NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Janssen**
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. Myeloma UK
   b. UK Kidney Association
4. **Evidence Review Group report** prepared by **York Centre for Reviews and Dissemination – factual accuracy check**
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8. **Evidence Review Group critique of company response to technical engagement** prepared by **York Centre for Reviews and Dissemination**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Daratumumab in combination for newly diagnosed systemic amyloid light-chain amyloidosis [ID3748]

Document B

Company evidence submission

June 2021

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List of abbreviations

Abbreviation	Definition
(HR)QoL	(Health-related) quality of life
1L	First-line
2L	Second-line
ADCC	Antibody-dependent cell mediated cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AIC	Akaike's information criterion
AL	Amyloid light chain
ANS	Autonomic nervous system
ARC	Amyloidosis Research Consortium
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
BCd	Bortezomib, cyclophosphamide and dexamethasone
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
BSH	British Society for Haematology
CD(4/8/38)	Cluster of differentiation (4/8/38)
CDC	Complement-dependent cytotoxicity
CHR	Complete haematologic response
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTd	Cyclophosphamide, thalidomide and dexamethasone
cTnT	Cardiac troponin T
CUA	Cost-utility analysis
CyBorD	Cyclophosphamide, bortezomib, dexamethasone (otherwise referred to as BCd)
DBCd	Daratumumab, bortezomib, cyclophosphamide and dexamethasone
DBMP	Daratumumab in combination with bortezomib, melphalan and prednisone
DFLC	Difference between involved and uninvolved free light chain
DLd	Daratumumab, lenalidomide and dexamethasone
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DVCd	Daratumumab, bortezomib, cyclophosphamide and dexamethasone
ECOG	Eastern Cooperative Oncology Group Performance Status
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool

EMN	European Myeloma Network
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0
EQ-5D-5L	EuroQol-5 Dimensions-5 Level
EVT	Event
FDA	U.S. Food and Drug Administration
FDT	Fixed dose treatment
FISH	Fluorescence in situ hybridisation
FLC	Free light chain
GCP	Good Clinical Practice
GHS	Global Health Status
GI	Gastrointestinal
HSUV	Health state utility value
HTA	Health technology assessment
IA(1/2)	Interim analysis 1/2
IAT	Indirect anti-globulin testing
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
iFLC	Involved free light chain
IPCW	Inverse probability of censoring weighting
IPD	Individual patient data
IRC	Independent Review Committee
IRR	Infusion-related reactions
ISA	International Society of Amyloidosis
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
KM	Kaplan-Meier
KRd	Carfilzomib, lenalidomide and dexamethasone
LS	Least squares
mAb	Monoclonal antibody
MCS	Mental Component Summary
Md	Melphalan and dexamethasone
MDSCs	Myeloid-derived suppressor cells
MHRA	Medicines & Healthcare Products Regulatory Agency
MM	Multiple myeloma
MOD-EFS	Major organ deterioration event-free survival
MOD-PFS	Major organ deterioration progression-free survival
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
NAC	National Amyloidosis Centre
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEL	Non-elective long stay

NHS	National Health Service
NHSCII	NHS cost inflation index
NICE	National Institute for Health and Care Excellence
NK	Natural killer
NR	No response
NT-proBNP	N-terminal prohormone brain natriuretic peptide
NT-proNBP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
ORR	Organ response rate
OS	Overall survival
PAS	Patient access scheme
PBd	Panbinostat, bortezomib and dexamethasone
PD	Progressive disease
PFS	Progression-free survival
PNS	Peripheral nervous system
PO	Orally
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QC	Qualty control
QTcF	QT interval as corrected by Fridericia's formula
RCT	Randomised controlled trial
Rd	Lenalinomide with dexomethasone
RDI	Relative dose intensity
rHuPH20	Recombinant human hyaluronidase PH20
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36 Health Survey Questionnaire
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
Tregs	Regulatory T cells
TSD	Technical Support Document
Tx	Treatment
ULN	Upper limit of normal
VAS	Visual analogue scale
VAT	Value added tax
VCd	Bortezomib, cyclophosphamide and dexamethasone

VGPR	Very good partial response
WTP	Willingness-to-pay

Introduction

Patients with systemic amyloid light chain (AL) amyloidosis experience poor prognosis, with an estimated four-year survival rate of 54%, and almost a third of patients die within one year of diagnosis.[1, 2] In current UK clinical practice, patients receive light chain suppressive chemotherapy, however, the majority of patients fail to achieve a complete haematologic response (CHR), which is the main aim of treatment, and many patients experience relapse with progression of organ damage.[3-6] There is a clear unmet need for an effective, well-tolerated treatment option to support the management of patients with this condition.

Daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone received European marketing authorisation for the treatment of adult patients with newly diagnosed AL amyloidosis on 21st June 2021.[7] Marketing authorisation for this indication with the MHRA is expected in [redacted], following the reliance route.

This submission presents the clinical and cost-effectiveness evidence for the use of daratumumab SC in combination with cyclophosphamide, bortezomib and dexamethasone within its marketing authorisation for the treatment of newly diagnosed patients with AL amyloidosis. The pivotal clinical trial, ANDROMEDA, referred to the cyclophosphamide, bortezomib and dexamethasone regimen as “CyborD”, but “BCd” is used throughout this submission to align with the terminology used in the NICE final scope.[8]

Overall, the data presented herein show that daratumumab SC in combination with BCd is superior to BCd alone in achieving deep, rapid haematologic and organ responses for patients with AL amyloidosis. In the ANDROMEDA trial, the proportion of patients achieving a CHR, and the rate at which they did so, was statistically significantly higher in the daratumumab SC with bortezomib, cyclophosphamide and dexamethasone (DBCd) treatment arm as compared with the BCd arm, and organ response rates were almost two-fold greater for patients treated with DBCd as compared with BCd alone. This was consistent across all pre-specified subgroups. The safety profile of DBCd was broadly consistent with the established safety profiles of daratumumab and BCd: TEAEs were generally manageable with no new safety concerns identified which is particularly important for patients when increasing the number of regimens within a combination therapy. Results from a *de novo* cost-utility analysis indicate that the introduction of DBCd to UK clinical practice represents a cost-effective use of NHS resources, with an incremental cost-effectiveness ratio (ICER) versus BCd alone falling below the willingness-to-pay (WTP) threshold of £30,000. If recommended, DBCd would be the first treatment specifically licensed for AL amyloidosis patients in the UK, representing a greatly needed step-change in the care available for these patients.

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

Summary of decision problem, the technology and clinical care pathway

Disease overview

- AL amyloidosis is a rare and debilitating condition and is the most frequent and severe form of amyloidosis in which amyloid fibrils are deposited in organs around the body. This causes debilitating symptoms which affect patients' quality of life, leading to significant morbidity, organ dysfunction and death.
- An annual incidence 1 in 100,000 people in the UK annually has been estimated, with incidence known to increase with age and to be higher amongst males.[9-12] AL amyloidosis typically presents systemically (93% of AL amyloidosis patients).
- The symptoms of AL amyloidosis are often non-specific, such as weight loss and fatigue, contributing to prolonged times for diagnosis and frequent misdiagnosis, with more severe symptoms developing as the condition progresses.
- The heart and kidneys are the most commonly affected organs and the type, number and extent of organ involvement is a key factor in influencing survival of these patients.[1, 13, 14] The Mayo Clinic Staging System is the most widely used staging system for AL amyloidosis, with prognosis worsening as patients progress through more advanced stages.[14-17]
- Over time, almost all patients experience progression of organ involvement and ultimately death, with heart failure representing the most common cause of mortality in these patients.[18-20]

Impact on patients

- Patients with AL amyloidosis suffer both physical and psychological burdens: from the wide-ranging symptoms of AL amyloidosis and the side effects associated with off-label chemotherapies, to the anxiety, depression and low self-worth associated with diagnosis of a life-limiting disease with a poor prognosis and no licensed treatment options; AL amyloidosis patients experience a significantly reduced quality of life.
- These burdens are exacerbated by prolonged wait times for a correct diagnosis, due in part to the rarity of the disease and lack of clinical knowledge surrounding it. This delayed diagnosis is associated with further disease progression and corresponding worsened prognoses.
- Patients who reach end-stage kidney failure become reliant on regular dialysis, which has a further substantial impact on patient quality of life.[21-23]

Current clinical care

- As AL amyloidosis is incurable, the primary therapeutic goal of its treatment is to achieve a rapid, deep and durable haematologic response.[24, 25]
- Before daratumumab, there were no therapies specifically licensed for the treatment of patients with AL amyloidosis; furthermore, there are no NICE guidelines currently available for its treatment.
- The majority ([redacted]%) of newly diagnosed patients are treated with BCd as a first-line therapy in the UK.[88] As such, BCd represents the standard of care for these patients and constitutes the sole comparator in this appraisal.

Unmet need

- The majority of patients currently fail to achieve a complete haematologic response (CHR) through treatment with the current standard of care in the UK, and organ response rates are poor.[27-31]
- There remains a high level of unmet need for a novel, effective and well-tolerated treatment for newly diagnosed AL amyloidosis patients that has the potential to induce a rapid, deep and durable haematologic response. Introduction of such a treatment option would improve patient prognosis and health-related quality of life (HRQoL), delay organ failure and prolong survival.

Daratumumab SC

- Daratumumab is a fully human monoclonal antibody that binds to CD38 on the surface of haematologic cells, including the clonal plasma cells that produce amyloidogenic immunoglobulin light-chain, to reduce native light-chain production and the associated organ toxicity in patients with systemic AL amyloidosis.
- Daratumumab has been shown to be efficacious and safe in multiple myeloma (MM) and has a licence for use in four different treatment regimens in MM indications in the European Union.[32]
- The efficacy and safety of daratumumab SC in combination with BCd has been assessed in the ANDROMEDA trial. DBCd was superior to BCd in achieving deep, rapid haematologic and organ responses and was associated with an improvement in HRQoL over time and a tolerable safety profile that raised no new safety concerns.

B.1.1 *Decision problem*

The objective of this appraisal is to determine the clinical and cost-effectiveness of DBCd, in line with its marketing authorisation, i.e. for the treatment of adult patients with newly diagnosed systemic light-chain (AL) amyloidosis.[32] The decision problem addressed in this submission, compared to that defined in the final scope issued by NICE, is summarised in Table 1.[8]

Table 1: The decision problem

	Final scope issued by NICE[8]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with newly diagnosed systemic amyloid light-chain amyloidosis	Adult patients with newly diagnosed systemic amyloid light-chain (AL) amyloidosis	• This is aligned with the licensed indication and the patient population included within the pivotal ANDROMEDA trial[32]
Intervention	DBCd	DBCd	• DBCd is aligned with the intervention arm in the ANDROMEDA trial
Comparator(s)	Established clinical management without daratumumab. This may include: • Bortezomib with dexamethasone, an alkylating treatment and/or immunomodulatory drugs (i.e. BCd) • Lenalidomide with dexamethasone (Rd) • Melphalan and dexamethasone (Md) • Autologous stem cell transplant (ASCT) with high dose melphalan • Best supportive care None of the comparators listed have a marketing authorisation in the UK for this indication.	BCd	• Although none of the comparators listed in the final scope currently have marketing authorisation in the UK for this indication, BCd is considered to represent standard of care for newly diagnosed AL amyloidosis patients in UK clinical practice as per expert clinical advice.[26] • Clinical expert feedback, elicited through a UK advisory board (April 2021),[26] indicated that in UK clinical practice: o The majority of newly diagnosed AL amyloidosis patients are treated with BCd. BCd represents the mainstay of treatment in AL amyloidosis, including those who are eligible for transplant and those who are elderly. o Only a minority of patients with pre-existing neuropathy would not receive bortezomib-based therapies in the first-line setting. Although, even in these cases, bortezomib may be used in an attenuated dose regimen. o Md is rarely used and only for patients who are contraindicated BCd. o Rd can be used in patients with neuropathy, but its use in the newly diagnosed setting is very rare, therefore only patients who have poor tolerability, or are contraindicated to, bortezomib, would receive Rd.

			o Very few patients receive ASCT due to organ involvement resulting in ineligibility, and those who do receive ASCT typically receive previous induction therapy (i.e. it is not a first-line treatment for newly diagnosed patients). o It is deemed unlikely that newly-diagnosed patients with such a life-limiting disease with a poor prognosis would receive best supportive care. • A real-world retrospective study of AL amyloidosis in 10 European countries, including the UK (the EMN23 study) supports that BCd represents the standard of care for patients: 75% of AL amyloidosis patients were found to receive bortezomib-based regimens at first-line.[17] • As such, the decision problem addressed in the submission will consider BCd as the sole relevant comparator due to its position as the mainstay of treatment for patients with newly diagnosed AL amyloidosis. • This is aligned with the ANDROMEDA trial, which provides direct evidence for the relative clinical efficacy and safety data of DBCd compared with BCd.
Outcomes	The outcome measures to be considered include: • Haematologic response rates • Organ response rates • Progression-free survival (PFS) • Major organ deterioration progression-free survival (MOD-PFS) • Overall survival (OS) • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Haematologic response rates • MOD-PFS • Major organ deterioration event-free survival (MOD-EFS) • Organ response rates • OS • Adverse events (AEs) • HRQoL	• Outcomes represent those collected in the ANDROMEDA trial, with the exception of PFS. • PFS was not collected in ANDROMEDA because: o In clinical practice, disease progression in AL amyloidosis patients may be evaluated according to a range of biomarkers, including haematologic, cardiac and renal biomarkers given the heterogeneity in presentation of the disease. o Haematologic response does not comprehensively describe the response status of patients with AL amyloidosis, whose clinical

	(HRQoL)		presentation and long-term outcomes additionally depend on adequate organ function, whilst assessment of organ response rates is based on the use of clinical biomarkers which are associated with limitations. o Instead of PFS, ANDROMEDA included MOD-PFS. MOD-PFS is a novel, composite endpoint developed to encompass the most clinically relevant and objective measures of the benefits of anti-plasma cell therapy: haematologic progression, major organ deterioration, and death. o Inclusion of MOD-PFS in ANDROMEDA was agreed upon following consultation with regulatory authorities (EMA and FDA).[33, 34] The full definition of MOD-PFS can be found in Section B.2.3. o Similarly, MOD-EFS is a composite endpoint of clinically observable endpoints which, as compared with MOD-PFS, additionally captures subsequent lines of therapy since it included initiation of subsequent non-cross resistant therapy adjudicated by the Independent Review Committee (IRC) as an event.
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 (QALY) • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being	The reference case has been adhered to.	NA – in line with final NICE scope

	compared • Costs will be considered from an NHS and Personal Social Services perspective (PSS) • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account		
Other considerations, including subgroups and issues related to equity or equality	If the evidence allows, subgroups based on the severity of heart failure may be considered.	Baseline cardiac stage was pre-specified for a subgroup analysis at the interim analysis data-cut and at the 12-month landmark analysis. However, the ANDROMEDA trial excluded newly diagnosed systemic AL amyloidosis patients with Mayo Clinic Cardiac Stage IIIb disease. In order to gain an insight into the haematologic response rates that would be required for DBCd to be a cost-effective option for patients in this subgroup, the company are exploring whether an analysis that utilises data for BCd from Mayo Stage IIIb patients from the EMN23 study can be conducted, but this is not yet available.	• Patients with Stage IIIb disease, according to the European Modification of the Mayo Clinic Cardiac Staging System have the most severe degree of cardiac involvement (see Section B.1.3.1 for details).[16] These patients therefore require a rapid and deep response to treatment to improve survival. • In the ANDROMEDA study, patients with Stage IIIb disease were excluded during the screening period from participating in the trial as they are not typically candidates for BCd at the specific dose and dosing schedule used in the trial.[35] It is important to note that 6 patients in the BCd arm and 2 patients in the DBCd arm with Stage IIIb cardiac disease were included in the study because their cardiac involvement progressed to this stage after study enrolment. • However, clinical expert opinion suggests that Stage IIIb patients comprise approximately 20% of the AL amyloidosis cohort observed in UK clinical practice, and clinicians would wish to treat such patients with DBCd in clinical practice should DBCd be recommended for use.[26] • Patients with Stage IIIb disease are not excluded

			from the licensed indication for DBCd.[32] • These patients have high risk systemic AL amyloidosis and an extremely poor prognosis.[26] • It is Janssen's view that it is important that any recommendation for DBCd in AL amyloidosis is not restricted in such a way to exclude patients with Stage IIIb disease, a group of more severe patients, who have an extremely poor prognosis and life expectancy.

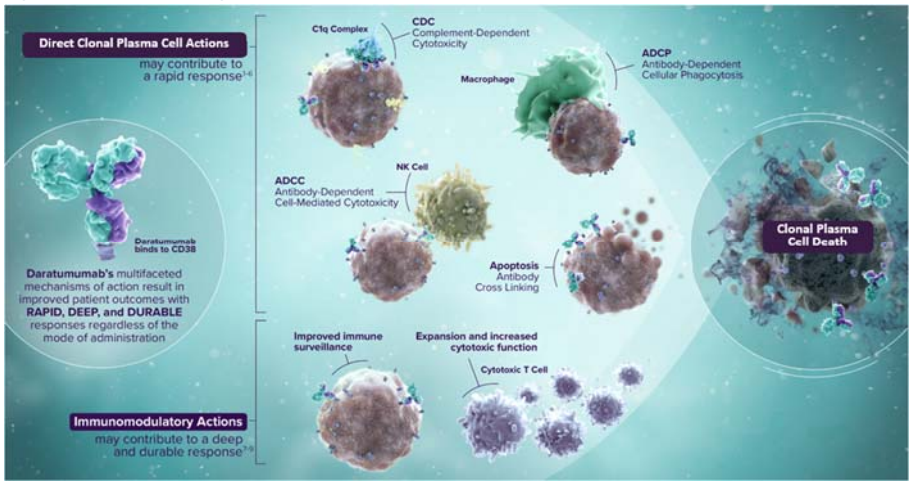
Abbreviations: AE: adverse event; AL: amyloid light-chain; ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; CTd: cyclophosphamide, thalidomide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; EMA: Europeans Medicines Agency; FDA: Food and Drugs Administration; HRQoL: health-related quality of life; Md: melphalan and dexamethasone; MOD-EFS: major organ deterioration event-free survival; MOD-PFS: major organ deterioration progression-free survival; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; PSS: Personal Social Services QALY: quality-adjusted life year; UK: United Kingdom.

B.1.2 *Description of the technology being appraised*

A description of the technology being appraised, daratumumab SC in combination with BCd, is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Daratumumab (Darzalex®) in combination with cyclophosphamide, bortezomib and dexamethasone
Mechanism of action	Daratumumab is a first-in-class, fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds to CD38, a multifunctional glycoprotein ectoenzyme that is frequently expressed on the cell surface of diverse haematologic malignancies, including clonal plasma cells that produce amyloidogenic immunoglobulin light-chain. Daratumumab has been shown to potently inhibit the *in vivo* growth of CD38-expressing (CD38+) tumour cells in patients with multiple myeloma MM.[32] *In vitro* studies show that daratumumab induces immune-mediated cell death in CD38+ tumour cells via several complementary mechanisms, including complement dependent cytotoxicity (CDC); antibody-dependent cell mediated cytotoxicity (ADCC); and antibody dependent cellular phagocytosis (ADCP). In addition, daratumumab has been shown to have immunomodulatory effects. Daratumumab leads to the rapid and sustained elimination of highly immunosuppressive subsets of CD38+ regulatory T cells (Tregs), CD38+ myeloid-derived suppressor cells (MDSCs), and CD38+ regulatory B cells, which suppress the destruction of malignant cells by the immune system.[36] This elimination, and the resultant modulation of CD38 enzymatic activity and destruction of the malignant myeloma cells, is thought to lead to the clonal expansion of CD8+ and CD4+ T cells and thus a further increase in the cytotoxic functioning of the immune system to destroy malignant cells.[36, 37] Although the clonal plasma cells in AL amyloidosis have a lower proliferation index and are therefore biologically distinct from those in MM, the clonal plasma cells that produce amyloidogenic light-chains are also CD38+, providing a biological rationale for the expectation of similar CD38 directed mechanisms in AL amyloidosis, and for the use of daratumumab in this indication.[32, 38, 39] Collectively, these actions reduce native light-chain production and the associated organ toxicity in patients with systemic AL amyloidosis (Figure 1).

	Figure 1: Summary of the mechanism of action of daratumumab in systemic AL amyloidosis  **Abbreviations:** ADCC: antibody-dependent cell-mediated cytotoxicity; ADPC: antibody-dependent cellular phagocytosis; AL: amyloid light chain; CDC: complement-dependent cytotoxicity; NK: natural killer. **Source:** Janssen (Data on File): Daratumumab AL Amyloidosis Scientific Communications Platform.[40]
Marketing authorisation/CE mark status	European marketing authorisation for daratumumab SC in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis was received on 21st June 2021.[32]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Daratumumab SC in combination with BCd has received marketing authorisation for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.[32] The current licensed indications for daratumumab are:[32] • "in combination with lenalidomide and dexamethasone (DLd) or with bortezomib, melphalan and prednisone (DBMP) for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant" • "in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant" • "in combination with lenalidomide and dexamethasone (DLd), or bortezomib and dexamethasone (DBd), for the treatment of adult patients with multiple myeloma who have received at least one prior therapy" • "as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy." **Contraindications:**[32] • Hypersensitivity to the active substance or to any of the following excipients: o Recombinant human hyaluronidase o L histidine o L histidine hydrochloride monohydrate o L methionine o Polysorbate 20

<table>
<tr><td></td><td>o Sorbitol (E420)
o Water for injections</td></tr>
<tr><td>Method of administration and dosage</td><td>
AL amyloidosis posology

Daratumumab 1,800 mg (15 mL vial; 120 mg daratumumab per mL) is available as a solution for subcutaneous (SC) injection administered over approximately 3–5 minutes according to the dosing schedule shown in Table 3.[32] As shown, in the ANDROMEDA trial from Week 25 onwards, daratumumab SC was administered every four weeks until disease progression or a maximum of 24 cycles (~2 years) from the first dose of treatment.[32, 35]

Table 3: Daratumumab SC dosing schedule for AL amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone (BCd), four-week cycle dosing regimen.
<table>
<tr><th>Weeks</th><th>Schedule</th></tr>
<tr><td>Weeks 1 to 8</td><td>Weekly (total of 8 doses)</td></tr>
<tr><td>Weeks 9 to 24</td><td>Every two weeks (total of 8 doses), beginning at Week 9</td></tr>
<tr><td>Week 25 onwards until disease progression[a]</td><td>Every four weeks, beginning at Week 25</td></tr>
</table>
[a] In the clinical trial, daratumumab was given until disease progression or a maximum of 24 cycles (~2 years) from the first dose of study treatment.
Source: Daratumumab SmPC.[32]

Daratumumab SC formulation is not intended for intravenous (IV) administration and should be given by subcutaneous injection only, using the doses specified.[32]

Drug administration should be performed by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available.[32]

It is anticipated that the concomitant medications of the regimen (cyclophosphamide, bortezomib and dexamethasone) will be administered to patients in line with the dosing schedules in the ANDROMEDA trial presented in Table 4. For further details of the additional components of the DBCd regimen, please refer to the respective SmPCs.[41-43] For further information regarding concomitant medications recommended to be administered alongside DBCd to manage the risk of infusion-related reactions, please see the daratumumab SmPC.[32]

Table 4: Dosing regimens for cyclophosphamide, bortezomib and dexamethasone in the ANDROMEDA trial
<table>
<tr><th>Medication</th><th>Dosing schedule</th></tr>
<tr><td>Cyclophosphamide, 300 mg/m^2 administered orally or IV[a]</td><td>Weekly dose on Days 1, 8, 15 and 22 in every 28-day cycle for a maximum of 6 cycles</td></tr>
<tr><td>Bortezomib, 1.3 mg/m^2 administered SC</td><td>Weekly dose on Days 1, 8, 15 and 22 in every 28-day cycle for a maximum of 6 cycles</td></tr>
<tr><td>Dexamethasone, 40 mg</td><td>Weekly dose on Days 1, 8, 15 and 22</td></tr>
</table>
[a] Maximum absolute weekly dose is 500 mg, irrespective of body surface area.
Abbreviations: IV: intravenous; SC: subcutaneous.
Source: ANDROMEDA clinical trial protocol.[35]
</td></tr>
<tr><td>Additional tests or investigations</td><td>Patients should be tested and screened prior to starting daratumumab treatment. Blood type, Rh, and indirect antiglobulin testing (IAT) should be undertaken before the first dose of daratumumab. Subject red blood cell</td></tr>
</table>

	phenotyping (standard or extended) is an alternative option to the IAT test, as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.[35]
List price and average cost of a course of treatment	List price 1,800 mg (fixed-dose 15 mL vial; 120 mg daratumumab per mL) = £4,320.00 (excl. VAT).
Patient access scheme (if applicable)	Daratumumab currently has a Patient Access Scheme (PAS) discount of [redacted]% from the list price in the UK. With the PAS, the pack price of daratumumab is £[redacted].

Abbreviations: ADCC: antibody-dependent cell mediated cytotoxicity; ADCDP: antibody dependent cellular phagocytosis; AL: amyloid light-chain; BCd: bortezomib, cyclophosphamide and dexamethasone; CDC: complement dependent cytotoxicity; DBd: daratumumab, bortezomib and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; DBMP: daratumumab, bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; IgG1κ: immunoglobulin G1 kappa; IV: intravenous; mAb: monoclonal antibody; MDSC: myeloid-derived suppressor cell; MM: multiple myeloma; SC: subcutaneous; Tregs: regulatory T cells.

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

B.1.3.1 Disease overview

Background to amyloidosis

Amyloidosis comprises a group of rare plasma cell disorders characterised by the formation of amyloid fibrils due to protein misfolding. The particular protein that misfolds is specific to the type of amyloidosis, but a common characteristic of all amyloidosis subtypes is the extracellular aggregation and accumulation of these fibrils within organs, resulting in impaired organ function and premature mortality.[44-46]

Types of amyloidosis may be differentiated based on clinical characteristics such as the pattern of tissue involvement (systemic versus localised), the role of underlying disease (primary versus secondary) and heritability of the condition (acquired versus hereditary), or according to the target tissue involved, such as in cardiac amyloidosis in which the heart is affected.[46-49] However, current guidelines from the International Society of Amyloidosis (ISA) recommend that amyloidosis should primarily be classified according to the amyloid precursor involved, given that this classification more closely reflects the underlying biology of the disease than the clinical classifications.[48]

AL amyloidosis

The most common and severe form of amyloidosis is immunoglobulin (Ig) light-chain (AL) amyloidosis, a rare and debilitating condition caused by an abnormality in certain cells found in the bone marrow, called plasma cells. While plasma cells in healthy people produce normal proteins (called 'light chain proteins') to help protect the body from infection, patients with AL amyloidosis produce erroneous forms of these proteins which create amyloid deposits when they enter the bloodstream. These proteins aggregate into thread-like strings (amyloid fibrils) that cannot be cleared easily. Over time, amyloid fibrils build up as AL amyloid deposits in tissues and organs. This gradually stops the organs functioning properly, causing debilitating symptoms

and ultimately leading to death. Unlike some other types of amyloidosis, AL amyloidosis is not hereditary.[44-46, 50]

AL amyloidosis has an annual incidence of approximately one case in every 100,000 people in the UK and accounts for approximately 60% of all amyloidosis cases.[9] AL amyloidosis may present locally, but the vast majority (93%) of patients have systemic involvement in which several organs are involved. Throughout this submission, the term 'AL amyloidosis' is used in reference to systemic AL amyloidosis.

Immunoglobulin heavy chain translocation (11;14) is one of the most prevalent chromosomal abnormalities in patients with AL amyloidosis, having an influence on prognosis via modification of the response to treatment.[14, 51] Translocation t(11;14), which involves the immunoglobulin heavy chain and genes encoding cyclin D1, is the most prevalent, found in approximately 39–57% of patients.[45, 52, 53] This translocation promotes proliferation of plasma cells and has been associated with a poor response to standard treatment.[54, 55]

The clinical presentation of amyloidosis varies according to the type, number and extent of organ involvement.[18, 19] In AL amyloidosis, the heart and kidneys are the most commonly affected organs, with approximately 50–70% of patients experiencing cardiac involvement, and up to 70% experiencing renal involvement.[18, 19, 56] Other sites that may be affected include the liver, gastrointestinal tract, soft tissue and peripheral nervous system, with most patients experiencing involvement across multiple organs.[1, 18, 57] Accordingly, patients often present with non-specific symptoms such as weight loss, fatigue, weakness, loss of appetite, bruising of ankles and legs, shortness of breath with minimal exertion, numbness, tingling or pain in hands or feet, blood pressure change, dizziness, GI symptoms such as diarrhoea or constipation, pain and/or kidney issues. This non-specificity of symptoms poses a challenge for diagnosis and can result in delays of several months or longer for an initial diagnosis.[58, 59] Although some symptoms, such as periorbital purpura and tongue enlargement, are specific to AL amyloidosis, they are less common, occurring in around 15% of patients.[59]

As the condition progresses, more severe symptoms develop, which may include heart failure. In addition, patients with kidney involvement may experience malabsorption, albuminuria and nephrotic-range proteinuria which impact the quality of life; if diagnosed late, kidney involvement can lead to end-stage renal failure.[18, 19, 57, 60]

The majority of patients with AL amyloidosis fail to achieve a CHR following standard therapy, and eventually, almost all patients experience haematologic relapse and progression of organ involvement, and ultimately death.[61]

Epidemiology

Systemic AL amyloidosis is a rare disease for which there is limited evidence on prevalence.[11, 12, 62-68] The main source of epidemiological information in the UK is the National Amyloidosis Centre (NAC). An analysis of patients in the UK NAC Database estimated a prevalence of 11,006 amyloidosis cases between 1987–2019, with AL amyloidosis cases representing 55% of the total (6,008). Another analysis of patients in England in the same database reported 174 cases of AL amyloidosis per 1 million individuals in 2008 and indicated that AL amyloidosis referral rates doubled during 2000 to 2008.[63, 66] These studies are summarised in Table 5.

Overall, the studies have generally reported low incidence rates of less than 1,000 new diagnoses each year. Acknowledging the rarity and severity of the disease and the absence of

authorised medicines for the treatment of this condition, daratumumab was granted orphan designation by the EMA in March 2020 for the treatment of AL amyloidosis.[69]

In general, the incidence of AL amyloidosis increases with age, with the highest rates reported in elderly patients (i.e. age ≥65 years).[10-12] Incidence is also higher among males, accounting for 54–58.5% of cases.[10, 11, 64]

Table 5: Prevalence of AL amyloidosis in the UK

Source	Region	Design and population	Prevalence
Pinney *et al*., (2013)[63]	England	Analysis of patients in England with systemic amyloidosis in the NAC database from 2000 to 2008.[a]	Crude prevalence of systemic amyloidosis:[b] • 2008: 1,051 cases • 2000: 435 cases Median survival increased significantly between 2000 and 20008 (p=0.02) and appeared to drive the increase in prevalence over time.
Ravichandran *et al*., (2020)[66]	United Kingdom	Analysis of patients in the United Kingdom with amyloidosis in the NAC database from 1987 to October 2019.	Number of prevalent amyloidosis cases: 11,006.[a] Number of AL amyloidosis cases: 6,008.

[a] Total population (N) not reported for either study.
[b] Systemic AL amyloidosis was reported as: "the most prevalent" type of systemic amyloidosis, although the proportion of patients with AL amyloidosis specifically was not reported. Although the NAC serves the entire population of England, the incidence of new referrals to the NAC decreases as distance from the NAC increases (R^2 = 0.64, P = 0.005).
Abbreviations: AL: light chain; NAC: National Amyloidosis Centre.

Disease prognosis and staging

As previously indicated, prognosis is poor for patients with AL amyloidosis, with nearly 30% of patients dying within the first year of diagnosis and an estimated 4-year survival rate of 54%.[1, 2] A key factor influencing survival is the type and number of organs involved, and prognosis is particularly poor in patients with multiple organ involvement.[1, 13, 14] Five-year survival has been shown to be 91% for patients with isolated renal involvement, compared to 42% among patients with multiple-organ involvement (p<0.001).[18] Notably, heart failure is the leading cause of death in patients with AL amyloidosis, and the presence and extent of cardiac involvement is among the strongest indicators of mortality risk.[20] If untreated, patients with cardiac involvement have a median survival of just six months from onset of heart failure.[70]

The most widely used staging system for AL amyloidosis was developed by the Mayo Clinic group in 2004 and revised in 2012.[14-16] The Mayo Clinic Staging System stratifies patients according to soluble serum cardiac biomarkers, as well as other important prognostic factors.[14, 15] Levels of the cardiac biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin T (TnT) form the basis of the staging system, with patients assigned to Stages I, II and III according to the number of these prognostic factors found to be elevated above defined thresholds.[14] In a 2013 revision to the Mayo system, Stage III patients were further categorised into Stages IIIa or IIIb based on whether the level of NT-proBNP was below (IIIa) or above (IIIb) 8,500 ng/L (Table 6).[16]

Table 6: Prognostic factors and thresholds for each stage of the Mayo Clinic Cardiac Staging System

Mayo Clinic Cardiac Stage	Stage definition
Stage I	NT-proBNP <332 ng/L **and** cTnT <0.035 µg/L
Stage II	**Either** NT-proBNP >332 ng/L **or** cTnT >0.035 µg/L
Stage IIIa	NT-proBNP >332 ng/L **and** cTnT >0.035 µg/L, **plus** NT-proBNP <8500 ng/L
Stage IIIb	NT-proBNP >332 ng/L **and** cTnT >0.035 µg/L, **plus** NT-proBNP >8500 ng/L

Abbreviations: cTnT: cardiac troponin T; NT-proBNP: N-terminal prohormone brain natriuretic peptide.
Source: Dispenzieri *et al.,* (2004);[15] Wechalekar *et al.,* (2013).[16]

Prognosis worsens as patients progress through more advanced Mayo stages; this is supported by data from the European Myeloma Network (EMN), which analysed the real-world treatment outcomes for 3,000 patients in 10 European countries, of which 38% were UK patients, during the period 2011 to 2018. In alignment with previous studies, the EMN23 study identified an inverse relationship between median survival and cardiac stage, as defined by the Mayo 2004 / European modification staging system: whilst median survival was not reached by patients with Stage I disease, patients with Stage II, IIIa and IIIb disease had a median survival of 67.0 months, 31.1 months and 4.5 months, respectively.[17]

Delays in diagnosis are also associated with the poor prognosis of patients with AL amyloidosis since patients are often diagnosed after the disease has progressed to more advanced stages.[38, 71] The EMN retrospective analysis found that many patients had advanced disease at the point of diagnosis, with 35% having Stage II disease at diagnosis, 22% with Stage IIIa and 16% with Stage IIIb.[72] Furthermore, a recent US claims analysis of 1,403 patients has shown that symptoms related to advanced disease progression appear <1 year before diagnosis, whilst the median time from onset of symptoms to diagnosis overall is 2.7 years.[73] Ultimately, delayed diagnosis in patients with AL amyloidosis significantly and adversely impacts survival rates because disease is more advanced with later diagnosis and irreversible organ damage has already occured.[59, 74]

B.1.3.2 Impact of AL amyloidosis on patients

AL amyloidosis has a significant impact on the lives of patients afflicted with this disease. Patients suffer from substantially reduced quality of life due to physical burdens from the wide-ranging symptoms and complications associated with the condition, in addition to side effects from currently available chemotherapy regimens. Patients suffer further psychologically, with many patients reporting anxiety, depression and low self-worth. These factors are compounded by delayed diagnosis and a lack of information around the disease.

Given the rarity of AL amyloidosis, Janssen conducted a patient workshop consisting of two online focus groups on 7th and 14th April 2021 to understand the psychological and emotional impact of AL amyloidosis on patients and carers in the UK. The methods for the workshop, which gathered insights from six patients with AL amyloidosis and one carer of a patient, are presented in Appendix N, and the full report is available in the reference pack.[75]

The burden of AL amyloidosis from a physical and emotional perspective, as well as the impact of barriers to diagnosis and treatment, is discussed further below.

Physical and emotional burden experienced by AL amyloidosis patients

AL amyloidosis, and its associated treatments, impose a substantial burden on patients and their carers, with the disease and its symptoms taking a major toll on quality of life. For the large proportion of AL amyloidosis patients with cardiac involvement, impaired heart functioning leads to shortness of breath, fatigue, and eventual development of congestive heart failure. Such physical impairment significantly affects patients' ability to conduct day-to-day activities and may lead to rapid onset of exhaustion. One participant at the patient workshop described his ability to walk as greatly impaired and his breathing as 'appalling'; he described that he is unable to bend down and expressed that he gets exhausted quickly.[75] Beyond cardiac problems, the systemic nature of AL amyloidosis means that the symptom burden is high, with fatigue, weakness, weight loss, muscle atrophy and neuropathy reported as the other symptoms that have the greatest impact on daily life.[76]

The physical burden of AL amyloidosis is supported quantitatively by the US prospective AL Amyloidosis Patient HRQoL Study, which compared the HRQoL of 341 AL amyloidosis patients with that of matched general population controls. This study identified that patients with newly diagnosed AL amyloidosis reported significantly lower scores across all subscales on the Short Form 36 Health Survey Questionnaire (SF-36v2) ($p<0.05$ for all comparisons) compared to the general population.[77] The study also underscored the relationship between cardiac involvement and reduced HRQoL, with 178 patients with cardiac involvement demonstrating significantly lower SF-36v2 scores compared to the general population.[77] Further, the subgroup of patients who did not meet cardiac response targets (≥30 reduction in NT-proBNP levels) had significantly worse mean SF-36v2 scores across all subscales compared to patients who did meet this target.[78]

With regards to treatment, many patients at the workshop indicated that it was difficult to separate feelings of ill health because of the disease versus feelings of ill health from treatment.[75] As discussed below, there are currently no approved therapies for AL amyloidosis in the UK, and off-label chemotherapies used in current clinical practice are associated with adverse events.[26]

Beyond their physical health, patients with AL amyloidosis experience significant mental health challenges. Findings from the patient workshop show that living with AL amyloidosis has a negative impact on the mental health of patients, which has worsened in the last year by the ongoing COVID-19 pandemic, causing delays in treatment and diagnosis. Patients expressed feelings of low self-worth, frustration at their declining physical ability and distress at their loss of independence. One individual indicated that he struggled at the time of diagnosis, noting that he did not want to talk with family and friends about his disease for months and that "the transplant cancellation was the lowest point in my life." The patients at the workshop were in agreement that the optimal treatment option would allow them to live as long as possible for as well as possible, without having to trade-off between the two.[75]

The impact of AL amyloidosis on patients' mental health is further supported by a large US study of 1,226 patients. High proportions of patients who had completed the SF-36v2 reported experiencing symptoms of anxiety (47%) and depression (37%), with many reporting that this disrupted their ability to work and reduced the amount of time spent on work and other activities.[79] In a further qualitative study of 199 AL amyloidosis patients, 63.0% reported that their diagnosis had made them feel frightened, 31.0% reported feeling depressed and 25.5% felt hopeless.[76] This reflects the poor prognosis and expected survival of patients diagnosed with AL amyloidosis, as described previously.

Barriers to diagnosis and treatment

Patients with AL amyloidosis experience a difficult journey due to delayed diagnoses and the lack of available support and disease information.[76, 80] A survey conducted by the US Amyloidosis Research Consortium (ARC), completed by 533 patients, family members or carers, including respondents from the UK, reported that just 37% of patients had received a diagnosis within six months, with 20% and 10% of patients waiting more than two years and three years, respectively.[76]

Non-specific symptoms and healthcare system barriers have both been cited as sources of the difficulties in establishing a diagnosis of AL amyloidosis.[76] AL amyloidosis may go undiagnosed due to patient interpretation of non-specific symptoms, such as fatigue, shortness of breath and muscle aches, as low priority concerns, or attributable to other less serious health conditions or to advancing age.[76, 81] Healthcare barriers mean that patients can struggle to get their physicians to investigate their observed symptoms and that these are subsequently frequently misdiagnosed. In the ARC study, cardiologists were the most frequently seen physician after the primary physician/general practitioner (24.5%), despite the fact that they were typically unlikely to diagnose the condition (doing so in only 22.6% of cases), with correct diagnoses more likely to come from haematologists or oncologists (34.1%).[76] Nearly half of AL amyloidosis patients in the ARC study reported having received a misdiagnosis.[76]

Aligned with this, several UK-based patients at the workshop described their journey to diagnosis as challenging due to the generic nature of the symptoms, with one patient recalling having been seen by several practitioners, including a nephrologist, who diagnosed multiple myeloma, before receiving the correct diagnosis from a haematologist. Some patients experienced a time to diagnosis of up to two years.[75]

The rarity of AL amyloidosis and the lack of any currently licensed treatment options for patients in the UK may contribute to the extended waiting time for diagnosis faced by patients. Introduction of DBCd to clinical practice following recommendation by NICE is likely to raise awareness of this rare disease, thus improving diagnosis rates and positively impacting patient outcomes and survival rates as a result.

Summary

Overall, the physical, psychological and social burdens of AL amyloidosis contribute to significantly reduced quality of life in patients, which is exacerbated further by healthcare barriers such as prolonged diagnosis time and misdiagnosis.

B.1.3.3 Description of the clinical care pathway

Treatment pathway for AL amyloidosis in the UK

As AL amyloidosis is incurable, the primary goal of treatment is to achieve a rapid, deep and durable haematologic response as this is associated with improved quality of life and prolonged survival.[24, 25] Haematologic response represents a key goal in medical society guidelines, which recommend at least VGPR as the target and preferably CHR.[3-6] An early and deep haematologic response has been established as a key prognostic factor for survival as demonstrated by studies assessing the impact of timing and depth of haematologic response in patients with newly diagnosed AL amyloidosis.[2, 82]

Currently, there are no therapies in the UK that are specifically licensed for the treatment of patients with AL amyloidosis. There are also no NICE guidelines currently available for treatment of AL amyloidosis and the latest UK guidelines from the British Society for Haematology (BSH) were published in 2014.[83] During a UK advisory board in April 2021, clinical experts agreed that the BSH guidelines may be used to inform the treatment of patients in UK clinical practice, but that advice from the NAC represents the most valuable resource to inform treatment in the UK at this time.[26]

The small, select group of AL amyloidosis patients who are eligible to undergo ASCT have greatly improved prognosis and survival outcomes.[15, 84, 85] ASCT can be a highly effective treatment option, but the proportion of patients who are eligible to receive this treatment option is small, with many patients ineligible due to their high comorbidity burden: eligibility criteria for ASCT vary by country, though patients are typically considered ineligible for ASCT if they have ≥2 affected organs, severe cardiac dysfunction, end-stage renal disease or high overall comorbidity burden.[6] Indeed, a treatment rate of approximately 5% can be estimated from data from the British Society of Blood and Marrow Transplantation and Cellular Therapy; this is likely to have been even lower in the year 2020/2021 due to an increased risk of infection associated with transplantation during the COVID-19 pandemic.[86, 87]

This low rate of treatment with ASCT is supported by feedback from a UK advisory board, in which clinicians suggested that <1% of AL amyloidosis patients receive ASCT as a first-line treatment option (i.e. without prior induction therapy), reflecting the advanced stage of disease at presentation of many patients in the UK.[26] The experts noted that only 10 to 12 patients have received ASCT without previous induction therapy in the last 10 years.[26] This indicates that many of the patients undergoing ASCT are not newly diagnosed systemic AL amyloidosis patients.

Accordingly, bortezomib-based regimens are considered to represent the mainstay of treatment for AL amyloidosis. This is supported by the EMN23 study, which found that, between 2011 to 2018, 75.0% of AL amyloidosis patients received first-line bortezomib-based regimens. Furthermore, ASCT was used in 10% and 2% of those younger or older than 65, respectively, mostly for patients at an earlier cardiac stage (14%, 4%, 3%, and 1% for Stages I, II, IIIa and IIIb, respectively).[17]

Based on the same clinical expert opinion, the standard of care for newly diagnosed patients in clinical practice in the UK is BCd, and approximately [redacted]% of patients are treated with BCd as first-line therapy.[88]

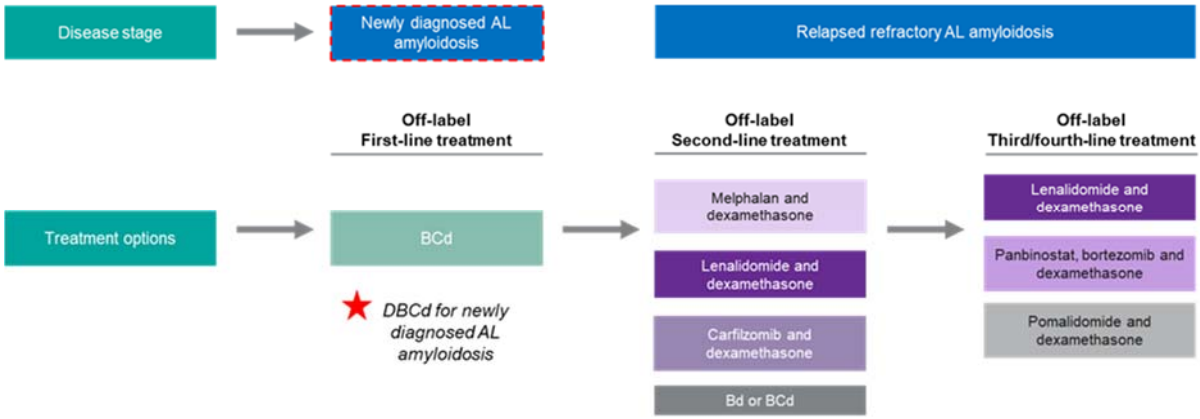
Clinical expert opinion suggests that, in the UK, melphalan in combination with dexamethasone is rarely used.[26] Lenalidomide with dexamethasone is an option only for patients with neuropathy, but it is very rarely used in newly diagnosed patients; typically, this treatment option is likely to be used only in patients who struggle with, or are contraindicated to, bortezomib.[26]

In the second line setting, clinical feedback was that patients may be re-treated with bortezomib-based regimens, particularly if they had responded well in the first-line setting. Carfilzomib, lenalidomide and dexamethasone (KRd) was indicated to not be used due to high levels of toxicity.

Based on clinical expert opinion elicited at the advisory board, the current treatment pathway for AL amyloidosis patients in the UK, and the expected treatment pathway should DBCd be recommended in this indication, is presented in Figure 2.[26] In this figure, the proportions of

patients who would receive each treatment following BCd or DBCd, as estimated by these clinicians, are also presented.

Figure 2: Current and expected pathway of care for AL amyloidosis patients in UK clinical practice



[a] Given the small proportion of newly-diagnosed AL amyloidosis patient who receive ASCT, this treatment is not considered as a comparator in this appraisal.
Abbreviations: ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone.

Unmet need

There is a high level of unmet need for patients with AL amyloidosis, with the disease causing progressive, irreversible damage to multiple organs that leads to significant HRQoL impairment, substantial treatment costs and a very poor long-term prognosis. Nearly one-third (30%) of patients die within the first year of diagnosis, with an estimated 4-year survival rate of just 54%.[2, 74] This burden is particularly high in patients with advanced Mayo Clinic Stage IIIa/IIIb disease, who represent approximately 55% of all presenting UK AL amyloidosis patients: median overall survival in patients with Mayo Clinic Stage IIIb at baseline is approximately 2.5–3.5 months as compared with about 9.5–25.9 months in patients with Mayo Clinical Stage IIIa.[72] This reflects that heart failure is currently the leading cause of death in patients with systemic AL amyloidosis, with a median survival of just six months from the onset of heart failure.[18-20] Survival rates are also particularly low for the large proportion of patients with multiple organ involvement.[18]

Few robust clinical trials have been conducted in patients with AL amyloidosis to date. As a result, available clinical evidence is primarily based on retrospective studies, with only a small number of Phase II or III trials. Available studies of bortezomib-based regimens (e.g. BCd) typically show high ORRs, however the majority of patients currently fail to achieve the primary therapeutic goal of a CHR. This in turn allows toxic amyloids to continue to build up in the organs.[27-29] Organ response rates (OrRRs), which indicate the effect of treatment on organ function, have also been shown to be poor for bortezomib-based therapies: across several studies, most AL amyloidosis patients receiving first-line bortezomib-based regimes have been observed to fail to achieve cardiac (13 to 29%) and renal responses (19 to 29%), increasing overall disease burden and mortality risk.[27, 28, 30, 31]

Limited efficacy and adverse events are still concerns with current therapy that may result in further HRQoL impairment.[89] Treatments that have been shown to be more effective, such as ASCT or organ transplantation, are restricted to small groups of eligible patients; unfortunately, AL amyloidosis patients often have multi-organ involvement which makes them unsuitably fit to undergo ASCT.

Additionally, most patients experience a protracted delay between symptom onset and initial diagnosis, meaning many patients have advanced disease at the time of diagnosis and are given a poor prognosis at this point.[1, 38] Aside from the more severe and life-limiting symptoms associated with later stages of disease, this delayed diagnosis and the lack of any licensed treatments for AL amyloidosis contribute to the psychological burdens of anxiety, depression and low self-worth reported by patients. It is likely that the availability of a treatment option recommended specifically for the treatment of AL amyloidosis in the UK would have the dual benefits of raising clinician and patient awareness of the disease and reducing the stress and anxiety associated with diagnosis.

Beyond the physical and emotional aspects of life with AL amyloidosis for patients, the direct treatment costs for the healthcare system are substantial. In particular, significant costs are associated with patients who require multiple lines of therapy. For patients who reach end-stage renal failure, renal replacement therapy is necessary; for patients who do not receive, or are not eligible for, a transplant, treatment is with dialysis. In addition to being extremely costly for the healthcare system, the substantial impact of dialysis on patient HRQoL is well-documented.[21-23] As such, a reduction in the proportion of patients who require this treatment would be an important benefit of DBCd treatment in AL amyloidosis patients with kidney involvement.

Accordingly, there is a substantial unmet need for a novel, effective and well-tolerated treatment for newly diagnosed AL amyloidosis patients that has the potential to induce a rapid, deep and durable haematologic response. By doing so, such a treatment will improve the poor prognosis associated with this disease, improve patient HRQoL, delay organ failure and prolong survival.

Daratumumab SC in combination with BCd

Daratumumab in combination with BCd has received marketing authorisation for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.[32] In this positioning, the sole relevant comparator to DBCd is BCd alone.

The efficacy and safety of DBCd has been compared directly to BCd in ANDROMEDA, a pivotal, randomised controlled trial of newly diagnosed AL amyloidosis patients. Within ANDROMEDA, DBCd has demonstrated a rapid and deep haematologic response, as well as high rates of cardiac and renal response, relative to BCd. The methodology and results of ANDROMEDA are presented in Section B.2.

NICE recommendation of DBCd as a treatment in this population in England and Wales would make it the first recommended treatment for AL amyloidosis patients specifically and would represent a step-change to patient care. The introduction of DBCd would fulfil a significant unmet need for a group of patients who suffer from a dearth of effective and tolerable treatment options and face an extremely limited prognosis and life expectancy.

B.1.4 *Equality considerations*

In the ANDROMEDA study, patients with Stage IIIb cardiac disease were excluded during the screening period from participating in the trial, as they are not typically candidates for BCd at the specific dose and dosing schedule used in the trial.[35] It is important to note, however, that between the time of screening and of the first study drug administration, eight patients progressed to cardiac Stage IIIb (six in the BCd arm; two in the DBCd arm).

As described above, patients with Stage IIIb cardiac disease have the most severe degree of cardiac involvement.[16] However, clinical expert opinion supports that patients would be treated with DBCd in clinical practice should DBCd be recommended for use in the UK, as this would fulfil a significant unmet need in these patients. Furthermore, clinical experts emphasised that Stage IIIb patients comprise at least 20% of the AL amyloidosis patients observed in UK clinical practice and that they would expect such patients to derive clinical benefit should DBCd be recommended by NICE.[26] Patients with Stage IIIb disease are not excluded from the licensed indication for DBCd.[32]

These patients have high risk systemic AL amyloidosis and an extremely poor prognosis: in the EMN23 study, patients with Stage IIIb cardiac disease had a median survival of just 4.5 months.[17] These patients with severe cardiac involvement were further identified to receive bortezomib-based therapies often, with 81% and 8% of Stage IIIa and IIIb patients reported to receive these therapies, respectively.[17] Results of an analysis for patients with cardiac Stage IIIb disease which aimed to evaluate the safety profile of daratumumab monotherapy in this high-risk population found that from 14 patients who had received the first dose of daratumumab at least three months prior to the cut-off date, 9 (64%) had a haematologic response of PR or better, of which 42% were VGPR and above.[90]

This is further supported by data from the ALCHemy trial, a UK-based prospective study of patients with systemic AL amyloidosis, in which Stage III patients who did not respond to treatment had a survival rate of 20% at four years. The Stage III patients who did achieve a complete or very good partial haematologic response had an approximate survival rate of 75% at four years, underscoring the importance of achieving a deep and rapid haematologic response in this poor prognostic group in order to increase overall survival. Furthermore, given that haematologic responses are associated with improved survival and organ response, these data illustrate the reason that the primary aim of therapy is achievement and maintenance of this response.[91] Overall, these data indicate that receipt of, and response to, treatment has the potential to improve significantly the prognosis of these typically poor prognosis patients, highlighting the importance that these patients have access to DBCd should it be recommended by NICE.

It is therefore Janssen's view that that any recommendation for DBCd in AL amyloidosis should not be restricted in such a way to exclude patients with Stage IIIb disease, a group of highly severe patients, who have an extremely poor prognosis and life expectancy and who have the potential to benefit greatly from new, effective treatment options.

B.2 Clinical effectiveness

Summary of clinical effectiveness evidence

The ANDROMEDA trial

- The efficacy and safety of DBCd as compared with BCd was assessed in the ANDROMEDA trial: a randomised, open-label, multinational, multicentre Phase III trial of adult patients with newly diagnosed systemic AL amyloidosis.
- Expert clinical opinion confirms that the baseline demographic and disease characteristics of the enrolled population is broadly comparable to the AL amyloidosis population seen in clinical practice in England and Wales.[26]
- Data are presented from a pre-specified interim analysis (IA1; median follow-up 11.4 months) and a 12-month landmark analysis (median follow-up 20.3 months).

Haematologic response

- Results for haematologic response from ANDROMEDA demonstrate that DBCd achieves a deeper and more rapid haematologic response compared with the existing standard of care for AL amyloidosis in the UK, BCd.
- A statistically significantly higher rate of CHR was achieved in the DBCd treatment arm relative to the BCd arm. Additionally, DBCd induced at least a VGPR at a faster rate than BCd.
- The significant improvement in CHR rate in patients treated with DBCd was also observed across all pre-specified subgroups, including poor prognostic groups and importantly across patients with more advanced disease (Stage II and IIIa, according to the Mayo Clinical Staging System).
- Given the well-established relationship between depth of haematologic response and OS, [2, 27, 82, 92, 93] it is reasonable to expect that the deeper and more rapid haematologic responses achieved following DBCd treatment will translate into long-term improvements in OS for newly diagnosed AL amyloidosis patients.
- Achievement of CHR represents the optimal response in terms of patient prognosis and survival and is recommended as a key target in clinical treatment guidelines.[3-6]

Organ response

- Patients treated with DBCd achieved almost doubled rates of both cardiac and renal response at six months relative to those treated with BCd, with these significant improvements being sustained after 12- and 18-months.
- Furthermore, patients were able to achieve organ responses more quickly when treated with DBCd relative to BCd, delaying organ progression and enabling patients to avoid the detrimental impacts of organ deterioration on their quality of life. Results demonstrating an increased time to organ progression for patients treated with DBCd relative to BCd provide additional support to this.
- DBCd is therefore expected to fulfil a significant unmet need amongst AL amyloidosis patients, with many failing to achieve organ responses with existing bortezomib-based therapies.[27, 28, 30, 31]

MOD-PFS and MOD-EFS

- The MOD-PFS endpoint allowed measurement of the time until patients experience significant progression of their disease, defined as the time from randomisation to one of the following events (whichever comes first): haematologic progression, end-stage cardiac or renal disease, or death.
- DBCd was shown to prolong the time to MOD-PFS relative to BCd, providing substantial benefits to patients in delaying serious deterioration of the heart and kidneys. This is expected to enable patients to avoid considerable negative impacts on their quality of life associated with end-stage organ failure.
- A further supplementary analysis of MOD-PFS, MOD-EFS, that incorporated patient switching to subsequent alternative therapies upon suboptimal response or worsening organ function as an event, further demonstrates the benefits of DBCd.
- The increased time to MOD-EFS events observed for DBCd as measured with this composite endpoint further highlights the ability of DBCd to increase the time during which AL amyloidosis

patients can avoid disease progression.

HRQoL

- Patients treated with DBCd in ANDROMEDA reported improved overall EQ-5D-5L utility scores. The results demonstrate that patients treated with DBCd experience improvements across important aspects of their quality of life as measured by the different scales in the EQ-5D-5L questionnaire.
- DBCd was associated with relatively stable EQ-5D-5L utility scores throughout the first six cycles of treatment, whilst patients in the BCd group reported a substantial decline during the same time period. From Cycle 7 onwards, as patients received subsequent daratumumab SC monotherapy, a consistent improvement in mean EQ-5D-5L utility scores was reported in the DBCd treatment group.
- Importantly, adding daratumumab SC to standard of care BCd combination therapy did not result in a detrimental effect on HRQoL, suggesting that DBCd may produce both improvements to clinical outcomes whilst at least maintaining patients' HRQoL.

Safety

- The occurrence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs, Grade III and IV) were broadly balanced across the treatment arms.
- TEAEs were generally manageable and did not lead to any increase in treatment discontinuation as compared with background therapy.
- Overall, DBCd was well tolerated, with a safety profile consistent with the established safety profiles of daratumumab SC and BCd and no new safety concerns were identified.

Conclusion

- In summary, the introduction of DBCd to UK clinical practice would provide a step-change in the care available for AL amyloidosis patients. Its use provides patients with a novel, highly effective therapeutic option with a tolerable safety profile which has the potential to improve patient prognosis and HRQoL, delay organ failure and prolong survival.

B.2.1 *Identification and selection of relevant studies*

A *de novo* clinical systematic literature review (SLR) of the published literature was conducted to identify relevant clinical evidence (RCTs and non-RCTs) on the clinical efficacy and safety of pharmacological therapies for adults with newly diagnosed AL amyloidosis. Of note, the SLR took a broad approach and therefore included additional therapies not considered in the decision problem addressed in this submission.

The SLR was conducted according to a pre-specified protocol and performed in accordance with the methodological principles detailed in the PROSPERO international prospective register of systematic reviews.[94] The SLR was conducted in February 2021.

In total, the SLR identified five unique interventional studies (reported in eleven records) and 52 observational studies that met the inclusion criteria of the review. All five interventional studies were RCTs, and four of the five were Phase III trials.

Full details of the SLR search strategy, study selection process and results are presented in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

Of the studies identified in the clinical SLR, the trial of direct relevance to the decision problem for this appraisal is ANDROMEDA (NCT03201965). ANDROMEDA is the pivotal registration trial, presented to the EMA in support of the marketing authorisation for daratumumab SC in

combination with BCd in adult patients with newly diagnosed systemic AL amyloidosis.[32] ANDROMEDA is a randomised, open-label, multinational, multicentre Phase III trial in patients at least 18 years of age with newly diagnosed systemic AL amyloidosis.[35] This study provides the main body of evidence for daratumumab SC in combination with the relevant comparator to this appraisal, BCd.

An overview of ANDROMEDA is presented in Table 7, and the methodology and results are presented in Section B.2.3 onwards.

Table 7: Clinical effectiveness evidence from ANDROMEDA

Study	ANDROMEDA (NCT03201965)		
Study design	Randomised, open-label, active-controlled, Phase III trial		
Population	Adult patients (aged ≥18 years) with newly diagnosed systemic AL amyloidosis, involvement in ≥1 organ(s), measurable haematologic disease and an ECOG performance score of 0–2		
Intervention(s)	Daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone (N=195)		
Comparator(s)	Bortezomib, cyclophosphamide and dexamethasone (N=193)		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	ANDROMEDA represents the primary source of efficacy and safety data for DBCd in this indication. Data reported from ANDROMEDA are relevant to the decision problem and have been used in the economic model.		
Reported outcomes specified in the decision problem[a]	• **Hematologic response** • Organ response rates • **MOD-PFS** • OS • **AEs** • **HRQoL**		
All other reported outcomes	• MOD-EFS • CHR at six- and 12-months • Time to haematologic response • Duration of haematologic response • Time to initiation of subsequent non-cross resistant anti-plasma cell therapy • Time to organ response • Time to organ progression		

[a] Endpoints in bold are those that are used to inform the cost-effectiveness model.
Abbreviations: AE: adverse event; AL: amyloid light-chain; BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ECOG: Eastern Cooperative Oncology Group Performance Status; HRQoL: health-related quality of life; MOD-PFS: major organ deterioration-progression free survival; SC: subcutaneous.
Source: Janssen ANDROMEDA Protocol.[35]

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

B.2.3.1 Trial design

ANDROMEDA is a randomised, open-label, multinational, multicentre Phase III trial, in patients at least 18 years of age, with newly diagnosed systemic AL amyloidosis.

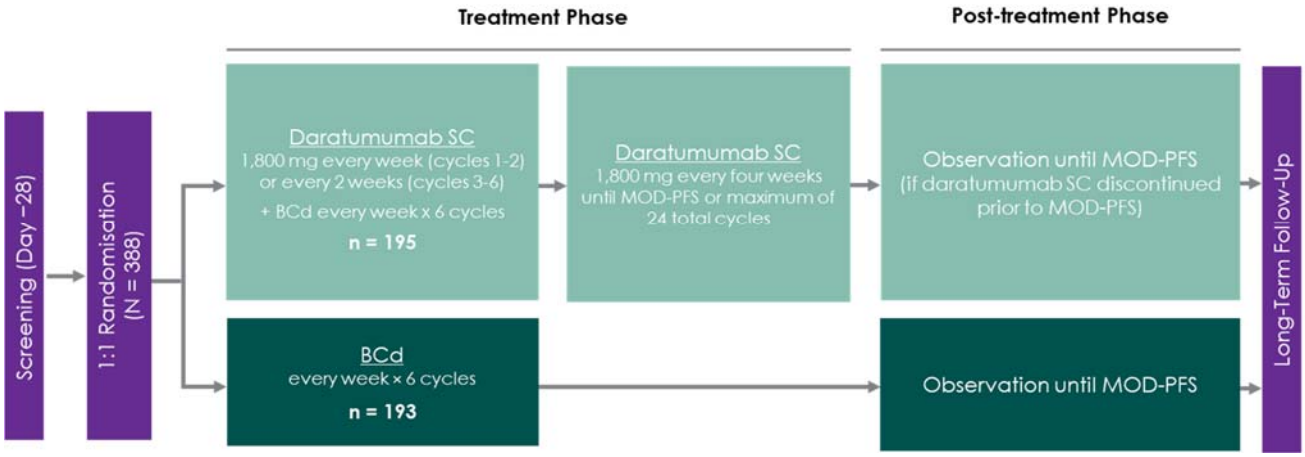
Patients were randomised in a 1:1 ratio to receive either BCd alone (Treatment Arm A) or DBCd (Treatment Arm B), following stratification according to the following factors:[35]

- Cardiac stage based on the Mayo Clinical Cardiac Staging System (Stages I, II, and IIIa)
- Countries that typically offer (List A) or do not offer (List B) ASCT for patients with AL amyloidosis
- Renal function (creatinine clearance [CrCl] ≥60 mL/min versus CrCl <60 mL/min)

The trial design consisted of four phases, including a Screening Phase (extending up to 28 days prior to Cycle 1, Day 1), a Treatment Phase (from Cycle 1, Day 1 until study treatment discontinuation), a Post-Treatment Observation Phase and a Long-term Follow-up Phase.

A schematic of the study design of the ANDROMEDA trial is presented in Figure 3.

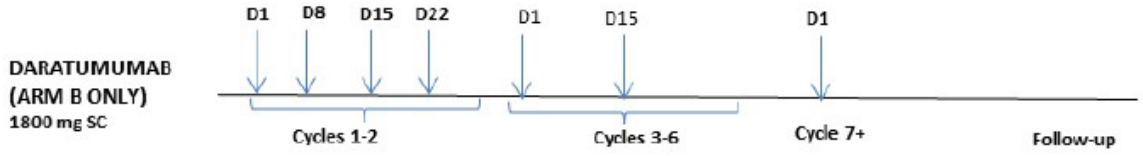
Figure 3: Design of the ANDROMEDA study



Each cycle is 28 days in length.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; SC: subcutaneous; MOD-PFS: major organ deterioration-progression free survival.
Source: Adapted from Kastritis *et al.*, (2020).[95]

During the Treatment Phase, patients in both the DBCd and BCd only arms received a maximum of six 28-day cycles of BCd therapy. Patients in the DBCd arm also received a fixed 1,800 mg dose of subcutaneous (SC) daratumumab, with weekly dosing during Cycles 1–2 and dosing every two weeks during Cycles 3–6. From Cycle 7 onwards, patients in the DBCd arm continued to receive daratumumab as monotherapy every four weeks until experiencing disease progression, starting a subsequent anti-plasma cell therapy, or a maximum of 24 cycles from the first dose of study treatment. An overview of the dosing schedule for the DBCd treatment arm is presented in Figure 4 below. A summary of the dosing schedule for the BCd arm is presented in Table 8 below.

Figure 4: Overview of ANDROMEDA daratumumab dosing schedule



Abbreviations: SC: subcutaneous.

B.2.3.2 Trial methodology

A summary of the methodology of ANDROMEDA is presented in Table 8 below.

Table 8: Summary of the ANDROMEDA trial methodology

Trial name	ANDROMEDA (NCT03201965)
Location	International: 140 sites in 22 countries, including the UK (2 sites)
Trial design	Randomised, open-label, active-controlled, Phase III trial
Eligibility criteria for participants	**Key inclusion criteria**: • Adult patients (≥18 years of age) • Histopathological diagnosis of amyloidosis based on detection by immunohistochemistry and polarising light microscopy of green bi-refringent material in congo red-stained tissue specimens (in an organ other than bone marrow) or characteristic electron microscopy appearance • Measurable disease of AL amyloidosis as defined by at least one of the following: o Serum M-protein ≥0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation performed at a central laboratory) o Serum free light chain ≥50 mg/L with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) ≥50 mg/ L • One or more organs impacted by AL amyloidosis according to consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis[24] • ECOG performance Status of 0, 1 or 2 **Key exclusion criteria**: • Patients with non-AL subtypes were excluded from the trial: Male subjects of 70 years of age or older with isolated cardiac involvement, and subjects of African descent (black subjects underwent mass spectrometry typing of AL amyloid in a tissue biopsy to rule out other types of amyloidosis such as age-related amyloidosis or hereditary amyloidosis (*ATTR* mutation) • Prior therapy for AL amyloidosis or MM including medications that target CD38, with the exception of 160 mg dexamethasone • Previous or current diagnosis of symptomatic MM, including the presence of lytic bone disease, plasmacytomas, ≥60% plasma cells in the bone marrow, or hypercalcemia • Evidence of significant cardiovascular conditions as specified below: o NT-ProBNP >8,500 ng/L (i.e. Mayo Clinic Cardiac Stage IIIb disease) o New York Heart Association (NYHA) classification IIIB or IV heart failure

	○ Heart failure that in the opinion of the investigator is on the basis of ischemic heart disease or uncorrected valvular disease and not primarily due to AL amyloid cardiomyopathy ○ Inpatient admission to a hospital for unstable angina or myocardial infarction within the last six months prior to first dose or percutaneous cardiac intervention with recent stent within six months or coronary artery bypass grafting within six months ○ For patients with congestive heart failure, cardiovascular-related hospitalisations within four weeks prior to randomisation ○ Patients with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but not placed ○ Screening 12-lead electrocardiogram showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >500 msec ○ Supine systolic blood pressure <90 mm Hg, or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of >20 mmHg despite medical management in the absence of volume depletion • Planned stem cell transplant during the first six cycles of protocol therapy are excluded
Study drugs	**In the DBCd arm:** • Daratumumab (1,800 mg) was administered via SC injection weekly for weeks 1–8, every two weeks for weeks 9–24 and every four weeks (one cycle) from week 25 onwards until disease progression or a maximum of 24 cycles (~2 years) from first dose of treatment. Each cycle was 28 days in length **In both the DBCd and BCd arms:** • Bortezomib was administered SC at a dose of 1.3 mg/m^2 once weekly for six 28-day cycles • Cyclophosphamide was administered orally or via IV infusion at 300 mg/m^2 once weekly (maximum weekly dose of 500 mg) for six 28-day cycles (dose can be rounded to the nearest pill size, e.g. a dose of 310 mg can be rounded to 300 mg if 10 mg pills are not available) • Dexamethasone was administered orally or via IV infusion at a total dose of 40 mg weekly for six 28-day cycles ○ On days of daratumumab dosing, patients in the DBCd arm received 20 mg on the day of daratumumab dosing as premedication and 20 mg on the day after daratumumab dosing. On weeks that daratumumab was not administered, or for patients in the BCd arm, dexamethasone was given at 40 mg weekly on a single day or divided into 2 days
Permitted and disallowed concomitant medication	• Concomitant administration of any other therapy for the intention of treating AL amyloidosis was prohibited including medications that target CD38 • Concurrent use of corticosteroids was prohibited, unless patients were on chronic steroids (maximum dose 20 mg/day prednisone equivalent) if they were being given for disorders other than amyloidosis • Concomitant administration of investigational agents was prohibited

	• Concurrent use of NEOD-1 was prohibited. Use of chronic doxycycline was prohibited. Administration of commercially available agents with activity against or under investigation for AL amyloidosis, including systemic corticosteroids were to be avoided. If steroids were given for other AEs, treatment duration greater than 14 days were to be avoided • Concomitant administration of strong CYP3A4 inducers was prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors were to be avoided and was not recommended in patients receiving bortezomib. If a strong CYP3A4 inhibitor must have been given in combination with bortezomib, patients were monitored for signs of bortezomib toxicity and considered a bortezomib dose reduction
Primary outcome	Overall CHR rate: defined as the overall proportion of patients who achieved CHR, as per independent review committee (IRC) assessment and confirmed by a subsequent assessment during or after study treatment. Evaluation of haematologic response was based on the consensus guidelines (see Table 9).[24]
Secondary outcomes	• MOD-PFS: a composite endpoint of clinically observable endpoints defined from randomisation to any one of the following events, whichever came first: o Death o Clinical manifestation of cardiac failure: defined as development of dyspnoea at rest (for at least 3 consecutive days) and due solely to amyloidosis cardiac deterioration, or need for cardiac transplant, left ventricular assist device, or intra-aortic balloon pump o Clinical manifestation of renal failure: defined as the development of end-stage renal disease (need for haemodialysis or renal transplant) o Development of haematologically progressed disease as per consensus guidelines • OrRR for kidney, heart, liver at six months: defined as the proportion of baseline organ involved patients who achieve confirmed organ response in each corresponding organ. Evaluation of organ response was based on the consensus guidelines (see Table 10)[24] • OS: measured from the date of randomisation to the date of the patient's death. If the patient was alive or the vital status is unknown, then the patient's data was censored at the date the patient was last known to be alive • CHR rate at six months: defined as the proportion of patients who achieve a complete haematologic response at six months, according to the consensus guidelines during or after the study treatment • Time to next treatment: defined as the time from the date of randomisation to the start date of subsequent AL amyloidosis (non-protocol) treatment. Death due to progressed disease prior to subsequent therapy was considered as an event. Otherwise, time to next treatment was censored at the date of death or the last date known to be alive • Haematologic VGPR or better rate: defined as the proportion of patients who achieve CHR or VGPR • Time to CHR (or VGPR or better): defined as the time between the date of randomisation and the first efficacy evaluation at which the patient met all criteria for CHR (or VGPR or better) • Duration of CHR (or VGPR or better): defined as the time between the date of initial documentation of CHR (or VGPR or better) to the date of first documented evidence of haematologic progressed disease. For patients who have not progressed, data was censored at the last disease assessment

	• Time to cardiac response, time to renal response, and time to liver response: defined as the time between the date of randomisation and the first efficacy evaluation at which the patient had each corresponding organ response. Definitions of organ response can be found in Table 10 • Duration of organ response: defined as the time between the date of initial documentation of each corresponding organ response to the date of first documented evidence of the corresponding organ progressive disease. For patients who did not have organ progression, data will be censored at the last disease assessment • Time to cardiac progression, time to renal progression, and time to liver progression: defined as the time from the date of randomisation to the date of each corresponding organ progression per consensus guidelines. Definitions of organ response can be found in Table 10 • Improvement in fatigue: defined as the change from baseline in the EORTC QLQ-C30 Fatigue scale score, improvement in mental functioning is defined as the change from baseline in the SF-36v2 Mental Component Summary • Improvement in HRQoL: defined as change from baseline in the EORTC QLQ-C30 Global Health Status scale score • Mean EQ-5D-5L utility scores ranging from zero (0.0) to 1 (1.0) with higher values representing better general health status of the individual
Pre-specified subgroups	• Sex (male, female) • Age (<65, ≥65) • Baseline weight (≤65 kg, 65–85 kg, >85 kg) • Race (white, Asian, others) • Baseline cardiac stage (I, II, IIIa/b) • Transplant typically offered in local country (list A, list B) • Baseline renal function (≥60 mL/min, <50 mL/min) • Cardiac involvement at baseline (yes, no) • Baseline renal stage (I, II, III) • Baseline alkaline phosphatase (abnormal, normal) • Baseline ECOG performance status (0, 1 or 2) • Cytogenic risk at study entry (high risk, low risk) • FISH t(11;14) (abnormal, normal)

Abbreviations: AE: adverse event; AL: amyloid light-chain; BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; dFLC: uninvolved free light chains; ECOG: Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L: EuroQol-5 Dimensions-5 Level; FISH: florescence in situ hybridisation; HRQoL: health-related quality of life; IRC: Independent Review Committee; IV: intravenous; MM: multiple myeloma; MOD-PFS: major organ deterioration-progression free survival; NYHA: New York Heart Association; OrRR: organ response rate; OS: overall survival; SC: subcutaneous; SF-36v2: Short Form 36 Health Survey Questionnaire; UK: United Kingdom; VGPR: very good partial response.
Source: Janssen ANDROMEDA Protocol.[35]

Rationale for choice of CHR as the primary endpoint

The primary endpoint used in ANDROMEDA was overall CHR, which was assessed via the consensus guidelines widely used in clinical practice in England to guide treatment options and assess patient prognosis.[24]

The rationale for selecting CHR as the primary endpoint in the trial was based primarily on its prognostic significance in relation to survival outcomes. The relationship between the timing and depth of haematologic response and improved OS is supported by a substantial body of evidence.[2, 27, 82, 92, 93] CHR therefore functions as a surrogate endpoint for survival, and was

selected in ANDROMEDA to enable modelling of survival in the absence of mature OS data from the trial.

Evaluation of haematologic response

The study protocol initially defined complete haematologic response as per Comenzo (2012) consensus guidelines criteria, which included achievement of a normalised free light chain (FLC) level and ratio, as well as negative serum and urine immunofixation.[24] However, this definition was later updated in line with subsequent publications that provided a broader understanding of the biological processes involved in AL amyloidosis.[18, 96, 97] The revised definition no longer required normalisation of the uninvolved FLC (uFLC) level and FLC ratio in patients who achieved an involved FLC (iFLC) level below the upper limit of normal (ULN). Disease evaluations were performed by a central laboratory.

Table 9 presents a summary of the criteria used to define the series of different haematologic response categories.

Rationale for choice of MOD-PFS as a major secondary endpoint

In clinical practice, disease progression in AL amyloidosis patients may be evaluated according to a range of biomarkers, including haematologic, cardiac and renal biomarkers given the heterogeneity in presentation of the disease. As a result of the complexities of using PFS to measure disease progression in AL amyloidosis, and to provide additional clinical context regarding the long-term durability of haematologic response and organ response, ANDROMEDA instead collected MOD-PFS. MOD-PFS is a novel, composite endpoint developed to encompass the most clinically relevant and objective measures of the benefits of anti-plasma cell therapy: haematologic progression, major organ deterioration, and death.

The use of MOD-PFS as a key secondary endpoint and measure of disease progression in the ANDROMEDA trial was approved following consultation with both the FDA and EMA.[33, 34]

Table 9: Summary of haematologic response endpoints and definitions based on the consensus guidelines

Response Category	Criteria
CHR	• Negative serum and urine immunofixation and normalisation of FLC levels and FLC ratios • Per clarifications during the trial based on recent evidence (recommended by the Steering Committee and agreed upon by the IRC, if iFLC level is lower than the upper limit of normal (ULN), normalisation of uninvolved FLC and FLC ratio is not required when determining CHR
VGPR	• Baseline[a] dFLC ≥50 mg/L: reduction in dFLC <40 mg/L • Baseline[a] dFLC <50 mg/L: ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
PR	• Baseline[a] dFLC ≥50 mg/L: a greater than 50% reduction in the dFLC • Baseline[a] dFLC <50 mg/L: ≥50% reduction in serum M-protein plus reduction in 24-hour urine M-protein by ≥90% or to <200 mg/24 hours
NR	• Less than a PR
Progression	• From CHR, abnormal FLC ratio (light chains must double) • From any response, 50% increase in serum M-protein to >0.5 g/dL or 50%

	increase in urine M-protein to >200 mg/day (a visible peak must be present) • Involved free light chain increase of 50% to >100 mg/L

[a] Baseline measurement defined as the closest non-missing measurement taken on or prior to the first study treatment administration.
Abbreviations: CHR: complete haematologic response; dFLC: difference between the involved and uninvolved free light chain; FLC: free light chain; iFLC: involved free light chain; IRC: Independent Review Committee; NR: no response; PR: partial response; ULN; upper limit of normal; VGPR: very good partial response.
Source: Comenzo *et al*., (2012).[24]

Table 10: Summary of organ response and progression criteria based on the consensus guidelines

Organ	Response	Progression
Heart	• NT-ProBNP response (>30% and >300 ng/l decrease in patients with baseline NT-proBNP>650 ng/l) or NYHA class response (>2 class decrease in subjects with baseline NYHA class 3 or 4)	• NT-proBNP progression (>30% and >300 ng/l increase[a]) or cTn progression (>33% increase) or ejection fraction progression (>10% decrease)
Kidney	• 50% decrease (at least 0.5 g/day) of 24-hour urine protein (urine protein must be >0.5g/day pre- treatment). Creatinine and creatinine clearance must not worsen by 25% over baseline	• 50% increase (at least 1 g/day) of 24-hour urine protein to >1 g/day or 25% worsening of serum creatinine or creatinine clearance
Liver	• 50% decrease in abnormal alkaline phosphatase value	• 50% increase of alkaline phosphatase above the lowest value

[a] Patients with progressive worsening renal function cannot be scored for NT-proBNP progression.
Abbreviations: NT-proBNP: N-terminal prohormone of brain natriuretic peptide; cTnT: cardiac troponin; NYHA: New York Heart Association.
Source: Comenzo *et al*., (2012).[24]

B.2.3.3 Baseline characteristics

Summaries of baseline demographic and disease characteristics of patients with AL amyloidosis included in ANDROMEDA are presented in Table 11 and Table 12, respectively. Overall, baseline demographics were well-balanced between the DBCd and BCd treatment arms. The median age was 64.0 years (range: 34–87), with 47.2% of the patients ≥65 years of age. Fifty-eight percent of patients were male. The majority of patients were white (75.8%) with an ECOG performance score of 0 (41.5%) or 1 (49.5%). Body weight subgroups were generally balanced between both treatment arms.[98]

Table 11: Baseline patient characteristics in ANDROMEDA (ITT population)

Characteristic	BCd (N=193)	DBCd (N=195)	Total (N=388)
Age, years			
Mean (SD)	64.0 (9.7)	62.2 (10.2)	[redacted]
Median	64.0	62.0	[redacted]
Range	(35–86)	(34–87)	[redacted]
<65, n (%)	[redacted]	[redacted]	[redacted]
≥65, n (%)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female	76 (39.4)	87 (44.6)	[redacted]
Male	117 (60.6)	108 (55.4)	[redacted]

Race, n (%)			
American Indian or Alaska Native	2 (1.0)	1 (0.5)	[redacted]
Asian	34 (17.6)	30 (15.4)	[redacted]
Black or African American	7 (3.6)	6 (3.1)	[redacted]
Native Hawaiian or Other Pacific Islander	1 (0.5)	0	[redacted]
White	143 (74.1)	151 (77.4)	[redacted]
Multiple	1 (0.5)	0	[redacted]
Unknown	5 (2.6)	7 (3.6)	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	13 (6.7)	9 (4.6)	[redacted]
Not Hispanic or Latino	176 (91.2)	179 (91.8)	[redacted]
Unknown	4 (2.1)	7 (3.6)	[redacted]
Weight, kg			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
≤65 kg, n (%)	74 (38.3)	62 (31.8)	[redacted]
65–85 kg, n (%)	74 (38.3)	96 (49.2)	[redacted]
>85 kg, n (%)	45 (23.3)	37 (19.0)	[redacted]
Height, cm			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Body surface area, m^2			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide, and dexamethasone DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide, and dexamethasone; ITT: intention-to-treat; SD: standard deviation.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020).[95]

Baseline disease characteristics were also well-balanced between the DBCd and BCd treatment arms. The median time since initial AL amyloidosis diagnosis to randomisation was 43.0 days. The median number of organs involved at baseline was 2, with 71.4% of patients having cardiac involvement, 59.0% of patients having kidney involvement, and 65.5% of patients having ≥2 organ involvement. 16.2% of patients were renal Stage III at baseline.[98]

Another key disease characteristic was Mayo Clinic Cardiac Stage at baseline. Disease staging in the ANDROMEDA trial was based primarily on the Mayo Clinic Staging systems described in Section B.1.3.1, but with some minor differences in the criteria used to categorise patients into stages. As compared with the criteria outlined in Table 6, the ANDROMEDA trial implemented an hs-cTnT threshold of 54 ng/L instead of a cTnT threshold of 0.035 µg/mL, and Stage III patients were divided into IIIa and IIIb based on the NT-proBNP threshold of 8,500 ng/L alone without consideration of a systemic blood pressure factor (threshold of 100 mg Hg) that was used to further divide Stage III patients in the 2013 revision of the Mayo staging system.[16] Approximately

one-third (36.6%) of patients were Mayo Clinic Cardiac Stage IIIa/b at baseline. It should be noted that although patients with Stage IIIb were excluded from ANDROMEDA, eight patients (two and six in the DBCd and BCd arms, respectively) who did not have Stage IIIb disease at screening, progressed to Stage IIIb at the time of first study dose administration.

Table 12: Baseline patient disease characteristics in ANDROMEDA (ITT population)

Characteristic	BCd (N=193)	DBCd (N=195)	Total (N=388)
Baseline ECOG score, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Time since initial AL diagnosis, days			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	43.0	48.0	[redacted]
Range	(5–1102)	(8–1611)	[redacted]
≤30, n (%)	[redacted]	[redacted]	[redacted]
30–60, n (%)	[redacted]	[redacted]	[redacted]
>60, n (%)	[redacted]	[redacted]	[redacted]
Isotype of AL based on either immunofixation or light chain, n (%)			
Lambda	[redacted] (77.2)	[redacted] (81.0)	[redacted]
Kappa	[redacted] (22.8)	[redacted] (19.0)	[redacted]
Organ involvement, n (%)			
Heart	137 (71.0)	140 (71.8)	277 (71.4)
Kidney	114 (59.1)	115 (59.0)	229 (59.0)
Liver	16 (8.3)	15 (7.7)	[redacted]
Gastrointestinal tract	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]
Nerve	[redacted]	[redacted]	[redacted]
PNS	[redacted]	[redacted]	[redacted]
ANS	[redacted]	[redacted]	[redacted]
Soft tissue	[redacted]	[redacted]	[redacted]
Number of organs involved			
Mean (SD)	2.0 (1.0)	2.0 (1.0)	[redacted]
Median	2.0	2.0	[redacted]
Range	(1–6)	(1–5)	[redacted]
1 organ, n (%)	68 (35.2)	66 (33.8)	[redacted]
2 organs, n (%)	77 (39.9)	76 (39.0)	[redacted]
≥3 organs, n (%)	48 (24.9)	53 (27.2)	[redacted]
Cardiac stage based on Mayo Clinic Cardiac Staging System[a], n (%)			
I	43 (22.3)	47 (24.1)	[redacted] (23.2)
II	80 (41.5)	76 (39.0)	[redacted] (40.2)
IIIa	64 (33.2)	70 (35.9)	[redacted]
IIIb	6 (3.1)	2 (1.0)	[redacted]

NYHA class, n (%)			
I	94 (48.7)	101 (51.8)	[redacted]
II	89 (46.1)	77 (39.5)	[redacted]
IIIA	10 (5.2)	17 (8.7)	[redacted]
Renal function status - creatinine clearance			
<60 mL/min	[redacted]	[redacted]	[redacted]
≥60 mL/min	[redacted]	[redacted]	[redacted]
Renal stage[b], n (%)			
I	[redacted] (52.3)	[redacted] (55.4)	[redacted]
II	[redacted] (38.3)	[redacted] (34.7)	[redacted]
III	[redacted] (9.3)	[redacted] (9.8)	[redacted]
Chronic kidney disease stage[c], n (%)			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
V (End stage renal disease)	[redacted]	[redacted]	[redacted]
Cytogenetic risk at study entry[d], n (%)			
High risk	19 (11.4)	17 (11.0)	36 (11.2)
Standard risk	147 (88.6)	138 (89.0)	285 (88.8)

[a] Cardiac stage is based on both NT-proBNP and hs-cTnT levels; [b] Renal stage is based on eGFR and proteinuria testing; [c] Chronic kidney disease stage is based on eGFR; [d] Cytogenetic risk is based on FISH or karyotype testing. High risk is defined as: 1) by FISH testing: t (4; 14), t(14; 16), and 17p deletion; or 2) by Karyotype testing: t (4; 14), 17p deletion.
Abbreviations: ANS: autonomic nervous system; BCd: bortezomib, cyclophosphamide, and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide, and dexamethasone; dFLC: difference in involved and uninvolved free light chains; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; FISH: florescence in situ hybridization; FLC: free light chain; iFLC: involved free light chain; hs-cTnT high sensitivity cardiac troponin T; ITT: intention-to-treat; NT-proNBP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; PNS: peripheral nervous system; SD: standard deviation.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020).[95]

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

B.2.4.1 Trial populations

The definitions of the ANDROMEDA study populations are presented in Table 13.

Table 13: Trial populations used for the analysis of endpoints of ANDROMEDA

Analysis set	Definition
ITT analysis set (N=388)	Included all randomised patients
Safety analysis set (N=381)	Includes randomised patients who received at least 1 administration of any study treatment
Haematologic response analysis set (N=369)	Includes randomised patients who have a confirmed diagnosis of amyloidosis and measurable disease at baseline. In addition,

	patients must have received at least 1 administration of study treatment and have at least 1 post-baseline disease assessment
Cardiac response analysis set (N=235)	Includes randomised patients with baseline NT-proBNP value ≥650 ng/L or baseline NYHA class 3 or 4. In addition, patients must have received at least 1 administration of study treatment and have at least one post-baseline NT-proBNP measurement (if baseline NT-proBNP ≥650 ng/L) or NYHA function evaluation (if baseline NYHA class 3 or 4)
Renal response analysis set (N=230)	Includes randomised patients with baseline urine protein >0.5 g/day. In addition, patients must have received at least 1 administration of study treatment and have at least one post-baseline urine protein (g/day) measurement
Liver response analysis set (N=24)	Includes randomised patients with baseline abnormal alkaline phosphatase value. In addition, patients must have received at least 1 administration of study treatment and have at least one post-baseline alkaline phosphatase measurement
Pharmacokinetic analysis set (N=183)	Includes randomised patients assigned to DBCd group who received at least 1 administration of daratumumab and have at least 1 pharmacokinetic sample concentration value after the first infusion
Immune response analysis set (N=182)	Includes randomised patients assigned to DBCd group who received at least 1 administration of daratumumab and had appropriate serum samples for detection of antibodies to daratumumab or rHuPH20

Abbreviations: DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide, and dexamethasone; ITT: intention-to-treat; NT-proNBP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; rHuPH20: recombinant human hyaluronidase PH20.
Source: Janssen ANDROMEDA Protocol[98]

B.2.4.2 Statistical methods

The statistical analyses used to analyse the primary endpoint (overall CHR rate as assessed by blinded IRC), alongside sample size calculations and methods for handling missing data, are presented in Table 14.

Table 14: Statistical methods for the primary analysis of ANDROMEDA

Hypothesis objective	• Null hypothesis: there is no difference in the overall CHR rate between daratumumab in combination with BCd compared to BCd alone, in patients with newly diagnosed AL amyloidosis • Alternative hypothesis (which informs the sample size calculation): daratumumab in combination with BCd will demonstrate a 15% improvement in the overall CHR rate compared to BCd alone, in patients with newly diagnosed AL amyloidosis
Analysis timepoints	In the ANDROMEDA trial protocol,[35] the following pre-specified interim analyses were planned: • A pre-specified interim analysis occurred after the first 30 subjects were treated for at least 1 cycle in each arm, with the purpose of providing a comprehensive evaluation of safety (IA1). (Note: in the ANDROMEDA trial protocol this interim analysis is referred to as IA1, but results of this analysis are **not** reported in the present submission) • A later pre-specified interim analysis occurred after at least 180 subjects had been treated for at least 6 cycles, with the purpose of evaluating cumulative interim efficacy and safety data (IA2). (Note: in the ANDROMEDA trial

	protocol this interim analysis is referred to as IA2, but is referred to as **IA1** in the present submission)
Statistical analysis	• All statistical hypothesis tests and 95% CI presented were 2-sided. For the primary endpoint, overall CHR rate, the hypothesis was tested at the 0.05 significance level (overall). An alpha level of 0.0001 (2-sided) was spent at the second interim analysis; the alpha spent at the primary analysis was 0.0499 (2-sided) by a user defined alpha spending function • Formal hypothesis testing of the major secondary endpoints, MOD-PFS and OS, was conducted at the primary analysis of CHR and when 200 MOD-PFS events were observed • If at the time of primary analysis, the primary endpoint of overall CHR rate was statistically significant, the following major secondary endpoints ordered below were to be sequentially tested, each with an overall two-sided alpha of 0.05, by utilising a hierarchical testing approach. The major secondary endpoints are ordered as follows: 1. MOD-PFS 2. OS • The significance level at the primary analysis was determined by the alpha-spending function specific to that endpoint: o For MOD-PFS, the exact information fraction at primary analysis was determined by the O'Brien-Fleming alpha spending function o For OS, the information fraction at primary analysis was determined by the observed number of death events divided by 156 total projected death events by the time of final OS analysis • If the null hypothesis for MOD-PFS endpoint failed to be rejected at the primary analysis, then OS was not tested until the next analysis timepoint (e.g. approximately 200 MOD-PFS events). If the null hypothesis for MOD-PFS endpoint was rejected at the primary analysis, it remained rejected and was not to be re-tested at the final OS analysis • By the time of primary analysis of CHR, 43.5% of total planned MOD-PFS events were observed, an alpha level of 0.00136 is used for this analysis of MOD-PFS based on Fleming alpha-spending function • For time-to-event endpoints (including MOD-PFS and OS), Kaplan-Meier estimates were presented along with a log-rank test stratified according to different factors to compare the two treatment arms (including cardiac risk, countries typically offering transplant to AL amyloidosis patients, and renal function). Median values and corresponding 95% CIs were obtained from the Kaplan-Meier estimates, Cox's regression applied to obtain the hazard ratio estimate and corresponding 95% CI
Sample size, power calculation	• The sample size for this study was based on the alternative hypothesis of a 15% improvement in overall CHR • Taking an estimated overall CHR rate of 25% for the BCd arm, adding a 15% improvement translates to an overall CHR rate of 40% for the DBCd arm • Approximately 360 patients (180 patients per arm) would provide more than 85% power to detect a 15% improvement in overall CHR using a likelihood ratio test with a 2-sided alpha of 0.05
Data management, patient withdrawals	• Patients were withdrawn from the study for any of the following reasons: o Lost to follow-up o Withdrawal of consent for study participation o Death o Sponsor terminates the study • If a patient was lost to follow-up, every reasonable effort was made by the study-site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow-up with the patient were documented • When a patient withdrew before completing the study, the reason for

	withdrawal was to be documented in the electronic case report form and in the source document. Study drug assigned to the withdrawn patient may not be assigned to another patient. Patients who withdrew from the study were not replaced • The patient could withdraw consent for use of samples for research. In such a case, samples were destroyed after they were no longer needed for the clinical study • See Table 8 for details on censoring of missing data for outcomes

Abbreviations: AL: amyloid light-chain; BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; MOD-PFS: major organ deterioration-progression free survival; OS: overall survival.
Source: Janssen ANDROMEDA Protocol.[35]

B.2.4.3 Participant flow in the relevant randomised controlled trials

A summary of patient flow in ANDROMEDA is presented in Appendix D.

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

RCTs captured in the clinical SLR were assessed for quality using the NICE clinical effectiveness quality assessment checklist, and non-RCTs and observational studies were assessed using the Newcastle-Ottawa scale. The results of these quality assessments are presented in Appendix D, and a summary of the quality assessment for ANDROMEDA is presented in Table 15 below.

Table 15: Quality assessment of the ANDROMEDA trial

	ANDROMEDA	
	Response	**Risk of bias**
Was randomisation carried out appropriately?	Yes. Centralised randomisation was carried out in ANDROMEDA, with patients randomly assigned to treatment arms using a computer-generated randomisation schedule prior to study initiation	Low
Was the concealment of treatment allocation adequate?	ANDROMEDA was an open-label trial, however, risk was mitigated through blinded IRC assessment of outcomes	Medium
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, demographic and baseline characteristics were well balanced between the two treatment groups, including key prognostic disease characteristics	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	ANDROMEDA was an open-label trial, which meant care providers and participants were not blinded to treatment allocation Outcomes were assessed by blinded IRC	Low

Were there any unexpected imbalances in drop-outs between groups?	No. Of the 388 patients that were randomised to receive study treatment (195 for DBCd; 193 for BCd), 193 were treated in the DBCd arm and 188 were treated in the BCd arm	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The ITT population included all randomised patients and was used for analysis of the primary endpoint and other endpoints unless otherwise stated, with the exception of time to and duration of both haematologic and organ specific responses	Low

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intention-to-treat.

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

Efficacy results from ANDROMEDA in this submission are presented from a pre-specified interim analysis (IA1; data cut-off 14th February 2020) and a 12-month landmark analysis (data cut-off 13th November 2020) and are based on a blinded IRC assessment of the outcomes investigated in the ANDROMEDA trial. The 12-month landmark analysis was not a pre-specified data cut, and instead was generated for conference purposes. The next pre-specified interim analysis for MOD-PFS and OS will occur when 200 MOD-PFS events have been observed in ANDROMEDA. Where possible, efficacy results for outcomes assessed in both the pre-specified interim analysis and 12-month landmark analysis are presented in parallel. For a number of outcomes, data are only available from the pre-specified interim analysis.

A summary of the outcomes from the pre-specified interim analysis and 12-month landmark analysis that are presented in the submission is provided in Table 16.

Table 16: Summary of ANDROMEDA data cuts

Data cut description	Median follow-up	Populations included	Outcomes presented in submission	Rationale for inclusion
Pre-specified interim analysis (IA1)	11.4 months (clinical data cut-off: 14th February 2020)	• ITT • Haematologic response-evaluable analysis set • Organ response-evaluable analysis set	**Primary endpoint:** • CHR **Secondary endpoints:** • MOD-PFS • MOD-EFS • OS • CHR at 6 and 12 months • Time to haematologic response (CHR or VGPR or better) • Duration of haematologic response (CHR or VGPR or better) • Time to initiation of subsequent non-cross resistant anti-plasma cell therapy • Organ response (cardiac, renal and liver) at six months • Time to cardiac, renal and liver response • Time to cardiac, renal and liver progression **Exploratory endpoints:** • EQ-5D-5L scores **Pre-specified subgroup analysis:** • CHR • MOD-PFS	Outcomes assessed at the pre-specified interim analysis (IA1) timepoint were selected for inclusion in the submission in alignment with the final scope issued by NICE. Outcomes presented were selected to demonstrate the benefits of DBCd in achievement of haematologic response (including the depth and duration of response), organ response rates, and the impact on patient QoL
12-month landmark analysis	20.3 months (clinical data cut-off: 13th November 2020)	• ITT • Haematologic response-evaluable analysis set • Organ response-evaluable analysis set	**Primary endpoint:** • CHR **Secondary endpoints:** • CHR at six months • Time to haematologic response (CHR, VGPR or better, and PR or better) • Organ response (cardiac, renal and liver) at 6, 12 and	Outcomes assessed as part of the 12-month landmark analysis were selected ahead of presentation at the 2021 American Society of Clinical Oncology (ASCO) conference, and demonstrate the

			18 months • Time to initiation of subsequent non-cross resistant anti-plasma cell therapy **Subgroup analysis:** • CHR	continued benefits of DBCd over a longer follow-up period

Abbreviations: CHR: complete haematologic response; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; EQ-5D-5L: EuroQol-5 Dimensions-5 Level; GHS: Global Health Status; ITT: intention-to-treat; MCS: Mental Component Summary; MOD-EFS: major organ deterioration-event free survival; MOD-PFS: major organ deterioration-progression free survival; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival; SF-36v2: Short Form 36 Health Survey Questionnaire; VGPR: very good partial response.

B.2.6.1 Haematologic response

As described in Section B.1.3.2, the primary therapeutic goal in the treatment of AL amyloidosis is to achieve a rapid, deep and durable haematologic response.[24, 25] This is a clinically meaningful outcome, as multiple studies have established the relationship between deeper haematologic response and improved prognosis for AL amyloidosis patients, with each successive category of response achieved associated with delayed disease progression, improved organ response rates and overall survival.[2, 27, 82] Haematologic response comprises a key goal in clinical guidelines for AL amyloidosis, which recommend that clinicians treat patients to target VGPR as a minimum, with CHR representing the optimal response in terms of patient prognosis and survival.[3-6]

Primary efficacy analysis

At a median follow-up duration of 11.4 months, as assessed by blinded IRC, the addition of daratumumab SC to BCd resulted in a statistically significant and clinically meaningful improvement in the overall CHR rate compared with BCd alone (53.3% vs 18.1%, respectively; odds ratio [OR]: 5.13; 95% CI: 3.22, 8.16; p<0.0001; Table 17). In the 12-month landmark analysis, with a median follow-up duration of 20.3 months, DBCd continued to give rise to a deeper haematologic response than BCd alone. A significantly greater proportion of patients achieved CHR in the DBCd group compared with BCd alone (59.0% vs 19.2%, respectively; OR: 5.90; 95% CI: 3.72, 9.37; p<0.0001; Table 17).

At a median follow-up duration of 11.4 months, the proportion of patients achieving VGPR or better was also statistically significant and clinically superior for DBCd compared with BCd alone (78.5% vs 49.2%, respectively; OR: 3.75; 95% CI: [redacted]; p<0.0001; Table 17). Similarly, in the 12-month landmark analysis, the proportion of patients achieving VGPR or better remained significantly greater in the DBCd group than in the BCd group (79.0% vs 50.3%; OR: 3.74; 95% CI: 2.39, 5.86; p<0.0001; Table 17).

Table 17: Summary of overall best confirmed haematologic response based on IRC assessment; ITT analysis set (14th February 2020 data cut-off and 13th November 2020 data cut-off)

	IA1				12-month landmark			
	Response rate % (95% CI[a])		Odds ratio (95% CI[b]) DBCd vs BCd	P-value[c]	Response rate % (95% CI[a])		Odds ratio (95% CI[b]) DBCd vs BCd	P-value[c]
	BCd (N=193)	DBCd (N=195)			BCd (N=193)	DBCd (N=195)		
Response								
CHR	18.1 (13.0, 24.3)	53.3 (46.1, 60.5)	5.13 (3.22, 8.16)	<0.0001	19.2 [redacted]	59.0 [redacted]	5.90 (3.72, 9.37)	<0.0001
VGPR	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
PR	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
NR	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
PD	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
NE	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
VGPR or better (CHR+VGPR)	49.2 [redacted]	78.5 [redacted]	3.75 [redacted]	<0.0001	50.3 [redacted]	79.0 [redacted]	3.74 (2.39, 5.86)	<0.0001
Overall response (CHR+VGPR+PR)	76.7 [redacted]	91.8 [redacted]	-	-	76.7 [redacted]	91.8 [redacted]	-	-

[a] 95% CIs are based on Clopper-Pearson exact test. [b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl ≥60 mL/min or CrCl <60 mL/min). An odds ratio > 1 indicates an advantage for DBCd. [c] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intention-to-treat; NE: not evaluable; NR: no response; PD: progressive disease; VGPR: very good partial response.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020);[95] Janssen ANDROMEDA 12-month landmark analysis (2021);[99] Kastritis *et al.,* (2021).[100]

Six- and 12-month CHR rates

A major secondary outcome was achievement of CHR at 6 and 12 months. At the pre-specified interim analysis (IA1), greater six- and 12-month CHR rates were observed in the DBCd arm compared with the BCd arm (six months: [redacted] vs [redacted], respectively [OR: [redacted]; 95% CI: [redacted], [redacted]]; 12 months: [redacted] vs [redacted], respectively [OR: [redacted]; 95% CI: [redacted], [redacted]]).

In the 12-month landmark analysis, the greater confirmed CHR rate at six months in the DBCd group compared with the BCd group was maintained. Results for the CHR rate at 12 months were not available from the 12-month landmark analysis.

Results for achievement of CHR at 6 and 12 months for the IA1 analysis and achievement of CHR at six months for the 12-month landmark analysis are reported in Table 18. Due to the median follow-up duration of 11.4 months at the IA1 analysis, a lower CHR rate at 12 months was anticipated, given the relatively high proportion of patients who had not yet reached 12 months of follow-up. The apparent reduction in CHR rate between the 6- and 12-month timepoint can therefore be explained by this short follow-up, rather than by loss of response.

Table 18: Summary of confirmed CHR at six- and 12-months based on IRC assessment, ITT analysis set (14th February 2020 data cut-off and 13th November 2020 data cut-off)

IA1						12-month landmark					
BCd (N=193)		DBCd (N=195)		DBCd vs BCd		BCd (N=193)		DBCd (N=195)		DBCd vs BCd	
n (%)	95% CI[a]	n (%)	95% CI[a]	Odds ratio (95% CI)[b]	P-value[c]	n (%)	95% CI[a]	n (%)	95% CI[a]	Odds ratio (95% CI)[b]	P-value[c]
6 months											
[redacted] (14.0)	[redacted]	[redacted] (49.7)	[redacted]	6.09 [redacted]	<0.0001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months											
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR

[a] 95% CIs are based on Clopper-Pearson exact test. [b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl ≥ 60 mL/min or CrCl <60 mL/min). An odds ratio > 1 indicates an advantage for DBCd. [c] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; CHR: complete haematologic response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; IRC: independent review committee; NR: not reported.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020);[95] Janssen ANDROMEDA 12-month landmark analysis (2021).[99]

Time to haematologic response

A major secondary endpoint was time to haematologic response. As discussed previously, early and profound reductions of amyloid light chains are associated with the greatest chance of organ improvement, delayed progression and prolonged overall survival.[72]

Among patients who achieved CHR at the pre-specified interim analysis (IA1), median time to CHR was 60 days in the DBCd arm and 85 days in the BCd arm. Among subjects who achieved VGPR or better, median time to VGPR was 17 days in the DBCd arm and 25 days in the BCd arm (Table 19).

In the 12-month landmark analysis, among patients who achieved CHR, median time to CHR was 2.04 months (approximately 62 days) in the DBCd group and 2.79 months (approximately 85 days) in the BCd group. Median time to VGPR or better was also shorter in the DBCd group (0.56 months; approximately 17 days) compared to the BCd group (0.82 months; approximately 25 days).

Results for time to haematologic response for the IA1 and 12-month landmark analyses are presented in Table 19.

Table 19: Summary of time to haematologic response based on IRC assessment; haematologic response-evaluable analysis set (14th February 2020 data cut-off and 13th November 2020 data cut-off)

	IA1 (days)		12-month landmark (months)	
	BCd (N=148)	DBCd (N=179)	BCd (N=148)	DBCd (N=179)
Time to CHR[a]				
n	35	104	37	115
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	85.00	60.00	2.79	2.04
Range	[redacted]	[redacted]	[redacted]	[redacted]
Time to VGPR or better[b]				
n	95	153	97	154
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	25.00	17.00	0.82	0.56
Range	[redacted]	[redacted]	[redacted]	[redacted]
Time to PR or better[c]				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]

VGPR or better includes CR and VGPR. PR or better includes CR, VGPR and PR. Hematologic response-evaluable set includes subjects who have a confirmed diagnosis of amyloidosis and measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post- baseline disease assessment. [a] Time from randomisation date up to the first response of complete hematologic response is summarised. [b] Time from randomisation date up to the first response of VGPR or better, whichever is the earliest, is summarised. [c] Time from randomisation date up to the first response of PR or better, whichever is the earliest, is summarised.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; IRC: independent review committee; SD: standard deviation; PR: partial response VGPR: very good partial response.

Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020);[95] Janssen ANDROMEDA 12-month landmark analysis (2021);[99] Kastritis *et al.,* (2021).[100]

Results from both the IA1 and 12-month landmark analysis demonstrate that DBCd is able to give rise to a more rapid haematologic response when compared with BCd, which in turn is expected to delay deterioration of organ condition.

Duration of haematologic response

Interim analysis (IA1): Data cut-off 14th February 2020

Another major secondary endpoint was the duration of haematologic response. A prolonged haematological response is critical for delaying disease progression and improving survival.

At the pre-specified interim analysis (IA1), with a median follow-up of 11.4 months, the median duration of CHR had not been reached in either treatment arm (range: [redacted] months for DBCd; [redacted] months for BCd). Of the [redacted] patients who achieved CHR in the DBCd arm, [redacted] patients died while in CHR and [redacted] patients relapsed following CHR. Of the [redacted] patients who achieved CHR in the BCd arm, [redacted] died while in CHR and [redacted] patients relapsed following CHR (Table 20).

Table 20: Summary of duration of CHR based on IRC assessment; responders in ITT analysis set (14th February 2020 data cut-off)

	BCd (N=148)	DBCd (N=179)
N	[redacted]	[redacted]
Number of events[a] (%)	[redacted]	[redacted]
Number of censored (%)	[redacted]	[redacted]
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75% quantile (95% CI)	[redacted]	[redacted]

[a] Events are defined as disease relapses, with deaths not counted as events.
Percentages are calculated with the number of subjects in each treatment group with available data as denominator.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; NE: not estimable.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off)[98]

Results for the duration of CHR are not available from the 12-month landmark analysis.

In summary, results for haematologic response from ANDROMEDA demonstrate that DBCd may give rise to a deeper and more rapid haematologic response compared to the existing standard of care for AL amyloidosis in the UK, BCd. This is a clinically meaningful outcome, as multiple studies have established the relationship between deeper haematologic response and improved prognosis for AL amyloidosis patients, with each successive category of response achieved associated with delayed disease progression, improved organ response rates and overall survival.[2, 27, 82]

B.2.6.2 Major organ deterioration progression-free survival (MOD-PFS)

As described in Section B.2.3.2, MOD-PFS is a composite endpoint of multiple clinically observable endpoints, defined as the time from patient randomisation to either clinical

manifestation of either cardiac or renal failure, development of haematologic progressive disease as per Comenzo *et al.,* (2012) consensus guidelines, or death (whichever comes first).[24]

Disease progression in AL amyloidosis is evaluated according to a range of different biomarkers in clinical practice (because of the heterogeneity in presentation of disease). Due to the complexity in defining PFS in AL amyloidosis, ANDROMEDA collected MOD-PFS, and use of this endpoint has been approved by the FDA and EMA as a clinically relevant measure of both disease and the benefits of anti-plasma cell therapy.[33, 34]

The treatment paradigm used in ANDROMEDA involved patients being switched to an alternative treatment following a suboptimal haematologic response or worsening organ function, which commonly occurs prior to disease progression in clinical practice. As a result, this may have interfered with evaluation of the MOD-PFS endpoint, for which haematologic progression is among the outcomes included in the composite endpoint. Therefore, the primary analysis for MOD-PFS in ANDROMEDA employed the inverse probability of censoring weighting (IPCW) method to adjust estimates of the treatment effect in the presence of subsequent non-cross resistant, anti-plasma cell therapy. Full statistical details of the IPCW analysis can be found in Appendix L.

To test the robustness of the primary analysis results, pre-specified sensitivity IPCW analyses which used a different variable selection modelling and weight calculation approach were also conducted. Pre-specified sensitivity analyses of MOD-PFS were also performed. This included naïve censoring of subsequent non-cross resistant, anti-plasma cell therapy. In addition, given that patients would be permitted to switch in clinical practice if they do not achieve an adequate response, a supplementary analysis of MOD-PFS based on IRC assessment without censoring for any subsequent non-cross resistant, anti-plasma cell therapy, was also conducted.

Interim analysis (IA1): Data cut-off 14th February 2020

At a median follow-up duration of 11.4 months, after adjusting for dependent censoring due to switching to subsequent non-cross resistant, anti-plasma cell therapy, a substantial improvement in MOD-PFS was observed for patients receiving DBCd compared with BCd alone. The hazard ratio for MOD-PFS for DBCd vs BCd based on the primary IPCW analysis was [redacted] (95% CI: [redacted], [redacted]); this indicates a reduced risk of experiencing a MOD-PFS event in the DBCd arm compared to the BCd arm. Median MOD-PFS was not reached in either treatment arm. While the nominal p-value for this interim analysis was [redacted], above the pre-specified significance threshold of [redacted], there is a clear, substantial difference in treatment effect between DBCd and BCd, as demonstrated by the clear separation of the two Kaplan-Meier curves after Month 6 (Figure 5).

Figure 5: Kaplan-Meier plot of MOD-PFS based on IRC assessment, IPCW analysis; ITT analysis set (14th February 2020 data cut-off)

Abbreviations: CI: confidence interval; CyBorD: cyclophosphamide, bortezomib, dexamethasone (otherwise referred to as BCd); Dara SC: daratumumab subcutaneous.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

The results from pre-specified sensitivity IPCW analyses, which used a different variable selection modelling and weight calculation approach, were consistent with the primary IPCW analysis. Further pre-specified sensitivity analyses of MOD-PFS such as naïve censoring of subsequent non-cross resistant, anti-plasma cell therapy were also performed, and a supplementary analysis of MOD-PFS based on IRC assessment without censoring for any subsequent non-cross resistant, anti-plasma cell therapy also demonstrated consistency with the results from the primary analysis (Table 21).

Table 21: Summary of primary, sensitivity and supplementary analysis of MOD-PFS based on IRC assessment; ITT analysis set (14th February 2020 data cut-off)

	DBCd versus BCd, HR (95% CI)	P-value
Primary analysis		
IRC assessment - IPCW (stepwise procedure used to select baseline covariates and time-dependent covariates for weight calculation)	[redacted]	[redacted]
Sensitivity analysis		
IRC assessment – naïve censoring of subsequent non-cross resistant, anti-plasma cell therapy therapy	[redacted]	[redacted]
Supplementary analysis		
IRC assessment – without censoring subsequent therapy[a]	[redacted]	[redacted]

[a] Refers to subsequent non-cross resistant, anti-plasma cell therapy.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; IRC: independent review committee; HR: hazard ratio; IPCW: inverse probability of censoring weight; MOD-EFS: major organ deterioration-event-free survival; MOD-PFS: major organ deterioration-progression-free survival.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Updated MOD-PFS results are not available from the 12-month landmark analysis.

Overall, the MOD-PFS results from the pre-specified interim analysis were robust and consistent, favouring the DBCd arm and demonstrating a substantial delay in haematologic progression, major organ deterioration, or death.

Increasing the length of time to major organ deterioration offers significant value for patients, given the very poor prognosis associated with progression of cardiac and renal disease to later stages.[20, 70] The development of end-stage organ failure is likely to have substantial negative impacts on patient quality of life, with an increasing burden of severe disease symptoms, increased frequency of hospital visits and the continuation of poorly tolerated chemotherapy treatments. Further, progression of AL amyloidosis to end-stage organ failure results in an increased burden to the NHS, such as the significant costs of dialysis to manage end-stage renal failure.[22, 23]

Major organ deterioration event-free survival (MOD-EFS)

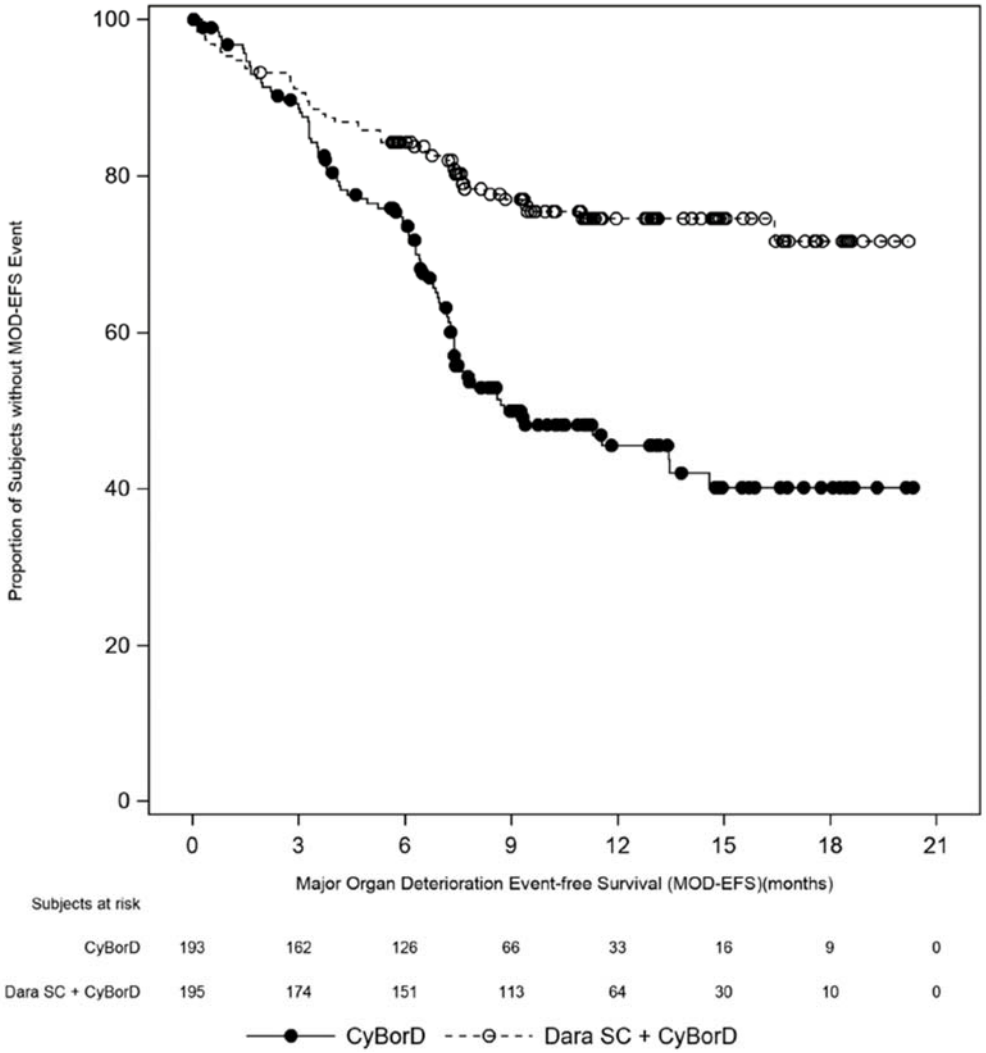
As discussed above, in ANDROMEDA, patients were able to switch to subsequent non-cross resistant, anti-plasma cell therapy before haematologic progression or major organ deterioration in cases where they experienced suboptimal haematologic response or worsening organ function. Initiation of subsequent therapy therefore represents a key measure of both the rate and depth of haematologic response, as patients with delayed or suboptimal response may need to switch to a subsequent therapy.

As a switch to subsequent therapy is not captured by MOD-PFS assessments, a supplementary analysis of MOD-PFS was explored which included subsequent non-cross resistant, anti-plasma cell therapy as an event. MOD-EFS is therefore a composite endpoint incorporating haematologic progression, major organ deterioration, initiation of any subsequent non-cross resistant anti-plasma cell therapy, or death, whichever event comes first.

Interim analysis (IA1): Data cut-off 14th February 2020

In the pre-specified interim analysis, the median MOD-EFS was [redacted] months in BCd treatment arm, and was not yet reached in the DBCd arm (HR: [redacted]; 95% CI: [redacted], [redacted]; nominal p-value: [redacted]; Figure 6). The hazard ratio indicates that there is a reduced risk of a MOD-EFS event in the DBCd group compared with the BCd group.

Figure 6: Weighted Kaplan-Meier plot of MOD-EFS based on IRC assessment; ITT analysis set (14th February 2020 data cut-off)



Abbreviations: CyBorD: cyclophosphamide, bortezomib, dexamethasone (otherwise referred to as BCd); Dara SC: daratumumab subcutaneous; IRC: independent review centre; MOD-EFS: major organ deterioration event-free survival.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020).[95]

Updated MOD-EFS results are not available from the 12-month landmark analysis.

B.2.6.3 Overall survival

Interim analysis (IA1): Data cut-off 14th February 2020

OS data were not mature at the time of the pre-specified interim analysis (IA1), with 56 deaths in total (27 in the DBCd arm and 29 in the BCd arm), including 1 randomised subject in the BCd arm who died without receiving study treatment (Table 22; Figure 7). The HR for survival was [redacted] (DBCd vs BCd; 95% CI: [redacted], [redacted]), and the nominal p-value was [redacted]. Median OS was not reached in either treatment arm, and the estimated 18-month OS was [redacted] in the DBCd arm and [redacted] in the BCd arm.

Table 22: Summary of OS; ITT analysis set (14th February 2020 data cut-off)

	BCd (N=193)	DBCd (N=195)
Number of events (%)	[redacted]	[redacted]
Number of censored (%)	[redacted]	[redacted]
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75% quantile (95% CI)	[redacted]	[redacted]
P-value[a]	-	[redacted]
Hazard ratio (95% CI)[b]	-	[redacted]
Six-month survival rate % (95% CI)	[redacted]	[redacted]
12-month survival rate % (95% CI)	[redacted]	[redacted]
18-month survival rate % (95% CI)	[redacted]	[redacted]

[a] P-value is based on a log-rank test stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥ 60 mL/min or CrCl <60 mL/min) as randomised. [b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min) as randomised. A hazard ratio <1 indicates an advantage for DBCd.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; OS: overall survival; NE: not evaluable.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Figure 7: Kaplan-Meier plot for OS; ITT analysis set (14th February 2020 data cut-off)

Abbreviations: CyBorD: cyclophosphamide, bortezomib, dexamethasone (otherwise referred to as BCd); Dara SC: daratumumab subcutaneous.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Updated OS results are not available from the 12-month landmark analysis.

