【ダラキューロ配合皮下注】

未治療の全身性 AL アミロイドーシスに関する費用対効果評価

[第 1.0 版]

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【提出日】2022 年 5 月 20 日

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Table of abbreviations

Abbreviation	Formal Description
1L	First-line
2L	Second-line
aCR	Amyloid complete response
AE	Adverse event
AIC	Akaike's information criterion
AL	Amyloid light-chain
ASCT	Autologous stem cell transplantation
ASMR	Amélioration du Service Médical Rendu
BIC	Bayesian information criterion
BMd	Bortezomib, melphalan, dexamethasone
BNF	British National Formulary
BNP	B-type natriuretic peptide
C2H	Core2 Health
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CUA	Cost-utility analysis
CyBorD	Cyclophosphamide, bortezomib, and dexamethasone
DCE	Discrete choice experiment
DCyBorD	Daratumumab, cyclophosphamide, bortezomib, and dexamethasone
dFLC	Difference in free light-chains
DNA	Deoxyribonucleic acid

ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EQ-5D	EuroQol-5 Dimension questionnaire
EQ-5D-5L	EuroQol-5 Dimension-5 Level questionnaire
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item
ER	Emergency room
FDT	Fixed daratumumab treatment
FLC	Free light-chain
FLCr	Free light-chain ratio
G	Grams
GHS	Global health status
HAS	French National Authority for Health
HBV	Hepatitis B Virus
HCRU	Healthcare resource use
Hr	Hour
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
iFLC	Involved free light-chains
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMiD	Immunomodulatory drug
IPD	Individual patient data
IQR	Interquartile range
IQWiG	Institute for Quality and Efficiency in Health Care
IRR	Infusion related reaction

ITT	Intent-to-treat
IV	Intravenous
Kg	Kilogram
KM	Kaplan-Meier
L	liter
LY	Life-year
M	Meter
Md	Melphalan and dexamethasone
MDV	Medical Data Vision
Mg	Milligrams
MHLW	Ministry of Health, Labor and Welfare
min	Minute
mL	Milliliters
MM	Multiple myeloma
MOD	Major organ deterioration
Mp	Melphalan, prednisone
N	Number
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
Ng	Nanograms
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported or no response
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association

OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PFS	Progression-free survival
PI	Package insert
PO	Oral
PR	Partial response
PSA	Probabilistic sensitivity analysis
Py	Person year
QALY	Quality-adjusted life year
RBd	REVLIMID® (lenalidomide), bortezomib, dexamethasone
RCT	Randomized controlled trial
Rd	REVLIMID® (lenalidomide), dexamethasone
RDI	Relative dose intensity
REML	Restricted maximum likelihood
rHuPH20	Vorhyaluronidase Alfa (Genetical Recombination)
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-12	Short-form 12
SF-36	Short-form 36
SG	Standard gamble
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMR	Service Médical Rendu
Tab	Tablet

TCd	Thalidomide, cyclophosphamide, dexamethasone
TEAE	Treatment-emergent adverse event
TNT	Time to next treatment
TSD	Technical Support Document
Tx	Treatment
UK	United Kingdom
USA	United States of America
VAS	Visual analog scale
VAT	Value-added tax
VGPR	Very good partial response

0 Abstract

The summary of analytical results for the target drug is summarized and described in **Table 0.1** below.

Table 0.1. Summary of analytical results

Name of technology subject to analysis [**Section 1.1**]	DARZQURO® SC (daratumumab and vorhyaluronidase alfa [genetical recombination] [rHuPH20]) in combination with bortezomib, cyclophosphamide, and dexamethasone (DCyBorD)
Evaluation results at health technology evaluation institutions in other countries [**Section 1.8**]	CADTH (Canada): Recommended with conditions HAS (France): Recommended IQWiG (Germany): Minor additional benefit NICE (UK): Not recommended (draft recommendation) SMC (Scotland): Under evaluation PBAC (Australia): Not recommended; two options of re-submission pathway are provided by PBAC
Target disease/population [**Section 2.1**]	Newly diagnosed Amyloid light-chain (AL) amyloidosis
Comparative technical name	Cyclophosphamide, bortezomib, and dexamethasone (CyBorD)
Analysis position and scope of costs [**Section 2.2**]	Public healthcare payer
Effectiveness indicators to be used [**Section 2.3**]	Life years (LYs) and quality-adjusted life years (QALYs)
Analysis period [**Section 2.4**]	35 years (i.e., lifetime)
Discount rate [**Section 2.5**]	2% (costs), 2% (effects)

Systematic Review Clinical Questions [**Section 3**]	P: Newly diagnosed AL amyloidosis patients I: DCyBorD C: CyBorD O: Efficacy (hematologic response, MOD-PFS, OS), safety and HRQoL
Summary of Results of Systematic Review [**Section 3**]	One RCT, the ANDROMEDA trial, was identified where eighteen records, all pertaining to ANDROMEDA, were identified by systematic review via database and registry searches in addition to hand-searching of pre-specified conference abstract lists
Results of Indirect Comparison [**Section 3**]	Not applicable
Presence or absence of additional usefulness [**Section 3**]	■ Presence of additional benefit □ "No additional usefulness" or "Cannot be determined" Evidence from the ANDROMEDA study demonstrates the presence of additional benefit for DCyBorD compared to CyBorD with respect to hematologic response, MOD-PFS, organ response, and HRQoL. • The rate of hematologic CR was significantly higher in the DCyBorD arm vs the CyBorD arm (53.3% vs. 18.1%; OR: 5.1 (95% CI: 3.2 to 8.2); p<0.001) in the primary analysis (median follow-up 11.4 months). At the median follow-up of 25.8 months, the CR rate continued to be higher (59.5% vs 19.2%; OR [95% CI], 6.03 [3.80–9.58]; p<0.0001). • MOD-PFS was significantly longer in the DCyBorD group than the CyBorD group (HR 0.58, 95% CI 0.36 to 0.93, p=0.02) in the

	primary analysis. • At 6 months, cardiac response and renal response favored DCyBorD compared with CyBorD among evaluable subjects. 41.5% of DCyBorD (95% CI 32.5 to 51.0) and 22.2% of CyBorD (95% CI 15.1 to 30.8) subjects achieve cardiac response; 53.0% (95% CI 43.5 to 62.3) of DCyBorD and 23.9% (95% CI 16.4 to 32.8) of CyBorD subjects had a renal response. Greater cardiac responses (53% vs. 24%) and renal response rate (58% vs. 26%) were achieved at 18 months. • Median time to improvement was shorter and median time to worsening was longer in the DCyBorD group than in the CyBorD group for EORTC QLQ-C30 GHS and fatigue scales and EQ-5D-5L VAS. The median time to improvement for global health status as measured by the EORTC QLQ-C30 was 7.83 months in the DCyBorD arm and 16.79 months in the CyBorD arm (hazard ratio = 1.53, 95% CI, 1.10 to 2.13). EORTC QLQ-30 global health status showed continued improvement in the DCyBorD arm after 6 months.
Overview of Cost-Effectiveness Analysis Methods [**Sections 4.1.1, 4.2, etc.**]	A CUA model was developed consisting of a decision tree paired with a Markov model where patients transition through independent health states and OS is stratified by hematologic response.
Summary of Results [**Section 5**]	Compared with CyBorD, DCyBorD was more effective (incremental 1.85 QALYs) and was associated with higher costs (¥ 10,414,642) over a 35-year horizon, resulting in an ICER of ¥ 5,626,171 per QALY gained.

Interval considered to have the highest probability of belonging to ICER	ICER threshold: ☐ 通常の品目 ☒ 配慮が必要な品目 (designated intractable disease) ☐ Cost reduction or dominant ☒ ≤ 7.5 million yen ☐ More than 7.5 million yen and ≤ 11.25 million yen ☐ More than 11.25 million yen and ≤ 15 million yen ☐ Over 15 million yen ☐ Equivalent (or inferior) efficacy and high cost

Abbreviations: AL = amyloid light chain; CUA = cost-utility analysis; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; ICER = incremental cost-effectiveness ratio; Lys = life years; OS = overall survival; QALY = quality adjusted life year; RCT = randomized controlled trial; SC = subcutaneous; SLR = systematic literature review.

1 Nature of drugs and medical devices subject to the study

1.1 Name

- 製品名
  ダラキューロ配合皮下注
- 一般名
  ダラツムマブ（遺伝子組換え）1800mg、ボルヒアルロニダーゼ　アルファ（遺伝子組換え）30000 単位（1 バイアル 15mL 中）

Regimen for the evaluation: DARZQURO® (daratumumab and vorhyaluronidase-alfa [rHuPH20]) in combination with cyclophosphamide, bortezomib, and dexamethasone. (DCyBorD)

1.2 Insurance Reimbursement Price

保険償還価格：15mL 1 バイアル 445,064 円 (2022 年 5 月 20 日時点)

算定方式：類似薬効比較方式(I)

算定上の最類似技術：ダラザレックス点滴静注 400mg

有用性系加算：有用性加算 II（A=5%）

2022 年 4 月薬価改定時の加算：希少疾病の効能追加等に係る加算（A=5%）

1.3 Mechanism of Therapeutic Effect

Daratumumab is a CD38-targeted human IgG1κ monoclonal antibody that functions as an immunotherapy directed toward CD38, an antigen that is highly and uniformly expressed on the surface of multiple myeloma (MM) cells and also on plasma cell clones responsible for amyloid light-chain (AL) amyloidosis (1). The specific mechanisms of action of daratumumab include both immune-mediated effects (ie, complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody dependent cell-mediated toxicity, antibody dependent cellular phagocytosis, and direct cellular apoptosis) and immunomodulatory effects (1-3). Vorhyaluronidase alfa (rHuPH20) reduces the

viscosity of the extracellular matrix by depolymerizing hyaluronian, a component of the extracellular matrix in the subcutaneous space. This facilitates the diffusion and absorption of therapeutic drugs.

1.4 Target Disease

Indications covered by public insurance

- Multiple myeloma
- Systemic AL Amyloidosis (Target disease of this analysis)

Systemic AL amyloidosis is a subtype of "systemic amyloidosis (Notification No. 28)" which has been designated as a designated intractable disease in Japan (4). AL amyloidosis is a rare, underdiagnosed disease characterized by the extracellular accumulation of insoluble amyloid fibril deposits on various organs and tissues (5, 6). Over time, these deposits disrupt tissue structure and cause organ dysfunction. AL amyloidosis is the most common and severe form of amyloidosis (7) and is a distinctly different plasma cell disorder from multiple myeloma (MM) (8). In MM, abnormal plasma cells proliferate and inhibit the production of normal blood cells. In AL amyloidosis, clonal plasma cells produce immunoglobulin (Ig) light chains that misfold and deposit systemically as amyloid in any organ outside the central nervous system (9). The deposition of these fibrils can affect multiple organs, most commonly the heart (50%-75%) and kidneys (70%), resulting in a variety of associated complications including malabsorption, nephrotic syndrome, and heart failure (7). Presenting symptoms of this disease, such as asthenia and dyspnea, generally overlap with those of other diseases; as a result, diagnosis is often delayed by several months or even years in some cases (10-13). Patients typically require at least three physician visits before their diagnosis and this delay is often challenging for patients, especially for those experiencing unpredictable symptoms (10, 13). Because of these delays, many patients are diagnosed after their disease has progressed to more advanced stages and organ damage has already occurred (14).

Studies pertaining to the incidence of systemic AL amyloidosis are sparse; as such, the incidence of AL amyloidosis both globally and in Japan remains unclear. United States (US)-based estimates range from 10 to 12 cases per

million per year, while studies based out of Argentina and Sweden report incidences of 6.1 and 3.0 cases per million person-years, respectively (15-17). In Japan, a 2019 study reported the estimated incidence of AL amyloidosis as 4.2 per million person-years (18). According to a recent Japanese study of 741 patients with AL amyloidosis, the median age at diagnosis was 65 years (range: 31-93) and men were more afflicted by the disease than women (59% male; 41% female) (19).

Number of people expected to use the drug for the disease to be analyzed

Based on the annual incidence of systemic AL amyloidosis (4.2 per 1 million) in Japan (18), it is estimated to have 500 adults with newly diagnosed AL Amyloidosis per year (20). Treatment for these patients is selected on the basis of individual patient risk status. It is estimated that [redacted] of newly diagnosed AL Amyloisis paitents may receive DCyBord based on a market research conducted by Janssen in 2021 (21). As the result, it is estimated that [redacted] adult patients will receive DCyBorD per year. Note that the market research result is aligned with patient risk profile in the ANDROMEDA trial (eligible portion of patient ranges from 60-80% of total based on an epidemiology study) (18, 22, 23).

1.5 Method of Use

1.5.1 Drug Dosing, Administration Route, and Frequency of Administration

DCyBorD consists of four individual drugs: daratumumab, cyclophosphamide, bortezomib, and dexamethasone. The route and frequency of administration, dose, and duration of treatment for DCyBorD are presented in **Table 1.1**.

Table 1.1. Drug dosing and administration for DCyBorD

Drug	Administration Route	Dose per Administration	Dosing Schedule
DARZQURO® (daratumumab and rHuPH20)	SC*	1,800 mg	• 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
Cyclophosphamide	PO	300 mg/m^2	• Weekly (Days 1, 8, 15, 22) for a maximum of 6 cycles
Bortezomib	SC	1.3 mg/m^2	• Weekly (Days 1, 8, 15, 22) for a maximum of 6 cycles
Dexamethasone	PO	40 mg	• Weekly (Days 1, 8, 15, 22) for a maximum of 6 cycles

* The daratumumab SC formulation uses a higher concentration of daratumumab compared to the IV formulation and reduces the infusion volume to 15 mL, which reduces the risk that patients with cardiac or renal comorbidities will experience signs or symptoms of volume overload (24). Daratumumab SC formulation is approved to treat AL Amyloidosis patients in Japan.

Abbreviations: DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; m = meter; mg = milligrams; PO = oral; rHuPH20 = vorhyaluronidase alfa; SC = subcutaneous.

Source: DARZQURO® package insert (25).

1.5.2 Co-medications

According to the DARZQURO® package insert (PI), co-medications should be used to reduce the infusion reaction caused by administration of this drug (25). Corticosteroids, antipyretic analgesics and antihistamines should be given one to three hours before the start of administration of this drug. In addition, in order to reduce the delayed infusion reaction, corticosteroids, etc. should be administered after administration of this drug as necessary (25).

1.5.3 Disease Monitoring Tests

According to the DARZQURO® PI (25), important basic precautions must be taken. Since myelosuppression may occur, blood and other tests should be performed regularly before and during administration of this drug. Additionally, hepatitis due to reactivation of hepatitis B virus (HBV) may occur due to administration of this drug. Therefore, hepatitis virus infection should be tested for prior to drug administration and appropriate measures should be taken before administration of this drug. Other precautions may be required for patients with specific complications or a history of disease, such as tumor lysis syndrome, pulmonary disease, bronchial asthma, or patients who are HBV carriers (25). If abnormalities related to tumor lysis syndrome are observed, patients should be treated (administration of physiological saline, therapeutic agents for hyperurinary acidemia, dialysis, etc.) until symptoms are resolved. If abnormalities related to interstitial lung disease are observed, administration of this drug should be discontinued, and chest CT, serum markers, etc. should be examined as necessary.

1.6 Positioning of the Drug in the Treatment of the Target Disease

Treatment for systemic AL amyloidosis focuses on destruction of the underlying plasma cell clone, thereby suppressing amyloidogenic Ig light-chain formation and preserving organ function (5, 26). Before DARZQURO®, no therapies were approved in Japan.

Due to lack of approved pharmacologic treatment regimens, CyBorD and other treatments have been used but result in suboptimal patient outcome; most patients fail to achieve hematologic complete response (CR) during first-line treatment (27, 28) and low rates of cardiac and renal response are observed (27, 29-33). As most treatments for systemic AL amyloidosis are associated with poor efficacy and/or unacceptably high safety risks, a strong need exists for an effective and approved first-line therapy that can rapidly induce high rates of CR and organ response, prolong survival, and improve health-related quality of life (HRQoL).

1.6.1 Position of DCyBorD in treatment flow

Recently updated local and clinical guidelines, including National Comprehensive Cancer Network (NCCN) guidelines and guidelines from the Japanese Society of Myeloma (JSM), now recommend that daratumumab combination therapy be used as a first-line treatment for this disease (**Table 1.2**) (34-36). In NCCN guidelines version 1.2022, DCyBorD is the only preferred regimen (Category 1) for newly diagnosed AL Amyloidosis as the primary therapy for hematopoietic cell transplant eligible candidates and non-eligible candidates. Other recommended regimens including CyBorD and other off label regimens are also included in **Table 1.2**. According to JSM guidelines, DCyBorD therapy for patients with newly diagnosed AL amyloidosis is recommended regardless of whether ASCT is indicated or not (level A recommendation / evidence level Ib) (36).

Table 1.2. NCCN Guideline for Systemic Light Chain Amyloidosis:

Therapy for newly diagnosed disease

Primary therapy for hematopoietic cell transplant eligible candidates and non-eligible candidates
Preferred Regimen • Daratumumab/cyclophosphamide/bortezomib/dexamethasone (category 1)
Other Recommended Regimens • Bortezomib± dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/melphalan/dexamethasone • Melphalan/dexamethasone

Abbreviations: NCCN = National Comprehensive Cancer Network.
Note: If not a candidate for hematopoietic cell transplant at initial diagnosis, reassess after two cycles of systemic therapy; All recommendations are category 2A unless otherwise indicated. Note: the order of regimens in each category is alphabetical and does not indicate preference.

Source: Adapted from NCCN Guidelines Version 1.2022 (Systemic Light Chain Amyloidosis) (35)

1.7 Major Adverse Events

The following major adverse events may occur as described in the DARZQURO® PI (25):

Infusion Reactions

Infusion reactions (24.9%) such as anaphylaxis, nasal congestion, cough, chills, bronchospasm, hypoxia, and dyspnea may occur. If any abnormalities are observed, administration of this drug should be interrupted or discontinued, appropriate measures should be taken, and the patient's condition should be carefully monitored until the symptoms resolve. If a severe infusion reaction is observed, appropriate measures, including discontinuation of administration of this drug should be taken.

Bone Marrow Suppression

Neutropenia (15.8%), thrombocytopenia (12.8%), lymphopenia (9.2%) and febrile neutropenia (1.2%) may occur.

Infections

Serious infection such as pneumonia (7.4%) and sepsis (0.7%) may occur. Reactivation of hepatitis B virus may occur.

Tumor lysis syndrome

Tumor lysis syndrome (incidence unknown). If abnormality is observed, take appropriate measures such as administration of normal saline, providing treatment for hyperuricemia, and dialysis. Continue monitoring patient's condition carefully until the symptoms resolve.

Interstitial lung disease

Interstitial lung disease (0.3%) If any abnormalities are observed, administration of this drug should be discontinued. Chest CT and serum marker test should be examined as necessary.

1.8 Results of Evaluation by Health Technology Assessment Bodies in Other Countries

A list of assessments in key countries is provided in **Table 1.3**. See **Table 1.4** for a summary of available cost-effectiveness evaluations in each country.

Table 1.3. List of assessments in key countries

Country	Institution Name	Evaluation results	List Price (Local currency)
United Kingdom	NICE	• Recommendation: Other (In review. Final recommendation not yet available) (37)	[redacted] per 1,800 mg per vial

		• Assessment Status: Draft The draft outcome is "not recommended" due to the uncertainty of cost-effectiveness. However, the clinical experts considered DCyBorD to be a step-change in managing newly diagnosed AL amyloidosis as the treatment extends life for at least an additional 3 months, compared to current NHS treatment. The second committee meeting is planned.	
	SMC	• Recommendation: Other (in review, result not available) • Assessment Status: Other (In review) (38)	
France	HAS	• Recommendation: recommended • Actual benefit (SMR): Important • Improvement in actual benefit (ASMR): IV (minor) vs CyBorD	[redacted] per 1800 mg vial.
Germany	IQWiG	• Minor additional benefit vs CyBorD	[redacted] per 1,800 mg vial*

Canada	CADTH	• Recommendation: recommended with clinical criteria and/or conditions (39) • Assessment Status: Final	[redacted] per 1,800 mg vial
Australia	PBAC	• Recommendation: Not recommended (40) • Assessment Status: PBAC nominated two re-submission pathways.	[redacted] per 1800 vial

Abbreviations: ASMR = amélioration du service médical rendu; BNF = British National Formulary; CADTH = Canadian Agency for Drugs and Technologies in Health; HAS = Haute Autorité de santé (French National Authority for Health); IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); mg = milligrams; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; SMR = service médical rendu; VAT = value-added tax. * Rote Liste https://www.doccheck.com/ (Accessed on May 10th, 2022).

Table 1.4. Details of cost-effectiveness evaluation in each country

Country	Institution Name	Presence or absence of evaluation results
United Kingdom	NICE	Under evaluation (draft guidance decision is available) (37)
	SMC	Under evaluation (SMC2447) (38)
France	HAS	Present (final guidance) (41)
Germany	IQWiG	Present (final guidance)
Canada	CADTH	Present (final guidance) (39)

Australia	PBAC	Present (40)

Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health; HAS = Haute Autorité de santé; IQWiG = Institute for Quality and Efficiency in Health Care; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium.

Details pertaining to the evaluation results for National Institute for Health and Care Excellence (NICE), Haute Autorité de santé (HAS), Institute for Quality and Efficiency in Health Care (IQWiG), Canadian Agency for Drugs and Technologies in Health (CADTH), and Pharmaceutical Benefits Advisory Committee (PBAC) are presented in **Table 1.5**, **Table 1.6**, **Table 1.7**, **Table 1.8**, and **Table 1.9**, respectively. Note: full details of these evaluation results have not been posted or are not available since the submissions are still under review.

Table 1.5. Details of draft evaluation results for NICE

Country	United Kingdom
Institution Name	NICE (37)
URL of evaluation results, etc.	https://www.nice.org.uk/guidance/indevelopment/gid-ta10656
Technology to be evaluated	Daratumumab SC for use in combination with cyclophosphamide, bortezomib and dexamethasone (DCyBorD)
Evaluation Results	Below is the information from appraisal evaluation document. Note that this document is not NICE final guidance on this technology. The recommendations below may change after consultation. • Daratumumab plus bortezomib, cyclophosphamide, and dexamethasone is not recommended, within its marketing authorization, for treating newly diagnosed systemic AL amyloidosis in adults.

	• This recommendation is not intended to affect treatment with daratumumab plus bortezomib, cyclophosphamide and dexamethasone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.
If a Conditional Recommendation, specify the condition	Not applicable
Disease subject to evaluation	Adults with newly diagnosed systemic AL amyloidosis
Usage	Daratumumab: 1,800 mg (15 mL vial; 120 mg per mL) injected subcutaneously over 3-5 minutes • Week 1 to 8: every week • Week 9 to 24: every 2 weeks • Week 25 until progression or maximum of 2 years: every 4 weeks Bortezomib: 1.3 mg/m^2 subcutaneously – max 6 cycles Cyclophosphamide: 300 mg/m^2 orally or IV – max 6 cycles Dexamethasone: 40 mg orally or IV Weekly dose on Days 1, 8, 15 and 22 in every 28-day cycle
Comparative Control	The committee agreed that, for people newly diagnosed with systemic AL amyloidosis, standard care in the NHS is bortezomib plus cyclophosphamide and

	dexamethasone (CyBorD or bortezomib in combination in the appraisal consultation document) and hence it is the most relevant comparator.
Key Incremental Cost Effectiveness Ratio Values	The cost-effectiveness estimates ranged from £34,000 to £62,000 per QALY.

Abbreviations: AL = amyloid light-chain; ASCT = autologous stem cell transplant; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; IV = intravenous; m = meter; Md = melphalan and dexamethasone; mg = milligrams; mL = milliliters; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; QALY = quality adjusted life-year; Rd = REVLIMID® (lenalidomide), dexamethasone; UK = United Kingdom.

Table 1.6. Details of evaluation results for HAS

Country	France
Institution Name	HAS (41)
URL of evaluation	https://www.has-sante.fr/jcms/p_3320599/fr/darzalex-amylose-systemique-a-chaines-legeres-daratumumab
Technology to be evaluated	Daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone (DCyBorD).
Evaluation Results	Opinion in favor of reimbursement in newly diagnosed systemic AL amyloidosis. Actual benefit (SMR): Substantial. The actual benefit of DARZALEX (daratumumab) is substantial in the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis, in combination

	with bortezomib + cyclophosphamide + dexamethasone. Improvement in actual benefit (ASMR): IV (minor); DCyBorD, provides a minor improvement in actual benefit (ASMR IV) compared to CyBorD, in the treatment of adult patients with systemic amyloidosis at newly diagnosed light chains (AL).
If a Conditional Recommendation, specify the condition	N/A
Disease subject to evaluation	Adult patients with newly diagnosed systemic AL amyloidosis
Usage	The recommended dose is 1800 mg of DARZALEX solution for injection by the subcutaneous route, administered over approximately 3 to 5 minutes, according to the following administration schedule: • Weeks 1 to 8: weekly doses (8 doses total). • Weeks 9 to 24: dose every 2 weeks, with the first dose on week 9. • From week 25 until disease progression: dose every 4 weeks, with the first dose on week 25.
Comparative Control	CyBorD
Key Incremental Cost	Not reported

Effectiveness Ratio Values	

Abbreviations: AL = amyloid light-chain; ASMR = amélioration du service médical rendu; CyBorD = cyclophosphamide, bortezomib, dexamethasone; HAS = Haute Autorité de santé; mg = milligram; N/A = not applicable; SMR = service médical rendu.

Table 1.7. Details of evaluation results for IQWiG

Country	Germany
Institution Name	IQWiG
URL of evaluation	https://www.g-ba.de/downloads/39-1464-5236/2022-01-20_AM-RL-XII_Daratumumab_D-715_EN.pdf
Technology to be evaluated	Daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone (DCyBorD).
Evaluation Results	Minor additional benefit for adults with newly diagnosed systematic AL amyloidosis for whom CyBorD is the appropriate therapy.*
If a Conditional Recommendation, specify the condition	Not applicable
Disease subject to evaluation	Adult patients with newly diagnosed systemic AL amyloidosis
Usage	The recommended dose is 1800 mg of DARZALEX solution for injection by the subcutaneous route, administered over approximately 3 to 5 minutes, according to the following administration schedule:

	• Weeks 1 to 8: weekly doses (8 doses total). • Weeks 9 to 24: dose every 2 weeks, with the first dose on week 9. • From week 25 until disease progression: dose every 4 weeks, with the first dose on week 25.
Comparative Control	CyBorD
Key Incremental Cost Effectiveness Ratio Values	Not applicable

Abbreviations: AL = amyloid light-chain; BSA = body surface area; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; IQWiG = Institute for Quality and Efficiency in Health Care; IV = intravenous; PO = oral. * population a1, which is aligned with the evaluation scope in Japan.

Table 1.8. Details of evaluation results for CADTH

Country	Canada
Institution Name	CADTH (39)
URL of evaluation results, etc.	https://www.cadth.ca/sites/default/files/DRR/2022/PC0257%20Darzalex%20-%20CADTH%20Final%20Rec%20Final.pdf
Technology to be evaluated	Daratumumab SC for use in combination with cyclophosphamide, bortezomib and dexamethasone (DCyBorD)
Evaluation	Reimburse with clinical criteria and/or conditions

Results	
If a Conditional Recommendation, specify the condition	1. Treatment with DCyBorD should only be initiated in adult patients (≥18 years) with newly diagnosed AL amyloidosis who meet all of the following criteria: i. Histopathological diagnosis of systemic AL amyloidosis based on detection by IHC and polarizing light microscopy of green bi-refringent in congo red-stained tissue specimens or characteristic electron microscopy appearance ii. Measurable disease by serum M-protein ≥0.5 g/dL or abnormal serum free light chain ratio or a difference between involved and uninvolved free light chains (dFLC) ≥50 mg/L iii. Involvement of at least 1 organ system iv. Adequate hematologic, hepatic and renal function (eGFR greater than or equal to 20 ml/min/1.73m^2) 2. Patients should have good performance status 3. Patients must not have any of the following: i. Prior therapy for AL amyloidosis or multiple myeloma including medications that target CD38 ii. Previous or current diagnosis of multiple myeloma including the presence of lytic bone disease, plasmacytomas, ≥60% plasma cells in the bone marrow, or hypercalcemia iii. Planned ASCT during the first 6 cycles of treatment 4. Treatment with daratumumab should be discontinued upon occurrence of any of the following: i. Evidence of hematologic progression or organ

	decompensation on treatment ii. Unacceptable toxicity iii. Renewal of daratumumab should be based on the absence of hematologic progression or organ function decompensation up to a maximum of 24 months. 5. Monitoring for hematologic response and progression should include the following: M-protein, free light chains (serum and urine), cardiac biomarkers (NT-proBNP/BNP and Troponin T), serum creatine, electrolytes, and alkaline phosphatase performed every month for the first 6 months of treatment, then every 3 months up to month 24. 6. Daratumumab should be given in combination with CyBorD for 6 months followed by daratumumab monotherapy (starting in week 25) until disease progression or a maximum of 2 years. 7. Daratumumab should be prescribed by a hematologist or oncologist with experience managing patients with amyloidosis or multiple myeloma in a cancer centre setting. 8. A reduction in price
Disease subject to evaluation	Newly diagnosed AL amyloidosis
Usage	The recommended dose is 1,800 mg administered subcutaneously, over 3 to 5 minutes, weekly (total of 8 doses) in weeks 1 to 8, every 2 weeks (total of 8 doses) in weeks 9 to 24, and every 4 weeks from week 25 onwards until disease progression or a maximum of 2 years.
Comparati	CyBorD

ve Control	
Key Incremental Cost Effectiveness Ratio Values	The incremental cost effectiveness ratio for DCyBorD was $67,484 per QALY compared with CyBorD.

Abbreviations: AL = amyloid light-chain; ASCT = autologous stem cell transplant; BNP = B-type natriuretic peptide; CADTH = Canadian Agency for Drugs and Technologies in Health; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; dFLC = difference between involved and uninvolved free light chains; eGFR = estimated glomerular filtration rate; IHC = immunohistochemistry; m = meter; mg = milligrams; mL = milliliter; L = liter; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; QALY = quality-adjusted life-year.

Table 1.9. Details of evaluation results for PBAC

Country	Australia
Institution Name	PBAC (40)
URL of evaluation result	https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-11/files/daratumumab-psd-november-2021.pdf
Technology to be evaluated	Daratumumab SC for use in combination with cyclophosphamide, bortezomib and dexamethasone (DCyBorD).
Evaluation Results	The PBAC recognized that there are no treatments on the PBS available specifically for this condition, and it considered that the addition of daratumumab SC plus CyBorD offered high added therapeutic value. However, PBAC considered that there were uncertainties in the cost effectiveness analysis. As a result, it was not recommended. The PBAC nominated

	the Early Resolution re-submission pathway for this submission.
If a Conditional Recommendation, specify the condition	N/A
Disease subject to evaluation	Newly diagnosed AL amyloidosis
Usage (*)	Daratumumab is administered subcutaneously at a dose of 1800 mg over approximately 3-5 minutes. It is administered weekly for the first 2 cycles (each cycle is 4 weeks in duration; a total of 8 doses over weeks 1 to 8), every two weeks from cycles 3 to 6 (a total of 8 doses over week 9 to 24) and then once every 4 weeks from cycle 7 (week 25+) onward until disease progression, the development of treatment-limiting toxicity, or a maximum of 24 cycles (≈2 years) from the first dose of treatment (whichever is first).
Comparative Control	Main comparator: CyBorD Secondary comparator: Melphalan and Dexamethasone
Key Incremental Cost Effectiveness Ratio Values	NR

Abbreviations: AL = amyloid light-chain; N/A = not applicable; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme.

2 Setting of analytical conditions for cost-effectiveness analysis

2.1 Analysis Populations

The analysis population includes newly diagnosed AL Amyloidosis patients based on the analytic framework agreed upon by an expert committee meeting on 24th December, 2021).

The model uses a cohort-based approach to model patients as they transition through health states. The model assumed a hypothetical cohort of 1,000 patients, with baseline characteristics that aligned with newly diagnosed AL amyloidosis adult patient characteristics in Japan.

The starting age and proportion of male subjects were set based on the ANDROMEDA global ITT population which are closely aligned with values for the Japanese population as reported by Shimazaki *et al.,* (2018) (19). For patient body weight and body surface area (BSA), model values were based on the Asian subjects included in the ANDROMEDA study (n=60) to more accurately reflect Japanese patient characteristics. In addition, a subgroup analysis was conducted using efficacy outcome of the Asian subjects from the ANDROMEDA trial (N=60; DCyBorD n=29; CyBorD n=31). Details pertaining to this subgroup analysis can be found in **Section 5.1.2.2.1**.

The ANDROMEDA trial included adult (≥18 years) patients newly diagnosed with AL amyloidosis who had ≥1 organ involved (24). Patients were excluded if they had received prior therapy for AL amyloidosis, if they had a previous or current diagnosis of symptomatic MM, or if they presented with evidence of significant cardiovascular conditions (New York Heart Association [NYHA] stage IIIB and IV). Furthermore, patients were excluded if they were planning to receive ASCT during the first six cycles of treatment (24). Base case patient demographics used in the model are presented in **Table 4.3**.

Comparative Controls

As agreed upon by the expert committee (24th December, 2021), CyBorD was selected as the most appropriate comparator based on the rationale that

CyBorD is widely used for systemic AL amyloidosis in Japan and is recommended by international clinical guidelines (35).

2.2 Analytical Position and Cost Range

The analysis was conducted from the perspective of the Japanese public healthcare system and included direct medical costs.

Cost parameters included in the model were first-line drug therapy costs, first-line drug administration costs, first-line co-medication costs, disease monitoring costs, AE management costs, second-line drug therapy costs, end-stage organ failure management costs, other health state-specific healthcare resource use costs, and end of life costs.

Drug costs were sourced from the Ministry of Health, Labor, and Welfare (MHLW) and were relevant as of May 2022. Medical fees were sourced from the current Japan medical fee points schedule as of May 2022 and were not inflated. Costs sourced from published literature were inflated to 2022 values using the Japanese Consumer Price Index for medical care (42). Where uncertainty existed, both sensitivity and scenario analyses were included to assess the impact of parameter uncertainty and using alternative parameters (see **Section 5.1.2**).

2.3 Effectiveness Indices

Effectiveness outcomes in the analysis are life-years (LYs) and quality-adjusted life years (QALYs).

2.4 Analysis Period

A lifetime horizon was selected for the model analysis period (per C2H guidelines) (43) since AL amyloidosis treatments have an impact on costs and outcomes over a patient's lifetime. Given the mean starting cohort age of ~63 years in the population of interest, the model predicted that >99% of patients in both treatment arms would die and the cohort population would be ~100 years old by 35 years. Thus, a 35-year time horizon would represent a lifetime

analysis and was deemed sufficiently long to capture all important differences in costs and outcomes. Furthermore, a 35-year time horizon is aligned with CADTH evaluation in Canada. A shorter time horizon of 20 years was explored in a scenario analysis (see **Section 5.1.2.2.2**)

2.5 Discount rate

A discount rate of 2.0% was applied for both costs and effects and sensitivity analyses were conducted using discount rates of 0% and 4% (see **Section 5.1.2.1**).

2.6 Summary of Determination of Analytic Framework

The contents of **Sections 2.1** to **2.5** are summarized in **Table 2.1**.

Table 2.1. Summary of determination of analytic framework

Population to be analyzed	Adult (≥18 years) patients newly diagnosed with AL amyloidosis
Comparative Control	CyBorD
Reason for selecting the comparator	CyBorD is generally widely used for systemic AL amyloidosis in Japan and is recommended by international clinical guidelines (35).
Analysis position and cost coverage	Japanese public healthcare system and included direct medical costs.
Effectiveness index	LYs and QALYs
Analysis period	Lifetime horizon (35 years)
Discount rate	2% per year for both costs and effects

Abbreviations: AL = amyloid light-chain; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; ICER = incremental cost-effectiveness ratio; LYs = life-years; MM = multiple myeloma; QALYs = quality-adjusted life-years; RCT = randomized controlled trial.

3 Additional Benefits

3.1 Clinical Questions

A systematic literature review (SLR) of randomized controlled trials (RCTs) to examine the additional benefit of DARZQURO® in combination with cyclophosphamide, bortezomib, and dexamethasone (DCyBorD) compared with cyclophosphamide, bortezomib, and dexamethasone alone (CyBorD) among patients newly diagnosed with systemic amyloid light-chain (AL) amyloidosis based on the decision of the expert committee meeting held on 24th December, 2021.

A search strategy was developed using the designated databases (see **Section 3.2**). The outcomes were efficacy, safety, and health-related quality of life (HRQoL). The time frame of the database literature search (eg, Ovid Medline, Ovid Embase, Cochrane) was from 1st January, 2005 to 19th January, 2022 as presented in **Table 3.1**. The time frame associated with the Ichushi Web database search was from inception to 7th February, 2022. The search of clinicaltrials.gov was not restricted by date. Conference abstract hand-searches were limited to the most recent two years (ie, 1st January, 2020 to 31st December, 2021).

Table 3.1. Research question for systematic review

Item	Description
Population	Newly diagnosed systemic AL amyloidosis
Intervention	DCyBorD
Comparator	CyBorD
Outcome	• Efficacy (hematologic response, MOD-PFS, OS) • Safety • HRQoL
Study design	Randomized controlled trial
Literature search period	Ovid/Embase/Cochrane • 1st January, 2005 to 19th January, 2022 Ichushi Web

	• Inception to 7th February, 2022 Clinicaltrials.gov • Inception to 24th January, 2022 Conference abstract repositories • 1st January, 2020 to 31st December, 2021

Abbreviations: CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; HRQoL = health-related quality of life; MOD-PFS: major organ deterioration progression-free survival; OS = overall survival.

3.2 Systematic Review

3.2.1 Literature Searches

- The following databases and registries were searched:
    - Ovid Medline
    - Ovid Medline Epub ahead of print, in-process, and other non-indexed citations and daily
    - Ovid Embase
    - Ovid EBM Reviews – Cochrane Central Register of Controlled Trials – CENTRAL
    - EBM Reviews – Cochrane Database of Systematic Reviews
    - Ichushi Web
    - clinicaltrials.gov
- Hand-searching of conference abstracts for pre-specified conference proceedings was also performed. Please refer to **Section 3.2.1.4** for a list of conferences for which hand-searching of abstracts was performed.

3.2.1.1 Search Strategy for Ovid and Cochrane Databases

The search strategy for Ovid and Cochrane databases was developed by an experienced information specialist and was peer-reviewed by another information specialist using the PRESS Checklist (44) prior to execution. Using the Ovid platform, databases searched included Embase, Medline (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline® Daily and Ovid Medline®), and Cochrane Controlled Register of Trials (CENTRAL). The search strategies included a combination of controlled vocabulary (eg, "Amyloidosis") and keywords (eg, "light chain, amyloid"). Vocabulary and syntax were adjusted across databases. In the search strategy, language was restricted to English and Japanese. Studies published earlier than 2005 were excluded based on the publication date (August 2005) of the consensus opinion for organ involvement and response by the 10th International Symposium in Amyloid and Amyloidosis, which was when uniform criteria to define organ involvement and response were developed (45). The search strategy for the Ovid and Cochrane searches is presented below in **Table 3.2**.

