, doubly robust estimation combining IPTW with regression adjustment was performed to provide additional protection against model misspecification and confirm the robustness of the results. Multivariate regression analysis was also conducted as a complementary method to validate the findings.

Doubly robust

The doubly robust estimation combined the IPTW weights with an outcome regression model. This approach offers the advantage of being consistent if either the propensity score model or the outcome regression model is correctly specified, providing two opportunities to control for confounding. The outcome regression model included the same baseline covariates used in the IPTW model.

Time-to-event outcomes from the DBLd arm of CEPHEUS and the DLd arm of MAIA were used to derive the hazard ratio (HR) for DBLd vs DLd on the log scale using IPTW-weighted Cox proportional hazard model regression, with the treatment indicator (DBLd or DLd) and all relevant baseline variables included as predictors. The log(HR) and its corresponding standard error (SE) for DBLd vs DLd were estimated based on the weighted Cox proportional hazard model. Robust sandwich estimate of SE was used to account for the IPTW weighting. The effect estimates were exponentiated and reported as a HR with 95% confidence intervals.

Binary outcomes from the DBLd arm of CEPHEUS and the DLd arm of MAIA were used to derive the odds ratio (OR) for DBLd vs DLd on the log scale using IPTW-weighted logistic regression, with the treatment indicator (DBLd or DLd) and all relevant baseline variables included as predictors. The log(OR) and its corresponding SE for DBLd vs DLd were estimated based on the weighted logistic regression model. Robust sandwich estimate of SE was used to account for the IPTW weighting. The effect estimates were exponentiated and reported as an OR with 95% confidence intervals.

Multivariate regression

For the multivariate regression analysis, Cox proportional hazard models were fitted for time-to-event outcomes (progression-free survival [PFS] and OS) and logistic regression models for binary outcomes (response rates), adjusting for the same set of baseline characteristics.

Time-to-event outcomes from the DBLd arm of CEPHEUS and the DLd arm of MAIA were used to derive the HR for DBLd vs DLd on the log scale using Cox proportional hazard model regression, where the treatment indicator (DBLd or DLd) and all relevant baseline variables were included as predictors. The log(HR) and its corresponding SE for DBLd vs DLd were estimated based on the cox proportional hazards model. The effect estimates were exponentiated and reported as a HR with 95% confidence intervals.

Binary outcomes and baseline data from the DBLd arm of CEPHEUS and the DLd arm of MAIA were used to derive the OR for DBLd vs DLd on the log scale using logistic regression, where the treatment indicator (DBLd or DLd) and all relevant baseline variables were included as predictors. The log(OR) and its corresponding SE for DBLd vs DLd were estimated based on the

logistic regression model. The effect estimates were exponentiated and reported as an OR with 95% confidence intervals.

Network meta-analysis

A6. Please clarify whether the search strategy referred to in Appendix M.1 is the original and first update search (not including the 2nd update) of the clinical SLR search strategy reported in Appendix B.1.1. If not, please provide the search strings.

Yes, the EAG is correct in that the search strategy for the network meta- analysis (NMA) in Appendix M.1 is based on the original and first update search (August 2024) reported in B.1.1 of the Appendices. Further details are also given in the NMA report provided as a reference with this response.

A7. Please clarify whether the complete reference lists for included studies and excluded studies, reported in Appendix B.1.3 for the clinical SLR, include the NMA studies. If not, please provide the included and excluded studies list(s) for the NMA.

The reference list for the clinical SLR (Appendix B.1.3) includes all studies included and excluded from the NMA. Notably, studies excluded from the NMA were those not included in the relevant clinical guidelines, and the following treatments could not be connected: bortezomib, cyclophosphamide and dexamethasone (BCd), daratumumab, bortezomib, cyclophosphamide and dexamethasone (DBCd), Isatuximab, carfilzomib, lenalidomide and dexamethasone (IsaKLd), Carfilzomib, cyclophosphamide and dexamethasone (KCd) and lenalidomide, cyclophosphamide and dexamethasone (LCd). These treatments were therefore excluded from the NMA due to the requirement of having a connected network for conducting an NMA. More information can be found in Section 4.1 of the NMA report provided with this response.

A8. We note there is inconsistency in the include/exclude status of the TMSG and IFM 01/01 studies in the NMA. These studies are included in the network diagram in CS Figure 27, yet the preceding paragraphs, and the narrative summary in Appendix M and Appendix M Table 108 do not list these as trials included in the NMA.

Furthermore, we note that both trials are listed in Appendix M Table 14 'Records included in the SLR but deprioritised for extraction due to intervention (not a key comparator)'. However, Table 111 includes the raw data for both studies for analysis of the OS outcome and Appendix M, Table 110 includes the raw data for IFM 01/01 for analysis of the PFS outcome (NB. TMSG 'inputs for PFS not available').

Our assumption is that these trials are not directly relevant to the NMA because the treatments evaluated (MP versus MPT) are not included in the decision problem. But they do help to connect the relevant treatments in the evidence network. Please could you clarify if we are correct in this assumption?

Tables 108, 110 and 111 in Appendix M mistakenly did not include the IFM 01/01 or TMSG studies. The NMA report provided as a reference with this response includes the corrected versions; please see Tables 3, 5 and 6. J&J confirms that both studies were included in the NMA to connect other relevant treatments in the network, per the EAG assumption.

Only OS data are available in the public domain for TMSG; therefore, this study is included in the OS network and not the PFS network.

A9. We note another inconsistency in the stated number of trials included in the NMA. In various places, including CS Appendix M Tables 108 and 109, it is stated that 9 trials were included in the NMA, whereas CS Appendix M Tables 110 lists 10 trials and Table 111 lists 11 trials (the two additional trials are TMSG and IFM 01/01 – see Question A8 above). The text that references Table 111 also mentions that there were 16 trials. Please can you explain this discrepancy?

J&J apologises for this error and confirms that 10 trials were used to inform the PFS network (since the TMSG study did not report PFS results) and 11 trials were used to inform the OS network (the TMSG study was included). '16 trials' was incorrectly reported.

A10. It is stated (CS section 2.10.5) that the choice between random effects and fixed-effect NMA model was informed by the Deviance Information Criterion (DIC) values, specifically fixed-effect was preferred unless the DIC of the random effects model was at least three points lower than that of the fixed-effect model.

- a) For each NMA outcome measure please provide the DIC model fit values for fixed-effect and random effects models.

As requested, the Deviance Information Criterion (DIC) values for the fixed effect (FE) and random effect (RE) models are provided in Table 2.

Table 2: DIC model fit values for the FE and RE models

	Response	HR	
		FE	RE {U[0, 1]}
Base case	OS		
	PFS		
Scenario: SWOG S0777: ITT population	OS		
	PFS		
Scenario: SWOG S0777: > 65 population	OS		
	PFS		

Abbreviations: DIC, Deviance Information Criterion; FE: fixed-effect; HR: hazard ratio; ITT: intent-to-treat; OS: overall survival; PFS: progression-free survival; RE: random effects.

- b) Please provide the results of the NMA using the corresponding effect model that was not selected. E.g. for OS and PFS (fixed-effect model selected) provide the random effects model results.

The NMA was conducted to provide supportive comparative efficacy estimates between DBLd and the relevant comparators (DLd, Ld and BMP). A FE model was chosen for both endpoints (PFS and OS) in the Company evidence submission due to a smaller DIC score compared to the RE model. Additionally, the FE model is deemed more appropriate given the small size of the network, which includes only one link connecting two treatments with multiple trials. Relying on the RE model with this network could introduce additional uncertainty, as the estimation of the random effects for most links is based on a single trial input. Therefore, the FE model provides a more reliable and parsimonious approach for this network.

For completeness, the results of the base case RE model are presented in Table 3 and Table 4, and can also be found in the accompanying NMA report provided as a reference with this response. These results are highly consistent with the base case FE model results presented in Section 2.10.5 of the Company evidence submission.

Of note, results in Table 3 and Table 4 are based on the 'no intent-to-transplant' subgroup population from SWOG S0777 as this subgroup was considered the best proxy for the ASCT-ineligible population in this NMA (in order to preserve the randomisation of the trial and in line with the committee's preferred assumptions in the draft guidance of ID3981).⁵ Consistent with the FE model results included in the Company evidence submission, the CEPHEUS and MAIA trials were adjusted for COVID-19 in the RE model results presented below.

Table 3: RE model base case NMA results for OS (adjusted for COVID-19)

OS HR (95% CrI)	DBLd	DLd	Ld	BMP
DBLd				
DLd				
Ld				
BMP				

Abbreviations: BMP: bortezomib, melphalan and prednisone; CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; OS: overall survival; RE: random effects.
Source: J&J Data on File. NMA Report.

Table 4: RE model base case NMA results for PFS (adjusted for COVID-19)

PFS HR (95% CrI)	DBLd	DLd	Ld	BMP
DBLd				
DLd				
Ld				
BMP				

Abbreviations: BMP: bortezomib, melphalan and prednisone; CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; PFS: progression-free survival; RE: random effects.

Source: J&J Data on File. NMA Report.

Alternative scenario analyses based on the ITT population and the >65 years of age patient population from SWOG S0777 are presented below, in line with the scenarios presented in Appendix M of the Company evidence submission. These results are highly consistent with the FE scenario results presented in Appendix M.

SWOG S0777 ITT population

Table 5 and Table 6 show RE model results for the relative treatment effects for OS and PFS, respectively, when using the ITT population from SWOG S0777, with CEPHEUS and MAIA results adjusted for COVID-19.

Table 5: RE model NMA results for OS (SWOG S0777 subgroup analysis; ITT population, adjusted for COVID-19)

OS HR (95% CrI)	DBLd	DLd	Ld	BMP
DBLd				
DLd				
Ld				
BMP				

Abbreviations: BMP: bortezomib, melphalan and prednisone; CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; OS: overall survival; RE: random effects.
Source: J&J Data on File. NMA Report.

Table 6: RE model NMA results for PFS (SWOG S0777 subgroup analysis; ITT population, adjusted for COVID-19)

PFS HR (95% CrI)	DBLd	DLd	Ld	BMP
DBLd				
DLd				
Ld				
BMP				

Abbreviations: BMP: bortezomib, melphalan and prednisone; CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; PFS: progression-free survival; RE: random effects.
Source: J&J Data on File. NMA Report.

SWOG S0777 >65 years of age subgroup

Table 7 and Table 8 show the RE model results for the relative treatment effects for OS and PFS, respectively, when using the >65 years of age subgroup from SWOG S0777, with CEPHEUS and MAIA results adjusted for COVID-19.

Table 7: RE model NMA results for OS (SWOG S0777 subgroup analysis; >65 years population, adjusted for COVID-19)

OS HR (95% CrI)	DBLd	DLd	Ld	BMP
DBLd				
DLd				
Ld				
BMP				

Abbreviations: BMP: bortezomib, melphalan and prednisone; CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; OS: overall survival; RE: random effects.
Source: J&J Data on File. NMA Report.

Table 8: RE model NMA results for PFS (SWOG S0777 subgroup analysis; >65 years population, adjusted for COVID-19)

PFS HR (95% CrI)	DBLd	DLd	Ld	BMP
DBLd				
DLd				
Ld				
BMP				

Abbreviations: BMP: bortezomib, melphalan and prednisone; CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; PFS: progression-free survival; RE: random effects.
Source: J&J Data on File. NMA Report.

A11. The company's decision problem excludes the comparator Isatuximab with bortezomib, lenalidomide and dexamethasone (IsaBLd; subject to NICE evaluation) because it has not (currently) received a positive recommendation from NICE and therefore cannot be considered routine clinical practice. We note that a trial of IsaBLd (IMROZ) is included in the NMA and is connected to the network via its comparator treatment arm bortezomib, lenalidomide and dexamethasone (BLd). The EAG notes that this allows an indirect comparison of IsaBLd to DBLd. Please provide an exploratory NMA including IsaBLd as a comparator and also model its cost-effectiveness. This is based on an assumption that final NICE guidance recommends IsaBLd for use in the NHS.

At the time of this response to the EAG's clarification questions, the NICE appraisal for IsaBLd is ongoing and IsaBLd has not received positive final guidance in this indication.⁵ As such, IsaBLd cannot be considered to represent routine clinical practice for ASCT-ineligible NDMM patients and J&J maintain that IsaBLd therefore does not represent a relevant comparator for DBLd in this indication. If a positive recommendation were to be made for IsaBLd, there would be only a brief period before the DBLd committee meeting, and during this short timeframe, it is anticipated that there would be limited uptake of IsaBLd and it therefore will not have become a standard of care.

However, in line with the EAG's request, J&J has presented results from an exploratory NMA of DBLd vs IsaBLd in Table 9 for completeness. Except where specified, the NMA was conducted in line with the methods presented as part of the original Company evidence submission.

Exploratory NMA of DBLd vs IsaBLd

As per the ingoing submission, the following trials are included in the NMA: CEPHEUS (ASCT-ineligible),⁶ MAIA,⁷ ALCYONE,⁸ FIRST,⁹ VISTA,¹⁰ Sacchi 2011,¹¹ IFM 99-06,¹² IMROZ,¹³ TMSG,¹⁴ IFM 01/01,¹⁵ and SWOG S0777¹⁴ (Table 108, Appendix M of the Company evidence

submission). Aligning to the Company evidence submission, the no-intent to transplant subgroup population of the SWOG S0777 trial was used in the base case NMA, and the MAIA population was also restricted to patients <80 to ensure consistency with the population of interest. Additionally, deaths due to COVID-19 were censored in both the CEPHEUS and MAIA trials in line with the Company's ingoing base case IPTW ITCs. All other trials included in the NMA were unadjusted for COVID-19 – this is not expected to impact results due to the majority of trials of interest being conducted prior to the pandemic. For completeness, both the FE and RE NMA results are presented below.

As shown, across both the FE and RE models, DBLd is associated with considerable numerical improvements in both OS and PFS compared with IsaBLd (Table 9). Specifically, DBLd reduced the risk of death by █% versus IsaBLd, and the risk of disease progression or death by █% demonstrating a clear trend in favour towards DBLd over IsaBLd in this indication.

Table 9: DBLd vs IsaBLd NMA results for OS (adjusted for COVID-19) and PFS (adjusted for COVID-19)

DBLd vs IsaBLd OR HR (95% CrI)	Fixed effects model	Random effects model
OS	██████████	██████████
PFS	██████████	██████████

Abbreviations: CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival.

Source: J&J Data on File. NMA Report

Since individual patient data (IPD) were not available to J&J for the IMROZ trial, it was not possible to adjust IMROZ trial data for any potential impact of COVID-19. J&J recognises that this is a limitation of the NMA presented and therefore, for completeness, results from an NMA with no adjustments for COVID-19 across any included trial are presented in Table 10. Of note, this unadjusted analysis is considered conservative as it is likely that IsaBLd in IMROZ was less heavily impacted by the COVID-19 pandemic than DBLd in CEPHEUS, based on the timing of the studies, as COVID-19 deaths made up 11.59% of all deaths in the IsaBLd arm of IMROZ (8 COVID-19 deaths out of 69 total deaths) compared to █ of all deaths in the DBLd arm of CEPHEUS █ COVID-19 deaths out of █ total deaths).^{6, 13} This difference is expected to be because of the timing of trial initiation and data cut-offs between the two trials. Considering both are quadruplet therapies consisting of an anti-CD38 monoclonal antibody given in combination with BLd, a similar proportion of COVID-19 deaths would be expected.

As shown in Table 10, across both the FE and RE models, in the unadjusted for COVID-19 analyses, DBLd is associated with a consistent numerical improvement in both OS and PFS outcomes compared with IsaBLd. Specifically, DBLd reduced the risk of death by █% versus IsaBLd, and the risk of disease progression or death by █% demonstrating a clear trend in favour towards DBLd over IsaBLd in this indication.

Table 10: DBLd vs IsaBLd NMA results for OS (unadjusted for COVID-19) and PFS (unadjusted for COVID-19)

DBLd vs IsaBLd OR HR (95% CrI)	Fixed effects model	Random effects model
OS	██████████	██████████
PFS	██████████	██████████

Abbreviations: CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival.
Source: J&J Data on File.

Cost-effectiveness analysis of DBLd vs IsaBLd

It was not feasible to conduct a robust cost-effectiveness analysis of DBLd vs IsaBLd in the timeframe available. However, J&J would like to highlight that, based on the exploratory NMA results above, which demonstrate a clear clinical benefit of DBLd over IsaBLd for both OS and PFS, and key aspects of the two treatments' dosing schedules (discussed below), it is expected that DBLd would be associated with both better efficacy and lower costs than IsaBLd (i.e. DBLd would dominate IsaBLd).

Per dosing regimens in the respective SmPCs, IsaBLd requires fifteen more infusions than DBLd over the first two years of treatment, and therefore incurs substantially higher drug acquisition and administration costs than DBLd when both treatments are modelled at list price.^{16, 17} The extra infusions for IsaBLd arise as isatuximab (as part of IsaBLd) is given once every two weeks (Q2W) until Week 76 (at which point it switches to Q4W), while daratumumab (as part of DBLd) is given once every four weeks (Q4W) after Week 24 until progression. At list price, the difference in the Year 1 and 2 total costs is £53,944 (costs of £133,015 for daratumumab and £186,959 for isatuximab). In the absence of TTD data for IsaBLd, if an assumption of the same time on treatment is taken for the two treatments, drug acquisition and administration costs associated with IsaBLd in this treatment setting are anticipated to be higher than those associated with DBLd based on the dosing schedules and intravenous (IV) administration.

To note, isatuximab is administered as an IV infusion, while daratumumab is administered subcutaneously. Per Table 77 of the Company evidence submission, IV administration costs are substantially higher than those for subcutaneous (SC) administration due to significantly longer nurse and hospital chair time with IV (several hours) compared to SC time (5 minutes). Considering both the acquisition costs at list price and administration costs, it is expected that DBLd would be cost saving to the NHS compared to IsaBLd. Furthermore, the SC route and reduced dosing schedule for DBLd has the potential to alleviate NHS resource burden, whilst also enhancing patient convenience through fewer lengthy hospital visits, as compared to IsaBLd.

Further, owing to the improved PFS of DBLd over IsaBLd (based on the NMA), fewer patients would be expected to require subsequent treatment, compounding the expected cost-saving associated with DBLd versus IsaBLd.

Considering the above factors, it is J&J's expectation that DBLd would dominate IsaBLd in this patient population and would therefore represent a cost-effective use of NHS resources for patients with ASCT-ineligible NDMM. However, as highlighted above, in the absence of positive NICE final guidance for IsaBLd in this indication, IsaBLd cannot be considered to represent routine clinical practice for ASCT-ineligible NDMM patients and at the time of this response, should not represent a relevant comparator for DBLd.

A12. Is there a separate NMA report (e.g. containing further information on the methods and results) available? If so, please could this be provided.

The NMA report for comparison between DBLd and the relevant comparators (DLd, Ld and BMP) has been provided as part of the reference pack accompanying this response (titled: 'J&J Data on File. NMA Report').

Section B: Clarification on cost-effectiveness data

B1. Priority question: The clinical study reports (CSRs) for CEPHEUS, MAIA and ALCYONE provided in the submission reference pack present data for the intention-to-treat populations of these trials. Please could you provide the Data on File information that is the source data for the patient characteristics, K-M data for overall survival, progression-free survival, time-to-discontinuation, and health state utilities for the ASCT-ineligible populations in this submission.

As agreed during the clarification call, there is no separate Data on File available for the ASCT-ineligible population data – these data were specifically generated for the development of this submission. As such, no additional files are provided as part of the accompanying reference pack.

B2. Priority question: Regarding the discontinuation of components of DBLd and DLd:

- 1) How is this accounted for in treatment acquisition costs?**
- 2) How is time-to-discontinuation measured if patients stop taking a component of a therapy?**

Based on the CEPHEUS and MAIA trials, the definition of time to treatment discontinuation (TTD) used in the economic model is based on when a patient has discontinued all components of DBLd or DLd, respectively.^{7, 18}

This means that in the economic model, patients cannot discontinue an individual component of the treatment regimen. A patient is assumed to incur the costs of all of the treatments as part of either DBLd or DLd, respectively, until they discontinue treatment and thus cease to incur further treatment acquisition costs.

It should be noted that, in line with the draft SmPC for daratumumab, the bortezomib component of DBLd is modelled to only be administered for a fixed number of eight cycles – after which point, patients discontinue bortezomib and continue receiving daratumumab, lenalidomide and dexamethasone until treatment discontinuation.¹⁷

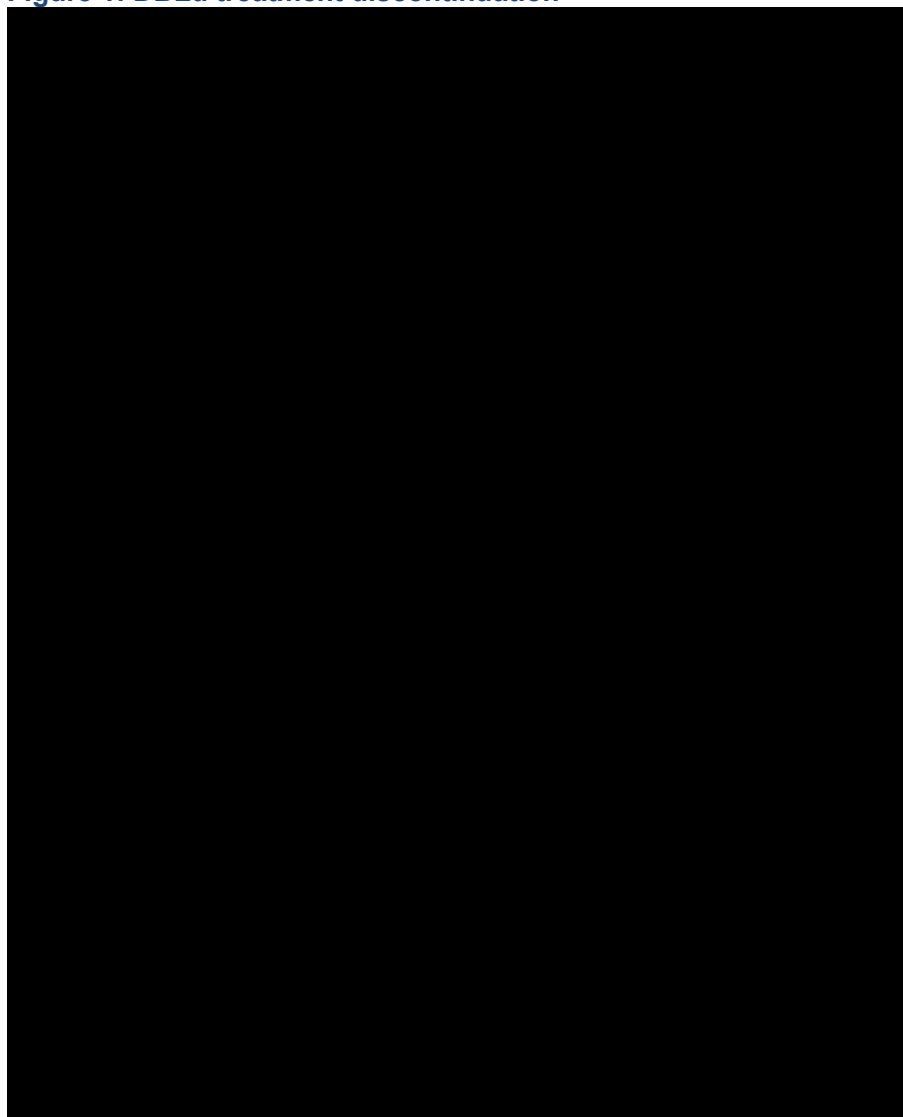
Thus, after the initial treatment period with bortezomib, patients receiving DBLd and DLd are effectively receiving the same long-term treatment regimen (i.e. daratumumab, lenalidomide and dexamethasone).

The individual components of therapies were not modelled separately, following the same approach used for TTD in TA917. Since the treatment dosing schedules for DBLd and DLd are the same after Week 24, discontinuation of individual components are expected to be similar between the two arms, as patients are receiving the same overall treatment (DLd).

Analysis from the naïve unadjusted comparison of component discontinuations in DBLd (based on the TIE population from CEPHEUS) and DLd (based on MAIA and excluding patients >80), shows that patients may stop taking [REDACTED] or [REDACTED] while continuing on [REDACTED], as shown in Figure 1 and Figure 2. The rates of discontinuation are similar for both treatments, with [REDACTED] (represented by yellow triangles) and [REDACTED] (represented by black triangles) being the primary treatments discontinued early. Given the [REDACTED], these discontinuations are unlikely to significantly impact overall treatment costs. Any small differences observed in the discontinuation rates of individual components between DBLd and DLd are likely due to minor differences in the patient populations across the trials. However, in practice, the actual treatment discontinuation rates would be similar between the treatment arms, considering it is the same treatment (DLd) given.

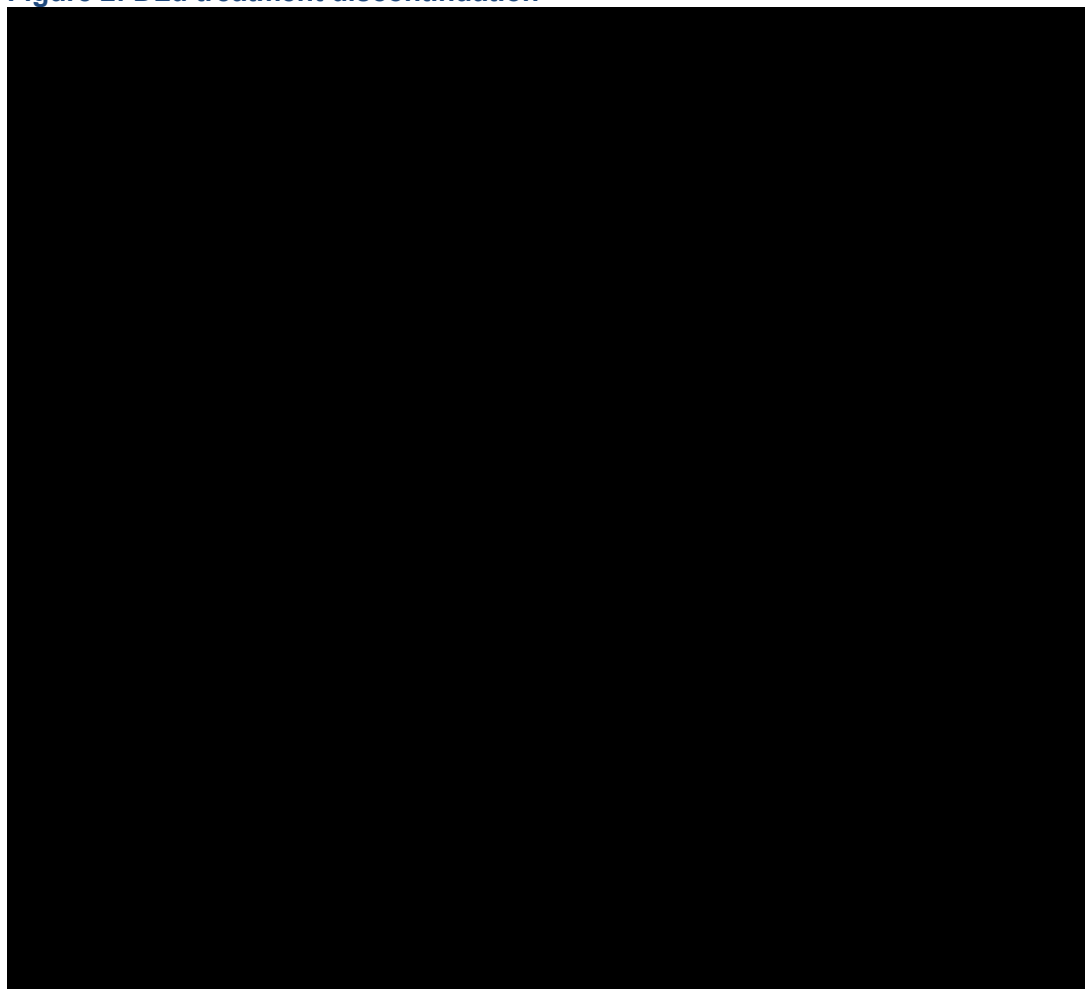
As such, it is assumed that the effects of modelling discontinuation of individual treatment components would be very similar across both DBLd and DLd, and therefore have a minimal impact on the economic model results.

Figure 1: DBLd treatment discontinuation



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone.

Figure 2: DLd treatment discontinuation



Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone.

B3. Priority question: CS 3.5.1 (p.159) states that bortezomib is given once a week in UK clinical practice, rather than twice a week as per the SmPC, and that in the model the full bortezomib dose is given once a week, rather than split to be twice weekly. However, in the model bortezomib appears to be given twice a week for two weeks (Cycles 1-8) in DBLd (Treatment Cost Calculation! AB12:AB35). Please clarify which dosing regimen is correct.

As noted by the EAG, the SmPC for bortezomib specifies twice weekly dosing of bortezomib. However, in UK clinical practice, the full dose of bortezomib ($2.6\text{mg}/\text{m}^2$) is given once weekly, as confirmed by clinical experts in both the November 2024 and more recent May 2025 UK Advisory Boards.¹ As such, it was considered most appropriate to align the model to clinical practice whereby bortezomib is administered once a week.

J&J acknowledge that the bortezomib dosing in the model is twice a week for two weeks. However, the modelled dose of bortezomib associated with each dose is half the full dose ($1.3\text{mg}/\text{m}^2$) and therefore the weekly dose administered in the model equates to the full dose of bortezomib required per patient weekly. As per Treatment Cost Calculation!AB12:AB35, only one administration cost per week is applied for the DBLd regimen and therefore the dosing costs

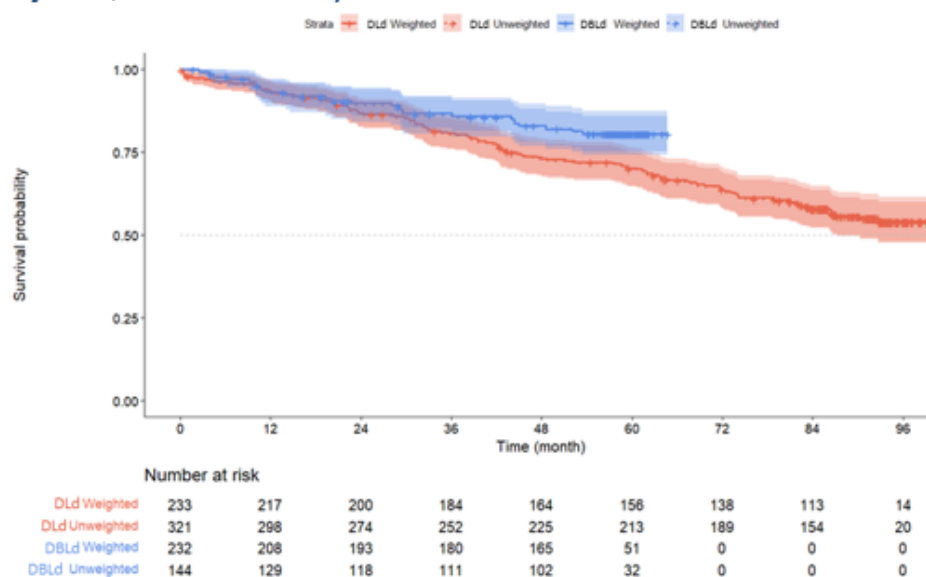
(acquisition and administration) for bortezomib as part of DBLd (and other bortezomib-containing regimens in the front-line setting) align to the once-a-week dosing schedule observed in UK clinical practice.

B4.a. Priority question: CEPHEUS SAP 5.3.2.1 states that “Subjects who have not progressed and are still alive at the cutoff date for analysis will be censored at the last disease assessment.” If patients were known to be alive and disease free on 07 May 2024 (clinical cut off), please clarify why they were censored earlier for overall survival (CS Figure 14) and progression-free survival (CS Figure 12) and not at the end of the study.

The PFS and OS censoring definitions stated in the CEPHEUS statistical analysis plan (SAP) are standard and consistent with those used in other clinical trials in Haematology and Oncology (such as MAIA and ALCYONE).^{19, 20} As such, patients were censored in accordance with these definitions. For clarity, based on the PFS quoted definition the EAG have given above, individual patients in CEPHEUS who were alive and progression-free based on data collected until the cut-off date were censored for PFS at the latest available disease assessment prior to the clinical cut-off date i.e. patients were not censored ‘earlier’ as suggested by the EAG. The date of the last available disease assessment reflects the last opportunity available to observe if progression had occurred, without having to make assumptions on the disease status of the patients between the last disease assessment and the date of clinical cut-off.

B4.b Priority question: A Similar early mass-censoring is seen at the end of the Kaplan-Meier curve in the MAIA trial (CS Figure 21 [PFS] and CS Figure 22 [OS], shown below). Please provide the reason for this censoring.

Figure 22: OS (censored for COVID-19) KM curves for DBLd and DLd (unadjusted and adjusted; base case model)



Footnotes: ATE weights are applied in this case. Patient volume was reweighted with weighted sum at time zero equals to unweighted sum at time zero.

Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; OS: overall survival.

Source: J&J Data on File.

As per the response to Question B4.a, the censoring approach was in accordance with the PFS and OS censoring definitions stated in the MAIA SAP.¹⁹ The censoring definitions in the MAIA SAP are aligned with those typically used in the analysis of time-to-event outcomes in other multiple myeloma trials, and at 87 months in MAIA, there are still a large number of patients at risk for DLd OS (■ DLd patients based on the unweighted KM curve). Therefore, the tail end of the KM remains largely informative, as it reflects observations on patients who are still known to be alive (e.g., at 87 months). Thus, this should not be considered a source of uncertainty.

The censoring observed at the end of the KM curve is not unusual, as it reflects the OS status of patients who are alive by the cut-off date. Patients treated with DLd have an improved overall survival and live longer compared to Ld, as demonstrated in the MAIA trial. Therefore, an increase in censoring towards the end of the curve is expected. Similar levels of censoring are seen across many other multiple myeloma trials, such as ALCYONE, CASTOR, POLLUX, CASSIOPEIA, and PERSEUS, suggesting this pattern is common as it demonstrates that a treatment is working effectively. Whilst J&J accept that censoring is higher towards the tail of the OS and PFS KM curves (because many patients treated with DLd in MAIA remain alive/progression-free at end of study follow-up), we do not consider this 'early' as it uses all available information i.e., happens at the patient's last disease assessment prior to clinical cut-off (for PFS) and at the date last known alive collected until the cut-off date (for OS).

B4.c. Priority question: Please would you run a scenario using truncated Kaplan-Meier data (Table 11), which removes the bulk censoring from both the CEPHEUS and MAIA overall survival and progression-free Kaplan-Meier survival curves, and recalculate the overall survival and progression-free survival parametric extrapolations for both studies.

Table 11: Kaplan-Meier (KM) truncation points for scenario analysis

Trial	Survival	End of KM curve	Model reference
CEPHEUS	OS	Cycle number: 58.04	DBLd! AJ57 (OS = 0.81)
	PFS		
MAIA	OS	Year: 6.51608	DLd! BU180 (OS = 0.61)
	PFS		

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; OS: Overall survival; PFS: progression-free survival.

Primarily, it is important to emphasise the censoring definitions are aligned with other haematology clinical trials, and the observed clustering of censored observations towards the tail end of the KMs are not unusual (as described in the response to B4a and B4b). As such, it is important to make use of all available data to model long term outcomes, particularly for OS, where long term OS follow-up reduces uncertainty. J&J have concerns with using truncated KM data based on earlier timepoints, particularly as in this case where there remain a high number of patients at risk, as this approach omits important trial data, which introduces unnecessary uncertainty in informing extrapolations as well as long-term outcomes.

OS

For DLd OS, the timepoint selected by the EAG is where there are still very high numbers of patients still at risk (■ patients), a number that remains high at 87 months (■ patients). This timepoint omits a notable portion of the KM curve which contains informative data regarding the

long-term survival profile for patients receiving DLd. Accordingly, around month 84, there are still some death events observed, and the KM curve remains stable. If there were very few patients left at risk, large drops in the KM would be noticeable with the occurrence of an event, which would suggest large uncertainty over the KM estimate at that time point. Similarly, for the DBLd OS timepoint, there are higher levels of censoring beyond Cycle 58, because patients are doing well and remain alive, and the numbers at risk at this selected timepoint are still very high (■ patients) and remain high after that e.g., at 57 months there are still ■ patients at risk. By artificially imposing a cut-off at this earlier timepoint, meaningful data that informs long term survival projections are being omitted, increasing uncertainty.

PFS

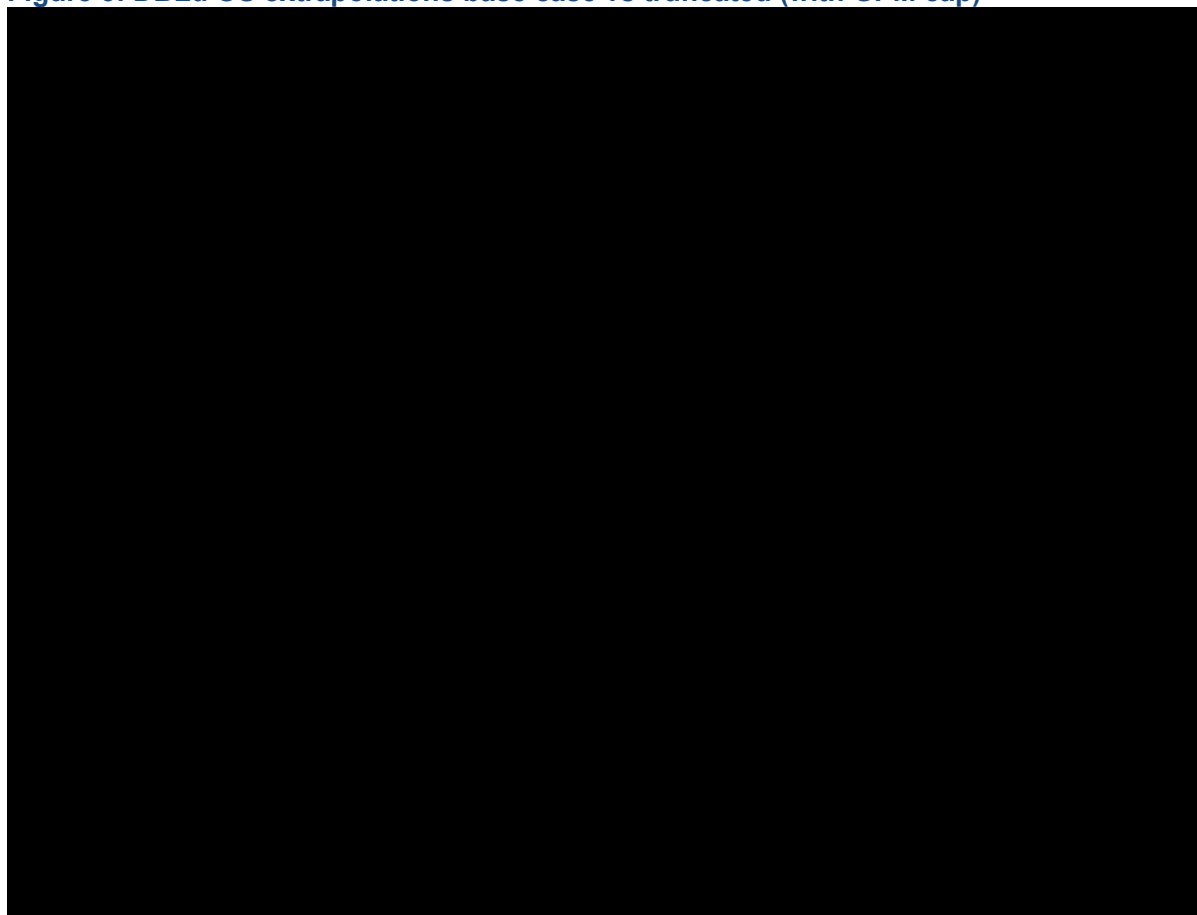
For DBLd PFS, the selected timepoint is unreasonable and omits important data, as the curve continues to drop with multiple events beyond the selected timepoint, with there being ■ patients still at risk. For DLd PFS, the proposed truncation has no impact on the long-term extrapolations, as the selected timepoint was beyond the follow-up of the trial (follow up of 64.5 months for PFS).

In a disease area where long-term follow-up data is always valuable, J&J do not consider using truncated KM data from an earlier point to be appropriate or informative, especially considering beyond the proposed truncation timepoint there are many patients still at risk, which provides information on patients being progression-free or alive.

Whilst J&J maintain that it is not appropriate to use truncated KM data based on earlier timepoints, for completeness and in line with the EAG's request, J&J have explored the impact of the truncated data on DBLd OS and PFS extrapolations and DLd OS extrapolations via a scenario analysis. As mentioned, it was not possible to truncate for DLd PFS, as the selected timepoint was beyond the trial follow-up.

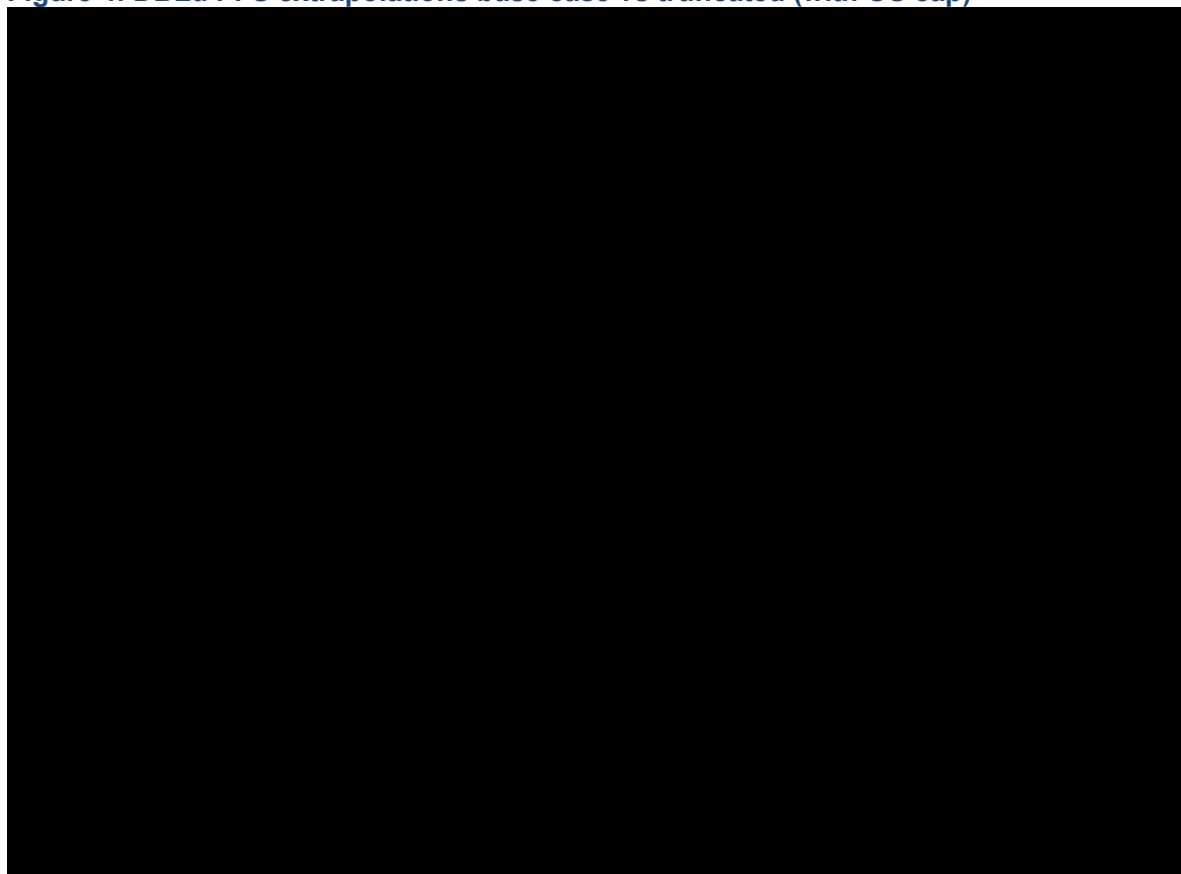
In line with the survival analysis described in the company evidence submission (section 3.3), seven standard parametric extrapolations were fitted to the truncated KM curves to estimate long-term survival outcomes. After capping the OS curves by general population mortality (GPM), and the PFS curves by the calibrated OS curve, the truncated extrapolations were very similar to the corresponding untruncated extrapolations as shown in Figure 3, Figure 4 and Figure 5.

Figure 3: DBLd OS extrapolations base case vs truncated (with GPM cap)



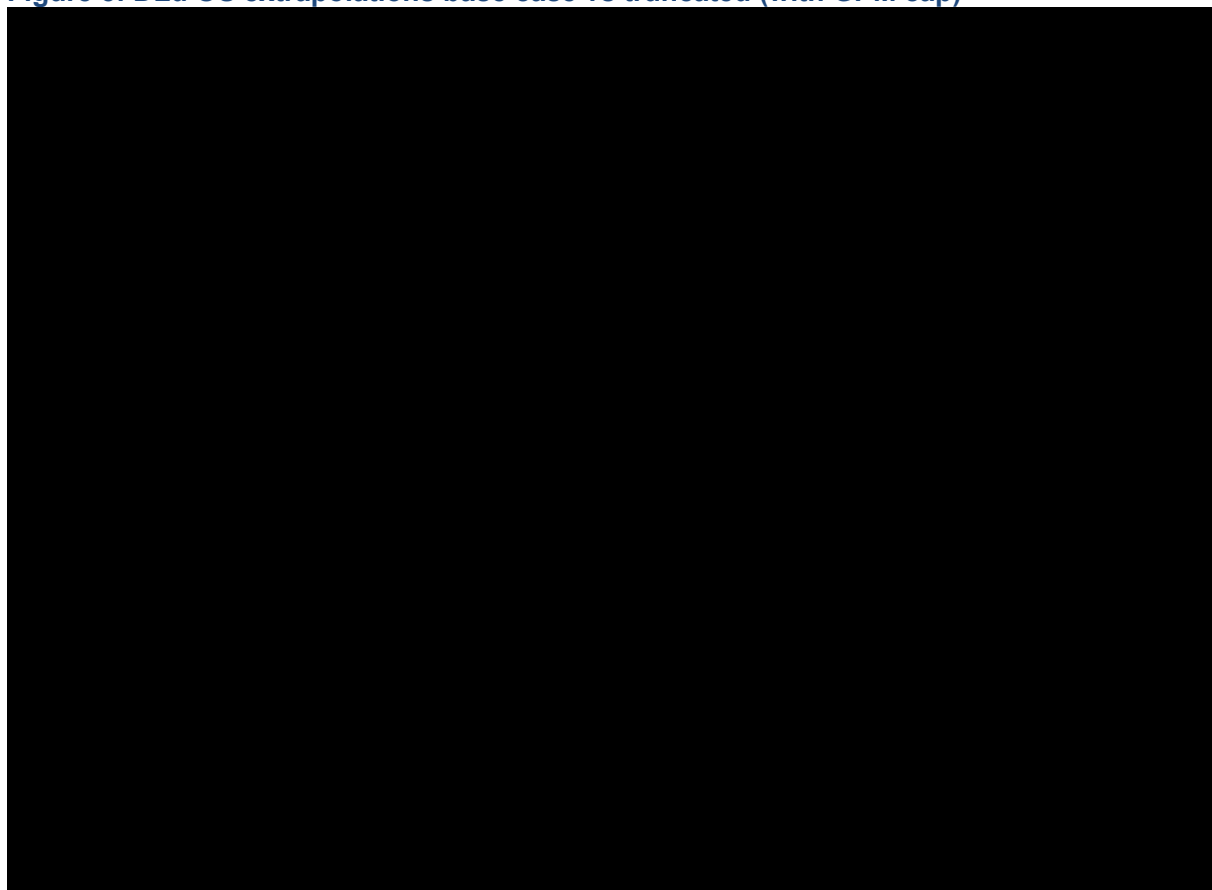
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; GPM: general population mortality; OS: overall survival.

Figure 4: DBLd PFS extrapolations base case vs truncated (with OS cap)



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; OS: overall survival; PFS: progression-free survival.

Figure 5: DLd OS extrapolations base case vs truncated (with GPM cap)

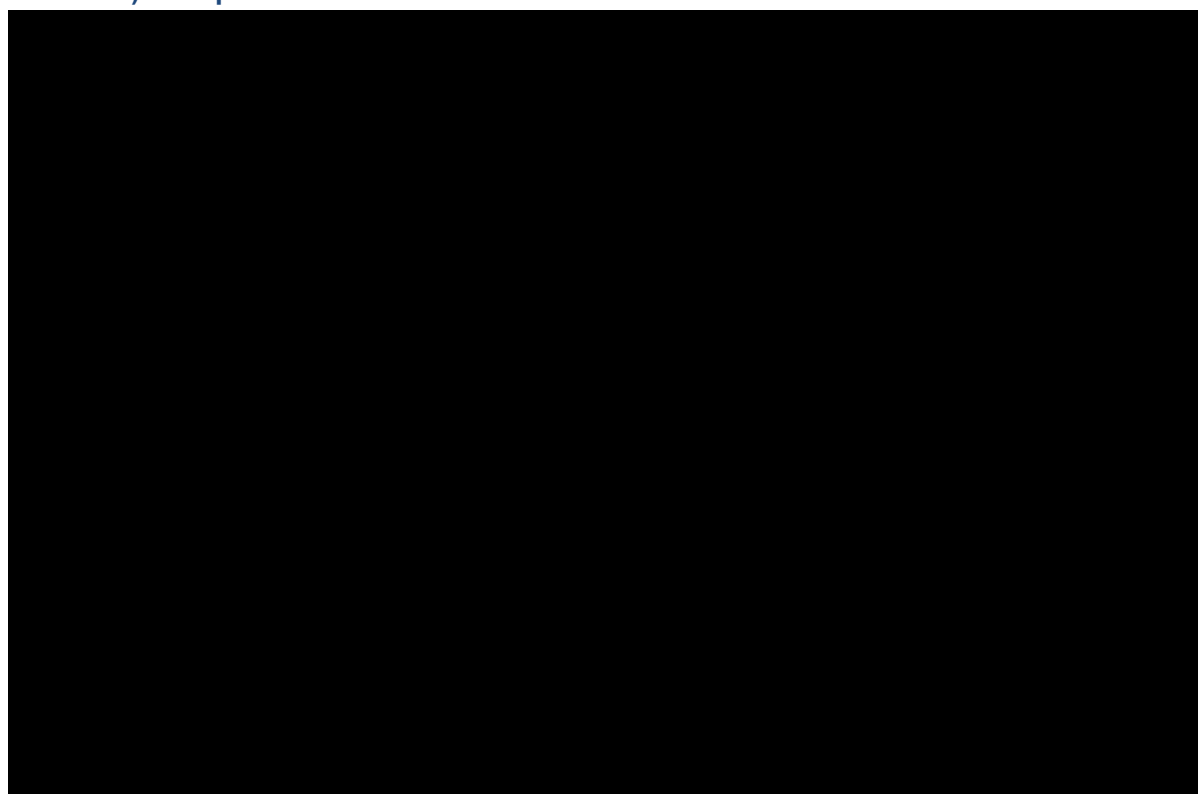


Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; GPM: general population mortality; OS: overall survival.

Following the original approach in the Company evidence submission, to conduct a scenario using truncated KM data, the curve with the best statistical fit was chosen, which was exponential across all endpoints. This was then calibrated to align with clinical expert estimates.