OS data from ANDROMEDA remain immature at currently available data cut offs. However, given the established relationship between haematological response and overall survival in AL amyloidosis,[2, 27, 82] results presented in Section B.2.6.1 illustrating the rapid and deep haematological response achieved with DBCd compared to BCd are expected to result in long-term survival benefits for patients treated with DBCd.

B.2.6.4 Time to subsequent non-cross resistant anti-plasma cell therapy

In line with the treatment paradigm for patients with AL amyloidosis and with the ANDROMEDA protocol, patients with suboptimal haematologic response or worsening organ function were permitted to start subsequent non-cross resistant, anti-plasma cell therapy prior to developing haematologic progression after three cycles of treatment.

Non-cross resistant anti-plasma cell therapy was defined as ASCT with high dose melphalan, melphalan plus dexamethasone, or any new combination regimen that included at least one new component that was different to the assigned study drugs received (i.e. bortezomib plus lenalidomide for both treatment arms and daratumumab SC for the BCd arm).

A summary of the proportion of patients that received different subsequent therapies in ANDROMEDA is presented in Table 23 below. More patients in the BCd arm ([redacted] patients [redacted]) received subsequent therapy (both cross-resistant and non-cross resistant), compared with those in the DBCd arm ([redacted] patients [redacted]). Of those patients who received subsequent therapy, [redacted] ([redacted]) patients in the BCd arm and [redacted] ([redacted]) in the DBCd arm received therapy that met the criteria for non-cross resistant subsequent therapy, in line with the definition above. The most common non-cross resistant subsequent therapy in the DBCd arm was melphalan ([redacted] [redacted]), and the most common therapy in the BCd arm was daratumumab IV (48/188 [redacted]).

Table 23: Summary of subsequent non-cross resistant, anti-plasma cell therapy by therapeutic class, pharmacologic class, and preferred term; safety analysis set (14th February 2020 data cut-off)

	BCd (N=188) n (%)	DBCd (N=193) n (%)	Total (N=381) n (%)
Subjects with one or more subsequent non-cross resistant anti-plasma cell therapies	79 (42.0)	19 (9.8)	[redacted]
Subjects with subsequent autologous stem cell transplant	20 [redacted]	13 [redacted]	[redacted]
Therapeutic class Pharmacologic class Drug			
Antineoplastic agents	[redacted]	[redacted]	[redacted]
Other antineoplastic agents	[redacted]	[redacted]	[redacted]
Daratumumab	48 [redacted]	0	[redacted]
Ixazomib	[redacted]	[redacted]	[redacted]
Isatuximab	[redacted]	[redacted]	[redacted]
Venetoclax	[redacted]	[redacted]	[redacted]
Alkylating agents	[redacted]	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]	[redacted]
Immunosuppressants	[redacted]	[redacted]	[redacted]
Immunosuppressants	[redacted]	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]	[redacted]
Macrolides, lincosamides and streptogramins	[redacted]	[redacted]	[redacted]
Clarithromycin	[redacted]	[redacted]	[redacted]
Corticosteroids for systemic use	[redacted]	[redacted]	[redacted]
Corticosteroids for systemic use, plain	[redacted]	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020).[95]

A summary of the time to subsequent non-cross resistant, anti-plasma cell therapy for both the pre-specified interim analysis and 12-month landmark analysis is presented in Table 24.

In the pre-specified interim analysis, more patients in the BCd arm ([redacted]) received subsequent non-cross resistant anti-plasma cell therapy compared with patients in the DBCd arm ([redacted]), whilst in the 12-month landmark analysis, the proportion of patients receiving non-cross resistant anti-plasma cell therapy remained higher in the BCd arm ([redacted]) compared with the DBCd arm ([redacted]) (Table 24).

In the pre-specified interim analysis, the median time to initiation of subsequent non-cross resistant anti-plasma cell therapy was not reached for subjects in the DBCd arm, and was 10.38 months in the BCd arm (HR: [redacted]; 95% CI: [redacted]; [redacted]; Table 24). In the 12-month landmark analysis, the median time to subsequent non-cross resistant anti-plasma cell therapy was still yet to be reached, whilst it was [redacted] (95% CI: [redacted]) in the BCd arm (Table 24).

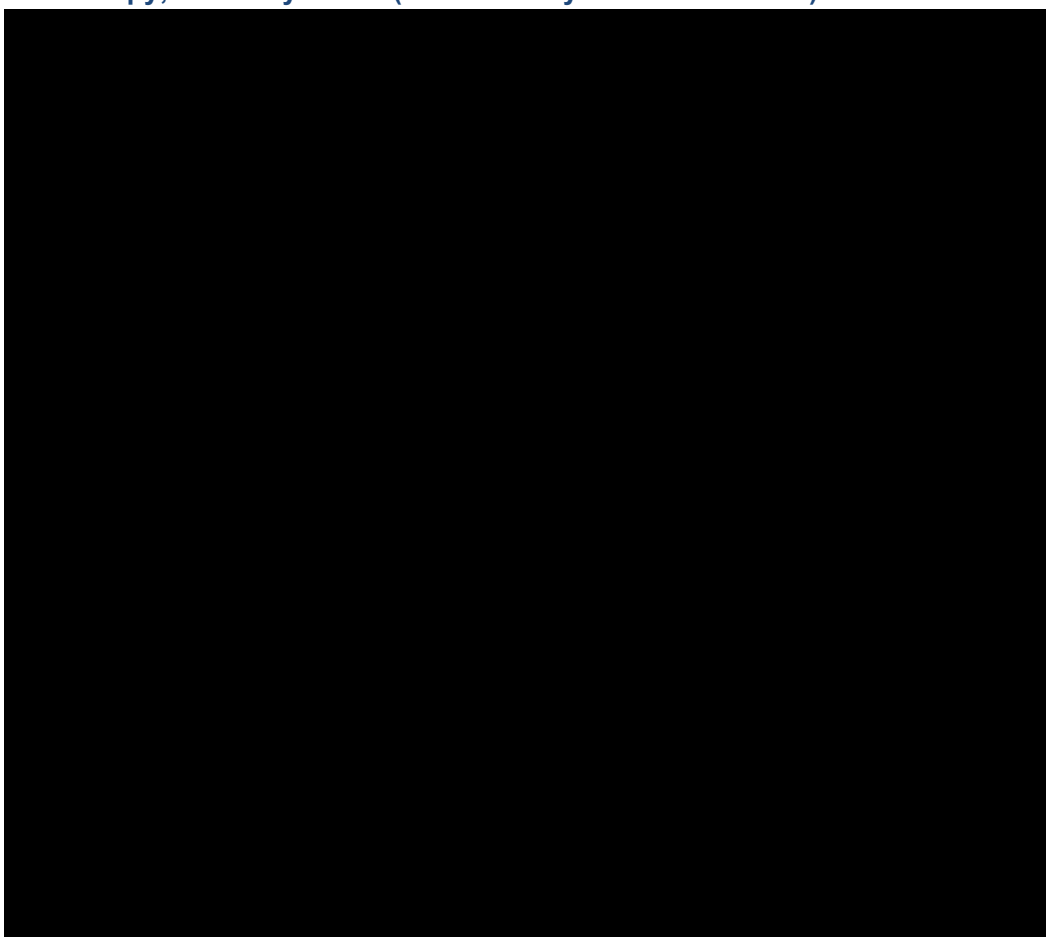
Kaplan-Meier curves for the time to first subsequent non-cross resistant anti-plasma cell therapy for both the pre-specified interim analysis (Figure 8) and 12-month landmark analysis (Figure 9) are also presented below. Separation of the Kaplan-Meier curves is observed after Month 3 in the case of both the IA1 and 12-month landmark analyses, with a clear treatment effect between DBCd and BCd observable at Month 6 (Figure 8 and Figure 9).

Table 24: Summary of time to first subsequent non-cross resistant anti-plasma cell therapy; ITT analysis set (14th February 2020 and 13th November 2020 data cut-off)

	IA1		12-month landmark	
	BCd (N=193)	DBCd (N=195)	BCd (N=193)	DBCd (N=195)
Time to first subsequent non-cross resistant anti-plasma cell therapy				
Number of events (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of censored (%)	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimate (months)				
25% quantile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75% quantile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P-value[a]	-	[redacted]	-	-
Hazard ratio (95% CI)[b]	-	[redacted]	-	-
Six-month subsequent non-cross resistant anti-plasma cell therapy free rate % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month subsequent non-cross resistant anti-plasma cell therapy free rate % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month subsequent non-cross resistant anti-plasma cell therapy free rate % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

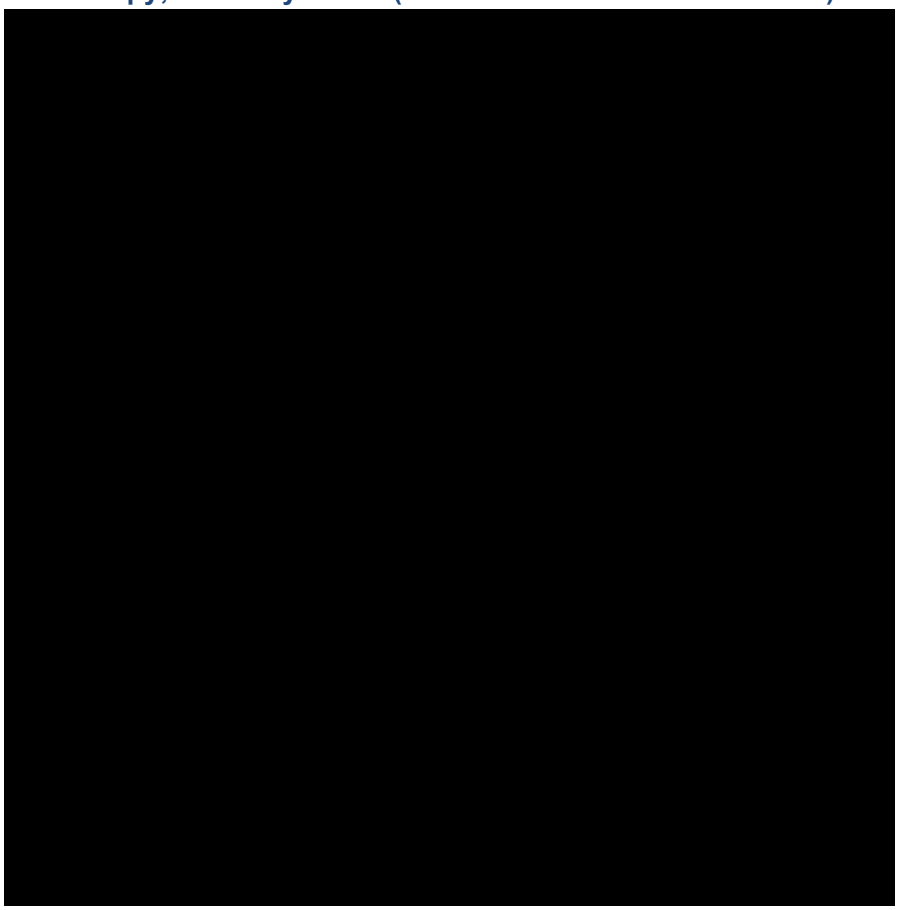
[a] p-value is based on a log-rank test stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min) as randomised. [b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min) as randomised. A hazard ratio <1 indicates an advantage for DBCd.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intention-to-treat; NE: not estimable.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Janssen ANDROMEDA 12-month landmark analysis (2021).[99]

Figure 8: Kaplan-Meier plot for time to first subsequent non-cross resistant anti-plasma cell therapy; ITT analysis set (14th February 2020 data cut-off)



Abbreviations: CyBorD: cyclophosphamide, bortezomib, dexamethasone (otherwise referred to as BCd); Dara SC: daratumumab subcutaneous; ITT: intention-to-treat.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Figure 9: Kaplan-Meier plot for time to first subsequent non-cross resistant anti-plasma cell therapy; ITT analysis set (13th November 2020 data cut-off)



Abbreviations: D-VCd: daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (otherwise referred to as DBCd); ITT: intention-to-treat; VCd: bortezomib, cyclophosphamide and dexamethasone (otherwise referred to as BCd).
Source: ANDROMEDA 12-month landmark analysis (November 2020).[99]

Overall, the time to initiation of subsequent non-cross resistant, anti-plasma cell therapy represents an additional measure of both the rate and depth of haematologic response, given that patients with suboptimal response or worsening of organ function may be switched onto subsequent therapies as early as after three cycles. As compared with BCd, treatment with DBCd increased the time to initiation of subsequent therapies.

B.2.6.5 Cardiac, renal and liver responses

In AL amyloidosis, the systemic nature of the disease results in amyloid deposition in organs throughout the body which can substantially impair organ function and may ultimately lead to organ failure.[45, 101, 102] Cardiac failure can lead to death, while renal failure can mean patients require renal replacement therapy and has significant impacts on patient quality of life, alongside greatly increasing costs to the NHS.[22, 23] Organ response therefore represents a key outcome in the ANDROMEDA trial to understand the relative effectiveness of DBCd vs BCd alone for delaying the amyloid deposition in organs which may ultimately lead to organ failure.

As was the case for evaluation of MOD-PFS, the option for patients to switch treatment to non-cross resistant, anti-plasma cell therapy in cases of suboptimal haematologic response or worsening organ function meant that analysis of organ response may have been affected by the treatment patients subsequently went on to receive. It was therefore necessary to conduct

analyses of organ responses both with and without censoring for subsequent non-cross resistant, anti-plasma cell therapy, to understand the effect of DBCd and BCd on organ response rates.

Organ response rate

Interim analysis (IA1): Data cut-off 14th February 2020

Of the [redacted] patients with baseline cardiac involvement, [redacted] were evaluable for cardiac response (DBCd: n=118; BCd: n=117). A substantially greater cardiac response was observed in the DBCd arm compared to the BCd arm; cardiac response rate at six months for patients in the DBCd arm was nearly twice that of patients in the BCd arm (41.5% vs 22.2%; OR: [redacted]; 95% CI: [redacted], [redacted]; p=0.0029; without censoring for subsequent non-cross resistant anti-plasma cell therapy). Results were consistent regardless of whether the analysis was conducted with or without censoring for subsequent non-cross resistant anti-plasma cell therapy.

There were [redacted] patients evaluable for renal response (DBCd: 113; BCd: 117). Similar to cardiac response, a substantially greater renal response was observed in the DBCd arm compared to the BCd arm. The renal response rate at six months was 53.8% in the DBCd arm compared with 27.4% in the BCd arm (OR: [redacted]; 95% CI: [redacted], [redacted]; p<0.0001; without censoring for subsequent non-cross resistant anti-plasma cell therapy). Again, the results were comparable regardless of whether the analysis was conducted with or without censoring for subsequent non-cross resistant anti-plasma cell therapy.

The liver response rate at six months was substantially higher in the DBCd arm compared with the BCd arm ([redacted] vs [redacted], respectively), both with and without censoring for subsequent non-cross resistant anti-plasma cell therapy. However, it is not possible to make definitive comparative conclusions with regards to liver response rates due to the limited number of evaluable patients ([redacted]; DBCd: n=[redacted]; BCd: n=[redacted]).

Cardiac and renal response rates at six months for the pre-specified interim analysis are presented in Table 25.

Table 25: Cardiac and renal six-month response rates (14th February 2020 data cut-off)

	DBCd vs BCd	
	Six-month response rate	Odds ratio (95% CI)
Cardiac response rate[a] (n=235 patients)		
IRC assessment with censoring for subsequent non-cross resistant anti-plasma cell therapy	[redacted]	[redacted]
IRC assessment without censoring for subsequent non-cross resistant anti-plasma cell therapy	41.5% vs 22.2%	[redacted]
Renal response rate[b] (n=230 patients)		
IRC assessment with censoring for subsequent non-cross resistant anti-plasma cell therapy	[redacted]	[redacted]
IRC assessment without censoring for subsequent non-cross resistant anti-plasma cell therapy	53.8% vs 27.4%	[redacted]

[a] Cardiac response was based on NT-proBNP response (>30% and >300 ng/L decrease in subjects with baseline NT-proBNP >650 ng/L) or NYHA class response (>2 class decrease in subjects with baseline NYHA class 3 or 4) per Comenzo (2012) consensus criteria.[24] [b] Renal response was defined as ≥30% decrease in proteinuria or proteinuria decreased to <0.5 g/24 hours in the absence of renal progression.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; IRC: independent review committee.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020).[95]

12-month landmark analysis: Data cut-off 13th November 2020

In the 12-month landmark analysis, updated results for organ response rates at six months are presented, along with organ response rates at the 12- and 18-month timepoints. In this later analysis timepoint, only results without censoring for subsequent non-cross resistant, anti-plasma cell therapy were available.

Among the [redacted] cardiac response-evaluable patients with cardiac involvement at baseline (DBCd: n=118; BCd: n=117), similarly to the interim analysis, cardiac response rates were substantially higher with DBCd arm compared to BCd. DBCd was associated with approximately [redacted] rates of cardiac response than BCd at 6, 12 and 18 months ([redacted] for all comparisons; Table 26). Compared to the interim analysis, organ response rates after longer follow-up were greater.

Similarly, among the renal response-evaluable patients with renal involvement at baseline (DBCd: n=117; BCd: n=113), DBCd was associated with approximately [redacted] rates of renal response at 6, 12 and 18 months ([redacted] for all comparisons; Table 27).

Table 26: Summary of cardiac response rate at 6, 12 and 18 months based on IRC assessment without censoring non-cross resistant anti-plasma cell therapy; cardiac response-evaluable analysis set (13th November 2020 data cut-off)

	BCd (N=117)		DBCd (N=118)		DBCd vs BCd	
	n (%)	95% CI[a]	n (%)	95% CI[a]	Odds ratio (95% CI)[b]	P-value[c]
Subjects with overall cardiac response during the study, n (%)	[redacted]	-	[redacted]	-	-	-
Cardiac response						
Cardiac response at 6 months	[redacted] (22.2)	[redacted]	[redacted] (41.5)	[redacted]	2.44 (1.35, 4.42)	0.0029
Cardiac response at 12 months	[redacted] (28.2)	[redacted]	[redacted] (56.8)	[redacted]	3.52 (2.00, 6.19)	<0.0001
Cardiac response at 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cardiac response is determined by evaluation of NYHA and NT-proBNP decrease from baseline. [a] 95% CIs are based on Clopper-Pearson exact test. [b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl ≥60 mL/min or CrCl <60 mL/min). An odds ratio > 1 indicates an advantage for DBCd. [c] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd; daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; IRC; independent review committee.
Source: Janssen ANDROMEDA 12-month landmark analysis (2021);[99] Kastritis *et al.,* (2021).[100]

Table 27: Summary of renal response rate at 6, 12 and 18 months based on IRC assessment without censoring non-cross resistant anti-plasma cell therapy; renal response-evaluable analysis set (13th November 2020 data cut-off)

	BCd (N=113)		DBCd (N=117)		DBCd vs BCd	
	n (%)	95% CI[a]	n (%)	95% CI[a]	Odds ratio (95% CI)[b]	P-value[c]
Subjects with overall renal response during the study, n (%)	[redacted]	-	[redacted]	-	-	-
Renal response						
Renal response at 6 months	[redacted] (27.4)	[redacted]	63 (53.8)	[redacted]	3.34 (1.88, 5.94)	<0.0001
Renal response at 12 months	[redacted] (27.4)	[redacted]	67 (57.3)	[redacted]	4.07 (2.26, 7.33)	<0.0001
Renal response at 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] 95% CIs are based on Clopper-Pearson exact test. [b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), Countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl ≥60 mL/min or CrCl <60 mL/min). An odds ratio > 1 indicates an advantage for DBCd. [c] P-value from the Cochran Mantel-Haenszel Chi-Squared test. Renal response indicates ≥30% decrease in proteinuria or drop in proteinuria below 0.5 g/24 hour in the absence or renal progression.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd; daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; IRC; independent review committee.
Source: Janssen ANDROMEDA 12-month landmark analysis (2021);[99] Kastritis *et al.,* (2021).[100]

Time to organ response

Interim analysis (IA1): Data cut-off 14th February 2020

The median times to cardiac, renal and liver responses as per IRC assessment are presented in Table 28. Cardiac and renal responses were reached more quickly in the DBCd group than in the BCd group, and this result was observed both with and without censoring for non-cross resistant anti-plasma cell therapy. The median time to cardiac response was [redacted] months in the DBCd group and [redacted] months in the BCd group, with censoring for subsequent therapy. The median time to renal response was also reached approximately one month earlier in the DBCd group, at [redacted] months compared with [redacted] months in the BCd group. The time to liver response was faster in the DBCd group without censoring for subsequent therapy, though the smaller sample size of evaluable patients precludes meaningful comparisons.

Table 28: Median time to cardiac, renal and liver response based on IRC assessment (14th February 2020 data cut-off)

	DBCd[a]	BCd[a]
Median time to cardiac response, months (range)		
Censoring for subsequent anti-plasma cell therapy	[redacted]	[redacted]
Without censoring for subsequent anti-plasma cell therapy	[redacted]	[redacted]
Median time to renal response, months (range)		
Censoring for subsequent anti-plasma cell therapy	[redacted]	[redacted]
Without censoring for subsequent anti-plasma cell therapy	[redacted]	[redacted]
Median time to liver response, months (range)		
Censoring for subsequent anti-plasma cell therapy	[redacted]	[redacted]
Without censoring for subsequent anti-plasma cell therapy	[redacted]	[redacted]

[a] The median time to organ response is reported for evaluable responding patients in the DBCd group (cardiac n=59; renal n=83; liver n=5) and in the BCd group (cardiac n=41; renal n=45; liver n=2).
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd; daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; IRC; independent review committee.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Cardiac, renal and liver progression rates at six months

Interim analysis (IA1): Data cut-off 14th February 2020

A summary of the proportion of evaluable patients with cardiac, renal and liver progression after six months is presented in Table 29.

Compared with the BCd group, numerically lower rates of cardiac, renal and liver progression were observed after six months among evaluable patients with organ involvement at baseline. At the six-month time point, 13.6% of evaluable patients in the DBCd group had experienced cardiac progression, compared with 19.7% in the BCd group.

Table 29: Cardiac, renal and liver progression rates at six months based on IRC assessment (14th February 2020 data cut-off)

	DBCd[a]	BCd[a]
Cardiac progression, n (%) 95% CI[b]	[redacted]	[redacted]
Renal progression, n (%) 95% CI[b]	[redacted]	[redacted]
Liver progression, n (%) 95% CI[b]	[redacted]	[redacted]

[a] The median time to organ response is reported for evaluable responding patients in the DBCd group (cardiac n = 59; renal n = 83; liver n = 5) and in the BCd group (cardiac n=41; renal n=45; liver n=2).
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd; daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Overall, DBCd resulted in a clinically meaningful, substantial improvement in cardiac and renal response rates when compared with BCd, with a nearly doubled rate of improvement at six months. These improvements, in combination with the increased rate of response, again provide a substantial benefit to patients in the context of the generally poor organ response rates achieved by those receiving treatment with existing bortezomib-based therapies.[27, 28, 30, 31] Greater organ response rates and delayed time to organ progression may also mean that patients avoid some of the substantial impacts that AL amyloidosis symptoms can have on their ability to carry out their daily lives, particularly those symptoms related to cardiac involvement.[76 77]

Similarly, these improvements to organ response rates would be expected to delay disease progression to late-stage organ failure, where the impacts for patients can be very severe. In the case of cardiac failure this can lead to death, while end-stage renal failure may require patients to begin dialysis or receive a kidney transplant.[18, 19, 57, 60]

Furthermore, the fact that the near two-fold improvements in organ response rate for DBCd compared with BCd observed in the pre-specified interim analysis were sustained in the 12-month landmark analysis suggests that the benefits to patients described may also be sustained in the short to medium term.

B.2.6.6 Health-related quality of life

In the ANDROMEDA trial, data from a series of health-related quality of life instruments were collected, namely the EORTC-QLQ-C30, SF-36v2 and EQ-5D-5L instruments. Detailed results from the EORTC-QLQ-C30 and SF-36v2 are presented in Appendix M. In summary, DBCd was associated with substantial benefits to patients based on all the above mentioned measures. During Cycles 1–6 of treatment, DBCd was associated with no decrement in overall HRQoL, fatigue, and mental health, as measured by EORTC-QLQ-C30 Global Health Status, EORTC-QLQ-C30 LS mean Fatigue and SF-36v2 Mental Component Summary (MCS) scores. In contrast, BCd was associated with worsening HRQoL during Cycles 1–6. In the context of evidence highlighting the overall HRQoL impairment experienced by AL amyloidosis patients

relative to the general population, as well as the high proportion of patients experiencing negative impacts on their mental health, the improvements to HRQoL associated with DBCd are expected to provide considerable value for many patients.[77, 79]

EQ-5D-5L

Interim analysis (IA1): Data cut-off 14th February 2020

EQ-5D-5L scores worsened in the BCd group during Cycles 1–6, whereas they remained relatively stable in the DBCd group (Figure 10). At Week 16 (Cycle 4), there was no change in LS mean EQ-5D-5L utility scores in the DBCd group ([redacted] points; 95% CI: [redacted], [redacted]), whereas scores decreased (i.e., worsened) significantly in the BCd group (-0.056 points; 95% CI: [redacted], [redacted]; unadjusted [redacted] vs DBCd). After Cycles 1–6, mean EQ-5D-5L utility scores continued to improve in the DBCd group throughout subsequent daratumumab SC monotherapy (Figure 10).

Figure 10: Mean EQ-5D-5L utility scores over time; ITT analysis set (14th February 2020 data cut-off)

Abbreviations: C: cycle; CyBorD: cyclophosphamide, bortezomib, dexamethasone (otherwise referred to as BCd); Dara SC: daratumumab subcutaneous; D: day; SE: standard error.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

There was also a significant difference in the mean change from baseline at Week 16 for the VAS score, again in favour of DBCd treatment (VAS LS mean change: DBCd: [redacted] [95% CI: [redacted], [redacted]]; BCd: [redacted] [95% CI: [redacted], [redacted]]; [redacted]).

These results support that DBCd is a well-tolerated regimen for AL amyloidosis. The addition of daratumumab SC to BCd was not found to have a detrimental effect on HRQoL, with this tolerability being maintained during Cycles 1–6 whilst patients received daratumumab in combination with BCd. Furthermore, improvements to HRQoL are observed once patients then begin the daratumumab SC monotherapy phase of treatment following Cycle 6.

The EQ-5D-5L utility scores results demonstrate that patients treated with DBCd experience improvements across important aspects of their quality of life. With the questionnaire measuring patients' level of mobility, general ability to look after themselves and conduct their daily activities, as well as their experience of pain, discomfort, anxiety and depression, the overall improvement in EQ-5D-5L utility scores suggests that treatment with DBCd is associated with improvements across at least some of these important aspects of quality of life. In the context of evidence highlighting the level of impact AL amyloidosis can have on patient quality of life,[77, 79] the improvements to HRQoL observed with DBCd treatment are expected to offer substantial benefit to patients.

As previously described, additional HRQoL outcomes were also assessed at the IA1 analysis, including the EORTC QLQ-C30 and SF-36v2 instruments, with the results presented in Appendix M.

B.2.7 *Subgroup analysis*

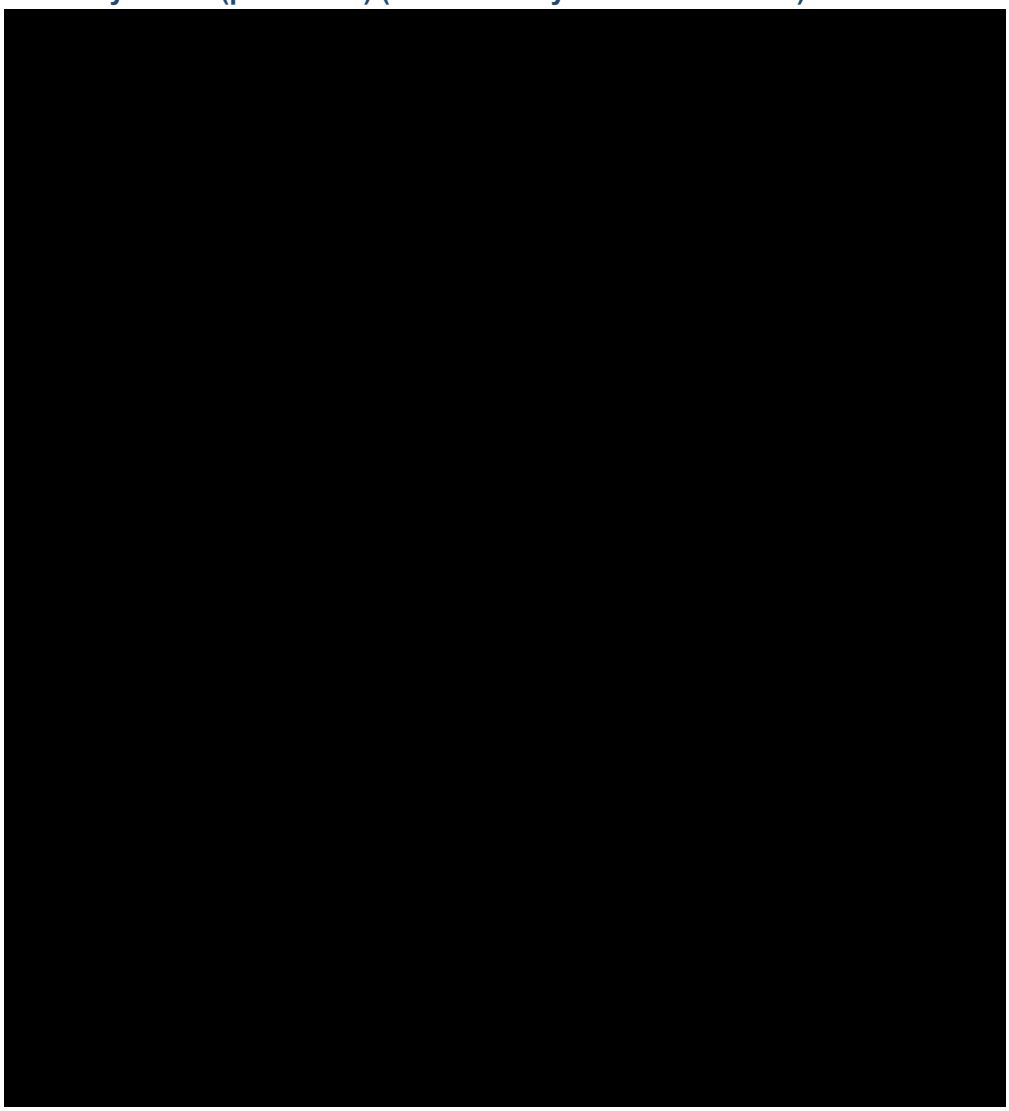
Results from subgroup analyses of the primary efficacy outcome, CHR, from both the pre-specified interim analysis and 12-month landmark analyses are presented below.

Interim analysis (IA1): Data cut-off 14th February 2020

Achievement of CHR was consistent across all pre-specified, clinically relevant subgroups, including baseline characteristics such as age, sex, race, renal function, hepatic function, and body weight, with greater rates of CHR achieved in the DBCd group compared to the BCd group for all analyses (Figure 11 and Figure 12). CHR rates achieved across body weight categories (≤65 kg, >65 to 85 kg, >85 kg) achieved in the DBCd arm were consistent with the overall population, whereas a lower CHR rate was observed in patients who were ≤65 kg in the BCd arm compared to the overall population. Of the 5 patients that were >120 kg, 2 of the 3 patients in the DBCd arms achieved CHR, while none of the 2 patients in the BCd arm achieved CHR.

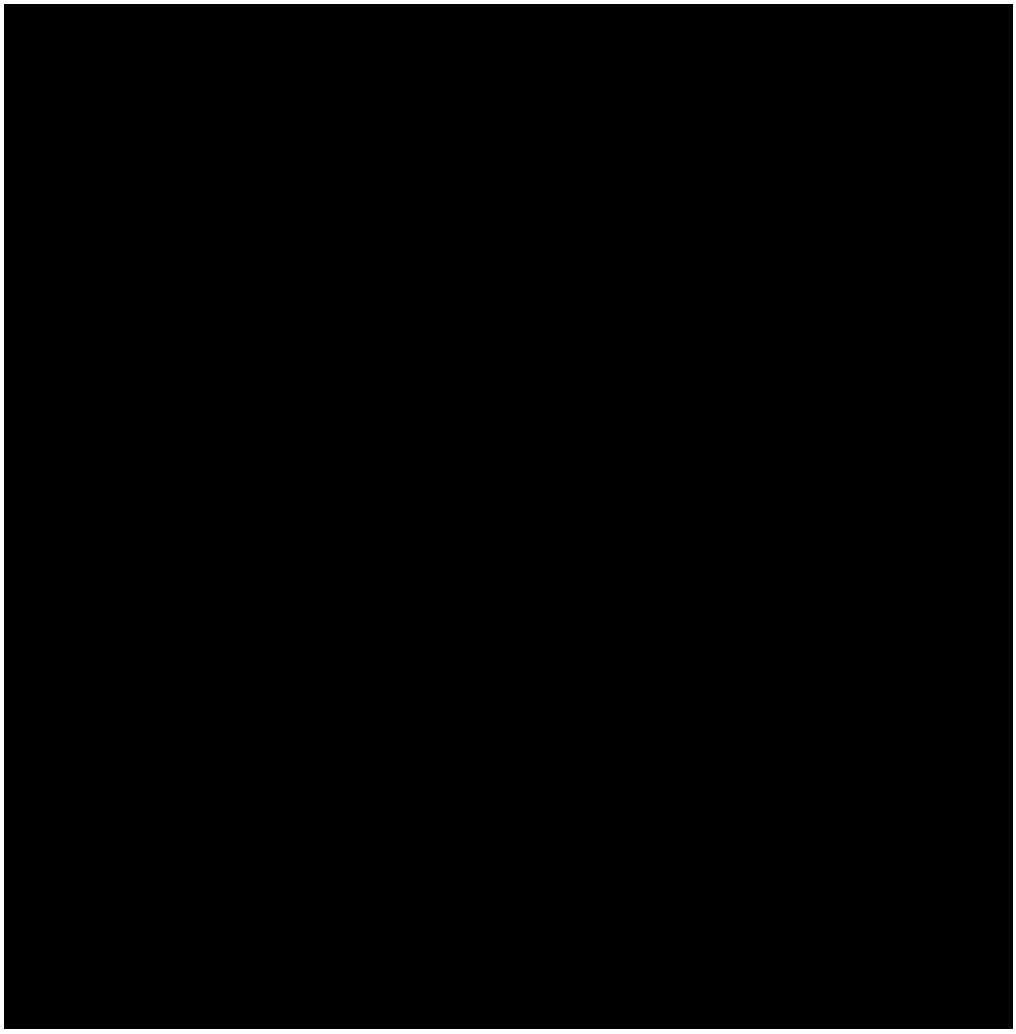
When stratified by the severity of cardiac involvement (a key prognostic factor) at baseline, patients in the DBCd group had similar rates of CHR across each cardiac stage (Stage I: 44.7%; Stage II: 53.9%; Stage IIIa/IIIb: 58.3%; Figure 11). In contrast, in the BCd group, the proportion of patients achieving CHR declined as cardiac involvement worsened, ranging from 27.9% at Stage I to just 10.0% at Stage IIIa/IIIb. The CHR rate was similarly high for patients both with and without translocation t(11;14) in the DBCd group (present: 54.9%; absent: [redacted]), whereas the CHR rate was lower among patients with this translocation in the BCd group (present: 12.7%; absent: [redacted]; Figure 12).[95, 98]

Figure 11: Forest plot of subgroup analysis of confirmed CHR based on IRC assessment; ITT analysis set (part 1 of 2) (14th February 2020 data cut-off)



Abbreviations: CyBorD: cyclophosphamide, bortezomib, dexamethasone (otherwise referred to as BCd); CI: confidence interval; Dara SC: daratumumab subcutaneous; EVT: event; IRC: independent review committee; ITT: intention-to-treat.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Figure 12: Forest plot of subgroup analysis of confirmed CHR based on IRC assessment; ITT analysis set (part 2 of 2) (14th February 2020 data cut-off)

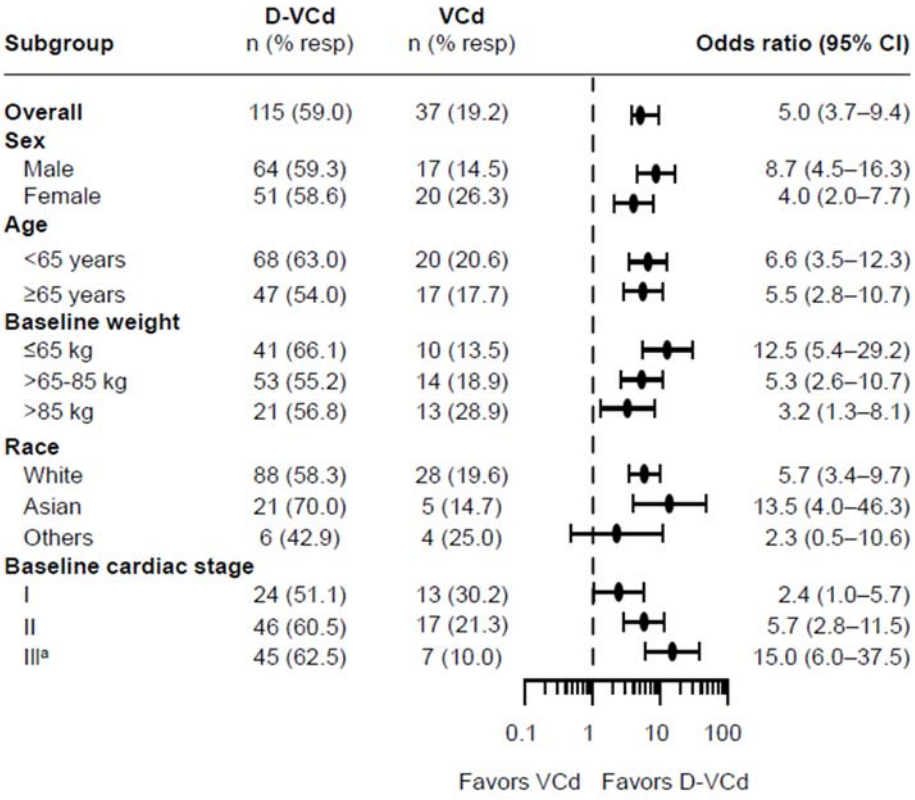


Abbreviations: CyBorD: cyclophosphamide, bortezomib, dexamethasone (otherwise referred to as BCd); CI: confidence interval; Dara SC; daratumumab subcutaneous; ECOG: eastern cooperative oncology score; EVT: event; FISH: fluorescence in situ hybridisation; IRC: independent review committee; ITT: intention-to-treat.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

12-month landmark analysis: Data cut-off 13th November 2021

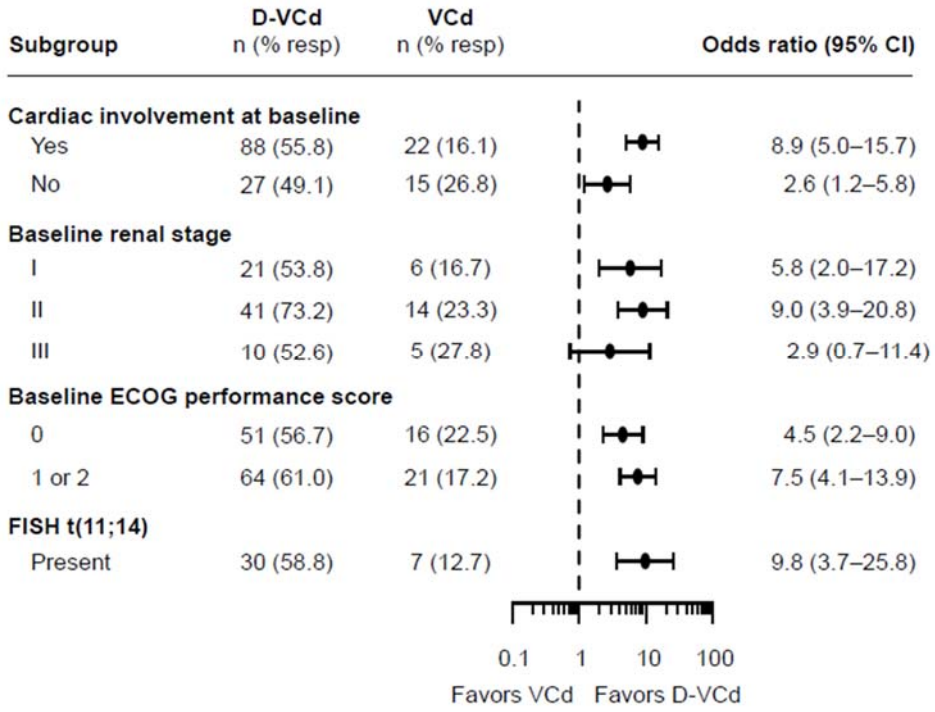
As per the interim analysis, DBCd continued to be associated with a greater achievement of CHR than BCd across all subgroup analyses in the 12-month landmark analysis (Figure 13Figure 14) including patients with Mayo Cardiac Stage III disease or t(11;14) translocation. When stratified by the severity of cardiac involvement at baseline, patients in the DBCd group had similar rates of CHR across each cardiac stage (Stage I: 51.1%; Stage II: 60.5%; Stage IIIa/IIIb: 62.5%; Figure 13). In contrast, similar to the results from the interim analysis, achievement of CHR declined in the BCd group with cardiac involvement worsening, ranging from 30.2% at Stage I to just 10.0% at Stage IIIa/IIIb. Finally, patients in the DBCd group continued to show similarly high CHR rates regardless of t(11;14) translocation (present: 58.8%; absent: [redacted]), whereas patients in the BCd group with this translocation had lower CHR rates (present: 12.7%; absent: [redacted]).

Figure 13: Forest plot of subgroup analysis of confirmed CHR based on IRC assessment; ITT analysis set (part 1 of 2) (13th November 2020 data cut-off)



Cardiac stage IIIa/IIIb includes both IIIa subjects and subjects that are IIIa at randomisation and progressed to IIIb at Cycle 1 Day 1.
Abbreviations: CHR: complete haematologic response; CI: confidence interval; D-VCd: daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (otherwise referred to as DBCd); IRC: independent review committee; VCd: bortezomib, cyclophosphamide and dexamethasone (otherwise referred to as BCd).
Source: Kastritis *et al.,* (2021).[100]

Figure 14: Forest plot of subgroup analysis of confirmed CHR based on IRC assessment; ITT analysis set (part 2 of 2) (13th November 2020 data cut-off)



Baseline renal stage is defined for subjects with baseline renal involvement.
Abbreviations: CHR: complete haematologic response; CI: confidence interval; D-VCd: daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (otherwise referred to as DBCd); ECOG: ECOG: eastern cooperative oncology score; FISH: fluorescence in situ hybridisation; IRC: independent review committee; VCd: bortezomib, cyclophosphamide and dexamethasone (otherwise referred to as BCd).
Source: Kastritis *et al.,* (2021).[100]

B.2.8 *Meta-analysis*

A clinical SLR conducted (Section B.2.1) identified ANDROMEDA as the only trial analysing the efficacy of DBCd in newly diagnosed AL amyloidosis. It was therefore not necessary to conduct a meta-analysis of multiple trials for DBCd in AL amyloidosis.

B.2.9 *Indirect and mixed treatment comparisons*

UK clinical experts confirmed that most patients (90-95%) with AL amyloidosis are treated with BCd on the NHS.[88] Further evidence that BCd represents the mainstay of treatment for AL amyloidosis in the UK comes from a retrospective observational analysis conducted by the EMN, where 75% of AL amyloidosis patients in ten countries in Europe were found to receive bortezomib-based regimens as first-line therapy. In line with this evidence, BCd thus represents the sole relevant comparator for this submission.[17]

Given that direct evidence for DBCd compared to BCd is available from the high-quality, RCT ANDROMEDA, it was not necessary to conduct an indirect comparison comparing the efficacy and safety of DBCd with that of other treatments.

B.2.10 *Adverse reactions*

Safety results summary

- Nearly all patients in both the DBCd and BCd treatment groups reported at least one TEAE (DBCd: 97.9%; BCd: 98.4%)
    - The most frequently reported TEAEs (≥25%) included diarrhoea, peripheral oedema, constipation, peripheral sensory neuropathy, nausea, fatigue, upper respiratory tract infection, and insomnia
- A similar proportion of patients in the DBCd and BCd treatment groups experienced Grade 3 or 4 TEAEs (DBCd: 59%; BCd: 57%)
    - The most commonly reported (≥5% in either group) included lymphopenia, pneumonia, diarrhoea, neutropenia, syncope, cardiac failure, anaemia, peripheral oedema and hypokalaemia
- The proportion of patients reporting serious TEAEs in each treatment group was broadly similar, with a slightly higher proportion reported in the DBCd arm (DBCd: 43.0%; BCd: 36.2%)
    - The most commonly reported serious TEAEs included pneumonia and cardiac failure/cardiac congestive failure combined
- A similarly low proportion of patients in both treatment groups reported AEs that led to discontinuation of study treatment (DBCd: 4.1%; BCd: 4.3%), and the incidence of Grade 3 or 4 AEs that led to discontinuation of treatment was also similarly low across both groups (DBCd: 3.1%; BCd: 2.7%)
- The incidence of all grade infusion-related reactions (IRRs) in the DBCd treatment group was 7.4%, which is consistent with that observed in other daratumumab SC studies; all grade injection site reactions were reported in 10.9% of patients treated with daratumumab
- At the time of the pre-specified interim analysis, 27 patients (14.0%) had died in the DBCd treatment arm and [redacted] patients ([redacted]) had died in the BCd treatment arm
- Overall, DBCd was found to be well-tolerated, with management TEAEs which did not lead to an increase in patient discontinuation and a safety profile consistent with the established safety profiles of daratumumab SC and BCd. Importantly, no new safety concerns were identified.

B.2.10.1 Treatment duration and dosage

Duration of exposure

A summary of exposure to study treatment in both treatment arms is presented in Table 30. A total of [redacted] patients received at least 1 administration of study treatment. The median number of cycles was 11 months in the DBCd arm and six months in the BCd arm (patients were permitted no more than 6 cycles in the BCd arm). A similar percentage of patients in both treatment arms received study treatment during the first 2 cycles, however from Cycle 3 onwards, more patients in the BCd arm discontinued study treatment compared with subjects in the DBCd arm. In the DBCd arm, [redacted] of patients completed 6 cycles of treatment compared with [redacted] of patients in the BCd arm.

With daratumumab SC treatment continuing beyond the initial 6 cycles of BCd, the treatment duration was expected to be longer in the DBCd arm. The median duration of study treatment was 9.6 months for the DBCd arm and 5.3 months for the BCd arm. Among patients in the DBCd arm, [redacted] received more than 6 cycles of therapy.

Treatment modifications

As specified in the trial protocol, dose reductions or escalations were not permitted for daratumumab, with daratumumab-related toxicities being managed by dose delays or dose skipped.

In compliance with the protocol, there were no dose reductions for daratumumab SC, though there were dose delays in [redacted] of patients, as well as doses skipped in [redacted] of patients. The proportion of patients with dose delays of cyclophosphamide, bortezomib, and dexamethasone was low in both treatment arms (cyclophosphamide: [redacted] vs [redacted]; bortezomib: [redacted] vs [redacted]; dexamethasone: [redacted] vs [redacted], respectively).

More subjects in the DBCd arm had skipped doses of cyclophosphamide, bortezomib, and dexamethasone compared with the BCd arm (cyclophosphamide: [redacted] vs [redacted]; bortezomib: [redacted] vs [redacted]; dexamethasone: [redacted] vs [redacted]). The proportion of subjects with dose reductions of cyclophosphamide, bortezomib, and dexamethasone was generally similar between arms (cyclophosphamide: [redacted] vs [redacted]; bortezomib: [redacted] and [redacted]; dexamethasone: [redacted] vs [redacted], respectively).

Table 30: Summary of exposure to study treatment, safety analysis set (14th February 2020 data cut-off)

	BCd (N=188)	DBCd (N=193)
Duration of study treatment, months		
N	188	193
Mean (SD)	[redacted]	[redacted]
Median	5.3	9.6
Range	(0.03–7.33)	(0.03–21.16)
Number of subjects treated within cycle, n (%)		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
>6	[redacted]	[redacted]
Maximum number of treatment cycles received		
N	188	193
Mean (SD)	[redacted]	[redacted]
Median	6.0	11.0
Range	(1–6)	(1–23)
Category, n (%)		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
>6	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; SD: standard deviation.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020).[95]

B.2.10.2 Adverse events

Safety results from ANDROMEDA presented in this submission are primarily from the pre-specified interim analysis (data cut-off 14th February 2020), on the basis that adverse events related to study treatment typically occur close to the beginning of treatment. As such, a longer duration of follow-up is not expected to present any further safety signals.

A number of safety outcomes were also assessed at the 12-month landmark analysis (data cut-off 13th November 2020), ahead of presentation of updated safety results from ANDROMEDA at a conference. For example, results for the most commonly reported (≥5%) Grade 3 or 4 TEAEs from this 12-month landmark analysis are presented in the submission, highlighting the change in incidence of reported adverse events once patients complete Cycle 6 and are receiving daratumumab SC monotherapy.

For both the pre-specified interim and 12-month landmark analyses, results are presented for the safety population.

Interim analysis (IA1): Data cut-off 14th February 2020

Nearly all patients in both treatment arms experienced at least one treatment-emergent adverse event (TEAE) (97.9% in the DBCd arm vs 98.4% in the BCd arm; Table 31). TEAEs occurring with an incidence of greater than 25% were generally balanced between treatment arms, with the exception of peripheral sensory neuropathy and upper respiratory tract infection which occurred at a higher incidence in the DBCd arm. TEAEs leading to discontinuation were also [redacted] between the treatment arms. Serious TEAEs and Grade 5 TEAEs were [redacted] in the DBCd arm, reflecting the longer treatment exposure in the DBCd arm and longer TEAE reporting period for patients treated with DBCd.

Table 31: Overall summary of treatment-emergent adverse events; safety analysis set (14th February 2020 data cut-off)

	BCd (N=188), n (%)	DBCd (N=193), n (%)
Any TEAE	[redacted] (98.4)	[redacted] (97.9)
At least one TEAE related to the treatment regimen[a]	[redacted]	[redacted]
At least one related to daratumumab	[redacted]	[redacted]
At least one related to cyclophosphamide	[redacted]	[redacted]
At least one related to bortezomib	[redacted]	[redacted]
At least one related to dexamethasone	[redacted]	[redacted]
Maximum toxicity grade		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Any serious TEAE	[redacted] (36.2)	[redacted] (43.0)
At least one related to the treatment regimen[a]	[redacted]	[redacted]
At least one related to daratumumab	[redacted]	[redacted]
At least one related to cyclophosphamide	[redacted]	[redacted]
At least one related to bortezomib	[redacted]	[redacted]
At least one related to dexamethasone	[redacted]	[redacted]
TEAE leading to discontinuation of daratumumab	[redacted]	[redacted]
Related to daratumumab	[redacted]	[redacted]
TEAE leading to discontinuation of cyclophosphamide	[redacted]	[redacted]
Related to cyclophosphamide	[redacted]	[redacted]
TEAE leading to discontinuation of bortezomib	[redacted]	[redacted]
Related to bortezomib	[redacted]	[redacted]
TEAE leading to discontinuation of dexamethasone	[redacted]	[redacted]
Related to dexamethasone	[redacted]	[redacted]
TEAE leading to discontinuation of study treatment[b]	8 (4.3)	8 (4.1)

Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03. [a] TEAEs related to at least 1 of the 4 components of study treatment: cyclophosphamide, bortezomib, dexamethasone and daratumumab. [b] TEAEs leading to discontinuation of all study treatment due to an adverse event on the end of treatment CRF page. [c] Site reporting error: site reported at least 1 AE as related to daratumumab in error, for 1 subject randomised to BCd arm.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CRF: case report form; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; SD: standard deviation; TEAE: treatment-emergent adverse event.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020).[95]

Table 32 summarises the most commonly reported (>10%) TEAEs by preferred term in the DBCd and BCd treatment arms. TEAEs in which differences in incidence of more than 5% between treatment arms were observed included diarrhoea, constipation, peripheral sensory neuropathy, upper respiratory tract infection, dyspnoea, thrombocytopenia, cough, asthenia, back pain and arthralgia. While these were all reported with greater incidence in the DBCd arm than in the BCd arm, it should be considered that the median treatment duration for DBCd was substantially longer (9.6 months) than the median treatment duration for BCd (5.3 months).

Table 32: Most commonly reported (>10% in either arm) treatment-emergent adverse events by preferred term; safety analysis set (14th February 2020 data cut-off)

	BCd (N=188), n (%)	DBCd (N=193), n (%)
Subjects with 1 or more TEAEs	[redacted] (98.4)	[redacted] (97.9)
Preferred term		
Diarrhoea	[redacted] (30.3)	[redacted] (35.8)
Oedema peripheral	[redacted] (36.2)	[redacted] (35.8)
Constipation	[redacted] (28.7)	[redacted] (34.2)
Peripheral sensory neuropathy	[redacted] (19.7)	[redacted] (31.1)
Fatigue	[redacted] (28.2)	[redacted] (26.9)
Nausea	[redacted] (27.7)	[redacted] (26.9)
Upper respiratory tract infection	[redacted] (11.2)	[redacted] (25.9)
Anaemia	[redacted] (23.4)	[redacted] (24.4)
Insomnia	[redacted] (25.0)	[redacted] (23.8)
Dyspnoea	[redacted]	[redacted]
Lymphopenia	[redacted] (14.9)	[redacted] (18.7)
Thrombocytopenia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Neutropenia	[redacted] (6.4)	[redacted] (10.9)
Pneumonia	[redacted] (6.4)	[redacted] (10.9)
Arthralgia	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]

Adverse events are reported using MedRA Version 22.1.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; TEAE: treatment-related adverse event.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020).[95]

Table 33 presents a summary of the most common (≥5% in either treatment arm) Grade 3 or 4 TEAEs experienced by patients in the DBCd and BCd treatment arms. Grade 3 or 4 TEAEs were

reported in 58.5% of patients in the DBCd arm and 57.4% of patients in the BCd arm and were well-balanced between arms.

Table 33: Most commonly reported (>5%) toxicity Grade 3 or 4 treatment-emergent adverse events by system organ class and preferred term; safety analysis set (14th February 2020 data cut-off)

	BCd (N=188), n (%)	DBCd (N=193), n (%)
Subjects with 1 or more toxicity Grade 3 or 4 TEAEs	[redacted] (57.4)	[redacted] (58.5)
Preferred term		
Lymphopenia	[redacted] (10.1)	[redacted] (13.0)
Pneumonia	[redacted] (4.3)	[redacted] (7.8)
Diarrhoea	[redacted] (3.7)	[redacted] (5.7)
Cardiac failure	[redacted]	[redacted]
Neutropenia	[redacted] (2.7)	[redacted] (5.2)
Syncope	[redacted] (6.4)	[redacted] (5.2)
Oedema peripheral	[redacted] (5.9)	[redacted] (3.1)
Hypokalaemia	[redacted]	[redacted]

Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are reported using MedRA Version 22.1.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; TEAE: treatment-related adverse event.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020)[95]

A summary of the most common treatment-emergent serious adverse events is presented in Table 34. In the DBCd treatment arm, 43% of patients reported ≥1 treatment-emergent serious adverse event (SAE) compared with 36.2% of patients in the BCd arm. The most commonly (≥5% in either treatment arm) reported treatment-emergent SAEs included pneumonia (DBCd 7.3%; BCd: 4.8%) and cardiac failure/cardiac failure congestive combined (DBCd: 6.7% [13/193]; BCd: 5.3% [10/188]). A difference in the incidence of >2% between treatment arms was observed for the following treatment-emergent SAEs: pneumonia (DBCd: 7.3%; BCd: 4.8%) and sepsis (3.1% and 0%, respectively) and cardiac arrest (3.6% and 1.6%, respectively; Table 33). Fluid overload was reported with ≥2% higher incidence in the BCd arm (DBCd: 0.5%; BCd: 2.7%).

Table 34: Most common (at least 2% in either arm) treatment-emergent serious adverse events by system organ class and preferred term; safety analysis set (14th February 2020 data cut-off)

	BCd (N=188), n (%)	DBCd (N=193), n (%)
Subjects with 1 or more TEAEs	68 (36.2)	83 (43.0)
System organ class **Preferred term**		
Infections and infestations	[redacted]	[redacted]
Pneumonia	9 (4.8)	14 (7.3)
Sepsis	0	6 (3.1)
Cardiac disorders	[redacted]	[redacted]
Cardiac failure	8 (4.3)	12 (6.2)
Cardiac arrest	3 (1.6)	7 (3.6)

Atrial fibrillation	2 (1.1)	4 (2.1)
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Dyspnoea	3 (1.6)	4 (2.1)
Pleural effusion	1 (0.5)	4 (2.1)
General disorders and administration site conditions	[redacted]	[redacted]
Sudden death	3 (1.6)	6 (3.1)
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	4 (2.1)	3 (1.6)
Metabolism and nutrition disorders	[redacted]	[redacted]
Fluid overload	5 (2.7)	1 (0.5)
Nervous system disorders	[redacted]	[redacted]
Syncope	6 (3.2)	3 (1.6)

Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedRA Version 22.1.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; TEAE: treatment-related adverse event.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020);[95] ANDROMEDA Study Results (clinicaltrials.gov).[103]

With use of the SC formulation of daratumumab in ANDROMEDA, it was necessary to explore the extent of IRRs relating to DBCd treatment. A summary of the proportion of patients in the DBCd treatment group that experienced treatment-emergent infusion-related reactions is presented in Table 35.

Of 193 patients who received DBCd, 7.3% experienced an IRR. IRRs were Grade 1 or 2 (manageable) and did not lead to treatment discontinuation. The incidence, preferred terms, severity and onset of IRRs were consistent with those previously reported for daratumumab SC.

Table 35: Number of patients with treatment-emergent infusion-related reactions by system organ class, preferred term and maximum toxicity grade; safety analysis set (14th February 2020 data cut-off)

	DBCd (N=193)			
	All Grades, n (%)	**Grade 3, n (%)**	**Grade 4, n (%)**	**Grade 5, n (%)**
Subjects with infusion-related reactions associated with daratumumab	14 (7.3)	0	0	0
Subjects with infusion-related reactions associated with daratumumab >1 infusion	[redacted]	0	0	0
System organ class **Preferred term**				
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Chills	3 (1.6)	0	0	0
Pyrexia	3 (1.6)	0	0	0
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Swelling face	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]

Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Throat tightness	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]	[redacted]
Hyperhidrosis	[redacted]	[redacted]	[redacted]	[redacted]
Rash pruritic	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	2 (1.0)	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Blepharospasm	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events are reported using MedRA Version 22.1. Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.0.
Abbreviations: DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Kastritis *et al.,* (2020).[95]

Deaths

27 patients (14.0%) died in the DBCd group, whilst [redacted] patients ([redacted]) died in the BCd group. In addition, one patient randomised to BCd died prior to receiving any treatment. Overall, deaths were primarily due to AL amyloidosis-related cardiomyopathy, reported either as TEAEs or disease progression, in both treatment arms. Cardiac disorders were the primary cause of death in both treatment groups, most commonly from cardiac arrest or failure (DBCd: [redacted] and [redacted], respectively; BCd: [redacted] and [redacted]). Compared with the BCd group, more patients in the DBCd group died from TEAEs ([redacted] and [redacted], respectively), with fewer patients dying from disease progression ([redacted] and [redacted]). Nearly all patients who died from TEAEs had cardiac involvement at baseline (DBCd: [redacted] patients; BCd: [redacted] patients); relatively few deaths from cardiac events or other causes were considered related to study treatment (DBCd: overall: [redacted]; cardiac: [redacted]; BCd:

overall: [redacted]; cardiac: [redacted]). No patients with Mayo Cardiac Stage I disease at baseline died due to a TEAE during follow-up.

12-month landmark analysis: Data cut-off 13th November 2020

In the 12-month landmark analysis (median follow-up 20.3 months), both DBCd and BCd remained well-tolerated, with no new safety concerns identified. As with the interim analysis, safety results should continue to be interpreted in the context of different treatment durations in the DBCd and BCd patient groups. The DBCd group continued to receive daratumumab SC monotherapy from Cycle 7 onwards and the median treatment duration was 18.5 months in this group, 3.5 times longer than the 5.3 months in the BCd group.

A summary of commonly reported (in ≥5% of patients) Grade 3 or 4 TEAEs is presented in Table 36. Grade 3 or 4 TEAEs were reported by [redacted] of patients in the DBCd group (56.0% for Cycles 1–6) and 57.4% of patients in the BCd group. From Cycle 7 onwards, when patients in the DBCd treatment arm were receiving daratumumab SC monotherapy, no Grade 3 or 4 TEAEs were reported in ≥5% of patients.

Table 36: Most commonly reported (≥5% in either arm) toxicity Grade 3 or 4 treatment-emergent adverse events by system organ class and preferred term; safety analysis set (13th November 2020 data cut-off)

	BCd, n (%)		DBCd, n (%)		
	Total (N=[redacted])	Cycles 1–6 (N=188)	Total (N=[redacted])	Cycles 1–6 (N=193)	Cycles 7+ (N=149)
Patients with 1 or more Grade 3 or 4 TEAEs	[redacted]	[redacted] (57.4)	[redacted]	[redacted] (56.0)	[redacted] (25.5)
System organ class/preferred term					
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted] (4.3)	16 (8.3)	12 (6.2)	5 (3.4)
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted] (10.1)	[redacted]	[redacted] (13.0)	[redacted] (3.4)
Neutropenia	[redacted]	[redacted] (2.7)	[redacted]	[redacted] (4.7)	[redacted] (1.3)
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted] (5.9)	[redacted]	[redacted] (3.1)	0
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted] (3.7)	[redacted]	[redacted] (5.7)	0
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted] (5.3)	[redacted]	[redacted] (1.6)	[redacted] (0.7)

Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted] (6.4)	[redacted]	[redacted] (5.2)	[redacted] (1.3)
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted] (2.7)	[redacted]	[redacted] (5.2)	[redacted] (2.0)

Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedRA Version 22.1. Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; TEAE: treatment-emergent adverse event.
Source: Janssen ANDROMEDA 12-month landmark analysis (2021);[99] Kastritis *et al.,* (2021).[100]

In summary, no new safety concerns were identified with the addition of daratumumab SC to BCd in patients with newly diagnosed AL amyloidosis, when compared with BCd alone. Indeed, for patients in the DBCd treatment arm, a marked decrease in the incidence of AEs was observed from Cycles 7 onwards, representing the time during which patients received daratumumab SC monotherapy. The favourable toxicity profile of DBCd makes daratumumab an attractive treatment option for all newly diagnosed AL amyloidosis patients, especially when considered in the context that daratumumab represents an add-on regimen.[89] Its safety profile was generally consistent with the established safety profiles of daratumumab SC, the BCd regimen and the underlying condition of AL amyloidosis. Further, the small administration volume for daratumumab SC offers benefit to AL amyloidosis patients with cardiac involvement, for whom volume overload is a concern. TEAEs were generally manageable and did not lead to any increase in treatment discontinuation compared with background therapy.

B.2.11 *Ongoing studies*

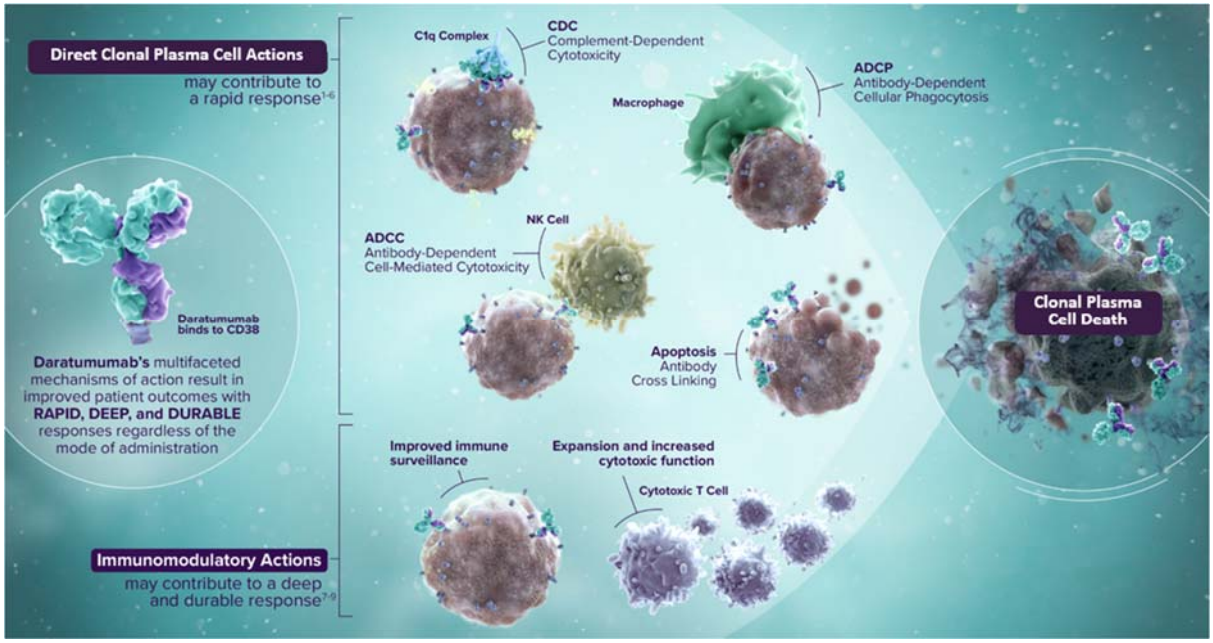
The ANDROMEDA trial is ongoing, however, the following analyses from ANDROMEDA are planned:

- 18-month landmark data cut-off: updated analyses for haematologic response and organ response ([redacted])
- 200 MOD-PFS event driven data cut-off: updated analyses for OS, MOD-PFS, haematologic response and organ response ([redacted])
- Final OS data cut-off: updated analyses have not yet been confirmed ([redacted])

B.2.12 *Innovation*

Daratumumab is a first-in-class, fully human IgG1κ mAb that binds to CD38, a protein that is overexpressed on the cell surface of diverse haematologic malignancies, including clonal plasma cells that produce the amyloidogenic immunoglobulin light-chain. High CD-38 expression is associated with adverse survival in AL amyloidosis.[104] Daratumumab works through a combination of immunomodulatory actions, which contribute to a deep and durable haematologic response, and direct clonal plasma cell actions, which contribute to a rapid haematologic response (Figure 15). Collectively, these actions are hypothesised to reduce native light-chain production and the associated organ toxicity in patients with systemic AL amyloidosis.

Figure 15: The multiple mechanisms of actions of daratumumab in AL amyloidosis



Abbreviations: ADCC: antibody-dependent cell-mediated cytotoxicity; ADPC: antibody-dependent cellular phagocytosis; AL: amyloid light chain; CDC: complement-dependent cytotoxicity; NK: natural killer.
Source: Janssen (Data on File): Daratumumab AL Amyloidosis Scientific Communications Platform.[40]

The significant improvements to haematologic and organ responses observed in patients treated with DBCd in the ANDROMEDA trial can be attributed to the innovative mechanisms of action of daratumumab. By reducing native light-chain production and subsequent organ toxicity, adding daratumumab SC to the BCd regimen was able to produce the significantly increased rates of achievement of CHR, reduced median time to CHR, and result in almost two-fold improvements in cardiac and renal response rates at six months. Although OS data were immature at the interim analysis, these improvements in haematologic and organ response associated with the addition of daratumumab SC to BCd are expected to translate into substantial improvements in overall survival compared with BCd alone.

There are currently no therapies in the UK licensed specifically for the treatment of patients with AL amyloidosis. Patients with AL amyloidosis are currently treated with a range of off-label treatment options that are typically used for MM. Many of these therapies demonstrate limited efficacy. Whilst use of BCd and other bortezomib-based therapies has led to some improvements in overall survival, most patients (59–79%) fail to achieve the primary therapeutic goal of CHR during first-line BCd therapy.[27, 28] OrRRs are also generally poor for bortezomib-based therapies.[27, 28, 30, 31] This lack of efficacy is compounded by the fact that available chemotherapies are poorly tolerated and are associated with frequent adverse events that may result in further HRQoL impairment.[89] Accordingly, there is a substantial unmet need for a novel, effective and well-tolerated treatment for newly diagnosed AL amyloidosis. Daratumumab SC can induce a rapid, deep and durable haematological response and consequently improve the poor prognosis and survival associated with this disease.

Patients with AL amyloidosis currently live with grief, distress, anger, and fear, finding out there is a lack of standard treatment for their condition. The benefits to patients of receiving an innovative treatment that provides significant clinical benefits and is tailored for their condition, in contrast to treatment with off-label therapies for MM, is not captured in the cost per QALY framework.

Treatment with daratumumab SC offers a convenient subcutaneous administration, fixed dose schedule, and finite treatment duration to patients (less or equal to 24 months). As the first and only approved therapy for AL amyloidosis, DBCd is expected to transform the treatment landscape and significantly improve clinical outcomes.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Strengths and limitations of the evidence base

ANDROMEDA was a high-quality, active-controlled Phase III RCT that directly compared DBCd against the relevant active (off-label) comparator BCd. ANDROMEDA was conducted in line with ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements. Steps taken to ensure the accuracy and reliability of the data included the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by sponsor representatives, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. The study had an open label design because of the difference in mode of administration for the trial drugs (daratumumab SC infusions are administered over a longer duration than bortezomib injections). However, the risk for bias was minimised since patients were randomised using a central interactive web response system (IWRS). In addition, outcomes were reviewed by an Independent Data Monitoring Committee (IDMC) which considered efficacy and safety outcomes to be robust. A summary of the quality of the ANDROMEDA trial is presented in Section B.2.5.

In the ANDROMEDA trial, patients in both the DBCd and BCd treatment arms who achieved a suboptimal haematologic response or worsening organ function were able to switch to an alternative treatment. This may be considered a limitation of the trial since, as described in Section B.2.6.2, this may have interfered with data collection for the MOD-PFS endpoint (given that disease progression is among the outcomes included in the composite). Further, because of the poor response of patients receiving BCd treatment, more patients in this arm of the trial received subsequent non-cross resistant, anti-plasma cell therapy compared with the DBCd arm. Overall, this necessitated adjustment of the MOD-PFS data for subsequent therapies through censoring, however, results were found to be consistent regardless of whether or not the analysis was carried out with this censoring. Patients who switched therapy following BCd treatment were permitted to receive off-label daratumumab-based regimens, ASCT or other treatments as a subsequent therapy.

Within ANDROMEDA, median MOD-PFS and median OS had not been reached at IA1. However, the substantially greater estimated 18-month MOD-PFS rate for DBCd (79.3%) compared with BCd (59.8%) suggests that the MOD-PFS results are durable over time and, given the established relationship between haematologic response and OS, higher achievement of a CHR in the DBCd arm indicates that treatment with DBCd is likely to lead to long-term improvements to OS.

Generalisability of ANDROMEDA to clinical practice in England

ANDROMEDA was a multicentre, international trial (two UK sites) that enrolled participants generally representative of AL amyloidosis patients in England. Expert clinical opinion indicated that whilst patients recruited in ANDROMEDA were slightly younger and fitter (in terms of ECOG performance status),[26] and excluded patients with cardiac Stage IIIb disease, baseline demographic and disease characteristics were otherwise broadly comparable to clinical practice

in England. This assessment is supported by a comparison of patient characteristics between the BCd arm of ANDROMEDA and the EMN23 study.[17] Results of this comparison are presented in Table 37 below. It should be noted however that, as previously mentioned in Section B.2.3.1, patients with cardiac Stage IIIb disease, were excluded from ANDROMEDA. This may partially explain some of the imbalances observed given that, according to data from EMN23, these patients represent approximately 16.0% of the total AL amyloidosis population included.[17]

Table 37: Comparison of patient characteristics between ANDROMEDA and EMN23

Characteristic	ANDROMEDA (N=388), n (%)	EMN23 (N=3,064), n (%) *or* %
Age, years		
Median	[redacted]	66
Sex, n (%)		
Female	[redacted]	41
Male	[redacted]	59
Cardiac stage based on Mayo Clinic Cardiac Staging System, n (%)		
I	[redacted]	17
II	[redacted]	35
IIIa	[redacted]	28
IIIb	[redacted]	16 [a]
Not reported	[redacted]	5
Organ involvement, n (%)		
Heart	[redacted]	2,131 (70)
Kidney	[redacted]	2,024 (66)
Liver	[redacted]	409 (13)
Gastrointestinal tract	[redacted]	215 (7)
Lung	[redacted]	26 (1)
Nerve	[redacted]	447 (15)
Soft tissue	[redacted]	609 (20)
Number of organs involved		
1 organ, n (%)	[redacted]	37
2 organs, n (%)	[redacted]	40
≥3 organs, n (%)	[redacted]	23
Not reported	[redacted]	-

[a] As per the Mayo Clinic 2012 staging system, this is reported as Stage IV. The 2012 revision to the staging system incorporated serum immunoglobulin free-light chain (dFLC) as a prognostic factor, assigning patients to Stages I, II, III and IV based on the number of prognostic factors, NT-proBNP, cTnT and dFLC, found to be elevated above defined thresholds.[14]
Abbreviations: EMN: European Myeloma Network.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[98] Palladini *et al.* (2021)[17]

As noted previously, BCd is considered to represent standard of care for newly diagnosed AL amyloidosis patients in clinical practice in England. This is aligned with the ANDROMEDA trial, which provides direct evidence for the relative clinical efficacy and safety data of DBCd compared with BCd. The primary endpoint used in ANDROMEDA was overall CHR, which was assessed via the consensus guidelines widely used in clinical practice in England to guide treatment options and assess patient prognosis.[24] PFS was not collected in ANDROMEDA as there is no accepted definition in AL amyloidosis. Instead, ANDROMEDA collected MOD-PFS, a

novel endpoint developed to encompass the most clinically relevant and objective measures of the benefits of anti-plasma cell therapy: haematologic progression, major organ deterioration, and death. Use of MOD-PFS as a key secondary endpoint and measure of disease progression in the ANDROMEDA trial was approved following consultation with both the FDA and the EMA, which acknowledge the challenges of collecting PFS data in AL amyloidosis.[33, 34]

Summary

Overall, the results of the ANDROMEDA study demonstrate that DBCd is an effective and tolerable treatment option as compared with the current standard of care in UK clinical practice, BCd. As compared with BCd-treated patients, DBCd gave rise to a deeper and more rapid haematologic response than BCd, and statistically significantly higher rates of cardiac and renal response at six months. These results can reasonably be expected to translate to long-term improvements in OS for these newly diagnosed amyloidosis patients who currently face a poor clinical prognosis. In addition, patients receiving DBCd in the ANDROMEDA trial reported overall stable or improved HRQoL as compared with substantial declines of those in the BCd treatment arm, and the safety profile of the regimen was tolerable and raised no new safety concerns. The introduction of DBCd to UK clinical practice would represent a step-change in care for patients, meeting a significant unmet need for a highly effective, tolerable treatment option which has the potential to improve patient prognosis and HRQoL, delay organ failure and prolong survival.

B.3 Cost effectiveness

Summary of cost effectiveness evidence

Cost-effectiveness model methodology

- An SLR of economic evaluations did not identify any prior cost-effectiveness analyses for pharmacologic interventions in newly diagnosed AL amyloidosis. Accordingly, a *de novo* cost-utility analysis was developed to assess the cost-effectiveness of DBCd compared to BCd in patients with newly diagnosed AL amyloidosis.
- The cost-effectiveness model adopts a decision tree-Markov structure. At the start of the decision tree, patients are assigned to receive either DBCd or BCd, following which they achieve a specified depth of haematologic response of complete response (CR), very good partial response (VGPR), partial response (PR) or no response (NR). Haematological response is assessed at six months in the base case, following which patients exit the decision tree and enter the Markov model.
- Patients' depth of haematologic response achieved in the decision tree subsequently informs which of three tracks within the Markov model they progress to: CR, VGPR or PR/NR. Patients who achieve CR and VGPR may continue first-line treatment for up to six treatment cycles; BCd patients subsequently discontinue and undergo observation, whereas DBCd patients may go on to receive daratumumab monotherapy for a maximum of up to 18 further cycles. In all three Markov model tracks, patients may progress to second-line treatment, end-stage organ failure and death. In agreement with well-established evidence from the literature,[2, 27, 82, 92, 93] patients' level of haematologic response informs their OS in the model.
- In line with the NICE reference case,[105] the analysis was conducted from the perspective of the NHS and PSS over a lifetime time horizon.
- With regards to efficacy, haematologic response rates for DBCd and BCd were sourced directly from the pivotal RCT for DBCd, ANDROMEDA, in addition to transitions to second-line therapy and end-stage organ failure. Long-term OS corresponding to different levels of haematologic response were sourced from Palladini *et al*., (2012).[2] Adverse event data for each intervention were sourced from ANDROMEDA.
- Health-related quality of life estimates for each category of haematologic response were sourced using EQ-5D-5L data (valued using UK-based tariffs) collected in ANDROMEDA, whilst decrements to utility associated with second-line therapy and end-stage organ failure were sourced from ANDROMEDA and Emin *et al*., (2016),[106] respectively.
- Due to a lack of UK-based cost and resource use data for AL amyloidosis identified in an SLR, a modified Delphi panel was conducted in order to source UK-specific estimates of resource use for each health state in the model. Unit costs were sourced from the NHS reference costs or the PSSRU.[107, 108]

Cost-effectiveness model results

- At the confidential PAS price, the ICER for DBCd vs BCd fell within the range considered to be cost-effective. At £23,446/QALY gained, it is below the NICE willingness-to-pay (WTP) threshold of £30,000. The probability of cost-effectiveness at WTP thresholds of £20,000 and £30,000 was [redacted]% and [redacted]%, respectively, indicating that DBCd has a high probability of cost-effectiveness. These results demonstrate DBCd to be a cost-effective option for the treatment of newly diagnosed AL amyloidosis versus the comparator relevant to UK clinical practice.
- Results of the sensitivity analyses demonstrate that the base case cost-effectiveness results exhibit little variation when the combined distributional uncertainty across model parameters is

taken into account. The most influential parameters driving the model were the CR health state utility value and the proportion of patients requiring haemodialysis

Cost-effectiveness model conclusions

- Overall, the introduction of DBCd into UK clinical practice is anticipated to bring substantial benefits to AL amyloidosis patients, for whom current standard of care (BCd) is unable to fulfil a significant unmet need for an effective, well-tolerated treatment that is able to induce rapid and deep response rate and improve survival rates. This analysis demonstrates that DBCd comprises a cost-effective treatment option that would offer value for money to the NHS.
- It should further be noted there are a number of benefits associated with DBCd that may not be captured in this analysis. DBCd is an innovative treatment, and if recommended, would represent the first treatment to be available for the treatment of newly diagnosed AL amyloidosis in the UK. This has benefits in terms of relieving patients' current stress and anxiety at the prospect of no available treatments, and will also serve to increase aware of this very rare disease among the clinical community, and in turn improve diagnosis rates and consequent clinical outcomes and survival for patients. These elements of value to patients and the clinical community are not captured in cost per QALY framework.

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify any relevant economic evaluations for the treatment of adult patients with newly diagnosed AL amyloidosis. The search was conducted in February 2021, with no studies meeting the criteria for inclusion in the review. The databases searches were supplemented with grey literature searches of HTA websites in March 2021, which confirmed that no further relevant economic evaluations have been published.

Full details of the SLR search strategy, study selection process and results are reported in Appendix G.

B.3.2 *Economic analysis*

The objective of this economic analysis was to assess the cost-effectiveness of DBCd compared with BCd alone for the treatment of patients with newly diagnosed AL amyloidosis in the UK.

As discussed in Section B.3.1, the SLR did not identify any studies evaluating the cost-effectiveness of DBCd in AL amyloidosis. Accordingly, a *de novo* cost-utility analysis has been conducted for the purpose of this appraisal. The cost-utility model adopted a decision tree-Markov structure, as follows:

- The decision tree assesses patients' haematologic response to treatment with DBCd or BCd among CR, VGPR, PR and NR at six months. After six months, patients exit the decision tree and enter the Markov model
- The Markov model captures the long-term trajectory of patients according to their level of haematologic response, and their transition through first-and later-line treatment and end-stage organ failure. Specifically, the Markov model contains a track for CR, VGPR and PR/NR
- Patients may transition to death at any point in the model, and OS is informed by category of haematologic response achieved
- This structure captures the disease course, including the wide-ranging clinical presentation of AL amyloidosis patients, and the treatment pathway of AL amyloidosis in UK clinical practice

In line with the NICE reference case,[105] the analysis was conducted from the perspective of the NHS and PSS and included direct medical costs only over a lifetime time horizon.

B.3.2.1 Patient population

This economic evaluation considers the cost-effectiveness of DBCd in adult patients with newly diagnosed AL amyloidosis. This is aligned with the licensed indication for daratumumab and the final NICE scope. The model is informed by data sourced from the pivotal ANDROMEDA trial (see Section B.2). Patients included in this study were considered generalisable to AL amyloidosis patients presenting in UK clinical practice by expert clinicians consulted within a UK advisory board, albeit slightly fitter (in terms of ECOG status and Mayo stage status), which was noted to be a common feature of clinical trials.[26]

The model is additionally informed by externally sourced data on patients with newly diagnosed AL amyloidosis from Palladini *et al*., (2012).[2] Palladini *et al*., (2012)[2] was a retrospective study of 816 AL amyloidosis patients from seven referral centres in Europe and the United States, including the UK (median follow-up time: 33 months). This data source was selected to inform OS by haematologic response in the Markov model.

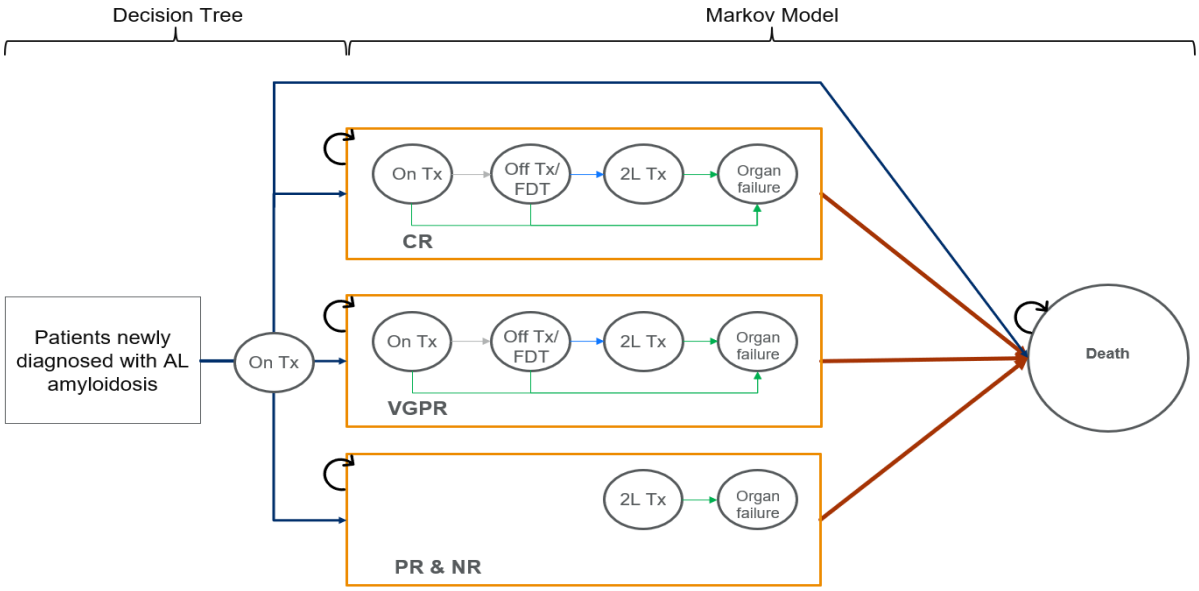
It is noted that data analysis is ongoing from a retrospective, observational, multicentre study on the management and outcomes of AL amyloidosis patients from 10 European countries, including the UK (EMN23 study).[17] This source is expected to provide a more recent source of data to inform OS that is more reflective of outcomes observed in current clinical practice. The company are currently working to incorporate these data into the model such that an analysis can be provided as soon as possible for the appraisal.

A limitation of the ANDROMEDA trial was the exclusion of patients with Mayo Stage IIIb disease. As described in Section B.1.4, the expert clinicians consulted indicated that a significant unmet need for an effective treatment exists in these patients, who are at a very high risk of death, and that they would expect such patients to derive clinical benefit from DBCd.[26] Despite the lack of data for Stage IIIb patients in ANDROMEDA, it is anticipated that standard of care data for such patients will be available from the EMN23 study. Accordingly, upon availability, the company will explore whether an analysis can be conducted that explores haematologic response rates that would be required for DBCd to be a cost-effective option in Mayo Stage IIIb AL amyloidosis patients.

B.3.2.2 Model structure

The model structure comprised a decision tree paired with a Markov model structure. In the context of AL amyloidosis, achieving a swift and deep haematologic response is the goal of first-line therapy as it prevents further organ damage and improves survival.[2] Accordingly, the structure of the model is based on the level of haematologic response achieved by the target population amongst non-response (NR)/partial response (PR), very good partial response (VGPR) and complete haematologic response (CHR). The model design was selected to appropriately reflect clinical practice and the disease course for patients with newly diagnosed AL amyloidosis. The Markov structure was better able to capture this compared to a traditional partitioned survival model, as well as reflecting the heterogeneity of outcomes in AL amyloidosis. The model structure is presented in Figure 16, with the decision tree and Markov elements described below.

Figure 16: Cost-effectiveness model structure



Abbreviations: AL: light-chain; CR: complete haematologic response (otherwise referred to as CHR); FDT: fixed daratumumab treatment; NR: no response; Off Tx/FDT: off-treatment / Fixed dose treatment; On Tx: on treatment; PR: partial response; (2L) Tx: (second-line) treatment; VGPR: very good partial response.

Decision tree

Upon entry into the decision tree segment of the model, all patients are alive and assigned to receive treatment with either DBCd or BCd. Within each cycle, patients are subsequently stratified by the level of haematologic response achieved amongst PR/NR, VGPR and CR, or death, as informed by IPD from the ANDROMEDA study. Within the model, the response categories of PR and NR were combined. This approach was guided by clinical expert opinion that such patients would be considered to have achieved a 'suboptimal' response and follow a similar treatment trajectory.

The model permits patients to exit the decision tree and enter the Markov portion of the model after either three or six cycles of treatment. Rationale exists for selecting both the three- and six-month options. The three-month option permits patients who only achieve PR or NR to exit the decision-tree after three months, and transition to an alternative therapy in order to try and achieve a superior response.[26] Alternatively, patients who achieve VGPR or CR in clinical practice would typically continue the same regimen up to cycle 6 (unless they experienced tolerability issues) in order to increase their depth of response and improve their long-term outcomes.[26] Given the rationale for both options, a six-month exit from the decision tree has been selected for the base case, whilst a three-month exit is explored in a scenario analysis. The six-month option enables the clinical value of DBCd, specifically the high and deep levels of haematologic response observed in ANDROMEDA (see Section B.2.6.1), to be recognised. This is also a conservative approach as QALYs in the BCd arm are likely to be overestimated as more patients in the BCd arm are PR/NR and they would accrue a better quality of life for longer due to the model structure.

Markov model

Upon exit from the decision tree, patients are stratified into one of three Markov tracks based on haematologic response achieved (i.e. CR, VGPR, or PR/NR) as outlined in Figure 16. Within each of these response levels, patients flow through the health states in a linear manner. Patients can either remain in the current state or transition to a later state, but cannot transition

back to a health state they previously transitioned from. Importantly, the health states for patients achieving CR or VGPR differ from the health states for patients achieving PR or NR, reflecting the expected treatment pathway each type of patient would follow in clinical practice.

Patients achieving complete haematologic response (CR) or very good partial response (VGPR)

The Markov tracks for CR and VGPR both have five health states, including 'First-line Treatment' (On Tx), 'Off First-line Treatment/fixed daratumumab treatment' (Off Tx/FDT), 'Second-line Treatment' (2L Tx), 'End-stage Organ Failure', and 'Death'. The first health state (1L Tx) is relevant only as a recurring health state when patients exit the decision tree after three cycles of treatment. In the base case analysis, patients with CR or VGPR can remain on-treatment for an additional three cycles (regardless of the treatment arm), after which they may transition to the 'Off Tx/FDT' or 'End-stage Organ Failure' states. Whilst in the 'Off Tx/FDT' health state, patients in the DBCd arm receive daratumumab monotherapy for a fixed treatment duration (up to a maximum of 24 cycles), whereas patients in the BCd arm stop any treatment and are observed (having completed their course of chemotherapy). The 'Off Tx/FDT' health state also captures patients in the DBCd arm who have discontinued treatment but have not transitioned to '2L Tx'. Regardless of their treatment arm, patients in the 'Off Tx/FDT' health state can remain in their current health state or transition to '2L Tx' or 'End-stage Organ Failure'. Of note, patients in the DBCd arm can remain in the 'Off Tx/FDT' health state beyond a maximum of 24 cycles of daratumumab, but these patients (similar to BCd patients) will not receive drug therapy and associated costs. Transitions to the '2L Tx' health state were informed by the 'time to subsequent non-cross anti-plasma cell therapy' outcome in the ANDROMEDA study.

In the '2L Tx' health state, patients go back onto treatment (due to haematologic or organ progression, or at the clinician's discretion) and will receive chemotherapy second line treatment. Patients can either remain in this health state or transition to 'End-stage Organ Failure'. The 'End-stage Organ Failure' health state encompasses patients that require solid organ (i.e. heart or kidney) transplant or dialysis. Patients can remain alive within this health state or die. At any cycle, patients can die and move from any health state to the absorbing "Death' health state. Transitions to the 'End-stage Organ Failure' state were informed by the MOD-PFS outcome (with the exclusion of death events contributing to the composite) from ANDROMEDA. Transitions to death from all health state were informed by Palladini *et al.,* (2012).[2]

Patients achieving partial response (PR) or no response (NR)

The Markov track for patients achieving PR or NR has three health states: '2L Tx', 'End-stage Organ Failure', and 'Death'. The primary difference between the Markov tracks for PR/NR and for CHR or VGPR is the absence of the '1L Tx' and 'Off Tx/FDT' health states. Regardless of whether patients exit the decision tree after three or six cycles of treatment, those with PR or NR haematologic responses will directly enter the '2L Tx' health state. This is aligned with clinical feedback, published literature and the ANDROMEDA trial protocol which all indicate that patients not achieving at least VGPR early in the course of treatment should switch to a different treatment regimen. In the '2L Tx' health state, patients return to receiving treatment (due to haematologic or organ progression, or at the clinician's discretion) and will receive treatment for refractory disease. Patients can either remain in this health state, or transition to 'End-stage Organ Failure'. As for patients with CHR or VGPR, patients can die and move from any health state to the absorbing 'Death' state. As per the CHR and VGPR Markov tracks, transitions to '2L Tx' and 'End stage organ failure' were informed by 'time to subsequent non-cross anti-plasma

cell therapy' and MOD-PFS outcomes from ANDROMEDA, whilst transitions to 'Death' were informed by Palladini *et al.,* (2012).[2]

Features of the economic analysis

In accordance with the NICE reference case, a lifetime time horizon of 35 years was adopted in order to fully capture the costs and benefits associated with DBCd or BCd treatment.

A half-cycle correction was applied to the calculation of life-years (LYs) and quality-adjusted life-years (QALYs) to account for the transition of patients from one health state to another happening in a continuous process, representing an average transition of halfway through a cycle (i.e. not at the beginning or end of a cycle)

A half-cycle correction was also applied to certain costs to avoid over- or under-estimating the value of a health state in alignment with patients transitioning from one health state to another part way through a cycle. More specifically, a half-cycle correction was applied to first-line drug therapy costs, first-line drug administration costs, first-line co-medication costs, healthcare resource use costs, first-line disease monitoring costs and recurring end-stage organ failure costs. Costs that were applied as a one-time cost (i.e. AE management, second-line drug therapy, solid organ transplant and end of life) were not half-cycle corrected.

Features of the economic analysis are summarised in Table 38.

Table 38: Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (35 years)	Consistent with the NICE reference case.[105] The mean starting age of the model patient population was 63 years and the model predicted that, after 35 years, >99% of patients in both treatment arms would have died.
Model structure	Decision tree combined with a Markov model	The decision tree component of the model permits patient stratification by haematologic response, thus reflecting the goal of first-line therapy of identifying early responders or non-responders at three or six cycles. Patients exit the decision tree at six months in the base case. The Markov model component includes multiple health states to capture the patient journey through the disease over the remainder of the cohort's lifetime (e.g. on/off treatment status, haematologic/organ progression necessitating subsequent therapy and progression to end-stage organ failure). Given the pre-progression heterogeneity of AL amyloidosis patients based on their treatment status and haematologic response, a three-state model (as has been submitted for previous daratumumab multiple myeloma indications)[109] would have been inadequate to reflect the complexity of this disease.
Treatment waning effect?	NA	No treatment waning effect is included within the model, as patients' stratification by haematologic response is informed by patients' initial response to treatment rather than the treatment received.
Source of utilities	Health state utility values were derived from EQ-5D-5L scores collected in the ANDROMEDA trial. These scores were then subsequently used to generate utility index values using the UK value set by van Hout *et al.,* (2012).[110]	In the base case, utility values stratified by haematologic response were informed by EQ-5D-5L data collected in the ANDROMEDA trial, weighted using UK tariffs.[111] Because the mean utility value for VGPR ([redacted]) was lower than the derived estimate for PR/NR ([redacted]) and could therefore be considered to have a lack of face validity, a more clinically plausible VGPR utility value was calculated as the mean of the CR and PR utility values ([redacted]). This assumption was explored in a scenario analysis where the utility value for VGPR was assumed to be the same as that for CR. Health state utilities were further explored based on feedback received from expert clinicians that they would expect any improvement in HRQoL to be delayed following initiation of treatment.[26] For this reason, a further scenario analysis was explored in which baseline utility values and post-treatment utility values at three months, six months and one year were sourced from clinicians, and used to inform a scenario

		analysis. It was not possible to derive HSUVs for these post-treatment timepoints from ANDROMEDA due to low numbers of EQ-5D responses at these timepoints.
Source of costs	Electronic market information tool (eMIT), the BNF, and the National schedule of NHS Costs (2018–19) Any cost sourced from published literature was inflated to 2020 values using the NHS cost inflation index (NHSCII) since it was the most recent inflation index available Costs included in the model were: • First-line drug therapy costs • First-line drug administration costs • First-line co-medication costs • First-line AE management costs • Disease monitoring costs • Second-line drug therapy costs • End-stage organ failure management costs • Health state-specific healthcare resource use costs • End of life costs	Established sources of costs within the NHS including BNF,[112] eMIT,[113] NHS Reference Costs 2018/19,[114] PSSRU.[115] In line with the NICE reference case.[105]
Resource use	The frequencies of healthcare resource use by the health states in the model structure were informed by a modified Delphi panel conducted with expert clinicians in the UK.[116] The report for the modified Delphi panel is supplied in the reference pack.	The SLR of cost and resource use (Appendix I) did not identify any high-quality studies providing resource use estimates for AL amyloidosis in the UK. Therefore, in order to source accurate estimates of healthcare resource use for the treatment of AL amyloidosis in the UK, a modified Delphi panel was conducted in which resource use estimates were gathered from seven UK-based expert healthcare professionals (clinicians and specialist nurses) with the aim of achieving consensus for all resource use inputs. The methodology of the Delphi panel is presented in a report provided in the reference pack.
Health effects measure	QALYs	Consistent with the NICE reference case.[105]

Half cycle correction applied?	Yes	A half-cycle correction was applied to the calculation of LYs, QALYs and costs to account for the transition of patients from one health state to another part-way through a cycle.

Abbreviations: AE: adverse event; AL: light-chain; CHR: complete haematologic response; eMIT: electronic market information tool; EQ-5D-5L: EuroQol-5 Dimensions-5 Level; LY: life year; NHSCII: NHS cost inflation index; NICE: National Institute for Health and Care Excellence; NR: no response; PR: partial response; PSSRU: Personal Social Services Research Unit; SLR: systematic literature review; QALY: quality-adjusted life year; VGPR: very good partial response.

B.3.2.3 Intervention technology and comparators

Intervention

The intervention included in the model was DBCd. The dosing schedule for daratumumab included in the model is consistent with the ANDROMEDA trial, as follows:

- Weeks 1 to 8: weekly (total of 8 doses)
- Weeks 9 to 24: every two weeks (for a total of 8 doses)
- Week 25 onwards: every four weeks until disease progression or a maximum of 24 cycles (~2 years)

It is noted that the SmPC for DBCd permits use of daratumumab monotherapy until progression (i.e. unlike the protocol of the ANDROMEDA trial, a 24-cycle discontinuation criterion is not stipulated).[32] However, feedback from the UK advisory board was that clinicians would likely prescribe daratumumab for up to 2 years, in line with the available clinical data from ANDROMEDA, and the fact that patients would likely not to wish to attend regular hospital visits beyond this length of time due to the burden to their wellbeing.[26, 32, 35]

The treatment protocol for BCd in the model was as follows, which was applied in both the DBCd and BCd arms:

- Bortezomib was administered SC at a dose of 1.3 mg/m^2 once weekly for six 28-day cycles
- Cyclophosphamide was administered orally at 300 mg/m^2 once weekly for six 28-day cycles
- Dexamethasone was administered orally at a total dose of 40 mg weekly for six 28-day cycles

Comparator

As described in Section B.1.3.3, BCd is the sole comparator considered in this cost-utility analysis.[26] Clinical expert feedback indicated that in UK clinical practice:

- Most newly diagnosed AL amyloidosis patients (approximately [redacted]%) are treated with BCd as a first-line therapy and it therefore represents the mainstay of treatment for these patients, including those who are eligible for transplant and those who are elderly[88]
- Lenalidomide and dexamethasone (Rd) can be used in patients with neuropathy, but its use in the newly diagnosed setting is very rare, therefore only patients who have poor tolerability, or are contraindicated to, bortezomib would receive Rd
- Melphalan and dexamethasone (Md) is rarely used, and only for patients who are contraindicated BCd
- Very few patients receive ASCT due to organ involvement resulting in ineligibility, and those who do receive ASCT typically receive previous induction therapy (i.e. it is not a first-line treatment for newly diagnosed patients). Indeed, recent clinical guidelines indicate DBCd or BCd as the preferred induction therapy prior to ASCT[3, 5]
- Best supportive care is not a preferred option for newly diagnosed AL amyloidosis patients, for whom front line treatment is recommended

The analysis has therefore been conducted to assess the cost-effectiveness of DBCd versus BCd alone.

B.3.3 *Clinical parameters and variables*

Clinical parameters and variables presented in Section B.3.3 are informed by the ANDROMEDA trial results from the interim analysis (IA1; data cut-off February 2020; median follow-up 11.4 months) and 12-month landmark analysis (data cut-off November 2020; median follow-up 20.3 months), in addition to Palladini *et al.,* (2012),[2] which informs OS in the Markov model.

Data from the interim analysis in ANDROMEDA were used to inform inputs pertaining to mortality and MOD-PFS since these outcomes were not reported in the 12-month landmark cut-off. All other inputs from ANDROMEDA that are included in the model, (patient stratification within the decision tree, time to subsequent non-cross resistant anti-plasma cell therapy and treatment duration) represent data from the 12-month landmark analysis.

B.3.3.1 Baseline characteristics

The baseline characteristics of the modelled cohort are based on the ANDROMEDA trial and are presented in Table 39. As described in Section B.3.2.1, expert clinicians consulted at the advisory board indicated that the ANDROMEDA trial population was largely generalisable to patients presenting in UK clinical practice.[26] Age and gender are included in the model in order to inform general mortality inputs, whilst body weight and body surface area (BSA) are included to inform drug acquisition costs of treatments that are dosed based on weight or BSA (e.g. bortezomib).[26] No differences in population characteristics are assumed between interventions.

Table 39: Baseline characteristics for the base case population

Component	Base case value
Mean age, years (SD)	[redacted]
Male, %	[redacted]
Mean weight, kg (SD)	[redacted]
Mean BSA, m^2 (SD)	[redacted]

Abbreviations: BSA: body surface area; SD: standard deviation.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

B.3.3.2 Efficacy in the decision tree

In the decision tree, patients are stratified by haematologic response. The proportion of patients in each treatment group achieving CR, VGPR, PR/NR or who died within each one-month window (i.e. one cycle) was informed by patient-level data from the ANDROMEDA trial (12-month landmark analysis). In the base case, exit from the decision tree was at six months (Table 40).[26] A two-month window was used to capture haematologic response data for patients in cycle six, thereby ensuring that all appropriate haematologic response data were captured, such as accounting for patients who may have experienced treatment delays. Where an alive patient's haematologic response status was not reported in a particular cycle, they were classified as PR/NR. This simplifying assumption was applied equally to both treatment groups to prevent overestimation of treatment benefit.

Table 40: Haematologic response distribution over six months within the decision tree (base case analysis)

Cycle	CR		VGPR		PR/NR		Dead	
	DBCd	BCd	DBCd	BCd	DBCd	BCd	DBCd	BCd
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

A scenario analysis was conducted in which patients were stratified by haematologic response at three months (Table 41). In alignment with the approach taken for the six-month analysis, haematologic response was determined for each month for cycles 1 and 2, and a two-month window approach was taken for capturing haematologic response data for patients in cycle three.

Table 41: Haematologic response distribution over three months within the decision tree

Cycle	CR		VGPR		PR/NR		Dead	
	DBCd	BCd	DBCd	BCd	DBCd	BCd	DBCd	BCd
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.
Source: ANDROMEDA 12-month landmark analysis (November 2020)[99]

B.3.3.3 Efficacy in the Markov model

Overall survival by haematologic response in the ANDROMEDA trial

Within the model, OS is informed by depth of haematologic response achieved following first-line treatment with DBCd or BCd. Specifically, OS is dependent upon survival extrapolations stratified by CR, VGPR, and PR/NR. As discussed in Section B.3.3.2, achievement of haematological response is directly related to treatment received (DBCd or BCd). Accordingly, the distribution of haematologic response achieved at the end of the decision tree (at six months in the base case) is assumed to predict treatment-specific OS over time. This assumption is supported by a substantial amount of evidence supporting the relationship between depth of haematologic response and improved OS for newly diagnosed AL amyloidosis,[2, 27, 82, 92, 93] and is aligned with the goal of front-line treatment to achieve the best haematologic response possible.[26] Conservatively, no additional treatment effect on DBCd compared to BCd in terms of improved survival was applied in the model, as data from ANDROMEDA are currently too immature to determine if this exists.

OS data from the ANDROMEDA trial was relatively immature at the time of the IA1 data cut-off. Accordingly, in order to inform long-term survival in the model, it was necessary to source external survival data for patients with newly diagnosed AL amyloidosis, stratified by haematologic response, and a targeted literature search was conducted to identify such studies. In the base case, OS stratified by haematologic response at six months is informed by Palladini *et al*., (2012).[2] Palladini *et al*., (2012) was a retrospective study of 816 AL amyloidosis patients from seven referral centres in Europe and the United States, including the UK (median follow-up time: 33 months). This data source was selected to inform the base case analysis given its large

sample size and inclusion of the UK setting. Importantly, this source is also in alignment with the six-month exit from the decision tree.

A scenario analysis whereby haematological response is assessed at three months is informed by Kastritis *et al*., (2020),[82] a study that aimed to evaluate the significance of an early and deep haematologic response in AL amyloidosis patients. The study included 227 patients with newly diagnosed AL amyloidosis treated with bortezomib-based regimens in Athens, Greece.[2]

In accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14,[117] the following methods were followed in order to identify the most appropriate parametric survival function for each category of haematologic response:

1. The OS Kaplan-Meier (KM) curves from Palladini *et al*., (2012) and Kastritis *et al.,* (2020) were digitised using DigitizeIt Software[2, 82]
2. In R 3.4.2, using the methods outlined in Guyot *et al*., (2012), individual patient level data were generated from the digitised KM data and number at risk[118]
3. Survival models (Exponential, Weibull, Gompertz, Log-normal, Log-logistic and Generalised Gamma) were fit to the individual patient level data using the flexsurvreg function of the flexsurv package
4. Parameters and model fit statistics (Akaike's information criterion [AIC] and Bayesian information criterion [BIC]) were calculated for each curve type

Subsequently, the most appropriate curve for data extrapolation was selected based on the following considerations:

- Visual inspection of the fit of each parametric survival function to the KM survival data
- The goodness of fit for each parametric survival function based on statistical analyses of AIC and BIC
- The face validity of the extrapolated curves with respect to predicting clinically plausible survival estimates for the patient population
    - The extrapolations were presented to UK expert clinicians at the advisory board to understand which survival functions most closely reflected duration of survival observed in newly diagnosed AL amyloidosis patients in the UK[26]

Survival analysis conducted for assessment of haematologic response at six months is presented in the main submission, whilst survival analysis conducted for haematologic response at three months is presented in Appendix O.

Overall survival for six-month PR/NR

As described in Section B.3.2.2, patients achieving either NR or PR are considered together in the model due to both types of response being considered 'suboptimal' in clinical practice and patients subsequently following a similar treatment pathway. The proportion of patients achieving PR and NR at six months, as reported in the ANDROMEDA trial, was used to apply weighting to a combined PR/NR OS curve, to reflect the patient population of suboptimal responders for each arm.

After digitising and extrapolating the PR and NR KM curves from Palladini *et al.,* (2012),[2, 82] the curves were visually assessed and shown to appropriately fit the PR and NR KM data. The PR

KM curve and its associated curve extrapolations are presented in Figure 17. The NR KM curve and its associated extrapolations are presented in Figure 18.

Within ANDROMEDA, patients that achieved a NR comprised [redacted] of all patients that were either PR or NR at the six-month landmark, irrespective of treatment arm. Because patients with NR represented a larger proportion of the weighting applied in generating the weighted PR/NR curve in the reference case, AIC and BIC for the PR curve were used to determine which parametric survival function was the best fit for the weighted PR/NR curve. The AIC and BIC statistics for the PR and NR curves are presented in Table 42. AIC/BIC values were similar across extrapolations, however, the Gompertz and exponential parametric survival functions were deemed to generate the best fit for patients with PR.

The full set of possible weighted extrapolations was presented to UK expert clinicians at an advisory board.[26] Feedback from expert clinicians was that all extrapolations were relatively optimistic, and they based their judgement of the most realistic extrapolation on survival estimates after one year, based on the fact that clinicians observe high rates of mortality in the year following patients' presentation at the clinic. Overall, the clinicians' preference was the Log-normal curve.

Accordingly, based on clinical expert opinion, the Log-normal curve was selected for the base case.

The PR and NR KM curves along with their respective weighted PR/NR survival curve extrapolations are depicted in Figure 19. Use of the Weibull function to generate the weighted PR/NR curve was explored in scenario analyses.

Figure 17: OS curve extrapolations for patients with PR from Palladini *et al.*, (2012) (six-month landmark)

[redacted]

Abbreviations: KM: Kaplan–Meier; OS: overall survival; PR: partial response.

Figure 18: OS curve extrapolations for patients with NR from Palladini *et al.*, (2012) (six-month landmark)

Abbreviations: KM: Kaplan–Meier; NR: no response; OS: overall survival.

Table 42: Model fit statistic for OS curve extrapolations for patients with NR or PR from Palladini *et al.*, (2012) (six-month landmark)

	NR		PR	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each response is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; NR: no response; OS: overall survival; PR: partial response.

Figure 19: Weighted PR and NR OS curve extrapolations from Palladini *et al.,* (2012) (six-month landmark)

Abbreviations: KM: Kaplan–Meier; NR: no response; OS: overall survival; PR: partial response.

Overall survival for six-month VGPR

After digitising and extrapolating the VGPR KM curve from Palladini *et al.,* (2012), the curves were visually assessed and shown to appropriately fit the VGPR KM data.[82] The VGPR KM curve and its associated curve extrapolations are presented in Figure 20.

The AIC and BIC statistics for the VGPR curve are presented in Table 43. According to AIC and BIC, the exponential extrapolation generated the best-fit for patients with VGPR.

The full set of possible weighted extrapolations was presented to UK expert clinicians at an advisory board.[26] As described above for 'Overall survival for six-month PR/NR', all extrapolations were considered relatively optimistic, and the clinicians based their judgement on survival predictions at one year. On this basis, they selected the Log-normal curve.

Accordingly, based on model fit statistics and clinical expert opinion, the Log-normal curve was selected for the base case, whilst the exponential was explored in a scenario analysis.

Figure 20: OS curve extrapolations for patients with VGPR from Palladini *et al.,* (2012) (six-month landmark)

Abbreviations: KM: Kaplan–Meier; NR: no response; OS: overall survival; VGPR: very good partial response.

Table 43: Model fit statistic for OS curve extrapolations for patients with VGPR from Palladini *et al.,* (2012) (six-month landmark)

	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; VGPR: very good partial response.

Overall survival for six-month CR

After digitising and extrapolating the CR KM curve from Palladini *et al.,* (2012), the curves were visually assessed and shown to appropriately fit the CR KM data.[82] The CR KM curve and its associated curve extrapolations are presented in Figure 21. Upon visual inspection, all tested extrapolations showed an appropriate fit, but all predicted a clinically implausible lifespan. Therefore, the model uses the selected curve extrapolation until the general population mortality hazard supersedes the hazards of the extrapolated curve data (for further detail, see the 'General population mortality' section below).

The AIC and BIC statistics for the CR curve are presented in Table 44. According to AIC and BIC, the exponential parametric survival function generated the best-fit for patients with CR.

The full set of possible weighted extrapolations was presented to UK expert clinicians at an advisory board.[26] As per the prior sections for PR/NR and VGPR, clinicians based their

extrapolation selection on survival predictions at one year, deeming the Gompertz function to be most suitable.

Accordingly, based on model fit statistics and clinical expert opinion, the Gompertz was selected for the base case.

Figure 21: OS curve extrapolations for patients with CR from Palladini *et al.,* (2012) (six-month landmark)

Abbreviations: CR: complete haematologic response; KM: Kaplan–Meier; NR: no response; OS: overall survival.

Table 44: Model fit statistic for OS curve extrapolations for patients with CR from Palladini *et al.,* (2012) (six-month landmark)

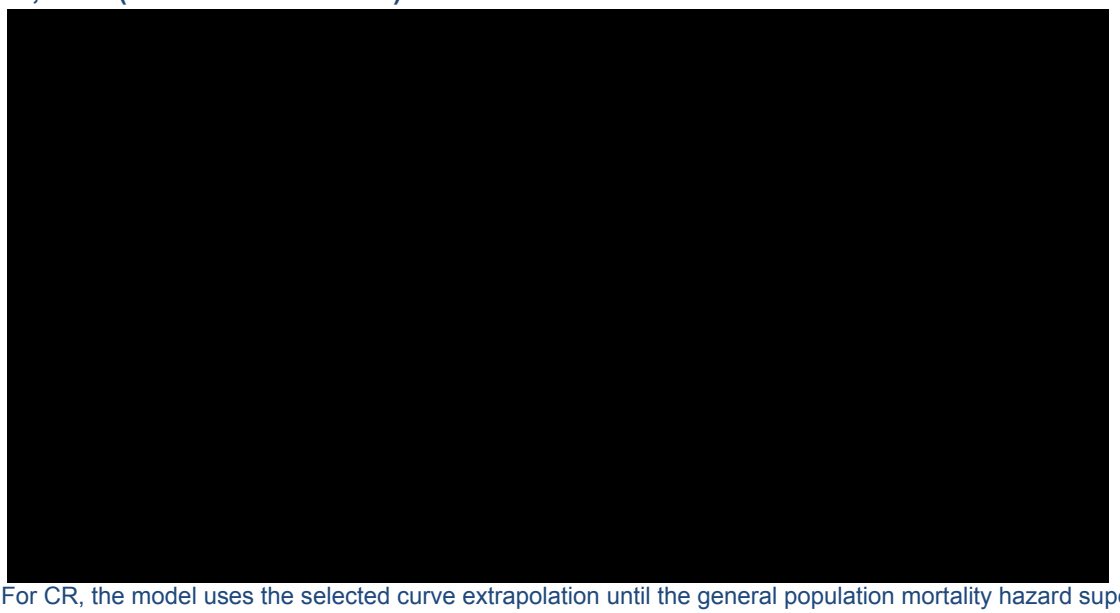
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CR: complete haematologic response; OS: overall survival.

Overall survival at six months

The OS extrapolations for each haematologic response of PR/NR, VGPR and CR selected to inform the base case are presented in Figure 22.

Figure 22: OS curve extrapolations stratified by haematologic response from Palladini *et al*., 2012 (six-month landmark)



For CR, the model uses the selected curve extrapolation until the general population mortality hazard supersedes the hazards of the extrapolated curve data.
Abbreviations: CR: complete haematologic response; KM: Kaplan-Meier; NR: non-response; PR: partial response; VGPR: very good non-partial response.

Overall survival by haematologic response in the EMN23 study

An additional external source of OS in AL amyloidosis patients stratified by haematologic response is the EMN23 study, a retrospective observational, multicentre study on the management and outcome of AL amyloidosis patients from 10 European countries, including the UK.[17] Overall, 3064 patients treated between 2011 and 2018, including 38% from the UK. The majority of patients were male (59%). Median age was 66 years, and 37%, 40%, and 23% of the patients had 1, 2, and 3 or more organs involved, respectively. A 17% of the patients were at cardiac stage (Mayo 2004/European modification) I, 35% at stage II, 28% at stage IIIa and 16% at stage IIIb, and for 5% the cardiac stage was unknown.

Due to the data availability and time constraints, it has not yet been possible to incorporate in the submission the EMN23 survival data into the cost-effectiveness model ahead of submission. However, the Company are currently working to incorporate these data into the model such that results are available during the timeframe of the appraisal.

General population mortality

In addition to disease-specific mortality from the OS extrapolations, the model also considered background mortality risk from the general population. General population mortality was obtained from the most recent life tables available from the UK Office for National Statistics.[119] The annual probabilities of death by sex and age were converted to rates of death and weighted for the percentage of males in the model, and then converted to per cycle probabilities of death by age. The model used the sex-weighted per cycle probability of death based on the mean patient age each cycle to ensure the hazard of death predicted by the extrapolations did not drop below that of the general population (i.e. predicted survival could not exceed general population survival). Therefore, in the model, if patient survival based on OS curve extrapolations exceeded that expected from general population mortality risk, the general population mortality hazard would be used instead.

Mortality distribution among health states

The probability of survival (based on OS curves and general population mortality; see the 'Overall survival by haematologic response' and 'General population mortality' sections for further details) determined the number of deaths per cycle within each Markov track. However, these sources were not able to inform which health states these deaths occurred in within each model. As such, in order to inform the distribution of mortality among health states, the state-specific probabilities of mortality from the ANDROMEDA trial (IA1) were used. All deaths that occurred over the trial period up to the interim analysis were reviewed to capture which health state each patient occupied before they died. Given that early, sudden deaths whilst on treatment is a possibility for patients with AL amyloidosis, deaths that occurred during the first six months and from six months to the end of follow-up in ANDROMEDA were reviewed and two mortality distributions were considered in the model to account for the potential difference in early- versus long-term health state-specific probabilities of mortality.

It was assumed that the mortality distribution among health states was the same regardless of haematologic response and treatment, such that the health state would dictate the risk of death, but the haematologic response would dictate the total number of deaths.

According to ANDROMEDA IPD, the majority of early deaths occurred whilst patients were in the '1L Tx' health state (Table 45). This aligns with published literature and clinical expert feedback where, for patients with AL amyloidosis, most deaths occur early in the treatment pathway due to irreversible cardiac dysfunction.[26, 74] The distributions of mortality for cycles 4–6 presented in Table 45 are utilised in the base case where a three-month decision tree exit is employed (mortality in cycles 1–3 is discussed in Section B.3.3.2). In the scenario analysis which employs a six-month decision tree exit, these distributions would not be used, as mortality would be informed by the risk of death in the decision tree.

In cycles seven and beyond, ANDROMEDA IPD indicated that the majority of deaths occurred in the 'End-stage Organ Failure' state (Table 46).

Table 45: Mortality distribution by health state for cycles four to six (ANDROMEDA; 14th February 2020 data cut-off)

Health state	Patients, n	Deaths by health state
1L Tx	[redacted]	[redacted]
Off Tx/FDT	[redacted]	[redacted]
2L Tx	[redacted]	[redacted]
End-stage Organ Failure	[redacted]	[redacted]
Total	[redacted]	**100%**

Abbreviations: 1L: first-line; 2L: second-line; FDT: fixed daratumumab treatment; Tx: treatment.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Table 46: Mortality distribution by health state for cycles seven and beyond (ANDROMEDA; 14th February 2020 data cut-off)

Health state	Patients, n	Deaths by health state
1L Tx	[redacted]	[redacted]
Off Tx/FDT	[redacted]	[redacted]
2L Tx	[redacted]	[redacted]
End-stage Organ Failure	[redacted]	[redacted]

Total	[redacted]	**100%**

Abbreviations: 1L: first-line; 2L: second-line; FDT: fixed daratumumab treatment; Tx: treatment.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

It was necessary to include an adjustment in the model to prevent health states from experiencing negative deaths. Specifically, for any cycle where the mortality distribution led to more deaths within a particular health state than the number of patients available, all patients were first removed from that health state, and the remainder were taken out of the health state with the highest number of patients. For example, if there were 5 alive patients in the '2L Tx' health state, but the mortality distribution required 7 deaths, all 5 patients would be removed from '2L Tx', with the remaining 2 patients taken from another health state with the highest number of patients in that cycle.

Health state transition probabilities

In the model, transition probability matrices were used to estimate the number of patients alive that would progress to another health state (except death, see mortality distribution section above). These transition probabilities varied by haematologic response but did not vary between treatment groups, such that progression to other health states was driven by depth of haematologic response rather than the treatment received. Assumed to be constant over time due to current data availability from the trial, these transition probabilities were generated using pooled data for DBCd- and BCd-treated patients from the ANDROMEDA trial.

