Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Darzalex SC

Active ingredient: Daratumumab

Sponsor: Janssen-Cilag Pty Ltd

October 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-rHuPH20	Anti-recombinant human PH20 hyaluronidase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate aminotransferase
CABG	Coronary artery bypass graft
C_{max}	Maximum plasma concentration
C_{trough}	Trough concentration
CyBorD	Cyclophosphamide, bortezomib and dexamethasone combination therapy (also known as VCd)
dFLC	Difference in involved and uninvolved free light chain
DLP	Data lock point
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration (United States of America)
FLC	Free light chains
hCR	Haematologic complete response
hPR	Haematologic partial response
hVGPR	Haematologic very good partial response
IA	Interim analyses
IACC	International Amyloidosis Consensus Criteria
IFE	Immunofixation

Abbreviation	Meaning
iFLC	Involved free light chain
IG	Immunoglobin
IRC	Independent review committee(s)
IRR	Infusion related reaction
LLN	Lower limit of normal
mCR	Modified complete response
MM	Multiple myeloma
MOD-EFS	Major organ deterioration event free survival
MOD-PFS	Major organ deterioration progression free survival
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
OS	Overall survival
RMP	Risk management plan
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
uFLC	Uninvolved free light chain
ULN	Upper limit of normal
US(A)	United States (of America)
VCd	Velcade (tradename for bortezomib), cyclophosphamide and dexamethasone combination therapy (also known as CyBorD)
VGPR	Very good partial response

Product submission

Submission details

Type of submission:	Extension of indications
Product name:	Darzalex SC
Active ingredient:	Daratumumab
Decision:	Approved
Date of decision:	6 October 2021
Date of entry onto ARTG:	6 October 2021
ARTG number:	322685
▼ *Black Triangle Scheme:*	No
Sponsor's name and address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Road, Macquarie Park, NSW 2113
Dose form:	Solution for injection
Strength:	120 mg/mL (1800 mg/15 mL)
Container:	Vial
Pack size:	1
Approved therapeutic use:	*Darzalex SC in combination with bortezomib, cyclophosphamide and dexamethasone, is indicated for the treatment of patients with light chain AL amyloidosis.*
Route of administration:	Subcutaneous injection
Dosage:	Darzalex SC (subcutaneous daratumumab) is to be used along with bortezomib, cyclophosphamide and dexamethasone combination in a regimen of 4-week long cycles for the treatment of patients with AL amyloidosis. The recommended dose is Darzalex SC 1800 mg administered subcutaneously, over approximately 3 to 5 minutes, according to the dosage schedule shown in the table below. For dosing instructions of medicinal products administered with Darzalex SC, see section 5.1 Pharmacodynamic properties, Clinical trials and the Product Information of the individual medicinal products.

Darzalex SC dosing schedule for AL amyloidosis, used in combination with bortezomib, cyclophosphamide and dexamethasone (known as CyBorD, or VCd); via a 4-week cycle dosing regimen:

Darzalex SC dosing schedule

Weeks	**Darzalex SC dosing schedule**
Weeks 1 to 8	Weekly (total of 8 doses)
Weeks 9 to 24	Every two weeks (total of 8 doses)
Weeks 25 onwards	Until disease progression every 4 weeks

Darzalex SC is for subcutaneous use only. Darzalex SC has different dosage and administration instructions than intravenous daratumumab. Do not administer Darzalex SC intravenously.

Serious infusion-related reactions can occur with administration of both Darzalex (intravenous daratumumab) or Darzalex SC (subcutaneous daratumumab). The rate of infusion-related reactions in clinical trials is higher with intravenous administration, compared to subcutaneous administration.

Darzalex and Darzalex SC should be administered by a healthcare professional, and the first subcutaneous dose (that is, first dose of Darzalex SC) in daratumumab-naïve patients should be administered in an environment where resuscitation facilities are available.

Before Darzalex SC therapy is commenced, clinicians should arrange for extended red cell phenotyping of patients (see section 4.4 Special warnings and precautions for use, Effects on laboratory tests, in the Product Information).

Pre- and post-injection medications (such as corticosteroids, antipyretics and antihistamines) should be administered. See 'Recommended concomitant medications' in the Product Information for further information.

For patients currently receiving Darzalex (daratumumab intravenous formulation), Darzalex SC solution for subcutaneous injection may be used as an alternative to the intravenous daratumumab formulation starting at the next scheduled dose.

See the Product Information for further information, including

Pregnancy category: C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on

the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Janssen-Cilag Pty Ltd (the sponsor) to register Darzalex SC (daratumumab) 1800 mg/15 mL solution for subcutaneous injection (vial) for the following proposed extension of indications:

> *Darzalex SC is indicated for the treatment of patients with light chain (AL) amyloidosis.*

Condition

Amyloidosis refers to a diverse group of rare diseases characterised by the production of abnormal proteins known as amyloid fibrils. Over time, accumulation of these amyloid fibrils results in amyloid build up (or amyloid deposits) in tissues of the body. Over time, the increase in amyloid deposits can impact the normal function of the organs affected. The presentation of amyloidosis varies depending on the site of amyloid accumulation. The formation of amyloid deposits may be limited to a specific organ, however systemic amyloidosis is most common, where amyloid deposits can affect many different tissues and organs.

There are many types of amyloidosis, each characterised by a different type of protein misfolding.[1] Systemic amyloid light chain (AL) amyloidosis (previously known as primary systemic amyloidosis) is the most common form of systemic amyloidosis with an annual incidence of about 1.2 cases per 100,000 population in Australia.[2,3]

Systemic amyloid light-chain (AL) amyloidosis can be defined as a protein misfolding and deposition disorder associated with monoclonal gammopathy.[2] AL amyloidosis results from an abnormality in plasma cells found in bone marrow. These plasma cells are responsible for the production of immunoglobulins (or antibodies). Immunoglobulins are composed of four protein chains: two light chains (either kappa or lambda light chains), and two heavy chains, of which there are several types. In AL (or amyloid + light chain) amyloidosis, the amyloid forming protein is derived from the free light chain component of the monoclonal immunoglobulin, most commonly the lambda chain.[2]

[1] Picken MM. The Pathology of Amyloidosis in Classification: A Review. *Acta Haematologica.* 2020; 143 (4): 322–334.
[2] Medical Scientific Advisory Group (MSAG) to Myeloma Australia (MFA). MSAG Clinical Practice Guideline for management of systemic AL amyloidosis (updated 2019). Myeloma Australia. Available at: https://myeloma.org.au/wp-content/uploads/2021/11/MSAG-Clinical-Practice-Guidelines_Managemen-of-Systemic-Amyloidosis-Oct19.pdf
[3] Wisniowski B, McLeod D, Adams R, et al. The epidemiology of amyloidosis in Australia. *Amyloid*. 2019;26(sup1):132-133.

These free light chains fold abnormally to form fibrils with a beta pleated sheet structure. The fibrils associate with serum amyloid P protein and glycosaminoglycans to form amyloid deposits in extracellular tissues that progressively accumulate and disrupt organ function.

Whilst most monoclonal light chains are not amyloidogenic, it is currently not possible to predict those that are. A major challenge with the prognosis and treatment of AL amyloidosis is high diversity of antibodies among individuals.[4,5] Although there are methods for high-throughput sequencing of antibody repertoires, it is not feasible to experimentally determine the amyloidogenicity for each antibody.[4]

Systemic AL amyloidosis is most commonly diagnosed in those over the age of 50, with a slight male predominance. AL amyloidosis can be difficult to recognise, with variable involvement of organs affected and a range of presentations. Patients are often diagnosed late, and an estimated 20% of patients die within six months of diagnosis.[2]

Systemic AL amyloidosis most commonly affects the heart, kidney, liver, gastrointestinal tract, carpal tunnels and nerves, with variable involvement of other organs.[2] At diagnosis, evidence of organ involvement is most prevalent in the heart (74%, with heart failure evident in 47%), kidneys (65%, with nephrosis in 42%), liver (17%), and the peripheral nervous syndrome (15% peripheral, 14% autonomic).[2,6,7,8]

Progressive infiltration leads to organ dysfunction and end stage complications including restrictive cardiomyopathy and nephrotic syndrome. Involvement of the peripheral nervous system occurs in more than 20% of cases, causing a predominantly sensory peripheral neuropathy with autonomic dysfunction.

Current treatment options

In Australia there are no treatments specifically registered for AL amyloidosis.

The treatment of AL amyloidosis is based on multiple myeloma approaches. The aim is to address the malignant clone and to allow the amyloid to clear by existing processes.

The Australian Clinical Practice guidelines;[2] note bortezomib based therapies are the preferred front line therapy, with the combination of melphalan and dexamethasone where there are contraindications to bortezomib, such as pre-existing autonomic neuropathy. High dose melphalan prior to autologous stem cell transplant is a therapeutic option but careful patient selection is required to reduce the risk of treatment related mortality.

