

Single Technology Appraisal

**Daratumumab with bortezomib,
lenalidomide and dexamethasone for
untreated multiple myeloma when an
autologous stem cell transplant is
suitable [ID6249]**

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

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](#)
 - a. [Clarification Responses](#)
 - b. [Addendum](#)
4. [Patient group, professional group and NHS organisation submissions](#) from:
 - a. [Myeloma UK](#)
5. [Expert personal perspectives](#) from:
 - [Mrs Sophie Tinley, patient expert nominated Myeloma UK](#)
6. [External Assessment Report](#) prepared by KSR
7. [External Assessment Report – factual accuracy check](#)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

Company evidence submission

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Company evidence submission for daratumumab in combination with bortezomib, lenalidomide and dexamethasone for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

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Abbreviations

Acronym	Definition
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike information criterion
ALL	Acute Lymphoblastic Leukaemia
ASCT	Autologous Stem Cell Transplantation
ATC	Average Treatment Effect for the Control
ATE	Average Treatment Effect
ATT	Average Effect of the Treatment
BCd	Bortezomib, Cyclophosphamide, Dexamethasone
Bd	Bortezomib, Dexamethasone
BeBd	Belantamab mafodotin, Bortezomib, Dexamethasone
BePd	Belantamab mafodotin, Pomalidomide, Dexamethasone
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body Surface Area
BTd	Bortezomib, Thalidomide, Dexamethasone
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module
EQ-5D-5L	European Quality of Life Five Dimension Five Level Questionnaire
CAA	Commercial Access Agreement
Cad	Carfilzomib, Dexamethasone
CaLd	Carfilzomib, Lenalidomide, Dexamethasone
CD38	Cluster of Differentiation 38 antigen (target in multiple myeloma)
CDC	Complement-Dependent Cytotoxicity
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CR	Complete Response
CRAB	Calcium, Renal, Anaemia, Bone
CRUK	Cancer Research UK
G-CSF	Granulocyte-Colony Stimulating Factor
CSR	Clinical Study Report
CTd	Cyclophosphamide, Thalidomide, Dexamethasone
CXDY	Cycle X Day Y
D	Daratumumab

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Acronym	Definition
DBd	Daratumumab, Bortezomib, Dexamethasone
DBLd	Daratumumab, Bortezomib, Lenalidomide, Dexamethasone
DBTd	Daratumumab, Bortezomib, Thalidomide, Dexamethasone
DCO	Data Cut-Off
DL	Dexamethasone, Lenalidomide
DLBd	Daratumumab, Lenalidomide, Bortezomib, Dexamethasone
DOR	Duration of Response
DSA	Deterministic Sensitivity Analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
Elran	Elranatamab
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EMN	European Myeloma Network
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
ESS	Effective Sample Size
FDA	Food and Drug Administration
FISH	Fluorescence in situ Hybridisation
FLC	Free Light Chains
GCP	Good Clinical Practice
GPM	Generalised Population Mortality
HDT	High-Dose Therapy
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSUV	Health State Utility Value
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IgG1κ	Human Immunoglobulin G1 Kappa
ILd	Ixazomib, Lenalidomide, Dexamethasone
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
INHB	Incremental Net Health Benefit
IPD	Individual Patient Data
IPTW	Inverse Probability of Treatment Weighting
IQR	Interquartile Range
IsaPd	Isatuximab, Pomalidomide, Dexamethasone

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Acronym	Definition
ISS	International Staging System
ITC	Indirect Treatment Comparison
ITT	Intent-To-Treat
IV	Intravenous
IWMG	International Myeloma Working Group
IWRS	Interactive Web Response System
KM	Kaplan-Meier
L	Lenalidomide
Ld	Lenalidomide, dexamethasone
LDH	Lactate Dehydrogenase
LS	Least Squared
LT	Liver Transplant
LYG	Life Year Gained
mAb	Monoclonal Antibody
MGUS	Monoclonal Gammopathy of Undetermined Significance
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple Myeloma
MRD	Minimal Residual Disease
MyPOS	Myeloma Patient Outcomes Scale
N	No
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NDMM	Newly Diagnosed Multiple Myeloma
NE	Not Evaluable
NGS	Next-Generation Sequencing
NHS	National Health Service
NI	No Information
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NCRAS	NHS Digital National Cancer Registration and Analysis Service
ONS	Office for National Statistics
OR	Overall Response Rate
OS	Overall Survival
PanBd	Panobinostat, Bortezomib, Dexamethasone
PAS	Patient Access Scheme
Pd	Pomalidomide, Dexamethasone
PD	Progressive Disease
PF	Progression-Free
PFS	Progression-Free Survival
PFS2	Second Progression-Free Survival (or sequential)

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Acronym	Definition
PH	Proportional hazard
PI	Proteasome Inhibitor
PK	Pharmacokinetics
PR	Partial Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-Reported Outcome
PS	Performance Status
PSA	Probabilistic Sensitivity Analysis
PSM	Propensity Score Matching
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q25	Lower quartile
Q2W	Every 2 Weeks
Q75	Upper quartile
QALY	Quality-Adjusted Life Year
QD	Once Daily
RCT	Randomised Controlled Trial
RDI	Relative Dose Intensity
RoB	Risk of Bias
RRMM	Relapsed/Refractory Multiple Myeloma
SBd	Selinexor, Bortezomib, Dexamethasone
SC	Subcutaneous
sCR	Stringent Complete Response
Sd	Selinexor, Dexamethasone
SD	Standard Deviation
SE	Standard Error
SFLC	Serum Free Light Chains
SLiM	60% clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of 100 or more with the involved serum free light chain being ≥ 100 mg/L, and Magnetic Resonance Imaging with more than one focal marrow lesion
SLR	Systematic Literature Review
SMD	Standardised Mean Difference
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SPEP	Serum Protein Electrophoresis
TA	Technology Appraisal
Tal	Talquetamab
TEAE	Treatment-Emergent Adverse Event
Tec	Teclistamab
TEM	Treatment Effect Modifier
TFI	Treatment-Free Interval

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Acronym	Definition
TSD	Technical Support Document
TTD	Time To Discontinuation
TTDD	Time To Disease Progression or Discontinuation
UK	United Kingdom
ULN	Upper Limit of Normal
UPEP	Urine Protein Electrophoresis
US	United States
VAS	Visual Analogue Scale
VAT	Value-Added Tax
VGPR	Very Good Partial Response
WTP	Willingness To Pay
Y	Yes

Company evidence submission for daratumumab in combination with bortezomib, lenalidomide and dexamethasone for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

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

1.1 *Decision problem*

This submission covers the full marketing authorisation for the technology in this indication: daratumumab in combination with bortezomib, lenalidomide and dexamethasone (DBLd) for the treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplant (ASCT).¹

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. Any differences between the decision problem addressed within this submission and the NICE final scope are 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	Adult patients with NDMM who are eligible for high-dose therapy- (HDT-) ASCT		N/A
Intervention	DBLd for induction and consolidation treatment followed by DL for maintenance treatment		In line with the NICE final scope for induction and consolidation (DBLd) and maintenance (daratumumab and lenalidomide [DL])
Comparator(s)	Induction and consolidation therapy • Daratumumab with bortezomib, thalidomide and dexamethasone (DBTd) • Bortezomib with thalidomide and dexamethasone (BTd) • Bortezomib, cyclophosphamide and dexamethasone (BCd) (off-label) • Bortezomib and dexamethasone (Bd) Maintenance therapy • Lenalidomide	Induction and consolidation therapy • DBTd Maintenance therapy • Lenalidomide	DBTd is considered the only relevant comparator for DBLd induction and consolidation therapy for patients with NDMM who are eligible for ASCT, and is recommended by NICE for this indication (TA763).² During the DBTd appraisal, the Committee's preferred assumption was that BTd was the most relevant comparator to DBTd from the comparators listed in the NICE scope, which also included CTd, Bd and BCd.² Given that TA763 subsequently demonstrated that DBTd is associated with significant survival benefits over BTd, DBTd is now the predominantly used treatment option in this setting.² The predominance of DBTd is supported by <u>new patient initiation data received from NHS England, which confirmed 1,587 new DBTd patient initiations for the 12-month period June 2024 to May 2025 (equivalent to 98.9% assuming an available pool [REDACTED])</u> (refer to Budget Impact Analysis for further details of patient pool estimate).³ In line with this, feedback from UK clinical experts at a May 2025 Advisory Board indicated that DBTd represents standard of care for HDT-ASCT eligible patients with NDMM in UK clinical practice, received by approximately 95–98% of patients.⁴ Consequently, BTd, BCd and Bd induction and consolidation therapies are not relevant comparators in this indication. With regards to maintenance treatment, feedback from UK clinical experts indicated that 95% of patients in UK clinical practice receive lenalidomide as maintenance therapy, which is recommended by NICE for this indication (TA680).⁵

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			As such, DBTd is considered to be the only relevant comparator to DBLd as an induction and consolidation treatment in this indication. Furthermore, lenalidomide is considered to be the only relevant comparator to DL as a maintenance treatment for this submission.
Outcomes	• Progression-free survival (PFS) • Overall survival (OS) • Response rates • Minimal residual disease (MRD) negativity status • Proportion of patients undergoing HDT-ASCT • Health-related quality of life (HRQoL) • Adverse events (AEs)		In line with the final scope.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	• The economic analysis aligns with that described in the NICE decision problem	N/A – A cost-effectiveness model has been conducted in line with the NICE reference case.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	- Costs will be considered from a National Health Service (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 availability and cost of biosimilar and generic products should be taken into account		

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; Bd: bortezomib and dexamethasone; BTd: bortezomib with thalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab and lenalidomide; HDT: high-dose therapy; HRQoL: health-related quality of life; MM: multiple myeloma; MRD: minimal residual disease; 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-DL, is presented in Table 2.

The summary of product characteristics (SmPC) and European public assessment report (EPAR) for DBLd in the indication of relevance to this submission are provided in the reference pack accompanying this submission (see Appendix A).^{1, 6}

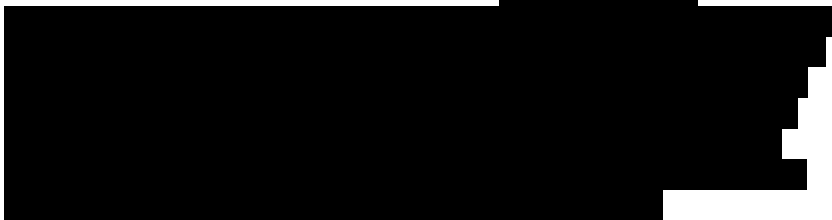
Table 2: Technology being evaluated

UK approved name and brand name	• Induction and consolidation: Daratumumab (Darzalex®) in combination with bortezomib, lenalidomide and dexamethasone • Maintenance: Daratumumab in combination with lenalidomide
Mechanism of action	Daratumumab Daratumumab is a first-in-class, fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds to cluster of differentiation 38 (CD38). CD38 is a cell surface glycoprotein found on the surface of many immune cells, including white blood cells, and overexpressed on the surface of MM cells.^{7, 8} 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.⁹ 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 myeloma cell apoptosis.^{9, 10} Figure 1: Mechanism of action of daratumumab Abbreviations: ADCC: antibody-dependent cell-mediated cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; CDC: complement-dependent cytotoxicity. Source: NICE TA763.² Daratumumab in combination with lenalidomide When compared with lenalidomide alone, daratumumab and lenalidomide act synergistically to enhance their anti-tumour effects.

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	Indeed, a mixed-model analysis revealed that daratumumab and lenalidomide induce lysis in 20% more MM cells than when compared with the expected additive effects of each agent alone. This synergistic effect can be attributed to the unique mechanisms of action of daratumumab and lenalidomide, as well as the potential for lenalidomide to enhance the daratumumab-mediated antibody-dependent cell-mediated cytotoxicity. ^{11, 12}
Marketing authorisation/CE mark status	UK marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) was granted for daratumumab (in combination with lenalidomide, bortezomib and dexamethasone) in the indication of relevance to this submission in November 2024 via the International Recognition Procedure route. ¹
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The licensed indication for daratumumab of relevance to this submission is; “<i>in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with NDMM who are eligible for ASCT.</i>”^{a,1} Other licensed indications for daratumumab in MM are:¹ • In combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with NDMM who are ineligible for ASCT transplant.¹ • In combination with bortezomib, thalidomide and dexamethasone (DBTd) for the treatment of adult patients with NDMM who are eligible for ASCT.¹ • In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy.¹ • In combination with pomalidomide and dexamethasone for the treatment of adult patients with MM who have received one prior therapy containing a proteasome inhibitor (PI) and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a PI and have demonstrated disease progression on or after the last therapy [daratumumab subcutaneous (SC) formulation only].¹ • As monotherapy for the treatment of adult patients with relapsed and refractory MM, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent (IMiD) and who have demonstrated disease progression on the last therapy.¹ Licensed indications for daratumumab in light chain amyloidosis are: • In combination with bortezomib, cyclophosphamide and dexamethasone (DBCd) for the treatment of adult patients with newly diagnosed systemic light chain amyloidosis [daratumumab SC formulation only].¹
Method of administration and dosage	• Daratumumab 1,800 mg solution for subcutaneous (SC) injection is available as a fixed dose with each 15 mL vial containing 120 mg daratumumab per mL.¹ • Induction: Daratumumab is administered once weekly for the first two Cycles (Weeks 1–8), followed by every two weeks for Cycles 3 and 4 (Weeks 9–16). • Stop for HDT and ASCT. • Consolidation: Daratumumab is administered every two weeks from Weeks 17–24. • Maintenance: Daratumumab is administered every four weeks from Week 25 onwards, until disease progression.^b

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	• 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.¹ • Detailed dosing information is provided in the SmPC.¹
Additional tests or investigations	A one-off blood sample to type and screen patients' serum is required prior to starting daratumumab. ¹³
List price and average cost of a course of treatment	• List price 1,800 mg (fixed-dose vial) = £4,320.00 (excl. VAT.).¹⁴
Patient access scheme/commercial arrangement (if applicable)	There is a commercial access agreement (CAA) in place for daratumumab. This makes daratumumab 

Footnotes: ^a In the SmPC, the dosing regimen for DBLd in HDT-ASCT eligible patients with NDMM includes DL maintenance and, as such, is licensed for the indication of relevance to this submission.¹ ^b Daratumumab can be discontinued for patients who have achieved MRD negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months.

Abbreviations: ASCT: autologous stem cell transplant; CD38: cluster of differentiation-38; CHMP: Committee for Medicinal Products for Human Use; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DLBd: daratumumab, bortezomib, lenalidomide and dexamethasone; EMA: European Medicines Agency; HDT: high dose therapy; IgG1κ: human immunoglobulin G1 kappa; IMiD: immunomodulatory agent; IMWG: International Myeloma Working Group; IV: intravenous; mAb: monoclonal antibody; MHRA: Medicines and Healthcare Products Regulatory Agency; MM: multiple myeloma; PI: proteasome inhibitor; 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 economic burden

- Multiple myeloma (MM) is a predominantly incurable, highly heterogeneous haematological cancer. Although a rare disease, the incidence rates of MM have risen in recent years and are expected to continue increasing.
- A high symptom burden exists in patients with MM, with fatigue, pain, tiredness and poor mobility reported by patients as the most prevalent issues.^{15, 16}
- All newly diagnosed patients eventually become refractory to therapy over time. With each relapse, prognosis worsens as it becomes more difficult to induce deep and durable responses to treatment.¹⁷⁻²² It is therefore crucial that the most effective treatments are used in the front-line setting, as patients may not survive or be fit enough to receive treatment at later lines.²³

An unmet need exists in patients with HDT-ASCT eligible NDMM for a more tolerable treatment option that achieves deeper, more durable responses

- In UK clinical practice, patients with newly diagnosed MM (NDMM) are initially assessed for suitability for high dose therapy (HDT) and autologous stem cell transplantation (ASCT). Eligibility for HDT-ASCT informs first-line treatment choice.²⁴
- For patients who are eligible to receive ASCT (estimated to be around one third of MM patients), daratumumab, in combination with bortezomib, thalidomide and dexamethasone (DBTd) represents the current standard of care for induction and consolidation therapy. Following consolidation therapy, lenalidomide (L) represents the standard of care for maintenance therapy.^{2, 24}
- The key unmet needs for HDT-ASCT eligible patients with NDMM can be broadly divided into the induction and consolidation phases, and maintenance treatment phases:

Induction and consolidation therapy:

- Thalidomide-containing therapies such as DBTd are associated with substantial adverse events (AEs) including neurotoxicities, somnolence and constipation. As well as adding to the already high burden of disease experienced by MM patients, the management of these toxicities is associated with substantial healthcare resource use.^{4, 25}
- There is an unmet need for an effective thalidomide-free induction and consolidation therapy which offers an improved tolerability profile to alleviate symptoms and enhance health-related quality of life (HRQoL). Input from UK clinical experts confirmed the strong desire for such a treatment across the medical community.⁴

Maintenance therapy

- Achieving a deep, durable response with sustained minimal residual disease-negativity (MRD-negativity) is associated with delayed progression and improved survival outcomes. Given the incurable nature of MM, these are key aims of treatment.⁴
- 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.
 - This suggests the criteria for Level 1 evidence, referenced in the NICE report of surrogate endpoints in HTA, is clearly met.
- The positive NICE recommendation of lenalidomide maintenance and its subsequent introduction to UK clinical practice has improved long-term outcomes. However, an unmet need remains for more personalised treatment options that can induce deeper, more durable responses to further delay progression.²⁶ Given that maintenance treatment is administered for a prolonged period of time, tolerability and optimisation of drug exposure are key to its viability post-ASCT.²⁷
- By delaying relapse, an effective maintenance therapy would delay the onset of cycling through costly subsequent treatments, and the increased healthcare resource use associated with

progression. This would represent significant cost-savings to the NHS, given that the cost of anti-MM medications accounts for up to 95% of direct MM costs in the UK, with novel, later-line therapies contributing disproportionately to this burden.²⁸

DBLd-DL would provide HDT-ASCT eligible NDMM patients with a more effective, tolerable treatment option, whilst reducing the long-term economic burden of MM to the NHS

- Daratumumab in combination with bortezomib, lenalidomide and dexamethasone (DBLd) for induction and consolidation therapy, followed by daratumumab and lenalidomide (DL) maintenance therapy is anticipated to be positioned as an alternative to DBTd induction and consolidation followed by lenalidomide maintenance therapy in HDT-ASCT eligible patients with NDMM.
- The key benefits of the introduction of DBLd-DL can be broadly divided into benefits at the induction and consolidation phase, and maintenance phase:

Induction and consolidation therapy:

- **A thalidomide-free treatment regimen:** As a second-generation immunomodulatory drug (IMiD), lenalidomide-based regimens are associated with a more tolerable safety profile than thalidomide-based induction and consolidation options.^{29, 30} As such, DBLd would offer patients an effective induction and consolidation therapy without the detrimental impact of thalidomide on their HRQoL.
- **Reduced AE management costs:** The availability of a non-thalidomide based regimen would minimise the need for monitoring and management of debilitating AEs, reducing the strain of MM on NHS resources.
- **Reduced drug acquisition costs:** DBLd represents further cost savings compared with DBTd due to the cheaper drug acquisition costs for lenalidomide versus thalidomide and the [REDACTED]

Maintenance therapy:

- **Deeper, more durable responses with higher rates of sustained MRD-negativity:** Daratumumab and lenalidomide act synergistically to induce lysis in more cells than each agent on its own. DL maintenance acts to continuously suppress MRD to prolong response duration, delay relapse and therefore extend progression-free survival (PFS)³¹ and offer the possibility of a functional cure for some patients with the best response.
- **Personalised maintenance treatment strategy:** Daratumumab maintenance therapy can be discontinued for patients who achieve sustained MRD-negativity for ≥ 12 months, having been on maintenance therapy for ≥ 24 months.³² This reduces the economic burden on the NHS, and treatment burden on patients whilst in remission.
- **Delayed onset of subsequent treatment cycling:** By delaying disease progression, DL maintenance also delays the onset of cycling through subsequent treatment regimens, therefore alleviating the immediate burden of high costs associated with anti-MM treatments, particular with later lines of therapy.

The introduction of DBLd-DL into the UK treatment pathway has the potential to **transform patient outcomes** for this important first remission across the induction, consolidation and maintenance phases. DBLd would address the significant unmet need for a more tolerable induction and consolidation therapy, **minimising toxicities** associated with the current thalidomide-based standard of care. The introduction of DL maintenance would further help to drive **deeper, more durable response** compared with L maintenance alone, translating to a delay in relapse, improved HRQoL and long-term outcomes, and the **prospect of functional cure** for best responders.

1.3.1 Disease overview

MM is a rare and incurable type of haematological cancer characterised by uncontrolled proliferation of malignant plasma cells in the bone marrow. This uncontrolled proliferation results

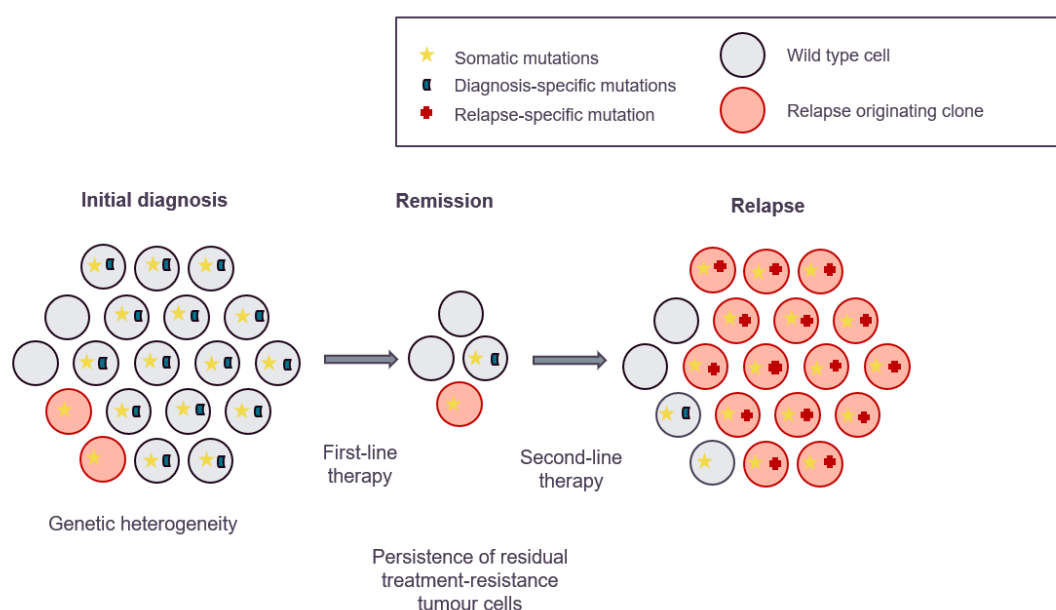
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in the over-production of an abnormal monoclonal immunoglobulin called M-protein. Over time, this protein accumulates in the bones, blood and multiple organs throughout the body. This leads to progressive morbidity and eventual mortality by impairing the body's ability to fight infection, and causing serious complications that require immediate medical treatment, including elevated **c**alcium levels (hypercalcemia), **r**enal impairment, **a**naemia and **b**one disease (CRAB) and other types of end stage organ failure.^{33, 34} Additional presenting features include fatigue and unremitting bone pain, recurrent or persistent infection and hyperviscosity (i.e. increased blood viscosity).³⁴⁻³⁶

MM is a highly heterogeneous disease with a variable clinical course. Furthermore, at a genetic level, heterogeneity exists in the form of mutations and genetic translocations.³⁷ This genetic heterogeneity means it is a difficult disease to treat and that clinical outcomes, including overall survival (OS), vary depending on a number of prognostic factors, including International Staging System (ISS) stage and whether the patient has high-risk chromosomal abnormalities.^{38, 39}

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.⁴⁰⁻⁴² As depicted in Figure 2, treatment-resistant subclones that have obtained resistance mutations via clonal evolution initially exist at low frequencies, but persist residually, ultimately 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.⁴³

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



Abbreviations: MM: multiple myeloma.

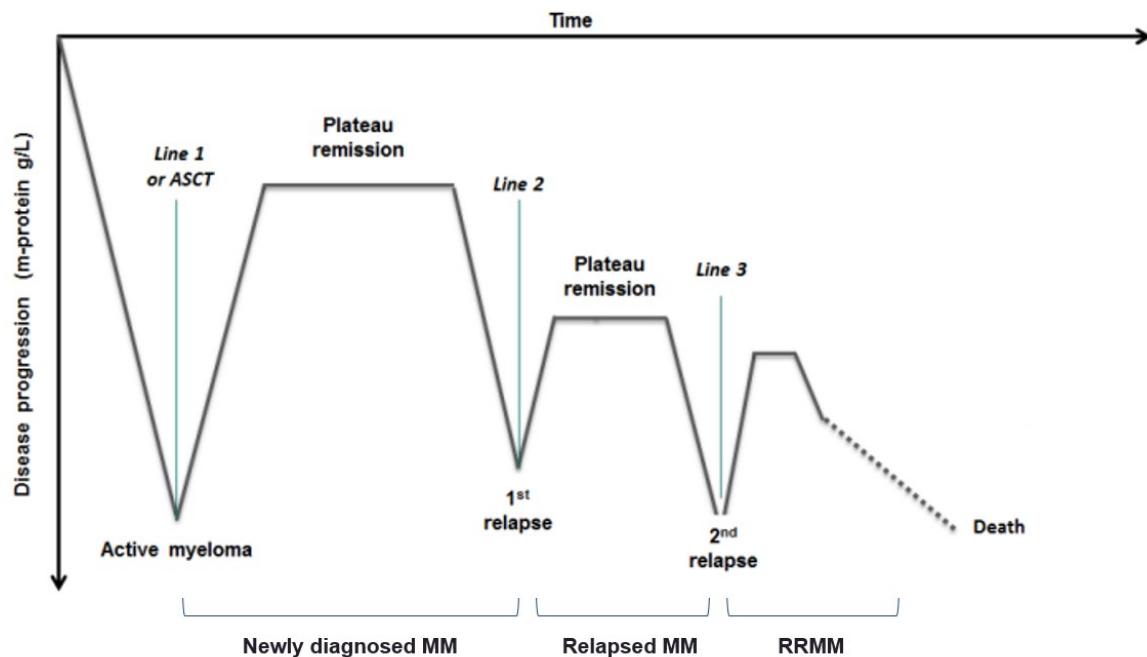
Source: Adapted from Vosberg and Greif (2019).⁴³

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).⁴⁴ Each subsequent relapse carries a cumulative risk of additional clones, which arise due to genetic mutations in myeloma cells.⁴⁵ Furthermore, with each relapse prognosis worsens as it becomes more difficult to induce deep and durable

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responses to treatment and attrition rates increase.¹⁷⁻²² As such, the prognosis of patients with relapsed/refractory disease is poorer than those with NDMM. A key challenge of treatment is therefore 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.²

Figure 3: Clinical model of disease progression in MM



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

Source: Adapted from TA763.²

The emergence of novel therapeutic agents and combinations has significantly enhanced both survival rates and HRQoL for patients with MM. Despite these advances, MM remains a predominantly incurable malignancy, and nearly all patients eventually experience relapse or fail to respond to treatment, becoming refractory to at least one class of drugs commonly used to treat MM.⁴⁶ Due to the refractory nature of the disease, it is therefore crucial that the most effective treatments are used in the front-line setting, as patients may not survive or be fit enough to receive treatment at later lines.²

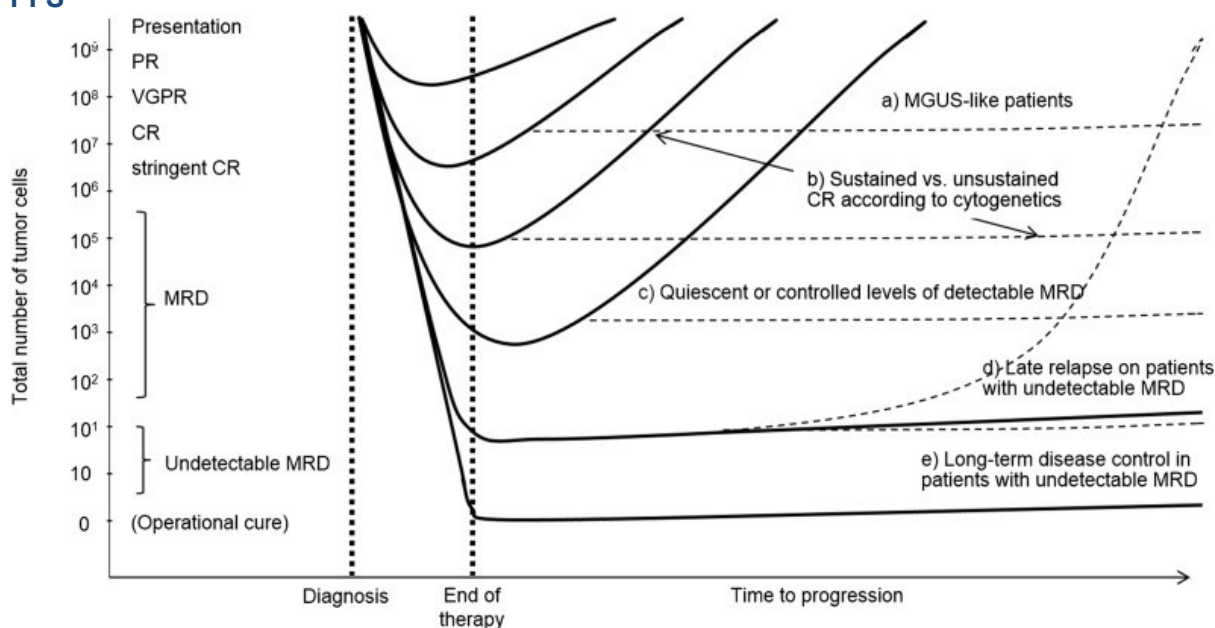
1.3.2 Depth of response and minimal residual disease

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.⁴⁷ It is therefore critical that measures of response are able to identify these small but clinically relevant populations of myeloma cells. MRD is the most sensitive measure of response currently available and is recommended in the International Myeloma Working Group (IMWG) response assessment criteria.⁴⁸

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 essential to assessing treatment effectiveness.⁴⁹ As described in section 5 of the daratumumab SmPC, when used in the indication of relevance to this submission, daratumumab can be discontinued for patients who have achieved MRD negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months.

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

Figure 4: Illustration of the relationship between achieving a deep response and extended PFS



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

Source: Paiva *et al.*, 2015.⁵⁰

As such, in the context of NDMM where it can often take many years to demonstrate a statistical survival advantage, it is necessary to assess the efficacy of treatments 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 correlated with substantial improvements in PFS and OS:

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- 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 HDT-ASCT eligible patients with NDMM, patients who achieved MRD-negative status had statistically significant PFS and OS improvements compared to those who were MRD positive (PFS HR: 0.33; 95% confidence interval [CI], 0.29-0.37; $p < 0.001$; OS HR: 0.45; 95% CI, 0.39-0.51; $p < 0.001$).⁵¹
- 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 endpoint 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]).⁵²
 - 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; OS: R^2 of 0.21 [95% CI: <0.01 to 0.53] for the NDMM population).⁵²
 - 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.⁵³ Among HDT-ASCT eligible patients, the global OR for the patient-level correlation between 9-month MRD-CR and PFS was 3.06 (95% CI: 2.09, 4.03), while the correlation between 12-month MRD-CR and PFS was 4.46 (95% CI: 3.19, 5.70). Of note, consistent results were observed for the correlation between MRD-CR and OS. Landmark Kaplan-Meier estimates of PFS and OS for HDT-ASCT eligible patients achieving MRD-CR at 9 months compared with those who did not are presented in Figure 5.⁵³
- An analysis of two RCTs in patients with MM found that patients with an MRD-negative status experienced an improved PFS compared with MRD-positive patients, but also that sustained MRD-negativity was associated with improved PFS versus a less durable MRD-negativity, highlighting the importance of achieving both a deep and durable response.^{54, 55}
- 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.⁵⁶

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 Company evidence submission template for daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

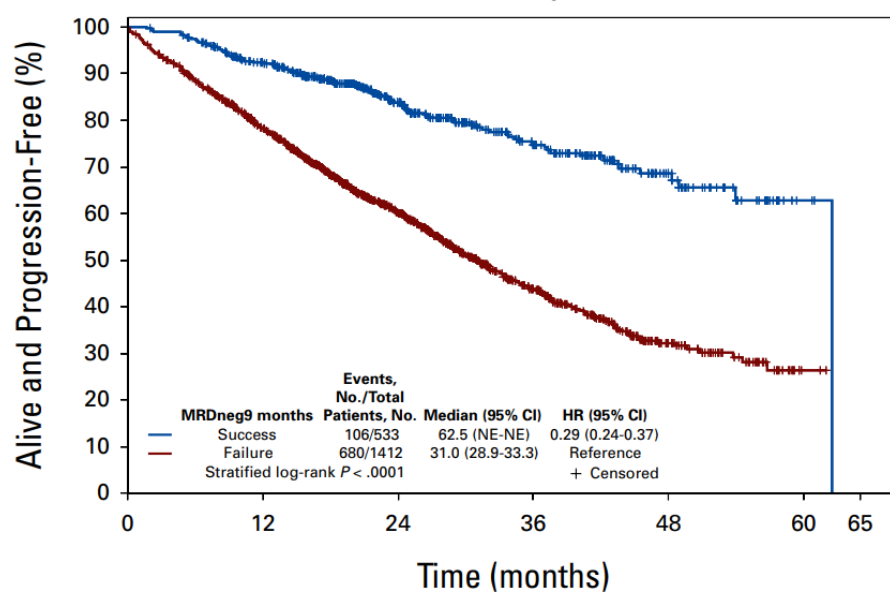
meta-analysis by Landgren *et al.* (2024), which demonstrated a strong observed correlation between treatment effect on MRD-negativity and long-term survival outcomes.⁵² The criteria for Level 1 evidence outlined by Ciani *et al.* (2017),⁵⁷ which is referenced in the NICE report of surrogate endpoints in health technology assessment (HTA),⁵⁸ is therefore clearly met. Level 1 evidence represents the highest possible strength of evidence as per the Ciani *et al.* (2017) criteria.⁵⁷

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.^{4, 59} At the May 2025 UK Advisory Board, clinical experts confirmed that they would expect MRD-negativity to translate to prolonged PFS in NDMM patients given sufficient follow-up.⁴ In line with this, MRD-negativity was accepted as a surrogate outcome for OS in the NICE appraisal for DBTd in the same indication.² In summary, there is a wealth of evidence to demonstrate that MRD-negativity is a powerful independent predictor of long-term survival in MM, demonstrated at the highest level of evidence (i.e., RCTs) in line with the NICE decision support unit (DSU) technical support document (TSD) 20.^{4, 60}

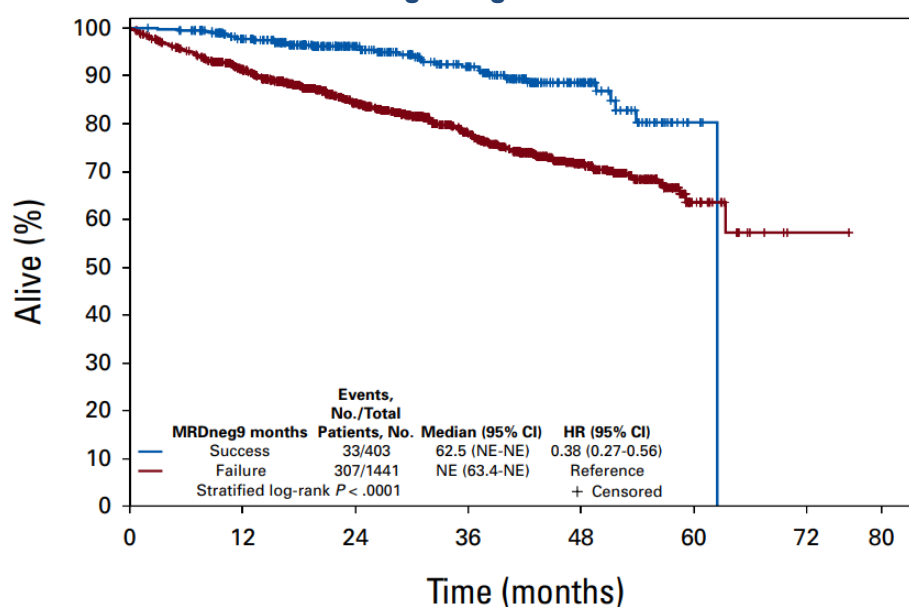
The role of MRD status as a major predictive factor of longer-term outcomes is illustrated by its use to inform disease management in UK clinical practice for other haematological cancers. For example, MRD testing is widely established and implemented across the NHS for those with acute lymphoblastic leukaemia (ALL), both during and after treatment in order to measure response and inform treatment choice.⁶¹ Although MRD testing is not currently routinely used in the NHS for patients with MM, it is expected that this would be established to support the initiation of MRD-dependent treatment decision-making, should such a treatment become available. Input from UK clinicians at a May 2025 Advisory Board confirmed that the adoption MRD-dependent treatment decision-making is encouraged by the clinical community, given the highly predictive nature of MRD status.⁴

Figure 5: Landmark analyses assessing prognostic values of 9-month MRD-CR status regarding PFS and OS in HDT-ASCT eligible patients with NDMM

A – 9-month MRD-CR status regarding PFS



B – 9-month MRD-CR status regarding OS



Abbreviations: ASCT: autologous stem cell transplant; CI: confidence interval; HDT: high dose therapy; 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).⁵³

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1.3.3 Epidemiology

Approximately 6,200 new MM cases were recorded in the UK from 2017–2019, accounting for just 2% of all new cancer cases.⁶² Owing to its rarity, NDMM has been granted an orphan disease designation both in Europe and the United States (US).^{63, 64} However, over the last decade, MM incidence rates have increased by approximately 15% 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.⁶² Specifically, projections indicate that, on average, there will be approximately 8,300 new cases of myeloma annually in the UK by 2038–2040.⁶²

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

- Age: MM most commonly affects individuals over the age of 65.⁶⁵
- Race: Individuals with African heritage experience MM at twice the frequency of Caucasian people, although the reason for this disparity remains unclear.⁶⁶
- 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]).⁶⁶
- 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.⁶⁷
- 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.⁶⁶ In England, between 2017–2019, incidence rates were 62% higher in males versus females.⁶²

Of relevance to this submission, HDT followed by ASCT represents standard of care for patients with NDMM who are fit enough to receive this intervention. Approximately 30% of MM patients in the UK are eligible for ASCT upon diagnosis, based on a real-world evidence study in patients with NDMM, with most eligible patients aged ≤65 years old.⁶⁸ This is broadly in line with the NICE appraisal for DBTd in the same indication (TA763), where an estimate of one-third was accepted.² 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.⁶²

1.3.4 Disease burden

Clinical burden

Patients with MM experience a particularly high clinical burden, and often present with recurring or persistent infection, fatigue and unremitting bone pain.⁶⁹ 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.⁷⁰ 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).⁷⁰ 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.^{71, 72}

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

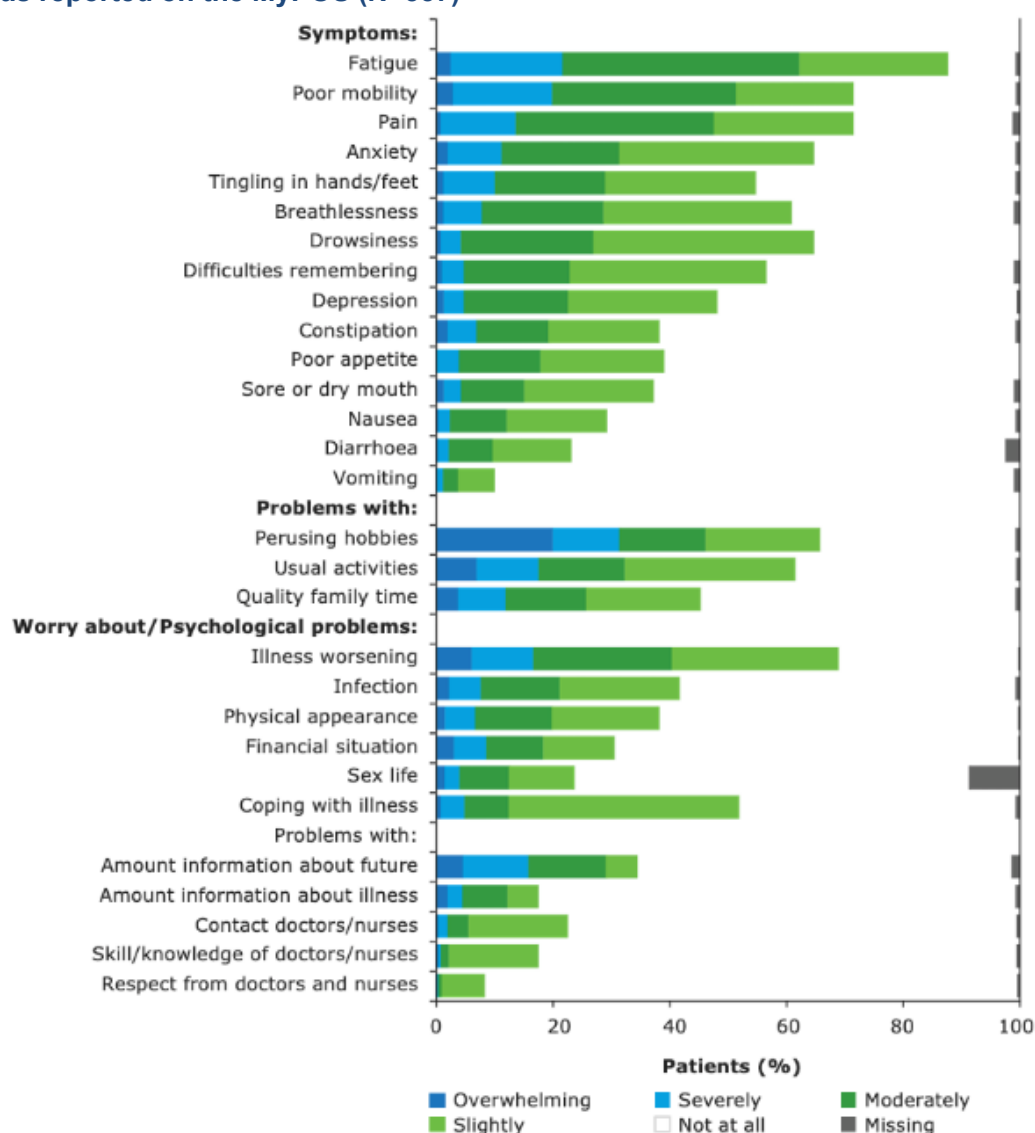
Figure 6.⁷³ A 2019 prospective, longitudinal cohort study of patients with MM in England (N=238) reported similar findings. Over half of patients reported fatigue (52.1%) and 40.3% reported moderate to overwhelming pain.¹⁵ These symptoms have a significant impact on patients' ability to carry out daily activities, contributing to reduced independence (

Figure 6).^{73, 74} Of particular note, 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.⁷³

Alongside the symptom burden, patients with MM face a substantial mortality burden. Although considerable progress in the treatment of MM has improved patient survival, the disease remains incurable. The introduction of novel agent-based combinations for patients with HDT-ASCT eligible NDMM has improved outcomes, and response rates have been shown to improve with the addition of a third agent.⁷⁵ However, all surviving patients will eventually relapse, with survival rates declining at each successive line of therapy.⁷⁶ Indeed, the 5-year survival rate for adults with MM (all stages) in England and Wales is 56% (estimated 2016–2020).⁶²

The broad clinical burden for patients with MM highlights the importance of effective treatments in the first-line setting which achieve deep and durable responses. As described in Section 1.3.2, such responses are expected to translate to delayed disease progression, extended PFS and, ultimately, prolonged survival. Furthermore, feedback from UK clinical experts confirmed that improving disease control and maintaining the progression-free state is a key aim of front-line treatment, to ensure patient HRQOL is maintained for as long as possible.^{4, 75, 76}

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.*, 2016⁷³

Impact on HRQoL

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.^{77, 78}

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 MM diagnosis as a ‘time bomb’, living in fear of a relapse.⁷⁹ Initial disease relapse is associated with a period of negative emotions, including hopelessness and a general sense of resignation.⁸⁰ Subsequent relapses are linked to increasing distress and pessimism.⁸⁰ As a result, HRQoL significantly

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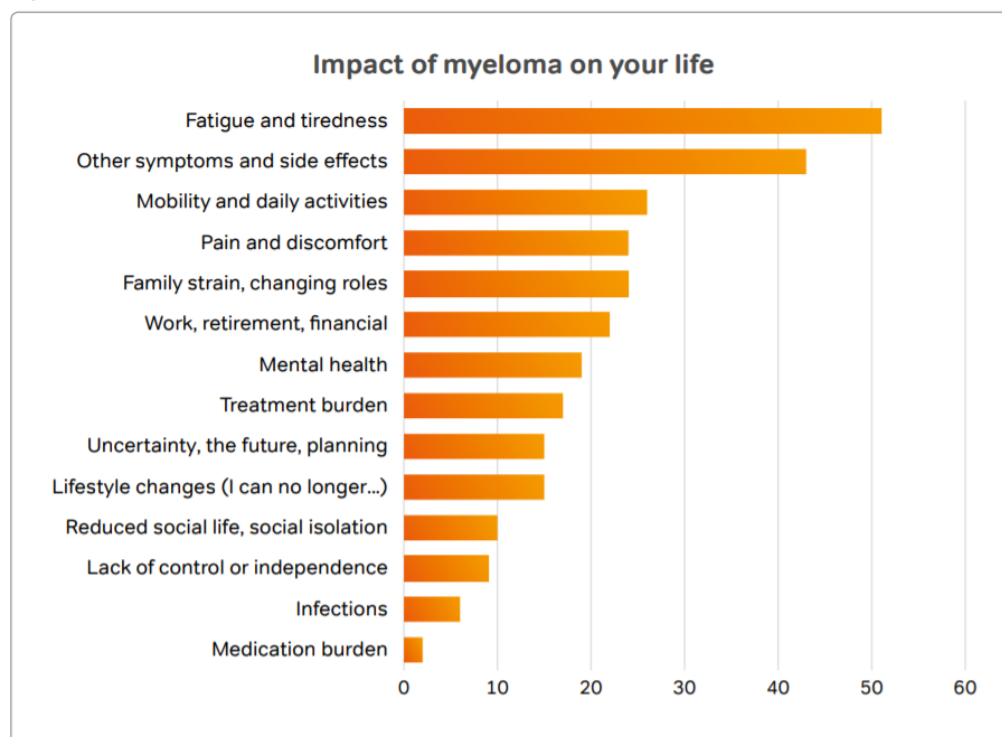
deteriorates with each relapse and subsequent line of treatment. Observational data from a UK cross-sectional study conducted by Myeloma UK, which included responses from 370 MM patients, demonstrated that patient HRQoL reduced following progression from their first treatment-free interval (TFI) to second-line treatment and subsequent lines of therapy.⁸¹ This study also showed that a longer TFI was significantly associated with improved patient HRQoL. These results highlight the value of effective first-line therapies, which are able to induce deep responses and therefore extend the TFI in patients.⁸¹

Uncertainty about the future causes ongoing anxiety and often affects patients' relationships with family and friends who may act as informal caregivers.⁸⁰ 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.⁷⁴ Furthermore, a systematic literature review and meta-analysis included 36 studies on symptoms associated with multiple myeloma 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) criteria, while 80.2% exhibited decreased cognitive functioning. These findings underscore the substantial impact that multiple myeloma has on the HRQoL of patients.¹⁶

Patient preferences

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 health technology assessments (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). Additionally, patients highlighted that MM affected their personal lives by reducing their sense of control/independence, altering their lifestyles, and causing financial strain. It's 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 newly diagnosed disease) 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 in a recent study conducted in Europe explored patient perceptions regarding MM and its treatment among 30 MM patients, 60% of whom had newly diagnosed disease.⁸⁴ The qualitative interviews highlighted that increased life expectancy, achieving remission or response, and reduced fatigue 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 (reported by 94% of respondents).⁸⁴ Given the association between relapse and a worsening symptom burden, treatments which achieve the deepest and most durable remissions will also provide the greatest relief from debilitating disease-related symptoms. Furthermore, 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 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; therefore, the bulk of care is provided by informal caregivers,

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typically comprised of patients' family and friends.⁸⁵ 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% report symptoms of depression.⁷⁴ A more recent prospective, cross-sectional study found that almost half of caregivers reported being diagnosed with stress, anxiety or depression due to their caring role in the year following MM diagnosis.⁸⁷ Furthermore, 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

Economic burden

Direct economic burden

In addition to the significant impact of disease on patient and caregiver HRQoL, MM is associated with a substantial financial burden. A 2015 retrospective medical chart review across the UK, France and Italy conducted to quantify the costs associated with MM found that the mean total healthcare costs associated with a single line of treatment were €51,717 (SD: 42,342). Furthermore, 95.0% of these costs were attributed to direct costs associated with anti-myeloma medications and, notably, the costs of these medications increased with line of therapy despite the regimens having comparable treatment durations.²⁸ This is in line with other studies which have highlighted the disproportionate contribution of novel, later line therapies to overall anti-MM drug costs.^{88, 89} This highlights the need for effective first-line treatments that delay the onset of patients cycling through expensive subsequent line treatments.

In addition, MM is associated with increased healthcare utilisation versus other disease areas. A UK-based study in 41,845 patients with MM found that the average number of MM-related hospital admissions per patient was more than three times higher than that of colon cancer (4.5 versus 1.4, respectively).⁹⁰ In the same study, the average cost per patient per year reported for MM-related admissions was nearly three times higher than that of the average patient in the NHS (£2,455 versus £870, respectively), further emphasising the high economic burden associated with MM.⁹⁰ The 2015 retrospective medical chart review detailed above also found that hospitalisation costs increase with each line of therapy.²⁸ Again, this highlights the unmet need for effective first-line treatments that extend remission for as long as possible, to delay the onset of financial costs associated with disease management following relapse, and cycling through expensive later-line therapies.

Indirect economic burden

The economic burden of MM extends beyond direct costs to the healthcare system to patients and their carers; the results of a SLR and meta-analysis including 34 studies on symptoms in MM found that financial difficulties occurred in 78.4% of patients with MM.¹⁶ Furthermore, the results of a targeted literature review carried out by J&J in 2023 found that caregivers reported financial difficulties as a result of a relative being diagnosed with MM; they reported that they may suffer from loss of wages, difficulty in paying bills, lack of sick leave and premature use of retirement funds.⁸⁵ Additionally, one study analysing results from an economic questionnaire from patients in a Phase II, multi-centre, international randomised controlled trial (RCT) (N=307), including Company evidence submission template for daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

sites in the UK, found that MM causes productivity losses, with carers losing an average of 104.5 working hours per year due to providing informal care.⁸⁹

These studies highlight the importance of the availability of effective treatments that can extend life, delay disease relapse and minimise symptom and psychological burden on patients. Furthermore, these studies also highlight the importance of additional treatments that are associated with reduced drug acquisition and disease management costs. Such treatments would minimise the economic burden on individuals, their carers and the NHS, as well as the subsequent productivity losses on society as a whole.⁹¹

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

1.3.5.1. Clinical care pathway

MM is a treatable but currently incurable disease. Consequently, the aim of treatment is to achieve deep and durable responses, translating to delayed disease progression and ultimately prolonged survival. Additionally, by inducing remission and delaying progression, treatments should alleviate the symptom burden and enhance patient HRQoL.⁴

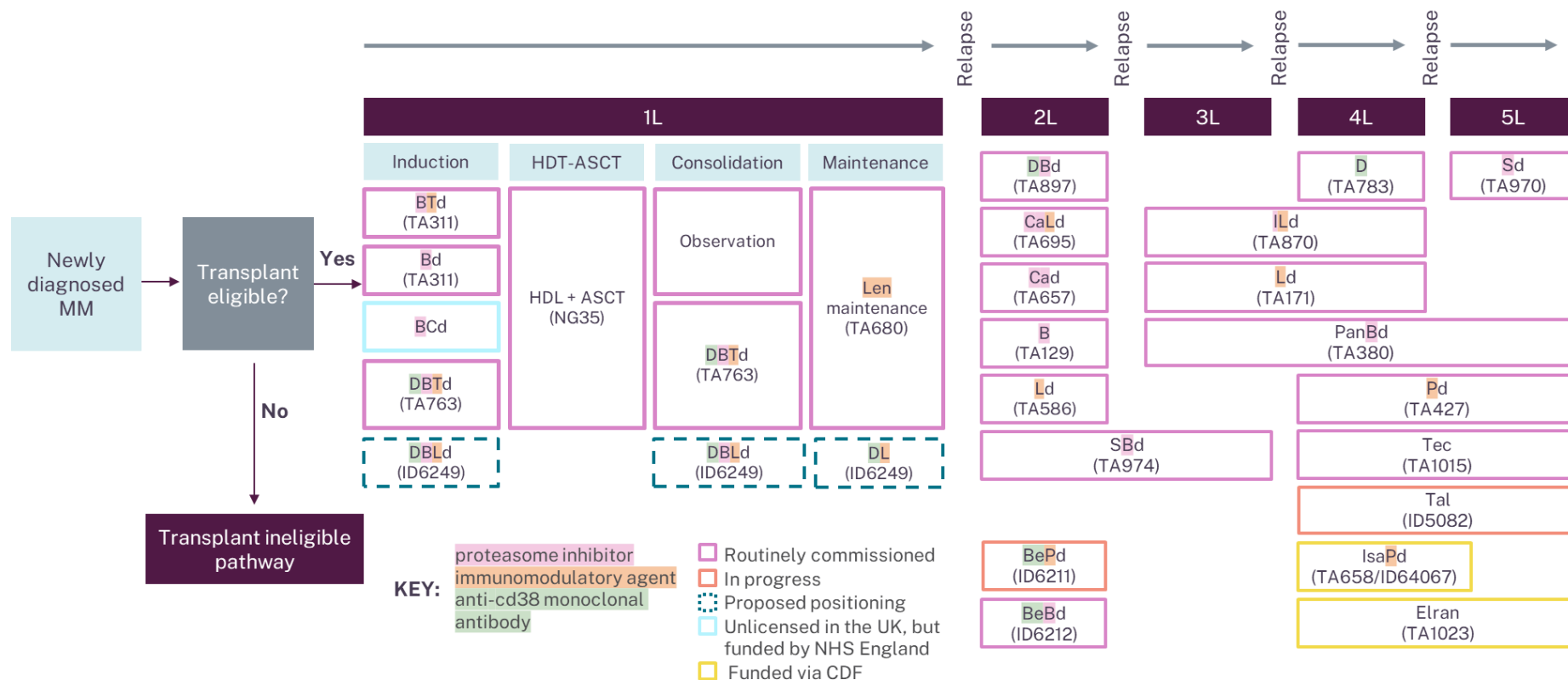
Treatment guidelines

Treatment guidelines for the management of MM are available from the European Society of Medical Oncology (ESMO), European Myeloma Network (EMN), National Comprehensive Cancer Network (NCCN) and NICE (NG35).^{24, 92-94} 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.²⁴ Various regimens have been recommended by NICE for the treatment of MM; however, several of these regimens are reserved for later treatment lines (Figure 8).²⁴

Description of the UK clinical care pathway

In the current NICE treatment guidelines, patients with NDMM are initially assessed for suitability for intensive treatment (i.e., HDT followed by ASCT) according to factors such as age, frailty and performance status.^{2, 24} 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 stage in life (74% of patients are diagnosed aged ≥ 65 years, as described in Section 1.3.3).⁶² As shown in Figure 8, NDMM patients are typically categorised into two subpopulations according to HDT-ASCT eligibility, with this categorisation informing first-line treatment choice and consequently the positioning of DBLd-DL.²⁴

Figure 8: Current treatment pathway for MM in the UK



Abbreviations: 1/2/3/4L/5L: 1st/2nd/3rd/4th/5th line; ASCT: autologous stem cell transplantation; BCd: bortezomib, cyclophosphamide and dexamethasone; Bd: bortezomib and dexamethasone; BePd: belantamab mafodotin, pomalidomide and dexamethasone; BeBd: Belantamab mafodotin, bortezomib and dexamethasone; BTd: bortezomib, thalidomide and dexamethasone; Cad: carfilzomib and dexamethasone; CaLd: carfilzomib, lenalidomide and dexamethasone; CD38: cluster of differentiation 38; D: daratumumab; DBd: daratumumab, bortezomib and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; Elran: elranatamab; HDT: high dose therapy; ILd: ixazomib, lenalidomide and dexamethasone; IsaPd: isatuximab, pomalidomide, dexamethasone; Ld: lenalidomide and dexamethasone; Len: lenalidomide; MM: Multiple Myeloma; NHS: National Health Service; PanBd: panobinostat, bortezomib and dexamethasone; Pd: pomalidomide and dexamethasone; RRMM: relapsed/refractory multiple myeloma; SBd: selinexor, bortezomib and dexamethasone; Sd: selinexor and dexamethasone; TA: technical appraisal; Tal: talquetamab; Tec: teclistamab; UK: United Kingdom.

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DBTd is the predominantly used induction regimen in this setting. This is supported by [REDACTED]
[REDACTED]
[REDACTED]

Post-ASCT, consolidation therapy is typically given for a short duration (2–4 cycles), to further deepen response and provide long-term disease control.⁹⁶ The only recommended consolidation therapy in UK clinical practice is DBTd.²

Following disease progression on maintenance therapy, patients become relapsed/refractory and initiate a subsequent line of therapy. Regardless of prior ASCT history, MM patients typically require multiple lines of treatment due to the relapsing and remitting nature of the disease, with treatment of relapsed/refractory MM being highly individualised and dependent on response to previous treatment. MM patients typically require multiple lines of treatment due to the relapsing and remitting nature of the disease. This usually involves combination therapies consisting of PIs (i.e. bortezomib, carfilzomib or ixazomib), IMiDs (i.e. thalidomide, lenalidomide or pomalidomide) and/or an anti-CD38 mAb (i.e. daratumumab) with dexamethasone added to further alleviate symptom burden. Almost all surviving patients with MM eventually relapse from, or become refractory to, existing treatment options.⁹⁷

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combination therapies) have been introduced in the UK. Teclistamab, a BCMA-targeting bispecific antibody (BsAb), has received a positive routine recommendation for use as a 4L+ treatment in triple-class exposed (TCE) RRMM patients (TA1015).⁹⁸ Elranatamab, a BCMA-targeting BsAb, is currently only available via the Cancer Drugs Fund (CDF) as a 4L+ treatment for TCE RRMM patients and therefore, is not part of routine UK clinical practice.⁹⁹ Belantamab mafodotin in combination with bortezomib and dexamethasone, a BCMA-targeting antibody drug conjugate (ADC), has received a positive draft recommendation (ID6212) as a 2L treatment for patients who are refractory to lenalidomide.¹⁰⁰

Therapies with other mechanisms of action, beyond PIs, IMiDs, anti-CD38 mAbs and BsAbs, such as selinexor have also been recently approved for use in both 2L (selinexor plus bortezomib and dexamethasone) and 5L (selinexor plus dexamethasone) for the treatment of RRMM.^{101, 102}

The available treatment options in UK clinical practice in the second-line setting and beyond are summarised in Figure 8 above for completeness.

1.3.5.2. Unmet need

Given the currently incurable nature of MM, the key aim of treatment is to achieve a deep, durable response at the first treatment line, which translates to more time spent in the progression-free state, improved patient well-being and, ultimately, extended survival. Amongst patients with the best response there maybe potential for functional cure i.e. survival outcomes in line with general population mortality. As MM is associated with a substantial disease burden on patients, it is essential that this clinical benefit does not come at the expense of patient HRQoL. There is an unmet need in HDT-ASCT eligible patients with NDMM for a tolerable treatment option which effectively induces deep responses, thereby extending PFS and OS, whilst minimising the economic burden of MM on the NHS.

Clinical burden

Current induction and consolidation treatment options are associated with a high toxicity burden, highlighting the need for more tolerable treatment options

One of the key challenges in the treatment of MM is to find options that effectively target and eliminate all clonal and subclonal mutations.^{7, 8} The recent introduction of DBTd to the treatment pathway has provided a step-change in efficacy for patients with NDMM.² However, thalidomide is associated with various toxicities including somnolence (i.e. drowsiness), constipation and neuropathy.²⁵ A 2024 RCT comparing carfilzomib in combination with thalidomide and dexamethasone (CTd) versus carfilzomib in combination with lenalidomide and dexamethasone (CLd) in patients with NDMM found a distinct discrepancy in AE profiles. Peripheral neuropathy was significantly associated with thalidomide (CTd: 41.3% versus CLd: 11.7%, p=0.0053).¹⁰³ Additionally, the incidence of other AEs, including neurological disorders, thromboembolic complications and oedema were notably higher in the CTd arm.¹⁰³ Similarly, in a Phase III RCT, 73.0% of patients with NDMM receiving melphalan with prednisone and thalidomide experienced overall grade ≥3 AEs, compared with 58.0% of patients receiving melphalan, prednisone and lenalidomide. Specifically, the proportion of grade ≥3 non-haematological toxicities were statistically significantly higher in the thalidomide-based therapy arm versus the lenalidomide arm (p=0.001).³⁰ This study demonstrates that thalidomide-based therapies are associated with a less tolerable safety profile than lenalidomide-based combinations.

Feedback from UK clinical experts emphasised the substantial burden of neurotoxicities on patient HRQoL, and the strong desire across the medical community for a complete move to treatment options which minimise such side effects. Quotes from patients with MM, provided as part of the Myeloma UK patient organisation submissions in the NICE submissions for DBTd (TA763) and Ld (TA587), highlight how neurotoxic symptoms exacerbate the significant clinical burden they experience.^{2, 104}

“I have permanent damage in my extremities, my feet constantly feel icy and like they don't belong to my body – when I touch between my knees and feet I can't really feel anything. It is because of this I trip up all of the time.”

“It can only be described as a feeling of walking on rocks. I had a constant burning sensation in my hands and feet, which got much worse at night and meant I struggled to sleep. This combined with having terrible fatigue related to my myeloma, meant that it impacted on my ability to do things.”

An unmet need therefore exists in HDT-ASCT eligible patients with NDMM for a thalidomide-free induction and consolidation therapy which is as effective, safer and more tolerable, to enhance the HRQoL of patients and their caregivers.

More personalised maintenance treatment strategies that induce deep and durable responses whilst optimising drug exposure are required to delay disease relapse and ultimately prolong survival

Results of a Phase III, open-label RCT of DBTd compared with BTd in patients with NDMM (N=1,085) found that the addition of daratumumab achieved impressive clinical benefits. However, outcomes remain sub-optimal, with only 64% of patients in the DBTd arm achieving MRD-negativity (at a threshold of 10^{-5}), and fewer than half achieving both MRD-negativity and a complete response or better ($\geq$ CR).⁷⁵ The introduction of lenalidomide maintenance therapy to clinical practice (replacing clinical observation) has improved long-term outcomes, as illustrated by a Phase III RCT assessing lenalidomide versus placebo maintenance after single ASCT for MM (N=460) found that the introduction of lenalidomide maintenance treatment significantly improved median time to progression (57.3 months for the lenalidomide group versus 28.9 months for the placebo group; HR: 0.57; $p < 0.0001$).²⁶ However, although the introduction of lenalidomide maintenance demonstrated improvements in time to disease progression and PFS for patients with MM, it remains an incurable disease, meaning that these patients ultimately still experience disease relapse. Therefore, there is a key unmet need for additional treatment options that can induce a deeper, more durable response to further delay disease progression and the need for later lines of treatment.

Furthermore, as maintenance treatment is given for a prolonged period of time, tolerability and safety are key to its viability post-ASCT.²⁷ Maintenance duration is related to the tolerability of the intervention and, although the duration length has yet to be optimised, 2–3 years appears to be preferred.¹⁰⁵ Cumulative toxicities arising from long-term exposure can lead to discontinuation and impact treatment duration, therefore highlighting the need for tolerable maintenance therapies.¹⁰⁶ Indeed, feedback from UK clinical experts during a May 2025 Advisory Board highlighted that around 20–30% of patients experience toxicity issues associated with L maintenance and therefore need to pause treatment, putting them at risk of relapse.⁴ As such, the option of a maintenance therapy which can be optimised to maximise effectiveness of

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maintenance therapy for the period of time in which patients can tolerate it would further reduce the clinical burden of disease.⁴

As described in Section 1.3.2, there is a well-established, biologically plausible relationship between achieving a deep treatment response, particularly (sustained) MRD-negativity, and improvements in PFS and OS. As such, an unmet need remains for additional treatment strategies that are able to induce higher rates of such responses and ultimately prolong survival or result in functional cure.²³

Economic burden

Management of toxicities associated with thalidomide-based induction and consolidation therapy contributes to the economic burden of MM

As noted above, there is a significant unmet need for more tolerable, thalidomide-free induction and consolidation regimens which would minimise the HRQoL impact of treatment on patients with NDMM by reducing the rate of neurotoxicity and other AEs. In addition, the management of neurotoxicity is associated with substantial healthcare resource use, often requiring ongoing monitoring, additional treatments to manage neuropathic pain and intensive care unit (ICU) admission for higher grade events.⁴ As such, the availability of a thalidomide-free treatment option would minimise such AE management and reduce the use of associated resources like ICU beds, alleviating the strain on NHS resources.

An unmet need exists for maintenance treatments which delay the initiation of cycling through costly subsequent treatments

As noted in Section 1.3.4, the cost of anti-MM medications is a key driver of the economic burden of MM in the UK. In particular, the need for multiple treatment lines following initial relapse contributes to the cumulative costs incurred by the NHS. Furthermore, given that hospitalisation costs increase with each line of therapy, each disease relapse and subsequent line of therapy represents a higher economic burden to the NHS.²⁸ By delaying progression, an effective maintenance therapy would not only extend survival and improve patient HRQoL, but also delay the onset of cycling through costly subsequent anti-MM treatments.

In conclusion, an unmet need exists in HDT-ASCT eligible patients with NDMM for:

- **A thalidomide-free induction and consolidation treatment option** which provides patients with the opportunity to receive effective treatment, whilst minimising the detrimental impact of thalidomide on their HRQoL during treatment. A move towards non-thalidomide based regimens would by extension, reduce the need for the management of AEs associated with thalidomide and help to relieve NHS resources.
- **An effective maintenance treatment** that achieves deeper, more durable responses and higher rates of MRD-negativity, including sustained MRD-negativity, all of which are associated with improved long-term survival outcomes. Disease relapse is associated with increase healthcare resource utilisation and cycling through costly subsequent treatments (Section 1.3.4). By delaying relapse, an effective maintenance treatment would extend the time until these costs are incurred. It would also potentially extend treatment-free periods, representing substantial cost savings for the NHS. A maintenance strategy which allows for more personalised optimisation of treatment duration would further minimise the economic burden of MM, whilst reducing the treatment burden on patients in remission.

1.3.5.3. Positioning of daratumumab in the UK MM treatment pathway

DBLd is anticipated to be positioned within its full marketing authorisation as an induction and consolidation therapy followed by DL maintenance therapy for patients with NDMM who are eligible for HDT-ASCT in UK clinical practice (Figure 8). As DBTd as an induction and consolidation therapy and lenalidomide as a maintenance therapy represent the predominantly used treatments in this setting, DBTd followed by lenalidomide maintenance is considered the only relevant comparator to DBLd induction and consolidation, and DL maintenance therapy in this setting.¹⁰⁷

The proposed positioning and relevant comparator to DBLd in this setting was supported by feedback received from UK clinical experts consulted as part of a recent 2025 UK Advisory Board who noted that, given DBLd is comprised of the same treatments as DBTd with the exception of lenalidomide replacing thalidomide, it is anticipated that DBLd will directly displace DBTd as an induction and consolidation treatment in UK clinical practice. Furthermore, it was noted that DL is expected to directly displace lenalidomide as a maintenance treatment.⁵

As described above, whilst effective, DBTd as a treatment for induction and consolidation is associated with a substantial toxicity burden, with UK clinical experts noting, in particular, the significant burden imposed by neurotoxicity.⁴ By contrast, DBLd is expected to be associated with an improved tolerability profile. Indeed, the Myeloma XI trial reported that the rate of peripheral neuropathy was significantly lower for a lenalidomide-based induction regimen (CLd) versus the thalidomide-based alternative (CTd) in patients with HDT-ASCT eligible NDMM.¹⁰⁸ In addition to reducing this disease burden on patients, the improved tolerability profile of lenalidomide versus thalidomide may translate to a reduction in hospital visits and ultimately alleviated AE management costs. This is particularly important given studies have shown that MM is associated with higher hospital admissions than other cancers (see section 1.3.4) and therefore further highlights the potential value of DBLd as a thalidomide-free regimen.⁹⁰ DBLd represents further cost savings for the NHS, compared with DBTd, due to the lower drug acquisition costs for lenalidomide versus thalidomide¹⁰⁹ and lower net price of daratumumab.

Furthermore, DL as a maintenance treatment has demonstrated the ability to induce continuous MRD suppression, to prolong response duration, delay disease relapse and extend PFS, all with minimal toxicity.^{31, 110} This is further supported by the evidence presented in TA917, which demonstrated that daratumumab and lenalidomide act synergistically to induce lysis in more MM cells than each agent on its own.¹² Therefore, the addition of daratumumab to lenalidomide in the maintenance setting would provide an additional efficacious treatment option for patients with MM, providing the prospect of functional cure for best responders. By delaying the onset of cycling through costly subsequent treatment options, DL maintenance would also alleviate the immediate burden of high costs associated with downstream MM treatment regimens. Moreover, patients may be able to discontinue daratumumab maintenance therapy once they have achieved sustained MRD-negativity for at least 12 months, and have been on maintenance treatment for at least 24 months.¹ Indeed, █% of patients who received DBLd-DL in the PERSEUS trial discontinued daratumumab based on this stopping rule, demonstrating the high likelihood of patients discontinuing daratumumab maintenance therapy in clinical practice, upon MRD testing being made available (see Section 1.3.2).³² This stopping rule represents further cost savings for the NHS, whilst also offering a more personalised maintenance treatment strategy to optimise drug exposure, reducing the treatment burden for patients in remission.

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In conclusion, the introduction of DBLd for induction and consolidation followed by DL maintenance treatment has the potential to address the existing unmet need in HDT-ASCT eligible patients with NDMM for an additional efficacious treatment option that provides deep and durable response rates, ultimately leading to improvements in patient HRQoL, delayed relapse and prolonged survival, whilst optimising treatment exposure. DBLd for induction and consolidation is also associated with an improved tolerability profile versus existing standard of care, and therefore anticipated to be associated with reduced AE management costs on top of reduced drug acquisition costs. Therefore, in addition to improving the burden of disease on patients, its introduction would also help to alleviate the existing economic burden of MM to the NHS, which is only anticipated to increase over time.

1.4 Equality considerations

No equality issues related to the use of daratumumab combination therapy (i.e. DBLd) for the treatment of HDT-ASCT eligible NDMM patients have been identified.

2 Clinical effectiveness

The PERSEUS trial provides the most relevant clinical efficacy and safety evidence for DBLd followed by DL maintenance in patients with NDMM who are eligible for HDT-ASCT

A systematic literature review (SLR) was conducted to identify clinical evidence for patients with newly diagnosed multiple myeloma (NDMM) eligible for high-dose therapy and autologous stem cell therapy (HDT-ASCT). Two viable sources of efficacy and safety data for daratumumab, bortezomib, lenalidomide and dexamethasone (DBLd) in the population of interest were identified, the Phase III PERSEUS trial and the Phase II GRIFFIN trial. In addition, the AURIGA trial was selected to inform the clinical efficacy and safety of DL maintenance.

PERSEUS is an ongoing, randomised, open-label, multicentre Phase III trial in patients with NDMM who are eligible for HDT-ASCT,³² and was the registrational trial supporting the label extension for daratumumab to cover the indication of relevance to this submission. As such, PERSEUS represents the principal source of clinical evidence for DBLd induction and consolidation followed by daratumumab in combination with lenalidomide (DL) maintenance therapy in this submission (referred to hereafter as the full treatment sequence; DBLd-DL).^{1, 111}

- PERSEUS is aligned with the decision problem specified in the NICE scope and the marketing authorisation for DBLd.^{1, 112} Furthermore, UK clinical experts consulted as part of a UK Advisory Board validated that the PERSEUS trial population is broadly generalisable to patients with NDMM in UK clinical practice.⁴ Supportive evidence is provided by the earlier study GRIFFIN, which informed the design of PERSEUS.
- The PERSEUS trial included four treatment stages: induction therapy, ASCT, consolidation therapy and maintenance therapy.³²

The AURIGA trial is the largest available RCT assessing the clinical efficacy and safety of DL versus L maintenance alone, and was considered the best available source of evidence for the comparative efficacy of DL versus L maintenance. This ongoing, randomised, open-label, multicentre, Phase III trial was conducted in anti-CD38-naïve patients with NDMM who were minimal residual disease- (MRD-) positive, and had achieved a very good partial response or better (≥VGPR) after induction therapy and HDT-ASCT.³¹

Patients in the DBLd arm of PERSEUS experienced an increased likelihood of achieving a deeper response to treatment compared to those in the BLd arm, translating to a reduced risk of disease progression

- The primary endpoint of progression-free survival (PFS) was met in the PERSEUS trial. The addition of daratumumab to bortezomib, lenalidomide and dexamethasone (BLd) and lenalidomide (L) resulted in a statistically significant improvement in PFS, with a 58% reduction in risk of disease progression or death compared with BLd alone (hazard ratio [HR]: 0.42; 95% confidence interval [CI]: 0.30, 0.59; p<0.001).¹¹⁰
 - Furthermore, the estimated PFS rate at 12 months and 24 months was █% (95% CI: █, █) and █% (95% CI: █, █), respectively.³²
 - At the 1st August 2023 data cut-off (DCO), with a median follow-up of 47.5 months, median PFS was █.^{32, 110} This is expected, given the effectiveness of both DBLd-DL and BLd-L as treatments alongside HDT-ASCT.

- Patients receiving DBLd-DL were more likely to respond to treatment compared to those receiving BLd-L, with the likelihood of achieving an overall objective response, VGPR, complete response (CR) or stringent complete response (sCR) increasing over time (post-induction overall response rate [ORR] odds ratio [OR]: [REDACTED]; 95% CI: [REDACTED]; p=[REDACTED]; post-consolidation ORR: OR: [REDACTED]; 95% CI: [REDACTED]; p=[REDACTED]; full treatment sequence ORR: OR: [REDACTED]; 95% CI: [REDACTED]; [REDACTED]).³²
- Notably, responses in the DBLd arm were deeper compared to those in the BLd arm across all phases of treatment. As early as post-induction, patients were [REDACTED] to experience ≥VGPR in the DBLd arm compared to BLd, and [REDACTED] in the likelihood of experiencing a ≥CR, ≥VGPR and a stringent CR (sCR) were observed across both the post-consolidation and full treatment sequences.
 - Across the full treatment sequences, patients in the DBLd arm were [REDACTED] as likely to achieve a ≥CR to treatment (OR: [REDACTED]; 95% CI: [REDACTED], [REDACTED]) versus the BLd arm.
- Amongst responders, median duration of response (DOR) was [REDACTED]. However, the proportion of patients who were still in response, and thus censored, was greater in the DBLd arm compared with the BLd arm ([REDACTED]% versus [REDACTED]%).³²
- Studies have demonstrated that achieving a deep, sustained response to therapy is prognostic for improved survival outcomes.²³ Furthermore, deeper treatment responses are associated with improvements in health-related quality of life (HRQoL) for MM patients.⁵⁶
- For those who experienced a complete response or better (≥CR) in the PERSEUS trial, MRD-negativity (at a threshold of 10^{-5}) was achieved by 47.5% of patients in the BLd arm (95% CI: [REDACTED], [REDACTED]) versus 75.2% of patients in the DBLd arm (95% CI: [REDACTED], [REDACTED]), with an OR of 3.40 (95% CI: 2.47, 4.69]; p<0.0001) for the full treatment sequence.^{32, 110}
 - The proportion of patients who converted from MRD-positive at post-consolidation to MRD-negative during maintenance treatment was significantly higher for those receiving DL maintenance versus L maintenance (60.2% versus 40.5%; p=0.0049).¹¹³
 - Achieving MRD-negativity, defined as having fewer than a set threshold of clonal plasma cells in the bone marrow, is a highly sensitive measure of the depth of response and a powerful independent predictor of long-term outcomes.¹¹⁴
- At the time of the 1st August 2023 DCO, median overall survival (OS) was [REDACTED] in either arm ([REDACTED]; 95% CI: [REDACTED], [REDACTED]), with a 27% reduction in risk of death for those receiving DBLd compared with BLd.³² As with PFS, this is to be expected given the effectiveness of both DBLd and BLd as treatment regimens, evidenced by the high rates of MRD-negativity achieved.
- No significant between-arm differences were observed across health-related quality of life (HRQoL) measures. This indicates that the addition of daratumumab to BLd induction and consolidation and L maintenance therapy does not detrimentally impact HRQoL.

Head-to-head data on full treatment sequence of relevance to this submission compared to UK Standard of Care is not available.

- PERSEUS was used to inform DBLd treatment benefit as part of an ITC used to compare DBLd vs DBTd with respect to Induction and Consolidation therapy
- AURIGA was used as a primary evidence base to inform a comparison of DL vs L maintenance therapy. PERSEUS provides supportive information

ITCs were conducted between PERSEUS and CASSIOPEIA to derive comparative efficacy estimates for DBLd induction and consolidation versus the comparators of relevance to UK clinical practice

- In the absence of direct head-to-head trial evidence comparing the effectiveness of DBLd-DL with its relevant comparator (DBTd-L) in UK clinical practice, indirect treatment comparisons (ITCs) were conducted between the PERSEUS and CASSIOPEIA trials.
- No efficacy data for the full treatment sequence for the comparator (i.e. DBTd-L) were available. Instead, ITCs using individual patient data (IPD) from the PERSEUS and CASSIOPEIA trials were used to compare the clinical effectiveness of DBLd and DBTd as induction and consolidation treatments in patients with NDMM who are eligible for HDT-ASCT.
- In the base case ITC approach, the PERSEUS population was re-weighted to match CASSIOPEIA via the inverse probability of treatment weighting (IPTW) approach, in line with NICE Technical Support Document 18.¹¹⁵

The ITCs demonstrated that DBLd is associated with deeper responses compared with DBTd in the induction and consolidation phase of treatment, which are expected to translate into long-term OS benefits

- Results of the induction and consolidation phase ITCs demonstrate that DBLd is at least as effective as DBTd. Patients receiving DBLd are almost [REDACTED] to experience a $\geq$ VGPR compared to patients receiving DBTd (OR: [REDACTED]; 95% CI: [REDACTED], [REDACTED]; p=[REDACTED]). DBLd was also associated with a benefit in terms of ORR and MRD-negativity.
 - Given the prognostic implications of deep treatment responses for long-term benefits, the clear response benefit associated with DBLd is expected to translate to a long-term OS benefit compared with DBTd.^{53 23, 54, 55, 116, 117}

The results from the base case ITC were consistent across the sensitivity analysis (all 14 covariates adjusted), scenario analyses using alternative ITC methodologies,¹¹⁸ and a sensitivity analysis where patients ≥ 65 years were not excluded from trial populations. This provides support for the robustness of the base case results.

The addition of daratumumab to lenalidomide maintenance therapy in the AURIGA trial resulted in significantly higher rates of MRD-negativity, including sustained MRD-negativity, translating to a reduced risk of disease progression

- The primary endpoint of MRD-negative conversion rate by 12 months from the start of maintenance therapy was met in the AURIGA trial (DL versus L: 50.5% versus 19.8%; OR: 4.51; 2.37, 8.57; p<0.0001).³¹
- The sustained MRD-negativity rate for patients receiving DL maintenance was three times higher than the rate for those receiving L maintenance (17.2% versus 5.0%; OR: 4.08; 95% CI: 1.43, 11.62; p=0.0065).³¹
- At the time of the 4th April 2024 data cut (median follow-up: 32.3 months), patients in the DL arm had a 47% reduction in the risk of disease progression or death, compared with the L arm (HR, 0.53; 95% CI: 0.29 – 0.97).³¹ A similar trend was observed for overall survival (HR, 0.50, 95% CI: 0.17 – 1.50).

Alongside substantial efficacy improvement, the addition of daratumumab to BLd induction and consolidation and L maintenance therapy was well-tolerated, with similar HRQoL and safety profiles observed across the two treatment arms in PERSEUS

- [REDACTED] were observed between the DBLd and BLd treatment arms across a range of patient-reported outcome (PRO) measures, including the EORTC QLQ-C30, the EORTC QLQ-MY20 (a MM-specific PRO measure consisting of four domains including disease symptoms and the side effects of treatment), and EQ-5D-5L measures. These results indicate that quadruplet therapy with DBLd followed by DL maintenance is not associated with any major detriment to patient HRQoL compared to triplet therapy with BLd followed by L maintenance.³²
- The incidence of treatment-emergent adverse events (TEAEs) was comparable between the BLd and DBLd treatment arms at each treatment phase ([REDACTED]% versus [REDACTED]% for the induction phase, [REDACTED]% versus [REDACTED]% for the pre-ASCT phase, [REDACTED]% versus [REDACTED]% for the ASCT phase [REDACTED]% versus [REDACTED]% for the consolidation phase and [REDACTED]% versus [REDACTED]% for the maintenance phase).^{32, 110}

The overall incidence of Grade 3 or 4 TEAEs was [REDACTED] in the DBLd arm versus the BLd arm during induction and consolidation. However, the incidence was [REDACTED] across arms during the maintenance phase, and fewer patients discontinued treatment due to TEAEs in the DBLd arm ([REDACTED]%) compared to the BLd arm ([REDACTED]%).³²

- Overall, these safety data support that DBLd-DL treatment was consistent with the known safety profiles of daratumumab, lenalidomide and BLd in isolation, with DBLd-DL treatment shown to be associated with clinically manageable side effects. Of particular note, no new safety signals were identified³²

The introduction of DBLd-DL therapy would represent a clear step-forward in the treatment pathway for patients in NDMM eligible for HDT-ASCT in UK clinical practice

- In the induction and consolidation phase, DBLd would displace DBTd as an equally or more efficacious treatment, which frees patients and clinicians from the burden associated with thalidomide-related toxicities. Induction and consolidation ITCs demonstrate that DBLd is at least as effective as DBTd in the induction and consolidation phase, with the potential to elicit a greater proportion of $\geq$ VGPR compared to DBTd.
- The key benefit associated with the full treatment sequence of DBLd-DL is the addition of daratumumab maintenance therapy – currently, in UK clinical practice, patients only receive maintenance therapy with lenalidomide following a response to induction and consolidation treatment.
 - The PERSEUS trial showed that three-quarters of patients receiving DBLd-DL achieved MRD-negativity, compared with less than half of those receiving BLd-L. A significantly higher proportion of patients who were MRD-positive post-consolidation converted to MRD-negative during maintenance in the DBLd-DL arm versus the BLd-L arm (60.2% versus 40.5%; $p=0.0049$).¹¹³ In the AURIGA trial, the overall conversion rate at median follow-up of 32.3 months was significantly higher for DL than L (60.6% versus 27.7%; $p<0.0001$)³¹. These findings highlight the deep, durable responses associated with the addition of daratumumab to lenalidomide maintenance.

- MRD-negativity is a biologically plausible surrogate of improved long-term outcomes.^{4, 51, 119-121} As such, these results are expected to translate to improved PFS and OS, offering patients the potential for functional cure.
- Whilst OS data remain immature, the strong prognostic association (level 1 evidence of correlation) between improved response rates and extended PFS and OS mean that this is expected to translate into a longer-term survival benefit. This underlines the importance of making DBLd-DL available to patients as soon as possible in the UK treatment pathway, based on the improved response rates observed compared to DBTd-L.

2.1 Identification and selection of relevant studies

Two systematic literature reviews (SLRs) were conducted to identify relevant clinical evidence on the efficacy and safety of treatments for patients with NDMM who are eligible for HDT-ASCT. One focused on treatments specifically in the induction and consolidation setting (referred to as the I+C SLR) and the other focused on treatments in the induction, consolidation and maintenance settings (hereafter referred to as I+C+M SLR).

The I+C SLR was originally conducted on the 31st May 2018 and was subsequently updated on the 30th April 2023 and 26th February 2025. Results of the I+C SLR informed the indirect treatment comparisons (ITCs) conducted for the induction and consolidation phases, presented in Section 2.10.

The I+C+M SLR was originally conducted on the 19th September 2023 and updated on the 26th February 2025. The I+C+M SLR was used to identify evidence relevant to the full treatment sequence (i.e., DBLd-DL) under assessment in this submission. Both 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.¹²²

As no head-to-head studies informing the full treatment sequence of relevance to this submission were identified, we performed a pragmatic re-evaluation of previously excluded studies in order to find additional evidence that could inform a comparison of DL vs. L maintenance.

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

The clinical SLRs identified two studies on DBLd in patients with NDMM who are HDT-ASCT eligible, the PERSEUS and GRIFFIN clinical trials. PERSEUS is an ongoing, randomised, open-label, multicentre, Phase III trial examining the efficacy and safety of DBLd induction and consolidation followed by DL maintenance versus BLd induction and consolidation followed by L maintenance in patients with NDMM who are deemed HDT-ASCT eligible. The GRIFFIN trial is an ongoing randomised, open-label, multicentre, Phase II trial in transplant eligible NDMM patients.¹¹¹ More details are given in Appendix N. As the registrational trial which led to the extension label for daratumumab to DBLd in HDT-ASCT eligible patients with NDMM, PERSEUS was considered the most appropriate source of clinical evidence for DBLd induction and consolidation followed by DL maintenance therapy in this submission.¹

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A summary of the pivotal PERSEUS trial is provided in Table 3.³² Data presented are based on the latest data cut-off (DCO) of the PERSEUS trial (1st August 2023) and are informed by the Sonneveld *et al.* 2024 publication and Clinical Study Report (CSR).¹¹⁰

Table 3: Clinical effectiveness evidence (PERSEUS trial)

Study	PERSEUS (NCT03710603)
Study design	Ongoing, randomised, open-label, multicentre, Phase III trial in patients with NDMM who are eligible for HDT-ASCT. The trial consisted of three phases: a screening phase, a treatment phase and a follow-up phase. The treatment phase was comprised of four key stages: • Induction therapy • ASCT • Consolidation therapy • Maintenance therapy (given until disease progression or unacceptable toxicity)
Population	Patients with NDMM who are deemed eligible for HDT-ASCT. As of 1st August 2023, 709 patients had been randomised to treatment (intent-to-treat [ITT] analysis set: DBLd + DL: 355; BLd + L: 354) and 698 patients treated (safety analysis set: DBLd + DL: 351; BLd + L: 347). See Section 2.4.1 for a more detailed description of analysis sets in the PERSEUS trial.
Intervention(s)	DBLd (induction and consolidation) followed by DL (maintenance) in the following dosing (all 28-day cycles): <u>Induction and consolidation:</u> • Subcutaneous daratumumab ○ Induction (4x 4-week cycles): 1,800 mg per week during Cycles 1 and 2, 1,800 mg every 2 weeks during Cycles 3 and 4 ○ Consolidation (2x 4-week cycles following HDT and ASCT: 1,800 mg every 2 weeks for both Cycles) • Subcutaneous bortezomib 1.3 mg/m² twice a week (Days 1, 4, 8, and 11) for induction and consolidation • Oral lenalidomide 25 mg on Days 1–21 of each Cycle for induction and consolidation • Oral or intravenous dexamethasone 40 mg on Days 1 through 4 and Days 9–12 of each Cycle for induction and consolidation <u>Maintenance:^a</u> • Subcutaneous daratumumab (1,800 mg every 4 weeks on Day 1) • Oral lenalidomide (10 mg on Days 1 to 28 of each cycle, until disease progression or unacceptable toxicity) Please refer to Section 2.2.2, Table 5 for full details of the dosing schedule.
Comparator(s)	BLd (induction and consolidation) followed by lenalidomide (maintenance) in the following dosing (all 28-day cycles): <u>Induction and consolidation:</u> • Subcutaneous bortezomib 1.3 mg/m² twice a week (Days 1, 4, 8, and 11) for induction and consolidation • Oral lenalidomide 25 mg on Days 1–21 of each Cycle for induction

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Study	PERSEUS (NCT03710603)
	and consolidation • Oral or intravenous dexamethasone 40 mg on Days 1 through 4 and Days 9–12 of each Cycle for induction and consolidation Maintenance: • Oral lenalidomide (10 mg on Days 1 to 28 of each 28-day cycle, until disease progression or unacceptable toxicity)
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 ¹¹²	• Proportion of patients undergoing HDT-ASCT • PFS • OS • Response rates: ○ Overall response rate (ORR) ○ sCR ○ ≥CR ○ ≥VGPR ○ CR ○ Partial response (PR) ○ Stable disease (SD) ○ Progressed disease (PD) • MRD-negativity status • AEs • HRQoL outcomes: ○ European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item (EORTC QLQ-C30) scores ○ European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module (EORTC QLQ-MY20) ○ European Quality of Life Five Dimension Five Level Questionnaire (EQ-5D-5L) scores

Footnotes: ^a In line with the licence for daratumumab, daratumumab maintenance treatment is to be administered until disease progression. Daratumumab can, however, be discontinued for patients who have achieved MRD-negativity that is sustained for 12 months, if they have been treated on maintenance for at least 24 months, as recommended by the SmPC.

Abbreviations: AEs: adverse events; ASCT: autologous stem cell transplantation; BLd: bortezomib, lenalidomide and dexamethasone; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab and lenalidomide; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; 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; NDMM: newly diagnosed multiple myeloma; OS: overall survival; PD: progressed disease; PFS: progression-free survival; sCR: stringent complete response; SD: stable disease; SmPC: summary of product characteristics; VGPR: very good partial response.

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Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO);³² Sonneveld *et al.* 2024.¹¹⁰

AURIGA was identified as the sole additional relevant DBLd study during pragmatic title and abstract re-evaluation. Neither the PERSEUS nor GRIFFIN trials included a second randomisation after consolidation and prior to maintenance initiation. However, the Phase III AURIGA trial assessed clinical efficacy and safety in patients randomised to either DL or L maintenance therapy alone in anti-CD38-naïve, MRD-positive patients who had achieved a $\geq$ VGPR after induction therapy and ASCT.³¹ As such, the AURIGA trial was considered as the best available source of evidence for the comparative efficacy of DL versus L maintenance and to inform long-term survival estimates in the economic analysis (see Section 3.3 for further details).

It is noted that the AURIGA trial population differs in some respects to that of the PERSEUS trial, and the population of relevance to this submission. However, evidence from alternative RCTs suggest that the AURIGA results are likely a conservative estimate of the expected outcomes of DL maintenance following daratumumab-based induction and consolidation therapy in clinical practice (see Section 2.13 for further details).

In the AURIGA trial, patients were randomly assigned in a 1:1 ratio to receive DL or L maintenance therapy, which was continued for a maximum of 36 cycles, or until disease progression, unacceptable toxicity or consent withdrawal. Key methodological details of the AURIGA trial are presented in Table 4, with a summary of the trial results in Section 2.6.2. An overview of the baseline characteristics for the trial population is presented in Appendix H.

Table 4: Clinical effectiveness evidence (AURIGA trial)

Study	AURIGA (NCT03710603)
Study design	Ongoing, randomised, open-label, multicentre, Phase III trial in patients with NDMM who: - Have received induction therapy followed by HDT-ASCT - Had achieved $\geq$VGPR - Were MRD-positive (at a threshold of 10^{-5}, according to next-generation sequencing [NGS]) - Had not received prior anti-CD38 therapy
Population	Patients with NDMM who were anti-CD38-naïve and MRD-positive, and had achieved a $\geq$ VGPR following induction and HDT-ASCT. At the primary analysis (4 th April 2024), 200 patients had been randomised 1:1 to treatment (ITT analysis set: DL maintenance: 99; L: 101).
Intervention(s)	DL maintenance in the following dosing (all 28-day cycles): Subcutaneous daratumumab 1,800 mg: - Cycles 1 and 2: weekly - Cycles 3–6: every two weeks - Cycle 7 onwards Oral lenalidomide 10 mg on Days 1–28 of each cycle. After three cycles, the dose could be increased to 15 mg, if tolerated, at the discretion of the investigator
Comparator(s)	L maintenance in the following dosing (all 28-day cycles): Oral lenalidomide 10 mg on Days 1–28 of each cycle. After three cycles, the dose could be increased to 15 mg, if tolerated, at the discretion of the investigator

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Study	AURIGA (NCT03710603)
Indicate if study supports application for marketing authorisation	No
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 ¹¹²	• PFS • OS • Response rates: ○ ORR ○ sCR ○ ≥CR ○ ≥VGPR ○ CR ○ PR ○ SD ○ PD • MRD-negativity status • AEs • HRQoL outcomes: ○ EORTC QLQ-C30 scores ○ EORTC QLQ-MY20 ○ EQ-5D-5L scores

Abbreviations: AEs: adverse events; ASCT: autologous stem cell transplantation; CR: complete response; DL: daratumumab and lenalidomide; EORTC QLQ-MY20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; 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; L: lenalidomide; MRD: minimal residual disease; NDMM: newly diagnosed multiple myeloma; OS: overall survival; PD: progressed disease; PFS: progression-free survival; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.

Source: Badros *et al.* 2025,³¹ ClinicalTrials.gov 2025.¹²³

2.2.1 Summary of trial methodology

Trial design

PERSEUS is an ongoing, randomised, open-label, multicentre, Phase III trial conducted at 115 study centres in 13 locations across Europe and Australia.³² An overview of the PERSEUS trial design is provided in Figure 9.

The trial consisted of 3 phases: a screening phase, a treatment phase, and a follow-up phase. The screening phase started up to 28 days before randomisation. The treatment phase extended from Cycle 1 Day 1 and consisted of 4-week cycles. This phase included four cycles of induction therapy, followed by ASCT, then two cycles of consolidation therapy, followed by maintenance therapy until disease progression or unacceptable toxicity. Patients entered the Follow-up Phase following documented disease progression or unacceptable toxicity leading to all study treatment

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discontinuation, or if a response of PR or better ($\geq$ PR) was not achieved by Day 1 of Cycle 7.³² Patients were followed up every four months until death or loss to follow-up.¹¹⁰

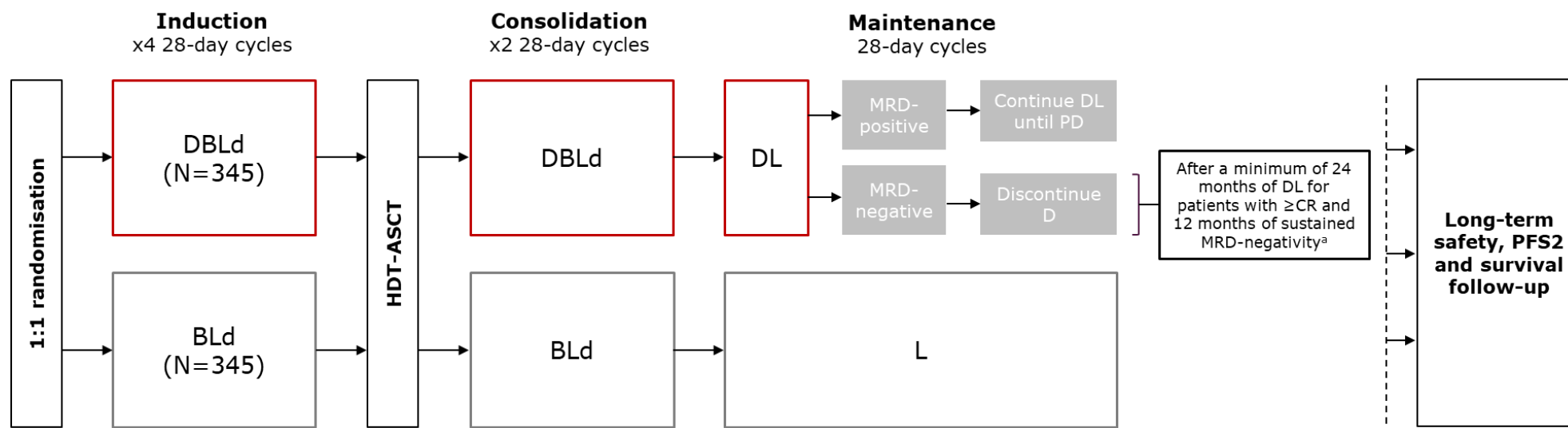
Patients were stratified by International Staging System (ISS) Stage I, II, or III disease (based upon laboratory results for β -2 microglobulin and albumin) and cytogenetics (standard risk or high risk as defined by presence of del17p, t[4;14] or t[14;16]) and then randomised in a 1:1 ratio into one of the following treatment arms:³²

- **Arm A:** BLd for induction and consolidation, followed by L maintenance until disease progression or unacceptable toxicity, henceforth referred to as the **BLd treatment arm**
- **Arm B:** DBLd for induction and consolidation followed by DL maintenance until disease progression or unacceptable toxicity, henceforth referred to as the **DBLd treatment arm**

Patients in the DBLd treatment arm who had a response of $\geq$ CR were permitted to stop therapy with daratumumab after a minimum of 24 months of maintenance therapy, if sustained MRD-negativity (at the threshold of 10^{-5}) was established for a minimum of 12 months. These patients continued L maintenance therapy until disease progression or unacceptable toxicity. After stopping daratumumab therapy, patients with sustained MRD-negativity should restart therapy with daratumumab if there is a recurrence of MRD at 10^{-4} or higher, or a confirmed loss of CR without IMWG-defined disease progression.³² However, it should be noted that this represents a minority of patients, with only █% of patients (i.e., only █ of █ patients in the DBLd-DL arm who stopped daratumumab and continued maintenance therapy) in PERSEUS re-starting daratumumab following loss of MRD-negative status.³²

A schematic of the trial is presented in Figure 9. Full details of patient disposition at the August 2023 DCO are provided in Section 2.4.3.

Figure 9: Study schematic of the PERSEUS trial



Footnotes: ^a Daratumumab therapy was restarted upon confirmed loss of CR or recurrence of MRD at 10^{-4} or higher.

Abbreviations: BLd: bortezomib, lenalidomide, and dexamethasone; CR: complete response; DBLd: daratumumab in combination with bortezomib, lenalidomide, and dexamethasone; DL: daratumumab with lenalidomide; L: lenalidomide; MRD: minimal residual disease; PD: progressive disease; PFS2: progression-free survival on the next line of therapy.

Source: Sonneveld *et al.* 2024 (Supplementary material: Statistical Analysis Plan).¹¹⁰

2.2.2 Trial methodology

A summary of the trial methodology, including the eligibility criteria of PERSEUS, is presented in Table 5 below.

Table 5: Summary of PERSEUS trial methodology

Trial name	PERSEUS
Location	Australia, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Spain, Switzerland, Turkey
Trial design	Ongoing, randomised, open-label, multicentre, Phase III trial in patients with NDMM who are eligible for HDT-ASCT. The trial consisted of three phases: a screening phase, a treatment phase and a follow-up phase. The treatment phase included induction therapy followed by ASCT and consolidation therapy, followed by maintenance therapy until disease progression or unacceptable toxicity.
Eligibility criteria for patients	Key inclusion criteria: • 18 to 70 years of age, inclusive • Monoclonal plasma cells in the bone marrow $\geq 10\%$ or presence of a biopsy proven plasmacytoma and documented multiple myeloma satisfying at least one of the CRAB criteria or biomarkers of malignancy criteria • Newly diagnosed patients for whom HDT-ASCT is part of the intended treatment plan • Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 Key exclusion criteria: • Prior or current systemic therapy or stem cell therapy for any plasma cell dyscrasia, with the exception of emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment Full inclusion and exclusion criteria can be found within Section 4 of the protocol (Sonneveld <i>et al.</i> 2024. Supplementary Material) included within the reference pack.¹¹⁰
Method of study drug administration	• Subcutaneous daratumumab ○ Induction (4 x 4-week cycles): 1,800 mg per week during Cycles 1 and 2, 1,800 mg every 2 weeks for Cycles 3 and 4 ○ Consolidation (2 x 4-week cycles following HDT and ASCT): 1,800 mg every 2 weeks for both Cycles ○ Maintenance: 1,800 mg every four weeks from Week 25 onwards^a • Subcutaneous bortezomib ○ Induction, consolidation (Cycles 1–6): 1.3 mg/m² bortezomib as a subcutaneous injection twice a week (Days 1, 4, 8, and 11) for 6 cycles

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	• Oral lenalidomide ○ Induction (Cycles 1–4): 25 mg on Days 1–21 of each Cycle ○ Consolidation (Cycles 5–6): 25 mg on Days 1–21 of each Cycle ○ Maintenance: 10 mg on Days 1 to 28 of each 28-day cycle, until disease progression or unacceptable toxicity • Oral or intravenous dexamethasone ○ Induction and consolidation: (Cycles 1–6): 40 mg on Days 1 through 4 and Days 9–12 of each Cycle
Permitted and disallowed concomitant medication	Permitted: • Colony-stimulating factors, erythropoietin, and transfusion of platelets and red cells • Loperamide is recommended for the treatment of diarrhoea, starting at the time of the first watery stool • Methods for the prevention of constipation are permitted (e.g. adequate hydration, high-fibre diet, and stool softeners, if needed) • Adequate hydration is 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) is permitted before treatment • Vaccination is allowed per local guidelines Disallowed: • Concomitant administration of strong CYP3A4 inducers is prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) should be avoided and is not recommended in patients receiving bortezomib • Other agents that target CD38 • Medications used for other indications that have antimyeloma properties • Approved or investigational treatments for multiple myeloma (including but not limited to conventional chemotherapies, IMiDs, or PIs) • Concomitant administration of investigational agents including administration of commercially available agents with activity against or under investigation for multiple myeloma • Administration of investigational, live attenuated, or replication-competent viral vector vaccines <4 weeks prior to the start of study treatment, during study treatment, or initiated <90 days after last dose of study treatment
Primary outcome	• PFS
Secondary and exploratory outcomes^b	• OS • ≥CR • DoR

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	• ORR • ≥VGPR • sCR • MRD-negative status with ≥CR • Time to response • Safety outcomes, including AEs • Duration of MRD-negativity • Pharmacokinetic (PK) outcomes • Immunogenicity • Patient-reported outcomes from the EORTC and EQ-5D-5L questionnaires • Stem cell yield after mobilisation • Time to engraftment post-ASCT • Proportion of patients undergoing HDT-ASCT
Pre-planned subgroups	Efficacy endpoints • Age (<65 versus ≥65 years) • Sex (male versus female) • Race (white versus other) • ISS (I versus II versus III) • Cytogenic risk (high versus standard versus indeterminate) • Type of MM (immunoglobulin G [IgG] versus non-IgG) • Baseline ECOG performance score (0 versus ≥1) Safety endpoint • Age (<50 versus 50–<65 versus ≥65) • Baseline hepatic function (normal versus impaired) • Sex (male versus female) • Race (White versus Other) • Baseline renal function (<60 mL/min/1.73m² versus 60 to <90 mL/min/1.73m² versus ≥90 mL/min mL/min/1.73m²) • Baseline body weight (≤65 kg versus >65 to ≤85 kg versus >85 kg)
Duration of study and follow-up	At the 1 st August 2023 DCO, median overall follow-up was 47.5 months (DBLd + DL: ■■■ months; BLd + L : ■■■ months) ¹¹⁰

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Footnotes: ^a Daratumumab can be discontinued for patients with a response of CR or better who have achieved MRD-negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months. After stopping daratumumab therapy, subjects with sustained MRD-negativity should restart therapy with daratumumab if there is a recurrence of MRD. ^b Bolded outcomes are presented in this submission.

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CD38: cluster of differentiation 38; CR: complete response; CRAB: calcium, renal, anaemia, bone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DCO: data cut-off; DL: daratumumab and lenalidomide; ECOG: Eastern Cooperative Oncology Group; HDT: high dose therapy; Ig: immunoglobulin; IMiD: immunomodulatory agent; ISS: International Staging System; MRD: minimal residual disease; NDMM: newly diagnosed multiple myeloma; ORR: overall response rate; OS: overall survival; PI: proteasome inhibitor; PK: pharmacokinetic; sCR: stringent complete response; ULN: upper limit of normal; VGPR: very good partial response; L: lenalidomide.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO);³² Sonneveld *et al.* 2024 (Supplementary material: PERSEUS trial Protocol and Statistical Analysis Plan).¹¹⁰

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Baseline characteristics and demographics

The definitions of the analysis sets in the PERSEUS trial and the disposition of patients are presented in Section 2.4. This submission focusses on the ITT analysis set, which included any patients who were randomly assigned to either the BLd or DBLd treatment arm at the August 2023 DCO. A summary of the baseline patient demographics and disease characteristics for the 709 patients in the ITT analysis set in the PERSEUS trial, is provided in Table 6 below.^{32, 110}

Patients in the BLd treatment arm had a median age of 59.0 years (range: 31, 70) and patients in the DBLd treatment arm had a similar median age of 61.0 years (range: 32, 70).¹¹⁰ The median time between diagnosis and the first dose was similar in patients in the BLd and DBLd treatment arms (1.12 years [range: 0.1, 184.6] versus 1.18 years [range: 0.0, 46.5]).¹¹⁰ Extramedullary disease (defined as the presence of one or more extramedullary soft-tissue lesions) was present in a similar proportion of patients in both the BLd and DBLd treatment arms (■ patients ■ versus ■ patients ■, respectively).³² Overall, baseline characteristics were well balanced between patients in the BLd and DBLd treatment arms.

Furthermore, stratification factors of cytogenetics and ISS stage were balanced between the 2 treatment arms. A total of ■ (■%) participants had a high-risk cytogenetic abnormality (presence of del[17p] [■%], t[4;14] [■%] or t[4;16] [■%]). The distribution of ISS stage was balanced between treatment arms, with 51.4% of participants overall reported as Stage I, 33.8% as Stage II, and 14.8% as Stage III.

Table 6: Summary of baseline demographic and disease characteristics

Characteristics	ITT analysis set		
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)
Age, years			
Median (range)	59.0 (31, 70)	61.0 (32, 70)	60.0 (31, 70)
Overall age group, n (%)			
<50	54 (15.3)	54 (15.2)	108 (15.2)
≥50 and <65	213 (60.2)	207 (58.3)	420 (59.2)
≥65	87 (24.6)	94 (26.5)	181 (25.5)
Sex, n (%)			
Female	149 (42.1)	144 (40.6)	293 (41.3)
Male	205 (57.9)	211 (59.4)	416 (58.7)
Race, n (%)			
White	323 (91.2)	330 (93.0)	653 (92.1)
Black or African American	4 (1.1)	5 (1.4)	9 (1.3)

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Characteristics	ITT analysis set		
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)
Asian	6 (1.7)	4 (1.1)	10 (1.4)
Native Hawaiian or other Pacific Islander	████	████	████
American Indian or Alaska Native	████	████	████
Not reported	18 (5.1)	12 (3.4)	30 (4.2)
Ethnicity, n (%)			
Hispanic or Latino	████	████	████
Not Hispanic or Latino	████	████	████
Missing	████	████	████
Body weight, kg^c			
Median (range)	████	████	████
Baseline ECOG, n (%)^d			
0	230 (65.0)	221 (62.3)	451 (63.6)
1	108 (30.5)	114 (32.1)	222 (31.3)
2	16 (4.5)	19 (5.4)	35 (4.9)
3	0	1 (0.3)	1 (0.1)
Type of myeloma by immunofixation or serum FLC assay, n (%)			
IgG	████	████	████
IgA	████	████	████
IgM	I	████	████
IgD	████	████	████
IgE	I	I	I
Light chain	████	████	████
Kappa	████	████	████
Lambda	████	████	████
FLC-Kappa ^e	████	████	████
FLC-Lambda ^f	I	████	████
Biclonal	████	████	████
Type of measurable disease, n (%)			
Serum	████	████	████
IgG	185 (52.3)	204 (57.5)	389 (54.9)
IgA	85 (24.0)	65 (18.3)	150 (21.2)

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Characteristics	ITT analysis set		
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)
Other ^g	11 (3.1)	13 (3.7)	24 (3.4)
Urine only	46 (13.0)	43 (12.1)	89 (12.6)
Serum FLC	27 (7.6)	29 (8.2)	56 (7.9)
Not evaluable (NE)	0	1 (0.3)	1 (0.1)
ISS Staging, n (%)^h			
Stage I	178 (50.4)	186 (52.4)	364 (51.4)
Stage II	125 (35.4)	114 (32.1)	239 (33.8)
Stage III	50 (14.2)	55 (15.5)	105 (14.8)
R-ISS Staging, n (%)ⁱ			
Stage I	██████	██████	██████
Stage II	██████	██████	██████
Stage III	██████	██████	██████
Time from MM diagnosis to randomisation, years			
Mean (SD)	██████	██████	██████
Median (range)	1.12 (0.1, 184.6)	1.18 (0.0, 46.5)	1.15 (0.0, 184.6)
Number of lytic bone lesions, n (%)			
None	██████	██████	██████
1–3	██████	██████	██████
4–10	██████	██████	██████
More than 10	██████	██████	██████
Number of extramedullary plasmacytomas, n (%)			
0	██████	██████	██████
≥1	██████	██████	██████
% Plasma cells, bone marrow biopsy/aspirate			
<10	██████	██████	██████
10–30	██████	██████	██████
>30	██████	██████	██████
Cytogenetic risk, n (%)^j			
Standard risk	266 (75.1)	264 (74.4)	530 (74.8)
High risk ^k	78 (22.0)	76 (21.4)	154 (21.7)
del(17p)	██████	██████	██████
t(4;14)	██████	██████	██████

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Characteristics	ITT analysis set		
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)
t(14;16)	██████	██████	██████
Indeterminate	10 (2.8)	15 (4.2)	25 (3.5)

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy. ^c One patient did not have baseline weight. The patient was randomised but not treated. ^d One patient had ECOG 0 at randomisation and worsened to ECOG 3 at baseline. ^e Includes patients without a positive immunofixation but with evidence of free light chain kappa by FLC testing. ^f Includes patients without a positive immunofixation but with evidence of free light chain lambda by FLC testing. ^g Includes patients with IgD, IgM, IgE and biclonal. ^h ISS staging is derived based on the combination of serum β2-microglobulin and albumin. ⁱ Determination is based on three factors: International Staging System (ISS); presence of chromosomal abnormalities of t(4; 14), t(14; 16), or del17p by FISH/Karyotype testing and serum lactate dehydrogenase (LDH) at baseline. ^j Cytogenetic risk is based on FISH. ^k Patients may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)].

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; 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; MM: multiple myeloma; NE: not evaluable; SD: standard deviation.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO; Table 4 and Table 5);³² Sonneveld *et al.* 2024.¹¹⁰

Generalisability to UK clinical practice

As part of TA763, J&J invested in obtaining real-world data 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 aim was to understand MM patient and disease characteristics in the UK clinical practice. A comparison of patient characteristics from the NCRAS dataset and the DBLd-DL arm of PERSEUS trial population is provided in Table 7 below, showing a very similar age between patients in the NCRAS dataset and PERSEUS DBLd-DL arm.

As is often the case with real world data sets, availability of data for baseline characteristics were not as comprehensive as those collected in clinical trials. Although, ECOG and ISS data were available in the NCRAS, it's impacted by high degree of missing data. Hence, the level of missing data for ECOG and ISS stage makes comparison somewhat challenging.

Table 7: Comparison of patient characteristics from the from NHS Digital NCRAS for England between January 2015 and December 2022 and DBLd-DL arm of the PERSEUS trial (at baseline)

	NCRAS dataset (n=██████)	PERSEUS DBLd-DL (n=355)
Mean age (SD)	██████	██████
Median age (range)	██████	61.0 (32, 70)
Female, n (%)	██████	144 (40.6)
Age category, n (%)		
<50 years	██████	██████
50-64 years	██████	██████
65 years and older	██████	94 (26.5)
ECOG score, n (%)		
0	██████	221 (62.3)

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	NCRAS dataset (n=████)	PERSEUS DBLd-DL (n=355)
1	████	114 (32.1)
2	████	19 (5.4)
3	████	1 (0.1)
4	████	-
Null	████	-
ISS stage, n (%)^a		
I	████	186 (52.4)
II	████	114 (32.1)
III	████	55 (15.5)
Null	████	-

Footnotes: ^a From 01/04/2021 onwards, the revised ISS (R-ISS) could be submitted by trusts.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System; NCRAS: National Cancer Registration and Analysis Service; SD: standard deviation.

Source: Sonneveld *et al.* 2024,¹¹⁰ NHS Digital NCRAS¹²⁴

Whilst a higher proportion of patients had an ECOG score of 0 and ISS stage of I in the PERSEUS trial compared to the NCRAS dataset, data for these factors were missing for half of the patients in the NCRAS dataset, therefore limiting the comparability of the two patient populations.

Nevertheless, feedback was gathered from UK clinical experts consulted during a May 2025 Advisory Board commenting on the generalisability of PERSEUS to UK clinical practice.⁴ Overall, the UK clinical experts noted that baseline characteristics of patients in the PERSEUS trial were generalisable to patients with HDT-ASCT NDMM in UK clinical practice:⁴

- One expert noted that the median age of 61.0 years for the DBLd arm of the PERSEUS trial is broadly generalisable however may be slightly younger than that expected of HDT-ASCT eligible patients with NDMM in UK clinical practice. However, it was highlighted that this is a common finding in clinical trials and given the median age of patients is only anticipated to decrease in the coming years, any discrepancies would not impact the generalisability of the trial results.⁴ Furthermore, NCRAS data in Table 7 suggests that the age of patients in the DBLd arm is in fact aligned with the UK patient population.
- One of the UK clinical experts noted that the ECOG PS profile of the PERSEUS trial population may differ slightly from ASCT-eligible NDMM patients in UK clinical practice, however that it is broadly generalisable. The expert noted that trials in patients with MM often do not include patients ECOG PS ≥2, despite them receiving transplants in UK clinical practice. The expert however acknowledged the challenge of including such patients in a clinical trial setting.
- The experts agreed that the remaining characteristics were broadly generalisable to patients in UK clinical practice.

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

2.4.1 Definitions of the patient population analysis sets

Analysis sets

Analysis sets in the PERSEUS trial relevant to this submission are outlined in Table 8 below. A total of 709 patients were included in the ITT analysis set which informs the efficacy evidence for this submission, whilst a total of 698 patients were included in the safety analysis set which forms the principal evidence base for the safety evidence for this submission.¹¹⁰

Table 8. PERSEUS analysis set definitions

Analysis set	Analysis set description	Number of patients		
		BLd arm ^a	DBLd arm ^b	Total
ITT analysis set (primary analysis set)	Patients who have been randomly assigned to either the BLd or DBLd treatment arm	354	355	709
Safety analysis set	All patients who have received at least one dose of treatment (partial or complete) in the trial	347	351	698

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.
Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intent-to-treat.
Source: Sonneveld *et al.* 2024 (Supplementary material: PERSEUS trial Protocol and Statistical Analysis Plan).¹¹⁰

2.4.2 Statistical analysis

Details of the statistical methods for the PERSEUS trial are presented in Table 9.

Table 9: Statistical methods for the primary analysis of PERSEUS

Trial name	PERSEUS
Hypothesis objective	Standard treatment strategy in HDT-ASCT eligible patients with NDMM: BLd induction followed by ASCT followed by BLd consolidation followed by maintenance therapy with lenalidomide alone New treatment strategy: To add daratumumab to the standard induction, consolidation and lenalidomide maintenance treatment phases. With the primary efficacy endpoint PFS, the null hypothesis is that there is no difference in PFS between the two treatment strategies in subjects with previously untreated multiple myeloma who are eligible for high-dose therapy
Statistical analysis	The treatment groups were: • BLd arm: BLd for induction and consolidation, followed by L maintenance • DBLd arm: DBLd for induction and consolidation followed by DL maintenance • Continuous variables were summarised using descriptive statistics such as mean, SD, median and range. Categorical variables were summarised using frequency and percentage • For the efficacy assessment of response and disease progression, a validated computerised algorithm was utilised to determine response and disease progression for each subject. This computerised algorithm is based on the IMWG response criteria (Durie 2006, Rajkumar 2011), and has been used and validated by an independent review • All statistical hypothesis tests and 95% confidence intervals presented are 2-sided
Sample size, power calculation	• It was assumed that median PFS is 63 months for the BLd arm, and the addition of daratumumab will decrease the risk of progression or death by 31% (HR=0.69; estimated median PFS of 91 months for DBLd arm). Assuming a 12-month accrual and 64-month of additional follow-up, approximately 690 patients (345/arm) were needed to achieve the 285 PFS events needed to achieve 85% power with a 2-sided alpha of 0.05 • Long-term follow-up for survival continued until approximately 310 deaths had been observed or 9 years had elapsed after the last patient was randomised, whichever occurred earlier. Per the protocol, this provided approximately 70% power to detect a 25% reduction in the risk of death (HR=0.75) with a log-rank test at a 2-sided alpha of 0.05. However, a hazard ratio of 0.71 or less will provide at least 80% power • A large Phase III trial (CASSIOPEIA, MMY3006) comparing DBLd with BTd in a similar study population

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	(N=1085), observed a hazard ratio (HR) of 0.66 from first randomisation censoring the events from the crossover BTd subjects after Part 1 of the trial with median follow-up of 18.8 months. As such, a HR would provide approximately 93.5% power for this study with 310 deaths. After the significance of PFS was established, testing of OS could continue as planned until a definitive conclusion on OS was reached
Data management, patient withdrawals	Discontinuation and withdrawal: • Patients were withdrawn from the trial for any of the following reasons: ○ Lost to follow-up ○ Withdrawal of consent for trial participation ○ Death ○ Sponsor terminates the trial • When a patient withdrew consent before completing the trial, the reason for withdrawal was documented in the electronic case report form (eCRF) and in the source document • Study treatment assigned to the withdrawn patients was not permitted to be assigned to another patient • Patients who withdrew were not replaced • If a patient discontinued study treatment and withdrew from the trial before the end of the treatment phase, End-of-Treatment assessments were obtained • If the reason for withdrawal from the trial 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; eCRF: electronic case report form; HR: hazard ratio; IMWG: International Myeloma Working Group; PFS: progression-free survival.

Source: Sonneveld *et al.* 2024 (Supplementary material: Statistical Analysis Plan).¹¹⁰

Definitions for outcome measures

A variety of outcomes were employed to explore the efficacy of DBLd induction and consolidation therapy followed by DL maintenance versus BLd induction and consolidation therapy followed by L maintenance in patients with NDMM who are eligible for HDT-ASCT. Definitions for these outcome measures are presented in Table 10.

Table 10. Definitions for outcome measures used in PERSEUS

Outcome measure	Definition
Primary outcome	
PFS	The time from the date of randomisation to the date of first disease progression (PD) according to the IMWG response criteria, or death due to any cause, whichever occurred earlier
Key secondary outcomes	
≥CR rate	The percentage of ITT patients who achieved CR or stringent CR (sCR) status anytime during the trial per the IMWG criteria. In addition, the specific response must have been achieved prior to start of subsequent therapies
Overall MRD-negativity rate	The proportion of ITT patients who achieved MRD-negativity (at or below the threshold of 10^{-5}) by bone marrow aspirate and achieved ≥CR (i.e. CR or sCR) at any time after the date of randomisation during the trial (and prior to progressive disease, subsequent therapy, or both)
OS	Measured from the date of randomisation to the date of death due to any cause. Patients who were lost to follow-up were censored at the time of lost to follow-up. Patients who died after consent withdrawal were considered as having an OS event. Patients who were still alive at the clinical cut-off date for the analysis were censored at the last known alive date
Post-consolidation MRD-negativity rate	The proportion of patients who achieved MRD-negativity (at or below the threshold of 10^{-5}) and achieved ≥CR at the end of the consolidation treatment phase
ORR, ≥VGPR rate and sCR rate	The percentage of ITT patients who achieved ≥PR status (PR, VGPR, CR or sCR), ≥VGPR status (VGPR, CR or sCR) and sCR status anytime during the trial per the IMWG criteria, respectively
ORR, ≥VGPR rate, ≥CR rate, and sCR rate for post-induction/post-ASCT/post-consolidation/full treatment sequence	The proportions of ITT patients who achieved ≥PR status, ≥VGPR, ≥CR, or sCR by the end date of the induction/ASCT/consolidation/maintenance treatment phase, per the IMWG criteria, respectively
Time to response	The time from the date of randomisation to the date of first documentation of a confirmed response (≥PR) for patients who had ≥PR as their best response
DOR	The date of first documentation of a confirmed response (≥PR) to the date of first documentation of a confirmed PD, according to IMWG criteria, or death due to PD, whichever occurs first, for patients who had ≥PR as their best response. Responders without PD were censored at the last disease evaluation prior to subsequent therapy

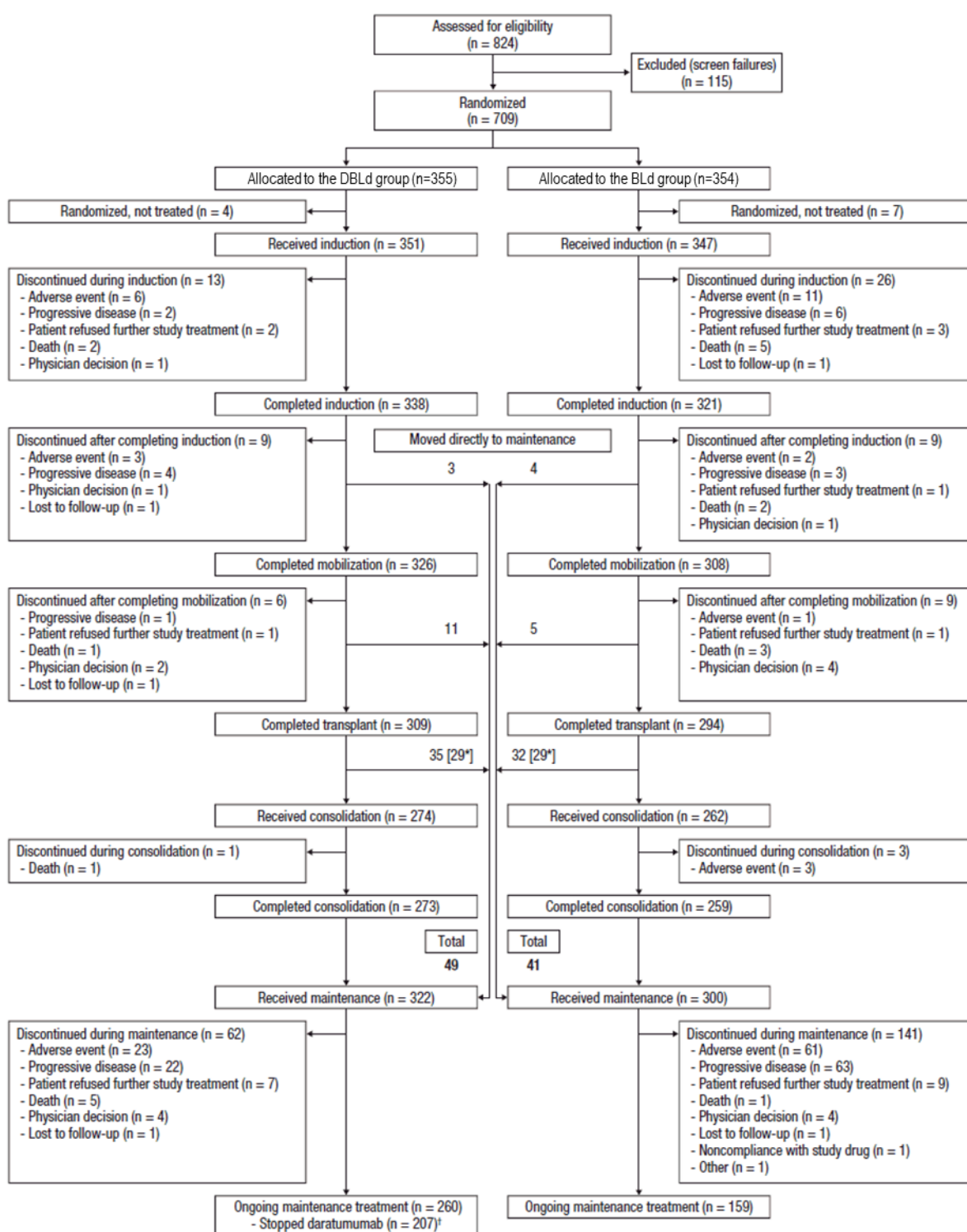
Abbreviations: ASCT: autologous stem cell transplant; CR: complete response; DOR: duration of response; IMWG: International Myeloma Working Group; ITT: intent-to-treat; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PR: partial response; sCR: stringent complete response; VGPR: very good partial response.
Source: Sonneveld *et al.* 2024 (Supplementary material: Statistical Analysis Plan).¹¹⁰

2.4.3 Study population and patient disposition

A consort diagram showing patient flow through the PERSEUS trial is shown in Figure 10. At the time of the 1st August 2023 DCO, 824 patients had been assessed for eligibility, of which a total of 709 patients (DBLd arm: 355; BLd arm: 354) were randomised. Of the 709 randomised patients, 351 patients in the DBLd arm and 347 patients in the BLd arm received study treatment.^{32, 110}

Fewer patients in the DBLd arm (91 [25.9%]) discontinued treatment compared with the BLd arm (188 [54.2%]).¹¹⁰ The majority of discontinuations occurred during induction and maintenance. Fewer patients in the DBLd arm discontinued treatment during induction and maintenance compared with the BLd arm (DBLd arm: 13 [3.7%]; BLd arm: 26 [7.5%] and DBLd arm: 62 [19.3%]; BLd arm: 141 [47.0%], respectively). The most common reasons for discontinuation of all components of study treatment (>10% of total in either arm) were AEs (DBLd arm: 9.1%; BLd arm: 22.5%) and progressive disease (DBLd arm: 8.3%; BLd arm: 20.7%). Full details of patient disposition are provided in Figure 10.³²

Figure 10: Consort diagram for PERSEUS trial



Footnote: *Patients who received Cycles 5 and 6 consecutive to induction therapy due to the COVID-19 pandemic

† After at least 24 months of maintenance therapy, daratumumab was discontinued in patients who achieved complete response or better and sustained MRD-negativity (at or below a sensitivity threshold of 10^{-5}) for 12 months; patients continued L maintenance therapy until disease progression or unacceptable toxicity.

Abbreviations: BId: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone.

Source: Sonneveld *et al.* 2024 (Supplementary Appendix).¹¹⁰

2.5 Critical appraisal of the relevant clinical effectiveness evidence

PERSEUS and AURIGA were assessed for risk of bias using the Cochrane RoB 2.0 Quality Assessment tool 2.0, as recommended by NICE.¹²⁵ The quality assessment was based on published sources for the trial, where possible, and supplemented with information provided in the trial protocol. Overall, both trials were associated with a low risk of bias. The results from the quality assessment for PERSEUS presented in Table 11. The AURIGA trial quality assessment is presented in Appendix M

Table 11: Quality assessment of PERSEUS 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 intervention and comparator by randomly permuted blocks using an interactive web-response system (IWRS)
1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Y	IWRS was employed for randomisation, ensuring allocation concealment.
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	The baseline characteristics were similar between the groups
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	Due to the open-label nature of the study, participants were aware of their treatment assignment
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	Due to the open-label nature of the study, carers and those delivering the assigned intervention were aware of their treatment assignment
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	There was no evidence of discontinuations or switches based on the CONSORT diagram
2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	Not applicable as there were no deviations reported
2.5 If Y/PY/Ni to 2.4: Were these deviations from intended intervention balanced between groups?	NA	Not applicable as there were no deviations reported
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was 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

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Study Question	Grade (yes/no/unclear)	Justification
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/Nl 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/Nl 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	The outcomes and their measurement methods were clearly defined
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Objective outcomes and standardized criteria were used for measurement
4.3 If N/PN/Nl to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were aware of the treatments due to the open-label design
4.4 If Y/PY/Nl to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA
4.5 If Y/PY/Nl 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	Data were in line with the well-documented, pre-specified analysis plan
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	The primary outcome had a single definition, and other analyses were 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	No evidence of selective reporting of outcomes
Risk of bias judgement	Low	-
Overall Risk of bias judgement	Low	

Abbreviations: IWRS: interactive web-response system; N: no; NA: not applicable; NI: no information; Y: yes.

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2.6 Clinical effectiveness results of the relevant studies

2.6.1 PERSEUS trial

PERSEUS is an ongoing, Phase III RCT of DBLd induction and consolidation therapy followed by DL maintenance versus BLd induction and consolidation therapy followed by L maintenance in HDT-ASCT eligible patients with NDMM. Efficacy analyses were performed in the ITT population, which comprised all patients who underwent randomisation to the DBLd or BLd treatment arms.³² Data in this submission are based on the latest, 1st August 2023, DCO of the PERSEUS trial (median follow-up for the DBLd arm: [REDACTED] months; median follow-up for the BLd arm: [REDACTED] months).³² Results in this section are presented for the full treatment sequence (including induction, consolidation and maintenance treatment) and by treatment phase, where available.

At the 1st August 2023 DCO, the PERSEUS trial demonstrated that DBLd induction and consolidation therapy followed by DL maintenance (DBLd arm) resulted in statistically significantly greater responses (sCR, ≥CR, ≥VGPR, MRD-negativity) as compared with BLd followed by L maintenance treatment (BLd arm).^{32, 110} These responses deepened over time from the induction to post-consolidation and maintenance treatment phases. As described in Section 1.3.2, a deep, sustained treatment response including MRD negativity is an important predictor for long-term survival outcomes. Furthermore, feedback from UK clinical experts from the May 2025 Advisory Board confirmed that it is biologically plausible that depth of response correlates with long-term outcomes, with MRD-negativity in particular considered as a suitable proxy for long-term survival benefit, and thereby meets the NICE criteria for surrogate endpoints.^{4, 50, 59} When considering the full treatment sequence, the PERSEUS study provides supportive albeit non-randomised evidence that addition of daratumumab to L maintenance therapy is associated with improved depth response versus L maintenance therapy alone.³² Post-consolidation, the DBLd treatment arm had a higher OR versus the BLd arm for all response endpoints including sCR and MRD-negativity.

PFS and OS data were not mature at the latest DCO, with neither median PFS nor median OS reached in either treatment arm. Given the generally good prognosis of HDT-ASCT eligible NDMM patients, immature survival data are expected in this front-line setting, whereby extensive follow-up would be required to obtain mature survival data, and are consistent with the availability of data in previously recommended treatments by NICE in the same indication.² Despite the relative immaturity, the available survival data obtained at the August 2023 DCO provided promising initial results; a consistent trend supporting the clinical benefit of survival achieved in the DBLd arm when compared with the BLd arm was observed. Given the correlation between deep sustained response and improved survival outcomes, this benefit is only anticipated to become more pronounced over time.

A summary of the key clinical efficacy results from the PERSEUS trial are presented in Table 12, with full discussion of each endpoint provided in the remainder of this section.

Table 12: Summary of key clinical efficacy results (PERSEUS trial)

Outcome	BLd arm ^a	DBLd arm ^b	DBLd arm versus BLd arm ^c (95% CI)
Survival outcomes (full treatment sequence)			
Median PFS	NE	NE	0.42 (0.30, 0.59); p<0.001
Median OS	■	■	0.73 (0.47, 1.14)
Response (post-consolidation), n (%)			
≥CR	■	■	■
≥VGPR	■	■	■
ORR	■	■	■
sCR	■	■	■
Response (full treatment sequence), n (%)			
≥CR	248 (70.1)	312 (87.9)	3.13 (2.11, 4.65)
≥VGPR	■	■	■
ORR	■	■	■
sCR	■	■	■
Overall MRD-negativity rate (10⁻⁵; post-consolidation), n (%)			
MRD-negativity rate (≥CR)	115 (32.5)	204 (57.5)	■
Overall MRD-negativity rate (10⁻⁵; full treatment sequence), n (%)			
MRD-negativity rate (≥CR)	168 (47.5)	267 (75.2)	3.40 (2.47, 4.69); p<0.0001
Sustained MRD-negativity rate (10⁻⁵; full treatment sequence), n (%)			
Sustained MRD-negativity rate (at or below 10 ⁻⁵)	105 (29.7)	230 (64.8)	4.42 (3.22, 6.08); p<0.0001
HRQoL (at consolidation initiation [Cycle 5 Day 1])			
EORTC QLQ-C30 Global Health Status; LS mean change from baseline (95% CI)	■	■	■
EQ-5D-5L utility score, LS mean change from baseline (95% CI)	■	■	■
EQ-5D-5L visual analogue scale, LS mean change from baseline (95% CI)	■	■	■
HRQoL (at maintenance initiation [Cycle 1 Day 1])			
EORTC QLQ-C30 Global Health Status; LS mean change from baseline (95% CI)	■	■	■
EQ-5D-5L utility score, LS mean change from baseline (95% CI)	■	■	■
EQ-5D-5L visual analogue scale, LS mean change from baseline (95% CI)	■	■	■

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy. ^c HRs presented for survival outcomes; ORs presented for response outcomes and MRD-negativity; absolute difference presented for HRQoL outcomes. A hazard ratio <1 indicates an advantage for DBLd.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; ≥CR: complete response or better; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer QoL questionnaire core 30; EQ-5D-5L: EuroQoL Group Five Dimensions Five Levels; HRQoL: health-related quality of life; LS: least squared; MRD: minimal residual disease; N/A: not applicable; ORR: Overall response rate ; OS: overall survival; PFS: progression-free residual disease; sCR: stringent complete response; ≥VGPR: VGPR or better

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO) Table 10, Table 13, Table 14,³² Sonneveld *et al.* (2024).¹¹⁰

2.6.1.1. Primary efficacy outcomes

Progression-free survival

The primary endpoint in the PERSEUS trial was PFS, defined as the time from the date of randomisation to the date of first PD according to the IMWG response criteria, or death due to any cause (whichever occurs earlier). As disease progression is associated with substantial reductions in patient HRQoL, prolonging the time patients are in a progression-free state is vital in ensuring patients maintain an improved quality of life for longer.¹²⁶ This view was supported by feedback received from UK clinical experts at an Advisory Board in which it was highlighted that as there is currently no cure for MM, increasing the time patients are in a progression-free state is a key treatment aim in this patient population.⁴ Furthermore, results from the 2019 Myeloma UK study conducted in 97 patients, found that patients placed high value on 'longer remission/treatment-free periods', highlighting the importance of PFS as an outcome.⁸² Additionally, a study of 560 myeloma patients conducted jointly by Myeloma UK, the European Medicines Agency (EMA) and the University of Groningen supported the importance of achieving a lasting remission for the majority of patients (75%).²

A summary of PFS results in the ITT analysis set is provided in Table 13. At the 1st August 2023 DCO, the primary endpoint of the PERSEUS trial was met. The addition of daratumumab to BLd induction and consolidation therapy and L maintenance treatment resulted in a statistically significant improvement in PFS, with a 58% reduction in risk of disease progression or death compared with BLd induction and consolidation treatment followed by L maintenance alone (HR: 0.42; 95% CI: 0.30, 0.59; p<0.001) in HDT-ASCT eligible NDMM patients.¹¹⁰ Furthermore, landmark estimates of PFS (summarised in Table 13) demonstrate a consistent trend of improved PFS associated with the DBLd versus the BLd treatment arms over time, with this benefit anticipated to increase with increased follow-up. This view is supported by the Kaplan-Meier (KM) plot of PFS presented in Figure 11 in which an early and increasing separation between the BLd and DBLd treatment arms is clearly observed over time, as well as the response data which are discussed in more detail below.

Table 13: PFS; ITT analysis set (full treatment sequence)

PFS Results	BLd arm ^a N=354	DBLd arm ^b N=355
Number of events, n (%)	103 (29.1)	50 (14.1)
Number of events censored, n (%)	██████	██████
6-month PFS rate, % (95% CI)	██████████	██████████
12-month PFS rate, % (95% CI)	██████████	██████████
24-month PFS rate, % (95% CI)	██████████	██████████
36-month PFS rate, % (95% CI)	██████████	██████████
48-month PFS rate, % (95% CI)	67.7 (62.2, 72.6)	84.3 (79.5, 88.1)

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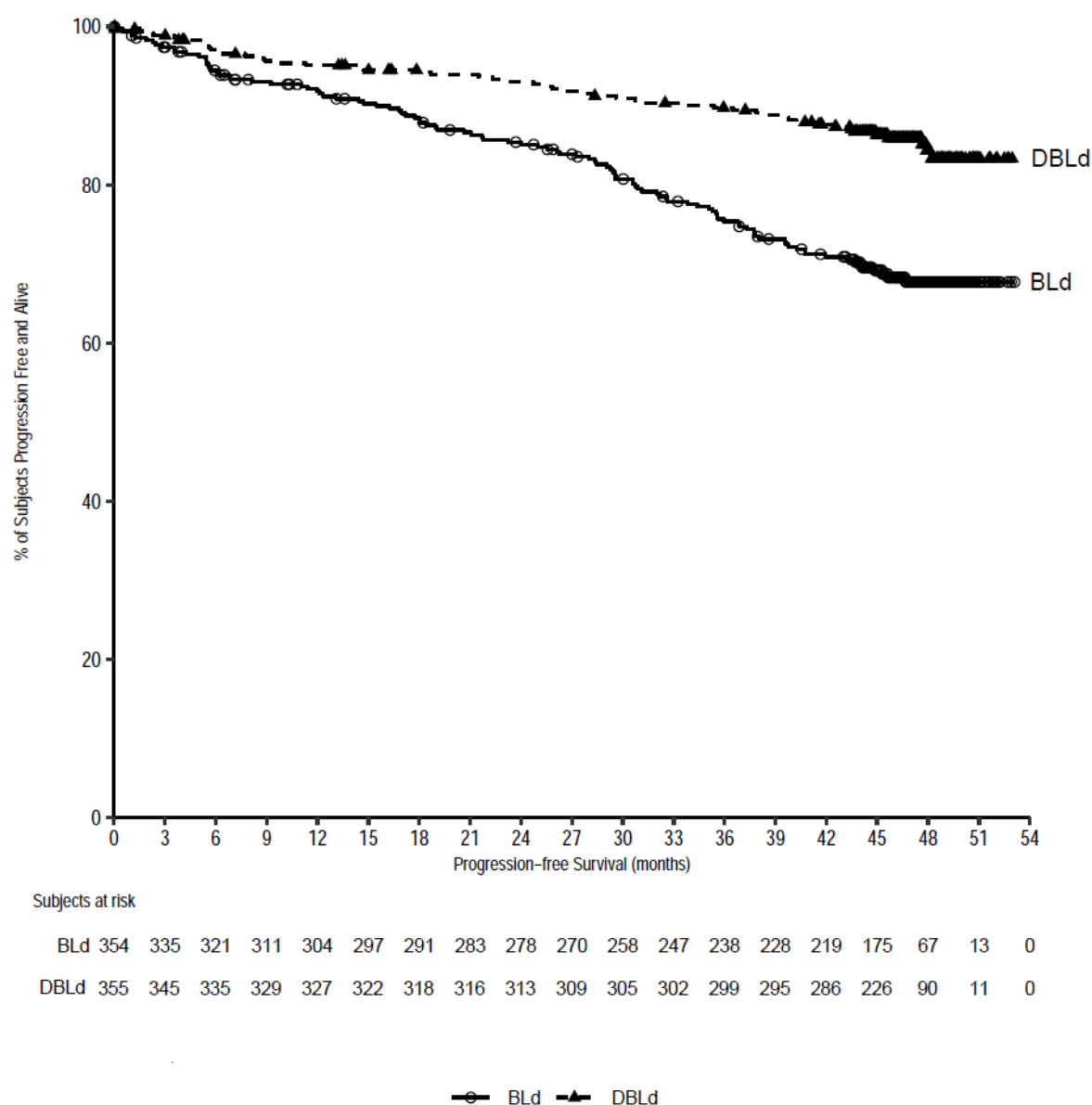
PFS Results	BLd arm ^a N=354	DBLd arm ^b N=355
60-month PFS rate, % (95% CI)	██████	██████
Median KM estimate, months		
Median (95% CI)	██████	██████
25% percentile (95% CI)	██████████	██████
75% percentile (95% CI)	██████	██████
HR (95% CI) ^c	0.42 (0.30, 0.59)	
P-value ^d	<0.001	

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy ^c p-value is based on the log-rank test stratified with ISS staging (I, II, versus III), and cytogenetic risk (high risk versus standard risk or unknown). ^d Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, versus III), and cytogenetic risk (high risk versus standard risk or unknown). A hazard ratio <1 indicates an advantage for DBLd.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; KM: Kaplan-Meier; ITT: intent-to-treat; NE: not evaluable; PFS: progression-free survival.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO) Table 8;³² Sonneveld *et al.* (2024).¹¹⁰

Figure 11: KM plot of PFS, ITT analysis set



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

Source: Sonneveld *et al.* (2024).¹¹⁰

2.6.1.2. Key secondary efficacy outcomes

Response rates

As detailed in Section 1.3.2, there is a growing body of evidence which indicates that achieving a deep, durable response to therapy is prognostic for improved survival outcomes. In particular, statistical methods quantifying the relationship as well as clinician feedback, have validated the clinical plausibility of the relationship between (sustained) MRD-negativity and long-term outcomes.⁵⁹ Furthermore, deeper treatment responses are associated with improvements in HRQoL in patients with MM.⁵⁶

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As highlighted above, survival data for first-line treatments are likely to be immature, owing to a 24-month survival rate of at least 90% in patients with HDT-ASCT eligible NDMM, placing further importance on response-based outcomes in this setting.² Response-based outcomes, along with other key secondary outcomes in the PERSEUS trial are outlined and defined in Table 10, Section 2.4.2.

Both the DBLd and BLd treatment arms were associated with high levels of response at all treatment periods; (post-induction, post-consolidation and the full treatment sequence [induction, consolidation and maintenance]). The DBLd arm was however associated with an increased likelihood of response versus the BLd arm from the post-consolidation treatment phase, with the odds ratio increasing over time; post-consolidation: ORR OR: ■■■; 95% CI: ■■■, ■■■; p■■■■; full treatment sequence ORR OR: ■■■; 95% CI: ■■■, ■■■; ■■■.

As well as an increased number of responders, the DBLd treatment arm was associated with deeper responses versus the BLd treatment arm. The DBLd treatment arm yielded a ■■■■ as early as post-induction (odds ratio [OR]: ■■■; 95% CI: ■■■, ■■■; p■■■■). This benefit is shown to increase over time, demonstrated by the increased OR for the DBLd arm versus the BLd arm for the end of consolidation versus the full treatment sequence results (OR: ■■■; 95% CI: ■■■, ■■■; p■■■■ versus OR: ■■■; 95% CI: ■■■, ■■■; p■■■■, respectively).³² Furthermore, by the end of the consolidation phase, ■■■■ rates were achieved in the DBLd arm compared with the BLd arm (sCR: ■■■ versus ■■■; OR: ■■■, 95% CI: ■■■, ■■■, p■■■■; ≥CR: ■■■ versus ■■■%; OR: ■■■, 95% CI: ■■■, ■■■, p■■■■).³² This trend was consistent in the full treatment sequence data; statistically significantly greater rates of both sCR and ≥CR were achieved for DBLd versus the BLd arm for the full treatment sequence (sCR: ■■■ versus ■■■; OR: ■■■, 95% CI: ■■■, ■■■, p■■■■; ≥CR: 87.9% versus 70.1%; OR: 3.13, 95% CI: ■■■, ■■■, p<0.0001.^{32, 110} In line with the ≥VGPR data, the benefit shown in sCR and ≥CR rates in the DBLd arm was shown to increase over time, demonstrated by increased ORs when comparing the post-consolidation to the full treatment sequence data (sCR: 1.56 versus 2.83; ≥CR: 1.51 versus 3.13).³²

Finally, deeper responses were observed over time between post-induction, post-consolidation and post-maintenance (full treatment sequence) for both the DBLd and BLd arms. As highlighted above however, the extent of this was greater for the DBLd versus the BLd arm, illustrated by the consistently increasing ORs (Table 14).³²

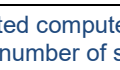
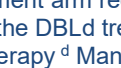
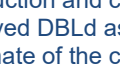
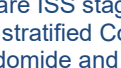
An overview of response rates by treatment phase in the ITT analysis set is provided in Table 14.