As per the ANDROMEDA trial protocol, all patients are modelled to transition out of the '1L Tx' health state after receiving six cycles of therapy, regardless of decision tree exit timepoint. Patients may transition from '1L Tx' to 'Off Tx/FDT (for CR and VGPR only) or to 'End-stage organ failure'.

Transition to end-stage organ failure

The probability of transitioning from '1L Tx' to 'End-stage organ failure' was generated using time-to-MOD-PFS data from the ANDROMEDA trial, stratified by haematologic response. Transition probabilities were based on MOD-PFS events including haematologic progression and major organ deterioration events but excluded deaths, to avoid over-estimating the proportion of patients that would move to the 'End-stage organ failure' state. Stratification was performed based on haematologic response at three months, which benefitted from a larger sample size for generation of extrapolation curves compared to stratification at six months.

The time-to-MOD-PFS haematologic response Kaplan-Meier curves are presented in Figure 23. The time-to-MOD-PFS data were still immature at the time of the interim analysis (87 out of 200 planned events had occurred); as such, the shapes of the MOD-PFS by haematologic response curves are unknown, and any extrapolation of these data beyond 10-months would be highly uncertain due to the limited sample size and short follow-up. Furthermore, the plateau in all the KM curves from the lack of long-term events seemed clinically implausible; rather, a continuous decline in the curves would be expected given that AL amyloidosis is a progressive disease. Given that these curves appear generally linear (between three months and before the curves plateau due to few events/patients), a constant transition probability was deemed reasonable as a simplistic and pragmatic assumption. Constant hazard rates were calculated from the curves and converted to a per-cycle probability. The monthly probability for MOD-PFS stratified by haematologic response is presented in Table 47.

Because patients from '1L Tx', 'Off Tx/FDT' and '2L Tx' can all transition to 'End-stage organ failure' at any given cycle, the monthly probability of MOD-PFS was further stratified based on the distribution of MOD-PFS events (excluding deaths) that occurred by health state in ANDROMEDA, as presented in Table 47. The transition probability is calculated as the monthly probability of a MOD-PFS event for a patient with the specified depth of haematologic response multiplied by the proportion of MOD-PFS events that occurred whilst a patient was on that line of treatment in ANDROMEDA. For example, the 0.02549% of transition from '1L Tx' to 'End-stage organ failure' for a patient with CR on first-line treatment was calculated as 0.21% multiplied by 12%. Given the small number of MOD-PFS events reported at the first clinical cut-off, a simplifying, and likely conservative, assumption was made that the transition probabilities from '2L Tx' to 'End-stage organ failure' are equivalent to those for '1L Tx' to 'End-stage organ failure' for all haematologic responses.

Figure 23: Time-to-MOD-PFS by hematologic response

The scale of x axis is months.
Abbreviations: CR: complete response; NR; no response; PR: partial response; VGPR: very good partial response.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Figure 24: Extrapolated time-to-MOD-PFS curves

Abbreviations: CR: complete response; NR; no response; PR: partial response; VGPR: very good partial response.

Table 47: Values informing transition probabilities to 'End-stage organ failure' by haematologic response

Transition to 'End stage organ failure'	CR	VGPR	PR/NR
From 1L Tx			
Monthly Probability of MOD-PFS, %	0.21%	1.03%	3.39%
Distribution of '1L Tx' MOD-PFS Events, %	12%	28%	60%
Calculated Transition Probability '1L Tx' to 'End-stage organ failure', %	0.02549%	0.28712%	2.03623%
From Off Tx/FDT			
Distribution of 'Off Tx/FDT' MOD-PFS Events, %	10%	35%	55%
Calculated Transition Probability 'Off Tx/FDT' to 'End-stage organ failure', %	0.0212%	0.3589%	1.8665%
From 2L Tx			
Transition probability '2L Tx' to 'End-stage organ failure', % [a]	0.02549%	0.28712%	2.03623%

[a] Due to a limited number of MOD-PFS events reported in ANDROMEDA, a simplifying assumption was made whereby the transition probabilities for '2L Tx' to 'End-stage Organ Failure' were assumed equivalent to those from '1L Tx' to 'End-stage Organ Failure'.
Abbreviations: 1L: first-line; 2L: second-line; FDT: fixed dose treatment; MOD-PFS: major organ deterioration-progression free survival; tx: treatment.

Transition to second-line treatment health state

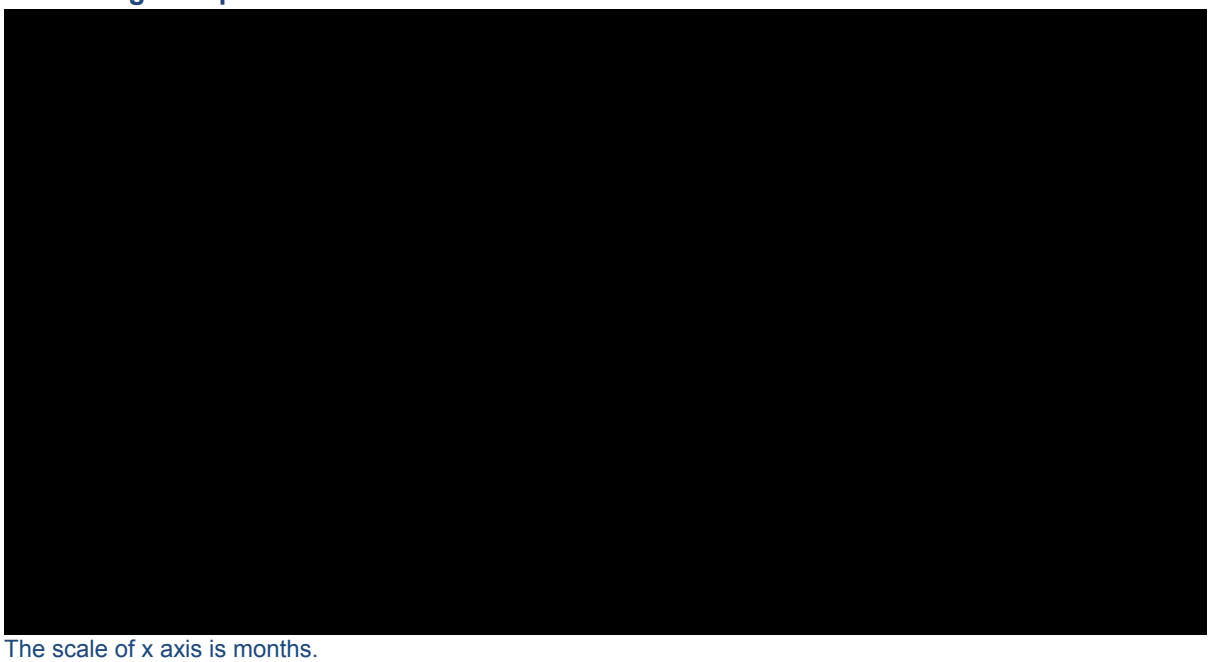
Patients with CR and VGPR in the 'Off Tx/FDT' health state can transition to 'End-stage organ failure' (described in the 'Transition to end-stage organ failure' section) or to '2L Tx'. Transition probabilities from 'Off Tx/FDT' to '2L Tx' were generated using the 'time to subsequent non-cross resistant anti-plasma cell therapy curves' derived from ANDROMEDA trial data (12-month landmark analysis), stratified by haematologic response. As for transition to 'End-stage organ

failure', stratification was also performed based on haematologic response at three months, which benefitted from a larger sample size for generation of extrapolation curves compared to stratification at six months. The time to subsequent non-cross resistant anti-plasma cell therapy by haematologic response is presented in Figure 25.

Follow-up data for this outcome was still immature from the trial, as shown by the low numbers at risk after ~10 months. Extrapolation of these curves would, therefore, introduce unnecessary complexity and uncertainty into the model. Given that these curves appear generally linear (between six months [when CR/VGPR patients are still on first-line therapy] and before the curves start to plateau around 10-months due to short follow-up), a constant transition probability was therefore deemed reasonable as a simplistic and pragmatic assumption. Moreover, as the plateau in the KM curves (from the lack of long-term events), particularly in the CR curve, would favour patients in the DBCd arm, the use of a constant transition probability would also be a conservative assumption. The constant hazard rate was calculated from the CR and VGPR time to subsequent non-cross resistant anti-plasma cell therapy curves and then converted to a per-cycle probability.

The per-cycle transition probabilities from 'Off Tx/FDT' to '2L Tx' were 0.42% for CR and 1.52% for VGPR. Given that patients with PR/NR would immediately switch to second-line treatment after exiting the decision tree, no transition probability for 'Off Tx/FDT' to '2L Tx' was calculated. All remaining patients that did not transition to another health state and did not die remained in the 'Off Tx/FDT' health state until the next cycle.

Figure 25: Time to subsequent non-cross resistant anti-plasma cell therapy stratified by hematologic response



The scale of x axis is months.
Abbreviations: CR: complete response; NR; no response; PR: partial response; VGPR: very good partial response.
Source: ANDROMEDA 12-month landmark analysis (November 2020).[99]

Figure 26: Extrapolated time-to-subsequent non-cross resistant anti-plasma cell therapy

Abbreviations: CR: complete response; NR; no response; PR: partial response; VGPR: very good partial response.

Transition probabilities for cycles 3–6

In the base case, exit from the decision tree is at three months. Given that in cycles 3 to 6, patients with CR and VGPR do not yet transition from '1L Tx' to 'Off Tx/FDT', and thus the transition probability from '1L Tx' to 'Off Tx/FDT' is 0%, the health state transition probabilities applicable to cycles 3 to 6 differ from those applied in cycles 7 and beyond (where patients may transition to 'Off Tx/FDT') for patients in the '1L Tx' state. The transition probabilities for CR, VGPR, and PR/NR applied in cycles 3 to 6, generated using ANDROMEDA IPD as described for 'End stage organ failure' and 'time to second-line treatment', are presented in Table 48.

Table 48: Transition probabilities stratified by haematologic response for cycles 3–6

From:	To:				
	1L Tx	Off Tx/FDT	2L Tx	End-stage Organ Failure	Total
CR					
1L Tx	99.97%	0%	-	0.025%	100%
Off Tx/FDT	-	99.56%	0.420%	0.021%	100%
2L Tx	-	-	99.97%	0.025%	100%
End-stage Organ Failure	-	-	-	100%	100%
VGPR					
1L Tx	99.71%	0%	-	0.29%	100%
Off Tx/FDT	-	98.12%	1.52%	0.36%	100%

2L Tx	-	-	99.71%	0.29%	100%
End-stage Organ Failure	-	-	-	100%	100%
PR/NR					
1L Tx	0%	-	97.96%	2.04%	100%
Off Tx/FDT	-	-	-	-	100%
2L Tx	-	-	97.96%	2.04%	100%
End-stage Organ Failure	-	-	-	100%	100%

Abbreviations: 1L: first-line; 2L: second-line; CR: complete response; FDT: fixed-dose treatment; MOD-PFS: major organ deterioration-progression free survival; NR; no response; PR: partial response; tx: treatment; VGPR: very good partial response.

Transition probabilities for cycles 7 and beyond

The transition probabilities for CR, VGPR, and PR/NR applied in cycles 7 and beyond, generated using ANDROMEDA IPD as described for 'End-stage organ failure' and 'time to second-line treatment', are presented in Table 49.

Table 49: Transition probabilities stratified by haematologic response for cycles 7 and beyond

From:	To:				
	1L Tx	**Off Tx/FDT**	**2L Tx**	**End-stage Organ Failure**	**Total**
CR					
1L Tx	0%	99.97%	-	0.025%	100%
Off Tx/FDT	-	99.56%	0.420%	0.021%	100%
2L Tx	-	-	99.97%	0.025%	100%
End-stage Organ Failure	-	-	-	100%	100%
VGPR					
1L Tx	0%	99.71%	-	0.29%	100%
Off Tx/FDT	-	98.12%	1.52%	0.36%	100%
2L Tx	-	-	99.71%	0.29%	100%
End-stage Organ Failure	-	-	-	100%	100%
PR/NR					
1L Tx	0%	-	97.96%	2.04%	100%
Off Tx/FDT	-	-	-	-	100%
2L Tx	-	-	97.96%	2.04%	100%
End-stage Organ Failure	-	-	-	100%	100%

Abbreviations: 1L: first-line; 2L: second-line; CR: complete response; FDT: fixed-dose treatment; MOD-PFS: major organ deterioration-progression free survival; NR; no response; PR: partial response; tx: treatment; VGPR: very good partial response.

Treatment exposure

In the model, first-line drug costs are calculated based on the treatment duration (i.e. the number of model cycles) and the proportion of patients receiving each treatment cycle over the treatment duration, analogous to patient discontinuation.

Treatment duration

In the base case, patients who only achieve NR or PR after six months must stop first-line treatment and immediately switched to a subsequent therapy. According to the ANDROMEDA 12-month landmark analysis, the ITT mean treatment duration for DBCd and BCd was [redacted] and [redacted] months, respectively.[99] In the base case, this translates to patients in the DBCd and BCd arms receiving [redacted] and [redacted] cycles of therapy, respectively. An additional 'maximum treatment duration' scenario was conducted, in which patients in the DBCd and BCd arms received 24 and 6 cycles of therapy, respectively. In each case, the corresponding number of cycles of treatment receive is calculated based on the treatment duration as presented in Table 50.

Table 50: Number of treatment cycles received in the base case and scenario analyses

Drug regimen	Treatment duration option	Treatment duration (months)	Calculated number of cycles
DBCd	Base case (ITT mean) (scenario 1)	[redacted]	[redacted]
	Maximum (scenario 2)	[redacted]	[redacted] [a]
	Base case (ITT mean) (scenario 1)	[redacted]	[redacted]
	Maximum (scenario 2)	[redacted]	[redacted]

[a] The number of cycles of treatment for patients in the DBCd arm is capped at 24 and the number of cycles for patients in the BCd arm is capped at 6 per the ANDROMEDA trial protocol.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone.
Source: ANDROMEDA 12-month landmark analysis (November 2020).[99]

Proportion of patients on first-line treatment

In the base case, patients with PR/NR at six months must move to subsequent treatment lines at this time, and thus receive first-line treatment for a maximum of six cycles. For patients with VGPR and CR, it is assumed that treatment would be received by all patients for the first six cycles regardless of the decision tree exit timepoint. This assumption that all patients would complete the full course of chemotherapy is based on ANDROMEDA trial data which show that [redacted]% of patients in the BCd arm received 6 cycles of treatment, and [redacted]% of patients in the DBCd arm received more than 6 cycles of treatment (i.e. by receiving 6 cycles of DBCd followed by daratumumab monotherapy); these data indicate that most patients completed the treatment course as per the trial protocol, and is supported by feedback from clinical experts that patients would remain on treatment if they were responding, unless they experienced poor tolerability.[26]

Beyond cycle 6, only patients achieving CR or VGPR (in the DBCd arm) were eligible to remain on first-line treatment. In the base case, a conservative assumption that all patients who are alive and have not progressed remain on treatment and thus incur treatment costs for the entire treatment duration – as per Table 50, this is [redacted] cycles and [redacted] cycles for DBCd and BCd, respectively. Given that most treatment discontinuations observed in the ANDROMEDA trial were due to progression or death, this assumption that all patients would choose to remain on treatment is considered reasonable albeit conservative.

B.3.3.4 Safety

The AEs considered in the model are based on the Grade III or IV AEs reported in >5% of patients in either treatment arm of the ANDROMEDA trial. Within the model, disutilities (see Section B.3.4 and costs (see Section B.3.5) associated with AEs are applied in cycle one to all patients in the appropriate treatment arm. The AEs included in the model and the probability of them occurring in each treatment arm are presented in Table 51.

Table 51: Adverse event probabilities used in the model base case

AE probability, %	DBCd	BCd
Cardiac failure	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Edema	[redacted]	[redacted]
Hypokalemia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Syncope	[redacted]	[redacted]

Abbreviations: AE: adverse event; BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone.

Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off)[98]

B.3.4 *Measurement and valuation of health effects*

Utility values for AL amyloidosis patients stratified by their initial haematologic response (CR, VGPR or PR/NR) were derived from the ANDROMEDA trial, which represented the most recent and relevant data in the population of interest during model development. Data from ANDROMEDA also informed a utility decrement for the '2L treatment' health state. These values were supplemented by Emin *et al*., (2016),[106] from which the utility values associated with 'End-stage organ failure' were sourced.

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

Health state utility values by haematologic response

As described in Section B.2.6.6, the ANDROMEDA trial collected HRQoL data using the EQ-5D-5L questionnaire.[35] These data were valued using a UK-based tariff, informed by van Hout *et al.,* (2012).[111] From these data, utility values could be derived for patients stratified by haematologic response. As the mean utility value for VGPR ([redacted]) was found to be lower than the mean utility value for PR/NR ([redacted]), it was considered that this value did not hold face validity. Therefore, a more clinically plausible VGPR utility value was calculated as the mean of the CR and PR/NR values, as presented in Table 52.

Table 52: Utility values for haematologic response derived from the ANDROMEDA trial

Haematologic response	Utility value	SE
CR	[redacted]	[redacted]
VGPR	[redacted][a]	[redacted]
PR/NR	[redacted]	[redacted]

[a] VGPR utility value was calculated as the mean of CR and PR.
Abbreviations: CR: complete response; NR: no response; PR: partial response; SE: standard error; VGPR: very good partial response.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Health state utilities were further explored based on feedback received from expert clinicians that they would expect any improvement in HRQoL to be delayed following initiation of treatment.[26] For this reason, a further scenario analysis was explored in which baseline utility values and post-treatment utility values at three months, six months and one year were sourced from clinicians to inform a scenario analysis. The utility values used in this scenario analysis are presented in Table 53.

Table 53: Utility values for haematologic response at baseline line and post-treatment derived from expert clinicians

Haematologic response	Baseline utility value	Three months post-treatment utility value	Six months post-treatment utility value	One year post-treatment utility value
CR	[redacted]	[redacted]	[redacted]	[redacted]
VGPR		[redacted]	[redacted]	[redacted]
PR/NR		[redacted]	[redacted]	[redacted]

* VGPR utility value was calculated as the mean of CR and PR.
Abbreviations: CR: complete response; NR: no response; PR: partial response; SE: standard error; VGPR: very good partial response.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Utility decrements for progression health states

Utility decrements for second line treatment and for end-stage organ failure were applied on a recurring per-cycle basis for as long as the patient remained within the respective health state. The second line treatment utility decrement was calculated as the difference between the mean baseline utility score and the mean utility value associated with 'progressive disease' from data collected in the ANDROMEDA trial.

Both structured and systematic literature reviews failed to identify data to inform a utility decrement for patients with end-stage organ failure due to AL amyloidosis. Therefore, a UK-based study on HRQoL for patients with advanced chronic heart failure (Emin *et al*., 2016) was used to calculate this utility value.[106] In this study, a utility value of 0.5 was reported for patients with chronic heart failure that had been assessed for heart transplant. According to trial data, the mean baseline utility value for patients in the ANDROMEDA trial was [redacted], meaning a difference between the baseline ANDROMEDA utility value and the utility value reported in Emin *et al*., (2016) was [redacted]. This value was utilised in the model to inform the utility decrement for patients in the end-stage organ failure' health state. A summary of progression-related health state utility values used in the model is presented in Table 54.

Table 54: Progression-related health state utility values

Health state	Recurring utility decrement	Source
Second-line treatment	[redacted]	ANDROMEDA CSR (14th February 2020 data cut-off).[98]
End-stage organ failure	[redacted]	ANDROMEDA CSR (14th February 2020 data cut-off)[98] and Emin *et al.,* (2016)[106]

Utility decrements for end-stage organ failure events

Utility decrements specific to end-stage organ failure interventions are applied in the model according to their occurrence. Since dialysis is a recurring treatment, its associated utility decrement is applied on a per-cycle basis to the proportion of patients requiring the intervention.

The decrement associated with dialysis (0.1) was sourced from a systematic literature review of utility-based HRQoL in chronic kidney disease treatments. According to this study, the utility value for patients on dialysis was 0.69, which represented a decrement of 0.1 compared to those with chronic kidney disease pre-treatment.[22]

For the utility decrement associated with solid organ transplant, there was no data source identified to inform this utility decrement, but a publication was available that provided the change in UK EQ-5D scores for pre- and post-liver transplantation (as a proxy for solid organ transplant) among 455 respondents.[22] The mean utility score at three months post-transplantation, after adjusting for informative dropout, was similar to the baseline utility score, suggesting that the transplantation event has a transient impact on quality of life. This supports its use as a one-time utility decrement in the model and that utilities are not significantly different following transplant. Due to the absence of data to parameterise this input and the brief HRQoL impact that would be expected, a conservative approach was taken which assumes that solid organ transplant was associated with no utility decrement.

A summary of end-stage organ failure utility decrements applied in the model is presented in Table 55.

Table 55: End stage organ failure utility decrements

Intervention	Recurring utility decrement	Source
Dialysis (recurring)	0.1	Wyld *et al.*, (2012)[22]
Organ transplant (one-time)	0	Assumption

B.3.4.2 Mapping

No mapping was performed in this analysis as EQ-5D-5L data were sourced directly from the ANDROMEDA trial.

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

An SLR was conducted in April 2021 to identify any relevant HRQoL data for people with newly diagnosed AL amyloidosis. In total, 13 studies reporting health-related quality of life data associated with the treatment of people with newly diagnosed AL amyloidosis were identified. None of the included studies reported utility values or mapping algorithms. Full details of the SLR search strategy, study selection process and results are reported in Appendix H.

Since the SLR yielded no results related to utility data associated with daratumumab treatment of adults with AL amyloidosis, the utility values collected in ANDROMEDA were applied in the base case.

B.3.4.4 Adverse reactions

As AEs can have a meaningful impact on patient quality of life, disutilities associated with Grade III or IV AEs reported in >5% of patients in either treatment arm of the ANDROMEDA trial are considered in the model (Table 56). Disutilities associated with treatment-related AEs in AL amyloidosis were not identified in the SLR for HRQoL. As such, an additional, more generic

literature search was conducted to identify AE disutility values related to oncology and/or chemotherapy; this search was successful in identifying published literature sources to inform each AE utility decrement. It was assumed that utility decrements associated with AEs would not last a whole cycle, and a duration of 21 days for all AEs was thus assumed in alignment with the definition of a non-elective long stay AE.[120]

In alignment with how AE costs are applied within the model, the total QALYs lost per treatment arm were calculated as a sum of the average QALYs lost per patient and was applied in cycle one to all patients in the appropriate treatment arm (Table 57). The impact of this one-time decrement is assumed to be minimal, given that treatment is a fixed course of therapy with limited duration.

Table 56: Adverse event utility decrements and durations

AE	One-time utility decrement	Duration of AE, days	Average QALY lost per event	Average QALY lost per patient		Source of utility decrement
				DBCd	BCd	
Cardiac failure	0.1034	21	0.006	0.0003	0.0002	Decrement: Sullivan 2011[121] Duration: Assumption*
Diarrhoea	0.176	21	0.010	0.0006	0.0004	Decrement: Stein 2008[122] Duration: Assumption*
Oedema	0.06	21	0.003	0.0001	0.0002	Decrement: Brown 2001[123] Duration: Assumption*
Hypokalemia	0.02	21	0.001	0.00002	0.0001	Decrement: Sullivan 2011[121] Duration: Assumption*
Lymphopenia	0.09	21	0.005	0.0007	0.0005	Decrement: Assumed equal to neutropenia Duration: Assumption*
Neutropenia	0.09	21	0.005	0.0003	0.0001	Decrement: Nafees 2008[124] Duration: Assumption*
Pneumonia	0.2	21	0.011	0.0009	0.0005	Decrement: Beusterien 2010[125] Duration: Assumption*
Syncope	0.0039	21	0.00022	0.00001	0.00001	Decrement: Sullivan 2011[121] Duration: Assumption*

Footnote: *Assumed 21-day duration for utility decrement in alignment with the definition of a “NEL” AE.
Abbreviations: AE: adverse event; BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NEL: non-elective long stay; QALY: quality-adjusted life-year.

Table 57: Total adverse event disutilities by treatment arm

Treatment arm	Mean total AE disutility per patient
DBCd	0.0029
BCd	0.0020

Abbreviations: AE: adverse event; BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the utility values used in the cost-effectiveness analysis is provided in Table 58.

Table 58: Summary of utility values for cost-effectiveness analysis

State	Utility value, mean	Reference in submission	Source
CR	[redacted]	Section B.3.4.1	ANDROMEDA trial data
VGPR	[redacted]		
PR/NR	[redacted]		
Progression to second line treatment	[redacted]	Section B.3.4.1	ANDROMEDA trial
Progression to end-stage organ failure	[redacted]		ANDROMEDA trial and Emin *et al.*, (2016)[106]
Dialysis in end-stage organ failure	0.100		Wyld *et al.*, (2012)[22]
DBCd	0.0029	Section B.3.4.1	Various literature sources
BCd	0.0020		

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

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

An SLR was conducted in February 2021 to identify any relevant healthcare resource use data for people with newly diagnosed AL amyloidosis. In total, 16 studies reporting resource use outcomes and costs associated with the treatment of people with newly diagnosed AL amyloidosis were identified, although only one was conducted in the UK.[126] Full details of the SLR search strategy, study selection process and results are reported in Appendix I.

The cost-utility analysis was conducted from the perspective of the NHS in England and therefore included only costs that would be incurred by the healthcare system. Appropriate sources of unit costs, such as NHS reference costs (2018–19),[108] the British National Formulary (BNF),[112] PSSRU,[107] and drugs and pharmaceutical electronic market information tool (eMIT)[113] were used for cost inputs in the model. Furthermore, in order to source accurate estimates of healthcare resource use for the treatment of AL amyloidosis in the UK, a modified Delphi panel was conducted in which resource use estimates were gathered from seven UK-based expert healthcare professionals (clinicians and specialist nurses) with the aim of achieving consensus for all resource use inputs. The Delphi questionnaire rounds were designed in collaboration with a 'lead clinician', who was a practising Consultant Haematologist in the NHS with substantial experience in treating AL amyloidosis. The methodology of the Delphi panel is presented in a report provided in the reference pack.

The following cost types were included in the model: first-line acquisition costs, first-line drug administration costs, first-line co-medication costs, disease monitoring costs, first-line AE

management costs, second-line drug acquisition costs, end-stage organ failure management costs, health state-specific healthcare resource use costs, and end of life costs.

B.3.5.1 Intervention and comparators' costs and resource use

First line drug acquisition costs

The dosing schedules for each medicine within the DBCd and BCd regimens are presented in Table 59.

Table 59: DBCd and BCd dosing regimens

Treatment	Dosing schedule
Daratumumab	Weekly for cycles 1–2 (Days 1, 8, 15, 22) Every 2 weeks for cycles 3–6 (Days 1, 15) Every 4 weeks for cycle 7+ (Day 1) For a maximum of 24 cycles
Bortezomib	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles
Cyclophosphamide	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles
Dexamethasone	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles

The duration of one cycle was 28 days.
Source: ANDROMEDA protocol[35]

Relative dose intensities and drug wastage were also considered in the cost calculations. Drug wastage was assumed to occur for all oral, SC, and IV therapies and was applied in drug cost calculations by incorporating the cost of an entire package or vial of drug even if its constituents were not completely depleted. Where relevant, RDIs were applied in calculating total per cycle drug costs. The mean RDIs for each drug regimen, as reported in the ANDROMEDA clinical study report, are presented in Table 60.

Table 60: Mean relative dose intensities

Drug regimen	RDI	Source
DBCd	[redacted]	ANDROMEDA CSR[98]
BCd	[redacted]	

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; RDI: relative drug intensity.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Drug formulations and the unit costs for each medicine used as part of the DBCd and BCd regimens are presented in Table 61.

Table 61: First-line drug acquisition costs

Treatment	Unit strength	Unit type	Units per pack	Price per pack	Price per unit	Source
Daratumumab (with PAS)	1,800 mg	Vial	1	[redacted]	[redacted]	BNF 2021[112]
Bortezomib	3.5 mg	Vial	1	£276.78	£276.78	eMIT 2021[113]
Cyclophosphamide	50 mg	Tab	100	£52.46	£0.52	eMIT 2021[113]
Dexamethasone	8 mg	Tab	50	£79.61	£1.59	eMIT 2021[113]

Abbreviations: BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool; PAS: patient access scheme.

Table 64 presents the calculated costs per dose and per cycle as used in the base case. The treatment regimen for DBCd has two phases, namely the initial phase of daratumumab plus BCd combination therapy for 6 cycles and the post-treatment daratumumab monotherapy phase for up to an additional 18 cycles. Within the first phase of treatment, the number of daratumumab administrations differs depending on the cycle. In cycles 1 and 2, daratumumab is administered four times per cycle (in combination with BCd).[35] In cycles 3 to 6, daratumumab is administered twice per cycle (in combination with BCd). Once patients enter the daratumumab monotherapy phase, daratumumab is administered once per cycle. Therefore, there are three different DBCd drug acquisition costs per cycle used in the model.

First-line drug acquisition costs for bortezomib and cyclophosphamide were calculated based on the mean patient body surface area (BSA; 1.84 m^2) as reported in the ANDROMEDA trial population.[98] Vials were assumed to be one-time use only. Therefore, it was assumed that vial sharing was not permitted, and the base case drug dosing calculations included wastage. Both daratumumab SC and dexamethasone are administered at a fixed dosage and therefore their associated drug acquisition costs are independent of body weight or BSA.

Table 62: Drug costs cycle

Treatment	Cost per Cycle
DBCd (Cycles 1–2)	[redacted]
DBCd (Cycles 3–6)	[redacted]
DBCd (Cycles 7+)	[redacted]
BCd	£1,159.95

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone.

First-line drug administration costs

The route of drug administration (i.e. SC or oral [PO]) and frequencies mirrored those outlined in the ANDROMEDA clinical trial protocol.[35] For each medicine, if there an option between IV and PO or SC (e.g. cyclophosphamide),[42] the non-IV route was selected for the analysis because fluid volume overload (that may result from IV infusion) is a safety concern associated with IV drug administration for patients with AL amyloidosis. As such, the safer administration option was assumed in the analysis. The administration routes of each drug in the DBCd and BCd regimens is presented in Table 63.

Table 63: Drug administration routes

Type of administration	Unit cost
DBCd	
Daratumumab SC	SC injection (hospital)
Bortezomib	SC injection (hospital)
Cyclophosphamide	Oral
Dexamethasone	Oral
BCd	
Bortezomib	SC injection (hospital)
Cyclophosphamide	Oral
Dexamethasone	Oral

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; IV: intravenous; SC: subcutaneous.

The SC administration cost was calculated based on the cost per hour of a band five nurse (£37.00)[115] and the time required to administer SC injections of daratumumab and bortezomib. According to the ANDROMEDA clinical study report, the median SC injection duration for daratumumab was five minutes.[98] Because no duration for SC injection of bortezomib was specified in the EMA product information document[127] or the bortezomib reconstitution booklet,[128] the SC injection time was assumed equivalent to daratumumab. In the analysis, a five-minute SC injection of daratumumab or bortezomib was associated with a cost of £3.08. Both cyclophosphamide and dexamethasone are administered PO and therefore do not incur any administration costs. A summary of drug administration costs included in the model is presented in Table 64. For a given treatment regimen, the total administration time was the sum of individual administration times for all drugs included within the regimen, as the combination of therapies were assumed to be given in sequence.

Table 64: Administration unit costs

Type of administration	Unit cost	Source
SC	£3.08	PSSRU 2019 (5 mins band five nurse time),[115] CSR[98]
PO	£0	Assumption

Abbreviations: IV: intravenous; PO: oral; SC: subcutaneous.

Co-medication costs

The model included pre- and post-treatment medications for both the DBCd and BCd regimens. Concomitant medications for each comparator were sourced from the ANDROMEDA clinical trial protocol.[35] Only the additional medications that were recommended or required for all patients on a therapy were included. Additional medications that were provided only to select patients or those that were administered per physician discretion were not included because the proportion of patients who would receive these medications was not explicitly reported. Per the ANDROMEDA clinical trial protocol,[35] paracetamol, dexamethasone, diphenhydramine, and montelukast were administered to patients receiving daratumumab to prevent infusion-related reactions. Co-medications for each drug therapy included in the CUA, and their respective administration frequencies, are presented in Table 65. The unit costs for co-medications were sourced from the BNF and the eMIT and are presented in Table 66.[112, 113] For a given treatment regimen, the total co-medication cost was based on the unit costs, frequency of dose, and the proportion of patients receiving each co-medication.

Table 65: First-line co-medications per drug regimen

Co-medication	Proportion of Patients Receiving Co-medication	Dose (mg)	Dose Frequency	Frequency Unit
DBCd				
Aciclovir	100%	400	2	per day
Diphenhydramine PO	100%	50	1	per daratumumab SC administration
Dexamethasone PO [a]	100%	20	5	per entire treatment duration
Montelukast	86%	10	1	per entire treatment duration
Methylprednisolone PO[b]	100%	20	10	per entire treatment duration
Paracetamol PO	100%	1,000	1	per daratumumab SC administration
BCd				
Aciclovir	100%	400	2	per day

[a] According to the ANDROMEDA clinical protocol, dexamethasone was to be administered as a pre-treatment prior to each dose of daratumumab monotherapy after completing six cycles of DBCd combination therapy. The dose frequency for dexamethasone represents one dose for each administration of daratumumab monotherapy. [b] According to the ANDROMEDA clinical protocol, patients receiving daratumumab monotherapy after completing six cycles of DBCd will receive an oral long- or intermediate-acting corticosteroid (e.g. methylprednisolone) on the two days following daratumumab administration.[35] The frequency for methylprednisolone represents two doses for each administration of daratumumab monotherapy.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; SC: subcutaneous.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[98]

Table 66: First-line co-medication unit costs

Co-medication	Drug units per Pack	Strength (mg)	Cost per pack	Source
Aciclovir	25	200	£0.52	eMIT 2021[113]
Diphenhydramine	30	10	£6.92	BNF 2021[112]
Dexamethasone	50	8	£79.61	eMIT 2021[113]
Montelukast	28	10	£0.71	eMIT 2021[113]
Methylprednisolone	30	2	£3.88	BNF 20[112]21
Paracetamol	100	500	£0.41	eMIT 2021[113]

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool.

B.3.5.2 Health-state unit costs and resource use

Disease monitoring costs

Monitoring costs are included in the model for the first-line 'On-Tx' health state and 'Off First-line Treatment/fixed daratumumab treatment' (Off Tx/FDT). Resource use frequencies were informed by the modified Delphi panel, whilst unit costs were sourced from the NHS Reference Costs 2018/19,[114] or alternatively, published literature sources. All monitoring unit costs are presented in Table 67. Frequency of resource use for disease monitoring in the 'On Tx', 'Off Tx/FDT' and 'Off Tx' health states are presented in Table 68.

Table 67: Disease monitoring costs per unit

Item	Unit cost	Source
Troponin T test	£2.79	NHS 2018/2019 (DAPS05)[114]
Serum FLC assessment	£1.10	NHS 2018/2019 (DAPS04)[114]
NT-proBNP assay	£27.10	Chapman 2015;[129] PSSRU 2020[107]
Cardiac MRI	£272.41	NHS 2018/2019 (RD08Z)[114]
Echocardiogram	£72.57	NHS 2018/2019 (RD51A)[114]
eGFR	£282.58	NHS 2018/2019 (RN27A)[114]
Urine protein:creatinine test	£3.46	Kerr 2012[130]
Liver panel	£6.69	NICE 2015[131]
Paraprotein test via serum electrophoresis/ immunofixation	£2.79	NHS 2018/2019 (DAPS04)[114]
Full blood count	£6.00	National Guideline Centre. Preoperative tests. 2015[131]

Abbreviations: eGFR: estimated glomerular filtration rate; FLC: free light-chains; MRI: magnetic resonance imaging; NHS: National Health Service; NT-proBNP: N-terminal prohormone brain natriuretic peptide; PSSRU: Personal Social Services Research Unit.

Table 68: Monitoring frequency of resource use by Markov health state

Item	On-treatment			FDT			Off-treatment		
	Proportion of Patients Requiring Item	Item Frequency	Frequency Unit	Proportion of Patients Requiring Item	Item Frequency	Frequency Unit	Proportion of Patients Requiring Item	Item Frequency	Frequency Unit
Troponin T test	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle
Serum FLC assessment	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle
NT-proBNP assay	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle
Cardiac MRI	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle
Echocardiogram	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	Per cycle
eGFR	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle
Urine protein:creatinine Test	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle
Liver panel	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle
Paraprotein test via serum electrophoresis/ immunofixation	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle
Full blood count	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle	[redacted]	[redacted]	per cycle

Abbreviations: eGFR: estimated glomerular filtration rate; FDT: fixed-dose treatment; FLC: free light-chains; MRI: magnetic resonance imaging; NHS: National Health Service; NT-proBNP: N-terminal prohormone brain natriuretic peptide; PSSRU: Personal Social Services Research Unit.
Source: Janssen modified UK Delphi panel. 2021[116]

Healthcare resource use costs

Healthcare resource use costs are included in the model for all Markov health states. Resource use frequencies were informed by the modified Delphi panel, whilst unit costs were sourced from the NHS Reference Costs 2018/19[114] and PSSRU 2020.[107] Healthcare resource use unit costs are presented in Table 69, whilst frequencies are presented in Table 70.

Table 69: Healthcare resource use unit costs

Item	Unit Cost	Source
Long hospital stay (≤24h)	£3,366.00	PSSRU 2020 (Non-elective inpatient long stay)[107]
Short hospital stay (>24h)	£602.00	PSSRU 2020 (Non-elective inpatient short stay)[107]
Accident and emergency visit	£166.00	NHS 2018/2019 (Unit cost for emergency visit)[114]
Intensive care unit	£1,428.00	NHS 2018/2019 (Critical care codes XC01Z:XC07Z)[114]
Haematologist visit	£59.50	PSSRU 2020 (Hospital-based doctors; assumed 30-min appointment)[107]
Specialist nurse visit	£25.00	PSSRU 2020 (Band 6 nurse)[107]
Nephrologist visit	£59.50	PSSRU 2020 (Hospital-based doctors; assumed 30-min appointment)[107]
Cardiologist visit	£59.50	PSSRU 2020 (Hospital-based doctors; assumed 30-min appointment)[107]

Abbreviations: NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

Table 70: Healthcare resource use frequencies in the Markov model

Item	On-treatment (first-line)		FDT/Off-treatment		Second-line treatment		End-stage organ failure	
	Proportion of patients requiring item	Frequency of resource utilisation per cycle	Proportion of patients requiring item	Frequency of resource utilisation per cycle	Proportion of patients requiring item	Frequency of resource utilisation per cycle	Proportion of patients requiring item	Frequency of resource utilisation per cycle
Accident and emergency visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long hospital stay (≤24h)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Short hospital stay (>24h)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensive care unit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematologist visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specialist nurse visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrologist visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiologist visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FDT: fixed-dose treatment
Source: Janssen modified UK Delphi panel, 2021.[116]

Second-line treatment regimen costs

As part of the advisory board with UK expert clinicians,[26] feedback was sought on the later-line treatment regimens used for AL amyloidosis in the UK and the proportions of patients typically receiving each treatment. In the base case, second-line treatments costs are applied upon entry into the 'Second-line' health state. A scenario analysis has also been conducted in which an additional third line of treatment is included, the cost of which is applied alongside the second-line therapies for simplicity. As not all patients may go on to receive third-line therapy, this may overestimate third-line costs.

Drug acquisition and administration costs were included when calculating the total cost of a later-line treatment regimen. Acquisitions costs were sourced from the BNF or eMIT,[112, 113] as applicable, whilst relevant administration costs were as per the 'First-line drug administration costs' section in B.3.5.1. Dosing schedules and treatment durations were informed by either the SmPCs for the treatments in each regimen or were assumptions.

The second-line therapies included in the model and the associated proportions are presented in Table 71 whilst treatment durations and total costs are presented in Table 72. The equivalent tables for third-line therapy are presented in Table 73 and Table 74, respectively.

Table 71: Second-line treatment regimen acquisition costs (base case)

Second-line treatment regimen	Proportion of patients receiving regimen
Lenalidomide + dexamethasone (Rd)	75%
Melphalan + dexamethasone (Md)	5%
Carfilzomib + dexamethasone (Kd)	10%
Bortezomib + cyclophosphamide + dexamethasone (BCd)	10%

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; Kd: carfilzomib and dexamethasone; Md: melphalan and dexamethasone; Rd: lenalidomide and dexamethasone.
Source: UK clinical expert advisory board.[26]

Table 72: Second-line treatment regimen duration and cost (acquisition and administration)

Second-line treatment regimen	Number of cycles	Total cost of treatment course	Source of treatment duration
Lenalidomide + dexamethasone (Rd)	6	£26,293.98	Assumption (same as BCd)
Melphalan + dexamethasone (Md)	18	£1,880.14	Jaccard *et al.*, 2007[132]
Carfilzomib + dexamethasone (Kd)	18	£209,329.19	Carfilzomib SmPC[133]
Bortezomib + cyclophosphamide + dexamethasone (BCd)	6	£7,033.61	Assumption (same as first-line treatment)

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; Kd: carfilzomib and dexamethasone; Md: melphalan and dexamethasone; Rd: lenalidomide and dexamethasone.

Table 73: Third-line treatment regimen acquisition costs (scenario analysis)

Third-line treatment regimen	Proportion of patients receiving regimen (DBCd arm)	Proportion of patients receiving regimen (BCd arm)

Panbinostat + bortezomib + dexamethasone (PBd)	0%	0%
Pomalidomide + dexamethasone (Pd)	70%	80%
Lenalidomide + dexamethasone (Rd)	30%	20%

Abbreviations: PBd: panbinostat, botezomib and dexamethasone; Pd: pomalidomide and dexamethasone; Rd: lenalidomide and dexamethasone.
Source: UK clinical expert advisory board[26]

Table 74: Third-line treatment regimen duration and cost (acquisition and administration)

Third-line treatment regimen	Number of cycles	Total cost of treatment course	Source of treatment duration
Panbinostat + bortezomib + dexamethasone (PBd)	16	£125,635.83	Panbinostat SmPC[134]
Pomalidomide + dexamethasone (Pd)	16	£142,653.50	Pomalidomide SmPC[135]
Lenalidomide + dexamethasone (Rd)	6	£26,293.98	Assumption (same as BCd)

Abbreviations: PBd: panbinostat, botezomib and dexamethasone; Pd: pomalidomide and dexamethasone; Rd: lenalidomide and dexamethasone.

End-stage organ failure costs

Treatment for end-stage organ failure was included in the model for the 'End-stage organ failure' health state. Informed by the Delphi panel lead clinician's guidance of treatments utilised for end-stage organ failure in NHS clinical practice, recurring costs were included for haemodialysis and peritoneal dialysis, whilst one-off costs were included for heart and kidney transplant. Unit costs were sourced from the NHS Reference Costs 2018/19 (Table 75 and Table 76),[114] whilst resource use frequencies were informed by the modified Delphi panel (Table 77 and Table 78).[116]

Table 75: Recurring treatments for end-stage organ failure unit costs

Item	Unit cost	Source
Cost per haemodialysis session	£214.00	NHS 2018/2019
Cost of peritoneal dialysis	£66.16	NHS 2018/2019, Continuous Ambulatory Peritoneal Dialysis, 19 years and over, LD11A

Table 76: One-off treatments for end-stage organ failure unit costs

Item	Unit cost	Source
Heart transplant	£55,937.00	NHS 2018/2019 (mean of ED04Z and ED05Z)
Kidney transplant	£12,629.00	NHS 2018/2019 (mean of LA01A, LA02A, and LA03A)

Table 77: Recurring treatments for end-stage organ failure resource use frequencies

Item	Proportion of end-stage organ failure patients requiring item	Frequency per cycle
Haemodialysis	[redacted]	[redacted]
Peritoneal dialysis	[redacted]	[redacted]

Source: Janssen modified UK Delphi panel, 2021.[116]

Table 78: One-off treatments for end-stage organ failure resource use frequencies

Item	Proportion of end-stage organ failure patients requiring item (one-off basis over model time horizon)
Heart transplant	[redacted]
Kidney transplant	[redacted]

Source: Janssen modified UK Delphi panel, 2021.[116]

B.3.5.3 Adverse reaction unit costs and resource use

AEs were defined as grade ≥3 AEs occurring in ≥5% of patients in either treatment arm of the ANDROMEDA trial. AE management costs were sourced from the 2018/2019 National Schedule of NHS costs (based on non-elective long [NEL] stay costs) to reflect the severity of grade ≥3 AEs.[114] A summary of AE management costs is presented in Table 79. The cost of AE management was applied in the model as a one-time cost per patient in the first cycle. Given the low AE rate and short duration of treatment as a fixed course of chemotherapy, a one-off cost has a minimal impact on the total cost of treatment.

Table 79: Adverse event unit costs

Adverse event (Grade ≥3 or NEL)	Unit cost	Code/Description	Source(s)/Notes
Cardiac failure	£2,957.33	Weighted cost: EB03A-E NEL	NHS 2018/2019[114]
Diarrhoea	£2,109.23	Weighted cost: FD01F-J NEL	NHS 2018/2019[114]
Edema	£2,432.30	Weighted cost: KC05G-N NEL	NHS 2018/2019[114]
Hypokalemia	£2,432.30	Weighted cost: KC05G-N NEL	NHS 2018/2019[114]
Lymphopenia	£3,288.93	SA08G NEL	NHS 2018/2019[114]
Neutropenia	£2,617.33	SA08G NEL	NHS 2018/2019[114]
Pneumonia	£2,701.77	Weighted cost: DZ11K-V NEL	NHS 2018/2019[114]
Syncope	£2,059.77	Weighted cost: EB08A-E NEL	NHS 2018/2019[114]

Abbreviations: NEL: non-elective long stay; NHS: National Health Service.

B.3.5.4 Miscellaneous unit costs and resource use

End of life costs

Patients who transition to the death health state can incur a one-time cost for end of life. Terminal care costs were included in the analysis and reflect those associated with the final month of life based on acute hospital care and physician visits.[136] The study informing this cost was a UK-based retrospective review of patient-level datasets to estimate hospital and non-hospital related costs in the final months of life and does not specifically reflect an AL amyloidosis patient subset. Terminal care costs were inflated from 2011 to 2020 Pounds Sterling using inflation rates from the NHS cost inflation index (NHSCII).[107] The terminal care cost included in the model is presented in Table 80 and is applied in full to all patients who died in each model cycle.

Table 80: End of life costs

Item	Cost	Source
End of Life Costs [a]	£3,561.88	Georghiou and Bardsley 2014;[136] PSSRU 2020[107]

[a] Represents terminal care costs for the final month of life.
Abbreviations: PSSRU: Personal Social Services Research Unit.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

A summary of the base case model inputs and settings are presented in Table 81.

Table 81: Summary of variables applied in the economic model base case

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution	Reference to section in submission
Model characteristics			
Time horizon	35 years	NA	Section B.3.2
Cycle length	28 days	NA	Section B.3.2
Discount rate effects	3.5%	NA	Section B.3.2
Discount rate costs	3.5%	NA	Section B.3.2
Patient characteristics			
Starting age, years	[redacted]	[redacted]	Section B.3.3.1
Proportion male	[redacted]	SE assumed to be 10% of the mean	Section B.3.3.1
Mean weight, kg	[redacted]	[redacted]	Section B.3.3.1
Mean body surface area, m^2	[redacted]	[redacted]	Section B.3.3.1
Efficacy data			
DBCd: Patient distribution at six monthsbased on haematologic response (six-month exit from decision tree)	CR: 50.3% VGPR: 21.5% PR/NR: 15.4% Dead: 12.8%	Not varied in order to align precisely with ANDROMEDA data	Section B.3.3.2
BCd: Patient distribution at six months based on haematologic response (six-month exit from decision tree)	CR: 14.0% VGPR: 27.5% PR/NR: 47.2% Dead: 11.4%	Not varied in order to align precisely with ANDROMEDA data	Section B.3.3.2
PR/NR survival function	Log-normal	Cholesky decomposition	Section B.3.3.3
VGPR survival function	Log-normal	Cholesky decomposition	Section B.3.3.3
CR survival function	Gompertz	Cholesky decomposition	Section B.3.3.3
Distribution of PR:NR patients	[redacted]	SE assumed to be 10% of the mean (Beta)	Section B.3.3.3

DBCd treatment duration, months	[redacted]	[redacted]	Section B.3.3.3
BCd treatment duration, months	[redacted]	[redacted]	Section B.3.3.3
First-line drug therapy costs (per cycle)			
DBCd (Cycles 1–2) DBCd (Cycles 3–6) DBCd (Cycle 7+)	[redacted]	Not varied in PSA	Section B.3.5.1
BCd	£1,159.95	Not varied in PSA	Section B.3.5.1
First-line drug dosing			
Daratumumab	Cycles 1–2: 1,800 mg; 4 administrations per cycle Cycles 3–6: 1,800 mg; 2 administrations per cycle Cycle 7+: 1,800 mg; 1 administration per cycle	NA	Section B.3.5.1
Bortezomib	1.3 mg/m^2; 4 administrations per cycle	NA	Section B.3.5.1
Cyclophosphamide	300 mg/m^2; 4 administrations per cycle	NA	Section B.3.5.1
Dexamethasone	40 mg; administrations per cycle	NA	Section B.3.5.1
First-line drug RDI			
DBCd	[redacted]	[redacted]	Section B.3.5.1
BCd	[redacted]	[redacted]	Section B.3.5.1
First-line drug administration costs (per cycle)			
DBCd (Cycles 1–2)	£24.64	SE assumed to be 10% of the mean	Section B.3.5.1
DBCd (Cycles 3–6)	£18.48	SE assumed to be 10% of the mean	Section B.3.5.1
DBCd (Cycles 7+)	£3.08	SE assumed to be 10% of the mean	Section B.3.5.1
BCd	£12.32	SE assumed to be 10% of the mean	Section B.3.5.1
First-line co-medication costs (per cycle)			
DBCd	£6.22	SE assumed to be 10% of the mean	Section B.3.5.1
BCd	£2.33	SE assumed to be 10% of the mean	Section B.3.5.1
First-line disease monitoring costs (per cycle)			
1L Tx	£297.66	SE assumed to be 10% of the mean	Section B.3.5.2
FDT	£311.35	SE assumed to be 10% of the mean	Section B.3.5.2

Off Tx	£167.33	SE assumed to be 10% of the mean	Section B.3.5.2
Adverse event management costs (average total cost)			
DBCd	£1,269.83	SE assumed to be 10% of the mean	Section B.3.5.3
BCd	£1,081.16	SE assumed to be 10% of the mean	Section B.3.5.3
AE utility decrement (average per patient)			
DBCd	0.0029	SE assumed to be 10% of the mean	Section B.3.4.4
BCd	0.0020	SE assumed to be 10% of the mean	Section B.3.4.4
Second-line drug therapy costs			
Total second-line drug therapy costs for DBCd patients	£41,450.77	SE assumed to be 10% of the mean	Section B.3.5.2
Total second-line drug therapy costs for BCd patients	£41,450.77	SE assumed to be 10% of the mean	Section B.3.5.2
Organ failure costs			
Recurring organ failure costs per cycle	£4,24.23	SE assumed to be 10% of the mean	Section B.3.5.2
Total one-off treatment costs	£1,064.53	SE assumed to be 10% of the mean	Section B.3.5.2
Healthcare resource use costs (per cycle)			
1L Tx	£145.70	SE assumed to be 10% of the mean	Section B.3.5.2
Off Tx/FDT	£85.00	SE assumed to be 10% of the mean	Section B.3.5.2
2L Tx	£206.86	SE assumed to be 10% of the mean	Section B.3.5.2
End-stage Organ Failure	£223.26	SE assumed to be 10% of the mean	Section B.3.5.2
End of life costs (total)			
Costs associated with final month of life	£3,561.88	SE assumed to be 10% of the mean	Section B.3.5.4
Utilities			
CR	[redacted]	[redacted]	Section B.3.4.1
VGPR	[redacted]	[redacted]	Section B.3.4.1
PR/NR	[redacted]	[redacted]	Section B.3.4.1
2L Tx health state utility decrement	[redacted]	SE assumed to be 10% of the mean	Section B.3.4.1
End-stage organ failure health state utility decrement	[redacted]	SE assumed to be 10% of the mean	Section B.3.4.1
Haemodialysis utility decrement	0.1	SE assumed to be 10% of the mean	Section B.3.4.1

Abbreviations: 1L: first-line; 2L: second-line; AE: adverse event; BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; CR: complete response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; FDT: fixed daratumumab treatment; NA: not applicable; NR: no response; PR: partial response; SE: standard error; Tx: treatment; VGPR: very good partial response.

B.3.6.2 Assumptions

A list of the assumptions made in the base case analysis and their justifications is provided in Table 82. Where appropriate, the exploration of the potential impact of these assumptions in a scenario analysis is noted.

Table 82: List of assumptions for the base case analysis

Model input	Description of base case assumption	Justification
OS surrogacy	Haematologic response is a treatment-independent surrogate for OS. Rates of haematologic response achieved at six months observed in ANDROMEDA are assumed to predict the OS curves for DBCd and BCd.	The relationship between depth of haematologic response and improved OS is strongly supported in published literature and by clinical expert opinion and is the basis for treatment guidelines recommending that the goal of AL amyloidosis therapy is to achieve at least VGPR.[2, 27, 31, 83, 92, 93, 137-140] Pooled survival data from ANDROMEDA stratified by CR vs. non CR status further supports this assumption; patients who achieved CR had prolonged OS compared with those with responses less than CR (HR: [redacted]).
Missing data in the decision tree	For the distribution of haematologic response in the decision tree, any non-evaluable haematologic response at a specific cycle was classified as PR/NR.	To use all the data available and to avoid overestimating treatment benefit, this was a simplistic assumption that was applied equally to both treatment groups.
Best overall haematologic response	Best overall haematologic response is achieved once patients exit the decision tree; upon exit from the decision tree, haematologic response does not change	The median time to haematologic response reported in the ANDROMEDA trial was 85 days for BCd patients and 60 days for DBCd patients. Therefore, CHR patients had achieved their best response prior to three months (i.e. the earliest possible exit from the decision tree).[98] Data from the ANDROMEDA trial also indicate that patients who respond to treatment have a durable response and continue to respond to treatment without haematologic progression.[98]
Partial and non-response	Patients achieving PR and NR were grouped together because they would be managed in a similar manner in clinical practice.	Patients achieving PR or NR are considered to have inadequate response to treatment and will proceed directly to second-line treatment.[45] This was supported by clinical expert opinion at the advisory board.[26]
Major organ failure in the decision tree	Major organ failure is not captured within decision tree.	Very few MOD events occurred in the first data cut of the trial, supporting that end stage organ failure would be unlikely to occur during the time span of the decision tree.
Long-term survival	Long-term survival by haematologic response (i.e. treatment-independent) was based on OS extrapolations of published data (Palladini *et al.,* (2012).[2] The OS curves for PR/NR, VGPR, and CR were generated based on independent extrapolations of their raw KM data.	To project long-term survival over the lifetime time horizon, methodological best practices were followed for extrapolating and choosing the most clinically plausible distributions.[117]

Risk of mortality	Risk of mortality of patients with AL amyloidosis in the model cannot be lower than the risk of mortality of the general population.	UK general population mortality rates were implemented in the model such that the extrapolations will be adjusted to ensure that the hazard of death at each cycle did not drop below that of the general population (ie, predicted survival could not exceed general population).
Transition probabilities over time	Mortality distributions (from cycles 4–6 and from cycle 7+) and transition probabilities are assumed to be constant over time.	There is not enough long-term trial data to indicate when/if health state-specific mortality risks and transition probabillities change over time. Since mortality risk by health state can change once patients finish treatment, mortality distributions pre- and post-cycle 6 were estimated. Very few deaths were captured in the trial after cycle 6 due to short follow-up; therefore, a fixed distribution assumption was applied. The KM curves used to estimate the transition probabilities were generally linear, and thus it was a pragmatic assumption to use a constant probability.
Probability of transition to end-stage organ failure	The transition probabilities for '1L Tx' to 'End-stage Organ Failure' are the same for '2L Tx' to 'End-stage Organ Failure'.	Due to a lack of MOD-PFS events reported at the first clinical cut-off, in which no events were reported for patients with VGPR while on second-line treatment, the transition probability for '1L Tx' to 'End-stage Organ Failure' was used instead of zero.
	The probabilities of transition to 'End-stage Organ Failure' from any other health state are informed by time-to-MOD-PFS data from the ANDROMEDA trial.	Ideally, the transition probabilities to 'End-stage organ failure' would be based strictly on events pertaining to cardiac or renal failure; however, as there were too few such events observed in ANDROMEDA at the time of CUA development, MOD-PFS was used (with death events removed). Although a potential limitation of using MOD-PFS is the risk of overestimating the transition probabilities to 'End-stage Organ Failure', this was considered a simplistic assumption implemented due to data immaturity
Movement to subsequent therapy based on haematologic response	All patients with VGPR and CR complete treatment and receive the first six cycles of treatment. Patients with PR/NR must switch to a subsequent therapy after six cycles of treatment.	As outlined in the ANDROMEDA protocol, patients were to receive 6 cycles of BCd (BCd arm) or 6 cycles of DBCd followed by up to 18 cycles of daratumumab monotherapy, unless they had a suboptimal (≤PR) haematologic response and could be switched to another therapy after six cycles.[35] Since there is no clinical rationale for patients with deep haematologic response (≥VGPR) to change their treatment, it was assumed that all patients in the BCd treatment arm with VGPR or CR would receive up to the full six cycles of BCd and then cease treatment. Similarly, all patients in the DBCd arm with VGPR or CR were assumed to receive the first six cycles of DBCd (in alignment with the ANDROMEDA CSR).[98] After the first six cycles, patients in the DBCd arm could continue with daratumumab monotherapy.

Drug administration	For any drug with multiple modes of administration, IV was not selected as the administration route of choice for estimating cost of administration.	IV infusion may cause fluid volume overload in patients with AL amyloidosis; therefore, the safer alternative mode was selected for costing.
Drug wastage	Drug wastage and RDI were accounted for in drug costs.	Important to accurately calculate the true (real-world) treatment cost for an average patient.
Cost of subsequent therapy	Subsequent therapy costs are applied as a one-time cost.	The duration of second-line therapy in AL amyloidosis is poorly reported in the literature. As such, the cost of subsequent therapy was applied as a one-time tariff.
HSUV for VGPR	Utility value assigned to VGPR is the mean of utility values for CR and PR.	The utility value for patients achieving VGPR derived from the ANDROMEDA IPD is lower than the utility values for PR and NR. It was a simplistic assumption for clinical plausibility to calculate the utility value for VGPR based on the utility values for CR and PR.
Utility decrements for 2L Tx and end-stage organ failure	The utility decrement applied for '2L Tx' is the difference between the mean baseline utility value and that of 'Progressive Disease" according to ANDROMEDA IPD.	Due to the paucity of data for decrements attributable to these health states, this was a simplifying assumption whereby 'progressive disease' is analogous to commencing second-line treatment.
AE management costs and disutilities	AE management costs/disutilities reflect grades 3 and 4 events and are applied as a one-time upfront cost/disutility in the first cycle.	Grade 3–4 AEs were assumed to be costly/severe events that would require hospitalisation and utility decrements. AEs were assumed to be treatment-emergent and because treatment is a fixed course of therapy with limited duration, AE management costs and disutilities were applied in the first cycle such that they would apply to all patients that received treatment.
AE disutility duration	AE utility decrements are applied for 21 days.	The costs for AE management were analogous with "NEL"; the definition of which is at least a 21-day inpatient hospitalisation. Therefore, the same timeframe was applied to the length of time that the corresponding utility decrement was applied for.

Abbreviations: AE: adverse event; BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; CSR: case study report; CUA: cost utility analysis; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; IPD: individual participant data; IV: intravenous; KM: Kaplan-Meier; MOD-PFS: major organ deterioration-progression free survival; NEL: non-elective long stay; NR: no response; OS: overall survival; PR: partial response; RDI: relative drug intensity; VGPR: very good partial response.

B.3.7 *Base-case results*

B.3.7.1 Base-case incremental cost-effectiveness analysis results

A summary of results in the base case analysis are presented in Table 83.

BCd and DBCd accumulated costs of [redacted] and [redacted], and total QALYs of [redacted] and [redacted], respectively. At the confidential PAS price, the ICER was within the range considered cost-effective; at £23,446/QALY, it falls below the NICE WTP threshold of £30,000. The probability of cost-effectiveness at WTP thresholds of £20,000 and £30,000 is presented in Table 84 at which DBCd had a cost-effectiveness probability of [redacted]% and [redacted]%, respectively. These results demonstrate DBCd to be a cost-effective option for the treatment of newly diagnosed AL amyloidosis versus the comparator relevant to UK clinical practice.

Table 83: Base case results

	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALY)
BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,446

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

Table 84: Probability of cost-effectiveness at a WTP threshold of £20,000 and £30,000

	WTP threshold £20,000	WTP threshold £30,000
BCd	[redacted]	[redacted]
DBCd	[redacted]	[redacted]

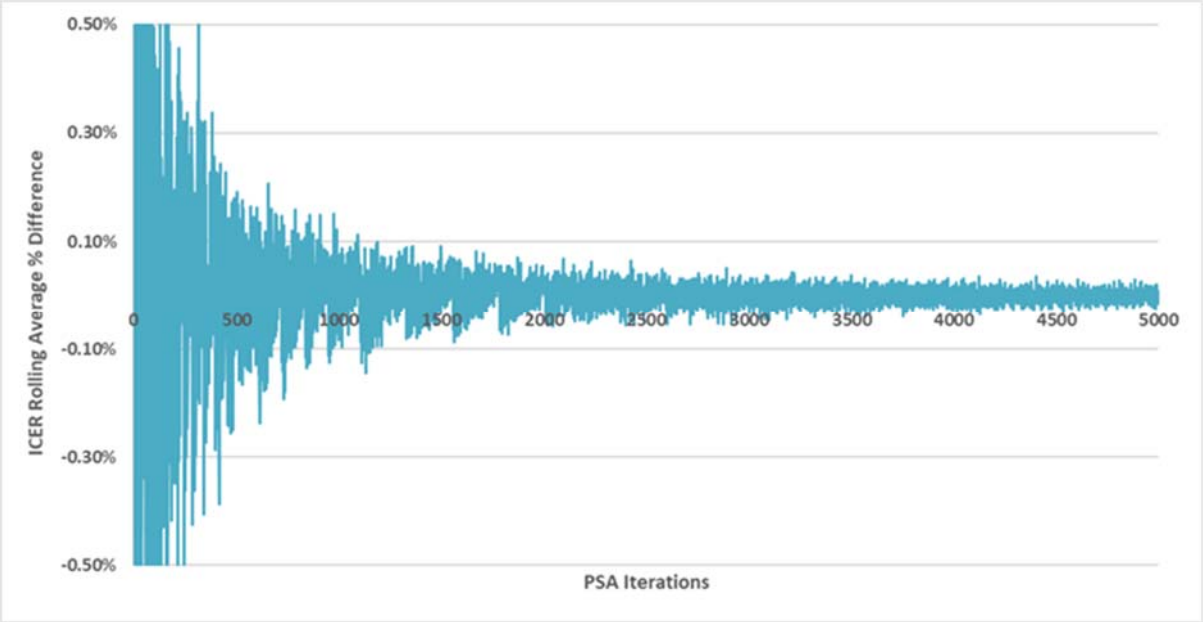
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; WTP: willingness-to-pay.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) with 5,000 iterations were performed in order to assess the uncertainty associated with model input parameters. Use of 5,000 iterations was deemed appropriate based on the results of an ICER convergence tests, shown in Figure 27.

Figure 27: Probabilistic ICER convergence plot



Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis.

The probabilistic base case results are presented in Table 85 and the cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve are presented in Figure 28 and Figure 29, respectively. The probabilistic base case results are in close alignment with the deterministic base case results. DBCd has a higher probability of being cost-effective than BCd at a WTP threshold of £30,000/QALY gained over the range of values tested in the model.

Table 85: Probabilistic base case results

	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALY)
BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,625

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

Figure 28: Cost effectiveness plane scatterplot

Abbreviations: BCd: bortezomib, cyclophosphamide, dexamethasone; D-BCd: daratumumab, bortezomib, cyclophosphamide, dexamethasone; QALY: quality-adjusted life year.

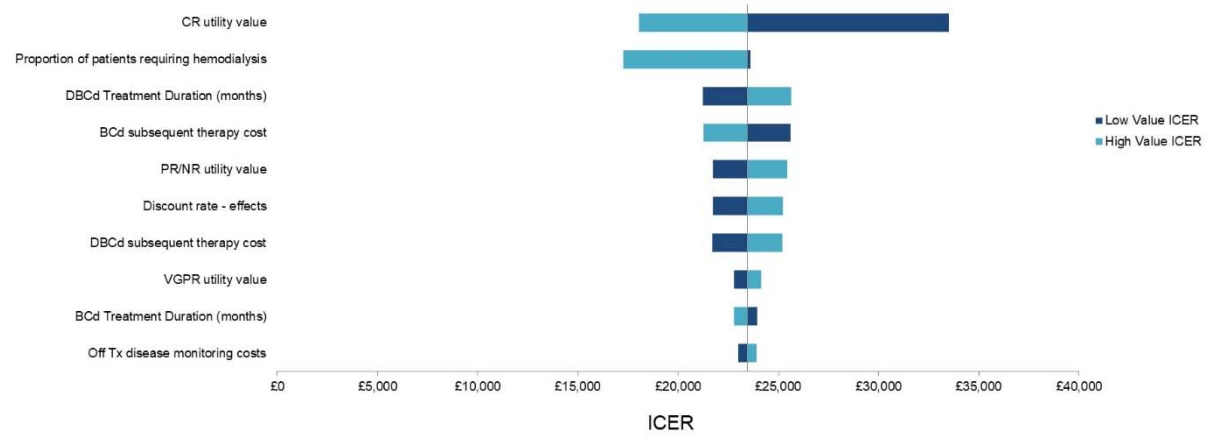
Figure 29: Cost-effectiveness acceptability curve

Abbreviations: BCd: bortezomib, cyclophosphamide, dexamethasone; D-BCd: daratumumab, bortezomib, cyclophosphamide, dexamethasone; CEAC: cost-effectiveness acceptability curve; QALY: quality-adjusted life year.

B.3.8.2 Deterministic sensitivity analysis

The ten most influential variables in the DSA for the analysis of DBCd versus BCd are presented as tornado plot in Figure 30. These results indicate that the most influential parameters on the ICER results at a £30,000 threshold were the CR health state utility value and the proportion of patients requiring haemodialysis. Overall, results were largely robust to parameter uncertainty, demonstrating the stability of the model.

Figure 30: Tornado plot (ICER)



Abbreviations: BCd: bortezomib, cyclophosphamide, dexamethasone; CR: complete response; DBCd: daratumumab, bortezomib, cyclophosphamide, dexamethasone; ICER: incremental cost-effectiveness ratio; NR: no response; PR: partial response; Tx: treatment; VGPR: very good partial response

B.3.8.3 Scenario analysis

A number of scenario analyses were explored in which model assumptions or parameters were altered. The scenario analyses carried out are presented in Table 86. The results of these scenario analyses are presented below in Table 87.

Table 86: Summary of scenario analyses

#	Scenario analysis value	Base case value	Rationale
1	OS extrapolations performed using curve choices with the best fit as per AIC and BIC statistics in situations where the statistical fit data and clinician choice at the advisory board differed	OS extrapolations performed using clinicians' choice in situations where the statistical fit data and clinician choice at the advisory board differed	In the base case, clinicians' choice of curve at the advisory board was selected since these were considered to hold the highest clinical validity. This scenario assesses the impact of curve choice based on statistical fit.
2	Maximum possible treatment duration assumed for patients in the DBCd and BCd arms (24 and 6 cycles, respectively)	Mean treatment duration for DBCd and BCd in the ANDROMEDA trial assumed for patients in the DBCd and BCd arms ([redacted] and [redacted] cycles, respectively)	This scenario explores the impact of all patients receiving therapy for the maximum duration that would be expected within clinical practice.
3	Three-month exit from decision tree	Six-month exit from the decision tree	In the base case, exit at six months is considered in order to permit patients who achieve a VGPR or CR the opportunity to increase their depth of response and improve their long-term outcomes.[26] This scenario assesses the impact of a three-month exit timepoint which permits patients who achieve a PR or NR to transition to an alternative therapy.[26]

			Curve choices of Generalised Gamma for PR/NR and exponential for VGPR and CR were selected based on clinical choice in the advisory board.[26]
4	Inclusion of third-line therapies	The costs and benefits of first- and second-line therapies only are included	This scenario assesses the impact of including the costs and benefits of these third-line therapies. Clinical feedback was that some patients may reach third-line therapy in the course of their treatment pathway.[26]
5	HSUVs as per clinician estimations at the advisory board	HSUVs derived from EQ-5D-5L data collected in the ANDROMEDA trial	Clinical expert opinion was that a delay between initiation of treatment and improvement of HRQoL would be expected. This scenario assesses the impact of implementing clinician-estimated HSUVs.

Abbreviations: AIC: Akaike's information criterion; BCd: bortezomib, cyclophosphamide and dexamethasone; BIC: Bayesian information criterion; CR: complete response; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; EQ-5D-5L: EuroQol-5 Dimensions-5 Level; HRQoL: health-related quality of life; HSUVs: health state utility values; NR: no response; OS: overall survival; PR: partial response; VGPR: very good partial response.

Table 87: Scenario analyses results

Scenario #	Treatment	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	ICER vs BCd (£/QALY)
Base case	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,446
1	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,751
2	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,841
3	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,383
4	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,806
5	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,446

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

B.3.8.4 Summary of sensitivity analyses results

Results of the sensitivity analyses demonstrate that the base case cost-effectiveness results exhibit little variation when the combined distributional uncertainty across model parameters is taken into account. The PSA results aligned closely with the deterministic base case results showing that DBCd is cost-effective versus BCd and indicating it to be a cost-effective use of resources in the NHS. As demonstrated by the DSA, the most influential parameters driving the model were the CR health state utility value, the unit cost of daratumumab and the proportion of patients requiring haemodialysis. Limited variation was observed in the majority of changes to the modelling approach that were explored in the scenario analyses: across all but one of the scenarios conducted, DBCd was associated with ICERs of less than £30,000 per QALY gained. Altogether, these results demonstrate the robustness of the model to uncertainty.

B.3.9 *Subgroup analysis*

No subgroup analyses were conducted.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

The model methodology was designed to align with NICE's preferred methods. The model was built to align with the NICE reference case, and used an NHS and PSS perspective and discount rates for cost and benefits of 3.5%.[105] The model used a lifetime time horizon in order to capture all costs and QALY gains associated with the interventions. EQ-5D-5L scores collected in the ANDROMEDA trial and valued using the UK value set by van Hout *et al.,* (2012).[110]

Expert opinion used to guide the modelling approach

Development of the cost-effectiveness model was closely guided by clinical experts in the field of AL amyloidosis. In particular, the clinical experts consulted confirmed that the model structure appropriately reflects the disease and treatment pathway for AL amyloidosis, and that assessment of haematologic response informs treatment decisions and is highly prognostic of OS.

Model inputs were also sourced from or validated by UK clinical experts. In particular, clinician feedback was sought regarding how well survival extrapolations were reflective of mortality observed in UK clinical practice, later-line treatments typically received by AL amyloidosis patients in UK clinical practice, as well as changes in HRQoL and expected patient utility values following treatment.[26] Furthermore, a modified Delphi panel was conducted in order to source healthcare resource use estimates reflective of UK clinical practice. As discussed in Section B.3.5, resource use estimates were gathered from seven UK-based expert healthcare professionals (clinicians and specialist nurses) with the aim of achieving consensus for all resource use inputs. The Delphi questionnaire rounds were designed in collaboration with a 'lead clinician', who was a practising Consultant Haematologist in the NHS with substantial experience in treating AL amyloidosis.

Validation of model overall survival estimates

Limited long-term OS data exist in the literature for newly diagnosed AL amyloidosis patients, however, in order to assess external validity of survival estimates from the model, OS data have

been sourced from a UK-based prospective observational study of AL amyloidosis patients treated with front-line bortezomib regimens from February 2010–August 2017 (Manwani *et al.,* 2019).[141] In line with the model base case, Manwani *et al.,* measured OS based on a six-month landmark assessment of haematologic response. Due to OS estimates for PR/NR patients not being published, it was not possible to use this study to inform the model. The median follow-up at time of publication was 32 months for living patients and 23 months for all patients.

In addition to external estimates of survival, OS predicted by the model has also been compared to values from Palladini *et al.,* 2012,[2] to confirm internal validity.

Model predicted survival estimates for 12, 24 and 36 months versus data from Palladini *et al.,* and Manwani *et al.,* are presented in Table 88, Table 89 and Table 90, respectively. Across all three points, the model survival estimates demonstrate close alignment with source study for OS stratified by haematologic response (Palladini *et al.*). With the exception of two optimistic OS predictions for CR patients at 24 and 36 months, in the majority of instances, the model conservatively predicts lower survival estimates compared to Manwani *et al*., These results demonstrate that the model has both good internal and external validity.

Table 88: Predicted survival at 12 months by haematologic response (six-month landmark)

Haematologic response	DBCd model (base case)	Palladini 2012[2]	Manwani 2019[141a]
CR	[redacted]	~98%	~100%
VGPR	[redacted]	~92%	~96%
PR	[redacted]	~79%	Not reported
NR		~56%	Not reported

[a] Haematologic response without stringent dFLC response.
Abbreviations: CR: complete response; DBCd: daratumumab, bortezomib, cyclophosphamide, dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Table 89: Predicted survival at 24 months by haematologic response (six-month landmark)

Haematologic response	DBCd model (base case)	Palladini 2012[2]	Manwani 2019[141a]
CR	[redacted]	~94%	~90%
VGPR	[redacted]	~82%	~86%
PR	[redacted]	~61%	Not reported
NR		~40%	Not reported

[a] Haematologic response without stringent dFLC response.
Abbreviations: CR: complete response; DBCd: daratumumab, bortezomib, cyclophosphamide, dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Table 90: Predicted survival at 36 months by haematologic response (six-month landmark)

Haematologic response	DBCd model (base case)	Palladini 2012 [2]	Manwani 2019 [a, 141]
CR	[redacted]	~90%	~80%
VGPR	[redacted]	~80%	~84%
PR	[redacted]	~54%	Not reported
NR		~30%	Not reported

[a] Haematologic response without stringent dFLC response.

Abbreviations: CR: complete response; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Technical validity

Quality-control (QC) procedures for verification of input data and coding were performed and two checklists (for technical and stress test checks) were used to ensure that the model generated accurate results which were consistent with input data and robust to extreme values. An independent reviewer who was not involved in model development performed the technical and stress test QC checks. As part of the technical QC, all model calculations were reviewed, including standalone formulae, equations and Excel macros programmed in VBA. The correct functioning of the sensitivity and scenario analyses was also reviewed. The stress test ensured that the expected effect is observed when key inputs are varied in the model (e.g. when utilities for all health states and for AEs are set to 0, all QALYs should result equal to 0).

B.3.11 *Interpretation and conclusions of economic evidence*

A *de novo* model was developed to evaluate the cost-effectiveness of DBCd vs BCd for the treatment of newly diagnosed AL amyloidosis patients in UK clinical practice.

At the confidential PAS price, the ICER for DBCd versus BCd fell within the range considered to be cost-effective. At £23,446/QALY, it is below the NICE WTP threshold of £30,000. The probability of cost-effectiveness at WTP thresholds of £20,000 and £30,000 was [redacted]% and [redacted]%, respectively, indicating that DBCd has a high probability of cost-effectiveness. These results demonstrate DBCd to be a cost-effective option for the treatment of newly diagnosed AL amyloidosis versus the comparator relevant to UK clinical practice.

Results of the PSA demonstrate that the base case cost-effectiveness results exhibit little variation when the combined distributional uncertainty across model parameters is taken into account. The most influential parameters driving the model in the DSA were the CR health state utility value and the proportion of patients requiring haemodialysis. Across all but one of the scenarios conducted, DBCd was associated with ICERs of less than £30,000 per QALY gained. Altogether, these results demonstrate the robustness of the model to uncertainty.

The results of the cost-effectiveness analysis reiterate the benefits that introduction of DBCd into clinical practice may offer patients and the NHS. As discussed in Section B.1, AL amyloidosis is associated with poor survival, with nearly 30% of patients dying within the first year of diagnosis.[1, 2] Results of the model illustrate that DBCd offers an extension to life compared to current standard of care (BCd) in the UK, with mean survival estimates of 13.3 and 8.6 years, respectively. This is in line with clinical expectations, in which achievement of a deep haematological response, as observed in a greater proportion of patients treated with DBCd compared to BCd in ANDROMEDA, is associated with substantially improved prognosis and overall survival.[2, 27, 82, 92, 93]

Furthermore, results of the model demonstrate a reduction in healthcare resource use costs associated with treatment of patients treated with DBCd compared to BCd. Importantly, a reduction in lifetime costs discounted for treatment of end stage organ failure per patient of £[redacted] was observed. Of note, patients who reach end-stage kidney failure who do not receive a kidney transplant are treated with dialysis. In addition to healthcare costs,[23] the substantial impact of dialysis on patient HRQoL is well-documented,[21, 22] and as such a reduction in the proportion of patients who require this treatment is an important benefit of DBCd treatment in AL amyloidosis patients with kidney involvement.

Strengths

As described in Section B.3.1, no cost-effectiveness analyses in AL amyloidosis have previously been conducted, and as such a *de novo* model was designed and built in order to closely reflect the complex natural history of AL amyloidosis and to align with the treatment pathway in UK clinical practice. The model was designed in close collaboration with clinicians, with inputs and assumptions further validated through expert clinical opinion sourced at a UK advisory board. Importantly, the basis of the model structure is achievement of haematologic response, for which there is strong evidence to support a relationship between improved haematologic response and improved overall survival.[2, 27, 82, 92, 93] The model Markov structure was further better able to capture this compared to a traditional partitioned survival model, as well as reflecting the heterogeneity of outcomes in AL amyloidosis. Importantly, the model structure captured end-stage organ failure, a key clinical outcome in AL amyloidosis.

A further strength of the analysis was the availability of haematologic response data from the high-quality, robust ANDROMEDA clinical trial, which directly compared DBCd to the comparator of interest for this appraisal, BCd, without need for an indirect comparison, thus minimising any uncertainty around treatment effect estimate in the analysis.

Due to the complex and severe nature of AL amyloidosis, healthcare resource use associated with treatment of the disease is high and multi-faceted. Accordingly, in order to generate robust healthcare resource use inputs that were as reflective of UK clinical practice as possible, a modified Delphi panel study was conducted, in which a healthcare resource use questionnaire was distributed among seven expert healthcare professionals, with the aim of achieving consensus on resource use frequency parameter inputs. Further details of the Delphi panel methodology are presented in the reference pack.

Evidence sources and model settings were also aligned with the NICE reference case,[105] with DBCd and BCd evaluated from the NHS/PSS perspective, over a lifetime horizon, with costs and benefits discounted at 3.5%.

Limitations

A limitation of the cost-effectiveness analysis was the immaturity of data from the pivotal ANDROMEDA study, necessitating use of external data in order to inform OS stratified by haematologic response. Nevertheless, the Palladini *et al.,* (2012) study was informed by a large sample size of patients, and included patients from the UK and other related European settings.[2] The company are further working on sourcing data from the EMN23 study, a retrospective, observational, multicentre study on the management and outcomes of AL amyloidosis patients from 10 European countries, including the UK (EMN23 study).[17] This source is expected to provide a more recent source of data to inform OS that is more reflective of outcomes observed in current clinical practice. The company are currently working to incorporate these data into the model such that an analysis can be provided as soon as possible for the appraisal.

An additional limitation is the lack of data available from ANDROMEDA for Mayo Stage IIIb patients to inform the cost-effectiveness analysis. However, it is anticipated that data for such patients will be available from the EMN23 study. Accordingly, upon availability, the company will explore whether a cost-effectiveness estimate for DBCd in this population can be provided that makes use of EMN23 data.

An additional limitation of the study was the short follow-up for the collection of EQ-5D-5L patients within the ANDROMEDA study. In the ANDROMEDA study, EQ-5D data were collected up to 24 cycles in DBCd arm and 6 cycles in the BCd arm, with limitations observations available with increasing cycles. Discussions with UK clinical experts at the advisory board was that an

improvement in HRQoL is often not observed in patients until up to one year post-treatment, and accordingly, benefits experienced by DBCd-treated patients in terms of HRQoL may not have been fully captured at the current data cut-off. As such, in order to populate this evidence gap, a scenario analysis was therefore conducted in which utility estimates post-one year of treatment were provided by clinicians, stratified by haematologic response. The results of this scenario analysis re-affirmed the base case that DBCd is a cost-effective treatment.

Overall, the introduction of DBCd into UK clinical practice is anticipated to bring substantial benefits to AL amyloidosis patients, for whom current standard of care (BCd) is unable to fulfil a significant unmet need for an effective, well-tolerated treatment that is able to induce rapid and deep response rate and improve survival rates. This analysis demonstrates that DBCd comprises a cost-effective treatment option that would offer value for money to the NHS.

B.4 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Clarification questions

July 2021

File name	Version	Contains confidential information?	Date
ID3748_Daratumumab_AL Amyloidosis_Company Clarification Responses_ACIC	N/A	Yes	30th July 2021

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

A1. PRIORITY. Please clarify whether the company considers daratumumab to be a candidate for the Cancer Drugs Fund (CDF). If yes, please clarify the data that would be collected, and which uncertainties it would likely resolve.

Light chain (AL) amyloidosis is a rare condition that often affects multiple organs, causing debilitating symptoms and ultimately leading to death; it is estimated to have a four-year survival rate of 54%, while almost a third of patients die within a year of diagnosis.[1, 2] Daratumumab in combination with BCd is the first treatment to be licensed for this debilitating condition.

The efficacy and safety of DBCd compared with BCd has been demonstrated in the ANDROMEDA trial, where patients receiving DBCd demonstrated rapid and deep haematologic responses, as well as high rates of cardiac and renal response. As a rare condition, the Company recognise that there are inherent uncertainties in the evidence base. The ANDROMEDA trial, however, is a robust Phase III randomised controlled trial providing evidence on the efficacy and safety of DBCd and BCd (current standard of care) in 195 and 193 patients, respectively. This level of evidence is particularly good for a rare condition such as AL amyloidosis.

Nonetheless, the Company acknowledge that, at the time of latest trial follow-up, uncertainty exists in long-term outcomes and in the relative effectiveness of DBCd in patients with Mayo Clinic Cardiac Stage IIIb.

As outlined in Section B.2.11 of the original Company Submission, further data cuts from the ANDROMEDA trial are expected as follows:

- 18-month landmark data cut-off: updated analyses for haematologic response, organ response and safety ([redacted])

- 200 MOD-PFS event driven data cut-off: pre-specified analyses for all endpoints described in the Statistical Analysis Plan. Among them: overall survival (OS), major organ deterioration progression-free survival (MOD-PFS), haematologic response, safety and organ response ([redacted])
- Final OS event driven data cut-off: updated analyses have not yet been confirmed ([redacted])

These further analyses will provide data on the longer-term time to event endpoints of DBCd and BCd in the newly diagnosed AL amyloidosis, including more mature OS estimates.

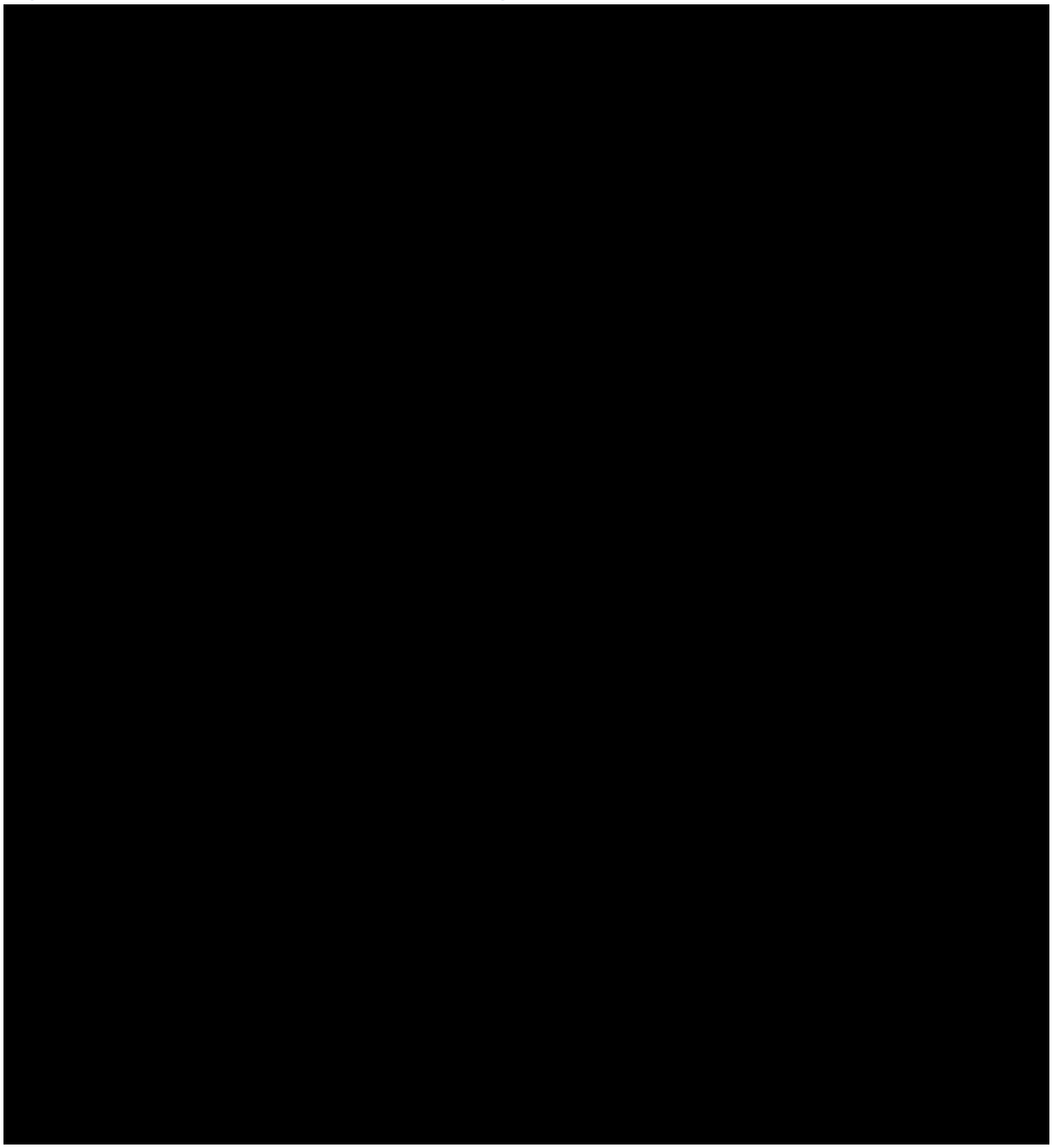
As discussed in Section B.1.1 of the original Company Submission, Mayo Clinic Cardiac Stage IIIb patients were excluded from the ANDROMEDA trial. As such, in order to gain insight into the haematologic response rates that would be required for DBCd to be a cost-effective option for patients in this subgroup, the Company are exploring the use of data from a retrospective real-world evidence study, the EMN23 study. No further data, to that presented in questions in Sections B.1 and B.2 below, from the EMN23 study are expected.

The Company have primarily positioned DBCd for routine commissioning within the NHS for patients with AL amyloidosis given the significant unmet need in this population and the fact that the ICER for DBCd (with the confidential PAS) versus BCd is well within the range normally considered a cost-effective use of NHS resources; considering that a lower ICER may compensate for any residual uncertainty in decision-making. Nevertheless, through preliminary discussion with NHS England, it was verbally confirmed by NHS England that daratumumab would be eligible for the CDF if this route were to be deemed most appropriate by the NICE Committee.

A2. PRIORITY. Company submission (CS), section B2. Please provide a CONSORT flowchart for patients in the ANDROMEDA trial, using an intention-to-treat (ITT) approach. Please provide the number of evaluable patients, deaths, withdrawals, and discontinuations before and after 6 cycles of treatment. Please provide clear reasons for exclusions/withdrawals at each stage.

The CONSORT diagram presenting the number of evaluable patients, deaths, withdrawals, and discontinuations before and after 6 cycles of treatment for patients in the ANDROMEDA study is presented in Figure 1. In Cycles 1 to 6, a higher proportion of patients discontinued from the BCd arm than the DBCd arm ([redacted] and [redacted], respectively), and a further [redacted] patients discontinued from the DBCd arm after Cycle 6.

Figure 1: ANDROMEDA trial CONSORT diagram



Progressive disease (MOD-PFS) included haematologic progression or major organ deterioration.
Abbreviations: ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intention to treat; MOD-PFS: major organ deterioration progression-free survival.

A3. PRIORITY. CS, section B.2.6.2. Treatment switching

1. **Please clarify how 'suboptimal response' was defined in relation to switching to non-cross resistant anti-plasma cell therapy.**

As per the ANDROMEDA trial protocol, suboptimal response was defined as any patient who had achieved a best response of partial response (PR) but who had worsening organ function on Cycle 4 Day 1.[3] These patients could discontinue protocol therapy to switch to a second line therapy.

As per the guidelines for use of subsequent therapy presented in the statistical analysis plan for the ANDROMEDA study, observation or daratumumab monotherapy until disease progression was recommended for patients with haematologic response (PR or better) with stable or improved major organ failure after six cycles of initial therapy. However, at this same timepoint, subsequent therapy was considered for patients with haematologic response (PR or better) with worsening organ function, haematologic non-response or disease progression with stable or improved organ function, and was recommended for patients with haematologic non-response or disease progression with worsening organ function.[4]

2. **Please provide the numbers of patients who switched to subsequent cross-resistant as well as non-cross resistant anti-plasma cell therapy in each study arm and by cycle (by therapeutic class, pharmacologic class, and preferred term), with reasons for switching (suboptimal haematologic response, worsening organ function, haematologic progression, other reasons).**

A summary of the number of ANDROMEDA patients who switched to subsequent cross-resistant and non-cross resistant anti-plasma cell therapies in each study arm and by cycle, by therapeutic class, pharmacologic class, and preferred term, is presented in Table 46 of Appendix 1 presented at the end of this document.

Non-cross resistant anti-plasma cell therapy for AL amyloidosis is defined as any anti-plasma cell therapy not included in the original protocol assigned treatment.[4] For example, for patients in the BCd arm that receive lenalidomide and bortezomib combination therapy as a subsequent line of treatment, the lenalidomide treatment will be considered as subsequent non-cross resistant anti-plasma cell therapy. Patients in the BCd arm who continued to receive BCd, or any component of the triplet, as a subsequent therapy, would be considered as having received subsequent cross-resistant anti-plasma cell therapy.

A summary of the reasons for patients switching onto first subsequent therapies in the ANDROMEDA trial is presented in Table 1. The Company are not however able to present the reasons for switching therapies by treatment cycle as these data cannot be broken down by cycle. The Company are also unable to present the reasons for patients switching onto second or later lines of subsequent therapies as these data were not collected in the ANDROMEDA trial.

Table 1: Summary of subsequent anti-amyloidosis therapy and reasons for initiation of first subsequent therapy; ITT analysis set (14th February 2020 data cut-off)

	BCd (N=193) n (%)	DBCd (N=195) n (%)	Total (N=388) n (%)
Number of lines of subsequent therapy received			
N	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
>1	[redacted]	[redacted]	[redacted]
Reasons for initiation of first subsequent therapy			
N	[redacted]	[redacted]	[redacted]
MOD-PFS due to haematologic progression	[redacted]	[redacted]	[redacted]

MOD-PFS due to major organ deterioration	[redacted]	[redacted]	[redacted]
Less than a haematologic partial response (PR) at Cycle 4	[redacted]	[redacted]	[redacted]
Autologous stem cell transplantation (ASCT)	[redacted]	[redacted]	[redacted]
Worsening of free light chains not meeting criteria for haematologic PD	[redacted]	[redacted]	[redacted]
Organ function worsening	[redacted]	[redacted]	[redacted]
Less than a CR after completion of Cycle 6	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Percentages are calculated with the number of patients in each treatment group with available data as the denominator.
Abbreviations: ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intention to treat; MOD-PFS: major organ deterioration progression-free survival; PD: progressive disease; PR: partial response.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[5]

3. **Please provide the haematologic response rates (complete response [CR], VGPR [very good partial response], PR [partial response], no response [NR]) for patients who switched treatment and how this was accounted for in the analysis of clinical outcomes.**

A summary of the best haematologic response rate for patients who switched to subsequent anti-amyloidosis therapies at the time of the pre-specified interim analysis (IA1) is presented in Table 2 (median follow-up: 11.4 months). As per the ANDROMEDA statistical analysis protocol, disease assessments after subsequent non-cross resistant, anti-plasma cell therapy for AL amyloidosis while on treatment strategy were not included for the overall analyses presented in the original Company Submission.[4] Therefore, patients who switched treatment will not have impacted the data or conclusions previously presented.

Table 2: Overall best haematologic response for patients who switched treatment to receive subsequent anti-amyloidosis therapy; ITT analysis set (14th February 2020 data cut-off)

Response, n (%)	BCd (n=[redacted])	DBCd (n=[redacted])	Total (n=[redacted])
CHR	[redacted]	[redacted]	[redacted]
VGPR	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]

Percentages are calculated with the number of subjects in each treatment group with available data as the denominator.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; NR: no response; PD: progressive disease; PR: partial response; VGPR: very good partial response.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[5]

A4. CS, section B.2.6. Please provide the number of patients censored due to loss of follow-up or non-occurrence of event for the time-to-event outcomes

reported in the interim analysis (IA1) and 12 month-landmark analyses of the ANDROMEDA trial.

Time-to-event outcomes assessed in the ANDROMEDA trial and presented in the Company Submission included: MOD-PFS; MOD-EFS; OS; time to cardiac, renal and liver response; time to best haematologic response; and time to subsequent non-cross resistant, anti-plasma cell therapy.

MOD-PFS

As described in Section B.2.6.2 of the Company Submission, the primary analysis of MOD-PFS at the pre-specified interim analysis (IA1) employed the inverse probability of censoring weighting (IPCW) method to adjust estimates of the treatment effect in the presence of subsequent non-cross resistant, anti-plasma cell therapy. Data on the number of patients censored due to loss of follow-up or non-occurrence of event are not available and the Company are therefore not able to provide this information for the MOD-PFS outcome.

MOD-PFS was not evaluated at the 12-month landmark analysis.

MOD-EFS

At IA1, the total number of patients censored as part of the analysis of MOD-EFS was [redacted] in the BCd arm, and [redacted] in the DBCd arm. However, data on the number of patients censored due to loss of follow-up or non-occurrence of event are not available and the Company are therefore not able to provide this information for the MOD-PFS outcome.

MOD-EFS was not evaluated at the 12-month landmark analysis.

OS

The total number of patients censored as part of analysis of OS at IA1 is presented in Table 22 of the original Company Submission. However, the number of patients censored due to loss to follow-up or non-occurrence of event is not available and the Company are therefore not able to provide this information for OS.

OS was not evaluated at the 12-month landmark analysis.

Time to cardiac, renal and liver response

At IA1, assessment of the time to cardiac, renal and liver response outcome was conducted only in patients who had achieved an organ response. Therefore, it was known that this group of patients had not been lost to follow-up, while patients who had not achieved an organ response (i.e., non-occurrence of event) were also not included as part of the analysis of this outcome. As such, no censoring was conducted for the time to cardiac, renal and liver response analysis.

Time to cardiac, renal and liver response was not evaluated at the 12-month landmark analysis.

Time to best haematologic response

Time to haematologic response was assessed at both the IA1 and 12-month landmark analyses. Similarly to the time to organ response outcome described above, analysis of time to best haematologic response was conducted only in patients that had achieved a haematologic

response. As described previously, no censoring for patients lost to follow-up or for non-occurrence of event was therefore conducted as part of this analysis.

Time to subsequent non-cross resistant treatment

Time to first subsequent non-cross resistant anti-plasma cell therapy was assessed at both the IA1 and 12-month landmark analysis, and the total number of censored patients at each of the IA1 and 12-month analyses is presented in Table 24 of the original Company Submission. However, the Company are not able to provide the specific number of patients that were censored due to loss of follow-up or of non-occurrence of event for this outcome at the IA1 or 12-month analyses.

A5. CS, sections B.2.3.2 and B.2.6. Please describe how overall confirmed haematologic response was defined. Please clarify whether the values reported in Table 17 represent the best response achieved during study follow-up, regardless of treatment phase. If yes, please provide the proportion of best confirmed haematologic response for each arm by 1st and subsequent treatment lines.

As per the ANDROMEDA clinical study report, overall complete haematologic response (CHR) rate was defined as the proportion of patients who achieved a CHR, confirmed by a subsequent assessment during or after the study treatment. Patients with positive serum immunofixation electrophoresis (IFE) and confirmed daratumumab IFE interference, that meet all other clinical criteria for complete haematologic response, were considered to have achieved CHR.[5]

Evaluation of CHR was based on the "Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis", published by Comenzo *et al*., (2012). Within these consensus guidelines, the criteria for CHR are "normalisation of the free light chain levels and ratio, negative serum and urine immunofixation".[6] However, with an increased understanding of the disease biology and publication of additional guidelines after the initiation of the ANDROMEDA study, it became apparent that there were limitations to the criteria for CHR provided by Comenzo *et al.*, (2012).[7-9] Based on Steering Committee's recommendations, and agreed upon by the Independent Review Committee (IRC), normalisation of uninvolved FLC (uFLC) level and FLC ratio were not required when determining CHR if iFLC was less than the upper normal limit.[5] Therefore, the definition of CHR used in the ANDROMEDA study was well-aligned with the latest clinical understanding within the field.

The Company can confirm that the values reported in Table 17 of the original Company Submission represent best haematologic response during study follow up, regardless of treatment phase.

The proportion of best confirmed haematologic response for each arm of the ANDROMEDA trial by first subsequent therapy line is presented in Table 2 above in response to Part 2 of Question A3 and, as noted previously, the Company are unable to present these data for the second subsequent therapy line as they were not collected in the ANDROMEDA trial.

A6. CS, section B.2. Major organ deterioration event-free survival (MOD-EFS) is defined as haematologic progression, major organ deterioration, initiation of

any subsequent non-cross resistant, anti-plasma cell therapy, or death, whichever comes first. Please clarify whether treatment switching due to disease progression be considered a single MOD-EFS event.

The Company can confirm that a patient switching treatment due to haematologic progression would be considered a single MOD-EFS event. The MOD-EFS endpoint captures a single event per patient (whichever of the events making up the composite occurs first). For patients switching treatment due to haematologic progression, the MOD-EFS event would be recorded as a haematologic progression event.

A7. CS, section B.2.3.3, page 44. The company submission states that "Disease staging in the ANDROMEDA trial was based primarily on the Mayo Clinic Staging systems … but with some minor differences in the criteria used to categorise patients into stages …". Please clarify why the cardiac staging criteria in ANDROMEDA differed from the Mayo system. Please explain the implications of these changes (p.44).

The Company would first like to clarify the nature of the two minor differences between the cardiac staging criteria used in the ANDROMEDA trial when compared with the Mayo 2004/European modification cardiac staging criteria, as described in the original Company Submission. The differences are outlined below, alongside rationale for why these aspects of the staging criteria differed in the ANDROMEDA trial, and rationale for why the implications are expected to be limited.

1. A minor difference in the measurement of cardiac troponin (cTnT) levels.

    - The original 2004 Mayo staging system, and subsequent European modification, used cTnT as part of the staging system with a threshold of 0.035 ng/mL for this marker. The difference described in the Company Submission lies in the fact that, in the ANDROMEDA trial, a high sensitivity cardiac troponin (hs-cTnT) assay was used instead, with a threshold of 54 ng/L used as part of the staging system.

    - In 2014, it was determined that an hs-cTnT threshold of 54 ng/L improved on the 35 ng/L threshold that was previously established for cTnT.[10]

    - Use of the hs-cTnT assay in ANDROMEDA is therefore well-aligned with the evolution of the Mayo Clinic Staging System, and the Company can confirm that no implications are expected as a result.

2. Inclusion of systolic blood pressure as a factor to divide stage III patients into the IIIa and IIIb subgroups.

    - The Company can confirm that systolic blood pressure was **not** used as a factor to stage patients in the ANDROMEDA trial, as outlined in the original Company Submission. However, the Company would also like to acknowledge an error in the statement that systolic blood pressure was used as a factor to divide cardiac stage III patients into IIIa and IIIb in the European modification of the Mayo system (alongside the NT-proBNP threshold of 8,500 ng/L).

- As such, the ANDROMEDA trial utilised the same NT-proBNP threshold of 8,500 ng/L to categorise patients as cardiac stage IIIa or IIIb as included in the Mayo staging system (Mayo 2004/European modification), and therefore a difference did not exist in relation to systolic blood pressure. The Company can therefore confirm that there are no further implications to consider.

A8. CS, section B.2.6.1. The time to haematologic response values in Table 19 suggest that the distribution of data is skewed. Please provide a histogram or similar plot to illustrate the distribution of time to haematologic response in each arm.

Histograms are presented below to illustrate the distribution of time to haematologic response in each arm of the ANDROMEDA trial. The distribution of CHR, VGPR and PR achievement using data from the first interim analysis (IA1) are presented in Figure 2, Figure 3 and Figure 4, respectively, and time to CHR, VGPR and PR using data from the 12-month landmark analysis are presented in Figure 5, Figure 6 and Figure 7, respectively.

Figure 2: Time to CHR for patients in the BCd arm (left panel) and DBCd arm (right panel) of the ANDROMEDA trial (IA1)

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.

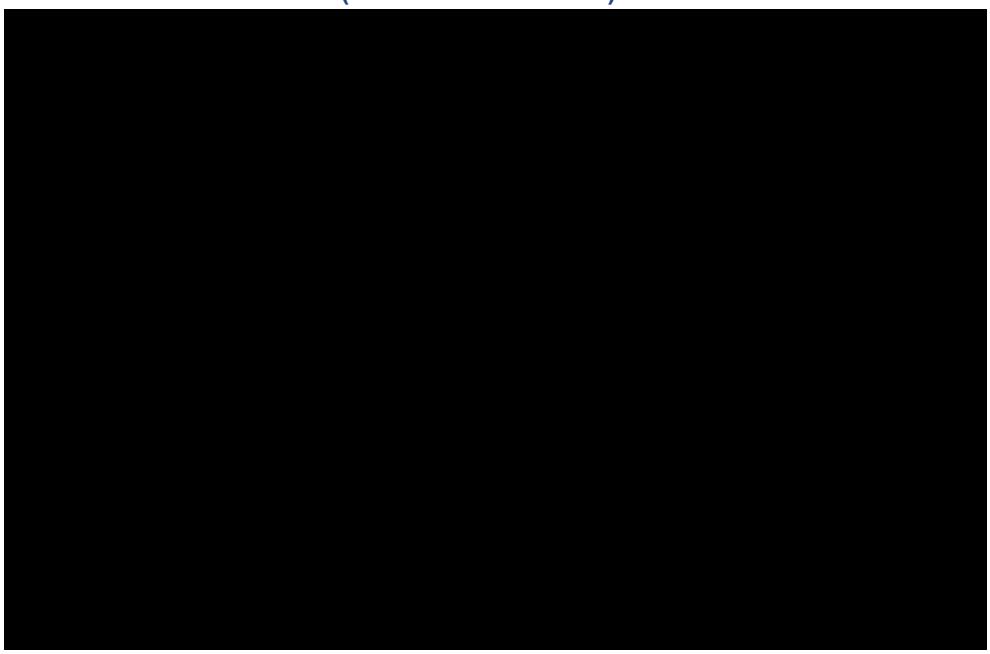
Figure 3: Time to VGPR or better for patients in the BCd arm (left panel) and DBCd arm (right panel) of the ANDROMEDA trial (IA1)

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; VGPR: very good partial response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.

Figure 4: Time to PR or better for patients in the BCd arm (left panel) and DBCd arm (right panel) of the ANDROMEDA trial (IA1)

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; PR: partial response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.

Figure 5: Time to CHR for patients in the BCd arm (left panel) and DBCd arm (right panel) of the ANDROMEDA trial (12-month landmark)



Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.

Figure 6: Time to VGPR or better for patients in the BCd arm (left panel) and DBCd arm (right panel) of the ANDROMEDA trial (12-month landmark)

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; VGPR: very good partial response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.

Figure 7: Time to PR or better for patients in the BCd arm (left panel) and DBCd arm (right panel) of the ANDROMEDA trial (12-month landmark)

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; PR: partial response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.

A9. CS, section B.2.6. Please clarify why the following outcomes were unavailable at the 12-month landmark analysis:

1. Complete haematologic response (CHR) rate at 12 months

As indicated in Section B.2.6 of the Company Submission, the 12-month landmark analysis (median follow-up: 20.3 months, clinical data cut-off: 13th November 2020) was not a pre-specified data cut, and instead was generated for conference purposes only. Therefore, not all outcomes were evaluated at this data cut-off.

Janssen have since undertaken analysis to determine the CHR rate at 12 months for patients in the ANDROMEDA trial at the 12-month landmark analysis, and results are presented in Table 3. These data confirm that CHR is maintained to this timepoint, with significantly higher CHR rates in the DBCd arm as compared with the BCd arm ([redacted] and [redacted], respectively; p[redacted]). This is in alignment with the results observed at the pre-specified interim analysis (IA1) presented in Table 18 of the original Company Submission.

Table 3: Confirmed complete haematologic response at 12 months based on IRC assessment (ITT analysis set)

	Response rate, % (95% CI[a])		DBCd vs BCd odds ratio (95% CI[b])	P-value[c]
	BCd (N=193)	DBCd (N=195)		
CHR	[redacted]	[redacted]	[redacted]	[redacted]

[a] CIs are based on Clopper-Pearson exact test. [b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl ≥60 mL/min or CrCl <60 mL/min). An odds ratio >1 indicates an advantage for DBCd. [c] P-value from the Cochran Mantel-Haenszel Chi-Squared test.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intention-to-treat.

2. Complete haematologic response (CHR) duration

3. Major organ deterioration-progression free survival (MOD-PFS)

4. MOD-EFS

5. Overall survival (OS)

The duration of CHR, MOD-PFS, MOD-EFS and OS were endpoints not evaluated at the 12-month landmark analysis, and therefore the Company are unable to present these data.

Table 16 of the original Company Submission presents the outcomes that were assessed at the 12-month landmark analysis and are thus available:

- Updated data on the primary endpoint, CHR
- Updated data on a selection of secondary endpoints (CHR at six months, time to haematologic response, organ response at 6, 12 and 18 months, and time to initiation of subsequent non-cross resistant anti-plasma cell therapy)
- Updated subgroup analysis for the primary endpoint, CHR

Section B: Clarification on cost-effectiveness data

B1. PRIORITY. CS, sections B.2.3.3 and B.3.2.1. Using data from the EMN23 study to inform cost-effectiveness.

The company submission states that "It is noted that data analysis is ongoing from a retrospective, observational, multicentre study on the management and outcomes of AL amyloidosis patients from 10 European countries, including the UK (EMN23 study). This source is expected to provide a more recent source of data to inform OS that is more reflective of outcomes observed in current clinical practice. The company are currently working to incorporate these data into the model such that an analysis can be provided as soon as possible for the appraisal" (p.98).

1. **Please provide details on when the data analysis from the EMN23 study is expected to be complete, and when an updated model with cost-effectiveness results based on data from this study is expected to be submitted to NICE.**

OS data by haematologic response from the EMN23 study are anticipated to be incorporated into an updated version of the cost-effectiveness model by the time of Technical Engagement.

2. **Please report the methods of this analysis and indicate how this data will be used in the model to inform cost effectiveness.**

The EMN23 study collected data from patients with AL amyloidosis and symptomatic organ involvement who initiated first-line treatment between 2004–2018.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] These analyses are not however available at present.

3. **If the analysis has been complete (or an interim analysis is available):**

    a) **Please provide full details of the study, methods used to analyse the data and inform the model, and revised set of cost-effectiveness results.**

No analyses with data from the EMN23 study are available for presentation at this time.

    b) **Please provide a revised version of the model incorporating the data from the EMN23 study, and with sufficient flexibility to switch**

between alternative sources of data. Please signpost the changes made to the model.

No analyses with data from the EMN23 study are available for presentation at this time.

4. **If it is not possible to provide revised cost-effectiveness results in response to clarification questions, please provide the following information (or indicate when this information will become available for each query below):**

    a) **The baseline characteristics of patients in the EMN23 study. Where possible, please provide the same level of detail as reported in Tables 11 and 12 of the company submission for the ANDROMEDA trial population, and confirm whether patients included are newly diagnosed AL amyloidosis receiving first-line therapy.**

Patient baseline characteristics at diagnosis from the EMN23 study cohort, who initiated first line treatment post-2010, are presented in Table 4 and Table 5, respectively. Where possible, these data have been presented in alignment with Table 11 and Table 12 of the original Company Submission; however, due to the retrospective and observational nature of the EMN23 study, data are not available for all characteristics. Furthermore, given EMN23 was a retrospective, observational study, all patients were newly diagnosed with AL amyloidosis however not all were receiving first-line treatment at the time of data collection (see Part C below for further information); a criterion for study inclusion based on time since diagnosis was not applied. Despite the above differences, many of the baseline characteristics in the EMN23 study align closely to those of the ANDROMEDA patient population. Patient characteristics such as age, weight and sex are highly comparable between the two studies. Further, disease characteristics including organ involvement and the number of organs involved are generally aligned between the ANDROMEDA and EMN23 patient populations.

Importantly, the EMN23 study included 3,065 patients, 55% of whom (n=1,690) were from the UK. Combined with the fact that EMN23 and ANDROMEDA patient populations were broadly comparable, and clinical experts have confirmed that patients in ANDROMEDA are generally reflective of patients with AL amyloidosis in the UK, the EMN23 study population is considered representative of patients with AL amyloidosis in the UK.

Notably, clinical experts have indicated that the exclusion of Mayo Clinic Cardiac Stage IIIb patients from the ANDROMEDA population (due to being considered too “unfit” to participate) marginally limited generalisability of the results. In contrast, as an observational study, the EMN23 study included these patients, representing around [redacted]% of the enrolled population.

Table 4: Baseline patient characteristics in EMN23

Characteristic	Total (N=3,065)
Age, years	
Mean (SD)	[redacted]
Median	66.0
Range	[redacted]
<65, n (%)	Not available
≥65, n (%)	Not available
Sex, n (%)	
Female	1,269 (41.4)
Male	1,796 (58.6)
Race, n (%)	
American Indian or Alaska Native	Not available
Asian	Not available
Black or African American	Not available
Native Hawaiian or Other Pacific Islander	Not available
White	Not available
Multiple	Not available
Unknown	Not available
Ethnicity, n (%)	
Hispanic or Latino	Not available
Not Hispanic or Latino	Not available
Unknown	Not available
Weight, kg	
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]
≤65 kg, n (%)	Not available
65–85 kg, n (%)	Not available
>85 kg, n (%)	Not available
Height, cm	
Mean (SD)	Not available
Median	Not available
Range	Not available
Body surface area, m^2	
Mean (SD)	Not available
Median	Not available
Range	Not available

Abbreviations: BCd: bortezomib, cyclophosphamide, and dexamethasone DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide, and dexamethasone; ITT: intention-to-treat; SD: standard deviation.

Table 5: Baseline patient disease characteristics in EMN23 (ITT analysis set)

Characteristic	Total (N=3,065)
Baseline ECOG score, n (%)	
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
Not reported	[redacted]
Time since initial AL diagnosis, months	
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]
≤30, n (%)	Not available
30–60, n (%)	Not available
>60, n (%)	Not available
Isotype of AL based on either immunofixation or light chain, n (%)	
Lambda	Not available
Kappa	Not available
Organ involvement, n (%)	
Heart	2,135 (69.7)
Kidney	2,024 (66.0)
Liver	409 (13.3)
Gastrointestinal tract	215 (7.0)
Lung	26 (0.9)
Nervous system	447 (14.6)
PNS	Not available
ANS	Not available
Soft tissue	609 (19.9)
Number of organs involved	
Mean (SD)	Not available
Median	Not available
Range	Not available
1 organ, n (%)	1,123 (36.6)
2 organs, n (%)	1,224 (39.9)
≥3 organs, n (%)	700 (22.8)
Not reported, n (%)	[redacted]
Cardiac stage based on Mayo Clinic Cardiac Staging System[a], n (%)	
I	512 (16.7)
II	1,066 (34.8)
IIIa	853 (27.8)
IIIb	485 (15.8)
Not reported	[redacted]

NYHA class, n (%)	
I	Not available
II	Not available
IIIA	Not available
Renal function status[b]	
Normal	[redacted]
Abnormal	[redacted]
Not reported	[redacted]
Renal stage, n (%)	
I	Not available
II	Not available
III	Not available
Chronic kidney disease stage, n (%)	
I	Not available
II	Not available
III	Not available
IV	Not available
V (End stage renal disease)	Not available
Cytogenetic risk at study entry, n (%)	
High risk	Not available
Standard risk	Not available

[a] Cardiac stage is based on both NT-proBNP and cTnT levels (I: NT-proBNP <332 ng/L and cTnT >0.035 µg/L; II: NT-proBNP >332 ng/L or cTnT >0.035 µg/L; IIIa: NT-proBNP >332 ng/L and cTnT >0.035 µg/L; IIIb: NT-proBNP >8500 ng/L and cTnT >0.035 µg/L). [b] Renal function status was evaluated according to investigators' assessments.
Abbreviations: ANS: autonomic nervous system; BCd: bortezomib, cyclophosphamide, and dexamethasone; cTnT cardiac troponin T; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide, and dexamethasone; dFLC: difference in involved and uninvolved free light chains; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; FISH: florescence in situ hybridisation; FLC: free light chain; iFLC: involved free light chain; ITT: intention-to-treat; NT-proNBP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; PNS: peripheral nervous system; SD: standard deviation.
Source: Palladini *et al.* (2021).[11]

b) The depth of haematologic response by Mayo Clinic Cardiac Stage.

The depth of haematologic response at three and six months by Mayo Clinic Cardiac Stage for all patients in the EMN23 study who commenced first line therapy post-2010 are presented in Table 6.

Table 6: Haematologic response at three and six months after initiation of first-line treatment by Mayo Clinic Cardiac Stage in patients in the EMN23 study who initiated treatment post-2010

Response	Mayo 2004/European Cardiac stage, n (%)				
	I	II	IIIa	IIIb	NA
Assessment at three months	n=[redacted]	n=[redacted]	n=[redacted]	n=[redacted]	n=[redacted]
CHR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

VGPR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assessment at six months	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**
CHR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VGPR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHR: complete haematologic response; NA: not applicable; NR: no response; PR: partial response; VGPR: very good partial response.

c) How patients in the study were treated in first and subsequent lines of therapy.

The first- and second-line treatment regimens received by patients in the EMN23 study who commenced first-line therapy post-2010 are presented in Table 7 and Table 8, respectively.

In alignment with UK clinical expert opinion gained at a Janssen-led advisory board, and information presented in Section B.1.3.3and Table 71 of the original Company Submission, the vast majority of patients in the EMN23 study received bortezomib-based therapies first-line. Immunomodulatory imide drugs-based regimens (such as those including lenalidomide), chemotherapy regimens (such as those including melphalan or carfilzomib) and bortezomib-based regimens were found to be the three most commonly received second-line therapy regimens for patients in the EMN23 study, which further aligns with the proportions estimated by clinicians (see Table 71 of original Company Submission). Therefore, it is reasonable to consider these data are broadly representative of AL amyloidosis treatment in the UK.

Table 7: First line treatment regimens for patients in the EMN23 study who initiated first-line treatment post-2010 (ITT analysis set)

Regimen group, n (%)	EMN23 patients (n=3,065)
Bortezomib-based	[redacted]
Immunomodulatory imide drugs-based[a]	[redacted]
Chemotherapy	[redacted]
Rituximab	[redacted]
Daratumumab	[redacted]
Steroids	[redacted]
ASCT	[redacted]
Clinical trial	[redacted]
Other regimen groups	[redacted]

[a] Example imides include lenalidomide and pomalidomide.
Abbreviations: ASCT: autologous stem cell transplant; ITT: intent-to-treat.

Table 8: Second line treatment regimens for patients in the EMN23 study who initiated first-line treatment post-2010 (ITT analysis set)

Regimen group, n (%)	EMN23 patients (n=[redacted])
Bortezomib-based	[redacted]

Immunomodulatory imide drugs-based[a]	[redacted]
Chemotherapy	[redacted]
Rituximab	[redacted]
Daratumumab	[redacted]
Steroids	[redacted]
ASCT	[redacted]
Clinical trial	[redacted]
Other regimen groups	[redacted]

[a] Example imides include lenalidomide and pomalidomide.
Abbreviations: ASCT: autologous stem cell transplant; ITT: intent-to-treat.

d) For first line treatment, please indicate the timepoints for assessment of response and how they align with the exit timepoint used in the decision tree. Please provide the treatment duration (with standard error) for first line treatment.

Response to first line treatment was assessed at three and six months in the EMN23 study, which is in alignment with the six-month exit timepoint used in the submitted Company base case. The model has been built to allow flexibility in selecting the decision tree exit timepoint and the OS data source informing the Markov model.

The median time on treatment for patients in the EMN23 study who initiated first-line treatment post 2010 was [redacted] months (95% CI: [redacted]). The standard error of these data is not available.

e) The Kaplan-Meier curves (with time, proportion of patients alive, and numbers at risk at each timepoint) for overall survival (OS) from assessment of response, by depth of haematologic response (complete response [CR], very good partial response [VGPR], partial response [PR] and no response [NR], separately). Please provide the same curves by depth of haematologic response and Mayo Clinic Cardiac Stage (for example, Mayo Stage I and CR; Mayo Stage II and CR; Mayo Stage IIIa and CR; Mayo Stage IIIb and CR; Mayo Stage I and VGPR; Mayo Stage II and VGPR; etc.), since Mayo Stage is a major prognostic factor for OS. If the latter is not possible, please use the EMN23 data to estimate the hazard ratios (or acceleration factors, as relevant) associated with depth of haematologic response (CR, VGPR, PR, NR) and Mayo Stage (Stage I, II, IIIa and IIIb).