The combination of cyclophosphamide, bortezomib and dexamethasone (CyBorD, also named VCd), while reasonably tolerated in AL amyloid may not be sufficient to address the plasma cell clone. Haematological complete responses seen with CyBorD range from 23 to 47%.

There is currently no standard of care for relapsed or refractory AL amyloidosis.

[4] Rawat, P., Prabakaran, R., Kumar, S. et al. Exploring the sequence features determining amyloidosis in human antibody light chains. *Sci Rep* 11, 13785 (2021).
[5] Blancas-Mejia LM , Misra P , Dick CJ , et al. Immunoglobulin light chain amyloid aggregation. *Chem Commun (Camb)*. 2018;54(76):10664-10674.
[6] Merlini G. CyBorD: stellar response rates in AL amyloidosis. *Blood* 2012; 119: 4343-45
[7] Gertz M et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Hematol* 2005; 79: 319-28
[8] Gertz M, Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion. *Amyloid* 2010; 17: 48-49

Daratumumab

Daratumumab is a fully human IgG1κ anti-CD38 monoclonal antibody that acts as a plasma cell depleting agent and as an immunomodulator.

Daratumumab SC is a combination of daratumumab, an immunoglobulin (Ig) G1κ anti-CD38 antibody and hyaluronidase, intended for subcutaneous use. Daratumumab binds to CD38 and inhibits the growth of CD38 expressing tumour cells by inducing apoptosis directly through fragment crystallizable region mediated cross-linking as well as by immune mediated tumour cell lysis through complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity and antibody dependent cellular phagocytosis.

This evaluation was facilitated through Project Orbis, an initiative of the United States (US) Food and Drug Administration (FDA) Oncology Center of Excellence (OCE). Under this project, the FDA, Health Canada, Swissmedic (Switzerland), and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

Regulatory status

Daratumumab is currently registered in Australia as concentration solution for intravenous infusion and a concentrated solution for subcutaneous injection.

Darzalex (daratumumab), for intravenous infusion has been registered in Australia since July 2017.[9,10]

This product, Darzalex SC (daratumumab), concentrated solution for subcutaneous injection, received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 8 September 2020.[11]

At the time the TGA considered this submission, Darzalex SC (daratumumab, concentrated solution for subcutaneous injection) was approved for the following indications:

> *Darzalex SC is indicated for the treatment of patients: with newly diagnosed multiple myeloma; who are eligible for autologous stem cell transplant. For use in combination with bortezomib, thalidomide and dexamethasone who are eligible for autologous stem cell transplant. For use in combination with:*
>
> - *bortezomib, melphalan and prednisone; or*
> - *lenalidomide and dexamethasone.*
>
> *with multiple myeloma who have received: at least one prior therapy. For use in combination with:*
>
> - *bortezomib and dexamethasone, or*
> - *lenalidomide and dexamethasone.*

[9] AUST R 281843: Darzalex (daratumumab) 400 mg/20 mL concentrated solution for (intravenous) infusion, vial.
[10] AUST R 281842: Darzalex (daratumumab) 100 mg/5 mL concentrated solution for (intravenous) infusion, vial.
[11] AUST R 322685: Darzalex SC (daratumumab) 1800 mg/15 mL solution for (subcutaneous) injection, vial.

at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent. For use as:

- *monotherapy*

At the time the TGA considered this submission, a similar submission had been approved in the European Union on 21 June 2021, the United States of America on 15 January 2021, Canada on 12 April 2021 and Switzerland on 14 April 2021.

A similar submission was under consideration in New Zealand (submitted on 19 May 2021) and Singapore (submitted on 30 April 2021).

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	5 November 2020	Approved on 21 June 2021	*Darzalex is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.*
United States of America	9 September 2020	Approved on 15 January 2021	*Darzalex Fasbro in combination with bortezomib, cyclophosphamide and dexamethasone (CyBorD) for the treatment of patients with newly diagnosed AL amyloidosis has accelerated approval.* *The indication is approved under accelerated approval based on response rate [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).*
Canada	18 September 2020	Approved on 12 April 2021	*Darzalex SC in combination with bortezomib, cyclophosphamide, and dexamethasone, for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis.*
Switzerland	25 September 2020	Approved on 14 April 2021	*Darzalex SC in combination with bortezomib, cyclophosphamide, and dexamethasone is indicted for the treatment of previously untreated patients with AL amyloidosis (light*

Region	Submission date	Status	Approved indications
			chain amyloidosis) who have not cardiac disease NYHA stage IIIB or stage IV newly diagnosed systemic light chain (AL) amyloidosis.
New Zealand	19 May 2021	Under consideration	Under consideration
Singapore	30 April 2021	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2020-04809-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	2 November 2020
First round evaluation completed	30 March 2021
Sponsor provides responses on questions raised in first round evaluation	30 April 2021
Second round evaluation completed	1 June 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 July 2021
Sponsor's pre-Advisory Committee response	22 July 2021
Advisory Committee meeting	6 August 2021
Registration decision (Outcome)	6 October 2021
Completion of administrative activities and registration on the ARTG	11 October 2021

Description	Date
Number of working days from submission dossier acceptance to registration decision*	208

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

The Delegate referred to the following guidelines as being applicable to this submission:

- EMA/CHMP/703715/2012 Rev.2 Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man Condition specific guidance
- EMA/CHMP/27994/2008/Rev 1 Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials

Quality

A full quality evaluation was conducted at the time this product received initial registration.

Nonclinical

A full nonclinical evaluation was conducted at the time this product received initial registration.

Clinical

Pharmacology

Population pharmacokinetics data

The evaluation found body weight, renal stage in AL amyloidosis, proteinuria and alkaline phosphatase were identified as significant covariates on daratumumab clearance and volume of distribution.

Sex, age, cardiac stage, renal function, hepatic function, baseline Eastern Cooperative Oncology Group (ECOG) performance status,[12] and anti-recombinant human PH20

[12] **ECOG Performance Status:** The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

hyaluronidase (anti-rHuPH20) status were not identified as covariates. The evaluation did not find the influence on the exposure of daratumumab from these covariates statistically significant or clinically relevant.

Flat dosing of 1800 mg resulted in a 37% higher maximum plasma concentration (C_{max}) in patients with a body weight < 50 kg, and a 23% lower trough concentration (C_{trough}), maximum in patients with baseline body weight > 85 kg compared with patients in the body weight range of 50 to ≤ 85 kg.

An exposure-response analysis for efficacy did not find any meaningful differences in haematological response in patients at the extremes of body weight. In an exposure-response analysis for safety, lower body weigh was associated with a higher incidence of any grade, and Grade 3 to 4 neutropenia and thrombocytopenia but no influence of body weight on cardiac and renal disorders was found.

Few AL amyloidosis patients who were non-White contributed to the population pharmacokinetic data in AL amyloidosis. The evaluation noted that from the data available there appeared higher exposures and a higher incidence of adverse events in these groups compared to White patients.

The evaluation considered the impact of body weight on safety and efficacy, however only nine patients with evaluable data had a body weight < 50 kg. In those patients, there was a higher risk of neutropenia and thrombocytopenia, but not cardiac and renal disorders in patients with patients with body weight < 50 kg. In those > 85 kg, efficacy was not compromised.

After a detailed analysis, the TGA evaluation concluded renal stage did not alter exposure in a clinically meaningful way and that dose adjustment based on renal stage was not warranted.

Immunogenicity

Daratumumab anti-drug antibodies (ADAs) were not found in the key Phase III Study AMY3001 (the Andromeda trial) population and anti-rHuPH20 antibodies were found in 6.1% of patients. ADAs to hyaluronidase did not affect daratumumab exposure.

Efficacy

Study AMY3001 (also referred to as the Andromeda trial) was a Phase III multicentre, multinational, open label, randomised study that randomised 388 patients with newly diagnosed AL amyloidosis that compared the addition of Darzalex SC to CyBorD multidrug

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work

2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5 – Dead

therapy (CyBorD being bortezomib, cyclophosphamide and dexamethasone multidrug therapy) compared to treatment with CyBorD therapy alone.[13]

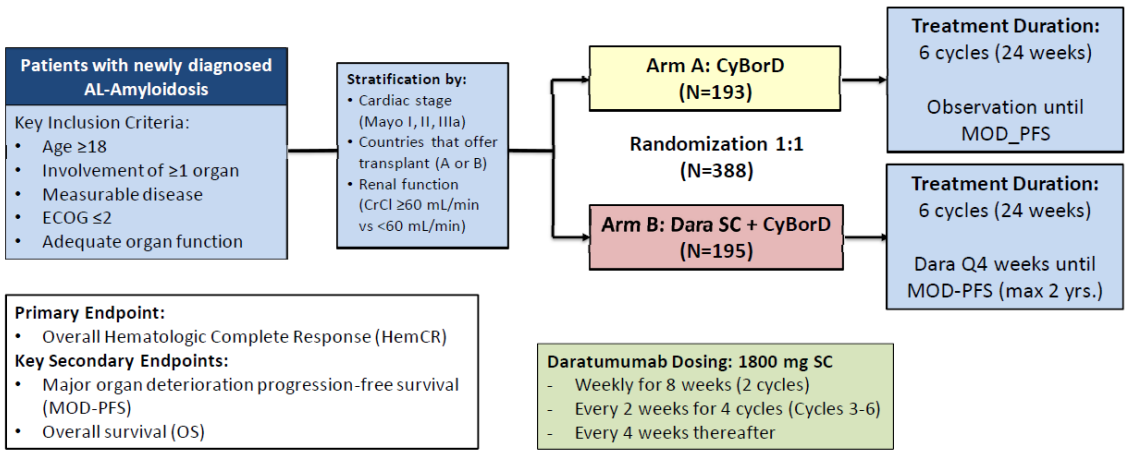
Study AMY3001 (Andromeda trial)

The first patient first visit was on 10 October 2017, with the data cut-off date for this analysis being 14 February 2020.