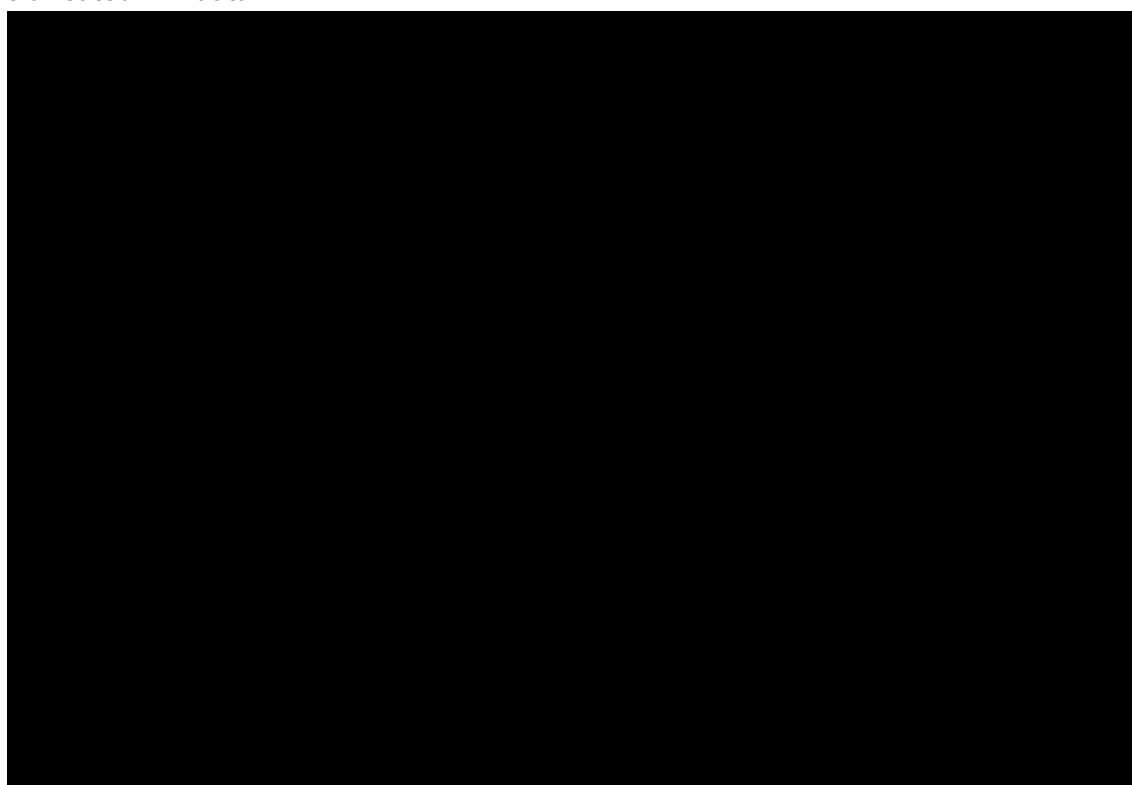
Figure 6 compares the selected DBLd OS GPM and PFS (capped by DBLd OS) extrapolations based on truncated and untruncated KM data from the CEPHEUS trial. Figure 7 compares the selected DLd OS (capped by GPM) extrapolations based on truncated and untruncated KM data from the MAIA trial. As shown in both Figure 6 and Figure 7, use of the truncated KM data has very minimal impact to the resulting extrapolations.

Figure 6: DBLd OS (calibrated, and capped by GPM) and PFS (calibrated and capped by DBLd OS) extrapolations with and without truncated KM data



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; GPM: general population mortality; KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival.

Figure 7: DLd OS (calibrated, and capped by GPM) extrapolations with and without truncated KM data



Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; GPM: general population mortality; KM: Kaplan-Meier; OS: overall survival.

Table 12 presents the cost-effectiveness results from the requested scenario analysis whereby DBLd OS and PFS, and DLd OS long-term extrapolations are based on the truncated KM data from the CEPHEUS and MAIA trials, respectively. As shown, DBLd dominates DLd in this scenario analysis (in line with the base case analysis; see Table 16 in Appendix A). Of note, in the analysis with only the discounted daratumumab price applied, the use of truncated KM data has a small impact on the ICER in favour of DBLd, driven by proportionately reduced costs for DBLd compared to DLd and the minimal differences observed across the long-term survival extrapolations (Figure 6 and Figure 7).

Table 12: Deterministic scenario analysis results (discounted daratumumab price)

Intervention	Total Costs	Total QALYs	Inc. Costs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	██████	██					
DLd	██████	██	██████	██	██████	██	██

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

B5. We note that the analyses of DBLd versus Ld and versus bortezomib-based therapies (BMP and BCd) are presented as pairwise results within the submission.

Please would you provide a fully incremental analysis of DBLd, DLd, Ld, BMP and BCd.

J&J does not consider it appropriate to present the cost-effectiveness results of DBLd versus all comparators (DLd, Ld, BMP and BCd) as a fully incremental analysis. A fully incremental analysis implies that the same population of patients could receive any of the treatment options. However, as detailed in the Company evidence submission and confirmed by UK clinical experts at the May 2025 UK Advisory Board, the introduction of DBLd into UK clinical practice would not displace the use of Ld or bortezomib-based therapies, given these treatments are typically reserved for distinct subgroups of patients with ASCT-ineligible NDMM.¹

Specifically, the doublet regimen, Ld, is now mainly reserved for patients who are not considered fit enough to receive a triplet regimen, or who live far from a hospital and prefer the convenience of an all oral option.²¹ Thus, these patients would also not be considered suitable for a quadruplet regimen such as DBLd. Although this comparison has been included in the cost-effectiveness analysis for completeness and in-line with the final scope, for the reasons outlined above and in the Company evidence submission, Ld is not considered a relevant comparator to DBLd. Further, bortezomib-based combination therapies are typically only used in patients with renal impairment, which represents a small proportion of the population under consideration. This was supported by clinical experts at the May 2025 UK Advisory Board who estimated that bortezomib-based combination treatments are only used in ~5% of patients in UK clinical practice.¹ Most patients with renal impairment currently receiving a bortezomib-based combination (BMP or BCd) would be unlikely to receive DBLd, as it is understood that the majority of these patients have multiple comorbidities that would preclude them from receiving a quadruplet combination.

DLd represents the only relevant treatment comparator to DBLd, although of note, the patients eligible for DLd and those who would be eligible for DBLd are not identical patient populations, given the addition of bortezomib would not be tolerated by all patients, as confirmed by clinical experts in the May 2025 Advisory Board.

B6. The model uses median time on treatment (median time to progression or median progression-free survival) to estimate 2L, 3L and 4L subsequent treatment costs, which will underestimate these costs. Is it possible to correct this and use mean data instead? If not, please provide a scenario using estimated means.

Unfortunately, it is not possible to leverage mean time on treatment data to inform estimates of subsequent treatment costs in the cost-effectiveness analysis since mean values for time on treatment for subsequent lines of therapy are rarely reported in the literature and not available in the public domain for regimens included in this analysis. Therefore, it is not possible to identify data to inform the EAG's requested calculations. Of note, the derivation of mean values for time-to-event data requires a complete dataset (i.e., where all patients have experienced an event), which is rare, particularly in indications such as multiple myeloma where there is the distinct possibility of prolonged disease remission among responders. The modelling approach taken in the Company evidence submission follows that accepted in TA917 and can be considered consistent for decision-making in this population.⁴

As highlighted by the EAG, the use of median values will slightly underestimate the subsequent treatment costs. J&J would like to highlight that more patients who receive DLd as a first-line

therapy progress on treatment and require subsequent lines of therapy than patients who receive DBLd at first line, and therefore the use of median values, as opposed to mean time on treatment (if available) represents a conservative modelling approach.

B7. There are some discrepancies between the drug costs used in the economic model and current eMIT prices (**Table 13**). Please would you update the model to use the EAG costs.

Table 13: Drug costs used within the economic model

Treatment	Price per vial/pack		Source
	Company	EAG	
Lenalidomide	£28.27	£36.10	eMIT 2024. Price per pack of 21 x 25 mg capsules; DHB148
Dexamethasone	£2.38	£2.19	eMIT 2024. Price per pack of 50 x 2 mg tablets; DFN018
Bortezomib	£97.54	£79.76	eMIT 2024. Price per vial of 2.5 mg powder for solution for injection; DLK037
Prednisolone	£12.78	£13.13	eMIT 2024. Price per pack of 56 x 25 mg tablets; DFN031
Cyclophosphamide	£153.00	£73.95	eMIT 2024. Price per pack of 100 x 50 mg tablets; DHA017

J&J acknowledges the discrepancies between the costs used in the economic model and the eMIT prices provided by the EAG. The economic model included with the Company evidence submission incorporated eMIT prices available at the time of submission. However, an updated dataset has been released since. Drug costs within the economic model have therefore been revised to reflect the latest eMIT values per EAG analyses. Please see Table 14 and Table 15 for the updated treatment and concomitant medication costs, respectively. Drug costs not included in these tables have not been changed as part of this response.

The impact of the updated drug costs on the ICER for DBLd vs DLd has been found to be negligible and, as such, there are no changes to any of the cost-effectiveness conclusions made in the original Company evidence submission. For completeness, the updated base case cost-effectiveness results for the comparison of DBLd vs DLd are presented in Appendix A.

Table 14: Updated treatment costs per vial/unit size

Treatment	Previous cost per vial/unit	Updated cost per vial/unit	Source
Bortezomib	£97.54	£79.76	eMIT 2025. Price per vial of Velcade 2.5 mg powder for solution for injection. Manufacturer: Takeda
Prednisolone	£12.78	£13.13	eMIT 2025. Price per pack of 56 prednisolone (generic) 25 mg tablets
Dexamethasone	£2.38	£2.19	eMIT 2025. Price per pack of 50 dexamethasone (generic) 2 mg tablets
Lenalidomide	£28.27	£36.10	eMIT 2025. Price per pack of 21 Revlimid 25 mg capsules. Manufacturer: Celgene Corporation
Cyclophosphamide	£153.00	£73.95	eMIT 2025. Price per pack of 100 cyclophosphamide (generic) 50 mg tablets: Baxter Healthcare Ltd

Abbreviations: eMIT: electronic market information tool.

Source: eMIT (2025)⁴

Concomitant medications

Updated treatment costs for concomitant medications, based on the latest eMIT values are included below in Table 15.

Table 15: Updated treatment costs for concomitant medications

Treatment	Previous cost per pack	Updated cost per pack	Source
Oral paracetamol	£0.79	£0.66	eMIT 2025. Price per pack of 100 500 mg tablets (generic)
Aciclovir	£1.91	£1.61	eMIT 2025. Price per pack of 56 400 mg dispersible tablets (generic)

Abbreviations: eMIT: electronic market information tool.

Source: eMIT (2025)⁴

Section C: Textual clarification and additional points

C1. The Darzalex/daratumumab SMPC supplied with the company reference pack does not include the DBLd combination for NDMM patients who are ineligible for ASCT in the list of therapeutic indications. Please supply the draft SMPC that includes the DBLd combination.

J&J would like to clarify that the draft SMPC supplied with the Company evidence submission reference pack does include the DBLd indication. The indication of relevance is provided on Page 32 of the SMPC (which represents the SC formulation); the indications listed prior relate to daratumumab IV, for which DBLd does not have an indication.

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Appendix A: Updated base case cost-effectiveness results (DBLd vs DLd)

The updated base case cost-effectiveness results are presented in Table 16 and Table 17.

Table 16: Deterministic base-case results (discounted daratumumab price)

Intervention	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	██████	8.59	██████						
DLd	██████	7.44	██████	██████	1.15	██████	Dominant	██████	██████

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 17: Probabilistic base-case results (discounted daratumumab price)

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
DBLd	██████	██████			
DLd	██████	██████	██████	██████	Dominant

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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.

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 UK charity dedicated to improving the lives and wellbeing of people living with myeloma and related conditions. Our 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 drug manufacturer (Johnson & Johnson) in the last 12 months. The table below shows the 2024 income from the relevant manufacturers and other pharmaceutical companies. Funding is received for a range of purposes and activities namely core grants, project specific work, honoraria, or sponsorship events. The funding received from the pharmaceutical industry in 2024 was approximately 4% of our annual income. <table border="1"> <thead> <tr> <th></th> <th>Core grant</th> <th>Research / Project</th> <th>Consultancy/ Honoraria</th> <th>Events</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Akt Health Communications Ltd</td> <td></td> <td></td> <td>240</td> <td></td> <td>240</td> </tr> <tr> <td>Alexion Pharma UK Ltd</td> <td></td> <td>10000</td> <td></td> <td></td> <td>10000</td> </tr> <tr> <td>The Binding Site Ltd</td> <td>25000</td> <td></td> <td></td> <td></td> <td>25000</td> </tr> <tr> <td>Bristol-Myers Squibb Pharmaceuticals Ltd</td> <td>10000</td> <td></td> <td></td> <td></td> <td>10,000</td> </tr> <tr> <td>Gilead Sciences</td> <td></td> <td>19000</td> <td></td> <td></td> <td>19,000</td> </tr> </tbody> </table>							Core grant	Research / Project	Consultancy/ Honoraria	Events	Total	Akt Health Communications Ltd			240		240	Alexion Pharma UK Ltd		10000			10000	The Binding Site Ltd	25000				25000	Bristol-Myers Squibb Pharmaceuticals Ltd	10000				10,000	Gilead Sciences		19000			19,000
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Gilead Sciences		19000			19,000																																					

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

	GlaxoSmithKline UK Limited			700		700	
	ITECHO Health Ltd		1500			6600	
	Johnson & Johnson / Janssen-Cilag Ltd	19400		200	13990	33590	
	Kyowa Kirin Ltd		5000			5000	
	Menarini Stemline UK Limited			1844	3423	5267	
	Merck Sharp and Dohme		15000			15000	
	Pfizer Limited		9391			9391	
	Oxford Biomedica UK Limited	5000				5000	
	Sebia				11192	11,192	
	Sanofi			720	33,990	34710	
	Takeda	20000		880	15389	36269	
	Totals	79400	59891	4584	77984	221,859	
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 and June-July 2025, 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 appraisals for daratumumab containing combinations. - 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

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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.” “The pain was unbelievable, and I’m not a big fan of taking medication at the best of times so being on pretty hardcore painkillers was quite hard work for a while.” <i>“Neuropathy in my feet is the only side effect I have experienced (other than some constipation). I’ve had to employ a part-time gardener due to neuropathy in my feet.”</i> Symptoms can be 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. 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 <i>“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.”</i> It is an incurable, relapsing and remitting cancer. The constant possibility of relapse has a huge psychological impact on patients. <i>“I think it’s the problem that you’re just in remission and you are going to get it again. How do you plan your life? I’ve planned a holiday for next April, but how will I be next April? Will I be okay?”</i>

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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)

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

	<i>“It makes you aware of your mortality. For a lot of my life, I felt invincible, but I’m not.”</i> <i>“I can put it to the back of my mind, but not fully. Sometimes I just fall asleep, I never used to do that. My wife copes by keeping herself busy, that’s important to her.”</i> 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. 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. 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. 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. 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 them²

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

	<i>“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.”</i> <i>“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.”</i>

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

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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. <i>"I thinking I am really lucky. I know that everyone's experience is different. My treatment worked well for me and I feel fit"</i> 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>"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."</i> The Myeloma UK Information Specialists have had over 400 calls and emails about HDT-SCT 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. <i>"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> <i>"I was told I was too old for SCT at 72, even although I saw myself as fit. I was told that it wasn't an option for me that the cut-off was 65."</i> <i>"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"</i>

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

	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>"I should have stayed on maintenance but in 2022 I made the decision to stop it. I had numbness in my feet and hands, and I was worried that if I carried on with the lenalidomide it would get worse and that it would affect my quality of life. At the time I stopped the numbness was travelling up my legs to my calves and even into my thighs"</i> <i>"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."</i> 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. <i>"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."</i> 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>"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."</i>

³ Myeloma UK (2024) Unmet need research: Diagnosing myeloma and its related conditions earlier and better, data on file

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

⁴Yong, K., et. al. (2016). Multiple myeloma: patient outcomes in real-world practice. British journal of haematology, 175(2), 252–264.

Advantages of the technology

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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 patients we spoke to about DVRD commented that it looked similar to the treatments they had because it contained some of the drugs they had as part of their initial treatment. They also said they would have been happy to get it as their initial treatment because it appeared to be more effective and therefore might keep their myeloma under control for longer. <i>“I think I’d have to discuss it with a consultant. I don’t know. If it was the best treatment, yes, obviously I would like it.”</i> <i>“The data looks good so I would say yes if I was given that option. The only thing is the side effects, especially the eyesight and risk of cataract. That would be a concern.”</i> DVRD delivers deep, sustained responses. In the CEPHEUS trial, 81% patients in the DVRD group had a complete response or better, 61% reached MRD-negativity and 49% had sustained MRD-negativity for 12 months or more.⁶ We believe the depth of responses DVRD delivers are higher than those delivered by the current standard of care. MRD negativity is associated with long remission times therefore this treatment has the potential to keep myeloma under control for longer than the current standard of care. Having a treatment option with high response rates also improves the quality of life of patients, reducing the anxiety associated with relapse and worry that the next treatment won’t work for them. Overall adding daratumumab to bortezomib, lenalidomide and dexamethasone did not increase overall toxicity. The adverse events were clinically manageable and consistent with the known toxicities of daratumumab, bortezomib, lenalidomide and dexamethasone. If approved, DVRD 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 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.

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	Reaching complete response, having undetectable levels of paraprotein is desirable for patients and has a huge psychological impact. <i>“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.”</i> <i>“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.”</i>

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

Disadvantages of the technology

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Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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. <i>“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.”</i> The mode of administration, with regular trips to the hospital, 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. <i>“It’s all very well saying that you’ve got to have injections, but you’ve got to go in for other things, you’ve got to go in to see your consultant... Because right now I have telephone conversations which is nice. I don’t have to go trailing in there. It’s a nightmare, it’s a nightmare for a lot of people, I’m sure. Parking is difficult. But you have to face whatever comes, I guess.”</i> Some patients particularly those who were in remission and no longer taking treatment felt that the continuous, ongoing nature of the treatment was a disadvantage. <i>“I have a super life, I have great friends, and I have dogs. I have always been really active. But I would find that [ongoing treatment] really difficult because I think that does cut you down an awful lot.”</i>

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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 organisation submission

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. DVRD gives patients who are on the borderline between transplant eligibility and ineligibility access to a treatment that delivers comparable results without having to balance the mortality risk and high side effect burden of having HDT-SCT. HDT-SCT is a very intensive treatment which has severe side effects, with patients spending 2-3 weeks in hospital and needing 3-6 months to recover. It is well established that side effect burden and recovery time are higher for less-fit patients and those with comorbidities. <i>“When they brought-up stem cell transplantation, I thought about my friend who was also diagnosed with myeloma. He had a SCT, and it was very grim. He took a long time to recover fully. I wanted to get treatment over and done with. Also, for me being 75/76 benefits didn’t outweigh the risks. If you only have 4-5-6 years on average, I didn’t want to spend one of those years in hospital, in recovery.”</i> <i>“When my mum was diagnosed, we had to decide between a stem cell transplant and standard chemotherapy early on. The transplant was only available in London, which brought up a lot of worries. We were trying to figure out how we’d manage the travel, who would support her while she was there, and how it would affect her emotionally. On top of that, because of her age and the stage of her myeloma, there was a real risk it wouldn’t work. Even if it did, we were told it might only give her one more year—five years instead of four with chemo. And as a carer, those choices don’t leave you—you carry the weight of them long after the moment has passed. I still wonder if we made the right call. “</i> <i>“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.”</i> 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.

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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 <i>eligible</i> for HDT-SCT have access to a quadruplet contain an anti-CD38 monoclonal antibody, a proteasome 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 CEPHEUS 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, DVRD 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 daratumumab to bortezomib, lenalidomide and dexamethasone did not increase overall toxicity.

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Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Patient expert statement

Multiple myeloma (untreated, stem cell transplant unsuitable)-daratumumab, bortezomib, lenalidomide and dexamethasone

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name

Dr David Owen, FRSB, OBE (2001: services to medical research and technology transfer)

2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. <u>(If you tick this box, the rest of this form will be deleted after submission.)</u>	☐
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: I am a talkative Welshman. I have spoken to other patients and find the Clinical Nurse Specialists very knowledgeable
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As a multiple myeloma patient and, currently in full remission, I have had only moderate impact on my life. Apart from some aches and pains in my hips and pelvis at the outset (responsive to Cocodamol 30), the major impact were dexamethasone on 1. my sleep pattern with too many sleepless nights and 2. diminishing clarity of sight. The Optician described "classical steroid cataracts. Dexamethasone was stopped. Sleep is better but, still not good. the cataracts are now repaired. I live as healthy a life as is reasonable to expect as an 81 year old. I spent almost 4 years as my wife's carer for a different bone marrow cancer; Mantle Cell Lymphoma. The "heavyweight" chemotherapy left her wheel chair dependent. As her carer my life was also transformed as caring was almost a full time task. I gave up most hobbies and was only to sustain a few work duties

	(Non-exec. Director at a number of biosciences companies). Fortunately, my wife was a most appreciative patient and our relationship was enhanced.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I have responded well to the first line daratumumab, lenalinomide, dexamethasone regime and am, currently, very pleased with my treatment. The myeloma may, of course, return in which case, I find comfort knowing that my doctors will have alternatives to help me. In the carer role, my wife had the hardest of treatments; all the classical adverse effects of “heavy” chemotherapy. Starting with R-CHOP followed by R-Chop plus cytosine. It took her to a point where a stem cell transplant was possible. That gave her 12-15 months of limited but, improved, life before the MCL returned. There was, clearly, a need for more effective and less damaging treatments. I understand (from a distance) that MCL can, now, be managed with better drugs, coupled with optimism that CAR-T is probably effective for some patients
10. Is there an unmet need for patients with this condition?	For myeloma, there is a need for alternatives should the daratumumab, lenalinomide, dexamethasone regime fails. I am aware of encouraging trial results with bi-specific antibodies and antibody-drug conjugates for multiple myeloma
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The focus is control of the myeloma with minimal adverse effects

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The dexamethasone impact on sleep cycle, possible elevated blood glucose levels and acceleration of cataract formation are negatives. These disadvantages apply to the front line therapy and are relevant in the potential new regime
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Don't know
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Don't know

Other issues

15. Are there any other issues that you would like the committee to consider?

No

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- My experience is that the front line therapy is effective
- Adverse effects are troublesome but, trivial compared with the lot of myeloma patients 10+ years ago
- It is re-assuring to know that there are/will be alternative treatments available should the current regime fail. In addition the topic under review in this process, bi-specific antibodies and antibody-drug conjugates are showing effective results in multiple myeloma.
-
-

Thank you for your time.

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External Assessment Group (EAG) Report Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Post factual accuracy check version

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Date completed	19/09/2025

Source of funding

This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme (HTA) Programme as project number NIHR176618.

Declared competing interests of the authors

None.

Acknowledgements

We thank the following for providing expert clinical advice to the project team and for reading and commenting on a draft of the report:

Dr Christopher Parrish, Associate Professor of Haematology, Leeds Institute of Clinical Trials Research, Honorary Consultant Haematologist, Leeds Teaching Hospitals NHS Trust.

We also thank Dr Keith Cooper, Principal Research Fellow, Southampton Health Technology Assessments Centre (SHTAC), and Dr Emma Maund, Research Fellow, Southampton Health Technology Assessments Centre (SHTAC), for providing a quality assurance review of the draft 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.

This report should be referenced as follows:

Kalita, N., Woods, L., Chinnery, F. Scott, D.A., Shepherd, J. Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when

a stem cell transplant is unsuitable: A Single Technology Appraisal. Southampton Health Technology Assessments Centre (SHTAC), 2025.

Contributions of authors

Neelam Kalita critically appraised health economic systematic review, critically appraised the economic evaluation, and drafted the report; Lois Woods critically appraised the clinical effectiveness systematic review and drafted the report; Fay Chinnery critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the indirect treatment comparisons and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project coordinator.

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- Text referenced on EAG report pages 24, 28, 133

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List of abbreviations

Acronym	Definition
AE	Adverse event
AIC	Akaike information criterion
AKI	Acute kidney injury
ASCT	Autologous stem cell transplant
ATC	Average treatment effect for the control
ATE	Average treatment effect
ATT	Average effect of the treatment
BCd = VCd	Bortezomib, cyclophosphamide and dexamethasone
BCP	Bortezomib, cyclophosphamide and prednisone
Bd	Bortezomib and dexamethasone
BeBd	Belantamab mafodotin, bortezomib and dexamethasone
BePomd	Belantamab mafodotin, pomalidomide and dexamethasone
BIC	Bayesian information criterion
BLd = VRd	Bortezomib, lenalidomide and dexamethasone
BMI	Body mass index
BMP = VMP	Bortezomib, melphalan and prednisone
BNF	British National Formulary
BP	Bortezomib and prednisone
BPI	Brief pain inventory
BSA	Body surface area
BSH	British Society for Haematology
CAA	Commercial access agreement
Cd	Carfilzomib and dexamethasone
CDF	Cancer drug fund
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CLd	Carfilzomib, lenalidomide and dexamethasone
COPD	Chronic obstructive pulmonary disease
CR	Complete response

Acronym	Definition
CRAB	Calcium levels (hypercalcemia), renal impairment, anaemia and bone disease
CRF	Case report form
CrI	Credible interval
CRUK	Cancer Research UK
CSR	Clinical study report
CUA	Cost-utility analysis
DBd	Daratumumab, bortezomib and dexamethasone
DBLd = DVRd	Daratumumab, bortezomib, lenalidomide and dexamethasone
DBMP=DVMP	Daratumumab, bortezomib, melphalan and prednisone
DBTd	Daratumumab, bortezomib, thalidomide and dexamethasone
DCO	Data cut-off
DIC	Deviance Information Criterion
DLd = DRd	Daratumumab, lenalidomide and dexamethasone
DNA	Deoxyribonucleic acid
DOR	Duration of response
DPomd	Daratumumab, pomalidomide and dexamethasone
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EEPRU	Economic Methods of Evaluation of Health and Care Interventions Policy Research Unit
EMA	European Medicines Agency
EMD	Extramedullary plasmacytoma;
EMN	European Myeloma Network
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment report
ESMO	European Society of Medical Oncology
ESS	Effective sample size
FDA	Food and Drug Administration
FE	Fixed effects
FISH	Fluorescence in situ hybridisation

Acronym	Definition
FLC	Free light chain
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GPM	General population mortality
HDT	High dose chemotherapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-relation quality of life
HSUV	Health state utility values
HTA	Heath technology assessment
ICER	Incremental cost-effectiveness ratio
Ig	Immunoglobulin
ILd	Ixazomib, lenalidomide and dexamethasone
iMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group;
INHB	Incremental net health benefit
IPD	Individual patient data
IPTW	Inverse probability of treatment weighting
IRC	Independent Review Committee
IRP	International Reliance Procedure
IRR	Injection related reactions
IsaBLd = IsaVRd	Isatuximab, bortezomib, lenalidomide and dexamethasone
IsaPomd	Isatuximab, pomalidomide and dexamethasone
ISS	International staging system
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system
KM	Kaplan-Meier
Ld = Rd	Lenalidomide and dexamethasone
LDH	Lactate dehydrogenase
LY	Life year
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison

Acronym	Definition
mAB	Monoclonal antibody
MGUS	Monoclonal gammopathy of undetermined significance
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MM	Multiple myeloma
MP	Melphalan and prednisone
MPT	Melphalan, prednisone and thalidomide
MRD	Minimal residual disease
MyPOS	Myeloma Patient Outcome Scale
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service
NDMM	Newly diagnosed multiple myeloma
NE	Not evaluable
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ONS	Office for National Statistics
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PaBd	Panobinostat, bortezomib and dexamethasone
PAR	Public assessment report
PAS	Patient access scheme
PD	Progressive disease
PF	Progression-free
PFS	Progression-free survival
PFS2	Progression-free survival on the next line of therapy
PI	Proteasome inhibitor
PK	Pharmacokinetics
Pomd	Pomalidomide and dexamethasone

Acronym	Definition
PRISMA	Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses
PR	Partial response
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSM	Partitional survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QLQ	Quality of life questionnaire
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random effects
RoB	Risk of bias
RRMM	Relapsed/refractory multiple myeloma
RWE	Real-world evidence
SAE	Serious adverse event
SBd	Selinexor, bortezomib and dexamethasone
SC	Subcutaneous
sCR	Stringent complete response
Sd	Selinexor and dexamethasone
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SmPC	Summary of Product Characteristics
SoC	Standard of care
TA	Technology appraisal
TD	Transplant deferred
TEAE	Treatment emergent adverse event
TEM	Treatment effect modifier
TFI	Treatment-free interval
TIE	Transplant ineligible
ToT	Time on treatment

Acronym	Definition
TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTP	Time to progression
UK	United Kingdom
USA	United States of America
VAT	Value added tax
VGPR	Very good partial response
WHO	World Health Organisation
WTP	Willingness to pay

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. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

Table 1 gives an outline of the key issues identified by the EAG.

Table 1 Summary of key issues

ID	Summary of issue	Impact on results	Report sections
1a	There is uncertainty in the exploratory network meta-analysis (NMA) for the indirect comparison of daratumumab, bortezomib, lenalidomide and dexamethasone (DBLd) versus Isatuximab, bortezomib, lenalidomide and dexamethasone (IsaBLd)	Unclear at present. Current estimates from the exploratory NMA indicate improved survival with DBLd but credible intervals are wide indicating no statistically significant difference.	3.4.2, 3.5.2 and 4.2.4
1b	There are no cost-effectiveness results comparing DBLd versus IsaBLd. IsaBLd was not included as a comparator in the company's economic model	Unclear at present. The company speculates that DBLd would be associated with both better efficacy and lower costs than IsaBLd. However, this is based on, as yet, untested assumptions and clinical effect estimates from the NMA which are uncertain (see issue 1a above)	3.4.2, 3.5.2 and 4.2.4
2	Uncertainty in the proportion of patients requiring second-line treatment.	An increase in total costs of DBLd, but DBLd continues to dominate DLd	5.2.2, 5.2.3 and 5.2.4

	Expert clinical advice suggests that the percentage of DBLd treated patients who receive second-line treatment is underestimated in the company's model. Survival data are immature currently, and the percentage progressing to second line is likely to increase.		

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 quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival
- Increasing progression free survival

Overall, the technology is modelled to affect costs by:

- Increasing total drug costs associated with DBLd compared with DLd
- Reducing the proportion of patients progressing to subsequent treatment

The modelling assumptions that have the greatest effect on the ICER are:

- The average subsequent treatment acquisition cost per model cycle (for both arms)
- The treatment acquisition cost of daratumumab (for both arms)
- The proportion of patients receiving subsequent treatment second-line, after having received DBLd first-line

1.3 EAG's key issues

Issue 1a There is uncertainty in the network meta-analysis (NMA) for the indirect comparison of daratumumab, bortezomib, lenalidomide and dexamethasone (DBLd) versus Isatuximab, bortezomib, lenalidomide and dexamethasone (IsaBLd)

Report section	3.4.2, 3.5.2 and 4.2.4
Description of issue and why the EAG has	(Please note that key issues 1a and 1b both relate to the same overarching key issue – the exclusion of comparator treatment IsaBLd from

identified it as important	the company submission. Key issue 1a focuses on implications for clinical effectiveness and Key issue 1b focuses on the implications for cost effectiveness). One of the comparator treatments in the NICE scope is the regimen of isatuximab, bortezomib, lenalidomide and dexamethasone (IsaBLd). This has recently been recommended by NICE for the same indication as this current appraisal (TA1098). The company did not include this comparator in their decision problem because a NICE recommendation (either positive or negative) on IsaBLd had not been made at that time. The EAG requested the company to include IsaBLd as a comparator (EAG clarification question A11) in their analysis. In response, the company provided an “exploratory” network meta-analysis (NMA) of IsaBLd vs. DBLd, for overall survival and progression free survival. This is the same NMA reported in the CS for DBLd versus the other comparators, provided by the company as a “supportive analysis” to the company’s primary indirect treatment comparison method - the inverse probability of treatment weighting (IPTW) approach using individual patient data (IPD). Without access to IPD from the pivotal IsaBLd study (the IMROZ trial) it will not be possible to apply the IPTW approach to the indirect comparison of DBLd versus IsaBLd. Instead, the NMA is the only source of evidence for DBLd versus IsaBLd, and it is subject to certain limitations such as the potential for bias due to inclusion of patient subgroup data for some of the trials. Given the uncertainty in the NMA results it would be prudent to consider an alternative ITC approach for consideration in decision making.
What alternative approach has the EAG suggested?	Alternative approaches to ITC such as a matched adjusted indirect comparison (MAIC). This would allow IPD from the pivotal DBLd trial (the CEPHEUS trial) (specifically the subgroup of patients who were ineligible for stem cell transplant) to be matched to aggregate data from the IMROZ trial.
What is the expected effect on the cost-effectiveness estimates?	Unclear at present. The company’s exploratory NMA showed numerical improvements in PFS and OS hazard ratios favouring DBLd, but with wide credible intervals which include 1, indicating uncertainty in the relative clinical effectiveness between DBLd and IsaBLd.
Could any additional evidence or analyses be provided to resolve this key issue?	Yes, an alternative approach to ITC as suggested above.

Issue 1b There are no cost-effectiveness results comparing DBLd versus IsaBLd

Report section	3.4.2, 3.5.2 and 4.2.4
Description of issue and why the EAG has identified it as important	(Please see key issue 1a above for the background to this key issue). The company did not include the comparator IsaBLd in their submission to NICE. In response to the EAG's request to update their analysis with the inclusion of this comparator (EAG clarification question A11) the company provided an exploratory network meta-analysis (NMA) of the clinical effectiveness of IsaBLd vs. DBLd. However, they did not incorporate this comparison into the economic model due to time constraints.
What alternative approach has the EAG suggested?	A fully incremental analysis of the cost effectiveness of DBLd, IsaBLd and DLd with an appropriate ITC (see key issue 1a). The economic model will need to be updated to include parameters relating to IsaBLd.
What is the expected effect on the cost-effectiveness estimates?	The company speculates that DBLd would be associated with both better efficacy and lower costs than IsaBLd. However, this is based upon assumptions around dosing regimens and time on treatment, and associated costs. It is also based on drug acquisition costs at list prices. Cost effectiveness estimates may change with application of patient access scheme (PAS) discounts, some of which are commercial in confidence and not known by the company. The EAG therefore considers the expected effect on cost effectiveness is currently uncertain.
Could any additional evidence or analyses be provided to resolve this key issue?	Yes, a fully incremental analysis as suggested above.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide, and dexamethasone.

Issue 2 Uncertainty in the proportion of patients requiring second-line treatment

Report section	4.2.5.1 and 4.2.5.2
Description of issue and why the EAG has identified it as important	We note that fewer patients in the DBLd arm receive second-line subsequent treatment (████) compared with patients in the DLd arm (81.25%). Our clinical expert considered it unlikely that the improvement in PFS in the DBLd arm would reduce the proportion of patients requiring second-line treatment by █████ compared with the DLd arm. Because median survival for the OS and PFS data from the CEPHEUS trial (DBLd arm) has not been reached, we would expect the proportion of patients requiring second-line treatment to increase with time.

What alternative approach has the EAG suggested?	We prefer to assume that 75% of patients in the DBLd arm receive second-line subsequent treatment, based on advice from our clinical expert.
What is the expected effect on the cost-effectiveness estimates?	The change increases DBLd total costs, but DBLd continues to dominate DLd (i.e. it is cheaper and more effective) in the company's base case after clarification.
Could any additional evidence or analyses be provided to resolve this key issue?	A later data cut from the CEPHEUS trial with data on the proportions of patients requiring subsequent treatment. The final data cut is expected in [REDACTED], though the company suggests this is not expected to reduce inherent long-term modelling uncertainty when considering a lifetime model time horizon.

1.4 Secondary issues identified by the EAG

Secondary issue 1 The modelled patient population characteristics may not necessarily be generalisable to clinical practice

Report section	4.2.3
Description of issue and why the EAG has identified it as important	The baseline characteristics of the modelled population were based on the autologous stem cell transplant (ASCT)-ineligible population in the CEPHEUS trial (mean age of patients: [REDACTED] years; proportion who are male: [REDACTED]). Clinical advice to the EAG is that patients seen in the NHS with newly diagnosed multiple myeloma (NDMM) ineligible for an ASCT are likely to be slightly older, with a higher proportion of males, compared with the estimates obtained from the CEPHEUS trial.
What alternative approach has the EAG suggested?	Based on expert clinical advice we prefer to use a mean age of 75 years and a proportion of 55% of patients who are male in our base case, to be more reflective of NHS practice.
What is the expected effect on the cost-effectiveness estimates?	DBLd continues to dominate DLd (i.e. it is cheaper and more effective) in the company's base case after clarification.
Could any additional evidence or analyses be provided to resolve this issue?	Further advice from clinical experts. Registry data (if available) may also be informative.

Abbreviations: ASCT, autologous stem cell transplant; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; NDMM, newly diagnosed multiple myeloma

Secondary issue 2 Second- and third-line subsequent treatment proportions do not reflect NHS practice

Report section	5.2.2, 5.2.3 and 5.2.4
Description of issue and why the EAG has identified it as important	The company's assumptions for treatments used at second and third line may not necessarily reflect clinical practice. The company's modelled subsequent treatment resource use is for patients receiving DLd at first line: • Second line: 0% patients receive bortezomib, 0% receive carfilzomib, lenalidomide and dexamethasone (CLd), 87.5% receive belantamab mafodotin, bortezomib and dexamethasone (BeBd) • Third line: 41.18% patients receive selinexor, bortezomib and dexamethasone (SBd), 17.65% receive panobinostat, bortezomib and dexamethasone (PanoBd), and 41.18% receive cyclophosphamide.
What alternative approach has the EAG suggested?	Clinical advice to the EAG is that for patients receiving DLd at first line in UK practice approximately 10% are likely to receive bortezomib, about 3-5% receive CLd and approximately 74% receive BeBd second-line. In addition, SBd use is likely to be nearer 10% than 40%, because availability is currently limited. The EAG considers that SBd scarcity applies to subsequent treatment for both DBLd and DLd. Draft NICE guidance for NICE TA ID6212 (published in June 2025) is that BeBd is recommended in adults with if they have had one previous line of therapy. The EAG's expert commented that it is difficult to predict the uptake of this new regimen, but considered the company's estimate to be a little high, noting that toxicity from this regimen might be prevent some patients from taking it. The EAG-preferred subsequent treatment resource use: • Second line (DLd): 10% receive bortezomib, 4% receive CLd, 73.5% receive BeBd • Third line (DBLd and DLd): 10% patients receive SBd; other third line subsequent treatments adjusted by Dirichlet calculation (PanoBd = 26.86%, cyclophosphamide = 62.67%)
What is the expected effect on the cost-effectiveness estimates?	DBLd continues to dominate DLd (i.e. it is cheaper and more effective) in the company's base case after clarification.
Could any additional evidence or analyses be provided to resolve this issue?	Further advice from clinical experts on the distribution of the subsequent treatments among patients in UK clinical practice. Registry data (if available) may also be informative.

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; BeBD, belantamab mafodotin, bortezomib and dexamethasone; CLd, carfilzomib, lenalidomide and dexamethasone; DBLd: daratumumab,

bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio, PBd, panobinostat, bortezomib and dexamethasone; SBd, selinexor, bortezomib and dexamethasone

1.5 Company's modelling errors identified by the EAG

We did not identify any technical calculation errors in the company's economic model.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 shows the impact on the ICERs for DBLd versus DLd, based on the EAG's preferred modelling assumptions. DBLd remains the dominant treatment in most cases (i.e. it is both less costly and more beneficial than DLd).

Table 2 Summary of EAG's preferred assumptions and ICER, DBLd vs DLd

Scenario	Incremental cost	Incremental QALYs	ICER (change from company's base case)
Company's deterministic base case (company model dated 21 Aug 2025)	██████	████	Dominant
Key issue 2: 75% of patients receiving DBLd 1L go on to receive subsq Tx 2L	████	████	Dominant
Mean age of patients: 75 years; proportion of males: 55%	██████	████	Dominant
EAG-preferred subsq Tx resource use	██████	████	Dominant
EAG's preferred base-case deterministic	██████	████	£14,903
EAG's preferred base-case probabilistic	██████	████	£17,078

EAG considers a disease severity modifier of 1.0 is appropriate

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio. QALY, quality-adjusted life-year; subseq Tx, subsequent treatment

1.7 Outline of confidential comparator or subsequent treatment prices

The cost-effectiveness results in this report include the confidential [REDACTED]. However, discounts for other therapies in the economic model are not included. Cost-effectiveness results including all appropriate PAS discounts are reported in a separate confidential addendum to this report. Therefore, the ICERs in this report do not reflect the actual prices that would be paid by the NHS.

Other treatments with commercial arrangements that have been taken into account in the confidential appendix include:

- Bortezomib
- Lenalidomide
- Carfilzomib
- Selinexor
- Belantamab mafadotin
- Panobinostat
- Ixazomib
- Pomalidomide
- Teclistamab

2 Background

This report critiques the company submission for daratumumab with bortezomib, lenalidomide and dexamethasone (DBLd) for untreated multiple myeloma when a stem cell transplant is unsuitable.

2.1 Critique of the company's description of underlying health problem

Multiple myeloma is a blood cancer in which there is an uncontrolled proliferation of malignant plasma cells produced in the bone marrow. This suppresses the production of other blood cells that fight infection, transport oxygen and enable blood clotting. Consequently, patients can experience bone pain, bone fractures, tiredness, infections, hypercalcaemia and kidney problems. The malignant myeloma cells undergo genetic mutations over the course of the disease, producing clones and subclones, which increases resistance to treatments over time.

The company submission (CS) provides a detailed description of multiple myeloma in terms of its biologic and genetic characteristics, course of disease, symptoms, prognostic risk factors, long-term outcomes, and epidemiology (CS sections 4.3.1 and 4.3.2). Key things of note include:

- The heterogeneous nature of the disease, with prognosis varying from patient to patient.

- The relapse-remission pattern of disease, driven by secondary genetic events giving rise to treatment-resistant subclones. This is referred to as clonal heterogeneity.
- The duration of remission diminishes at each subsequent treatment line. This is caused by production of additional clones, a consequence of genetic mutations.
- It is important to achieve a deep and durable response to first line treatment, measured by the amount of malignant myeloma cells residing in the bone marrow. This is known as 'minimal residual disease' (MRD) negativity and is associated with increased progression-free survival and overall survival.

The CS also gives a comprehensive account of the effects of multiple myeloma on patients and carers, in terms of health-related quality of life (HRQoL), activities of daily living, prevalence and severity of symptoms (CS section 4.3.3).

2.2 Critique of the company's overview of current service provision

The CS cites clinical guidelines on the management of multiple myeloma produced by the British Society for Haematology (BSH),¹ European Society of Medical Oncology (ESMO),² European Myeloma Network (EMN),³ National Comprehensive Cancer Network (NCCN)⁴ and NICE (NG35)⁵ (CS section 4.3.4). The CS points out that the NCCN and EMN guidelines have recently included DBLd as a recommended treatment option in newly diagnosed transplant-ineligible patients. The CS considers the NICE guideline (NG35) (last updated October 2018) is most relevant to UK clinical practice. This is in addition to NICE guidance on multiple myeloma treatments produced since the guideline was published (TA917, TA587 and TA228, listed below).

In clinical practice the starting point for newly diagnosed patients is to determine suitability for intensive treatment, comprising high dose chemotherapy followed by autologous stem cell transplant (ASCT). The CS states that many patients are not fit enough to undergo ASCT and are considered transplant ineligible. The NICE recommended treatment options for transplant ineligible patients include:

- Daratumumab with lenalidomide and dexamethasone (DLd) for untreated multiple myeloma when a stem cell transplant is unsuitable (TA917)⁶
- Lenalidomide plus dexamethasone (Ld) for previously untreated multiple myeloma (TA587)⁷

- Bortezomib in combination with an alkylating agent and a corticosteroid if the patient is unable to tolerate or has contraindications to thalidomide (TA228)⁸
- Thalidomide in combination with an alkylating agent and a corticosteroid (TA228)⁸

The company considers DLd to be the current standard of care for the transplant ineligible patient population, with an estimated market share of 82.5%. Very few patients are said to be treated with the other options. For example, Ld may be given to patients unable to tolerate a triplet therapy regimen (and hence, would not be considered for a quadruplet therapy such as DBLd. Bortezomib containing regimens are used in patients with renal impairment, which the CS estimates as being around 5% of the patient population. Thalidomide treatment regimens are no longer in use.

The EAG's expert clinical adviser agrees with the company that DLd is the current standard of care, estimating it to be used by over 90% of patients at first line. The expert commented that Ld is not significantly less toxic than DLd but it is significantly less effective and hence why DLd is the preferred option. However, some patients may choose Ld over DLd out of preference for oral only regimen (daratumumab is administered parentally and thus requires hospital appointments). Bortezomib containing regimens such as bortezomib, melphalan and prednisone (BMP) and bortezomib, cyclophosphamide and dexamethasone (BCd) are being phased out in most centres.

2.2.1 Background information on DBLd

The anticipated marketing authorisation of daratumumab relevant to this NICE technology appraisal is

[REDACTED] (CS section 4.1). Of note, daratumumab is also indicated for use as part of other regimens across the multiple myeloma transplant eligible and ineligible treatment pathways (see Figure 1 below).

The CS describes the mechanism of action of daratumumab noting that it has distinct direct and indirect antitumour activities. One of the indirect activities is an immunomodulatory function, which involves off tumour, on target depletion of tumour promoting CD38-positive immunosuppressive cells. In patients with a response to treatment this additional mechanism contributes to "augmentation of anti-tumour immune responses to recognise and drive further the elimination of tumour cells" (CS Table 2).

The CS notes that the introduction of DLd (recommended by NICE in 2023 (TA917)) significantly has improved outcomes for transplant ineligible patients compared to the then standard of care, Ld. However, the CS reports that only around a third of patients achieve MRD negativity and less than a fifth sustain MRD negativity for more than a year (this is known as 'durable MRD'). It is suggested that, given the pivotal role MRD plays as a prognostic factor of long-term outcomes, there is unmet need for a more efficacious treatment regimen.

The CS discusses the rationale for a quadruplet treatment regimen in place of the current triplet regimen standard of care, DLd. It is noted that introduction of bortezomib to other drug regimens has been shown to prolong survival in multiple myeloma patients, both transplant eligible and ineligible, hence the addition of bortezomib to DLd (i.e. DBLd – the technology under appraisal). The company suggests that a synergistic effect is achieved through the combination of the distinct modes of action of the DBLd constituent drugs: an anti-CD38 monoclonal antibody (daratumumab); a proteasome inhibitor (bortezomib); an immunomodulatory drug (lenalidomide) and a glucocorticoid (dexamethasone). Multiple biological pathways are targeted with the aim of maximising cytotoxicity and leading to deeper and more durable responses than regimens with fewer pathways.

The CS contends there is unmet need for a quadruplet combination therapy which can address clonal heterogeneity, to achieve higher rates of MRD negativity and sustained MRD negativity. In turn it is suggested that this would improve outcomes including tumour response and survival.

2.2.2 The position of DBLd in the care pathway

CS Figure 8, reproduced below as Figure 1, is the company's illustration of the transplant ineligible care pathway, comprising NICE recommended treatments and technologies currently under appraisal, across multiple lines of therapy. The figure shows the proposed position of DBLd as a first line treatment in the transplant ineligible population. The CS states that the positioning has support from UK clinical experts the company consulted. It is anticipated that DBLd, if recommended by NICE, would displace DLd as the standard first line treatment in this patient population. DBLd would not, however, displace Ld as this is used by patients unable to tolerate a triplet combination (i.e. DLd) and hence would not tolerate a quadruplet combination.

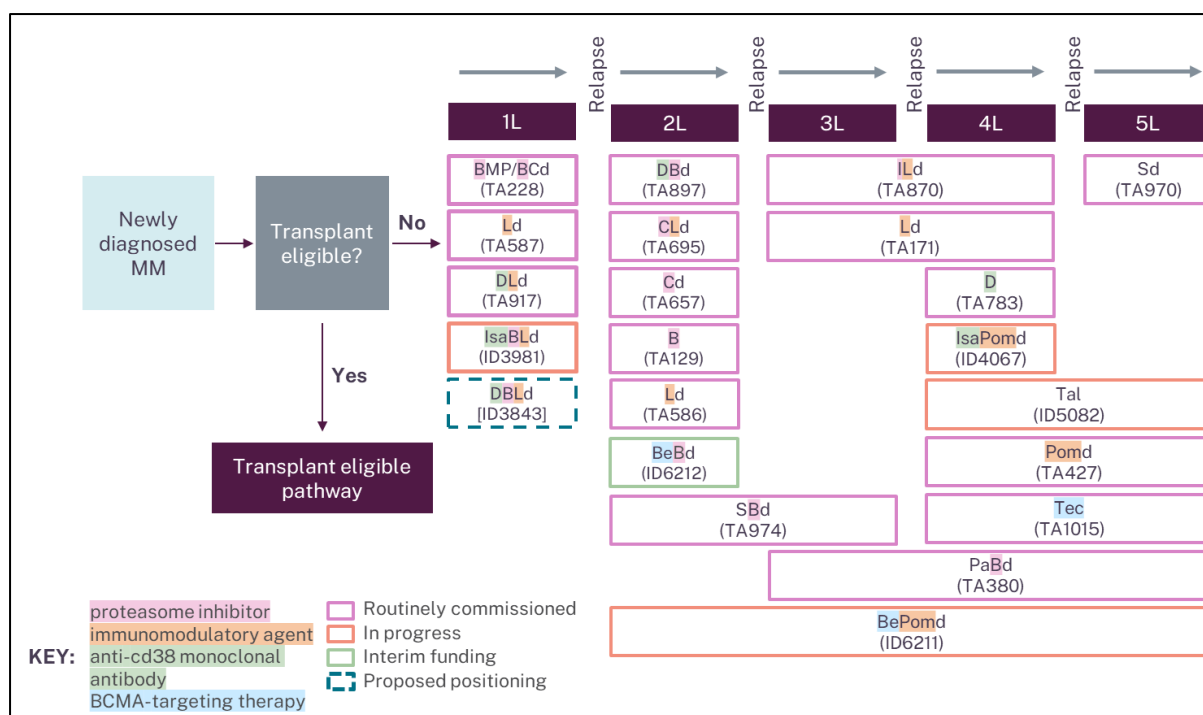


Figure 1 The company's illustration of the care pathway for transplant-ineligible multiple myeloma patients

NB. The figures in parentheses refer to existing NICE guidance (TA) or NICE appraisals in progress (ID number)

Of note, NICE have recently recommended a quadruplet regimen, isatuximab, bortezomib, lenalidomide and dexamethasone (IsaBLd) for untreated multiple myeloma in adults when an autologous stem cell transplant is unsuitable (TA1098, 24th September 2025). This provides an additional first line treatment option in the transplant ineligible population and is therefore a relevant comparator to DBLd in this technology appraisal (we discuss the comparator treatments in more detail in section 2.3).

The EAG's clinical adviser agrees with the company's proposed position of DBLd as a first-line treatment. The expert commented that in practice bortezomib would likely be given as a weekly injection rather than twice weekly as was the case in the pivotal CEPHEUS trial (see section 3.2.1). They also noted that there is widespread acceptance that weekly and twice-weekly are equivalent in terms of efficacy, and that weekly offers a better toxicity profile.

The preference for weekly injections accords with clinical practice for bortezomib when included as part of other regimens. The reduction in the number of hospital visits for bortezomib injections would be appealing to many patients. The expert acknowledged the likely increase in toxicity from the addition of bortezomib would mean that patients at the

frailer end of the spectrum would choose DLd rather than DBLd. Thus, in practice DBLd would tend to be offered to younger fitter patients, until there is more evidence available on toxicity in older more frail patients. Overall, however, the addition of the fourth drug to the regimen would be attractive to many patients and clinicians.

The expert also suggested that if DBLd is recommended by NICE there may be an increase in the proportion of patients being classed as transplant ineligible. The improvement in outcomes attributable to DBLd is almost comparable to the outcomes of treatment in patients who have had a transplant. The prospect of effective treatment with DBLd may increase preference for the transplant ineligible pathway in patients on the borderline of eligibility. On the issue of the criteria for assessing transplant eligibility, the expert noted there is a lack of consensus and there is widespread variation in practice. In the expert's practice the key factors considered are age and physical fitness, function and comorbidities.

2.3 Critique of the company's definition of decision problem

Table 3 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this. The main observation from Table 3 is that, generally, the decision problem matches the scope of the appraisal. There only area of disagreement is the comparator treatments. The company regard DLd to be the only clinically relevant comparator from the scope, and *in principle* they exclude the other comparators on the basis that these are rarely used in practice. Nonetheless, they include the comparators in their assessment of clinical effectiveness and cost effectiveness (the exception is IsaBLd which is currently not modelled).