As outlined in response to Part 2 of Question B1 above, it is anticipated that Kaplan-Meier graphs plotting OS by haematologic response in the EMN23 study will be produced, but these analyses are not available at the present time.

f) The Kaplan-Meier curves (with time, proportion of patients, and numbers at risk at each timepoint) for time from first line treatment to patients experiencing significant progression of their disease by depth of haematologic response (CR, VGPR, PR and NR, separately).

It is anticipated that Kaplan-Meier graphs plotting PFS by haematologic response in the EMN23 study will be produced, but these analyses are not available at the present time.

g) Any health-related quality of life data that was collected in the study. Please provide full details, including mean and standard errors of utility values by timepoint, by haematologic response status, by Mayo Stage, and number of individuals at each timepoint.

No HRQoL data were collected in the EMN23 study.

B2. PRIORITY. CS, sections B.2.3.3 and B.3.2.1. Patients with Mayo Clinic Cardiac Stage IIIb disease.

The company submission states that "Despite the lack of data for Stage IIIb patients in ANDROMEDA, it is anticipated that standard of care data for such patients will be available from the EMN23 study. Accordingly, upon availability, the company will explore whether an analysis can be conducted that explores haematologic response rates that would be required for DBCd to be a cost-effective option in Mayo Stage IIIb AL amyloidosis patients" (p.98).

1. **Please provide details on when the data analysis for patients with Mayo Clinic Cardiac Stage IIIb from the EMN23 study is expected to be complete, and when an updated model with cost-effectiveness results for this subgroup of patients is expected to be submitted to NICE.**

It is anticipated that this analysis using data from the EMN23 study will be incorporated into an updated version of the cost-effectiveness model by the time of Technical Engagement.

2. **Please provide the baseline characteristics of patients with Mayo Clinic Cardiac Stage IIIb from the EMN23 study at treatment initiation. Where possible, please provide the same level of detail as reported in Tables 11 and 12 of the company submission for the ANDROMEDA trial population.**

The age at diagnosis for patients in the EMN23 study with Mayo Clinic Cardiac Stage IIIb is presented in Table 9. Although this information was collected at the time of diagnosis rather than at the time of treatment initiation, the median time from diagnosis to initiation of treatment was only 0.7 months.

These data represent the only baseline characteristic data available for this subgroup of patients. While additional baseline characteristics were collected for the broader EMN23 patient cohort (as presented in B1, Part 4), these data for the cardiac Stage IIIb patients specifically were not collected as per the EMN23 study protocol and thus are not available for presentation.

Table 9: Patient age at diagnosis for patients in EMN23 with Mayo 2004/European Cardiac Stage IIIb who initiated first-line treatment post-2010

	Stage IIIb patients (N=485)
Age at diagnosis, years	
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]
Q1–Q3	[redacted]

Abbreviations: Q1: first quartile; Q3: third quartile; SD: standard deviation.

3. **Please provide information on how this subgroup of patients were treated by line of therapy.**

The first- and second-line treatment regimens received by Mayo Clinic Stage IIIb patients in the EMN23 study who commenced first-line therapy post-2010 are presented in Table 10 and Table 11, respectively.

In alignment with the ITT data presented in response to Question B1, Part 4c, these data show a reasonable overlap with the expert opinion of UK-based clinicians at a Janssen-led advisory board on the treatments received by AL amyloidosis patients in UK clinical practice. In the first-line setting, bortezomib-based regimens remain the standard of care; in the second-line setting, immunomodulatory imide drugs-based, chemotherapy and bortezomib-based regimens were the most commonly received, aligning with the clinician-estimated proportions presented in Table 71 of the original Company Submission. Therefore, these data indicate the data are broadly generalisable to the UK.

Table 10: First line treatment regimens for Mayo 2004/European Cardiac Stage IIIb patients who initiated first-line treatment post-2010

Regimen group, n (%)	Stage IIIb patients (n=[redacted])
Bortezomib-based	[redacted]

Immunomodulatory imide drugs-based	[redacted]
Chemotherapy	[redacted]
Rituximab	[redacted]
Daratumumab	[redacted]
Steroids	[redacted]
ASCT	[redacted]
Clinical trial	[redacted]
Other regimen groups	[redacted]

Abbreviations: ASCT: autologous stem cell transplant.

Table 11: Second-line treatment regimens for Mayo 2004/European Cardiac Stage IIIb patients who initiated first-line treatment post-2010 and went on to receive second-line treatment

Regimen group, n (%)	Stage IIIb patients receiving second-line treatment (n=[redacted])
Bortezomib-based	[redacted]
Immunomodulatory imide drugs-based	[redacted]
Chemotherapy	[redacted]
Rituximab	[redacted]
Daratumumab	[redacted]
Clinical trial	[redacted]
Other regimen groups	[redacted]

Abbreviations: ASCT: autologous stem cell transplant.

4. **Please provide full details on the planned methods to be used to model long-term health outcomes and costs in this subgroup of patients. Please provide the following information:**

    a) **Please indicate whether the same model structure is expected to be used to inform the cost-effectiveness of DBCd in this subgroup of patients. If a different model structure is expected to be used, please provide details about the revised model structure, model inputs and justification for the revisions.**

It is anticipated that the model structure that will be used to inform the cost-effectiveness of DBCd in this subgroup of patients will be the same as the current model structure.

    b) **Please provide details on the methods, data and assumptions used to inform overall survival and disease progression in patients with Mayo Clinic Cardiac Stage IIIb disease, conditional on haematologic response, and how the transition probabilities used in the model will be derived.**

The EMN23 study is anticipated to provide haematologic response rates for the Mayo Clinic Cardiac Stage IIIb subgroup at three and six months which could be used to inform the proportion of patients achieving CR, VGPR, and PR/NR at three and six months in the BCd arm. These data are deemed to be appropriate given that approximately [redacted] of Mayo Clinic Cardiac Stage IIIb patients received a bortezomib-based regimen at first line in the EMN study (Table 10).

It is anticipated that the Company will explore how best to optimise the use of these data within an updated economic model in time for the Technical Engagement step of the appraisal process, at which time detail of the analysis methodology will be provided.

5. **FIf it is not possible to provide cost-effectiveness results for the subgroup of patients with Mayo Clinic Cardiac Stage IIIb disease from the EMN23 study in response to clarification questions, please provide cost-effectiveness results for this subgroup based on an analysis of the overall survival curves and data presented in Manwani et al. (2018) [reference 140 of the CS]. This study reports outcomes of 179 UK patients with Mayo Clinic Cardiac Stage IIIb disease and treated with upfront bortezomib, cyclophosphamide, and dexamethasone from ALchemy. If feasible, please provide a revised version of the model and details on data inputs and assumptions used for this subgroup. Please signpost the changes made to the model.**

The patients included in the analysis presented in Manwani *et al.*, (2018), were UK-based patients with Mayo Clinic Cardiac Stage IIIb disease and included patients from the ALchemy study.[7] The ALchemy study recruited UK-based patients from the National Amyloidosis Centre.[12]

Similar to the EMN23 study, a considerable proportion of patients in the Manwani *et al.*, (2018) publication were recruited from the National Amyloidosis Centre in the UK, suggesting the results are generalisable to typical UK clinical practice. However, the EMN23 study has the advantage that CHR and VGPR rates are reported separately, whereas they are reported as a grouped outcome in Manwani *et al.*, (2018). Crucially, the separate reporting of these outcomes aligns with feedback received by Janssen from UK clinicians that a deeper haematologic response would be anticipated to correlate with improved overall survival, and it further aligns with the design of the ANDROMEDA study and the model structure.

As outlined above in response to Part 1 of Question B2, it is anticipated that cost-effectiveness data for the Mayo Clinic Cardiac Stage IIIb disease patient subgroup of the EMN23 study will be available by the Technical Engagement step of the appraisal process. Therefore, cost-effectiveness data for this subgroup informed by data presented in Manwani *et al.*, (2018) have not been provided in lieu of provision of these data informed by EMN23 data at the next stage of the appraisal process.

B3. PRIORITY. CS, sections B.1.4 and B.3.3.3. ALchemy study.

The ALchemy study is an ongoing, prospective, observational study of newly diagnosed patients with AL amyloidosis in the UK. Ravichandran et al. (2021) [please see reference below] reports the outcomes of patients from ALchemy who were treated with upfront bortezomib-based regimes. Figure 1B of this study reports the distribution of patients by depth of response at 3 timepoint assessments: ITT cohort at 1-month; landmark cohort at 1-month, 3-months and 6-months. Figure 2 provides the Kaplan-Meier curves for overall survival by depth of haematologic response for the same cohorts. Given that this study provides a relevant baseline for NHS patients, please provide the following information:

1. **Please comment on the relevance of this study for informing baseline outcomes for the comparator BCd.**

The Company appreciate interest in the ALchemy study given that it recruited a UK-only cohort but note that some limitations are associated with this analysis. The study cohort is relatively small in size (N=1,194) and recruited only bortezomib-treated patients from the National Amyloidosis Centre (NAC). In addition, the median OS had not been reached by the time data are published.

While the Company recognise that the EMN23 study is a broader European cohort, 55% were from the UK supporting that the cohort is broadly generalisable to UK clinical practice. Since the EMN23 study cohort is larger in size (N=3,065) than the ALchemy study and the median OS has been reached, these data may be considered to be more robust for the purposes of economic modelling. The increased sample size is of particular interest given the increased potential to address the uncertainties inherently associated with real-world evidence studies, such as the lack of randomisation.

Nevertheless, the Company acknowledge interest in both datasets and will explore feasible scenario analyses by the time of the Technical Engagement step of the appraisal process.

2. **Please compare the haematologic response distribution over 6 months of patients in the ANDROMEDA study for the BCd arm with patients from the Ravichandran et al. (2021) study.**

The haematologic response distribution at six months of patients in the Ravichandran *et al.,* (2021), study and in the BCd arm of the ANDROMEDA study are presented in Table 12.[12] For the ANDROMEDA data, a window of Days 153–213 was used to capture patient haematologic responses for Cycle 6. This is in alignment with the methodology outlined in the ANDROMEDA CSR for calculation of the landmark six-month CHR rate.

In alignment with the findings presented in Ravichandran *et al*., (2021), a higher proportion of patients in the BCd arm of the ANDROMEDA trial had a very good partial response than complete haematologic response at six months, although response rates were generally lower in ANDROMEDA than reported in Ravichandran *et al*., (2021).

Table 12: Haematologic response distribution at six months in the Ravichandran et al., (2021) study and in the BCd arm of the ANDROMEDA study

Haematologic response, n (%)	Ravichandran *et al*., (2021) (N=948)	ANDROMEDA (N=193)
CHR	294 (31)	[redacted]
VGPR	323 (34)	[redacted]
PR	194 (20.5)	[redacted]
NR	104 (11)	[redacted]
NA	33 (3.5)	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; NA: not applicable; NR: no response; PR: partial response; VGPR: very good partial response.
Source: Ravichandran et al., (2021).[12]

3. **Please provide revised cost-effectiveness results and an updated model for a scenario analysis where the haematologic response distribution for BCd is derived from the Ravichandran et al. (2021) study, while the depth of response for the daratumumab-based regimen is calculated from relative risk (or odds ratios) estimated from a comparison of DBCd and BCd from the ANDROMEDA trial and applied to the haematologic response distribution for BCd from Ravichandran et al. (2021). Please include separate scenarios with the response assessed at 1-month, 3-months and 6-months as the exit point from the decision tree. Please signpost the changes made to the model.**

Unfortunately, has been unable to conduct these analyses within the timeframe available for response to these clarification questions. The feasibility of incorporating these data into the updated model ahead of the Technical Engagement step of the appraisal process will be investigated.

4. **Please provide extrapolated overall survival curves by haematologic response and timepoint of assessment based on Figures 2B, 2C and 2D of Ravichandran et al. (2021), that is, please follow the approach outlined on page 108 of the company submission for extrapolating overall survival Kaplan Meier data from Palladini et al. (2012). This involves digitising the overall survival Kaplan Meier curves presented in Figure 2 of Ravichandran et al. (2021), recreating the individual patient level data generated from the digitised data and number at risk, and**

fitting parametric survival models to extrapolate beyond the time horizon of the data. Please include the data obtained from the digitised Kaplan Meier curves, recreated individual patient level data, and full details of the extrapolation methods used.

As noted above, these analyses have not been conducted but the feasibility of their inclusion in the model at the Technical Engagement step of the appraisal process will be investigated.

5. **Please provide a revised set of cost-effectiveness results where the cost-effectiveness of DBCd is assessed using both the haematologic response distribution at various assessment timepoints (for example, 1-, 3-, and 6-month exit points from the decision tree) and extrapolated overall survival curves (by haematologic response) from Ravichandran et al. (2021) for the comparator BCd. Please provide the revised version of the model with sufficient flexibility to permit this analysis. Please signpost the changes made to the model.**

As noted above, these analyses have not been conducted but the feasibility of their inclusion in the model at the Technical Engagement step of the appraisal process will be investigated.

Reference: Ravichandran et al (2021). Impact of early response on outcomes in AL amyloidosis following treatment with frontline Bortezomib. Blood Cancer Journal, 11:118; doi:10.1038/s41408-021-00510-7

B4. PRIORITY. CS, section B.3.2.2. Model structure – timing of response assessment.

In the model, the exit timepoint from the decision tree is 6 months for the base case analysis and 3 months in a scenario analysis.

1. **Please justify the use of a 6-month assessment timepoint for stratifying patients by haematologic response in the base case given that current guidelines for the management of AL amyloidosis in UK clinical practice suggests that the assessment timepoint for response is at 3 months (see Wechalekar et al. 2015, reference below).**

Rationale exists for selecting both the three- and six-month options. Whilst the assessment timepoint in UK clinical practice is suggested to be three months, which enables patients who have a suboptimal response to treatment to attempt an alternative treatment, clinical expert opinion received by Janssen is that patients who achieve VGPR or CR in clinical practice would

typically continue the same regimen up to cycle 6, unless they experienced tolerability issues, in order to increase their depth of response and improve their long-term outcomes.[13, 14]

An abbreviated version of Table 17 from Section B.2.6.1 of the original Company Submission is presented in Table 13, which summarises the overall best confirmed haematologic response at IA1 and the 12-month landmark analysis of the ANDROMEDA trial. In the DBCd arm, while the proportion of patients achieving a VGPR or better (VGPR or CHR) or any overall response (CHR, VGPR or PR) remained approximately stable between the IA1 and 12-month landmark analyses, CHR rates rose while VGPR rates fell, evidencing an overall deepening of response from VGPR to CHR with time on DBCd therapy. As such, a six-month exit from the decision tree enables the model to capture the deepening of response over time in patients who demonstrate a VGPR, as informed by the ANDROMEDA data. As discussed further in Section B.2.6.1 of the original Company Submission, the relationship between depth of haematologic response and improved prognosis and overall survival for AL amyloidosis patients is well established. Therefore, this timepoint was selected as the base case, whilst a three-month exit was explored in a scenario analysis.

Further, as described in B.3.2.2 of the original Company Submission, use of a six-month exit from the decision tree as the base case is a conservative approach. This is because use of a six-month exit prolongs the time for which patients are in the decision tree, and thus delays the time of stratification into haematologic response categories in the Markov model. Therefore, the accrual of QALYs within the comparator BCd group is likely overestimated, as these patients would otherwise transition directly to the '2L Tx' health state, which is associated with a lower utility.

Table 13: Summary of overall best confirmed haematologic response based on IRC assessment; ITT analysis set (14th February 2020 data cut-off and 13th November 2020 data cut-off)

Response	IA1, % (95% CI[a])		12-month landmark, % (95% CI[a])	
	BCd (N=193)	DBCd (N=195)	BCd (N=193)	DBCd (N=195)
CHR	18.1 (13.0, 24.3)	53.3 (46.1, 60.5)	19.2 [redacted]	59.0 [redacted]
VGPR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
NE	[redacted]	[redacted]	[redacted]	[redacted]
VGPR or better (CHR+VGPR)	49.2 [redacted]	78.5 [redacted]	50.3 [redacted]	79.0 [redacted]
Overall response (CHR+VGPR+PR)	76.7 [redacted]	91.8 [redacted]	76.7 [redacted]	91.8 [redacted]

[a] 95% CIs are based on Clopper-Pearson exact test.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intention-to-treat; NE: not evaluable; NR: no response; PD: progressive disease; VGPR: very good partial response.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[5] Kastritis *et al.,* (2020);[15] Janssen ANDROMEDA 12-month landmark analysis (2021);[16] Kastritis *et al.,* (2021).[17]

2. **Please provide the cost-effectiveness results for a scenario analysis where the assessment of response is conducted at 1 month, in line with**

the proposals outlined by Kastritis et al. (2021) [reference 82 in CS] and Ravichandran et al. (2021) [reference included in this document]. Please signpost the changes made to the model.

The Company acknowledge that conclusions within Kastritis *et al*., (2021) and Ravichandran *et al*., (2021) suggest that the achievement of a response at the earlier timepoint of one month translates to improved overall survival.[12, 18] Indeed, the rapid and deep haematologic response achieved with DBCd compared with BCd is expected to result in survival benefits for patients treated with DBCd (for example, see Section B.2.6.3 of the original Company Submission). While expert clinicians consulted at a UK advisory board similarly noted that early response translates into improved survival, they also suggested that haematologic response typically deepens over time and that it is important to prevent prematurely switching patients to subsequent lines of therapy.[13] Clinicians noted the importance of avoiding a situation in which patients have received several lines of therapy in a short period of time and are facing a lack of other treatment options.[13] Kastritis *et al*., (2021) also acknowledged that haematological response can improve and deepen over time.[18]

As such, the Company acknowledge that the timing of assessment of haematologic response is important for clinical research purposes due to the consequences for survival and that patients' responses may be assessed regularly. However, the Company understand that the decision on whether to switch patients is not routinely taken at one month in NHS clinical practice and thus consider that exit from the decision tree at one month is not clinically appropriate. An additional scenario analysis with assessment of response at one month has therefore not been conducted as it is not deemed to be reflective of clinical practice.

Reference: Wechalekar AD, Gillmore JD, Bird J, Cavenagh J, Hawkins S, Kazmi M, et al. Guidelines on the management of AL amyloidosis. Br J. Haematol. 2015;168:186–206.

B5. PRIORITY. Flexibility of economic model.

The submitted model is not sufficiently flexible to use alternative sources of data for overall survival extrapolation and alternative timepoints for exit from the decision tree. Furthermore, the company submission does not provide the output of the Markov trace.

1. **Please provide a revised model that de-links the exit decision tree timepoint (timing of the assessment of response) from the data source used to inform overall survival. Please ensure that the model is sufficiently flexible to incorporate alternative sources of data for overall survival and time to MOD-PFS. Please signpost the changes made to the model.**

In the current version of the cost-effectiveness model, there are two OS data sources: Palladini *et al.,* (2012) and Kastritis *et al*., (2020), which provide OS based on response recorded at six months following the initiation of treatment and OS based on response recorded at three months following the initiation of treatment, respectively. As previously discussed, the Company are to explore incorporation of additional OS sources into an updated economic model at the Technical Engagement step of the appraisal process. These options will be integrated into the model in such a way that any data source providing OS based on response at six months will be selectable when the six-month decision tree exit is active, and any data source providing OS based on response at three months will be selectable when the three-month decision tree exit is active.

The Company acknowledge that the ERG would like to vary only one parameter at a time, such that selection of the decision tree exit timepoint does not influence the OS data source selected, but do not consider it to be clinically appropriate to adapt the model in such a way that a six-month OS data source could be used while the three-month decision tree exit is active, or vice versa. This would ignore the clinical relationships between responses achieved at certain timepoints (in this case, three and six months) and OS and during clinical validation of the model structure at an advisory board, the importance of alignment between the timepoints used for the decision tree and the assessment of haematologic response was significantly underscored by clinicians.

Furthermore, misalignment between the timepoints used for the decision tree exit and the assessment of haematologic response is not feasible within the model structure. Use of a six-month OS data source when a three-month decision tree exit is active would result in a ‘gap’ in data for patient deaths in Cycles 4–6. It would be inappropriate to use the six-month OS source during this period, given that this can only be appropriately applied after six-months following the initiation period. Use of ANDROMEDA data to inform patient deaths in Cycles 4–6 would be equally inappropriate as these data reflect patients who were treated for six cycles regardless of response, whereas the three-month exit ought to capture a scenario in which patients with PR/NR at three months discontinue from first line treatment. In addition, recently published data from the ALchemy study confirm that OS by depth of haematologic response differs depending on whether data from the three- or six-month landmark analysis is considered. This is supported by data from the ANDROMEDA study in which deepening haematologic response between Cycles 4 and 6 of treatment was observed in some patients.

On the other hand, use of a six-month decision tree exit with a three-month data source would result in an overlap of data for patient deaths in Cycles 4–6. The six-month exit is intended to capture a scenario in which patients are treated for six months regardless of response, and so using data from a source in which patients were not treated for six months result in the benefits of treatment for six months not being captured while the costs of treatment for six months are incurred. The only three-month OS source to which the Company currently have access is Kastritis *et al.,* (2021); unfortunately, it is unclear from the published literature available whether patients in this trial were treated beyond three months.

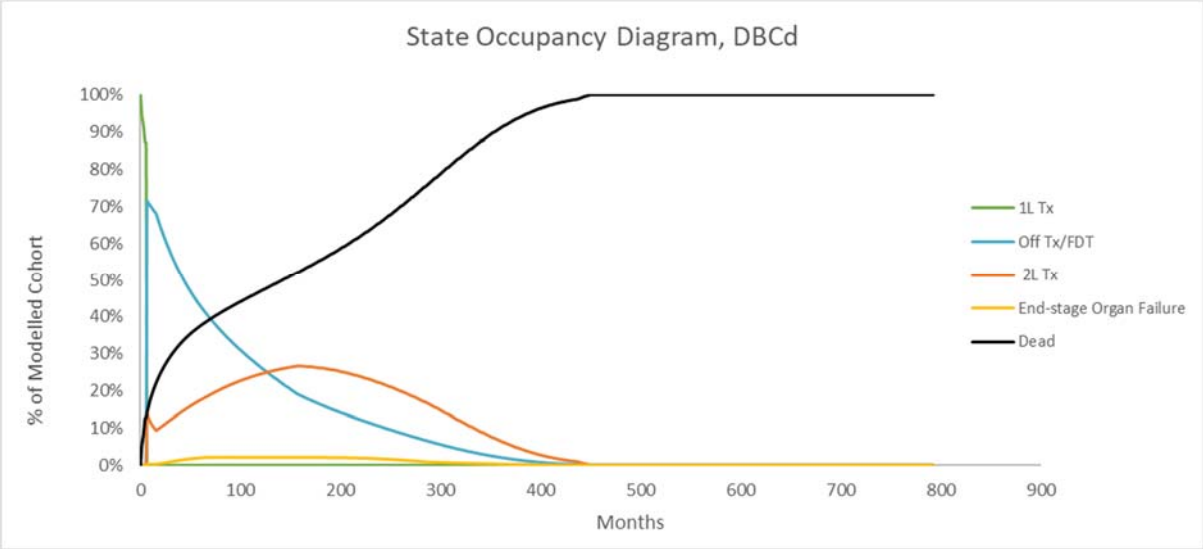
Therefore, for both clinical and structural reasons, the Company do not consider it appropriate to edit the model such that the decision tree exit timepoint and timing of haematologic response can be misaligned, and no edits have been made to the model in this respect.

It is anticipated that additional flexibility will be added to the model to incorporate alternative data sources to inform OS and MOD-PFS could be added by the time of the Technical Engagement step of the appraisal process.

2. **Please provide a revised model that calculates the proportion of patients in each health state by treatment (known as the Markov trace) over time. Please create a plot of the Markov trace by treatment over time. Please signpost the changes made to the model.**

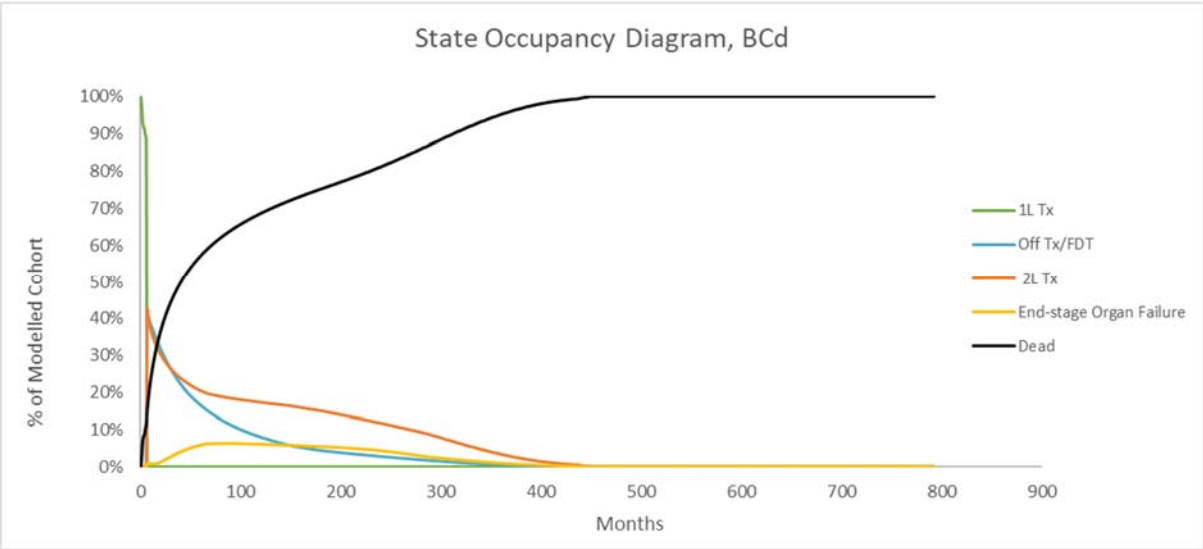
State occupancy diagrams which present the proportion of patients in each health state (1L Tx, OffTx/FDT, 2L Tx, End-stage Organ Failure or Dead) across the model time horizon for the DBCd and BCd arms of the model are presented in Figure 8 and Figure 9, respectively.

Figure 8: State occupancy diagram for the DBCd arm



Abbreviations: DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone.

Figure 9: State occupancy diagram for the BCd arm



Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone.

B6. PRIORITY. CS, sections B.2.6.1, B.3.2.2, B.3.3.3 and B.3.5.1. Details on data used in the cost-effectiveness model

The company submission is sparse on detail about some of the data used in the cost-effectiveness model, specifically the distributions by depth of haematologic response by cycle and relative dose intensities.

1. **Please clarify how the data in Table 40 (page 106) for haematologic response distribution over 6 months relates to the data presented in Table 17 of the company submission. Please clarify how the haematologic response distributions for each cycle in Tables 40 and 41 of the company submission were calculated.**

The data presented in Table 17 of the original Company Submission are the overall best haematologic response at any time in the ANDROMEDA trial, where the data in Table 40 on page 106 represent the best haematologic response achieved in each cycle. For cycles 1 to 5, these data are for a 30-day window: Day 0–30 for Cycle 1, Day 31–61 for Cycle 2, Day 62–91 for Cycle 3, Day 92–121 for Cycle 4 and Day 122–152 for Cycle 5. In alignment with the methodology outlined in the ANDROMEDA CSR for calculation of the landmark six-month CHR rate, a larger window (Days 153–213) was used to capture patient haematologic responses for Cycle 6.

For each month, the number of patients who achieved a best response of a CHR, VGPR, PR/NR and had died was recorded. From these data, the proportion of patients who had died or who had achieved a CHR, a VGPR or a PR/NR was calculated by dividing the number of patients with each outcome by the ITT analysis set (DBCd: N=195; BCd: N=193). In alignment with the ANDROMEDA CSR, all patients that were not recorded as CHR, VGPR, PR, NR, or dead in a given month were assigned as NR.

2. **Please clarify whether any adjustment was made to the data presented in Tables 40 and 41 to account for treatment switching in the ANDROMEDA trial. If yes, please provide details on the methods used and corresponding results.**

In alignment with the ANDROMEDA trial protocol and as discussed further in response to Part 3 of Question A3, patients that switched to a subsequent non-cross resistant anti-plasma cell therapy were considered to have a NR from that point onwards. The number of patients per month who were designated to have a NR as a result of switching to subsequent non-cross resistant anti-plasma cell therapy is presented in Table 14.

Table 14. Patients designated NR after switching to subsequent non-cross resistant anti-plasma cell therapy

Cycle (month)	Patients designated NR, n	
	DBCd	BCd

1	0	0
2	0	0
3	0	0
4	1	8
5	0	9
6	5	14

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; NR: no response.

3. **Please provide details on the methods and results of the analyses that inform the transition probabilities (from p.116), the mortality distribution by health state (from p.115) and relative dose intensities (p.129), as this was not provided; including any adjustments made to account for treatment switching.**

Transition probabilities to MOD-PFS

Kaplan-Meier curves for time-to-MOD-PFS (excluding death events) were derived using ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months); these are presented in Figure 23 of the original Company Submission. These curves were subsequently smoothed using a linear function (Figure 24 of the original Company Submission), from which the constant hazard rate for each haematologic response was calculated as shown in Table 15. From this constant hazard rate, the per-cycle probability of MOD-PFS (excluding death) stratified by haematologic response was calculated (Table 15) using the following formula:

$$Probability = 1-exp(-rate)$$

Because patients from '1L Tx', 'Off Tx/FDT' and '2L Tx' can all transition to 'End-stage organ failure' in any given cycle, the monthly probability of MOD-PFS was further stratified based on the distribution of MOD-PFS events (excluding deaths) that occurred by health state in ANDROMEDA. ANDROMEDA IPD was used to determine the number and proportion of MOD-PFS events stratified by health state (Table 16). In general, a small number of MOD-PFS events were reported at the first clinical cut-off, leading to some unrealistic values for patients on second-line therapy (for example, no MOD-PFS events occurred for patients with VGPR). Therefore, due to a lack of data availability, a simplifying and conservative assumption was made whereby the transition probabilities for '2L Tx' to 'End-stage Organ Failure' were assumed equivalent to those for '1L Tx' to 'End-stage Organ Failure' for all haematologic responses. Therefore, the distribution of MOD-PFS events used to calculate transition probabilities were as presented in Table 17 (also presented within Table 47 of the original Company Submission). This is a conservative assumption because the probability of transitioning to 'End-stage Organ Failure' is likely underestimated in later stages of the model. As DBCd slows patient progression through the model versus BCd, this assumption is likely to introduce bias against DBCd.

The distribution of MOD-PFS events (Table 17) and the monthly probability of MOD-PFS (Table 15) were used to calculate transition probabilities based on health state and haematologic response (Table 18; final values presented in Table 47 of Document B of the original Company Submission). Any patient that switched to a subsequent non-cross resistant anti-plasma cell

therapy within the first one to four months of treatment was designated as a non-responder (NR). No additional adjustments were made due to treatment switching.

Table 15: Hazard rates and per-cycle probabilities for time-to-MOD-PFS (excluding death)

	CHR	VGPR	PR/NR
Hazard Rate	0.00213	0.01031	0.03453
Probability	0.00212	0.01025	0.03394

Abbreviations: CHR: complete haematologic response; MOD-PFS: major organ deterioration progression-free survival; NR: no response; PR: partial response; VGPR: very good partial response.

Table 16: MOD-PFS events (excluding death) by health state

	MOD-PFS events, n (%)		
	1L Tx	Off Tx	2L Tx
CR	3 (12)	2 (10)	1 (10)
VGPR	7 (28)	7 (35)	0 (0)
PR+NR	9+6=15 (60)	5+6=11 (55)	3+6=9 (90)
Total	25 (100)	20 (100)	10 (100)

Abbreviations: 1L: first-line; 2L: second-line; CHR: complete haematologic response; MOD-PFS: major organ deterioration progression-free survival; NR: no response; PR: partial response; Tx: treatment; VGPR: very good partial response.

Table 17: Distribution of MOD-PFS events as used in model

	1L Tx (%)	Off Tx (%)	2L Tx (%)
CR	12%	10%	12%
VGPR	28%	35%	28%
PR+NR	60%	55%	60%
Total	100%	100%	100%

Abbreviations: 1L: first-line; 2L: second-line; CHR: complete haematologic response; MOD-PFS: major organ deterioration progression-free survival; NR: no response; PR: partial response; Tx: treatment; VGPR: very good partial response.

Table 18: Transition probability (to 'End-stage Organ Failure' health state) calculations

	1L Tx → End-stage Organ Failure	Off Tx → End-stage Organ Failure	2L Tx → End-stage Organ Failure
CR	12%*0.21% = **0.025%**	10%*0.21% = **0.021%**	12%*0.21% = **0.025%**
VGPR	28%*1.03% = **0.287%**	35%*1.03% = **0.359%**	28%*1.03% = **0.287%**
PR+NR	60%*3.39% = **2.036%**	55%*3.39% = **1.867%**	60%*3.39% = **2.036%**

Abbreviations: 1L: first-line; 2L: second-line; CHR: complete haematologic response; MOD-PFS: major organ deterioration progression-free survival; NR: no response; PR: partial response; Tx: treatment; VGPR: very good partial response.

Transition probability to second-line treatment

The transition from 'Off Tx/FDT' to '2L Tx' was generated using the time to subsequent non-cross resistant anti-plasma cell therapy curves from ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months) stratified by haematologic response. For curve generation, the three-month stratification of hematologic response was selected for use, rather than stratification at six-months, due to larger sample size. Given that these curves appear mostly linear, a constant transition probability was deemed reasonable. These curves were digitised and the inverse data was used to graph curves that were smoothed using a linear

function – this is presented in Figure 26 of the original Company Submission. The constant hazard rate (Table 19) was calculated and then converted to a per-cycle probability stratified by haematologic response (Table 19) using the following formula:

$$Probability = 1-exp(-rate)$$

The per-cycle transition probabilities from 'Off Tx/FDT' to '2L Tx' were 0.42% for CR and 1.52% for a VGPR. For a PR/NR, a transition probability is not applicable since all patients with this haematologic response will automatically switch to second-line treatment after exit from the decision tree.

Table 19: Time-to-subsequent non-cross resistant anti-plasma cell therapy hazard rates and per-cycle probabilities

	CR	VGPR	PR/NR
Hazard Rate	0.004206	0.015343	0.064429
Probability	0.004197	0.015226	Not applicable

Abbreviations: CHR: complete haematologic response; NR: no response; PR: partial response; VGPR: very good partial response.

Mortality distribution

ANDROMEDA IPD (based on the primary analysis; February 2020; median follow-up: 11.4 months) were used to determine the number of patients that died from each health state in the first six months (180 days) or Month 7 and beyond, as presented in Table 20. The number of deaths per health state were used to calculate the mortality distributions for Cycles 4–6 (Table 45 of the original Company Submission) and for Cycles 7+ (Table 46 of the original Company Submission).

Table 20: Distribution of deaths by health state

	Total (all treated patients)	1–6 months	7+ months
1L Tx	381	35	0
Off Tx	218	4	2
2L Tx	95	3	1
End-stage organ failure	46	3	5

"1L Tx" is from first exposure to first treatment to the earlier of: 30 days after last exposure to treatment *or* first exposure of second treatment. "Off Tx" is from 30 days after last exposure to first treatment to first exposure of second treatment. "2L Tx" is on or after date of first exposure to second treatment. "End-stage Organ Failure" is after any MOD-PFS event had occurred (excluding death).
Abbreviations: 1L: first-line; 2L: second-line; MOD-PFS: major organ deterioration progression-free survival; Tx: treatment.

Relative dose intensities

The relative dose intensities presented in the original Company Submission, as reported in the safety set of the ANDROMEDA trial at 11.4 months median follow-up, are presented in Table 21 below.

Table 21: Relative dose intensities (safety analysis set)

Relative dose intensity	BCd (N=188)	DBCd (N=193)
Cyclophosphamide, %		
N	[redacted]	[redacted]

Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range (min, max)	[redacted]	[redacted]
Bortezomib, %		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range (min, max)	[redacted]	[redacted]
Dexamethasone, %		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range (min, max)	[redacted]	[redacted]
Daratumumab, %		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range (min, max)	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; SD: standard deviation.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[5]

B7. CS, section B.3.5.2. Subsequent lines of therapy

The company used feedback from UK expert clinicians to inform subsequent lines of therapy for 2nd line (base-case analysis) and 3rd line treatments (scenario analysis). It assumes that patients incur the costs at entry into the 2nd line therapy (and 3rd line, respectively) health states. In the model, this occurs at the cycle following exit from the decision tree for patients who achieved partial (PR) or no response (NR), or over time when patients' relapse for complete (CR) and very good partial response (VGPR).

1. Please provide justification for including the costs of 2nd and 3rd line therapies upfront, since this approach is likely to overestimate the costs of subsequent therapies as not all patients will be alive to receive the full course of treatment and others will discontinue treatment.

As noted in Table 82 in Section B.3.6.2 of the original Company Submission, the application of subsequent therapy costs as a one-time cost was a simplification assumption taken due to the natural history data and treatment patterns for patients with relapsed or refractory AL amyloidosis being poorly documented; in particular, treatment duration of second- and third-line therapies is not well reported in the literature. Uncertainty in subsequent therapy distribution and duration is inherent in orphan diseases such as AL amyloidosis where no licensed treatments exist and

clinical practice is consequently varied. Given this lack of approved subsequent therapies for AL amyloidosis, the relevant Summary of Product Characteristics or published studies were used to inform dosing and administration frequencies and durations for all off-label subsequent therapies applied in the model.

Upon reviewing articles cited by the National Comprehensive Cancer Network (NCCN) for previously treated disease, variability was noted with respect to the maximum allowable number of cycles administered to patients receiving the same treatment regimen. For example, two studies reported outcomes for patients treated with lenalidomide, cyclophosphamide, and dexamethasone (LCd). In the first study, a maximum of 24 cycles of LCd was permitted (with a cap of 12 cycles specifically for cyclophosphamide); however, in the second study, a maximum of 9 cycles of LCd was permitted.[19, 20] In other instances, the treatment duration was poorly defined since treatment could continue until disease progression, the patient withdrew consent, or until the development of unacceptable toxicities.[20, 21] Taken together, variability and ambiguity in the various regimens used in subsequent therapy and their associated treatment durations reported for patients receiving subsequent therapies was the driving factor in choosing a simple yet flexible approach of applying an upfront cost associated with subsequent therapy in the model.

2. Please provide the cost-effectiveness results (and revised model) for a scenario where the costs of 2nd line therapy (and 3rd line) are adjusted to reflect dose adjustments, discontinuations, and deaths during the course of treatment. Please signpost the changes made to the model.

As discussed in Part 1 above, the absence of licensed treatments in orphan diseases is often associated with uncertainty in subsequent therapy distribution and duration. The Company have not been able to identify any available data with which to determine an appropriate adjustment to the costs of second- and third-line therapies in order to reflect dose adjustments, discontinuations and deaths during the course of treatment. However, the Company acknowledge a need to address these uncertainties as far as possible and thus performed several scenario analyses to test the effect of various proportional reductions in the second- and third-line therapy costs.

Therefore, several scenario analyses were performed to test the effect of various proportional reductions in the second- and third-line therapy costs. The Company note that these reductions are arbitrary and are provided in order to determine how influential adjustments to subsequent therapy costs are on the base case results, rather than to provide clinically appropriate estimations suitable for decision-making. Furthermore, the Company note that since the OS source considered in these analyses does not provide information on subsequent treatment therapy distributions, the adjustments presented impact costs only while the survival assumptions remain unchanged, further limiting the appropriateness of this scenario. All cost-effectiveness data presented account for the updated utilities approach described in Question B10 and correction of the model errors described in Question B14.

The cost-effectiveness results for scenarios in which second-line therapy costs are reduced are presented in Table 22. The cost-effectiveness results for scenarios in which both second- and third-line subsequent therapy costs are reduced are presented in Table 23.

The effect on ICERs in each of these scenario analyses is limited and does not affect any of the conclusions of cost-effectiveness: even a 70% reduction in both second- and third-line therapy

costs results in a cost-effective ICER that falls below the £30,000/QALY willingness-to-pay threshold. Overall, DBCd remains a cost-effective option versus BCd in these scenarios which can reasonably be considered to be extremely conservative.

A setting has been added to the revised model to allow for a set reduction to be applied to the subsequent therapy costs.

Table 22: Cost-effectiveness results for scenarios in which second-line therapy costs are reduced

Reduction in second-line therapy costs	ICER	Impact on ICER vs base case (£/QALY)
0% (no change)	£23,509	£0
20%	£23,941	+£432
50%	£24,590	+£1,081
70%	£25,022	+£1,513

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 23: Cost-effectiveness results for scenarios in which second- and third-line therapy costs are reduced

Reduction in second- and third-line therapy costs	ICER	Impact on ICER vs scenario including third-line subsequent therapy costs (£/QALY)
0% (no change)	£14,835	£0
20%	£17,002	+£2,167
50%	£20,253	+£5,418
70%	£22,420	+£7,585

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

3. Feedback from ERG's clinical advisors suggests that bortezomib-based regimens are unlikely to be used as 2nd line therapy in patients who have previously received bortezomib as a 1st line therapy. Please provide the cost-effectiveness results (and revised model) for a scenario where 2nd line therapy does not include bortezomib. Please signpost the changes made to the model.

At a Janssen-led advisory board, UK-based clinical experts confirmed that some patients who received bortezomib-based regimens such as BCd in the first-line setting would be re-treated with BCd second-line, particularly if they had shown a long response.[13] Based on this feedback that re-treatment with BCd occurs in around 10% of AL amyloidosis patients, bortezomib-based regimens were included as a second-line treatment option. However, for completeness, a setting has been added to the revised model to allow for bortezomib regimens to be excluded from second-line therapies. In this case, all other second-line therapy options are re-weighted proportionately, to ensure that treatment shares sum to 100%. All cost-effectiveness data presented account for the updated utilities approach described in Question B10 and correction of the model errors described in Question B14.

Cost-effectiveness results for this scenario in which second-line therapies are included but bortezomib regimens are not included as a second-line therapy option are presented in Table 24.

The results demonstrate that the removal of bortezomib-based therapies as a second-line therapy option has only a minimal impact on the base case ICER, decreasing it by £200. Consequently, no conclusions of cost-effectiveness are affected and DBCd remains a cost-effective option versus BCd in this scenario.

Table 24: Cost-effectiveness results for scenario in which bortezomib-based therapies are removed as a second-line option for those who received these therapies at first-line

	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALY)
BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,309

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

4. The publication by Ravichandran et al. (2021) [reference included below] reports the baseline characteristics, treatments and outcomes of patients included in the ALchemy study who were treated with up-front bortezomib-based regimens. Table SA3 of the Supplementary data to this study reports the distribution of treatments received by patients in subsequent lines of treatment. Please provide the cost-effectiveness results (and revised model) for the following scenarios, signposting the changes made to the model:

    i. the distribution of treatments for 2nd line in Ravichandran et al. (2021) is used to inform the 2nd line therapies in the model (excluding daratumumab, that is, recalculate the distribution of patients without including the patients treated with daratumumab).

For this scenario, therapies with a treatment share of less than 1% (rituximab, ixazomib, ibrutinib, platinum, and allogeneic HSCT) were not included, as these therapies are unlikely to have a material impact on the weighted average cost for second-line treatment. The treatment shares for the other therapies were re-weighted proportionately in order to sum to 100%.

As Table SA3 in the Ravichandran *et al.,* (2021) paper reports the principal agents of subsequent therapy regimens only, it was necessary to make assumptions regarding the full regimen received; these assumptions are listed in Table 25. Where regimens matched those used in the base case analysis of subsequent therapies, the same treatment durations were assumed. For bendamustine monotherapy, a treatment duration of 7 cycles was assumed, based on its SmPC which reports an average treatment duration of 6.8 cycles for bendamustine in the treatment of multiple myeloma.[22] For thalidomide monotherapy, a treatment duration of 12 cycles was assumed, based on the maximum treatment duration specified in its SmPC.[23]

The results of this scenario are presented in Table 26. and they demonstrate that modelling second-line therapies as informed by Ravichandran *et al.,* (2021) has a minimal impact on the base case ICER, increasing it by £977. Consequently, no conclusions of cost-effectiveness are affected and DBCd remains a cost-effective option versus BCd in this scenario. All cost-

effectiveness data presented account for the updated utilities approach described in Question B10 and correction of the model errors described in Question B14.

A setting has been added to the revised model so that this scenario can be easily run. The scenario is compatible with the scenarios requested in question Parts 2 and 3 of this question: adjustment to reflect dose adjustments, discontinuations, and deaths during the course of treatment, and the removal of bortezomib based therapies for second line.

Table 25: Second-line treatment weightings in the scenario in which second-line therapies are informed by Ravichandran et al., (2021)

Principle agent	Assumed therapy	Proportion of second-line patients receiving therapy
Bortezomib	VELCADE® + Cyclophosphamide + Dexamethasone (VCd)	8%
Lenalidomide	REVLIMID® + Dexamethasone (Rd)	55%
Melphalan	Melphalan + Dexamethasone (Md)	11%
Autologous HSCT	Autologous HSCT (one time event)	11%
Pomalidomide	Imnovid® + Dexamethasone (Pd)	2%
Carfilzomib	Kyprolis® + Dexamethasone (Kd)	1%
Bendamustine	Bendamustine monotherapy [a]	8%
Thalidomide	Thalidomide monotherapy	4%
Cyclophosphamide	VELCADE® + Cyclophosphamide + Dexamethasone (VCd)	2%

[a] Bendamustine is used in combination with prednisone in treatment for multiple myeloma. However, no price for prednisone was available on the latest versions of the eMIT or BNF, and therefore bendamustine was modelled as a monotherapy.
Abbreviations: HSCT: hematopoietic stem-cell transplantation
Source: Ravichandran *et al*., (2021).[12]

Table 26: Cost-effectiveness results for scenario in which second-line therapies are informed by Ravichandran *et al.*, (2021)

	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALY)
BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,486

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

ii. the distribution of treatments for 2nd and 3rd line in Ravichandran et al. (2021) is used to inform the 2nd and 3rd line therapies in the model (excluding daratumumab).

As with the scenario presented above in Part 4i of Question B7, therapies with a treatment share of less than 1% were not included, as these therapies are unlikely to have a material impact on the weighted average costs for second-line, or third-line treatment. These were rituximab, ixazomib, venetoclax, ibrutinib, platinum, and allogeneic HSCT for second-line treatment and thalidomide, ixazomib, venetoclax, ibrutinib, platinum, and allogeneic HSCT for third-line

treatment. The treatment shares for the other therapies were re-weighted proportionately to ensure that they summed to 100%.

As with the scenario presented above in Part 4i of Question B7, assumptions regarding the full regimen received were necessary given that Table SA3 of Ravichandran *et al.,* (2021) reports the principal agents of subsequent therapy regimens only; these assumptions are provided in Table 27. The same assumptions regarding treatment duration were made as for the second-line scenario. All cost-effectiveness data presented account for the updated utilities approach described in Question B10 and correction of the model errors described in Question B14.

The results of this scenario are presented in Table 28. As above, the results demonstrate that using second- and third-line therapies as informed by Ravichandran *et al.,* (2021) does not affect conclusions of cost-effectiveness, with DBCd remaining a cost-effective option versus BCd.

Table 27: Second- and third-line treatment weightings in the scenario in which second- and third-line therapies are informed by Ravichandran *et al.*, (2021)

Principle agent	Assumed therapy	Proportion of second-line patients receiving therapy	Proportion of third-line patients receiving therapy
Bortezomib	VELCADE® + Cyclophosphamide + Dexamethasone (VCd)	8%	2%
Lenalidomide	REVLIMID® + Dexamethasone (Rd)	55%	58%
Melphalan	Melphalan + Dexamethasone (Md)	11%	2%
Autologous HSCT	Autologous HSCT (one time event)	11%	12%
Panabinostat	Farydak® + VELCADE® + Dexamethasone (PBd)	0%	5%
Pomalidomide	Imnovid® + Dexamethasone (Pd)	2%	13%
Carfilzomib	Kyprolis® + Dexamethasone (Kd)	1%	2%
Bendamustine	Bendamustine monotherapy*	8%	6%
Thalidomide	Thalidomide monotherapy	4%	0%
Cyclophosphamide	VELCADE® + Cyclophosphamide + Dexamethasone (VCd)	2%	0%

*Bendamustine is used in combination with prednisone in treatment for multiple myeloma. However, no price for prednisone was available on the latest versions of the eMIT or BNF, and therefore bendamustine was modelled as monotherapy.
Abbreviations: HSCT: hematopoietic stem-cell transplantation
Source: Ravichandran *et al*., (2021).[12]

Table 28: Cost-effectiveness results for scenario in which second- and third-line therapies are informed by Ravichandran et al., (2021)

	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALY)
BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,073

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

Conclusion

Despite the inherent uncertainty associated with subsequent therapy distributions and durations in rare diseases such as AL amyloidosis, none of the scenarios presented in response to Question B7 have had a substantial impact on the cost-effectiveness results and all results indicate DBCd remains a cost-effective treatment option versus BCd.

B8. CS, sections B.3.2.2, B.3.3.2 and B.3.3.3. Model structure: pooling together patients with partial response (PR) and no response (NR).

The company combines response categories of PR and NR in the model.

1. Please provide justification for combining these response categories when there are clear differences in overall survival and time to MOD-PFS for PR and NR.

As discussed in Section B.3.2.2 of the original Company Submission, clinical expert opinion received by Janssen suggests that patients with a PR or NR are similarly classified as having a sub-optimal response and would be managed similarly in typical UK clinical practice by switching treatments. Therefore, combining these response categories in the decision tree was deemed a reasonable and appropriate reflection of clinical practice. This model structure was validated by a UK clinician to be an appropriate representation of the AL amyloidosis disease and care pathway, with no concerns raised regarding the combination of PR and NR response categories.

Furthermore, although the model uses only one curve for the PR and NR response categories, the PR/NR model inputs are nonetheless informed by all available data from both the PR and NR response levels: the PR/NR OS curve accounts for PR-specific and NR-specific OS by combining these data using a weighted average based on the ANDROMEDA distribution.

2. Please provide a revised version of the model with sufficient flexibility in the model structure to separate out the categories of PR and NR in order to enable separate data on PR and NR to be included in the model. Please signpost the changes made to the model.

As noted above, based on clinical expert opinion, the Company deems the current model approach, which combines the PR and NR response categories by a weighted average, is a reasonable reflection of clinical practice. Splitting these response categories within the economic

modelling would add undue complexity to the analysis; The Company do not believe that this additional complexity is warranted given that these patients are managed in the same way in clinical practice and since it introduces further uncertainty into the model. As such, no edit to the model structure has been made.

3. Please provide a revised set of cost-effectiveness results (and model inputs) where the categories of PR and NR are not combined. This includes providing updated data for Tables 40 and 41 of the company submission for haematologic response over time separated by PR and NR, and updated transition probabilities for PR and NR separately.

As noted above, based on clinical expert opinion, the Company deems that the current model approach provides a reasonable reflection of clinical practice without adding undue complexity and uncertainty into the model. As such, no edit to the model has been made.

4. The company submission states that "Where an alive patient's haematologic response status was not reported in a particular cycle, they were classified as PR/NR" (p.106). Please clarify how much data was missing from the ANDROMEDA trial to inform haematologic response status in each cycle, why these data were missing, and why the missing data were classified as PR/NR status.

A summary of the number of patients with missing data per treatment and cycle is presented Table 29. Within the model, patients with missing data were classified as NR to produce response estimates that align with the pre-specified ITT analysis of the primary endpoint as reported in the ANDROMEDA publication. All randomised patients in the ITT analysis were included in the denominator of the haematologic response calculations, but patients who had missing data were not evaluable for response status. As such, in order to use all available response data, it was assumed that these patients were NR. Specific reasons for missing data are not available.

Table 29: Patients in the decision tree with missing data by cycle

Cycle	DBCd (n=195), n (%)	BCd (n=193), n (%)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intent-to-treat.

5. Please clarify the source of data used to plot Figure 24 of the company submission (extrapolated time-to-MOD-PFS curves) and explain how it relates

to inputs used in the model. Please note that there is no cross-reference to this figure in the text.

The Company apologise that Figure 24 was not cross-referenced in the original Company Submission. This figure presents the smoothed curves (CR, VGPR, and PR/NR) from Figure 23 of the Company Submission: time-to-MOD-PFS data was used to generate the constant hazard rate and, subsequently, the monthly probability for MOD-PFS stratified by health state. The monthly probability for MOD-PFS stratified by health state was used to calculate the transition probability to end-stage organ failure.

B9. CS, sections B.2.3.2, B.3.2.2 and B.3.3.3. Probability of end-stage organ disease.

The transition probability to the health state of 'end-stage organ disease' is based on the probability of major organ deterioration-progression free survival (MOD-PFS) excluding deaths. The company submission states that "The 'End-stage Organ Failure' health state encompasses patients that require solid organ (i.e. heart or kidney) transplant or dialysis" (p.100). MOD-PFS is defined as "a composite endpoint of clinically observable endpoints defined from randomisation to any one of the following events, whichever came first: death, clinical manifestation of cardiac failure (…), clinical manifestation of renal failure (…), development of haematologically progressed disease as per consensus guidelines" (p.40).

1. Please clarify how the composite outcome of MOD-PFS from the ANDROMEDA trial, excluding deaths, maps to the health state of 'end-stage organ disease' because MOD-PFS includes not only clinical manifestations of cardiac or renal failure but also haematologically progressed disease, which is not end-stage organ failure.

In light of the limited number of events observed in the ANDROMEDA trial at the time of IA1, all major organ deterioration and haematologic progression events were considered to be events when calculating the transition probability to the End-stage Organ Failure health state. This assumption was essential to retain the necessary sample size to derive transition probabilities and represents an inherent limitation in an analysis where few events have occurred. In this case, using the probability of MOD-PFS (excluding deaths) to calculate a transition probability to the End-stage Organ Failure health state based solely on events relating to cardiac or renal failure was not feasible.

Although a proportion of the MOD-PFS events recorded at the time of IA1 were haematologic progression events, haematologic progression of disease is likely to increase the risk that patients progress to the later stages of AL amyloidosis in which end-stage organ failure may occur. Increasing levels of abnormal free light chain proteins and amyloid deposition in organs is

expected to contribute to further deterioration of these organs, thereby increasing the risk of patients reaching end-stage organ failure.[24]

2. Please report the number of patients who had MOD-PFS by depth of haematologic response, and provide the percentage breakdown of patients by the endpoints that constitute the MOD-PFS outcome.

At the time of IA1, 87 MOD-PFS results had been observed, representing 43.5% of the 200 planned events. The number of patients with MOD-PFS by depth of haematologic response and the proportion of patients with the endpoints that constitute the composite MOD-PFS outcome are presented in Table 30 and Table 31, respectively.

Table 30: Patients with MOD-PFS by depth of haematologic response at IA1

Haematologic response (IA1)	Patients with MOD-PFS, n (%)	
	BCd (N=193)	DBCd (N=195)
CHR	[redacted]	[redacted]
VGPR	[redacted]	[redacted]
PR	[redacted]	[redacted]
NR	[redacted]	[redacted]
NE	[redacted]	[redacted]
Total	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; NE: not evaluable; NR: no response; PR: partial response; VGPR: very good partial response.

Table 31: Summary of major organ deterioration progression-free survival (MOD-PFS) based on IRC assessment, IPCW analysis; ITT analysis set (14th February 2020 data cut-off)

	BCd (N=193)	DBCd (N=195)	DBCd vs BCd
Number of events, n (%)	[redacted]	[redacted]	-
Haematologic PD	[redacted]	[redacted]	-
Major organ deterioration	[redacted]	[redacted]	-
Death	[redacted]	[redacted]	-
Hazard ratio (95% CI)[a]	-	-	[redacted]
p-value[b]	-	-	[redacted]

[a] Hazard ratio and 95% CI are from unstratified weighted Cox proportional hazards model including treatment group as the sole explanatory variable by using IPCW method. A hazard ratio <1 favours DBCd. [b] p-value is from IPCW log-rank test (i.e. score test from unstratified IPCW weighted Cox proportional hazards model).
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; PD: progressive disease.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[5]

3. Please explain how the probability of MOD-PFS, which informs the transition matrices in the model, was calculated from the results of the IPCW analysis. Please also comment on any assumptions made in this analysis and the plausibility of these assumptions.

Details on the methods and results of the analyses informing transition probabilities to MOD-PFS are described in the response to Part 3 of Question B6 above.

It should be noted that the data used to calculate the probability of (transition to) 'End-stage Organ Failure' was not calculated based on the results of the IPCW analysis. Rather, raw ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months) was used to derive time-to-MOD-PFS KM curves, stratified by patient hematologic response at the 3-month landmark (which provided a larger sample size than responses at the 6-month landmark). As described in the response to B6, Part 3, the only adjustment made with respect to treatment switching was assigning "NR" to any patient that commenced subsequent non-cross resistant anti-plasma cell therapy in months 1–4.

Assumptions made in this analysis and their associated plausibility

1. Based on the available data from ANDROMEDA, transition probabilities to the 'End-stage Organ Failure' health state are constant over time.
    a) Generally, the MOD-PFS-free survival KM curves appear to have a constant rate of decline (i.e., are linear). Therefore, the curves were smoothed using a linear function to derive constant hazard rates and transition probabilities to inform transitions to 'End-stage Organ Failure'.
2. Transition probabilities to 'End-stage Organ Failure' were calculated by including all MOD-PFS events except death (i.e., all first-described incidences of end-stage renal failure, end-stage cardiac failure, and hematologic progression).
    a) Due to data immaturity at the time of the first clinical cut-off, and the exclusion of death as a MOD-PFS event, only a small number of 'major organ deterioration' events had occurred; therefore, in order to conduct more robust data re-analyses, hematologic progression events were also included in the derivation of transition probabilities to 'End-stage Organ Failure'. Although MOD-PFS (excluding death) only captures the *first* instance of either major organ deterioration event or hematologic progression, it was assumed that including hematologic progression events in the transition probability calculation is reasonable since progression events typically precede (and would, in turn, lead to) major organ deterioration.[25, 26] Furthermore, due to the time-to-MOD-PFS data immaturity at the first clinical data cut-off, including a higher number of "MOD-PFS" events in the transition probability calculation was viewed as a plausible estimate of the expected number of 'major organ deterioration' events for a progressive disease like AL amyloidosis that would occur with longer trial follow-up.
    b) The transition probabilities for '2L Tx' to 'End-stage Organ Failure' were assumed equivalent to those for '1L Tx' to 'End-stage Organ Failure' for all hematologic responses. Due to data immaturity at the time of the first clinical cut-off, an unrealistic number of MOD-PFS events (ie, zero) resulted for patients with VGPR on second-line therapy. Therefore, a simplifying (and likely conservative) assumption was made whereby the same number of events were used to calculate the transition probabilities from '1L Tx' to 'End-stage Organ Failure' and '2L Tx' to 'End-stage Organ Failure'.

4. Please clarify if, in Table 47 of the company submission, the monthly probability of MOD-PFS refers to events from any health state.

The Company can confirm that the above interpretation is correct.

B10. CS, sections B.2.6.6, B.3.4.1 and B.3.4.4. Health-related quality of life (HRQoL).

1. Related to Figure 10 of the company submission:

    a. Please provide the EQ-5D values (mean and standard error) which underpin Figure 10 by trial arm; and by haematologic response status (including number of individuals by category and trial arm).

The EQ-5D-5L utility values by trial arm of the ANDROMEDA study that underpin Figure 10 of the original Company Submission are presented in Table 32. The EQ-5D-5L utility values of patients in the ANDROMEDA trial by best haematologic response are presented in Table 33.

In the ANDROMEDA trial, EQ-5D-5L utility values were gathered for the period of time in which patients were receiving treatment and no further values were obtained after treatment was stopped. The Company acknowledge that the lack of available EQ-5D-5L utility values for patients in the BCd arm of the trial after Cycle 6, once treatment has stopped, precludes comparison with patients in the DBCd arm after this point, and that the number of patients with recorded EQ-5D-5L utility value data decreases over time.

Despite this, the data from Cycle 7 onwards indicate an improvement in EQ-5D-5L utility values with time for patients in the DBCd arm who were receiving daratumumab monotherapy, which is consistent with the tolerable safety profile of daratumumab SC as described in the original Company Submission. Furthermore, this is supported by expert clinical opinion, with UK-based clinicians indicating that improvements to HRQoL over time would be expected in patients receiving treatment.[13]

Table 32: Summary of EQ-5D-5L utility scores by visit from the ANDROMEDA trial (ITT analysis set) (14th February 2020 data cut-off)

	Utility score				
	N	Mean	SD	SE[a]	Median
BCd					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBCd					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Standard errors associated with the mean utility scores were calculated by dividing the standard deviation for each cycle by the square root of the number of patients with recorded EQ-5D-5L utility scores in that cycle.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; EQ-5D-5L: EuroQol-5 Dimensions-5 Level; NA: not applicable; SD: standard deviation; SE: standard error.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[5]

Table 33: EQ-5D-5L utility scores by best haematologic response and by visit from the ANDROMEDA trial (ITT analysis set) (14th February 2020 data cut-off)

	CR (N=139)					VGPR (N=109)					PR/NR (N=125)				
	N	Mean	SD	SE[a]	Med.	N	Mean	SD	SE[a]	Med.	N	Mean	SD	SE[a]	Med.
BCd															
Baseline	[redacted]														
Cycle 2 Day 1	[redacted]														
Cycle 3 Day 1	[redacted]														
Cycle 4 Day 1	[redacted]														
Cycle 5 Day 1	[redacted]														
Cycle 6 Day 1	[redacted]														
DBCd															
Baseline	[redacted]														
Cycle 2 Day 1	[redacted]														
Cycle 3 Day 1	[redacted]														
Cycle 4 Day 1	[redacted]														
Cycle 5 Day 1	[redacted]														
Cycle 6 Day 1	[redacted]														
Cycle 7 Day 1	[redacted]														
Cycle 9 Day 1	[redacted]														
Cycle 11 Day 1	[redacted]														
Cycle 13 Day 1	[redacted]														
Cycle 15 Day 1	[redacted]														
Cycle 17 Day 1	[redacted]														
Cycle 19 Day 1	[redacted]														
Cycle 21 Day 1	[redacted]														
Cycle 23 Day 1	[redacted]														

[a] Standard errors associated with the mean utility scores were calculated by dividing the standard deviation for each cycle by the square root of the number of patients with recorded EQ-5D-5L utility scores in that cycle.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; EQ-5D-5L: EuroQol-5 Dimensions-5 Level; Med.: median; NA: not applicable; SD: standard deviation; SE: standard error.

b. The company submission states that “At Week 16 (Cycle 4), there was no change in LS mean EQ-5D-5L utility scores in the DBCd group ([redacted] points; 95% CI: [redacted]), whereas scores decreased (that is, worsened) significantly in the BCd group ([redacted] points; 95% CI: [redacted]; unadjusted [redacted] vs DBCd)”. This does not appear to describe the data shown in Figure 10. Please provide further clarification of the discrepancy.

The Company apologise for this error and can confirm that the observed discrepancy is due to the above data relating to the LS mean change from baseline in EQ-5D-5L utility scores, rather than mean utility scores over time as presented in Figure 10 of the original Company Submission. For clarity, the LS mean change from baseline in EQ-5D-5L utility scores to which the above refers are presented in Table 34 below.

Table 34: Change from baseline in EQ-5D-5L utility score; mixed model for repeated measures; ITT analysis set (14th February 2020 data cut-off)

Timepoint	BCd (N=193)		DBCd (N=195)		Difference (DBCd – BCd) LSM[a] cfb (95% CI)	P-value
	n	LSM cfb (95% CI)	n	LSM cfb (95% CI)		
Baseline	[redacted]		[redacted]			
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] LSM 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 value, treatment, time in week, treatment-by-time interaction, and randomisation stratification factors — cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min) as fixed effects and individual subject as random effect. Note: visit window is derived by including all scheduled visits with available EQ-5D-5L assessment.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; cfb: change from baseline; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; EQ-5D-5L: EuroQol-5 Dimensions-5 Level; ITT: intent-to-treat; LSM: least square means.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off).[5]

c. Please clarify why EQ-5D (and other HRQoL) data were not collected after cycle 6 in the BCd arm of the ANDROMEDA trial. If this data was collected, please provide the values (mean and standard error) at each cycle; and by haematologic response status (including number of individuals).

EQ-5D-5L data are not available after Cycle 6 in the BCd arm of the ANDROMEDA trial. As mentioned in Part A of this question, EQ-5D-5L data were collected in both arms of the ANDROMEDA trial only for the period of time in which patients were receiving treatment. After treatment was stopped, no further values were obtained.

2. Related to Table 52 of the company submission:

   a. Please provide details on how these utility estimates were calculated from the data collected in the ANDROMEDA trial. Specifically,

      i. Please clarify which ANDROMEDA trial data were used (for example, timepoint based on a specific treatment cycle or mean across all cycles; includes both treatment arms or one specific arm; number of individuals that the data relates to).

The utility data presented in Section B.3.4.1 of Document B of the original Company Submission were derived by valuing the EQ-5D-5L data collected in the ANDROMEDA trial directly. However, the Company have since updated this approach to align with the NICE reference case. The EQ-5D-5L data have been cross-walked to the EQ-5D-3L based on the algorithm presented in van Hout *et al.*, 2012, before being valued using the UK-specific tariff by Dolan *et al.*, (1997).[27, 28]

The updated health state utility values (HSUVs) implemented in the updated model are presented in Table 35; the previous HSUVs presented in Table 52 of the original Company Submission are additionally presented for reference. In alignment with the original approach, the utility value for VGPR was calculated as the mean of the CR and PR/NR values given that it was deemed clinically implausible for it to be lower than the PR/NR value. For further discussion of this, please see Part B of this question below.

These utility data were derived using the mean of EQ-5D-5L data up to Cycle 6 for both arms, after which BCd treatment, and thus collection of EQ-5D-5L data, stopped. The number of patients from which these data were derived per health state is presented below in Table 36 in Part 3b of Question B10.

Table 35: Original and updated utility values for haematologic response derived from the ANDROMEDA trial

Haematologic response	Utility value (SE)	
	Original Company Submission	Updated values
CR	[redacted]	[redacted]
VGPR[a]	[redacted]	[redacted]
PR/NR	[redacted]	[redacted]

[a] VGPR utility value was calculated as the mean of CR and PR.
Abbreviations: CR: complete response; NR: no response; PR: partial response; SE: standard error; VGPR: very good partial response.

ii. Please clarify which methodology was used to derive these values (for example, based on mean values or a regression model. If the latter, please provide details on the regression model, including how standard errors were calculated).

The Company confirm that the mean and standard deviation values presented are a simple calculation without any additional methodology such as regression models.

b. Please explain why the mean utility value for VGPR ([redacted]) was found to be lower than the mean utility value for PR/NR ([redacted]).

As outlined in Part 2ai above, the updated model includes health state utility values derived by cross-walking the EQ-5D-5L data from the ANDROMEDA trial to the EQ-5D-3L and subsequently valuing it using a UK-specific tariff. Therefore, the data quoted in this question refer to the original VGPR and PR/NR values. However, in the updated EQ-5D-3L analysis the utility value for VGPR remained lower than that of PR/NR ([redacted] and [redacted], respectively).

Several factors could contribute to a lower mean utility value for VGPR than for PR/NR in the ANDROMEDA trial, but it is likely that the early timepoint at which utility values in ANDROMEDA were recorded was particularly influential. Expert clinical opinion received by Janssen is that improvements to HRQoL would be expected to increase with increasing time on treatment.[13] Therefore, the collection of utility data at this early stage in ANDROMEDA may have meant that the full benefits of differing levels of treatment response on HRQoL were not adequately captured. This is particularly the case given that utility data were not collected after Cycle 6 in the BCd arm whereas the clinical experts estimated the greatest improvements in quality of life may occur at approximately a year after treatment initiation.[13]

In addition to this, the lack of sensitivity of the EQ-5D instrument may have precluded clear differentiation of mean utility values for these haematologic response categories that is reflective of the differing symptom improvement and prognoses between types of response.

Where utility values are deemed clinically implausible from clinical trial results, it is not uncommon for alternative approaches to the application of utilities to be adopted, either using observed data or data from the literature. Given that the Company are not aware that any appropriate utility data for AL amyloidosis exist from the literature to inform VGPR, the approach adopted was deemed most methodologically sound. Utility value estimates provided by expert clinicians in the cost-effectiveness analysis were explored in a scenario analysis

3. Related to Table 54 of the company submission:

    a. Please provide details on how the utility decrements were calculated (for example, number of patients, and full details of the methodology used).

The recurring utility decrement for the second line treatment health state was calculated in the updated EQ-5D-3L analysis outlined in Part 2ai above to be [redacted]. For each subject that had at least one hematologic answer as "Progressive Disease" (n = [redacted]) an individual decrement in utility was calculated by subtracting their individual mean utility value before reaching a "Progressive Disease" state, from their individual mean utility value while in a "Progressive Disease" state. The value of [redacted] was then calculated as the mean over all individual decrements.

The recurring utility decrement for the End-stage Organ Failure health state was calculated in the updated EQ-5D-3L analysis outlined in Part 2ai above to be [redacted]. This value was derived by subtracting the utility score associated with patients assessed for heart transplant, as reported in Emin *et al.*, (2016), (0.5, n=194) from the ANDROMEDA baseline utility score ([redacted], n=[redacted]).[29]

    b. Please provide uncertainty estimates (for example, standard error) calculated with appropriate methods (in particular, please provide the standard error for the mean baseline utility of [redacted] from the ANDROMEDA trial).

The mean baseline utility from the ANDROMEDA trial that was calculated in the updated EQ-5D-3L analysis was [redacted].

The mean utility scores, number of patients, standard deviation (SD) and quantiles of utility scores for baseline, CHR, VGPR, PR, NR and PD as derived in the updated EQ-5D-3L analyses are presented in Table 36. As described in the response to Part 3a above, the baseline utility and progressive disease utility values were used in calculating the utility decrement associated with "End-stage Organ Failure". As a calculated value, there is no explicit uncertainty value associated with this decrement. Therefore, for the revised model, an uncertainty estimate for the "End-stage Organ Failure" utility decrement was determined online.[30] A revised uncertainty estimate for the second-line treatment utility decrement was calculated in the updated EQ-5D-3L analysis; this has also been included in the revised model. These uncertainties are presented in Table 37.

Table 36: Summary of EQ-5D-3L utility score by haematologic response state

EQ-5D-3L Utility Score	N	Mean	SD	Quantiles		
				25th	50th	75th
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VGPR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHR: complete haematologic response; EQ-5D-5L: EuroQol-5 Dimensions-5 Level; NR: no response; PD: progressive disease; PR: partial response; SD: standard deviation; VGPR: very good partial response.

Table 37: Uncertainty associated with calculated utility decrements

Utility Decrement For:	Calculated Standard Error Used in Revised Model[a]	Standard Error Used in Company Submission
2L Tx	[redacted]	[redacted]
End-stage Organ Failure	[redacted]	[redacted]

[a] Calculations performed with no error correlation between the two variables identified (https://statpages.info/erpropgt.html).

4. For the utility decrement related to dialysis, please justify the use of the haemodialysis mean utility value of 0.69 and not the peritoneal dialysis mean utility value of 0.72 from Wyld et al. (2012), noting that the model appears to refer to this parameter as peritoneal dialysis in resource use and costing.

Resource use and costing was included in the model for both haemodialysis and peritoneal dialysis; however, the Company acknowledge oversight in not accounting for both types of dialysis in the utility inputs. Nevertheless, variation of dialysis utility between 0.69 and 0.72 is anticipated to have a minimal effect on the cost-effectiveness results given the similarity in these figures, the relatively small proportion of patients to whom this disutility is applied in the model, and that no utility decrements were identified as key model drivers in the tornado diagram presented in Figure 30 of the original Company Submission.

5. For the disutilities due to adverse events applied in the model, please provide details of the literature search used to identify evidence sources to inform these disutilities.

The HRQoL SLR (detailed in Appendix H of the original Company Submission) identified no published literature detailing AL amyloidosis-associated adverse event (AE) disutility values. As such, disutility values for AEs were sourced from alternative published literature sources identified from a search for articles reporting AE disutilities associated with chemotherapy or more generic databases of EQ-5D scores. A PubMed/MEDLINE search, conducted on 5th February 2021, for articles published in the last 10 years using the search terms [("catalogue" OR "systematic review") AND ("utilities" OR "utility values" OR "EQ-5D")] yielded 417 articles.

From this search, two articles were identified which served as resources for informing utility values or sources of utility values in the model. The first article, Shabaruddin *et al*., (2013), is an SLR of utility values for chemotherapy-related AEs that is cited by 50 other articles.[31] This systematic review included the studies by Brown *et al*., (2001),[32] Beusterien *et al*., (2010),[33] and Nafees *et al*., (2008)[34] which reported the utility decrements used in the model for oedema, pneumonia, and neutropenia, respectively. Notably, all three articles have been cited in previous submissions to, and guidelines published by, the National Institute for Health and Care Excellence (NICE).[35-40] The second article, Sullivan *et al*., (2011), is a UK-specific catalogue of EQ-5D scores from which multiple utility decrements (i.e., for cardiac failure, hypokalemia, and syncope) were sourced.[41] Finally, a recently published article by Stein *et al*., (2018)[42] was

identified via hand-searching of other cost-effectiveness studies; the utility decrement for diarrhoea was sourced from this article.[43-45]

B11. CS, section B.3.8.1. Probabilistic sensitivity analysis.

The following issues have been identified with the model programming for the probabilistic analysis. Please correct these issues in the model and signpost the changes made to the model.

1. The depth of haematologic response is not sampled in the probabilistic sensitivity analysis. Please amend the model to include parameter uncertainty for the depth of haematologic response.

The model submitted alongside these responses has been amended to include parameter uncertainty for the depth of haematologic response.

2. Please revise the standard errors used to draw simulations of the model inputs, to use standard errors obtained from their relevant data source where possible rather than assuming 10% of the mean value. Please provide a list of the parameters updated in the model.

Based on the updated EQ-5D-3L utility analyses, updated standard errors have been provided in the revised model for the following inputs as summarised in Table 38.

These updated EQ-5D-3L utility analyses provided the standard errors for the CR utility value, PR/NR utility value, and second line treatment utility decrement. However, as outlined in response to Part 2a of Question B10, the VGPR utility value was calculated as an average of the CHR and PR/NR utility values; as such, its associated standard error was calculated online using the standard errors of the CHR and PR/NR.[30] The standard error for the end-stage organ failure decrement was calculated as described in response to Part 3b of Question B10.

Aside from these changes, standard errors for model inputs have been utilised where they were available from the source. In cases where a standard error was not available or could not be calculated, a standard error of 10% has been assumed.

Table 38: Revised input parameters and standard errors in the economic model

Parameter	Input (standard error)
CHR utility value	[redacted]
VGPR utility value	[redacted]
PR/NR utility value	[redacted]
Second-line treatment utility decrement	[redacted]
End stage organ failure decrement	[redacted]

Abbreviations: CHR: complete haematologic response; PR: partial response; NR: no response; VGPR: very good partial response.

B12. CS, sections B.1.1 and B.1.2 and Reference 116 (Janssen. [Data on File]. HCRU in AL Amyloidosis UK Delphi Panel Report., 2021). Autologous stem cell therapy in the cost-effectiveness model.

The model does not appear to include autologous stem cell therapy (ASCT) as part of the subsequent therapies (2nd or 3rd line) after 1st line therapy with DBCd or BCd. However, the results of the company's modified Delphi panel on resource use states that 13% of patients would have ASCT as part of 1st line therapy and the off-treatment period (Tables 2 and 3) and 11% as part of 2nd line therapy (Table 4). In the footnotes of Tables 2 to 4 in Reference 116, it states that "[redacted]", and that more realistic estimates are [redacted] respectively.

1. Please justify the rationale for not including ASCT as part of the costs associated with the subsequent therapy health states.

The Company understand that a very small proportion of AL amyloidosis patients receive ASCT as a second- or third-line therapy. As described in the original Company Submission, most AL amyloidosis patients are unable to receive ASCT as they do not meet the eligibility criteria for this therapy. Though the criteria vary by country, in general patients are precluded from receiving ASCT if they have involvement of ≥2 organs, severe cardiac dysfunction and/or end-stage renal disease, or an overall high comorbidity burden.[46] With the very low number of patients expected to receive ASCT as second- or third-line therapy, ASCT was not included as part of the costs associated with the subsequent therapy health states to avoid incorporating unwarranted uncertainty into the economic modelling.

2. Please provide a revised set of cost-effectiveness results (and model inputs) where the costs of ASCT are included. Please signpost the changes made to the model.

A revised set of cost-effectiveness results (and model inputs) with inclusion of ASCT costs as part of the subsequent therapy health states have not been provided, in line with the rationale described in response to Part 1 of Question B12.

B13. CS, section B.3.8.3. Cost-effectiveness results of scenario 3.

The company submission reports that the ICER for scenario 3 (3-month assessment of response) is £42,383/QALY (Table 87, p.152), while the cost-effectiveness model produces £43,188/QALY. Please clarify the discrepancy.

This is a typographical error in the original Company Submission and the Company can confirm that the ICER of £43,188 produced by the original cost-effectiveness model is correct. These results have now been updated based on a revised utilities approach (see Question B10) and correction of two model errors (see Question B14). Updated results are presented in response to Part 2 of Question B14 below.

B.14. PRIORITY. CS, Excel model. Potential errors identified in company's cost-effectiveness model.

After further exploration of the company's cost-effectiveness model, the ERG has identified 2 potential errors in the cells of the Excel worksheets.

1. **Under the scenario where the assessment of response takes place at 3 months (that is, after 3 treatment cycles), there appears to be an error in the worksheet 'Intervention', cell DC1780 which has a large impact on the ICER.**

   The model appears to incorrectly add the 'costs of subsequent therapy' for patients who are in PR/NR in cell DC1780. Notably, the formula in this cell differs for worksheet 'Comparator' compared to worksheet 'Intervention'. The formula appears to be correct for cycle 4 in the intervention worksheet, where the costs of subsequent therapy are accounted for given the number of patients who achieved PR/NR at the response assessment in cycle 3 and have transitioned to the health state 'second line therapy' in cycle 4. In summary, the cell in worksheet currently reads:

   DC1780=IF(decision_tree_exit="6 Months",0,c_2L_drug_DVCd*((Q1779-AQ1780)*p_c36_1L_2L_DVCd_prnr))

   when it should read DC1780=0. It reads DC1780=0 for worksheet 'Comparator'. Please clarify.

The Company thank the ERG for highlighting this modelling error in the submitted model. The Company agree with the model edit suggested above and can confirm that this has been implemented in the model version submitted alongside these responses.

Updated cost-effectiveness results, including results for this scenario where the assessment of response takes place at three months, are provided below in Table 39 in Part 2 of this response. These updated results include correction of both errors highlighted within Question B14. Similarly, the Company can confirm that all additional scenario results presented within this response document include correction of these errors.

2. **In sheet 'Comparator', the formula for the calculation of the 1st line therapy monitoring costs of patients who achieved PR/NR refers to the incorrect cell reference.**

   It currently reads:

   CU1778=AVERAGE(Q1778*c_1L_DisMon*INDEX('1L Drug Administration Costs'!$I$71:$J$77,MATCH(C1779,'1L Drug Administration Costs'!$I$71:$I$77,0),2),Q1779*c_1L_DisMon*INDEX('1L Drug Administration Costs'!$I$71:$J$77,MATCH(C1779,'1L Drug Administration Costs'!$I$71:$I$77,0),2))

   When it should read:

   CU1778=AVERAGE(Q1778*c_1L_DisMon*INDEX('1L Drug Administration Costs'!$D$71:$E$94,MATCH(C1778,'1L Drug Administration Costs'!$D$71:$D$94,0),2),Q1779*c_1L_DisMon*INDEX('1L Drug Administration Costs'!$D$71:$E$94,MATCH(C1779,'1L Drug Administration Costs'!$D$71:$D$94,0),2))

   Please clarify.

The Company thank the ERG for highlighting this error in the submitted model. The Company agree with the model edit suggested above and can confirm that this has been implemented in the model version submitted alongside these responses.

Following correction of the errors identified in Parts 1 and 2 of this question, updated cost-effectiveness results for the base case and scenario analyses have been produced. Please note that these updated results also account for the updated utilities approach described in Question B10. As summarised in Table 86 of the original Company Submission, the scenario analyses were as follows:

1. OS extrapolations performed using curve choices with the best fit as per AIC and BIC statistics in situations where the statistical fit data and clinician choice at the advisory board differed

2. Maximum possible treatment duration assumed for patients in the DBCd and BCd arms (24 and 6 cycles, respectively)

3. Three-month exit from decision tree

4. Inclusion of third-line therapies

5. HSUVs as per clinician estimations at the advisory board

The updated cost effectiveness data for the base case and these scenarios are presented in Table 39.

Correcting these two errors had a minimal impact on the ICERs for the base case and Scenarios 1, 2, 4 and 5. However, correcting these two errors reduces the ICER for Scenario 3, assessment of response at three months, by £8,773, bringing the result closer to a £30,000 per QALY willingness to pay threshold.

Table 39: Cost effectiveness results following model updates (update of Table 87 from the original Company Submission)

Scenario	Treatment	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	ICER vs BCd (£/QALY)	Impact on ICER of correcting errors (£/QALY)
Base case	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,509	−£29
1	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,845	−£29
2	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,942	−£101
3	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,774	−£8,773
4	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,835	−£29
5	BCd	[redacted]	[redacted]	[redacted]	-	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,373	−£24

All results include the updated utilities approach discussed in Question B10. The impact on the ICER presented in the right-hand column relates to the isolated impact of correcting the errors outlined in Question B14.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

Section C: Textual clarification and additional points

Decision problem, description of the technology and clinical care pathway

C1. CS, sections B.1.3.3 and B.3.5.2. The company submission states that "…the proportions of patients who would receive each treatment following BCd or DBCd, as estimated by these clinicians, are also presented [in figure 2]" (p.30). These proportions are not presented in figure 2. Please clarify whether these proportions are the same as those presented in Table 71 (p.137).

The Company can confirm that the proportions missing from Figure 2 are in full alignment with those presented in Table 71. These proportions were confirmed by the clinicians as reasonably accurate estimates of therapy typical of UK clinical practice at the recent Janssen-led advisory board.[13]

C2. CS, section B.1.3.3. In the company submission, the paragraph beginning "Few robust clinical trials have been conducted in patients with AL amyloidosis to date …" (p.31) appears to contain contradictory statements about the effects of BCd on organ response rates (ORRs). Please clarify.

The Company does not believe that contradictory statements have been made in this section of the original Company Submission however further clarification may be warranted. Bortezomib-based regimens can be associated with considerable overall response rates (ORRs) as defined by haematologic response, although a high proportion achieve a VGPR or PR only and fail to achieve a CHR. Despite this, overall disease burden and mortality risk remain substantial for patients receiving these therapies due to typically poor organ response rates (OrRRs) leading to severe clinical outcomes such as heart and renal failure. This highlights the current unmet need for the introduction of a treatment option for AL amyloidosis that is associated with deep, rapid and sustained haematologic responses as well as significant improvements in OrRRs and strengthens the clinical relevance of the composite endpoint MOD-PFS in ANDROMEDA.

C3. CS, section B.1.4. The company submission states that "Results of an analysis…found that from 14 patients who had received the first dose of daratumumab at least three months prior to the cut-off date, 9 (64%) had a haematologic response of PR or better, of which 42% were VGPR and above.[90]" (p.33). Reference 90 (Kastristis et al. 2021) does not appear to report any data relating to daratumumab. Please clarify if this is the correct reference. If not, please

provide the correct reference and confirm that the remaining references in the company submission are correct.

Please note that reference 90 within the original Company Submission refers to a poster by Kastritis *et al*. that was presented at the European Hematology Association (EHA) congress in 2021 (abstract number: EP1036). The reference is as follows:

Kastritis E, Monique, C, Dimopoulos, A et al. Daratumumab Monotherapy in Newly Diagnosed Patients With Stage 3B Light Chain (AL) Amyloidosis: A Phase II Multicenter Study by the European Myeloma Network. Presented at EHA, 2021.

This is the correct reference; the data described within the Company Submission are presented in Figure 2 of the poster, rather than in the abstract. Unfortunately, the poster cannot be shared within the reference pack as the Company do not own the copyright to do so, and it is not freely available online to those who did not attend the conference.

Literature Searches

C4. PRIORITY. CS, Appendices D and G. Missing Search Strategies. Please provide further details of the searches for: clinical trials and conference proceedings listed in Appendix D, D.1.1, page 6 and the grey literature searches in Appendix G, G.1.1, page 40. Please provide full details of the date of the searches, dates of conferences searched, how they were searched (that is, paper copies or online), any search terms used, and the number of hits.

Regarding the SLR of clinical evidence (detailed in Appendix D of the original Company Submission), database searches were conducted on the February 12th 2021. Searches of the conference proceedings of interest (25th European Hematology Association [EHA] Annual Congress and the 62nd American Society of Hematology [ASH] Annual Meeting) were conducted on March 15th 2021. The 25th EHA Annual Congress was held from 11th to 21st June 2020, while the ASH Annual Meeting took place from 2nd to 10th December 2020. With regards to the number of hits from conference searches, a total of eight abstracts were identified from searches of the congress proceedings. A search of the EHA open access database of congress abstracts, using the search term “amyloidosis” and restricting to January 1st to December 31st 2020, produced 26 hits. Of these, one abstract (abstract #LB2604, Kastritis et al., [2020])[15] was identified as relevant for inclusion in the clinical evidence SLR. One other potentially relevant abstract was also identified, however this abstract was already captured in the database searches and so was not included. Hand searching of the online database of the ASH 2020 “Volume 136, Issue Supplement 1” was also conducted using the search term “amyloidosis”. This search produced 67 hits that were individually screened. From these, seven abstracts (six describing ANDROMEDA and one described a trial for ixazomib) were identified as relevant for inclusion in the clinical evidence SLR (Table 40).

Table 40: Summary of included studies from ASH 2020 hand searches

Publication(s)	Trial/study drug
Minnema M, Dispenzieri, A., Merlini, G., Comenzo, R., Kastritis, E., Wechalekar, A., Grogan, M., Witteles, R., Ruberg, F., Maurer, M., Tran, N., Qin, X., Vasey, S., Tromp, B., Weiss, B., Vermeulen, J., Jaccard, A. (2020) Outcomes By Cardiac Stage in Newly Diagnosed AL Amyloidosis: Results from Andromeda. Blood 136 (Supplement 1): 44-45.	ANDROMEDA
Wechalekar A, Palladini G, Merlini G, Comenzo R, Jaccard A et al. (2020) Rapid and deep hematologic responses are associated with improved major organ deterioration-progression-free survival in newly diagnosed AL amyloidosis: results from ANDROMEDA. Blood 136 (Supplement 1): 6-7.	ANDROMEDA
Comenzo R, Kastritis, E., Minnema, M., Wechalekar, A., Jaccard, A., Sanchorawala, V., Lee, H., Gibbs, S., Mollee, P., Venner, C., Lu, J., Gatt, M., Suzuki, K., Kim, K., Cibeira, M., Beksac, M., Libby, E., Valent, J., Hungria, V., Wong, S., Rosenzweig, M., Bumma, N., Chauveau, D., Dimopoulos, M., ran, N., Qin, X., Vasey, S., Tromp, B., Weiss, B., Vermeulen, J., Merlini, G. (2020) Reduction in Absolute Involved Free Light Chain and Difference Between Involved and Uninvolved Free Light Chain Is Associated With Prolonged Major Organ Deterioration Progression-Free Survival in Patients With Newly Diagnosed AL Amyloidosis Receiving Bortezomib, Cyclophosphamide, and Dexamethasone With or Without Daratumumab: Results From ANDROMEDA (#552) 62nd American Society of Hematology Annual Meeting & Exposition. Dec 5-8, 2020.	ANDROMEDA
Suzuki K, Wechalekar, A., Kim, K., Shimazaki, C., Kim, J.S., Ikezoe, T., Min, C., Zhou, F., Iida, S., Katoh, N., Fujisaki, T., Shin, H., Tran, N., Qin, X., Vasey, S., Tromp, B., Weiss, B., Vermeulen, J., Comenzo, R., Kastritis, E., Lu, J. (2020) Subcutaneous Daratumumab (DARA SC) + Bortezomib, Cyclophosphamide, and Dexamethasone (VCd) in Asian Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: Subgroup Analysis from the Phase 3 Andromeda Study. Blood 136 (Supplement 1): 11.	ANDROMEDA
Palladini G, Milani, P., Celant, S., Summa, V., Affronti, G., Olimpieri, P.P., Petraglia, S., Foli, A., Nuvolone, M., Merlini, G., Russo, P. (2020) The Italian Medicines Agency Prospective Registry of Bortezomib-Based Treatment in AL Amyloidosis. Blood 136 (Supplement 1): 22.	ANDROMEDA
Sanchorawala V, Palladini, G., Minnema, M., Jaccard, A., Lee, H., Gibbs, S., Mollee, P., Venner, C., Lu, J., Schönland, S., Gatt, M., Suzuki, K., Kim, K., Cibeira, M.T., Beksac, M., Libby, E., Valent, J., Hungria, V., Wong, S., Rosenzweig, M., Bumma, N., Chauveau, D., Gries, K., Fastenau, J., Tran, N., Qin, X., Vasey, S., Tromp, B., Weiss, B., Vermeulen, J., Merlini, G., Comenzo, R., Kastritis, E., Wechalekar, A. (2020) Health-Related Quality of Life in Patients With AL Amyloidosis Treated With Daratumumab, Bortezomib, Cyclophosphamide, and Dexamethasone: Results From the Phase 3 ANDROMEDA Study. (#1640) American Society of Hematology. December 5-8, 2020.	ANDROMEDA
Muchtar E, Gertz, M.A., Laplant, B., Buadi, F.K., Leung, N., Peterson, S.M., Bergsagel, P.L., Fonder, A., Hwa, Y.L., Hobbs, M.A., Helgeson, D.K., Vossen, A.M., Gonsalves, W.I., Lacy, M.Q., Kapoor, P., Siddiqui, M.A., Larsen, J., Warsame, R.M., Hayman, S.R., Go, R.S., Dingli, D., Kourelis, T., Dispenzieri, A., Rajkumar, S.V., Kumar, S.K. (2020) Phase 2 Trial of Ixazomib, Cyclophosphamide and Dexamethasone for Treatment of Previously Untreated Light Chain Amyloidosis. Blood (Supplement 1):52-53.	Ixazomib

ASH: American Society of Hematology.

Regarding the SLR of cost-effectiveness evidence (detailed in Appendix G of the original Company Submission), database searches were conducted on 3rd February 2021 and the grey literature search of health technology assessment (HTA) websites were all conducted between

25th and 31st March 2021. All searches of HTA websites were guided by the CADTH Grey Matters Checklist. A summary of the search terms used and number of hits for each of the grey literature searches are detailed in Table 41.

Table 41: Grey literature resources with hits resulting from amyloidosis search

Resource	Search terms used	Number of records retrieved[a]
Canadian Agency for Drugs and Technologies in Health (CADTH)	Amyloidosis	25
Health Quality Ontario (HQO)	Amyloidosis	2
International Network of Agencies for Health Technology Assessment (INAHTA)	Amyloidosis	1
Australian Institute for Health Technology Assessment (AIHTA)	Amyloidosis	12
French National Authority for Health (HAS)	Amyloidosis	16
Health Service Executive; Irish Health Repository (Lenus)	Amyloidosis	22
National Health Care Institute Netherlands	Amyloidosis	1
Agency for Health Quality and Assessment of Catalonia (AQuAS)	Amyloidosis	2
Sahlgrenska University Hospital	Amyloidosis	1
National Institute for Health and Care Excellence (NICE)	Amyloidosis	12
NICE: Guidance and Advice List	Amyloidosis	2
National Institute for Health Research (NIHR)	Amyloidosis	9
NIHR Evaluation, Trials, and Studies Coordinating Centre (NETSCC)	Amyloidosis	4
National Health Service (NHS) England	Amyloidosis	4
ECRI Institute	Amyloidosis	3
Institute for Clinical and Economic Review (ICER)	Amyloidosis	9
Federal Reserve Bank of St. Louis. Economic Research Division (IDEAS database)	Amyloidosis	1
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	Systemic Amyloidosis[b]	16
	Light Chain Amyloidosis[b]	8
National Centre for Pharmacoeconomics (NCPE)	Amyloidosis	4
NHS Economic Evaluation Database (EED), economic evaluations of health care interventions (NHS CRD Databases)	Amyloidosis	16
University of Aberdeen Health Economics Research Unit (HERU)	Amyloidosis	1

[a] All resulting hits were screened and excluded due to (1) irrelevant topic (eg, non-AL amyloidosis), (2) a lack of relevant information provided, (3) date of publication, or (4) reporting on DBCd for AL amyloidosis (ie, the Company Submission).
[b] "Systemic amyloidosis" and "light chain amyloidosis" are recommended search terms that appear on the ISPOR website when "amyloidosis" is entered into the search bar; therefore, these search terms were used when searching the ISPOR site rather than simply "amyloidosis".

C5. PRIORITY. CS, section B.3.4.4. Missing Search Strategies. The company submission refers to an additional search for Adverse Reactions (p.125-126). However, no strategies or further details are listed in the Appendices. Please clarify.

The SLR for AE disutilities refers to the SLR for HRQoL studies, detailed in Appendix H of the original Company Submission. Given that this SLR identified no published literature detailing AL amyloidosis-associated AE disutility values, an additional, more generic search for articles reporting AE disutilities associated with chemotherapy or more generic databases of EQ-5D scores was conducted. The details of this search are further described in our response to question B10 (Part 5) above.

C6. PRIORITY. CS, Appendices D, G, H, I and N. Missing Search Dates. Please provide details of the exact dates of each of the searches throughout the entirety of the appendices in DD/MM/YYY format.

The exact dates of each search are provided in Table 42.

Table 42: Date of searches for reviews

Review topic	Date of searches
Clinical evidence (Appendix G of original Company Submission)	
Database searches	12/02/2021
ClinicalTrials.gov searches	15/02/2021
Conference proceedings searches	25/03/2021–31/03/2021
Cost-effectiveness evidence (Appendix G of original Company Submission)	
Database searches	03/02/202
Grey literature search HTA websites	31/03/2021
HRQoL evidence (Appendix H of original Company Submission)	
Database searches	14/04/2021
Grey literature search HTA websites	31/03/2021
Cost and healthcare resource use evidence (Appendix I of original Company Submission)	
Database searches	04/02/2021
Grey literature search HTA websites	31/03/2021
AL amyloidosis patient experiences (Appendix N of original Company Submission)	
PubMed and Google Scholar	24/03/2021

Abbreviations: HTA: Health Technology Assessment.

C7. CS, Appendix D. Results Retrieved. Please clarify why there were 0 results for the searches of ClinicalTrials.gov, listed in Appendix D (p.20). As the search strategy is not documented it cannot be determined how many results were originally

retrieved by the search, or if there was an error in the strategy. Please confirm that no relevant evidence was missed.

All relevant results from searching ClinicalTrials.gov had been previously identified in the systematic database (literature) searches; that is, these studies would be removed as duplicates with the database searches. Since no additional studies were identified with the search of ClinicalTrials.gov, the results were recorded as zero. The search strategy and corresponding date(s) of the searches within ClinicalTrials.gov are presented in Table 43.

Table 43: Search strategy for ClinicalTrials.gov

Date of search	Search strategy	Number of records retrieved	Number of records screened	Number of relevant records identified	Number of recorded included after de-duplication against database searches
February 15, 2021	Condition or disease: Other terms: "AL Amyloidosis" Country: Study type: Study results: Status: All studies Outcome Measure:	190	190	7	0[a]

[a] All relevant records identified were identified in the SLR; therefore, no unique records were identified by searching ClinicalTrials.gov.

C8. CS, Appendix H. Errors in Documentation. In Appendix H, Table 14 (p.50) please clarify whether there should be an additional line (line 166: '77 or 165') to pool the results of both databases. This line misses the records from MEDLINE which means the results from this database were excluded from the final results listed. Nonetheless, section H.2.1 (p.52) lists the figure for both databases combined (reporting 3220 citations). This appears to be an error in documenting the strategy. Please correct the error and provide assurance that no relevant evidence was missed.

The Company confirm that it is not an error in the search strategy itself and is rather an oversight regarding the presentation of the strategy in the report. The records from MEDLINE were included in the final results that were screened in duplicate, as shown in the PRISMA diagram (Figure 4 in Section H.2.1 of the original Company Submission).

The correct documentation of the strategy is shown in Table 44 below, with the additional line 166 included (in highlight).

Table 44: Search strategy for MEDLINE and Embase (HRQoL SLR)

#	Searches	Results
1	"Value of Life"/	142972
2	Quality of Life/	710619

3	quality of life.ti,kf.	205472
4	((instrument or instruments) adj3 quality of life).ab.	8454
5	Quality-Adjusted Life Years/	41828
6	quality adjusted life.ti,ab,kf.	35589
7	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	58434
8	disability adjusted life.ti,ab,kf.	8429
9	daly*.ti,ab,kf.	7923
10	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	71088
11	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	4827
12	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	1417
13	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	16538
14	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	99
15	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	892
16	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	50150
17	(hye or hyes).ti,ab,kf.	216
18	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	100
19	(pqol or qls).ti,ab,kf.	1066
20	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	1379
21	nottingham health profile*.ti,ab,kf.	2761
22	sickness impact profile.ti,ab,kf.	2315
23	exp health status indicators/	350665
24	(health adj3 (utilit* or status)).ti,ab,kf.	176634
25	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	34200
26	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	27177
27	disutilit*.ti,ab,kf.	1496
28	rosser.ti,ab,kf.	230
29	willingness to pay.ti,ab,kf.	16133
30	standard gamble*.ti,ab,kf.	2012
31	(time trade off or time tradeoff).ti,ab,kf.	3550
32	tto.ti,ab,kf.	2951
33	(hui or hui1 or hui2 or hui3).ti,ab,kf.	4149
34	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	47380

35	duke health profile.ti,ab,kf.	203
36	functional status questionnaire.ti,ab,kf.	286
37	dartmouth coop functional health assessment*.ti,ab,kf.	26
38	(WHOQOL or WHOQOL-BREF).ti,ab,kf.	7911
39	(chronic respiratory questionnaire or chronic respiratory disease questionnaire or CRQ).ti,ab,kf.	1670
40	(St* George* Hospital questionnaire or SGRQ).ti,ab,kf.	5441
41	DIsability REIated to COPD Tool.ti,ab,kf.	7
42	london handicap scale.ti,ab,kf.	204
43	((modified medical research council dyspn?ea or MMRC) adj scale).ti,ab,kf.	1006
44	"MRC-D".ti,ab,kf.	3
45	(airways questionnaire or AQ20).ti,ab,kf.	109
46	(breathing problems questionnaire or BPQ or "BPQ-S").ti,ab,kf.	274
47	COPD activity rating scale.ti,ab,kf.	4
48	COPD assessment test.ti,ab,kf.	2990
49	(clinical COPD questionnaire or CCQ).tw,kf.	911
50	(("10" or ten) adj item respiratory illness questionnaire).ti,ab,kf.	3
51	"RIQ-MON10".ti,ab,kf.	2
52	"cost of illness"/	48282
53	(cost? adj3 illness*).ti,ab,kf.	7339
54	exp Disability Evaluation/	221376
55	((disabil* or disabled or impaired or impairment*) adj3 (estimat* or evaluat* or instrument or instruments or measur* or scale? or score? or weight? or valu*)).ti,ab,kf.	107094
56	burden*.ti,ab,kf.	617313
57	(toll or tolls).ti,ab,kf.	109488
58	exp Severity of Illness Index/	280048
59	((disease* or illness* or sickness*) adj3 sever* adj2 (estimat* or evaluat* or instrument or instruments or measur* or scale? or score? or weight? or valu*)).ti,ab,kf.	21259
60	((disease* or illness* or sickness*) adj2 impact?).ti,ab,kf.	25149
61	Absenteeism/	27232
62	absentee*.ti,ab,kf.	15693
63	Presenteeism/	1923
64	presentee*.ti,ab,kf.	4169
65	productivit*.ti,ab,kf.	142707
66	((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kf.	297795
67	((work* or employ*) adj5 abilit*).ti,ab,kf.	29630
68	(time adj1 away).ti,ab,kf.	1756
69	Sick Leave/	12120
70	((sick or medical) adj leave).ti,ab,kf.	12663
71	or/1-70 [QoL/DISEASE BURDEN]	2838439

72	exp amyloidosis/	74274
73	amyloidos$.ti,ab,kw,kf.	58501
74	or/72-73 [Amyloidosis]	85790
75	71 and 74	4335
76	exp animals/ not humans.sh.	32006278
77	75 not 76	1303
78	77 use ppez	1134
79	socioeconomics/	143736
80	exp quality of life/	734708
81	quality of life.ti,kw.	240406
82	((instrument or instruments) adj3 quality of life).ab.	8454
83	quality-adjusted life year/	41828
84	quality adjusted life.ti,ab,kw.	35744
85	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw.	58802
86	disability-adjusted life year/	2489
87	disability adjusted life.ti,ab,kw.	8445
88	daly*.ti,ab,kw.	8042
89	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	71377
90	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw.	4840
91	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw.	1421
92	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw.	16605
93	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	99
94	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw.	892
95	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kw.	50364
96	(hye or hyes).ti,ab,kw.	220
97	(health* adj2 year* adj2 equivalent*).ti,ab,kw.	103
98	(pqol or qls).ti,ab,kw.	1068
99	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw.	1388
100	nottingham health profile*.ti,ab,kw.	2774
101	nottingham health profile/	535
102	sickness impact profile.ti,ab,kw.	2355
103	sickness impact profile/	9593
104	health status indicator/	26863
105	(health adj3 (utilit* or status)).ti,ab,kw.	178145

106	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.	34327
107	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw.	27254
108	disutilit*.ti,ab,kw.	1500
109	rosser.ti,ab,kw.	231
110	willingness to pay.ti,ab,kw.	16301
111	standard gamble*.ti,ab,kw.	2032
112	(time trade off or time tradeoff).ti,ab,kw.	3584
113	tto.ti,ab,kw.	2961
114	(hui or hui1 or hui2 or hui3).ti,ab,kw.	4163
115	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw.	47442
116	duke health profile.ti,ab,kw.	203
117	functional status questionnaire.ti,ab,kw.	287
118	dartmouth coop functional health assessment*.ti,ab,kw.	26
119	(WHOQOL or WHOQOL-BREF).ti,ab,kw.	7949
120	(chronic respiratory questionnaire or chronic respiratory disease questionnaire or CRQ).ti,ab,kw.	1673
121	"St. George Respiratory Questionnaire"/	3539
122	(St* George* Hospital questionnaire or SGRQ).ti,ab,kw.	5457
123	DIsability RElated to COPD Tool.ti,ab,kw.	7
124	london handicap scale.ti,ab,kw.	204
125	((modified medical research council dyspn?ea or MMRC) adj scale).ti,ab,kw.	1004
126	"MRC-D".ti,ab,kw.	3
127	(airways questionnaire or AQ20).ti,ab,kw.	110
128	(breathing problems questionnaire or BPQ or "BPQ-S").ti,ab,kw.	274
129	COPD activity rating scale.ti,ab,kw.	4
130	COPD assessment test.ti,ab,kw.	2995
131	(clinical COPD questionnaire or CCQ).ti,ab,kw.	912
132	(("10" or ten) adj item respiratory illness questionnaire).ti,ab,kw.	3
133	"RIQ-MON10".ti,ab,kw.	2
134	"cost of illness"/	48282
135	(cost? adj3 illness*).ti,ab,kw.	8034
136	disability/	116365
137	((disabil* or disabled or impaired or impairment*) adj3 (estimat* or evaluat* or instrument or instruments or measur* or scale? or score? or weight? or valu*)).ti,ab,kw.	106801
138	disease burden/	48673
139	burden*.ti,ab,kw.	618487
140	(toll or tolls).ti,ab,kw.	110614
141	"severity of illness index"/	270928

142	((disease* or illness* or sickness*) adj3 sever* adj2 (estimat* or evaluat* or instrument or instruments or measur* or scale? or score? or weight? or valu*)).ti,ab,kw.	21294
143	((disease* or illness* or sickness*) adj2 impact?).ti,ab,kw.	25219
144	absenteeism/	27232
145	absentee*.ti,ab,kw.	15987
146	presenteeism/	1923
147	presentee*.ti,ab,kw.	4269
148	productivity/	57314
149	productivit*.ti,ab,kw.	143517
150	((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kw.	297925
151	((work* or employ*) adj5 abilit*).ti,ab,kw.	29710
152	(time adj1 away).ti,ab,kw.	1759
153	medical leave/	7141
154	((sick or medical) adj leave).ti,ab,kw.	12866
155	or/79-154 [QoL/DISEASE BURDEN]	2789940
156	exp *amyloidosis/	52183
157	AL amyloidosis/	3192
158	amyloidos$.ti,ab,kw.	58406
159	or/156-158 [Amyloidosis]	72487
160	(exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) and (human/ or normal human/ or human cell/)	41579186
161	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/	53095322
162	161 not 160	11516136
163	155 and 159	3398
164	163 not 162 [Remove Animals]	3107
165	164 use oemezd	2086
166	**78 or 165 [All results - MEDLINE & Embase]**	**3220**

Database(s): Embase 1974 to 2021 April 13, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to April 13, 2021.

C9. CS, Appendix I. Errors in Documentation. In Appendix I, section I.1.1 (p.68), please clarify whether ‘grey literature sources for HRQoL evidence’ should be ‘cost and healthcare resource use identification, measurement and valuation studies’.

The Company confirm that this sentence should be modified to read: “The grey literature search of HTA websites for the economic evidence SLR (see Section G.1) encompassed cost and healthcare resource use identification, measurement and valuation studies”.

C10. CS, Appendix N. Errors in Documentation. In Appendix N, Table 34 (p.106), there appears to be a mistake in line 1: ‘Amyloid*OR’ should have a space after *.

Please correct the error and provide assurance that no relevant evidence was missed.

The Company acknowledge that this was a typographical error in the write up of the search and that correct search, using the line '(Amyloid* OR Light Chain) AND (Preference OR Experience OR Choice OR Wellbeing OR QoL OR Quality of Life) AND (Treatment OR Diagnosis)', was originally used. As such, no relevant evidence was missed.

C11. CS, Appendix D. Emtree Headings used outside of Embase. In Appendix D, Table 2 (p.13), please clarify why there are Emtree headings used in a search of Cochrane Central, Cochrane CDSR, DARE, and ACP Journal Club. These databases use MeSH not Emtree. The following are Emtree terms only and not MeSH terms: daratumumab/ pomalidomide/ carfilzomib/. Please confirm that no relevant evidence was missed.

The Company confirm the Emtree headings for daratumumab, pomalidomide and carfilzomib were erroneously used in the Cochrane Central, Cochrane CDSR, DARE, and ACP Journal Club search strategies.

Since these Emtree terms do not have an equivalent in the MeSH database, the proper syntax in the mentioned databases for these three interventions would be searched using appropriate keywords, without any controlled vocabulary terms. Therefore, in the absence of corresponding MeSH terms, Emtree alongside key words were implemented in our search. While it was incorrect to include Emtree in the search strategy, the Emtree terms were, in essence, redundant and had no impact on the final results, as keyword search terms for daratumumab, pomalidomide, and carfilzomib were appropriately applied. As shown in the search strategy in Appendix D, Table 2, the database either returned zero results (ie, ignored the command with the controlled vocabulary terms, as seen for carfilzomib/) or returned results corresponding to the terms listed in the subject headings field of the record that would have also been picked up by the keyword command line (as seen for daratumumab/ and pomalidomide/).

To confirm that no relevant evidence was missed, the search strategy was re-run (on July 20th, 2021) with and without the controlled vocabulary terms in question. The "corrected" search and the "uncorrected original search" produced the same number of hits (Table 45). In addition, NOT statements were used to combine the sets and understand the impact on the number of results; 0 results were retrieved. This confirmed that the "corrected" results are congruent with our original search and proved that the presence of these terms did not affect the final set of results screened.

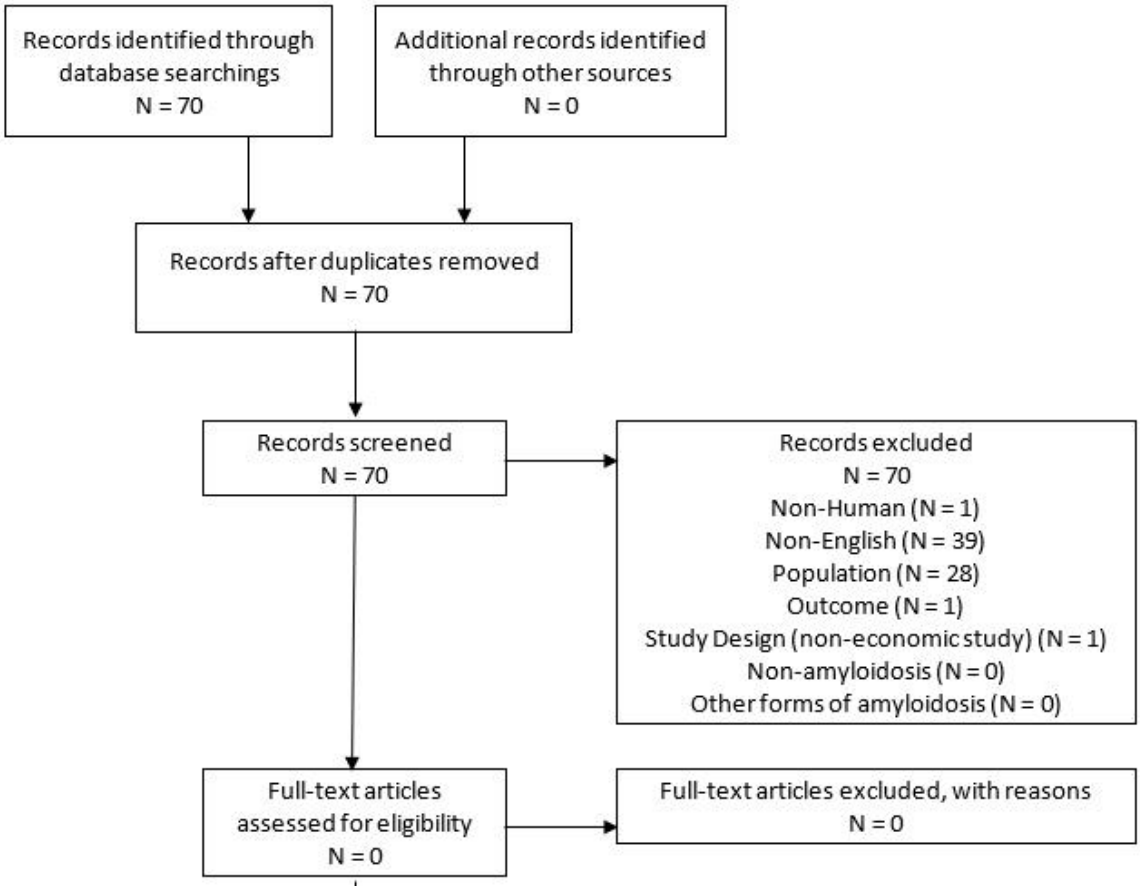
Table 45: Results of original and corrected searches

#	Searches	Results
49	45 or 46 or 47 or 48 [All results – uncorrected original search]	326
90	86 or 87 or 88 or 89 [All results – corrected search]	326

C12. CS, Appendix I. Search Limits. Please clarify why Appendix I, Table 22 (p.68-73) limits the search to English.

The search strategy in Appendix I.1.1 was designed by an information specialist based on the PICOS (Appendix I, Table 23) criteria and mistakenly included a filter for English language. Since the PICOS specified only including English-language studies (non-English was excluded at screening), it is expected that there was minimal impact on the final number of studies included in the SLR. To confirm that no relevant articles were missed due to limiting the search to English, the search strategy was re-run (on July 19th, 2021) after removing the language filter from the strategy. This "corrected" search produced 70 additional records, which were all subsequently screened and excluded at title/abstract (due primarily to incorrect patient population and being non-English as per the PICOS criteria; see Figure *10* below).

Figure *10*: PRISMA diagram for corrected search limits (resource use and indirect costs SLR)



Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

C13. CS, Appendix N. Search Strategies. Please provide details of the exact search strategies for PubMed and Google Scholar separately, as they cannot be searched concurrently. For PubMed, please list the fields searched and the platform this was searched on. Please provide an exact date against each search.

PubMed was searched on March 24th 2021, using the terms '((Amyloidosis[Title] OR Amyloid[Title] OR Light Chain)[Title]) AND ((Preference[Title] OR Experience[Title] OR

Choice[Title] OR Wellbeing[Title] OR QoL[Title] OR 'Quality of Life')[Title])' with a date filter applied ('2015/1/1–2021/3/24'). The Title field was searched and the platform was https://pubmed.ncbi.nlm.nih.gov/.

Google Scholar was searched on March 24th 2021. The original search terms used were '(Amyloid* OR Light Chain) AND (Preference OR Experience OR Choice OR Wellbeing OR QoL OR 'Quality of Life')' with a date filter applied (2015–2021; Google Scholar does not allow for the search to be narrowed to a specific day). In order to narrow down the number of results, an additional search was run using the terms '(Amyloid* OR Light Chain) AND (Preference OR Experience OR Choice OR Wellbeing OR QoL OR 'Quality of Life') AND (Treatment OR Diagnosis)', again with a date filter applied (2015–2021).

References

C14. PRIORITY. Please provide copies of the following company documents referenced in Document B:

1. **HTA Advisory Board Meeting Minutes (Ref # 26)**
2. **Daratumumab AL Amyloidosis Scientific Communications (Ref # 40)**
3. **Verbal communications with UK expert clinicians (Ref # 88)**

The Company confirm that these documents will be provided as soon as they are available, which is anticipated to be by approximately Friday 13th August.

Appendix 1

Table 46: Summary of patients switching to subsequent cross-resistant and non-cross resistant anti-plasma cell therapy, by treatment arm and cycle (by therapeutic class, pharmacologic class and preferred term); safety analysis set (14th February 2020 data cut-off)

			Patients per cycle[a]																		
	Term	Treatment arm	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Patients with one or more subsequent anti-plasma cell therapies (cross and non-cross resistant)		BCd	[redacted]																		
		DBCd	[redacted]																		
Therapeutic class	Antibacterials for systemic use	BCd	[redacted]																		
	Antibacterials for systemic use	DBCd	[redacted]																		
	Antineoplastic agents	BCd	[redacted]																		
	Antineoplastic agents	DBCd	[redacted]																		
	Corticosteroids for systemic use	BCd	[redacted]																		
	Corticosteroids for systemic use	DBCd	[redacted]																		
	Immunosuppressants	BCd	[redacted]																		
	Immunosuppressants	DBCd	[redacted]																		
Pharmacologic class	Alkylating agents	BCd	[redacted]																		
	Alkylating agents	DBCd	[redacted]																		

	Corticosteroids for systemic use, plain	BCd																		
	Corticosteroids for systemic use, plain	DBCd																		
	Immunosuppressants	BCd																		
	Immunosuppressants	DBCd																		
	Macrolides, lincosamides and streptogramins	BCd																		
	Other antineoplastic agents	BCd																		
	Other antineoplastic agents	DBCd																		
	Tetracyclines	BCd																		
	Tetracyclines	DBCd																		
Drug	Bortezomib	BCd																		
	Bortezomib	DBCd																		
	Carfilzomib	BCd																		
	Clarithromycin	BCd																		
	Cyclophosphamide	BCd																		
	Cyclophosphamide	DBCd																		
	Cyclophosphamide monohydrate	BCd																		
	Daratumumab	BCd																		

	Daratumumab	DBCd	[redacted]																		
	Dexamethasone	BCd	[redacted]																		
	Dexamethasone	DBCd	[redacted]																		
	Doxycycline	BCd	[redacted]																		
	Doxycycline	DBCd	[redacted]																		
	Isatuximab	BCd	[redacted]																		
	Ixazomib	BCd	[redacted]																		
	Ixazomib citrate	BCd	[redacted]																		
	Ixazomib citrate	DBCd	[redacted]																		
	Lenalidomide	BCd	[redacted]																		
	Lenalidomide	DBCd	[redacted]																		
	Melphalan	BCd	[redacted]																		
	Melphalan	DBCd	[redacted]																		
	Melphalan hydrochloride	BCd	[redacted]																		
	Methylprednisolone	BCd	[redacted]																		
	Pomalidomide	BCd	[redacted]																		
	Pomalidomide	DBCd	[redacted]																		
	Prednisone	BCd	[redacted]																		
	Venetoclax	BCd	[redacted]																		

[a] Each cycle was 28 days in length.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone.