The clinical study report date was 18 August 2020.

Study AMY3001 was conducted at 140 sites across 22 countries.

Figure 1: Study AMY3001 (ANDROMEDA trial) design



Abbreviations: AL-amyloidosis: amyloid light-chain amyloidosis; CrCl = creatinine clearance; Dara = daratumumab; ECOG = Eastern Cooperative Oncology Group; HemCR = overall haematologic complete response; MOD-PFS = major organ deterioration progression-free survival; OS = overall survival; Q4 = every four; SC = subcutaneous.

CyBorD refers to cyclophosphamide, bortezomib and dexamethasone combination therapy (also known as VCd).

A total 388 patients were randomised. Enrolment was stratified by the European Modification of the Mayo Cardiac Staging system;[14] by the countries that offer transplant for AL amyloidosis (yes versus no) and baseline creatinine clearance (< 60 mL/min versus ≥ 60 mL/min). Treatment ran in 4-week (28 day) cycles, for 6 full cycles (24 weeks total).

The treatment arms were as follows:

- Daratumumab + CyBorD arm (daratumumab + cyclophosphamide, bortezomib and dexamethasone combination therapy)
  - Daratumumab dosing:
    - daratumumab 1800 mg given subcutaneous every week for 8 weeks (for 2 x 4 week cycles); then
    - every two weeks for 4 x 4-week cycles; then
    - every four weeks until first of disease progression, start of subsequent therapy, or 2 years from treatment commencement

[13] CyBorD (bortezomib, cyclophosphamide and dexamethasone) multidrug combination therapy is also known as VCd (Velcade (bortezomib), cyclophosphamide and dexamethasone.
[14] The European version of the 2004 Mayo system identifies patients with very high NT-proBNP levels as having very poor outcomes and splits stage III into two stages (IIIa and IIIb) based on the 8500 ng/L cut-off for NT-proBNP.

  - CyBorD dosing:
    - dexamethasone 40 mg every week (Days 1, 8, 15, and 22 of a cycle) or divided into 2 days; plus
    - cyclophosphamide 300 mg/m^2 (max 500 mg oral or intravenously); plus
    - bortezomib 1.3 mg/m^2 subcutaneously (Day 1, 8, 15, and 22 of a cycle).
- CyBorD only arm (cyclophosphamide, bortezomib and dexamethasone combination therapy).
  - Patients were given the same dosage regimen as detailed above (without daratumumab).

Patient flow

The patient flow as at 14 February 2020 was as follows:

- Received allocated treatment:
  - Daratumumab + CyBorD arm: 193 of 195 patients
  - CyBorD only arm: 188 of 193 patients
- Discontinued intervention:
  - Daratumumab + CyBorD arm: 52 of 193 patients (26.9%)
  - CyBorD only arm: 68 of 188 patients (36.2%)
- Discontinued due to adverse events
  - Daratumumab + CyBorD arm: 8 of 193 patients (4.1%)
  - CyBorD only arm: 8 of 188 patients (4.2%)
- Discontinued due to death:
  - Daratumumab + CyBorD arm: 20 of 193 patients (10.4%)
  - CyBorD only arm: 14 of 188 patients (7.4%)
- Discontinued due to progressive disease:
  - Daratumumab + CyBorD arm: 2 of 193 patients (1%)
  - CyBorD only arm: 11 of 188 patients (5.9%)
- Received subsequent therapy for AL amyloidosis:
  - Daratumumab + CyBorD arm: 5 of 193 patients (2.6%)
  - CyBorD only arm: 23 of 188 patients (12.2%)
- Received autologous stem cell transplant:
  - Daratumumab + CyBorD arm: 12 of 193 patients (6.2%)
  - CyBorD arm: 3 of 188 (1.6%)
- Received subsequent non-cross resistant, anti-plasma cell therapy:
  - Daratumumab + CyBorD arm: (9.8%)
  - CyBorD only arm: (42%)

Key inclusion criteria

Key inclusion criteria were patients:

- ≥ 18 years, and with no prior therapy

- ≥ 1 organ impacted
- Histopathologic diagnosis of systemic AL amyloidosis
  - Immunohistochemistry and polarizing light microscopy of green birefringent material in Congo Red stained tissue in organ not bone marrow, or unbranched 10 nm thick fibrils on electron microscopy (bone marrow only disease excluded)
  - If of African descent or male ≥ 70 years with cardiac involvement only, using mass spectrometry typing of amyloid deposits in a tissue biopsy
- measurable disease defined by ≥ 1 of:
  - serum free light-chain (FLC) ≥ 50 mg/L with abnormal κ:λ ratio, or
  - difference between involved FLC (iFLC) and uninvolved FLC (uFLC) ≥ 50 mg/L, or
  - serum M protein ≥ 5g/L
- Pre-treatment laboratory values:
  - Absolute neutrophil count ≥ 1 x 10^9/L;
  - haemoglobin ≥ 80 g/L;
  - platelet count ≥ 50 x 10^9/L;
  - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal (ULN);
  - total bilirubin ≤ 1.5 x ULN;
  - estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m^2
- ECOG performance status of 0 to 2;[12]

Key exclusion criteria

Key exclusion criteria included:

- Prior therapy for AL amyloidosis of multiple myeloma (MM) including CD38-targeted agents (could have had dexamethasone or equivalent)
- Planned stem cell transplant during first 6 cycles of therapy
- Any form of non-AL amyloidosis
- Previous or current diagnosis of MM
- Significant cardiovascular conditions, for example:
  - N-terminal pro hormone brain natriuretic peptide (NT-proBNP) > 8500 mg/L
  - New York Heart Association (NYHA);[15] class IIIb or IV cardiac failure;
  - Heart failure due to ischaemic heart disease or uncorrected valvular heart disease unrelated to AL amyloid cardiomyopathy;

[15] The New York Heart Association (NYHA) criteria categorise heart failure into four classes based on patient symptoms and function.
Class I: No limitation of ordinary physical activity.
Class II: Slight limitation of ordinary physical activity. No symptoms at rest.
Class III: Marked limitation of ordinary physical activity. No symptoms at rest.
Class IV: Symptoms on any physical activity or at rest.

  - Inpatient admission for unstable angina or myocardial infarction in last 6 months; or stent or coronary artery bypass graft in last 6 months
  - If heart failure, no related hospitalisation within 4 weeks of randomisation
  - sustained ventricular tachycardia or aborted ventricular fibrillation; atrioventricular nodal or sinoatrial nodal dysfunction without pacemaker/ implantable cardioverter defibrillator;
  - QT corrected > 500 msec without pacemaker,
  - supine blood pressure < 90 mmHg or symptomatic orthostatic hypotension
- Chronic obstructive pulmonary disease forced expiratory volume in one second < 50% predicted, or moderate/severe persistent asthma in last 2 years or uncontrolled asthma any classification
- Peripheral neuropathy of Grade 2 (sensory) or Grade 1 (painful)

Study endpoint

Primary endpoint: overall haematologic complete response rate (hCR) by independent review committees (IRC)

Key secondary endpoints: Major organ deterioration progression free survival (MOD-PFS), major organ deterioration event free survival (MOD-EFS) and overall survival (OS)

Other secondary endpoints: hCR at 6 months; ≥ hVGPR ; time to and duration of haematologic response (≥VGPR; CR); ; organ response rate; improvement in patient reported fatigue according to the European Organization for the Research and Treatment of Cancer Quality of Life,[16] and time to next treatment.