Table 3 Summary and critique of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with untreated multiple myeloma when a stem cell transplant is unsuitable	[REDACTED]	The population addressed in the company submission is line with the NICE final scope. However, to align with the anticipated wording for the indication of interest in the draft daratumumab summary of product characteristics (SmPC), the target population is described as [REDACTED] " throughout the submission.	For clarity NDMM (as referred to in the CS) refers to 'newly diagnosed multiple myeloma' and is analogous to 'untreated multiple myeloma' as per the NICE scope. In effect, both refer to multiple myeloma patients who are treatment naïve. NB, although the scope and decision problem are aligned, the patient population is narrower than the anticipated marketing authorisation. The anticipated indication for DBLd is in "[REDACTED]" A separate NICE appraisal of DBLd in patients who are suitable for transplant is in progress (ID6249)
Intervention	DBLd	DBLd	N/A – in line with the NICE final scope	In line with the NICE final scope.
Comparator(s)	Daratumumab with lenalidomide and dexamethasone (DLd)	Daratumumab with lenalidomide and dexamethasone (DLd)	DLd represents the current National Health Service (NHS) standard of care (SoC) which was confirmed by a UK Advisory Board meeting	Please note, despite the company's justification for omitting Ld and bortezomib-containing regimens as comparators from the decision problem, they have, nonetheless,

	• Lenalidomide with dexamethasone (Ld) • Bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone) • Isatuximab with bortezomib, lenalidomide and dexamethasone (IsaBLd; subject to NICE evaluation)	• Lenalidomide with dexamethasone (Ld) • Bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone)	in May 2025 when clinical experts estimated that DLd accounts for 82.5% (range: 70–90%) of the treatment share for ASCT-ineligible NDMM patients.⁹ [REDACTED] As such, DLd is considered the main comparator in this submission. Following the NICE recommendation for DLd in 2023 (TA917), J&J understand the doublet regimen, Ld, is now mainly reserved for patients who are not considered fit enough to receive a triplet regimen, or who live far from a	included these as comparators in their submission for completeness. However, for interest we comment <i>in principle</i> below on the company's rationale for excluding these comparators. • Ld. Given that Ld tends to be used in patients unable to tolerate BLd it follows that they would similarly not be able to tolerate DBLd. The EAG therefore accepts that Ld would not necessarily be a relevant comparator to DBLd. • Bortezomib containing therapies. Expert clinical advice to the EAG agrees with the company that these regimens (e.g. BCd and BMP) are rarely used now in this patient population. This supports the company's proposed omission • IsaBLd. The company notes that this had not yet received a positive NICE recommendation and therefore they did not include it as a comparator. As we discuss in section 3.4 and 3.5, we requested the company to include IsaBLd as a comparator, to inform decision making should NICE make a positive recommendation for IsaBLd from NICE (clarification question A 11). The company

			hospital and prefer the convenience of an all oral option. Similarly, these patients would not be considered suitable for a quadruplet regimen such as DBLd, so Ld is not considered a relevant comparator in this submission. This was confirmed by clinical experts consulted during the May 2025 UK Advisory Board meeting and as part of an ongoing appraisal for IsaBLd in this indication. Bortezomib combination therapies are typically only used in a small proportion of patients with renal impairment. This was supported by clinical experts at the May 2025 UK Advisory Board who estimated that bortezomib-based treatments are only used in ~5% of patients.³ Therefore, J&J do not consider bortezomib combination therapies to be a relevant comparator	provided an indirect comparison of the clinical effectiveness of IsaBLd vs. DBLd, but they have not yet incorporated this into the economic model.

			to DBLd in this indication, considering their minimal usage in UK clinical practice. However, for completeness, and in line with the final scope, analyses versus Ld and bortezomib-based therapies are presented within this submission. At the time of this submission, the NICE appraisal for IsaBLd is ongoing and IsaBLd has not received a positive recommendation in this indication. As such, IsaBLd cannot be considered to represent routine clinical practice for ASCT-ineligible NDMM patients and therefore does not represent a relevant comparator for DBLd.	
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates	• Overall survival (OS) • Progression-free survival (PFS) • Response rates	N/A – in line with the NICE final scope.	In line with the NICE final scope.

	• Time to treatment discontinuation (TTD) • Minimal residual disease (MRD) negativity • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)	• Time to treatment discontinuation (TTD) • Minimal residual disease (MRD) negativity • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)		
Economic analysis	Please note, standard NICE reference case requirements are listed in the scope, but for brevity the EAG has not reproduced them here.	The economic analysis aligns with that described in the NICE decision problem	N/A	In line with the NICE final scope.
Subgroups	None identified	None identified	N/A – No subgroups have been identified for which DBLd is expected to be more clinically effective and cost effective. J&J do not consider there are any other groups that should be examined separately.	N/A
Special considerations including issues related to equity or equality	None	None	-	-

3 Clinical effectiveness

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 and 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Section 3.4 and Section 3.5 critique the indirect comparisons presented by the company.

3.1 Critique of the methods of review

The company carried out a systematic literature review (SLR) to identify clinical efficacy and safety evidence for the DBLd treatment combination and relevant comparators. Searches were initially carried out in November 2020, and the review was updated in August 2024 and in April 2025. The company also carried out a combined economic SLR and a separate SLR to identify quality of life evidence, discussed below in the cost-effectiveness section of this report (sections 4.1 and 4.2.6.1).

We summarise our assessment of the clinical SLR in Table 39 in the Appendices of this report. Overall, we found the SLR was conducted to a good standard, all relevant documentation was provided, and it is up to date with no gaps in coverage for search dates or sources. It is not likely to have missed any relevant studies.

The SLR identified 27 unique studies (90 publications), from the original search and both update searches, that evaluated all relevant treatments for ASCT-ineligible patients with NDMM (CS section 5.1; CS Appendix B.1.3; CS Appendix Figure 1). One relevant RCT was identified evaluating the DBLd treatment combination in the ASCT-ineligible NDMM population: the CEPHEUS trial, discussed in section 3.2 below.

3.2 Critique of the methods of the trials of the technology of interest

The company identified one RCT evaluating DBLd in untreated transplant-ineligible MM patients: the CEPHEUS trial.¹⁰ CEPHEUS (NCT03652064) is the only trial that provides efficacy data for the DBLd combination in the NDMM ASCT-ineligible population thus supporting its marketing authorisation with the regulatory bodies. We summarise the main characteristics of the CEPHEUS trial in section 3.2.1 below.

3.2.1 CEPHEUS study characteristics

Error! Reference source not found. shows the general characteristics of the CEPHEUS trial.

Table 4 CEPHEUS study characteristics

Role in this evaluation	Company pivotal trial supporting marketing authorisation. • Source of efficacy and safety data for DBLd versus BLd reported for the ASCT-ineligible subgroup in CS sections 5.3 to 5.8 and CS Appendix K, (and for the overall trial ITT population reported in CS Appendix L). • Source of efficacy data for DBLd in the company's indirect treatment comparisons, and therefore for OS, PFS and TTD DBLd outcomes (adjusted via IPTW methods) in the economic model. • Direct source of ASCT-ineligible baseline characteristics data (CS section 6.2.1; CS Table 52), AE rates (CS section 6.3.5), and base case utilities (CS section 53) for the economic model.
Study type	Ongoing, randomised, open-label, multicentre, Phase III trial comparing DBLd to BLd. Randomisation: 1:1; stratified by International Staging System (ISS) and age/transplant eligibility.
Patient group	Newly diagnosed multiple myeloma and either, • <70 years and ineligible for ASCT (ASCT-ineligible), • <70 years and refused (deferred) ASCT, or • ≥70 years (ASCT-ineligible). • ITT (randomised) population: DBLd N=197, BLd N=198, Total N=395 • ASCT-ineligible population: DBLd N=144 (73%), BLd N=145 (73%), Total N=289 (73%)
ASCT-ineligible criteria	Age ≥65 years or age 18-65 years with comorbid conditions likely to have a negative impact on tolerability of high-dose chemotherapy for stem cell transplant (CEPHEUS protocol section 5.1).
Intervention	Daratumumab, bortezomib, lenalidomide and dexamethasone (DBLd). Dosing for each component is detailed in CS Table 3. This regimen adds bortezomib to the current NHS standard of care regimen daratumumab, lenalidomide and dexamethasone (DLd) (NB. DLd is not a comparator in this trial)

Comparator	Bortezomib, lenalidomide and dexamethasone (BLd). Dosing for each component is detailed in CS Table 3. (NB. BLd is not a regimen used in the NHS).
Duration	First participant screened November 2018; latest data cut May 2024 for the final PFS analysis, duration of follow-up: 58.7 months (range: 0.1-64.7) for the overall trial population. Final data cut, for the final overall survival analysis, expected in [REDACTED].
Location	International across North and South America, Europe, Israel, and Japan. Nine sites in the UK; N=25 UK participants.

Source: CS sections 5.2, 5.3, 5.12; CS Tables 3 and 4; Usmani 2025¹⁰

Abbreviations: AE, adverse events; ASCT, autologous stem cell transplant; BLd, bortezomib, lenalidomide, dexamethasone; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DLd, daratumumab, lenalidomide, dexamethasone; IPTW, inverse probability of treatment weighting; ISS, International Staging System; ITT, intention to treat; LD, lenalidomide, dexamethasone; OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation; UK, United Kingdom.

The ASCT-ineligible population is a subgroup of the overall CEPHEUS trial population, consisting of those who, according to the trial inclusion criteria, are <70 years and ineligible for ASCT and those who are ≥70 years (and ineligible for ASCT). Those included in the trial who are <70 years and for whom transplant was not planned as the initial therapy ('transplant deferred', also referred to in the CS as patients who refused transplant) are not relevant to the company's decision problem. The ASCT-ineligible population is the majority trial population (N= 289/395; 73%), but it is not a pre-specified subgroup listed in the study statistical analysis plan (CEPHEUS SAP section 2.5). The EAG considers this a post-hoc subgroup of the trial,

The comparator in the CEPHEUS trial is bortezomib, lenalidomide and dexamethasone (BLd). BLd is not a treatment in the UK clinical pathway for ASCT-ineligible NDMM (section 2.2.2 above) and as such is not included in the NICE scope or company decision problem (section 2.3 above). In UK clinical practice the most widely used treatment in this indication is DLd. Importantly, therefore, CEPHEUS does not provide the *relevant comparative* evidence for this appraisal.

The trial is ongoing, and the data cut off for the final overall survival analysis is not expected until [REDACTED].

3.2.2 CEPHEUS population baseline characteristics

Baseline characteristics for the CEPHEUS trial are reported for the ASCT-ineligible population in CS Table 6 (and for the overall trial population in CS Table 5).

The baseline characteristics of the ASCT-ineligible population are similar to the those of the overall trial population. This is not unexpected because age/transplant eligibility was a stratification factor at randomisation. The ASCT-ineligible population was slightly older (median age 72 years; ■■■ ≥70 years) than the overall trial population (median age 70 years; 55.4% ≥70 years). However, this did not automatically translate to a less fit population on comparison of the ECOG and frailty scores of the overall and ASCT-ineligible trial populations. It is not implausible that the overall trial results could be relevant to an ASCT-ineligible population.

Focusing on the ASCT-ineligible population (CS Table 6), the baseline characteristics are similar across both DBLd and BLd arms with the following exceptions:

- **ECOG scores.** There were slightly more participants with ECOG performance status 2 (signifying that the patient is capable of all self-care but unable to carry out any work activities) in the DBLd arm (11.8%) compared to the BLd arm (6.9%), corroborated with slightly fewer participants with a frailty score of 0 (i.e. assessed as fit according to the Myeloma Geriatric Assessment score) in the DBLd arm (56.9%) compared to the BLd arm (60.7%).
- **Gender.** Overall, the proportions of male and female ASCT-ineligible participants in the trial were about even, however, the DBLd arm had slightly fewer male participants (45.1%) compared to the BLd arm (56.6%).

The participants in the DBLd arm may be slightly less fit but this would make the results for DBLd in comparison to BLd more conservative. Sex is a prognostic factor (CS Table 29) and the EAG's clinical expert advised that males in the general MM population generally fare worse. The expert noted that fewer male participants in the DBLd arm than in the BLd arm means it is less challenging to make DBLd effective, therefore results could favour DBLd due to gender imbalance between arms in the CEPHEUS trial.

The ASCT-ineligible participants in the CEPHEUS trial can be generally considered as representative of ASCT-ineligible patients in NHS clinical practice. The EAG's clinical expert

noted that the median age at diagnosis in the UK is 71, which is between the median ages of 70 (overall trial population) and 72 (ASCT-ineligible trial population). The EAG's clinical expert advised that multiple myeloma is more common in men than women, but this is not reflected in the trial whereby the ASCT-ineligible population had 49.1% female participants and 50.9% male participants overall.

3.2.3 CEPHEUS risk of bias assessment

The company, using the Cochrane Risk of Bias (RoB) 2.0 tool,¹¹ assessed the CEPHEUS trial to be at low risk of bias (CS Table 11 with justifications; summary in CS Appendix Table 21).

The EAG checked the company's RoB assessment and noted our agreement with the company's judgements (see Table 40 in Appendix 7.2 of this report). Note that the Cochrane RoB 2.0 tool is designed to assess the risk of bias for each trial outcome independently, but the company assessment considers all outcomes together. The study design is open label and there is potential for attrition and detection bias, which would affect the patient reported outcomes but is less likely to affect the survival and response outcomes as these are more objective endpoints. Therefore, we assess the efficacy outcomes for survival and response in CEPHEUS as having 'some concerns' due to raising concerns in at least one domain, that is for 'bias in measurement of the outcome', but low for all other domains.

3.2.4 CEPHEUS statistical methods

The statistical methods for the CEPHEUS trial are reported in CS Table 8 and the trial Statistical Analysis Plan (SAP).

Analysis populations: Both overall and ASCT-ineligible trial populations were analysed according to an intention to treat (ITT) analysis, defined as all patients randomly assigned to either DBLd or BLd for the efficacy outcomes. It is not explicitly stated whether or not all patients were analysed in the same trial arm they were randomised to. The safety analysis sets (for overall and ASCT-ineligible populations) were all participants who were randomised and received at least one administration of any study treatment (CS Table 7).

Sample size calculation: The power calculation was based on the ITT population and required 180 participants to be randomised to each arm (CS Table 8), with a total of 360 patients overall. Recruitment exceeded this target with a total of 395 patients randomised.

The sample size of the ASCT-ineligible population (n=289) is smaller than the overall trial population (n=395). Whilst this is still a sizeable proportion (73.1%) of the overall sample it is not statistically powered to detect a significant difference between DBLd and BLd for the MRD negativity rate, risk of progression, or death.

Analysis of outcomes: Appropriate, standard statistical methods were applied: Cochran Mantel Haenszel tests and Mantel-Haenszel odds ratios for the primary outcome of MRD negativity rate and other binary secondary outcomes; stratified log-rank tests, KM method and stratified Cox's regression model for time-to-event-outcomes; time to response was compared descriptively.

Methods to account for multiplicity: for the overall trial population, the key secondary outcomes of $\geq$ CR rate, PFS and sustained MRD negativity rate, were sequentially tested only if the results for the primary outcome of MRD negativity rate were statistically significant. This approach appears to be applied in the analysis of the ASCT-ineligible population (as well as the ITT population), this sub-population is not statistically powered for the primary outcome.

Handling of missing data: Neither the amount of missing data nor the methods for handling missing data are reported in the CS. The SAP states that no data imputation will be applied for missing safety and efficacy evaluations (CEPHEUS SAP section 2.8). The CSR states that ■■■% of bone marrow samples for MRD testing were evaluable with a ■■■% rate of successful calibration (CSR section 5.1.2.2) so there is no great concern about missing data for MRD negativity. For OS, PFS, PFS2 and other time-to-event outcomes, missing data was managed by the usual censoring rules for clinical trials (CEPHEUS SAP sections 5.3.2.1 and 5.4.2). Only ■■■ PFS events were censored due to missing disease evaluations for the final PFS analysis (CSR section 5.1). Sensitivity analyses of patient reported outcomes used the mixed model for repeated measures, missing at random, method.

Sensitivity analyses: adjustments for COVID-19: primary and secondary outcomes were adjusted for deaths due to COVID-19, i.e. COVID-19 deaths were censored (CS section 5.4.1, page 60). In the ASCT-ineligible population ■■■ of participants died due to COVID-19. Most deaths occurred during the year ■■■ and the majority occurred in ■■■ (CS section 5.4.1). Additionally, there were more deaths in the DBLd arm than in the BLd arm in both the overall trial population and the ASCT-ineligible population. The company suggest that this is

likely due to the immunosuppressive effects of anti-CD38 monoclonal antibodies of which daratumumab is one. Both unadjusted and adjusted results are reported for the CEPHEUS trial in the CS; and the adjusted results inform the economic model. The EAG consider it is reasonable to censor the COVID-19 deaths because the adjusted results are more generalisable to a current NHS multiple myeloma population, and it enables a more like-for-like comparison with the comparator trials in the ITCs.

EAG conclusion on statistical methods: The trial population has been analysed using an ITT approach, which is appropriate in clinical trials. The sample size for the overall trial population was sufficient to provide the necessary statistical power and was analysed appropriately. However, the ASCT-ineligible population is a post-hoc subgroup of the ITT population, and it is not statistically powered for the outcomes measured. We find it reasonable to adjust for COVID-19 deaths, especially as the unadjusted results are also reported for comparison

3.3 Critique of the results of the trials of the technology of interest

The results of the CEPHEUS trial provide efficacy evidence for DBLd in comparison with BLd, however to reiterate, BLd is not a comparator in this appraisal. For completeness we summarise the trial results for DBLd in comparison with BLd. The EAG considers it informative to examine how DBLd compares with BLd since this is primary aim of this randomised study. Also, because the DBLd arm of the trial informs indirect comparisons with comparators in the decision problem, notably DLd (see section 3.4 and 3.5 below)..Thus it is a useful starting point from which to view the results of these indirect comparisons.

Below we summarise and comment on the efficacy results of the CEPHEUS trial that relate to the primary outcome (MRD negativity rate) and the outcomes used in the economic model (PFS and OS). Results are for the ASCT-ineligible sub-population, except where stated for the overall population for the MRD negativity rate outcome.

3.3.1 CEPHEUS MRD negativity rate results

The primary outcome of the CEPHEUS trial was the proportion of patients (overall trial population) achieving MRD negativity rate at 10^{-5} which was analysed at the primary analysis (data cut off 08 April 2021), reported in CS section 5.6.1. Table 5 below shows that the primary outcome was met and that the difference in the proportion of participants

achieving MRD negativity 10^{-5} was significantly greater in the DBLd arm compared to the BLd arm. The company state that statistically and clinically meaningful results were achieved for the overall trial population at both the primary analysis and the final PFS analysis (data cut off 07 May 2024). Although we cannot ascribe statistical significance to the results for the ASCT-ineligible population, we observe that the odds of achieving MRD negativity 10^{-5} are similar to the overall trial population, favouring DBLd.

Table 5 Proportion of patients achieving MRD negativity rate 10^{-5} (CEPHEUS)

Population and timepoint	Median follow-up (months)	BLd	DBLd	Difference OR (95% CI) p-value
Overall trial population Primary MRD analysis (Primary outcome)		%	%	
Overall trial population Final PFS analysis	58.71	39.4%	60.9%	2.37 (1.58, 3.55) p<0.0001
ASCT-ineligible Final PFS analysis	58.71	39.3%	60.4%	2.365 (1.471, 3.802) p=0.0004

Source: CS Tables 13 and 14. Abbreviations: ASCT, autologous stem cell transplant; BLd, bortezomib, lenalidomide and dexamethasone; CI, confidence interval; DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; MRD, minimal residual disease; OR, odds ratio; PFS, progression free survival.

Treatment in CEPHEUS was not adapted to MRD negativity response, nor is MRD commonly measured in clinical practice to inform treatment decisions. However, the EAG's clinical expert commented that, as a measure of depth of response, these results translate into improved real-world outcomes.

Further results, for the ASCT-ineligible population, that explore sustained MRD negativity, MRD-negativity landmark rates over time, OS for participants who achieve MRD negativity, PFS by MRD status, and MRD-negative rate at a more sensitive threshold of 10^{-6} , are reported in CS section 5.6.2 and CS Appendix K. For brevity we have not summarised these here, but we note that they were favourable for DBLd versus BLd and the company expect them to translate to the long-term outcomes of PFS and OS.

3.3.2 CEPHEUS progression free survival results

The PFS results for the ASCT-ineligible population are reported for the final PFS analysis (data cut off 07 May 2024) in CS section 5.6.2. Table 6 below shows that the participants in

the DBLd arm were █% (unadjusted for COVID-19) or █% (adjusted for COVID-19) more likely to achieve progression free survival than those in the BLd arm. The confidence intervals and p-values show the results as statistically significant, but the sample size for the ASCT-ineligible population was not powered to demonstrate statistical significance so we should be cautious interpreting the results as such. However, the EAG’s clinical expert advises that the hazard ratio of █ is indisputably clinically meaningful.

Table 6 PFS results (CEPHEUS; ASCT-ineligible population)

Final PFS analysis	Median KM estimate, months		Difference HR (95% CI) p-value
	BLd	DBLd	
Unadjusted	49.61 █	█	0.51 (0.35, 0.74) p=0.0003
Adjusted for COVID-19	█	█	█

Source: CS Tables 17 and 18. Abbreviations: ASCT, autologous stem cell transplant; BLd, bortezomib, lenalidomide and dexamethasone; CI, confidence interval; DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; HR, hazard ratio; KM, Kaplan-Meier; NE, non-evaluable; PFS, progression free survival.

Table 6 above shows that median PFS █ in the DBLd arm. Additionally, PFS events were recorded in █ of the population (█% in the BLd arm and █% in the DBLd arm; CS Table 17), and there were slightly fewer events when adjusted for COVID-19 (CS Table 18).

PFS2 (progression free survival on the next line of therapy) results for the ASCT-ineligible population are reported for the final PFS analysis (data cut off 07 May 2024), in CS section 5.6.3. The results reported in CS Tables 23 and 24 demonstrate a benefit for treating with DBLd compared to BLd. However, the data are not yet mature as median PFS2 was not reached in the DBLd arm, and the proportion of participants experiencing the event (PFS2) was small: █% in the BLd arm and █% in the DBLd arm (smaller when adjusting for COVID-19).

3.3.3 CEPHEUS overall survival results

The OS results for the ASCT-ineligible population are reported for the final PFS analysis (data cut off 07 May 2024) in CS section 5.6.3. Table 7 below shows that the participants in the DBLd arm were █% (unadjusted for COVID-19) or █% (adjusted for COVID-19) more likely to survive than those in the BLd arm.

Table 7 OS results (CEPHEUS; ASCT-ineligible population)

Final PFS analysis	Median KM estimate, months		Difference HR (95% CI) p-value
	BLd	DBLd	
Unadjusted	██████████	██████████	0.66 (0.42, 1.03) p=0.0682
Adjusted for COVID-19	██████████	██████████	0.55 (0.34, 0.90) p=0.0159

Source: CS Tables 21 and 22. Abbreviations: ASCT, autologous stem cell transplant; BLd, bortezomib, lenalidomide and dexamethasone; CI, confidence interval; DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; HR, hazard ratio; KM, Kaplan-Meier; NE, non-evaluable; OS, overall survival; PFS, progression free survival.

The confidence intervals and p-values do not show the results as statistically significant in the unadjusted analysis. The COVID-19 adjusted results are more favourable towards DBLd by about █████ percentage points showing that, although only █ of deaths in the ASCT-ineligible population were due to COVID-19, adjusting the results has an observable effect. Although we believe that adjusting for COVID-19 is reasonable (section 3.2.4 above), the sample size for the ASCT-ineligible population is smaller and not statistically powered so the COVID-19 adjustments may also be at increased risk of bias. Whilst our clinical expert finds the OS results plausible, Table 7 shows that they are not yet mature; the final data cut is not expected until █████ (CS section 5.12), though the company suggests these results are unlikely to add much certainty in estimating long-term survival (Issue 5, company factual accuracy check form). Therefore, we advise caution when interpreting the OS results.

EAG conclusion on efficacy results: The results are favourable for DBLd compared to BLd and demonstrate that participants tend to remain progression free for longer when receiving DBLd. Overall survival estimates show a benefit for DBLd but with some uncertainty as the data are immature. The CS interprets the efficacy results in terms of statistical significance, but the post-hoc ASCT-ineligible population is not statistically powered for any outcomes.

3.3.4 CEPHEUS HRQoL results

HRQoL results for the ASCT-ineligible population are reported in least squares plots for EORTC QLQ-30, EORTC-QLQ-MY20 and EQ-5D-5L (CS section 5.6.4 and Appendix K.2). The plots (CS Figures 15 and 16, CS Appendix Figures 22-25) consistently show that both DBLd and BLd both effect some █████ in HRQoL and █████ in symptoms. The

residuals for each treatment [REDACTED] throughout the plot meaning that the results for both arms are [REDACTED].

The company describe the results as supporting [REDACTED] in HRQoL, symptoms or functioning by adding daratumumab to BLd. We agree, and this aligns with recent literature by demonstrating that adding another treatment to the combination does not affect quality of life detrimentally.¹²

3.3.5 CEPHEUS subgroup analyses

Subgroup analyses of the ASCT-ineligible population were reported for the MRD negativity rate at 10⁻⁵ outcome in CS section 5.8 and for PFS in CS Appendix Figure 26. The equivalent subgroup analyses for the ITT population are reported in CS Appendix L.4 and CEPHEUS CSR Figure 7. The pre-specified subgroups were sex, age, renal function, region, weight, International Staging System (ISS), cytogenetic risk, and ECOG performance status (CEPHEUS SAP Table 1), but the results for the renal function at baseline subgroups were not reported in the CS or CSR.

MRD negativity rate: CS Figure 17 shows that the odds ratio of achieving MRD negativity 10⁻⁵ varies by subgroup. However, most subgroups favour the DBLd combination. Several subgroups have confidence intervals that cross the null line (female sex, North America region, >85 kg weight, ISS stage II, high cytogenetic risk, and ECOG performance status 0), but as some of the subgroups are quite small and none are statistically powered, we can only say that there is a general trend towards favouring DBLd compared to BLd for achieving MRD negativity in most of the subgroups. The results are very similar to the subgroup results for MRD negativity rate in the overall trial population (CS Appendix Figure 35).

PFS: CS Appendix Figure 26 shows a forest plot of hazard ratios demonstrating that treatment with DBLd is consistently more favourable to achieving progression free survival compared to BLd. Several subgroups have confidence intervals that cross the null line and as the sample sizes are quite small we can only say there is a general trend towards favouring DBLd compared to BLd for achieving progression free survival in most of the subgroups. The results are [REDACTED] to the subgroup results for PFS in the overall trial population (CSR Figure 7).

3.3.6 CEPHEUS Safety results

Safety results are reported in CS section 5.11 and are provided for the safety ASCT-ineligible analysis set which included all patients who were randomised and received at least 1 dose of study treatment. All ASCT-ineligible participants (100% in both arms) experienced treatment emergent adverse events (TEAEs).

The CS summarises TEAEs, TEAEs leading to study treatment discontinuation, AEs relating to COVID-19, the most common TEAEs, the most common Grade 3 or 4 TEAEs, serious adverse events, and deaths.

CS section 5.11.3 reports the most common TEAEs, with a frequency of $\geq 10\%$ in either treatment arm (CS Table 48), including a sub list of those with a frequency of $\geq 30\%$ in either treatment arm: diarrhoea, peripheral sensory neuropathy, neutropenia, thrombocytopenia, oedema peripheral, constipation, fatigue, COVID-19, anaemia, insomnia, upper respiratory tract infection, hypokalaemia. With the addition of hypokalaemia and insomnia, these adverse events are in keeping with the known safety profile of daratumumab according to the draft SMPC (section 4.8) ¹³ which lists adverse events with a frequency of $\geq 20\%$ patients as: injection related reactions (IRRs) (at a lower rate than for the intravenous formulation), fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral neuropathy, upper respiratory tract infection, musculoskeletal pain and COVID-19. Although both hypokalaemia and insomnia are listed as “very common”/ $\geq 1/10$ in Table 8 of the draft SMPC.¹³

Grade 3 or 4 TEAEs are reported for the frequencies $\geq 10\%$ (CS section 5.11.4) and $\geq 5\%$ (CS Table 49) in either treatment arm. The most common TEAEs at Grade 3 or 4 were neutropenia, thrombocytopenia, hypokalaemia, pneumonia, anaemia, diarrhoea, lymphopenia and fatigue. The rates were similar across arms, but they were greater in the DBLd arm for neutropenia (DBLd 43.8%; BLd 31.7%), thrombocytopenia (DBLd 30.6%; BLd 23.2%) and hypokalaemia (DBLd ■%; BLd ■%).

Serious adverse events are reported for the frequencies $\geq 5\%$ (CS section 5.11.5) and $\geq 2\%$ (CS Table 50) in either treatment arm. The most common serious adverse events were pneumonia, COVID-19, pulmonary embolism and diarrhoea; rates were similar across arms, but they were greater in the DBLd arm for COVID-19 (DBLd ■%; BLd ■%) and pulmonary embolism (DBLd ■%; BLd ■%).

Deaths are reported in CS section 5.11.6, including CS Table 51. By the time of the final PFS analysis 79 participants in the CEPHEUS trial had died. Fewer patients in the DBLd arm had died (22.9%) compared to the BLd arm (32.4%). However, more patients died of COVID-19 in the DBLd arm (██████%) than in the BLd arm (██████%), which as discussed in section 3.2.4 above is not unexpected due to the immunosuppressive action of daratumumab as an anti-CD38 monoclonal antibody. Deaths due to adverse events were only ████████ in the DBLd arm (██████%) compared to the BLd arm (██████%), whereas deaths due to disease progression were ████████ in the DBLd arm (██████%) compared to the BLd arm (██████%). We do not note any cause for concern in the mortality rates in the trial.

Note that the CEPHEUS trial adds daratumumab (considered less toxic than bortezomib) to a regimen already containing bortezomib (DBLd versus BLd). Whereas the main comparator in this appraisal is DLd, so bortezomib (considered more toxic than daratumumab) would be added to the DLd regimen that is current standard of care in the NHS. Both daratumumab and bortezomib have known safety profiles as they are recommended in other multiple myeloma indications. Additionally, the comparator (BLd) is not a recommended treatment in NHS clinical practice. However, the CEPHEUS trial provides an opportunity to assess whether any new safety concerns might be raised for any of the component treatments and to understand how tolerable the specific quadruplet regimen DBLd is. Adverse events were not compared in the ITCs, therefore there is no comparative safety evidence for DBLd compared to DLd, Ld or BMP. The CEPHEUS trial is the only safety evidence provided in the CS, in addition to the summary of safety evidence for daratumumab provided in the draft SMPC.

EAG conclusion on safety results: The types of adverse events that occurred in the ASCT-ineligible population the CEPHEUS trial are consistent with the known safety profile of daratumumab shown in pooled trial results in the draft SMPC,¹³ and according to our clinical expert whereby adding daratumumab to other regimens does see an increase in haematological toxicity and infection rates, both of which are manageable. The frequency of some adverse events is ████████ in the quadruplet regimen of DBLd compared to the triplet regimen of BLd.

3.4 Critique of studies included in the indirect treatment comparison

As there are no known trials directly comparing DBLd to any of the comparators in the NICE scope for this appraisal, the company conducted a series of indirect treatment comparisons, using specialist methods for evidence synthesis detailed in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 17¹⁴ and 18.¹⁵ Two main approaches were used – indirect treatment comparisons (ITCs) using individual patient data (IPD), and network meta-analysis (NMA). A third approach is an anchored matched-adjusted indirect comparison (MAIC) using real world evidence (provided for one of the treatment comparisons).

- **Indirect treatment comparisons**, using IPD and inverse probability of treatment weighting (IPTW) methods, the results of which inform the economic model, for the following decision problem comparisons:
 - DBLd versus DLd
 - DBLd versus Ld
 - DBLd versus BMP

This is the main approach to indirect comparison presented in the CS.

- **A “supportive” network meta-analysis (NMA)**, with the same comparisons as the ITC analysis above, that is DBLd versus DLd, Ld and BMP. (NB. The NMA also included an indirect comparison between DBLd and IsaBLd but the results were not reported in the CS. Subsequently the results have been reported in response to EAG clarification question A11). The NMA was conducted in addition to the ITC described above, to provide “supportive comparative efficacy estimates”. The network includes a total of 11 trials, including the treatments in the NICE scope/decision problem and other treatments which do not feature in the NICE scope/decision problem. The purpose of the latter is to allow all relevant treatments to connect to the network, given the absence of common comparators.
- **An anchored matched-adjusted indirect comparison (MAIC)** using real world evidence is reported, to support the necessary assumption that BMP and BCd are equivalent in efficacy, thus allowing the ITC results comparing DBLd vs BMP (see above) to be a proxy for ITC results for DBLd vs BCd. This was necessary because no clinical

trial data for BCd was identified in the CS. We consider that the BMP combination fulfils the NICE scope for the comparator “Bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone)”. Our clinical expert, in common with the company, advised that BMP and BCd are hardly used in the NHS now. Therefore, we will not cover this analysis in detail in this report, instead we focus on the IPTW ITCs and NMA for the comparison between DBLd versus DLd.

3.4.1 Inverse probability of treatment weighting (IPTW) indirect treatment comparisons

3.4.1.1 Rationale for the IPTW indirect treatment comparisons

The company present their rationale for the IPTW ITCs in CS section 2.10.1. Their choice of approach stems from the company having access to IPD for two comparator trials- the MAIA trial (DLd versus Ld),^{16 17} and the ALCYONE trial¹⁸ (DBMP versus BMP), plus the IPD for DBLd from the CEPHEUS trial.

Table 8 below gives an overview of the comparisons made and the trials informing each comparison.

The evidence identified for the comparator Ld also comes from the MAIA trial and the evidence for BMP is from the ALCYONE trial (DBMP versus BMP).¹⁸ Both MAIA and ALCYONE trials were conducted in ASCT-ineligible NDMM populations. None of the trials are connected by a common comparator, therefore, each trial contributes a single arm to each treatment comparison with DBLd, using the single DBLd arm from the CEPHEUS trial.¹⁰

Table 8 IPTW indirect treatment comparisons using individual patient data

Comparison	Method	Trial A name (treatment vs comparator)	Trial B name (treatment vs comparator)
DBLd vs DLd	IPTW	CEPHEUS (<u>DBLd</u> vs BLd)	MAIA (<u>DLd</u> vs Ld)
DBLd vs Ld	IPTW	CEPHEUS (<u>DBLd</u> vs BLd)	MAIA (DLd vs <u>Ld</u>)
DBLd vs BMP (proxy for BCd)	IPTW	CEPHEUS (<u>DBLd</u> vs BLd)	ALCYONE (DBMP vs <u>BMP</u>)

Underlining in the table denotes the trial arm included in the ITC.

Abbreviations: BMP, bortezomib, melphalan, prednisone; BLd, bortezomib, lenalidomide, dexamethasone; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DBMP, daratumumab, bortezomib, melphalan, prednisone; DLd, daratumumab, lenalidomide; Ld, lenalidomide, dexamethasone; IPTW, inverse probability of treatment weighting; MAIC, matched adjusted indirect comparison.

The algorithm to assist with method selection in NICE TSD18¹⁵ (Population-adjusted indirect comparisons (MAIC and STC)) recommends that if IPD is available for all the studies and the studies do not form a connected network then the NICE TSD17¹⁴ guidance (methods for comparative individual patient data) should be followed. We discuss these methods later in section 3.5.1.1.

3.4.1.2 Identification, selection and feasibility assessment of studies for the IPTW indirect treatment comparisons

Studies for the ITCs were identified via the clinical SLR which we find to be well-conducted and not likely to miss any relevant studies (section 3.1 and Table 39). As noted above in section 3.1, the SLR identified 27 unique studies (90 publications), from the original search and both update searches, that evaluated all relevant treatments for ASCT-ineligible patients with NDMM; these are the included studies prioritised for this appraisal due to evaluating a comparator in scope.

The 27 studies are listed in CS Appendix Table 13. Tables 15 to 20 in the CS Appendix summarise the key study characteristics, outcomes and results for all 27 studies, however there is no discussion of the studies' suitability for inclusion in ITCs; the CS simply states the SLR identified the MAIA RCT which evaluated the efficacy and safety of DLd compared with Ld (CS Appendix B.1.4).

3.5 The EAG notes that the following included/prioritised studies also evaluated DLd, but the company's inclusion/exclusion screening decisions for these are not reported: MCC-20130/Baz 2022:¹⁹ DLd or DdB determined by investigator choice; and IFM2017-03:^{20,21} DLd vs Ld. We do not think that these studies are feasible for comparison with the CEPHEUS trial and our justifications are in

Table 43 in Appendix 7.5.

The CS assessed the feasibility of an ITC between CEPHEUS and MAIA in CS section 5.10.2. They concluded that the study designs of the two trials were similar enough to enable an ITC (full comparison in CS Appendix Table 24).

Both trials include the relevant population: ASCT-ineligible NDMM. They had similar inclusion criteria, but the main differences were that CEPHEUS excluded those with a frailty score of ≥ 2 which automatically excludes patients over 80 years, whereas MAIA included these patients. Also, MAIA only recruited ASCT-ineligible patients whereas CEPHEUS also included patients who refused (deferred) ASCT (CS Appendix B.1.6). However, they had a similar definition of ASCT-ineligible (CS Table 27). For the purposes of this analysis patients refusing ASCT were removed from the CEPHEUS population and patients over 80 years old were removed from the MAIA population to enable the trials to be better matched.

Both trials measure relevant outcomes that are similarly defined (CS Tables 4, 26 and 28). The company found it feasible to compare treatments for the following outcomes: OS, PFS, PFS2, TTD, MRD negative CR rate, $\geq$ CR, sCR, $\geq$ VGPR and ORR. However, the EAG note that the timepoints for comparison of OS are not consistent because the data is reported at different stages in the trials: in MAIA for the final analysis (median follow up 89.3 months), and in CEPHEUS for the final PFS analysis (median follow up 58.7 months) with the final OS analysis not due until [REDACTED].

The EAG notes that both trials included UK sites, and both trials are considered broadly generalisable to NHS practice according to our clinical expert advisor and to the EAG's clinical experts advising TA917⁶ regarding MAIA. Our clinical expert advises that the MAIA trial has a younger population than in clinical practice as transplant -ineligible patients are often older than 78 and will often have ECOG PS >2 .

The company identified another trial of potential relevance - the IMROZ trial²² which evaluated the regimen IsaBLd compared to BLd in the ASCT-ineligible population. The IMROZ trial can be connected to the CEPHEUS trial via the common comparator BLd, as shown in the network diagram in CS Figure 27, (reproduced as Figure 2 below - see section 3.5.2). Potential methods for indirectly comparing DBLd with IsaBLd are not discussed in the CS, as at that time IsaBLd had not yet received a positive recommendation for use in the NHS by NICE (see NICE TA1098, published 24th September 2025). The IsaBLd comparison with DBLd is discussed further in the NMA sections 3.5.2 and 3.6.2 below.

3.5.1.1 Clinical heterogeneity assessment of studies included in the IPTW

Indirect treatment comparisons

A separate heterogeneity assessment was not carried out for CEPHEUS and MAIA for the DBLd versus DLd and DBLd versus Ld ITCs. The feasibility assessment incorporated consideration of similarity between the trials (see section 3.4.1.2 above). Differences in the population baseline characteristics were accounted for as part of the IPTW weighting methods (see section 3.6.1 below), except that an initial decision was made to exclude all participants in the MAIA trial who were over 80 years old because the oldest ASCT-ineligible patient in the CEPHEUS trial was 80 years old at baseline and approximately 14% of the participants in MAIA were over 80 (CS Figure 18). This was done prior to the IPTW reweighting process.

3.5.1.2 Risk of bias in the studies included in the IPTW indirect treatment comparisons

Risk of bias in the CEPHEUS trial has been discussed in section 3.2.3 above, determined by the company and EAG as at low risk of bias using the Cochrane RoB 2.0 tool for the outcomes included in the ITCs.

Risk of bias in the MAIA and ALCYONE trials, both RCTs, were also assessed by the company to be at low risk of bias in all domains using the Cochrane RoB 2.0 tool (CS Appendix Table 21).

The EAG assessed the MAIA and ALCYONE trials using the Cochrane RoB 2.0 tool in Table 41, in Appendix 7.3. We agree with the CS that the ALCYONE trial is probably at low risk of bias, we have some concerns around the effect of no blinding on assessment of some outcomes, but the RoB tool questions and algorithm lead to a judgement of low risk of bias.

We have similar concerns for the MAIA trial regarding lack of blinding, but our main concern with MAIA is the lack of clarity around the effect of patient crossover after the second interim analysis, when participants in the Ld (comparator) arm could receive daratumumab.¹⁷ For OS and TTD estimates, the CS uses data on file from a time point beyond the second interim analysis (the final OS analysis, median follow up 89.3 months). The CSR for the MAIA trial reports that [REDACTED] of patients in the Ld arm received a subsequent therapy compared to [REDACTED] of patients in the DLd arm. Of the [REDACTED] Ld patients, [REDACTED] received a daratumumab-containing therapy as first subsequent therapy and [REDACTED] received a

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daratumumab containing regimen as any subsequent therapy. The number of Ld patients who received DLd (i.e. crossed over to the experimental arm) as first subsequent treatment was [REDACTED]. The most used regimens at first subsequent therapy in the Ld arm were bortezomib-containing, including BCd, Bd, and BMP (around [REDACTED] of patients in each), followed by DBd ([REDACTED] patients). It therefore appears that there was a disproportionate amount of treatment switching between the trial arms. Only a small proportion of Ld patients switched to DLd, and this alone is unlikely to bias OS and TTD estimates in favour of the Ld arm. However, the combined effect of other subsequent daratumumab regimens in the Ld arm suggests possible bias for OS and TTD in favour of the Ld arm. This potentially biases against DLd when compared indirectly with DBLd. There doesn't appear to be any available analyses adjusting outcomes measured after crossover/treatment switching in the trial. It is

3.5.2 Network meta-analysis

3.5.2.1 Rationale for the network meta-analysis (NMA)

The company's rationale for the NMA is to provide supportive comparative efficacy estimates (CS section 5.10.5) in addition to the ITC IPTW approach discussed above. The CS does not compare the relative merits and limitations of the two approaches. However, the ITC IPTW analysis is the company's primary approach to indirect comparison.

3.5.2.2 Identification, selection and feasibility assessment of studies included in the network meta-analysis

The company used the original and first update searches of the clinical SLR to identify relevant studies for the NMA (CS Appendix M.1 and clarification response A6). The EAG has not identified any further studies that could be included from the results of the second update search conducted in April 2025.

The company selected studies that evaluated treatments recommended in international guidelines for the relevant population, ASCT-ineligible NDMM. The selection criteria in CS Appendix Table 107 are broader than for the main clinical effectiveness evidence which is focused on the decision problem treatments (i.e. DBLd, DLd, BMP, and Ld). We consider it appropriate to identify studies of additional treatments which may be needed to create a connected network. Clarification question response A7 outlines the additional recommended

treatments for ASCT-ineligible NDMM that were identified and excluded by the company because they could not be connected to a network. The EAG consider this is appropriate.

The company identified 11 studies with OS data, 10 of which also had PFS data (clarification question responses A8 and A9). All the included studies are RCTs: CEPHEUS,¹⁰ IMROZ,²² SWOG S0777,^{23 24} MAIA,¹⁷ FIRST,²⁵ Sacchi 2011,²⁶ IFM 01/01,²⁷ IFM 99-06,²⁸ TMSG,²⁹ VISTA,³⁰ ALCYONE.¹⁸ Please note that tables 3 to 6 in the confidential NMA report supplied with the company's clarification response supersede CS Appendix Tables 108, 110 and 111, which had mistakenly omitted some of the included trials.

Figure 2 below reproduces the company's network diagram (CS Figure 27) with some minor EAG adaptations to the labelling of treatments for consistency (all regimens are now labelled by their generic name, rather than brand name). We have also introduced colour coding to distinguish between trials of treatments in the decision problem (shaded in blue) and trials of other treatments which are necessary to form a connected network (shaded in orange). For example, the melphalan and prednisone (MP) and the melphalan, prednisone and thalidomide (MPT) regimens (orange) are not in the decision problem, but they are in the network because they form a link, via the VISTA trial, with BMP (blue) which is relevant to the decision problem.

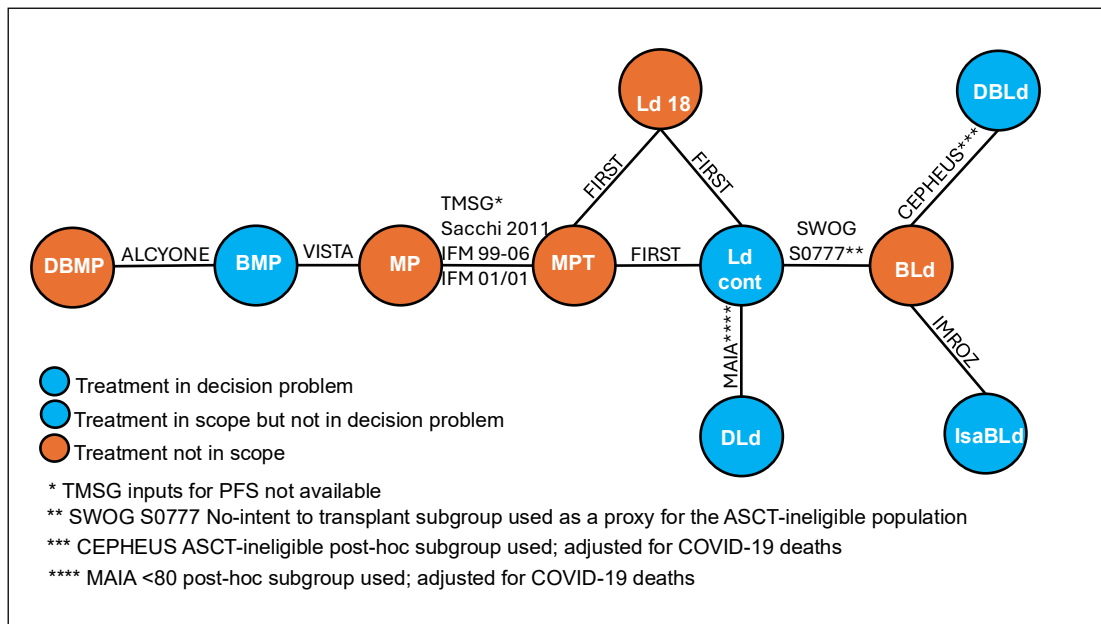


Figure 2 Network diagram of studies included in the NMA

Source: adapted from CS Figure 27.

Abbreviations: BLd, bortezomib, lenalidomide and dexamethasone; BMP, bortezomib, melphalan and prednisone; DBMP, daratumumab, bortezomib, melphalan and prednisone; DLd, daratumumab, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone; Ld18, lenalidomide and dexamethasone 18 months; Ld cont, lenalidomide and dexamethasone continuous; MP, melphalan and prednisone; MPT, melphalan, prednisone and thalidomide.

3.5.2.3 Clinical heterogeneity assessment of studies included in the network meta-analysis

The CS assessed study design and participant baseline characteristics for feasibility and heterogeneity. Study outcomes that matched any outcomes investigated in the CEPHEUS trial were inclusion criteria for the NMA SLR (CS Appendix Table 107). The CS reports NMA results for PFS and OS only and it is not reported whether any other outcomes were feasible for comparison.

Design: The assessment of study design in the company NMA report includes trial phase, population, location and blinding (NMA report Table 3). The assessment also considered the enrolment period and study inclusion criteria but omitted the IFM 01/01 trial from the comparison (CS Appendix Table 108). The CEPHEUS and SWOG S0777 trials were the only two studies which enrolled mixed populations of transplant ineligible patients and

patients who were eligible for transplant but had chosen to defer this until a later time. All studies enrolled participants pre- the COVID-19 pandemic except CEPHEUS and IMROZ. The study locations varied, some trials were international, some European, one was USA only (SWOG S0777) and others focused on Italy (Sacchi 2011) or Turkey (TMSG).

Age: There were some age differences between the trials. Although CS Appendix M.1 notes that Sacchi 2011, IFM 99-06, and IMROZ focused on ≥ 65 -year-olds, the Sacchi 2011 trial participants were much older with median age 79 and 76 years across the two trial arms (NMA report Table 4; CS Appendix Table 109). The trial publication states that 33% of participants were over 80 years old.²⁶ Most other trials had a median age of between 71 and 73 years, (once patients ≥ 80 years were removed from the analysis of the MAIA trial). The eligibility criteria for the IFM 99-06 study was patients aged between 65 and 75 years, with 41% of patients over 70 years at baseline.²⁸ IMROZ also excluded patients over 80 years and included patients under 65 if they had comorbidities that made them ineligible for transplant.²³ The median age of the ITT population in the SWOG S0777 trial was 63 years.²³ This makes the SWOG S0777 population about eight to ten years younger than the median age of all other trials in the network.

Performance status: The Sacchi trial is one of only two trials that included patients with an ECOG performance score of up to 3, resulting in 9% and 12% of patients with ECOG performance scores 3-4 in each trial arm at baseline.²⁶ If Sacchi 2011 was removed from the network, BMP would remain connected via three other trials (TMSG, IFM 99-06 and IFM 01/01). Although we are not focusing on the BMP comparator in this report, any potential sensitivity analysis excluding Sacchi 2011 would not disconnect the BMP comparator from the network.

Participant subgroups: As well as being US-focused and having a much younger trial population, the SWOG S0777 trial is potentially confounded as 35% of the ITT participants received ASCT.³¹ The base case NMA used the 'no intent to transplant' sub- group from the SWOG S0777 trial, and sensitivity analyses explored using the ITT population (i.e. mixed population of transplant eligible/ineligible participants) and also the subgroup of participants ≥ 65 years of age. Whichever population is used from the SWOG S0777 trial it introduces uncertainty into the results. SWOG S0777 is also essential to the network as without this trial the CEPHEUS trial cannot connect to the MAIA or ALCYONE trials, effectively preventing an

indirect comparison of DBLd with all but one of the comparators in the NICE Scope – IsaBLd would be the only remaining connected comparator.

Follow up duration: There are differences in median follow up periods for PFS ranging from 16.3 months to 84 months (NMA Report Table 5; CS Appendix Table 110). However, the tables do not show the relevance of the analysis timepoint and whether median PFS had been reached. Median PFS is [REDACTED] in the CEPHEUS data (CS Table 17). In the study publication for IMROZ, the other most recent trial, median PFS was not reached in the IsaBLd arm.²² Similarly, there are differences in median follow up used for OS from the trials, ranging from 23 months to 89.3 months (NMA report Table 6; CS Appendix Table 111). Furthermore, the tables do not show the relevance of the analysis timepoint or whether median OS was reached. Median OS is [REDACTED] for either treatment arm in the CEPHEUS data (CS Table 21).

Study design phase: All studies are phase III evaluations except Sacchi 2011 which is the only phase II trial included.

EAG comments on NMA clinical heterogeneity

The trials included in the NMA are heterogeneous in terms of factors such as geographical study location, participant age range, impact/experience of COVID-19 and follow-up periods for analysis of OS / and maturity of PFS and OS data.

Furthermore, other trial characteristics such as dosing regimens, outcome definitions and outcome measures are not discussed in the CS. If we focus on the transplant ineligible population subgroups in SWOG S0777 (i.e, remove the transplant-deferred subgroup), and in CEPHEUS (i.e. remove transplant-refused sub-group), and the age subgroup in MAIA (i.e. remove the >80 years old sub-group), the trials appear more homogenous. The exception is the Sacchi 2011 trial which had a notably older and frailer population.

3.5.2.4 Risk of bias in studies included in the network meta-analysis

There are no assessments of risk of bias reported specifically for studies included in the NMA. However, the risk of bias assessments for RCTs identified in the clinical SLR in CS Appendix Table 21 provides a summary of risk of bias in each domain for five of the eleven trials included in the NMA: ALCYONE, CEPHEUS, FIRST, MAIA and SWOG S0777. The company assessed them all to be at low risk of bias in all domains, except SWOG S0777

which was assessed as having 'some concerns' due to the randomisation process (CS Appendix Table 21). No justifications for the company's summary risk of bias assessments were provided. It is unclear why risk of bias assessments for the VISTA, Sacchi 2011, IFM 99-06, IMROZ, IFM 01/01 and TMSG trials are not reported.

The EAG did a risk of bias assessment using the RoB 2.0 tool on the CEPHEUS, MAIA, ALCYONE and IMROZ trials (see Table 40, Table 41 and Table 42 in Appendix 7.2, 7.3 and 7.4 of this report, respectively. See also section 3.5.1.2 above). We prioritised these trials because collectively they include all the comparators specified in the scope for this NICE appraisal. Generally, we find all the trials at low risk of bias for the outcomes reported in the NMA. However, there is potential risk of bias arising from crossover/treatment switching affecting the OS and TTD outcomes in the MAIA trial, as we have commented on earlier (see section 3.5.1.2). We also note the open label study designs and that this may bias outcomes measured less objectively, such as patient reported outcomes.

EAG comment on risk of bias in the NMA trials

The company's approach to risk of bias assessment is inconsistent and lacks transparency. The CS does not report a risk of bias assessment for all the studies included in their NMA. A summary risk of bias assessment is given of five of the 11 trials in the NMA, as part of a wider set of "prioritised studies" from the SLR. No justifications for the company's summary risk of bias assessments were provided. The EAG has assessed the key comparator trials for risk of bias and generally finds the risk to be low, though there is some uncertainty regarding the impact of patient crossover..