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43. Stein E, Xie J, Duchesneau E, et al. Cost Effectiveness of Midostaurin in the Treatment of Newly Diagnosed FLT3-Mutated Acute Myeloid Leukemia in the United States. Pharmacoeconomics 2019;37:239-253.
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NICE National Institute for Health and Care Excellence

Patient organisation submission

Daratumumab in combination for newly diagnosed systemic amyloid light-chain Amyloidosis [ID3748]

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

NICE National Institute for Health and Care Excellence

<table>
<tr><td>1.Your name</td><td>[redacted]</td></tr>
<tr><td>2. Name of organisation</td><td>Myeloma UK</td></tr>
<tr><td>3. Job title or position</td><td>[redacted]</td></tr>
<tr><td>4a. Brief description of the organisation (including who funds it). How many members does it have?</td><td>Myeloma UK is the only organisation in the UK dealing exclusively with myeloma and related conditions including AL Amyloidosis. Our broad and innovative range of services cover every aspect of myeloma and related conditions from providing information and support, to improving standards of treatment and care through research and campaigning. We receive no government funding 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. We are not a membership organisation.</td></tr>
<tr><td>4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]</td><td>
<table>
<tr><th>Name of Company</th><th>Grants and project specific funding</th><th>Gifts, Honoraria and Sponsorship</th><th>Total (£)</th></tr>
<tr><td>Celgene</td><td>110,000</td><td>12,337</td><td>122,337</td></tr>
<tr><td>Janssen-Cilag</td><td>20,000</td><td>327</td><td>20,327</td></tr>
</table>
The table above shows the audited 2019 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work including clinical trials, and gifts, honoraria or sponsorship.
</td></tr>
</table>

If so, please state the name of manufacturer, amount, and purpose of funding.	
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 has been gathered from the AL Amyloidosis patients and carers we engage with through our research and services programmes, including: - Nine semi-structured telephone interviews with AL Amyloidosis patients about living with AL Amyloidosis, their experience, and expectations of treatment. Participants included newly diagnosed and relapsed/refractory AL Amyloidosis patients who have received all treatments or part treatments of the combination being appraised. - Two patients who were interviewed are also participants in the ongoing ANDROMEDA clinical trial which compares Daratumumab (Darzalex®) in combination with cyclophosphamide, bortezomib (Velcade®) and dexamethasone (Dara CyBord) to cyclophosphamide, bortezomib (Velcade®) and dexamethasone (CyBord). - It has also been informed by analysis of the experiences and views of patients, family members and carers gathered via our Myeloma UK Infoline, Patient and Family AL Amyloidosis Infodays and posts to our online Discussion Forum.
Living with the condition	
6. What is it like to live with the condition? What do carers	**What is it like to live with AL Amyloidosis?**

experience when caring for someone with the condition?	*"Sometimes the hardest part for me is dealing with the mental impact. You are constantly reminded there is no cure. You have to maintain and treasure what you have for as long as possible. Treatment can slow the clock but thinking about the future is sometimes very hard. I suspect many patients will feel the same."* AL Amyloidosis is a highly individual and complex condition. There is currently no cure, but treatment can halt its progress and improve quality of life. The term 'amyloidosis' is a general term used for a group of conditions where an abnormal protein, called amyloid, accumulates in the tissues. The build-up of amyloid protein is called an 'amyloid deposit'. Deposits can occur in various organs or tissues and cause problems. In AL Amyloidosis abnormal plasma cells in the bone marrow produce light chains that form amyloid proteins. The amyloid protein is only broken down very slowly by the body and so starts to build up in the tissues and organs. This gradually damages them and causes symptoms. This build-up can happen almost anywhere in the body; each patient has a different pattern of amyloid deposition, with different organs affected. Amyloid can affect two or more organs at the same time and can build up in the kidneys, heart, liver, spleen, nerves, or digestive system. AL Amyloidosis is incurable. It can be treated but it is a relapsing-remitting condition. This means you can have periods of remission after treatment, when the AL Amyloidosis is not active or causing symptoms, but it will become active again after a period of time. AL Amyloidosis is rare condition, with approximately 500 – 600 people diagnosed in the UK each year. The 1-year mortality rate is estimated to be around 40%.[1] **Symptoms and complications of AL amyloidosis** AL Amyloidosis can cause a number of symptoms and affect the body in several ways. This is because the amyloid protein can be deposited in almost any organ in the body, except from the brain. The symptoms you have will depend on which organ or organs are most affected by amyloid deposits. Most

[1] Gertz MA. (2018) Immunoglobulin light chain amyloidosis: 2018 update on diagnosis, prognosis, and treatment. American Journal of Hematology 93(9): 1169- 1180

	patients will have more than one organ affected by amyloid deposits. The organ that is most affected is referred to as the 'dominant organ'. The most common symptoms of AL Amyloidosis include, fatigue, weakness, weight loss and loss of appetite. Further complications can be caused by the build-up of amyloid deposits in the body including, kidney disease, heart problems, digestive problems, neuropathy, skin changes and macroglossia (enlargement of tongue). *"The big difference is in my energy levels. Before I was ill, I would play 5 a side every week and be running two to three times a week. Now I can do a walk and that would be it."* Symptoms and complication will vary between patients and will depend on which area of the body or organ(s) are affected by the amyloid deposits. *"The scans and x-rays show that my kidneys, heart and lungs where all affected by the amyloid. I had stage 3 heart condition. At one point they did talk about a heart transplant. I also had stage 3 kidney amyloid. The doctors also spoke about putting me on dialysis, but it never got that far."* Around 15% of myeloma patients will also have the associated condition of AL Amyloidosis. *"I went for a kidney biopsy as they suspected it might have been AL Amyloidosis. After waiting for a local hospital appointment, I then had a bone marrow biopsy as they wanted to check if I might have myeloma. It was confirmed in April 2019 that I had both AL Amyloidosis and myeloma. I have never been ill or had any serious health issue before. It came completely out of the blue." - Patient on the ANDROMEDA Clinical trial* **What do carers experience?** Carers and family members may have to devote time to accompanying patients to hospital appointments and caring responsibilities can impact on their ability to work or spend time on other activities. AL Amyloidosis shares some of the same characteristics as myeloma, for example that it is incurable, and we know that this can lead to a heavy psychological burden for carers and family including the feeling that their lives are "on hold". When discussing the effect of an AL Amyloidosis diagnosis on their families and carers participants who were interviewed stated:

	"It is always harder for family than it is for you. The better treatment you get the better for the people around you. It puts them at ease." *"My husband took it very seriously. I never really want to know except what I have to do that day, my husband looked ahead more."* *"It affects not just me but my family also…. In March 2020 when lockdown happened my wife and both my children were working from home and available to help with my recovery.* *"I have a 13-year-old son and my main aim is to stay alive until he is 18....During treatment I felt isolated. I was just waiting to get better and move forward. This was mainly for my son as I didn't want to be known as the ill mum." Patient on the ANDROMEDA Clinical Trial*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are currently no approved treatments for AL Amyloidosis available through the NHS. Treatment is directed at the underlying bone marrow disorder. The aim of chemotherapy is to decrease the number of abnormal plasma cells which will proportionately reduce production of the amyloid forming light chain protein. Unfortunately, regression of amyloid is slow, and it often takes 6-12 months after the end of chemotherapy for patients to experience a significant improvement in health. Because of the serious nature of AL Amyloidosis, it is desirable to suppress the bone marrow disorder as quickly and completely as possible. Treatment for AL Amyloidosis is currently based on anti-myeloma therapy including immunomodulatory drugs (e.g., thalidomide) and proteasome inhibitors (e.g., bortezomib) and has to be tailored to the individual patient in terms of their age, comorbidities, extent of amyloid organ involvement and the patient's treatment preferences. There is also a greater treatment-related toxicity in patients with AL Amyloidosis compared to that seen in patients with multiple myeloma and dose reductions are required.

	The current standard treatment of care for newly diagnosed AL Amyloidosis involves patients receiving the triplet combination of cyclophosphamide, bortezomib (Velcade®) and dexamethasone (CyBord). *"I was treated with Velcade, cyclophosphamide and dexamethasone. All indications from the blood tests show that I have made good progress. My heart, lungs and kidneys have also improved."* *"I had tiredness from the illness. In terms of side effects from treatment itchiness was my biggest issue. Also, the first and second month of treatment I wouldn't really sleep. Apart from that just general tiredness from the illness."* If patients cannot tolerate the Velcade due to peripheral neuropathy then will they receive lenalidomide (Revlimid®) and dexamethasone (Rd). About one fifth of newly diagnosed patients with AL Amyloidosis may be suitable for consideration of high dose chemotherapy and stem cell transplantation as first-line treatment.[2] *"The SCT was the hardest treatment in terms of falling off a cliff. I can clearly remember speaking to the consultant on the 2nd or 3rd day being happy and feeling buoyant. The following morning the sickness hit and I was exhausted."* *"You don't fully understand the debilitating nature of the SCT until you go through it. Doing basic things were hard. I lost a lot of strength and stamina, and it took many months for it to come back."* In general, management of AL Amyloidosis is aimed at achieving deep, durable responses with very close monitoring for early detection of relapse/refractory disease. Further studies have shown that achieving an early response is associated with better outcomes. [3]

[2] Al Hamed, R., Bazarbachi, A.H., Bazarbachi, A. *et al.* Comprehensive Review of AL amyloidosis: some practical recommendations. *Blood Cancer J.* **11,** 97 (2021). https://doi.org/10.1038/s41408-021-00486-4

[3] Manwani R, Foard D, Mahmood S, Sachchithanantham S, Lane T, Quarta C, et al. Rapid hematologic responses improve outcomes in patients with very advanced (stage IIIb) cardiac immunoglobulin light chain amyloidosis. Haematologica. 2018;103:e165–e8. & Rezk T, Lachmann HJ, Fontana M, Sachchithanantham S, Mahmood S, Petrie A, et al. Prolonged renal survival in light chain amyloidosis: speed and magnitude of light chain reduction is the crucial factor. Kidney Int. 2017;92:1476–83.

	The ALchemy Clinical trial, (part funded by Myeloma UK), is an ongoing prospective observational study of newly diagnosed AL Amyloidosis seen at the UK National Amyloidosis Centre (NAC) from February 2010 until August 2019. Findings showed that patients who achieve an early deep response have a superior survival and better organ responses than those who achieve a deep response later. **The key finding is that benefit of rapid response is seen across all disease stages.**[4]
8. Is there an unmet need for patients with this condition?	There is a significant unmet need for approved treatments in AL Amyloidosis. As stated above, there is currently no standard NICE approved treatment for AL Amyloidosis available through the NHS. Treatment for AL Amyloidosis is currently based on anti-myeloma therapy. This will be the first licensed treatment to be assessed by NICE for AL Amyloidosis and if approved will become the standard of care for newly diagnosed AL Amyloidosis. Given that AL Amyloidosis is such a heterogeneous condition there is a need for a range of treatment options with different mechanisms of action for newly diagnosed and relapsed/refractory patients. It is therefore extremely important to the AL Amyloidosis community that this treatment is being appraised is a first step in developing a more complete treatment pathway. *"When I was first diagnosed, we were wondering whether I would see Christmas or see summer. Then the treatment kicks in and you get hope."*
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients value treatments which are effective and control their AL Amyloidosis. **Clinical Trial Results** Data from the Phase III ANDROMEDA trial indicates that the addition of daratumumab to CyBord for newly diagnosed AL Amyloidosis can induce faster and deeper responses to the treatment.

[4] Ravichandran, S., Cohen, O.C., Law, S. *et al.* Impact of early response on outcomes in AL Amyloidosis following treatment with frontline Bortezomib. *Blood Cancer J.* **11,** 118 (2021). https://doi.org/10.1038/s41408-021-00510-7

	The main efficacy measure of the ANDROMEDA trial was the overall complete haematologic response rate (CHR). In the most up to date data released from the clinical trial the overall haematologic CR rate continued to be higher in the Dara CyBord arm compared to the CyBord arm (59% vs 19%; odds ratio [OR] 5.9; 95% CI 3.7–9.4; *P*< 0.0001). More patients achieved a very good partial response or better (≥VGPR) with Dara CyBord compared to CyBord (79% vs 50%; OR 3.7; 95% CI 2.4–5.9; *P*< 0.0001).[5] The secondary endpoint was Major organ deterioration progression-free survival (MOD-PFS) – time free from haematologic progression, development of end-stage cardiac or renal disease, or death. At a median follow-up of 11.4 months, MOD-PFS favoured treatment with daratumumab as well (hazard ratio = 0.58; p=0.0224).[6] Further to this the median treatment duration was 18.5 months for Dara CyBord and 5.3 months for CyBord with 40% in the Dara CyBord arm still on treatment. Finally, the clinical trial also investigated organ response rates, which almost doubled with the addition of daratumumab. The 6-month cardiac response rate was 42% for Dara CyBord compared with 22% for CyBord alone (p=0.0029), and the 6-month renal response rates were 54% and 27%, respectively (p<0.0001). Data from the ANDROMEDA clinical trial clearly shows the benefit of using daratumumab to treat AL Amyloidosis. This will be the first monoclonal antibody used to treated newly diagnosed patients with AL Amyloidosis and we consider this a step change in the treatment options for patients. *“My numbers came down in two months. They came straight down and have stayed low ever since. Both the amyloid and the myeloma have been low ever since. It’s a great feeling that I reacted so quickly. I just*

[5] Efstathios Kastritis, Vaishali Sanchorawala, Giampaolo Merlini, and on behalf of the ANDROMEDA study group: Subcutaneous daratumumab + bortezomib, cyclophosphamide, and dexamethasone (VCd) in patients with newly diagnosed light chain (AL) amyloidosis: Updated results from the phase 3 ANDROMEDA study. Journal of Clinical Oncology 2021 39:15

[6] Kastritis E, Palladini G, Minnema MC, et al. Subcutaneous daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (CyborD) in patients with newly diagnosed light chain (AL) amyloidosis: primary results from the phase 3 Andromeda study. Abstract LB2604. Presented as part of EHA25 Virtual, June 14, 2020.

	want it to work. I would not care if it took months, but I know I am lucky as I am one of those who responded so quickly to the treatment." Patient on the ANDROMEDA Clinical trial Further studies have shown that using daratumumab in AL Amyloidosis is a highly effective agent that produced rapid and deep haematologic responses without increasing toxicity.[7] Daratumumab is an innovative technology which we consider has potential to make a significant and substantial impact. *"Daratumumab compared to VCD is unbelievable. It took many cycles of VCD to get my FLC ratio down and it never got as far as the Daratumumab."* Results from the ANDROMEDA Clinical trial shows that adding Daratumumab to the standard treatment combination of CyBord resulted in deeper and more robust rapid hematologic responses and improved clinical outcomes, compared with CyBord alone, in patients with newly diagnosed AL Amyloidosis. **Treatment Administration** In the ANDROMEDA trial all patients received CyBord weekly for 6 28-day cycles. Cyclophosphamide 300 mg/m^2 is given orally (by mouth) or intravenously (injection into a vein) and bortezomib 1.3 mg/m^2 subcutaneously (injection under the skin) on days 1, 8, 15, and 22 of each cycle for up to 6 cycles. Dexamethasone 40 mg was given orally or intravenously weekly for each cycle for up to 6 cycles. With the inclusion of subcutaneous Daratumumab this treatment will be fairly simple for patients to receive. We know from our engagement with patients that they value treatments which do not take up too much time to receive. We also know that patients have greatly valued receiving the subcutaneous formulation of daratumumab during the COVID pandemic as it can cut down time spent in hospital or be taken at home and thus reduce the risk of being exposed to infection.

[7] Gregory P. Kaufman, Stanley L. Schrier, Richard A. Lafayette, Sally Arai, Ronald M. Witteles, Michaela Liedtke; Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. *Blood* 2017; 130 (7): 900–902. doi: https://doi.org/10.1182/blood-2017-01-763599

	"The last four cycles of Daratumumab have been subcutaneous. This is a really big advantage as now I am in hospital for one hour instead of four and it frees up a bed in the hospital and the nurses time looking after me." Finally, the fixed duration of treatment with six cycles of Dara CyBord followed by two years of maintenance treatment with daratumumab can provide patients with a level of certainty that the treatment has an end point. Following this, there will hopefully be an extended and possibly treatment-free remission which is highly valued by patients.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	**Side Effects** Patients value treatments with fewer side effects with low severity ratings which stop when treatment ends. However, in practice patients will accept varying levels of toxicity in a treatment if it delivers good survival benefit. The most common grade 3/4 side effects reported in the ANDROMEDA clinical trial were similar across both arms including low lymphocyte levels (13% Dara CyBord arm vs 10% CyBord arm), pneumonia (8% vs 4%), heart failure (6% vs 5%), low neutrophil levels (5% vs 3%), fainting/ temporary loss of consciousness (5% vs 6%) and swelling in the lower legs or hands (3% vs 6%). *"For the first 6 months the Velcade had an effect on me. As time has gone on, I have put on a lot of weight. I have not changed my diet or my eating habits, I do some exercise also, but I have put on some weight." Patient on the ANDROMEDA Clinical trial* *"I also lost my sense of taste; everything tasted a bit burnt or plasticky which was pretty awful. I had lots of support at home which was fortunate." Patient on the ANDROMEDA Clinical trial*

	"During treatment I had a lot of tiredness. On most days I would need a nap in the afternoon. At the start of treatment, it was about a half hour nap and now it can be as short as ten minutes, but I wake up and I am good to go." Patient on the ANDROMEDA Clinical trial *"Whilst in hospital I had retention of a lot of fluid. The reduced incidence of grade 3/4 swelling in the hands/feet looks positive. The swelling for me created a lot of pressure on my heart. The data looks a lot better here in the Dara CyBord arm."* Infusion related reactions with daratumumab occurred in 7% of patients, all were grade 1-2 and most occurred during the first infusion. This is a well-known side effect of daratumumab which clinicians are experienced in dealing with. When considering side effects, the most discussed impact of treatment is usually associated with the steroid the patient receives (i.e. dexamethasone) "*The steroid has the biggest impact on me. I wake up at 3am on a Thursday morning the day after treatment, regular as clockwork as the steroids seem to put me into overdrive."* *"The most significant side effects I experience are with the dexamethasone. It causes sleeplessness and gut disturbances. I had a lot of refluxes but the biopsy and examination on that proved clear. It has gradually improved."* Overall, the side effect profile of Dara CyBord is similar to CyBord and therefore patients can expect no reduction in quality of life when receiving this quadruplet combination. Patient engagement in Myeloma UK has shown that most patients see side effects as something that has to be managed in their daily lives or tolerated for an effective treatment that keeps their AL Amyloidosis in remission.

	"All of the side effects I have had with treatment were and are manageable. A day or two of bad sleep is minor compared to the upside. You can only comment on the side effects that you personally experience which for me have been minimal."
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.	At the scoping workshop carried out in December 2020 a question was posed around the inclusion of AL Amyloidosis patients with Cardiac 3b involvement. The chair cited that there was a lack of evidence for this sub-group of patients in the clinical trial data. In the ANDROMEDA clinical trial there were no patients with Cardiac 3b involvement participating in the trial. We understand from clinicians that many patients who present with Cardiac 3b involvement are either older or particularly unwell and are usually unable to take part in clinical trials. We would advocate strongly for access to this treatment for patients with cardiac 3b involvement and cite further evidence for showing inclusion. Approximately 20% of patients have advanced (stage 3b) cardiac involvement at diagnosis. Treatment of these patients remains an unmet need. However, if a profound response is reached within 1 month, OS can improve, even in these subjects.[8] In the ALchemy trial conducted in the UK at the NAC recently published results show that patients achieving an early deep haematologic response have a significantly superior survival irrespective of cardiac involvement.[9]

[8] Manwani R, Foard D, Mahmood S, et al. Rapid hematologic responses improve outcomes in patients with very advanced (stage IIIb) cardiac immunoglobulin light chain amyloidosis. Haematologica. 2018;103(4):e165-e168

[9] Ravichandran, S., Cohen, O.C., Law, S. *et al.* Impact of early response on outcomes in AL Amyloidosis following treatment with frontline Bortezomib. *Blood Cancer J.* **11,** 118 (2021). https://doi.org/10.1038/s41408-021-00510-7

	Studies have shown the effectiveness and tolerability of daratumumab as a treatment for AL Amyloidosis patients with cardiac 3b involvement, including in the USA[10] and in real word studies as a front-line treatment in Austria.[11] Clinical trial data from the ANDROMEDA study shows that daratumumab can produce early and deep haematological responses in patients which will have a significant impact in the patients' overall survival. Based on the evidence above and the clinical experts' opinion we would advocate for patients with level 3b cardiac involvement to be eligible to be treated with Dara CyBord.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**N/A**

[10] Gregory P. Kaufman, Stanley L. Schrier, Richard A. Lafayette, Sally Arai, Ronald M. Witteles, Michaela Liedtke; Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood 2017; 130 (7): 900–902. doi

[11] G. Jeryczynski, M. Antlanger, F. Duca, C. Binder-Rodriguez, T. Reiter, I. Simonitsch-Klupp, D. Bonderman, R. Kain, M.-T. Krauth, H. Agis,First-line daratumumab shows high efficacy and tolerability even in advanced AL amyloidosis: the real-world experience ESMO Open 6:2, 2021, 100065, ISSN 2059-7029,

Other issues	
13. Are there any other issues that you would like the committee to consider?	Dara CyBord also presents the first NICE appraisal for a treatment directly related to AL Amyloidosis. This is significant for the patient population as it gives recognition to the disease and its own treatment pathway can begin to be developed.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- There is significant unmet need for this patient population. Dara CyBord presents the first licensed treatment to be assessed by NICE for AL Amyloidosis. If approved, it will become the standard treatment for newly diagnosed AL Amyloidosis.
- Data from the Phase III ANDROMEDA trial indicates that the addition of daratumumab to CyBord for newly diagnosed AL Amyloidosis can induce faster and deeper responses to the treatment without increasing toxicity. In AL Amyloidosis the depth and speed of response correlates directly with improved outcomes for patients.
- The quadruplet treatment is relatively easily to take involving two tablets and two subcutaneous injections which patients value as it cuts down on time spent in hospital and gives them more control over their lives.
- The side effect profile for Dara CyBord is comparable to the current standard of care of CyBord meaning patients who receive this quadruplet treatment will not experience a decrease in Quality of Life.
- Patients with cardiac 3b involvement should not be excluded from accessing this treatment. Evidence from other clinical trials including ALchemy shows that patients who achieve an early deep haematologic response have a significantly superior survival irrespective of cardiac involvement. Daratumumab has also demonstrated its efficacy for patients with cardiac 3b involvement in other studies.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Daratumumab in combination for newly diagnosed systemic amyloid light-chain amyloidosis [ID3748]

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this 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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	UK Kidney Association

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The UK Kidney Association (Renal Association) is the leading professional body for the UK renal community. We welcome members working in clinical renal care, treating and caring for people with kidney disease, and those working in research, or related sciences and fields. For 70 years, the Renal Association has been energetic in promoting and sharing research to improve outcomes for people with kidney disease. We have taken a lead in the education of clinicians and scientists and more recently we've evolved to take a major role in training doctors and developing clinical services. We are transforming the way kidney care and research is delivered in the UK and beyond. Funding is obtained from membership fees, including industry memberships.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator	No

products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to suppress the underlying clone which is the source of the AL amyloid fibrils and to prevent further disease progression. If successful this can result is disease regression but this is not universal.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The treatment response is assessed through measurement of the reduction in clonal markers. This is via sequential measurements of monoclonal protein using protein electrophoresis and through testing serum free light chains. The target is a complete clonal response with normalisation of the abnormal serum free light chain and no detection of monoclonal immunoglobulin. This may not be achievable and a >90% reduction in the dFLC (the difference between the abnormal serum free light chain and the 'normal' serum free light chain) is associated with stabilisation of disease and/or regression and is usually deemed an acceptable response (Palladini et al JCO 2012).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need in this condition. Amyloid is a condition which can present in an indolent way with a wide variety of symptoms making diagnostic pathways varied and leading to delayed diagnosis. The prognosis can be varied depending on organ involvement and access to treatment is not uniform across the UK. Access to disease specific treatment rests on having the disease classified as myeloma so that patients are able to access chemotherapy. There is a wealth of literature to support the use of chemotherapy in improving patient outcomes in AL amyloidosis. Side effects from treatment are often more challenging in this patient population as they may have organ involvement which results in symptoms which are exacerbated by the side effects from chemotherapy and result in early cessation of treatment.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Amyloid is currently treated by a local haematologists. There are centres in the UK with specific expertise where patients may be referred to and this is recommended but not mandated as there is no currently funded treatment centres within the UK. Treatment of AL amyloidosis is with chemotherapy used in line with national guidance for the treatment of multiple myeloma. This is usually initially with Bortezomib, cyclophosphamide and dexamethasone and further lines of chemotherapy are delivered depending on disease response after the first 2-3 months and at subsequent clonal relapse.
• Are any clinical guidelines used in the treatment of the	There is a NICE approved guideline which was published in 2014 entitled: Guidelines on the management of AL amyloidosis. This sets out recommendations on treatment but acknowledges that there is no

condition, and if so, which?	'standard treatment' as treatment needs to be tailored to the individual patient.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care can be complex prior to the diagnosis being made as patients may present to a variety of specialists. Once there is a histological diagnosis the pathway is defined. It involves referral to the National Amyloidosis Centre for either face to face review or expert advice if the patient is too unwell to travel. Once the diagnosis is confirmed the management is directed at treatment of the underlying clone in haematology clinic, preferably under a haematologist with specialist knowledge and expertise in amyloid. Further diagnostic work-up is required with bone marrow biopsy, PET CT, cardiac work-up and review of clinical systems to determine the organ involvement. There may be differences in opinion regarding suitability for treatment as in some patients prognosis may be poor and perceived benefit from treatment can be a very difficult decision. Experience of the treating physician may also have an impact on the delivery of chemotherapy. Access to chemotherapy can vary across the UK. National guidance regarding diagnosis of myeloma remains as >10% plasma cells on bone marrow biopsy. AL amyloidosis is commonly associated with a low level clone with <10% plasma cells. Not all units have access to treatment if the clone is not at this level as they may not be able to define the condition as myeloma. The view of national experts is that AL amyloidosis is 'myeloma defining' but this is not currently backed up by haematology bodies. This means that access to treatment may change depending on postcodes, for second and third line treatments IFR applications and blue teq forms are required and therefore can depend on the local commissioning bodies.
• What impact would the technology have on the current pathway of care?	A NICE approved treatment for AL amyloidosis would take away the need for classification as 'myeloma' and improve access to first line treatment as it would be able to be used in a more uniform way across the UK. However, the impact on second and third line treatment would need to be considered as it would need to ensure that these treatments remain available to patients.
10. Will the technology be used (or is it already used) in the same way as current care	Daratumumab is not currently used as first line treatment for Multiple Myeloma in the UK. It has a licence by the European Medicines Agency (EMA) for use across Europe as both monotherapy and in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone in relapsed and/or refractory patients. NICE have approved Daratumumab monotherapy as Fourth line treatment in England and Wales.

in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Access to Daratumumab upfront in patients with AL amyloidosis would enable these patients access to a combination therapy that is currently only available as fourth line treatment.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This treatment should be used in specialist clinics with the set up and expertise to manage these complex patients who often require multi-disciplinary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Haematology clinics have been using Daratumumab now for several years and have experience in this. I wouldn't anticipate additional training to be required, the monitoring associated would be the same as current practice.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The ANDROMEDA study compared Daratumumab in combination with Bortezomib, cyclophosphamide and dexamethasone (BCd) vs BCd in patients with newly diagnosed AL amyloidosis. There were significantly more patients achieving a complete response (CR) and very good partial response (VGPR) and the time to haematologic response was faster in the DBCd group. This in turn was associated with nearly double the patients achieving both cardiac and renal responses.
• Do you expect the technology to increase length of life more than	Patients with cardiac amyloid have a poor prognosis and the depth and speed of the clonal response is essential for improving patient outcomes. Patients often have significant morbidity from fluid retention in both cardiac and renal disease which can result in early termination of treatment. Based on the results of

current care?	the ANDROMEDA study I would anticipate an increase in the length of life of these patients.
• Do you expect the technology to increase health-related quality of life more than current care?	I would expect an improvement in quality of life. Daratumumab has been shown to have fewer side effects such as fluid retention which can be the reason for cessation of treatment and poor quality of life. This is particularly the case in patients with nephrotic syndrome from renal amyloid and cardiac involvement or a combination of the two which is very difficult to manage.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This combination would be particularly suited to nephrotic patients in whom drugs such as thalidomide are very difficult to use due to the fluid retention and pro thrombotic effects. The speed of response is particularly important for patients who have cardiac disease. The ANDROMEDA study excluded patients with stage IIIb cardiac disease and patients with an eGFR <20ml/min so information on benefit is more limited in these groups.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	The Daratumumab infusion if administered intravenously (especially initially) can take longer to administer than current first line treatment and requires monitoring for 4 hours after the first infusion, after the initial infusion patients can go home after 30 minutes. A subcutaneous delivery method is now available; this method was used in the ANDROMEDA study. Infusion reactions are the main side effect which may impede delivery and results in slower delivery of the drug.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Diagnostic criteria for AL amyloidosis will be required. Lack of clonal response at cycle 3 would result in consideration of switching to second line therapy. Testing for clonal response happens at monthly intervals already so no additional testing would be required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This is dependent on the timing of the QALY assessment. Patients can feel significantly worse during their treatment than they did at presentation but if they survive and complete chemotherapy the quality of life benefits happen after the treatment has finished and in the subsequent years when disease stability ensues.
16. Do you consider the technology to be innovative in its potential to make a	The treatment itself has the potential to improve life expectancy and quality of life as Daratumumab appears to be more efficacious in the clinical trial setting than standard of care. The process of licensing an up front treatment for AL amyloidosis will also impact on access to treatment in its own right, potentially

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	changing the landscape of treatment for these patients.
• Is the technology a 'step-change' in the management of the condition?	Yes, as AL amyloidosis has not previously had its own licensed treatment this would be a step change in the management of the condition.
• Does the use of the technology address any particular unmet need of the patient population?	The may be better adherence to treatment as Daratumumab has been well tolerated in patients with AL amyloidosis, some patients with significant neuropathy may not be able to have Bortezomib and if licensed in combination with different agents it would enable more flexibility for patients who are difficult to treat due to Amyloid disease side effects.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The commonest side effect is an infusion reaction which should not affect quality of life in the medium to longer term. Cytopenias, deranged LFTs can occur and may result in the need for transfusions or GCSF in some patients. Rarely neuropathy can occur, however this is also a potential side effect of Bortezomib based therapy and patients are required to report symptoms as soon as they occur. Painful peripheral neuropathy as a

	permanent side effect of treatment has potential for long term impact on quality of life. In patients who present with significant neuropathy this can mean restrictions on the use of Bortezomib, as Daraumumab has a much lower risk of peripheral neuropathy it may be easier to use for patients with neuropathy.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The ANDROMEDA study compared Dara BCd with BCd. The schedule of Bortezomib, cyclophosphamide and dexamethasone and doses were the same as those in clinical practice and diagnostic criteria for patients with AL amyloidosis were the same as standard practice. Patients with an eGFR of <20ml/min and stage IIIb cardiac disease patients were excluded.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are; overall patient survival, clonal response and progression to end stage renal failure. These were measured in the trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None to my knowledge
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Real world data in the literature show rapid clonal responses and the literature reports that it is well tolerated in this disease group. This is in line with the clinical trial data.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	The ANDROMEDA clinic trial excluded patients with an eGFR of <20ml/min and those patients with stage IIIb cardiac disease. Arguably these groups of patients have the most to gain from a rapid response with a well tolerated drug. Daratumumab can be given in renal failure and therefore patients with significant renal impairment or those with end stage kidney disease should not be excluded. Patients with stage IIIb cardiac disease will need careful consideration. If an experienced physician feels they may tolerate treatment then exclusion from receiving this treatment if approved would mean having to have a combination of treatment

	that takes longer to work with potentially more side effects and potentially worse outcomes.
21b. Consider whether these issues are different from issues with current care and why.	No patient group are currently excluded from treatment. Shared decision making with the patient regarding whether they want to embark on treatment in the knowledge the prognosis may be very poor happens in clinical practice with some patients deciding to take a palliative care approach and others having a very limited amount of treatment at a reduced dose to determine tolerability. This would remain the approach with Daratumumab.
Topic-specific questions	
22. How would you diagnose and assess the extent of heart failure in people with AL amyloidosis in NHS practice?	The extent of heart failure is assessed in several ways. Firstly a clinical assessment is required incorporating NHYA symptoms via the patient history, discussion about exercise tolerance, and examination looking at the volume status of the patient. Secondly via biochemical markers, troponin T and NT-proBNP measurements, oxygen saturations and basic observations. At the initial presentation diagnostic imaging is also used, including echocardiography and cardiac MRI scanning.
23. To what extent the New York Heart Association (NYHA) classification is used in the UK to classify the extent of heart failure?	This is used commonly and is a quick way of conveying information regarding severity of heart failure symptoms, however it is not used to stage the disease in AL amyoidosis. The MAYO staging system is used routinely in studies and in clinical practice. This involvement the measurement of Tropoinin T and NT-proBNP.
24. If NYHA scale is not used,	I would ask the patient more generally about their symptoms and exercise tolerance or ability to perform

how would you identify a group of patients corresponding to level IIIb NYHA heart failure?	daily tasks and use the MAYO staging system.
25. How is this population (with level IIIb NYHA heart failure or corresponding severity) is currently treated in the UK? Is it any different to how would you treat people with no or less severe heart failure?	Patients with NYHA class IIIb symptoms in general have a poor outcome in AL amyloidosis. This measure would not be used in isolation when considering whether the patient would benefit from treatment with chemotherapy. Age, ECOG performance status, cardiac biomarkers to define the MAYO staging are also used in discussion with the patient. Consideration is also given to other organ involvement such as autonomic dysfunction which can be particularly difficult to manage. The degree of fluid overload in patients with a combination of cardiac and renal disease can mean NYHA scoring may also be misleading. In those patients deemed suitable for treatment dose reduction of Bortezomib is usually required to determine tolerability and initiation of treatment may initially be with Bortezomib and dexamethasone alone first with cyclophosphamide added in after the first few weeks. Patients with MAYO stage III disease are admitted for their first dose of Bortezomib and have cardiac monitoring.
26. Would you expect the outcomes to differ for this population (with level IIIb NYHA heart failure or corresponding severity), compared with those with no or	Prognosis in the most severely affected cardiac patients is poor, however if this group was excluded from treatment it may mean an inability to offer treatment at all. In some (very rare) cases upfront chemotherapy has been used to achieve a clonal response in order to have a cardiac transplant and then subsequent bone marrow transplant. This group of patients potentially has the most to gain from this treatment as a rapid response is so important for them.

less severe heart failure?	
27. What proportion of people with AL amyloidosis are expected to have level IIIb heart failure (or corresponding severity) in the UK?	Up to 80% of patients have been reported to have cardiac involvement at presentation. Data on the proportion of patients presenting with NYHA IIIb symptoms is not readily available in the published literature. The estimated number of patients attending the UK National Amyloidosis Centre with stage IIIb disease is around 15%.

Key messages

27. In up to 5 bullet points, please summarise the key messages of your submission.

- Access to treatment for patients with AL amyloidosis in the UK is not uniform across the NHS.
- Treatment with Daratumumab in combination as upfront therapy has been shown to be superior to standard chemotherapy.
- AL amyloidosis is very different clinically to Multiple Myeloma but current treatment is the same and does not take into account disease specific side effects/limitations.
- Exclusion of patients with advanced cardiac and renal disease would affect a significant proportion of patients who have the most to gain from the treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Daratumumab in combination for newly diagnosed systemic amyloid light-chain amyloidosis [ID3748]

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Helen Lachmann is Vice Chair of the MHRA Expert Advisory Group on Clinical Trials, Vaccines and Biologics and potentially could be asked in that respect to comment on new licence applications for daratumumab and other novel agents targeting plasma cell disorders.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Sumayya Anwer critiqued the clinical effectiveness review and contributed to the writing of Sections 2 and 3. Sofia Dias reviewed the ERG additional analyses, led the critical appraisal of the clinical evidence and takes joint responsibility for the report as a whole. Rita Faria performed the critical review of the economic analyses, conducted the ERG additional analyses, and wrote Sections 4, 5 and 6 of the report. Helen Fulbright critiqued the search strategies, wrote the search strategy sections and provided editorial support. Mark Rodgers performed the critical review of the clinical evidence, and wrote sections 2 and 3 of the report. Claire Rothery performed the critical review of the economic analyses, contributed to the writing of Sections 4, 5 and 6 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole. Pedro Saramago performed the critical review of the economic analyses and provided technical support for the ERG additional analyses.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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List of abbreviations

Abbreviation	Definition
1L Tx	First-line treatment
2L Tx	Second-line treatment
AE	Adverse event
AIC	Akaike's information criterion
AL	Amyloid light chain
ANS	Autonomic nervous system
ASCT	Autologous stem cell transplant
BCd	Bortezomib, cyclophosphamide and dexamethasone
CDF	Cancer Drugs Fund
CE	Cost-effectiveness
cfb	Change from baseline
CR	Complete haematologic response
CI	Confidence interval
CONSORT	CONsolidated Standards of Reporting Trials
CR	Complete response
CS	Company submission
CSR	Clinical study report
CyBorD	Cyclophosphamide, bortezomib, dexamethasone (otherwise referred to as BCd)
Dara SC	Daratumumab subcutaneous
DBCd	Daratumumab, bortezomib, cyclophosphamide and dexamethasone
dFLC	Difference between involved and uninvolved free light chain
ECOG	Eastern Cooperative Oncology Group Performance Status
eMIT	Drugs and pharmaceutical electronic market information tool
EMN	European Myeloma Network
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0
EQ-5D-5L	EuroQol-5 Dimensions-5 Level
ERG	Evidence Review Group
FDA	U.S. Food and Drug Administration
FDT	Fixed dose treatment
FLC	Free light chain
HBV	Hepatitis B virus
HemPFS	Hematologic progression-free survival
HRG	Healthcare resource group
HRQoL	Health-related quality of life
IA1	Interim analysis 1
ICER	Incremental cost-effectiveness ratio

iFLC	Involved free light chain
IgG1κ	Immunoglobulin G1 kappa
IPCW	Inverse probability of censoring weighting
IRC	Independent Review Committee
IRR	Infusion-related reactions
ISR	Injection site reactions
ITT	Intention-to-treat
IWRS	Interactive web response system
KM	Kaplan-Meier
LS(M)	Least square (means)
LY	Life years
mAb	Monoclonal antibody
MCS	Mental Component Summary
Md	Melphalan and dexamethasone
MHRA	Medicines & Healthcare Products Regulatory Agency
MM	Multiple myeloma
MOD-EFS	Major organ deterioration event-free survival
MOD-PFS	Major organ deterioration progression-free survival
NA	Not Applicable
N/A	Not Applicable
NAC	(UK) National Amyloidosis Centre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	No response
NYHA	New York Heart Association
Off Tx	Off treatment
On Tx	On first-line treatment
OS	Overall survival
PAS	Patient access scheme
PCS	Physical Component Summary
Pd	Pomalidomide and dexamethasone
PD	Progressive disease
PfC	Points for clarification
PFS	Progression-free survival
PICOS	Population, Intervention, Comparison, Outcomes, and Study design
PNS	Peripheral nervous system
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses

PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
Rd	Lenalinomide with dexomethasone
SC	Subcutaneous
SD	Standard deviation
SF-36	Short Form 36 Health Survey Questionnaire
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TECH-VER	TECHnical VERification
ULN	Upper limit of normal
VGPR	Very good partial response

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 provides an overview of the key issues.

Table 1: Overview of the ERG's key issues

ID	Summary of issue	Report sections
1.	The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis that is not restricted to exclude patients with Mayo Clinic Cardiac Stage IIIb disease	2.3
2.	Absence of clinical trial data for patients with Mayo Clinic Cardiac Stage IIIb disease	3.2.1.2
3.	Immaturity of overall survival data from the ANDROMEDA clinical trial	3.2.3.1
4.	Lack of medium-to-long term adverse event data for daratumumab in AL amyloidosis	3.2.4.8
5.	Timing of response assessment for depth of haematologic response	4.2.2.2
6.	Source of data for overall survival, stratified by haematologic response	4.2.6.2
7.	Baseline source of haematologic response distribution for BCd	4.2.6.2
8.	Combining suboptimal haematologic response categories in the model	4.2.2.2
9.	Health-related quality of life utility values used in the model	4.2.8.2
10.	Maximum treatment duration with daratumumab	4.2.4.2
11.	Underestimation of the administration costs of DBCd and BCd	4.2.9.2
12.	Impact of DBCd on autologous stem cell transplant rates	4.2.9.2
13.	Approach to the costs of second- and third-line therapies in the model	4.2.9.2
14.	Potential of daratumumab for the Cancer Drugs Fund (CDF)	6.4

Abbreviations: AL: Amyloid light chain; BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone.

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are (i) a haematologic response assessment timepoint after three treatment cycles rather

than after six treatment cycles; (ii) the use of the UK ALchemy study to inform baseline haematologic response distribution for bortezomib, cyclophosphamide and dexamethasone (BCd) rather than the ANDROMEDA trial; (iii) the use of the UK ALchemy study to inform overall survival stratified by depth of haematologic response; (iv) utility values are adjusted by age; (v) second-line therapies are based on those used in the ALchemy study; and (vi) third-line therapy costs are included with a 20% reduction in upfront costs of second- and third-line therapies to reflect treatment discontinuations, dose adjustments and death during the course of treatment.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients who achieve complete haematologic response (CR), as CR is associated with better health-related quality of life, lower risk of progression (to second-line therapy and end-stage organ failure) and greater life expectancy.

Overall, the technology (daratumumab with bortezomib, cyclophosphamide and dexamethasone, DBCd) is modelled to affect costs by:

- Greater acquisition costs compared to BCd (the comparator);
- Increasing the life expectancy of patients who use healthcare services;
- Reducing the proportion of patients who require subsequent therapies.

The modelling assumptions that have the greatest effect on the ICER are:

- Timing of the haematologic response assessment after three treatment cycles rather than after six treatment cycles;
- Data source used to inform overall survival (i.e. life expectancy in the model);
- Administration costs of daratumumab and bortezomib.

1.3 The decision problem: summary of the ERG's key issues

Issue 1 The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis that is not restricted to exclude patients with Mayo Clinic Cardiac Stage IIIb disease

Report section	Section 2.3
Description of issue and why the ERG has identified it as important	The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis in the entire licensed population, including patients with Mayo Clinic Cardiac Stage IIIb disease, who have the most severe degree of cardiac involvement and have high risk systemic AL amyloidosis with a very poor prognosis. The company submission states that, in UK clinical practice, patients with Stage IIIb disease are expected to comprise approximately 20% of the AL amyloidosis cohort. The ERG notes that the NICE scope includes consideration of subgroups based on severity of heart failure if evidence allows. However, the company submitted no evidence to assess the clinical effectiveness or cost-effectiveness of DBCd compared to BCd in a subpopulation of patients with Stage IIIb disease.
What alternative approach has the ERG suggested?	The company should provide evidence on the clinical effectiveness and cost-effectiveness of DBCd compared to BCd in a subgroup of patients with Mayo Clinic Cardiac Stage IIIb. The nature of the evidence that could be provided is discussed in Issue 2. The ERG has provided evidence on the cost-effectiveness of DBCd in the entire licensed population (including patients with Mayo Clinic Cardiac Stage IIIb and patients with less severe disease) under the critical assumptions that (i) the relative effectiveness of DBCd versus BCd for the depth of haematologic response, as observed in the ANDROMEDA trial, generalises to the entire licensed population; (ii) the health-related quality of life, safety and probability of progression observed in the ANDROMEDA trial also generalises to the entire licensed population; and (iii) the UK ALchemy study[1] for overall survival stratified by depth of haematologic response for BCd provides the best available baseline data. Without evidence assessing the relative effectiveness of DBCd compared to BCd for different severity levels of disease, the ERG is unable to provide cost-effectiveness results for subgroups of patients.
What is the expected effect on the cost-effectiveness estimates?	The ERG is unable to predict what the expected cost-effectiveness results would be in a subpopulation with Mayo Clinic Cardiac Stage IIIb given the lack of evidence on relative effectiveness in this subpopulation. In addition to evidence on the relative effectiveness of DBCd vs. BCd in this subpopulation, the model would require evidence on overall survival, stratified by depth of haematologic response, in patients with Mayo Clinic Cardiac Stage IIIb. The ERG expects overall survival to be lower in patients with Stage IIIb disease, but the impact on cost-effectiveness results is unknown.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence on the clinical effectiveness and cost-effectiveness of DBCd in a subpopulation with Mayo Clinic Cardiac Stage IIIb.

	The ERG notes that, in response to ERG points for clarification, the company have indicated that it expects to provide additional evidence for this subpopulation at Technical Engagement.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2 Absence of clinical trial data for patients with Mayo Clinic Cardiac Stage IIIb disease

Report section	3.2.1.2
Description of issue and why the ERG has identified it as important	The ANDROMEDA trial excludes patients with Mayo Clinic Cardiac Stage IIIb – a high clinical need subgroup that comprises approximately 20% of AL amyloidosis patients in the UK. It is therefore unclear how the benefits and harms of DBCd relative to BCd for Stage IIIb patients compare to the benefits and harms estimated for patients with less severe cardiac involvement.
What alternative approach has the ERG suggested?	In the absence of any other comparative trials, it is not possible to estimate the relative treatment effect of daratumumab in patients with newly diagnosed AL amyloidosis and Mayo Clinic Cardiac Stage IIIb.
What is the expected effect on the cost-effectiveness estimates?	As noted under Issue 1, and given the lack of evidence, the ERG is unable to predict what is the expected effect on cost-effectiveness. The cost-effectiveness results based on data from the pivotal ANDROMEDA trial that excludes patients with Stage IIIb disease is unlikely to generalise to patients with very severe cardiac involvement and poor prognosis. Overall survival, conditional on haematologic response, would be expected to be lower for patients with more severe cardiac involvement. However, the impact of treatment with DBCd relative to BCd on outcomes in Stage IIIb disease is unknown; and it is not clear if the ANDROMEDA trial evidence which informs other parameters of the model generalises to this subpopulation. Therefore, the impact on the cost-effectiveness of DBCd is also unknown.
What additional evidence or analyses might help to resolve this key issue?	Further clarification of the relative effects of daratumumab in cardiac Stage IIIb patients would require trial evidence from the UK (or similar population), which is unlikely to exist at present. However, the company has indicated that they expect to provide an exploratory analysis investigating the cost-effectiveness of DBCd for this subpopulation at Technical Engagement.

Issue 3 Immaturity of overall survival data from the ANDROMEDA clinical trial

Report section	3.2.3.1
Description of issue and why the ERG has identified it as important	Mature overall survival (OS) data from the ANDROMEDA trial were not available at the time of the company submission, with median OS not being reached in either treatment arm. In the absence of long-term OS data from the trial to inform the cost-effectiveness model, OS is informed by depth of

	haematologic response achieved following first-line treatment with DBCd or BCd after six cycles of treatment (base-case analysis). After six cycles of treatment, external survival data, stratified by haematologic response, was sourced to inform OS over time. The ERG considers that the assumption that OS depends only on depth of haematologic response may be overly simplistic and may bias the model predictions of long-term OS.
What alternative approach has the ERG suggested?	In the absence of mature OS trial data, the ERG considers the company's approach to be acceptable but there is considerable uncertainty surrounding the predicted treatment-specific OS over time. The ERG proposes an alternative source of external survival data, conditional on haematologic response, which closely reflects outcomes in a UK population and has longer follow-up; this is discussed under Issue 6.
What is the expected effect on the cost-effectiveness estimates?	The expected effect of mature trial data for OS on the cost-effectiveness estimates will depend on how closely the treatment-specific survival outcomes from the trial relate to the current modelling assumption that treatment-specific survival over time can be predicted based solely on the distribution of haematologic response achieved at the response assessment time point (e.g., after three or six cycles of treatment) and external survival data, stratified by haematologic response, from observational studies.
What additional evidence or analyses might help to resolve this key issue?	The ANDROMEDA trial is ongoing and the company have indicated that the following analyses are planned: • 18-month landmark data cut-off: updated analyses for haematologic response and organ response ([redacted]) • 200 MOD-PFS event driven data cut-off: updated analyses for OS, MOD-PFS, haematologic response and organ response (publication expected [redacted]) • Final OS data cut-off: updated analyses have not yet been confirmed ([redacted]). Given the model structure and the ANDROMEDA trial sample size and follow-up period, the ERG considers that these analyses could be used to validate the cost-effectiveness model predictions for overall survival, which represents the main driver of cost-effectiveness of DBCd relative to BCd.

Issue 4 Lack of medium-to-long term adverse event data for daratumumab in AL amyloidosis

Report section	3.2.4.8
Description of issue and why the ERG has identified it as important	While the ANDROMEDA treatment protocol permitted up to 24 cycles of daratumumab treatment, median length of follow-up in the most recent analysis was 20.3 months and median duration of daratumumab treatment was 18.5 months. Adverse event data for longer treatment or follow-up times are not currently available. As daratumumab is a monoclonal antibody therapy, the ERG's clinical advisors noted general concerns about the possible effect on infections beyond the period observed in the trial.

What alternative approach has the ERG suggested?	There is currently limited evidence on the longer-term use of daratumumab for any indication. The ERG have looked further at 40-month data from multiple myeloma, in which AEs were largely consistent with those observed in ANDROMEDA.
What is the expected effect on the cost-effectiveness estimates?	The AEs considered in the model are based on Grade III or IV AEs reported in > 5% of patients in either treatment arm of the ANDROMEDA trial. Infections beyond the period observed in the trial are mostly anticipated to be treatable Grade I or II events that would not be expected to significantly affect the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Complete ANDROMEDA follow-up data and observational/post-marketing surveillance data will be needed to understand the longer-term safety of daratumumab in patients with AL amyloidosis.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 5 Timing of response assessment for depth of haematologic response

Report section	Section 4.2.2.2 Timing of response assessment Item 1; Item 2.
Description of issue and why the ERG has identified it as important	In the company's base case analysis, patients are stratified by haematologic response after six monthly treatment cycles, which is inconsistent with UK clinical practice and guidelines[2, 3] that suggest response assessment occurs after three treatment cycles.
What alternative approach has the ERG suggested?	The ERG considers that the response assessment timepoint for stratifying patients by haematologic response in the base case should be consistent with current guidelines for the management of AL amyloidosis in UK clinical practice that suggest the assessment timepoint for response is after three months (approximately three treatment cycles).[2] Furthermore, a scenario analysis should be considered to assess the impact of early response to treatment after one treatment cycle, in line with proposals outlined by Ravichandran et al, 2021 and Kastritis et al (2021).[1, 4]
What is the expected effect on the cost-effectiveness estimates?	The timing of the response assessment has a large impact on the cost-effectiveness results: • In the company's scenario analysis (scenario 3), which assumes that the response assessment occurs after three treatment cycles rather than after six cycles in the company's base-case, and replicated in ERG Scenario 1, the ICER increases from £23,509/QALY to £33,774/QALY • Under the ERG's preferred assumptions, which includes response assessment after three treatment cycles, the ICER is £62,660/QALY. The impact of assuming that the response assessment occurs after one treatment cycle is unknown.

What additional evidence or analyses might help to resolve this key issue?	An additional scenario analysis that considers the impact of early response to treatment after one treatment cycle. The ERG requested this at points for clarification, but the company did not present results of this scenario.

Issue 6 Source of data for overall survival, stratified by haematologic response

Report section	Section 4.2.6.2 Overall survival Item 8; item 9
Description of issue and why the ERG has identified it as important	A key assumption in the model is that the distribution of haematologic response achieved at the response assessment timepoint (e.g., after three or six cycles of first-line treatment with DBCd or BCd) can predict treatment-specific overall survival over time. In the model, the source of overall survival data, stratified by depth of haematologic response and extrapolated over the long-term is a key driver of cost-effectiveness. In the base-case analysis after six treatment cycles, the source of data for overall survival is Palladini et al (2012),[5] while in the scenario analysis after three treatment cycles, the source is Kastritis et al (2021).[4] Palladini et al (2012) is a retrospective study of 816 AL amyloidosis patients from seven centres in Europe and the United States, with only 18% of patients from the UK and 3.2% treated with upfront bortezomib, while Kastritis et al (2021) included 227 patients in Greece and no UK patients.
What alternative approach has the ERG suggested?	The ALchemy study is an ongoing, prospective, observational study of newly diagnosed patients with AL amyloidosis in the UK treated with upfront bortezomib. Ravichandran et al (2021)[1] reports OS by depth of haematologic response at three timepoint assessments of 1-month, 3-months and 6-months after treatment with upfront bortezomib-based regimes. This study is based on 1194 AL amyloidosis patients seen at the UK National Amyloidosis Centre from 2010-2019 and the ERG considers it to provide the most relevant source of OS data, stratified by haematologic response. The ERG have extrapolated the OS curves by haematologic response and timepoint of assessment based on Ravichandran et al (2021)[1] using the same approach as the company for extrapolating OS data from Palladini et al (2012)[5] and Kastritis et al (2021).[4]
What is the expected effect on the cost-effectiveness estimates?	The source of overall survival data has a large impact on the cost-effectiveness results: • ERG Scenario 6 uses overall survival data based on the ALchemy study[1] at the six month landmark (and assuming the response assessment after six treatment cycles), which increases the ICER from £23,509/QALY to £36,612/QALY. • ERG Scenario 7 uses overall survival data based on the ALchemy study[1] at the three month landmark (and assuming the response assessment after three treatment cycles), which increases the ICER from £33,774/QALY (company scenario

	analysis with response assessment after three treatment cycles) to £47,671/QALY. • The ERG base-case uses the overall survival data based on the ALchemy study[1] at the three month landmark as per ERG Scenario 7; the ICER is £62,660/QALY
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that this key issue is resolved in the ERG's base-case assumptions.

Issue 7 Baseline source of haematologic response distribution for BCd

Report section	Section 4.2.6.2 Depth of haematologic response Item 7
Description of issue and why the ERG has identified it as important	The company uses the haematologic response distribution after six treatment cycles (base-case analysis) in the DBCd and BCd arms from the ANDROMEDA trial to inform the proportion of patients in each treatment group by depth of haematologic response and death in the decision tree model. However, the ERG considers the ALchemy study[1] to be the most relevant source to inform the baseline haematologic response distribution for BCd, at the relevant response assessment timepoint. This is because the ALchemy study includes a large proportion of all patients with newly diagnosed AL amyloidosis in the UK, and all patients are treated with upfront bortezomib-based regimens (although not all patients received BCd as exactly defined in the ANDROMEDA trial). Furthermore, the ALchemy study[1] includes 15.4% of patients with Mayo Clinic Cardiac Stage IIIb disease, which have been excluded from the pivotal ANDROMEDA trial. Therefore, using the ALchemy study to inform the distribution of patients by depth of haematologic response for BCd is expected to align better with the population in whom the company seeks a recommendation, which includes patients with Mayo Clinic Cardiac Stage IIIb.
What alternative approach has the ERG suggested?	The ERG suggests using the ALchemy study to provide the baseline haematologic response distribution for the comparator BCd at the relevant response assessment timepoint (Issue 5), while the depth of response for the daratumumab-based regimen (DBCd) is calculated from odds ratios estimated from a comparison of DBCd and BCd from the ANDROMEDA trial and applied to the haematologic response distribution for BCd from the ALchemy study, in line with the recommendations in NICE Technical Support Document 5.[6] The ERG notes that a feature of this approach is that the ordering of the conditioning into dichotomous categories, which is required to calculate the distribution by depth of haematologic response for the multiple categories of CR, VGPR and PR/NR, can affect the joint distribution, but these differences are small.

What is the expected effect on the cost-effectiveness estimates?	The approach to inform the distribution by depth of haematologic response has limited impact on the cost-effectiveness results: • ERG Scenario 5 uses the BCd baseline based on the ALchemy study[1] at the six month landmark (and assuming the response assessment occurs after six treatment cycles), which increases the ICER from £23,509/QALY to £29,194/QALY. • ERG Scenarios 3 and 4 use the BCd baseline based on the ALchemy study[1] at the three month landmark (and assuming the response assessment occurs after three treatment cycles), which increases the ICER from £33,774/QALY (company scenario analysis with response assessment after three treatment cycles) to £34,094/QALY (ERG Scenario 3) and £36,948/QALY (ERG Scenario 4); ERG Scenarios 3 and 4 vary in terms of the ordering of the conditioning of the multiple haematologic categories. • The ERG base-case uses the BCd baseline based on the ALchemy study[1] at the three month landmark after three treatment cycles, as per ERG Scenario 3; the ICER is £62,660/QALY.
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that this key issue is resolved in the ERG's base-case assumptions.

Issue 8 Combining suboptimal haematologic response categories in the model

Report section	Section 4.2.2.2 Pooling patients with PR and NR in the same trace; Item 3
Description of issue and why the ERG has identified it as important	The model structure pools together patients with partial response (PR) and no response (NR) into a combined group of PR/NR based on the simplifying assumption that these patients are considered to have achieved a suboptimal response and follow a similar treatment trajectory. However, the combined group may result in an underestimation of OS when compared to estimation of OS in the respective groups separately.
What alternative approach has the ERG suggested?	The ERG suggests removing this simplifying assumption and permit sufficient flexibility within the model structure to separate out the categories of PR and NR in order to enable separate data on PR and NR to be included in the model.
What is the expected effect on the cost-effectiveness estimates?	The model structure that combines PR/NR is likely to favour DBCd, given that DBCd reduces the proportion of patients who achieve PR/NR compared to BCd in the base case analysis.
What additional evidence or analyses might help to resolve this key issue?	A model structure with sufficient flexibility to separate out the categories of PR and NR.

Issue 9 Health-related quality of life utility values used in the model

Report section	Section 4.2.8 Health related quality of life Item 10; Item 11; Item 12
Description of issue and why the ERG has identified it as important	The ERG has three main concerns with the utility values used in the model: (1) The company's base-case analysis does not adjust utilities by age over time, which is a standard approach.[7] (2) The company's model assumes that the utility decrements for the progression-related health states of second-line treatment and end-stage organ failure are conditional on response to first-line treatment, but it is unclear why patients in these health states would not have the same utility value, irrespective of previous response to treatment or previous lines of therapy. (3) The EQ-5D utility values by haematologic response are highly uncertain given the lack of face validity of the utility values derived for VGPR; the short follow-up period to cycle six to inform long-term utility values; and the limited data for health-related quality of life during the progression-related health states of second-line treatment and end-stage organ failure.
What alternative approach has the ERG suggested?	To resolve these concerns, the ERG has conducted the following additional analyses: (1) In ERG Scenario 8, utility values are adjusted by age over time;[7] (2) In ERG Scenario 9, the utility values on second-line therapy or end-stage organ failure do not differ by depth of haematologic response achieved on first-line therapy. Regarding concern (3), the ERG notes that health-related quality of life data in the form of SF-36v2 scores has been collected from patients in the ALchemy study at baseline and response assessment study visits of 3-, 6- and 12-months. These data could potentially be used to map the SF-36 scores to EQ-5D utility values using a published algorithm,[8] in order to validate the EQ-5D utility values from the ANDROMEDA trial.
What is the expected effect on the cost-effectiveness estimates?	The alternative approaches to concerns (1) and (2) discussed above have a minor impact on the cost-effectiveness results: • ERG Scenario 8, with adjustment of utility values by age[7] increases the ICER from £23,509/QALY to £25,293/QALY. • ERG Scenario 9, with utility values for second-line therapy and end-stage organ failure independent of depth of haematologic response achieved with first-line therapy, increases the ICER from £23,509/QALY to £23,862/QALY. • The ERG base-case adjusts the utility values by age[8]; the ICER is £62,660/QALY The impact of using the SF-36v2 scores from the ALchemy study to estimate utilities is unknown.
What additional evidence or analyses might help to resolve this key issue?	The ERG's third concern, relating to uncertainty in the EQ-5D utility values by haematologic response, may be addressed with evidence from the ALchemy study. Specifically, the SF-36v2 scores from the ALchemy study could be mapped to EQ-5D utility values and compared with the ANDROMEDA trial

	estimates and/or incorporated in the model. Furthermore, it may be possible for additional utility evidence to be collected as part of the ALchemy study.

Issue 10 Maximum treatment duration with daratumumab

Report section	Section 4.2.4 Interventions and comparators Item 6
Description of issue and why the ERG has identified it as important	The company's base-case analysis assumes that patients receive daratumumab treatment as observed in the ANDROMEDA trial (up to a maximum of 24 treatment cycles; mean treatment duration = [redacted] cycles) but the SmPC for daratumumab does not include a 24-cycle treatment discontinuation criterion. No patients in the daratumumab arm appeared to have reached the maximum permitted treatment duration of 24 cycles in the ANDROMEDA trial at the time of the IA1 analysis. If daratumumab was recommended in line with its licensed treatment duration, the proportion of patients on treatment beyond 24 cycles and their overall treatment duration is uncertain. If patients continue to receive daratumumab treatment beyond 24 cycles in UK clinical practice, the costs of treatment in the model may be underestimated. Given the lack of evidence on the effect of continuing daratumumab treatment beyond 24 cycles, the impact on health outcomes is unclear. The model structure is not sufficiently flexible to permit daratumumab monotherapy to continue for more than 24 cycles.
What alternative approach has the ERG suggested?	The ERG suggests providing additional flexibility within the model structure to permit daratumumab treatment to continue beyond 24 cycles. However, the ERG notes that the effect on health outcomes would remain unclear because of a lack of evidence on the long-term effects of permitting daratumumab treatment beyond 24 cycles.
What is the expected effect on the cost-effectiveness estimates?	If daratumumab is taken for a longer period of time, the costs of treatment increase, which will increase the ICER. Given the lack of evidence on the effect of continuing daratumumab treatment beyond 24 cycles, the impact on QALYs is unclear.
What additional evidence or analyses might help to resolve this key issue?	A model structure with sufficient flexibility to permit daratumumab treatment to continue beyond 24 cycles if considered reflective of UK practice. Additional evidence of the effects of long-term treatment with daratumumab. The ERG notes that a Cancer Drugs Fund (CDF) recommendation is unlikely to resolve these uncertainties given that the CDF period is usually 2 years and ANDROMEDA trial protocol specified that treatment is stopped at 24 cycles.

Issue 11 Underestimation of the administration costs of DBCd and BCd

Report section	Section 4.2.9.2 Administration cost of daratumumab and bortezomib

	Item 13
Description of issue and why the ERG has identified it as important	The model assumes that the cost of subcutaneous administration for daratumumab and bortezomib corresponds to the cost of 5 minutes of a band 5 nurse at £3.08[9] and zero cost for cyclophosphamide and dexamethasone because their administration is oral. However, daratumumab and bortezomib require preparation in the pharmacy or in the ward, and the first four administrations of daratumumab are expected to require the patient to stay for a few hours for monitoring. Furthermore, the NHS guidance for national cost collection[10-12] specifies that, in recording the costs of chemotherapy, trusts should use the relevant healthcare resource group (HRG) codes for the procurement of chemotherapy and for the delivery of chemotherapy at £2,110 and £241-£332, respectively. Therefore, if these costs are representative of the administration and procurement costs in the NHS, the administration costs of DBCd and BCd are likely to be underestimated in the model.
What alternative approach has the ERG suggested?	The ERG has presented Scenario 10, which uses the aforementioned NHS Reference Costs for the administration of bortezomib-based chemotherapy to inform the administration costs of daratumumab and bortezomib.
What is the expected effect on the cost-effectiveness estimates?	ERG Scenario 10, which uses the aforementioned NHS Reference Costs, increases the ICER from £23,509/QALY to £30,800/QALY.
What additional evidence or analyses might help to resolve this key issue?	Information on the relevant HRG codes for the procurement and administration of DBCd and BCd in the NHS.

Issue 12 Impact of DBCd on autologous stem cell transplant rates

Report section	Section 4.2.9.2 Cost of autologous stem cell transplant Item 17
Description of issue and why the ERG has identified it as important	The company's base-case analysis does not include the costs of autologous stem cell transplant (ASCT), although some patients receive it as subsequent therapy, as observed in the ANDROMEDA trial ([redacted] of patients on BCd and [redacted] of patients on DBCd received ASCT) and in the UK ALchemy study[1, 13] (7% of patients on first-line therapy, 9% as second-line and 3% as third-line). ASCT is a costly procedure (e.g. unit cost = £15,065[12]). The ERG notes that the company's scenario using the ALchemy study to inform the distribution of patients by second- and third-line therapy include the unit costs of ASCT. In addition to the impact on costs, if DBCd affects the proportion of patients who subsequently have ASCT, their health outcomes may be affected as well.
What alternative approach has the ERG suggested?	The ERG considers that the costs of ASCT should be included, given that this is a treatment used in clinical practice and its effect on health outcomes is implicit in the overall survival curves which inform the model. Therefore, the ERG considers that the company's scenario (in response to the ERG's points for clarification) which uses the ALchemy study to inform the

	distribution of patients by second- and third-line treatments is more likely to reflect clinical practice. The ERG did not include the costs of ASCT as part of first-line therapy given the uncertainty about the extent to which the proportion of patients undergoing ASCT may change with DBCd.
What is the expected effect on the cost-effectiveness estimates?	The exclusion of the costs of ASCT from the second- and third-line treatments in the company's base-case analysis is likely to be conservative against DBCd because a smaller proportion of patients who have DBCd progress to second-line therapy. The ERG notes that this issue is addressed in ERG Scenario 11 and ERG base-case, which uses the ALchemy study to inform the distribution of patients by second- and third-line therapies and includes the unit cost of ASCT. The ERG is unable to predict the effect of including ASCT as part of first-line therapy given that it is unclear how DBCd will change ASCT rates.
What additional evidence or analyses might help to resolve this key issue?	Evidence on the ASCT rates with DBCd and its impact on long-term health outcomes.

Issue 13 Approach to the costs of second- and third-line therapies in the model

Report section	Section 4.2.9.2 Approach to the costs of second- and third-line treatments Item 14, Item 15, Item 16
Description of issue and why the ERG has identified it as important	The ERG has three main concerns regarding the approach used to estimate costs of second- and third-line treatments in the model: (1) The costs of second-line therapy (included in the base-case analysis) and third-line therapy (included in a scenario analysis) are calculated by assuming that all patients who progress to subsequent lines of therapy receive the full set of treatment cycles, without accounting for deaths, treatment discontinuation and dose adjustments over the duration of treatment on subsequent lines of therapy. Hence the costs are likely to be overestimated. (2) In the company's base-case, the type of treatment and distribution of patients by second- and third-line therapies were derived from UK clinical expert opinion received at a Janssen-led advisory board,[14] whilst there is evidence from the UK ALchemy study[13] to inform these distributions. The ERG notes that the company presented a scenario in response to the ERG's points for clarification, which used the distributions from the UK ALchemy study.[13] (3) In the company's scenario analysis, the calculation of the distribution of patients on third-line treatment refers to the actual number of patients on third-line treatment. However, the ERG considers it more appropriate to calculate the distribution of patients by treatment at third-line out of those treated at second-line given that these costs are

	applied at entry to the health state 'On second line treatment'. Therefore, the costs of third-line treatment are overestimated in this scenario. The overestimation of costs of second- and third-line therapy is likely to favour the cost-effectiveness of DBCd given that fewer patients progress to second-line therapy when treated with DBCd at first-line.
What alternative approach has the ERG suggested?	To resolve these concerns, the ERG has conducted the following additional analyses: (1) The ERG reduced the costs of second- and third-line treatments by 20% to account for deaths, treatment discontinuation and dose adjustments over the treatment duration; 20% reflects the lower bound of the company's scenario analysis in response to ERG points for clarification. (2) The ERG adopts the company's scenario analysis (in response to ERG points for clarification) where the distribution of patients by type of second- and third-line therapies was obtained from the UK ALchemy study,[13] given that it is more likely to reflect UK clinical practice and ensures that the costing of subsequent treatments aligns with overall survival in the model. (3) The ERG recalculated the distribution of patients by third-line therapy when using the ALchemy study; which applies both second- and third-line treatments are included and the distribution of patients by treatments is informed by the ALchemy study.[13]
What is the expected effect on the cost-effectiveness estimates?	The ERG's preferred assumptions have a limited impact on the cost-effectiveness results: • ERG Scenario 11, which uses the distribution of second-line treatments from the ALchemy study, increases the ICER from £23,509/QALY to £24,486/QALY. • ERG Scenario 12, which includes third-line therapy costs and reduces the costs of second- and third-line therapies by 20% to account for dose adjustments, treatment discontinuations and deaths, reduces the ICER from £23,509/QALY to £17,002/QALY.
What additional evidence or analyses might help to resolve this key issue?	Evidence on deaths, treatment discontinuation and dose adjustments over the treatment duration on second- and third-line therapies in UK clinical practice. Either an adjustment to the model structure is required to incorporate these costs in the model or an adjustment to the upfront costs at entry into the health state 'On second line treatment' is required.

1.6 Other key issues: summary of the ERG's view

Issue 14 Potential of daratumumab for the Cancer Drugs Fund (CDF)

Report section	Section 6.4 Conclusions of the cost effectiveness section
Description of issue and why the ERG has identified it as important	In their response to ERG points for clarification, the company stated that while they have positioned DBCd for routine commissioning within the NHS, they have had preliminary discussions with NHS England and verbal confirmation that, if deemed appropriate by the NICE Committee, daratumumab would be eligible for the CDF. There is uncertainty associated with long-term overall survival, health-related quality of life utility values by depth of haematologic response, administration costs of DBCd and BCd, and relative effectiveness of DBCd versus BCd in patients with Mayo Clinic Cardiac Stage IIIb that the CDF may help address. Additionally, the company has indicated that further analyses of the ANDROMEDA trial are planned in [redacted].
What alternative approach has the ERG suggested?	Given the model structure and the sample size and follow-up period of the ANDROMEDA trial, the ERG considers it unlikely that it would be feasible to use the ANDROMEDA trial to inform the model's overall survival by haematological response. These further analyses, however, could be used to validate the cost-effectiveness model predictions for overall survival, which are the main driver of cost-effectiveness. The additional time in the CDF would allow for data from the ALchemy study to mature, and reduce the uncertainty in the overall survival extrapolation, as well as providing time to explore the potential of the ALchemy study to inform health-related quality of life utility values in the model.
What is the expected effect on the cost-effectiveness estimates?	The ERG is unable to predict the expected effect on the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	To reduce uncertainty in long-term overall survival, comparison of the cost-effectiveness model predictions to further analyses of overall survival based on the ANDROMEDA trial data is warranted. Furthermore, if the ALchemy study continues to follow-up UK patients, further analyses of overall survival with a later data-cut based on the ALchemy study could be used in the cost-effectiveness model. To reduce uncertainty in health-related quality of life utility values by depth of haematologic response, analysis of the existing ALchemy study SF-36 v2 data, mapped to EQ-5D utility values, and comparison with the ANDROMEDA trial EQ-5D values is warranted. Furthermore, if feasible, longer term health-related quality of life data may be collected in the ALchemy study. To reduce uncertainty in the administration costs, evidence on the HRGs and NHS costs associated with the administration of DBCd and BCd could be collected.

	To reduce uncertainty on the clinical effectiveness of DBCd versus BCd in patients with Mayo Clinic Cardiac Stage IIIb, additional data collection on the characteristics and outcomes of patients who receive DBCd in UK clinical practice would be warranted, with appropriate analysis to account for the potential for bias in observational studies. Alternatively, a randomised controlled trial comparing DBCd vs BCd in this subpopulation would address this issue.

1.7 Summary of ERG's preferred assumptions and resulting ICER

Table 2 summarises the ERG's preferred assumptions and resulting ICER. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.

Table 2: Summary of ERG's preferred assumptions and resulting ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base-case	[redacted]	[redacted]	£23,509
ERG Scenario 3: ALchemy baseline[1] and three cycle response time point; conditioning order: alive, CR, VGPR.	[redacted]	[redacted]	£34,094 (+£10,585)
ERG Scenario 7: Overall survival based on ALchemy[1] 3 months response time point; CR - Weibull; VGPR - Weibull; PR/NR - Weibull	[redacted]	[redacted]	£47,671 (+£24,162)
ERG Scenario 8: Health-related quality of life: adjust utility by age[7]	[redacted]	[redacted]	£25,293 (+1,1784)
ERG Scenario 11: Costs: Second-line therapies based on the ALchemy study[13]	[redacted]	[redacted]	£24,486 (+£977)
ERG Scenario 12: Costs: Including third line therapy costs and reduce costs of second- and third-line therapy	[redacted]	[redacted]	£17,002 (-£6,507)
ERG base-case ERG Scenarios 3 + 7 + 8 + 11 + 12	[redacted]	[redacted]	£62,660 (+£39,151)

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. CR: complete response. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: evidence review group. ICER: incremental cost-effectiveness ratio. NR: No Response. PR: Partial Response. VGPR: very good partial response.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In this report, the ERG has reviewed the clinical and cost-effectiveness evidence in the Company Submission (CS) in support of daratumumab (Darzalex) for newly diagnosed systemic amyloid light-chain (AL) amyloidosis. Daratumumab was granted European marketing authorisation for the treatment of adult patients with newly diagnosed AL amyloidosis on 21st June 2021. Marketing authorisation for this indication with the MHRA is expected in [redacted], following the reliance route.

In this section, the ERG critiques the company's proposed treatment pathway, positioning of daratumumab, and its definition of the decision problem when compared with the NICE scope.

2.2 Background

Section 1.3 of the CS provides a brief and accurate overview of AL amyloidosis, its aetiology, epidemiology, prognosis and staging.

2.2.1 Treatment pathway

The CS correctly states that there are currently no therapies in the UK that are specifically licenced for the treatment of patients with AL amyloidosis and no NICE guidelines for this condition (p.30).

The CS (figure 2, p.31) illustrates the current and expected treatment pathway for AL amyloidosis patients in UK clinical practice, based on clinical expert opinion. In the pathway, patients with newly diagnosed AL amyloidosis receive off-label treatment with bortezomib, cyclophosphamide, and dexamethasone (BCd) as first-line therapy. Patients who develop relapsed refractory AL amyloidosis are subsequently eligible for a range of alternative second and third/fourth off-label treatments. This proposed pathway appears to be broadly reflective of UK clinical practice. As proposed in the pathway, daratumumab would be given as first-line treatment in combination with BCd (dartumumab plus BCd is abbreviated to DBCd). Therefore, DBCd and BCd are respectively the intervention and comparator of interest for this appraisal.

The ERG's clinical advisors agreed that bortezomib-based regimens are considered the mainstay of treatment, with the standard of care for newly diagnosed patients in UK clinical practice being BCd (the CS estimates [redacted] of patients receive BCd as first-line therapy). They also agreed that lenalidomide and dexamethasone (Rd) can be used in patients with neuropathy, but its use in the newly diagnosed setting is very rare, and would only be used in patients who have poor tolerability, or

are contraindicated to, bortezomib. Melphalan and dexamethasone (Md) is rarely used, and only for patients who are contraindicated BCd.

The CS states that autologous stem cell transplant (ASCT) was not considered as a comparator in the appraisal due to the small proportion of newly diagnosed AL amyloidosis patients who receive this as first-line treatment (estimated as < 1% by the company's clinical advisory board). The ERG's clinical advisors agreed that very few patients are eligible for ASCT due to organ involvement, and those who do receive ASCT typically receive previous induction therapy (i.e. it is not a first-line treatment for newly diagnosed patients). Indeed, recent clinical guidelines indicate bortezomib-based regimens as the preferred induction therapy prior to ASCT.[2, 15] Hence, ASCT can be part of the first-line treatment as well as second- or third-line treatment for patients who did not have a good haematologic response. There is uncertainty regarding the extent to which the proportion of patients undergoing ASCT may change with DBCd compared to treatment with BCd, with the impact on cost-effectiveness results remaining unclear. Possible implications are discussed in section 4.2.9.2.

The ERG's clinical advisors broadly agreed with the second line (melphalan and dexamethasone; lenalidomide and dexamethasone, carfilzomib and dexamethasone; bortezomib and dexamethasone or BCd) and third/fourth line (lenalidomide and dexamethasone; panobinostat, bortezomib and dexamethasone; pomalidomide and dexamethasone) treatment options outlined in the treatment pathway. Pages 137-8 of the CS report the proportions of patients assumed to receive each treatment at second and third line.

The ERG clinical advisors did however note that patients who progress following bortezomib-based treatment are unlikely to have bortezomib treatment again due to funding constraints, unless they progressed many years after first-line treatment. They also noted that some of the dosages and administration schedules of the treatment regiments used for second- and third-line therapies in the model may not necessarily reflect their usage in UK clinical practice. Section 4.2.9.2 of the ERG report critiques the company's approach to incorporating the costs of these treatments in the model.

While patients diagnosed with both amyloidosis and multiple myeloma (MM) might be eligible for MM therapies approved for NHS use in England and Wales through the Cancer Drugs Fund, this population does not match the decision problem and is not considered further.

2.2.2 Company's proposed positioning

The CS proposes daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (DBCd) as first-line treatment for newly diagnosed AL amyloidosis. Section B.1.2 of the CS describes daratumumab as a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds to CD38, a multifunctional glycoprotein ectoenzyme that is frequently

expressed on the cell surface of diverse haematologic malignancies, including clonal plasma cells that produce amyloidogenic immunoglobulin light-chain. It describes how daratumumab reduces native light-chain production and related organ toxicity through a combination of immunomodulatory and direct clonal plasma cell actions.

The ERG agrees with the positioning of (DBCd) as first-line treatment. The ERG's clinical advisors noted the crucial importance of attaining a rapid, deep and long-lasting clonal response in patients with AL amyloidosis. They stated that the quicker the treatment response, the faster patients will stabilise and be better able to tolerate complex chemotherapy and the greater the chance of clinically meaningful reduction of amyloid deposits. They considered daratumumab an attractive and easy to use option in sometimes very fragile patients, due to its relatively good tolerability (based on experience of its use in multiple myeloma).

The ERG's clinical advisors would use DBCd in all patients who would otherwise have received bortezomib-based treatment (including those with the most advanced Mayo Cardiac Stage IIIa/b disease). Exceptions might be patients with severe neuropathy (likely less than 5-6%) and some elderly patients due to logistical issues.

2.3 Critique of company's definition of decision problem

Table 3 summarises the decision problem as defined in the NICE scope and the CS.

The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis that is not restricted by subgroups based on severity of cardiac involvement. More specifically, the company seeks a recommendation that includes patients classified according to Mayo Clinic Cardiac Staging with Stage IIIb disease, who have the most severe degree of cardiac involvement and have high risk systemic AL amyloidosis with a very poor prognosis. The company submission states that in UK clinical practice, patients with Stage IIIb disease are expected to comprise approximately 20% of the AL amyloidosis cohort.

However, the ANDROMEDA trial population does not fully reflect the patient population seen in practice, primarily due to its exclusion of Mayo Cardiac Stage IIIb patients. The CS states: *"patients with Stage IIIb disease were excluded during the screening period from participating in the trial as they are not typically candidates for BCd at the specific dose and dosing schedule used in the trial"*. The ERG's clinical advisors suggested that Stage IIIb patients would receive BCd, but due to their fragility, they may receive one drug at a time, over a 3-week period, with doses increased slowly. In some patients, the bortezomib or steroid dose may be reduced where necessary. The exclusion of these patients from ANDROMEDA therefore appears justified for the stated reason, however this

means that there is an absence of evidence on the effectiveness of daratumumab in this important clinical subgroup.

In addition, as noted in the CS (p.93), patients recruited to ANDROMEDA were slightly younger and fitter (in terms of ECOG performance status) than the UK population. It is unclear the extent to which this is attributable to the exclusion of Mayo cardiac stage IIIb patients or additional factors.

While noting that ANDROMEDA permitted a maximum of 24 cycles of daratumumab, the SmPC dosing schedule does not explicitly propose a maximum treatment duration. It states that daratumumab treatment continue every four weeks from week 25 onwards until disease progression.[16] The ERG clinical advisors commented that patients are unlikely to continue treatment beyond 24 cycles due to lack of evidence about longer treatment durations. However, the ERG clinical advisors also noted that if there was an option of continuing beyond 24 cycles, the majority of patients who are still on daratumumab treatment at this point are likely to be tolerating the drug reasonably well and not have progressed; hence they may remain on daratumumab treatment.

Overall survival (OS) data in the ANDROMEDA trial were immature, meaning that ANDROMEDA cannot currently provide a direct estimate of the effect of DBCd on survival. The alternative approach to estimate the effects of DBCd on overall survival involved (1) using depth of haematologic response from ANDROMEDA as a surrogate endpoint, (2) obtaining survival conditional on depth of haematologic response from external observational evidence, and (3) extrapolating long-term survival. This approach raises several important concerns around uncertainty, over-simplification and bias that are explored in detail in section 4.2.6 of the ERG report.

Table 3 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with newly diagnosed systemic amyloid light-chain amyloidosis	Adult patients with newly diagnosed systemic amyloid light-chain (AL) amyloidosis	This is aligned with the licensed indication and the patient population included within the pivotal ANDROMEDA trial. [17]	The population is consistent with the NICE scope. However, the trial population does not fully reflect the patient population seen in practice, primarily due to the exclusion of Mayo cardiac stage IIIb patients from the ANDROMEDA trial.
Intervention	DBCd	DBCd	DBCd is aligned with the intervention arm in the ANDROMEDA trial	The intervention is consistent with the NICE scope. ANDROMEDA permitted a maximum of 24 cycles of daratumumab (mean treatment duration = [redacted] cycles), though the SmPC dosing schedule does not explicitly propose a maximum treatment duration.
Comparator(s)	Established clinical management without daratumumab. This may include: • Bortezomib with dexamethasone, an alkylating treatment and/or immunomodulatory drugs (i.e. BCd) • Lenalidomide with dexamethasone (Rd)	BCd	Although none of the comparators listed in the final scope currently have marketing authorisation in the UK for this indication, BCd is considered to represent standard of care for newly diagnosed AL amyloidosis patients in UK clinical practice as per expert clinical advice.[18] Clinical expert feedback, elicited through a UK advisory board (April 2021),[18] indicated that in UK clinical practice:	The company's decision problem is restricted to only one comparator (BCd), and so is much narrower than the NICE scope. However, the ERG's clinical advisors agree that for the vast majority of newly diagnosed patients, BCd is the current

	• Melphalan and dexamethasone (Md) • Autologous stem cell transplant (ASCT) with high dose melphalan • Best supportive care None of the comparators listed have a marketing authorisation in the UK for this indication.		• The majority of newly diagnosed AL amyloidosis patients are treated with BCd. BCd represents the mainstay of treatment in AL amyloidosis, including those who are eligible for transplant and those who are elderly. • Only a minority of patients with pre-existing neuropathy would not receive bortezomib-based therapies in the first-line setting. Although, even in these cases, bortezomib may be used in an attenuated dose regimen. • Md is rarely used and only for patients who are contraindicated BCd. • Rd can be used in patients with neuropathy, but its use in the newly diagnosed setting is very rare, therefore only patients who have poor tolerability, or are contraindicated to, bortezomib, would receive Rd. • Very few patients receive ASCT due to organ involvement resulting in ineligibility, and those who do receive ASCT typically receive previous induction therapy (i.e. it is not a first-line treatment for newly diagnosed patients). • It is deemed unlikely that newly-diagnosed patients with such a life-limiting disease with a poor	preferred treatment (see Section 2.2.1).

			prognosis would receive best supportive care. A real-world retrospective study of AL amyloidosis in 10 European countries, including the UK (the EMN23 study) supports that BCd represents the standard of care for patients: 75% of AL amyloidosis patients were found to receive bortezomib-based regimens at first-line.[19] As such, the decision problem addressed in the submission will consider BCd as the sole relevant comparator due to its position as the mainstay of treatment for patients with newly diagnosed AL amyloidosis. This is aligned with the ANDROMEDA trial, which provides direct evidence for the relative clinical efficacy and safety data of DBCd compared with BCd.	
Outcomes	The outcome measures to be considered include: • Haematologic response rates • Organ response rates • Progression-free survival (PFS) • Major organ deterioration progression-free survival (MOD-PFS)	The outcome measures to be considered include: • Haematologic response rates • MOD-PFS • Major organ deterioration event-free survival (MOD-EFS) • Organ response rates • OS	Outcomes represent those collected in the ANDROMEDA trial, with the exception of PFS. PFS was not collected in ANDROMEDA because: • In clinical practice, disease progression in AL amyloidosis patients may be evaluated according to a range of biomarkers, including haematologic, cardiac and renal	The outcomes are broadly consistent with the NICE scope. OS data in the ANDROMEDA trial were immature; the economic model uses observational data on the relationship between haematologic response and OS rather than using OS data

	• Overall survival (OS) • Adverse effects of treatment • Health-related quality of life (HRQoL)	• Adverse events (AEs) • HRQoL	biomarkers given the heterogeneity in presentation of the disease. • Haematologic response does not comprehensively describe the response status of patients with AL amyloidosis, whose clinical presentation and long-term outcomes additionally depend on adequate organ function, whilst assessment of organ response rates is based on the use of clinical biomarkers which are associated with limitations. • Instead of PFS, ANDROMEDA included MOD-PFS. MOD-PFS is a novel, composite endpoint developed to encompass the most clinically relevant and objective measures of the benefits of anti-plasma cell therapy: haematologic progression, major organ deterioration, and death. • Inclusion of MOD-PFS in ANDROMEDA was agreed upon following consultation with regulatory authorities (EMA and FDA).[17, 20]The full definition of MOD-PFS can be found in CS Section B.2.3. • Similarly, MOD-EFS is a composite endpoint of clinically observable endpoints which, as compared with MOD-PFS, additionally captures subsequent lines of therapy since it	collected in the ANDROMEDA trial. The analysis of MOD-PFS was complicated by patients in ANDROMEDA being allowed to switch therapy following suboptimal haematologic response or worsening organ function.

			included initiation of subsequent non-cross resistant therapy adjudicated by the Independent Review Committee (IRC) as an event.	
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 (QALY) • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective (PSS) • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any	The reference case has been adhered to.	NA – in line with final NICE scope	In line with NICE scope.

	managed access arrangement for the intervention will be taken into account			
Subgroups **Special considerations including issues related to equity or equality**	If the evidence allows, subgroups based on the severity of heart failure may be considered.	Baseline cardiac stage was pre-specified for a subgroup analysis at the interim analysis data-cut and at the 12-month landmark analysis. However, the ANDROMEDA trial excluded newly diagnosed systemic AL amyloidosis patients with Mayo Clinic Cardiac Stage IIIb disease. In order to gain an insight into the haematologic response rates that would be required for DBCd to be a cost-effective option for patients in this subgroup, the company are exploring whether an analysis that utilises data for BCd from Mayo Stage IIIb patients from the EMN23 study can be conducted, but this is not yet available.	• Patients with Stage IIIb disease, according to the European Modification of the Mayo Clinic Cardiac Staging System have the most severe degree of cardiac involvement (see CS Section B.1.3.1 for details). These patients therefore require a rapid and deep response to treatment to improve survival. • In the ANDROMEDA study, patients with Stage IIIb disease were excluded during the screening period from participating in the trial as they are not typically candidates for BCd at the specific dose and dosing schedule used in the trial.[21] It is important to note that 6 patients in the BCd arm and 2 patients in the DBCd arm with Stage IIIb cardiac disease were included in the study because their cardiac involvement progressed to this stage after study enrolment. • However, clinical expert opinion suggests that Stage IIIb patients comprise approximately 20% of the AL amyloidosis cohort observed in UK clinical practice, and clinicians would wish to treat such patients	ANDROMEDA excludes patients with Mayo Clinic Cardiac Stage IIIb even though they comprise up to 20% of AL amyloidosis patients in the UK. Therefore, the CS does not provide any evidence on the effects of daratumumab in this high clinical need subgroup.

			with DBCd in clinical practice should DBCd be recommended for use.[18] • Patients with Stage IIIb disease are not excluded from the licensed indication for DBCd.[16] • These patients have high risk systemic AL amyloidosis and an extremely poor prognosis.[18] • It is Janssen's view that it is important that any recommendation for DBCd in AL amyloidosis is not restricted in such a way to exclude patients with Stage IIIb disease, a group of more severe patients, who have an extremely poor prognosis and life expectancy.	

Abbreviations: AE: adverse event; AL: amyloid light-chain; ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; CS: company submission; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; EMA: Europeans Medicines Agency; FDA: Food and Drugs Administration; HRQoL: health-related quality of life; Md: melphalan and dexamethasone; MOD-EFS: major organ deterioration event-free survival; MOD-PFS: major organ deterioration progression-free survival; NA: Not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; PSS: Personal Social Services QALY: quality-adjusted life year; Rd: lenalidomide and dexamethasone; UK: United Kingdom.
Source: Adapted from company submission Table 1.

3 CLINICAL EFFECTIVENESS

After receiving the CS, the ERG submitted several points for clarification (PfC) to the company. Any additional or corrected data provided by the company have been incorporated into the analyses and discussion of this ERG report where appropriate.

3.1 Critique of the methods of review(s)

The company conducted a *de novo* systematic literature review (SLR) to identify relevant clinical evidence on the efficacy and safety of pharmacological therapies for adults with newly diagnosed AL amyloidosis. Both randomised controlled trials (RCTs) and non-randomised controlled trials (non-RCTs) were considered for inclusion. Details of the SLR are reported in Appendix D of the CS.

3.1.1 Searches

The original company submission included searches to identify clinical evidence for adults newly diagnosed with AL amyloidosis. A detailed description of the searches and most of the search strategies were included in Appendix D (pp. 5-33).

In response to the ERG's PfCs, a further document was provided by the company, which included additional search strategies and corrections to errors identified by the ERG.

An appraisal of the literature searches is presented in Appendix 9.1.1

3.1.2 Study Selection

The study selection process is described in the CS Appendix D.1.2. The PICOS eligibility criteria for the SLR is reported in Table 3 in Appendix D of the CS. RCTs and non-RCTs conducted on adults who were newly diagnosed with AL amyloidosis were included in the review. Patients could be treatment naïve or those requiring first-line treatment. Patients in eligible studies could be receiving any of the following treatments:

a) Daratumumab in combination with BCd;
b) BCd, or any combinations of the following chemotherapies: melphalan, cyclophosphamide, bendamustine, bortezomib, lenalidomide, pomalidomide, thalidomide, dexamethasone, melphalan-dexamethasone;
c) Ixazomib, methylprednisolone, prednisolone, prednisone, carfilzomib, doxycycline;
d) Placebo

All outcomes were eligible for study selection. Only English language studies were included. Studies published before 2005 were excluded, as these studies would have been published prior to the publication of the consensus opinion for organ involvement and response by the 10th International

Symposium in Amyloid and Amyloidosis,[22] and the company reasoned that studies prior to 2005 would likely have used inconsistent definitions of organ involvement and response to treatment.

A PRISMA flow diagram summarising the company's SLR selection process is presented in Figure 1, in Appendix D of the CS. Fifty-nine unique studies were included for the analysis, five of which were RCTs and fifty-four were observational studies. A summary of the included RCTs is presented in Table 5 in Appendix D of the CS; and the included observational studies are summarised in Table 6 in Appendix D of the CS.

Of the studies identified in the SLR, only one RCT, the company's own ANDROMEDA trial[23] was considered relevant to this appraisal. No other trial or observational study evaluated daratumumab.

3.1.2.1 Points for Critique

The SLR study selection process was broadly appropriate. While the company does not specify reasons to eventually exclude the studies that were identified in the SLR, the ERG believes that it is likely that ANDROMEDA is the only RCT relevant to the decision problem.

In the absence of long-term OS data from ANDROMEDA to inform the cost-effectiveness model, external survival data on patients with newly diagnosed AL amyloidosis, stratified by haematologic response were sought. Two relevant observational studies (Palladini et al., 2012[5] and Kastritis et al., 2021[4]), that were ultimately found and incorporated in the company's economic model (see section 4.2) were identified in a targeted literature search. Palladini et al. (2012) was a multi-centre retrospective study of AL amyloidosis patients in Europe (including the UK), and the US. Kastritis et al. (2021) was conducted in Greece on patients with newly diagnosed AL amyloidosis. The ERG was unable to ascertain why these studies were missed in the SLR.

A third observational study, EMN23[19] was also identified by the company. EMN23 is a retrospective, multicentre study conducted in 10 European countries, including the UK. However, EMN23 could not be incorporated into the company's economic model due to constraints with time and availability of data. The company plans to include the study in the economic model during the appraisal.

3.1.3 Quality Assessment

The risk of bias for included studies from the SLR was assessed by two reviewers, working independently and evaluations were compared. The company assessed the quality of RCTs using the NICE clinical effectiveness quality assessment checklist,[24] and the quality of reporting for comparative observational studies using the Newcastle Ottawa scale.[25] The results of these quality assessments are reported in Table 7 and 8 in Appendix D of the CS.

However, ANDROMEDA was the only study that informed the company's economic analysis, and the company provided a more detailed bias assessment for the study in Section B.2.5 of the CS (p49).

3.1.3.1 Points for Critique

With the exception of the ANDROMEDA trial, none of the studies identified in the SLR informed the clinical or cost-effectiveness evidence presented in this appraisal. Therefore, there will be no further discussion of these studies in the ERG report.

A critique of the ANDROMEDA trial, including a comparison of the company and ERG's risk of bias assessments can be found in section 3.2.1.3.

3.1.4 Evidence Synthesis

Section D.1.3 of the CS states that, as there was only one high-quality RCT (ANDROMEDA) comparing DBCd to BCd, it was not necessary to perform any evidence synthesis or conduct an indirect comparison to compare the efficacy and safety of DBCd to BCd.

3.1.4.1 Points for Critique

Given the absence of (a) other trials comparing DBCd to BCd and (b) alternative first-line treatment options to compare against DBCd or BCd, the decision not to conduct an evidence synthesis or indirect comparison is appropriate.

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

3.2.1 Trial Design and Methods

3.2.1.1 ANDROMEDA

Section B.2.3 of the CS (p.37) summarises the design and methodology of the ANDROMEDA trial. Briefly, this was an open-label, multinational, multicentre trial comparing DBCd with BCd in adults with newly diagnosed AL amyloidosis. Both treatment arms received a maximum of six 28-day cycles of BCd therapy. Patients in the DBCd arm also received daratumumab until Major Organ Deterioration Progression-Free Survival (MOD-PFS; see section 3.2.3.1) or up to a maximum of 24 cycles. The primary outcome was overall complete haematologic response (CR) rate. Secondary outcomes assessed: the depth, speed and durability of haematologic response; MOD-PFS; Major Organ Deterioration Event-Free Survival (MOD-EFS; see section 3.2.3.1) overall survival (OS); the rate, speed and duration of organ (heart, kidney, liver) response; improvement in fatigue; time to next treatment; health related-quality of life; and safety.

3.2.1.2 Points for Critique

Participant eligibility criteria

The ANDROMEDA trial population does not fully reflect the patient population seen in practice, primarily due to the exclusion of Mayo Cardiac Stage IIIb patients, a subgroup of patients with particularly poor prognosis. These patients were excluded because they are *"not typically candidates for BCd at the specific dose and dosing schedule used in the trial"* (CS table 1, p.19). However, the ERG's clinical advisors suggested that while Stage IIIb patients would receive a more gradual dose escalation, they would nevertheless receive BCd and be eligible for DBCd. This is of particular importance in the current appraisal, where the company selected depth of haematologic response as a surrogate endpoint for survival in the absence of mature OS data from ANDROMEDA. Crucially, to make inferences for the whole population requires assumptions to be made about the depth of response in Mayo Stage IIIb patients relative to that observed in the (less severe) ANDROMEDA trial population (see section 4.2.6.2).

Use of interim analyses

The ANDROMEDA trial is ongoing. The CS reports results from two interim analyses: a pre-specified interim analysis (IA1; median follow-up 11.4 months) and a 12-month landmark analysis (median follow-up 20.3 months). Table 16 (p.51) of the CS summarises the outcomes reported for these two data cuts. The use of these interim analyses means that some time-to-event outcomes (OS, MOD-PFS, duration of haematologic response) have yet to reach median values in either treatment arm.

Treatment duration

Though the SmPC dosing schedule does not explicitly propose a maximum treatment duration, ANDROMEDA permitted a maximum of 24 cycles of daratumumab. The dosing schedules used in the trial were appropriate. Median treatment durations for DBCd vs BCd was 9.6 vs. 5.3 months in the interim analysis (IA1) and 18.5 vs. 5.3 months in the 12-month landmark analysis. The number of patients receiving treatment at each cycle was not available in the CS, but it appears from the clinical study report that no patients in the daratumumab arm had reached the maximum treatment duration of 24 cycles in the IA1 analysis.[23]

Reported clinical effectiveness outcomes

Table 7 (p.36) of the CS lists the clinical effectiveness outcomes from ANDROMEDA. Most outcomes collected according to the ANDROMEDA trial protocol were reported in the CS. Exceptions were serum free light chain measurements, and haematologic progression-free survival (HemPFS). HemPFS recorded haematologic progression based on IRC assessment or death, disaggregated from the composite MOD-PFS outcome (see section 3.2.3.1). While the protocol listed

duration of organ response (time from initial documentation of organ response to first documented evidence of organ progressive disease), the CS only reported progression data as rates at 6 months.

Table 4 Outcomes reported in the ANDROMEDA trial protocol/clinical study report vs CS

Source	Outcome
CS and protocol/clinical study report	- Overall CR rate - Major Organ Deterioration Progression-Free Survival (MOD-PFS) - Major Organ Deterioration Event-Free Survival (MOD-EFS)* - OS - CR at 6 and 12 months - Time to haematologic response (CR or VGPR or better) - Duration of haematologic response (CR or VGPR or better) - Time to initiation of subsequent non-cross resistant anti-plasma cell therapy - Organ response (cardiac, renal and liver) at 6, 12, and 18 months - Time to cardiac, renal and liver response - Cardiac, renal, and liver progression rates at 6 months - Improvement in fatigue: defined as the change from baseline in the EORTC QLQ-C30 Fatigue scale score - Improvement in HRQoL: defined as change from baseline in the EORTC QLQ-C30 Global Health Status scale score - EQ-5D-5L scores - SF-36 v2 scores
Protocol/clinical study report only	- Haematologic progression-free survival (HemPFS) - Duration of organ response - Time to cardiac, renal and liver progression - FLC Response and Time to iFLC <ULN and iFLC ≤20 mg/L and dFLC <10 mg/L

*reported in statistical analysis plan, but not study protocol

Abbreviations: CR: complete response; CS: company submission; HRQoL: health-related quality of life; OS: overall survival; VGPR: very good partial response.

CONSORT flowchart, discontinuation and switching to subsequent anti-plasma cell therapies

At PfC, the ERG requested that the company provide a CONSORT flowchart for patients in the ANDROMEDA trial, using an intention-to-treat (ITT) approach, reporting the number of evaluable patients, deaths, withdrawals, and discontinuations before and after 6 cycles of treatment, along with clear reasons for exclusions/withdrawals at each stage (Figure 1). It can be seen that during cycles 1 to 6, [redacted] of patients discontinued from the BCd arm compared with [redacted] from the DBCd arm. A further [redacted] patients discontinued from the DBCd arm after Cycle 6.

Figure 1 ANDROMEDA trial CONSORT diagram

Abbreviations: AL: amyloid light-chain; ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ITT: Intention-to-treat; MOD-PFS: major organ deterioration progression-free survival.
Source: Company response to Points for Clarification Figure 1.

The ANDROMEDA trial protocol allowed patients to switch to an alternative treatment following a suboptimal haematologic response or worsening organ function. In response to an ERG request, the company clarified that suboptimal response was defined as any patient who had achieved a best response of partial response (PR) but who had worsening organ function on Cycle 4 Day 1 (i.e. after three cycles of initial therapy). However, participating clinics could also propose early treatment-

switching for patients who did not meet this criterion but for whom subsequent therapy might be considered optimal.

The company further clarified that observation (in the BCd arm) or daratumumab monotherapy until disease progression or a maximum of 24 cycles (in the DBCd arm) was recommended for patients with haematologic response (PR or better) with stable or improved major organ failure after six cycles of initial therapy. However, at this same timepoint, subsequent therapy was *considered* for patients with haematologic response (PR or better) with worsening organ function, haematologic non-response or disease progression with stable or improved organ function, and was *recommended* for patients with haematologic non-response or disease progression with worsening organ function.

It can be seen from Figure 1 that the proportion of patients who received AL amyloidosis subsequent therapy during cycles 1-6 was greater in the BCd arm [redacted] than the DBCd arm [redacted].

In response to a further point for clarification, the company provided a summary of the reasons for patients switching onto the first subsequent therapy in the ANDROMEDA trial (Table 5), based on the IA1 interim analysis. Reasons for switching onto second or later lines of therapy were not collected in the ANDROMEDA trial.

Table 5 shows that the proportion of participants switching to one or more subsequent lines of anti-amyloidosis therapy was [redacted]. Some differences in the reasons for switching can be seen between study arms: patients in the BCd arm were somewhat more likely to switch because of a [redacted]. This may indicate greater efficacy of initial treatment in the DBCd arm. However, there was potential for this treatment switching paradigm to interfere with outcome measurement in the ANDROMEDA trial (see section 3.2.3.1).

Table 5 Summary of subsequent anti-amyloidosis therapy and reasons for initiation of first subsequent therapy; ITT analysis set (14th February 2020 data cut-off)

	BCd (N=193) n (%)	DBCd (N=195) n (%)	Total (N=388) n (%)
Number of lines of subsequent therapy received			
N	XXX	XXX	XXX
1	XXX	XXX	XXX
>1	XXX	XXX	XXX
Reasons for initiation of first subsequent therapy			
N	XXX	XXX	XXX
MOD-PFS due to haematologic progression	XXX	XXX	XXX

MOD-PFS due to major organ deterioration	[redacted]	[redacted]	[redacted]
Less than a haematologic PR at Cycle 4	[redacted]	[redacted]	[redacted]
Autologous stem cell transplantation (ASCT)	[redacted]	[redacted]	[redacted]
Worsening of free light chains not meeting criteria for haematologic PD	[redacted]	[redacted]	[redacted]
Organ function worsening	[redacted]	[redacted]	[redacted]
Less than a CR after completion of Cycle 6	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Percentages are calculated using the number of patients in each treatment group with available data as the denominator
Abbreviations: ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ITT: intention-to-treat; MOD-PFS: major organ deterioration progression-free survival; PD: progressive disease; PR: partial response.
Source: Company response to Points for Clarification Table 1.

The numbers of ANDROMEDA patients who switched to subsequent cross-resistant and non-cross resistant anti-plasma cell therapies in each study arm and by cycle, by therapeutic class, pharmacologic class, and preferred term, are presented in Table 46 of Appendix 1 of the company's response to PfC.

3.2.1.3 Risk of bias

Table 15 (p.49-50) of the CS reports the company's assessment the risk of bias for ANDROMEDA. Table 6 below compares the company and ERG risk of bias assessments for this trial.

The CS rated ANDROMEDA as having a low risk of bias with respect to: randomisation method; baseline comparability of groups; blinding of participants, providers and outcome assessors; attrition between groups; selective outcome reporting; and intention to treat analysis. It rated the risk of selection bias due to concealment of treatment allocation as 'medium'.

The ERG's risk of bias judgements differed from the CS ratings on two domains: Firstly, the ERG considered ANDROMEDA to be at low risk of selection bias due to allocation concealment, as a centralised interactive web response system was used to randomly assign subjects to study treatment and dispense the study agent. Secondly, the ERG agreed that efficacy outcomes based on objective measures such as biomarker thresholds (haematologic and organ response/progression) or significant clinical events (organ response/progression, overall survival) are likely to be at low risk of bias in an open label RCT, but subjective HRQoL measures may be at higher risk of bias, particularly when one trial arm consists of the comparator treatment plus a novel new agent. However, data for the period where comparative data are available from ANDROMEDA, there is not any obvious evidence of bias in EQ-5D-5L scores (CS figure 10; PfC response table 33).

Table 6 Comparison of company and ERG risk of bias assessments for ANDROMEDA

	ANDROMEDA			
	CS response	**ERG response**	**CS risk of bias judgement**	**ERG risk of bias judgement**
Was randomisation carried out appropriately?	Yes. Centralised randomisation was carried out in ANDROMEDA, with patients randomly assigned to treatment arms using a computer-generated randomisation schedule prior to study initiation	Agree	Low	Low
Was the concealment of treatment allocation adequate?	ANDROMEDA was an open-label trial, however, risk was mitigated through blinded IRC assessment of outcomes	Allocation was concealed by use of a centralised interactive web response system to assign subjects to study treatment and dispense the study agent	Medium	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, demographic and baseline characteristics were well balanced between the two treatment groups, including key prognostic disease characteristics	Agree	Low	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	ANDROMEDA was an open-label trial, which meant care providers and participants were not blinded to treatment allocation Outcomes were assessed by blinded IRC	Patient-reported quality of life measures were subjective and subject to bias. Most efficacy outcomes included an objective component i.e. predefined biomarker thresholds or significant clinical events (e.g. haemodialysis or renal/cardiac transplant). Hematologic and organ response/ progression were adjudicated by an IRC.	Low	Low for OS, haematologic and organ response/progression Medium for EORTC QLQ-C30, EQ-5D-5L, and SF-36 v2 scores
Were there any unexpected imbalances in drop-outs between groups?	No. Of the 388 patients that were randomised to receive study treatment (195 for DBCd; 193 for BCd), 193 were treated in the DBCd arm and 188 were treated in the BCd arm	Agree	Low	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None	Agree	Low	Low for ANDROMEDA clinical trial report, though not all outcomes were

				reported in the CS (see Table 4)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The ITT population included all randomised patients and was used for analysis of the primary endpoint and other endpoints unless otherwise stated, with the exception of time to and duration of both haematologic and organ specific responses	Agree	Low	Low

Abbreviations: CS: company submission; BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ERG: evidence review group; IRC: independent review committee; ITT: intention-to-treat; OS: overall survival.

3.2.2 Population

Section B.2.3.3 (p.43-6) of the CS reports the baseline characteristics of the ANDROMEDA trial. Table 37 (p.94) of the CS also provides a comparison of baseline characteristics between ANDROMEDA and the EMN23 observational study to illustrate the generalisability of ANDROMEDA to clinical practice in England. The ERG identified a further observational study, the ALchemy study,[1] which was published soon after receiving the CS. The ERG's clinical advisors estimate that ALchemy reports data from around two-thirds of all UK AL amyloidosis patients assessed between February 2010 and August 2019. The ERG considers this study to report a population that better represents NHS clinical practice. Baseline characteristics of patients included in the 3 studies are presented in Table 7.

3.2.2.1 Points for Critique

The ERG's clinical advisors agreed that baseline patient characteristics were well-balanced between the two ANDROMEDA treatment arms.

While the EMN23 study appears to be a useful source of evidence of AL amyloidosis treatment population data, the ERG believes that the UK ALchemy observational study[1] more closely reflects the NHS treatment population (see section 3.5 for further details). Table 7 therefore compares the baseline characteristics of ANDROMEDA with both EMN23 and ALchemy. The ERG's clinical advisors noted that the main differences between the trial and observational patient characteristics relate to cardiac Stage IIIb patients (15-16% of patients in the ALchemy and EMN23 studies had cardiac Stage IIIb disease, while these were excluded from ANDROMEDA), and physical fitness (patients in ANDROMEDA tended to be fitter, as measured by ECOG performance status). This raises the question of the extent to which the effects observed the ANDROMEDA trial can be generalised to the substantial subgroup of cardiac Stage IIIb patients who typically have the poorest prognosis and greatest clinical need (see section 3.5).

Table 7 Comparison of baseline patient characteristics between ANDROMEDA, ALchemy and EMN23

	ANDROMEDA	ALchemy (Ravichandran 2021)[1]	EMN23 (PfC Response)
Number of participants	388	1194	3065
Age, years			
Mean (SD)	[redacted]	-	[redacted]
Median	[redacted]	66.0	66.0
Range	[redacted]	(29-88)	[redacted]
<65, n (%)	[redacted]	-	-
≥65, n (%)	[redacted]	-	-
Sex, n (%)			
Female	[redacted]	481 (40.3)	1269 (41.4)
Male	[redacted]	713 (59.7)	1796 (58.6)
Weight, kg			
Mean (SD)	[redacted]	-	[redacted]
Median	[redacted]	-	[redacted]
Range	[redacted]	-	[redacted]
≤65 kg, n (%)	[redacted]	-	-
65–85 kg, n (%)	[redacted]	-	-
>85 kg, n (%)	[redacted]	-	-
Baseline ECOG score, n (%)			
0	[redacted]	0-2 1117 (93.6)	[redacted]
1	[redacted]		[redacted]
2	[redacted]		[redacted]
3	-	>2 77 (6.4)	[redacted]
4	-		[redacted]
Not reported	-	-	[redacted]
Time since initial AL diagnosis			
Mean (SD)	[redacted]	-	[redacted]
Median	[redacted]	-	[redacted]
Range	[redacted]	-	[redacted]
≤30, n (%)	[redacted]	-	-
30–60, n (%)	[redacted]	-	-
>60, n (%)	[redacted]	-	-
Isotype of AL based on either immunofixation or light chain, n (%)			
Lambda	[redacted]	936 (78.4)	-
Kappa	[redacted]	258 (21.6)	-
Organ involvement, n (%)			
Heart	277 (71.4)	791 (66.2)	2135 (69.7)
Kidney	229 (59.0)	802 (67.3)	2024 (66.0)
Liver	[redacted]	139 (11.6)	409 (13.3)
Gastrointestinal tract	[redacted]	48 (4)	215 (7.0)
Lung	[redacted]	-	26 (0.9)
Nerve	[redacted]	-	447 (14.6)
PNS	[redacted]	85 (7.1)	-

ANS	[redacted]	82 (6.9)	-
Soft tissue	[redacted]	187 (15.7)	609 (19.9)
Number of organs involved			
1 organ, n (%)	[redacted]	-	1123 (36.6)
2 organs, n (%)	[redacted]	-	1224 (39.9)
≥3 organs, n (%)	[redacted]	-	700 (22.8)
Not reported, n (%)	-	-	[redacted]
Cardiac stage based on Mayo Clinic Cardiac Staging System[a], n (%)			
I	[redacted] (23.2)	183 (15.3)	512 (16.7)
II	[redacted] (40.2)	409 (34.3)	1066 (34.8)
IIIa	[redacted]	418 (35)	853 (27.8)
IIIb	[redacted]	184 (15.4)	485 (15.8)
Not reported		-	[redacted]
Renal function status - creatinine clearance			
<60 mL/min	[redacted]	-	-
≥60 mL/min	[redacted]	-	-
Normal	-	-	[redacted]
Abnormal	-	-	[redacted]
Not reported	-	-	[redacted]

[a] For ANDROMEDA-Cardiac stage is based on both NT-proBNP and hs.cTnT levels.

Abbreviations: AL: amyloid light-chain; ANS: autonomic nervous system; BCd: bortezomib, cyclophosphamide, and dexamethasone DBCd: daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone; ECOG: eastern cooperative oncology group; ITT: intention-to-treat; PNS: peripheral nervous system; SD: standard deviation.

Source: Adapted from company submission Table 12.

3.2.3 Effectiveness

The results of ANDROMEDA presented in the CS are based primarily on a planned interim analysis (IA1; median follow-up 11.4 months, February 2020 data cut-off) and supplemented by a 12-month landmark analysis (median follow-up 20.3 months, November 2020 data cut-off). The latter analysis was not a pre-specified data cut, and according to the CS, a subset of outcomes was evaluated "for conference purposes only".

Table 16 (p.51) of the CS lists the outcomes that were assessed at the 12-month landmark analysis. These were: CR (overall and subgroup analyses); CR at six months; time to haematologic response; organ response at 6, 12 and 18 months; and time to initiation of subsequent non-cross resistant anti-plasma cell therapy. In response to a point for clarification, the company did not provide the rationale for selecting this particular set of outcomes for the 12-month landmark analysis, but did provide the results of an additional analysis to determine CR at 12 months for patients in the 12-month landmark analysis (see section 3.2.3.1).

The ANDROMEDA trial is ongoing, with the following planned analyses:

- 18-month landmark data cut-off: updated analyses for haematologic response and organ response ([redacted])
- 200 MOD-PFS event driven data cut-off: updated analyses for OS, MOD-PFS, haematologic response and organ response ([redacted])
- Final OS data cut-off: updated analyses have not yet been confirmed ([redacted])

Section B.2.6 of the CS reported the clinical effectiveness outcomes listed in Table 4.

3.2.3.1 Points for Critique

Depth of haematologic response

Table 17 (p.54) of the CS summarised overall best confirmed haematologic response for both IA1 and 12-month-landmark analyses. These indicated that DBCd is associated with a clinically and statistically significant improvement in the primary outcome of CR relative to BCd. DBCd was also associated with a significant improvement in very good partial response (VGPR) or better (i.e. achievement of CR or VGPR).

Table 18 (p.56) of the CS summarised confirmed CR at 6- and 12-month timepoints. In their response to PfCs, the company also provided data on CR rate at 12 months from the 12-month landmark analysis. All available information on CR at 6 and 12 months is collated in Table 8 below. These results from both analyses show significantly higher rates of complete response for DBCd than BCd.

Table 2 of the company's response to PfC provides overall best haematologic response for patients who switched treatment to receive subsequent anti-amyloidosis therapy, noting that response assessments after switching were not included in the overall analyses.

Table 8 Summary of confirmed CR at six- and 12-months based on IRC assessment, ITT analysis set (14th February 2020 data cut-off and 13th November 2020 data cut-off)

IA1						12-month landmark					
BCd (N=193)		DBCd (N=195)		DBCd vs BCd		BCd (N=193)		DBCd (N=195)		DBCd vs BCd	
n (%)	95% CI[a]	n (%)	95% CI[a]	Odds ratio (95% CI)[b]	P-value[c]	n (%)	95% CI[a]	n (%)	95% CI[a]	Odds ratio (95% CI)[b]	P-value[c]
6 months											
[redacted] (14.0)	[redacted]	[redacted] (49.7)	[redacted]	6.09 [redacted]	<0.0001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months											
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] 95% CIs are based on Clopper-Pearson exact test,and correspond to the percentage response rate. [b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl ≥ 60 mL/min or CrCl <60 mL/min). An odds ratio > 1 indicates an advantage for DBCd. [c] P-value from the Cochran Mantel-Haenszel Chi-Squared test.

Abbreviations: AL: amyloidosis light-chain; BCd: bortezomib, cyclophosphamide, and dexamethasone; CI: Confidence Interval; DBCd: daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone; IA1: Interim Analysis 1; IRC: independent review committee; ITT: intention-to-treat; IWRS: Interactive web response system.

Source: Company submission Table 18, Company response to PfCs Table 3

Rapidity of haematologic response

Table 19 (p.57) of the CS summarised time to haematologic response. Based on the 12-month landmark analysis, median time to CR was shorter in the DBCd arm than the BCd arm (62 days vs 85 days). Median time to VGPR or better was also shorter in the DBCd group (17 days vs 25 days). The ERG's clinical advisors considered these gains to be small and unlikely to make much difference to survival or potential for improvement in amyloidotic organ function; the important clinical benefit of daratumumab is increasing the proportion of patients achieving CR.

It should also be noted that time to haematologic response within each reported category (CR, VGPR or better, PR) was highly variable, with relatively large standard deviations and wide range of values that substantially overlapped between treatment arms. Figures 2-7 of the Company's response to PfC A8 illustrates the distribution of time to haematologic response in each arm of the ANDROMEDA trial.

Durability of haematologic response

Table 20 (p.58) of the CS reported duration of haematologic response, defined as time to relapse after achieving CR. With a median follow-up of 11.4 months, most responders (100% in the DBCd arm, 94.3% in the BCd arm) had sustained CR without relapse. Consequently, the currently available data from ANDROMEDA do not provide any useful information on duration of haematologic response.

Major organ deterioration progression-free survival (MOD-PFS)

Due to numerous ways in which disease progression can be defined and measured in AL amyloidosis, the ANDROMEDA trial collected MOD-PFS, a novel composite measure that captured time from randomisation to cardiac or renal failure, haematologic progressive disease, or death.

Figure 5 (p.60) of the CS shows a divergence of the BCd and DBCd Kaplan-Meier (KM) curves from month 6, indicating a lower risk of MOD-PFS among DBCd patients. However, it should be noted that median MOD-PFS was not reached in either treatment arm at the reported median follow-up duration (11.4 months).

As acknowledged in the CS, the opportunity for patients in ANDROMEDA to switch to an alternate treatment following suboptimal haematologic response or worsening organ function may have interfered with the evaluation of MOD-PFS, which incorporates haematologic progression as an outcome. The CS presented three analyses to assess the impact of patients switching to subsequent non-cross resistant anti-plasma cell therapy on MOD-PFS: the primary analysis using inverse probability of censoring weighting (IPCW) to adjust treatment estimates in the presence of treatment switching; a sensitivity analysis using naïve censoring of patients who switched treatments; and a supplementary analysis without any censoring of patients who switched. Table 21 (p.60) of the CS

shows that hazard ratio estimates were largely unaffected by the handling of patients receiving subsequent non-cross resistant anti-plasma cell therapy.

Haematologic PFS (HemPFS)

While MOD-PFS has the advantage of capturing haematologic progression, cardiac and renal failure within a single measure, it is a novel outcome that may be challenging to interpret and compare with existing evidence. For this reason, the ANDROMEDA statistical analysis plan outlined separate analyses for "haematologic PFS" (HemPFS; defined as hematologic progression, or death, whichever comes first) and organ-based progression. While landmark analyses on organ response and progression were presented in the CS (p.73-4), HemPFS was not.

A summary of HemPFS data from the ANDROMEDA clinical trial report is presented in Table 9 and Figure 2. These indicate that HemPFS observed in the two treatment arms of ANDROMEDA is similar to MOD-PFS.

Table 9 Summary of Hematologic Progression-free Survival (HemPFS) Based on IRC Assessment; ITT analysis set; IA1 analysis

	BCd (n=193)	DBCd (n=195)
Number of events (%)	[redacted]	[redacted]
Number censored (%)	[redacted]	[redacted]
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75% quantile (95% CI)	[redacted]	[redacted]
p-value[a]		[redacted]
Hazard ratio (95% CI)[b]		[redacted]
6-month HemPFS rate, % (95% CI)	[redacted]	[redacted]
12-month HemPFS rate, % (95% CI)	[redacted]	[redacted]
18-month HemPFS rate, % (95% CI)	[redacted]	[redacted]

[a]p-value is based on a log-rank test stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl>=60 mL/min or CrCl <60 mL/min) as randomized. [b]Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl>=60 mL/min or CrCl <60 mL/min) as randomized. A hazard ratio <1 indicates an advantage for DBCd.

Abbreviations: AL: amyloidosis light-chain; BCd: bortezomib, cyclophosphamide, and dexamethasone; CI: Confidence Interval; DBCd: daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone; NE: not estimable.

Source: CSR Table TEFHPFS01.

Figure 2 Kaplan-Meier Plot for Haematologic Progression-free Survival (HemPFS) Based on IRC Assessment; Intent-to-treat Analysis Set; IA1 analysis

Abbreviations: CyBorD: cyclophosphamide-bortezomib-dexamethasone (otherwise referred to as BCd); Dara SC: daratumumab subcutaneous.

Source: CSR Figure 12.

Major organ deterioration event-free survival (MOD-EFS)

Figure 6 (p.62) of the CS shows the Kaplan-Meier curves for MOD-EFS in the ANDROMEDA trial. MOD-EFS incorporated treatment-switching events into the MOD-PFS composite measure. The justification for this was that switching to a subsequent therapy might be considered a proxy measure for suboptimal or delayed haematologic response.

As would be expected, there is a notably greater separation between the Kaplan-Meier curves for MOD-EFS than MOD-PFS, due to the larger proportion of patients switching to subsequent therapy in the BCd arm (see section 3.2.1.1).

Overall survival (OS)

Section B.2.6.3 (p.62-4) of the CS reported OS data from the IA1 interim analysis of ANDROMEDA. The immaturity of these data means there is insufficient direct trial evidence to establish the effect of daratumumab on overall survival in patients with newly diagnosed AL amyloidosis.

In the absence of data from ANDROMEDA, survival in the model is predicated on the relationship between level of haematologic response and OS from observational study data, with long-term extrapolation (see section 4.2.2).