Endpoint definitions

- Complete haematologic response rate (hCR) was defined according to International Amyloidosis Consensus Criteria (IACC) guidelines:[17]
  - normalisation of free light chain (FLC) levels and ratio, and
  - negative urine immunofixation (IFE).
  - Negative serum and urine immunofixation without normalised free light chain ratio because suppression of uninvolved free light chain (uFLC) < lower limit of normal (LLN) (FLC normal ratio abnormal or normal) with normalised involved free light chain (iFLC) levels classified as modified complete response (mCR).
- Very good partial haematologic response (hVGPR):
  - reduction of difference in involved and uninvolved free light chain (dFLC) to < 40 mg/L in patients with measurable difference between involved and uninvolved FLC (dFLC ≥ 50 mg/L
  - partial response(hPR): Decreased in dFLC > 50% in patients with measurable difference between involved and uninvolved FLC (dFLC ≥ 50 mg/L)
- Major organ deterioration progression free survival (MOD-PFS):

[16] A questionnaire developed to assess the quality of life of cancer patients. It has been translated and validated into over 100 languages and is used in each year in more than 5,000 studies worldwide. Further information can be found on qol.eortc.org

[17] Guidelines prepared by the Medical Scientific Advisory Group (MSAG) to provide Australian clinicians with a current, practical and evidence based approach to the management of AL amyloidosis. They can be found on myeloma.org.au

  - First of death, clinical manifestation of cardiac or renal failure, or haematologic progressive disease (consensus guidelines).
- Cardiac failure defined:
  - need for left ventricular assist device, intra-aortic balloon pump, or cardiac transplant
- Renal failure defined:
  - development of end stage renal disease requiring haemodialysis or renal transplant.

Definitions of organ response or deterioration

- Cardiac response:
  - > 30% improvement and > 30 ng/L decrease in NT-proBNP in patients with a baseline of ≥ 650 ng/L
- Cardiac progression:
  - > 30% and > 300ng/L increase in NT-proBNP, ≥ 33% increase in cardiac troponin levels, or ≥ 10%
- Renal response:
  - ≥ 30% decrease in proteinuria and decrease in proteinuria < 0.5 g/24 hours without renal progression.
- Renal progression:
  - ≥ 25% increase in eGFR.
- Hepatic response:
  - 50% decrease in abnormal alkaline phosphatase (ALP)
- Hepatic progression:
  - 50% increase in ALP above the lowest value

Haematologic progression

Defined according to International Amyloidosis Consensus Criteria (IACC) guidelines:[17]

- Starting from complete response (CR), a change to abnormal FLC ratio (involved FLC ≥ 2x and ≥ ULN) or reappearance of the involved monoclonal protein on immunofixation;
- Starting from complete response (CR), very good partial response (VGFR), or a partial response (PR), a 50% increase in serum M-protein > 0.5 g/dL or a 50% increase in urine M-protein to > 200 mg/day (must have visible peak); or FLC increase of 50% to > 100 mg/L.

Haematologic responses were evaluated weekly for cycle 1, every 4 weeks for cycles 2 to 6 and every other month thereafter until MOD-PFS, death, withdrawal of consent to participate or the end of the study.

Statistical analysis

Patients were randomised to 1:1 ratio.

Interim analyses: Two interim analyses (IA) planned;

- Interim analysis 1 (IA1) for safety after 30 completed one cycle;
- Interim analysis 2 (IA2) after 180 completed six cycles.

- The primary analysis for hCR performed after all patients completed 6 cycles of treatment.

The sample size for the study was based on the alternative hypothesis of a 15% improvement in overall haematologic complete response (hCR). Taking hCR estimated to be 25% for the CyBorD only arm and adding 15% improvement givens and overall hCR of 40% for the daratumumab SC + CyBorD arm.

Around 360 (180 subject per arm) would provide more than 85% power to detect a 15% improvement in overall hCR using a likelihood ratio test with a 2-sided alpha of 0.05. The post-treatment observation phase will continue until 200 major organ deterioration – MOD-PFS events have been observed. The 200 events will provide approximately 80% power to detect a 33% reduction in the risk of haematologic progression, major organ deterioration or death with a log-rank test (two sided alpha 0.05).

There were two amendments to the statistical analysis plan. The second introduced an Inverse probability of censoring weights method used for primary analysis of MOD-PFS.

Primary endpoint: (haematologic complete response) (overall hCR) tested at 0.05 (2-sided) significance level overall, p = 0.0499 (2-sided) at the primary analysis after 0.0001(2-sided) alpha spent at IA2.

Key secondary MOD-PFS tested at 0.05 (2-sided) significance level overall using O'Brien-Fleming alpha spending function as implemented by the Lan-DeMets method: Inverse probability of censoring weights method used for primary analysis of MOD-PFS. This was to be tested at p = 0.00136 significance level using an O'Brien Fleming spending function;[18] for this is an interim analysis for this endpoint at the time of primary analysis of hCR.

If both hCR and MOD-PFS were statistically significant OS would be test to an overall alpha of 0.05 (2 sided) using O'Brien-Fleming spending function.

Protocol amendments and deviations

Major amendments: Three amendments to the protocol were considered unlikely to have impacted the interpretation of the study.

Important Protocol Deviations: Major protocol deviations were infrequent (n = 17 and balanced between the two arms (daratumumab + CyBorD arm: 4.1%; CyBorD only arm: 4.7%).

Demographic and disease characteristics

Table 3 summarises the baseline demographic and disease characteristics of Study AMY3001 (the ANDROMEDA trial).

Table 3: Study AMY3001 (Andromeda trial) Summary of the baseline demographic and disease characteristics

Baseline demographics and disease characteristics		CyBorD (n = 193)	Daratumumab + CyBorD (n = 195)
Age	Median (years, range)	64 (35-86)	62 (34-87)
Age group	< 65 years	97 (50.3%)	108 (55.4%)

[18] Also known as an alpha spending function, an approach of distributing (spending) the type I error (denoted alpha) over the duration of a sequential A/B test. Alpha-spending makes it possible to perform sequential testing while maintaining the overall error probability of the procedure.

Baseline demographics and disease characteristics		CyBorD (n = 193)	Daratumumab + CyBorD (n = 195)
	≥ 65 years	96 (49.7%)	87 (44.6%)
Sex	Male	117 (60.6%)	108 (55.4%)
	Female	76(39.4%)	87 (44.6%)
Race	White Asian	143 (74.1%) 34 (17.6%)	151 (77.4%) 30(15.4%)
Weight	Median (range)	70 (38, 134.6)	73 (41.5, 141.5)
	≤ 65 kg	74 (38.3%)	62 (31.8%)
	> 65 to 85 kg	74 (38.3%)	96 (49.2%)
	> 85 kg	45 (23.3%)	37 (19.0%)
ECOG status	0 1 2	71 (36.8%) 106 (54.9%) 16 (8.3%)	90 (46.2%) 86 (44.1%) 19 (9.7%)
Time since AL amyloidosis diagnosis	Median (days, range)	43 (5, 1102)	48 (8, 1611)
	≤ 30	55 (28.5%)	51 (26.2%)
	> 30 to 60	83 (43.0%)	74 (37.9%)
	> 60	55 (28.5%)	70 (35.9%)
Number of organs involved	Median (range)	2 (1-6)	2 (1-5)
Organ involvement	Heart Kidney Liver GI tract Nerve Soft tissue	137 (71.0%) 114 (59.1%) 16 (8.3%) 29 (15.0%) 33 (17.1%) 55 (28.5%)	140 (71.8%) 115 (59.0%) 15 (7.7%) 30 (15.4%) 42 (21.5%) 51 (26.2%)
Cardiac Staging	I II IIIa IIIb	43 (22.3%) 80 (41.5%) 64 (33.2%) 6 (3.1%)	47 (24.1%) 76 (39.0%) 70 (35.9%) 2 (1%)
NYHA class	I	94 (48.7%)	101 (51.8%)

Baseline demographics and disease characteristics		CyBorD (n = 193)	Daratumumab + CyBorD (n = 195)
	II IIIA	89 (46.1%) 10 (5.2%)	77 (39.5%) 17 (8.7%)
Renal function (creatinine clearance)	<60 mL/min ≥60 mL/min	62 (32.1%) 131 (67.9%)	69 (35.4%) 126 (64.6%)
Cytogenetic risk	High Standard	19 (11.4%) 147 (88.6%)	17 (11%) 138 (89%)

Abbreviations: CyBorD = cyclophosphamide, bortezomib and dexamethasone combination therapy; ECOG = Eastern Cooperative Oncology Group; NYHA = New York Heart Association;

Results for the primary endpoint

The primary endpoint was:

- Complete haematologic response rate (hCR) defined according to International Amyloidosis Consensus Criteria (IACC) guidelines (by independent review committee) :[17]
  - normalisation of free light chain (FLC) levels and ratio, and
  - negative urine immunofixation (IFE).
  - Negative serum and urine immunofixation without normalised free light chain ratio because suppression of uninvolved free light chain (uFLC) < lower limit of normal (LLN) (FLC normal ratio abnormal or normal) with normalised involved free light chain (iFLC) levels classified as modified complete response (mCR).

The results for the primary endpoint were as follows:

- CyBorD only treatment arm: 18.1% (95% confidence interval (CI): 13%, 24.3%)
- Daratumumab + CyBorD treatment arm: 53.3% (95% CI: 46.1%, 60.5%)
- Odds ratio: 5.13 (95% CI: 3.22, 8.16), p < 0.0001.