Table 3.2. Search strategy for Ovid and Cochrane databases

Search strategy for: (1) Ovid Medline and Epub ahead of print, in-process, in-data-review and other non-indexed citations and daily, (2) Ovid Embase, (3) EBM Reviews – Cochrane Central Register of Controlled Trials, (4) EBM Reviews – Cochrane Database of Systematic Reviews.		
Date of search: January 19, 2022		
Resulting number of publications: 117		
#	**Searches**	**Results**
1	exp Amyloidosis/ or Plaque, Amyloid/ or (amyloido$ or beta-amyloido$ or betaamyloido$ or paraamyloido$ or "para-amyloido$" or beta fibrillos$ or betafibrillos$ or (amyloid$ adj3 (AL or light-chain or primary or systemic or senile or abeta or fibril? or tumo?r Or deposit? or plaque?)) or (amyloid$ adj2 (neuropathy or neuropathi$ or	189360

	polyneuropathy or polyneuropathi$ or polyneuritic$ or poly-neuropathy or poly-neuropathi$ or poly-neuritic$)) or cerebral amyloid? angiopath$ or (abeta adj4 amyloido$) or famil$ mediterranean fever? or ((HCHWA or FMF or MWS or UDA) and amyloido$) or ((muckle wells or Wohlwill Andrade) adj2 (syndrome$ or disease?)) or (neuritic plaque? or senile plaque?)).ti,ab,kw,kf. [Amyloidosis Terms]	
2	(daratumumab$ or darzalex$ or dalinvi$ or jnj54767414 or jnj-54767414 or 945721-28-8 or 4Z63YK6E0E or ((CD38 or CD-38) adj2 (monoclonal antibod$ or mab or moab or humax)) or D-VCd).ti,ab,kw,kf,rn. [Daratumumab Terms]	6811
3	1 and 2	539
4	(randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly or trial or groups).ab. or drug therapy.fs. [RCTs – MEDLINE sensitive Filter – Cochrane HSSS, 2019]	14314646
5	exp Randomized Controlled Trials as Topic/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or (equivalence trial or pragmatic clinical trial).pt. or (randomised or randomi#ation? or RCT or placebo$ or ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$ or dumm$)) or ((study or trial or CT) adj3 (phase 2 or phase 2a or phase 2b or phase 2c or phase Ii or phase IIa or phase IIb or phase IIc or phase 3 or phase 3a or phase 3b or phase 3c or phase III or phase IIIa or phase IIIb or phase IIIc or "phase? 2/3" or "phase? II/III")) or open label$).tw,kf. [PHASE 2-3, OPEN LABEL - ADDITIONAL TERMS TO SUPPLEMENT RCTs FILTER]	2280495
6	4 or 5 [RCTs only]	14636281
7	3 and 6	387
8	exp Animals/ not Humans/	17080928
9	7 not 8 [ANIMAL-ONLY REMOVED]	315

10	(address or autobiography or bibliography or biography or comment or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt.	4595454
11	9 not 10 [OPINION PIECES REMOVED]	280
12	exp Child/ not (exp Adult/ and exp Child/)	3403086
13	exp Infant/ not (exp Adult/ and exp Infant/)	1729334
14	11 not (12 or 13) [CHILD AND INFANT - ONLY REMOVED]	280
15	14 use ppez [MEDLINE records]	55
16	exp amyloidosis/ or plaque, amyloid/ or (amyloido$ or beta-amyloido$ or betaamyloido$ or paraamyloido$ or "para-amyloido$" or beta fibrillos$ or betafibrillos$ or (amyloid$ adj3 (AL or light-chain or primary or systemic or senile or abeta or fibril? or tumo?r Or deposit? or plaque?)) or (amyloid$ adj2 (neuropathy or neuropathi$ or polyneuropathy or polyneuropathi$ or polyneuritic$ or poly-neuropathy or poly-neuropathi$ or poly-neuritic$)) or cerebral amyloid? angiopath$ or (abeta adj4 amyloido$) or famil$ mediterranean fever? or ((HCHWA or FMF or MWS or UDA) and amyloido$) or ((muckle wells or Wohlwill Andrade) adj2 (syndrome$ or disease?)) or (neuritic plaque? or senile plaque?)).ti,ab,kw,kf. [Amyloidosis Terms]	189360
17	daratumumab/ or (daratumumab$ or darzalex$ or dalinvi$ or jnj54767414 or jnj-54767414 or 945721-28-8 or 4Z63YK6E0E or ((CD38 or CD-38) adj2 (monoclonal antibod$ or mab or moab or humax)) or D-VCd).ti,ab,kw,rn. [Daratumumab Terms]	6807

18	16 and 17	539
19	Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or (crossover or cross over) or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or (assigned or allocated) or (controlled adj7 (study or design or trial)) or (volunteer or volunteers)).ti,ab.	10645734
20	(Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or ((((case adj control$) and random$) not randomi?ed controlled) or (nonrandom$ not random$) or "Random field$" or (random cluster adj3 sampl$)).ti,ab. or (Systematic review not (trial or study)).ti. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or ("update review" or (databases adj4 searched)).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/))	5432169
21	19 not 20 [RCTs – Embase sensitive Filter – Cochrane HSSS, 2019]	9727876
22	phase 2 clinical trial/ or phase 3 clinical trial/ or (equivalence trial or pragmatic clinical trial).pt. or (randomised or	2058379

	randomi#ation? or RCT or placebo* or ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)) or ((study or trial or CT) adj3 (phase 2 or phase 2a or phase 2b or phase 2c or phase Ii or phase IIa or phase IIb or phase IIc or phase 3 or phase 3a or phase 3b or phase 3c or phase III or phase IIIa or phase IIIb or phase IIIc or "phase? 2/3" or "phase? II/III")) or open label*).tw,kw. [PHASE 2-3, OPEN LABEL - ADDITIONAL TERMS TO SUPPLEMENT RCTs FILTER]	
23	21 or 22	9964913
24	18 and 23	158
25	(exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) [ANIMAL-ONLY REMOVED]	11774963
26	24 not 25 [ANIMAL-ONLY REMOVED]	156
27	(comment or editorial or news or newspaper article or (letter not (letter and randomized controlled trial))).pt. [OPINION PIECES REMOVED]	4159298
28	26 not 27 [OPINION PIECES REMOVED]	156
29	exp adolescent/ not (exp adult/ and exp adolescent/)	1288676
30	exp child/ not (exp adult/ and exp child/)	3403086
31	fetus/ not (fetus/ and exp adult/)	233252
32	28 not (29 or 30 or 31) [UNDER 18 REMOVED]	156
33	conference abstract.pt.	4313905
34	32 not 33 [CONFERENCE ABSTRACTS REMOVED]	69
35	32 and 33	87
36	24 not 25 [ANIMAL-ONLY REMOVED]	156
37	34 or 36 [MOST RECENT 2 YEARS CONF ABSTRACTS	116

	RETAINED]	
38	37 use oemezd [EMBASE RECORDS, MOST RECENT 2 YEARS CONF ABSTRACTS RETAINED]	68
39	exp Amyloidosis/ or Plaque, Amyloid/ or (amyloido$ or beta-amyloido$ or betaamyloido$ or paraamyloido$ or "para-amyloido$" or beta fibrillos$ or betafibrillos$ or (amyloid$ adj3 (AL or light-chain or primary or systemic or senile or abeta or fibril? or tumo?r Or deposit? or plaque?)) or (amyloid$ adj2 (neuropathy or neuropathi$ or polyneuropathy or polyneuropathi$ or polyneuritic$ or poly-neuropathy or poly-neuropathi$ or poly-neuritic$)) or cerebral amyloid? angiopath$ or (abeta adj4 amyloido$) or famil$ mediterranean fever? or ((HCHWA or FMF or MWS or UDA) and amyloido$) or ((muckle wells or Wohlwill Andrade) adj2 (syndrome$ or disease?)) or (neuritic plaque? or senile plaque?)).ti,ab,kw. [Amyloidosis Terms]	188319
40	(daratumumab$ or darzalex$ or dalinvi$ or jnj54767414 or jnj-54767414 or 945721-28-8 or 4Z63YK6E0E or ((CD38 or CD-38) adj2 (monoclonal antibod$ or mab or moab or humax)) or D-VCd).ti,ab,kw. [Daratumumab Terms]	5358
41	39 and 40	401
42	exp Child/ not (exp Adult/ and exp Child/)	3403086
43	exp Infant/ not (exp Adult/ and exp Infant/)	1729334
44	41 not (42 or 43) [CHILD AND INFANT - ONLY REMOVED]	401
45	44 use cctr [CENTRAL records]	35
46	(amyloido$ or beta-amyloido$ or betaamyloido$ or paraamyloido$ or "para-amyloido$" or beta fibrillos$ or betafibrillos$ or (amyloid$ adj3 (AL or light-chain or primary or systemic or senile or abeta or fibril? or tumo?r Or deposit? or plaque?)) or (amyloid$ adj2 (neuropathy or neuropathi$ or polyneuropathy or polyneuropathi$ or	172177

	polyneuritic$ or poly-neuropathy or poly-neuropathi$ or poly-neuritic$)) or cerebral amyloid? angiopath$ or (abeta adj4 amyloido$) or famil$ mediterranean fever? or ((HCHWA or FMF or MWS or UDA) and amyloido$) or ((muckle wells or Wohlwill Andrade) adj2 (syndrome$ or disease?)) or (neuritic plaque? or senile plaque?)).ti,ab,kw. [Amyloidosis Terms]	
47	(daratumumab$ or darzalex$ or dalinvi$ or jnj54767414 or jnj-54767414 or 945721-28-8 or 4Z63YK6E0E or ((CD38 or CD-38) adj2 (monoclonal antibod$ or mab or moab or humax)) or D-VCd).ti,ab,kw. [Daratumumab Terms]	5358
48	46 and 47	390
49	48 use coch	0
50	15 or 38 or 45 or 49	158
51	limit 50 to yr="2005 -Current"	158
52	limit 51 to english language [Limit not valid in CDSR; records were retained]	153
53	limit 51 to japanese [Limit not valid in CDSR; records were retained]	1
54	52 or 53	154
55	remove duplicates from 54	117

3.2.1.2 Search Strategy for Ichushi Web

Five searches were performed using Ichushi Web which combined the terms "daratumumab" (in English) and the English and Japanese translations of "amyloidosis" (ie, "アミロイドーシス"). Ultimately, 402 records (ie, 382 from search 4 and 20 from search 5) from Ichushi Web underwent screening for inclusion. The search strategy and results for the Ichushi Web search are presented below in **Table 3.3**.

Table 3.3. Search strategy for Ichushi Web

Search formula for Ichushi Web		
Date of search: February 7, 2022		
Search 1*	(TH or amyloidosis / AL)	19,064 hits
Search 2*	(Amyloidosis / TH or Amyloidosis / AL)	19,991 hits
Search 3	#1 OR #2	20,521 hits
Search 4	(Daratumumab / TH or Daratumumab / AL)	382 hits
Search 5	#1 AND #4	20 hits
Search 4 + Search 5 total records screened		**402**

*The search included both English and Japanese translations of "amyloidosis".

3.2.1.3 Search Strategy for Clinicaltrials.gov

The search of the clinicaltrials.gov registry was performed by specifying the term "amyloidosis" as the "condition/disease" and entering "daratumumab" in the search bar for "other terms". The search strategy for clinicaltrials.gov is presented below in **Table 3.4**.

Table 3.4. Search strategy for clinicaltrials.gov

Search formula for clinicaltrials.gov
Date of search: January 24, 2022
Used keyword: "amyloidosis" (condition/disease), "daratumumab" (other terms)
Number of records: 13

3.2.1.4 Strategy for Hand-searching Pre-specified Conference Abstracts

The search also included hand-searching of the following conference proceedings from the years 2020 and 2021:

- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)
- European Hematology Association (EHA)
- JSM
  Note: the JSM 2020 45th annual meeting was cancelled due to the COVID-19 pandemic, therefore, only abstracts from JSM 2021 were included in this search
- Japanese Society of Hematology (JSH)

A summary of the search strategy for conference abstract hand-searching is presented below in **Table 3.5.**

Table 3.5. Strategy for hand-searching pre-specified conference abstracts

Search formula for conference abstracts*
Date of search: January 24, 2022 (ASCO, EHA, ASH); February 7, 2022 (JSM, JHA)
Used keyword**: "daratumumab", "amyloidosis"
Number of unique abstracts screened ASCO: 39 EHA: 13 ASH: 60 JSM: 81 JSH: 1,034

*Only conference abstracts from 2020 and 2021 were reviewed.

**For ASCO, ASH, and EHA conference searches, the terms "daratumumab" and

"amyloidosis" were searched in English. For JSM and JSH, the program of abstracts from each conference were screened manually (ie, without the use of keywords or search terms).
Abbreviations: ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; EHA = European Hematology Association; JSH = Japanese Society of Hematology; JSM = Japanese Society of Myeloma.

3.2.2 Study Selection

Study screening was performed by two independent reviewers using the systematic review software DistillerSR (Evidence Partners, Ontario, Canada). After the removal of duplicate citations, titles and abstracts were reviewed for study eligibility according to pre-specified inclusion and exclusion criteria established using the population, intervention, comparators, outcomes, and study design (PICOS) framework (see **Table 3.6** below). Non-English and non-Japanese publications were excluded during title and abstract screening provided that the publication language was known. Studies that met the inclusion criteria and those that could not be excluded due to insufficient information were further reviewed at the full-text screening phase. The study selection criteria excluded conference abstracts or posters older than two years from the dates of the search. It was expected that full-text publications associated with conference abstracts and posters dated prior to 2020 would be published by the time the search was conducted. During both screening phases, any discrepancies between the two reviewers were resolved by consensus or by a third reviewer.

Data extraction was performed for all records that met all inclusion criteria. Information from the full-text articles was extracted by one reviewer and validated by a second reviewer. A third reviewer was consulted to resolve discrepancies, as necessary.

Table 3.6. PICOS framework for study inclusion and exclusion

Item	Inclusion Criteria	Exclusion Criteria
Population	Humans only; women and men ≥18 years of age Newly diagnosed amyloid light-chain (AL) amyloidosis	Non-human <18 years of age Relapsed/refractory or previously treated AL amyloidosis Other forms of amyloidosis (eg, senile, familial/hereditary, and secondary), multiple myelomas, or lymphomas as primary diagnosis
Intervention	DCyBorD	N/A
Comparators	CyBorD	All other therapies
Outcomes*	Efficacy Safety HRQoL	N/A
Study design	RCTs	Pre-clinical or pilot studies Non-randomized, single-arm, or observational studies Case reports, case series, expert opinion articles, editorials, letters Narrative (non-systematic) reviews SLR/MA
Study	English or Japanese	All other languages

Item	Inclusion Criteria	Exclusion Criteria
language		
Date restrictions	Full-text studies published in 2005 or later Conference abstracts and posters from the last two years (January 2020 and later)	Published studies dated earlier than 2005 Conference abstracts and posters prior to 2020

*Outcomes were not specified during the literature search stage. Efficacy, safety, and HRQoL outcomes were used only during full-text article screening to identify articles relevant for inclusion.

Abbreviations: CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; HRQoL = health-related quality of life; MA = meta-analysis; N/A = not applicable; PICOS = population, intervention, comparator, outcome, study design; RCT = randomized controlled trial; SLR = systematic literature review.

3.2.3 Quality Assessment

Per C2H guidelines (43), quality assessment of included records is not required since the only data source identified in the SLR was an RCT.

3.2.4 Search Results

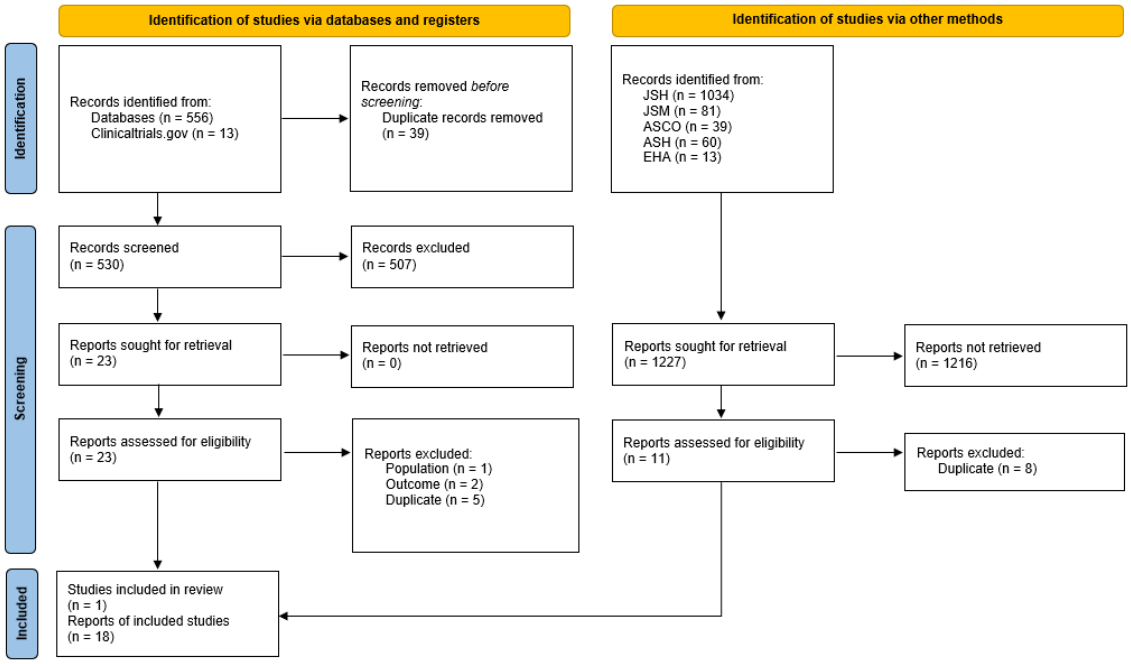
The database searches for RCTs comparing DCyBorD and CyBorD for first-line pharmacologic treatment of AL amyloidosis identified 530 citations that underwent title and abstract screening; this included 115[i] unique records from Ovid/Embase/Cochrane searches, 402 records from Ichushi Web, and 13 records from clinicaltrials.gov. Of these, 507 were excluded during title and abstract screening because they did not meet the pre-specified inclusion criteria (see PICOS in **Section 3.2.2**). Among the 23 remaining citations, 8 were excluded at the full-text screening phase for not meeting the pre-specified inclusion criteria or due to inadequate reporting. After title and abstract and full-text screening of the database searches was completed, 15 records (46-60)

[i] Initial database searches retrieved 117 records; however, 2 duplicate records were removed prior to screening.

were identified for inclusion in the SLR, all of which pertained to the ANDROMEDA trial.

Three additional relevant records were identified by performing hand-searching of EHA, ASCO, ASH, JSM, and JSH conference websites (61-63). Notably, all relevant records identified in the conference hand-searches pertained to the ANDROMEDA trial. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (64, 65) flow diagram for the selection of these studies is presented in **Figure 3.1**.

Figure 3.1. PRISMA flow diagram



Abbreviations: ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; EHA = European Hematology Association; JSH = Japanese Society of Hematology; JSM = Japanese Society of Myeloma; n = number; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3.2.5 Clinical studies identified in the systematic literature review

The only clinical study identified in the SLR was the ANDROMEDA trial. A summary of this phase 3 RCT is presented in **Table 3.7**.

Table 3.7. Summary of the ANDROMEDA randomized controlled trial

Clinical study	Intervention	Comparator	Sample size	Statistics	Primary analysis publication
ANDROMEDA	DCyBorD	CyBorD	DCyBorD: n=195 CyBorD: n=193	The Kaplan-Meier method was used to evaluate time-to-event variables. Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards regression model. Between group differences with respect to CR were tested with the use of a stratified Cochran–Mantel–Haenszel test, and corresponding relative risk and odds ratios, 95% CIs, and P values were reported.	Kastritis *et al.*, (2021) (50)

Abbreviations: CI = confidence interval; CR = hematologic complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone.

3.2.6 Summary of Additional Benefit

3.2.6.1 ANDOMEDA clinical trial

The SLR search strategy and screening process were robust and aimed to identify RCTs reporting efficacy, safety, and HRQoL when comparing DCyBorD and CyBorD in patients newly diagnosed with AL amyloidosis. All relevant articles identified in this SLR (resulting from both database and grey literature searches) pertained to the ANDROMEDA trial. Database searches identified 2 relevant full-text articles (50, 57), 12 relevant conference abstracts (46-49, 51-56, 58, 59), and one record retrieved via a search of clinicaltrials.gov (60). Targeted searching of key conference websites (see **Section 3.2.1.4**) identified three additional records (61-63) related to the ANDROMEDA study. All relevant records identified are summarized in **Table 3.8**.

Table 3.8. List of identified studies pertaining to ANDROMEDA

Author (Year)	Title	Record Type	Source
Kastritis *et al.*, (2021) (50)	Daratumumab-based treatment for immunoglobulin light-chain amyloidosis.	Publication	Database search
Palladini *et al.*, (2020) (57)	Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA.	Publication	Database search
Comenzo *et al.*, (2021) (47)	Subcutaneous Daratumumab with Bortezomib, Cyclophosphamide, and Dexamethasone in Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: 18-Month Analysis of the Phase 3 ANDROMEDA Study	Conference abstract (ASH)	Database search
Grogan *et al.*, (2021) (48)	Effect of daratumumab, bortezomib, cyclophosphamide, and dexamethasone on cardiac function and health-related quality of life in patients with newly-diagnosed AL amyloidosis with cardiac involvement: Results from the phase 3 ANDROMEDA study.	Conference abstract (ACC)	Database search
Havasi *et al.*, (2021) (56)	Effect of daratumumab/ bortezomib/ cyclophosphamide/ dexamethasone on renal function and HRQoL in patients with newly diagnosed AL amyloidosis with renal involvement: results from the phase 3 ANDROMEDA study.	Conference abstract (Kidney International Reports)	Database search

Author (Year)	Title	Record Type	Source
Havasi *et al.*, (2021) (59)	Effect of daratumumab (DARA) + Bortezomib, Cyclophosphamide, Dexamethasone (VCd) on Renal Organ Response and Health-Related Quality of Life (HRQoL) in patients with Systemic Light Chain (AL) Amyloidosis: ANDROMEDA Japanese Subgroup	Conference abstract (Japanese Society of Nephrology)	Database search
Kastritis *et al.*, (2021) (49)	Subcutaneous daratumumab ± bortezomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed light chain amyloidosis: Updated results from the phase 3 Andromeda study.	Conference abstract (ASCO)	Database search
Kastritis *et al.*, (2021) (58)	Updated results from phase 3 ANDROMEDA study of patients with newly diagnosed light chain amyloidosis treated with bortezomib, cyclophosphamide, and dexamethasone plus subcutaneous daratumumab.	Conference abstract (EHA); abstract #S189	Database search
Kumar *et al.*, (2021) (51)	Evaluating the impact of cytogenetic abnormalities on treatment outcomes in patients with AL amyloidosis: sub-analyses from the ANDROMEDA study	Conference abstract	Database search
Comenzo *et al.*, (2020) (46)	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	Conference abstract (ASH); oral presentation #552	Database search

Author (Year)	Title	Record Type	Source
	Survival in Patients With Newly Diagnosed AL Amyloidosis Receiving Bortezomib, Cyclophosphamide, and Dexamethasone With or Without Daratumumab: Results From ANDROMEDA.		
Minnema *et al.*, (2020) (52)	Outcomes by Cardiac Stage in Newly Diagnosed AL Amyloidosis: Results From ANDROMEDA.	Conference abstract (ASH); poster #1392	Database search
Sanchorawala *et al.*, (2020) (53)	Health-Related Quality of Life in Patients With AL Amyloidosis Treated With Daratumumab, Bortezomib, Cyclophosphamide, and Dexamethasone: Results From the Phase 3 ANDROMEDA Study.	Conference abstract (ASH); poster #1640	Database search
Suzuki *et al.*, (2020) (54)	Subcutaneous Daratumumab (DARA SC) + Bortezomib, Cyclophosphamide, and Dexamethasone (CyBorD) in Asian Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: Subgroup Analysis from the Phase 3 Andromeda Study.	Conference abstract (ASH); poster #653	Database search
Wechalekar *et al.*, (2020) (55)	Rapid and Deep Hematologic Responses Are Associated With Improved Major Organ Deterioration Progression-Free Survival in Newly Diagnosed AL Amyloidosis: Results From ANDROMEDA.	Conference abstract (ASH); poster #2305	Database search
Clinicaltrials.gov	A Study to Evaluate the Efficacy and Safety of Daratumumab in	NCT Record;	Registry search

Author (Year)	Title	Record Type	Source
(2022) (60)	Combination With Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared to CyBorD Alone in Newly Diagnosed Systemic Amyloid Light-chain (AL) Amyloidosis.	NCT03201965	
Comenzo *et al.*, (2021) (61)	Daratumumab/bortezomib/cyclophosphamide/dexamethasone (D-VCd) for pts with AL amyloidosis: ANDROMEDA	Conference abstract (JSH)	JSH conference repository
Suzuki *et al.*, (2021) (63)	Subcutaneous daratumumab + bortezomib/ cyclophosphamide/ dexamethasone (D-VCD) in newly diagnosed al amyloidosis: Asian subgroup analysis from ANDROMEDA	Conference abstract (JSM)	JSM conference repository
Kastritis *et al.*, (2020) (62)	Subcutaneous Daratumumab + Cyclophosphamide, Bortezomib, and Dexamethasone (CyBorD) in Patients With Newly Diagnosed Light Chain (AL) Amyloidosis: Primary Results From the Phase 3 ANDROMEDA Study.	Conference abstract (EHA); abstract #LB2604	EHA conference repository

Abbreviations: ACC = American College of Cardiology; AL = amyloid light chain; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DARA = daratumumab; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; D-VCD = daratumumab, VELCADE® (bortezomib), cyclophosphamide, dexamethasone; EHA = European Hematology Association; JSH = Japan Society of Hematology; JSM = Japan Society of Myeloma; SC = subcutaneous.

The following outcome measures were used to evaluate the additional benefit of DCyBorD compared to CyBorD:

- Primary outcomes: Overall complete hematologic response rate
- Secondary outcomes: major organ deterioration progression free survival (MOD-PFS), overall survival (OS), hematologic response, and organ response.
- Patient-reported outcomes (PROs) and adverse events (AEs)

3.2.7 ANDROMEDA Study Details

A summary of data from the only clinical trial (ANDROMEDA) relevant to the research question is provided in **Table 3.9**.

Table 3.9. Summary of relevant literature related to the ANDROMEDA study

Study name	ANDROMEDA
Bibliographic information for ANDROMEDA primary publication	Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC, Sanchorawala V, Gibbs S, Mollee P, Venner CP, Lu J. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. New England Journal of Medicine. 2021 Jul 1;385(1):46-58.
Clinicaltrials.gov registry information (60)	NCT03201965
Study sites (50)	Multicenter (109 sites in 22 countries)
Study enrollment period (50)	May 3, 2018 – August 15, 2019
Target population (50)	Recruited patients with newly diagnosed systemic AL amyloidosis.
Eligibility criteria (50)	• Eligible patients were aged ≥18 years. • Histopathologic diagnosis of systemic AL amyloidosis (affecting one or more organs). • Measurable hematologic disease.

Key exclusion criteria (50)	• Previous therapy for AL amyloidosis. • Symptomatic multiple myeloma according to International Myeloma Working Group criteria. • Eastern Cooperative Oncology Group performance-status score of more than 2 (on a 5-point scale in which higher numbers indicate greater disability). • Estimated glomerular filtration rate of less than 20 ml per minute per 1.73 m^2 of body surface area. • Evidence of a severe cardiovascular condition including an N-terminal pro– B-type natriuretic peptide level of more than 8500 ng per liter, a systolic blood pressure of less than 90 mm Hg, or a New York Heart Association classification of stage IIIB or IV at screening.

Details of interventional method (50)	• <u>DCyBorD group (n=195)</u>
	• Daratumumab component
	  ○ Dosing: 1800 mg of daratumumab co-formulated with rHuPH20 2000 U/mL.
	  ○ Patients received daratumumab via SC injection once weekly (cycles 1 and 2), every 2 weeks (cycles 3–6), and then every 4 weeks until disease progression, the start of subsequent therapy, or for a maximum of 24 cycles from the start of the trial, whichever occurred first.
	  ▪ Each cycle consisted of 28 days.
	• Cyclophosphamide component
	  ○ Dosing: 300 mg/m^2 of

	cyclophosphamide. ○ Patients received cyclophosphamide as an oral or IV weekly dose for a maximum of 6 cycles. • Bortezomib component ○ Dosing: 1.3 mg/m^2 of bortezomib. ○ Patients received bortezomib via SC injection weekly for a maximum of 6 cycles. • Dexamethasone component* ○ Dosing: 40 mg of dexamethasone weekly. ○ Patients received dexamethasone as an oral or IV weekly dose for a maximum of 6 cycles.
Details of comparator method (50)	<u>CyBorD group (n=193)</u> • Cyclophosphamide component ○ Dosing: 300 mg/m^2 of cyclophosphamide. ○ Patients received cyclophosphamide as an oral or IV weekly dose for a maximum of 6 cycles. • Bortezomib component ○ Dosing: 1.3 mg/m^2 of bortezomib. ○ Patients received bortezomib via SC injection weekly for a maximum of 6 cycles. • Dexamethasone component* ○ Dosing: 40 mg of dexamethasone weekly. ○ Patients received dexamethasone as an oral or IV weekly dose for a maximum of 6 cycles.
Study design (50)	Phase 3 randomized controlled trial.

	Randomization was stratified according to cardiac stage (I, II, or IIIA on the basis of the European modification of the Mayo Clinic Cardiac Staging System (33)), availability of transplantation in the local country, and renal function.
Blinding method (50)	Open label
Primary endpoint (50)	• Hematologic CR rate (or Complete Hematologic Response, CHR)
Key secondary endpoints (50)	• MOD-PFS • Organ response • OS • Hematologic complete response at 6-months • Hematologic VGPR or better • Time to/duration of hematologic complete response • Time to next treatment • Reduction in fatigue
Statistical methods (50)	• The Kaplan-Meier method was used to estimate time-to-event distributions. • Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards regression model. • The infusion-related reaction rate and rates of very good partial response or better were compared between groups using a stratified Cochran-Mantel-Hansel test.
Sample size (50)	• DCyBorD group: n=195 • CyBorD group: n=193
Follow-up period	• Primary analysis: Median 11.4 months (range 0.03 to 21.3 months) (50) • Interim analysis: Median 15.7 months (range 0.0 to 24.1 months) (61) • 12-month landmark analysis: NR (49, 58)

	• 18-month landmark analysis: Median 25.8 months (47)

Patient demographics (50)	DCyBorD group vs CyBorD group: the demographic and clinical characteristics of the patients at baseline were balanced between the groups.
	• Male, n (%):108 (55.4) vs 117 (60.6)
	• Median age (range), years: 62 (34-87) vs 64 (35-86)
	• Median time since initial diagnosis (range), days: 48 (8-1,611) vs 43 (5-1,102)
	• Median dFLC (range), mg/liter: 200 (2-4,749) vs 186 (1-9,983)
	• Median number of involved organs (range): 2 (1-5) vs 2 (1-6)
	• Median NT-proBNP level (range), ng/liter: 1388.6 (51-10182) vs 1746.0 (51-12950)
	• Median eGFR (range), ml/min/1.73 m^2: 77.8 (21-126) vs 76.2 (20-121)
	• Cardiac (Mayo) stage
	  ○ Stage I, n (%): 47 (24.1) vs 43 (22.3)
	  ○ Stage II, n (%): 76 (39.0) vs 80 (41.5)
	  ○ Stage IIIA, n (%): 70 (35.9) vs 64 (33.2)
	  ○ Sage IIIB, n (%): 2 (1.0) vs 6 (3.1)
	• Renal stage
	  ○ Stage I, n/total n (%): 107/193 (55.4) vs 101/193 (52.3)
	  ○ Stage II, n/total n (%): 67/193 (34.7) vs 74/193 (38.3)
	  ○ Stage III, n/total n (%): 19/193 (9.8) vs 18/193 (9.3)

Efficacy results (47, 49, 50, 57, 58, 60-62)	**Safety Run-in Results in 28 patients (DCyBorD arm only; July 2019; median follow-up 17.6 months) (57)** • Overall hematologic response rate was 96%, with a complete hematologic response in 15 (54%) patients. • 23 (82%) patients achieved VGPR or better. • PR or better was achieved by 20 (71%) patients at 1 month, 22 (79%) patients at 3 months, and 17 (61%) patients at 6 months. • Renal response occurred in 6 of 16 (38%), 7 of 15 (47%), and 10 of 15 (67%) patients. • Cardiac response occurred in 6 of 16 (38%), 6 of 13 (46%), and 8 of 13 (62%) patients at 3, 6, and 12 months, respectively • Hepatic response occurred in 2 of 3 (67%) patients at 12 months. • 5 patients died. **Primary Analysis (February 2020; median follow-up 11.4 months) (50, 60)** • CR was achieved in 104 patients (53.3%) in the DCyBorD group and 35 patients (18.1%) in the CyBorD group (RR ratio: 2.9 (95% CI: 2.1 to 4.1), p<0.001; OR: 5.1 (95% CI: 3.2 to 8.2), p<0.001). o At 6-months, 49.7% of DCyBorD subjects and 14.0% of CyBorD subjects achieved CR (RR ratio: 3.5 [95% CI 2.4 to 5.2]; OR 6.1 [95% CI 3.7 to 10.0]; p<0.001 for both comparisons). o At 6-months, VGPR or better was achieved by 78.5% of DCyBorD

	subjects and 49.2% of CyBorD subjects (RR ratio 1.6 [95% CI 1.4 to 1.9]; OR 3.8 [95% CI 2.4 to 5.9]). ○ Median time to CR was 60 days for DCyBorD subjects and 85 days for CyBorD subjects. • MOD-PFS was significantly longer in the DCyBorD group than the CyBorD group (HR 0.58, 95% CI 0.36 to 0.93, p=0.02; see **Figure 3.2**). • Among subjects who were evaluable for cardiac response (ie, 118 in DCyBorD and 117 in CyBorD groups), 41.5% of DCyBorD (95% CI 32.5 to 51.0) and 22.2% of CyBorD (95% CI 15.1 to 30.8) subjects had a cardiac response at 6-months. • Among subjects who were evaluable for renal response (ie, 117 in DCyBorD and 113 in CyBorD groups), 53.0% (95% CI 43.5 to 62.3) of DCyBorD and 23.9% (95% CI 16.4 to 32.8) of CyBorD subjects had a renal response at 6-months. • Overall survival data were immature at the time of the primary analysis and did not differ substantially between the two groups. **Updated/Interim Results (Median follow-up 15.7 months) (61)** • The overall CR rate continued to be higher with DCyBorD than CyBorD (56.9% vs 18.7%; OR 5.68; 95% CI 3.58-9.00; p<0.0001).

	12-month Landmark Analysis (November 2020; median follow-up not reported) (49, 58)
	• The overall CR rate continued to be higher with DCyBorD than CyBorD (59% vs 19%; OR 5.9; 95% CI 3.7–9.4; p<0.0001).
	  ○ More patients achieved a VGPR or better (≥VGPR) with DCyBorD than CyBorD (79% vs 50%; OR 3.7; 95% CI 2.4–5.9; p<0.0001).
	  ○ Among responders, median time from randomization to ≥VGPR was shorter for DCyBorD than CyBorD (0.56 vs 0.82 months).
	• Cardiac response rates were higher with DCyBorD than CyBorD at 6 months (42% vs 22%) and at 12 months (57% vs 28%)
	• Renal response rates for DCyBorD vs CyBorD were 54% vs 27% at 6 months and 57% vs 27% at 12 months.
	• A total of 71 deaths** occurred (DCyBorD, n = 31; CyBorD, n = 40).
	
	18-month Landmark Analysis (May 2021; median follow-up 25.8 months) (47)
	• The rate of hematologic CR was significantly higher in the DCyBorD arm vs the CyBorD arm (59.5% vs 19.2%; OR [95% CI], 6.03 [3.80–9.58]; p<0.0001).
	  ○ More patients achieved a VGPR or better (≥VGPR) (DCyBorD vs CyBorD, 79.0% vs 50.3%; OR [95% CI], 3.74 [2.39–5.86]; p<0.0001)
	  ○ Among patients who responded, the median time from randomization to

	≥VGPR was shorter in the DCyBorD arm (0.56 months) vs the CyBorD arm (0.82 months). • Comparable to the cardiac response analysis at 6 months (DCyBorD vs CyBorD, 42% vs 22%), greater cardiac response rates were achieved with DCyBorD compared with CyBorD at 18 months (53% vs 24%). • Renal response rates remained superior with DCyBorD vs CyBorD alone at 18 months (58% vs 26% compared with 6 months [54% vs 27%]). • A total of 79 deaths** occurred (DCyBorD, N=34; CyBorD, N=45). OS will be analyzed and major organ deterioration PFS will be updated after approximately 200 events have occurred.
Safety results (47, 49, 50, 57, 58)	**Safety Run-in Results (July 2019; median follow-up 17.6 months; pertains to DCyBorD arm only) (57, 60)** • 26 (93%) patients experienced TEAEs considered related to study treatment; TEAEs in 21 (75%) patients were considered related to daratumumab. • Serious TEAEs occurred in 12 (43%) patients and included fall and acute kidney injury (11% each) and pneumonia and cellulitis (7% each; cellulitis not related to injection site). • An IRR occurred in 1 (4%) patient, comprising chest discomfort, cough, hypotension, oropharyngeal pain, and sneezing, all of which were grade 1. • A total of 6 injection-site reactions occurred

	in 3 (11%) patients. ○ All injection-site reactions were grade 1 and included erythema, bruising, and skin discoloration; none led to changes in treatment. • No new safety concerns were identified with DCyBorD compared with daratumumab monotherapy (IV or SC) or CyBorD alone. • Daratumumab SC is associated with low rates of IRRs, few injection-site reactions, and reduced administration times compared with Daratumumab IV. **Primary Analysis (February 2020; median follow-up 11.4 months) (50, 60)** • The most common AEs of grades 3 or 4 were lymphopenia (13.0% in the daratumumab group and 10.1% in the control group), pneumonia (7.8% and 4.3%, respectively), cardiac failure (6.2% and 4.8%), diarrhea (5.7% and 3.7%), syncope (5.2% and 6.4%), neutropenia (5.2% and 2.7%), peripheral edema (3.1% and 5.9%), and hypokalemia (1.6% and 5.3%). • The incidence of grade 3 or 4 infections was 16.6% in the daratumumab group and 10.1% in the control group. • SAEs occurred in 43.0% of patients in the DCyBorD arm and 36.2% of patients in the CyBorD arm. • The most common SAE reported was pneumonia, which occurred in 7.3% and 4.8% of subjects in the DCyBorD and CyBorD arms, respectively.