Table 14: Summary of response rates; ITT analysis set, based on time of assessment^a

Response rates	BLd arm ^b N=354		DBLd arm ^c N=355		OR (95% CI) ^d	P-value ^e
	n (%)	95% CI	n (%)	95% CI		
Post-induction						
≥CR (sCR + CR)	75 (21.2)	██████████	80 (22.5)	██████████	██████████	0.6680
≥VGPR (sCR + CR + VGPR)	257 (72.6)	██████████	301 (84.8)	██████████	██████████	██████████
ORR	321 (90.7)	██████████	334 (94.1)	██████████	██████████	██████████
sCR	25 (7.1)	██████████	34 (9.6)	██████████	██████████	██████████

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Response rates	BLd arm ^b N=354		DBLd arm ^c N=355		OR (95% CI) ^d	P-value ^e
	n (%)	95% CI	n (%)	95% CI		
	50 (14.1)		46 (13.0)		-	-
VGPR	182 (51.4)		221 (62.3)		-	-
PR	64 (18.1)		33 (9.3)		-	-
SD					-	-
PD					-	-
NE					-	-
Post-ASCT						
≥CR (sCR + CR)	83 (23.4)		99 (27.9)			
≥VGPR (sCR + CR + VGPR)	260 (73.4)		303 (85.4)			
ORR	322 (91.0)		334 (94.1)			
sCR	29 (8.2)		38 (10.7)			
CR	54 (15.3)		61 (17.2)		-	-
VGPR	177 (50.0)		204 (57.5)		-	-
PR	62 (17.5)		31 (8.7)		-	-
SD					-	-
PD					-	-
NE					-	-
Post-consolidation						
≥CR (sCR + CR)	123 (34.7)					
≥VGPR (sCR + CR + VGPR)	291 (82.2)					
ORR	326 (92.1)					
sCR	46 (13.0)					
CR	77 (21.8)				-	-
VGPR	168 (47.5)				-	-
PR	35 (9.9)				-	-
SD					-	-
PD					-	-
NE					-	-
Full treatment sequence						
≥CR (sCR + CR)	248 (70.1)		312 (87.9)			
≥VGPR (sCR + CR + VGPR)	316 (89.3)		338 (95.2)			

Response rates	BLd arm ^b N=354		DBLd arm ^c N=355		OR (95% CI) ^d	P-value ^e
	n (%)	95% CI	n (%)	95% CI		
ORR	332 (93.8)	(90.7, 96.1)	343 (96.6)	(94.2, 98.2)		
sCR	158 (44.6)		246 (69.3)			
CR	90 (25.4)		66 (18.6)		-	-
VGPR	68 (19.2)		26 (7.3)		-	-
PR	16 (4.5)		5 (1.4)		-	-
SD	9 (2.5)		4 (1.1)		-	-
PD	1 (0.3)		2 (0.6)		-	-
NE	12 (3.4)		6 (1.7)		-	-

Footnotes: ^a Tumour response was assessed with the use of a validated computerised algorithm in accordance with the IMWG response criteria. Percentages are calculated with the number of subjects in each group as denominator. ^b Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^c Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy ^d Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are ISS staging (I, II, versus III) and cytogenetic risk (high risk versus standard risk). ^e P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CR: complete response; ≥CR: complete response or better; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; IMWG: International Myeloma Working Group; L: lenalidomide; NE: not evaluable; OR: odds ratio; ORR: overall response rate; PD: progressive disease; PR: partial response; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.

Source: Sonneveld *et al.* 2024,¹¹⁰ J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): Table 10, Table 17–19.³²

MRD-negativity

As described in Section 1.3.2, MRD-negativity is a highly sensitive measure of the depth of response and a powerful independent predictor of long-term outcomes.¹¹⁴ Clear evidence from multiple randomised trials and meta-analyses, as well as validation from UK clinical experts consulted during a May 2025 Advisory Board, highlight the significance and biological plausibility of MRD-negativity as a surrogate measure for improved survival outcomes.^{4, 51-55} MRD negativity was also recently accepted by the FDA as a predictor for longer term outcomes including PFS and OS for NDMM and can be considered Level 1 evidence (representing the highest possible strength of evidence as a surrogate endpoint). Furthermore, MRD-negativity was accepted as a surrogate endpoint for OS in the recent NICE appraisal for DBTd in the same indication (TA763).²

In PERSEUS, MRD-negativity rate was defined as the proportion of patients in the ITT population who achieved both MRD-negativity (at a threshold of one tumour cell per 10⁻⁵ white cells in bone marrow aspirate) and a ≥CR at any time after the date of randomisation (and prior to disease progression, receipt of subsequent therapy, or both).³² Of note, the requirement for a ≥CR means the definition of MRD-negativity rate is more stringent than typical definitions in other MM clinical trials.^{127, 128} Sustained MRD-negativity was defined as two consecutive MRD-negative results (at or below a threshold of 10⁻⁵) at least 12 months apart, without any MRD-positive (at a threshold of 10⁻⁴ or higher) results in between.¹¹⁰

In the ITT analysis set, the DBLd arm achieved a significantly higher MRD-negativity rate compared with the BLd arm at the post-consolidation timepoint (57.5% versus 32.5%; OR: 

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95% CI: [REDACTED], [REDACTED]; p [REDACTED]; Table 15).³² Importantly, in line with the response data presented above, the OR for DBLd versus the BLd arm increased when comparing the post-consolidation to the full treatment sequence data, demonstrating an increasing benefit in the DBLd arm over time (full treatment sequence MRD-negativity rate: 75.2% versus 47.5%; OR: 3.40; 95% CI: 2.47, 4.69; p<0.0001).^{32, 113} As the full treatment sequence data included maintenance treatment, this increasing OR also supports an improved efficacy of DL maintenance (DBLd arm) versus L maintenance therapy alone (BLd arm).

Table 15: Summary of overall MRD-negativity rate by NGS at or below 10⁻⁵ in patients with ≥CR post-consolidation and full treatment sequence; ITT analysis set

MRD-negativity rate	BLd arm ^a N=354	DBLd arm ^b N=355
	n (%)	n (%)
Post-consolidation		
MRD-negativity rate (at or below 10 ⁻⁵)	115 (32.5)	204 (57.5)
95% CI ^c		
OR (95% CI) ^d		
P-value ^e		
Full treatment sequence		
MRD-negativity rate (at or below 10 ⁻⁵)	168 (47.5)	267 (75.2)
95% CI ^c		
OR (95% CI) ^d	3.40 (2.47, 4.69)	
P-value ^e	<0.001	
Sustained MRD-negativity rate (at or below 10 ⁻⁵)	105 (29.7)	230 (64.8)
95% CI ^c		
OR (95% CI)	4.42 (3.22, 6.08)	
P-value ^e	<0.001	

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy. ^c Exact 95% confidence interval. ^d Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are ISS staging (I, II, versus III) and cytogenetic risk (high risk versus standard risk). ^e P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; ITT: intent-to-treat; L: lenalidomide; MRD: minimal residual disease; NGS: next-generation sequencing; OR: odds ratio.

Source: Rodríguez-Otero *et al.* 2024,¹¹³ J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): Table 11, Table 14.³²

The benefit of DL maintenance versus L maintenance in PERSEUS is further supported by the data presented in Table 16, which show that the proportion of patients who achieved sustained MRD-negativity during the maintenance phase was significantly higher for patients receiving DL maintenance (DBLd arm) versus L maintenance therapy alone (BLd arm). The same was true for the rate of patients who converted from MRD-positive post-consolidation to MRD-negative during the maintenance phase.¹¹³ As shown in Section 2.8, a subgroup analysis of sustained MRD-negativity showed that the benefit of DBLd followed by DL maintenance over BLd with L maintenance was consistent across all subgroups.

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Table 16: Summary of MRD-negativity outcomes by NGS during the maintenance phase; ITT analysis set

MRD-negativity rate	BLd arm ^a N=121	DBLd arm ^b N=88
	%	%
Sustained MRD-negativity for ≥12 months during the maintenance phase		
Sustained MRD-negativity rate (at or below 10 ⁻⁵)	17.4	38.6
P-value	0.0006	
Conversion rate during maintenance phase		
MRD-positive (post-consolidation) to MRD-negative conversion rate (at or below 10 ⁻⁵)	40.5	60.2
P-value	0.0049	

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; ITT: intent-to-treat; L: lenalidomide; MRD: minimal residual disease; NGS: next-generation sequencing; OR: odds ratio.

Source: Rodríguez-Otero *et al.* 2024.¹¹³

Overall survival

At the time of the 1st August 2023 DCO, median OS was not reached in either treatment arm (■; 95% CI: ■, ■) at a median follow-up of 47.5 months. As highlighted above, given the relatively good prognosis (median OS of approximately 160 months)¹²⁹ of this patient population, immature OS data is expected in the first-line setting with extensive follow-up required to obtain mature OS data. The current data cut from PERSEUS is also consistent with the availability of data in previously recommended treatments by NICE in the same indication.² Despite this, the available OS data show promising initial results, with an estimated HR of 0.73 (95% CI: ■) in favour of the DBLd treatment arm.³² Whilst this result was ■, a clear early separation in KM curves can be observed between treatment arms (Figure 12), which is maintained until high censoring towards the end of follow-up. This separation is only anticipated to increase over time, as follow-up increases. This is supported by the fact that the DBLd treatment arm was associated with a ■ versus the BLd treatment arm as early as post-induction.³² As noted above, there is an extensive body of evidence highlighting the link between achieving a deep, sustained treatment response on improved survival outcomes and therefore these results are highly predictive of superior long-term survival outcomes with DBLd + DL versus BLd + L.¹³⁰

A summary of OS is provided in Table 17 and a KM plot illustrating OS in the DBLd and BLd treatment arms is presented in Figure 12.

Table 17: OS in patients in the ITT analysis set (full treatment sequence)

OS	BLd arm ^a N=354	DBLd arm ^b N=355
Number of events, n (%)	44 (12.4)	34 (9.6)
Number of censored	■	■
12-month OS rate, % (95% CI)	■	■
24-month OS rate, % (95% CI)	■	■

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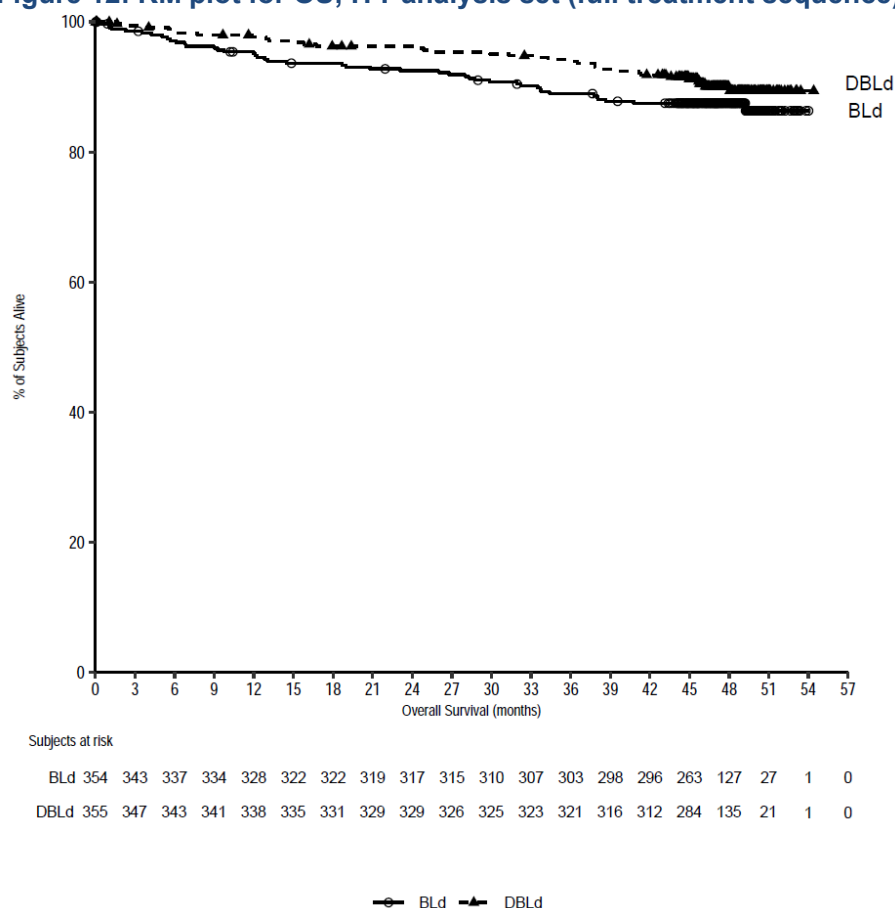
36-month OS rate, % (95% CI)		
48-month OS rate, % (95% CI)		
60-month OS rate, % (95% CI)		
Median KM estimate, months (95% CI)		
25% percentile		
Median		
75% percentile		
HR (95% CI) ^c	0.73 (0.47, 1.14)	

Footnote: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy ^c Hazard ratio from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and cytogenetic risk (high risk versus standard risk or unknown). A hazard ratio < 1 indicates an advantage for the DBLd arm.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; L: lenalidomide; NE: not evaluable; OS: overall survival.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): Table 12.³²

Figure 12: KM plot for OS; ITT analysis set (full treatment sequence)



Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intent-to-treat; KM: Kaplan-Meier; OS: overall survival.

Source: Sonneveld *et al.* (2024).¹¹⁰

Duration of response

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DOR was calculated among responders (with a $\geq$ PR) for the full treatment sequence from the date of initial documentation of a response to the date of first documented evidence of progressive disease as defined in the IMWG criteria, or death due to any cause.

Among responders, median DOR in the ITT analysis set was [REDACTED] at a median follow-up of 47.5 months (Table 18).³² This highlights the benefits achieved by both treatments in terms of response, as median DOR was [REDACTED] due to a large number of patients still being in response and, as such, being censored. Of note however, a greater proportion of patients were censored (i.e., still in response) in the [REDACTED] arm compared with the [REDACTED] arm ([REDACTED] versus [REDACTED]) at the most recent (1st August 2023) DCO.³²

Table 18: DOR in patients in the ITT analysis set (full treatment sequence)^a

DOR	BLd arm ^b N=332	DBLd arm ^c N=343
Number of events, n (%) ^d	██████	██████
Number of events censored, n (%)	██████	██████
Median KM estimate, months		
25% percentile (95% CI)	██████████	██████████
Median (95% CI)	██████	██████
75% percentile (95% CI)	██████████	██████████

Footnotes: ^a Response PR or better. ^b Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^c Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy ^d Number of events refers to number of responders (or complete responders, or stringent complete responders) who developed disease progression or died due to disease progression.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; DOR: duration of response; ITT: intent-to-treat; KM: Kaplan-Meier; L: lenalidomide.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TEFDOR01.³²

Time to response

At the 1st August 2023 DCO, for responders, the median time to first response (defined as a ≥PR) and the median time to ≥CR were similar between the two treatment arms (DBLd arm: █████ months versus BLd arm: █████ months and DBLd arm: █████ months versus BLd arm: █████ months, respectively).³² Median time to best response and median time to sCR however were longer in the DBLd arm compared with the BLd arm (DBLd arm: █████ months versus █████ months and DBLd arm: █████ months versus █████ months, respectively).³² Of note however, several studies in patients with NDMM have found that achieving a more gradual response is associated with deeper responses which translate to longer PFS and DOR.^{116, 117} The longer time to response for the DBLd arm compared with BLd may also relate to the higher rate of patients achieving a response in the DBLd arm. As such, the acquisition of response would be expected to plateau faster in the BLd arm, when compared with the DBLd arm where patients continue to experience a response in the early maintenance phase.

A summary of time to response for patients in the ITT analysis set in PERSEUS is provided in Table 19.

Table 19: Time to response; ITT analysis set (full treatment sequence)^a

Time to response	BLd arm ^b N=332	DBLd arm ^c N=343
Time to first response, months		
n	██	██
Mean (SD)	██████	██████
Median (range)	██████████	██████████
Time to best response, months		
n	██	██
Mean (SD)	██████	██████
Median (range)	██████████	██████████
Time to ≥VGPR, months		

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Time to response	BLd arm ^b N=332	DBLd arm ^c N=343
n	■	■
Mean (SD)	■	■
Median (range)	■	■
Time to ≥CR, months		
n	■	■
Mean (SD)	■	■
Median (range)	■	■
Time to sCR or better, months		
n	■	■
Mean (SD)	■	■
Median (range)	■	■

Footnote: ^a Response PR or better. ^b Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^c Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; ITT: intent-to-treat; L: lenalidomide; sCR: stringent complete response; SD: standard deviation; VGPR: very good partial response.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TEFTTR01.³²

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

Progression-free survival on the subsequent line of therapy (PFS2) was defined as the time interval between the date of randomisation to the date of progressive disease on the next line of subsequent treatment or death, whichever comes first. PFS2 has been proposed as an alternative surrogate endpoint to OS in oncology clinical trials, particularly as a method of negating the confounding effect of subsequent line therapies.¹³¹

At a median follow-up of 47.5 months, PFS2 data remained immature with only ■ (■%) events in the DBLd arm and ■ (■%) events in the BLd arm. Despite the low number of events, a strong trend for improved outcomes for patients in the DBLd arm versus the BLd arm was observed (HR: ■; 95% CI: ■; ■).³² These results demonstrate that the observed PFS benefit in the DBLd arm is maintained beyond the next line of therapy received.

A summary of PFS2 is provided in Table 20 and a KM plot illustrating PFS2 in the DBLd versus the BLd arm is presented in Table 20.³²

Table 20: Progression-free survival on next line of therapy; ITT analysis set (full treatment sequence)

PFS2	BLd arm ^a N=354	DBLd arm ^b N=355
Number of events, n (%)	■	■
Number of censored, n (%)	■	■
12-month PFS2 rate, % (95% CI)	■	■
24-month PFS2 rate, % (95% CI)	■	■
36-month PFS2 rate, % (95% CI)	■	■
48-month PFS2 rate, % (95% CI)	■	■

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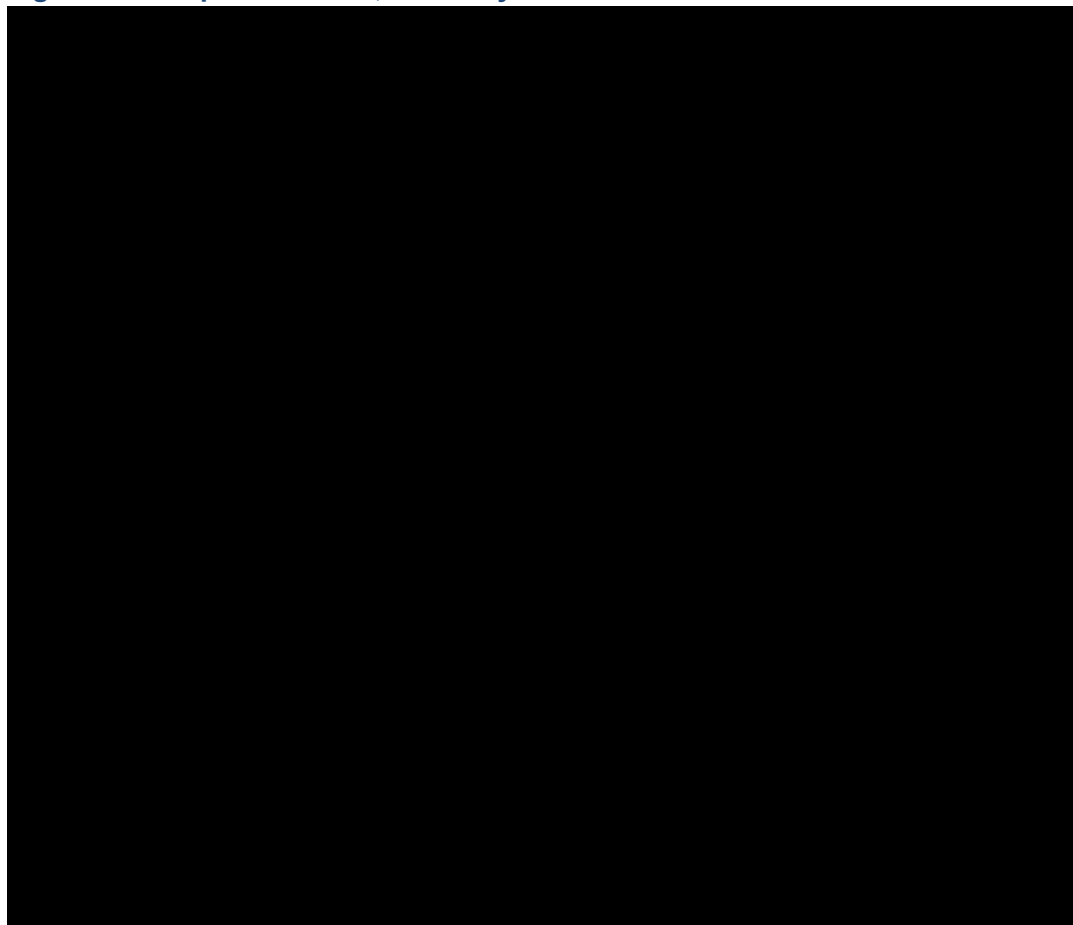
PFS2	BLd arm ^a N=354	DBLd arm ^b N=355
60-month PFS2 rate, % (95% CI)		
Median KM estimate, months (95% CI)		
25% percentile		
Median		
75% percentile		
HR (95% CI) ^c		
P-value ^d		

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy. ^c Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. A hazard ratio <1 indicates an advantage for DBLd. ^d p-value is based on the log-rank test.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; L: lenalidomide; NE: not evaluable; PFS2: progression-free survival on next line of therapy.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TEF PFS2.³²

Figure 13: KM plot for PFS2; ITT analysis set



Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ITT: intent-to-treat; KM: Kaplan-Meier; PFS2: progression-free survival on next line of therapy.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): Figure 10.³²

2.6.1.3. Patient-reported outcomes

In PERSEUS, functional status and well-being were assessed using several pre-specified patient-reported outcome (PRO) tools, including the EORTC QLQ-C30 scale, EQ-5D-5L and EORTC QLQ-MY20 at:

- Baseline (Cycle 1 Day 1)
- During induction (Cycle 3 Day 1)
- Post-induction (pre-ASCT; within two weeks of completing Cycle 4)
- Consolidation initiation (Cycle 5 Day 1)
- Maintenance initiation (Cycle 7 Day 1) and then every 12 weeks until progressed disease
- End of treatment

Of note, the compliance rate for PRO assessments was high and comparable between both treatment arms. Compliance at baseline was >■% and >■% for the majority of timepoints, ranging from ■% to ■% through Cycle 34 for the EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L.³²

Across the different HRQoL measures, DBLd-DL resulted in durable improvements in overall HRQoL, MM symptoms and functioning, with no differences in HRQoL between treatment arms observed. These findings indicate that the addition of daratumumab to BLd induction and consolidation and L maintenance therapy did not have a detrimental impact on patient HRQoL. Further details of the results for each HRQoL measure are presented below.

EORTC QLQ-C30

The EORTC QLQ-C30 includes 30 items, resulting in five functional scales, one Global Health Status scale, three symptom scales and six single items. A higher score on the functional scales represents a greater level of functioning, whereas a higher score on the symptom scales represents a worse level of symptoms. Baseline EORTC QLQ-C30 scores were comparable across treatment arms (Table 21).³²

The proportion of patients with a clinically meaningful improvement in EORTC QLQ-C30 scores at each cycle up to the final maintenance timepoints was comparable between treatment arms (Cycle 34 Day 1; DBLd versus BLd: global health status 37.8% versus 36.8%, physical functioning 39.5% versus 41.1%, pain 48.9% versus 50.0%, fatigue 46.5% versus 53.1%).¹¹⁰ Results for the change from baseline in EORTC QLQ-C30 scores for induction, pre-ASCT, consolidation, maintenance and end of treatment phases in the PERSEUS trial are presented in Table 22. For conciseness, for the maintenance phase, results are presented for the maintenance initiation (maintenance Cycle 1, Day 1) and the final maintenance timepoints (Cycle 34 Day 1) only. For completeness, results for other timepoints in the maintenance phase are presented in the Clinical Study Report provided in the reference pack alongside the submission.³²

Results from the improvements in outcomes including Global Health Status, pain symptom score, fatigue symptom score and physical functioning from baseline to consolidation initiation were comparable over time for the DBLd and BLd arms (least squared [LS] mean difference in change from baseline at Cycle 5 Day 1: [redacted] [95% CI: [redacted]; p=[redacted]], [redacted] [95% CI: [redacted]; p=[redacted]], [redacted] [95% CI: [redacted]; p=[redacted]] and [redacted] [95% CI: [redacted]; p=[redacted]], respectively [Table 22]). Similarly, improvements in these outcomes were also comparable over time for the DBLd and BLd arms from baseline to maintenance initiation (LS mean difference in change from baseline at maintenance Cycle 1 Day 1: [redacted] [95% CI: [redacted]; p=[redacted]], [redacted] [95% CI: [redacted]; p=[redacted]], [redacted] [95% CI: [redacted]; p=[redacted]] and -[redacted] [95% CI: [redacted]; p=[redacted]], respectively).³²

Of particular note, clinically meaningful reductions in pain (≥ 10 points) were found for both treatment arms, by maintenance Cycle 4 Day 1 in the DBLd arm (LS mean difference in change from baseline: [redacted] [95% CI: [redacted], [redacted]]) and in the BLd arm (LS mean difference in change from baseline: [redacted] [95% CI: [redacted], [redacted]]) and extended through maintenance Cycle 34 Day 1.³² Most scores showed numerical improvement in both arms from induction through maintenance. [redacted] were observed between arms in the time to improvement or worsening.

Overall, these results support that the addition of daratumumab to BLd induction and consolidation therapy and L maintenance therapy does not have a negative impact on patient HRQoL.

Table 21: Baseline values for EORTC QLQ-C30; ITT analysis set^a

Subscale score (mean, SD)	BLd arm ^c	DBLd arm ^b
Global health status	[redacted]	64.24 (23.06)
Symptom scales		
Fatigue	[redacted]	31.71 (24.73)
Nausea and vomiting	[redacted]	[redacted]
Pain score	[redacted]	32.79 (30.42)
Functional scales		
Cognitive functioning	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]
Physical functioning	[redacted]	74.19 (27.06)
Role functioning	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]

Footnote: ^a All the scores are presented in the range of 0-100 after linear transformation from raw scores (in the range of 1-4). A higher score indicates better health on the global health and functional scales (physical, role, emotional, cognitive, and social) and greater symptom severity on the symptom scales (fatigue, nausea/vomiting, pain, dyspnea, Insomnia, appetite loss, constipation and diarrhea). ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy. ^c Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy
Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer QoL questionnaire core 30; ITT: intent-to-treat; L: lenalidomide; SD: standard deviation.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TPROQLQ02.³²

Table 22: Change from baseline in EORTC QLQ-C30 scores for induction, pre-ASCT, consolidation and maintenance phases; ITT analysis set

	BLd arm ^a N=354	DBLd arm ^b N=355	Difference (95% CI) ^c	P-value
Global health status score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	████████	████████	████████	████
Pre-ASCT	████████	████████	████████	████
Consolidation Cycle 5 Day 1	████████	████████	████████	████
Maintenance Cycle 1 Day 1	████████	████████	████████	████
Maintenance Cycle 34 Day 1	████████	████████	████████	████
Pain symptom score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	████████	████████	████████	████
Pre-ASCT	████████	████████	████████	████
Consolidation Cycle 5 Day 1	████████	⌵	████████	████
Maintenance Cycle 1 Day 1	████████	████████	████████	████
Maintenance Cycle 34 Day 1	████████	⌵	████████	████
Fatigue symptom score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	████████	████████	████████	████
Pre-ASCT	████████	████████	████████	████
Consolidation Cycle 5 Day 1	████████	████████	████████	████
Maintenance Cycle 1 Day 1	████████	████████	████████	████
Maintenance Cycle 34 Day 1	████████	⌵	████████	████
Physical functioning score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	████████	████████	████████	████
Pre-ASCT	████████	████	████████	████
Consolidation Cycle 5 Day 1	████████	████████	████████	████
Maintenance Cycle 1 Day 1	████	████████	████████	████
Maintenance Cycle 34 Day 1	████████	████████	████████	████

Footnote: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy. ^c least squares means are derived based on the mixed effects model with repeated measures, in which the dependent variable is change from baseline in score, and independent variables are baseline, visit, treatment, visit by treatment interaction, and randomization stratification factors ISS staging (I, II, III), and cytogenetic risk (high risk versus standard risk or unknown) as fixed effects and individual subject as random effect.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer QoL questionnaire core 30; ITT: intent to treat; L: lenalidomide; LS: least squared.
Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TPROQLQ11.³²

EQ-5D-5L

The EQ-5D-5L instrument measures and characterises health status using the utility scores for EQ-5D scale across five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the visual analogue scale (VAS) for the respondent's self-rated health state. A low utility score indicates a worse health state, whereas a low VAS score indicates low symptom severity.^{132, 133}

The proportion of patients with a clinically meaningful improvement in EQ-5D-5L VAS scores at each cycle up to the final maintenance timepoints was comparable between treatment arms (Cycle 34 Day 1; DBLd versus BLd: 49.7% versus 43.9%).¹¹⁰ Changes from both baseline to consolidation initiation and baseline to maintenance initiation for EQ-5D-5L VAS and utility scores were [REDACTED] different between treatment arms, with comparable slight improvements seen with VAS scores in both treatment arms (LS mean difference in change from baseline at Cycle 5 Day 1: baseline to consolidation initiation: [REDACTED] [95% CI: [REDACTED], [REDACTED]; p=[REDACTED]; baseline to maintenance initiation: [REDACTED] [95% CI: [REDACTED], [REDACTED]; p=[REDACTED]; Table 23; Figure 14).

Table 23: Change from baseline in EQ-5D-5L scores at induction, pre-ASCT, consolidation and maintenance phases; ITT analysis set

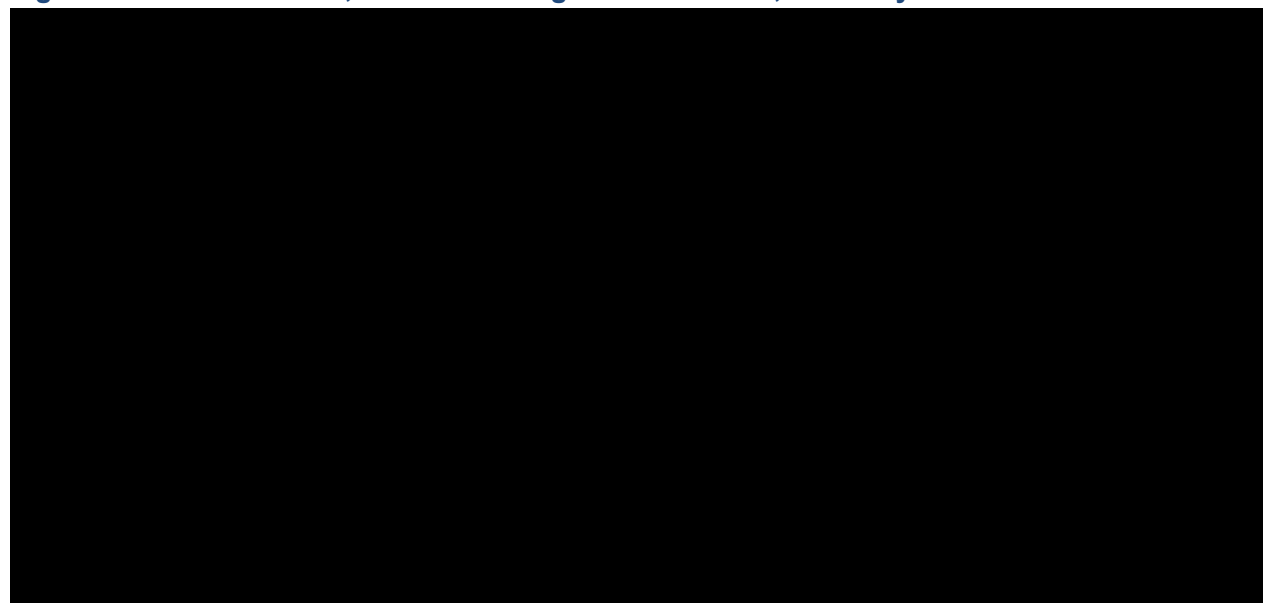
	BLd arm ^a N=332	DBLd arm ^b N=343	Difference (95% CI)	P-value
Utility score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Pre-ASCT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Consolidation Cycle 5 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Maintenance Cycle 1 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Maintenance Cycle 34 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
VAS score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Pre-ASCT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Consolidation Cycle 5 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Maintenance Cycle 1 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Maintenance Cycle 34 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; EQ-5D-5L: EuroQol Group Five Dimensions Five Levels; ITT: intent to treat; L: lenalidomide; LS: least squared; VAS: visual analogue scale.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TPROEQ07 and TPROEQ07A.³²

Figure 14: EQ-5D-5L VAS, LS mean change from baseline; ITT analysis set



Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; CXDY: Cycle X Day Y; DL: daratumumab with lenalidomide; EQ-5D-5L: EuroQol Group Five Dimensions Five Levels; ITT: intent to treat; L: lenalidomide; LS: least squared; VAS: visual analogue scale.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TPROEQ07.³²

EORTC QLQ-MY20

The EORTC QLQ-MY20 scale is a MM-specific PRO measure consisting of 20 items within four domains, including disease symptoms, side effects of treatment, future perspectives and body image.¹³⁴ Scores range from 0 to 100 with higher scores indicating worse symptoms (for disease symptoms and side effects of treatment domains) or better support/functioning (for future perspective and body image domains).¹³⁵

The proportion of patients with a clinically meaningful improvement in EORTC QLQ-MY20 scores at each cycle up to the final maintenance timepoints was similar across the DBLd and BLd treatment arms (Cycle 34 Day 1; DBLd versus BLd: 47.3% versus 49.1%).¹¹⁰ Changes from both baseline to consolidation initiation (Cycle 5 Day 1) and baseline to maintenance initiation for EORTC QLQ-MY20 disease symptom scale scores were [REDACTED] between treatment arms, with comparable slight improvements in scores seen in both treatment arms (LS mean difference in change from baseline at Cycle 5 Day 1: [REDACTED] [95% CI: [REDACTED], [REDACTED]; p=[REDACTED]; LS mean difference in change from baseline at maintenance initiation: [REDACTED] [95% CI: [REDACTED], [REDACTED]; p=[REDACTED]; Table 24).

Overall, patients treated with DBLd-DL experienced a HRQoL improvement from baseline that was apparent by the time maintenance began, and was sustained throughout the maintenance

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treatment phase across the different HRQoL measures. No differences in symptoms and/or functioning between treatment arms was observed. These findings indicate that the addition of daratumumab to BLd induction and consolidation and L maintenance therapy did not have a detrimental impact on patient HRQoL.

Table 24: Change from baseline in EORTC QLQ-MY20 scores at induction, pre-ASCT, consolidation and maintenance phases

	BLd arm ^a N=332	DBLd arm ^b N=343	Difference (95% CI)	P-value
Disease symptom scale score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	██████████	██████████	██████████	████
Pre-ASCT	██████████	██████████	██████████	████
Consolidation Cycle 5 Day 1	██████████	██████████	██████████	████
Maintenance Cycle 1 Day 1	██████████	██████████	██████████	████
Maintenance Cycle 34 Day 1	██████████	██████████	██████████	████

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20; ITT: intent to treat; L: lenalidomide; LS: least squared.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TPROMY05.³²

2.6.2 AURIGA trial

AURIGA is an ongoing, Phase III RCT of DL versus L maintenance in patients who have received induction and HDT-ASCT. Specifically, it enrolled patients who, despite achieving $\geq$ VGPR, had detectable MRD post-ASCT. Efficacy analyses were performed in the ITT population, which comprised all patients who underwent randomisation to the DL or L treatment arms.¹²³ Data in this submission are based on the latest DCO, 4th April 2024, with a median follow-up of 32.3 months (DL: 33.2 months; L: 30.3 months).^{31, 123}

A summary of the key efficacy outcomes are presented in Table 25. The AURIGA trial met its primary endpoint of the MRD-negative conversion rate by 12 months from the start of maintenance therapy. The overall MRD-negativity conversion rate for the DL arm was double that of the L arm (60.6% versus 27.7%; $p < 0.0001$), whilst the rate of sustained MRD-negativity was three times higher in the DL arm compared with the L arm (17.2% versus 5.0%; $p = 0.0065$). At a median follow-up of 32.3 months, PFS favoured DL over L, with a 47% risk reduction in disease progression or death ($p = 0.0361$).³¹

The results of the AURIGA trial demonstrate that DL maintenance treatment is associated with a statistically significantly greater likelihood of achieving MRD-negativity compared to the standard of care maintenance treatment currently used in the UK, lenalidomide. AURIGA phase III trial confirmed the benefit of DL maintenance with 2.7x MRD-negativity rates of conversion and a 47% PFS risk reduction versus L. These results are supported by the MRD-negative treatment effect observed in PERSEUS for DBLd-DL versus BLd-L (full treatment sequence MRD-

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negativity rate: 75.2% versus 47.5%; OR: 3.40; 95% CI: 2.47, 4.69; $p < 0.0001$). Refer to Section 2.6.1.2

As described in Section 1.3.2, it is critical that patients with NDMM achieve a deep and durable response, in particular MRD negativity, at the first-line stage of the treatment pathway, in order to prolong the period that they are progression free, delay reductions in HRQoL and the requirement for expensive subsequent therapies, and ultimately extend patients' survival for as long as possible. These results therefore illustrate that the introduction of DL maintenance treatment would represent a substantial improvement to the treatment pathway for transplant-eligible NDMM patients in the UK.

Table 25: Summary of key clinical efficacy results (AURIGA trial)

Outcome	L arm (N=101)	DL arm (N=99)	DL arm versus L arm (95% CI)
Survival outcomes			
Median PFS (months)	NE	37.9	0.53 (0.29, 0.97); 0.0361
Median OS (months)	■	■	■
12-month MRD-negativity conversion rate (10^{-5}), n (%)^a			
MRD-negativity rate	19 (19.8)	50 (50.5)	4.51 (2.37, 8.57); $p < 0.0001$
Overall MRD-negativity conversion rate (10^{-5}), n (%)^b			
MRD-negativity rate	28 (27.7)	60 (60.6)	4.12 (2.26, 7.52); $p < 0.0001$
Sustained MRD-negativity rate (10^{-5}), n (%)^c			
Sustained MRD-negativity rate	5 (5.0)	17 (17.2)	4.08 (1.43, 11.62); $p = 0.0065$

Footnote: ^a Defined as the proportion of patients who achieved MRD-negative status (threshold 10^{-5}) by 12 months after the initiation of maintenance treatment and before progressive disease or subsequent antimyeloma therapy. ^b Defined as the proportion of patients who achieved MRD-negative status any time after the date of randomisations. ^c Defined as patients who achieved MRD-negative status (at 10^{-5}) in two bone marrow aspirate assessments with a minimum of 12 months apart, without any assessment showing MRD-positive status in between assessments.

Abbreviations: CI: confidence interval; DL: daratumumab with lenalidomide; L: lenalidomide; MRD: minimal residual disease; NE: not evaluable; OS: overall survival; PFS: progression-free survival.

Source: Badros *et al.* 2024,¹³⁶ Badros *et al.* 2025,³¹ J&J Data on File AURIGA Clinical Study Report (April 2024 DCO) Table 14.¹³⁷

At the April 2024 DCO, 99.0% of patients in both arms experienced TEASs (Table 26). Serious AEs were reported in 30.2% of DL patients and 22.4% of L patients. The proportion of patients with TEAEs leading to discontinuation of daratumumab was 8.3%. The most common TEAS are reported in Table 27.

Table 26: Summary of TEAEs from the AURIGA trial; safety analysis set

TEAEs, n (%)	DL N=96	L N=98
Any TEAE	95 (99.0%)	97 (99.0%)
At least one related ^a	94 (97.9%)	92 (93.9%)
At least one related to daratumumab	88 (91.7%)	0
At least one related to lenalidomide	90 (93.8%)	92 (93.9%)

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Maximum toxicity grade		
Grade 1	4 (4.2%)	4 (4.1%)
Grade 2	19 (19.8%)	27 (27.6%)
Grade 3	58 (60.4%)	56 (57.1%)
Grade 4	12 (12.5%)	9 (9.2%)
Grade 5	2 (2.1%)	1 (1.0%)
Any serious TEAE	29 (30.2%)	22 (22.4%)
At least one related ^a	15 (15.6%)	5 (5.1%)
At least one related to daratumumab	9 (9.4%)	0
At least one related to lenalidomide	13 (13.5%)	5 (5.1%)
TEAEs leading to discontinuation of treatment per disposition CRF	12 (12.5%)	7 (7.1%)
TEAEs leading to discontinuation of any treatment component	14 (14.6%)	8 (8.2%)
At least one related ^a	12 (12.5%)	7 (7.1%)
At least one related to daratumumab	4 (4.2%)	0
At least one related to lenalidomide	12 (12.5%)	7 (7.1%)
TEAEs leading to discontinuation of daratumumab	8 (8.3%)	0
TEAEs leading to discontinuation of lenalidomide	14 (14.6%)	8 (8.2%)
Death due to TEAEs	2 (2.1%)	1 (1.0%)
At least one related ^a	1 (1.0%)	0
At least one related to daratumumab	1 (1.0%)	0
At least one related to lenalidomide	1 (1.0%)	0

Footnotes: ^a TEAEs related to at least 1 of the 2 components of study treatment: lenalidomide or daratumumab.

^b Includes those who had AEs with action taken as drug withdrawn to at least one component of study treatment.

^c Includes those subjects indicated as having discontinued treatment due to an AE at the end of treatment.

Abbreviations: AE: adverse event; CRF: case report form; DL: daratumumab with lenalidomide; L: lenalidomide; TEAE: treatment-emergent adverse event.

Source: J&J IM Data on File AURIGA Clinical Study Report (April 2024 DCO) Table 17.¹³⁷

Table 27: Summary of most common TEAEs of any grade; safety analysis set

TEAEs, n (%)	DL N=96	L N=98
Infections and infestations	<u>81 (84.4%)</u>	<u>69 (70.4%)</u>
COVID-19	28 (29.2%)	29 (29.6%)
Upper respiratory tract infection	40 (41.7%)	26 (26.5%)
Blood and lymphatic system disorders	<u>74 (77.1%)</u>	<u>69 (70.4%)</u>
Neutropenia	62 (64.6%)	60 (61.2%)
Thrombocytopenia	23 (24.0%)	28 (28.6%)
Anaemia	22 (22.9%)	17 (17.3%)
Gastrointestinal disorders	<u>83 (86.5%)</u>	<u>76 (77.6%)</u>
Diarrhoea	59 (61.5%)	54 (55.1%)
Constipation	22 (22.9%)	26 (26.5%)
Nausea	26 (27.1%)	26 (26.5%)
General disorders and administration site conditions	<u>77 (80.2%)</u>	<u>67 (68.4%)</u>
Pyrexia	<u>18 (18.8%)</u>	<u>16 (16.3%)</u>
Asthenia	<u>12 (12.5%)</u>	<u>14 (14.3%)</u>
Fatigue	44 (45.8%)	46 (46.9%)
Oedema peripheral	<u>12 (12.5%)</u>	<u>14 (14.3%)</u>
Nervous system disorders	<u>62 (64.6%)</u>	<u>55 (56.1%)</u>
Peripheral sensory neuropathy	<u>12 (12.5%)</u>	<u>13 (13.3%)</u>
Musculoskeletal and connective tissue disorders	<u>72 (75.0%)</u>	<u>68 (69.4%)</u>
Back pain	31 (32.3%)	20 (20.4%)
Skin and subcutaneous tissue disorders	<u>67 (69.8%)</u>	<u>55 (56.1%)</u>
Rash	21 (21.9%)	17 (17.3%)
Respiratory, thoracic and mediastinal disorders	<u>70 (72.9%)</u>	<u>60 (61.2%)</u>
Cough	37 (38.5%)	36 (36.7%)
Psychiatric disorders	<u>26 (27.1%)</u>	<u>18 (18.4%)</u>
Insomnia	<u>15 (15.6%)</u>	<u>8 (8.2%)</u>

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Abbreviations: DL: daratumumab with lenalidomide; L: lenalidomide; TEAE: treatment-emergent adverse event.
Source: Badros *et al.* 2025,³¹; J&J IM Data on File AURIGA Clinical Study Report (April 2024 DCO) Table 18.¹³⁷

Patient reported outcomes in AURIGA were collected through the EORTC QLQ-C30 and the EQ-5D questionnaires (Table 28). EQ-5D-5L health utility index and VAS assessment showed that general HRQoL and overall health status were maintained with DL.

Table 28: Change from baseline in EORTC QLQ-C30 scores from AURIGA trial; ITT analysis set

	DL N=96	L N=98
EORTC QLQ-C30		
<i>Global health status score, LS mean change from baseline (95% CI)</i>		
Baseline	<u>77.75</u>	<u>72.76</u>
Cycle 13 Day 1	<u>-1.73</u>	<u>6.47</u>
End of treatment	<u>-6.20</u>	<u>-3.98</u>
Post-treatment follow-up	<u>-21.67</u>	<u>-8.33</u>
EQ-5D-5L		
<i>Utility</i>		
Baseline	<u>0.81</u>	<u>0.79</u>
Cycle 13 Day 1	<u>0.00</u>	<u>0.00</u>
End of treatment	<u>0.01</u>	<u>-0.02</u>
Post-treatment follow-up	<u>-0.13</u>	<u>-0.06</u>
VAS		
Baseline	<u>80.24</u>	<u>81.28</u>
Cycle 13 Day 1	<u>1.96</u>	<u>-1.68</u>
End of treatment	<u>3.28</u>	<u>-5.79</u>
Post-treatment follow-up	<u>-3.20</u>	<u>4.60</u>
EORTC QLQ-MY20		
<i>Disease symptom scales</i>		
Baseline	<u>19.69</u>	<u>21.59</u>
Cycle 13 Day 1	<u>-0.49</u>	<u>-2.20</u>

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	DL N=96	L N=98
End of treatment	<u>-2.84</u>	<u>4.18</u>
Post-treatment follow-up	<u>1.11</u>	<u>5.56</u>

Abbreviations: DL: daratumumab with lenalidomide; L: lenalidomide; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer QoL questionnaire core 30; EQ-5D-5L: EuroQol Group Five Dimensions Five Levels; ITT: intent to treat; LS: least squared.

Source: J&J IM Data on File AURIGA Clinical Study Report (April 2024 DCO) TPROQLQ02, TPROEQ02, TPROMY02.¹³⁷

2.7 Subsequent treatments used in the relevant studies

A summary of the subsequent therapies received by patients in both the DBLd and BLd treatment arms at the August 2023 DCO in PERSEUS are summarised in Table 29 below.

Fewer participants in the DBLd arm (■ [■%]) received subsequent anti-myeloma therapies compared with the BLd arm (■ [■%]). Subsequent ASCT was reported for ■ (■%) patients in the DBLd arm and ■ (■%) participants in the BLd arm. The most commonly received subsequent treatments were dexamethasone (■%), daratumumab (■%) and carfilzomib (■%) in the BLd arm and dexamethasone (■%), carfilzomib (■%) and pomalidomide (■%) in the DBLd arm.³²

PFS2 data are presented in Section 2.6.1.2. Although immature, these data demonstrate that the observed PFS benefit in the DBLd arm, compared with the BLd arm, is maintained beyond the next line of therapy received.

Table 29: Summary of subsequent anti-myeloma therapy; safety analysis set

Patients receiving subsequent therapies, n (%)	BLd arm ^a ■	DBLd arm ^b ■
Total number of subjects with 1 or more subsequent antimyeloma therapies^c	■	■
Surgery	■	■
Radiotherapy	■	■
Allogenic transplant	■	1
Autologous transplant	■	■
Systemic therapy	■	■
Therapeutic class/pharmacologic class/drug^{d,e}		
Antineoplastic agents	■	■
Other antineoplastic agents	■	■
Carfilzomib	■	■
Bortezomib	■	■
Cisplatin	■	■
Venetoclax	■	■
CAR T-cells nos	■	■

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Patients receiving subsequent therapies, n (%)	BLd arm ^a	DBLd arm ^b
Mezigdomide		
Carboplatin		
Ciltacabtagene autoleucel		
Idecabtagene vicleucel		
Panobinostat		
Selinexor		
Tinostamustine		
Monoclonal antibodies and antibody drugs		
Daratumumab		
Isatuximab		
Belantamab mafodotin		
Teclistamab		
Elranatamab		
Elotuzumab		
Modakafusp alfa		
Talquetamab		
Alkylating agents		
Cyclophosphamide		
Melphalan		
Bendamustine		
Carmustine		
Lomustine		
Cytotoxic antibiotics and related substances		
Doxorubicin		
Doxorubicin hydrochloride		
Pegylated liposomal doxorubicin		
Plant alkaloids and other natural products		
Etoposide		
Vincristine		
Antimetabolites		
Fludarabine		
Cytarabine		
Fludarabine phosphate		
Corticosteroids for systemic use		
Dexamethasone		
Prednisone		
Dexamethasone phosphate		
Dexamethasone sodium phosphate		

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Patients receiving subsequent therapies, n (%)	BLd arm ^a	DBLd arm ^b
Methylprednisolone		
Prednisolone		
Immunosuppressants		
Pomalidomide		
Lenalidomide		
Thalidomide		
Iberdomide		
Antithymocyte immunoglobulin		
Ciclosporin		
Mycophenolate mofetil		
Investigational drug		

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy. ^c Percentages are calculated with the number of subjects in each arm as denominators. ^d Coded using WHO Drug Dictionary, March 2023 version. ^e Percentages are calculated with the number of subjects who received subsequent systemic therapies in each arm as denominators.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CAR T-cell: chimeric antigen receptor T-cells; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; L: lenalidomide.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): Table 6.³²

2.8 Subgroup analysis

Subgroup analyses were performed on the PFS, $\geq$ CR and overall MRD negativity rate endpoints in the ITT analysis set for the full treatment sequence, including clinically relevant subgroups based on age, ISS stage, cytogenetic risk, and baseline ECOG score. Subgroup analyses of PFS, $\geq$ CR, overall MRD-negativity and sustained MRD-negativity (full treatment sequence) are summarised in Figure 15, Figure 16, Figure 17 and Figure 18, respectively.^{32, 110}

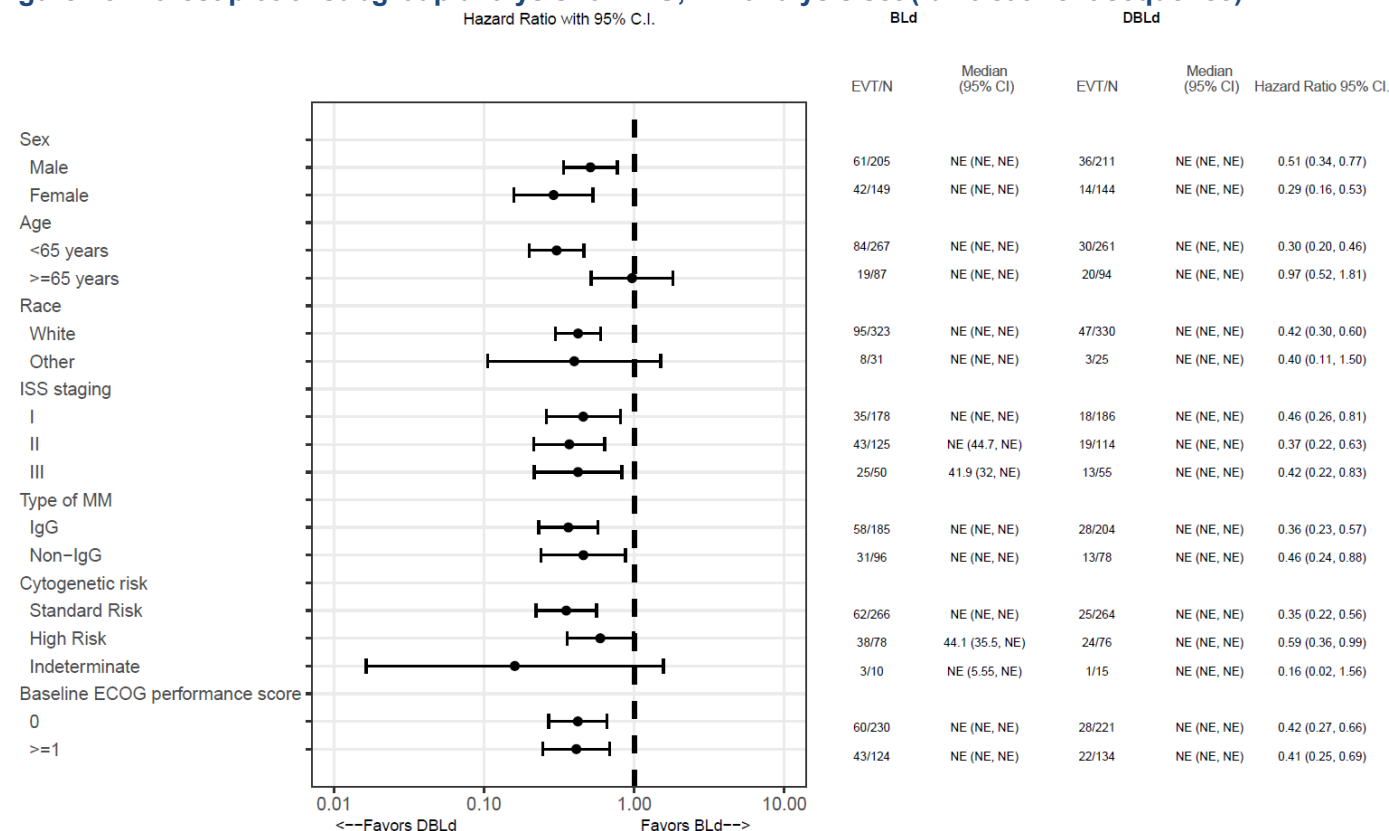
For PFS, the benefit was generally consistent across clinically relevant prespecified subgroups (age, ISS stage, cytogenetic risk, and baseline ECOG performance score) demonstrating a statistically significantly greater improvement in patients in the DBLd arm compared with patients in the BLd arm, with the exception of the ≥ 65 years subgroup, the indeterminate cytogenetic risk subgroup and the race 'other' subgroup. These subgroups still favoured DBLd, however the results were not statistically significant (HR: 0.97 [95% CI: 0.52, 1.81], HR: 0.16 [95% CI: 0.02, 1.56] and HR: 0.40 [95% CI: 0.11, 1.50], respectively (Figure 15). Given that the study was not powered to detect differences in subgroups and owing to the small patients numbers associated with these subgroups however, these results should be interpreted with caution.

For subgroup analyses of overall $\geq$ CR rate and MRD-negativity, the response benefit was consistent across most clinically relevant prespecified subgroups; most analyses demonstrated statistically significant improvements in the DBLd arm compared with BLd arm, with the exception of the ≥ 65 years, ISS Stage III, high cytogenetic risk and race 'other' subgroups for $\geq$ CR rate (Figure 15) and race 'other' for MRD-negativity (Figure 17).¹¹⁰ As noted above, however, these observed differences are anticipated to be a reflection of small patient numbers and therefore a lack of statistical power to detect differences in treatment effects within these subgroups and as such these results should be interpreted with caution (Figure 17).

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For subgroup analyses of sustained MRD-negativity (MRD-negativity for at least 12 months; at a threshold of 10^{-6}), the response benefit was consistent across all prespecified subgroups, with statistically significant improvements in the DBLd arm compared with BLd arm for all analyses (Figure 18).¹¹³

Figure 15: Forest plot of subgroup analysis for PFS; ITT analysis set (full treatment sequence)



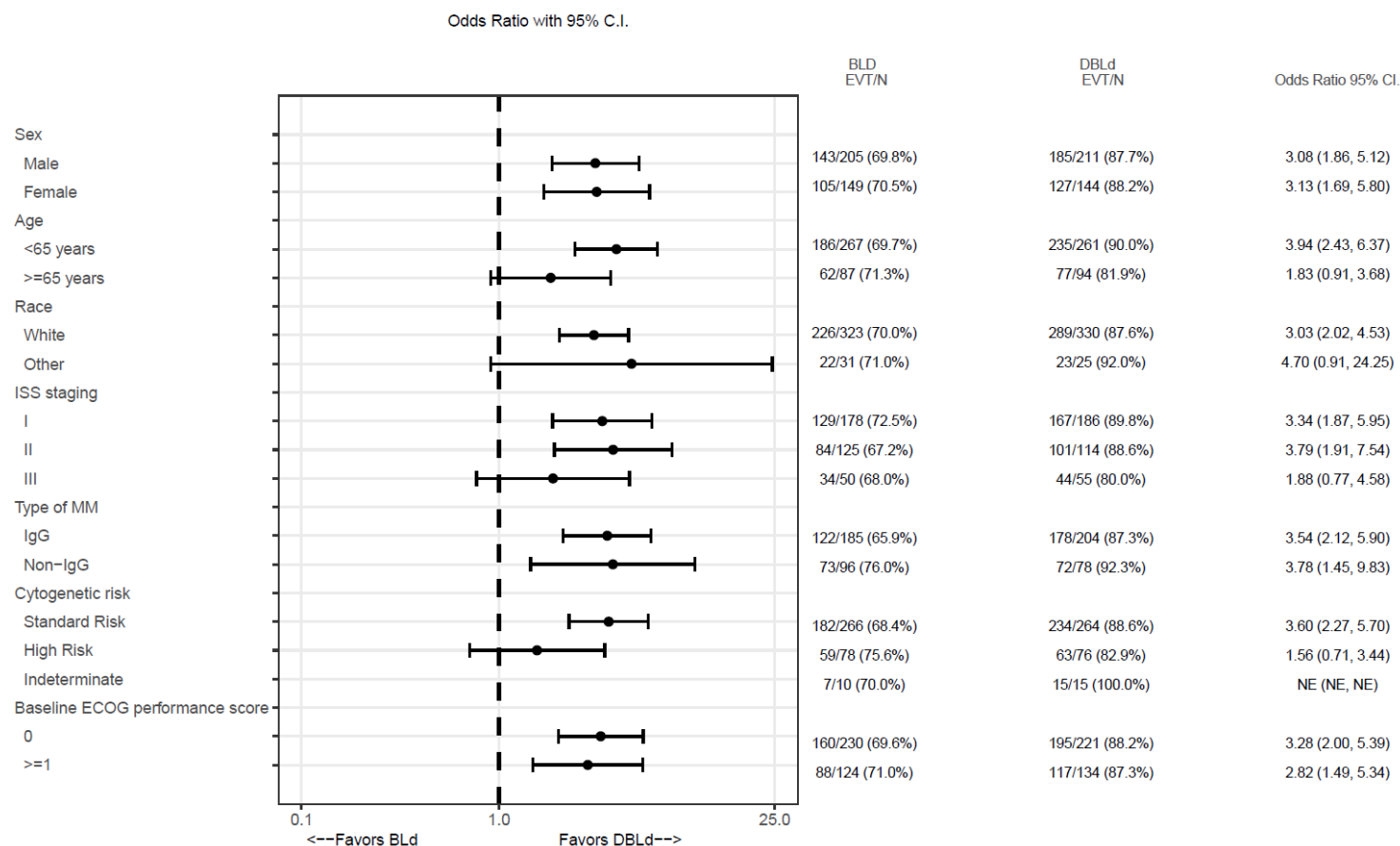
Footnotes: ^a Cytogenetic risk is based on FISH. ^b Patient may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)]

Abbreviations: BLD: bortezomib, lenalidomide, and dexamethasone; CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IgG: immunoglobulin G; ISS: International Staging System; ITT: intent-to-treat; MM: multiple myeloma; NE: not evaluable; PFS: progression-free survival.

Source: Sonneveld *et al.* (2024).¹¹⁰

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Figure 16: Forest plot of subgroup analysis for ≥CR; ITT analysis set (full treatment sequence)



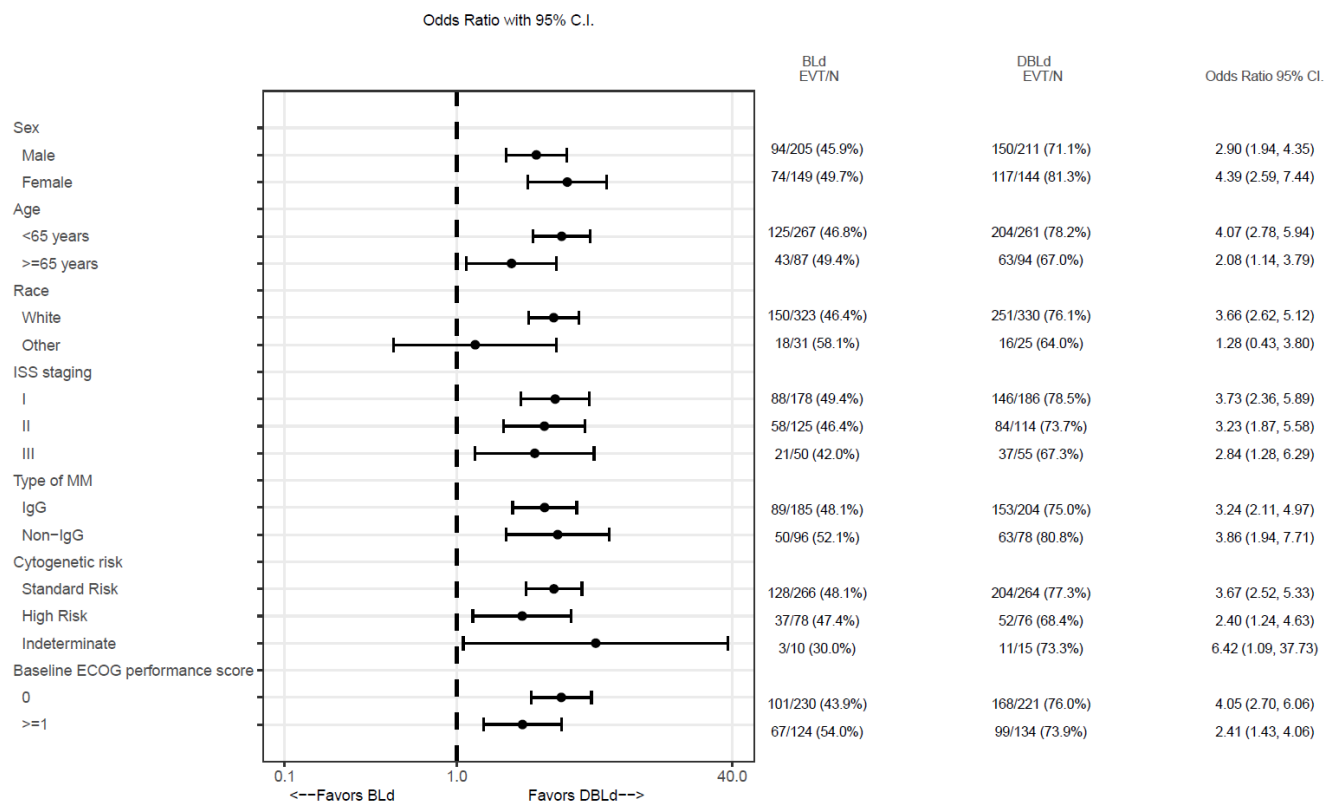
Footnotes: ^a Cytogenetic risk is based on FISH. ^b Patient may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)]

Abbreviations: BLd: bortezomib, lenalidomide, and dexamethasone; CI: confidence interval; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IgG: immunoglobulin G; ISS: International Staging System; ITT: intent-to-treat; MM: multiple myeloma.

Source: Sonneveld *et al.* 2024 (Supplementary Appendix).¹¹⁰

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Figure 17: Forest plot of overall MRD-negativity rate by NGS at or below 10^{-5} in patients with $\geq$ CR, ITT analysis set (full treatment sequence)



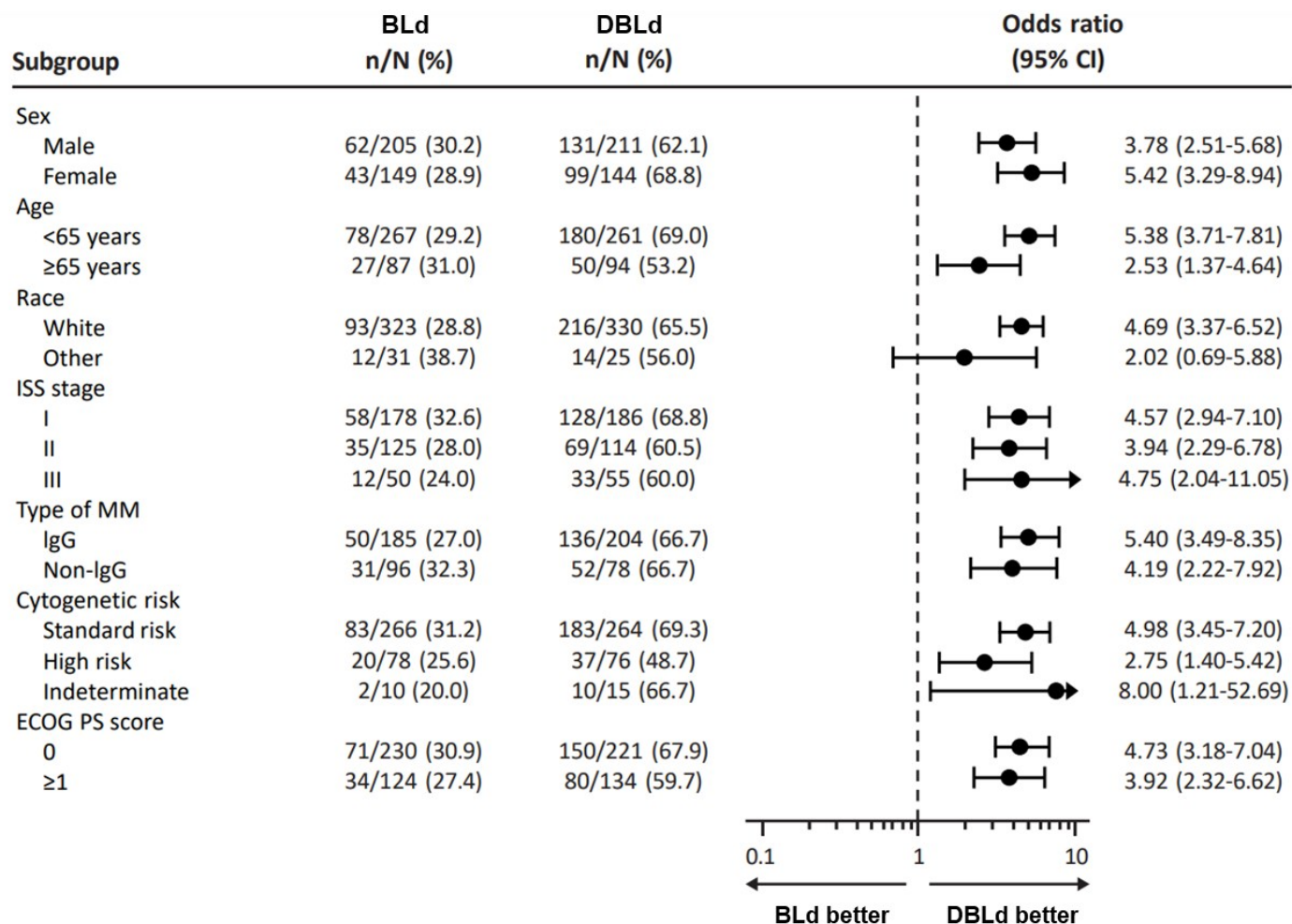
Footnotes: ^a Cytogenetic risk is based on FISH. ^b Patient may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)].

Abbreviations: BLd: bortezomib, lenalidomide, and dexamethasone; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG: Eastern Cooperative Oncology Group; IgG: immunoglobulin G; ISS: International Staging System; ITT: intent-to-treat; MM: multiple myeloma; MRD: minimal residual disease; NGS: next generation sequencing.

Source: Sonneveld *et al.* 2024 (Supplementary Appendix).¹¹⁰

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Figure 18: Forest plot of sustained MRD-negativity rate (at least 12 months apart) by NGS at or below 10^{-5} , ITT analysis set (full treatment sequence)



Abbreviations: BLd: bortezomib, lenalidomide, and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG: Eastern Cooperative Oncology Group; IgG: immunoglobulin G; ISS: International Staging System; ITT: intent-to-treat; MRD: minimal residual disease; NGS: next generation sequencing.

Source: Rodríguez-Otero *et al.* 2024.¹¹³

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2.9 Meta-analysis

PERSEUS is the only RCT for DBLd induction and consolidation followed by DL maintenance therapy which aligns with the decision problem (Section 1.1) and technology (Section 1.2) of relevance to this submission. As such, no meta-analysis was required.

2.10 Indirect and mixed treatment comparisons

Summary of Indirect Treatment Comparisons

- In the absence of direct trial evidence comparing the effectiveness of daratumumab, bortezomib, lenalidomide and dexamethasone (DBLd) followed by daratumumab with lenalidomide (DL) maintenance with its relevant comparator (daratumumab, bortezomib, thalidomide and dexamethasone [DBTd] followed by lenalidomide [L] maintenance)] in UK clinical practice, indirect treatment comparisons (ITCs) were conducted between PERSEUS and CASSIOPEIA in order to obtain relative efficacy estimates.
- No efficacy data for the full treatment sequence for the comparator (i.e. DBTd-L) were available. Instead, indirect treatment comparisons (ITCs) using individual patient data (IPD) from the PERSEUS and CASSIOPEIA trials were used to compare the clinical effectiveness of DBLd and DBTd as induction and consolidation treatments in patients with NDMM who are eligible for HDT-ASCT.
- Note, comparative effectiveness of DL versus L maintenance was informed by direct evidence from the Phase III AURIGA and PERSEUS studies.

ITC methodology

- The results of the feasibility assessment comparing the PERSEUS and CASSIOPEIA trials indicated that the two trials were sufficiently comparable for an ITC to be conducted for the induction and consolidation phases (Section 2.10.2).
- In the base case ITC approach, the PERSEUS population was re-weighted to match the CASSIOPEIA population via the inverse probability of treatment weighting (IPTW) approach, in line with NICE technical support document (TSD) 18.¹¹⁵ This IPTW approach adjusted for seven key prognostic variables using an average treatment effect (ATE) approach, where each patient's weight was determined by the inverse of their propensity score of belonging to the treatment or control group.
- One noted difference between the trials was that the CASSIOPEIA trial population was limited to patients up to 65 years, versus 70 years in the PERSEUS population. To align these populations, patients in PERSEUS ≥65 years were excluded from the base case ITC.

The results of the induction and consolidation ITCs demonstrated deeper responses for DBLd versus DBTd expected to translate to improved long-term survival outcomes

- During the induction and consolidation phase, patients receiving DBLd are almost [REDACTED] to experience a very good partial response or better (≥VGPR) compared to patients receiving DBTd (odds ratio [OR] [REDACTED]; 95% CI [REDACTED]–[REDACTED]; p=[REDACTED]); this difference was statistically significant. DBLd was also associated with a response benefit in terms of ORR (OR: [REDACTED]; 95% CI [REDACTED]–[REDACTED]; p = [REDACTED] and rates of MRD-negativity (OR: [REDACTED]; 95% CI [REDACTED]–[REDACTED]; p = [REDACTED])

- PFS and OS data are unavoidably immature, as median follow-up in the DBLd arm was restricted by the duration of induction and consolidation treatment (approximately 10-months). As such, results of the time-to-event outcomes are not a true reflection of the outcomes expected in clinical practice.
- The base case results were consistent across the various sensitivity analyses exploring alternate covariate adjustment (all covariates adjusted), alternative ITC methodologies outlined in NICE DSU TSD 17 (multivariate and double robust regressions),¹¹⁸ and alternate age restrictions on the PERSEUS trial population (patients >65 years were no longer excluded). This provides strong support for the robustness of the base case results to residual confounding which is an unavoidable limitation associated with unanchored ITC.

Conclusions

- The induction and consolidation ITCs demonstrate that DBLd is more effective than DBTd with statistically significant deeper $\geq$ VGPR, along with higher ORR and MRD-negativity rates.
- In light of the robust (Level 1) evidence and clinical expert support for the biological plausibility that depth of response will translate into commensurate improvements in PFS and OS, the clear response benefit associated with DBLd during induction and consolidation is expected to translate into a longer-term survival benefit.

2.10.1 Overview of the indirect treatment comparisons conducted

As previously highlighted in Section 1.3.4, DBTd-L is the only induction-consolidation-maintenance treatment sequence that is both established and used substantially in UK clinical practice for the treatment of patients with HDT-ASCT eligible NDMM.¹⁰⁷ As such, it is the only relevant comparator to DBLd-DL in this submission.

A clinical SLR was conducted in May 2018 and subsequently updated in April 2023 and February 2025 to identify studies of relevant induction-consolidation comparator therapies for patients with HDT-ASCT eligible NDMM. Additionally, a clinical SLR was conducted in September 2023 and updated in February 2025 to identify studies of relevant induction, consolidation and maintenance therapies in patients with HDT-ASCT eligible NDMM.

The reviews did not identify any clinical studies directly comparing the efficacy of DBLd induction and consolidation therapy with DBTd induction and consolidation therapy, nor DBLd followed by DL maintenance versus DBTd followed by L maintenance. Similarly, no studies assessing either of these treatments with a common comparator were identified, thus excluding the feasibility of conducting a network meta-analysis (NMA).

The SLRs identified one RCT investigating DBTd as an induction and consolidation therapy: the CASSIOPEIA trial was a two-part RCT in patients with HDT-ASCT eligible NDMM (an overview of the CASSIOPEIA trial is provided in Section 2.10.3). The first phase of the trial evaluated the efficacy and safety of DBTd compared with BTd as induction and consolidation treatments. In the second phase, patients were re-randomised 1:1 to receive daratumumab maintenance therapy or observation.⁷⁵ As such, the CASSIOPEIA trial does not provide comparative data for the full treatment sequence of relevance to the relevant comparator in this submission – i.e. DBTd-L.

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Therefore, it was not possible to perform an ITC comparing the full treatment sequences of DBLd-DL versus DBTd-L with the available evidence.

However, an ITC comparing the efficacy of DBLd and DBTd as induction and consolidation treatments was possible with the available data, and performed using clinical evidence from PERSEUS and CASSIOPEIA, respectively. Given that PERSEUS and CASSIOPEIA have the same sponsor, and therefore access to IPD, in line with NICE DSU TSD 17, population adjustment-based methods were explored to conduct an ITC.¹³⁸

The ITCs aimed to obtain relative efficacy estimates for DBTd versus DBLd, as induction and consolidation treatments, for the following five outcomes ($\geq$ VGPR, ORR, MRD-negativity, OS and PFS).

2.10.2 Feasibility assessment

When conducting ITCs, in order to ensure that any differences in outcomes between the intervention groups may be attributed to the difference in interventions, there should be no systematic differences between studies other than the interventions being compared. Accordingly, the suitability of comparing PERSEUS and CASSIOPEIA in an ITC was determined by assessing whether the studies are sufficiently homogenous, similar and consistent across their populations and outcomes. Specifically, CASSIOPEIA was evaluated versus PERSEUS based on the following parameters:

- Study design
- Risk of bias
- Treatment characteristics
- Patient inclusion/exclusion criteria
- Baseline characteristics
- Outcomes

Further details on each of these parameters, and the conclusions from the feasibility assessment, are detailed below. Results of the feasibility assessment are presented in full Appendix B.6.

Study design

The comparability of the PERSEUS and CASSIOPEIA study design was evaluated according to key variables, including study type, phase, study setting (i.e., time of randomisation), population, number of patients and country/institutions. An overview of the study designs of both trials is presented in Appendix B.6. PERSEUS and CASSIOPEIA were comparable across all evaluated variables.

Risk of bias

The risk of bias of PERSEUS and CASSIOPEIA was assessed using the Cochrane Risk of Bias 2.0 tool, as per NICE and Cochrane guidance. Both studies scored 'low' in all risk of bias categories, with no notable risk identified.^{139, 140} The results of the quality assessment are presented in Table 11 for PERSEUS, and Appendix B.8 for CASSIOPEIA.

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Treatment characteristics

The comparability of treatment characteristics between PERSEUS and CASSIOPEIA was evaluated according to key variables including treatment type, frequency, dosing, administration and duration.

Both trials consisted of four four-week cycles of induction therapy, followed by two four-week cycles of consolidation therapy. It should be noted that daratumumab was administered subcutaneously in PERSEUS and intravenously in CASSIOPEIA, however the different daratumumab administration routes are not expected to impact efficacy outcomes.¹⁴¹

Patient inclusion/exclusion criteria

The eligibility criteria for PERSEUS and CASSIOPEIA were compared by evaluating inclusion criteria relating to type of MM, age and ECOG PS, as well as major exclusion criteria.

A full comparison of the eligibility criteria across CASSIOPEIA and PERSEUS are presented in Appendix B.6. No major discernible differences were found except for age, where CASSIOPEIA only recruited patients aged up to 65 years while PERSEUS included patients aged up to 70 years. Measures were undertaken in the ITC to correct for this difference, as described in Section 2.10.4.

Baseline characteristics

The comparability of patient characteristics between PERSEUS and CASSIOPEIA was evaluated according to key variables including age, sex, region, race, ECOG PS, ISS stage, cytogenetic risk, creatine clearance and MM type.

CASSIOPEIA and PERSEUS underwent a rigorous evaluation to ascertain their comparability and concordance in terms of baseline characteristics. A summary of the baseline values for key variables (i.e., covariates of adjustment; see Section 2.10.5) that were considered relevant for the ITC is presented in Appendix B.6. Variables appeared to be well balanced between PERSEUS and CASSIOPEIA, with the exception of ECOG PS and ISS from the base case variables. Specifically, the PERSEUS trial population generally had a lower ECOG PS and ISS stage, indicative of higher levels of patient functioning and a less advanced disease stage, respectively, when compared with CASSIOPEIA. Both of these factors were adjusted for in the ITC (see Section 2.10.5).

Outcomes

When conducting an ITC, ensuring consistency in outcome definitions and censoring rules is paramount. A thorough examination of definitions for PFS and OS was conducted across PERSEUS and CASSIOPEIA to pinpoint any disparities that could introduce bias in the ITCs. The comparability and similarity of PFS, OS and response of CASSIOPEIA were evaluated against the PERSEUS trial based on several criteria including definition, availability of data, assessment criteria and type of assessment, and median follow-up and survival (full details presented in Appendix B.6). Overall, outcomes were broadly similar across both trials.

In the PERSEUS trial, MRD status was evaluated utilizing the NGS method. Conversely, in the CASSIOPEIA trial, a subgroup of patients underwent MRD testing through both NGS and flow cytometry. To facilitate an MRD ITC between these two trials, the NGS MRD statuses were imputed for analysis. A concordance analysis was performed on those patients who had Company evidence submission template for daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

undergone testing with both assays to assess the level of agreement between the two methodologies. Furthermore, to predict the NGS MRD status in CASSIOPEIA patients who were only assessed using flow cytometry, a predictive model was developed. The predicted NGS outcome in CASSIOPEIA was compared to the observed NGS in PERSEUS in an ITC.

Owing to no major differences in study design, risk of bias, treatment characteristics, patient eligibility criteria, baseline characteristics and outcomes between the PERSEUS and CASSIOPEIA trials, the feasibility assessment concluded that the studies were sufficiently comparable to conduct an ITC.

2.10.3 Data sources

Efficacy evidence for DBLd and DBTd as induction and consolidation therapies were derived from the PERSEUS and CASSIOPEIA trials, respectively, to inform the induction and consolidation set of ITCs.

Further information on data sources informing the ITCs are provided below.

PERSEUS

PERSEUS is an ongoing, randomised, multicentre, open-label Phase III trial which investigated the clinical efficacy and safety of DBLd induction and consolidation followed by DL maintenance compared with BLd followed by L maintenance in patients with HDT-ASCT eligible NDMM. Full details of the trial methodology are presented in Section 2.2.2.

CASSIOPEIA

CASSIOPEIA was a randomised, multicentre, open-label Phase III trial which compared DBTd to BTd in patients with HDT-ASCT eligible NDMM. This trial represented the pivotal clinical trial in the NICE appraisal for DBTd (TA763).² A total of 886 patients across 111 European centers were randomised in a 1:1 ratio, stratified by ISS stage and cytogenetic risk, to receive DBTd or BTd as induction and consolidation therapy (induction/consolidation phase). Patients who achieved a $\geq$ PR at Day 100 post-transplant underwent a second randomisation (1:1) to either observation or maintenance therapy with daratumumab every 8 weeks until disease progression, or for a maximum of two years (maintenance phase).⁷⁵

The primary endpoint for the induction and consolidation phase of the trial was the proportion of patients who achieved a sCR after consolidation. Key secondary efficacy endpoints included OS and PFS from first randomisation, the proportion of patients who were MRD-negative after consolidation, and the proportion of patients who achieved $\geq$ CR. For the maintenance phase of the trial, the primary endpoint was PFS, with key secondary outcomes including time to progression, OS, and the proportion of patients who achieved $\geq$ CR or MRD-negativity. The unpublished clinical DCO (May 2019) from CASSIOPEIA was used to inform the ITC, with a median follow-up of [REDACTED] months. A summary of the CASSIOPEIA trial is presented in Table 30. The risk of bias was estimated to be low (Appendix B).

Table 30: CASSIOPEIA trial design and methodology¹²⁸

Trial name	CASSIOPEIA (NCT02541383)
Location	Patients were treated across 111 European sites including: France (70 sits), Belgium (13 sites) and the Netherlands (28 sites)

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Trial design	Randomised, open-label, active-controlled, parallel-group, multicentre, Phase III trial to investigate the efficacy and safety of DBTd as an induction and consolidation therapy, and daratumumab as maintenance, in patients with previously untreated MM eligible for ASCT. The 'treatment phase' was conducted in two parts: • Part 1: Induction/ASCT/consolidation phase (1:1 randomisation) ○ The consolidation phase of treatment began approximately 30 days after ASCT • Part 2: Maintenance phase (1:1 re-randomisation of patients achieving at least a PR after consolidation) ○ Patients who had not achieved a response enter the follow-up phase, and are followed until disease progression or death, even if they received subsequent treatment^a
Intervention (Part 1)	• DBTd as an induction and consolidation therapy (N=543 randomised)
Comparator (Part 1)	• BTd as an induction and consolidation therapy (N=542 randomised)
Intervention (Part 2)	Following re-randomisation: • Daratumumab as maintenance therapy (N=442) of which (N=229 had received DBTd induction and consolidation therapy and N=213 had received BTd induction and consolidation therapy)
Comparator (Part 2)	Following re-randomisation: • Observation as maintenance therapy (N=444) of which (N=229 had received DBTd induction and consolidation therapy and N=215 had received BTd induction and consolidation therapy)
Key inclusion/exclusion criteria	Inclusion criteria: • Diagnosis of previously untreated MM • Have a confirmed diagnosis and eligible for high-dose chemotherapy and autologous stem cell transplantation, and an ECOG PS 0–2 Exclusion criteria: • Previous treatment for MM • Primary amyloidosis, plasma cell leukaemia or smouldering MM • Prior or concurrent exposure to systemic therapy or ASCT for any plasma cell dyscrasia, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment, or received an investigational drug or used an invasive investigational medical device within 4 weeks before Cycle 1, Day 1 Full inclusion and exclusion criteria can be found in Section 4 of the protocol (Moreau <i>et al.</i> 2024. Supplementary Material) included within the reference pack.¹²⁸
Method of study drug administration	Four 28-day cycles of induction therapy followed by two 28-day cycles of consolidation therapy in the following dosing: • Intravenous daratumumab: ○ Induction: 16 mg/kg once weekly in Cycles 1 and 2; once every two weeks for Cycles 3 and 4 ○ Consolidation: once every two weeks for Cycles 5 and 6 • Subcutaneous bortezomib: ○ Induction: 1.3 mg/m² twice weekly (with an option to change to once weekly in the event of toxicity) on Days 1, 4, 8, and 11 for Cycles 1–4

	○ Consolidation: 1.3 mg/m² twice weekly (with an option to change to once weekly in the event of toxicity) on Days 1, 4, 8, and 11 for Cycles 5 and 6 • Oral thalidomide: ○ Induction: 100 mg per day for Cycles 1–4 ○ Consolidation: 100 mg per day for Cycles 5 and 6 • Oral or intravenous dexamethasone: ○ Induction: 40 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 of Cycles 1 and 2; 40 mg on Days 1 and 2, and 20 mg on subsequent dosing days (Days 8, 9, 15, 16) of Cycles 3 and 4 ○ Consolidation: 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5 and 6 The following dosing was used in the maintenance phase: • Intravenous daratumumab: 16 mg/kg once every eight weeks until documented disease progression (limited to a maximum of two years)
Primary outcomes	Part 1: Post-consolidation sCR rate; assessed by computer algorithm and defined as the percentage of patients achieving CR in addition to having a normal serum free light chain (FLC) ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry. Post-consolidation response was assessed at Day 100 post-ASCT. Part 2: PFS from second randomisation: time from randomisation to either confirmed PD or death, whichever comes first
Key secondary endpoints^b	Part 1: • PFS: time from the initial randomisation to either confirmed PD or death, whichever comes first • Time to progression: time from the initial randomisation to confirmed PD, or death due to PD, whichever occurs first • ≥CR rate (post-ASCT/consolidation): proportion of patients who achieved CR or better by the end of consolidation assessed by computer algorithm • MRD-negativity rate (post-ASCT/consolidation): proportion of patients who achieved MRD-negative status by the end of consolidation assessed by computer algorithm • sCR rate (post-induction): proportion of patients who achieved sCR prior to high-dose therapy/ASCT assessed by computer algorithm • PFS2: time from initial randomisation to time of subsequent progression on next-line of therapy after disease progression on study treatment • OS: measured from the date of initial randomisation to the date of patient's death. If the patient is alive or vital status is unknown, then the patient's data was censored at the date the patient was last known to be alive Part 2: • Time to progression (from second randomisation): time from second randomisation to confirmed PD, or death due to PD, whichever occurs first • ≥CR rate: proportion of patients who have achieved a CR or better during the trial • MRD-negativity rate: proportion of patients who have achieved MRD-

	negative status by the end of the trial • PFS2 (from second randomisation): time from the second randomisation to time of subsequent progression on next line of therapy after disease progression on study treatment • OS (from second randomisation): time from the second randomisation to the date of death
Pre-planned subgroups	• Sex (male, female) • Age (<50 years, ≥50 years) • Site (IFM, Hovon) • ISS staging (I, II, III) • Cytogenetic risk (high risk, standard risk) • Baseline renal function (CrCl) (>90 mL/min, ≤90 mL/min) • Baseline hepatic function (normal, impaired) • Type of MM (IgG, non-IgG) • ECOG performance score (0, ≥1)
Duration of study and follow-up	The latest clinical DCO was September 2023, with a median follow-up time of 80.1 months (IQR 75.7–85.6 months). However, the clinical DCO informing the ITC was May 2019, with a median follow-up time of [REDACTED] months.

Footnotes: ^a If a patient's study treatment was discontinued before the end of the treatment regimen, the patient moved into the follow-up phase. ^b Response outcomes assessed in accordance with the IMWG criteria.

Abbreviations: ASCT: autologous stem cell transplantation; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DCO: data cut-off; ECOG PS: eastern cooperative oncology group performance status; IQR: interquartile range; ISS: international staging system; IWMG: International Myeloma Working Group; MM: multiple myeloma; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; PRO: patient-reported outcome; sCR: stringent complete response; VGPR: very good partial response.

2.10.4 Analysis methods

As described above, given PERSEUS and CASSIOPEIA were sponsored by the Company, IPD were available from both trials. As such, population-adjustment methods were considered for the analysis in line with NICE DSU TSD 17.¹³⁸

The ITC employed inverse probability treatment weighting (IPTW) as the base case approach, with alternative adjustment methods employed as scenario analyses. These methods are described in further detail below.

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 prognostic factors of interest. In these situations, multivariable regression and propensity score analyses – both of which are established methods recognised by NICE¹¹⁸ – 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.^{142, 143}

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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.¹⁴⁴

In the base case analysis, IPTW was the method used to control for differences in baseline characteristics that could introduce bias between the CASSIOPEIA and PERSEUS trials. 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. This method aims to address the correlation between baseline characteristics and the probability of being in a treatment group by using logistic regression and is part of the recommended method from the NICE DSU TSD 18.¹¹⁵

IPTW is a particularly useful approach 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.

It was important to ensure that both PERSEUS and CASSIOPEIA had completely overlapping populations, as differences in population inclusion criteria could result in overrepresentation of certain baseline characteristics, thus biasing the probability of allocation. As noted in the results of the feasibility assessment described in Section 2.10.2, the only major difference in the eligibility criteria of the two trials was with respect to age. CASSIOPEIA only recruited patients aged up to 65 years, whilst PERSEUS included those aged up to 70 years (including 94 patients aged ≥ 65 years).¹¹⁰ In order to better align the trial populations, the patient population in PERSEUS was limited to those up to 65 years of age. Inclusion and exclusion criteria were compared with any differences considered with respect to potential bias as described in Section 2.10.2. A sensitivity analysis, including the population of patients aged over 65 years in the DBLd arm of PERSEUS, was also conducted, with results presented in Section 2.10.9.

Weights were calculated for each patient using the formula “1/propensity score” for the treatment group (PERSEUS patients treated with DBLd) and “1/(1 - propensity score)” for the control group (CASSIOPEIA patients). This means that individuals with a lower probability of exposure to the treatment of interest received larger weights, thus increasing their relative influence on the comparison. Including these weights in the analysis made the allocation of patients to each clinical trial independent of the variables included in the propensity score model. Conceptually, the model aimed 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 PERSEUS and CASSIOPEIA 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), average treatment effect (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.¹³⁸ 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.¹³⁸ Considering the

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above, and that it is unclear whether one of the PERSEUS or CASSIOPEIA trials is more generalisable to UK clinical practice, employing the ATE approach (over other approaches such as ATC or ATT) is the most appropriate approach.

Proportional hazards

The proportional hazards (PH) assumption was assessed via log-cumulative hazard plots and Schoenfeld residuals of the survival outcome data from PERSEUS and CASSIOPEIA. No evidence of violation of the PH assumption was observed, indicating that the use of a HR as a summary measure for the time-to-event ITCs for PFS and OS was appropriate. Full details of the PH assessments can be found in Appendix L.

Scenario analyses

To explore the impact of using alternative adjustment methods, various methodologies outlined in NICE DSU TSD 17 were explored in scenario analyses, including multivariate regression and the double robust method, for both sets of ITCs.¹³⁸ Further details on these methods is provided below, with results presented in Section 2.10.8.

Multivariate regression

Multivariate regression is a statistical technique used to model outcomes by simultaneously accounting for the influence of multiple covariates, specifically baseline characteristics, that impact treatment effects. Given that the distribution of such variables is likely to differ between the PERSEUS and CASSIOPEIA trials, multivariate regression models the relationship between these baseline characteristics and the outcome of interest. This allows for predicting the effects of different treatment regimens in a patient population similar to that of the PERSEUS trial.

By allowing for the control of potential confounding variables and the assessment of the independent effect of each factor on efficacy outcomes, multivariate regression enhances the accuracy of efficacy estimates and improves the generalisability of the findings to broader patient populations. Furthermore, because multivariate regression does not rely on propensity scores, it conserves sample size, allowing for greater statistical power and a higher degree of certainty when specified correctly.

Double robust method

IPTW models rely on adjustments at the patient level without fully accounting for the effect of baseline characteristics on outcomes. For example, age might influence treatment allocation as a continuous variable but affect efficacy outcomes more as a categorical factor.

A method to address this issue is the double robust regression method. This approach models both treatment allocation and outcomes using the same set of regressors, allowing for simultaneous estimation of their effects on both treatment allocation and outcomes, without relying solely on reweighting at the patient level. Moreover, the double robust method handles extreme weights better, resulting in more reliable estimates even in the presence of highly skewed propensity scores.

2.10.5 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)/prognostic factor (PF), and that these factors are imbalanced between the trials under consideration. Baseline covariates of interest were identified based on a literature review. To further explore potential TEMs/PFs, based on the framework outlined in NICE DSU TSD 18, a review of stratification factors in PERSEUS (ISS and cytogenetic risk) was performed.¹¹⁵ Additionally, the results of pre-specified subgroup analyses conducted in PERSEUS and CASSIOPEIA were reviewed for evidence suggesting that a baseline characteristic could be a potential TEM. In total, 14 covariates were identified, of which seven were deemed to be priority PFs/TEMs (Table 31). The full list of covariates, and those selected as priority PFs/TEMs for the ITC, was validated by UK clinical experts during an advisory board in May 2025.⁴ In the base case model, the seven priority PFs and TEMs were adjusted, whilst all PFs and TEMs were adjusted for as a sensitivity analysis, as shown in Table 31 below.

Table 31: Identification of TEMs and PFs for the ITC:

Variable	Base case (priority covariates adjusted)	Sensitivity analysis (all covariates adjusted)
Age (≥50 versus <50 years)	✓	✓
Sex	✓	✓
ECOG PS	✓	✓
ISS stage	✓	✓
Baseline cytogenetic risk (high risk [defined as presence of del(17p) or t(4;14)] versus standard risk)	✓	✓
Type of MM (IgG versus non-IgG)	✓	✓
Haemoglobin levels (<10 versus ≥10 g/dL)	✓	✓
LDH (≥280 versus <280 U/L)		✓
Creatine clearance category (<90 versus ≥90 mL/min)		✓
MM diagnostic criteria satisfied: ≥1 CRAB feature versus SLiM-only		✓
Presence versus absence of extramedullary plasmacytomas		✓
Serum calcium (corrected; ≥2.75 versus <2.75 mmol/L)		✓
Bone lesions (≥1 versus none)		✓
Platelet levels (<150 versus ≥150 x 10 ⁹ /L)		✓

Abbreviations: CRAB: hyperCalcemia, Renal, Anemia, Bone; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ITC: indirect treatment comparison; LDH: lactate dehydrogenase; MM: multiple myeloma; PF: prognostic factor; SLiM: ≥60% clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of 100 or more with the involved serum free light chain being ≥100 mg/L, and Magnetic Resonance Imaging with more than one focal marrow lesion; TEM: treatment effect modifiers.

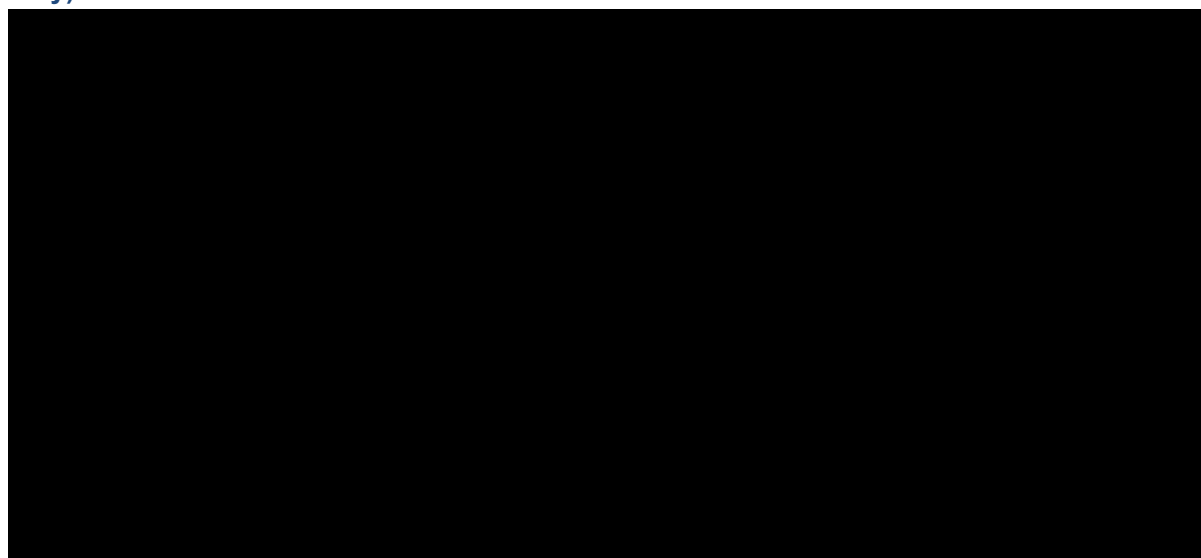
2.10.6 Assessment of overlap

IPTW weight distribution

For the base case (Figure 19; Table 32) and sensitivity analysis (all covariates adjusted) of both sets of ITCs (Figure 20; Table 33), the weight distribution followed a lognormal pattern. Additionally, the median and mean weights in both models were relatively close. In both models, a small number of patients had weights exceeding six, particularly in the sensitivity analysis (all covariates adjusted) where at least three patients had a weight over six.

However, adding the weight of these patients was found to be inferior to 10% of the effective sample size (ESS) in both the base case and sensitivity analysis (all covariates adjusted). Therefore, it was not considered to be overly contributing to the reweighted population. Consequently, the propensity score model ensured a balanced representation of the population, avoiding biases that could arise from over- or under-representation of specific patient groups during the comparison of DBLd versus DBTd as induction and consolidation therapies.

Figure 19: DBLd versus DBTd weight distribution: base case (priority covariates adjusted only)



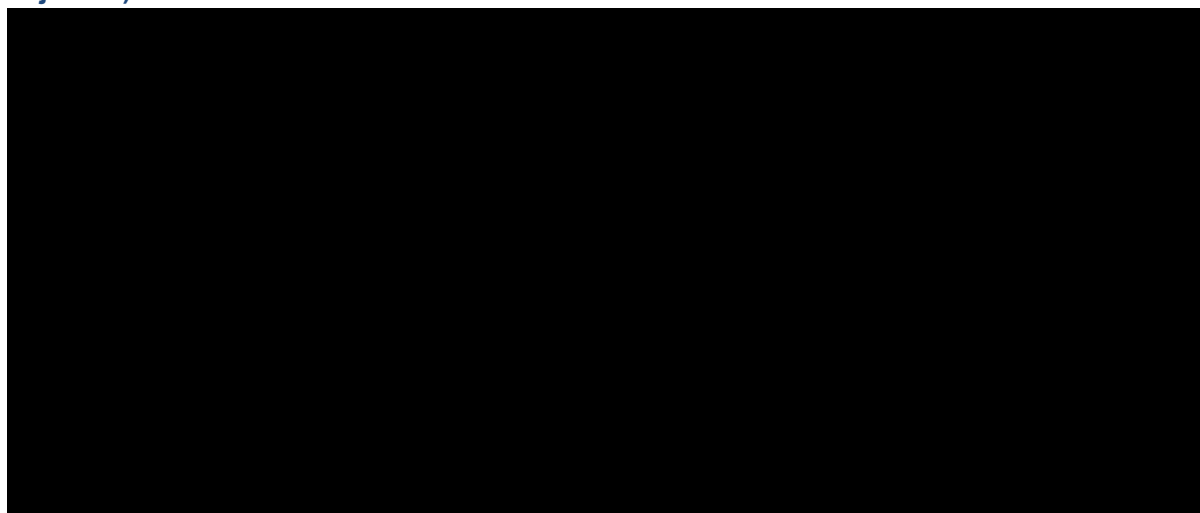
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone.

Table 32: DBLd versus DBTd weight distribution: base case

	Mean	SD	Median	Q25	Q75	Min	Max
Weights	■	■	■	■	■	■	■
Rescaled weights	■	■	■	■	■	■	■

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; Q25: lower quartile; Q75: upper quartile; SD: standard deviation.

Figure 20: DBLd versus DBTd weight distribution: sensitivity analysis (all covariates adjusted)



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone.

Table 33: DBLd versus DBTd weight distribution: sensitivity analysis (all covariates adjusted)

	Mean	SD	Median	Q25	Q75	Min	Max
Weights	■	■	■	■	■	■	■
Rescaled weights	■	■	■	■	■	■	■

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; Q25: lower quartile; Q75: upper quartile; SD: standard deviation.

Baseline characteristics before and after IPTW

The extent of overlap between populations with respect to the covariates identified for adjustment (Section 2.10.5) was evaluated before and after IPTW. Standardised mean differences (SMDs) were used to evaluate the differences for each variable included in the analysis, with a SMD greater than 0.2 indicating a substantial difference between the populations.

Unweighted

SMDs calculated before weighting are presented in Table 34 for the base case model (priority covariates adjusted) and Table 35 for the sensitivity analysis (all covariates adjusted). In the DBLd arm in PERSEUS, a greater proportion of patients receiving DBLd in PERSEUS had an ECOG PS of 0, and ISS stage I disease, whilst fewer patients had a bone lesion, compared with those receiving DBTd in CASSIOPEIA. The majority of variables had small SMDs (i.e., ≤ 0.2), indicating that the trial populations across PERSEUS and CASSIOPEIA were well-matched prior to adjustment. SMDs were greater than 0.2 for a small proportion of the variables, including bone lesions, lactate dehydrogenase (LDH), ECOG PS 0 or 1, and ISS stage I or II.

Weighted

Overall, IPTW resulted in well-matched populations across the base case and sensitivity analysis (all covariates adjusted). Specifically, in the base case model, only three variables (presence of extramedullary plasmacytomas, LDH and bone lesions) had SMDs above the threshold of 0.2.

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Therefore the weighting approach was deemed to be broadly successful. Furthermore, in the sensitivity analysis explored, no variables had SMDs exceeding 0.2.

Table 34: Baseline characteristics before and after matching: base case model

Variable	Unweighted			Weighted		
	DBTd	DBLd	SMD	DBTd	DBLd	SMD
n ESS	■	■	I	■	■	I
Age: ≥50 years (%)	■	■	■	■	■	■
Sex: Male (%)	■	■	■	■	■	■
ECOG performance status (%)						
0	■	■	■	■	■	■
1	■	■	■	■	■	■
2	■	■	■	■	■	■
ISS (%)						
I	■	■	■	■	■	■
II	■	■	■	■	■	■
III	■	■	■	■	■	■
Baseline Cytogenetic profile: Standard risk (%)	■	■	■	■	■	■
Type of MM at diagnosis: IgG (%)	■	■	■	■	■	■
Haemoglobin levels: LT10 (%)	■	■	■	■	■	■
LDH: ≥280 (%)	■	■	■	■	■	■
Creatine clearance category: LT90 ml/min (%)	■	■	■	■	■	■
CRAB versus SLiM: Any CRAB (%)	■	■	I	■	■	I
Presence of extramedullary plasmacytomas: 0 (%)	■	■	■	■	■	■
Calcium corrected: Normal (%)	■	■	■	■	■	■
Bone lesions: 1 (%)	■	■	■	■	■	■
Platelet levels: LT150 (%)	■	■	■	■	■	■

Abbreviations: CRAB: calcium elevation, renal insufficiency, anaemia, and bone lesions; LT: liver transplant; MM: multiple myeloma; ISS: international staging system; ECOG: eastern cooperative oncology group; ESS: effective sample size; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; ISS: International Staging System; SLiM: ≥60% clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of 100 or more with the involved serum free light chain being ≥100 mg/L, and Magnetic Resonance Imaging with more than one focal marrow lesion; SMD: standardised mean difference; IgG: immunoglobulin G; LDH: lactate dehydrogenase.

Table 35: Baseline characteristics before and after matching: sensitivity analysis (all covariates adjusted)

Variable	Unweighted			Weighted		
	DBTd	DBLd	SMD	DBTd	DBLd	SMD
n ESS	■	■	I	■	■	I
Age: ≥50 years (%)	■	■	■	■	■	■
Sex: Male (%)	■	■	■	■	■	■

Variable	Unweighted			Weighted		
	DBTd	DBLd	SMD	DBTd	DBLd	SMD
ECOG performance status (%)						
0	■	■	■	■	■	■
1	■	■	■	■	■	■
2	■	■	■	■	■	■
ISS (%)						
I	■	■	■	■	■	■
II	■	■	■	■	■	■
III	■	■	■	■	■	■
Baseline Cytogenetic profile: Standard risk (%)	■	■	■	■	■	■
Type of MM at diagnosis: IgG (%)	■	■	■	■	■	■
Haemoglobin levels: LT10 (%)	■	■	■	■	■	■
LDH: ≥280 (%)	■	■	■	■	■	■
Creatine clearance category: LT90 ml/min (%)	■	■	■	■	■	■
CRAB versus SLiM: Any CRAB (%)	■	■	I	■	■	I
Presence of extramedullary plasmacytomas: 0 (%)	■	■	■	■	■	■
Calcium corrected: Normal (%)	■	■	■	■	■	■
Bone lesions: 1 (%)	■	■	■	■	■	■
Platelet levels: LT150 (%)	■	■	■	■	■	■

Abbreviations: CRAB: calcium elevation, renal insufficiency, anaemia, and bone lesions; LT: liver transplant; MM: multiple myeloma; ISS: international staging system; ECOG: eastern cooperative oncology group; ESS: effective sample size; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; ISS: International Staging System; SLiM: ≥60% clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of 100 or more with the involved serum free light chain being ≥100 mg/L, and Magnetic Resonance Imaging with more than one focal marrow lesion; SMD: standardised mean difference; IgG: immunoglobulin G; LDH: lactate dehydrogenase.

2.10.7 Base case and sensitivity analysis (all covariate adjusted) results

2.10.7.1. Induction and consolidation treatment outcomes

Results of the comparative effectiveness of DBLd and DBTd, from induction to the end of consolidation, are presented below.

≥VGPR

≥VGPR results for both the unadjusted and adjusted base case and sensitivity analysis (all covariate adjusted), for DBTd versus DBLd are presented in Table 36.

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The ≥VGPR event rates were [REDACTED] in both the DBTd and DBLd arms. For the unadjusted and adjusted base case model, the OR was [REDACTED] and [REDACTED] favoured [REDACTED] over [REDACTED] (adjusted base case OR [REDACTED]; 95% CI: [REDACTED]–[REDACTED]; p [REDACTED]), indicating that the odds of achieving a ≥VGPR were [REDACTED] with DBLd compared with DBTd. The significantly deeper responses observed for DBLd over DBTd following induction and consolidation therapy reflect the increased potency of lenalidomide (a second-generation IMiD) versus thalidomide which is expected to translate to improved long-term outcomes given the well-established association between depth of response and PFS/OS in multiple myeloma.

Similar results were obtained in the sensitivity analysis (all covariates adjusted) – notably, the sensitivity analysis (all covariates adjusted) produced [REDACTED] than the base case model, suggesting that residual bias might have led to [REDACTED] of the DBLd effect on the response rate.

Table 36: ≥VGPR results of the ITC (induction and consolidation)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	OR (95% CI)	p-value
Unadjusted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Base case	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sensitivity analysis (all covariates adjusted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

An OR >1 favours DBLd, and an OR <1 favours DBTd. *Statistically significant p-value.

Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, and dexamethasone; HR: hazard ratio; ITC: indirect treatment comparison; IPTW: inverse probability treatment weighting; OR: odds ratio; VGPR: very good partial response.

ORR

ORR results for the unadjusted and adjusted base case, and sensitivity analysis (all covariates adjusted), for DBTd versus DBLd are presented in Table 37.

The ORR event rates were [REDACTED] in both the DBLd and DBTd arms, and the OR favoured [REDACTED] over [REDACTED] in the unadjusted, base case and sensitivity analysis (all covariates adjusted). Whilst the ORs were consistently [REDACTED], they were [REDACTED] for the unadjusted and base case model. However, [REDACTED] the odds of achieving an overall response were [REDACTED] (OR [REDACTED]; 95% CI: [REDACTED]–[REDACTED]; p [REDACTED]).

Table 37: ORR results of the ITC (induction and consolidation)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	OR (95% CI)	p-value
Unadjusted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Base case	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sensitivity analysis (all covariates adjusted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

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An OR >1 favours DBLd, and an OR <1 favours DBTd. *Statistically significant p-value.

Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, and dexamethasone; HR: hazard ratio; ITC: indirect treatment comparison; IPTW: inverse probability treatment weighting; OR: odds ratio; ORR: objective response rate.

MRD-negativity (regardless of CR status)

MRD-negativity (regardless of CR status) results for the unadjusted and adjusted base case, and sensitivity analysis (all covariates adjusted), for DBTd versus DBLd are presented in Table 38.

The MRD-negativity (regardless of CR status) rate [REDACTED] in the unadjusted, base case and sensitivity analysis (all covariates adjusted). Whilst not statistically significant, the consistency of results supports the notion of deeper rates of MRD negativity for DBLd following induction and consolidation compared with current standard of care which is expected to translate to an improvement in long-term survival outcomes.

Table 38: MRD-negativity results of the ITC (induction and consolidation)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	OR (95% CI)	p-value
Unadjusted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Base case	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sensitivity analysis (all covariates adjusted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

An OR >1 favours DBLd, and an OR <1 favours DBTd. *Statistically significant p-value.

Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, and dexamethasone; HR: hazard ratio; ITC: indirect treatment comparison; IPTW: inverse probability treatment weighting; MRD: minimum residual disease; OR: odds ratio.

PFS

PFS results for the unadjusted and adjusted base case, and sensitivity analysis (all covariates adjusted), for DBTd versus DBLd are presented in Table 39. Associated KM curves for the base case and sensitivity analysis (all covariates adjusted) are presented in Appendix J.

The median follow-up for time-to-event data for DBLd ([REDACTED] months) was restricted by the length of induction and consolidation treatment, as patient outcomes required censoring at the initiation of maintenance treatment. This limitation would not be resolved regardless of the availability of data from a longer follow-up period. Results of the PFS ITC presented below should therefore be interpreted with caution.

In the unadjusted model, the HR for DBLd versus DBTd was slightly in favour of [REDACTED] (HR [REDACTED]; 95% CI: [REDACTED]–[REDACTED]; p[REDACTED]), but this difference was [REDACTED].

Results from the adjusted models were consistent with this, finding a numerical, but [REDACTED], benefit in favour of [REDACTED] (HR [REDACTED]; 95% CI: [REDACTED]–[REDACTED]; p[REDACTED]). As with the base case, the sensitivity analysis (all covariates adjusted) favoured [REDACTED], although [REDACTED], as expected in line with the slightly [REDACTED] event rate for the [REDACTED] compared with the [REDACTED] arm.

Table 39: PFS results of the ITC (induction and consolidation)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	HR (95% CI)	p-value
Unadjusted	■	■	■	■
Base case	■	■	■	■
Sensitivity analysis (all covariates adjusted)	■	■	■	■

An HR <1 favours DBLd, and an HR >1 favours DBTd. *Statistically significant p-value.

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

OS

OS results for the unadjusted model and adjusted base case, and sensitivity analysis (all covariates adjusted), for DBTd versus DBLd are presented in Table 40. Associated KM curves for the base case and sensitivity analysis (all covariates adjusted) in Appendix J.

While the OS HR was greater than one, suggesting ■ in favour of DBTd (HR ■; 95% CI: ■–■), this result was ■ (p■). It is also important to note that, as these ITCs are based on the induction and consolidation phase of treatment only, a very small proportion of patients died in either treatment arm (■% and ■% of patients, during the induction and consolidation phase with DBTd and DBLd, respectively), these results must therefore be interpreted with extreme caution. As noted above, the limited median follow-up for time-to-event data for DBLd (■ months), which was restricted by the length of induction and consolidation treatment, should be considered when interpreting results from the OS ITC.

This ■ in the adjusted base case and sensitivity analysis (all covariates adjusted), but were ■ any of the analyses. For the same reasons, these point estimates must be interpreted with caution, and the KM curves indicate that OS is wholly comparable between treatment arms across the induction and consolidation treatment period.

Table 40: OS results of the ITC (induction and consolidation)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	HR (95% CI)	p-value
Unadjusted	■	■	■	■
Base case	■	■	■	■
Sensitivity analysis (all covariates adjusted)	■	■	■	■

An HR <1 favours DBLd, and an HR >1 favours DBTd. *Statistically significant p-value.

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

2.10.8 Scenario analyses results

2.10.8.1. Induction and consolidation treatment outcomes

The results for scenario analyses for $\geq$ VGPR, ORR, MRD-negativity, PFS and OS, which explored double robust and multivariate regression as alternative ITC methodologies, are presented in Table 41 for the induction and consolidation treatment phase.

For the induction and consolidation treatment set of ITCs, the scenario analyses results were consistent with those obtained via IPTW (Section 2.10.7). Given the short median follow-up for PFS and OS data for DBLd in the ITCs (an unavoidable limitation as patient outcomes required censoring at the initiation of maintenance treatment), reliable conclusions cannot be drawn for time-to-event endpoints. However, DBLd demonstrated deeper responses when compared with DBTd, with [REDACTED]

[REDACTED]. Deep durable responses are strong prognostic markers for improved long-term outcomes. As such, the response benefit associated with DBLd is expected to translate to improved PFS and OS outcomes over DBTd.

The consistency of the results across the base case and scenario analyses demonstrates their robustness, and provides strong evidence to support the assertion that DBLd is at least comparable in efficacy to DBTd induction and consolidation therapy. Indeed, given the statistically significant higher rates of $\geq$ VGPR and numerical trend in favour of DBLd for intermediate response-based endpoints including rates of MRD negativity, long-term clinical equivalence is considered a conservative assumption.

Table 41: Results of ITC scenario analyses (induction and consolidation)

Model	DBTd	DBLd	Adjusted ITC					
			IPTW		Double robust		Multivariate regression	
	% of events	% of events	OR/HR ^a (95% CI)	p-value)	OR/HR ^a (95% CI)	p-value	OR/HR ^a (95% CI)	p-value
≥VGPR								
Unadjusted	████	████	██████████	████	██████████	████	██████████	████
Priority variables adjusted	████	████	██████████	████	██████████	████	██████████	████
All variables adjusted	████	████	██████████	████	██████████	████	██████████	████
ORR								
Unadjusted	████	████	██████████	████	██████████	████	██████████	████
Priority variables adjusted	████	████	██████████	████	██████████	████	██████████	████
All variables adjusted	████	████	██████████	████	██████████	████	██████████	████
MRD-negativity (regardless of CR status)								
Unadjusted	████	████	██████████	████				
Priority variables adjusted	████	████	██████████	████				
All variables adjusted	████	████	██████████	████				
PFS								
Unadjusted	████	████	██████████	████	██████████	████	██████████	████
Priority variables adjusted	████	████	██████████	████	██████████	████	██████████	████
All variables adjusted	████	████	██████████	████	██████████	████	██████████	████
OS								
Unadjusted	████	████	██████████	████	██████████	████	██████████	████
Priority variables adjusted	████	████	██████████	████	██████████	████	██████████	████
All variables adjusted	████	████	██████████	████	██████████	████	██████████	████

* Statistically significant p-value. **Footnotes:** ^a ORs and HRs are presented for response and survival outcomes, respectively. An OR >1 favours DBLd, and an OR <1 favours DBTd. An HR <1 favours DBLd, and an HR >1 favours DBTd.

Abbreviations: CI: confidence interval; CR: complete response; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; ITC: indirect treatment comparison; MRD: minimal residual disease; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; VGPR: very good partial response

2.10.9 Sensitivity analysis (full population from PERSEUS) results

In the base case ITC, the patient population from PERSEUS was limited to those up to, and including, 65 years of age, compared to 70 years in the ITT population, to better align with the CASSIOPEIA patient population. A sensitivity analysis was conducted using the full population from PERSEUS, without excluding patients aged >65 years of age.

An assessment of overlap was conducted and found that the propensity score model ensured a balanced representation of the population, avoiding biases that could arise from over- or under-representation of specific patient groups during the comparison of DBLd versus DBTd. Full details of the assessment of overlap are presented in Appendix K.

Results

The sensitivity analysis (full PERSEUS population) was conducted via IPTW for the unadjusted model, the model with priority covariates adjusted for, and the model with all fourteen identified covariates adjusted for. The sensitivity analysis also involved scenario analyses which explored the utilisation of double robust and multivariate regression. Findings for the sensitivity analyses (full PERSEUS population) were broadly consistent with the base case analysis, where the PERSEUS population was limited to those aged up to and including 65 years (Section 2.10.7). These findings demonstrate the robustness of the results of both sets of ITCs, irrespective of whether the PERSEUS population is limited to those aged up to and including 65 years, and support the comparative efficacy of DBLd and DBTd as induction and consolidation treatments.

Full results are presented in Appendix J.

2.10.10 Uncertainties in the indirect and mixed treatment comparisons

Lack of comparator efficacy data reporting on full comparator treatment sequence of interest in submission (i.e. DBTd-L)

As noted in Section 2.10.1 no studies reported efficacy data for the full comparator treatment sequence, DBTd-L and as such ITCs comparing the efficacy for DBLd-DL and DBTd-L could not be performed. The conclusions derived from the ITCs performed are therefore, only focused on the induction and consolidation phases. The benefit of adding daratumumab to L maintenance therapy could not be investigated through the ITCs. The AURIGA trial described in Section 2.2, which compared the clinical efficacy of DL and L maintenance therapy, was considered the best available source of evidence to inform the comparative efficacy of the maintenance phase of the DBLd-DL versus DBTd-L treatment sequence. As such, this trial was used to inform long-term survival estimates in the cost-effectiveness model (see Section 3.3 for further details), with the PERSEUS study providing supportive evidence.

Assessment of time-to-event outcomes (PFS and OS) during induction and consolidation

In the PERSEUS trial, patients were randomised to DBLd followed by DL maintenance, or BLd followed by L maintenance. To derive an estimate of the treatment effect for DBLd induction and consolidation therapy alone, to inform the induction and consolidation ITCs, patient outcomes were censored at the initiation of maintenance treatment for time-to-event outcomes. As such, the median follow-up for PFS and OS in the DBLd arm (12 months) was restricted by the duration of induction and consolidation treatment. This represents an unavoidable limitation for the induction and consolidation ITCs, as no amount of additional follow-up would be able to resolve this uncertainty. As such, outcomes for PFS and OS ITCs should be interpreted with caution with respect to the treatment effects for DBLd versus DBTd induction and consolidation.

The uncertainty surrounding the comparative PFS and OS data is mitigated by the availability of biologically plausible, clinically meaningful surrogate endpoints, including response rates and MRD-negativity.⁴ There is an extensive body of evidence highlighting the significance of achieving deep, sustained treatment responses (Section 0) and the subsequent benefits on long-term survival outcomes. The results of the ITCs presented in Section 2.10.7 show that [REDACTED], and [REDACTED] of patients achieving a $\geq$ VGPR. As such, it can reasonably be concluded that, by achieving a deep, durable response in the induction and consolidation phase, DBLd is likely to result in a long-term survival benefit versus DBTd.¹⁴⁵⁻¹⁴⁸

Potential for residual confounding given the unanchored nature of the ITCs

As with all unanchored ITCs, one of the inherent uncertainties in the analysis is the potential for residual bias. For an unanchored ITC to be valid, all PFs and TEMs must be adjusted for, however it is possible that residual bias remains in the analyses as a result of differences between the PERSEUS and CASSIOPEIA trial populations that were unaccounted for. The risk of such residual bias is, however, minimal, as the availability of individual patient data (IPD) from the PERSEUS and CASSIOPEIA trials enabled the use of propensity-based ITC methodologies. This allows for a more robust matching process compared to MAICs, where MAICs only match

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reported, aggregated baseline characteristics. Furthermore, the process to identify the most important covariates to include in the analysis and improve matching was extensive and conducted in line with NICE DSU TSD 18.¹¹⁵ In support of the minimal risk of residual bias, the small SMDs observed pre-adjustment reflect that the PERSEUS and CASSIOPEIA populations exhibited high overlap even prior to weighting. The overlap was increased further following weighting, with SMDs only slightly exceeding 0.2 for three non-priority variables in the base case model, and no variables in the model with all covariates adjusted (as shown in Table 34 and Table 35 of Section 2.10.6). The robustness of base case results to residual confounding is supported by the consistency of findings between the base case and sensitivity analysis with all covariates adjusted for, along with the multivariate regression and double robust methods explored.

In addition, to further align the PERSEUS and CASSIOPEIA patient populations to minimise residual bias, the base case model limited the PERSEUS population to those aged up to, and including, 65 years. The importance of exploring this adjustment to maximise the exchangeability of trials in line with NICE TSD 18 was confirmed by feedback received from UK health economic experts during a May 2025 Advisory Board.^{4, 115} It is however acknowledged that excluding patients aged >65 years to better match the PERSEUS and CASSIOPEIA trials may potentially limit the generalisability of the ITC results to older populations. It should however be noted that given the majority of HDT-ASCT eligible patients in the UK are expected to be aged ≤65 years old, as those diagnosed later in life would likely not be fit enough to receive HDT with ASCT (see Section 1.3.2), any generalisability issues are anticipated to be minimal.^{62, 149} Furthermore, to address any such generalisability concerns, a sensitivity analysis was conducted in which the full PERSEUS population was included, with results demonstrating that the base case analysis results are robust to such age restrictions in the PERSEUS trial population.

2.10.11 Conclusions of the indirect and mixed treatment comparisons

During the induction and consolidation phase, patients receiving DBLd experienced deeper responses compared to patients receiving DBTd, and were almost [REDACTED] to experience a ≥VGPR

The CASSIOPEIA trial was considered to represent the most appropriate source of evidence for the induction and consolidation comparator of relevance in this submission, DBTd. The ITCs showed that patients who received DBLd were significantly more likely to achieve a ≥VGPR (OR: [REDACTED], 95% CI: [REDACTED], [REDACTED]) compared to DBTd, and demonstrated a [REDACTED] and the rate of MRD-negativity. Overall, these results support that DBLd is more effective than DBTd as an induction and consolidation treatment at achieving deeper responses.

Measurement of time-to-event outcomes for induction and consolidation is inherently limited, however, achieving a deep response is a strong prognostic markers for survival outcomes, and therefore [REDACTED] associated with DBLd are expected to translate into long-term OS benefits when compared to DBTd

As described in Section 2.10.10, the median follow-up for PFS and OS in the DBLd arm was restricted by induction and consolidation treatment duration, as patient outcomes were censored at the initiation of maintenance treatment. This represents an unavoidable limitation of the

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induction and consolidation ITCs for PFS and OS, meaning the comparative efficacy estimates for DBLd versus DBTd are not a true reflection of the outcomes expected in clinical practice. However, there is an extensive body of evidence highlighting the prognostic implications of deep responses to treatment, including MRD-negativity, and subsequent benefits to long-term OS.^{51, 53-55, 119-121} As discussed in Section 1.3.2, the biological plausibility of using depth of response as predictors of long-term survival outcomes was further confirmed by feedback received from UK clinical experts at a May 2025 Advisory Board, whilst the NICE appraisal for DBTd (TA763), MRD-negativity was accepted as a surrogate outcome for OS.^{2, 4, 53} DBLd [REDACTED] at induction and consolidation, whilst also achieving a benefit in terms of ORR and MRD-negativity rates, when compared with DBTd. It is therefore reasonable to expect that DBLd would inevitably result in a long-term OS benefit when compared with DBTd.

The results of the induction and consolidation ITCs were shown to be robust across an extensive range of sensitivity and scenario analyses, which were consistent with the base case results

The base case results were consistent across various the sensitivity analyses exploring alternate covariate adjustment (all covariates adjusted), alternative ITC methodologies outlined in NICE DSU TSD 17 (multivariate and double robust regressions),¹¹⁸ and alternate age restrictions on the PERSEUS trial population (where patients >65 years were no longer excluded). This provides support for the robustness of the base case results, and therefore confidence in the conclusion that DBLd is at least comparable to DBTd in the induction and consolidation phase.

2.11 Adverse reactions

The safety data presented in the sections below are based on the results of the safety analysis set from the PERSEUS trial at the 1st August 2023 DCO. The safety analysis set included all patients who had received at least one dose of study treatment (partial or complete) in the trial.³² Full details on the safety analysis set are presented in Table 8; Section 2.4.1.

2.11.1 Treatment duration and dosage

A summary of treatment duration and dose intensity of patients in the BLd and DBLd arm in the PERSEUS trial is provided in Table 42.

The median duration of study treatment was comparable between arms ([REDACTED] months for BLd arm and [REDACTED] months for DBLd arm). Similarly, median dose intensity for bortezomib, lenalidomide and dexamethasone was comparable between the BLd and DBLd treatment arms ([REDACTED] mg/cycle versus [REDACTED] mg/cycle for bortezomib, [REDACTED] mg/cycle versus [REDACTED] mg/cycle for lenalidomide, and [REDACTED] mg/cycle versus [REDACTED] mg/cycle for dexamethasone, respectively).³²

Table 42: Summary of the treatment duration and dose intensity for the full treatment sequence; Safety analysis set

	BLd arm ^a N=347	DBLd arm ^b N=351
Duration of study drug (months)^c		
Mean (SD)	[REDACTED]	[REDACTED]
Median	[REDACTED]	45.73

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	BLd arm ^a N=347	DBLd arm ^b N=351
Range	██████████	0.49, 54.34
Daratumumab dose intensity (mg/cycle)		
Mean (SD)	-	██████████
Median	-	██████
Range	-	██████████
Bortezomib dose intensity (mg/cycle)		
Mean (SD)	██████████	██████████
Median	████	████
Range	██████	██████
Lenalidomide dose intensity (mg/cycle)		
Mean (SD)	██████████	██████████
Median	████	████
Range	██████	██████
Dexamethasone dose intensity (mg/cycle)		
Mean (SD)	██████████	██████████
Median	████	████
Range	██████	██████

Footnote: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy. ^c Duration of induction/Pre-ASCT/ASCT/consolidation treatment: (a) For subjects received consolidation after having received ASCT, from first induction dose date to the last consolidation dose date. (b) For subjects received ASCT after 6 cycles of induction, from first induction dose date to the day before maintenance treatment start date, or the date of end-of-treatment visit, whichever is earlier. Subjects who received both ASCT and consolidation, or received ASCT after 6 cycles of induction were taken into account for this calculation.

Abbreviations: BLd: bortezomib, lenalidomide, and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; SD: standard deviation.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO; Table 7 and TSIX04).³²

2.11.2 Summary of treatment-emergent adverse events

A summary of TEAEs at the August 2023 DCO is provided in Table 43.¹¹⁰

The incidence of TEAEs was comparable between the BLd and DBLd treatment arms at each treatment phase (████ versus █████ for the induction phase; █████ versus █████ for the pre-ASCT phase; █████ versus █████ for the ASCT phase; █████ versus █████ for the consolidation phase and █████% versus █████% for the maintenance phase).^{32, 110} Of note, the percentage of patients who discontinued treatment because of at least one TEAE was marginally lower in the DBLd arm compared to the BLd arm at each treatment phase. Furthermore, the number of TEAEs related to study drug leading to death were comparably low between arms (BLd arm: █████% versus DBLd arm: █████%).³² Of note, these results show that the addition of daratumumab to standard of care BLd + L is not linked to reduced tolerability or safety concerns.

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Table 43: Summary of treatment-emergent adverse events for the full treatment sequence; safety analysis set

TEAEs, n (%)	BLd arm ^a N=█	DBLd arm ^b N=█
TEAE leading to discontinuation of study drug ^c	█	█
COVID-19	█	█
TEAE leading to discontinuation of daratumumab ^d	I	█
At least one related to daratumumab	I	█
TEAE leading to discontinuation of bortezomib ^d	█	█
At least one related to bortezomib	█	█
TEAE leading to discontinuation of lenalidomide ^d	█	█
At least one related to lenalidomide	█	█
TEAE leading to discontinuation of dexamethasone ^d	█	█
At least one related to dexamethasone	█	█
Any TEAE	█	█
Study drug-related ^e	█	█
Maximum toxicity grade		
Grade 1	█	█
Grade 2	█	█
Grade 3	█	█
Grade 4	█	█
Grade 5	█	█
Any serious TEAE	█	200 (57.0)
Study drug-related ^e	█	█
TEAE with outcome death	█	█
Study drug-related ^e	█	█

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TEAEs, n (%)	BLd arm ^a N=■	DBLd arm ^b N=■
Death due to COVID-19	■	■
COVID-19 TEAEs	■	■
COVID-19 serious TEAEs	■	■

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy ^c Includes those patients indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page ^d Includes those patients indicated as having discontinued specific study treatment due to an adverse event on the adverse event CRF page. ^e TEAEs related to at least 1 of the 4 study treatments: daratumumab, bortezomib, lenalidomide and dexamethasone.

Abbreviations: BLd: bortezomib, lenalidomide, and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; DL: daratumumab with lenalidomide; L: lenalidomide; TEAE: treatment-emergent adverse event.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TSFAE01P.³²

2.11.3 Most common treatment-emergent adverse events

The most common TEAEs, defined as occurring in 10% of patients or more in either treatment arm, in the safety analysis set for the induction phase were neutropenia (DBLd arm: █%; BLd arm: █%), peripheral sensory neuropathy (DBLd arm: █%; BLd arm: █%) and constipation (DBLd arm: █%; BLd arm: █%).³² For the consolidation phase, the most common TEAEs were thrombocytopenia (DBLd arm: █%; BLd arm: █%), neutropenia (DBLd arm: █%; BLd arm: █%) and peripheral sensory neuropathy (BLd arm: █%; DBLd arm: █%). For the maintenance phase, the most common TEAEs were diarrhea (DBLd arm: █%; BLd arm: █%), COVID-19 (DBLd arm: █%; BLd arm: █%) and neutropenia (DBLd arm: █%; BLd arm: █%) (Table 44).

Despite peripheral sensory neuropathy being one of the most common TEAEs in the induction and consolidation phases, it is important to note that the incidence of such events remained relatively low in both arms throughout the trial at <█% in both the DBLd and BLd arms during the consolidation and maintenance phases. This is in sharp contrast to the proportions of patients who are anticipated to experience neurotoxicity events in clinical practice on currently available thalidomide containing regimens in this setting. The high neurotoxicological burden associated with thalidomide containing regimens was highlighted in a 2024 RCT in 123 patients in which 41.3% of patients experienced a neurotoxic event versus 11.7% in patients receiving a thalidomide sparing regimen (CLd).¹⁰³ The need for thalidomide-free treatment options was highlighted in a 2025 UK Advisory Board, where UK clinical experts confirmed that the neurotoxicity associated with thalidomide is seen as a major issue across the medical community and there is therefore a desire to move to thalidomide sparing therapies which would prevent this.⁴

Overall, the incidence of TEAEs was comparable between treatment arms, with the exception of neutropenia, which occurred more frequently in the DBLd arm in the induction and maintenance phase.³² Furthermore, the incidence of TEAEs were comparable by treatment phase between treatment arms (induction: █% versus █%; consolidation: █% versus █%; maintenance: █% versus █% for the DBLd and BLd arm, respectively).³² These data provide evidence to support that the addition of daratumumab to BLd induction and consolidation and L maintenance therapy is not associated with a decreased tolerability profile. This was supported by feedback from UK clinicians at a 2025 UK Advisory Board, who noted that daratumumab is overall a very tolerable treatment.⁴

Table 44: Summary of most common TEAEs of any grade by treatment phase; safety analysis set

TEAEs, n (%)	BLd arm ^a					DBLd arm ^b				
	Induction n N=	Pre-ASCT N=	ASCT N=	Consolidation n N=	Maintenance N=	Induction n N=	Pre-ASCT N=	ASCT N=	Consolidation n N=	Maintenance N=
Infections and infestations										
COVID-19										
Upper respiratory tract infection										
Blood and lymphatic system disorders										
Neutropenia										
Thrombocytopenia										
Anaemia										
Gastrointestinal disorders										
Diarrhoea										
Constipation										
Nausea										
General disorders and administration site conditions										

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TEAEs, n (%)	BLd arm ^a					DBLd arm ^b				
	Induction n N=	Pre-ASCT N=	ASCT N=	Consolidation n N=	Maintenance n N=	Induction n N=	Pre-ASCT N=	ASCT N=	Consolidation n N=	Maintenance n N=
Pyrexia										
Asthenia							1			
Fatigue										
Oedema peripheral										
Nervous system disorders										
Peripheral sensory neuropathy										
Musculoskeletal and connective tissue disorders										
Back pain								1		
Skin and subcutaneous tissue disorders										
Rash							1			
Respiratory, thoracic and mediastinal disorders										
Cough								1		
Psychiatric disorders										
Insomnia		1								

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Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy

Abbreviations: BLd: bortezomib, lenalidomide, and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; TEAE: treatment-emergent adverse event.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): Table 23.³²

2.11.4 Grade 3–4 treatment-emergent adverse events

A summary of the incidence of Grade 3 or 4 TEAEs by treatment phase is provided in Table 45 below.

The overall incidence of Grade 3 or 4 TEAEs was higher in the DBLd arm compared with the BLd arm during induction and consolidation however was similar across treatment arms during maintenance (Table 45).³² The most common Grade 3 or 4 TEAEs occurring at a $\geq 10\%$ frequency in either treatment arm were neutropenia (DBLd arm: █%; BLd arm: █%) and thrombocytopenia (DBLd arm: █%; BLd arm: █%) for the induction phase, thrombocytopenia (DBLd arm: █%; BLd arm: █%) and neutropenia (DBLd arm: █%; BLd arm: █%) for the consolidation phase, and neutropenia (DBLd arm: █%; BLd arm: █%) and thrombocytopenia (DBLd arm: █%; BLd arm: █%) for the maintenance phase (Table 45).³²

Table 45: Summary of most common TEAEs of Grade 3 or 4 by treatment phase; safety analysis set

TEAEs, n (%)	BLd arm ^a					DBLd arm ^b				
	Induction N=■	Pre-ASCT N=■	ASCT N=■	Consolidation N=■	Maintenance N=■	Induction N=■	Pre-ASCT N=■	ASCT N=■	Consolidation N=■	Maintenance N=■
Blood and lymphatic system disorders	■	■	■	■	■	■	■	■	■	■
Neutropenia	■	■	■	■	■	■	■	■	■	■
Thrombocytopenia	■	■	■	■	■	■	■	■	■	■
Febrile neutropenia	■	■	■	■	■	■	■	■	■	■
Anaemia	■	■	■	■	■	■	■	■	■	■
Infections and infestations	■	■	■	■	■	■	■	■	■	■
Pneumonia	■	■	■	■	■	■	■	■	■	■
Gastrointestinal disorders	■	■	■	■	■	■	■	■	■	■
Diarrhoea	■	■	■	■	■	■	■	■	■	■
Stomatitis	■	■	■	■	■	■	■	■	■	■
Nervous system disorders	■	■	■	■	■	■	■	■	■	■
General disorders and administration site conditions	■	■	■	■	■	■	■	■	■	■
Fatigue	■	■	■	■	■	■	■	■	■	■
Investigations	■	■	■	■	■	■	■	■	■	■
Alanine aminotransferase increased	■	■	■	■	■	■	■	■	■	■

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TEAEs, n (%)	BLd arm ^a					DBLd arm ^b				
	Induction N=■	Pre-ASCT N=■	ASCT N=■	Consolidation N=■	Maintenance N=■	Induction N=■	Pre-ASCT N=■	ASCT N=■	Consolidation N=■	Maintenance N=■
Respiratory, thoracic and mediastinal disorders	■	■	■	■	■	■	■	■	■	■
Metabolism and nutrition disorders	■	■	■	■	■	■	■	■	■	■
Skin and subcutaneous tissue disorders	■	■	■	■	■	■	■	■	■	■
Vascular disorders	■	■	■	■	■	■	■	■	■	■
Cardiac disorders	■	■	■	■	■	■	■	■	■	■
Hepatobiliary disorders	■	■	■	■	■	■	■	■	■	■
Psychiatric disorders	■	■	■	■	■	■	■	■	■	■
Neoplasms benign, malignant and unspecified	■	■	■	■	■	■	■	■	■	■
Musculoskeletal and connective tissue disorders	■	■	■	■	■	■	■	■	■	■

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy

Abbreviations: BLd: bortezomib, lenalidomide, and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; TEAE: treatment-emergent adverse event.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): Table 25.³²

2.11.5 Adverse events of special interest

Based on previous experience with daratumumab in humans, in vitro studies, and animal toxicological findings, adverse events of special interest in the PERSEUS trial included systemic administration-related reactions (sARRs) and infusion-related reactions (IRRs), local injection-site reactions, infections and infestations and cytopenia.³² The results for each adverse event of special interest (AESI) are discussed below.

Firstly, sARRs were defined as systemic reactions related to daratumumab subcutaneous (SC) administration and IRRs were defined as systemic reactions related to daratumumab administration, regardless of the route of administration. There was a low incidence of sARRs reported in the DBLd arm (■ (■%) patients), and the majority were Grade 1 or 2 events. The most frequently reported ($\geq 2\%$ in all participants) sARRs were pyrexia in ■ (■%) patients and chills in ■ (■%) patients. Four Grade 3 or 4 sARRs were reported in ■ (■%) participants (respiratory failure, bronchospasm, tachycardia, and bronchitis) and all were reported as treatment-emergent serious adverse events (SAEs) that required hospitalisation.³²

Secondly, injection-site reactions were experienced by ■ (■%) patients in the DBLd arm. Of note, all injection-site reactions were Grade 1 or 2 and did not lead to dose modification or discontinuation of study treatment. The most frequently reported (≥ 2 patients) injection-site reactions in the DBLd arm were injection site erythema in ■ (■%) participants and injection site rash, erythema, and rash in ■ (■%) patients each.³²

Furthermore, the overall incidence of infections and infestations was slightly higher in the DBLd arm compared with the BLd arm (DBLd arm: 86.9%; BLd arm: 76.7%) and mainly occurred during induction (DBLd arm: ■%; BLd arm: ■%) and maintenance (DBLd arm: ■%; BLd arm: ■%). The most common infections ($\geq 10\%$ incidence in either treatment arm) were:³²

- COVID-19 (DBLd arm: ■%; BLd arm: ■%)
- Upper respiratory tract infection (DBLd arm: ■%; BLd arm: ■%)
- Bronchitis (DBLd arm: ■%; BLd arm: ■%)
- Pneumonia (DBLd arm: ■%; BLd arm: ■%)
- Nasopharyngitis (DBLd arm: ■%; BLd arm: ■%)

Lastly, a summary of the incidence of treatment-emergent cytopenia by treatment arm and treatment phase is provided in Table 46.

Any grade treatment-emergent cytopenia (comprising neutropenia, anemia, thrombocytopenia, and lymphopenia group terms) was reported in ■% of patients in the DBLd arm and ■% of participants in the BLd arm.³² Of note however, the overall incidence of cytopenia was higher in the DBLd arm compared with the BLd arm for the induction treatment phase (DBLd arm: ■% versus BLd arm: ■%), but was lower versus the BLd arm for consolidation and maintenance phases (consolidation: DBLd arm: ■% versus BLd arm: ■%; maintenance: DBLd arm: ■% versus BLd arm: ■%).³² Overall, these safety data support that DBLd-DL treatment was consistent with the known safety profiles of daratumumab, lenalidomide and BLd in isolation, with DBLd-DL treatment shown to be associated with clinically manageable side effects. Of particular note, no new safety signals were identified.³²

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Table 46: Treatment-emergent cytopenia by preferred term for induction, pre-ASCT, ASCT, consolidation and maintenance treatment phases; safety analysis set

TEAEs, n (%)	BLd arm ^a					DBLd arm ^b				
	Induction N=█	Pre-ASCT N=█	ASCT N=█	Consolidat ion N=█	Maintenan ce N=█	Induction N=█	Pre-ASCT N=█	ASCT N=█	Consolida tion N=█	Maintenan ce N=█
Total number of patients with treatment-emergent cytopenia	████	██	████	████	████	████	██	████	████	████
Neutropenia	████	██	████	████	████	████	██	████	████	████
Febrile neutropenia	██	██	████	█	██	██	██	████	██	██
Anaemia	████	██	████	████	████	████	██	████	████	████
Thrombocytopenia	████	██	████	████	████	████	██	████	████	████
Lymphopenia	██	█	█	████	████	████	█	█	████	████

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy

Abbreviations: BLd: bortezomib, lenalidomide, and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; TEAE: treatment-emergent adverse event.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TSFAE15A and TSFAE15B.³²

2.12 Ongoing studies

The latest DCO of the PERSEUS trial (1st August 2023), the principal evidence base for patients with NDMM who are eligible for HDT-ASCT, is presented in this submission; no further DCOs are expected to become available within the timeframe of this submission. No other studies in DBLd-DL in this indication are ongoing.

2.13 Interpretation of clinical effectiveness and safety evidence

In totality, the evidence demonstrates that the DBLd regimen has the potential to address a significant unmet need in the front-line MM transplant eligible patient population:

- A clear unmet need exists in this patient population for a thalidomide-sparing, induction and consolidation therapy that is associated with comparable efficacy and a more tolerable safety profile
- As demonstrated using data from the PERSEUS trial, and an ITC incorporating CASSIOPEIA induction and consolidation, patients who received DBLd were statistically significantly more likely to achieve $\geq$ VGPR compared to DBTd. DBLd was also associated with a numerical benefit over DBTd with respect to rates of overall response and MRD-negativity.
- Clinical Expert opinion indicates that DBLd will provide a more favourable safety profile than DBTd.
- In the UK, an unmet need remains for the introduction of more effective maintenance treatment regimens which can capitalise on the effectiveness of induction and consolidation treatment and provide patients with an extended first remission, with the ultimate aim of keeping myeloma under control for a sufficiently long period of time to allow patients to live out the remainder of their lives with their loved ones
- The AURIGA trial demonstrated that the addition of daratumumab to lenalidomide maintenance therapy resulted in deeper, more durable responses including MRD-negativity that translated to improved PFS and OS compared to lenalidomide maintenance alone. This benefit was associated with a manageable change in adverse events. Supportive evidence is also provided by the PERSEUS study.
- Given the prognostic utility of MRD-negativity in NDMM, DBLd followed by DL maintenance is therefore expected to result in long-term survival benefits for patients with NDMM eligible for HDT-ASCT. Despite challenges in compiling the evidence base, J&J consider that decision makers can feel confident that DBLd provides substantial long-term benefit versus UK standard of care. Results from PERSEUS (median follow-up of 47.5 months) and AURIGA (median follow-up of 32.3 months) trials show that the benefits of treatment persist over time as both PFS and OS curves continue to separate with longer follow-up. Furthermore, as detailed in the SPC, MRD can be used to guide treatment ensuring that patients receive daratumumab until they achieve a sustained response likely to result in favourable long term outcomes (Table 2, footnote)

Summary of unmet need

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As highlighted in Section 1.3.4, the recent introduction of DBTd induction and consolidation therapy to the treatment pathway has provided a step-change in efficacy for ASCT-eligible patients with NDMM.² However, while efficacious, thalidomide is associated with numerous severe toxicities including somnolence (i.e. drowsiness), constipation and neuropathy which have a substantial determinantal impact on patient HRQoL.²⁵

A clear unmet need therefore exists in this patient population for a similarly if not more effective, but thalidomide-sparing, induction and consolidation therapy that is associated with a more tolerable safety profile. This view was supported by feedback received from UK clinical experts at a May 2025 Advisory Board, where experts noted that the high levels of neurotoxicity associated with thalidomide are seen as a major issue across the medical community and that there is therefore an existing unmet need for novel thalidomide-sparing therapies that would prevent this.⁴

Additionally, given almost all patients respond to initial treatment for NDMM,^{32, 128} a key challenge in the NDMM treatment paradigm remains prolonging that response and the corresponding period of PFS for as long as possible (Section 1.3.4). The introduction of L maintenance therapy in 2021 represented a significant step forward, with the Myeloma XI trial demonstrating the clear benefits of providing maintenance therapy after initial induction and consolidation treatment.¹⁵⁰ However, as NDMM remains incurable, treatment aims remain focused on extending PFS in patients and therefore prolonging patient HRQoL for as long as possible. Feedback from UK clinical experts during a May 2025 Advisory Board highlighted that around 20–30% of patients experience toxicity issues associated with L maintenance and therefore need to pause treatment, putting them at risk of relapse.⁴ In line with this, █% of patients in the BLd arm of the PERSEUS trial (i.e., receiving L maintenance) discontinued lenalidomide due to any TEAE, whilst █% discontinued due to a lenalidomide-related TEAE.¹⁵¹ The experts added that the introduction of a lenalidomide-based induction and consolidation therapy would substantially reduce the burden of AEs for patients, whilst the addition of daratumumab to lenalidomide maintenance would maximise the effectiveness of maintenance therapy for the period of time in which patients can tolerate it.⁴ Therefore, an unmet need remains for the introduction of more effective maintenance treatment regimens which can capitalise on the effectiveness of induction and consolidation treatment and provide patients with an extended first remission, with the ultimate aim of keeping myeloma under control for a sufficiently long period of time to allow patients to live out the remainder of their lives with their loved ones.

Principal findings from the PERSEUS trial

Pivotal evidence for DBLd (followed by DL maintenance) in this submission is provided by the PERSEUS trial. PERSEUS is an ongoing, randomised, open-label, multicentre, Phase III trial examining the efficacy and safety of DBLd induction and consolidation followed by DL maintenance versus BLd induction and consolidation followed by L maintenance in patients with NDMM who are deemed HDT-ASCT eligible. Evidence in this submission is based on the latest 1st August 2023 DCO, with a median follow-up of █ months (DBLd arm) and █ months (BLd arm), respectively.³²

Patients in the DBLd arm were significantly more likely to experience a response to treatment versus the BLd arm. Responses in the DBLd arm were deeper, with patients █ to achieve an sCR and a ≥VGPR versus the BLd arm

Disease control was highlighted as the most important attribute for a MM treatment by patients in a 2019 Myeloma UK study, and deep and durable responses represent the first, crucial step towards this.⁸² In the PERSEUS trial, treatment in the DBLd arm was shown to result in greater clinical benefit across a range of response outcomes during the induction, consolidation and maintenance phases of treatment versus the BLd arm.³²

Specifically, patients receiving DBLd were more likely to respond to treatment compared to those receiving BLd – with the likelihood of response increasing over time through the post-induction (OR: ■■■, 95% CI: ■■■, ■■■); post-consolidation (OR: ■■■; 95% CI: ■■■, ■■■; and full treatment sequence phases (OR: ■■■; 95% CI: ■■■).