Subsequent non-cross resistant anti-plasma cell therapy

Section B.2.6.4 (p.64-6) of the CS reported the time to subsequent non-cross resistant anti-plasma cell therapy. As noted in section 3.2.1, more patients received subsequent therapy in the BCd arm ([redacted]) than DBCd arm ([redacted]), and a similar difference was observed for subsequent therapy defined as non-cross resistant (42% vs 9.8%; CS table 23). In addition, the KM curves in figures 8 and 9 of the CS show that the time to first subsequent non-cross resistant anti-plasma cell therapy was shorter among patients receiving BCd. The rate of switching in the BCd noticeably increased soon after the 3- and 6-month assessment timepoints: this observation appears to reflect the ANDROMEDA treatment switching rules at each timepoint (see section 3.2.1) and the end of the BCd regimen at 6 months.

Organ response rate

Tables 25-27 (p.71-2) of the CS report organ response rates from the ANDROMEDA trial. These indicate statistically significantly greater cardiac and renal response rates among DBCd patients than BCd patients at 6, 12 and (from the 12-month landmark analysis), 18 months. These data suggest that the gains in haematologic response associated with DBCd are likely to translate into substantial increases in organ response. While liver response rates also favoured DBCd, the small number of evaluable patients preclude a meaningful comparison between groups.

Time to organ response

Table 28 (p.73) of the CS reports time to organ response with/without censoring for subsequent anti-plasma cell therapy. While DBCd was associated with shorter median time to cardiac and renal response, the range of values was highly variable, and the difference in median time to response relatively small (equivalent to [redacted] days for cardiac response, and [redacted] days for renal response). The small number of patients evaluable for liver response again precluded a meaningful comparison on this outcome.

Cardiac, renal and liver progression

Table 29 (p.74) of the CS reports cardiac, renal and liver progression rates at six months based on the IA1 analysis. While the CS states that rates of organ progression were numerically lower in the DBCd group, the number of events was small, and differences between groups were not statistically significant. Based on the currently available interim analysis, there is insufficient evidence to show that DBCd substantially delays time to organ progression.

Health-related quality of life

Section B.2.6.6 of the CS partially reported health related quality of life (HRQoL) data collected in the ANDROMEDA trial. Figure 10 (p.75) illustrates the observed mean EQ-5D-5L utility scores over time. This showed broadly similar scores for BCd and DBCd arms during the first 6 cycles of treatment, with increasing scores for the DBCd arm at later cycles.

An error in the CS means that the text on p.75 does not refer to the mean observed utility scores presented in Figure 10, but to the least square mean change from baseline in EQ-5D-5L utility scores. These latter data were presented in table 34 of the company's response to PfCs and are reproduced in Table 10 below. The CS points to a statistically significant decrease in utility score for the BCd arm compared to no change from baseline for DBCd arm at 16 weeks. However, the difference between arms was not statistically significant at other timepoints, and the clinical significance of estimates for each timepoint are subject to considerable uncertainty.

Table 10 Change from baseline in EQ-5D-5L utility score; mixed model for repeated measures; ITT analysis set (14th February 2020 data cut-off)

Timepoint	BCd (N=193)		DBCd (N=195)		Difference (DBCd – BCd) LSM[a] cfb (95% CI)	P-value
	n	LSM cfb (95% CI)	n	LSM cfb (95% CI)		
Baseline	[redacted]		[redacted]			
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] LSM 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 value, treatment, time in week, treatment-by-time interaction, and randomisation stratification factors — cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min) as fixed effects and individual subject as random effect. Note: visit window is derived by including all scheduled visits with available EQ-5D-5L assessment.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; cfb: change from baseline; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; EQ-5D-5L: EuroQol-5 Dimensions-5 Level; ITT: intent-to-treat; LSM: least square means.

As noted in the response to PfCs, HRQoL data were only collected while patients were on study treatment, and the number of patients with recorded EQ-5D-5L utility value data decreases over time. Therefore, ANDROMEDA does not provide any evidence on the difference in HRQoL between DBCd and BCd arms after six months, and the estimates for the DBCd arm tend to become increasingly uncertain over time.

Results from the EORTC-QLQ-C30 (Global Health Status and Fatigue) and SF-36v2 (Mental Component Summary (MCS) and Physical Component Summary (PCS)) measures were presented in Appendix M of the CS. LS mean change scores from baseline for Global Health Status, fatigue, and

MCS scores worsened for most of the first six cycles in the BCd arm, while DBCd scores did not significantly differ from baseline. As for the EQ-5D-5L scores, no comparative data were available after 6 months, and the uncertainty for DBCd values increased as the number of patients with available data decreased over time.

Subgroup analyses

Section B.2.7 of the CS reported the results of subgroup analyses for the primary outcome of complete haematologic response (CR) from ANDROMEDA. These showed achievement of CR to be broadly consistent across all pre-specified subgroups (sex, age, baseline weight, race, baseline cardiac stage, countries that typically do or do not offer transplant, baseline renal function, cardiac involvement at baseline, baseline renal stage, baseline alkaline phosphatase, baseline ECOG performance, cytogenetic risk at study entry, FISH t(11;14) translocation). The CS pointed to an increase in relative effect estimate with increasing severity of baseline Mayo cardiac stage, due to poorer response rates for BCd in patients with more severe disease. Other differences in relative effect due to variation in BCd response were noted for baseline weight and presence/absence of FISH t(11;14) translocation.

Subgroup results reported in both the IA1 and 12-month landmark analyses appeared to be consistent.

Appendix E of the CS showed MOD-PFS to be broadly consistent across all pre-specified subgroups.

3.2.4 Adverse Events

Adverse events (AEs) were presented in Section B.2.10.2 of the CS. The company reported safety results from the interim analysis, which used a data cut-off of 14th February 2020. The company believed that a longer follow-up would not present further safety signals as adverse events related to the study treatment would occur early on during the treatment. The company also presented some safety results for the 12-month landmark (using a data cut-off of 13th November 2020) analysis to highlight the change in the incidence of reported AEs when patients were only receiving daratumumab monotherapy after completing six cycles of treatment. All safety results were presented for the safety population.

3.2.4.1 Treatment-emergent adverse events

Almost all patients in ANDROMEDA experienced at least one treatment-emergent adverse event (TEAE) at the IA1 analysis point. [redacted] patients (98.4%) of the patients in the BCd treatment arm (N=188), and [redacted] patients (97.9%) of the patients in the DBCd treatment arm (N=193) experienced at least one TEAE. A brief summary of TEAEs is provided in Table 11, more details, including TEAEs related to individual treatment components, are provided in Table 31 of the CS. The DBCd treatment arm experienced more serious TEAEs (n=[redacted], 43.0% in the DBCd arm, compared to n=[redacted],

36.2% in the BCd arm) and Grade 5 TEAEs ([redacted] in the DBCd arm, compared to [redacted] in the BCd arm). The company attributed this to the longer treatment exposure and longer reporting period for patients in the DBCd treatment arm.

Table 11. Summary of treatment-emergent adverse events (TEAEs) in ANDROMEDA

	BCd (N=188)	DBCd (N=193)
Any TEAE, n (%)	[redacted] (98.4)	[redacted] (97.9)
At least one related to treatment regimen [a], n (%)	[redacted]	[redacted]
Any serious TEAEs, n (%)	[redacted] (36.2)	[redacted] (43.0)
At least one related to the treatment regimen [a], n (%)	[redacted]	[redacted]
TEAE leading to discontinuation of study treatment [b], n (%)	8 (4.3)	8 (4.1)
Deaths, n (%)	[redacted]	27 (14.0)
Deaths due to TEAEs, n (%)	[redacted]	[redacted]

† In Table 32 of the CSR, it was reported that there were [redacted] patients with TEAEs with an outcome of death. ‡ In Table 32 of the CSR, it was reported that there were [redacted] patients with TEAEs with an outcome of death. [a] TEAEs related to at least 1 of the 4 components of study treatment: cyclophosphamide, bortezomib, dexamethasone and daratumumab. [b] TEAEs leading to discontinuation of all study treatment due to an adverse event on the end of treatment.
Abbreviations: BCd: bortezomib, cyclophosphamide, and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide, and dexamethasone; TEAE: treatment-emergent adverse events.
Source: Adapted from: CS (Table 31), and CSR (Table 31)

The most commonly (> 10%) reported TEAEs are presented in Table 32 in the CS. TEAEs where the difference in incidence was at least 5% between the two treatment arms are summarised in Table 12. For all these TEAEs, the greater incidence was observed in the DBCd treatment arm, which the Company attributed to the longer treatment duration of patients in the DBCd arm.

Table 12 Most commonly reported (> 10%) TEAEs with at least 5% difference in incidence in treatment arms.

	BCd (N=188)	DBCd (N=193)
Patients with ≥ 1 TEAEs, n (%)	[redacted] (98.4)	[redacted] (97.9)
TEAE, n (%)		
Diarrhoea	[redacted] (30.3)	[redacted] (35.8)
Constipation	[redacted] (28.7)	[redacted] (34.2)
Peripheral sensory neuropathy	[redacted] (19.7)	[redacted] (31.1)
Upper respiratory tract infection	[redacted] (11.2)	[redacted] (25.9)
Dyspnoea	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cough	[redacted]	[redacted]

Asthenia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide, and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide, and dexamethasone; TEAE: treatment-emergent adverse events.

Source: Adapted from CS Table 32

3.2.4.2 Grade 3 and 4 TEAEs

A summary of the most common (≥ 5%) Grade 3 or 4 TEAEs experienced by patients in ANDROMEDA is presented in Table 33 of the CS. Grade 3 or 4 TEAEs were consistent between the BCd ([redacted]; 57.4%) and DBCd ([redacted]; 58.5%) treatment arms.

3.2.4.3 Treatment-emergent serious adverse events

The most common treatment-emergent serious adverse events (serious TEAEs) were summarised in Table 34 of the CS. In the DBCd treatment arm, 43.0% (n=83) of patients reported at least one serious TEAE compared to 36.2% (n=68) of patients in the BCd treatment arm. Infections and infestations (n=[redacted], [redacted]% in the DBCd arm; n=[redacted], [redacted]% in the BCd arm) was the most commonly observed class of serious TEAE, particularly pneumonia (n=14, 7.3% in the DBCd arm; n=9, 4.8% in the BCd arm), and sepsis (n=6, 3.1% in the DBCd arm; n=0 in the BCd arm).

3.2.4.4 Infusion-related reactions

As daratumumab is a subcutaneous treatment, infusion-related reactions (IRRs) would be an AE of interest. According to the SmPC,[16] daratumumab for subcutaneous injection can cause severe and/or serious IRRs including anaphylactic reactions. To avoid the risk of IRRs patients were pre-medicated with anti-histamines, anti-pyretics, and corticosteroids prior to each daratumumab treatment.[21]

In ANDROMEDA, 7.3% (n=14) of patients in the DBCd treatment arm (N=193) experienced an IRR. All patients experienced a Grade 1 or Grade 2 IRR which did not lead to treatment discontinuation. A smaller percentage of patients [redacted] experienced an IRR in more than one daratumumab infusion.

3.2.4.5 Deaths

At the time of the IA1 analysis (median follow-up: 11.4 months), 27 patients (14.0%) in the DBCd treatment arm died, whereas [redacted] patients ([redacted]) died in the BCd treatment arm. A further patient (who was randomised to the BCd arm) died prior to receiving any treatment. Deaths were overall due to AL amyloidosis-related cardiomyopathies, either as TEAEs or due to disease progression. More patients in the DBCd treatment arm died due to TEAEs ([redacted]) compared to the BCd treatment

arm ([redacted]). On the other hand, more patients in the BCd treatment arm ([redacted]) died due to disease progression compared to patients in the DBCd treatment arm ([redacted]).

Cardiac disorders were the primary cause of death in ANDROMEDA. In the DBCd treatment arm, [redacted] and [redacted] of patients died due to cardiac arrest and cardiac failure respectively. In the BCd treatment arm, [redacted] of patients died due to cardiac arrest, whereas [redacted] of patients died due to cardiac failure.

Almost all patients ([redacted] patients in the BCd treatment arm, and [redacted] patients in the DBCd treatment arm) who died due to TEAEs in the trial had cardiac involvement at baseline, which was defined as patients categorised on stage II, IIIa and IIIa on the Mayo Scale, or class IIIb on the New York Heart Association (NYHA). Relatively few deaths, from any cause, were related to study treatment.

3.2.4.6 Other Adverse Events

The SmPC for daratumumab also presented selected adverse events of concern that were considered by the company in the protocol and assessed during in CSR, although they were not mentioned in the CS. These adverse events are briefly summarised in this section.

Hepatitis B virus reactivation

The SmPC for daratumumab states that the hepatitis B virus (HBV) was reactivated in some patients, sometimes with fatal consequences.[16] It was recommended that HBV screening should be performed prior to treatment. In the protocol, the company identified patients who could potentially reactivate for HBV, and the patients at risk would be tested and manged for potential reactivation.

[redacted]

Injection site reactions

Similar to IRRs, described in Section 3.2.4.4, as daratumumab is a subcutaneous treatment, patients, injection site reactions (ISRs) were also an adverse event to be considered. In ANDROMEDA [redacted]

3.2.4.7 12-month landmark analysis

No new safety concerns were identified at the later cut-off point. Unlike patients in the BCd treatment arm, patients in the DBCd treatment arm continued to receive treatment beyond the first six cycles. A summary of TEAEs, compared to the safety results reported for the IA1 analysis is reported in Table

13. At the later cut-off point of the 12-month landmark analysis, [redacted] were reported compared to the IA1 analysis.

Table 13 Summary of TEAEs reported in the 12-month landmark analysis, compared to IA1 results

	IA1 Analysis		12- Month Landmark Analysis			
	(Total) BCd (N=188)	(Total) DBCd (N=193	BCd	DBCd		
			Cycles 1-6 (N=188)	Total (N=193)	Cycles 1-6 (N=193)	Cycles 7 + (N=149)
Patients with ≥ 1 TEAE, n (%)	[redacted] (98.4)	[redacted] (97.9)	[redacted] (98.4)	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 serious TEAEs, n (%)	[redacted] (36.2)	[redacted] (43.0)	[redacted] (36.2)	[redacted]	[redacted]	[redacted]
TEAE leading to discontinuation of study treatment [b], n (%)	8 (4.3)	8 (4.1)	[redacted]	[redacted]		
Deaths, n (%)	[redacted]	27 (14.0)	[redacted]	[redacted]		
Deaths due to TEAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		

† In Table 32 of the CSR, it was reported that there were [redacted] patients with TEAEs with an outcome of death. ‡ In Table 32 of the CSR, it was reported that there were [redacted] patients with TEAEs with an outcome of death. †† In Table TSFAE09 of the 12-month landmark analysis results, it was reported that there were [redacted] of patients with TEAEs with an outcome of death. ‡‡ In Table TSFAE09 of the 12-month landmark analysis results, it was reported that there were [redacted] of patients with TEAEs with an outcome of death.

Abbreviations: BCd: bortezomib, cyclophosphamide, and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide, and dexamethasone; TEAE: treatment-emergent adverse events.

Source: Adapted from: CS (Table 31), CSR (Table 31), and 12-month landmark analysis results for ANDROMEDA Tables TSIDS01B, TSFDTH01, and TSFAE02B.

A summary of the most commonly reported TEAEs for the 12-month landmark analysis, categorised according to cycle numbers, is presented in Table 14. The incidence of upper respiratory tract infections and peripheral sensory neuropathy were [redacted] in the DBCd treatment arm compared to the BCd treatment arm. In the DBCd treatment arm, the incidence of TEAEs in cycles 7+ is generally lower compared to cycles 1-6, with the exception of upper respiratory tract infections, which remain consistent over the two time periods.

Table 14 Most commonly reported (≥ 25%) treatment-emergent adverse events reported for the 12-month landmark analysis (safety-analysis data set).

	BCd	DBCd

	Total (N=[redacted])	Cycles 1-6 (N=188)	Total (N=[redacted])	Cycles 1-6 (N=193)	Cycles 7 + (N=149)
Patients with ≥1 TEAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide, and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide, and dexamethasone; TEAE: treatment-emergent adverse events.

Source: ANDROMEDA 12-month landmark analysis

A summary of commonly reported Grade 3 and 4 TEAEs for patients in the DBCd arm is presented in Table 36 of the CS. In the first six cycles, 56% ([redacted]) of patients experienced at least one Grade 3 or 4 TEAEs, but in subsequent cycles (i.e., 7+), 25.5% ([redacted]) of patients experienced at least one Grade 3 or 4 TEAE.

3.2.4.8 Points for Critique

The safety outcomes were generally well-reported and were consistent with those detailed in the SmPC for daratumumab. Nearly all patients in ANDROMEDA (97.9% of the patients in the DBCd treatment arm, and 98.4% of the patients in the BCd treatment arm) experienced at least one TEAE, but most of these TEAEs were low grade and manageable.

A limitation of the safety data is that it is over a short follow-up period and no longer-term data are currently available for daratumumab. The company does not expect further safety signals over a longer follow up. However, the ERG's clinical advisors consider low-grade infections to be a potential concern over the longer term.

Most deaths in ANDROMEA were due to cardiac myopathies, either as TEAEs or due to disease progression, and all patients who died due to cardiac disorders in the trial had cardiac involvement at baseline. However, as ANDROMEDA did not include patients with Mayo IIIb status, the ERG believes the number of deaths reported in ANDROMEDA underestimate the number of deaths that would be observed in clinical practice.

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

N/A

3.4 Critique of the indirect comparison and/or multiple treatment comparison

N/A

3.5 Additional work on clinical effectiveness undertaken by the ERG

3.5.1 Observational studies to inform overall survival based on haematologic response

Because overall survival data from ANDROMEDA trial were immature, the trial cannot currently provide a direct estimate of the effect of DBCd on survival. The company's alternative approach for estimating the effects of DBCd on overall survival involved (1) using depth of haematologic response from ANDROMEDA as a surrogate endpoint, (2) obtaining survival conditional on depth of haematologic response from external observational evidence, and (3) extrapolating long-term survival.

The ERG are aware of four possible sources of evidence that could inform estimates of the probability of death over time, stratified by haematologic response. These are:

- Palladini et al. (2012)[5]
- Kastritis et al. (2021)[4]
- EMN23[19]
- ALchemy (2021)[1]

Two of these studies were identified in a targeted search and are used in the company's economic model (see section 4.2.6). Palladini et al. (2012) is a retrospective study of 816 AL amyloidosis patients from seven referral centres in the US and Europe, including the UK (median follow-up was 33 months). This was used in the base case to inform the probability of death over time, stratified by haematologic response at six cycles.[5] Kastritis et al (2021) is a retrospective study of 227 newly diagnosed patients treated with bortezomib-based regimens in Greece (median follow-up was 48 months) and is used in a scenario analysis for response assessment after three cycles.[4]

The company chose Palladini et al (2012) over Kastritis et al (2021) to inform the base-case analysis based on its inclusion of UK patients, having a larger sample size, and using a six-cycle response assessment time point.

EMN23 is a retrospective observational, multicentre study on the management and outcome of AL amyloidosis patients from 10 European countries, including the UK.[19] As it is not fully published, the ERG can only comment on information provided by the company. The CS describes EMN23 as *"…a*

more recent source of data to inform OS that is more reflective of outcomes observed in current clinical practice" (p.98). However, the company stated that data availability and time constraints precluded them from incorporating EMN23 survival data into the cost-effectiveness model ahead of submission. Additional information on EMN23 was provided in response to PfC B1.

The ALchemy study is a prospective study of 1194 patients assessed by the UK National Amyloidosis Centre (NAC). The ERG identified a journal article reporting overall survival stratified by haematologic response from the ALchemy study, published in June 2021.[1, 13]

3.5.1.1 Applicability of observational studies to current UK clinical practice

Table 15 summarises the key characteristics of the four observational studies and Table 16 compares the available baseline participant data for these four studies against ANDROMEDA.

While Palladini et al. (2012) and Kastritis et al. (2021) may have been the best available sources at the time of preparation of the CS, they have significant limitations. The Palladini et al. (2012) study recruited participants from 2002-2010, so may be less applicable to the current decision problem given that bortezomib-based therapies only became widely used from 2010. The study appeared to have a population with less severe cardiac disease than any other source (31% Mayo Cardiac Stage I) and included a relatively small proportion of UK patients (18%; n=147) among its international sample. The Kastritis et al. (2021) study included just 227 patients from a single centre in Athens, Greece.

In contrast to the two studies used in the CS, the ALchemy study reports a large prospectively collected dataset (n=1194) comprising of UK patients recruited by the NAC.[3] The NAC is predominantly a tertiary referral service open to all NHS patients in England and Scotland with suspected or proven amyloidosis, treating around 80% of UK patients. The ERG's clinical advisors estimate this study reports around two-thirds of all UK AL amyloidosis patients assessed between February 2010 and August 2019. Consequently, it is likely to be the cohort that most closely reflects the current UK clinical population and treatment context. In addition, the study reports overall survival for haematologic response assessed at 1, 3, and 6 months. This captures both the assessment points addressed in the CS model plus 1-month assessment of response, which the ERG's clinical advisors suggest is becoming an increasingly common point at which treatment decisions are made.

While the EMN23 study has the largest overall sample size (3065 patients, 55% from the UK), all UK patients were recruited via the NAC and therefore the majority of included patients are also likely to be in ALchemy. While length of follow-up for EMN23 is unknown, it is separated into pre-2010 and post-2010 cohorts. In response to the ERG's clarification questions, the company stated that they plan to use the more applicable post-2010 cohort. This would likely result in a dataset with a similar

observation period and length of follow-up as the ALchemy study. However, the ERG clinical advisors considered that the ALchemy study reflects the standard of care in the UK better than the EMN23 study because some countries have a slightly different standard of care (e.g. using melphalan early and switch if poor response) and because assessment of response occurs at different timepoints in different countries (e.g. in France, the haematologic response assessment is typically undertaken at 1 month). The EMN23 study also interprets the internationally recommended response criteria in a different way from the ALchemy study, leading to slightly different results. The ERG's clinical advisor familiar with both studies noted that ALchemy study interpretation is the same as the interpretation in the UK clinical care, using a strict interpretation of the response criteria, whilst EMN23 has a looser interpretation.

For these reasons, the ERG considers the ALchemy study to be the most appropriate source of data for estimating overall survival stratified by haematologic response in an NHS context. While EMN23 is also a good candidate, there may be a trade-off between its larger sample size and its incorporation of non-UK data.

3.5.1.2 Applicability of BCd outcomes observed in ANDROMEDA to UK clinical practice

While the ERG considers the ANDROMEDA trial to be the best source of data for assessing the effectiveness of DBCd *relative* to BCd, it does not necessarily represent the expected *absolute* outcomes (i.e. proportion of patients achieving each level of haematologic response) for DBCd and BCd that would be observed in UK clinical practice.

The ERG considers the ALchemy study to provide the most accurate estimate of the effect of BCd treatment on haematologic response in recent UK clinical practice. In addition to the reasons stated above, ALchemy exclusively includes UK patients treated with upfront bortezomib-based regimens, while the ANDROMEDA trial is a multinational RCT.

As noted by the company, there are some differences between the response rates observed in the BCd arm of the ANDROMEDA trial and those of the ALchemy study (see response to PfC B3, table 12). This suggests that the absolute outcomes observed in the ANDROMEDA trial may not generalise to the UK setting, even if the relative effectiveness of DBCd vs BCd is considered generalisable.

To estimate the distribution of patients by depth of haematologic response for DBCd in the UK population, the ERG considers that the most appropriate approach is to apply the relative effectiveness estimates of DBCd vs. BCd from the ANDROMEDA trial to the baseline distribution for BCd from the ALchemy study (see section 4.2.6.2 of the ERG report for further details and discussion).

Table 15 Key characteristics of studies reporting OS stratified by haematologic response

	Palladini 2012[5]	Kastritis 2021[4]	EMN23 (Palladini 2021)[19]*	ALchemy (Ravichandran 2021a)[1]
Number of patients	816	227	3064	1194 (ITT cohort); 1133 (1-month landmark cohort)
Recruitment period	2002-2010	Not Reported	2011-2018	February 2010 - August 2019
Geographic setting	EU / USA (18% from UK)	Greece	Austria (1.9%), Czech Republic (0.6%), France (5.8%), Germany (13.8%), Greece (5.8%), Italy (27.0%), Netherlands (3.6%), Portugal (0.6%), Spain (2.9%), UK (38.0%).	UK
Clinical Setting	Seven referral centres in the European Union and the United States	Secondary care (Department of Clinical Therapeutics, Athens, Greece)	Not Reported	UK National Amyloidosis Centre (NAC): predominantly but not exclusively a tertiary referral service open to all NHS patients in England and Scotland with suspected or proven amyloidosis. All patients are seen at the NAC at baseline, and then at least every six months for a comprehensive assessment. All investigations were done at the NAC, where data was collected and analysed. Patients were treated at their local centres as per nationally agreed protocols.
Patient selection criteria (where stated)	Only patients with AL amyloidosis recorded in the referral centre databases who had been evaluated for response 3 and/or 6 months after initiation of first-line therapy were included	Consecutive patients	Treatment information and efficacy outcomes for patients who participated in an interventional clinical trial have been excluded from the analysis.	Patients with a difference between involved and uninvolved free light chain (dFLC) < 20mg/l at diagnosis were excluded due to a lack of validated response criteria in this patient group.
All newly diagnosed?	Yes	Yes	Yes	Yes
Assessment period	3 and/or 6 months	1 and 3 months	Not Reported	1, 3, 6 months
1st line treatment	Melphalan plus dexamethasone 364 (44.6%) Autologous stem-cell transplantation 129 (15.9%) Thalidomide based 119 (14.6%) Lenalidomide based 43 (5.3%) Bortezomib based 26 (3.2%) Dexamethasone alone 24 (2.9%) Melphalan plus prednisone 20 (2.4%) Other 91 (11.1%)	Bortezomib	Bortezomib-based 2291 (74.7%) Immunomodulatory imide drugs-based 59 (1.9%) Chemotherapy 266 (8.7%) Rituximab 66 (2.2%) Daratumumab 21 (0.7%) Steroids 11 (0.4%) ASCT 170 (5.5%) Clinical trial 142 (4.6%) Other regimen groups 39 (1.3%)	Upfront bortezomib-based regimens

2nd line/subsequent treatments	N/A	Not Reported	Bortezomib-based 199 (20.2%) Immunomodulatory imide drugs-based 410 (41.7%) Chemotherapy 119 (12.1%) Rituximab 46 (4.7%) Daratumumab 54 (5.5%) Steroids 1 (0.1%) ASCT 96 (9.8%) Clinical trial 26 (2.6%) Other regimen groups 33 (3.4%)	Not Reported
Length of follow-up	Median follow-up for living patients = 33 months (IQR 20 to 48) OS curves up to 48 months	Median follow-up 48 months OS curves up to ~150 months	Not Reported	Median follow-up not reported OS curves up to 125 months
Numbers at risk, censored at key follow-up times	Not Reported	Not Reported	Not Reported	Deaths in 1st month, n=61 Deaths within 3 months, n=156 Deaths within 6 months, n=246 No reported loss to follow-up within the cohorts
Reports OS by CR, VGPR, PR and NR?	Reports (a) survival hazard rates (from 3 and 6 month landmarks) and (b) overall HRs with CR as the reference category. ***Survival hazard rates from 6-month landmark of 649 patients based on hematologic response:*** CR: 97 patients; 3.6 deaths/100 py VGPR: 233 patients; 9.6 deaths/100 py PR: 140 patients; 23.7 deaths/100 py NR: 179 patients; 47.2 deaths/100 py Stage I: 103/432 (24%) Stage II: 223/432 (52%) Stage III: 106/432 (24%) ***Survival hazard rates from 3-month landmark of 300 patients based on hematologic response:*** CR: 37 patients; 1.0 deaths/100 py VGPR: 122 patients; 7.4 deaths/100 py PR: 47 patients; 19.9 deaths/100 py NR: 94 patients; 32.9 deaths/100 py	KM curves comparing (a) ≥VGPR, PR, NR for 1 month response (b) CR, VGPR, PR and NR for 3 months response	No	**Overall survival based on haematologic response** ***ITT cohort; 1-month haematologic response:*** CR (n=137): Median not reached. 87%, 83%, 68%, 63% of patients alive at the end of 1, 2, 5, 10 years VGPR (n=270): Median not reached. 92%, 87%, 71%, 59% of patients alive at the end of 1, 2, 5, 10 years PR (n=252): Median OS 61 months (95% CI: 43.42–78.57) NR (n=413): Median OS 22 months (95% CI: 14.54–29.45) ***1-month landmark; 1-month haematologic response:*** CR (n=137): Median not reached. 87%, 83%, 68%, 63% of patients alive at the end of 1, 2, 5, 10 years VGPR (n=270): Median not reached. 92%, 87%, 72%, 58% of patients alive at the end of 1, 2, 5, 10 years PR (n=252): Median OS 60 months (95% CI 42.42–77.57)

	Stage I: 44/184 (24%) Stage II: 108/184 (59%) Stage III: 32/184 (17%) ***Overall HR (95% CI)*** CR: 1 (reference) VGPR: 2.67 (1.26 to 5.66) PR: 6.24 (2.96 to 16.15) NR: 12.34 (6.03 to 25.35)			NR (n=352): Median OS 32 months (95% CI 25.36–38.63) ***3-month landmark; 3-month haematologic response*** CR (n=290): Median not reached. 93%, 88%, 69%, 55% of patients alive at the end of 1, 2, 5, 10 years VGPR (n=303): Median not reached. 91%, 84%, 65%, 51% of patients alive at the end of 1, 2, 5, 9 years PR (n=213): Median OS 47 months (95% CI 27.51–66.48) NR (n=179): Median OS 23 months (95% CI 15.93–30.06) **6-month landmark*; 6-month haematologic response*** CR (n=294): Median not reached. 93%, 88%, 74%, 63% of patients alive at the end of 1, 2, 5, 10 years VGPR (n=323): Median not reached. 93%, 86%, 61%, 51%of patients alive at the end of 1, 2, 5, 10 years PR (n=194): Median OS 42 months (95% CI27.91–56.09) NR (n=104): Median OS 22 months (95% CI 16.39–27.60)
Reports HRQoL by CR, VGPR, PR and NR?	No	No	No	No
Reports haematologic response by Mayo stage?	Numbers not reported: "The proportion of stage III patients was not significantly different among the four hematologic response groups"	Only partially (CR and VGPR grouped as ≥ VGPR). ***Median OS of patients achieving ≥ VGPR vs PR vs NR at 1 month by Mayo stage (years)*** ≥VGPR (n=69): 12.1 (Stage I); 6 (Stage II); 5 (Stage III) PR (n=64): 12 (Stage I); 4.9 (Stage II); 2 (Stage III) NR (n=94): 7 (Stage I); 1.9 (Stage II); 0.5 (Stage III)	No	Only partially (response classed as ≥ VGPR or < VGPR) ***Median OS of patients achieving ≥ VGPR vs < VGPR at 1 month by Mayo stage.*** Mayo stage I: Median not reached vs was 88 months (95% CI 72.65–103.35) Mayo stage II: Median not reached vs 58 months (95% CI 41–74.99 months) Mayo stage IIIa: Median 74 months vs 30 months (95% CI 23.69–36.30)

		Median OS of patients achieving ≥ VGPR vs PR vs NR at 3 months by Mayo stage (years) ≥VGPR (n=95): 12 (Stage I); 6 (Stage II); 3.4 (Stage III) PR (n=60): 12 (Stage I); 3.9 (Stage II); 0.6 (Stage III) NR (n=52): 3.2 (Stage I); 1.8 (Stage II); 1 (Stage III)		Stage IIIb: median 31 months (95% CI 11.05–50.95) vs 7 months (95% CI 3.03–10.96)
Reports Kaplan-Meier curves?	Yes	Yes	Yes (survival by Mayo stage)	Yes

*Includes additional information provided in company's response to points for clarification. **Abbreviations:** AL: amyloid light-chain; CI: confidence interval; CR: complete response; dFLC: difference between involved and uninvolved free light chain; HR: hazard ratio; HRQoL: health-related quality of life; IQR: interquartile range; ITT: intention-to-treat; KM: Kaplan-Meier; N/A: not applicable; NR: no response; OS: overall survival; PR: partial response; VGPR: very good partial response.

Table 16: Baseline characteristics of studies reporting OS stratified by haematologic response

	ANDROMEDA[26]	Palladini 2012[5]	Kastritis 2021[4]	ALchemy (Ravichandran 2021)[1]	EMN23 (PfC Response)
Number of participants	388	816	227	1194	3065
Age, years					
Mean (SD)	[redacted]				[redacted]
Median	[redacted]	63.0	65.0	66.0	66.0
Range	[redacted]	IQR (55-71)	(10-84)	(29-88)	[redacted]
Sex, n (%)					
Female	[redacted]	327 (40.1)	43%	481 (40.3)	1269 (41.4)
Male	[redacted]	489 (59.9)	57%	713 (59.7)	1796 (58.6)
Weight, kg					
Mean (SD)	[redacted]				[redacted]
Median	[redacted]				[redacted]
Range	[redacted]				[redacted]
Baseline ECOG score, n (%)					
0	[redacted]			0-2 1117 (93.6)	[redacted]
1	[redacted]				[redacted]
2	[redacted]				[redacted]
3				>2 77 (6.4)	[redacted]
4					[redacted]
Not reported					[redacted]
Time since initial AL diagnosis					
Mean (SD)	[redacted]				[redacted]
Median	[redacted]				[redacted]
Range	[redacted]				[redacted]
⩽30, n (%)	[redacted]				
30–60, n (%)	[redacted]				
>60, n (%)	[redacted]				
Isotype of AL based on either immunofixation or light chain, n (%)					
Lambda	[redacted]	615 (75.4)		936 (78.4)	
Kappa	[redacted]	201 (24.6)		258 (21.6)	
Organ involvement, n (%)					
Heart	277 (71.4)	529 (64.8)	69%	791 (66.2)	2135 (69.7)
Kidney	229 (59.0)	556 (68.1)	70%	802 (67.3)	2024 (66.0)
Liver	[redacted]	131 (16.1)	19%	139 (11.6)	409 (13.3)
Gastrointestinal tract	[redacted]			48 (4)	215 (7.0)
Lung	[redacted]				26 (0.9)
Nerve	[redacted]				447 (14.6)
PNS	[redacted]	153 (18.8)	23%	85 (7.1)	
ANS	[redacted]			82 (6.9)	
Soft tissue	[redacted]			187 (15.7)	609 (19.9)

Number of organs involved					
Mean (SD)	XXX				
Median	XXX	2			
Range	XXX	IQR: 1-2			
1 organ, n (%)	XXX				1123 (36.6)
2 organs, n (%)	XXX				1224 (39.9)
⩾3 organs, n (%)	XXX				700 (22.8)
Not reported, n (%)					XXX
Cardiac stage based on Mayo Clinic Cardiac Staging System[a], n (%)					
I	XXX (23.2)	160/517 (30.9)	18%	183 (15.3)	512 (16.7)
II	XXX (40.2)	226/517 (43.7)	52.5%	409 (34.3)	1066 (34.8)
IIIa	XXX	III: 131/517 (25.3)	18%	418 (35)	853 (27.8)
IIIb	XXX	-	11.5%	184 (15.4)	485 (15.8)
Not reported					XXX
NYHA class, n (%)					
I	XXX				
II	XXX				
IIIA	XXX	III or IV: 156/582 (26.8)			
Renal function status[b] - creatinine clearance					
<60 mL/min	XXX				
⩾60 mL/min	XXX				
Normal					XXX
Abnormal					XXX
Not reported					XXX

[a] For ANDROMEDA-Cardiac stage is based on both NT-proBNP and hs.cTnT levels. [b] For EMN23- Renal function status was evaluated according to investigators' assessment.

Abbreviations: AL: amyloid light-chain; ANS: autonomic nervous system; BCd: bortezomib, cyclophosphamide, and dexamethasone DBCd: daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone; ECOG: eastern cooperative oncology group; eGFR: estimated glomerular filtration rate; ITT: intention-to-treat; NYHA: New York heart association; PNS: peripheral nervous system; SD: standard deviation.

Source: Adapted from company submission Table 12.

3.6 Conclusions of the clinical effectiveness section

The clinical effective evidence for DBCd versus BCd is based on a single trial (ANDROMEDA). The study appears to be at low risk of bias for most domains, though the strength of conclusions that can be drawn are limited by incomplete follow-up for several outcomes.

ANDROMEDA shows that DBCd is associated with improved haematologic response, reporting a clinically and statistically significant improvement in the primary outcome of complete haematologic response (CR) relative to BCd. While median times to CR and VGPR or better were also shorter for DBCd, these values were of less clinical significance than the proportion of patients achieving deep haematologic response. Due to the variability of time to haematologic response within each reported category (CR, VGPR or better, PR), the relative effect of DBCd on speed of response remains uncertain. Due to the small number of patients with relapse after achieving CR in the ANDROMEDA interim analysis, the relative effect of DBCd on duration of haematologic response cannot yet be established.

Cardiac and renal response rates were significantly higher in DBCd- than BCd-treated patients, likely due to the substantial gains in depth of haematologic response.

While the observed gains in haematologic response might also reasonably be expected to translate into improvements in overall survival (OS), the immaturity of directly observed OS data in ANDROMEDA means that the relative effect of DBCd on OS is highly uncertain. Section 3.5.1 discusses the selection of alternative sources of survival data conditional on haematologic response. Section 4.2 provides a detailed discussion around the subsequent modelling of haematologic response and overall survival in newly diagnosed AL amyloidosis.

After 6 months of treatment, absolute HRQoL values appear to increase in patients receiving DBCd. However, as these data were not collected in the ANDROMEDA BCd arm, the relative effect of DBCd on quality of life after this timepoint is unknown.

The available ANDROMEDA data did not raise any new safety concerns and suggested that daratumumab is tolerable. However, as the trial was powered for effectiveness and only interim analyses are currently available (median length of follow-up 20.3 months; median duration of daratumumab treatment 18.5 months), the effects of DBCd in terms of rare and longer-term adverse effects remain uncertain or unknown.

Patients classified according to Mayo Clinic Cardiac Staging with Stage IIIb disease have the most severe degree of cardiac involvement and have high risk systemic AL amyloidosis with a very poor prognosis. However, patients with Stage IIIb disease were excluded from the ANDROMEDA trial, so the effects of DBCd in this important patient subgroup are unknown. More significantly for the current appraisal, the ANDROMEDA trial population does not appear to be generalizable to the UK population. Baseline levels of haematologic response in the BCd arm of ANDROMEDA differ from the UK-based ALchemy study (see response to PfC B.3.2) that includes patients with Mayo Clinic Cardiac Stage IIIb disease. Section 3.5.1.2 makes the argument for using the ALchemy study rather

than ANDROMEDA to inform baseline levels of haematologic response in the economic model. Though the ERG considered ALchemy to be a more appropriate source of absolute baseline haematologic response levels, the ERG's clinical advisors expect to see a similar relative treatment effect for DBCd compared to BCd in Mayo Clinic Cardiac Stage IIIb patients as was observed in the less severe ANDROMEDA population.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

4.1.1 Summary of company's submission

The company's systematic literature review did not identify any economic evaluations for the treatment of adult patients with newly diagnosed AL amyloidosis. See Appendix G of the CS for a detailed description of the searches and results from the review.

4.1.2 Points for critique

The ERG is satisfied with the company's review of the cost-effectiveness evidence. In the CS, there was insufficient information on the grey literature searches in Appendix G, G.1.1, p40. In response to ERG points for clarification, the company provided the full details requested. The review appears to have been conducted to a high standard and is well reported.

4.2 Summary and critique of the company's submitted economic evaluation

The company submitted a *de-novo* model that adopted a decision tree structure to assess patients' haematologic response to treatment with first-line DBCd or BCd and a Markov model to estimate long-term health outcomes and costs conditional on haematologic response achieved. In the model, patients are assessed for haematologic response after six (base-case analysis) or three (scenario analysis) 28-day cycles, at which point depth of response is classified as having achieved complete response (CR), very good partial response (VGPR), partial response (PR) or no response (PR), with some patients having died. Following assessment of response, patients who achieve CR or VGPR, either (i) remain on treatment with fixed dose daratumumab monotherapy if their initial treatment was DBCd (for a maximum period of 24 cycles); or (ii) discontinue treatment if their initial treatment was BCd (i.e., come off treatment altogether). Patients on either fixed dose daratumumab treatment or off-treatment are at risk of relapse and movement to subsequent second-line treatment. Patients who achieve PR or NR start a second-line therapy immediately after the assessment of haematologic response. All patients are at risk of end-stage organ failure and death. The risk of these events depends on their depth of haematologic response, line of therapy, and whether they are off-treatment (or on

daratumumab monotherapy), and whether they have had end-stage organ failure. The depth of haematologic response achieved with first-line treatment determines long-term overall survival.

DBCd is modelled to affect quality-adjusted life years (QALYs) by increasing the proportion of patients who achieve CR because CR is associated with better health-related quality of life, lower risk of progression to second-line therapy and end-stage organ failure (thereby reducing the costs associated with progression) and greater life expectancy. DBCd directly increases NHS costs due to its greater acquisition costs compared to BCd, and indirectly by increasing the life expectancy of patients who use healthcare services.

4.2.1 NICE reference case checklist

Table 17 NICE reference case checklist

Element of health technology assessment	Reference case[27]	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate, the time horizon is 35 years, by when more than 99% of the cohort have died.
Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate. The systematic review identified the ANDROMEDA trial as the only RCT on DBCd.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The CS is appropriate. HRQoL was measured with EQ-5D-5L. The EQ-5D-5L data was mapped to EQ-5D-3L values with the van Hout et al algorithm.[28]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS base-case is appropriate.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
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	The CS is appropriate. Resources obtained from modified Delphi panel with seven UK-based clinical experts. Unit costs from national representative sources.[9, 12, 29]

Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
CS: company submission; DBCd: daratumumab with bortezomib; cyclophosphamide and dexamethasone; EQ-5D: standardised instrument for use as a measure of health outcome; HRQoL: health-related quality of life; PSS: personal social services; QALYs: quality-adjusted life years; RCT: randomised controlled trial.		

4.2.2 Model structure

4.2.2.1 Summary of company submission

The model is a cohort model, with a decision tree embedded in a Markov model (see Figure 3). The decision tree calculates the number of patients by depth of haematologic response with first-line treatment on DBCd or BCd at the response assessment time point, which is after six cycles of treatment in the base-case analysis and after three cycles of treatment in a scenario analysis. At the response assessment time point, patients are classified according to their depth of haematologic response: CR, VGPR, or PR/NR (within the model the response categories of PR and NR are combined). At this point, patients exit the decision tree and enter the long-term Markov model. The cycle length used in the model is 4-weeks long, and a half-cycle correction is implemented.

The health states included in the Markov model are:

- 'On first line treatment (On Tx)', which represents the time when patients are on first line treatment, but this health state is only relevant as a recurring health state when patients exit the decision tree after three cycles of treatment (scenario analysis) rather than the base case of six cycles of treatment.
- 'Off-treatment or on fixed dose treatment (Off Tx/FDT)', which represents the time when patients who achieve CR or VGPR are not on any active treatment (Off Tx), including those who have discontinued treatment but have not yet progressed to 2L treatment, or are on daratumumab monotherapy for a fixed treatment duration (FDT). Only patients who receive first-line treatment with DBCd may receive daratumumab monotherapy (up to a maximum of 24 cycles), whereas patients who receive first-line BCd stop treatment.
- 'On second line treatment (2L Tx)', which represents the time when patients are on second or subsequent lines of therapy due to haematologic or organ progression, or at the clinician's discretion. The resource use associated with second line chemotherapy used in the model includes: lenalidomide + dexamethasone (75%), melphalan + dexamethasone (5%), carfilzomib + dexamethasone (10%) and BCd (10%).
- 'End-stage organ failure', which encompasses patients that require solid organ (i.e. heart or kidney) transplant or dialysis.

- Death. At any cycle, patients can die and move from any health state to death.

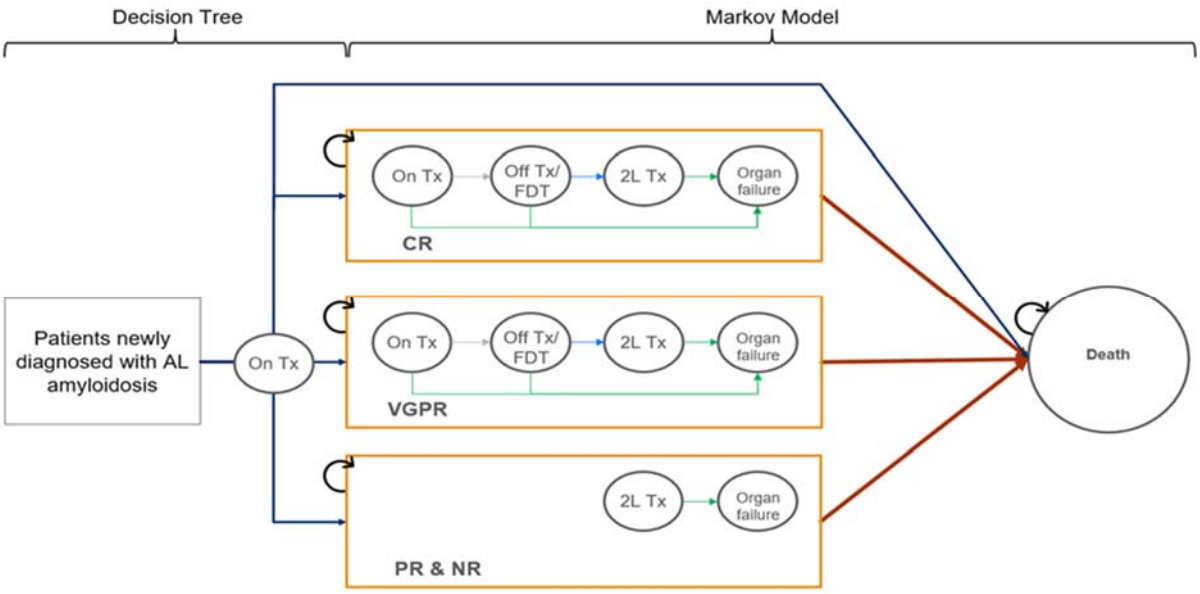
The company justified the response assessment at six cycles for the base-case analysis for two reasons: (i) to recognise the effectiveness of DBCd in improving haematologic response over six treatment cycles rather than a shorter period of treatment; and (ii) to act as a conservative approach given that more patients treated with BCd are expected to have a suboptimal response of PR/NR and these patients would remain in the health state "on first line treatment" for longer where they would accrue better health-related quality of life than that inferred by subsequent lines of therapy. In response to ERG points for clarification, the company stated: "*Whilst the assessment timepoint in UK clinical practice is suggested to be three months, which enables patients who have a suboptimal response to treatment to attempt an alternative treatment, clinical expert opinion received by Janssen is that patients who achieve VGPR or CR in clinical practice would typically continue the same regimen up to cycle 6, unless they experienced tolerability issues, in order to increase their depth of response and improve their long-term outcomes*" (company's response to the ERG points for clarification document, B4.1 p28). The company also noted that modelling the assessment of response at six cycles allowed the model to capture the deepening of response over time for patients who had VGPR.

Patients enter the model at the beginning of treatment on either DBCd or BCd, in the state 'On first line treatment'. Patients in the state 'On first line treatment' are at risk of death. After the response assessment, patients with CR and VGPR mostly transit to the state 'Off-treatment or on fixed dose treatment', with a small proportion having 'End-stage organ failure'. Patients in the state 'Off-treatment or on fixed dose treatment' are at risk of progressing to the states 'On second line treatment', 'End-stage organ failure' or 'Death'. After the response assessment, patients with PR or NR transit to the state 'On second line treatment'; a small (but greater proportion than patients with CR or VGPR) transit to 'End-stage organ failure'. Patients in the state 'On second line treatment' are at risk of 'End-stage organ failure' or 'Death'.

The model combines patients who achieve PR and NR at the response assessment time point. The company justified this approach because both outcomes are considered suboptimal responses in UK clinical practice, and patients are expected to follow a similar treatment pathway where they both start second line therapy following response assessment. The ERG requested at points for clarification additional flexibility within the model structure to separate out the categories of PR and NR in order to enable separate data on PR and NR to be included in the model, but the company declined to provide a revised version of the model. The company justified this decision on the grounds that the model structure is a reasonable reflection of clinical practice and that any change would introduce undue complexity and uncertainty to the analysis, which the company considered as unwarranted

given that these patients are expected to be managed in the same way in clinical practice (see company's response to ERG points for clarification document, B8.2).

Figure 3: Cost-effectiveness model structure (reproduced from CS Figure 16, page 99)



Abbreviations: AL: light-chain; CR: complete haematologic response; FDT: fixed daratumumab treatment; NR: no response; Off Tx/FDT: off-treatment / fixed dose treatment; On Tx: on treatment; PR: partial response; (2L) Tx: (second-line) treatment; VGPR: very good partial response.

4.2.2.2 ERG critique

The ERG considers the model structure to be broadly representative of the natural course of the disease and the expected effects of DBCd and BCd on health outcomes and healthcare costs. The ERG has three main concerns regarding the model structure, which relate to (i) the timing of the response assessment for first line treatment; (ii) the assumption that overall survival (i.e. life expectancy) depends only on the depth of haematologic response achieved at the response assessment timepoint; and (iii) the pooling of patients who achieve PR and NR into a single Markov trace. Each of these concerns are discussed below in turn.

Timing of response assessment

Firstly, the base-case assumption that the response assessment takes place after six treatment cycles is inconsistent with UK clinical practice and guidelines.[2, 3]The UK clinical practice guideline states: "*Monitoring of response to treatment with FLC or M-protein should be measured after each cycle of chemotherapy during treatment and every 1–3 months thereafter (Grade 1c). The aim is to switch to an alternative regimen as soon as the current one is proving ineffectual, which may be assessed after three cycles of therapy or earlier if appropriate (Grade 1c).*"[2] The website of the National Amyloidosis Centre also states: "*Soon after the ALchemy study began, it became clear that patients*

were benefiting from the more intensive monitoring after the first 3 cycles of chemotherapy, monthly blood samples and treatment forms from the local doctors. As a result, we have incorporated all of these into our standard clinical practice for all patients."[3] Feedback provided to the company by its clinical advisor is consistent: "*Stopping rule: if the patient has not responded by month 3, then patient needs to switched treatment"*.[30] The ERG clinical advisors confirmed that the response assessment to determine whether treatment should continue is typically conducted after three treatment cycles in the UK.

In the model, under the scenario where the response assessment occurs after three treatment cycles, patients who achieve CR or VGPR continue treatment with DBCd or BCd, while patients who achieve PR or NR transit to the health state 'second line therapy'. This is in line with the company's view that: "*Whilst the assessment timepoint in UK clinical practice is suggested to be three months, which enables patients who have a suboptimal response to treatment to attempt an alternative treatment, clinical expert opinion received by Janssen is that patients who achieve VGPR or CR in clinical practice would typically continue the same regimen up to cycle 6, unless they experienced tolerability issues, in order to increase their depth of response and improve their long-term outcomes*" (company's response to ERG points for clarification document, B4.1 p28). For these reasons, the ERG considers a response assessment time point after three treatment cycles to be more consistent with UK clinical practice and current guidelines.

> ***item 1. The ERG considers that the response assessment time point used in the model should be consistent with UK clinical practice and guidelines that suggests response assessment after three treatment cycles.***

The ERG notes that some patients may discontinue first-line therapy earlier than three treatment cycles. The ERG clinical advisors noted that patients are monitored monthly, with some patients having an earlier response assessment when clearly not responding to first-line treatment. Furthermore, Kastritis et al (2021)[4], which was used by the company to inform overall survival by haematologic response in the scenario analysis that uses a three-cycle assessment time point, proposes assessing response after one treatment cycle rather than three cycles. Ravichandran et al (2021)[1], which reports the outcomes of patients in the UK ALchemy study, states "*Our practice now is to measure serum-FLCs frequently (once a week at least for the initial cycles) and consider therapy modification for those cases where a partial response is not achieved by 1 month and, for those with >PR at one month, where patients have <VGPR by 2 months*. (p7)".

In response to ERG points for clarification, the company acknowledged that recent evidence and feedback from UK expert clinicians suggest that good haematologic response following one month of treatment translates into improved overall survival.[1, 4] However, UK expert clinicians noted that "(…)

haematologic response typically deepens over time and that it is important to prevent prematurely switching patients to subsequent lines of therapy. Clinicians noted the importance of avoiding a situation in which patients have received several lines of therapy in a short period of time and are facing a lack of other treatment options" (company's response to ERG points for clarification document, B4.2 p30). For these reasons, the company concluded that a one-month response assessment does not reflect UK clinical practice, although it recognised its importance for clinical research purposes. Therefore, the company did not conduct a scenario analysis assuming a one-month response assessment.

The ERG considers that the response assessment at one month may not be standard clinical practice at the time of this appraisal but occurs in some patients and may become more widespread in the future. Therefore, the ERG considers that a one-month response assessment should warrant a scenario analysis in order to assess the impact of early response to treatment at one month, in line with proposals outlined by Ravichandran et al, 2021 and Kastritis et al (2021).[1, 4]

> ***item 2. The ERG considers that a scenario analysis should assess the impact of early response to treatment at one month, in line with proposals outlined by Ravichandran et al, 2021 and Kastritis et al (2021).***[1, 4]

Prognostic factors affecting overall survival

Secondly, the ERG considers that the assumption that overall survival depends only on the depth of haematologic response achieved at the assessment time point of six months is overly simplistic and may bias the model predictions; however, the impact on the cost-effectiveness results is unclear. If other independent prognostic factors are expected to have an impact on life expectancy, such as Mayo Clinic Cardiac Stage, [1, 4] and these differ between the response groups in the ANDROMEDA trial and between patients included in studies informing overall survival by haematologic response, the model may mis-predict overall life expectancy. The impact on cost-effectiveness results is unclear as this will depend on the magnitude of differences in independent prognostic factors between groups. This will be discussed further in Section 4.2.6.2Treatment effectiveness and extrapolation.

Pooling patients with PR and NR in the same trace

Thirdly, the pooling of patients who achieve either PR or NR together in the model may result in an underestimation of overall survival for the 'suboptimal response' group when compared to estimation of overall survival in the respective groups separately. This is likely to favour DBCd, given that DBCd reduces the proportion of patients who achieve PR/NR compared to BCd. Patients who achieve PR are expected to experience better overall survival than patients who achieve NR.[1, 4, 31] In the model, overall survival for the combined PR/NR group is calculated as a weighting of the separate PR and NR overall survival curves where the weighting is based on the proportion of patients achieving

PR and NR at six months in the ANDROMEDA trial. The limitation is that, over time, patients who achieve PR are expected to survive longer and hence become a greater proportion of patients alive. By calculating overall survival as the weighted average of the two groups at one response assessment timepoint in time (i.e. 6 cycles in the base case analysis), the model underestimates overall survival for the pooled PR/NR group. Therefore, the ERG requested the company to present a revised version of the model which does not combine patients who achieve PR and NR, but the company declined with the view that their modelling approach was a reasonable reflection of clinical practice and avoided unwarranted complexity. The ERG believes that the pooling of PR and NR patients in the same trace is not appropriate given the different mortality risks for these separate categories.

item 3. The model structure should have sufficient flexibility to separate out the response categories of PR and NR because of different mortality risks in each category.

4.2.3 Population

4.2.3.1 Summary of company submission

The patient population in the model comprises adults with newly diagnosed AL amyloidosis. The baseline characteristics are based on the average patient population in the ANDROMEDA trial, that is [redacted] years of age, [redacted] % male, weighing [redacted] Kg and with a body surface area of [redacted] m^2.

No separate subgroup populations are considered in the company's base case analysis. However, the company seeks a recommendation for DBCd in patients who have Mayo Clinic Cardiac Stage IIIb disease, which is the most severe degree of cardiac involvement. In the ANDROMEDA study, patients with Stage IIIb disease were excluded during the screening period from participating in the trial. As this trial is the only source of efficacy data for DBCd compared with BCd, and the depth of haematologic response in the model is informed by the results of the ANDROMEDA trial for both BCd and DBCd, the company's cost-effectiveness analysis does not consider a population with Stage IIIb disease.

4.2.3.2 Points for critique

As discussed in Section 3.5.1.2. the ERG has concerns about how well the patient population of the ANDROMEDA trial aligns with the population seen in UK clinical practice. The baseline characteristics from the ANDROMEDA trial for the average UK patient population are not too dissimilar when compared to the patient characteristics of the ALchemy study, but the exclusion of patients with Stage IIIb disease from participating in the trial limits the generalisability to the UK population with newly diagnosed AL amyloidosis. As discussed in Section 3.2.1.2, the ERG notes that the ALchemy study included 15.4% of patients with Mayo Clinic Cardiac Stage IIIb, which the ERG clinical advisors indicated is reflective of the UK patient population.[1] Therefore, the ERG considers the ALchemy study to be more generalisable to the UK patient population than the ANDROMEDA

trial. This is reinforced further by the company's desire to seek a recommendation in all patients with newly diagnosed AL amyloidosis, including those with Mayo Clinic Cardiac Stage IIIb disease.

item 4: The ALchemy study is more generalisable to the UK patient population than the ANDROMEDA trial.

The company has not provided any evidence to allow an assessment of response to treatment in a subpopulation with Stage IIIb disease. The cost-effectiveness results based on data from the pivotal ANDROMEDA trial that excludes patients with Stage IIIb disease is unlikely to generalise to a subpopulation of patients with very severe cardiac involvement and extremely poor prognosis. This is because patients with Stage IIIb disease are not expected to achieve the same level of depth of haematologic response as patients with less severe disease. In response to ERG points for clarification, the company has indicated that the EMN23 study is anticipated to provide haematologic response rates for the Mayo Clinic Cardiac Stage IIIb subgroup at three and six months, which could be used to inform the proportion of patients achieving different depths of haematologic response at three and six months for BCd (where approximately 82% of Stage IIIb patients in the EMN23 study received a bortezomib-based regime). The company indicated that this data is expected to be available and incorporated into the cost-effectiveness model at the time of Technical Engagement. The ERG notes that the ERG preferred approach and data source for depth of haematologic response and overall survival provides evidence on the cost-effectiveness of DBCd for the entire patient population in the NICE scope (see Section 4.2.6.2 and 6.1.1.3), but assumes that the relative effect of DBCd vs. BCd from the ANDROMEDA trial is applicable to all patients regardless of cardiac involvement.

item 5: In the absence of evidence from the ANDROMEDA trial, an assessment of the cost-effectiveness of DBCd relative to BCd for a subpopulation with Mayo Clinic Cardiac Stage IIIb disease remains an area of uncertainty.

4.2.4 Interventions and comparators

4.2.4.1 Summary of company's submission

The intervention is DBCd as per the NICE scope. The cost-effectiveness of DBCd is assessed using the same dose as that used in the ANDROMEDA trial:

- Daratumumab (D): 1800 mg SC once weekly in weeks 1-8, then every two weeks in weeks 9-24, then every four weeks until disease progression or a maximum of 24 cycles.
- Bortezomib (B) was administered SC at a dose of 1.3 mg/m2 once weekly for six 28-day cycles
- Cyclophosphamide (C) was administered orally at 300 mg/m2 once weekly for six 28-day cycles

- Dexamethasone (d) was administered orally at a total dose of 40 mg weekly for six 28-day cycles

As discussed in Section 2.3, the company restricted the comparison to BCd, where the treatment protocol for BCd in the model was the same for both the DBCd and BCd groups.

4.2.4.2 Points for critique

As discussed in Section 2.3, the ERG is satisfied that restricting the comparators to BCd only is appropriate given that the majority of newly diagnosed patients are treated with BCd as first-line therapy in UK clinical practice.

The ERG notes that daratumumab's SmPC does not include a 24-cycle discontinuation criterion,[17] which is included in the model (following the ANDROMEDA trial protocol[21]). It is not clear what was the proportion of patients on treatment at 24 cycles in the ANDROMEDA trial, who discontinued treatment due to the maximum treatment duration in the protocol. The ERG clinical advisors commented that patients are unlikely to continue treatment beyond 24 cycles due to lack of evidence about longer treatment durations. The ERG clinical advisors noted that, if there was an option of continuing beyond 24 cycles, the majority of patients who are still on daratumumab treatment at this point are likely to be tolerating the drug reasonably well and not have progressed; hence may remain on daratumumab treatment. If patients continue to receive daratumumab beyond 24 cycles in practice, the costs of treatment in the model may be underestimated. Given the lack of evidence on the effect of continuing daratumumab treatment beyond 24 cycles, the impact on health outcomes is unclear. The model structure is not sufficiently flexible to permit daratumumab monotherapy to continue for more than 24 cycles.

> ***item 6: The company's base-case assumption that patients receive daratumumab monotherapy (following a positive response to DBCd at the assessment timepoint) for up to a maximum of 24 cycles (mean treatment duration = [redacted] cycles), as observed in the ANDROMEDA trial, may underestimate costs if some patients continue daratumumab for longer, which the SmPC permits. The effect on QALYs is unclear.***

4.2.5 Perspective, time horizon and discounting

4.2.5.1 Summary of company's submission

The analysis is conducted from the perspective of the NHS and PSS over a 35-year lifetime horizon, at which point the model predicts that 99% of the patient cohort have died.

4.2.5.2 Points for critique

The company's submission adheres to the NICE Methods Guide[27] and the approach used by the company is appropriate.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Summary of company's submission

The model includes four elements related to treatment effectiveness and extrapolation of effects over the long-term, which are discussed below in turn: (i) the distribution of patients by depth of haematologic response; (ii) overall survival (i.e. probability of all-cause death) by depth of haematologic response; (iii) the probability of progression to end-stage organ disease; and (iv) the probability of progression to second-line therapy. The efficacy of DBCd compared to BCd is assessed based on the distribution of patients by depth of haematologic response at the assessment timepoint of six cycles in the base case analysis (and three cycles in a scenario analysis). The depth of haematologic response achieved at the assessment timepoint is assumed to predict treatment-specific overall survival, progression to end-stage organ disease, and to second-line therapy over the long-term.

Depth of haematologic response

Figure 4 shows the difference in the distribution of patients by depth of haematologic response (CR, VGPR, PR and NR) and in the proportion of patients who died between the DBCd and BCd arms of the ANDROMEDA trial when the assessment of response occurs after six treatment cycles (company's base-case) or after three cycles (company's scenario analysis). DBCd compared to BCd increases the proportion of patients who achieve CR and reduces the proportion who achieve PR or NR, with a smaller difference in the proportion of patients who achieve VGPR or death, after both six and three treatment cycles. After three treatment cycles, the difference in depth of haematologic response between DBCd and BCd is less pronounced compared to six-cycles.

Figure 4: Difference in haematologic response and proportion of patients who died when the response assessment is at six (base-case) or three cycles (scenario).

Figure plotted using data presented in Tables 40 and 41 of CS p106-107.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

In response to ERG points for clarification, the company explained that the distribution of patients by haematologic response used in the model referred to the 30-day window specific per cycle as follows: Day 0–30 for Cycle 1, Day 31–61 for Cycle 2, Day 62–91 for Cycle 3, Day 92–121 for Cycle 4, Day 122–152 for Cycle 5, and Days 153-213 for Cycle 6. The proportions were calculated in terms of the number of patients in the ITT analysis dataset (DBCd: N=195; BCd: N=193). The patients who were not recorded as having one of the four categories of haematologic response, or as having died, were assigned as NR (see company's response to ERG points for clarification document, B6.1 p33). The

patients who switched to a subsequent non-cross resistant anti-plasma cell therapy were considered to have NR from that point onwards (see company's response to ERG points for clarification document, B6.2 p33).

Also, in their response to ERG points for clarification, the company compared the haematologic response distribution at six months for patients in the ANDROMEDA trial, allocated to the BCd arm, to the distribution at six months for patients in the ALchemy study (see company's response to ERG points for clarification document, B3.2 p26). The company noted that: "*a higher proportion of patients in the BCd arm of the ANDROMEDA trial had a very good partial response than complete haematologic response at six months, although response rates were generally lower in ANDROMEDA than reported in Ravichandran et al., (2021).*" (company's response to ERG points for clarification document, p27). The ERG requested a scenario be provided which used the haematologic response distribution for BCd from the ALchemy study as a baseline in the model,[1] with depth of response for the daratumumab-based regimen calculated from relative risk (or odds ratios) estimated from a comparison of DBCd and BCd from the ANDROMEDA trial and applied to the baseline haematologic response distribution for BCd obtained from the ALchemy study. In response, the Company stated that it was unable to provide this scenario within the timeframe of points for clarification, but that inclusion of these data would be investigated in time for the Technical Engagement step of the appraisal process (see company's response to ERG points for clarification document, B3.3 p27).

Overall survival

After the response assessment timepoint, overall survival in the model over the long-term is independent of treatment received and only depends on depth of haematologic response, i.e., the distribution of haematologic response achieved at the response assessment timepoint is assumed to predict treatment-specific overall survival over time.

In the base-case analysis, Palladini et al. (2012) is used to inform the probability of death over time, stratified by depth of haematologic response at six cycles,[5] while Kastritis et al (2021) is used in a scenario analysis for response assessment after three cycles.[4] Palladini et al. is a retrospective study of 816 AL amyloidosis patients from seven referral centres in the US and Europe, including the UK (median follow-up was 33 months), which reports overall survival data following either a 6-month and 3-month response assessment timepoint.[5] Kastritis et al. is a retrospective study of 227 newly diagnosed patients treated with bortezomib-based regimens in Greece (median follow-up was 48 months), which reports overall survival following either a 3-month and 1-month response assessment timepoint.[4] Both studies were identified by the company from a targeted literature search, but no details on how the search was conducted are reported in the CS. The company justified the choice of

Palladini et al[5] to inform the base-case analysis because of the inclusion of UK patients, larger sample size, and alignment with the six-cycle response assessment timepoint.

In order to obtain long-term data on probability of death over time, the company extrapolated the overall survival Kaplan-Meier data from these studies by fitting different parametric survival models. This was achieved by (1) digitising the published Kaplan-Meier curves on overall survival; (2) recreating the individual patient level data from the digitised curves and number at risk in each time period;[32] and (3) fitting standard parametric survival models to the recreated individual level data. The company states that the selection of parametric models for the base-case analysis was based on visual inspection of fit, statistical goodness of fit, and face validity according to UK expert clinicians.

Table 18 summarises the parametric survival models selected to inform the base-case and scenario analyses stratified by depth of haematologic response, together with the rationale given in the CS for their choice.

Table 18: Parametric survival models informing the probability of death (overall survival) in the model

Depth of haematologic response	Parametric survival model when the response assessment is at 6-months		Rationale	Parametric survival model when the response assessment is at 3-months	Rationale
	Base-case	Scenario			
Complete response	Gompertz	Not reported but using exponential has the same results as those reported in the company's response to ERG points for clarification.	Gompertz model had the most realistic estimates of survival at 1-year based on expert clinician feedback. Visual inspection suggested similar goodness of fit between parametric models. All curves predicted implausible lifespan. Therefore, the model uses the general population mortality as the minimum value for the probability of death.	Exponential	Expert clinicians preferred the exponential curve given survival at 1-year. The exponential curve had the best statistical fit to the observed data.
Very good partial response	Log-normal	Exponential	Log-normal model had the most realistic estimates of survival at 1-year based on expert clinician feedback. Exponential model had the best statistical goodness of fit.	Exponential	Expert clinicians preferred the exponential curve given survival at 1-year, although all curves were found to be relatively optimistic.
Partial or no response	Log-normal	Weibull	Log-normal model had the most realistic estimates of survival at 1-year based on expert clinician feedback. Similar statistical goodness of fit between models.	Generalised Gamma	Expert clinicians preferred the generalised gamma curve given survival at 1-year, although all curves were found to be relatively optimistic.

One important point to note is that the probability of death in the model is calculated as the maximum between the probability of death obtained from parametric survival models and the probability of death from sex- and age-matched general population values in order to ensure that the death rate in the model was equal or above that of the general population, i.e., predicted survival could not exceed general population survival.

Figure 5 shows the extrapolated overall survival curves over time by haematologic response status. The Kaplan-Meier curves are in full, the parametric extrapolations are in dashed lines, and the overall survival curves which relate to the probability of death in the model are in dotted lines; the general population survival curve is presented as the full line in black, for comparison.

Figure 5: Overall survival curve extrapolations in the company's base-case (response assessment after six treatment cycles), adapted from the company's model

Abbreviations: CR: complete response; NR: no response; KM: Kaplan-Meier; OS; overall survival PR: partial response; VGPR: very good partial response.

The stepped curves represent the Kaplan-Meier data obtained from the digitisation and recreation of individual patient level data from Palladini et al (2012)[5], while the curves with dashed lines represent

the extrapolated survival curves. The curve labelled 'CR (model)' is the adjusted overall survival curve for CR used in the model, where the adjustment is made to ensure that the survival curve is not greater than the general population mortality risk. The general population mortality curve is presented in black to aid comparison.

In the model, the probability of death does not enter the transition matrix that informs the transitions between health states. In other words, the source of overall survival by haematologic response cannot inform which health states in the model that the deaths occurred in. Instead, the probability of death determines the proportion of the cohort alive at each cycle, by depth of haematologic response, with deaths being apportioned to the health states separately. The distribution of deaths by health state was based on the state-specific probability of death from the ANDROMEDA trial (IA1 analysis; see CS Tables 45-46, p115). The distribution of deaths in cycles 4-6 is used for cycles 4-6 when the assessment of response is after three cycles (company's scenario analysis), with the distribution in cycles 7+ used in the model to apportion the deaths by health states for cycles 7+. This means that the mortality distribution among health states is assumed to be the same regardless of treatment received or depth of haematologic response.

The company's submission refers to the EMN23 study as a potential source of data on overall survival. The EMN23 study is a retrospective study of AL amyloidosis in 10 European countries with 3,065 patients, 55% of whom were from the UK. The company stated: "*The company are currently working to incorporate these data into the model such that an analysis can be provided as soon as possible for the appraisal*" (company's submission document B, p98). In response to ERG points for clarification, the company stated that: "*OS data by haematologic response from the EMN23 study are anticipated to be incorporated into an updated version of the cost-effectiveness model by the time of Technical Engagement*" (see company's response to ERG points for clarification document, B1.1 p15). The company added: "[redacted]" (company's response to ERG points for clarification document, B1.2 p15). [redacted] (see company's response to ERG points for clarification document, B1.4 Table 7 p20).

Progression to end-stage organ disease

In the model, patients can progress to the health state 'End-stage organ failure' from any of the (alive) health states following the response assessment. The company calculated the probability of progression to 'End-stage organ failure' using time to MOD-PFS data from the ANDROMEDA trial (IA1 analysis), stratified by depth of haematologic response at three months, excluding deaths, assuming constant probabilities over time. To calculate the transition probabilities from each health

state to the state of 'End-stage organ failure', the company multiplied the probability of progression given the specific level of haematologic response by the proportion of MOD-PFS events that occurred whilst a patient was on that line of treatment in the ANDROMEDA trial. The probabilities are reported in the CS Table 47 (p118). The calculations and assumptions are explained in the company's response to ERG points for clarification document (see B6.3 p34-35 and B9.3 p47, respectively). Specifically, the company justified assuming constant transition probabilities given that the MOD-PFS-free survival curves suggested a constant hazard rate. The company argued that the inclusion of all MOD-PFS events excluding deaths (that is, all first-described incidences of end-stage renal failure, end-stage cardiac failure, and haematologic progression) was unlikely to overestimate the number of end-state organ disease events as haematologic progression typically precedes and may lead to major organ deterioration. The assumption that the transition probabilities from 'On second line treatment' to 'End-stage organ failure' were the same as the transition probabilities from 'On first-line treatment' was required due to the small number of events; the company notes that this is likely to be a conservative assumption.

Progression to second line therapy

In the model, patients who achieve PR or NR at the response assessment time point progress to the health state 'On second line treatment' unless progression to the state 'End-stage organ failure' or 'Death' has occurred. Patients who achieve CR or VGPR, who transit to the health state 'Off-treatment or on fixed daratumumab therapy' are at risk of progressing to the health state 'On second line treatment' in each model cycle. The company calculated the probability of progression to second-line therapy using time to subsequent non-cross resistant anti-plasma cell therapy data from the ANDROMEDA trial (12-month landmark analysis), stratified by depth of haematologic response. The stratification was based on haematologic response after three cycles due to a larger sample size compared to stratification after six cycles. A constant transition probability was deemed a reasonable assumption for pragmatic reasons. The probabilities are reported in the CS Tables 48-49 (p120-121).

4.2.6.2 Points for critique

The CS provides the rationale for the selection of data sources and methodology used to inform treatment effectiveness in the model. In general terms, the ERG considers the company's approach to treatment effectiveness as appropriate, but there are a number of limitations that may favour the cost-effectiveness of DBCd relative to BCd and increase the uncertainty surrounding the decision. These concerns relate to the inputs informing: (i) the depth of haematologic response at the assessment timepoint, (ii) the probability of death (or overall survival), and (iii) the probability of progression to the state 'End-stage organ failure'.

Depth of haematologic response

The ERG considers that the ANDROMEDA trial provides the best source of data for assessing the relative effectiveness of DBCd compared to BCd; however, it does not necessarily represent the expected absolute outcomes (i.e., distribution of patients by depth of haematologic response) for DBCd and BCd that would be observed in UK clinical practice. The ERG considers the ALchemy study to be a better representation of baseline haematologic response distribution for BCd, at the relevant response assessment timepoint, in UK clinical practice.[1] This is because the ALchemy study includes a large proportion of all patients with newly diagnosed AL amyloidosis in the UK, and all treated with upfront bortezomib-based regimens, while the ANDROMEDA trial was not designed specifically to reflect the absolute outcomes in the UK population, but rather to compare outcomes (and estimate relative effects) across balanced groups. Furthermore, the ERG clinical advisors considered that the ALchemy study reflects the standard of care in the UK better than the EMN23 study. This is because some countries have a slightly different standard of care (e.g. using melphalan early and switch if poor response) and assessment of response occurs at different timepoints in different countries (e.g. in France, the haematologic response assessment is typically undertaken at 1 month for patients with cardiac AL). As noted by the company, there are some differences between the response rates observed in the BCd arm of the ANDROMEDA trial and those of the ALchemy study. This suggests that the absolute outcomes observed in the ANDROMEDA trial (i.e. distribution of patients by haematologic response category) may not generalise to the UK setting, even if the relative effectiveness of DBCd vs BCd is considered generalisable.

To estimate the distribution of patients by depth of haematologic response for DBCd in the UK population, the ERG considers that the most appropriate approach is to apply the relative effectiveness estimates of DBCd vs. BCd from the ANDROMEDA trial to the baseline distribution for BCd from the ALchemy study. This approach follows the recommendations presented in the NICE Technical Support Document 5 that supports the use of baseline outcomes relevant to the healthcare setting as the absolute natural history under standard treatment to which the relative treatment effects from an RCT are applied to obtain absolute outcomes under the treatment arm.[6] This assumes that the relative effectiveness of DBCd vs BCd, as observed in the ANDROMEDA trial, generalises to the UK setting, but it does not require the assumption that absolute outcomes in the BCd arm of the trial generalises to the UK as an alternative UK baseline is available from the ALchemy study.

Furthermore, using the ALchemy study to inform the distribution of patients by depth of haematologic response for BCd (baseline) is expected to align better with the population in whom the company seeks a recommendation. As discussed in Section 2.2.2, the company seeks a recommendation in all patients with newly diagnosed AL amyloidosis, as per the NICE scope, including patients with Mayo Clinic Cardiac Stage IIIb. While the ANDROMEDA trial excluded patients with Mayo Clinic Cardiac

Stage IIIb, the ALchemy study includes 15.4% (184/1194) of patients with Stage IIIb disease.[1] The ERG clinical advisors suggested that DBCd (when compared to BCd) would be expected to have the same (or similar) relative treatment effect in patients with Mayo Clinic Cardiac Stage IIIb to that identified for patients in the ANDROMEDA trial, i.e., absolute survival outcomes will differ for patients with Mayo Clinic Cardiac Stage IIIb by depth of haematologic response but a similar relative increase for DBCd compared to BCd would be expected for the probability that patients achieve complete response status conditional on survival to the response assessment timepoint.

> ***item 7. The ERG considers the ALchemy study[1] to be the most relevant source to inform the baseline haematologic response distribution for BCd, at the relevant response assessment timepoint, while the distribution for DBCd is informed by the relative treatment effect from the ANDROMEDA trial and applied to the haematologic response distribution for BCd from the ALchemy study.***

Overall survival

The ERG considers that the ALchemy study provides the best available evidence on the long-term outcomes of UK patients with newly diagnosed AL amyloidosis. As discussed previously, this study includes 1,194 newly diagnosed UK patients with AL amyloidosis who were treated with first-line bortezomib based-regimens between 2010-2019 at the UK National Amyloidosis Centre, and provides haematologic response status at one-, three- and six-months following initiation of first-line treatment. It also provides the respective Kaplan-Meier curves for overall survival, stratified by depth of haematologic response. [1] Therefore, the ALchemy study is expected to represent the best source of long-term outcomes for UK patients as seen in clinical practice, in line with recent past practices and current guidelines for the management of newly diagnosed AL amyloidosis. In contrast, and as discussed previously and in Section 3.6, the studies that the company uses to inform overall survival are mostly set in countries other than the UK, [4, 5] and in the study used in the base-case (Palladini et al., 2012[5]), patients were treated between 2002-2010 with migratorily regimens other than bortezomib.

The ALchemy study[1] is also expected to be more generalisable to the UK than the [redacted] of the EMN23 study that the company is planning to use as a basis for informing overall survival in the model at Technical Engagement for the following reasons: Firstly, [redacted], while all patients in the ALchemy study[1] were treated with upfront bortezomib-based regimens, which is the main first-line treatment regimen used in the UK. Secondly, of the entire EMN23 study, 55% (1,690/3,065) of patients were from the UK (see response to ERG points for clarification document, p16), while it is not clear what proportion from the UK is included in the [redacted]. Thirdly, and as discussed earlier, the ERG clinical advisors considered the ALchemy study to be a better reflection of the standard of care seen in

the UK than the EMN23 study, which includes countries with slightly different treatment protocols. Fourthly, the ALchemy study includes 15.4% of patients with Mayo Clinic Cardiac Stage IIIb,[1] in whom the company seeks a recommendation. Furthermore, using the ALchemy study[1] for the baseline distribution by depth of haematologic response alongside overall survival allows for consistency in the distribution of other prognostic factors, such as Mayo Clinic Stage (as discussed in Section 4.2.2.2). For these reasons, the ERG considers that the ALchemy study[1] is the best source of evidence to inform overall survival in the model.

> ***item 8. The ALchemy study[1] is the best source of available evidence to inform overall survival, stratified by depth of haematologic response, to inform expected outcomes in UK clinical practice.***

The ERG has major concerns that the company's base-case analysis, with the response assessment informed after six treatment cycles and overall survival informed by Palladini et al (2012),[5] overestimates overall survival for UK patients with CR. In the model, the probability of death is estimated as the largest of the hazard rate predicted by the survival curves and the age- and sex-matched general population mortality (see Figure 5 for reference). This results in the company's base-case using the age- and sex-matched general population hazard rate to inform the probability of death of patients with CR from approximately 4.4 years onwards from the timepoint of response assessment, which is unlikely to be plausible in UK clinical practice, i.e., it effectively assumes that patients treated for newly diagnosed AL amyloidosis with first-line treatment and achieving CR have the same mortality risk as the age- and sex-matched general population from 4.4 years following response assessment. Since a greater proportion of patients achieve CR with DBCd in the model, this approach is likely to favour the cost-effectiveness of DBCd relative to BCd.

> ***item 9. Overall survival of patients with CR in the company's base-case analysis (assuming haematologic response assessment after six treatment cycles) is likely to be overestimated.***

Progression to end-stage organ disease and to second-line therapy

The ERG considers the approach used to calculate transition probabilities to the health states of 'End-stage organ failure and 'On second-line treatment', based on data from the ANDROMEDA trial, to be appropriate in the absence of an alternative UK source. The ERG notes that these probabilities are subject to uncertainty given a number of assumptions required to estimate them and the small number of events on which they are based. However, the impact of this uncertainty on the cost-effectiveness results is expected to be small (for example, multiplying all transition probabilities to the health state of 'end-stage organ disease' by 10 reduces the ICER by £1,333/QALY).

4.2.7 Safety

4.2.7.1 Summary of company's submission

The model includes treatment-specific adverse events based on those classified as Grade 3 or 4 with a minimum incidence of 5% in either arm of the ANDROMEDA trial (see Table 51, p123 of CS). Adverse events affect both costs and QALYs in the model with a one-off QALY reduction and cost increase assumed to occur in the first cycle of the model. These are summarised in Section 4.2.8 Health related quality of life (for the QALY reductions) and Section 4.2.9 Resource use and costs (for the cost increases).

4.2.7.2 Points for critique

The ERG has no major concerns with the approach used by the company to model adverse events.

4.2.8 Health related quality of life

4.2.8.1 Summary of company's submission

The CS considers health-related quality of life (or health state utility values) related to (i) depth of haematologic response (CR, VGPR, PR/NR); (ii) utility decrements due to progression to second-line therapy, end-stage organ failure and haemodialysis; and (iii) utility decrements associated with treatment-related adverse events.

The company conducted a systematic literature review to identify studies that reported health-related quality of life data for patients with AL amyloidosis, or mapping algorithms to derive utility values (see CS Appendix H). Thirteen studies were identified for data-extraction: three RCTs (including the ANDROMEDA trial) and ten observational studies, with six studies focused on newly diagnosed or treatment-naïve patients. No studies reported EQ-5D utility values (with the exception of the ANDROMEDA trial), but most reported health-related quality of life scores with potential for mapping to utility values: three studies reported EORTC QLQ-C30, one study reported EQ-5D-5L visual analogue scale scores, and 12 studies reported SF-36 scores. Of these studies, one of the studies reporting EORTC QLQ-C30 was based on a UK population,[33] while one study reporting SF-36 included UK patients.[34] The company did not use any of the studies identified in the systematic review to inform health-related quality of life in the model because none of the studies reported EQ-5D utility values and none provided sufficient information to map other health-related quality of life measures, such as SF-36, to EQ-5D.

Utility values for AL amyloidosis patients stratified by depth of haematologic response at the response assessment timepoint (six treatment cycles in the base case analysis) were derived from the ANDROMEDA trial, which collected data using the EQ-5D-5L questionnaire. In response to ERG points for clarification, the company updated the approach used in the original CS (Section B.3.4.1 of

Document B) to align with the NICE Reference Case, where EQ-5D-5L data were cross-walked to the EQ-5D-3L based on the algorithm in van Hout et al (2012)[28] and then valued using a UK-specific tariff. The company also presented a scenario analysis where the utility values by haematologic response were elicited from expert clinicians (see CS Table 53 p123).

Once patients enter the health states of 'On second-line treatment' and 'End-stage organ failure', they experience a decrement in utility on a recurring per-cycle basis for the duration that the patient remains in that health state. The utility decrement associated with 'On second-line treatment' was calculated as the difference between the mean utility value at baseline and the mean utility value associated with 'progressive disease' from data collected in the ANDROMEDA trial. The utility decrement associated with 'End-stage organ failure' consisted of two components: (i) a reduction due to end-stage organ failure, calculated as the difference between the mean utility value at baseline in the ANDROMEDA trial and the utility value of patients with advanced heart failure who had been assessed for heart transplant reported in Emin et al (2016)[35]; and (ii) a reduction due to haemodialysis, which was obtained from a published systematic literature review of utilities related to chronic kidney disease treatments (Wyld et al (2012)[36], multiplied by the proportion of patients who are expected to have haemodialysis of [redacted]% (obtained from a modified Delphi panel of expert clinicians).

Table 19 summarises the utility values used in the company's updated cost-effectiveness analysis at response to ERG points for clarification.

Table 19: Utility values used in the model (updated at response to ERG points for clarification)

Item	Model input	Sources
Health states 'On first line therapy' and Off treatment or on fixed daratumumab therapy'		
Complete response (CR)	[redacted]	For CR and PR/NR the utility values were estimated from the EQ-5D-5L data collected directly from patients in the ANDROMEDA trial and valued with UK tariff using the van Hout et al (2012)[28] algorithm (see Table 35, p55 of response to ERG point for clarification document). For VGPR, the values were calculated as the mean of the values for CR and PR/NR, as the mean value for VGPR ([redacted]) was lower than the mean value for PR/NR.
Very good partial response (VGPR)	[redacted]	
Partial or no response (PR/NR)	[redacted]	
Health state 'On second line therapy'		
Complete response (CR)	[redacted]	Based on the utility on 'first line therapy', reduced by the disutility associated with second line therapy of [redacted] (see p56 of response to ERG point for clarification document). This disutility associated with second line therapy was estimated as the difference between the mean baseline utility score ([redacted]) and the mean utility value associated with 'progressive disease' in the ANDROMEDA trial.
Very good partial response (VGPR)	[redacted]	
Partial response or no response (PR/NR)	[redacted]	
Health state 'End-stage organ failure		

Complete response (CR)	[redacted]	Based on the utility on 'first line therapy', reduced by the disutility due to end-stage organ failure ([redacted] (see p56 of response to ERG point for clarification document) and disutility due to haemodialysis (0.10)[36] given the proportion of patients who have haemodialysis ([redacted] %; obtained from the modified Delphi panel of expert clinicians[14]). The disutility due to end-stage organ failure was estimated as the difference between the mean baseline utility in the ANDROMEDA trial ([redacted]) and the utility of patients with chronic heart failure that had been assessed for heart transplant (0.5).[35]
Very good partial response (VGPR)	[redacted]	
Partial response or no response (PR/NR)	[redacted]	
One-off reduction in quality-adjusted life years due to adverse events		
DBCd	0.0029	Based on the disutility related to specific adverse events (see CS Table 56 p126), their incidence in the ANDROMEDA trial (see CS Table 51 p123), and assuming that adverse events affect utility over 21 days.
BCd	0.0020	
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone.		

4.2.8.2 Points for critique

The approach used by the company to estimate health-related quality of life is considered to be generally appropriate. However, there are a number of concerns related to the utility values used in the model. Firstly, the EQ-5D utility values derived from the ANDROMEDA trial are limited to a very short period of assessment. In the ANDROMEDA trial, EQ-5D-5L data were only gathered for the period of time in which patients received treatment. This means that there is no available data for patients in the BCd arm of the trial after six treatment cycles, when treatment with BCd was stopped. EQ-5D-5L data was collected beyond cycle six in the DBCd arm of the trial because these patients received daratumumab monotherapy. The data from cycle 7 onwards indicates an improvement in EQ-5D-5L utility values over time but this data is limited to the DBCd arm and involves a decreasing number of patients with recorded values over time. The lack of data for the BCd arm after cycle six precludes a comparison with DBCd after this timepoint. As a result, the utility values used in the model were derived using the mean of EQ-5D-5L data across the first six treatment cycles only and across both treatment arms, stratified by depth of haematologic response (CR, VGPR and PR/NR). Secondly, the mean EQ-5D utility value for VGPR derived from the trial data was lower than that for PR/NR ([redacted] and [redacted], respectively). Due to the lack of face validity of the utility value for VGPR, the company used the mean of the CR and PR/NR values (note this appears to be a weighted mean although details are not provided in the CS) to derive a value for VGPR of [redacted]. In response to ERG points for clarification, the company indicates that several factors could contribute to the lower mean utility value for VGPR compared to PR/NR in the ANDROMEDA trial: (i) the early timepoint at which utility values were recorded in the trial may mean that the benefits of differing levels of treatment response on health-related quality of life are not adequately captured; and (ii) a lack of

sensitivity of the EQ-5D instrument may preclude a clear differentiation in mean utility values by depth of haematologic response. The ERG clinical advisors supported the view that improvements in health-related quality of life would be expected to peak at approximately nine to 12 months from the point of treatment initiation and continue to improve for a further 2-3 years, but at a much slower pace, before stabilising. This may suggest that the early timepoint of up to six treatment cycles in the ANDROMEDA trial is not sufficiently long to capture the impact of treatment on health-related quality of life. As a consequence, the utility values applied in the model by depth of haematologic response are highly uncertain. This is further exacerbated by the fact that survival in the model is stratified by the distribution of haematologic response achieved at the response assessment timepoint and therefore the utility values by depth of haematologic response are extrapolated over the long-term.

In the absence of alternative data to inform the utility values, the company conducted an exploratory scenario analysis to elicit utility values from expert clinicians for utility at baseline and at three months, six months and one-year post-treatment. However, very few details were provided in the CS on the derivation of the values derived from expert clinicians. Furthermore, the ERG notes that the NICE Reference Case specifies that health-related quality of life, or changes in health-related quality of life, should be measured directly by patients. When this is not possible the Reference Case states that data should be obtained from the person who acts as their carer in preference to healthcare professionals. It is further reinforced that in some circumstances where EQ-5D data may not be the most appropriate source, alternative health-related quality of life measures should be accompanied by a carefully detailed account of the methods used to generate the data, their validity, and how these methods affect the utility values.[27] The company have not provided adequately justified alternative utility values. Furthermore, the baseline utility value of [redacted] used in the scenario analysis from expert clinicians is considerably lower than that obtained from the ANDROMEDA trial of [redacted] suggesting either a lack of face validity of the values derived from expert clinicians or a lack of validity of the EQ-5D values from the trial, even for baseline mean utility.

The ERG notes that health-related quality of life data in the form of SF-36v2 scores has been collected from patients in the ALchemy study at baseline and response assessment study visits of 3-, 6- and 12-months. Although the outcomes of this data are not yet publicly available, it is likely to represent an important source to validate the EQ-5D utility values from the ANDROMEDA trial. For example, it should be possible to map, even where individual level data are not available, the SF-36 data to EQ-5D using the algorithm by Ara et al (2008).[8] The ERG explored this option in relation to obtaining the eight mean absolute SF-36 summary dimension scores from ALchemy at baseline and follow-up time points but it was not possible to obtain this data within the timescales of submitting the ERG report.

item 10. The utility values applied in the model by depth of haematologic response are highly uncertain.

A third concern in relation to the health-related quality of life utility values used in the model relates to the utility decrements for the progression-related health states of 'On second-line treatment' and 'End-stage organ failure'. For second-line treatment the utility decrement of [redacted] was based on the difference between the mean baseline utility score and the mean utility value associated with 'progressive disease' from the ANDROMEDA trial. The definition of progression disease in this context is unclear. At response to ERG points for clarification, the company stated that for each subject that had at least one haematologic answer as 'progressive disease' ([redacted]), the individual decrement in utility was calculated by comparing utility data before and after reaching the progressive disease state and then the mean was calculated over all individual decrements to derive a disutility associated with second-line treatment. The ERG is concerned that this decrement is based on a very small sample size and a loosely defined definition of progression that is subsequently used to inform the utility values for patients on second-line therapies. Furthermore, the method of implementing a disutility for this health state in the model implies that patients on second-line therapy have different utility values depending on their depth of haematologic response achieved with first-line therapy, i.e., those who respond better to treatment at first-line (e.g., CR or VGPR) who subsequently progress to second-line treatment, due to lack of treatment response with first-line therapies, are assumed to have a better quality of life on second-line therapies than those on second-line treatment with poorer response with first-line therapies (e.g., PR/NR). The ERG believes that this may not be the case given that some patients with PR to first-line therapies may achieve CR or VGPR with second-line therapies. This latter issue is considered further in Section 6 of ERG additional analyses.

For the state 'End-stage organ failure', the disutility value of [redacted] was derived by subtracting the utility score associated with patients assessed for heart transplant in a UK-based study by Emin et al. (2016)[35] from the ANDROMEDA baseline utility score. Although the company did not report a systematic literature review to identify health-related quality of life utility values for patients with advanced chronic heart failure, the ERG has identified a recent review of health state utility values for patients with heart failure.[37] This review supports the company's choice of Emin et al. (2016)[35] as a relevant source of UK-based EQ-5D data for patients with advanced heart failure. However, the ERG notes that using this study to derive a disutility value for the state 'End-stage organ failure' involves the assumption that the baseline utility of patients with advanced heart failure in Emin et al. (2016)[35] would have the same baseline utility of patients in the ANDROMEDA trial if they did not have advanced heart failure, with the same health conditions, age and gender distribution as patients in the ANDROMEDA trial. Given the difference between end-stage organ failure due to AL amyloidosis and advanced heart failure, it is difficult to assess the validity of this assumption. An alternative

approach would be to calculate the increase in utility, reported in Emin et al (2016),[35] for patients assessed for heart transplantation (EQ-5D index score of 0.50) to post-transplantation (EQ-5D index score of 0.74) and assume that it represents the disutility due to advanced heart failure. This results in a disutility value of 0.24, which, when compared to the decrement of [redacted] applied in the model, has minimal impact on the ICER results. The ERG's main concern related to the utility values for the state 'End-stage organ failure' is the use of a decrement applied to utility values conditional on response to first-line treatment, which implies that patients with end-stage organ failure have different utility values depending on their depth of haematologic response achieved with first-line therapies, i.e., a higher utility value for end-stage organ failure is incorporated in the model for patients who previously responded better to treatment with first-line therapies (e.g., CR or VGPR) compared to patients who did not respond well to treatment at first-line (PR/NR). The ERG believes that all patients with end-stage organ failure should have the same utility value, whilst in this health state, irrespective of previous response to treatment or previous lines of therapy. This issue is considered further in Section 6 of ERG additional analyses.

item 11. The utility decrements for the progression-related health states of second-line treatment and end-stage organ failure are conditional on response to first-line treatment, but it is unclear why patients in these health states would not have the same utility value, irrespective of previous response to treatment or previous lines of therapy.

A fourth concern in relation to the health-related quality of life utility values used in the base-case analysis is the assumption that these values are not age-dependent over time. A more appropriate approach involves reflecting the decreasing utility of patients as they age through the model over time.[7] The model permits this option but it was not selected in the base-case analysis. This issue has been addressed in the ERG's base-case in Section 6.

item 12. Age-adjusted utility values should be incorporated in the model to reflect the decreasing utility of patients as they age through the model over time.

A fifth concern relates to the inappropriate use of arbitrary standard errors for utility values used in the probabilistic sensitivity analysis. Following response to ERG points for clarification, the company revised the standard errors for the utility values used in the model to reflect the variation from the mean value and the available sample size from the ANDROMEDA trial (see p58 of response to ERG point for clarification document). Although these have been implemented appropriately in the updated model following ERG points for clarification, the ERG has some remaining concerns that the standard deviation and standard error has been confused for the uncertainty estimates on mean utility values used in the model. However, the implications on the probabilistic ICER results are minimal.

At points for clarification, the ERG requested further details in relation to the utility decrements associated with dialysis, organ transplant and adverse events included in the model. The ERG is satisfied with the response and expects these utility decrements to have minimal impact on ICER results.

4.2.9 Resource use and costs

4.2.9.1 Summary of company's submission

The CS includes costs related to (i) first-line drug acquisition costs; (ii) drug administration costs; (iii) co-medication and adverse event costs; (iv) second-line treatment costs (and third line treatment costs in a scenario analysis); and (v) costs associated with disease monitoring and management.

The company conducted a systematic literature review to identify healthcare resource use data for newly diagnosed AL amyloidosis. Two studies were identified that included data from UK patients: McCausland et al (2019), which was an international study with UK centres, and Attwood et al (2019),[38] which reported outcomes related to eight UK patients with cardiac AL amyloidosis.[34] Neither study was used to inform resource use and costs in the model.

The company based the estimates of the use of healthcare services mostly from a modified Delphi panel with seven UK-based clinical experts, complemented with data from the ANDROMEDA trial. Unit costs were obtained from national sources.[9, 12, 29]

Table 20 summarises the costs included in the model. The cost of first-line drug therapy, administration, and co-medication depend on time on treatment. The base-case analysis uses the ITT mean treatment duration as observed in the ANDROMEDA trial (12-month landmark analysis), corresponding to [redacted] cycles for DBCd and [redacted] cycles for BCd.

Table 20: Costs used in the model

Item	Model input	Sources
First-line drug therapy costs per cycle		
DBCd cycles 1-2	[redacted]	Calculated based on the dosage of DBCd and BCd from the ANDROMEDA trial (see CS Table 59 p129), the cohort average body surface area (see CS Table 39 p106), mean relative dose intensity (see CS Table 60 p129), and unit costs (see CS Table 61 p131) including vial wastage. Includes confidential PAS discount for daratumumab (confidential price is £[redacted] per vial with 1800mg daratumumab).
DBCd cycles 3-6	[redacted]	
DBCd cycles 7+	[redacted]	
BCd	£ 1,159.95	
First-line administration costs per cycle		
DBCd cycles 1-2	£ 24.64	Calculated based on the frequency of subcutaneous injections, 5 minutes median time to administer
DBCd cycles 3-6	£ 18.48	

DBCd cycles 7+	£ 3.08	daratumumab,[23] and on the cost per hour of a band five nurse (£37)[9] per subcutaneous injection (see CS Table 64 p131). Oral drugs were assumed to have zero administration costs.
BCd	£ 12.32	
First-line co-medication costs per cycle		
While on first-line therapy with DBCd	£ 6.22	Calculated based on the concomitant medications recorded in the ANDROMEDA trial [23] which were recommended or required for all patients (see CS Table 65 p132), and the unit costs from national sources (see CS Table 66 p132).
While on first-line therapy with BCd	£ 2.33	
First-line adverse event costs; one-off cost		
First-line therapy with DBCd	£ 1,269.83	Calculated based on the proportion of patients experiencing adverse events in the ANDROMEDA trial (see CS Table 51 p123) and the unit cost for a non-elective long stay for the specific adverse events (see CS Table 79 p139).[29].
First-line therapy with BCd	£ 1,081.16	
Disease monitoring costs per cycle		
Health state 'On first-line therapy'	£ 297.66	Calculated based on the frequency of monitoring tests elicited via the modified Delphi panel of UK expert clinicians[14] (see CS Table 68 p134) and unit costs from national sources (see CS Table 67 p133).
Health state 'Off Treatment/Fixed Daratumumab Therapy' while on daratumumab monotherapy	£ 311.35	
Health state 'Off Treatment/Fixed Daratumumab Therapy' while off treatment	£ 167.33	
Hospital visits by state per cycle		
Health state 'On first-line therapy'	£ 145.70	Calculated given the frequency of visits to hospital elicited via the modified Delphi panel of UK expert clinicians[14] (see CS Table 70 p136) and unit costs from national sources (see CS Table 69 135).
Health state 'Off treatment/fixed daratumumab therapy'	£ 85.00	
Health state 'On second-line treatment'	£ 206.86	
Health state 'End-stage organ failure'	£ 223.36	
Second-line treatment costs (one-off cost at entry into health state 'second line therapy)		
Following first-line therapy with DBCd	£ 41,450.77	Calculated based on the distribution of patients by treatment regimens that were derived from UK clinical expert opinion received at a Janssen-led advisory board[14] (see CS Table 71 p137), their dosing schedule, the cohort mean body weight and body surface area, and publicly available drug prices including wastage.
Following first-line therapy with BCd	£ 41,450.77	
End-stage organ failure costs		
Management costs per cycle	[redacted]	Calculated based on the proportion of patients requiring haemodialysis and peritoneal dialysis and the frequency of sessions elicited from the modified Delphi panel of UK expert clinicians[14] (see CS Table 77 p139), and national unit costs (see CS Table 75 p138).[29]
Transplant and surgical costs (one-off cost)	[redacted]	Calculated based on the proportion of patients who have a heart transplantation, kidney transplantation and cardiac assist device elicited from the modified Delphi panel of UK expert clinicians[14] (see CS Table 78 p139), and national unit costs (see CS Table 76 p138).[29].
End-of-life costs		

One-off cost	£ 3,561.88	Based on Georghiou and Bardsley 2014[39] inflated to 2020.[9]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone.

In the model, patients are assigned the costs of second-line treatments (and third-line treatments in a scenario analysis) when they progress to the health state 'On second-line treatment'. The treatment regimens and the distribution of patients by regimen were elicited from the modified Delphi panel of UK expert clinicians[14] (see CS Table 71 p137), various sources for the dosing schedule, and publicly available drug prices. The ERG notes that some of these drugs are subject to confidential discounts.

The company's approach to implementing the costs of second- and third-line treatments in the model assumes that all patients who progress receive the full dose of subsequent treatments, without accounting for dose adjustments, treatment discontinuation, and deaths that would occur during the course of treatment. Additionally, in the scenario analysis that includes the costs of third-line treatments, the model assumes that all patients who progress to the health state 'On second-line treatment' would receive the full dose of both second- and third-line treatments (again without accounting for dose adjustments, discontinuation and deaths that would occur during the course of treatment). In response to ERG points for clarification that queried this approach, the company explained that it was driven by the limited evidence and the variability in clinical practice for subsequent treatments (see company's response to ERG points for clarification document, B7 question 1, p37-38). The company explained that it was not able to identify data to inform such adjustments and, therefore, the company was unable to present a scenario accounting for dose adjustments, discontinuations, and deaths during the course of treatment.

The model includes the costs of BCd as one of the second-line treatments (10% of patients who progress to second-line treatment) despite this forming first-line treatment. Following the response to ERG points for clarification, the company noted that UK clinical expert feedback suggests that bortezomib-based regimens could be used in second-line, particularly in patients who have had a long response to first-line treatment (see company's response to ERG points for clarification document, B7 question 3, p39-40).

The model does not include the costs of autologous stem cell therapy (ASCT) as part of the subsequent therapies after first-line treatment with DBCd or BCd. In response to ERG points for clarification, the company justified the exclusion of the costs of ASCT given the small proportion of patients who receive ASCT as second- or third-line treatments.

In response to ERG points for clarification, the company presented three additional scenarios regarding the costs of second- and third-line therapies:

- Scenarios that reduced the costs of second-line therapy by varying the reduction between 20% and 70%. The ICER results increased by £432-£1,513/QALY when compared to the company's revised base-case results. When third-line therapy costs are included and second- and third-line therapy costs are reduced between 20% and 70%, the ICER results are increased by £2,167-£7,585/QALY (see company's response to ERG points for clarification document, B7 question 2, p38-39).
- A scenario where bortezomib-based regimens are not included as part of second-line therapy, which reduced the ICER by £200/QALY compared to the company's revised base-case (see company's response to ERG points for clarification document, B7 question 3, p39-40)
- Scenarios using the UK ALchemy study (Ravichandran et al, 2021b)[13] to calculate the costs of second-line therapy based on the therapies used at second-line in the ALchemy study. This increased the ICER by £977/QALY compared to the company's revised base-case result. Cost-effectiveness results for a scenario in which both second- and third-line therapies are informed by Ravichandran et al (2021b) [13]was also presented, which reduced the ICER by £1,436/QALY (see company's response to ERG points for clarification document, B7 question 4, p40-43). The ERG notes that this scenario includes the cost of ASCT assuming that 11% of patients who had second-line therapies and 12% of patients who had third-line therapies received ASCT (unit cost = £15,065)[12].

4.2.9.2 Points for critique

The ERG considers that, in general, the costs informing the model are appropriate but have noted some limitations. Key issues relate to the administration costs associated with first-line therapy, the costs of second- and third-line therapies, the costs of ASCT, and minor issues relating to the costs of first-line therapy.

Administration cost of daratumumab and bortezomib

The model uses the cost of 5 minutes of a band 5 nurse at £3.08[9] and zero cost for cyclophosphamide and dexamethasone, as their administration is oral. The ERG clinical advisors explained that both bortezomib and daratumumab require preparation, and daratumumab requires a period of observation after its administration. After the first dose, the patient is kept under observation for 4 hours, after the second dose for 2 hours and after the third and fourth dose observation for 1 hour, with no observation period required in subsequent doses. The administration of BCd and of DBCd would be conducted as a day case or as an outpatient visit.

The NHS guidance for national cost collection specifies that, in recording the costs of chemotherapy, trusts should use the relevant healthcare resource group (HRG) codes for the procurement of chemotherapy and for the delivery of chemotherapy.[40] The HRG code for procurement of chemotherapy relates to the average cycle and includes all costs associated with procuring each drug cycle and costs of supportive drugs.[10, 40] For bortezomib-based regimens, the HRG codes are as follows:

- For procurement per cycle, the HRG code is bortezomib, dexamethasone and cyclophosphamide SA10Z – Procure Chemotherapy Drugs for regimens in Band, for which the average cost weighted by activity is £2,110.[10, 12]
- For the first delivery of the cycle, the HRG code is SB12Z – Deliver Simple Parental Chemotherapy at First Attendance, for which the average cost weighted by activity is £241.[12]
- For subsequent deliveries in the same cycle, the HRG code is SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle, for which the average cost weighted by activity is £332.[12]

If these HRG codes apply to the subcutaneous delivery of DBCd and BCd, the administration costs used in the model are likely to be an underestimation of the administration costs to the NHS.

> ***item 13. The model may underestimate the administration costs of daratumumab and bortezomib, which is likely to favour the cost-effectiveness of DBCd given its longer treatment duration.***

Approach to the costs of second- and third-line treatments

As noted above, the model assigns the costs of second-line treatments (and third-line treatments in a scenario analysis) when patients progress to the health state 'On second-line treatment'. The ERG considers that this approach may result in the costs of second- and third-line treatments being overestimated because it assumes that all patients who progress to second-line (and third-line in the scenario) therapy receive the full set of treatment cycles, without accounting for deaths, treatment discontinuation and dose adjustments. The ERG notes that the company agrees that this approach overestimates the costs of third-line therapy: "*As not all patients may go on to receive third-line therapy, this may overestimate third-line costs*." (Company submission document B p137). Overestimating the costs of subsequent treatments is likely to favour the cost-effectiveness of DBCd as fewer patients progress to second-line therapy when treated with DBCd at first-line.

> ***item 14. The costs of second-line treatments (and third-line treatments in a scenario analysis) are likely to be overestimated, which is likely to favour the cost-effectiveness of DBCd given that fewer patients progress to second-line therapy when treated with DBCd at first-line.***

The model includes the costs of BCd as one of the second-line therapies. The ERG clinical advisors noted that patients who progress following bortezomib treatment are unlikely to have bortezomib treatment again due to funding constraints, unless they progressed many years after first-line treatment. The ERG notes that the company's scenario where bortezomib-based regimens are not included as part of second-line therapy reduced the ICER by £200/QALY compared to the company's revised base-case results. Therefore, the ERG considers that, although the use of BCd as part of subsequent treatments is an area of uncertainty it is expected to have a minor impact on cost-effectiveness results.

The ERG considers that the company's scenario (in response to ERG points for clarification) where the distribution of patients by type of second- and third-line therapies was obtained from the UK ALchemy study is more likely to reflect UK clinical practice than those derived from UK clinical expert opinion received at a Janssen-led advisory board.[13, 14] This study reports the treatments of patients included in the ALchemy study who were treated with up-front bortezomib-based regimens (and whose long-term outcomes are reported in Ravichandran et al., 2021a).[1] As discussed in Section 4.2.6.2, the ERG considers that the ALchemy study represents a more appropriate source of overall survival by depth of haematologic response given that it reflects outcomes of UK patients treated with up-front bortezomib as per UK clinical practice. Therefore, using the ALchemy study for the type of treatments and distribution of patients receiving these treatments ensures that the costing of subsequent treatments aligns with overall survival in the model.

> ***item 15. To inform the costs of second- and third-line treatments, the ALchemy study is more likely to reflect UK clinical practice, and therefore represents a better source of data to inform the type and distribution of patients receiving second- and third-line therapies.***

To inform the distribution of patients by type of second- and third-line therapies, the company used the ALchemy study for subsequent therapies as reported in Ravichandran et al. (2021b)[13] and calculated the proportion of patients in each treatment with > 1% share and excluded daratumumab. This is appropriate to calculate the distribution of patients by treatment at second-line in the model. However, it is not appropriate to use the distribution of patients by third-line treatment reported in Ravichandran et al. (2021b)[13] without adjustment because of constraints within the company's model structure. The model structure is limited to including only one health state of 'On second-line treatment', i.e., the model structure does not explicitly include a health state for 'On third-line treatment'. Therefore, the costs of subsequent therapies, both second- and third-line, are incorporated in the health state of 'On second-line treatment' at the point of entry to this state. The ERG considers it more appropriate to calculate the distribution of patients by treatment at third-line out of those treated at second-line, i.e., the distribution of patients who have third-line treatment should be relative to the number of patients who received second-line treatment. The impact on costs can be exemplified

with the lenalidomide + dexamethasone regimen. Under the company's approach, and in the scenario analysis including third-line therapy costs, 55% of patients have lenalidomide + dexamethasone at second-line and 58% have it at third-line. In the cost calculation by the company, this means that 113% of patients who progress to second-line therapy in the model have lenalidomide + dexamethasone, which is clearly incorrect.

> ***item 16. To inform the costs of second- and third-line treatments for patients who progress to the health state of 'second-line therapy', the calculation of the distribution of patients who have third-line treatment should be relative to the number of patients who received second-line treatment.***

The ERG notes that some of the drugs used for subsequent treatments are subject to confidential discounts. Therefore, cost-effectiveness results based on confidential prices for these drugs are reported in the confidential appendix.

Cost of autologous stem cell transplantation

The company's base-case analysis does not include the costs of ASCT, although some patients receive it as subsequent therapy. The modified Delphi panel concluded that [redacted]% of patients would have ASCT during the off-treatment period (Table 3 p17) and [redacted]% as part of second line therapy (Table 4 p19).[14] As footnotes to these tables, it is noted that "*Further follow-up with the lead clinician of the Delphi panel indicated that the estimates for ASCT provided by participants were significant over-estimates due to participants likely interpreting the question as asking about the proportion of total patients who receive an ASCT (given an ASCT is only received once by each patient)*", and that more realistic estimates are [redacted]% and [redacted]% respectively.[14] Furthermore, in the ANDROMEDA trial, [redacted]% of patients on BCd and [redacted]% of patients on DBCd had ASCT (see CS, Table 23 p65). In the ALchemy study, where all patients were treated with upfront bortezomib, 87/1194 (7%) patients had an ASCT as part of first-line therapy,[1] while 9% (34/376) had an ASCT as second-line and 3% (10/117) had an ASCT as third-line.[13]

While the model does not include the costs of ASCT in the 'Off-treatment or on fixed daratumumab therapy' health state, the company presented a scenario following ERG points for clarification where the type of treatment and distribution of patients by treatment at second- and third-line therapy is based on the ALchemy study,[13] including ASCT. However, the ERG notes that the cost of ASCT used in the model comprises only the unit cost of the procedure without follow-up costs, therefore, it may represent an underestimation of the costs of ASCT. Nonetheless, this scenario which includes the cost of ASCT is considered better at reflecting the costs in UK clinical practice than excluding these costs from the model as in the company's base-case.

Whether the exclusion of the costs of ASCT affects the cost-effectiveness results depends on the extent to which treatment with DBCd affects the proportion of patients who subsequently have ASCT. The ERG clinical advisors considered that it was very uncertain whether and how treatment with DBCd would affect the proportion of people who subsequently have ASCT. For example, DBCd may reduce it by increasing the proportion of patients who achieve CR, precluding the need for ASCT. Conversely, DBCd may increase it if the patients who have not achieved a good haematologic response and are fit enough may be more likely to undergo this procedure, as other second-line therapies are less effective. The ERG clinical advisors emphasised that the number of patients considered for ASCT is small and considered on an individual basis.

The ERG considers that the extent to which the proportion of patients undergoing ASCT may change with DBCd is an area of uncertainty. Changes in the proportion of patients undergoing ASCT can affect costs because ASCT is a costly procedure (e.g. unit cost = £15,065[12]). Furthermore, it can affect health outcomes because the overall survival curves on which the probability of death in the model is based includes a proportion of patients who had ASCT as part of their clinical management. Although the number of patients who have ASCT is small, the costs of ASCT are high, hence it is not clear the extent to which this uncertainty may affect the cost-effectiveness results.

> ***item 17. There is uncertainty regarding the extent to which the proportion of patients undergoing ASCT may change with DBCd compared to treatment with BCd, with the impact on cost-effectiveness results remaining unclear.***

Minor issues

The ERG noted a number of minor issues related to resource use and costs used in the model as follows:

- The company obtained the unit cost of bortezomib, cyclophosphamide and dexamethasone from eMIT 2020, which is appropriate. However, the cost of dexamethasone was based on the cost of 8 mg soluble tablets (£1.59 per tablet) when the cost per two tablets of dexamethasone 4 mg is lower (£0.52 per two tablets). The impact on the ICER is negligible (ICER reduces by £10/QALY).
- Daratumumab's SmPC specifies that patients should be screened for hepatitis B virus before treatment initiation, and patients with positive serology should be monitored for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of daratumumab treatment.[17] However, the model does not account for the cost of testing or additional monitoring. Given that the cost of testing and the proportion of affected patients is likely to be small, the impact on the ICER is expected to be small.

- The dosages and administration schedules of the treatment regiments used for second- and third-line therapies were based on various sources that may not necessarily reflect their usage in UK clinical practice. The ERG clinical advisors reviewed the dosing schedules used to calculate the costs in the model and had some minor comments. Specifically, lenalidomide + dexamethasone is used until toxicity or progression in reduced dose in those who respond (while the model assumes a treatment duration of six cycles). Other comments were that the melphalan + dexamethasone is given for 6-8 cycles (while the model assumed 18 cycles); carfilzomib's dose at cycle 2+ is 45 mg/m2 (while the model assumes 56mg/m2); thalidomide is given usually for up to 8 cycles at 50-100mg (while the model assumes 12 cycles at 200mg); and pomalidomide is given up to toxicity and progression in those who respond at a reduced dose of 3 mg (rather than over 16 cycles at 4 mg). The ERG notes that implementing the changes related to lenalidomide and pomalidomide requires information on the proportion of responders, the time to toxicity and time to progression in order to be implemented within the company's model structure, which was not possible to obtain within the timelines of submitting the ERG report and the expected impact is small relative to the other important model considerations about overall survival and its extrapolation over time.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Summary of company's submission

All analyses presented in the CS include the confidential PAS discount for daratumumab. Following response to ERG points for clarification, the company presented a revised model – termed henceforth the company's updated model. In this model, a number of technical errors identified by the ERG were corrected, health-related quality of life utility values were updated (derived by cross-walking the EQ-5D-5L data from the ANDROMEDA trial to the EQ-5D-3L and subsequently valuing it using a UK-specific tariff, and using data generated standard errors in the probabilistic analysis rather than assuming an arbitrary value of 10% of the mean value), and the probabilistic analysis revised to include sampling uncertainty in the distribution by depth of haematologic response.

Table 21 shows the company's updated base-case deterministic (reported in the company's response to ERG points for clarification and confirmed by the ERG using the company's updated model) and probabilistic cost-effectiveness results (results obtained by the ERG using the company's updated model). The deterministic ICER for DBCd relative to BCd is £23,509/QALY and the probabilistic ICER is £24,715/QALY. For the probabilistic cost-effectiveness results, the cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve for the original model (before ERG points for

clarification) are presented in Figures 28 and 29 (p148) of CS, respectively. The company's response to ERG points for clarification did not report the probabilistic cost-effectiveness results.

The confidential appendix to this ERG report provides the company's updated base-case results with confidential PAS discounts applied to the drugs comprising second- and third-line therapy where relevant, as provided by the companies holding the marketing authorisation for each product.

Table 21: Company's base-case results (adapted from Table 39 p63 of company's response to ERG points for clarification and obtained from the updated model)

Option	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER, /QALY
Deterministic results					
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£23,509
Probabilistic results					
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 24,715
The company's response to ERG points for clarification did not report the probabilistic results. Hence the results presented here were obtained by running the model over 5,000 simulations given the results of convergence tests presented in the company's submission (Figure 27, p148).					

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

5.1.2 Points for critique

The results of the company's updated model are similar to the company's original model for the base-case analysis.

For the company's base-case results, Figure 6 shows the difference in health state occupancy for DBCd relative to BCd (using the updated model). DBCd increases the time in the health states 'off treatment or on fixed dose treatment' and 'second-line treatment', while the difference in occupancy in the states of 'first-line treatment' and 'end-stage organ failure' is minimal.

Figure 6: Difference in state occupancy between DBCd and BCd according to company's revised base-case (calculated using the revised company's model

Abbreviations: Off Tx/FDT: off-treatment / fixed dose treatment; On Tx: on treatment; (2L) Tx: (second-line) treatment.

To aid understanding of the key drivers of cost-effectiveness, the ERG used the model results to plot the distribution of QALY gains by health state and depth of haematologic response in Figure 7, while the difference in costs between DBCd and BCd is shown in Figure 8. The QALY gain is driven by the gains in CR patients, mostly in the state 'Off treatment or on fixed daratumumab therapy' and to a smaller extent in the state 'On second line treatment'. The additional costs are driven by the greater costs of first line therapy in all patients, and to a smaller extent, disease monitoring costs of CR patients before progressing to second line therapy (cost category '1L Disease Monitoring Costs').

Figure 7: Incremental discounted QALYs by health state and response (plotted using the results of the company's revised model)

Abbreviations: AL: amyloid light-chain; CR: complete haematologic response; FDT: fixed daratumumab treatment; NR: no response; Off Tx/FDT: off-treatment / fixed dose treatment; On Tx: on treatment; PR: partial response; (2L) Tx: (second-line) treatment; VGPR: very good partial response.

Figure 8: Incremental discounted costs by health state and response (plotted using the results of the company's revised model)

Abbreviations: AL: amyloid light-chain; CR: complete haematologic response; FDT: fixed daratumumab treatment; NR: no response; Off Tx/FDT: off-treatment / fixed dose treatment; On Tx: on treatment; PR: partial response; (2L) Tx: (second-line) treatment; VGPR: very good partial response.

The ERG identified a number of minor issues with the probabilistic sensitivity analysis conducted by the company, some of which were corrected by the company in their response to ERG points for clarification (see response to ERG points for clarification document, B11., p58). Some issues remained in the updated model: parameter uncertainty was included in the cohort characteristics (age, body weight, and body surface), where differences are due to patient variability rather than parameter uncertainty; and parameter uncertainty was excluded in the organ transplantation cost and proportion

of patients requiring transplantation. Within the time constraints of this report, it was not feasible for the ERG to address these issues in the probabilistic analysis. However, the ERG expects that the impact on the mean cost-effectiveness results is very small because the mean probabilistic ICER is similar to the deterministic ICER.

5.2 Company's sensitivity analyses

5.2.1 Summary of company's submission

The company conducted univariate deterministic sensitivity analysis on a wide range of model inputs and plotted the ten most influential parameters on a tornado plot (see CS Figure 30 p150). The most influential input was the HRQoL weight for CR (ICER increased to £33,518/QALY when HRQoL of CR is reduced from [redacted]; results using the company's original model) and the proportion of patients on haemodialysis (ICER reduced to £17,253/QALY when the proportion increased from 9% to 100%; results using the company's original model).