A range of sensitivity and supplementary analyses were conducted. Of the 139 patients who achieved hCR based on IRC assessment, 22 patients in the daratumumab + CyBorD arm and 9 patients CyBorD only arm did not have normalisation of the FLC ratio, despite a negative serum and urine immunofixation and iFLC < ULN. A sensitivity analysis removing these patients from the hCR data did not substantially influence the results (odds ratio: 4.8; 95% CI 2.9, 8.1; p<0.0001).

Subgroup analyses were consistent with the primary analysis for all variables tested.

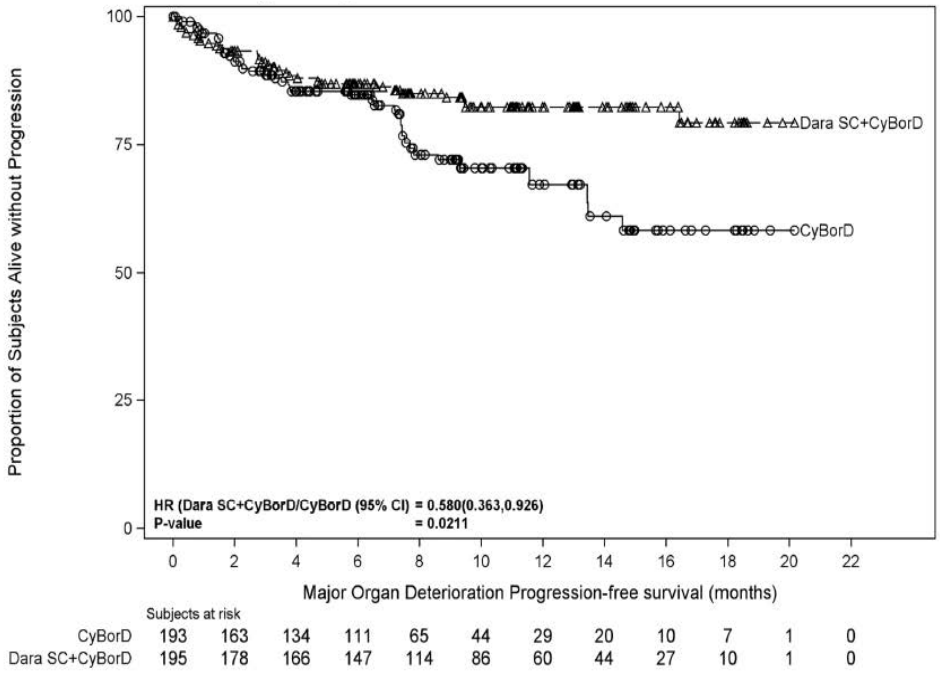
Key secondary efficacy analysis

The analysis used an inverse probability of censoring weighting (IPCW)[19] method by Robins and Finkelstein;[20] to adjust estimates of a treatment effect for subsequent non-cross resistant anti-plasma cell therapy.

For the major organ deterioration-progression free survival (MOD-PFS):

- Median follow up was 11.4 months; 43.5% of events accrued.
- Primary analysis (using the IPCW method) hazard ratio (HR) 0.58 (95% CI: 0.36, 0.93), p = 0.0211 (interim analysis p threshold = 0.00136, so p = 0.0211 is a non-significant result)
- Similar results were found in an analysis without adjustment for subsequent non-cross resistant anti-plasma cell therapy.

Figure 2: Study AMY3001 (ANDROMEDA trial) Inverse probability weighted Kaplan-Meier plot for major organ deterioration progression free survival (MOD-PFS), in months, by independent review committee assessment



Abbreviations: CyBorD = cyclophosphamide, bortezomib and dexamethasone combination therapy; Dara SC = daratumumab subcutaneous.

For major organ deterioration, event free survival (MOD-EFS); that is haematologic progression, major organ deterioration, initiation of subsequent non-cross resistant, anti-plasma cell therapy, or death, whichever occurs first:

- Median MOD-EFS was not reached in the daratumumab + CyBorD arm and was 8.8 months in the CyBorD only arm. The hazard ratio for the comparison of daratumumab + CyBorD versus CyBorD only arm was 0.39 (95% CI: 0.27, 0.56).

[19] The Inverse Probability of Censoring Weighting (IPCW) is an alternative method, which attempts to reduce the bias caused by treatment change recreating a scenario where any patient switched to the alternative treatment arm.
[20] Robins JM. et al. Correcting for non-compliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics*, 2000; 56:779-788.

For overall survival:

- Overall survival was not tested at the primary analysis because MOD-PFS did not meet statistical significance.
- Fifty-six subjects (14.7%) died (daratumumab + CyBorD arm : 27 subjects; CyBorD only arm: 29 subjects).

Organ responses:

- Cardiac response at 6 months (daratumumab + CyBorD 41.5% versus CyBorD only arm 22.2%), odds ratio: 2.44 (95% CI:1.35, 4.42)
- Renal response at 6 months (daratumumab + CyBorD 53.8% versus CyBorD only arm 27.4%), odds ratio: 3.34 (95% CI:1.88, 5.94)

Not all secondary outcomes are reported but are included in the evaluation.

Measures of and time to deep haematologic responses for daratumumab + CyBorD versus CyBorD only arm:

- involved free light chain (iFLC) ≤ 20 mg/L (70.8% versus 20.2%; median time to iFLC ≤ 20 mg/L: 24 versus 32 days)
- dFLC < 10 mg/L (64.1% versus 30.6%; median time to dFLC < 10 mg/L: 29 verses 56 days).

Subsequent therapy

For the CyBorD only treatment arm, 90 CyBorD patients received any subsequent therapy, 40% after 3 to 6 cycles and 51.1% after 6 cycles of treatment. Of those, 72 received daratumumab as monotherapy (24 out of 48; 6 out of 24 achieved complete response (CR) or very good partial response (VGPR) or in combination (24 out of 48; 8 out of 24 achieved CR/VGPR).

Subsequent non-cross resistant, anti-plasma cell therapy was received by 79 CyBorD only patients and 19 daratumumab + CyBorD patients, of whom 63 out of 79 CyBorD only patients and 18 out of 19 daratumumab + CyBorD patients received the treatment before experiencing a haematological progression or major organ deterioration. Two daratumumab + CyBorD patients and 12 CyBorD patients had a MOD-PFS event after receiving the subsequent therapy, with a median time to subsequent event < 60 days.

Relapsed/refractory AL amyloidosis

The sponsor is not seeking an indication in the relapsed/refractory setting.

Safety

Exposure

The median duration of treatment was longer in the daratumumab + CyBorD arm (9.6 months) compared to the CyBorD only arm (5.3 months). The median number of cycles was 11 (range: 1 to 23) in the daratumumab + CyBorD arm and 6 (range: 1 to 6) in the CyBorD arm. In the daratumumab + CyBorD arm, 82.4% of subjects completed 6 cycles of treatment, compared to 64.4% of subjects in the CyBorD only arm.

Treatment-emergent adverse events

The following is a summary of the treatment emergent adverse events (TEAEs) including any Grade and Grade 3 or 4 events occurring at ≥ 2% in any treatment arm in Study AMY3001 (the ANDROMEDA trial).

Table 4: Study AMY3001 (ANDROMEDA trial) Summary of Grades 3 or 4, or Any Grade treatment-emergent adverse events occurring in greater than or equal to two percent of trial participants, but System Organ Class and Preferred Term

MedDRA System Organ Class/ Preferred term	CyBorD only arm		Daratumumab + CyBorD arm	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Blood and lymphatic system disorders				
Anaemia	44 (23.4%)	9 (4.8%)	46 (23.8%)	8 (4.1%)
Lymphopenia	28 (14.9%)	19 (10.1%)	36 (18.7%)	25 (13.0%)
Thrombocytopenia	22 (11.7%)	5 (2.7%)	32 (16.6%)	6 (3.1%)
Neutropenia	12 (6.4%)	5 (2.7%)	20 (10.4%)	9 (4.7%)
Leukopenia	7 (3.7%)	2 (1.1%)	11 (5.7%)	2 (1.0%)
Cardiac disorders				
Cardiac failure	20 (10.6%)	9 (4.8%)	21 (10.9%)	15 (7.8%)
Arrhythmia	10 (5.3%)	2 (1.1%)	18 (9.3%)	6 (3.1%)
Gastrointestinal disorders				
Constipation	54 (28.7%)	0	64 (33.2%)	2 (1.0%)
Diarrhoea	57 (30.3%)	7 (3.7%)	59 (30.6%)	11 (5.7%)
Nausea	52 (27.7%)	0	46 (23.8%)	3 (1.6%)
Abdominal pain	28 (14.9%)	1 (0.5%)	28 (14.5%)	2 (1.0%)
Vomiting	21 (11.2%)	1 (0.5%)	22 (11.4%)	0
Abdominal distension	12 (6.4%)	0	10 (5.2%)	0
Dyspepsia	12 (6.4%)	1 (0.5%)	5 (2.6%)	0
General disorders and administration site conditions				
Fatigue	73 (38.8%)	8 (4.3%)	72 (37.3%)	11 (5.7%)
Oedema peripheral	73 (38.8%)	14 (7.4%)	72 (37.3%)	9 (4.7%)
Pyrexia	16 (8.5%)	1 (0.5%)	24 (12.4%)	0
Injection Site Reactions	0	0	18 (9.3%)	0
Injection site erythema	21 (11.2%)	0	17 (8.8%)	0