3.6 Critique of the indirect treatment comparison and network meta-analysis

In the following sub-sections we critique the methods used by the company to conduct indirect comparisons, starting with the IPTW approach and then NMA.

3.6.1 IPTW indirect treatment comparisons

3.6.1.1 Methods of the IPTW indirect treatment comparisons

The inverse probability of treatment weighting (IPTW) is a method used to adjust for confounding in observational studies. It uses propensity scores to balance patient

characteristics between treatment and comparator groups by weighting each person by the inverse probability of receiving their treatment. Propensity scores represent the conditional probability that an individual is assigned to an intervention based on their baseline observed covariates. In the CS the IPTW is used to control for differences in baseline characteristics which could bias comparisons between CEPHEUS (DBLd) and MAIA (DLd).

The processes of matching each population comparison are reported for DBLd versus DLd in CS section 5.10.2, and for DBLd versus Ld and DBLd versus BMP in CS Appendix B.1.7.

3.6.1.1.1 Weighting

The CS states that the average treatment effect (ATE) was used in the weighting of study participants. The ATE measures the average differences in outcomes between patients who receive the treatment of interest and those who do not, as if the patients under consideration were randomly allocated to treatments. The CS considers this is one of the most commonly used approaches to weighting in IPTW analyses and one which is “typically of interest in NICE appraisals” (CS page 92). The CS states a preference for the ATE over alternatives such as the average treatment effect for the control (ACT), and the average effect of the treatment (ATT). This is because it is unclear, in the company’s view, whether the CEPHEUS or the MAIA trial is more generalisable to UK clinical practice. The ATE is suited where the treatment is applicable to the entire population represented by the data. The EAG infers this means it applies to both the CEPHEUS (treatment) and MAIA (control) trials (i.e. ‘the entire population’) as opposed to just one of the trials (i.e. treatment or control). The EAG therefore considers the ATE to be the appropriate choice in this instance.

The company’s approach of using propensity score weighting for the base case is appropriate given they have access to IPD for both intervention and comparator trials (CEPHEUS, MAIA and ALCYONE).

3.6.1.1.2 Identifying covariates

IPTW methods require identification of all potential treatment effect modifiers and prognostic factors to avoid potential risk of bias from imbalanced distribution of these modifiers/factors across studies at baseline. The CS identified 14 prognostic factors/effect modifiers (covariates) for adjustment in the base case and sensitivity analyses of DBLd versus DLd and DBLd versus Ld (CS Table 29). (Note that it is not stated whether each covariate is a prognostic factor or a treatment effect modifier).

The covariates were identified from what appears to be a comprehensive process (CS Section 2.10.2) involving:

- A literature review examining evidence of effect modifiers in RCTs, and previous population-adjusted indirect comparisons.
- A second literature review examining which covariates have been adjusted for in prior indirect treatment comparisons in the transplant ineligible setting.
- Regression analysis assessing the prognostic association between covariates and PFS and OS, based on pooled IPD from CEPHEUS, MAIA, and ALCYONE.
- A list of potential covariates was generated from the above and discussed and refined by clinical experts based on “the importance of variables.”
- A final list of covariates was agreed based on “clinical plausibility, missing data and collinearity” and validated with UK clinical experts in May 2025.

The CS does not provide further details of the above process (except for validation of covariates with clinical experts in May 2025⁹) therefore the EAG is unable to assess each of the steps taken, but in general the establishment of covariates for adjustment in the ITC appears to be thorough. The EAG’s clinical expert confirmed that no potential prognostic factors/effect modifiers are missing from the company’s list.

Of the 14 covariates listed, 11 were prioritised for adjustment in the base case. The remaining three covariates (race, time since initial multiple myeloma diagnosis and calcium levels) were added in a sensitivity analysis. The specific reasons for relegating these three covariates from the base case to sensitivity analysis are not given.

3.6.1.1.3 Overlap assessment

The degree to which the 14 covariates overlapped the CEPHEUS (DBLd) and MAIA (DLd) study populations was measured using standardised mean differences (SMD) for each covariate (CS Table 30). SMDs greater than 0.1 indicate a substantial difference between the populations. Prior to the adjustment there was a high degree of overlap for all covariates (SMDs within a ± 0.2 threshold), which further improved following the adjustment (SMDs

within a ± 0.1 threshold). This indicates that the two patient populations were well balanced in the base case comparison of DBLd versus DLd.

3.6.1.1.4 Base case analyses

The CS reports the ITC results according to a base case, and sensitivity analyses as follows:

- Unadjusted ITC using IPTW
- The base case ITC using IPTW with 11/14 covariates adjusted for; Covid adjusted
- Sensitivity analysis ITC using IPTW, with all covariates adjusted for; Covid adjusted
- Sensitivity analysis ITC using IPTW, with all covariates adjusted for; unadjusted for COVID-19

3.6.1.1.5 Scenario analyses

The CS reports scenario analyses around the IPTW methodology using multivariate regression and doubly robust analyses (CS section 5.10.2), as recommended by the NICE DSU TSD17.¹⁴

In response to EAG clarification question A5, the company justified their choice of two these approaches and elaborated on how they were applied. In brief,

- The doubly robust approach combines the IPTW weights with an outcome regression model. The has the advantage of being consistent if either the propensity score model or the outcome regression model is correctly specified, providing two opportunities to control for confounding. The outcome regression model included the same baseline covariates used in the IPTW model.
- The multivariate regression analysis fitted Cox proportional hazard models to time-to-event outcomes (PFS and OS) and logistic regression models for binary outcomes (response rates), adjusting for the same set of baseline characteristics (predictors). The multivariate regression analysis was conducted as a complimentary method to validate the findings

The EAG considers that both the methods are appropriate for minimising confounding and testing the robustness of the ITC results.

The scenario analyses were applied to the ITC base case analysis (adjusted for COVID-19; adjusted for 11/14 covariates) for all outcomes in the DBLd versus DLd comparison only. This is acceptable as DLd is considered the main comparator of interest.

The programming code for the ITCs is provided in CS Appendix B.1.9.

3.6.1.2 Results of the IPTW indirect treatment comparisons

The results of ITCs are reported across CS sections 5.10.2, 5.10.3 and CS appendix B.1.8. Here we focus on the results of the DBLd comparisons with DLd, Ld and BMP for the OS, PFS and TTD outcomes as these are used in the economic model.

PFS: The PFS results in Table 9 below show that DBLd is more effective at reducing the risk of disease progression or death than DLd, Ld or BMP. Compared to DLd, DBLd reduces the risk of progression or death by 45% (HR 0.55; 95% CI 0.38, 0.79, $p=0.001$), and this is statistically significant. Results for the sensitivity analysis that includes all covariates in the adjustment are very similar to the base case results, but there is a greater difference (seven percentage points) between results for the base case and the sensitivity analysis that does not adjust for COVID-19 deaths. The CS also reports the Kaplan Meier curves for the DLd and Ld comparisons which both show a sustained difference in treatment effect throughout (CS Figure 21 and CS Appendix Figure 9). There are no Kaplan Meier curves reported for the BMP comparison.

Table 9 Overview of ITC results for PFS

Analyses		DBLd versus comparator HR (95% CI), p-value		
		DLd	Ld	BMP
IPTW Base case	11/14 covariates adjusted; ^a adjusted for COVID- 19	0.55 (0.38, 0.79) $p=0.001$	0.30 (0.21, 0.43) $p<0.0001$	0.16 (0.10, 0.25) p -value not reported
IPTW sensitivity analysis	All covariates adjusted; adjusted for COVID- 19	0.54 (0.37, 0.79) $p=0.001$	0.31 (0.21, 0.45) $p<0.0001$	0.16 (0.10, 0.25) p -value not reported

IPTW sensitivity analysis	11/14 covariates adjusted; ^a unadjusted for COVID-19	0.62 (0.44, 0.88) p=0.007		

Source: CS Table 32; CS Appendix Tables 34 and 38.

Abbreviations: BMP, bortezomib, melphalan, prednisone; CI, confidence interval; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DLd, daratumumab, lenalidomide, dexamethasone; HR, hazard ratio; IPTW, inverse probability of treatment weighting; Ld, lenalidomide, dexamethasone; PFS, progression free survival.

^a does not adjust for covariates of race, time since initial multiple myeloma diagnosis, and calcium levels.

OS: The OS results in Table 10 below show that treatment with DBLd is more effective at reducing the risk of death than DLd, Ld or BMP. Compared to DLd, DBLd reduces the risk of death by 37% (HR 0.63; 95% CI 0.41, 0.98; p=0.040) and this is statistically significant. Results for the sensitivity analysis that includes all covariates in the adjustment are very similar to the base case results. However, there is a greater difference (seventeen percentage points) between results for the base case and the sensitivity analysis that does not adjust for COVID-19 deaths. Results from both sensitivity analyses are less certain as the confidence intervals cross 1. The CS also reports the Kaplan Meier curves for the DLd and Ld comparisons which show a sustained difference in treatment effect from about 12 months (Ld comparison) and 24 months (DLd comparison) (CS Figure 22 and CS Appendix Figure 10). There are no Kaplan Meier curves reported for the BMP comparison.

Table 10 Overview of ITC results for OS

Analyses		Comparison, DBLd versus... HR (95% CI) p-value		
		DLd	Ld	BMP
IPTW Base case	11/14 covariates adjusted; ^a adjusted for COVID-19	0.63 (0.41, 0.98) p=0.040	0.43 (0.28, 0.66) p<0.0001	0.36 (0.23, 0.57) p-value not reported
IPTW sensitivity analysis	All covariates adjusted; adjusted for COVID-19	0.65 (0.41, 1.02) p=0.060	0.44 (0.29, 0.69) p<0.0001	0.39 (0.24, 0.62) p-value not reported
IPTW sensitivity analysis	11/14 covariates adjusted; ^a unadjusted	0.80 (0.53, 1.19) p=0.262		

for COVID-
19

Source: CS Table 33; CS Appendix Tables 35 and 39.

Abbreviations: BMP, bortezomib, melphalan, prednisone; CI, confidence interval; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DLd, daratumumab, lenalidomide, dexamethasone; HR, hazard ratio; IPTW, inverse probability of treatment weighting; Ld, lenalidomide, dexamethasone; OS, overall survival.

^a does not adjust for covariates of race, time since initial multiple myeloma diagnosis, and calcium levels).

TTD: The TTD results in Table 11Table 10 below show that treatment with DBLd is more effective at reducing the risk of discontinuing treatment than DLd, Ld or BMP. Compared to DLd, DBLd reduces the risk of discontinuing treatment by

Results for the sensitivity analysis that includes all covariates in the adjustment are to the base case results. However, there is a greater difference (percentage points) between results for the base case and the sensitivity analysis that does not adjust for COVID-19 deaths, which also are less certain. The CS also reports the Kaplan Meier curves for the DLd and Ld comparisons which show a difference in treatment effect from (DLd comparison; CS Figure 23) and (CS Appendix Figure 11). There are no Kaplan Meier curves reported for the BMP comparison.

Table 11 Overview of ITC results for TTD

Analyses		Comparison, DBLd versus... HR (95% CI) p-value		
		DLd	Ld	BMP
IPTW Base case	11/14 covariates adjusted; ^a			
	adjusted for COVID-19			
IPTW sensitivity analysis	All covariates adjusted;			
	adjusted for COVID-19			
IPTW sensitivity analysis	11/14 covariates adjusted; ^a			
	unadjusted for COVID-19			

Source: CS Table 34; CS Appendix Tables 36 and 40.

Abbreviations: BMP, bortezomib, melphalan, prednisone; CI, confidence interval; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DLd, daratumumab, lenalidomide, dexamethasone; HR, hazard ratio; IPTW, inverse probability of treatment weighting; Ld, lenalidomide, dexamethasone; TTD, time to treatment discontinuation.

^a does not adjust for covariates of race, time since initial multiple myeloma diagnosis, and calcium levels).

3.6.1.2.1 Results of IPTW ITC scenario analyses

The results for the scenario analyses on the base case using the doubly robust and multivariate regression methods for the DBLd versus DLd comparison are reported in CS Table 38. The results are very similar across the scenarios: the hazard ratios only differ by a few percentage points, and the odds ratios are similar for the various response rate outcomes, although for all outcomes there is greater benefit attributed to DBLd using the standard IPTW method. The confidence intervals for the doubly robust and multivariate regression results are slightly wider than the CIs when using the standard IPTW method, indicating greater uncertainty.

Results for the MRD negative CR rate, and the other response rates of $\geq$ CR, sCR, $\geq$ VGPR and ORR, are reported in CS Tables 36 and 37 for the DBLd versus DLd comparison. They all show odds ratios in favour of treatment with DBLd, consistent across the sensitivity analyses. Results for the response rates for the treatment comparisons of DBLd versus Ld and DBLd versus BMP are also consistently in favour of treatment with DBLd (CS Appendix Tables 37 and 41).

The ITC results overall show DBLd has superior efficacy over the DLd, Ld and BMP comparator regimens. We should be cautious in interpreting the OS results and because the CEPHEUS data is immature whereas the OS results available for MAIA and ALCYONE reflect a longer follow-up period.

3.6.2 Network meta-analysis

3.6.2.1 Methods of the network meta-analysis

The NMA methods are reported in CS section 5.10.5, CS Appendix M, Clarification responses A10, A11 and A12, and the separate company NMA report.

The company conducted Bayesian NMAs for PFS and OS. The included studies are shown in Figure 2 above (see section 3.5.2) which shows that data inputs for three of the trials, CEPHEUS, MAIA and SWOG S0777, were based on sub-populations of the total trial population (we discuss this further in section 3.5.1.2). The rationale for the COVID-19 adjustments in CEPHEUS and MAIA are clearly described in CS section 5.10.5, in line with

the rationale and data used for the IPTW ITCs. Furthermore, the company discuss the rationale for the unadjusted for COVID-19 analyses between DBLd and IsaBLd in clarification response A11, providing the results for both adjusted and unadjusted NMAs for this comparison.

Statistical heterogeneity in the network was assessed using the deviance information criterion (DIC) to compare model fit between fixed effect and random effects, results of which are reported in clarification response A10a. The company use the fixed effect results for their base case and report the random effects results in clarification response A10b. We agree the choice of fixed effect is reasonable in lieu of using informative priors for the random effect. However, the fixed effect model is likely to underestimate uncertainty due to the heterogeneity present in the included trials (section 3.5.2.3)..

WinBUGS 1.4 software was used to carry out the analyses (NMA report section 4.2), and the programming code for the fixed-effect model is provided in CS Appendix M.3.

EAG comment on NMA methods

We believe the statistical methods for the NMAs are appropriate, and results are transparently provided. However, the heterogeneity in the network and use of subgroup data in some trials potentially increases the risk of bias, though this is offset by ASCT eligibility being a stratification factor in the randomisation to trial arms.

3.6.2.2 Results of the network meta-analysis

We summarise the NMA results below in Table 12 for PFS and in

Table 13 for OS. DBLd was [REDACTED] for progression free survival than DLd, Ld and BMP, and the results are [REDACTED]. However, the benefit of DBLd compared to IsaBLd is [REDACTED] given the overlapping credible intervals. There is [REDACTED] between DBLd and IsaBLd when the data is not adjusted for COVID-19 deaths.

Table 12 Overview of NMA results for PFS

Outcome	Comparison, DBLd versus... OR (95% CrI)			
	DLd	Ld	BMP	IsaBLd
PFS (Fixed effect; adjusted for COVID-19; base case)				
PFS (Random effects; adjusted for COVID-19)				
PFS (Fixed effect; unadjusted)	Not reported	Not reported	Not reported	
PFS (Random effects; unadjusted)	Not reported	Not reported	Not reported	

Source: CS Table 45; Clarification responses A10 and A11.

Abbreviations: BMP, bortezomib, melphalan, prednisone; CrI, credible interval; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DLd, daratumumab, lenalidomide, dexamethasone; FE, fixed effect; Ld, lenalidomide, dexamethasone; OR, odds ratio; PFS, progression free survival; RE, random effects.

As shown in

Table 13 below, DBLd was [REDACTED] for overall survival than DLd, Ld and BMP, however the credible intervals show the results as uncertain. The results for the DBLd versus IsaBLd comparison [REDACTED]. The unadjusted results were not reported for the DLd, Ld and BMP comparisons, but the unadjusted results for the IsaBLd comparison show that adjusting for COVID-19 deaths [REDACTED] the treatments, with [REDACTED]. DBLd reduced the risk of death by [REDACTED] in the unadjusted analysis compared to [REDACTED] in the adjusted analysis. This remains [REDACTED]

Table 13 Overview of NMA results for OS

Outcome	Comparison, DBLd vs... HR (95% CrI)

	DLd	Ld	BMP	IsaBLd
OS (Fixed effect; adjusted for COVID-19; base case)				
OS (Random effects; adjusted for COVID-19)				
OS (Fixed effect; unadjusted)	Not reported	Not reported	Not reported	
OS (Random effects; unadjusted)	Not reported	Not reported	Not reported	

Source: CS Table 44; Clarification responses A10 and A11.

Abbreviations: BMP, bortezomib, melphalan, prednisone; CrI, credible interval; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DLd, daratumumab, lenalidomide, dexamethasone; FE, fixed effect; HR, hazard ratio; Ld, lenalidomide, dexamethasone; PFS, progression free survival; RE, random effects.

3.7 Additional work on clinical effectiveness done by the EAG

The EAG has not done any additional work on clinical effectiveness at the current time.

3.8 Conclusions of the clinical-effectiveness section

3.8.1 The CEPHEUS trial

The evidence for the clinical effectiveness of DBLd in adult patients with newly diagnosed multiple myeloma comes from the pivotal CEPHEUS trial. This is an on-going, phase III, open-label, multi-centre RCT of 395 patients, which has been used to support license applications to regulatory bodies. The EAG considers this to be a well-designed study with generally low risk of bias and reasonable generalisability to UK clinical practice, with a few exceptions as discussed in this report. (e.g. the patient age profile). Despite its strengths it must be remembered that the comparison treatment in the CEPHEUS trial, BLd, is not used in the NHS and is therefore not relevant as a comparator in this NICE appraisal. The results of the trial show statistically significant differences across a range of outcomes in favour of

DBLd. However, this does not necessarily infer that DBLd will be similarly superior in effects in relation to the comparators in the NICE scope.

3.8.2 The IPTW indirect treatment comparisons

The relative effectiveness of DBLd versus the comparators in the NICE scope is based entirely on evidence from indirect treatment comparisons. There is no randomised head-to-head data for DBLd to inform the economic modelling, or to facilitate a consistency check between direct and indirect comparison evidence. A strength of the CS is that it presents two different methods of ITC, allowing the results of each to be compared for consistency and hence inform judgments about robustness of the findings.

The primary approach to indirect comparison presented in the CS is the IPTW ITC, which makes use of IPD available to the company from trials of DBLd and some of the comparators. The advantage is that differences in baseline patient characteristics between trials, which may be a source of confounding, can be somewhat compensated for by adjustments to the respective trial arms to match patients on observable characteristics using propensity scores. The IPTW ITC was conducted according to methodological guidance from the NICE DSU and has been implemented comprehensively. The results indicate that DBLd is associated with statistically significant and clinically meaningful improvements in outcomes including PFS, OS, tumour response rates and MRD negative complete response rates, compared to existing treatment (except for IsaBLd which has not been included in the IPTW ITC).

3.8.3 The network meta-analysis (NMA)

To reinforce the findings of the ITC, the company provided an alternative approach to indirect comparison using network meta-analysis. The NMA follows a Bayesian approach using standard statistical methods commonly used in NICE appraisals. Reassuringly, the results of the NMA generally accord with those of the IPTW ITC, with significant improvements in PFS and OS relative to existing treatments. However, the NMA is subject to certain limitations with potential for some uncertainty in the findings. The evidence network is sparse with some interventions (including DBLd) connected only by a single trial arm. The lack of common comparators linking trials means it has been necessary to create an extended network incorporating trials of treatments outwith the scope, to create a fully connected network.

Another issue affecting the NMA is that two of the trials (CEPHEUS and SWOG S0777) include mixed patient populations. In CEPHEUS patients were either ASCT ineligible or had refused (deferred) ASCT. Data for the ASCT ineligible subgroup is used in the NMA, which technically breaks randomisation, however, ASCT eligibility was a stratification factor in the randomisation so this is protective against bias in the results. We reiterate that the ASCT-ineligible sub-population of the CEPHEUS trial is not a pre-specified subgroup and, despite comprising 73% of the ITT population, it was not statistically powered to demonstrate superiority of DBLd relative to the comparator in the trial (BLd).

The SWOG S0777 trial included patients in whom immediate transplant was intended and patients in whom transplant was not currently intended. The latter group comprised a mix of patients who were ASCT-ineligible or who were ASCT-eligible but chose to decline or defer transplant. Separate results for the ASCT ineligible patients were not reported, so for the purposes of the NMA the company use the results for the no-intent to transplant subgroup as a proxy for ASCT ineligibility. Intent to transplant was a stratification factor in the randomisation procedure, and, in common with the CEPHEUS trial above, protects against bias. Reassuringly, the results of scenario analyses based on the ITT population in the SWOG trial were similar to the results of the base case which was based on a sub-population. No such scenario analysis for the DBLd arm of the CEPHEUS trial (i.e. based on the ITT population) is available, for comparison with the results based on the ASCT-ineligible population.

Overall, the EAG considers both approaches to ITC have merits as well as potential limitations and both are informative for decision making. Of the two approaches we regard the IPTW approach as being the most appropriate method for the available data.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 summarises the company's review of the cost-effectiveness evidence and section 4.2 describes and critiques the company's economic evaluation. Section 5 reports results from the company's economic analyses, the EAG's validation of the model, and the additional analyses conducted by the EAG.

4.1 Critique of the review of cost-effectiveness evidence

The company summarises the results of their systematic review of cost-effectiveness evidence in CS section B.3.1 and CS Appendix E. The methods and results of the published economic evaluations are described in CS Appendix E. The searches were originally conducted in April and May 2021 and subsequently updated in August 2024 and April 2025. The EAG considers that the search methods are appropriate.

The CS identified 18 publications from 17 unique studies that reported data for the relevant comparators for the current appraisal (CS Appendix E Table 59). Only one of these studies, which was an abstract, Ashcroft et al 2018,³² was UK-based. The treatments assessed in this study were daratumumab, bortezomib, melphalan, prednisone (DBMP), BMP, and Ld. A partitioned survival model was used to analyse cost-effectiveness for a lifetime horizon from the NHS perspective. The ICER for DBMP vs Ld was reported as €202,903 per QALY, and that of BMP vs Ld as €43,030 per QALY. The remaining studies were based in the USA, Taiwan, China, Singapore, Austria, Canada, and Serbia. We do not consider these remaining studies to add relevant additional information. The searches did not find any cost-effectiveness studies for DBLd versus the relevant comparators in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

See sections 4.2.6 and 4.2.7, respectively, for discussion of the reviews of sources of evidence for quality of life ('utility') and resource use and costs.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 14 summarises the EAG's view on whether the company's economic analysis complies with methodological criteria specified in the NICE reference case checklist.³³ We consider that the company's approach is reasonable and meets those outlined in the NICE reference case.

Table 14 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comments on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	Yes, for patients (carer outcomes are not included)
Perspective on costs	NHS and Personal Social Services	Yes
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes, cost-utility analysis. The company report pairwise ICERs, not fully incremental results.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, the time horizon is lifetime in the base case
Synthesis of evidence on health effects	Based on systematic review	Yes
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.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	Yes, EQ-5D-5L data collected from patients in the clinical trial
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, utilities are mapped UK population values using the Hernández-Alava et al. (2017) function ³⁴
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	Yes. The severity modifier is not applicable
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: Produced by the EAG based on information from the company's submission and model EQ-5D, European Quality of Life Working Group Health Status Measure 5 Dimensions; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PSS, personal social services; QALY, quality-adjusted life year.

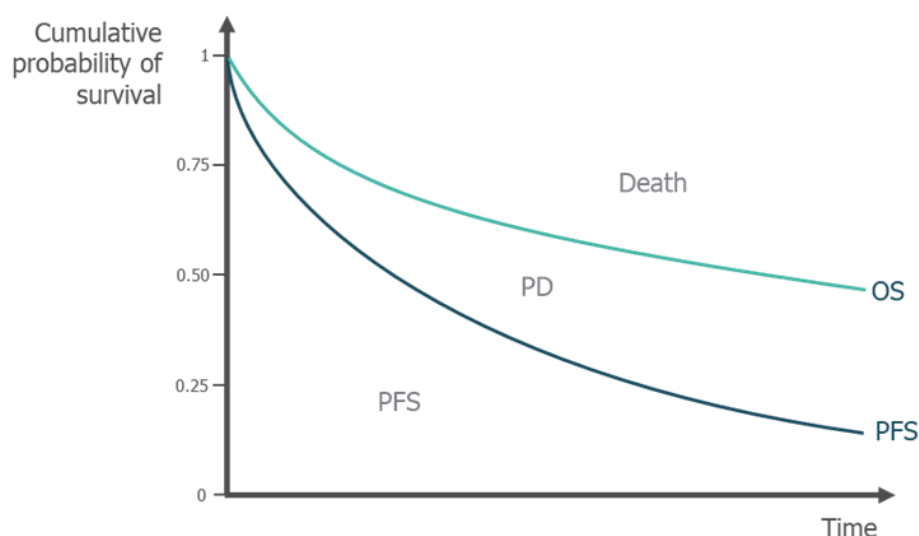
4.2.2 Model structure

The company's model structure is described in CS section B.3.2.2. It is a partitioned survival model, programmed in Microsoft Excel with a time horizon of 28 years and a cycle length of four weeks. The model structure comprises three health states: pre-progression, post-progression, and death. The occupancy of health states over time is estimated using the PFS and OS extrapolations. To illustrate, the proportions of patients occupying the health states is estimated as follows:

- Pre-progression: the proportion alive (based on OS) and progression-free (based on PFS)
- Post-progression: the proportion alive (based on OS extrapolations) minus the proportion of patients alive and PF (based on PFS extrapolations)
- Death state: the proportion who had died (based on OS extrapolations)

To account for patients discontinuing treatment before progression, time on treatment (ToT) was determined to apply specific health-state costs. The structure is illustrated in CS Figure 28 (reproduced in

Figure 3 below).



Abbreviations: OS: overall survival; PD: progressed disease; PFS: progression-free survival.

Figure 3 Company's economic model structure

Source: Reproduced from CS Figure 28

EAG comment on model structure

The model structure is appropriate. It is the same approach as that used in the company submissions in previous technology appraisals in this indication, area and accepted by the NICE appraisal committee, such as for TA917.

4.2.3 Population

The base case population for the company's economic analysis is patients with ASCT-ineligible NDMM. The baseline characteristics of the modelled population were based on the ASCT-ineligible population in the CEPHEUS trial, shown in Table 15. Age and gender determine general population mortality, whereas mean body weight and body surface area inform drug dosage, and therefore drug costs.

Table 15 Baseline characteristics of the modelled population

Characteristic	Value	Source
Mean age of patients (years)	65	CEPHEUS trial (ASCT-ineligible population)
Mean weight of patients (kg)	75	
Mean BSA of patients (m ²)	1.9	
Male (%)	50	

Source: Reproduced from CS Table 52

Abbreviations: BSA: Body Surface Area; ASCT: Autologous stem cell transplantation

The company argued that the CEPHEUS ASCT-ineligible population is broadly reflective of patients in UK clinical practice. This is based on a real-world evidence data set from the National Cancer Registration and Analysis Service (NCRAS) that included patients with multiple myeloma in England between January 2015 and December 2022 ³⁵. The mean age in the NCRAS cohort was ■■■ years, which is slightly higher than that of CEPHEUS population. Furthermore, the proportion of males in the NCRAS cohort was ■■■ compared to ■■■ in CEPHEUS. Consultation with our clinical expert indicated that, in general, patients with NDMM are likely to be older with higher proportion of males compared to the estimates obtained from the CEPHEUS trial. We test the impact of changing the mean age and proportion of males on the overall cost-effectiveness results in EAG analyses (see Section 5.2).

EAG comments on the population

The baseline characteristics of the company's modelled population are based on the CEPHEUS trial. Based on our expert clinical advice and real-world evidence dataset from NCRAS, we view that patients with NDMM in UK clinical practice are likely to be older, with higher proportion of males than those in the CEPHEUS trial. We test these assumptions in EAG analyses.

4.2.4 Interventions and comparators

The modelled intervention is DBLd with a dosing regimen outlined in CS Table 69. The comparators included are: DLd, Ld, BMP and BCd. These match those specified in the NICE scope. The scope also included IsaBLd as a comparator subject to NICE evaluation. NICE guidance, published on 24th September 2025, recommends IsaBLd as a treatment option for untreated multiple myeloma in adults when an autologous stem cell transplant is unsuitable (TA1098). NICE expects that the company include this comparator in their analyses. However, as mentioned earlier, the company did not include it in their submission because at that time, a decision for IsaBLd had not been made. We requested that the company include IsaBLd as a comparator (EAG clarification question A11). In response, the company provided an indirect comparison (NMA) of IsaBLd vs. DBLd, but did not incorporate this comparison into the economic model. Instead, they speculate on the likely cost-effectiveness of DBLd vs IsaBLd based on assumptions, expert clinical advice and best available evidence.

Of the four included comparators, viz., DLd, Ld, BMP and BCd, the company considers DLd as the primary comparator against DBLd. Further discussions were presented in earlier sections, see Sections 2.2 and 2.3. Briefly, the company justified their approach (in response to the EAG clarification question B5), stating that Ld is generally used by patients who cannot tolerate a triplet regimen, or who do not live near a hospital and would prefer the convenience of an oral treatment. Consequently, they do not consider that a quadruplet option such as DBLd would be deemed suitable for these patients. Additionally, they commented that bortezomib-based combination therapies are usually used in patients with renal impairment (estimated to be about 5% of patients in UK clinical practice by clinical experts at the company's May 2025 UK Advisory Board). As most of these patients have multiple comorbidities, quadruplet regimens like DBLd are likely to be regarded as inappropriate for these patients.

Clinical advice to the EAG was that over 90% of patients with NDMM who are ASCT-ineligible currently receive treatment with DLd and almost none are treated with BCd. Our clinical expert also explained that BMP is rarely used in the UK and considered that Ld would likely only be used by patients preferring an oral therapy or not fit enough to receive triplet therapy with DLd. Consequently, our report focuses on the comparison of DBLd with DLd only.

We discuss the dosing regimens of the intervention and the comparator, along with subsequent treatments, in section 4.2.7.

EAG comments on the intervention and comparator

The company have not included IsaBLd as a comparator in their economic analyses. NICE guidance, published on 24th September 2025, recommends IsaBLd as a treatment option for untreated multiple myeloma in adults when an autologous stem cell transplant is unsuitable. We agree with the company that, of the four included comparators, DLd is the most relevant comparator based on clinical expert opinion.

4.2.5 Treatment effectiveness and extrapolation

The economic model fitted independent survival extrapolations for OS, PFS and TTD to patient-level data from the ASCT-ineligible ITT populations of CEPHEUS for DBLd and DLd. The company adjusted the COVID-related mortality in their survival extrapolations and capped PFS and TTD to ensure that PFS is less than OS and TTD is less than PFS,

respectively, for clinical plausibility. Furthermore, they used the age-and gender-matched general population mortality (obtained from the ONS life tables 2017-2019) to cap OS across the intervention and comparator. No treatment effect waning was implemented, which is appropriate based on the treatment mechanism and consistent with the recent NICE appraisal of IsaBLd (NICE TA1098).

4.2.5.1 Overall survival

COVID-19 adjusted Kaplan-Meier estimates for OS for the average treatment effect (ATE)-weighted ASCT-ineligible population of the CEPHEUS trial are provided in CS Figures 29 and 30 for DBLd and in CS Figures 32 and 33 for DLd, respectively. CS Section B.3.3.2 reports how parametric survival models were fitted to these data to produce extrapolations for use in the economic model. Seven standard parametric survival distributions were used, viz., exponential, Weibull, lognormal, loglogistic, Gompertz, generalised gamma and gamma. The fitted curves for DBLd are shown in CS Figures 29 and 30, and for DLd in CS Figures 32 and 33, respectively. Goodness-of-fit statistics (Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)) and landmark survival estimates (at 10, 15 and 20 years) are reported in CS Tables 54 and 55 for DBLd, and in CS Tables 56 and 57 for DLd. The cost-effectiveness model includes a general population mortality cap adjustment to ensure that the mortality risk for the modelled population cannot be lower than that expected for members of the general population of the same age and sex.

The company tested the assumptions of proportional hazard (adjusted for COVID-19) for DBLd versus DLd, shown in CS Appendix N. The company states that while the proportional hazard assumptions were not violated for PFS (COVID-19 adjusted), these were violated for OS (COVID-19 adjusted) based on the hazard plots. Therefore, they chose to fit parametric curves to each treatment arm independently to ensure consistency between PFS and OS.

The CS reported that the company used visual inspection, statistical goodness-of-fit and expert opinion on the plausibility of the long-term survival estimates from UK clinical experts to choose the parametric distribution for their base case and alternatives for scenario analysis. The exponential distribution provided the best fit based on AIC and BIC statistics; however, the predicted survival rates were much higher than the company's clinical experts' estimates (see CS Tables 55 and 57). The CS states that clinical feedback and estimates were given central consideration for the choice of the company's base case extrapolation.

Therefore, to ensure clinical face validity of the base case curve selection, they adopted a calibration approach by attenuating the curves to align the extrapolations with the most clinically plausible estimates of long-term survival for DBLd (shown in Figure 6 below) and DLd (shown in Figure 7). This approach was previously used and accepted in TA1015.

For the base case, the company chose:

- For DBLd, the exponential distribution attenuated to increase the hazard of death in each cycle from Year 5 onwards so that the exponential curve resulted in 10, 15, and 20-year survival of 50%, 22.5% and 10% respectively (see Figure 6).
- For DLd, the attenuation factor (derived using a multiplier applied to the general population mortality) was applied to the exponential extrapolation from Year 7 onwards so that the 10, 15, and 20-year survival estimates were 40%, 20% and 4.5% respectively (see Figure 7).

Figure 4 to Figure 7 below shows the company's fitted extrapolations for DBLd and DLd.

Table 16 reports the company's overall survival estimates for ASCT-ineligible patients with NDMM, based on extrapolated results from the CEPHEUS trial, which include adjustments for general population mortality.

Table 16 The company's OS estimates

Parametric function	Estimated survival		
	5 years	10 years	20 years
DBLd			
Exponential			
Weibull			
LogNormal			
LogLogistic			
Gompertz			
Gen Gamma			
Gamma			
DLd			
Exponential			
Weibull			
LogNormal			
LogLogistic			
Gompertz			
Gen Gamma			
Gamma			

Source: Produced by the EAG from the company's revised model received on 21st August 2025

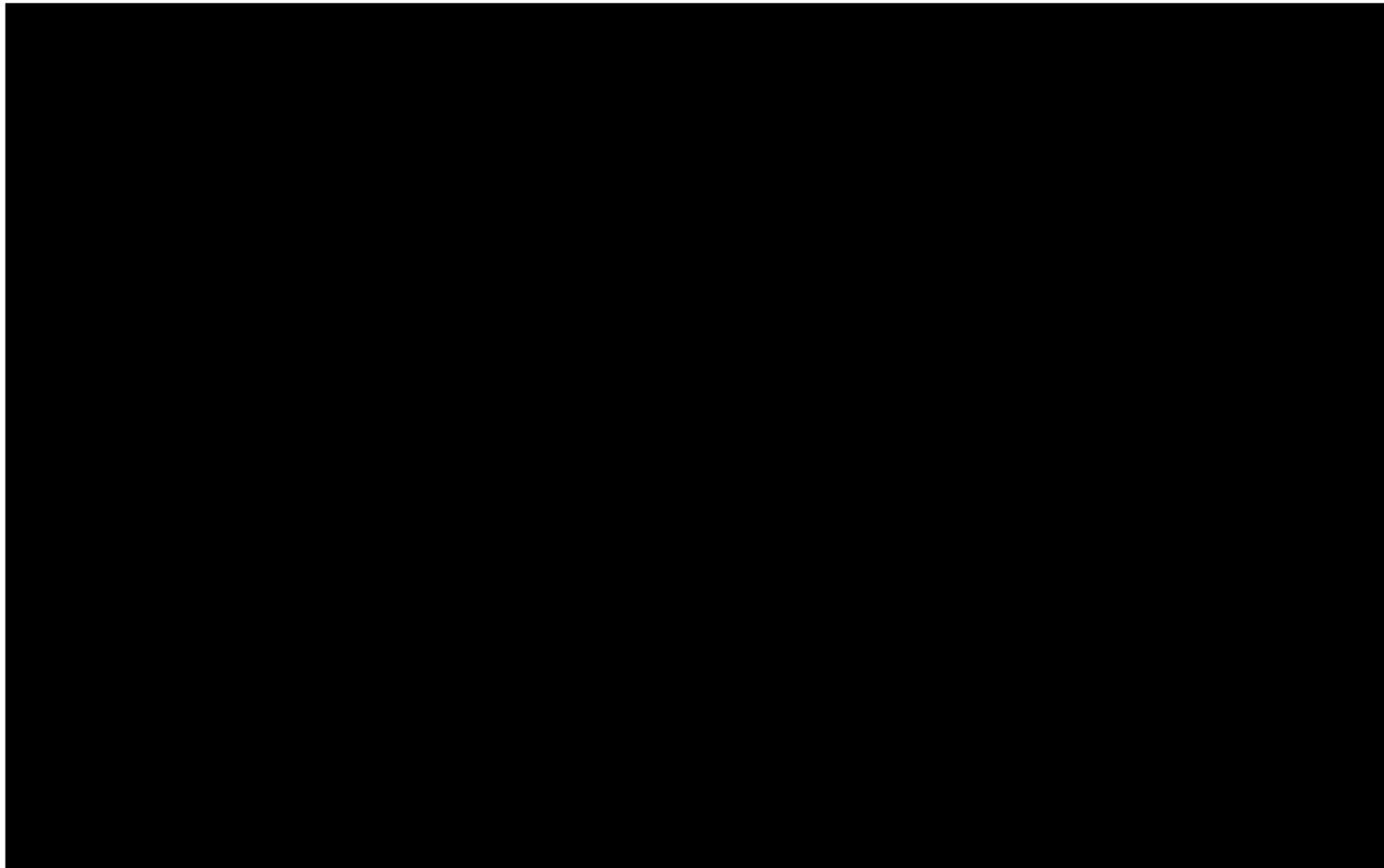


Figure 4 DBLd OS extrapolation (COVID-19 adjusted) with GPM cap

Source: Produced by the EAG from the company's economic model

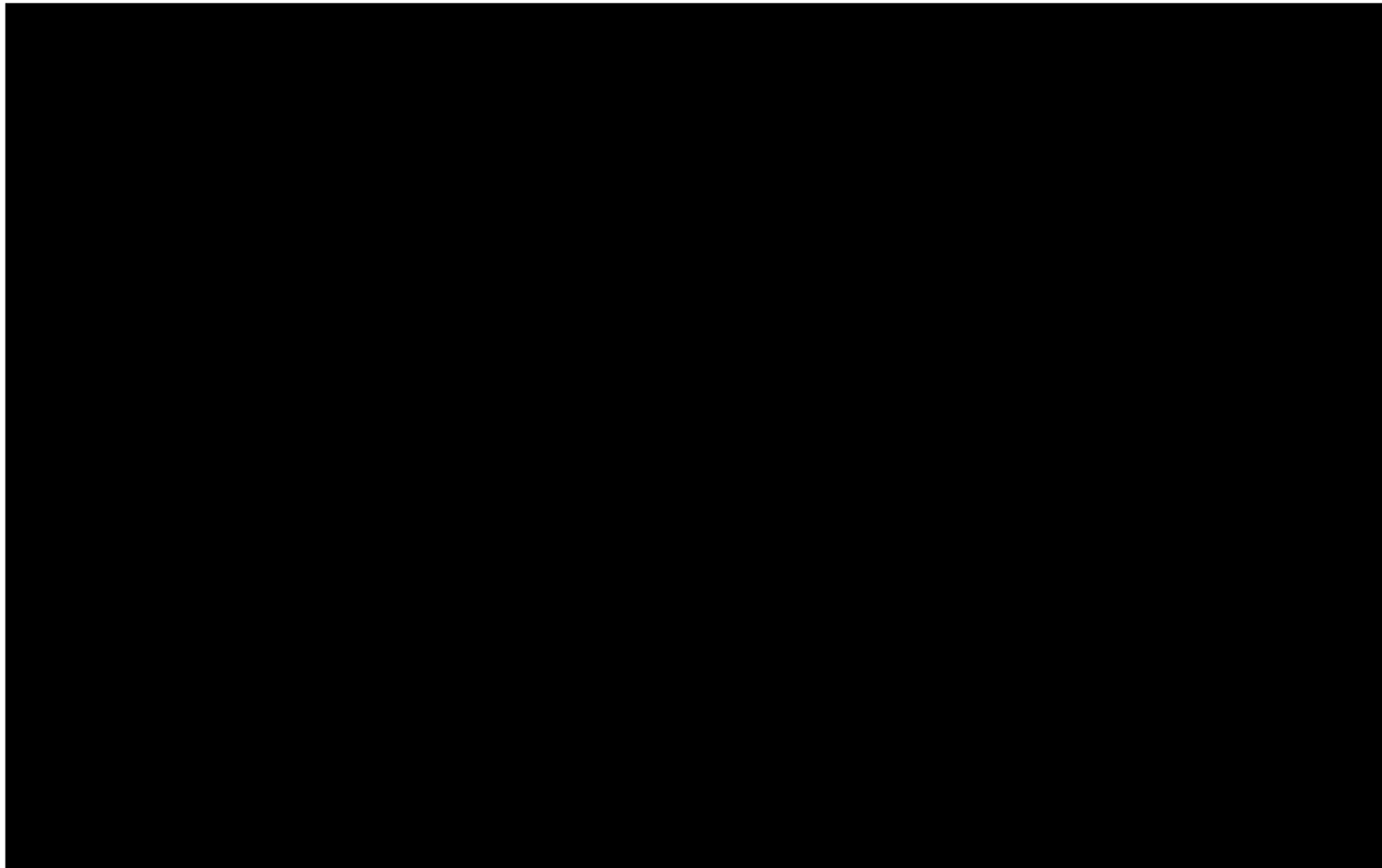


Figure 5 DLd OS extrapolation (COVID-19 adjusted) with GPM cap

Source: Produced by the EAG from the company's economic model

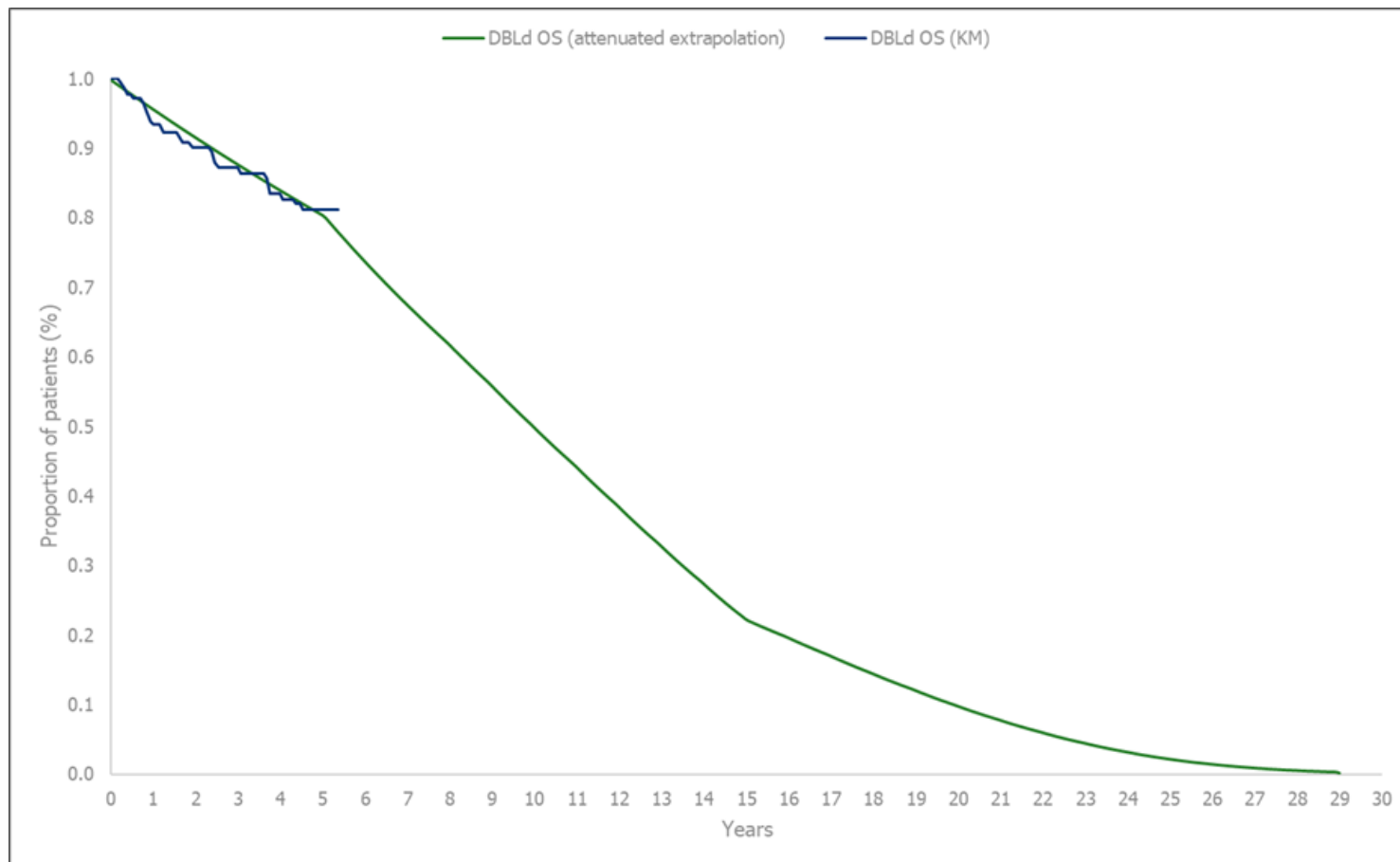


Figure 6 Attenuated exponential curve fitted to DBLd OS extrapolation (COVID-19 adjusted)

Source: Reproduced from CS Figure 31

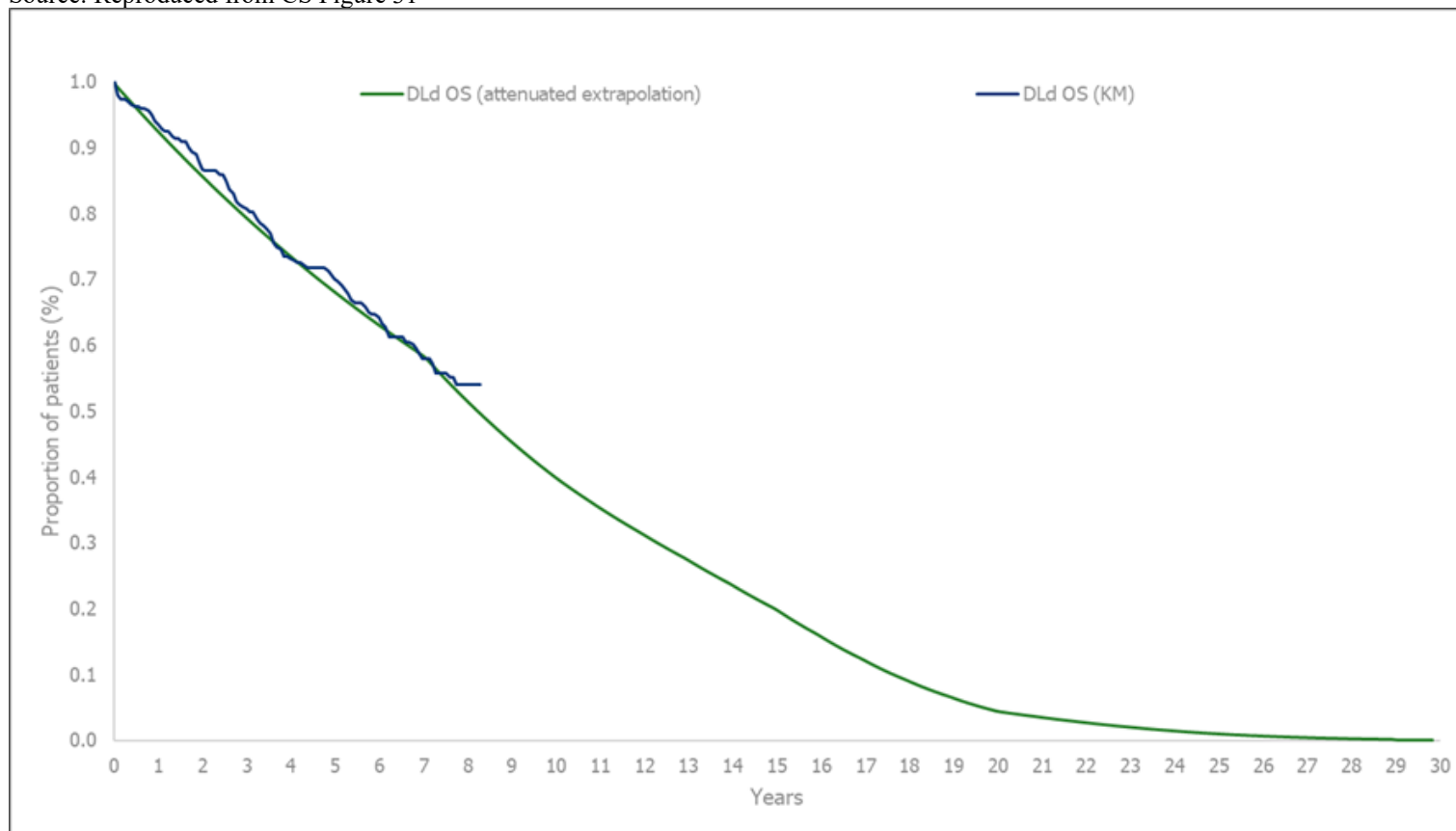


Figure 7 Attenuated exponential curve fitted to DLd OS extrapolation (COVID-19 adjusted)

Source: Reproduced from CS Figure 34

The EAG has several observations regarding the company's approach to modelling OS. These are summarised below.

We note that most patients were censored for OS before the end of the clinical cut-off date in both CEPHEUS and MAIA. This appears to result in a flattening of the OS KM curve, notably in CEPHEUS for about the last year (approximately one-fifth of the duration) of the study (see Figure 8).

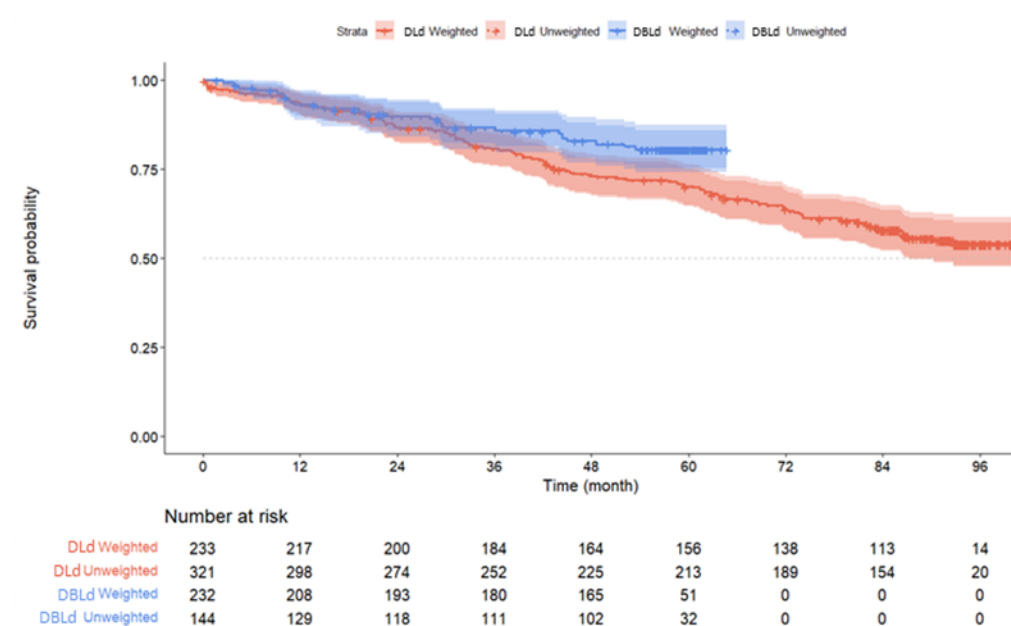


Figure 8 OS (censored for COVID-19) KM curves for DBLd and DLd (unadjusted and adjusted; base case model)

Source: Reproduced from CS Figure 22

Footnotes: ATE weights are applied in this case. Patient volume was reweighted with weighted sum at time zero equals to unweighted sum at time zero.