The CS reports five scenario analyses as summarised in Table 22 (for detailed results see the company's response to ERG points for clarification document, Table 39 p63). The scenario with the greatest impact on the cost-effectiveness results was Scenario 3 (ICER=£33,774/QALY), in which the response assessment occurs after three treatment cycles, rather than six cycles as in the base case analysis, and the probability of death by depth of haematologic response is informed by extrapolation of OS data from Kastritis et al.[4]

Table 22: Results of company's scenario analysis (adapted from company's response to ERG points for clarification, Table 87 p63, and confirmed using the company's updated model)

Scenario	ICER DBCd vs BCd, /QALY
Company's updated base-case (deterministic)	£23,509
1) using alternative parametric models for the survival extrapolations based on Palladini et al.[5]	£23,845
2) assuming that all patients receive the maximum treatment durations for DBCd and BCd of 24 and 6 cycles respectively	£27,942
(3) assuming that patients are assessed for response at three months and have the survival predicted by fitting parametric models to the data reported in Kastritis et al.[4]	£33,774
(4) inclusion of the costs of third line therapies assuming that all patients who progress to second line are treated with third line therapies	£14,835
5) informing utilities by depth of haematologic response according to the estimates elicited from expert clinicians	£19,373
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.	

5.2.2 Points for critique

The ERG notes that the results of the scenario analysis using the company's updated model are similar to those using the company's original model, with the exception of scenario 3, which assumes that the assessment of response is after three treatment cycles rather than six treatment cycles in the base-case analysis.

The company conducted extensive deterministic sensitivity analyses, with the model set up to conduct additional scenarios which were not presented in the report. The sensitivity analysis was appropriate in the model inputs and structural assumptions which were included but was limited in scope.

5.3 Model validation and face validity check

5.3.1 Summary of company submission

The company validated the model structure with clinical experts, as well as sourcing and/or validating model inputs (survival extrapolations, HRQoL, healthcare resource use) with experts. The company validated the predicted overall survival by comparing the proportion of patients alive by depth of haematologic response (assessed at 6 months) at 12, 24 and 36 months to those reported in Palladini et al. (used to inform survival in the model)[5] and Manwani et al. (2019).[41] Manwani et al. reports the outcomes of 915 newly diagnosed patients treated with upfront bortezomib-based regimen in the UK between 2010-2017 – this is an early cut-off of the ALchemy study reported in Ravichandran et al (2021).[1] The company concluded that the model's predicted survival aligned well with Palladini et al.,[5] but resulted in underprediction of OS compared to Manwani et al.[41] for CR and VGPR patients at 12 months and VGPR patients at 12, 24 and 36 months, and optimistic for CR patients at 24 and 36 months. The CS reports that the model inputs were verified, checklists were used for technical implementation, stress tests were conducted, and the model was reviewed independently.

5.3.2 Points for critique

The ERG considers that the company's validation procedure was appropriate. As discussed in Section 4.2.6.2, the ERG has concerns that Palladini et al. is not generalisable to current UK clinical practice and may result in an overestimation of survival of patients who achieved CR. These concerns are reinforced by the results of the company's comparison of predicted survival with Manwani et al., which the ERG considers to be more generalisable to the UK than Palladini et al.

The ERG reviewed the model in detail and applied the TECHnical VERification (TECH-VER) checklist.[42] The ERG identified two errors in the calculation of the costs for DBCd: (i) an incorrect cell reference (Comparator!CU1778:CU2638) for the calculation of the first line therapy administration costs, which had a negligible impact on the ICER; and (ii) the calculation of

subsequent therapy costs for PR/NR at cycle 3 (Intervention!DC1780) in addition to cycle 4, when it should only take place at cycle 4, which had a large impact on the ICER results for scenario 3. The company submitted an updated model with these errors corrected following ERG points for clarification.

However, the ERG considered that the model was coded in a way that could hinder model validation given the various links between cells and changing the formulas within columns in the trace.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

A summary of the main issues identified and critiqued in Section 4 along with the scenario where the ERG addresses each issue in its additional analyses is shown in Table 23. The ERG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where possible, the ERG explored alternative assumptions and model inputs in the scenario analysis to the company's updated base-case analysis (ERG Scenarios 1-12). The ERG's base-case consists of the set of assumptions and model inputs that the ERG considers to be most appropriate for assessing the cost-effectiveness of DBCd relative to BCd. A thorough description of the ERG scenario analyses are presented in Section 6.1.1, while the impact on the cost-effectiveness results is presented in Section 6.2. The effect of making changes simultaneously on elements that are considered to form part of the ERG's preferred base case assumptions is presented in Section 6.3.

The ERG did not perform any corrections to the company's updated model. The errors identified and referred to in Section 5, were identified by the ERG at points for clarification and corrected by the company by providing an updated version of the electronic model.

The ERG notes that some of the drugs which form part of second- and third-line treatments are subject to confidential PAS discounts. The cost-effectiveness results given these confidential discounts are presented in the confidential appendix.

Table 23: Summary of the main issues identified by the ERG in Section 4 and ERG analyses

Critique item and description		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
The ERG considers that:		ERG's Scenarios	ERG's Base-case		
1	***The response assessment time point used in the model should be consistent with UK clinical practice and guidelines that suggests response assessment after three treatment cycles.***	Sc. 1	Yes	No	Yes
2	***A scenario analysis should assess the impact of early response to treatment at one month.***	No	No	Yes	Unclear
3	***The model structure should have sufficient flexibility to separate out the response categories of PR and NR because of different mortality risks in each category.***	No	No	Yes	Unclear
4	***The ALchemy study is more generalisable to the UK patient population than the ANDROMEDA trial.***	Sc. 2	Partly	No	Yes
5	***In the absence of evidence from the ANDROMEDA trial, an assessment of the cost-effectiveness of DBCd relative to BCd for a subpopulation with Mayo Clinic Cardiac Stage IIIb disease remains an area of uncertainty.***	No	No	Yes	Unclear
6	***The company's base-case assumption that patients receive daratumumab monotherapy (following a positive response to DBCd at the assessment timepoint) up to 24 cycles (mean treatment duration = [redacted] cycles), as observed in the ANDROMEDA trial, may underestimate costs if some patients continue daratumumab for longer, which the SmPC permits. The effect on QALYs is unclear.***	No	No	Yes	Unclear
7	***The ALchemy study[1] to be the most relevant source to inform the baseline haematologic response distribution for BCd, at the relevant response assessment timepoint, while the distribution for DBCd is informed by the relative treatment effect from the ANDROMEDA trial and applied to the haematologic response distribution for BCd from the ALchemy study.***	Sc. 3-5	Yes	No	Yes
8	***The ALchemy study[1] is the best source of available evidence to inform overall survival, stratified by depth of haematologic response, to inform expected outcomes in UK clinical practice.***	Sc. 6-7	Yes	Yes	Yes
9	***Overall survival of patients with CR in the company's base-case analysis (assuming haematologic response assessment after six treatment cycles) is likely to be overestimated.***	Sc. 6-7	Yes	No	Yes
10	***The utility values applied in the model by depth of haematologic response are highly uncertain.***	No	No	Yes	Unclear
11	***The utility decrements for the progression-related health states of second-line treatment and end-stage organ failure are conditional on response to first-line treatment, but it is unclear why patients in these health states would not have the same utility value, irrespective of previous response to treatment or previous lines of therapy.***	Sc. 9	No	Yes	No
12	***Age-adjusted utility values should be incorporated in the model to reflect the decreasing utility of patients as they age through the model over time.***	Sc. 8	Yes	No	No
13	***The model may underestimate the administration costs of daratumumab and bortezomib, which is likely to favour the cost-effectiveness of DBCd given its longer treatment duration.***	Sc. 10	No	Yes	Yes

Critique item and description		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
The ERG considers that:		ERG's Scenarios	ERG's Base-case		
14	***The costs of second-line treatments (and third-line treatments in a scenario analysis) are likely to be overestimated, which is likely to favour the cost-effectiveness of DBCd given that fewer patients progress to second-line therapy when treated with DBCd at first-line.***	Sc. 12	Yes	Yes	No
15	***To inform the costs of second- and third-line treatments, the ALchemy study[13] is more likely to reflect UK clinical practice, and therefore represents a better source of data to inform the type and distribution of patients receiving second- and third-line therapies.***	Sc. 11	Yes	Yes	No
16	***To inform the costs of second- and third-line treatments for patients who progress to the health state of 'second-line therapy', the calculation of the distribution of patients who have third-line treatment should be relative to the number of patients who received second-line treatment.***	Sc. 12	Yes	No	No
17	***There is uncertainty regarding the extent to which the proportion of patients undergoing ASCT may change with DBCd compared to treatment with BCd, with the impact on cost-effectiveness results remaining unclear.***	No	No	Yes	No

Abbreviations: ASCT: autologous stem cell transplant. BCd: bortezomib, cyclophosphamide and dexamethasone. CR: complete response. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: evidence review group. ICER: incremental cost-effectiveness ratio. NR: No Response. PR: Partial Response. Sc.: scenario. VGPR: very good partial response.

6.1.1 Issues explored by the ERG in additional analyses

6.1.1.1 ERG Scenario 1: Haematologic response assessment after three treatment cycles

As discussed in Section 4.2.2.2, the ERG considers that the response assessment timepoint used in the model should be after three treatment cycles (item 1). This timing is consistent with UK clinical practice guidelines[2] and supported by both the ERG and the company's clinical advisors.

ERG Scenario 1 is equivalent to the company's updated scenario 3 analysis, where the company used a 3-month response assessment timepoint. In this scenario, the distribution of patients by depth of haematologic response is based on data from the ANDROMEDA trial after three treatment cycles (see Figure 4 of this document and Table 41 of CS p107) and overall survival (i.e. probability of all-cause death), stratified by haematologic response from Kastritis et al. (2021).[4] Kastritis et al. is a retrospective study of 227 newly diagnosed patients treated with bortezomib-based regimens in Greece (median follow-up was 48 months), and reports overall survival by haematologic response following either a 3-month or 1-month response assessment timepoint.[4]

Figure 9 shows the overall survival curves used in the model for this scenario. The solid lines represent the Kaplan-Meier curves based on Kastritis et al. (2021),[4] the dashed lines represent the extrapolation of overall survival from the Kaplan-Meier data, and the dotted lines represent the overall survival curves used in the model after adjustment by the general population mortality risk (note that the hazard rate of death in the model is the maximum of the hazard rate predicted by the overall survival curve and the age- and sex-matched general population mortality hazard rate). The parametric distributions selected for the overall survival extrapolation are the same as the ones selected by the company: exponential for CR and VGPR, and generalised gamma for PR or NR. Figure 9 also shows the Kaplan-Meier curve for patients who achieve PR and NR separately. The overall survival curve extrapolation is a single curve for PR and NR because these categories are combined in the model by a weighted average of the extrapolations for PR and NR by the proportion of patients who achieve PR versus NR.

Figure 9: Overall survival in the model; response assessment after three treatment cycles (adapted from the company's model)

Abbreviations: CR: complete response; NR: no response; KM: Kaplan-Meier; OS; overall survival PR: partial response; VGPR: very good partial response.

6.1.1.2 ERG Scenario 2: Patient population age and gender based on the ALchemy study

As discussed in Section 4.2.3.2 and 4.2.6.2 (item 4), the ERG considers that the patient population in the ALchemy study[1] is more generalisable to the UK patient population in clinical practice than the population in the ANDROMEDA trial. This is because the ALchemy study includes a large proportion of all patients with newly diagnosed AL amyloidosis in the UK, and all treated with upfront bortezomib-based regimens, including 15.4% patients with Mayo Clinic Cardiac Stage IIIb disease. In contrast, the ANDROMEDA trial is a multinational clinical trial which did not include patients with Mayo Clinic Cardiac Stage IIIb disease.

ERG Scenario 2 uses the median age (66 years) and gender breakdown (59.7% male) of the ALchemy study, as reported in Ravichandran et al. (2021a).[1] Median age is used because Ravichandran et al. (2021a)[1] does not report the mean age. The mean weight and mean body surface area (used in the model to calculate costs) are unchanged from the company's base-case because Ravichandran et al. (2021a)[1] does not report these baseline characteristics. Given the limited set of characteristics in

Ravichandran et al. (2021a)[1] and the similarity in median age and gender breakdown with the ANDROMEDA study (median age = [redacted] years; [redacted]% male (see CS Table 11 p43)), the ERG does not include this scenario as part of its base-case.

6.1.1.3 ERG Scenarios 3, 4 and 5: Baseline haematologic response distribution based on the ALchemy study

As discussed in Section 4.2.6.2 (item 7), the ERG considers the ALchemy study to be the most relevant source to inform the baseline haematologic response distribution for BCd, at the relevant response assessment timepoint, while the distribution for DBCd is informed by the relative treatment effect from the ANDROMEDA trial and applied to the haematologic response distribution for BCd from the ALchemy study. This follows from the ERG's conclusion that the ALchemy study[1] is more generalisable to the UK patient population in clinical practice than the population in the ANDROMEDA trial, while the ANDROMEDA trial provides the best source of data for assessing the relative effectiveness of DBCd compared to BCd. Furthermore, using the ALchemy study[1] to inform the distribution of patients by depth of haematologic response for BCd is expected to align better with the population in whom the company seeks a recommendation, which includes patients with Mayo Clinic Cardiac Stage IIIb.

In ERG Scenarios 3-5, the ERG uses the distribution of patients by depth of haematologic response from the ALchemy study at different timepoints (ERG Scenarios 3-4 uses three-month response assessment, while ERG Scenario 5 uses six-month response assessment)[1] to represent expected outcomes with BCd and the ANDROMEDA trial to inform the relative effect for DBCd. To calculate the absolute haematologic response distribution for DBCd, it is necessary to condition the multiple categories (CR, VGPR, PR/NR and dead) into dichotomous categories in a series of steps, to ensure the resulting probabilities sum to 1. For example, in ERG Scenario 3, the first dichotomous categorisation is the proportion of patients who are alive vs. the proportion of patients who died; then the next dichotomous categorisation is the proportion of patients who achieve CR vs. the proportion of patients who do achieve CR conditional on being alive; then the next dichotomous categorisation is the proportion of patients who achieve VGPR vs. the proportion of patients who do not achieve VGPR conditional on being alive and not having achieved CR. At each step, the baseline odds of achieving the haematologic response category for BCd is based on the ALchemy study, and the odds ratio for the effect of DBCd relative to BCd from the ANDROMEDA trial is applied to the baseline odds to calculate the odds for DBCd. The odds are then converted to probabilities and the joint probability distribution is estimated in a process akin to rolling back a decision tree.

One key feature associated with calculating the odds of response for multiple categories is that the ordering of the conditioning into dichotomous categories can affect the joint distribution because the transformations are non-linear, although these differences are typically small. For this reason, the

ERG explored an alternative ordering in ERG Scenario 4, where the categories were conditioned as follows: the first dichotomous categorisation is the proportion of patients who are alive vs. the proportion of patients who died; then the next dichotomous categorisation is the proportion of patients who achieve PR/NR vs. the proportion of patients who do not achieve PR/NR conditional on being alive; then the next dichotomous categorisation is the proportion of patients who achieve CR vs. the proportion of patients who do not achieve CR conditional on being alive and not having achieved PR/NR.

Figure 10 to Figure 12 show the absolute difference in haematologic response between DBCd and BCd when obtained directly from the ANDROMEDA trial as used in the company's model (bars in blue) compared to the difference obtained using the baseline distribution from ALchemy and the relative effect from ANDROMEDA (bars in orange) at three treatment cycles (ERG Scenarios 3 and 4, with different ordering of the conditioning) and at six treatment cycles (ERG Scenario 5). Table 24 shows the corresponding haematologic response distributions. Note that worksheets 'ERG_S3_4_3months' and 'ERG_S5_6months' in the ERG version of the updated model contain the calculations used in these scenarios.

Figure 10, which relates to ERG Scenario 3, shows the difference in haematologic response distribution when the response assessment takes place at three treatment cycles, and assuming the conditioning order of alive, then CR, then VGPR. The proportion of patients achieving CR with DBCd is greater than that observed in the ANDROMEDA trial ([redacted]% in ANDROMEDA vs. [redacted]% calculated), the proportion of patients achieving VGPR is smaller ([redacted]% in ANDROMDA vs. [redacted]% calculated), while the reduction in patients with PR/NR is not as pronounced ([redacted]% in ANDROMEDA vs. [redacted]% calculated) and there is slighter increase in the proportion of patients who died ([redacted]% in ANDROMEDA vs. [redacted]% calculated). Figure 11, which relates to ERG Scenario 4, shows the difference in haematologic response distribution for the same timing of response assessment at three treatment cycles but for a different conditioning order: alive, then PR/NR, then CR. The distributions are similar to those obtained under ERG Scenario 3, but the increase in the proportion of patients who achieve CR is not as pronounced ([redacted]% in ANDROMEDA vs. [redacted]% calculated in ERG Scenario 3 compared to [redacted]% in ANDROMEDA vs. [redacted]% calculated in ERG Scenario 4). Figure 12, which relates to ERG Scenario 5, shows the difference in haematologic response distribution at six treatment cycles, assuming the conditioning order of alive, then CR, then VGPR. The proportion of patients achieving CR with DBCd is smaller than that observed in the ANDROMEDA trial ([redacted]% in ANDROMEDA vs. [redacted]% calculated), the proportion of patients achieving VGPR is smaller ([redacted]% in ANDROMDA vs. [redacted]% calculated), while the reduction in patients with PR/NR is not as pronounced ([redacted]% in ANDROMEDA vs. [redacted]% calculated) and there is slight increase in the proportion of patients who died ([redacted]% in ANDROMEDA vs. [redacted]% calculated).

Figure 10: Absolute differences in the depth of haematologic response based on ANDROMEDA (blue bars) and using the relative effect from ANDROMEDA applied to the ALchemy baseline (orange bars) at three treatment cycles; conditioning order of alive, then CR, then VGPR as used in ERG Scenario 3.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Figure 11: Absolute differences in the depth of haematologic response based on ANDROMEDA (blue bars) and using the relative effect from ANDROMEDA applied to the ALchemy baseline (orange bars) at three treatment cycles; conditioning order of alive, then PR/NR, then CR as used in ERG Scenario 4.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Figure 12: Absolute differences in the depth of haematologic response based on ANDROMEDA (blue bars) and using the relative effect from ANDROMEDA applied to the ALchemy baseline (orange bars) at six treatment cycles; conditioning order of alive, then CR, then VGPR as used in ERG Scenario 5

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Table 24: Distribution of depth of haematologic response in the company's base-case and scenarios and in the ERG Scenarios 3-5

	CR	VGPR	PR/ NR	Dead
ANDROMEDA trial; three-cycle response assessment				
BCd	[redacted]	[redacted]	[redacted]	[redacted]
DBCd	[redacted]	[redacted]	[redacted]	[redacted]
ANDROMEDA trial; six-cycle response assessment				
BCd	[redacted]	[redacted]	[redacted]	[redacted]
DBCd	[redacted]	[redacted]	[redacted]	[redacted]
ALchemy study[1] baseline and relative effect from ANDROMEDA trial; three-cycle response assessment Conditioning order: alive, then CR, then VGPR.				

BCd	25%	27%	34%	14%
DBCd	[redacted]	[redacted]	[redacted]	[redacted]
ALchemy study[1] baseline and relative effect from ANDROMEDA trial; three-cycle response assessment Conditioning order: alive, then PR, then CR.				
BCd	25%	27%	34%	14%
DBCd	[redacted]	[redacted]	[redacted]	[redacted]
ALchemy study[1] baseline and relative effect from ANDROMEDA trial; six-cycle response assessment Conditioning order: alive, then CR, then VGPR.				
BCd	25%	28%	26%	21%
DBCd	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

6.1.1.4 ERG Scenarios 6 and 7: Overall survival based on the ALchemy study

As discussed in Section 4.2.6.2 (items 8-9), the ERG considers that the ALchemy study is the best source of available evidence to inform overall survival, stratified by depth of haematologic response, in order to inform expected outcomes in UK clinical practice. As discussed earlier, this is because the ALchemy study includes a large proportion of all UK patients with AL amyloidosis and the patients in the ALchemy study (N=1,194) were all treated with first-line bortezomib based-regimens in line with the comparator BCd and as per current UK clinical care. This makes ALchemy more appropriate to inform the cost-effectiveness model than the study used by the company in its base-case, which was an international study reporting the outcomes of 816 patients who were treated between 2002-2010, a minority (3.2%) with BCd,[5] and the study used by the company in its scenario analysis, which was a Greek study reporting the outcomes of 227 patients treated with BCd.[4] The ALchemy study is also preferred over the EMN23 study or its [redacted], which is an international study (in [redacted]), which the company plans to present results at technical engagement. The ERG's preference for the ALchemy study is supported by feedback from the ERG clinical advisors, who considered the ALchemy study to be a better reflection of the standard of care seen in UK clinical practice than the EMN23 study. Furthermore, and as discussed earlier, the ALchemy study includes 15.4% patients with Mayo Clinic Cardiac Stage IIIb disease.

Therefore, the ERG considers that using the ALchemy study to inform overall survival in the model, stratified by depth of haematologic response, and in combination with using the baseline depth of haematologic response for BCd as observed in UK practice and includes patients with Mayo Clinic Cardiac Stage IIIb (as in ERG Scenarios 3-5), provides the best available evidence to inform a recommendation for the entire UK patient population as outlined in the NICE scope. However, the ERG emphasises that this assumes that the relative effectiveness of DBCd compared to BCd, as

observed in the ANDROMEDA trial, is generalisable to all newly diagnosed AL amyloidosis patients, despite the fact that this trial excluded patients with Stage IIIb disease.

In order to extrapolate the overall survival Kaplan-Meier data, stratified by depth of haematologic response, from the ALchemy study, the ERG followed a similar procedure to that used by the company when extrapolating overall survival data from Palladini et al. and Kastritis et al. The process involved: (1) digitising the published Kaplan-Meier curves on overall survival from Ravichandran et al, (2021); (2) recreating the individual patient level data from the digitised curves and number at risk in each time period;[32] and (3) fitting standard parametric survival models to the recreated individual level data. In line with the company's approach in selecting the parametric survival curves, the ERG assessed visual fit to the Kaplan-Meier curves, statistical goodness of fit, and face validity given the feedback from the ERG clinical advisors. This feedback was that, at 15-years after first-line treatment, the ERG clinical advisors expected 25%-30% of patients who achieve CR to be alive, with a similar but slightly lower estimate for patients who achieve VGPR; and very few of the patients with PR or NR to be alive at 15-years, with patients who achieved NR having poorer outcomes than patients who achieve PR.

For ERG Scenario 6, with the response assessment after six treatment cycles, the ERG selected the exponential parametric model for patients with CR and VGPR, and the Weibull parametric model for patients with PR and NR. In selecting the parametric models, the ERG first excluded the parametric models which predicted implausible proportions of patients alive at 15-years, given the feedback from ERG clinical advisors. For patients with CR, these were the Weibull (43% alive at 15-years), the Gompertz (47%), the lognormal (56%), the log-logistic (49%) and the gamma (21%). The remaining parametric models were the exponential (35% alive at 15-years) and the generalised gamma (35%). The ERG then considered the statistical goodness-of fit of the remaining models (the AIC for the exponential model was 384 and for generalised gamma was 386). The visual fit to the Kaplan-Meier curves was similarly good for the two remaining parametric models.

The ERG then examined the parametric models for patients with VGPR. The parametric models with implausible predictions at 15 years were the Gompertz (15% alive at 15-years), the lognormal (41%), the log-logistic (36%), and the generalised gamma (14%). The remaining parametric models were the exponential (24%), the Weibull (23%) and the gamma (27%). Of the remaining parametric models, the best fitting model in terms of statistical fit was the exponential model (AIC = 482), with slightly worse fit for the Weibull model (AIC=484) and the gamma (AIC=486). The ERG considered the feedback from the clinical advisors that patients with CR are expected to have better outcomes than patients with VGPR. Therefore, to ensure that patients with CR had always better survival in the model than patients with VGPR, the ERG selected the exponential model for both groups.

The ERG conducted a similar process to select the parametric survival models for patients with PR and NR. The first consideration was that the company's model structure requires that the same parametric model is selected for both PR and NR as these categories are combined in the model. The ERG excluded the parametric models that had implausible predictions at 15-years: Gompertz (PR: 24%; NR: 16%), lognormal (PR: 18%; NR 13%), log-logistic (PR: 19%; 8%); generalised gamma (PR: 20%; NR: 7%). The remaining parametric models were the exponential (PR: 5%; NR: 1%), the Weibull (PR: 9%; NR: 5%); and the gamma (PR: 5%; NR: 0%). The ERG then considered the statistical and visual goodness-of-fit: for PR, the AIC for the exponential curve was 510, for the Weibull curve was 509, and for the gamma curve was 503; for NR, the AIC for the exponential curve was 383, for the Weibull curve was 370, and for the gamma curve was 372. For both PR and NR, the gamma curve had a poorer visual fit to the Kaplan-Meier data than the Weibull and the exponential curve, and the visual fit of the Weibull was better than that of the exponential. Therefore, the Weibull model was selected.

The full set of curves is shown in the Appendix 9.2 Figure 20 to Figure 24 for the six month response assessment timepoint from the ALchemy study.

Figure 13 shows the overall survival curves, stratified by depth of haematologic response, based on the ALchemy study at six treatment cycles. The Kaplan-Meier curves are represented in solid lines, while the parametric extrapolations are represented in dashed lines, and the overall survival curves used in the model are represented in dotted lines. The general population survival curve is presented as a solid black line to aid interpretation. In contrast to the company's base-case analysis using Palladini et al. for overall survival extrapolation, the overall survival curve for patients who achieve CR is well below the general population survival curve. Therefore, the issue highlighted by the ERG in item 9, related to concerns that overall survival for CR in the company's base-case analysis is likely to be overestimated is not an issue when the ERG's preferred survival curves based on the ALchemy study are used in the model.

Figure 13: ERG Scenario 6 overall survival Kaplan-Meier and ERG preferred extrapolations based on the ALchemy study,[1] with the response assessment at six months; general population survival shown for comparison

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; KM: Kaplan-Meier; NR: no response; PR: partial response; VGPR: very good partial response.

For ERG Scenario 7, with the response assessment after three treatment cycles instead of six cycles, the ERG selected the Weibull parametric model for extrapolation of overall survival curves for all response categories. The same process for selecting the parametric models as used in ERG Scenario 6 was followed. The parametric models which predicted implausible proportions of patients alive at 15-years for patients with CR were the log-normal (46%), the log-logistic (41%), the gamma (34%) and the generalised gamma (20%). The remaining parametric models were the exponential (32%), the Weibull (31%) and the Gompertz (25%). The AIC for the exponential model was 373 and for both the Weibull and Gompertz models was 375, and the visual fit to the Kaplan-Meier curves was similarly good for the three remaining parametric models.

The ERG then examined the parametric models for patients with VGPR. The parametric models with implausible predictions at 15 years were the Gompertz (34%), the lognormal (42%), the log-logistic (37%), and the generalised gamma (37%). The remaining parametric models were the exponential

(25%), the Weibull (28%) and the gamma (22%). Of the remaining parametric models, the best fitting model in terms of statistical fit was the exponential model (AIC = 461), with similar fit by the Weibull (AIC=462) and slightly worse for the gamma models (AIC=464). To ensure that the patients with CR had always better survival in the model than patients with VGPR, the ERG selected the Weibull curve for both groups.

For PR and NR, the ERG excluded the parametric models that had implausible predictions at 15-years: Gompertz (PR: 30%; NR: 23%), lognormal (PR: 22%; NR 16%), log-logistic (PR: 21%; 8%); generalised gamma (PR: 26%; NR: 10%). The remaining parametric models were the exponential (PR: 7%; NR: 1%), the Weibull (PR: 12%; NR: 8%); and the gamma (PR: 6%; NR: 0%). For PR, the AIC for the exponential curve was 529, for the Weibull curve was 528, and for the gamma curve was 523; for NR, the AIC for the exponential curve was 660, for the Weibull curve was 629, and for the gamma curve was 628. However, for both PR and NR, the gamma curve had a poor visual fit to the Kaplan-Meier data. Between the exponential and the Weibull models, the ERG selected the Weibull model because it had better statistical and visual fit to the observed data for both PR and NR.

The full set of curves is shown in Appendix 9.2 Figure 15 to Figure 19 for the three month response assessment timepoint from the ALchemy study.

Figure 14 shows the overall survival curves, stratified by depth of haematologic response, based on the ALchemy study at three treatment cycles. The Kaplan-Meier curves are represented in solid lines, the parametric extrapolations in dashed lines, and the overall survival curves used in the model in dotted lines; the general population survival curve is presented as the solid black line to aid interpretation. Similar to ERG Scenario 6, the survival models provide overall survival curves well below the general population survival curve, resolving the issue highlighted by the ERG in item 9.

Figure 14: ERG Scenario 7 overall survival Kaplan-Meier and ERG preferred extrapolations based on the ALchemy study[1], with the response assessment at three months; general population survival shown for comparison

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; KM: Kaplan-Meier; NR: no response; PR: partial response; VGPR: very good partial response.

6.1.1.5 ERG Scenario 8: Adjusting health-related quality of life utility values by age over time

As discussed in Section 4.2.8.2 (item 12), the ERG considers that age-adjusted utility values should be incorporated in the model to reflect the decreasing utility of patients as they age through the model over time.[7] This adjustment is incorporated in ERG Scenario 8.

6.1.1.6 ERG Scenario 9: Assuming that health-related quality of life utility values on second-line therapy or end-stage organ failure do not differ by depth of haematologic response achieved on first-line therapy.

As discussed in Section 4.2.8.2 (item 11), the ERG has concerns about the company's assumption that that patients on second-line therapy and with end-stage organ disease have different utility values depending on their depth of haematologic response achieved with first-line therapy. That is, patients who respond better to treatment at first-line (e.g., CR or VGPR) who subsequently progress to the state 'On second-line treatment' or who progress to the state 'End-stage organ failure' are assumed to have a better quality of life on second-line therapies than those on second-line treatment with poorer

response with first-line therapies (e.g., PR/NR). The ERG believes that this may not be the case given that some patients with PR to first-line therapies may achieve CR or VGPR with second-line therapies. For this reason, the ERG presents a scenario where the utility of the health states 'On second-line therapy' and 'end-stage organ failure' is calculated as the difference between the mean baseline utility from the ANDROMEDA trial of [redacted] and the decrements due to progression and end-stage organ failure as used in the company's base-case. Table 25 compares the utility values used in the company's base-case and in ERG scenario 9.

Table 25: Utility values used in the company's base-case and in ERG scenario 9

Item	Company's base-case	ERG Scenario 9
Health state 'On second line treatment'		
Complete response (CR)	[redacted]	[redacted]
Very good partial response (VGPR)	[redacted]	
Partial response or no response (PR/NR)	[redacted]	
Health state 'end-stage organ failure'		
Complete response (CR)	[redacted]	[redacted]
Very good partial response (VGPR)	[redacted]	
Partial response or no response (PR/NR)	[redacted]	

6.1.1.7 ERG Scenario 10: Administration costs of DBCd and BCd based on NHS Reference Costs for bortezomib-based chemotherapy

As discussed in Section 4.2.9.2 (item 13), the ERG has concerns that the model may underestimate the administration costs of daratumumab and bortezomib, which is likely to favour the cost-effectiveness of DBCd given its longer treatment duration. Feedback from the ERG's clinical advisors suggested that daratumumab and bortezomib require preparation in the pharmacy or in the ward, and the first four administrations of daratumumab are expected to require the patient to stay for a few hours for monitoring. Furthermore, the NHS guidance for national cost collection specifies that, in recording the costs of chemotherapy, trusts should use the relevant healthcare resource group (HRG) codes for the procurement of chemotherapy and for the delivery of chemotherapy.[40] Therefore, the ERG presents a scenario (ERG Scenario 10) using these unit costs to inform the administration costs of daratumumab and bortezomib:

- For procurement per cycle, the HRG code is bortezomib, dexamethasone and cyclophosphamide SA10Z – Procure Chemotherapy Drugs for regimens in Band,[10] for which the average cost weighted by activity is £2,110.[12]
- For the first delivery of the cycle, the HRG code is SB12Z – Deliver Simple Parental Chemotherapy at First Attendance, for which the average cost weighted by activity is £241.[12]

- For subsequent deliveries in the same cycle, the HRG code is SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle, for which the average cost weighted by activity is £332[12]

For comparison, the company's base-case uses the cost of 5 minutes of a band 5 nurse at £3.08 for the administration of daratumumab and bortezomib.[9]

6.1.1.8 ERG Scenario 11: Second-line therapy costs based on the ALchemy study

As discussed in Section 4.2.9.2 (item 15), the ERG considers that the ALchemy study is more likely to reflect UK clinical practice, and therefore represents a better source of data to inform the type and distribution of patients receiving second- and third-line therapies.[13] Furthermore, using the ALchemy study for the type of treatments and distribution of patients receiving these treatments ensures that the costing of subsequent treatments aligns with overall survival in the model.

ERG Scenario 11 is the same as the scenario presented by the company in response to ERG points for clarification, where the ERG requested use of the ALchemy study to inform second-line therapy costs. The cost of second-line treatments in the company base-case analysis is £41,451 per patient, while in ERG Scenario 11 it is £22,719.

6.1.1.9 ERG Scenario 12: Including third-line therapy costs based on the ALchemy study, reduced by 20% to account for deaths, treatment discontinuation and dose adjustments over the treatment duration

As discussed in Section 4.2.9.2 (item 14 and item 16), the ERG considers that the calculation of the distribution of patients who have third-line treatment should be relative to the number of patients who receive second-line treatment, given that these costs are applied in the model to patients at entry into the health state 'second-line therapy'. The costs of third-line treatments in the company's scenario analysis in response to ERG points for clarification is likely to be overestimated because it is not calculated relative to the number of patients who received second-line therapies in the ALchemy study. Furthermore, the ERG considers that the calculation of costs of both second- and third-line treatments in the model are likely to be overestimated because the total upfront costs at entry to the second-line health state do not account for dose adjustments, treatment discontinuations and deaths during treatment. Overestimating the costs of subsequent treatments is likely to favour the cost-effectiveness of DBCd as fewer patients progress to second-line therapy when treated with DBCd at first-line.

ERG Scenario 12 includes an adjustment to third-line therapy costs to reflect the cost of subsequent treatments in clinical practice, and a 20% reduction to account for dose adjustments, treatment discontinuations and deaths during treatment with second- and third-line therapies. The option to apply a cost reduction was included in the company's model, with the ERG choosing 20% as the lower bound of the company's scenario analysis in response to ERG points for clarification.

Additionally, the ERG corrected the calculation of the distribution of patients by third-line therapy when using the ALchemy study; however, this correction is only applied when ERG Scenario 12 is applied jointly with ERG Scenario 11, i.e., when the distribution of patients by treatments is informed by the ALchemy study.[13]

Table 26 shows the distribution of patients by treatment in the company's scenario analysis including second-line therapies and in ERG Scenarios 11 and 12. The cost of second- and third-line therapies used in ERG Scenario 12 amount to £119,357 and £128,666 per patient upon progression to the health state 'second-line therapy', following first-line treatment with DBCd and BCd, respectively. When ERG Scenarios 11 and 12 are applied simultaneously, the cost of second- and third-line therapies, the cost is £28,120 per patient (for both the DBCd and BCd options). The difference is mostly driven by the smaller proportion of patients in costlier treatments and the correction of the calculation of the distribution of patients in third-line treatments, with 20% reduction to account for dose adjustments, treatment discontinuations and deaths during treatment having a smaller effect.

Table 26: Distribution of second- and third-line treatments used in the company's base-case and ERG Scenarios

Treatment line	Treatments	First-line = DBCd	First-line = BCd
Company's base-case			
Second-line	Lenalidomide + Dexamethasone	75%	75%
	Melphalan + Dexamethasone	5%	5%
	Carfilzomib + Dexamethasone	10%	10%
	Bortezomib + Cyclophosphamide + Dexamethasone	10%	10%
Third-line	Panabinostat + Bortezomib + Dexamethasone	0%	0%
	Pomalidomide + Dexamethasone (Pd)	70%	80%
	Lenalidomide + Dexamethasone (Rd)	30%	20%
ERG Scenarios 11 and 12			
Second-line (ERG Scenario 11)	Bortezomib (assumed Bortezomib + Cyclophosphamide + Dexamethasone)	8%	
	Lenalidomide (assumed Lenalidomide + Dexamethasone)	55%	
	Melphalan (assumed Melphalan + Dexamethasone)	11%	
	Autologous stem cell transplant	11%	
	Pomalidomide (assumed equal to Pomalidomide + Dexamethasone)	2%	
	Carfilzomib (assumed Carfilzomib + Dexamethasone)	1%	
	Bendamustine	8%	
	Thalidomide	4%	
	Cyclophosphamide (assumed Bortezomib + Cyclophosphamide + Dexamethasone)	2%	
	Bortezomib (assumed Bortezomib + Cyclophosphamide + Dexamethasone)	8%	

Third-line (ERG Scenarios 11 and 12)	Bortezomib (assumed Bortezomib + Cyclophosphamide + Dexamethasone)	1%
	Lenalidomide (assumed Lenalidomide + Dexamethasone)	16%
	Melphalan (assumed Melphalan + Dexamethasone)	1%
	Autologous stem cell transplant	3%
	Panabinostat (assumed equal to third line Panabinostat + Bortezomib + Dexamethasone)	1%
	Pomalidomide (assumed equal to Pomalidomide + Dexamethasone)	3%
	Carfilzomib (assumed Carfilzomib + Dexamethasone)	1%
	Bendamustine	2%
	Bortezomib (assumed Bortezomib + Cyclophosphamide + Dexamethasone)	1%

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Table 27 shows the results of the ERG scenarios, with Table 28 showing the summary results (ICER for each scenario). The ERG scenarios with the largest impact on the ICER are those relating to: (i) the timing of the response assessment (after six vs. three treatment cycles); (ii) the source of data used to inform overall survival in the model (Palladini et al (2012)[5] when the assessment is after six treatment cycles and Kastritis et al (2021)[4] when the assessment is after three treatment cycles vs. the ALchemy study[1]); (iii) ERG scenario 10 where the administration costs of bortezomib and daratumumab are based on HRG codes for chemotherapy procurement and administration and NHS Reference Costs; and (iv) ERG Scenario 12 where third-line therapy costs are appropriately adjusted and the costs of second- and third-line therapy reduced by 20%. Scenarios that have a small impact on the ICER are ERG Scenario 2 on the age and gender distribution of the patient population, ERG Scenarios 8 and 9 on health-related quality of life, and ERG Scenario 11 on the source of the treatment distribution to calculate the costs of second-line therapies. ERG Scenarios 3-5, using the ALchemy study[13] to provide the baseline distribution by depth of haematologic response for BCd results in only a small impact on the ICER when the response assessment is at six treatment cycles, but has a material impact at three treatment cycles. The latter is mostly driven by the change in the timing of response assessment rather than the source of baseline distribution.

Table 27: Cost-effectiveness results of the ERG scenario analyses

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
-	Company's base-case	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£23,509
1	Assessment response time point after 3 treatment cycles, using Kastritis et al (2021)[4] to inform the overall survival curves (company scenario analysis)	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£33,774
2	Patient population age and gender based on the ALchemy study[1].	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£25,436
3	ALchemy[1] study used to inform baseline haematologic response distribution for BCd after three treatment cycles: conditioning order for relative effect of alive, CR, and VGPR.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£34,094
4	ALchemy[1] study used to inform baseline haematologic response distribution for BCd after three treatment cycles: conditioning order for relative effect of alive, PR/NR, and VGPR.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£36,948
5	ALchemy[1] study used to inform baseline haematologic response distribution for BCd after six treatment cycles: conditioning order for relative effect of alive, CR, and VGPR.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£29,194
6	Overall survival based on ALchemy[1] after six treatment cycles (CR – Exponential distribution; VGPR - Exponential; PR/NR – Weibull)	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£36,612
7	Overall survival based on ALchemy[1] after three treatment cycles (CR – Weibull distribution; VGPR - Weibull; PR/NR – Weibull)	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£47,671
8	Health-related quality of life: utility values adjusted by age.[7]	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£25,293
9	Health-related quality of life: utility values for progression-related health states independent of response to first-line treatment.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£23,862
10	Costs: Administration costs based on NHS Reference Costs[12, 40]	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£30,800
11	Costs: Second-line therapies based on the ALchemy study. [13]	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£24,486
12	Costs: Including third line therapy costs and a 20% reduction in upfront costs of second- and third-line therapies to account for dose adjustments, treatment discontinuation, and deaths during treatment.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£17,002

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. CR: complete response. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: evidence review group. ICER: incremental cost-effectiveness ratio. NR: No Response. PR: Partial Response. VGPR: very good partial response.

Table 28: Summary cost-effectiveness results (ICER) for the ERG scenario analyses

Scenario #	Name	ICER, /QALY
1	Assessment response time point after 3 cycles, using Kastritis et al (2021)[4] to inform the overall survival curves (company scenario analysis)	£33,774
2	Patient population age and gender based on the ALchemy study.[1]	£25,436
3	ALchemy[1] study used to inform baseline haematologic response distribution for BCd after three treatment cycles: conditioning order for relative effect of alive, CR, and VGPR.	£34,094
4	ALchemy[1] study used to inform baseline haematologic response distribution for BCd after three treatment cycles: conditioning order for relative effect of alive, PR/NR, and VGPR.	£36,948
5	ALchemy[1] study used to inform baseline haematologic response distribution for BCd after six treatment cycles: conditioning order for relative effect of alive, CR, and VGPR.	£29,194
6	Overall survival based on ALchemy[1] after six treatment cycles (CR – Exponential distribution; VGPR - Exponential; PR/NR – Weibull)	£36,612
7	Overall survival based on ALchemy[1] after three treatment cycles (CR – Weibull distribution; VGPR - Weibull; PR/NR – Weibull)	£47,671
8	Health-related quality of life: utility values adjusted by age.[7]	£25,293
9	Health-related quality of life: utility values for progression-related health states independent of response to first-line treatment.	£23,862
10	Costs: Administration costs based on NHS Reference Costs.[12, 40]	£30,800
11	Costs: Second-line therapies based on the ALchemy study.[13]	£24,486
12	Costs: Including third line therapy costs and a 20% reduction in upfront costs of second- and third-line therapies to account for dose adjustments, treatment discontinuation, and deaths during treatment.	£17,002

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. CR: complete response. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: evidence review group. ICER: incremental cost-effectiveness ratio. NR: No Response. PR: Partial Response. VGPR: very good partial response.

6.3 ERG's preferred assumptions

The ERG preferred assumptions are:

- The timing of the response assessment is after three treatment cycles, consistent with UK clinical practice and guidelines[2] – item 1.
- The ALchemy study[1] is more generalisable to the UK patient population than the ANDROMEDA trial – item 2.
- The ALchemy study[1] is the most relevant available source to inform the baseline haematologic response distribution for BCd, while the distribution for DBCd is informed by the relative treatment effect from the ANDROMEDA trial and applied to the haematologic response distribution for BCd from the ALchemy study – item 7.
- The ALchemy study[1] is the best source of available evidence to inform overall survival, stratified by depth of haematologic response, to inform expected survival outcomes in UK clinical practice – item 8.

- Age-adjusted utility values should be incorporated in the model to reflect the decreasing utility of patients as they age through the model over time[7] – item 12.
- To inform the costs of second- and third-line treatments, the ALchemy study[13] is more likely to reflect UK clinical practice, and therefore represents a better source of data to inform the type and distribution of patients receiving second- and third-line therapies – item 15.
- To inform the costs of second- and third-line treatments for patients who progress to the health state of 'On second-line treatment', the calculation of the distribution of patients who have third-line treatment should be relative to the number of patients who received second-line treatment – item 16.
- A 20% reduction in the costs of second- and third-line therapies is applied in the model to account for dose adjustments, treatment discontinuations and deaths during treatment because the model structure only permits inclusion of upfront costs of subsequent lines of therapy – item 14.

Table 29 shows the ERG's preferred assumptions, which form the ERG base-case, and their cumulative impact on the ICER, while Table 30 shows detailed results cumulatively. The ERG base-case ICER is £62,660/QALY.

Table 29 ERG's preferred model assumptions

Scenario number	Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
3	**ALchemy study used to inform baseline haematologic response distribution for BCd after three treatment cycles (conditioning order for relative effect from the ANDROMEDA trial of alive, CR, and VGPR)** The timing of the response assessment is after three treatment cycles, consistent with UK clinical practice and guidelines.[2] The ALchemy study[1] is more generalisable to the UK patient population than the ANDROMEDA trial. The ALchemy study[1] is the most relevant available source to inform the baseline haematologic response distribution for BCd, while the distribution for DBCd is informed by the relative treatment effect from the ANDROMEDA trial and applied to the haematologic response distribution for BCd from the ALchemy study.	4.2.3.2 4.2.6.2	£34,094
3+7	**Overall survival based on ALchemy after three treatment cycles (CR – Weibull distribution; VGPR - Weibull; PR/NR – Weibull)**The ALchemy study[1] is the best source of available evidence to inform overall survival, stratified by depth of haematologic response, to inform expected survival outcomes in UK clinical practice.	4.2.6.2	£56,215
3+7+8	**Health-related quality of life: utility values adjusted by age** Age-adjusted utility values should be incorporated in the model to reflect the decreasing utility of patients as they age through the model over time.[7]	4.2.8.2	£59,830
3+7+8+11	**Costs: Second-line therapies based on the ALchemy study** To inform the costs of second- line treatments, the ALchemy study[13] is more likely to reflect UK clinical practice, and therefore represents a better source of data to inform the type and distribution of patients receiving second- and third-line therapies.	4.2.9.2	£63,806
2+7+8+11+12 (ERG base-case)	**Costs: Including third line therapy costs and a 20% reduction in upfront costs of second- and third-line therapies.** To inform the costs of second- and third-line treatments for patients who progress to the health state of 'second-line therapy', the calculation of the distribution of patients who have third-line treatment should be relative to the number of patients who received second-line treatment. Given the model structure does not explicitly account for dose adjustments, treatment discontinuations and deaths during treatment, a 20% reduction on the cost of second- and third-line therapies is applied.	4.2.9.2	£62,660

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: evidence review group. ICER: incremental cost-effectiveness ratio.

Table 30: Detailed cost-effectiveness results for the ERG preferred model assumptions

Scenario #	Summary name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
-	Company's base-case	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£23,509
3	ALchemy study used to inform baseline haematologic response distribution for BCd after three treatment cycles (conditioning order for relative effect from the ANDROMEDA trial of alive, CR, and VGPR)	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£34,094
3+7	Overall survival based on ALchemy after three treatment cycles (CR – Weibull distribution; VGPR - Weibull; PR/NR – Weibull)	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£56,215
3+7+8	Health-related quality of life: utility values adjusted by age.[7]	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£59,830
3+7+8+11	Costs: Second-line therapies based on the ALchemy study[13]	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£63,806
3+7+8+11+12 (ERG base-case)	Costs: Including third line therapy costs and a 20% reduction in upfront costs of second- and third-line therapies	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
		DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£62,660

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. CR: complete response. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: evidence review group. ICER: incremental cost-effectiveness ratio. NR: No Response. PR: Partial Response. VGPR: very good partial response.

6.4 Conclusions of the cost effectiveness section

The company submitted a *de novo* decision model to assess the cost-effectiveness of DBCd versus BCd for newly diagnosed AL amyloidosis. The ERG considers that the model structure is broadly appropriate to inform decision-making but does not agree with the timing of response assessment, which is after six treatment cycles in the company's base-case analysis. The ERG considers that the timing of response assessment in the model should correspond to the timing in UK clinical practice, i.e. after three treatment cycles (approximately three months)[2] (item 1), as per the ERG base-case. At this point, patients who achieve CR or VGPR continue treatment with DBCd or BCd, and patients who achieve PR or NR switch to second-line therapy, in line with clinical practice.

In informing the model, the company assumed that the most relevant source of evidence to inform the depth of haematologic response distribution for BCd and DBCd was the ANDROMEDA trial. To inform overall survival (i.e., life expectancy) conditional on depth of haematologic response, the company used the study by Palladini et al. (2012)[5] when the response assessment is after six treatment cycles and the study by Kastritis et al. (2021)[4] when the response assessment is after three treatment cycles. The company have indicated that they plan to present overall survival by haematologic response based on the EMN23 study at Technical Engagement.

While the ERG agrees that the ANDROMEDA trial is the relevant source of evidence to inform the relative effectiveness of DBCd vs. BCd, the ERG believes that the ALchemy study[1] provides the best available evidence on the outcomes of UK patients with newly diagnosed AL amyloidosis, treated with BCd. The ALchemy study[1] includes 1,194 UK patients treated between 2010-2019 with upfront bortezomib-based regimens and who comprise a large proportion of all UK patients with newly diagnosed AL amyloidosis. In contrast, the studies proposed by the company to inform overall survival in the model are either international studies with a proportion of UK patients, some of whom were not treated with the current standard of care with bortezomib (Palladini et al., 2012[5] and EMN23 study) or studies set outside the UK (Kastritis et al., 2021[4]). Therefore, the ERG uses the ALchemy study[1] to inform overall survival in the model, conditional on the depth of haematologic response.

For consistency with the ERG's view that the ALchemy study provides the best available evidence to inform outcomes in the model, the ERG prefers to use this study to inform the baseline distribution by depth of haematologic response for BCd, at the response assessment timepoint, and to calculate the distribution for DBCd by applying the relative effectiveness from the ANDROMEDA trial to this baseline distribution. This approach, which follows recommendations presented in the NICE Technical Support Document 5,[6] assumes that the relative effectiveness of DBCd vs BCd, as observed in the ANDROMEDA trial, generalises to the UK setting. It does not require the assumption that

absolute outcomes in the BCd arm of the trial generalises to the UK because an alternative UK baseline is available from the ALchemy study.

An additional strength of using the ALchemy study is that it allows the ERG base-case to provide evidence on the cost-effectiveness of DBCd vs BCd for the entire patient population with newly diagnosed AL amyloidosis, that includes patients with Mayo Clinic Cardiac Stage IIIb. However, this still assumes that the relative effectiveness for DBCd vs. BCd from the ANDROMEDA trial is generalisable to patients with Mayo Clinic Cardiac Stage IIIb disease. This is because the ALchemy study[1] includes 15.4% patients with Mayo Clinic Cardiac Stage IIIb, which the ERG considers to be representative of the UK patient population. However, the ERG acknowledges that this assumption extrapolates beyond the evidence collected in the ANDROMEDA trial, which excluded patients with Mayo Clinic Cardiac Stage IIIb. The company's base-case, which relies on the ANDROMEDA trial for the depth of haematologic response for both BCd and DBCd does not provide evidence for the cost-effectiveness of DBCd in patients with Mayo Clinic Cardiac Stage IIIb. Furthermore, the ERG highlights that the available evidence does not allow to stratify the cost-effectiveness results by Mayo Clinic Cardiac Stage.

The ERG's base-case assumes that the response assessment takes place after three treatment cycles and uses the ALchemy study to inform both the baseline depth of haematologic response for BCd and overall survival by response in the model. The assumptions with the largest impact on the ICER are the timing of the response assessment (ICER increases from £23,509 to £33,774/QALY) and using the ALchemy study for the source of overall survival in the model (ICER increases to £56,215/QALY). The other changes that comprise the ERG base-case have a smaller impact on the cost-effectiveness results. The ERG base-case ICER is £62,660/QALY. The ERG highlights that these results include the confidential PAS discount on daratumumab but not for the treatments used in second- and third-line treatments. Results with these confidential discounts are reported in the confidential PAS appendix.

Some uncertainties and limitations in the evidence base could not be fully explored by the ERG and the impact on the ICER remains unclear, as summarised in Table 23. Two of the areas with remaining uncertainty relate to the model structure that combines PR and NR despite different overall survival (item 3) and the impact of early response assessment after one treatment cycle, which can occur in clinical practice (item 2).

Another area of uncertainty with unclear impact on the ICER relates to the utility values used in the model by depth of haematologic response. The ERG notes that the utility values used in the model are highly uncertain because they are mostly based on EQ-5D data collected in the ANDROMEDA trial from baseline to the response assessment timepoint at cycle six. The ERG has concerns regarding the

EQ-5D data collected in the ANDROMEDA trial given the lack of face validity of the utility values derived for VGPR; the short follow-up period to cycle six to inform long-term utility values; and the limited data for health-related quality of life during the progression-related health states of second-line treatment and end-stage organ failure. The ERG notes that health-related quality of life data in the form of SF-36v2 scores has been collected from patients in the ALchemy study at baseline and response assessment study visits of 3-, 6- and 12-months, which could be used to validate or supplement the EQ-5D utility values from the ANDROMEDA trial. However, it was not possible to obtain this data within the timescales of submitting the ERG report.

The ERG also notes that if daratumumab were to be considered for the Cancer Drugs Fund, the ANDROMEDA trial is ongoing. The company has indicated that further analyses are planned in [redacted]. Given the model structure and the ANDROMEDA trial sample size and follow-up period, the ERG considers it to be unlikely that it would be feasible to use the ANDROMEDA trial to inform the model's overall survival by haematologic response. Nonetheless, these further analyses could be used to validate the cost-effectiveness model predictions for overall survival, which represents the main driver of cost-effectiveness of DBCd relative to BCd. Additionally, the period in the Cancer Drugs Fund would allow for the ALchemy study data to mature and reduce the uncertainty in the overall survival extrapolations, as well as time to explore the potential of the ALchemy study in informing health-related quality of life in the model. Furthermore, the data collected as part of the Cancer Drugs Fund may help inform the administration costs of DBCd and BCd in the model, which the ERG explored as an area of uncertainty in item 13 and Scenario 10.

7 END OF LIFE

End-of-life considerations do not apply because life expectancy with current clinical care (comprising BCd as first-line therapy) exceeds 24 months.

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9 APPENDICES

9.1 Critique of literature searches

9.1.1 Clinical effectiveness and safety searches

Table 31 ERG appraisal of evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	Missing Search Strategies: In the original submission, there was insufficient information on the searches for clinical trials and conference proceedings (listed in Appendix D, D.1.1, page 6). In response to the PfCs, the company provided the full details requested. Incomplete Data: In the original submission, 0 results were listed for the search of ClinicalTrials.gov (listed in Appendix D, page 20) and the search strategy was omitted. In the response to PfCs, the strategy was provided and the total hits for the search were documented and explained. It was then clear that the 0 results referred to 0 unique results from the database as the 190 records retrieved were all duplicates. Missing Dates: In the original submission, details of the exact dates of each of the searches throughout the entirety of the appendices had not been provided. In the response to PfCs, this data was provided in DD/MM/YYY format as requested.
Were appropriate sources searched?	YES	A good range of relevant databases, conference proceedings, grey literature sources and trials registry databases were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date in the strategy.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the intervention.
Were appropriate search terms used?	PARTLY	The search of ClinicalTrials.gov could have used broader terminology to describe the condition than simply 'AL amyloidosis'. However, this may not have achieved much further relevant evidence (if any) and the other searches were very thorough. Emtree Headings used outside of Embase: Emtree headings daratumumab/, pomalidomide/, and carfilzomib/ were used in a search of Cochrane Central, Cochrane CDSR, DARE, and ACP Journal Club (Appendix D, Table 2, page 13). These databases use MeSH not Emtree. However, the company acknowledged this error, re-ran the searches, and provided assurance that no relevant evidence was missed. This is convincing as there are no equivalent MeSH terms for these Emtree headings and the other search terms were very thorough.
Were any search restrictions applied appropriate?	NOT APPLICABLE	No restrictions were applied in the search strategy.
Were any search filters used validated and referenced?	NOT APPLICABLE	No search filters were used.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE; **Abbreviations:** PfCs: points for clarification.

9.1.2 Cost and Healthcare Resource Identification, Measurement and Valuation Searches

Search strategy

The original company submission included searches to identify cost and healthcare resource identification, measurement and valuation studies for adults newly diagnosed with AL amyloidosis. A detailed description of the searches and most of the search strategies were included in Appendix I (pp. 68-98).

In response to the ERG's PfCs, a further document was provided by the company, which included additional search strategies and corrections to errors identified by the ERG.

Table 32 ERG appraisal of evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	Missing Search Strategies: In the original submission, there was insufficient information on the searches for grey literature (listed in Appendix G, G.1.1, page 40 and referred to in Appendix I, page 68). In response to the PfCs, the company provided the full details requested. Missing Dates: In the original submission, details of the exact dates of each of the searches throughout the entirety of the appendices had not been provided. In the response to PfCs, this data was provided in DD/MM/YYY format as requested. Errors in Documentation: In Appendix I, I.1.1, page 68, the reference to 'grey literature sources for HRQoL evidence' was queried with the company who confirmed that this should have read: 'The grey literature search of HTA websites for the economic evidence SLR (see Section G.1) encompassed cost and healthcare resource use identification, measurement and valuation studies'.
Were appropriate sources searched?	YES	Relevant databases and grey literature sources were searched.
Was the timespan of the searches appropriate?	YES	The searches were limited from 2010 to the present to retrieve the most relevant and current costs for treatment.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study type.
Were appropriate search terms used?	YES	Very thorough search terms were used.
Were any search restrictions applied appropriate?	YES	Animal papers were removed appropriately. English Language Limits: Appendix I, Table 22, pages 68-73 limited the search to English, which was queried with the company. In response to the PfCs, the company indicated this limit was applied in error, re-ran the search, and provided assurance no relevant evidence was missed.

Were any search filters used validated and referenced?	PARTLY	Search filters were used but not fully referenced.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.1.3 Cost-Effectiveness Searches

Search strategy

The original company submission included searches to identify cost-effectiveness studies for adults newly diagnosed with AL amyloidosis. A detailed description of the searches and most of the search strategies were included in Appendix G (pp. 39-45).

In response to the ERG's PfCs, a further document was provided by the company, which included additional search strategies and corrections to errors identified by the ERG.

Table 33 ERG appraisal of evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	Missing Search Strategies: In the original submission, there was insufficient information on the grey literature searches in Appendix G, G.1.1, page 40. In response to the PfCs, the company provided the full details requested. Missing Dates: In the original submission, details of the exact dates of each of the searches throughout the entirety of the appendices had not been provided. In the response to PfCs, this data was provided in DD/MM/YYY format as requested.
Were appropriate sources searched?	YES	A good range of relevant databases and grey literature sources were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study type.
Were appropriate search terms used?	YES	Very thorough search terms were used.
Were any search restrictions applied appropriate?	YES	Animal papers were removed appropriately.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not fully referenced.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.1.4 Health-Related Quality of Life Searches

Search strategy

The original company submission included searches to identify health-related quality of life studies for adults newly diagnosed with AL amyloidosis. A detailed description of the searches and most of the search strategies were included in Appendix H (pp. 45-67).

In response to the ERG's PfCs, a further document was provided by the company, which included additional search strategies and corrections to errors identified by the ERG.

Table 34 ERG appraisal of evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	Missing Search Strategies: In the original submission, there was insufficient information on the searches for grey literature (listed in Appendix G, G.1.1, page 40 and referred to in Appendix H, page 45). In response to the PfCs, the company provided the full details requested. An additional search for adverse event disutility data was mentioned in the main submission document (Document B, B.3.4.4, pages 125-126) but no strategies or further details were listed in Appendix H. The strategy was listed in the company's response to PfCs (B10, part 5, p. 57) but was not documented clearly. Missing Dates: In the original submission, details of the exact dates of each of the searches throughout the entirety of the appendices had not been provided. In the response to PfCs, this data was provided in DD/MM/YYY format as requested. Errors in Documentation: In the original submission of Appendix H, there should have been an additional line in Table 14 on page 50, to pool the results of both databases. However, H.2.1, page 52 lists the figure for both databases combined (correctly reporting 3220 citations). This was an error in documenting the strategy, which was corrected by the company in the response to PfCs with assurances that no relevant evidence was missed.
Were appropriate sources searched?	YES	Relevant databases and grey literature sources were searched, although the use of more databases could potentially have retrieved further relevant evidence.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study type.
Were appropriate search terms used?	YES	Very thorough search terms were used.
Were any search restrictions applied appropriate?	YES	Animal papers were removed appropriately.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not fully referenced.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.1.5 Patient and Carer Experience Searches

Search strategy

The original company submission included searches to retrieve real-world data of patient and carer experiences of AL amyloidosis. A description of the searches and one of the search strategies was included in Appendix N (pp. 105-112).

In response to the ERG's PfCs, a further document was provided by the company, which included the additional search strategy and corrections to errors identified by the ERG.

Table 35 ERG appraisal of evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	Missing Search Strategies Only the strategy for Google Scholar was provided in the original submission, with incomplete details. In response to the PfCs, more detailed information was provided on the search. The strategy for PubMed was also provided with the further requested information on this search. Missing Dates: In the original submission, details of the exact dates of each of the searches throughout the entirety of the appendices had not been provided. In the response to PfCs, this data was provided in DD/MM/YYY format as requested. Errors in Documentation: In the original submission of Appendix N, there was a mistake in line 1, Table 34, page 106: 'Amyloid*OR' should have a space after *. In the response to PfCs, the company noted this was a typographical error in documenting the strategy and made assurances that no relevant evidence was missed. Google Scholar Search Documentation: In line with best practice, it would have been better to describe the version of Google Scholar used, the geographical location the search was conducted, and note whether the search was performed in incognito mode to limit personalisation bias.
Were appropriate sources searched?	YES	A search of social media sources or dedicated social media databases (e.g. socialmention.com or social-searcher.com) could have been provided additional relevant evidence. However, this was a rapid review which is why few sources have been searched. There are limitations to using Google Scholar since this database is subject to personalisation bias; the results retrieved can also vary by the user's location and the version of Google Scholar used.
Was the timespan of the searches appropriate?	YES	The search of Google Scholar limited studies by date 2015-2021 in the strategy, which was appropriate for a rapid review on real-word data. In the response to PfCs (which provided the search strategy for PubMed) it was evident that the search of PubMed was date limited by 2015/1/1–2021/3/24. This was appropriate for a rapid review on real-word data.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the outcome.
Were appropriate search terms used?	YES	The terms used were narrow and focused which was appropriate for a rapid review on real-word data.

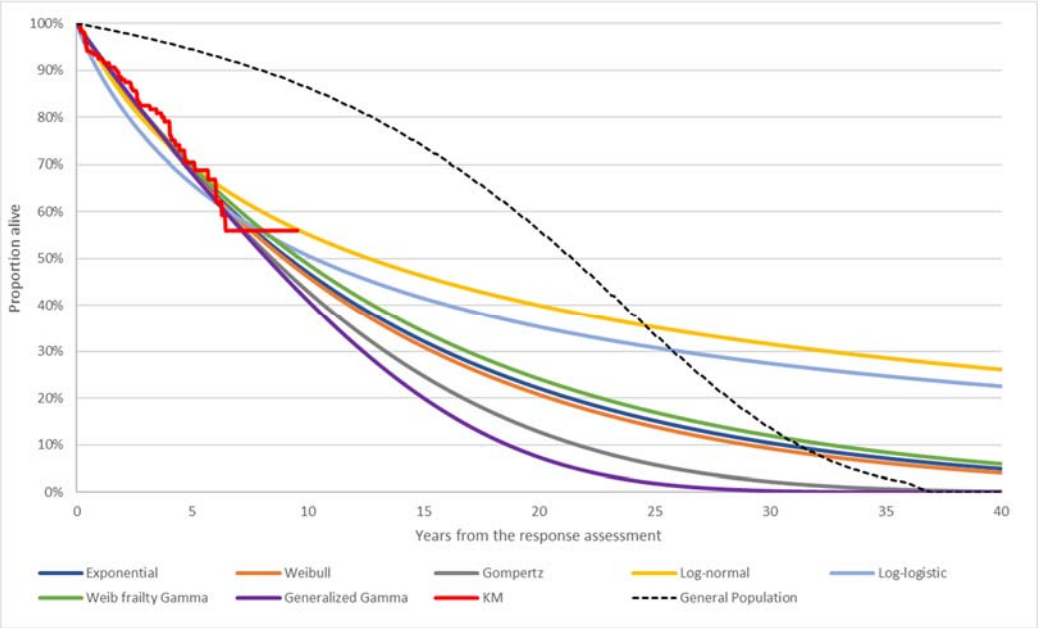
Were any search restrictions applied appropriate?	NOT APPLICABLE	No restrictions were applied. However, this was only apparent following the response to PfCs which provided the strategies for each database separately.
Were any search filters used validated and referenced?	NOT APPLICABLE	No search filters were used in either database. However, this was only apparent following the response to PfCs which provided the strategies for each database separately.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.2 Overall Survival extrapolation plots

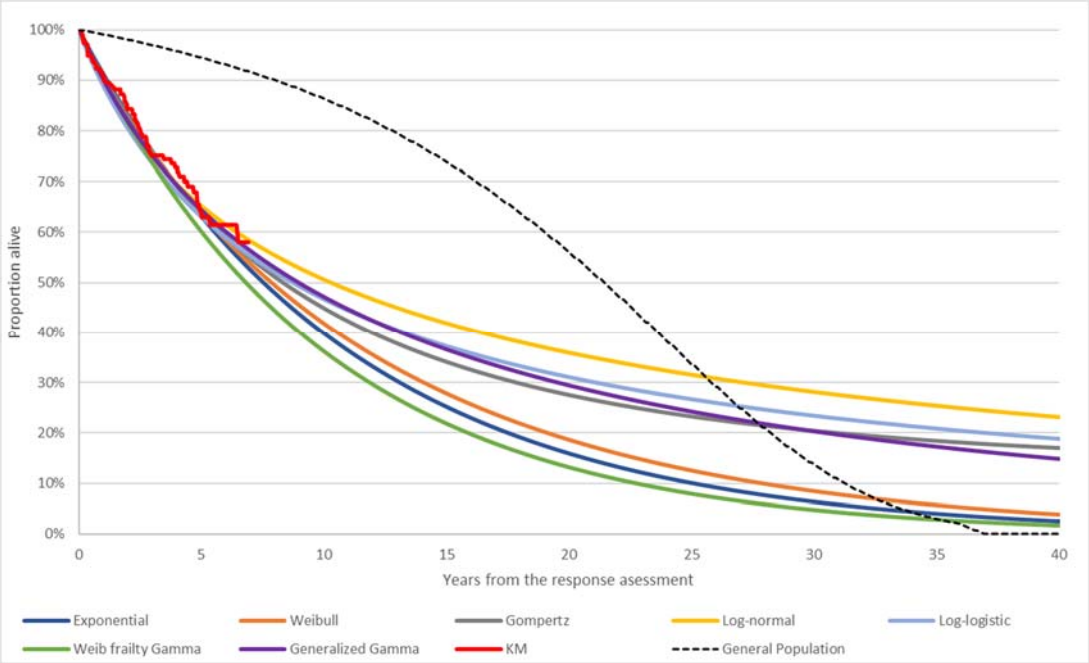
9.2.1 Assessment of haematologic response at 3 months

Figure 15 Overall survival Kaplan-Meier curve and parametric extrapolations for patients with complete response (CR) at three months based on Ravichandran et al (2021a) [1]



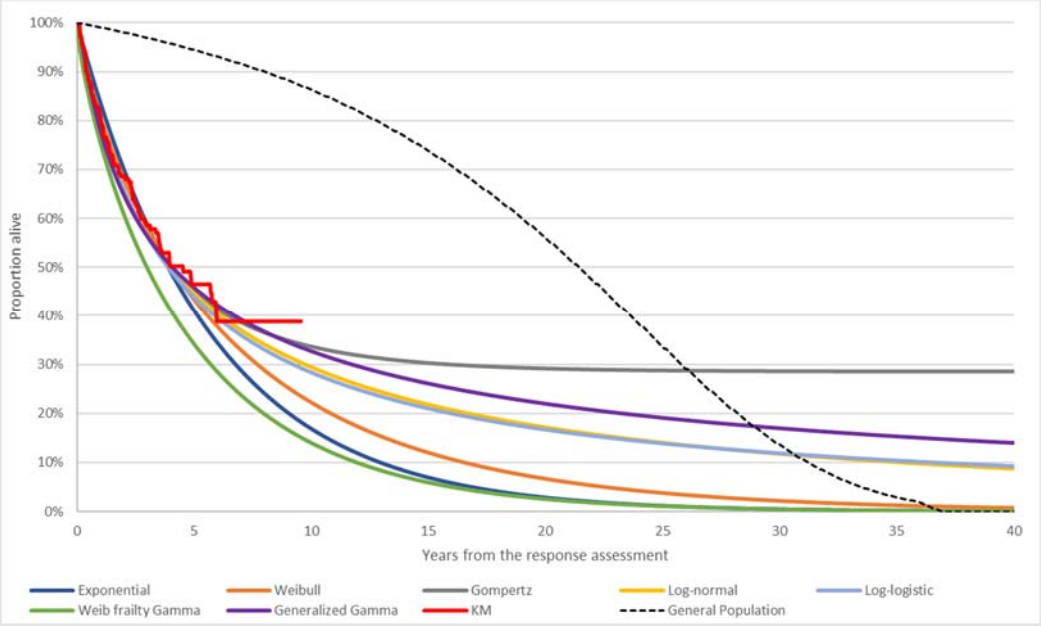
Kaplan-Meier (KM) Data: Ravichandran et al. (2021a)[1]

Figure 16 Overall survival Kaplan-Meier curve and parametric extrapolations for patients with very good partial response (VGPR) at three months based on Ravichandran et al (2021a) [1]



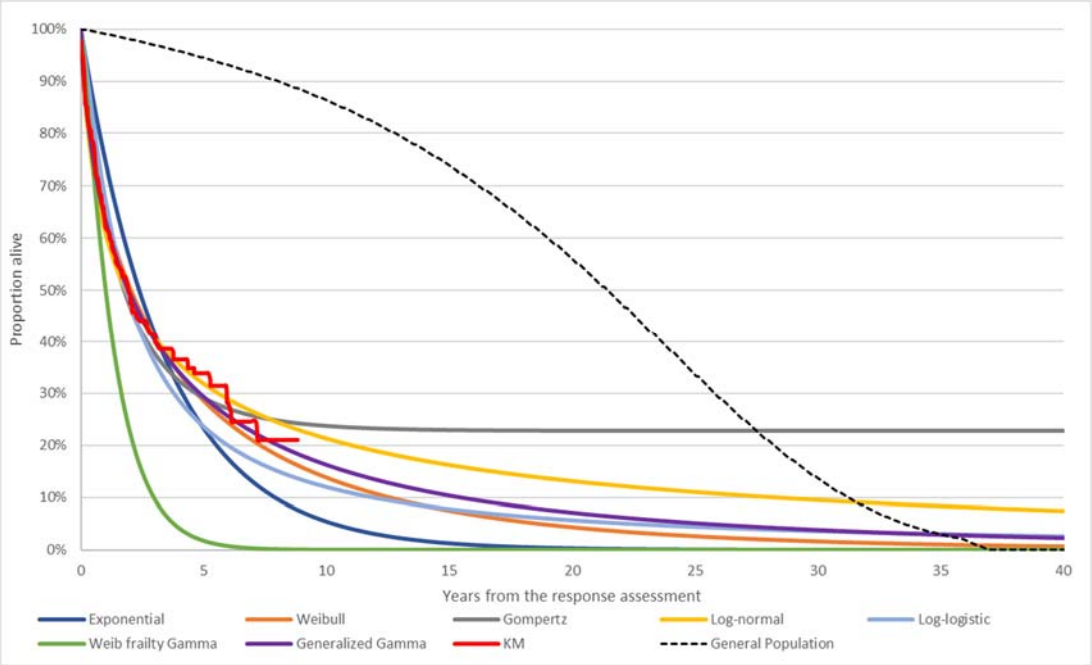
Kaplan-Meier (KM) Data: Ravichandran et al. (2021a)[1]

Figure 17 Overall survival Kaplan-Meier curve and parametric extrapolations for patients with partial response (PR) at three months based on Ravichandran et al (2021a) [1]



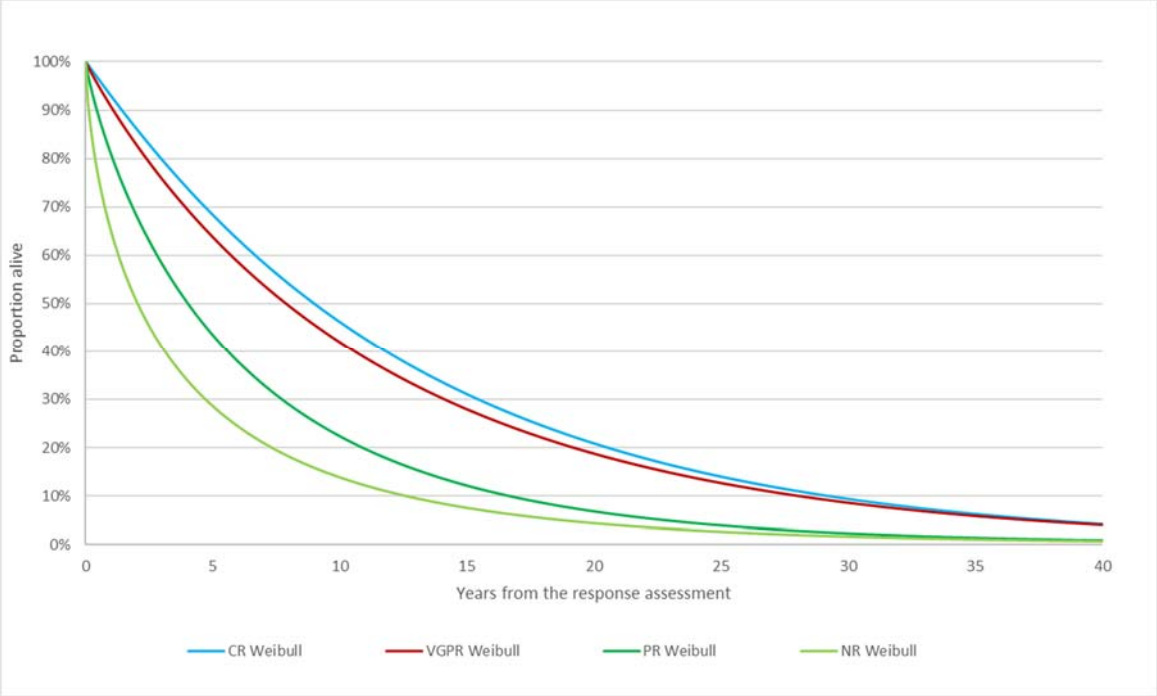
Kaplan-Meier (KM) Data: Ravichandran et al. (2021a)[1]

Figure 18 Overall survival Kaplan-Meier curve and parametric extrapolations for patients with no response (NR) at three months based on Ravichandran et al (2021a) [1]



Kaplan-Meier (KM) Data: Ravichandran et al. (2021a)[1]

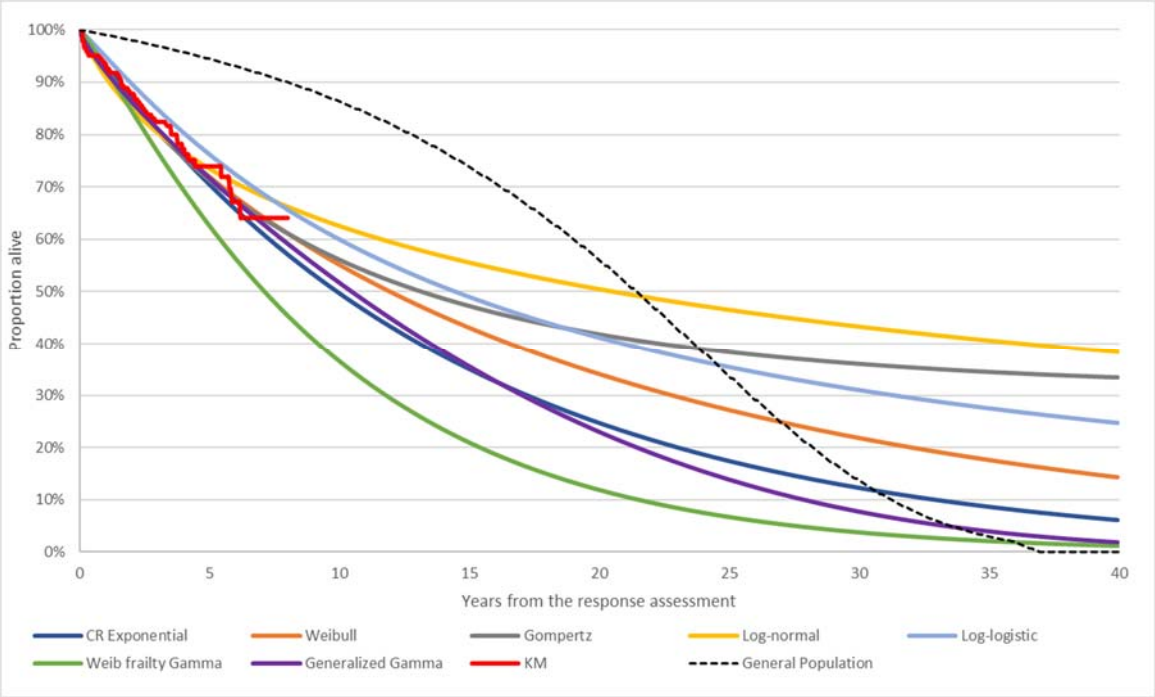
Figure 19 Extrapolation of 3-month survival: selected plausible distributions for all response types†



† The functional form of distribution selected for PR and NR must be the same.

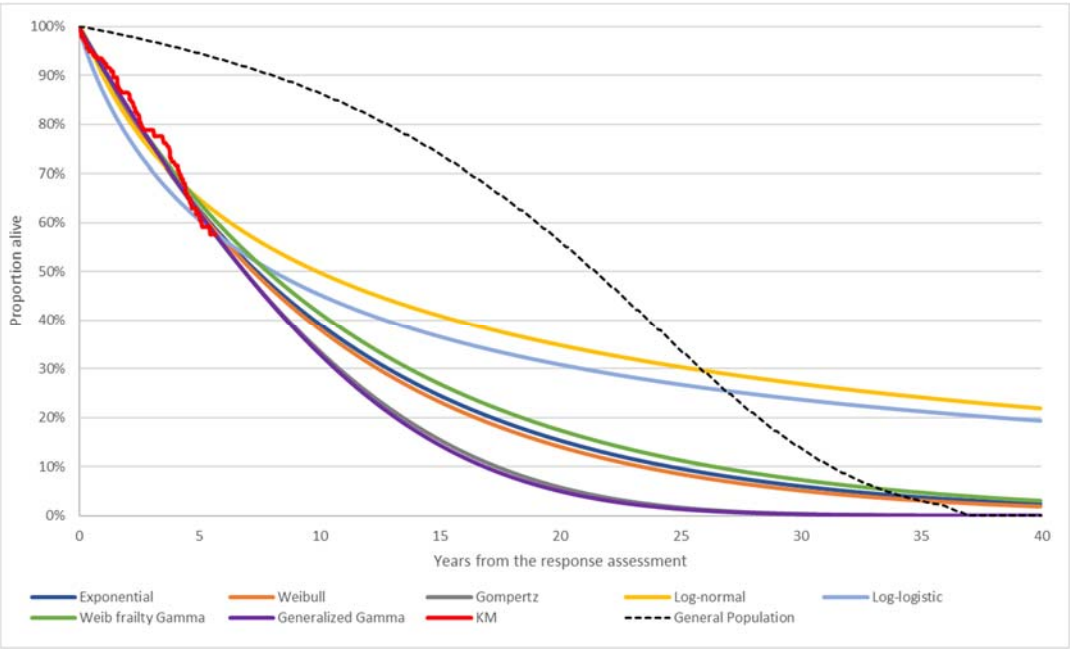
9.2.2 Assessment of haematologic response at 6 Months

Figure 20 Overall survival Kaplan-Meier curve and parametric extrapolations for patients with complete response (CR) at six months based on Ravichandran et al (2021a) [1]



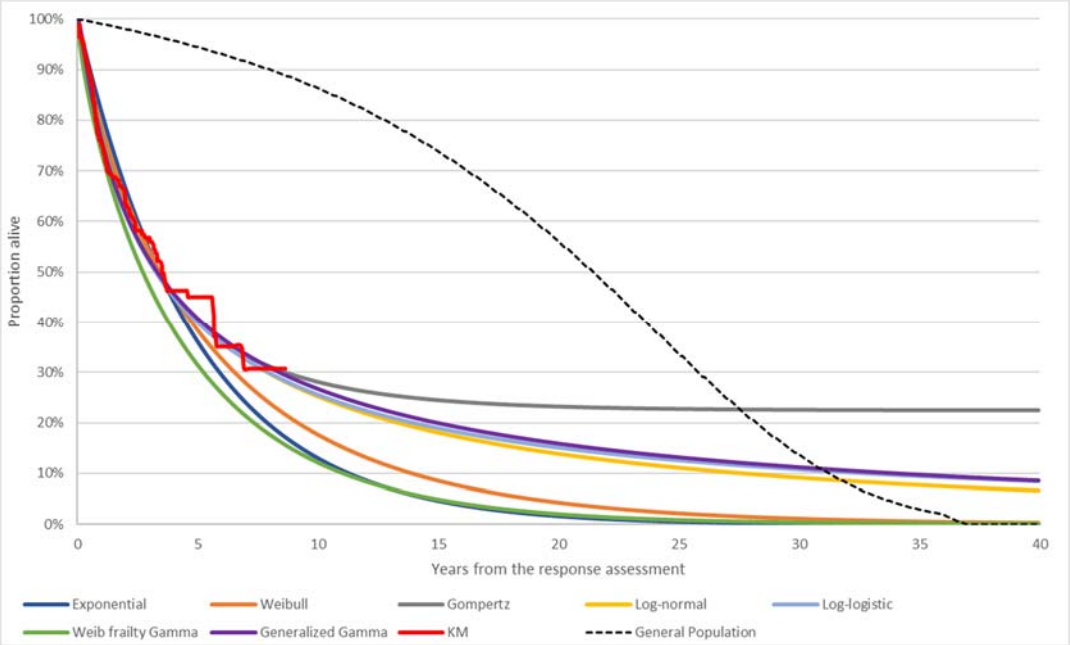
Kaplan-Meier (KM) Data: Ravichandran et al. (2021a)[1]

Figure 21 Overall survival Kaplan-Meier curve and parametric extrapolations for patients with very good partial response (VGPR) at six months based on Ravichandran et al (2021a) [1]



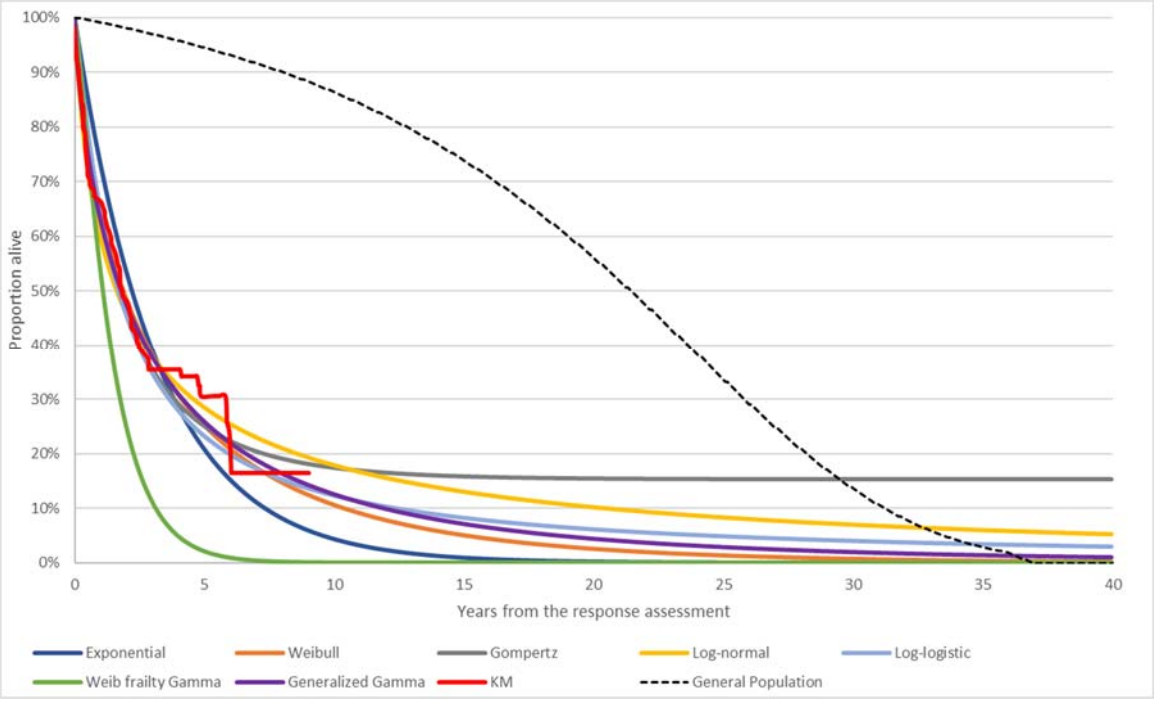
Kaplan-Meier (KM) Data: Ravichandran et al. (2021a)[1]

Figure 22 Overall survival Kaplan-Meier curve and parametric extrapolations for patients with partial response (PR) at six months based on Ravichandran et al (2021a) [1]



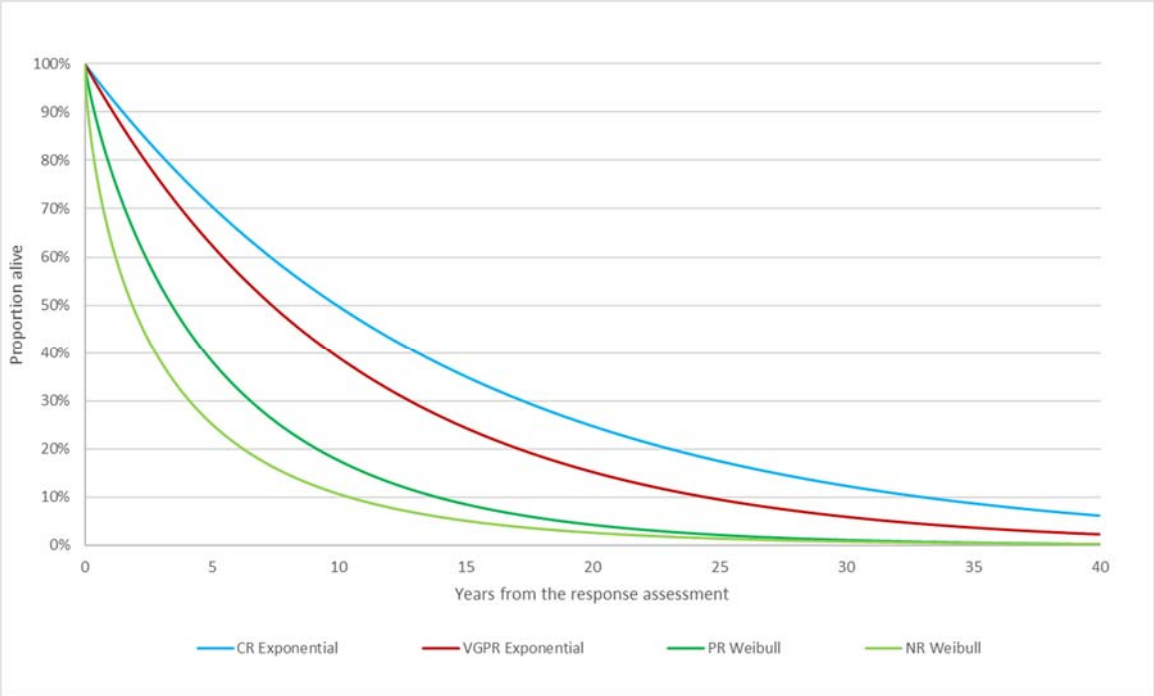
Kaplan-Meier (KM) Data: Ravichandran et al. (2021a)[1]

Figure 23 Overall survival Kaplan-Meier curve and parametric extrapolations for patients with no response (NR) at six months based on Ravichandran et al (2021a) [1]



Kaplan-Meier (KM) Data: Ravichandran et al. (2021a)[1]

Figure 24 Extrapolation of six-month survival: selected plausible distributions for all response types†



† The functional form of distribution selected for PR and NR must be the same.

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Technical engagement response form

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **15 October 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, 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 during engagement 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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Janssen & Cilag Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis that is not restricted to exclude patients with Mayo Clinic Cardiac Stage IIIb disease	**YES**	Following discussion at the Technical Engagement meeting, Janssen have considered the comments from the ERG on how best to model the full population of AL amyloidosis patients, including patients with Mayo Clinic Cardiac Stage IIIb disease. Janssen consider the approach taken by the ERG, using real world evidence (RWE) in all patients to inform the baseline (standard of care, BCd) response rate, to be reasonable. However, Janssen note that there are limitations associated with this approach; in particular, the use of different evidence sources for baseline haematologic responses and the relative benefits of DBCd versus BCd introduces internal inconsistency to the model, requiring the assumption that the treatment effect from ANDROMEDA is applicable to Stage IIIb patients. As such, Janssen propose two revised base cases, one using RWE response rates in all patients from a study conducted by the European Myeloma Network (the EMN23 study) which included patients with Mayo Clinic Cardiac Stage IIIb disease, to inform the baseline response rate, and one using response rates from ANDROMEDA to ensure internal consistency. Both base case analyses use evidence from the EMN23 study to inform overall survival (OS) in the model. ***RWE responses base case*** Feedback received during the Technical Engagement Process reaffirms the significant unmet need for an efficacious and tolerable treatment regimen in Mayo Clinic Cardiac Stage IIIb patients. Feedback from the UK Kidney Association (Technical Engagement Papers, page 300) is that patients and clinicians do, and should continue to, discuss and decide

		treatment options based on individual patient preference and circumstance: "*No patient group are currently excluded from treatment. Shared decision making with the patient regarding whether they want to embark on treatment in the knowledge the prognosis may be very poor happens in clinical practice with some patients deciding to take a palliative care approach and others having a very limited amount of treatment at a reduced dose to determine tolerability. This would remain the approach with daratumumab*." The availability of DBCd across all of AL amyloidosis patients provides patients and clinicians with choice, which is essential in the management of rare diseases. There is a scarcity of treatment options for patients with Mayo Clinic Cardiac Stage IIIb disease because they are often deemed to be too frail to receive any off-label regimens that may be used in AL amyloidosis. As described in response to Issues 6 and 7, Janssen provide an RWE responses base case using the EMN23 study to inform baseline haematologic response rates for the BCd arm and OS estimates stratified by haematologic response. These data from the EMN23 study have become available to Janssen since the original Company Submission. This revised approach builds upon and strengthens the analysis performed by the ERG in which data derived from the ALchemy trial were used to reflect a population which included Mayo Clinic Cardiac Stage IIIb patients. In line with the ALchemy study, the EMN23 study includes patients from the full population for which Janssen seek reimbursement for DBCd, namely patients of all stages of the Mayo Clinic Cardiac staging system, including the most severe group with the worst prognosis, Stage IIIb (which comprised [redacted]% of patients included in the post-2010 period of the EMN23 study). However, as detailed in response to Issue 6, the EMN23 study represents a superior source of real-world clinical data as compared with the ALchemy study, due to the availability of more mature data and a larger sample size (including a similarly sized UK-based population), which together provide greater certainty in the evidence as compared with ALchemy. Despite these notable strengths, this revised RWE responses base case is associated with some limitations. The use of different evidence sources to inform baseline haematologic response outcomes (EMN23) and the relative efficacy of DBCd and BCd (ANDROMEDA) introduces internal inconsistency to the model, which necessitates an assumption that the relative treatment benefit associated with DBCd in the ANDROMEDA trial is generalisable to

		patients with Mayo Clinic Cardiac Stage IIIb disease. This is a conservative assumption, given subgroup evidence from ANDROMEDA which demonstrates that the relative treatment effect of DBCd increases with increasing severity of disease according to the Mayo Clinic Cardiac staging system, as described below. Results of subgroup analyses of the primary efficacy outcome in ANDROMEDA, complete haematologic response (CHR), by baseline haematologic response and the associated interaction test statistics are presented in Appendix 4. Data from the 12-month landmark analysis show that DBCd resulted in high CHR rates across all Mayo Clinic Cardiac stages with a trend towards greater CHR rates in patients with more advanced disease: Stage I: [redacted]%; Stage II: [redacted]%; Stage IIIa/IIIb: [redacted]%. By contrast, achievement of CHR declined for BCd-treated patients with worsening cardiac involvement, decreasing from [redacted]% for Stage I patients to [redacted]% at Stage II, and reaching just [redacted]% for Stage IIIa/IIIb patients.[1] Data from the IA1 analysis allow the same conclusions to be drawn. Whilst the interaction test statistics are not significant, risk ratio (RR), odds ratio (OR) and risk difference (RD) statistics consistently show significant differences in response rates within subgroups using data from both the IA1 and 12-month analysis data cut-offs. The upward trend for relative efficacy of DBCd versus BCd increasing with cardiac stage indicating a better treatment effect with advancing cardiac involvement following treatment with DBCd. Overall, this subgroup evidence from ANDROMEDA supports the assumption of strong relative benefit for DBCd versus BCd in the Mayo Clinic Cardiac Stage IIIb patient population. Accordingly, Janssen consider the results of the RWE responses base case to be highly conservative. ***ANDROMEDA base case*** As outlined above, the approach suggested by the ERG to derive the relative benefits of DBCd versus BCd from the ANDROMEDA trial and apply these to an external source of haematologic response rates for BCd-treated patients is associated with the introduction of internal inconsistency within the model. To address this, Janssen provide a base case in

		which six-month haematologic response rates from the ANDROMEDA trial are used, thus providing robust internal consistency. As with the RWE responses base case, this approach is associated with some limitations. Derivation of the baseline haematologic response rates from ANDROMEDA means that these rates are derived from a population which does not include patients with Mayo Clinic Cardiac Stage IIIb. In addition, the OS estimates stratified by haematologic response in the ANDROMEDA base case remain informed by the EMN23 study, as in the RWE responses base case. Although this base case has a higher level of internal consistency than the RWE responses base case, the baseline level of response may be overestimated since Mayo Clinic Cardiac Stage IIIb patients were not enrolled in ANDROMEDA. Subgroup analyses from ANDROMEDA suggest, however, that baseline response may be overestimated to a greater extent for the BCd arm than the DBCd arm meaning this base case is conservative. ***Conclusion*** The results of the revised RWE responses base case and ANDROMEDA base case analyses are presented in Appendix 2, and demonstrate conservative ICERs of £32,744/QALY gained and £32,692/QALY gained, respectively. It is expected with longer follow up data from ANDROMEDA, the relative treatment effect in favour of DBCd to improve due to a deepening of haematologic response in the study. Considering that this is an orphan disease where patients have extremely poor prognosis and significant unmet need, the results of the ANDROMEDA base case show clearly that DBCd is a plausibly cost-effective use of NHS resources. Patients with Mayo Clinic Cardiac Stage IIIb disease meet NICE's end of life criteria, given that they have the poorest survival prospects of approximately six months, and DBCd is highly likely to extend their lives by more than three months (given the incremental life years observed in the RWE and ANDROMEDA base cases: [redacted] years and [redacted] years (undiscounted), respectively. As such, Janssen consider flexibility in the cost-effectiveness threshold is warranted.

		There are limitations inherently associated with each of these approaches, consequential to the imperfect level of information available in a rare condition such as AL amyloidosis. Janssen considers, however, that the true ICER is likely to fall below the two ICERs presented and that the submitted cost-effectiveness results provide the Committee with sufficient evidence required to evaluate DBCd in the full licensed population. Moreover, the similarity in results produced by the two conservative modelling approaches provides confidence regarding the likely upper bound of the true ICER.
Key issue 2: Absence of clinical trial data for patients with Mayo Clinic Cardiac Stage IIIb disease	**YES**	Please refer to Janssen's response to Issue 1; as described above, Janssen have provided a highly conservative revised RWE responses cost-effectiveness analysis that incorporates patients with Mayo Clinic Stage IIIb disease.
Key issue 3: Immaturity of overall survival data from the ANDROMEDA clinical trial	**NO**	Janssen is in agreement that at the time of latest trial follow-up, uncertainty exists in long-term outcomes. As such, for current decision-making, Janssen is leveraging a robust external real-world evidence source of data, with longer follow-up, and the greatest level of maturity of OS data, the EMN23 study, to inform long-term survival predictions (see Key issue 6). Future data cuts with longer follow-up periods from the ANDROMEDA trial will provide greater insight into the overall survival of AL amyloidosis patients treated with DBCd relative to those treated with BCd. More mature overall survival data are expected from the 200 MOD-PFS event-driven data cut-off from ANDROMEDA, now anticipated to be in [redacted], which is within the timeframe DBCd would spend in the CDF if the committee were to deem this appropriate. This additional, more mature data would provide an opportunity to validate the assumptions of the current cost-effectiveness model.
Key issue 4: Lack of medium-to-long term adverse event data for daratumumab in AL amyloidosis	**YES**	The currently available safety data for daratumumab in AL amyloidosis is derived from ANDROMEDA, a robust, Phase III randomised controlled trial (RCT) involving 195 and 193 patients within the DBCd and BCd (current standard of care) trial arms, respectively. Since AL amyloidosis is a rare disease, the availability of safety data from a Phase III RCT is significant and represents an important advance in the evidence base. While the safety data from ANDROMEDA are currently not medium-to-long term, there are long-term safety data available for daratumumab in the multiple myeloma (MM) patient population as indicated by the ERG (ERG report, page 17); the Phase III POLLUX study

		provides safety data for daratumumab in MM patients after more than four years (54.8 months) of follow up.[2] The European Public Assessment Report (EPAR) for daratumumab in AL amyloidosis states: "*The safety profile is in general as expected in the context of the patient population, the backbone therapy and the known safety profile of daratumumab SC*" (page 116) and concludes that there no new safety findings or adverse drug reactions have been observed.[3] This is in alignment with the conclusions of the ERG that the safety outcomes of ANDROMEDA are generally well-reported and "*consistent with those detailed in the SmPC for daratumumab*" (ERG Report, page 63), with the majority of reported TEAEs being low grade and manageable. Therefore, the safety data available from the ANDROMEDA study and from daratumumab in MM are aligned, suggesting that the limited safety follow up currently available in the AL amyloidosis population should not be considered a significant area of uncertainty. The ERG noted a concern regarding "*the possible effect on infections beyond the period observed in the trial*" (ERG report, page 16). While reports of any grade and Grade 3 or 4 infections and infestations were more frequent in the DBCd arm of ANDROMEDA than the BCd arm, the treatment discontinuation rate was low in both the DBCd and BCd trial arms ([redacted] and [redacted], respectively).[1] Notably, any grade and treatment-emergent infections decreased from Cycle 7 onwards in the DBCd arm compared with Cycles 3–6 ([redacted] versus [redacted], respectively) and Grade 3 or 4 treatment-emergent infections decreased from Cycle 7 onwards in the DBCd arm ([redacted] compared with [redacted] and [redacted] during Cycles 1–2 and Cycles 3–6, respectively).[1] These results indicate a clear downward trend in the occurrence of infections once patients switch from DBCd to daratumumab monotherapy, and therefore suggest that the increased risk of infection with daratumumab treatment does not persist in the long-term. This conclusion is supported by evidence from patients newly diagnosed with MM, where the risk of infection has been identified to be greatest in the first three months after diagnosis, and treatment with antibiotic prophylaxis for 12 weeks has been found to manage the short-term risk effectively.[4] Finally, it should be noted that, when presented with data from ANDROMEDA during an advisory board, UK clinicians suggested that it would be unlikely that AL amyloidosis patients would be treated with daratumumab (DBCd) beyond two years (see response to Issue 10 for

Commented [PMC[1]: 28 Oct 2021 results from MAIA (pre-specified IAIII) median follow up 56.2 months https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00466-6/fulltext

		further details). As such, a lack of long-term safety data should not be considered a key uncertainty because daratumumab is not anticipated to be administered beyond 2 years in clinical practice, with ANDROMEDA expected to provide sufficiently informative safety data over this treatment period.
Key issue 5: Timing of response assessment for depth of haematologic response	**YES**	A six-month decision tree exit timepoint has been retained in Janssen's revised base cases for technical engagement due to the importance of comprehensive capturing the deepening response rates over time to robustly inform long-term outcomes within the model. Haematologic responses deepen over time. This is supported by feedback from expert clinicians consulted at a UK advisory board,[5] as well as published real-world evidence in AL amyloidosis by Kastritis et al. (2021)[6] and Ravichandran et al. (2021).[7] In the ALchemy study, a progressive improvement in the proportion of patients achieving a deeper (≥VGPR) between 3 and 6 months was observed (CHR: 27.9%; 31.0%; VGPR: 29.2%; 34.0% at 3 and 6 months, respectively). In line with this, it was observed that the numbers at risk in each of the response categories changed with the assessment time point (over 1, 3 and 6 months), with numbers at risk for CR and VGPR increasing, and decreasing for PR and NR over time.[7] The deepening of response over time seen in AL amyloidosis patients is also supported by the results of the ANDROMEDA trial. As presented in Table 1 below (which is a reproduction of Table 17 in Section B.2.6.1 of the original Company Submission), although the proportion of patients in the DBCd arm achieving a VGPR or better (VGPR or CHR) or any overall response (CHR, VGPR or PR) remained approximately stable between the IA1 and 12-month landmark analyses, CHR rates rose, while VGPR rates fell, evidencing an overall deepening of response from VGPR to CHR with time on DBCd therapy. In the BCd arm of the ANDROMEDA trial, the proportion of patients achieving a CHR increased from 18.1% to 19.2% between the IA1 and 12-month landmark analyses, despite patients no longer receiving BCd between these timepoints (BCd was received for a maximum of six cycles). The deepening of response over time has also been noted in MM patients; a clinical expert noted that the efficacy of autologous stem cell transplant (ASCT) in MM patients is similarly not assessed immediately after these procedures, to reflect the time taken for plasma cells to respond.[8]

In accordance with the above evidence, newly diagnosed AL amyloidosis patients in clinical practice would typically continue the same regimen (unless they experience tolerability issues) in order to increase their depth of response and improve their long-term outcomes.[5]

Table 1: Summary of overall best confirmed haematologic response based on IRC assessment; ANDROMEDA ITT analysis set (14th February 2020 data cut-off and 13th November 2020 data cut-off)

Response	IA1, % (95% CI[a])		12-month landmark, % (95% CI[a])	
	BCd (N=193)	DBCd (N=195)	BCd (N=193)	DBCd (N=195)
CHR	18.1 (13.0, 24.3)	53.3 (46.1, 60.5)	19.2 [redacted]	59.0 [redacted]
VGPR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
NE	[redacted]	[redacted]	[redacted]	[redacted]
VGPR or better (CHR+VGPR)	49.2 [redacted]	78.5 [redacted]	50.3 [redacted]	79.0 [redacted]
Overall response[b]	76.7 [redacted]	91.8 [redacted]	76.7 [redacted]	91.8 [redacted]

[a] 95% CIs are based on Clopper-Pearson exact test. [b] Overall response defined as CHR+VGPR+PR.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intention-to-treat; NE: not evaluable; NR: no response; PD: progressive disease; VGPR: very good partial response.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[1] Kastritis *et al.,* (2020);[9] Janssen ANDROMEDA 12-month landmark analysis (2021);[10] Kastritis *et al.,* (2021).[11]

As well as enabling haematologic responses to be comprehensively captured, a clinical expert advised that OS extrapolations based on exiting the decision tree at six months would be more reflective of long-term OS observed in practice, as compared with those based on three-month data, given that it takes time for plasma cells to respond to treatment.[8] This is of particular relevance, as the ERG raised concerns regarding the assumption adopted in

		the model that "*overall survival depends only on the depth of haematologic response achieved*" (ERG report, page 16); clinical opinion is that this assumption is mitigated through the use of six-month data. For these reasons, a six-month decision tree exit timepoint is maintained in the revised base cases. However, Janssen acknowledge that UK treatment guidelines suggest that patients may undergo response assessment at three months, with a view to potentially switching treatment in attempt to improve the response of those patients who are achieving suboptimal levels of response (i.e. a response below VGPR) to treatment (ERG report, page 79). This is captured by the three-month exit within the model, whereby patients who achieve PR/NR at three months can move to the '2L Tx' health state. Therefore, a scenario analysis has been conducted in which a three-month exit timepoint is considered; the results for this scenario are presented in Appendix 3. The results of this scenario show that consideration of a three-month exit timepoint results in ICERs of £38,520/QALY gained and £42,620/QALY gained in the RWE responses and ANDROMEDA base cases, respectively. Considering the important decision modifiers that apply, including the rarity of AL amyloidosis and its severity, particularly in the Mayo Clinic Cardiac Stage IIIb patients, these results still indicate that DBCd is likely to represent a cost-effective use of NHS resources. In addition, there are important limitations to the three-month decision exit point, with regards to the data that inform the model, which limit its use for decision-making. Specifically, three-month exit data have a comparatively lower ability to capture clinical outcomes. This is because haematologic responses improve and deepen over time, and this instability in the response data reduces its ability to predict long-term survival. In addition, importantly, while the three-month exit of the model is able to capture the costs of patients who achieve a CHR or VGPR and stay on treatment, it is not able to capture the deepening of response over time that has been demonstrated in both clinical trials and real-world studies, as described above. **One-month decision tree exit** Regarding the ERG's suggestion to include an additional scenario analysis whereby a response assessment is conducted at one-month (ERG report, page 81), Janssen

		acknowledge that the achievement of a response at the earlier timepoint of one month translates to improved overall survival.[6, 7] However, as described above, the use of landmark analyses at a timepoint where response rates have stabilised is important for informing long-term extrapolations, whereas the assessment of response at one month would not provide the most accurate projections of long-term survival for AL amyloidosis patients due to deepening of response over time and instability of the data. Further, as noted in Janssen's response to clarification questions, UK-based clinicians consulted at an advisory board explained that it is important to prevent prematurely switching patients (unless a response is not achieved whatsoever) to subsequent lines of therapy, noting the importance of avoiding a situation whereby patients have received several lines of therapy in a short period of time and are facing a lack of other treatment options.[5] Finally, as noted by the ERG, only a small minority of patients who are very clearly not showing a response to treatment undergo a response assessment at one month with a potential view to switch treatment. As such, it is not standard NHS clinical practice to consider treatment switching at one month and Janssen therefore do not consider exit from the decision tree at one month to be clinically appropriate. An additional scenario analysis with assessment of response at one month was therefore not conducted.
Key issue 6: Source of data for overall survival, stratified by haematologic response	**YES**	In the original Company Submission, a study conducted by Palladini *et al.* (2012) was used as the external source of OS data to inform survival in the economic analysis.[12] As outlined in response to Key Issue 1, data from the EMN23 study have become available since this submission. The EMN23 study is a more recent source of data and provides superior generalisability to the UK population than the Palladini *et al.* (2012) study, and therefore now represents Janssen's preferred source of external OS data to inform economic analyses.[13] The EMN23 study is a real-world, retrospective, observational study on the management and outcomes of AL amyloidosis patients from 10 European countries, including the UK. Detailed baseline characteristics of patients recruited in the EMN23 study, as well as the treatment regimens received by these patients, are presented in Janssen's response to clarification questions (Parts 4a and 4c of Question B1, respectively).

		While the ALchemy study provides an alternative source of OS data stratified by haematologic response, Janssen considers that the EMN23 study is a superior source of evidence for decision-making at this time for the reasons outlined below. ***Sample size and generalisability to UK clinical practice*** As compared with the ALchemy study, the EMN23 study has a greater sample size, which is of particular value in an orphan disease. While the ALchemy study represents a UK-only population of 1,194 patients, the EMN23 study also recruited a large overall sample of 1,156 UK-based patients in the post-2010 cohort (which includes patients who initiated first-line treatment for AL amyloidosis between 2011–2018, a time period considered to most accurately reflect the current approach to treatment of AL amyloidosis in the UK). Furthermore, the UK-based patient populations recruited to the EMN23 and ALchemy trials overlap, with many patients recruited to both studies from the UK National Amyloidosis Centre (NAC). As such, the comparability of the patient populations recruited to the EMN23 and ALchemy studies is as expected. Overall, the large sample of UK patients included in the post-2010 cohort of the EMN23 study suggests its generalisability to typical clinical practice in the UK. ***Data maturity*** Importantly, the EMN23 study holds an advantage over the ALchemy study in relation to the maturity of survival data available. The immaturity of survival data in the ALchemy study is demonstrated by the overlapping Kaplan-Meier curves for patients achieving CR and VGPR at the three-month analysis timepoint, with expert clinical opinion indicating that this clinically implausible result is likely to be reflective of immature data.[8] The lack of face validity for the CR and VGPR survival at the three-month timepoint therefore represents a limitation of the ERG base case approach, which employs a three-month exit from the decision tree. Further, no significant differences were observed in survival for patients achieving CR and VGPR at any of the one-month, three-month and six-month timepoints, with median OS values not reached for these two response categories at any timepoint.

		By contrast, the EMN23 study reports a long follow-up period of [redacted] (range: [redacted]–[redacted]) for patients treated in the post-2010 period, and median haematologic response was reached for all response categories, with statistically significant between-response differences in OS.[14] Further, survival extrapolations derived from EMN23 six-month OS per haematologic response data underwent validation by a UK-based expert clinician, with this process indicating that the extrapolations generated clinically plausible long-term survival estimates.[8] Whilst the additional maturity may in part be derived from study patients outside of the UK, Janssen argue that the greater maturity of survival data in the EMN23 study reduces uncertainty in the model OS estimates, supporting its use as the external source of OS data to inform the model. Indeed, NICE frequently places significant value in evidence which can aid or reduce decision uncertainty at time of evaluation, thus reaffirming the relevance of EMN23. ***Conclusion*** Overall, Janssen consider that the EMN23 study is broadly equivalent to the ALchemy study in terms of the UK-based sample size and subsequent generalisability to UK clinical practice, while at the same time providing a more mature source of survival information. Further details on the survival analysis conducted using EMN23 data are presented in Appendix 1. The results for the revised RWE and ANDROMEDA base cases in which the six-month exit timepoint informed by OS data from the EMN23 study are presented in Appendix 2.
Key issue 7: Baseline source of haematologic response distribution for BCd	**YES**	As discussed in more detail in response to Key Issue 1 above, Janssen present two revised base cases: the RWE responses base case which considers baseline haematologic response rates derived from the EMN23 study, in alignment with Janssen's preferred source of external OS data (see response to Key Issue 6), and the ANDROMEDA base case which considers baseline haematologic response rates derived from the ANDROMEDA trial. ***RWE responses base case*** In alignment with the choice of external OS source, Janssen's revised RWE responses base case approach considers baseline haematologic response rates at six months as derived from the post-2010 population of the EMN23 study. The same approach was used to

calculate EMN23-based response rates for DBCd as was used in the ERG's model to calculate ALchemy-based response rates for DBCd. This involved the application of ANDROMEDA-based relative risks (DBCd versus BCd) to response rates from EMN23. The conditioning order was as preferred by the ERG: alive, CR, VGPR.

In order to derive the BCd response rates from EMN23, it was necessary to make an assumption regarding patients that were marked as 'NA' in the six-month landmark response analysis, and that did not die before six months. It was assumed that these patients were distributed among the response categories (CR, VGPR, PR/NR) in the same proportions as observed for the patients that were not marked as 'NA'.

The response rates thus derived from the EMN23 study are presented in Table 2.

Table 2: Baseline haematologic response rates used in the revised RWE responses base case

Cycle	Proportion of patients at six months			
	CR	VGPR	PR/NR	Dead
DBCd				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
BCd				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]

6	[redacted]	[redacted]	[redacted]	[redacted]	

Presented figures are rounded to the nearest 1% and thus may not sum to 100%.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

ANDROMEDA base case

In order to permit robust internal consistency between the haematologic response rates used and the relative benefits of DBCd versus BCd, the ANDROMEDA base case considers six-month haematologic response rates derived from the ANDROMEDA trial, as presented in Table 3, which is a reproduction of Table 40 in Section B.3.3.2 of the original Company Submission.

Table 3: Baseline haematologic response rates used in the revised ANDROMEDA base case

Cycle	Proportion of patients at six months			
	CR	VGPR	PR/NR	Dead
DBCd				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
BCd				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]

		6 [redacted] [redacted] [redacted] [redacted] Presented figures are rounded to the nearest 1% and thus may not sum to 100%. **Abbreviations:** BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response. ***Conclusions*** The results for Janssen's revised RWE responses base case and ANDROMEDA base case approaches, in which the above response rates are implemented, are presented in Appendix 2.
Key issue 8: Combining suboptimal haematologic response categories in the model	**NO**	As outlined in response to clarification questions (Part 1 of Question B8), pooling of patients with PR and NR within the model is appropriate. This approach is informed by all available data from both the PR and NR response categories and reflects the standard of care in UK clinical practice, given that all patients with a sub-optimal haematologic response would be expected to be managed similarly by switching treatments. A clinical expert from the NAC confirmed that patients achieving a PR or NR could be grouped as their long-term outcomes are expected to be similar, whereas differentiation of patients who achieve a CHR or VGPR is clinically significant since this has a considerable impact on their expected long-term outcomes. As discussed during the Technical Engagement meeting, Janssen calculated the overall survival estimates for PR and NR independently, but also stratified by treatment arm. Results from these analyses indicated that if PR and NR were to be modelled independently, as requested by the ERG, results would be expected to be similar to those obtained using the PR/NR pooling method. However, improved survival for DBCd patients and lower survival for BCd patients at all time points may be expected. Therefore, pooling patients who achieve a PR/NR is likely to be a conservative estimate of overall survival, which may favour BCd. In addition, the results indicate that the slight underestimation of survival for patients with PR in the pooled PR/NR approach is compensated by the overestimation of survival for patients with NR. As such, Janssen do not agree that the current pooling method underestimates

		survival for the sub-optimal response group. The calculations described above have been supplied alongside this response. However, Janssen acknowledge the preference of the ERG for a model in which the PR and NR categories are separated. Therefore, this structural adaptation is currently being explored. This structural adaption involves substantial model revisions across multiple worksheets, including the model engine trace sheets and the creation of new inputs that require data. As such, re-analysis and re-calculation of the trial data for PR and NR to inform transition probabilities is required. Janssen apologise that this will fall outside of the timeframe for this Technical Engagement response.
Key issue 9: Health-related quality of life utility values used in the model	**NO**	Janssen are aligned with the view of the ERG that application of age-adjustment of utilities in this appraisal is appropriate (ERG Report, Item 12). Therefore, this adjustment has been applied to all economic analyses presented in this response. With respect to uncertainty surrounding the utility values implemented (ERG Report, Item 10), Janssen acknowledge the limitations associated with the health-related quality of life data collected in the ANDROMEDA trial, given that these data were collected for the period of time in which patients were receiving treatment and no further values were obtained following treatment cessation. In particular, expert UK clinicians consulted noted that the benefits of treatment on HRQoL are only likely to be observed after approximately one year. This is highlighted by feedback received as part of this Technical Engagement process, that "*regression of amyloid is slow, and it often takes 6-12 months after the end of chemotherapy for patients to experience a significant improvement in health*" (Technical Engagement Papers, Myeloma UK, page 278) and that "*quality of life benefits happen after the treatment has finished and in the subsequent years when disease stability ensues*" (Technical Engagement Papers, UK Kidney Association, page 296). Therefore, Janssen agree with the ERG that longer-term utilities data would be valuable. As outlined in response to Issue 6, Janssen consider the EMN23 study to be the most appropriate source of data to supplement data collected in the ANDROMEDA trial. However, no health-related quality of life (HRQoL) data were collected in the EMN23 study, as stated in Janssen's response to clarification questions (Part G of Question B1). As such, Janssen

		have investigated the availability of additional HRQoL data from the ALchemy study, as suggested by the ERG, but have not identified any available HRQoL data stratified by depth of haematologic response. However, should the NICE Committee consider a CDF recommendation for DBCd to be appropriate, provided utility data stratified by haematologic response are available (currently unclear), it may be possible to validate utility estimates used in the model.
Key issue 10: Maximum treatment duration with daratumumab	**YES**	Data from the ANDROMEDA trial show that [redacted]/195 ([redacted]%) patients received daratumumab for 24 cycles, although the mean treatment duration was substantially lower at [redacted] cycles (12-month landmark analysis, 20.3 months median follow-up).[10] UK clinicians at an advisory board were in agreement that treatment of AL amyloidosis patients with DBCd beyond two years in clinical practice would be unlikely, particularly since this may be burdensome to the patients, who would have to attend the clinic each time. As such, it was suggested that the ANDROMEDA trial protocol, which limited daratumumab treatment to a maximum of 24 cycles, would likely be adhered to in clinical practice given that ANDROMEDA provides the only currently available relevant data regarding the efficacy of daratumumab in this patient population. This lack of clinical evidence for longer treatment durations was similarly noted by the clinical experts consulted by the ERG (ERG report, page 31). That patients may not favour receipt of daratumumab for more than two years in clinical practice is supported by feedback received as part of this Technical Engagement process from Myeloma UK: "*the fixed duration of treatment with six cycles of Dara CyBord followed by two years of maintenance treatment with daratumumab can provide patients with a level of certainty that the treatment has an end point*" (Technical Engagement Papers, page 283). Based on this clinical expert opinion that daratumumab treatment for longer than 24 cycles is not likely to be clinically appropriate, coupled with evidence submitted by a patient group that its longer term use may not reflect patient preferences, it is considered that treatment with DBCd beyond two years is not likely to be reflective of clinical practice. Despite this, given data from the ANDROMEDA trial that [redacted]% of patients received daratumumab therapy for 24 cycles, a scenario has been performed in which all patients in the DBCd arm were modelled to receive daratumumab for the maximum treatment duration

<table>
<tr><td></td><td></td><td>of 24 cycles. Duration of BCd treatment was maintained at 4.36 cycles, reflecting the mean treatment duration received in the BCd arm of the ANDROMEDA trial. The results for this scenario are presented in Appendix 3.

The results of this scenario in the RWE responses and ANDROMEDA base cases show increases in the ICER to £41,049/QALY gained and £40,746/QALY gained, respectively. These results indicate DBCd to be a cost-effective use of NHS resources given the decision modifiers that apply to this appraisal. However, due to the lack of data informing health outcomes up to Cycle 24, this scenario is limited in its consideration of the additional costs associated with longer daratumumab treatment duration without any additional health benefits gained. Therefore, these results are provided for completeness and are not considered to be suitable for decision-making.</td></tr>
<tr><td>Key issue 11: Underestimation of the administration costs of DBCd and BCd</td><td>YES</td><td>The administration costs for the DBCd and BCd regimens have been aligned with those used and accepted by the NICE Committee in a previous daratumumab appraisal in untreated multiple myeloma (NICE appraisal ID1510).[15] There is no clear rationale for additional or different administration costs in the newly diagnosed AL amyloidosis setting. These administration costs, updated from Table 77 of the original Company Submission in NICE appraisal ID1510 to reflect the most recent cost year (2019/20), are provided in Table 4. As described in Section B.3.5.1 of the original Company Submission, where an option between intravenous (IV) and oral or subcutaneous (SC) administration was available (e.g. for cyclophosphamide), the non-IV route was selected for the analysis because fluid volume overload (that may result from IV infusion) is a safety concern associated with IV drug administration for patients with AL amyloidosis. In clinical practice, the oral chemotherapies (cyclophosphamide and dexamethasone) would be administered together and thus the first administration cost is applied once to cover both treatments.