Notably, responses in the DBLd arm were deeper compared to those in the BLd arm across all phases of treatment. As early as post-induction, patients ■■■ to experience $\geq$ VGPR in the DBLd arm compared to BLd, and ■■■ in the likelihood of experiencing a $\geq$ CR, $\geq$ VGPR and an sCR were observed across both the post-consolidation and full treatment sequences. Across the full treatment sequences, patients in the DBLd arm were over three times as likely to achieve a $\geq$ CR to treatment (OR: 3.13; 95% CI: 2.11, 4.65) versus the BLd arm.³² These deep responses were sustained for a prolonged period of time, with the median DoR ■■■ at the time of the latest DCO.³² Improvements in depth and duration of response are important indicators of long-term survival, with substantial evidence indicating deep, sustained responses to therapy are strongly prognostic for improved survival outcomes.²³

Similarly, patients in the DBLd arm were statistically significantly more likely to achieve MRD-negativity both at post-consolidation and over the full treatment sequences. Across the full treatment sequences, patients in the DBLd arm were over three times more likely to achieve MRD-negativity (OR: 3.40, 95% CI: 2.47, 4.69) versus the BLd arm. These results are of particular importance - MRD-negativity represents the eradication of all detectable myeloma cells, and is therefore a powerful independent predictor of long-term survival outcomes.¹¹⁴

The increased rates of deeper responses and MRD-negativity in the DBLd arm of PERSEUS translated to a 58% reduction in the risk of disease progression or death versus the BLd arm over the full treatment sequences

The primary endpoint in the PERSEUS trial was PFS; as disease progression is associated with substantial reductions in patient HRQoL, prolonging the time patients are in a progression-free state is vital in ensuring patients maintain an improved quality of life for longer.¹²⁶ This view was supported by feedback received from UK clinical experts at a May 2025 Advisory Board in which it was highlighted that as there is currently no cure for MM, increasing the time patients are in a progression-free state is a key treatment aim in this patient population.⁴ Furthermore, results from the 2019 Myeloma UK study conducted in 97 patients, found that patients placed high value on 'longer remission/treatment-free periods', highlighting the importance of PFS as an outcome not only from a clinical perspective but for patients.⁸²

The PERSEUS trial demonstrated that the increased rates of response, and particularly, increased rates of $\geq$ CR and MRD-negativity, translated to statistically significant improvements in PFS for patients in the DBLd arm compared to the BLd arm. Of note, patients in the DBLd arm were associated with a statistically significant 58% reduced risk of disease progression or death compared with the BLd arm (HR: 0.42; 95% CI: 0.30, 0.59; $p < 0.001$).¹¹⁰

Median OS was [REDACTED] of PERSEUS. This is to be expected, given the effectiveness of both DBLd and BLd as treatment regimens, as well as the availability of multiple subsequent lines of treatment for patients with NDMM. As such, patients can live for an extended period following disease progression, and substantial additional follow-up would be required for mature OS data to be obtained. However, the early results of PERSEUS indicate a clear trend towards improved OS for the DBLd arm, with a 27% reduced risk of death compared to the BLd arm (HR: 0.73, 95% CI: [REDACTED], [REDACTED]). With the strong prognostic links between improved response rates and prolonged progression-free survival with long-term survival benefits, it is expected that the magnitude of OS benefit will increase with additional follow-up in the PERSEUS trial.

Alongside substantial efficacy improvements, the addition of daratumumab to BLd induction and consolidation and L maintenance therapy was well-tolerated, with similar HRQoL and safety profiles observed across the two treatment arms

[REDACTED] were observed between the DBLd and BLd treatment arms across a range of PRO measures, including the EORTC QLQ-C30, the EORTC QLQ-MY20 (a MM-specific PRO measure consisting of four domains including disease symptoms and the side effects of treatment), and EQ-5D-5L measures. These results indicate that quadruplet therapy with DBLd followed by DL maintenance is not associated with any major detriment to patient HRQoL compared to triplet therapy with BLd followed by L maintenance.³²

PERSEUS also demonstrated that DBLd followed by DL maintenance and BLd followed by L maintenance are associated with comparable safety profiles. At the latest DCO, the incidence of TEAEs were comparable between the BLd and DBLd treatment arms at each treatment phase ([REDACTED]% versus [REDACTED]% for the induction phase, [REDACTED]% versus [REDACTED]% for the pre-ASCT phase, [REDACTED]% versus [REDACTED]% for the ASCT phase, and [REDACTED]% versus [REDACTED]% for the consolidation phase).^{32, 110} Of note however, fewer patients discontinued treatment due to TEAEs in the DBLd arm ([REDACTED]%) compared to the BLd arm ([REDACTED]%).^{32, 110} These data provide evidence to support that the addition of daratumumab to BLd induction and consolidation and L maintenance therapy is not associated with a decreased tolerability profile. This was supported by feedback received from UK clinical experts at a 2025 UK Advisory Board, who noted that daratumumab is overall a very tolerable treatment.⁴

Comparative efficacy evidence between DBLd and DBTd for induction and consolidation

As described in Section 1.3.5, DBTd (followed by L maintenance) represents the only relevant comparator to DBLd (followed by DL maintenance) in UK clinical practice for HDT-ASCT eligible patients with NDMM. This was confirmed by UK clinical experts during a recent Advisory Board.

The PERSEUS trial did not include DBTd (followed by L maintenance), meaning that ITCs were required to generate comparative efficacy estimates that are relevant to UK clinical practice. However, no data for the full comparator treatment sequence were available. As such, ITCs were conducted comparing DBLd versus DBTd induction and consolidation therapy across $\geq$ VGPR, ORR, MRD-negativity, PFS and OS

The CASSIOPEIA trial was considered to represent the most robust source of evidence for the comparator induction and consolidation treatment regimen. As the Company was also the sponsor of the CASSIOPEIA trial, IPD was available from both PERSEUS and CASSIOPEIA, allowing the use of robust IPTW-based ITC approaches. Full details of the ITC methodology can be found in Section 2.10.4.

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During the induction and consolidation phase, DBLd demonstrated deeper responses than DBTd, with DBLd [REDACTED] to elicit a ≥VGPR or better versus DBTd

Induction and consolidation ITCs between PERSEUS and CASSIOPEIA showed that patients who received DBLd were [REDACTED] to achieve ≥VGPR (OR: [REDACTED], 95% CI: [REDACTED], [REDACTED]) compared to DBTd. DBLd was also associated with a benefit over DBLd for rates of overall response and MRD-negativity.

To derive an estimate of the treatment effect for DBLd induction and consolidation therapy alone, to inform the induction and consolidation ITCs, patient outcomes were censored at the initiation of maintenance treatment for time-to-event outcomes. Median follow-up in the DBLd arm (9.7 months) was therefore restricted to the length of induction and consolidation treatment, representing an inherent limitation of the induction and consolidation ITCs which cannot be resolved with further follow-up. As such, outcomes for the PFS and OS ITCs do not represent a true reflection of the comparative treatment effects for DBLd versus DBTd.

An extensive body of evidence highlighting the prognostic implications of deep responses to treatment and to long-term OS (Section 1.3.2).^{53, 23, 54, 55, 116, 117} The response benefit associated with DBLd is therefore expected to result in a long-term OS benefit when compared with DBTd. Aligned to guidance provided in the NICE report of surrogate endpoints in HTA, the biological plausibility of using depth of response as a predictor of long-term survival outcomes was confirmed by feedback received from UK clinical experts during a May 2025 Advisory Board, as well as a wealth of Level 1 evidence (the highest possible strength of evidence).^{4, 59}

Taken together, the induction and consolidation ITCs demonstrated a clear response benefit associated with DBLd when compared with DBTd, which is inevitably expected to translate to a long-term OS benefit for DBLd over DBTd.

Comparative efficacy of DL and L maintenance therapy

DBTd-L represents the current standard of care for HDT-ASCT eligible patients with NDMM and, as such, is the only relevant comparator to DBLd-DL in this submission (Section 1.1). As noted above, CASSIOPEIA represents the best source of evidence for DBTd induction and consolidation therapy and, as such, was used to inform the ITCs comparing DBLd and DBTd as induction and consolidation therapies (Section 2.10). However, at the time of submission, no trials investigating the full comparator treatment sequence of DBTd-L were available. The Phase III AURIGA trial was considered as the best available source of evidence for the comparative efficacy of DL versus L maintenance and inform long-term survival estimates in the economic analysis (see Section 3.3 for further details).

The AURIGA trial demonstrated that the addition of daratumumab to lenalidomide maintenance therapy resulted in deeper, more durable responses that translated to improved PFS and OS

The AURIGA trial is an ongoing, randomised, open-label Phase III trial in patients with NDMM who had received prior induction therapy and HDT-ASCT. At the latest DCO (4th May 2024), the addition of daratumumab to lenalidomide maintenance therapy resulted in deeper, more durable responses, with an overall MRD-negativity conversion rate two times higher in the DL versus L arm, and rates of sustained MRD-negativity three times higher.³¹

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As detailed in Section 1.3.2, obtaining a deep, durable response, in particular MRD-negativity, is a biological plausible surrogate for improved long-term survival outcomes. Indeed, the greater rates of MRD-negativity, including sustained MRD-negativity, in the DL arm when compared with the L maintenance arm, clearly translated to an improvement in PFS and OS. The addition of daratumumab to L maintenance resulted in a statistically significant, 47% reduction in the risk of progression or death (HR: 0.53; 95% CI: 0.29, 0.97; $p=0.0361$), and a 50% reduction in the risk of death (HR: 0.50; 95% CI: 0.17, 1.50; $p=0.2081$).³¹ The introduction of DL maintenance treatment to clinical practice is therefore anticipated to lead to substantially improved long-term outcomes for NDMM patients in the UK.

Generalisability of the AURIGA trial to the population of relevance to this submission

It is noted that the AURIGA trial population differs in some respects to that of the PERSEUS trial, and the indication of relevance to this submission. In particular, patients receiving DL maintenance in the PERSEUS trial had received prior daratumumab therapy (i.e., anti-CD38-experienced) during induction/consolidation, whilst those in the AURIGA trial were anti-CD38-naïve and were MRD-positive at the end of consolidation.³¹

Nevertheless, it is expected that the treatment effect observed in the AURIGA trial is at least maintained for DL versus L in a broader population of patients receiving daratumumab as part of induction and consolidation therapy. For example, in the CASSIOPEIA trial there was no difference in outcomes for patients who received daratumumab as maintenance treatment after prior daratumumab induction and consolidation when compared with those who were not daratumumab-experienced.¹²⁸ These findings indicate that, although patients enrolled into AURIGA were anti-CD38-naïve, the comparative efficacy estimates for DL versus L maintenance are likely to be maintained in clinical practice following DBLd induction and consolidation.

AURIGA shows clear clinical benefit of DL maintenance in an MRD-positive post-consolidation cohort, a benefit that is likely to be at least maintained in a broader NHS population that includes MRD-negative patients. This is supported by a comparison of the DL vs L treatment effect observed in AURIGA for the non-sustained MRD-negative subgroup (for both PFS (HR: ■■■, 95% CI: ■■■■■) and OS (HR: ■■■, 95% CI: ■■■■■)) relative to the ITT population including both sustained and non-sustained responders (PFS HR: 0.53, 95% CI: 0.29 – 0.97) and OS (HR: ■■■, 95% CI: ■■■■■)). This shows a diminished treatment effect for non responders for both PFS and OS and provides indirect evidence that the treatment effect of DL versus L is likely to be stronger in patients that respond well to treatment, including those that are MRD negative post consolidation. Of note, non-sustained responders in AURIGA represented 83% and 95% of the DL and L populations respectively signalling the strength of the treatment effect observed for the sustained MRD-negative subgroup.

Strengths and limitations of the evidence base

PERSEUS was carried out in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP), alongside applicable regulatory and country-specific requirements. Measures to ensure data accuracy and reliability included selecting qualified investigators and suitable study sites, reviewing protocol procedures with investigators and study-site staff prior to the study, conducting periodic monitoring visits by the sponsor, and, where applicable, directly transmitting clinical laboratory data from a central laboratory into the sponsor's database.

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As such, the PERSEUS trial represents a robust source of evidence for DBLd (followed by DL maintenance), and was considered to be at low risk of bias based on the Cochrane RoB 2.0 Quality Assessment tool 2.0, recommended by NICE (Section 2.5).¹²⁵ Furthermore, UK clinical experts confirmed that the patient population in PERSEUS is generalisable ASCT-eligible NDMM patients in UK clinical practice.

As the comparator in PERSEUS, BLd, is not relevant to UK clinical practice, there was no trial evidence to inform the efficacy of DBTd followed by lenalidomide maintenance. As such, J&J has considered the efficacy of the induction & consolidation and maintenance treatment phases separately. First, it was necessary to conduct ITCs to derive comparative efficacy evidence between DBLd and DBTd for induction & consolidation. While this is a limitation, a thorough and robust approach to the ITC was taken by the Company, as evidenced by the following:

- The Company were the sponsor of both the PERSEUS and CASSIOPEIA trials, allowing a robust approach to the trial-versus-trial ITC using IPTW weighting. Following adjustment, the two patient populations were well-matched, and alternative adjustments suggested that the base case analysis may be conservative
- The results of the ITC were consistent across an extensive range of sensitivity and scenario analyses exploring alternative matching approaches and covariates that were adjusted for, demonstrating the robustness of the base case results
- In light of the aforementioned points, HTA experts consulted by the Company reinforced that the ITC analyses presented were methodologically robust and appropriate for comparing DBLd and DBTd

Second, in the absence of re-randomisation in PERSEUS following induction & consolidation, J&J has leveraged the Phase III AURIGA study to inform the treatment effect of DL versus L maintenance alone. Whilst results from AURIGA are not fully generalisable to the decision problem due to differences in the population (excluded MRD-negative patients) and prior daratumumab exposure, evidence from the AURIGA and CASSIOPEIA studies indicate that the treatment effect of DL versus L is expected to at least be maintained in a broader population of patients receiving a daratumumab based induction and consolidation regimen and patients achieving MRD-negativity following induction, HDT-ASCT and consolidation.

Whilst immature survival data for the full treatment sequence (DBLd-DL) may introduce uncertainty, there is an extensive body of evidence published for patients with MM that highlights the prognostic links between deep, sustained treatment responses and subsequent long-term survival benefits.^{51, 53} The use of these surrogate endpoints in lieu of mature OS data should therefore not be considered to represent a major source of uncertainty in this submission and is in line with the accepted approach used in prior appraisals in this indication.²

Overall summary

Overall, the introduction of DBLd (followed by DL maintenance) into the UK clinical pathway for NDMM would fulfil a substantial unmet need for a novel, effective, well-tolerated induction and consolidation treatment option for patients with HDT-ASCT-eligible NDMM, who currently experience substantial AEs as well as the existing unmet need for more effective maintenance treatment regimens in current UK clinical practice.

In the induction and consolidation phase, DBLd would replace DBTd as an at least equally efficacious treatment, which frees patients and clinicians from the burdens associated with

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thalidomide-related toxicities. Induction and consolidation ITCs demonstrate that DBLd is at least as effective as DBTd in the induction and consolidation phase, with a greater potential to elicit a VGPR or better when compared to DBTd.

The key benefit associated with the full treatment sequence of DBLd followed by DL maintenance is the addition of daratumumab maintenance therapy. Currently, in UK clinical practice, patients only receive maintenance therapy with lenalidomide following a response to induction and consolidation treatment. Results of the PERSEUS and AURIGA trials highlight that addition of daratumumab to lenalidomide maintenance results in significant benefits in terms of response, particularly MRD-negativity conversion and sustained MRD-negativity rates. The stopping rule for daratumumab per the PERSEUS protocol means DL represents a more personalised maintenance strategy, allowing for optimisation of drug exposure in order to minimise the treatment burden for patients in remission.

Whilst OS data remain immature, the strong prognostic links associated with improved response rates and MRD-negativity, including sustained MRD-negativity, mean that DBLd followed by DL maintenance is also likely to result in long-term survival benefits for patients with NDMM eligible for HDT-ASCT.^{23, 116, 117} Finally, it is important to highlight that feedback received from UK clinical experts at a May 2025 Advisory Board indicated that the introduction of daratumumab to lenalidomide maintenance therapy in UK clinical practice would result in patients achieving a deeper response versus lenalidomide maintenance therapy alone, thereby reducing the chance of patients losing their response if they have to pause lenalidomide maintenance treatment due to toxicities.⁴ It was reiterated that the current proportion of patients having to pause L maintenance therapy due to toxicities is high (20–30%) of patients.

It is therefore evident that the introduction of DBLd followed by DL maintenance therapy would represent another clear step forward in the UK treatment paradigm for patients with NDMM eligible for HDT-ASCT, giving patients the best chance possible at achieving a deep and sustained response and extended first remission. This would, ultimately, keep a patient's myeloma under control long enough to allow them to live out the remainder of their lives with their loved ones, and even offers the potential for a functional cure.

3 Cost-effectiveness analysis

Summary of cost-effectiveness model

- A cost-utility model was developed to estimate the cost-effectiveness of daratumumab, bortezomib, lenalidomide with dexamethasone followed by daratumumab with lenalidomide maintenance therapy (DBLd-DL) versus daratumumab, bortezomib, thalidomide and dexamethasone followed by lenalidomide maintenance (DBTd-L) as a treatment for adult patients with newly diagnosed multiple myeloma (NDMM) who are eligible for high-dose therapy (HDT) and autologous stem cell therapy (ASCT).
 - The analysis was conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS).
- Similar to previous NICE evaluations of multiple myeloma (MM) therapies, the model was a partitioned survival model (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 patients in the DBLd arm of the PERSEUS trial (intent-to-treat [ITT] analysis set).

Survival inputs

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- During the **induction and consolidation phases**, DBLd and DBTd were assumed to have equivalent treatment efficacy, a conservative estimate of the comparative efficacy of these treatments given the deeper responses observed for DBLd
- No trials reporting data for the **full treatment sequence** of the relevant comparator (DBTd-L) were identified in the clinical systematic literature review (SLR). As detailed in Section 2.2 above, whilst it is difficult to isolate the treatment effect of DL versus L maintenance therapy in PERSEUS, AURIGA is a phase III, head-to-head randomised controlled trial (RCT) which compares DL versus L maintenance therapies. Therefore, AURIGA represented the best available evidence to inform the maintenance treatment efficacy in the economic model.
- AURIGA compared the efficacy of DL and L in MRD+ patients who had achieved a very good partial response or better ($\geq$ VGPR) after induction therapy and ASCT
 - To derive proxy efficacy outcomes for DBTd-L, relative treatment effects for L versus DL were applied to adjust the PFS and OS extrapolations for patients receiving DBLd-DL in the PERSEUS trial from the onset of maintenance therapy

Base case extrapolations: OS, PFS and TTD

Overall survival (OS) and progression-free survival (PFS)

- Seven standard parametric distributions were fitted to Kaplan-Meier data (exponential, Weibull, loglogistic, lognormal, Gompertz, Gamma and Generalised Gamma)
- The choice of base case extrapolations were based upon statistical fit, long-term clinical plausibility and assessment of internal validity including assessment of hazard function plots. Graphical assessment of fit was not feasible given the immaturity of PERSEUS trial data
 - Generalised Gamma was selected in the base case for PFS, and the exponential curve for OS, broadly aligning with clinician estimates for both DBLd-DL and DBTd-L

Time-to-discontinuation (TTD)

- During the induction and consolidation phase, treatment duration for DBLd and DBTd were modelled using observed TTD data from the PERSEUS and CASSIOPEIA trials, respectively
- In line with the license for daratumumab, daratumumab maintenance treatment is to be administered until disease progression.¹ It can, however, be discontinued for patients who have achieved MRD-negativity that is sustained for 12 months, if they have been treated on maintenance for at least 24 months. TTD for DL maintenance was modelled separately for the following populations to reflect the stopping criteria for daratumumab:
 - Patients who, after a minimum of two years of maintenance therapy, **discontinued daratumumab** after achieving sustained MRD-negativity for at least 12 months
 - Due to the maturity of data, observed Kaplan-Meier TTD were applied
 - Patients who **discontinued daratumumab** but did not achieve sustained MRD-negativity at the latest DCO
 - Based on assessment of internal validity, statistical fit and long-term clinical plausibility, the exponential extrapolation was applied to PERSEUS TTD data in the base case
 - Patients who discontinued lenalidomide:
 - Based on assessment of internal validity, statistical fit and long-term clinical plausibility, the exponential extrapolation was applied to PERSEUS TTD data in the base case
- Treatment duration for L maintenance therapy following DBTd induction and consolidation therapy was derived by fitting extrapolations to the TTD data for patients in the PERSEUS trial who received bortezomib, lenalidomide and dexamethasone followed by L maintenance (BLd-L). This is a simplifying assumption which assumes that the addition of daratumumab to induction and consolidation therapies would not influence the treatment duration of L maintenance therapy.
 - Based on assessment of internal validity, statistical fit and long-term clinical plausibility, the exponential extrapolation was applied in the base case

- Scenario analyses were explored using alternative approaches for modelling survival:
 - Extrapolation of pooled DBLd-DL data from the PERSEUS and GRIFFIN trials
 - The GRIFFIN trial is an ongoing randomised, open-label, multicentre, Phase II trial in transplant-eligible patients with NDMM, which was identified in the I+C+M clinical SLR (as described in Section 2.2). However, given that PERSEUS was the registrational trial which led to the extension label for daratumumab to DBLd in HDT-ASCT eligible patients with NDMM, PERSEUS was considered the most appropriate clinical evidence source informing the efficacy data for DBLd-DL in the ongoing submission.

Model inputs

- Adverse events (AEs) during induction and consolidation were modelled based on the PERSEUS and CASSIOPEIA trials for DBLd-DL and DBTd-L, respectively. AEs during maintenance for DL and L were based on the AURIGA trial.
- In the base case economic analysis, utility data were derived from the PERSEUS trial
 - EQ-5D-3L utilities were derived for the PF health state (induction, ASCT and consolidation phases) and PD health state
- Cost inputs used in the model (drug acquisition and administration, ASCT, AEs, monitoring costs, concomitant medication and end-of-life cost) are aligned with the accepted inputs used in previous evaluations in NDMM^{2, 152}

Summary of cost-comparison and cost-effectiveness results

- For induction and consolidation, a cost-comparison analysis was conducted based on the ITC results presented in Section 2.11 that show DBLd efficacy is (conservatively) expected to be at least comparable to DBTd. Results from the cost-comparison show DBLd is expected to reduce the economic burden to the NHS through reduced drug acquisition and AE management costs, delivering a cost saving of [REDACTED].
- Overall, the base case incremental cost-effectiveness ratio demonstrated that DBLd-DL is a cost-effective use of NHS resource at a willingness-to-pay (WTP) threshold of £30,000 per quality-adjusted life year (QALY). DBLd-DL was also associated with a positive incremental net health benefit (INHB) versus DBTd-L
- 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 [REDACTED]
- Additionally, in all base case analyses, DBLd-DL was associated with positive incremental life years gained (LYGs; [REDACTED]) and QALYs ([REDACTED]) versus DBTd-L. These results highlight the improvement in both quality and length of life that DBLd-DL may offer patients mainly driven by improved PFS, keeping patients from relapsing and requiring subsequent treatment cycles.
- Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) demonstrated that the base case cost-effectiveness results were robust to an extensive number of sensitivity analyses.
- The parameters with the greatest impact on the ICER were OS and PFS extrapolations for DBTd-L, and PFS for DBLd-DL impacting efficacy.
- Scenario analyses conducted to address sources of uncertainty in the model demonstrated that, whilst there was variation in the INHB, cost-effectiveness conclusions remained unchanged with DBLd-DL remaining dominant versus DBTd-L at a WTP threshold of £30,000 per QALY
- Overall, these results demonstrate that DBLd-DL could address a significant unmet need for an effective and well-tolerated treatment option which induces deep and durable responses, translating to an anticipated increase in PFS and OS and providing patients with the prospect of functional cure. This benefit is achieved whilst representing a cost-effective use of NHS

resources

- These economic results omit important benefits that cannot be captured in the QALY, meaning the base case results likely represent a conservative estimate of the true cost-effectiveness of DBLd-DL in UK clinical practice. These benefits include:
 - Improved long-term survival benefits anticipated with DBLd-DL compared to DBTd-L, not captured due to simplified model assumption of equivalent efficacy of induction and consolidation therapies
 - Improved HRQoL associated with a thalidomide-free treatment option
 - The value of hope associated with the prospect of achieving deeper, more durable responses and functional cure
 - Value of personalised treatment regimens enabling de-escalation of maintenance treatment whilst maintaining a progression-free period

3.1 Published cost-effectiveness studies

SLRs were conducted to identify the cost-effectiveness (economic evaluations), health-state utility values (HSUVs), and cost/resource use evidence associated with treatment options for HDT-ASCT eligible patients with NDMM. The SLR to identify economic evaluations and cost/resource use was conducted in parallel (referred to hereafter as the economic SLR), with full details presented in Appendix E and G respectively. Details on the HRQoL SLR to identify evidence relating to HRQoL, PRO and HSUVs are presented in Appendix F.

The economic SLR was originally conducted on 19th September 2023 and updated on 8th May 2025. Across the searches, a total of 43 publications met the inclusion criteria of the economic SLR. Among the included studies, all of which reported data on HDT-ASCT eligible patients with NDMM, 17 were economic evaluations including five published cost utility analyses (CUAs) and eight HTA submissions. No studies reported data on patients who received DBLd induction and consolidation followed by DL maintenance, or DBTd followed by L maintenance. As such, none of these studies were considered relevant for the purpose of this submission as they did not contain an economic evaluation comparing DBLd-DL with DBTd-L from a UK perspective. Full details of the SLR methodology used to identify the economic evaluations relevant to this submission, is provided in Appendix E.

3.2 Economic analysis

As outlined above, no relevant economic evaluations comparing DBTd-DL to DBTd-L from a UK perspective were identified in the SLR. As such, a *de novo* cost-utility analysis has been conducted for the purpose of this evaluation and is described below. The economic analysis was developed in accordance with 'Modeling Good Research Practices' disseminated by the International Society of Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making (ISPOR-SMDM).¹⁵³

The aim of this economic analysis was to determine the cost-effectiveness of DBLd-DL versus DBTd-L as a treatment for adult patients with NDMM who are eligible for HDT-ASCT. The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS), taking into account direct costs and health benefits only.

The economic evaluation was conducted in line with the NICE reference case:

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- Health outcomes were measured both in terms of life years gained (LYG) and quality-adjusted life years (QALYs) gained
- The primary outcome measure for the economic evaluation was the incremental cost-effectiveness ratio (ICER; cost per QALY gained) for the comparison of DBLd-DL versus DBTd-L
- Clinical effectiveness for DBLd-DL and DBTd-L was measured through OS and PFS (see Section 3.3)
- All relevant costs were considered including drug acquisition costs, administration costs, ASCT costs, monitoring costs, AE costs, costs associated with concomitant and subsequent medicines, resource use and end-of-life costs (see Section 3.5)
- The model used a lifetime horizon (equivalent to 40 years). This was considered to be a sufficient length of time to capture all important differences in costs or outcomes between the technologies being compared, given that the mean age of patients within the PERSEUS trial was ■■■ years at DBLd-DL treatment initiation³²
- The discount rate is set to 3.5% for both costs and health benefits

3.2.1 *Patient population*

The patient population for the economic evaluation was adult patients with NDMM who are eligible for HDT-ASCT (Section 1.1). This population is in line with the decision problem for this submission, the marketing authorisation for DBLd in the UK and the patient population of the PERSEUS trial (Section 2.3).^{32, 154}

The characteristics of patients entering the model were based on the baseline characteristics of patients in the DBLd arm of the ITT analysis set in the PERSEUS trial. UK clinical experts consulted as part of a 2025 UK advisory board validated that the PERSEUS trial population, and therefore the patient population utilised in the economic analysis, is broadly generalisable to patients with NDMM in UK clinical practice.⁴ As presented in Section 2.3.1, the mean age of patients in the DBLd arm in the PERSEUS trial aligns with that of the NCRAS dataset (■■■ vs. ■■■ respectively), further supporting the generalisability of the PERSEUS DBLd ITT population to UK clinical practice. Moreover, when compared to the NICE appraisal for DBTd (TA763) wherein the mean age of patients was 56.6 years, the PERSEUS trial population age informing the current economic analysis was considered more comparable to UK clinical practice than TA763.²

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

A summary of the relevant patient baseline characteristics used in the model are presented in Table 47.

Table 47: Summary of baseline characteristics used in the economic analysis

Characteristics	Value	Source
Mean age, years	■	PERSEUS trial, ITT analysis set (DBLd-DL arm) ³²
Proportion of female patients, %	■	PERSEUS trial, ITT analysis set (DBLd-DL arm) ³²
Mean body weight, kg	■	PERSEUS trial, ITT analysis set (DBLd-DL arm) ³²
Mean BSA, m ²	■	PERSEUS trial, ITT analysis set (DBLd-DL arm) ³²

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab with lenalidomide BSA: body surface area; ITT: intention-to-treat.

3.2.2 Model structure

The economic analysis used a partitioned survival model (PSM) approach with three mutually exclusive health states:

- Progression-free (PF)
- Progressed disease (PD)
- Death

The occupancy of health states over time was derived from extrapolation of data from the PERSEUS trial for DBLd-DL, and application of relative treatment effect estimates from the AURIGA trial to derive outcomes for DBTd-L (as detailed in Section 3.3.1). The proportion of patients occupying each health state was calculated using the PFS and OS survival extrapolations, as described below and shown in Figure 21:

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

To maintain the logical consistency of the patient flow within the economic analysis, the following adjustments were applied:

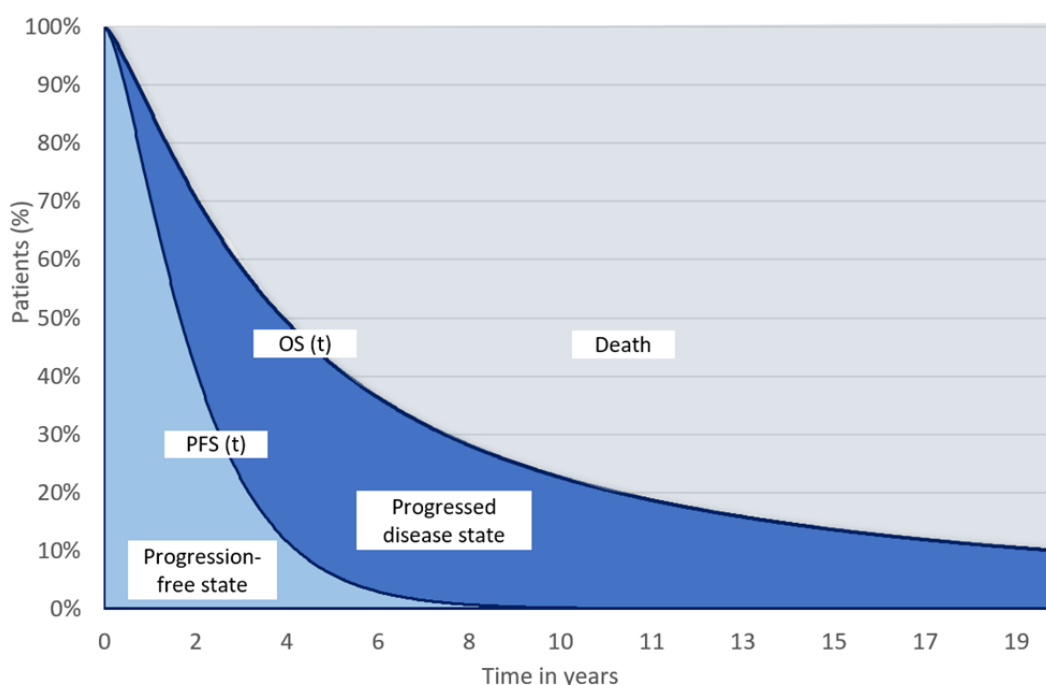
- The mortality risk at each model cycle was bound by age-matched general population predictions, sourced from the latest available Office for National Statistics (ONS) Life Tables¹⁵⁵
- A limit was built into the model to ensure that PFS could not exceed OS. The limit was applied to the per-cycle hazard of progression or death, and hazard of death. As such, if the hazard of death exceeds that of progression or death, the maximum hazard was assumed

Patients may have discontinued DBLd-DL or DBTd-L for reasons other than disease progression. As such, time to treatment discontinuation (TTD) was used to determine the time on treatment (ToT). This allowed for the application of specific health state costs, such as treatment

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acquisition, treatment administration and monitoring, to be applied only while patients are on or off treatment, while also allowing patients to occupy the PF and PD health state costs, regardless of whether they are on treatment.

Figure 21: Structure of PSM



Abbreviations: PFS: progression-free survival; OS: overall survival.

Given the 28-day treatment cycles of DBLd-DL and DBTd-L, the model used a 28-day cycle length (see Section 3.2.3). This was in line with approach used in TA763. A half cycle correction was applied in line with modelling best practices, to avoid systemic over- or under-estimation of costs and outcomes.¹⁵⁶

Justification for model structure

A PSM was deemed the most appropriate structure to inform the cost-effectiveness of DBLd induction and consolidation with DL maintenance as the modelled health states are considered to accurately reflect the natural disease course for patients with HDT-ASCT NDMM. The key outcomes in this setting, PFS and OS, are time-to-event outcomes, and the PSM approach allows for the observed data from the PERSEUS trial to be directly and intuitively replicated within the economic model. This means the model is expected to accurately reflect disease progression and the observed survival profile of patients treated with DBLd-DL or DBTd-L.

The PSM was also considered appropriate because, given the similarity between the treatment arms in terms of the treatment pathway following disease progression, there is limited advantage in being able to model the subsequent lines of therapy as individual health states. By directly modelling study-observed events, the PSM approach is also likely to provide estimates of survival that closely match the observed survival from the original studies. Additionally, uncertainty in long-term survival can also be explored via the use of alternative distributions to extrapolate survival (see Section 3.11).

Finally, as MM is a chronic, incurable disease, there is no requirement for functionality to move backwards between the health states, supporting the use of a PSM for the cost-effectiveness analysis. The choice of model structure is aligned with extensive precedent for the use and acceptance of PSMs in previous NICE appraisals in the MM setting, including the appraisal for DBTd.^{2, 157-164}

Table 48: Features of the economic analysis

Factor	Previous evaluation	Current evaluation	
	TA763	Chosen values	Justification
Model structure	Response-based PSM, with survival outcomes stratified based on post-consolidation MRD-negativity status	Standard PSM	A PSM accurately reflects disease progression and the observed survival profile of HDT-ASCT eligible patients with NDMM, and is in line with precedent in previous NICE evaluations in MM ¹⁵⁷⁻¹⁶⁴
Time horizon	Lifetime (40 years)	Lifetime (40 years)	A time horizon of 40 years was deemed sufficient to cover the remaining lifetime of patients in the model, based on a patient starting age of [REDACTED] years, and is therefore considered sufficient to capture any differences in costs or outcomes between the technologies being compared. This approach is consistent with the NICE reference case
Cycle length	28 days	28 days	To align with the 28-day treatment cycles for DBLd-DL and DBTd-L
Half cycle correction	Applied	Applied	Half cycle correction was included in the economic model. To reduce systemic over/underestimation of costs and other outcomes, in line with the recommended best practice ¹⁵⁶
Treatment waning effect?	None OS and PFS (post-landmark) are modelled to be dependent on post-consolidation response and, for DBTd, survival inputs are based on the application of HRs (OS and PFS) to the BTd arm. In the model, the long-term effect of treatment was therefore modelled in terms of differences in post-consolidation response and via the application of HRs to the BTd arm.	None	No treatment waning effect was applied in the model. The assumption of no waning effect was in line with the GRIFFIN trial findings wherein clinical benefit was demonstrated to persist with no treatment waning effect observed after stopping daratumumab therapy, following a fixed maintenance treatment duration of 24 months. PERSEUS and AURIGA provide supportive evidence of a persistent treatment benefit. ¹³⁷

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Factor	Previous evaluation	Current evaluation	
	TA763	Chosen values	Justification
	In the base case analysis, the same HRs were applied for the entire duration of the remaining time in the model		As well as not being included in TA763, treatment waning was not considered in the previous NICE appraisals of daratumumab at later lines of therapy (TA573 and TA510).
Source of utilities	EQ-5D-5L data from CASSIOPEIA were used to derive utility values for the PF health state (including separate values for induction therapy, post-induction to post-consolidation response, and PF post-consolidation). The utility value used in TA311 for the '2nd line and 3rd line' health states from van Agthoven et al. (2004) were used for the PD health state • PF induction therapy=0.57 • PF post-induction to post-consolidation response=0.68 • PF post-consolidation=0.73 • PD=0.69	The utility values were derived from a univariate linear regression analysis of EQ-5D-5L data from the PERSEUS trial, which were then cross-walked to EQ-5D-3L based on Hernandez-Alava et al. (2017) dataset: • PF (induction therapy): [REDACTED] • PF (transplantation): [REDACTED] • PF (consolidation therapy): [REDACTED] • PF (maintenance): [REDACTED] • PD (second-, third- and fourth-line treatment): [REDACTED]	For consistency with the patient population and source of efficacy inputs used in the model, utility values derived from the PERSEUS EQ-5D-5L data, cross-walked to EQ-5D-3L, were preferred in the base case analysis.
Source of costs	NHS reference costs and the British National Formulary (BNF) Costs included: • Drug acquisition and administration for 1st line and subsequent therapies • Concomitant medications (e.g. prophylaxis) • ASCT costs • Monitoring costs • Management of adverse events (grade 3 and above, with incidence $\geq 5\%$, plus any grade nausea and upper respiratory tract infections) • End-of-life cost	NHS reference costs, BNF, electronic market information tool (eMIT), Personal Social Services Research Unit (PSSRU) Costs included: • Drug acquisition and administration for 1st line and subsequent therapies • ASCT costs • Concomitant medications (e.g. prophylaxis) • Monitoring costs	Cost assumptions used in the model (administration costs, incidence of adverse events, monitoring costs, end-of-life cost) have been based on previous appraisals in MM, including previous daratumumab appraisals (TA763, TA573 and TA510). The cost of MRD testing using flow cytometry was estimated based on details from the NICE clonoSEQ technology briefing (2021).¹⁶⁵

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Factor	Previous evaluation	Current evaluation	
	TA763	Chosen values	Justification
		• Terminal care costs • Management of AEs • MRD testing costs	

Abbreviations: AE: adverse event; ASCT: autologous stem-cell transplant; British National Formulary; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, dexamethasone; DL: daratumumab with lenalidomide; eMIT: electronic market information tool; HR: hazard ratio; L: lenalidomide; MRD: minimal residual disease; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PSSRU: Personal Social Services Research Unit; TA: technology appraisal.

3.2.3 *Intervention technology and comparators*

Intervention: DBLd-DL

The intervention included in the economic analysis was DBLd as an induction therapy prior to ASCT, a consolidation therapy post-ASCT, and DL as maintenance therapy. The treatment protocols included in the model for induction therapy, ASCT, consolidation and maintenance therapy in the DBLd-DL arm are consistent with the PERSEUS trial (refer to Table 68 in Section 3.5.1 for full details), and the SmPC-recommended posology for daratumumab:^{1, 110}

- Four 28-day cycles of DBLd as induction therapy
- High-dose chemotherapy and ASCT
- Two 28-day cycles of DBLd as consolidation therapy
- 28-day cycle of DL as maintenance therapy (see Section 3.3.1.6 for details of the stopping rule applied for daratumumab during maintenance therapy)

Timely access to ASCT was not possible for some patients in the PERSEUS trial due to COVID-19.³² Patients who could not receive a transplant as scheduled received an additional 2 cycles of induction therapy.³² Patients who received the additional induction therapy then did not receive consolidation. Therefore, the duration of induction and consolidation for all patients in PERSEUS was similar, and aligned with the duration in the CASSIOPEIA trial.^{32, 75}

Comparator: DBTd-L

The comparator included in the economic analysis was DBTd as an induction therapy prior to ASCT, a consolidation therapy post-ASCT, and L as maintenance therapy. The treatment protocols included in the model for induction therapy, ASCT, consolidation and maintenance therapy for DBTd-L are consistent with the CASSIOPEIA trial (for induction, ASCT and consolidation therapies only, given that patients did not receive L maintenance therapy in CASSIOPEIA; refer to Table 68 in Section 3.5.1 for full details), and the SmPC-recommended posology for daratumumab for induction and consolidation therapy and lenalidomide for maintenance therapy:^{1, 128, 166}

- Four 28-day cycles of DBTd as induction therapy
- High-dose chemotherapy and ASCT
- Two 28-day cycles of DBTd as consolidation therapy
- 28-day cycles of L as maintenance therapy

Similarly, the treatment protocols in the model for maintenance therapy are consistent with the AURIGA trial.

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 28-day model cycle was determined for DBLd-DL and DBTd-L from cumulative survival probabilities from PFS and OS extrapolations, while separate TTD extrapolations were used to determine the proportion of patients in the model who remained on treatment. Efficacy data for DBLd induction and consolidation followed by DL maintenance were derived from the latest DCO of the PERSEUS trial (1st August 2023; trial methodology and results presented in Section 2.6). Due to the immaturity of PERSEUS survival data, a scenario analysis using pooled data for DBLd-DL from the PERSEUS and GRIFFIN trials were explored (see Section 3.3.2 for further details). However, it should be noted that neither median PFS nor OS is reached in the GRIFFIN trial (median follow-up: 49.6 months). As such, data immaturity is to be expected for earlier-line treatments, particularly given the availability of more effective later-line treatment options. As described in Section 2.2, the GRIFFIN trial is an ongoing randomised, open-label, multicentre, Phase II trial investigating DBLd-DL versus BLd-L in transplant-eligible NDMM patients.¹¹¹

Survival inputs were modelled separately for the induction and consolidation phase and the maintenance phase, as described below.

3.3.1.1. Survival inputs: Induction and consolidation

KM data for the DBLd arm of the PERSEUS trial were used to inform the efficacy of DBLd-DL in the model. A pragmatic approach was taken to modelling the induction and consolidation treatment phases, whereby DBLd and DBTd were assumed to have equal efficacy with regards to PFS and OS. This is considered highly conservative given the ITC results for induction and consolidation presented in Section 2.10.7, which indicated a response benefit associated with DBLd over DBTd. This included statistically significantly deeper responses for DBLd, with patients almost [REDACTED] more likely to achieve a [REDACTED] compared with DBTd. A numerical non-significant benefit in ORR and MRD-negativity was also observed in patients receiving DBLd compared to DBTd.

3.3.1.2. Survival inputs: Full treatment sequence

No trials reporting data for the full treatment sequence of the relevant comparator in this submission are available, i.e. DBTd induction and consolidation followed by L maintenance, as confirmed by the clinical SLR (Section 2.2). Furthermore, it is difficult to isolate the treatment effect of DL versus L maintenance from the PERSEUS trial due to the lack of a second randomisation after consolidation and prior to maintenance initiation. The Company therefore consider the Phase III AURIGA trial as the best available data source to inform the relative efficacy of DL versus L maintenance alone. The AURIGA trial investigated clinical efficacy in MRD-positive patients randomised to DL or L maintenance therapy who had achieved a $\geq$ VGPR after induction therapy and ASCT.³¹ Data from the AURIGA and PERSEUS trials were combined in order to derive proxy efficacy outcomes for the comparator full treatment sequence.³¹

Whilst the PERSEUS and AURIGA trial populations differ in some respects including prior exposure to daratumumab during induction and consolidation, evidence from CASSIOPEIA and AURIGA support the assertion the treatment effect of DL versus L is expected to be at least maintained in a broader population of patients including anti-CD38 experienced and MRD-negative patients post consolidation. Refer to Section 2.13.

Furthermore, a comparison of the demographic and disease characteristics of patients in the PERSEUS and AURIGA trials indicate that the two populations are comparable. Furthermore, similar efficacy outcomes for DL maintenance were observed in both trials, with 60.2% and 60.6% converting from MRD-positive to MRD-negative during maintenance therapy (at a threshold of 10^{-5}). In both trials, MRD-negativity rates increased over time for those receiving DL maintenance, plateauing after 24 months of maintenance.^{31, 113} The comparability of the PERSEUS and AURIGA trial populations and observed treatment effects suggest that it is reasonable to utilise treatment effect data from the AURIGA trial to derive proxy efficacy estimates. A comparison of key baseline and efficacy data (i.e., MRD-negativity conversion rates at prespecified landmark timepoints in subjects who achieved $\geq$ CR) are presented in Appendix M. Further details on the generalisability of the AURIGA trial to the relevant patient population in this submission are presented in Section 2.13 and indicate that the application of the relative treatment effect from this trial to the DBLd-DL arm are likely to be at least maintained.

Data from AURIGA were therefore used to inform the comparative efficacy of DL and L maintenance therapy following DBLd and DBTd induction and consolidation, respectively. The relative treatment effects for L versus DL maintenance, summarised in Table 49, were applied to adjust the PFS and OS extrapolations for patients receiving DBLd-DL in the PERSEUS trial from the onset of maintenance therapy (approximately 9.7 months from randomisation) to obtain a proxy survival function for DBTd-L patients.

The PH assumption was assessed via log-cumulative hazard plots and Schoenfeld residuals of the survival outcome data from AURIGA. No evidence of violation of the PH assumption was observed, indicating that the use of a HR as a summary measure for treatment effect in terms of PFS and OS was appropriate. Full details of the PH assessments can be found in Appendix M.

Table 49: Summary of treatment effects (DL versus L maintenance) from AURIGA trial for PFS and OS (MRD-positive patients)

Survival results	PFS	OS
HR (DL versus L)	0.53	■
95% CI	0.29, 0.97	■■■■■
P-value	0.036	■

Abbreviations: CI: confidence interval; DL: daratumumab with lenalidomide; HR: hazard ratio; L: lenalidomide; PFS: progression-free survival; OS: overall survival.
Source: J&J Data on File. AURIGA Clinical Study Report (April 2024 DCO) Table 14;¹³⁷ Badros *et al.* (2024).¹³⁶

Scenario analysis

As described above, the AURIGA trial was conducted in patients who were MRD+ and anti-CD38 naïve at the end of consolidation. The treatment benefit observed in this study is expected to be at least maintained in the broader population. Further exploration of the treatment effect in AURIGA for subgroups stratified by sustained MRD-negativity status showed a diminished treatment effect of DL vs L (for both PFS (HR: ■, 95% CI: ■■■■■) and OS (HR: ■, 95% CI: ■■■■■)) in the non-sustained MRD-negative subgroup, compared to the treatment effect of the Company evidence submission template for daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

entire cohort (Table 49). This shows that the treatment effect in the broader population is expected to be similar or better. Given a very wide confidence interval that includes 1 for the treatment effect on OS, we conducted a scenario assuming that the OS HR between DL and L maintenance is 1, indicative of equal efficacy during the maintenance period. As described in Section 2.6.2, this scenario is not considered to be clinically plausible given the superior efficacy demonstrated in the AURIGA trial, and supported by PERSEUS, in response- and survival-based outcomes. In addition, all clinical experts estimated that DL would always be superior over the long term in terms of both PFS and OS.

3.3.1.3. Extrapolation of survival

The follow-up period for the PERSEUS trial was shorter than the model time horizon and, as such, extrapolations of the observed OS, PFS and TTD data were required. In accordance with the NICE DSU TSD 14 guidance, a range of standard parametric distributions (e.g. exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were explored.¹⁶⁷ Each model was assessed in terms of goodness-of-fit statistics (Akaike information criterion [AIC] and the Bayesian information criteria [BIC]), visual inspection of the hazard function, assessment of hazard function plots and survival extrapolations versus the observed data in PERSEUS, and clinical plausibility of long-term survival predictions.

The choice of distribution for the base case for each endpoint was informed considering:

- **Statistical fit:** AIC and BIC statistics were generated for each extrapolation, the best fit to the observed data is the extrapolation with the lowest AIC and BIC
- **Clinical validation of long-term extrapolations:** Clinician feedback was sought from England-based clinicians with expertise in the treatment and management of patients with MM in the NHS. Clinicians were asked to provide plausible estimates of the proportions of patients in clinical practice expected to be progression-free and alive at 10, 15 and 25 years, as well as patients expected to remain on treatment at 5, 8 and 10 years

Graphical assessment of fit, involving visual inspection to determine how well the predicted extrapolation captured the shape of the observed Kaplan-Meier data, was of limited use given the immaturity of PERSEUS trial data.

3.3.1.4. Overall survival

DBLd with DL maintenance

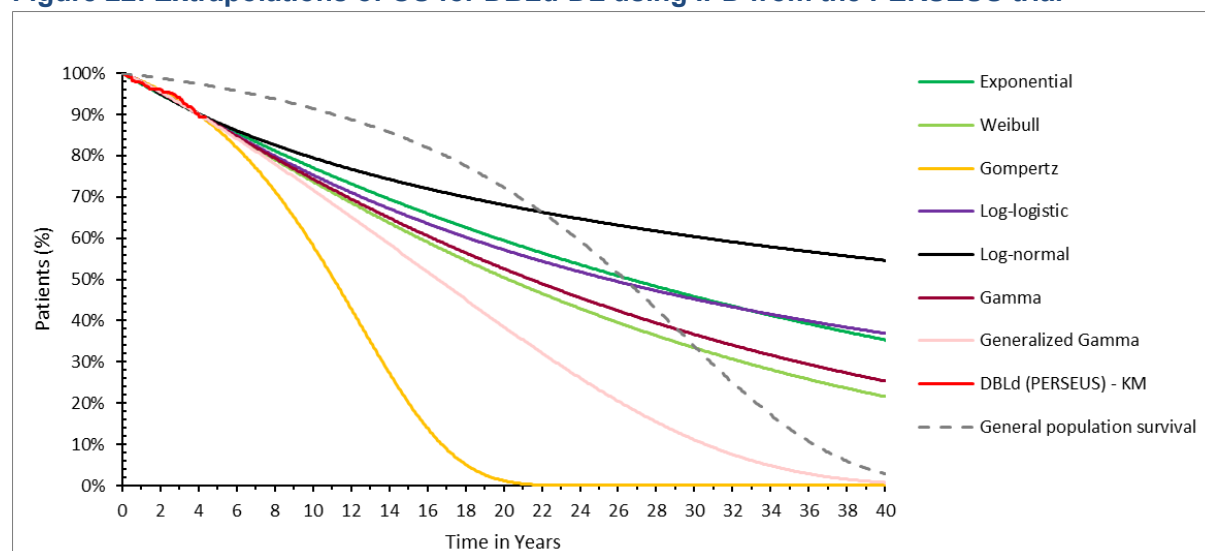
Long-term OS extrapolations for DBLd-DL were obtained by fitting standard parametric distributions to observed OS data from the intervention arm of the PERSEUS trial (1st August 2023; Section 2.6). Each of the extrapolations are presented in Figure 22 below, with goodness-of-fit statistics of each of the extrapolations presented in Table 50. Long-term estimates of OS elicited from UK clinicians consulted in an Advisory Board held in May 2025 are provided in Table 51. Long-term estimates of OS for each parametric curve are also presented in Table 51, with the accompanying smoothed hazard plots presented in Figure 23.

Mortality for patients with NDMM 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 was at least equal to general population mortality (GPM) at any timepoint, age- and gender-matched GPM was used in the cycle where the predicted rate of death was lower than the GPM. The age- and

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gender-matched GPM used to cap OS across all interventions and comparators was based on life tables for England from the 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 TA917.¹⁶⁸

Figure 22: Extrapolations of OS for DBLd-DL using IPD from the PERSEUS trial



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival.

Table 50: Goodness-of-fit statistics for DBLd-DL OS extrapolations

Survival model	DBLd-DL			
	AIC	BIC	AIC rank	BIC rank
Exponential	318.177	322.049	1	1
Weibull	319.385	327.129	3	3
Gompertz	318.417	326.162	2	2
Log-logistic	319.615	327.360	5	5
Log-normal	320.866	328.611	6	6
Gamma	319.457	327.201	4	4
Generalised Gamma	321.164	332.780	7	7

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

Table 51: Comparison of predicted survival rates for DBLd-DL OS extrapolations (with GPM cap)

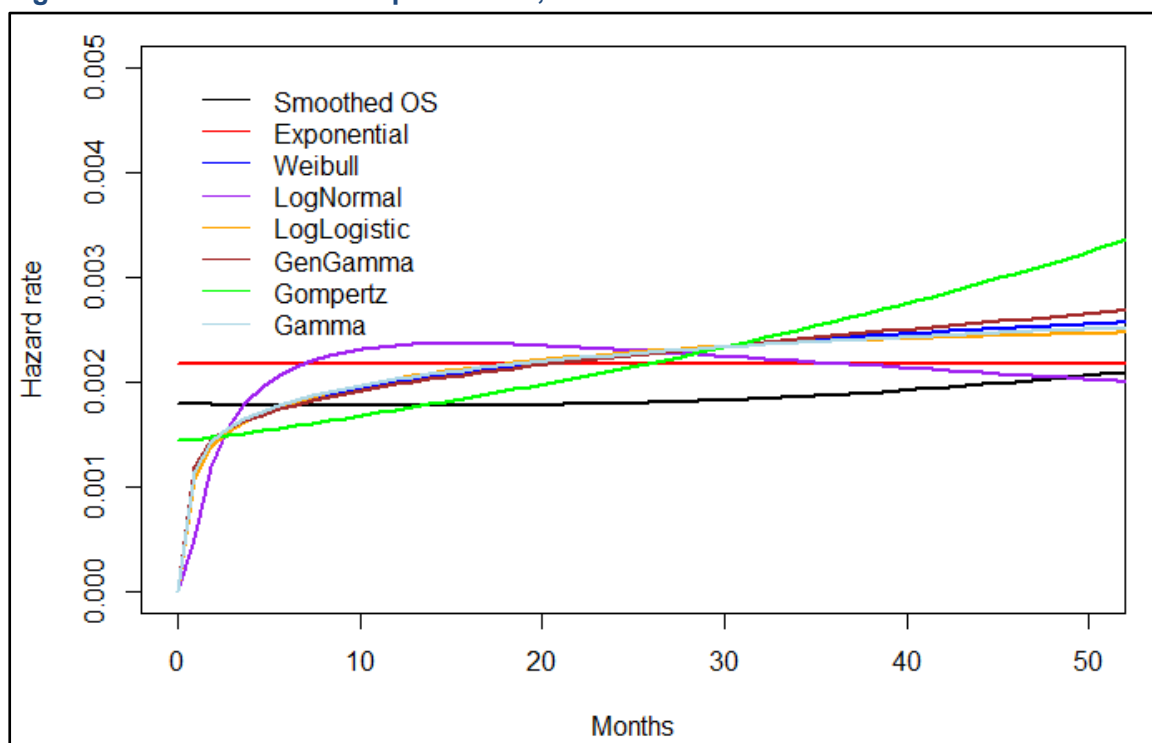
Survival model	DBLd-DL			
	Mean OS (months)	OS survival rates (% , mean [range])		
		10 years	15 years	25 years
Clinical expert estimates				

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Survival model	DBLd-DL			
	Mean OS (months)	OS survival rates (% , mean [range])		
		10 years	15 years	25 years
Clinical expert estimates	NA	77 [75, 80]	67 [65,70]	38 [25, 53]
Extrapolations				
Exponential	255.0	77.0	67.7	44.4
Weibull	237.7	73.6	61.3	38.6
Gompertz	129.6	57.9	20.0	0.0
Log-logistic	249.4	75.3	65.3	42.8
Log-normal	265.9	79.4	72.5	47.8
Gamma	241.9	74.3	62.7	40.1
Generalised Gamma	204.7	71.6	55.1	23.1

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; GPM: general population mortality; NA: not applicable; OS: overall survival.

Figure 23: Smoothed hazard plot for OS; DBLd-DL



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; OS: overall survival.

Curve selection process

Figure 23 shows that in the PERSEUS trial, DBLd-DL is associated with an OS hazard rate which remains constant initially, before gradually increasing after two years. The exponential extrapolation has a constant hazard of death and therefore broadly aligns with this trend and shows internal validity. In contrast, the Weibull, Gompertz, Generalised Gamma, Gamma and loglogistic extrapolations increase over time from the outset, and therefore lack internal validity.

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The lognormal extrapolation shows an increasing hazard initially then, after three years, decreases over time. Overall, the exponential extrapolation was the only fit which followed the observed hazards.

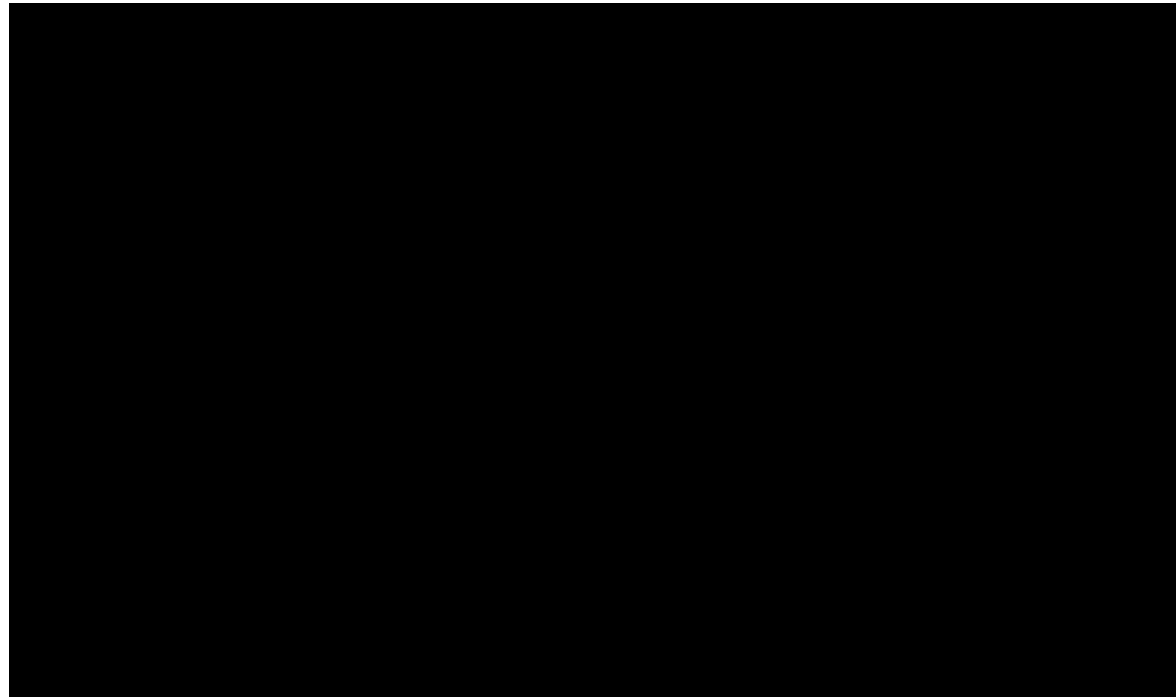
Furthermore, the exponential extrapolation also provided the best statistical fit to the observed PERSEUS OS data with respect to both AIC and BIC data (Table 50). Out of all the extrapolations, the long-term OS survival rates estimated by the exponential extrapolation are most closely aligned with the clinician estimates at the 10- and 15-year timepoints. Whilst the 25-year OS rate estimated by the exponential extrapolation is higher than the mean clinician estimates, this still falls within the range of estimates provided by the clinicians, suggesting its clinical plausibility. As such, the exponential was chosen as the base case curve selection. This aligns with the accepted approach in the NICE appraisal for DBTd (TA763).²

DBTd with L maintenance

As described in Section 3.3.1, the relative treatment benefit of DL versus L maintenance, derived from the AURIGA trial, was applied to adjust the chosen extrapolation of the DBLd-DL arm of the PERSEUS trial from the onset of maintenance therapy (~9.7 months from randomisation). This generated a proxy OS extrapolation (presented in Figure 24:) for DBTd induction and consolidation followed by L maintenance in the absence of trial data for the full treatment sequence.

Long-term estimates of OS estimated by clinicians and the predicted estimates by DBTd-L extrapolation (derived from the application of the AURIGA HR on the chosen DBLd-DL OS extrapolation) are presented in Table 52. The long-term OS estimates derived from the application of the AURIGA HR to the selected DBLd-DL extrapolation were therefore within the range of clinical expert estimates provided across all three landmark timepoints (10, 15, 25 years), confirming its clinical validity. The DBTd-L extrapolations generated are therefore a suitable proxy for extrapolating DBTd-L OS in the absence of trial data.

Figure 24: OS exponential extrapolation for DBLd-DL, and DBTd-L derived from application of AURIGA relative treatment effect (for maintenance phase) on the selected DBLd-DL extrapolation (using IPD from PERSEUS)



Footnotes: Extrapolations shown are with the GPM cap applied.

Abbreviations: DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab-lenalidomide; KM: Kaplan-Meier; GPM: general population mortality; IPD: individual patient data; L: lenalidomide; OS: overall survival.

Table 52: Comparison of predicted survival rates by clinical expert estimates and DBTd-L OS extrapolation (with GPM cap)

Survival model	DBTd-L			
	Mean OS (months)	OS survival rates (% , mean [range])		
		10 years	15 years	25 years
Clinical expert estimates				
Clinical expert estimates	NA	68 [60, 70]	55 [45, 65]	30 [15, 45]
DBTd-L extrapolation derived from application of AURIGA HR applied on selected DBLd-DL extrapolation				
Exponential	194.1	60.7	46.9	27.1

Abbreviations: DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; GPM: general population mortality; L: lenalidomide; NA: not applicable; OS: overall survival.

3.3.1.5. Progression-free survival

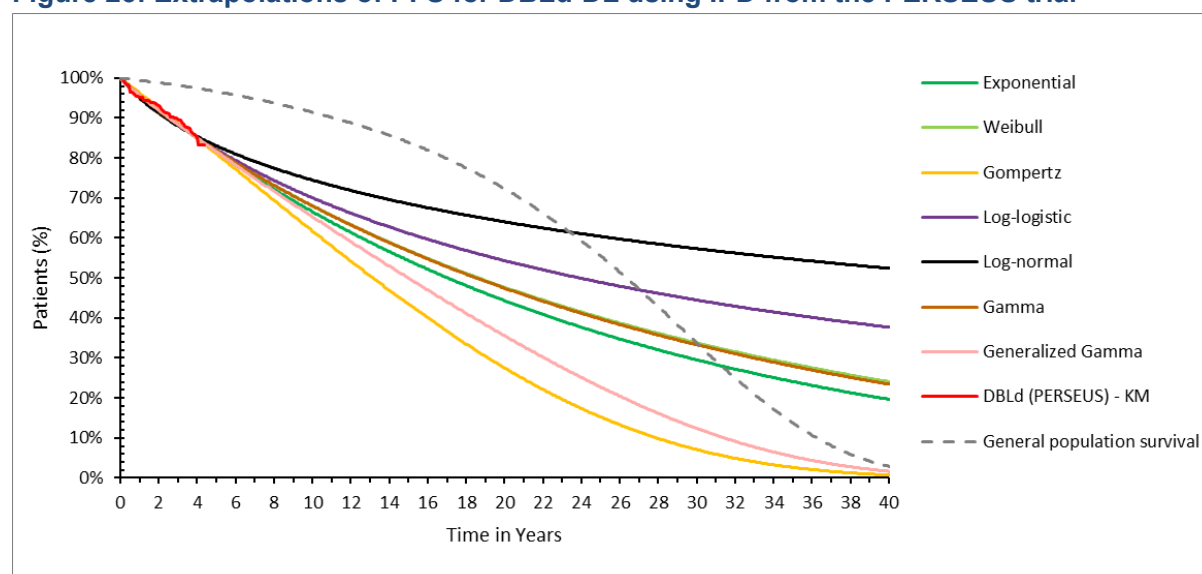
DBLd with DL maintenance

To model long-term DBLd-DL PFS, extrapolations were fitted to the observed PFS data from the PERSEUS trial. The PFS extrapolations implemented in the model include a cap to ensure that PFS did not exceed OS for DBLd-DL to ensure clinical plausibility. Each of the extrapolations are presented in Figure 25 below, with goodness-of-fit statistics of each of the extrapolations

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presented in Table 53. Long-term estimates of PFS for each parametric extrapolation are provided in Table 54, and the accompanying smoothed hazard plots are presented in Figure 26.

Figure 25: Extrapolations of PFS for DBLd-DL using IPD from the PERSEUS trial



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; IPD: individual patient data; KM: Kaplan-Meier; PFS: progression-free survival.

Table 53: Goodness-of-fit statistics for DBLd-DL PFS extrapolations

Survival model	DBLd-DL			
	AIC	BIC	AIC rank	BIC rank
Exponential	422.265	426.137	1	1
Weibull	424.087	431.831	3	3
Gompertz	424.091	431.835	4	4
Log-logistic	424.584	432.328	5	5
Log-normal	428.23	435.975	7	6
Gamma	424.035	431.779	2	2
Generalised Gamma	425.623	437.239	6	7

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

Table 54: Comparison of predicted survival rates for DBLd-DL PFS extrapolations (with OS cap)

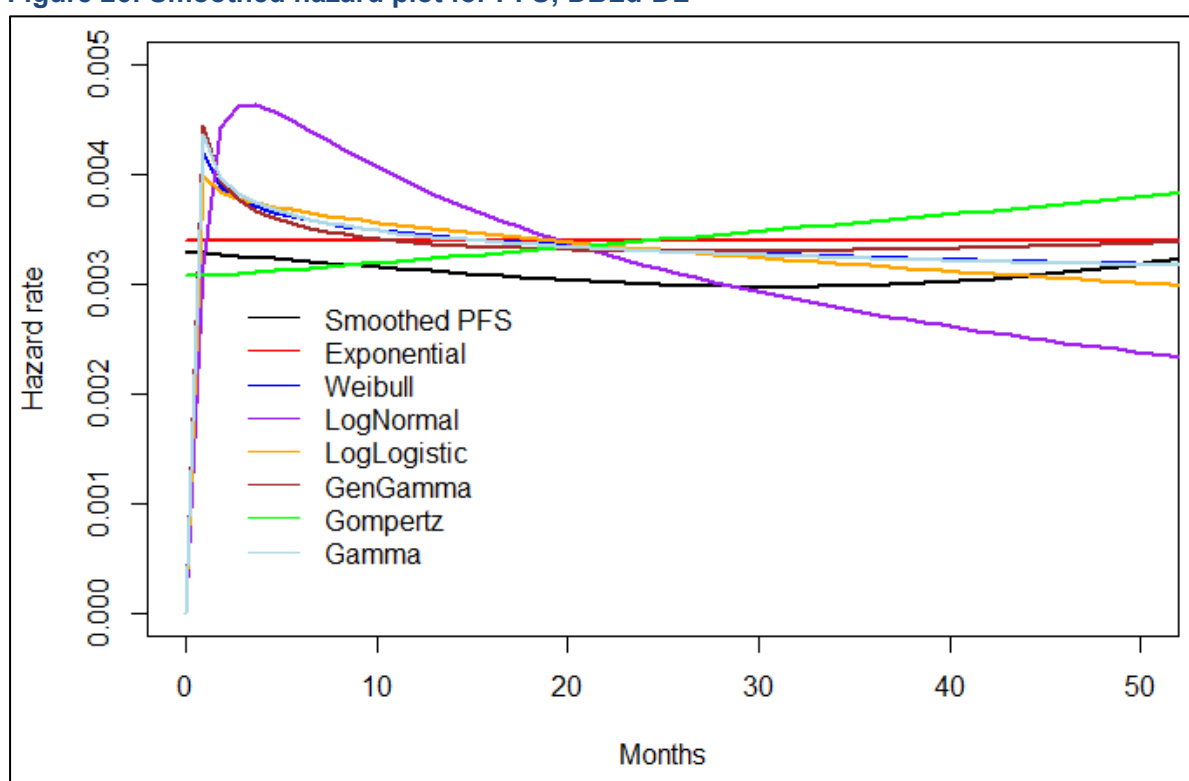
Survival model	DBLd-DL			
	Mean PFS (months)	Proportion of patients progression-free (% mean [range])		
		10 years	15 years	25 years
Clinical expert estimates				
Clinical expert estimates	NA	64 [60, 65]	48 [45, 55]	21 [15, 35]
Extrapolations				
Exponential	223.1	66.5	54.3	36.1

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Survival model	DBLd-DL			
	Mean PFS (months)	Proportion of patients progression-free (% mean [range])		
		10 years	15 years	25 years
Weibull	230.3	68.0	56.8	40.0
Gompertz	173.1	61.6	43.4	15.1
Log-logistic	240.9	70.0	61.1	44.4
Log-normal	249.9	74.4	68.5	44.4
Gamma	229.9	67.9	56.7	39.6
Generalised Gamma	193.8	65.2	49.9	22.6

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; GPM: general population mortality; NA: not applicable; PFS: progression-free survival.

Figure 26: Smoothed hazard plot for PFS; DBLd-DL



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; PFS: progression-free survival.

Curve selection process

Figure 26 shows that in the PERSEUS trial, DBLd-DL is associated with a PFS hazard rate that declines slightly at the beginning of the observed period, then increases gradually from 25 months onwards. The lognormal and loglogistic extrapolations both show a declining hazard of progression or death towards the end of the observed period, therefore lacking internal validity. The Gompertz extrapolation exhibits an increasing hazard over time, in contrast with the observed data. The Generalised Gamma, Weibull and Gamma extrapolations all show an initial steep increasing hazard then gradually decrease over time and the exponential fit showed a

constant hazard over time. All models showed a similar statistical fit to the observed data based on AIC/BIC statistics.

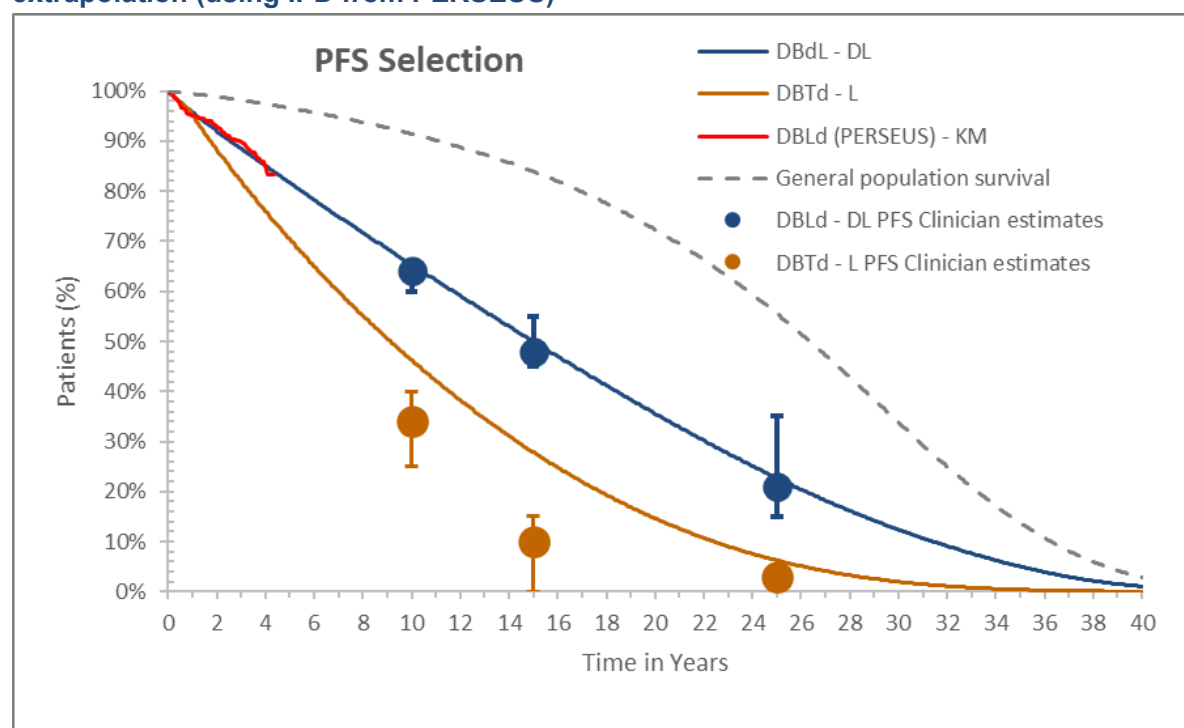
When considering the comparison of predicted PFS rates by the extrapolations with clinician estimates, the Generalised Gamma curve was most closely aligned with the clinician estimates at all three timepoints, and therefore was selected as the base case extrapolation.

DBTd with L maintenance

Long-term PFS extrapolations for DBTd-L were obtained in line with the methods used for the derivation of the OS extrapolations. That is, the relative treatment benefit of DL versus L maintenance, derived from the AURIGA trial, was applied to adjust the chosen extrapolation of the DBLd-DL arm of the PERSEUS trial from the onset of maintenance therapy (~9.7 months from randomisation). This generated a proxy PFS extrapolation (presented in Figure 27:) for DBTd induction and consolidation followed by L maintenance in the absence of trial data for the full treatment sequence.

Long-term estimates of PFS by clinicians and the predicted estimates by the DBTd-L extrapolation (derived from the application of the AURIGA HR on the chosen DBLd-DL PFS extrapolation) are shown in Table 55. The long-term PFS estimates derived from the application of the AURIGA HR to the selected DBLd-DL extrapolation were above the 10 and 15-year clinical estimates but in line with the 25-year clinical expert estimates, and represented the best available proxy PFS extrapolation for DBTd-L in the absence of trial data. The proxy PFS extrapolation for DBTd-L is conservative, suggesting that applying the AURIGA treatment effect maybe conservative when applied to a broad population.

Figure 27: PFS extrapolation for DBLd-DL, and DBTd-L derived from application of AURIGA relative treatment effect (for maintenance phase) on the selected DBLd-DL extrapolation (using IPD from PERSEUS)



Footnotes: Extrapolations shown are with the OS cap applied.

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Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; KM: Kaplan-Meier; IPD: individual patient data; L: lenalidomide; PFS: progression-free survival; OS: overall survival.

Table 55: Comparison of predicted survival rates by clinical expert estimates and DBTd-L PFS extrapolation (with OS cap)

Survival model	DBTd-L			
	Mean PFS (months)	Proportion of patients progression-free (% mean [range])		
		10 years	15 years	25 years
Clinical expert estimates				
Clinical expert estimates	NA	34 [25, 40]	10 [0, 15]	3 [0, 5]
DBTd-L extrapolation derived from application of AURIGA HR applied on selected DBLd-DL extrapolation				
Generalized Gamma	129.9	46.2	28.0	6.2

Abbreviations: DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; GPM: general population mortality; L: lenalidomide; NA: not applicable; OS: overall survival; PFS: progression-free survival.

3.3.1.6. Time to treatment discontinuation

Induction and consolidation phase for DBLd and DBTd

Due to the maturity of the trial data, treatment duration for DBLd and DBTd during the induction and consolidation treatment phases was modelled using observed TTD data (i.e., the observed percentage of patients who continued receiving treatment over time throughout the induction and consolidation phases) from the PERSEUS and CASSIOPEIA trials, respectively (Table 56).

TTD was capped by the duration of the induction and consolidation treatment phases in the trials, to reflect the fact that the therapies had a fixed duration.

Table 56: Observed TTD during induction and consolidation phases of the PERSEUS and CASSIOPEIA trials

Number of 28-day treatment cycles	DBLd	DBTd
Induction phase		
At least 1 cycle	████	████
At least 2 cycles	████	████
At least 3 cycles	████	████
At least 4 cycles	████	████
Consolidation phase		
At least 1 cycle	████	████
2 cycles	████	████
Source	PERSEUS ³²	CASSIOPEIA ¹²⁸

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, dexamethasone; TTD: time to treatment discontinuation.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO; TSIX01);³² J&J Data on File. CASSIOPEIA Clinical Study Report (August 2023 DCO; Table 8).¹²⁸

Maintenance phase for DBLd-DL

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In line with the licence for daratumumab, daratumumab maintenance treatment is to be administered until disease progression.¹ Daratumumab can, however, be discontinued for patients who have achieved MRD-negativity that is sustained for 12 months, if they have been treated on maintenance for at least 24 months, as recommended by the SmPC.¹ For DL maintenance therapy, following DBLd induction and consolidation, TTD was modelled separately for the following populations, to reflect the stopping criteria for daratumumab:

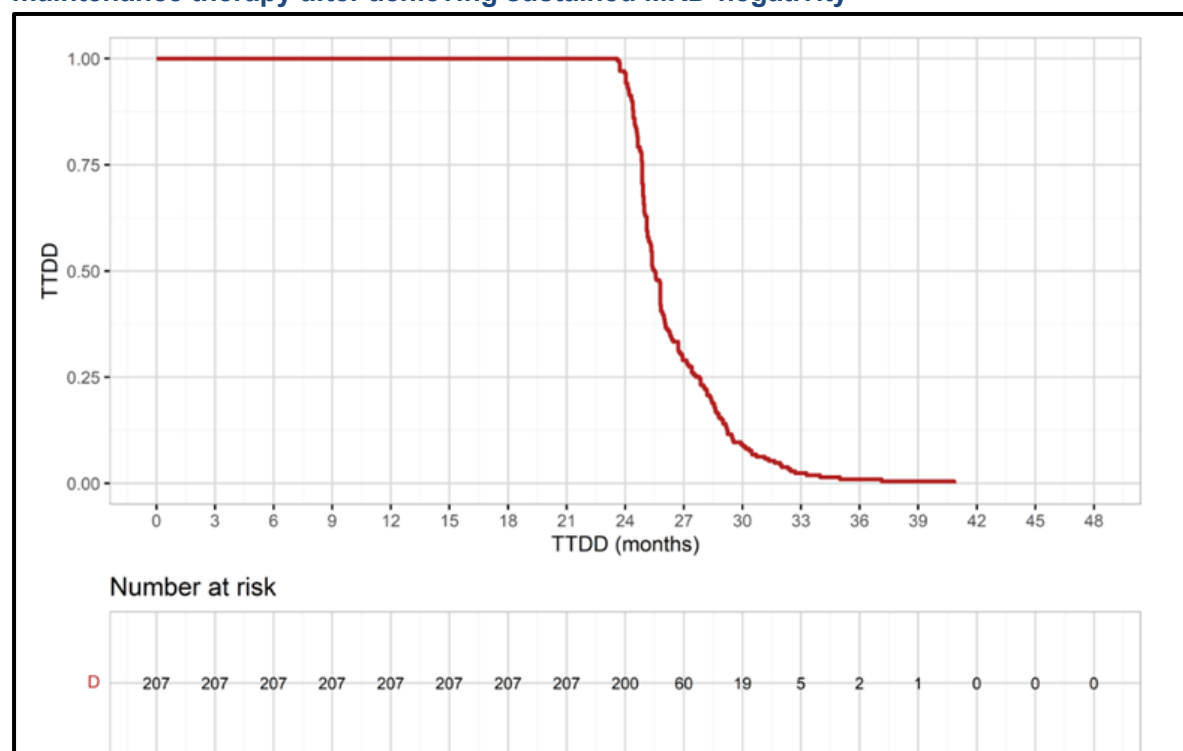
- Patients who, after a minimum of two years of maintenance therapy, **discontinued daratumumab** after achieving sustained MRD-negativity for at least 12 months
- Patients who **discontinued daratumumab** but did not achieve sustained MRD-negativity at the latest DCO
- Patients who **discontinued lenalidomide** (*Note: independently modelled data for discontinuation of daratumumab and discontinuation of lenalidomide was applied for patients receiving DL*)

DL maintenance following DBLd induction and consolidation: extrapolations for discontinuation of daratumumab with sustained MRD-negativity

Mature data were available for the cohort of patients who discontinued daratumumab maintenance therapy due to sustained MRD-negativity. Observed KM data were therefore applied in the model for these patients, as presented in Figure 28 below. A scenario analysis was also explored, where TTD for this group of patients was modelled based on a fixed duration of two years.

For the other two groups of patients, extrapolations were fitted to TTD data from the PERSEUS trial (as detailed below).

Figure 28: Observed Kaplan-Meier data for patients who discontinued daratumumab maintenance therapy after achieving sustained MRD-negativity



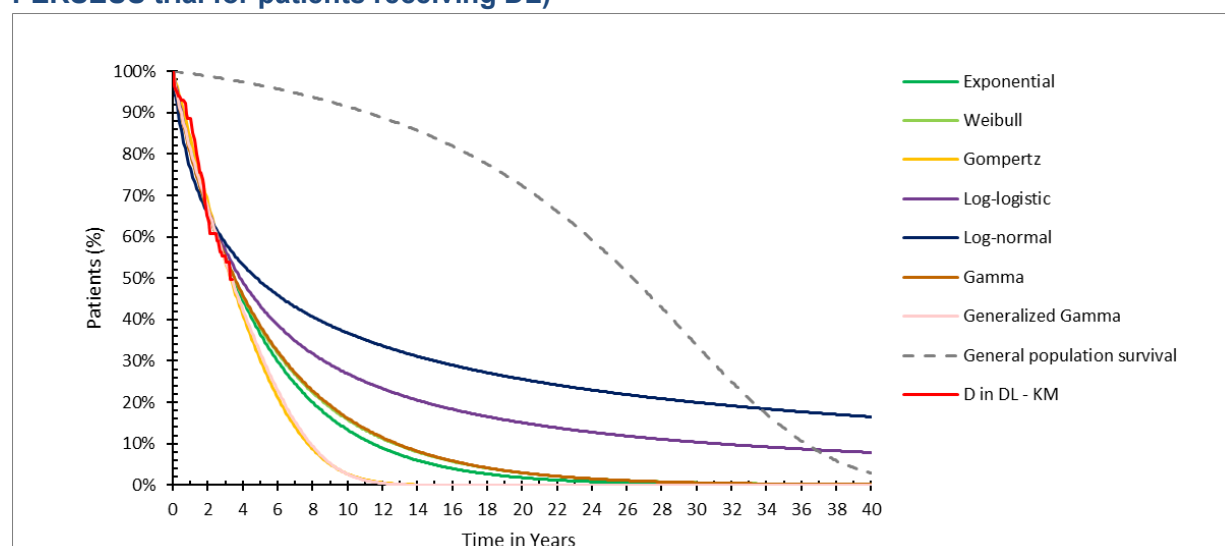
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Abbreviations: D: daratumumab; MRD: minimal residual disease; TTDD: time to treatment discontinuation duration.

DL maintenance following DBLd induction and consolidation: extrapolations for discontinuation of daratumumab without sustained MRD-negativity

As described above, treatment duration for patients who received DL maintenance following DBLd induction and consolidation, but discontinued daratumumab during the maintenance phase without meeting the stopping criteria of sustained MRD-negativity, was modelled by fitting extrapolations to TTD data from the PERSEUS trial. Each of the extrapolations are presented in Figure 29 below, with goodness-of-fit statistics of each of the extrapolations presented in Table 57. Long-term estimates of TTD for each parametric extrapolation are provided in Table 58, and the accompanying smoothed hazard plots are presented in Figure 30.

Figure 29: Extrapolation of TTD for DBLd-DL patients without sustained MRD-negativity who discontinued daratumumab maintenance therapy (modelled using IPD from the PERSEUS trial for patients receiving DL)



Footnotes: TTD capped by PFS in the model.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab with lenalidomide; IPD: individual patient data; KM: Kaplan-Meier; MRD: minimal residual disease; PFS: progression-free survival; TTD: time to treatment discontinuation.

Table 57: Goodness-of-fit statistics for TTD extrapolations for DBLd-DL patients without sustained MRD-negativity who discontinued daratumumab maintenance therapy

Survival model	Daratumumab discontinuation without sustained MRD-negativity			
	AIC	BIC	AIC rank	BIC rank
Exponential	278.1	280.8	1	1
Weibull (PH)	279.8	285.3	5	4
Gompertz	279.3	284.8	3	2
Log-logistic	283.6	289.1	6	6
Log-normal	298.5	304	7	7
Gamma	279.3	284.8	4	3
Generalised Gamma	279.1	287.4	2	5

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab with lenalidomide; MRD: minimal residual disease; TTD: time to discontinuation.

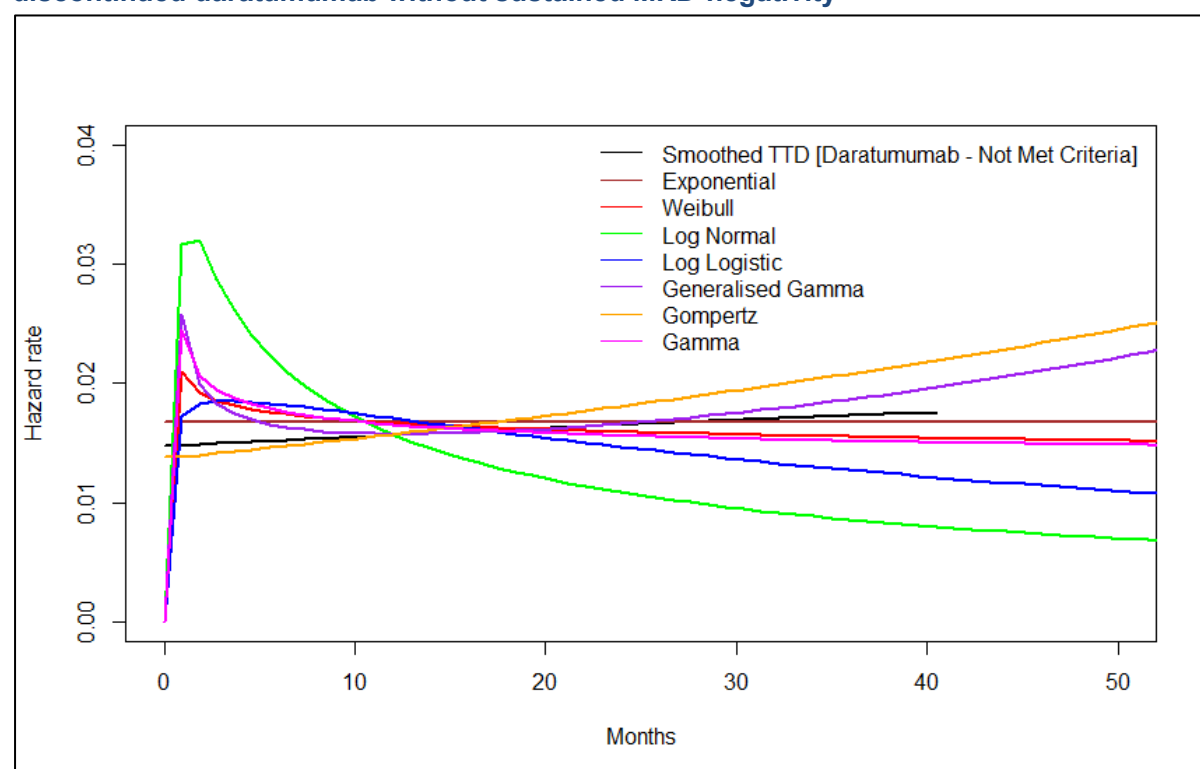
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Table 58: Comparison of predicted TTD rates for DBLd-DL patients without sustained MRD-negativity who discontinued daratumumab maintenance therapy

Survival model	Daratumumab discontinuation without sustained MRD-negativity			
	Median TTD (years)	Patients on treatment (% , mean [range])		
		5 years	8 years	10 years
Clinical expert estimates				
Clinical expert estimates	NA	36 [35, 37]	20 [19, 20]	12 [10, 15]
Extrapolations				
Exponential	3.4	36.2	19.8	13.3
Weibull	3.5	37.8	22.2	15.7
Gompertz	3.4	29.7	8.5	2.7
Log-logistic	3.9	43.0	31.6	26.8
Log-normal	4.8	49.0	40.6	36.7
Gamma	3.6	38.1	22.6	16.1
Generalised Gamma	3.3	31.4	9.2	2.6

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab with lenalidomide; MRD: minimal residual disease; NA: not applicable; TTD: time to discontinuation.

Figure 30: Smoothed hazard plot for TTD extrapolations for DBLd-DL patients who discontinued daratumumab without sustained MRD-negativity



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab with lenalidomide; MRD: minimal residual disease; TTD: time to discontinuation.

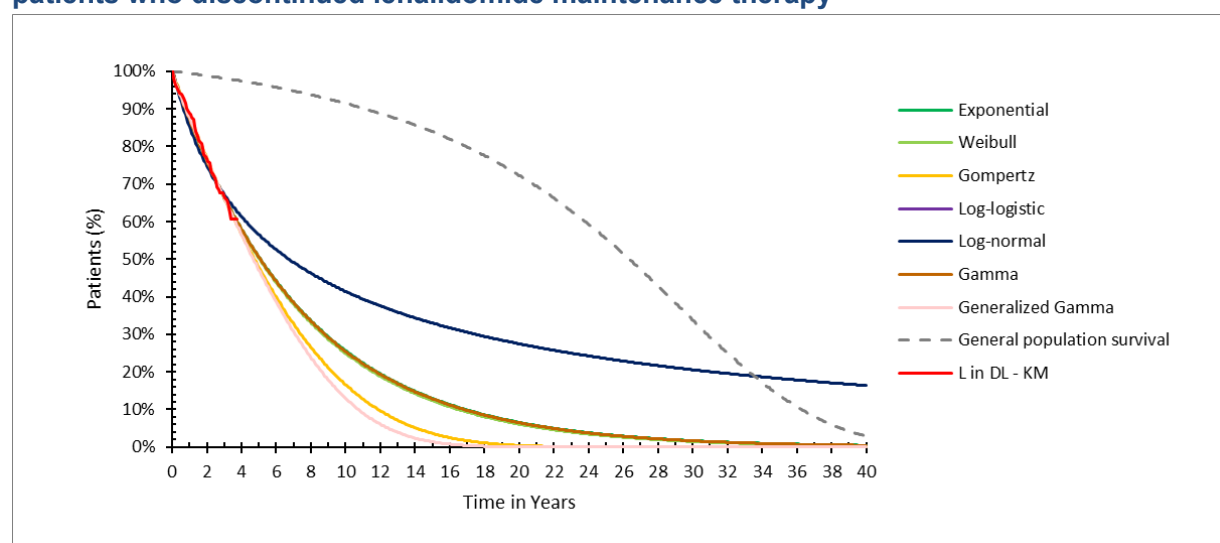
As shown in Table 57, the exponential extrapolation showed the best statistical fit with the observed data in terms of AIC and BIC. In addition, the exponential fit showed a constant hazard over time, following the observed hazards most closely, and closely aligned with the long-term TTD clinician estimates across all three timepoints at 5, 8 and 10 years. As such, considering Company evidence submission template for daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

both statistical fit, assessment of hazard plots and alignment with clinical plausibility, the exponential curve was deemed most appropriate and selected for the base case economic analysis.

DL maintenance following DBLd induction and consolidation: extrapolations for discontinuation of lenalidomide

Treatment duration for patients who received DL maintenance following DBLd induction and consolidation, but discontinued lenalidomide during the maintenance phase, was modelled by fitting extrapolations to TTD data from the PERSEUS trial. Each of the extrapolations are presented in Figure 31 below, with goodness-of-fit statistics of each of the extrapolations presented in Table 59. Long-term estimates of TTD for each parametric extrapolation are provided in Table 60, and the accompanying smoothed hazard plots are presented in Figure 31.

Figure 31: Extrapolation of TTD for using IPD from the PERSEUS trial for DBLd-DL patients who discontinued lenalidomide maintenance therapy



Footnotes: TTD capped by PFS in the model.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab with lenalidomide; IPD: individual patient data; KM: Kaplan-Meier; PFS: progression-free survival.

Table 59: Goodness-of-fit statistics for TTD extrapolations for DBLd-DL patients who discontinued lenalidomide maintenance therapy

Survival model	Lenalidomide discontinuation			
	AIC	BIC	AIC rank	BIC rank
Exponential	660.5	664.3	1	1
Weibull	662.5	670	3	3
Gompertz	662.0	669.5	2	2
Log-logistic	664.4	671.9	6	5
Log-normal	673.8	681.3	7	7
Gamma	662.5	670.0	4	4
Generalised Gamma	663.5	674.8	5	6

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

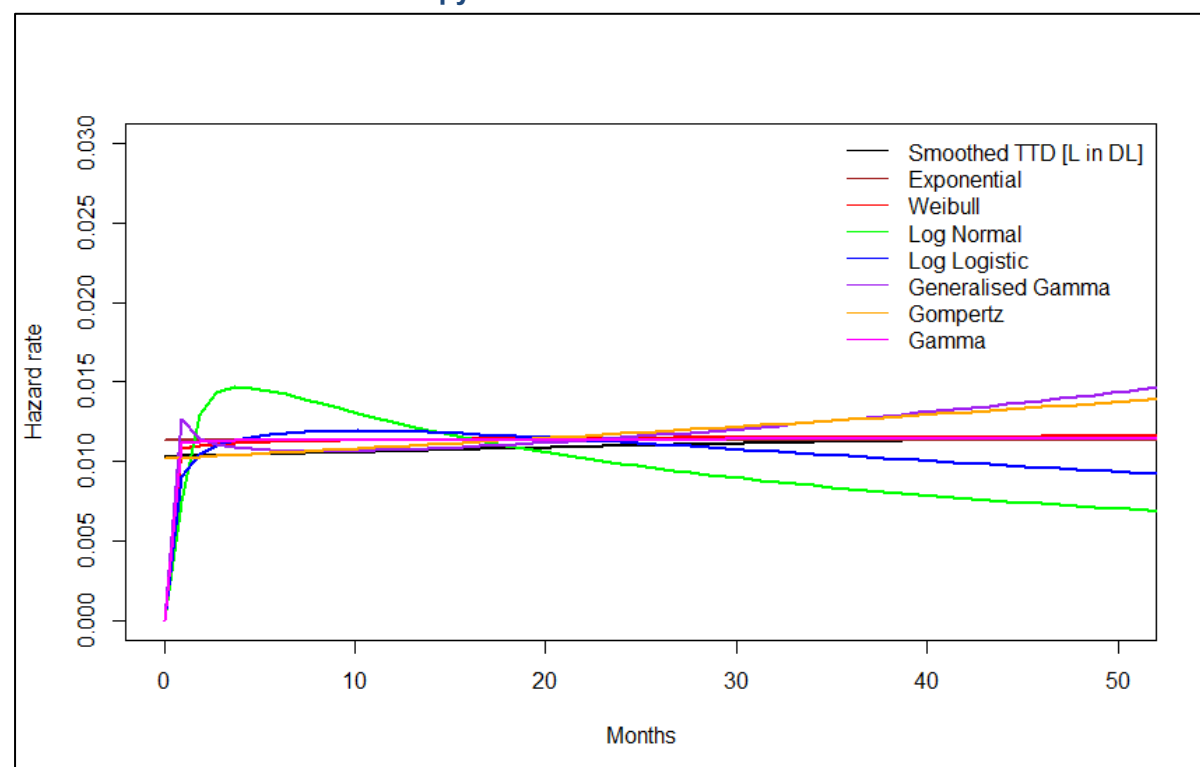
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Table 60: Comparison of predicted TTD rates for DBLd-DL patients who discontinued lenalidomide maintenance therapy

Survival model	Lenalidomide discontinuation			
	Median TTD (years)	Patients on treatment (% , mean [range])		
		5 years	8 years	10 years
Clinical expert estimates				
Clinical expert estimates	NA	51 [50,53]	34 [32, 35]	25 [24, 25]
Extrapolations				
Exponential	5.1	50.2	33.4	25.5
Weibull	5.0	49.9	32.9	24.8
Gompertz	4.7	47.3	26.3	16.4
Log-logistic	5.7	52.8	40.0	34.3
Log-normal	6.7	56.3	46.1	41.3
Gamma	5.1	50.1	33.3	25.3
Generalized Gamma	4.7	46.7	23.5	12.8

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab with lenalidomide; MRD: minimal residual disease; NA: not applicable; TTD: time to discontinuation.

Figure 32: Smoothed hazard plot for TTD for DBLd-DL patients who discontinued lenalidomide maintenance therapy



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab with lenalidomide; MRD: minimal residual disease; TTD: time to discontinuation.

The exponential, Weibull and gamma extrapolations showed constant and were therefore in line with the observed hazards in the PERSEUS trial (Figure 32). When comparing the fitted model statistics, hazards and long-term estimates, the exponential extrapolation showed the best

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statistical fit with the observed data in terms of AIC and BIC (Table 59) and produced long-term estimates that are close to clinicians' estimates. As such, this curve was selected for the base case economic analysis.

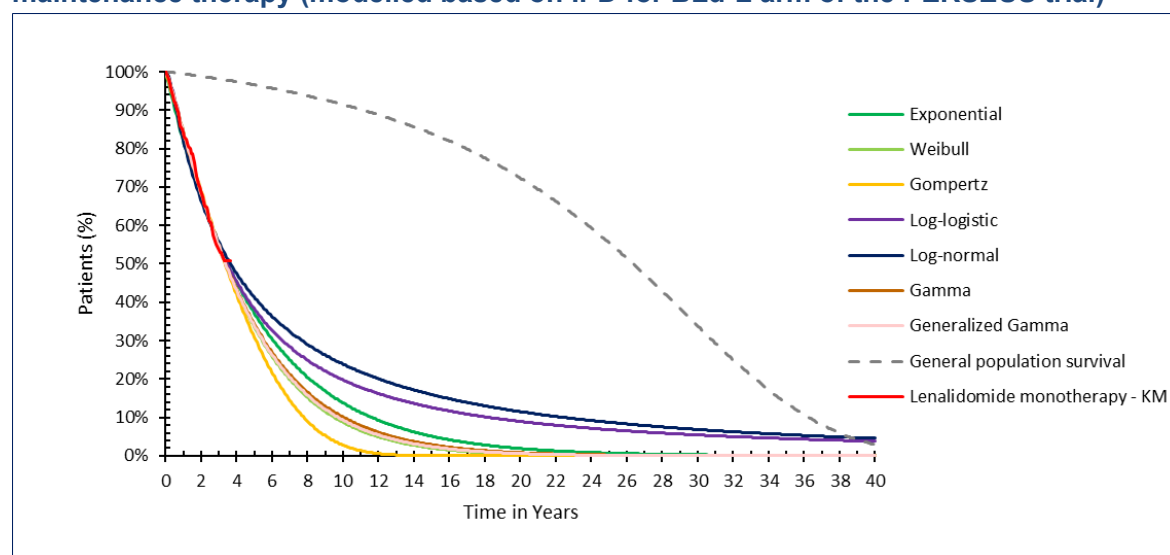
Treatment restarting following discontinuation of daratumumab during maintenance phase

The PERSEUS trial protocol allowed patients to restart daratumumab, after previously discontinuing due to sustained MRD-negativity, upon confirmed loss of CR, or recurrence of MRD (at a threshold of $\geq 10^{-4}$). However, only [REDACTED] patients restarted daratumumab out of the [REDACTED] patients who discontinued after meeting the stopping criteria. Given the low number of patients restarting, there is insubstantial information to draw conclusions about these patients. Furthermore, feedback from UK clinical experts confirmed that patients in clinical practice are unlikely to restart daratumumab maintenance and would instead initiate a new treatment regimen.⁴ As such, the base case economic analysis assumed that no patients would restart daratumumab.

Maintenance phase for DBTd-L

Treatment duration for lenalidomide maintenance therapy for the DBTd-L comparator arm was modelled by fitting extrapolations to the TTD data for the BLd-L arm in the PERSEUS trial where patients received L maintenance therapy. Each of the extrapolations are presented in Figure 33 below, with goodness-of-fit statistics of each of the extrapolations presented in Table 61. Long-term estimates of TTD for each parametric extrapolation are provided in Table 62, and the accompanying smoothed hazard plots are presented in Figure 34.

Figure 33: Extrapolation of TTD for DBTd-L patients who discontinued lenalidomide maintenance therapy (modelled based on IPD for BLd-L arm of the PERSEUS trial)



Footnotes: TTD capped by PFS in the model.

Abbreviations: L: lenalidomide; IPD: individual patient data; KM: Kaplan-Meier; PFS: progression-free survival; TTD: time to treatment discontinuation.

Table 61: Goodness-of-fit statistics for DBTd-L patients who discontinued lenalidomide maintenance therapy (modelled based on IPD for BLd-L arm of the PERSEUS trial)

Survival model	Lenalidomide discontinuation			
	AIC	BIC	AIC rank	BIC rank
Exponential	740.3	744.0	4	1
Weibull	739.0	746.4	1	2
Gompertz	740.0	747.4	2	3
Log-logistic	740.1	747.5	3	4
Log-normal	746.7	754.1	6	7
Gamma	739.0	746.4	1	2
Generalised Gamma	741.0	752.1	5	5

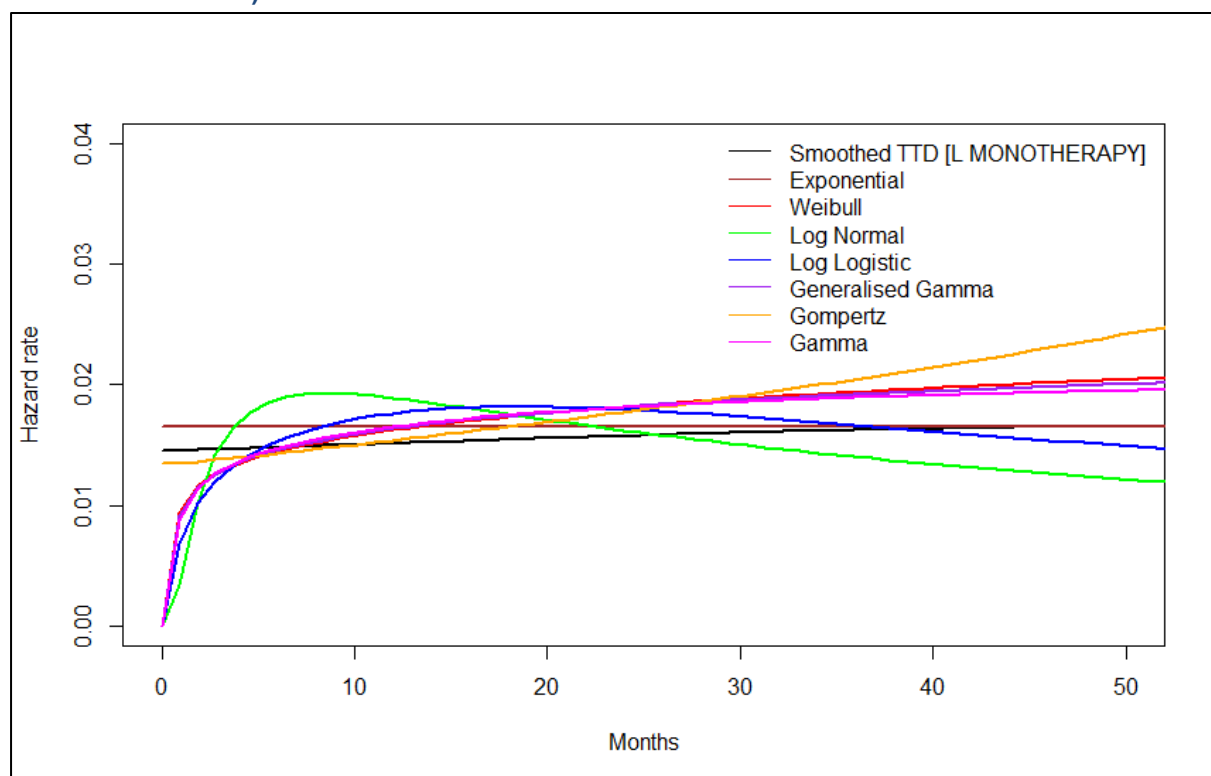
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BLd: bortezomib, lenalidomide, dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, dexamethasone; IPD: individual patient data; L: lenalidomide; TTD: time to discontinuation.

Table 62: Comparison of predicted TTD rates for DBTd-L patients who discontinued lenalidomide maintenance therapy (extrapolation modelled based on IPD for BLd-L arm of the PERSEUS trial)

Survival model	Lenalidomide discontinuation			
	Median TTD (years)	Patients on treatment (% , mean [range])		
		5 years	8 years	10 years
Clinical expert estimates				
Clinical expert estimates	NA	36 [35, 37]	20 [18, 20]	13 [10, 15]
Extrapolations				
Exponential	3.5	36.7	20.3	13.7
Weibull	3.4	33.0	15.0	8.6
Gompertz	3.3	30.3	8.8	2.7
Log-logistic	3.5	37.9	24.7	19.7
Log-normal	3.6	40.9	28.9	23.8
Gamma	3.4	33.8	16.4	10.0
Generalized Gamma	3.4	33.3	15.6	9.2

Abbreviations: BLd: bortezomib, lenalidomide, dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, dexamethasone; IPD: individual patient data; L: lenalidomide; TTD: time to discontinuation.

Figure 34: Smoothed hazard plot for TTD extrapolations for discontinuation of lenalidomide maintenance therapy for DBTd-L (modelled based on IPD for BLd-L arm of the PERSEUS trial)



Abbreviations: BLd: bortezomib, lenalidomide, dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, dexamethasone; L: lenalidomide; MRD: minimal residual disease; TTD: time to discontinuation.

Whilst the Gamma and Weibull distributions had the same AIC statistics, demonstrating the best statistical fit, none of the distributions apart from generalised gamma and log-normal had significantly different values. Beyond statistical fit, the exponential had consistent hazards in line with the observed hazards in the PERSEUS trial (as per Figure 34) with long-term extrapolations that were closely aligned with clinician estimates. Therefore, the exponential distribution was selected as the base case thereby, also maintaining the consistency of treatment discontinuation assumptions across the three treatment cohorts.

3.3.2 Scenario analyses for modelling survival

Due to the relatively strong prognosis for patients with HDT-ASCT eligible NDMM, immaturity of survival data is a common challenge in this setting. As such, alternative approaches for modelling survival were performed, the results of which are presented in 3.11.3.

Scenario A: Extrapolation of pooled DBLd-DL data from the PERSEUS and GRIFFIN trials

Due to the immaturity of OS and PFS data from the PERSEUS trial, a scenario analysis was conducted pooling PERSEUS data with the more mature data from the GRIFFIN trial. The GRIFFIN trial is an ongoing Phase II RCT comparing DBLd induction and consolidation followed by DL maintenance, with BLd induction and consolidation followed by L maintenance in patients with NDMM who are deemed HDT-ASCT eligible.¹⁶⁹

3.3.3 Adverse events

In the base case economic analysis, AEs for DBLd during the induction, ASCT and consolidation phases were informed by the PERSEUS trial. AEs for DBTd during the induction, ASCT and consolidation phases were informed by the CASSIOPEIA trial. AEs for DL and L during the maintenance phase were informed by the AURIGA trial.^{31, 32, 75} AEs of Grade 3 or 4 occurring in $\geq 5\%$ of patients in the PERSEUS, CASSIOPEIA or AURIGA trials were included in the base case economic analysis. Requiring that events must have occurred in at least 5% of patients in either trial was considered appropriate 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. The disutilities associated with AEs are presented in Section 3.4.4, and the costs associated with AE management in Section 3.5.3.

The model uses the cumulative probabilities of AE occurrence during induction, ASCT and consolidation, as these are assumed to be independent of both PFS and treatment duration. To account for differences in exposure time, treatment-specific cumulative probabilities for the ITT populations over the whole duration of the induction, ASCT and consolidation phases were used to calculate an overall cost of AEs. A per-patient overall AE cost and utility decrement was applied as a one-time lump sum and one-off decrement, respectively at the start of induction treatment. For maintenance, the treatment-specific probabilities of AE occurrence were derived from the maintenance phase of the AURIGA trial to inform the overall AE costs. A per-patient overall AE cost and utility decrement was applied as a one-time lump sum and one-off decrement, respectively at the start of maintenance treatment.

The cumulative probabilities of AE occurrence during the induction and consolidation phases, as well as the probabilities for AEs in the maintenance phase, are shown in Table 63 and Table 64, respectively.

Table 63: Incidence of Grade 3/4 AEs (occurring in 5% of patients in PERSEUS or CASSIOPEIA) included in the base case economic analysis (induction and consolidation phases)

Adverse event	DBLd	DBTd
Neutropenia	████	27.60%
Lymphopenia	████	17.00%
Thrombocytopenia	████	11.00%
Febrile neutropenia	████	████
Stomatitis	████	12.70%
Peripheral sensory neuropathy	████	8.80%
Anaemia	████	████
Pneumonia	████	████
Diarrhoea	████	████
Source	PERSEUS ³²	CASSIOPEIA ⁷⁵

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, dexamethasone.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): Table 25.³² CASSIOPEIA: At least 5% Grade 3/4 Treatment-emergent Adverse Events During Induction/ASCT/Consolidation Phase (June 2018 DCO): Table TSFAE03A_3006;⁷⁵ Moreau *et al.* 2024.¹²⁸

Table 64: Incidence of Grade 3/4 AEs (occurring in 5% of patients in AURIGA) included in the base case economic analysis (maintenance phase)

Adverse event	DL	L
Neutropenia	46.9%	41.8%
Leukopenia	9.4%	6.1%
Lymphopenia	10.4%	5.1%
Diarrhoea	3.1%	5.1%
Hypokalemia	7.3%	6.1%
Hypertension	7.3%	4.1%
Pneumonia	5.2%	4.1%
Source	AURIGA ³¹	

Abbreviations: AE: adverse event; BLd: bortezomib, lenalidomide and dexamethasone; DCO: data cut-off; DL: daratumumab and lenalidomide; L: lenalidomide.

Source: Badros et al. 2024: Table 2.³¹

3.4 Measurement and valuation of health effects

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

In the PERSEUS trial, patients completed PRO measures related to their HRQoL, including the EORTC-QLQ-C30, EORTC-QLQ-MY20 and the EQ-5D-5L questionnaires.¹¹⁰

EQ-5D-5L data were collected at the following time points:¹¹⁰

- Twice during induction (Day 1 of Cycles 1 and 3)
- Once prior to ASCT (within 2 weeks of completing Cycle 4)
- Once during the consolidation phase (Day 1 of Cycle 5)
- Throughout maintenance therapy (Day 1 of Cycle 7, then every 12 weeks until progression)

Further details on the HRQoL data collected in the PERSEUS trial are provided in Section 2.6.1.3.

3.4.2 Mapping

HRQoL data were collected in the PERSEUS trial using the EQ-5D-5L. In accordance with the NICE methods manual regarding the use of EQ-5D-5L to derive utility values, the EQ-5D-5L descriptive scores from PERSEUS 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).^{107, 170} The resulting utility values for DBLd-DL derived from the mapping are presented in Section 3.4.5.

3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify evidence on HRQoL, PROs and utilities in HDT-ASCT eligible patients with NDMM for the full treatment sequence (induction, consolidation and maintenance treatment phases) (see Appendix F). The HRQoL SLR was originally conducted on 19th September 2023 and subsequently updated on 13th May 2025.

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In total, a total of 44 unique HRQoL studies were identified. However, none of these elicited utility values from a UK population using EQ-5D, and therefore none were in line with the NICE reference case. Two studies (one RCT [Ludwig *et al.* 2013] and one RWE study [Abonour *et al.* 2018]) reported EQ-5D utility data for HDT-ASCT eligible NDMM patients but were not deemed suitable due to the following reasons.

Ludwig *et al.* 2013 reported utilities for patients who received BTd induction therapy with and without cyclophosphamide.¹⁷¹ As per TA763, DBTd has shown improved clinical outcomes compared to BTd and therefore, utilities from a BTd patient population would not be representative of the expected utilities for DBTd treatment.² Moreover, data from Ludwig *et al.* 2013 is outdated, having been published more than 10 years ago. Utilities were also only collected for patients receiving induction therapy rather than the full treatment sequence and therefore, Ludwig *et al.* 2013 was not considered relevant for use in the economic analysis.¹⁷¹

Abonour *et al.* 2018 reported utilities for patients in a US registry who received ASCT and did or did not receive maintenance therapy.¹⁷² The study excluded patients who received consolidation therapy prior to maintenance, and reported utilities which were implausibly high when compared to UK population norms for individuals aged 55–64 years, given the clinical burden of MM.¹⁷² The utilities reported in Abonour *et al.* 2018 were higher than utilities derived from the PERSEUS trial and utilities used in previous NICE appraisals for patients with HDT-ASCT eligible NDMM.^{2, 173} As such, utilities from the study were not considered relevant for use in the economic analysis. This approach aligns with that taken in the evaluation for DBTd induction and consolidation therapy (TA763).²

Apart from these two RCTs, EQ-5D-5L data for patients receiving DBLd-DL and BLd-L from GRIFFIN and PERSEUS were both reported in Silbermann *et al.* 2023 and Sonneveld *et al.* 2024, respectively.^{174, 175} Given the availability of EQ-5D-5L data for DBLd-DL from the PERSEUS trial which represent the main treatment of interest to this submission and the registrational trial supporting the label extension for daratumumab maintenance therapy, the utilities for patients receiving other treatments (i.e., beyond DBLd-DL) are inherently less relevant. Hence, utility values were derived as noted in Section 3.4.2.

3.4.4 Adverse reactions

One-off decrements in utility were applied in the base case economic analysis based on the proportion of patients who experienced AEs associated with induction, ASCT or consolidation (Table 63), or maintenance therapy (Table 64) during the PERSEUS and CASSIOPEIA trials. The duration of AEs, and the AE disutilities, applied were informed by previous NICE evaluations for daratumumab-based combination therapies in patients with NDMM.^{12, 176} A summary of AE durations and disutilities is presented in Table 65.

Table 65: Summary of AE durations and disutilities included in the base case economic analysis

AE	Utility decrement	Duration of AE (weeks)	Source
Febrile neutropenia	-0.39	4.00	TA763 ¹⁷⁶
Peripheral sensory neuropathy	-0.07	4.00	
Stomatitis	-0.15	4.00	

AE	Utility decrement	Duration of AE (weeks)	Source
Anaemia	-0.31	25.71	TA917 ¹²
Diarrhoea	-0.10	1.71	
Lymphopenia	-0.07	2.21	
Neutropenia	-0.15	1.00	
Pneumonia	-0.19	1.00	
Thrombocytopenia	-0.31	1.00	
Leukopenia	-0.07	2.10	
Hypokalemia	-0.07	1.63	
Hypertension	-0.15	1.63	

Abbreviation: AE: adverse event; TA: technology appraisal.

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

To align with the exact population which efficacy data were derived from, utility data for the induction, ASCT, consolidation and maintenance treatment phases were taken from the PERSEUS trial for the base case economic analysis.

EQ-5D-5L utility data were similar between the two treatment arms in the PERSEUS trial (see Section 3.4.3), with no significant differences in the LS mean change from baseline up to maintenance cycle 34 day 1 (difference in utility score [95% CI] measured at initiation cycle 3 day 1 up till maintenance cycle 34 day 1: [REDACTED]). As such, the utility values were pooled across treatment arms to increase sample size in the analysis, with equal utilities applied for DBLd-DL, and DBTd-L.

The compliance rates for EQ-5D-5L at baseline were above [REDACTED]% in both treatment arms, and were above [REDACTED]% for most timepoints up to Cycle 34 of maintenance therapy. All values collected post-censoring for PFS were excluded since, after the censoring date, the pre- and post-PD states cannot be determined. Overall, there were [REDACTED] missing visits (1.5% of the total visits), of which [REDACTED] ([REDACTED]%) had a missing progression status due to censoring for progression prior to the PRO assessment date. The remaining [REDACTED] visits ([REDACTED]%) were off-treatment visits for the PF health state where treatment phase (i.e., induction, consolidation or maintenance) could not be determined.

Details of the utilities applied to the PF and PD health state are presented below.

PF health state

The derivation of utilities for the induction, ASCT and consolidation treatment phases was based on descriptive statistics and least-squared adjusted means output from a univariate linear regression model. The number of observations with non-missing utility values and the distribution of observed utility values (i.e., mean, mean, standard error [SE], SD, median, IQR, minimum and maximum) were summarised by treatment phase. For the maintenance phase, the average utility was calculated using a repeated-measures linear mixed-effects model. A subject random intercept was used to account for repeated measures of individuals during maintenance and over multiple cycles before progression. The derived utilities are presented below in Table 66.

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PD health state

Patients who experienced a progression event during the PERSEUS trial were grouped together to estimate the mean post-progression EQ-5D-5L utility value. For patients who progressed, but did not die, post-progression utility was defined as the average utility at the date of, or after, confirmed progression (based on a computerised algorithm). All post-progression observations after the date of confirmed progression were used in these analyses regardless of whether they were per-protocol scheduled or unscheduled visits. A subject random intercept was used to account for repeated measures of individuals over multiple cycles and post-PD assessments. The derived utilities are presented below in Table 66.

In the base case economic analysis, utilities were also age-adjusted over the model time horizon in line with UK population norm values for EQ-5D, as reported in the HSE 2014 dataset by NICE DSU, using methods outlined in Hernandez *et al.* (2014).¹⁷⁷

Table 66. Summary of utilities used in the base case economic analysis

Treatment phases	Mean (SE)	Source
PF		PERSEUS EQ-5D-5L data, cross-walked to UK EQ-5D-3L value set (August 2023 DCO)
Induction		
ASCT		
Consolidation		
Maintenance		
PD		

Abbreviations: ASCT: autologous stem-cell transplant; PF: progression-free; PD: progressed disease; SE: standard error.

Scenario analysis

In the NICE appraisal for DBTd (TA736), utility values were sourced from the CASSIOPEIA trial for the PF health state, and TA311 for the PD health state (Table 67). The PF utilities sourced from PERSEUS for this submission were higher than those used in TA763.

The utility used for the PD health state was lower in TA763 (sourced from the Van Agthoven *et al.* 2004 study used in the NICE appraisal for Bd [TA311]) compared with value used in the base case economic analysis in this submission.^{152, 176, 178} This difference is likely a reflection of the increasing availability of more efficacious and tolerable subsequent treatments for patients with relapsed/refractory MM over time, with the Van Agthoven *et al.* 2004 study conducted around 15 years before the PERSEUS trial.^{110, 178}

The utilities used in the NICE appraisal for DBTd underestimate HRQoL in patients with NDMM.² Nevertheless, a scenario analysis was conducted using these pessimistic utility values.

Table 67: Summary of utilities used in the NICE appraisal for DBTd (TA763), and explored in a scenario analysis

Treatment phases	Mean (SE)	Source
PF		
Induction	0.57 (0.009)	Utility for induction (CASSIOPEIA) ²
ASCT	0.57 (0.009)	

Treatment phases	Mean (SE)	Source
Consolidation	0.68 (0.007)	Utility for post-induction to post-consolidation response (CASSIOPEIA) ²
Maintenance	0.73 (0.005)	Utility for post-consolidation (CASSIOPEIA) ²
PD	0.69 (0.010)	Utility for second- and third-line treatment (TA311 ¹⁷³ ; sourced from Van Agthoven <i>et al.</i> 2004) ¹⁷⁸

Abbreviations: ASCT: autologous stem-cell transplant; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; NICE: National Institute for Health and Care Excellence; PF: progression-free; PD: progressed disease; SE: standard error.

3.5 Cost and healthcare resource use identification, measurement and valuation

The health economic analysis was conducted from the perspective of the NHS in England and therefore only included costs that would be incurred by the health system. Appropriate sources of unit costs, such as NHS reference costs 2023–2024, BNF and drugs and pharmaceutical eMIT costs were used for cost inputs in the model. Specifically, the following cost components were considered in the model:

- Drug acquisition and administration costs, for intervention and comparators
- Costs associated with management of AEs, for intervention and comparators
- Costs of HDT-ASCT
- Cost of concomitant medications
- Monitoring costs
- Cost of subsequent treatments
- Cost of terminal care
- Cost of MRD testing (for DBLd-DL arm only)

As part of the economic SLR conducted in patients with HDT-ASCT eligible NDMM, no studies that reported direct cost or resource data specific to the UK were identified. Full details of the SLR search strategy, study selection process and results are reported in Appendix G.

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1. Induction, consolidation, ASCT and maintenance phase

Drug acquisition costs

The dosing regimens for induction, consolidation and maintenance therapies are presented in Table 68. These were based on treatment protocols specified for the PERSEUS and CASSIOPEIA trials, with the exception that for DBTd, the dose of daratumumab was based on the SC formulation (1,800 mg fixed dose) in the economic analysis, which is now available as a result of a licence extension in June 2020, rather than the IV formulation of daratumumab used in the CASSIOPEIA trial.

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The unit and total costs per administration associated with individual therapies within the induction, consolidation and maintenance regimens included in the model are presented in Table 69 (daratumumab and bortezomib vials) and Table 70 (lenalidomide, thalidomide and dexamethasone tablets). For bortezomib, which requires BSA-based dosing, the administration cost was calculated using the mean BSA (1.73 m²) of patients in the PERSEUS trial.³² In the base case analysis, wastage was considered as it was assumed that there would be no vial sharing in clinical practice. Therefore, the number of vials required per administration was rounded up to the nearest whole integer (Table 69). The impact of wastage is expected to have a negligible impact on the base case economic analysis results, as bortezomib is the only drug where vial sharing might be considered and is common to both DBLd-DL and DBTd-L.

In the base case economic analysis presented in this submission, the cost per vial of bortezomib is based on the tender price. However, the cost of bortezomib may vary in different regions because of negotiated procurement discounts and use of generic versions of the drug.

As discussed in Section 3.2.3, the proportion of patients who remain on induction, consolidation and maintenance therapy was derived from observed TTD and, where relevant, long term extrapolations using data from PERSEUS.

Additionally, in clinical practice, patients do not always receive the full doses of their assigned treatment. Therefore, data from clinical trials may better reflect the efficacy of the dose received rather than the intended dose. To account for this, dose intensity was considered in the base case economic analysis by adjusting the drug acquisition cost in proportion to doses received in the trial (i.e., the relative dose intensity [RDI]; calculated as the average of doses per treatment cycle received, divided by doses per cycle, according to the trial design) received in the PERSEUS or CASSIOPEIA trial. As shown in Table 71, dose intensity was considered separately for each component of a combination treatment.

Concomitant medication costs

The cost of concomitant medications was also included in the model during the induction and consolidation treatment phases, based on the concomitant medications received in the PERSEUS and CASSIOPEIA trials.^{32, 151} For example, costs for prophylactic antithrombotic medicines, such as warfarin, were included in the model – these are recommended for patients receiving lenalidomide or thalidomide.^{64, 166} For patients receiving daratumumab, pre-infusion medications (antipyretic/analgesics, antihistamine and antibiotics) were included.¹ The cost of antiviral treatment for patients receiving bortezomib for the prevention of herpes zoster reactivation was also included in the model.¹

A summary of the concomitant medications used in the economic analysis, and their costs, is provided in Table 72. The proportion of patients receiving each concomitant medication during the induction phase was informed by the PERSEUS and CASSIOPEIA trials, whilst the proportions for consolidation were assumed to be the same as induction (Table 73). The total cost of concomitant medications was applied at each induction and consolidation treatment cycle depending on the proportion of patients remaining on treatment (according to TTD), along with the main treatment costs. Concomitant medications for subsequent treatments received were not included in the model.

Administration costs

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Administration of IV treatment requires an outpatient visit that may involve additional nursing and pharmacist preparation time, whilst SC treatment administration requires an outpatient visit with a specialist cancer nurse. The cost of administration for induction, consolidation, maintenance and subsequent therapies (see Section 3.5.1.2) was included in the economic analysis – these costs are summarised in Table 74.

The cost for treatments administered by SC administration (i.e., daratumumab and bortezomib) was applied for each administration. In the base case economic analysis, no additional cost was applied for oral treatment regimens (i.e., lenalidomide, thalidomide and dexamethasone). A scenario analysis was conducted in which administration costs for oral treatments was applied.

ASCT costs

The costs associated with ASCT were applied in the model for the proportion of progression-free patients modelled to receive ASCT following induction therapy (Table 75). The proportion of patients assumed to undergo ASCT following DBLd induction therapy was based on the PERSEUS trial (█████%).³² Following DBTd induction therapy, █████% of patients were assumed to undergo ASCT, based on the CASSIOPEIA trial.¹⁵¹ These proportion of transplanted patients for DBLd and DBTd are therefore considered comparable. Furthermore, following disease progression, patients under 70 years could receive a second ASCT – this was therefore considered in the model as a subsequent therapy, based on the data from the PERSEUS trial. Post-progression, █████% of patients receiving DBLd underwent a second ASCT, and the rate was assumed to be equal for DBTd.

The ASCT costs considered in this economic analysis captured the cost of stem cell mobilisation and the cost of the transplant procedure itself, and are presented in Table 75.

Table 68: Summary of intervention and comparator dosing regimens

Treatment	Treatment phase	Duration of treatment	Drugs per cycle	Source
Intervention				
DBLd	Induction	4x 4-week cycles	Daratumumab – 1,800 mg SC per week for 2 cycles, then every 2 weeks for 2 cycles	PERSEUS ¹¹⁰ RDIs presented in Table 71
			Bortezomib – 1.3 mg/m ² SC twice a week, for 2 weeks	
			Lenalidomide – 25 mg oral QD for first three weeks of each cycle	
			Dexamethasone – 40 mg oral on Days 1–4 and Days 9–12 of each cycle	
	Consolidation	2x 4-week cycles	Daratumumab – 1,800 mg SC every two weeks for 2 cycles	
			Bortezomib – 1.3 mg/m ² SC twice a week for 2 weeks	
			Lenalidomide – 25 mg oral QD for first three weeks of each cycle	
			Dexamethasone – 40 mg oral on Days 1–4 and Days 9–12 of each cycle	
DL	Maintenance	Until sustained-MRD negativity ^a	Daratumumab – 1,800 mg SC every four weeks	
		4-week cycles until disease progression or unacceptable toxicity	Lenalidomide – 10 mg oral QD, increased to 15 mg after 3 cycles ^b	
Comparator				
DBTd	Induction	4x 4-week cycles	Daratumumab – 1,800 mg SC per week for 2 cycles, then every 2 weeks for 2 cycles	CASSIOPEIA protocol (with the exception of the daratumumab dose, which is based on the SC formulation) ⁷⁵
			Bortezomib – 1.3 mg/m ² SC twice a week for 2 weeks	
			Thalidomide – 100 mg oral QD	
			Dexamethasone – Cycles 1 and 2: 40 mg oral twice a week	
			Dexamethasone – Cycles 3 and 4: 40 mg twice a week in Week 1, 20 mg twice a week Weeks 2 and 3; oral	
	Consolidation	2x 4-week cycles	Daratumumab – 1,800 mg SC every two weeks for 2 cycles	RDIs presented in Table 71
			Bortezomib – 1.3 mg/m ² SC twice a week for 2 weeks	
			Thalidomide – 100 mg oral QD	
			Dexamethasone – 20 mg oral twice a week for Weeks 1–3	

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Treatment	Treatment phase	Duration of treatment	Drugs per cycle	Source
L	Maintenance	4-week cycles until disease progression or unacceptable toxicity	Lenalidomide – 10 mg oral QD, increased to 15 mg after 3 cycles ^b	PERSEUS protocol ¹¹⁰

Footnotes: ^a Daratumumab can be discontinued for patients with a response of CR or better who have achieved MRD-negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months. After stopping daratumumab therapy, subjects with sustained MRD-negativity should restart therapy with daratumumab if there is a recurrence of MRD. As detailed in Section 3.3.1.6, it was assumed that no patients would restart daratumumab after discontinuation, based on results from the PERSEUS trial and UK clinical opinion. ^b The dose of lenalidomide is increased if well-tolerated. The economic analysis assumes the dose increases from Week 13.

Abbreviations: L: lenalidomide; QD: once daily; SC: subcutaneous; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; MRD: minimal residual disease; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone.

Table 69: Drug acquisition costs for first-line treatment (daratumumab and bortezomib)

Treatment	Dose per administration	Total dose per administration	Vial size	Cost per vial	Vials per administration	Cost per administration	Source
Daratumumab	1,800 mg	1,800 mg	1,800 mg	£4,320	1	£4,320	BNF 2025 ¹⁴
Bortezomib	1.3 mg/m ²	█ mg	3.5 mg	£55.87	1	£55.87	eMIT 2024 ¹⁰⁹

Table 70: Drug acquisition costs for first-line treatment (lenalidomide, thalidomide and dexamethasone)

Treatment	Unit size	Pack size	Cost per pack	Source
Lenalidomide	25 mg	21	£28.27	eMIT 2024 ¹⁰⁹
Thalidomide	50 mg	28	£280.62	eMIT 2024 ¹⁰⁹
Dexamethasone	2 mg	50	£2.38	eMIT 2024 ¹⁰⁹

Table 71: Summary of RDIs for induction, consolidation and maintenance treatment

Treatment	Component	RDI	Source
Induction			
DBLd	Daratumumab	█	PERSEUS ³²
	Bortezomib	█	
	Lenalidomide	█	
	Dexamethasone	█	
DBTd	Daratumumab	█	CASSIOPEIA ¹⁵¹

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Treatment	Component	RDI	Source
	Bortezomib	████	
	Thalidomide	████	
	Dexamethasone	████	
Consolidation			
DBLd	Daratumumab	████	PERSEUS ³²
	Bortezomib	████	
	Lenalidomide	████	
	Dexamethasone	████	
DBTd	Daratumumab	████	CASSIOPEIA ¹⁵¹
	Bortezomib	████	
	Thalidomide	████	
	Dexamethasone	████	
Maintenance			
DL	Daratumumab	████	PERSEUS ³²
	Lenalidomide	████	
L	Lenalidomide	████	

Abbreviations: L: lenalidomide; QD: once daily; SC: subcutaneous; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; MRD: minimal residual disease; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone.

Table 72: Concomitant medication regimens unit costs

Concomitant medication	Dosing regimen	Strength	Drug units per pack	Cost per pack	Cost per administration	Source
Thalidomide/lenalidomide (prophylaxis for thrombosis)						
Antithrombotic: warfarin	3 mg	3 mg	28	£0.40	£1.54	eMIT 2024 (DBH083, Warfarin) ¹⁰⁹
Daratumumab						
Antipyretic/analgesic: oral paracetamol; pre-infusion	825 mg	500 mg	100	£0.79	£0.01	eMIT 2024 (DDM003, Paracetamol) ¹⁰⁹

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Concomitant medication	Dosing regimen	Strength	Drug units per pack	Cost per pack	Cost per administration	Source
Antihistamine: oral/IV hydroxyzine; pre-infusion	37.5 mg	30 mg	30	£0.75	£0.03	BNF 2025 (Hydroxyzine 25mg tablets - Medreich Plc) ¹⁷⁹
Bortezomib						
Antiviral prophylaxis: oral acyclovir	400	800	35	£2.06	£0.03	eMIT 2024 (DER025, Acyclovir) ¹⁰⁹
Other						
Antibiotics: oral amoxicillin	960	500	100	£4.06	£0.08	eMIT 2024 (DEA397, Amoxicillin) ¹⁰⁹
Biphosphonate: oral alendronic acid	4	70	4	£0.26	£0.00	eMIT 2024 (DFF047, Alendronic acid) ¹⁰⁹
Antacid: omeprazole	150 mg	20	28	£0.33	£0.09	eMIT 2024 (DAI012, Omeprazole) ¹⁰⁹

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; IV: intravenous.

Table 73: Proportion of patients receiving concomitant medications during induction and consolidation therapy with DBLd or DBTd

Induction and consolidation regimen		Concomitant medication							Source
		Analgesics	Antacid	Antibiotics	Antithrombotic	Antiviral prophylaxis	Bisphosphonate	Antihistamine	
DBLd	Daratumumab	■	■	■	■	■	■	■	PERSEUS ^{32,a}
	Bortezomib	■	■	■	■	■	■	■	
	Lenalidomide	■	■	■	■	■	■	■	
	Dexamethasone	■	■	■	■	■	■	■	
DBTd	Daratumumab	■	■	■	■	■	■	■	CASSIOPEIA ^{151,a}
	Bortezomib	■	■	■	■	■	■	■	
	Thalidomide	■	■	■	■	■	■	■	
	Dexamethasone	■	■	■	■	■	■	■	

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Footnotes: ^a Rates of concomitant medication use for consolidation phase assumed equal to induction.

Abbreviations: DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone.

Table 74: Summary of drug administration costs included in the economic analysis

Drug	Administration parameter	Cost	Source
Daratumumab, bortezomib, teclistamab	Subcutaneous administration	£115.36	NHS National Schedule of Costs 2023/24; N10AF Specialist Nursing, Cancer Related, Adult, Face to face
Bortezomib	Subcutaneous administration	£115.36	
Carfilzomib, cyclophosphamide, elotuzumab, belantamab mafodotin	First IV administration	£597.91	NHS National Schedule of Costs 2023/24; SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance, Total HRG
	Subsequent IV administration	£430.23	NHS National Schedule of Costs 2023/24; SB15Z Deliver Subsequent Elements of a Chemotherapy Cycle, Total HRG

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

Table 75: ASCT costs included in the economic analysis

Description	Cost	Source
Stem cell mobilisation	£1,856.67	NHS National Schedule of Costs 2023/24; SA34Z Peripheral Blood Stem Cell Harvest, Total HRG
Transplantation	£24,356.40	NHS National Schedule of Costs 2023/24; SA26A, SA38A, SA39A, SA40Z Peripheral Blood Stem Cell Transplant; weighted average of all unit costs

Footnotes: ^a Proportion of patients undergoing initial and 2nd ASCT based on the PERSEUS trial. ^b Proportion of patients undergoing initial ASCT based on the CASSIOPEIA trial. The proportion undergoing a 2nd ASCT was assumed equal to the PERSEUS trial).

Abbreviations: ASCT: autologous stem cell transplantation; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; QD: once daily; G-CSF: granulocyte-colony stimulating factor; BNF: British National Formulary; eMIT: electronic market information tool; HRG: healthcare resource group.

3.5.1.2. Subsequent treatments

As shown in Section 1.3.5.1, several treatments have been recommended by NICE for patients with relapsed/refractory MM. To reflect that patients are expected to receive treatment following progression from induction, ASCT, consolidation and maintenance therapy, the model includes the cost of subsequent therapies across the second, third and fourth lines. In accordance with the NICE position statement on the inclusion of therapies recommended via the CDF, only those treatments that have been recommended for routine funding by NICE, and not via the CDF, have been considered as subsequent therapies.¹⁰⁷ Additionally, as noted in the 'ASCT costs' section above, and in Table 75, some patients may receive a 2nd ASCT post-progression. As such, this was also included in the base case economic analysis as a subsequent treatment. It was assumed that 2.85% of patients receiving DBLd-DL and DBTd-L would receive a 2nd ASCT post-progression, based on the PERSEUS trial data.

Distribution of subsequent treatments

Subsequent treatment costs were modelled based on subsequent treatments received by HDT-ASCT eligible patients with MM who have progressed on first-line treatment according to UK clinical expert opinion.⁴ This approach is more informative to UK decision making as opposed to modelling subsequent treatments received by patients in the international trials, as these include treatment regimens which are not routinely commissioned in the UK. Table 76, Table 77 and Table 78 present a breakdown of the subsequent treatments received by HDT-ASCT eligible patients with MM who have progressed on first-line, second-line and third-line treatments, respectively, based on UK clinical expert opinion.

Application of subsequent therapy costs

The median treatment duration of each subsequent treatment was taken from clinical trials and used to model a TTD curve, assuming an exponential distribution (i.e., constant rate of treatment discontinuation). The modelled TTD was used to calculate the proportion of patients who stop receiving treatment over time and, therefore, stop accruing treatment-related costs. These were weighted by market share. The incidence of progression in each model cycle was tracked using an aggregated PFS curve, to calculate the proportion of patients who remain progression-free over time, and would switch to a subsequent line of treatment. For the second and third treatment lines, an aggregated PFS curve was derived by generating a weighted average of the median PFS for subsequent treatments in the given line of therapy, by their respective market share, to derive an exponential curve.

Overviews of the breakdown of drug acquisition costs for the subsequent treatments are presented in Table 80 (SC/IV-administered; dosing regimens in Table 79) and Table 81 (orally-administered). Administration costs are presented in Table 74.

Table 76: Summary of second-line subsequent treatment distributions following induction, consolidation and maintenance therapy with DBLd-DL or DBTd-L

		Distribution of second-line regimen according to first-line regimen received (%)		Median treatment duration (months)	Source of median treatment duration	Median PFS (months)	Source of median PFS
		DBLd-DL	DBTd-L				
Second-line regimen	DBd	0.00	0.00	23.2	NICE (TA897) ¹⁸⁰	27.0	NICE (TA897) ¹⁸⁰
	Cad	10.00	10.00	6.6	ENDEAVOR study ¹⁸¹	22.2	ENDEAVOR study (based on mean PFS) ¹⁸¹
	CaLd	5.00	5.00	19.1	ASPIRE study ¹⁸²	29.6	ASPIRE study ¹⁸²
	SBd	5.00	5.00	21.0	Assumed equal to PFS	21.0	NICE (TA974) ¹⁰¹
	BeBd	80.00	80.00	36.6	Assumed equal to PFS	36.6	NICE (ID6212) ¹⁰⁰

Abbreviations: BeBd: belantamab mafodotin, bortezomib and dexamethasone; Cad: carfilzomib with dexamethasone; CaLd: carfilzomib, lenalidomide with dexamethasone; DBd: daratumumab, bortezomib and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone ; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone ; DL: daratumumab with lenalidomide; L: lenalidomide; NICE: National Institute for Health and Care Excellence; PFS: progression-free survival; SBd: selinexor, bortezomib and dexamethasone.

Table 77: Summary of third-line subsequent treatment distributions

		Distribution of third-line regimen according to second-line regimen received (%)					Median treatment duration (months)	Source of median treatment duration	Median PFS (months)	Source of median PFS
		DBd	Cad	CaLd	SBd	BeBd				
Third-line regimen	ILd	22.41	14.94	0.00	0.00	5.00	17.7	NICE (TA870) ¹⁸³	22.0	NICE (TA870) ¹⁸³
	SBd	28.01	28.01	24.31	0.00	50.00	13.0	Assumed equal to PFS	13.0	NICE (TA974) ¹⁰¹
	Ld	7.47	3.73	0.00	0.00	0.00	11.1	Assumed equal to PFS	11.1	NICE (TA586) ¹⁸⁴
	PanBd	20.54	31.75	56.73	81.63	20.00	12.5	Assumed equal to PFS	12.5	NICE (TA380) ¹⁸⁵

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		Distribution of third-line regimen according to second-line regimen received (%)					Median treatment duration (months)	Source of median treatment duration	Median PFS (months)	Source of median PFS
		DBd	Cad	CaLd	SBd	BeBd				
	CTd	21.57	21.57	18.96	18.37	25.00	8.7	Kwon <i>et al.</i> 2016	8.7	Kwon <i>et al.</i> 2016

Abbreviations: BeBd: belantamab mafodotin, bortezomib and dexamethasone; Cad: carfilzomib with dexamethasone; CaLd: carfilzomib, lenalidomide with dexamethasone; DBd: daratumumab, bortezomib and dexamethasone; ILd: ixazomib, lenalidomide, dexamethasone; Ld: lenalidomide with dexamethasone; NICE: National Institute for Health and Care Excellence; PanBd: panobinostat, bortezomib, dexamethasone; PFS: progression-free survival; SBd: selinexor, bortezomib and dexamethasone.

Table 78: Summary of fourth-line subsequent treatment distributions

		Distribution of fourth-line regimen according to third-line regimen received (%)				Median treatment duration (months)	Source of median treatment duration	Median PFS (months)	Source of median PFS
		ILd	SBd	Ld	PanBd				
Fourth-line regimen	Teclistamab	50.00	60.00	50.00	56.00	11.3	Assumed equal to PFS	11.3	Liu, L. & Krishnan, A. 2023 ¹⁸⁶
	Pd	20.00	26.00	20.00	24.00	4.0	Assumed equal to PFS	4.0	NICE (TA427) ¹⁸⁷
	D	20.00	8.00	20.00	16.00	3.7	Assumed equal to PFS	3.7	NICE (TA783) ¹⁸⁷
	PanBd	10.00	6.00	10.00	4.00	4.0	Assumed equal to PFS	4.0	Assumption

Abbreviations: BeBd: belantamab mafodotin, bortezomib and dexamethasone; CTd: cyclophosphamide, thalidomide and dexamethasone; D: daratumumab; ILd: ixazomib, lenalidomide, dexamethasone; Ld: lenalidomide with dexamethasone; NICE: National Institute for Health and Care Excellence; PanBd: panobinostat, bortezomib, dexamethasone; Pd: pomalidomide with dexamethasone; PFS: progression-free survival; SBd: selinexor, bortezomib and dexamethasone.

Table 79: Dosing regimens for subsequent treatments (IV/SC)

Treatment	Dose per administration	Total dose per administration	Source
Belantamab mafodotin	2.5 mg/kg	█ mg	Belantamab mafodotin SmPC
Cyclophosphamide	300 mg/m ²	█ mg	Cyclophosphamide SmPC
	350 mg/m ²	█ mg	
Carfilzomib	20 mg/m ²	█ mg	Carfilzomib SmPC

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Treatment	Dose per administration	Total dose per administration	Source
	27 mg/m ²	■ mg	
	36 mg/m ²	■ mg	
	56 mg/m ²	■ mg	
Elotuzumab	10 mg/kg	■ mg	Elotuzumab SmPC
	20 mg/kg	■ mg	
Teclistamab	0.1 mg/kg	■ mg	Teclistamab SmPC
	0.3 mg/kg	■ mg	
	1.5 mg/kg	■ mg	

Abbreviations: IV: intravenous; SC: subcutaneous; SmPC: summary of product characteristics.

Table 80: Drug acquisition costs for subsequent treatments (IV/SC)

Treatment	Vial size	Cost per vial	Source
Belantamab mafodotin	70 mg	£11,784.00	NICE (ID6212)
	100 mg	£16,848.00	
Cyclophosphamide	1000 mg	£13.11	eMIT 2024
	1000 mg	£13.11	
Carfilzomib	10 mg	£176.00	BNF 2025
	30 mg	£528.00	
	60 mg	£1,056.00	
Elotuzumab	300 mg	£1,085.00	BNF 2025
	400 mg	£1,446.00	
Teclistamab	30 mg	£775.14	BNF 2025
	153 mg	£3,952.78	

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool.

Table 81: Drug acquisition costs for subsequent treatments (oral)

Treatment	Dose per administration	Unit size	Pack size	Cost per pack	Source
Ixazomib	4 mg	4 mg	3	£6,336.00	BNF 2025
Panobinostat	20 mg	20 mg	6	£4,656.00	BNF 2025
Pomalidomide	4 mg	4 mg	21	£7,995.60	BNF 2025
Selinexor	100 mg	20 mg	20	£2,300.00	BNF 2025

Abbreviations: BNF: British National Formulary.

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 depending on whether a patient was in the PF or PD health state (Table 82). The type and frequency of monitoring visits and tests included during the PF health state (split by induction, consolidation and maintenance) was based on the CASSIOPEIA study protocol, recommendation in the ESMO clinical guideline, and those used in previous NICE appraisals for HDT-ASCT eligible NDMM.^{75, 93, 173} The type and frequency of monitoring visits and tests included during the PD health state was based on post-progression resource use in a previous NICE appraisal in the front-line MM setting.¹⁸⁸ The medical resource frequency in each health state is assumed to be the same for DBLd with DL maintenance, and DBTd with L maintenance, in alignment with the approach taken in the NICE appraisal for DBTd.²

The frequency of monitoring resource use for each health state is presented in Table 82, and an overview of the monitoring unit costs is presented in Table 83.

End-of-life costs

A terminal care cost for patients who die during the progression-free or post-progression health state was accrued as a one-off cost at the time of death. The cost applied in the model (£13,409.00) was sourced from PSSRU 2024 unit costs (Jones *et al.* 2024). It was calculated based on the costs of hospital care (including inpatient, outpatient and, accident and emergency) as well as social care (including residential/nursing and home care).¹⁸⁹

Table 82: Frequency of routine follow-up care use by health state

Item	Frequency per cycle			
	PF (induction)	PF (consolidation)	PF (maintenance)	PD
Haematologist initial visit	0.25	-	-	-
Haematologist follow-up visit	0.50	0.50	0.13	0.23
Full blood count	0.14	0.14	0.14	0.39
Urine disease evaluations (UPEP)	0.13	0.13	0.13	0.10
Liver function tests	0.10	0.10	0.10	-
Calcium	0.13	0.13	0.13	-
Serum free light chain (SFLC)	0.03	0.03	0.03	-
Serum disease evaluations (SPEP)	0.13	0.13	0.13	0.19
Source	CASSIOPEIA ⁷⁵	Assumed equal to PF (induction)	CASSIOPEIA ⁷⁵	NICE TA228; ¹⁸⁸ Picot <i>et al.</i> 2011

Abbreviations: NHS: National Health Service; PD: progressed disease; PF: progression-free; SFLC: serum free light chain; SPEP: serum disease evaluations; UPEP: urine disease evaluations.

Table 83: Unit costs for routine follow-up tests and visits

Item	Unit cost	Source
Haematologist initial visit	£296.72	NHS National Schedule of Costs 2023/24; 303; WF01B Clinical Haematology; Non-Admitted Face-to-Face Attendance, First. Includes both consultant and non-consultant led (in line with TA917) ¹²
Haematologist follow-up visit	£192.29	NHS National Schedule of Costs 2023/24; 303; WF01A Clinical Haematology; Non-Admitted Face-to-Face Attendance, Follow-up. Includes both consultant and non-consultant led (in line with TA917) ¹²
Full blood count	£3.10	NHS National Schedule of Costs 2023/24; PATH05; DAPS Haematology
UPEP	£1.53	NHS National Schedule of Costs 2023/24; PATH04; DAPS Clinical biochemistry
Liver function tests	£10.68	NHS National Schedule of Costs 2023/24; PATH04; DAPS Clinical biochemistry value multiplied by seven

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Item	Unit cost	Source
Calcium	£1.53	NHS National Schedule of Costs 2023/24; PATH04; DAPS Clinical biochemistry
SFLC	£1.53	NHS National Schedule of Costs 2023/24; PATH04; DAPS Clinical biochemistry
SPEP	£1.53	NHS National Schedule of Costs 2023/24; PATH04; DAPS Clinical biochemistry

Abbreviations: NHS: National Health Service; SFLC: serum free light chain; SPEP: serum disease evaluations; UPEP: urine disease evaluations.

3.5.3 Adverse reaction unit costs and resource use

The cost of managing AEs experienced by patients during the induction, ASCT, consolidation and maintenance treatment phases was included in the base case economic analysis. The unit costs per event were based on NHS reference costs 2023–2024 and are presented in Table 84. The proportions of patients experiencing each AE in the DBLd-DL and DBTd-L arms during the induction and consolidation treatment phases are detailed in Section 3.3.3, Table 63. The proportion of patients experiencing each AE in the DBLd-DL and DBTd-L arms during the maintenance treatment phases are detailed in Section 3.3.3, Table 64.

The total cost of AE management was £[REDACTED] and £[REDACTED] for DBLd-DL and DBTd-L, respectively, during the induction and consolidation treatment phases. The total cost of AE management was £[REDACTED] and £[REDACTED] for DBLd-DL and DBTd-L, respectively, during the maintenance phase.