Abbreviations: ATE: average treatment effect; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; KM: Kaplan-Meier; OS: overall survival.

In their response to EAG Clarification Question B4, the company explain that patients were censored according to definitions stated in the CEPHEUS and MAIA statistical analysis plans. Further, they state that these definitions are consistent with those used in other multiple myeloma clinical trials. The censoring observed at the end of the KM curves reflects the survival status of patients who are alive by the clinical cut-off date. For OS, censoring occurs at the date the patient was last known to be alive, collected until the cut-off date, and PFS censoring occurs at the patient's last disease assessment before the clinical cut-off. They conducted a scenario analysis based on the EAG request, whereby the long-term

extrapolations of OS curves for DBLd and DLd (and the PFS of DLd) are based on the truncated KM data from the CEPHEUS and MAIA trials, respectively. This change does not have any significant impact on the overall cost-effectiveness results. Further details of the scenario can be found in Table 12 of the company's response to EAG Clarification Question B4.

The EAG agrees with the company that the visual fit of the extrapolations to the observed CEPHEUS data indicated that the trajectories of all extrapolations were similar. Furthermore, we also note that according to AIC/BIC scores, the exponential has the best fit, closely followed by the remaining distributions having a very similar fit for the DBLd arm. And, for the DLd arm, the exponential has the best fit, closely followed by Weibull and loglogistic distributions.

With respect to the company's calibration approach, whereby curves were attenuated to align extrapolations with the 10-, 15- and 20-year estimates obtained from their UK clinical experts advisory board, the company calibrated the exponential extrapolation after year 5 in the model (within the model, the attenuations were at 10-year, 15-year and 20-year time points). They argued that calibrating the attenuation post 5 years was appropriate, as the median follow-up in the CEPHEUS is 58.71 months at the latest data cut. Furthermore, they justified their approach by citing a previous NICE appraisal on teclistamab, TA1015, where this approach was used and accepted by the committee. The company states that the attenuation factor is derived by applying a multiplier to the general population mortality rate. The EAG agrees that the model in the current appraisal uses the same attenuation method as applied in TA1015. Within the economic model, we note that the company uses the following steps:

1. Calculates the hazard at the start time point of interest (e.g. start of attenuation @ 5 years), using the unattenuated OS extrapolation
2. Calculates the hazard at the end time point of interest (e.g. attenuation time point 1 @ 10 years), using the clinical expert estimates of survival at that time point
3. Calculates the cumulative hazard between the two timepoints of interest using the probability of death per cycle (maximum of the raw extrapolation or general population mortality)
4. The multiplier is the ratio of the two cumulative hazard estimates
5. This multiplier is then applied to calculate the OS attenuated extrapolation

Based on the above steps, the company obtain different multipliers for each time period, i.e., 0-5 years, 10-15 years and 15-20 years and between DBLd and DLd, because the hazards are calculated from probabilities of survival at each timepoint, which vary over time and between each treatment arm. The company applies the attenuation at different time points for OS: year 5 for DBLd and Year 7 for DLd with the different time points selected due to the different length of follow-up across the two studies (58.7 months and 89.3 months in CEPHEUS and MAIA respectively).

Consultation with our clinical expert suggested the company's survival estimate for DBLd at 20 years is quite high, given the average age at diagnosis is 75 years. For a comparative reference, our clinical expert suggests that approximately 30% of the patients in the DLd are likely to be alive at 10 years; and about 15% and 5% at 15 years and 20 years, respectively. We conduct scenarios to test the impact of varying the company's survival assumptions in EAG analyses, see Section 5.2.2.

EAG comments on OS extrapolation

We view there is uncertainty around the company's calibration approach, specifically, the multiplier applied to the general population mortality. Whilst we acknowledge there may be an improvement in the OS estimates for DBLd compared to those of the DLd arm, advice from our clinical expert suggests the company's estimates may be overestimated, particularly at 10 years and 20 years for both arms, and at 5 years in the DBLd arm. We conducted scenario analyses varying the survival estimates and the attenuation time points (section 5.2).

Considering that all the modelled survival distributions have a similar fit to the OS Kaplan-Meier estimates, and there is an uncertainty regarding the method applied to derive the multipliers for the attenuation, we retain the company's base case OS ,base case to test the impact of alternative assumptions on survival estimates, see Section 5.2.

4.2.5.2 Progression-free survival

COVID-19 adjusted Kaplan-Meier estimates of PFS for DBLd and DLd from the ATE-weighted ASCT-ineligible population of CEPHEUS are presented in CS Figures 35 and 37. The parametric curves, including the exponential, Weibull, lognormal, loglogistic, Gompertz,

generalised gamma and gamma, fitted to each arm are also provided in these figures. The hazard plots for the outcomes of PFS are given in CS Appendix N. As with OS, the company assume that:

- Proportional hazards do not hold, and models are fitted independently for each arm.
- The exponential curve provided the best fit for both arms based on AIC/BIC statistics
- An attenuation factor is applied to the exponential extrapolation from Year 5 onwards for both arms, shown in CS Figures 36 and 38, respectively.

Table 17 The company's PFS estimates

Parametric function	Estimated survival					
	5 years		10 years		20 years	
DBLd						
Exponential						
Weibull						
LogNormal						
LogLogistic						
Gompertz						
Gen Gamma						
Gamma						
DLd						
Exponential						
Weibull						
LogNormal						
LogLogistic						
Gompertz						
Gen Gamma						
Gamma						

Source: Produced by the EAG from the company's revised model received on 21st August 2025

EAG comments on PFS extrapolation

We note that the assumption of proportional hazard holds for the PFS. However, the company model the two treatment arms independently to be consistent with the approach applied for OS. We view this as a reasonable adjustment. Furthermore, changing the distributions or the attenuation time points has a small impact on the overall cost-effectiveness results (see EAG scenarios in Section 5.2). We agree with the company that the best-fitting curve for both DBLd and DLd is the exponential distribution. However, the CEPHEUS trial is immature so the median PFS is not met for DBLd. The median PFS is met for the DLd arm in the MAIA trial. Further details are available in Section 3.3.2.

4.2.5.3 Time to treatment discontinuation

The parametric curves were fitted to DBLd and DLd individually on the COVID-19 adjusted TTD outcomes from the ASCT-ineligible CEPHEUS population. The KM estimates, along with the parametric survival model fits for DBLd and DLd, are provided in CS Figures 39 and 42, respectively, and the hazard plots are provided in CS Appendix N. The company argue that the proportional hazards assumption does not hold for TTD and fits parametric curves independently for each treatment. We note that the company apply the PFS cap to ensure that TTD is less than PFS. For their base case, the company selects the Gompertz distribution for DBLd (without attenuation) and the Weibull distribution for DLd (also without attenuation). They conducted scenario analyses by applying an attenuated exponential model for DBLd and an attenuated Gompertz model for DLd. These scenarios did not influence the direction of the overall cost-effectiveness results.

We note that the exponential distribution provides the best fit of the TTD KM data for DBLd and Gompertz for DLd. However, long-term predictions do not match their clinical experts' predictions, which is why they chose the Gompertz distribution for DBLd and the Weibull for DLd arm, respectively. We run EAG scenarios using alternative distributions (i.e., exponential and Gompertz) for the two treatment arms, see Section 5.2.

Table 18 The company's TTD estimates (with PFS cap)

Parametric function	Estimated survival		
	5 years	10 years	20 years
DBLd			
Exponential			
Weibull			
LogNormal			
LogLog			
Gompertz			
Gen Gamma			
Gamma			
DLd			
Exponential			
Weibull			
LogNormal			
LogLog			
Gompertz			
Gen Gamma			
Gamma			

Source: Produced by the EAG from the company's revised model received on 21st August 2025

CS Table 65 presents a comparison of the predicted survival rates for DLd TTD extrapolations against their clinical expert estimates (reproduced below in Table 19).

Consultation with our clinical expert indicated that the company's estimates for the proportion of patients on treatment at 10-, 15- and 20 years are overestimated. Our expert suggested that in the UK clinical practice, the proportion of patients remaining on treatment is likely to be less than 5% at 10 years and none at 20 years. Based on this, we run scenarios using Gompertz and generalised gamma distributions for extrapolating TTD for the DLd arm, see Section 5.2.

Table 19 Predicted time to treatment discontinuation (TTD) extrapolations

	TTD rates (%)		
	10 years	15 years	20 years
Clinical expert estimates	■	■	■
Company extrapolation (Weibull)	■	■	■
Exponential	■	■	■
LogNormal	■	■	■
LogLogistic	■	■	■
Gompertz	■	■	■
Gen Gamma	■	■	■
Gamma	■	■	■

Source: CS Table 65

EAG comments on TTD extrapolation

Like OS and PFS, the company fits independent distributions to DBLd and DLd to extrapolate the TTD Kaplan-Meier data. However, unlike OS and PFS, they do not apply an attenuation factor. We consider this appropriate because the estimates obtained at 10-, 15-, and 20 years from the Gompertz distribution are a reasonable match to those provided by the clinical experts' (the company's and the EAG's) estimates. We assess the impact of using alternate distributions to extrapolate the long-term TTD estimates in the DLd arm in Section 5.2.

4.2.5.4 Adverse events

The economic model included treatment-emergent grade 3 and grade 4 adverse events with an incidence $\geq 5\%$ for each of the treatment arms. CS Table 66 reports the included adverse events and their incidence rates. These rates were based on the ASCT-ineligible population of the CEPHEUS trial for DBLd, the MAIA trial for DLd and Ld, and the ALCYONE trial for BMP. The company assumes the same adverse event rates for BCd as BMP. Changes in utility and costs associated with adverse events were applied in the first cycle of the model.

4.2.6 Health-related quality of life

The company describe their approach to estimating health-related quality of life (utility) for the cost-effectiveness analysis in CS section B.3.4.

Base case utilities for the progression-free and progressed disease health states are estimated from EQ-5D-5L data for the ASCT-ineligible population in the CEPHEUS trial. EQ-5D-5L were mapped to the EQ-5D-3L using Hernandez Alava et al. 2020.³⁶ The utilities are modelled per health state, but the progression-free state is split into prior to 8 weeks and after 8 weeks. The company justified their approach by stating that it reflected improvement in patient utility values, which improved with increasing time spent in the PF state. Furthermore, they stated that this approach is consistent with that accepted in TA1015. Age-adjustment of utilities is applied.

Results are also reported for scenario analyses where time-independent utilities (sourced from CEPHEUS) are applied for both PFS and PD; time-dependent utilities are applied to both PFS and PD states, and the utilities derived from the MAIA trial are applied. See the subsections below for further discussion.

4.2.6.1 Systematic literature review for utilities

The company's review of utility studies identified 77 publications reporting 46 unique studies on patient-reported outcomes and utilities in patients with ASCT-ineligible NDMM. The company discuss these findings in CS Appendix F but notes that the clinical trials for DBLd and DLd (CEPHEUS and MAIA, respectively) represent the most relevant sources of utility data for the current appraisal.

4.2.6.2 Utility estimates from trial data

The methods used to analyse the EQ-5D-5L data from the CEPHEUS trial (ASCT-ineligible population) are described in CS sections B.3.4.1, 3.4.2 and 3.4.5.

In the CEPHEUS trial, HRQoL data were collected using EQ-5D-5L and EORTC QLQ-C30 on Day 1 of Cycles 1-8 and then every third cycle thereafter until the disease progressed and at Weeks 8 and 16 after disease progression. Thereafter, EQ-5D-5L data were collected every 16 weeks, at the start of subsequent therapy, and four weeks after the start of subsequent therapy. The scores of EQ-5D-5L were mapped to EQ-5D-3L using the Hernández-Alava et al. (2017)³⁷ function using the Economic Methods of Evaluation of Health and Care Interventions Policy Research Unit (EEPRU) dataset (Hernandez Alava et al 2020³⁷), as recommended by NICE.³³ The company do not provide any information on the number of missing utility observations. Therefore, it is unclear if imputation was necessary or undertaken.

The CS stated that, as both DBLd and DLd are daratumumab-based regimens, it was appropriate to assume equal utilities (i.e., treatment-independent utilities) for both the treatment arms. To account for the treatment-specific impact of adverse events on QoL, adverse event disutilities were applied. The approach is similar to that used in TA917 and ID3981.

For the base case, utility values for PFS were modelled based on the cycle number, i.e., one utility value was used for cycles 0-8 and another value for cycles 9 onwards. The company terms this approach “time-dependent” and states that this is based on the recent appraisal of teclistamab in RRMM (TA1015³⁸) For the PD health state, a time-independent utility value (i.e. applying one utility value across all cycles for this health state) was used due to a lack of sufficient granularity in the data. The base case utilities used in the model are shown in CS Table 68 and reproduced below in Table 20. For consistency, we use the company’s phrases “time-dependent” and “time-independent” in this report.

Table 20 Base case utilities used in the model

Health state	Utility	SD	95% Confidence Interval
Pre-progression (treatment cycle 0-8)	0.85	0.02	0.81 to 0.89
Pre-progression (treatment cycle 9+)	0.84	0.02	0.80 to 0.88
Post-progression	0.75	0.02	0.71 to 0.79

Abbreviations: SD Standard Deviation

Source: Reproduced from CS Table 68 and the company's economic model

One-off utility decrements were applied in the model for the proportion of patients experiencing treatment-emergent adverse events. CS Table 67 provides the duration and utility decrements associated with adverse events included in the company model. This approach is consistent with that accepted in TA917.

4.2.6.3 General population utilities and age adjustment

The model includes an adjustment to reflect the declining quality of life with age and variation by gender, based on the UK-HSE 2014 estimates. This adjustment is correctly applied and in accordance with NICE guidance.³³ We confirm that the modelled utility in the progression-free health state remains lower than expected utility for people of the same age and gender in the general population based on the estimates of general population utility in England reported by HSE 2014.

EAG comment on utilities

The methods used to estimate health state utilities in the CEPHEUS trial are consistent with the NICE guidelines.³³ We agree with the company's approach to split the PFS state into two: one up to 8 weeks and the other, after 8 weeks. Overall, we note that changing the utilities has a limited impact on the overall cost-effectiveness results, as shown in Section 5.2.2.

4.2.7 Resources and costs

4.2.7.1 Systematic literature review for costs and resource use

Results from the systematic review of evidence for cost and resource use are reported in CS Appendix G. The review included 46 publications reporting 39 unique studies. None of the included studies were previous NICE appraisals in multiple myeloma.

In the following sections, we report the company's resource use and cost assumptions used in their cost-effectiveness model.

4.2.7.2 Dosing regimens

The dosing regimens for the intervention and the comparators are summarised in CS Table 69. These are obtained from the CEPHEUS trial (for DBLd), the MAIA trial (DLd and Ld), the ALCYONE trial (BMP) and the NHS Chemotherapy Protocol in MM (BCd).³⁹ For bortezomib, the full dose was given once a week, rather than twice weekly as per the SmPC. The company pointed out that this adjustment was based on their UK Advisory Boards and made to reflect UK clinical practice. They conducted a scenario analysis where the bortezomib dosing was given twice daily as per the SmPC- this was applied to all bortezomib treatments, DBLd, BMP and BCd.

4.2.7.3 Drug acquisition costs

Unit costs for the intervention and comparator drugs, sourced from the British National Formulary and the UK government electronic Market Information Tool (eMIT), are reported in CS Table 70. Costs of the concomitant medications (used as a single cost with the main treatment costs in the first model cycle) are reported in CS Table 76. For the daratumumab arm, the company applied

[REDACTED] We noted some discrepancies between the drug costs used in the economic model and current eMIT prices, which the company updated in their response to clarification question B7. We discuss this further in Section 5.2.

The company apply relative dose intensity (RDI) to the costs of the intervention and comparator drugs in the base case. RDIs were obtained from the ASCT-ineligible cohort in CEPHEUS (for DBLd and DLd), MAIA (for Ld) and ALCYONE (for BMP and bortezomib as part of BCd).

The mean Body Surface Area (BSA) of patients in the CEPHEUS trial was used to estimate the cost per administration for bortezomib. In the base case, no vial sharing was assumed for any treatments for which this was relevant. In these instances, the number of vials required per administration was rounded up to the nearest whole integer.

4.2.7.4 Subsequent treatment use

The company applied the cost of subsequent therapy (across second-line, third-line and fourth-line line) as a weighted average to each cycle in the progressed disease health state. Further information on the estimation of associated costs is in CS Section 3.5.1. Briefly, the weighted acquisition and administration costs were estimated based on treatment dosing regimens, time-on-treatment for each subsequent treatment, relevant treatment share and relevant attrition rates for each subsequent treatment. CS Table 71 presents the proportion of patients with a PFS receiving first-line subsequent (reproduced below Table 21). For the first and second lines, attrition rates were obtained from the pivotal trials. For the transitions between second and third line, and third and fourth line, the rates were obtained from a published source by Yong et al.(2016).⁴⁰ In these cases, the attrition rates were applied to the same proportions (see CS Table 72, reproduced in Table 22). The company adjusted the proportions in the third and fourth lines by estimating these relative to the previous lines (see CS Table 73, reproduced below in Table 23). The final proportions of patients with treatment at each line are presented in CS Table 74 (reproduced in Table 24)

Table 21 Proportion of patients with a subsequent treatment among patients with PFS event by treatment at 1st Line

	DBLd	DLd
PFS, n (%)	■ (100)	160 (100)
Progressive disease, n (%)	■ (■)	112 (70)
Progressive disease with subsequent treatment, n (%)	■	91 (81)
Death, n (%)	■	48 (30)
Source	CEPHEUS (ASCT-ineligible)	MAIA

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone DLd:

daratumumab, lenalidomide, and dexamethasone; PFS: progression-free survival.

Source: Reproduced from CS Table 71

Table 22 Attrition rates for subsequent lines of therapy from Yong et al.

	Proportion with a treatment at each LoT (%)	Proportion with a treatment at each LoT, re-based to 100% (%)	Proportion with a treatment at each LoT, relative to the previous line (%)
1 st line	95%	100.00%	100%
2 nd line	61%	64.21%	64.21%

3rd line	38%	40.00%	62.30%
4th line	15%	15.79%	39.47%

Abbreviations: LoT: line of therapy.

Source: Reproduced from CS Table 72

Table 23 Proportion of patients with treatment estimated from clinical trials and Yong et al., relative to the previous line of treatment

	DBLd	DLd	Source
1st line	100%	100%	Assumption
2nd line	████	81.25%	Clinical trials - progressive disease with subsequent treatment (CS Table 71)
3rd line	62.30%	62.30%	Yong <i>et al.</i> (2016) ⁴¹
4th line	39.47%	39.47%	Yong <i>et al.</i> (2016) ⁴¹

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone DLd: daratumumab, lenalidomide, and dexamethasone.

Source: Reproduced from CS Table 73

Table 24 Final proportion of patients with treatment applied in the company model, relative to the 1st line of treatment

	DBLd	DLd	Source
1st line	100.00%	100.00%	Calculation
2nd line	████	81.25%	
3rd line	████	50.61%	
4th line	████	19.98%	

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone DLd: daratumumab, lenalidomide, and dexamethasone.

Source: Reproduced from CS Table 74

It is noteworthy that fewer patients in the DBLd arm receive subsequent treatment compared to those in the DLd arm. The company explains this by the significant PFS benefits of DBLd, compared to DLd (PFS HR: 0.55). They also argued that those receiving DBLd would be much older following disease progression on DBLd compared to DLd, and therefore less likely to receive further subsequent treatments. However, our clinical expert points out that there is a ~3.5% drop in the proportion of patients receiving the second line treatment when comparing DLd vs Ld (81.25% in the DLd arm receive the second line compared to 84.8% in the Ld arm). Based on this, it appears unlikely that the uplift in PFS from DBLd vs DLd would drop the estimate by █████. Furthermore, OS data for the DBLd arm is immature so it is likely

that the proportion will increase with time. We run scenario analyses varying this estimate, see Section 5.2

CS Table 75 (reproduced below in Table 25) presents the distribution of patients receiving subsequent treatment in the economic model. The company obtained these estimates based on their clinical experts' opinions. Further, they stated that the estimates were re-weighted, where applicable, to remove subsequent treatments not routinely available in the UK, as well as combinations of treatments, which would be unlikely in clinical practice. We validated these estimates with our expert, who viewed the estimates as reasonable, except for a few exceptions in the proportions receiving second line in the DLd. In UK practice, approximately 10% of these patients are likely to receive bortezomib, about 3-5% CLd and approximately 74% BeBd, respectively, as second-line. In addition, our expert highlighted that SBd is scarce and its use is likely to be nearer ~10% than 40% at third line. The EAG considers that SBd scarcity applies to subsequent treatment in both arms. We ran exploratory scenarios to test the impact of varying these estimates on the cost-effectiveness results, see Section 5.2.

Table 25 Distribution of patients to subsequent therapies used in company model

Line:		2 nd line (%)					
Subsequent therapy:	Ld	Cd	DBd	B	CLd	SBd	BeBd
DBLd	0.00	9.38	0.00	0.00	0.00	3.13	87.50
DLd	0.00	9.38	0.00	0.00	0.00	3.13	87.50
Line:		3 rd line (%)					
Subsequent therapy:	Ld	PanoBd	ILd	SBd	Cyclo	CLd	-
DBLd	0.00	17.65	0.00	41.18	41.18	0.00	-
DLd	0.00	17.65	0.00	41.18	41.18	0.00	-
Line:		4 th line (%)					
Subsequent therapy:	PomDex	Teclistamab	-	-	-	-	-
All treatments	■	■	-	-	-	-	-

Abbreviations: B: bortezomib; BeBd: belantamab mafodotin with bortezomib; CLd: carfilzomib, lenalidomide and dexamethasone; Cyclo: cyclophosphamide; DBd: daratumumab, bortezomib and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ILd: ixazomib, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PanoBd: panobinostat, bortezomib and dexamethasone; PomDex: pomalidomide and dexamethasone; SBd: selinexor, bortezomib and dexamethasone; UK: United Kingdom.

Source: Reproduced from CS Table 75

4.2.7.5 Administration costs

The economic model incorporated the administration cost for both first-line treatments and subsequent therapies (see CS Table 77). They applied a one-off cost on treatment initiation for oral chemotherapy, whereas for subcutaneous injection-based therapies (such as daratumumab), a cost was applied for each administration. This is in line with the assumptions in NICE TA917 (Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable).⁶

4.2.7.6 Health state resource use and costs

4.2.7.6.1 Monitoring costs

Assumptions regarding the use of the monitoring resource and costs (CS Table 78 and reproduced below in Table 26) were based on previous NICE appraisals, including TA917, TA897, TA763 and SMC2302.^{6 42-44} Frequency of monitoring visits and tests were based on time on treatment: patients were assumed to receive “on treatment” monitoring for as long as patients were on front-line or subsequent treatment, whereas the “off-treatment” monitoring costs were applied when not on active treatment (e.g. pre-progression, but after discontinuing treatment). The company pointed out that this was most relevant for those receiving BMP, as patients spent longer periods in the “off treatment” before progressing. Overall, our expert viewed the estimates as reasonable, except for a few (see Table 26). We anticipate the effects on overall results will be negligible as the associated costs are minimal.

Table 26 Frequency of monitoring used in the company model

Item	Frequency per cycle (company)		Frequency per cycle (EAG expert opinion)	
	On-treatment	Off-treatment	On-treatment	Off-treatment
Haematologist visit	0.92	0.32	1	0.32
Full blood count	0.84	2.56	1	1
Biochemistry	0.76	1.32	1	1.32
Protein electrophoresis	0.52	0.72	0.75	0.72
Immunoglobulin	0.48	0.76	0.48	0.76
Urinary light chain excretion	0.20	0.20	0.20	0.20

Source: CS Table 78 and based on EAG expert opinion

4.2.7.6.2 End of life costs

The model includes a cost of £13,409 for end of life, representing the cost of terminal care. This cost, obtained from the PSSRU 2024, is applied to the proportion of patients dying in each cycle.

4.2.7.7 Adverse events costs

The model includes costs for treatment-related adverse events of grade ≥ 3 experienced by more than 5% of patients, see CS Table 79.

EAG comments on resource use and costs

The company's overall approach to estimating resource use and costs is mostly reasonable, although we noted some discrepancies that we addressed in EAG's additional analysis (see Section 5). These included varying assumptions on the proportions of patients receiving subsequent treatments and updated treatment costs.

5 Cost-effectiveness results

Section 5.1 summarises the company's cost-effectiveness results, section 5.2 presents the EAG's additional work and preferred assumptions, and section 5.3 explores decision modifiers, including the company's and EAG's preferred QALY weighting for severity.

Our report only considers the comparison of DBLd with DLd, as previously stated in Section 4.2.4.

5.1 Company's cost-effectiveness results

5.1.1 Company's base case

In response to clarification question B7, the company updated their base case model to include the latest eMIT costs for bortezomib, prednisolone, dexamethasone, lenalidomide and cyclophosphamide (shown in Table 14 in the company's response to clarification questions), and the concomitant medications paracetamol and aciclovir (response to clarification questions Table 15). These changes had a negligible effect on total treatment costs, decreasing DBLd total costs from [REDACTED] to [REDACTED] and increasing DLd total costs

from [REDACTED] to [REDACTED] DBLd continues to dominate DLd, i.e. it is cheaper and more effective.

Table 27 presents the deterministic base case results from the company's revised model (dated 21 Aug 2025) and Table 28 shows the updated probabilistic base case results. The EAG notes that the deterministic and probabilistic ICERs are consistent.

Table 27 Company's deterministic base-case cost-effectiveness results

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
DBLd	[REDACTED]	[REDACTED]	-	-	-
DLd	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant

Source: Company model (21 Aug 2025)

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

The EAG and the company consider a disease severity modifier of 1.0 is appropriate.

Table 28 Company's probabilistic base-case cost-effectiveness results

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
DBLd	[REDACTED]	[REDACTED]	-	-	-
DLd	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant

Source: Revised company model (21 Aug 2025)

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

The EAG and the company consider a disease severity modifier of 1.0 is appropriate.

5.1.2 Company's sensitivity and scenario analyses

5.1.2.1 Deterministic sensitivity analyses

Deterministic sensitivity analysis results for DBLd versus DLd using the company's revised base case are presented as a tornado diagram in Figure 9, showing the effect on the ICER result. The analyses included the following parameters:

- Proportion of patients who are male
- Treatment acquisition costs for the intervention and comparators
- Treatment administration costs
- Subsequent treatment costs
- Hazard ratios for OS, PFS and TTD (for Ld, BMP and BCd comparisons)
- One-off adverse event costs
- Monitoring and resource use costs
- Health state utilities

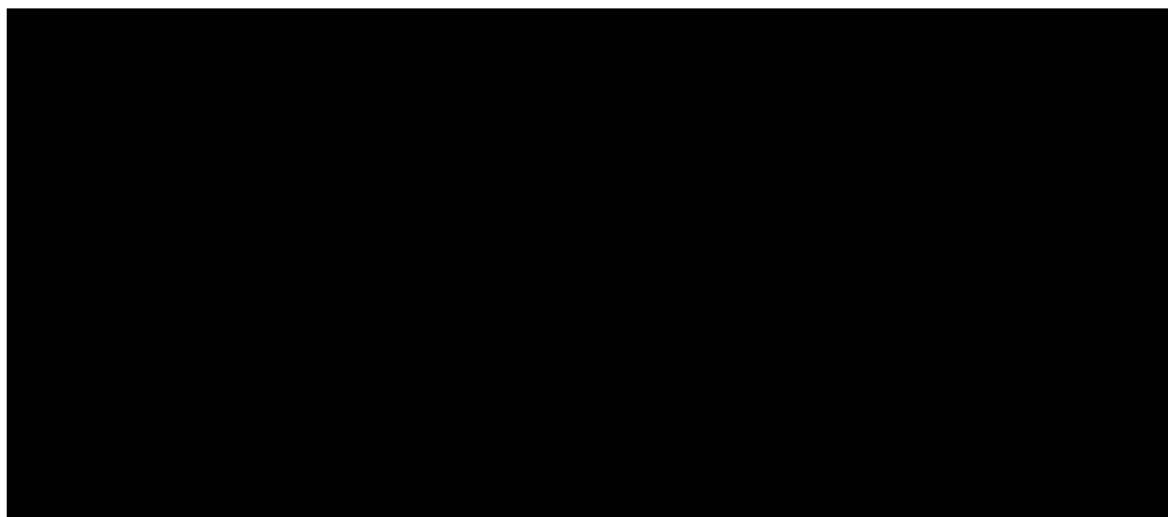


Figure 9 Deterministic sensitivity analysis, company base case

Source: Revised company model (21 Aug 2025)

Abbreviations: AE, adverse event; BOR, bortezomib; DARA, daratumumab; DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; substx, subsequent treatment

Patient age at baseline and the survival curves for progression-free survival, overall survival and time to treatment discontinuation have not been varied in the deterministic sensitivity

analyses. Lower and upper limits of a parameter were defined by the 95% confidence intervals around the mean, if the standard error of the mean was available. Otherwise, inputs were varied by $\pm 10\%$.

The parameters with the largest impact on the results were the cost of subsequent therapies and daratumumab acquisition costs. The CS highlights that the model uses list prices for all subsequent treatments. The company expects that once applicable PAS discounts are applied, the subsequent treatments are likely to have less influence on the ICER result.

5.1.2.2 Scenario analyses

The company conducted several scenario analyses to explore parameter assumptions and structural uncertainties of the economic model. The rationales for the scenario analyses are given in CS Table 86. The scenarios used data that were not included in the base case, and we consider the parameters tested by the company to be reasonable:

- 1 Alternative utility values
 - a. CEPHEUS (EQ-5D-3L cross-walked); assuming time-independence
 - b. CEPHEUS (EQ-5D-3L cross-walked); assuming time-dependence across both PF and PD health states
 - c. MAIA (EQ-5D-3L cross-walked)
- 2 Twice weekly bortezomib dosing to align with the SmPC
- 3 Alternative extrapolations for TTD
- 4 Discounting of 1.5% for both costs and health benefits
- 5 OS, PFS and TTD estimates for DBLd and DLd (from the CEPHEUS and MAIA trials)

The changes made to the model as part of the company's response to clarification questions did not affect the scenario results. DBLd continues to dominate DLd in all scenarios in the company's revised model (Table 29). The EAG was able to replicate these analyses.

Table 29 Company scenario analysis results, company revised base case

Scenario		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company base case				Dominant
1a	Utility Source: CEPHEUS (EQ-5D-3L cross-walked)			Dominant
1b	Utility Source: CEPHEUS time dependant (EQ-5D-3L cross-walked)			Dominant
1c	Utility Source: MAIA (EQ-5D-3L cross-walked):			Dominant
2	Frequency of administration of bortezomib: Twice weekly			Dominant
3	Apply TTD attenuation for DBLd			Dominant
4	Discounting 1.5%			Dominant
5	Use COVID-unadjusted data for DBLd and DLd: Independent extrapolation (COVID-unadjusted)			Dominant

Source: Revised company model (21 Aug 2025)

Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life-year

The EAG requested the company run a scenario using Kaplan-Meier data that excludes the censoring at the tail of both the CEPHEUS and MAIA overall survival and progression-free survival Kaplan-Meier curves, and recalculate the overall survival and progression-free survival parametric extrapolations for both studies. Full details of the scenario analysis and the company's response are given in the EAG clarification question B4.c. We note that using the truncated Kaplan-Meier data had little effect on the DBLd overall survival and progression-free survival extrapolations (Company Response to Clarification Questions Figure 6) or on the DLd overall survival extrapolation (Company Response to Clarification Questions Figure 7). The results of this scenario are shown in Table 30; DBLd dominates DLd. The EAG was able to reproduce the result of this scenario.

Table 30 Company scenario analysis result, truncated Kaplan-Meier survival data

Intervention	Total Costs	Total QALYs	Inc. Costs	Incremental QALYs	ICER
DBLd					
DLd					Dominant

Source: Reproduced from Clarification Response Table 12

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

In addition to the scenarios described above, we consider that the company could also have tested using an alternative:

- Patient age at model entry
- Proportions of patients receiving subsequent treatment in the DBLd arm

We explore the effect of these alternatives in scenario analyses in the section 5.2.2.

5.1.2.3 Probabilistic sensitivity analyses

The company conducted a probabilistic sensitivity analysis (PSA), estimated using 1,000 iterations, to assess parameter uncertainty in the model results. Table 28 shows the mean probabilistic base case ICER result from the company's revised model; Figure 10 and Figure 11 present the scatter plot and cost-effectiveness acceptability curve (CEAC) from the company's revised model.



Figure 10 Probabilistic sensitivity analysis scatter plot, company revised base case

Abbreviations: QALYs: quality-adjusted life years; WTP: willingness to pay.



Figure 11 Cost-effectiveness acceptability curve, company revised base case

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone

CS Section 3.11.1 states the choice of distributions used in the PSA were: gamma for costs; beta for proportions, and lognormal for HRs. In addition, we note that the 1-gamma distribution was used for utilities. We consider the choice of distributions to be appropriate and that the parameters included in the PSA are reasonable.

We note that the probabilistic results are stable and consistent with the deterministic results. DBLd compared with DLd has a probability of ■ and ■ of being cost-effective at a willingness-to-pay threshold of £20,000 and £30,000, respectively.

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

5.2.1.1 Company model validation

The company's approach to validating their model is described in CS section B.3.14.1, which states that the validation aligns with best practice.⁴⁵ Briefly, the model structure, source data and statistical analysis design were reviewed by external experts, including health economic and UK clinical experts in MM, at the company's May 2025 Advisory Board. Internal validity was assessed by health economists not involved in developing the model, and followed a pre-specified test plan. External validity relied on clinical feedback regarding key inputs and assumptions. Where possible, UK sources of data have been used, and the model mirrors the approach taken in previous appraisals, TA917 (DLd for untreated multiple myeloma when a stem cell transplant is unsuitable)⁶ in particular.

EAG comments on the company's model validation

We consider the company's approach to be reasonable and follows the suggestions for best practice.⁴⁵ The company's May 2025 Advisory Board involved five clinical experts and two health economists. The EAG considers the number and location of the clinical experts to be reasonable and that the clinical expert opinion sought by the company covers all the important model inputs. We also consider the health economists at the Advisory Board to be suitably experienced and qualified.

5.2.1.2 EAG model validation

The EAG checked the economic model for transparency and validity. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses
- Checking the individual equations within the model
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks)

5.2.1.3 Comparison with other studies

We conducted a targeted literature search for evidence on the effectiveness of DLd in treating patients with NDMM who are transplant-ineligible. A 2025 systematic review and meta-analysis on the efficacy of daratumumab combined with standard therapy in high-risk multiple myeloma⁴⁶ included 11 studies. However, only five studies involved patients with newly diagnosed multiple myeloma. None of these five studies investigated the use of DLd, except for the MAIA trial; the others considered bortezomib-containing therapies (with or without daratumumab). The GRIFFIN trial⁴⁷ evaluated the use of DBLd for patients with NDMM, but involved participants who were transplant eligible.

The EAG considers that the best comparative data for DLd for this appraisal comes from the MAIA trial, and the CS presents these data for the comparator arm.

5.2.1.4 Company corrections to the company model

None, other than updating eMIT costs as explained in section 5.1.1.

5.2.1.5 EAG corrections to the company model

We did not identify any technical calculation errors in the company's economic model.

5.2.2 EAG's exploratory analyses using the company's base case

We investigate uncertainties concerning key aspects of the company's economic model through additional scenario analyses summarised in Table 31

Table 31 Summary of EAG's exploratory analyses using the company's base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	The mean age of patients is ■ years, and the proportion of males is ■	The mean age of patients is 75 years, and the proportion of males is 55%	Based on the clinical advice to the EAG. Our expert viewed that these patient characteristics better reflect the NHS patient population of people with NDMM who are ineligible for ASCT.	4.2.3
2	Company's OS and PFS estimates at 10 and 15 years for DBLd and DLd	Reduce OS and PFS survival estimates by 10% at 10 years and by 5% at 15 years for both DBLd and DLd	Clinical advice to the EAG was that the DLd survival estimates were optimistic and that it is expected that DBLd would offer a survival benefit over DLd	4.2.5.1 and 4.2.5.2
3	DLd attenuation point at 7 years for OS	DLd attenuation point at 5 years for OS	OS and PFS attenuation points for DLd match DBLd	4.2.5.1
4	DLd attenuation point at 5 years for PFS	DLd attenuation point at 7 years for PFS	The DLd OS attenuation point is 7 years	4.2.5.2
5	TTD: Gompertz distribution for DBLd (without attenuation) and the Weibull distribution for DLd (without attenuation)	TTD: exponential distribution for DBLd (without attenuation) and the Gompertz distribution for DLd (without attenuation)	The exponential and Gompertz are the best-fitting curves according to AIC/BIC scores	4.2.5.3
6	TTD: Gompertz distribution for DBLd (without attenuation) and the Weibull distribution for DLd (without attenuation)	TTD: Gompertz distribution for DBLd (without attenuation) and the Gompertz distribution for DLd (without attenuation)	Exploratory analysis based on clinical advice to the EAG	4.2.5.3
7	TTD: Gompertz distribution for DBLd (without attenuation) and the	TTD: Gompertz distribution for DBLd (without attenuation) and the generalised	Exploratory analysis based on clinical advice to the EAG	4.2.5.3

	Weibull distribution for DLd (without attenuation)	gamma distribution for DLd (without attenuation)		
8	████ of patients receiving DBLd 1L go on to receive 2L line subsequent treatment	████ of patients receiving DBLd 1L go on to receive 2L subsequent treatment.	Clinical advice to the EAG was that █████ was low; proportion likely to be higher, but DBLd would be expected to be lower than DLd.	4.2.7.4
9	████ of patients receiving DBLd 1L go on to receive 2L line subsequent treatment	████ of patients receiving DBLd 1L go on to receive 2L subsequent treatment	Exploratory analysis: same proportion as patients receiving 2L subsequent treatment in DLd arm i.e. █████	4.2.7.4
10	Company-preferred subsq Tx resource use: - DLd 2L: 0% receive bortezomib, 0% receive CLd, 87.5% receive BeBd - DBLd and DLd 3L: 41.18% receive SBd, 17.65% receive PBd, 41.18% receive cyclophosphamide	EAG-preferred subsq Tx resource use: - DLd 2L: 10% receive bortezomib, 4% receive CLd, 73.5% receive BeBd - DBLd and DLd 3L: 10% patients receive SBd; other 3L subsequent treatments adjusted by Dirichlet calculation (PBd = 26.86%, cyclophosphamide = 62.67%)	Clinical advice to the EAG was that - For patients receiving DLd 1L in UK practice approximately 10% are likely to receive bortezomib, about 3-5% CLd and approximately 74% BeBD at 2L - SBd availability is currently limited	4.2.7.4

Source: EAG created table

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; ASCT, autologous stem cell transplant; BeBD, belantamab mafodotin, bortezomib and dexamethasone; CLd, carfilzomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; NDMM, newly-diagnosed multiple myeloma; OS, overall survival; PBd, panobinostat, Bortezomib and dexamethasone; PFS, progression-free survival; SBd, selinexor, bortezomib and dexamethasone; subsq Tx, subsequent treatment; TTD, time to treatment discontinuation

Table 32 Deterministic results of EAG’s exploratory analyses using the company’s base case

Exploratory analysis number	Scenario applied to company’s base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Company base case		██████	████	Dominant
1	Mean age of patients: 75 years; proportion of males: 55%	██████	████	Dominant
2	Reduce OS and PFS survival estimates	██████	████	Dominant
3	OS: DLd attenuation point at 5 years	██████	████	Dominant
4	PFS: DLd attenuation point at 7 years	██████	████	Dominant
5	TTD: exponential for DBLd; Gompertz for DLd	██████	████	£3,013
6	TTD: Gompertz for DBLd; Gompertz for DLd	██████	████	Dominant
7	TTD: Gompertz for DBLd; generalised gamma for DLd	██████	████	Dominant
8	██████ of patients receiving DBLd 1L go on to receive subsq Tx 2L	████	████	Dominant
9	██████ of patients receiving DBLd 1L go on to receive subsq Tx 2L	██████	████	£11,964
10	EAG-preferred subsq Tx resource use	██████	████	Dominant

Source: EAG created table; company and EAG consider a disease severity modifier of 1.0 is appropriate

Abbreviations: 1L, first-line, 2L, second-line; 3L, third-line; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; subsq Tx, subsequent treatment; TTD, time to treatment discontinuation

5.2.3 EAG's preferred assumptions

Based on our scenario analyses using the company's model, summarised in Table 31, we have identified several key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- Mean age of patients is 75 years, and the proportion of males is 55% (EAG report section 4.2.3)
- 75% of patients receiving DBLd first-line go on to receive subsequent treatment second-line (EAG report section 4.2.7.4)
- EAG-preferred subsequent treatment resource use:
 - DLd 2L: 10% receive bortezomib, 4% receive CLd, 73.5% receive BeBd
 - DBLd and DLd 3L: 10% patients receive SBd; other 3L subsequent treatments adjusted by Dirichlet calculation (PBd = 26.86%, cyclophosphamide = 62.67%) (EAG report section 4.2.7.4)

When using the EAG's preferred assumptions, the ICER increases to £14,903 per QALY for DBLd compared with DLd (Table 33).

Table 33 Results using EAG's preferred model assumptions

Preferred assumption	Exploratory analysis number	Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	Cumulative ICER £/QALY
Company's base case	Not applicable	DBLd	██████	██████	██████	██████	Dominant
		DLd	██████	██████			
+ Mean age of patients: 75 years; proportion of males: 55%	1	DBLd	██████	██████	██████	██████	Dominant
		DLd	██████	██████			
+ 75% of patients receiving DBLd 1L go on to receive subsq Tx 2L	4	DBLd	██████	██████	██████	██████	£1,943
		DLd	██████	██████			
+ EAG-preferred subsq Tx resource use	6	DBLd	██████	██████	██████	██████	£14,903
		DLd	██████	██████			
EAG's base case	Not applicable	DBLd	██████	██████	██████	██████	£14,903
		DLd	██████	██████			

Source: EAG created table; EAG considers a disease severity modifier of 1.0 is appropriate

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio, Incr., incremental; QALY, quality-adjusted life-year; SBd, selinexor, bortezomib and dexamethasone; subsq Tx, subsequent treatment

5.2.4 Scenario analyses using EAG's preferred assumptions

We performed a range of scenario analyses using the EAG base case to explore the impact of changing some model assumptions on the final cost-effectiveness results, summarised in Table 34 below. Results are shown in Table 35; these were most sensitive to reducing the proportion of patients receiving subsequent treatment in the second line, after having received DBLd first-line (scenario 2), altering the choice of parametric curve to model DLd time to treatment discontinuation (scenarios 9 and 10) and altering the attenuation points for OS and PFS for DLd (scenarios 11 and 12).

Table 34 Summary of EAG's scenario analyses using EAG's preferred assumptions

Scenario	EAG's base-case assumption	EAG's scenario
1	Mean age of patients: 75 years; proportion of males: 55%	Mean age of patients: [REDACTED] years; proportion of males: [REDACTED]
2	75% of patients receiving DBLd 1L go on to receive subsq Tx 2L	[REDACTED] of patients receiving DBLd 1L go on to receive subsq Tx 2L
3	EAG-preferred subsq Tx resource use: • DLd 2L: 10% receive bortezomib, 4% receive CLd, 73.5% receive BeBd • DBLd and DLd 3L: 10% patients receive SBd; other 3L subsequent treatments adjusted by Dirichlet calculation (PBd = 26.86%, cyclophosphamide = 62.67%)	Company-preferred subsq Tx resource use: • DLd 2L: 0% receive bortezomib, 0% receive CLd, 87.5% receive BeBd • DBLd and DLd 3L: 41.18% receive SBd, 17.65% receive PBd, 41.18% receive cyclophosphamide
4	Utility Source: CEPHEUS EQ-5D-5L	Utility Source: CEPHEUS (EQ-5D-3L cross-walked)
5	Utility Source: CEPHEUS EQ-5D-5L	Utility Source: CEPHEUS time dependant (EQ-5D-3L cross-walked)
6	Utility Source: CEPHEUS EQ-5D-5L	Utility Source: MAIA (EQ-5D-3L cross-walked)
7	COVID-adjusted data for DBLd and DLd: Independent extrapolation	COVID-unadjusted data for DBLd and DLd: Independent extrapolation
8	Company's base case OS and PFS Kaplan-Meier data	Use truncated OS and PFS Kaplan-Meier data (described in EAG report section 5.1.2.2)
9	TTD: Gompertz distribution for DBLd and the Weibull distribution for DLd	TTD: Gompertz for DBLd; Gompertz for DLd
10	TTD: Gompertz distribution for DBLd and the Weibull distribution for DLd	TTD: Gompertz for DBLd; generalised gamma for DLd
11	OS: DLd attenuation point at 7 years	OS: DLd attenuation point at 5 years
12	PFS: DLd attenuation point at 5 years	PFS: DLd attenuation point at 7 years

Source: EAG created table; EAG considers a disease severity modifier of 1.0 is appropriate
Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; SBd, selinexor, bortezomib and dexamethasone; subsq Tx, subsequent treatment; TTD, time to treatment discontinuation

Table 35 Results of EAG's deterministic scenario analyses using EAG's preferred assumptions

Scenario	Scenario applied to EAG's base case	Incr. costs (£)	Incr. QALYs	ICER £/QALY
EAG base case		■	■	£14,903
1	Mean age of patients: ■ years; proportion of males: ■	■	■	£12,522
2	■ of patients receiving DBLd 1L go on to receive subsq Tx 2L	■	■	Dominant
3	Company-preferred subsq Tx resource use	■	■	£1,943
4	Utility Source: CEPHEUS (EQ-5D-3L cross-walked)	■	■	£15,665
5	Utility Source: CEPHEUS time dependant (EQ-5D-3L cross-walked)	■	■	£14,912
6	Utility Source: MAIA (EQ-5D-3L cross-walked)	■	■	£14,719
7	COVID-unadjusted data for DBLd and DLd: Independent extrapolation	■	■	£3,356
8	Use truncated OS and PFS Kaplan-Meier data	■	■	Dominant
9	TTD: Gompertz for DBLd; Gompertz for DLd	■	■	£18,274
10	TTD: Gompertz for DBLd; generalised gamma for DLd	■	■	£18,836
11	OS: DLd attenuation point at 5 years	■	■	£23,966
12	PFS: DLd attenuation point at 7 years	■	■	£7,774

Source: EAG created table; EAG considers a disease severity modifier of 1.0 is appropriate
Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life-year; SBd, selinexor, bortezomib and dexamethasone; subsq Tx, subsequent treatment

5.3 Decision modifiers

5.3.1 QALY weighting for severity

CS section 3.6 states that no severity modifier is applicable for this appraisal. We calculated the absolute and proportional QALY shortfall for the company's base case, using the baseline participant characteristics of the ASCT-ineligible population from the CEPHEUS trial of █████ male and mean age of █ years (CS Table 52). The QALYs for patients with NDMM are taken from the DLd arm of the company model. The proportional QALY shortfall in the company base case is █████ (Table 38).

We also calculated the absolute and proportional QALY shortfall using the EAG base case and obtained similar results to the company's revised base case (Table 38). We agree that a severity modifier is not applicable.

Table 36 Summary of the company's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Reference to section in submission or rationale
Sex distribution	█ male	CS Table 80
Starting age	█ years	CS Table 80
Discount rate	3.5%	CS Table 80

Table 37 Summary of EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Reference to section in submission or rationale
Sex distribution	55.0% male	4.2.3
Starting age	75 years	4.2.3
Discount rate	3.5%	CS Table 80

Table 38 Summary of the company's and EAG's base-case QALY shortfall analyses and preferred QALY weighting

	Expected total QALYs for the general population	Expected total QALYs for people living with a condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company's base case	8.34	████	████	████	None
EAG's base case	7.24	████	████	████	None

5.3.2 Uncaptured benefits

CS section 3.13 proposes that benefits not captured in the QALY calculation include:

- Reducing discrepancies between ASCT-ineligible and ASCT-eligible patients
- Giving patients hope associated with a new treatment
- Providing an additional treatment choice

The EAG notes that, if approved, DBLd would be a new quadruplet therapy available to ASCT-ineligible patients, offering more choice in disease management.

5.3.3 Health inequalities

CS section 1.4 states that no equality considerations related to the use of DBLd for the treatment of ASCT-ineligible NDMM patients were identified.

5.4 Confidential comparator and subsequent treatment prices

The cost-effectiveness results in this report include the confidential ██████████. However, discounts for other therapies in the economic model are not included. Cost-effectiveness results, including all the appropriate PAS discounts, are reported in a separate confidential addendum to this report. Therefore, the ICERs in this report do not reflect the actual prices that would be paid by the NHS.

Other treatments with commercial arrangements that have been taken into account in the confidential appendix include:

- Bortezomib
- Lenalidomide
- Carfilzomib
- Selinexor
- Belantamab mafadotin
- Panobinostat
- Ixazomib
- Pomalidomide
- Teclistamab

Analyses included in the confidential appendix:

- Company analyses
 - Deterministic base case results
 - Probabilistic base case results
 - Deterministic sensitivity analyses
 - Deterministic scenario analyses
- EAG analyses
 - EAG preferred assumptions and their cumulative effect on the company's base case
 - Scenario analyses
 - Probabilistic base case results

5.5 Conclusions of the cost-effectiveness section

We consider that the company conducted a thorough systematic review of the cost-effectiveness evidence. The searches did not find any economic evaluations comparing DBLd with the relevant comparators in patients with NDMM who are ineligible for ASCT.

Consequently, the company developed a de novo model to estimate the cost-effectiveness DBLd compared with DLd for patients with NDMM. The EAG considers the structure of the model to be appropriate and consistent with previous economic models for NDMM. In general, we consider that the model is well constructed and

coded and that the parameters have been selected according to best practice as described in the NICE process and methods manual.³³

However, in contrast to the NICE scope, the company did not submit a comparison of DBLd with IsaBLd, which we identify as a key issue and discuss in the sections 1.3 and 4.2.4.

The EAG disagrees with several of the assumptions in the company's model. Our preferred model assumptions are the following:

- Mean age of patients is 75 years and the proportion of males is 55% (EAG report section 4.2.3)
- 75% of patients receiving DBLd first-line go on to receive subsequent treatment second-line (EAG report section 4.2.7.4)
- EAG-preferred subsequent treatment resource use:
 - DLd 2L: 10% receive bortezomib, 4% receive CLd, 73.5% receive BeBd
 - DBLd and DLd 3L: 10% patients receive SBd; other 3L subsequent treatments adjusted by Dirichlet calculation (PBd = 26.86%, cyclophosphamide = 62.67%) (EAG report section 4.2.7.4)

These changes result in an ICER of £14,903 per QALY for DBLd versus DLd, compared with DBLd being “dominant” (i.e. less costly and more effective) in the company's revised base case (Table 35). The EAG's base case is sensitive to the proportion of patients receiving DBLd first-line who go on to receive second-line subsequent treatment and to using the truncated Kaplan-Meier data for overall survival and progression-free survival (Table 35).