MedDRA System Organ Class/ Preferred term	CyBorD only arm		Daratumumab + CyBorD arm	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Infusion Related Reactions	0	0	14 (7.3%)	0
Chills	4 (2.1%)	0	10 (5.2%)	1 (0.5%)
Infections and infestations				
Upper respiratory tract infection	40 (21.3%)	1 (0.5%)	55 (28.5%)	2 (1.0%)
Pneumonia	16 (8.5%)	10 (5.3%)	22 (11.4%)	15 (7.8%)
Conjunctivitis	5 (2.7%)	0	11 (5.7%)	0
Sepsis	1 (0.5%)	1 (0.5%)	10 (5.2%)	9 (4.7%)
Herpes zoster	12 (6.4%)	2 (1.1%)	9 (4.7%)	0
Hordeolum	11 (5.9%)	0	8 (4.1%)	0
Injury, poisoning and procedural complications				
Contusion	6 (3.2%)	0	10 (5.2%)	0
Fall	8 (4.3%)	0	10 (5.2%)	0
Investigations				
ALT increased	10 (5.3%)	1 (0.5%)	15 (7.8%)	3 (1.6%)
Blood creatinine increased	16 (8.5%)	2 (1.1%)	15 (7.8%)	4 (2.1%)
AST increased	8 (4.3%)	1 (0.5%)	12 (6.2%)	2 (1.0%)
GGT increased	11 (5.9%)	6 (3.2%)	11 (5.7%)	2 (1.0%)
Blood ALP increased	11 (5.9%)	1 (0.5%)	6 (3.1%)	1 (0.5%)
Metabolism and nutrition disorders				
Hypokalaemia	28 (14.9%)	10 (5.3%)	21 (10.9%)	3 (1.6%)
Decreased appetite	23 (12.2%)	0	18 (9.3%)	0
Hyponatraemia	7 (3.7%)	5 (2.7%)	14 (7.3%)	5 (2.6%)
Hyperglycaemia	7 (3.7%)	1 (0.5%)	11 (5.7%)	4 (2.1%)
Hypocalcaemia	9 (4.8%)	0	10 (5.2%)	1 (0.5%)
Hypoalbuminaemia	11 (5.9%)	5 (2.7%)	8 (4.1%)	1 (0.5%)

MedDRA System Organ Class/ Preferred term	CyBorD only arm		Daratumumab + CyBorD arm	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Musculoskeletal and connective tissue disorders				
Back pain	11 (5.9%)	0	17 (8.8%)	1 (0.5%)
Muscle spasms	10 (5.3%)	0	16 (8.3%)	1 (0.5%)
Muscular weakness	11 (5.9%)	1 (0.5%)	16 (8.3%)	3 (1.6%)
Myalgia	7 (3.7%)	0	15 (7.8%)	0
Pain in extremity	9 (4.8%)	0	12 (6.2%)	0
Arthralgia	9 (4.8%)	0	10 (5.2%)	0
Nervous system disorders				
Peripheral sensory neuropathy	37 (19.7%)	4 (2.1%)	54 (28.0%)	
Dizziness	26 (13.8%)	0	28 (14.5%)	5 (2.6%)
Headache	18 (9.6%)	0	23 (11.9%)	0
Dysgeusia	11 (5.9%)	0	15 (7.8%)	1 (0.5%)
Paraesthesia	12 (6.4%)	0	14 (7.3%)	0
Syncope	12 (6.4%)	12 (6.4%)	14 (7.3%)	0
Tremor	2 (1.1%)	0	10 (5.2%)	10 (5.2%)
Psychiatric disorders				
Insomnia	47 (25.0%)	2 (1.1%)	41 (21.2%)	0
Anxiety	12 (6.4%)	2 (1.1%)	6 (3.1%)	0
Renal impairment	11 (5.9%)	4 (2.1%)	8 (4.1%)	
Respiratory and thoracic and mediastinal disorders				
Dyspnoea	37 (19.7%)	7 (3.7%)	41 (21.2%)	6 (3.1%)
Cough	20 (10.6%)	0	28 (14.5%)	1 (0.5%)
Epistaxis	3 (1.6%)	0	10 (5.2%)	1 (0.5%)
Pleural effusion	10 (5.3%)	1 (0.5%)	9 (4.7%)	1 (0.5%)
Skin and subcutaneous tissue disorders				
Rash	13 (6.9%)	0	12 (6.2%)	0

MedDRA System Organ Class/ Preferred term	CyBorD only arm		Daratumumab + CyBorD arm	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Erythema	3 (1.6%)	0	11 (5.7%)	0
Vascular disorders				
Hypotension	21 (11.2%)	5 (2.7%)	26 (13.5%)	4 (2.1%)
Orthostatic hypotension	11 (5.9%)	0	6 (3.1%)	2 (1.0%)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CyBorD = cyclophosphamide, bortezomib and dexamethasone combination therapy GGT = gamma glutamyl transferase;

Treatment discontinuations occurred in around 4% of each treatment arm, with all but one occurring in Cycles 1 to 6.

Common TEAEs leading to treatment cycle delays or dose modifications in the daratumumab + CyBorD arm were peripheral sensory neuropathy, upper respiratory tract infection, thrombocytopenia, fatigue and peripheral oedema. In the CyBorD only arm the common TEAEs leading to treatment cycle delays or dose modifications were sensory neuropathy and peripheral oedema.

Haematological abnormalities are summarised in the Table 6. Grade 3 or 4 febrile neutropenia occurred in 1% of the daratumumab + CyBorD arm but not in the CyBorD only arm. All grade bleeding events were also more common in the daratumumab + CyBorD (29.5%) than in the CyBorD only arm (13.8%).

Treatment-emergent adverse haematological events

The following table summarises the haematological events in Study AMY3001 (the ANDROMEDA trial) based on the safety population. The median duration of treatment was 9.6 months for the daratumumab + CyBorD arm, and 5.3 month for the CyBorD only arm.

Table 5: Study AMY3001 (ANDROMEDA trial) Summary of All Grade, Grade 3, and Grade 4 haematological events

	Daratumumab + CyBorD (N=193)			CyBorD only (N=188)		
	All Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Anaemia	125 (65)	11 (6)	0	131 (70)	12 (6)	0
Thrombocytopenia	87 (45)	4 (2)	2 (1)	75 (40)	6 (3)	1 (1)
Leukopenia	112 (58)	9 (5)	5 (3)	85 (45)	8 (4)	0
Neutropenia	56 (29)	6 (3)	6 (3)	34 (18)	7 (4)	0
Lymphopenia	153 (79)	67 (53)	35 (18)	132 (70)	74 (39)	12 (6)

Abbreviation: CyBorG = cyclophosphamide, bortezomib and dexamethasone combination therapy.

Serious adverse events including fatal events

The following table summarises serious adverse events including deaths in Study AMY3001 (Andromeda trial)

Table 6: Study AMY3001 (ANDROMEDA trial) Summary of serious adverse events and deaths

Event	CyBorD only arm (n = 188)	Daratumumab + CyBorD arm (n = 193)
Serious Adverse Events (SAEs)		
Any SAE	36.2%	43%
SAEs in > 2% of either arm		
Pneumonia	4.8%	7.3%
Cardiac failure	4.3%	6.2%
Atrial fibrillation	1.1%	2.1%
Dyspnoea	1.6%	2.1%
Pleural effusion	0.5%	2.1%
Sudden death	1.6%	3.1%
Diarrhoea	2.1%	1.6%
Fluid overload	2.7%	0.5%
Syncope	3.2%	1.6%
Deaths		
In cycles 1 to 6	4.3%	4.1%
After cycle 6	N/A	0.5%
Drug dosing interruption		
Due to adverse event	60.6%	67.9%
Grade ≥ 3 event	31.4%	33.7%

Abbreviation: CyBorD = cyclophosphamide, bortezomib and dexamethasone combination therapy; SAE = serious adverse event.

Beyond the first 6 months, 2 out of 193 patients from the daratumumab + CyBorD arm and 8 out of 188 patients of the CyBorD only arm died.

Serious cardiac events

While many of the safety findings in the submission were consistent with the expected safety profile of daratumumab, of particular interest were the cardiac events. Grade 3 to 4 cardiac adverse events, and serious cardiac events occurred in 9.6%, and 13.3% of the

CyBorD only arm and 11.4%, and 15.5% of the daratumumab + CyBorD only arm respectively.

An analysis of Grade 5 toxicity or cardiac serious adverse events (SAEs) by Mayo Cardiac Staging;[15] was conducted. For Cardiac stages I, II and IIIa/IIIb 2.4%, 8.9%, and 25.4% of the CyBorD only arm and 0%, 13.3%, and 27.8% of the daratumumab + CyBorD arm, respectively had Grade 5 toxicity or cardiac SAE.