Table 84: Summary of AE costs used in the base case economic analysis

AE	Unit cost	Source ^a
Neutropenia	£2,058.15	NHS National Schedule of Costs 2023/24, weighted average of SA08G-SA08J (Other Haematological or Splenic Disorders with CC score 0-6+)
Lymphopenia	£2,058.15	
Thrombocytopenia	£2,515.70	NHS National Schedule of Costs 2023/24, weighted average of SA12G-SA12K (Thrombocytopenia with CC score 0–8+)
Febrile neutropenia	£2,522.59	NHS National Schedule of Costs 2023/24, weighted average of SA35A-SA35E (Agranulocytosis with CC score 0-13+)
Stomatitis	£1,367.81	NHS National Schedule of Costs 2023/24, weighted average of CB02A-CB02F (Non-malignant, ear, nose, mouth, throat or neck disorders, with interventions (with CC score 1-4) and without interventions (with CC score 0-5+)
Peripheral sensory neuropathy	£1,263.06	NHS National Schedule of Costs 2023/24, weighted average of WH08A-WH08B (Unspecified pain with CC score 0 and 1+)
Anaemia	£1,544.29	NHS National Schedule of Costs 2023/24, weighted average of SA04H-SA04L (Iron Deficiency Anaemia with CC Score 0–14+)
Pneumonia	£2,655.55	NHS National Schedule of Costs 2023/24, weighted average of DZ11K-DZ11V (Lobar, Atypical or Viral Pneumonia, with Multiple Interventions (CC Score 0–14+), with Single Intervention (CC Score 0–13+) and without Interventions (CC Score 0–14+))
Diarrhoea	£1,798.79	NHS National Schedule of Costs 2023/24, weighted average of FD01A-FD01J (Gastrointestinal Infections with Multiple Interventions (CC Score 0–4+), and without Interventions (CC Score 0–8+))
Leukopenia	£1,887.11	NHS National Schedule of Costs 2023/24, weighted average of SA08G–SA08J: Other Haematological or Splenic Disorders, with CC Score 0–6+, nonelective long stay and short stay
Hypokalemia	£1,792.32	NHS National Schedule of Costs 2023/24, Weighted average of KC05G–KC05N: Fluid or Electrolyte Disorders, with Interventions (CC Score 0–5+) and without Interventions (CC Score 0–5+), nonelective long stay and

AE	Unit cost	Source ^a
Hypertension	£801	NHS National Schedule of Costs 2023/24, EB04Z: Hypertension, non-elective long stay and short stay

^a Non-elective long-stay and short stay.

Abbreviations: AE: adverse event; NHS: National Health Service.

3.5.4 *Miscellaneous unit costs and resource use*

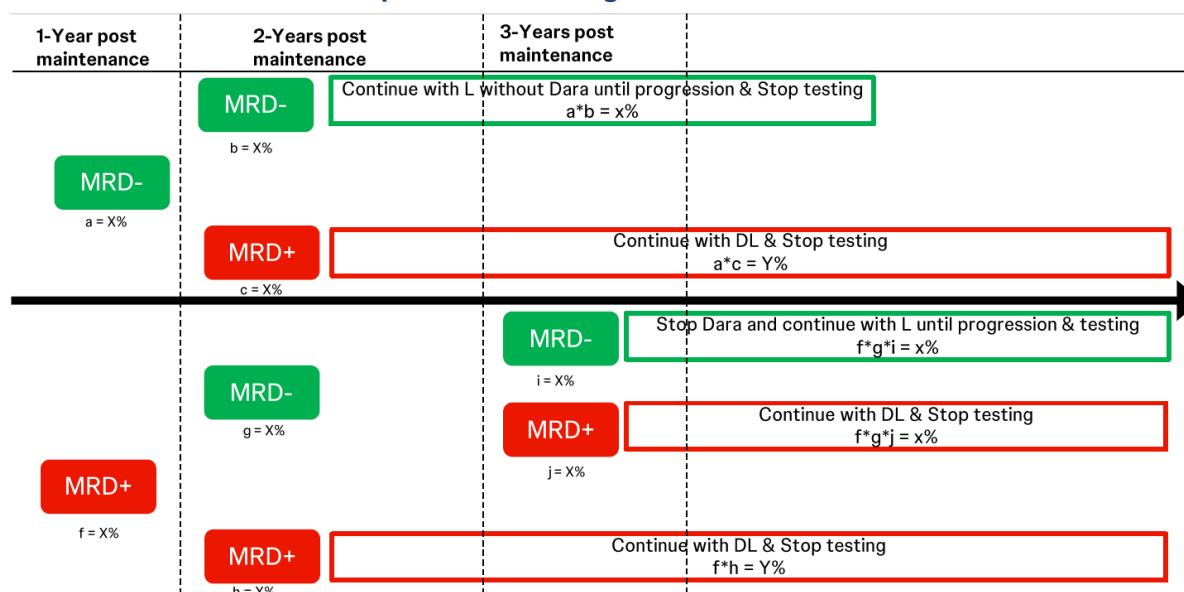
MRD testing costs

As detailed in Section 3.3.1.6, daratumumab can be discontinued for patients who have achieved MRD-negativity that is sustained for 12 months, if they have received maintenance treatment for at least 24 months, as per the stopping rule for daratumumab maintenance outlined in its licence.¹ This is illustrated in Figure 35.

To reflect the fact that MRD testing is used to inform treatment decisions for patients receiving DL maintenance, MRD testing costs were included in the economic base case analysis for patients in the DBLd-DL arm. All patients would undergo a minimum of two tests, one at 1-year post-maintenance and another at 2-years post-maintenance. These patients could subsequently discontinue daratumumab if they are MRD-negative at each of these tests. Alternatively, if patients are MRD-positive when tested at 1-year post-maintenance, they would require additional tests at 2- and 3-years post-maintenance in order to meet the required stopping criteria. Data from clinical trials of patients receiving DL maintenance indicate that the rate of conversion from MRD-positive to MRD-negative plateaus from 1-year post-maintenance, so testing beyond 3-years post-maintenance is not deemed necessary as the chance of patients achieving MRD-negativity at this point is minimal. As such, MRD testing costs were applied as one-off costs at Years 1, 2 and 3 of the maintenance phase for the proportion of patients who would undergo MRD testing (Table 85).

The unit cost of MRD testing was assumed to be £300 (£359.98 in 2024 prices), using flow cytometry, based on the NICE clonoSEQ technology briefing (2021).¹⁶⁵ This is in line with input from UK clinical experts, who indicated that MRD testing across the UK is primarily carried out using flow cytometry rather than next-generations sequencing; use of flow cytometry would be sufficient for implementation of the PERSEUS regimen in UK clinical practice and hence this cost represents the most appropriate cost to use in the model when considering the decision problem.⁴

Figure 35: Illustrative diagram for utilisation of MRD testing to inform decision-making for patients receiving DL maintenance



Footnotes: Placeholder values have been used to illustrate decision-making process with MRD-testing.

Abbreviations: MRD: minimal residual disease; DL: daratumumab with lenalidomide; L: lenalidomide.

Table 85: Proportion of patients in DBLd-DL arm receiving MRD testing during maintenance phase

Proportion of patients receiving MRD testing during maintenance phase	Year 1	Year 2	Year 3	Source
DBLd-DL	100.00%	100.00%	8.73%	PERSEUS

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; MRD: minimal residual disease. The proportion of patients requiring a third test was based on the proportion of patients who had their first negative MRD test after 2 years in the PERSEUS trial.

3.6 Severity

Based on the QALY shortfall calculator published by Schneider et al. (2022), DBLd-DL in HDT-ASCT eligible patients with NDMM does not meet the criteria for the application of a QALY modifier.¹⁹⁰

3.7 Uncertainty

Long-term uncertainty in survival estimates despite use of the latest DCO from the PERSEUS trial

Long-term extrapolation of the PFS and OS data from the PERSEUS trial were required, which is inevitably associated with uncertainty. Although data from the latest DCO (1st August 2023) were used, PFS and OS data were immature, with neither median PFS nor median OS reached in either treatment arm.

This uncertainty was mitigated by eliciting survival estimates from UK clinical experts as part of this submission, which, in line with NICE TSD 14, were incorporated to inform the modelled long-term extrapolations of survival for HDT-ASCT eligible patients with NDMM treated with DBLd-DL.

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or DBTd-L.¹⁶⁷ The selected extrapolation curves for OS, PFS and TTD for DBLd-DL as well as the proxy extrapolations generated for DBTd-L were broadly in line with the clinician estimates received, and therefore clinically plausible. The Committee preferred assumptions from TA763 for the DBTd extrapolations were also used to externally validate the survival estimates simulated in the ingoing submission for DBTd-L.² This ensured that choice of the most suitable extrapolation considered external validity.

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. This provides confidence that the high level of MRD negativity observed for DBLd-DL in PERSEUS will translate to improved long-term outcomes versus DBTd-L with the potential of functional cure for the best responders.

Direct clinical data for the relevant comparator, DBTd with L maintenance, are not available. As such, comparative efficacy estimates for this full treatment sequence were derived from multiple sources

No trials were identified reporting on the relevant comparator for the full treatment sequence, DBTd followed by L maintenance. To overcome this limitation, modelling for the comparator was taken in two stages. First, DBTd and DBLd as induction and consolidation therapies were conservatively assumed to have equal efficacy, modelled based on PERSEUS data for DBLd. The relative treatment effect of DL vs. L maintenance was derived from AURIGA and applied to the PERSEUS data for DBLd-DL arm, in order to estimate PFS and OS for DBTd-L.

As detailed in Section 3.3, the model assumes equal efficacy between DBLd and DBTd induction and consolidation therapies. Given the ITC results presented in Section 2.10, whereby DBLd has a response benefit over DBTd, in particular statistically significantly deeper responses, with patients almost two times more likely to achieve a $\geq$ VGPR response, this assumption remains highly conservative and underestimates the comparative efficacy of DBLd versus DBTd. As described in Section 1.3.2, given that achieving a deep, durable response is a strong prognostic marker for survival outcomes, the response benefit observed with DBLd would be expected to translate to longer-term survival outcomes. Indeed, this is supported by input from UK clinical experts who confirmed that DBLd is at least as effective, if not more, than DBTd as induction and consolidation therapies for HDT-ASCT eligible patients with NDMM.

3.8 Managed access proposal

This submission does not have a proposal for managed access. Whilst there is an upcoming final analysis expected for the PERSEUS trial in 2028, the collection of mature survival data is anticipated to require a significant duration of time. This is due to the strong correlation between deep sustained response and improved survival outcomes, as highlighted in Sections 1.3.1 and 2.6 and the indication being in the first-line setting.^{23, 56, 191} This means that patients who achieve deep and durable responses, as well as MRD-negativity, as is expected with DBLd-DL would therefore, remain disease progression-free for longer. As such, median PFS or OS is not anticipated to be reached at the point of the final analysis for DBLd-DL.

Indeed, this is in line with the long-term outcomes for the CASSIOPEIA trial (median follow-up of 80.1 months from first randomisation; September 2023 DCO) wherein median PFS was not reached in patients who received DBTd induction and consolidation therapies followed by daratumumab maintenance therapy.¹²⁸ Furthermore, with the availability of effective, later-line

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treatment regimens, which extend patient prognosis by ~2 years (i.e., teclistamab in the 4L+ setting), it is likely that the timeframe for the availability of DBLd-DL in the CDF would not allow for mature PFS or OS data to be collected.

Clinical expert feedback gathered from the 2025 UK advisory board highlighted the detrimental neurotoxicity associated with thalidomide and clear clinician preference to switch to lenalidomide from thalidomide during induction and consolidation phases.⁴ As such, it is critical to provide a thalidomide-free treatment option like lenalidomide for NDMM transplant-eligible patients as quickly as possible.

Although MM is incurable, DBLd-DL induces deep and durable sustained MRD-negativity in patients, with the potential of functional cure for best responders. As such, these patients would benefit from improved HRQoL due to the prolonged time spent progression-free. This would also result in lower downstream costs for the NHS incurred from expensive subsequent therapies.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of inputs used in the base case analysis is presented in Table 86.

Table 86: Summary of variables applied in the economic analysis

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission	
Model settings				
Discount rate (costs and benefits)	3.5%		Section 3.2	
Time horizon	Lifetime (40 years)			
Patient baseline characteristics				
Mean age, years	█		Section 3.2.1	
Proportion of male patients (%)	█			
Mean body weight, kg	██			
Mean BSA, m ²	█			
Survival inputs				
	PFS	OS	TTD	
DBLd-DL	Generalized gamma	Exponential	I+C: Observed TTD data M: See below	Section 3.3.1
DBTd-L (Equal efficacy assumed between DBLd-DL and DBTd-L during I+C phases [0 to 10 months])	1.89 PFS HR applied to DBLd-DL PFS curve at 10 months timepoint reflecting end of DBTd	2.00 OS HR applied to DBLd-DL OS curve at 10 months timepoint reflecting end of DBTd	I+C: Observed data M: See below	

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Variable	Value		Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	consolidation phase	consolidation phase		
TTD for maintenance phase of DBLd-DL	Discontinuation of daratumumab following achieving sustained MRD-negativity for ≥12 months and received maintenance treatment for 24 months	Discontinuation of daratumumab but did not achieve sustained MRD-negativity at latest DCO	Discontinuation of lenalidomide	
	Observed TTD data (i.e., not fixed duration)	Exponential	Exponential	
AEs for induction and consolidation phases				
	DBLd-DL	DBTd-L		Section 3.3.3
Neutropenia	████	27.60%		
Lymphopenia	████	17.00%		
Thrombocytopenia	████	11.00%		
Febrile neutropenia	████	████		
Stomatitis	████	12.70%		
Peripheral sensory neuropathy	████	8.80%		
Anaemia	████	████		
Pneumonia	████	████		
Diarrhoea	████	████		
AEs for maintenance phase				
	DL	L		Section 3.3.3
Neutropenia	████	████		
Leukopenia	████	████		
Lymphopenia	████	████		
Diarrhoea	████	████		
Hypokalemia	████	████		
Hypertension	████	████		
Pneumonia	████	████		
Utility inputs				
Health state	Mean (SE)			Section 3.4.5
Progression-free				
PF (induction)	████████			
PF (ASCT)	████████			
PF (consolidation)	████████			

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Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission		
PF (maintenance)					
Progressed disease					
PD					
Adverse event disutility					
	Utility decrement	Duration of AE (weeks)	Section 3.4.4		
Febrile neutropenia	-0.39	4.00			
Peripheral sensory neuropathy	-0.07	4.00			
Stomatitis	-0.15	4.00			
Anaemia	-0.31	25.71			
Diarrhoea	-0.10	1.71			
Lymphopenia	-0.07	2.21			
Neutropenia	-0.15	1.00			
Pneumonia	-0.19	1.00			
Thrombocytopenia	-0.31	1.00			
Leukopenia	-0.07	2.10			
Hypokalemia	-0.07	1.63			
Hypertension	-0.15	1.63			
Resource use (frequency per cycle)					
	PF (induction)	PF (consolidation)	PF (maintenance)	PD	Section 3.5.2
Haematologist initial visit	0.25	-	-	-	
Haematologist follow-up visit	0.50	0.50	0.13	0.23	
Full blood count	0.14	0.14	0.14	0.39	
UPEP	0.13	0.13	0.13	0.10	
Liver function tests	0.10	0.10	0.10	-	
Calcium	0.13	0.13	0.13	-	
SFLC	0.03	0.03	0.03	-	
SPEP	0.13	0.13	0.13	0.19	
MRD testing (DBLd-DL arm only during maintenance phase)					
Proportion of patients receiving MRD testing	Year 1	Year 2	Year 3	Section 3.5.4	
DBLd-DL	100.00%	100.00%	8.73%		
Drug acquisition costs					
Drug	Cost per pack/vial				Section 3.5.1
Daratumumab	£4,320				
Bortezomib	£55.87				
Lenalidomide	£28.27				

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Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Thalidomide	£280.62		
Dexamethasone	£2.38		
ASCT costs			
Stem cell mobilisation	£1,856.67		Section 3.5.1
Transplantation	£24,356.40		
Concomitant medications			
Concomitant medication	Cost per pack		Section 3.5.1
Antithrombotic (warfarin)	£0.40		
Antipyretic/analgesic (Paracetamol)	£0.79		
Antihistamine (hydroxyzine)	£0.75		
Antiviral (acyclovir)	£2.06		
Antibiotics (amoxicillin)	£4.06		
Biphosphonate (alendronic acid)	£0.26		
Antacid (omeprazole)	£0.33		
Administration costs			
Drug	Cost per administration		Section 3.5.1
Daratumumab	£115.36		
Bortezomib	£115.36		
Carfilzomib, cyclophosphamide, elotuzumab, belantamab mafodotin (first IV administration)	£597.91		
Carfilzomib, cyclophosphamide, elotuzumab, belantamab mafodotin (subsequent IV administration)	£430.23		
Monitoring costs			
Haematologist initial visit	£296.72		Section 3.5.1.2
Haematologist follow-up visit	£192.29		
Full blood count	£3.10		
UPEP	£1.53		
Liver function tests	£10.68		
Calcium	£1.53		
SFLC	£1.53		
SPEP	£1.53		

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Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission				
MRD testing costs							
MRD test	£359.98		Section 3.5.4				
AE costs							
Neutropenia	£2,058.15		Section 3.5.3				
Lymphopenia	£2,058.15						
Thrombocytopenia	£2,515.70						
Febrile neutropenia	£2,522.59						
Stomatitis	£1,367.81						
Peripheral sensory neuropathy	£1,263.06						
Anaemia	£1,544.29						
Pneumonia	£2,655.55						
Diarrhoea	£1,798.79						
Leukopenia	£1,887.11						
Hypokalemia	£1,792.32						
Hypertension	£801						
Subsequent treatment distribution							
	Distribution of 2L regimen according to 1L regimen received (%)			Section 3.5.1.2			
Second-line regimen	DBLd-DL		DBTd-L		Median treatment duration (months)		
DBd	0.00		0.00		23.2		
Cad	10.00		10.00		6.6		
CaLd	5.00		5.00		19.1		
SBd	5.00		5.00		21.0		
BeBd	80.00		80.00		36.6		
	Distribution of third-line regimen according to second-line regimen received (%)				Median treatment duration (months)		
Third-line regimen	DBd	Cad	CaLd			SBd	BeBd
ILd	22.41	14.94	0.00		0.00	28.57	17.7
SBd	28.01	28.01	24.31		0.00	35.71	13.0
Ld	7.47	3.73	0.00		0.00	9.52	11.1
PanBd	20.54	31.75	56.73		81.63	26.19	12.5
CTd	21.57	21.57	18.96	18.37	0.00	8.7	
	Distribution of fourth-line regimen according to third-line regimen received (%)			Median treatment duration (months)			
Fourth-line regimen	ILd	SBd	Ld		PanBd		
Teclistamab	50	60	50		56	11.3	
Pd	20	26	20	24	4.0		

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Variable	Value			Measurement of uncertainty and distribution: CI (distribution)		Reference to section in submission
D	20	8	20	16	3.7	
PanBd	10	6	10	4	4.0	

Abbreviations: BeBd: belantamab mafodotin, bortezomib and dexamethasone; Cad: carfilzomib with dexamethasone; CaLd: carfilzomib, lenalidomide with dexamethasone; D: daratumumab; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; I+C: induction and consolidation; ILd: ixazomib, lenalidomide, dexamethasone; L: lenalidomide; Ld: lenalidomide with dexamethasone; M: maintenance; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival; PD: progressed disease; PF: progression-free; QW/Q2W: once weekly/twice weekly; SBd: selinexor, bortezomib and dexamethasone; SD: stable disease; SPEP: serum protein electrophoresis; TTD: time to treatment discontinuation; UPEP: urine protein electrophoresis.

3.9.2 Assumptions

A summary of the assumptions utilised in the base case economic analysis can be found in Table 87.

Table 87: Summary of assumptions in the base case economic analysis

Parameter	Assumption	Justification
Clinical effectiveness		
Induction and consolidation therapy	Efficacy of DBLd and DBTd as induction and consolidation therapies was assumed to be equal. As such, PERSEUS trial data for DBLd were utilised for both treatment arms	Results of the induction and consolidation ITCs, presented in Section 2.10.7, indicate that DBLd improves depth of response compared with DBTd including a significant increase in the rate of $\geq$ VGPR. Whilst survival data during the induction & consolidation phases of treatment remains inherently immature, improved responses are expected to translate to long-term survival benefit for DBLd patients. Furthermore, input from UK clinical experts confirmed that DBLd is expected to be at least as effective, if not more, than DBTd. This assumption therefore represents a conservative estimate of the comparative efficacy of DBLd and DBTd during the induction and consolidation phases.
Survival models		
Approach to modelling survival	A standard PSM with three mutually exclusive health states (PF, PD and death) was chosen to inform the cost-effectiveness modelling of DBLd-DL.	The choice of a standard PSM was deemed appropriate as the modelled health states were considered to accurately reflect the natural disease course and is in line with the use and acceptance of PSMs in previous NICE appraisal in the MM setting, including that of DBTd (TA763). ^{2, 157-164}
Extrapolation of PFS and OS for DBLd-DL and DBTd-L	Exponential distribution for the extrapolation of OS. Generalized Gamma distribution for the extrapolation of PFS.	The choice of parametric distribution for the base case economic analyses was predominantly based on long-term clinical plausibility, using feedback from UK clinical experts collected as part of this appraisal, and validated based on committee-preferred survival curves in TA763. ² Due to the immaturity of PFS and OS data from the PERSEUS trial, consideration of statistical fit and visual inspection was deemed less important. This approach was validated by UK health economic experts.
Application of HR comparing L and DL maintenance therapies from AURIGA trial to derive DBTd-L extrapolation from the chosen DBLd-DL extrapolation	Relative treatment effect for L versus DL maintenance in AURIGA was applied to adjust the chosen extrapolation for patients receiving DBLd-DL in the PERSEUS trial from the onset of maintenance therapy (approximately 9.7 months from	In the absence of trials reporting data for the full treatment sequence of DBTd induction and consolidation therapies followed by L maintenance, data from the AURIGA trial comparing DL and L maintenance therapies in HDT-ASCT eligible NDDM patients were taken to derive the relative treatment effect.

Parameter	Assumption	Justification
	randomisation) to obtain a proxy survival function for DBTd-L	Given that DBLd and DBTd induction and consolidation therapies were assumed to have equal efficacy, the treatment effect observed in AURIGA was applied to the chosen DBLd-DL extrapolation from onset of maintenance to obtain a proxy extrapolation for the full treatment sequence of DBTd-L. This represented the best approach to derive survival extrapolation for DBTd-L in the absence of trial data reporting efficacy data for the full comparator treatment sequence in this submission.
Costs		
Proportion of patients receiving subsequent treatments and distribution of subsequent treatments	Subsequent treatments in the 2nd, 3rd and 4th lines were included in the model, based on treatments that had been recommended by NICE for relapsed/refractory MM. All patients were assumed to eventually progress to subsequent lines of treatment due to the inevitable relapsed/refractory nature of MM. Estimates of median progression for modelled subsequent treatments were taken from the literature. The distribution of patients across the available treatments at each line of therapy was based on estimates from clinical experts in England. To accurately reflect clinical practice, the distribution of each subsequent treatment was contingent on the treatment received in the previous line.	The costs of subsequent therapies were included in the economic analysis to reflect the reality that patients with NDMM inevitable experience relapsed and refractory disease.
Vial sharing	No vial sharing was assumed.	In the base case economic analysis, it was assumed that vials would not be shared or pooled across administrations. As such, drug wastage was assumed if the amount of drug required for a single dose was not an exact multiple of vial size.
AE costs	AE costs incurred during the induction and consolidation phases of treatment were modelled based on the proportion of patients who experienced AEs associated with induction, ASCT or consolidation in PERSEUS for the DBLd-DL arm and CASSIOPEIA for DBTd-L arm. A per-patient overall AE cost was applied as a one-time lump sum at the start of induction treatment.	The PERSEUS and CASSIOPEIA trials represented the best available evidence which captured the AEs experienced by patients receiving DBLd and DBTd induction and consolidation therapies, respectively. In the absence of data for the AEs experienced during the maintenance phase by patients receiving DBTd-L, it was deemed most appropriate to use the proportion of AEs experience by patients who received DL and

Parameter	Assumption	Justification
	AEs experienced by DL and L patients during the maintenance phase were modelled based on the proportion of patients experiencing AEs observed in AURIGA. A per-patient overall AE cost was applied as a one-time lump sum at the start of maintenance treatment.	L in the AURIGA trial for the DBLd-DL and DBTd-L treatment sequence respectively.
Utility values		
Treatment-independent HSUVs	In the base case analysis, equal HSUVs by health state were assumed for DBLd-DL and DBTd-L, derived from PERSEUS.	To align with the exact population which efficacy data were derived from, it was deemed appropriate to model utilities for DBLd-DL and DBTd-L based on the utility data from the PERSEUS trial for the base case economic analysis.
AE disutilities	To account for the impact of treatment-specific AEs, a one-off decrement in utilities was applied to the induction/ASCT/consolidation phases based on the proportion and duration of AEs experienced by patients in PERSEUS and CASSIOPEIA trials for DBLd-DL and DBTd-L, respectively. A one-off decrement in utilities was applied to the maintenance phase based on the proportion and duration of AEs experienced by patients in AURIGA receiving DL and L maintenance therapies.	Owing to the differences in safety profile between thalidomide and lenalidomide, AE disutilities were applied to account for the differences in AEs experienced by patients receiving DBLd-DL and DBTd-L. This was applied as a one-off decrement in utilities at the start of the induction treatment (for the cumulative AEs experienced during induction, ASCT and consolidation) as well as maintenance treatment (for the AEs experienced during maintenance).

Abbreviations: CDF: Cancer Drugs Fund; DL: disease level; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; HSUV: health-state utility values; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; L: lenalidomide; ITC: indirect treatment comparison.

3.10 Base-case results

Results of the economic analysis are presented in Section 3.10 below.

3.10.1 Base-case cost-comparison analysis results: induction and consolidation

The base-case cost-comparison results for DBLd versus DBTd at the [REDACTED] are presented in Table 88.

For induction and consolidation, the key change with the new DBLd treatment versus current standard of care DBTd is the substitution of the thalidomide component of the regimen with lenalidomide. The results of the ITCs presented in Section 2.10.7 provide evidence for the assumption (albeit conservative) of comparative efficacy of DBLd and DBTd as induction and consolidation therapies. The validity of this assumption was confirmed by UK clinical experts.⁴ As such, the cost-comparison analysis was conducted, as DBLd is expected to reduce the economic burden to the NHS through reduced drug acquisition and AE management costs. As shown in Table 88, there is a cost differential of [REDACTED] between DBLd and DBTd, showing DBLd to be cost-saving in terms of drug acquisition and concomitant medications for the treatment of patients with HDT-ASCT eligible NDMM during the induction and consolidation treatment phases.

As detailed in Section 3.14, the economic model overestimates the cost of AEs associated with DBLd versus DBTd. In practice, the safety profile of DBLd is expected to be substantially improved compared with DBTd, as confirmed by UK clinical expert feedback, which should translate to reduced AE management costs.

Table 88: Base-case cost-comparison analysis results (discounted daratumumab price)

Results	DBLd	DBTd	DBLd versus DBTd
Induction			
Drug acquisition	[REDACTED]	[REDACTED]	[REDACTED]
Administration	[REDACTED]	[REDACTED]	[REDACTED]
Concomitant medications	[REDACTED]	[REDACTED]	[REDACTED]
Monitoring	[REDACTED]	[REDACTED]	[REDACTED]
ASCT			
Transplant	[REDACTED]	[REDACTED]	[REDACTED]
Consolidation			
Drug acquisition	[REDACTED]	[REDACTED]	[REDACTED]
Administration	[REDACTED]	[REDACTED]	[REDACTED]
Concomitant medications	[REDACTED]	[REDACTED]	[REDACTED]
Monitoring	[REDACTED]	[REDACTED]	[REDACTED]
All treatment phases			
AEs	[REDACTED]	[REDACTED]	[REDACTED]
Overall			
Total	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: AE: adverse event; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone.

3.10.2 Base-case incremental cost-effectiveness analysis results: induction, consolidation & maintenance

The base-case deterministic and probabilistic cost-effectiveness results for DBLd-DL versus DBTd-L at the [REDACTED] are presented in Table 89 and Table 90. These results are based on list prices for all other treatments, with the exception of those with prices available in eMIT.

For maintenance phase, the only change with the new treatment versus the current standard of care is replacing lenalidomide monotherapy with daratumumab in combination with lenalidomide. The efficacy of DL versus L has been informed by the only head-to-head phase III AURIGA trial.

The deterministic base case cost-effectiveness results show that over a 40-year time horizon, the total costs associated with DBLd-DL are estimated to be [REDACTED], compared with [REDACTED] for patients receiving treatment with DBTd-L (incremental cost of [REDACTED]). The total QALYs are estimated to be higher for patients receiving DBLd-DL compared to patients receiving DBTd-L ([REDACTED] versus [REDACTED]; incremental QALYs: [REDACTED]), resulting in an ICER for DBLd-DL of £24,218 per QALY gained versus DBTd-L. INHB result at £30,000 WTP threshold was positive, indicating DBLd-DL represents a cost-effective use of NHS resources vs DBTd-L. Furthermore, DBLd-DL was also associated with positive incremental LYGs ([REDACTED] LYG) versus DBTd-L, highlighting the improvement in both quality and length of life that DBLd-L may offer to patients in this setting. These results are intuitive given the doubling of the MRD negativity conversion rate observed in AURIGA for DL versus L maintenance (DL: 60.6% vs L: 27.7%; $p < 0.0001$) and the three times higher rate of sustained MRD-negativity (17.2% vs 5.0%; $p = 0.0065$).

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-eligible 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 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, DBLd-DL was found to be a cost-effective use of NHS resources when compared to DBTd-L at a willingness-to-pay (WTP) threshold of £30,000/QALY in the deterministic analysis.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J.

Table 89: Deterministic base-case results (discounted daratumumab price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20,000	INHB at £30,000
DBLd-DL	████	████	████	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	████	████	████	████	████	████	£24,218	████	████

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; ICER, incremental cost-effectiveness ratio; INHB: incremental net health benefit; L: lenalidomide; LYG, life years gained; QALYs, quality-adjusted life years.

Table 90: Probabilistic base case results (discounted daratumumab price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
DBLd-DL	████	██	██	-	-	-	-
DBTd-L	████	██	██	████	██	██	£25,880

Abbreviations: DBLd-DL: daratumumab + bortezomib + lenalidomide + dexamethasone; DBTd-L: daratumumab + bortezomib + thalidomide + dexamethasone with lenalidomide follow-up; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; 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,

3.11 Exploring uncertainty

Parameter uncertainty in the model was assessed via 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 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. Of note, this section focuses on the comparison of DBLd-DL versus DBTd-L with the discounted daratumumab prices to model uncertainty, as this is considered most informative for decision-making.

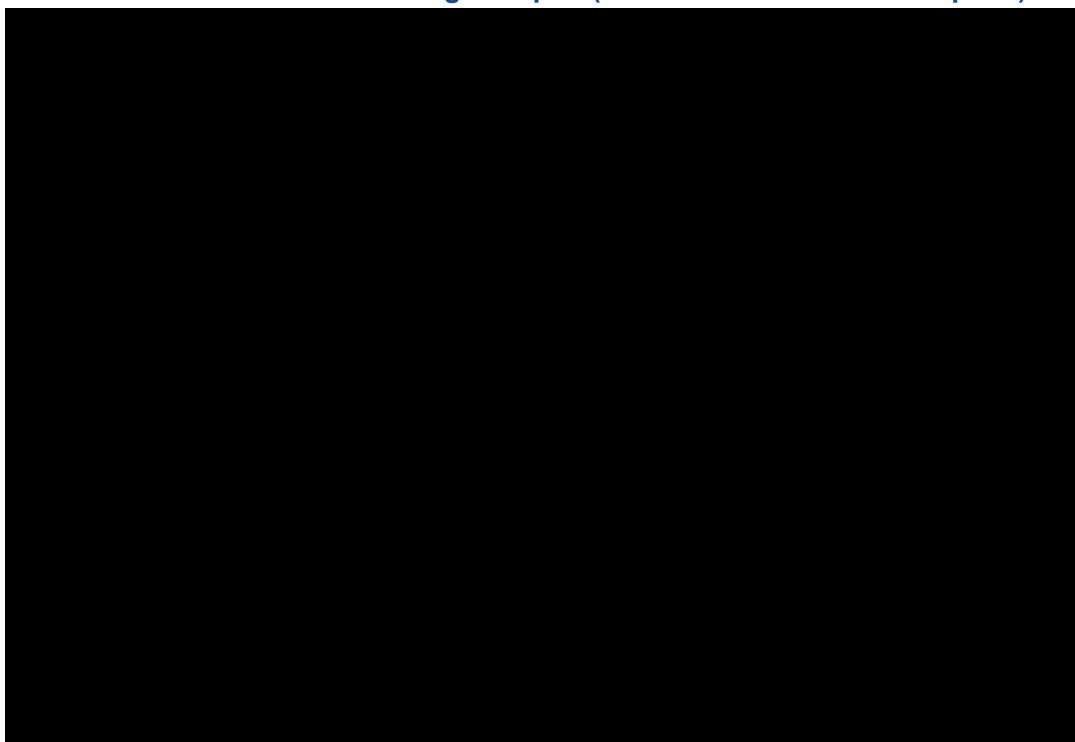
3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results were robust to those variations. A Monte-Carlo simulation with 2,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions. Estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Where no such data were available, SEs were estimated as 10% of the mean value.

PSA results with daratumumab at PAS price

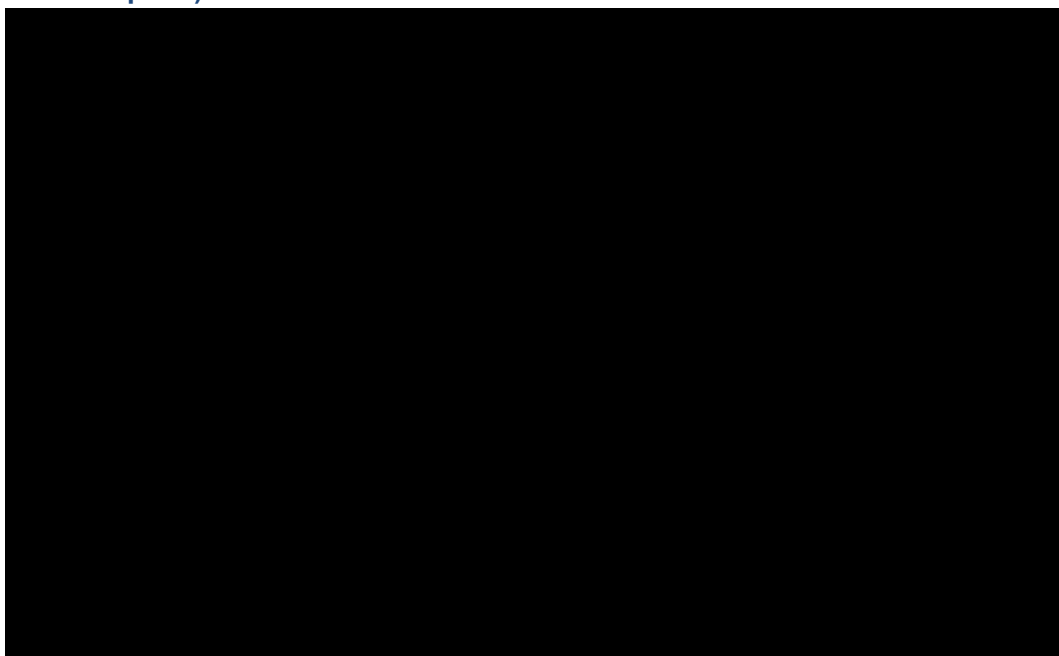
An incremental QALYs convergence plot for the PSA is presented in Figure 36 below which demonstrates that the simulations stabilised after approximately 200 iterations for the with-PAS analysis. The scatter plot shows that there is an expected spread of values, all appearing in the northeast, southeast and southwest quadrants. The results led to a mean probabilistic ICER of £25,880/QALY, demonstrating that the base case results are robust to uncertainty surrounding model inputs. This is despite the wide confidence interval for OS HR for DBTd-L. The probabilistic cost-effectiveness planes for DBLd-DL versus DBTd-L with discounted daratumumab prices is presented in Figure 37. The cost-effectiveness acceptability plots are presented in Figure 38; the PSA found the probabilities of DBLd-DL being dominant to be  and of resulting in health loss but still cost saving to be .

Figure 36: Incremental QALYs convergence plot (discounted daratumumab price)



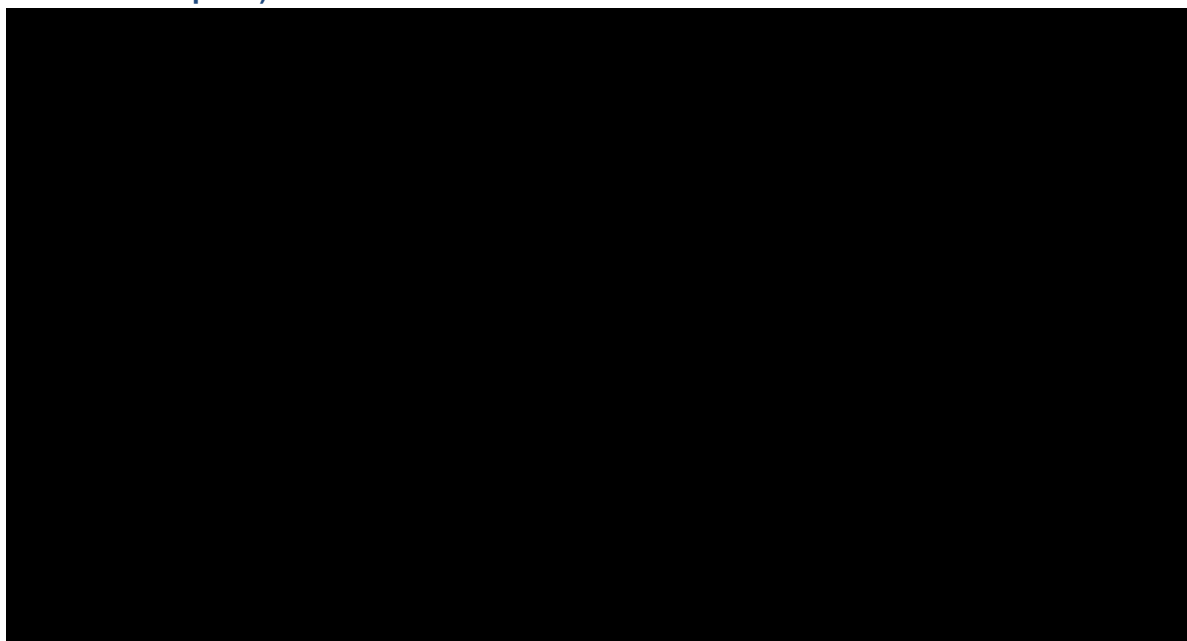
Abbreviations: PAS: patient access scheme; QALY: quality adjusted life years

Figure 37: Probabilistic cost-effectiveness plane for DBLd-DL versus DBTd-L (discounted daratumumab price)



Abbreviations: PAS: patient access scheme; QALYs: quality adjusted life years; WTP: willingness-to-pay threshold.

Figure 38: Cost-effectiveness acceptability curve for DBLd-DL versus DBTd-L (discounted daratumumab price)



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; PAS: patient access scheme; QALYs: quality adjusted life years; WTP: willingness-to-pay threshold.

3.11.2 Deterministic sensitivity analysis

DSA was undertaken to explore the impact of changing key model parameter values on the NHB. 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 $\pm 20\%$.

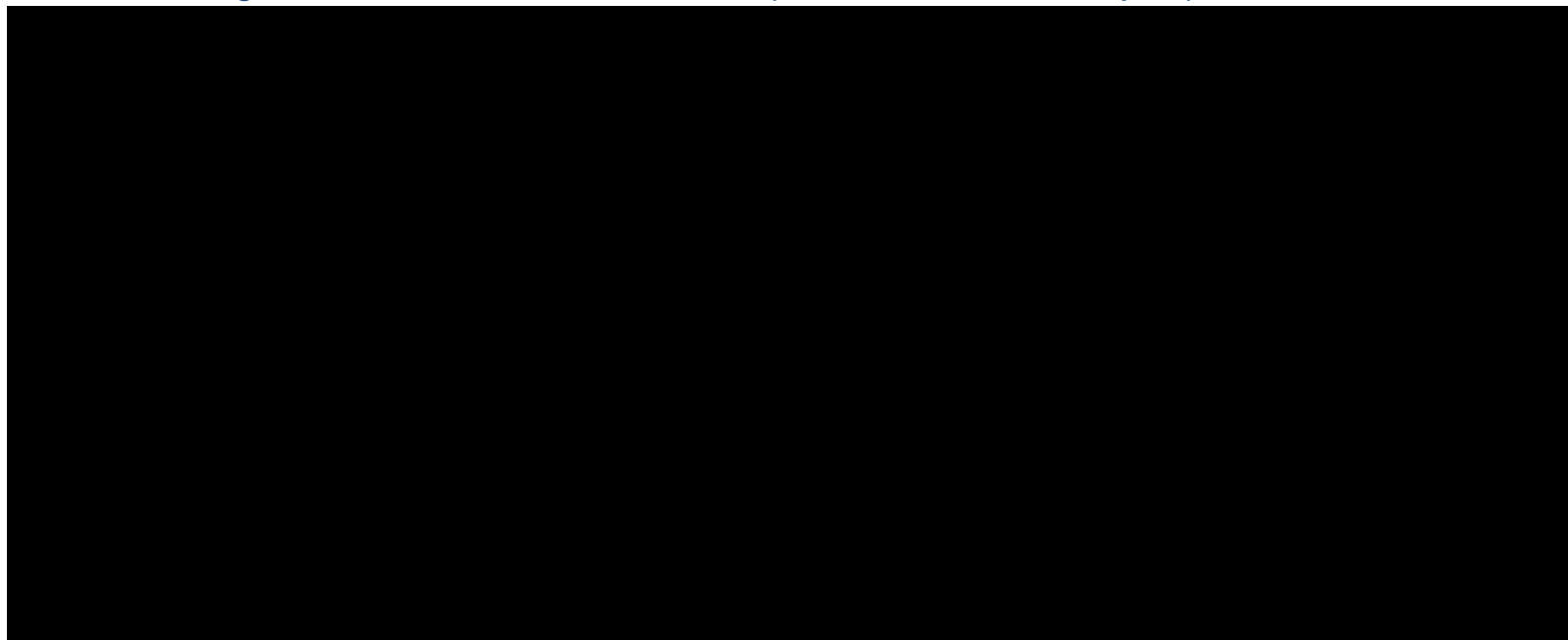
The tornado diagram showing the top 10 most influential parameters on the incremental net health benefit (INHB) in the base case economic analysis of DBLd-DL versus DBTd-L at discounted daratumumab prices is presented in Figure 39.

The incremental NHB was found to be most sensitive to DL versus L treatment effect (OS and PFS hazard ratios) and patient age at baseline. It is implausible that treatment with DBTd-L improves overall survival compared with DBLd-DL. The Phase III AURIGA study provides direct head-to-head evidence of the relative benefit of adding daratumumab to lenalidomide maintenance. Whilst J&J acknowledge issues regarding generalisability of the AURIGA study, there is evidence to suggest that the treatment effect in favour of DL maintenance would be at least maintained in a broader population of patients including those MRD-negative post consolidation, and prior exposed to anti-CD38 therapy (refer to Section 2.13). Moreover, long term survival estimates that assume an OS benefit for DBLd-DL versus DBTd-L were supported by feedback from 4 UK expert haematologists.

J&J acknowledge uncertainty of the overall survival treatment effect point estimate from AURIGA represented by the wide confidence interval spanning 1 due to small number of events observed in the trial. However, this uncertainty has been fully explored in scenario analysis which assumed equivalence between treatments (OS HR=1) – refer Section 3.11.3. This is considered highly conservative, and resulted in DBLd-DL being dominant against DBTd-L.

The average age of the patients with newly diagnosed multiple myeloma in the NHS is 59 years, which is consistent with the NCRAS mean age of 58.7 years. Therefore, assuming plausible treatment effects (PFS HR < 0.65 and OS HR < 1) and NHS practice average age of 59 years, results in positive NHB , demonstrating minimal uncertainty around parameters evaluated and that DBLd-DL remains a cost-effective treatment option versus DBTd-L.

Figure 39: DSA tornado diagram for DBLd-DL versus DBTd-L, INHB (discounted daratumumab price)



Abbreviations: ASCT: autologous stem cell transplantation; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DSA: deterministic sensitivity analysis; HR: hazard ratio; INHB: incremental net health benefit; PAS: patient access scheme; PFS: progression-free survival; OS: overall survival.

3.11.3 Scenario analysis

For the comparison of DBLd-DL versus DBTd-L, a number of scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the economic analysis. A complete list of the scenario analyses explored, along with the rationale for their selection, is presented in Table 91. The results for all scenario analyses conducted are presented in Table 92. In conclusion, the scenario analyses demonstrate that the results of the base case analysis are robust to uncertainties in the model inputs and assumptions, with the ICERs for DBLd-DL remaining below £30,000/QALY for all scenarios with the exception of a highly conservative scenario setting the OS HR equal to 1 where DBLd-DL is dominant, and a scenario exploring TTD extrapolations which was marginally above the upper end of the NICE cost-effectiveness range.

Table 91: Summary of scenario analyses

Model element	Base case	Scenario analysis	Description and Rationale
Utility values	HSUVs were assumed to be equal for both DBLd-DL and DBTd-L for each health state, and derived from the EQ-5D-5L data from PERSEUS for DBLd-DL, crosswalked to the UK EQ-5D-3L value set: PF (Induction), mean (SE): [REDACTED] PF (ASCT), mean (SE): [REDACTED] PF (Consolidation), mean (SE): [REDACTED] PF (Maintenance), mean (SE): [REDACTED] PD, mean (SE): [REDACTED]	1: Utility values informed by TA763 PF (Induction), mean (SE): 0.57 (0.009) PF (ASCT), mean (SE): 0.57 (0.009) PF (Consolidation), mean (SE): 0.68 (0.007) PF (Maintenance), mean (SE): 0.73 (0.005) PD, mean (SE): 0.69 (0.010)	In the base case analysis, HSUVs were informed based on the PERSEUS trial data. This scenario analysis explores an alternative source of utility data (i.e. CASSIOPEIA for PF health state and TA311 for PD health state). The temporal differences between the two trials and source for the PD health state should be taken into account to contextualise the observed differences in utility values, as noted in Section 3.4.5.
TTD modelling for daratumumab discontinuation for patients receiving DL maintenance	TTD for daratumumab discontinuation in patients who achieve sustained MRD-negativity for ≥12 months, after being on a minimum of 2 years of maintenance therapy, was modelled based on the observed TTD KM data in PERSEUS.	2: Fixed duration for daratumumab discontinuation for patients receiving DL maintenance	A scenario analysis was explored, where TTD for this group of patients was modelled based on a fixed duration of two years.
TTD modelling for daratumumab for patients receiving DL maintenance and who do not meet stopping criteria	TTD for discontinuation in patients who do not achieve sustained MRD-negativity status, was modelled based on the exponential survival curve	3: An alternative log-logistic curve is selected to model TTD for patients who do not achieve sustained MRD-negative status	In this scenario analysis, a pessimistic curve is explored as a scenario.
Maintenance therapy OS efficacy	Relative treatment effect derived from AURIGA trial applied to derive DBTd-L survival extrapolations based on DBLd-DL extrapolations (informed by PERSEUS ITT data)	4: Assumption of equal OS efficacy between DL and L maintenance therapies	This scenario analysis investigates the impact of assuming equal efficacy of maintenance therapies on survival by setting the OS HR to 1. Whilst implausibly conservative, this analysis is provided to fully explore parameter uncertainty

Model element	Base case	Scenario analysis	Description and Rationale
DBLd-DL efficacy source	The registrational trial, PERSEUS, which supported the label extension for daratumumab to cover the indication of relevance in the submission, informed the DBLd-DL efficacy data.	5: Pooled data (PERSEUS + GRIFFIN)	This scenario analysis pools the efficacy data for DBLd-DL from both PERSEUS and GRIFFIN trials, thereby increasing the overall patient population.
Discounting both costs and health benefits at 1.5%	Discounts costs and benefits at 3.5%	6. Assuming a discount of 1.5% for both costs and health benefits	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 (40 years) and therefore it was considered appropriate to explore discounting costs and outcomes at a 1.5% rate.

Abbreviations: 3L: 3 level; 5L: 5 level; ASCT: autologous stem cell transplant; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab, lenalidomide; EQ-5D: EuroQoL-5 Dimensions; HDT: high dose treatment; HR: hazard ratio; HSUV: health state utility value; ITT: intent-to-treat; KM: Kaplan-Meier; L: lenalidomide; MRD: minimal residual disease; NDMM: newly diagnosed multiple myeloma; PD: progressed disease; PF: progression-free; PSM: partitioned survival model; SE: standard error; TTD: time to discontinuation; .

Table 92: Summary of scenario analysis results for DBLd-DL and DBTd-L (probabilistic; discounted daratumumab price)

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£QALY)	%Δ from base case
Base Case	■	■	£24,218	-
1 Utility values from TA763	■	■	£25,933	+7.1%
2 Fixed duration for patients discontinuing daratumumab	■	■	£23,552	-2.8%

3	TTD for patients who do not achieve sustained MRD-negative status (log-logistic curve)	████	██	£30,817	+27.2
4	Maintenance therapy OS efficacy (HR=1)	████	██	Dominant	-
5	DBLd-DL efficacy source	████	██	£23,436	-3.2%
6	Discounting at 1.5%	████	██	£24,619	+1.7%

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab, lenalidomide

3.12 Subgroup analysis

As noted in Section 1, no subgroups were considered relevant to this appraisal and, as such, no subgroup analyses were included in the cost-effectiveness analysis.

3.13 Benefits not captured in the QALY calculation

Improved long-term survival benefit anticipated with DBLd-DL compared to DBTd-L which is not captured in the economic model due to the simplifying model assumption of equal efficacy for DBLd and DBTd induction and consolidation therapies

As noted in Section 3.3.1.1, equal efficacy was assumed for the modelling of the induction and consolidation treatment phases for DBLd-DL and DBTd-L. Given the response benefit of DBLd observed over DBTd in the ITC analysis results detailed in Section 2.10.7, this assumption is highly conservative and therefore, underestimates the relative treatment effect of DBLd compared to DBTd during the induction and consolidation phases. This is further supported by the increased potency of lenalidomide (a second-generation IMiD) compared to thalidomide. As such, the significantly deeper responses observed for treatment with DBLd is anticipated to translate to an overall improvement in long-term outcomes which remains underestimated in the current economic model.

Improved HRQoL associated with a thalidomide-free treatment option

The poor safety profile associated with DBTd as an induction and consolidation therapy compounds the psychological burden of the MM for patients. A high proportion of patients receiving thalidomide-containing regimens can expect to experience neurotoxicity events, and UK clinical experts confirmed that this toxicity is widely seen as a major issue across the medical community.^{4, 103} Although the disutility associated with peripheral sensory neuropathy is incorporated, the economic analysis does not capture the fear and anxiety experienced by patients knowing they may experience such AEs, as well as the impact of this psychological and clinical burden on patients friends and families. As described in detail in Section 1.3.4, substantial reduction in HRQoL is experienced by MM caregivers

Value of hope associated with the prospect of a functional cure provided by a new treatment option which achieves unprecedented deep and durable responses, including sustained MRD-negativity

As described in Section 1.3.4, MM is an incurable disease and patients with MM live in fear of relapse. As such, the aims of treatment are to achieve deep, durable responses which translate to extended PFS, whilst maintaining HRQoL. Any therapies which delay the treatment-free interval before initiation of a second-line treatment are therefore incredibly valuable to patients, highlighting the value of effective first-line therapies. This is illustrated by statements from patients with MM: *“The most difficult part of living with myeloma is knowing that relapse is inevitable... Time in remission, treatment free, is a gift.”*²

DBLd-DL offers patients a treatment option with a deep, sustained treatment response and, given the extensive body of evidence highlighting the link between achieving a deep, sustained treatment response on improved survival outcomes, these results are highly predictive of superior long-term survival outcomes with DBLd -DL.¹³⁰ The poorer response outcomes associated with subsequent treatment options used in UK clinical practice are indicative of the reduced prognosis associated with each relapse patients experience.^{192, 193}

Moreover, in the AURIGA trial which compared the treatment effect of DL and L maintenance therapies, the rate of conversion for MRD-positivity to MRD-negativity (at 10^{-5}) during maintenance therapy doubled for the DL maintenance group compared to L maintenance group (60.6% versus 27.7%; $p < 0.001$).^{31, 137} Patients receiving DL maintenance also had a significantly higher rate of sustained MRD-negativity (at 10^{-5}) of ≥ 12 months compared to L maintenance therapy (17.2% versus 5.0%; $p = 0.0065$).^{31, 137} Given MRD-negativity is a biologically plausible surrogate of improved long-term outcomes and superior results of DL maintenance over L maintenance therapy in AURIGA, the introduction of daratumumab to current lenalidomide maintenance therapy is anticipated to translate to improved PFS and OS.^{4, 51, 119-121}

Input from UK clinical experts also highlighted that approximately 20% of patients who initiate lenalidomide maintenance discontinue therapy due to tolerability issues.⁴ The addition of daratumumab means that, in clinical practice, patients will be able to receive a more effective maintenance therapy, therefore achieving a more sustained response, before the combination therapy is discontinued due to challenges with lenalidomide tolerance.

The value of hope associated with the prospect of functional cure offered by the prolonged remission and survival with improved HRQoL associated with DBLd-DL, cannot be fully captured in the economic analysis.

Value of personalised treatment regimens enabling de-escalation of maintenance treatment required by patients whilst maintaining progression-free period

With the introduction of DBLd-DL, patients would be able to discontinue daratumumab maintenance therapy once they have achieved sustained MRD negativity for at least 12 months and have been on maintenance treatment for at least 24 months.¹ Indeed, 59.0% of patients who received DBLd-DL in the PERSEUS trial had discontinued daratumumab based on this stopping rule, demonstrating the high plausibility of patients discontinuing daratumumab maintenance therapy in clinical practice.³² The introduction of DL maintenance treatment therefore, enables personalised de-escalation of maintenance therapy based on their MRD status.

3.13.1 Validation of cost-effectiveness analysis

Face validity

Model validations were performed in alignment with best practices.¹⁹⁴ The model structure, source data and statistical analysis design were reviewed by external experts, including health economic and UK clinical experts in MM.¹⁹⁵ Of note, and as discussed in Section 3.3, a thorough validation process was conducted in order to inform the derivation and selection of base case extrapolations used in the economic analysis.

Internal validity

Quality-control procedures for verification of input data and coding were performed by two peer reviewers not involved in the model development and in accordance with a pre-specified test plan. The process involved checking the intermediate calculations for references, implementation and evaluation of the face validity of predicted results. The expected functions of parameters were checked with extreme value sensitivity analysis. The process also involved checking the functionality of any build-in macro programs. Quality check was a repeatable process that produced a checklist spreadsheet indicating the specific tasks performed and their results returned. Throughout the validation process a comprehensive and rigorous quality check was fulfilled, including validating the logical structure of the model, mathematical formulas, sequences

of calculations and the values of numbers supplied as model inputs. Unexpected model behaviour, implementation and typing errors were all identified by this review.

The appropriateness of distributions used in the probabilistic analysis of the model was also checked. Following the validation, correction of any identified errors or bugs was incorporated in the revised model.

External validity

Clinical feedback was also used to validate key inputs and assumptions utilised in the model, including subsequent treatment choices and monitoring frequencies. Where possible, UK sources were used for model inputs and similar inputs and approaches to those used in prior appraisal were adopted.

3.14 Interpretation and conclusions of economic evidence

As described in Section 1.3.5.2, there remains a substantial unmet need for patients with HDT-ASCT eligible patients NDMM in the UK for a thalidomide-free induction and consolidation treatment, combined with an effective maintenance treatment that induces a deep and durable response. As confirmed by UK clinical experts, neurotoxicity events associated with thalidomide-containing induction and consolidation regimens are widely seen as a major issue across the medical community, with a strong consensus in the clinical community to move away from thalidomide-based regimens.^{4, 103} Furthermore, given the incurable nature of MM, it is critical that patients are treated with the most effective treatment available at first-line in order to induce a deep and durable response, with a view to maximising the time patients spend progression-free, their HRQoL, as well as their survival.

DBLd-DL is a novel induction, consolidation and maintenance treatment regimen that is anticipated to fulfil this unmet need, and this economic analysis demonstrates that its introduction would represent a cost-effective use of NHS resources. DBLd-DL was associated with a probabilistic ICER of £25,880 per QALY versus the relevant comparator to UK clinical practice: DBTd-L. Importantly, all scenario analyses conducted remained cost-effective when considering the cost-effectiveness threshold of £20,000–£30,000 per QALY, illustrating the robustness of the model to variation in inputs, and further supporting the cost-effectiveness of DBLd-DL to the NHS.

Strengths

The economic analysis was associated with a number of strengths. Firstly, the efficacy of the intervention was informed by the registrational, phase III RCT, PERSEUS. The results of the quality assessment of the PERSEUS trial demonstrated that it is a methodologically robust and well-reported trial, with results considered to be of low risk of bias (Section 2.5). UK clinical experts further confirmed that the PERSEUS trial is considered generalisable to patients with ASCT-eligible NDMM in UK clinical practice.⁴ Similarly, the phase III RCT, AURIGA, was used to inform the relative treatment efficacy between DL and L maintenance treatment, and was also found to be at low risk of bias in the quality assessment (Appendix M).

The economic analysis itself aligned closely with the NICE reference case, including assessing costs from an NHS and PSS perspective, using a lifetime horizon to capture all cost and QALY gains, and discounting costs and benefits at a rate of 3.5% per annum. Furthermore, the analysis aligned as far as possible with committee preferences from TA763, which assessed DBTd in

HDT-ASCT eligible NDMM, including leveraging the committee-preferred survival curves to externally validate survival extrapolations for DBTd-L.¹⁷⁶

PFS, OS, and TTD curves in the model were informed as far as possible by the Kaplan-Meier data from the relevant studies. Extrapolations for DBLd-DL and DBTd-L were also broadly in line with the clinician feedback elicited as part of the May 2025 Advisory Board, thereby confirming their clinical plausibility. Indeed, deviation from the chosen curves is likely to reduce clinical plausibility. The prognostic value of MRD negativity (level 1 evidence) and other response outcomes captured during the clinical trials indicates that the long-term outcomes predicted by the model may be viewed with confidence. There is a totality of evidence indicating that use of the PERSEUS regimen in NHS practice would result in meaningful long-term benefits to patients.

Limitations

The modelling assumption of equal efficacy assumed between DBTd and DBLd induction and consolidation therapies remains conservative given the results of the ITCs presented in Section 2.9.8.1, wherein DBLd demonstrated deeper responses compared to DBTd in terms of [REDACTED]. Given that deep, durable responses are strong prognostic markers for improved long-term outcomes, the benefit observed with DBLd would be expected to translate to improvements observed for both PFS and OS. Therefore, the modelling approach assuming equal efficacy is a conservative approach and underestimates the long-term benefits which would be observed with DBLd.

A key limitation of the economic analysis was the absence of efficacy data for the full treatment sequence of the comparator, DBTd-L. Whilst efficacy was assumed to be equal between DBTd and DBLd induction and consolidation therapies in the model, this absence necessitated identification of an alternative comparative efficacy source for DL versus L maintenance treatment. The AURIGA trial was a Phase III RCT which investigated the clinical efficacy of DL and L maintenance therapy in patients who had achieved a $\geq$ VGPR after induction therapy and ASCT.³¹ Data from the AURIGA and PERSEUS trials were combined in order to derive proxy efficacy outcomes for the full comparator treatment sequence. Specifically, the relative treatment effects for L versus DL maintenance were applied to adjust the PFS and OS extrapolations for patients receiving DBLd-DL in the PERSEUS trial from the onset of maintenance therapy (approximately 9.7 months from randomisation), to obtain a proxy survival function for DBTd-L. This approach made best use of available randomised data for DL and L maintenance treatment.

The detrimental effects of neurotoxicity associated with thalidomide-based regimens cannot be understated. Whilst the incidence of peripheral sensory neuropathy observed in the CASSIOPEIA trial is representative of the neurotoxicities expected with thalidomide-based treatments, the Company acknowledge that overall AE costs in the cost-effective analysis for DBLd-DL are higher than that of DBTd-L (£[REDACTED] versus £[REDACTED]). This is an inherent limitation due to the differences in the data sources used to inform AE rates for DBLd-DL and DBTd-L, resulting in an underestimate of the “true” economic impact of thalidomide-containing regimens. The reasons for higher AE management costs for DBLd compared to DBTd during induction and consolidation phases can be attributed to the following reasons. Firstly, the patient population included in the CASSIOPEIA trial is considered fitter than that of the PERSEUS trial. Specifically, CASSIOPEIA recruited patients aged up to 65 years only, whilst PERSEUS included patients aged up to 70 years (Section 2.10). This may have led the PERSEUS population having a greater susceptibility to adverse events in general. However, UK clinical experts confirmed their expectation that lenalidomide-based regimens are expected to be substantially better tolerated

than thalidomide-containing regimens in real-world practice. This negative cost differential for AEs for DBLd-DL vs DBTd-L in the analysis is therefore considered to be an anomaly, but is nevertheless conservative.

Conclusions

This cost-effectiveness analysis demonstrates that DBLd-DL meets the cost-effectiveness threshold, and therefore represents value for money for the NHS versus existing standard of care, DBTd-L. A positive NICE recommendation for this novel induction, consolidation and maintenance regimen will prevent the need for patients to be treated with poorly tolerated, thalidomide-containing regimens that pose a substantial burden on patients, their families and the healthcare system. Moreover, the introduction of daratumumab-lenalidomide maintenance therapy would facilitate personalisation of maintenance regimens by allowing patient to de-escalate their treatment if they achieve sustained MRD-negativity for ≥ 12 months and have been on maintenance therapy for ≥ 24 months.

DBLd-DL further induces deep and durable sustained MRD-negativity in patients, with the hope of functional cure for best responders whilst enabling de-escalation of maintenance therapy. As such, these patients would benefit from improved HRQoL due to the extended time spent progression-free as well as prolonged overall survival, enabling patient to spend more time with loved ones. Additionally, a prolonged response to first-line treatment will result in lower downstream costs for the NHS incurred from cycling through expensive subsequent therapies. In conclusion, DBLd-DL is anticipated to fulfil the substantial unmet need for an highly effective, tolerable first-line treatment for NDMM transplant-eligible patients, whilst representing a cost-effective use of NHS resources.

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Single technology appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is suitable [ID6249]

Summary of Information for Patients (SIP)

July 2025

File name	Version	Contains confidential information	Date
ID6249_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) as induction and consolidation therapy followed by daratumumab and lenalidomide (DL, commonly also referred to as DR) maintenance for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible 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:

In November 2024, the Medicines and Healthcare Products Regulatory Agency (MHRA) granted marketing authorisation for daratumumab (Darzalex®) in combination with lenalidomide, bortezomib, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. This approval was achieved through the International Recognition Procedure.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 Innovative Medicine (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}

MM 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

Approximately 6,200 new MM cases were recorded in the UK from 2017–2019, accounting for just 2% of all new cancer cases.⁷ However, over the last decade, MM incidence rates have increased by approximately 15% 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.⁷ Specifically, projections indicate that, on average, there will be approximately 8,300 new cases of myeloma annually in the UK by 2038–2040.⁷

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.⁷ 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.^{8, 9}

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.¹⁰

Patients with MM face a heavy burden of health issues, often dealing with ongoing or repeated infections, tiredness and severe bone pain.^{10, 11} 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.¹²

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.^{13, 14} Additionally, 37% of patients expressed worries about their future health, 34% often thought about their disease, and 21% were afraid of dying.¹³ In the UK, 27.4% of MM patients showed signs of anxiety, and 25.2% had symptoms of depression.¹⁵

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.¹⁶

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.¹⁶ 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.^{16, 17}

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:¹⁸⁻²⁰

- 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.¹³ 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.^{13, 21} 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.¹³ Patients who are diagnosed later in life tend to have a much worse quality of life compared to those who are diagnosed early.¹³

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.

In the current NICE treatment guidelines for MM (NG35), patients with newly diagnosed multiple myeloma (NDMM) are initially assessed for suitability for intensive treatment (i.e., High dose therapy following autologous stem cell transplantation (HDT-ASCT)) according to factors such as age, frailty and performance status.^{22, 23} A brief overview of the treatment pathway for transplant eligible patients is described below:

Induction therapy

Prior to receiving stem cell transplant patients receive induction therapy to reduce the number of malignant plasma cells in the bone marrow and achieve some form of remission.²⁴ There are currently four induction therapies recommended by NICE for patients with previously untreated MM who are eligible for ASCT; these include bortezomib, either in combination with dexamethasone (Bd) or with thalidomide and dexamethasone (BTd), and daratumumab in combination with bortezomib, thalidomide and dexamethasone (DBTd).²⁵ Bortezomib with cyclophosphamide and dexamethasone (BCd) has not been assessed by NICE but is occasionally used off-label as an induction therapy.²⁵

HDT-ASCT, also commonly referred as stem cell transplantation

Stem cell transplantation is an intensive treatment option and involves giving high doses of chemotherapy (typically melphalan) to kill the myeloma cells and then infusing stem cells back into the patient, allowing the bone marrow to recover.^{22, 26}

Consolidation therapy

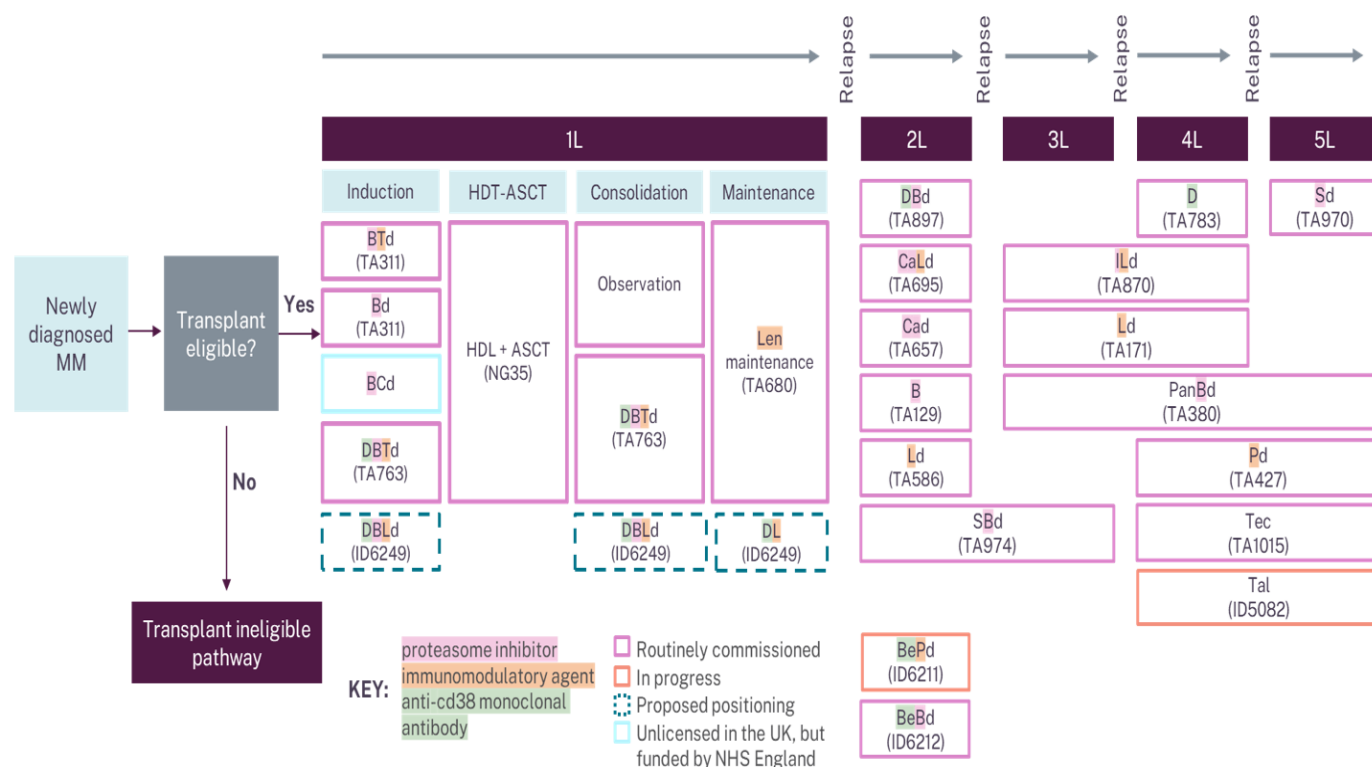
Following transplant, consolidation therapy is typically given for a short duration to further deepen response and provide long-term disease control.²⁷ The only recommended consolidation therapy in UK clinical practice is DBTd.^{23, 28}

Maintenance therapy

Following completion of consolidation therapy, patients receive long-term maintenance therapy with lenalidomide to suppress residual disease, with the aim of extending the duration of response and ultimately survival.²⁹ Lenalidomide is the current standard of care maintenance treatment in the UK: according to clinical experts in a recent advisory board, this treatment is given to 95% of patients.³⁰

The current clinical pathway of care for patients with NDMM in the UK, along with the proposed positioning of DBLd followed by DL (here after referred as DBLd-DL), is provided in Figure 1.

Figure 1: Current treatment pathway for MM in the UK and proposed positioning of DBLd-DL



Abbreviations: 1/2/3/4L/5L: 1st/2nd/3rd/4th/5th line; ASCT: autologous stem cell transplantation; BCd: bortezomib, cyclophosphamide and dexamethasone; Bd: bortezomib and dexamethasone; BePd: belantamab mafodotin, pomalidomide and dexamethasone; BeBd: Belantamab mafodotin, bortezomib and dexamethasone; BTd: bortezomib, thalidomide and dexamethasone; Cad: carfilzomib and dexamethasone; CaLd: carfilzomib, lenalidomide and dexamethasone; CD38: cluster of differentiation 38; D: daratumumab; DBd: daratumumab, bortezomib and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; Elran: elranatamab; HDT: high dose therapy; ILd: ixazomib, lenalidomide and dexamethasone; IsaPd: isatuximab, pomalidomide, dexamethasone; Ld: lenalidomide and dexamethasone; Len: lenalidomide; MM: Multiple Myeloma; NHS: National Health Service; PanBd: panobinostat, bortezomib and dexamethasone; Pd: pomalidomide and dexamethasone; RRMM: relapsed/refractory multiple myeloma; SBd: selinexor, bortezomib and dexamethasone; Sd: selinexor and dexamethasone; TA: technical appraisal; Tal: talquetamab; Tec: teclistamab; UK: United Kingdom.

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.³¹ 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.³¹

Key findings from European studies on treatment valuation

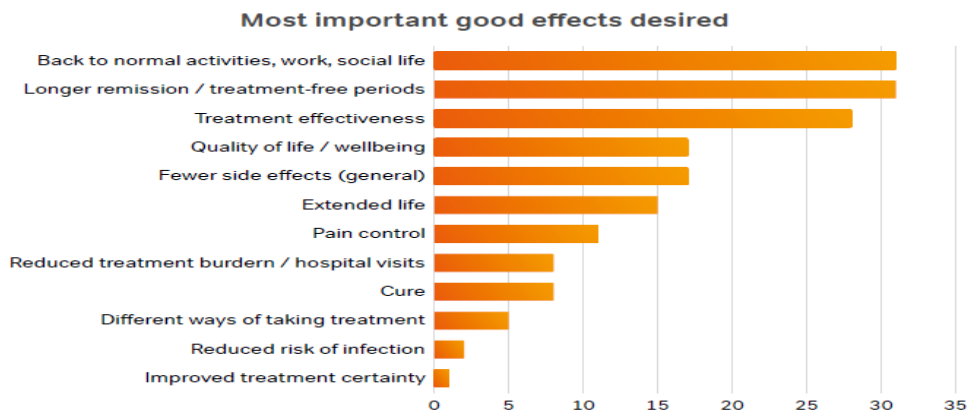
Another recent European study looking at patients with newly diagnosed multiple myeloma suggested that:³²

- 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, where patients may struggle with their memory, attention or speech, affecting their everyday lives

NICE survey insights on patient considerations

A survey carried out by the National Institute of Health and Care Excellence (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):

Figure 2: Treatment effects most desired by MM patients



Source: Myeloma UK (2019).³³

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.³³

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. ³⁴

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.³⁴

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 correctly, often producing abnormal proteins that cause MM. By binding to CD38, daratumumab helps the body’s immune system recognise and attack the harmful MM cells, aiding their destruction.¹⁸⁻²⁰

In the treatment relevant to this appraisal, daratumumab is combined with bortezomib, lenalidomide and dexamethasone (during induction and consolidation) and with lenalidomide (during maintenance). The key benefits of the introduction of DBLd-DL as a treatment option for newly diagnosed transplant eligible MM patients can be broadly divided by treatment phase:

DBLd during induction and consolidation treatment phase:

1. The current standard of care, DBTd, is a thalidomide-based treatment regimen associated with side effects including drowsiness, constipation and peripheral neuropathy which add to the already high disease burden

experienced by MM patients.³⁵ By contrast, DBLd is a thalidomide-free regimen that can provide patients the opportunity to receive effective treatment, whilst minimising the negative impact of thalidomide on their quality of life due to a potentially improved side effect profile associated with lenalidomide.

2. As a second-generation immunomodulatory drug (IMiD), lenalidomide-based regimens are associated with a more tolerable safety profile than thalidomide-based induction and consolidation options.^{36, 37} As such, DBLd could offer patients an effective induction and consolidation therapy without the detrimental impact of thalidomide on their health related quality of life.

In summary, if recommended, DBLd-DL will address the significant unmet need as a potentially more tolerable induction and consolidation therapy, minimising toxicities associated with the current thalidomide-based standard of care and alleviating associated health related quality of life burden.

DL maintenance therapy:

1. DL work well together to destroy more MM cells than either drug could on its own. When combined, these two treatments enhance each other's effects, making them more effective in fighting the cancer.^{38, 39} Therefore, the addition of daratumumab to lenalidomide maintenance therapy helps to continuously suppress minimal residual disease (MRD) to prolong response duration, delay disease relapse and extend progression free survival (PFS). This would extend the duration patients continue to receive maintenance therapy whilst remaining disease progression-free. More details regarding MRD and PFS are provided in Section 3d (current clinical trials)
2. DL maintenance is given for a minimum of 2-years with patients who achieve 12-months sustained MRD-negativity able to stop daratumumab (refer to Section 3c, Administration and dosing). This personalised approach to maintenance treatment ensures optimised drug exposure; patients that achieve deep, durable responses are able to benefit from treatment de-escalation when they receive oral lenalidomide monotherapy, thus avoiding the need to travel into hospital.
3. DL combination serves as an effective maintenance therapy that can slow the progression of the disease, helping MM patients to live longer and feel better during their treatment journey. By delaying disease progression, patients will spend longer in a good health state and potentially avoid the negative psychological impact and emotional burden associated with repeat cycles of relapse and remission.

The introduction of DL maintenance therapy would induce deeper and more durable responses including sustained MRD-negativity, with an option for patients to even discontinue daratumumab maintenance. This would translate into delayed disease progression, and extension of the period patients remain disease progression-free.

The summary of product characteristics (SMPC) for the treatment is currently not available.

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, Daratumumab is meant to be used along with other medicines. Here's a breakdown of each of the drugs involved:

Daratumumab (D)

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. It is administered during induction, consolidation and maintenance.¹⁸

Bortezomib (B)

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. It is administered during induction and consolidation.¹⁸

Lenalidomide (L)

Lenalidomide acts on the immune system to target MM, specifically, by enhancing the activity of anti-tumour T-cell and natural killer cell responses that help to eliminate MM cells. It also exerts a direct anti-proliferative effect on MM cells, whilst indirectly impairing their growth by blocking the formation of new blood vessels.^{40, 41} Furthermore, the immune-modifying effects of lenalidomide help to increase the activity of daratumumab when used in combination. Overall, by disrupting the tumour microenvironment and enhancing immune responses, lenalidomide supports the maintenance of durable treatment responses.⁴²

Dexamethasone (d)

Dexamethasone is a steroid, which helps control the immune response by reducing inflammation and lowering blood pressure, and is commonly used alongside cancer drugs. It is administered only during induction and consolidation.^{18 43}

MM can have a lot of different types of cancer cells (called clonal heterogeneity). This variety can make it harder to treat the disease because some of the cancer cells may not be affected by a single treatment.²³ By administering DBLd-DL, it can effectively target and eliminate more of the harmful cancer cells. This combination allows for a stronger overall treatment without adding serious side effects to those that might come from each drug individually.^{44, 45}

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?

Patients are given daratumumab as an injection under the skin by a trained healthcare professional in a hospital. The maintenance treatment with DL is given until the patient meets the following criteria: 1) received maintenance for at least 24-months ; 2) achieved sustained MRD negativity for 12-months.

Following which there could be two options: 1) patients stop daratumumab treatment if MM could not be found by a bone marrow biopsy (MRD negative) for a minimum 12-months apart and continue with L; 2) patients continue DL treatment if multiple myeloma was still present (MRD positive) or MRD negativity is not sustained. Patients continue maintenance treatment their until multiple myeloma gets worse or the treatment is no longer tolerable. Below is the dosing schedule for DBLd-DL:

Table 2: Daratumumab dosing schedule in combination with bortezomib, lenalidomide, and dexamethasone

Daratumumab as an injection - Dosage: 1800mg - Schedule: ➤ Induction (Cycles 1-2): once a week ➤ Induction (Cycles 3-4): every 2 weeks ➤ Consolidation (2 x 4 week Cycle): injected every 2 weeks for both the Cycles ➤ Maintenance: 1,800 mg every 4 weeks on Day 1 Daratumumab maintenance treatment is to be administered until disease progression. Daratumumab can, however, be discontinued for patients who have achieved MRD-negativity that is	Bortezomib as an injection - Dosage: 1.3mg/m² (this means the amount depends on the patient's body size) - Schedule: ➤ Induction and consolidation: Injected twice a week on days 1, 4, 8, and 11, and then stopped

sustained for 12 months, if they have been treated on maintenance for at least 24 months	
Lenalidomide as a tablet - Dosage: 25mg (1 tablet) during Induction and consolidation and 10mg (1 tablet) during maintenance - Schedule: ➤ Induction and consolidation: taken daily from days 1 through 21 ➤ Maintenance: on days 1 to 28 of each 28-day cycle, until disease progression or unacceptable toxicity	Dexamethasone as a tablet or an injection - Dosage: 40 mg - Schedule ➤ Induction and consolidation: days 1 through 4 and Days 9–12 of each Cycle

Impact on patients and caregivers
Caregivers may need to help patients get to and from the hospital for their daratumumab treatments.

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.

PERSEUS

The PERSEUS clinical trial assessed if the combination treatment of DBLd-DL was better at delaying the time before patients' MM got worse, or patients died than in the comparator arm of BLd-L in patients with newly diagnosed multiple myeloma who were eligible to receive autologous stem cell transplant (clinical trial number: NCT03710603). This ongoing international Phase 3 trial involves patients from 115 study centres in 13 locations across Europe and Australia. A total of 709 transplant-eligible patients with newly diagnosed MM were included in the PERSEUS trial.⁴⁵

To participate in the trial, patients needed to be aged between 18 to 70 years, have newly diagnosed MM, an Eastern Cooperative Oncology Group performance score of 0-2 (indicating their health status), and be eligible for a stem cell transplant.⁴⁵ Further details can be found on the clinical trial website (link: <https://www.clinicaltrials.gov/study/NCT03710603>).

The main goal of the study (primary end point) was to measure 'progression-free survival' (PFS) i.e. to measure the length of time from when a patient was randomised to a treatment to when their multiple myeloma got worse (progressed) or they died. Other important objectives (key secondary end points) of the trial included:

- Minimal residual disease negativity (MRD negative): it measures if a patient has any remaining (or residual) multiple myeloma cancer cells in the bone marrow during or after treatment. Patients were MRD negative if no multiple myeloma cells were detected in a sample of 100,000 healthy cells (called the 10^{-5} threshold (10^{-5})).⁴⁶ Achieving MRD negativity is associated with better treatment outcomes^{47, 48}
- Sustained MRD negativity rate: checking how many patients maintained an MRD negative status (no detectable disease) at different timepoints i.e. patient has no sign of MM cells at two back-to-back tests (at least 12 months apart), with no positive MRD result (presence of multiple myeloma) in between⁴⁶
- Overall survival rates: tracking how long patients lived overall during the trial⁴⁶
- Overall response rate (partial response or better): finding out what percentage of patients showed at least some improvement in their condition during or after treatment⁴⁶

GRIFFIN

There is one more trial investigating DBLd-DL in patients who are newly diagnosed and eligible for a transplant, known as the GRIFFIN trial. This non registrational Phase 2 trial compares DBLd-DL to BLd-L, although there are notable differences with PERSEUS in terms of study endpoints and dosing schedule.⁴⁹

AURIGA

The AURIGA clinical trial directly compared DL maintenance with L maintenance alone after stem cell transplant; a comparison very relevant to the current treatment pathway in the UK. The primary endpoint of this study was the proportion of patients who achieved MRD-negative status (to a certain threshold termed “ 10^{-5} ”) by 12-months after the start of maintenance treatment and before their myeloma got worse (progressed) or received subsequent therapy. Whilst patients in this study had not yet received daratumumab (or other treatments of the same class) and were MRD-positive after transplant, it provides important insights regarding the clinical efficacy of adding daratumumab to current UK standard of care maintenance therapy.⁵⁰

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.

There is no direct head-to-head evidence comparing DBLd-DL against current UK standard of care (DBTd-L). In addition, no studies have investigated the treatment sequence DBTd-L to inform an indirect treatment comparison against DBLd-DL. Instead, J&J has made the best use of available data to consider how well the new treatment works relative to existing standard of care for induction and consolidation (I&C) and maintenance (M) separately.

Induction & Consolidation (I&C)

Indirect treatment comparison (ITC) is a method used in healthcare research to compare how effective different treatments are, especially when there are no direct studies comparing them. It allows researchers to analyse existing data to make good comparisons between treatments. This can help healthcare providers make informed decisions about which treatments may work best for patients.

J&J used patient-level data from the PERSEUS and CASSIOPEIA trials to perform an ITC of DBLd versus the UK relevant standard of care, DBTd. CASSIOPEIA was a phase III trial investigating DBTd versus BTd before and after transplant. The primary endpoint for the I&C phase of the trial was the proportion of patients who achieved a stringent complete response (sCR) after consolidation.⁵¹ sCR means that the MM patient has achieved a very high level of remission where the myeloma/cancer is not completely gone, but the tests confirm that there are no traces of it, under very strict criteria.

After statistical adjustment to ensure comparability of the data from each study, results show that treatment with DBLd leads to a statistically significant higher rates of very good partial response or better ($\geq$ VGPR), with comparable overall response (ORR) and MRD-negativity rates vs. DBTd. No statistically significant differences were observed for either PFS or OS which was expected given the length of the study data available (median follow-up ~10-months). Overall, these results show that DBLd helps to achieve deeper responses and is at least as effective as DBTd as an I&C treatment.

Maintenance

Neither the PERSEUS nor GRIFFIN studies were designed to study the contribution of DL maintenance therapy to the main (primary) or secondary endpoints in isolation from the treatment effect of DBLd during I&C. Therefore, as noted above in Section 3d, results from the AURIGA study were used. The AURIGA trial investigated the clinical efficacy of adding daratumumab to lenalidomide vs lenalidomide alone during the maintenance phase.

In summary, results from AURIGA show that the addition of daratumumab to standard of care lenalidomide maintenance resulted in improved rates of MRD-negative conversion (from MRD-positive), deeper responses, and improved PFS rates.⁵⁰ These results therefore support the addition of daratumumab to standard of care lenalidomide maintenance for stem cell transplant eligible NDMM patients.

- Results from AURIGA show that the proportion of patients converting from MRD-positive to MRD-negative status by 12-months from the start of maintenance was statistically significantly higher for DL than L monotherapy

- At median follow-up of 32.3 months, DL achieved a higher overall MRD-negative (10^{-5}) conversion rate and greater Complete Response rate
- PFS also favoured DL versus L representing a 47% reduction in the risk of disease progression or death.⁵⁰

Some summary statistics are displayed in Table 3, below:

Table 3: Results from the AURIGA trial

Measure	Treatment Favoured (DL or L)	Statistical Description (DL vs. L)
Patients converting from MRD-positive to MRD-negative status by 12-months from the start of maintenance	DL	50.5% vs 18.8%; odds ratio [OR]: 4.51; 95% confidence interval [CI]: 2.37-8.57; $P < 0.0001$
MRD-negative (10^{-5}) conversion rate at median length follow up 32.3 months	DL	60.6% vs 27.7%; OR, 4.12; 95% CI, 2.26-7.52; $P < .0001$
Complete response rate or better at median length follow up 32.3 months	DL	75.8% vs 61.4%; OR, 2.00; 95% CI, 1.08-3.69; $P = .0255$
PFS	DL	Hazard ratio of 0.53 (95% CI, 0.29-0.97)

As noted above in Section 3d, patients in AURIGA were MRD-positive following their transplant and had not yet received daratumumab (or a treatment of the same class as daratumumab) which is not fully reflective of what normally occurs in UK clinical practice. AURIGA is, however, the best available data to understand the clinical effectiveness of maintenance treatment with DL vs L.

There is evidence to suggest that the relative benefit of adding daratumumab to lenalidomide maintenance is at least maintained for patients who have received DBLd I&C treatment, and those that attain MRD-negative status post consolidation. For example, with regards to I&C daratumumab use, data from the CASSIOPEIA trial shows patients that received daratumumab (as DBTd) during I&C and maintenance experienced comparable outcomes to those who did not receive it during I&C.

Data from AURIGA also shows a diminished treatment effect for the non-sustained MRD-negative subgroup for both PFS and OS and provides indirect evidence that the treatment effect of DL versus L is likely to be stronger in patients that respond well to treatment, including those that are MRD-negative post consolidation.

In the AURIGA study, nearly 10% of patients in each treatment arm had “unknown” cytogenetic risk at the start of the study. There were some differences in risk factors between patients in the two treatment arms. However, any impact of this is likely to make study results look less favourable for DL maintenance than they might otherwise do; underscoring the benefit of DL versus L maintenance for ASCT-eligible NDMM patients.^{46, 52} For further analysis and discussion regarding the attempt to indirectly compare DBLd-DL versus the UK relevant standard of care (DBTd-L), please refer to Section 2 of Company Submission.

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 PERSEUS trial (amongst others) to gather information on any symptoms experienced by patients, their physical and emotional wellbeing and the impact of their disease on social interactions.^{46, 45} Such outcomes are sometimes described in terms of Health Related Quality of Life (HRQoL).

During induction, consolidation and maintenance, HRQoL was measured using 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), European Quality of Life 5-Dimension 5-Levels (a general health questionnaire with 5 dimensions and 5 levels per Dimension) and a visual analogue scale. The results indicated a greater improvement in HRQoL and physical functioning, as well as reductions in symptoms with DBLd-DL compared BLd-L. ⁴⁶

Overall, DBLd-DL treatment can lead to lasting improvements in patients' overall quality of life, MM symptoms, and daily functioning. With these positive results, DBLd-DL should be considered as a new standard treatment option for transplant-eligible patients with newly diagnosed MM. More details regarding quality of life are presented in Section 2 of the Company Submission.

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. Results are provided below by treatment phase:

Induction and consolidation:

The analysis of Grade 3/4 adverse events (AEs) reveals distinct variances between the DBLd and DBTd treatment groups in the PERSEUS and CASSIOPEIA studies. Neutropenia stands out as a significant adverse event, demonstrating a heightened risk for patients in the DBLd cohort. Conversely, lymphopenia appears to be more prevalent among those receiving DBTd treatment, indicating differing safety profiles between the therapies. Additional AEs such as thrombocytopenia, febrile neutropenia, and stomatitis are also more frequently associated with the DBLd group.

Maintenance:

During the maintenance phase of treatment in the PERSEUS study, the incidence of Grade 3/4 adverse events (AEs) displayed notable differences between the DL and L treatment groups. Neutropenia emerged as a significant concern, with a higher occurrence in the L cohort compared to the DL group, indicating a greater risk associated with the L treatment. Additionally, diarrhoea was reported more frequently among patients receiving DL, while the incidence in the L group was markedly lower.

The data presented below is for the transplant eligible population, comparing versus BLd-L (PERSEUS in-trial comparator).

Overall, the DBLd-DL safety profile was consistent with known safety profiles for daratumumab and BLd-L in this patient population. In the PERSEUS trial, treatment with DBLd-DL was well-tolerated, with fewer deaths as a result of side-effects than in the group treated with BLd-L. ⁴⁵

The appearance of more serious (also called "Grade 3 or 4") adverse events were slightly higher in the DBLd-DL group than the BLd-L group (91.5% vs 85.6%). The overall incidence of Grade 3 or 4 adverse events was higher in the DBLd arm versus the BLd arm during induction and consolidation. However, the incidence was similar across arms during the maintenance phase. ⁴⁵ The most common Grade 3 or 4 adverse events (≥10%) are present in table below.

Table 3: Common grade 3 or 4 treatment adverse event

Side effect	Symptoms	Patients who experienced side effects with DBLd-DL
Diarrhoea	Passing of loose or watery stools more than three times a day	10.5

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	4.3
Neutropenia (low white blood cells)	Feeling sick, extreme tiredness and getting frequent infections	62.1
Thrombocytopenia	Bruising easily, tiny red spots under the skin and unusual bleeding from the gums or nose	29.1
Febrile neutropenia		9.4
Anaemia (low red blood cell count)	Feeling extreme tiredness, weakness, pale skin, cold hands and feet, dizziness and shortness of breath	6.0
Pneumonia	Coughing, fever, chills, shortness of breath, chest pain, fatigue, and loss of appetite	10.5

It is important to note that despite slightly higher AE's in DBLd-DL arm compared to BLD-L it did not cause a higher rate of discontinuation of treatment in the DBLd group.⁴⁵ 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.

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 effectively manage any infusion-related reactions that may occur, it is crucial for patients to receive daratumumab from a healthcare professional in a setting equipped with resuscitation facilities. This ensures that any reactions can be promptly addressed should they arise.^{53, 54}

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)⁵⁵
- Growth factors (a type of supportive medicine that stimulates the bone marrow to make blood cells)⁵⁵

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 patients newly diagnosed with multiple myeloma (MM), timely disease management is crucial. Delaying treatment can increase risk of drug resistance, making it increasingly difficult to respond effectively to subsequent treatments. Each recurrence or relapse not only worsens the disease prognosis but also complicates efforts to achieve strong and lasting treatment results.⁵⁶⁻⁵⁸ Disease control was highlighted as the most important attribute for a MM treatment by patients in a 2019 Myeloma UK study, and deep and durable responses represent the first, crucial step towards this.⁵⁹

This underscores the importance of providing effective therapy during the initial treatment phases, which include induction, consolidation, and maintenance. When patients experience relapses and require additional treatments, these therapies often prove less effective, reducing their chances of survival. Moreover, frequent relapses can lead to treatment discontinuation, which negatively impacts patients' health outcomes and quality of life.^{56, 60-62}

It is essential to optimize first-line treatment options for MM patients. Early initiation of therapy can help maintain better health for a longer period and enhance overall quality of life. Adopting a proactive approach not only helps delay the likelihood of relapse but also contributes to improved overall health outcomes.⁶³

As induction and consolidation therapy, DBLd is expected to improve the toxicity profile associated with current standard of care (DBTd) due to the substitution of lenalidomide for thalidomide. Whilst both lenalidomide and thalidomide are immunomodulatory drugs (IMiDs), as a second-generation IMiD, lenalidomide is generally considered more potent and less toxic compared with thalidomide which is associated with a number of side-effects including neurotoxicity. As referred to in Section 3e above, the improved efficacy of DBLd over DBTd is supported by results from the I&C ITC which show statistically significant improvement in rates of patients achieving $\geq$ VGPR responses.

For maintenance, the key benefit of adding daratumumab to lenalidomide maintenance is considered to be the deeper, more durable responses and higher rates of MRD negativity/sustained MRD negativity that are expected to translate to improved long-term outcomes including progression-free and overall survival. AURIGA shows clear clinical benefit of DL maintenance versus L in a group of patients who are MRD-positive after I&C treatment. The magnitude of benefit for patients treated in the NHS is likely to be of a similar size or greater, as outlined in Section 3e above and detailed further in Section 2 of the Company Submission.

Hence, combining daratumumab with lenalidomide during the maintenance phase works better than existing options to destroy more cancer cells. DL maintenance plays a vital role in maintaining MRD negativity that leads to longer-lasting responses, delaying the return of cancer, and extending the time before the disease worsens

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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
- As with all treatments there can be side-effects. However, clinical trial evidence indicate that DBLd-DL has a manageable safety profile.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Economic Model Structure

The economic model for this submission assesses the costs and quality of life of patients over a lifetime for those receiving DBLd-DL compared to the current standard of care treatment in the UK, DBTd-L. The model simulates a patient's treatment journey over a 40-year time horizon through a set of different health states (before disease progression, after disease progression, and death). The model accounts for resources and costs for managing the disease, treating side effects as well as the impact on quality of life and survival of patients.

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.

Survival inputs

- In the absence of direct head-to-head data, a pragmatic approach was taken to modelling the induction and consolidation treatment phases, with DBLd and DBTd assumed to have equivalent efficacy. J&J consider this a highly conservative assumption given the statistically significant deeper very good partial response or better ($\geq$ VGPR) responses indicated by the I&C ITC.
- For maintenance, the AURIGA study serves as the best available evidence to inform the relative benefit of adding daratumumab to lenalidomide monotherapy for the economic model. AURIGA specifically evaluated the efficacy of DL versus L in minimal residual disease-positive (MRD+) patients who had achieved a $\geq$ VGPR following induction therapy and autologous stem cell transplantation. More details regarding survival inputs are presented in Section 3 of the Company Submission.

Modelling how much a treatment improves quality of life

Quality of life in the model is based on data from PERSEUS, 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)

Uncertainty

There is often uncertainty in modelled long-term predictions of survival as trial data are only available for a certain duration of follow-up and therefore different extrapolation methods were implemented to derive long term estimates. To mitigate this uncertainty, best practice approaches aligned with NICE Technical Support Document 14 have been used to incorporate insights from UK clinical experts' expectations for survival.⁶⁴ Additionally, external validation following NICE precedent, particularly from TA763, reinforces the robustness of the standard of care, providing further confidence in the derived estimates.⁶⁵

Cost effectiveness results

The cost-effectiveness results for DBLd-DL versus DBTd-L is confidential, but can be found in Section 3 of the Company Submission. Confidential discounts for the comparators and subsequent treatments (that are used in the model) are not available to J&J. Therefore, the Company cannot determine the true cost-effectiveness of the treatment upfront. Instead, this information will be reviewed by the NICE committee to help them make decisions about whether to approve it.

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, the introduction of DBLd followed by DL maintenance therapy would represent a clear step-forward for transplant eligible newly diagnosed MM patients in UK clinical practice. By using multiple drugs with different mechanisms of action, DBLd-DL leverages the synergistic benefit of different classes leading to deeper and more durable responses. This approach is expected to translate to 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 represents a step change to current standard of care, delivering transformative outcomes not previously seen in the transplant eligible setting.

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>

Furter information on the PERSEUS trial:

- Study Details | Daratumumab, VELCADE (Bortezomib), Lenalidomide and Dexamethasone Compared to VELCADE, Lenalidomide and Dexamethasone in Subjects With Previously Untreated Multiple Myeloma | ClinicalTrials.gov

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>

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.⁶⁶

Biopsy: A process in which a very small part of tissue in the body is removed to look for signs of disease.⁶⁷

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.⁶⁸

Minimal residual disease: A term used to describe a very small number of cancer cells that remain in the body during or after treatment.⁶⁶

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.⁶⁶

Multiple myeloma: A type of cancer that begins in plasma cells.⁶⁶

Plasma cell: A type of white blood cell that makes large amounts of a specific antibody.⁶⁶

Progression: The course of a disease, such as cancer, as it spreads in the body.⁶⁶

Relapse: Return of the signs and symptoms of a disease after a period of improvement.⁶⁶

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.⁶⁶

Stem cell transplant: The process of providing a patient with healthy stem cells that can replace diseased cells intentionally destroyed by therapy.⁶⁶

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

Clarification questions

August 2025

File name	Version	Contains confidential information	Date
ID6249_Daratumumab EAG Clarification Questions Response [REDACTED]	1.0	Yes	22nd August 2025

Note: Revised Company base case

A revised Company base-case is included as an Addendum to this Clarification Questions response. This represents the Company submission model, when accounting for the following corrections to inputs and calculations:

- updating any eMIT costs used within the model to use the December 2024 data cut;
- using the higher cost for subcutaneous injection of £115.36 (NHS National Schedule of Costs 2023/24; N10AF Specialist Nursing, Cancer Related, Adult, Face to Face); and
- correcting the probability of diarrhoea in maintenance to use the AURIGA trial, in line with the other adverse events.

In addition, J&J identified and fixed a referencing error in the DBLd and DBTd model 'Engine' sheets, which impacted fourth-line treatment acquisition and administration costs. Further details regarding the correction (and other updates based on clarification questions) and updated base case results are provided in the Addendum.

Section A: Clarification on effectiveness data

Literature searches

A 1. Appendices E, F and G state that the Cochrane Library was searched for the economic and health-related quality of life (HRQoL) systematic literature reviews (SLRs), via cochranelibrary.com for the original search and EBM Reviews for the update.

Please confirm which individual databases within this resource (e.g. CDSR, CENTRAL, NHS EED, DARE etc.) were searched for the original and update searches for both of these SLRs.

For the original searches of the economic and HRQoL systematic literature reviews (SLRs), the Cochrane Library was searched via cochranelibrary.com. The individual databases searched included the Cochrane Database of Systematic Reviews (CDSR) and CENTRAL. NHS EED and DARE were not searched, and no new records have been added to these databases since 2015 (DARE) and 2016 (NHS EED). However, DARE abstracts critically appraising systematic reviews of health and social care interventions were made available in PubMed in 2015, and a PubMed search was conducted to support identification of relevant economic evaluations. This approach ensured coverage of relevant content from DARE despite its archival status and aligns with current best practice, given that NHS EED and DARE have not been updated for nearly a decade.

For the update searches, NHS EED and DARE were not searched, again as the Centre for Reviews and Dissemination (CRD) has confirmed that while archives are maintained, no new records have been added since 2015 (DARE) and 2016 (NHS EED). The search for the update was conducted on 08 May 2025, which is well beyond the last update of these databases, and therefore their inclusion would not have contributed any new or relevant evidence. This approach aligns with current best practice and ensures that the review reflects the most up-to-date and actively maintained sources

Decision problem

A 2. Priority question. Table 1 of the company submission (CS) lists comparators separately for induction and maintenance. The company has responded to the scope by carrying out a cost comparison for induction and consolidation treatment (daratumumab, bortezomib, lenalidomide and dexamethasone (DBLd) vs. standard of care (SoC) (daratumumab, bortezomib, thalidomide and dexamethasone (DBTd), as well as a cost effectiveness analysis (CEA) of DBLd followed by

daratumumab plus lenalidomide (DL) maintenance vs. DBTd followed by L maintenance.

a) Please clarify what is assumed to follow induction and consolidation in the cost comparison i.e. is it only SoC, which is L for both intervention and comparator.

As indicated in Section 1.1 of the company submission (CS), lenalidomide (L) monotherapy is the only maintenance therapy reimbursed in the UK, with UK clinical experts indicating it is received by 95% of patients with high-dose therapy (HDT)-autologous stem cell transplant (ASCT) eligible newly diagnose multiple myeloma (NDMM).¹ In the cost-comparison, lenalidomide maintenance is therefore assumed to follow induction and consolidation therapy with either daratumumab, bortezomib, lenalidomide and dexamethasone (DBLd), or its relevant comparator daratumumab, bortezomib, thalidomide and dexamethasone (DBTd).

The cost-comparison was included so as to facilitate earlier access to induction and consolidation in the event that the Committee requires additional information to determine a recommendation for the full treatment sequence. In the scenario that the full treatment sequence (DBLd induction and consolidation followed by DL maintenance) was still awaiting a decision by the NICE committee, Johnson and Johnson (J&J) consider DBLd induction and consolidation suitable for initial reimbursement. This is based on at least comparable efficacy of DBLd and DBTd, coupled with the substantial cost savings DBLd would offer the NHS due to lower drug acquisition costs associated with lenalidomide compared to thalidomide as well as the improved tolerability profile of lenalidomide-based treatment regimens and, consequently, reduced adverse event (AE) management costs. While Section 3.10.1 of the CS presents higher AE managements associated with DBLd compared to DBTd, this can be attributed to the differences in the trials informing the AE rates for DBLd and DBTd which has been detailed in J&J's response to B24 below. Safety concerns with thalidomide-based regimens, and consequently detrimental impact on patient HRQoL have been highlighted by clinicians consulted as part of the May 2025 Advisory Board; clinicians voiced clear preference to move away from thalidomide-based regimens.¹

As such an initial recommendation of DBLd induction and consolidation would serve to ensure that the benefits of this regimen are achieved without delay.

b) If this is the case, please can you clarify that the company anticipates that DBLd might be followed by L, as opposed to DL, in clinical practice?

In UK clinical practice, DBLd induction and consolidation therapy is expected to be followed by daratumumab and lenalidomide (DL) maintenance, should DL be reimbursed.

As detailed in the response to question A2a), the cost-comparison was included to aid the NICE committee in making decisions at different times for DBLd induction and consolidation versus the full treatment sequence of DBLd with DL maintenance. If DBLd were to be made available in UK clinical practice as an induction/consolidation therapy, but DL maintenance was yet to be reimbursed, DBLd would be followed by the standard of care maintenance therapy (i.e., L maintenance).

- c) If this is not the case then DBLd would be followed by DL, so please clarify how a cost comparison can be valid given the cost and QALY increase shown in the CEA.**

As described in the response to question A2b), DBLd induction and consolidation therapy is expected to be followed by DL maintenance. As such, J&J conducted a cost-utility analysis to explore the cost-effectiveness of this full treatment sequence compared with its relevant comparator, DBTd with L maintenance. Given the at least comparable efficacy of DBLd and DBTd as induction and consolidation therapies, a cost-comparison analysis was also conducted to illustrate the significant cost savings DBLd would offer the NHS during the induction and consolidation phases. As described in response to question A2a), the results of the cost-comparison could inform an initial recommendation for DBLd, whilst the full treatment sequence (DBLd with DL) is still being considered. Providing the cost-comparison to facilitate early access to induction and consolidation is important to bring access in England and Wales in line with Scotland and Northern Ireland where guidance has already been extended to include DBLd alongside DBTd.

A 3. Priority question. Table 1 notes that DBTd is the only relevant induction and consolidation treatment given the observation of █████ use in NHS England data.

- a) Please provide an explanation as to why this figure is not 100%: is there a subgroup of patients for whom another treatment is more appropriate?**

As described in Section 1.1 of the CS, DBTd represents the only relevant comparator to DBLd in the induction and consolidation treatment phase. This is based on NHS usage data indicating that almost 100% of HDT-ASCT eligible patients with NDMM receive DBTd in clinical practice. The overwhelmingly predominant use of DBTd was further confirmed in an Advisory Board conducted in May 2025, where UK clinical experts were in agreement that almost 100% of patients receive DBTd in clinical practice.¹ The experts noted that the remaining patients reflects the very occasional use of bortezomib, cyclophosphamide and dexamethasone (BCd), given that cyclophosphamide can be preferred in some cases of renal impairment, due to the toxicity concerns associated with thalidomide.¹ This small group of infrequently-treated patients reflects a remnant and declining practice that does not represent a clinically definable subgroup.

In summary, DBTd represents the only relevant comparator to DBLd induction and consolidation in UK clinical practice. Given that the vast majority of HDT-ASCT eligible patients with NDMM in UK clinical practice are currently treated with DBTd, the analysis presented in the CS can be considered representative of the entire population under consideration for this appraisal.

- b) If such a subgroup exists then would that subgroup also be eligible for the intervention, and, if this is the case, then please conduct the appropriate clinical effectiveness assessment and economic analyses versus the comparator for this subgroup.**

As detailed in the response to question A2a), the proportion of HDT-ASCT eligible patients with NDMM who do not receive DBTd in UK clinical practice is negligible and does not represent a clinically definable subgroup. As such, clinical and economic analyses were not conducted for the small minority of patients who do not receive DBTd.

Systematic review

A 4. Please describe what exactly ‘pragmatic re-evaluation of previously excluded studies in order to find additional evidence that could inform a comparison of DL vs. L maintenance’ means and supply all relevant prioritisation or eligibility criteria.

The AURIGA trial was not initially included in the induction, consolidation and maintenance phases SLR (referred to as the I+C+M SLR), in line with its eligibility criteria, given that it only assessed treatment in the maintenance phase. This initial screening did not identify evidence that was sufficient to address the decision problem.

Therefore, to determine whether any studies were available that were conducted in the population of relevance to this submission (i.e., HDT-ASCT eligible patients with NDMM) and provided evidence on the comparative efficacy of DL versus L, the title/abstract of studies which were excluded at the full-text review stage of the I+C+M SLR, as they were restricted to the maintenance phase only, were re-screened. Subsequent targeted searches in Google Scholar were conducted to ensure all relevant publications reporting on any studies of interest had been captured. A list of the 67 studies which were pragmatically re-evaluated can be found in the Appendix submitted alongside the response to clarification questions. Through this pragmatic re-evaluation, AURIGA was found to be the only available source of evidence for the comparative efficacy of DL versus L maintenance (as outlined in the response to B2e).

Following the original Company submission, J&J has conducted exploratory analysis to isolate the treatment effect for DL versus L leveraging patient level data from the PERSEUS trial (necessary as there was no second randomisation after consolidation, prior to maintenance initiation). Please refer to our response to question B3b below for further details.

A 5. Please confirm how many reviewers were involved in risk of bias assessment and whether the same method used for study selection (in duplicate independently with a third arbitrator when necessary) were employed.

As part of the clinical SLRs, risk of bias was assessed using the Cochrane RoB 2.0 Quality Assessment tool 2.0, as recommended by NICE– the results of these assessments can be found in the Appendix submitted alongside the response to clarification questions.² The risk of bias assessment was performed by a single reviewer and checked by a second reviewer. Any discrepancies that arose during their reviews were resolved through discussion or the intervention of a third reviewer. This method aligns with that used for study selection at both the title and abstract and full-text screening stages, in line with the methodological principles of conduct for SLRs as detailed in the University of York Centre for Reviews and Dissemination’s (CRD’s) “Guidance for Undertaking Reviews in Health Care”.³ The same approach was taken when conducting the risk of bias assessment for the AURIGA trial, which was not included in the clinical SLRs.

Clinical effectiveness evidence

A 6. We acknowledged the information provided on trial generalisability and NHS patient data as detailed in table 7 of the CS. Please also provide the breakdown of baseline characteristics for any England/Wales based patients involved in the relevant trials.

As noted in Table 5 (Section 2.2.2) of the CS, the PERSEUS trial was conducted in 13 locations across Europe and Australia, but these locations did not include any in the UK. The GRIFFIN trial was conducted in the USA, and the AURIGA trial across the USA and Canada.^{4, 5} As such, no patients based in England- or Wales- were enrolled in these trials.

A 7. The CS reference number 4 is listed as pertaining to a May 2025 Advisory Board commenting on the generalisability of PERSEUS to UK clinical practice. However, based on reviewing the references in the CS, number 4 is missing. Please provide this document detailing all clinical advice and opinion on these matters.

J&J apologise for the error in the reference list, which resulted in Reference number 3 and 4 showing as unlabelled in the reference list. The correct citations for reference number 3 and 4 are given below, and the error has been corrected in the updated version of the CS submitted alongside the response to clarification questions.

3. J&J Data on File. NHS England Patient Initiation Data (2024-2025).

4. J&J Data on File. Advisory Board Meeting Minutes. May 2025.

Indirect treatment comparison (ITC)

A 8. Priority question. The CS states: “Baseline covariates of interest were identified based on a literature review. To further explore potential TEMs/PFs, based on the framework outlined in NICE DSU TSD 18, a review of stratification factors in PERSEUS (ISS and cytogenetic risk) was performed. Additionally, the results of pre-specified subgroup analyses conducted in PERSEUS and CASSIOPEIA were reviewed for evidence suggesting that a baseline characteristic could be a potential TEM.” Precisely how were covariates selected for the ITC:

a) Which came from the literature review, which were identified from stratification factors, and which came from subgroup analyses?

Baseline covariates of interest were identified based on:

1. A literature review of treatment effect modifiers (TEMs) and prognostic factors (PFs) as reported in previous clinical trials and population-adjusted indirect treatment comparisons (ITCs) conducted in the HDT-ASCT eligible NDMM setting⁶
2. The literature review was supplemented by:
 - a) A review of the stratification factors in the PERSEUS trial (international staging system [ISS] and cytogenetic risk)
 - b) Analyses of the role of candidate baseline covariates as TEMs and PFs based on PERSEUS trial data

As such, the potential for characteristics to be PFs or TEMs was assessed by considering findings from all of the methods described above – criteria used to select covariates are provided in the response to question A8b. This approach was based on the framework outlined in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.⁷

b) What were the criteria that were applied to select from each of these sources?

Clinical experts reviewed the results of the literature review and PERSEUS analyses to select and rank the baseline covariates based on their importance as PFs and TEMs. The result of this process yielded the base case set of covariates, which were considered to be the most important as PFs/TEMs, as well as a larger set of TEMs and PFs which were adjusted as part of a sensitivity analysis (Table 31 of the CS). The selection of both sets of covariates was completed *a priori*, that is, prior to the ITC analyses being conducted.

Clinical validation for the set of characteristics identified as PFs and TEMs, as well as the covariates prioritised for adjustment in the base case ITC, was provided by input from UK clinical experts as part of an Advisory Board conducted in May 2025.¹

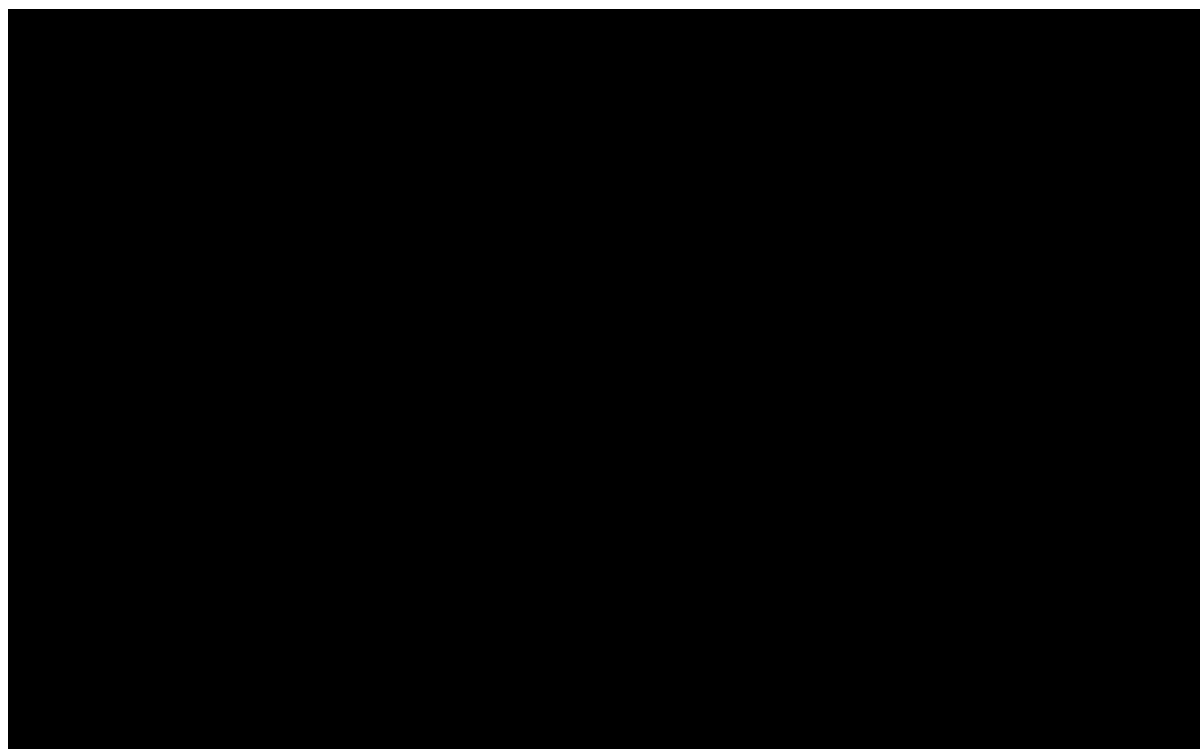
c) Please consider other scenarios for the ITC with different choices of covariates.

As detailed in Section 2.10.9 of the CS, findings from the base case ITC (where the seven covariates were adjusted for) and the sensitivity analyses (where all 14 covariates were adjusted for) were broadly consistent, indicating that adjusting for different covariates had minimal impact on the results. This is further supported by results of a step-wise covariate analysis conducted by J&J, presented in Figure 1, which illustrates the minimal impact of adjusting for each covariate on very good partial response or better ($\geq$ VGPR) with the exception of presence of extramedullary plasmacytomas (already included in the Company sensitivity analysis). The biological plausibility of using depth of response as a predictor of long-term survival outcomes is well-established, as discussed in Section 1.3.2 of the CS. DBLd [REDACTED] at induction and consolidation, whilst also achieving a benefit in terms of objective response rate (ORR) and MRD-negativity rates, when compared with DBTd. As such, the benefit of DBLd in terms of response outcome is reasonably expected to result in a long-term OS benefit versus DBTd, as discussed further in the Company response to B1.

Overall, the robust methodology used to identify the full, and priority, set of covariates, the consistency of results across the base case and sensitivity analysis (all 14 covariates adjusted),

and the limited impact of each covariate in the step-wise analysis of a robust surrogate outcome ($\geq$ VGPR), confirm that the ITC results presented are robust to the impact of PFs/TEMs.

Figure 1: ITC Step-wise covariate adjustment for DBLd compared with DBTd in terms of $\geq$ VGPR



Footnotes: ¹p-value: 0 '****' 0.001 '***' 0.01 '**' 0.05 '.' 0.1 ' ' 1.

Abbreviations: CRAB: hyperCalcemia, Renal, Anemia, Bone; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide, and dexamethasone; ECOG: Eastern Cooperative Oncology Group; ISS: international staging system; IPTW: inverse probability treatment weighting; ITC: indirect treatment comparison; LDH: lactate dehydrogenase; MM: multiple myeloma; OR: odds ratio; Slim: $\geq$ 60% clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of 100 or more with the involved serum free light chain being $\geq$ 100 mg/L, and Magnetic Resonance Imaging with more than one focal marrow lesion.

Section B: Clarification on cost-effectiveness data

Clinical effectiveness parameters and assumptions

B 1. Priority. During the induction and consolidation phases, DBLd and DBTd were assumed to have equivalent treatment efficacy in terms of OS and PFS. Please explain what is assumed to differ between DBLd and DBTd in induction and consolidation, apart from the drug acquisition costs.

Although DBLd and DBTd were assumed to have equivalent treatment efficacy in terms of progression-free survival (PFS) and overall survival (OS) during the induction and consolidation phases of the model, this should be considered a pragmatic, highly conservative assumption in the economic analysis. The ITC results presented in Section 2.10 of the CS demonstrated that

treatment with DBLd resulted in statistically significantly deeper responses than DBTd, with patients almost twice as likely to achieve a $\geq$ VGPR response. Since achieving a deep and durable response is a strong prognostic marker for survival outcomes (as outlined in Section 1.3.2 of the CS), this response benefit observed with DBLd is expected to translate to longer-term survival improvement. This was supported by UK clinical experts at the May 2025 Advisory Board, who confirmed that DBLd is at least as effective, if not more, than DBTd as induction and consolidation therapies for HDT-ASCT eligible patients with NDMM.¹

The key differences between DBLd and DBTd induction and consolidation in the model are based on data from the PERSEUS and CASSIOPEIA trials, respectively, and are listed below, not including drug acquisition costs:

- Relative drug intensities (RDI) – although derived from different sources, the RDIs for DBLd and DBTd were broadly similar, as presented in Section 3.5.1.1, Table 71 of the CS.
- Proportion of patients receiving autologous stem cell transplant (ASCT) – it should be noted that these proportions however are broadly similar (DBLd: ██████% versus DBTd: ██████% based on PERSEUS and CASSIOPEIA, respectively)^{8, 9}
- Proportion of patients receiving concomitant medications (Table 73, CS)
- AE rates – in the model, these data are sourced from the PERSEUS and CASSIOPEIA trials for DBLd and DBTd, respectively. In clinical practice, a substantially improved tolerability profile is expected for DBLd compared with DBTd owing to the neurotoxicity burden associated with thalidomide, as described in Section 1.3.5.2 and Section 1.3.5.3 of the CS. Improved tolerability of lenalidomide-based therapies compared to thalidomide-based therapies was clinically validated by UK clinical experts consulted at the May 2025 Advisory Board.¹ This is further supported by data from the Myeloma XI trial, which provides evidence from a randomised controlled setting demonstrating significantly lower rates of peripheral neuropathy for a lenalidomide-based induction regimen (carfilzomib in combination with lenalidomide and dexamethasone [CLd]) versus a thalidomide-based alternative (carfilzomib in combination with thalidomide and dexamethasone [CTd]) in patients with HDT-ASCT eligible NDMM.¹⁰ However, as highlighted in the company response to B24, owing to trial differences, the overall AE costs for DBLd are higher than DBTd in the model, and therefore represent a highly conservative estimate of the true economic benefit from lenalidomide-based regimens compared to thalidomide-based regimens.

B 2. Priority. On page 148 of the CS it is stated that data from the AURIGA trial represented the best available evidence to inform the treatment efficacy in the maintenance phase of the economic analysis instead of the PERSEUS trial. AURIGA is a phase III, head-to-head RCT which compares DL versus L maintenance therapies AURIGA in patients who have received induction and HDT-ASCT. Regarding this approach:

- Please explain if patients in the AURIGA trial have received the same treatments in induction and consolidation as patients in the current**

economic analysis. Please provide details on the number of patients and alternative treatment options that these patients received during induction and consolidation.

The AURIGA trial exclusively investigated treatment in the maintenance phase, with patients enrolled if they had NDMM and had received prior induction therapy followed by HDT-ASCT. A summary of the induction therapies received by patients in the AURIGA trial is presented in Table 1. At least 60% of patients received bortezomib, lenalidomide and dexamethasone (BLd) as induction therapy in both arms (L arm: 70/101 [69.3%]; DL arm: 62/99 [62.6%]). Only a minority of patients in the trial were confirmed to have received consolidation therapy following HDT-ASCT (total: [REDACTED] L arm: [REDACTED]; DL arm: [REDACTED]).¹¹ There were no restrictions on induction or consolidation regimens received by patients prior to enrolment in the AURIGA trial.¹² However, all patients must have been anti-CD38-naïve to be eligible for enrolment and as such, could not have received DBLd or DBTd.¹²

Table 1: Summary of induction therapies in the AURIGA trial

	L (N=101)	DL (N=99)	Total (N=200)
Patients with ≥1 induction therapy, n (%)	[REDACTED]	[REDACTED]	[REDACTED]
Therapy combination, n (%)			
BLd	[REDACTED]	[REDACTED]	[REDACTED]
BCLd	[REDACTED]	[REDACTED]	[REDACTED]
BCd	[REDACTED]	[REDACTED]	[REDACTED]
BCaLd	[REDACTED]	[REDACTED]	[REDACTED]
BLMd	[REDACTED]	[REDACTED]	[REDACTED]
BL	[REDACTED]	[REDACTED]	[REDACTED]
BCaLPd	[REDACTED]	[REDACTED]	[REDACTED]
Bd	[REDACTED]	[REDACTED]	[REDACTED]
BCLMVd	[REDACTED]	[REDACTED]	[REDACTED]
BILMd	[REDACTED]	[REDACTED]	[REDACTED]
CaCd	[REDACTED]	[REDACTED]	[REDACTED]
CaLd	[REDACTED]	[REDACTED]	[REDACTED]
CLd	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: BCaLd: bortezomib, carfilzomib, lenalidomide and dexamethasone; BCaLPd: bortezomib, carfilzomib, lenalidomide, pomalidomide and dexamethasone; BCd: bortezomib, cyclophosphamide and dexamethasone; BCLd: bortezomib, cyclophosphamide, lenalidomide and dexamethasone; BCLMVd: bortezomib, cyclophosphamide, lenalidomide, melphalan, vincristine and dexamethasone; Bd: bortezomib and dexamethasone; BILMd: bortezomib, ixazomib, lenalidomide, melphalan and dexamethasone; BL: bortezomib and lenalidomide; BLd: bortezomib, lenalidomide and dexamethasone; CaCd: carfilzomib, cyclophosphamide and dexamethasone; CLd: cyclophosphamide, lenalidomide and dexamethasone.

Source: J&J Data on File (AURIGA Clinical Study Report; 2024 DCO).¹¹

b) Please discuss the impact of informing efficacy in the maintenance phase using data from the AURIGA trial, if these patients had received

different treatments than DBLd/DBTd during induction and consolidation.

It is not expected that the treatment received at induction or consolidation would substantially impact the comparative efficacy of DL versus L maintenance therapy. This is illustrated by the similar efficacy outcomes observed for DL maintenance in the PERSEUS and AURIGA trials, with 60.2% and 60.6% converting from MRD-positive to MRD-negative during maintenance therapy (at a threshold of 10^{-5}), respectively. A comparable trend for patients in the DL maintenance arm of both trials was similarly observed with regards to MRD-negativity rates, which increased over time before plateauing at 24 months.^{5, 13}

This is further supported by the data from the CASSIOPEIA trial data, as described in Section 2.13 of the CS (page 145). The trial suggests that there were no difference in outcomes for patients who received daratumumab as maintenance treatment after prior daratumumab induction and consolidation when compared with those who were not daratumumab-experienced.¹⁴ As such, the comparative efficacy estimates for DL versus L maintenance from the AURIGA trial, where patients were anti-CD38-naïve, are likely to be maintained in clinical practice following DBLd induction and consolidation. It should be noted that trends in data from the CASSIOPEIA trial can be used to qualitatively explore the impact of prior daratumumab exposure on outcomes following daratumumab maintenance, the exact treatment regimens used in the induction, consolidation and maintenance phases of the trial differ from those being assessed in the current appraisal. As such, these data can be leveraged for qualitative interpretation only, rather than quantitative.

c) On page 160 of the CS it is stated that ‘the PERSEUS and AURIGA trial populations differ in some respects including prior exposure to daratumumab during induction and consolidation’. Please explain in detail these differences.

The key differences between the PERSEUS and AURIGA trial populations are outlined below:

- **Daratumumab exposure:** patients in the DBLd arm of the PERSEUS trial received daratumumab-based treatment during the induction and consolidation phases, making them anti-CD38-experienced, whilst patients were all anti-CD38-naïve when initiating maintenance therapy in the AURIGA trial^{12, 15}
- **Consolidation therapy:** consolidation therapy with DBLd or BLd was administered as part of the trial regimen in PERSEUS, whilst consolidation therapy was received by a minority of patients (██████████), prior to enrolment, in the AURIGA trial^{11, 12}
- **MRD and response status:** patients enrolled in the AURIGA trial were MRD-positive and achieved a $\geq$ VGPR following induction therapy and ASCT.¹⁵ In the PERSEUS trial, patients were enrolled and randomised prior to induction or consolidation therapy, and initiated maintenance therapy irrespective of their MRD or response status

Whilst the differences in the AURIGA and PERSEUS trial populations are acknowledged, the use of comparative efficacy estimates for DL versus L maintenance therapy from the AURIGA trial was considered the best approach. As detailed in the response to B2a), similarity in maintenance efficacy outcomes between the PERSEUS and AURIGA trial suggest that differences in prior treatment do not substantially impact the generalisability of AURIGA trial results. This is

supplemented by evidence from the CASSIOPEIA trial, which suggests that the prior exposure to daratumumab does not notably impact the effect of daratumumab maintenance. The response to question B2d) highlights that the $\geq$ VGPR and MRD-positive status of the AURIGA trial population is not expected to significantly impact the generalisability of maintenance therapy outcomes.

This means that the comparative efficacy of DL versus L in AURIGA is representative of what would be expected for patients who receive DBLd or DBTd induction and consolidation therapy in UK clinical practice.

d) The AURIGA trial enrolled anti-CD38-naïve patients with NDMM who were minimal residual disease- (MRD-) positive, and had achieved a very good partial response or better ($\geq$ VGPR) after induction therapy and HDT-ASCT. Does this mean that patients in the AURIGA trial were potentially ‘better off’ than those in the PERSEUS trial?

J&J do not consider the patients enrolled in the AURIGA trial to be ‘better off’ than those in the PERSEUS trial. As discussed in Section 1.3.2 of the CS, MRD-negativity following induction and consolidation is a well-established surrogate for improved long-term PFS and OS outcomes. As such, the MRD-positive status of patients enrolled in the AURIGA trial means they are not expected to be ‘better off’ than those in the PERSEUS trial post-consolidation.

Distribution of IMWG responses by treatment arm for MRD-positive patients at post-consolidation in the PERSEUS trial is presented in Table 2 below, indicating that [REDACTED] % and [REDACTED] % of patients in the DBLd and BLd arms, respectively, had achieved a $\geq$ VGPR after induction therapy and HDT-ASCT. Whilst the proportion of MRD-positive patients achieving $\geq$ VGPR following induction therapy in the PERSEUS trial is therefore less than the AURIGA trial (i.e., 100% of patients), on balance, a sizeable proportion of patients in the PERSEUS trial had achieved MRD-negativity following consolidation.

In PERSEUS, following consolidation, 57.5% and 32.5% of patients in the DBLd and BLd arms respectively were MRD-negative (at or below 10^{-5}). Therefore, in comparison to MRD-positive patients in the AURIGA trial, the patient population in PERSEUS had a more favourable overall disease biology, with greater potential to achieve good outcomes.

The NDMM patient population who would receive DBLd followed by DL maintenance therapy in the NHS would comprise MRD-negative and MRD-positive patients post-consolidation and therefore, in comparison, the rate of MRD-negativity achieved by the MRD-positive AURIGA trial population remains a true estimate of the treatment effect of DBLd-DL in clinical practice.

Table 2: Distribution of IMWG responses by treatment arm for MRD-positive patients at post-consolidation timepoint in PERSEUS

Response rates	DBLd (N=151)	BLd (N=239)	All (N=390)
	n (%)	n (%)	n (%)
$\geq$ CR (sCR + CR)	[REDACTED]	[REDACTED]	[REDACTED]
$\geq$ VGPR (sCR + CR + VGPR)	[REDACTED]	[REDACTED]	[REDACTED]
ORR (sCR + CR + VGPR+PR)	[REDACTED]	[REDACTED]	[REDACTED]
sCR	[REDACTED]	[REDACTED]	[REDACTED]
CR	[REDACTED]	[REDACTED]	[REDACTED]

Response rates	DBLd (N=151)	BLd (N=239)	All (N=390)
	n (%)	n (%)	n (%)
VGPR	██████████	██████████	██████████
PR	██████████	██████████	██████████
SD	██████████	██████████	██████████
PD	██████████	██████████	██████████
NE	██████████	██████████	██████████

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; CR: complete response; ≥CR: complete response or better; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; IMWG: International Myeloma Working Group; L: lenalidomide; NE: not evaluable; OR: odds ratio; ORR: overall response rate; PD: progressive disease; PR: partial response; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.

Source: J&J Data on File. PERSEUS Post-Hoc Analysis: IMWG response data (MRD-positive)¹⁶.

Furthermore, the clear clinical benefit of DL maintenance in the MRD-positive post-consolidation cohort is expected to be *at least* maintained in a broader population of patients that includes MRD-negative patients, such as the PERSEUS trial cohort and the UK patient population. This is supported by a comparison of the DL versus L treatment effect observed in AURIGA for the non-sustained MRD-negative subgroup (PFS HR: ██████████; 95% CI: ██████████; OS HR: ██████████, 95% CI: ██████████) relative to the intent-to-treat (ITT) population which included both sustained and non-sustained responders (PFS HR: 0.53, 95% CI: 0.29 – 0.97; OS HR: ██████████, 95% CI: ██████████). Comparing these treatment effects shows that the treatment effect in terms of PFS and OS is diminished in non-sustained responders and therefore provides indirect evidence that the treatment effect of DL versus L is expected to be stronger in patients who respond well to treatment, such as patients who are MRD-negative post-consolidation. As such, the relative treatment effect estimates derived from AURIGA are conservative when applied to the broader population.

e) Please explain if the key reason to use the AURIGA trial data to inform efficacy in the maintenance is the randomisation of patients to the DL or L treatment arms in maintenance that did not happen in the PERSEUS trial. If differently, please provide a detailed explanation.

As described in Section 2.2 and Section 3.3.1.2 of the CS, no trial investigating the full treatment sequence for the comparator of relevance to this submission (DBTd induction and consolidation therapy followed by DL maintenance) was identified in the clinical SLR. As there was no second randomisation after consolidation in the PERSEUS trial, isolating the treatment effect of DL versus L maintenance therapy presented a methodological challenge.¹² Combined with the strengths of the AURIGA trial outlined in Section 2.13 of the CS and the company response to B3c), these are the reasons why the AURIGA trial was considered the best available randomised evidence to inform the comparative efficacy of DL versus L maintenance therapy and, consequently, long-term survival inputs for the full treatment sequence in the economic analysis. J&J have also presented a PERSEUS re-weighted analysis as part of the Company response to B3 below. This analyses, conducted following the original submission, attempts to isolate the effect of DL versus L maintenance on PFS and OS, and was broadly consistent with the relative efficacy estimates from the AURIGA trial.

f) Data in this submission from the AURIGA trial are based on the DCO of April 2024. Please clarify whether longer follow-up data are now available.

A 2-year DCO of 3rd March 2025 from the AURIGA trial has been collected but data are currently unavailable to be used to inform the submission and relevant model inputs. However, J&J are exploring the potential to present this evidence later in the submission process.

g) A scenario analysis assuming equal OS between DL and L maintenance was included due to the non-significant OS hazard ratio. However, the submission states that this scenario is not considered clinically plausible, citing superior efficacy demonstrated in the AURIGA trial and supported by PERSEUS in terms of response and survival outcomes. Given that OS differences in PERSEUS are also not statistically significant, please clarify which evidence is used to support a difference in OS between treatment arms. Additionally, the submission notes that all clinical experts estimated DL would be superior to L in the long term for both PFS and OS. However, a reference for this expert opinion is missing. Please provide the source or documentation for this statement.

A clear trend indicating an OS benefit was observed for the DBLd-DL arm of the PERSEUS trial (HR: 0.73; 95% CI: 0.47, 1.14), and the DL arm of the AURIGA trial (HR: [REDACTED]), when compared with BLd-L, and L maintenance, respectively.^{11, 12}

Input from clinical experts who took part in an Advisory Board, conducted by J&J in May 2025, supports superiority of DL over L in the long term for both PFS and OS.¹ All experts provided higher PFS and OS proportions for DL, supporting its expected superiority over L.¹

Documentation for this Advisory Board can be found in the meeting minutes – as noted in the response to question A7, the minutes (reference number 4 of the CS: J&J Data on File. Advisory Board Meeting Minutes. May 2025) were shared as part of the reference pack in the CS.¹

Furthermore, as detailed in Section 1.3.2 of the submission, MRD-negativity, including sustained MRD-negativity, is an appropriate surrogate endpoint in myeloma for long-term survival outcomes such as PFS and OS. As per guidance from the NICE report of surrogate endpoints in HTA, the appropriateness of MRD-negativity as a surrogate was confirmed through clinical expert opinion and Level 1 evidence (i.e., supporting evidence from RCTs).¹⁷ A response benefit of DL over L maintenance therapy was observed in the AURIGA trial, with overall MRD-negativity conversion rates of 60.6% and 27.7% observed for the DL and L maintenance arms, respectively.⁵ This aligned with the benefit observed for DBLd-DL in the PERSEUS trial, where 60.2% of patients in the DBLd-DL arm converted from MRD-positive post-consolidation to MRD-negative during the maintenance phase, compared with 40.5% in the BLd-L arm.¹³ These data therefore provide surrogate evidence for the long-term OS benefit expected for patients receiving DL maintenance in clinical practice, and support the clinical implausibility of a scenario with equal OS assumed between DL and L maintenance.

Further to this, a statistically significant PFS benefit was observed for the DBLd-DL arm of the PERSEUS trial (HR: 0.42 [95% CI: 0.30, 0.59; $p < 0.001$] and DL arm of the AURIGA trial (HR: 0.53 [95% CI: 0.29, 0.97; $p = 0.0361$]) when compared with BLd-L and L maintenance therapy.^{11, 12} PFS was the primary endpoint in PERSEUS, with the median PFS not reached at the time of the latest data-cut despite a median follow-up of [REDACTED] months (DBLd arm) and [REDACTED] months (BLd arm). PFS is a well-established prognostic endpoint in MM.¹⁸ As such, given the statistically significant PFS benefit observed, an assumption of equivalent long-term OS benefit of DL versus L is considered clinically implausible.

Overall, results from the PERSEUS and AURIGA trials highlight the deep, sustained responses patients achieve following treatment with DL maintenance therapy. There is a strong body of Level 1 evidence (the highest possible strength of evidence) highlighting the prognostic implications of these responses for improved long-term survival outcomes, such as PFS and OS. The expected survival benefits patients would derive from the addition of daratumumab to lenalidomide maintenance are further supported by input from UK clinical experts.

h) Finally, please comment on whether longer follow-up data would be expected to resolve the current uncertainty in the OS projections.

J&J recognise that the high proportion of patients alive and responding well to DBLd-DL means uncertainty exists in the OS projections. The effectiveness of DBLd induction and consolidation therapy, and DL maintenance, was clearly demonstrated by the deep, durable responses observed in the PERSEUS. As highlighted in Section 1.3.2 of the CS, there is a strong correlation between deep, sustained responses, particularly MRD-negativity, and improved survival outcomes. This means that patients who achieve such responses, as well as MRD-negativity, would remain progression-free for longer.^{1, 19-24} This is in line with the statistically significant PFS benefit observed in the AURIGA trial for patients receiving DL maintenance therapy compared to L maintenance therapy (HR: 0.53 (95% CI: 0.29, 0.97; $p = 0.0361$)), as noted above.⁵

Additionally, the availability of multiple lines of effective treatments for patients in the UK following disease progression on either treatment also contributes to the relatively good prognosis of this patient population in UK clinical practice.²⁵ For example, even in the 4L+ setting, teclistamab extends patient prognosis by ~2 years.²⁶

Indeed, even with the availability of longer follow-up data from the CASSIOPEIA trial (median follow-up of 80.1 months from first randomisation; September 2023 DCO), median PFS was not reached in patients who received DBTd induction and consolidation therapy followed by daratumumab maintenance therapy.¹⁴

Whilst the availability of longer-term follow-up data from the AURIGA trial is expected to improve precision of the PFS and OS hazard ratio point estimates, cost-effectiveness of DBLd-DL has been demonstrated to be robust to scenarios varying the OS HR (refer Section 3.11.3 of the original Company submission), while the PFS benefit of DL vs L results from AURIGA are statistically significant and not a source of material unresolved uncertainty. As such, we believe that the current data available informing the model would be sufficient to inform decision making. J&J are exploring whether a later data cut-off from AURIGA will be available to inform the appraisal. More data may improve precision but are unlikely to resolve uncertainty.

B 3. Priority. Page 148 of the CS states that it is ‘difficult’ to isolate the treatment effect of DL versus L maintenance therapy in the PERSEUS trial.

a) Please explain if it is possible to isolate the treatment effect of DL versus L maintenance therapy using data from the PERSEUS trial.

As there was no second randomisation after consolidation in the PERSEUS trial design, further analysis is required to attempt to isolate the treatment effect of DL vs L. J&J has explored analyses outlined in B3b below to provide relative efficacy estimates for DL versus L. The results of the PERSEUS re-weighted analyses indicate PFS benefit for DL over L maintenance therapy, congruent with the results from the AURIGA. These results are important as they are consistent with AURIGA trial results and provide reassuring consistency in the DL versus L treatment effect during maintenance.

b) If possible, please provide relative efficacy evidence for DL versus L maintenance based on the PERSEUS data and run a scenario analysis using this data.

In order to isolate the effect of DL versus L maintenance on PFS and OS following DBLd induction, HDT-ASCT, and DBLd consolidation, the following post hoc analysis was performed using individual patient-level data from the PERSEUS trial. The analysis included n=322 DBLd-DL patients and n=299 BLd-L patients who initiated maintenance therapy (DL or L monotherapy) and who had not progressed prior to the start of maintenance therapy.

PERSEUS patients initiating L maintenance were then re-weighted using inverse probability of treatment weighting (average treatment effect in the treated; IPTW-ATT) to resemble the patients initiating DL maintenance with respect to measured baseline patient characteristics at randomisation as well as post-consolidation MRD-negativity status (assessed with NGS at a threshold of 10^{-5}). The objective of the re-weighting of patients receiving L maintenance therapy was to estimate comparative PFS and OS for DL versus L maintenance strategies in patients with similar baseline characteristics and post-consolidation MRD-negativity status. This exercise was done with the primary base case covariate set (age, sex, ECOG PS, ISS stage, baseline cytogenetic risk, type of MM, haemoglobin levels and LDH) and sensitivity analysis covariate set (base case covariate case plus creatinine clearance, MM diagnostic criteria satisfied, presence versus absence of extramedullary plasmacytomas, serum calcium, bone lesions and platelet levels) similar to the ITC analysis.

Both PFS and OS from the start of maintenance therapy were then evaluated for DL maintenance versus L maintenance under three scenarios:

- L maintenance as observed in patients who had not progressed at the start of maintenance (i.e., without weighting) in PERSEUS,
- L maintenance with patients re-weighted to resemble DL patients with respect to post-consolidation MRD-negativity status and the base case baseline covariate set, and

- L maintenance with patients re-weighted to resemble DR patients with respect to post-consolidation MRD-negativity status and the sensitivity analysis baseline covariate set.

Results are presented in Table 3, with the corresponding PFS and OS Kaplan-Meier plots presented in Figure 2 and Figure 3, respectively. The HR for PFS aligns with the observed data in the AURIGA trial and there is a trend towards a benefit of OS attributable to DL maintenance treatment. It is important to note that all scenarios exhibit similar OS curves for L, owing to the limited number of these OS events.

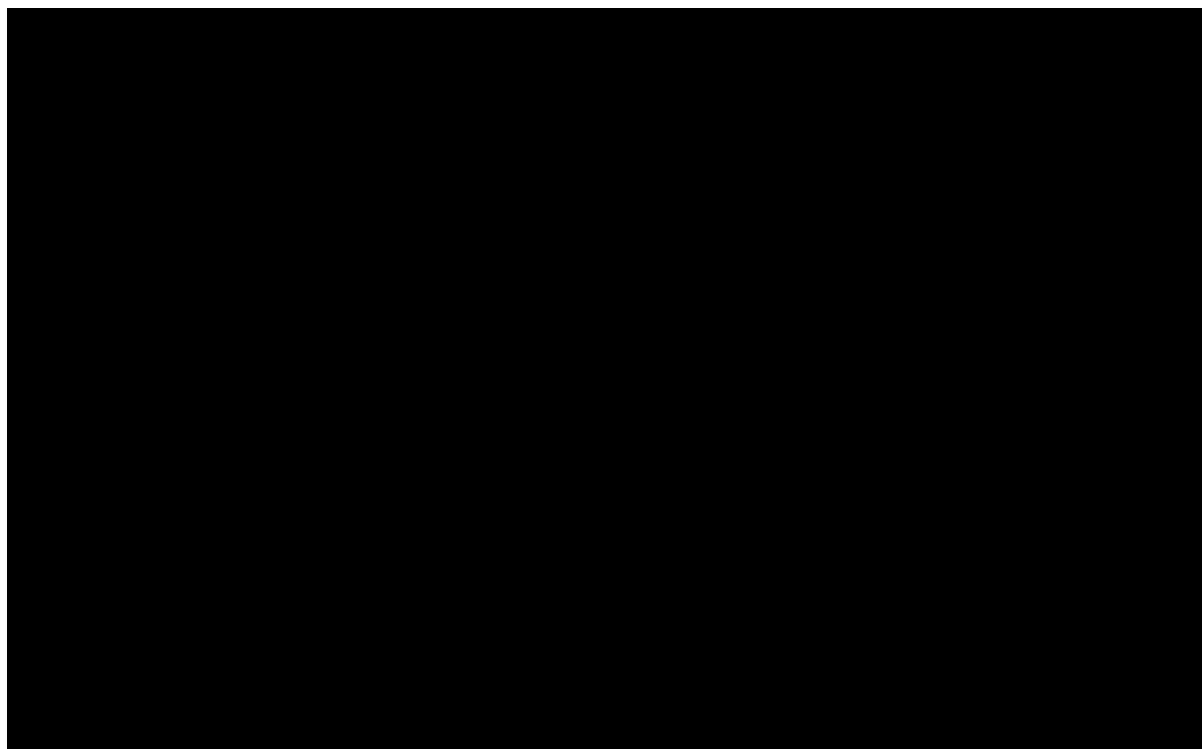
A scenario analysis was conducted using the re-weighted data that included sensitivity analysis baseline covariate, with the results presented in Table 4 showing the impact of this treatment effect on the overall economic results (a change of the ICER from the base case of £23,986/QALY to dominant). The difference in results is driven by the diminished OS treatment effect in the current analysis where patients on DBTd-L progress early and spend more time cycling through subsequent treatments resulting in significant increases in costs. The risk of death is similar to patients in the DBLd-DL arm who spend more time in the progression-free state and less time in the progressed disease state.

Table 3: Overview of PFS and OS results (before and after re-weighting) for DL versus L maintenance therapy in PERSEUS

Comparison	PFS HR (95% CI)	OS HR (95% CI)
DL vs L maintenance (unweighted)	██████████	██████████
DL vs L maintenance (weighted; base case baseline covariate set)	██████████	██████████
DL vs L maintenance (weighted; sensitivity analysis baseline covariate set)	██████████	██████████

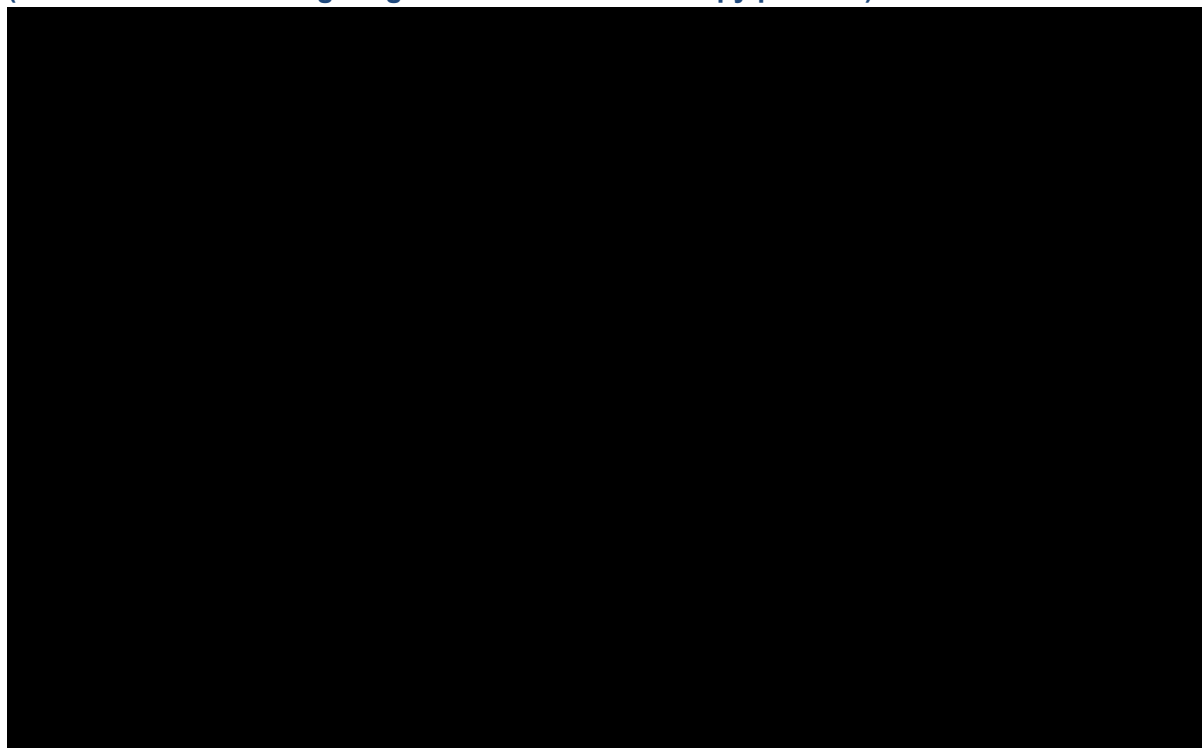
Abbreviations: CI: confidence interval; DL: daratumumab and lenalidomide; HR: hazard ratio; L: lenalidomide; OS: overall survival; PFS: progression-free survival.