6 References

1. Sive J, Cuthill K, Hunter H, et al. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. *British Journal of Haematology* 2021;193(2)
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7 Appendices

7.1 Appendix 1 EAG appraisal of systematic review methods

Table 39 EAG appraisal of systematic review methods for the clinical SLR

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The aims of the review are clearly stated (CS Appendix B.1.1) and the eligibility criteria are in PICOT format (CS Appendix Table 12).
Were appropriate sources of literature searched?	Yes	Core healthcare databases including MEDLINE, Embase, and Cochrane databases, as well as several relevant conferences, HTA agency websites, ClinicalTrials.gov, and reference lists of relevant systematic reviews and network meta-analyses identified in the database searches (CS Appendix B.1.1).
What time period did the searches span and was this appropriate?	Yes	From database inception up to April 2025 with no gaps in coverage between updates; conference abstracts since 2019 (CS Appendix B.1.1).
Were appropriate search terms used and combined correctly?	Yes	The company used appropriate search terms for the disease. We queried the statement in CS Appendix B.1.5 that “the clinical SLR identified seven observational studies” and the company clarified that although the searches targeted RCTs they would also identify non-randomised studies (clarification response A1). However, the EAG has since noticed these are the same seven observational studies identified in SLR3 for the TA917 appraisal with the same two studies selected to inform the [same?] unanchored MAIC that is presented in the CS for this appraisal. The search strings are provided (CS Appendix Tables 1 to 11).
Were inclusion and exclusion criteria specified? If so, were	Yes	The eligibility criteria are specified in CS Appendix B.1.2 and they are relevant to

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
these criteria appropriate and relevant to the decision problem?		the decision problem (CS Appendix Table 12).
Were study selection criteria applied by two or more reviewers independently?	Yes	Both title and abstract screening and full-text screening were carried out by two independent reviewers, disagreements were resolved by discussion, and if necessary, a third reviewer made the final decision (CS Appendix B.1.2).
Was data extraction performed by two or more reviewers independently?	Yes	Data extraction was carried out by one reviewer and independently verified by a second reviewer, discrepancies and missing data were discussed, and if necessary, a third reviewer made the final decision (CS Appendix B.1.2).
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The Cochrane RoB 2.0 tool was used to assess the identified RCTs and summary assessments are provided (CS Appendix Table 21). The assessment of the CEPHEUS trial is provided with justification statements (CS Table 11).
Was a risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	The conduct (e.g. number of reviewers) of the risk of bias assessment was not reported.
Is sufficient detail on the individual studies presented?	Yes	Relevant trial publications and documents, included/excluded studies lists, and methodological reports were provided either at submission or clarification stage. CS Appendix B gives thorough discussion of the included studies. Not all trial publications were provided for the studies included in the NMA. Additionally, the EAG had to source later trial publications reporting later analyses, and supplementary appendices reporting baseline characteristics for example.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were	Yes	The company carried out ITCs, using inverse probability of treatment weighting methods, and an NMA. These are

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
appropriate methods used?		discussed in sections 3.4 and 3.6 of this report.

Abbreviations: HTA, health technology assessment; ITC, indirect treatment comparison; NMA, network meta-analysis; PICOD, population, intervention, comparator(s), outcomes, design of study; PICOT, population, intervention, comparator(s), outcomes, time point; RCTs, randomised controlled trials; RoB, Risk of Bias; SLR, systematic literature review.

7.2 EAG risk of bias assessment for the CEPHEUS trial

Table 40 below reproduces CS Table 11 detailing the company's risk of bias assessment of the CEPHEUS trial. We have appended a fourth column indicating our agreement, or otherwise, with the company's assessment.

Table 40 Risk of bias assessment for the CEPHEUS trial using Cochrane RoB 2.0

Study Question	Grade (yes/no/unclear)	Justification	EAG assessment
Bias arising from the randomisation process			
1.1 Was the allocation sequence random?	Y	Patients were randomly assigned (1:1) to DBLd or BLd by randomly permuted blocks using an IWRS. Randomisation was stratified by ISS disease stage (I, II or III) and age or transplant eligibility (<70 years and transplant ineligible, <70 years and transplant deferred or ≥70 years). There was no selection of patients.	Agree. Randomisation was based on randomly permuted blocks and stratified by ISS stage and transplant eligibility. We assume randomisation was implemented correctly due to use of an IWRS.
1.2 Was the allocation sequence concealed until participants were	Y	IWRS used for randomisation.	Agree. We assume the IWRS concealed the allocation sequence.

recruited and assigned to interventions?			
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	The baseline characteristics were similar.	Agree. Baseline characteristics for both the overall trial population, and the ASCT-ineligible group relevant to this appraisal, were similar.
Risk of bias judgement	Low		Low
Bias due to deviations from intended interventions, effect of assignment to intervention			
2.1. Were participants aware of their assigned intervention during the trial?	Y	Open-label.	Agree. Open-label trial.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	Open-label.	Agree. Open-label trial.
2.3. If Y/PY/Ni to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	N	No evidence of discontinuations or switches due to trial context based on the information provided in the CONSORT diagram.	Agree. The CONSORT diagram for the overall trial population is in CS Appendix Figure 27, and additionally the CONSORT diagram for the ASCT-ineligible population shows the same (CS Figure 10).
2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA	NA
2.5 If Y/PY/Ni to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis used	Agree. ITT analysis used for both the overall trial population and for the ASCT-ineligible population relevant to this appraisal.
2.7 If N/PN/Ni to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	NA	NA
Risk of bias judgement	Low		Low

Bias due to missing outcome data			
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcomes were consistently reported for the same number of randomised patients.	Agree.
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA	NA
Risk of bias judgement	Low		Low
Bias in measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	N	Outcomes and measurement clearly defined.	Agree. Response outcomes were measured according to IMWG recommended criteria by the investigator. Disease evaluations performed by central laboratory (or exceptionally by local laboratory). A validated computer algorithm was used for data analysis and reporting (protocol 8.2.1).
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Objective outcomes (OS) and some subjective but standardised criteria used; although it was unclear if ORR was assessed by investigator or IRC.	Agree
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y	Open-label.	Agree. Open-label trial.
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by	N	Objective outcomes (OS) and some subjective but standardised criteria used; although it	Unclear, dependent on outcome assessed. PN due to lack of clarity around investigator or

knowledge of intervention received?		was unclear if ORR was assessed by investigator or IRC.	independent review committee. PY for some outcomes such as patient reported outcomes.
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA	Partly agree, dependent on outcome assessed. NA for survival and response outcomes. PN for patient reported outcomes.
Risk of bias judgement	Low		Low for survival and response outcomes. Some concerns for patient reported outcomes.
Bias in selection of the reported result			
5.1. Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Methods well-reported with outcomes defined.	Agree
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Primary outcome had one definition; other analyses clearly and transparently defined.	Agree
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N		Agree
Risk of bias judgement	Low		Low
Overall Risk of bias judgement	Low		Low for survival and response outcomes Some concerns for the patient reported outcomes (i.e. The study is judged to raise some concerns in at least one

			domain (domain 4 above) for this result, but not to be at high risk of bias for any domain.)

Source: CS Table 11 with EAG comments.

Abbreviations: ASCT, autologous stem cell transplant; BLd, bortezomib, lenalidomide, dexamethasone; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; ITT, intention to treat; IWRS, interactive web response system; NA, not applicable; PN, probably no; PY, probably yes; OS, overall survival; ORR, overall response rate.

7.3 EAG risk of bias assessments for the MAIA and ALCYONE trials included in the ITCs

Table 41 EAG risk of bias assessments for MAIA and ALCYONE trials

Study Question	EAG assessment of MAIA	EAG assessment of ALCYONE
Bias arising from the randomisation process		
1.1 Was the allocation sequence random?	Yes. An IWRS was used to assign patients 1:1 using randomly permuted blocks and we assume it was implemented correctly.	Yes. Patients were randomly assigned in a 1:1 ratio, by permuted block randomisation, using IWRS which we assume was implemented correctly.
1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Yes. We assume the IWRS method concealed the allocation sequence.	Yes. We assume the IWRS method concealed the allocation sequence.
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No. Demographic and baseline characteristics reported in Table 1 of the 2021 study publication do not show any differences between groups.	No. Table S1 of the 2020 study publication shows that patient demographic and disease characteristics at baseline were similar between groups.
Risk of bias judgement	Low	Low
Bias due to deviations from intended interventions, effect of assignment to intervention		
2.1. Were participants aware of their assigned intervention during the trial?	Yes. There was no masking to treatment assignments.	Yes. There was no masking to treatment assignments.

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes. There was no masking to treatment assignments.	Yes. There was no masking to treatment assignments.
2.3. If Y/PY/Nl to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Yes. A protocol amendment based on positive results of the second interim analysis allowed crossover for patients receiving Ld to receive DLd.	PN. The patient flow diagram in Figure S1 of the 2025 publication does not indicate any deviations. Crossover is not reported in the study publications, but the study SAP suggests methods for analysing OS in the case of crossover to the daratumumab treatment arm (ALCYONE SAP section 4.3.5.2).
2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	PY in favour of the Ld comparator.	Not applicable
2.5 If Y/PY/Nl to 2.4: Were these deviations from intended intervention balanced between groups?	No. crossover occurred in the Ld comparator arm to the DLd arm. ar.	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY. The primary analysis population was the ITT population. No adjustments for crossover appear to have been made in the 2025 study publication since the second interim analysis nor in the CSR for the final OS analysis.	Yes. Outcomes were analysed for the intent-to-treat analysis set.
2.7 If N/PN/Nl to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable	Not applicable
Risk of bias judgement	Some concerns – lack of information on crossover analyses; open label trial may introduce bias for less objective outcomes such as patient reported quality of life.	Some concerns - open label trial may introduce bias for less objective outcomes such as patient reported quality of life.
Bias due to missing outcome data		

3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes. CSR for final OS analysis provided. Company had access to IPD for the ITCs.	Yes. CSR for final OS analysis provided. Company had access to IPD for the ITCs.
3.2 If N/PN/Ni to 3.1: Is there evidence that the result was not biased by missing outcome data?	Not applicable	Not applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable	Not applicable
3.4 If Y/PY/Ni to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable	Not applicable
Risk of bias judgement	Low	Low
Bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	Yes. Outcomes were measured in line with IMWG guidelines.	Yes. Outcomes were measured in line with IMWG guidelines.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No. Disease evaluations were performed by central laboratory using IMWG consensus recommendations for treatment response criteria	No. Disease evaluations were performed by central laboratory using IMWG consensus recommendations for treatment response criteria
4.3 If N/PN/Ni to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	PY. There was no masking of treatment assignments. Study publications do not differentiate between assessors, investigators, participants, etc. in this respect.	PY. There was no masking of treatment assignments. Study publications do not differentiate between assessors, investigators, participants, etc. in this respect.
4.4 If Y/PY/Ni to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN. Use of central laboratory and following IMWG guidelines and response criteria.	PN. Use of central laboratory and following IMWG guidelines and response criteria.
4.5 If Y/PY/Ni to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable	Not applicable

Risk of bias judgement	Low	Low
Bias in selection of the reported result		
5.1. Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes. The reported results were analysed according to methods outlined in the trial SAP.	Yes. The reported results were analysed according to methods outlined in the trial SAP.
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No. The reported results are presented in the CS by prespecified outcome type, e.g. primary, key secondary, secondary.	No. The reported results were for prespecified outcomes measured at prespecified analysis timepoints.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No. Multiple timepoints were available for OS and PFS, but it is appropriate to select PFS results from the final PFS analysis and OS from the final OS analysis (CS 5.10.2).	No. The CS confirms that all PFS, TTD, binary outcome, and OS results were informed by the latest data cut off of June 2019 (CS Appendix B.1.6, page 96).
Risk of bias judgement	Low	Low
Overall Risk of bias judgement	Some concerns (in one domain) associated with being open label, and the lack of information around the extent of and/or any adjustments made for crossover from Ld to DLd.	Some concerns (in one domain) associated with being open label

Sources: Facon 2021,¹⁷ Facon 2025,⁴⁸ 89mo CSR⁴⁹ (MAIA); Mateos 2020,¹⁸ Mateos 2025,⁵⁰ June 2019 CSR⁵¹ (ALCYONE).

Abbreviations: ASCT, autologous stem cell transplant; BLd, bortezomib, lenalidomide, dexamethasone; CSR, clinical study report; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; IMWG, International Myeloma Working Group; IPD, individual patient data; ISS, International Staging System; ITT, intention to treat; IWRS, interactive web response system; Ld, lenalidomide, dexamethasone; PN, probably no; PY, probably yes; OS, overall survival; SAP, statistical analysis plan.

7.4 EAG risk of bias assessment for the IMROZ trial

Table 42 EAG risk of bias assessment for IMROZ trial

Study Question	EAG assessment of IMROZ
Bias arising from the randomisation process	
1.1 Was the allocation sequence random?	Yes. Patients were randomly assigned in a 3:2 ratio to IsaBLd or BLd.
1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Probably yes. Random assignment was carried out using an interactive response technology (study protocol). The assignment process is likely to have been concealed.
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No. Table 1 in the study publication shows baseline demographic and disease characteristics are similar.
Risk of bias judgement	Low
Bias due to deviations from intended interventions, effect of assignment to intervention	
2.1. Were participants aware of their assigned intervention during the trial?	Yes. Open label trial.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes. Open label trial.
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Probably no. Crossover was planned for in the protocol. The CONSORT diagram in Figure S1 shows 25 patients crossed over to receive Isa-Ld (not IsaBLd) as a proportion of participants in that arm discontinuing treatment due to disease progression. "Post crossover efficacy data (e.g, ORR, BOR and DOR) will be analyzed separately and for exploratory purpose. The crossover arm will be considered as a next line treatment" (study protocol).
2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Not applicable
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes. Intention-to-treat analysis was used for all the efficacy analyses.

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
Risk of bias judgement	Low
Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Probably yes. The amount of missing data is not reported. Methods to impute missing dates, censoring, and sensitivity analyses to assess the impact of missing data are all appropriate.
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Not applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Risk of bias judgement	Low
Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	Yes.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No. An independent review committee, whose members were unaware of the treatment assignments, determined disease response and progression.
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Risk of bias judgement	Low
Bias in selection of the reported result	
5.1. Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes.

5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No. Results are reported from analyses carried out according to the pre-specified statistical analysis plan.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No. Results are reported from analyses carried out according to the pre-specified statistical analysis plan.
Risk of bias judgement	Low
Overall Risk of bias judgement	Low

Sources: Facon 2024, supplementary appendices include protocol and statistical analysis plan.²²

Abbreviations: BLd, bortezomib, lenalidomide, dexamethasone; BOR, best overall response; IsaBLd, isatuximab, bortezomib, lenalidomide, dexamethasone; Isa-Ld, isatuximab, lenalidomide, dexamethasone; ISS, International Staging System; IWRS, interactive web response system; Ld, lenalidomide, dexamethasone.

7.5 EAG assessment of additional DLd studies in the included / prioritised list

Table 43 EAG assessment of additional DLd studies in the included/prioritised list

Included / prioritised study evaluating DLd	Baz 2022¹⁹ MCC-20130 (NCT04151667)⁵²	IFM2017-03^{20 21}

Brief details	DLd or DdB determined by investigator choice. The source cited is a conference abstract (not provided with the CS), but on searching for it we identified another abstract published in 2024 with the final results. ⁵³ The study details for Baz 2022 match another study listed in CS Appendix Table 13, MCC-20130 (NCT04151667), and we believe them to be the same study.	DLd vs Ld; phase 3 RCT; the population was NDMM ASCT-ineligible and ≥ 65 years but also required an ECOG proxy frailty score ≥ 2 .
EAG justification for not including in ITCs	Although this was a Phase II study in the relevant population, the dosing regimen does not match NHS practice. It has a small sample size and would not be a meaningful comparison as only 12 patients received the addition of lenalidomide to the daratumumab + dexamethasone regimen after the initial two cycles of Dd. It also does not appear to measure overall survival.	Eighty-four percent of participants were over the age of 75 years and 61% over the age of 80 years. This is an older, frailer subgroup of the ASCT-ineligible population relevant to this appraisal, although no subgroups were specified in the scope or decision problem. However, it would be difficult to match the population with CEPHEUS and would introduce significant heterogeneity into an NMA. There is limited information in the conference abstract, e.g. no baseline characteristics. Additionally, dexamethasone was only administered for two cycles in the DLd arm because this study was investigating a dexamethasone-sparing regimen.

7.6 Further details of studies included in the NMA

Table 44 provides details of characteristics of the studies included in the NMA where the EAG identified the most heterogeneity, plus brief EAG commentary on studies which potentially might provide data to inform economic modelling.

Table 44 EAG tabulation of studies included in the NMA

Study	Comparison	Role in NMA	Location	Population	Age at baseline (median and range)	Fitness score	EAG comment / limitations
CEPHEUS ¹⁰	DBLd vs BLd	Informs PFS and OS; comparator of interest	North America, Latin America, Asia Pacific, Europe	NDMM; ASCT-ineligible and ASCT-deferred	ASCT-ineligible subgroup: 72 (51, 80)	ECOG PS 0-2	Use of post-hoc ASCT-ineligible subgroup
IMROZ ²²	IsaBLd vs BLd	Informs PFS and OS; comparator of interest	North America, Asia Pacific, Europe	NDMM; ASCT-ineligible	72 (55-80)	ECOG PS 0-2	-
SWOG S0777 ^{23 24}	BLd vs Ld	Informs PFS and OS; connects CEPHEUS and IMROZ to the rest of the network	USA	NDMM; no intent for immediate ASCT	No intent to treat subgroup (base case): Not reported ITT population: 63 (IQR 56-71) >65 subgroup: Not reported	ECOG PS 0-3	Younger trial population, and sensitivity analysis using subgroup >65 years old also limitations. Use of prespecified 'no intent' to transplant group; potential confounding for proportion of participants in ITT population who did receive transplant.
MAIA ^{17 48}	DLd vs Ld	Informs PFS and OS; comparators of interest	North America, Latin America, Asia Pacific, Europe	NDMM; ASCT-ineligible	73 (IQR 70 -78) CS Figure 18 shows 103 (14%) patients older than 80 years	ECOG PS 0-2	Includes patients >80 years; NMA base case removes participants >80 years old breaks trial randomisation.

FIRST ²⁵	MPT vs Ld	Informs PFS and OS	USA, Canada, Europe, Asia Pacific	NDMM; ASCT-ineligible	73 (40-92) Approximately 35% older than 75 years	ECOG PS 0-2	-
Sacchi 2011 ²⁶	MPT vs MP	Informs PFS and OS	Italy	NDMM; ASCT-ineligible	77 (66-89) 33% older than 80 years	ECOG PS 0-3	Older and frailer trial population. Patients >80 not removed as with MAIA.
IFM 01/01 ²⁷	MPT vs MP	Informs PFS and OS	France, Belgium	NDMM; age >75 years	78.5 (75-89) 36% older than 80 years	WHO PI 0-2; 3/4 (7%)	Older trial population. Patients >80 not removed as with MAIA.
IFM 99-06 ²⁸	MPT vs MP	Informs PFS and OS	France, Belgium, Switzerland	NDMM; ASCT-ineligible	43% (MPT) and 43% (MP) older than 70 years	WHO PI 3-4 (8%)	-
TMSG ²⁹	MPT vs MP	Informs OS	Turkey	NDMM; ASCT-ineligible	69 (MPT) and 72 (MP); range not reported; 10.3% over 80 years (MPT) 15.8% over 80 years (MP)	WHO PI 0-4	Turkish setting may not be generalisable to NHS clinical practice.
VISTA ^{30 54}	BMP vs MP	Informs PFS and OS	US, Canada, Europe, Latin America, Asia Pacific	NDMM; ASCT-ineligible	71 (48-91); 30% ≥75 years	Karnofsky PS ≥70 (33-35%)	-
ALCYONE ^{18 50}	DBMP vs BMP	Informs PFS and OS; comparator of interest	North America, Latin America, Asia Pacific, Europe	NDMM, ASCT-ineligible	-	ECOG PS 0-2	3 or 4 times removed from the other comparators of interest. Extended network has less certainty.

Abbreviations: ASCT, autologous stem cell transplant; BLd, bortezomib, lenalidomide, dexamethasone; BMP, bortezomib, melphalan, prednisone; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DBMP, daratumumab, bortezomib, melphalan, prednisone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IsaBLd, isatuximab, bortezomib, lenalidomide, dexamethasone; ITT, intention to treat; Ld, lenalidomide, dexamethasone; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PS, performance status; WHO PI, World Health Organization Performance Index [score].

Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

EAG report – factual accuracy check and confidential information check

“Datappa 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 Friday 3rd October 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 **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Following the recent positive NICE recommendation for IsaBLd for patients with untreated multiple myeloma when a stem cell transplant is unsuitable [TA1098], J&J have informed NICE and the EAG that J&J will be submitting an addendum detailing a comprehensive cost-effectiveness analysis of DBLd vs IsaBLd in the target population. Please refer to the submission addendum for full details relating to this comparison. This present document addresses factual and confidentiality highlighting inaccuracies identified in the EAG report.

Principal factual inaccuracies

Issue 1 Lack of clarity in reporting of clinical expert feedback relating to subsequent treatment distributions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
For the Secondary issue 2 (Second- and third-line subsequent treatment proportions do not reflect NHS practice) detailed in the EAG report, the EAG states that “Clinical advice to the EAG is that for patients receiving DBLd / DLd at first line in UK practice: Second line: approximately 10% are likely to receive bortezomib, about 3-5% receive CLd and approximately 74% receive BeBd. In addition, SBd availability is currently limited.”. This indicates that the clinical expert consulted by the EAG considered that the subsequent treatment distributions following treatment with DLd or DBLd at first line would be equivalent. This is in line with clinical expert feedback received by J&J as part of a May 2025 advisory board with four England based clinical experts, and as a result, the subsequent treatment distributions informing the Company base case analysis (see Table 75 of the CS).	J&J request the EAG include clarification in their report regarding the clinical expert feedback on subsequent treatment distributions following first-line treatment with DLd or DBLd in this indication.	It is currently unclear and inconsistently reported throughout the report whether the EAG’s clinical expert feedback refers to subsequent treatments following DLd or both DBLd and DLd. The report should therefore be updated to mitigate the present inconsistencies across discussion of the subsequent treatment distributions in the EAG report.	We thank the company for highlighting the discrepancy. Our expert’s estimates for second line bortezomib, CLd and BeBd use were for patients receiving DLd first line. We acknowledge that this means that second-line treatment is different for DBLd

However, on Page 93 of the EAG report where this issue is discussed in further detail, there is a misalignment in the reporting of the clinical expert feedback, and therefore J&J seeks clarity from the EAG. Specifically, on Page 93 of the EAG report, the EAG state that the clinical expert “viewed the [Company] estimates as reasonable, except for a few exceptions in the proportions receiving second line in the DLd”. There is no comment on the subsequent treatment distributions following first-line treatment with DBLd. J&J also note that the EAG’s preferred subsequent treatment resource use distributions (as per the EAG report, and in the EAG’s base case model; see Table 1) vary between patients treated with DBLd and patients treated with DLd.

Table 1: EAG preferred subsequent treatment distributions following DBLd or DLd at first line

1st Line Treatment	Ld	Cd	DBd	B	CLd	SBd	BeBd
DBLd	0.00%	9.38%	0.00%	0.00%	0.00%	3.13%	87.50%
DLd	0.00%	9.38%	0.00%	10.00%	4.00%	3.13%	73.50%

Abbreviations: B: bortezomib, BeBd: belantamab mafodotin, bortezomib and dexamethasone; Cd: carfilzomib and dexamethasone; CLd: carfilzomib, lenalidomide and dexamethasone; DBd: daratumumab, bortezomib and dexamethasone; DBLD: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; EAG: External Assessment Group; Ld: lenalidomide and dexamethasone; SBd: selinexor, bortezomib and dexamethasone

As such, there is an inconsistency in the reporting of the clinical expert feedback on subsequent treatment distributions following treatment with DLd (and/or DBLd); it is unclear whether feedback relates to subsequent treatments following DLd or both DLd and

and DLd in our base case, but this is not a factual inaccuracy. We consider further clinical advice on this matter would be beneficial.

Our expert’s comment regarding SBd availability concerned third-line treatment where 41.18% patients receive SBd in the company’s base case (DBLd and DLd). Our expert thought SBd use is likely nearer 10% due to SBd scarcity, which we consider applies to both treatment arms.

We have edited the secondary issue and the text in the

DBLd. In relation to this inconsistency, J&J wish to highlight that clinical expert feedback received as part of an advisory board with four England-based clinical experts indicated that subsequent treatment distributions following DBLd or DLd at first line would be equal. Likewise, in the recent NICE appraisal of IsaBLd in ASCT-ineligible NDMM, the Committee concluded that the proportions of people having subsequent treatments should be equal for people who have had IsaBLd or DLd at first line, further justifying this approach. ¹			main report (p.93) for clarity.

Issue 2 Uncertainty associated with crossover in MAIA and IMROZ

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG highlight concerns regarding crossover in the MAIA and IMROZ trials, noting that this might introduce bias to the NMA comparison with DBLd. For example, on Page 51, Section 3.4.1.4, the EAG note “We consider that crossover is likely to bias results in favour of the Ld arm, so the OS and TTD results reported for the DLd arm could be conservative therefore underestimating the efficacy of DLd when compared to DBLd in the ITC.” Likewise, on Page 56, Section 3.4.2.4 the report notes “there is some uncertainty regarding the impact of patient crossover in some trials.”	This section should be amended to state that the impact of crossover in MAIA is unlikely to introduce uncertainty due to the small number of patients who crossed over. Additionally, it should be clarified that the impact of crossover in the IMROZ trial does not introduce uncertainty, as	Whilst no formal crossover was permitted in the CEPHEUS trial, patients in CEPHEUS were also able to receive treatment with an anti-CD38 regimen following disease progression on BLd. This means that there were no key differences between the BLd arms of CEPHEUS and IMROZ, which were both aligned with UK clinical practice, meaning that this should not be considered to	We have amended the text in section 3.4.1.4 to acknowledge the small number of Ld patients who crossed over to DLd. However, we have also noted the sizeable proportion of patients who received daratumumab containing regimens as subsequent therapy in the Ld arm and we suggest that this in itself could bias in

J&J would like to highlight that only a small proportion of patients in the Ld arm of MAIA received DLd as a second-line treatment (■ out of a total of ■ patients who received a subsequent therapy).² Instead, the majority of patients in the Ld arm of MAIA that received an anti-CD38 at second-line were treated with DBd (■ out of ■ patients) which represents a licensed and reimbursed option in England. Therefore, the OS treatment effect observed in MAIA is unlikely to be conservative, as anti-CD38 exposure following disease progression with Ld is closely aligned with UK clinical practice.	subsequent treatments in the IMROZ trial aligns with UK clinical practice, and subsequent therapies received in the BLd arm of IMROZ (receiving an anti-CD38) is similar to what is observed in the BLd arm of CEPHEUS.	represent a source of uncertainty in the NMA. As highlighted, the impact of crossover on MAIA is also not expected to introduce any uncertainty, considering subsequent therapies received are closely aligned with UK clinical practice.	favour of Ld (for the outcomes of OS and TTD)., In turn, this could bias against DLd when compared to DBLd in the NMA

Issue 3 Reference to bias in the NMA due to loss of randomisation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the EAG report, the EAG highlight that use of a sub-population of trials (such as CEPHEUS, SWOG S0777 and MAIA) in the NMA may introduce bias through compromising the effect of randomisation in each trial. For example on Page 64, Section 3.5.2.1, the EAG state that “CEPHEUS, MAIA and SWOG S0777, were based on sub-populations of the total trial population. This breaks randomisation in the trials and which may increase baseline imbalances in the	The EAG report should clarify throughout that the risk of bias due to potential imbalances in patient characteristics between treatment arms in the ASCT-ineligible subgroup of CEPHEUS (and SWOG S0777) is limited because	This ensures consistency and accuracy in recognising that the stratification of patients in the studies by ASCT eligibility offsets the risk of bias when analysing results for the ASCT-ineligible subgroup.	We have reworded the text to emphasise that stratification by ASCT eligibility / intent to transplant is protective against bias in the sub-group analysis.

subgroups potentially biasing in the relative effect estimates in each trial.” Likewise, on Page 65, Section 3.5.2.1 the EAG highlight that “the heterogeneity in the network and use of subgroup data in some trials potentially increases the risk of bias.” In places, the EAG correctly acknowledge that the risk of bias due to potential imbalances in patient characteristics between treatment arms in the ASCT-ineligible subgroup of CEPHEUS is offset because randomisation was preserved with ASCT eligibility included as a stratification factor in studies. However, this acknowledgement is not reflected in each section of the EAG report where this point is raised.	randomisation was preserved with ASCT eligibility included as a stratification factor in the study. This is acknowledged by the EAGs comment on Page 68, Section 3.7.3: “This risk of bias is offset, to some extent, by the inclusion of ASCT eligibility as a stratification factor in the randomisation in both trials”. Equivalent sentences should also be added to the earlier discussion of this matter on Pages 64 and 65 of the EAG report.		

Issue 4 Reference to the attenuation method in TA1015

Description of problem	Description of proposed amendment	Justification for amendment	
Whilst not a factual inaccuracy, J&J note that the EAG were unable to access Appendix N of TA1015	To clarify that the attenuation method used	For completeness.	We thank the company for providing the relevant

to confirm the methodology used to calibrate the long-term PFS and OS estimates as part of that appraisal. As such, to aid the EAG, J&J have since detailed the relevant section of TA1015 Appendix N in the Appendices accompanying this response for completeness.	in TA1015 has since been provided by J&J.		section of TA1015 Appendix N. After reviewing the document we agree that the attenuation method used by the company is the same as that in TA1015. We have therefore removed Key Issue 2 and any reference to it in the EAG report.

Issue 5 Reference to the final data cut of CEPHEUS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
J&J note that the EAG reference that the final data cut of CEPHEUS is expected in [REDACTED]. Whilst correct, J&J wish to reiterate that this final OS data cut is not expected to reduce inherent long-term modelling uncertainty when considering a lifetime model time horizon. The current data still represents almost five years of follow up, with the limited additional data from the final OS, unlikely to substantially change any long-term modelling. As detailed in the CS, there is sufficient evidence on the basis of MRD negativity and robust ITCs versus UK relevant comparators, to demonstrate the long-	When referencing the final data cut for CEPHEUS, add further wording to explain that this final OS data cut is not expected to reduce inherent long-term modelling uncertainty given the first-line treatment setting and attenuation approach to survival modelling.	For completeness.	Though not a factual inaccuracy we have amended the report to reflect the company's assertion that the final OS data cut is unlikely to change long-term modelling. We reiterate that the OS results from the CEPHEUS trial are based on the comparison of DBLd versus a treatment which is not within the scope of this NICE

term benefits of DBLd for ASCT-ineligible NDMM patients. Of note, the attenuation approach leveraged to model long-term survival for DBLd (and DLd) in the CS lowered the survival curves considerably, and therefore the survival curves likely already represent conservative estimates of survival; any uncertainty associated with the modelled curves would likely only result in improved estimates of survival and cost-effectiveness.			appraisal. Hence, the long-term survival estimates for DBLd versus DLd, IsaBLd and other comparators in the scope are estimated via indirect comparisons. We note that survival estimates in the ImROZ trial of IsaBLd is similarly based on interim analyses. Thus, the long-term survival with DBLd versus IsaBLd is currently unknown.

Issue 6 EAG description of attenuation time point

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG reference the time points for the attenuation to be uncertain, “The company applies the attenuation at different time points for OS: year 5 for DBLd and Year 7 for DLd. We consider this as an area of uncertainty.” (Page 83) and run scenarios using alternative attenuation timepoints for PFS and OS for DLd.	“The company applies the attenuation at different time points for OS: year 5 for DBLd and Year 7 for DLd, with the different timepoints selected due to the different length of follow-	To clarify the time points chosen are based on the evidence available which does not represent an additional source of uncertainty.	We have added this information for clarity, updating the text on page 83, as per the company’s suggestion.

The time points selected are based on the data available from trial follow up. As the CEPHEUS data cut was just under 5 years (58.7 months), a timepoint of 5-years was selected, for MAIA, the OS data cut was 89.3 months, therefore a 7-year timepoint was chosen. The time points selected were based on the follow-up of the trials, and this should be clarified.	up across the two studies (58.7 months and 89.3 months in CEPHEUS and MAIA respectively)".		

Minor factual inaccuracies

Issue 7 Reporting of NMA results (DBLd vs IsaBLd)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 66, Section 3.5.2.2 The EAG report incorrectly states in relation to the NMA results that "The unadjusted results were not reported for the DLd, Ld and BMP comparisons, but the unadjusted results for the IsaBLd comparison show that adjusting for COVID-19 deaths [REDACTED] the treatments, with an [REDACTED]." As per Table 13 of the EAG report (copied below for completeness; Table 2), the adjustment for COVID-	Correct the statement describing the DBLd vs IsaBLd OS NMA results to read as follows: The unadjusted results were not reported for the DLd, Ld and BMP comparisons, but the results for the IsaBLd comparison show that adjusting for COVID-19 deaths [REDACTED] the	To maintain the factual accuracy of the reporting of the DBLd vs IsaBLd OS NMA results.	Thank you for highlighting this inaccuracy. Correction made as suggested.

19 rather [REDACTED] between the treatments, with a [REDACTED].		treatments, with [REDACTED]		
Table 2: Overview of NMA results for OS (DBLd vs IsaBLd)				
Outcome	Comparison, DBLd vs IsaBLd HR (95% CrI)			
OS (Fixed effect; adjusted for COVID-19; base case)	[REDACTED]			
OS (Random effects; adjusted for COVID-19)	[REDACTED]			
OS (Fixed effect; unadjusted)	[REDACTED]			
OS (Random effects; unadjusted)	[REDACTED]			

Issue 8 Reporting of Company approach to attenuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 82, Section 4.2.5.1 The EAG report states the following when detailing J&J's approach to attenuation:	Amend step 2 reported in the EAG report to read as follows: "2. Calculates the hazard at the end time point of interest (e.g. attenuation time point 1 @ 10 years), using the	To maintain the factual accuracy of the reporting of J&J's approach to attenuation of extrapolations.	We thank the company for the correction and have updated the text as requested.

“2. Calculates the hazard at the end time point of interest (e.g. attenuation time point 1 @ 10 years), using the unattenuated OS extrapolation” This is factually inaccurate as the hazard is calculated at the end time point of interest using the clinical expert estimates of survival at that time point, rather than the unattenuated extrapolation.	clinical expert estimates of survival at that time point”		

Issue 9 Reporting of Company approach to applying multipliers

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 82, Section 4.2.5.1 The EAG incorrectly report that J&J obtain different multipliers for each time period, including for the 20+ timepoint. Whilst multipliers are obtained for 0-5 years, 10-15 years and 15-20 years, no multiplier is leveraged for 20+ years.	Remove reference to the 20+ year time period from the following sentence in the EAG report: “Based on the above steps, the company obtain different multipliers for each time period, i.e., 0-5 years, 10-15 years, 15-20 years, 20+ years and between DBLd and DLd, because the hazards are calculated from probabilities of survival at	To maintain the factual accuracy of the reporting of J&J’s approach to attenuation of extrapolations.	We thank the company for the correction and have updated the text as requested.

	each timepoint, which vary over time and between each treatment arm.”		

Issue 10 Derivation of Company base case utility values

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 87 Section 4.2.6 The EAG incorrectly report that the base case utilities for the progression-free and progressed disease health states are estimates from the ITT population of the CEPHEUS trial. In fact, utility values are estimated from EQ-5D-5L data collected from the ASCT-ineligible population specifically.	Amend the following sentence “Base case utilities for the progression-free and progressed disease health states are estimated from EQ-5D-5L data for the ITT population in the CEPHEUS trial” to “Base case utilities for the progression-free and progressed disease health states are estimated from EQ-5D-5L data for the ASCT-	To maintain the factual accuracy of the reporting of J&J’s derivation of base case utility values.	We thank the company for the correction and have updated the text as requested.

	ineligible population in the CEPHEUS trial".		

Issue 11 EAG QALY shortfall analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 38, Page 111, Section 5.3.1 The EAG report presents results from J&J's and the EAG's respective QALY shortfall analyses. However, the EAG's base QALY shortfall analysis results presented in the EAG report are not accurate against the QALY shortfall analysis in the EAG model. J&J have identified that the presented EAG shortfall analysis instead corresponds to the York QALY shortfall calculator (using the inputs from Table 37 of the EAG report). J&J note that the conclusions from the QALY shortfall analysis remain consistent (i.e. that no QALY weighting should be applied) regardless of the calculator used, although for clarity, the EAG report should be amended.	The EAG's base case QALY shortfall analysis results in Table 38 of the EAG report should either be updated to be based on the EAG model QALY shortfall analysis, or a clear footnote added to specify that results are based on the York QALY shortfall calculator.	To maintain full transparency in the reporting of the EAG QALY shortfall analysis.	We thank the company for the correction and have updated Table 38 using results from the QALY shortfall analysis in the EAG base case, as requested.

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21, Section 1.4 The EAG have incorrectly referred to BeBd as a <i>quadruplet</i> regimen in the following sentence relating to BeBd: “The EAG’s expert commented that it is difficult to predict the uptake of this new regimen, but considered the company’s estimate to be a little high, noting that toxicity from this quadruplet regimen might be prevent some patients from taking it.”	Refer to BeBd as a triplet regimen as follows: “The EAG’s expert commented that it is difficult to predict the uptake of this new regimen, but considered the company’s estimate to be a little high, noting that toxicity from this triplet regimen might be prevent some patients.”	To maintain factual accuracy around the describing of BeBd.	This has been corrected.
Page 26, Section 2.2.1 The EAG report states that “less than a fifth sustain MRD negativity for more than a year (this is known as ‘durable MRD’).” This present wording does not accurately capture the definition of durable MRD, which as detailed on Page 37, Section 1.3.4 of the CS, is defined as having MRD negativity for <i>at least</i> 12 months.	Please amend the text as follows: “less than a fifth sustain MRD negativity for at least 12 months (this is known as ‘durable MRD’).”	Update to improve the factual accuracy of the definition of durable MRD.	This is not a factual inaccuracy. No change made.
Throughout the report, incorrect section numbers of the CS have been referred to.	Check that CS section references are correct throughout the report.	Using accurate section numbers to reference the CS	Amended as requested

		will improve the usability of the report.	
Throughout the report, the EAG have used underlining of > and < instead of ≥ and ≤ symbols.	Replaced underlined > and < with ≥ and ≤ symbols.	Use of underlining instead of symbols may lead to errors when underlining is required for CIC or other reasons.	Amended as requested
Page 35, Section 3.2.1 The EAG incorrectly state the ASCT-ineligible criteria for CEPHEUS to be “[REDACTED]” [REDACTED] [REDACTED] [REDACTED]	Correct the “>65” to “≥65”.	The correct age in the first part of the criteria is ≥65 as per Page 45, Section 2.3.1 and Table 4, Page 47, Section 2.3.2 of the CS. Please also remove the confidentiality highlighting from the full criteria (see confidentiality highlighting inaccuracies section below).	Amended as requested
Page 37, Section 3.2.2 The EAG incorrectly state that 55.3% of the overall trial population are ≥70 years of age.	Correct the value of 55.3% to 55.4% .	The correct value is 55.4% as per Page 50, Section 2.3.3, Table 5 of the CS.	Amended as requested
Page 37, Section 3.2.2 The EAG incorrectly state that 56% of participants in the DBLd arm have a frailty score of 0.	Correct the value of 56% to 56.9% .	The correct value is 56.9% as per Page 54, Section 2.3.3, Table 6 of the CS. Note that, for consistency, values should	Amended as requested

		be reported to 1 decimal place.	
Page 41, Section 3.3.1 The following sentence in the EAG report does not make sense in its current form, and therefore the key message is unclear to the reader: “However, the EAG’s clinical expert commented that, as a measure of depth of response, these results to translate into improved real-world outcomes.”	Dependent on the feedback received by the clinical expert, please amend the text as follows: “However, the EAG’s clinical expert commented that, as a measure of depth of response, these results are expected to translate into improved real-world outcomes.”	Update to ensure the statement reads correctly and the key feedback shared by the clinical expert is captured comprehensively.	We have made a minor edit to this sentence.
Page 41, Section 3.3.1 The EAG incorrectly state that the data cut-off date for the final PFS analysis was 04 May 2024.	Correct the data of 04 May 2024 to 07 May 2024.	The correct data cut-off date is 07 May 2024 as per Page 66, Section 2.6 of the CS.	Amended as requested
Page 42, Section 3.3.2 There is an additional close bracket after “(unadjusted for COVID-19)”.	Remove the additional close bracket after (unadjusted for COVID-19).	Correction of this typographical error will improve the overall readability of the report.	Amended as requested
Page 42, Section 3.3.2 There is a missing close bracket and full stop after “(CS Table 18”	Add a close bracket and full stop after (CS Table 18).	Correction of this typographical error will improve the overall readability of the report.	Amended as requested

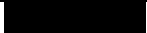
Page 45, Section 3.3.6 The EAG incorrectly state that 39 participants in the CEPHEUS trial had died at the time of the final PFS analysis.	Correct the value of 39 to 79.	The correct value is 79 as per Page 122, Section 2.11.6, Table 51 of the CS.	Amended as requested
Page 50, Section 3.4.1.2 The EAG have omitted a decimal place when reporting that median follow-up was 89 months in MAIA.	Correct the value of 89 months to 89.3 months.	The correct value is 89.3 months as per Page 86, Section 2.10.2 of the CS. Reporting values to 1 decimal place will improve the consistency of the report.	Amended as requested
Page 59, Section 3.5.1.1.3 There is a missing letter 'd' and full stop after "DBLd versus DL".	Correct the sentence to end with "DBLd versus DLd."	Correction of this typographical error will improve the overall accuracy and readability of the report.	Amended as requested
Page 62, Section 3.5.1.2 There is an erroneous cross reference to Table 10 immediately after the Table 11 cross reference.	Remove the erroneous "Table 10" cross-reference.	Correction of the typographical error will improve the overall readability of the report.	Amended as requested
Page 62, Section 3.5.1.2 The EAG incorrectly report the p-value for the TTD DBLd versus DLd base case IPTW analysis as [REDACTED].	Correct the value of [REDACTED] to [REDACTED]	The correct value is [REDACTED] as per Page 101, Section 2.10.2, Table 34 of the CS.	Amended as requested

Page 63, Section 3.5.1.2, Table 11 The EAG incorrectly report the p-value for the TTD DBLd versus DLd base case IPTW analysis as [REDACTED].	Correct the value of [REDACTED] to [REDACTED]	The correct value is [REDACTED] as per Page 101, Section 2.10.2, Table 34 of the CS.	Amended as requested
Page 67, Section 3.7.2 The following sentence is unclearly written: “There is no randomised head-to-head data for DBLd to inform the economic modelling, or provide check on consistency between direct and indirect comparison evidence.”	Please amend the text as follows: “There is no randomised head-to-head data for DBLd to inform the economic modelling, or to facilitate a consistency check between direct and indirect comparison evidence.”	Update to improve clarity.	Amended as requested
Page 68, Section 3.7.3 There is a typographical error in the sentence “The lack of common comparators linking trials means it has been necessary to create an extended network incorporating trials of treatments outwith the scope, to create a fully connected network.”	Please amend the text as follows: “The lack of common comparators linking trials means it has been necessary to create an extended network incorporating trials of treatments out of the scope, to create a fully connected network.”	Update to ensure the statement reads correctly.	Not a typographical error. The word outwith is a Scottish English preposition meaning outside; beyond.
Page 67, Section 3.7.1 There is a typographical error in the sentence “The evidence for the clinical effectiveness of DBLd in adult patens with	Please amend the text as follows: “The evidence for the clinical effectiveness of DBLd in adult patients with newly diagnosed multiple myeloma comes from the pivotal CEPHEUS trial	Update to ensure the statement reads correctly.	Amended as requested

newly diagnosed multiple myeloma comes from the pivotal CEPHEUS trial.”			
Page 75, Section 4.2.5 There is a typographical error in the following sentence: “No treatment effect waning was implemented, which is appropriate based on the treatment mechanism and consistent with the recent NICE appraisal of IsaBLd (NICE TA1098)”,	Amend the statement to be “No treatment effect waning was implemented, which is appropriate based on the treatment mechanism and consistent with the recent NICE appraisal of IsaBLd (NICE TA1098)”	Correction of the typographical error will improve the overall readability of the report.	Amended as requested
Table 34, Page 109, Section 5.2.4 The L in DLd is not capitalised.	Correct the Dld to DLd in the following bullet point: “DBLd and Dld 3L: 10% patients receive SBd; other 3L subsequent treatments adjusted by Dirichlet calculation (PBd = 26.86%, cyclophosphamide = 62.67%)”	Correction of this typographical error will improve the overall accuracy and readability of the report.	Amended as requested
Page 114, Section 5.5 There is a missing table number for the cross reference in the following sentence: “These changes result in an ICER of £14,903 per QALY for DBLd versus DLd, compared with DBLd being “dominant” (i.e.	Update the cross reference to be “Table 33”.	To improve the improve the overall readability and accessibility of the report.	Amended as requested

less costly and more effective) in the company's revised base case (Table)."			

Confidentiality highlighting inaccuracies

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 35, Section 3.2.1	The ASCT-ineligible criteria for CEPHEUS do not require CiC highlighting as per the CS (Page 45, Section 2.3.1 and Table 4, Page 47, Section 2.3.2)	"Age ≥65 years or age 18-65 years with comorbid conditions likely to have a negative impact on tolerability of high-dose chemotherapy for stem cell transplant" (noting the correction to "≥65" as per the typographical errors section above).	Amended as requested
Page 42, Section 3.3.2, Table 6	The first NE value in the Median KM unadjusted estimate cell for DBLd requires CiC highlighting as per the CS (Page 66, Section 2.6, Table 12)		Amended as requested
Page 60, Section 3.5.1.2	The data values and statements describing the PFS results do not require CiC highlighting as per the CS (Page 98, Section 2.10.2, PFS Base case and sensitivity analysis results (DBLd versus DLd))	"Compared to DLd, DBLd reduces the risk of progression or death by 45% (HR 0.55; 95% CI 0.38, 0.79, p=0.001), and this is statistically significant. Results for the sensitivity analysis that includes all covariates in the adjustment are very similar to the base case results, but there is a greater difference (seven percentage	Amended as requested

		points) between results for the base case and the sensitivity analysis that does not adjust for COVID-19 deaths.”	
Page 61, Section 3.5.1.2, Table 9	The values in the cell for the IPTW Base case DLd comparison analysis do not require CiC highlighting, as per the CS (Page 99, Section 2.10.2, Table 32)	“0.55 (0.38, 0.79) p=0.001”	Amended as requested
Page 61, Section 3.5.1.2, Table 9	The values in the cell for the IPTW sensitivity analysis, unadjusted for COVID-19, comparison to DLd do not require CiC highlighting, as per the CS (Page 99, Section 2.10.2, Table 32)	“0.62 (0.44, 0.88) p=0.007”	Amended as requested
Page 61, Section 3.5.1.2	The data values and statements describing the OS results do not require CiC highlighting as per the CS (Page 99, Section 2.10.2, OS Base case and sensitivity analysis results (DBLd versus DLd))	“Compared to DLd, DBLd reduces the risk of death by 37% (HR 0.63; 95% CI 0.41, 0.98; p=0.040) and this is statistically significant. Results for the sensitivity analysis that includes all covariates in the adjustment are very similar to the base case results. However, there is a greater difference (seventeen percentage points) between results for the base case and the sensitivity analysis that does not adjust for COVID-19 deaths.”	Amended as requested
Page 62, Section 3.5.1.2, Table 10	The values in the cell for the IPTW Base case DLd comparison analysis do not	“0.63 (0.41, 0.98) p=0.040”	Amended as requested

	require CiC highlighting, as per the CS (Page 100, Section 2.10.2, Table 33)		
Page 62, Section 3.5.1.2, Table 10	The values in the cell for the IPTW sensitivity DLd comparison analysis (adjusted for COVID-19) do not require CiC highlighting, as per the CS (Page 100, Section 2.10.2, Table 33)	“0.65 (0.41, 1.02) p=0.060”	Amended as requested
Page 62, Section 3.5.1.2, Table 10	The values in the cell for the IPTW sensitivity DLd comparison analysis (unadjusted for COVID-19) do not require CiC highlighting, as per the CS (Page 100, Section 2.10.2, Table 33)	“0.80 (0.53, 1.19) p=0.262”	Amended as requested
Page 62, Section 3.5.1.2	The narrative statements describing the TTD results require CiC highlighting, as they describe values and figures that are marked as CiC in the CS (Page 100-1, Section 2.10.2, Table 34 and Figure 23) and the CS Appendices (Page 121, Figure 11).	“...which also are less certain [REDACTED]. The CS also reports the Kaplan Meier curves for the DLd and Ld comparisons which show a difference in treatment effect from [REDACTED] [REDACTED] (DLd comparison; CS Figure 23) and [REDACTED] [REDACTED] (CS Appendix Figure 11).”	Amended as requested
Page 63, Section 3.5.1.2.1	The wording ‘in favour of’ does not require CiC highlighting as the results being described do not have CiC	“They all show odds ratios in favour of treatment with DBLd, consistent across the sensitivity analyses.”	Amended as requested

	highlighting in the CS (Page 103-4, Section 2.10.2, Table 36 and Table 37)		
EAG CEM; Tab: Settings; Cell: D60 (Age at model entry; proportion male drop down)	The age at model entry; proportion male drop down box in the model should be CiC highlighted, given the Company base case inputs are based on unpublished ASCT-ineligible data from the CEPHEUS trial (see Table 52, Page 127, Section 3.2.1 of the CS).	EAG CEM; Tab: Settings; Cell: D60 – CiC highlighted	We thank the company for the correction and have updated the model as requested.
EAG CEM; Tab: Settings; Cell: D69 (Proportion of patients receiving subseq. Tx 2L in DBLd drop down)	The Proportion of patients receiving subseq. Tx 2L in DBLd drop down box in the model should be CiC highlighted, given the Company base case inputs for DBLd attrition rates are based on unpublished ASCT-ineligible data from the CEPHEUS trial (see Table 71, Page 164, Section 3.5.1 of the CS).	EAG CEM; Tab: Settings; Cell: D69 – CiC highlighted	We thank the company for the correction and have updated the model as requested.

References

1. National Institute for Health and Care Excellence (NICE). Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [TA1098]. Final guidance. Available at: <https://www.nice.org.uk/guidance/ta1098/documents/674> [Accessed: September 2025].
2. J&J Data on File. MAIA Clinical Study Report. November 2023.

Appendix

Appendix A: Methodology for calibrating long-term PFS and OS (as detailed in TA1015)

As detailed in Appendix N of the CS for teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (TA1015), the methodology for calibration long-term PFS and OS in TA1015 was as follows:

OS and PFS per cycle hazards beyond 5 years were modified in order to match the long-term OS and PFS estimates of teclistamab with the clinical expert input. The adjustment starts after year 5 given it is expected that the survival trend would not change immediately after the end of the follow-up in the MajesTEC-1 study.

Beyond 5 years, per cycle OS hazard from the original model was replaced by general population mortality per cycle between year 5 to year 10, multiplied by a constant so that the cumulative hazard at year 10 results in the 10-year survival estimate provided by clinical expert opinion. The same method is used between years 10 and 15: the general population mortality between year 10 and 15 was multiplied by a different constant so that the cumulative hazard at year 15 results in the survival estimate provided by clinical expert opinion for year 15. The constant used between years 5 and 10 was [REDACTED], and was calculated by dividing the difference of cumulative hazard needed to reach 10% survival (e.g. [REDACTED]) and the cumulative hazard at the time of start of OS hazard adjustment ([REDACTED]) by the sum of the general population mortality per cycle during this period ([REDACTED]). The constant used between years 10 and 15 was [REDACTED], and was calculated by dividing the difference of cumulative hazard needed to reach 3% survival ([REDACTED]) and the cumulative hazard at year 10 ([REDACTED]) by the sum of the general population mortality per cycle during this period ([REDACTED]).

PFS was adjusted using the same adjustment start time (5 years) and method as described above for OS estimates. However, instead of using the general population mortality as a reference, the per cycle hazard from the original PFS extrapolation was used to calculate the constant in the first period ([REDACTED]) and the second period ([REDACTED]). The cumulative PFS hazard at 5 years was [REDACTED].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Addendum to Company Submission

October 2025

File name	Version	Contains confidential information	Date
ID3843_Daratumumab_NICE_ Addendum [CON]	V1.0	Yes	21 st October 2025

1 Introduction

At the time of the Company submission, the NICE appraisal for IsaBLd was ongoing and IsaBLd had not received positive final guidance in this indication. As such, IsaBLd did not represent routine clinical practice for ASCT-ineligible NDMM patients, and therefore could not be considered to represent a relevant comparator in this indication.

Following Clarification Questions, IsaBLd has now received a positive recommendation from NICE on the 24th September 2025. It is important to note that given the recency of this recommendation, uptake of IsaBLd is still expected to be limited, and therefore it is unlikely that IsaBLd represents standard of care in current UK clinical practice.

However, in response to the EAG's request, J&J have provided full details of clinical and cost-effectiveness analyses comparing DBLd versus IsaBLd in the sections below. Section 2 of this response provide details of two ITCs comparing the two treatments – the base case NMA approach previously provided as part of Clarification Question A11 (Section 2.2), and a supportive MAIC (Section 2.3), as requested by the EAG. Section 3 of this response provides details of the cost-effectiveness analysis between DBLd versus IsaBLd, and the results of this analysis are presented in Section 4.

2 ITCs between DBLd and IsaBLd

2.1 *Introduction*

The IMROZ trial is the most relevant trial to inform the efficacy of IsaBLd in this indication, as per the evidence informing TA1098. The IMROZ trial had a common comparator arm – BLd – with the CEPHEUS trial, allowing IMROZ to be included in a connected network of evidence.