The following seeks to quantify haematological and cardiac response against the risk of cardiac death for each of the treatment arms.

Table 7: Study AMY3001 (ANDROMEDA trial) Cardiac outcomes and complete haematologic response by baseline cardiac stage

	CyBorD			Dara SC + CyBorD		
	HemCR	Cardiac Response	Death	HemCR	Cardiac Response	Death
All patients	35/193 (18.1%)	26/117 (22.2%)	29/193 (15.0%)	104/195 (53.3%)	49/118 (41.5%)	27/195 (13.8%)
Baseline cardiac stage						
Mayo Clinic Cardiac Staging I	12/43 (27.9%)	-	1/43 (2.3%)	21/47 (44.7%)	-	0
Mayo Clinic Cardiac Staging II	16/80 (20.0%)	16/54 (29.6%)	9/80 (11.3%)	41/76 (53.9%)	28/55 (50.9%)	8/76 (10.5%)
Mayo Clinic Cardiac Staging III	7/70 (10.0%)	10/63 (15.9%)	19/70 (27.1%)	42/72 (58.3%)	21/63 (33.3%)	19/72 (26.4%)
NYHA class						
CLASS I	20/94 (21.3%)	12/35 (34.3%)	6/94 (6.4%)	48/101 (47.5%)	21/42 (50.0%)	5/101 (5.0%)
CLASS II	12/89 (13.5%)	12/73 (16.4%)	21/89 (23.6%)	47/77 (61.0%)	25/63 (39.7%)	14/77 (18.2%)
CLASS IIIA	3/10 (30.0%)	2/9 (22.2%)	2/10 (20.0%)	9/17 (52.9%)	3/13 (23.1%)	8/17 (47.1%)

Abbreviations: CyBorD = cyclophosphamide, bortezomib and dexamethasone combination therapy; Dara SC = subcutaneous daratumumab subcutaneous (+ recombinant human hyaluronidase PH20 (rhuPH20)); HemCR = haematologic complete response based on IRC; cardiac response = cardiac response based on IRC at 6 months.

Of the 49 out of 90 patients from the CyBorD only arm who received subsequent therapy crossed over to daratumumab intravenously (IV). Of those, one patient with progressive cardiac disease prior to crossing to daratumumab IV died of cardiac failure.

Case narratives were provided for three CyBorD only treated patients and 6 daratumumab + CyBorD treated patients who had sudden cardiac death. The two daratumumab + CyBorD treated deaths occurred one and 3 days after the commencement of daratumumab + CyBorD. Both had Mayo Cardiac Stage IIIa cardiac involvement. In the sponsor's analysis of treated patients, the early death events in Study AMY3001 (the ANDROMEDA trial) 45 patients died in the first 6 months (25 out of 193 daratumumab + CyBorD treated patients, and 20 out of 188 CyBorD-only treated patients), mostly due to amyloid cardiomyopathy.

Among other events renal and hepatobiliary disorders occurred in similar proportion of patients in each treatment arm.

Risk management plan

The most recently evaluated European Union (EU)-risk management plan (RMP) was version 7.4 (dated 17 June 2020; data lock point (DLP) 29 January 2020) and Australia specific annex (ASA) version 8.0 (dated 18 August 2020). In support of the extended indications, the sponsor has submitted EU-RMP version 8.1 (dated 3 September 2020; DLP 10 August 2020) and ASA version 9.0 (dated 11 September 2020). At Round 2, the sponsor

has submitted EU-RMP version 8.3 (dated 15 March 2021; DLP 10 August 2020) and ASA version 10.0 (dated 12 March 2021) in support of the application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 9: Summary of safety concerns. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 8: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs' test)	✓	–	✓	✓*
	Hepatitis B virus reactivation	✓	–	✓	–
Important potential risks	Nil	–	–	–	–
Missing information	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	✓	✓†	✓	–

*Additional Risk Minimisation Activities include educational material for health care professionals (HCPs) and Blood Banks and a Patient Alert Card (PAC). (A Dear HCP letter was distributed regarding Hepatitis B reactivation but distribution was completed in February 2019).

† Multicentre prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis.

The summary of safety concerns are acceptable including the removal of Missing Information 'Use in pregnancy and lactation' and 'Reproductive and developmental toxicity.' Use in these populations is unlikely due to the age at diagnosis of patients with multiple myeloma and amyloidosis and therefore data are unlikely to be ascertained.

Only routine pharmacovigilance activities have been proposed. However, an overseas regulator has requested the sponsor conduct a post-marketing clinical trial in newly diagnosed and relapsed/refractory AL amyloidosis for all serious cardiovascular adverse events, and all deaths. This study should be added to the pharmacovigilance plan for Australia. At second round of evaluation, the requested study has been added to the updated EU-RMP and ASA and also *'Use in patients with AL amyloidosis who have pre-existing cardiac involvement'* has been added as Missing Information to the summary of safety concerns.

As previously routine and additional risk minimisation activities have been proposed. Routine activities include a follow-up questionnaire for Interference for Blood Typing (Minor Antigens) and Haemolytic Transfusion Reactions. Additional risk minimisation activities include health care professionals and Blood Bank educational material and a Patient Alert Card. This educational material needed to be updated with the new indication prior to approval by the TGA.

Risk-benefit analysis

Delegate's considerations

AL amyloidosis is a life threatening and rare condition, often diagnosed late and with multiple organ involvement.

There are no registered therapies with CyBorD (cyclophosphamide, bortezomib and dexamethasone) combination therapy. The CyBorD combination has been used for some time in the treatment AL amyloidosis and appears in current Australian guidelines.[2] Daratumumab added to this combination compared with the combination alone allows the attribution of efficacy and safety to daratumumab in the context of this condition.

Efficacy is assessed by complete haematological response, as defined by Palladini.[21] The modified complete haematological response used for the primary analysis included 22 patients from the daratumumab + CyBorD arm, and 9 patients from the CyBorD-only treatment arm that did not meet the full complete response criteria. A sensitivity analysis did not meaningfully change the odds ratio for the difference between the two arms that has a point estimate of approximately five.

The data are immature; 43.5% of the events for the major organ deterioration-progression free survival (MOD-PFS) had accrued with a median follow up of 11.4 months. The IPCW method;[19] was used because of concerns about the influence of subsequent therapies on the interpretation of the results. This technique aims to account for situations where treatments after discontinuation of treatment but still within the study period can influence the ultimate outcome for the patient, such as switching to treatment in a comparator arm, another treatment or discontinuing altogether. The advice of the Advisory Committee of Medicine (ACM) is requested regarding the interpretation of the Kaplan-Meier outputs using this method.

As statistical significance for MOD-PFS was not reached, overall survival was described and the data were immature. Cardiac and renal response data appear promising, although there is a correlation between improvement in renal function and clearance of N-terminal prohormone brain natriuretic peptide (NT-proBNP) that may be a confounding factor for this component of the cardiac response.

Clinically, a reduction in free light chain is accepted in Australia as correlating with improved survival.[2] The difference in involved and uninvolved free light chain < 10 mg was 64% in the daratumumab + CyBorD arm versus 30.6% in the CyBorD-only arm and the median time to onset was 29 days in the daratumumab + CyBorD arm and 56 days in the CyBorD arm.

The safety profile of daratumumab has been established in the setting of multiple myeloma. While generally similar, concern arose from early cardiac deaths, higher in the daratumumab + CyBorD. There is a lag to onset of organ function improvement in amyloidosis treatment. Patients will likely need additional support in the lag between the reduction of amyloid production from the clone and clearance of amyloid by other processes. Pathologies that result from the presence of amyloid are likely to continue in the meantime, and this would be expected in both arms of the study. At Baseline, 3.5% more patients in the daratumumab + CyBorD arm than in the CyBorD-only arm had NYHA Class IIIA;[15] functional symptoms. A 2.4% excess of early death was reported in the daratumumab + CyBorD arm compared with the CyBorD arm in the first six months of treatment. One patient from the CyBorD arm who moved to subsequent daratumumab IV therapy and who had deteriorating cardiac function died of cardiac failure. The

[21] Palladini G, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis : safety run-in results ANROMEDA, Blood, 2020, 136(1): 71-80.

administration instructions for the IV formulation require an infusion of a minimum of 500 mL and up to 1000 mL if the first dose is given on a single day. A relatively small number of patients contributed events to the analysis, and in the context of the imbalance in NYHA IIIA;[15] patients between the groups at Baseline it is difficult to discern the impact of the treatment from the impact of the underlying disease.

The sponsor has chosen the subcutaneous form (Darzalex SC) of daratumumab for study. The volume of infusion required for the intravenous formulation (Darzalex) is potentially problematic for patients with cardiac and/or renal disease.