	• The percentage of patients who had AEs that led to discontinuation of trial treatment was 4.1% in the DCyBorD group and 4.3% in the CyBorD group. • Local injection-site reactions to any agent occurred in 54 patients (28.0%) in the DCyBorD group and 45 patients (23.9%) in the CyBorD group. • A total of 21 patients (10.9%) in the DCyBorD group had local injection-site reactions related to daratumumab, all of which were grade 1 or 2. **12-month Landmark Analysis (November 2020; median follow-up not reported) (49, 58)** • From cycle 7 onward in the DCyBorD group, no grade 3/4 TEAE occurred in ≥5% of pts. • There were no systemic administration-related reactions with DCyBorD after cycle 6. **18-month Landmark Analysis (May 2021; median follow-up 25.8 months) (47)** • In the DCyBorD arm, only 1 additional grade 3/4 TEAE occurred over 18 months compared with 12 months (119 [61.7%] vs 118 [61.1%] patients) and no additional IRRs were reported.
Patient-reported outcomes (53)	• Median time to improvement was shorter and median time to worsening was longer in the DCyBorD group than in the CyBorD group for EORTC QLQ-C30 GHS and fatigue scales and EQ-5D-5L VAS. • Least squares mean scores for EORTC QLQ-C30 GHS and fatigue, EQ-5D-5L VAS, and

	SF-36 MCS remained stable in the DCyBorD group but worsened compared with baseline in the CyBorD group. • The greatest between-group differences in PRO score changes from baseline were observed at Week 16 (Cycle 4). • After Cycle 6, patients in the DCyBorD group reported improvements in mean GHS and fatigue scores that continued while on treatment.
Efficacy results – impact of cytogenic abnormalities on treatment outcomes (51)	• Among ANDROMEDA subjects, 321 were tested for cytogenic abnormalities. • In the DCyBorD and CyBorD arms, respectively, 42.9% vs 40.0% had t(11;14), 25.4% vs 20.3% had amp1q21, 16.2% vs 22.0% had del13q14, and 6.7% vs 6.1% had del17p13. • At a median follow-up of 20.3 months, the hematologic CR rate was higher with DCyBorD vs CyBorD across all four cytogenic subgroups, ranging from 56-72% vs 0-14% ($p<0.05$). • Organ response rates were numerically higher with DCyBorD in all subgroups except for cardiac response rate in the del17p13 subgroup. • Rates of deep hematologic response were not impacted by t(11;14) and amp1q21 in patients treated with DCyBorD but were generally lower in CyBorD-treated patients with t(11;14) and amp1q21.
Efficacy results – reduction in absolute involved free light	• Rates of deep hematological responses by all criteria strongly favored the DCyBorD treatment arm.

chain and difference between involved and uninvolved free light chains (46)	○ Overall hematologic CR rate for DCyBorD vs CyBorD was 53% vs 18%, respectively. ○ Hematologic response rate for subjects with iFLC≤20 mg/L (regardless of FLCr) receiving DCyBorD vs CyBorD was 71% and 20%, respectively. ○ Hematologic response rate for subjects with dFLC<10 mg/L (regardless of FLCr) receiving DCyBorD vs CyBorD was 64% and 31%, respectively. • MOD-PFS was longer in patients achieving deep hematological responses regardless of which criteria for deep hematologic response was utilized.
Efficacy results – rapid and deep hematologic responses and MOD-PFS (55)	• MOD-PFS was longer in patients with CR/VGPR at 1- and 3-months compared to patients with lower levels of response. • CR/VGPR at 1 and 3 months was associated with reduced risk of death or major organ deterioration in a multivariate analysis adjusting for baseline difference between involved and uninvolved free light chains and cardiac stage, (HR: 0.399, p=0.0006 and HR: 0.262, p=0.0003, respectively). • At 1 and 3 months, cardiac and renal response rates were higher in those who achieved early and deep hematologic responses (CR and VGPR).
Efficacy and safety results – Asian	• Overall CR rate was 59% for DCyBorD and 10% for CyBorD (OR 13.2; 95% CI 3.3-53.7; p<0.0001).

subgroup analysis (54, 63)	○ DCyBorD vs CyBorD achieved higher rates of VGPR or better (≥VGPR; 93% vs 61%). • MOD-PFS favored DCyBorD-treated patients (HR 0.21; 95% CI, 0.06-0.75, P=0.0079). • A total of 12 deaths occurred (DCyBorD, n=3; CyBorD, n=9). • The most common (≥10%) grade 3/4 TEAEs were lymphopenia (DCyBorD 35%/CyBorD 32%), neutropenia (10%/3%), diarrhea (10%/7%), pneumonia (7%/10%), cardiac failure (7%/10%), hypokalemia (7%/10%), anemia (3%/10%), thrombocytopenia (3%/10%), hypoalbuminemia (3%/10%), and syncope (3%/10%). • TEAEs leading to treatment discontinuation occurred in 1 patient in each treatment arm. • Please refer to **Appendix A** for a more detailed description of the ANDROMEDA Asian subgroup analysis.
Efficacy and safety results – outcomes by cardiac stage (52)	• Hematologic CR rates were higher in the DCyBorD group than in the CyBorD group in patients with cardiac stages I, II, and III at baseline. • HRs for MOD-PFS were 0.33, 0.55 and 0.66 for cardiac stages I, II and III, respectively, favoring DCyBorD. • Cardiac and renal response rates at 6 months were also higher in the DCyBorD group regardless of cardiac stage at baseline. • Rates of any grade AEs were similar in patients with and without cardiac involvement at baseline.

	• Across both treatment arms, rates of serious TEAEs were higher in patients with cardiac involvement at baseline than in those without.
Efficacy and HRQoL results – outcomes for patients with cardiac involvement (48)	• 140 and 137 patients in the DCyBorD and CyBorD groups had cardiac involvement, respectively. • At 6-months, 41.5% of DCyBorD and 22.2% of CyBorD patients with cardiac involvement had a cardiac response (p=0.0029). • GHS and fatigue scores remained stable with DCyBorD but worsened with CyBorD. • The greatest between-group differences were at cycles 4 and 5 (GHS LS mean difference: 6.2 [95% CI 1.1 to 11.3, p=0.0174]; fatigue LS mean difference: -11.4 [95% CI -17.6 to -5.3, p=0.0003]). • Over six cycles, higher percentages of DCyBorD vs CyBorD subjects had meaningful improvements (≥1 point) in shortness of breath (33.3% vs 26.6%) and feeling weak (31.1% vs 12.5%) and tired (24.4% vs 10.9%). • Overall, DCyBorD resulted in higher rates of cardiac response with the PRO results suggesting improvement in fatigue-related parameters in AL amyloidosis patients with cardiac involvement.
Efficacy and HRQoL results – outcomes for patients with renal involvement (56, 59)	• 115 and 114 patients in the DCyBorD and CyBorD groups had renal involvement, respectively. • At 6-months, 53.8% of DCyBorD and 27.4% of CyBorD patients had a renal response (p<0.0001).

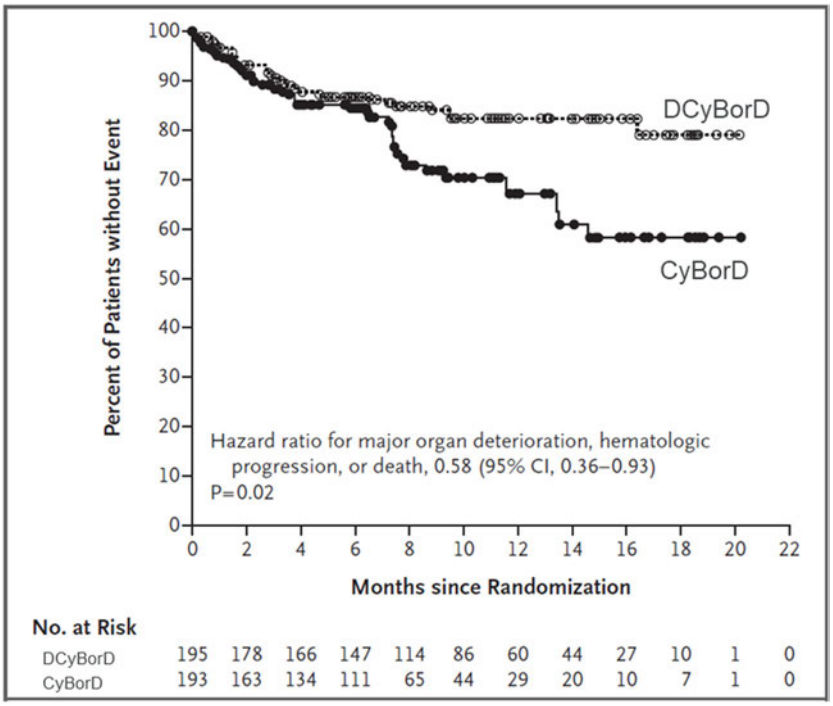
	• GHS and fatigue scores remained stable with DCyBorD but worsened with CyBorD by cycle 3 with the greatest between-group differences were observed at cycle 5. • More DCyBorD than CyBorD patients experienced ≥1-point improvement in shortness of breath or feeling weak/tired by 'a little or more'. • Overall, DCyBorD increased renal response with indications of improvement in fatigue-related HRQoL parameters.
Limitations	• Open label design. Patients and physicians were not blinded to treatment.

* For patients who were older than 70 years of age, were underweight (body-mass index [the weight in kilograms divided by the square of the height in meters], <18.5), or had hypervolemia, poorly controlled diabetes mellitus, or previous unacceptable side effects associated with glucocorticoid therapy, dexamethasone could be administered at a dose of 20 mg weekly at the discretion of their physician.

**OS will be analyzed and MOD-PFS will be updated after approximately 200 events have occurred.

Abbreviations: AE = adverse event; AL = amyloid light-chain; CI = confidence interval; dFLC = difference in free light chains; CR = hematologic complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; eGFR = estimated glomerular filtration rate; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; EQ-5D-5L = EuroQol 5-dimensional descriptive system; GHS = global health status; Hg = mercury; IRR = infusion-related reaction; ITT = intent-to-treat; IV = intravenous; HR = hazard ratio; HRQoL = health-related quality of life; MCS = mental component summary; mg = milligrams; min = minute; mL = milliliters; MOD-PFS = major organ deterioration progression-free survival; ng = nanograms; NT-proBNP = N-terminal pro-hormone B-type natriuretic peptide; OR = odds ratio; OS = overall survival; PR = partial response; rHuPH20 = recombinant human hyaluronidase PH20 enzyme; PRO = patient-reported outcome; RR = relative risk; SAE = serious adverse event; SC = subcutaneous; SF-36 = Short Form-36; TEAE = treatment-emergent adverse event; VAS = visual analog scale; VGPR = very good partial response.

Figure 3.2. Kaplan-Meier estimates of MOD-PFS from ANDROMEDA



Abbreviations: CI = confidence interval; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone.

Source: Adapted from Kastritis *et al*., 2021 (50).

3.3 Clinical Questions (Different controlled or single-arm studies)

Not applicable.

3.4 Systematic Review (Different controlled or single-arm studies)

Not applicable.

3.5 Reanalysis of Existing Data

A summary of published re-analyses of Asian subgroup data and Japanese subjects from the ANDROMEDA study is presented below in **Table 3.10**.

Table 3.10. Summary of ANDROMEDA post-hoc analyses

Author and Year	Title	Sample Size	Results
Suzuki *et al*., (2020) (54), Suzuki *et al*., (2021) (63)	Subcutaneous Daratumumab (DARA SC) + Bortezomib, Cyclophosphamide, and Dexamethasone (CyBorD) in Asian Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: Subgroup Analysis	60 (DCyBorD: 29; CyBorD: 31)	Among 388 patients in the ANDROMEDA RCT, 60 were Asian. Since this abstract reports the results of a post-hoc analysis from the ANDROMEDA trial, the statistical analysis methods and number of institutions are as outlined in **Table 3.9**. In the Asian sub-population, the baseline characteristics were well balanced between arms and consistent with the global ITT population. Same statistical analysis methods were performed in the Asian sub-population. 63.3% were male, mean (median) age is 64 (65.5). The overall hematologic CR rate was 59% for DCyBorD and 10% for CyBorD (OR 13.2; 95% CI 3.3, 53.7; p<0.0001). DCyBorD vs CyBorD achieved higher rates of ≥VGPR (93% vs 61%, respectively).

Author and Year	Title	Sample Size	Results
	from the Phase 3 Andromeda Study.		MOD-PFS favored DCyBorD-treated patients (HR 0.21; 95% CI 0.06, 0.75, p=0.0079). A total of 12 deaths occurred (DCyBorD, n=3; CyBorD, n=9). The most common (≥10%) grade 3/4 TEAEs were lymphopenia (DCyBorD 35%/CyBorD 32%), neutropenia (10%/3%), diarrhea (10%/7%), pneumonia (7%/10%), cardiac failure (7%/10%), hypokalemia (7%/10%), anemia (3%/10%), thrombocytopenia (3%/10%), hypoalbuminemia (3%/10%), and syncope (3%/10%). TEAEs leading to treatment discontinuation occurred in 1 patient in each treatment arm. The safety profile is consistent with the overall study population. Results observed in the Asian patient cohort were generally consistent with those observed in the overall analysis population.
Havasi *et al*., (2021) (59)	Effect of daratumumab (DARA) + Bortezomib, Cyclophosphamide,	17 (DCyBorD: 8; CyBorD: 9)	Among 388 patients in the ANDROMEDA RCT, 17 were Japanese. Since this abstract reports the results of a post-hoc analysis from the ANDROMEDA trial, the statistical analysis methods and number of institutions are as outlined in **Table 3.9**. The baseline characteristics of patients in the two treatment arms were

Author and Year	Title	Sample Size	Results
	Dexamethasone (VCd) on Renal Organ Response and Health-Related Quality of Life (HRQoL) in patients with Systemic Light Chain (AL) Amyloidosis: ANDROMEDA Japanese Subgroup		not comparable due to the small number of Japanese patients. At 6 months, 63% DCyBorD versus 50% CyBorD renal-response evaluable patients had a renal response. Over 6 cycles, more DCyBorD patients experienced ≥1—point improvement in "shortness of breath", "feeling weak" and "felt tired". GHS and fatigue scores remained relatively stable at most cycles; the greatest between-group differences were observed at cycle 5. Result observed in the Japanese patient cohort were generally consistent with those observed in the overall analysis population.

Abbreviations: AL = amyloid light chain; CI = confidence interval; CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DARA = daratumumab; DARA SC = subcutaneous daratumumab; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; GHS = global health status; HR = hazard ratio; HRQoL = health-related quality of life; ITT = intent-to-treat; L = liter; MOD-PFS = major organ deterioration progression free survival; OR = odds ratio; RCT = randomized controlled trial; TEAE = treatment-emergent adverse event; VCd = VELCADE®, cyclophosphamide, dexamethasone; VGPR = very good partial response.

3.6 Details of Meta-Analysis

Not applicable.

3.7 Results of Indirect Comparison and Network Meta-Analysis

Not applicable.

3.8 Evaluation of Additional Benefit

3.8.1 Additional Benefit Assessment for DCyBorD vs CyBorD Based on ANDROMEDA Trial

For the main evaluation of additional benefit, individual endpoints were compared for DCyBorD and CyBorD and the results are presented in **Table 3.11**. Overall survival is not reported since data were immature at the time of the primary analysis.

Table 3.11. Additional benefit assessment for the ANDROMEDA trial

Study population	Newly diagnosed AL amyloidosis
Intervention	DCyBorD
Comparator	CyBorD
Outcomes	• Hematologic response • MOD-PFS • Organ response (cardiac and renal response rates) • Safety (AEs, rate of discontinuation) • Patient-reported outcomes (eg, HRQoL)
Presence or absence of additional usefulness	Evidence from the ANDROMEDA study demonstrates the presence of additional benefit for DCyBorD compared to CyBorD with respect to hematologic response, MOD-PFS, organ response, and HRQoL.

Data to support judgment	□ Meta-analysis of RCTs ■ Single clinical trial (18 associated unique records) □ Prospective, controlled, observational study □ Indirect comparison of RCTs □ Comparison of single-arm studies □ No relevant clinical study data □ Other
Reason for judging the presence or absence of additional usefulness	**Hematologic response** • Primary results from the ANDROMEDA study (50, 62) indicated that the proportion of subjects achieving CR was significantly greater in the DCyBorD arm compared to the CyBorD arm (53.3% vs 18.1%; OR: 5.1 (95% CI: 3.2 to 8.2); p<0.001)). • As reported in the ANDROMEDA primary analysis (50, 62), at 6-months, more DCyBorD subjects than CyBorD subjects had achieved CR (49.7% vs 14.0%, respectively [RR ratio: 3.5 with 95% CI: 2.4 to 5.2; OR 6.1 with 95% CI 3.7 to 10.0; p<0.001 for both comparisons]) and ≥VGPR (78.5% vs 49.2%, respectively [RR ratio: 1.6 with 95% CI 1.4 to 1.9; OR 3.8 with 95% CI 2.4 to 5.9]) and the median time to CR was shorter for subjects receiving DCyBorD (60 days) compared to CyBorD (85 days). • An ANDROMEDA interim analysis (median follow-up 15.7 months) indicated that, similar to the primary results, subjects in the DCyBorD arm had a higher overall CR rate compared to those in the CyBorD arm (p<0.0001) (61). • Similar hematologic response data were reported for both the ANDROMEDA 12-month landmark (49, 58) and 18-month landmark (47) analyses with higher rates of CR, higher rates of ≥VGPR,

	and shorter time to response for subjects receiving DCyBorD compared to CyBorD. Notably, at the 18-month landmark data cut (median follow-up of 25.8 months), the CR rate continued to be higher for subjects receiving DCyBorD compared to CyBorD (59.5% vs 19.2%; OR [95% CI], 6.03 [3.80–9.58]; p<0.0001). • Similar results were observed in an ANDROMEDA Asian subgroup analysis (54) with higher overall CR rates for DCyBorD compared to CyBorD (59% vs 10%, respectively) and higher rates of ≥VGPR for DCyBorD compared to CyBorD (93% vs 61%, respectively). • Regardless of baseline cardiac stage, hematologic CR rates were higher in the DCyBorD group compared to the CyBorD group (52). • Rates of deep hematologic response were not impacted for patients with t(11;14) and amp1q21 cytogenic abnormalities; however, rates of deep hematologic response were generally lower for patients with these abnormalities that were treated with VCd (51). • Regardless of which criteria was used to define "deep hematologic response", rates of hematologic response strongly favored the DCyBorD arm compared to the CyBorD arm (46). **MOD-PFS** • Data from the ANDROMEDA primary analysis (50, 62) indicated that survival free from major organ deterioration or hematologic progression (ie, MOD-PFS) was longer for subjects in the DCyBorD arm compared to those in the CyBorD arm (HR 0.58, 95% CI 0.36 to 0.93, p=0.02).

	○ The Kaplan-Meier curve for MOD-PFS based on the primary analysis is presented in **Figure 3.2**. • Similar results were reported in the Asian subgroup analysis (54) where MOD-PFS favored subjects treated with DCyBorD compared to those treated with CyBorD (HR 0.21; 95% CI, 0.06-0.75, p=0.0079). • Compared to subjects receiving CyBorD, subjects receiving DCyBorD had improved MOD-PFS regardless of cardiac stage (HRs for cardiac stage I, II, and III were 0.33, 0.55, and 0.66, respectively) (52). **Organ response** • At 6 months, cardiac response and renal response favored DCyBorD compared with CyBorD among evaluable subjects: 41.5% of DCyBorD (95% CI 32.5 to 51.0) and 22.2% of CyBorD (95% CI 15.1 to 30.8) subjects achieve cardiac response; 53.0% (95% CI 43.5 to 62.3) of DCyBorD and 23.9% (95% CI 16.4 to 32.8) of CyBorD subjects had a renal response (50). Greater cardiac responses (53% vs. 24%) and renal response rate (58% vs. 26%) were achieved at 18 months (47). • Regardless of baseline cardiac stage, 6-month cardiac and renal response rates were higher in the DCyBorD arm compared to the CyBorD arm (52). **Safety** • The safety profiles of daratumumab and bortezomib, cyclophosphamide, and

	dexamethasone in this trial were consistent with their known profiles and the underlying disease (50). • No new safety concerns were identified with DCyBorD compared with daratumumab monotherapy (IV or SC) or CyBorD alone (57). **HRQoL** • Median time to improvement was shorter and median time to worsening was longer in the DCyBorD group than in the CyBorD group for EORTC QLQ-C30 GHS and fatigue scales and EQ-5D-5L VAS (53).The median time to improvement for GHS as measured by the EORTC QLQ-C30 was 7.82 months in the DCyBorD arm and 16.79 months in the CyBorD arm (hazard ratio = 1.53, 95% CI, 1.10 to 2.13). EORTC QLQ-30 global health status showed continued improvement in the DCyBorD arm after 6 months (53). • Compared to the CyBorD group, the DCyBorD group had higher percentages of patients (with renal and/or cardiac involvement) with meaningful improvements in shortness of breath and feeling weak/tired over six cycles (48, 56). • HRQoL measures (EORTC QLQ-C30 GHS and fatigue, EQ-5D-5L VAS, and SF-36 MCS) remained stable in the DCyBorD group but worsened compared with baseline in the CyBorD group (48, 53, 56).

Abbreviations: AEs = adverse events; CI = confidence interval; CR = hematologic complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; EQ-5D-5L = EuroQol 5-dimensional descriptive system; GHS = global health status; HR = hazard ratio; HRQoL = health-related quality of life; IV = intravenous; MCS =

mental component summary; MOD-PFS = major organ deterioration progression-free survival; OR = odd ratio; QoL = quality of life; RCT = randomized controlled trial; RR = relative risk; SC = subcutaneous; SF-36 = Short Form-36; VAS = visual analog scale; QoL = quality of life; VGPR = very good partial response.

4 Details of Analytical Methods

4.1 Analytical Procedures

4.1.1 Calculation of cost-effectiveness

An economic model was developed de novo to conduct a CUA for DCyBorD compared to CyBorD for patients newly diagnosed with AL amyloidosis.

Achieving a swift and deep hematologic response is the goal of first-line therapy as it prevents further organ damage and improves survival in patients with AL amyloidosis (66). The level of hematological response (better response) is correlated with lower risk of progression and longer OS (additional details provided in **Appendix C**) (27, 33, 67-76). The model was, therefore, developed based on the importance of hematologic response in AL amyloidosis. In clinical practice, hematologic response is assessed at each cycle of the treatment course. Based on expert opinion and current clinical practice (35), the hematologic response at 3 months allows clinicians to consider changing therapies if the current treatment is not effective.

The CUA model consists of a decision tree paired with a Markov model where patients transition through independent health states and OS is stratified by hematologic response. The cycle length selected for the model was 28 days to align with the duration of treatment cycles and observation timepoints in the ANDROMEDA trial (24). In general, costs that are applied on a per-cycle basis were calculated based on a 28-day cycle. In some instances where ANDROMEDA individual patient data (IPD) were used to inform inputs (eg, distribution of patients in the decision tree) and were only reported/calculated on a monthly basis, a simplifying assumption was made where one month was equivalent to one model cycle.

4.1.1.1 Model Structure

The CUA model was developed in Microsoft® Excel and consisted of a hybrid cohort model that included a decision tree treatment component. The decision tree allowed for patient stratification by hematologic response to identify responders or non-responders after three cycles of treatment. Patients were distributed into 1 of 3 hematologic response categories: "complete response [CR]", "very good partial response [VGPR]" or combined "partial or no response [PR & NR]" or death.

The decision tree was followed by a Markov model to capture the patient disease course after being assessed for their initial response to treatment. The Markov model includes 11 Markov health states, as shown in **Figure 4.1**.

- Remain on first-line treatment ('1L Tx')
- Off first-line treatment (if previously on CyBorD) or on fixed daratumumab (monotherapy) treatment (if previously on DCyBorD) ('Off Tx/FDT')
- Second-line treatment ('2L Tx')
- End-stage organ failure
- Death

For patients in the response category of "CR" or "VGPR", after they complete their first-line treatment regimen or transition to receive daratumumab monotherapy (ie, patients in the off treatment or fixed daratumumab treatment ['Off Tx/FDT'] health state), patients are monitored and may eventually experience disease relapse necessitating second-line treatment.

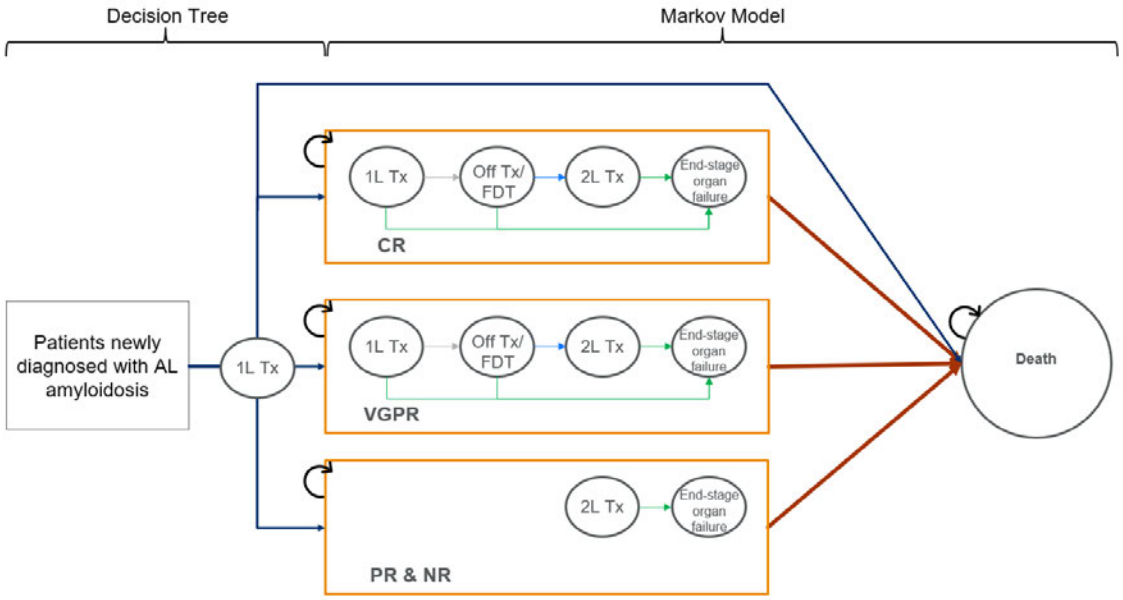
Patients in the response category "PR & NR" move immediately to second-line treatment.

In this model, it is assumed that patients with relapsed/refractory disease received one line of subsequent therapy based on clinical feedback that later line therapies provide risk/toxicity that outweighs their potential benefits. This was also observed in the ANDROMEDA trial where the majority of patients ([redacted]) received only one line of subsequent therapy (77).

Ultimately patients experience disease progression or death, which is captured in the 'End-stage Organ Failure' health state and "death" health states.

Patients can die and move to "death", the absorbing health state, at any time.

Figure 4.1. Model structure diagram



Abbreviations: 1L = first-line; 2L = second-line; AL = amyloid light-chain; CR = complete response; FDT = fixed daratumumab treatment; NR = no response; PR = partial response; Tx = treatment; VGPR = very good partial response.

4.1.1.1.1 Decision Tree

Within the decision tree, all patients are either alive on first-line treatment and are stratified based by hematologic response (ie, CR, very good partial response [VGPR], or partial/no response [PR/NR]), or dead. End-stage organ failure was not considered in the decision tree, as very few organ deterioration events were reported in the ANDROMEDA trial during the first three cycles of treatment initiation, suggesting that organ failure is a consequence of disease progression that would occur in the long-term rather than during the first three

cycles of the model. In the main analysis, patients exit the decision tree after three cycles. This timeframe was included in the model and selected for the main analysis because it aligns with our understanding of current clinical practice in Japan whereby patients that do not achieve, at minimum, VGPR would switch to a subsequent line of therapy (78-80). As stated earlier, patients who do not achieve ≥VGPR are at serious risk of irreparable organ damage. Rather than waiting for a deepening of response, a change of therapy offers the best chance to achieve a deep response and prolong survival. It is therefore common clinical practice to switch therapy after 3 cycles of treatment if a deep response is not achieved. Given this, patients achieving PR and NR were combined because these patients would switch to another treatment regimen without undergoing an observation period or continuing with their current therapy.

The option to exit the decision tree after six months was included for flexibility, based on the six-month responder landmark analysis in the ANDROMEDA trial and the time by which a patient's best hematologic response is expected to be fully established (78, 79). Six-month exit from the decision tree was explored as a scenario analysis (**Section 5.1.2.2.2**).

4.1.1.1.2 Markov Model

Upon exit from the decision tree, patients are stratified into one of three Markov models based on their hematologic response achieved (ie, CR, VGPR, or PR/NR) as outlined in **Figure 4.1**. Patients flow through the individual health states in an irreversible manner; that is, they can remain in their current state or transition to a progressive state but they cannot transition back to a health state they previously transitioned from. The health states for patients achieving CR or VGPR differ from patients achieving PR or NR, as described below. For information pertaining to health state transition probabilities, please refer to **Section 4.2.1.4.**

Patients Achieving CR or VGPR:

As outlined in **Figure 4.1** and **Table 4.1**, the Markov models for CR and VGPR have five identical health states: (1) 1L Tx, (2) Off Tx/FDT, (3) 2L Tx, (4) End-stage Organ Failure, (5) Death. The first health state (1L Tx) is relevant only as a recurring health state when the three-month exit from the decision tree is

selected, because patients with CR or VGPR will remain on-treatment for an additional three cycles (regardless of their respective treatment arm), after which they will transition to the 'Off Tx/FDT' or 'End-stage Organ Failure' states.

While in the 'Off Tx/FDT' health state, patients in the DCyBorD arm receive daratumumab monotherapy for a fixed treatment duration (up to a maximum of 24 cycles) whereas patients in the CyBorD arm stop any treatment and are observed (ie, have completed their 6 cycles of therapy). Patients in the DCyBorD arm who remain in the 'Off Tx/FDT' health state beyond a maximum of 24 cycles of daratumumab (and who have not transitioned to '2L Tx' or 'End-stage Organ Failure') will no longer receive drug therapy and associated costs (similar to CyBorD patients). 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' as per transition probabilities derived using ANDROMEDA data.

In the '2L Tx' health state, patients will start receiving 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 with major organ deterioration that require hemodialysis due to end-stage renal failure. Patients can remain alive within this health state (up to the end of the time horizon) or die.

At any cycle, patients can die and move from any health state to the absorbing 'Death' state.

Patients Achieving Partial Response or No Response:

As outlined in **Figure 4.1** and **Table 4.1**, the Markov model for patients achieving PR or NR has three health states: (1) 2L Tx, (2) End-stage Organ Failure, (3) Death. The primary difference between the Markov models for PR/NR and for CR or VGPR is the absence of the '1L Tx' and 'Off Tx/FDT' health states. According to published literature and our understanding of current clinical practice in Japan, patients who do not achieve a satisfactory response (ie, PR or NR) early in their treatment course should immediately switch to a different treatment regimen (66, 80-82). Thus, those with PR or NR

hematologic responses will directly enter the '2L Tx' health state from the decision tree.

In the '2L Tx' health state, patients commence second-line treatment for relapsed/refractory disease. Patients can either remain in this health state or transition to 'End-stage Organ Failure'.

The 'End-stage Organ Failure' health state encompasses patients with major organ deterioration (ie, renal failure). Patients can remain alive within this health state (up to the end of the time horizon) or die.

At any cycle, patients can die and move from any health state to the absorbing "Death' health state.

Additional details pertaining to the various health states included in the base case model are provided in **Table 4.1**.

Table 4.1. Overview of decision tree and health states in the main analysis

	Description and Patient Flow	Associated Costs and/or Utilities*
Decision Tree		
CR VGPR PR/NR	• Patients newly diagnosed with AL amyloidosis commence treatment with either DCyBorD or CyBorD • Patients remain either alive and stratified by their hematologic response within the decision tree for three cycles, or dead	• Drug therapy costs • Drug administration costs • Co-medication costs • First-line disease monitoring costs** • AE management costs (one-time cost) • Incidental healthcare resource use costs† • CR, VGPR, PR/NR utilities • AE utility decrements (one-

		time decrement)
Death	• Absorbing state • Patients can die within the decision tree or from any health state	• End of life costs (one-time cost)
Markov Model		
'1L Tx' (CR or VGPR only)	Entry to this health state is attained by patients receiving first-line treatment that achieved CR or VGPR within the decision tree (ie, within 3-months) All patients transition out of this health state once they have completed six cycles of treatment (regardless of treatment arm) Patients leaving this health state will transition to 'Off Tx/FDT', 'End-stage Organ Failure', or 'Death'	• Drug therapy costs • Drug administration costs • Co-medication costs • First-line disease monitoring costs • Incidental healthcare resource use costs† • CR, VGPR, PR/NR utilities
'Off Tx/FDT' (CR or VGPR only)	Represents patients in the CyBorD arm that have completed their treatment course (six cycles) and are being observed Represents patients in the DCyBorD arm receiving daratumumab monotherapy up to a maximum of 24 cycles, or being observed	• First-line disease monitoring costs** • Incidental healthcare resource use costs† • For patients treated by DCyBorD only: Daratumumab (monotherapy) drug costs, administration cost, and co-medication costs

	Patients enter this state from the '1L Tx' health state Patients can remain in this health state or may transition to '2L Tx', 'End-stage Organ Failure', or 'Death'	• CR, VGPR, PR/NR utilities
'2L Tx'	Represents patients receiving second-line therapy due to relapsed (for CR or VGPR) or refractory (for PR/NR) disease Patients can enter this health state only from the 'Off Tx/FDT' state (for CR or VGPR) or directly from the decision tree (for PR/NR) Patients can remain in this health state or transition to 'End-stage Organ Failure' or 'Death' states	• Second-line drug therapy costs (one-time cost) • Incidental healthcare resource use costs† • CR, VGPR, PR/NR utilities • '2L Tx' utility decrement
'End-stage Organ Failure'	Represents patients that progress to end-stage organ failure. Patients can enter this health state from the '1L Tx' (for CR or VGPR), 'Off Tx/FDT' (for CR or VGPR), or '2L Tx' health states (for CR, VGPR, or PR/NR) Patients can remain in this health state until the end of the simulation or transition to 'Death'	• Recurring end-stage organ failure costs (ie, hemodialysis) • Incidental healthcare resource use costs† • CR, VGPR, PR/NR utilities • End-stage organ failure health state utility decrement • Hemodialysis utility decrement

*All costs and decrements are recurring (ie, per-cycle) unless specifically stated otherwise.
**Reflects costs associated with routine/planned disease monitoring and assessments.
†Reflects costs associated with additional incidental healthcare resource utilization, for example, emergency room visits.
Abbreviations: 1L = first-line; 2L = second-line; AE = adverse event; AL = amyloid light-chain; CR = complete response; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; FDT = fixed daratumumab treatment; NR = no response; PR =partial response; Tx = treatment; VGPR = very good partial response.

A half-cycle correction was applied to the calculation of LYs and QALYs and to certain costs to avoid over- or under-estimating the value of a health state in alignment with patients transitioning part way through a cycle. Half-cycle corrections are used to reflect the fact that some patient transitions can occur at any point within the cycle (ie, at cycle start or cycle end). A half-cycle correction is used with the expectation that patients will, on average, transition about half-way through a model cycle. Therefore, half of the costs and benefits are assigned in each state to avoid under- or over-estimating the value of the health state. In the model, half-cycle corrections have been applied by averaging the costs and benefits between two cycles. 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, disease monitoring costs, recurring end-stage, and organ failure costs. Costs that were applied as a one-time cost (ie, AE management, second-line drug therapy, and end of life) were not half-cycle corrected since the timing of events within that cycle is irrelevant.

4.1.2 Model assumptions

Several assumptions were required in the model and are summarized in **Table 4.2**.

Table 4.2. Model assumptions and rationale

Assumption	Rationale/Support
Hematologic response is a treatment-independent surrogate for OS. Rates of hematologic response achieved at three-months observed in ANDROMEDA are assumed to predict the OS curves for DCyBorD and CyBorD.	The relationship between depth of hematologic 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 (32, 33, 68-70, 72-74, 76, 83-85).
For the distribution of hematologic response in the decision tree, any non-evaluable hematologic response at a specific cycle was classified as PR/NR.	This conservative approach is to use all the data available and to avoid overestimating treatment benefit. In addition, this assumption was applied equally to both treatment groups.
Best overall hematologic response is achieved once patients exit the decision tree (ie, upon exit from the decision tree, a patient's hematologic response does not change).	The median time to hematologic complete response reported in the ANDROMEDA trial was 85 days for CyBorD patients and 60 days for DCyBorD patients. Therefore, patients had achieved their best response prior to three months (ie, the earliest possible exit from the decision tree) (78). Data from the ANDROMEDA trial also indicates that patients who respond to treatment have a durable response and continue to respond to treatment (78).
Patients achieving PR and NR were grouped together.	Patients achieving less than VGPR (PR or NR) are considered to have inadequate response. In addition,

	patient outcomes and clinical practice are similar for both (66, 80)).
Major organ failure is not captured in the decision tree (first 3 months). It is captured in the Markov model.	Very few MOD events occurred in the first data cut of the trial (February 2020; median follow-up: 11.4 months) (78), supporting that end stage organ failure would happen in long-term. Further, patients with severe organ involvement (NYHA classification IIIB or IV heart failure) were not suitable for DCyBorD or CyBorD treatment and were excluded from the study population.
A retrospective study Kastritis *et al*., (2020) was used to estimate the OS associated with different hematologic responses independent of treatment. The OS curves for PR/NR, VGPR, and CR were generated based on independent extrapolations of their raw KM data.	Published OS curves from Kastritis *et al*., (2020) were available up to a maximum of ~12 years (71). To project long-term survival over the lifetime time horizon, methodological best practices were followed for extrapolating and choosing the most clinically valid distributions. The proportional hazards assumption did not hold for the KM curves; therefore, separate extrapolations were performed for CR, VGPR, PR, and NR. With this approach, the resulting long-term survival also appeared clinically valid.
Risk of mortality of patients with AL amyloidosis in the model cannot be lower than the risk of mortality of the general population.	Japanese general population mortality rates (86) 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).
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 probabilities 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.
The transition probabilities for '1L Tx' to 'End-stage Organ Failure' are the same for '2L Tx' to 'End-stage Organ Failure'.	Due to lack of data to inform this transition probability from the ANDROMEDA study, we assumed the transition probability of '2L Tx' to 'End-stage Organ Failure' should be at least the same as the transition probability for '1L Tx' to 'End-stage Organ Failure'.
All patients with VGPR and CR will complete the full six cycles of treatment. Patients with PR/NR will immediately switch to a subsequent	As outlined in the ANDROMEDA protocol, patients were to receive 6 cycles of CyBorD (CyBorD arm) or 6 cycles of DCyBorD followed by up to

therapy after three cycles of treatment if three-month exit from the decision tree is selected (as in the main analysis).	18 cycles of daratumumab monotherapy, unless they had a suboptimal (≤PR) hematologic response and could be switched to another therapy after 3 cycles in accordance with clinical expert feedback on real-world practices (24, 79, 80). Since there is no clinical rationale for patients with deep hematologic response (≥VGPR) to change their treatment regimen, it was assumed that all patients in the CyBorD treatment arm with VGPR or CR would receive up to the full 6 cycles of CyBorD and then cease treatment. Similarly, all patients in the DCyBorD arm with VGPR or CR were assumed to receive the first six cycles of DCyBorD (in alignment with the ANDROMEDA CSR) (78). After the first 6 cycles, patients in the DCyBorD arm could continue with daratumumab monotherapy in accordance with the values specified on "Time on Treatment" sheet.
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 and would, therefore, not be appropriate in these patients.
Drug wastage and RDI were accounted for in drug costs.	Important to accurately calculate the true (real-world) treatment cost for an average patient.
Subsequent therapy costs are applied	The duration of second-line therapy

as a one-time cost.	was poorly reported in the literature. As such, the cost of subsequent therapy was applied as a one-time tariff to avoid overestimating costs.
Subsequent therapy costs for '2L Tx' health state reflect patients receiving one subsequent line of therapy.	Real-world evidence and clinical expert feedback indicate that most patients do not receive multiple lines of subsequent therapy (70, 87-89). Furthermore, the majority of patients ([redacted]) in the ANDROMEDA trial only received one subsequent line of therapy (78).
The number of cycles of treatment used to calculate second-line therapy costs was 6 for Rd, 4 for BMd, 6 for CyBorD, 4 for TCd, and 6 for DCyBorD.	Best available data sources in AL amyloidosis: Rd: Sanchorawala *et al*., (2007) (median number of cycles completed by study subjects was 6) (90); BMd: Palladini *et al*., (2014) (median number of treatment cycles received was 4) (91); CyBorD: ANDROMEDA protocol (assumed the maximum number of cycles per the ANDROMEDA protocol) (24); TCd: Venner *et al*., (2014) (median number of treatment cycles received was 4); Wechalekar *et al*., (2007) (76, 92); DCyBorD: ANDROMEDA protocol (although daratumumab could be administered up to a maximum of 24 cycles, a total of 6 cycles was used in

	the model as a conservative assumption since long-term administration/adherence data are not available from the ANDROMEDA trial) (24).
The utility decrement applied for '2L Tx' is the difference between the mean utility value prior to reaching a 'progressive disease' state and the mean utility value once in a 'progressive disease' state 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/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 could require hospitalization 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.
Incidental healthcare resource use (proportion of patients requiring each item and usage frequency) for patients in '2L Tx' and 'End-stage Organ Failure' health states is equivalent to that of patients in the '1L Tx' health state.	AL Amyloidosis a designated intractable disease with low prevalence in Japan. We attempted to leverage MDV data to inform incidental healthcare resource use by health state (see **Appendix H**). However, due to a paucity of data from the database, the incidental healthcare resource use for '2L Tx' and 'End-stage Organ Failure' health

	states were assumed to be equal to '1L Tx' to be conservative.
The relative reduction in incidental healthcare resource use between '1L Tx' and 'Off Tx/FDT' health states was assumed equal to the relative reduction in healthcare resource use for patients in their first- and second-year post-diagnosis with AL amyloidosis as reported by Quock *et al.*, (2018) (93).	Healthcare resource use values reported by Quock *et al.*, (2018) (93) for the first- and second-year diagnosis were assumed to approximately with the timeframe that patients would be on first-line treatment and have completed first-line treatment, respectively. Relative reductions in healthcare resource use between first- and second-year post-diagnosis were applied as a best-available estimate of the healthcare resource use for patients in the 'Off Tx/FDT' health state.
No patients received solid organ transplant or implantation of a cardiac assist device.	Solid organ transplant in patients with AL amyloidosis is very rare in clinical practice (82, 94). In addition,  (95).