Only aggregate published data were available for the IMROZ trial, precluding the consideration of a similar IPTW ITC that was used in the Company submission to inform comparative efficacy between DBLd and DLd.

As such, two ITC approaches were considered to compare DBLd versus IsaBLd. Based on the high degree of similarity between the patient populations and the similar study designs in CEPHEUS and IMROZ, the NMA approach detailed below (previously presented in response to Clarification Question A11) is considered to represent the base case approach to comparative efficacy versus IsaBLd. To explore the potential uncertainty around the assumption of balanced treatment effect modifiers that underpins the NMA, and as requested by the EAG, a supportive anchored MAIC was also conducted between the CEPHEUS and IMROZ trials, detailed in Section 2.3 below.

2.2 NMA

NMA Methodology

As previously detailed in response to Clarification Question A11, the ASCT-ineligible subgroup in CEPHEUS, and the no-intent to transplant subgroup population of the SWOG S0777 trial were used in the base case NMA. It is important to note that in both cases, these subgroups were defined by stratification factors. As such, whilst the use of subgroups breaks randomisation, baseline characteristics remain closely balanced in both arms of the respective studies, minimising any uncertainty.

The base case NMA approach did not adjust for COVID-19 deaths in either the CEPHEUS or IMROZ trials. This is a limitation of the evidence base - since individual patient data (IPD) were not available to J&J for the IMROZ trial, it was not possible to adjust IMROZ trial data for any potential impact of COVID-19. For completeness, results from an NMA where the CEPHEUS trial data were adjusted for COVID-19 are also provided below.

Whilst neither analysis is truly reflective of the comparative efficacy in clinical practice, the unadjusted analysis used in the base case is likely to be particularly conservative. This is because IsaBLd results in IMROZ were less heavily impacted by the COVID-19 pandemic than DBLd in CEPHEUS, based on the timing of the studies. COVID-19 deaths made up 11.59% of all deaths in the IsaBLd arm of IMROZ (8 COVID-19 deaths out of 69 total deaths) compared to ████ of all deaths in the DBLd arm of CEPHEUS (█ COVID-19 deaths out of ███ total deaths).^{1, 2} This difference is expected to be because of the timing of trial initiation and data cut-offs between the two trials. Considering both are quadruplet therapies consisting of an anti-CD38 monoclonal antibody given in combination with BLd, a similar proportion of COVID-19 deaths would be expected, therefore suggesting the treatment benefit estimated in the CEPHEUS trial is likely underestimated compared to the efficacy results from the IMROZ trial.

As such, the unadjusted base case NMA represents a conservative estimate of the comparative efficacy of DBLd versus IsaBLd, with a scenario analysis conducted to explore a plausible lower-bound to the true treatment effect of DBLd where CEPHEUS IPD was adjusted for COVID-19.

Results

The results of the NMA are summarised below – as previously presented in response to Clarification Question A11. For completeness, both fixed effect (FE) and random effect (RE) NMA results were explored. All of the results were highly consistent between the two approaches, indicating that the choice of a FE versus RE model was considered to represent a minimal source of uncertainty.

As shown, across both the FE and RE models, DBLd was associated with considerable numerical improvements in both OS and PFS compared with IsaBLd. In the base case NMA – which did not adjust for COVID-19 – DBLd reduced both the risk of death and the risk of disease progression by ███% versus IsaBLd, demonstrating a clear trend in favour of DBLd over IsaBLd in this indication. As discussed above, this analysis is likely to be conservative, given that COVID-19 disproportionately impacted CEPHEUS compared to IMROZ.

As shown in Table 2, across both the FE and RE models, the magnitude of benefit increased in the scenario analysis adjusting for COVID-19 in CEPHEUS. Specifically, DBLd reduced the risk

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of death by █% versus IsaBLd, and the risk of disease progression or death by █% demonstrating a clear trend in favour towards DBLd over IsaBLd.

Table 1: DBLd vs IsaBLd NMA results for OS (unadjusted for COVID-19) and PFS (unadjusted for COVID-19)

DBLd vs IsaBLd OR HR (95% CrI)	Fixed effects model	Random effects model
OS	██████████	██████████
PFS	██████████	██████████

Abbreviations: CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; NMA: network meta-analysis; OR: odds ratio; OS: overall survival; PFS: progression-free survival.

Source: J&J Data on File.

Table 2: DBLd vs IsaBLd NMA results for OS (adjusted for COVID-19) and PFS (adjusted for COVID-19)

DBLd vs IsaBLd OR HR (95% CrI)	Fixed effects model	Random effects model
OS	██████████	██████████
PFS	██████████	██████████

Abbreviations: CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; NMA: network meta-analysis; OR: odds ratio; OS: overall survival; PFS: progression-free survival.

Source: J&J Data on File.

2.3 MAIC between DBLd vs IsaBLd

Overview

The base case NMA approach assumes that there is no significant heterogeneity in treatment effect modifiers between the patient populations in CEPHEUS and IMROZ. Whilst this represents a reasonable assumption, given the similarity in trial designs, it is possible some heterogeneity exists between the two trials. Therefore, a supportive matching adjusted indirect comparison (MAIC) was additionally conducted to explore the potential impact of any heterogeneity on the comparative efficacy results.

Given that there is a common comparator arm (BLd) between the CEPHEUS and IMROZ trial populations, an anchored MAIC using the individual patient data (IPD) from CEPHEUS was considered to represent the next best approach (outside of the NMA) to conduct an ITC, in line with the guidance provided in NICE TSD 18.³

MAIC Methodology

The data for CEPHEUS in the MAIC was informed by the ASCT-ineligible ITT analysis set, to align with the patient population of relevance in this submission, as well as the IMROZ trial population. Individual patient data were available from the CEPHEUS trial; however, only aggregate data were available from the IMROZ trial.

A summary of baseline characteristics in the CEPHEUS trial (ASCT-ineligible population) and IMROZ prior to adjustment is presented in Table 3, below. Almost all of the baseline characteristics already fell within an SMD threshold ± 0.2 prior to adjustment, indicating a high

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level of alignment between the two trial populations, and providing support for the base case NMA approach. Only [REDACTED] characteristic used in the base case – [REDACTED] was observed to have an SMD falling slightly outside of this threshold, however the patient numbers for this characteristic were small reducing the risk of bias. [REDACTED] also fell out of the SMD threshold, however this is not included in the base model, only the full model sensitivity analyses (see Table 4).

Table 3 - Baseline characteristics of CEPHEUS and IMROZ trials.

Characteristics		CEPHEUS (ASCT-ineligible)		IMROZ		SMD between CEPHEUS (ASCT-ineligible) and IMROZ trials
		DBLd (n=144)	BLd (n=145)	IsaBLd (n=265)	BLd (n=181)	
R-ISS, %*	Stage I/II or missing	[REDACTED]	[REDACTED]	88.3	86.7	[REDACTED]
	Stage III	[REDACTED]	[REDACTED]	10.9	11.6	[REDACTED]
Cytogenetic Risk, %	Unknown/missing	13.2	11.0	6.8	3.9	[REDACTED]
	Standard	72.9	76.6	78.1	77.3	[REDACTED]
	High	13.9	12.4	15.1	18.8	[REDACTED]
Age (years), %	<65 years	[REDACTED]	[REDACTED]	3.0	5.0	[REDACTED]
	65-69 years	[REDACTED]	[REDACTED]	26.0	27.5	[REDACTED]
	70-74 years	[REDACTED]	[REDACTED]	37.6	43.4	[REDACTED]
	75-80 years	[REDACTED]	[REDACTED]	26.0	31.5	[REDACTED]
ECOG PS, %	0	36.1	39.3	46.4	43.6	[REDACTED]
	1	52.1	53.8	42.3	45.9	[REDACTED]
	≥2 †	11.8	6.9	11.3	10.5	[REDACTED]
Type of MM, %*	IgG	63.9	53.8	64.5	63.5	[REDACTED]
	Non-IgG	36.1	46.2	35.5	33.2	[REDACTED]
eGFR, %	<60 ml/min /1.73 m ²	[REDACTED]	[REDACTED]	24.9	34.3	[REDACTED]
EMD, %	EMD present	6.3	8.3	6.8	3.3	[REDACTED]
Sex, %	Male	45.1	56.6	54.0	51.9	[REDACTED]
Time since initial MM diagnosis (years)	Median, Range	[REDACTED]	[REDACTED]	0.1 (0.0-4.1)	0.1 (0.0-3.1)	[REDACTED]
Race, % *	White	[REDACTED]	[REDACTED]	72.5	72.4	[REDACTED]

Frailty based on simplified IMWG frailty score, %	Frail	■	■	27.5	31.5	■

Abbreviations: ASCT; autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: Daratumumab, bortezomib, lenalidomide and dexamethasone; ECOG: Eastern Cooperative Oncology Group performance score; eGFR: Estimated glomerular filtration rate; EMD: extramedullary disease; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; IMWG: International Myeloma Working Group; ITT: intent to treat; MM: multiple myeloma; R-ISS: revised International Staging System; SMD: standard mean difference.

* Missing race, RISS or type of multiple myeloma are classified as non-white, non-stage III, or non-IgG respectively

† 1 patient in the IsaVRd arm of IMROZ had an ECOG PS score of 3 and is categorized as ≥2.

The selection of baseline covariates used for the ITC was aligned with the approach taken to inform the IPTW ITC between DBLd and DLd, as previously detailed in the Company submission (Section 2.10.2). As part of their report, the EAG confirmed that this approach was thorough, and that no potential covariates were missing from the list.

The final variables adjusted for were then adapted slightly, based on the availability of published data for IMROZ – as detailed in Table 4. Sensitivity analyses which adjusted for additional baseline covariates (aligned with the ITC in the original Company submission) were also performed, as shown in Table 4.

Table 4: Variables adjusted for in the base and sensitivity MAICs.

		Covariate
Base model	R-ISS	• Stage I or II • Stage III • Not classified
	Cytogenetic risk	• Standard • High • Unknown/missing
	Age	• <65 yr • 65-69 yr • 70-74 yr • 75-80 yr
	ECOG PS	• 0 • 1 • 2+
	Myeloma type	• IgG • Non-IgG
	Frailty	
	EMD	
	Sex	
	eGFR <60 ml per minute per 1.73 m ²	
Full model (Sensitivity)	Median duration since initial Dx with MM	
	Race	

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Abbreviations: Dx: diagnosis; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eGFR: estimated glomerular filtration rate; EMD: extramedullary disease; IgG: immunoglobulin G; MAIC: matching adjusted indirect comparison; MM: multiple myeloma; R-ISS: revised international staging system;.

Results

A summary of the unadjusted, base case and sensitivity MAIC results are presented in Table 5 below. Across all of the analyses, treatment with DBLd [REDACTED] the risk of disease progression (base case PFS HR: [REDACTED], [95% CI: [REDACTED]] and death (base case OS HR: [REDACTED] [95% CI: [REDACTED]]) when compared to IsaBLd - consistent with the results of the NMA (although the magnitude of benefit was [REDACTED]).

KM curves for the base case MAIC are presented in Figure 1 and Figure 2 below for PFS and OS respectively. The DBLd and IsaBLd curves begin to separate at ~30 months, with the benefit in favour of DBLd persisting throughout the duration of follow-up. The improved survival for DBLd is supported by NMA results that demonstrate a [REDACTED] of achieving deeper responses with DBLd compared with IsaBLd:⁴

- The probability of DBLd having superior MRD-negative complete response was [REDACTED]% compared to IsaBLd (OR: [REDACTED]; CrI: [REDACTED])
- The probability of DBLd having superior complete response or better rate was [REDACTED]% compared to IsaBLd (OR: [REDACTED]; CrI: [REDACTED])

The separation in the OS curves is also be supported by a lower PFS2 hazard ratio observed in CEPHEUS (DBLd: [REDACTED]%, BLd: [REDACTED]%, HR: [REDACTED]; CI: [REDACTED]) when naively compared with the PFS2 data from IMROZ (IsaBLd: 31.7%, BLd: 41.4%, HR: 0.697; CI: 0.51, 0.952), suggesting DBLd provides greater and more durable clinical benefit to patients.

It is important to note that the results of the MAIC should be interpreted with caution, as the effects of COVID-19 was not adjusted for as part of the matching process. As previously detailed, the COVID-19 pandemic impacted the CEPHEUS trial disproportionately compared to IMROZ – comprising [REDACTED]% of deaths in the DBLd arm of CEPHEUS, compared to 11.59% in the IsaBLd arm of IMROZ. The disproportionate impact of COVID-19 across the two studies is likely to explain why the OS Kaplan Meier curve for DBLd initially tracks below the IsaBLd curve before the benefit of deeper responses translates to improved long-term survival outcomes (see Figure 2).

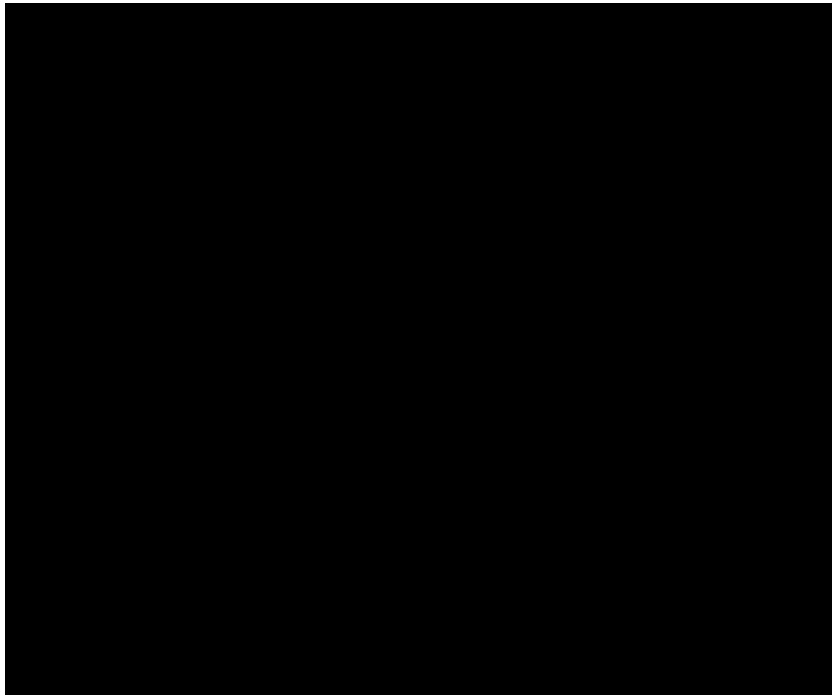
Without taking this imbalance into account, it is likely that the results of the MAIC are therefore conservative and represent an upper-bound to the true treatment effect for DBLd versus IsaBLd.

Table 5: Summary of MAIC results for DBLd versus IsaBLd

	PFS, HR (95% CI)	OS, HR (95% CI)
Unadjusted	[REDACTED]	[REDACTED]
Base case MAIC	[REDACTED]	[REDACTED]
Sensitivity analysis MAIC	[REDACTED]	[REDACTED]

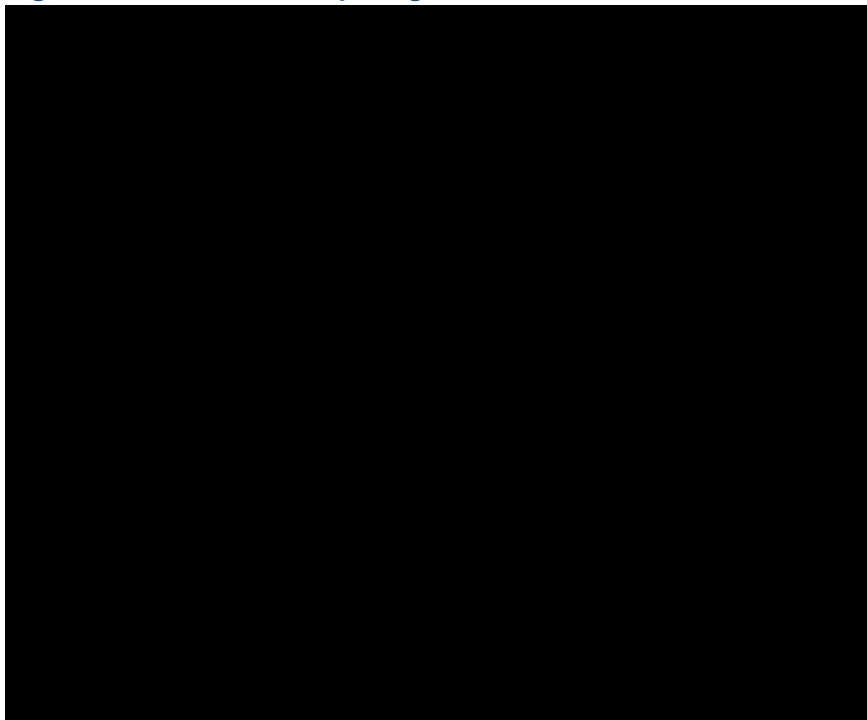
Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; MAIC: matching adjusted indirect comparison; OS: overall survival; PFS: progression-free survival.

Figure 1: KM curves comparing DBLd vs IsaBLd for the MAIC (PFS)



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; KM: Kaplan-Meier; MAIC: matching adjusted indirect comparison; PFS: progression-free survival; Wt; weighted.

Figure 2: KM curves comparing DBLd versus IsaBLd for the MAIC (OS)



Abbreviations: DBLd/DVRd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd/IsaVRd: isatuximab, bortezomib, lenalidomide and dexamethasone; KM: Kaplan-Meier; MAIC: matching adjusted indirect comparison; PFS: progression-free survival; VRd: bortezomib, lenalidomide and dexamethasone; Wt; weighted.

2.4 Conclusions

In the absence of direct evidence comparing DBLd versus IsaBLd, a comprehensive range of ITCs were conducted (using both NMA and MAIC methodologies) and scenarios explored (both COVID-19 adjusted and unadjusted), in line with the recommendations provided in NICE TSD 18.³ In the absence of sufficient published data for TTD, only ITCs for PFS and OS could be conducted.

The results across all of the ITCs showed that DBLd reduced the risk of death and disease progression or death when compared to IsaBLd. The magnitude of effect varied, ranging between a ■% to ■% reduction in the risk of death across the various ITC results that were explored. One possible explanation for this could be the reduced number of doses associated with daratumumab (as part of DBLd) when compared to isatuximab (as part of IsaBLd). The increased dosing intensity associated with IsaBLd could result in a greater proportion of patients discontinuing individual components of the regimen, and therefore deriving less benefit from the quadruplet regimen relative to DBLd.

The NMA was chosen as the base case for the ITC considering the similarity in trial designs and patient populations between CEPHEUS and IMROZ, with no significant differences in treatment effect modifiers. This is supported by all but ■ of the key baseline characteristics in the base model falling within an SMD threshold of ± 0.2 .

One key limitation across all of the ITCs is the absence of individual patient data from the IMROZ trial. Both the CEPHEUS and IMROZ trials were impacted by the COVID-19 pandemic, although with only aggregate data available from IMROZ, only the CEPHEUS trial can be adjusted to account for this. Because of this, the base case NMA and MAIC did not include adjustment for COVID-19, although a scenario NMA analysis where CEPHEUS was adjusted for COVID-19 was also explored to provide a lower-bound to the true treatment effect of DBLd.

This therefore means that the base case NMA results, which indicate that DBLd reduces the risk of death by ■% (OS HR: ■) and the risk of disease progression or death by ■% (PFS HR: ■), are likely to represent a conservative estimate of the true comparative effectiveness between DBLd and IsaBLd due to the disproportionate impact of COVID-19 on the two trials, accounting ■ the proportion of deaths in CEPHEUS (■%) compared to IMROZ (11.59%).

3 Cost-effectiveness analysis of DBLd vs IsaBLd

3.1 Overview

Based on the results of the ITCs, a cost-effectiveness analysis for DBLd versus IsaBLd was conducted. The approach to modelling DBLd was unchanged from the approach previously detailed in the Company base case – the new approaches included to model IsaBLd are detailed below.

3.2 Clinical effectiveness inputs

The efficacy for DBLd was aligned with the approaches previously described in Section 3.3 of the Company submission. Briefly, extrapolations were independently fitted to the ATE-weighted KM data from the ASCT-ineligible subgroup of CEPHEUS. The best statistically fitting extrapolations were then calibrated to align with clinical expert estimates of survival for DBLd.

At the time of the May 2025 advisory board ran by the Company, IsaBLd was not recommended by NICE. As such, and following advice received by J&J from the health economic advisors that such a comparison would be off NICE process, long-term estimates of survival were not obtained from the panel of clinical experts. Given the short timeframe to perform a cost-effectiveness comparison of DBLd versus IsaBLd (within 4-weeks of the IsaBLd Final Guidance), absence of long-term estimates from clinical advisors, and the request from the EAG to keep model changes to DBLd to a minimum, a pragmatic approach was taken by leveraging the ITC-generated HRs to inform cost-effectiveness (note, if independent models had been fitted to the IsaBLd Kaplan-Meier curves, the approach to estimate PFS and OS for DBLd would have had to substantially change as calibration would have needed to be removed).

The first step was to assess proportional hazards (PH), and whether it held between DBLd and IsaBLd. As the base case NMA represents an anchored comparison, the PH assumption was tested separately for both the transplant-ineligible population in CEPHEUS and IMROZ. The results from the Schoenfeld plots (presented in Appendix A) showed that the PH assumption holds for both PFS and OS in both trials. By extension, the PH assumption can be considered to hold in the comparison between DBLd and IsaBLd. Results from the loglog plots were less conclusive, suggesting a potential violation for OS in IMROZ and a small crossing in the plots for PFS in CEPHEUS. However, given both treatments include component drugs with the same mechanism of action, it was considered that the totality of evidence was sufficient to support proportional hazards, and a hazard ratio approach was taken forward to inform the cost-effectiveness comparison.

Efficacy estimates for IsaBLd were generated by applying the PFS and OS HRs from the base-case NMA to the DBLd extrapolations to obtain corresponding extrapolations for IsaBLd. This approach allows uncertainty related to the treatment effect from the ITCs to be fully explored, whilst also mitigating the absence of clinical expert estimates of survival for IsaBLd that would be required for a calibration approach.

In the base case economic analysis, the HRs (unadjusted for COVID-19) from the FE NMA (PFS HR: ■■■; OS HR: ■■■) were used to generate PFS and OS curves for IsaBLd. Scenario analyses

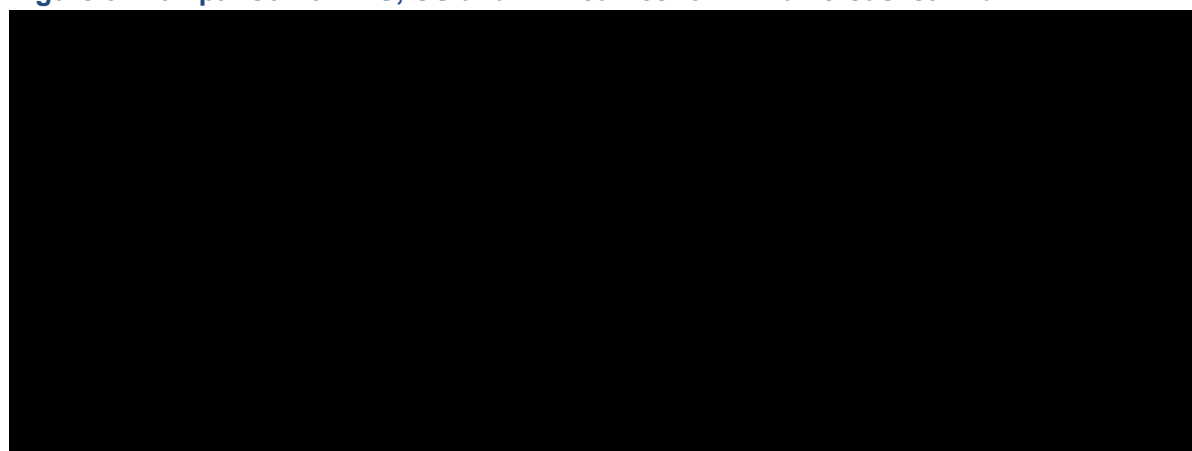
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were explored (Section 4.2) using the HRs (adjusted for COVID-19 in CEPHEUS), as well as the HRs from the MAIC.

Insufficient TTD data were published for IsaBLd to allow a TTD ITC to be conducted between DBLd and IsaBLd. Therefore, in the absence of further information, an assumption was included in the economic analysis whereby the TTD curve for IsaBLd was set equal to the TTD curve for DBLd. As both treatments include the same MoA of an anti-CD38 in combination with BLd, this was considered a reasonable assumption. An additional scenario was considered where the PFS HR between DBLd and IsaBLd (HR: [REDACTED]) was applied to the DBLd TTD curve to derive a TTD curve for IsaBLd (Section 4.2).

A summary of the DBLd and IsaBLd base case PFS, OS and TTD extrapolations are presented in Figure 3 below.

Figure 3: Comparison of PFS, OS and TTD curves for DBLd versus IsaBLd



Footnotes: The OS extrapolations presented in Figure 3 are capped by general population mortality. TTD extrapolations are capped by PFS, and PFS extrapolations are capped by OS, respectively. The IsaBLd extrapolations are also capped so that they can never fall below the DLd extrapolations for each endpoint, to support clinical plausibility of modelled outcomes.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; OS: overall survival; PFS: progression free survival; TTD: time to treatment discontinuation.

As part of the updated economic model, a minor change has been applied to the calibration methodology, to ensure that the curve is capped by general population mortality both before and after calibration is applied. This change does not impact the Company base case results versus IsaBLd or DLd, but has a very minor impact on the results of the EAG's base case versus DLd. Further details can be found in Appendix B.

3.3 *Adverse Events*

In line with the approach detailed in Section 3.3.5 of the Company submission, Grade 3 or 4 AEs with an incidence of $\geq 5\%$ for any treatment were included in the economic analysis. For IsaBLd, AEs were based on the IMROZ trial.⁵

Based on the AEs included for IsaBLd, two new AEs were additionally considered for DBLd - peripheral sensory neuropathy and syncope.

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A summary of the AEs included in the economic analysis for DBLd versus IsaBLd is provided in Table 6 below.

Table 6: Summary of AEs for DBLd and IsaBLd in the base case economic analysis

Adverse Event	DBLd	IsaBLd
Neutropenia	████	54.37%
Lymphopenia	████	60.08%
Thrombocytopenia	████	30.04%
Leukopenia	████	31.56%
Anaemia	████	17.49%
Pneumonia	████	20.15%
Hypokalaemia	████	0.00%
Pulmonary embolism	████	4.94%
Hyperglycaemia	████	0.00%
Diarrhoea	████	7.60%
Fatigue	████	7.98%
Hypertension	████	0.00%
Asthenia	████	2.66%
Acute kidney injury	████	0.00%
Chronic kidney disease	████	0.00%
Cataract	████	15.59%
Peripheral sensory neuropathy	████	7.22%
Syncope	████	5.70%

Abbreviations: AE: adverse event; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone.

3.4 Utility Values

Patients treated with IsaBLd were assumed to experience the same utility values across all health states in the economic model as those treated with either DBLd or DLd, based on the CEPHEUS trial, as previously detailed in Table 68 of the Company submission.

Two new AEs were included in the economic model for the comparison with IsaBLd – the disutility values associated with these AEs are presented in Table 7, below.

Table 7: Duration and utility decrement associated with new AEs included in the economic model for the comparison versus IsaBLd

Adverse Event	Utility	Duration (days)	Disutility
Peripheral sensory neuropathy	-0.02	50	-0.003
Syncope	0.00	14	0.000

Abbreviations: AE: adverse event; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone.

3.5 Cost inputs

Unless specified, all cost inputs for IsaBLd were aligned with the corresponding cost inputs used for DBLd as detailed previously in Section 3 of the Company submission.

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Drug acquisition costs

The dosing regimen and associated drug acquisition costs for IsaBLd are presented in Table 8 and Table 9, below.

As previously detailed in Section 3.5.1 of the Company submission, the model accounts for relative dosing intensity (RDI), to reflect that patients receiving therapy may not necessarily receive the full course of therapy due to dose reductions or skipped doses. RDI for each of the components of the IsaBLd regimen was based on data from the IMROZ trial used as part of TA1098; a scenario analysis was conducted where the RDI for the bortezomib, lenalidomide and dexamethasone components of the regimen was set equal to the equivalent components of the DBLd regimen.

It is important to note that, based on the dosing regimens in their respective SmPCs, IsaBLd requires fifteen more administrations than DBLd over the first two years of treatment, as described in the response to Clarification Question A11. Therefore, IsaBLd incurs substantially higher drug acquisition and administration costs than DBLd when both treatments are modelled at list price.^{6, 7}

The extra infusions for IsaBLd arise as isatuximab (as part of IsaBLd) is given once every two weeks (Q2W) until Week 76 (at which point it switches to Q4W), while daratumumab (as part of DBLd) is given once every four weeks (Q4W) after Week 24 until progression. It is also notable that isatuximab is administered as an IV infusion lasting several hours, while daratumumab is administered as a short 3-5 minute subcutaneous injection, resulting in a higher resource burden on the NHS.^{8, 9}

Table 8: Summary of dosing regimens for IsaBLd

Treatment	Treatment cycle duration	Dosing regimen	Source/Justification
IsaBLd	6 week treatment cycle for Cycles 1–4, 4-week cycle for Cycle 5 until disease progression	Isatuximab - 10 mg/kg C1: days 1, 8, 15, 22, 29; C2-4 days 1, 15, 29; C5-17 days 1, 15; C18+ day 1	Isatuximab SmPC; TA1098
		Bortezomib - 1.3 mg/kg Day 1, 4, 8, 11, 22, 25, 29, 32*	
		Lenalidomide - 25 mg C1-4: Day 1–14 and 22-35; C5+: Day 1–21	
		Dexamethasone - C1-4: Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, 33; C5+: Day 1, 8, 15, 22. IV administration on days where isatuximab is administered, and oral administration otherwise.	

Abbreviations: C: Cycle; IV: Intravenous; mg/kg: milligrams per kilogram; SmPC: Summary of Product Characteristics; TA: NICE technology appraisal number; IsaBLd: isatuximab, bortezomib, lenalidomide, and dexamethasone.

Footnotes: *To align with UK clinical practice, bortezomib doses are modelled to be given once weekly as advised in the November 2024 and May 2025 Advisory Boards.

Table 9: Summary of drug costs for IsaBLd

Intervention	Drug	Total dose per administration	Vial/unit size (mg)	Price per vial/pack (£)	Price per administration	RDI	Source
IsaBLd	Isatuximab	741.80 mg	100	£506.94	£4,055.51	93.58%	BNF 2025. Price per vial for Sarclisa 100/500 mg concentrate for solution for infusion. RDI: Median value from IMROZ trial, per TA1098
			500	£2,534.69			
	Bortezomib	2.38 mg	2.5	£79.76	£79.76	90.28%	eMIT 2025. Price per vial of Velcade 2.5 mg powder for solution for injection. RDI: Median value from IMROZ trial, per TA1098
	Lenalidomide	25.00 mg	25.0	£36.10	£1.72	77.74%	eMIT 2025. Price per pack of 21 Revlimid 25 mg capsules. RDI: Median value from IMROZ trial, per TA1098
	Dexamethasone	20.00 mg	2.0	£2.19	£0.44	81.58%	eMIT 2025. Price per pack of 50 dexamethasone (generic) 2 mg tablets. RDI: Median value from IMROZ trial, per TA1098
	Dexamethasone	40.00 mg	2.0	£2.19	£0.88		eMIT 2025. Price per pack of 50 dexamethasone (generic) 2 mg tablets. RDI: Median value from IMROZ trial, per TA1098

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; mg: milligram; RDI: relative dose intensity; TA: NICE technology appraisal number

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Subsequent treatments

Subsequent treatments were modelled in line with the approach detailed in Section 3.5.1 of the Company submission.

In the IMROZ trial, of the 50 patients who experienced disease progression, 36 (72%) received a subsequent treatment (Table 10). As such, 72% of patients who received 1L treatment with IsaBLd were modelled to receive a 2L subsequent treatment – the proportions of patients who received 3L and 4L treatments were then calculated based on the proportions reported by Yong et al (2016). The final proportions of patients receiving subsequent treatment at each line following IsaBLd are reported in Table 11. A scenario has also been provided assuming a proportion of 75% for both IsaBLd and DBLd to align with the EAG base case in the EAG report.

Given the similarity between DBLd and IsaBLd, patients were assumed to receive the same distribution of subsequent treatments following either DBLd or IsaBLd. Subsequent treatment distributions for DBLd are detailed in Table 75, Section 3.5.1 of the Company submission.

Table 10: Proportion of patients with a subsequent treatment among patients with a PFS event by treatment at 1st line

	IsaBLd
PFS, n (%)	84 (100)
Progressive disease, n (%)	50 (60)
Progressive disease with subsequent treatment, n (%)	36 (43)
Death, n (%)	34 (40)
Source	IMROZ

Abbreviations: IsaBLd: Isatuximab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival; n: number

Table 11: Final proportion of patients with treatment applied in the cost-effectiveness model, relative to the 1st line of treatment

	IsaBLd	Source
1 st line	100%	Calculation, based on IMROZ and Yong et al. (2016)
2 nd line	72%	
3 rd line	62.3%	
4 th line	39.47%	

Abbreviations: IsaBLd: Isatuximab, bortezomib, lenalidomide and dexamethasone.

Concomitant Medications

Patients receiving IsaBLd were modelled to receive concomitant medications with an antipyretic, antihistamine and an H2 antagonist – as detailed in Table 12 below.

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Table 12: Concomitant medication dosing regimens for IsaBLd^a

Treatment	Dosing regimen	Source	Dose	Number of Units	Admins Per Cycle
Antipyretic: oral paracetamol pre-infusion	1000 mg per administration	As specified in Isatuximab SmPC, aligning with TA1098	1,000 mg	2	2.00
Antihistamine: oral/IV diphenhydramine pre-infusion	50 mg per administration		50 mg	2	2.00
H2 antagonist: oral cimetidine pre-infusion	50 mg per administration		50 mg	1	2.00

Footnotes: ^a As a simplifying assumption, it is assumed that concomitant medication dosing is based on the Cycle 5-17 dosing regimen of IsaBLd.

Abbreviations: IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; IV: intravenous; SmPC: Summary of Product Characteristics; TA: NICE technology appraisal number.

Table 13: Concomitant medication costs for IsaBLd

Treatment	Dosing regimen	Unit size	Units per pack	Cost per pack	Cost per unit	Source
Antipyretic: oral paracetamol	1,000 mg per administration of isatuximab	500 mg	100	£0.66	£0.01	Dosing regimen: Isatuximab SmPC Drug costs: Paracetamol: eMIT 2024; Price per pack of 100 500 mg oral tablets (generic) Diphenhydramine: MIMS 2021 Cimetidine: eMIT 2025; Price per pack of 60 400 mg dispersible tablets (generic)
Antihistamine: oral/IV diphenhydramine	50 mg per administration of isatuximab	25 mg	20	£3.16	£0.16	
H2 antagonist: oral cimetidine	50 mg per administration of isatuximab	400 mg	60	£4.69	£0.08	

Abbreviations eMIT: electronic market information tool; IV: intravenous; MIMS: Monthly Index of Medical Specialities; QD: daily; SmPC: Summary of Product Characteristics.

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Adverse events

Two new AEs were included in the economic model for the comparison with IsaBLd – the costs associated with these AEs are presented in Table 14, below.

Table 14: Costs associated with new AEs included in the economic model for the comparison versus IsaBLd

Adverse Event	Costs	Source	Details
Peripheral sensory neuropathy	£2,106.05	NHS Reference Costs 2023/2024	DZ09J-Q: Weighted Average of Pulmonary Embolus with Interventions (CC Score 9+) and without interventions (CC Score 0–12) NEL and NES. Aligns with TA1098.
Syncope	£1,539.54		EB08A-E: Weighted Average of Syncope or collapse (CC Score 0–13+), NEL and NES

Abbreviations: AE: adverse event; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; CC complications and comorbidities; NEL: Non-Elective Long Stay; NES: Non-Elective Short Stay; TA: NICE technology appraisal number

4 Cost-Effectiveness Results

4.1 Base case results

DBLd vs IsaBLd

The deterministic and probabilistic base case cost-effectiveness results for DBLd versus IsaBLd are presented in Table 15 and Table 16. The results show that at the DBLd (at the discounted daratumumab price) dominates IsaBLd (at list price for isatuximab). DBLd was associated with a saving of £[REDACTED] and [REDACTED] additional QALYs per patient, compared to IsaBLd.

Table 15: Deterministic base-case results (discounted daratumumab price)

Intervention	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER	INHB at £20,000	INHB at £30,000
DBLd	[REDACTED]	8.59	[REDACTED]						
IsaBLd	[REDACTED]	7.99	[REDACTED]	[REDACTED]	0.59	[REDACTED]	Dominant	[REDACTED]	[REDACTED]

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; LY: life years; QALYs: quality-adjusted life years.

Table 16: Probabilistic base-case results (discounted daratumumab price)

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
DBLd	[REDACTED]	[REDACTED]			
IsaBLd	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant

Footnotes: HRs for OS and PFS between DBLd and IsaBLd were excluded from the PSA, on the basis that the capping of IsaBLd OS and TTD by GPM and DLd led to capping overriding the variation and to clinically implausible iterations. Additionally, as correlated parameters, allowing PFS and OS to be varied without correlation in the PSA could result in clinically implausible iterations. Instead, any uncertainty around the most appropriate HRs was explored in separate scenario analyses, detailed in Section 4.2, which explored the use of HRs from the COVID-19 NMA and the MAIC between CEPHEUS and IMROZ as potential bounds to any uncertainty around the true treatment effect between DBLd and IsaBLd.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; QALYs: quality-adjusted life years.

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Fully Incremental Analysis

Table 17: Fully incremental analysis results of the analysis between DBLd, DLd and IsaBLd (discounted daratumumab prices as part of DBLd and DLd; list price for isatuximab)

Treatment	Total costs	Total QALYs	Dominated?	Extendedly dominated?	Fully incremental ICER
DLd	██████	██	I	I	I
DBLd	██████	██	█		██████
IsaBLd	██████	██	█		██████

Notes: The economic results for DBLd and DLd have changed slightly compared to the previous Company base case, due to additional AEs included in the economic model following the addition of IsaBLd.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; QALYs: quality-adjusted life years.

4.2 Sensitivity and scenario analyses

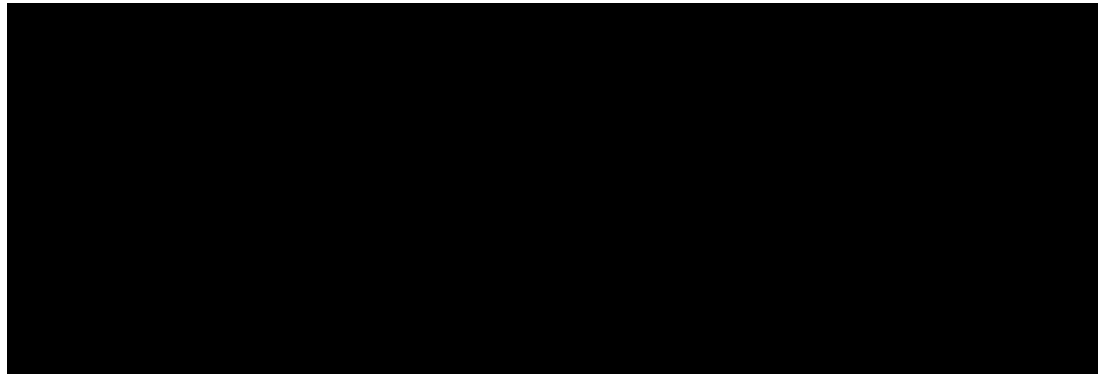
A full range of sensitivity and scenario analyses for DBLd versus DLd were previously presented in Section 3.11 of the CS. This section focusses on a range of sensitivity and scenario analyses comparing DBLd versus IsaBLd.

Deterministic Sensitivity Analysis

The tornado diagram showing the key drivers of the DSA in the economic analysis of DBLd versus IsaBLd is presented in Figure 4. The key model drivers were the HRs for both OS and PFS between DBLd and IsaBLd. However, for the reasons previously detailed in Section 2 of this response, the base case NMA HRs (which are not adjusted for COVID-19) are likely to be conservative, given the disproportionate impact of the COVID-19 pandemic on CEPHEUS compared to IMROZ. Any uncertainty around the most appropriate PFS and OS values is explored in scenario analyses, using the COVID-19 adjusted NMA HRs, as well as HRs obtained from the MAIC between CEPHEUS and IMROZ.

It is noted that the DSA presented in Figure 4 uses the discounted price for DBLd and the list price for IsaBLd.

Figure 4: DSA tornado diagram (DBLd versus IsaBLd)



Footnotes: When comparing the discounted price of DBLd versus the list price of IsaBLd, both the upper and lower bound OS HRs cause the ICER to increase. When the OS HR becomes more favourable for DBLd, this causes the ICER to become less negative, and therefore increases. When the OS HR becomes less favourable for DBLd, this causes the ICER to move into the southwest cost-effective quadrant (meaning the ICER is positive), which also causes the ICER to increase.

Abbreviations: AE: adverse event; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; IV: intravenous; OS: overall survival; QALY: quality-adjusted life year; SC: subcutaneous; Subtx: subsequent treatment.

Company evidence submission template for daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Scenario Analysis

A number of scenario analyses were conducted to explore the sensitivity of the cost-effectiveness model results to different input parameter assumptions. Full details including justification for all scenario analyses conducted are provided in Table 18. The results for all scenario analyses conducted are presented in Table 19.

In summary, results of the scenario analyses demonstrate that the base case analysis is robust to uncertainty in key input parameter assumptions, with DBLd dominating IsaBLd across all scenarios explored. As noted above, the base case already adopts a conservative relative efficacy assumption, given it uses the NMA unadjusted for COVID-19. As such, the additional scenarios that explore more conservative relative efficacy assumptions (the MAIC and equivalent efficacy) are likely to underestimate the true QALY gain expected with DBLd over IsaBLd and overestimate the resultant ICERs.

Table 18: Summary of scenario analyses (DBLd versus IsaBLd)

Scenario	Description of scenario analysis	Rationale
1a: IsaBLd PFS/OS	Use of COVID-adjusted HRs from NMA (PFS HR: ■■■, OS HR: ■■■)	In the base case analysis, the PFS and OS HRs are based on the base case NMA, detailed in Section 2.2 of this addendum document. This NMA was unadjusted for COVID-19, as individual patient data (IPD) were not available to J&J for the IMROZ trial and therefore it was not possible to adjust IMROZ trial data for any potential impact of COVID-19. The uncertainty of this is explored with an alternative scenario analysis where the CEPHEUS trial was adjusted for COVID-19.
1b: IsaBLd PFS/OS	Use of the base MAIC estimates to inform the efficacy of IsaBLd (PFS HR: ■■■, OS HR: ■■■)	
2: IsaBLd TTD	IsaBLd TTD is derived by applying the PFS HR between DBLd and IsaBLd to the DBLd TTD curve	To fully explore uncertainty regarding TTD, this scenario explores a shorter treatment duration for IsaBLd versus DBLd. To maintain internal consistency of the relationship between treatment arms for PFS and TTD, the PFS HR from the base case NMA is applied to the DBLd TTD curve to derive the IsaBLd TTD curve. J&J consider this highly conservative as, in the absence of robust ITC evidence, the treatment duration for IsaBLd would reasonably be expected to be similar to a comparable anti-CD38 containing quadruplet regimen.

Company evidence submission template for daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

		One possible justification for this approach would be increased AEs associated with intravenous administration of isatuximab compared with subcutaneous administration for daratumumab, and the increased inconvenience for patients/carers travelling in to hospital for more frequent and lengthy hospital visits (IV administration for isatuximab lasts several hours compared with a 3-5 minute subcutaneous injection for daratumumab, and there are 15 additional hospital visits for IsaBLd compared with DBLd in the first 2-years of starting treatment).^{8,9} Indeed, the clinical expert in TA1098 confirmed that some people may stop treatment early because of reasons such as toxicity or a desire to avoid repeated hospital visits. This also supports the consistent efficacy benefit observed for DBLd versus IsaBLd in both the NMA and MAIC ITCs as it is reasonable to assume improved efficacy associated with longer treatment exposure to a highly efficacious anti-CD38 containing quadruplet regimen.
3a: Alternative efficacy combined with alternative TTD 1	Use of COVID-adjusted HRs from NMA with IsaBLd TTD applying the PFS HR between DBLd and IsaBLd to the DBLd TTD curve	To explore a combined scenario of alternative efficacy with more conservative treatment duration assumptions, when using the COVID-adjusted HRs from the NMA, combined with the IsaBLd TTD informed by applying the PFS HR between DBLd and IsaBLd to the DBLd TTD curve. This combines scenarios 1a and 2.
3b: Alternative efficacy combined with alternative TTD 2	Use of MAIC HRs with IsaBLd TTD applying the PFS HR between DBLd and IsaBLd to the DBLd TTD curve	To explore a combined scenario when using the MAIC estimates to inform the efficacy of IsaBLd, combined with the IsaBLd TTD informed by applying the PFS HR between DBLd and IsaBLd to the DBLd TTD curve. This combines scenarios 1b and 2. J&J consider this highly conservative as it assumes a higher efficacy for IsaBLd versus the base case, but with a shortened treatment duration.
4: Equivalent efficacy between DBLd and IsaBLd	Use of a HR of 1 for OS and PFS to inform the efficacy of IsaBLd to explore a highly conservative scenario	To explore a highly conservative scenario, the PFS and OS HRs have been set to 1, which assumes equivalent efficacy between IsaBLd and DBLd. This scenario is likely to represent an extremely conservative approach with respect to the efficacy, as an efficacy benefit is demonstrated throughout the ITC approaches in both the NMAs and the MAIC.
5: IsaBLd RDI	RDI for BLd are set equal to BLd as part of the DBLd treatment regimen, based on CEPHEUS	In the base case analysis, the RDI for the bortezomib, lenalidomide and dexamethasone components of DBLd and IsaBLd are separately informed by the CEPHEUS and IMROZ trials, respectively. However, as BLd are aligned across the two regimens, then this scenario explores using the same RDI for these components, based on data from the CEPHEUS trial.

Company evidence submission template for daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

6: Subsequent treatment attrition rates	Attrition rates are aligned with the EAG base case	In the base case analysis, the proportion of patients who experience disease progression and receive subsequent treatment following either DBLd and IsaBLd were based on the CEPHEUS and IMROZ trials, respectively. However, this scenario explores the use of using an equal rate of attrition for both DBLd and IsaBLd, set to 75%, in line with the EAG's feedback.
7: Subsequent treatment distributions	Subsequent treatment distributions are aligned with the EAG base-case	In the base case, the subsequent treatment distributions for both DBLd and IsaBLd were based on the distributions previously detailed in Section 3.5.1 of the Company submission. This scenario explores the use of an alternative subsequent treatment distributions, in line with the EAG's feedback.
8: Baseline characteristics	The modelled starting age and % male are aligned with the EAG base-case	In the base case economic analysis, the starting age in the model was based on data from the ASCT-ineligible subgroup in CEPHEUS, to align with the efficacy data. However, this scenario explored the use of a slightly older starting age of 75, and a higher % of males (55%) in line with the EAG's preferred assumptions based on their clinical expert feedback.
9. Company base case with EAG settings	Combination of Scenarios 6, 7 and 8, to align with the EAG settings based on the EAG report	This scenario combines Scenarios 6, 7 and 8, to present a combined scenario that is closely aligned with the EAG's preferred base case settings relating to the comparison against DLd, stated in the EAG report.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; IPD: individual patient data; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NMA: network meta-analysis; OS: overall survival; PD: progressed disease; PFS: progression-free survival; RDI: relative dose intensity; TTD: time to treatment discontinuation.

Table 19: Summary of scenario analysis results – DBLd versus IsaBLd (deterministic; discounted daratumumab prices)

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case		██████	██	Dominant
1a	IsaBLd efficacy: COVID-19 adjusted OS and PFS HRs	██████	██	Dominant
1b	IsaBLd efficacy: MAIC OS and PFS HRs	██████	██	Dominant
2	IsaBLd TTD: apply PFS HR to DBLd	██████	██	Dominant
3a	Alternative efficacy combined with alternative TTD 1	██████	██	Dominant
3b	Alternative efficacy combined with alternative TTD 2	██████	██	Dominant
4	Equivalent efficacy between IsaBLd and DBLd	██████	██	Dominant
5	IsaBLd RDIs: Equal to RDIs for BLd in DBLd	██████	██	Dominant
6	EAG proportion receiving subsequent treatment	██████	██	Dominant

Company evidence submission template for daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

7	EAG subsequent treatment mix	██████	██	Dominant
8	EAG preferred patient characteristics	██████	██	Dominant
9	Company base case with EAG settings	██████	██	Dominant

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ICER: incremental cost effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; RDI: relative dose intensity; TTD: time to treatment discontinuation.

4.3 **Conclusions**

In response to the EAG's request, J&J have provided full details of clinical and cost-effectiveness analyses comparing DBLd versus IsaBLd. It is important to reiterate that as a very recently recommended treatment regimen, the uptake of IsaBLd is expected to be limited, and therefore it is unlikely that IsaBLd represents standard of care in UK clinical practice.

The results were consistent across both the NMA analyses and MAIC comparing CEPHEUS and IMROZ showed that DBLd [REDACTED] the risk of both death or disease progression or death when compared to IsaBLd. Without IPD from the IMROZ trial, it was not feasible to adjust for COVID-19 across both trials – as such, the base case NMA analysis is likely to be conservative, given the disproportionate impact of COVID-19 on CEPHEUS compared to IMROZ.

Based on these NMA results, the economic model showed that treatment with DBLd would represent a cost-effective use of NHS resources, with a cost saving of £[REDACTED] and a QALY gain of [REDACTED] when compared to IsaBLd. Varying key input parameter assumptions in the scenario analyses by exploring upper and lower bounds for relative efficacy estimates and varying treatment duration assumptions, continued to demonstrate an increase in QALYs with DBLd versus IsaBLd and the ICER being dominant.

The less frequent dosing schedule of DBLd and a subcutaneous route of administration means DBLd will significantly reduce the burden of administration for the NHS when compared to isatuximab (which requires more frequent administrations via lengthy IV infusions).

The eased burden of administration will also result in enhanced convenience for both patients and their carers through fewer lengthy hospital visits, likely resulting in further QALY gains that are not captured in the base case economic analysis. For this reason, as well as the conservative nature of the base case NMA which does not consider the impact of COVID-19, the base case cost-effectiveness results are likely to underestimate the true incremental QALYs between DBLd and IsaBLd in NHS clinical practice.

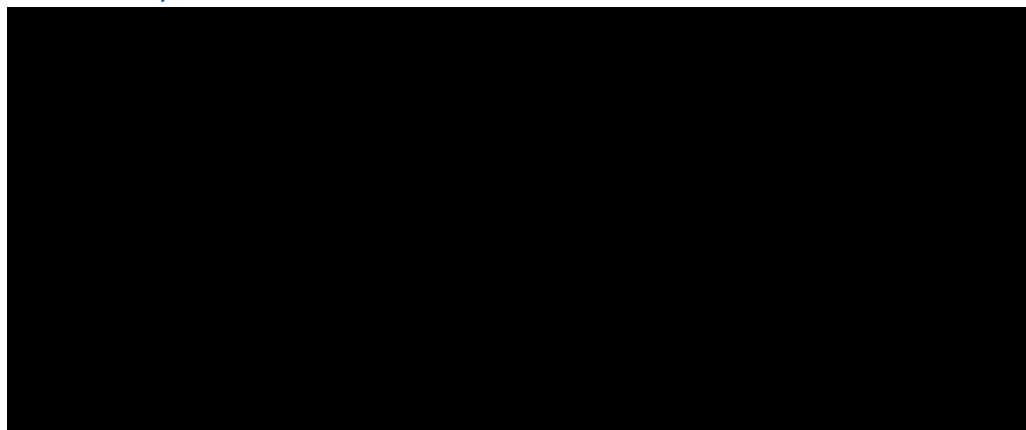
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Appendix A: CEPHEUS and IMROZ PH Tests

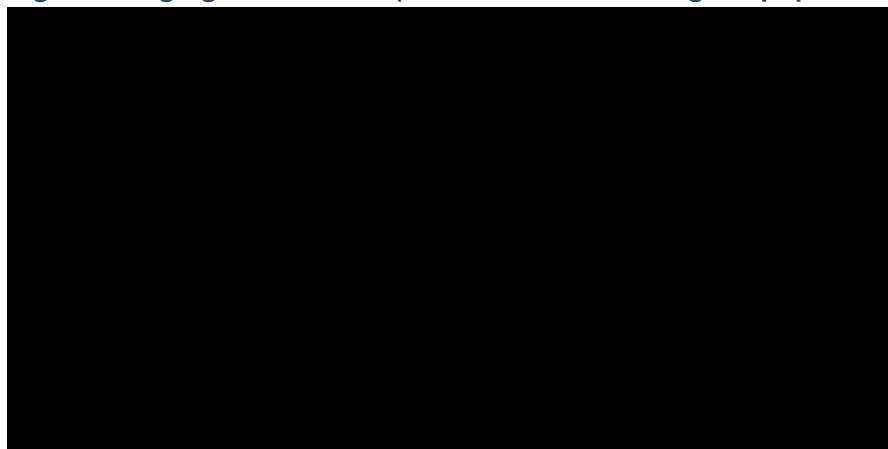
A summary of the PH tests in CEPHEUS and IMROZ are presented in Figure 5 to Figure 12 below.