Flat dosing is reasonable for most patients although patients of body weight less than 50 kg may be more at risk of neutropenia and febrile neutropenia. This is also a recognised consideration for the use of subcutaneous dosing in patients with multiple myeloma, for which registration has been granted in Australia, and the relatively small number of patients < 50 kg (9 patients) on which these analyses are based. The incidence of other adverse events such as anaemia and cardiac and renal disorders was similar across the weight groupings in AL amyloidosis. The evaluator was satisfied the proposed dose reaches the serum level needed to achieve 99% CD38 target that was determined for multiple myeloma.

From the evidence presented, and subject to the advice of the ACM, the addition of daratumumab to cyclophosphamide, bortezomib and dexamethasone (CyBorD), would seem a reasonable option for treatment for patients early in their disease and treatment course. The balance of benefits and harms is uncertain for patients who present with NYHA class IIIA functional symptoms and there is no evidence to support the use of this combination in patients with NYHA Class IIIB and IV symptoms.

Indication

The proposed indication is broad and could be interpreted as suitability for use as monotherapy. For AL amyloidosis, daratumumab without concurrent use of a proteasome inhibitor (bortezomib), chemotherapy agent (cyclophosphamide) and corticosteroid (dexamethasone) has not been demonstrated. The sponsor has only demonstrated benefit in combination with the CyBorD (bortezomib, cyclophosphamide and dexamethasone) combination, and as has occurred internationally this should be reflected in the wording of the indication. Whether there should be additional limits to the population either through the wording of the indication, precautionary statements or other means is an issue upon which the advice of the ACM is sought.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***It is noted the United States (US) Food and Drug Administration (FDA) granted accelerated approval for daratumumab for the proposed indication. What plans does the sponsor have for generating additional data to confirm the clinical benefit in this population of further characterise the potential cardiovascular risk in this population?***

Confirmatory efficacy data

The primary endpoint of Study AMY3001 (Andromeda trial) was overall haematologic complete response rate. This endpoint was selected, as the treatment goal in AL amyloidosis is to achieve a deep haematologic response which are associated with superior outcomes and increased chances for organ response.

Secondary endpoints of Major organ deterioration progression free survival (MOD-PFS) and overall survival within Study AMY3001 will provide confirmatory data of the longer term clinical benefits of adding daratumumab subcutaneously to CyBorD for treatment of AL amyloidosis. As specified in the statistical analysis plan, overall survival is a major secondary endpoint and included in the formal hierarchical hypothesis testing. The marketing authorisation holder can commit to provide the final overall survival analysis post-approval with a projected submission of June 2025.

Characterisation of cardiovascular risk

To further characterise cardiac adverse events in AL amyloidosis patients treated with daratumumab, the sponsor is also planning a multicentre, prospective, observational study of daratumumab-based therapy in newly diagnosed AL amyloidosis patients. A brief synopsis is provided below:

- Study title: A multicentre, prospective, observational study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis.
- Primary objective: The primary objective of the study is to further characterise cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome.
- Patient population: Patients with light chain amyloidosis who initiate subcutaneous daratumumab based therapy. The sponsor plans to recruit at least 100 patients across multiple sites in the USA and other countries.
- Data collection sources: Data collection for patients with AL amyloidosis will include, but may not be limited to: demographic data; baseline disease characteristics including cardiac parameters as appropriate to determine cardiac risk status; treatment regimen and dosing; haematologic response as per standard of care; serious adverse events with a focus on major cardiac events including non-fatal myocardial infarction, cardiac failure, arrhythmia, as well as fatal cardiac events and events of sudden death. Management and outcome of major cardiac events, including hospitalisations, will be analysed. Data collection will be considered complete for a participating patient if data are available for 2 years following initiation of daratumumab therapy (or until initiation of subsequent treatment, withdrawal of consent, death, or loss to follow-up).
- Study duration: The overall duration of the study, including recruitment and follow-up, is anticipated to be approximately 5 years.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***Does the ACM consider the complete haematologic response and MOD-PFS (major organ deterioration progression free survival) response acceptable surrogates for disease outcome in AL amyloidosis?***

The ACM advised that haematologic response, including complete response, is a strong and reliable predictor of overall survival in AL amyloidosis. As haematologic response is based on measurement of the serum free light chain, which is causing the disease, the ACM did not consider this to be a surrogate marker but rather an actual measure of disease levels.

The ACM noted that MOD-PFS is driven by haematologic progression (rise in the amyloid forming free light chains), severe cardiac failure, severe renal disease and death. The ACM considered MOD-PFS to be a reasonable surrogate for disease outcome.

2. Does the ACM have any concerns about the approach to the statistical analysis of MOD-PFS by the sponsor?

Overall, the ACM did not have any major concerns about the sponsor's approach to statistical analysis of MOD-PFS. While the analysis has low power, the ACM were satisfied that the sponsor has noted that the analysis of MOD-PFS is interim, and that the interim analysis was not based on the number of events.

The ACM advised that the inverse probability of censoring weighting (IPCW)[19] technique used within the analysis, while not common, appears to be a valid statistical technique in this scenario given the nature of the data and that this is an interim analysis. However, the ACM noted that the IPCW technique is based on a number of assumptions, including exchangeability. The ACM advised that to confirm assumptions are met the sponsor could be asked to investigate exchangeability and confirm that exchangeability has been met.

3. The data are immature, however there is a clinical unmet need. Overall, does the ACM consider the evidence is sufficient to support the use of daratumumab in AL amyloidosis?

The ACM advised that in AL amyloidosis, especially those with cardiac involvement, the need for effective and approved treatments is critical and a real area of unmet need. The ACM agreed that the results of the surrogate endpoints from the trial are strongly associated with an improvement in survival; the complete response rate is strongly and consistently associated with improved overall survival, the cardiac organ response is strongly associated with improved overall survival, and the renal organ response is strongly associated with reduced risk of end stage renal failure. The ACM were of the opinion that the current preliminary data supports use of daratumumab in AL amyloidosis.

4. What measures does the ACM advise to mitigate the potential risk of an imbalance in early cardiac death and cardiac adverse events?

The ACM did not have any specific concerns relating to the risk of early cardiac death and cardiac adverse events with daratumumab treatment. The ACM emphasised that AL amyloidosis is a very serious disease with terrible outcomes for those with cardiac involvement, and there does not appear to be any evidence that daratumumab is causing more cardiac harm than the disease itself. There has also been no evidence of daratumumab causing direct cardiac toxicity. The ACM noted that the proposed imbalance in early cardiac death and cardiac adverse events is based on very small numbers of patients and were of the opinion that this is not sufficient to warrant a safety signal.

5. Does the ACM have any other advice applicable to this submission?

The ACM emphasised that 'AL' is not an abbreviation and noted that in some places in the Product Information (PI)/Consumer Medicine Information (CMI) is says 'light chain (AL) amyloidosis' but should instead state 'light chain AL amyloidosis'.

The ACM advised that while Mayo 2004;[22] cardiac stage 3B patients were not included in the trial, they should not be excluded from the proposed indication as they have quite severe disease and limited treatment options.

[22] The Mayo 2004 staging is based on the presence and severity of heart damage, which is assessed by serum levels of cardiac troponin T (TnT) cut off level of 0.035 mcg/L and NT-proBNP level of 332 ng/L to place AL amyloidosis patients into three groups: (1) stage I, normal levels of both, (2) stage II, an elevated level of either but not both, and (3) stage III, elevated levels of both.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Darzalex SC in combination with bortezomib, cyclophosphamide and desxamethasone, is indicated for the treatment of patients with light chain AL amyloidosis.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Darzalex SC (daratumumab) 1800 mg/15 mL solution for injection vial, for the following extension of indications:

> *Darzalex SC in combination with bortezomib, cyclophosphamide and dexamethasone, is indicated for the treatment of patients with light chain AL amyloidosis.*

As such, the full indications at this time were:

> *Darzalex SC is indicated for the treatment of patients:*
>
> – *with newly diagnosed multiple myeloma:*
>
> - *who are eligible for autologous stem cell transplant. For use in combination with:*
>
> *bortezomib, thalidomide, and dexamethasone.*
>
> - *who are ineligible for autologous stem cell transplant. For use in combination with:*
>
> *bortezomib, melphalan and prednisone, or*
>
> *lenalidomide and dexamethasone.*
>
> – *with multiple myeloma who have received:*
>
> - *at least one prior therapy. For use in combination with:*
>
> *bortezomib and dexamethasone, or*
>
> *lenalidomide and dexamethasone.*
>
> - *at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent. For use as:*
>
> *monotherapy.*
>
> *Darzalex SC in combination with bortezomib, cyclophosphamide and dexamethasone, is indicated for the treatment of patients with light chain AL amyloidosis.*

The above extension of indications are inclusive of the previous approved indications.

Specific conditions of registration applying to these goods

- The Darzalex SC EU- RMP (version 8.3, dated 15 March 2021, data lock point 10 August 2020), with Australian specific annex (version 10.0, dated 12 March 2021), included with submission PM-2020-04809-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Conduct a multicentre, prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis for all serious cardiovascular adverse events, and all deaths. On completion the clinical study report should be provided for evaluation.
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Darzalex SC approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au