Abbreviations: 1L = first-line; 2L = second-line; AE = adverse event; AL = amyloid light-chain; BMd = bortezomib, melphalan, dexamethasone; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; CR = complete response; CSR = clinical study report; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; FDT = fixed daratumumab treatment; IPD = individual participant data; IV = intravenous; KM = Kaplan-Meier; MOD = major organ deterioration; NR = no response; OS = overall survival; PR = partial response; Rd = REVLIMID® (lenalidomide), dexamethasone; RDI = relative dose intensity; TCd = thalidomide, cyclophosphamide, dexamethasone; Tx = treatment; VGPR = very good partial response.

4.2 Parameters Used in the Analysis

Table 4.3 provides a summary of the model inputs used in the main analysis. Please refer to the corresponding sections for additional details.

Table 4.3. Model parameters used for the analysis

Variable Name	Value	SD or SE*	Distribution* (if applicable)	Rationale
Model Settings				
Time horizon	35 years	N/A	N/A	C2H guidelines indicate that the time horizon should be sufficiently long to capture important differences in costs and outcomes between the technologies being compared (96, 97). Given that AL amyloidosis survival has improved in recent years with the introduction of bortezomib-based treatments, a time horizon of >30 years is possible for some patients to capture their full lifespan. A time horizon of 35 years was selected since <1% of modelled patients are alive at this time. 35 years is selected since <1% of modelled cohort are alive at this time. We believe the time horizon is appropriate to capture the cost and effectiveness over patients' lifetime. The same time horizon was used in the CADTH evaluation in Canada.

Discount rate - effects	2.0%	N/A	N/A	Both cost and effectiveness should be discounted at a rate of 2% per year as per current C2H guidelines (43).
Discount rate - costs	2.0%	N/A	N/A	
Patient Characteristics				
Starting age (years)	[redacted]	[redacted]	Normal	Mean age and the proportion of male subjects are based on all subjects included in the ANDROMEDA study (78). Starting patient age and the proportion of male subjects were closely aligned with the Japanese population reported by Shimazaki *et al*., (2018) (19) (median age: 65; percent male subjects: 58.8%); therefore, ANDROMEDA values were used to inform the main analysis. Body weight and BSA is based on the Asian subjects included in the ANDROMEDA study (n=60) to better reflect Japanese patient characteristics (98).
Proportion male	[redacted]	[redacted]	Beta	
Mean weight (kg)	[redacted]	[redacted]	Normal	
Mean body surface area (m^2)	[redacted]	[redacted]	Normal	
Efficacy Data				
DCyBorD arm: Hematologic response and death distribution at three months (exit from	CR: [redacted] VGPR: [redacted] PR/NR: [redacted]	N/A	N/A	ANDROMEDA IPD post hoc analysis (18-month landmark data cut, data on file) (98).

decision tree)	Dead: [redacted]			
CyBorD arm: Hematologic response and death distribution at three months (exit from decision tree)	CR: [redacted] VGPR: [redacted] PR/NR: [redacted] Dead: [redacted]	N/A	N/A	
PR/NR survival function	Weibull	N/A	N/A	After digitizing and extrapolating the PR and NR KM curves from Kastritis *et al*., (2020), the Weibull parametric survival function was a good visual fit to the PR and NR KM data and generated the curve of best-fit for the larger proportion of patients with PR/NR (71).
CR survival function	Exponential	N/A	N/A	According to clinical validity, visual assessment, and curve fit statistics, the Exponential parametric survival function generated the curve of best-fit for patients with CR (71).
VGPR survival function	Log-logistic	N/A	N/A	According to clinical validity, visual assessment, and curve fit statistics, the Log-logistic parametric survival function generated the curve of best-fit for patients with VGPR (71).
Proportion of patients in	[redacted]	[redacted]	Beta	ANDROMEDA IPD post hoc analysis (18-month

PR (vs. NR at exit from decision tree)		[redacted]		landmark data cut, data on file) (98). Proportion of patients in PR = Number of PR patients/total number of PR and NR patients. The proportion is used to apply weighting to the blended PR/NR OS curve to reflect the patient population of suboptimal responders.
DCyBorD Treatment duration (in months)	24.00	0	N/A	Maximum treatment duration for patients in the DCyBorD arm that achieved CR or VGPR per ANDROMEDA protocol (24).
CyBorD Treatment duration (in months)	6.00	0	N/A	Maximum treatment duration for patients in the CyBorD arm that achieved CR or VGPR per ANDROMEDA protocol (24).
DCyBorD Time on Treatment**	Cycles 1-6: 100% Cycle 7: [redacted] Cycles 8-23: range [redacted] Cycle 24: [redacted]	N/A	N/A	Cycles 1-6: assumption that patients achieving CR or VGPR will continue their current treatment regimen; Cycles 7-24: ANDROMEDA IPD post hoc analysis (18-month landmark data cut, data on file) (98). During the course of treatment, patients are expected to discontinue treatment for a variety of reasons (toxicity, patient choice, etc.). Treatment discontinuation was observed in the ANDROMEDA trial, and values determined using ANDROMEDA IPD were

				used to inform treatment discontinuation applicable in the model.
CyBorD Time on Treatment	Cycles 1-6: 100%	N/A	N/A	Cycles 1-6: assumption that patients achieving CR or VGPR will continue their current treatment regimen to a maximum of 6 cycles.
First-line Drug Costs				
DCyBorD (Cycles 1-2) DCyBorD (Cycles 3-6) DCyBorD (Cycle 7+)	¥ 1,937,112.40 ¥ 1,046,984.40 ¥ 445,064.00	N/A	N/A	NHI Price List, (2022) (99).
CyBorD	¥ 156,856.40	N/A	N/A	
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	N/A	N/A	Aligned with product label (25) and ANDROMEDA protocol (24).

	Cycle 7+: 1,800 mg; 1 administration per cycle			
Bortezomib	1.3 mg/m^2; 4 administrations per cycle	N/A	N/A	
Cyclophosphamide	300 mg/m^2; 4 administrations per cycle	N/A	N/A	
Dexamethasone	40 mg; 4 administrations per cycle	N/A	N/A	
First-line Drug Relative Dose Intensity (RDI)				
DCyBorD RDI (daratumumab)	[redacted]	[redacted]	Beta	ANDROMEDA CSR (data on file) (78).
DCyBorD RDI (bortezomib)	[redacted]	[redacted]	Beta	
DCyBorD RDI	[redacted]	[redacted]	Beta	

(cyclophosphamide)				
DCyBorD RDI (dexamethasone)	[redacted]	[redacted]	Beta	
CyBorD RDI (bortezomib)	[redacted]	[redacted]	Beta	
CyBorD RDI (cyclophosphamide)	[redacted]	[redacted]	Beta	
CyBorD RDI (dexamethasone)	[redacted]	[redacted]	Beta	
First-line Drug Administration Costs per cycle				
DCyBorD (Cycles 1-2)	¥ 3,120.00	312	Gamma	Unit costs: Saeki *et al.,* (2020) (100), Japan MHLW Medical Fee Schedule, (2022) (101), NHI Price List, (2022) (99). Frequency: ANDROMEDA protocol (24).
DCyBorD (Cycles 3-6)	¥ 2,680.00	268	Gamma	
DCyBorD (Cycles 7+)	¥ 220.00	22	Gamma	
CyBorD	¥ 2,240.00	224	Gamma	
First-line Co-medication Costs				
DCyBorD	¥ 1,907.80	190.78	Gamma	Unit costs: NHI Price List, (2022) (99). Type and frequency: ANDROMEDA protocol (24).
CyBorD	¥ 1,663.20	166.32	Gamma	

First line (Routine) Disease Monitoring Costs				
1L Tx	¥ 23,618.90	2367.89	Gamma	Unit costs: Japan MHLW Medical Fee Schedule, (2022) (101). Type and frequency: ANDROMEDA protocol (24).
FDT	¥ 8,798.90	882.89	Gamma	
Off Tx	¥ 5,360.00	536.00	Gamma	
Adverse Event Management Costs				
DCyBorD	¥ 101,069.34	10106.93384	Gamma	Cost per event: Japan MHLW Medical Fee Schedule, (2022) (101), Inoue *et al*., (2020) (102), NHI Price List 2022 (99), Usami *et al*., (2014) (103), Akashi *et al*., (2012) (104), MDV data analysis (See **Appendix H**) (94). Proportion of patients experiencing AEs: Janssen Data on File 2021 (ANDROMEDA 18-month landmark analysis) (105).
CyBorD	¥ 68,610.25	6861.02495	Gamma	
AE Utility Decrements				
DCyBorD	[redacted]	[redacted]	Gamma	Decrement per event: Nafees *et al*., (2008) (106), Onouchi *et al*., (2014) (107), Beusterien *et al*., (2010) (108), Ishida *et al*., (2012) (109), Stein *et al*., (2018) (110), Shiroiwa *et al*., (2009) (111), Brown *et al*., (2001) (112), Saito *et al*., (2014) (113), Sullivan *et al*.,
CyBorD	[redacted]	[redacted]	Gamma	

				(2011) (114), Usami *et al*., (2014) (103), Akashi *et al*., (2012) (104), Inoue *et al*., (2020) (102). Proportion of patients experiencing AEs: Janssen Data on File 2021 (ANDROMEDA 18-month landmark analysis) (105).
Second-line Drug Therapy Costs				
Second-line drug therapy proportions for DCyBorD patients	Rd: [redacted]% BMd: [redacted]% CyBorD: [redacted]% TCd: [redacted]%	N/A	N/A	Best available data sources from: Shimazaki *et al*., (2018) (19); Janssen Japan internal assumption.
Second-line drug therapy proportions for CyBorD patients	Rd: [redacted]% BMd: [redacted]% CyBorD: [redacted]% TCd: [redacted]% DCyBorD: [redacted]%	N/A	N/A	
Second-line drug therapy costs for DCyBorD patients	¥ 1,323,417.67	132341.7668	Gamma	Unit cost: ANDROMEDA CSR (78), NHI Price List, (2022) (99). Proportion of 2L patients receiving regimen: Shimazaki

Second-line drug therapy costs for CyBorD patients	¥ 1,667,882.67	166788.2668	Gamma	*et al*., (2018) (19), Janssen Japan Internal Assumption.
End-stage Organ Failure Costs				
Recurring organ failure costs per cycle	¥ 353,434.64	35343.46388	Gamma	Unit cost: Takura *et al*., (2019) (115). Proportion of patients requiring treatment: ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95), MDV database analysis (See **Appendix H**, Data on File) (94).
Incidental Healthcare Resource Use Costs				
1L Tx	¥ 91,319.33	9131.933401	Gamma	Unit cost: Japan MHLW Medical Fee Schedule, (2022) (101) (inpatient hospitalization code: A105, outpatient visit code: A002) (101), MDV database analysis (See **Appendix H**, Data on File) (94). Proportion of patients requiring item: Janssen Japan Data on File, (2021) (116).
Off Tx/FDT	¥ 50,258.17	5025.816914	Gamma	
2L Tx	¥ 91,319.33	9131.933401	Gamma	
End-stage Organ Failure	¥ 91,319.33	9131.933401	Gamma	

End of Life Costs				
Costs associated with final month of life	¥ 662,205.59	66220.55901	Gamma	Japan Medical Association, (2007) (117).
Utilities				
CR	[redacted]	[redacted]	Beta	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) re-analysis with Japanese tariff (95). Utility value assigned to VGPR is the mean of utility value of CR ([redacted]) and PR ([redacted]). PR/NR utility value is weighted average of PR and NR utility values ([redacted]%*PR utility ([redacted])+[redacted]%*NR utility([redacted]))§
VGPR	[redacted]	[redacted]	Beta	
PR/NR	[redacted]	[redacted]	Beta	
2L Tx health state utility decrement	[redacted]	[redacted]	Gamma	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) re-analysis with Japanese tariff; utility decrement associated with 'progressed disease' (95).
End-stage organ failure health state utility decrement	[redacted]	[redacted]	Gamma	Calculated as the difference between the baseline utility value for all ANDROMEDA patients and the utility value from patients with advanced chronic heart failure listed for heart transplant per Emin *et al*., (2016)

				(118).
Hemodialysis utility decrement	0.1	0.01	Gamma	Recurring utility value decrement applied to all patients commencing hemodialysis. Calculated as the difference between patients with chronic kidney disease pre-hemodialysis and after commencing hemodialysis per Wyld *et al*., (2012) (119).
Transition Probabilities†				
CR transition probability (cycle 4-6): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
CR transition probability (cycle 4-6): 1L Tx to Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	All patients with CR in '1L Tx' that have not transitioned to 'End-stage organ failure' will remain on 1L Tx for cycles 4-6.
CR transition probability (cycle 4-6): Remain in 1L Tx	[redacted]	Dirichlet	Dirichlet	
CR transition probability (cycle 4-6): Off Tx/FDT to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

CR Transition probability (cycle 4-6): Off Tx/FDT to 2L Tx	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months, data on file) (120).
CR Transition probability (cycle 4-6): Remain in Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	All patients with CR in 'Off Tx/FDT' who have not transitioned to '2L Tx' or 'End-stage organ failure' will remain in the 'Off Tx/FDT' health state.
CR transition probability (cycle 4-6): 2L Tx to End-stage Organ Failure‡	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
CR transition probability (cycle 4-6): Remain in 2L Tx	[redacted]	Dirichlet	Dirichlet	All patients with CR in '2L Tx' who have not transitioned to 'End-stage organ failure' will remain on 2L Tx.
VGPR transition probability (cycle 4-6): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
VGPR transition probability (cycle 4-6): 1L Tx to Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	All patients with VGPR in '1L Tx' that have not transitioned to 'End-stage organ failure' will remain in '1L Tx' for cycles 4-6.

VGPR transition probability (cycle 4-6): Remain in 1L Tx	[redacted]	Dirichlet	Dirichlet	
VGPR transition probability (cycle 4-6): Off Tx/FDT to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
VGPR transition probability (cycle 4-6): Off Tx/FDT to 2L Tx	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months, data on file) (120).
VGPR transition probability (cycle 4-6): Remain in Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	All patients with VGPR in 'Off Tx/FDT' that have not transitioned to '2L Tx' or 'End-stage organ failure' will remain in the 'Off Tx/FDT' health state.
VGPR transition probability (cycle 4-6): 2L Tx to End-stage Organ Failure‡	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
VGPR transition probability (cycle 4-6): Remain in 2L Tx	[redacted]	Dirichlet	Dirichlet	All patients with VGPR in '2L Tx' that have not transitioned to 'End-stage organ failure' will remain in 2L Tx.

PR/NR transition probability (cycle 4-6): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
PR/NR transition probability (cycle 4-6): 1L Tx to 2L Tx	[redacted]	Dirichlet	Dirichlet	All patients with PR/NR in '1L Tx' that have not transitioned to 'End-stage organ failure' will transition to '2L Tx'.
PR/NR transition probability (cycle 4-6): Remain in 1L Tx	[redacted]	Dirichlet	Dirichlet	
PR/NR transition probability (cycle 4-6): 2L Tx to End-stage Organ Failure‡	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
PR/NR transition probability (cycle 4-6): Remain in 2L Tx	[redacted]	Dirichlet	Dirichlet	All patients with PR/NR in '2L Tx' that have not transitioned to 'End-stage organ failure' will remain in '2L Tx'.
CR transition probability (cycle 7+): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

CR transition probability (cycle 7+): 1L Tx to Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	All patients remaining in the '1L Tx' health state (ie, have not transitioned to end-stage organ failure) will transition to the 'Off Tx/FDT' health state after cycle 6.
CR transition probability (cycle 7+): Remain on 1L Tx	[redacted]	Dirichlet	Dirichlet	
CR transition probability (cycle 7+): Off Tx/FDT to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
CR Transition probability (cycle 7+): Off Tx/FDT to 2L Tx	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months, data on file) (120).
CR Transition probability (cycle 7+): Remain in Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	All patients with CR in 'Off Tx/FDT' who have not transitioned to '2L Tx' or 'End-stage organ failure' will remain in the 'Off Tx/FDT' health state.
CR transition probability (cycle 7+): 2L Tx to End-stage Organ Failure‡	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

CR transition probability (cycle 7+): Remain on 2L Tx	[redacted]	Dirichlet	Dirichlet	All patients with CR in '2L Tx' who have not transitioned to 'End-stage organ failure' will remain in the '2L Tx' health state.
VGPR transition probability (cycle 7+): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
VGPR transition probability (cycle 7+): 1L Tx to Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	All patients with VGPR in '1L Tx' who have not transitioned to 'End-stage organ failure' will transition to the 'Off Tx/FDT' health state after cycle 6.
VGPR transition probability (cycle 7+): Remain on 1L Tx	[redacted]	Dirichlet	Dirichlet	
VGPR transition probability (cycle 7+): Off Tx/FDT to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
VGPR transition probability (cycle 7+): Off Tx/FDT to 2L Tx	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months, data on file) (120).

VGPR transition probability (cycle 7+): Remain in Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	All patients with VGPR in 'Off Tx/FDT' who have not transitioned to '2L Tx' or 'End-stage organ failure' will remain in the 'Off Tx/FDT' health state.
VGPR transition probability (cycle 7+): 2L Tx to End-stage Organ Failure‡	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
VGPR transition probability (cycle 7+): Remain on 2L Tx	[redacted]	Dirichlet	Dirichlet	All patients with VGPR in '2L Tx' who have not transitioned to 'End-stage organ failure' will remain in the '2L Tx' health state.
PR/NR transition probability (cycle 7+): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
PR/NR transition probability (cycle 7+): 1L Tx to 2L Tx	[redacted]	Dirichlet	Dirichlet	All patients with PR/NR in '1L Tx' who have not transitioned to 'End-stage organ failure' will transition to '2L Tx' since the patients failed to achieve CR or VGPR.
PR/NR transition probability (cycle 7+): Remain on 1L Tx	[redacted]	Dirichlet	Dirichlet	

PR/NR transition probability (cycle 7+): 2L Tx to End-stage Organ Failure‡	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
PR/NR transition probability (cycle 7+): Remain on 2L Tx	[redacted]	Dirichlet	Dirichlet	All patients with PR/NR in '2L Tx' who have not transitioned to 'End-stage organ failure' will remain on 2L Tx.
Mortality Distributions				
Mortality Distribution (cycles 4-6): 1L Tx	[redacted]	Dirichlet	Dirichlet	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
Mortality Distribution (cycles 4-6): Off 1L Tx/FDT	[redacted]	Dirichlet	Dirichlet	
Mortality Distribution (cycles 4-6): 2L Tx	[redacted]	Dirichlet	Dirichlet	
Mortality Distribution (cycles 4-6): End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	
Mortality Distribution	[redacted]	Dirichlet	Dirichlet	

(cycles 7+): 1L Tx				
Mortality Distribution (cycles 7+): Off 1L Tx/FDT	[redacted]	Dirichlet	Dirichlet	
Mortality Distribution (cycles 7+): 2L Tx	[redacted]	Dirichlet	Dirichlet	
Mortality Distribution (cycles 7+): End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	
Mortality Distribution, Decision tree (Assigning end of life costs): CR	[redacted]	Dirichlet	Dirichlet	
Mortality Distribution, Decision tree (Assigning end of life costs): VGPR	[redacted]	Dirichlet	Dirichlet	
Mortality Distribution, Decision tree (Assigning end of life costs): PR/NR	[redacted]	Dirichlet	Dirichlet	

* Only applicable if a probabilistic analysis is run.

** The proportion of patients remaining on treatment decreases gradually from [redacted]% (cycle 7) to [redacted]% (cycle 24) as observed in the

ANDROMED trial (18-month landmark analysis IPD) (98); patient proportions for cycles 8-23 are located on the 'Time on Treatment' sheet in the model.

† CR and VGPR criteria as defined in the ANDROMEDA CSR (78); transition probabilities are applicable to both DCyBorD and CyBorD.

§ Weighting applied in the calculation of the PR/NR utility value was derived using the number of patients for which the respective utility values were recorded. For PR and NR, there were [redacted] and [redacted] measures, respectively (combined total of [redacted] measures). Therefore, the weighting applied for PR was [redacted]% and the weight applied for NR was [redacted]%.

‡ Due to a limited number of MOD-PFS events reported, 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; AE = adverse event; AL = amyloid light-chain; C2H = Center for Outcomes Research and Economic Evaluation for Health; CR = complete response; CSR = clinical study report; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; FDT = fixed daratumumab treatment; HR = hazard ratio; IPD = individual participant data; kg = kilogram; KM = Kaplan-Meier; m = meter; mg = milligram; MHLW = Ministry of Health, Labor, and Welfare; N/A = not applicable; NR = no response; PR = partial response; RDI = relative dose intensity; SD = standard deviation; Tx = treatment; VGPR = very good partial response.

4.2.1 Efficacy Parameters

Efficacy parameters in the model were derived from three studies: ANDROMEDA, Kastritis *et al*., (2020), and Palladini *et al*., (2012). As described in **Section 4.1.1.1**, the model structure was developed based on the use of hematologic response as a measure of treatment efficacy. Therefore, to inform the model, decision tree data and OS curves stratified by hematologic response were needed. Hematologic response data from ANDROMEDA was used to inform parameters for the decision tree (see **Section 4.2.1.1**). However, because [redacted]% of patients were still alive in the ANDROMEDA trial at the time of the first clinical cut-off (February 2020; median follow-up: 11.4 months), statistically robust long-term extrapolation of effectiveness was limited by the ANDROMEDA OS KM data immaturity. As such, external published data (ie, Kastritis *et al*., [2020] and Palladini *et al*., [2012]) identified through a targeted literature search was used to inform long-term OS in the Markov model (see **Section 4.2.1.1**).

Kastritis *et al*., (2020) was a retrospective study aimed to evaluate the significance of an early and deep hematologic response in patients treated first-line with bortezomib-based regimens (71). Data from this study was used to inform long-term OS in the main analysis (ie, 3-month decision tree exit).

The study by Palladini *et al*., (2012) was a retrospective study aimed to identify and validate criteria for response to first-line treatment in AL amyloidosis (74). Data from this study is used to inform long-term OS in the model only if 6-month decision tree exit is selected (included as a scenario analysis in **Section 5.1.2.2**). A summary of the three studies used to inform OS in the model is provided in **Table 4.4**.

Table 4.4. Summary of studies informing efficacy in economic model

	ANDROMEDA (50, 78)	Kastritis *et al.*, (2020) (71)	Palladini *et al.*, (2012) (74)
Study Purpose in Context of Economic Model	Informs rates of hematologic response within decision tree.	Informs efficacy (parametric survival curves and HRs) for long-term OS when 3-month exit from decision tree is selected.	Informs efficacy (parametric survival curves and HRs) for long-term OS when 6-month exit from decision tree is selected.
Study Design	RCT	Retrospective	Retrospective
Number of patients	388	227	816
Patient Population	Newly diagnosed	Newly diagnosed	Newly diagnosed
Publication Year	2021	2020	2012
First-line Regimens Received	DCyBorD (50%) CyBorD (50%)	Bortezomib-based (100%)	Md (44.6%) ASCT (15.9%) Thalidomide (14.6%) REVLIMID® (5.3%) Bortezomib-based (3.2%) Dexamethasone (2.9%)

			Mp (2.4%) Other (11.1%)
Median Follow-up	11.4 months (primary analysis)	48 months	33 months
Statistical Methods	The Kaplan-Meier method was used to estimate time-to-event distributions. Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards regression model. The infusion-related reaction rate and rates of very good partial response or better were compared between groups using a stratified Cochran-Mantel-Hansel test.	Descriptive statistics were reported as medians with range values. All efficacy analyses are on an ITT basis, unless otherwise specified. For between groups comparisons the chi-square test was used. Time to event was calculated from the date of first treatment until the date of death or other event or until the date of last follow up if the respective event has not occurred. Analyses were performed using SPSS.	Survival was calculated from the time of evaluation of response. Cox models were fitted to compute HRs and 95% CIs for death. To measure model performance, the Harrell concordance statistic and the Royston explained variation were computed. The ability of the selected response criteria to identify groups of patients with different survival was tested in the validation cohort. Survival curves were plotted using the Kaplan-Meier method. STATA 11 and MedCalc 11 were used

			for computation.
Age (median, years)	64.0 (range: 34-87)	65 (range: 40-84)	63 (IQR: 55-71)
Sex (% male)	58.0%	57%	59.9%
Organ Involvement (#, median) Kidney (%) Heart (%) Liver (%)	2 (range:1-6) 59.0% 71.4% 8.0%	NR 70% 69% 19%	2 (IQR: 1-2) 68.1% 64.8% 16%
Mayo Cardiac Stage (%) I II III IIIa IIIb	 23.2% 40.2% NR 34.5% 2.1%	 18% 52.5% 29.5%* 18% 11.5%	 30.9% 43.7% 25.4% NR NR
NT-proBNP (ng/L, median)	2307.9 (range: 51-12950)	NR	1587 (IQR: 351-4,670)
dFLC (mg/L, median)	187.1 (range: 1-9983)	194 (range: 50-8987)	157 (IQR: 70-460)

* Calculated based on the percentage of patients with Mayo stage IIIa and IIIb.

Abbreviations: ASCT = autologous stem cell transplant; CI = confidence interval; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; dFLC = difference in free light-chains; HR = hazard ratio; IQR = interquartile range; ITT = intent-to-treat; Md = melphalan, dexamethasone; Mp = melphalan, prednisone; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; OS = overall survival; RCT = randomized controlled trial.

Sources: ANDROMEDA CSR (78), Kastritis *et al*., (2021) (50), Kastritis *et al*., (2020) (71), Palladini *et al*., (2012) (74).

4.2.1.1 Modelling Effectiveness in the Decision Tree

The decision tree highlighted the treatment benefit of DCyBorD; that is, affording patients deeper hematologic response earlier in the treatment course. Patient-level data from the ANDROMEDA 18-month landmark analysis (May 2021; median follow-up: 25.8 months) (98) was used to inform the decision tree with respect to the proportion of patients in each treatment group achieving CR, VGPR, and PR/NR or who died within each one-month window (assumed to be equal to one model cycle). Of note, a two-month window was used to capture hematologic response data at the decision tree exit timepoint (ie, cycle 3 in the main analysis) to be consistent with the assumed method for reporting landmark CR rate in the ITT landmark analysis. In essence, the decision tree reflects a snapshot of patients' hematologic response status at each assessment timepoint. For any instance where an alive patient's hematologic response status was not reported in a particular cycle, they were classified as PR/NR (a simplistic assumption that was applied equally to both treatment groups in order to avoid overestimating treatment benefit). The patient distribution within the 3-month decision tree is shown in

Table 4.5**.**

Table 4.5. Hematologic response (3-month) distribution within the decision tree

Cycle	CR		VGPR		PR/NR		Dead	
	DCyBorD	CyBorD	DCyBorD	CyBorD	DCyBorD	CyBorD	DCyBorD	CyBorD
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: CyBorD = cyclophosphamide, bortezomib, dexamethasone; CR = complete response; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; NR = no response; PR = partial response; VGPR = very good partial response.

Source: ANDROMEDA 18-month landmark analysis (May 2021; median follow-up: 25.8 months, data on file) (98).

4.2.1.2 Modelling Effectiveness in the Markov Model

Survival curve extrapolation was performed as described in the NICE Technical Support Document (TSD) 14 for survival analysis for economic evaluations (121). Cox proportional hazard assumptions were tested for OS data, and pairwise hazard ratios (HRs) were calculated (see **Appendix D**). Parameters and model fit statistics (ie, Akaike's information criterion [AIC], Bayesian information criterion [BIC]) were calculated for each curve type and are presented below in **Table 4.6**. A list of all parametric survival functions, extrapolation parameters, and covariance matrices used in the model are presented in **Appendix E**.

Table 4.6. Fit statistics for OS based on 3-month hematologic response (Kastritis *et al.*, [2020] (71))

		Exponential	Weibull	Gompertz	Log-normal	Log-logistic	Gamma	Generalized Gamma
NR	AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VGPR	AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CR	AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike's information criterion; BIC = Bayesian information criterion; CR = complete response; NR = no response; OS = overall survival; PR = partial response; VGPR = very good partial response.

Within the decision tree (see **Section 4.2.1.1**), the number of deaths in each cycle was dependent on treatment (as reported in the ANDROMEDA trial), rather than on hematologic response. In contrast, OS in the Markov model was dictated by depth of hematologic response as a surrogate for OS, according to the KM curves published by Kastritis *et al*., (2020) (71). That is, OS is dependent on the survival curves stratified by CR, VGPR, and PR/NR regardless of which treatment regimen patients receive. Therefore, the distribution of hematologic response achieved at the end of the decision tree was assumed to predict treatment-specific OS over time. This assumption is supported by the wealth of evidence supporting the relationship between depth of hematologic response and improved OS (21, 32, 33, 62, 68-70, 72-74, 76, 84, 85), and is aligned with the goal of AL amyloidosis treatment to achieve the best hematologic response possible (66).

Overall Survival for 3-month PR/NR:

After digitizing and extrapolating the PR and NR KM curves based on the reconstructed pseudo-IPD from Kastritis *et al*., (2020) (71), the curves were visually assessed. The PR KM curve and its associated curve extrapolations are presented in **Figure 4.2** and the survival rate over time for patients with PR is presented in **Table 4.7**. The NR KM curve and its associated extrapolations are presented in **Figure 4.3** and the survival rate over time for patients with NR is presented in **Table 4.8**. All curves were shown to appropriately fit the PR and NR KM data, but the Exponential, Weibull, and Gamma extrapolations appeared most clinically plausible and were further considered for the main analysis.

According to ANDROMEDA IPD (18-month landmark analysis; May 2021; median follow-up 25.8 months, data on file) (98), patients that achieve PR comprise [redacted]% of all patients that are PR or NR at the three-month landmark irrespective of treatment arm. Because patients with PR represented a larger proportion of the weighting applied in generating the blended PR/NR curve in the main analysis, AIC and BIC values for the PR curve were used to determine which parametric survival function should be used for the blended PR/NR curve. According to AIC and BIC (**Table 4.6**), the Weibull parametric survival function was the best statistical fit and was therefore selected for the main analysis. Of note, the Weibull survival function was also clinically plausible and a good visual fit to the NR KM curve.

The proportion of patients in PR and NR at three months, as reported in the ANDROMEDA trial, was used to apply weighting to the blended PR/NR OS curve to reflect the patient population of suboptimal responders (78). The PR and NR KM curves along with their respective blended PR/NR survival curve extrapolations are depicted in **Figure 4.4**. Using the next best fitting curve (Gamma function) to generate the blended PR/NR curve was explored in scenario analyses (**Section 5.1.2.2.2).**

Figure 4.2. OS curve extrapolations for patients with PR from Kastritis et al., (2020)

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

Table 4.7. Survival rate over time for patients with PR

Time Point (Month)	Survival Rate	At Risk*	Number of Events	Censoring Number**
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	NR
[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]	[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]	[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]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	

*Only the starting number at risk was reported by Kastritis *et al*., (2020) (71); all remaining numbers at risk were generated by creating pseudo-IPD during the curve extrapolation process according to the methods described by Guyot *et al*., (2012) (122).

**Because pseudo-IPD was used in the curve extrapolation process, the number of censors is not available.

Abbreviations: IPD = individual patient data; NR = not reported.

Figure 4.3. OS curve extrapolations for patients with NR from Kastritis et al., (2020) (71)

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

Table 4.8. Survival rate over time for patients with NR

Time Point (Month)	Survival Rate	At Risk*	Number of Events	Censoring Number**
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	NR
[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]	[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]	
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[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	

*Only the starting number at risk was reported by Kastritis *et al*., (2020) (71); all remaining numbers at risk were generated by creating pseudo-IPD during the curve extrapolation process according to the methods described by Guyot *et al*., (2012) (122).

**Because pseudo-IPD was used in the curve extrapolation process, the number of censors is not available.

Abbreviations: IPD = individual patient data; NR = not reported.

Figure 4.4. Blended PR and NR OS curve extrapolations

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

Overall Survival for 3-month CR and VGPR

In the model, OS for patients with CR or VGPR was generated by extrapolating individual KM curves as opposed to using HRs since the proportional hazards assumption was violated based on the log-cumulative hazards for CR vs PR and NR (see **Appendix D**). After digitizing and extrapolating the CR and VGPR curves from Kastritis *et al*., (2020) (71), the curves were assessed for visual and statistical fit to the CR and VGPR KM data. The KM curves with their associated extrapolations using all seven parametric survival functions for patients with CR and VGPR are presented in **Figure 4.5** and **Figure 4.6**, respectively. The survival rate over time for patients with CR and VGPR are presented below in **Table 4.9** and **Table 4.10**, respectively.

For CR, the Exponential function was selected for the main analysis since it appeared clinically plausible and was the curve of best-fit according to visual assessment and AIC/BIC (**Table 4.6**). For VGPR, the Log-logistic extrapolation appeared realistic and clinically plausible and was the curve of best-fit according to AIC/BIC (**Table 4.6**) and was therefore selected for the main analysis. Using the next best-fitting curves for CR (Weibull function) and VGPR (Gamma function) were explored in scenario analyses (**Section 5.1.2.2.2).**

Figure 4.5. OS curve extrapolations for patients with CR from Kastritis et al., (2020) (71)

Abbreviations: CR = complete response; KM = Kaplan-Meier; OS = overall survival.

Table 4.9. Survival rate over time for patients with CR

Time Point (Month)	Survival Rate	At Risk*	Number of Events	Censoring Number**
[redacted]	[redacted]	[redacted]	[redacted]	NR
[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]	
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[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	

*Only the starting number at risk was reported by Kastritis *et al*., (2020) (71); all remaining numbers at risk were generated by creating pseudo-IPD during the curve extrapolation process according to the methods described by Guyot *et al*., (2012) (122).

**Because pseudo-IPD was used in the curve extrapolation process, the number of censors is not available.

Abbreviations: IPD = individual patient data; NR = not reported.

Figure 4.6. OS curve extrapolations for patients with VGPR from Kastritis et al., (2020) (71)

Abbreviations: KM = Kaplan-Meier; OS = overall survival; VGPR = very good partial response.

Table 4.10. Survival rate over time for patients with VGPR

Time Point (Month)	Survival Rate	At Risk*	Number of Events	Censoring Number**
[redacted]	[redacted]	[redacted]	[redacted]	NR
[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]	[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]	[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]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	

*Only the starting number at risk was reported by Kastritis *et al*., (2020) (71); all remaining numbers at risk were generated by creating pseudo-IPD during the curve extrapolation process according to the methods described by Guyot *et al*., (2012) (122).

**Because pseudo-IPD was used in the curve extrapolation process, the number of censors is not available.

Abbreviations: IPD = individual patient data; NR = not reported.

4.2.1.3 Mortality Distribution

Within the Markov model, the extrapolated OS curves were used to determine the transitions to death (ie, the number of patients who died between cycles *n* and *n+1*). The number of patients alive in each health state per cycle was determined using both mortality distribution and transition probabilities.

The probability of survival determined the number of deaths per cycle, but not which health states those deaths came from. Instead of assuming an equal risk of death across health states, the state-specific probabilities of mortality from the trial were used. In addition, because early, sudden deaths (while on treatment) are possible in patients with AL amyloidosis, two different mortality distributions were considered in the model to account for the potential change in early vs. long-term health state-specific probabilities of mortality. All deaths that occurred over the trial period (during the first 6-months and from post-6-

months to end of follow-up) were reviewed in the patient-level data to see which health state the patient was in before they died.

The number of patients that died during each cycle were removed from specific health states according to their respective mortality distribution (**Table 4.11** and **Table 4.12**). Appropriately removing "dead" patients in cycle *n* was necessary to avoid overestimating the number of patients who would be transitioning into cycle *n+1*. According to ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95), the majority of early deaths occurred while patients were in the '1L Tx' health state (**Table 4.11**). 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 (77, 123). In cycles seven and beyond (**Table 4.12**), ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95) indicated that the majority of deaths occurred in the 'End-stage Organ Failure' health state. 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 then the remainder would be taken out of the health state with the highest number of patients. The remaining alive patients in each cycle were distributed amongst the various health states according to their respective transition probabilities.

Table 4.11. Mortality distribution by health state for cycles four to six

Health State	Deaths by Health State (%)
1L Tx	[redacted]
Off Tx/FDT	[redacted]
2L Tx	[redacted]
End-stage Organ Failure	[redacted]
Total	100%

Abbreviations: 1L = first-line; 2L = second-line; FDT = fixed daratumumab treatment; Tx = treatment.

Source: ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

Table 4.12. Mortality distribution by health state for cycles seven and beyond

Health State	Deaths by Health State (%)
1L Tx	[redacted]
Off Tx/FDT	[redacted]
2L Tx	[redacted]
End-stage Organ Failure	[redacted]
Total	100%

Abbreviations: 1L = first-line; 2L = second-line; FDT = fixed daratumumab treatment; Tx = treatment.

Source: ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

4.2.1.4 Health State Transition Probabilities

Calculation of Health State Transition Probabilities to End-stage Organ Failure

Transition probability matrices were used to estimate the number of alive patients that would progress to another health state (except death) in the Markov model. In the main analysis, the transition probabilities between the Markov model health states (ie, the health states in the orange box as shown in the model structure diagram in **Figure 4.1**) varied by hematologic response but were assumed to be the same between treatment groups; that is, hematologic response drives the progression to other health states rather than being directly impacted by the treatment received. These transition probabilities were generated using pooled patient-level data for DCyBorD and CyBorD for the MOD-PFS and time-to-subsequent-therapy outcomes from the ANDROMEDA

trial and are described further below. Given the current data availability from the trial, constant transition probabilities were used.

The transition probability to 'End-stage Organ Failure' was generated using ANDROMEDA IPD pertaining to time-to-MOD-PFS (which included hematologic progression and major organ deterioration events but excluded deaths according to the primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95) stratified by hematologic response irrespective of treatment arm (note that the stratification of hematologic response was based on the 3-month timepoint due to larger sample size for generating the curves). Since extrapolation would be highly uncertain due to the lack of long-term events, constant hazard rates were instead calculated from the curves (**Figure 4.7**) and converted to a per-cycle probability. The monthly probability for MOD-PFS stratified by hematologic response is presented in **Table 4.13** and the MOD-PFS rate over time for patients with CR, VGPR, and PR/NR is presented in **Appendix F**.