Figure 2: Comparison of PFS outcomes for DL versus L maintenance therapy in PERSEUS (before and after re-weighting of L maintenance therapy patients)



Abbreviations: DR or DL: daratumumab and lenalidomide; D-VRd or DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IPTW: inverse probability of treatment weighting; R or L: lenalidomide; MRD: minimal residual disease; PFS: progression-free survival

Figure 3: Comparison of OS outcomes for DL versus L maintenance therapy in PERSEUS (before and after re-weighting of L maintenance therapy patients)



Abbreviations: DR or DL: daratumumab and lenalidomide; D-VRd or DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; IPTW: inverse probability of treatment weighting; R or L: lenalidomide; OS: overall survival

Table 4: Deterministic scenario results (PERSEUS re-weighted HRs; discounted daratumumab price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20,000	INHB at £30,000
Base case¹									
DBLd-DL	██████	██	██	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	██████	██	██	██████	██	██	£23,986	██	██
Scenario									
DBLd-DL	██████	██	██	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	██████	██	██	██████	██	██	dominant	██	██

Footnote: ¹An error has been identified and corrected in the 'DBLd Engine' and 'DBTd Engine' tabs of the model, which impacted the fourth-line subsequent treatment acquisition and administration costs for both DBLd-DL and DBTd-L. These results reflect the correct base case.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; L: lenalidomide; LYG: life years gained; QALY: quality-adjusted life year.

c) Please discuss the advantages and disadvantages of using the PERSEUS trial data as compared to isolating the effect from the AURIGA trial (as per company's base case analysis).

The PERSEUS trial provides direct observed evidence for the full treatment sequence (DBLd-DL) for the intervention considered as part of the decision problem, with a patient population consisting of both MRD-positive and MRD-negative patients at the end of consolidation. As noted in the company response to B2d, the PERSEUS trial population is more representative of the MRD-negativity status in the NDMM population who would receive DBLd-DL in the NHS and the AURIGA trial data represents a conservative estimate of the true treatment effect.

However, whilst J&J have provided a proxy method to isolate the treatment effect of DL vs L in the PERSEUS trial, this does break randomisation which may not be fully accommodated for using statistical reweighting. It is, however, an important confirmatory analysis confirming the treatment effect of DL versus L. As such, the PERSEUS re-weighted data represents non-randomised evidence, unlike the AURIGA trial which provides phase III randomised evidence and is specifically designed to isolate the treatment effect of adding daratumumab to L maintenance therapy. Deriving the DL versus L maintenance effect from the AURIGA trial instead of reweighted PERSEUS trial data also means that a larger population sample size is used with no additional need for matching of patients.

Taken together, the results of the re-weighting exercise outlined in B2b to isolate the effect of DL versus L maintenance therapy confirm a robust PFS benefit (HR: █████ (95% CI: █████) congruent with the PFS benefit observed in the AURIGA trial (HR: 0.53 (95% CI: 0.29, 0.97)).⁵ Similarly, a trend showing improved OS with DL compared to L maintenance therapy is observed for the re-weighted PERSEUS trial data that supports the clear OS benefit trend observed for DL maintenance therapy in the AURIGA trial as well as clinical expert feedback received.¹ Results

from both the PERSEUS re-weighting analyses and AURIGA trial indicate a consistent treatment effect and therefore, reduce uncertainty associated with the use of the AURIGA trial to inform the maintenance treatment effect in the Company base case analysis.

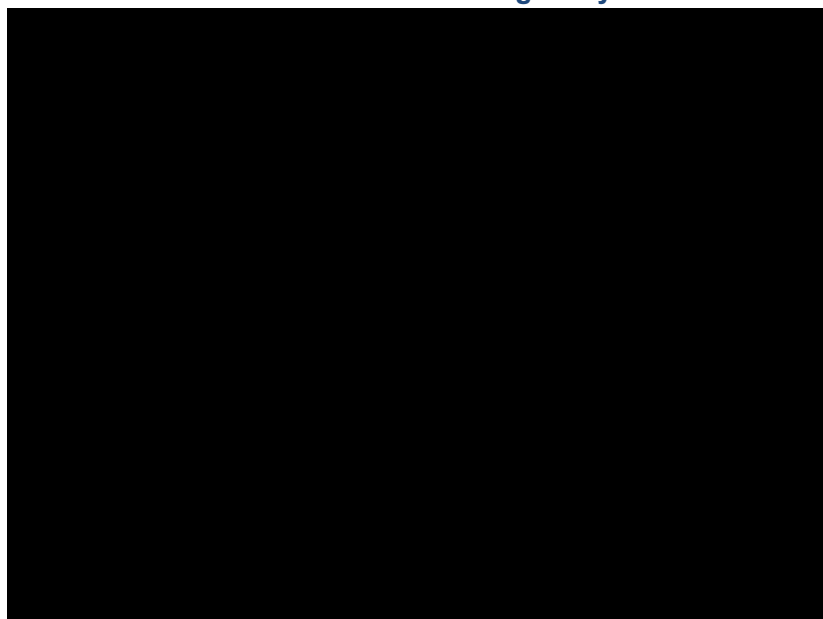
- d) Page 48 of the CS reports that the proportion of patients converting MRD-positive at post-consolidation to MRD-negative during maintenance treatment was significantly higher for those receiving DL maintenance versus L maintenance in the PERSEUS trial (60.2% versus 40.5%; $p=0.0049$). Given that MRD-negativity is mentioned throughout the CS as a biologically plausible surrogate of improved long-term outcomes, please explain if and how these results could be included in the economic model.**

As detailed in Section 1.3.2 and Section 2.6.1.2 of the CS, there is strong evidence indicating that MRD-negativity is a surrogate for improved long-term outcomes. MRD-negativity has been implicitly accounted for in the economic model given that the overall PERSEUS patient population included patients with deep and sustained responses demonstrated by MRD-negativity, and sustained MRD-negativity rates observed, respectively.

A summary of the overall MRD-negativity rate in the PERSEUS trial is presented in Table 15 of the CS wherein 75.2% and 47.5% of patients in the DBLd-DL and BLd-L treatment arms respectively achieved MRD-negativity (at or below 10^{-5}).^{8, 13} Similarly, 64.8% and 29.7% of patients in the DBLd-DL and BLd-L treatment arms achieved sustained MRD-negativity (at or below 10^{-5}), respectively.^{8, 13} As a surrogate for improved long-term outcomes, these patients with MRD-negativity, in particular sustained MRD-negativity, would therefore drive the overall PFS and OS outcomes observed in the ITT population. The relationship between sustained MRD-negativity and improved long-term outcomes can be observed from the Kaplan-Meier plots for PFS (Figure 4) and OS (Figure 5) for the DBLd-DL arm, where outcomes were significantly greater for those experiencing sustained MRD-negativity compared with those who did not.

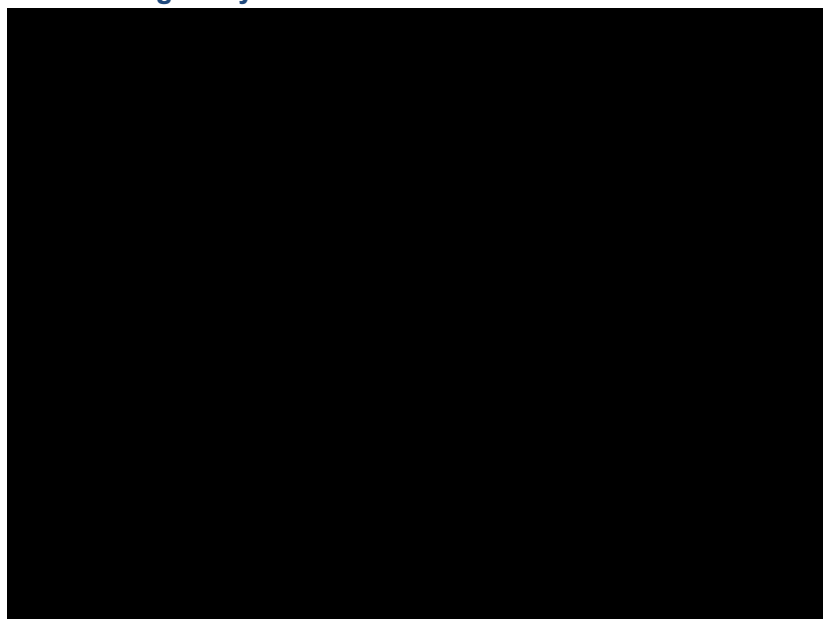
Owing to the fewer sustained MRD-negativity events particularly in the BLd-L arm, splitting the patient population by MRD status in the model would reduce the patient population and increase uncertainty. Therefore, whilst it was not deemed appropriate to further split the patient population by MRD status, patients who have achieved MRD-negativity, in particular sustained MRD-negativity, are anticipated to drive the overall PFS and OS outcomes.

Figure 4: Kaplan-Meier plot for PFS in the DBLd arm of the PERSEUS trial, according to 12-month sustained MRD-negativity status



Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; MRD: minimal residual disease; PFS: progression-free survival; RMST: restricted mean survival time.

Figure 5: Kaplan-Meier plot for OS in the DBLd arm of the PERSEUS trial, according to 12-month sustained MRD-negativity status.



Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; MRD: minimal residual disease; OS: overall survival; RMST: restricted mean survival time.

B 4. Priority. The immaturity of PFS and OS data from the PERSEUS trial is highlighted as a key limitation throughout the company submission, particularly in relation to alternative model fits for these outcomes. As

the data used in this submission are based on the August 2023 DCO, please clarify whether longer follow-up data are now available.

Longer follow-up data from a later data cut-off (DCO), beyond the August 2023 DCO used in the submission, are not currently available and a final analysis for the PERSEUS trial is not expected until 2028. However, as detailed in the response to B2h), the good prognosis of patients with HDT-ASCT eligible NDMM plus the fact that a high proportion of patients are responding very well to DBLd-DL means uncertainty in long term estimates is inevitable. The collection of mature survival data from the PERSEUS trial is therefore anticipated to require a significant duration of time and, as such, it is not expected that the immaturity of PFS and OS data from the PERSEUS trial will be resolved at the final analysis.

B 5. Priority. TTD for L maintenance therapy following DBTd induction and consolidation therapy was derived from the BLd-L arm of the PERSEUS trial. This approach assumes that adding daratumumab to the induction and consolidation phases does not affect the duration of L maintenance therapy.

a) Please comment on the clinical plausibility of this assumption.

J&J acknowledges that clinical evidence outlining the impact of the addition of daratumumab during induction and consolidation on the duration of lenalidomide maintenance as a monotherapy remains limited. Therefore, J&J have explored alternative scenarios presented in B5b and B5c which indicate minimal impact on the ICER.

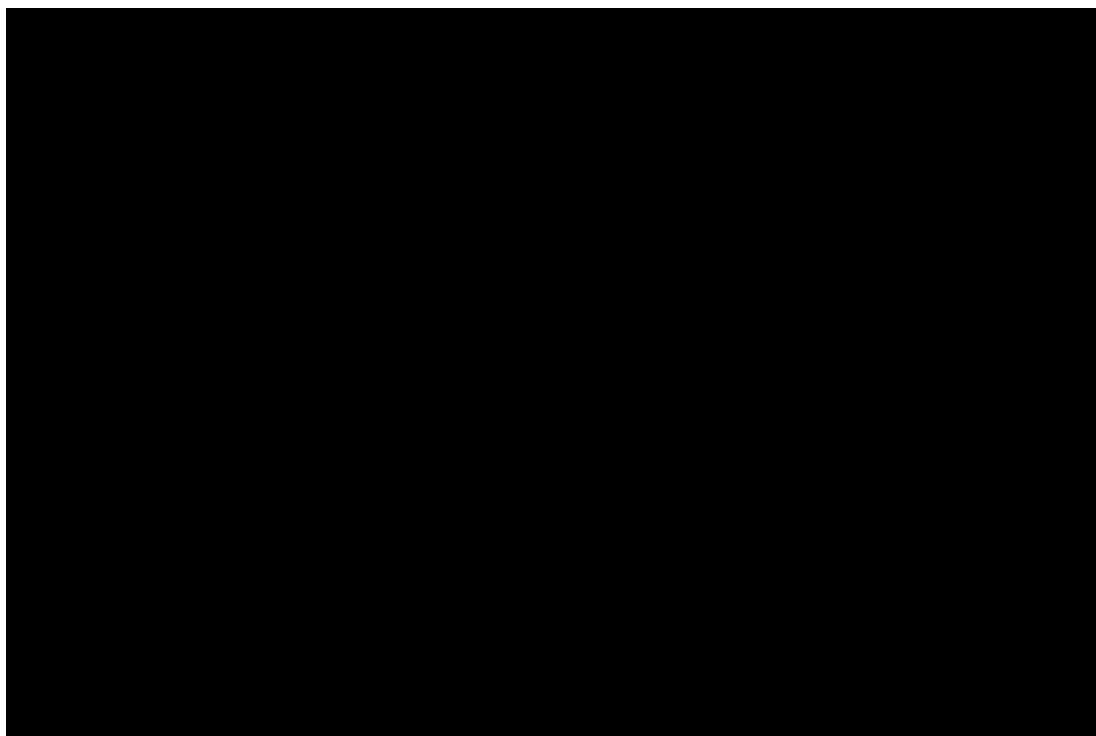
b) Additionally, clarify whether TTD data for L maintenance therapy is available from the AURIGA trial. If so, please conduct a scenario analysis using that data.

TTD data for L maintenance therapy from the AURIGA trial are available and presented in Figure 6 below. As requested by the EAG, J&J has therefore conducted a scenario analysis using the AURIGA trial data, results of which are presented in Table 5. This option can be selected in the model (Cell H84 in the 'Settings' sheet of the model). The impact on the ICER is very small (+1.08% change of the ICER from the updated deterministic base case of £23,986/QALY to £24,244/QALY).

The extrapolations of TTD using IPD from AURIGA for L maintenance therapy, with the goodness-of-fit statistics and long-term estimates of TTD for each parametric extrapolation presented in Figure 7 below.

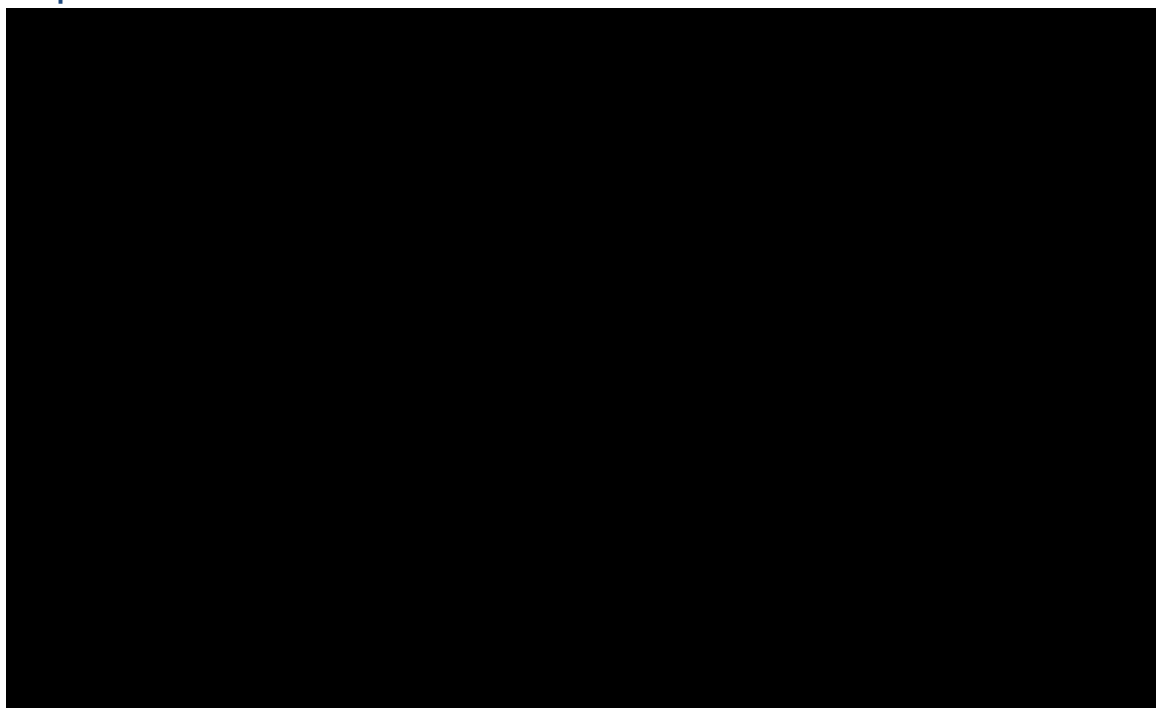
When comparing the fitted model statistics, and long-term estimates, the exponential extrapolation showed the best statistical fit with the observed data in terms of AIC and BIC (Figure 7) although it produced long-term estimates that are lower than clinicians' estimates. As such, this curve was selected for this scenario analysis representing a pessimistic assumption that fewer people remain on L maintenance treatment.

Figure 6: Observed KM data for TTD in the AURIGA trial



Abbreviations: CI: confidence interval; DR: daratumumab and lenalidomide; KM: Kaplan–Meier; R: lenalidomide; TTD: time to treatment discontinuation.

Figure 7: Extrapolation of TTD using IPD from the AURIGA trial for L discontinuation in the L maintenance arm, with goodness-of-fit statistics and long-term estimates derived for each parametric distribution



Footnotes: Three patients who withdrew before starting treatment (no treatment start date) were censored at day 1.

Abbreviations: R: lenalidomide; TTD: time to treatment discontinuation.

Table 5: Deterministic scenario results (TTD data for L maintenance therapy from AURIGA; discounted daratumumab price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20,000	INHB at £30,000
Base case¹									
DBLd-DL	██████	████	████	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	██████	████	████	██████	████	████	£23,986	████	████
Scenario									
DBLd-DL	██████	████	████	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	██████	████	████	██████	████	████	£24,244	████	████

Footnote: ¹An error has been identified and corrected in the 'DBLd Engine' and 'DBTd Engine' tabs of the model, which impacted the fourth-line subsequent treatment acquisition and administration costs for both DBLd-DL and DBTd-L. These results reflect the correct base case.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; L: lenalidomide; LYG: life years gained; QALY: quality-adjusted life year; TTD: time to treatment discontinuation.

- c) To reflect the stopping criteria for daratumumab in the maintenance phase, TTD for DBLd–DL was adjusted using data from patients who discontinued lenalidomide therapy during maintenance (in addition to the two other adjustment rules). Please run a scenario analysis where TTD for L maintenance in the DBTd–L arm is informed using the same subgroup of patients (i.e. those who discontinued lenalidomide in the DBLd–DL arm). Additionally, please explain why the BLd–L arm was preferred over the DBLd–DL arm to inform TTD data for lenalidomide maintenance?**

As requested by the EAG, J&J have incorporated a scenario analysis where TTD for L maintenance in the DBTd-L arm is informed using TTD for patients who discontinue L in the DBLd-DL arm of the PERSEUS trial. The extrapolations and smoothed hazard plot for TTD in the PERSEUS DBLd-DL arm have been presented in Figures 32 and 33 of the CS. This option to implement the scenario can be selected in the model (Cell M45 in 'Tx Efficacy' sheet of the model). Results of the scenario (Table 6) show a very small impact on the ICER (-1.49% change of the ICER from the base case of £23,986/QALY to £23,629/QALY).

The BLd-L arm was preferred over the DBLd-DL in the company base case as it is not expected that patients on L monotherapy would have the same duration of treatment as patients on DL.

Table 6: Deterministic scenario results (TTD data for L maintenance therapy from PERSEUS DBLd-L arm; discounted daratumumab price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20,000	INHB at £30,000

Base case ¹									
DBLd-DL	████	██	██	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	████	██	██	████	██	██	£23,986	██	██
Scenario									
DBLd-DL	████	██	██	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	████	██	██	████	██	██	£23,629	██	██

Footnote: ¹An error has been identified and corrected in the 'DBLd Engine' and 'DBTd Engine' tabs of the model, which impacted the fourth-line subsequent treatment acquisition and administration costs for both DBLd-DL and DBTd-L. These results reflect the correct base case.

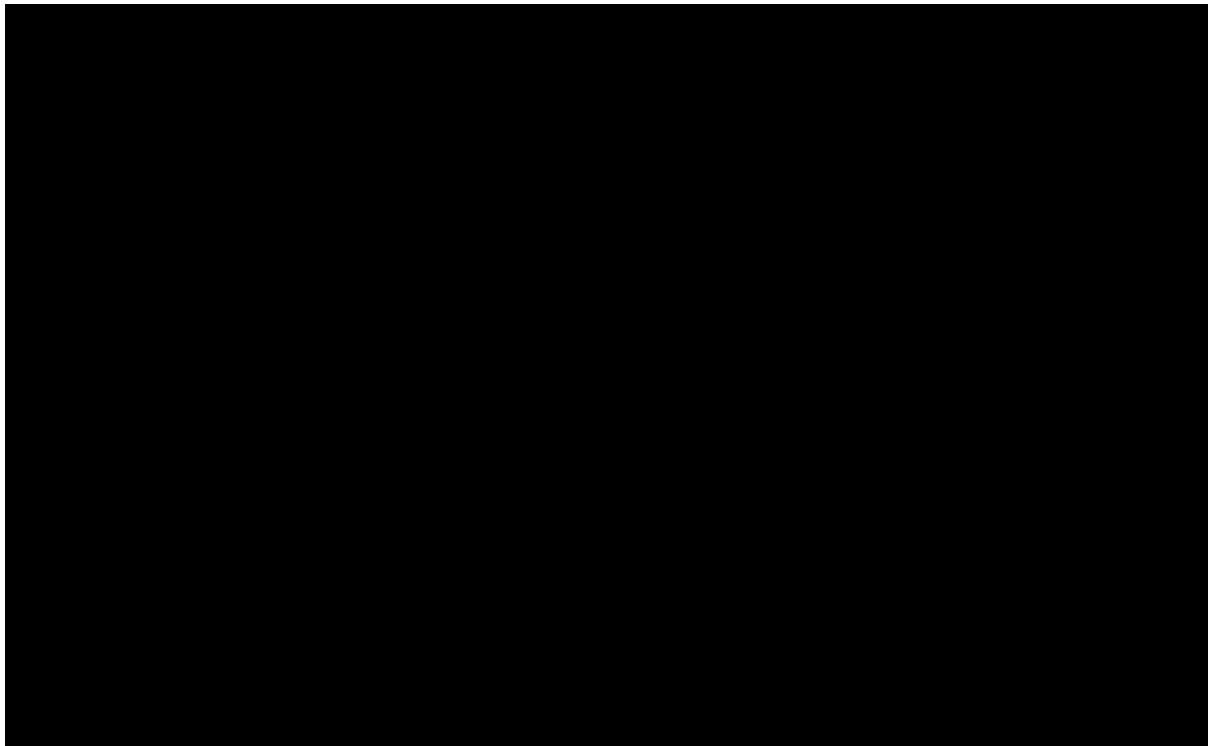
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; L: lenalidomide; LYG: life years gained; QALY: quality-adjusted life year; TTD: time to treatment discontinuation.

B 6. Priority. In Table 48 of the CS it is reported that the assumption of no treatment waning is based on findings from GRIFFIN and supported by the PERSEUS and AURIGA data.

a) Please provide more detail on the specific evidence from these trials that supports a sustained treatment effect after stopping daratumumab (e.g. relevant time-to-event outcomes or post-treatment follow-up data).

In the PERSEUS trial, the number of OS and PFS events among patients who stopped daratumumab maintenance after meeting the stopping rule was small (one and two events for OS and PFS respectively) (Figure 8), thereby providing evidence of sustained treatment effect even after cessation of daratumumab. If waning was occurring, a greater number of events would have been observed in this cohort of patients who stopped daratumumab treatment approximately 30-36 months after randomisation.

Figure 8: OS and PFS outcomes in patients who discontinued daratumumab after achieving 12 months sustained MRD negativity after 24 months of starting maintenance therapy



In addition, the time-varying hazard ratios for both OS and PFS demonstrate that there is no treatment effect waning (Table 7).

Table 7: Time varying OS and PFS hazard ratios

Endpoint	Follow up duration (months)	Events in DBLd	Events in BLd	Hazard Ratio	95% CI	P-value
PFS	≤6					
	≤12					
	≤18					
	≤24					
	≤30					
	≤36					
	≤42					
	≤48					
	≤54					
	≤60					
OS	≤6					
	≤12					
	≤18					
	≤24					
	≤30					
	≤36					
	≤42					
	≤48					
	≤54					

	≤60								

Abbreviations: CI: confidence interval; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; OS: overall survival; PFS: progression-free survival

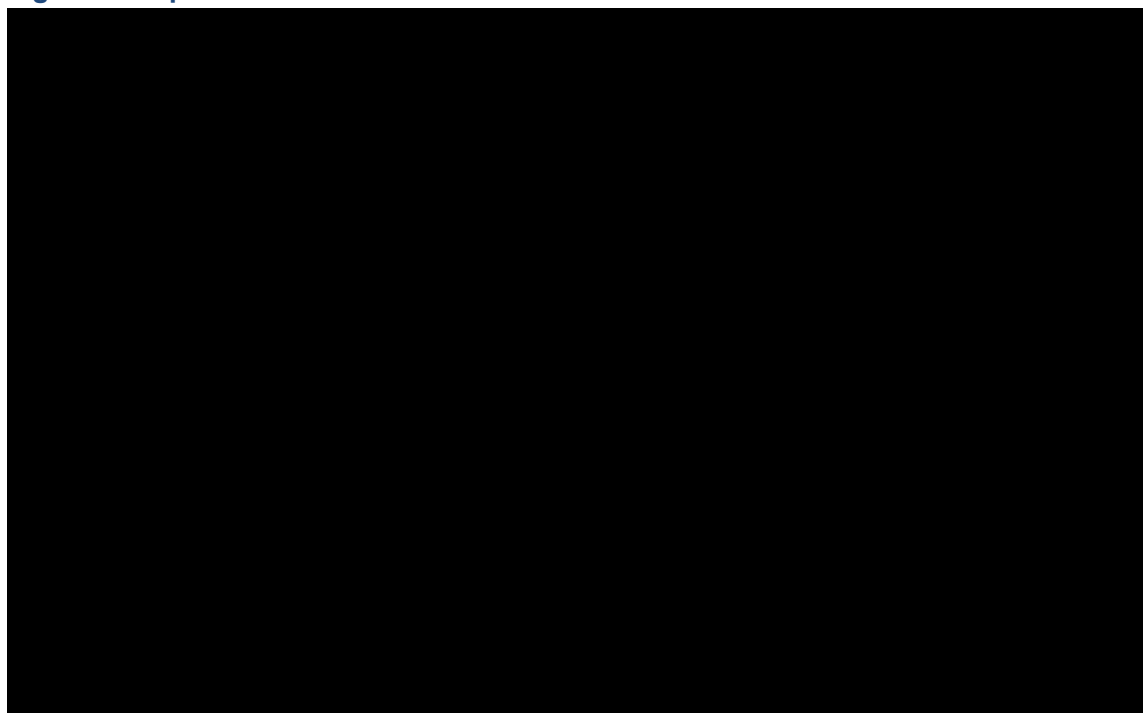
Consideration of the plausibility of treatment effect waning was discussed in TA763 extensively, with the Company citing longer-term trial data, such as the GIMEMA study and a CASSIOPEIA data cut with almost 4 years of follow-up, which provided compelling evidence that deeper responses translate to significant improvements in long-term outcomes.^{27, 28} Furthermore, treatment waning was not considered in previous NICE appraisals of daratumumab in first-line, and later-line, settings.²⁹⁻³¹ Discussions from the TA763 Committee meetings consequently concluded that it was reasonable to assume that the effect of a deepening response would be maintained over a lifetime following daratumumab combination treatment in relation to daratumumab-containing induction and consolidation treatment regimens.²⁸

Whilst TA763 did not evaluate DL maintenance therapy, given the strong evidence supporting the link between intermediate response outcomes and long-term survival outcomes (as detailed in Section 1.3.2 of the CS), the same conclusion regarding the absence of treatment waning can be made for patients receiving DL maintenance therapy. As described previously, the AURIGA trial provides evidence for a deepened response achieved by patients receiving DL maintenance therapy compared to L maintenance therapy, demonstrated by the higher rate of sustained MRD negativity (lasting ≥6 months; 35.4% versus 13.9%, respectively).¹¹ This is also supported by the statistically significant improvement in MRD-negativity reported for patients receiving DBLd-DL compared to BLd-L in the PERSEUS trial, with a MRD-negativity rate of 75.2% compared to 47.5% (p<0.0001).^{8, 13}

This is further supported by evidence from the GRIFFIN trial, where patients received maintenance therapy for a 2-year fixed-duration. Whilst OS data from GRIFFIN remains immature, PFS results demonstrate sustained benefit for the DL arm with continued separation of the curves beyond 36-months i.e. after 2-years fixed maintenance treatment duration (Figure 9**Error! Reference source not found.**).⁴

Considering the TA763 Committee-preferred assumptions for treatment waning, evidence for sustained MRD-negativity with DL maintenance therapy and the appropriateness of MRD-negativity as a surrogate endpoint for long-term OS outcomes, and evidence for the sustained treatment effect following DBLd-DL, it is clinically plausible for no treatment effect waning to be observed with DBLd induction and consolidation followed by DL maintenance therapy.

Figure 9: Kaplan-Meier for PFS in the GRIFFIN trial



Footnotes: Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.

Abbreviations: D-RVd: daratumumab, bortezomib, lenalidomide and dexamethasone; HR: hazard ratio; PFS: progression-free survival; RVd: bortezomib, lenalidomide and dexamethasone.

Source: Voorhees *et al.* 2023.⁴

- b) Additionally, if treatment waning were to be applied in the analysis, please indicate and justify one or more plausible alternative scenarios (e.g. linear or exponential waning over time, or reduced treatment effect after discontinuation), and provide scenario analyses accordingly.**

Treatment waning is inappropriate as there is no precedence, and results from PERSEUS demonstrate that there is no evidence of treatment waning. It is important to emphasise that such an exploration is based on conjecture as these model settings will be arbitrary, given the absence of evidence regarding if, or when, the treatment effect might decline over time.

In the economic model, clinical plausibility of long-term OS is addressed through use of clinical expert assumptions to guide curve choices. The evidence from patients who stopped daratumumab and not being associated with a loss of treatment effect supports the inappropriateness of waning, arbitrarily diminishing OS beyond clinical expectations. In addition, the availability of effective subsequent treatment with substantive evidence of improving outcomes is likely to maintain or even improve outcomes over time.

- c) The economic model seems to be including a functionality of treatment waning (sheet Tx efficacy). Please explain how this has been**

implemented in the model and why it is not part of the company's sensitivity analysis.

The functionality of treatment waning included in the economic model is an artifact of an earlier global model build which is intended to be adapted by local markets to address a variety of different decision problems. Given the discussion in part b above, J&J consider it inappropriate to explore treatment waning scenarios in the context of the current decision problem. It would also be double counting given the methods used to derive curves already.

This scenario has not been incorporated into the sensitivity analysis within the current submission, as it is deemed inappropriate given the clinical evidence in B6a and rationale outlined in B6b above.

B 7. Priority. Tables 51 and 54 of the CS present the predicted OS and PFS survival rates for the DBLd–DL arm alongside clinical experts' expectations. Please include the 5-year OS and PFS survival predictions in both tables. Please also provide a comparison of the modelled OS and PFS predictions against the observed OS and PFS data from the PERSEUS trial, using the most recent available data cut-off.

Table 8 and Table 9 have been updated from Tables 51 and 54 from CS to include the 5-year OS and PFS survival predictions for DBLd-DL with capping by OS and GPM, respectively. The Company would like to apologise for an error in the extraction of the mean OS, mean PFS, and survival rates at 25 years that are presented in Table 51 and 54 of CS. The OS and PFS survival predictions for DBLd-DL in these tables are not capped by OS and GPM; the corrected values (with caps for OS and GPM) are reported in the tables provided in response to this question.

Further, Table 10 and Table 11 have been added to compare the observed PERSEUS data with the relevant survival extrapolations, over the time period covered by the KM (up to 4.4 years). Clinical expert estimates were only sought for the period beyond the KM, and therefore are not provided in these tables. These tables show close alignment of the short-term extrapolations with the observed KM.

As discussed in Section 3.3.1.4 and 3.3.1.5 of the CS, base case curve extrapolations were chosen based on statistical fit, long-term clinical plausibility and observed hazards. The exponential curve was selected for OS in the base case, based on the suitability of observed hazards (initially constant with a gradual increase after two years), statistical fit (lowest AIC/BIC) and alignment with clinician estimates at all time points. Generalised gamma was chosen for the PFS curve for similar reasons, with all models showing similar statistical fit, but the generalised gamma deemed most appropriate based on the observed hazard (initial decline followed by a gradual incline after 25 months) and alignment with clinician estimates all three time points.

Table 8: Comparison of predicted survival rates for DBLd-DL OS extrapolations (with GPM cap)

copy

Survival model	DBLd-DL				
	Mean OS (months)	OS survival rates (% , mean [range])			
		5 years	10 years	15 years	25 years
Clinical expert estimates					
Clinical expert estimates	NA	NA	77 [75, 80]	67 [65,70]	38 [25, 53]
Extrapolations					
Exponential	255.0	87.7	77.0	67.7	44.4
Weibull	237.7	87.2	73.6	61.3	38.6
Gompertz	129.6	86.1	57.9	20.0	0.0
Log-logistic	249.4	87.3	75.3	65.3	42.8
Log-normal	265.9	87.9	79.4	72.5	47.8
Gamma	241.9	87.2	74.3	62.7	40.1
Generalised Gamma	204.7	87.0	71.6	55.1	23.1

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; GPM: general population mortality; NA: not applicable; PFS: progression-free survival.

Table 9: Comparison of predicted survival rates for DBLd-DL PFS extrapolations (with OS cap)

copy

Survival model	DBLd-DL				
	Mean PFS (months)	Proportion of patients progression-free (% , mean [range])			
		5 years	10 years	15 years	25 years
Clinical expert estimates					
Clinical expert estimates	NA	NA	64 [60, 65]	48 [45, 55]	21 [15, 35]
Extrapolations					
Exponential	223.1	81.4	66.5	54.3	36.1
Weibull	230.3	81.7	68.0	56.8	40.0
Gompertz	173.1	80.8	61.6	43.4	15.1
Log-logistic	240.9	82.0	70.0	61.1	44.4
Log-normal	249.9	82.9	74.4	68.5	44.4
Gamma	229.9	81.7	67.9	56.7	39.6
Generalised Gamma	193.8	81.4	65.2	49.9	22.6

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; NA: not applicable; OS: overall survival; PFS: progression-free survival.

Table 10: Comparison of predicted survival rates for DBLd-DL OS extrapolations versus PERSEUS KM data (with GPM cap)

Survival model	DBLd-DL		
	OS survival rates (%)		
	1 year	2 years	4 years
PERSEUS			

Survival model	DBLd-DL		
	OS survival rates (%)		
	1 year	2 years	4 years
KM Data ¹	97.7	96.0	89.4
Extrapolations			
Exponential	97.2	94.8	90.0
Weibull	97.8	95.3	89.9
Gompertz	98.0	95.7	89.8
Log-logistic	97.8	95.2	89.9
Log-normal	97.5	94.8	90.0
Gamma	97.7	95.2	89.9
Generalised Gamma	97.8	95.3	89.9

Footnote: ¹The KM OS data are based on observed patient outcomes directly related to disease progression and survival within the study. Therefore, they have not been capped by GPM.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; GPM: general population mortality; KM: Kaplan-Meier; OS: overall survival.

Table 11: Comparison of predicted survival rates for DBLd-DL PFS extrapolations versus PERSEUS KM data (with OS cap)

Survival model	DBLd-DL		
	Proportion of patients progression-free (%)		
	1 year	2 years	4 years
PERSEUS			
KM Data ¹	95.1	92.7	83.3
Extrapolations			
Exponential	95.7	91.9	84.8
Weibull	95.4	91.7	84.8
Gompertz	96.0	92.3	84.7
Log-logistic	95.4	91.6	84.9
Log-normal	94.7	90.9	85.2
Gamma	95.4	91.7	84.8
Generalised Gamma	95.5	91.8	84.7

Footnote: ¹The KM PFS data are based on observed patient outcomes directly related to disease progression and survival within the study. Therefore, they have not been capped by OS.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival.

B 8. Priority. Table 52 and Table 55 of the company submission present the predicted OS and PFS survival rates for the DBTd-L arm alongside clinical experts' expectations. However, these tables only include predictions based on the exponential model for OS and the generalised gamma model for PFS. Please update both tables to: 1) include survival predictions from all parametric models considered in the analysis, and 2) include the 5-year OS and PFS survival predictions for each model.

In the original CS, predicted OS and PFS survival rates were only provided based on the exponential and generalised gamma extrapolations (respectively) as DBTd-L are derived from a hazard ratio, applied to the selected DBLd-DL curve. For completeness, these have been updated with the findings for OS (capped by general population mortality) reported in Table 12 and PFS (capped by the selected OS curve) reported in Table 13. The Company would like to apologise for an error in the extraction of the generalised gamma extrapolation for PFS presented in Table 55 which were extracted for DBLd-DL as opposed to DBTd-L; the corrected values are reported in response to this question. The values have been corrected in the updated version of the CS submitted alongside the response to clarification questions.

Table 12: Comparison of predicted survival rates by clinical expert estimates and DBTd-L OS extrapolation (with GPM cap)

DBTd-L					
Survival model	Mean OS (months)	OS survival rates (% , mean [range])			
		5 years	10 years	15 years	25 years
Clinical expert estimates					
Clinical expert estimates	NA	NA	68 [60, 70]	55 [45, 65]	30 [15, 45]
DBTd-L extrapolation derived from application of AURIGA HR applied on selected DBLd-DL extrapolation					
Exponential	194.1	78.6	60.7	46.9	27.1
Weibull	167.6	77.3	55.3	38.3	17.2
Gompertz	98.4	75.4	34.2	4.1	0.0
Log-logistic	185.8	77.6	57.7	43.4	25.1
Log-normal	216.7	78.8	64.3	54.5	35.5
Gamma	173.4	77.5	56.2	40.1	19.6
Generalised Gamma	139.3	77.0	52.2	31.0	5.4

Abbreviations: DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; GPM: general population mortality; HR: hazard ratio; L: lenalidomide; NA: not applicable; OS: overall survival.

Table 13: Comparison of predicted survival rates by clinical expert estimates and DBTd-L PFS extrapolation (with OS cap)

Survival model	DBTd-L				
	Mean PFS (months)	Proportion of patients progression-free (% , mean [range])			
		5 years	10 years	15 years	25 years
Clinical expert estimates					
Clinical expert estimates	NA	NA	34 [25, 40]	10 [0, 15]	3 [0, 5]
DBTd-L extrapolation derived from application of AURIGA HR applied on selected DBLd-DL extrapolation					
Exponential	150.1	70.0	47.8	32.6	15.0
Weibull	159.1	70.6	49.9	35.7	18.3
Gompertz	104.7	68.9	41.3	14.5	0.0
Log-logistic	176.2	71.1	52.8	40.9	24.9
Log-normal	203.4	73.0	59.5	51.0	33.4
Gamma	158.6	70.7	49.9	35.5	18.0

Survival model	DBTd-L				
	Mean PFS (months)	Proportion of patients progression-free (%; mean [range])			
		5 years	10 years	15 years	25 years
Generalised Gamma	129.9	70.1	46.2	28.0	6.2

Abbreviations: DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; HR: hazard ratio; L: lenalidomide; NA: not applicable; OS: overall survival; PFS: progression-free survival.

B 9. Priority. Table 56 of the CS presents the observed TTD during induction and consolidation phases of DBLd and DBTd. While TTD appears comparable during the induction phase, a lower % of patients remain on treatment during the consolidation phase in the DBLd arm compared to the DBTd arm. Please explain the reason behind this difference. Given that thalidomide-containing regimens are presented to be associated with higher rates of adverse events, wouldn't the opposite trend be expected?

The PERSEUS trial was conducted during the COVID-19 pandemic, which had a notable global impact on patient enrolment, whilst the CASSIOPEIA trial was conducted prior to the pandemic. This key difference in the timing of study enrolment contributed to the lower-than-expected proportion of patients receiving consolidation treatment with DBLd, when compared with the DBTd arm in CASSIOPEIA. In particular, as noted in our response to question B12a below, a number of patients in PERSEUS skipped consolidation and received six cycles of induction therapy instead when an ASCT could not be received as scheduled due to the pandemic.

As the EAG notes, it is expected that a lower, or at least similar, proportion of patients would remain on DBTd than DBLd by consolidation in clinical practice. This is based on a significant body of evidence on the poor tolerability profile associated with thalidomide-containing regimens, as detailed in Section 1.3.5.2 of the CS.³²⁻³⁴ In support of this, feedback from UK clinical experts during an Advisory Board in May 2025 highlighted the substantial burden of neurotoxicities and other AEs on patient HRQoL.¹

B 10. In section 3.13 of the CS it is mentioned that UK clinical experts noted that around 20% of patients stop lenalidomide maintenance due to tolerability issues. Adding daratumumab allows patients to receive a more effective maintenance treatment and potentially achieve a more sustained response before discontinuation due to lenalidomide-related side effects. However, it is unclear why this would be expected, as the addition of daratumumab could reasonably be assumed to increase treatment burden and potentially worsen tolerability. Data from the PERSEUS trial showed that the incidence of Grade 3 or 4 TEAEs was [REDACTED] in the DBLd arm versus the BLd arm during induction and

consolidation while being ██████ in consolidation (section 2 of the CS). Also in page 92 of the CS, it is mentioned that serious AEs were reported in 30.2% of DL patients and 22.4% of L patients in the AURIGA trial. Please clarify and justify the rationale behind this claim/expectation.

Results from the maintenance phase of the PERSEUS trial indicate that the incidence of Grade 3 or 4 TEAEs was comparable for the DBLd-DL and BLd-L arms (█████% versus ██████%), whilst the proportion of patients experiencing a TEAE leading to treatment discontinuation in the BLd-L arm was over twice that of the DBLd-DL arm (19.0% versus 7.1%). As such, the PERSEUS trial provides strong evidence indicating that the addition of daratumumab maintenance treatment does not increase the treatment burden and worsen tolerability.⁸ This observation is consistent with other clinical trials. For example, in the Phase III MAIA trial, which evaluated the efficacy and safety of daratumumab, lenalidomide and dexamethasone (DLd) and Ld in HDT-ASCT ineligible patients with NDMM, the overall discontinuation rate was lower in the DLd versus Ld arm (64.0% versus 85.2%), as was the rate of discontinuations due to TEAEs (14.6% versus 23.8%). This difference was in spite of the substantially longer treatment duration in the DLd versus Ld arm (47.5 months versus 22.6 months), resulting in a longer AE reporting window for the former.³⁵ More broadly, daratumumab has consistently been found to have a good safety profile, and is considered to be a well-tolerated treatment.³⁶ In contrast with observations from the PERSEUS and MAIA trials, the incidence of serious AEs were slightly higher for those receiving DL versus L maintenance in the AURIGA trial (DL: 30.2% versus L: 22.4%; Table 26 of the CS).¹¹ However, it should be noted that in the AURIGA trial, treatment duration was notably longer in the DL arm (30.7 months) when compared with the L arm (20.6 months), resulting in a longer AE reporting window for DL therapy.⁵ The slight difference in serious AE rates should therefore be interpreted in the context of this extended reporting window.

Taken together, these trials provide strong evidence that it is not reasonable to assume that the addition of daratumumab to lenalidomide would worsen tolerability in clinical practice. When considering this in tandem with the substantial efficacy benefit of DL maintenance therapy compared to L maintenance therapy observed in AURIGA, with almost double the overall MRD-negativity conversion rate (60.6% versus 27.7%; $p < 0.0001$), it can be concluded that patients receiving DL are deriving substantially greater clinical benefit for the duration of time in which they undergo maintenance treatment compared to L alone.⁵ These deeper responses consequently offer greater flexibility for patients receiving DL to undergo lenalidomide adjustments to manage tolerability issues with this drug, compared with those receiving L maintenance. Indeed, in the AURIGA trial, the proportion of patients with lenalidomide dose adjustments was higher in the DL versus L arm (█████% versus ██████%), resulting in a lower RDI for the DL arm (█████% versus ██████%).¹¹ As such, the addition of daratumumab to L maintenance is expected to allow for a more tolerable treatment experience overall as well as substantial efficacy gains.

Intervention and comparators

B 11. Priority. On page 37 of the CS it is stated that based on input from clinical experts, 95% of patients receive lenalidomide maintenance therapy. Please explain why this figure is not 100%. Are there other

maintenance therapies currently used in clinical practice in the UK? If so, please clarify what these are and explain why they have not been included in the economic analysis.

Lenalidomide maintenance therapy currently represents the only relevant comparator to DL in UK clinical practice as it is the only maintenance therapy recommended by NICE for HDT-ASCT eligible patients with NDMM. For this reason, the vast majority of patients in the UK are expected to receive L maintenance and, as such, the analysis can be considered representative of the entire population. There are likely to be a very small minority of patients who are not suitable for L maintenance, and instead go on to observation following their ASCT. The reasons for this include patient choice, tolerability concerns and inadequate marrow recovery post-ASCT. These patients who are ineligible for L maintenance are also unlikely to be eligible for DL maintenance. This small minority of patients are not deemed relevant to the decision problem and hence are not included in the economic analysis presented in the CS.

B 12. Priority. In the PERSEUS trial, some patients did not receive ASCT as scheduled due to COVID-19 and instead received two additional cycles of induction therapy, without subsequent consolidation.

a) How many patients in the trial followed this modified treatment pathway (i.e. additional induction cycles instead of transplant and consolidation)?

Of the 709 patients randomised to treatment in the PERSEUS trial, 90 patients received maintenance but skipped consolidation therapy. The majority of these (██████████%) skipped consolidation as they received six cycles of induction therapy instead. The proportion of patients who received six cycles of induction therapy was comparable between treatment arms (DBLd: ██████% [██████]; BLd: ██████% [██████]).⁸ The majority of these patients (29 in each treatment arm) received an ASCT following their 6-cycle induction therapy.¹² Additionally, ██████ patients in the PERSEUS trial received maintenance without undergoing an ASCT or consolidation therapy. All but ██████ of these patients received six cycles of induction therapy.⁸

b) What are the implications of this deviation for the model outcomes, including the cost comparison and cost effectiveness outcome?

Minimal implications are expected from both a cost and efficacy perspective, because of some patients receiving two additional cycles of induction therapy (a total of six) instead of the two cycles of consolidation therapy. Specifically, the regimen received by patients for induction (pre-ASCT) and consolidation (post-ASCT) is identical, and therefore, there are no differences in costs incurred on a per-patient basis.

We'd expect minimal impact on efficacy given (i) skipping consolidation was balanced between the arms and (ii) the two approaches (skipping/not skipping) are viewed as interchangeable in recent EHA-EMN guideline update. Specifically, the guidelines state that 4-6 cycles of induction are recommended but if only 4 induction cycles are given then 2 cycles of consolidation should also be considered. To date, consolidation therapy after ASCT has not been established as a SOC approach. In patients who have received only four cycles of DBLd induction, two cycles of DBLd consolidation should be considered.

With respect to efficacy, this deviation is not expected to impact the outcome of the cost-comparison model where we have conservatively assumed equivalence of induction and consolidation between treatments while for the cost utility analysis, any difference in absolute outcomes is expected to have a minimal impact on cost-effectiveness due to application of a hazard ratio to the DBLd-DL reference curve. In addition, the consistency of the treatment effects observed in AURIGA and PERSEUS supports the minimal expected impact of this deviation.

- c) What would this mean as compared to the respective inputs from the CASSIOPEIA trial?

The CASSIOPEIA trial was conducted prior to the COVID-19 pandemic. As such, the modified treatment pathway available to patients in PERSEUS, where patients received an additional two cycles of induction therapy when an ASCT could not be received as scheduled due to the pandemic, was not required in CASSIOPEIA.

It should also be noted that the proportion of patients who underwent an ASCT as planned in the PERSEUS and CASSIOPEIA trials was comparable (██████% and ██████%, respectively).^{8, 9} This indicates that the COVID-19 pandemic did not substantially impact whether or not patients ultimately received their transplant, and, subsequently, the inputs in the economic analysis.

- d) In the current post-COVID setting, is it realistic to assume that 100% of patients would receive ASCT as planned? If not, what proportion should be assumed in the base case or explored in sensitivity analysis?

In the PERSEUS trial, ██████% of patients underwent ASCT as planned, with only a minority of patients not undergoing ASCT due to COVID-19.⁸ The proportion of patients receiving their ASCT as planned was comparable to that of the CASSIOPEIA trial (██████%), which was conducted prior to the pandemic.⁹ The similarity between the proportion of patients receiving ASCT in CASSIOPEIA and PERSEUS suggests that COVID-19 did not significantly influence the overall proportion of patients receiving ASCT or similar treatments. This indicates that in trials, and in clinical practice, a subset of patients would likely not receive their planned ASCT for various reasons, such as disease progression, physician's decision, AEs following induction therapy or stem cell mobilisation. As such, it is not realistic to assume that 100% of patients in clinical practice would receive ASCT as planned, even in a post-COVID setting. The proportion of patients undergoing ASCT in the PERSEUS and CASSIOPEIA trials can therefore be assumed to be reflective of UK clinical practice.

Health-related Quality of Life

- B 13. Priority.** Table 48 of the CS presents the utility values estimated from the EQ-5D-5L data of the PERSEUS trial as compared to the utility values used in TA763. Please justify why the utility values in the current submission are consistently higher than the utility values in TA763. Please provide alternative sources estimating utility values in induction, transplantation, consolidation therapy, maintenance and subsequent line of therapies.

The company acknowledges that the utility values applied in the economic analysis, derived from the PERSEUS trial, are higher than those used in the NICE appraisal for DBTd (TA763). The discrepancy in values for the progression-free (PF) health state can, in part, be attributed to the temporal differences between the two trials, with CASSIOPEIA enrolling patients between 2015 and 2017, and PERSEUS between 2019 and 2020.^{12, 14} The recent advancements in MM management mean that the prognosis for patients with NDMM enrolled in PERSEUS was substantially improved compared to those enrolled in CASSIOPEIA, leading to higher utility values for the PERSEUS trial population.

Furthermore, a utility of 0.57 for NDMM patients receiving induction therapy and undergoing ASCT, as derived from CASSIOPEIA, is notably lower than utilities reported in previous NICE appraisals for relapsed/refractory MM, thus lacking face validity. In the NICE appraisal for teclistamab (TA1015) in patients who had progressed on at least three prior therapies, those in the PF health state receiving pomalidomide with dexamethasone had a utility of 0.610.²⁶ Given that each relapse is associated with a decline in patients' physical, emotional and mental well-being, it appears that the utilities derived from the CASSIOPEIA trial are likely to substantially underestimate patient HRQoL.³⁷

The utility used in TA763 for the PD health state was sourced from the Van Agthoven *et al.* 2004 study used in the NICE appraisal for bortezomib with dexamethasone [Bd; TA311]), and, as described in Section 3.4.5 of the CS, was notably lower than utility value used in the ingoing submission's base case economic analysis.^{29, 38, 39} This is likely due to the increasing availability of more efficacious and tolerable subsequent treatments for patients with relapsed/refractory MM over time, with the Van Agthoven *et al.* 2004 study conducted around 15 years before the PERSEUS trial.^{12, 38}

Overall, the temporal differences between the PERSEUS trial, CASSIOPEIA trial and Van Agthoven *et al.* 2004 study should be taken into account to contextualise the discrepancies in utility values. Given the advancing progress of MM management with time, it is most appropriate to use values from the most recently available trial data. Furthermore, as presented in Section 3.11.3 of the CS, a scenario analysis using the utility values from TA763 had minimal impact on the ICER (£24,218 per QALY in the base case versus £25,933 per QALY in the scenario analysis). Given that DBLd-DL was found to be cost-effective irrespective utility values used, highlighting that results are robust to changes in these inputs, alternative sources were not considered necessary.

It should be noted that EQ-5D-5L utility values derived from the PERSEUS trial were cross-walked to the UK EQ-5D-3L value set, as described in Table 48 of the CS. As such, EQ-5D-3L utility values were used in the economic analysis – mention of EQ-5D-5L in Section 3.4.5 of the CS are typographical errors.

B 14. Priority. The utility value in the PD health state appears higher than those in the three PF health states. Please comment on the clinical plausibility of this outcome. Additionally, only one utility value has been applied to the PD health state across second-, third-, and fourth-line treatments. Please justify this approach and comment on whether quality of life would be expected to deteriorate with subsequent lines of therapy.

The trend in the utility values can be explained by the psychological impact of diagnosis, and HRQoL burden of treatments, which patients with HDT-ASCT NDMM experience:

- **PF (induction):** upon diagnosis with MM, patients are faced with significant psychological stress due to uncertainty about the future and anxiety surrounding their prognosis.⁴⁰ This mental distress is compounded by the burden of treatment, which represents a significant change in the day-to-day lives of patients. Moreover, until patients have responded to treatment, they would experience the symptomatic burden of MM, which is anticipated to have a substantial negative impact on their HRQoL. These are together reflected by the relatively low utility value for the PF induction health state, compared with the PD state.
- **PF (ASCT):** ASCT is an intensive treatment option associated with an increased risk of side effects as a result of compromised immunity and organ function.⁴¹ It also involves giving HDT (typically melphalan) to kill the myeloma cells and then infusing stem cells back into the patient, allowing the bone marrow to recover.^{42, 43} The HDT which patients receive prior to ASCT is associated with a number of AEs, such as alopecia, anorexia, nausea and vomiting, impacting patient HRQoL. Due to this treatment-related burden associated with HDT-ASCT, the relatively low utility value in this health state compared with the PD state, is therefore clinically plausible
- **PF (consolidation) and PF (maintenance):** the gradual increase in utilities from the preceding health states is reflective of the declining clinical and mental burden on patients, as they become accustomed to their disease and treatments. Furthermore, many experience a response during these phases of treatment, leading to improved HRQoL levels.

Taken together, the higher utility value in the PD health state compared with the PF induction, ASCT and consolidation health states are considered reflective of the treatment trajectory that HDT-ASCT eligible patients follow upon diagnosis.

With regards to the application of one utility value applied to the PD health state across second-, third- and fourth-line treatments, the company acknowledges that HRQoL would be expected to deteriorate with each subsequent line of therapy. This underscores the importance of introducing additional early-line treatment options such as DBLd-DL. It would however require substantial additional model complexity to be able to model individual later lines of therapy explicitly, requiring the addition of several additional health states to track patients through each line – for which, sufficient, appropriate data is unlikely to be readily available.

As such, as a simplifying assumption, a single utility value has been applied to the PD health state, based on utility in the PD state in the PERSEUS trial. This utility value is likely to overestimate utility throughout the entirety of the PD health state as most patients in PERSEUS only reached one subsequent line of therapy (proportion of patients receiving ≥ 1 subsequent therapies: █% [████] for DBLd-DL versus █% [████] for BLd-L). However, the impact of this assumption is likely to be conservative, considering a greater proportion of patients reach the PD health state in the DBTd-L arm compared to the DBLd-DL arm. Accordingly, if subsequent utilities were modelled granularly, then patients in the DBTd-L would move through these health states more rapidly than patients receiving DBLd-DL, thus accumulating a lower utility and fewer QALYs, ultimately resulting in a reduced ICER for DBLd-DL versus DBTd-L.

B 15. The CS states that EQ-5D-5L data for patients receiving DBLd-DL and BLd-L from the GRIFFIN and PERSEUS trials are reported in Silbermann et al. (2023) and Sonneveld et al. (2024), respectively. Please provide further detail on the utility values reported in these publications, including the health states or time points at which they were measured, and how they compare to the utility values used in the current submission.

The Sonneveld *et al.* (2024) publication provides details of the patient-reported outcome (PRO) measures, such as the EQ-5D-5L questionnaire, administered in the PERSEUS trial.¹² Details of EQ-5D-5L data collection are provided in Section 3.4.1 of the CS. The resulting EQ-5D-5L utilities are provided in the PERSEUS clinical study report, shared in the reference pack alongside the CS, and were used to derive the utilities included in the Company's economic analysis. The Least Squares (LS) mean change from baseline in PROs, including EQ-5D-5L VAS, at Maintenance Cycle 34 were reported in a conference abstract presented at the American Society of Hematology (ASH) Annual Meeting (Sonneveld *et al.* [2024]).⁴⁴

In the GRIFFIN trial, EQ-5D-5L data were collected at the following timepoints:

- Day 1 of Cycles 1, 2 and 3
- Day 21 of Cycle 4 (i.e., end of induction therapy)
- Day 21 of Cycle 6 (i.e., end of consolidation therapy)
- Months 6, 12, 18 and 24 of maintenance therapy

The resulting EQ-5D-5L utility scores are provided in the GRIFFIN clinical study report, shared alongside the response to clarification questions. A summary of these data at key timepoints are presented in Table 15

Given that EQ-5D-5L data were collected and reported by timepoint in the GRIFFIN trial, and utility values were not aggregated by health state, they cannot be compared with the values used in the company's economic analysis. However, a naïve comparison of the utility scores collected in the two trials, as presented in Table 14 and Table 15, indicates that these data are broadly comparable, with the PERSEUS values representing a more conservative measure of patient health-related quality of life (HRQoL).

Table 14: EQ-5D-5L utility scores at baseline, induction, consolidation and maintenance phase in the PERSEUS trial; ITT analysis set

	BLd arm ^a	DBLd arm ^b
Baseline	■	■
Induction Cycle 3 Day 1	■	■
Pre-ASCT	■	■
Consolidation Cycle 5 Day 1	■	■
Maintenance Cycle 7 Day 1	■	■
Maintenance Cycle 25 Day 1	■	■

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.

Abbreviations: ASCT: autologous stem cell transplant; BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; EQ-5D-5L: EuroQol Group Five Dimensions Five Levels; ITT: intent to treat; L: lenalidomide.

Source: J&J Data on File. PERSEUS Clinical Study Report (August 2023 DCO): TPR0MY05.⁸

Table 15: EQ-5D-5L utility scores at baseline, induction, consolidation and maintenance phase in the GRIFFIN trial; ITT analysis set

	BLd arm ^a	DBLd arm ^b
Baseline	■	■
Induction Cycle 3 Day 1	■	■
Induction Cycle 4 Day 21	■	■
Consolidation Cycle 6 Day 21	■	■
Month 6 of maintenance	■	■
Month 24 of maintenance	■	■

Footnotes: ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.

Abbreviations: BLd: bortezomib, lenalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; EQ-5D-5L: EuroQol Group Five Dimensions Five Levels; ITT: intent to treat; L: lenalidomide.

Source: J&J Data on File. GRIFFIN Clinical Study Report (January 2019 DCO): tproeq02.⁴⁵

Resource use and costs

B 16. Priority. Regarding drug acquisition costs, the company explained on page 183 of the CS that the dosing regimens for induction, consolidation and maintenance therapies were based on treatment protocols specified for the PERSEUS and CASSIOPEIA trials. However, for DBTd, the dose of daratumumab was based on the subcutaneous (SC) formulation (1,800 mg fixed dose), available as a result of a licence extension in June 2020, rather than on the IV formulation of daratumumab used in the CASSIOPEIA trial. Please provide further explanation on why this was done and on the implications for the effectiveness of the treatment. Please also explain whether or not this could also be relevant for the DBLd treatment arm.

In TA763 base case analysis, daratumumab was modelled based on the SC formulation following the licence extension, with a scenario analysis conducted where the weight-based dose and IV formulation of daratumumab (16 mg/kg) was used in drug acquisition and administration cost calculations for DBTd. This was found to have a limited effect on the ICER.²⁸

The EMA has accepted evidence of non-inferiority for SC versus IV daratumumab, based on the COLUMBA trial.⁴⁶

As per TA763, it is therefore expected that in clinical practice, the majority of patients would receive daratumumab administration (for DBLd or DBTd) by SC, as it represents an equally efficacious, more convenient route of administration for patients, as well as a lower cost and an increase in NHS capacity.²⁸ Data collected by J&J confirm that <2% of total daratumumab volume is administered intravenously in the NHS. Therefore, the modelling of daratumumab for both DBLd and DBTd based on the SC formulation remains appropriate.

B 17. Priority. According to Table 74 of the CS, the administration costs for subcutaneous administration were set at £115.36. However, in the electronic model (sheet 'Costs), this cost is listed as £12.82 (with a note stating that this "represents 5 minutes out of 45 of the unit cost to administer SC injection"). Please resolve this discrepancy. Furthermore, if the subcutaneous administration cost is indeed £12.82, and not £115.36, then please justify whether this is a realistic unit cost. One could argue that £12.82 appears quite low, considering that subcutaneous administration requires a hospital outpatient visit with a specialist cancer nurse (even if the injection itself takes only a few minutes).

J&J acknowledges that the administration cost of £12.82 could represent an underestimate and, as such, have amended the cost of subcutaneous administration to £115.36 (NHS National Schedule of Costs 2023/24; N10AF Specialist Nursing, Cancer Related, Adult, Face to face). However, it should be noted that the true administration cost is expected to be lower in clinical practice, given that the full 45 minutes of time would not be required to administer a single SC injection. This expectation is supported by patient expert feedback provided in TA763 regarding SC administration of daratumumab, in which a patient stated: "Because the daratumumab is now an injection instead of an infusion, I take my pre-meds before leaving for the hospital, and I can be in and out in about 15 minutes".²⁸

The deterministic economic results, with the administration cost of £115.36 applied instead of £12.82, are presented in Table 16, which reflects a marginal increase compared to the company base case ICER.

Table 16: Deterministic scenario results (revised subcutaneous administration costs; discounted daratumumab price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20,000	INHB at £30,000
Base case¹									
DBLd-DL	████	████	████	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	████	████	████	████	████	████	£23,986	████	████
Scenario									
DBLd-DL	████	████	████	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	████	████	████	████	████	████	£25,829	████	████

Footnote: ¹An error has been identified and corrected in the 'DBLd Engine' and 'DBTd Engine' tabs of the model, which impacted the fourth-line subsequent treatment acquisition and administration costs for both DBLd-DL and DBTd-L. These results reflect the correct base case.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; L: lenalidomide; LYG: life years gained; QALY: quality-adjusted life year.

B 18. On page 184 of the CS, it is mentioned that the cost per vial of bortezomib was based on the tender price. Table 69 of the CS mentions that the cost of bortezomib was sourced from Electronic Market Information Tool (eMIT, 2024). Please provide a reference. That is also relevant for the other eMIT prices used in the analyses.

The costs sourced from eMIT in the CS base case use the July 2024 values, as opposed to the December 2024 vales – a comparison of which is provided in Table 18. Updating these to the December 2024 for all relevant inputs gives the deterministic results presented in Table 17, with a negligible impact on cost-effectiveness results.

Table 17: Deterministic scenario results (revised eMIT costs; discounted daratumumab price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20,000	INHB at £30,000
Base case¹									
DBLd-DL	████	████	████	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	████	████	████	████	████	████	£23,986	████	████
Scenario									

DBLd-DL	████	████	████	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	████	████	████	████	████	████	£24,111	████	████

Footnote: ¹An error has been identified and corrected in the 'DBLd Engine' and 'DBTd Engine' tabs of the model, which impacted the fourth-line subsequent treatment acquisition and administration costs for both DBLd-DL and DBTd-L. These results reflect the correct base case.

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; eMIT: electronic market information tool; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; L: lenalidomide; LYG: life years gained; QALY: quality-adjusted life year.

Table 18: July and December 2024 eMIT costs

Treatment	July 2024	December 2024	NPC Code
	Price per vial/pack		
Bortezomib 2.5mg powder for solution for injection vials/pack size 1	£97.54	£79.76	DLK037
Bortezomib 3.5mg powder for solution for injection vials/pack size 1	£55.87	£20.30	DHA323
Lenalidomide 10mg capsules/pack size 21	£27.55	£41.24	DHA385
Lenalidomide 15mg capsules/pack size 21	£30.76	£21.59	DHA386
Lenalidomide 20mg capsules/pack size 21	£43.27	£28.08	DHK053
Lenalidomide 25mg capsules/pack size 21	£28.27	£36.10	DHB148
Dexamethasone 2mg tablets/pack size 50	£2.38	£2.19	DFN018
Thalidomide 50mg capsules/pack size 28	£280.62	£240.67	DHB163
Cyclophosphamide 1g powder for solution for injection vials/pack size 1	£13.11	£12.80	DHA014
Cyclophosphamide 2g powder for solution for injection vials/pack size 1	£27.50	£27.50	DOU014
Melphalan 50mg powder and solvent for solution for injection vials/pack size 1	£24.04	£21.32	DHA179
Paracetamol 500mg tablets/pack size 100	£0.79	£0.66	DDM003
Omeprazole 20mg gastro-resistant capsules/pack size 28	£0.33	£0.39	DAI012
Amoxicillin 500mg capsules/pack size 100	£4.06	£6.85	DEA397
Warfarin 3mg tablets/pack size 28	£0.40	£0.41	DBH083
Aciclovir 800mg dispersible tablets/pack size 35	£2.06	£2.02	DER025
Alendronic acid 70mg tablets/pack size 4	£0.26	£0.35	DFF047

Abbreviations: eMIT: electronic market information tool; g:gram; mg: milligram; NPC: National Product Code.

B 19. Table 71 of the CS shows that, in the induction phase of treatment, the relative dose intensity for daratumumab in the DBLd arm is [REDACTED]%.

Please explain how this percentage was calculated from the percentages given in the sheet ‘Drug Costs_Induction’ of the electronic model (that is, [REDACTED]%, [REDACTED]%, and [REDACTED]%).

The RDI for daratumumab in the DBLd arm during the induction phase is [REDACTED]% in Cycles 1–2, [REDACTED]% in Cycles 3–4 and [REDACTED]% in Cycles 5–6. During Cycles 1–2, daratumumab is administered a total of eight times and during Cycles 3–4, it is administered a total of four times. In the economic analysis, most patients only receive 4 cycles of induction treatment. The exception to this was patients who received an additional two cycles of induction therapy (i.e., Cycles 5–6) because timely access to ASCT was not possible for some patients in the PERSEUS trial due to the COVID-19 pandemic. The [REDACTED]% figure was applied for these patients in Cycles 5–6 of their induction therapy.

The [REDACTED]% is the RDI for daratumumab in the DBLd arm, as presented in Table 71 of the CS, and is calculated as a weighted average of the RDIs during Cycles 1–2 and 3–4, taking into account the number of administrations within each set of cycles. In the exceptional case that patients receive Cycle 5–6 of induction therapy as described above, a RDI of [REDACTED]% is used for these patients.

Health-state unit costs and resource use

B 20. Ongoing monitoring costs were included in the model, with a distinction made between the induction, consolidation, and maintenance phases of treatment (page 196 of CS). Apparently, no monitoring costs were included for the HDT-ASCT phase of treatment. Please provide a rationale for this.

Patients are monitored during both the induction and consolidation phases. Since patients receive induction, then proceed straight to receiving ASCT, which is immediately followed by consolidation therapy, monitoring before and after ASCT is captured by the ongoing monitoring costs during the induction and consolidation phases. This approach was also employed, and accepted, in the NICE appraisal for DBTd (TA763).²⁸

Adverse Events

B 21. Priority. On page 199 of the CS, it is stated that during the maintenance phase, the total cost of adverse event management was [REDACTED] for DBLd-DL and [REDACTED] for DBTd-L. However, in the electronic model (sheet ‘Base case results’), the costs of adverse event management during the maintenance phase are reported as [REDACTED] for DBLd and [REDACTED] for DBTd. Please clarify or resolve this discrepancy.

J&J thanks the EAG for flagging these discrepancies. The values reported in the CS were incorrect due to a typographical error. The values of £[REDACTED] for DBLd and £[REDACTED] for DBTd, however, are also not the total AE management costs during the maintenance phase for the base case economic analysis. The correct values should in fact be £[REDACTED] for DBLd and £[REDACTED] for DBTd. This discrepancy is due to the settings in the model not reflecting the base case economic analysis. Specifically, the source of DBLd data, as the reference curve, should be 'PERSEUS' (base case) rather than 'Pooled PERSEUS & GRIFFIN' (scenario analysis). An updated economic model set to the correct base case settings is provided alongside this clarification response.

The response to B 24. further discusses the model drivers behind this result.

B 22. Priority. On page 178 of the CS it is stated that AEs of Grade 3 or 4 occurring in $\geq 5\%$ of patients in the PERSEUS or CASSIOPEIA trials were included in the base case economic analysis. However, Table 63 also includes diarrhoea which was estimated to occur at [REDACTED]% of patients in the PERSEUS trial and [REDACTED]% in the CASSIOPEIA trial. Please confirm if this AE was included in the economic model and/or if a different rule was applied for the inclusion of AEs.

As shown in Table 63 and Table 64 of the CS, Grade 3/4 AE rates were sourced from the PERSEUS and CASSIOPEIA trial for the induction and consolidation phases, and AURIGA trial for the maintenance phase, respectively. Grade 3/4 AEs were included in the economic analysis if they occurred in $\geq 5\%$ in the DBLd or DBTd induction and consolidation arms, or the DL or L maintenance arms. In the L maintenance arm of the AURIGA trial, 5.1% of patients experienced Grade 3/4 diarrhoea and, as such, this AE was included in the model.⁵ The Company acknowledges, and apologises for, the typographical error on page 178 of the CS, which should state "AEs of Grade 3 or 4 occurring in $\geq 5\%$ of patients in the PERSEUS, CASSIOPEIA or AURIGA trials were included in the base case economic analysis", to correctly reflect the rule applied here. The wording has also amended in the updated version of the CS submitted alongside the response to clarification questions.

The Company would also like to note that the proportion of patients experiencing Grade 3/4 diarrhoea during the maintenance phase was incorrectly inputted as [REDACTED]% and [REDACTED]% for the DL and L arms, respectively. In line with Table 64 of the CS, the values should be [REDACTED]% and [REDACTED]% for the DL and L arms, respectively.⁵ These inputs, and the corresponding source, have been corrected in the updated version of the model shared alongside the response to clarification questions.

Cost-effectiveness results

B 23. Priority. Tables 88 and 89 present the deterministic results from the company's base case; however, these do not align with the results produced by the electronic model. For instance, the model estimates a base-case ICER of £23,436 per QALY gain, whereas an ICER of £24,218

is reported in Table 89. Similar inconsistencies are observed for the company's sensitivity analyses. Please ensure that the results presented in the report are consistent with those generated by the model by providing either an updated version of the model or an updated version of the submission. Consistency between outcomes in the model and report should also be ensured across all sensitivity analyses, including the DSA, PSA, and scenario analyses (in Table 92 of the CS).

J&J thanks the EAG for flagging these discrepancies. This discrepancy is due to the settings in the model not reflecting the base case economic analysis. Specifically, the source of DBLd data, as the reference curve, should be 'PERSEUS' (base case) rather than 'Pooled PERSEUS & GRIFFIN' (scenario analysis; 'Tx Efficacy' sheet, I27). Therefore, the base case cost-comparison analysis results (Table 88), deterministic base case results (Table 89) and scenario analysis results (Table 92) as well as the DSA and PSA results presented within the CS are correct.

B 24. Priority. Please explain the drivers behind the differences in estimated ASCT and AE costs between the DBLd and DBTd arms, as presented in Table 88. Furthermore, the company has stated that thalidomide-containing regimens are associated with higher rates of adverse events. Why is this not reflected in higher AE-related costs for the DBTd arm?

The proportion of patients receiving ASCT for the DBLd and DBTd arms was modelled based on the proportion of ASCT received by patients in PERSEUS (██████%) and CASSIOPEIA (██████%), respectively.^{8, 9} This results in a marginally higher costs for DBTd of £██████.

As outlined in the CS, the company has highlighted the significant safety concerns with thalidomide-containing regimens. Notably, while efficacious, thalidomide is associated with numerous severe toxicities including neuropathy, somnolence (i.e. drowsiness) and constipation, which have a substantial determinantal impact on patient HRQoL.³² This is congruent with the feedback received from UK clinical experts who highlighted the high levels of neurotoxicity associated with thalidomide and emphasised on the clear unmet need for novel, thalidomide-sparing therapies.¹

The company acknowledges that the overall AE costs for DBLd are higher than DBTd (£██████ versus £██████). However, as detailed in Section 3.14 of the CS, this is a limitation associated with the different data sources used to inform the AE rates for DBLd and DBTd, PERSEUS and CASSIOPEIA, respectively. Of note, patients who included in the CASSIOPEIA trial are considered fitter than patients included in PERSEUS, owing to the enrolment of patients up to 65 years compared to 70 years, respectively. Older patients with MM typically have an enhanced susceptibility to AEs, whilst steroid treatments are known to cause a range of AEs.^{47, 48} Indeed, differences in the protocol-defined dosing schedule of dexamethasone in the PERSEUS and CASSIOPEIA trials resulted in an overall lower cumulative dose of dexamethasone received by patients in the CASSIOPEIA versus PERSEUS trial (██████ mg versus ██████ mg, respectively), which may have also led to an increased incidence of AEs).^{8, 49}

As such, the older age and greater cumulative dexamethasone for patients receiving DBLd in the PERSEUS trial likely confounded the AE rates when compared to DBTd in the CASSIOPEIA trial. In practice, it is therefore expected that the improved safety profile of lenalidomide-based regimens versus thalidomide-based combinations would result in reduced AE management costs for patients receiving DBLd as an induction and consolidation therapy, in line with UK clinical expert input. Therefore, the base case analysis remains a conservative estimate of the true economic benefit from DBLd compared to DBTd.

B 25. Priority. It is noted that the electronic model is very slow to open and run. In particular, the PSA took over two hours to complete. Please review the model's performance and advise whether any steps can be taken to improve its efficiency.

The model's performance has been reviewed, and appropriate actions have been implemented to enhance it. This includes making structural changes to the model, such as removing placeholders related to induction, consolidation, and maintenance treatments and other redundant components. The current estimated DSA runtime is under three minutes, while the PSA runtime at 1,000 iterations, including plotting the cost-effectiveness acceptability curve, is approximately half an hour. However, these runtime estimates also depend on the computer's performance. Additionally, the model convergence is achieved at 500 iterations, therefore 1,000 iterations should be sufficient to produce robust PSA results.

B 26. Table 92 of the company submission presents the results of scenario analyses. It is noted that, under the scenario where the OS hazard ratio is set to 1 (i.e. assuming no survival benefit for DL versus L maintenance), the cost effectiveness of DBLd–DL appears to improve? As this result seems counterintuitive, please provide a detailed explanation of the mechanism underlying this outcome.

These results are driven by the increase in OS for DBTd-L resulting in increased costs which are not outweighed by the increased QALYs obtained. Specifically, patients spend an increased amount of time in the post progression health states where they accrue significantly more subsequent treatment costs. However, it should be acknowledged that several subsequent treatments include unknown PAS discounts which might change the interpretation of the results, when included.

Section C: Textual clarification and additional points

C 1. The CS frequently refers to "Table" without including the corresponding table numbers. Please ensure that all table references are correctly cross-referenced and numbered throughout the document. Please provide an updated version of the CS with all table numbers properly in place throughout the text.

The cross-references have now been updated so, for each instance where a table is referenced, the table number is now included. An updated version of the CS, with these amended cross-references, has been shared alongside the response to clarification questions.

C 2. Table 63 of the company submission presents the incidence of adverse events (AEs) for the DBLd and DBTd arms during induction and consolidation. It is noted that the percentage for lymphopenia in the DBLd arm used in the economic model (████%) differs from the value reported in Table 63 (████%). Please clarify which percentage is correct and should be used in the model. Additionally, please explain why some adverse event rates in the DBTd arm are marked as confidential while others are not.

J&J thanks the EAG for identifying this error. The correct value should be █████% as currently used in the economic model. This error has been corrected in the updated version of the CS submitted alongside the response to clarification questions.

The Moreau *et al.* 2024 publication reported safety data for the maintenance phase of the CASSIOPEIA trial. Any data in Table 63 of the CS which were reported in this publication have not been marked as confidential. The remaining AE rates in the DBTd arm have been marked as confidential as these data are confidential and not currently planned for publication.¹⁴ The source in the footnote of Table 63 has been amended to reflect this in the updated version of the CS submitted alongside the response to clarification questions.

C 3. Table 64 of the company submission presents the incidence of adverse events (AEs) for the DBLd and DBTd arms during maintenance. It is noted that the percentages in the economic model for diarrhoea in both arms differ from the values reported in Table 64. Please clarify which percentages are correct and should be used in the model.

As described in the response to question B22, the proportion of patients experiencing Grade 3/4 diarrhoea during the maintenance phase was incorrectly inputted as █████% and █████% for the DL and L arms, respectively. In line with Table 64 of the CS, the values should be █████% and █████% for the DL and L arms, respectively.⁵ These inputs, and the corresponding source, have been corrected in the updated version of the model shared alongside the response to clarification questions. J&J apologises for this error, and corrected this in the updated version of the CS submitted alongside the response to clarification questions.

C 4. Page 181 of the CS states that the derived utilities are presented below in Table 63. This should be Table 66 following the numbering.

J&J thanks the EAG for flagging this error. This cross-reference has now been corrected in the updated CS shared alongside the response to clarification questions.

C 5. On page 184 of the CS, it is stated that the administration cost of bortezomib was calculated using the mean body surface area (BSA) of patients in the PERSEUS trial, reported as 1.89m². However, both the electronic model (sheet 'Costs') and Table 47 of the CS mention a mean BSA of 1.90 m². Please clarify or resolve this discrepancy.

J&J thanks the EAG for flagging this error. The reported value of 1.89 m² was a typographical error. The correct value for the body surface area (BSA) of the overall cohort of patients in the PERSEUS trial is indeed 1.90 m², in line with Section 3.2.2 of the CS, and was the value used in the base case economic analysis. This error has been corrected in the updated version of the CS submitted alongside the response to clarification questions.

C 6. References are missing for Tables 69 to 72 in the company submission. Please provide the appropriate references for the data presented in these tables.

The relevant references have been added for Table 69 to 72 of the CS in Table 19 to Table 22 below. These references have also been added to the tables in the updated version of the CS submitted alongside the response to clarification questions.

Table 19: Drug acquisition costs for first-line treatment (daratumumab and bortezomib) (Table 69 in CS)

Treatment	Dose per administration	Total dose per administration	Vial size	Cost per vial	Vials per administration	Cost per administration	Source
Daratumumab	1,800 mg	1,800 mg	1,800 mg	£4,320	1	£4,320	BNF 2025 ⁵⁰
Bortezomib	1.3 mg/m ²	█████ mg	3.5 mg	£55.87	1	£55.87	eMIT 2024 ⁵¹

Table 20: Drug acquisition costs for first-line treatment (lenalidomide, thalidomide and dexamethasone) (Table 70 in CS)

Treatment	Unit size	Pack size	Cost per pack	Source
Lenalidomide	25 mg	21	£28.27	eMIT 2024 ⁵¹
Thalidomide	50 mg	28	£280.62	eMIT 2024 ⁵¹
Dexamethasone	2 mg	50	£2.38	eMIT 2024 ⁵¹

Table 21: Summary of RDIs for induction, consolidation and maintenance treatment (Table 71 in CS)

Treatment	Component	RDI	Source
Induction			
DBLd	Daratumumab	█████	PERSEUS ⁸
	Bortezomib	█████	
	Lenalidomide	█████	
	Dexamethasone	█████	

Treatment	Component	RDI	Source
DBTd	Daratumumab	██████████	CASSIOPEIA ⁹
	Bortezomib	██████████	
	Thalidomide	██████████	
	Dexamethasone	██████████	
Consolidation			
DBLd	Daratumumab	██████████	PERSEUS ⁸
	Bortezomib	██████████	
	Lenalidomide	██████████	
	Dexamethasone	██████████	
DBTd	Daratumumab	██████████	CASSIOPEIA ⁹
	Bortezomib	██████████	
	Thalidomide	██████████	
	Dexamethasone	██████████	
Maintenance			
DL	Daratumumab	██████████	PERSEUS ⁸
	Lenalidomide	██████████	
L	Lenalidomide	██████████	

Abbreviations: L: lenalidomide; QD: once daily; SC: subcutaneous; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; MRD: minimal residual disease; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone.

Table 22: Concomitant medication regimens unit costs (Table 72 in CS)

Concomitant medication	Dosing regimen	Strength	Drug units per pack	Cost per pack	Cost per administration	Source
Thalidomide/lenalidomide (prophylaxis for thrombosis)						
Antithrombotic: warfarin	3 mg	3 mg	28	£0.40	£1.54	eMIT 2024 (DBH083, Warfarin) ⁵¹
Daratumumab						
Antipyretic/analgesic: oral paracetamol; pre-infusion	825 mg	500 mg	100	£0.79	£0.01	eMIT 2024 (DDM003, Paracetamol) ⁵¹
Antihistamine: oral/IV hydroxyzine; pre-infusion	37.5 mg	30 mg	30	£0.75	£0.03	BNF 2025 (Hydroxyzine 25mg tablets - Medreich Plc) ⁵²
Bortezomib						
Antiviral prophylaxis: oral acyclovir	400	800	35	£2.06	£0.03	eMIT 2024 (DER025, Acyclovir) ⁵¹
Other						
Antibiotics: oral amoxicillin	960	500	100	£4.06	£0.08	eMIT 2024 (DEA397, Amoxicillin) ⁵¹

Concomitant medication	Dosing regimen	Strength	Drug units per pack	Cost per pack	Cost per administration	Source
Biphosphonate: oral alendronic acid	4	70	4	£0.26	£0.00	eMIT 2024 (DFF047, Alendronic acid) ⁵¹
Antacid: omeprazole	150 mg	20	28	£0.33	£0.09	eMIT 2024 (DAI012, Omeprazole) ⁵¹

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; IV: intravenous.

C 7. In Table 77 on Page 192 of the CS, the summary of third line subsequent treatment distributions is shown. For the belantamab mafodotin (BeBd) column, the percentages differ from what is presented in the corresponding tab in the model. Please clarify and ensure consistency in the model/supporting tables in the CS.

J&J thank the EAG for pointing out this discrepancy, which arose due to an error in the CS. The correct treatment distribution, which align with the values applied in the economic analysis, is presented below in Table 23. The amended values have been *italicised*, for clarity. The values have also been corrected in the updated version of the CS submitted alongside the response to clarification questions.

Table 23: Summary of third-line subsequent treatment distributions (Table 77 in CS)

		Distribution of third-line regimen according to second-line regimen received (%)					Median treatment duration (months)	Source of median treatment duration	Median PFS (months)	Source of median PFS
		DBd	Cad	CaLd	SBd	BeBd				
Third-line regimen	ILd	22.41	14.94	0.00	0.00	<i>5.00</i>	17.7	NICE (TA870) ⁵³	22.0	NICE (TA870) ⁵³
	SBd	28.01	28.01	24.31	0.00	<i>50.00</i>	13.0	Assumed equal to PFS	13.0	NICE (TA974) ⁵⁴
	Ld	7.47	3.73	0.00	0.00	<i>0.00</i>	11.1	Assumed equal to PFS	11.1	NICE (TA586) ⁵⁵
	PanBd	20.54	31.75	56.73	81.63	<i>20.00</i>	12.5	Assumed equal to PFS	12.5	NICE (TA380) ⁵⁶
	CTd	21.57	21.57	18.96	18.37	<i>25.00</i>	8.7	Kwon <i>et al.</i> 2016	8.7	Kwon <i>et al.</i> 2016

Abbreviations: BeBd: belantamab mafodotin, bortezomib and dexamethasone; Cad: carfilzomib with dexamethasone; CaLd: carfilzomib, lenalidomide with dexamethasone; DBd: daratumumab, bortezomib and dexamethasone; ILd: ixazomib, lenalidomide, dexamethasone; Ld: lenalidomide with dexamethasone; NICE: National Institute for Health and Care Excellence; PanBd: panobinostat, bortezomib, dexamethasone; PFS: progression-free survival; SBd: selinexor, bortezomib and dexamethasone

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**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single technology appraisal

**Daratumumab in combination for newly
diagnosed multiple myeloma when stem cell
transplant is suitable [ID6249]**

Addendum

22nd August 2025

File name	Version	Contains confidential information	Date
ID6249_Daratumumab_NICE_Addendum to Clarification Letter Response_REDACTED	V1.0	Yes	22 nd August 2025

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1 Base-Case Results

1.1 Base-case cost-comparison analysis results: induction and consolidation

The revised base-case presented in this section represents the company submission model, when accounting for corrections to inputs and calculations. These include fixing a referencing error in each of the model ‘Engine’ sheets, which impacted fourth-line treatment costs; correcting the probability of diarrhoea in maintenance to use the AURIGA trial, in line with the other adverse events; updating any eMIT costs used within the model to use the December 2024 data cut; and using the higher cost for subcutaneous injection of £115.36 (NHS National Schedule of Costs 2023/24; N10AF Specialist Nursing, Cancer Related, Adult, Face to Face).

Table 1: Base-case cost-comparison analysis results (discounted daratumumab price)

Results	DBLd	DBTd	DBLd versus DBTd
Induction			
Drug acquisition	████	████	████
Administration	████	████	██
Concomitant medications	█	█	█
Monitoring	████	████	█
ASCT			
Transplant	████	████	██
Consolidation			
Drug acquisition	████	████	████
Administration	████	████	██
Concomitant medications	█	█	█
Monitoring	████	████	█
All treatment phases			
AEs	████	████	████
Overall			
Total	████	████	████

Abbreviations: AE: adverse event; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone. Company evidence submission template for daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

1.2 Base-case incremental cost-effectiveness analysis results: induction, consolidation & maintenance

Table 2: Deterministic base-case results (discounted daratumumab price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20,000	INHB at £30,000
DBLd-DL	████	████	████	Ref	Ref	Ref	Ref	Ref	Ref
DBTd-L	████	████	████	████	████	████	£25,888	████	████

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DL: daratumumab with lenalidomide; ICER, incremental cost-effectiveness ratio; INHB: incremental net health benefit; L: lenalidomide; LYG, life years gained; QALYs, quality-adjusted life years.

Table 3: Probabilistic base case results (discounted daratumumab price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
DBLd-DL	████	██	██	Ref	Ref	Ref	Ref
DBTd-L	████	██	██	████	██	██	£27,699

Abbreviations: DBLd-DL: daratumumab + bortezomib + lenalidomide + dexamethasone; DBTd-L: daratumumab + bortezomib + thalidomide + dexamethasone with lenalidomide follow-up; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; 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,

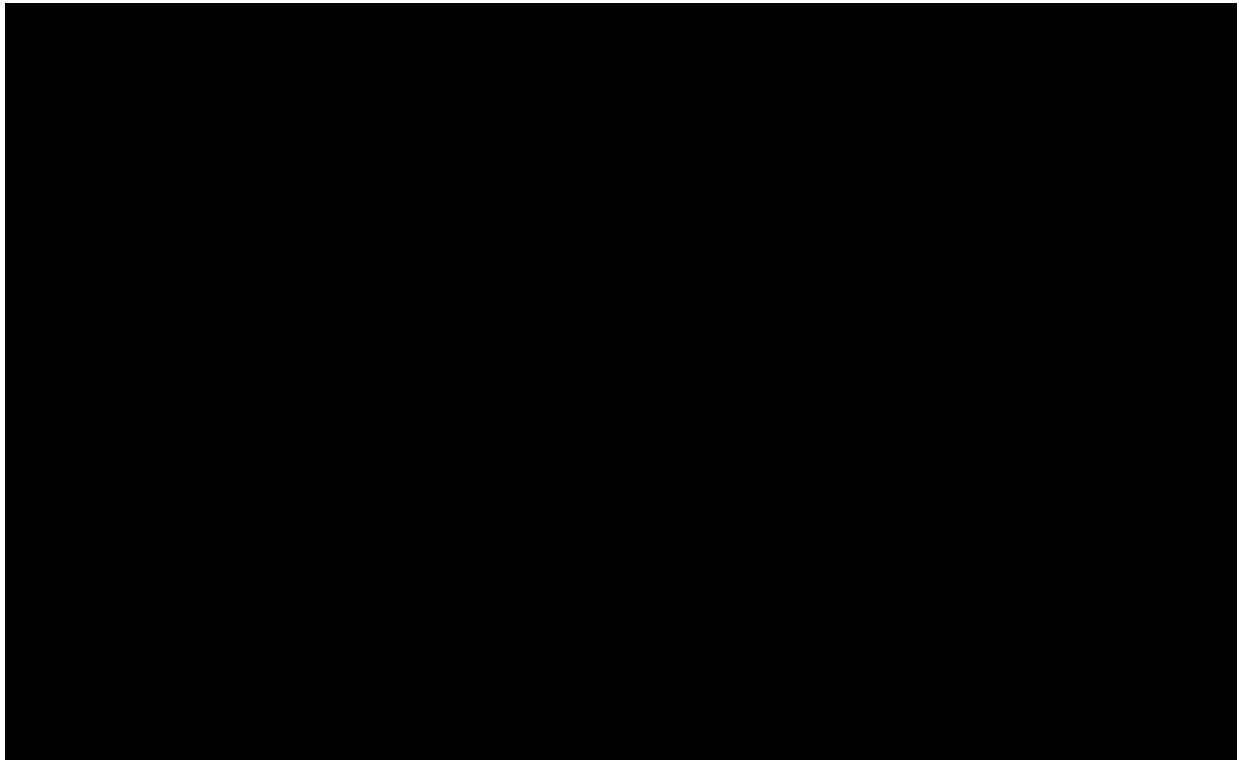
2 Exploring uncertainty

2.1 *Probabilistic sensitivity analysis*

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results were robust to those variations. A Monte-Carlo simulation with 2,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions. Estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Where no such data were available, SEs were estimated as 10% of the mean value.

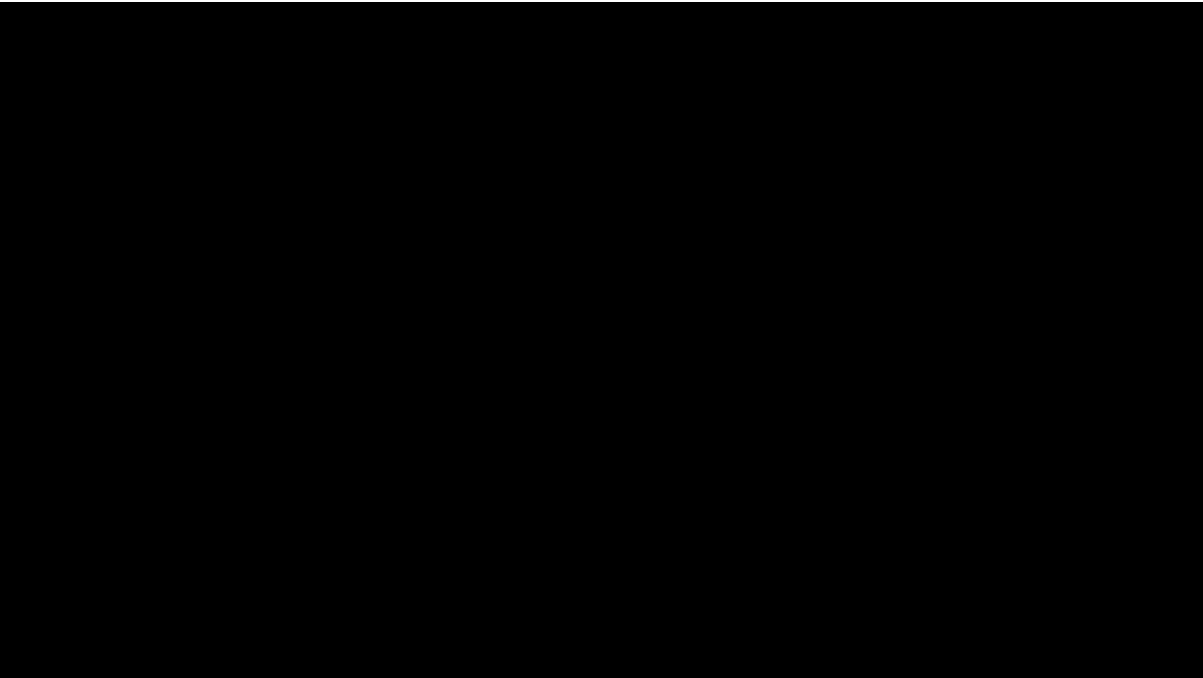
PSA results with daratumumab at PAS price

Figure 1: Incremental QALYs convergence plot (discounted daratumumab price)



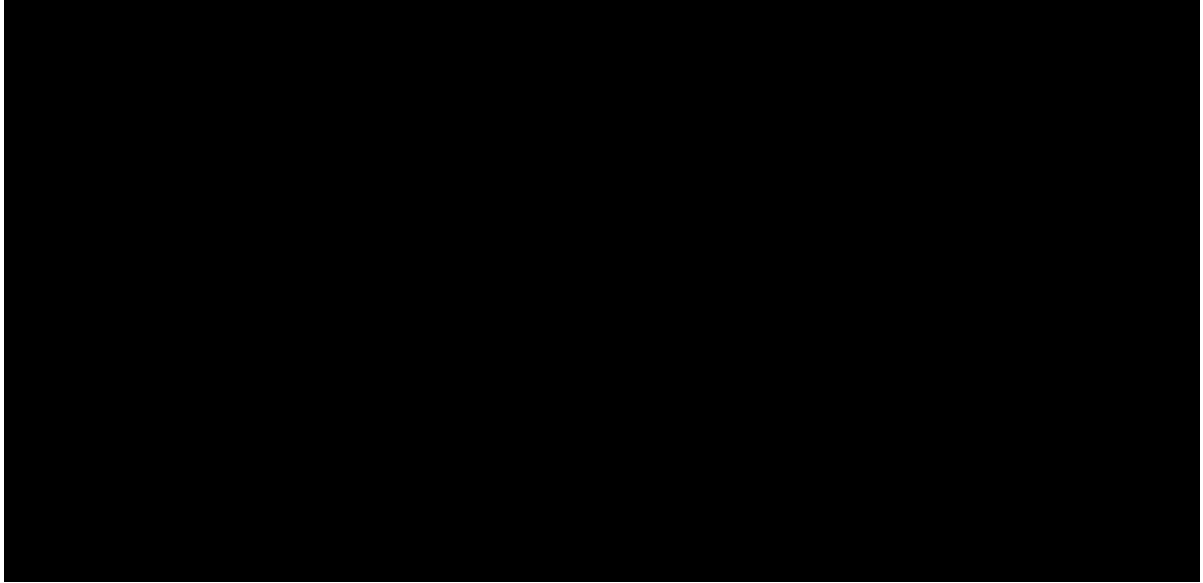
Abbreviations: PAS: patient access scheme; QALY: quality adjusted life years

Figure 2: Probabilistic cost-effectiveness plane for DBLd-DL versus DBTd-L (discounted daratumumab price)



Abbreviations: PAS: patient access scheme; QALYs: quality adjusted life years; WTP: willingness-to-pay threshold.

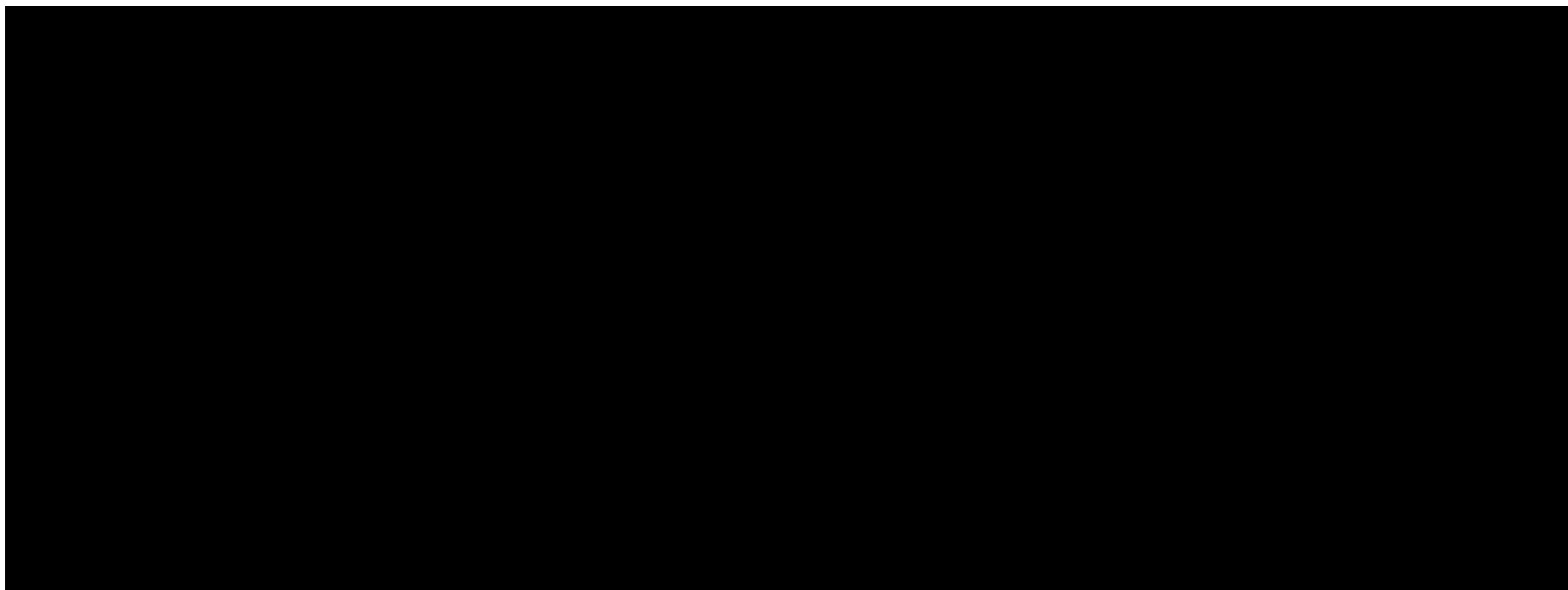
Figure 3: Cost-effectiveness acceptability curve for DBLd-DL versus DBTd-L (discounted daratumumab price)



Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; PAS: patient access scheme; QALYs: quality adjusted life years; WTP: willingness-to-pay threshold.

2.2 *Deterministic sensitivity analysis*

Figure 4: DSA tornado diagram for DBLd-DL versus DBTd-L, INHB (discounted daratumumab price)



Abbreviations: ASCT: autologous stem cell transplantation; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DSA: deterministic sensitivity analysis; HR: hazard ratio; INHB: incremental net health benefit; PAS: patient access scheme; PFS: progression-free survival; OS: overall survival.

Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

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> </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
	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																															

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable
[ID6249]

	Gilead Sciences		19000			19,000	
	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 had daratumumab containing induction treatment followed by high-dose therapy and stem cell transplantation (HDT-SCT) as part of their initial treatment. These interviews						

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

	were conducted between June-July 2025, they provide valuable real-world experience and insight data of what it is like living with myeloma. - Short online questionnaire conducted in July 2025 and completed by nine patients who had MRD tests as part of their treatment for 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.

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Living with the condition

Patient organisation submission

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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. <i>“The worst thing about the brace was that it really impacted my fitness. It really limited the amount of exercise I can do, and I know you feel 10 years older than I did before my diagnosis. I’m hoping to get back to you my usual fitness levels soon.”</i> <i>“I’m a social person, so not being able to spend time with my friends and family was massive.”</i> <i>“The tiredness – not being tired the fatigue. It is like the plugs been pulled out. I am talking to you now, animated, focused but I know that in the afternoon I will have no energy, and it just doesn’t fill back up even if I rest.”</i> Symptoms are often severe at diagnosis. Many patients are diagnosed with severe complications such as spinal fracture, or reduced kidney function. Therefore, many newly diagnosed patients need support and treatment for associated complications as well as myeloma. This can lead to a higher burden for carers especially when a newly diagnosed is admitted to hospital or struggling with their mobility. 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.

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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)

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	<i>“The hardest part is knowing it’s still there. It’s not quite a loaded gun but it’s that uncertainty. I have my blood test on Fridays and then have to wait the weekend and Monday to find out the result on Tuesday.”</i> <i>“When we had a plan, it was easier, now what’s not so easy is knowing what comes next, that is the unpredictable nature of the condition.”</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. Many patients also spoke about the impact myeloma has had on their overall fitness and how they can’t be as active as they used to be. <i>“It is huge it is life changing, it something that you never think it would be you. It has changed perspective for all of us. I am taking ill health retirement because for the first time I have to think shorter term not longer term. That was a huge mind shift before it was when I retire, we’ll do this. But now we have a now plan – the plan we had for ten years’ time we will do as soon I am well enough to do it. That plan is very different, the places we wanted to go and the things we wanted to do – we’ve talked, and I have accepted that our life is very different now.”</i> <i>“I call it my new norm, because it’s a completely different feeling to how I was feeling before I started on the treatment. I think it’s going to take a while. Most of the time I’m fine but there’s days when I think I’d just like to curl up and go asleep and can everyone leave me alone for a day or two.”</i> <i>“The physical side makes it really difficult – when you are used to being fit healthy, on the go, working full time, to not have that is really difficult.”</i> <i>“I used to be really busy person. I used to come down and clean for my mother. I used to do her shopping, I used to do my own. I was 100 miles an hour. I can’t do that anymore. My physicality is reduced. My stamina is reduced. I don’t feel like I have strength anymore.”</i> 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.

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	Patients who get HDT-SCT as part of their initial treatment tend to be the younger, fitter patients. They are more likely to be working at the time of diagnosis and therefore the financial impact of myeloma is greater due to the need to take time off work for treatment. Many of the patients we spoke to decided to take ill-health retirement following their diagnosis. <i>“They said all along that once I was in remission I could return to go back to teaching, but I worked with young children nursery age and early years children. I weighed up the risks of being around them with all their germs and things. Even when I’m in remission I’ve had to accept that I’m still immunosuppressed, so I decided that I wasn’t going to go back to work.”</i> Patients were aware that their life may be shortened, and their future plans limited by myeloma. This is challenging to deal with and is felt more acutely by younger patients. <i>“After they told me, I couldn’t manage it very well. I was absolutely terrified. I thought, am I going to die immediately? Because I had got things that I wanted to do for heaven’s sake. I was only 67. I thought, I don’t want my life to be over yet, I want to do things.”</i> <i>“There’s a lot of emotional changes. The fact that you’ve had your life mapped out – I mean, I never wanted to retire. I was fit and healthy. All of these have an emotional scar as well, you know, I’ve not been able to go on holiday with my friends, things like that.”</i> It is also important to acknowledge that younger patients are more likely to have children or elderly patients they are caring for, and partners who are working. Therefore, fatigue, regular hospital visits and reduced mobility has a wider impact on their family and the family dynamics. <i>“It has been a total life changer really for the whole family.”</i> <i>“To see mum with no hair, with no energy – it is really hard for the family dynamic.”</i>

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

	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. <i>“It’s hard for them (my family) and they don’t always get the support they need.”</i> <i>“I think its affected my family more than its affected me, because I’m the one that’s being treated and have all the professionals around. It’s the family that sometimes need a bit more support... I think the effect is on them more than me because I’m going through it and I know how I feel, and they’ve got to walk around on eggshells if I’m having a bad day.”</i> 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 <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>

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 an autologous stem cell transplant is suitable
[ID6249]

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 was confident we could treat it - I was approved for daratumumab and got the latest treatment. It was a psychological boost to be on the best treatment available on the NHS.”</i> Initial treatment for myeloma patients who are eligible for high-dose therapy and stem cell transplantation is very intensive with the initial phases of induction, high dose chemotherapy, stem cell transplant and consolidation taking over a year to complete. During this time patients have frequent hospital visits and typically spend 2-6 weeks in hospital when having the high-dose chemotherapy and stem cell transplantation. <i>“The only good point of the stem cell transplant was that it worked, because it was awful. It was definitely the worst time. You know, the sickness, diarrhoea, hair loss, loss of appetite, fatigue, everything. I was in hospital for just under 3 weeks and I kept telling myself this is a horrible time, but it will pass. I wasn’t in any pain, but it was horrible, uncomfortable, disgusting, but I just knew it would be a short time in my life in order to get better.”</i> <i>“You become very vulnerable. I was on my own in isolation. I couldn’t open a window – the air has to be filtered, the water has to be filtered. And, you know, I only allowed my husband to come and see me, and he would sit at the far end of the room wearing a mask because he was frightened of giving me something.”</i> <i>“Until it started and until they showed me the course, I didn’t realise how long it was going to be. It almost became a whole year of my life of sitting on and off in a hospital chair waiting for someone to be seen.”</i> 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. <i>“It’s the horrible side effects I don’t like. They’re horrible. Dexamethasone kept me up all night. Daratumumab made everything taste of metal. Bortezomib gave me the eye problem. Thalidomide was like a little horror story lurking, I thought I don’t really want this.”</i> <i>“I felt like the thalidomide was like a tranquiliser, it did make feel really quite sluggish. I know that it is highly toxic.”</i>

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“The worst was probably the dex. It was a lot. I couldn’t sleep. Or I got up at two or three o’clock and was just pacing the room. I went down at 4 for breakfast. It also affected my mood. I got aggressive. I didn’t know I was. I would get fixated on things. I was completely unaware, I thought I was just being normal. My family were the ones suffering, not me. We had to come up with a plan.”

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

Peripheral neuropathy is a common side effect caused by myeloma treatments in particular bortezomib and thalidomide. Peripheral neuropathy can be extremely painful and causes numbness and loss of function in the hands and feet.

“The neuropathy, in my fingers, it’s like coming inside from being out in really cold, freezing weather. Thankfully, I was never at a stage I couldn’t drive.”

Some patients found the injections in the stomach hard to deal with, particularly the large daratumumab injections, because of the swelling, bruising, and scarring they caused. This was often compounded by the number of injections they had to get – bortezomib, daratumumab, GCSF, supportive treatments. However, overall patients felt the injections were better than infusions because they are much faster.

“For me I found the injections under the skin really difficult because there were so many – when I started treatment even my blood thinners were going in there. My stomach was really badly swollen from where the injections were. I can still see the marking now.”

“The good thing about [DVTD] is that it’s just jabs in the stomach. When someone says chemo, you instantly think of being given chemo intravenously and sat up in hospital for five hours a day. It wasn’t that, it was literally just in and out to have a jab once a week, so that was a great thing.”

³ Myeloma UK (2024) Unmet need research: Diagnosing myeloma and its related conditions earlier and better, data on file
Patient organisation submission

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. <i>“You hear of so many people these days who get cancer but whenever I hear of them it's a cancer that can be cured. So, it always goes across my mind that they're going to get their treatment and be fit and well again. The hardest part for me to get used to was the incurable bit.”</i> 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.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

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[ID6249]

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 <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> The patients we spoke to about daratumumab with bortezomib, lenalidomide and dexamethasone (DVRD) commented that it looked similar to the treatments they had because it contained 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>“It’s similar to what I’ve had and the ease of the actual treatment, I think it’s good. You don’t get anywhere without some side effects.”</i> <i>“It’s exactly like what I’ve had. The only changes that I heard that they were going to do was the change between the thalidomide to lenalidomide.”</i> <i>“I’m very much whatever treatment brings the best success, I’m willing to take. I’m prepared to put up with anything if it works.”</i> DVRD delivers deep, sustained responses. We believe the depth of responses DaraVRD 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. 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>

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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.

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	<i>“I had the bone marrow biopsy 100 days after my transplant, and I had no cancerous cells that were detected. I did it, and I was chuffed to bits when he said there was no residual disease.”</i> 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. A key advantage of the regimen being assessed in this appraisal is that it doesn't contain thalidomide. Whilst thalidomide is effective, it is known to have significant side effects and to be hard to tolerate. It is associated with a higher risk of peripheral neuropathy than lenalidomide. Peripheral neuropathy has a significant impact on the lives of myeloma patients and carers. It affects the dexterity of hands and feet and causes chronic pain and tingling which can make some daily tasks more challenging. Some patients saw the MRD testing and associated stopping rule for daratumumab as an advantage because it would mean that they no longer needed to come into the hospital for further treatment. However, other patients were apprehensive about the test and how it would impact them if they found out they were MRD-positive. <i>“I was offered an MRD test. I got some information about it. Me and my husband decided I would rather not know. The result wouldn't change what we want to do. I think psychologically I think that could be harder. We decided no.”</i> <i>I would be happy to come off Daratumumab if MRD was negative as the less therapies the better.</i> Patients who have had MRD tests as part of their treatment felt that MRD should be offered to all patients, particularly when there was a clinical reason to do so. MRD tests were seen as a useful tool to assess how well a treatment has worked, to inform the next stage of treatment but to also provide reassurance. <i>“To know I am MRD negative means I can put myeloma to the back of my mind for a bit. I'm only 45 with a young son so I want to focus on getting back to work and enjoying my life. The test result has helped me do that.”</i>

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	<i>“The biggest advantage [of MRD testing] for me is the reassurance that there is no sign of myeloma and that the treatment I have received so far has worked extremely well.”</i> <i>“Treatment could be adjusted based on MRD tests. For example, trials might show that it is safe for those who are MRD negative to discontinue lenalidomide after a while. For younger patients, we need to balance pushing the cancer back with damaging our bodies with toxic drugs.”</i> <i>“Everyone should have a relatively regular MRD check given it’s the most sensitive test we have for myeloma.”</i>

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Disadvantages of the technology

Patient organisation submission

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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.⁶ 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. 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. The mode of administration, with regular trips to the hospital, was considered a slight disadvantage by some patients. Continued monthly injections would 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. For others, it could limit the ability to get back to normal life and limit their travel plans. 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. They were also aware that the monthly injections would likely coincide with other regular appointments and tests. <i>“It sounds really weird this, but I actually enjoyed going into hospital. Where I went at [the hospital], the people there are fantastic. I made so many friends and every time I walked in it was ‘hello, how are you?’ and you’d sit down and chat. You’d actually forget that you’re there for treatment.”</i> The need for additional bone marrow biopsies to assess MRD status were seen as a slight disadvantage, because bone marrow biopsies are often painful and are something that patients don’t want to have if they don’t need to. However, most patients felt the benefits of the MRD testing and the possibility of stopping treatment outweighed the disadvantages. <i>“They weren’t pleasant, I’d say that’s the only pain I’ve felt is when I had the bone marrow biopsies. But if they’re only once or twice a year or two years then that’s not a problem.”</i>

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	<i>“My doctors talked me through that [biopsies], and I wouldn’t go through with that again. I mean that was the new treatment, but I could not face the bone marrow biopsy again. It was horrific.”</i>

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.	This treatment would be hugely beneficial to patients who don’t achieve a complete response with the current standard of care. DVRD gives people access to daratumumab maintenance which has been shown to improve complete response rates.

⁶ 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

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We don't anticipate that a positive recommendation would impact people protected by the equality legislation differently to the wider population. As with all treatments the costs incurred by hospital visits and time off work will have a more significant impact on people with lower incomes.

Other issues

13. Are there any other issues that you would like the committee to consider?	Whilst the MRD related stopping rule for daratumumab is generally seen as an advantage by most patients, it is not for all. There needs to be flexibility within the recommendation for patients to continue or restart maintenance when clinically appropriate or when bone marrow biopsies are unsuitable. For example, in patients with high-risk, highly aggressive myeloma, stopping daratumumab could be detrimental and lead to earlier relapse. If the implementation of the stopping rule is too strict some patients may opt against the treatment to avoid bone marrow biopsies.

Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• The patient population covered in this appraisal make up almost one third of all myeloma patients. They are generally younger and fitter and therefore eligible for HDT-SCT. • 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. • DRVD delivers deep, durable responses that are higher than the current standard of care. • 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. • Adding daratumumab to bortezomib, lenalidomide and dexamethasone did not increase overall toxicity.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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Patient organisation submission

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable
[ID6249]

Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with multiple myeloma or caring for a patient with multiple myeloma. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

<<[Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable ID6249]>>

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm on Thursday 27 November 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

<<[Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable ID6249]>>

Part 1: Living with this condition or caring for a patient with multiple myeloma

Table 1 About you, multiple myeloma, current treatments and equality

1. Your name	Sophie Tinley
2. Are you (please tick all that apply)	☒ A patient with multiple myeloma ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with multiple myeloma ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with multiple myeloma? If you are a carer (for someone with multiple myeloma) please share your experience of caring for them	I was diagnosed with Myeloma in Jan 2020 at the age of 47 through an admission to A&E, following a brief period of aggressively progressing symptoms. Having always been fit and healthy, this came as a real shock. Few people are ever prepared for any kind of cancer diagnosis, but surely no-one can be prepared for an incurable diagnosis out of the blue. With a teenager and pre-teen at home with my husband and Covid around the corner, an incurable diagnosis followed by a 9-week, non-weight bearing, hospital stay was difficult, in fact it was traumatic for the whole family. The impact of a diagnosis such as this is far reaching, well beyond the patient themselves. With a starting point of light chains at 39,000 and high-risk genetics, everything was thrown at me. Induction had ups and downs in terms of side effects and my response. But I received great care, and the Covid pandemic didn't significantly impact the treatment I received. I managed to achieve normal Myeloma markers and get through tandem stem cell transplants throughout 2020. The response of my 12-year daughter to my remission will be forever engrained in my memory; "does that mean I don't have to worry about you anymore mummy?" I was fortunate in the timing of my diagnosis and treatment, in that Lenalidomide maintenance was approved by NICE within 3 months of my transplants and I started this maintenance in Feb 2021, have been on it and in remission ever since. Whilst I suffer from some of the standard side effects of this treatment, (mainly GI issues and fatigue), they are manageable and to me are a small price to pay for ongoing remission. I am able to live a relatively 'normal' life with this treatment and now ensure I make the most of life, working part time, fulfilling various voluntary roles and making everlasting memories with my family. I am grateful I have a life to make the most of; something which in the depths of winter in a Nottingham Hospital

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	bed, with Covid looming and an uncertain world on the horizon for everyone, let alone just me, didn't always seem possible.
7a. What do you think of the current treatments and care available for multiple myeloma on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	The care I have received at Nottingham City Hospital has been exemplary, particularly in the early days of diagnosis, induction treatment and stem cell transplants. It is heartening to know there is an increasing range of treatment available on the NHS which should enable a longer period of living with the condition. However, this needs to be considered alongside the side effects and being able to live well with these treatments over (hopefully) a prolonged period of time. There are still treatments which have significant side effects and the need for regular hospital visits which both have a detrimental impact on quality of life. Not all patients have had the quality of care I have received, and many are not fortunate to have lengthy remission times with their treatment. Many patients have also suffered significantly more than I have with side effects of ongoing treatments.
8. If there are disadvantages for patients of current NHS treatments for multiple myeloma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Side effects are often a significant disadvantage. At the point of diagnosis many patients are suffering with their initial symptoms e.g. bone issues, alongside the emotional impact of having an incurable diagnosis; induction treatment with significant side effects can further impact their ability to come to terms with their diagnosis mentally and physically. It is also incredibly important for patients to be in the best place to manage the impact of an upcoming stem cell transplant – physically and emotionally; therefore, managing the side effects of the induction treatment is an important part in achieving this. The emotional impact of treatment is a significant issue for many Myeloma patients, often most acute when treatment isn't as successful as hoped, so the risk of not reaching remission in induction treatment is a disadvantage. Ultimately the aim is to achieve as good a remission as possible at induction stage to give a patient the best chance of success in the stem cell transplant and to maintain this remission for as long as possible. This is not always achieved with current treatment – putting patients at a disadvantage into the future; emotionally if not medically. Another disadvantage is the plethora of treatment at the outset of a patients Myeloma diagnosis and how overwhelming this is, e.g. induction treatment followed

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	by HD-SCT then a different maintenance regime with an all or nothing approach. The emotional impact of this cannot be underestimated, with an inability to see beyond each stage for many patients and a lack of understanding of what the future treatment regime looks like due to it changing and the potential for being overwhelmed with so much information at a very difficult time. The unpredictability of outcome at induction stage can have a significant impact on a patient, particularly if they are not responding as well/quickly as hoped. There can be an inability to comprehend the next stages of treatment as it is less clear than they may have imagined with a continual trauma in the background of an incurable diagnosis.
9a. If there are advantages of Daratumumab with bortezomib, lenalidomide and dexamethasone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does Daratumumab with bortezomib, lenalidomide and dexamethasone help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	An advantage of this regime is a generally improved impact of side effects, e.g. lenalidomide has a lower risk of neuropathy than thalidomide. Although some side effects are potentially more likely, these can potentially be managed such as infection risk. The reduction in risk of neuropathy has an impact of quality of life on a daily and ongoing basis and will enable increased opportunity of self-care both through this treatment and into the future. The addition of a fourth drug into the combination should provide an improved outcome at induction stage and beyond. The impact on the emotional strength and stability of a patient with the potential of a better outcome must not be underestimated. Emotional strength is a key contributor to living well with Myeloma and 'getting through' HD-SCT is an early test of this. Having a good outcome at induction stage and the prospect of longer remission is a key stepping stone to this early emotional strength. The advantage of the 4-phase approach will have a medical advantage, but also an advantage to a patient's ability to understand the treatment plan. It clearly sets out the plan for the foreseeable future, with a consistent drug regime and clear plan. The ability to tailor treatment as the maintenance progresses is a positive development. It ensures patients are not subjected to treatment which they don't need, and will definitely be an advantage to emotional wellbeing for those who respond well enough to enable this tailored approach. These points together all address the disadvantages laid out in question 8.

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10. If there are disadvantages of Daratumumab with bortezomib, lenalidomide and dexamethasone over current treatments on the NHS please describe these. For example, are there any risks with Daratumumab with bortezomib, lenalidomide and dexamethasone ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The main disadvantage of this regime is the increased need for hospital visits with Daratumumab. However, the prospect of a better outcome will outweigh this for many people. Also, the prospect of a more tailored approach for MRD-ve patients to this in the maintenance phase is a welcome mitigation to this disadvantage. There is also some disadvantage in that with an increased number of drugs being used throughout the treatment, there is an increased risk of side effects, reactions to drugs and potentially a perceived build-up of impact on the body. But as a patient, my view is the benefit of the outcome should outweigh this risk for the majority of patients. Daratumumab in particular has a high risk of reaction in the first few doses, but this seems to be already managed in the way it is given with pre-meds and close observation.
11. Are there any groups of patients who might benefit more from Daratumumab with bortezomib, lenalidomide and dexamethasone or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	This appraisal is relevant to those patients suitable for autologous stem cell transplants, therefore is likely to be the patients who are 'younger/fitter'. I think this will therefore be as equally beneficial to all patients who fall within this category, providing an increased chance of a good outcome.
12. Are there any potential equality issues that should be taken into account when considering multiple myeloma and Daratumumab with bortezomib, lenalidomide and dexamethasone? Please explain if you think any groups of people with this condition are particularly disadvantage	I am not aware of any issue to consider here.

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Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Multiple Myeloma is an incurable disease; it goes without saying the treatments with the most successful outcomes are the most desirable. But this must be considered within the 'incurable, but treatable' landscape. Treatment is for life, so as well as having successful outcomes, treatment must be tolerable for patients with minimal or manageable side effects to enable the patient to live <i>well</i> as well as long with the condition. The development of new, better treatments gives patients not only a metaphorical lifeline, but a literal one. The approval of this appraisal feels like one of those lifelines, given to the patient at the outset which will help frame their whole Myeloma life. I hope my lived experience and views described here will assist in the positive outcome of this approval.

Patient expert statement

<<[Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable ID6249]>>

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Living with an incurable condition such as Myeloma is traumatic, new treatment provides a lifeline, especially early on.
- The treatment with the best outcomes are the most desirable to patients
- But being able to live WELL is also very important
- A clear, consistent treatment pathway will help patients emotionally as well as medically
- The ability to have some tailoring to the treatment is an exciting development.

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<<[Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable ID6249]>>



in collaboration with:

Erasmus School of
Health Policy
& Management



Maastricht University

Daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AdViSHE	Assessment of the Validation Status of Health-Economic decision models
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike information criterion
AIFA	Italian Medicines Agency
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplantation
ASH	American Society of Hematology
ATC	Average treatment effect for the control
ATE	Average treatment effect
ATT	Average effect of the treatment
BCd	Bortezomib, cyclophosphamide and dexamethasone
Bd	Bortezomib and dexamethasone
BDd	Bortezomib, doxorubicin and dexamethasone
BeBd	Belantamab mafodotin, bortezomib and dexamethasone
BIC	Bayesian information criterion
BLd	Bortezomib, lenalidomide and dexamethasone
BNF	British National Formulary
BSA	Body surface area
BTd	Bortezomib with thalidomide and dexamethasone
CAA	Commercial Access Agreement
Cad	Carfilzomib with dexamethasone
CADTH	Canadian Agency for Drugs and Technologies in Health
CaLd	Carfilzomib, lenalidomide with dexamethasone
CD38	Cluster of Differentiation 38 antigen (target in multiple myeloma)
CDA	Canada's Drug Agency
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CON	Confidential
CR	Complete response
CRAB	Calcium elevation, renal insufficiency, anaemia, and bone lesions
CRF	Case report form
CS	Company submission
CTd	Cyclophosphamide, thalidomide and dexamethasone
CXDY	Cycle X Day Y
D	Daratumumab
DARE	Database of Abstracts of Reviews of Effects
DBd	Daratumumab, bortezomib and dexamethasone
DBLd	Daratumumab, bortezomib, lenalidomide and dexamethasone
DBTd	Daratumumab, bortezomib, thalidomide and dexamethasone
DCO	Data cut-off
DL	Dexamethasone with lenalidomide
DOR	Duration of response
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
EBM	Evidence-Based Medicine

ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EED	Economic Evaluation Database
EHA	European Hematology Association
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	European Quality of Life Five Dimension Five Level Questionnaire
ESHPM	Erasmus School of Health Policy & Management
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EUHEA	European Health Economics Association
EUR	Erasmus University Rotterdam
FE	Fixing errors
FISH	Fluorescence in situ hybridisation
FLC	Free light chains
FV	Fixing violations
G-BA	Gemeinsamer Bundesausschuss
GPM	Generalised population mortality
HAS	Haute Autorité de Santé
HCRU	Health care resource use
HDT	High-dose therapy
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSUV	Health-state utility value
HTA	Health Technology Assessment
I+C	Induction and consolidation
I+C+M	Induction, consolidation and maintenance
ICER	Incremental cost-effectiveness ratio
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IHEA	International Health Economics Association
ILd	Ixazomib, lenalidomide and dexamethasone
IMiD	Immunomodulatory drug
iMTA	Institute for Medical Technology Assessment
IMWG	International Myeloma Working Group
INHB	Incremental net health benefit
IPD	Individual patient data
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
IQWiG	Institute for Quality and Efficiency in Health Care
IsaBLd	Isatuximab, bortezomib, lenalidomide and dexamethasone
ISCIH	Institute of Health Carlos III
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISS	International Staging System
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system

KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
L	Lenalidomide
Ld	Lenalidomide with dexamethasone
LDH	Lactate dehydrogenase
LS	Least squared
LT	Liver transplant
LYs	Life years
LYG	Life years gained
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MJ	Matters of judgement
MM	Multiple myeloma
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
N/A	Not applicable
NCPE	National Centre for Pharmacoeconomics
NCRAS	NHS Digital National Cancer Registration and Analysis Service
NDMM	Newly diagnosed multiple myeloma
NE	Not evaluable
NGS	Next-generation sequencing
NHS	National Health Service
NI	No Information
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NL	The Netherlands
NMA	Network meta-analysis
NR	Not reported
NSC	National Schedule of Costs
ONS	Office for National Statistics
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PanBd	Panobinostat, bortezomib and dexamethasone
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
Pd	Pomalidomide with dexamethasone
PD	Progressive disease
PF	Prognostic factor
PF	Progression-free
PFS	Progression-free survival
PFS2	Second progression-free survival (or sequential)
PH	Proportional hazards
PI	Proteasome inhibitor
PK	Pharmacokinetics
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year

QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RoB	Risk of bias
RWE	Real world evidence
SAE	Serious adverse event
SBd	Selinexor, bortezomib and dexamethasone
SC	Subcutaneous
sCR	Stringent complete response
SD	Stable disease
SD	Standard deviation
SE	Standard error
SLiM	60% clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of 100 or more with the involved serum free light chain being ≥ 100 mg/l, and magnetic resonance imaging with more than one focal marrow lesion
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SMDM	Society for Medical Decision Making
SmPC	Summary of product characteristics
SoC	Standard of care
SPEP	Serum protein electrophoresis
TA	Technology Appraisal
TE	Transplant eligible
TEAE	Treatment-emergent adverse event
Tec	Teclistamab
TEM	Treatment effect modifier
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTDD	Time to treatment discontinuation duration
TTP	Time to progression
UK	United Kingdom
ULN	Upper limit of normal
UMC+	University Medical Centre+
UPEP	Urine protein electrophoresis
US	United States
VAS	Visual analogue scale
VGPR	Very good partial response

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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. If possible, 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 presents the key model outcomes. Section 1.3 discusses the decision problem (DP), Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues relate to the cost effectiveness (CE). A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (DP), 3 (clinical effectiveness) and 4 (CE) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	Uncertainty as to the intervention.	2.2
2	Uncertainty as to the comparator for a small percentage of patients.	2.3
3	Lack of comparison of complete treatment sequence.	3.12, 3.25, 3.3 and 3.4
4	In the base-case ITC, lack of balance of three priority covariates.	3.3 and 3.4
5	The immaturity of the survival data (OS, PFS and TTD) included in the appraisal.	4.2.6.1, 4.2.6.2 and 4.2.6.3
6	The lack of validation efforts on the model outcomes.	5.2.1
7	The economic model fails to capture the full impact of including subsequent lines of treatment.	4.2.2, 4.2.5 and 5.2.1
ITC = indirect treatment comparison; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation		

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the following:

- Assuming a Gompertz distribution for daratumumab, bortezomib, lenalidomide, and dexamethasone – dexamethasone with lenalidomide (DBLd-DL) progression-free survival (PFS).
- Using time to treatment discontinuation (TTD) data from the lenalidomide (L) arm of AURIGA to inform TTD for daratumumab, bortezomib, thalidomide, and dexamethasone – lenalidomide (DBTd-L).

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, based on the company's base-case results, the new technology is modelled to affect QALYs by:

- Increasing total QALYs due to patients remaining longer in the maintenance phase of treatment and shorter in post-progression. This is caused by an improvement in overall survival (OS) and PFS.
- Slightly reducing QALYs due to adverse events (AEs).

Overall, based on the company's base-case results, the new technology is modelled to affect costs by:

- Decreasing total costs during the induction, autologous stem cell transplantation (ASCT) and consolidation phases.
- Increasing total costs during the maintenance phase, mostly due to daratumumab (D) acquisition costs. The increase in costs in the maintenance phase is approximately [REDACTED] higher than the reduction in costs during the induction, ASCT and consolidation phases.
- Reducing costs associated to subsequent lines of treatment and terminal care.

In most scenarios explored by the company, changes in ICERs were relatively modest compared with the base-case analysis. However, the EAG considered that the number of scenarios explored by the company was not sufficient to provide a balanced overview of the current structural uncertainty. The EAG explored a substantially larger number of scenario analyses and based on these concluded that the model results were sensitive to changes in certain key assumptions, which was not captured by the company's scenario analyses.

1.3 The decision problem (DP): summary of the EAG's key issues

The DP addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is uncertainty as to the intervention (Table 1.2) as well as on certain comparators (Table 1.3).

Table 1.2: Key issue 1: Uncertainty as to the intervention

Report Section	2.2
Description of issue and why the EAG has identified it as important	The scope and DP seem to match. However, the company has responded to the scope by carrying out a cost comparison for induction and consolidation treatment (DBLd) versus SoC (DBTd), as well as a CEA of DBLd followed by DL maintenance versus DBTd followed by L maintenance. This means that effectively there are two interventions, i.e. the complete sequence (induction, consolidation and maintenance) or induction and consolidation only (followed by SoC).
What alternative approach has the EAG suggested?	None.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG understand that it is up to the committee which intervention or interventions to consider, and which method of analysis i.e. CEA or cost comparison.
CE = cost effectiveness; CEA = cost-effectiveness analysis; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; DP = decision problem; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; L = lenalidomide; SoC = standard of care	

Table 1.3: Key issue 2: Uncertainty as to the comparator for a small percentage of patients

Report Section	2.3
Description of issue and why the EAG has identified it as important	The company stated that DBTd was used by █████% patients according to NHS England data. The EAG clinical expert also supports DBTd as SoC.
What alternative approach has the EAG suggested?	The EAG requested clarification as to SoC for the remainder of patients to which the company responded that very small percentage of patients not treated with DBTd are treated with BCd, “...given that cyclophosphamide can be preferred in some cases of renal impairment, due to the toxicity concerns associated with thalidomide.”
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Further data or expert opinion could be employed to check whether BCd is the only other treatment and its indication. This could then inform a decision as to whether a formal clinical effectiveness or CEA is required for these patients.
BCd = bortezomib, cyclophosphamide and dexamethasone; CE = cost effectiveness; CEA = cost-effectiveness analysis; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; SoC = standard of care	

1.4 The clinical effectiveness evidence: summary of the EAG’s key issues

Table 1.4: Key issue 3: Lack of evidence for a comparison of the complete treatment sequence

Report Sections	3.12, 3.25, 3.3 and 3.4
Description of issue and why the EAG has identified it as important	The company could find no evidence to compare DBLd induction and consolidation followed by DL maintenance with DBTd induction and consolidation followed by L maintenance. Therefore, they compared DBLd with DBTd in the induction and consolidation phase only via an ITC using the intervention arm of the pivotal PERSEUS trial and the intervention arm (DBTd) of the CASSIOPEIA trial. They compared DL with L in the maintenance phase only via another RCT i.e. AURIGA. In the economic model, only the results from AURIGA were used to inform the treatment effect (difference between intervention and comparator), with the assumption that there was no difference in effectiveness occurring in the induction and consolidation phase. Whilst this does appear to be conservative, given that the ITC does appear to show an advantage in short term outcomes i.e. up to the beginning of maintenance, this does mean that the results of the pivotal trial are not used to inform the treatment effect in the economic analysis. Also, although the SLR to look for studies to compare the complete sequence seems to be adequate, the search for studies to compare DL with L in the maintenance phase was pragmatic, using only the records excluded at full text from the search to inform the SLR of the complete sequence i.e. induction, consolidation and maintenance.
What alternative approach has the EAG suggested?	None.

Report Sections	3.12, 3.25, 3.3 and 3.4
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	To locate maintenance phase trials, the company could screen all references excluded at the title and abstract stage of the SLR designed to find trials of the full sequence. It is unclear to the EAG what other approach could be taken if, as it appears there is no evidence by which the full treatment sequences can be compared. Also, if the appropriateness of the ITC, and the fact that it is censored prior to maintenance also needs to be considered as a component in the comparison of the treatment sequence.
CE = cost effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = dexamethasone with lenalidomide; EAG = External Assessment Group; ITC = indirect treatment comparison; L = lenalidomide; RCT = randomised controlled trial; SLR = systematic literature review	

Table 1.5: Key issue 4: In the base-case ITC, lack of balance of three priority covariates

Report Sections	3.3 and 3.4
Description of issue and why the EAG has identified it as important	In the base-case ITC analyses, three priority covariates (presence of extramedullary plasmacytomas, LDH and bone lesions) between the DBTd population and the DBLd population were not well balanced after matching.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	There is probably nothing that can be done to address this issue.
CE = cost effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; EAG = External Assessment Group; ITC = indirect treatment comparison; LDH = lactate dehydrogenase	

1.5 The CE evidence: summary of the EAG's key issues

A full summary of the CE evidence review conclusions can be found in Section 5.4 of this report. The EAG's summary and detailed critique can be found in Section 4, the company's CE results are presented in Section 5.1, and the EAG's amendments to the company's model and results are in Section 5.2. The key issues in the CE evidence are discussed in Tables 1.6, 1.7 and 1.8 below.

Table 1.6: Key issue 5: Survival data (OS, PFS and TTD) immature

Report Sections	4.2.6.1, 4.2.6.2 and 4.2.6.3
Description of issue and why the EAG has identified it as important	There is uncertainty in the long-term OS and PFS predictions based on the alternative extrapolations and in the relative treatment effectiveness, driven by the precision of the PFS and OS HRs estimates. Some uncertainty is inevitable due to the immaturity of the survival data from the PERSEUS and AURIGA trials, which reflects a generally good prognosis of HDT-ASCT-eligible

Report Sections	4.2.6.1, 4.2.6.2 and 4.2.6.3
	NDMM patients, the high proportion achieving durable responses to DBLd-DL, and the availability of effective subsequent therapies. There is also uncertainty around TTD assumptions. The option to treat until progression resulted in large ICERs due to the high costs of D treatment which under this assumption are extended over time. The model results are also sensitive to changes in the extrapolation curve for TTD for MRD+ patients. If the company considers a functional cure plausible, fitting survival models such as mixture cure models is an option to include functional cure in the economic model.
What alternative approach has the EAG suggested?	The EAG explored scenario analyses assuming different (standard) extrapolations for PFS, OS and TTD.
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Long-term data, where available. With the current data, explore more flexible extrapolations methods (if for example functional cure is deemed plausible).
ASCT = autologous stem cell transplant; CE = cost effectiveness; D = daratumumab; EAG = External Assessment Group; HDT = high-dose therapy; HRs = hazard ratios; ICER = incremental cost-effectiveness ratio; NDMM = newly diagnosed multiple myeloma; MRD = minimal residual disease; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation	

Table 1.7: Key issue 6: The validity of the model outcomes not sufficiently explored

Report Section	5.2.1
Description of issue and why the EAG has identified it as important	Previous daratumumab appraisals such as TA763 were used to validate the model structure, input parameters and assumptions. This could have been used to validate the results for the comparator arm (DBTd-L) in this appraisal to confirm that either they are in line or to explain the differences. The EAG highlighted a [REDACTED] difference in total life years estimated for DBTd-L in TA763 (14.66) and the current appraisal ([REDACTED]). From all the OS extrapolations explored by the company, the log-normal distribution results in the highest life years estimated for DBTd-L ([REDACTED]), which is slightly more than [REDACTED] less than the estimate in TA763. This raises some concerns regarding the validity of the model results and further exploration of this potential issue is therefore recommended. Additionally, there is a large deviation between the deterministic and PSA results. The EAG was not able to identify the cause of this discrepancy at the time this report was completed.
What alternative approach has the EAG suggested?	Explore scenario analyses where life years estimated for DBTd-L are closer to those in TA763. Explore and explain or resolve the large deviation between the deterministic and PSA results.
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Use TA763 (or other relevant evidence) to validate the results for the comparator arm (DBTd-L) in this appraisal.

Report Section	5.2.1
CE = cost effectiveness; CS = company submission; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; EAG = External Assessment Group; L = lenalidomide; OS = overall survival; TA = Technology Appraisal	

Table 1.8: Key issue 7: The economic model fails to capture the full impact of including subsequent lines of treatment

Report Sections	4.2.2, 4.2.5 and 5.2.1
Description of issue and why the EAG has identified it as important	The company included 2nd, 3rd and 4th line treatment in the model, but only on the costs side. Utilities remain constant after progression and survival probabilities do not seem to have been adjusted for subsequent lines of treatment. Assuming constant utilities upon progression, while a simplifying assumption, has a relatively small impact on model outcomes and is likely conservative with respect to the incremental QALYs gained, as a higher proportion of patients transition to the PD health state in the DBTd-L arm compared with the DBLd-DL arm. It seems reasonable to assume that survival prognosis gets worse as patients progress to subsequent treatment lines. If this is not properly captured in the economic model, then the estimated LYs and QALYs are likely overestimated. This raises some concerns regarding the second key issue since in comparison with TA763, the current appraisal estimates substantially less LYs for the comparator arm. If the current analyses underestimate LYs and QALYs because they fail to capture the impact of subsequent lines of treatment, then the discrepancy might be even larger. The company also indicated that most patients in PERSEUS received only one subsequent line of therapy (with the proportion of patients receiving one or more subsequent lines of therapy in the PERSEUS trial being ■■■% in the BLd-L arm and ■■■% in the DBLd-DL arm). This means for example that ■■■% of patients in the BLd-L arm did not get subsequent lines of therapies.
What alternative approach has the EAG suggested?	Include impact of subsequent lines of treatment in both survival and HRQoL (but not feasible with current data).
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Collect survival and HRQoL data for subsequent treatment lines.
CE = cost effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; EAG = External Assessment Group; HRQoL = health-related quality of life; L = lenalidomide; LYs = life years; QALYs = quality-adjusted life years; TA = Technology Appraisal	

1.6 Secondary issues identified by the EAG

No secondary key issues were identified by the EAG.

1.7 Company's modelling errors identified by the EAG

The EAG encountered several inconsistencies encountered between the data reported in the CS and used in the economic model. This was flagged by the EAG in the clarification letter but, although some improvements were made by the company, these inconsistencies remained in the documents submitted by the company in response to the clarification letter. When these inconsistencies were identified, the EAG assumed that the values in the economic model were the correct ones.

1.8 Summary of the EAG's preferred assumptions and resulting ICER

The step-by-step changes made by the EAG to derive its base-case and the cumulative impact of each change can be seen in Table 1.7. The change with the largest impact on the results was assuming a Gompertz distribution for DBTd-DL PFS. Implementing the two EAG's preferred changes yielded an ICER of £38,483 per QALY gained, when DBLd-DL is compared to DBTd-L. The EAG's base-case ICER increased thus by approximately 49% compared to the company's base-case ICER.

Table 1.9: Cumulative impact of EAG's preferred assumptions (deterministic)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company base-case (after clarification)					
DBLd-DL	██████	██████	██████	██████	25,888
DBTd-L	██████	██████			
EAG Step 1 – Gompertz distribution for DBTd-DL PFS					
DBLd-DL	██████	██████	██████	██████	38,296
DBTd-L	██████	██████			
EAG Step 2 – Step 1 + TTD data from L arm of AURIGA to inform TTD for DBTd-L					
DBLd-DL	██████	██████	██████	██████	38,483
DBTd-L	██████	██████			
Based on the model submitted following clarification DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Inc. = incremental; L = lenalidomide; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation					

1.9 Outline of confidential comparator or subsequent treatment prices

A confidential appendix to this EAG report includes analyses using confidential comparator prices. The treatments that have commercial arrangements can be found in Section 5.4 of this report.

2. Critique of company's definition of decision problem (DP)

Table 2.1: Statement of the DP (as presented by the company)

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
Population	Adult patients with NDMM who are eligible for HDT-ASCT		N/A	DP and scope are the same.
Intervention	DBLd for induction and consolidation treatment followed by DL for maintenance treatment	In line with the NICE final scope for induction and consolidation (DBLd) and maintenance (DL)	DBLd for induction and consolidation treatment followed by DL for maintenance treatment	The intervention is in line with the NICE scope. However, the company has conducted a CEA for the complete sequence i.e. induction, consolidation and maintenance, and a cost only comparison for the induction and consolidation phase only i.e. DBLd followed by SoC, which is L (as opposed to DL).
Comparator(s)	Induction and consolidation therapy • DBTd • BTd • BCd (off-label) • Bd Maintenance therapy • L	Induction and consolidation therapy • DBTd Maintenance therapy • L	DBTd is considered the only relevant comparator for DBLd induction and consolidation therapy for patients with NDMM who are eligible for ASCT and is recommended by NICE for this indication (TA763). During the DBTd appraisal, the Committee's preferred assumption was that BTd was the most relevant comparator to DBTd from the comparators listed in the NICE scope, which also included CTd, Bd and BCd. Given that TA763 subsequently demonstrated that DBTd is associated with significant survival benefits over BTd, DBTd is now the predominantly	The comparators are in line with the NICE scope, although a small percentage of patients seem to be treated with BCd.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
			used treatment option in this setting. The predominance of DBTd is supported by new patient initiation data received from NHS England, which confirmed 1,587 new DBTd patient initiations for the 12-month period June 2024 to May 2025 (equivalent to 98.9% assuming an available pool of █████ HDT-ASCT eligible patients with NDMM) (refer to Budget Impact Analysis for further details of patient pool estimate). In line with this, feedback from UK clinical experts at a May 2025 Advisory Board indicated that DBTd represents standard of care for HDT-ASCT eligible patients with NDMM in UK clinical practice, received by approximately 95–98% of patients. Consequently, BTd, BCd and Bd induction and consolidation therapies are not relevant comparators in this indication. With regards to maintenance treatment, feedback from UK clinical experts indicated that 95% of patients in UK clinical practice receive L as maintenance therapy, which is recommended by NICE for this indication (TA680). As such, DBTd is considered to be the only relevant comparator to DBLd as	

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
			an induction and consolidation treatment in this indication. Furthermore, L is considered to be the only relevant comparator to DL as a maintenance treatment for this submission.	
Outcomes	PFS OS Response rates MRD negativity status Proportion of patients undergoing HDT-ASCT HRQoL AEs		In line with the final scope.	DP in line with the scope.
Economic analysis	The reference case stipulates that the CE of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and CE should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a NHS and PSS perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	The economic analysis aligns with that described in the NICE DP	N/A	As per the NICE reference case.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
	technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			
Based on Table 1 of the CS¹ AE = adverse event; ASCT = autologous stem cell transplant; BCd = bortezomib, cyclophosphamide and dexamethasone; Bd = bortezomib and dexamethasone; BTd = bortezomib with thalidomide and dexamethasone; CE = cost effectiveness; CEA = cost-effectiveness analysis; CS = company submission; CTd = cyclophosphamide, thalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; DP = decision problem; EAG = External Assessment Group; HDT = high-dose therapy; HRQoL = health-related quality of life; L = lenalidomide; MM = multiple myeloma; MRD = minimal residual disease; N/A = not applicable; 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; QALY = quality-adjusted life year; SoC = standard of care; TA = Technology Assessment; UK = United Kingdom				

2.1 Population

The population defined in the scope, and the decision problem (DP) is: Adult patients with newly diagnosed multiple myeloma (NDMM) who are eligible for high-dose therapy- (HDT-) autologous stem cell transplantation (ASCT).^{1, 2}

EAG comment: The scope and DP populations are the same.

2.2 Intervention

The intervention in the scope and the DP is daratumumab, bortezomib, lenalidomide, and dexamethasone (DBLd) for induction and consolidation followed by daratumumab with lenalidomide (DL) maintenance.

EAG comment: The scope and DP seem to match. However, the company has responded to the scope by carrying out a cost comparison for induction and consolidation treatment (DBLd) versus standard of care (SoC) daratumumab, bortezomib, thalidomide and dexamethasone (DBTd), as well as a cost effectiveness analysis (CEA) of DBLd followed by DL maintenance versus DBTd followed by lenalidomide (L) maintenance. The EAG therefore asked the company to clarify what is assumed to follow induction and consolidation in the cost comparison i.e. is it only SoC, which is L for both intervention and comparator, to which the company responded that this is indeed the case.³ Therefore, there appear to be in effect two interventions, one of which is for induction and consolidation only, and the other which includes DL for maintenance. The uncertainty as to which is the appropriate intervention therefore constitutes a key issue.

2.3 Comparators

The comparators in the scope are:²

For induction/consolidation:

- Bortezomib with dexamethasone or with dexamethasone and thalidomide
- Bortezomib with cyclophosphamide and dexamethasone (off-label)
- Daratumumab with bortezomib, thalidomide and dexamethasone

For maintenance:

- Lenalidomide

In the DP they are:

- Induction and consolidation therapy
 - DBTd
- Maintenance therapy
 - Lenalidomide

The company stated that DBTd was used by [REDACTED] patients according to National Health Service (NHS) England data.¹

EAG comment: As mentioned in Section 2.2, it has been clarified that there are two interventions in the company submission (CS), which implies two comparators, but not entirely as indicated in the scope or the DP i.e. for induction and maintenance the comparator is as shown, but there is no separate comparison for the maintenance phase, but instead the complete sequence of DBTd followed by L in the CEA.

The company also clarified that most patients are treated with DBLd according to the May 2025 Advisory Board, and that the very small percentage of patients not treated with DBTd are treated with bortezomib, cyclophosphamide and dexamethasone (BCd), “...given that cyclophosphamide can be preferred in some cases of renal impairment, due to the toxicity concerns associated with thalidomide.”³ Although the EAG clinical expert confirmed that SoC is DBTd, there remains some uncertainty as to the comparator, which therefore constitutes a key issue.

2.4 Outcomes

The outcomes in the DP were those in the NICE scope.

EAG comment: None.

2.5 Other relevant factors

None.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.¹ The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.⁴ The External Assessment Group (EAG) has presented only the major limitations of each search strategy in the report.

Appendix B of the CS details two systematic literature reviews (SLRs) conducted to identify relevant clinical evidence on the efficacy and safety of treatments for patients with NDMM who are eligible for HDT-ASCT.⁵

EAG comment:

- Two SLRs were conducted to identify relevant clinical evidence on the efficacy and safety of treatments for patients with NDMM who are eligible for HDT-ASCT. The first focused on treatments specifically in the induction and consolidation setting (the induction and consolidation [I+C] SLR), and the second focused on treatments in the induction, consolidation and maintenance settings (the I+C+M SLR).
- The CS, Appendix B and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{1, 3, 5}
- The I+C SLR was conducted in May 2018 and updated in April 2023 and February 2025. The I+C+M SLR was conducted in September 2023 and updated in February 2025.
- For both SLRs, the following databases were searched: Embase, MEDLINE (including MEDLINE In Process), the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE). In addition to the above, the Cochrane Central Register of Controlled Trials (CENTRAL) was searched for the original and first update, and the Health Technology Assessment (HTA) Database and the NHS Economic Evaluation Database (NHS EED) were searched for the second update.
- The conferences of five key organisations were reviewed for relevant abstracts between January 2018 and February 2025, through the Embase search and via relevant websites: American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Hematology Association (EHA), International Myeloma Working Group (IMWG), International Society for Pharmacoeconomics and Outcomes Research (ISPOR).
- The websites of the following HTA organisations were searched in April 2025: National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Canada's Drug Agency (CDA), Pharmaceutical Benefits Advisory Committee (PBAC), National Centre for Pharmacoeconomics (NCPE).
- The National Institutes of Health (NIH) ClinicalTrials.gov trials registry was searched in April 2025 to identify potentially relevant ongoing clinical trials, and reference lists were scanned.
- For the I+C SLR the searches were limited to records published since 1995. For the I+C+M SLR the searches were limited to records published since 2000. No language limits were applied to any of the searches.
- All database strategies searched for a range of terms for NDMM. The population facet was then combined with a study design filter for randomised controlled trials (RCTs). The study design filters

contained a range of free-text terms for RCTs and clinical trials. The EAG believes that the addition of subject headings (Medical subject headings [MeSH]/Emtree) to these strategies, or the use of published objectively-derived filters could have improved the identification of potentially relevant RCTs.