Figure 5: Schoenfeld residual test for PFS (CEPHEUS ASCT-ineligible population, DBLd versus BLd)



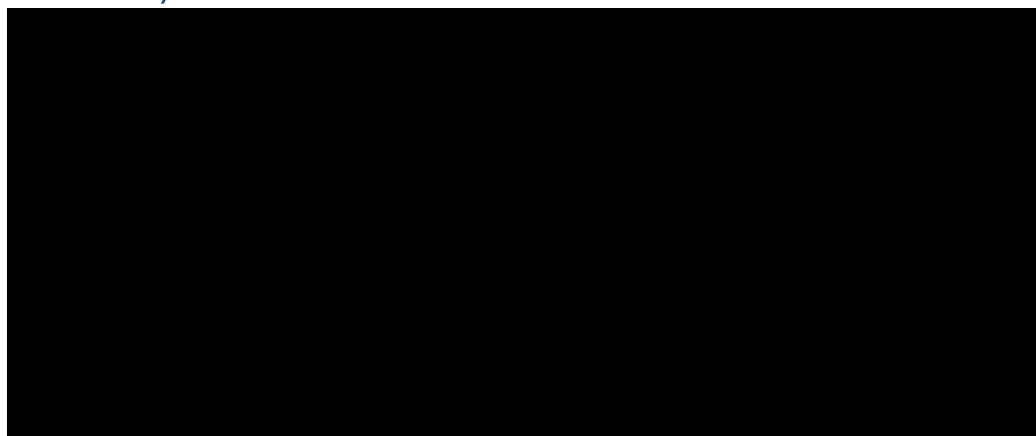
Abbreviations: ASCT: autologous stem-cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival.

Figure 6: loglog Plot for PFS (CEPHEUS ASCT-ineligible population, DBLd versus BLd)



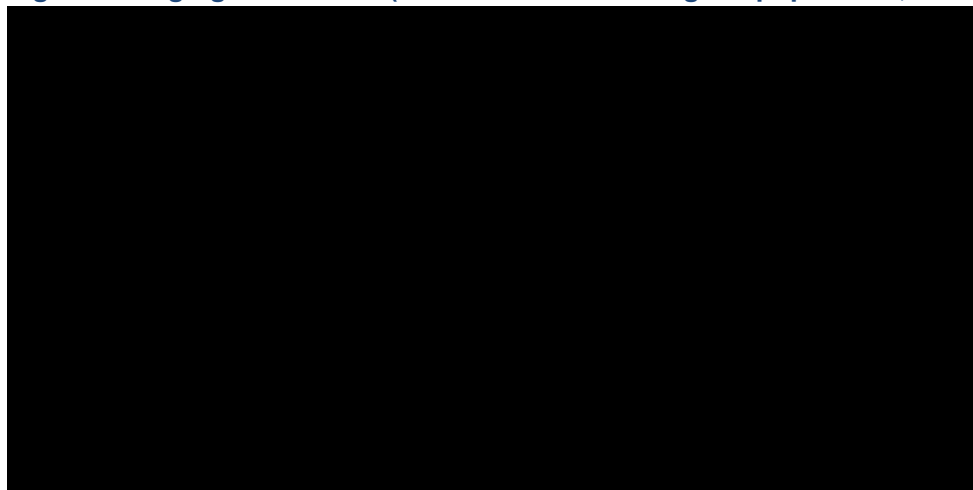
Abbreviations: ASCT: autologous stem-cell transplant; VRd: bortezomib, lenalidomide and dexamethasone; DVRd: daratumumab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival.

Figure 7: Schoenfeld residual test for OS (CEPHEUS ASCT-ineligible population, DBLd versus BLd)



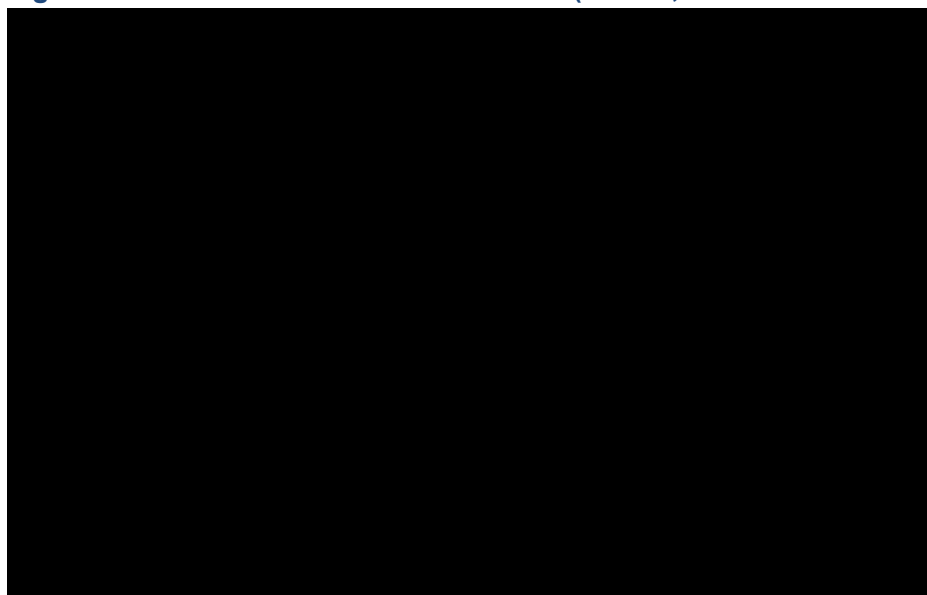
Abbreviations: ASCT: autologous stem-cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; OS: overall survival.

Figure 8: Loglog Plot for OS (CEPHEUS ASCT-ineligible population, DBLd versus BLd)



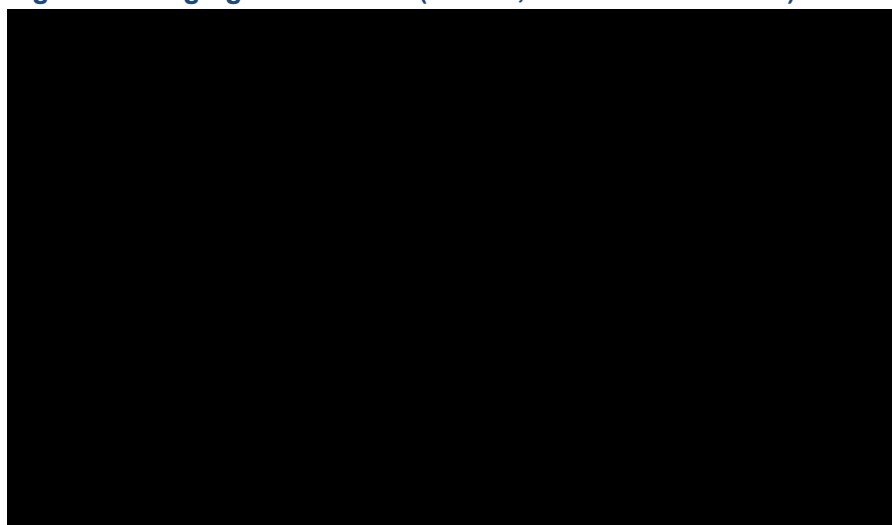
Abbreviations: ASCT: autologous stem-cell transplant; VRd: bortezomib, lenalidomide and dexamethasone; DVRd: daratumumab, bortezomib, lenalidomide and dexamethasone; OS: overall survival.

Figure 9: Schoenfeld residual test for PFS (IMROZ, IsaBLd versus BLd)



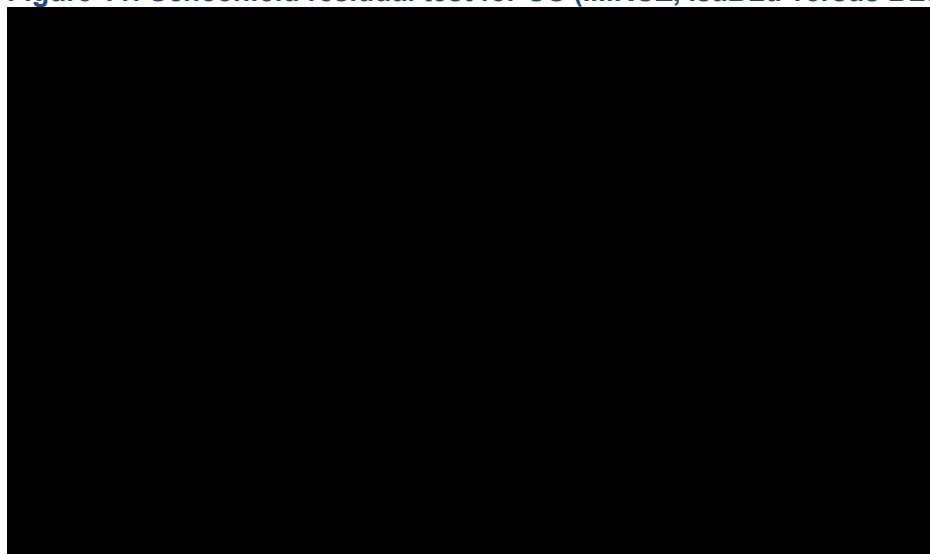
Abbreviations: VRd: bortezomib, lenalidomide and dexamethasone; IVRd: isatuximab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival.

Figure 10: Loglog Plot for PFS (IMROZ, IsaBLd versus BLd)



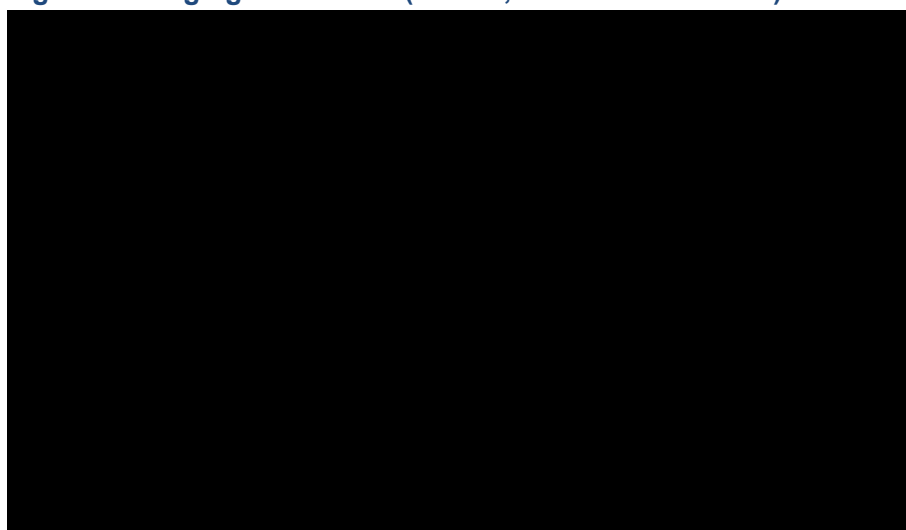
Abbreviations: VRd: bortezomib, lenalidomide and dexamethasone; IVRd: isatuximab, bortezomib, lenalidomide and dexamethasone; PFS: progression-free survival.

Figure 11: Schoenfeld residual test for OS (IMROZ, IsaBLd versus BLd)



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

Figure 12: Loglog Plot for OS (IMROZ, IsaBLd versus BLd)



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

Appendix B: Minor Change to Calibration Approach

As part of this analysis, a minor change to the calibration methodology has been incorporated in the latest model. Previously, the OS curves were capped by general population mortality, and were then calibrated to align with the long-term clinical expert estimates of survival. In the Company base case, this resulted in the hazard of death being increased in both the DBLd and DLd arms, as the capped OS curves resulted in OS estimates that were higher than the clinician expert estimates at all timepoints.

However, as the modelled starting age increases, then the capped OS curves can start to fall below the clinician expert estimates of survival. As such, in some scenarios – including the EAG's base case – the calibration methodology could previously result in the hazard of death falling below general population mortality. The model has now been updated to ensure that the calibrated curves cannot have a hazard of death that is lower than general population mortality, regardless of the chosen starting age in the economic model.

This change does not impact the Company base case versus DLd, but does have a very minor impact on the EAG's base case. The updated results of the EAG's base case and EAG's scenario analyses are provided in Table 20 and Table 21 – which are updated versions of Table 33 and Table 35 from the EAG report.

Table 20 Results using EAG's preferred model assumptions

Preferred assumption	Exploratory analysis number	Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	Cumulative ICER £/QALY
Company's base case	Not applicable	DBLd	████	██	████	██	████
		DLd	████	██			
+ Mean age of patients: 75 years; proportion of males: 55%	1	DBLd	████	██	████	██	████
		DLd	████	██			
+ 75% of patients receiving DBLd 1L go on to receive subsq Tx 2L	4	DBLd	████	██	████	██	████
		DLd	████	██			
+ EAG-preferred subsq Tx resource use	6	DBLd	████	██	████	██	████
		DLd	████	██			
EAG's base case	Not applicable	DBLd	████	██	████	██	████
		DLd	████	██			

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr.: incremental; QALY: quality-adjusted life-year; Tx: treatment

Notes: This table is an updated version of Table 33 of the EAG report. Based on the comparison versus IsaBLd, the two additional AEs were also included in the model for DBLd and DLd. This resulted in a very minor change to the results of the Company base case analysis

Table 21 Results of EAG's deterministic scenario analyses using EAG's preferred assumptions

Scenario	Scenario applied to EAG's base case	Incr. costs (£)	Incr. QALYs	ICER £/QALY
EAG base case		████	██	████
1	Mean age of patients: █ years; proportion of males: █	████	██	████
2	████ of patients receiving DBLd 1L go on to receive subsq Tx 2L	████	██	████
3	Company-preferred subsq Tx resource use	████	██	████
4	Utility Source: CEPHEUS (EQ-5D-3L cross-walked)	████	██	████

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5	Utility Source: CEPHEUS time dependant (EQ-5D-3L cross-walked)	████	██	████
6	Utility Source: MAIA (EQ-5D-3L cross-walked)	████	██	████
7	COVID-unadjusted data for DBLd and DLd: Independent extrapolation			
8	Use truncated OS and PFS Kaplan-Meier data	████	██	████
9	TTD: Gompertz for DBLd; Gompertz for DLd	████	██	████
10	TTD: Gompertz for DBLd; generalised gamma for DLd	████	██	████
11	OS: DLd attenuation point at 5 years	████	██	████
12	PFS: DLd attenuation point at 7 years	████	██	████

Notes: This table is an updated version of Table 35 of the EAG report.

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life-year; SBd, selinexor, bortezomib and dexamethasone; subsq Tx, subsequent treatment

External Assessment Group (EAG) Report

Addendum

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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Date completed	28 th November 2025

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1 Introduction

This report critiques the company's Addendum to the company submission (CS) for the NICE technology appraisal of *'Daratumumab with bortezomib, lenalidomide and dexamethasone (DBLd) for untreated multiple myeloma when a stem cell transplant is unsuitable'* (ID3843). The CS was submitted to NICE in July 2025 and the Addendum was submitted on 22nd October 2025. The Addendum was produced in response to the EAG and NICE's request to the company to include the treatment regimen isatuximab, bortezomib, lenalidomide and dexamethasone (IsaBLd) as a comparator to DBLd in their assessment of clinical effectiveness and cost effectiveness of DBLd.

The NICE appraisal of IsaBLd (TA1098) was in progress when the current appraisal of DBLd began (ID3843). IsaBLd had been included as one of the comparator treatments to DBLd in the NICE scope for ID3843 "(subject to NICE evaluation)". However, the company did not include IsaBLd in their submission because a NICE recommendation on IsaBLd had not been made at that time. Subsequently on 24th September 2025 NICE guidance was published recommending IsaBLd as a treatment option for untreated multiple myeloma in adults when an autologous stem cell transplant is unsuitable (TA1098).

In their Addendum the company report the results of an indirect treatment comparison of DBLd versus IsaBLd for survival outcomes (overall survival and progression free survival). The survival estimates inform an update of the company's economic model to provide cost effectiveness estimates for DBLd versus IsaBLd. An updated economic model accompanies the company's Addendum.

Below we recap the methodological approaches to indirect treatment comparison (ITC) used by the company in their submission (Section 2.1) and in response to an EAG clarification question request in July 2025 (Section 2.2). We previously critiqued these analyses in the external assessment group (EAG) report, and we summarise

them here for context. Section 2.3 describes and critiques the NMA and the matched adjusted indirect comparison of DBLd versus IsaBLd in the company's Addendum (October 2025). Readers who do not require the recap may therefore prefer to start reading from Section 2.3 onwards. In section 3 we review and critique the company's updated economic analysis and provide updated company and EAG base case and scenario/ sensitivity analyses. An accompanying confidential addendum reports cost effectiveness estimates based on Patient Access Scheme (PAS) drug discount prices for all treatments, where applicable.

2 Critique of the indirect treatment comparison

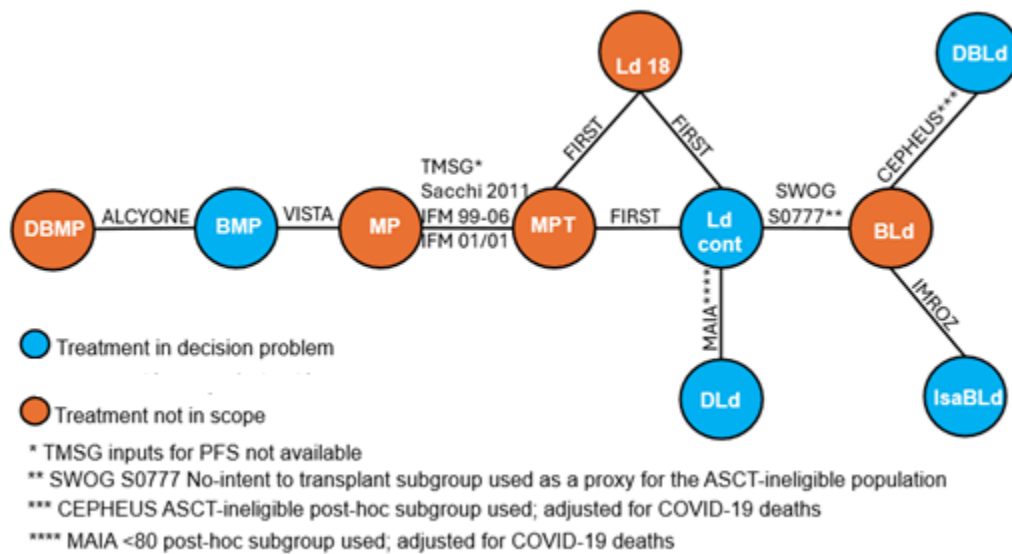
2.1 The company submission (July 2025)

In their submission (July 2025) the company reported two different methods of indirect treatment comparison (ITC).

1. **The inverse probability of treatment weighting method (IPTW).** The primary approach to indirect comparison presented in the CS is the IPTW. This uses individual patient data (IPD) from the DBLd arm of the pivotal CEPHEUS trial¹ and IPD from the relevant arms of key comparator trials (i.e. the DLd arm of the MAIA trial;² the BMP arm of the ALCYONE trial).³ The company chose the IPTW approach because they had access to the IPD for these trials (they were the sponsor of all three trials). The IPTW approach was used for the following decision problem comparisons: DBLd versus DLd; DBLd versus Ld and DBLd versus BMP.

Bayesian network meta-analysis (NMA). The second approach reported in the CS was a Bayesian network meta-analysis of the same indirect comparisons made using the IPTW approach. Eleven randomised controlled trials were included in the NMA to form a fully connected evidence network

(CS Figure 27, adapted and reproduced below as



2. Figure 1). In the CS the relative effect estimates for all possible treatment comparisons are tabulated in a matrix (CS Table 44 and 45), expressed as hazard ratios with 95% credible intervals. The results were adjusted for Covid-19.

Of note, even though IsaBLd was not a comparator in the CS at that time, the pivotal IMROZ trial of IsaBLd is included in the network (Figure 1 below).⁴ However, its inclusion is not strictly necessary as it does connect any other relevant treatments to the network. Therefore, the only reason for it to be included is to enable the comparison of IsaBLd to the other relevant treatments. The EAG assumes that the company included IMROZ in readiness for potentially including IsaBLd as a comparator at later time.

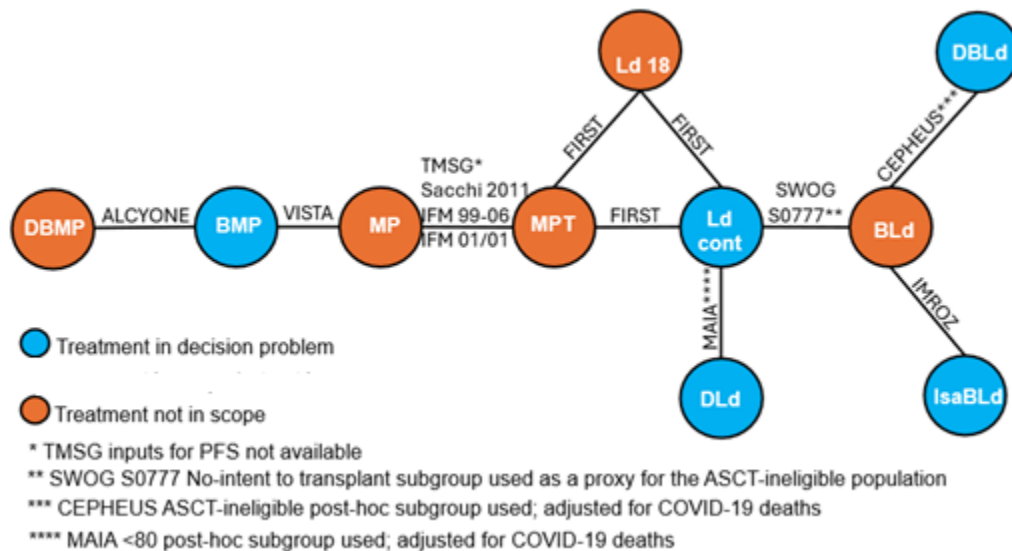


Figure 1 Network diagram of studies included in the NMA

Source: adapted from CS Figure 27.

Abbreviations: BLd, bortezomib, lenalidomide and dexamethasone; BMP, bortezomib, melphalan and prednisone; DBMP, daratumumab, bortezomib, melphalan and prednisone; DLd, daratumumab, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone; Ld18, lenalidomide and dexamethasone 18 months; Ld cont, lenalidomide and dexamethasone continuous; MP, melphalan and prednisone; MPT, melphalan, prednisone and thalidomide.

2.2 Clarification on the company submission (August 2025)

On the expectation that a positive recommendation for IsaBLd was a possibility, the EAG requested the company to include IsaBLd as a comparator (EAG clarification question A11). In their response to EAG clarification questions, the company provided results of a network meta-analysis (NMA) for the comparison of DBLd versus IsaBLd, on overall survival and progression free survival.

2.2.1 Bayesian network meta-analysis (DBLd versus IsaBLd)

The NMA was conducted using the same evidence network and the same statistical modelling methods as presented in the CS for the other comparators (i.e. a Bayesian

NMA model, an evidence network of 11 RCTs, analysis adjusted for Covid-19 deaths, effect estimates for survival outcomes (OS and PFS)).

The results of the NMA (Table 9 and Table 10, company response to clarification questions, August 2025) showed numerical improvements in PFS and OS hazard ratios favouring DBLd, but with wide credible intervals [REDACTED] (and therefore [REDACTED]). The Covid 19 adjusted results showed lower HRs compared to the unadjusted results, indicating greater benefit for DBLd. Further detail on these results is reported in Section **Error! Reference source not found.** below.

The EAG notes that the company report relative effects only for the comparison of DBLd versus IsaBLd. This contrasts with the presentation of the NMA results in the CS (CS Table 44 and 45), whereby the relative effect estimates for all possible treatment comparisons were tabulated. Whilst comparisons between IsaBLd and the other comparator treatments were not within the scope of this appraisal, the EAG nonetheless would have preferred a consistent approach for completeness and for comparison with the results of other NMAs featuring IsaBLd as a treatment (where available).

Importantly, the company's response to clarification question A11 did not include an updated cost effectiveness analysis for DBLd versus IsaBLd due to time constraints. In the EAG report (19th September 2025) we suggested the need for a fully incremental analysis of the cost effectiveness of DBLd, IsaBLd and DLd, noting that the economic model would need to be updated to include input parameters relating to IsaBLd.

2.2.2 Alternative approaches to indirect treatment comparison (DBLd versus IsaBLd)

In their response to clarification question A11, the company explained that they couldn't replicate the IPTW approach for the indirect comparison of IsaBLd versus DBLd because they have no access to the IPD from the pivotal RCT of IsaBLd, the IMROZ trial. The EAG concurs that this would not be possible without access to the IMROZ trial IPD. The consequence is that, with one exception, each comparison in this appraisal (e.g. DBLd versus DLd; DBLd versus Ld and DBLd versus BMP)

benefits from analysis using two different methods of indirect comparison (i.e. IPTW and NMA). In contrast, IsaBLd was (at that time) the only comparator analysed using just a single approach (NMA only). Both IPTW and NMA approaches have advantages and limitations, hence it is useful to compare their respective effect estimates to gauge the degree of consistency and certainty in the findings, and provide the appraisal committee with greater confidence in their decision making.

To address this inequity the EAG suggested an alternative to the IPTW approach for DBLd versus IsaBLd (see Key issue 1a of the EAG report (September 2025)). For example, we proposed a matched adjusted indirect comparison (MAIC), subject to feasibility. A MAIC would use the available IPD from the pivotal DBLd trial (the CEPHEUS trial - specifically the subgroup of patients who were ineligible for stem cell transplant) to be matched with aggregate data for patients receiving IsaBLd from the IMROZ trial (see 2.3.2 below for more detail).

2.3 Company's Addendum to their submission (October 2025)

2.3.1 Bayesian network meta-analysis (DBLd versus IsaBLd)

In their Addendum the company report the same NMA results for the comparison of DBLd versus IsaBLd as previously presented in response to clarification question A11 (see section 2.2.2). The company consider the NMA (unadjusted for Covid-19) to be the base case approach to comparative efficacy versus IsaBLd.

Table 1 and Table below show the relative effect estimates for DBLd (NB. These tables replicate Tables 12 and 13 previously reported in the EAG report, we have included them here for ease of reference). Based on a fixed-effect model, adjusted for Covid-19 mortality, DBLd is statistically significantly more effective than DLd, Ld and BMP as can be seen by the HRs (which range from [REDACTED] for PFS and [REDACTED] for OS) and credible intervals (which are [REDACTED] in each case). When a random-effects model is used the HRs remain the same, but the credible intervals become wider [REDACTED], which is to be expected from random-effects models.

There is a marked difference in results, however, for the comparison of DBLd to IsaBLd. For PFS (Table 1) the fixed-effect HR [REDACTED], adjusted for Covid-19, favours

RE; adjusted for COVID- 19)	██████████ ██	██████████ ██	██████████ ██	██████████
FE; unadjusted for COVID- 19	Not reported	Not reported	Not reported	██████████ (Base case)
RE; unadjusted for COVID- 19	Not reported	Not reported	Not reported	██████████
Source: CS Table 44; Clarification responses A10 and A11. Abbreviations: BMP, bortezomib, melphalan, prednisone; CrI, credible interval; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DLd, daratumumab, lenalidomide, dexamethasone; FE, fixed effect; HR, hazard ratio; Ld, lenalidomide, dexamethasone; PFS, progression free survival; RE, random effects.				

Adjusted versus unadjusted effect estimates (Covid-19 deaths)

The CEPHEUS trial and the IMROZ trial were both affected by Covid-19 related deaths, though the proportion of deaths was greater in CEPHEUS than IMROZ (██████ of all deaths in the DBLd arm of CEPHEUS, versus 11.59% of all deaths in the IsaBLd arm of IMROZ).

The company report both adjusted and unadjusted NMA results, nominating the unadjusted analysis as their base case and the adjusted analysis as scenario analyses. In the adjusted analysis all Covid-19 deaths are censored but only in the CEPHUS trial, for which the company has access to the IPD. The company is unable to censor patients in the IMROZ trial as only aggregate data are publicly available. Censoring Covid-19 deaths in one but not both trials is a potential risk of bias. The EAG concurs with the company's choice of the unadjusted analyses (in which neither trial is censored) for their base case. The company regards the unadjusted analysis as a conservative option due to the disproportionally greater impact of Covid-19 deaths in the CEPHUS trial, resulting in higher HRs compared to the adjusted analyses. Please note that for DBLd versus DLd, Ld and BMP results given (in the CS) are for the Covid-19 adjusted analysis only.

Fixed versus random effects

In their Addendum the company do not fully report details of the NMA model fitting process. For example, the deviance information criterion (DIC) values for each outcome and the resulting selection of models are absent. The EAG assume that the company favours, *a priori*, the fixed effect model, for the same reasons given in the CS for the NMA comparing DBLd versus DLd, Ld and BMP (relating to the sparseness of the network – CS section 2.10.5). For completeness the company's Addendum presents the NMA effect estimates for random effects and fixed effect models. The company notes the high degree of consistency in effect estimates between these models, and therefore choosing between the models is a "minimal source of uncertainty". The EAG agrees that there is consistency in the HRs between random and fixed effect models, but we note inconsistency in the width of the credible intervals (wider in random effects, as we mention above). We would have preferred to have seen the model fitting values for each outcome and a clear statement on which model was selected.

2.3.2 Matched adjusted indirect comparison (MAIC)

The second approach to the indirect comparison of DBLd vs IsaBLd in the company's Addendum is a MAIC. The company's rationale for this approach is to explore the impact of heterogeneity between the CEPHEUS and IMROZ trials on the comparative efficacy results. The company acknowledges the possibility of heterogeneity between the two trials impacting the NMA results even though the fixed-effect analysis used in their base case assumes no significant heterogeneity. The company regard the "supportive" MAIC as being the next best approach to indirect comparison following the NMA, citing methodological guidance in NICE Decision Support Unit (DSU) Technical Support Document 18. 'Methods for population-adjusted indirect comparisons'.⁵ The EAG agrees with the company's justification for using the MAIC approach in this instance.

As seen in Figure 1 earlier, the CEPHEUS and IMROZ trials have a common comparator arm (bortezomib, lenalidomide and dexamethasone, BLD) which links the DBLd arm of CEPHEUS with the IsaBLd arm of IMROZ, thus allowing an anchored MAIC. An anchored MAIC has the benefit of preserving the effects of randomisation within each trial, which reduces the risk of bias from confounders.

Comparison of the patient baseline characteristics of the two trials showed that there was a “high level of agreement” between the two trial populations (Table 3, company Addendum). This is evidenced by baseline characteristics falling within a standardised mean difference (SMD) threshold ± 0.2 in all cases, except for cytogenic risk (unknown/missing) where the SMD was slightly in excess of the threshold (SMD = 0.23) and race (White) (SMD = 0.203).

Regarding the selection of baseline covariates for the MAIC, the company state this is “aligned” to the selection process they used in their IPTW ITC (CS section 2.10.2). In the EAG report we commented that the covariates used in the IPTW ITC were identified from what appears *in general* to be a comprehensive process (e.g. literature reviews, previous population-adjusted indirect comparisons; regression analyses, discussion with clinical experts). The caveat to this is we could not independently appraise the individual components of the process as little information had been given on these (except for details of the company’s discussion with clinical experts). Reassuringly, expert clinical guidance to the EAG confirmed that no potential prognostic factors/effect modifiers are missing from the company’s list.

Table 4 of the company’s Addendum lists the 9 covariates adjusted for in the MAIC base model and an additional two included in the full model (sensitivity analysis), bringing the total of covariates to 11. The reason why the two additional two covariates (race and median duration since initial multiple myeloma diagnosis) were not included in the base model is not reported. The EAG cross-referenced the list of MAIC covariates to the list of the IPTW covariates (CS Table 29) (the latter including a total of 14 covariates of which 11 were prioritised). We observe general consistency between MAIC and the IPTW in terms of selected covariates, except for three covariates from the IPTW which are not mentioned in the MAIC (LDH, calcium levels and anaemia). The EAG considers the selection of covariates for the MAIC to be reasonable based on the company’s assertion that it is aligned to the covariate selection process used in the IPTW ITC. However, further detail specific to the selection of the MAIC covariates would have been useful.

Beyond the establishment of the covariates, the Addendum gives very limited detail on the other statistical characteristics of the MAIC. Notably, there is no comparison of patient characteristics (including the covariates) before and after matching, and

hence whether there were any imbalances which could cause confounding. Furthermore, the number of patients before and after matching (the effective sample size), is not stated, thus the degree of lost data is unknown.

The results of the MAIC for the comparison of DBLd versus IsaBLd are reported below in Table 3 for the base case MAIC, the sensitivity analysis MAIC and for an unadjusted analysis (NB. it is not clear in the Addendum what ‘unadjusted’ specifically refers to, but we note that Covid-19 mortality was “not adjusted for as part of the matching process”). Reassuringly the EAG observes that these results are broadly consistent with the results of the NMA, albeit with the MAIC estimating slightly higher HRs, which the company regard as being conservative. In common with the NMA, the credible intervals [REDACTED], indicating no statistically significant difference between the treatments.

Table 3 Summary of MAIC results for DBLd versus IsaBLd

Analysis	PFS, HR (95% CI)	OS, HR (95% CI)
Unadjusted	[REDACTED]	[REDACTED]
Base case MAIC	[REDACTED]	[REDACTED]
Sensitivity analysis MAIC	[REDACTED]	[REDACTED]

Source: Table 5, Company Addendum (October 2025)
Abbreviations: BMP, bortezomib, melphalan, prednisone; CrI, credible interval; DBLd, daratumumab, bortezomib, lenalidomide, dexamethasone; DLd, daratumumab, lenalidomide, dexamethasone; FE, fixed effect; HR, hazard ratio; Ld, lenalidomide, dexamethasone; PFS, progression free survival; RE, random effects.

However, we urge caution in the interpretation of these results. Without further information on its statistical properties the EAG is unable to fully critically appraise the MAIC. We therefore regard the results of the MAIC as uncertain.

2.4 Conclusions on clinical effectiveness

The company have indirectly compared the efficacy of DBLd with IsaBLd via NMA and via a “supportive” MAIC. Thus, an alternative set of effect estimates is now available for each comparison in the NICE scope.

The NMA represents the company’s base case estimate of survival outcomes as regards the comparison between DBLd with IsaBLd. The EAG concurs with this

choice. Despite some limitations (e.g. a sparse network, use of subgroups) the NMA is of a reasonable standard. The NMA shows a statistically significant difference favouring DBLd when compared to DLd, Ld and BMP in terms of survival and disease progression. However, the difference between DBLd versus IsaBLd is more modest and not statistically significant. The width of the credible intervals indicates uncertainty in for this comparison. As

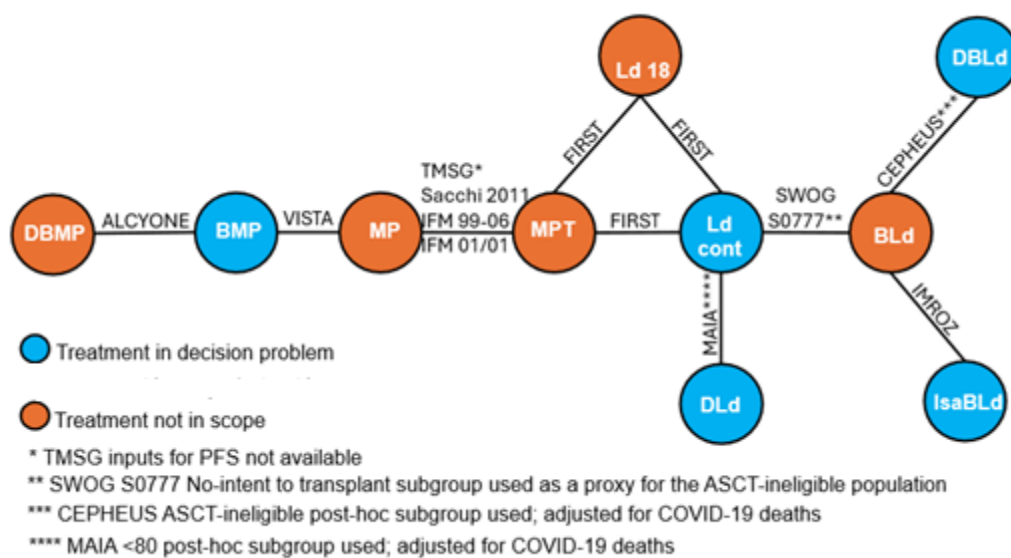


Figure 1 shows, DBLd is compared to IsaBLd via a common comparator (BLd), independently from the other treatments in the network. In effect it is more appropriate to refer to this analysis as a pairwise adjusted indirect comparison.

The company's MAIC, comparing DBLd to IsaBLd, shows some consistency with the NMA in the relative treatment effect estimates. This suggests robustness in the estimates based on the NMA. However, we urge caution in the interpretation of the results of the MAIC as limited details on its methodology prevent us from fully appraising its methodological soundness.

3 Cost effectiveness

3.1 Company's revised base case

The company provided a revised model dated 21-10-2025, which includes:

- Data for two new adverse events (peripheral sensory neuropathy and syncope) that were considered for DBLd and DLd, based on the adverse events included for IsaBLd analysis
- A change to the calibration methodology for OS to ensure that the hazard of death could not fall below general population mortality (GPM), as occurred in the EAG base case

The company describes the revisions to the model in the Addendum to the CS Appendix B.

The EAG agrees that the OS hazard of death should not fall below the GPM. We note that the company have applied a modifier to the 'Required multiplier on hazard by third time point' in the DBLd trace, which prevents the attenuated OS extrapolation from exceeding the unattenuated OS extrapolation with the GPM cap applied. A similar modification is not applied in the DLd trace, because the attenuated OS extrapolation never exceeds the unattenuated OS extrapolation with the GPM cap applied in the DLd arm. The IsaBLd attenuated OS extrapolation is governed by the DBLd OS HR, so a similar OS modification is not needed.

The EAG successfully validated the revised model (dated 21-10-2025) by applying the updates to the 21-08-2025 version of the model (Table 4). The revisions to the model impacted both the company's and EAG's base case for DBLd versus DLd, because the model now includes costs and disutilities for two additional adverse events as well as the change to the OS calibration methodology.

The change to the company's base case was negligible as shown in Table 5 and Table 6. The Addendum to the CS Appendix B provides the updated results of the EAG's base case and EAG's scenario analyses for DBLd versus DLd. We reproduce the EAG's results, and results for the company's analyses for DBLd versus DLd, using the revised model (dated 21-10-2025), in a confidential addendum applying all appropriate PAS discounts and Medicines Procurement and Supply Chain (MPSC) costs.

Table 4 Validation of revised company model (21-10-2025), EAG base case, DBLd vs DLd

Description of change	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
EAG base case (21-08-2025 model)	■	■	£14,903
Add cost and utility data for the two new adverse events (peripheral sensory neuropathy and syncope)	■	■	£15,148
Add change to the OS calibration methodology	■	■	£11,695
EAG base case results, Addendum to the CS Appendix B, Table 20	■	■	£11,697
Source: EAG created table Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; OS, overall survival; QALY, quality-adjusted life-year			

Table 5 Company base case results (DBLd vs DLd), original company model (dated 21-08-2025)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
DBLd	■	■			
DLd	■	■	■	■	Dominant
Source: Company model (dated 21-08-2025) Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life-year					

Table 6 Company base case results (DBLd vs DLd), revised company model (dated 21-10-2025)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
DBLd	■	■			
DLd	■	■	■	■	Dominant
Source: Company model (21-10-2025) Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life-year					

3.1.1 Utility values

The EAG agrees with the company's approach of assuming that the utilities for each health state are the same regardless of treatment (i.e. treatment-independent utilities). The Addendum to the CS Table 7 shows the disutilities and duration associated with the two additional adverse events (peripheral sensory neuropathy and syncope) now included in the model.

3.1.2 Proportional hazards assessment: IsaBLd scenario

The company describes their approach to assessing proportional hazards (PH) in Addendum to the CS section 3.2. Briefly, the PH assumption was tested separately for both the transplant-ineligible population in CEPHEUS (DBLd vs BLd) and in IMROZ (IsaBLd vs BLd) using Schoenfeld plots and loglog plots (figures shown in Addendum to the CS Appendix A).

The EAG notes that the Schoenfeld plots suggest that PH holds for both OS and PFS, but that the loglog plots cross for PFS in CEPHEUS (Addendum to the CS Appendix A Figure 6) and OS for IsaBLd vs BLd (Addendum to the CS Appendix A Figure 13). However, we agree with the company that the majority of the evidence supports that PH holds.

The HRs (unadjusted for COVID-19) from the NMA (PFS HR: ■■■; OS HR: ■■■) were used to generate PFS and OS curves for IsaBLd. The company test using HRs adjusted for COVID-19 in CEPHEUS, and HRs from the MAIC in scenario analyses (Addendum to the CS Table 19). The Addendum to the CS Figure 3 presents the PFS, OS and TTD curves for DBLd and IsaBLd.

3.1.3 Adverse events

The company's model considers adverse events, grade 3 or 4 with an incidence of $\geq 5\%$ for any treatment. Data for IsaBLd were taken from the IMROZ trial and included two extra adverse events to those included in the main CS (Table 7). These adverse events were included in the economic analysis for DBLd versus IsaBLd.

Table 7 Additional adverse events considered in the DBLd vs IsaBLd analyses

Adverse event	DBLd	DLd	IsaBLd
Peripheral sensory neuropathy	■	■	7.22%
Syncope	■	■	5.70%
Source: Adapted from Addendum to the CS Table 6 Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone			

3.1.4 Costs

3.1.4.1 Drug acquisition costs

The dosing regimen and drug acquisition costs for IsaBLd are given in the Addendum to the CS Table 8 and Table 9. The company's base case uses data from the IMROZ trial to inform the relative dosing intensity (RDI) for the components of IsaBLd (as reported in TA1098). The company conducted a scenario analysis setting the RDI for the bortezomib, lenalidomide and dexamethasone components of IsaBLd equal to the equivalent constituents of the DBLd regimen (Addendum to the CS Table 19).

3.1.4.2 Subsequent treatments

The company calculates the proportion of patients receiving subsequent treatment following IsaBLd from the IMROZ trial, using the same methodology as for DBLd and DLd (CS section 3.5.1). In IMROZ, of the 50 patients who experienced disease progression, 36 (72%) received a subsequent treatment. Table 8 presents the proportions of patients receiving subsequent treatment, by treatment line, in the company's base case. The company conducted a scenario setting the proportion receiving treatment second line to 75% for both IsaBLd and DBLd (Addendum to the CS Table 19). The EAG prefers to use this assumption in our base case (section 3.3.1).

The company's base case assumes that patients receive the same distribution of subsequent treatments following either DBLd or IsaBLd. The EAG considers this to be a reasonable assumption, given that the two treatments have three constituents in common.

Table 8 Proportion of patients progressing to a further line of subsequent treatment having received a previous line of treatment, company base case

First-line treatment	Second-line	Third-line	Fourth-line
DBLd		62.30%	39.47%
DLd	81.25%	62.30%	39.47%
IsaBLd	72.00%	62.30%	39.47%
Source: Company model (dated 21-10-2025) Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone			

3.1.4.3 Concomitant medications

Patients receiving IsaBLd in the company's model receive an antipyretic, antihistamine and an H2 antagonist as concomitant medications.

Table 9 presents the total concomitant medications cost, per model cycle (i.e. every 4 weeks) for each treatment.

Table 9 Total concomitant medications cost, company base case

Treatment	Cost per cycle
Daratumumab	£1.47
Bortezomib (DBLd)	£0.15
Bortezomib (IsaBLd)	£0.15
Isatuximab (IsaBLd)	£0.81
Source: Company model (dated 21-10-2025) Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone	

3.1.4.4 Adverse events

The costs associated with treating the additional adverse events (peripheral sensory neuropathy and syncope) are shown in Addendum to the CS Table 14. Table 10 presents the one-off costs and disutility associated with treating adverse events for each treatment.

Table 10 One-off costs and utility decrement associated with adverse events, company model

Treatment	Costs	Utility Decrement

DBLd	£4,301	-0.026
DLd	£4,477	-0.032
IsaBLd	£5,561	-0.035
Source: Company model (dated 21-10-2025) Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone		

Addendum to the CS Table 6 summarises the proportions of patients experiencing each adverse event for DBLd and IsaBLd. The EAG notes that markedly more patients receiving IsaBLd experienced lymphopenia and leukopenia (both with an associated cost of £2,058) than those receiving DBLd, potentially accounting for the majority of the higher total costs associated with adverse events.

3.2 Company revised base case results

Table 11 and Table 12 present the results of the company's deterministic and probabilistic base case. Table 13 shows the fully incremental analysis between DBLd, DLd and IsaBLd. DBLd dominates both IsaBLd and DLd, i.e. it is cheaper and more effective.

Table 11 Deterministic base-case results, company base case

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	INHB at £20,000	INHB at £30,000
DBLd							
IsaBLd					Dominant		
Source: partially reproduced from Addendum to the CS Table 15 Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; INHB, incr. net health benefit; QALY, quality-adjusted life-year							

Table 12 Probabilistic base-case results, company base case

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
DBLd					
IsaBLd					Dominant
Source: partially reproduced from Addendum to the CS Table 16 Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; INHB, incr. net health benefit; QALY, quality-adjusted life-year					

Table 13 Fully incremental analysis results of the analysis between DBLd, DLd and IsaBLd

Intervention	Total costs	Total QALYs	Dominated?	Fully incremental ICER
DBLd	██████	██████		
DLd	██████	██████	██████	Dominated
IsaBLd	██████	██████	██████	Dominated
Source: partially reproduced from Addendum to the CS Table 17 Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; INHB, incr. net health benefit; QALY, quality-adjusted life-year				

3.2.1 Company's sensitivity and scenario analyses

Addendum to the CS Figure 4 presents the Tornado plot of the company's deterministic sensitivity analysis (DSA). Addendum to the CS Table 18 describes the summary of the company scenario analyses and Table 19 presents the results of these analyses, for DBLd versus IsaBLd. We reproduce these results in a confidential addendum, applying all appropriate PAS discounts and MPSC costs.

The Addendum to the CS states that *"the HRs for OS and PFS between DBLd and IsaBLd were excluded from the PSA, on the basis that the capping of IsaBLd OS and TTD by GPM and DLd led to capping overriding the variation and to clinically implausible iterations. Additionally, as correlated parameters, allowing PFS and OS to be varied without correlation in the PSA could result in clinically implausible iterations."* (Addendum to the CS Table 16 footnote).

Although not explicitly explained, the EAG assumes that the HRs for OS and PFS were excluded from the PSA, because using the upper 95% credible interval (CrI) of the PFS HR and the lower 95% CrI of the OS HR gives clinically implausible results, for example. We note that the upper and lower 95% CrI s for the HRs for both OS and PFS for DBLd vs IsaBLd were tested individually in the DSA (Addendum to the CS, Figure 4, Tornado plot) and we explore the effect of using the upper and lower 95% CrIs for the OS and PFS HRs in our scenario analyses (section 3.3.2).

3.3 EAG's additional analyses

3.3.1 EAG's preferred assumptions

We disagree with some key aspects of the company base case. As per the EAG report, our preferred model assumptions are the following:

- Mean age of patients is 75 years, and the proportion of males is 55%
- 75% of patients receiving DBLd and IsaBLd first-line go on to receive subsequent treatment second-line
- EAG-preferred subsequent treatment resource use:
 - DBLd and IsaBLd 3L: 10% patients receive SBd; other 3L subsequent treatments adjusted by Dirichlet calculation (PBd = 26.86%, cyclophosphamide = 62.67%)

The Addendum to the CS Table 19 shows the effect of each individual change on the company's base case. Table 14 presents the cumulative effect of the EAG's preferences. When using the EAG's preferred assumptions, DBLd dominates IsaBLd i.e. it is cheaper and more effective. Table 15 shows the fully incremental analysis between DBLd, IsaBLd and DLd.

Table 14 Cumulative results using EAG's preferred model assumptions

Preferred assumption	Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	Cumulative ICER £/QALY
Company revised base case	DBLd	████████	████	████████	████	Dominant
	IsaBLd	████████	████			
+ Mean age of patients: 75 years; proportion of males: 55%	DBLd	████████	████	████████	████	Dominant
	IsaBLd	████████	████			
+ 75% of patients receiving DBLd and IsaBLd 1L go on to receive subsq Tx 2L	DBLd	████████	████	████████	████	Dominant
	IsaBLd	████████	████			
+ EAG-preferred subsq Tx resource use	DBLd	████████	████	████████	████	Dominant
	IsaBLd	████████	████			
EAG's base case	DBLd	████████	████	████████	████	Dominant
	DLd	████████	████			
Source: EAG created table						
Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; INHB, incr. net health benefit; QALY, quality-adjusted life-year						

Table 15 Fully incremental analysis results of the analysis between DBLd, DLd and IsaBLd, EAG base case

Treatment	Total costs	Total QALYs	Incr. costs (£)	Incr. QALYs	Fully incremental ICER (£/QALY)
DLd	██████	██████			-
DBLd	██████	██████	██████	██████	£11,697
IsaBLd	██████	██████	██████	██████	DBLd dominates IsaBLd
Source: partially reproduced from Addendum to the CS Table 17					
Abbreviations: DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; INHB, incr. net health benefit; QALY, quality-adjusted life-year					

3.3.2 Scenario analyses using EAG's preferred assumptions

We performed a range of scenario analyses using the EAG base case to explore the impact of changing some model assumptions on the final cost-effectiveness results (Table 16).

Table 16 EAG's scenario analyses using EAG's preferred assumptions

No	Scenario	Incr. costs (£)	Incr QALYs	ICER (£/QALY)
	EAG base case	██████	████	Dominant
1	Mean age of patients: █████ years; proportion of males: █████	██████	████	Dominant
2	██████ of patients receiving DBLd 1L go on to receive subsq Tx 2L; 72% of patients receiving IsaBLd 1L go on to receive subsq Tx 2L	██████	████	Dominant
3	Company-preferred subsq Tx resource use: DBLd and IsaBLd 3L: 41.18% receive SBd, 17.65% receive PBd, 41.18% receive cyclophosphamide	██████	████	Dominant
4	IsaBLd efficacy: MAIC OS and PFS HRs	██████	████	Dominant
5	Equivalent efficacy (i.e. OS and PFS HR = 1) between IsaBLd and DBLd	██████	████	Dominant
6	Use lower 95% CI for OS (██████) and PFS (██████) HR; fixed effects model	██████	████	£369,798
7	Use upper 95% CI for OS (██████) and PFS (██████) HR; fixed effects model	██████	████	Dominant
Source: EAG created table Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; CI, credible interval; DBLd, daratumumab, bortezomib, lenalidomide and dexamethasone; HR, hazard ratio; IsaBLd, isatuximab, bortezomib, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; INHB, incr. net health benefit; MAIC, matching-adjusted indirect comparison; OS, overall survival; PBd, pabinosat, bortezomib, dexamethasone; PFS, progression-free survival; QALY, quality-adjusted life-year; SBd, selinexor, bortezomib and dexamethasone; subsq Tx, subsequent treatment				

3.3.3 EAG sensitivity analyses

We present results for our deterministic sensitivity analysis and probabilistic sensitivity analysis in a confidential addendum, applying all appropriate PAS discounts and MPSC costs.

3.4 Conclusions of the cost-effectiveness section

The company updated their model to include adverse events relevant to IsaBLd and to correct the OS calibration methodology to prevent the calibrated curves from having a hazard of death lower than the mortality of the general population. The EAG successfully validated the revised model, and we consider that the company's change to the OS calibration methodology has been applied appropriately.

The company presented results comparing DBLd with IsaBLd using their revised model. We disagreed with some aspects of the model (discussed in section 3.3.1). However, in both the company and EAG base case DBLd dominates IsaBLd i.e. it is cheaper and more effective.

4 References

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