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 (**Table 4.13**). Owing to some unrealistic values for patients on second-line therapy (eg, no MOD-PFS events occurred for patients with VGPR), a simplifying (and likely 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 hematologic responses (**Table 4.13**).

Ideally, the transition probabilities 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 (excluding death) was used to allow for sufficiently robust re-analyses. 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.

Figure 4.7. Time-to-MOD-PFS (excluding death) by 3-month hematologic response ([redacted])

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

Source: ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file).

Table 4.13. Values informing transition probabilities to 'End-stage Organ Failure'

Hematologic Response	CR	VGPR	PR/NR
Monthly Probability of MOD-PFS (a)	[redacted]	[redacted]	[redacted]
Distribution of '1L Tx' MOD-PFS Events (b)	[redacted]	[redacted]	[redacted]
Calculated Transition Probability '1L Tx' to 'End-Stage Organ Failure' (a x b)	[redacted]	[redacted]	[redacted]
Distribution of 'Off Tx/FDT' MOD-PFS Events (c)	[redacted]	[redacted]	[redacted]
Calculated Transition Probability 'Off Tx/FDT' to 'End-Stage Organ Failure' (a x c)	[redacted]	[redacted]	[redacted]
Transition Probability '2L Tx' to 'End-stage Organ Failure' (a x b)*	[redacted]	[redacted]	[redacted]

*Due to a limited number of MOD-PFS events reported, 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; CR = complete response; FDT = fixed daratumumab treatment; MOD-PFS = major organ deterioration progression-free survival; NR = no response; PR = partial response; Tx = treatment; VGPR = very good partial response.

Source: ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file).

Calculation of Health State Transition Probabilities to Second-line Therapy

All patients in PR/NR would transition directly to the '2L Tx' state from the decision tree, but the transition probabilities for CR and VGPR patients from 'Off

Tx/FDT' to '2L Tx' were generated using the time to subsequent therapy curves from ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months, data on file) stratified by 3-month CR or VGPR hematologic responses (**Figure 4.8**). Since extrapolation would be highly uncertain due to the lack of long-term events (particularly in the CR curve), a constant hazard rate was instead calculated from the time to subsequent therapy curves for CR and VGPR and then converted to a per-cycle probability. The per-cycle transition probabilities from 'Off Tx/FDT' to '2L Tx' were [redacted]% for CR and [redacted]% for VGPR. The subsequent therapy rate over time for patients with CR and VGPR is presented in **Appendix G**.

Figure 4.8. Time to subsequent therapy stratified by 3-month hematologic response ([redacted])

Abbreviations: CR = complete response; VGPR = very good partial response.

Source: ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months, data on file) (124).

Transition Probabilities for Cycles Four to Six

With a three-month exit from the decision tree (as in the main analysis), the health state transition probabilities applicable to cycles four to six differ from those applied in cycles seven and beyond for CR and VGPR patients in the '1L

Tx' health state. This is due to the fact that, within cycles four to six, CR and VGPR patients do not yet transition from '1L Tx' to 'Off Tx/FDT' (hence, [redacted]% transition probability from '1L Tx' to 'Off Tx/FDT' for cycles 4-6); this transition occurs only after patients have received the maximum six cycles of therapy (see below for transition probabilities in cycles 7+). A summary of transition probabilities for CR, VGPR, and PR/NR are presented in **Table 4.14**, **Table 4.15**, and **Table 4.16**, respectively.

Table 4.14. CR transition probabilities for cycles 4-6 (DCyBorD and CyBorD)

		To				
		1L Tx	Off Tx/FDT	2L Tx	End-stage Organ Failure	Total
From	1L Tx	[redacted]	[redacted]	-	[redacted]	[redacted]
	Off Tx/FDT	-	[redacted]	[redacted]	[redacted]	[redacted]
	2L Tx	-	-	[redacted]	[redacted]	[redacted]
	End-stage Organ Failure	-	-	-	[redacted]	[redacted]

Abbreviations: 1L = first-line; 2L = second-line; CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; FDT = fixed daratumumab treatment; Tx = treatment.

Table 4.15. VGPR transition probabilities for cycles 4-6 (DCyBorD and CyBorD)

		To				
		1L Tx	Off Tx/FDT	2L Tx	End-stage Organ Failure	Total
From	1L Tx	[redacted]	[redacted]	-	[redacted]	[redacted]
	Off Tx/FDT	-	[redacted]	[redacted]	[redacted]	[redacted]
	2L Tx	-	-	[redacted]	[redacted]	[redacted]
	End-stage Organ Failure	-	-	-	[redacted]	[redacted]

Abbreviations: 1L = first-line; 2L = second-line; CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; FDT = fixed daratumumab treatment; Tx = treatment.

Table 4.16. PR/NR transition probabilities for cycles 4-6 (DCyBorD and CyBorD)

		To				
		1L Tx	Off Tx/FDT	2L Tx	End-stage Organ Failure	Total
From	1L Tx	[redacted]	-	[redacted]	[redacted]	[redacted]
	Off Tx/FDT	-	-	-	-	-
	2L Tx	-	-	[redacted]	[redacted]	[redacted]
	End-stage Organ Failure	-	-	-	[redacted]	[redacted]

Abbreviations: 1L = first-line; 2L = second-line; CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab,

cyclophosphamide, bortezomib, dexamethasone; FDT = fixed daratumumab treatment; Tx = treatment.

Transition Probabilities for Cycles Seven and Beyond

A summary of transition probabilities for patients with CR, VGPR, and PR/NR utilized in cycle seven and beyond is presented in **Table 4.17**, **Table 4.18**, and **Table 4.19,** respectively.

Table 4.17. CR transition probabilities for cycles 7+ (DCyBorD and CyBorD)

		To				
		1L Tx	Off Tx/FDT	2L Tx	End-stage Organ Failure	Total
From	1L Tx	[redacted]	[redacted]	-	[redacted]	[redacted]
	Off Tx/FDT	-	[redacted]	[redacted]	[redacted]	[redacted]
	2L Tx	-	-	[redacted]	[redacted]	[redacted]
	End-stage Organ Failure	-	-	-	[redacted]	[redacted]

Abbreviations: 1L = first-line; 2L = second-line; CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; FDT = fixed daratumumab treatment; Tx = treatment.

Table 4.18. VGPR transition probabilities for cycles 7+ (DCyBorD and CyBorD)

		To				
		1L Tx	Off Tx/FDT	2L Tx	End-stage Organ Failure	Total
From	1L Tx	[redacted]	[redacted]	-	[redacted]	[redacted]
	Off Tx/FDT	-	[redacted]	[redacted]	[redacted]	[redacted]
	2L Tx	-	-	[redacted]	[redacted]	[redacted]
	End-stage Organ Failure	-	-	-	[redacted]	[redacted]

Abbreviations: 1L = first-line; 2L = second-line; CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; FDT = fixed daratumumab treatment; Tx = treatment.

Table 4.19. PR/NR transition probabilities for cycles 7+ (DCyBorD and CyBorD)

		To				
		1L Tx	Off Tx/FDT	2L Tx	End-stage Organ Failure	Total
From	1L Tx	[redacted]	-	[redacted]	[redacted]	[redacted]
	Off Tx/FDT	-	-	-	-	-
	2L Tx	-	-	[redacted]	[redacted]	[redacted]
	End-stage Organ Failure	-	-	-	[redacted]	[redacted]

Abbreviations: 1L = first-line; 2L = second-line; CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab,

cyclophosphamide, bortezomib, dexamethasone; FDT = fixed daratumumab treatment; Tx = treatment.

4.2.2 Safety Parameters

The safety data source that informed the model was the ANDROMEDA trial (see **Section 1.7**). As AEs can have a meaningful impact on both the cost of treatment and quality of life, the CUA model included grade 3 or 4 AEs occurring in 5% or more patients in any treatment arm in the ANDROMEDA trial per the 18-month landmark analysis (May 2021; median follow-up 25.8 months, data on file) (98). **Table 4.20** summarizes the AEs included in the model and the percentage of patients experiencing each AE in each treatment arm.

Table 4.20. Percentage of patients experiencing common (occurring at ≥5% frequency) grade ≥3 adverse events

Adverse Event	DCyBorD	CyBorD
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: CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone;
Source: ANDROMEDA 18-month landmark analysis (May 2021; median follow-up: 25.8 months, data on file) (98).

4.2.3 Details of QOL values

An SLR was conducted in January 2022 (see **Section 3**) with the intention of identifying any sources reporting HRQoL values for subjects being treated with DCyBorD for newly diagnosed AL amyloidosis. However, only the ANDROMEDA trial was identified in the SLR. The ANDROMEDA clinical trial collected patient-reported outcomes (PROs), including the EuroQol-5 dimension-5 level (EQ-5D-5L) instrument, the short-form 36 (SF-36) questionnaire, and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30). An additional targeted literature search was performed to identify utility values related to other proxy malignancies, organ failure, and/or chemotherapy treatment. This targeted search was successful in identifying utility values that were not available in ANDROMEDA. Therefore, EuroQol-5-dimension (EQ-5D) utility values in the model were sourced from both ANDROMEDA and published literature sources. A summary of utility values included in the model are presented in **Sections 4.2.3.1**, **4.2.3.2**, **4.2.3.3**, and **4.2.3.4**. The model also includes the option for incorporating age-adjusted utility values as a baseline value in the calculation of QALYs according to the methods of Ara and Brazier (2010) (125); however, age-adjusted utility values were not implemented in the main analysis.

Table 4.21. Summary of utility values used in model

Variable Name	Country of Measurement	Details of Measured Population	Scale used	Number of measures	Reference
Patients with CR	Global	Utility value from patients that achieve hematologic CR at any timepoint in ANDROMEDA (with Japan-specific utility weights applied).	EQ-5D-5L (VAS)	[redacted]	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95); see **Section 4.2.3.1**.
Patients with VGPR	Global	Utility value from patients that achieve hematologic VGPR at any timepoint in ANDROMEDA (with Japan-specific utility weights applied).	EQ-5D-5L (VAS)	[redacted]	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95); see **Section 4.2.3.1**.
Patients with PR or NR	Global	Utility value from patients that achieve hematologic PR/NR at	EQ-5D-5L (VAS)	[redacted]	ANDROMEDA IPD (primary analysis;

		any timepoint in ANDROMEDA (with Japan-specific utility weights applied).			February 2020; median follow-up: 11.4 months, data on file) (95); see **Section 4.2.3.1**.
'2L Tx' health state	Global	Calculated by subtracting the individual mean utility values before reaching a progressed disease state from the mean utility value once disease progression has occurred based on ANDROMEDA IPD (with Japan-specific utility weights applied).	EQ-5D-5L (VAS)	[redacted]	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95); see **Section 4.2.3.3**.
'End-stage organ failure' health state	UK	Calculated as the difference between the baseline utility value for all ANDROMEDA patients and the utility value from patients with advanced chronic heart failure listed for heart transplant per Emin *et*	EQ-5D (VAS)	[redacted]	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95); Emin *et al*., (2016) (118); see

		al., (2016) (118).			**Section 4.2.3.3**.
Patients receiving hemodialysis	Various*	Utility decrement from a published SLR of utility-based HRQoL in chronic kidney disease treatments. Calculated as the difference between patients with chronic kidney disease pre-hemodialysis and after commencing hemodialysis.	SF-36 and SF-12 used to calculate EQ-5D	N=207**	Wyld *et al*., (2012) (119); see **Section 4.2.3.4**.
Lymphopenia (AE Disutility)	N/A	Assumed to be equivalent to that of neutropenia.	N/A[c]	N/A†	Disutility: assumed equal to neutropenia Duration of AE: assumed equal to neutropenia; See **Section 4.2.3.2**.
Neutropenia (AE Disutility)	UK (decrement) Japan	Utility decrement from a published study reporting health state utility values for	SG	N=100	Disutility: Nafees *et al*., (2008) (106) Duration of AE:

	(duration)	patients receiving treatment for non-small cell lung cancer. Duration of decrement sourced from published study on Japanese patients receiving treatment for neuropathic pain.			Onouchi *et al*., (2014) (107); See **Section 4.2.3.2**.
Pneumonia (AE Disutility)	UK (decrement) Japan (duration)	Utility decrement from a published study reporting utility values for patients receiving treatment for chronic lymphocytic leukemia. Duration of decrement sourced from published study on healthcare-associated pneumonia.	SG	N=89	Disutility: Beusterien *et al*., (2010) (108); Duration of AE: Ishida *et al*., (2012) (109); See **Section 4.2.3.2**.
Diarrhoea (AE Disutility)	USA (decrement) Japan (duration)	Utility decrement from a published study reporting utility values for patients receiving treatment for acute myeloid leukemia.	DCE	N=300	Disutility: Stein *et al*., (2018) (110); Duration of AE: Shiroiwa *et al*., (2009) (111);

		Duration of decrement sourced from published cost-effectiveness study on the treatment of colon cancer.			See **Section 4.2.3.2**.
Edema (AE Disutility)	UK (decrement) Japan (duration)	Utility decrement from a published study reporting utility values for patients receiving treatment for advanced breast cancer. Duration of decrement sourced from published study on patients receiving treatment for secondary lower limb lymphedema.	SG	N=30	Disutility: Brown *et al*., (2001) (112); Duration of AE: Saito *et al*., (2014) (113); See **Section 4.2.3.2**.
Hypokalemia (AE Disutility)	UK (decrement) Japan (duration)	Utility decrement from a published catalogue of EQ-5D scores including a wide variety of chronic conditions. Duration of decrement sourced from published study on patients receiving treatment	EQ-5D	N=1,037	Disutility: Sullivan *et al*., (2011) (114) Duration of AE: Usami *et al*., (2014) (103); See **Section 4.2.3.2**.

		with liposomal-amphotericin B.			
Syncope (AE Disutility)	UK (decrement) Japan (duration)	Utility decrement from a published catalogue of EQ-5D scores including a wide variety of chronic conditions. Duration of decrement sourced from published case report of a patient with syncope resulting from atrioventricular block.	EQ-5D	N=183	Disutility: Sullivan *et al*., (2011) (114); Duration of AE: Akashi *et al*., (2012) (104); See **Section 4.2.3.2**.
Cardiac failure (AE Disutility)	UK (decrement) Japan (duration)	Utility decrement from a published catalogue of EQ-5D scores including a wide variety of chronic conditions. Duration of decrement sourced from published cost-effectiveness study on transcatheter aortic valve implantation.	EQ-5D	N=590	Disutility: Sullivan *et al*., (2011) (114); Duration of AE: Inoue *et al*., (2020) (102); See **Section 4.2.3.2**.

* This study was a systematic review and meta-analysis; therefore, no specific country is associated with the utility value reported.

** The 207 utility estimates reported for this study included a combination of hemodialysis and peritoneal dialysis; however, the utility value

used in the model was specific to hemodialysis.

† Disutility values for lymphopenia were assumed to be equal to those for neutropenia.

Abbreviations: AE = adverse event; CR = complete response; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCE = discrete choice experiment; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; EQ-5D = EuroQol-5 Dimension questionnaire; EQ-5D-5L = EuroQol-5 Dimension-5 Level questionnaire; HRQoL = health-related quality of life; SF-12 = short-form 12 health survey; SF-36 = short-form 36 health survey; SG = standard gamble; TEAE = treatment emergent adverse event; UK = United Kingdom; USA = United States of America; VAS = visual analog scale; VGPR = very good partial response.

4.2.3.1 Hematologic Response Health State Utility Values from ANDROMEDA

Hematologic response state utility values used in the model were based on the EQ-5D-5L data collected in the ANDROMEDA trial (pooled treatment data). The EQ-5D-5L values used in the main analysis were calculated using Japan-specific utility weights (95). Because the mean utility value for VGPR ([redacted]) did not meet initial face validity (ie, was lower than the value for PR), a more clinically plausible VGPR utility value was calculated as the mean of CR and PR utility values for use in the model. The mean hematologic response-specific utility values used in the model are presented in **Table 4.22**. Notably, when compared to Japanese EQ-5D-5L population norms (126) the utility values used in the model meet face validity; that is, the utility values of patients with AL amyloidosis (in the model) never exceed the mean Japanese EQ-5D-5L population norms for any age group.

Table 4.22. ANDROMEDA utility values by hematologic response

Hematologic Response	Utility Value*
CR	[redacted]
VGPR	[redacted]
PR/NR	[redacted]

* Determined using Japan-specific utility weights.

** VGPR utility value was calculated as the mean of CR and PR.

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

Source: ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

4.2.3.2 Utility Decrements for Adverse Events

Health state utility values in the model were the same regardless of treatment, but disutilities associated with AEs were included to distinguish between patients receiving DCyBorD and CyBorD. Utility decrements associated with all grade ≥3 AEs that occurred in at least 5% of patients in either treatment arm were included in the main analysis. Disutilities associated with treatment-related AEs in AL amyloidosis were not identified in the SLR. As such, a broad 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 and Japanese data sources were used wherever possible.

The AE disutility value and the length of its application (duration of each grade ≥3 AE) were used to calculate the average QALY lost per event. The average QALY lost per event and the proportion of patients experiencing the respective AEs was then used to calculate the average QALY lost per patient (**Table 4.23**). The total QALYs lost per treatment arm (**Table 4.23**) was calculated as a sum of the average QALYs lost per patient and was applied in cycle one to all patients in each treatment arm (aligns with how AE costs were also applied). 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 4.23. Adverse event utility decrements and durations

AE	One-time Utility Decrement	Duration of Adverse Event (Days)	Average QALY Lost per Event*	Average QALY Lost per Patient		Data Source/Notes
				DCyBorD	CyBorD	
Cardiac failure	0.1034	30	0.008	0.0005	0.0002	Decrement: Sullivan *et al.*, (2011) (114). Duration: Inoue *et al.*, (2020) (102).
Diarrhoea	0.176	12	0.006	0.0003	0.0002	Decrement: Stein *et al.*, (2008) (110). Duration: Shiroiwa *et al.*, (2009) (111).
Edema	0.06	7	0.001	0.00004	0.0001	Decrement: Brown *et al.*, (2001) (112). Duration: Saito *et al.*, (2014) (113).
Hypokalemia	0.02	14.4	0.001	0.00002	0.00004	Decrement: Sullivan *et al.*,

						(2011) (114). Duration: Usami *et al.,* (2014) (103).
Lymphopenia	0.09	8	0.002	0.0003	0.0002	Decrement: Assumed same decrement as neutropenia (106). Duration: Onouchi *et al.,* (2014) (107).
Neutropenia	0.09	8	0.002	0.0001	0.0001	Decrement: Nafees *et al*., (2008) (106). Duration: Onouchi *et al.,* (2014) (107).
Pneumonia	0.2	15	0.008	0.0007	0.0004	Decrement: Beusterien *et al*., (2010) (108). Duration: Ishida *et al.,* (2012) (109).
Syncope	0.0039	20	0.0002	0.00001	0.00001	Decrement: Sullivan *et al*., (2011) (114). Duration: Akashi *et al.,*

						(2012) (104).

* The AE disutility value and the length of its application were used to calculate the average QALY lost per event (eg, for cardiac failure, average QALY lost per event = 0.1034 x (30/365 year) ≈ 0.008). It was assumed that the duration of grade ≥3 AEs would not last an entire cycle.

Abbreviations: AE = adverse event; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; QALY = quality adjusted life-year.

Table 4.24. Total adverse event disutilities by treatment arm

Drug Regimen	Mean Total AE Disutility per Patient
DCyBorD	0.0020
CyBorD	0.0012

Abbreviations: AE = adverse event; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone.

4.2.3.3 Utility Decrements for Progression Health States

Utility decrements for '2L Tx' and 'End-stage Organ Failure' were applied on a recurring per-cycle basis for as long as the patient remains within the respective health state. The '2L Tx' utility decrement was calculated by subtracting the individual mean utility values *before* reaching a progressed disease state from the mean utility value once disease progression has occurred based on ANDROMEDA IPD with Japan-specific utility weights applied (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

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 study on HRQoL for patients with advanced chronic heart failure was used to calculate this utility value (118). In this study, a utility value of 0.5 was reported for patients with chronic heart failure that had been assessed for heart transplant (118). According to ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file), the mean baseline utility value (with Japan-specific utility weights applied) was [redacted] (95). The difference between the baseline ANDROMEDA utility value and the utility value reported by Emin *et al*., (2016) was utilized in the model to inform the utility decrement for patients in the 'End-stage Organ Failure' health state (ie, [redacted]). A summary of progression-related health state utility values used in the model is presented in **Table 4.25**.

Table 4.25. Summary of progression-related health state utility decrements

Health State	Recurring Utility Decrement	Source
2L Tx	[redacted]	ANDROMEDA IPD with Japan-specific utility weight applied (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
End-stage Organ Failure	[redacted]	Emin *et al.*, (2016) (118) and ANDROMEDA IPD with Japan-specific utility weight applied (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

Abbreviations: 2L = second-line; IPD = individual participant data; Tx = treatment.

4.2.3.4 Utility Decrements for End-stage Organ Failure Events

Patients in the 'End-stage Organ Failure' state would experience hemodialysis, but solid organ transplant was excluded from the main analysis (see **Section 4.2.4.5**). Since hemodialysis is a recurring treatment, its associated utility decrement is applied on a per-cycle basis to the proportion of patients requiring the intervention (see **Section 4.2.4.5**).

The decrement associated with hemodialysis (0.1) was sourced from a published SLR of utility-based HRQoL in chronic kidney disease treatments. According to this study, the utility value for patients on hemodialysis was 0.69, which represented a decrement of 0.1 compared to those with chronic kidney disease pre-hemodialysis (119). A summary of end-stage organ failure utility decrements applied in the model is presented in **Table 4.26**.

Table 4.26. Summary of end-stage organ failure utility decrements

Intervention	Utility Decrement	Source
Hemodialysis (recurring)	0.1	Wyld *et al.*, (2012) (119).

4.2.4 Details of cost parameters

All costs used in the model reflect current (2022) Japanese values or, where applicable, were inflated to 2022 Japanese Yen using the Japanese Consumer Price Index for medical care (42).

4.2.4.1 First-line Drug Therapy Costs

4.2.4.1.1 First-line Drug Acquisition Costs

Table 4.27 provides the drug formulations and unit costs for each therapy. Drug costs were obtained from the Japan MHLW NHI Price List (99).

Table 4.27. Drug acquisition costs

Treatment	Unit Strength	Unit Type	Units per Pack	Price per Pack	Price per Unit	Source
Daratumumab	1,800 mg	Vial	1	¥ 445,064.00	¥ 445,064.00	NHI Price List, (2022) (99)
Cyclophosphamide	50 mg	Tab	100	¥ 2,590.00	¥ 25.90	
Bortezomib	3 mg	Vial	1	¥ 38,694.00	¥ 38,694.00	
Dexamethasone	4 mg	Tab	100	¥ 2,870.00	¥ 28.70.00	

Abbreviations: mg = milligram; MHLW = Ministry of Health, Labour, and Welfare; Tab = tablet.

The general dosing schedule for each therapy, according to the ANDROMEDA trial protocol, is summarized in **Table 4.28**.

Table 4.28. Drug dosing schedules per ANDROMEDA

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
Cyclophosphamide	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles
Bortezomib	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

Source: ANDROMEDA Protocol (24).

Relative dose intensities (RDIs) and drug wastage were considered in the cost calculations. RDIs were applied in calculating total per cycle drug costs. The mean RDIs for each drug regimen, as reported in the ANDROMEDA CSR, are presented in **Table 4.29**. Drug wastage was assumed to occur for all 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 based on current clinical practice in Japan. Vials were assumed to be one-time use only in accordance with the drug PI and local clinical practice. Therefore, it was assumed that vial sharing was not permitted, and the drug dosing calculations included wastage.

Table 4.29. Mean relative dose intensities (RDI)

Drug Regimen	RDI
DCyBorD	Daratumumab: [redacted] Cyclophosphamide: [redacted] Bortezomib: [redacted] Dexamethasone: [redacted]
CyBorD	Cyclophosphamide: [redacted] Bortezomib: [redacted] Dexamethasone: [redacted]

Abbreviations: CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; RDI = relative dose intensity.

Source: ANDROMEDA CSR (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (78).

Table 4.30 presents the calculated costs per dose and per cycle as used in the main analysis. Three different DCyBorD drug acquisition costs are presented because the number of daratumumab administrations differs depending on the treatment cycle (see **Table 4.28**).

First-line drug acquisition costs for bortezomib and cyclophosphamide were calculated based on the mean patient BSA ([redacted] m^2) as reported in the ANDROMEDA Asian sub-population. 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 (24).

Table 4.30. Drug costs per cycle

Treatment	Cost per Cycle
DCyBorD (Cycles 1-2)	¥ 1,937,112.40
DCyBorD (Cycles 3-6)	¥ 1,046,984.40

DCyBorD (Cycles 7+)	¥ 445,064.00
CyBorD	¥ 156,856.40

Abbreviations: CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone.

4.2.4.1.2 First-line Drug Administration Costs

In the CUA, the route of drug administration (ie, SC or oral [PO]) mirrored those outlined in the ANDROMEDA clinical trial protocol (24). Treatments administered SC were assumed to require an outpatient visit per the ANDROMEDA protocol (24).

The SC administration cost was ¥220.00 per the Japan MHLW Medical Fee Schedule (code G000) (101). Oral drugs were assumed to be administered at home and therefore only included a per-cycle pharmacy dispensing fee of ¥680 (code F400-3) in the administration cost (101). A summary of drug administration costs included in the model is presented in **Table 4.31**.

Table 4.31. First-line drug administration unit costs

Type of Administration	Unit Cost
SC	¥220
PO	¥680

Abbreviations: PO = oral; SC = subcutaneous.

Sources: Japan MHLW Medical Fee Schedule (Intradermal, subcutaneous and intramuscular injection [per injection], code: G000); dispensing fee (code F400-3) (101).

A summary of the per-cycle first-line drug administration costs is presented in **Table 4.32**. Similar to first-line drug acquisition costs (**Table 4.30**), the cost of DCyBorD administration depends on the cycle (see **Table 4.28**).

Table 4.32. First-line drug administration costs per cycle

Drug Regimen	Cost per Cycle
DCyBorD (Cycles 1-2)	¥ 3,120.00
DCyBorD (Cycles 3-6)	¥ 2,680.00
DCyBorD (Cycles 7+)	¥ 220.00
CyBorD	¥ 2,240.00

Abbreviations: CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone.

4.2.4.1.3 First-line Co-medication Costs

The model included pre- and post-treatment medications for both DCyBorD and CyBorD regimens. Concomitant medications for each comparator were sourced from the ANDROMEDA clinical trial protocol (24). Only the additional medications that were recommended or required for all patients on a therapy were included. Co-medications for each drug therapy included in the CUA, and their respective administration frequencies, are presented in **Table 4.33**. The unit costs for co-medications were sourced from the Japan MHLW NHI Price List (99) and are presented in **Table 4.34**. 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. A per-cycle summary of first-line co-medications for DCyBorD and CyBorD is presented in **Table 4.35**.

Table 4.33. First-line co-medications per drug regimen

Co-medication	Proportion of Patients Receiving Co-medication	Dose (mg)	Dose Frequency	Frequency Unit
DCyBorD				
Aciclovir	[redacted]	200	[redacted]	per Day

Diphenhydramine PO	[redacted]	25	[redacted]	per Daratumumab SC Administration
Dexamethasone PO	[redacted]	20	[redacted]*	per Entire Treatment Duration
Montelukast	[redacted]	10	[redacted]	per Entire Treatment Duration
Methylprednisolone PO	[redacted]	20	[redacted]	per Entire Treatment Duration
Paracetamol PO	[redacted]	650	[redacted]	per Daratumumab SC Administration
CyBorD				
Aciclovir	[redacted]	200	[redacted]	per Day

* 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 DCyBorD combination therapy (24). The dose frequency for dexamethasone represents one dose for each administration of daratumumab *monotherapy* (ie, cycle 7 and beyond).

** According to the ANDROMEDA clinical protocol, patients receiving daratumumab monotherapy after completing six cycles of DCyBorD will receive an oral long- or intermediate-acting corticosteroid (eg, methylprednisolone) on the two days following daratumumab administration (24). The frequency for methylprednisolone represents two doses for each administration of daratumumab *monotherapy* (ie, cycle 7 and beyond).

Abbreviations: CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; mg = milligrams; PO = oral; SC = subcutaneous.

Sources: ANDROMEDA trial protocol (24); ANDROMEDA CSR (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (78).

Table 4.34. First-line co-medication unit costs

Co-medication	Drug Units per Pack	Strength (mg)	Cost per Pack	Source
Aciclovir	100	400	¥ 3,960.00	NHI Price List 2022 (99).
Diphenhydramine	500	10	¥ 2,950.00	
Dexamethasone	100	4	¥ 2,870.00	
Montelukast	100	10	¥ 1,990.00	
Methylprednisolone	100	4	¥ 1,350.00	
Paracetamol	100	500	¥ 760.00	

Abbreviations: mg = milligrams; MHLW = Ministry of Health, Labour and Welfare.

Table 4.35. First-line co-medication costs per cycle

Drug Regimen	Co-medication Cost per Cycle
DCyBorD	¥ 1,907.80
CyBorD	¥ 1,663.20

Abbreviations: CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone.

4.2.4.1.4 Summary of First-line Treatment Costs

The total first-line treatment cost was calculated by combining the first-line drug acquisition cost (see **Section 4.2.4.1.1**) with the treatment administration (see **Section 4.2.4.1.2**) and co-medication (see **Section 4.2.4.1.3**) costs. **Table 4.36** summarizes the total first-line treatment cost per cycle for each treatment arm.

Table 4.36. Summary of treatment costs per cycle

Cost Item	DCyBorD Cost	CyBorD Cost	Source/Notes
Drug Acquisition	Cycles 1-2: ¥ 1,937,112.40 Cycles 3-6: ¥ 1,046,984.40 Cycles 7+: ¥ 445,064.00	¥ 156,856.40	see **Section 4.2.4.1.1**
Treatment Administration	Cycles 1-2: ¥ 3,120.00 Cycles 3-6: ¥ 2,680.00 Cycles 7+: ¥ 220.00	¥ 2,240.00	see **Section 4.2.4.1.2**
Co-medications	¥ 1,907.80	¥ 1,663.20	see **Section 4.2.4.1.3**
Total Treatment Cost (per Cycle)	Cycles 1-2: ¥1,942,140.20 Cycles 3-6: ¥1,051,572.20 Cycles 7+: ¥447,191.8	¥160,759.60	-

Abbreviations: CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone.

4.2.4.1.5 First-line Treatment Exposure

In the model, first-line drug costs are based on two parameters: 1) the treatment duration (ie, number of treatment cycles) and 2) the percentage of patients receiving each treatment cycle over the treatment duration (ie, analogous to treatment discontinuation).

With respect to the treatment duration in the main analysis, all patients eligible for treatment were assumed to receive the maximum treatment duration (ie, 24 cycles for the DCyBorD arm and 6 cycles in the CyBorD arm). A summary of the treatment durations used in the main analysis is presented in **Table 4.37**.

Table 4.37. Treatment duration of DCyBorD and CyBorD used in the main analysis

Drug Regimen	Treatment Duration (Months)	Calculated Number of Cycles*
DCyBorD	24.00	24.00
CyBorD	6.00	6.00

* Per the ANDROMEDA protocol, the maximum number of cycles of treatment is 24.0 and 6.00 for subjects in the DCyBorD and CyBorD arms, respectively (24).

Abbreviations: CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone.

Source: ANDROMEDA protocol (24).

With respect to the percentage of patients remaining on first-line treatment over time (ie, "time on treatment)") in the main analysis, it is reasonable to expect that a proportion of pre-progression patients would discontinue treatment prior to completion of their anticipated treatment duration for various reasons (eg, toxicity, patient choice, etc.). Indeed, discontinuation was observed in the ANDROMEDA trial and is reflected in the ITT efficacy informing the model. Because this parameter only pertains to patients that achieve CR or VGPR, who are assumed to complete at least the full 6-courses of combination therapy (ie, DCyBorD), the proportion of alive patients who received each cycle of daratumumab monotherapy (from cycles 7-24) was informed by ANDROMEDA IPD by pooling data for patients achieving CR and VGPR after six cycles of therapy (18-month landmark analysis; May 2021; median follow-up: 25.8 months, data on file) (98). The proportion of patients in the DCyBorD arm remaining on treatment for cycles 7 and beyond is presented in **Table 4.38**. All patients in the CyBorD arm that achieved CR or VGPR were assumed to stay on treatment for the entirety of their treatment duration, up to a maximum of six

cycles. Because CyBorD is not administered beyond six cycles, time on treatment data do not apply after cycle 6.

Table 4.38. Proportion of patients in DCyBorD arm that received treatment up to 24 cycles

Cycle	1-6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Patients on Treatment (%)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* It is possible for the percentages to go up in subsequent cycles because each cycle is a "snapshot" of the number of patients who are alive and stay on drug. Taking cycles 19 and 20 as an example, these data should be interpreted as [redacted] of patients who are alive in model cycle 19 would receive and incur the cost of the 19th cycle of daratumumab monotherapy" and "[redacted]% of patients who are alive in model cycle 20 would receive and incur the cost of the 20th cycle of daratumumab monotherapy". It would be incorrect to interpret these data like a time-to-event curve where [redacted] of patients starting the drug at day 0 have remained on treatment at cycle 20".

Abbreviations: DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone.

Source: ANDROMEDA IPD (18-month landmark analysis; May 2021; median follow-up: 25.8 months, data on file) (98).

4.2.4.2 First-line Disease Monitoring Costs

Monitoring of treated patients included routine (or pre-planned) laboratory tests that occurred while a patient was in the '1L Tx' or 'Off Tx/FDT' health state. The frequency of routine disease monitoring varied depending on whether a patient was receiving drug therapy (DCyBorD or CyBorD), receiving daratumumab monotherapy (ie, FDT), or receiving no treatment (24). Specific tests and their associated frequencies for DCyBorD and for CyBorD were as outlined in the ANDROMEDA clinical trial protocol (24).

For patients in the '1L Tx' and 'Off Tx/FDT' health states (**Table 4.39** and **Table 4.40**), all routine disease monitoring items were applicable to 100% of the patient population except for hepatitis B virus (HBV; the proportion was based on the weighted mean percentage of patients with prior exposure to HBV per baseline serology as reported in the ANDROMEDA CSR (78). For patients that were off-treatment (ie, cycle 7+ in the CyBorD arm and patients in the DCyBorD arm post-daratumumab monotherapy), the frequency of routine disease monitoring was reduced compared to patients receiving daratumumab monotherapy for a fixed treatment duration (**Table 4.41)**. These patients did not undergo hematology or serum chemistry assessments or HBV deoxyribonucleic acid (DNA) tests. For all remaining routine disease monitoring items, the frequency of administration was the same as for patients treated with daratumumab monotherapy for a fixed treatment duration. Notably, routine physician visits to assess disease status were captured (along with incidental physician visits) on the 'Healthcare Resource Use' sheet (additional details provided in **Section 4.2.4.6**).

The unit cost for each routine disease monitoring item was sourced from the Japan Medical Fee Schedule (101). All unit costs are summarized in **Table 4.42**. The frequency of use for each resource (**Table 4.39**, **Table 4.40**, and **Table 4.41**) and the unit costs (**Table 4.42**) were used to calculate the total routine disease monitoring cost per cycle for each health state (**Table 4.43**).

Table 4.39. Frequency of resource use for routine disease monitoring ('1L Tx')

Item	Proportion of Patients Requiring Item	Item Frequency	Frequency Unit	Reference/Notes
Hematology Assessment	[redacted]	[redacted]	per Week	ANDROMEDA protocol (24).
Serum Chemistry Assessment	[redacted]	[redacted]	Every Other Week	ANDROMEDA protocol (24).
HBV DNA Test	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Troponin T Test	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Serum Disease Evaluation	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Urine Disease Evaluation	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Serum FLC Assessment	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
NT-proBNP Assay	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).

* Weighted mean percentage of patients with prior exposure to HBV per baseline serology as reported in the ANDROMEDA CSR (primary analysis; February 2020; median follow-up: 11.4 months) (78).

** Routine HBV DNA testing occurred every 12 weeks during treatment (24); a value of [redacted] per cycle was entered into the model to best represent 1 test per 12 weeks.

† Routine serum FLC testing occurred 4 times in cycle 1 and then once per cycle for cycles 2-6 (ie, total of 9 serum FLC tests while on treatment) (24); a value of [redacted] assessments per cycle was entered into the model to reflect 9 assessments over 6 cycles.

Abbreviations: DNA = deoxyribonucleic acid; FLC = free light-chains; HBV = Hepatitis B Virus; NT-proBNP = N-terminal prohormone brain natriuretic peptide.

Table 4.40. Frequency of resource use for routine disease monitoring ('FDT')

Item	Proportion of Patients Requiring Item	Item Frequency	Frequency Unit	Reference/Notes
Hematology Assessment	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Serum Chemistry Assessment	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
HBV DNA Test	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Troponin T Test	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Serum Disease	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).

Evaluation				
Urine Disease Evaluation	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Serum FLC Assessment	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
NT-proBNP Assay	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).

* Weighted mean percentage of patients with prior exposure to HBV per baseline serology as reported in the ANDROMEDA CSR (primary analysis; February 2020; median follow-up: 11.4 months) (78).

** Routine HBV DNA testing occurred every 12 weeks during treatment (24); a value of [redacted] per cycle was entered into the model to best represent 1 test per 12 weeks.

Abbreviations: DNA = deoxyribonucleic acid; FLC = free light-chains; HBV = Hepatitis B Virus; NT-proBNP = N-terminal prohormone brain natriuretic peptide.

Table 4.41. Frequency of resource use for routine disease monitoring ('Off Tx')

Item	Proportion of Patients Requiring Item	Item Frequency	Frequency Unit	Reference/Notes
Hematology Assessment	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).

Serum Chemistry Assessment	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
HBV DNA Test	[redacted]	[redacted]	per Cycle	Assumption based on ANDROMEDA protocol (24).
Troponin T Test	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Serum Disease Evaluation	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Urine Disease Evaluation	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
Serum FLC Assessment	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).
NT-proBNP Assay	[redacted]	[redacted]	per Cycle	ANDROMEDA protocol (24).

* HBV testing occurred every 12 weeks for up to 6 months after the last dose of study treatment (24); HBV testing was assumed not to occur while 'Off Tx' as a simplifying assumption.

Abbreviations: DNA = deoxyribonucleic acid; FLC = free light-chains; HBV = Hepatitis B Virus; NT-proBNP = N-terminal prohormone brain natriuretic peptide.

Table 4.42. Routine disease monitoring unit costs

Item	Unit Cost	Source(s)/Notes
Hematology Assessment	¥ 2,100.00	Japan MHLW Medical Fee Schedule (codes D400-1 B-V, D026-3, D005-2, D005-3, and D005-5) (101).
Serum Chemistry Assessment	¥ 1,220.00	Japan MHLW Medical Fee Schedule (code D007 and D015-1)* (101).
HBV DNA Test	¥ 2,630.00	Japan MHLW Medical Fee Schedule (code D023-4) (101).
Troponin T Test	¥ 1,120.00	Japan MHLW Medical Fee Schedule (code D007-29) (101).
Serum Disease Evaluation	¥ 2,180.00	Japan MHLW Medical Fee Schedule (code D015-24) (101).
Urine Disease Evaluation	¥ 2,180.00	Japan MHLW Medical Fee Schedule (code D015-24) (101)
Serum FLC Assessment	¥ 3,880.00	Japan MHLW Medical Fee Schedule (code D015-29) (101).
NT-proBNP Assay	¥ 1,360.00	Japan MHLW Medical Fee Schedule (code D008-22) (101).

* Blood chemistry test is based on D007. The total number of tests included is greater than 10 and costs ¥1,060. Additionally, D015-1 is included for an additional CRP test.

Abbreviations: DNA = deoxyribonucleic acid; FLC = free light-chains; HBV = Hepatitis B Virus; NT-proBNP = N-terminal prohormone brain natriuretic peptide.