- The EAG noted that an RCT filter was applied to searches of the Cochrane Library. The databases within this resource are already pre-filtered by study design, and therefore the use of a filter could be considered to be overly restrictive.
- Overall, the clinical effectiveness searches were well structured, transparent and reproducible, and contained a good range of search terms, synonyms and subject headings.

3.1.2 Inclusion criteria

The company confirmed in the CS that they conducted two SLRs to identify relevant clinical evidence on the efficacy and safety of treatments for patients with NDMM who are eligible for HDT-ASCT.¹ The first SLR was described as being focused on treatments specifically in the induction and consolidation setting (Table 3.1) (referred to as the I+C SLR); while the second SLR focused on treatments in the induction, consolidation and maintenance settings (Table 3.2) (referred to as I+C+M SLR).¹

Table 3.1: Eligibility criteria used for the I+C clinical SLR

	Inclusion	Exclusion
Population	HDT-ASCT eligible patients with NDMM	• Patients without a primary diagnosis of MM • Patients with previously-treated MM • Patients with transplant-ineligible MM
Interventions/comparators	• Licensed treatments, treatments used in routine care, or treatments under investigation provided as a single-agent or a combination treatment • These include, but are not limited, to the following: ○ DBLd ○ DBTd ○ BLd ○ BTd ○ BCd ○ BDd ○ ILd ○ CTd ○ IsaBLd	• Interferon alpha used as monotherapy or in combination • Studies evaluating the preferred sequence of treatments • Treatments aimed at managing complications of MM that are not provided as part of best supportive care or as a combination treatment with a drug of interest (i.e., calcium, zoledronic acid, antibiotics, or bisphosphonate)

	Inclusion	Exclusion
Outcomes	Morbidity and survival outcomes: ○ OS ○ PFS ○ TTP ○ PFS2 Response outcomes including, but not limited to: ○ ORR ○ sCR ○ CR ○ VGPR ○ PR ○ SD ○ DOR ○ MRD Safety outcomes including, but not limited to: • Discontinuations due to AEs • Grade 3/4 AEs	Publications that do not report on clinical efficacy or safety outcomes (i.e., study protocols [which were listed in a bibliography list but not explored further])
Study design	RCTs (phase II and III)	• Single-arm studies • Case reports/case-series • Comments and editorials • Animal/in-vitro studies • Observational studies • SLRs^a
Time point	• During and post-induction (pre-transplantation) • Post-ASCT and before the start of consolidation • Post-consolidation • Before maintenance (in those studies that provide maintenance treatment) • Long-term survival outcomes	
Date limit	• Publications indexed in electronic databases since January 1995 • Abstracts and other material from conferences from 2018	• Conference abstracts or materials presented prior to 2018
Language restrictions	English language only	Non-English language publications

	Inclusion	Exclusion
Based on Table 9, CS Appendices⁵ AE = adverse event; ASCT = autologous stem cell transplant; BCd = bortezomib, cyclophosphamide and dexamethasone; BDd = bortezomib, doxorubicin and dexamethasone; BLd = bortezomib, lenalidomide and dexamethasone; CR = complete response; CS = company submission; CTd = carfilzomib, thalidomide and dexamethasone; (D)BLd = (daratumumab) bortezomib, lenalidomide and dexamethasone; (D)BTd = (daratumumab) bortezomib, thalidomide, dexamethasone; DOR = duration of response; HDT = high-dose therapy; I+C = induction and consolidation; ILd = ixazomib, lenalidomide, and dexamethasone; IsaBLd = isatuximab, bortezomib, 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 = second progression-free survival (or sequential); PR = partial response; RCT = randomised controlled trial; sCR = stringent complete response; SD = stable disease; SLR = systematic literature review; TTP = time to progression; VGPR = very good partial response		

Table 3.2: Eligibility criteria for the I+C+M clinical SLR

	Inclusion	Exclusion
Population	HDT-ASCT eligible patients with NDMM	- Patients without a primary diagnosis of MM - Patients with previously-treated MM - Patients with transplant-ineligible MM
Intervention/Comparators	- Licensed treatments, treatments used in routine care, or treatments under investigation provided as a single-agent or a combination treatment. - These include, but are not limited, to the following: - DBLd - DBTd - BLd - BTd - BCd - BDd - ILd - CTd - IsaBLd AND at least one identifiable maintenance treatment	- Interferon alpha used as monotherapy or in combination. - Studies evaluating the preferred sequence of treatments. - Treatments aimed at managing complications of MM that are not provided as part of best supportive care or as a combination treatment with a drug of interest (i.e., calcium, zoledronic acid, antibiotics, or bisphosphonate).
Outcomes	Morbidity and survival outcomes: - OS - PFS - TTP - PFS2	Publications that do not report on clinical efficacy or safety outcomes (i.e., study protocols [which were listed in a bibliography list but not explored further])

	Inclusion	Exclusion
	Response outcomes including, but not limited to: ○ ORR ○ sCR ○ CR ○ VGPR ○ PR ○ SD ○ DOR ○ MRD Safety outcomes including, but not limited to: ○ Discontinuations due to AEs ○ Grade 3/4 AEs	
Study Design	RCTs (phase II and III)	• Single-arm studies • Case reports/case-series • Comments and editorials • Animal/in-vitro studies • Observational studies • SLRs^a
Time Point	• During and post-induction (pre-transplantation) • Post-ASCT • Post-consolidation • Before maintenance (in those studies that provide maintenance treatment) • Long-term survival outcomes	
Date Limit	• Publications indexed in electronic databases since 2000 • Abstracts and other material from conferences from 2018	• Publications index in 1999 or previous years • Conference abstracts or materials presented prior to 2018
Language	English language	Non-English language publications
Based on Table 18, CS Appendices.⁵ Footnotes: a search strategy included SLRs, and the bibliographies of relevant SLRs were reviewed for any additional studies. AE = adverse event; ASCT = autologous stem cell transplant; BCd = bortezomib, cyclophosphamide and dexamethasone; BDd = bortezomib, doxorubicin and dexamethasone; BLd = bortezomib, lenalidomide and dexamethasone; CR = complete response; CS = company submission; CTd = carfilzomib, thalidomide and dexamethasone; (D)BLd = (daratumumab) bortezomib, lenalidomide and dexamethasone; (D)BTd = (daratumumab) bortezomib, thalidomide, dexamethasone; DOR = duration of response; HDT = high-dose therapy; I+C = induction and consolidation; ILd = ixazomib, lenalidomide, and dexamethasone; IsaBLd = isatuximab, bortezomib, 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 = second progression-free survival (or sequential); PR = partial response; RCT = randomised controlled trial; sCR = stringent complete response; SD = stable disease; SLR = systematic literature review; TTP = time to progression; VGPR = very good partial response		

EAG comment: Note from the DP (see Sections 2.2 and 2.3), that these SLRs were intended to find evidence for the complete sequence of treatments i.e. induction, consolidation and maintenance, or induction and consolidation only, given the two possible interventions i.e. DBLd followed by DL maintenance, or DBLd only. Given that the only difference between the two SLRs was that the second added a criterion of requiring a maintenance phase treatment, it is unclear why a single SLR was not conducted, with studies being divided according to whether there was a maintenance treatment. However, this should not preclude the identification of both those with and those without maintenance.

Given that the company did not find any studies that compared the complete sequence of DBLd followed by lenalidomide with dexamethasone (Ld) with SoC in the form of DBTd followed by L, they then decided to compare induction and consolidation treatments only and, separately, maintenance treatments only, the former via an indirect treatment comparison (ITC) (see Sections 3.3 and 3.4). The latter required an additional search for maintenance only treatments in order to compare DL with L.

The EAG were concerned about company claiming that a process of ‘*pragmatic re-evaluation of previously excluded studies in order to find additional evidence that could inform a comparison of DL vs. L maintenance*’ was conducted. The company was asked to provide clarification on this. In their response, the company stated that:³ “*The AURIGA trial was not initially included in the induction, consolidation and maintenance phases SLR (referred to as the I+C+M SLR), in line with its eligibility criteria, given that it only assessed treatment in the maintenance phase. This initial screening did not identify evidence that was sufficient to address the decision problem.*”³. The company went on to say that: “*...to determine whether any studies were available that were conducted in the population of relevance to this submission (i.e., HDT-ASCT eligible patients with NDMM) and provided evidence on the comparative efficacy of DL versus L, the title/abstract of studies which were excluded at the full-text review stage of the I+C+M SLR, as they were restricted to the maintenance phase only, were re-screened. Subsequent targeted searches in Google Scholar were conducted to ensure all relevant publications reporting on any studies of interest had been captured. A list of the 67 studies which were pragmatically re-evaluated can be found in the Appendix submitted alongside the response to clarification questions. Through this pragmatic re-evaluation, AURIGA was found to be the only available source of evidence for the comparative efficacy of DL versus L maintenance.*”

The EAG considers that this approach may well have been prone to bias and error and may risk excluding studies that were not initially identified. Ultimately, only those studies initially included at first stage screening were revisited while targeted Google Scholar checks are not systematically implemented searches to identify evidence: it is unclear as to how Google Scholar was searched, terms that were used, or language limits. The company do seem to take a conservative approach in the economic model by assuming equal effectiveness, in terms of overall survival (OS) and progression-free survival (PFS), in the induction and consolidation phase in the base-case CEA of the complete treatment sequence, which might mitigate this problem with the maintenance phase. Nevertheless, the lack of rigour implies uncertainty as to the evidence to inform DL versus L maintenance, and thus the comparison of the complete sequence, which implies a key issue.

3.1.3 Critique of screening and data extraction

Appendix B of the CS⁵ states that two independent reviewers screened abstracts for inclusion and where disagreements existed and consensus could not be reached, a third investigator resolved the disagreement. All included studies were then retrieved for full text screening and again screened by two independent reviewers with the involvement of a third where necessary.

EAG comment: This process would be an optimal method to minimise the likelihood of error and bias. However, when the company was asked by the EAG to describe the process of critical appraisals (see Section 3.1.4) they responded by saying that this was conducted by one reviewer and checked by a second. The company then went on to say that:³ *“This method aligns with that used for study selection at both the title and abstract and full-text screening stages.”* It is clear that this response creates uncertainty as the company have now claimed to have implemented two distinct methods during screening. For clarity, both these methods are legitimate and reasonable, but the method as initially described in the CS which utilises two independent reviewers is more robust and reliable than the use of one reviewer with a second conducting checks and so this raises the likelihood of error and bias being present.

Additionally, it is unclear as to which process was utilised for data extraction. There is no information provided and while it is likely reasonable to assume that data extraction followed a similar method as screening, the ambiguity over the conflicting information on screening methods coupled with the lack of reporting means that there is uncertainty and as such a higher likelihood of error and bias must also be considered for the process of data extraction.

3.1.4 Quality assessment

The company provided details on the critical appraisals of the included evidence within the CS and the associated appendices. The PERSEUS and AURIGA were assessed for risk of bias using the Cochrane RoB 2.0 Quality Assessment tool 2.0 and the company also emphasise that: *‘The quality assessment was based on published sources for the trial, where possible, and supplemented with information provided in the trial protocol’*.¹

EAG comment: Like the process of data extraction, it was unclear how the critical appraisal of the relevant trials had been conducted. The EAG requested clarification on this matter and in their response the company stated that:³ *“The risk of bias assessment was performed by a single reviewer and checked by a second reviewer. Any discrepancies that arose during their reviews were resolved through discussion or the intervention of a third reviewer.”* This method is not as robust as appraisals being conducted in duplicate and independently, however it is a reasonable approach to minimise error and bias.

Tables 3.3 and 3.4 below contains the risk of bias (RoB) appraisal of the relevant trials. The final column contains comments from the EAG where appropriate if the EAG view differed to that of the company.

Table 3.3: RoB of PERSEUS

Study question	Grade (Yes/No/Unclear)	Justification	EAG comment
Bias arising from the randomisation process			
1.1 Was the allocation sequence random?	Y	Patients were randomly assigned (1:1) to intervention and comparator by randomly permuted blocks using an IWRS	N/A
1.2 Was the allocation sequence concealed until	Y	IWRS was employed for randomisation,	N/A

Study question	Grade (Yes/No/Unclear)	Justification	EAG comment
participants were recruited and assigned to interventions?		ensuring allocation concealment.	
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	The baseline characteristics were similar between the groups	Minor differences at the 5% level in the type of measurable disease with those in the BLd arm having less IgG detection compared to the DBLd arm (52.3% versus 57.5%) but more IgA detection (24% versus 18.3%). May not be clinically or statistically relevant but suggests unequal weighting.
RoB 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	Due to the open-label nature of the study, participants were aware of their treatment assignment	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	Due to the open-label nature of the study, carers and those delivering the assigned intervention were aware of their treatment assignment	N/A
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	There was no evidence of discontinuations or switches based on the CONSORT diagram	N/A
2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	N/A	N/A as there were no deviations reported	N/A
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	N/A	N/A as there were no deviations reported	N/A
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used	N/A
2.7 If N/PN/NI to 2.6: Was there potential for a	N/A	N/A	N/A

Study question	Grade (Yes/No/Unclear)	Justification	EAG comment
substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?			
RoB judgement	Low	-	N/A
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	N/A
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	N/A	N/A	N/A
RoB judgement	Low	-	
Bias in measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	N	The outcomes and their measurement methods were clearly defined	N/A
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Objective outcomes and standardised criteria were used for measurement	N/A
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were aware of the treatments due to the open-label design	N/A
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N/A	N/A	N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by	N/A	N/A	N/A

Study question	Grade (Yes/No/Unclear)	Justification	EAG comment
knowledge of intervention received?			
RoB 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	Data were in line with the well-documented, pre-specified analysis plan	N/A
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	The primary outcome had a single definition, and other analyses were transparently defined	N/A
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	No evidence of selective reporting of outcomes	N/A
RoB judgement	Low	-	
Overall RoB judgement	Low		
Based on Table 11, CS ¹ BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; EAG = External Assessment Group; IgA = immunoglobulin A; IgG = immunoglobulin G; IWRS = interactive web response system; ITT = intention-to-treat; N = no; N/A = not applicable; NI = no information; RoB = risk of bias; Y = yes			

Table 3.4: RoB of AURIGA

Study question	Grade (Yes/No/Unclear)	Justification	EAG comment
Bias arising from the randomisation process			
1.1 Was the allocation sequence random?	Y	Patients were randomly assigned (1:1) to DL or L maintenance using an IWRS with randomly permuted blocks.	N/A
1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Y	The study utilised an IWRS ensuring allocation concealment until assignment.	N/A

Study question	Grade (Yes/No/Unclear)	Justification	EAG comment
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	Baseline characteristics were generally balanced between the groups as presented in the results.	N/A
RoB judgement	Low	-	N/A
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	This was an open-label study, so participants were aware of their treatment assignment.	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	Open-label design meant that carers were aware of the treatment assignments.	N/A
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 the need to switch treatments due to the trial context was indicated.	N/A
2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	N/A	N/A due to no deviations reported.	N/A
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	N/A	N/A	N/A
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	The study used an ITT analysis approach to estimate the effects.	N/A
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 randomised?	N/A	N/A since appropriate analysis was used.	N/A
RoB judgement	Low	-	N/A

Study question	Grade (Yes/No/Unclear)	Justification	EAG comment
Bias due to missing outcome data			
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcomes were reported for all randomised patients.	N/A
3.2 If N/PN/Ni to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A since data availability was adequate.	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A	N/A
3.4 If Y/PY/Ni to 3.3: Is it likely that missingness in the outcome depended on its true value?	N/A	N/A	N/A
RoB judgement	Low	-	N/A
Bias in measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	N	The outcomes were well-defined and appropriate measurement methods were used.	N/A
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Objective outcomes were measured using standardised criteria, which mitigates differences in measurement.	N/A
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 design means assessors were aware of the treatment received.	N/A
4.4 If Y/PY/Ni to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	Standardised criteria were employed, reducing the influence of awareness.	N/A
4.5 If Y/PY/Ni to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N/A	N/A	N/A
RoB judgement	Low	-	N/A

Study question	Grade (Yes/No/Unclear)	Justification	EAG comment
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 finalised before unblinded outcome data were available for analysis?	Y	The methods and outcomes were clearly reported and aligned with pre-specified plans.	N/A
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	The primary outcome was singularly defined, with clear reporting of other analyses.	N/A
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	No evidence suggests selective reporting among the analyses.	N/A
Risk of bias judgement	Low	-	N/A
Overall risk of bias judgement	Low		
Based on Table 87 CS Appendices ⁵ CS = company submission; DL = daratumumab and lenalidomide; EAG = External Assessment Group; IWRS = interactive web response system; L = lenalidomide; ITT = intention-to-treat; N = no; N/A = not applicable; NI = no information; RoB = risk of bias; Y = yes			

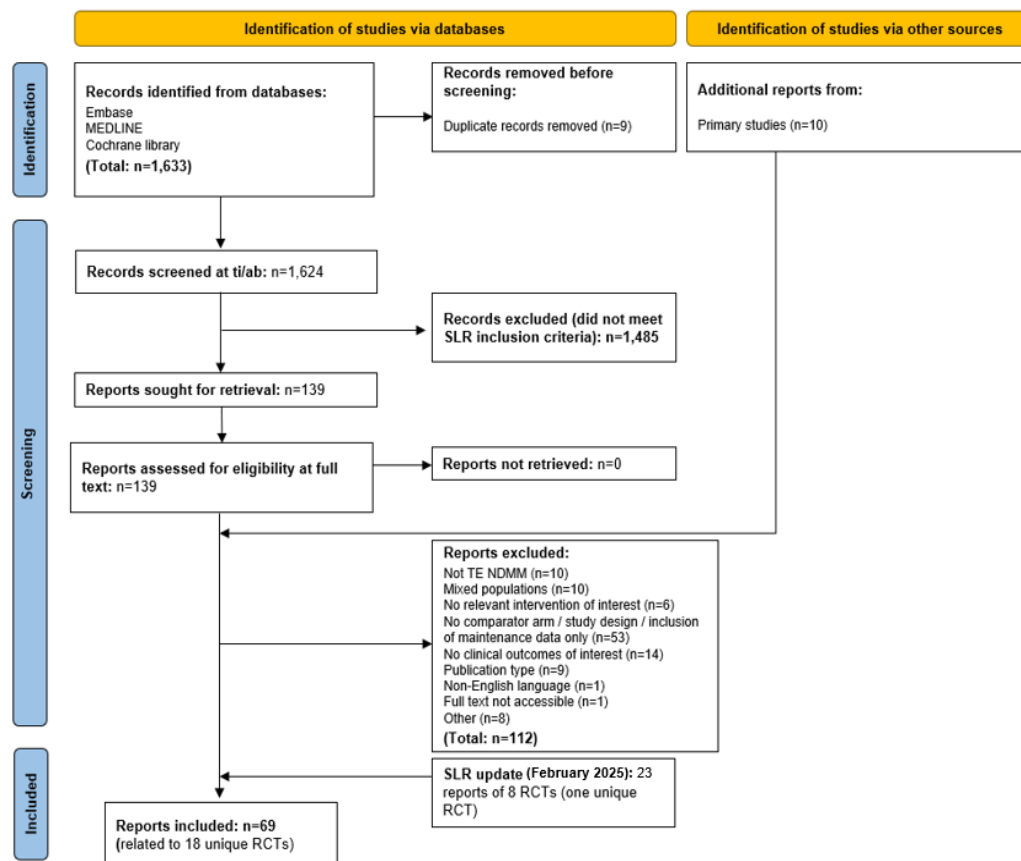
3.1.5 Evidence synthesis

It was not possible to conduct direct comparative analysis full treatment sequence of relevance to this submission compared to United Kingdom (UK) SoC so evidence was identified from the PERSEUS trial to inform DBLd treatment benefit as part of an ITC used to compare DBLd versus DBTd with respect to induction and consolidation therapy (see Sections 3.3 and 3.4 of this report), while the AURIGA trial was used as a primary evidence base to inform a comparison of DL versus L maintenance therapy (see Section 3.2).

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

3.2.1 Study retrieval

As described in Section 3.1.1 above, two searches were conducted for two separate SLRs to identify evidence relevant for this submission. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowcharts detailing the process of study selection in each SLR are provided below.

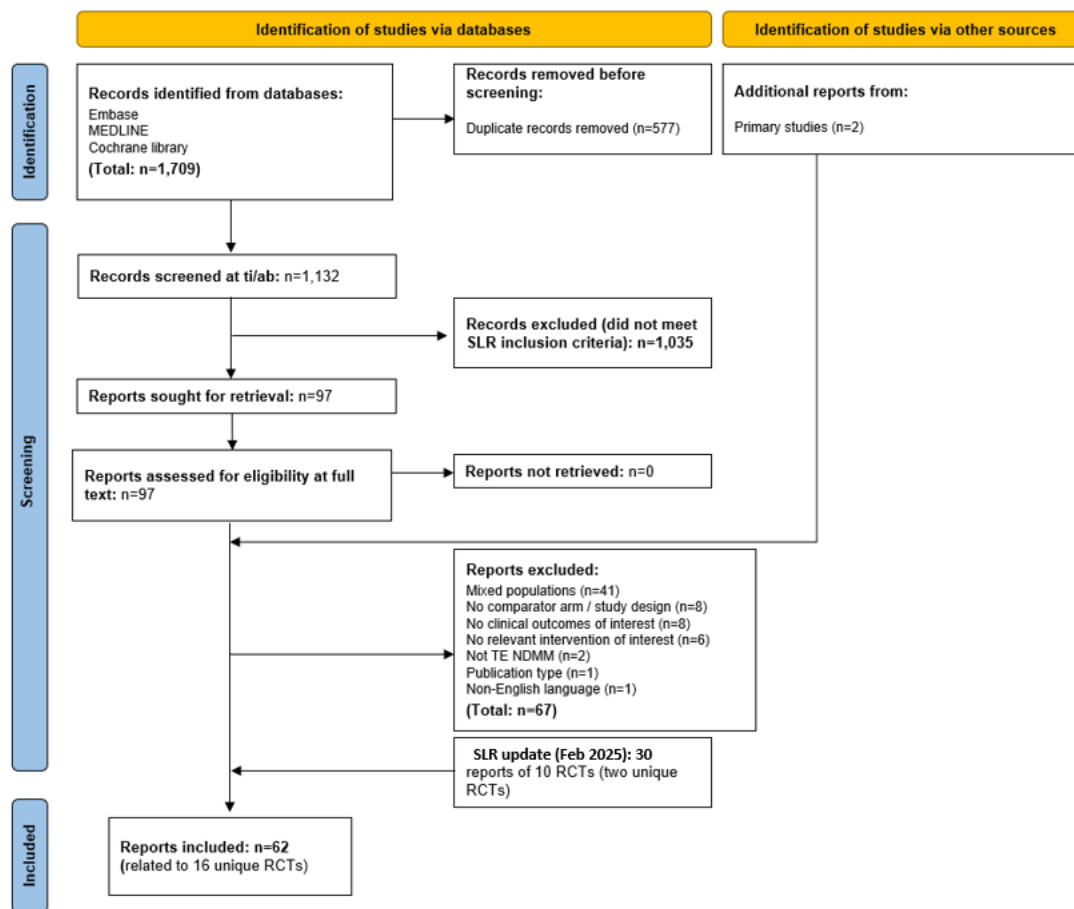
Figure 3.1: Overall PRISMA flow diagram for the I+C clinical SLR

Based on Figure 4, CS Appendices⁵

CS = company submission; I+C = induction and consolidation; NDMM = newly diagnosed multiple myeloma; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomised controlled trial; SLR = systematic literature review; TE = transplant eligible

The original SLR was conducted on 31 May 2018, with two updates on 30 April 2023 and 26 February 2025. The latest SLR update was performed to identify efficacy and safety data for DBLd in I+C phase, and all relevant comparators in RCTs involving NDMM patients who are HDT-ASCT eligible. As can be seen above in Figure 3.1, 18 unique RCTs reported in 69 citations were identified.¹

The second SLR was conducted on 19 September 2023 with an update on 26 February 2025. This update was performed to identify efficacy and safety data for DBLd I+C followed by DL maintenance, and all relevant comparators in RCTs involving NDMM patients who are HDT-ASCT eligible. As can be seen below in Figure 3.2, 16 unique RCTs reported in 62 citations were eligible for inclusion in the SLR.¹

Figure 3.2: Overall PRISMA flow diagram for the I+C+M clinical SLR

Based on Figure 7, CS Appendices⁵

CS = company submission; I+C+M = induction, consolidation and maintenance; NDMM = newly diagnosed multiple myeloma; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomised controlled trial; SLR = systematic literature review; TE = transplant eligible

The SLRs identified the PERSEUS multicentre, Phase III trial examining the efficacy and safety of DBLd I+C followed by DL maintenance versus bortezomib plus lenalidomide and dexamethasone (BLd) I+C followed by L maintenance in patients with NDMM who are deemed HDT-ASCT eligible. As the registrational trial which led to the extension label for daratumumab to DBLd in HDT-ASCT eligible patients with NDMM, PERSEUS was considered the most appropriate source of clinical evidence for DBLd induction and consolidation followed by DL maintenance therapy in this submission.¹ The details of which are summarised in the next Sections of this report.

3.2.2 Summary of details of PERSEUS trial

The PERSEUS trial provides the most relevant evidence and is an ongoing, randomised, open-label, multicentre, Phase III trial. The study is conducted across 115 study centres in 13 locations in Europe and Australia.¹ A summarised overview of the trial characteristics is described in Table 3.5 and Figure 3.3 below.

Table 3.5: Clinical effectiveness evidence (PERSEUS trial)

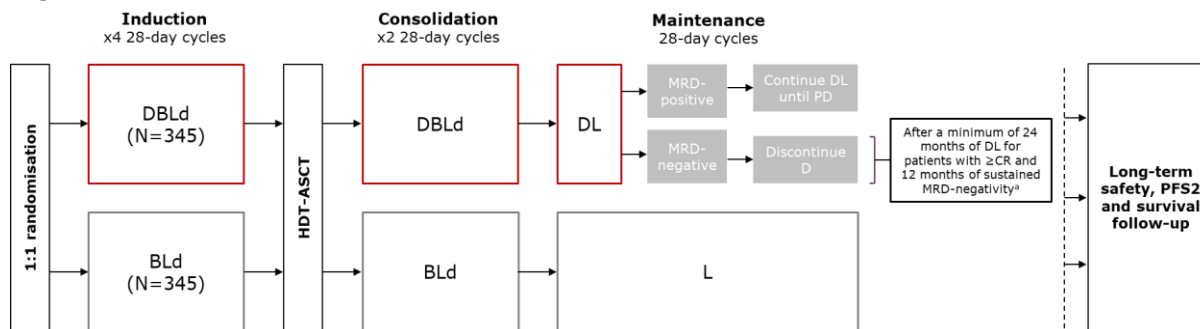
Study	PERSEUS (NCT03710603)
Study design	Ongoing, randomised, open-label, multicentre, Phase III trial in patients with NDMM who are eligible for HDT-ASCT. The trial consisted of three phases: a screening phase, a treatment phase and a follow-up phase. The treatment phase was comprised of four key stages: • Induction therapy • ASCT • Consolidation therapy • Maintenance therapy (given until disease progression or unacceptable toxicity)
Population	Patients with NDMM who are deemed eligible for HDT-ASCT. As of 1 August 2023, 709 patients had been randomised to treatment (ITT analysis set: DBLd + DL: 355; BLd + L: 354) and 698 patients treated (safety analysis set: DBLd + DL: 351; BLd + L: 347).
Intervention(s)	DBLd (I+C) followed by DL (maintenance) in the following dosing (all 28-day cycles): Induction and consolidation: Subcutaneous daratumumab Induction (4 x 4-week cycles): 1,800 mg per week during Cycles 1 and 2, 1,800 mg every 2 weeks during Cycles 3 and 4 Consolidation (2 x 4-week cycles following HDT and ASCT: 1,800 mg every 2 weeks for both Cycles) Subcutaneous bortezomib 1.3 mg/m² twice a week (Days 1, 4, 8, and 11) for I+C Oral L 25 mg on Days 1–21 of each Cycle for I+C Oral or IV dexamethasone 40 mg on Days 1 through 4 and Days 9–12 of each Cycle for I+C <u>Maintenance:</u>^a Subcutaneous daratumumab (1,800 mg every 4 weeks on Day 1) Oral L (10 mg on Days 1 to 28 of each cycle, until disease progression or unacceptable toxicity)
Comparator(s)	BLd (I+C) followed by L (maintenance) in the following dosing (all 28-day cycles): <u>Induction and consolidation:</u> Subcutaneous bortezomib 1.3 mg/m² twice a week (Days 1, 4, 8, and 11) for I+C Oral L 25 mg on Days 1–21 of each Cycle for I+C Oral or IV dexamethasone 40 mg on Days 1 through 4 and Days 9–12 of each Cycle for I+C <u>Maintenance:</u> Oral L (10 mg on Days 1 to 28 of each 28-day cycle, until disease progression or unacceptable toxicity)
Indicate if study supports application for	Yes

Study	PERSEUS (NCT03710603)
marketing authorisation	
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the DP⁶	Proportion of patients undergoing HDT-ASCT • PFS • OS Response rates: • Overall response rate (ORR) • sCR • ≥CR • ≥VGPR • CR • PR • SD • PD • MRD-negativity status AEs HRQoL outcomes: • EORTC QLQ-C30 scores • EORTC QLQ-MY20 • EQ-5D-5L scores

Based on Table 3, CS¹

^aIn line with the licence for daratumumab, daratumumab maintenance treatment is to be administered until disease progression. Daratumumab can, however, be discontinued for patients who have achieved MRD-negativity that is sustained for 12 months, if they have been treated on maintenance for at least 24 months, as recommended by the SmPC.

AEs = adverse events; ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide and dexamethasone; CR = complete response; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab and lenalidomide; EORTC QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; EQ-5D-5L = European Quality of Life Five Dimension Five Level Questionnaire; HDT = high-dose therapy; HRQoL = health-related quality of life; I+C = induction and consolidation; ITT = intent-to-treat; MRD = minimal residual disease; IV = intravenous; N/A = not applicable; NDMM = newly diagnosed multiple myeloma; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; SD = stable disease; SmPC = summary of product characteristics; VGPR = very good partial response

Figure 3.3: Overview of the PERSEUS trial

Based on Figure 9 of the CS¹

^aDaratumumab therapy was restarted upon confirmed loss of CR or recurrence of MRD at 10-4 or higher.

BLd = bortezomib, lenalidomide, and dexamethasone; CR = complete response; CS = company submission; DBLd = daratumumab in combination with bortezomib, lenalidomide, and dexamethasone; DL = daratumumab with lenalidomide; L = lenalidomide; MRD = minimal residual disease; PD = progressive disease; PFS2 = progression-free survival on the next line of therapy

The trial design consists of three phases:¹

- Screening phase: Commencing up to 28 days before randomisation
- Treatment phase: Extended on from Cycle 1 Day 1 and consisted of 4-week cycles. This phase included four cycles of induction therapy, followed by ASCT, then two cycles of consolidation therapy, followed by maintenance therapy until disease progression or unacceptable toxicity.
- Follow-up phase: Patients entered the Follow-up Phase following documented disease progression or unacceptable toxicity leading to all study treatment discontinuation, or if a response of partial response (PR) or better ($\geq$ PR) was not achieved by Day 1 of Cycle 7. Patients were followed up every 4 months until death or loss to follow-up.

Stratification occurred by International Staging System (ISS) Stage I, II, or III disease (based upon laboratory results for β -2 microglobulin and albumin) and cytogenetics (standard risk or high risk as defined by presence of del17p, t[4;14] or t[14;16]) and then randomised in a 1:1 ratio into one of the two treatment arms:¹

- Arm A: BLd for induction and consolidation, followed by L maintenance until disease progression or unacceptable toxicity, henceforth referred to as the BLd treatment arm
- Arm B: DBLd for induction and consolidation followed by DL maintenance until disease progression or unacceptable toxicity, henceforth referred to as the DBLd treatment arm

Those in Arm B who had a response of $\geq$ CR were permitted to stop therapy with daratumumab after a minimum of 24 months of maintenance therapy, if sustained MRD-negativity (at the threshold of 10-5) was established for a minimum of 12 months.¹ These patients continued L maintenance therapy until disease progression or unacceptable toxicity.¹ After stopping daratumumab therapy, patients with sustained MRD-negativity should restart therapy with daratumumab if there is a recurrence of MRD at 10-4 or higher, or a confirmed loss of CR without IMWG-defined disease progression.¹ This represents only █% of patients (i.e., only █ of █ patients in the DBLd-DL arm who stopped daratumumab and continued maintenance therapy) in PERSEUS re-starting daratumumab following loss of MRD-negative status.¹

Further details of the PERSEUS trial can be found in Table 3.6 below.

Table 3.6: Summary of PERSEUS trial methodology

Trial name	PERSEUS
Location	Australia, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Spain, Switzerland, Turkey
Trial design	Ongoing, randomised, open-label, multicentre, Phase III trial in patients with NDMM who are eligible for HDT-ASCT. The trial consisted of three phases: a screening phase, a treatment phase and a follow-up phase. The treatment phase included induction therapy followed by ASCT and consolidation therapy, followed by maintenance therapy until disease progression or unacceptable toxicity.
Eligibility criteria for patients	Key inclusion criteria: 18 to 70 years of age, inclusive. Monoclonal plasma cells in the bone marrow $\geq 10\%$ or presence of a biopsy proven plasmacytoma and documented MM satisfying at least one of the CRAB criteria or biomarkers of malignancy criteria. Newly diagnosed patients for whom HDT-ASCT is part of the intended treatment plan. ECOG PS score of 0, 1, or 2 Key exclusion criteria: Prior or current systemic therapy or stem cell therapy for any plasma cell dyscrasia, with the exception of emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment. Full inclusion and exclusion criteria can be found within Section 4 of the protocol (Sonneveld <i>et al.</i> 2024. Supplementary Material) included within the reference pack.⁷
Method of study drug administration	Subcutaneous daratumumab Induction (4 x 4-week cycles): 1,800 mg per week during Cycles 1 and 2, 1,800 mg every 2 weeks for Cycles 3 and 4 Consolidation (2 x 4-week cycles following HDT and ASCT): 1,800 mg every 2 weeks for both Cycles Maintenance: 1,800 mg every 4 weeks from Week 25 onwards^a Subcutaneous bortezomib Induction, consolidation (Cycles 1–6): 1.3 mg/m² bortezomib as a subcutaneous injection twice a week (Days 1, 4, 8, and 11) for 6 cycles Oral L Induction (Cycles 1–4): 25 mg on Days 1–21 of each Cycle Consolidation (Cycles 5–6): 25 mg on Days 1–21 of each Cycle Maintenance: 10 mg on Days 1 to 28 of each 28-day cycle, until disease progression or unacceptable toxicity Oral or IV dexamethasone Induction and consolidation: (Cycles 1–6): 40 mg on Days 1 through 4 and Days 9–12 of each Cycle
Permitted and disallowed concomitant medication	Permitted: Colony-stimulating factors, erythropoietin, and transfusion of platelets and red cells.

	Loperamide is recommended for the treatment of diarrhoea, starting at the time of the first watery stool. Methods for the prevention of constipation are permitted (e.g. adequate hydration, high-fibre diet, and stool softeners, if needed). Adequate hydration is 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) is permitted before treatment. Vaccination is allowed per local guidelines. Disallowed: Concomitant administration of strong CYP3A4 inducers is prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) should be avoided and is not recommended in patients receiving bortezomib. Other agents that target CD38. Medications used for other indications that have antimyeloma properties. Approved or investigational treatments for multiple myeloma (including but not limited to conventional chemotherapies, IMiDs, or PIs). Concomitant administration of investigational agents including administration of commercially available agents with activity against or under investigation for MM. Administration of investigational, live attenuated, or replication-competent viral vector vaccines <4 weeks prior to the start of study treatment, during study treatment, or initiated <90 days after last dose of study treatment.
Primary outcome	PFS
Secondary and exploratory outcomes ^b	OS ≥CR DOR ORR ≥VGPR sCR MRD-negative status with ≥CR Time to response Safety outcomes, including AEs Duration of MRD-negativity PK outcomes Immunogenicity Patient-reported outcomes from the EORTC and EQ-5D-5L questionnaires Stem cell yield after mobilisation Time to engraftment post-ASCT Proportion of patients undergoing HDT-ASCT
Pre-planned subgroups	Efficacy endpoints Age (<65 versus ≥65 years) Sex (male versus female) Race (white versus other)

	ISS (I versus II versus III) Cytogenic risk (high versus standard versus indeterminate) Type of MM (IgG versus non-IgG) Baseline ECOG PS (0 versus ≥ 1) Safety endpoint Age (<50 versus 50–<65 versus ≥ 65) Baseline hepatic function (normal versus impaired) Sex (male versus female) Race (White versus Other) Baseline renal function (<60 mL/min/1.73 m ² versus 60 to <90 mL/min/1.73 m ² versus ≥ 90 mL/min/1.73 m ²) Baseline body weight (≤ 65 kg versus >65 to ≤ 85 kg versus >85 kg)
Duration of study and follow-up	At the 1 August 2023 DCO, median overall follow-up was 47.5 months (DBLd + DL: ■■■ months; BLd + L : ■■■ months)
Based on Table 5 of the CS ¹ ^a Daratumumab can be discontinued for patients with a response of CR or better who have achieved MRD-negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months. After stopping daratumumab therapy, subjects with sustained MRD-negativity should restart therapy with daratumumab if there is a recurrence of MRD. ^b Bolded outcomes are presented in this submission. AEs = adverse events; ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide and dexamethasone; CD38 = cluster of differentiation 38 antigen; CR = complete response; CRAB = calcium elevation, renal insufficiency, anaemia, and bone lesions; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DCO = data cut-off; DL = daratumumab and lenalidomide; DOR = duration of response; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; EQ-5D-5L = European Quality of Life Five Dimension Five Level Questionnaire; HDT = high-dose therapy; Ig = immunoglobulin; IMiD = immunomodulatory agent; ISS = International Staging System; I+C = induction and consolidation; ITT = intent-to-treat; MRD = minimal residual disease; IV = intravenous; N/A = not applicable; NDMM = newly diagnosed multiple myeloma; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PI = proteasome inhibitor; PK = pharmacokinetic PR = partial response; sCR = stringent complete response; SD = stable disease; SmPC = summary of product characteristics; ULN = upper limit of normal; VGPR = very good partial response	

3.2.3 Statistical analysis of PERSEUS trial

This Section summarises the statistical methodology, presents and described in the CS.¹

Two datasets were described in the CS relevant to the PERSEUS trial, namely the intention-to-treat (ITT) and the safety analysis sets. Seven hundred and nine patients were included in the ITT analysis set which informs the efficacy evidence for this submission, whilst a total of 698 patients were included in the safety analysis set which forms the principal evidence base for the safety evidence for this submission.¹

Table 3.7: PERSEUS analysis set definitions

Analysis set	Analysis set description	Number of patients		
		BLd arm ^a	DBLd arm ^b	Total
ITT analysis set (primary)	Patients who have been randomly assigned to either the BLd or DBLd treatment arm	354	355	709

Analysis set	Analysis set description	Number of patients		
		BLd arm ^a	DBLd arm ^b	Total
analysis set)				
Safety analysis set	All patients who have received at least one dose of treatment (partial or complete) in the trial	347	351	698

Based on Table 8, CS¹

^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy.

^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy.

BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = dexamethasone with lenalidomide; I+C = induction and consolidation; ITT = intent-to-treat; L = lenalidomide

Table 3.8: Statistical methods for the primary analysis of PERSEUS

Trial name	PERSEUS
Hypothesis objective	Standard treatment strategy in HDT-ASCT eligible patients with NDMM: BLd induction followed by ASCT followed by BLd consolidation followed by maintenance therapy with L alone New treatment strategy: To add daratumumab to the standard induction, consolidation and L maintenance treatment phases. With the primary efficacy endpoint PFS, the null hypothesis is that there is no difference in PFS between the two treatment strategies in subjects with previously untreated MM who are eligible for HDT
Statistical analysis	The treatment groups were: BLd arm: BLd for induction and consolidation, followed by L maintenance DBLd arm: DBLd for induction and consolidation followed by DL maintenance Continuous variables were summarised using descriptive statistics such as mean, SD, median and range. Categorical variables were summarised using frequency and percentage. For the efficacy assessment of response and disease progression, a validated computerised algorithm was utilised to determine response and disease progression for each subject. This computerised algorithm is based on the IMWG response criteria (Durie et al 2006, Rajkumar et al 2011) and has been used and validated by an independent review. All statistical hypothesis tests and 95% CIs presented are 2-sided.
Sample size, power calculation	It was assumed that median PFS is 63 months for the BLd arm, and the addition of daratumumab will decrease the risk of progression or death by 31% (HR = 0.69; estimated median PFS of 91 months for DBLd arm). Assuming a 12-month accrual and 64-month of additional follow-up, approximately 690 patients (345/arm) were needed to achieve the 285 PFS events needed to achieve 85% power with a 2-sided alpha of 0.05. Long-term follow-up for survival continued until approximately 310 deaths had been observed or 9 years had elapsed after the last patient was randomised, whichever occurred earlier. Per the protocol, this provided approximately 70% power to detect a 25% reduction in the risk of death (HR = 0.75) with a log-rank test at a 2-sided alpha of 0.05. However, a HR of 0.71 or less will provide at least 80% power.

	A large Phase III trial (CASSIOPEIA, MMY3006) comparing DBLd with BTd in a similar study population (N=1,085), observed a HR of 0.66 from first randomisation censoring the events from the crossover BTd subjects after Part 1 of the trial with median follow-up of 18.8 months. As such, a HR would provide approximately 93.5% power for this study with 310 deaths. After the significance of PFS was established, testing of OS could continue as planned until a definitive conclusion on OS was reached.
Data management, patient withdrawals	Discontinuation and withdrawal: Patients were withdrawn from the trial for any of the following reasons: • Lost to follow-up • Withdrawal of consent for trial participation • Death • Sponsor terminates the trial When a patient withdrew consent before completing the trial, the reason for withdrawal was documented in the eCRF and in the source document. Study treatment assigned to the withdrawn patients was not permitted to be assigned to another patient. Patients who withdrew were not replaced. If a patient discontinued study treatment and withdrew from the trial before the end of the treatment phase, End-of-Treatment assessments were obtained. If the reason for withdrawal from the trial was withdrawal of consent, then no additional assessments were allowed.
Based on Table 9, CS¹ ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide and dexamethasone; BTd = bortezomib with thalidomide and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab and lenalidomide; eCRF = electronic case report form; HDT = high-dose therapy; HR = hazard ratio; IMWG = International Myeloma Working Group; L = lenalidomide; MM = multiple myeloma; NDMM = newly diagnosed multiple myeloma; OS = overall survival; PFS = progression-free survival; SD = stable disease	

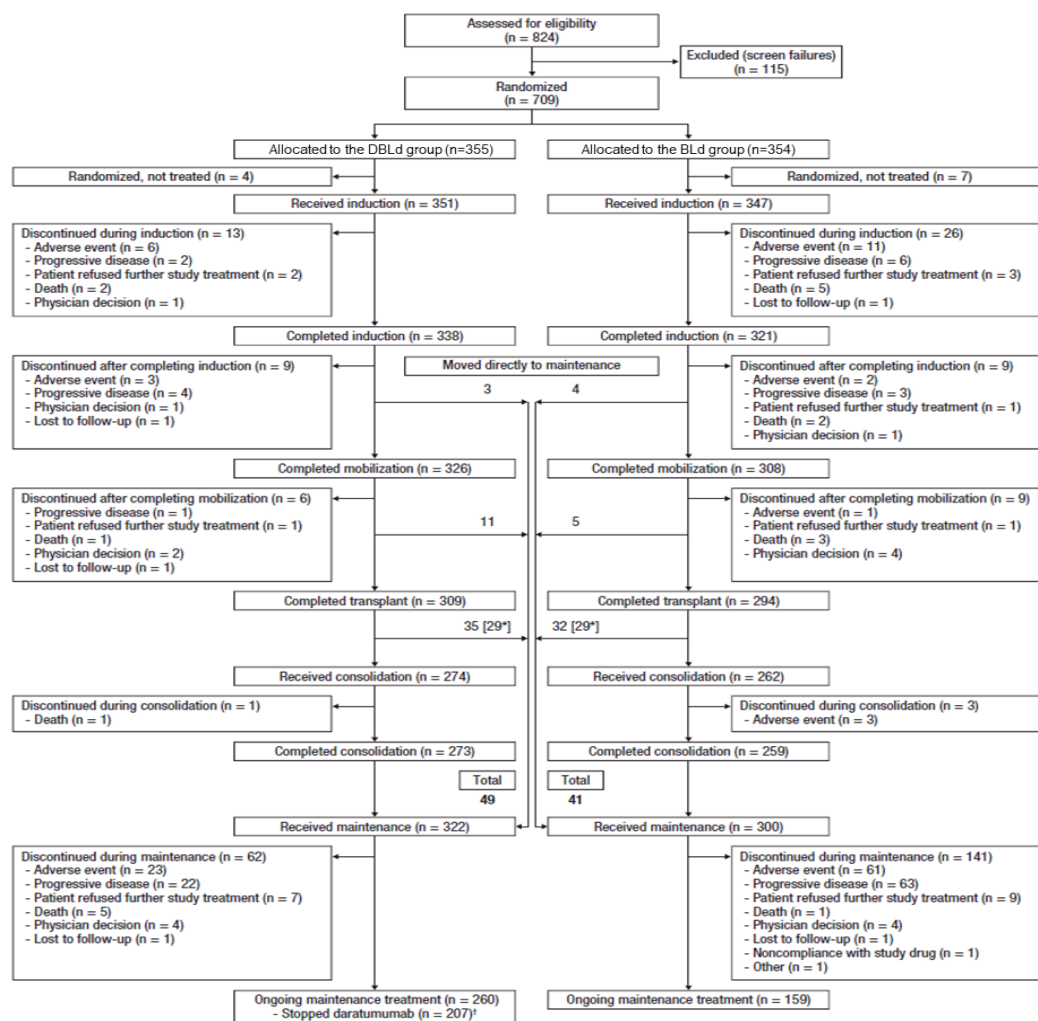
Multiple outcomes were employed to explore the efficacy of DBLd I+C therapy followed by DL maintenance versus BLd I+C therapy followed by L maintenance. The Table below summarises these outcomes as presented in the CS.¹

Table 3.9: Definitions for outcome measures used in PERSEUS

Outcome measure	Definition
Primary outcome	
PFS	The time from the date of randomisation to the date of first disease progression according to the IMWG response criteria, or death due to any cause, whichever occurred earlier.
Key secondary outcomes	
≥CR rate	The percentage of ITT patients who achieved CR or sCR status anytime during the trial per the IMWG criteria. In addition, the specific response must have been achieved prior to start of subsequent therapies.
Overall MRD-negativity rate	The proportion of ITT patients who achieved MRD-negativity (at or below the threshold of 10 ⁻⁵) by bone marrow aspirate and achieved ≥CR (i.e. CR or sCR) at any time after the date of randomisation during the trial (and prior to progressive disease, subsequent therapy, or both).

Outcome measure	Definition
OS	Measured from the date of randomisation to the date of death due to any cause. Patients who were lost to follow-up were censored at the time of lost to follow-up. Patients who died after consent withdrawal were considered as having an OS event. Patients who were still alive at the clinical cut-off date for the analysis were censored at the last known alive date.
Post-consolidation MRD-negativity rate	The proportion of patients who achieved MRD-negativity (at or below the threshold of 10^{-5}) and achieved $\geq$ CR at the end of the consolidation treatment phase.
ORR, $\geq$ VGPR rate and sCR rate	The percentage of ITT patients who achieved $\geq$ PR status (PR, VGPR, CR or sCR), $\geq$ VGPR status (VGPR, CR or sCR) and sCR status anytime during the trial per the IMWG criteria, respectively.
ORR, $\geq$ VGPR rate, $\geq$ CR rate, and sCR rate for post-induction/post-ASCT/post-consolidation/full treatment sequence	The proportions of ITT patients who achieved $\geq$ PR status, $\geq$ VGPR, $\geq$ CR, or sCR by the end date of the induction/ASCT/consolidation/maintenance treatment phase, per the IMWG criteria, respectively.
Time to response	The time from the date of randomisation to the date of first documentation of a confirmed response ($\geq$ PR) for patients who had $\geq$ PR as their best response.
DOR	The date of first documentation of a confirmed response ($\geq$ PR) to the date of first documentation of a confirmed PD, according to IMWG criteria, or death due to PD, whichever occurs first, for patients who had $\geq$ PR as their best response. Responders without PD were censored at the last disease evaluation prior to subsequent therapy.
Based on Table 10, CS ¹ ASCT = autologous stem cell transplant; CR = complete response; CS = company submission; DOR = duration of response; IMWG = International Myeloma Working Group; ITT = intention-to-treat; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PD = progressed disease; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; VGPR = very good partial response	

At the time of the 1 August 2023 data cut-off (DCO), 824 patients had been assessed for eligibility, 709 patients (DBLd arm: 355; BLd arm: 354) were randomised. Of these, 351 patients in the DBLd arm and 347 patients in the BLd arm received study treatment.¹ There were fewer patients in the DBLd arm (91 [25.9%]) who discontinued treatment compared with the BLd arm (188 [54.2%]). Most discontinuation occurred in the induction and maintenance phases. There were less patients in the DBLd arm who discontinued treatment during induction and maintenance than in the BLd arm (DBLd arm: 13 [3.7%]; BLd arm: 26 [7.5%] and DBLd arm: 62 [19.3%]; BLd arm: 141 [47.0%], respectively). The most common reasons for discontinuation of all components of study treatment ($>10\%$ of total in either arm) were due to adverse events (AEs) (DBLd arm: 9.1%; BLd arm: 22.5%) and progressive disease (PD) (DBLd arm: 8.3%; BLd arm: 20.7%).¹

Figure 3.4: Consort diagram for PERSEUS trial

Based on Figure 10 of the CS¹

Footnote:

*Patients who received Cycles 5 and 6 consecutive to induction therapy due to the COVID-19 pandemic.

†After at least 24 months of maintenance therapy, daratumumab was discontinued in patients who achieved CR or better and sustained MRD-negativity (at or below a sensitivity threshold of 10–5) for 12 months; patients continued L maintenance therapy until disease progression or unacceptable toxicity.

BLd = bortezomib, lenalidomide and dexamethasone; CR = complete response; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; L = lenalidomide; MRD = minimal residual disease

EAG comment: PERSEUS appears to be a well conducted RCT, and the only issue is that it could not be used to compare the full treatment sequence either directly or through an anchored ITC.

3.2.4 Baseline characteristics PERSEUS trial

This submission focusses on the ITT analysis set, which included any patients who were randomly assigned to either the BLd or DBLd treatment arm at the August 2023 DCO.¹

Patients in the BLd treatment arm had a median age of 59.0 years (range: 31, 70) and patients in the DBLd treatment arm had a similar median age of 61.0 years (range: 32, 70). The median time between diagnosis and the first dose was similar in patients in the BLd and DBLd treatment arms (1.12 years [range: 0.1, 184.6] versus 1.18 years [range: 0.0, 46.5]). Extramedullary disease (defined as the presence of one or more extramedullary soft-tissue lesions) was present in a similar proportion

of patients in both the BLd and DBLd treatment arms (■■ patients [■■%] versus ■■ patients [■■%], respectively).

EAG comment: Overall, baseline characteristics were well balanced between patients in the BLd and DBLd treatment arms although there were a few noticeable differences at the 5% level in the type of measurable disease with those in the BLd arm having less immunoglobulin G (IgG) detection compared to the DBLd arm (52.3% versus 57.5%) but more immunoglobulin A (IgA) detection (24% versus 18.3%). The EAG emphasises that such differences at the 5% level do not necessarily reflect clinically meaningful differences, but we highlight them to ensure that such considerations inform interpretation of results.

Table 3.10: Summary of baseline demographic and disease characteristics

Characteristics	ITT analysis set		
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)
Age, years			
Median (range)	59.0 (31, 70)	61.0 (32, 70)	60.0 (31, 70)
Overall age group, n (%)			
<50	54 (15.3)	54 (15.2)	108 (15.2)
≥50 and <65	213 (60.2)	207 (58.3)	420 (59.2)
≥65	87 (24.6)	94 (26.5)	181 (25.5)
Sex, n (%)			
Female	149 (42.1)	144 (40.6)	293 (41.3)
Male	205 (57.9)	211 (59.4)	416 (58.7)
Race, n (%)			
White	323 (91.2)	330 (93.0)	653 (92.1)
Black or African American	4 (1.1)	5 (1.4)	9 (1.3)
Asian	6 (1.7)	4 (1.1)	10 (1.4)
Native Hawaiian or Other Pacific Islander	■■	■■	■■
American Indian or Alaska Native	■■	■■	■■
Not reported	18 (5.1)	12 (3.4)	30 (4.2)
Ethnicity, n (%)			
Hispanic or Latino	■■	■■	■■
Not Hispanic or Latino	■■	■■	■■
Missing	■■	■■	■■
Body weight, kg ^c			
Median (range)	■■■■	■■■■	■■■■
Baseline ECOG PS, n (%) ^d			

Characteristics	ITT analysis set		
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)
0	230 (65.0)	221 (62.3)	451 (63.6)
1	108 (30.5)	114 (32.1)	222 (31.3)
2	16 (4.5)	19 (5.4)	35 (4.9)
3	0	1 (0.3)	1 (0.1)
Type of myeloma by immunofixation or serum FLC assay, n (%)			
IgG			
IgA			
IgM			
IgD			
IgE			
Light chain			
Kappa			
Lambda			
FLC-Kappa ^c			
FLC-Lambda ^f			
Biclonal			
Type of measurable disease, n (%)			
Serum	281 (79.4)		
IgG	185 (52.3)	204 (57.5)	389 (54.9)
IgA	85 (24.0)	65 (18.3)	150 (21.2)
Other ^g	11 (3.1)	13 (3.7)	24 (3.4)
Urine only	46 (13.0)	43 (12.1)	89 (12.6)
Serum FLC	27 (7.6)	29 (8.2)	56 (7.9)
NE	0	1 (0.3)	1 (0.1)
ISS Staging, n (%) ^h			
Stage I	178 (50.4)	186 (52.4)	364 (51.4)
Stage II	125 (35.4)	114 (32.1)	239 (33.8)
Stage III	50 (14.2)	55 (15.5)	105 (14.8)
R-ISS Staging, n (%) ⁱ			
Stage I			
Stage II			
Stage III			
Time from MM diagnosis to randomisation, years			

Characteristics	ITT analysis set		
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)
Mean (SD)			
Median (range)			
Number of lytic bone lesions, n (%)			
None			
1–3			
4–10			
More than 10			
Number of extramedullary plasmacytomas, n (%)			
0			
≥1			
% Plasma cells, bone marrow biopsy/aspirate			
<10			
10–30			
>30			
Cytogenetic risk, n (%) ^j			
Standard risk	266 (75.1)	264 (74.4)	530 (74.8)
High risk ^k	78 (22.0)	76 (21.4)	154 (21.7)
del(17p)			
t(4;14)			
t(14;16)			
Indeterminate	10 (2.8)	15 (4.2)	25 (3.5)
Based on Table 6 of the CS^l ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy; ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy; ^c One patient did not have baseline weight. The patient was randomised but not treated; ^d One patient had ECOG PS 0 at randomisation and worsened to ECOG PS 3 at baseline; ^e Includes patients without a positive immunofixation but with evidence of free light chain kappa by FLC testing; ^f Includes patients without a positive immunofixation but with evidence of free light chain lambda by FLC testing; ^g Includes patients with IgD, IgM, IgE and biclonal; ^h ISS staging is derived based on the combination of serum β2-microglobulin and albumin; ⁱ Determination is based on three factors: ISS; presence of chromosomal abnormalities of t(4; 14), t(14; 16), or del17p by FISH/Karyotype testing and serum LDH at baseline; ^j Cytogenetic risk is based on FISH; ^k Patients may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)]. BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = dexamethasone with lenalidomide; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FISH = fluorescence in situ hybridisation; FLC = free light chain; Ig = immunoglobulin; ISS = International			

Characteristics	ITT analysis set		
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)
Staging System; ITT = intention-to-treat; L = lenalidomide; LDH = lactate dehydrogenase; MM = multiple myeloma; NE = not evaluable; SD = standard deviation			

To address the issue of generalisability to relevant patients in NHS clinical practice in England and Wales, the company obtained real-world data from the NHS Digital National Cancer Registration and Analysis Service (NCRAS) including patients diagnosed with multiple myeloma (MM) in England between January 2015 and December 2022 inclusive.¹ A comparison of patient characteristics from the NCRAS dataset and the DBLd-DL arm of PERSEUS trial population is provided below in Table 3.11.

Table 3.11: Comparison of patient characteristics from the NHS Digital NCRAS for England between January 2015 and December 2022 and DBLd-DL arm of the PERSEUS trial (at baseline)

	NCRAS dataset (n=██████)	PERSEUS DBLd-DL (n=355)
Mean age (SD)	██████	██████
Median age (range)	██████	██████
Female, n (%)	██████	██████
Age category, n (%)		
<50 years	██████	██████
50-64 years	██████	██████
65 years and older	██████	94 (26.5)
ECOG PS score, n (%)		
0	██████	221 (62.3)
1	██████	114 (32.1)
2	██████	19 (5.4)
3	██████	1 (0.1)
4	██████	-
Null	██████	-
ISS stage, n (%) ^a		
I	██████	186 (52.4)
II	██████	114 (32.1)
III	██████	55 (15.5)
Null	██████	-
Based on Table 7, CS ¹ ^a From 1 April 2021 onwards, the revised ISS (R-ISS) could be submitted by trusts. CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ISS = International Staging System; NCRAS = National Cancer Registration and Analysis Service; NHS = National Health Service; SD = standard deviation		

The company acknowledge in the CS that availability of data for baseline characteristics were limited and that although Eastern Cooperative Oncology Group Performance Status (ECOG PS) and ISS data were available in the NCRAS, it was impacted by a high degree of missing data. Hence, the level of

missing data for the ECOG PS and ISS stage makes comparison somewhat challenging.¹ Whilst a higher proportion of patients had an ECOG PS score of 0 and ISS stage of I in the PERSEUS trial compared to the NCRAS dataset, data for these factors were missing for half of the patients in the NCRAS dataset, therefore limiting the comparability of the two patient populations.¹

EAG comment: The EAG requested information that may be available on any patients involved in the trial that were based in England and Wales. The company responded to this request stating that:³ “...the PERSEUS trial was conducted in 13 locations across Europe and Australia, but these locations did not include any in the UK...”. The EAG, noting the lack of UK based representation, is concerned regarding the generalisability of the trial to relevant NHS patients based in England and Wales. The company in their submission stated that feedback was gathered from UK clinical experts on the generalisability of PERSEUS to UK clinical practice.¹ Their overall view was that baseline characteristics of patients in the PERSEUS trial were generalisable to patients with HDT-ASCT NDMM in UK clinical practice.¹ However, some points were noted with the following comments:

- *One expert noted that the median age of 61.0 years for the DBLd arm of the PERSEUS trial is broadly generalisable however may be slightly younger than that expected of HDT-ASCT eligible patients with NDMM in UK clinical practice. However, it was highlighted that this is a common finding in clinical trials and given the median age of patients is only anticipated to decrease in the coming years, any discrepancies would not impact the generalisability of the trial results. Furthermore, NCRAS data suggests that the age of patients in the DBLd arm is in fact aligned with the UK patient population¹.*
- *One of the UK clinical experts noted that the ECOG PS profile of the PERSEUS trial population may differ slightly from ASCT-eligible NDMM patients in UK clinical practice, however that it is broadly generalisable. The expert noted that trials in patients with MM often do not include patients ECOG PS ≥ 2 , despite them receiving transplants in UK clinical practice. The expert however acknowledged the challenge of including such patients in a clinical trial setting¹.*
- *The experts agreed that the remaining characteristics were broadly generalisable to patients in UK clinical practice¹.*

In conclusion, the EAG consider that the PERSEUS trial is sufficiently generalisable to UK clinical practice, whilst noting that only the induction and maintenance phase was used in the comparison with SoC i.e. DBTd via an ITC (see Section 3.3 and 3.4). This is because neither the induction and consolidation phase nor the maintenance phase of the comparator in the trial represented SoC.

3.2.5 Summary of details of AURIGA trial

AURIGA was identified as the sole additional relevant DBLd study. The PERSEUS trial did not include a second randomisation after consolidation and prior to maintenance initiation. However, the Phase III AURIGA trial assessed clinical efficacy and safety in patients randomised to either DL or L maintenance therapy alone in anti-CD38-naïve, MRD-positive patients who had achieved a $\geq$ VGPR after induction therapy and ASCT. Therefore the AURIGA trial was considered to be the best available source of evidence for the comparative efficacy of DL versus L maintenance and to inform long-term survival estimates in the economic analysis.¹

In this trial patients were randomly assigned in a 1:1 ratio to receive DL or L maintenance therapy, which was continued for a maximum of 36 cycles, or until disease progression, unacceptable toxicity or consent withdrawal. Trial characteristics are summarised in the Table below.

Table 3.12: Clinical effectiveness evidence (AURIGA trial)

Study	AURIGA (NCT03710603)
Study design	Ongoing, randomised, open-label, multicentre, Phase III trial in patients with NDMM who: • Have received induction therapy followed by HDT-ASCT • Had achieved $\geq$VGPR • Were MRD-positive (at a threshold of 10⁻⁵, according to NGS) • Had not received prior anti-CD38 therapy
Population	Patients with NDMM who were anti-CD38-naïve and MRD-positive and had achieved a $\geq$ VGPR following induction and HDT-ASCT. At the primary analysis (4 April 2024), 200 patients had been randomised 1:1 to treatment (ITT analysis set: DL maintenance: 99; L: 101).
Intervention(s)	DL maintenance in the following dosing (all 28-day cycles): Subcutaneous daratumumab 1,800 mg: Cycles 1 and 2: weekly Cycles 3–6: every 2 weeks Cycle 7 onwards Oral L 10 mg on Days 1–28 of each cycle. After three cycles, the dose could be increased to 15 mg, if tolerated, at the discretion of the investigator
Comparator(s)	L maintenance in the following dosing (all 28-day cycles): Oral L 10 mg on Days 1–28 of each cycle. After three cycles, the dose could be increased to 15 mg, if tolerated, at the discretion of the investigator
Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the DP ⁶	PFS OS Response rates: • ORR • sCR • $\geq$CR • $\geq$VGPR • CR • PR • SD • PD • MRD-negativity status AEs

Study	AURIGA (NCT03710603)
	HRQoL outcomes: • EORTC QLQ-C30 scores • EORTC QLQ-MY20 • EQ-5D-5L scores
Based on Table 4 of the CS ¹ AEs = adverse events; ASCT = autologous stem cell transplantation; CR = complete response; DL = daratumumab and lenalidomide; DP = decision problem; EORTC QLQ-MY20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; EQ-5D-5L = European Quality of Life Five Dimension Five Level Questionnaire; HDT = high-dose therapy; HRQoL = health-related quality of life; ITT = intention-to-treat; L = lenalidomide; MRD = minimal residual disease; N/A = not applicable; NDMM = newly diagnosed multiple myeloma; ORR = overall response rate; OS = overall survival; PD = progressed disease; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response	

3.2.5.1 Baseline characteristics AURIGA trial

The company emphasise in the CS that the AURIGA trial population differs in some respects to that of the PERSEUS trial, and the population of relevance to this submission. They go on to state that ‘evidence from alternative RCTs suggest that the AURIGA results are likely a conservative estimate of the expected outcomes of DL maintenance following daratumumab-based induction and consolidation therapy in clinical practice.’¹

Table 3.13: Comparison of patient demographic and baseline characteristics in AURIGA and PERSEUS

Characteristics	AURIGA		PERSEUS	
	DL maintenance (N=99)	L maintenance (N=101)	BLd arm ^a (N=354)	DBLd arm ^b (N=355)
Age				
Median (range)	63 (55, 77)	62 (35,78)	59.0 (31, 70)	██████████
Overall age group, n (%)				
<50	61 (61.6)	61 (60.4)	██████	██████
≥50 and <65			██████	██████
≥65	38 (38.4)	42 (42.6)	██████	██████
Sex, n (%)				
Female	38 (38.4)	43 (42.6)	149 (42.1)	144 (40.6)
Male	61 (61.6)	58 (57.4)	205 (57.9)	211 (59.4)
Race, n (%)				
White	67 (67.7)	68 (67.3)	323 (91.2)	330 (93.0)
Black or African American	20 (20.2)	24 (23.8)	4 (1.1)	5 (1.4)
Asian	5 (5.1)	1 (1.0)	6 (1.7)	4 (1.1)

Characteristics	AURIGA		PERSEUS	
	DL maintenance (N=99)	L maintenance (N=101)	BLd arm ^a (N=354)	DBLd arm ^b (N=355)
Native Hawaiian or Other Pacific Islander	0	0	██████	██████
American Indian or Alaska Native	0	1 (1.0)	██████	██████
Not reported	2 (2.0)	2 (2.0)	18 (5.1)	12 (3.4)
Other*	██████	██████	2 (0.6)	-
Ethnicity, n (%)				
Hispanic or Latino	██████	██████	██████	██████
Not Hispanic or Latino	██████	██████	██████	██████
Missing	██████	██████	██████	██████
Body weight, kg^c				
Median (range)	██████████	██████████	73.0 (37.0, 167.6)	75.4 (44.5, 125.0)
Baseline ECOG PS, n (%)^d				
0	45 (45.5)	55 (54.5)	230 (65.0)	221 (62.3)
1	52 (52.5)	44 (43.6)	108 (30.5)	114 (32.1)
2	2 (2.0)	2 (2.0)	16 (4.5)	19 (5.4)
3	0	0	0	1 (0.3)
Type of myeloma by immunofixation or serum FLC assay, n (%)				
IgG	NR	NR	██████	██████
IgA	NR	NR	██████	██████
IgM	NR	NR	█	██████
IgD	NR	NR	██████	██████
IgE	NR	NR	█	█
Light chain	NR	NR	██████	██████
Kappa	NR	NR	██████	██████
Lambda	NR	NR	██████	██████
FLC-Kappa ^e	NR	NR	██████	██████
FLC-Lambda ^f	NR	NR	█	██████
Biclonal	NR	NR	██████	██████
Type of measurable disease, n (%)				
Serum	NR	NR	██████	██████

Characteristics	AURIGA		PERSEUS	
	DL maintenance (N=99)	L maintenance (N=101)	BLd arm ^a (N=354)	DBLd arm ^b (N=355)
IgG	NR	NR	185 (52.3)	204 (57.5)
IgA	NR	NR	85 (24.0)	65 (18.3)
Other ^g	NR	NR	11 (3.1)	13 (3.7)
Urine only	NR	NR	46 (13.0)	43 (12.1)
Serum FLC	NR	NR	27 (7.6)	29 (8.2)
Not evaluable	NR	NR	0	1 (0.3)
ISS Staging, n (%)^h				
	████	████		
Stage I	████	████	████	186 (52.4)
Stage II	████	████	████	114 (32.1)
Stage III	████	████	████	55 (15.5)
R-ISS Staging, n (%)ⁱ				
Stage I	NR	NR	████	████
Stage II	NR	NR	████	████
Stage III	NR	NR	████	████
Time from MM diagnosis to randomisation, years				
Mean (SD)	12.1 (6.9)	12.2 (5.0)	████	████
Median (range)	10.8 (5.0, 72.4)	11.2 (5.2, 43.1)	1.12 (0.1, 184.6)	1.18 (0.0, 46.5)
Number of lytic bone lesions, n (%)				
	N=95	N=99		
None	45 (47.4)	40 (40.4)	████	████
1–3	20 (21.1)	18 (18.2)	████	████
4–10	10 (10.5)	14 (14.1)	████	████
More than 10	20 (21.1)	27 (27.3)	████	████
Number of extramedullary plasmacytomas, n (%)				
0	98 (99.0)	101 (100.0)	████	████
≥1	1 (1.0)	0	████	████
% Plasma cells, bone marrow biopsy/aspirate				
<10	NR	NR	████	████
10–30	NR	NR	████	████
>30	NR	NR	████	████
Cytogenetic risk, n (%)^j				

Characteristics	AURIGA		PERSEUS	
	DL maintenance (N=99)	L maintenance (N=101)	BLd arm ^a (N=354)	DBLd arm ^b (N=355)
	N=89	N=92		
Standard risk	63 (68.5)	66 (74.2)	266 (75.1)	264 (74.4)
High risk ^k	22 (23.9)	15 (16.9)	78 (22.0)	76 (21.4)
del(17p)	13 (14.1)	3 (3.4)	██████	██████
t(4;14)	10 (10.9)	12 (13.5)	██████	██████
t(14;16)	6 (6.5)	7 (7.9)	██████	██████
Indeterminate	7 (7.6)	8 (9.0)	10 (2.8)	15 (4.2)
Based on Table 85, CS Appendices⁵ ^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy. ^c One patient did not have baseline weight. The patient was randomised but not treated. ^d One patient had ECOG PS 0 at randomisation and worsened to ECOG PS 3 at baseline. ^e Includes patients without a positive immunofixation but with evidence of free light chain kappa by FLC testing. ^f Includes patients without a positive immunofixation but with evidence of free light chain lambda by FLC testing. ^g Includes patients with IgD, IgM, IgE and biclonal. ^h ISS staging is derived based on the combination of serum β2-microglobulin and albumin. ⁱ Determination is based on three factors: ISS; presence of chromosomal abnormalities of t(4; 14), t(14; 16), or del17p by FISH/Karyotype testing and serum lactate dehydrogenase (LDH) at baseline. ^j Cytogenetic risk is based on FISH ^k Patients may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)] BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = dexamethasone with lenalidomide; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FISH = fluorescence in situ hybridisation; FLC - free light chain; Ig = immunoglobulin; ISS = International Staging System; ITT = intention-to-treat; L = lenalidomide; MM = multiple myeloma; SD = standard deviation				

EAG comment: The EAG were concerned about the comparability of the two trial populations and requested clarification on this matter, particularly given that AURIGA was used instead of PERSEUS for the comparison of maintenance treatment. The company had also highlighted these differences in the CS¹ and responded to the request³ describing the key differences between the PERSEUS and AURIGA trial populations. They state that:

‘Daratumumab exposure: patients in the DBLd arm of the PERSEUS trial received daratumumab-based treatment during the induction and consolidation phases, making them anti-CD38-experienced, whilst patients were all anti-CD38-naïve when initiating maintenance therapy in the AURIGA trial’³

‘Consolidation therapy: consolidation therapy with DBLd or BLd was administered as part of the trial regimen in PERSEUS, whilst consolidation therapy was received by a minority of patients (██████%) (██████%), prior to enrolment, in the AURIGA trial’³

‘MRD and response status: patients enrolled in the AURIGA trial were MRD-positive and achieved a $\geq$ VGPR following induction therapy and ASCT. In the PERSEUS trial, patients were enrolled and

randomised prior to induction or consolidation therapy, and initiated maintenance therapy irrespective of their MRD or response status’³

The company while acknowledging those differences claim ‘that the use of comparative efficacy estimates for DL versus L maintenance therapy from the AURIGA trial was considered the best approach’³. They go on to state that ‘similarity in maintenance efficacy outcomes between the PERSEUS and AURIGA trial suggest that differences in prior treatment do not substantially impact the generalisability of AURIGA trial results’³. Evidence from the CASSIOPEIA trial was also cited (see Section 3.4) which suggests that the prior exposure to daratumumab does not notably impact the effect of daratumumab maintenance. The company also state that ‘the $\geq$ VGPR and MRD-positive status of the AURIGA trial population is not expected to significantly impact the generalisability of maintenance therapy outcomes.’³ They conclude that the comparative efficacy of DL versus L in AURIGA is representative of what would be expected for patients who receive DBLd or DBTd I+C therapy in UK clinical practice. The EAG acknowledges these arguments made by the company, although the differences between patients who receive maintenance therapy in PERSEUS and AURIGA does cause uncertainty. This also highlights the importance of ensuring that methods to retrieve studies were robust, which the EAG questions in Section 3.1, and includes as part of the key issue regarding the lack of comparison of complete treatment sequence.

3.2.6 Efficacy results

3.2.6.1 PERSEUS trial

In Section 2.6.1, the company reported that “PERSEUS is an ongoing, Phase III RCT of DBLd induction and consolidation therapy followed by DL maintenance versus BLd induction and consolidation therapy followed by L maintenance in HDT-ASCT eligible patients with NDMM. Efficacy analyses were performed in the ITT population, which comprised all patients who underwent randomisation to the DBLd or BLd treatment arms. Data in this submission are based on the latest, 1st August 2023, DCO of the PERSEUS trial (median follow-up for the DBLd arm: █████ months; median follow-up for the BLd arm: █████ months).”¹ Further details can be found in Table 3.14 below.

Table 3.14: Summary of key clinical efficacy results

Outcome	BLd arm ^a	DBLd arm ^b	DBLd arm versus BLd arm ^c (95% CI)
Survival outcomes (full treatment sequence)			
Median PFS	████	████	0.42 (0.30, 0.59); p<0.001
Median OS	████	████	0.73 (0.47, 1.14)
Response (post-consolidation), n (%)			
$\geq$ CR	████	████	████
$\geq$ VGPR	████	████	████
ORR	████	████	████
sCR	████	████	████
Response (full treatment sequence), n (%)			
$\geq$ CR	248 (70.1)	312 (87.9)	3.13 (2.11, 4.65)
$\geq$ VGPR	████	████	████
ORR	████	████	████

Outcome	BLd arm ^a	DBLd arm ^b	DBLd arm versus BLd arm ^c (95% CI)
sCR			
Overall MRD-negativity rate (10-5; post-consolidation), n (%)			
MRD-negativity rate ($\geq$ CR)	115 (32.5)	204 (57.5)	
Overall MRD-negativity rate (10-5; full treatment sequence), n (%)			
MRD-negativity rate ($\geq$ CR)	168 (47.5)	267 (75.2)	3.40 (2.47, 4.69); p<0.0001
Sustained MRD-negativity rate (10-5; full treatment sequence), n (%)			
Sustained MRD-negativity rate (at or below 10 ⁻⁵)	105 (29.7)	230 (64.8)	4.42 (3.22, 6.08); p<0.0001
HRQoL (at consolidation initiation [Cycle 5 Day 1])			
EORTC QLQ-C30 Global Health Status; LS mean change from baseline (95% CI)			
EQ-5D-5L utility score, LS mean change from baseline (95% CI)			
EQ-5D-5L VAS, LS mean change from baseline (95% CI)			
HRQoL (at maintenance initiation [Cycle 1 Day 1])			
EORTC QLQ-C30 Global Health Status; LS mean change from baseline (95% CI)			
EQ-5D-5L utility score, LS mean change from baseline (95% CI)			
EQ-5D-5L VAS, LS mean change from baseline (95% CI)			
Based on Table 12 of the CS ¹			
^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy.			
^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.			
^c HRs presented for survival outcomes; ORs presented for response outcomes and MRD-negativity; absolute difference presented for HRQoL outcomes. A HR <1 indicates an advantage for DBLd			
BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; $\geq$ CR = complete response or better; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer QoL questionnaire core 30; EQ-5D-5L = EuroQol Group Five Dimensions Five Levels; HR = hazard ratio; HRQoL = health-related quality of life; L = lenalidomide; LS = least squared; MRD = minimal residual disease; N/A = not applicable; OR = odds ratio; ORR = overall response rate ; OS = overall survival; PFS = progression-free survival; sCR = stringent complete response; VAS = visual analogue scale; $\geq$ VGPR = very good partial response or better			

3.2.6.1.1 Primary efficacy outcomes - PFS

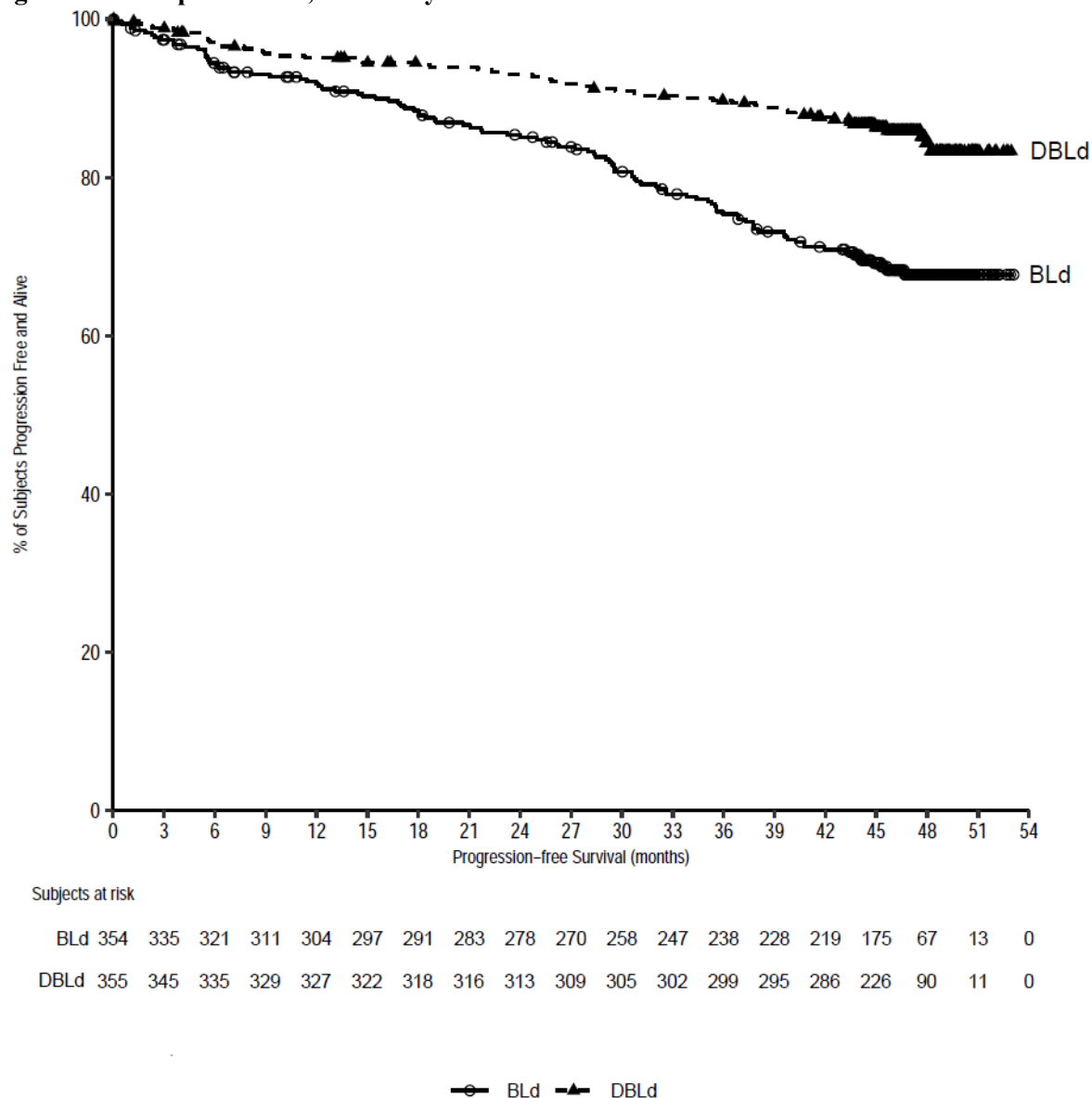
The company reported that “At the 1st August 2023 DCO, the primary endpoint of the PERSEUS trial was met. The addition of daratumumab to BLd induction and consolidation therapy and L maintenance treatment resulted in a statistically significant improvement in PFS, with a 58% reduction in risk of disease progression or death compared with BLd induction and consolidation treatment followed by L

maintenance alone (HR: 0.42; 95% CI: 0.30, 0.59; $p < 0.001$) in HDT-ASCT eligible NDMM patients. Furthermore, landmark estimates of PFS demonstrate a consistent trend of improved PFS associated with the DBLd versus the BLd treatment arms over time, with this benefit anticipated to increase with increased follow-up. This view is supported by the Kaplan-Meier (KM) plot of PFS in which an early and increasing separation between the BLd and DBLd treatment arms is clearly observed over time, as well as the response data.”¹ The further details can be found in Table 3.15 and Figure 3.5 below.

Table 3.15: PFS; ITT analysis set (full treatment sequence)

PFS Results	BLd arm ^a N=354	DBLd arm ^b N=355
Number of events, n (%)	103 (29.1)	50 (14.1)
Number of events censored, n (%)		
6-month PFS rate, % (95% CI)		
12-month PFS rate, % (95% CI)		
24-month PFS rate, % (95% CI)		
36-month PFS rate, % (95% CI)		
48-month PFS rate, % (95% CI)	67.7 (62.2, 72.6)	84.3 (79.5, 88.1)
60-month PFS rate, % (95% CI)		
Median KM estimate, months		
Median (95% CI)		
25% percentile (95% CI)		
75% percentile (95% CI)		
HR (95% CI) ^c	0.42 (0.30, 0.59)	
P-value ^d	<0.001	
Based on Table 13 of the CS ¹		
^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy.		
^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.		
^c p-value is based on the log-rank test stratified with ISS staging (I, II, versus III), and cytogenetic risk (high risk versus standard risk or unknown).		
^d HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, versus III), and cytogenetic risk (high risk versus standard risk or unknown). A HR <1 indicates an advantage for DBLd.		
BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = dexamethasone with lenalidomide; HR = hazard ratio; ISS = International Staging System; ITT = intention-to-treat; KM = Kaplan-Meier; L = lenalidomide; PFS = progression-free survival		

Figure 3.5: KM plot of PFS, ITT analysis set



Based on Figure 11 of the CS¹

BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; ITT = intention-to-treat; KM: Kaplan-Meier; PFS = progression-free survival

3.2.6.1.2 Key secondary efficacy outcomes - response rates

The company stated that “Both the DBLd and BLd treatment arms were associated with high levels of response at all treatment periods; (post-induction, post-consolidation and the full treatment sequence [induction, consolidation and maintenance]). The DBLd arm was however associated with an increased likelihood of response versus the BLd arm from the post-consolidation treatment phase, with the odds ratio increasing over time; post-consolidation: ORR OR: [REDACTED]; 95% CI: [REDACTED], [REDACTED]; p [REDACTED]; full treatment sequence ORR OR: [REDACTED]; 95% CI: [REDACTED], [REDACTED]; [REDACTED]

As well as an increased number of responders, the DBLd treatment arm was associated with deeper responses versus the BLd treatment arm. The DBLd treatment arm yielded a [REDACTED] as early as post-induction

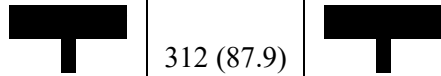
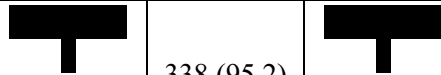
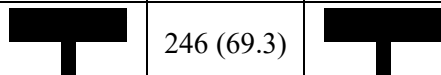
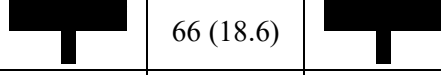
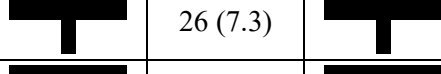
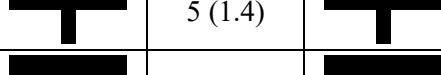
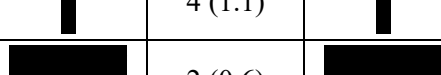
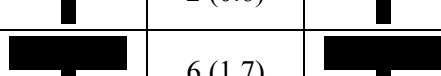
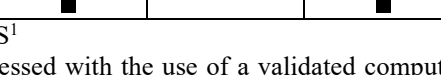
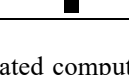
(odds ratio [OR]: [REDACTED]; 95% CI: [REDACTED]; p [REDACTED]). This benefit is shown to increase over time, demonstrated by the increased OR for the DBLd arm versus the BLd arm for the end of consolidation versus the full treatment sequence results (OR: [REDACTED]; 95% CI: [REDACTED]; p [REDACTED] versus OR: [REDACTED]; 95% CI: [REDACTED]; p [REDACTED], respectively). Furthermore, by the end of the consolidation phase, [REDACTED] rates were achieved in the DBLd arm compared with the BLd arm (sCR: [REDACTED] versus [REDACTED]; OR: [REDACTED], 95% CI: [REDACTED], p [REDACTED]; $\geq$ CR: [REDACTED] versus [REDACTED]; OR: [REDACTED], 95% CI: [REDACTED], p [REDACTED]). This trend was consistent in the full treatment sequence data; statistically significantly greater rates of both sCR and $\geq$ CR were achieved for DBLd versus the BLd arm for the full treatment sequence (sCR: [REDACTED] versus [REDACTED]; OR: [REDACTED], 95% CI: [REDACTED], p [REDACTED]; $\geq$ CR: 87.9% versus 70.1%; OR: 3.13, 95% CI: [REDACTED], $p < 0.0001$. In line with the $\geq$ VGPR data, the benefit shown in sCR and $\geq$ CR rates in the DBLd arm was shown to increase over time, demonstrated by increased ORs when comparing the post-consolidation to the full treatment sequence data (sCR: 1.56 versus 2.83; $\geq$ CR: 1.51 versus 3.13).

Finally, deeper responses were observed over time between post-induction, post-consolidation and post-maintenance (full treatment sequence) for both the DBLd and BLd arms. As highlighted above however, the extent of this was greater for the DBLd versus the BLd arm, illustrated by the consistently increasing ORs.^{”1} Further details can be found in Table 3.16 below.

Table 3.16: Summary of response rates; ITT analysis set, based on time of assessment^a

Response rates	BLd arm ^b N=354		DBLd arm ^c N=355		OR (95% CI) ^d	P-value ^e
	n (%)	95% CI	n (%)	95% CI		
Post-induction						
≥CR (sCR + CR)	75 (21.2)		80 (22.5)			0.6680
≥VGPR (sCR + CR + VGPR)	257 (72.6)		301 (84.8)			
ORR	321 (90.7)		334 (94.1)			
sCR	25 (7.1)		34 (9.6)			
	50 (14.1)		46 (13.0)		-	-
VGPR	182 (51.4)		221 (62.3)		-	-
PR	64 (18.1)		33 (9.3)		-	-
SD					-	-
PD					-	-
NE					-	-
Post-ASCT						
≥CR (sCR + CR)	83 (23.4)		99 (27.9)			
≥VGPR (sCR +	260 (73.4)		303 (85.4)			

Response rates	BLd arm ^b N=354		DBLd arm ^c N=355		OR (95% CI) ^d	P-value ^e
	n (%)	95% CI	n (%)	95% CI		
CR + VGPR)						
ORR	322 (91.0)		334 (94.1)			
sCR	29 (8.2)		38 (10.7)			
CR	54 (15.3)		61 (17.2)		-	-
VGPR	177 (50.0)		204 (57.5)		-	-
PR	62 (17.5)		31 (8.7)		-	-
SD					-	-
PD					-	-
NE					-	-
Post-consolidation						
≥CR (sCR + CR)	123 (34.7)					
≥VGPR (sCR + CR + VGPR)	291 (82.2)					
ORR	326 (92.1)					
sCR	46 (13.0)					
CR	77 (21.8)				-	-
VGPR	168 (47.5)				-	-
PR	35 (9.9)				-	-
SD					-	-
PD					-	-
NE					-	-
Full treatment sequence						

Response rates	BLd arm ^b N=354		DBLd arm ^c N=355		OR (95% CI) ^d	P-value ^e
	n (%)	95% CI	n (%)	95% CI		
≥CR (sCR + CR)	248 (70.1)		312 (87.9)			
≥VGPR (sCR + CR + VGPR)	316 (89.3)		338 (95.2)			
ORR	332 (93.8)	(90.7, 96.1)	343 (96.6)	(94.2, 98.2)		
sCR	158 (44.6)		246 (69.3)			
CR	90 (25.4)		66 (18.6)		-	-
VGPR	68 (19.2)		26 (7.3)		-	-
PR	16 (4.5)		5 (1.4)		-	-
SD	9 (2.5)		4 (1.1)		-	-
PD	1 (0.3)		2 (0.6)		-	-
NE	12 (3.4)		6 (1.7)		-	-

Based on Table 14 of the CS¹

^a Tumour response was assessed with the use of a validated computerised algorithm in accordance with the IMWG response criteria. Percentages are calculated with the number of subjects in each group as denominator.

^b Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy.

^c Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy.

^d Mantel-Haenszel estimate of the common OR for stratified tables is used. The stratification factors are ISS staging (I, II, versus III) and cytogenetic risk (high risk versus standard risk).

^e P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.

ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; CR = complete response; ≥CR = complete response or better; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; I+C = induction and consolidation; IMWG = International Myeloma Working Group; ISS = International Staging System; ITT = intention-to-treat; L = lenalidomide; NE = not evaluable; OR = odds ratio; ORR = overall response rate; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response

3.2.6.1.3 Key secondary efficacy outcomes - MRD-negativity

In PERSEUS, minimal residual disease (MRD)-negativity rate was defined as the proportion of patients in the ITT population who achieved both MRD-negativity (at a threshold of one tumour cell per 10⁻⁵ white cells in bone marrow aspirate) and a ≥complete response (≥CR) at any time after the date of randomisation (and prior to disease progression, receipt of subsequent therapy, or both). Of note, the requirement for a ≥CR means the definition of MRD-negativity rate is more stringent than typical definitions in other MM clinical trials. Sustained MRD-negativity was defined as two consecutive

MRD-negative results (at or below a threshold of 10^{-5}) at least 12 months apart, without any MRD-positive (at a threshold of 10^{-4} or higher) results in between.

The company reported that “In the ITT analysis set, the DBLd arm achieved a significantly higher MRD-negativity rate compared with the BLd arm at the post-consolidation timepoint (57.5% versus 32.5%; OR: [REDACTED]; 95% CI: [REDACTED]; $p < [REDACTED]$). Importantly, in line with the response data presented above, the OR for DBLd versus the BLd arm increased when comparing the post-consolidation to the full treatment sequence data, demonstrating an increasing benefit in the DBLd arm over time (full treatment sequence MRD-negativity rate: 75.2% versus 47.5%; OR: 3.40; 95% CI: 2.47, 4.69; $p < 0.0001$). As the full treatment sequence data included maintenance treatment, this increasing OR also supports an improved efficacy of DL maintenance (DBLd arm) versus L maintenance therapy alone (BLd arm).”¹ Further details can be found in Table 3.17 below.

The company also reported that “The benefit of DL maintenance versus L maintenance in PERSEUS is further supported by the data, which show that the proportion of patients who achieved sustained MRD-negativity during the maintenance phase was significantly higher for patients receiving DL maintenance (DBLd arm) versus L maintenance therapy alone (BLd arm). The same was true for the rate of patients who converted from MRD-positive post-consolidation to MRD-negative during the maintenance phase.” The company also mentioned that “a subgroup analysis of sustained MRD-negativity showed that the benefit of DBLd followed by DL maintenance over BLd with L maintenance was consistent across all subgroups.”¹ Further details can be found in Table 3.18 below.

Table 3.17: Summary of overall MRD-negativity rate by NGS at or below 10^{-5} in patients with $\geq$ CR post-consolidation and full treatment sequence; ITT analysis set

MRD-negativity rate	BLd arm ^a N=354	DBLd arm ^b N=355
	n (%)	n (%)
Post-consolidation		
MRD-negativity rate (at or below 10 ⁻⁵)	115 (32.5)	204 (57.5)
95% CI ^c		
OR (95% CI) ^d		
P-value ^e		
Full treatment sequence		
MRD-negativity rate (at or below 10 ⁻⁵)	168 (47.5)	267 (75.2)
95% CI ^c		
OR (95% CI) ^d	3.40 (2.47, 4.69)	
P-value ^e	<0.001	
Sustained MRD-negativity rate (at or below 10 ⁻⁵)	105 (29.7)	230 (64.8)
95% CI ^c		
OR (95% CI)	4.42 (3.22, 6.08)	
P-value ^e	<0.001	
Based on Table 15 of the CS ¹		
^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy.		
^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy		
^c Exact 95% CI.		

^d Mantel-Haenszel estimate of the common OR for stratified tables is used. The stratification factors are ISS staging (I, II, versus III) and cytogenetic risk (high risk versus standard risk).

^e P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.

BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; CR = complete response; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; ISS = International Staging System; ITT = intention-to-treat; L = lenalidomide; MRD = minimal residual disease; NGS = next-generation sequencing; OR = odds ratio

Table 3.18: Summary of MRD-negativity outcomes by NGS during the maintenance phase; ITT analysis set

MRD-negativity rate	BLd arm ^a N=121	DBLd arm ^b N=88
	%	%
Sustained MRD-negativity for ≥12 months during the maintenance phase		
Sustained MRD-negativity rate (at or below 10 ⁻⁵)	17.4	38.6
P-value	0.0006	
Conversion rate during maintenance phase		
MRD-positive (post-consolidation) to MRD-negative conversion rate (at or below 10 ⁻⁵)	40.5	60.2
P-value	0.0049	
Based on Table 16 of the CS ¹		
^a Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy.		
^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy.		
BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; I+C = induction and consolidation; ITT = intention-to-treat; L = lenalidomide; MRD = minimal residual disease; NGS = next-generation sequencing; OR = odds ratio		

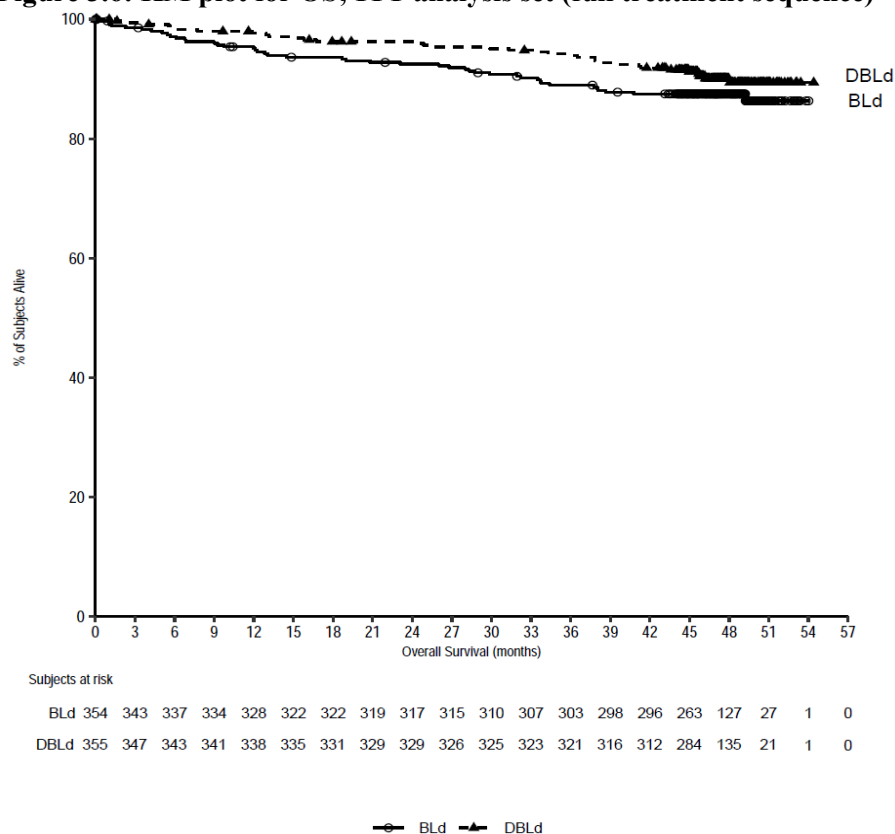
3.2.6.1.4 Key secondary efficacy outcomes - OS

The company reported that “At the time of the 1st August 2023 DCO, median OS was not reached in either treatment arm (■■■■; 95% CI: ■■■■, ■■■■) at a median follow-up of 47.5 months. As highlighted above, given the relatively good prognosis (median OS of approximately 160 months) of this patient population, immature OS data is expected in the first-line setting with extensive follow-up required to obtain mature OS data. The current data cut from PERSEUS is also consistent with the availability of data in previously recommended treatments by NICE in the same indication. Despite this, the available OS data show promising initial results, with an estimated HR of 0.73 (95% CI: ■■■■) in favour of the DBLd treatment arm. Whilst this result was ■■■■, a clear early separation in KM curves can be observed between treatment arms, which is maintained until high censoring towards the end of follow-up. This separation is only anticipated to increase over time, as follow-up increases. This is supported by the fact that the DBLd treatment arm was associated with a ■■■■ versus the BLd treatment arm as early as post-induction. As noted above, there is an extensive body of evidence highlighting the link between achieving a deep, sustained treatment response on improved survival outcomes and therefore these results are highly predictive of superior long-term survival outcomes with DBLd + DL versus BLd + L.”¹ The further details can be found in Table 3.19 and Figure 3.6 below.

Table 3.19: OS in patients in the ITT analysis set (full treatment sequence)

OS	BLd arm ^a N=354	DBLd arm ^b N=355
Number of events, n (%)	44 (12.4)	34 (9.6)
Number of censored	■■■■	■■■■
12-month OS rate, % (95% CI)	■■■■	■■■■
24-month OS rate, % (95% CI)	■■■■	■■■■
36-month OS rate, % (95% CI)	■■■■	■■■■

48-month OS rate, % (95% CI)		
60-month OS rate, % (95% CI)		
Median KM estimate, months (95% CI)		
25% percentile		
Median		
75% percentile		
HR (95% CI) ^c	0.73 (0.47, 1.14)	
Based on Table 17 of the CS ¹		
Footnote:		
^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy.		
^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy.		
^c HR from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and cytogenetic risk (high risk versus standard risk or unknown). A HR <1 indicates an advantage for the DBLd arm.		
BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; HR = hazard ratio; ISS = International Staging System; ITT = intention-to-treat; KM = Kaplan-Meier; L = lenalidomide; NE = not evaluable; OS = overall survival		

Figure 3.6: KM plot for OS; ITT analysis set (full treatment sequence)Based on Figure 12 of the CS¹

BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival

3.2.6.1.5 Key secondary efficacy outcomes – duration of response (DOR)

The company reported that “Among responders, median DOR in the ITT analysis set was [REDACTED] at a median follow-up of 47.5 months. This highlights the benefits achieved by both treatments in terms of response, as median DOR was [REDACTED] due to a large number of patients still being in response and, as such, being censored. Of note however, a greater proportion of patients were censored (i.e., still in response) in the [REDACTED] arm compared with the [REDACTED] arm ([REDACTED] versus [REDACTED]) at the most recent (1st August 2023) DCO.”¹ Further details can be found in Table 3.20 below.

Table 3.20: DOR in patients in the ITT analysis set (full treatment sequence)^a

DOR	BLd arm ^b N=332	DBLd arm ^c N=343
Number of events, n (%) ^d	[REDACTED]	[REDACTED]
Number of events censored, n (%)	[REDACTED]	[REDACTED]
Median KM estimate, months		
25% percentile (95% CI)	[REDACTED]	[REDACTED]
Median (95% CI)	[REDACTED]	[REDACTED]
75% percentile (95% CI)	[REDACTED]	[REDACTED]
Based on Table 18 of the CS¹ ^a Response PR or better. ^b Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy. ^c Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy. ^d Number of events refers to number of responders (or complete responders, or stringent complete responders) who developed disease progression or died due to disease progression. BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; DOR = duration of response; I+C = induction and consolidation; ITT = intention-to-treat; KM = Kaplan-Meier; L = lenalidomide; PR = partial response		

3.2.6.1.6 Key secondary efficacy outcomes - time to response

The company reported that “At the 1st August 2023 DCO, for responders, the median time to first response (defined as a $\geq$ PR) and the median time to $\geq$ CR were similar between the two treatment arms (DBLd arm: [REDACTED] months versus BLd arm: [REDACTED] months and DBLd arm: [REDACTED] months versus BLd arm: [REDACTED] months, respectively). Median time to best response and median time to sCR however were longer in the DBLd arm compared with the BLd arm (DBLd arm: [REDACTED] months versus [REDACTED] months and DBLd arm: [REDACTED] months versus [REDACTED] months, respectively). Of note however, several studies in patients with NDMM have found that achieving a more gradual response is associated with deeper responses which translate to longer PFS and DOR. The longer time to response for the DBLd arm compared with BLd may also relate to the higher rate of patients achieving a response in the DBLd arm. As such, the acquisition of response would be expected to plateau faster in the BLd arm, when compared with the DBLd arm where patients continue to experience a response in the early maintenance phase.”¹ Further details can be found in Table 3.21 below.

Table 3.21: Time to response; ITT analysis set (full treatment sequence)^a

Time to response	BLd arm ^b N=332	DBLd arm ^c N=343
Time to first response, months		
n	██████	██████
Mean (SD)	██████████	██████████
Median (range)	██████████	██████████
Time to best response, months		
n	██████	██████
Mean (SD)	██████████	██████████
Median (range)	██████████	██████████
Time to ≥VGPR, months		
n	██████	██████
Mean (SD)	██████████	██████████
Median (range)	██████████	██████████
Time to ≥CR, months		
n	██████	██████
Mean (SD)	██████████	██████████
Median (range)	██████████	██████████
Time to sCR or better, months		
n	██████	██████
Mean (SD)	██████████	██████████
Median (range)	██████████	██████████
Based on Table 19 of the CS ¹ Footnote: ^a Response PR or better. ^b Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy. ^c Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy. BLd = bortezomib, lenalidomide and dexamethasone; CR = complete response; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; I+C = induction and consolidation; ITT = intention-to-treat; L = lenalidomide; sCR = stringent complete response; SD = standard deviation; VGPR = very good partial response		

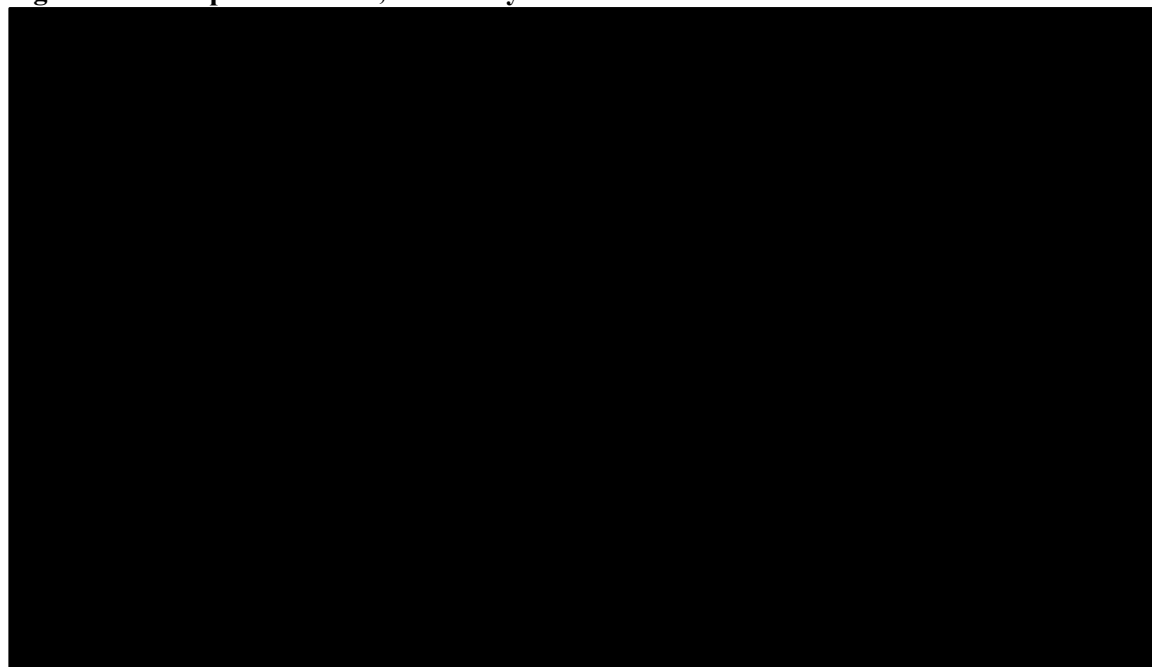
3.2.6.1.7 Key secondary efficacy outcomes – PFS on next line of therapy

The company reported that “At a median follow-up of 47.5 months, PFS2 data remained immature with only ███ (████%) events in the DBLd arm and ███ (████%) events in the BLd arm. Despite the low number of events, a strong trend for improved outcomes for patients in the DBLd arm versus the BLd arm was observed (HR: ███; 95% CI: █████; █████). These results demonstrate that the observed PFS benefit in the DBLd arm is maintained beyond the next line of therapy received.”¹ Further details can be found in Table 3.22 and Figure 3.7 below.

Table 3.22: PFS on next line of therapy; ITT analysis set (full treatment sequence)

PFS2	BLd arm ^a N=354	DBLd arm ^b N=355
Number of events, n (%)	██████	██████

PFS2	BLd arm ^a N=354	DBLd arm ^b N=355
Number of censored, n (%)		
12-month PFS2 rate, % (95% CI)		
24-month PFS2 rate, % (95% CI)		
36-month PFS2 rate, % (95% CI)		
48-month PFS2 rate, % (95% CI)		
60-month PFS2 rate, % (95% CI)		
Median KM estimate, months (95% CI)		
25% percentile		
Median		
75% percentile		
HR (95% CI) ^c		
P-value ^d		
Based on Table 20 of the CS¹ ^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy. ^c HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. A HR <1 indicates an advantage for DBLd. ^d p-value is based on the log-rank test. BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; CI = confidence interval; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; HR = hazard ratio; I+C = induction and consolidation; ITT = intention-to-treat; KM = Kaplan-Meier; L = lenalidomide; NE = not evaluable; PFS2 = progression-free survival on next line of therapy		

Figure 3.7: KM plot for PFS2; ITT analysis set

Based on Figure 13 of the CS¹

BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; ITT = intention-to-treat; KM = Kaplan-Meier; PFS2 = progression-free survival on next line of therapy

3.2.6.1.8 Patient-reported outcomes - EORTC QLQ-C30

The company reported that “The proportion of patients with a clinically meaningful improvement in EORTC QLQ-C30 scores at each cycle up to the final maintenance timepoints was comparable between treatment arms (Cycle 34 Day 1; DBLd versus BLd: global health status 37.8% versus 36.8%, physical functioning 39.5% versus 41.1%, pain 48.9% versus 50.0%, fatigue 46.5% versus 53.1%).”

The company stated that “Results from the improvements in outcomes including Global Health Status, pain symptom score, fatigue symptom score and physical functioning from baseline to consolidation initiation were comparable over time for the DBLd and BLd arms (least squared [LS] mean difference in change from baseline at Cycle 5 Day 1: [REDACTED] [95% CI: [REDACTED]; p [REDACTED]], [REDACTED] [95% CI: [REDACTED]; p [REDACTED]], [REDACTED] [95% CI: [REDACTED]; p [REDACTED]] and [REDACTED] [95% CI: [REDACTED]; p [REDACTED]], respectively). Similarly, improvements in these outcomes were also comparable over time for the DBLd and BLd arms from baseline to maintenance initiation (LS mean difference in change from baseline at maintenance Cycle 1 Day 1: [REDACTED] [95% CI: [REDACTED]; p [REDACTED]], [REDACTED] [95% CI: [REDACTED]; p [REDACTED]] [95% CI: [REDACTED]; p [REDACTED]] and [REDACTED] [95% CI: [REDACTED]; p [REDACTED]] respectively). Of particular note, clinically meaningful reductions in pain (≥ 10 points) were found for both treatment arms, by maintenance Cycle 4 Day 1 in the DBLd arm (LS mean difference in change from baseline: [REDACTED] [95% CI: [REDACTED]]) and in the BLd arm (LS mean difference in change from baseline: [REDACTED] [95% CI: [REDACTED]]) and extended through maintenance Cycle 34 Day 1. Most scores showed numerical improvement in both arms from induction through maintenance. [REDACTED] were observed between arms in the time to improvement or worsening.”

The company summarised that “Overall, these results support that the addition of daratumumab to BLd induction and consolidation therapy and L maintenance therapy does not have a negative impact on patient HRQoL”.¹ Further details can be found in Table 3.23 and Table 3.24 below.

Table 3.23: Baseline values for EORTC QLQ-C30; ITT analysis set^a

Subscale score (mean, SD)	BLd arm ^c	DBLd arm ^b
Global health status	[REDACTED]	64.24 (23.06)
Symptom scales		
Fatigue	[REDACTED]	31.71 (24.73)
Nausea and vomiting	[REDACTED]	[REDACTED]
Pain score	[REDACTED]	32.79 (30.42)
Functional scales		
Cognitive functioning	[REDACTED]	[REDACTED]
Emotional functioning	[REDACTED]	[REDACTED]
Physical functioning	[REDACTED]	74.19 (27.06)
Role functioning	[REDACTED]	[REDACTED]
Social functioning	[REDACTED]	[REDACTED]

Based on Table 21 of the CS¹

^a All the scores are presented in the range of 0-100 after linear transformation from raw scores (in the range of 1-4). A higher score indicates better health on the global health and functional scales (physical, role, emotional, cognitive, and social) and greater symptom severity on the symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea); ^b Patients in the DBLd treatment arm received DBLd as induction and consolidation therapy, followed by DL maintenance therapy; ^c Patients in the BLd treatment arm received BLd as induction and consolidation therapy, followed by L maintenance therapy.

BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer QoL questionnaire core 30; ITT = intention-to-treat; L = lenalidomide; SD = standard deviation

Table 3.24: Change from baseline in EORTC QLQ-C30 scores for induction, pre-ASCT, consolidation and maintenance phases; ITT analysis set

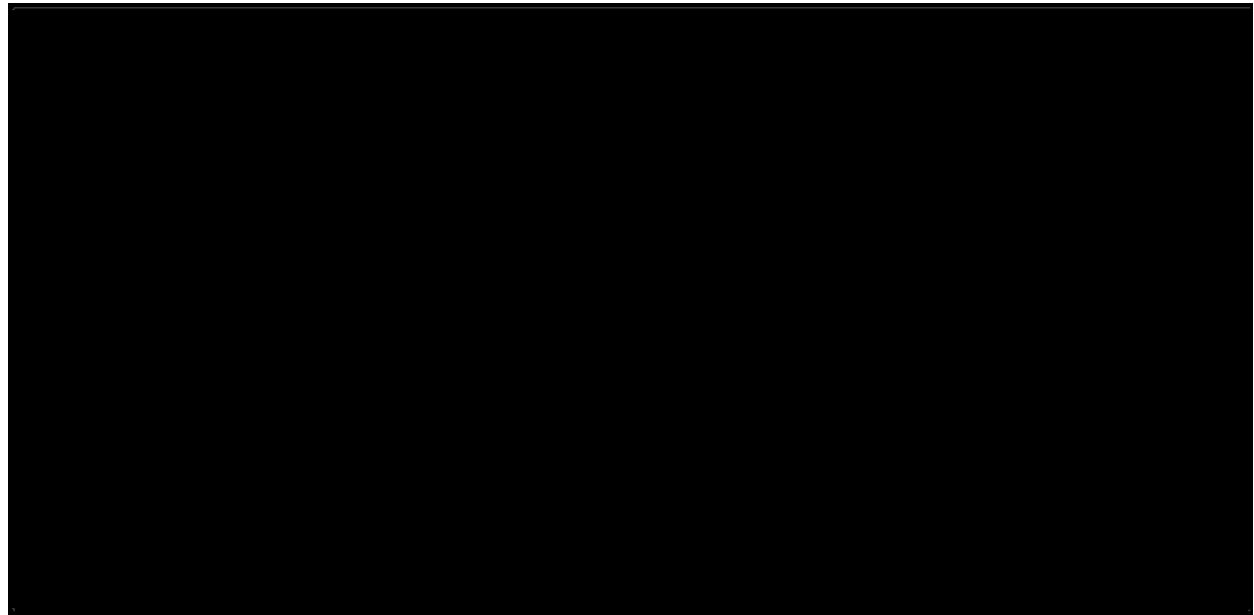
	BLd arm^a N=354	DBLd arm^b N=355	Difference (95% CI)^c	P-value
Global health status score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1				
Pre-ASCT				
Consolidation Cycle 5 Day 1				
Maintenance Cycle 1 Day 1				
Maintenance Cycle 34 Day 1				
Pain symptom score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1				
Pre-ASCT				
Consolidation Cycle 5 Day 1				
Maintenance Cycle 1 Day 1				
Maintenance Cycle 34 Day 1				
Fatigue symptom score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1				
Pre-ASCT				
Consolidation Cycle 5 Day 1				
Maintenance Cycle 1 Day 1				
Maintenance Cycle 34 Day 1				
Physical functioning score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1				
Pre-ASCT				
Consolidation Cycle 5 Day 1				
Maintenance Cycle 1 Day 1				
Maintenance Cycle 34 Day 1				
Based on Table 22 of the CS ¹ ^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy; ^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy ^c LS means are derived based on the mixed effects model with repeated measures, in which the dependent variable is change from baseline in score, and independent variables are baseline, visit, treatment, visit by treatment interaction, and randomisation stratification factors ISS staging (I, II, III), and cytogenetic risk (high risk versus standard risk or unknown) as fixed effects and individual subject as random effect. ASCT = autologous stem cell transplant; BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; I+C = induction and consolidation; ITT = intention-to-treat; L = lenalidomide; LS = least squared; SD = standard deviation				

3.2.6.1.9 Patient-reported outcomes - EQ-5D-5L

The company reported that “The proportion of patients with a clinically meaningful improvement in EQ-5D-5L VAS scores at each cycle up to the final maintenance timepoints was comparable between treatment arms (Cycle 34 Day 1; DBLd versus BLd: 49.7% versus 43.9%). Changes from both baseline to consolidation initiation and baseline to maintenance initiation for EQ-5D-5L VAS and utility scores were [REDACTED] different between treatment arms, with comparable slight improvements seen with VAS scores in both treatment arms (LS mean difference in change from baseline at Cycle 5 Day 1: baseline to consolidation initiation: [REDACTED] [95% CI: [REDACTED], [REDACTED]; p=[REDACTED]]; baseline to maintenance initiation: [REDACTED] [95% CI: -[REDACTED], [REDACTED]; p=[REDACTED]])”.¹ Further details can be found in Table 3.25 below.

Table 3.25: Change from baseline in EQ-5D-5L scores at induction, pre-ASCT, consolidation and maintenance phases; ITT analysis set

	BLd arm ^a N=332	DBLd arm ^b N=343	Difference (95% CI)	P-value
Utility score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Pre-ASCT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Consolidation Cycle 5 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Maintenance Cycle 1 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Maintenance Cycle 34 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
VAS score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Pre-ASCT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Consolidation Cycle 5 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Maintenance Cycle 1 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Maintenance Cycle 34 Day 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 23 of the CS ¹				
^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy.				
^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy.				
ASCT = autologous stem cell transplant; BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; EQ-5D-5L = EuroQol Group Five Dimensions Five Levels; ITT = intention-to-treat; L = lenalidomide; LS = least squared; VAS = visual analogue scale				

Figure 3.8: EQ-5D-5L VAS, LS mean change from baseline; ITT analysis set

Based on Figure 14 of the CS¹

^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy.

^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy.

ASCT = autologous stem cell transplant; BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; CXDY = Cycle X Day Y; DL = daratumumab with lenalidomide; EQ-5D-5L = EuroQol Group Five Dimensions Five Levels; ITT = intention-to-treat; L = lenalidomide; LS = least squared; VAS = visual analogue scale

3.2.6.1.10 Patient-reported outcomes - EORTC QLQ-MY20

The company reported that “*The proportion of patients with a clinically meaningful improvement in EORTC QLQ-MY20 scores at each cycle up to the final maintenance timepoints was similar across the DBLd and BLd treatment arms (Cycle 34 Day 1; DBLd versus BLd: 47.3% versus 49.1%). Changes from both baseline to consolidation initiation (Cycle 5 Day 1) and baseline to maintenance initiation for EORTC QLQ-MY20 disease symptom scale scores were [REDACTED] between treatment arms, with comparable slight improvements in scores seen in both treatment arms (LS mean difference in change from baseline at Cycle 5 Day 1: [REDACTED] [95% CI: [REDACTED], [REDACTED]; p=[REDACTED]]; LS mean difference in change from baseline at maintenance initiation: [REDACTED] [95% CI: [REDACTED], [REDACTED]; p=[REDACTED]).*”

The company summarised that “*patients treated with DBLd-DL experienced a HRQoL improvement from baseline that was apparent by the time maintenance began, and was sustained throughout the maintenance treatment phase across the different HRQoL measures. No differences in symptoms and/or functioning between treatment arms was observed. These findings indicate that the addition of daratumumab to BLd induction and consolidation and L maintenance therapy did not have a detrimental impact on patient HRQoL.*”¹ Further details can be found in Table 3.26 below.

Table 3.26: Change from baseline in EORTC QLQ-MY20 scores at induction, pre-ASCT, consolidation and maintenance phases

	BLd arm ^a N=332	DBLd arm ^b N=343	Difference (95% CI)	P-value
Disease symptom scale score, LS mean change from baseline (95% CI)				
Induction Cycle 3 Day 1	████████	████████	████████	████████
Pre-ASCT	████████	████████	████████	████████
Consolidation Cycle 5 Day 1	████████	████████	████████	████████
Maintenance Cycle 1 Day 1	████████	████████	████████	████████
Maintenance Cycle 34 Day 1	████████	████████	████████	████████
Based on Table 24 of the CS ¹				
^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy.				
^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy.				
ASCT = autologous stem cell transplant; BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; EORTC QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20; I+C = induction and consolidation; L = lenalidomide; LS = least squared				

EAG comment: The daratumumab-based regimen (DBLd I+C followed by DL maintenance) demonstrated a statistically significant and clinically meaningful improvement in efficacy outcomes compared to the SoC (BLd I+C followed by L maintenance) in transplant-eligible patients with NDMM. This benefit was observed across multiple endpoints including PFS, depth of response, and MRD negativity, with no detrimental impact on health-related quality of life (HRQoL). OS data remain immature but show an early trend in favour of the daratumumab arm. However, the EAG notes that this comparison is not relevant to the DP and was not used in any ITC or to inform the economic model.

3.2.6.2 AURIGA trial

AURIGA is an ongoing, Phase III RCT of DL versus L maintenance in patients who have received induction and HDT-ASCT. Specifically, it enrolled patients who, despite achieving $\geq$ very good partial response (VGPR), had detectable MRD post-ASCT. Efficacy analyses were performed in the ITT population, which comprised all patients who underwent randomisation to the DL or L treatment arms. Data in this submission are based on the latest DCO, 4 April 2024, with a median follow-up of 32.3 months (DL: 33.2 months; L: 30.3 months).

The AURIGA trial met its primary endpoint of the MRD-negative conversion rate by 12 months from the start of maintenance therapy. The overall MRD-negativity conversion rate for the DL arm was double that of the L arm (60.6% versus 27.7%; $p < 0.0001$), whilst the rate of sustained MRD-negativity was three times higher in the DL arm compared with the L arm (17.2% versus 5.0%; $p = 0.0065$). At a median follow-up of 32.3 months, PFS favoured DL over L, with a 47% risk reduction in disease progression or death ($p = 0.0361$).

The results of the AURIGA trial demonstrate that DL maintenance treatment is associated with a statistically significantly greater likelihood of achieving MRD-negativity compared to the SoC maintenance treatment currently used in the UK, lenalidomide. AURIGA phase III trial confirmed the benefit of DL maintenance with 2.7 x MRD-negativity rates of conversion and a 47% PFS risk reduction versus L. These results are supported by the MRD-negative treatment effect observed in PERSEUS for DBLd-DL versus BLd-L (full treatment sequence MRD-negativity rate: 75.2% versus 47.5%; odds ratio [OR]: 3.40; 95% confidence interval [CI]: 2.47, 4.69; $p < 0.0001$).

The company summarised that “it is critical that patients with NDMM achieve a deep and durable response, in particular MRD negativity, at the first-line stage of the treatment pathway, in order to prolong the period that they are progression free, delay reductions in HRQoL and the requirement for expensive subsequent therapies and ultimately extend patients’ survival for as long as possible. These results therefore illustrate that the introduction of DL maintenance treatment would represent a substantial improvement to the treatment pathway for transplant-eligible NDMM patients in the UK”.¹ Further details can be found in Table 3.27 below.

The company also reported that “Patient reported outcomes in AURIGA were collected through the EORTC QLQ-C30 and the EQ-5D questionnaires. EQ-5D-5L health utility index and VAS assessment showed that general HRQoL and overall health status were maintained with DL”.¹ Further details can be found in Table 3.28 below.

Table 3.27: Summary of key clinical efficacy results

Outcome			DL arm versus L arm (95% CI)
Survival outcomes			
Median PFS (months)	NE	37.9	0.53 (0.29, 0.97); 0.0361
Median OS (months)			
12-month MRD-negativity conversion rate (10⁻⁵), n (%)^a			
MRD-negativity rate	19 (19.8)	50 (50.5)	4.51 (2.37, 8.57); p<0.0001
Overall MRD-negativity conversion rate (10⁻⁵), n (%)^b			
MRD-negativity rate	28 (27.7)	60 (60.6)	4.12 (2.26, 7.52); p<0.0001
Sustained MRD-negativity rate (10⁻⁵), n (%)^c			
Sustained MRD-negativity rate	5 (5.0)	17 (17.2)	4.08 (1.43, 11.62); p=0.0065
Based on Table 25 of the CS ¹			
^a Defined as the proportion of patients who achieved MRD-negative status (threshold 10 ⁻⁵) by 12 months after the initiation of maintenance treatment and before progressive disease or subsequent antimyeloma therapy.			
^b Defined as the proportion of patients who achieved MRD-negative status any time after the date of randomisations.			
^c Defined as patients who achieved MRD-negative status (at 10 ⁻⁵) in two bone marrow aspirate assessments with a minimum of 12 months apart, without any assessment showing MRD-positive status in between assessments.			
CI = confidence interval; CS = company submission; DL = daratumumab with lenalidomide; L = lenalidomide; MRD = minimal residual disease; NE = not evaluable; OS = overall survival; PFS = progression-free survival			

Table 3.28: Change from baseline in EORTC QLQ-C30 scores from AURIGA trial; ITT analysis set

	DL, N=96	L, N=98
EORTC QLQ-C30		
<i>Global health status score, LS mean change from baseline (95% CI)</i>		
Baseline	77.75	72.76
Cycle 13 Day 1	-1.73	6.47
End of treatment	-6.20	-3.98
Post-treatment follow-up	-21.67	-8.33
EQ-5D-5L		

	DL, N=96	L, N=98
Utility		
Baseline	0.81	0.79
Cycle 13 Day 1	0.00	0.00
End of treatment	0.01	-0.02
Post-treatment follow-up	-0.13	-0.06
VAS		
Baseline	80.24	81.28
Cycle 13 Day 1	1.96	-1.68
End of treatment	3.28	-5.79
Post-treatment follow-up	-3.20	4.60
EORTC QLQ-MY20		
Disease symptom scales		
Baseline	19.69	21.59
Cycle 13 Day 1	-0.49	-2.20
End of treatment	-2.84	4.18
Post-treatment follow-up	1.11	5.56
Based on Table 28 of the CS ¹ CI = confidence interval; CS = company submission; DL = daratumumab with lenalidomide; L = lenalidomide; EORTC QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire core 30; EQ-5D-5L = EuroQol Group Five Dimensions Five Levels; ITT = intention-to-treat; LS = least squared; VAS = visual analogue scale		

EAG comment: In the AURIGA trial, the DL maintenance regimen demonstrated a statistically significant and clinically meaningful improvement in efficacy outcomes compared to L maintenance alone in transplant-eligible NDMM patients. The primary endpoint and key secondary endpoints were met, showing superior MRD conversion and a PFS benefit, with no detrimental impact on HRQoL.

3.2.7 Subgroup analyses

Subgroup analyses were performed on the PFS, $\geq$ CR and overall MRD negativity rate endpoints in the ITT analysis set for the full treatment sequence, including clinically relevant subgroups based on age, ISS stage, cytogenetic risk, and baseline ECOG PS score.

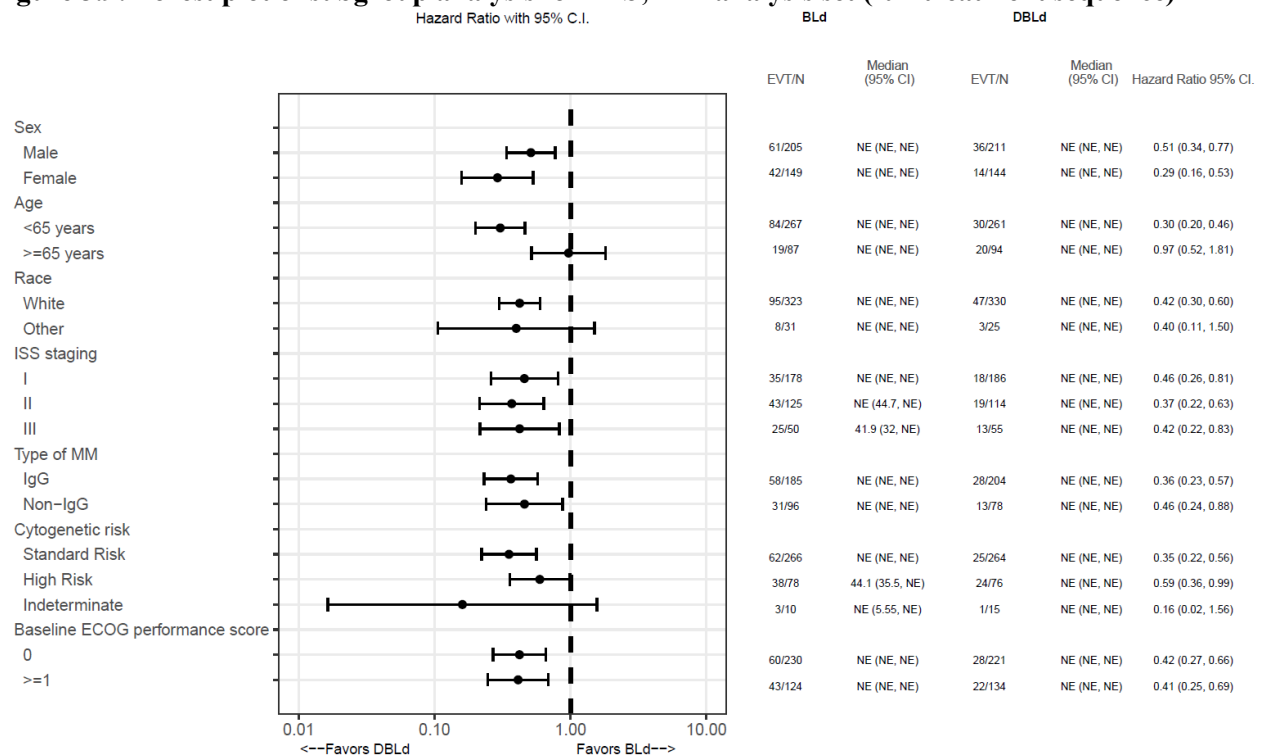
In Section 2.8, the company reported that “For PFS, the benefit was generally consistent across clinically relevant prespecified subgroups (age, ISS stage, cytogenetic risk, and baseline ECOG performance score) demonstrating a statistically significantly greater improvement in patients in the DBLd arm compared with patients in the BLd arm, with the exception of the ≥ 65 years subgroup, the indeterminate cytogenetic risk subgroup and the race ‘other’ subgroup. These subgroups still favoured DBLd, however the results were not statistically significant (HR: 0.97 [95% CI: 0.52, 1.81], HR: 0.16 [95% CI: 0.02, 1.56] and HR: 0.40 [95% CI: 0.11, 1.50], respectively. Given that the study was not powered to detect differences in subgroups and owing to the small patients numbers associated with these subgroups however, these results should be interpreted with caution.

For subgroup analyses of overall $\geq$ CR rate and MRD-negativity, the response benefit was consistent across most clinically relevant prespecified subgroups; most analyses demonstrated statistically

significant improvements in the DBLd arm compared with BLd arm, with the exception of the ≥ 65 years, ISS Stage III, high cytogenetic risk and race 'other' subgroups for $\geq$ CR rate and race 'other' for MRD-negativity. As noted above, however, these observed differences are anticipated to be a reflection of small patient numbers and therefore a lack of statistical power to detect differences in treatment effects within these subgroups and as such these results should be interpreted with caution.

For subgroup analyses of sustained MRD-negativity (MRD-negativity for at least 12 months; at a threshold of 10^{-6}), the response benefit was consistent across all prespecified subgroups, with statistically significant improvements in the DBLd arm compared with BLd arm for all analyses.¹ Further details can be found in Figure 3.9, Figure 3.10, Figure 3.11 and Figure 3.12.

Figure 3.9: Forest plot of subgroup analysis for PFS; ITT analysis set (full treatment sequence)



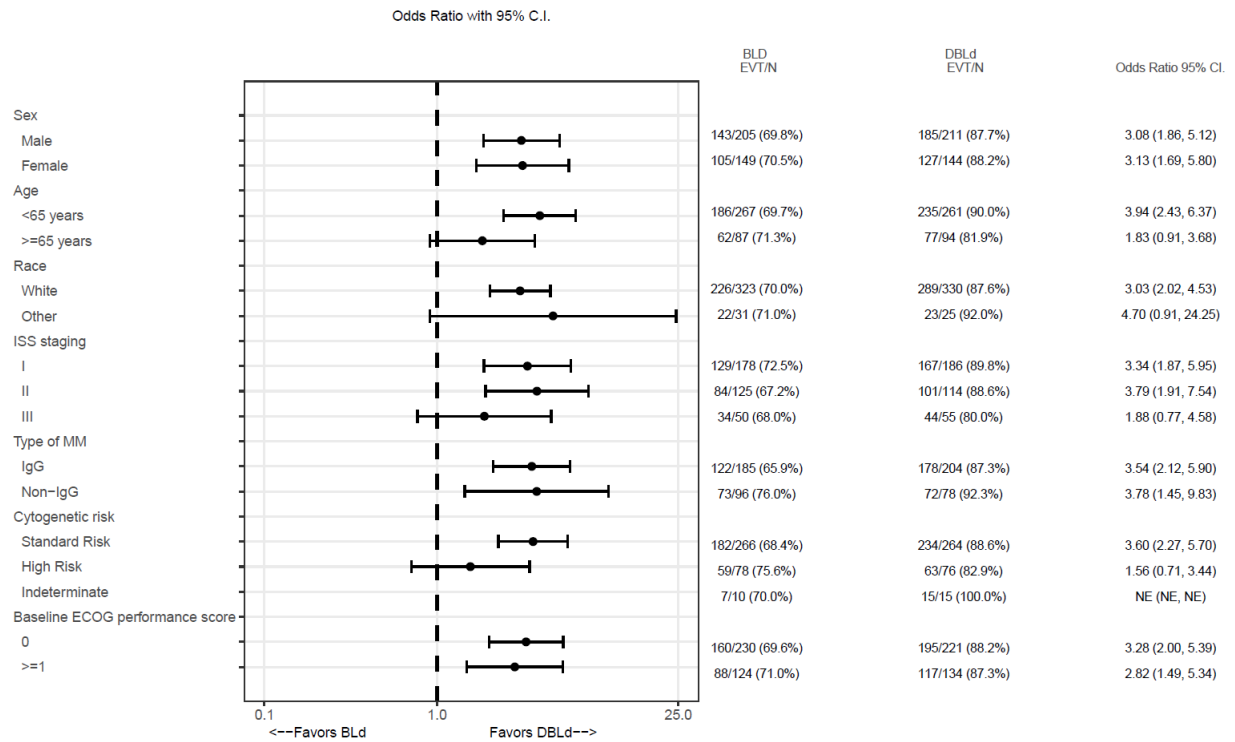
Based on Figure 15 of the CS¹

^a Cytogenetic risk is based on FISH.

^b Patient may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)].

BLd = bortezomib, lenalidomide, and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; HR = hazard ratio; IgG = immunoglobulin G; ISS = International Staging System; ITT = intention-to-treat; MM = multiple myeloma; NE = not evaluable; PFS = progression-free survival

Figure 3.10: Forest plot of subgroup analysis for $\geq$ CR; ITT analysis set (full treatment sequence)



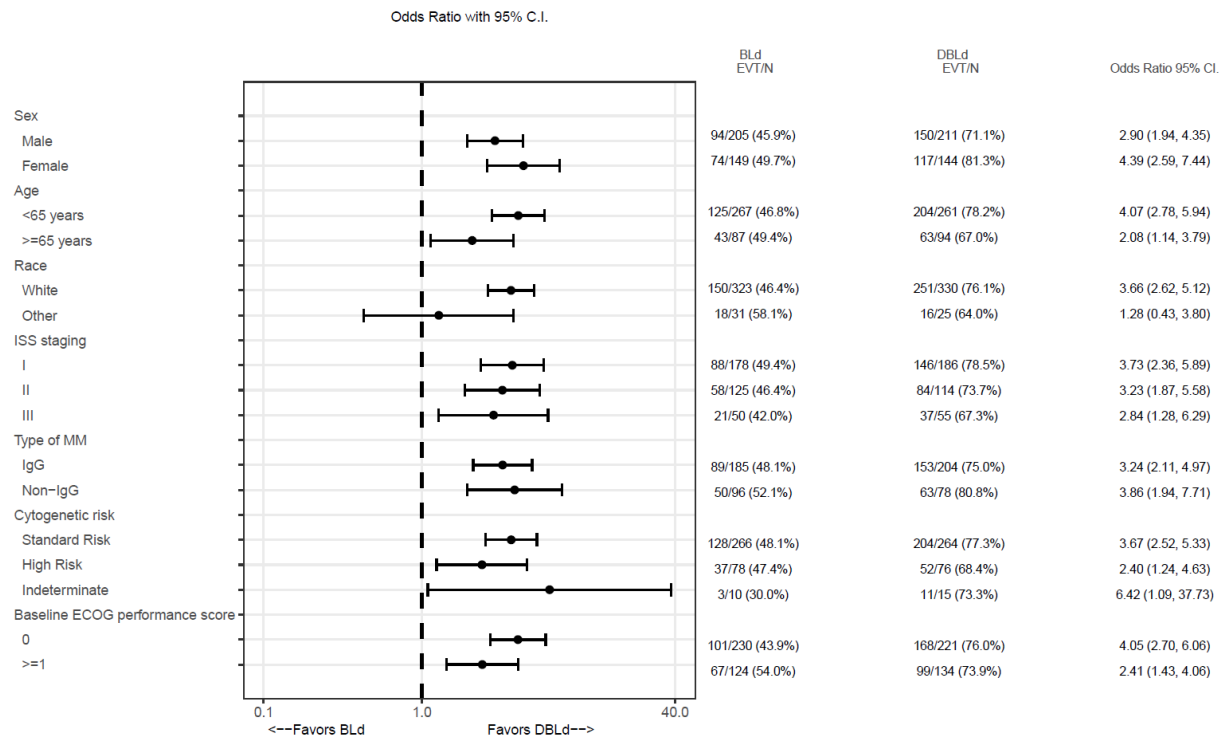
Based on Figure 16 of the CS¹

^a Cytogenetic risk is based on FISH.

^b Patient may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)]

BLd = bortezomib, lenalidomide, and dexamethasone; CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; HR = hazard ratio; IgG = immunoglobulin G; ISS = International Staging System; ITT = intention-to-treat; MM = multiple myeloma; NE = not evaluable; PFS = progression-free survival

Figure 3.11: Forest plot of overall MRD-negativity rate by NGS at or below 10^{-5} in patients with $\geq$ CR, ITT analysis set (full treatment sequence)

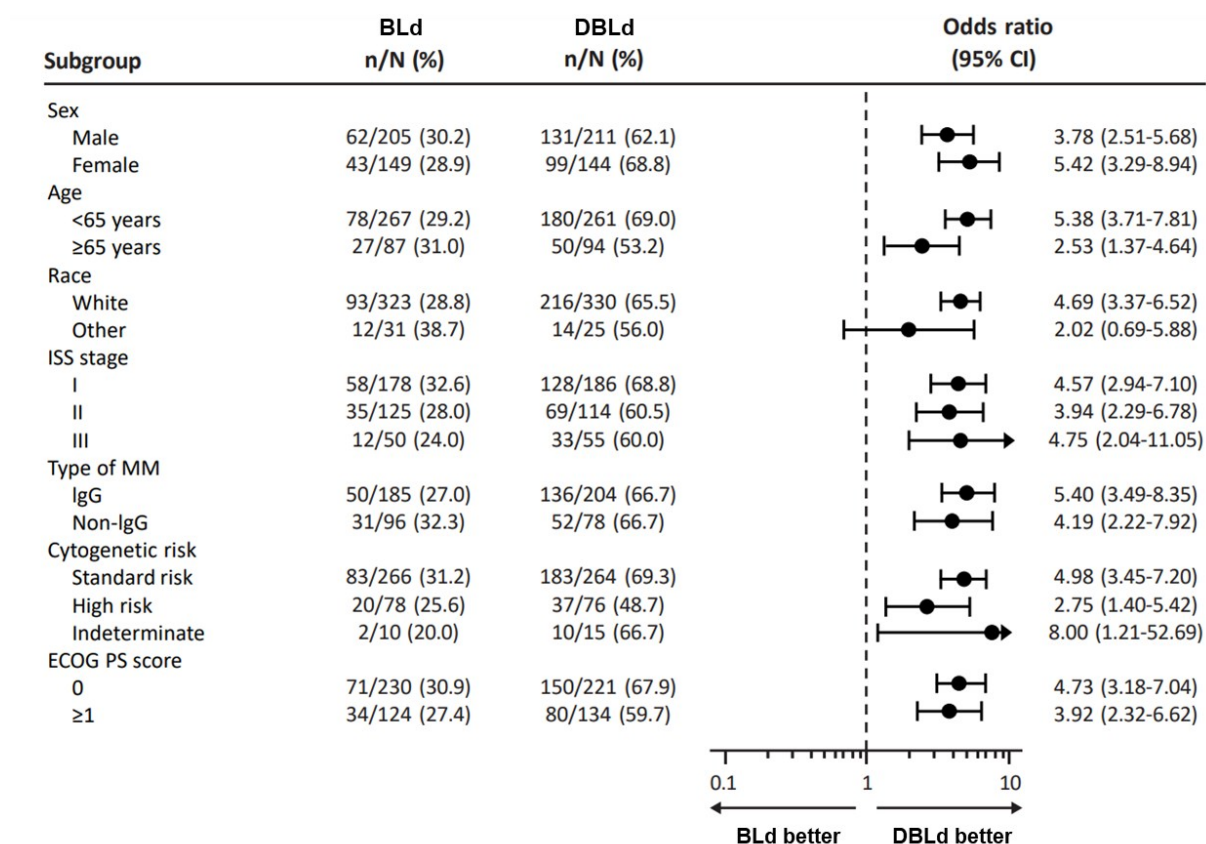


Based on Figure 17 of the CS¹

^a Cytogenetic risk is based on FISH.

^b Patient may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)].

BLd = bortezomib, lenalidomide, and dexamethasone; CI = confidence interval; CR = complete response; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; IgG = immunoglobulin G; ISS = International Staging System; ITT = intention-to-treat; MM = multiple myeloma; MRD = minimal residual disease; NGS = next generation sequencing

Figure 3.12: Forest plot of sustained MRD-negativity rate (at least 12 months apart) by NGS at or below 10^{-5} , ITT analysis set (full treatment sequence)

Based on Figure 18 of the CS¹

BLd = bortezomib, lenalidomide, and dexamethasone; CI = confidence interval; CR = complete response; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IgG = immunoglobulin G; ISS = International Staging System; ITT = intention-to-treat; MM = multiple myeloma; MRD = minimal residual disease; NGS = next generation sequencing

EAG comment: The treatment benefit of the daratumumab-based regimen (DBLd-DL) over the standard regimen (BLd-L) was generally consistent across pre-specified clinically relevant subgroups for the key efficacy endpoints of PFS, CR rate ($\geq$ CR), and MRD negativity. While some subgroups showed non-statistically significant results, this is likely attributable to a lack of statistical power due to small patient numbers rather than a true absence of treatment effect.

3.2.8 Safety results

3.2.8.1 PERSEUS trial

The safety data presented below are based on the results of the safety analysis set from the PERSEUS trial at the 1 August 2023 DCO. The safety analysis set included all patients who had received at least one dose of study treatment (partial or complete) in the trial.¹

3.2.8.1.1 Treatment duration and dosage

The company reported that “The median duration of study treatment was comparable between arms (██████ months for BLd arm and ██████ months for DBLd arm). Similarly, median dose intensity

for bortezomib, lenalidomide and dexamethasone was comparable between the BLd and DBLd treatment arms (████ mg/cycle versus █████ mg/cycle for bortezomib, █████ mg/cycle versus █████ mg/cycle for lenalidomide, and █████ mg/cycle versus █████ mg/cycle for dexamethasone, respectively)".¹ Further details can be found in Table 3.29 below.

Table 3.29: Summary of the treatment duration and dose intensity for the full treatment sequence; safety analysis set

	BLd arm ^a , N=347	DBLd arm ^b , N=351
Duration of study drug (months)^c		
Mean (SD)	████	████
Median	████	45.73
Range	████	0.49, 54.34
Daratumumab dose intensity (mg/cycle)		
Mean (SD)	-	████
Median	-	████
Range	-	████
Bortezomib dose intensity (mg/cycle)		
Mean (SD)	████	████
Median	████	████
Range	████	████
Lenalidomide dose intensity (mg/cycle)		
Mean (SD)	████	████
Median	████	████
Range	████	████
Dexamethasone dose intensity (mg/cycle)		
Mean (SD)	████	████
Median	████	████
Range	████	████
Based on Table 42 of the CS ¹		
^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy.		
^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy.		
^c Duration of induction/pre-ASCT/ASCT/consolidation treatment: (a) for subjects received consolidation after having received ASCT, from first induction dose date to the last consolidation dose date. (b) For subjects received ASCT after 6 cycles of induction, from first induction dose date to the day before maintenance treatment start date, or the date of end-of-treatment visit, whichever is earlier. Subjects who received both ASCT and consolidation or received ASCT after 6 cycles of induction were taken into account for this calculation.		
ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide, and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; I+C = induction and consolidation; L = lenalidomide; SD = standard deviation		

3.2.8.1.2 Summary of treatment-emergent adverse events (TEAEs)

The company reported that “The overall incidence of Grade 3 or 4 TEAEs was higher in the DBLd arm compared with the BLd arm during induction and consolidation however was similar across treatment arms during maintenance. The most common Grade 3 or 4 TEAEs occurring at a $\geq 10\%$ frequency in either treatment arm were neutropenia (DBLd arm: █████%; BLd arm: █████%) and thrombocytopenia

(DBLd arm: ■■■%; BLd arm: ■■■%) for the induction phase, thrombocytopenia (DBLd arm: ■■■%; BLd arm: ■■■%) and neutropenia (DBLd arm: ■■■%; BLd arm: ■■■%) for the consolidation phase, and neutropenia (DBLd arm: ■■■%; BLd arm: ■■■%) and thrombocytopenia (DBLd arm: ■■■%; BLd arm: ■■■%) for the maintenance phase.”¹ Further details can be found in Table 3.30 below.

Table 3.30: Summary of TEAEs for the full treatment sequence; safety analysis set

TEAEs, n (%)	BLd arm ^a , N=347	DBLd arm ^b , N=351
TEAE leading to discontinuation of study drug ^c	████	████
COVID-19	████	████
TEAE leading to discontinuation of daratumumab ^d	████	████
At least one related to daratumumab	████	████
TEAE leading to discontinuation of bortezomib ^d	████	████
At least one related to bortezomib	████	████
TEAE leading to discontinuation of lenalidomide ^d	████	████
At least one related to lenalidomide	████	████
TEAE leading to discontinuation of dexamethasone ^d	████	████
At least one related to dexamethasone	████	████
<i>Any TEAE</i>	████	████
Study drug-related ^e	████	████
<i>Maximum toxicity Grade</i>		
Grade 1	████	████
Grade 2	████	████
Grade 3	████	████
Grade 4	████	████
Grade 5	████	████
<i>Any serious TEAE</i>	████	████
Study drug-related ^e	████	████
<i>TEAE with outcome death</i>	████	████
Study drug-related ^e	████	████

TEAEs, n (%)	BLd arm ^a , N=347	DBLd arm ^b , N=351
Death due to COVID-19	████	████
<i>COVID-19 TEAEs</i>	████	████
COVID-19 serious TEAEs	████	████
Based on Table 43 of the CS¹ ^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy. ^c Includes those patients indicated as having discontinued treatment due to an AE on the end of treatment CRF page. ^d Includes those patients indicated as having discontinued specific study treatment due to an AE on the AE CRF page. ^e TEAEs related to at least 1 of the 4 study treatments: DBLd. AE = adverse event; BLd = bortezomib, lenalidomide, and dexamethasone; CRF = case report form; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; DL = daratumumab with lenalidomide; I+C = induction and consolidation; L = lenalidomide; TEAE = treatment-emergent adverse event		

3.2.8.1.3 Most common TEAEs

The company reported that “*The most common TEAEs, defined as occurring in 10% of patients or more in either treatment arm, in the safety analysis set for the induction phase were neutropenia (DBLd arm: █%; BLd arm: █%), peripheral sensory neuropathy (DBLd arm: █%; BLd arm: █%) and constipation (DBLd arm: █%; BLd arm: █%). For the consolidation phase, the most common TEAEs were thrombocytopenia (DBLd arm: █%; BLd arm: █%), neutropenia (DBLd arm: █%; BLd arm: █%) and peripheral sensory neuropathy (BLd arm: █%; DBLd arm: █%). For the maintenance phase, the most common TEAEs were diarrhea (DBLd arm: █%; BLd arm: █%), COVID-19 (DBLd arm: █%; BLd arm: █%) and neutropenia (DBLd arm: █%; BLd arm: █%).*

Despite peripheral sensory neuropathy being one of the most common TEAEs in the induction and consolidation phases, it is important to note that the incidence of such events remained relatively low in both arms throughout the trial at <█% in both the DBLd and BLd arms during the consolidation and maintenance phases. This is in sharp contrast to the proportions of patients who are anticipated to experience neurotoxicity events in clinical practice on currently available thalidomide containing regimens in this setting. The high neurotoxicological burden associated with thalidomide containing regimens was highlighted in a 2024 RCT in 123 patients in which 41.3% of patients experienced a neurotoxic event versus 11.7% in patients receiving a thalidomide sparing regimen (CLd). The need for thalidomide-free treatment options was highlighted in a 2025 UK Advisory Board, where UK clinical experts confirmed that the neurotoxicity associated with thalidomide is seen as a major issue across the medical community and there is therefore a desire to move to thalidomide sparing therapies which would prevent this.”