Table 4: Administration costs used in revised base case
<table>
<tr><th>Drug</th><th>Parameter</th><th>Cost</th><th>Source</th></tr>
<tr><td>Daratumumab (SC)</td><td>Subcutaneous administration</td><td>£99.30</td><td>NHS Reference Costs 2019/20. N10AF: Specialist Nursing, Cancer Related, Adult, Face to face</td></tr>
</table>
</td></tr>
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		<table><tr><td></td><td>Blood test (prior to first administration)</td><td>£2.53</td><td>NHS Reference Costs 2019/20. DAPS05: Haematology</td></tr><tr><td>Bortezomib</td><td>Subcutaneous administration</td><td>£99.30</td><td>NHS Reference Costs 2019/20. N10AF: Specialist Nursing, Cancer Related, Adult, Face to face</td></tr><tr><td>Oral chemotherapies (cyclophosphamide and dexamethasone)</td><td>First administration only</td><td>£210.82</td><td>NHS Reference Costs 2019/20. SB11Z Outpatient: Deliver Exclusively Oral Chemotherapy</td></tr></table> **Abbreviations:** IV: intravenous; SC: subcutaneous. The results for the revised base cases in which these updated administration costs are considered are presented in Appendix 2.
Key issue 12: Impact of DBCd on autologous stem cell transplant rates	**YES**	A Delphi panel with UK clinicians, conducted by Janssen, indicated that ASCT may be used as a treatment option at later line of treatment; however, as acknowledged by the ERG, the extent to which this treatment option would be used should DBCd be introduced to clinical practice remains unclear. As such, a scenario analysis assessing the impact of including ASCT as a second-line treatment in AL amyloidosis was conducted. In this scenario, [redacted]% of patients are modelled to receive second-line ASCT in both the DBCd and BCd arms; this value was sourced from patients in the EMN23 study who initiated first-line treatment post-2010 as presented in Table 8 of Janssen's responses to Part C of ERG Clarification Question B1. The cost of ASCT was modelled to be £15,065.25 (NHS Reference Costs 2019/2020, SA26A).[16] Proportions of patients receiving other second-line regimens were re-scaled to account for ASCT, and the same assumptions regarding deaths, dose reductions and discontinuation of treatment, and proportions of patients receiving third-line treatment, as described in response to Issue 13, were applied. The results of this scenario analysis are provided in Appendix 3. These results indicate that, with ICERs of £32,951/QALY gained and £32,892/QALY gained for the RWE responses and ANDROMEDA base cases, respectively, the conclusion that DBCd represents a cost-

		effective use of NHS resources is not altered in this scenario, particularly given the conservative nature of the model and the decision modifiers that are relevant to consider in this appraisal. In addition to this, Janssen consider it important to note that daratumumab is expected to improve ASCT efficacy, and consequently long-term survival, following ASCT.A limitation of this scenario, therefore is that it considers additional costs only. Evidence of improved efficacy of ASCT post daratumumab is supported by evidence from the CASSIOPEIA study, a randomised, open-label, Phase III trial, 1,085 patients with newly-diagnosed multiple myeloma were randomised to receive bortezomib, thalidomide and dexamethasone with or without the addition of daratumumab (BTd or DBTd, respectively) before and after ASCT. At the time of assessment after transplantation, a higher proportion of patients in the DBTd arm had achieved the primary endpoint of a stringent complete response than in the BTd arm (29% and 20%, respectively).[17] These data suggest that the addition of daratumumab to the treatment regimen is likely to improve survival outcomes with ASCT, and thus that the efficacy of ASCT may differ between BCd- and DBCd-treated patients. However, this is not reflected in the scenario analysis results presented in Appendix 3. Therefore, these results are provided for completeness and can be considered to be conservative.
Key issue 13: Approach to the costs of second- and third-line therapies in the model	**YES**	Janssen agree with the ERG that the application of a 20% adjustment factor to account for treatment discontinuations, dose adjustments during the course of treatment and deaths represents an improvement to the modelling approach to subsequent therapies. In addition, Janssen agree that inclusion of both second- and third-line therapies is appropriate, and that third-line therapies should be costed as a proportion of second-line therapy costs, to reflect that not all patients who receive second-line therapies go on to receive third-line therapies. In order to do this, the proportion of patients who received third line therapy as compared with second-line therapy in the ALchemy study was calculated (31%). Therefore, all third line drug therapy costs were multiplied by 31% before being applied to all patients entering the '2L Tx' health state. These changes (20% adjustment factor and inclusion of third line therapies with costs relative to the second line) have been implemented in Janssen's revised base cases, presented in Appendix 2.

		Janssen acknowledge the preference of the ERG to apply treatment regimens and distribution of second-line therapies as reported in the ALchemy study. However, in the revised base cases, these regimens and distributions remain sourced from the UK clinical advisory board. This is because the clinical experts in attendance at the advisory board provided the full treatment regimens, including all component therapies where combination therapies were used, as compared with the data available from the ALchemy study, which are limited in that they report only the principal agent of a treatment regimen (see Janssen's response to Part 4i of ERG Clarification Question B7). In addition, the scenario analyses presented in response to Part 4 of ERG clarification Question B7 indicate that use of the ALchemy study to inform second-line therapies or second- and third-line therapies (Tables 26 and 28 of the Clarification response document, respectively), had a negligible impact on the ICER and did not affect the cost-effectiveness conclusions drawn. Therefore, no further scenarios are presented here.
Key issue 14: Potential of daratumumab for the Cancer Drugs Fund (CDF)	**NO**	As previously indicated in Janssen's response to clarification questions (Question A1), Janssen have primarily positioned DBCd for routine commissioning within the NHS for patients with newly diagnosed AL amyloidosis. This positioning reflects the significant unmet need in this population, and the fact that the ICER for DBCd (with the confidential PAS for daratumumab applied) versus BCd is for the ANDROMEDA base case may be considered a cost-effective effective use of NHS resources, given the significant unmet need and burden that exists in AL amyloidosis. Nevertheless, if the Committee deem a CDF recommendation for DBCd to be most appropriate, Janssen is in agreement that this would present an opportunity to collect valuable additional information to reduce uncertainty in the economic analysis. Specifically, longer follow-up periods would provide the opportunity to gain greater insight into the following points: • OS in newly diagnosed AL amyloidosis patients treated with DBCd as compared with BCd-treated patients from ANDROMEDA • Effectiveness of DBCd in patients with Mayo Clinic Cardiac Stage IIIb disease, which would be captured from patients treated in the NHS within the time period in which DBCd is funded on the CDF, and longer-term data from the ALchemy study

		• The impact of DBCd treatment on patients' HRQoL. As noted in response to Issue 9, no HRQoL data were collected in the EMN23 study; as such, longer-term HRQoL data from the ALchemy study may be valuable (should this be stratified by haematologic response) despite the limitations with the dataset described in Issue 6 As outlined above, whilst there is the potential for collection of evidence on patients with Cardiac Stage IIIb disease and HRQoL data the ALchemy study, it is important to note that at the current time, ALchemy does not provide a robust evidence base for long-term OS, in either the full target population or Stage IIIb patients (nor does it provide HRQoL data). In contrast, at present, the EMN23 study provides the most mature OS estimates currently available and is generalisable source to the UK, as discussed in response to Issue 6. Accordingly, ALchemy data will be collected during the management access time period to validate the estimates currently available from the EMN23 study. For completeness, Janssen wish to highlight that a CDF recommendation will not be able to provide certainty around areas such as treatment effect difference for DBCd versus BCd on haematologic response rates, the long-term extrapolations of OS from EMN23 data or the distribution of subsequent therapies. In addition to providing an opportunity to resolve several remaining areas of uncertainty, a recommendation for use of DBCd as part of the CDF would permit patient access to this valuable therapy option. Patients with AL amyloidosis have a high disease burden and a poor prognosis, with nearly a third (30%) of patients dying within the first year of diagnosis and an estimated four-year survival rate of just 54%.[12, 18] Given this, access to DBCd, a highly effective therapeutic option with a tolerable safety profile, which has the potential to improve patient prognosis and HRQoL, delay organ failure and prolong survival, would be highly significant for patients in England and Wales. This significance is highlighted by feedback received as part of this Technical Engagement process from patient groups, who reported that the availability of DBCd would represent a step-change in the management of AL amyloidosis that could "*potentially [change] the landscape of treatment for these patients*" (Technical Engagement papers, UK Kidney Association, pages 296–297).

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Please see the response to Appendix 2 below, in which the updated Company base cases are outlined.

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Appendix 1: Survival analysis using a six-month decision tree exit timepoint (EMN23 study)

Survival analysis was conducted to generate appropriate extrapolations to the OS data from the EMN23 study, in line with guidance from the NICE Decision Support Unit Technical Support Document 14.[19]

Overall survival for six-month PR/NR

As described in the original Company Submission, patients achieving either NR or PR in the current model are considered together to reflect the clinical management of disease and to balance model complexity. The proportion of patients achieving PR and NR at six months, as reported in the ANDROMEDA trial, was used to apply weighting to a combined PR/NR OS curve, to reflect the patient population of suboptimal responders for each arm.

After digitisation of the PR and NR KM curves from the EMN23 study and application of parametric survival curves, a sense check was conducted to confirm that the extrapolations appropriately fitted the PR and NR KM data. The PR KM curve and its associated curve extrapolations are presented in Figure 1. The NR KM curve and its associated extrapolations are presented in Figure 2.

Within ANDROMEDA, patients that achieved a NR comprised [redacted] of all patients that were either PR or NR at the six-month landmark, irrespective of treatment arm. Because patients with NR represented a larger proportion of the weighting, AIC and BIC statistics for the NR curve were primarily used to determine which parametric survival function held the best statistical fit to the data. The AIC and BIC statistics for the NR (and PR) curves are presented in Table 5.

AIC/BIC values were similar across extrapolations, with the generalised gamma parametric survival function deemed to generate the best fit for patients with NR. However, the Weibull curve resulted in the least overlap between curves for other haematologic response categories. Following presentation of the extrapolation curves to a UK-based expert clinician, the Weibull curve was selected for the base case, with this choice representing the curve with greatest clinical plausibility.

The PR and NR KM curves along with their respective weighted PR/NR survival curve extrapolations are depicted in Figure 3.

Figure 1: OS curve extrapolations for patients with PR from EMN23 study

Abbreviations: KM: Kaplan–Meier; PR: partial response.

Figure 2: OS curve extrapolations for patients with NR from EMN23 study

Abbreviations: KM: Kaplan–Meier; NR: no response.

Table 5: Model fit statistic for OS curve extrapolations for patients with NR or PR from EMN23 study

	PR		NR	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each response is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; PR: partial response.

Figure 3: Weighted PR and NR OS curve extrapolations from EMN23 study

[redacted]

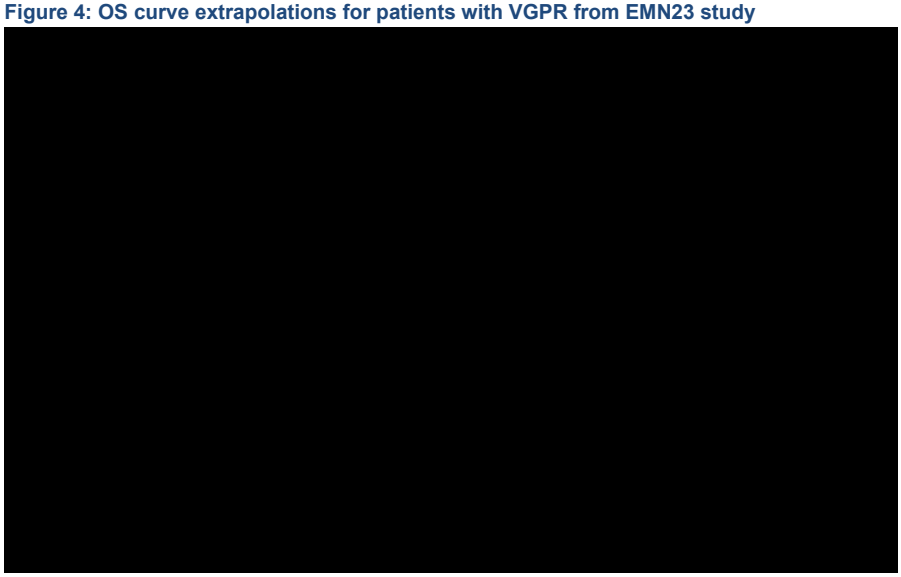
Abbreviations: KM: Kaplan–Meier; NR: no response; PR: partial response.

Overall survival for six-month VGPR

After digitisation of the VGPR KM curve from the EMN23 study and application of parametric survival curves, a sense check was conducted to confirm that the extrapolations appropriately fitted the VGPR KM data.[6] The VGPR KM curve and its associated curve extrapolations are presented in Figure 4.

The AIC and BIC statistics for the VGPR curve are presented in Table 6. According to AIC and BIC, the Weibull extrapolation generated the best fit, with this curve also resulting in minimal overlap with the survival estimates for other haematologic response categories. Following presentation of the extrapolation curves to a UK-based expert clinician, the Weibull curve was selected for the base case, with this choice representing the curve with greatest clinical plausibility.

Figure 4: OS curve extrapolations for patients with VGPR from EMN23 study



Abbreviations: KM: Kaplan–Meier; VGPR: very good partial response.

Table 6: Model fit statistic for OS curve extrapolations for patients with VGPR from EMN23 study

	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; VGPR: very good partial response.

Overall survival for six-month CR

After digitisation of the CR KM curve from the EMN23 study and application of parametric survival curves, a sense check was conducted to confirm that the extrapolations appropriately fitted the CR KM data.[6] The CR KM curve and its associated curve extrapolations are presented in Figure 5. Upon visual inspection, all tested extrapolations showed an appropriate fit, but all predicted a clinically implausible lifespan. Therefore, the model uses the selected curve extrapolation until the general population mortality hazard supersedes the hazards of the extrapolated curve data (for further detail, see the 'General population mortality' section below), at which point the hazards of general population mortality apply.

The AIC and BIC statistics for the CR curve are presented in Table 7, which showed that whilst the Log-normal survival function generated the best fit overall, there was minimal difference in statistical fit between curves. The Weibull curve also resulted in minimal overlap with the curves for other haematologic response categories. Following presentation of the extrapolation curves to a UK-based expert clinician, the Weibull curve was considered to be relatively pessimistic and the exponential curve was instead selected for the base case as this curve provided the greatest clinical plausibility.

Figure 5: OS curve extrapolations for patients with CR from EMN23 study

Abbreviations: CR: complete response; KM: Kaplan–Meier.

Table 7: Model fit statistic for OS curve extrapolations for patients with CR from EMN23 study

	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CR: complete haematologic response; OS: overall survival.

Overall survival at six months

The OS extrapolations for each haematologic response of PR/NR, VGPR and CR selected to inform the revised base case are presented in Figure 6.

Figure 6: OS curve extrapolations stratified by haematologic response from the EMN23 study

Abbreviations: CR: complete haematologic response; KM: Kaplan-Meier; NR: no response; PR: partial response; VGPR: very good partial response.

Appendix 2: Revised economic base case results

As discussed in response to Key Issues 1 and 6, two revised base cases are presented:

- **RWE responses base case:** Baseline haematologic response rates derived from the EMN23 study
- **ANDROMEDA base case:** Baseline haematologic response rates derived from the ANDROMEDA study

The settings employed in both of these base cases are as follows:

- Overall survival extrapolations derived from EMN23 data – see response to Key Issue 1 and Appendix 1
- Six-month decision tree exit timepoint – see response to Key Issue 5
- Inclusion of age-adjusted utilities – see response to Key Issue 9
- Updated administration costs – see response to Key Issue 11
- Subsequent therapies updated to include a 20% adjustment factor and inclusion of third-line therapies with costs relative to the second line (subsequent therapy distributions remain sourced from the UK clinical advisory board) – see response to Key Issue 13

The results for these revised base case analyses are presented in Table 8 (RWE responses base case) and Table 9 (ANDROMEDA base case). Results of the ANDROMEDA base case indicate that, bearing in mind important decision modifiers, such as the rarity of AL amyloidosis

and severity of disease, particularly in Mayo Clinic Cardiac Stage IIIb patients, that DBCd is highly likely to represent a cost-effective use of NHS resources.

Table 8: Revised RWE responses base case results

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,744

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; RWE: real world evidence.

Table 9: Revised ANDROMEDA base case results

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
BCd	[redacted]	[redacted]	[redacted]	-	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,692

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Appendix 3: Scenario analysis results

Issue 5

Table 10: Scenario analysis results: three-month decision tree exit timepoint

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
RWE responses base case					
BCd	[redacted]	[redacted]	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	38,520
ANDROMEDA base case					
BCd	[redacted]	[redacted]	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	42,620

Footnote: PR/NR: Generalised Gamma; VGPR: log-logistic; CR: log-logistic
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; RWE: real world evidence.

Issue 10

Table 11: Scenario analysis results: maximum daratumumab treatment duration (24 cycles)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
RWE responses base case					
BCd	[redacted]	[redacted]	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	41,049
ANDROMEDA base case					

BCd	[redacted]	[redacted]	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	40,746

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; RWE: real world evidence.

Issue 12

Table 12: Scenario analysis results: inclusion of ASCT as a second-line treatment option with proportion receiving ASCT sourced from EMN23 study

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
RWE responses base case					
BCd	[redacted]	[redacted]	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£32,951
ANDROMEDA base case					
BCd	[redacted]	[redacted]	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£32,892

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; RWE: real world evidence.

Appendix 4: Interaction test statistics

Table 13: Interaction test statistics, response rates at six months (IA1 and 12-month landmark analyses)

Variable	Subgroup	DBCd, n/N (%)	BCd, n/N (%)	OR (95% CI); p value	RR (95% CI); p-value	RD (95% CI); p-value	p-interaction value
IA1 analysis							
All	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE
Baseline Mayo Clinic Cardiac stage	I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	IIIa/IIIb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
12-month landmark analysis							
All	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE
Baseline Mayo Clinic Cardiac stage	I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	IIIa/IIIb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; NE: not evaluable; OR: odds ratio; RD: risk difference; RR: risk ratio; QALYs: quality-adjusted life years.

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Clinical expert statement & technical engagement response form

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please return this form by **5pm** on **15th October 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with systemic amyloid light-chain amyloidosis and current treatment options	
About you	
1. Your name	**Dr Carol Whelan**
2. Name of organisation	**British Society for Heart Failure (BSH)**
3. Job title or position	**Consultant Cardiologist at National Amyloidosis Centre, Royal Free Hospital and Councillor on board of BSH**
4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with systemic amyloid light-chain amyloidosis? ☐ a specialist in the clinical evidence base for systemic amyloid light-chain amyloidosis or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **x** other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**
The aim of treatment for systemic amyloid light-chain amyloidosis	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	This condition is at present incurable. The main aim of treatment is to switch off the abnormal production of the amyloidogenic free light chains in the bone marrow. This is to prevent further deposition of amyloid fibrils ie progression in vital organs and encourage regression of the amyloid fibrils in these organs. This leads to reduction in symptoms due to improved organ function and so improving quality of life and survival. A further aim is that the response to treatment is prolonged and sustained reducing the need for further lines of treatment in the future.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	A clinically significant treatment response is defined by the production of the abnormal free light chains (either kappa or lambda) returning to a normal level ie complete response or CR. A very good partial response (VGPR) whilst not as good as a result as a CR is also a clinically significant treatment response.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in systemic amyloid light-chain amyloidosis?	Yes. The diagnosis is still often made too late and there is still a significant early mortality of patients despite receiving current treatment.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	There is not a licensed treatment for AL amyloidosis so the treatments offered are based on current myeloma treatments. First line treatment is usually a combination of bortezemib, cyclophosphamide and dexamethasone or methylprednisolone. The patient is monitored for their response to treatment and 2nd, 3rd and 4th line treatments are then considered if appropriate.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The British Society of Haematology published guidelines in 2014 for systemic AL amyloidosis.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Patients are usually referred to the National Amyloidosis Centre (NAC) in London for the diagnosis to be confirmed (or refuted). They will then be discussed at a multi-disciplinary meeting at the NAC where the treatment regime is recommended to the local treating haematologist. Patients are then followed up at the NAC and locally to monitor treatment responses and need for further treatments. Usually the treatment recommended by the NAC is prescribed by the local treating haematologist. However, there can be variance in treatments allowed 1st/2nd or 3rd line across the country.

• What impact would the technology have on the current pathway of care?	It would not impact on the current pathway other than it would be added in to the existing treatments recommended.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is currently used 2nd line in patients who have not responded to 1st line treatment or who have relapsed despite 1st line treatment.
• How does healthcare resource use differ between the technology and current care?	By giving it 1st line rather than 2nd line.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist haematology clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Very little. It is given as subcutaneous injection so easy administration.
13. Do you expect the technology to provide clinically meaningful	Yes. The results from the Andromeda study showed impressive results in terms of haematological and cardiac responses for those patients receiving the technology upfront.

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not that I am aware.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	It is easily given by subcutaneous injection. Patients are monitored for a few hours after administration so the appropriate clinic environment and skillset of staff is important.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients received it for up to 24 cycles with an average of 16 cycles in the Andromeda study. It would be good to have flexibility in the duration of treatment rather than hard stop rules.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Potential for not requiring additional treatment as 2nd line due to excellent 1st line response will provide substantial benefit to patients.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes. Currently, AL amyloidosis is still seen by many clinicians as a fatal condition which is futile to treat. With this technology and improved responses, there is potential for clinicians to diagnose earlier and improve patient survival and quality of life.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. By addressing the early mortality still seen despite treatment by improving the early response.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is potential for treatment related infection which would need to be highlighted to patients and clinicians.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The Alchemy study is UK based from the National Amyloidosis Centre involving thousands of patients.
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Haematological and cardiac response to treatment which were addressed in the Andromeda trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Unaware of this.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	The Alchemy data is real world data.
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis that is not restricted to exclude patients with Mayo Clinic Cardiac Stage IIIb disease	It makes sense for data to be presented on the impact of the technology on patients in this stage if available from the company.
Key issue 2: Absence of clinical trial data for patients with Mayo Clinic Cardiac Stage IIIb disease	

Key issue 3: Immaturity of overall survival data from the ANDROMEDA clinical trial	Data from patients with myeloma can help form this.
Key issue 4: Lack of medium-to-long term adverse event data for daratumumab in AL amyloidosis	Data from patients with myeloma can help form this.
Key issue 5: Timing of response assessment for depth of haematologic response	Data from the Alchemy trial suggests that the response assessment should be at 3 months and in fact demonstrates a benefit for a 1 month assessment.
Key issue 6: Source of data for overall survival, stratified by haematologic response	
Key issue 7: Baseline source of haematologic response distribution for BCd	
Key issue 8: Combining suboptimal haematologic response categories in the model	

Key issue 9: Health-related quality of life utility values used in the model	
Key issue 10: Maximum treatment duration with daratumumab	Flexibility for treatment duration will be helpful but long term data are lacking.
Key issue 11: Underestimation of the administration costs of DBCd and BCd	
Key issue 12: Impact of DBCd on autologous stem cell transplant rates	
Key issue 13: Approach to the costs of second- and third-line therapies in the model	
Key issue 14: Potential of daratumumab for the Cancer Drugs Fund (CDF)	

Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Systemic AL amyloidosis is a fatal disease with early mortality despite treatment
- Diagnosis is often delayed.
- Cardiac involvement drives prognosis
- The technology has shown excellent haematological and cardiological responses
- It will be game changing to have an approved treatment for AL amyloidosis.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **15th October 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with systemic amyloid light-chain amyloidosis and current treatment options
About you

NICE National Institute for Health and Care Excellence

1. Your name	Dr Charlotte Manisty
2. Name of organisation	British Cardiovascular Society
3. Job title or position	British Cardiovascular Society representative for this appraisal. Consultant Cardiologist, Clinical lead for Cardio-Oncology, Barts Health NHS Trust and UCLH.
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with systemic amyloid light-chain amyloidosis? ☐ a specialist in the clinical evidence base for systemic amyloid light-chain amyloidosis or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you	☐ yes

tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for systemic amyloid light-chain amyloidosis	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Treatment of systemic light chain amyloidosis aims to reduce light chain production and hence further amyloid deposition in organs, alongside managing complications arising from organ damage (primarily cardiac and renal). From a haematological perspective, the aim is to achieve a deep and lasting remission, and from a systemic perspective, to support organ function and prevent further deterioration.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Response is split into • haematological response – defined according to established criteria from consensus guidelines based on dFLC • Organ response (cardiac, renal, liver) – based on blood biomarkers – again according to consensus guidelines The treatment target is complete haematological response with normalisation of FLC and FLC ratios, but a clinically significant treatment response would be a VGPR with ideally regression of organ response (>30% reduction in NTproBNP or reduction in NYHA Class or 50% reduction in proteinuria with stable creatinine if renal involvement).

10. In your view, is there an unmet need for patients and healthcare professionals in systemic amyloid light-chain amyloidosis?	There is a clear unmet need. This is a disease that is generally currently diagnosed late once significant organ involvement is present, and for which currently there are no licensed treatments. Treatment options currently are via off-label use of multiple myeloma therapies, which not only frequently fail to achieve the CHR but also commonly have low organ response rates. Patients often also develop significant toxicity from these regimens, leading to markedly impaired quality of life. Cardiac amyloidosis is now being more frequently diagnosed due to increasing detection via cardiology testing (especially due to greater availability of cardiovascular MRI). In addition, the availability of a range of emerging therapeutic options for transthyretin amyloidosis has increased awareness of red flag markers and diagnostic strategies for cardiac amyloid in general. Currently however if patients are found to have AL rather than TTR cardiac amyloid, the lack of licensed treatments is challenging for clinicians and patients alike, and means that treatment initiation may be delayed leading to worse outcomes, despite increasing rates of detection and improved survival once treatment is initiated (Barrett et al JACC HF 2019).
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Current treatment is based on use of multiple myeloma therapies to achieve a haematological response, and then management of cardiac complications (fluid overload, rhythm abnormalities etc) with appropriate supportive treatments (diuretics, antiarrhythmics, pacing etc). Most patients are able to receive 4-6 cycles of a combination of proteasome inhibitor (bortezemib) or immunomodulatory therapy (thalidomide), chemotherapy (cyclophosphamide) and steroid (dexamethasone). These regimens are successful in about 65-70% of patients. For patients at high risk with significant cardiac involvement, most will receive a modified regimen with lower doses of treatment or alternatives including melphalan and steroids or lenalidomide. For a small group of patients whose disease is detected early and in whom there is minimal organ involvement, high dose chemotherapy with stem cell rescue may be an option. Treatment is generally multidisciplinary and includes involvement of the haematologist and other specialists required to manage the secondary organ involvement (renal, cardiac, neurological).

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Current clinical guidelines generally followed in the UK arise from the British Committee for Standards in Haematology (Wechalekar AD et al *Br J Haematol* 2015 and the National Amyloidosis Centre). These are broadly in line with the NCCN 2021 Guidelines, although daratumumab is included as a first line therapy option in the NCCN Guidelines (more recently published).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is defined, and the majority of patients will be under the care of, or at least discussed with, the National Amyloidosis Centre. This means that treatment pathways are consistent. Patients however differ considerably in co-morbidities, stage of presentation, toxicity from therapies etc, meaning that treatment does have to be individualised to incorporate these systemic factors.
• What impact would the technology have on the current pathway of care?	Availability of daratumumab as a treatment for AL amyloidosis, which in the ANDROMEDA study was found to be superior to standard BCd therapy (itself not licensed for use in amyloid), should enable deeper and more rapid haematological responses as well as improved organ response rates in patients. Daratumumab would be administered in conjunction with standard BCd and then continued as a single agent until disease progression or for up to a maximum of 24 cycles. Given that data has shown that early remission is important for improved survival, availability of a licensed drug with evidence for remission being induced earlier should improve outcomes and reduce organ progression/ improve organ remission.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Administration of first line daratumumab for AL amyloidosis will be a new therapeutic option, and in fact the only licensed treatment available in the UK for this indication.

• How does healthcare resource use differ between the technology and current care?	Patients will receive daraumumab in combination with the BCd treatment that they currently receive (generally 6 cycles), and therefore the resource use will not differ significantly for this phase, apart from the cost of the drug. Patients will then continue to receive single agent daratumumab for up to 24 cycles – this will be given every 4 weeks, as a subcutaneous injection that will be administered in hospital generally via a chemotherapy day unit. There will be additional cost and staffing implications with this, although this will be minimal and would be expected to be offset by the reduction in resource used to manage organ complications (heart failure admissions, dialysis etc).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Patients will receive treatment under the care of specialist haemato-oncology units (generally secondary/ tertiary care) with the majority of patients receiving input from the National Amyloidosis Centre at some point during their care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The treatment is already used in multiple myeloma and therefore no new facilities, equipment or training would be expected. There will however be increased patient attendance as outlined above for administration of daratumumab beyond the initial 24 weeks of treatment.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There are currently no licensed/ funded treatments in UK via NHS for cardiac amyloidosis. Data from ANDROMEDA would suggest significant clinical benefits compared to the current care.
• Do you expect the technology to increase length of life more than current care?	The phase III ANDROMEDA study only has data available for overall survival to 14th February 2020, where the HR was 0.91 (DBCd vs BCd, 95% CI: 0.53, 1,53), however median OS was not reached in either treatment arm and the curves in the Kaplan Meier curves were beginning to diverge. Given that previous data has shown that early durable remission is associated with improved survival, and ANDROMEDA results for achieving CHR were over 5 fold higher with DBCd (vs BCd) with significantly lower time to

	haematological response (median time to CHR 60 vs 85 days), this is likely to be associated with increased length of life. Forthcoming ANDROMEDA results with longer follow-up should provide more definitive data to address this question.
• Do you expect the technology to increase health-related quality of life more than current care?	Health related quality of life is currently significantly impacted in patients with AL amyloidosis predominantly by the progression of organ involvement with cardiac failure and renal dysfunction. This means that patients experience debilitating symptoms related to organ involvement (shortness of breath, fatigue, oedema, dizziness) and commonly require frequent hospital admissions for diuresis or haemodialysis, meaning that their quality of life even between administration of BCd/ other treatments is poor. It is expected that higher and earlier rates of durable haematological remission, combined with regression of organ involvement should significantly improve quality of life. This is supported by the data from ANDROMEDA showing a reduction in major organ deterioration progression-free survival by almost half (HR 0.58)
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients who are MAYO IIIb at screening were not included in ANDROMEDA (although some were stage IIIb at treatment initiation). This patient population represents about 1 in 5 patients in UK newly diagnosed with AL amyloid and therefore there is less evidence for survival benefit in this patient group (haematological response is not likely to be significantly different, but survival from organ involvement and toxicity may be different). This population is however the group of patients for whom a rapid haemtological and organ response may be most important, and therefore availability of daratumumab to IIIb patients should be strongly considered – particularly given the recelty published Alchemy trial results.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	As above, patients will require attendance for administration of treatment for an extended period (up to 24 cycles) as compared to standard BCd treatment. Daratumumab is however generally well tolerated with patients not reporting significantly increased toxicity as compared to BCd, and treatment can be administered quickly via subcutaneous injection, meaning that prolonged hospital attendance is not necessary. There is no requirement for additional

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	monitoring or tests as patients with AL amyloidosis are closely monitored – both by their treating haematologists, but also by the professionals managing their organ involvement.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Current monitoring assesses for clonal response, and there are established disease staging and response criteria available. There may be a need for a formal criteria for continuation of treatment beyond cycle 6 and beyond 24 weeks (to be determined by haematology).
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The QALY assessment may not be able to fully capture the utility values and cost of organ progression – for heart failure this would include administration of diuretics, regular attendance at heart failure clinics, community heart failure nurse support, pacemaker implantation where necessary, hospitalisation for heart failure, administration of medications to support postural hypotension etc. Similar costs would be associated with renal dysfunction (although I note that dialysis was included).
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The results of ANDROMEDA highlight the potential for daratumumab to deliver significant improvements to haematological and organ response rates than found with current treatment options. Availability of a treatment would also likely have the secondary impact of increasing awareness of AL amyloidosis, thereby potentially driving earlier diagnosis and expediting treatment.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Clearly so – particularly given the lack of availability of treatments approved for use in AL amyloidosis and the poor prognosis and low quality of life that these patients currently suffer.
• Does the use of the technology address any particular unmet need of the patient population?	Clear unmet need, as there is currently no licensed treatment for AL amyloidosis.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Daratumumab is generally well tolerated, and data from the ANDROMEDA study suggests that the majority of the side effects reported in the Dara-BCd arm related to bortezemib with little incremental toxicity from the addition of daratumumab and few patients unable to complete treatment.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	The patient population included in ANDROMEDA have some differences to UK population, as highlighted already in the ERG response, and the ALCHEMY population are more representation. Specifically, the exclusion of patients with advanced organ involvement (Mayo Stage IIIb or significant renal involvement) in ANDROMEDA means the evidence of efficacy in this population is limited, however these patients may be the group in greatest need of such a therapy.

• If not, how could the results be extrapolated to the UK setting?	Data from EMN23 which included several patients with IIIb AL amyloidosis suggested that daratumumab is tolerated and has reasonable efficacy in this population, and ALCHemy suggests that survival was good in those patients receiving daratumumab as second or subsequent lines of therapy, who have a deep haematological response, with subsequent organ response to treatment.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes relate to patient survival, clonal response and organ progression/ regression – these were measured. Other important markers that are particularly relevant in this population would include quality of life indicators (measured) and specific organ-related outcomes (eg heart failure hospitalisation etc) which there would not have been sufficient power to address,
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not that I am aware of.

22. How do data on real-world experience compare with the trial data?	We are currently unable to give daratumumab first line for AL amyloidosis and hence cannot comment on this from our patient experience. However our experience, and that from ALCHemy shows that response in those patients receiving daratumumab as a later line of therapy is good, even in those with advanced disease.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	If patients with stage IIIb amyloid were excluded from access (in line with ANDROMEDA), this would mean that these patients faced inequity of access, and there is no evidence currently suggesting that they would not derive similar benefit from Dara BCd and they may potentially experience greater incremental benefit.
23b. Consider whether these issues are different from issues with current care and why.	All patients currently face the same challenges with access to treatment (ie there are no treatments currently licensed for amyloid), therefore this would be a new equality issue.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis that is not restricted to exclude patients with Mayo Clinic Cardiac Stage IIIb disease	I would strongly support this recommendation. The data (albeit limited) from EMN23 and ALCHemy suggest that there is potentially significant benefit from daratumumab in this patient group. We know that the drug is safe as it given in the second and subsequent line of treatment setting, and the ALChemy data suggests that the benefits will be significant if patients respond from the haematological perspective.
Key issue 2: Absence of clinical trial data for patients with Mayo Clinic Cardiac Stage IIIb disease	As above – there is information that can be extrapolated from other studies, however no direct evidence currently available.

Key issue 3: Immaturity of overall survival data from the ANDROMEDA clinical trial	It would be helpful to see a further analysis of survival data (the last data in the submission was from February 2020) – when would we expect to see this data? However whilst survival is clearly important, other data including QoL and organ progression/ regression rates is extremely important.
Key issue 4: Lack of medium-to-long term adverse event data for daratumumab in AL amyloidosis	There is longer term adverse event data in multiple myeloma and some for second/ subsequent line use in AL amyloid. The short term adverse event data did not raise any concerns. This issue does not concern me.
Key issue 5: Timing of response assessment for depth of haematologic response	The clarification to this point provided by the company appears reasonable.
Key issue 6: Source of data for overall survival, stratified by haematologic response	
Key issue 7: Baseline source of haematologic response distribution for BCd	The data differs between ANDROMEDA and UK ALCHemy data with lower haematological response to BCd in ANDROMEDA, meaning that perhaps the difference in response rates between arms may have been somewhat overestimated in ANDROMEDA.
Key issue 8: Combining suboptimal haematologic response categories in the model	I do not see this as a significant issue because we would be aiming for at least VGPR.

Key issue 9: Health-related quality of life utility values used in the model	As discussed in the ERG and then the subsequent clarification questions, there are some discrepancies (EQ-5D values lower for VGPR than for PR/NR) and the impact of organ involvement on QoL values may be underestimated in the model. Once patients develop cardiac involvement, the severity of their symptoms and hence the impact on their quality of life is generally significant (commonly NYHA class 3+), and conventional heart failure treatments have limited or no efficacy. I would therefore expect the heart failure values inputted to underestimate the true impact on QoL.
Key issue 10: Maximum treatment duration with daratumumab	From a cardiovascular perspective, medium to long term toxicity is not anticipated and with more sustained clonal suppression, it would be expected that organ regression would be greater.
Key issue 11: Underestimation of the administration costs of DBCd and BCd	The incremental administration costs for DBCd over BCd would not be great (four weekly subcutaneous daratumumab administration), and therefore I would not consider this a significant issue.
Key issue 12: Impact of DBCd on autologous stem cell transplant rates	There is no data to support this, however it might be expected that more patients would be eligible for autologous SCT if there are deeper and more durable response rates to dara BCd. However in general it is organ involvement (particularly cardiac and renal) that excludes ASCT and, whilst organ response rates may be higher, the time course is such that significant improvements in cardiac and renal parameters would take many months even despite CHR.
Key issue 13: Approach to the costs of second- and third-line therapies in the model	

Key issue 14: Potential of daratumumab for the Cancer Drugs Fund (CDF)	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Availability of daratumumab for first line treatment of AL amyloid would meet an unmet need and represent a step change in treatment options for patients.
- ANDROMEDA supports improved outcomes over standard BCd treatment – both in terms of faster, deeper and more sustained haematological responses and also for organ regression.
- Quality of life is currently poor in patients with amyloid – particularly for those with organ involvement. Although organ regression takes time, the more rapid and sustained haematological response should reduce organ progression and increase regression.
- Daratumumab appears well tolerated and administration is relatively straightforward with little additional cost related to administration.
- Patients with Mayo Stage IIIb amyloidosis should not be excluded from access to daratumumab. They represent a large minority of patients, with potentially the greatest potential to benefit.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

Your privacy

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

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- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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NICE National Institute for Health and Care Excellence

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PART 1 – Treating a patient with systemic amyloid light-chain amyloidosis and current treatment options	
About you	
1. Your name	**Dr Jennifer Pinney**
2. Name of organisation	**UK Kidney Association**
3. Job title or position	**Consultant Nephrologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with systemic amyloid light-chain amyloidosis? ☐ a specialist in the clinical evidence base for systemic amyloid light-chain amyloidosis or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation	☐ yes

submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures**
The aim of treatment for systemic amyloid light-chain amyloidosis	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity	

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in systemic amyloid light-chain amyloidosis?	
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase	

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The use of the technology	
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monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	

• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in	

the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when	

considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis that is not restricted to exclude patients with Mayo Clinic Cardiac Stage IIIb disease	The clinical trial #NCT02841033 provides evidence that Daratumumab is well tolerated in patients with stage II and III cardiac disease when used as monotherapy in the relapsed setting. Of the 22 patients recruited to this study, twenty (91%) had cardiac stage II and III disease. 50% of the patients achieved a cardiac- organ response (Shelton *et al* Blood 2020). This study is not the equivalent population given the relapsed setting and therefore those with the most severe disease are not likely to have survived to be recruited, it does provide some information regarding the safety of Daratumumab in the advanced cardiac patients. Real world data regarding outcomes is challenging, the UK Alchemy study is the best current data in the absence of a mandated registry for all patients diagnosed with AL amyloidosis. It does however only incorporate those well enough for a referral to the NAC in London. There will always remain a small proportion of patients who are too frail to withstand treatment and these patients are usually the Stage IIIb patients. The treating haematologist will weigh up the perceived benefit for these patients on a case by case basis. Exclusion of the stage IIIb patients from treatment will make it difficult to gather the evidence base for benefit and given the high risk of death in this patient group, proving benefit would be relatively short if this group are studied.

Key issue 2: Absence of clinical trial data for patients with Mayo Clinic Cardiac Stage IIIb disease	
Key issue 3: Immaturity of overall survival data from the ANDROMEDA clinical trial	
Key issue 4: Lack of medium-to-long term adverse event data for daratumumab in AL amyloidosis	While it is anticipated that some patients may stay on Daratumumab until disease progression in the ANDROMEDA study most did not receive treatment for this length of time and therefore analysis of longer-term adverse event data may not be achievable. A comparison of hospital admissions in both arms following cessation of treatment using HES data would be a potential way of determining longer term adverse event.
Key issue 5: Timing of response assessment for depth of haematologic response	The UK NAC have shown benefit from early assessment of haematological response and potential switch to second line therapy. However, this is not based on the combination of DBCd. In reality patients may have an assessment of response at 3 months but the potential for switching to second line treatment does tend to happen at around the 6 month point unless the patient is not tolerating treatment due to side effects. Assessment of response at both 3 and 6 months would have been a better approach.
Key issue 6: Source of data for overall survival, stratified by haematologic response	
Key issue 7: Baseline source of haematologic response	

distribution for BCd	
Key issue 8: Combining suboptimal haematologic response categories in the model	
Key issue 9: Health-related quality of life utility values used in the model	EQ5D is a well-recognised quality of life measure and acceptable for the study population. True improvement in quality of life is more likely to be seen later on during follow-up after cessation of treatment for a period of months and would be more useful at 12 months.
Key issue 10: Maximum treatment duration with daratumumab	The current use of Daratumumab in multiple myeloma is as second line treatment in combination with Bortezomib for 32 weeks then monthly Daratumumab until disease progression. It is also used as monotherapy in patients who have had 3 previous lines of treatment and again continues until disease progression with no maximum time. While treatment of AL amyloidosis differs in that some patients who are lower risk may not require continuous treatment until disease progression, stipulating a maximum timeframe for Daratumumab would take away the option of carrying on with treatment. This is especially pertinent for the small proportion of patients with concomitant multiple myeloma with a high proportion of plasma cells in their bone marrow.
Key issue 11: Underestimation of the administration costs of DBCd and BCd	I have requested estimated pharmacy costs for Daratumumab, this information has not yet come through but will be available during the meeting in December. In patients with stage III cardiac disease they are required to initiate treatment as an in-patient with cardiac monitoring, this is because of the potential effects of Bortezomib and risk of arrhythmia. This would not be different with DBCd and therefore the additional cost with this group would only be the make-up of the drug in pharmacy and delivery by a nurse on the ward.
Key issue 12: Impact of DBCd on autologous stem cell transplant	

rates	
Key issue 13: Approach to the costs of second- and third-line therapies in the model	
Key issue 14: Potential of daratumumab for the Cancer Drugs Fund (CDF)	Proposing Daratumumab for the cancer drugs fund would enable time for more data on benefit for those patients treated with stage IIIb cardiac disease, these patients have potentially the most to gain from the treatment as rapid effective treatment is absolutely essentially for survival but whether there is a true impact on survival or quality of life in these patients has not been determined by the company and it would allow time for this data to be collected.
Are there any important issues that have been missed in ERG report?	Currently AL amyloidosis is treated by defining the disease as multiple myeloma. If Daratumumab was licensed for AL amyloidosis it would be the first licensed treatment for this disease in its own right. It is important to consider whether there will be an impact on further lines of treatment in the future and whether there would be an impact on these patients continuing to have access to drugs licensed for multiple myeloma as second- and third-line treatment. The ANDROMEDA study did not include patients who presented with stage V CKD or those on dialysis. Inclusion of this group of more severely affected patients may have had an impact on the renal response data presented and also potentially impacts on the potential costs as an improved survival outcome in those with very severe renal function may mean proportionately more patients surviving on dialysis for longer which has a cost implication.
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • Cardiac stage IIIb patients were not included in the ANDROMEDA study. These patients have the most to gain from a rapid clonal	

response and further OS data is required including these patients in order to understand the potential benefit to these patients specifically.

- Patients with very advanced kidney disease were not included in the study, Daratumumab does not require dose adjustment in haemodialysis patients, it is not stipulated whether all renal patients will be included in the potential use of DBCd as upfront treatment including those on renal replacement therapy.
- The true benefit of DBCd will only be apparent when looking at the longer-term outcome data at 24 months + with OS and progression free survival rates and EQ5D at that stage.
- ANDROMEDA showed significant haematological and organ response rates for patients treated with DBCd vs BCd. NICE approval for a treatment in AL amyloidosis in its own right would not only confer a potential outcome benefit but also provide the first real treatment pathway for these patients. The psychological burden of being defined as having myeloma is difficult to quantify. If approved this technology would change the way in which we counsel patients about the disease and is an unmet need in this disease.
-

Thank you for your time.

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……

Your privacy

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Thank you for agreeing to give us your views on this treatment 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.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **15th October 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

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. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want 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 15 pages.

PART 1 – Living with or caring for a patient with systemic amyloid light-chain amyloidosis and current treatment options	
About you	
1.Your name	**Huw Stiley**
2. Are you (please tick all that apply):	☑ a patient with systemic amyloid light-chain amyloidosis? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with systemic amyloid light-chain amyloidosis? ☐ 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 below and provide answers where 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/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with systemic amyloid light-chain amyloidosis? If you are a carer (for someone with systemic amyloid light-chain amyloidosis) please share your experience of caring for them.	Being diagnosed and then living with AL Amyloidosis has completely changed my life. Learning that you have a very rare medical condition is a difficult message to receive. Being told that the condition is incurable is devastating. Learning that your options are limited because there are no approved Amyloid treatment options introduces a significant level of uncertainty and anxiety into your life. AL Amyloid has an immediate and permanently life reducing impact of your life, something that you are constantly reminded off and is something that effects the people close to you, in my instance, my Wife (also my carer) and my Children.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for systemic amyloid light-chain amyloidosis on the NHS?	The historical treatments I have received are not as well defined as other medical conditions. The treatment pathways are therefore not obvious or easy to access. The vast majority of medical people I have come into contact with have never heard of AL Amyloid, knowledge is limited at a local level. Having a rare medical condition brings its own challenges when viewed in the context of the resource

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	limitations of the NHS. The NAC team in London however are absolutely superb. I am not aware off or in close contact with other AL Amyloid patients.
8. If there are disadvantages for patients of **current NHS treatments** for systemic amyloid light-chain amyloidosis (for example how daratumumab in combination is given or taken, side effects of treatment etc) please describe these	My SCT was extremely tough and I took many many months to recover. A SCT is a debilitating and a much harder treatment option when compared to Daratumumab. Your entire life goes on hold whilst you prepare and then receive the SCT treatment. The risks and side effects are huge. I would describe a SCT as putting you into “survival mode”, you are literally fighting to survive the treatment, then months focusing on recovering and hoping the treatment works.
Advantages of this treatment	
9a. If there are advantages of daratumumab in combination over current treatments on the NHS please describe these. For example, the impact 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?	When on a weekly treatment regime, the cumulative side effects can reduce your strength and stamina due to lack of physical activity over a prolonged period of time, however when on a monthly treatment regime, the recovery time between treatments can be measured in days which dramatically improves your quality of life allowing you to undertake more tasks and activities during your non treatment weeks, ie going shopping, taking a walk and some exercise. When given as an infusion Daratumumab is time consuming, a treatment session can take several hours, the injection option by comparison is so much quicker and with no additional side effects. It is also a better use of hospital resources.

9c. Does daratumumab in combination help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	My time in hospital can now be measured as a few hours every 4 weeks allowing me time to recover, and then up to 2 or 3 weeks to do some normal things. Daratumumab is a much less severe treatment regime where the side effects are manageable, ie the neuropathy, disturbed sleep (from steroids), constipation or sickness.
Disadvantages of this treatment	
10. If there are disadvantages of daratumumab in combination over current treatments on the NHS please describe these? For example, are there any risks with daratumumab in combination? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	A Stem Cell Transplant SCT comes with a high risk off contracting a serious infection and subsequent risk to your life. When assessing potential side effects nothing compares with a Consultant quoting you a percentage chance of death from the treatment option you are being presented with. Based on your age and other underlying health conditions you may not even be offered a SCT, therefore the potential side effects of Daratumumab by comparison to other AL Amyloid treatments were not perceived as a disadvantage to me.
Patient population	
11. Are there any groups of patients who might benefit more from daratumumab in combination or any who may benefit less? If so, please describe them and explain why.	Of the treatments I have received, Daratumumab would I feel be a far gentler and less brutal treatment option for anyone who has other health conditions, is less active or lives on their own. My Daratumumab treatment continued during the Covid Pandemic which was reassuring when other treatments may have been halted.

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	
Equality	
12. Are there any potential equality issues that should be taken into account when considering systemic amyloid light-chain amyloidosis and daratumumab in combination? 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	I am not aware or have any knowledge of equality issues and am therefore not able to comment.

More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	AL Amyloid is an incurable disease, Daratumumab offers some hope for those who have been diagnosed with the condition, that there is a recognised treatment pathway available on the NHS.

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.]

Issue 5: When are patients assessed for treatment response in clinical practice? After 3 or 6 months?	
15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages
16. In up to 5 sentences, please summarise the key messages of your statement: • • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

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We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **15 October 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, 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 during engagement 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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Myeloma UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1:	NO	As stated in our evidence submission we would advocate strongly for access to this treatment for patients with cardiac 3b involvement and cite further evidence for showing inclusion. Approximately 20% of patients have advanced (stage 3b) cardiac involvement at diagnosis. Treatment of these patients remains an unmet need. However, if a

		profound response is reached within 1 month, OS can improve, even in these subjects.[1] In the ALchemy trial conducted in the UK at the NAC recently published results show that patients achieving an early deep haematologic response have a significantly superior survival irrespective of cardiac involvement.[2] We note that the submitting company will provide additional evidence for this subpopulation at technical engagement. Studies have shown the effectiveness and tolerability of daratumumab as a treatment for AL Amyloidosis patients with cardiac 3b involvement, including in the USA[3] and in real word studies as a front-line treatment in Austria.[4] Clinical trial data from the ANDROMEDA study shows that daratumumab can produce early and deep haematological responses in patients which will have a significant impact in the patients' overall survival. Based on the evidence above and the clinical experts' opinion we would advocate for patients with level 3b cardiac involvement to be eligible to be treated with Dara CBD.
Key issue 2:	**No**	As stated above we would note that some studies internationally show the effectiveness of treating patients with stage IIIb cardiac AL Amyloidosis with a daratumumab based regimen.

[1] Manwani R, Foard D, Mahmood S, et al. Rapid hematologic responses improve outcomes in patients with very advanced (stage IIIb) cardiac immunoglobulin light chain amyloidosis. Haematologica. 2018;103(4):e165-e168

[2] Ravichandran, S., Cohen, O.C., Law, S. *et al.* Impact of early response on outcomes in AL Amyloidosis following treatment with frontline Bortezomib. *Blood Cancer J.* **11,** 118 (2021). https://doi.org/10.1038/s41408-021-00510-7

[3] Gregory P. Kaufman, Stanley L. Schrier, Richard A. Lafayette, Sally Arai, Ronald M. Witteles, Michaela Liedtke; Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood 2017; 130 (7): 900–902. doi

[4] G. Jeryczynski, M. Antlanger, F. Duca, C. Binder-Rodriguez, T. Reiter, I. Simonitsch-Klupp, D. Bonderman, R. Kain, M.-T. Krauth, H. Agis,First-line daratumumab shows high efficacy and tolerability even in advanced AL amyloidosis: the real-world experience ESMO Open 6:2, 2021, 100065, ISSN 2059-7029,

Key issue 3:	**YES/NO**	No Comments
Key issue 4:	**NO**	We would emphasise that in our patient engagement the side effect profile of Daratumumab in combination with CBD has been similar to the side effect profile experience by treatment with CBD alone. We understand that there is currently limited evidence in long term use of Daratumumab in patients with AL Amyloidosis and that the ERG have looked at further data from multiple myeloma were AE's are said to be largely consistent with those observed in the ANDROMEDA clinical trial. In our engagement with patients who have myeloma and have received Daratumumab for that length time Patients have described it as 'kind' treatment which is well tolerated.
Key issue 5:	No	As discussed in the Technical Engagement meeting, we agree with the Clinical Experts who stated that assessment for depth of haematological response can take place after 3 cycles of treatment however in practice this can range from 3 to 6 cycles of treatment depending on clinical judgement and/or practice or hospital capacity.
Key issue 6:	**YES/NO**	No comments
Key issue 7:	**YES/NO**	No comments
Key issue 8:	**YES/NO**	No comments
Key issue 9:	**YES/NO**	No comments
Key issue 10:	**N**o	We note the comments made by the ERG and NICE on treatment with Daratumumab monotherapy for greater than the 24 months outlined in the ANDROMEDA Clinical trial. From a patient perspective our engagement has shown that patients will receive a treatment for as long as possible as long as it is effectively controlling their disease and keeping them remission. However, the

		fixed duration of treatment with six cycles of Dara CyBord followed by two years of maintenance treatment with daratumumab can provide patients with a level of certainty that the treatment has an end point. Following this, there will hopefully be an extended and possibly treatment-free remission which is highly valued by patients.
Key issue 11:	**NO**	We would agree with the clinical expert opinion that adding daratumumab to the administration costs of BCD would not impact on service capacity. Patients with newly diagnosed AL Amyloidosis will receive BCD and its associated costs as the current standard treatment. The costs of receiving and administering daratumumab should be already known with myeloma patients receiving daratumumab in clinics since 2017.
Key issue 12:	**YES/NO**	No comments
Key issue 13:	**YES/NO**	No comments
Key issue 14:	**YES/NO**	We note the uncertainties raised by the ERG associated with long-term overall survival, health-related quality of life utility values by depth of haematologic response, administration costs of DBCd and BCd, and relative effectiveness of DBCd versus BCd in patients with Mayo Clinic Cardiac Stage IIIb that the CDF may help address. We support this treatment being placed in the CDF to allow further analyses to be performed on these issues and strongly advocate access for this treatment to the whole patient population including patients with Cardiac stage IIIb.
Key issue 15:	**YES/NO**	No comments

Key issue 16:	**YES/NO**	No comments

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

NICE National Institute for Health and Care Excellence

Technical engagement response form

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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, 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 during engagement 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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Society for Heart Failure**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1:	YES – background on NTproBNP measurements and AL amyloidosis grading	The staging of stage 3 AL amyloidosis is based on levels of NTproBNP below (a) or above (b) 8500ng/L. Although this biomarker has been shown to predict mortality in amyloidosis, it is important to understand that the value of NTproBNP is neither fixed nor steadily progressive over time. NTproBNP varies considerably both on a day to day basis and depending on the fluid volume status of the patient. NTproBNP can be decreased from levels above 8500ng/L to levels well below 8500ng/L (eg < 3000ng/L) in patients with AL cardiac amyloidosis simply with fluid offloading. As the disease progresses and cardiac amyloid deposition steadily increases over time, mean NTproBNPs of a population with AL cardiac amyloid will increase, but both between patients and in the same patient at different time points there will be large variations in NTproBNP (both up and down) depending on fluid loading. If patients with stage 3b cardiac AL amyloid at diagnosis were to be excluded from therapy, the ERG would need to consider that many patients will have subsequent NTproBNP levels below this threshold and be aware that some patients may be excluded simply because their fluid balance status has been managed less effectively than others.
Key issue 2:	**NO**	Further data on effectiveness of Daratumumab in patients with advanced disease would be beneficial. However the limitations of the grading of AL amyloidosis

		based on a biomarker with known large temporal and fluid loading/HF management variations persist.
Key issue 3:	**NO**	No additional comments
Key issue 4:	**NO**	No additional comments
Key issue 5:	**NO**	No additional comments
Key issue 6:	**NO**	No additional comments
Key issue 7:	**NO**	No additional comments
Key issue 8:	**NO**	No additional comments
Key issue 9:	**NO**	No additional comments
Key issue 10:	**NO**	No additional comments
Key issue 11:	**NO**	No additional comments
Key issue 12:	**NO**	No additional comments
Key issue 13:	**NO**	No additional comments
Key issue 14:	**NO**	No additional comments
Key issue 15:	**NO**	No additional comments

Key issue 16:	**NO**	I agree that Daratumumab appears appropriate for consideration for the Cancer Drug Fund, given its utility in patients with myeloma, the adverse prognosis associated with the diagnosis and the current ongoing uncertainties regarding long term outcomes while further data is collected.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	N/A	**NO**	N/A

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	**N/A**	N/A
Company's preferred base case following technical engagement	**Incremental QALYs: N/A**	**Incremental costs: N/A**	**N/A**

Single Technology Appraisal (STA)

Daratumumab in combination for newly diagnosed systemic amyloid light-chain amyloidosis [ID3748]

ERG addendum: review of company's response to technical engagement

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The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 Overview

This addendum to the Evidence Review Group (ERG) report presents the ERG's critique of the additional evidence provided by the company in their response to a number of key issues that were raised by the ERG in its report, which were discussed at technical engagement.

The technical engagement covered 14 key issues for consideration. The company's response to technical engagement indicated that they accepted the ERG's judgement on some aspects of Issues 1, 7, 9, 11, 12; and mostly agreed with the ERG on issues 13 and 14. Table 1 summarises the issues and whether the ERG considers them resolved, unresolved, and their remaining uncertainty. The ERG critique to the company's response on all issues is presented in Section 2. The results of the company and ERG's updated analysis are presented in Section 3.

Table 1: Summary of the key issues

Issue		**Resolved?**
1	The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis that is not restricted to exclude patients with Mayo Clinic Cardiac Stage IIIb disease	Partially resolved with large uncertainty remaining
2	Absence of clinical trial data for patients with Mayo Clinic Cardiac Stage IIIb disease	Unresolved
3	Immaturity of overall survival data from the ANDROMEDA clinical trial	Unresolved
4	Lack of medium-to-long term adverse event data for daratumumab in AL amyloidosis	Partially resolved with some uncertainty remaining
5	Timing of response assessment for depth of haematologic response	Unresolved
6	Source of data for overall survival, stratified by haematologic response	Unresolved
7	Baseline source of haematologic response distribution for BCd	Unresolved
8	Combining suboptimal haematologic response categories in the model	Unresolved
9	Health-related quality of life utility values used in the model	Partially resolved with uncertainty remaining
10	Maximum treatment duration with daratumumab	Unresolved
11	Underestimation of the administration costs of DBCd and BCd	Partially resolved with uncertainty remaining
12	Impact of DBCd on autologous stem cell transplant rates	Unresolved but small impact
13	Approach to the costs of second- and third-line therapies in the model	Resolved
14	Potential of daratumumab for the Cancer Drugs Fund (CDF)	Resolved

2 Description and critique of additional evidence

2.1 Issue 1: The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis that is not restricted to exclude patients with Mayo Clinic Cardiac Stage IIIb disease

2.1.1 Background

The company sought a recommendation for DBCd in the entire licensed population of patients with newly diagnosed AL amyloidosis, including patients with Mayo Clinic Cardiac Stage IIIb disease, henceforth referred to as patients with Stage IIIb disease. Patients with Stage IIIb disease have the most severe degree of cardiac involvement and have high risk systemic AL amyloidosis with a very poor prognosis. However, in its original submission, the company submitted no evidence to assess the clinical effectiveness or cost-effectiveness of DBCd compared to BCd in these patients, who were excluded from the ANDROMEDA trial.

2.1.2 The ERG's position

The ERG provided evidence on the cost-effectiveness of DBCd in the entire licensed population (including patients with Stage IIIb and patients with less severe disease) by informing the (baseline) haematologic response distribution with BCd from the UK ALchemy study.[1] This approach assumes that: (i) the relative effectiveness of DBCd versus BCd in deepening haematologic response, as observed in the ANDROMEDA trial, is generalisable to the entire licensed population; (ii) the health-related quality of life, safety and probability of progression observed in the ANDROMEDA trial also generalises to the entire licensed population; and (iii) the UK ALchemy study[1] provides the best available baseline data for overall survival stratified by depth of haematologic response for patients on BCd. The ERG requested additional evidence on the clinical effectiveness and cost-effectiveness of DBCd in patients with Stage IIIb disease.

2.1.3 The company's response

The company considered the approach taken by the ERG (using real-world evidence to inform haematologic response distribution with the standard of care BCd) to be reasonable. However, the company had concerns about internal inconsistency due to a different evidence source being used for relative effectiveness (ANDROMEDA trial) and baseline haematologic response (UK ALchemy study). Furthermore, the company indicated a preference to use the EMN23 study, an international study, to provide evidence for baseline haematologic response rather than the UK ALchemy study.

The company proposed two revised base-cases for its updated analyses:

a. A base-case employing the ERG's approach to the baseline distribution of haematologic response, but using the EMN23 study (post-2010 subset) rather than the ALchemy study to inform the distribution with BCd; henceforth referred to as company's base-case (a).
b. A base-case using the original company's approach, in which the haematologic response distributions for BCd and DBCd were obtained from the ANDROMEDA study; henceforth referred to as company's base-case (b). The company presented base-case (b) to address their concern regarding internal inconsistency in base-case (a).

(Note, for both revised company base-cases (a) and (b), the company uses data from the EMN23 study to inform overall survival conditional on haematologic response in response to Issue 6 - see Issue 6 discussion below).

The company prefers the EMN23 study to inform the baseline haematologic response distribution with BCd in base-case (a) over the ERG preferred ALchemy study because the follow-up is longer and it has a larger sample size, reducing the level of sampling uncertainty. The company notes that the subset of patients treated after 2010 (termed the post-2010 subset) in the EMN23 study includes [redacted]% of patients with Stage IIIb disease, similar to the 15.4% in the UK ALchemy study.

The company considers that the assumption that the relative treatment effectiveness with DBCd from the ANDROMEDA trial is generalisable to patients with Stage IIIb disease is conservative. In the company's interpretation, the subgroup evidence from ANDROMEDA (which did not include patients with Stage IIIb disease at baseline) suggests that the relative treatment effect of DBCd increases with increasing severity of disease.

The company considers that patients with Stage IIIb disease meet NICE's end-of-life criteria, given that their expected overall survival is approximately six months (source not provided), and the company's model predicts that DBCd is likely to extend their life by more than three months (specifically, [redacted] years in base-case (a) and [redacted] years in base-case (b)).

2.1.4 ERG's critique

The ERG considers that the approach of using a UK observational study to inform the baseline distribution by haematologic response is more appropriate than using the distribution observed in the ANDROMEDA trial. The ERG disagrees that this approach gives rise to internal consistency issues. The aim of the cost-effectiveness analysis is to predict what would happen if the alternative options (in this case BCd and DBCd) were used in UK clinical practice. As such, the most relevant source of data to inform the outcomes with BCd in UK clinical practice is the ALchemy study, because it is an observational study reporting the outcomes of patients in UK clinical practice who were treated with bortezomib-based regimens.

The absolute haematologic response distribution observed in the ANDROMEDA trial may not generalise to UK clinical practice because the ANDROMEDA trial was not designed specifically to reflect the absolute outcomes in the UK population, but rather to compare outcomes (and estimate relative effects) across balanced treatment groups. As noted by the company in their response to points for clarification, there are some differences between the response distribution observed in the BCd arm of the ANDROMEDA trial and that of the ALchemy study. This suggests that the absolute outcomes observed in the ANDROMEDA trial (i.e. distribution of patients by haematologic response category) may not generalise to the UK setting, even if the relative effectiveness of DBCd vs BCd is considered generalisable. The approach preferred by the ERG follows the recommendations presented in the NICE Technical Support Document 5 that supports the use of baseline outcomes relevant to the healthcare setting as the absolute natural history under standard treatment to which the relative treatment effects from an RCT are applied to obtain absolute outcomes under the treatment arm.[2]

The ERG reiterates that the ALchemy study is more relevant to the UK than the EMN23 study to inform the baseline haematologic response distribution with BCd and the overall survival stratified by haematologic response. The ALchemy study comprised 1,194 UK patients treated between 2010-2019 with upfront bortezomib, who are a large proportion of all patients with newly diagnosed AL amyloidosis in the UK.[1]

The EMN23 study includes [redacted] patients from 10 European countries, where [redacted] (company's response to ERG points for clarification document, Table 7). In the entire EMN23, [redacted] of patients were from the UK (company's response to ERG points for clarification document, p.16), while it is not clear what proportion from the UK is included in the post-2010 subset or how its follow-up compares to the ALchemy study. The ERG report (p.66) acknowledged the larger sample size of the EMN23 study but this larger sample is likely to be informed by non-UK patients.

The ERG's clinical advisors considered that the ALchemy study reflects the standard of care in the UK better than the EMN23 study. For example, the ERG clinical advisors noted that some countries have a slightly different standard of care (e.g. using melphalan early and switch if poor response) and assessment of response occurs at different timepoints in different countries (e.g. in France, the haematologic response assessment is typically undertaken at 1 month for patients with cardiac AL amyloidosis). Furthermore, the ERG's clinical advisors who are familiar with both studies noted that the ALchemy study's interpretation of the response criteria is the same as the interpretation in UK clinical care, using a strict interpretation, whilst EMN23 has a looser interpretation, which may lead to different results. In addition, a UK clinical expert responding to Technical Engagement stated: "*Real world data regarding outcomes is challenging, the UK Alchemy study is the best current data in the*

absence of a mandated registry for all patients diagnosed with AL amyloidosis." (Dr Jennifer Pinney, p.12). As such, the ERG reiterates that the ALchemy study is the most relevant source of data to represent the UK standard of care.

The ERG notes that the company did not submit additional information on the design and findings of the EMN23 study apart from the data included as part of the Excel model (haematologic response distribution and Kaplan-Meier estimates for overall survival) and the evidence provided at the points for clarification. As far as the ERG is aware, the only peer-reviewed published information on the EMN23 study are conference abstracts/posters, which do not include full details of the population characteristics and follow-up times or survival by heamatologic response presented in the company's response to technical engagement.[3-5] For these reasons, the ERG was unable to critically appraise the EMN23 study in detail.

The ERG does not share the company's interpretation of the subgroup analysis of the ANDROMEDA trial that generalises the relative effectiveness of DBCd vs BCd from the trial population to patients with Stage IIIb disease is conservative. The ERG notes that the ANDROMEDA trial did not include patients with Stage IIIb disease, and the newly cited interaction test statistics are not significant. The difference in relative effect for Mayo Stage I, II, and IIIa subgroups is acknowledged in the ERG report (p.58). However, given (a) how much poorer prognosis is in patients with Stage IIIb disease ("patients with Stage II, IIIa and IIIb disease had a median survival of 67.0 months, 31.1 months and 4.5 months, respectively" CS p.27, citing EMN23 data), and (b) the company's assertion that haematologic response improves over time (see Issue 5), it is plausible that a proportion of stage IIIb patients would not survive long enough to achieve complete haematologic response. Therefore, the assumption of a larger relative effect among Stage IIIb patients than the less severe patients observed in ANDROMEDA trial may not be valid, and the true relative effectiveness of DBCd vs. BCd in Stage IIIb patients remains highly uncertain.

The ERG considers that the company did not present sufficient evidence to support the conclusion that patients with Stage IIIb disease meet NICE's end-of-life criteria. The end-of-life criteria require evidence that the technology increases overall survival for at least an additional 3 months compared to current NHS treatments, in addition to patients having a short life expectancy. The estimates quoted by the company refer to the entire patient population in whom the company seeks the recommendation, of which patients with Stage IIIb disease are approximately 15%, and the assumptions discussed above hold (see 2.1.2 The ERG's position). It is therefore unclear whether the extension to life criterion would be met for patients with Cardiac IIIb disease as no evidence in this subgroup has been provided.

If the company was to seek a recommendation only in the subgroup of patients with Stage IIIb disease, to know if the end-of-life criteria are met for this specific subgroup using the cost-effectiveness model, the company should adapt the model to use data only from the subgroup of patients with Stage IIIb disease from the EMN23 study (or preferably the ALchemy study) to inform haematologic response distribution and to inform overall survival conditional on haematologic response. This subgroup analysis would require the assumptions that (i) the relative effectiveness of DBCd versus BCd for the depth of haematologic response, as observed in the ANDROMEDA trial in patients with Stage I-IIIa disease generalises to patients with Stage IIIb; and (ii) the health-related quality of life, safety and probability of progression observed in the ANDROMEDA trial also generalises to patients with Stage IIIb. Additionally, the company should provide evidence that these assumptions are appropriate.

In the entire patient population, the estimate of overall survival with the current standard of care with BCd is [redacted] years, well above the end-of-life criterion of 24 months. Therefore, the ERG is satisfied that the end of life criteria are not met.

2.2 Issue 2: Absence of clinical trial data for patients with Mayo Clinic Cardiac Stage IIIb disease

2.2.1 Background

As discussed in Issue 1, the ANDROMEDA trial excluded patients with Mayo Clinic Cardiac Stage IIIb – a high clinical need subgroup that comprises approximately 20% of AL amyloidosis patients in the UK. It was therefore unclear how the benefits and harms of DBCd relative to BCd for Stage IIIb patients compare to the benefits and harms estimated for patients with less severe cardiac involvement.

2.2.2 The ERG's position

The ERG noted that no trial evidence is available on patients with Stage IIIb disease and that the company had indicated that they would provide exploratory analysis investigating the cost-effectiveness of DBCd for this subpopulation at Technical Engagement.

2.2.3 The company's response

The company referred to Issue 1 for their response.

2.2.4 The ERG's critique

The ERG reiterates that no trial evidence is available for patients with Stage IIIb disease and no exploratory analysis in this subpopulation has been presented by the company. Therefore, the benefits and harms of DBCd relative to BCd for Stage IIIb patients remain uncertain.

2.3 Issue 3: Immaturity of overall survival data from the ANDROMEDA clinical trial

2.3.1 Background

Mature overall survival data from the ANDROMEDA trial were not available at the time of the company submission, with median overall survival not being reached in either treatment arm. Hence, the model uses the depth of haematologic response as a surrogate for overall survival and uses overall survival data stratified by haematologic response from external studies.

2.3.2 The ERG's position

In the absence of mature overall survival trial data, the ERG considers the company's approach to be acceptable but notes the considerable uncertainty surrounding the predicted treatment-specific overall survival estimates over time. The ERG considered that the assumption that overall survival depends only on depth of haematologic response may be overly simplistic and may bias the model predictions of long-term overall survival. The ERG suggested that the planned future analyses of the ANDROMEDA trial could be used to validate the cost-effectiveness model predictions for overall survival.

2.3.3 The company's response

The company agreed that the analysis planned in [redacted], of 200 MOD-PFS event-driven data cut-off from ANDROMEDA, would provide more mature overall survival data and could validate the assumptions of the cost-effectiveness model.

2.3.4 The ERG's critique

As no new data have been presented by the company, the ERG's critique points remain. It is noted that if daratumumab is recommended within the CDF, additional data would become available that could resolve some of this uncertainty.

2.4 Issue 4: Lack of medium-to-long term adverse event data for daratumumab in AL amyloidosis

2.4.1 Background

While the ANDROMEDA treatment protocol permitted up to 24 months of daratumumab treatment, median length of follow-up in the most recent analysis was 20.3 months and median duration of daratumumab treatment was 18.5 months. Adverse event data for longer treatment or follow-up times are not currently available.

As daratumumab is a monoclonal antibody therapy, the ERG's clinical advisors noted general concerns about the possible effect on infections beyond the period observed in the trial.

2.4.2 The ERG's position

The ERG stated that there is currently limited longer-term evidence on the safety of daratumumab.

2.4.3 The company's response

The company indicated that the Phase III POLLUX study[6] provides safety data for daratumumab in multiple myeloma (MM) patients after more than four years (54.8 months) of follow up. They also refer to the lack of major safety concerns raised in the EPAR, ERG report or SmPC.

With regard to infections, they noted numerically lower rates of infection in the DBCd arm of ANDROMEDA from cycle 7 onwards, and references a study showing risk of infection in patients with newly diagnosed MM to be greatest in the first three months after diagnosis.

The company stated that it has also been advised that treatment with daratumumab is unlikely to continue beyond 2 years, and that ANDROMEDA will ultimately report safety data over this period.

2.4.4 The ERG's critique

The ERG can confirm that safety data reported at 54.8 months of follow-up in the POLLUX multiple myeloma study are largely consistent with the 40-month follow-up data referenced in the ERG report (p.17), and with safety data from ANDROMEDA.

As noted in the ERG report (p.60), infections and infestations (n=[redacted], [redacted] in the DBCd arm; [redacted], [redacted] in the BCd arm) was the most commonly observed class of serious treatment emergent adverse event (TEAE) in ANDROMEDA. This class included pneumonia (n=14, 7.3% in the DBCd arm; n=9, 4.8% in the BCd arm), and sepsis (n=6, 3.1% in the DBCd arm; n=0 in the BCd arm). While the ERG accepts that slightly higher rates of infection were observed during earlier periods of ANDROMEDA and the quoted MM study, it is not possible to establish whether the event rates observed in the ANDROMEDA trial are due to natural history, treatment effects or chance.

The ERG agree that safety data from ANDROMEDA and external sources on daratumumab are largely reassuring, and noted in the ERG report that most infections beyond the ANDROMEDA trial period are anticipated to be treatable Grade I or II events. Such events would not affect the cost-effectiveness estimates (because AEs considered in the model are based on Grade III or IV AEs reported in > 5% of patients).

Nevertheless, until complete ANDROMEDA follow-up data and observational/post-marketing surveillance data are available, there will be some uncertainty around the effects of daratumumab in the longer-term.

The likely duration of daratumumab treatment is discussed under Issue 10 below.

2.5 Issue 5: Timing of response assessment for depth of haematologic response

2.5.1 Background

In the company's original base case analysis, patients were assessed for their haematologic response after six treatment cycles (approximately six months), with patients' overall survival being dependent on haematologic response at this time point.

2.5.2 The ERG's position

The ERG considered that the response assessment timepoint for stratifying patients by haematologic response in the base case should be consistent with current guidelines for the management of AL amyloidosis in UK clinical practice that suggest the assessment timepoint for response is after three months (approximately three treatment cycles).[7] Furthermore, a scenario analysis should be considered to assess the impact of early response to treatment after one treatment cycle, in line with proposals outlined by Ravichandran et al, 2021 and Kastritis et al (2021).[1, 8]

2.5.3 The company's response

The company maintained that the haematologic response assessment after six treatment cycles is more appropriate than after three treatment cycles because haematologic response improves over time, as observed in the ANDROMEDA trial, in Kastristis et al.[8] and in the ALchemy study.[1] The company also notes that one of their clinical experts advised that the overall survival extrapolations based on the haematologic response assessment after six treatment cycles were more reflective of overall survival observed in clinical practice. The company presented a scenario analysis for haematologic response assessment after three treatment cycles, as suggested in the UK clinical guidelines.[7] The ICER increased from £32,744/QALY to £38,520/QALY in base-case (a) and from £32,692/QALY to £42,620/QALY in base-case (b).

The company did not provide a scenario for haematologic response assessment after one treatment cycle because this scenario would not capture the deepening of response over time and requires the use of unstable data. The company considered that only a small proportion of patients who have not achieved a response are switched after one treatment cycle in clinical practice.

2.5.4 The ERG's critique

The ERG maintains its view that the timing of haematologic response assessment in the model should reflect UK clinical practice and guidelines, which suggest this should be carried out after three treatment cycles. This is supported by a clinical expert who responded to Technical Engagement: "*Data from the Alchemy trial suggests that the response assessment should be at 3 months and in fact demonstrates a benefit for a 1 month assessment.*" (Dr Carol Whelan, p.13). The ERG considers that the assessment after six treatment cycles is a relevant scenario, but should not constitute the base-case

analysis, given the UK clinical guidelines and the UK expert clinical testimony that: "*In reality patients may have an assessment of response at 3 months but the potential for switching to second line treatment does tend to happen at around the 6 month point unless the patient is not tolerating treatment due to side effects. Assessment of response at both 3 and 6 months would have been a better approach*." (Dr Jennifer Pinney, p.13). The ERG considers that a one-month response assessment warrants a scenario analysis in order to assess the impact of early response to treatment at one month, in line with proposals outlined by Ravichandran et al. and Kastritis et al.[1, 8]

In response to the company's comment that haematologic response improves over time, the ERG notes that the overall survival curves which inform the probability of death in the model are stratified by haematologic response at the specific time point. Therefore, these overall survival curves given haematologic response at three months reflect the deepening of the haematologic response over time.

2.6 Issue 6: Source of data for overall survival, stratified by haematologic response

2.6.1 Background

A key assumption in the model is that the distribution of haematologic response achieved at the response assessment timepoint (e.g., after three or six cycles of first-line treatment with DBCd or BCd) can predict treatment-specific overall survival over time. In the model, the source of overall survival data, stratified by depth of haematologic response and extrapolated over the long-term is a key driver of cost-effectiveness. In the original submission, the company informed overall survival based on the Palladini et al. study in the base-case analysis and the Kastritis et al. study in a scenario analysis.[8, 9]

2.6.2 The ERG's position

The ERG believes that overall survival stratified by haematologic response should be based on UK data and informed by the UK ALchemy study for the reasons presented in section 2.1.4.

2.6.3 The company's response

The company has revised their base-case to use data from the EMN23 study (post-2010 subset) to inform overall survival stratified by haematologic response in the cost-effectiveness model. The company considers the EMN23 study to be more appropriate than the ALchemy study due to its larger sample size ([redacted] patients in the EMN23 study post-2010 subset vs 1,194 patients in the ALchemy study), large proportion of UK patients (n=1,156 patients) and longer follow-up period. The company reported that the follow-up of the EMN23 study (post-2010 subset) is [redacted] but it is unclear if this statistic refers to the median follow-up. The company has concerns regarding the maturity of the ALchemy study data because the Kaplan-Meier curves for overall survival in patients with complete response (CR) and very good partial response (VGPR) cross, with expert clinical opinion indicating

that this is clinically implausible and likely to be reflective of immature data. However, the company do not compare the length of follow-up of the two studies, possibly because median follow-up for ALchemy has not been published.

In their revised base-cases, the company used the exponential distribution to extrapolate the overall survival of patients with CR, and the Weibull extrapolation for patients with VGPR and for patients with partial response (PR) and no response (NR). Figure 1 shows the extrapolated overall survival curves over time by haematologic response status for the company's revised base-case, using the EMN23 study data and for the haematologic response assessment after six treatment cycles. The Kaplan-Meier curves are in solid lines, the parametric extrapolations are in dashed lines, and the overall survival curves which directly inform the probability of death in the model are in dotted lines; the general population survival curve is presented as the solid black line, for comparison.

Figure 2 shows the same overall survival curves, but for the haematologic response assessment after three treatment cycles (rather than six cycles) and based on the EMN23 (post-2010 subset). As the company did not report which parametric distributions were used in their scenario for the response assessment after three treatment cycles, the figure shows the same parametric distributions as were used for the extrapolation stratified by the haematologic response assessment after six treatment cycles: exponential curve for patients with CR, and Weibull curves for patients with VGPR, PR, and NR. This results in an ICER of £38,520/QALY under base-case (a) using the EMN23 study baseline, which is the same as reported by the company; and £43,468/QALY using base-case (b), using the ANDROMEDA baseline, which is slightly different to the ICER of £42,620/QALY reported by the company in their response document.

Figure 1: Overall survival stratified by haematologic response after six treatment cycles used in the company's revised base-case (EMN23 study post-2010 subset)

Adapted from the company's revised model.

Abbreviations: CR: complete response; NR: no response; KM: Kaplan-Meier; OS; overall survival PR: partial response; VGPR: very good partial response.

Figure 2: Overall survival stratified by haematologic response after three treatment cycles used in the company's revised base-case (EMN23 study post-2010 subset)

Adapted from the company's revised model.

Abbreviations: CR: complete response; NR: no response; KM: Kaplan-Meier; OS; overall survival PR: partial response; VGPR: very good partial response.

2.6.4 The ERG's critique

As discussed in section 2.1.4, the ERG maintains that the UK ALchemy study is the most relevant source of overall survival data to inform the cost-effectiveness model. Although the EMN23 study has a larger sample size, the ERG has concerns that this additional data is contributed by mostly non-UK patients, whose characteristics and prognosis may not generalise to the UK. It is not clear if the EMN23 study (post-2010 subset) has a longer follow-up than the ALchemy study as suggested by the company because the ALchemy study has not reported the median follow-up.[1] If the EMN23 study (post-2010 subset) has a longer follow-up, these data may not be from UK patients, hence may not be generalisable to the UK. The implication is that the possible longer follow-up and larger sample size of the EMN23 study may not provide evidence that is generalisable to the UK. The ERG has not been provided with full details of the EMN23 study so cannot comment further.

Figure 3 to Figure 10 show the Kaplan-Meier curves of the ALchemy study and the EMN23 study (post-2010 subset) and their extrapolations, which, in the model, form the basis of the overall survival

curves (and the probability of death) for the ERG and company's base-cases, respectively. The EMN23 study (post-2010 subset) data is represented in blue, and the ALchemy study data is represented in orange; for both, the solid lines are used for the Kaplan-Meier curve and dashed lines for the extrapolations. For both the haematologic response assessment after three- and six treatment cycles, the extrapolation curves fit visually well to the observed data and the curves follow a similar pattern:

- In patients with CR, the Kaplan-Meier and extrapolation curves are similar between the two studies, with the EMN23 study (post-2010 subset) extrapolation predicting slightly higher survival compared to the ALchemy study extrapolation.
- In patients with VGPR, the Kaplan-Meier curve based on the EMN23 study (post-2010 subset) is lower than the Kaplan-Meier curve based on the ALchemy study; the extrapolation curves follow the same pattern.
- In patients with PR, the Kaplan-Meier curve based on the EMN23 study (post-2010 subset) starts being above the Kaplan-Meier curve based on the ALchemy study, crossing around 5 years; hence, the extrapolation curve based on the ALchemy study is above the curve based on the EMN23 study (post-2010 subset) from this point onwards.
- In patients with NR, the Kaplan-Meier curve based on the EMN23 study (post-2010 subset) is lower than the Kaplan-Meier curve based on the ALchemy study; the extrapolation curves follow the same pattern.

Figure 3: Overall survival in patients with CR, stratified by response after six treatment cycles

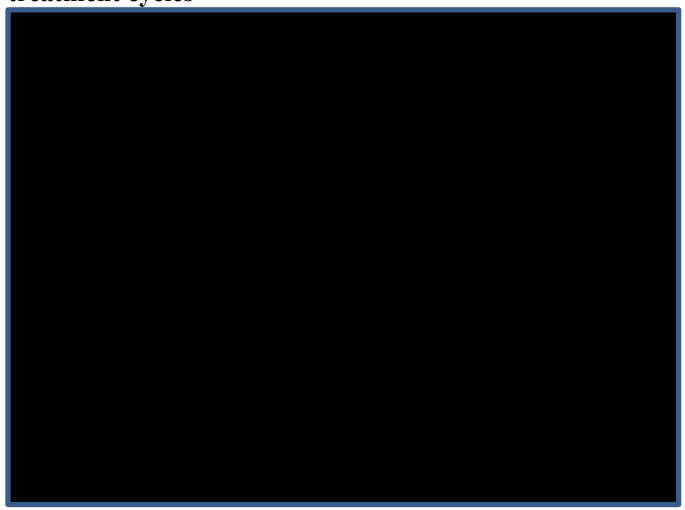

Figure 4: Overall survival in patients with VGPR, stratified by response after six treatment cycles

Figure 5: Overall survival in patients with PR, stratified by response after six treatment cycles

Figure 6: Overall survival in patients with NR, stratified by response after six treatment cycles

Figure 7: Overall survival in patients with CR, stratified by response after three treatment cycles

Figure 8: Overall survival in patients with VGPR, stratified by response after three treatment cycles

Figure 9: Overall survival in patients with PR, stratified by response after three treatment cycles

Figure 10: Overall survival in patients with NR, stratified by response after three treatment cycles

In assessing the face validity of the extrapolation curves, the ERG suggests considering the feedback from the ERG clinical advisors. This feedback was that, at 15-years after first-line treatment, the ERG clinical advisors expected 25%-30% of patients who achieve CR to be alive, with a similar but slightly lower estimate for patients who achieve VGPR; and very few patients with PR or NR to be alive at 15-years, with patients who achieve NR having poorer outcomes than patients who achieve PR (see ERG report p127).

Table 2 compares the ERG clinical advisors' feedback with the extrapolated curve predictions at 15-years. The main difference between the extrapolation curves based on the EMN23 study (post-2010 subset) and those based on the ALchemy study is in the predictions for overall survival of patients with VGPR. The curves based on the EMN23 study (post-2010 subset) predict a lower survival at 15-years than those based on the ALchemy study, and lower than the ERG clinical advisors' feedbacks. The differences with the predictions at 15-years for patients with CR, PR and NR are smaller in magnitude. The curves based on the EMN23 study (post-2010 subset) predict slightly higher survival for patients with CR compared to the curves based on the ALchemy study and compared to the ERG clinical advisors' feedback. For patients with PR and NR, the curves based on the EMN23 study (post-2010 subset) predict slightly higher survival than the curves based on the ALchemy study; both are broadly in line with the ERG clinical advisors' feedback.

Table 2: Comparison of ERG clinical advisors' feedback on survival at 15 years to the predictions by the extrapolation curves based on the EMN23 study (post-2010 subset) and ALchemy study

Haematologic response → Extrapolation based on ↓	**CR**	**VGPR**	**PR**	**NR**
Feedback from ERG clinical advisors	~ 25-30%	Similar to CR but slightly lower	Few patients	Very few patients
Response assessment after six treatment cycles				
EMN23 study (post-2010 subset)	[redacted]	[redacted]	[redacted]	[redacted]
ALchemy study	35%	24%	9%	5%
Response assessment after three treatment cycles				
EMN23 study (post-2010 subset)	[redacted]	[redacted]	[redacted]	[redacted]
ALchemy study	31%	28%	12%	8%

Abbreviations: CR: complete response; NR: no response; PR: partial response; VGPR: very good partial response.

2.7 Issue 7: Baseline source of haematologic response distribution for BCd

2.7.1 Background

In the original company's base-case, the company used haematologic response distribution after six treatment cycles in the DBCd and BCd arms from the ANDROMEDA trial to inform the proportion of patients in each treatment group by depth of haematologic response and death in the decision tree model.

2.7.2 The ERG's position

Following the ERG's view that the ALchemy study is the most relevant source to inform the baseline haematologic response distribution for BCd, the ERG used the haematologic response distribution with bortezomib-based regimens in the ALchemy study to inform the baseline distribution for BCd and applied the relative effectiveness of DBCd vs BCd from the ANDROMEDA trial to estimate the absolute response distribution for DBCd.

2.7.3 The company's response

As discussed in Issue 1, the company presented two revised base-cases: base-case (a) using the EMN23 study (specifically the post-2010 subset) to inform the baseline haematologic response distribution, similar to the ERG's base-case using the ALchemy study, and base-case (b) using the ANDROMEDA trial as per the company's original base-case. The company took the same approach for base-case (a) as the ERG. Due to data limitations, the company assumed that patients who were categorised as 'NA' (not available) in the EMN23 study and who had not died were assumed to be distributed among the response categories (CR, VGPR, PR/NR) in the same proportions as observed for the patients that were not marked as 'NA'.

2.7.4 The ERG's critique

The ERG reiterates that the ALchemy study is the most relevant source to inform the baseline haematologic response distribution for BCd in UK clinical practice.

The haematologic response distributions and proportion of patients who die according to the three alternative sources for the baseline: the ANDROMEDA trial, the EMN23 study (post-2010 subset) and the ALchemy study, are shown in Figure 11 for the response assessment after six treatment cycles and in Figure 12 for the response assessment after three treatment cycles. The results were mostly consistent across the two timings for response assessments: the ALchemy study had the [redacted] proportion of patients achieving CR (e.g. after six treatment cycles: [redacted] ALchemy vs [redacted] EMN23 vs [redacted] ANDROMEDA) and the [redacted] proportion of patients achieving PR and NR (e.g. after six treatment cycles: [redacted] ALchemy vs [redacted] EMN23 vs [redacted] ANDROMEDA). At the assessment of response after six treatment cycles, the proportion of patients with VGPR was [redacted] in the ALchemy study ([redacted] ALchemy vs [redacted] ANDROMEDA vs [redacted] EMN23), while after three treatment cycles it was [redacted] in ANDROMEDA ([redacted] ANDROMEDA vs [redacted] ALchemy vs [redacted] EMN23). The proportion of patients who died was consistently higher in the ALchemy study (e.g. after six treatment cycles: [redacted] ALchemy vs [redacted] EMN23 vs [redacted] ANDROMEDA).

Figure 11: Standard of care haematologic response assessment distribution and proportion of patients who died after six treatment cycles

Figures plotted using data presented in the company's model; EMN23 and ANDROMEDA study data also presented in the company's response to technical engagement.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Figure 12: Standard of care haematologic response assessment distribution and proportion of patients who died after three treatment cycles

Figures plotted using data presented in the company's model; EMN23 and ANDROMEDA study data also presented in the company's response to technical engagement.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Figure 13 compares the change in haematologic response and proportion of patients who died when the response assessment is after six treatment cycles (company's base-case) and Figure 14 after three treatment cycles (company's scenario and ERG base-case) when using the ANDROMEDA study, the EMN23 study, or the ALchemy study for the BCd baseline. Under the scenario that the haematologic response assessment takes place after six treatment cycles, the absolute change in haematologic response is similar across the different baseline sources (Figure 13). Under the company's preferred assumptions, using the EMN23 study for the baseline, results in an ICER of £32,744/QALY (company's base-case (a)); using the ANDROMEDA trial for the baseline, results in an ICER of £32,692/QALY (company's base-case (b)); and using the ALchemy study for the baseline, results in an ICER of £40,634/QALY.

Assuming that the haematologic response assessment takes place after three treatment cycles, the absolute change in haematologic response is also similar across the sources for the BCd baseline (Figure 14). Under the company's preferred assumptions, using the EMN23 study for the baseline,

results in an ICER of £38,520/QALY (company's base-case (a)); using the ANDROMEDA trial for the baseline, results in an ICER of £43,468/QALY (company's base-case (b)); and using the ALchemy study for the baseline, results in an ICER of £45,554/QALY.

Figure 13: Change in haematologic response and proportion of patients who died when the response assessment is at six treatment cycles depending on whether the ANDROMEDA trial, the EMN23 study or the ALchemy study are used to inform the baseline

Figures plotted using data presented in the company's model; EMN23 and ANDROMEDA study data also presented in the company's response to technical engagement.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Figure 14: Change in haematologic response and proportion of patients who died when the response assessment is at three treatment cycles depending on whether the ANDROMEDA trial, the EMN23 study or the ALchemy study are used to inform the baseline

Figures plotted using data presented in the company's model; EMN23 and ANDROMEDA study data also presented in the company's response to technical engagement.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

2.8 Issue 8: Combining suboptimal haematologic response categories in the model

2.8.1 Background

The model structure pooled together patients with PR and NR into a combined group of PR/NR based on the simplifying assumption that these patients are considered to achieve a suboptimal response and follow a similar treatment trajectory. The limitation is that, over time, patients who achieve PR are expected to survive longer and hence become a greater proportion of patients alive. By calculating overall survival as the weighted average of the two groups at the response assessment timepoint, the model underestimates overall survival for the pooled PR/NR group.

2.8.2 The ERG's position

The ERG had concerns that this simplifying assumption may favour DBCd given that fewer patients achieve PR and NR; hence the ERG suggested that the model structure should be revised to have sufficient flexibility to separate out these two categories.

2.8.3 The company's response

The company considered that the pooling of patients with PR and NR within the model was appropriate because it reflects clinical practice in that these patients are managed in a similar way. The company referred to an exploratory analysis where the company calculated overall survival for PR and NR independently and by treatment arm, which had similar results to the approach pooling both groups. Additionally, the company considered that modelling PR and NR patients separately may result in better overall survival if patients are treated with DBCd. The company noted that revising the model structure could not be completed within the timelines of the Technical Engagement.

2.8.4 The ERG's critique

The ERG notes that the request to model patients who achieved PR and NR separately was made to the company at Points for Clarification but has not been provided to date. The ERG welcomes the exploratory analysis by the company but are unable to comment given that the methodology and detailed results have not been provided. The ERG maintains its concerns with this simplifying assumption.

2.9 Issue 9: Health-related quality of life utility values used in the model

2.9.1 Background

The company's base-case did not adjust utilities by age over time, which is a standard approach used in cost-effectiveness models to reflect changes in utility over time.[10] Furthermore, the company's base-case assumed that the utility decrements for the progression-related health states of second-line treatment and end-stage organ failure are conditional on response to first-line treatment, but it was unclear why patients in these health states would not have the same utility value, irrespective of previous response to treatment or previous lines of therapy. The ERG also noted that the EQ-5D utility values by haematologic response used in the model were highly uncertain because of the lack of face validity of the utility values derived for VGPR; the short follow-up period to cycle six to inform long-term utility values; and the limited data for health-related quality of life during the progression-related health states of second-line treatment and end-stage organ failure (see ERG report section 4.2.8.2).

2.9.2 The ERG's position

The ERG's base-case included utility values adjusted by age over time.[10] The ERG presented a scenario (ERG Scenario 8) where the utility values on second-line therapy or end-stage organ failure do not differ by depth of haematologic response achieved on first-line therapy, which had a minor impact on the ICER. To reduce the uncertainty related to the utility values, the ERG noted that health-related quality of life data in the form of SF-36v2 scores has been collected from patients in the ALchemy study at baseline and response assessment study visits of 3-, 6- and 12-months. These data

could potentially be used to map the SF-36 scores to EQ-5D utility values using a published algorithm,[11] in order to validate the EQ-5D utility values from the ANDROMEDA trial.

2.9.3 The company's response

The company agreed with the ERG that the application of age-adjusted utilities over time was appropriate and revised their base-case analyses accordingly. The company acknowledged the uncertainty in the utility values and agreed that data on utilities over the longer term is relevant. The company noted that the EMN23 study did not collect health-related quality of life data and that health-related quality of life data stratified by haematologic response from the ALchemy study could not be identified.

2.9.4 The ERG's critique

The ERG welcomes the revision to the company's base-case to include age-adjusted utilities. The ERG notes that the company did not provide evidence to justify the assumption that utility decrements for the progression-related health states of second-line treatment and end-stage organ failure depend on response to first-line treatment. However, the impact of this assumption on the ICER is small.

The ERG emphasises that the health-related quality of life data used in the model is very uncertain given the data limitations. The uncertainty is likely to have a large impact on the cost-effectiveness results, which the ERG was unable to explore quantitively due to the data limitations. Therefore, the ERG suggests that the ALchemy study data on health-related quality of life data stratified by haematologic response is requested from the study authors for the purpose of informing this appraisal.

2.10 Issue 10: Maximum treatment duration with daratumumab

2.10.1 Background

The company's base-case analysis assumes that patients receive daratumumab treatment as observed in the ANDROMEDA trial (up to a maximum of 24 treatment cycles; mean treatment duration = [redacted] cycles) but the SmPC for daratumumab does not include a 24-cycle treatment discontinuation criterion. No patients in the daratumumab arm appeared to have reached the maximum permitted treatment duration of 24 cycles in the ANDROMEDA trial at the time of the IA1 analysis, though [redacted] reached 24 cycles in the 12-month Landmark analysis. If daratumumab was recommended in line with its licensed treatment duration, the proportion of patients on treatment beyond 24 cycles and their overall treatment duration is uncertain. If patients continue to receive daratumumab treatment beyond 24 cycles in UK clinical practice, the costs of treatment in the model may be underestimated. Given the lack of evidence on the effect of continuing daratumumab treatment beyond 24 cycles, the impact on health outcomes is unclear. The model structure is not sufficiently flexible to permit daratumumab monotherapy to continue for more than 24 cycles.

2.10.2 The ERG's position

The ERG suggests providing additional flexibility within the model structure to permit daratumumab treatment to continue beyond 24 cycles. However, the ERG notes that the effect on health outcomes would remain unclear because of a lack of evidence on the long-term effects of permitting daratumumab treatment beyond 24 cycles.

2.10.3 The company's response

The company noted that, while mean treatment duration with daratumumab in the ANDROMEDA trial was [redacted] cycles in the 12-months landmark analysis, [redacted] 195 ([redacted]) patients received daratumumab for 24 cycles. The company heard from UK expert clinicians that treatment beyond two years would be unlikely given the lack of evidence for longer treatment durations and burden to patients. The company presented a new scenario in which all patients who receive DBCd have the maximum treatment duration of 24 cycles, assuming that the health outcomes are unchanged from the base-case – the ICER increased from £32,744/QALY to £41,049/QALY in base-case (a) and £32,692/QALY to £40,746/QALY in base-case (b).

2.10.4 The ERG's critique

The ERG notes that the uncertainty regarding the proportion of patients who will receive daratumumab for more than 24 cycles remains unresolved because the ANDROMEDA trial had a 24-cycle stopping rule. As shown by the new company scenario, if daratumumab is taken for a longer period of time, the ICER increases.

The ERG clinical advisors commented that patients are unlikely to continue treatment beyond 24 cycles due to lack of evidence about the effects of longer treatment durations. The ERG clinical advisors noted that, if there was an option of continuing beyond 24 cycles, the majority of patients who are still on daratumumab treatment at this point are likely to be tolerating the drug reasonably well and not have progressed; hence it may be desirable for them to remain on daratumumab treatment.

The comment by an UK clinical expert to Technical Engagement suggests that a small proportion of patients may have longer treatment durations: "*While treatment of AL amyloidosis differs in that some patients who are lower risk may not require continuous treatment until disease progression, stipulating a maximum timeframe for Daratumumab would take away the option of carrying on with treatment. This is especially pertinent for the small proportion of patients with concomitant multiple myeloma with a high proportion of plasma cells in their bone marrow*." (Dr Jennifer Pinney, p14). Given the lack of evidence on the effect of continuing daratumumab treatment beyond 24 cycles, the impact on QALYs is unclear.

2.11 Issue 11: Underestimation of the administration costs of DBCd and BCd

2.11.1 Background

The original company's base-case assumed that the cost of subcutaneous administration for daratumumab and bortezomib corresponds to the cost of 5 minutes of a band 5 nurse at £3.08[12] and zero cost for cyclophosphamide and dexamethasone because their administration is oral. However, daratumumab and bortezomib require preparation in the pharmacy or in the ward, and the first four administrations of daratumumab are expected to require the patient to stay for a few hours for monitoring. Furthermore, the NHS guidance for national cost collection[13-15] specifies that, in recording the costs of chemotherapy, trusts should use the relevant healthcare resource group (HRG) codes for the procurement of chemotherapy at £2,110 and for the delivery of chemotherapy and £241 for simple parental chemotherapy at first attendance and £332 for subsequent elements of a chemotherapy cycle. Therefore, if these costs are representative of the administration and procurement costs in the NHS, the administration costs of DBCd and BCd are likely to be underestimated in the model.

2.11.2 The ERG's position

The ERG presented a scenario which uses the aforementioned NHS Reference Costs for the administration of bortezomib-based chemotherapy to inform the administration costs of daratumumab and bortezomib. The ICER increased from £23,509/QALY to £30,800/QALY. This assumption was not included in the ERG base-case due to the uncertainty regarding whether these unit costs were reflective of the administration costs of DBCd and BCd to the NHS. The ERG asked for information on the relevant HRG codes for the procurement and administration of DBCd and BCd in the NHS.

2.11.3 The company's response

The company did not provide additional evidence on the relevant HRG codes for the procurement and administration of DBCd and BCd in the NHS. In the company's revised base-case analyses, the administration costs for DBCd and BCd are now based on the administration costs used in a previous appraisal of daratumumab in untreated multiple myeloma (NICE appraisal ID1510[16]).

2.11.4 The ERG's critique

The ERG welcomes the revision of the administration costs of DBCd and BCd to align with a previous NICE appraisal. However, the administration costs are smaller than those based on the NHS guidance for national cost collection:[13-15] £241-£332 vs £99.30; it is unclear whether the unit cost of specialist nursing (as proposed by the company) is more relevant to administration of chemotherapy than the unit cost of the healthcare resource group for chemotherapy delivery (as in the ERG scenario), and whether the unit cost for procurement of chemotherapy should be included. The ERG has now updated its base-case to include the company's proposed administration costs but notes that

the uncertainty regarding the most appropriate values remains unresolved. Clarification on the relevant HRG codes for the procurement and administration of DBCd and BCd in the NHS would resolve this issue.

2.12 Impact of DBCd on autologous stem cell transplant rates

2.12.1 Background

The company's base-case analysis did not include the costs of autologous stem cell transplant (ASCT), although some patients receive it as subsequent therapy, as observed in the ANDROMEDA trial ([redacted] of patients on BCd and [redacted] of patients on DBCd received ASCT) and in the UK ALchemy study[1, 17] (7% of patients on first-line therapy, 9% as second-line and 3% as third-line). ASCT is a costly procedure (e.g. unit cost = £15,065[15]). The ERG noted that the company's scenario using the ALchemy study to inform the distribution of patients by second- and third-line therapy included the unit costs of ASCT. In addition to the impact on costs, if DBCd affects the proportion of patients who subsequently have ASCT, their health outcomes may also be affected.

2.12.2 The ERG's position

The ERG considers that the costs of ASCT should be included because this is a treatment used in UK clinical practice and its effect on health outcomes is implicit in the overall survival curves that inform the model. Therefore, the ERG considers that the company's scenario (in response to ERG's points for clarification) which used the ALchemy study to inform the distribution of patients by second- and third-line treatments is more likely to reflect clinical practice. The ERG did not include the costs of ASCT as part of first-line therapy given the uncertainty about the extent to which the proportion of patients undergoing ASCT may change with DBCd. The ERG asked for evidence on the ASCT rates with DBCd and its impact on long-term health outcomes.

2.12.3 The company's response

The company presented a new scenario analyses in response to technical engagement in which [redacted] of patients receive ASCT as a second-line treatment, based on the ASCT rates in the EMN23 study – the ICER increased from £32,692/QALY to £32,892/QALY in base-case (b). This scenario includes the ASCT impact on costs but not on health outcomes. The company considers this scenario conservative as daratumumab is expected to improve survival post-ASCT, given that the CASSIOPEIA trial found that a greater proportion of patients with multiple myeloma who had daratumumab before and after ASCT had achieved complete response.[18]

2.12.4 The ERG's critique

The ERG agrees that the CASSIOPEIA trial suggests that patients who receive daratumumab, bortezomib, thalidomide, and dexamethasone (DBTd) alongside ASCT as part of their first-line

treatment may have better prognosis than patients who have ASCT and BTd without daratumumab, although the CASSIOPEIA trial is in a different population (multiple myeloma rather than AL amyloidosis). However, uncertainty remains on the magnitude of the effect and, importantly, on whether the proportion of patients who have ASCT will be larger or smaller with DBCd than with BCd. The ERG considers that this uncertainty is likely to have a small impact on expected cost-effectiveness because the proportion of patients who have ASCT is relatively small.

2.13 Issue 13: Approach to the costs of second- and third-line therapies in the model

2.13.1 Background

The ERG expressed concerns that the costs of second- and third-line treatments were overestimated in the model, which was likely to favour DBCd as fewer patients progress to second-line therapy when treated with DBCd at first-line. The concerns were:

(1) The costs of second-line therapy (included in the base-case analysis) and third-line therapy (included in a scenario analysis) were calculated by assuming that all patients who progress to subsequent lines of therapy receive the full set of treatment cycles, without accounting for deaths, treatment discontinuation and dose adjustments over the duration of treatment on subsequent lines of therapy. Hence the costs were likely to be overestimated.

(2) In the company's base-case, the type of treatment and distribution of patients by second- and third-line therapies were derived from UK clinical expert opinion received at a Janssen-led advisory board,[19] whilst there is evidence from the UK ALchemy study[17] to inform these distributions. The ERG noted that the company presented a scenario in response to the ERG's points for clarification, which used the distributions from the UK ALchemy study.[17]

(3) In the company's scenario analysis, the calculation of the distribution of patients on third-line treatment referred to the actual number of patients on third-line treatment. However, the ERG considered it more appropriate to calculate the distribution of patients by treatment at third-line out of those treated at second-line given that these costs are applied at entry to the health state 'On second line treatment'. Therefore, the costs of third-line treatment were overestimated in this scenario.

2.13.2 The ERG's position

The ERG conducted additional scenario analyses to resolve these concerns, which subsequently informed the ERG base-case, as follows:

(1) The ERG reduced the costs of second- and third-line treatments by 20% to account for deaths, treatment discontinuation and dose adjustments over the treatment duration; 20% reflects the lower bound of the company's scenario analysis in response to ERG points for clarification.

(2) The ERG adopts the company's scenario analysis (in response to ERG points for clarification) where the distribution of patients by type of second- and third-line therapies was obtained from the UK ALchemy study,[17] given that it is more likely to reflect UK clinical practice and ensures that the costing of subsequent treatments aligns with overall survival in the model.

(3) The ERG recalculated the distribution of patients by third-line therapy when using the ALchemy study; which applies both second- and third-line treatments are included and the distribution of patients by treatments is informed by the ALchemy study.[17]

2.13.3 The company's response

The company revised its base-case analyses as follows:

(1) The company agreed with the application of a 20% reduction of the costs of second- and third-line treatments by 20% to account for deaths, treatment discontinuation and dose adjustments over the treatment duration.

(2) The company agreed with the inclusion of the costs of second- and third-line therapies but preferred to source the type of regimens and proportion of patients receiving each regimen from the UK clinical advisory board rather than from the ALchemy study; this was the UK clinical advisory board provided detailed information on the regimens which facilitates the costings.

(3) The company agreed that the distribution of patients by third-line therapy should refer to the number of patients on second-line therapy and adjusted the distribution of patients on third line therapy accordingly.

2.13.4 The ERG's critique

The ERG is satisfied with the company's response, although the ERG maintains that the ALchemy study is a more relevant source of evidence to inform the type of regimens and proportion of patients by type of regimen in subsequent therapies in UK clinical practice. Hence the ERG maintains their preferred assumptions and continues to use the ALchemy study to inform the ERG base-case.

2.14 Issue 14: Potential of daratumumab for the Cancer Drugs Fund (CDF)

2.14.1 Background

In their response to ERG points for clarification, the company stated that while they have positioned DBCd for routine commissioning within the NHS, they have had preliminary discussions with NHS England and verbal confirmation that, if deemed appropriate by the NICE Committee, daratumumab would be eligible for the CDF. There is uncertainty associated with long-term overall survival, health-related quality of life utility values by depth of haematologic response, administration costs of DBCd and BCd, and relative effectiveness of DBCd versus BCd in patients with Mayo Clinic Cardiac Stage IIIb that the CDF may help address.

2.14.2 The ERG's position

The ERG considers that, if daratumumab was recommended for the CDF, the additional time would allow for data from the ALchemy study to mature and reduce the uncertainty in the overall survival extrapolation, as well as providing time to explore the potential of the ALchemy study to inform health-related quality of life utility values in the model. Furthermore, further analyses of the longer-term data collected in the ANDROMEDA study could be used to validate the predictions of the cost-effectiveness model.

2.14.3 The company's response

The company reiterated that they have primarily positioned DBCd for routine commissioning but would accept a CDF recommendation. The CDF recommendation would allow for evidence to be gathered regarding overall survival of DBCd vs BCd in the ANDROMEDA trial, outcomes of patients with Stage IIIb disease via NHS data collection and the ALchemy study, and the impact of DBCd treatment on health-related quality of life via the ALchemy study.

2.14.4 The ERG's critique

The ERG has nothing further to add to its previous comments and to the company's response.

3 Results

3.1 Company analysis

3.1.1 Modelling assumptions

In response to the issues noted by the ERG and following technical engagement, the company updated their base case cost-effectiveness analyses and provided two new base-cases. The following ERG-preferred assumptions are incorporated within the company's revised model:

- Issue 9: Health-related quality of life utility values are adjusted by age over time.

- Issue 11 and 13: The costs of subsequent therapies are reduced to account for discontinuations, dose reductions and deaths; the costs of third-line therapies are included; and the distribution of patients by third-line therapies are recalculated as suggested by the ERG. However, the company continues to prefer to use the UK clinical advisory board to inform the type of regimens and proportion of patients receiving each regimen while the ERG prefers to use the ALchemy study.

In addition, the following assumptions have been altered in the company's revised model:

- Issues 1 and 7: The company now proposes two revised base-cases, one of which uses the EMN23 study (post-2010 subset) to inform the baseline haematologic response distribution with BCd.
- Issues 6: Overall survival stratified by haematologic response is based on the survival analysis of the EMN23 study (post-2010 subset) in both the company's revised base-cases.
- Issue 11: The administration costs in the company's base-cases are based on the administration costs used in a previous appraisal of daratumumab in untreated multiple myeloma (NICE appraisal ID1510[16]).

The company maintain their original position on the following assumptions, which differ from the ERG's preferred assumptions:

- Issue 5: The company maintains that the timing of the haematologic response assessment should take place at six treatment cycles, rather than three treatment cycles in the ERG preferred assumptions.
- Issue 8: The company maintains that the pooling of patients with PR and NR in the model structure is appropriate.
- Issue 13: As discussed earlier, the company continues to prefer to use the UK clinical advisory board to inform the type of regimens and proportion of patients receiving each regimen while the ERG prefers to use the ALchemy study.

3.1.2 Company's cost-effectiveness results

Table 3 shows the deterministic cost-effectiveness results for the company's revised base-case analyses, and Table 4 shows the corresponding probabilistic cost-effectiveness results. The company base-cases produce similar ICER results at £32,744/QALY and £32,692/QALY for base-case (a) using EMN23 study (post-2010 cohort) to inform baseline haematologic response distribution and base-case (b) using the ANDROMEDA trial to inform baseline haematologic response distribution, respectively. Table 5 summarises the results of the company's scenario analyses.

Table 3: Company's revised base-case analyses – deterministic results

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (/QALY)
Base-case (a): using EMN23 study (post-2010 cohort) to inform baseline haematologic response distribution					
BCd	[redacted]	[redacted]	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 32,744
Base-case (b): using the ANDROMEDA trial to inform baseline haematologic response distribution					
BCd	[redacted]	[redacted]	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£32,692

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 4: Company's revised base-case analyses – probabilistic results (95% confidence intervals in brackets)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (/QALY)
Base-case (a): using EMN23 study (post-2010 cohort) to inform baseline haematologic response distribution					
BCd	[redacted]	[redacted]			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 31,930.10
Base-case (b): using the ANDROMEDA trial to inform baseline haematologic response distribution					
BCd	[redacted]	[redacted]			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 31,869.21

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 5: Summary of company's scenario analyses (deterministic)

Scenario	ICER, £/QALY	
	Base-case (a)	Base-case (b)
Company's base-case assumptions	32,744	32,692
Issue 5: Timing of the haematologic response assessment after three treatment cycles.	38,520	42,620
Issue 10: Daratumumab treatment duration is 24 cycles.	41,049	40,746
Issue 12: ASCT included in the second-line treatment regimens; proportion obtained from EMN23 study.	32,951	32,892

Abbreviations: ASCT: autologous stem cell transplant. BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life year.

3.2 ERG analysis

The ERG's preferred assumptions and base-case remain, as per the ERG report, with the exception of the administration costs which now follow those proposed in the company's revised base-case (i.e., the administration costs are now based on those used in a previous appraisal of daratumumab in

untreated multiple myeloma [NICE appraisal ID1510[16]]). Table 6 presents the results of the ERG's preferred assumptions when applied to the company's revised base case (b), with a detailed breakdown of total costs and QALYs shown in Table 8, while corresponding results for the ERG base-case from a probabilistic analysis are shown in Table 7.

The ICER of the ERG's preferred base-case is £66,373/QALY (probabilistic; £65,964/QALY). The alternative assumptions for Issue 13 (approach to the costs of second- and third-line therapies in the model) and Issue 6 (source of data for overall survival, stratified by haematologic response) have a limited impact on the ICER results: the company's revised base case ICER increases from £32,692/QALY to £36,821/QALY (Issue 13) and £33,261/QALY (Issue 6), when the changes are applied individually, and to £38,109/QALY when Issues 13 and 6 are applied cumulatively.

Using the ALchemy study to inform the baseline haematologic response distribution has a large impact on the ICER results: the ICER increases from £32,692/QALY to £40,634/QALY when this is the only change applied. This is driven by a higher proportion of patients with CR and VGPR, a lower proportion of patients with PR/NR, and a greater proportion of patients who died in the ALchemy study compared to the EMN23 study (post-2010 subset) (see Figure 11). When the relative effectiveness of DBCd vs BCd from the ANDROMEDA trial is applied to this baseline haematologic response distribution, the improvement in the proportion of patients with CR is slightly smaller, the reduction in patients with VGPR is higher and the reduction in patients with PR/NR is smaller when compared to the ANDROMEDA trial or EMN23 study (post-2010 subset) for the baseline distribution (see Figure 13). The impact of changes to the distribution of patients by haematologic response is propagated through the model via the overall survival curves stratified by haematologic response, which inform the probability of death in the model.

The timing of the haematologic response distribution has the largest individual impact on the ICER: the ICER increases from £32,692/QALY to £43,468/QALY. This is for two reasons. Firstly, due to the smaller improvement in the haematologic response distribution with DBCd after three treatment cycles compared to six treatment cycles (see Figure 13 and Figure 14). Secondly, the overall survival curves stratified by the haematologic response assessment after three treatment cycles are slightly lower for patients with CR compared with the curves stratified by the haematologic response assessment after six treatment cycles, while the overall survival curves for patients with VGPR, PR and NR are slightly higher. Therefore, the comparative benefits in terms of overall survival from achieving CR are not as pronounced when using the haematologic response assessment after three treatment cycles compared to after six treatment cycles.

When the ERG's preferred assumptions to the model are implemented cumulatively, there is a large increase in the company's revised base case ICER. The combination of ALchemy study to inform the

baseline haematologic response distribution for BCd (Issue 7), ALchemy study to inform the proportion of patients on second- and third-line therapies (Issue 13), and ALchemy study to inform the overall survival stratified by haematologic response (Issue 6) increases the ICER from £32,692/QALY to £50,065/QALY. This large impact is mostly due to the combined effect of smaller absolute improvements in haematologic response distribution, and particularly the larger reduction in patients with VGPR when using the ALchemy study baseline, and the better overall survival of patients with VGPR in the ALchemy study compared to the EMN23 study (post-2010 subset). Combining the ERG preferred assumptions for Issues 6, 7 and 13 with the timing of the haematologic response distribution after three treatment cycles (Issue 5), increases the ICER further to £65,964/QALY. This is due to the reasons discussed above: smaller improvement in haematologic response distribution and smaller differences in overall survival between patients with CR and VGPR (and to smaller extent, PR and NR).

The ERG refers the committee to the addendum with the company's and ERG's base-case results with confidential prices included for subsequent therapies.

Table 6: ERG preferred assumptions and resulting ICERs

Issue	Preferred assumption	ICER, /QALY	
		Individual (*)	Cumulative(*)
Company's base-case (b) using ANDROMEDA trial to inform baseline haematologic response distribution with BCd		£32,692 (**)	
Issue 13: Approach to the costs of second- and third-line therapies in the model	**Costs: Proportion of patients on second- and third-line therapies based on the ALchemy study** To inform the costs of second- and third-line treatments, the ALchemy study[17] is more likely to reflect UK clinical practice, and therefore represents a better source of data to inform the type and distribution of patients receiving second- and third-line therapies. ERG3	£36,821	£36,821
Issue 6: Source of data for overall survival, stratified by haematologic response	**Overall survival based on the ALchemy study (CR – Weibull distribution; VGPR - Weibull; PR/NR – Weibull)** The ALchemy study[1] is the best source of available evidence to inform overall survival, stratified by depth of haematologic response, to inform expected survival outcomes in UK clinical practice.	£33,261	£38,109
Issue 7: Baseline source of haematologic response distribution for BCd	**ALchemy study used to inform the baseline haematologic response distribution for BCd (conditioning order for relative effect from the ANDROMEDA trial of alive, CR, and VGPR)** The ALchemy study[1] is more generalisable to the UK patient population than the ANDROMEDA trial and the EMN23 study. The ALchemy study[1] is the most relevant available source to inform the baseline haematologic response distribution for BCd, while the distribution for DBCd is informed by the relative treatment effect from the ANDROMEDA trial and applied to the haematologic response distribution for BCd from the ALchemy study.	£40,634	£50,065

Issue 5: Timing of response assessment for depth of haematologic response	**The timing of the response assessment is after three treatment cycles, consistent with UK clinical practice and guidelines.**[7]	£43,468	£65,964
	ERG base-case	£65,964	

(*) Individual ICER refers to the results when the alternative assumptions are applied individually; **Cumulative ICER** refers to the results when the alternative assumptions are applied cumulatively, in the order as indicated by the order of issues in the table.

(**) The company presented two base-cases, with similar results. Base-case (a) uses the baseline haematologic distribution from the EMN23 study; the ICER is £ 32,744/QALY.

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: evidence review group. ICER: incremental cost-effectiveness ratio.

Table 7: ERG base-case – probabilistic results (95% confidence intervals in brackets)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (/QALY)
BCd	[redacted]	[redacted]			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 66,373.36

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 8: Detailed cost-effectiveness results for each of the ERG's preferred assumptions

Scenario	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
Changes to the company model done individually						
Company's base-case	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£32,692
Costs: Second- and third-line therapies based on the Alchemy study	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£36,821
Overall survival based on the ALchemy study: CR - Weibull; VGPR - Weibull; PR/NR – Weibull; haematologic response assessment after six treatment cycles.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£33,261
ALchemy baseline; conditioning order: alive, CR, VGPR ; haematologic response assessment after six treatment cycles.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£40,634
Haematologic response assessment after three treatment cycles; ANDROMEDA baseline; overall survival based on the EMN23 (post-2010 subset) study.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£43,468
Changes to the company model done cumulatively						
Company's base-case	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£32,692
Costs: Second- and third-line therapies based on the Alchemy study	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£36,821
Overall survival based on the ALchemy study: CR - Weibull; VGPR - Weibull; PR/NR – Weibull; haematologic response assessment after six treatment cycles.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£38,109
ALchemy baseline; conditioning order: alive, CR, VGPR ; haematologic response assessment after six treatment cycles.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£50,065
Haematologic response assessment after three treatment cycles; ALchemy baseline; overall survival based on the ALchemy study.	BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£65,964

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. CR: complete response. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: evidence review group. ICER: incremental cost-effectiveness ratio. NR: No Response. PR: Partial Response. VGPR: very good partial response.

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