Table 4.43. First-line disease monitoring costs per cycle

Health State	Cost per Cycle
1L Tx	¥ 23,618.90
FDT	¥ 8,798.90
Off Tx	¥ 5,360.00

Abbreviations: 1L = first-line; FDT = fixed daratumumab treatment; Tx = treatment.

4.2.4.3 Adverse Event Costs

The criteria for identifying AEs was defined as grade ≥3 AEs occurring in ≥5% of patients in either treatment arm of the ANDROMEDA trial. The proportion of patients experiencing AEs for each therapy were presented in **Table 4.20**. AE management costs were sourced from a variety of Japan-specific sources (99, 101, 102, 111, 116, 127, 128). A summary of AE management costs is presented in **Table 4.44.** The AE cost per patient was calculated by multiplying the percentage of patients experiencing each AE (**Table 4.20**) by the cost per event (**Table 4.44**) and summing all AEs per treatment arm (**Table 4.45**). 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, it was assumed that a one-off cost would have minimal impact on the total cost of treatment.

Table 4.44. Adverse event unit costs

Adverse Event (Grade ≥3)	Unit Cost	Code/Description	Source(s)
Cardiac failure	¥987,886.10	Heart failure hospitalization cost	Inoue *et al.,* (2020) (102).
Diarrhoea	[redacted]	Cost to treat diarrhea per MDV database analysis for MM (May 2021)	MDV analysis, Data on File (2021) (94); see **Appendix H**
Edema	¥784.80	Assumed cost of an outpatient clinical visit plus the cost of seven-day treatment with furosemide (40 mg per day)	Japan MHLW Medical Fee Schedule, (2022; code A002); Saito *et al.*, (2014) (113); NHI Price List, (2022) (99); Sattar *et al.,* (2018) (129).
Hypokalemia	¥240,827.27	Cost of inpatient hospitalization (specialized hospital) and potassium supplementation for total of 14.4 days	Usami *et al.*, (2014) (103); Japan MHLW Medical Fee Schedule, (2022) (101); NHI Price List, (2022) (99).
Lymphopenia	[redacted]	Cost to treat lymphopenia per MDV database analysis for MM (May 2021)	MDV analysis, Data on File (2021) (94); see **Appendix H**
Neutropenia	[redacted]	Cost to treat neutropenia per MDV	MDV analysis, Data on File

		database analysis for MM (May 2021)	(2021) (94); see **Appendix H**
Pneumonia	[redacted]	Cost to treat pneumonia per MDV database analysis for MM (May 2021)	MDV analysis, Data on File (2021) (94); see **Appendix H**
Syncope	¥333,400.00	Cost of 20-day inpatient hospitalization	Akashi *et al*., (2012) (104); Japan MHLW Medical Fee Schedule 2022 (101).

Abbreviations: MDV = Medical Data Vision; mg = milligrams; MM = multiple myeloma; N/A = not applicable.

Table 4.45. Total adverse event costs per patient

Drug Regimen	Total AE Cost per Patient
DCyBorD	¥ 101,069.34
CyBorD	¥ 68,610.25

Abbreviations: AE = adverse event; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone.

4.2.4.4 Second-line Drug Therapy Costs

4.2.4.4.1 Second-line Drug Acquisition Costs

For first-line therapy, AL amyloidosis patients cease treatment following receipt of a fixed treatment course (80). While off-treatment, patients are observed until commencing second-line (subsequent) therapy is warranted (at the physician's discretion) (80).

Once patients enter the '2L Tx' health state, they incur a one-time cost for subsequent therapy. Because the duration of second-line treatment was poorly reported in the literature, the cost of subsequent therapy was applied as a one-time tariff to avoid overestimating costs. In the CUA, subsequent therapy costs represented drug therapy costs and treatment administration costs. Only one subsequent line of therapy was included in the CUA based on real-world evidence (including a study based in Asia) and clinical expert feedback that most patients do not receive multiple lines of subsequent therapy (70, 88, 89). In further support of this, according to ANDROMEDA data from the first clinical cut-off, most patients that commenced second-line therapy only received one subsequent line of therapy (DCyBorD: [redacted]%; CyBorD: [redacted]%) (78). Subsequent therapy costs were assigned based on whether patients received DCyBorD or CyBorD. According to clinical guidelines, published literature, and market research conducted by Janssen, Japanese patients that received first-line DCyBorD will receive second-line bortezomib, melphalan, and dexamethasone (BMd), CyBorD, thalidomide, cyclophosphamide, and

dexamethasone (TCd), and REVLIMID® (lenalidomide) and dexamethasone (Rd) (19, 116, 130). Japanese patients that received first-line CyBorD will receive second-line BMd, CyBorD, TCd, Rd, or DCyBorD (19, 116, 130). A summary of the second-line drug therapy regimens included in the model, and the proportion of patients receiving each regimen, is provided in **Table 4.46**. Scenario analyses varying the proportion of CyBorD patients that receive second-line TCd and DCyBorD are presented in **Section 5.1.2.2.2**.

Table 4.46. Second-line therapy drug regimens

In 2L Therapy, DCyBorD Patients Receive:	Proportion of Patients Receiving Regimen
Rd	[redacted]
BMd	[redacted]
CyBorD	[redacted]
TCd	[redacted]
In 2L Therapy, CyBorD Patients Receive:	**Proportion of Patients Receiving Regimen**
Rd	[redacted]
BMd	[redacted]
CyBorD	[redacted]
TCd	[redacted]
DCyBorD	[redacted]

Abbreviations: BMd = bortezomib, melphalan, dexamethasone; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; TCd = thalidomide, cyclophosphamide, dexamethasone; Rd = REVLIMID® (lenalidomide) and dexamethasone.

Source: Shimazaki *et al.*, (2018) (19), Janssen Japan Internal Assumption.

Second-line drug therapy dosage and administration frequencies were sourced from published literature of patients with AL amyloidosis rather than their product monographs because no indicated dosing regimen for second-line drugs exists in AL amyloidosis. Costs of second-line therapy drugs were sourced from the Japan MHLW NHI Price List (99). To determine the DCyBorD-specific subsequent therapy cost, the total costs for Rd, BMd, CyBorD, and TCd were calculated based on the proportion of patients receiving each regimen (**Table 4.46**) and the dosage and administration frequencies (**Table 4.47**) and cost of the individual drug components (**Table 4.48**). The total second-line therapy cost was applied to all DCyBorD patients that commenced second-line therapy. A similar approach was taken to determine the total cost of second-line treatment for patients that received first-line CyBorD.

Table 4.47. Second-line drug therapy dosage

Second-line Drug Regimen	Treatment Cycle Length (Days)	# Cycles	Dose per Administration	Administrations per Cycle	Source
Rd					
REVLIMID® (lenalidomide)	28	6	25 mg	21	Sanchorawala *et al.*, (2007) (90).
Dexamethasone	28	6	20 mg	3	Sanchorawala *et al.*, (2007) (90).
BMd					
Bortezomib	28	4	1.3 mg/m^2	4	Palladini *et al.*, (2014) (91).
Melphalan	28	4	0.22 mg/kg	4	
Dexamethasone	28	4	40 mg	4	
CyBorD					
Cyclophosphamide	28	6	300 mg/m^2	4	ANDROMEDA protocol (24).
Bortezomib	28	6	1.3 mg/m^2	4	
Dexamethasone	28	6	40 mg	4	

TCd					
Thalidomide	21	4	200 mg	21	Venner (2014) (92); Wechalekar (2007) (76).
Cyclophosphamide	21	4	500 mg	3	
Dexamethasone	21	4	40 mg	8	
DCyBorD					
Daratumumab	28	6	1,800 mg	Cycle 1-2: 4 Cycle 3-6: 2	ANDROMEDA protocol (24).
Cyclophosphamide	28	6	300 mg/m^2	4	
Bortezomib	28	6	1.3 mg/m^2	4	
Dexamethasone	28	6	40 mg	4	

Abbreviations: BMd = bortezomib, melphalan, dexamethasone; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; kg = kilogram; m = meters; mg = milligrams; TCd = thalidomide, cyclophosphamide, dexamethasone; Rd = REVLIMID® (lenalidomide), dexamethasone.

Table 4.48. Second-line drug therapy units and costs

Second-line Drug	Drug Units	Unit Strength	Price per Pack or Vial	Unit Cost
Cyclophosphamide	100	50 mg	¥ 2,590.00	¥ 25.90
Daratumumab	1	1800 mg	¥ 445,064.00	¥ 445,064.00
Dexamethasone	100	4 mg	¥ 2,870.00	¥ 28.70
Melphalan	25	2 mg	¥ 3,665.00	¥ 146.60
REVLIMID® (lenalidomide)	10	5 mg	¥ 80,853.00	¥ 8,085.30
Thalidomide	28	100 mg	¥ 192,732.00	¥ 6,883.29
Bortezomib	1	3 mg	¥ 38,694.00	¥ 38,694.00

Abbreviations: mg = milligrams.

Sources: NHI Price List, 2022 (99).

4.2.4.4.2 Second-line Drug Administration Costs

Similar to first-line drug therapy, administration costs were included in calculating the total second-line drug therapy costs. The route of drug administrations for all second-line therapy drugs were sourced from published literature (see **Table 4.47** for individual sources). All costs associated with second-line drug administration are the same as those outlined for first-line therapy drug administration (see **Section 4.2.4.1.2** and **Table 4.31**). A summary of the administration routes (**Table 4.49**) and per-cycle second-line drug administration costs is presented in **Table 4.50**.

Table 4.49. Second-line drug therapy administration routes

Drug	Administration Route
Cyclophosphamide	PO
Daratumumab	SC
Dexamethasone	PO
Melphalan	PO
REVLIMID® (lenalidomide)	PO
Thalidomide	PO
Bortezomib	SC

Abbreviations: PO = oral; SC = subcutaneous.

Source: ANDROMEDA protocol (24), Sanchorawala *et al*., (2007) (90), Palladini *et al.,* (2014); (91) Venner *et al.,* (2014) (92), Wechalekar *et al.,* (2007) (76).

Table 4.50. Second-line drug administration costs per cycle

Drug Regimen	Cost per Cycle	Total 2L Drug Administration Cost*
Rd	¥4,080.00	¥ 24,480.00
BMd	¥2,240.00	¥ 8,960.00
CyBorD	¥2,240.00	¥ 13,440.00
TCd	¥5,440.00	¥ 21,760.00
DCyBorD Cycles 1-2 Cycles 3-6	 ¥ 3,120.00 ¥ 2,680.00	 ¥ 16,960.00

*Total cost of 2L drug administration includes both the drug cost and number of administrations per cycle as outlined in **Table 4.47**.

Abbreviations: BMd = bortezomib, melphalan, dexamethasone; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib,

and dexamethasone; TCd = thalidomide, cyclophosphamide, dexamethasone; Rd = REVLIMID® (lenalidomide), dexamethasone.

4.2.4.4.3 Summary of Second-line Treatment Costs

Second-line therapy costs included both drug acquisition costs (see **Section 4.2.4.4.1**) and treatment administration costs (see **Section 4.2.4.4.2**). A summary of the total second-line drug costs is presented in **Table 4.51**.

Table 4.51. Total second-line drug therapy costs

Item	Cost
Second-line therapy for DCyBorD patients	¥ 1,323,417.67
Second-line therapy for CyBorD patients	¥ 1,667,882.67

Abbreviations: CyBorD = cyclophosphamide, bortezomib, and dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone.

4.2.4.5 End-stage Organ Failure Costs

According to ANDROMEDA IPD of MOD-PFS (primary analysis; February 14, 2020, data on file), [redacted] (95). [redacted]. This aligns with clinical expert feedback and published literature whereby the majority of early deaths occur in patients with cardiac involvement due to arrythmia/cardiac dysfunction and therefore, may not survive long enough to receive solid organ transplant or implantation of a cardiac assist device (68, 77, 79, 89). Furthermore, an analysis of the Japan MDV database (94) (see **Appendix H**) and published literature sources also indicate that solid organ transplant is very uncommon in patients with AL amyloidosis (80, 82, 94, 131). Therefore, it was considered a reasonable assumption that all patients in the 'End-stage organ failure' health state would have kidney failure.

Table 4.52 provides a summary of end-stage organ failure support costs and frequencies used in the model. The cost and frequency of hemodialysis were sourced from published literature at ¥383,939.58 (inflated) per month with three sessions per week (ie, 12 sessions per cycle) (115). The monthly cost and weekly frequency were used to calculate the cost per hemodialysis session of ¥29,452.89, which resulted in a per-cycle end-stage organ failure-related cost of ¥ 353,434.64. A summary of total end-stage organ failure-related costs is presented in **Table 4.53**. This cost was applied to each patient in the 'End-stage Organ Failure' health state on a per-cycle basis.

Table 4.52. Frequencies and costs associated with recurring end-stage organ failure support

Item	Proportion of End-Stage Organ Failure Patients Requiring Item	Frequency per Cycle	Cost	Source
Hemodialysis	[redacted]	12	¥ 29,452.89 (per hemodialysis session)	Proportion: MOD-PFS data from ANDROMEDA IPD (primary analysis; February 2020; median follow-up 11.4 months, data on file) (95). Frequency and cost: Takura *et al.*, (2019) (115).

Abbreviations: IPD = individual patient data; MOD-PFS = major organ deterioration-progression free survival.

Table 4.53. Total end-stage organ failure costs

Item	Cost
Recurring End-stage Organ Failure Costs per Cycle	¥ 353,434.64

4.2.4.6 Healthcare Resource Use Costs

Healthcare resource use costs for disease management in the model reflected *incidental* emergency room visits, inpatient hospitalizations, and physician/outpatient department visits. Note that data pertaining to physician/outpatient visits was sourced from the MDV database and did not discern between incidental visits and those that were part of routine disease monitoring (see **Section 4.2.4.2**). Therefore, both *incidental and routine* physician visits were both captured as "healthcare resource use" and not "disease monitoring" to avoid double-counting these costs.

Japan-specific values (albeit not specific to AL amyloidosis due to the absence of data in the literature and medical fee schedules) informed the costs associated with each healthcare resource use item. According to the MHLW Medical Fee Schedule, the cost of a visit to the emergency department is ¥10,500.00 (101). The cost for an inpatient hospitalization was calculated to be [redacted]. This value was the product of the mean length of hospitalization for patients with AL amyloidosis (ie, [redacted] days per the Japan MDV database analysis; see **Appendix H**) (94) and the basic hospitalization fee per day (ie, ¥16,670) for specialized hospitals (code: A105) per the MHLW Medical Fee Schedule (101). Finally, the cost of an outpatient department visit (code A002) is ¥740.00 (101). A summary of the healthcare resource use costs included in the model is presented in **Table 4.54**.

Table 4.54. Healthcare resource unit costs

Item	Unit Cost	Source
Emergency Room Visit	¥ 10,500.00	Japan MHLW Medical Fee Schedule (101).
Inpatient Department*	¥ [redacted]	Japan MHLW Medical Fee Schedule (101); MDV database analysis, data on file (2021) (116).
Outpatient Department	¥ 740.00	Japan MHLW Medical Fee Schedule (101).

* Patients with AL Amyloidosis are most likely to be hospitalized in specialized hospitals (専門病院) that provide advanced and specialized medical care for patients (101).

The frequencies of incidental healthcare resource use and proportion of patients utilizing such resources were sourced (or estimated) from mean estimates from the Japan MDV database analysis (see **Appendix H**) for '1L Tx', '2L Tx' and 'End-stage organ failure' health states (132). Due to a paucity of data in the Japan MDV database (see **Appendix H**) (94), assumptions were required pertaining to incidental healthcare resource use in 'Off Tx/FDT', '2L Tx', and 'End-stage Organ Failure' health states. For the '2L Tx' and 'End-stage Organ Failure' health states, all incidental healthcare resource use values were assumed to be the same as subjects in the '1L Tx' health state.

For the 'Off Tx/FDT' health state, the proportion of patients requiring incidental healthcare resource use was assumed to be the same as the '1L Tx' health state. The frequency of use in the 'Off Tx/FDT' health state was calculated based on a published literature source reporting healthcare resource utilization by patients with AL amyloidosis (93). This article (Quock *et al*., [2018] (93)) describes healthcare resource utilization for incident patients in their first- and second-year post-diagnosis with AL amyloidosis. In the first-year post-diagnosis, incident patients had a mean of 0.73 visits to the emergency

department (ie, an average of [redacted] visits per cycle), 1.05 inpatient hospitalizations (ie, an average of [redacted] inpatient hospitalizations per cycle), and an average of 49.2 non-emergency department outpatient visits (ie, an average of [redacted] outpatient visits per cycle) (93). Patients in their second-year post-diagnosis had a reported annual average of 0.63 emergency department visits (ie, an average of [redacted] emergency department visits per cycle), 0.57 inpatient hospitalizations (ie, an average of [redacted] inpatient hospitalizations per cycle), and 39.7 outpatient visits (ie, an average of [redacted] outpatient visits per cycle) (93). In the model, a simplifying assumption was made whereby the relative reductions in first- and second-year post-diagnosis healthcare resource use from Quock *et al*., (2018) (93) for each of emergency room (ER) visits (-13.7%), inpatient hospitalizations (-45.7%), and outpatient visits (-19.3%) were applied to '1L Tx' values sourced from the Japanese AL amyloidosis database to estimate the healthcare resource use for patients in the 'Off Tx/FDT' health state. The resulting frequency of resource utilization for 'Off Tx/FDT' was [redacted] emergency room visits, [redacted] inpatient hospitalizations, and [redacted] outpatient visits per cycle.

A summary of incidental healthcare resource use frequencies used in the model is presented in **Table 4.55**. Healthcare resource unit costs and frequencies were used to calculate the health state-associated costs per cycle as outlined in **Table 4.56**.

Table 4.55. Incidental healthcare resource use frequencies by health state

Item	1L Tx		Off Tx/FDT		2L Tx		End-stage Organ Failure	
	% Patients Requiring Item	Frequency of Use per Cycle	% Patients Requiring Item	Frequency of Use per Cycle	% Patients Requiring Item	Frequency of Use per Cycle	% Patients Requiring Item	Frequency of Use per Cycle
Emergency Room Visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inpatient Department	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient Department	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Assumed equivalent for '1L Tx', 'Off Tx/FDT', '2L Tx', and 'End-stage Organ Failure'.

**Calculated using the % reduction between '1L Tx' and 'Off Tx' per Quock *et al*., 2018 (93).

Abbreviations: 1L = first-line; 2L = second-line; FDT = fixed daratumumab treatment; Tx = treatment.

Source: Japan MDV database analysis, data on file (2021) (94); Quock *et al*., (2018; Off Tx/FDT) (93).

Table 4.56. Calculated incidental healthcare resource use costs per cycle

Item	1L Tx	Off Tx/FDT	2L Tx	End-stage Organ Failure
Emergency Room Visit	¥ 316.58	¥ 273.21	¥ 316.58	¥ 316.58
Inpatient Department	¥ 88,793.12	¥ 48,201.98	¥ 88,793.12	¥ 88,793.12
Outpatient Department	¥ 2,209.63	¥ 1,782.98	¥ 2,209.63	¥ 2,209.63
Total Cost per Cycle	¥ 91,319.33	¥ 50,258.17	¥ 91,319.33	¥ 91,319.33

Abbreviations: 1L = first-line; 2L = second-line; FDT = fixed daratumumab treatment; Tx = treatment.

4.2.4.7 End of Life Costs

Patients who transition to the death health state incur a one-time cost for end of life. Terminal medical care costs in the analysis reflect those associated with the final month of life and were sourced from the 2007 Japan Medical Association Working Paper (note that the cost does not specifically reflect an AL amyloidosis patient subset) (117). The terminal care cost included in the model is presented in **Table 4.57** and is applied in full to all patients who die in each model cycle.

Table 4.57. End of Life Costs

Item	Cost	Source
End of Life Costs*	¥ 662,205.59	Japan Medical Association (2007) (117).

* Represents terminal care costs for the final month of life.

5 Analytical Results

5.1 Results of Basic Analysis (Analysis using an analytical framework determined by the specialized organization for cost-effectiveness assessments)

Cost Utility analysis is performed as additional benefit of DCyBorD comparing to CyBorD as confirmed by the result of SLR.

x Cost-effectiveness analysis (Calculate the incremental cost-effectiveness ratio)
☐ Cost-Minimization Analysis (compare costs as well as benefits)

5.1.1 Incremental Cost, Incremental Effectiveness, and Incremental Cost Effectiveness Ratio for Main Analysis

The discounted deterministic results for DCyBorD versus CyBorD are summarized below. The total and incremental QALYs and costs, along with the incremental cost effectiveness ratio (ICER), expressed as costs per QALY gained, are shown in **Table 5.1**. Compared with CyBorD, DCyBorD was more effective (1.85 QALYs) and was associated with higher costs (¥10,414,642.44) over a 35-year horizon, resulting in an ICER of ¥5,626,171.29 per QALY gained. A detailed breakdown of analysis costs is presented in **Table 5.2**.

Table 5.1. Summary of analysis results

	Efficacy (QALY)	Incremental effect (QALY)	Expenses (yen)	Incremental costs (yen)	ICER (Costs/QALY)
DCyBorD	5.63	1.85	¥ 23,435,292.91	¥ 10,414,642.44	¥ 5,626,171
CyBorD	3.78		¥ 13,020,650.47		

Abbreviations: CyBorD = bortezomib, cyclophosphamide, dexamethasone; DCyBorD = daratumumab, bortezomib, cyclophosphamide, dexamethasone; QALY = quality adjusted life-year.

Table 5.2. Detailed results of analysis costs (discounted result)

	DCyBorD	CyBorD
Total 1L Drug Therapy Costs	[redacted]	[redacted]
Total 1L Drug Administration Costs	[redacted]	[redacted]
Co-medication Costs	[redacted]	[redacted]
Healthcare Resource Use Costs	[redacted]	[redacted]
Adverse Event Management Costs	[redacted]	[redacted]
1L Disease Monitoring Costs	[redacted]	[redacted]
Subsequent Therapy Drug Costs	[redacted]	[redacted]
End-stage Organ Failure Costs	[redacted]	[redacted]
End of Life Costs	[redacted]	[redacted]
Total Costs	¥ 23,435,293	¥ 13,020,650

Abbreviations: 1L = first-line; CyBorD = bortezomib, cyclophosphamide, dexamethasone; DCyBorD = daratumumab, bortezomib, cyclophosphamide, dexamethasone.

5.1.2 Sensitivity analysis

5.1.2.1 One-way sensitivity analysis

A one-way sensitivity analyses was performed to identify parameters to which the model results (in terms of ICER) are most sensitive (ie, model drivers) by adjusting the default value to a low and high value. All inputs were varied by increasing or decreasing the default value by 20% (except where estimates could not exceed 100% or an otherwise specified maximum value) with the exception of the discount rate for cost and effects which were varied at 0% (low value) and 4% (high value). The one-way sensitivity inputs are summarized in **Table 5.3**. Patient distributions within the decision tree and transition probabilities were not incorporated into the one-way sensitivity analyses, as one input cannot be varied without also varying the other dependent inputs.

The results of the one-way sensitivity analyses for DCyBorD versus CyBorD suggest that the top five model drivers were the CR utility value, the daratumumab unit cost, the discounting rate for effects, the PR/NR utility value, and the ongoing organ failure support cost per cycle. These results make sense, as the CR utility value, daratumumab unit cost, and discounting rate for effects value would affect the incremental QALYs and/or incremental costs for the DCyBorD arm, whereas the PR/NR utility value and ongoing organ failure support cost per cycle would more so affects the CyBorD arm. Notably, when inputted as 0% and 4%, the discounting of costs was not identified as a significant model driver. Results of the one-way sensitivity analysis are presented in **Table 5.3**. The resulting tornado diagram plots the most impactful parameters in order, based on the greatest percent change from the main analysis, and is presented in **Figure 5.1.**

Table 5.3. Results of one-way sensitivity analyses

Variable	Default Value	Low Value Tested (-20%)	High Value Tested (+20%)	Low Value ICER	High Value ICER
Time horizon	35	28	42	¥5,799,668.62	¥5,619,364.36
Discount rate - costs	2.0%	0%	4%	¥5,650,142.62	¥5,615,550.20
Discount rate - effects	2.0%	0%	4%	¥4,446,823.77	¥6,927,930.00
Proportion of male subjects	[redacted]	[redacted]	[redacted]	¥5,603,098.49	¥5,654,271.75
Proportion of PR patients at exit from decision tree	[redacted]	[redacted]	[redacted]	¥5,706,760.00	¥5,564,235.32
Daratumumab Unit Cost	¥445,064.00	¥356,051.20	¥534,076.80	¥4,353,387.84	¥6,898,954.73
Cyclophosphamide Unit Cost	¥2,590.00	¥2,072.00	¥3,108.00	¥5,626,095.18	¥5,626,247.39
Bortezomib Unit Cost	¥38,694.00	¥30,955.20	¥46,432.80	¥5,613,537.97	¥5,638,804.60
Dexamethasone Unit Cost	¥2,870.00	¥2,296.00	¥3,444.00	¥5,626,077.58	¥5,626,264.99
DCyBorD Treatment Duration (months)	24.00	19.2	24.00*	¥ 5,231,076.84	¥ 5,626,171.29
CyBorD Treatment Duration (months)	6.00	4.8	6.00*	¥ 5,659,585.00	¥ 5,626,171.29
DCyBorD RDI (Daratumumab)	[redacted]	[redacted]	[redacted]	¥5,626,171.29	¥5,626,171.29
DCyBorD RDI (Cyclophosphamide)	[redacted]	[redacted]	[redacted]	¥5,625,570.30	¥5,626,471.78

DCyBorD RDI (bortezomib)	[redacted]	[redacted]	[redacted]	¥5,626,171.29	¥5,626,171.29
DCyBorD RDI (Dexamethasone)	[redacted]	[redacted]	[redacted]	¥5,625,505.32	¥5,626,171.29
CyBorD RDI (Cyclophosphamide)	[redacted]	[redacted]	[redacted]	¥5,626,687.72	¥5,625,913.07
CyBorD RDI (bortezomib)	[redacted]	[redacted]	[redacted]	¥5,626,171.29	¥5,626,171.29
CyBorD RDI (Dexamethasone)	[redacted]	[redacted]	[redacted]	¥5,626,743.55	¥5,626,171.29
DCyBorD Drug Admin Costs (Cycles 1-2)	¥3,120.00	¥2,496.00	¥3,744.00	¥5,625,366.57	¥5,626,976.00
DCyBorD Drug Admin Costs (Cycles 3-6)	¥2,680.00	¥2,144.00	¥3,216.00	¥5,625,307.83	¥5,627,034.75
DCyBorD Drug Admin Costs (Cycles 7+)	¥220.00	¥176.00	¥264.00	¥5,625,910.87	¥5,626,431.71
CyBorD Drug Admin Costs	¥2,240.00	¥1,792.00	¥2,688.00	¥5,627,287.89	¥5,625,054.68
Co-medication cost for DCyBorD	¥1,907.80	¥1,526.24	¥2,289.36	¥5,622,806.27	¥5,629,536.31
Co-medication cost for CyBorD	¥1,663.20	¥1,330.56	¥1,995.84	¥5,627,000.37	¥5,625,342.21
Healthcare resource use - 1L Tx	¥91,319.33	¥73,055.47	¥109,583.20	¥5,618,717.51	¥5,633,625.07
Healthcare resource use - Off Tx/FDT	¥50,258.17	¥40,206.54	¥60,309.80	¥5,447,892.09	¥5,804,450.48
Healthcare resource use - 2L Tx	¥91,319.33	¥73,055.47	¥109,583.20	¥5,608,780.93	¥5,643,561.64

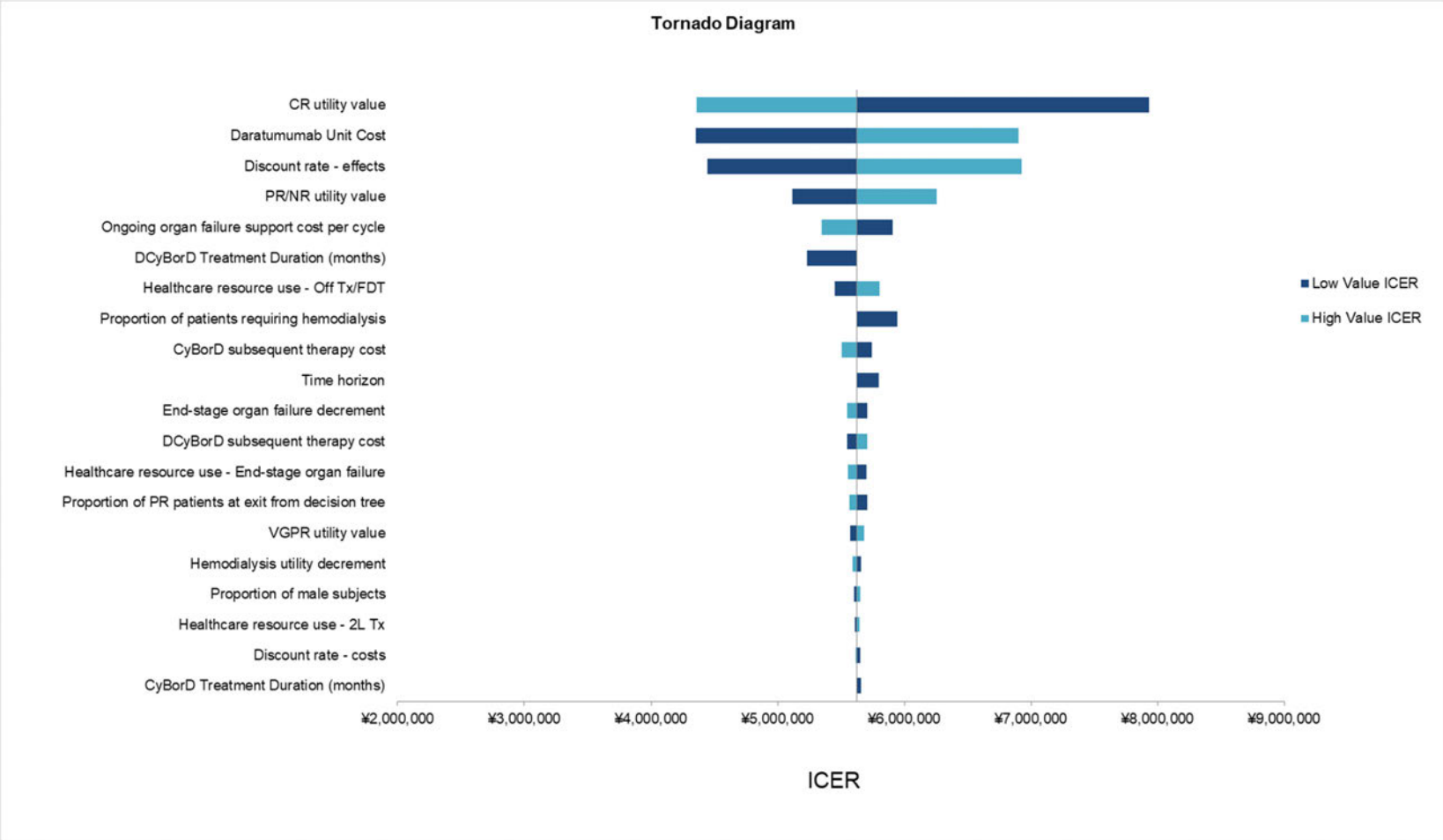
Healthcare resource use - End-stage organ failure	¥91,319.33	¥73,055.47	¥109,583.20	¥5,698,641.41	¥5,553,701.17
DCyBorD AE management costs	¥101,069.34	¥80,855.47	¥121,283.21	¥5,615,251.40	¥5,637,091.17
CyBorD AE management costs	¥68,610.25	¥54,888.20	¥82,332.30	¥5,633,584.18	¥5,618,758.40
DCyBorD AE disutility	0.001962086	0.001569669	0.002354503	¥5,624,978.85	¥5,627,364.24
CyBorD AE disutility	0.001172057	0.000937646	0.001406469	¥5,626,883.84	¥5,625,458.92
1L Tx disease monitoring costs	¥23,618.90	¥18,895.12	¥28,342.68	¥5,624,243.44	¥5,628,099.14
1L FDT disease monitoring costs	¥8,798.90	¥7,039.12	¥10,558.68	¥5,615,755.87	¥5,636,586.71
Off Tx disease monitoring costs	¥5,360.00	¥4,288.00	¥6,432.00	¥5,613,467.21	¥5,638,875.37
DCyBorD subsequent therapy cost	1,323,417.67	¥1,058,734.13	¥1,588,101.20	¥5,548,638.50	¥5,703,704.07
CyBorD subsequent therapy cost	1,667,882.67	¥1,334,306.13	¥2,001,459.20	¥5,744,220.71	¥5,508,121.86
Ongoing organ failure support cost per cycle	¥353,434.64	¥282,747.71	¥424,121.57	¥5,906,653.51	¥5,345,689.06
Proportion of patients requiring hemodialysis	[redacted]	[redacted]	[redacted]	¥5,942,807.46	¥5,626,171.29
End of life cost	¥662,205.59	¥529,764.47	¥794,646.71	¥5,628,080.22	¥5,624,262.36
CR utility value	[redacted]	[redacted]	[redacted]	¥7,932,073.66	¥4,358,987.06
VGPR utility value	[redacted]	[redacted]	[redacted]	¥5,573,301.91	¥5,680,053.33
PR/NR utility value	[redacted]	[redacted]	[redacted]	¥5,112,894.67	¥6,254,002.15

2L Tx utility decrement	[redacted]	[redacted]	[redacted]	¥5,622,234.11	¥5,630,113.98
End-stage organ failure decrement	[redacted]	[redacted]	[redacted]	¥5,705,308.00	¥5,549,199.91
Hemodialysis utility decrement	0.1000	0.0800	0.1200	¥5,660,608.43	¥5,592,150.62

* High value tested is not 20% greater than the default value so as to not exceed a pre-specified maximum value.

Abbreviations: 1L = first-line; 2L = second-line; AE = adverse event; CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; FDT = fixed daratumumab treatment; ICER = incremental cost-effectiveness ratio; RDI = relative drug intensity; Tx = treatment; NR = no response; PR = partial response; VGPR = very good partial response.

Figure 5.1. Tornado diagram depicting results of one-way sensitivity analysis



Abbreviations: 2L – second-line; CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; FDT = fixed daratumumab treatment; ICER = incremental cost-effectiveness ratio; NR = no response; PR = partial response; Tx = treatment; VGPR = very good partial response.

5.1.2.2 Scenario analyses

5.1.2.2.1 Asian subgroup analysis

As an alternative to the main analysis (which involved the ANDROMEDA ITT population), a scenario analysis was conducted using Asian subjects from the ANDROMEDA trial (N=60; DCyBorD n=29; CyBorD n=31). In this subgroup analysis, parameters pertaining to patient demographics, hematologic response stratification in the decision tree, and weighting for the PR/NR combined curve were revised to reflect the subjects residing in Asian countries. A summary of the parameters used to inform the Asian subgroup analysis is presented in **Table 5.4**. Compared to main analysis, using the Asian subgroup data resulted in a reduction in the ICER by ¥1,021,664.91 (~18%) given that, based on the ANDROMEDA-derived hematologic response data in the decision tree, Asian subjects in the DCyBorD arm have more rapid and deeper hematologic response compared to the DCyBorD arm of the ITT population. As such, the model predicts that Asian subjects incur greater incremental costs (¥1,188,274.88), LYs (0.81), and QALYs (0.67) compared to the model using the ITT population parameters. Despite the increase in incremental costs in the Asian subgroup analysis, the incremental QALYs gained offset the incremental costs, resulting in a reduced ICER compared to the main analysis. A summary of results of the Asian subgroup analysis is presented in **Table 5.5**.

Table 5.4. Summary of parameters for Asian subgroup analysis

Parameter Description	Parameter							
Starting age (years)	[redacted]							
Proportion of male subjects (%)	[redacted]							
Average patient body weight (kg)	[redacted]							
Body surface area (m^2)	[redacted]							
Weighting for PR/NR combined curve	PR: [redacted]							
Decision tree	DCyBorD				CyBorD			
	CR	VGPR	PR/NR	Death	CR	VGPR	PR/NR	Death
Cycle 1	[redacted]							
Cycle 2	[redacted]							
Cycle 3	[redacted]							

Abbreviations: CyBorD = cyclophosphamide, bortezomib, dexamethasone; CR = complete response; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; kg = kilograms; m = meters; NR = no response; PR = partial response; VGPR = very good partial response.

Source: ANDROMEDA IPD (18-month landmark analysis; median follow-up 25.8 months, data on file) (98).

Table 5.5. Summary of Asian subgroup analysis results

Result	Value
Incremental LYs	2.96
Incremental QALYs	2.52
Incremental Costs	¥ 11,602,917
Cost per QALY (ICER)	¥ 4,604,506

Abbreviations: ICER = incremental cost-effectiveness ratio; LYs = life-years; QALY = quality adjusted life-year.

5.1.2.2.2 Scenario analyses to test uncertainty in model inputs and assumptions

To test the impact of uncertainty in key model inputs and assumptions, several scenario analyses were conducted based on the ANDROMEDA ITT population. The inputs and results are summarized in **Table 5.6**. In general, DCyBorD is associated with higher total costs and total QALYs in all scenarios. Shortening the time horizon led to a ~18% increase in the main analysis ICER because the lifetime LY and QALY benefits associated with DCyBorD could not be fully accrued in this scenario. Selecting six-month exit from the decision tree resulted in a large (~19%) reduction in the ICER due to increased LYs and QALYs gained from using OS data from Palladini *et al*., (2012) (74), which showed higher survival rates relative to the OS curves from Kastritis et al., (2020) (71). The scenario varying the proportion of CyBorD patients receiving second-line TCd (14% to 19%) and DCyBorD (5% to 0%) resulted in a ~2% increase in the main analysis ICER. Conversely, the scenario varying the proportion of CyBorD patients receiving second-line TCd (14% to 9%) and DCyBorD (5% to 10%) resulted in a ~2% decrease in the main analysis ICER. Importantly, using alternate survival functions to extrapolate OS for CR, VGPR, and/or PR/NR did not have a large impact on the ICER (range ¥5,595,917.14 to ¥5,742,501.19), supporting the robustness of the results irrespective of which survival function is selected.

Table 5.6. Summary of scenario analysis inputs and results

Scenario	Default Value(s)	Alternative Value(s)	Incremental LYs	Incremental QALYs	Incremental Costs	Costs per QALY
Main analysis	N/A	N/A	2.15	1.85	¥ 10,414,642.44	¥ 5,626,171.29
Shortened time horizon	35 years	20 years	1.76	1.55	¥ 10,294,301.88	¥ 6,661,649.86
Use alternative Kastritis et al., (2020) curve extrapolations to inform PR/NR OS	Weibull	Gamma	2.16	1.85	¥ 10,531,364.47	¥ 5,683,006.85
Use alternative Kastritis et al., (2020) curve extrapolations to inform CR OS	Exponential	Weibull	2.10	1.82	¥ 10,403,225.21	¥ 5,716,213.45
Use alternative Kastritis et al., (2020) curve extrapolations to inform VGPR OS	Log-logistic	Gamma	2.16	1.86	¥ 10,406,056.87	¥ 5,595,917.14
Use alternative Kastritis et al., (2020) curve extrapolations combinations to inform PR/NR, CR, and VGPR OS (2)	PR/NR: Weibull CR; Exponential VGPR: Log-logistic	PR/NR: Gamma CR; Weibull VGPR: Gamma	2.13	1.83	¥ 10,511,361.67	¥ 5,742,501.19
6mo decision tree exit with	Decision tree:	Decision tree:	4.07	3.16	¥ 14,451,779.10	¥ 4,579,152.49

Scenario	Default Value(s)	Alternative Value(s)	Incremental LYs	Incremental QALYs	Incremental Costs	Costs per QALY
best-fit extrapolations for CR, VGPR, PR/NR	3mo CR raw curve: Exponential VGPR raw curve: Log-logistic PR/NR raw curve: Weibull	6mo CR raw curve: Exponential VGPR raw curve: Exponential PR/NR raw curve: Weibull				
'2L Tx' for CyBorD patients: % receiving DCyBorD = [redacted]*	[redacted]	[redacted]	2.15	1.85	¥ 10,640,297.41	¥ 5,748,074.03
'2L Tx' for CyBorD patients: % receiving DCyBorD = [redacted]*	[redacted]	[redacted]	2.15	1.85	¥ 10,188,987.47	¥ 5,504,268.54

* Scenario analysis results were generated by manually running the model analysis.