EAG comment: The EAG agree with the company that the incidence of TEAEs was comparable between treatment arms, with the exception of neutropenia, which occurred more frequently in the DBLd arm in the induction and maintenance phase.

Table 3.31: Summary of most common TEAEs of any Grade by treatment phase; safety analysis set

TEAEs, n (%)	BLd arma					DBLd armb				
	Induction ████	Pre-ASCT ████	ASCT ████	Consolidation ████	Maintenance ████	Induction ████	Pre-ASCT ████	ASCT ████	Consolidation ████	Maintenance ████
Infections and infestations	████ T	████	████ T	████	████	████ T	████ T	████ T	████	████
COVID-19	████	████	I	████	████	I	████	I	████	████
Upper respiratory tract infection	████	████	████ T	████	████	████ T	████	████	████	████
Blood and lymphatic system disorders	████ T	████	████ T	████	████	████ T	████	████ T	████	████
Neutropenia	████ T	████	████ T	████	████	████ T	████	████	████	████
Thrombocytopenia	████ T	████	████ T	████	████	████ T	████	████	████	████
Anaemia	████ T	████	████ T	████	████	████ T	████	████	████	████
Gastrointestinal disorders	████ T	████	████ T	████	████	████ T	████	████ T	████	████
Diarrhoea	████ T	████	████ T	████	████	████ T	████	████	████	████
Constipation	████ T	I	I	████	████	████ T	████	I	████	████
Nausea	████	████	████ T	████	████	████ T	████	████	████	████

TEAEs, n (%)	BLd arma					DBLd armb				
	Induction ████	Pre-ASCT ████	ASCT ████	Consolidation ████	Maintenance ████	Induction ████	Pre-ASCT ████	ASCT ████	Consolidation ████	Maintenance ████
General disorders and administration site conditions	████ █	████	████ █	████	████	████ █	████	████ █	████	████
Pyrexia	████ █	████	████ █	████	████	████ █	████	████ █	████	████
Asthenia	████ █	████	████ █	████	████	████ █	█	████	████	████
Fatigue	████ █	████	████ █	████	████	████ █	████	████	████	████
Oedema peripheral	████ █	████	████ █	████	████	████ █	████	████	████	████
Nervous system disorders	████ █	████ █	████ █	████	████	████ █	████ █	████ █	████	████
Peripheral sensory neuropathy	████ █	████	████ █	████	████	████ █	████	████ █	████	████
Musculoskeletal and connective tissue disorders	████ █	████	████ █	████	████	████ █	████	████	████	████
Back pain	████	████	████ █	████	████	████	████	█	████	████
Skin and subcutaneous tissue disorders	████ █	████	████ █	████	████	████ █	████	████	████	████
Rash	████ █	████	████ █	████	████	████ █	█	████	████	████

TEAEs, n (%)	BLd arma					DBLd armb				
	Induction ████	Pre-ASCT ████	ASCT ████	Consolidation ████	Maintenance ████	Induction ████	Pre-ASCT ████	ASCT ████	Consolidation ████	Maintenance ████
Respiratory, thoracic and mediastinal disorders	████ T	████	████ T	████	████	████ T	████	████	████	████
Cough	████	████	████ T	████	████	████	████	████ I	████	████
Psychiatric disorders	████ T	████	████ T	████	████	████ T	████	████	████	████
Insomnia	████ T	████ I	████ T	████	████	████ T	████	████	████	████
Based on Table 44 of the CS¹ ^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy. ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide, and dexamethasone; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; I+C = induction and consolidation; TEAE = treatment-emergent adverse event										

3.2.8.1.4 Grade 3–4 TEAEs

The company stated that “The overall incidence of Grade 3 or 4 TEAEs was higher in the DBLd arm compared with the BLd arm during induction and consolidation however was similar across treatment arms during maintenance. The most common Grade 3 or 4 TEAEs occurring at a $\geq 10\%$ frequency in either treatment arm were neutropenia (DBLd arm: █%; BLd arm: █%) and thrombocytopenia (DBLd arm: █%; BLd arm: █%) for the induction phase, thrombocytopenia (DBLd arm: █%; BLd arm: █%) and neutropenia (DBLd arm: █%; BLd arm: █%) for the consolidation phase, and neutropenia (DBLd arm: █%; BLd arm: █%) and thrombocytopenia (DBLd arm: █%; BLd arm: █%) for the maintenance phase.”¹ Further details can be found in Table 3.32 below.

Table 3.32: Summary of most common TEAEs of Grade 3 or 4 by treatment phase; safety analysis set

TEAEs, n (%)	BLd arm ^a					DBLd arm ^b				
	Induction N=	Pre-ASCT N=	ASCT N=	Consolidation N=	Maintenance N=	Induction N=	Pre-ASCT N=	ASCT N=	Consolidation N=	Maintenance N=
Blood and lymphatic system disorders										
Neutropenia										
Thrombocytopenia										
Febrile neutropenia										
Anaemia										
Infections and infestations										
Pneumonia										
Gastrointestinal disorders										
Diarrhoea										
Stomatitis										
Nervous system disorders										
General disorders and administration site conditions										

TEAEs, n (%)	BLd arm ^a					DBLd arm ^b				
	Induction n N=	Pre-ASCT N=	ASCT N=	Consolidation N=	Maintenance N=	Induction N=	Pre-ASCT N=	ASCT N=	Consolidation N=	Maintenance N=
Fatigue										
Investigations										
Alanine aminotransferase increased										
Respiratory, thoracic and mediastinal disorders										
Metabolism and nutrition disorders										
Skin and subcutaneous tissue disorders										
Vascular disorders										
Cardiac disorders										
Hepatobiliary disorders										
Psychiatric disorders										
Neoplasms benign, malignant and unspecified										

TEAEs, n (%)	BLd arm ^a					DBLd arm ^b				
	Induction n N=	Pre-ASCT N=	ASCT N=	Consolidation N=	Maintenance N=	Induction N=	Pre-ASCT N=	ASCT N=	Consolidation N=	Maintenance N=
Musculoskeletal and connective tissue disorders										
Based on Table 45 of the CS ¹ ^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy. ^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy. ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide, and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; I+C = induction and consolidation; L = lenalidomide; TEAE = treatment-emergent adverse event										

3.2.8.1.5 Adverse events of special interest (AESI)

The company stated that “There was a low incidence of sARRs reported in the DBLd arm (■ [■%] patients), and the majority were Grade 1 or 2 events. The most frequently reported ($\geq 2\%$ in all participants) sARRs were pyrexia in ■ (■%) patients and chills in ■ (■%) patients. Four Grade 3 or 4 sARRs were reported in ■ (■%) participants (respiratory failure, bronchospasm, tachycardia, and bronchitis) and all were reported as treatment-emergent serious adverse events (SAEs) that required hospitalisation.

Injection-site reactions were experienced by ■ (■%) patients in the DBLd arm. Of note, all injection-site reactions were Grade 1 or 2 and did not lead to dose modification or discontinuation of study treatment. The most frequently reported (≥ 2 patients) injection-site reactions in the DBLd arm were injection site erythema in ■ (■%) participants and injection site rash, erythema, and rash in ■ (■%) patients each.

The overall incidence of infections and infestations was slightly higher in the DBLd arm compared with the BLd arm (DBLd arm: 86.9%; BLd arm: 76.7%) and mainly occurred during induction (DBLd arm: ■%; BLd arm: ■%) and maintenance (DBLd arm: ■%; BLd arm: ■%). The most common infections ($\geq 10\%$ incidence in either treatment arm) were:

- COVID-19 (DBLd arm: ■%; BLd arm: ■%)
- Upper respiratory tract infection (DBLd arm: ■%; BLd arm: ■%)
- Bronchitis (DBLd arm: ■%; BLd arm: ■%)
- Pneumonia (DBLd arm: ■%; BLd arm: ■%)
- Nasopharyngitis (DBLd arm: ■%; BLd arm: ■%)

Any grade treatment-emergent cytopenia (comprising neutropenia, anemia, thrombocytopenia, and lymphopenia group terms) was reported in ■% of patients in the DBLd arm and ■% of participants in the BLd arm. Of note however, the overall incidence of cytopenia was higher in the DBLd arm compared with the BLd arm for the induction treatment phase (DBLd arm: ■% versus BLd arm: ■%), but was lower versus the BLd arm for consolidation and maintenance phases (consolidation: DBLd arm: ■% versus BLd arm: ■%; maintenance: DBLd arm: ■% versus BLd arm: ■%). Overall, these safety data support that DBLd-DL treatment was consistent with the known safety profiles of daratumumab, lenalidomide and BLd in isolation, with DBLd-DL treatment shown to be associated with clinically manageable side effects. Of particular note, no new safety signals were identified.”¹ Further details can be found in Table 3.33 below.

Table 3.33: Treatment-emergent cytopenia by preferred term for induction, pre-ASCT, ASCT, consolidation and maintenance treatment phases; safety analysis set

TEAEs, n (%)	BLd arm ^a					DBLd arm ^b				
	Induction N=████	Pre-ASCT N=████	ASCT N=████	Consoli- dation N=████	Main- tenance N=████	Induction N=████	Pre-ASCT N=████	ASCT N=████	Consoli- dation N=████	Main- tenance N=████
Total number of patients with treatment-emergent cytopenia	████	████	████	████	████	████	████	████	████	████
Neutropenia	████	████	████	████	████	████	████	████	████	████
Febrile neutropenia	████	████	████	████	████	████	████	████	████	████
Anaemia	████	████	████	████	████	████	████	████	████	████
Thrombocytopenia	████	████	████	████	████	████	████	████	████	████
Lymphopenia	████	████	████	████	████	████	████	████	████	████

Based on Table 46 of the CS¹^a Patients in the BLd treatment arm received BLd as I+C therapy, followed by L maintenance therapy.^b Patients in the DBLd treatment arm received DBLd as I+C therapy, followed by DL maintenance therapy.

ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide, and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; I+C = induction and consolidation; L = lenalidomide; TEAE = treatment-emergent adverse event

3.2.8.2 AURIGA trial

In Section 2.6.2, the company reported: “At the April 2024 DCO, 99.0% of patients in both arms experienced TEASs. Serious AEs were reported in 30.2% of DL patients and 22.4% of L patients. The proportion of patients with TEAEs leading to discontinuation of daratumumab was 8.3%.” Further details can be found in Table 3.34 and Table 3.35.

Table 3.34: Summary of TEAEs from the AURIGA trial; safety analysis set

TEAEs, n (%)	DL, N=96	L, N=98
<i>Any TEAE</i>	95 (99.0%)	97 (99.0%)
At least one related ^a	94 (97.9%)	92 (93.9%)
At least one related to daratumumab	88 (91.7%)	0
At least one related to lenalidomide	90 (93.8%)	92 (93.9%)
<i>Maximum toxicity Grade</i>		
Grade 1	4 (4.2%)	4 (4.1%)
Grade 2	19 (19.8%)	27 (27.6%)
Grade 3	58 (60.4%)	56 (57.1%)
Grade 4	12 (12.5%)	9 (9.2%)
Grade 5	2 (2.1%)	1 (1.0%)
<i>Any serious TEAE</i>	29 (30.2%)	22 (22.4%)
At least one related ^a	15 (15.6%)	5 (5.1%)
At least one related to daratumumab	9 (9.4%)	0
At least one related to lenalidomide	13 (13.5%)	5 (5.1%)
<i>TEAEs leading to discontinuation of treatment per disposition CRF</i>	12 (12.5%)	7 (7.1%)
<i>TEAEs leading to discontinuation of any treatment component</i>	14 (14.6%)	8 (8.2%)
At least one related ^a	12 (12.5%)	7 (7.1%)
At least one related to daratumumab	4 (4.2%)	0
At least one related to lenalidomide	12 (12.5%)	7 (7.1%)
<i>TEAEs leading to discontinuation of daratumumab</i>	8 (8.3%)	0
<i>TEAEs leading to discontinuation of lenalidomide</i>	14 (14.6%)	8 (8.2%)
<i>Death due to TEAEs</i>	2 (2.1%)	1 (1.0%)
At least one related ^a	1 (1.0%)	0
At least one related to daratumumab	1 (1.0%)	0
At least one related to lenalidomide	1 (1.0%)	0
Based on Table 26 of the CS ¹		
^a TEAEs related to at least 1 of the 2 components of study treatment: lenalidomide or daratumumab.		
^b Includes those who had AEs with action taken as drug withdrawn to at least one component of study treatment.		
^c Includes those subjects indicated as having discontinued treatment due to an AE at the end of treatment.		
AE = adverse event; CRF = case report form; CS = company submission; DL = daratumumab with lenalidomide; L = lenalidomide; TEAE = treatment-emergent adverse event		

Table 3.35: Summary of most common TEAEs of any Grade; safety analysis set

TEAEs, n (%)	DL, N=96	L, N=98
Infections and infestations	81 (84.4%)	69 (70.4%)
COVID-19	28 (29.2%)	29 (29.6%)
Upper respiratory tract infection	40 (41.7%)	26 (26.5%)
Blood and lymphatic system disorders	74 (77.1%)	69 (70.4%)
Neutropenia	62 (64.6%)	60 (61.2%)
Thrombocytopenia	23 (24.0%)	28 (28.6%)
Anaemia	22 (22.9%)	17 (17.3%)
Gastrointestinal disorders	83 (86.5%)	76 (77.6%)
Diarrhoea	59 (61.5%)	54 (55.1%)
Constipation	22 (22.9%)	26 (26.5%)
Nausea	26 (27.1%)	26 (26.5%)
General disorders and administration site conditions	77 (80.2%)	67 (68.4%)
Pyrexia	18 (18.8%)	16 (16.3%)
Asthenia	12 (12.5%)	14 (14.3%)
Fatigue	44 (45.8%)	46 (46.9%)
Oedema peripheral	12 (12.5%)	14 (14.3%)
Nervous system disorders	62 (64.6%)	55 (56.1%)
Peripheral sensory neuropathy	12 (12.5%)	13 (13.3%)
Musculoskeletal and connective tissue disorders	72 (75.0%)	68 (69.4%)
Back pain	31 (32.3%)	20 (20.4%)
Skin and subcutaneous tissue disorders	67 (69.8%)	55 (56.1%)
Rash	21 (21.9%)	17 (17.3%)
Respiratory, thoracic and mediastinal disorders	70 (72.9%)	60 (61.2%)
Cough	37 (38.5%)	36 (36.7%)
Psychiatric disorders	26 (27.1%)	18 (18.4%)
Insomnia	15 (15.6%)	8 (8.2%)
Based on Table 27 of the CS ¹ CS = company submission; DL = daratumumab with lenalidomide; L = lenalidomide; TEAE = treatment-emergent adverse event		

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

The company conducted an ITC to estimate the relative efficacy between DBLd-DL and DBTd-L for the treatment of patients with HDT-ASCT eligible NDMM. The company stated that, given that DBTd-L was the only induction-consolidation-maintenance treatment sequence that was used substantially in

UK clinical practice for the treatment of patients with HDT-ASCT eligible NDMM, DBTd-L was the only relevant comparator to DBLd-DL in this evidence submission.¹

The company made the following statement:¹

- “A clinical SLR was conducted in May 2018 and subsequently updated in April 2023 and February 2025 to identify studies of relevant induction-consolidation comparator therapies for patients with HDT-ASCT eligible NDMM. Additionally, a clinical SLR was conducted in September 2023 and updated in February 2025 to identify studies of relevant induction, consolidation and maintenance therapies in patients with HDT-ASCT eligible NDMM.
- The reviews did not identify any clinical studies directly comparing the efficacy of DBLd induction and consolidation therapy with DBTd induction and consolidation therapy, nor DBLd followed by DL maintenance versus DBTd followed by L maintenance. Similarly, no studies assessing either of these treatments with a common comparator were identified, thus excluding the feasibility of conducting a network meta-analysis (NMA).
- The SLRs identified one RCT investigating DBTd as an induction and consolidation therapy: the CASSIOPEIA trial was a two-part RCT in patients with HDT-ASCT eligible NDMM. The first phase of the trial evaluated the efficacy and safety of DBTd compared with BTd as induction and consolidation treatments. In the second phase, patients were re-randomised 1:1 to receive daratumumab maintenance therapy or observation. As such, the CASSIOPEIA trial does not provide comparative data for the full treatment sequence of relevance to the relevant comparator in this submission – i.e. DBTd-L. Therefore, it was not possible to perform an ITC comparing the full treatment sequences of DBLd-DL versus DBTd-L with the available evidence. However, an ITC comparing the efficacy of DBLd and DBTd as induction and consolidation treatments was possible with the available data, and performed using clinical evidence from PERSEUS and CASSIOPEIA, respectively. Given that PERSEUS and CASSIOPEIA have the same sponsor, and therefore access to IPD, in line with NICE DSU TSD 17, population adjustment-based methods were explored to conduct an ITC.”⁸

The ITC was conducted to estimate relative efficacy for five outcomes ($\geq$ VGPR, overall response rate [ORR], MRD-negativity, OS and PFS) between DBTd and DBLd as I+C treatments.¹

The company conducted a feasibility assessment to assess the suitability of comparing PERSEUS and CASSIOPEIA in an ITC, i.e. whether the included studies were sufficiently homogenous across their populations and outcomes. A range of domains including study design, risk of bias, treatment characteristics, patient inclusion/exclusion criteria, baseline characteristics and outcomes were assessed.¹

Table 3.36 presents key study design features between the PERSEUS and CASSIOPEIA trials. The PERSEUS trial was an ongoing, randomised, multicentre, open-label Phase III trial which assessed the clinical efficacy and safety of DBLd I+C followed by DL maintenance compared with BLd followed by L maintenance in patients with HDT-ASCT eligible NDMM.¹

The CASSIOPEIA trial was a randomised, multicentre, open-label Phase III trial which assessed the comparative efficacy of DBTd versus bortezomib with thalidomide and dexamethasone (BTd) in patients with HDT-ASCT eligible NDMM. There was a total of 886 patients across 111 European centers who were randomised in a 1:1 ratio (stratified by ISS stage and cytogenetic risk) to receive DBTd or BTd as I+C therapy (induction/consolidation phase). In the CASSIOPEIA trial, patients who achieved a $\geq$ PR at Day 100 post-transplant underwent a second randomisation (1:1) to either

observation or maintenance therapy with daratumumab every 8 weeks until disease progression or for a maximum of 2 years (maintenance phase).¹

Table 3.36: Comparison of key study design features between the PERSEUS and CASSIOPEIA trials

Study of interest	Study design	Trial phase	Blinding	Number of patients	Country (institutions)
PERSEUS	RCT	III	Open-label	DBLd: 355 BLd: 354	Global (multicentre)
CASSIOPEIA	RCT	III	Open-label	DBTd: 543 BTd: 542	Europe (multicentre)

Based on Table 20 of Appendix of the CS¹
 BLd = bortezomib, lenalidomide and dexamethasone; BTd = bortezomib, thalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; RCT = randomised controlled trial

Table 3.37 below presents a comparison of key patient characteristics between the PERSEUS and CASSIOPEIA trials. The company assessed the comparability of patient characteristics between PERSEUS and CASSIOPEIA based on key variables including age, sex, region, race, ECOG PS, ISS stage, cytogenetic risk, creatine clearance and MM type. The baseline characteristics appeared to be well balanced between PERSEUS and CASSIOPEIA trials, except for two baseline characteristics (ECOG PS and ISS stage). The patients in the PERSEUS trial had a lower ECOG PS and ISS stage, which suggested higher levels of patient functioning and a less advanced disease stage, when compared with those patients in the CASSIOPEIA trial. It should be noted that the two baseline variables of ECOG PS and ISS stage were adjusted for in the ITC analyses.¹

Table 3.37: Comparison of key patient characteristics between the PERSEUS and CASSIOPEIA trials

Characteristics	PERSEUS		CASSIOPEIA	
	DBLd (N=355)	BLd (N=354)	DBLd (N=543)	BLd (N=542)
Age, years				
Median (range)	61.0	59.0	59.0 (22–65)	58.0 (26–65)
<65 (%)	73.5	75.4	NR	NR
≥65 (%)	26.5	24.6	0	0
Sex, %				
Male	59.4	57.9	58.2	58.9
Race, %				
White	93.0	91.2	NR	NR
Asian	1.1	1.7	NR	NR
Black/African American	1.4	1.1	NR	NR
Other	1.1	0.8	NR	NR
Unknown/NR	3.4	5.1	NR	NR

Characteristics	PERSEUS		CASSIOPEIA	
	DBLd (N=355)	BLd (N=354)	DBLd (N=543)	BLd (N=542)
ECOG PS, %				
0	62.3	65.0	49.0	47.0
1	32.1	30.5	41.0	42.0
2	5.4	4.5	10.0	10.0
Cytogenic risk, %				
Standard	74.4	75.1	85.0	84.0
High-risk	21.4	22.0	15.0	16.0
ISS stage, %				
I	52.4	50.4	38.0	42.0
II	32.1	35.4	47.0	43.0
III	15.5	14.2	15.0	15.0
Myeloma type				
IgG	■	■	61.0	58.0
IgA	■	■	15.0	18.0
IgM	■	■	NR	NR
IgD			NR	NR
IgE			NR	NR
Light chain	■	■	9.0	7.0
Based on Table 22 of Appendix of the CS ¹ BLd = bortezomib, lenalidomide and dexamethasone; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Ig = immunoglobulin; ISS = International Staging System; NR = not reported				

3.3.1 Data sources

The data for DBLd and DBTd as I+C therapies in the ITC were derived from the PERSEUS and CASSIOPEIA trials. The primary outcome for the I+C phase of the trial was the proportion of patients who achieved a stringent complete response (sCR) after consolidation. The key secondary efficacy endpoints included OS and PFS from first randomisation, the proportion of patients who were MRD-negative after consolidation, and the proportion of patients who achieved $\geq$ CR. For the maintenance phase of the trial, the primary endpoint was PFS, while key secondary outcomes included time to progression, OS, and the proportion of patients who achieved $\geq$ CR or MRD-negativity. The unpublished data of clinical DCO (May 2019) with a median follow-up of ■ months from the CASSIOPEIA trial were used to inform the ITC analyses.¹

Table 3.38 presents a summary of trial design and methodology for the CASSIOPEIA trial.

Table 3.38: CASSIOPEIA trial design and methodology

Trial name	CASSIOPEIA (NCT02541383)
Location	Patients were treated across 111 European sites including: France (70 sites), Belgium (13 sites) and the Netherlands (28 sites)

Trial design	Randomised, open-label, active-controlled, parallel-group, multicentre, Phase III trial to investigate the efficacy and safety of DBTd as an I+C therapy, and daratumumab as maintenance, in patients with previously untreated MM eligible for ASCT. The 'treatment phase' was conducted in two parts: Part 1: Induction/ASCT/consolidation phase (1:1 randomisation) The consolidation phase of treatment began approximately 30 days after ASCT Part 2: Maintenance phase (1:1 re-randomisation of patients achieving at least a PR after consolidation) Patients who had not achieved a response enter the follow-up phase, and are followed until disease progression or death, even if they received subsequent treatment
Intervention (Part 1)	DBTd as an I+C therapy (N=543 randomised)
Comparator (Part 1)	BTd as an I+C therapy (N=542 randomised)
Intervention (Part 2)	Following re-randomisation: Daratumumab as maintenance therapy (N=442) of which (N=229 had received DBTd I+C therapy and N=213 had received BTd I+C therapy)
Comparator (Part 2)	Following re-randomisation: Observation as maintenance therapy (N=444) of which (N=229 had received DBTd I+C therapy and N=215 had received BTd I+C therapy)
Key inclusion/exclusion criteria	Inclusion criteria: Diagnosis of previously untreated MM Have a confirmed diagnosis and eligible for high-dose chemotherapy and ASCT, and an ECOG PS 0–2 Exclusion criteria: Previous treatment for MM Primary amyloidosis, plasma cell leukaemia or smouldering MM Prior or concurrent exposure to systemic therapy or ASCT for any plasma cell dyscrasia, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment, or received an investigational drug or used an invasive investigational medical device within 4 weeks before Cycle 1, Day 1 Full inclusion and exclusion criteria can be found in Section 4 of the protocol (Moreau et al 2024. Supplementary Material) included within the reference pack.⁹
Method of study drug administration	Four 28-day cycles of induction therapy followed by two 28-day cycles of consolidation therapy in the following dosing: IV daratumumab: Induction: 16 mg/kg once weekly in Cycles 1 and 2; once every 2 weeks for Cycles 3 and 4 Consolidation: once every 2 weeks for Cycles 5 and 6 Subcutaneous bortezomib: Induction: 1.3 mg/m² twice weekly (with an option to change to once weekly in the event of toxicity) on Days 1, 4, 8, and 11 for Cycles 1–4

	Consolidation: 1.3 mg/m² twice weekly (with an option to change to once weekly in the event of toxicity) on Days 1, 4, 8, and 11 for Cycles 5 and 6 Oral thalidomide: Induction: 100 mg per day for Cycles 1–4 Consolidation: 100 mg per day for Cycles 5 and 6 Oral or IV dexamethasone: Induction: 40 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 of Cycles 1 and 2; 40 mg on Days 1 and 2, and 20 mg on subsequent dosing days (Days 8, 9, 15, 16) of Cycles 3 and 4 Consolidation: 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5 and 6 The following dosing was used in the maintenance phase: IV daratumumab: 16 mg/kg once every 8 weeks until documented disease progression (limited to a maximum of 2 years)
Primary outcomes	Part 1: Post-consolidation sCR rate; assessed by computer algorithm and defined as the percentage of patients achieving CR in addition to having a normal serum FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence or 2- to 4-colour flow cytometry. Post-consolidation response was assessed at Day 100 post-ASCT. Part 2: PFS from second randomisation: time from randomisation to either confirmed PD or death, whichever comes first
Key secondary endpoints^b	Part 1: PFS: time from the initial randomisation to either confirmed PD or death, whichever comes first Time to progression: time from the initial randomisation to confirmed PD, or death due to PD, whichever occurs first ≥CR rate (post-ASCT/consolidation): proportion of patients who achieved CR or better by the end of consolidation assessed by computer algorithm MRD-negativity rate (post-ASCT/consolidation): proportion of patients who achieved MRD-negative status by the end of consolidation assessed by computer algorithm sCR rate (post-induction): proportion of patients who achieved sCR prior to high-dose therapy/ASCT assessed by computer algorithm PFS2: time from initial randomisation to time of subsequent progression on next-line of therapy after disease progression on study treatment OS: measured from the date of initial randomisation to the date of patient's death. If the patient is alive or vital status is unknown, then the patient's data was censored at the date the patient was last known to be alive Part 2: Time to progression (from second randomisation): time from second randomisation to confirmed PD, or death due to PD, whichever occurs first ≥CR rate: proportion of patients who have achieved a CR or better during the trial MRD-negativity rate: proportion of patients who have achieved MRD-negative status by the end of the trial

	PFS2 (from second randomisation): time from the second randomisation to time of subsequent progression on next line of therapy after disease progression on study treatment OS (from second randomisation): time from the second randomisation to the date of death
Pre-planned subgroups	Sex (male, female) Age (<50 years, ≥50 years) Site (IFM, Hovon) ISS staging (I, II, III) Cytogenetic risk (high risk, standard risk) Baseline renal function (CrCl) (>90 mL/min, ≤90 mL/min) Baseline hepatic function (normal, impaired) Type of MM (IgG, non-IgG) ECOG PS (0, ≥1)
Duration of study and follow-up	The latest clinical DCO was September 2023, with a median follow-up time of 80.1 months (IQR 75.7–85.6 months). However, the clinical DCO informing the ITC was May 2019, with a median follow-up time of [REDACTED] months.
Based on Table 30 of the CS¹ ^a If a patient's study treatment was discontinued before the end of the treatment regimen, the patient moved into the follow-up phase. ^b Response outcomes assessed in accordance with the IMWG criteria. ASCT = autologous stem cell transplantation; BTd = bortezomib, thalidomide and dexamethasone; CR = complete response; CS = company submission; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DCO = data cut-off; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FLC = free light chains; I+C = induction and consolidation; Ig = immunoglobulin; IMWG = International Myeloma Working Group; IQR = interquartile range; ISS = International Staging System; ITC = indirect treatment comparison; IV = intravenous; MM = multiple myeloma; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; sCR = stringent complete response; VGPR = very good partial response	

EAG comment: The company seem to have correctly identified that an ITC using any method is not feasible for comparison of the full treatment sequence i.e. induction, consolidation, and maintenance. They have therefore sought studies to conduct an ITC only for I+C i.e. excluding maintenance and thus treating DBLd and DBTd as I+C. Therefore, the EAG need to point out that any ITC for this comparison will not provide an estimate of the comparison between the full sequences i.e. DBLd followed by DL versus DBTd followed by L. There are further methodological problems with excluding maintenance in that the PERSEUS and CASSIOPEIA trials have different maintenance treatments, and the latter re-randomises at the start of the maintenance period. The company address this by censoring at the initiation of maintenance treatment, which appears to be appropriate. However, the validity of this approach needs to be considered as part of the key issues regarding lack of comparison of the full treatment sequence.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company conducted an ITC by using individual patient data (IPD) based on the PERSEUS and CASSIOPEIA trials. The ITC analysis used inverse probability treatment weighting (IPTW) as the base-case approach. The company further used alternative adjustment methods (multivariate regression and double robust method) as sensitivity analyses.¹

In terms of weighting approaches by using IPTW, the company made the following statement:¹ “There are multiple weighting approaches available using IPTW; average treatment effect for the control (ATC), average treatment effect (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. 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 data⁸ Considering the above, and that it is unclear whether one of the PERSEUS or CASSIOPEIA trials is more generalisable to UK clinical practice, employing the ATE approach (over other approaches such as ATC or ATT) is the most appropriate approach.”

3.4.1 Identification of covariates

The company identified baseline covariates of interest based on a literature review. With an aim to further explore potential treatment effect modifier (TEM)/prognostic factor (PF), the company also performed a review of stratification factors in the PERSEUS trial (ISS and cytogenetic risk).¹⁰ Additionally, the results of pre-specified subgroup analyses being conducted in PERSEUS and CASSIOPEIA were assessed for evidence that suggests that a baseline characteristic could be a potential TEM. A total of 14 covariates were identified, of which seven covariates were deemed to be priority PFs/TEMs (see Table 3.39 below). The company further stated that the full list of covariates and those selected as priority PFs/TEMs for the ITC were validated by UK clinical experts during an advisory board in May 2025.¹

It should be noted that the seven priority PFs and TEMs were adjusted for in the base-case ITC analyses, and all PFs and TEMs were adjusted for in sensitivity analyses.¹

Table 3.39: Identification of TEMs and PFs for the ITC:

Variable	Base-case (priority covariates adjusted)	Sensitivity analysis (all covariates adjusted)
Age (≥ 50 versus < 50 years)	✓	✓
Sex	✓	✓
ECOG PS	✓	✓
ISS stage	✓	✓
Baseline cytogenetic risk (high risk [defined as presence of del(17p) or t(4;14)] versus standard risk)	✓	✓
Type of MM (IgG versus non-IgG)	✓	✓
Haemoglobin levels (< 10 versus ≥ 10 g/dL)	✓	✓
LDH (≥ 280 versus < 280 U/l)		✓
Creatine clearance category (< 90 versus ≥ 90 mL/min)		✓
MM diagnostic criteria satisfied: ≥ 1 CRAB feature versus SLiM-only		✓
Presence versus absence of extramedullary plasmacytomas		✓

Variable	Base-case (priority covariates adjusted)	Sensitivity analysis (all covariates adjusted)
Serum calcium (corrected; ≥ 2.75 versus < 2.75 mmol/l)		✓
Bone lesions (≥ 1 versus none)		✓
Platelet levels (< 150 versus $\geq 150 \times 10^9/l$)		✓
Based on Table 31 of the CS ¹ CRAB = calcium elevation, renal insufficiency, anaemia, and bone lesions; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FLC = free light chain; Ig = immunoglobulin; ISS = International Staging System; ITC = indirect treatment comparison; LDH = lactate dehydrogenase; MM = multiple myeloma; MRI = magnetic resonance imaging; PF = prognostic factor; SLiM = $\geq 60\%$ clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of 100 or more with the involved serum FLC being ≥ 100 mg/l, and MRI with more than one focal marrow lesion; TEM = treatment effect modifiers		

3.4.2 Baseline characteristics before and after IPTW

The company assessed the degree of overlap between populations relating to the covariates identified for adjustment before and after IPTW. Standardised mean differences (SMDs) were used to assess the differences for each covariate included in the analysis.¹

Table 3.40 shows baseline characteristics before and after matching for the base-case ITC where the priority covariates were adjusted for. In the base-case ITC, the majority of priority covariates between the DBTd population and the DBLd population were well balanced after matching. However, it should be noted that three priority covariates (presence of extramedullary plasmacytomas, lactate dehydrogenase [LDH] and bone lesions) had SMDs above the threshold of 0.2, which indicates that the distribution of these three covariates were not well balanced after matching.¹

Table 3.41 shows baseline characteristics before and after matching for sensitivity analyses where all covariates were adjusted for. In the sensitivity analyses of ITC, the distribution of all these covariates between the DBTd population and the DBLd population were well balanced after matching.¹

Table 3.40: Baseline characteristics before and after matching: base-case model

Variable	Unweighted			Weighted		
	DBTd	DBLd	SMD	DBTd	DBLd	SMD
n ESS	████	████	████	████	████	████
Age: ≥ 50 years (%)	████	████	████	████	████	████
Sex: Male (%)	████	████	████	████	████	████
ECOG PS (%)						
0	████	████	████	████	████	████
1	████	████	████	████	████	████
2	████	████	████	████	████	████
ISS (%)						
I	████	████	████	████	████	████
II	████	████	████	████	████	████
III	████	████	████	████	████	████
Baseline cytogenetic profile: Standard risk (%)	████	████	████	████	████	████

Variable	Unweighted			Weighted		
	DBTd	DBLd	SMD	DBTd	DBLd	SMD
Type of MM at diagnosis: IgG (%)						
Haemoglobin levels: LT10 (%)						
LDH: ≥ 280 (%)						
Creatine clearance category: LT90 ml/min (%)						
CRAB versus SLiM: any CRAB (%)						
Presence of extramedullary plasmacytomas: 0 (%)						
Calcium corrected: normal (%)						
Bone lesions: 1 (%)						
Platelet levels: LT150 (%)						
Based on Table 34 of the CS ¹ CRAB = calcium elevation, renal insufficiency, anaemia, and bone lesions; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS = effective sample size; FLC = free light chain; IgG = immunoglobulin G; ISS = International Staging System; LDH = lactate dehydrogenase; LT = liver transplant; MM = multiple myeloma; MRI = magnetic resonance imaging; SLiM = $\geq 60\%$ clonal plasma cells in the bone marrow, involved/uninvolved FLC ratio of 100 or more with the involved serum FLC being ≥ 100 mg/l, and MRI with more than one focal marrow lesion; SMD = standardised mean difference						

Table 3.41: Baseline characteristics before and after matching: sensitivity analysis (all covariates adjusted)

Variable	Unweighted			Weighted		
	DBTd	DBLd	SMD	DBTd	DBLd	SMD
n ESS						
Age: ≥ 50 years (%)						
Sex: Male (%)						
ECOG PS (%)						
0						
1						
2						
ISS (%)						
I						
II						
III						
Baseline cytogenetic profile: Standard risk (%)						
Type of MM at diagnosis: IgG (%)						
Haemoglobin levels: LT10 (%)						
LDH: ≥ 280 (%)						

Variable	Unweighted			Weighted		
	DBTd	DBLd	SMD	DBTd	DBLd	SMD
Creatine clearance category: LT90 ml/min (%)						
CRAB versus SLiM: any CRAB (%)						
Presence of extramedullary plasmacytomas: 0 (%)						
Calcium corrected: normal (%)						
Bone lesions: 1 (%)						
Platelet levels: LT150 (%)						
Based on Table 35 of the CS ¹ CRAB = calcium elevation, renal insufficiency, anaemia, and bone lesions; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS = effective sample size; FLC = free light chain; IgG = immunoglobulin G; ISS = International Staging System; LDH = lactate dehydrogenase; LT = liver transplant; MM = multiple myeloma; MRI = magnetic resonance imaging; SLiM = $\geq 60\%$ clonal plasma cells in the bone marrow, involved/uninvolved FLC ratio of 100 or more with the involved serum FLC being ≥ 100 mg/l, and MRI with more than one focal marrow lesion; SMD = standardised mean difference						

3.4.3 ITC results: base-case and sensitivity analysis (all covariates adjusted)

3.4.3.1 I+C treatment outcomes

The results of $\geq$ VGPR for both the unadjusted and adjusted base-case and sensitivity analysis (all covariates adjusted) for DBTd versus DBLd from induction to the end of consolidation are presented in Table 3.42 below. For the adjusted base-case model, the OR was [REDACTED] and favoured [REDACTED] compared with [REDACTED] (adjusted base-case OR [REDACTED]; 95% CI: [REDACTED]; p [REDACTED]).¹

Similar results were obtained in the sensitivity analyses where all covariates were adjusted. It should be noted that the sensitivity analysis where all covariates were adjusted for resulted in [REDACTED] than the one from the base-case model.¹

Table 3.42: $\geq$ VGPR results of the ITC (I+C)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	OR (95% CI)	p-value
Unadjusted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Base-case	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sensitivity analysis (all covariates adjusted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 36 of the CS ¹ An OR >1 favours DBLd, and an OR <1 favours DBTd. * Statistically significant p-value. CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide, and dexamethasone; I+C = induction and consolidation; ITC = indirect treatment comparison; IPTW = inverse probability treatment weighting; OR = odds ratio; VGPR = very good partial response				

The results of ORR for the unadjusted and adjusted base-case, and sensitivity analysis (where all covariates were adjusted) for DBTd versus DBLd are presented in Table 3.43. The ORR event rates were [REDACTED] in both the DBLd and DBTd arms, and the OR for ORR favoured [REDACTED] compared with [REDACTED] in the base-case and sensitivity analysis (all covariates adjusted), but the results were [REDACTED] for the base-case model.¹

[REDACTED] the odds of achieving an overall response were [REDACTED] (OR [REDACTED]; 95% CI: [REDACTED]; p [REDACTED]).¹

Table 3.43: ORR results of the ITC (I+C)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	OR (95% CI)	p-value
Unadjusted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Base-case	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sensitivity analysis (all covariates adjusted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 37 of the CS ¹ An OR >1 favours DBLd, and an OR <1 favours DBTd. * Statistically significant p-value. CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide, and dexamethasone; I+C = induction and consolidation; ITC = indirect treatment comparison; IPTW = inverse probability treatment weighting; OR = odds ratio; ORR = overall response rate				

The results of MRD-negativity (regardless of CR status) for the unadjusted and adjusted base-case, and sensitivity analysis (all covariates adjusted), for DBTd versus DBLd are presented in Table 3.44 below. There were [REDACTED] in the MRD-negativity (regardless of CR status) rate between DBLd and DBTd in the base-case model and sensitivity analysis where all covariates were adjusted for.¹

Table 3.44: MRD-negativity results of the ITC (I+C)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	OR (95% CI)	p-value
Unadjusted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Base-case	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sensitivity analysis (all covariates adjusted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 38 of the CS ¹ An OR >1 favours DBLd, and an OR <1 favours DBTd. * Statistically significant p-value. CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide, and dexamethasone; I+C = induction and consolidation; ITC = indirect treatment comparison; IPTW = inverse probability treatment weighting; MRD = minimal residual disease; OR = odds ratio				

The results of PFS for the unadjusted and adjusted base-case, and sensitivity analysis (all covariates adjusted) for DBTd versus DBLd are presented in Table 3.45 below. It should be noted that the median follow-up for time-to-event data for DBLd ([REDACTED] months) was limited by the length of I+C treatment because the patient outcomes required censoring at the initiation of maintenance treatment. Therefore, this limitation was not resolved regardless of the availability of data from a longer follow-up.¹

Based on the adjusted models, there was a [REDACTED] difference in PFS between DBTd and DBLd (HR [REDACTED]; 95% CI: [REDACTED]–[REDACTED]; p [REDACTED]). Similar results were also found in the sensitivity analysis where all covariates were adjusted for.¹

Table 3.45: PFS results of the ITC (I+C)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	HR (95% CI)	p-value
Unadjusted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Base-case	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sensitivity analysis (all covariates adjusted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 39 of the CS ¹ An HR <1 favours DBLd, and an HR >1 favours DBTd. * Statistically significant p-value. CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; I+C = induction and consolidation; ITC = indirect treatment comparison; IPTW = inverse probability treatment weighting; PFS = progression-free survival				

The results of OS for the unadjusted model and adjusted base-case, and sensitivity analysis (all covariates adjusted) for DBTd versus DBLd are presented in Table 3.46 below. The company reported: “While the OS HR was greater than [REDACTED], suggesting [REDACTED] in favour of DBTd (HR [REDACTED]; 95% CI: [REDACTED]), this result was [REDACTED] (p [REDACTED]). It is also important to note that, as these ITCs are based on the induction and consolidation phase of treatment only, a very small proportion of patients died in either treatment arm ([REDACTED]% and [REDACTED]% of patients, during the induction and consolidation phase with DBTd and DBLd, respectively), these results must therefore be interpreted with extreme caution. As noted above, the limited median follow-up for time-to-event data for DBLd ([REDACTED] months), which was restricted by the length of induction and consolidation treatment, should be considered when interpreting results from the OS ITC. This [REDACTED] in the adjusted base case and sensitivity analysis (all covariates adjusted), but were [REDACTED] any of the analyses.”¹

Table 3.46: OS results of the ITC (I+C)

Model	DBTd	DBLd	Adjusted ITC (IPTW)	
	% of events	% of events	HR (95% CI)	p-value
Unadjusted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Base-case	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sensitivity analysis (all covariates adjusted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 40 of the CS ¹ An HR <1 favours DBLd, and an HR >1 favours DBTd. * Statistically significant p-value. CI = confidence interval; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; I+C = induction and consolidation; ITC = indirect treatment comparison; IPTW = inverse probability treatment weighting; OS = overall survival				

3.4.4 Results of sensitivity analyses for induction and consolidation treatment outcomes

The company further conducted the double robust and multivariate regression as sensitivity analyses for the I+C treatment outcomes.

The results for sensitivity analyses for $\geq$ VGPR, ORR, MRD-negativity, PFS and OS are presented in Table 3.47 below. For the I+C treatment set of ITCs, the sensitivity analyses results were consistent with those results of IPTW.

Table 3.47: Results of ITC scenario analyses (I+C)

Model	DBTd	DBLd	Adjusted ITC					
	% of events	% of events	IPTW		Double robust		Multivariate regression	
			OR/HR ^a (95% CI)	p-value)	OR/HR ^a (95% CI)	p-value	OR/HR ^a (95% CI)	p-value
≥VGPR								
Unadjusted								
Priority variables adjusted								
All variables adjusted								
ORR								
Unadjusted								
Priority variables adjusted								
All variables adjusted								
MRD-negativity (regardless of CR status)								
Unadjusted								
Priority variables adjusted								
All variables adjusted								
PFS								
Unadjusted								
Priority variables adjusted								
All variables adjusted								
OS								
Unadjusted								
Priority variables adjusted								
All variables adjusted								
Based on Table 41 of the CS ¹ * Statistically significant p-value; ^a ORs and HRs are presented for response and survival outcomes, respectively; An OR >1 favours DBLd, and an OR <1 favours DBTd. An HR <1 favours DBLd, and an HR >1 favours DBTd. CI = confidence interval; CR = complete response; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; I+C = induction and consolidation; ITC = indirect treatment comparison; IPTW = inverse probability treatment weighting; MRD = minimal residual disease; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; VGPR = very good partial response								

3.4.5 Results of sensitivity analysis: including full population from PERSEUS

The company further conducted sensitivity analyses by using the full population from PERSEUS, without excluding patients >65 years of age. The company stated that: *“In the base case ITC, the patient population from PERSEUS was limited to those up to, and including, 65 years of age, compared to 70 years in the ITT population, to better align with the CASSIOPEIA patient population.”*¹ The sensitivity analysis also involved alternative analyses by using the double robust model and multivariate regression.¹ The sensitivity analysis by including full PERSEUS population was conducted via IPTW for the unadjusted model, the model where priority covariates were adjusted for, and the model where all covariates were adjusted for. The findings from the sensitivity analyses by including full PERSEUS population were generally consistent with the base-case analysis of ITC.¹

EAG comment: In the ITC analyses, the data for DBLd and DBTd as I+C therapies were derived from two trials (PERSEUS and CASSIOPEIA). The company conducted an ITC by using IPD based on the PERSEUS and CASSIOPEIA trials. The ITC analysis used IPTW as the base-case approach. The company further used alternative adjustment methods (multivariate regression method and double robust method) as sensitivity analyses. The EAG considers that the indirect comparison analysis approach used by the company appears to be appropriate, and is in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 17.⁸

The results of ITC sensitivity analyses by using multivariate regression and double robust method were generally consistent with those from the base-case ITC.

In the base-case of ITC analyses where priority covariates were adjusted for, the majority of priority covariates between the DBTd population and the DBLd population were well balanced after weighting. However, it should be noted that three priority covariates (presence of extramedullary plasmacytomas, LDH and bone lesions) had SMDs above the threshold of 0.2, which indicates that the distribution of these three covariates were not well balanced after matching. Therefore, this might have introduced uncertainties on the validity of results from the base-case ITC analyses, which constitutes a key issue.

In addition, the validity of the ITC only for I+C treatment (excluding maintenance treatment phase) needs to be considered as part of the key issue regarding the lack of evidence for the comparison between the full sequences treatments (DBLd followed by DL versus DBTd followed by L).

3.5 Additional work on clinical effectiveness undertaken by the EAG

None.

3.6 Conclusions of the clinical effectiveness Section

The CS, Appendix B and response to clarification^{1,3,5} provided sufficient details for the EAG to appraise the two sets of literature searches conducted to identify relevant clinical evidence on the efficacy and safety of treatments for patients with NDMM who are eligible for HDT-ASCT. The I+C SLR was conducted in May 2018 and updated in April 2023 and February 2025. The I+C+M SLR was conducted in September 2023 and updated in February 2025. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of bibliographic databases, conference proceedings, HTA organisations and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

Two SLRs were conducted, which were intended to find evidence for the complete sequence of treatments i.e. induction, consolidation and maintenance, or I+C only, given the two possible interventions i.e. DBLd followed by Ld maintenance, or DBLd only. The EAG considers that they seem to have been conducted well enough for this purpose, and the result was finding one RCT, PERSEUS to compare the complete sequence with BLd followed by L maintenance. Given that the company did not find any studies that compared the complete sequence of DBLd followed by DL with SoC in the form of DBTd followed by L, they then decided to compare I+C treatments only and, separately, maintenance treatments only, the former via an ITC. The latter required an additional search for maintenance only treatments in order to compare DL with L, given that PERSEUS could not be used for this purpose as the I+C treatments also varied between the arms. This led to finding one study, the AURIGA RCT, to inform this comparison. The EAG were concerned about the company claiming that a process of *'pragmatic re-evaluation of previously excluded studies in order to find additional evidence that could inform a comparison of DL vs. L maintenance'* was conducted. The EAG considers that this approach may well have been prone to bias and error and may risk excluding studies that were not initially identified. The company do seem to take a conservative approach in the economic model by assuming equal effectiveness in terms of OS and PFS in the I+C phase, which might mitigate this problem with the maintenance phase. Nevertheless, the lack of rigour implies uncertainty as to the evidence to inform DL versus L maintenance, which implies a key issue.

In PERSEUS, patients on DBLd I+C followed by DL maintenance had a statistically significant and clinically meaningful improvement in efficacy outcomes compared to the SoC (BLd I+C followed by L maintenance). This benefit was observed across multiple endpoints including PFS, depth of response, and MRD negativity, with no detrimental impact on HRQoL. OS data remain immature but show an early trend in favour of the daratumumab arm. However, the EAG notes that this comparison is not relevant to the DP and was not used in any ITC or to inform the economic model.

The ITC compared the DBLd arm of PERSEUS with the DBTd arm of the CASSIOPEIA in the I+C phase only. This necessitated the censoring of data for survival outcomes, i.e. PFS and OS. The company conducted the ITC by using IPD from the PERSEUS and CASSIOPEIA trials, which used IPTW as the base-case approach to adjust for selection bias. The company also used alternative adjustment methods (multivariate regression method and double robust method) as sensitivity analyses. The EAG considers that this approach used by the company appears to be appropriate and is in accordance with DSU TSD 17. For $\geq$ VGPR, using the adjusted base-case model (where all covariates were adjusted for), the OR [REDACTED] favoured [REDACTED] compared with [REDACTED]. The OR for ORR favoured [REDACTED] compared with [REDACTED] in the base-case (seven priority PFs and TEMs were adjusted for) and sensitivity analysis (all covariates adjusted for), but the results were [REDACTED] for the base-case model. There were [REDACTED] in the MRD-negativity (regardless of CR status) rate between DBLd and DBTd in the base-case model and sensitivity analysis. The EAG agrees with the company that the PFS and OS results need to be regarded with caution given the use of censoring at the start of the maintenance phase.

In AURIGA, it was demonstrated that DL maintenance had a statistically significant and clinically meaningful improvement in efficacy outcomes compared to L maintenance alone, including in PFS and OS.

Overall, there was no comparison between the intervention of the complete sequence of DBLd followed by DL and SoC in the form of DBTd followed by L in any evidence presented by the company. There was an ITC between only the I+C treatments, which the EAG considers should be limited to short term outcomes (pre-maintenance phase only), which seemed to show an advantage to DBLd. There was also

an RCT that showed an advantage to DL over L in the maintenance phase. In total, this does seem to show an advantage for the intervention of DBLd followed by DL versus the comparator of DBTd followed by L. However, this conclusion needs to be considered in the light of the robustness of the SLR to locate the comparator trials, the ITC methodology, and the piecewise nature of the evidence.

4. Cost effectiveness (CE)

4.1 Critique of the review of CE evidence

This Section pertains mainly to the review of CEA studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to CE presented in the CS. Therefore, the following Section includes searches for the CEA review, health-state utility values (HSUVs), and cost/resource use.

4.1.1 Searches performed for CE Section

The following paragraphs contain summaries and critiques of all searches related to CE, HRQoL and cost/health care resource use (HCRU) identification presented in the CS.¹ The CADTH evidence-based checklist for the PRESS, was used to inform this critique.⁴ The EAG has presented only the major limitations of each search strategy in the report.

Appendices E, F and G of the CS provide details of searches conducted to identify relevant studies on CE, HRQoL and cost/HCRU in patients with NDMM who are eligible for HDT-ASCT.⁵ The searches were conducted in September 2023 and updated in May 2025.

EAG comment:

- A single set of searches was undertaken to identify relevant studies on CE, and cost/HCRU in the treatment of HDT-ASCT eligible patients with NDMM. A separate set of searches was undertaken to identify evidence relating to HRQoL, patient-reported outcomes (PROs) and utilities in patients with NDMM who are eligible for HDT-ASCT. The CS, Appendices E, F and G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{1, 3, 5}
- The following databases were searched on 19 September 2023 (updated on 8 May 2025) for the CE and cost/HCRU searches, and on 19 September (updated on 13 May 2025) for the HRQoL searches: MEDLINE and MEDLINE In Process (via PubMed for the original SLR and Ovid for the update), Embase and CDSR and CENTRAL (via the Cochrane Library for the original searches and Evidence-Based Medicine [EBM] Reviews for the update). The CDSR and CENTRAL HRQoL update searches were conducted on 8 May 2025.
- A publication date limit of 2000+ was applied to the MEDLINE and Embase searches. No language limit was applied to any of the searches.
- The conferences of seven key organisations were reviewed for relevant abstracts between January 2018 and February 2025, through the Embase search and via relevant websites: ASCO, ASH, EHA, IMWG, ISPOR, International Health Economics Association (IHEA), European Health Economics Associations (EUHEA).
- The websites of the following HTA organisations were searched for material published between 2018 and 2025: NICE, SMC, CDA formerly CADTH, PBAC, Haute Autorité de Santé (HAS), Gemeinsamer Bundesausschuss (G-BA), Institute for Quality and Efficiency in Health Care (IQWiG), Italian Medicines Agency (AIFA), Institute of Health Carlos III (ISCI)
- All database strategies searched for a range of terms for NDMM. This was then combined with study design filters containing terms for costs and economic evaluations, cost/HCRU and HRQoL.
- All searches were well structured, transparent and reproducible and searches contained a good range of search terms, synonyms and subject headings. None of the study design filters used were

referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.

4.1.2 Inclusion/exclusion criteria

In- and exclusion- criteria for the review on CE studies, costs/resource use and utilities are presented by the company in Appendices E, F and G of the CS.⁵

All SLRs excluded patients “without intent for immediate transplant.” It is unclear what “intent” exactly means and how it is related to the patient population of the current appraisal that indicates “eligible.” Furthermore, there is a non-negligible proportion of patients in the economic model who do not receive ASCT. Therefore, it is unclear whether patients “without intent for immediate transplant” are the same as those not receiving ASCT. This exclusion criterion potentially would return less relevant studies.

In addition, the CE and cost/resource use SLR excludes studies during maintenance treatment and short-term post-maintenance treatment. It is also unclear why these were chosen as exclusion criteria given that maintenance is explicitly modelled by the company. Therefore, it is possible that relevant studies may have been missed.

4.1.3 Findings of the CE review

The PRISMA flow diagram for the CE and resource use SLR can be found in Figure 11 of Appendix E of the CS.⁵

In total, 43 studies were identified; from these, 17 were economic evaluations and 26 costs/resource use studies. The economic evaluation studies included five published cost utility analyses and eight HTA submissions. None of them reported data on patients who received DBLd I+C followed by DL maintenance, or DBTd followed by L maintenance. Therefore, none of these studies were considered relevant by the company for the current submission. From the costs/resource use studies, 19 reported on HCRU in patients with NDMM, with four studies (across five publications) only including patients with HDT-ASCT eligible patients with NDMM. It is not mentioned whether or to what extent these studies were considered relevant for the current submission.

In addition, the PRISMA diagram for the HRQoL/utilities SLR was shown in Figure 14 of Appendix F of the CS.⁵ In total, 44 publications were identified, from which 30 were real world evidence (RWE) studies and 14 were RCTs. Also here, it is not mentioned whether or to what extent these studies were considered relevant for the current submission.

4.1.4 Conclusions of the CE review

The CS, Appendices E, F and G and response to clarification^{1, 3, 5} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on CE, HRQoL and cost/HCRU in the treatment of HDT-ASCT eligible patients with NDMM. Searches were conducted in September 2023 and updated in May 2025. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases and conference proceedings were searched. Overall, the EAG has no major concerns about the literature searches conducted. Since no economic models to address the current DP were identified by the company, a de novo model was built, which is discussed in the remainder of this Section.

4.2 Critique of the submitted economic evaluation

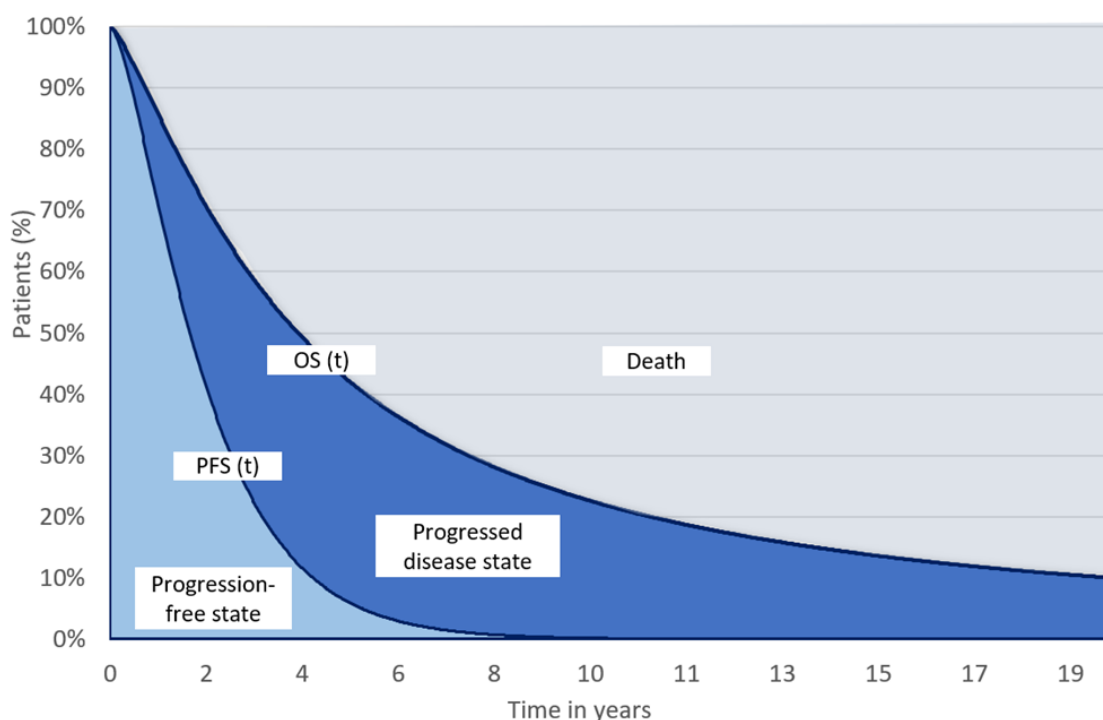
4.2.1 NICE reference case checklist

Table 4.1: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case
Perspective on costs	NHS and PSS	As per the reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	As per the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the reference case
Synthesis of evidence on health effects	Based on systematic review	As per the reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	As per the reference case
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	As per the reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	As per the reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per the reference case
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	As per the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case
CS = company submission; EAG = External Assessment Group; EQ-5D = EuroQoL-5 Dimensions; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom		

4.2.2 Model structure

The company developed a partitioned survival model (PSM) in Microsoft Excel® including three mutually exclusive health states: progression-free (PF), progressive disease (PD), and death. A schematic representation of the model structure is provided in Figure 4.1.

Figure 4.1: Schematic conceptual model structure

Based on Figure 22 of the CS¹

CS = company submission; PFS = progression-free survival; OS = overall survival

Health state occupancy was derived from extrapolation of PFS and OS data. For DBLd-DL, survival outcomes were taken directly from the PERSEUS trial. Outcomes for DBTd-L were generated by applying relative treatment effect estimates from the AURIGA trial.

Two adjustments were applied to maintain logical consistency. Firstly, mortality risk per cycle was bound by age-matched general population estimates, sourced from the Office for National Statistics (ONS) Life Tables.¹¹ Secondly, PFS was constrained not to exceed OS, with the maximum hazard applied when the hazard of death exceeded the hazard of progression or death.

Time on treatment was determined using time to treatment discontinuation (TTD), recognising that patients may discontinue therapy for reasons other than progression. This enabled treatment-related costs (acquisition, administration, monitoring) to be applied only while patients remained on treatment, while allowing PF and PD state costs to accrue regardless of treatment status.

The economic analysis was conducted from the NHS and PSS perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was 28 days, consistent with the treatment schedule for DBLd-DL and DBTd-L and aligned with the approach in TA763,¹² with a lifetime time horizon (i.e., 40 years) and a half-cycle correction applied.

The company considered a PSM the most appropriate structure to evaluate the CE of DBLd I+C with DL maintenance, as it reflects the natural course of disease for patients with NDMM eligible for HDT-ASCT. The key outcomes, PFS and OS, are time-to-event endpoints, and the PSM framework allows direct replication of observed data from PERSEUS, generating survival estimates consistent with trial evidence.

The PSM was further justified as the treatment arms follow similar care pathways after progression, reducing the need to model post-progression therapies as separate states. By directly modelling

observed events, the PSM was expected to closely match observed survival, with long-term uncertainty explored through alternative parametric extrapolations.

Finally, as MM is an incurable condition with unidirectional progression, there was no need to model backwards transitions between states. The use of a PSM was consistent with precedent from multiple NICE Technology Appraisals (TAs) in MM, including TA657 and TA763.¹²⁻²⁰

4.2.3 Population

The modelled population comprises adults with NDMM eligible for HDT-ASCT. This aligns with the DP, the marketing authorisation for DBLd in the UK, and the population of the PERSEUS trial.^{6, 21} Baseline characteristics were derived from the DBLd arm of the ITT population in PERSEUS. UK clinical experts consulted in 2025 confirmed that this trial population is broadly generalisable to UK clinical practice.²² Mean age in PERSEUS was consistent with NCRAS data (■■■■ versus ■■■■ respectively), and is considered more reflective of UK practice than the population in TA763 (mean age 56.6 years).¹²

Age and sex are included in the model for general population mortality and utilities. Mean baseline body weight and body surface area (BSA) are included to determine drug dosing and acquisition costs. A summary of baseline characteristics used in the model is provided in Table 4.2.

Table 4.2: Baseline characteristics used in the economic analysis

Characteristics	Value	Source
Mean age, years	████	PERSEUS trial, ITT analysis set (DBLd-DL arm) ²¹
Proportion of female patients, %	████	
Mean body weight, kg	████	
Mean BSA, m ²	████	
Based on Table 47 of the CS ¹ BSA = body surface area; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide, dexamethasone; DL = daratumumab with lenalidomide; ITT = intention-to-treat		

EAG comment: The company included 2nd, 3rd and 4th line treatment in the model, but only on the costs side, as explained in Section 4.2.8 of this report. Utilities remain constant after progression (see Section 4.2.7) and survival probabilities do not seem to have been adjusted for subsequent lines of treatment (see Section 4.2.6). The EAG considers it reasonable to assume that survival prognosis gets worse as patients progress to subsequent treatment lines. If this is not properly captured in the economic model, then the estimated life years (LYs) and quality-adjusted life years (QALYs) are likely overestimated. This raises some concerns because in comparison with TA763, the current appraisal estimates substantially less LYs for the comparator arm, as explained in Section 5.2.1. If the current analyses underestimate LYs and QALYs because they fail to capture the impact of subsequent lines of treatment, then the discrepancy might be even larger. Furthermore, it might also be in contradiction with the company's statement that "*the associated advances in MM management, which has potentially improved prognosis for NDMM patients and led to higher utility values*" (see Section 4.2.7). The company used this argument to assume that in the current appraisal, utilities are higher than in TA763. Following this line of reasoning, it could be argued that improvements in life expectancy compared to TA763 could also be expected. However, for the comparator arm in the current appraisal the opposite seems to be happening. Finally, in clarification response B14 the company indicated that most patients in PERSEUS trial only reached one subsequent line of therapy (the proportion of patients receiving one or more subsequent lines of treatments was ■■■■% in the BLd-L arm and ■■■■% in the DBLd-DL arm).

This means for example that ■■■% of patients in the BLd-L arm did not get subsequent lines of therapies.

4.2.4 Interventions and comparators

The intervention is DBLd-DL, consisting of DBLd induction prior to ASCT, DBLd consolidation post-ASCT, and DL maintenance therapy. Treatment protocols in the model mirror those of PERSEUS and the summary of product characteristics (SmPC) posology for daratumumab: four 28-day induction cycles; high-dose chemotherapy and ASCT; two 28-day consolidation cycles; and 28-day DL maintenance cycles.^{7, 23} COVID-19-related delays in ASCT in PERSEUS led to additional induction cycles for some patients and no consolidation, resulting in a total treatment duration consistent with CASSIOPEIA.^{24, 25}

The comparator is DBTd-L, comprising DBTd induction prior to ASCT, DBTd consolidation post-ASCT, and L maintenance therapy. Induction, ASCT, and consolidation are consistent with CASSIOPEIA, while maintenance is aligned with the AURIGA trial and SmPC guidance for daratumumab and lenalidomide.^{9, 23, 26} Protocols are defined as four 28-day induction cycles, high-dose chemotherapy and ASCT, two 28-day consolidation cycles, and 28-day L maintenance cycles.

EAG comment: The EAG refers to the key issues identified in Sections 2.2 and 2.3, which might have implications for the cost effectiveness analysis.

4.2.5 Perspective, time horizon and discounting

The company conducted the economic analysis in accordance with the ‘Modelling Good Research Practices’ disseminated by the ISPOR and the Society for Medical Decision Making (SMDM).²⁷ The analysis was conducted in line with NICE reference case. The perspective assumed was that of the NHS and PSS, taking into account direct costs and health benefits only. The health economic model used a lifetime horizon, equivalent to 40 years, which was considered as a sufficient length of time to capture the potential differences in costs and outcomes between the technologies being compared. The discount rate was set to 3.5% for both costs and health benefits.

4.2.6 Treatment effectiveness and extrapolation

To inform the PSM model the company derived efficacy data for DBLd I+C followed by DL maintenance, from the latest DCO in the PERSEUS trial (1 of August 2023). Given the immaturity of the PERSEUS trial survival data, scenario analyses using pooled data for DBLd-DL from the PERSEUS and GRIFFIN trials were explored.

Kaplan-Meier (KM) data for the DBLd arm of the PERSEUS trial were used to inform the efficacy of the DBLd-DL in the model. For the I+C phases DBLd and DBTd were assumed to have equal efficacy regarding PFS and OS. Given that the follow-up period in PERSEUS was shorter than the model time-horizon, extrapolations of the observed OS, PFS and TTD data were required. The company explored a range of standard parametric distributions (i.e. exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) in accordance with the NICE DSU TSD 14 guidance.²⁸ The choice of distribution for the base-case was informed considering statistical fit criteria, visual assessment of the hazard functions and survival curves, and clinical validation of long-term extrapolations.

Data from the AURIGA and PERSEUS trials were combined to derive proxy efficacy outcomes for the comparator full treatment sequence given the absence of trials reporting data for it, i.e., DBTd I+C followed by L maintenance. Specifically, the relative treatment effects for L versus DL maintenance,

as estimated from the AURIGA trial, were applied to adjust the PFS and OS extrapolations for patients receiving DBLd-DL in the PERSEUS trial from the onset of maintenance therapy (approximately 9.7 months from randomisation), in order to derive a proxy survival function for DBTd-L patients. With this approach the company assumed that the treatment benefit observed in the AURIGA trial would be at least maintained in the broader population.

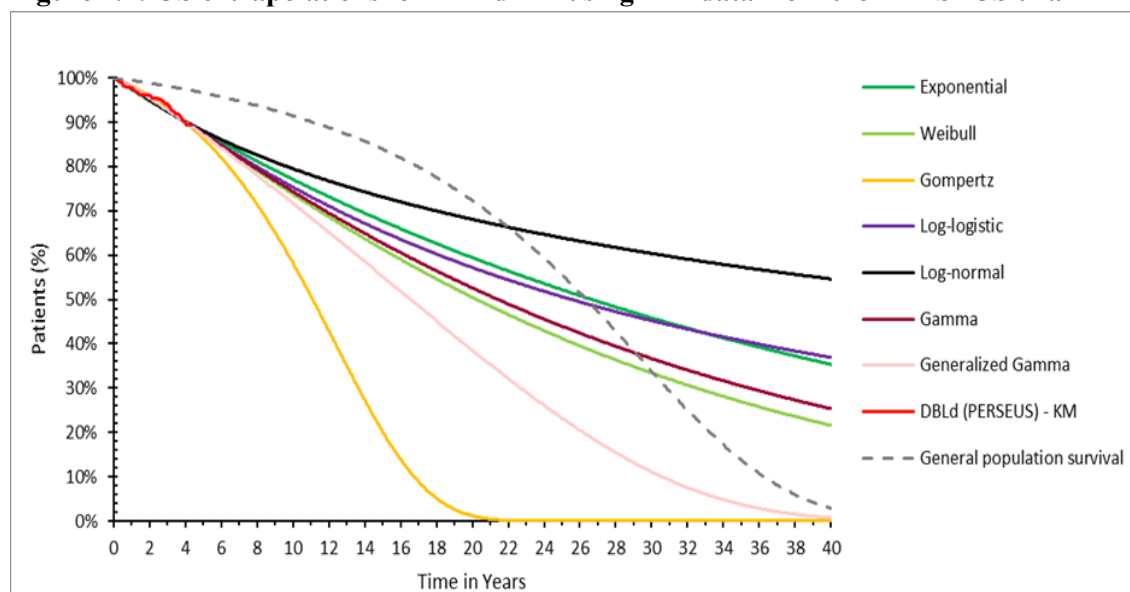
To estimate the relative treatment effects, the proportional hazards (PH) assumption was evaluated using log-cumulative hazard plots and Schoenfeld residuals based on survival data from the AURIGA trial. No violations of the PH assumption were identified, thereby justifying the application of HRs to summarise relative treatment effects on PFS and OS. Details of the PH assessments are reported in Appendix M of the CS.⁵

4.2.6.1 Overall Survival

4.2.6.1.1 DBTd with DL maintenance

For DBLd with DL maintenance, the exponential extrapolation provided the best statistical fit to the observed PERSEUS OS data with respect to both Akaike information criterion (AIC) and Bayesian information criterion (BIC) data, followed by the Gompertz and the Weibull distributions (see Table 50 of the CS).¹ Figure 4.2 below shows the OS extrapolations for DBLd-DL arm combined with the KM data from the PERSEUS trial. The long-term OS rates estimated by the exponential extrapolation also aligned most closely with the clinician estimates at the 10 and 15 years, as shown in Table 4.3. Finally, Figure 4.3 shows that in the PERSEUS trial, DBLd-DL exhibited a constant OS hazard initially, increasing gradually after 2 years. Of the models tested, the exponential extrapolation was deemed to align with this pattern demonstrating internal validity, whereas other parametric functions either increased from baseline or showed inconsistent trends. The exponential distribution was therefore chosen as the base-case curve selection.

Figure 4.2: OS extrapolations for DBLd-DL using KM data from the PERSEUS trial

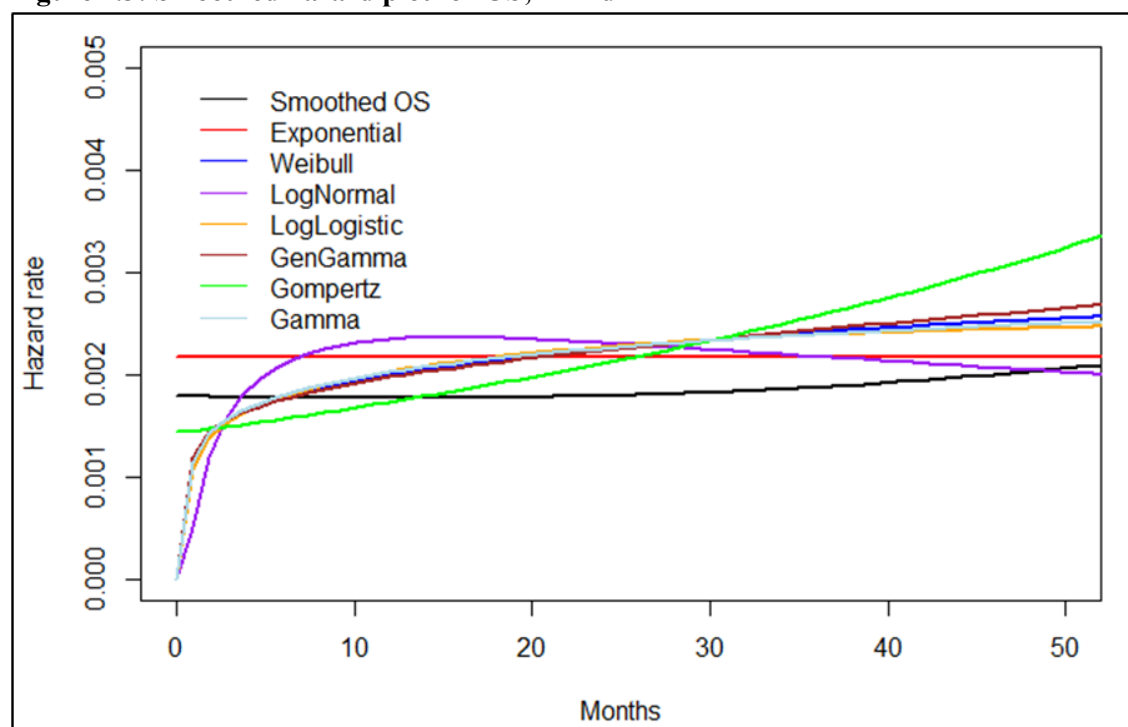


Based on Figure 22 of the CS¹

CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; KM = Kaplan-Meier; OS = overall survival

Table 4.3: Predicted DBLd-DL OS versus clinical expert expectations (with GPM cap)

Survival model	Mean OS (months)	OS rates (%)			
		5 years	10 years	15 years	25 years
Clinical Expert Estimates					
Expected [range]	N/A	N/A	77 [75, 80]	67 [65,70]	38 [25, 53]
Extrapolations					
Exponential	255.0	87.7	77.0	67.7	44.4
Weibull	237.7	87.2	73.6	61.3	38.6
Gompertz	129.6	86.1	57.9	20.0	0.0
Log-logistic	249.4	87.3	75.3	65.3	42.8
Log-normal	265.9	87.9	79.4	72.5	47.8
Gamma	241.9	87.2	74.3	62.7	40.1
Generalised Gamma	204.7	87.0	71.6	55.1	23.1
Based on Table 8 of the response to the request for clarification ²⁹ DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; N/A= not applicable; OS = overall survival; GPM = general population mortality					

Figure 4.3: Smoothed hazard plot for OS; DBLd-DL

Based on Figure 23 of the CS¹

CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; OS = overall survival

4.2.6.1.2 DBTd with L maintenance

The relative treatment benefit with an OS HR of [REDACTED] (95% CI: [REDACTED]; p-value: [REDACTED]) for DL versus L, as estimated from the AURIGA trial, was used to adjust the chosen extrapolation for the DBLd-DL arm of the PERSEUS trial from the onset of maintenance therapy. This, in turn, generated a

proxy for the OS extrapolation for DBTd I+C followed by L maintenance in the absence of trial data for the full treatment sequence. The company concluded that long-term estimates of OS for DBTd-L derived from the application of the AURIGA OS HR to the DBLd-DL extrapolation were within the range of the clinical expert estimates provided for the 10-, 15- and 25-year landmark timepoints, as shown in Table 4.4.

The company conducted a scenario analysis assuming equal OS between DL and L (HR=1), although considered this clinically implausible given trial evidence (AURIGA, PERSEUS) and expert opinion consistently favouring DL for long-term PFS and OS.

Table 4.4: Predicted DBTd-L OS versus clinical expert expectations (with GPM cap)

Survival Model	Mean OS (months)	OS rates (%)			
		5 years	10 years	15 years	25 years
Clinical Expert Estimates					
Expected [range]	N/A	N/A	68 [60, 70]	55 [45, 65]	30 [15, 45]
Extrapolations					
Exponential	194.1	78.6	60.7	46.9	27.1
Weibull	167.6	77.3	55.3	38.3	17.2
Gompertz	98.4	75.4	34.2	4.1	0.0
Log-logistic	185.8	77.6	57.7	43.4	25.1
Log-normal	216.7	78.8	64.3	54.5	35.5
Gamma	173.4	77.5	56.2	40.1	19.6
Generalised Gamma	139.3	77.0	52.2	31.0	5.4
Based on Table 12 of the response to the request for clarification ²⁹ DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; L = lenalidomide; N/A= not applicable; OS = overall survival; GPM = general population mortality					

EAG comment: To estimate long-term OS of DBLd-DL and DBTd-L patients, the company used data from the PERSEUS and the AURIGA trials. The immaturity of OS and PFS data from the PERSEUS trial is highlighted as a key limitation throughout the CS and is particularly evident when reviewing alternative model extrapolations (as shown in Figure 4.2). The immaturity in survival data inflates uncertainty around the economic outcomes and limits the reliability of predictions for decision making.

To inform both OS and PFS, the company used survival data from PERSEUS from the August 2023 DCO. The EAG requested any longer follow-up data that may now be available and that can perhaps resolve part of this uncertainty. In clarification response B4, the company indicated that longer-term follow-up data are not currently available and that a final PERSEUS analysis is not expected until 2028. The company further suggested that some uncertainty in long-term estimates is inevitable given the good prognosis of HDT-ASCT-eligible NDMM patients, the high proportion responding well to DBLd-DL, and the availability of effective subsequent therapies in the UK (clarification responses B4 and B2f).²⁹ The company concluded that mature PFS and OS data from PERSEUS are unlikely to resolve this uncertainty even at the final analysis.

The estimated HRs from the AURIGA trial were based on the April 2024 DCO. The HR for OS was estimated at [REDACTED] (95% CI: [REDACTED]; p-value: [REDACTED]) for DL versus L, with a wide CI indicating that the results are not statistically significant. In response to clarification question B2f,²⁹ the company confirmed that a 2-year DCO from 3 March 2025 has been collected, but these data were not yet

available to inform the submission or relevant model inputs. The company indicated they are exploring presenting this evidence later in the appraisal process. The company further commented that in the CASSIOPEIA trial, even after extended follow-up (median 80.1 months from randomisation; September 2023 DCO), median PFS was not reached for patients treated with DBTd I+C followed by daratumumab maintenance.

The EAG concludes that the immaturity of the survival data from the two trials introduces uncertainty in two ways. Firstly, there is uncertainty in the long-term OS predictions based on the alternative extrapolations, as shown in Figure 4.2. Secondly, there is uncertainty in the relative treatment effectiveness, driven by the precision of the PFS and OS HRs estimates.

The EAG understands the company's perspective that uncertainty may persist even with longer follow-up data and acknowledges the reasoning. However, the EAG does not concur with the company's belief that the current data informing the model are sufficient to support decision making (clarification response B2h).²⁹ The EAG considers that additional long-term follow-up data from AURIGA or PERSEUS that could assist in reducing current uncertainty and improve model precision, should be incorporated into this appraisal, and welcomes the company to submit any additional available data from these trials.

Regarding OS extrapolations in the current analysis, the EAG has no major objections to the company's preferred option for extrapolating OS (exponential), although assuming a constant hazard function over time may be a strong assumption. The observed hazard function shown in Figure 4.3 shows an increasing (but modest) hazard over time, which is not captured by the exponential distribution (constant hazard), which in the long-term might result in an overestimation of OS. However, the EAG does not consider that any of the alternative extrapolations presented by the company offer a better fit. Therefore, to address the immaturity of the PERSEUS survival data, the EAG conducted scenario analyses using different OS and PFS extrapolation options.

Regarding the OS HR estimated from the AURIGA trial, the company explored a scenario assuming an OS HR of 1 between DL and L maintenance, representing equal efficacy during the maintenance period. Under this assumption, DBLd-DL dominated DBTd-L (there is a small gain in QALYs for DBLd-DL due to PFS benefit, but the longer survival for DBTd-L in this scenario made it a more costly alternative), indicating that the model is sensitive to the magnitude of the relative treatment effects. Dominance for DBLd-DL was also maintained in the company's post-hoc analysis, which re-weighted data from the PERSEUS trial to estimate OS and PFS HRs for DBLd-DL versus BLd-L in the maintenance phase (see clarification response B3).²⁹ The company validated OS predictions using clinical expert feedback. The EAG notes that previous daratumumab appraisals, such as TA763, could also have been used to validate the comparator arm (DBTd-L) to ensure consistency or explain differences (see Section 5.2.1 for more details). Given the wide CIs around the HRs, the EAG ran alternative scenarios.

Finally, the company did not assume any treatment waning effects in the analysis. In response to clarification question B6,²⁹ the company indicated that in the PERSEUS trial, very few OS and PFS events occurred after patients stopped daratumumab maintenance, suggesting the treatment effect was sustained even after discontinuation. Furthermore, in the AURIGA trial, DL maintenance led to deeper responses than L, with higher sustained MRD negativity (≥ 6 months: 35.4% versus 13.9%). The company also referred to the previous NICE TAs of daratumumab (both first-line and later-line), which also did not apply waning assumptions.^{18, 30, 31} The possibility of waning was discussed in TA763, but evidence from long-term trial data (e.g., GIMEMA, CASSIOPEIA with ~4 years' follow-up) suggested that deeper treatment responses lead to sustained improvements in long-term outcomes. Based on these

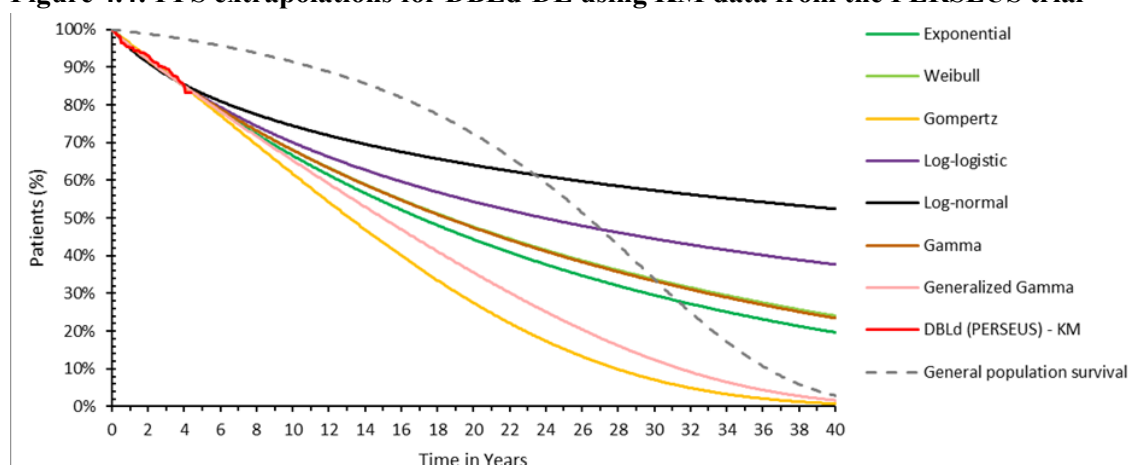
discussions, the TA763 Committee concluded that it was reasonable to assume the benefits of deep responses from daratumumab combination therapy would be maintained over a lifetime.¹² The EAG acknowledges the company's response and considers it reasonable. Nonetheless, given the immaturity of the survival data, the EAG maintains that uncertainty around long-term survival and therefore treatment effectiveness remains.

4.2.6.2 PFS

4.2.6.2.1 DBLd with DL maintenance

Extrapolations were fitted to the observed PFS data from the PERSEUS trial to model long-term DBLd-DL PFS as shown in Figure 4.4. The extrapolations implemented included a cap to ensure PFS did not exceed OS for DBLd-DL. The hazard of the PFS declined initially and increased from 25 months onwards as shown in Figure 4.5. According to the CS, although all extrapolations demonstrated comparable statistical fit in terms of AIC/BIC criteria (see Table 4.5), several extrapolation options lacked internal validity based on the long-term PFS rates estimated by the alternative extrapolation options against the clinician estimates (see Table 4.5). The generalised gamma model was considered by the company to align most closely with clinician-elicited estimates across timepoints and was therefore selected in the base-case extrapolation.

Figure 4.4: PFS extrapolations for DBLd-DL using KM data from the PERSEUS trial



Based on Figure 23 of the CS¹

CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; KM = Kaplan-Meier; PFS = progression-free survival

Table 4.5: AIC/BIC statistics for DBLd-DL PFS extrapolations

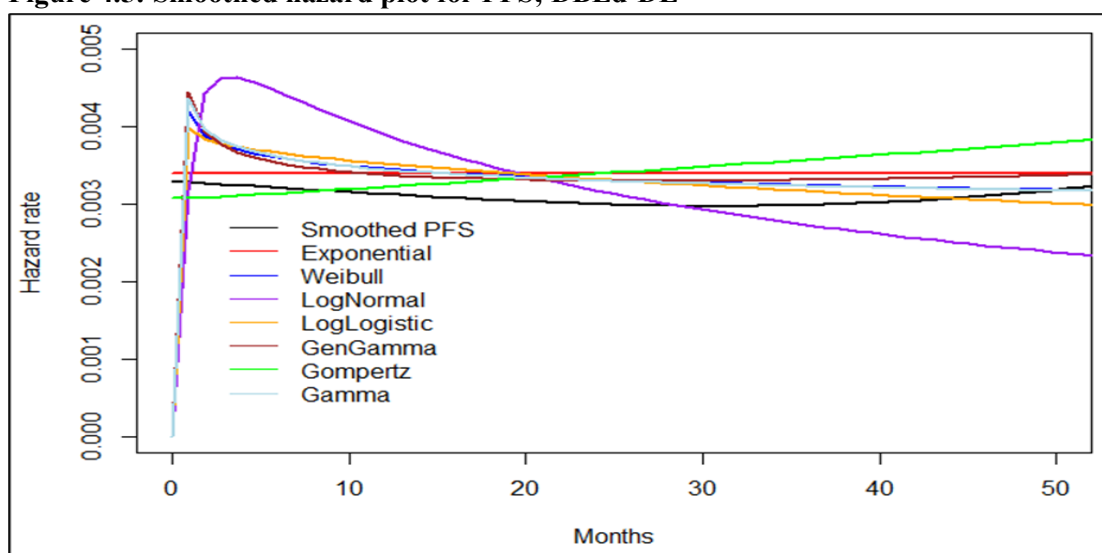
Survival model	DBLd-DL			
	AIC	BIC	AIC rank	BIC rank
Exponential	422.265	426.137	1	1
Weibull	424.087	431.831	3	3
Gompertz	424.091	431.835	4	4
Log-logistic	424.584	432.328	5	5
Log-normal	428.23	435.975	7	6
Gamma	424.035	431.779	2	2
Generalised Gamma	425.623	437.239	6	7

Based on Table 53 of the CS¹

Survival model	DBLd-DL			
	AIC	BIC	AIC rank	BIC rank
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; PFS = progression-free survival				

Table 4.6: Predicted DBTd-DL PFS versus clinical expert expectations (OS cap applied)

Survival model	Mean PFS (months)	PFS rates (%)			
		5 years	10 years	15 years	25 years
Clinical expert estimates					
Expected [range]	N/A	N/A	64 [60, 65]	48 [45, 55]	21 [15, 35]
Extrapolations					
Exponential	223.1	81.4	66.5	54.3	36.1
Weibull	230.3	81.7	68.0	56.8	40.0
Gompertz	173.1	80.8	61.6	43.4	15.1
Log-logistic	240.9	82.0	70.0	61.1	44.4
Log-normal	249.9	82.9	74.4	68.5	44.4
Gamma	229.9	81.7	67.9	56.7	39.6
Generalised Gamma	193.8	81.4	65.2	49.9	22.6
Based on Table 9 of the response to the request for clarification ²⁹ DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; N/A= not applicable; OS = Overall survival; PFS = progression-free survival					

Figure 4.5: Smoothed hazard plot for PFS; DBLd-DL

Based on Figure 26 of the CS¹

CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; PFS = progression-free survival

4.2.6.2.2 DBTd with L maintenance

The long-term PFS extrapolations for DBTd-L were obtained in line with the methods for the derivation of the OS extrapolation: the relative treatment benefit with a PFS HR of 0.53 (95% CI: 0.29, 0.97; p-

value: 0.036) for DL versus L maintenance derived from the AURIGA trial was applied to adjust the chosen extrapolation of the DBLd-DL arm of the PERSEUS trial from the onset of maintenance therapy. This way a proxy PFS extrapolation generated for DBTd-L in the absence of trial data for the full sequence.

Long-term estimates of PFS by clinical experts were also obtained for DBTd-L, as shown in Table 4.7. The company stated that long-term PFS estimates derived from the application of the AURIGA HR to the selected DBLd-DL extrapolation were above the 10- and 15-year clinician estimates but in line with the 25-year clinical expert estimates. This was considered the best available proxy PFS extrapolation for DBTd-L in absence of trial data.

Table 4.7: Predicted DBTd-L PFS versus clinical expert expectations (OS cap applied)

Survival model	Mean PFS (months)	PFS rates (%)			
		5 years	10 years	15 years	25 years
Clinical expert estimates					
Expected [range]	N/A	N/A	34 [25, 40]	10 [0, 15]	3 [0, 5]
Extrapolations					
Exponential	150.1	70.0	47.8	32.6	15.0
Weibull	159.1	70.6	49.9	35.7	18.3
Gompertz	104.7	68.9	41.3	14.5	0.0
Log-logistic	176.2	71.1	52.8	40.9	24.9
Log-normal	203.4	73.0	59.5	51.0	33.4
Gamma	158.6	70.7	49.9	35.5	18.0
Generalised Gamma	129.9	70.1	46.2	28.0	6.2
Based on Table 13 of the response to the request for clarification ²⁹ DBLd = daratumumab, bortezomib, thalidomide and dexamethasone; L = lenalidomide; N/A= not applicable; OS = overall survival; PFS = progression-free survival					

EAG comment: The issues arising from the immature OS data in the PERSEUS and AURIGA trials, as summarised in the EAG comments in Section 4.2.6.1, similarly affect PFS extrapolations, contributing to uncertainty around long-term outcomes and limiting the reliability of predictions for decision making. Furthermore, similarly to OS, the EAG considers that previous daratumumab appraisals, such as TA763, could have been used to validate PFS predictions for the comparator arm (DBTd-L) to ensure consistency or explain differences (see Section 5.2.1 for more details).

For PFS extrapolations in the company's base-case analysis, the generalised gamma model was selected because, although all models demonstrated similar statistical fit, it most closely matched clinician-elicited PFS estimates and better reflected observed hazard trends than the alternative models according to the company. However, the EAG noted that generalised gamma would be the least preferred model according to BIC and the second least preferred model according to AIC criteria in Table 4.5. Moreover, when comparing long-term predictions with clinician-elicited PFS estimates in Table 4.7 it is noted that for DBTd-L, the generalised gamma overestimates PFS at all three time points, with the bigger deviation observed at 15-year predictions. For DBTd-DL, PFS predictions based on generalised gamma are marginally above the upper bound of the clinicians' range for the 10-year estimates (see Table 4.6).

On the other hand, the Gompertz model scores better in terms of AIC and BIC criteria shown in Table 4.5, while it also more closely resembles clinicians' based PFS expected values for both arms

simultaneously: for DBTd-L the 10-year long-term prediction is slightly above the upper bound, whilst for DBTd-DL the 15-year prediction is slightly below the lower bound of the range. The company dismissed the Gompertz model as they argued it assumed an increasing hazard over time which is inconsistent with observed data. The EAG does not agree with this assessment. Figure 4.5 illustrates that treatment DBLd-DL presents a PFS hazard rate that initially declines slightly and then gradually increases from 25 months onward. While it is true that the Gompertz hazard function does not fully capture this, the same applies to all the other extrapolations considered by the company. As also stated in the CS,¹ the generalised gamma, Weibull and gamma extrapolations all show an initial steep increasing hazard then gradually decrease over time. Given the immaturity of the data, the EAG's preference would be to use the most conservative option between the two PFS extrapolation models (Gompertz versus generalised gamma). Therefore, the EAG's base-case use the Gompertz for PFS extrapolations that more closely matches clinicians-elicited preferences for both arms.

The estimated HRs for PFS from the AURIGA trial, based on the April 2024 DCO, was estimated at 0.53 (95% CI: 0.29, 0.97; p-value: 0.036) for DL versus L. To illustrate the impact of this parameter on model outcomes alternative scenario analysis was included in the EAG's scenario analyses.

4.2.6.3 Time to treatment discontinuation (TTD)

4.2.6.3.1 TTD for the I+C phases of DBLd and DBTd

Treatment duration for DBLd and DBTd during I+C was modelled using observed TTD data from the PERSEUS and CASSIOPEIA trials, respectively.^{9, 21} TTD was capped by the duration of the I+C phases in the trials to reflect the therapies' fixed duration.

4.2.6.3.2 TTD for the maintenance phase of DBLd-DL

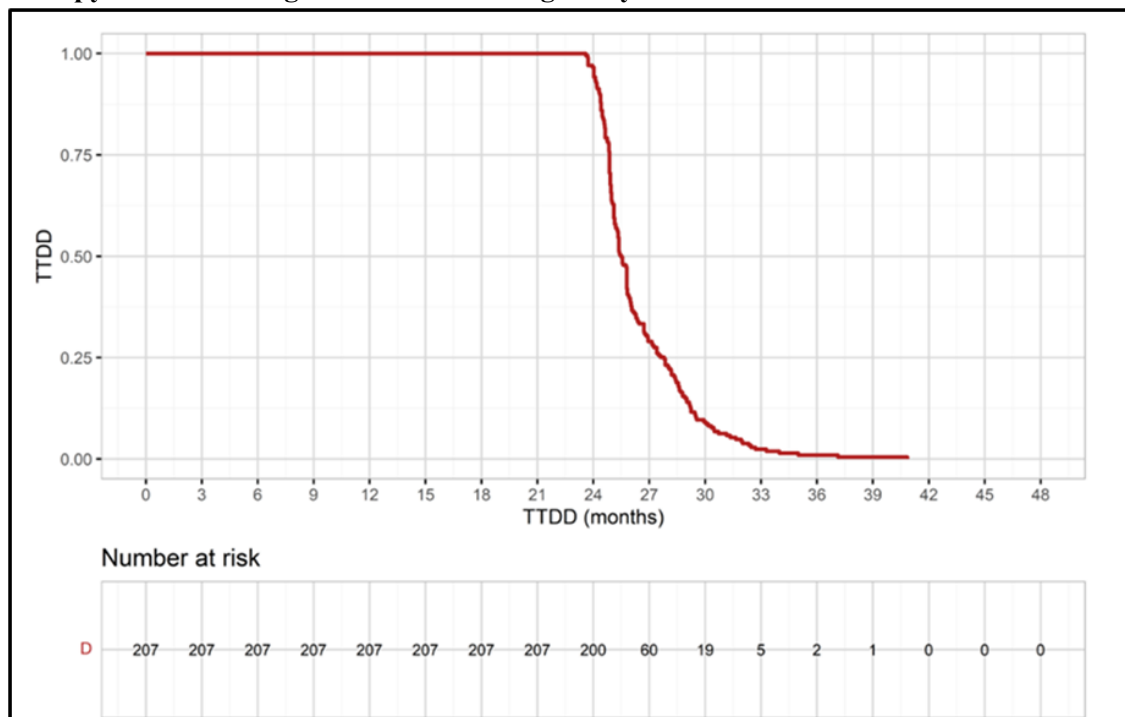
Following DBLd I+C, TTD for DL maintenance was capped by PFS and modelled separately for different sub-populations to reflect alternative stopping criteria for daratumumab:

- Patients who, after a minimum of 2 years of maintenance therapy, discontinued daratumumab after achieving sustained MRD-negativity for at least 12 months.
- Patients who discontinued daratumumab but did not achieve sustained MRD-negativity at the latest DCO.
- Patients who discontinued L (independently modelled data for discontinuation of daratumumab and discontinuation of L were applied for patients receiving DL).

TTD of DBLd-DL: discontinuation of daratumumab with sustained MRD-negativity

Data were available for the cohort of patients in the PERSEUS trial who discontinued daratumumab maintenance therapy due to sustained MRD-negativity. Mature KM data in Figure 4.6 were therefore applied in the model for these patients. In an scenario analysis, TTD was modelled with a fixed 2-year duration.¹ For the other two groups of patients, extrapolations were fitted to TTD data from the PERSEUS trial.

Figure 4.6: Observed KM data for patients who discontinued daratumumab maintenance therapy after achieving sustained MRD-negativity in the PERSEUS trial



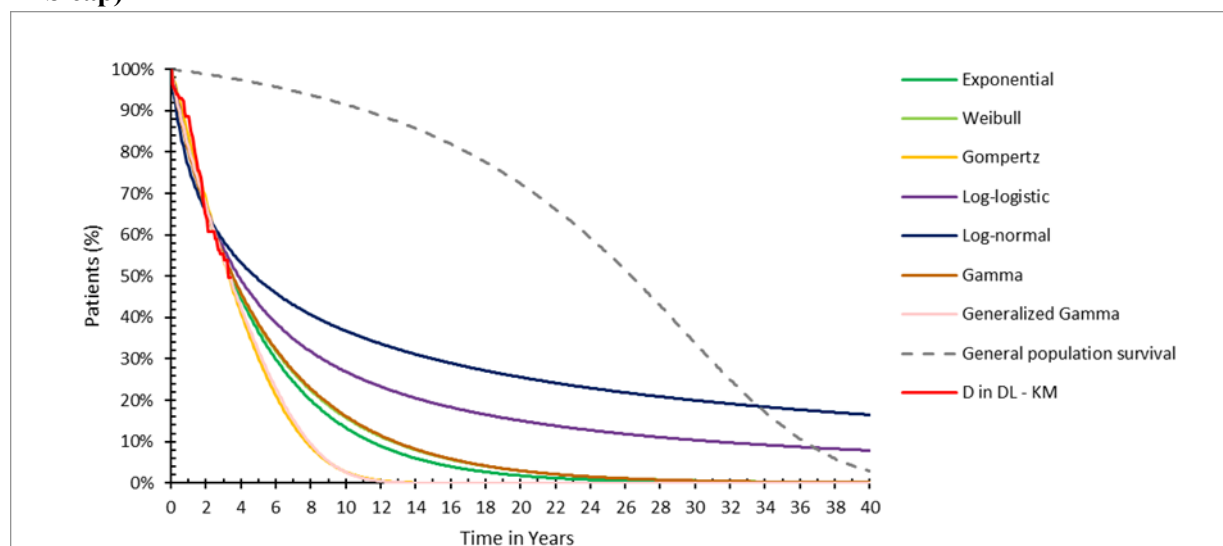
Based on Figure 28 of the CS¹

CS = company submission; KM = Kaplan-Meier; MRD = minimal residual disease; TTDD = time to treatment discontinuation duration.

TTD of DBLd-DL: discontinuation of daratumumab without sustained MRD-negativity

Treatment duration for patients who received DL maintenance following DBLd I+C but discontinued daratumumab during the maintenance phase without meeting the stopping criteria of sustained MRD-negativity was modelled fitting extrapolations to TTD data from patients in the PERSEUS trial receiving DL maintenance therapy. Goodness-of-fit statistics for each of the extrapolations were presented, and long-term TTD estimates for each parametric extrapolations are provided in Figure 4.7. The exponential extrapolation showed the best statistical fit with the observed data in terms of AIC and BIC (see Table 57 of the CS).¹ It also closely aligned with the long-term TTD clinical estimates at 5, 8, and 10 years in Table 4.8. The exponential curve was therefore chosen by the company as most appropriate for the base-case economic analysis.

Figure 4.7: TTD KM data from the PERSEUS trial and extrapolations for DBLd-DL patients without sustained MRD-negativity who discontinued daratumumab maintenance therapy (with PFS cap)



Based on Figure 30 of the CS¹

CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; KM = Kaplan-Meier; MRD = minimal residual disease; PFS = progression free survival; TTD = time to treatment discontinuation

Table 4.8: Predicted TTD survival versus clinical expert expectations for DBLd-DL patients without sustained MRD-negativity who discontinued daratumumab maintenance therapy

Survival model	Median TTD (years)	Patients on treatment (% , mean [range])		
		5 years	8 years	10 years
Clinical expert estimates				
Expected [range]	N/A	36 [35, 37]	20 [19, 20]	12 [10, 15]
Extrapolations				
Exponential	3.4	36.2	19.8	13.3
Weibull	3.5	37.8	22.2	15.7
Gompertz	3.4	29.7	8.5	2.7
Log-logistic	3.9	43.0	31.6	26.8
Log-normal	4.8	49.0	40.6	36.7
Gamma	3.6	38.1	22.6	16.1
Generalised Gamma	3.3	31.4	9.2	2.6

Based on Table 58 of the CS¹

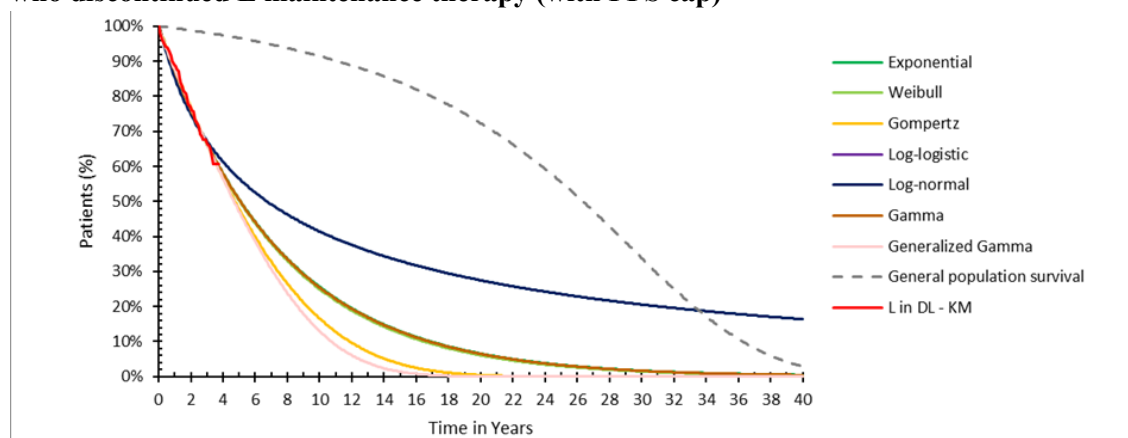
CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; MRD = minimal residual disease; N/A = not applicable; TTD = time to treatment discontinuation

TTD of DBLd-DL: discontinuation of L

Treatment duration for patients who received DL maintenance after DBLd I+C but discontinued L during the maintenance phase was modelled by fitting extrapolations to TTD data from the PERSEUS trial as shown in Figure 4.8. Given good statistical fit in terms of AIC and BIC (see Table 59 of the

CS),¹ and the production of long-term estimates close to clinician estimates in Table 4.9, the exponential extrapolation curve was selected for the base-case economic analysis.

Figure 4.8: TTD KM data from the PERSEUS trial and extrapolations for DBLd-DL patients who discontinued L maintenance therapy (with PFS cap)



Based on Figure 31 of the CS¹

CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; KM = Kaplan-Meier; L = lenalidomide; PFS= progression-free survival; TTD = time to treatment discontinuation

Table 4.9: Predicted TTD survival versus clinical expert expectations for DBLd-DL patients who discontinued L maintenance therapy

Survival model	Median TTD (years)	Patients on treatment (% , mean [range])		
		5 years	8 years	10 years
Clinical expert estimates				
Expected [range]	N/A	51 [50,53]	34 [32, 35]	25 [24, 25]
Extrapolations				
Exponential	5.1	50.2	33.4	25.5
Weibull	5.0	49.9	32.9	24.8
Gompertz	4.7	47.3	26.3	16.4
Log-logistic	5.7	52.8	40.0	34.3
Log-normal	6.7	56.3	46.1	41.3
Gamma	5.1	50.1	33.3	25.3
Generalised Gamma	4.7	46.7	23.5	12.8
Based on Table 60 of the CS ¹				
CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; N/A = not applicable; TTD = time to treatment discontinuation				

4.2.6.3.3 Treatment restarting following discontinuation of daratumumab during maintenance phase

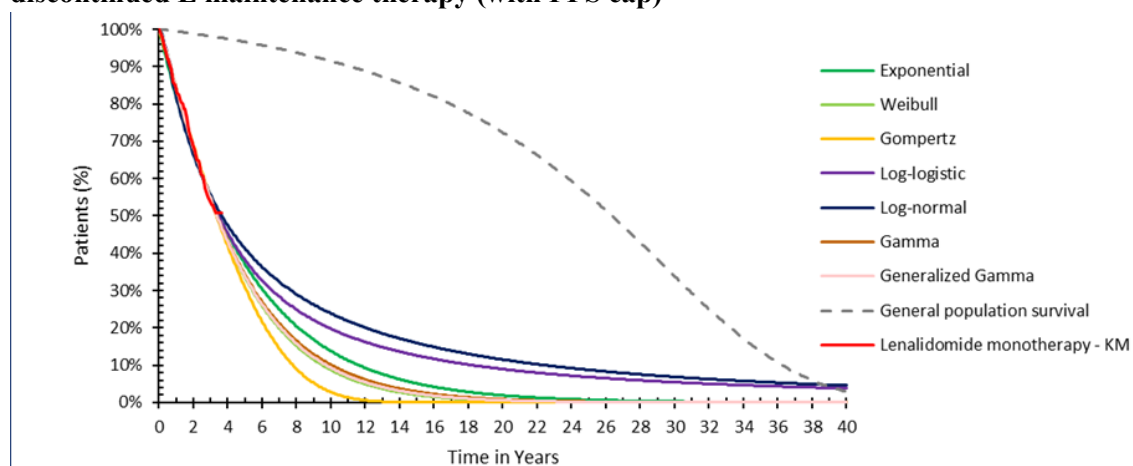
Given a low number of patients restarting treatment with daratumumab in the PERSEUS trial (■■■ patients restarted daratumumab out of the ■■■ patients who discontinued after meeting the stopping criteria), and the confirmation from UK clinical experts regarding the unlikelihood of restarting

daratumumab treatment, the base-case economic analysis assumed no patients would restart the medication.

4.2.6.3.4 Maintenance phase for DBTd-L

Treatment duration for L maintenance therapy for the DBTd-L comparator arm was modelled by fitting extrapolations to the TTD data for the BLd-L arm in the PERSEUS trial, where patients received L maintenance therapy, as shown in Figure 4.9. The exponential distribution was chosen as most appropriate for the base-case analysis given constant hazards in line with observed hazards in the PERSEUS trial, along with alignment with clinician long-term estimates presented in Table 4.10.

Figure 4.9: TTD KM data from the PERSEUS trial and extrapolations for BLd-L patients who discontinued L maintenance therapy (with PFS cap)



Based on Figure 33 of the CS¹

CS = company submission; BLd = bortezomib, lenalidomide and dexamethasone; L = lenalidomide; KM = Kaplan-Meier; PFS = progression-free survival; TTD = time to treatment discontinuation

Table 4.10: Predicted TTD survival versus clinical expert expectations for BLd-L patients who discontinued L maintenance therapy

Survival model	Median TTD (years)	Patients on treatment (% , mean [range])		
		5 years	8 years	10 years
Clinical expert estimates				
Expected [range]	N/A	36 [35, 37]	20 [18, 20]	13 [10, 15]
Extrapolations				
Exponential	3.5	36.7	20.3	13.7
Weibull	3.4	33.0	15.0	8.6
Gompertz	3.3	30.3	8.8	2.7
Log-logistic	3.5	37.9	24.7	19.7
Log-normal	3.6	40.9	28.9	23.8
Gamma	3.4	33.8	16.4	10.0
Generalised Gamma	3.4	33.3	15.6	9.2

Based on Table 62 of the CS¹

CS = company submission; BLd = bortezomib, lenalidomide and dexamethasone; L = lenalidomide; N/A = not applicable; TTD = time to treatment discontinuation

EAG comment: To inform treatment duration for L maintenance therapy in the DBTd-L arm, the company used data from the BLd-L arm of the PERSEUS trial. This approach implicitly assumes: i) the addition of daratumumab during I+C in the BLd-L treatment pathway does not affect the duration of L maintenance; and ii) the choice between DBTd or BLd at I+C does not influence the subsequent effect of L maintenance.

In clarification response B5,²⁹ the company acknowledged that clinical evidence on the impact of adding daratumumab during I+C on the duration of L maintenance as a monotherapy is limited, but did not provide any additional supportive evidence.

In response to question B5b,²⁹ the company confirmed that TTD data for L maintenance therapy from the AURIGA trial are available and conducted a scenario analysis using this data. The EAG remains unclear on why the company preferred the PERSEUS trial data to inform TTD in the maintenance phase of both arms, given that the relative treatment effectiveness in the maintenance phase of the company's base-case is informed by HRs derived from AURIGA. Importantly, patients in the AURIGA trial were anti-CD38-naïve and therefore could not have received DBLd or DBTd during I+C. That means that whether using TTD data from the AURIGA or the PERSEUS trial, an assumption remains that daratumumab in earlier phases does not influence L maintenance duration.

Nonetheless, as shown in Table 1 of the clarification response,²⁹ [REDACTED] of patients in the L arm of AURIGA received BLd at induction, while the remainder received other induction regimens. Given that L-based therapies are associated with improved tolerability compared to thalidomide-based therapies and improved response benefit, which is in turn expected to be translated to longer-term survival improvement (see clarification response B1), one could also expect shorter treatment duration for DBTd-L patients relative to BLd-L patients.²⁹ Clinical experts in the Advisory Board Meeting were asked to “*provide estimates for the proportion of patients expected to continue receiving DL or L maintenance therapy*” and were not specifically asked to provide estimates for the proportion of patients receiving DBTd-L.²² The company on the other hand considered the TTD curves from the AURIGA trial to be conservative when compared to the expected values from the clinical experts (clarification response B5).²⁹

In the absence of robust clinical evidence on the treatment duration of DBTd-L sequence, the EAG considers it more appropriate to use the TTD data from the L arm of AURIGA to inform TTD for DBTd-L in the base-case. The EAG considers this approach appropriate, firstly because OS and PFS for the DBTd-L arm in this appraisal are already informed by relative effectiveness estimates from the AURIGA trial, and secondly because the heterogeneous induction regimens in the AURIGA L arm may better capture the potential impact of DBTd versus BLd on subsequent L maintenance. Finally, in response to clarification question B2f,²⁹ the company indicated they may present longer-term survival data from the AURIGA trial (2-year DCO from 3 March 2025). The availability of these data would also provide more mature TTD data for the L maintenance arm and improve the validity of model predictions.

4.2.6.4 AEs

Base-case economic analysis AEs for DBLd during induction, ASCT and consolidation phases, as well as DL and L during maintenance phases, were informed by the PERSEUS trial. AEs for the comparator DBTd during the induction, ASCT and consolidation phases were informed by the CASSIOPEIA trial. Grade 3 or 4 AEs occurring in at least 5% of patients in the PERSEUS or CASSIOPEIA trials were included in the base-case economic analysis. This 5% threshold was considered appropriate to capture AEs that would impact patients consistently enough to have real-world setting validity.

In the economic model, cumulative probabilities of AE occurrence during induction, ASCT and consolidation were used as these were considered independent of PFS and treatment duration. Treatment-specific cumulative probabilities for the ITT population over the whole duration of the induction, ASCT and consolidation phases were used to calculate the cost of AEs. A per-patient overall AE cost and utility decrement was applied as a one-time lump sum and one-off decrement at the start of induction and start of maintenance. For maintenance, treatment-specific probabilities of AE occurrence were obtained from the maintenance phase of the AURIGA trial to inform AE costs. The cumulative probabilities of AE occurrence during I+C phases, and the probabilities of AEs in the maintenance phase (along with their associated costs) are shown in Table 4.19 in the “Resource use and costs” Section of this report.

4.2.7 *HRQoL*

The company performed an SLR to identify studies assessing the HRQoL, PROs and/or utilities in HDT-ASCT eligible patients with NDMM for the full treatment sequence including I+C+M treatment phases. For details on the SLR we refer to Appendix F of the CS.⁵

Out of the 44 unique HRQoL studies, two (one RCT by Ludwig et al. 2013, and one RWE study by Abonour et al. 2018) reported EQ-5D utility data for HDT-ASCT eligible NDMM patients.^{32, 33}

The RCT by Ludwig et al. 2013 reported utilities for patients who received BTd induction therapy with and without cyclophosphamide but was not considered relevant for the economic analysis for the following reasons:

- Following TA763, DBTd showed improved clinical outcomes in comparison to BTd.^{12, 34} Thus, utilities from a BTd population were not considered representative of the expected utilities for DBTd treatment.
- Data from Ludwig et al. 2013 were considered out of date given its publication date.³³
- Utilities in Ludwig et al. 2013 were only collected for patients receiving induction therapy rather than the full treatment sequence.³³

The RWE study by Abonour et al. 2018, reported utilities for patients in a United States (US) registry who received ASCT and did or did not receive maintenance therapy.³² The study was also considered not suitable for the economic analysis given the following reasons:

- The study excluded patients that had received consolidation therapy prior to maintenance and reported utilities considered implausibly high when compared to UK population norms for individuals aged 55-64, given the clinical burden of MM.
- Moreover, these utilities were higher than the utilities derived from the PERSEUS trial and the utilities used in previous NICE TAs for patients with HDT-ASCT eligible NDMM. This approach aligns with the approach taken in the evaluation for DBTd I+C therapy (TA763).^{12, 34}

None of the other 42 identified HRQoL studies elicited utility values from a UK population using the EQ-5D, and therefore, were not considered in line with the NICE reference case.

EQ-5D-5L data for patients receiving DBLd-DL and BLd-L from GRIFFIN and PERSEUS were both reported in Silbermann et al. 2024 and Sonneveld et al. 2024, respectively.^{35, 36} In response to clarification question 15, the company provided a naïve comparison of the utility values from the PERSEUS compared to the GRIFFIN trial, with scores presented in Table 4.11.²⁹ The naïve comparison suggests the data are broadly similar across trial arms and also broadly comparable between trials, though the PERSEUS values appear slightly more conservative in reflecting patient quality of life (QoL).

Table 4.11. EQ-5D-5L utility scores at baseline, I+C+M phase in the PERSEUS and GRIFFIN trials; ITT analysis sets

PERSEUS trial	BLd-L	DBLd-DL	Source
Baseline	████	████	PERSEUS Clinical Study Report ²¹
Induction Cycle 3 Day 1	████	████	
Pre-ASCT	████	████	
Consolidation Cycle 5 Day 1	████	████	
Maintenance Cycle 7 Day 1	████	████	
Maintenance Cycle 25 Day 1	████	████	
GRIFFIN trial	BLd-L	DBLd-DL	Source
Baseline	████	████	GRIFFIN Clinical Study Report ³⁷
Induction Cycle 3 Day 1	████	████	
Induction Cycle 4 Day 21	████	████	
Consolidation Cycle 6 Day 21	████	████	
Month 6 of maintenance	████	████	
Month 24 of maintenance	████	████	
Based on Tables 14 and 15 of the EAG Clarification Questions Response. ²⁹ ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide and dexamethasone; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DL = daratumumab with lenalidomide; EAG = External Assessment Group; EQ-5D-5L = EuroQol Group Five Dimensions Five Levels; I+C+M = induction, consolidation and maintenance; ITT = intention-to-treat; L = lenalidomide			

The company preferred using PERSEUS data in their base-case analysis because EQ-5D-5L data were available in the registrational trial for DBLd-DL, which is the main treatment of interest supporting the daratumumab maintenance label extension, and also because utilities from other treatments were considered less relevant for the current submission. Therefore, the company mapped PERSEUS trial EQ-5D-5L data to derive EQ-5D-3L utility values for the economic analysis. The mapping approach involved mapping the EQ-5D-5L descriptive scores from the PERSEUS trial, onto the 3L UK value set using the mapping function developed by Hernandez-Alava et al. 2017 through the NICE DSU, using the EEPRU dataset (Hernandez-Alava 2020), in accordance with the NICE methods manual.^{38, 39}

4.2.7.1 HSUVs

For the base-case economic analysis, the company used utility data from the PERSEUS trial for the induction, ASCT, consolidation and maintenance treatment phases. The company considered the EQ-5D-5L utility data between the 2 treatment arms in the PERSEUS trial as similar (shown in Table 4.11 above), without significant differences in the least squared (LS) mean change from baseline up to maintenance cycle 34 day 1.²¹ Given this, utility values were pooled across treatment arms to increase sample size in the analysis, and were applied in the economic analysis to both DBLd-DL and DBTd-L arms.

Compliance rates for EQ-5D-5L at baseline were above █████ in both treatment arms, and above █████ for most timepoints up to cycle 34 for maintenance therapy. Post-censoring-collected PFS values were excluded given that the pre- and post-PD states cannot be determined after the censoring date.

4.2.7.1.1 PF health State

Utilities for induction, ASCT and consolidation treatment phases were derived based on descriptive statistics and LS adjusted means output from a univariate linear regression model. The number of observations with non-missing utility values and the distribution of observed utility values were summarised by treatment phase. For the maintenance phase, the average utility was calculated using a repeated-measures linear-mixed-effects model with a random intercept per subject to account for repeated measurements of the same patients during maintenance and over multiple pre-progression cycles. The final utility values per health state are presented in Table 4.12.

4.2.7.1.2 PD health state

Patients experiencing a progression event during the PERSEUS trial were grouped to estimate the mean post-progression EQ-5D-5L utility value. For patients that progressed but did not die, post-progression utility was defined as the average utility at the date of, or after, confirmed progression based on a computerised algorithm. All post-progression observations, whether scheduled or unscheduled, were included in the analyses, with a subject-specific random intercept used to account for repeated measurements across cycles and post-progression assessments

For the base-case analysis the company employed utility age-adjustment over the model time horizon, in line with the UK population norm values for EQ-5D, as reported in the HSE 2014 dataset by NICE DSU, using methods from Hernández-Álava et al. 2022.³⁹

4.2.7.1.3 AEs

The company also applied one-off decrements in utility to account for the proportion of patients who experienced AEs associated with induction, ASCT or consolidation, or maintenance therapy during the PERSEUS and CASSIOPEIA trials. The duration of AEs and the AE disutilities were informed by previous NICE evaluations for daratumumab-based combination therapies in patients with NDMM.^{12, 40}

4.2.7.1.4 Summary of the utilities used in the economic model

A summary of the health state utilities, AE durations and disutilities is presented in Table 4.12. In a scenario analysis the company used the HSUVs that were used in the NICE TA for DBTd (TA763),¹² which were sourced from the CASSIOPEIA trial for the PF health state, and TA311 for the PD health state.⁴¹

Table 4.12: EQ-5D utilities used in the CEA

Treatment phases	Base-case		Scenario analysis (TA763) ¹²	
	Mean (SE)	Source	Mean (SE)	Source
PF - Induction		PERSEUS EQ-5D-5L data, cross-walked to UK EQ-5D-	0.57 (0.009)	Utility for induction (CASSIOPEIA) ¹²
PF - ASCT			0.57 (0.009)	
PF - Consolidation			0.68 (0.007)	Utility for post-induction to post-consolidation response (CASSIOPEIA) ¹²

PF - Maintenance		3L value set ^{21, 39}	0.73 (0.005)	Utility for post-consolidation (CASSIOPEIA) ¹²
PD			0.69 (0.010)	NICE TA311 and Van Agthoven et al. 2004 ^{41, 42}
AEs	Duration (weeks)		Mean disutility	Source
Febrile neutropenia	4		-0.39	TA763 ¹²
Peripheral sensory neuropathy	4		-0.07	
Stomatitis	4		-0.15	
Anaemia	25.71		-0.31	TA917 ⁴⁰
Diarrhoea	1.71		-0.10	
Lymphopenia	2.21		-0.07	
Neutropenia	1		-0.15	
Pneumonia	1		-0.19	
Thrombocytopenia	1		-0.31	
Leukopenia	2.1		-0.07	
Hypokalemia	1.63		-0.07	
Hypertension	1.63		-0.15	
Based on Table 65 and Table 66 of the CS ¹ AEs = adverse events; ASCT = autologous stem cell transplantation; CEA = cost-effectiveness analysis; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; NICE = National Institute for Health and Care Excellence; PD = progressive disease; SE = standard error; TA = Technology Appraisal; UK = United Kingdom				

EAG comment: The EAG was unable to identify the mixed model analyses that the company conducted to estimate utility values for the maintenance and PD health states. Nonetheless, in general the EAG finds the company's approach to estimating utilities reasonable. Following clarification question (B13), the company acknowledged that utility values from PERSEUS exceed those used in TA763, and explained that the discrepancy is likely reflecting the later enrolment period of PERSEUS (2019–2020) versus CASSIOPEIA (2015–2017) and the associated advances in MM management, which has potentially improved prognosis for NDMM patients and led to higher utility values.²⁹ The EAG considers the company's explanation plausible and prefers to include the utility values from TA763 in scenario analysis.

In clarification response B14, the company explained that the higher utilities assigned to the PD health state compared with PF induction, ASCT, and consolidation reflect the psychological impact of diagnosis and HRQoL burden of the treatment trajectory of HDT-ASCT-eligible patients after diagnosis. The company also acknowledged that applying a single utility value to the PD health state is a simplifying assumption, likely leading to an overestimation of utility across the PD period, as most patients in PERSEUS received only one subsequent line of therapy (the proportion of patients receiving one or more subsequent lines of treatments was █% in the BLd-L arm and █% in the DBLd-DL arm) (clarification response B14). They further noted that this assumption is likely conservative for the health economic outcomes, since a higher proportion of patients reach the PD health state in the DBTd-L arm compared with the DBLd-DL arm.²⁹

4.2.8 Resources and costs

In line with the study perspective (NHS in England), the following cost components were included in the economic model: drug acquisition costs, costs of concomitant medications, drug administration costs, costs of HDT-ASCT, monitoring costs, cost of terminal care, costs associated with management of AEs, cost of MRD testing (for DBLd-DL arm only) and cost of subsequent treatments. Section 4.2.8.2 to 4.2.8.10 describe how resource use and costs were determined for each cost category.

4.2.8.1 Resource use and costs data identified in the review

The company's SLR identified 43 studies; from which 17 were economic evaluations and 26 costs/resource use studies. From the costs/resource use studies, 19 reported on HCRU in patients with NDMM, with four studies (across five publications) only including patients with HDT-ASCT eligible patients with NDMM. It is not mentioned whether or to what extent these studies were considered relevant for the current submission. Further details can be found in Appendix E of the CS.⁵

4.2.8.2 Drug acquisition costs

Drug acquisition costs for the individual therapies within the I+C+M phases included in the model are presented in Table 4.13. These calculations were based on the dosing regimens (detailed in Table 68 of the CS) that were derived from the treatment protocols specified in the PERSEUS and CASSIOPEIA trials.¹ One exception was that for DBTd, daratumumab dose was based on the subcutaneous (SC) formulation (fixed dose of 1,800 mg), which was available as a result of a licence extension in June 2020, rather than on the intravenous (IV) formulation of daratumumab used in the CASSIOPEIA trial.

Table 4.13: Drug acquisition costs

Daratumumab and bortezomib							
	Dose per admin.	Total dose per admin.	Vial size	Cost per vial	Vials per admin.	Cost per admin.	Source
Daratumumab	1,800 mg	1,800 mg	1,800 mg	£4,320	1	£4,320	BNF 2025 ⁴³
Bortezomib	1.3 mg/m ²	█ mg	3.5 mg	£20.30 ^a	1	£20.30 ^a	eMIT 2024 ⁴⁴
Lenalidomide, thalidomide and dexamethasone							
	Unit size		Pack size		Cost per pack		Source
Lenalidomide	25 mg		21		£36.10 ^a		eMIT 2024 ⁴⁴
Thalidomide	50 mg		28		£240.67 ^a		
Dexamethasone	2 mg		50		£2.19 ^a		
Based on Tables 69 and 70 of the CS ¹							
^a Cost sourced from the electronic model. These differed from those presented in the CS, as the company provided an updated base-case analysis during the clarification phase, using updated eMIT costs (December 2024 prices, replacing July 2024 prices) which were not available at the time of submission.							
admin = administration; BNF = British National Formulary; CS = company submission; eMIT = Electronic Market Information Tool; mg = milligram							

In the base-case analysis, drug wastage was accounted for, as it was assumed no vial sharing would occur in clinical practice. Therefore, the number of vials required per administration was rounded up to the nearest whole integer. The impact of wastage on the model results was expected to be negligible, as bortezomib is the only drug where vial sharing might be considered and is common to both DBLd-DL and DBTd-L.

In clinical trials, patients do not always receive the full intended doses of their assigned treatment, but often receive fewer doses than plan, which may also occur in clinical practice. Therefore, clinical trial data may better reflect the efficacy of the dose received rather than the intended dose. To account for this, dose intensity was considered in the cost calculations of the base-case analysis by adjusting the drug acquisition cost in proportion to the doses received in the PERSEUS or CASSIOPEIA trial (i.e., the relative dose intensity (RDI), calculated as the average number of doses per treatment cycle received, divided by the doses per cycle according to the trial design). As shown in Table 4.14, dose intensity was considered separately for each component of a combination treatment.

Table 4.14: RDIs for I+C+M therapy

Treatment	Component	RDI	Source
Induction			
DBLd	Daratumumab	██████	PERSEUS ²¹
	Bortezomib	██████	
	Lenalidomide	██████	
	Dexamethasone	██████	
DBTd	Daratumumab	██████	CASSIOPEIA ⁴⁵
	Bortezomib	██████	
	Thalidomide	██████	
	Dexamethasone	██████	
Consolidation			
DBLd	Daratumumab	██████	PERSEUS ²¹
	Bortezomib	██████	
	Lenalidomide	██████	
	Dexamethasone	██████	
DBTd	Daratumumab	██████	CASSIOPEIA ⁴⁵
	Bortezomib	██████	
	Thalidomide	██████	
	Dexamethasone	██████	
Maintenance			
DL	Daratumumab	██████	PERSEUS ²¹
	Lenalidomide	██████	
L	Lenalidomide	██████	
Based on Table 71 of the CS ¹ CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL= daratumumab with lenalidomide; I+C+M = induction, consolidation and maintenance; L = lenalidomide; RDI = relative dose intensity			

EAG comment: As noted above, for DBTd, the daratumumab dose was based on the SC formulation (a fixed dose of 1,800 mg) following a licence extension, rather than on the IV formulation of daratumumab used in the CASSIOPEIA trial. When asked for clarification,²⁹ the company explained that in previous TA763,¹² daratumumab had also been modelled using the SC formulation. In TA763, a scenario analysis was conducted in which the weight-based IV dose of daratumumab (16 mg/kg) was used in the cost calculations for DBTd. This was found to have only a limited effect on the incremental-cost effectiveness ratio (ICER). Furthermore, the company highlighted that the European Medicines

Agency (EMA) has accepted evidence of non-inferiority for SC versus IV daratumumab, based on the COLUMBA trial.⁴⁶ The company concluded that, in current clinical practice, the vast majority of patients would be expected to receive daratumumab by the SC route (for DBLd or DBTd), as it represents an equally efficacious, less costly, and more convenient route of administration for patients. On this basis, the company considered modelling daratumumab for both DBLd and DBTd using the SC formulation to be appropriate. The EAG agrees that this seems to be a reasonable approach.

In response to clarification question B18,²⁹ the company explained that drug acquisition costs for bortezomib, as well as for lenalidomide, thalidomide, and dexamethasone, were sourced from eMIT using July 2024 values (with references added in Tables 69 and 70 of the CS).¹ In the updated electronic model, these unit prices were revised to December 2024 values. Updating the unit prices had only a minor impact on the ICER, increasing it from £23,986 to £ 24,111, as shown in the company's response to clarification question B18.²⁹ Although the prices of bortezomib, lenalidomide, thalidomide, and dexamethasone were updated in the electronic model, this was not done in Tables 69 and 70 of the CS, which still report the July 2024 values.¹ This explains why the prices listed in Table 4.13 above differ from those in Tables 69 and 70 of the CS.

RDI was incorporated into the cost calculations of the company's base-case analysis, to reflect that in clinical trials patients did not always receive the full intended doses of their assigned treatment but often received fewer doses than planned. It remains uncertain, however, whether, and to what extent, this occurs in routine clinical practice. Setting the RDI for all treatment components to 100% had a minimal impact on the model results.

4.2.8.3 Costs of concomitant medications

The cost of concomitant medications was included in the model during the induction and consolidation treatment phases. These medications comprised analgesics, antacids, antibiotics, antithrombotics, antiviral prophylaxis, bisphosphonates, and antihistamines. The proportions of patients receiving each concomitant medication are presented in Table 4.15. For the induction phase, these proportions were based on concomitant medication use in the PERSEUS and CASSIOPEIA trials,^{21, 45} while the proportions for the consolidation phase were assumed to be the same as for induction. Concomitant medications for subsequent treatments were not included in the model.

The total cost of concomitant medications was applied in each I+C treatment cycle, depending on the proportion of patients remaining on treatment (according to TTD). The calculations were based on the unit prices shown in Table 4.16.

Table 4.15: Proportion of patients receiving concomitant medications during I+C therapy

Treatment		Concomitant medication							Source
		Analgesics	Antacid	Antibiotics	Antithrombotic	Antiviral prophylaxis	Bisphosphonate	Antihistamine	
DBLd	Daratumumab	████	█	████	█	█	█	████	PERSEUS ²¹
	Bortezomib	█	█	█	█	█	████	█	
	Lenalidomide	█	████	█	████	████	█	█	
	Dexamethasone	█	█	█	█	█	█	█	
DBTd	Daratumumab	████	█	████	█	█	█	████	CASSIOPEIA ⁴⁵
	Bortezomib	█	█	█	█	█	████	█	
	Thalidomide	█	████	█	████	████	█	█	
	Dexamethasone	█	█	█	█	█	█	█	

Based on Table 73 of the CS¹
CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; I+C = induction and consolidation

Table 4.16: Unit costs of concomitant medications

Concomitant medication		Dosing regimen	Strength	Drug units per pack	Cost per pack ^a	Cost per administration ^a	Source
Analgesics	Oral paracetamol	825 mg	500 mg	100	£0.66	£0.01	eMIT 2024 (DDM003, Paracetamol) ⁴⁴
Antacid	Omeprazole	150 mg	20 mg	28	£0.39	£0.11	eMIT 2024 (DAI012, Omeprazole) ⁴⁴
Antibiotics	Oral amoxicillin	960 mg	500 mg	100	£6.85	£0.13	eMIT 2024 (DEA397, Amoxicillin) ⁴⁴
Antithrombotic	Warfarin	3 mg	3 mg	28	£0.41	£0.01	eMIT 2024 (DBH083, Warfarin) ⁴⁴
Antiviral prophylaxis	Oral acyclovir	400 mg	800 mg	35	£2.02	£0.03	eMIT 2024 (DER025, Acyclovir) ⁴⁴
Bisphosphonate	Oral alendronic acid	4 mg	70 mg	4	£0.35	£0.00	eMIT 2024 (DFF047, Alendronic acid) ⁴⁴
Antihistamine	Oral/IV hydroxyzine	37.5 mg	30 mg	30	£0.75	£0.03	BNF 2025 (Hydroxyzine 25mg tablets - Medreich Plc) ⁴⁷

Based on Table 72 of the CS¹

^a Cost sourced from the electronic model. Except for antihistamine, these differed from those presented in the CS, as the company provided an updated base-case analysis during the clarification phase, using updated eMIT costs (December 2024 prices, replacing July 2024 prices) which were not available at the time of submission.

BNF = British National Formulary; CS = company submission; eMIT = Electronic Market Information Tool; IV = intravenous; mg = milligram

EAG comment: In the CS (Table 72),¹ the cost per administration of warfarin was listed as £1.54. According to the EAG, this should be £0.01. This corresponds to the cost per administration that the company used in its electronic model.⁴⁸ The cost per administration of £0.01 for warfarin was included in Table 4.16 above.

Next to this, after the clarification phase the costs per pack (and consequently the costs per administration) were updated in the electronic model to reflect Electronic Market Information Tool (eMIT) December 2024 prices (replacing the July 2024 values). The only exception was the cost of antihistamine, which was not updated as it was sourced from the BNF. This explains the discrepancies between the costs listed in Table 4.16 and those in Table 72 of the CS,¹ which had not been updated to December prices.

4.2.8.4 Drug administration costs

Drug administration costs were included in the economic analysis for induction, consolidation, maintenance, and subsequent therapies, under the assumptions described next. Administration of IV treatment requires one outpatient visit that may involve additional nursing and pharmacist preparation time. Administration of SC treatment (i.e., daratumumab and bortezomib) requires one outpatient visit with a specialist cancer nurse. The associated costs are summarised in Table 4.17. In the base-case analysis, no additional costs were applied for oral treatment regimens (i.e., L, thalidomide, and dexamethasone). However, a scenario analysis was conducted in which administration costs for oral treatments were included.

Table 4.17: Drug administration costs

Drug	Administration parameter	Cost	Source
Daratumumab, bortezomib, teclistamab	SC administration	£115.36	NHS National Schedule of Costs 2023/24; N10AF Specialist Nursing, Cancer Related, Adult, Face to face
Bortezomib			
Carfilzomib, cyclophosphamide, elotuzumab, belantamab mafodotin	First IV administration	£597.91	NHS National Schedule of Costs 2023/24; SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance, Total HRG
	Subsequent IV administration	£430.23	NHS National Schedule of Costs 2023/24; SB15Z Deliver Subsequent Elements of a Chemotherapy Cycle, Total HRG
Based on Table 74 of the CS ¹ CS = company submission; HRG = healthcare resource group; IV = intravenous; NHS = National Health Service; SC = subcutaneous			

EAG comment: In the company's economic model,⁴⁸ the administration costs for SC administration was listed as £12.82, rather than £115.36 as stated in the CS.¹ After the clarification phase (see clarification question B17),²⁹ the cost of SC administration was amended to £115.36, which had a small positive impact on the ICER. In its response to that clarification question, the company added that, in clinical practice, the true administration cost is expected to be lower (than £115.36), as the full 45 minutes of time assumed in the unit cost would not be required to administer a single SC injection.

4.2.8.5 Costs of HDT-ASCT

The costs associated with ASCT were applied in the model for the proportion of PF patients modelled to receive ASCT following induction therapy. The proportion of patients assumed to undergo ASCT following DBLd induction therapy was based on the PERSEUS trial and set at [REDACTED]%. Following DBTd induction therapy, [REDACTED]% of patients were assumed to undergo ASCT, based on the CASSIOPEIA trial. Furthermore, following disease progression, patients under 70 years could receive a second ASCT – this was therefore considered in the model as a subsequent therapy. Based on data from the PERSEUS trial, [REDACTED]% of patients receiving DBLd underwent a second ASCT post-progression. For DBTd, this proportion was assumed to be equal.

The ASCT costs considered in the analysis captured the cost of stem cell mobilisation and the cost of the transplant procedure itself. As shown in Table 75 of the CS,¹ these were set at £1,856.67 and £24,356.40, respectively, sourced from the NHS National Schedule of Costs 2023/24.

EAG comment: In the economic model, it was assumed that [REDACTED]% of the patients in the DBLd arm and [REDACTED]% of the patients in the DBTd arm undergo ASCT following induction therapy. One could question whether these proportions are affected by the COVID-19 pandemic, raising the possibility that currently 100% of patients might receive their planned ASCT. In response to clarification question B12,²⁹ the company explained that COVID-19 did not significantly influence the overall proportion of patients receiving ASCT in either the PERSEUS or CASSIOPEIA trial. The company emphasised that in trials, and in clinical practice, a subset of patients is unlikely to receive their planned ASCT for various reasons, such as disease progression, physician's decision, AEs following induction therapy, or stem cell mobilisation. As such, it is not realistic to assume that 100% of patients in clinical practice would receive ASCT, even in a post-COVID setting. The proportions used in the model can thus be considered reflective of UK clinical practice. For that matter, the EAG noted that assuming that 100% of patients (in both the DBLd arm and the DBTd arm) undergo ASCT following induction therapy had only a minor impact on the base-case ICER.

4.2.8.6 Monitoring costs

Ongoing monitoring costs were included in the economic model, with the frequency of monitoring visits and tests depending on whether a patient was in the PF or PD health state (see Table 4.18). The type and frequency of monitoring visits and tests included during the PF health state (split by induction, consolidation, and maintenance) were informed by the CASSIOPEIA study protocol, recommendations in the European Society for Medical Oncology (ESMO) clinical guideline, and those used in a previous NICE TA (TA311) for HDT-ASCT eligible NDMM.^{24, 41, 49} The type and frequency of monitoring during the PD health state was based on post-progression resource use in a previous NICE TA (TA228) in the front-line MM setting.⁵⁰ The frequency of medical resource use in each health state was assumed to be the same for DBLd with DL maintenance, and DBTd with L maintenance, in alignment with the approach taken in NICE TA TA763 for DBTd.¹² Costs were derived by multiplying the frequencies of monitoring resource use by the corresponding unit costs presented in Table 4.18.

Table 4.18: Frequency (by health state) and unit costs of routine follow-up care

Item	Frequency per cycle				Unit cost (£)	Source
	PF (induction) ^a	PF (consolidation) ^b	PF (maintenance) ^c	PD ^d		
Haematologist initial visit	0.25	-	-	-	296.72	NHS NSC 2023/24; 303; WF01B Clinical Haematology; Non-Admitted Face-to-Face Attendance, First. Includes both consultant and non-consultant led (in line with TA917) ⁵¹
Haematologist follow-up visit	0.50	0.50	0.13	0.23	192.29	NHS NSC 2023/24; 303; WF01A Clinical Haematology; Non-Admitted Face-to-Face Attendance, Follow-up. Includes both consultant and non-consultant led (in line with TA917) ⁵¹
Full blood count	0.14	0.14	0.14	0.39	3.10	NHS NSC 2023/24; PATH05; DAPS Haematology
Urine disease evaluations (UPEP)	0.13	0.13	0.13	0.10	1.53	NHS NCS 2023/24; PATH04; DAPS Clinical biochemistry
Calcium	0.13	0.13	0.13	-		
Serum free light chain	0.03	0.03	0.03	-		
Serum disease evaluations (SPEP)	0.13	0.13	0.13	0.19		
Liver function tests	0.10	0.10	0.10	-	10.68	NHS NSC 2023/24; PATH04; DAPS Clinical biochemistry value, multiplied by seven
Based on Tables 82 and 83 of the CS¹ ^a Source: CASSIOPEIA²⁴ ^b Assumed equal to PF (induction) ^c Source: CASSIOPEIA²⁴ ^d Source: NICE TA228⁵⁰; Picot et al. 2011 CS = company submission; NHS = National Health Service; NSC = National Schedule of Costs; PD = progressive disease; PF = progression-free; SPEP = serum protein electrophoresis; TA = Technology Appraisal; UPEP = urine protein electrophoresis						

EAG comment: As mentioned above, monitoring costs were included in the economic model for the induction, consolidation, and maintenance phases of treatment, as well as for the PD health state. In response to clarification question B20,²⁹ the company provided a rationale for not including monitoring costs for HDT-ASCT. The company explained that patients are monitored during both the I+C phases. Since patients first receive induction, then proceed straight to receiving ASCT, which is immediately followed by consolidation therapy, monitoring before and after ASCT is captured by the ongoing monitoring costs during the I+C phases - an approach also applied in NICE TA (TA763) for DBTd.¹²

The EAG understands that this approach, also used in TA763, accounts for monitoring costs during the I+C phases. However, the EAG is unclear whether additional monitoring costs, specific to HDT-ASCT, should have been included separately in the cost calculations. After all, such monitoring costs seem not to be covered by the unit cost of HDT-ASCT (£1,856.67 for stem cell mobilisation and £24,356.40 for the transplant procedure itself, as presented in Section 4.2.8.5) and patients in the model may spend more than one cycle in HDT-ASCT. Nevertheless, the EAG expects that including potential monitoring costs for HDT-ASCT would be unlikely to substantially affect the CE results.

4.2.8.7 Cost of terminal care

A terminal care cost was applied as a one-off cost at the time of death for patients who died. Based on Personal Social Services Research Unit (PSSRU) 2024-unit costs,⁵² the cost applied in the model was £13,409. This included costs of hospital care (inpatient, outpatient, and accident & emergency services) as well as social care (residential/nursing and home care).

4.2.8.8 Costs associated with management of AEs

The cost of managing AEs occurring during the induction, ASCT, consolidation, and maintenance treatment phases was included in the base-case economic analysis. The proportions of patients experiencing specific AEs in the DBLd-DL and DBTd-L arms during the I+C treatment phases, as well as during the maintenance treatment phase, are given in Table 4.19. The unit costs per event, derived from NHS reference costs 2023-2024, are also presented in Table 4.19.

Table 4.19: Incidence of Grade 3/4 AEs (I+C+M phases) and their unit costs

AE	Incidence				Unit cost (£)	Source
	I+C phases ^a		Maintenance phase ^b			
	DBLd	DBTd	DL	L		
Neutropenia	████	27.60%	46.9%	41.8%	2,058.15	NHS NSC 2023/24, weighted average of SA08G-SA08J (Other Haematological or Splenic Disorders with CC score 0-6+)
Lymphopenia	████ ^c	17.00%	10.4%	5.1%		
Thrombocytopenia	████	11.00%	-	-	2,515.70	NHS NSC 2023/24, weighted average of SA12G-SA12K (Thrombocytopenia with CC score 0–8+)
Febrile neutropenia	████	████	-	-	2,522.59	NHS NSC 2023/24, weighted average of SA35A-SA35E (Agranulocytosi with CC score 0-13+)
Stomatitis	████	12.70%	-	-	1,367.81	NHS NSC 2023/24, weighted average of CB02A-CB02F (Non-malignant, ear, nose, mouth, throat or neck disorders, with interventions (with CC score 1-4) and without interventions (with CC score 0-5+)
Peripheral sensory neuropathy	████	8.80%	-	-	1,263.06	NHS NSC 2023/24, weighted average of WH08A-WH08B (Unspecified pain with CC score 0 and 1+)
Anaemia	████	████	-	-	1,544.29	NHS NSC 2023/24, weighted average of SA04H-SA04L (Iron Deficiency Anaemia with CC Score 0–14+)
Pneumonia	████	████	5.2%	4.1%	2,655.55	NHS NSC 2023/24, weighted average of DZ11K-DZ11V (Lobar, Atypical or Viral Pneumonia, with Multiple Interventions (CC Score 0–14+), with Single Intervention (CC Score 0–13+) and without Interventions (CC Score 0–14+))

AE	Incidence				Unit cost (£)	Source
	I+C phases ^a		Maintenance phase ^b			
	DBLd	DBTd	DL	L		
Diarrhoea	████	████	3.1%	5.1%	1,798.79	NHS NSC 2023/24, weighted average of FD01A-FD01J (Gastrointestinal Infections with Multiple Interventions (CC Score 0–4+), and without Interventions (CC Score 0–8+))
Leukopenia	-	-	9.4%	6.1%	1,887.11	NHS NSC 2023/24, weighted average of SA08G–SA08J: Other Haematological or Splenic Disorders, with CC Score 0–6+, nonelective long stay and short stay
Hypokalemia	-	-	7.3%	6.1%	1,792.32	NHS NSC 2023/24, weighted average of KC05G–KC05N: Fluid or Electrolyte Disorders, with Interventions (CC Score 0–5+) and without Interventions (CC Score 0–5+), nonelective long stay and short stay
Hypertension	-	-	7.3%	4.1%	801	NHS NSC 2023/24, EB04Z: Hypertension, non-elective long stay and short stay
Based on Tables 63, 64, and 84 of the CS ¹						
^a Source: PERSEUS (DBLd) ²¹ and CASSIOPEIA (DBTd) ²⁴						
^b Source: AURIGA ⁵³						
^c Percentage taken from the updated CS after clarification (a different percentage was mentioned in the original CS)						
AEs = adverse events; CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab and lenalidomide; I+C+M = induction, consolidation and maintenance; L = lenalidomide; NHS = National Health Service; NSC = National Schedule of Costs						

EAG comment: On page 178 of the CS,¹ the company explained that Grade 3 or 4 AEs occurring in $\geq 5\%$ of patients in the PERSEUS or CASSIOPEIA trials were included in the base-case analysis. This 5% threshold was considered appropriate to capture AEs that would impact patients consistently enough to have validity in a real-world setting where AEs are monitored less strictly compared with a clinical trial setting. However, the EAG noted that diarrhoea was also included as an AE, despite being reported in only [REDACTED]% of patients in the PERSEUS trial and [REDACTED]% in the CASSIOPEIA trial. In response to clarification question B22,²⁹ the company clarified that the rule applied should have been described as “*AEs of Grade 3 or 4 occurring in $\geq 5\%$ of patients in the PERSEUS, CASSIOPEIA or AURIGA trials were included in the base case economic analysis.*” This explains why diarrhoea was included as an AE in the model.

The EAG also noted that the percentage for lymphopenia in the DBLd arm used in the electronic model ([REDACTED]%) differed from the value reported in the CS ([REDACTED]%, as shown in Table 63 of the CS).^{1, 48} In response to clarification question C2,²⁹ the company explained that the correct value should be [REDACTED]% and that the CS has been updated accordingly. Furthermore, in this response, the company clarified that a publication by Moreau et al. reported safety data for the maintenance phase of the CASSIOPEIA trial.⁹ This explains why some data in Table 63 of the CS,¹ as well as in Table 4.19 above (that is, the data that were reported in this publication) were not marked as confidential.