Abbreviations: 2L = second-line; CyBorD = cyclophosphamide, bortezomib, dexamethasone; CR = complete response; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; LYs = life-years; N/A = not applicable; NR = no response; OS = overall survival; PR = partial response; QALYs = quality-adjusted life-years; Tx = treatment; VGPR = very good partial response.

5.1.2.3 Probabilistic sensitivity analysis

The PSA shows the overall uncertainty of the cost-effectiveness results for D-VCd compared to VCd. Common distributions used in a PSA are beta, gamma, log-normal, normal, and Dirichlet (133). The choice of distribution was selected based on recommendations by Briggs *et al*., (2006) (133). Survival estimates were sampled using Cholesky decomposition matrices.

For all inputs, when possible, the standard error (SE; alternatively, standard deviation [SD] or 95% confidence interval [CI] were used to calculate SE) from the data source were used to define parameter uncertainty. Otherwise, when not reported, the SE was assumed to be 10% of the default value. This was assumed to represent a reasonable degree of uncertainty and provided realistic values. Mean deterministic values (ie, point estimates), SEs, and distribution types used for each parameter included in the PSA are provided in **Table 5.7**. The PSA was conducted using 3,000 iterations (the maximum number of iterations in the model is 10,000).

The results of the PSA were aligned with the deterministic main analysis and are presented in **Table 5.8**. The mean total incremental costs from the PSA were marginally higher than the deterministic results; however, the overall trends in relative costs were the same. The mean total incremental QALYs from the PSA were lower than the deterministic analysis; however, the overall trends remained unchanged. In comparing the deterministic and probabilistic ICERs, the overall conclusion regarding cost effectiveness remained unchanged; that is, when compared to CyBorD, DCyBorD was more costly and more effective and did not exceed the threshold (for products requiring special consideration) of ¥7,500,000 per QALY.

The incremental cost-effectiveness plane (or scatter plot) of incremental costs versus incremental QALYs for DCyBorD versus CyBorD from 3,000 iterations is presented in **Figure 5.2**. All probabilistic iterations were in the North-East quadrant indicating that DCyBorD was more costly and more effective than CyBorD. The cost-effectiveness acceptability curve (CEAC), showing the probability of being the most cost-effective therapy at different willingness to pay thresholds, is presented in **Figure 5.3**. At a willingness to pay threshold greater than ¥6,200,000, DCyBorD had a higher probability of being more cost-effective than CyBorD.

Table 5.7. Summary of mean values and their distributions included in the probabilistic sensitivity analysis

Parameter	Mean Value Used in Main Analysis	SE/SD	Distribution	Value Used in PSA	Source(s)/Notes
Model Characteristics					
Time Horizon	35 Years	N/A	N/A	N/A	See **Section 2.4.**
Discount rate effects	2%	N/A	N/A	N/A	See **Section 2.5**; C2H guidelines (43).
Discount rate costs	2%	N/A	N/A	N/A	
Patient Characteristics					
Baseline patient age	[redacted]	[redacted]	Normal	[redacted]	See **Section 4.2**; ANDROMEDA CSR (78).
Proportion male	[redacted]	[redacted]	Beta	[redacted]	
Patient body weight	[redacted]	[redacted]	Normal	[redacted]	
Patient body surface area	[redacted]	[redacted]	Normal	[redacted]	
Efficacy Data*					
PR/NR survival function	Weibull	N/A	N/A	N/A	See **Section 0.1.1.1**; Kastritis *et al.*, (2020) (71).

CR survival function	Exponential	N/A	N/A	N/A	See **Section 0.1.1.1**; Kastritis *et al*., (2020) (71).
VGPR survival function	Log-logistic	N/A	N/A	N/A	See **Section 0.1.1.1**; Kastritis *et al*., (2020) (71).
Proportion pts PR (at exit from decision tree)	[redacted]	[redacted]	Beta	[redacted]	See **Section 0.1.1.1;** ANDROMEDA IPD 18-month landmark analysis (May 2021; median follow-up 25.8 months, data on file) (98).
DCyBorD Treatment duration (# months)	24.00	0	N/A	N/A	See **Section 4.2.4.1.5**;

					ANDROMEDA protocol (24).
CyBorD Treatment duration (# months)	6.00	0	N/A	N/A	See **Section 4.2.4.1.5**; ANDROMEDA protocol (24).
First-line Drug Therapy Costs					
DCyBorD (Cycles 1-2) DCyBorD (Cycles 3-6) DCyBorD (Cycle 7+)	¥ 1,937,112.40 ¥ 1,046,984.40 ¥ 445,064.00	N/A	N/A	N/A	See **Section 4.2.4.1.1**; Japan MHLW NHI Price List, (2022) (99).
CyBorD	¥ 156,856.40	N/A	N/A	N/A	See **Section 4.2.4.1.1**; Japan MHLW NHI Price List, (2022) (99).

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	N/A	N/A	N/A	See **Section 4.2.4.1.1**; Kastritis *et al*., (2021) (50).
Cyclophosphamide	300 mg/m^2; 4 administrations per cycle	N/A	N/A	N/A	See **Section 4.2.4.1.1**; Kastritis *et al*., (2021) (50).
Bortezomib	1.3 mg/m^2; 4 administrations per cycle	N/A	N/A	N/A	See **Section 4.2.4.1.1**; Kastritis *et al*., (2021) (50).
Dexamethasone	40 mg; administrations per cycle	N/A	N/A	N/A	See **Section 4.2.4.1.1**; Kastritis *et al*., (2021) (50).

First-line Drug RDI					
DCyBorD RDI (Daratumumab)	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.4.1.1**; ANDROMEDA CSR (78).
DCyBorD RDI (Cyclophosphamide)	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.4.1.1**; ANDROMEDA CSR (78).
DCyBorD RDI (Bortezomib)	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.4.1.1**; ANDROMEDA CSR (78).
DCyBorD RDI (Dexamethasone)	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.4.1.1**; ANDROMEDA CSR (78).

CyBorD RDI (Cyclophosphamide)	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.4.1.1**; ANDROMEDA CSR (78)
CyBorD RDI (Bortezomib)	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.4.1.1**; ANDROMEDA CSR (78).
CyBorD RDI (Dexamethasone)	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.4.1.1**; ANDROMEDA CSR (78).
First-line Drug Administration Costs					
DCyBorD administration costs (Cycles 1-2)	¥3,120.00	¥312.00	Gamma	¥2,866.08	See **Section 4.2.4.1.2**;

DCyBorD administration costs (Cycles 3-6)	¥ 2,680.00	¥268.00	Gamma	¥2,727.64	ANDROMEDA protocol (24); Japan MHLW Medical Fee Schedule (101); NHI Price List (99).
DCyBorD administration costs (Cycles 7+)	¥220.00	¥22.00	Gamma	¥269.33	
CyBorD administration costs	¥2,240.00	¥224.00	Gamma	¥2,331.96	
First-line Co-medication Costs					
DCyBorD Co-medication costs	¥1,907.80	¥190.78	Gamma	¥1,970.11	See **Section 4.2.4.1.3**; ANDROMEDA protocol (24); ANDROMEDA CSR (78); NHI Price List (99).

CyBorD Co-medication costs	¥1,663.20	¥166.32	Gamma	¥1,692.46	See **Section 4.2.4.1.3**; ANDROMEDA protocol (24); ANDROMEDA CSR (78); NHI Price List (99).
First-line Disease Monitoring Costs					
1L Tx	¥23,618.90	¥2,361.89	Gamma	¥27,056.10	See **Section 4.2.4.1.5**; ANDROMEDA protocol (24); ANDROMEDA CSR (78); Japan MHLW Medical Fee Schedule (101)
FDT	¥8,798.90	¥879.89	Gamma	¥8,047.15	
Off Tx	¥5,360.00	¥536.0	Gamma	¥5,727.54	

AE Management Costs					
DCyBorD	¥101,069.34	¥10,106.93	Gamma	¥106,951.98	See **Section 4.2.4.3**; ANDROMEDA IPD 18-month landmark analysis (May 2021; median follow-up 25.8 months, data on file) (98); Inoue, 2020 (102); Japan MHLW Medical Fee Schedule (code A002) (101); Janssen Japan Data on File 2021 (116); Akashi *et al*., (2012) (104); Usami *et al*., (2014)
CyBorD	¥68,610.25	¥6,861.04	Gamma	¥65,640.24	

					(103); NHI Price List (99).
AE Utility Decrements					
DCyBorD	0.001962086	0.000196209	Gamma	0.001915308	See **Section 4.2.3.2**; Sullivan *et al*., (2011) (114); Stein *et al*., (2008) (110); Brown *et al*., (2001) (112); Nafees *et al*., (2008) (106); Beusterien *et al*., (2010) (108); Inoue *et al.,* (2020) (102); Shiroiwa *et al.,* (2009) (111); Saito et al., (2014) (113);
CyBorD	0.001172057	0.000117206	Gamma	0.001150156	

					Usami et al., (2014) (103); Onouchi *et al.,* (2014) (107); Ishida et al., (2012) (109); Akashi et al., (2012) (104).
Second-line Drug Therapy Costs					
DCyBorD	¥1,323,417.67	¥132,341.77	Gamma	¥1,460,213.23	See **Section 4.2.4.4**; ANDROMEDA Protocol (24); Shimazaki *et al*., (2018) (19); JSH clinical guidelines (130); Janssen Japan internal assumption; NHI Price List (99);

					Sanchorawala *et al*., (2007) (90); Palladini *et al.,* (2014) (91); Venner *et al.,* (2014) (92); Wechalekar *et al.,* (2007) (76).
CyBorD	¥1,667,882.67	¥166,788.27	Gamma	¥1,642,205.58	See **Section 4.2.4.4**; ANDROMEDA Protocol (24); Shimazaki *et al*., (2018) (19); JSH clinical guidelines (130); Janssen Japan internal assumption; NHI Price List (99); Sanchorawala *et al*., (2007) (90); Palladini

					et al., (2014) (91); Venner *et al.,* (2014) (92); Wechalekar *et al.,* (2007) (76).
End-stage Organ Failure Costs					
Recurring end-stage organ failure costs per cycle	¥353,434 .64	¥35,343.46	Gamma	¥349,103.45	See **Section 4.2.4.5**; ANDROMEDA IPD (primary analysis February 2020, median follow-up: 11.4 months, data on file) (95); Takura *et al.,* (2019) (115).
Healthcare Resource Use Costs					

1L Tx	¥91,319.33	¥9,131.93	Gamma	¥88.308.16	See **Section 4.2.4.6**; NHI Price List (99); Japan MHLW Medical Fee Schedule (101); Janssen Japan Data on File 2021 (116).
Off Tx/FDT	¥50,258.17	¥5,025.82	Gamma	¥50,503.92	See **Section 4.2.4.6**; Japan MHLW Medical Fee Schedule (101); NHI Price List (99); Janssen Japan Data on File 2021 (116).
2L Tx	¥91,319.33	¥9,131.93	Gamma	¥80,713.41	See **Section 4.2.4.6**; NHI Price List (99); Japan

					MHLW Medical Fee Schedule (101); Janssen Japan Data on File 2021 (116).
End-stage Organ Failure	¥91,319.33	¥9,131.93	Gamma	¥82,896.25	See **Section 4.2.4.6**; Japan MHLW Medical Fee Schedule (101); NHI Price List (99); Janssen Japan Data on File 2021 (116).
End of Life Costs					
Costs associated with final month of life	¥662,205.59	¥66,220.56	Gamma	¥466,209.24	See **Section 4.2.4.7**; Japan Medical Association (2007) (117).

Utilities					
CR	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.3.1**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
VGPR	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.3.1**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

PR/NR	[redacted]	[redacted]	Beta	[redacted]	See **Section 4.2.3.1**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
2L Tx health state utility decrement	[redacted]	[redacted]	Gamma	[redacted]	See **Section 4.2.3.3**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

End-stage organ failure health state utility decrement	[redacted]	[redacted]	Gamma	[redacted]	See **Section 4.2.3.3**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95); Emin *et al*., (2016) (118).
Hemodialysis utility decrement	0.1	0.01	Gamma	0.116676643	See **Section 4.2.3.4**; Wyld *et al*., (2012) (119).
Parametric Survival Functions					
NR: Weibull Shape	[redacted]	Cholesky Decomposition	Cholesky Decomposition	[redacted]	See **Section 0.1.1.1** and **Appendix E**; Kastritis *et al*., (2020) (71).
NR: Weibull Scale	[redacted]	Cholesky Decomposition	Cholesky Decomposition	[redacted]	

PR: Weibull Shape	[redacted]	Cholesky Decomposition	Cholesky Decomposition	[redacted]	
PR: Weibull Scale	[redacted]	Cholesky Decomposition	Cholesky Decomposition	[redacted]	
CR: Exponential Rate	[redacted]	Cholesky Decomposition	Cholesky Decomposition	[redacted]	See **Section 0.1.1.1** and **Appendix E**; Kastritis *et al*., (2020) (71).
VGPR: Log-logistic Shape	[redacted]	Cholesky Decomposition	Cholesky Decomposition	[redacted]	
VGPR: Log-logistic Scale	[redacted]	Cholesky Decomposition	Cholesky Decomposition	[redacted]	
Transition Probabilities					
DCyBorD CR transition probability (cycle 7+): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020;

					median follow-up: 11.4 months, data on file) (95).
DCyBorD CR transition probability (cycle 7+): 1L Tx to Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4.**
DCyBorD CR transition probability (cycle 7+): Remain on 1L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4.**
DCyBorD CR transition probability (cycle 7+): Off Tx/FDT to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up:

					11.4 months, data on file) (95).
DCyBorD CR Transition probability (cycle 7+): Off Tx/FDT to 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (18-month landmark analysis; May 2021; median follow-up: 25.8 months, data on file) (98).
DCyBorD CR Transition probability (cycle 7+): Remain in Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.

DCyBorD CR transition probability (cycle 7+): 2L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
DCyBorD CR transition probability (cycle 7+): Remain on 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4.**
DCyBorD VGPR transition probability (cycle 7+): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020;

					median follow-up: 11.4 months, data on file) (95).
DCyBorD VGPR transition probability (cycle 7+): 1L Tx to Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.
DCyBorD VGPR transition probability (cycle 7+): Remain on 1L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.
DCyBorD VGPR transition probability (cycle 7+): Off Tx/FDT to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up:

					11.4 months, data on file) (95).
DCyBorD VGPR transition probability (cycle 7+): Off Tx/FDT to 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**;ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months, data on file) (120).
DCyBorD VGPR transition probability (cycle 7+): Remain in Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.
DCyBorD VGPR transition probability (cycle 7+): 2L Tx to	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD

End-stage Organ Failure					(primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
DCyBorD VGPR transition probability (cycle 7+): Remain in 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4.**
DCyBorD PR/NR transition probability (cycle 7+): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

DCyBorD PR/NR transition probability (cycle 7+): 1L Tx to 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**;ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months, data on file) (120).
DCyBorD PR/NR transition probability (cycle 7+): Remain on 1L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.
DCyBorD PR/NR transition probability (cycle 7+): 2L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020;

					median follow-up: 11.4 months, data on file) (95).
DCyBorD PR/NR transition probability (cycle 7+): Remain on 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.
DCyBorD CR transition probability (cycle 4-6): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
DCyBorD CR transition probability	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.

(cycle 4-6): 1L Tx to Off Tx/FDT					
DCyBorD CR transition probability (cycle 4-6): Remain in 1L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.
DCyBorD CR transition probability (cycle 4-6): Off Tx/FDT to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
DCyBorD CR Transition probability	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**;ANDROMEDA IPD (12-month

(cycle 4-6): Off Tx/FDT to 2L Tx					landmark analysis; November 2020; median follow-up: 20.3 months, data on file) (120).
DCyBorD CR Transition probability (cycle 4-6): Remain in Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.
DCyBorD CR transition probability (cycle 4-6): 2L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).

DCyBorD CR transition probability (cycle 4-6): Remain in 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4.**
DCyBorD VGPR transition probability (cycle 4-6): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
DCyBorD VGPR transition probability (cycle 4-6): 1L Tx to Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.

DCyBorD VGPR transition probability (cycle 4-6): Remain in 1L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4.**
DCyBorD VGPR transition probability (cycle 4-6): Off Tx/FDT to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
DCyBorD VGPR transition probability (cycle 4-6): Off Tx/FDT to 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**;ANDROMEDA IPD (12-month landmark analysis; November 2020;

					median follow-up: 20.3 months, data on file) (120).
DCyBorD VGPR transition probability (cycle 4-6): Remain in Off Tx/FDT	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.
DCyBorD VGPR transition probability (cycle 4-6): 2L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
DCyBorD VGPR transition probability	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.

(cycle 4-6): Remain in 2L Tx					
DCyBorD PR/NR transition probability (cycle 4-6): 1L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
DCyBorD PR/NR transition probability (cycle 4-6): 1L Tx to 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**; ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-

					up: 20.3 months, data on file) (120).
DCyBorD PR/NR transition probability (cycle 4-6): Remain in 1L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.
DCyBorD PR/NR transition probability (cycle 4-6): 2L Tx to End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**;ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
DCyBorD PR/NR transition probability (cycle 4-6): Remain in 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.4**.

Mortality Distribution: 1L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	See **Section 4.2.1.3**; ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months, data on file) (95).
Mortality Distribution: Off 1L Tx/FDT	[redacted]	Dirichlet	Dirichlet	[redacted]	
Mortality Distribution: 2L Tx	[redacted]	Dirichlet	Dirichlet	[redacted]	
Mortality Distribution: End-stage Organ Failure	[redacted]	Dirichlet	Dirichlet	[redacted]	
Mortality Distribution, Decision tree (Assigning end of life costs): CR	[redacted]	Dirichlet	Dirichlet	[redacted]	
Mortality Distribution, Decision tree	[redacted]	Dirichlet	Dirichlet	[redacted]	

(Assigning end of life costs): VGPR					
Mortality Distribution, Decision tree (Assigning end of life costs): PR/NR	[redacted]	Dirichlet	Dirichlet	[redacted]	

*CR and VGPR criteria as defined in the ANDROMEDA CSR (78).

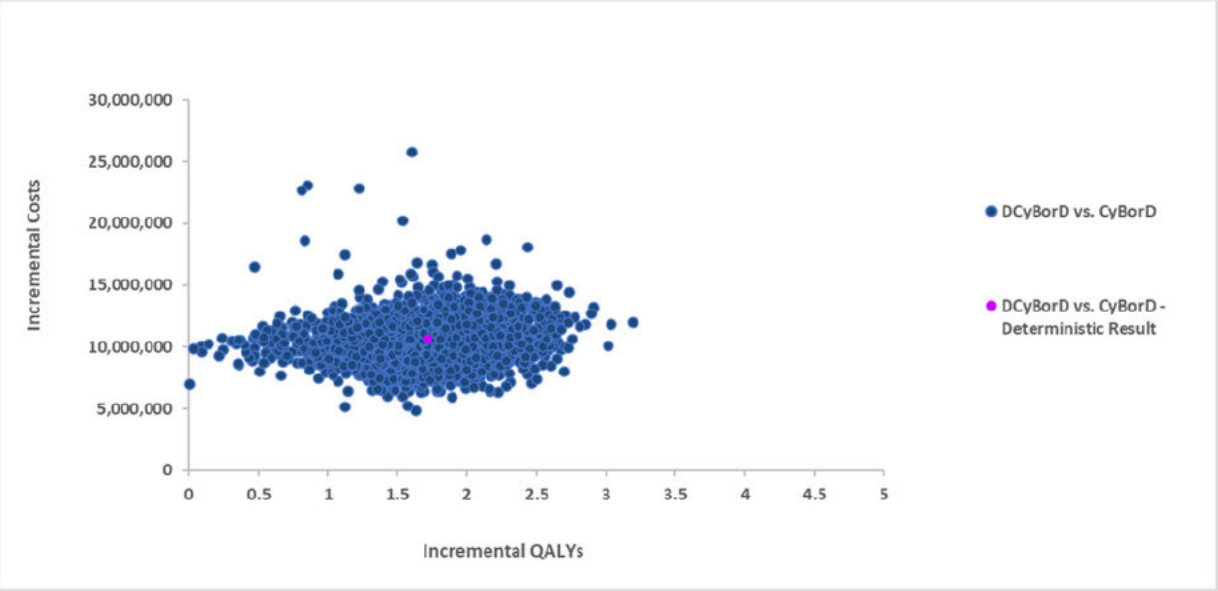
Abbreviations: 1L = first-line; 2L = second-line; AE = adverse event; C2H = Core2 Health; CR = complete response; CSR = clinical study report; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; FDT = fixed daratumumab treatment; IPD = individual patient data; m = meter; mg = milligrams; MHLW = Ministry of Health Labor and Welfare; NA = not applicable; N/A = not applicable; NR = no response; PR = partial response; PSA = probabilistic sensitivity analysis; RDI = relative dose intensity; SD = standard deviation; SE = standard error; Tx = treatment; VGPR = very good partial response.

Table 5.8. Mean discounted costs and quality adjusted life-years from the probabilistic scenario analysis

Treatment	Total Costs	Total QALYs	Incremental Costs (yen)	Incremental QALYs	ICER (Costs/QALYs)
DCyBorD	¥ 22,791,550.91	5.43	¥ 10,688,614.56	1.72	¥ 6,217,913.62
CyBorD	¥ 12,102,936.35	3.71			

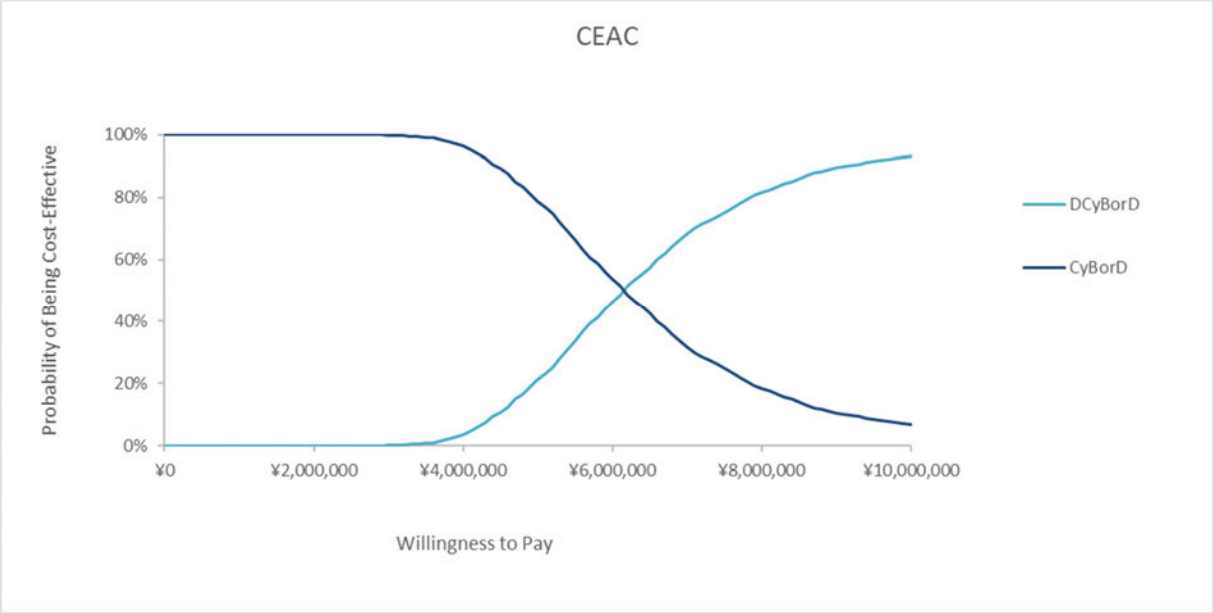
Abbreviations: CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; ICER = incremental cost-effectiveness ratio; QALYs = quality adjusted life-years.

Figure 5.2. Scatter plot of incremental costs versus incremental quality adjusted life-years



Abbreviations: CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; QALYs = quality adjusted life-years.

Figure 5.3. Cost-effectiveness acceptability curve



Abbreviations: CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone.

5.1.3 Validity of the analysis

The model underwent internal validation for model calculations and logic testing by the model programmer, as well as a thorough review of all calculations and data inputs for accuracy and logic by a reviewer not involved with the initial model programming and by another health economic vendor.

Treatment-specific survival results (for patients who receive DCyBorD and for patients who receive CyBorD) predicted from the model were, moreover, compared with observed outcomes from ANDROMEDA. For example, the 3-month hematologic response distribution of patients on DCyBorD or CyBorD and the extrapolated OS curves for CR, VGPR, and PR/NR reproduced a similar number of patients alive by 6 months as observed in the pivotal trial (note that OS estimates from ANDROMEDA at longer timepoints were not considered for validation, given that median follow-up time at the

primary analysis data cut-off was <12 months). Furthermore, the recommended OS extrapolation functions produced survival estimates that were similar to those from published studies reporting survival outcomes in bortezomib-treated AL amyloidosis populations in an assessment of external validation of the CyBorD arm. For example, the 1-year OS rates for patients with newly diagnosed AL amyloidosis who were treated with bortezomib-based regimens ranged from 66% to 80% (BMD, 15% Mayo stage III) (77, 134, 135). Our model predicted a similar 1-year OS of 77% for CyBorD.

A targeted literature search revealed a paucity of Japanese (and/or Asian) studies reporting OS for patients newly diagnosed with AL amyloidosis treated with bortezomib-based regimens. Most studies identified were not appropriate for model validation purposes due to (a) differences in population (ie, a relapsed/refractory patient population) (136) or (b) small sample sizes in the enrolled population (68, 137) or in the population treated with bortezomib-based regimens (70) leading to OS curves with large "steps" from which it would be inappropriate to extrapolate long-term survival estimates. One recent retrospective study reported OS for 20 patients (65% of whom were newly diagnosed) treated with bortezomib and dexamethasone (Bd) (138). The 1-year OS rate for these patients was 90% which suggests the model-predicted 1-year OS of 77% may be a conservative estimate for the Japanese patient population.

Our model predicted a CyBorD median OS of 3.45 years and 64%, 54%, and 46% survival at 2-years, 3-years, and 4-years, respectively, which aligns with real-world median OS values (range from 40.51 months [3.38 years] (72) to 72 months [6 years] (135)) and OS rates at 2-years (range from 47% (123) to 62% (33)), 3-years (range from 42% (123) to 55%) (33), and 4-years (range from 38% (123) to 43% (72)).

Importantly, the model was validated with clinical and HTA experts at a global advisory board in June 2021 with seven experts (three clinicians and four health economists).

This included a review of the model face validity in terms of model design, modelled survival rates by treatment (with extrapolations from the 3-month landmark OS curves from Kastritis *et al*., [2020] (71)), appropriateness of data sources, and key input estimates and clinical assumptions about AL amyloidosis. Overall, the advisors felt that the global model design and assumptions were sound and that the results could be seen as a conservative estimate of the anticipated survival gains from ANDROMEDA. Clinician feedback about the disease that was relevant for model design is provided in **Appendix B**.

Owing to the lack of any published economic models and data sources with long-term patient outcomes in AL amyloidosis treated with DCyBorD, the model could not undergo cross validation or predictive validation.

5.1.4 Interpretation of Analysis Results

Study Population	Adults (≥18 years) newly diagnosed with AL amyloidosis
Comparative Control	CyBorD
ICER reference value	☐ Usual products ☒ Products requiring consideration
Interval considered to have the highest probability of belonging to ICER	☐ Cost reduction or dominants ☒ ≤ 7.5 million yen ☐ > 7.5 million yen and ≤ 11.25 million yen ☐ > 11.25 million yen and ≤ 15 million yen ☐ Over 15 million yen ☐ Comparable effectiveness (Or worse) and high cost
Reason for such judgment	• AL amyloidosis is a designated intractable disease for which regulatory approved, effective therapies are lacking. As such, DCyBorD for the treatment of AL amyloidosis is a product requiring special consideration. • The results of the main analysis were well-supported by 8 deterministic scenario analyses and the probabilistic sensitivity analysis. • The model was robust to the use of different parametric survival functions to inform OS for CR, VGPR, and PR/NR. • Compared with CyBorD, DCyBorD was more costly (¥10,414,642) and more effective (2.15 LYs and 1.85 QALYs), with an ICER of ¥5,626,171 per QALY gained. • The higher costs and improved efficacy associated with DCyBorD treatment were a result of improved hematologic response leading to longer survival.

Abbreviations: CR = complete response; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; ICER = incremental cost-effectiveness ratio; NR = no response; OS = overall survival; PR = partial response; QALYs = quality adjusted life-years; VGPR = very good partial response.

5.1.5 Weight of price adjustment ratio

The estimated number of patients treated by DCyBorD is shown below (refer to section 1.4):

Population	Patient number
Newly diagnosed AL Amyloidosis	[redacted]

5.1.6 Higher prices

Not applicable.

5.2 Analysis Including Public Care Costs and Productivity Losses

Not applicable.

5.3 Other Analyses

Not applicable.

6 Data for reanalysis

Software used	Version	File name	Media
Microsoft® Excel® for Microsoft 365 MSO	Version 2202 (Build 16.0.14931.20216	FINAL_ DCyBorD AL Amyloidosis CUA_Main Analysis_v1.0	MHLW:CD-R C2H: Email
Microsoft® Excel® for Microsoft 365 MSO	Version 2202 (Build 16.0.14931.20216)	FINAL_ DCyBorD AL Amyloidosis CUA_Scenario Analysis_Asian_v1.0	MHLW: CD-R C2H: Email

7 Implementation system

Not applicable.

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Appendix A ANDOMEDA Asian subgroup analysis

Table A.1. Summary of Asian subgroup analysis from the ANDROMEDA trial

Study name	ANDROMEDA
Bibliographic information	(1) Suzuki, K, Wechalekar, A, Kim, K, Shimazaki, C, Kim, JS, Ikezoe, T, Min, CK, Zhou, F, Iida, S, Katoh, N, Fujisaki, T, Shin, HJ, Tran, NP, Qin, X, Vasey, SY, Tromp, B, Weiss, BM, Vermeulen, J, Comenzo, RL, Kastritis, E, Lu, J. Subcutaneous Daratumumab (DARA SC) + Bortezomib, Cyclophosphamide, and Dexamethasone (CyBorD) in Asian Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: Subgroup Analysis from the Phase 3 Andromeda Study. Conference abstract; American Society of Hematology. 2020 Dec 5-8. (2) Suzuki K, Wechalekar, A, Kim, K, Shimazaki, C, Kim, JS, Ikezoe, T, Min, CK, Zhou, F, Iida, S, Katoh, N, Fujisaki, T, Shin, HJ, Tran, NP, Qin, X, Vasey, SY, Tromp, B, Weiss, BM, Vermeulen, J, Comenzo, RL, Kastritis, E, Lu, J. Subcutaneous daratumumab + bortezomib/ cyclophosphamide/ dexamethasone (D-VCD) in newly diagnosed AL amyloidosis: Asian subgroup analysis from ANDROMEDA. 2021.
Clinicaltrials.gov registry information (50)	NCT03201965
Study sites (50)	Multicenter (109 sites in 22 countries)
Study enrollment period (50)	May 3, 2018 – August 15, 2019
Target population (50)	Recruited patients with newly diagnosed systemic AL amyloidosis.
Eligibility criteria (50)	• Eligible patients were aged ≥18 years. • Histopathologic diagnosis of systemic AL amyloidosis (affecting one or more organs). • Measurable hematologic disease.
Key exclusion criteria (50)	• Not reported.

Details of interventional method (50, 54, 63)	• DCyBorD group (ITT population): n = 195
	• DCyBorD group (Asian subgroup): n=29
	• Daratumumab component
	  ○ Dosing: 1800 mg of daratumumab co-formulated with rHuPH20 2000 U/mL.
	  ○ Patients received daratumumab via SC injection once weekly (cycles 1 and 2), every 2 weeks (cycles 3–6), and then every 4 weeks until disease progression,

	the start of subsequent therapy, or for a maximum of 24 cycles from the start of the trial, whichever occurred first. ▪ Each cycle consisted of 28 days. • Cyclophosphamide component o Dosing: 300 mg/m^2 of cyclophosphamide. o Patients received cyclophosphamide as an oral or IV weekly dose for a maximum of 6 28-day cycles. • Bortezomib component o Dosing: 1.3 mg/m^2 of bortezomib. o Patients received bortezomib via SC injection weekly for a maximum of 6 28-day cycles. • Dexamethasone component* o Dosing: 40 mg of dexamethasone weekly. o Patients received dexamethasone as an oral or IV weekly dose for a maximum of 6 28-day cycles.
Details of comparators (50, 54, 63)	• CyBorD group (ITT population): n = 193 • CyBorD group (Asian subgroup): n=31 • Cyclophosphamide component o Dosing: 300 mg/m^2 of cyclophosphamide. o Patients received cyclophosphamide as an oral or IV weekly dose for a maximum of 6 cycles. • Bortezomib component o Dosing: 1.3 mg/m^2 of bortezomib. o Patients received bortezomib via SC injection weekly for a maximum of 6 cycles. • Dexamethasone component* o Dosing: 40 mg of dexamethasone weekly. o Patients received dexamethasone as an oral or IV weekly dose for a maximum of 6 28-day cycles.
Study design (50)	Phase 3 randomized controlled trial. • Randomization was stratified according to cardiac stage (I, II, or IIIA on the basis of the European modification of the Mayo Clinic Cardiac Staging System (33)), availability of transplantation in the local country, and renal function.
Blinding method (50)	Open label
Primary endpoint (50, 54, 63)	• Hematologic complete response
Key secondary endpoints (54, 63)	• MOD-PFS • Organ response • OS • Hematologic complete response at 6-months • Hematologic VGPR or better

	• Time to/duration of hematologic complete response • Time to next treatment • Reduction in fatigue
Statistical methods (50)	• The Kaplan-Meier method was used to estimate time-to-event distributions. • Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards regression model. • The infusion-related reaction rate and rates of very good partial response or better were compared between groups using a stratified Cochran-Mantel-Hansel test.
Sample size (54, 63)	• DCyBorD ITT Population (n=195) • DCyBorD Asian patients (n=29) • CyBorD ITT population (n=193) • CyBorD Asian patients (n=31)
Follow-up period (54, 63)	ITT Population: Median, 11.4 months (range 0.03 to 21.3 months) Asian subgroup: Median, 9.4 months**
Baseline characteristics (for entire Asian sub-population) (54, 63)	• Subjects were recruited from China, Japan, and Korea. • Median age was 66 years • 70% and 58% had heart and kidney involvement, respectively. • 60% had ≥2 organs involved. • Cardiac stage I, II and IIIA/B were 28%, 28%, and 43%, respectively.
Treatment duration for Asian subgroup (54, 63)	DCyBorD group vs CyBorD group (median) • 9.2 months vs 5.3 months
Efficacy for Asian subgroup (54, 63)	Overall hematologic complete response rate • 59% for DCyBorD and 10% for CyBorD (OR, 13.2; 95% CI, 3.3-53.7; p<0.0001). VGPR or better rate • DCyBorD vs CyBorD achieved higher rates of very good partial response or better (≥VGPR; 93% vs 61%). MOD-PFS • MOD-PFS favored DCyBorD-treated patients (HR 0.21; 95% CI, 0.06-0.75, P=0.0079). OS • A total of 12 deaths occurred (DCyBorD, n=3; CyBorD, n=9).
Safety in Asian population (54, 63)	Most common (≥10%) Grade 3-4 TEAEs • Lymphopenia (DCyBorD: 35%; CyBorD: 32%) • Neutropenia (DCyBorD: 10%; CyBorD: 3%)

	• Diarrhea (DCyBorD: 10%; CyBorD: 7%) • Pneumonia (DCyBorD: 7%; CyBorD: 10%) • Cardiac failure (DCyBorD: 7%; CyBorD: 10%) • Hypokalemia (DCyBorD: 7%; CyBorD: 10%) • Anemia (DCyBorD: 3%; CyBorD: 10%) • Thrombocytopenia (DCyBorD: 3%; CyBorD: 10%) • Hypoalbuminemia (DCyBorD: 3%; CyBorD: 10%) • Syncope (DCyBorD: 3%; CyBorD: 10%) TEAEs leading to treatment discontinuation • Occurred in 1 patient in each treatment arm.
Conclusion (54, 63)	Addition of DCyBorD was superior to CyBorD alone in Asian patients, resulting in deeper hematologic responses and improved clinical outcomes.

*For patients who were older than 70 years of age, were underweight (body-mass index [the weight in kilograms divided by the square of the height in meters], <18.5), or had hypervolemia, poorly controlled diabetes mellitus, or previous unacceptable side effects associated with glucocorticoid therapy, dexamethasone could be administered at a dose of 20 mg weekly at the discretion of their physician.

**Range not reported for Asian subgroup.

Abbreviations: CI = confidence interval; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DCyBorD = DCyBorD = daratumumab, cyclophosphamide, bortezomib, dexamethasone; eGFR = estimated glomerular filtration rate; HR = hazard ratio; ITT = intent-to-treat; m = meter; mg = milligrams; min = minute; mL = milliliter; OR = odds ratio; OS = overall survival; TEAE = treatment-emergent adverse event.

Appendix B Clinical feedback on model design

Since no economic models were developed previously for AL amyloidosis, clinician validation (including an advisor from Japan) was influential in supporting the development of a decision tree and Markov model with multiple health states in order to appropriately reflect the patient journey through the disease course and current clinical practice (eg, hematologic response as the goal of therapy, timing of when to switch treatments). Clinical expert opinions were collected in various occasions including an advisory board, the experts are from Australia, Brazil, Canada, China, Japan, UK, and US. A summary of clinical feedback received pertaining to the model design is presented in **Table B.1**.

Table B.1. Clinical feedback received pertaining to model design

Model Design Topic	Feedback Received
Model structure	Model structure appropriately represents the disease and treatment pathway for patients with AL amyloidosis.
Correlation between hematologic response and OS	Hematologic response correlates with OS more in amyloidosis than in other cancers. CR is a good prognostic factor for OS. Hematologic response as reported by Palladini *et al.*, (2012) (74) is a valid approach to inform OS in the model. The available evidence supports a relationship between hematologic response and OS.
Decision tree/assessing hematologic response	Patients will switch to second-line therapy if they do not achieve an adequate response after three cycles. 3-months is a reasonable time to assess whether a patient will be a responder or non-responder 6-months is also an appropriate time point since hematologic response will be established by then (ie, patients that achieved CR are likely to remain in CR) Treatment decisions are based on hematologic response and not organ response since organ response is delayed.
Health states	CR is the cleanest definition of a 'responder' CR and VGPR should be separate health states. Anything less than VGPR after first-line therapy is considered a suboptimal hematologic response. PR and NR can be combined into one health state since outcomes and clinical practice are similar for both. The model structure and health states align with the disease process and patient journey.
Patient survival/death	20-30% of patients have such severe disease at diagnosis that they die within one year regardless of treatment (due to organ/cardiac failure).

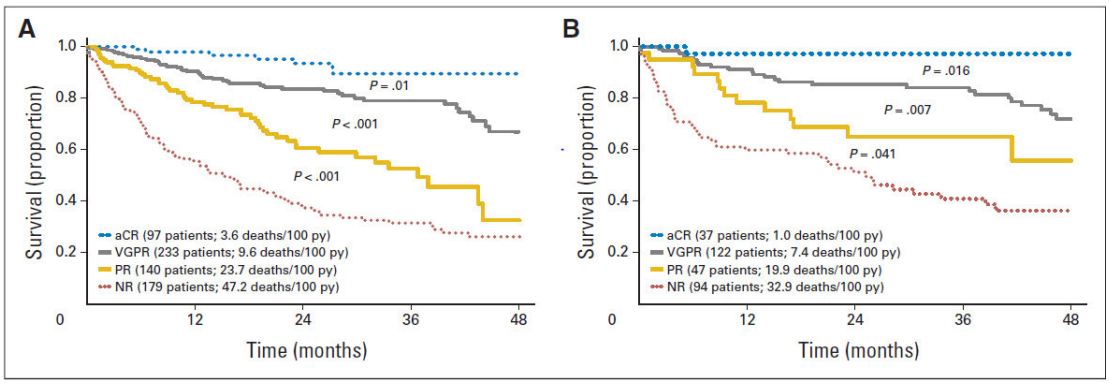
	Early death is the major driver of treatment discontinuation. Most deaths are from arrythmias (sudden death due to cardiac dysfunction) and will occur while patients are on 1L Tx.
End-stage organ failure	Solid organ transplant is extremely rare. Costs in end-stage organ failure will be attributed to dialysis. Patients may progress to end-stage organ failure from any preceding health state.

Abbreviations: 1L = first-line; AL = amyloid light-chain; CR = complete response; NA = not applicable; NR = no response; OS = overall survival; PR = partial response; Tx = treatment; VGPR = very good partial response.

Appendix C Correlation Between Hematologic Response and Overall Survival

In the context of AL amyloidosis, achieving a swift and deep hematologic response is the goal of first-line therapy as it prevents further organ damage and improves survival (66). Hematologic response is assessed at each cycle of the treatment course as an early response measure is used by clinicians to evaluate treatment efficacy due to its prognostic correlation with OS (74). Better OS in patients with hematologic response compared with those who had no response has been observed in numerous published studies (including studies based in Japan) (27, 33, 67, 69, 71-76), and univariate and multivariate analyses have found hematologic response to be a predictor of survival (33, 67, 69, 71, 74, 76). Indeed, a 2012 retrospective study including 816 patients diagnosed with AL amyloidosis between 2002-2010 reported that hematologic response had a prognostic correlation with OS with significant differences in survival based on patient three- or six-month hematologic response (**Figure C.1**) (74). Since the advent of bortezomib-based treatment regimens in 2010, similar trends in OS have been observed with respect to hematologic response. A 2015 study of 230 newly diagnosed patients treated with CyBorD reported significantly higher OS among patients that achieved ≥VGPR compared to either PR or NR (**Figure C.2**) (33). Similarly, a 2020 study of 227 patients treated upfront with bortezomib-based regimens showed significantly better OS for patients that achieving CR or VGPR at both one- and three-month landmarks (**Figure C.3**) (71).

Figure C.1. OS by hematologic response as reported by Palladini *et al*., (2012)

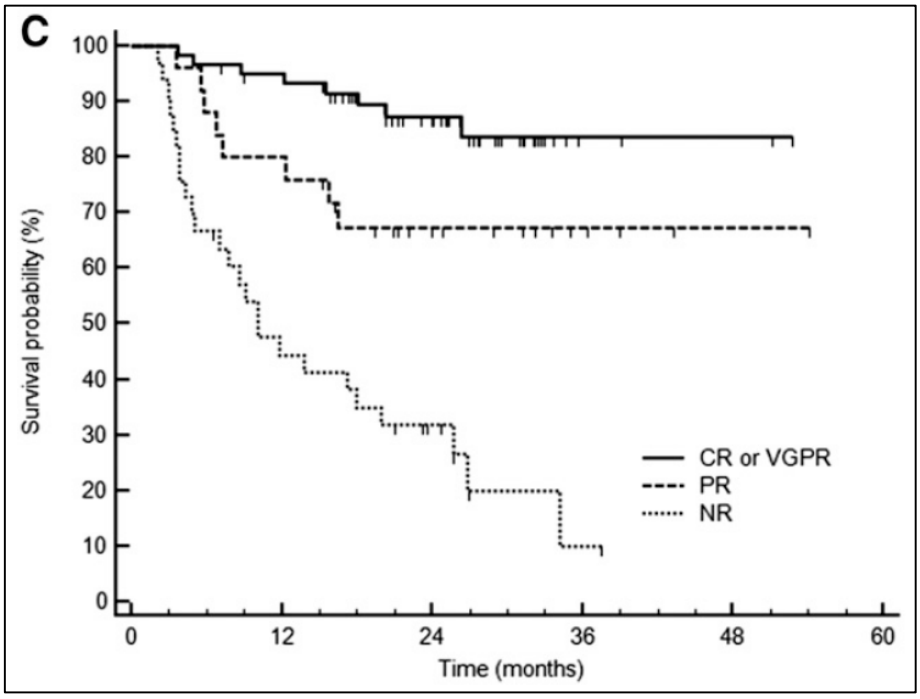


(A) OS based on patient six-month hematologic response; (B) OS based on patient three-month hematologic response.

Abbreviations: aCR = amyloid complete response; NR = no response; OS = overall survival; PR = partial response; py = person-year; VGPR = very good partial response.

Source: Palladini *et al*., (2012) (74).

Figure C.2. OS by hematologic response as reported by Palladini *et al*., (2015)

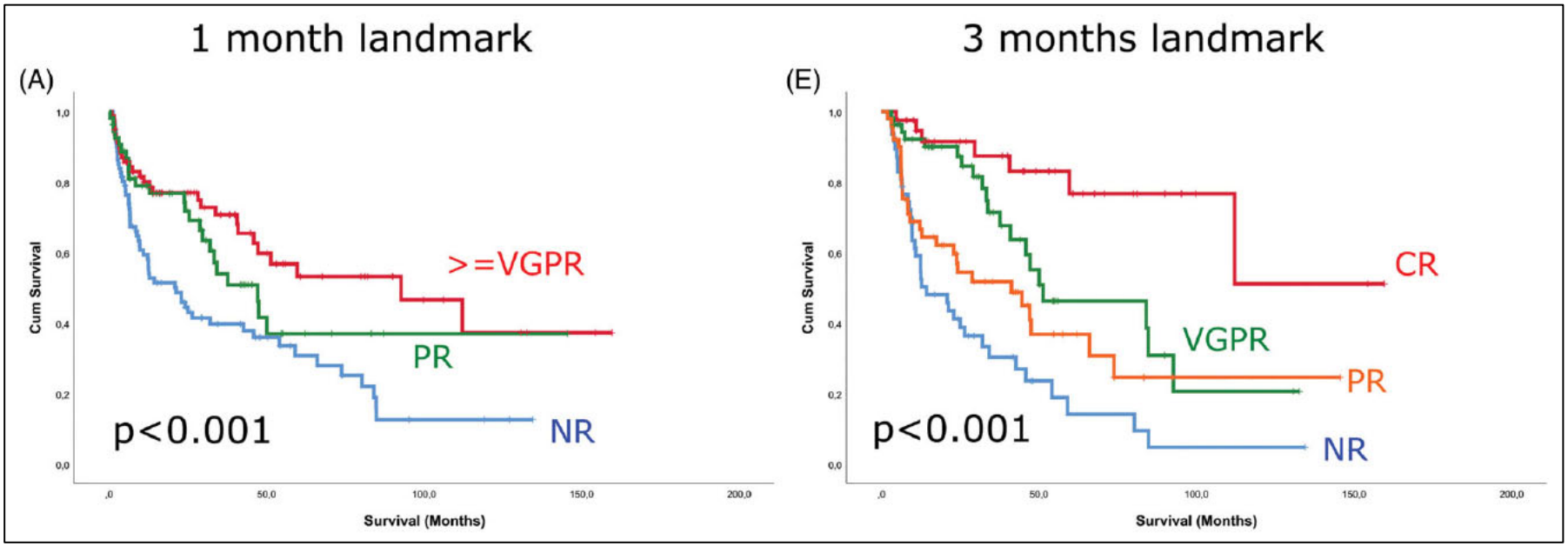


Abbreviations: CR = complete response; NR = no response; OS = overall survival; PR = partial

response; VGPR = very good partial response.

Source: Palladini *et al*., (2015) (33).

Figure C.3. OS by hematologic response as reported by Kastritis *et al*., (2020) (71)

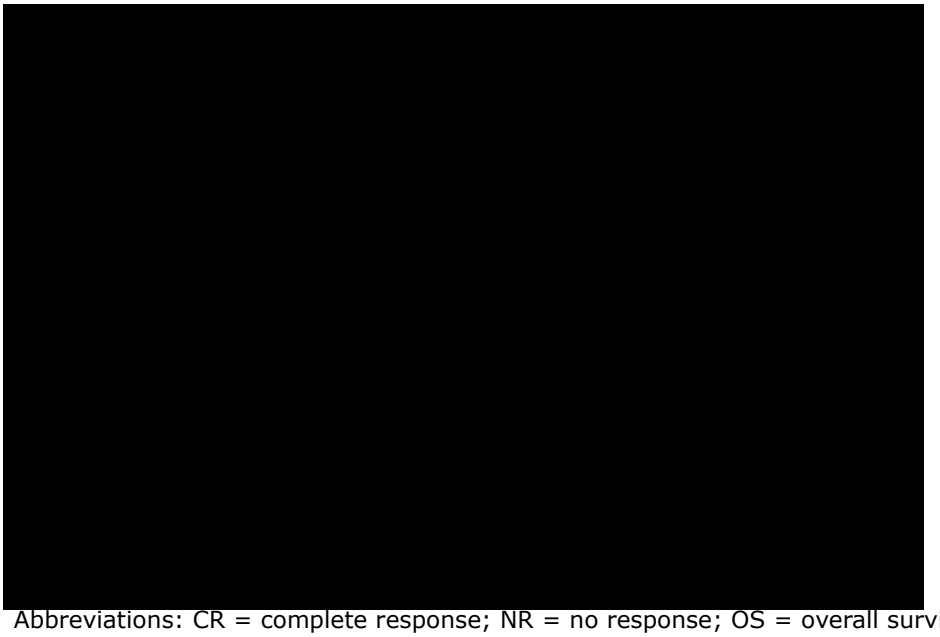


Abbreviations: CR = complete response; NR = no response; OS = overall survival; PR = partial response; VGPR = very good partial response.

Source: Kastritis *et al*., (2020) (31).

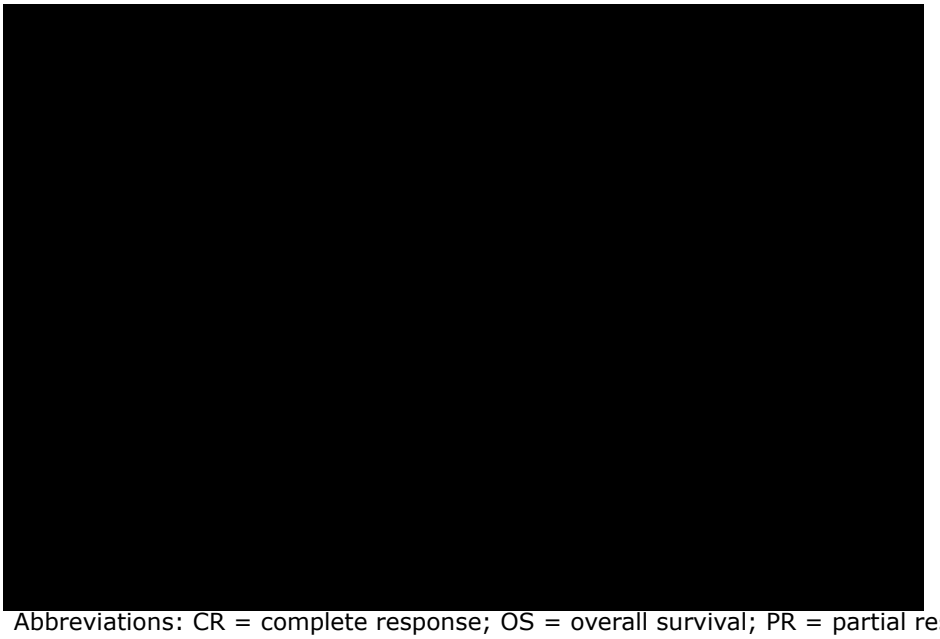
Appendix D Log-cumulative Hazard Plots for OS per Kastritis *et al*., (2020) (71)

Figure D.1. Log-cumulative hazard plot for OS: CR vs. NR ([redacted])



Abbreviations: CR = complete response; NR = no response; OS = overall survival.

Figure D.2. Log-cumulative hazard plot for OS: CR vs. PR ([redacted])

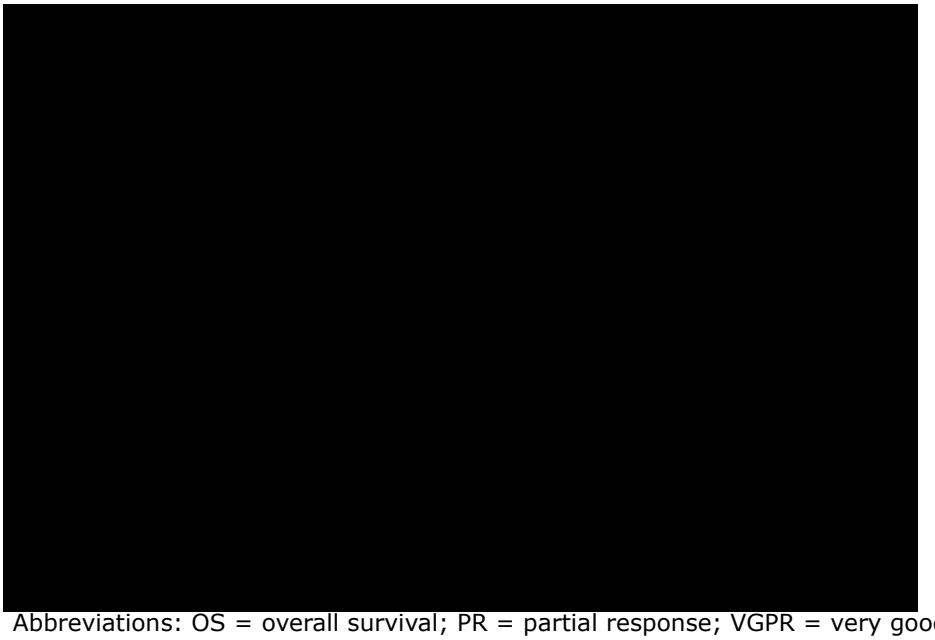


Abbreviations: CR = complete response; OS = overall survival; PR = partial response.

Figure D.3. Log-cumulative hazard plot for OS: VGPR vs. NR ( )

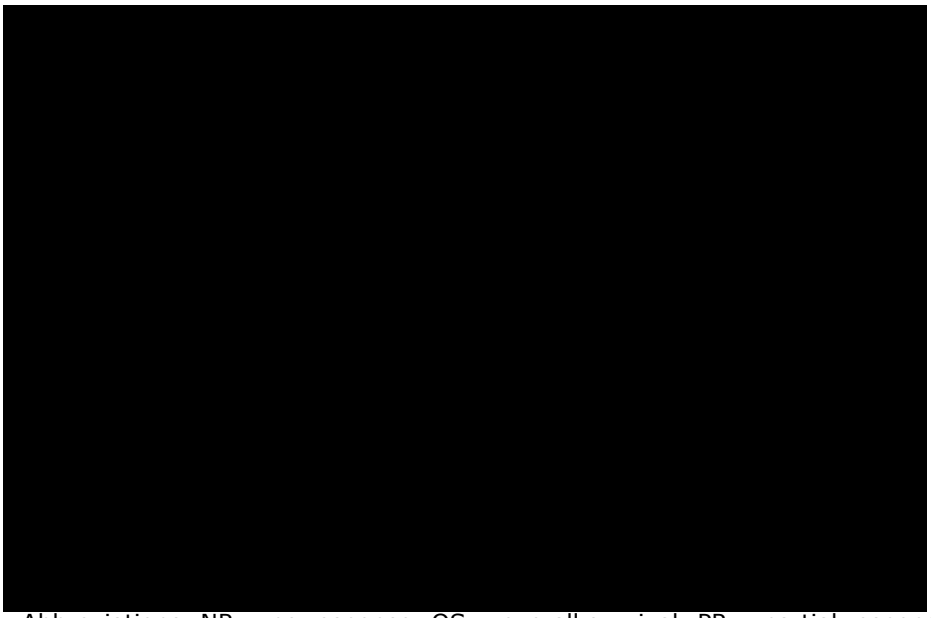
Abbreviations: NR = no response; OS = overall survival; VGPR = very good partial response.

Figure D.4. Log-cumulative hazard plot for OS: VGPR vs. PR ([redacted])



Abbreviations: OS = overall survival; PR = partial response; VGPR = very good partial response.

Figure D.5. Log-cumulative hazard plot for OS: PR vs. NR ([redacted])



Abbreviations: NR = no response; OS = overall survival; PR = partial response.

Appendix E Extrapolation parameters and covariance matrix

Appendix E.1 Parametric survival functions

Exponential

Equation $S(t) = \exp(-rate * t)$

Treatment Effect

$$rate_{treatment} = rate_{control} * \exp(covariate)$$

Weibull

Equation $S(t) = \exp\left(-scale * t^{shape}\right)$

Treatment Effect

$$scale_{treatment} = scale_{control} * \exp(covariate)$$

Gompertz

Equation $S(t) = \exp\left(\left(\frac{rate}{shape}\right) * (1 - \exp(shape * t)\right)$

Treatment Effect

$$rate_{treatment} = rate_{control} * \exp(covariate)$$

Log-normal

Equation $S(t) = 1 - normdist\left(\frac{\ln(t) - meanlog}{sdlog}, 0, 1, True\right)$

Treatment Effect

$$meanlog_{Treatment} = meanlog_{Control} + \text{covariate}$$

Log-logistic

Equation $S(t) = \frac{1}{1 + \exp\left(-\ln(scale) * (shape)\right) * t^{shape}}$

Treatment Effect

$$scale_{treatment} = scale_{control} * \exp(covariate)$$

Generalized Gamma

Equation

$S(t) = 1 - \text{GAMMADIST}(\lambda * t^{\delta}, \gamma, 1, \text{TRUE}), \text{when } \delta > 0$

$S(t) = \text{GAMMADIST}(\lambda * t^{\delta}, \gamma, 1, \text{TRUE}), \text{when } \delta < 0$

Note: δ will be < 0 (i.e. negative when Q < 0)

Where:

$$\lambda = \gamma * \exp(-mu)^{\delta}$$

$$\gamma = \frac{1}{Q^2}$$

$$\delta = \frac{Q}{sigma}$$

Treatment Effect

$$mu_{Treatment} = mu_{Control} + \text{covariate}$$

Appendix E.2 Extrapolation parameters and covariance matrices for Kastritis *et al.*, (2020) (71)

Note: all curve extrapolation covariance matrices were generated using Cholesky decomposition matrices.

No Response (NR)

Table E.1. Extrapolation parameters for patients with NR

	Extrapolation Parameters							
Survival Function	**rate**	**shape**	**scale**	**mean log**	**sdlog**	**mu**	**sigma**	**Q**
Exponential	[redacted]	-	-	-	-	-	-	-
Weibull	-	[redacted]	[redacted]	-	-	-	-	-
Gompertz	[redacted]	[redacted]	-	-	-	-	-	-
Log-normal	-	-	-	[redacted]	[redacted]	-	-	-
Log-logistic	-	[redacted]	[redacted]	-	-	-	-	-
Gamma	[redacted]	[redacted]	-	-	-	-	-	-

	[redacted]	[redacted]						
Generalized gamma	-	-	-	-	-	[redacted]	[redacted]	[redacted]

Table E.2. Covariance matrix for NR Exponential OS extrapolation

Variable	rate
rate	[redacted]

Abbreviations: NR = no response; OS = overall survival.

Table E.3. Covariance matrix for NR Weibull OS extrapolation

Variable	shape	scale
shape	[redacted]	[redacted]
scale	[redacted]	[redacted]

Abbreviations: NR = no response; OS = overall survival.

Table E.4. Covariance matrix for NR Gompertz OS extrapolation

Variable	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Abbreviations: NR = no response; OS = overall survival.

Table E.5. Covariance matrix for NR Log-normal OS extrapolation

Variable	meanlog	sdlog
meanlog	[redacted]	[redacted]
sdlog	[redacted]	[redacted]

Abbreviations: NR = no response; OS = overall survival.

Table E.6. Covariance matrix for NR Log-logistic OS extrapolation

Variable	shape	scale
shape	[redacted]	[redacted]

scale	[redacted]	[redacted]

Abbreviations: NR = no response; OS = overall survival.

Table E.7. Covariance matrix for NR Gamma OS extrapolation

Variable	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Abbreviations: NR = no response; OS = overall survival.

Table E.8. Covariance matrix for NR Generalized gamma OS extrapolation

Variable	mu	sigma	Q
mu	[redacted]	[redacted]	[redacted]
sigma	[redacted]	[redacted]	[redacted]
Q	[redacted]	[redacted]	[redacted]

Abbreviations: NR = no response; OS = overall survival.

Partial Response (PR)

Table E.9. Extrapolation parameters for patients with PR

	Extrapolation Parameters							
Survival Function	**rate**	**shape**	**scale**	**meanlog**	**sdlog**	**mu**	**sigma**	**Q**
Exponential	[redacted]	-	-	-	-	-	-	-
Weibull	-	[redacted]	[redacted]	-	-	-	-	-
Gompertz	[redacted]	[redacted]	-	-	-	-	-	-
Log-normal	-	-	-	[redacted]	[redacted]	-	-	-
Log-logistic	-	[redacted]	[redacted]	-	-	-	-	-
Gamma	[redacted]	[redacted]		-	-	-	-	-

	[redacted]	[redacted]						
Generalized gamma	-	-	-	-	-	[redacted]	[redacted]	[redacted]

Table E.10. Covariance matrix for PR Exponential OS extrapolation

Variable	rate
rate	[redacted]

Abbreviations: OS = overall survival; PR = partial response.

Table E.11. Covariance matrix for PR Weibull OS extrapolation

Variable	shape	scale
shape	[redacted]	[redacted]
scale	[redacted]	[redacted]

Abbreviations: OS = overall survival; PR = partial response.

Table E.12. Covariance matrix for PR Gompertz OS extrapolation

Variable	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Abbreviations: OS = overall survival; PR = partial response.

Table E.13. Covariance matrix for PR Log-normal OS extrapolation

Variable	meanlog	sdlog
meanlog	[redacted]	[redacted]
sdlog	[redacted]	[redacted]

Abbreviations: OS = overall survival; PR = partial response.

Table E.14. Covariance matrix for PR Log-logistic OS extrapolation

Variable	shape	scale
shape	[redacted]	[redacted]

scale	[redacted]	[redacted]

Abbreviations: OS = overall survival; PR = partial response.

Table E.15. Covariance matrix for PR Gamma OS extrapolation

Variable	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Abbreviations: OS = overall survival; PR = partial response.

Table E.16. Covariance matrix for PR Generalized gamma OS extrapolation

Variable	mu	sigma	Q
mu	[redacted]	[redacted]	[redacted]
sigma	[redacted]	[redacted]	[redacted]
Q	[redacted]	[redacted]	[redacted]

Abbreviations: OS = overall survival; PR = partial response.

Very Good Partial Response (VGPR)

Table E.17. Extrapolation parameters for patients with VGPR

	Extrapolation Parameters							
Survival Function	**rate**	**shape**	**scale**	**meanlog**	**sdlog**	**mu**	**sigma**	**Q**
Exponential	[redacted]	-	-	-	-	-	-	-
Weibull	-	[redacted]	[redacted]	-	-	-	-	-
Gompertz	[redacted]	[redacted]	-	-	-	-	-	-
Log-normal	-	-	-	[redacted]	[redacted]	-	-	-
Log-logistic	-	[redacted]	[redacted]	-	-	-	-	-
Gamma	[redacted]	[redacted]	-	-	-	-	-	-

Generalized gamma	-	-	-	-	-	[redacted]	[redacted]	[redacted]

Table E.18. Covariance matrix for VGPR Exponential OS extrapolation

Variable	rate
rate	[redacted]

Abbreviations: OS = overall survival; VGPR = very good partial response.

Table E.19. Covariance matrix for VGPR Weibull OS extrapolation

Variable	shape	scale
shape	[redacted]	[redacted]
scale	[redacted]	[redacted]

Abbreviations: OS = overall survival; VGPR = very good partial response.

Table E.20. Covariance matrix for VGPR Gompertz OS extrapolation

Variable	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Abbreviations: OS = overall survival; VGPR = very good partial response.

Table E.21. Covariance matrix for VGPR Log-normal OS extrapolation

Variable	meanlog	sdlog
meanlog	[redacted]	[redacted]
sdlog	[redacted]	[redacted]

Abbreviations: OS = overall survival; VGPR = very good partial response.

Table E.22. Covariance matrix for VGPR Log-logistic OS extrapolation

Variable	shape	scale
shape	[redacted]	[redacted]

scale	[redacted]	[redacted]

Abbreviations: OS = overall survival; VGPR = very good partial response.

Table E.23. Covariance matrix for VGPR Gamma OS extrapolation

Variable	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Abbreviations: OS = overall survival; VGPR = very good partial response.

Table E.24. Covariance matrix for VGPR Generalized gamma OS extrapolation

Variable	mu	sigma	Q
mu	[redacted]	[redacted]	[redacted]
sigma	[redacted]	[redacted]	[redacted]
Q	[redacted]	[redacted]	[redacted]

Abbreviations: OS = overall survival; VGPR = very good partial response.

Complete Response (CR)

Table E.25. Extrapolation parameters for patients with CR

	Extrapolation Parameters							
Survival Function	**rate**	**shape**	**scale**	**meanlog**	**sdlog**	**mu**	**sigma**	**Q**
Exponential	[redacted]	-	-	-	-	-	-	-
Weibull	-	[redacted]	[redacted]	-	-	-	-	-
Gompertz	[redacted]	[redacted]	-	-	-	-	-	-
Log-normal	-	-	-	[redacted]	[redacted]	-	-	-
Log-logistic	-	[redacted]	[redacted]	-	-	-	-	-
Gamma	[redacted]	[redacted]	-	-	-	-	-	-

Generalized gamma	-	-	-	-	-	[redacted]	[redacted]	[redacted]

Table E.26. Covariance matrix for CR Exponential OS extrapolation

Variable	rate
rate	[redacted]

Abbreviations: CR = complete response; OS = overall survival.

Table E.27. Covariance matrix for CR Weibull OS extrapolation

Variable	shape	scale
shape	[redacted]	[redacted]
scale	[redacted]	[redacted]

Abbreviations: CR = complete response; OS = overall survival.

Table E.28. Covariance matrix for CR Gompertz OS extrapolation

Variable	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Abbreviations: CR = complete response; OS = overall survival.

Table E.29. Covariance matrix for CR Log-normal OS extrapolation

Variable	meanlog	sdlog
meanlog	[redacted]	[redacted]
sdlog	[redacted]	[redacted]

Abbreviations: CR = complete response; OS = overall survival.

Table E.30. Covariance matrix for CR Log-logistic OS extrapolation

Variable	shape	scale
shape	[redacted]	[redacted]

scale	[redacted]	[redacted]

Abbreviations: CR = complete response; OS = overall survival.

Table E.31. Covariance matrix for CR Gamma OS extrapolation

Variable	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Abbreviations: CR = complete response; OS = overall survival.

Table E.32. Covariance matrix for CR Generalized gamma OS extrapolation

Variable	mu	sigma	Q
mu	[redacted]	[redacted]	[redacted]
sigma	[redacted]	[redacted]	[redacted]
Q	[redacted]	[redacted]	[redacted]

Abbreviations: CR = complete response; OS = overall survival.

Appendix F MOD-PFS Rates Over Time

Table F.1. MOD-PFS rates over time for patients with CR

Time Point (Month)	MOD-PFS Rate	At Risk*	Number of Events	Censoring Number**
[redacted]	[redacted]	[redacted]	[redacted]	NR
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	

*Only the starting number at risk was reported by Kastritis et al., (2020) (71); all remaining numbers at risk were generated by creating pseudo-IPD during the curve extrapolation process according to the methods described by Guyot *et al.*, (2012) (122).

**Because pseudo-IPD was used in the curve extrapolation process, the number of censors is not available.

Abbreviations: IPD = individual patient data; MOD-PFS = major organ deterioration progression-free survival; NR = not reported.

Table F.2. MOD-PFS rates over time for patients with VGPR

Time Point (Month)	MOD-PFS Rate	At Risk*	Number of Events	Censoring Number**
[redacted]	[redacted]	[redacted]	[redacted]	NR
[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]	

*Only the starting number at risk was reported by Kastritis et al., (2020) (71); all remaining numbers at risk were generated by creating pseudo-IPD during the curve extrapolation process according to the methods described by Guyot *et al.*, (2012) (122).

**Because pseudo-IPD was used in the curve extrapolation process, the number of censors is not available.

Abbreviations: IPD = individual patient data; MOD-PFS = major organ deterioration progression-free survival; NR = not reported.

Table F.3. MOD-PFS rates over time for patients with PR or NR

Time Point (Month)	MOD-PFS Rate	At Risk*	Number of Events	Censoring Number**
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	NR
[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]	[redacted]	[redacted]	[redacted]	

*Only the starting number at risk was reported by Kastritis *et al*., (2020) (71); all remaining numbers at risk were generated by creating pseudo-IPD during the curve extrapolation process according to the methods described by Guyot *et al*., (2012) (122).

**Because pseudo-IPD was used in the curve extrapolation process, the number of censors is not available.

Abbreviations: IPD = individual patient data; MOD-PFS = major organ deterioration progression-free survival; NR = not reported.

Appendix G Time-to-subsequent Therapy Rates Over Time

Table G.1. Time-to-subsequent therapy rates over time for patients with CR

Time Point (Month)	Time to Next Treatment Rate	At Risk*	Number of Events	Censoring Number**
[redacted]	[redacted]	[redacted]	[redacted]	NR
[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]	

*Only the starting number at risk was reported by Kastritis *et al.*, (2020) (71); all remaining numbers at risk were generated by creating pseudo-IPD during the curve extrapolation process according to the methods described by Guyot *et al.*, (2012) (122).

**Because pseudo-IPD was used in the curve extrapolation process, the number of censors

is not available.

Abbreviations: IPD = individual patient data; NR = not reported.

Table G.2. Time-to-subsequent therapy rates over time for patients with VGPR

Time Point (Month)	Time to Next Treatment Rate	At Risk*	Number of Events	Censoring Number**
[redacted]	[redacted]	[redacted]	[redacted]	NR
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
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*Only the starting number at risk was reported by Kastritis *et al*., (2020) (71); all remaining numbers at risk were generated by creating pseudo-IPD during the curve extrapolation process according to the methods described by Guyot *et al*., (2012) (122).

**Because pseudo-IPD was used in the curve extrapolation process, the number of censors is not available.

Abbreviations: IPD = individual patient data; NR = not reported.

Appendix H Medical Data Vision (MDV) database analysis

Table H.1. Methodology for MDV database analysis

Item	Description
Data source	Retrospective claims data obtained from the Medical Data Vision (MDV) database were analyzed from 01 January 2003 to 31 Aug 2020. The MDV database comprises standardized health-care insurance claims data provided by hospitals in Japan, which is using the Japanese Diagnosis and Procedure Combination (DPC) fixed-payment reimbursement system for over 36 million individuals since the year 2003 and contains about 6 hundred patients with AL amyloidosis.
Study Design and Patient Population	• Adult patients (age 20 or above) with a diagnosis of AL Amyloidosis were considered for this analysis. AL Amyloidosis diagnosis was defined as the presence of at least one record with a confirmed AL amyloidosis diagnosis code (ICD-10 code E858 in combination with the Japanese disease code 8845844). • Index diagnosis date was defined as the date on which the patient had first record of confirmed AL amyloidosis diagnosis. The baseline period was the 3-month period before the index diagnosis date and the follow-up period consisted of ≥60 days from the index diagnosis date; however, patients who died within this 60-day period were included for fairness consideration.
Outcomes evaluated	• Emergency Room Visit: Proportion of Patients Requiring Item, Frequency of Resource Utilization • Inpatient Hospitalization: Proportion of Patients Requiring Item, Length of hospitalization, Frequency of Resource Utilization • Outpatient Visit: Proportion of Patients Requiring Item, Frequency of Resource Utilization

	• Adverse event cost: [Cost of adverse event from Multiple Myeloma HTA submission is leveraged in this submission]

Abbreviations: AL = amyloid light-chain; DPC = Diagnosis and Procedure Combination; HTA = health technology assessment; MDV = Medical Data Vision.

Table H.2. Protocol for Estimating incidental medical Resource Utilization Costs in the AL Amyloidosis

Steps	Description
Emergency Room Visit	
Step 1	Identify the first diagnosis of AL amyloidosis in the database, then identify the 1st AL amyloidosis regimen following the diagnosis
Step 2	Identify the 1st AL amyloidosis regimen and its first administration date (D1)
Step 3	Identify the 2nd AL amyloidosis regimen and its first administration date (D2)
Step 4	Identify the 3rd AL amyloidosis regimen and its first administration date (D3)
Step 5	Identify the first record of ESRF disease name after D1 and its first record date (ESRF_start)
Step 6	Identify the end of timeframe – either the end of follow up or death (End_date)
Step 7	Exclude patients who died within 6 months from the first diagnosis
Step 8	Calculate the % patients who experienced an emergency room visit between D1 and D3, to estimate % of patient requiring ER in the following health states, '1L Tx', 'Off Tx/FDT', and '2L Tx'
Step 9	Calculate the % patients who experienced an emergency room visit between ESRF_start and End_date to estimate % of patient requiring ER in the health state of ESRF
Step 10	Frequency of utilization of ER is calculated for '1L Tx', '2L Tx', and ESRF. The frequency is converted to frequency per 28-day cycle.[ii] Due to a paucity of data, emergency room visit frequencies for '2L Tx' and 'End-stage Organ Failure' were assumed equivalent to '1L Tx'. The frequency of ER utilization for 'Off Tx/FDT' was estimated based on the percent reduction in emergency room utilization between the first- and second-years post-diagnosis per Quock *et al*., (2018) (93).[iii]

[ii] Calculating the frequency of events per 28-day cycle involved dividing the number of events by the entire duration during which the events occurred and multiplying by 28 (ie, [n events/duration in days)]*28).

[iii] Relative reductions in HCRU between the first- and second-years post-diagnosis with AL amyloidosis were used as a proxy by which to estimate the reduction in HCRU between '1L Tx' and 'Off Tx/FDT'. For example, the relative reduction in emergency room visits (per 28-day cycle) between first- and

Steps	Description
Inpatient Hospitalization	
Step 1	Calculate the % patients who experienced an inpatient hospitalization between D1 and D3, to estimate % of patient requiring hospitalization in the following health states: '1L Tx', 'Off Tx/FDT', and '2L Tx'.
Step 2	Calculate the % patients who experienced an inpatient hospitalization between ESRF_start and End_date to estimate % of patient requiring hospitalization in the health state of ESRF .
Step 3	Extract the records of hospitalization and calculate the average length of hospitalization.
Step 4	Frequency of utilization of inpatient hospitalizations calculated for '1L Tx', '2L Tx', and ESRF. The frequency is converted to frequency per 28-day cycle.[iv] Due to a paucity of data, the inpatient hospitalization frequencies for '2L Tx' and 'End-stage Organ Failure' were assumed equivalent to '1L Tx'. The frequency of hospitalization utilization for 'Off Tx/FDT' was estimated based on the percent reduction in inpatient hospitalizations between the first- and second-years post-diagnosis per Quock *et al*., (2018) (93).[v]
Outpatient Visit	
Step 1	Calculate the % patients who experienced an outpatient visit between D1 and D3, to estimate % of patient requiring outpatients in the following health states, '1L Tx', 'Off Tx/FDT', and '2L Tx'.
Step 2	Calculate the % patients who experienced an outpatient visit between ESRF_start and End_date to estimate % of patient requiring outpatients in the health state of ESRF.
Step 3	Frequency of utilization of outpatient visit was calculated for '1L Tx', '2L Tx', and 'End-stage Organ Failure'. The frequency is

second-year post-diagnosis was calculated to be [redacted]. This reduction was applied to values for '1L Tx' from the MDV database analysis to obtain an estimated 28-day frequency of emergency room visits in the 'Off Tx/FDT' health state (ie, [redacted]).

[iv] Calculating the frequency of events per 28-day cycle involved dividing the number of events by the entire duration during which the events occurred and multiplying by 28 (ie, [n events/duration in days)]*28).

[v] Relative reductions in HCRU between the first- and second-years post-diagnosis with AL amyloidosis were used as a proxy by which to estimate the reduction in HCRU between '1L Tx' and 'Off Tx/FDT'. For example, the relative reduction in inpatient visits (per 28-day cycle) between first- and second-year post-diagnosis was calculated to be 0.543. This reduction was applied to values for '1L Tx' from the MDV database analysis to obtain an estimated 28-day frequency of inpatient visits in the 'Off Tx/FDT' health state (ie, [redacted]).

Steps	Description
	converted to frequency per 28-day cycle.[vi] Due to a paucity of data, outpatient visit frequencies for '2L Tx' and 'End-stage Organ Failure' were assumed equivalent to '1L Tx'. The frequency of outpatient visit utilization for 'Off Tx/FDT' was estimated based on the percent reduction in outpatient visits between the first- and second-years post-diagnosis per Quock *et al*., (2018) (93).[vii]
Adverse event cost [Cost of adverse event from Multiple Myeloma HTA submission is leveraged in this submission]	
Step 1	Identify the first diagnosis of MM in the database, then identify the 1st MM regimen following the diagnosis.
Step 2	Identify the 1st MM regimen and its first administration date (MM_D1)
Step 3	Identify the first record of AE disease name after MM_D1 and its first record date (AE_start)
Step 4	Identify the sequentially continuous record of AE as monthly from AE_start and identify the last of the record in the sequence as AE end record (AE_end)
Step 5	Identify the date one month before from the AE_start (AE_oneM_before)
Step 6	Identify AE-related drug cost items between AE_start and AE_end and exclude AE-related drug cost items which occurred between AE_oneM_before and AE_start
Step 7	Calculate AE-related drug cost between AE_start and AE_end (NDMM_AE_cost)
Step 8	Identify the 2nd MM regimen and its first administration date (MM_D2)
Step 9	Repeat the steps to calculate AE cost after MM_D2 (RRMM_AE_cost)
Step 10	Calculate the weighted average cost from NDMM_AE_cost and RRMM_AE_cost

[vi] Calculating the frequency of events per 28-day cycle involved dividing the number of events by the entire duration during which the events occurred and multiplying by 28 (ie, [n events/duration in days)]*28).

[vii] Relative reductions in HCRU between the first- and second-years post-diagnosis with AL amyloidosis were used as a proxy by which to estimate the reduction in HCRU between '1L Tx' and 'Off Tx/FDT'. For example, the relative reduction in outpatient visits (per 28-day cycle) between first- and second-year post-diagnosis was calculated to be [redacted]. This reduction was applied to values for '1L Tx' from the MDV database analysis to obtain an estimated 28-day frequency of outpatient visits in the 'Off Tx/FDT' health state (ie, [redacted]).

Abbreviations: AE = adverse event; AL = amyloid light-chain; ER = emergency room; ESRF = End-stage renal failure, FDT = fixed daratumumab treatment; HTA = health technology assessment; MDV = Medical Data Vision; NDMM = newly diagnosed multiple myeloma, RRMM = relapsed and refractory multiple myeloma.