In the economic model,⁴⁸ the proportion of patients experiencing diarrhoea during the maintenance phase was incorrectly inputted as [REDACTED]% and [REDACTED]% for the DL and L arms, respectively. In the updated model, the company corrected these values to [REDACTED]% and [REDACTED]% for the DL and L arms, respectively (see also the company’s response to clarification question C3).²⁹

On page 199 of the CS,¹ the total cost of AE management during the maintenance phase was reported as £[REDACTED] for DBLd-DL and £[REDACTED] for DBTd-L, whereas in the economic model these costs were reported as £[REDACTED] for DBLd and £[REDACTED] for DBTd.⁴⁸ In their response to clarification question B21,²⁹ the company resolved this discrepancy by explaining that both the values reported in the CS and those reported in the economic model were incorrect (due to a typographical error in the CS and due to wrong settings in the electronic model). According to the company, the correct values are £[REDACTED] for DBLd and £[REDACTED] for DBTd. However, in the updated electronic model, these costs were reported as £[REDACTED] and £[REDACTED], respectively. The EAG assumed that these costs were correct (as also reported in Table 5.2 below).

4.2.8.9 Cost of minimal residual disease testing

In line with the licence for daratumumab, daratumumab maintenance treatment is administered until disease progression. However, daratumumab can be discontinued for patients who achieve sustained MRD-negativity for 12 months, if they have received maintenance treatment for at least 24 months (see Section 3.3.1.6 of the CS).¹ To reflect that MRD testing is used to guide treatment decisions in patients receiving DL maintenance, MRD testing costs were included in the base-case analysis for the DBLd-DL arm.

All patients would undergo a minimum of two tests: one at 1-year post-maintenance and another one at 2-years post-maintenance. Patients could discontinue daratumumab if MRD-negativity is achieved at both assessments. Patients who were MRD-positive at the 1-year test would require additional testing at 2- and 3-years post-maintenance in order to meet the stopping criteria. Data from clinical trials of DL maintenance indicate that conversion rates from MRD-positive to MRD-negative plateau from 1-year post-maintenance, so testing beyond year 3 was not deemed necessary, as the likelihood of achieving

MRD-negativity thereafter is minimal. As such, MRD testing costs were applied as one-off costs at years 1, 2, and 3 of maintenance, for the proportion of patients undergoing MRD testing (i.e., 100% at year 1, 100% at year 2, and 8.73% at year 3). Of note, the proportion requiring a third test at year 3 was based on the proportion of patients who had their first negative MRD test after 2 years in the PERSEUS trial.

The unit cost of MRD testing was assumed to be £359.98, using flow cytometry, based on the NICE clonoSEQ technology briefing (2021).⁵⁴ This is in line with input from UK clinical experts, who indicated that MRD testing across the UK is predominantly carried out using flow cytometry rather than next-generation sequencing.²²

4.2.8.10 Cost of subsequent treatments

To reflect that patients with relapsed/refractory MM are expected to receive treatment following progression from induction, ASCT, consolidation, and maintenance therapy, the model incorporated the cost of subsequent therapies across 2nd, 3rd, and 4th lines of treatment. In accordance with the NICE position statement on the inclusion of therapies recommended via the Cancer Drugs Fund, only treatments recommended for routine funding by NICE (and not via the Cancer Drugs Fund) were considered as subsequent therapies.⁵⁵ Where relevant, second ASCTs post-progression were also included as subsequent treatment (as noted in Section 4.2.7.5).

Subsequent treatment costs were modelled based on the therapies received by HDT-ASCT eligible patients with MM who progressed following 1st line treatment, informed by UK clinical expert opinion.²² This approach was considered more relevant for UK decision making than relying on subsequent treatments received by patients in the international trials, which include treatment regimens not routinely commissioned in the UK. Table 4.20 presents a breakdown of subsequent treatments received by HDT-ASCT eligible patients with MM who progressed after 1st line, 2nd line, and 3rd line treatment, respectively.

Median treatment durations for each subsequent treatment were derived from clinical trials and used to model TTD curves, assuming an exponential distribution (i.e., a constant rate of treatment discontinuation). These modelled TTD curves were used to calculate the proportion of patients discontinuing treatment over time and, therefore, ceasing to accrue treatment-related costs. The incidence of progression in each model cycle was tracked using an aggregated PFS curve, to calculate the proportion of patients who remain progression-free over time and would switch to a subsequent line of treatment. For the 2nd- and 3rd-line therapies, an aggregated PFS curve was derived by generating a weighted average of the median PFS for subsequent treatments in the given line of therapy to derive an exponential curve. Overviews of dosing regimens and drug acquisition costs for subsequent treatments are presented in Table 4.21. Administration costs, presented in Table 4.17, were also included in the calculations.

Table 4.20: Distribution of 2nd-line, 3rd-line, and 4th-line subsequent treatments

		Distribution of treatments					Treatment duration		PFS			
							Median (months)	Source		Median (months)	Source	
2nd-line treatments		1st-line regimen received										
		DBLd-DL		DBTd-L								
	DBd	0.00%		0.00%		23.2	NICE TA897 ³⁰		27.0	NICE TA897 ³⁰		
	Cad	10.00%		10.00%		6.6	ENDEAVOR study ⁵⁶		22.2	ENDEAVOR study ^{a56}		
	CaLd	5.00%		5.00%		19.1	ASPIRE study ⁵⁷		29.6	ASPIRE study ⁵⁷		
	SBd	5.00%		5.00%		21.0	Assumed equal to PFS		21.0	NICE TA974 ⁵⁸		
	BeBd	80.00%		80.00%		36.6			36.6	NICE ID6212 ⁵⁹		
3rd-line treatments		2nd-line regimen received										
		DBd	Cad	CaLd	SBd	BeBd ^b						
	ILd	22.41%	14.94%	0.00%	0.00%	5.00%	17.7	NICE TA870 ⁶⁰		22.0	NICE TA870 ⁶⁰	
	SBd	28.01%	28.01%	24.31%	0.00%	50.00%	13.0	Assumed equal to PFS		13.0	NICE TA974 ⁵⁸	
	Ld	7.47%	3.73%	0.00%	0.00%	0.00%	11.1			11.1	NICE TA586 ⁶¹	
	PanBd	20.54%	31.75%	56.73%	81.63%	20.00%	12.5			12.5	NICE TA380 ⁶²	
	CTd	21.57%	21.57%	18.96%	18.37%	25.00%	8.7	Kwon et al. 2017		8.7	Kwon et al. 2017 ⁶³	
See 4th-line treatments		3rd-line regimen received										
		ILd	SBd	Ld	PanBd	CTd ^c						
	Tec	50.00%	60.00%	50.00%	56.00%	50.00%	11.3	Assumed equal to PFS		11.3	Liu & Krishnan 2023 ⁶⁴	
	Pd	20.00%	26.00%	20.00%	24.00%	20.00%	4.0			4.0	NICE TA427 ⁶⁵	
	D	20.00%	8.00%	20.00%	16.00%	20.00%	3.7			3.7	NICE TA783 ¹⁷	
	PanBd	10.00%	6.00%	10.00%	4.00%	10.00%	4.0			4.0	Assumption	

	Distribution of treatments	Treatment duration		PFS	
		Median (months)	Source	Median (months)	Source
Based on Tables 76, 77, and 78 of the CS ¹					
^a Based on mean PFS.					
^b Percentages taken from the updated CS after clarification (different percentages were mentioned in the original CS).					
^c Percentages taken from the electronic model, since 4th-line treatments following 3rd-line CTd were erroneously omitted from Table 78 of the CS.					
BeBd = belantamab mafodotin, bortezomib and dexamethasone; Cad = carfilzomib with dexamethasone; CaLd = carfilzomib, lenalidomide with dexamethasone; CS = company submission; CTd = cyclophosphamide, thalidomide and dexamethasone; D = daratumumab; DBd = daratumumab, bortezomib and dexamethasone; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; ILd = ixazomib, lenalidomide and dexamethasone; L = lenalidomide; Ld = lenalidomide with dexamethasone; NICE = National Institute for Health and Care Excellence; PanBd = panobinostat, bortezomib and dexamethasone; Pd = pomalidomide with dexamethasone; PFS = progression-free survival; SBd = selinexor, bortezomib and dexamethasone; TA = Technology Appraisal; Tec = teclistamab					

Table 4.21: Dosing regimens and drug acquisition costs for subsequent treatments

Treatment	Dosing regimen			Costs		
Oral	Dose per administration	Unit size	Pack size	Cost per pack (£)	Source	
Ixazomib	4 mg	4 mg	3	6,336.00	BNF 2025 ⁴³	
Panobinostat	20 mg	20 mg	6	4,656.00	BNF 2025 ⁴³	
Pomalidomide	4 mg	4 mg	21	7,995.60	BNF 2025 ⁴³	
Selinexor	100 mg	20 mg	20	9,200.00 ^a	BNF 2025 ⁴³	
IV/SC	Dose per administration	Total dose per administration	Source	Vial size	Cost per vial	Source
Belantamab mafodotin	2.5 mg/kg	██████ mg	Belantamab mafodotin SmPC	70 mg	11,784.00	NICE ID6212 ⁵⁹
				100 mg	16,848.00	
Cyclophosphamide	300 mg/m ²	██████ mg	Cyclophosphamide SmPC	1000 mg	12.80 ^a	eMIT 2024 ⁴⁴
	350 mg/m ²	██████ mg		1000 mg	12.80 ^a	
Carfilzomib	20 mg/m ²	██████ mg	Carfilzomib SmPC	10 mg	176.00	BNF 2025 ⁴³
	27 mg/m ²	██████ mg				
	36 mg/m ²	██████ mg		30 mg	528.00	
	56 mg/m ²	██████ mg		60 mg	1,056.00	
Elotuzumab	10 mg/kg	██████ mg	Elotuzumab SmPC	300 mg	1,085.00	BNF 2025 ⁴³
	20 mg/kg	██████ mg		400 mg	1,446.00	
Teclistamab	0.1 mg/kg	██████ mg	Teclistamab SmPC	30 mg	775.14	BNF 2025 ⁴³
	0.3 mg/kg	██████ mg				
	1.5 mg/kg	██████ mg		153 mg	3,952.78	

Based on Table 79, 80, and 81 of the CS¹

^a Unit price taken from the electronic model (a different price was mentioned in the CS).

BNF = British National Formulary; CS = company submission; eMIT = Electronic Market Information Tool; IV = intravenous; mg = milligram; NICE = National Institute for Health and Care Excellence; SC = subcutaneous; SmPC = summary of product characteristics

EAG comment: The EAG noted that the distribution of 3rd-line treatments following 2nd-line treatment belantamab mafodotin, bortezomib and dexamethasone (BeBd) that was reported in Table 77 of the CS (i.e., 28.57%, 35.71%, 9.52%, 26.19%, and 0.00%) differed from the distribution included in the electronic model (i.e., 5%, 50%, 0%, 20%, and 25%).^{1, 48} In response to clarification question C7,²⁹ the company clarified that those reported in the electronic model were the correct values.

A further discrepancy was identified between the CS and the electronic model regarding the cost per pack for selinexor (unit size 20 mg; pack size 20). In the CS (Table 81), the cost was reported as £2,300, whereas in the electronic model it was entered as £9,200.^{1, 48} The EAG assumed that the price used in the electronic model was correct (it corresponds to the list price of selinexor reported in TA974).⁵⁸

After clarification, the cost per vial of cyclophosphamide was updated in the economic model to reflect eMIT December 2024 prices (presented as a scenario alongside the July 2024 values).⁴⁴ However, this was not done in Table 80 of the CS,¹ which explains the difference between the price for cyclophosphamide in Table 4.21 of this report and that in Table 80 of the CS.

Finally, the EAG noted that cyclophosphamide, thalidomide, and dexamethasone (CTd) was listed in Table 77 of the CS as a 3rd-line treatment, but not in in Table 78 of the CS, which presents the 4th-line treatments by prior 3rd-line treatment received.¹ This raises the question of whether 4th-line treatments following CTd were included in the analysis. From the electronic model, it seems that they indeed were included, using the same distribution that was used for ixazomib, lenalidomide and dexamethasone (ILd) and lenalidomide with dexamethasone (Ld).

5. Cost effectiveness (CE) results

5.1 Company's CE results

5.1.1 Company's base-case

In Section 3.10 of the CS, the company presented their CE results using a discounted price for daratumumab.¹ The results shown in Table 5.1 correspond to the revised base-case produced by the company after accounting for corrections to inputs and calculations during the clarification phase. These corrections include the following:

- Fixing a referencing error in each of the model 'Engine' sheets, which impacted 4th-line treatment costs.
- Correcting the probability of diarrhoea in the maintenance phase to use the AURIGA trial, in line with the other AEs.
- Updating eMIT costs used within the model to use the December 2024 data cut. This relates to the costs of therapies within the induction, consolidation, and maintenance regimens (i.e., bortezomib, lenalidomide, thalidomide, and dexamethasone) as well as to the costs of concomitant medications and those of cyclophosphamide (one of the subsequent treatments included in the model).
- Using the higher cost for SC injection of £115.36 (NHS National Schedule of Costs 2023/24; N10AF Specialist Nursing, Cancer Related, Adult, Face to Face).

The company's base-case deterministic discounted CE results for DBLd-DL compared to DBTd-L indicated that DBLd-DL was more costly and also more effective than DBTd-L with an ICER of £25,888 per QALY gained. Disaggregated discounted costs and QALYs are shown in Table 5.2 and Table 5.3, respectively.

Table 5.1: Company base-case deterministic CE results (discounted daratumumab price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
DBLd-DL	██████	██████	██████	██████	██████	██████	25,888
DBTd-L	██████	██████	██████	-	-	-	-

Based on Table 2 of the addendum to the clarification letter response.²⁹
 CE = cost-effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Table 5.2: Disaggregated cost results (discounted daratumumab price, discounted)

	DBLd-DL (£)	DBTd-L (£)	Increment (£)
Induction/ASCT/consolidation			
Drug acquisition	██████	██████	██████
Drug administration	██████	██████	██
Concomitant medications	█	█	██
Routine monitoring	██████	██████	█
AE management	██████	██████	██
ASCT	██████	██████	██

	DBLd-DL (£)	DBTd-L (£)	Increment (£)
Maintenance			
Drug acquisition	████	████	████
Drug administration	████	█	████
Concomitant medications	██	██	██
Routine monitoring	████	████	████
MRD testing	██	█	██
AE management	████	████	██
Second-line Treatment			
Drug acquisition	████	████	████
Drug administration	████	████	██
Routine monitoring	████	████	█
3rd-line Treatment			
Drug acquisition	████	████	██
Drug administration	██	██	██
Routine monitoring	██	██	██
4th-line Treatment			
Drug acquisition	████	████	██
Drug administration	██	██	██
Routine monitoring	████	████	████
Terminal care	████	████	████
Total	████	████	████
Based on economic model submitted with the response to the clarification letter. ⁴⁸ AE= adverse event; ASCT = autologous stem cell transplantation; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; L = lenalidomide; MRD = minimal residual disease			

Table 5.3: Disaggregated QALY results (discounted daratumumab price, discounted)

	DBLd-DL	DBTd-L	Increment
Induction	████	████	████
ASCT	████	████	████
Consolidation	████	████	████
Maintenance	████	████	████
Post-progression	████	████	████
Disutilities	████	████	██
Total	████	████	████
Based on economic model submitted with the response to the clarification letter. ⁴⁸ ASCT = autologous stem cell transplantation; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; L = lenalidomide			

In addition, the company presented separately, disaggregated costs result for the I+C phase, since for this phase the company assumed equal efficacy. These can be seen in Table 5.4.

Table 5.4: Disaggregated cost results – I+C phase (discounted daratumumab price, discounted)

	DBLd (£)	DBTd (£)	Increment (£)
Induction			
Drug acquisition	██████	██████	██████
Administration	██████	██████	██
Concomitant medications	█	█	█
Monitoring	██████	██████	█
Autologous stem cell transplantation			
Transplant	██████	██████	██
Consolidation			
Drug acquisition	██████	██████	██████
Administration	██████	██████	██
Concomitant medications	█	█	█
Monitoring	██████	██████	█
All treatment phases			
Adverse events	██████	██████	██
Overall			
Total	██████	██████	██████
Based on Table 1 of Addendum to clarification letter response. ³ DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone			

Overall, based on the company's base-case results, the new technology is modelled to affect QALYs by:

- Increasing total QALYs due to patients remaining longer in the maintenance phase of treatment and shorter in post-progression. This is caused by an improvement in OS and PFS.
- Slightly reducing QALYs due to AEs.

Overall, based on the company's base-case results, the new technology is modelled to affect costs by:

- Decreasing total costs during the induction, ASCT and consolidation phases.
- Increasing total costs during the maintenance phase, mostly due to D acquisition costs. The increase in costs in the maintenance phase is approximately ██████ higher than the reduction in costs during the induction, ASCT and consolidation phases.
- Reducing costs associated to subsequent lines of treatment and terminal care.

5.1.2 Company's sensitivity and scenario analyses

5.1.2.1 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) in which all relevant input parameters were sampled simultaneously from their corresponding probability distributions over 2,000 iterations. Details of the input parameters and the probability distributions used in the PSA can be found in the "PSA Inputs" and the "Parameters" sheets of the economic model. Input parameters were estimated based on the uncertainty presented in their data sources wherever possible, otherwise, standard errors (SEs) were assumed to be 10% of the mean value. The average PSA results are summarised in Table 5.5. Although the resulting ICER is in line with the deterministic one shown in Table 5.3, there

are substantial differences between the deterministic results (total costs, £[REDACTED]; total QALYs, [REDACTED]) and probabilistic results (total costs, £[REDACTED] total QALYs, [REDACTED] for the comparator arm.

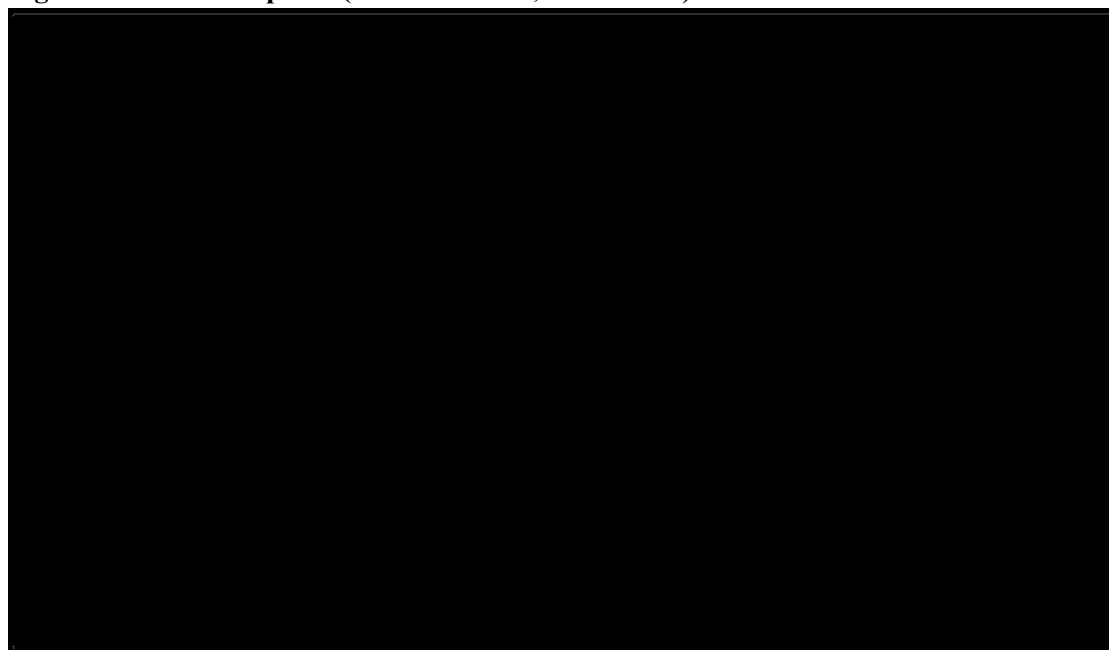
Table 5.5: Company base-case probabilistic CE results (discounted daratumumab price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
DBLd-DL	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	27,699
DBTd-L	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-

Based on Table 3 of the addendum to the clarification letter response.²⁹
 CE = cost-effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

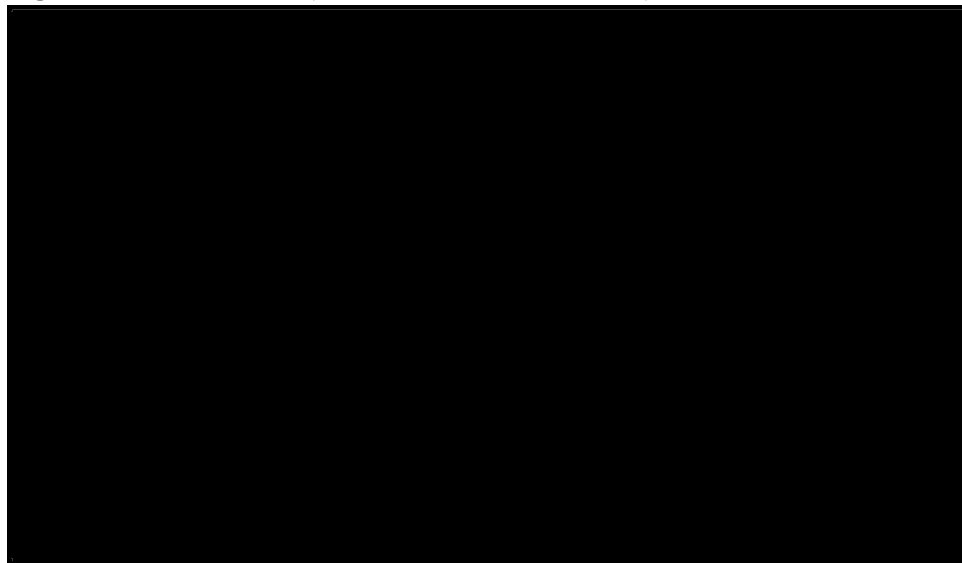
The company also plotted the PSA outcomes on a CE-plane (Figure 5.1). The majority (i.e., [REDACTED]%) of the outcomes reported positive incremental QALYs for DBLd-DL versus DBTd-L. Cost outcomes were spread across NE and SE quadrants mostly, with some outcomes in the SW quadrant. A cost-effectiveness acceptability curve (CEAC) was also calculated (see Figure 5.2). The CEAC plot indicates that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that DBLd-DL is a cost-effective alternative to DBTd-L was [REDACTED]% and [REDACTED]%, respectively.

Figure 5.1: PSA CE-plane (daratumumab, discounted)



Based on Figure 2 of the addendum to the clarification letter response.²⁹

CE = cost-effectiveness; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.2: PSA CEAC (daratumumab, discounted)

Based on Figure 3 of the addendum to the clarification letter response²⁹

CEAC = cost-effectiveness acceptability curve; PSA = probabilistic sensitivity analysis

EAG comment: As mentioned above, there is a substantial difference between the deterministic and probabilistic results for the comparator arm. This could be caused by skewed distribution assumed for the OS/PFS HRs.

When input parameters could not be estimated based on the uncertainty presented in their data sources wherever possible, the company assumed SEs to be 10% of the mean value. This choice is arbitrary and seems to be low for those parameters informed by clinical experts and for costs for which the SE would be expected to be higher than 10% in general.

5.1.2.2 Deterministic sensitivity analysis (DSA)

The company also conducted a DSA where key input parameters were varied using a lower and upper bound value of the mean $\pm$ SE. Where SEs were not available, the inputs were arbitrarily varied by $\pm 20\%$. A tornado diagram showing the top 10 most influential parameters on the incremental net health benefit (INHB) is presented in Figure 5.3. This represents updated results after clarification.

The INHB was most sensitive to the OS and PFS HRs, patient age at baseline, and the parameters of the survival curves used for extrapolation. Annual discount rates and the proportion of patients receiving ASCT were also among the top 10 of most influential parameters.

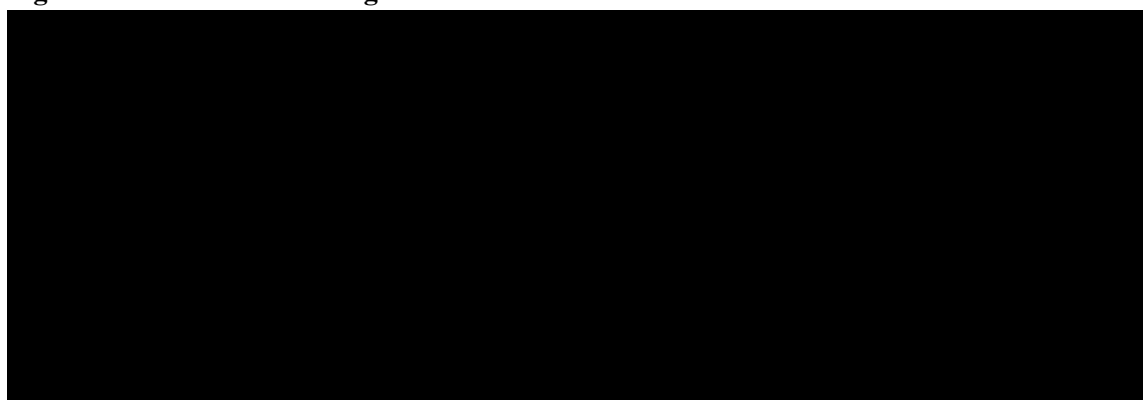
EAG comment: The company indicated that it is implausible that treatment with DBLd-DL would reduce OS compared with DBTd-L.¹ The Phase III AURIGA study provides direct head-to-head evidence of the relative benefit of adding daratumumab to L maintenance. Whilst J&J acknowledge issues regarding generalisability of the AURIGA study, there is evidence to suggest that the treatment effect in favour of DL maintenance would be at least maintained in a broader population of patients including those MRD-negative post consolidation, and prior exposed to anti-CD38 therapy. Moreover, long term survival estimates that assume an OS benefit for DBLd-DL versus DBTd-L were supported by feedback from four UK expert haematologists.

The company acknowledged uncertainty in the OS treatment effect point estimate from AURIGA, reflected in the wide CI spanning 1 (■■■■ to ■■■■), but considered that this was caused by the small number of events observed in the trial. However, this uncertainty has been explored in a scenario

analysis that assumed equivalence between treatments (OS HR = 1 – see Table 5.6). The company considered this scenario highly conservative, and resulted in DBLd-DL being dominant against DBTd-L. It should be noted that dominance is achieved due to a small gain in QALYs obtained by DBLd-DL effect delaying PFS. While maintenance costs are higher for DBLd-DL, large savings are accrued in the post-progression phase, mainly in drug acquisition costs of 2nd line treatments.

Finally, the company explained that the average age of patients with newly diagnosed MM in the NHS is 59 years, which is consistent with the NCRAS mean age of 58.7 years. Therefore, assuming plausible treatment effects (PFS HR <0.65 and OS HR <1) and the NHS practice average age of 59 years, results in positive INHB, demonstrating minimal uncertainty around parameters evaluated and that DBLd-DL remains a cost-effective treatment option versus DBTd-L. However, the EAG is unclear why the company indicated that PFS HR <0.65 and OS HR <1 are *plausible* treatment effects. This seems subjective and not in line with the 95% CIs for OS and PFS reported by the company in this submission.

Figure 5.3: DSA tornado diagram for INHB



Based on Figure 4 of the addendum to the clarification letter response.²⁹

DSA = deterministic sensitivity analysis; INHB = incremental net health benefit

5.1.2.3 Scenario analysis

The company presented the results of six scenario analyses to assess the robustness of the model against alternative inputs and assumptions. In these scenarios, different assumptions were made regarding:

- The source of the utility values (scenario 1),
- The duration for daratumumab discontinuation for patients receiving DL maintenance (scenario 2),
- TTD for patients who do not achieve sustained MRD-negative status (scenario 3),
- The difference in OS efficacy between DL and L maintenance therapies (scenario 4),
- The source of the DBLd-DL efficacy data (scenario 5),
- The discount rates for both costs and health outcomes (scenario 6).

The results of these scenario analyses, in terms of incremental costs, incremental QALYs, and ICER are shown in Table 5.6.

EAG comment: In most scenarios explored by the company, changes in ICERs were relatively modest compared with the base-case analysis. One exception was the third scenario, which assumed a log-logistic TTD curve for patients who do not achieve sustained MRD-negative status. This made the ICER for DBLd-DL less favourable, increasing it from £25,888 per QALY to £32,946 per QALY gained. The largest impact, however, came from the scenario that assumed equal OS efficacy between DL and L maintenance therapies. In this case, DBLd-DL resulted in only a minor QALY gain, but was also associated with considerable cost savings, making DBLd-DL the dominant strategy. As mentioned

above, this is caused by a small gain in QALYs obtained by DBLd-DL effect delaying PFS. Maintenance costs are higher for DBLd-DL, but large savings are accrued in post-progression, mainly in drug acquisition costs of 2nd line treatments. In any case, the EAG considers that the number of scenarios explored by the company is not sufficient to provide a balanced overview of the current structural uncertainty. In Section 5.2.4, a substantially larger number of scenario analyses are presented by the EAG.

Table 5.6: Company scenario analysis results (daratumumab, discounted)

Scenario number	Scenario description	Base-case assumption	Inc. Costs (£)	Inc. QALYs	ICER	ICER % change versus base-case
0. Base-case	N/A	N/A	██████	██████	25,888	N/A
1. Utility values from TA763	PF (Induction), mean (SE): 0.57 (0.009) PF (ASCT), mean (SE): 0.57 (0.009) PF (Consolidation), mean (SE): 0.68 (0.007) PF (Maintenance), mean (SE): 0.73 (0.005) PD, mean (SE): 0.69 (0.010)	HSUVs were assumed to be equal for both DBLd-DL and DBTd-L for each health state and derived from the EQ-5D-5L data from PERSEUS for DBLd-DL, cross-walked to the UK EQ-5D-3L value set.	██████	██████	27,721	7.08%
2. Fixed duration for patients discontinuing daratumumab	Fixed duration for daratumumab discontinuation for patients receiving DL maintenance	TTD for daratumumab discontinuation in patients who achieve sustained MRD-negativity for ≥ 12 months, after being on a minimum of 2 years of maintenance therapy, was modelled based on the observed TTD KM data in PERSEUS.	██████	██████	25,175	-2.76%
3. TTD for patients who do not achieve sustained MRD-negative status (log-logistic curve)	Log-logistic TTD curve for patients who do not achieve sustained MRD-negative status	TTD for discontinuation in patients who do not achieve sustained MRD-negativity status, was modelled based on the exponential survival curve	██████	██████	32,946	27.26%

Scenario number	Scenario description	Base-case assumption	Inc. Costs (£)	Inc. QALYs	ICER	ICER % change versus base-case
4. Maintenance therapy OS efficacy (HR=1)	4: Assumption of equal OS efficacy between DL and L maintenance therapies	Relative treatment effect derived from AURIGA trial applied to derive DBTd-L survival extrapolations based on DBLd-DL extrapolations (informed by PERSEUS ITT data)			DBLd-DL dominates	N/A
5. DBLd-DL efficacy source	5: Pooled data (PERSEUS + GRIFFIN)	The registrational trial, PERSEUS, which supported the label extension for daratumumab to cover the indication of relevance in the submission, informed the DBLd-DL efficacy data.			24,997	-3.44%
6. Discounting at 1.5%	6. Assuming a discount of 1.5% for both costs and health benefits	Discounts costs and benefits at 3.5%			26,060	0.66%
Based on Table 91 of the CS and the economic model submitted in response to the clarification letter.^{1, 48} CS = company submission; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; HR = hazard ratio; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; Inc. = incremental; ITT = intention-to-treat; KM = Kaplan-Meier; L = lenalidomide; MRD = minimal residual disease; N/A = not applicable; OS = overall survival; PD = progressed disease; PF = progression free; QALY = quality-adjusted life year; SE = standard error; TTD = time to treatment discontinuation						

5.2 EAG's additional analyses

5.2.1 *Model validation and face validity check*

In the validation Section of the CS (3.13.1),¹ the company indicated that face, internal, and external validation of the de novo CE model was undertaken in line with ISPOR-SMDM Modelling Good Research Practices.⁶⁶

Face validity included the model structure, source data (including the appropriateness of the distributions used in the probabilistic analysis of the model and the derivation and selection of base-case extrapolations used in the economic analysis) and statistical analysis design. All these aspects were reviewed by external experts, including health economic and UK clinical experts in MM.⁶⁷

Internal validity refers to quality-control procedures for verification of input data and coding. This was conducted by two reviewers not involved in the model development and in accordance with a pre-specified test plan. This was a repeatable process resulting in a checklist spreadsheet indicating the validation tasks performed and their results. Unexpected model behaviour, implementation and typing errors were identified and corrected. This technical verification process involved the following:

- Checking intermediate calculations for references, implementation and evaluation of the face validity of predicted results.
- Extreme value analysis.
- Checking the functionality of any build-in macro programs.
- Validating the logical structure of the model, mathematical formulas, sequences of calculations and the values of numbers supplied as model inputs.

By “external” validation, the company refers to the feedback provided by clinical experts used to validate key inputs and assumptions in the economic model, including subsequent treatment choices and monitoring frequencies. The company also indicated that where possible, UK sources and previous appraisals were used to inform model inputs and assumptions. While this validation exercise is valuable, the EAG would like to point out that this not what is commonly referred to as external validation – and considers this validation as part of face validity of the model structure or the validity of the input data.

The validation efforts performed on the model, as presented by the company, are categorised according to the Types of validation used in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool,⁶⁸ and summarised in Table 5.7.

EAG comment: The EAG acknowledges the company have performed various validation efforts and have no major concerns regarding the face validity of the conceptual model, the validity of the input data or the technical model verification.

There is however a lack of validation of the model outcomes. Previous daratumumab appraisals such as TA763 were used to validate the model structure, input parameters and assumptions. The EAG considers that this (or other relevant publications/HTA submission) could have been used to validate the results for the comparator arm (DBTd-L) in this appraisal to confirm that either they are in line or to explain the differences. The EAG would like to highlight a difference of [REDACTED] years in total LYs estimated for DBTd-L in TA763 (14.66) and the current appraisal ([REDACTED]).¹² From all the OS extrapolations explored by the company, the log-normal distribution results in the highest LYs estimated for DBTd-L ([REDACTED]), which is slightly more than [REDACTED] less than the estimate in TA763.

This raises some concerns regarding the validity of the model results and further exploration of this potential issue is therefore recommended.

The EAG would also like to point out several inconsistencies encountered between the data reported in the CS and used in the economic model. This was flagged by the EAG in the clarification letter but, although some improvements were made by the company, these inconsistencies remained in the documents submitted by the company in response to the clarification letter. When these inconsistencies were identified, the EAG assumed that the values in the economic model were the correct ones.

Table 5.7: Validation efforts performed on the company's model

Validation type	Sub-type	Description of company's activities	EAG comments
Conceptual model	Face validity	Validated via UK clinical experts and health economists.	Expert-informed; details scattered across documents.
	Cross validity	Through economic SLR, including previous NICE appraisals.	Conceptual alignment confirmed; differences justified.
Input data	Face validity	Validated via UK clinical experts and health economists.	Expert-informed; details scattered across documents
	Model fit testing	OS and PFS estimated using standard parametric curves. Utility values were derived from a univariate linear regression analysis of EQ-5D-5L data from the PERSEUS trial.	Goodness-of-fit statistics calculated. Validity of the long-term extrapolations discussed with experts. No details provided.
Computerised model (technical verification)	External review	Model verified by two reviewers not involved in the model development.	Inconsistencies encountered between the data reported in the CS and used in the economic model. There is a large deviation between the deterministic and PSA results. The EAG was not able to identify the cause of this discrepancy at the time this report was completed.
	Extreme value testing	Extreme value analysis conducted following a pre-specified testing plan.	No further details provided.
	Trace testing	Available in Model “Engine” sheets.	Trace testing evident.
	Unit testing	Quality control included functionality of any build-in macro programs.	Details not provided.
Model outcomes	Face validity	Assumed outcomes were reviewed by experts during advisory processes.	Not explicitly confirmed.

Validation type	Sub-type	Description of company's activities	EAG comments
	Cross validation	Not reported.	TA763 could have been used to validate the results for the comparator arm in this appraisal. Further exploration is recommended.
	Alternative input data	Not reported beyond scenario analyses.	Details not provided.
	Empirical data (dependent)*	Not reported.	Details not provided.
	Empirical data (independent)*	Not reported.	Details not provided.
Compiled by the EAG from the CS¹ *The distinction between dependent and independent validation of model outcomes against empirical data, refers to whether the empirical data used for validation were employed to develop the model (dependent) or not (independent). BSA = body surface area; CS = company submission; EAG = External Assessment Group; EQ-5D = EuroQoL-5 Dimensions; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; PSA = probabilistic sensitivity analysis; RDI = relative dose intensity; SLR = systematic literature review; TA = Technology Appraisal; UK = United Kingdom			

5.2.2 EAG's exploratory analyses using company's base-case

No exploratory analyses using the company's base-case were conducted by the EAG.

EAG comment: As explained in the next Section of this report, the EAG's preferred assumptions do not differ substantially from those of the company. For that reason, the EAG's exploratory analyses were conducted using the EAG's preferred assumptions only.

5.2.3 EAG's preferred assumptions

The changes made by the EAG (to the model received with the response to the clarification letter) can be subdivided into the following categories (according to Kaltenthaler et al 2016):⁶⁹

- Fixing errors ([FE]; correcting the model where model was unequivocally wrong).
- Fixing violations ([FV]; correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to).
- Matters of judgement ([MJ]; amending the model where the EAG considers that reasonable alternative assumptions are preferred).

After the proposed changes were implemented in the company's model, additional scenario analyses were also explored by the EAG in order to assess the impact of alternative assumptions on the CE results.

The adjustments made by the EAG, to define the EAG base-case (using the base-case after clarification as starting point) are listed below.

5.2.3.1 Fixing errors

No errors were found by the EAG in the model provided in response to the clarification letter, with the exception of the discrepancies between the CS and the economic model identified by the EAG. When these were identified, the EAG assumed that the values in the economic model were the correct ones, but the opposite could be true.

5.2.3.2 Fixing violations

No violations were identified by the EAG.

5.2.3.3 Matters of judgement

1. Gompertz distribution for DBTd-DL PFS (see Section 4.2.6.2).
2. TTD data from the L arm of AURIGA to inform TTD for DBTd-L (see Section 4.2.6.3)

5.2.4 EAG base-case results

The step-by-step changes made by the EAG to derive its base-case and the cumulative impact of each change can be seen in Table 5.8. The change with the largest impact on the results was assuming a Gompertz distribution for DBTd-DL PFS. Implementing the two EAG's preferred changes yielded an ICER of £38,483 per QALY gained, when DBTd-DL is compared to DBTd-L. The EAG's base-case ICER increased thus by approximately 49% compared to the company's base-case ICER.

Table 5.8: Cumulative impact of EAG's preferred assumptions (deterministic)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company base-case (after clarification)					
DBLd-DL	██████	██████	██████	██████	25,888
DBTd-L	██████	██████			
EAG Step 1 – Gompertz distribution for DBTd-DL PFS					
DBLd-DL	██████	██████	██████	██████	38,296
DBTd-L	██████	██████			
EAG Step 2 – Step 1 + TTD data from L arm of AURIGA to inform TTD for DBTd-L					
DBLd-DL	██████	██████	██████	██████	38,483
DBTd-L	██████	██████			
Based on the model submitted following clarification. ⁴⁸ DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; ICER = incremental cost-effectiveness ratio; Inc. = incremental; L = lenalidomide; LYG = life years gained; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation					

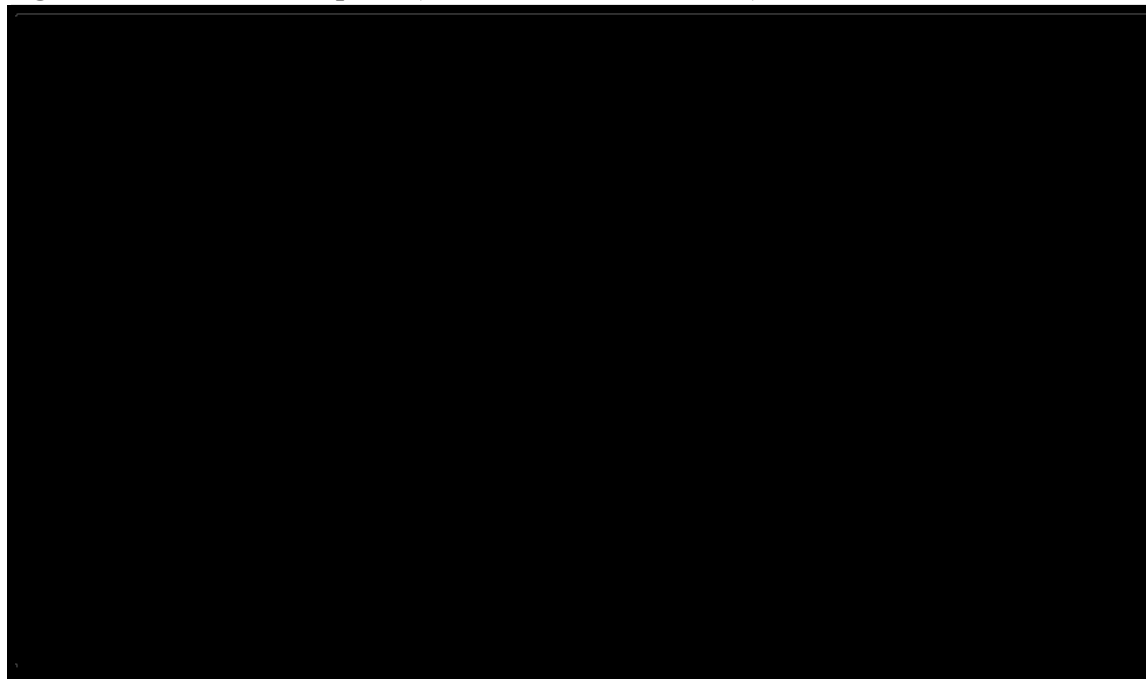
For the PSA, the EAG prefers changing the SEs to 20% deviation from the mean instead of 10% to reflect the expected larger uncertainty for those parameters informed by clinical experts and for costs. The average EAG PSA results are summarised in Table 5.9 and, as highlighted in Section 5.1.2.1, there is a large deviation with respect to the deterministic results shown in Table 5.8. The EAG was not able to identify the cause of this discrepancy at the time this report was completed, which constitutes a key issue for the cost-effectiveness evidence.

Table 5.9: EAG base-case probabilistic CE results (discounted daratumumab price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
DBLd-DL	██████	██████	██████	██████	██████	██████	DBLd-DL dominates
DBTd-L	██████	██████	██████	-	-	-	-
Based on the model submitted during the factual accuracy check phase. CE = cost-effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year							

The EAG PSA outcomes on the CE-plane can be seen in Figure 5.4. Compared to the company's CE-plane in Figure 5.1, the EAG PSA resulted in a wider cloud of outcomes (due to assuming 20% SEs instead of 10%). The majority (i.e., █████%) of the outcomes reported positive incremental QALYs for DBLd-DL versus DBTd-L. Cost outcomes were mostly spread across NE and SE quadrants, with some outcomes in the SW and NW quadrants. A CEAC was also calculated (see Figure 5.5), which indicated that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that DBLd-DL is a cost-effective alternative to DBTd-L was █████% and █████%, respectively.

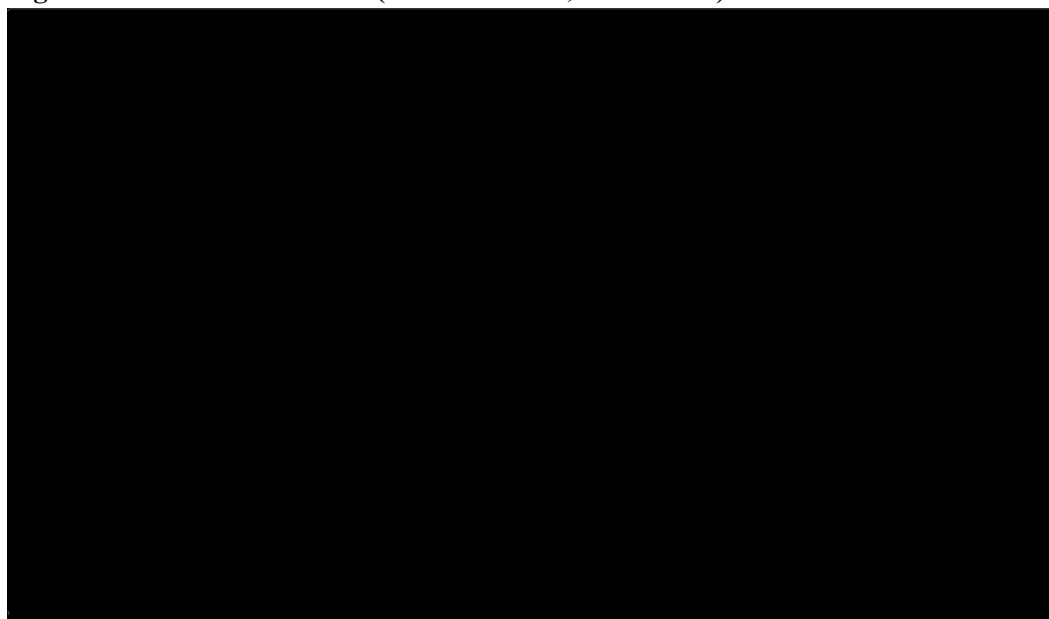
Figure 5.4: EAG PSA CE-plane (daratumumab, discounted)



Based on the model submitted during the factual accuracy check phase.

CE = cost-effectiveness; EAG = External Assessment Group; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.5: EAG PSA CEAC (daratumumab, discounted)



Based on the model submitted during the factual accuracy check phase.

EAG = External Assessment Group; CEAC = cost-effectiveness acceptability curve; PSA = probabilistic sensitivity analysis

5.2.5 Scenario analyses using EAG's preferred assumptions

Table 5.9 shows the results of the EAG's exploratory analyses changing one assumption from the EAG's base-case individually. The scenarios (all deterministic) explored by the EAG are the following:

- Source of survival data: choosing pooled data from PERSEUS and GRIFFIN trials.

- OS scenarios: selecting alternative extrapolations for OS (Weibull, log-logistic, log-normal and Gamma – other extrapolations not presented because they were deemed too implausible) and OS HR (limits of the reported 95% CI).
- PFS scenarios: selecting alternative extrapolations for PFS (generalised Gamma – other extrapolations not presented because they were deemed too implausible) and PFS HR (limits of the reported 95% CI).
- Treatment effect waning: incorporating DBLd-DL treatment effect waning by specifying starting point and duration.
- TTD scenarios: exploring the option treat to progression and alternative extrapolation curves.
- Utility scenarios: using utilities from NICE TA763 and decreasing utilities in 3rd and 4th lines of treatment to reflect a worsening in HRQoL.
- Cost scenarios: assuming second line treatment mix from PERSEUS.

Changes in OS and PFS assumptions result in a wide range of ICERs – from dominance to very high ICERs. This is not surprising given the immaturity of the survival data, as highlighted by the EAG in Section 4.2.6 of this report. Assuming treatment effect waning also had a substantial impact on the model results, which can lead to high ICERs. Similar to OS and PFS, there is also uncertainty around TTD assumptions. The option to treat until progression resulted in large ICERs due to the high costs of D treatment which under this assumption are extended over time. The model results are also sensitive to changes in the extrapolation curve for TTD for MRD+ patients. Changes in utilities had a moderate impact on the ICER. Finally, using second line treatment mix from PERSEUS decreased the ICER by approximately £11,000.

Overall, the results of the scenario analyses explored by the EAG indicate that the model results can be sensitive to changes in certain key assumptions. This was not captured by the company's scenario analyses in Section 5.1.2.3.

Table 5.10: Results of EAG's exploratory analyses using EAG's base-case

Exploratory analysis number	Scenario applied to EAG's base-case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
0	EAG base-case	██████	██████	38,483
1	Source of survival data (PERSEUS and GRIFFIN pooled)	██████	██████	18,988
2	OS Weibull	██████	██████	53,613
3	OS log-logistic	██████	██████	44,970
4	OS log-normal	██████	██████	DBLd-DL dominates
5	OS Gamma	██████	██████	52,662
6	OS HR = ██████	██████	██████	84,037
7	OS HR = ██████	██████	██████	646,677 (in SW quadrant of CE-plane)
8	PFS gen. Gamma	██████	██████	26,073
9	PFS HR = ██████	██████	██████	DBLd-DL dominates

Exploratory analysis number	Scenario applied to EAG's base-case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
10	PFS HR = [REDACTED]	[REDACTED]	[REDACTED]	181,248
11	Tx effect waning (start = cycle 66 [5 years], duration 50 cycles [3.8 years])	[REDACTED]	[REDACTED]	89,951
12	Tx effect waning (start = cycle 132 [10 years], duration 50 cycles [3.8 years])	[REDACTED]	[REDACTED]	72,050
13	Tx effect waning (start = cycle 132 [10 years], duration 100 cycles [7.6 years])	[REDACTED]	[REDACTED]	69,970
14	TTD – Treat to progression (D within DL)	[REDACTED]	[REDACTED]	152,166
15	TTD – D within DL for MRD+ log-normal	[REDACTED]	[REDACTED]	50,370
16	TTD – D within DL for MRD+ gen Gamma	[REDACTED]	[REDACTED]	35,759
17	TTD – D within DL for MRD+ treat to progression	[REDACTED]	[REDACTED]	80,023
18	TTD – L within DL treat to progression	[REDACTED]	[REDACTED]	39,147
19	TTD – L within L treat to progression	[REDACTED]	[REDACTED]	37,792
20	Utilities sourced from NICE TA763	[REDACTED]	[REDACTED]	41,222
21	Decrease utility in 3 rd and 4 th line of treatment	[REDACTED]	[REDACTED]	38,387
22	Second line treatment mix from PERSEUS	[REDACTED]	[REDACTED]	27,821
Based on the economic model after clarification⁴⁸ CE = cost-effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; D = daratumumab; DL = dexamethasone with lenalidomide; EAG = External Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; L = lenalidomide; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation				

5.2.6 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

5.2.7 Overview of the EAG key issues related to the CEAs

Table 5.10 summarises the CE key issues categorised according to the sources of uncertainty as defined by Grimm et al 2020:⁷⁰

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide CIs, small sample sizes, or immaturity of data)

- Bias and indirectness (e.g., there is a mismatch between the DP and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the sources of uncertainty can help determine whether additional clarifications, evidence and/or analyses might help to resolve the key issue. Table 5.10 also includes suggested alternative approaches, expected effects on the CE, whether it is reflected in the EAG exploratory analyses, and if additional evidence or analyses might help to resolve the identified key issues.

Table 5.11: Overview of key issues related to the CE

Key issues	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Survival data (OS, PFS and TTD) immature	4.2.6.1 4.2.6.2 4.2.6.3	Imprecision	Explore scenario analyses assuming different (standard) extrapolations for PFS, OS and TTD.	+/-	No/Explored	Long-term data, where available, should help reducing the uncertainty related to this key issue. With the current data, explore more flexible extrapolations methods (if for example functional cure is deemed plausible).
Validity of the model outcomes not sufficiently explored	5.2.1	Transparency Bias & indirectness	Highlight a [REDACTED] difference in total life years estimated for DBTd-L in TA763 (14.66) and the current appraisal ([REDACTED]). Explore scenario analyses where life years estimated for DBTd-L are closer to those in TA763.	+/-	No	Use TA763 (or other relevant evidence) to validate the results for the comparator arm (DBTd-L) in this appraisal. In addition, explore the large deviation between the deterministic and PSA results.
The economic model fails to capture the full impact of including subsequent lines of treatment	4.2.2 5.2.1	Methods Bias & indirectness Unavailability	Include impact of subsequent lines of treatment in both survival and HRQoL.	+/-	No	Collect survival and HRQoL data for subsequent treatment lines.
^a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator ^b Explored CE = cost-effectiveness; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; EAG = External Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; L = lenalidomide; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; TA = Technology Assessment; TTD = time to treatment discontinuation						

5.3 Decision modifiers

5.3.1 *QALY weighting for severity*

The company has not presented a case for a QALY weighting for severity. The EAG agrees with this approach.

5.3.2 *Uncaptured benefits*

The uncaptured benefits proposed by the company in Section 3.13 of the CS are described below.¹

5.3.2.1 Improved long-term survival benefit anticipated with DBLd-DL compared to DBTd-L which is not captured in the economic model due to the simplifying model assumption of equal efficacy for DBLd and DBTd induction and consolidation therapies

Equal efficacy was assumed for DBLd-DL and DBTd-L during the induction and consolidation phases. The company acknowledged that this assumption is conservative, as ITC results indicated superior response rates for DBLd compared with DBTd. This is consistent with the greater potency of L relative to thalidomide. The company considered that the deeper responses associated with DBLd are likely to improve long-term outcomes, which may therefore be underestimated in the current analysis.

EAG comment: The EAG would like to note that any additional benefit associated to the I+C phases is likely to have a minor impact on the CE results.

Regarding the company's second claim, whether treatment with DBLd has some long-term effect compared to DBTd seems difficult to prove. Because maintenance treatments in the current submission are DL versus L, it seems unlikely that the effect (if any) of the previous therapy in induction and/or consolidation phases can be identified.

5.3.2.2 Improved HRQoL associated with a thalidomide-free treatment option

The company indicated that DBTd as an I+C therapy is associated with a poor safety profile, where a high proportion of patients receiving thalidomide-containing regimens are expected to experience neurotoxicity events, which was confirmed by UK clinical experts.^{22, 71} While the economic model includes disutility for neuropathy, it does not account for the additional fear and anxiety associated with the expectation of AEs. The wider impact of these toxicities also extends to families and caregivers, who experience a marked reduction in HRQoL.

EAG comment: The EAG considers this claim plausible. However, as mentioned above, any additional benefit associated to the I+C phases is likely to have a minor impact on the CE results.

5.3.2.3 Value of hope associated with the prospect of a functional cure provided by a new treatment option which achieves unprecedented deep and durable responses, including sustained MRD-negativity

The company noted that wider value elements, including the "hope" associated with the prospect of functional cure through prolonged remission and survival with improved HRQoL, are not fully captured in the economic analysis.

EAG comment: The EAG considers that elements such as the value of hope fall outside the NICE reference case and therefore should not be incorporated into the company's base-case. If the company

considers a functional cure plausible, fitting survival models such as mixture cure models is an option to include functional cure in the economic model. While this might be possible in theory, given the immaturity of the available survival data, it is unlikely that these models are able to reduce the uncertainty associated with the long-term predictions.

5.3.2.4 Value of personalised treatment regimens enabling de-escalation of maintenance treatment required by patients whilst maintaining progression-free period

In the PERSEUS trial, DBLd-DL maintenance included a stopping rule for daratumumab. Patients who had received at least 24 months of maintenance and achieved sustained MRD negativity for ≥ 12 months were eligible to discontinue treatment. In the trial, █% of patients on DBLd-DL discontinued daratumumab under this rule, supporting the plausibility of treatment de-escalation in clinical practice.²¹ This approach allows for personalised discontinuation of daratumumab maintenance based on MRD status.

EAG comment: The EAG has no comments regarding this point.

5.3.3 Health inequalities

The company has not presented any information about health inequalities related to this submission.

5.4 Conclusions of the CE Section

The CS, Appendices E, F and G and response to clarification^{1, 3, 5} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on CE, HRQoL and cost/HCRU in the treatment of HDT-ASCT eligible patients with NDMM. Searches were conducted in September 2023 and updated in May 2025. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases and conference proceedings were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The CE-specific key issues highlighted by the EAG throughout this report are summarised in Table 5.10 and they are as follows:

- 1) The immaturity of the survival data (OS, PFS and TTD) included in the appraisal.
- 2) The lack of validation efforts on the model outcomes.
- 3) The economic model fails to capture the full impact of including subsequent lines of treatment.

The first key issue relates to the immaturity of survival data from the trials presented in this submission. The immaturity in survival data inflates uncertainty around the economic outcomes and limits the reliability of predictions for decision making. There is uncertainty in the long-term OS predictions based on the alternative extrapolations and in the relative treatment effectiveness, driven by the precision of the PFS and OS HRs estimates. Given the immaturity of the data, the EAG's preference would be to use the most conservative options. Also, if the company considers a functional cure plausible, fitting survival models such as mixture cure models is an option to include functional cure in the economic model. While this might be possible in theory, given the immaturity of the available survival data, it is unlikely that these models are able to reduce the uncertainty associated with the long-term predictions. To address to some extent the immaturity of the PERSEUS survival data, the EAG conducted scenario analyses using different OS and PFS extrapolation options. Changes in OS and PFS assumptions result in a wide range of ICERs – from dominance to very high ICERs. This is not surprising given the immaturity of the survival data. Assuming treatment effect waning also had a substantial impact on the model results, which can lead to high ICERs. Similar to OS and PFS, there is also uncertainty around

TTD assumptions. The option to treat until progression resulted in large ICERs due to the high costs of D treatment which under this assumption are extended over time. The model results are also sensitive to changes in the extrapolation curve for TTD for MRD+ patients. Long-term data, where available, should help reducing the uncertainty related to this key issue.

The second key issue relates to the lack of validation of the model outcomes. Previous daratumumab appraisals such as TA763 were used to validate the model structure, input parameters and assumptions. The EAG considers that this (or other relevant publications/HTA submission) could have been used to validate the results for the comparator arm (DBTd-L) in this appraisal to confirm that either they are in line or to explain the differences. The EAG would like to highlight a [REDACTED] difference in total LYs estimated for DBTd-L in TA763 (14.66) and the current appraisal ([REDACTED]).¹² From all the OS extrapolations explored by the company, the log-normal distribution results in the highest LYs estimated for DBTd-L ([REDACTED]), which is slightly more than [REDACTED] less than the estimate in TA763. This raises some concerns regarding the validity of the model results and further exploration of this potential issue is therefore recommended. In addition, there is a large deviation between the deterministic and PSA results. The EAG was not able to identify the cause of this discrepancy at the time this report was completed, which constitutes a key issue for the cost-effectiveness evidence.

The third key issue concerns economic model inability to capture the full impact of including subsequent lines of treatment. The company included 2nd, 3rd and 4th line treatment in the model, but only on the costs side. Utilities remain constant after progression and survival probabilities do not seem to have been adjusted for subsequent lines of treatment. Assuming constant utilities upon progression, while a simplifying assumption, has a relatively small impact on model outcomes as shown in the EAG scenario analysis and is likely conservative with respect to the incremental QALYs gained, as a higher proportion of patients transition to the PD health state in the DBTd-L arm compared with the DBLd-DL arm. The EAG considers it reasonable to assume that survival prognosis gets worse as patients progress to subsequent treatment lines. If this is not properly captured in the economic model, then the estimated LYs and QALYs are likely overestimated. This raises some concerns regarding the sixth key issue since in comparison with TA763, the current appraisal estimates substantially less LYs for the comparator arm. If the current analyses underestimate LYs and QALYs because they fail to capture the impact of subsequent lines of treatment, then the discrepancy might be even larger. Furthermore, it might also be in contradiction with the company's statement that "*the associated advances in MM management, which has potentially improved prognosis for NDMM patients and led to higher utility values*". The company used this argument to assume that in the current appraisal utilities are higher than in TA763. Following this line of reasoning, it could be argued that improvements in life expectancy compared to TA763 could also be expected. However, for the comparator arm in the current appraisal the opposite seems to occur. The company also indicated that most patients in PERSEUS received only one subsequent line of therapy (the proportion of patients receiving one or more subsequent lines of treatments was [REDACTED]% in the BLd-L arm and [REDACTED]% in the DBLd-DL arm). This means for example that [REDACTED]% of patients in the BLd-L arm did not get subsequent lines of therapies.

In an attempt to (partially) overcome some of these concerns, the EAG defined a new preferred base-case by:

1. Assuming a Gompertz distribution for DBLd-DL PFS.
2. Using TTD data from the L arm of AURIGA to inform TTD for DBTd-L.

The results of the EAG's base-case analysis indicated that DBLd-DL was more costly and more effective than DBTd-L with an estimated ICER of £38,483 per QALY gained. The EAG's base-case

ICER increased by approximately 49% compared to the company's base-case ICER, and this was mostly due to changing the PFS extrapolations.

For the PSA, the EAG prefers changing the SEs to 20% deviation from the mean instead of 10% to reflect the expected larger uncertainty for those parameters informed by clinical experts and for costs. The average EAG PSA results indicated that there is a large deviation with respect to the deterministic results. As mentioned above, the EAG was not able to identify the cause of this discrepancy at the time this report was completed.

The EAG did not conduct any exploratory analyses using the company's base-case. This was because the EAG's preferred assumptions did not differ substantially from those of the company. For that reason, the EAG's exploratory analyses were conducted using the EAG's preferred assumptions only. The scenarios (all deterministic) explored by the EAG were the following:

- Source of survival data: choosing pooled data from PERSEUS and GRIFFIN trials.
- OS scenarios: selecting alternative extrapolations for OS (Weibull, log-logistic, log-normal and Gamma – other extrapolations not presented because they were deemed too implausible) and OS HR (limits of the reported 95% CI).
- PFS scenarios: selecting alternative extrapolations for PFS (generalised Gamma – other extrapolations not presented because they were deemed too implausible) and PFS HR (limits of the reported 95% CI).
- Treatment effect waning: incorporating DBLd-DL treatment effect waning by specifying starting point and duration.
- TTD scenarios: exploring the option treat to progression and alternative extrapolation curves.
- Utility scenarios: using utilities from NICE TA763 and decreasing utilities in 3rd and 4th lines of treatment to reflect a worsening in HRQoL.
- Cost scenarios: assuming second line treatment mix from PERSEUS.

Overall, the results of the scenario analyses explored by the EAG indicate that the model results can be sensitive to changes in certain key assumptions, which was not captured by the company's scenario analyses.

In conclusion, the three CE-related key issues identified by the EAG, and the additional exploratory analyses, indicate that there are substantial uncertainties remaining in this appraisal, which can have impact on decision-making.

6. References

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Single Technology Appraisal

Daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 21st 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 [REDACTED] should be highlighted in turquoise and all information submitted as '[REDACTED]' in pink.

Principal factual inaccuracies

Issue 1 Reference to the company's cost-utility and cost-comparison analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
For Key issue 1 (Uncertainty as to the intervention [Table 2.1, Page 15, Section 1.3]), the EAG report states that the inclusion of a cost-effectiveness analysis for the full treatment sequence (DBLd followed by DL maintenance) as well as a cost-comparison analysis for the induction and consolidation phase (DBLd) means there are "effectively two	J&J request that the EAG re-word the response to the question "What is the expected effect on CE estimates?" in Table 1.2 of the report from "Unknown" to "None".	Given that the cost-comparison analysis is a standalone analysis from the cost-effectiveness analysis, it is factually inaccurate to imply cost-comparison results for DBLd induction and consolidation may impact the cost-effectiveness analysis for the full treatment sequence (DBLd-DL). As such, the EAG report should be updated to clarify this. DBLd induction and consolidation therapy would be followed by DL maintenance in UK clinical practice, should DL be reimbursed. As such, a cost-effectiveness analysis was included for this full treatment sequence. A cost-comparison analysis comparing DBLd and DBTd during the induction and consolidation phases was included in the Company's ongoing submission to support as early as possible access for DBLd induction and consolidation only, if the Committee required additional information/time to consider the full treatment sequence including DL maintenance. The cost-comparison analysis enables the Committee to understand the cost savings to the NHS associated with replacing thalidomide in the current standard of care with lenalidomide, and updates the [REDACTED] [REDACTED]	Not a factual inaccuracy. The EAG has added to the table to clarify that the implications depend on the method of evaluation.

interventions”, and that the expected effect of this on CE estimates is “Unknown”.			

Issue 2 EAG description of the clinical trial data informing the economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
For Key Issue 3 (Lack of evidence for a comparison of the complete treatment sequence [Table 1.4, Page 16, Section 1.3]), the EAG report outlines that DBTd and DBLd as induction and consolidation treatments were compared through an ITC, whilst DL and L maintenance were compared directly using data from the AURIGA trial. Whilst this description is correct, the EAG report then states that only results from the AURIGA trial were used in the Company’s economic analysis, whilst results	Statements suggesting that data from the PERSEUS trial were not used to inform the economic analysis are inaccurate. J&J therefore request the EAG report wording is amended throughout to clarify that the economic model was informed by efficacy data from the PERSEUS trial, as well as the AURIGA trial.	During the induction and consolidation phases, PFS and OS were assumed to be equal for DBLd and DBTd. As the EAG report notes, this is a highly conservative assumption as ITC results (Section 2.10 of the Company Submission) demonstrate that patients who receive DBLd achieve statistically significantly deeper responses than DBTd. Kaplan-Meier data for the DBLd arm of the PERSEUS trial were directly implemented in the economic model and used to inform the assumption of equal PFS and OS for the induction and consolidation phase. As such, it is incorrect to state that PERSEUS data were not used in the economic analysis.	Amended to clarify that the EAG are referring to the treatment effect.

of the pivotal trial, PERSEUS, were not: <i>“They compared DL with L in the maintenance phase only via another RCT i.e. AURIGA. In the economic model, only the results from AURIGA were used, with the assumption that there was no difference in effectiveness occurring in the induction and consolidation phase.”</i> <i>“Whilst this does appear to be conservative, given that the ITC does appear to show an advantage in short term outcomes i.e. up to the beginning of maintenance, this does mean that the results of the pivotal trial are not used in the economic analysis.”</i>		For the maintenance phase, HRs from the AURIGA trial were applied to the PERSEUS Kaplan-Meier data to adjust the PFS and OS extrapolations for patients receiving DBLd-DL in the PERSEUS trial from the onset of maintenance therapy. In addition, J&J provided an exploratory analysis as part of their response to Clarification Question 3(b), which re-weighted individual patient-level data from the PERSEUS trial to isolate the effect of DL versus L maintenance on PFS and OS. The results of this analysis showed that DBLd-DL was dominant against DBTd-L, providing reassurance in the results of the base case analysis. In summary, it is misleading to infer that only results from AURIGA were used in the economic model when data from PERSEUS was used directly to inform the economic analysis for both the induction & consolidation and maintenance treatment phases.	

Issue 3 Reference to literature reviews

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
It is factually inaccurate to suggest a lack of rigour and risk of bias/error with regards the SLR search for maintenance only treatments comparing DL with L. The EAG report describes two clinical SLRs conducted to identify evidence for the full treatment sequence, and the induction and consolidation phases only, both of which were deemed by the EAG to be appropriate for use (e.g., Page 27, Section 3.1.1; Page 32, Section 3.1.2; Page 116, Section 3.6). As these SLRs did not capture any trials investigating the full treatment sequence comparator, a pragmatic re-evaluation was conducted to identify studies comparing DL with L maintenance therapy. The EAG noted a lack of rigour, implying uncertainty as to the evidence to	J&J requests that the EAG remove wording throughout around the “lack of rigour” and “uncertainty” involved in the approach taken to capture relevant evidence to inform estimates of the comparative efficacy of DBLd-DL and its comparator.	As noted by the EAG in their report, J&J conducted two robust, fit-for-purpose SLRs to identify relevant evidence for the full treatment sequence comparator and for the induction and consolidation phases. This was in line with the submission decision problem. Pragmatic searches took place after J&J initial completion of these SLRs and determined that there was no ideal evidence to address the decision problem given the UK Standard of Care and comparisons required. To our understanding these follow the recommendations made by the EAG in their report i.e. a title and abstract screen of prior excluded studies (further details provided below). It is inaccurate to suggest that the Company’s approach to identifying studies to address the decision problem were prone to bias, given that additional steps were taken to supplement the robust SLRs in light of their findings .i.e.,	Not a factual inaccuracy.

inform DL versus L maintenance.		pragmatic but reproducible searches were performed to identify comparative efficacy data for DL versus L maintenance We note for reassurance, that J&J have full visibility of the clinical development programme for daratumumab, including trials exploring the safety and efficacy of DL maintenance therapy for patients with HDT-ASCT eligible NDMM. This indicates that the approach to sourcing evidence does not represent a source of uncertainty in this appraisal; we do however, acknowledge that there are limitations in the evidence base that exists. J&J would like to clarify the methodological approaches taken across the literature review stages, to address any uncertainty raised by the EAG in Sections 3.1.2–3.1.4 of their report: • Title/abstract and full-text review (SLR): each record was screened by two independent reviewers against a pre-defined eligibility criteria, with any	

		remaining disagreements resolved by a third investigator. • Data extraction (SLR): data for each included study were extracted into a pre-defined extraction grid by a single reviewer, and verified by a second independent reviewer. Any discrepancies that arose during their reviews were resolved through discussion with, or intervention by, a third reviewer • Pragmatic review: Title/abstracts of studies excluded at the full-text review stage of the I+C+M SLR - specifically those restricted to the maintenance phase - were pragmatically re-screened by two independent reviewers with any remaining disagreements resolved by a third investigator to identify any evidence relevant to the comparative efficacy of DL versus L. Targeted searches in Google Scholar were also conducted to ensure completeness. Further details are provided in section A3.4 of the 'response to clarification question'.	

		• Risk of bias assessment: risk of bias assessments were conducted by a single independent reviewer, and verified by a second independent reviewer. Any discrepancies that arose during their reviews were resolved through discussion with, or intervention by, a third reviewer.	

Issue 4 Alternative survival data and extrapolation methods to address uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG acknowledge in their report that uncertainty in PFS and OS estimates would persist with longer-term follow up data (e.g., Page 127, Section 4.2.6.1.2). Despite this, the EAG included immaturity of survival data as a key issue (Key Issue 5), and state that the current data informing the model is not sufficient to support decision making. The EAG suggest that the addition of longer-term AURIGA or PERSEUS data would reduce	J&J requests that the EAG amend wording in their report suggesting that availability of longer-term PERSEUS or AURIGA data, or use of alternative extrapolation methods such as mixture cure, might address uncertainty in PFS and OS estimates. Similarly, suggestions that the current model is not sufficient for decision making due to immature survival data should also be removed. Additionally, J&J request it is acknowledged	J&J wish to reiterate that the immaturity of data from the PERSEUS and AURIGA trials are inherent to survival data in the front-line setting for patients with HDT-ASCT eligible NDMM, given the excellent prognosis of these patients relative to those with transplant-ineligible or relapsed/refractory MM, and the ability of treatments in this setting to extend life beyond trial duration. This limitation is consistent with the availability of data in previously recommended treatments by NICE in the same setting. Median follow-up at the latest DCOs for the PERSEUS and AURIGA trials were comparable to	Not a factual inaccuracy. The EAG did not state that the current data informing the model or the model itself are not sufficient to support decision making and maintains that long-term follow up data can assist in improving precision of HR estimates as also supported by the company in clarification response B2h. Furthermore, alternative model extrapolations such as mixture cure models, if deemed

uncertainty and improve model precision (e.g., Table 1.6, Page 17, Section 1.4; Page 127, Section 4.2.6.1.2; Page 130, Section 4.2.6.2.2). The EAG report adds that the use of flexible extrapolation methods, such as mixture cure models, could be feasible and would address uncertainty with the current data.	that, whilst data from the PERSEUS and AURIGA trials are immature, this is inherent to survival data in the front-line setting for patients with HDT-ASCT eligible NDMM, and so this immaturity would not be addressed by future data cuts nor alternative statistical methods.	that of the DCOs for CASSIOPEIA and MYELOMA XI used to inform the NICE appraisals for DBTd induction and consolidation, and lenalidomide maintenance, respectively: • PERSEUS (August 2023 DCO): 47.5 months¹ • AURIGA (April 2024 DCO): 32.3 months² • CASSIOPEIA:³ ○ Primary DCO (June 2018): 18.8 months ○ Post-hoc DCO (May 2019): 29.2 months • MYELOMA XI (October 2017 DCO): 31 months⁴ Furthermore, as detailed in the Company Submission, the deep, sustained responses achieved by patients receiving DBLd-DL are associated with improved long-term survival. Our position is that further follow up data from PERSEUS would be of limited value, given the need to compare to lenalidomide maintenance therapy in this appraisal. We will investigate the potential to submit	plausible by the company, can help reduce uncertainty when combined with longer-term data. The EAG acknowledges that some uncertainty may persist due to the prognosis of the patient population and the subsequent treatments as summarised on page 127. For this reason, the EAG added the following statement in Table 1.6: “Some uncertainty is inevitable due to the immaturity of the survival data from the PERSEUS and AURIGA trials, which reflects a generally good prognosis of HDT-ASCT–eligible NDMM patients, the high proportion achieving durable responses to DBLd-DL, and the availability of effective subsequent therapies.” Additionally, on page 127 clarification response B2f should be clarification response B2h. This has been corrected.

		additional longer term follow up data from AURIGA, although given the study date, this is anticipated to be of confirmatory value only. Overall, whilst upcoming data cuts are expected for PFS and OS, the collection of mature survival data is anticipated to require a significant duration of time – these data are not expected to reduce inherent long-term modelling uncertainty when considering a lifetime model time horizon. J&J notes that NICE aims to produce useful and usable guidance – this aim would not be achieved by waiting many years for survival data to mature, substantially delaying access to treatment.³ This is an inherent limitation of the appraisal process, rather than an indication that the economic model is unsuitable. We note that mixture cure models have high data requirements. Fitting such models could increase uncertainty because a) as far as we are aware, there is no current expert consensus on how to define nor model MM functional cure and b) any issue of data maturity would persist; specifically, but not limited to the	

		fraction of patients that could be regarded as cured.	

Issue 5 Validation of model outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
In Key Issue 6, the EAG report has noted that the model results for DBTd-L obtained from the NICE appraisal for DBTd-L (TA763) could have been used to validate results in the current submission (e.g., Table 1.6, Page 17, Section 1.5; Page 167, Section 5.2.1). Specifically, the EAG report notes that the current Company base-case estimates a total of [REDACTED] LYs for DBTd-L, and that using a log-normal distribution for OS extrapolations, which yields the highest LYs estimate for DBTd-L, results in the total LYs for DBTd-L ([REDACTED]) being just over [REDACTED] lower than the estimate in TA763 (14.66).	The EAG quotes the total LYs estimated for DBTd-L in TA763 as 14.66, which is factually inaccurate. This figure is based on the initial submission, and subsequent model iterations had LYs results redacted in the committee papers. In addition, the wording around the difference between total LYs estimated for DBTd-L in TA763 and the current submission being “large” should be removed. J&J also notes that the statement “<i>Highlight a large difference in total life years estimated for DBTd-L in TA763 (14.66) and the current appraisal ([REDACTED])</i>” in Table 1.7,	J&J would like to clarify that the final submitted model in TA763 estimated total LYs of [REDACTED] for DBTd-L. J&J also note that a HR of 0.89 (consistent with results from the inverse probability of treatment weighting [IPTW] re-weighted analysis of PERSEUS data provided by J&J in response to Clarification Question B3(b) received from the EAG) implies 13.53 LYs for DBTd-L which is consistent with the value of [REDACTED] from TA763. Finally, the difference in total LYs estimated for DBTd-L in TA763 and the current submission is purely a numerical difference. J&J does not consider it appropriate to objectively describe this difference as ‘large’, without any measures of uncertainty to suggest this is the case. As such, this wording should be	Not a factual inaccuracy. The EAG had no access to redacted values. The EAG would like to thank the company for providing the updated value of [REDACTED] LYs and would like to point out that [REDACTED] LYs for DBTd-L in the current appraisal is still over [REDACTED] lower than the estimate in TA763. The EAG acknowledges that “large” is a subjective interpretation so it has been replaced by [REDACTED] years. The EAG is unclear regarding the placeholder statement on page 18, therefore no action was taken.

	Page 18, Section 1.5 appears to be a placeholder statement and therefore should also be removed.	amended, for accuracy, to simply state that there is a difference in total LYs estimated for DBTd-L in TA763 and the current appraisal.	
	J&J requests that the EAG amends their report to acknowledge that the lack of validation against results in the TA763 does not represent a key issue for decision making and clarify that the expected effect on the cost-effectiveness estimates is a reduction in the ICER rather than “Unclear”.	In Scenario 4 presented in the Company Submission, applying an OS HR of 1 during the maintenance phase, rather than the OS for DL versus L from the AURIGA trial, results in DBLd-DL dominating DBTd-L. This highlights that increasing the OS HR used in the Company base-case, such that the total LYs for DBTd-L are brought in line with the estimates from TA763, only improves the cost-effectiveness of DBLd-DL. Therefore, the suggestion in the EAG report that the lack of validation against TA763 contributes to uncertainty in decision making, by presenting this as a key issue, is misrepresentative.	Not a factual inaccuracy. The EAG maintains that the validity of the model outcomes has not been sufficiently explored and that this remains a key issue.

Issue 6 Reference to subsequent treatments in PERSEUS

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
As part of Key Issue 7, the EAG report has described the proportion of patients in the PERSEUS trial who received a subsequent line of therapy as of the latest DCO (e.g., Table 1.8, Page 19, Section 1.5; Page 122, Section 4.2.3). Based on these results, the EAG state that the PERSEUS trial may not be representative of the modelled patient population due to few patients having received subsequent therapies at the latest DCO.	J&J requests that the EAG removes suggestion that the PERSEUS patient population is not representative of the modelled population from Table 1.8, Page 19, Section 1.4 and Page 123, Section 4.2.3.	It is misleading to infer that the PERSEUS trial may not be representative of the patient population included in the economic model. Whilst up to four lines of subsequent treatment have been included in the economic model for completeness, both DBTd-L and DBLd-DL are efficacious front-line treatment strategies that will delay, or in some cases negate, the necessity to cycle through multiple lines of subsequent therapy for patients that achieve deep and durable responses. EAG report Key Issue 7 ultimately relates to data immaturity rather than representativeness of the PERSEUS trial to the modelled population. This is an inherent limitation when modelling outcomes in the front-line setting where the prognosis for patients eligible for ASCT, relative to transplant-ineligible or RRMM, is excellent. Whilst it is not realistic to capture mature subsequent treatment data within the standard	The following sentence has been removed from the EAG report but the key issue is maintained: "This also raises the concern as to whether the PERSEUS trial is representative of the patient population included in the economic model where all these subsequent lines of therapies are included but very few patients in the trial were getting them."

		timeframe of clinical trials, J&J consider that long-term modelling uncertainty has been extensively explored as part of the sensitivity and scenario analysis included in Section 4 of the Company Submission. As such, and given the demonstrated robustness of the Company base-case to sensitivity/scenario analysis explored, this should not be considered a separate (unquantified) key area of decision making uncertainty.	
	J&J requests that the EAG clarify that proportion of patients who received one or more subsequent lines of therapy in the PERSEUS trial was [REDACTED]% in the BLd-L arm and [REDACTED]% in the DBLd-DL arm on Table 1.8, Page 19, Section 1.5; Page 122, Section 4.2.3; Page 178, Section 5.4.	As detailed in Section 2.7 of the Company Submission, the proportion of patients receiving subsequent therapies in the PERSEUS trial refers to those who received one or more subsequent lines, not the proportion who received only one subsequent line of therapy. The EAG report should also correctly name the comparator treatment arm in the PERSEUS trial as BLd-L, rather than DBTd-L.	The report was amended as per company's clarification response B14 stating that most patients in PERSEUS only reached one subsequent line of therapy (proportion of patients receiving one or more subsequent therapies: [REDACTED]% [REDACTED] for DBLd-DL versus [REDACTED]% [REDACTED] for BLd-L).

Issue 7 Adjustment of survival probabilities to account for subsequent lines of treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
As part of Key Issue 7, the EAG report states that survival probabilities “<i>do not seem to have been adjusted for subsequent lines of treatment</i>”, suggesting that the Company’s economic model is unable to capture the full impact of subsequent lines of treatment on survival (e.g., Table 1.8, Page 19, Section 1.7; Page 177–178, Section 5.4).	J&J requests that the EAG reword relevant sections of the report to acknowledge that the impact of subsequent treatments on survival is captured in the model. For example, the following wording would more accurately represent the model’s capabilities: “Whilst the impact of subsequent treatments on overall survival is not explicitly modelled in the company’s economic analysis, the EAG acknowledge that when comparing the sum of the proportion of patients who progress in subsequent lines versus those who are alive and on subsequent treatment, the resulting values are identical, thus validating that the PFS and OS curves accurately	PFS is calculated for subsequent treatments in the model using the mean and median treatment durations, in order to calculate the probability of disease progression whilst on each subsequent treatment line. As the EAG states, this is only used to calculate incurred costs. However, when comparing the summed proportion of patients who progress on subsequent treatments in the model engine with the summed proportion of patients who are alive and on subsequent treatment across all subsequent treatment lines (based on median and mean treatment durations for each subsequent treatment), the resulting values are almost identical. This suggests that the PFS and OS curves used in the model accurately reflects the survival on subsequent treatment lines. Whilst J&J acknowledge that the impact of subsequent treatments on survival was not explicitly modelled, the above indicates that further adjustments to survival probabilities to account for	Not a factual inaccuracy. When multiple lines of treatments are included in an economic model, survival and HRQoL data should also be representative of these subsequent treatment lines.

	reflect survival on subsequent treatments.”	subsequent treatment were not considered necessary. Taken together, J&J considers it a misrepresentation to state that the model is not capable of capturing this and that this represents an issue for decision making. Furthermore, the approach taken in the Company Submission is also consistent with previous NICE appraisals for daratumumab, including TA917, in which this criticism was not raised. ⁵	

Issue 8 Adjustment of utilities to account for subsequent lines of treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
As part of Key Issue 7, the EAG report states that the current analyses that assumes that utilities remain constant after progression underestimate QALYs because they fail to capture the impact of subsequent lines of treatments.	J&J requests that the EAG amends their report to acknowledge that the assumption of constant utilities post-progression does not represent a key issue for decision making and clarify that it is a conservative assumption.	The small number of patients reaching subsequent lines means that the assumption of constant utilities post-progression has a minimal impact on the model results. Indeed, exploratory scenario applied to EAG base-case 21 (Table 5.9 of the EAG report) shows that decreasing utilities in the 3 rd and 4 th line of treatment results in very little deviation from the EAG base-case where constant post-progression utilities are used.	Amended. The following text was added in Table 1.8 and page 117 of the report: “Assuming constant utilities upon progression, while a simplifying assumption, has a relatively small impact on model outcomes and is likely conservative with respect to the incremental QALYs gained, as a higher proportion of patients transition to the PD health state in

		Furthermore, using constant post-progression utility values is highly conservative, as the EAG base-case shows that DBTd-L acquires more QALYs post-progression compared with DBLd-DL. As such, reducing utilities after each subsequent line of therapy would result in a greater decrease in post-progression QALYs for DBTd-L, ultimately reducing the ICER.	the DBTd-L arm compared with the DBLd-DL arm.”

Issue 9 Results of EAG’s exploratory analyses using EAG’s base-case

Description of problem	Description of proposed amendment	Justification for amendment					EAG comment
J&J cannot replicate exploratory analysis number 6, 7, 9, 10 and 21 in Table 5.9 in the report.	J&J requests that the EAG provide specific details (sheets and cells changed to produce the numbers they report). The results for scenarios 6, 7, 9 and 10 should match the	J&J have obtained the following results using the EAG model for the four scenarios noted (6, 7, 9 and 10). However, J&J have been unable to generate results for scenario 21, as the utility values used by the EAG have not been shared.					The EAG apologises for the confusion and acknowledges that this was not clear. Please see below: Scenario 6 and 7: Data - Parametric Fits G104 Scenario 9 and 10: Data - Parametric Fits T104
		Exploratory analysis #	Scenario applied to EAG’s base-case	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	
		0	EAG base-case	■	■	38,483	
		6	OS HR = ■ (EAG)	■	■	84,037	

	deterministic sensitivity analysis results as we demonstrate here. For scenario 21, J&J requests that the EAG provide the utilities they used and the implementation in the model.	<table><tr><td>-</td><td>OS HR = █████ (J&J)</td><td>█████</td><td>███</td><td>86,750</td></tr><tr><td>7</td><td>OS HR = █████ (EAG)</td><td>█████</td><td>███</td><td>646,677^a</td></tr><tr><td>-</td><td>OS HR = █████ (J&J)</td><td>█████</td><td>███</td><td>708,088^a</td></tr><tr><td>9</td><td>PFS HR = 0.29 (EAG)</td><td>█████</td><td>███</td><td>DBLd-DL dominates</td></tr><tr><td>-</td><td>PFS HR = 0.29 (J&J)</td><td>█████</td><td>███</td><td>DBLd-DL dominates</td></tr><tr><td>10</td><td>PFS HR = 0.97 (EAG)</td><td>█████</td><td>███</td><td>181,248</td></tr><tr><td>-</td><td>PFS HR = 0.97 (J&J)</td><td>█████</td><td>███</td><td>181,879</td></tr><tr><td>21</td><td>Decreased utility in 3rd and 4th line of treatment (EAG)</td><td>█████</td><td>███</td><td>38,387</td></tr><tr><td>-</td><td>Decreased utility in 3rd and 4th line of treatment (J&J)^b</td><td>███</td><td>███</td><td>N/A</td></tr></table> Footnotes: ^aIn Southwest quadrant of the cost-effectiveness plane ^bJ&J could not determine the utilities used.	-	OS HR = █████ (J&J)	█████	███	86,750	7	OS HR = █████ (EAG)	█████	███	646,677 ^a	-	OS HR = █████ (J&J)	█████	███	708,088 ^a	9	PFS HR = 0.29 (EAG)	█████	███	DBLd-DL dominates	-	PFS HR = 0.29 (J&J)	█████	███	DBLd-DL dominates	10	PFS HR = 0.97 (EAG)	█████	███	181,248	-	PFS HR = 0.97 (J&J)	█████	███	181,879	21	Decreased utility in 3 rd and 4 th line of treatment (EAG)	█████	███	38,387	-	Decreased utility in 3 rd and 4 th line of treatment (J&J) ^b	███	███	N/A	Scenario 21: Apply difference in utility between PF maintenance and 2nd line (██████████) to 3rd and 4th line (██████████, respectively). In any case, the differences between the EAG and company scenarios are minor and do not change the conclusions from the report.
-	OS HR = █████ (J&J)	█████	███	86,750																																												
7	OS HR = █████ (EAG)	█████	███	646,677 ^a																																												
-	OS HR = █████ (J&J)	█████	███	708,088 ^a																																												
9	PFS HR = 0.29 (EAG)	█████	███	DBLd-DL dominates																																												
-	PFS HR = 0.29 (J&J)	█████	███	DBLd-DL dominates																																												
10	PFS HR = 0.97 (EAG)	█████	███	181,248																																												
-	PFS HR = 0.97 (J&J)	█████	███	181,879																																												
21	Decreased utility in 3 rd and 4 th line of treatment (EAG)	█████	███	38,387																																												
-	Decreased utility in 3 rd and 4 th line of treatment (J&J) ^b	███	███	N/A																																												
The EAG conducted a scenario exploring the	J&J requests that this scenario be removed as it is inappropriate given	In line with the licence for daratumumab, daratumumab maintenance treatment is to be administered until disease progression. As used in the PERSEUS trial, daratumumab can, however, be discontinued for patients who have achieved MRD-negativity that is sustained for 12			The EAG considers that this exploratory scenario could still be interesting for the																																											

impact of treating with DL until progression: Scenario 14 (Table 5.9 of the EAG report): TTD – Treat to progression (D within DL)	the evidence base within the submission. This is because MRD-guided treatment is the expected clinical practice if DBLd-DL is recommended for us in the UK. In addition, this scenario deviates the model from the evidence base. As such it is not relevant when considering whether DBLd represents good value NHS resources. Furthermore, it would be incorrect to incorporate the cost of MRD testing when running the scenario; the use of	months, if they have been treated on maintenance for at least 24 months, as recommended by the SmPC. In the PERSEUS trial, about two thirds of the trial participants in the DBLd-DL arm stopped receiving the daratumumab element of the DL maintenance after 2 years of treatment. Therefore, the modelling approach for TTD of daratumumab within DL should be stratified based on sustained MRD test treatment guiding criteria. To determine eligibility, patients are tested for MRD status over time to check if they had achieved sustained MRD-negativity and if they had at least two years of DL maintenance. For patients who meet the criteria, the TTD data is mature such that in both the company and EAG base cases, the Kaplan Meier curve is selected. There is no uncertainty to explore on TTD for daratumumab in patients who meet the treatment guiding criteria.⁶ MRD testing alongside DBLd-DL treatment, if approved, is expected clinical practice in the UK. Secondly, if patients are to be treated until disease progression regardless of their MRD status, they do not require MRD testing as MRD results are not needed to make treatment decisions, and therefore the cost of MRD testing should not be included in the analysis.	Appraisal Committee. However, it acknowledges that MRD should be zero. This has been changed accordingly.

	the MRD test is to guide treatment.		
The EAG included scenarios that focused on different assumptions on treatment waning, i.e., scenarios 11,12 and 13 in Table 5.9 of the EAG report.	J&J requests that these 3 scenarios be removed as they are speculative and not evidence-based. All long-term OS and PFS predictions for DBLd-DL based on these scenarios are inconsistent with elicited survival estimates from clinical experts and artificially undervalue the expected benefit of DBLd-DL to HDT-ASCT eligible patients with NDMM.	Our position is that implementation of treatment waning in the economic model is inappropriate. This is because it: 1. deviates from the evidence base generated by expert elicitation of expected long-term survival outcomes following DBLd-DL. 2. Is not supported by evidence from the PERSEUS or AURIGA trials 3. Is inconsistent with the precedent of prior appraisals 1. The 3 scenarios explored resulted in OS and PFS projections that were lower than the clinical estimates elicited, hence underestimating the expected benefit of DBLd-DL. 2. Results from PERSEUS do not provide any evidence of treatment waning, and so presentation of these scenarios is misleading. In the PERSEUS trial, the number of OS and PFS events among patients who stopped daratumumab maintenance after meeting the MRD-guided stopping criteria was small (one and two events for OS and PFS respectively). Further, inspection of the time-varying hazard ratios for both OS and PFS in PERSEUS do not indicate that there is a treatment waning signal (J&J response to Clarification Question B6 (b)). It is important to emphasise that this exploration is based on	Not a factual inaccuracy. The EAG considers that these exploratory scenarios could still be interesting for the Appraisal Committee.

		model settings that are arbitrary, given the absence of evidence regarding if, or when, the treatment effect might decline over time. 3. Insight from prior appraisals may prove useful in exploring this topic in a more nuanced way. In TA917⁵, clinical experts considered that there was no evidence or biological justification to support treatment effect waning. In TA763³ the Committee concluded that it was reasonable to assume that the effect of a deepening response would be maintained over a lifetime with no waning of treatment effect following DBTd induction and consolidation therapy. Given induction and consolidation is for a fixed duration of six cycles, it is reasonable to expect that patients receiving a further minimum of two years of DL maintenance therapy would similarly sustain the treatment benefit over a lifetime time horizon.	

Issue 10 EAG description of PSA results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG report has described that some functionalities in the economic model submitted after clarification result in errors. Specifically, the EAG report states that “the probabilistic	J&J apologises for the errors encountered by the EAG after running the PSA. These errors have been resolved in the model submitted alongside this response and, as such, J&J	First, J&J would like to apologise for this and now have fixed the PSA errors when the Gompertz curve is selected for PFS.	The EAG still experiences issues with the PSA which is not able to run in all computers. However, since we managed to run the PSA in one computer, we suspect that the problem might also be on our

sensitivity analysis (PSA) and scenarios including assuming wastage, changing relative dose intensity (RDI), patient weight or body surface area (BSA), returned errors in the cost calculations.” (Page 19, Section 1.7). The EAG report states that for the PSA, the EAG prefers changing the SEs to 20% deviation from the mean. The EAG report also claims that, compared to the company’s CE-plane in Figure 5.1 of the report, the EAG PSA is expected to result in a wider cloud of outcomes spread over the four quadrants. Additionally, the EAG report states that, since the EAG’s base-case ICER is also higher than the company’s base-case ICER, the estimated probabilities that DBLd-DL is a cost-effective alternative to DBTd-L at the common thresholds of £20,000 and	kindly requests that the EAG modifies the following descriptions of expected PSA outcomes now that the model can run the PSA with the EAG base-case assumptions: • The EAG’s claim that the EAG base-case PSA is expected to result in a wider cloud of outcomes spread over the four quadrants is inaccurate • Speculation that the estimated probabilities that DBLd-DL is a cost-effective alternative to DBTd-L at £20,000 and £30,000 per QALY would be lower than those obtained in the Company’s base-case (40% and 43%) is inaccurate	J&J have also fixed the mis-referencing of patient weight and BSA in the Parameters Sheet, in the version of the model provided alongside this response, so that they can be included in the DSA analysis. J&J would like to note that assuming wastage, and changing RDIs, can be done in cells H35 and H36, respectively, of the Sheet “Costs”. To change the RDI option in Sheet “Costs”, cell H36, please change cell I9 to FALSE in Sheet “Cost Comparison”. When wastage is not included in the analysis, the EAG base-case ICER of £38,483 per QALY gained is reduced to £36,488 per QALY gained, whereas when RDI is not included in the analysis, the ICER changes to £38,994 per QALY gained. No errors were observed when these selections were made by J&J. Overall, these results indicate that scenarios exploring changes to RDI or wastage have minimal impact on model results. J&J have also changed the SEs to 20% deviation from the mean for both DSA and PSA analyses, in line with the	side, so we have decided to remove the statements regarding the errors. Also, since the impact of wastage, RDI, etc. on the model results seem to be minor, we have also removed the statements regarding these scenarios. The EAG PSA has also been included in the EAG report. There is a large deviation between the deterministic and probabilistic results. This was already hinted in the EAG report but the company has not provided additional clarification on this point. Given the problems the EAG has experienced running the PSA and the lack of time to explore this properly, the EAG was not able to identify the cause of this discrepancy at the time this report was completed. Since NICE prefers the PSA results over the deterministic ones, resolving or explaining this discrepancy seems crucial and, in the meantime, this constitutes a key

£30,000 per QALY gained, would be lower than those obtained in the company's base-case.		EAG's suggestion. The distribution of PSA simulations using the EAG base-case are ■% in the Northeast, ■% in the Southeast, ■% in the Southwest and ■% in the Northwest, showing a large concentration of simulations in only two quadrants. Overall, the PSA simulations based on the EAG base-case and assumptions resulted in improved probabilities of cost-effectiveness of ■% and ■% at £30,000 and £20,000 per QALY gained, values that are different from the EAG's predictions. This confirms that speculation by the EAG that the estimated probabilities of the cost-effectiveness of DBLd-DL are in fact lower than those presented in the Company's Submission is inaccurate. These results are heavily influenced by the wide OS HR and acquisition costs for subsequent treatments.	issue for the cost-effectiveness evidence.

Minor factual inaccuracies

Issue 11 Wording around the percentage of patients treated with BCd should be improved for clarity

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The following wording is included in Table 2.1, Page 21, Section 2 of the EAG report: “The comparators are in line with the NICE scope, although a small percentage of patients seem to be treated with BCd.”	“The comparators are in line with the NICE scope, although a very small percentage of patients seem to be treated with BCd.”	Given that the percentage of patients treated with BCd was <2% according to NHSE data, it should be highlighted here that this percentage is very small, to align with the wording in Section 2.3 of the EAG report.	Not a factual inaccuracy.

Issue 12 Incorrect categorisation of MRD-negativity status and AEs

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Categorisation of AEs under ‘response rates’ in Table 3.5 and Table 3.12 of the EAG report.	AEs should be moved to not fall under the ‘response rates’ heading.	It is incorrect to categorise AEs under ‘response rates’.	Amended.

Issue 13 Incorrect values reported for the Company base-case probabilistic CE results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment																								
The Company base-case probabilistic CE results in Table 5.5, Page 161 of the EAG report do not align with Table 3 of the addendum to the clarification response letter provided by the Company.	Table 5.5 should be updated as follows (updated values bolded): <table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total LY G</th><th>Total QALYs</th><th>Inc. Costs (£)</th><th>Inc. LY G</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th></tr><tr><td>DBLd-DL</td><td></td><td></td><td></td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>DBTd-L</td><td></td><td></td><td></td><td></td><td></td><td></td><td>29,940</td></tr></table>	Technologies	Total costs (£)	Total LY G	Total QALYs	Inc. Costs (£)	Inc. LY G	Inc. QALYs	ICER (£/QALY)	DBLd-DL				-	-	-	-	DBTd-L							29,940	Values in the original Table 5.5 were incorrect as per Table 3 of the addendum to the clarification response letter provided by the Company. Additionally, given that DBLd-DL is the reference arm, incremental	Not a factual inaccuracy. The results presented in Table 5.5 of the EAG report correspond to those in Table 3 of the addendum to the clarification response letter provided by the company, file name “ID6249_Daratumumab_NICE_Addendum to Clarification Letter Responses_CON – 230825.docx”. They are also the same as those in the model submitted in response to the Clarification Letter, file name “ID6249_Daratumumab_NICE_CEM_22Aug2025_CON - 230825 [CON].xlsm”. Also, the comparator (SoC) should be the ‘reference arm’ in an incremental analysis.
Technologies	Total costs (£)	Total LY G	Total QALYs	Inc. Costs (£)	Inc. LY G	Inc. QALYs	ICER (£/QALY)																				
DBLd-DL				-	-	-	-																				
DBTd-L							29,940																				

Furthermore, the incremental costs, LYs, QALYs and ICER were presented in the 'DBLd-dL' row in the EAG report.		costs, LYs, QALYs and the ICER should be presented for DBTd-L.	

Issue 14 Incorrect numbering of key issue

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 1.2, Page 19, Section 1.5 states that "This raises some concerns regarding the second key issue since in comparison with TA763, the current appraisal estimates substantially less LYs for the comparator arm".	"This raises some concerns regarding the sixth key issue since in comparison with TA763, the current appraisal estimates substantially less LYs for the comparator arm".	Incorrect numbering of key issue.	Amended.

Issue 15 Incorrect treatment mentioned for induction and consolidation phase

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 2.1, Page 21, Section 2 states “However, the company has conducted a CEA for the complete sequence i.e. induction, consolidation and maintenance, and a cost only comparison for the induction and consolidation phase only i.e. DBLd followed by SoC, which is L (as opposed to DL).”	Please remove the wording “followed by SoC”.	Given that SoC is not part of the induction plus consolidation phase, it is incorrect to include mention of ‘followed by SoC’ in this sentence.	Not a factual inaccuracy. This is SoC for maintenance.

Issue 16 Incorrect inclusion of ISS stage as a key difference between patients in the PERSEUS and CASSIOPEIA trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 102, Section 3.3 states “The patients in the PERSEUS trial had a lower ECOG PS and ISS stage, which suggested higher levels of patient functioning and a less advanced disease stage, when compared	Please remove mention of ISS stage here, given the difference was minimal, such that the sentence reads as follows: “The patients in the PERSEUS trial had a lower ECOG PS, which suggested higher levels of	The difference in ISS stage between patients in the PERSEUS versus CASSIOPEIA trial was minimal and therefore should not be included in this sentence.	Not a factual inaccuracy.

with those patients in the CASSIOPEIA trial”.	patient functioning when compared with those patients in the CASSIOPEIA trial”		

Issue 17 Incorrect classification of additional scenario as an updated base-case

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
It is stated on Page 157, Section 4.2.8.10 that “After clarification, the cost per vial of cyclophosphamide was updated in the economic model to reflect eMIT December 2024 prices (replacing the July 2024 values). ⁷ ”	“After clarification, the cost per vial of cyclophosphamide was updated in the economic model to reflect eMIT December 2024 prices (presented as a scenario alongside the July 2024 values). ⁷ ”	The original wording was incorrect given that this update was presented as a scenario rather than to replace the July 2024 values.	Amended.

Issue 18 Wording around the longer time in the maintenance phase translating to improved OS and PFS is unclear

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
It is stated on Page 15, Section 1.2 that “Increasing total QALYs due to patients remaining longer in the maintenance phase of treatment and shorter in post-progression. This is caused by	“Increasing total QALYs due to patients remaining longer in the maintenance phase of treatment and shorter in post-progression. This therefore translates to an improvement in overall	Whilst not a factual inaccuracy, this wording should be improved as suggested for clarity.	Not a factual inaccuracy. Also, the direction of causality is correct i.e. improvement in OS and PFS (as observed) leads to

an improvement in overall survival (OS) and PFS.”	survival (OS) and PFS given patients are in the maintenance phase for longer.”		more time in that health state (as modelled).

Issue 19 Incorrect presentation of incremental costs, LYs, QALYs and ICER in the base-case CE results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment																								
In Table 5.1, Page 158, Section 5.1.1, the incremental costs/ LYs, QALYs and ICER are presented in the ‘DBLd-dL’ row.	Please update Table 5.1 as follows (changes in bold): <table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Inc. Costs (£)</th><th>Inc. LYG</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th></tr><tr><td>DBLd-DL</td><td>■</td><td>■</td><td>■</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>DBTd-L</td><td>■</td><td>■</td><td>■</td><td>■</td><td>■</td><td>■</td><td>25,888</td></tr></table>	Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	DBLd-DL	■	■	■	-	-	-	-	DBTd-L	■	■	■	■	■	■	25,888	Given that DBLd-dL is the reference arm, incremental costs, LYs, QALYs and the ICER should be presented for DBTd-L.	Not a factual inaccuracy. Also, the comparator (SoC) should be the ‘reference arm’ in an incremental analysis.
Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)																				
DBLd-DL	■	■	■	-	-	-	-																				
DBTd-L	■	■	■	■	■	■	25,888																				

Issue 20 Reference to updated Company base-case and corrections in re-submitted Company Submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On Page 143, Section 4.2.8, the EAG report states that “prices of bortezomib, lenalidomide,	Remove the following statements on Page 143, Section 4.2.8: “Although the	J&J re-submitted the Company Submission to correct any inaccurate values that were	Not a factual inaccuracy.

thalidomide, and dexamethasone were updated in the electronic model, this was not done in Tables 69 and 70 of the CS, which still report the July 2024 values”.	prices of bortezomib, lenalidomide, thalidomide, and dexamethasone were updated in the electronic model, this was not done in Tables 69 and 70 of the CS, which still report the July 2024 values. This explains why the prices listed in Table 4.13 above differ from those in Tables 69 and 70 of the CS.” Add a footnote to Table 4.13 and Table 4.16 in the EAG report to state that “Drug costs sourced from eMIT provided in this table differ from those presented in the CS as the company provided an updated base-case alongside their responses to Clarification Questions, using updated eMIT costs (December 2024 prices, replacing July 2024 prices) which were not available at the time of submission.”	included in the original Submission. J&J also provided an updated base-case alongside their response to Clarification Questions, following corrections to errors in the model itself, and updated eMIT drug costs (as detailed in Section 5.1.1, Page 158 of the EAG report). However, J&J intentionally did not update the eMIT costs in the re-submitted Company Submission, as this would have misaligned with the base-case results included here. Wording in the EAG report should therefore be updated to clarify this.	Nevertheless, to clarify the reason for the differences with the prices mentioned in the CS, the footnote to Table 4.13 was changed from “Cost sourced from the electronic model (a different value was mentioned in the CS)” into “Cost sourced from the electronic model. These differed from those presented in the CS, as the company provided an updated base-case analysis during the clarification phase, using updated eMIT costs (December 2024 prices, replacing July 2024 prices) which were not available at the time of submission.” Similarly, the footnote to Table 4.16 was changed into “Cost sourced from the electronic model. Except for antihistamine, these differed from those presented in the CS, as the company provided an updated base-case analysis during the clarification phase, using updated eMIT costs (December 2024 prices, replacing July 2024 prices) which were not available at the time of submission.”

Issue 21 Costs of adverse events during the ASCT phase

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On Page 152, Section 4.2.8, the EAG report suggests that costs of AEs were not included separately for the ASCT phase, which raises the possibility that they were omitted.	Remove statements or suggestions that the cost of AEs during ASCT were not accounted for in the Company's economic analysis (e.g., Remove "Examination of the electronic model suggests that costs of AEs were not included separately for the ASCT phase, which raises the possibility that they were omitted").	As the EAG report notes on Page 152, Section 4.2.8, the CS and model specifies that the costs of managing AEs is informed by the incidence of AEs which occurred across induction, ASCT, consolidation and maintenance phases. For example, the cumulative incidence of anaemia during the induction/ASCT/consolidation phases was █% as per the CS (Table 63) and the model. This accounts for the incidence of Grade 3/4 AEs in the induction (n=█), pre-ASCT (n=█), ASCT (n=█) and consolidation phases (n=█), which, when summed, gives █% (█ = █, █ = █%). As the model and CS specifies that the cost of AEs during ASCT were captured, it is misleading to state that there is a possibility they were omitted.	Amended. The EAG now understands that the incidence rates listed in Table 63 of the CS actually also include the AEs occurring during the ASCT phase (although the table's caption refers to the "induction and consolidation phases"). Therefore, the following paragraph was removed from the EAG report (Section 4.2.8.8): "In addition, the EAG is unclear whether AEs were included separately for ASCT. Section 3.5.3 of the CS states that "the cost of managing AEs experienced by patients during the induction, ASCT, consolidation and maintenance treatment phases was included in the base case economic analysis".¹ Similarly, Section 3.3.3 of the CS suggests that AEs during ASCT were included,¹ and the electronic model (sheet 'Adverse events') refers to the "cumulative probability of AEs during

			induction/ASCT/consolidation”.⁴⁸ However, Tables 63 and 64 of the CS do not present incidence rates of AEs during ASCT, but only present probabilities for AEs in the induction, consolidation, and the maintenance phases.¹ Examination of the electronic model suggests that costs of AEs were not included separately for the ASCT phase, which raises the possibility that they were omitted.”

Issue 22 Appropriateness of the induction and consolidation phase ITC

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
In Table 1.4, Page 16, Section 1.4, the EAG report states "The appropriateness of the ITC, censored prior to maintenance also needs to be considered." However, the table does not provide any context as to why the appropriateness of the might need to be considered ITC.	Remove "The appropriateness of the ITC, censored prior to maintenance also needs to be considered." from Table 1.4, Page 16, Section 1.4.	In Table 1.4, the description of Key Issue 4 provides an outline of the approach taken to the ITC, and summarises the SLR and pragmatic review methodology. As no context or suggestion as to why the ITC itself might be considered inappropriate, this concluding statement should be removed for clarity.	Amended. Note that this issue is about the lack of comparison of the complete sequence and the alternative approaches that were or might be taken.

Issue 23 Impact of subsequent treatments on survival

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On Page 157, Section 4.2.8, the EAG report states “that 4th-line treatments following CTd should have been included in the model” and “it was not entirely clear whether 4th-line treatments following CTd were included in the model”.	Remove any statements from the EAG report which imply that 4th-line treatments following patients who received CTd in the 3rd-line were not included in the model.	J&J acknowledges that the column showing 4th-line treatments following 3rd-line CTd in Table 78 of the CS was erroneously omitted, and apologises for the error, 4th-line treatments for those who received 3rd-line CTd were captured in the model. This is shown in the ‘MKT %4th line’ tab of the model (Cells T20–T28). Given that these treatments are clearly shown in the model, suggestions in the EAG report that they were not included are misleading, and potentially a misrepresentation of the economic analysis.	The EAG understands that 4th-line treatments following CTd were actually included in the analysis, even though Table 78 of the CS suggested otherwise. Therefore, the paragraph of the EAG report that discussed this issue (in Section 4.2.8.10) was changed into: “Finally, the EAG noted that cyclophosphamide, thalidomide, and dexamethasone (CTd) was listed in Table 77 of the CS as a 3rd-line treatment, but not in in Table 78 of the CS, which presents the 4th-line treatments by prior 3rd-line treatment received.¹ This raises the question of whether 4th-line treatments following CTd were included in the analysis. From the electronic model, it seems that they indeed were included, using the same distribution that was used for ixazomib, lenalidomide and dexamethasone (ILd) and lenalidomide with dexamethasone (Ld).” Furthermore, we changed Table 4.20 of the EAG report to include 4th-line treatments following 3rd-line CTd.

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
As noted in the 'Principal factual inaccuracies' section above (Issue 5) here is a repeated sentence in Table 1.7, Page 18, Section 1.5 that should be removed.	Please remove the following sentence from the 'what alternative approach has the EAG suggested' row of Table 1.7: "Highlight a large difference in total life years estimated for DBTd-L in TA763 (14.6"6) and the current appraisal (■■■■)." "	It appears that this sentence has been mistakenly added to this row, given that it is repeated from the row above.	Amended.
There is a reference from the Company submission mistakenly included in Table 2.1, Page 21, Section 2.	Please remove the '2' from the end of the following sentence in Table 2.1: "During the DBTd appraisal, the Committee's preferred assumption was that BTd was the most relevant comparator to DBTd from the comparators listed in the NICE scope, which also included CTd, Bd and BCd.2"	This is an old reference from the Company submission that is not used in the EAG report.	Corrected.

On Page 82, Section 3.2.7 there is a reference mistakenly included from the Company submission that is no longer needed.	Please remove the '110' from the end of the following sentence: “...with the exception of the ≥65 years, ISS Stage III, high cytogenic risk and race 'other' subgroups for ≥CR rate and race 'other' for MRD-negativity.110”.	This is an old reference from the Company submission that is not used in the EAG report.	Corrected.
There is a word missing in the following sentence on Page 101, Section 3.3: “The company conducted feasibility assessment to assess the suitability of comparing PERSEUS and CASSIOPEIA in an ITC, i.e. whether the included studies were sufficiently homogenous across their populations and outcomes.”	“The company conducted a feasibility assessment to assess the suitability of comparing PERSEUS and CASSIOPEIA in an ITC, i.e. whether the included studies were sufficiently homogenous across their populations and outcomes.”	Incorrect grammar used.	Corrected.
On Page 107, Section 3.4 there is a full stop is missing from the end of the following sentence: “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. ⁸ ”	“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. ⁸ ”	Incorrect grammar used.	Not a factual inaccuracy – this is a quote from the CS.

population represented by the data. ⁸			
On Page 108, Section 3.4.2, there is a spelling mistake in the following sentence: “...which indidates that the disbritution of these three covariates were not well balanced after matching. ⁹ ”	“...which indicates that the disbritution of these three covariates were not well balanced after matching. ⁹ ”	Spelling mistake.	Corrected.
On Page 108, Section 3.4.2 there is a spelling mistake in the following sentence: “In the sensitivity analyses of ITC, the distribution of all these covariates between the DBTd poluaition and the DBLd population were well balanced after matching. ⁹ ”	“In the sensitivity analyses of ITC, the distribution of all these covariates between the DBTd poluaition and the DBLd population were well balanced after matching. ⁹ ”	Spelling mistake.	Corrected.
On Page 110, Section 3.4.3.1 there is a grammar mistake in the following sentence: “The results of ≥VGPR for both the unadjusted and adjusted base-case and sensitivity analysis (all covariate adjusted) for DBTd versus DBLd from induction to the end of	“The results of ≥VGPR for both the unadjusted and adjusted base-case and sensitivity analysis (all covariates adjusted) for DBTd versus DBLd from induction to the end of consolidation are presented in Table 3.42 below.”	Incorrect grammar used.	Corrected.

consolidation are presented in Table 3.42 below.”			
On Page 110, Section 3.4.3.1 there is wording missing from the following sentence: “It should be noted that the sensitivity analysis where all covariates were adjusted for higher ORs than the one from the base-case model. ⁹ ”	“It should be noted that the sensitivity analysis where all covariates were adjusted for resulted in higher ORs than the one from the base-case model. ⁹ ”	Wording is missing from this sentence.	Corrected.
There is a typo on Page 115, Section 3.4.5 in the following sentence: “Therefore, this might have introduced uncertainties on the validity of results from the base-case ITC analyses, which constitutes a key issue.”	“Therefore, this might have introduced uncertainties on the validity of results from the base-case ITC analyses, which constitutes a key issue.”	Typo.	Corrected.
There is a typo on Page 116, Section 3.6 in the following sentence: “Given that the company did not find any studies that compared the complete sequence of DBLd	“Given that the company did not find any studies that compared the complete sequence of DBLd followed by dL with SoC in the form of DBTd followed by L...”	Typo.	Corrected.

followed by Ld with SoC in the form of DBTd followed by L...			
There is a typo on Page 122, Section 4.2.3 in the following sentence: "Utilities remain constant after progression (see Section 4.2.7) and survival probabilities do not seem to have neem adjusted for subsequent lines of treatment (see Section 4.2.6)."	"Utilities remain constant after progression (see Section 4.2.7) and survival probabilities do not seem to have been adjusted for subsequent lines of treatment (see Section 4.2.6)."	Typo.	Corrected.
There is a typo in the heading of Table 4.3, Page 125, Section 4.2.6.1.1 that reads "Predicted DBTd-DL OS versus clinical expert expectations (with GPM cap)"	"Predicted DBLd -DL OS versus clinical expert expectations (with GPM cap)"	Typo.	Corrected.
There is a typo on Page 127, Section 4.2.6.1.2 in the following sentence: "However, The EAG does not consider that any of the alternative extrapolations presented by the company offer a better fit"	"However, the EAG does not consider that any of the alternative extrapolations presented by the company offer a better fit"	Typo.	Corrected.

There is a typo in the footnote of Table 5.4, Page 160, Section 5.1.1 in the following sentence: “Based on economic model submitted with the response to the clarification letter. ¹⁰ ”	“Based on Table 1 of Addendum to clarification letter response . ¹⁰ ”	Typo.	Corrected.
There is a typo on Page 163, Section 5.1.2.2 in the following sentence: “The company considered this scenario highly conservative, and resulted in DBLd-DL being dominant against DBTdL”	“The company considered this scenario highly conservative, and resulted in DBLd-DL being dominant against dL ”	Typo.	Corrected.
There is a typo on Page 163, Section 5.1.2.2 in the following sentence: “While maintenance costs ae higher for DBLd-DL, large savings are accrued in the post-progression phase, mainly in drug acquisition costs of 2nd line treatments.”	“While maintenance costs are higher for DBLd-DL, large savings are accrued in the post-progression phase, mainly in drug acquisition costs of 2nd line treatments.”	Typo.	Corrected.

There is a typo in the footnote of Figure 4.5, Page 125, Section 4.2.6.2.1 in the following sentence: “Based on Figure 24 of the CS ⁹ ”	“Based on Figure 26 of the CS ⁹ ”	Typo.	Corrected.
There is a typo in the footnote of Figure 4.6, Page 132, Section 4.2.6.3.2 in the following sentence: “Based on Figure 29 of the CS ⁹ ”	“Based on Figure 28 of the CS ⁹ ”	Typo.	Corrected.
There is a typo in the footnote of Figure 4.7, Page 133, Section 4.2.6.3.2 in the following sentence: “Based on Figure 30 of the CS ⁹ ”	“Based on Figure 29 of the CS ⁹ ”	Typo.	Corrected.
There is a typo in the footnote of Figure 4.8, Page 134, Section 4.2.6.3.2 in the following sentence: “Based on Figure 32 of the CS ⁹ ”	“Based on Figure 31 of the CS ⁹ ”	Typo.	Corrected.
There is a typo in the footnote of Figure 4.8, Page 135, Section 4.2.6.3.4 in the following sentence: “Based on Figure 34 of the CS ⁹ ”	“Based on Figure 33 of the CS ⁹ ”	Typo.	Corrected.

There is a typo on Page 134, Section 4.2.7.1.2 in the following sentence: "...as reported in the HSE 2014 dataset by NICE DSU, using methods from Hernández-Álava et al. 2022. ¹¹ "	"...as reported in the HSE 2014 dataset by NICE DSU, using methods from Hernández-Álava <i>et al.</i> 2014 . ¹¹ "	Typo.	Not a factual inaccuracy – the company cite the same 2022 reference.

Confidentiality highlighting inaccuracies

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
Page 22, Section 2	The number of HDT-ASCT eligible patients with NDMM used in the budget impact analysis is confidential and therefore requires CiC highlighting.	"Equivalent to 98.9% assuming an available pool of ■■■ HDT-ASCT eligible patients with NDMM."	Amended.
Page 43, Section 3.2.2	The number and proportion of patients in the DBLd-DL arm of the PERSEUS trial who re-started	"This represents only ■■■% of patients (i.e., only ■■ of ■■■ patients in the DBLd-DL arm who stopped daratumumab and continued maintenance therapy) in PERSEUS re-starting daratumumab following loss of MRD-negative status."	Amended.

	daratumumab following a loss of MRD-negative status are not published and therefore require CiC highlighting.		
Page 52, Section 3.2.4	The number and proportions of patients with extramedullary disease in the BLd and DBLd treatment arms of the PERSEUS trial are not published and therefore require CiC highlighting.	“Extramedullary disease (defined as the presence of one or more extramedullary soft-tissue lesions) was present in a similar proportion of patients in both the BLd and DBLd treatment arms (■ patients [■%] versus ■ patients [■%], respectively).”	Amended.
Table 3.10, Page 52, Section 3.2.4	The median age of patients in the DBLd arm and the total population in the ITT analysis set of the PERSEUS trial is published and therefore does not require CiC highlighting.	“Median age, years (range): DBLd arm: 61.0 (32, 70) Total: 60.0 (31, 70)“	Amended.

Table 3.10, Page 52, Section 3.2.4	The number and percentage of patients in the BLd and DBLd arms in the ITT analysis set of the PERSEUS trial in the overall age groups <50 and ≥50, <65 are published and therefore do not require CiC highlighting.	<table><tr><th rowspan="2">Characteristic</th><th colspan="2">ITT analysis set</th></tr><tr><th>BLd arm^a (N=354)</th><th>DBLd arm^b (N=355)</th></tr><tr><td colspan="3">Overall age group, n (%)</td></tr><tr><td><50</td><td>54 (15.3)</td><td>54 (15.2)</td></tr><tr><td>≥50 and <65</td><td>213 (60.2)</td><td>207 (58.3)</td></tr></table>	Characteristic	ITT analysis set		BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Overall age group, n (%)			<50	54 (15.3)	54 (15.2)	≥50 and <65	213 (60.2)	207 (58.3)	Amended.													
Characteristic	ITT analysis set																													
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)																												
Overall age group, n (%)																														
<50	54 (15.3)	54 (15.2)																												
≥50 and <65	213 (60.2)	207 (58.3)																												
Table 3.10, Page 53, Section 3.2.4	The number and percentage of patients with each baseline ECOG PS in each treatment arm of the ITT analysis set in the PERSEUS trial are published and therefore do not require CiC highlighting.	<table><tr><th rowspan="2">Characteristic</th><th colspan="3">ITT analysis set</th></tr><tr><th>BLd arm^a (N=354)</th><th>DBLd arm^b (N=355)</th><th>Total (N=709)</th></tr><tr><td colspan="4">Baseline ECOG PS, n (%)^d</td></tr><tr><td>0</td><td>230 (65.0)</td><td>221 (62.3)</td><td>451 (63.6)</td></tr><tr><td>1</td><td>108 (30.5)</td><td>114 (32.1)</td><td>222 (31.3)</td></tr><tr><td>2</td><td>16 (4.5)</td><td>19 (5.4)</td><td>35 (4.9)</td></tr><tr><td>3</td><td>0</td><td>1 (0.3)</td><td>1 (0.1)</td></tr></table>	Characteristic	ITT analysis set			BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)	Baseline ECOG PS, n (%) ^d				0	230 (65.0)	221 (62.3)	451 (63.6)	1	108 (30.5)	114 (32.1)	222 (31.3)	2	16 (4.5)	19 (5.4)	35 (4.9)	3	0	1 (0.3)	1 (0.1)	Amended.
Characteristic	ITT analysis set																													
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)																											
Baseline ECOG PS, n (%) ^d																														
0	230 (65.0)	221 (62.3)	451 (63.6)																											
1	108 (30.5)	114 (32.1)	222 (31.3)																											
2	16 (4.5)	19 (5.4)	35 (4.9)																											
3	0	1 (0.3)	1 (0.1)																											
Table 3.10, Page 53,	The number and percentage of patients with each of the following types of	<table><tr><th rowspan="2">Characteristic</th><th>ITT analysis set</th></tr><tr><th>BLd arm^a (N=354)</th></tr></table>	Characteristic	ITT analysis set	BLd arm ^a (N=354)	Amended.																								
Characteristic	ITT analysis set																													
	BLd arm ^a (N=354)																													

Section 3.2.4	measurable disease and all ISS stages in the BLd arm of the ITT analysis set in the PERSEUS trial are published and therefore do not require CiC highlighting: • IgG • IgA • Other^g • Urine only • Serum FLC • NE	<table><tr><th colspan="2">Type of measurable disease, n (%)</th></tr><tr><td>Serum</td><td>281 (79.4)</td></tr><tr><td>IgG</td><td>185 (52.3)</td></tr><tr><td>IgA</td><td>85 (24.0)</td></tr><tr><td>Other^g</td><td>11 (3.1)</td></tr><tr><td>Urine only</td><td>46 (13.0)</td></tr><tr><td>Serum FLC</td><td>27 (7.6)</td></tr><tr><td>NE</td><td>0</td></tr><tr><th colspan="2">ISS Staging, n (%)^h</th></tr><tr><td>Stage I</td><td>178 (50.4)</td></tr><tr><td>Stage II</td><td>125 (35.4)</td></tr><tr><td>Stage III</td><td>50 (14.2)</td></tr></table>	Type of measurable disease, n (%)		Serum	281 (79.4)	IgG	185 (52.3)	IgA	85 (24.0)	Other ^g	11 (3.1)	Urine only	46 (13.0)	Serum FLC	27 (7.6)	NE	0	ISS Staging, n (%) ^h		Stage I	178 (50.4)	Stage II	125 (35.4)	Stage III	50 (14.2)	
Type of measurable disease, n (%)																											
Serum	281 (79.4)																										
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Stage I	178 (50.4)																										
Stage II	125 (35.4)																										
Stage III	50 (14.2)																										
Table 3.10, Page 54, Section 3.2.4	The median time from MM diagnosis to randomisation for patients in each treatment arm of the ITT analysis set in the PERSEUS trial are published and therefore do not require CiC highlighting.	<table><tr><th rowspan="2">Characteristic</th><th colspan="3">ITT analysis set</th></tr><tr><th>BLd arm^a (N=354)</th><th>DBLd arm^b (N=355)</th><th>Total (N=709)</th></tr><tr><th colspan="4">Time from MM diagnosis to randomisation, years</th></tr><tr><td>Mean (SD)</td><td>██████</td><td>██████</td><td>██████</td></tr><tr><td>Median (range)</td><td>1.12 (0.1, 184.6)</td><td>1.18 (0.0, 46.5)</td><td>1.15 (0.0, 184.6)</td></tr></table>	Characteristic	ITT analysis set			BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)	Time from MM diagnosis to randomisation, years				Mean (SD)	██████	██████	██████	Median (range)	1.12 (0.1, 184.6)	1.18 (0.0, 46.5)	1.15 (0.0, 184.6)	Amended.					
Characteristic	ITT analysis set																										
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)																								
Time from MM diagnosis to randomisation, years																											
Mean (SD)	██████	██████	██████																								
Median (range)	1.12 (0.1, 184.6)	1.18 (0.0, 46.5)	1.15 (0.0, 184.6)																								

Table 3.10, Page 54, Section 3.2.4	The number and percentage of patients with each of the following cytogenetic risk classifications in the BLd arm of the ITT analysis set in the PERSEUS trial are published and therefore do not require CiC highlighting: • Standard risk • High risk • Indeterminate	<table> <tr> <th rowspan="2">Characteristic</th><th colspan="3">ITT analysis set</th></tr> <tr> <th>BLd arm^a (N=354)</th><th>DBLd arm^b (N=355)</th><th>Total (N=709)</th></tr> <tr> <td colspan="4">Cytogenetic risk, n (%)^j</td></tr> <tr> <td>Standard risk</td><td>266 (75.1)</td><td>264 (74.4)</td><td>530 (74.8)</td></tr> <tr> <td>High risk^k</td><td>78 (22.0)</td><td>76 (21.4)</td><td>154 (21.7)</td></tr> <tr> <td>del(17p)</td><td>██████</td><td>██████</td><td>██████</td></tr> <tr> <td>t(4;14)</td><td>██████</td><td>██████</td><td>██████</td></tr> <tr> <td>t(14;16)</td><td>██████</td><td>██████</td><td>██████</td></tr> <tr> <td>Indeterminate</td><td>10 (2.8)</td><td>15 (4.2)</td><td>25 (3.5)</td></tr> </table>	Characteristic	ITT analysis set			BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)	Cytogenetic risk, n (%)^j				Standard risk	266 (75.1)	264 (74.4)	530 (74.8)	High risk ^k	78 (22.0)	76 (21.4)	154 (21.7)	del(17p)	██████	██████	██████	t(4;14)	██████	██████	██████	t(14;16)	██████	██████	██████	Indeterminate	10 (2.8)	15 (4.2)	25 (3.5)	Amended.
Characteristic	ITT analysis set																																					
	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Total (N=709)																																			
Cytogenetic risk, n (%)^j																																						
Standard risk	266 (75.1)	264 (74.4)	530 (74.8)																																			
High risk ^k	78 (22.0)	76 (21.4)	154 (21.7)																																			
del(17p)	██████	██████	██████																																			
t(4;14)	██████	██████	██████																																			
t(14;16)	██████	██████	██████																																			
Indeterminate	10 (2.8)	15 (4.2)	25 (3.5)																																			
Table 3.11, Page 55, Section 3.2.4	The number and proportion of patients in the DBLd-DL arm of the PERSEUS trial aged 65 years or older is published and therefore does not require CiC highlighting.	“PERSEUS DBLd-DL (n=355) 65 years and older: 94 (26.5)”	Amended.																																			

Table 3.11, Page 55, Section 3.2.4	The number and proportion of patients in the DBLd-DL arm of the PERSEUS trial with ECOG PS scores of 0, 1 and 2 is published and therefore does not require CiC highlighting.	“PERSEUS DBLd-DL (n=355) ECOG PS score, n (%) 0: 221 (62.3) 1: 114 (32.1) 2: 19 (5.4)”					Amended.																																																				
Table 3.13, Page 58, Section 3.2.5	Throughout Table 13.3, incorrect CiC highlighting is used for baseline characteristics of patients in both the PERSEUS and AURIGA trials, given that some of these data are published.	<table><tr><th rowspan="2">Characteristics</th><th colspan="2">AURIGA</th><th colspan="2">PERSEUS</th></tr><tr><th>DL maintenance (N=99)</th><th>L maintenance (N=101)</th><th>BLd arm^a (N=354)</th><th>DBLd arm^b (N=355)</th></tr><tr><td colspan="5">Age</td></tr><tr><td>Median (range)</td><td>63 (55, 77)</td><td>62 (35,78)</td><td>59.0 (31, 70)</td><td>61.0 (32, 70)</td></tr><tr><td colspan="5">Overall age group, n (%)</td></tr><tr><td><50</td><td rowspan="2">61 (61.6)</td><td rowspan="2">61 (60.4)</td><td>██████</td><td>██████</td></tr><tr><td>≥50 and <65</td><td>██████</td><td>██████</td></tr><tr><td>≥65</td><td>38 (38.4)</td><td>42 (42.6)</td><td>██████</td><td>██████</td></tr><tr><td colspan="5">Sex, n (%)</td></tr><tr><td>Female</td><td>38 (38.4)</td><td>43 (42.6)</td><td>149 (42.1)</td><td>144 (40.6)</td></tr><tr><td>Male</td><td>61 (61.6)</td><td>58 (57.4)</td><td>205 (57.9)</td><td>211 (59.4)</td></tr></table>					Characteristics	AURIGA		PERSEUS		DL maintenance (N=99)	L maintenance (N=101)	BLd arm ^a (N=354)	DBLd arm ^b (N=355)	Age					Median (range)	63 (55, 77)	62 (35,78)	59.0 (31, 70)	61.0 (32, 70)	Overall age group, n (%)					<50	61 (61.6)	61 (60.4)	██████	██████	≥50 and <65	██████	██████	≥65	38 (38.4)	42 (42.6)	██████	██████	Sex, n (%)					Female	38 (38.4)	43 (42.6)	149 (42.1)	144 (40.6)	Male	61 (61.6)	58 (57.4)	205 (57.9)	211 (59.4)	Amended.
Characteristics	AURIGA		PERSEUS																																																								
	DL maintenance (N=99)	L maintenance (N=101)	BLd arm ^a (N=354)	DBLd arm ^b (N=355)																																																							
Age																																																											
Median (range)	63 (55, 77)	62 (35,78)	59.0 (31, 70)	61.0 (32, 70)																																																							
Overall age group, n (%)																																																											
<50	61 (61.6)	61 (60.4)	██████	██████																																																							
≥50 and <65			██████	██████																																																							
≥65	38 (38.4)	42 (42.6)	██████	██████																																																							
Sex, n (%)																																																											
Female	38 (38.4)	43 (42.6)	149 (42.1)	144 (40.6)																																																							
Male	61 (61.6)	58 (57.4)	205 (57.9)	211 (59.4)																																																							

		Race, n (%)				
		White	67 (67.7)	68 (67.3)	323 (91.2)	330 (93.0)
		Black or African American	20 (20.2)	24 (23.8)	4 (1.1)	5 (1.4)
		Asian	5 (5.1)	1 (1.0)	6 (1.7)	4 (1.1)
		Native Hawaiian or Other Pacific Islander	0	0		
		American Indian or Alaska Native	0	1 (1.0)		
		Not reported	2 (2.0)	2 (2.0)	18 (5.1)	12 (3.4)
		Other*			2 (0.6)	-
		Ethnicity, n (%)				
		Hispanic or Latino				
		Not Hispanic or Latino				
		Missing				
		Body weight, kg ^c				
		Median (range)			73.0 (37.0, 167.6)	75.4 (44.5, 125.0)
		Baseline ECOG PS, n (%) ^d				
		0	45 (45.5)	55 (54.5)	230 (65.0)	221 (62.3)
		1	52 (52.5)	44 (43.6)	108 (30.5)	114 (32.1)
		2	2 (2.0)	2 (2.0)	16 (4.5)	19 (5.4)

		3	0	0	0	1 (0.3)	
		Type of myeloma by immunofixation or serum FLC assay, n (%)					
		IgG	NR	NR	██████	██████	
		IgA	NR	NR	██████	██████	
		IgM	NR	NR	██████	██████	
		IgD	NR	NR	██████	██████	
		IgE	NR	NR	██████	██████	
		Light chain	NR	NR	██████	██████	
		Kappa	NR	NR	██████	██████	
		Lambda	NR	NR	██████	██████	
		FLC-Kappa ^e	NR	NR	██████	██████	
		FLC-Lambda ^f	NR	NR	██████	██████	
		Biclonal	NR	NR	██████	██████	
		Type of measurable disease, n (%)					
		Serum	NR	NR	██████	██████	
		IgG	NR	NR	185 (52.3)	204 (57.5)	
		IgA	NR	NR	85 (24.0)	65 (18.3)	
		Other ^g	NR	NR	11 (3.1)	13 (3.7)	
		Urine only	NR	NR	46 (13.0)	43 (12.1)	
		Serum FLC	NR	NR	27 (7.6)	29 (8.2)	
		Not evaluable	NR	NR	0	1 (0.3)	

		ISS Staging, n (%) ^h					
			N= 91	N=98			
		Stage I	40 (44.0)	38 (38.8)	178 (50.4)	186 (52.4)	
		Stage II	28 (30.8)	37 (37.8)	125 (35.4)	114 (32.1)	
		Stage III	23 (25.3)	23 (23.5)	50 (14.2)	55 (15.5)	
		R-ISS Staging, n (%) ⁱ					
		Stage I	NR	NR	██████	██████	
		Stage II	NR	NR	██████	██████	
		Stage III	NR	NR	██████	██████	
		Time from MM diagnosis to randomisation, years					
		Mean (SD)	12.1 (6.9)	12.2 (5.0)	██████	██████	
		Median (range)	10.8 (5.0, 72.4)	11.2 (5.2, 43.1)	1.12 (0.1, 184.6)	1.18 (0.0, 46.5)	
		Number of lytic bone lesions, n (%)					
			N=95	N=99			
		None	45 (47.4)	40 (40.4)	██████	██████	
		1–3	20 (21.1)	18 (18.2)	██████	██████	
		4–10	10 (10.5)	14 (14.1)	██████	██████	
		More than 10	20 (21.1)	27 (27.3)	██████	██████	
		Number of extramedullary plasmacytomas, n (%)					
		0	98 (99.0)	101 (100.0)	██████	██████	

		<table><tr><td>≥1</td><td>1 (1.0)</td><td>0</td><td>██████</td><td>██████</td></tr><tr><td colspan="5">% Plasma cells, bone marrow biopsy/aspirate</td></tr><tr><td><10</td><td>NR</td><td>NR</td><td>██████</td><td>██████</td></tr><tr><td>10–30</td><td>NR</td><td>NR</td><td>██████</td><td>██████</td></tr><tr><td>>30</td><td>NR</td><td>NR</td><td>██████</td><td>██████</td></tr><tr><td colspan="5">Cytogenetic risk, n (%)^j</td></tr><tr><td></td><td>N=89</td><td>N=92</td><td></td><td></td></tr><tr><td>Standard risk</td><td>63 (68.5)</td><td>66 (74.2)</td><td>266 (75.1)</td><td>264 (74.4)</td></tr><tr><td>High risk^k</td><td>22 (23.9)</td><td>15 (16.9)</td><td>78 (22.0)</td><td>76 (21.4)</td></tr><tr><td>del(17p)</td><td>13 (14.1)</td><td>3 (3.4)</td><td>██████</td><td>██████</td></tr><tr><td>t(4;14)</td><td>10 (10.9)</td><td>12 (13.5)</td><td>██████</td><td>██████</td></tr><tr><td>t(14;16)</td><td>6 (6.5)</td><td>7 (7.9)</td><td>██████</td><td>██████</td></tr><tr><td>Indeterminate</td><td>7 (7.6)</td><td>8 (9.0)</td><td>10 (2.8)</td><td>15 (4.2)</td></tr></table>	≥1	1 (1.0)	0	██████	██████	% Plasma cells, bone marrow biopsy/aspirate					<10	NR	NR	██████	██████	10–30	NR	NR	██████	██████	>30	NR	NR	██████	██████	Cytogenetic risk, n (%) ^j						N=89	N=92			Standard risk	63 (68.5)	66 (74.2)	266 (75.1)	264 (74.4)	High risk ^k	22 (23.9)	15 (16.9)	78 (22.0)	76 (21.4)	del(17p)	13 (14.1)	3 (3.4)	██████	██████	t(4;14)	10 (10.9)	12 (13.5)	██████	██████	t(14;16)	6 (6.5)	7 (7.9)	██████	██████	Indeterminate	7 (7.6)	8 (9.0)	10 (2.8)	15 (4.2)	
≥1	1 (1.0)	0	██████	██████																																																																
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t(4;14)	10 (10.9)	12 (13.5)	██████	██████																																																																
t(14;16)	6 (6.5)	7 (7.9)	██████	██████																																																																
Indeterminate	7 (7.6)	8 (9.0)	10 (2.8)	15 (4.2)																																																																
Page 61, Section 3.2.5	The number and percentage of patients in the AURIGA trial who received consolidation treatment prior to enrolment is not published and	“Consolidation therapy: consolidation therapy with DBLd or BLd was administered as part of the trial regimen in PERSEUS, whilst consolidation therapy was received by a minority of patients (██████ (██████%)), prior to enrolment, in the AURIGA trial.”			Amended.																																																															

	therefore require CiC highlighting.				
Page 62, Section 3.2.6.1	Median follow-up results for patients in the PERSEUS trial are not published and therefore require CiC highlighting.	“Data in this submission are based on the latest, 1st August 2023, DCO of the PERSEUS trial (median follow-up for the DBLd arm: █████ months; median follow-up for the BLd arm: █████ months).”			Amended.
Table 3.1.4, Page 62, Section 3.2.6.1	Row headings for each outcome do not require CiC highlighting given these are not confidential.	CiC highlighting should be removed from all row headings throughout Table 3.1.4.			Amended.
Table 3.1.4, Page 62, Section 3.2.6.1.1	Median PFS results for the full treatment sequence in the PERSEUS trial are published and therefore do not require CiC highlighting.	Outcome	BLd arm ^a	DBLd arm ^b	Amended.
		Survival outcomes (full treatment sequence)			
		Median PFS	NE	NE	
		Median OS	████	████	
Table 3.1.5, Page	The numbers of patients in the BLd and DBLd arms in the ITT analysis set	“BLd arm N=354 DBLd arm N=355”			Amended.

64, Section 3.2.6.1	of the PERSEUS trial are published and therefore do not require CiC highlighting.																																										
Page 68, Section 3.2.6.1.3	The OR, 95% CI and p-value for MRD-negativity rate in the ITT analysis set of the PERSEUS trial are not published and therefore require CiC highlighting.	“The company reported that “In the ITT analysis set, the DBLd arm achieved a significantly higher MRD-negativity rate compared with the BLd arm at the post-consolidation timepoint (57.5% versus 32.5%; OR: ■■■■; 95% CI: ■■■■, ■■■■; p<■■■■.”	Amended.																																								
Table 3.27, Page 80, Section 3.2.6.2	Throughout Table 3.27, incorrect CiC highlighting is used for clinical efficacy results of the PERSEUS trial, given that some of these data are published. Furthermore, row headings in this table have CiC highlighting incorrectly applied.	<table border="1"> <thead> <tr> <th>Outcome</th><th>L arm (N=101)</th><th>DL arm (N=99)</th><th>DL arm versus L arm (95% CI)</th></tr> </thead> <tbody> <tr> <td colspan="4">Survival outcomes</td></tr> <tr> <td>Median PFS (months)</td><td>NE</td><td>37.9</td><td>0.53 (0.29, 0.97); 0.0361</td></tr> <tr> <td>Median OS (months)</td><td>■■■■</td><td>■■■■</td><td>■■■■■■■■■■</td></tr> <tr> <td colspan="4">12-month MRD-negativity conversion rate (10-5), n (%)^a</td></tr> <tr> <td>MRD-negativity rate</td><td>19 (19.8)</td><td>50 (50.5)</td><td>4.51 (2.37, 8.57); p<0.0001</td></tr> <tr> <td colspan="4">Overall MRD-negativity conversion rate (10-5), n (%)^b</td></tr> <tr> <td>MRD-negativity rate</td><td>28 (27.7)</td><td>60 (60.6)</td><td>4.12 (2.26, 7.52); p<0.0001</td></tr> <tr> <td colspan="4">Sustained MRD-negativity rate (10-5), n (%)^c</td></tr> <tr> <td>Sustained MRD-negativity rate</td><td>5 (5.0)</td><td>17 (17.2)</td><td>4.08 (1.43, 11.62); p=0.0065</td></tr> </tbody> </table>	Outcome	L arm (N=101)	DL arm (N=99)	DL arm versus L arm (95% CI)	Survival outcomes				Median PFS (months)	NE	37.9	0.53 (0.29, 0.97); 0.0361	Median OS (months)	■■■■	■■■■	■■■■■■■■■■	12-month MRD-negativity conversion rate (10-5), n (%)^a				MRD-negativity rate	19 (19.8)	50 (50.5)	4.51 (2.37, 8.57); p<0.0001	Overall MRD-negativity conversion rate (10-5), n (%)^b				MRD-negativity rate	28 (27.7)	60 (60.6)	4.12 (2.26, 7.52); p<0.0001	Sustained MRD-negativity rate (10-5), n (%)^c				Sustained MRD-negativity rate	5 (5.0)	17 (17.2)	4.08 (1.43, 11.62); p=0.0065	Amended.
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Table 3.28, Page 80, Section 3.2.6.2	Throughout Table 3.28, incorrect CiC highlighting is used for change from baseline in EORTC QLQ-C30 scores from AURIGA trial, given that some of these data are published.	Amended.		
			DL, N=96	L, N=98
		EORTC QLQ-C30		
		<i>Global health status score, LS mean change from baseline (95% CI)</i>		
		Baseline	77.75	72.76
		Cycle 13 Day 1	-1.73	6.47
		End of treatment	-6.20	-3.98
		Post-treatment follow-up	-21.67	-8.33
		EQ-5D-5L		
		<i>Utility</i>		
		Baseline	0.81	0.79
		Cycle 13 Day 1	0.00	0.00
		End of treatment	0.01	-0.02
		Post-treatment follow-up	-0.13	-0.06
		VAS		
		Baseline	80.24	81.28
		Cycle 13 Day 1	1.96	-1.68
		End of treatment	3.28	-5.79
		Post-treatment follow-up	-3.20	4.60
		EORTC QLQ-MY20		
		<i>Disease symptom scales</i>		
		Baseline	19.69	21.59
		Cycle 13 Day 1	-0.49	-2.20
		End of treatment	-2.84	4.18
		Post-treatment follow-up	1.11	5.56

Table 3.30, Page 88, Section 3.2.8.1.2	The number and percentage of patients experiencing any serious TEAE in the DBLd arm of the PERSEUS trial are not published and therefore require CiC highlighting.	“DBLd arm, N [REDACTED]			Amended.
Table 3.31, Page 91, Section 3.2.8.1.3	All data points in Table 3.31 for the summary of most common TEAEs of any grade by treatment phase are not published and therefore require CiC highlighting.	Any serious TEAE: [REDACTED] ([REDACTED])”			
Table 3.37, Page 102, Section 3.3	Baseline characteristics of patients in the PERSEUS trial are published and therefore do not require CiC highlighting.	Please apply CiC highlighting to all data points in Table 3.31, including all N numbers.			Corrected
		</			

		Other	1.1	0.8		
Page 103, Section 3.3.1	Incorrect highlighting is applied to the word 'of'.	“The unpublished data of clinical DCO (May 2019) with a median follow-up of [REDACTED] months from the CASSIOPEIA trial were used to inform the ITC analyses. ⁹ ”				Amended.
Table 3.38, Page 104, Section 3.3.1	Median follow-up time for the May 2019 DCO of the CASSIOPEIA trial is not published and therefore requires CiC highlighting.	“However, the clinical DCO informing the ITC was May 2019, with a median follow-up time of [REDACTED] months.”				Amended.
Page 111, Section 3.4.3.1 and Page 116, Section 3.6	The statistical significance of the results of the differences in MRD-negativity rate between DBLd and DBTd in the ITC is not published and therefore require CiC highlighting.	“There were [REDACTED] in the MRD-negativity (regardless of CR status) rate between DBLd and DBTd in the base-case model and sensitivity analysis where all covariates were adjusted for.”				Amended.
Page 112, Section 3.4.3.1	The OS HR from the ITC is not published and therefore	“The company reported: “While the OS HR was greater than [REDACTED], suggesting [REDACTED] in favour of DBTd (HR [REDACTED] ; 95% CI: [REDACTED]), this result was [REDACTED] (p [REDACTED]).”				Amended.

	requires CiC highlighting.																													
Page 129 and Page 131, Section 4.2.6.2.2	In line with Table 25 in the Company Submission, the relative treatment benefit HR results for PFS for DL versus L maintenance derived from the AURIGA trial do not require CiC highlighting.	Page 129 “The long-term PFS extrapolations for DBTd-L were obtained in line with the methods for the derivation of the OS extrapolation: the relative treatment benefit with a PFS HR of 0.53 (95% CI: 0.29, 0.97; p-value: 0.036) for DL versus L maintenance derived from the AURIGA trial was applied to adjust the chosen extrapolation of the DBLd-DL arm of the PERSEUS trial from the onset of maintenance therapy.” Page 131 “The estimated HRs for PFS from the AURIGA trial, based on the April 2024 DCO, was estimated at 0.53 (95% CI: 0.29, 0.97; p-value: 0.036) for DL versus L.”			Amended.																									
Page 150, Table 4.19, Section 4.2.8.8	Incidence of Grade 3/4 AEs for the maintenance phase of the PERSEUS trial are published and therefore do not require CiC highlighting.	<table><tr><th rowspan="2">AE</th><th colspan="2">Maintenance phase</th></tr><tr><th>DL</th><th>L</th></tr><tr><td>Neutropenia</td><td>46.9%</td><td>41.8%</td></tr><tr><td>Lymphopenia</td><td>10.4%</td><td>5.1%</td></tr><tr><td>Pneumonia</td><td>5.2%</td><td>4.1%</td></tr><tr><td>Diarrhoea</td><td>3.1%</td><td>5.1%</td></tr><tr><td>Leukopenia</td><td>9.4%</td><td>6.1%</td></tr><tr><td>Hypokalemia</td><td>7.3%</td><td>6.1%</td></tr><tr><td>Hypertension</td><td>7.3%</td><td>4.1%</td></tr></table>	AE	Maintenance phase		DL	L	Neutropenia	46.9%	41.8%	Lymphopenia	10.4%	5.1%	Pneumonia	5.2%	4.1%	Diarrhoea	3.1%	5.1%	Leukopenia	9.4%	6.1%	Hypokalemia	7.3%	6.1%	Hypertension	7.3%	4.1%		Amended.
AE	Maintenance phase																													
	DL	L																												
Neutropenia	46.9%	41.8%																												
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Hypokalemia	7.3%	6.1%																												
Hypertension	7.3%	4.1%																												
Page 161, Section 5.1.2.1	The total costs and total QALYs from the probabilistic and deterministic results	“Although the resulting ICER is in line with the deterministic one shown in Table 5.3, there are substantial differences between the deterministic results (total costs, £[REDACTED]; total QALYs,			The CiC marking has																									

	are confidential and therefore require CiC highlighting. The total costs and total QALYs for the probabilistic results were also incorrect as per Table 3 in the addendum to the clarification response letter and should be updated in line with the suggested sentence (changes bolded).	██████████) and probabilistic results (total costs, £██████████; total QALYs, ██████████) for the comparator arm.”	been amended. As mentioned above in Issue 13, the EAG has sourced the PSA results from the correct addendum.
Page 177, Section 5.3.2.4	The percentage of patients on DBLd-DL who discontinued daratumumab under the stopping rule in the PERSEUS trial is not published and therefore requires CiC highlighting.	“In the trial, ██████████% of patients on DBLd-DL discontinued daratumumab under this rule, supporting the plausibility of treatment de-escalation in clinical practice.”	Amended.

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11. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. NICE DSU Report [Internet]. Sheffield: Decision Support Unit, ScHARR, University of Sheffield, 2022 [accessed 23.5.25]:23.