

**7.02 DARATUMUMAB,  
Solution for I.V. infusion 100 mg in 5 mL vial,  
Solution for I.V. infusion 400 mg in 20 mL vial,  
Solution for S.C. injection 1,800 mg in 15 mL vial,  
Darzalex<sup>®</sup>,  
Janssen-Cilag Pty Ltd.**

**1 Purpose of submission**

- 1.1 The Standard Re-entry resubmission requested Section 100 (Efficient Funding of Chemotherapy Program) Authority Required (telephone/online) listings for the intravenous (IV) (public and private hospitals) and subcutaneous (SC) (related benefits) formulations and a General Schedule Authority Required (telephone/online) listing for the SC formulation of daratumumab for use in combination with lenalidomide and dexamethasone (DLd) for the treatment of transplant ineligible, newly diagnosed multiple myeloma (TI NDMM).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SoC), comprised of lenalidomide in combination with dexamethasone (Ld) and bortezomib plus lenalidomide and dexamethasone (BLd). The key components of the clinical issues addressed by the resubmission are presented in Table 1.

**Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the March 2025 resubmission)**

Component	Description
Population	Patients with transplant ineligible (TI) newly diagnosed multiple myeloma (NDMM).
Intervention	Daratumumab, administered in combination with lenalidomide, and dexamethasone (DLd). Daratumumab is administered either intravenously (IV) by infusion at a dose of 16 mg/kg, or subcutaneously (SC) at a dose of 1800 mg. It is administered weekly for the first 2 cycles (each cycle is 4 weeks in duration; a total of 8 doses), every two weeks from cycles 3 to 6 (a total of 8 doses) and then once every 4 weeks from cycle 7 onwards until disease progression, or the development of treatment-limiting toxicity. Lenalidomide is administered orally by 25 mg capsule on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or intravenously once a week.
Comparator	Consistent with the March 2023 submission, the March 2025 resubmission nominated two comparators, as these are the regimens that will be most commonly replaced in clinical practice; <ul style="list-style-type: none"> <li>• Lenalidomide in combination with dexamethasone (Ld);</li> <li>• Bortezomib, in combination with lenalidomide and dexamethasone (BLd)</li> </ul>
Outcomes	Progression-free survival (PFS), overall survival (OS), overall response rate (ORR), adverse events (AEs).
Clinical claim	<p>Compared with Ld, DLd demonstrated statistically and clinically superior comparative efficacy based on PFS, OS and other secondary outcomes in the MAIA, including ORR and MRD-negativity. These outcomes are key goals of therapy in TI NDMM.</p> <p>Further, whilst the safety data are not adjusted for the longer exposure to DLd treatment and thus biased against DLd, DLd has a similar overall incidence of any grade TEAEs and is associated with a higher incidence of grade 3 or 4 AEs and SAEs compared with Ld alone and therefore has an inferior safety profile. However, these AEs are manageable and do not require discontinuation of daratumumab. The nature of higher incidence of adverse events versus Ld is expected given daratumumab is added to Ld and DLd a significantly longer duration of treatment and exposure compared with Ld. The profile of AEs observed with DLd are consistent with the known safety profile of daratumumab and lenalidomide which are available on the PBS. Thus, clinicians are experienced in their management.</p> <p>Compared with BLd, given the non-inferior efficacy between Ld and BLd in NDMM patients who are aged 65 years or older (a proxy for transplant ineligibility), adding daratumumab to Ld demonstrates statistically and clinically superior efficacy (i.e. PFS and OS). DLd has at worst a non-inferior, but likely superior safety profile compared with BLd.</p> <p>Therefore, DLd is superior to both Ld and BLd in terms of efficacy. DLd is inferior to Ld and at worst non-inferior, but likely superior to BLd in terms of safety.</p>

Source: Table 1-1, p20 of the March 2025 resubmission.

AEs = adverse events; BLd = bortezomib, lenalidomide and dexamethasone; DLd = daratumumab, lenalidomide and dexamethasone; IV = intravenous; Ld = lenalidomide and dexamethasone; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; PFS = progression-free survival; ORR = overall response rate; OS = overall survival; SC = subcutaneous; TEAE = treatment emergent adverse events; TI = transplant ineligible.

Blue shading indicates data previously seen by the PBAC.

## 2 Background

### Registration status

2.1 Daratumumab, intravenous (IV) and subcutaneous (SC) formulations were registered by the Therapeutic Goods Administration (TGA) on 30 April 2020 in combination with Ld for patients with newly diagnosed multiple myeloma who are ineligible for

autologous stem cell transplant (ASCT), which corresponds to the requested PBS listing.

2.2 Daratumumab is indicated for the treatment of multiple myeloma for the following indications:

**Newly diagnosed multiple myeloma:**

- Patients eligible for autologous stem cell transplant (ASCT). For use in combination with: bortezomib, thalidomide, and dexamethasone.
- Patients ineligible for ASCT. For use in combination with: 1) bortezomib, melphalan and prednisone, or 2) lenalidomide and dexamethasone.

**Relapsed and refractory multiple myeloma multiple myeloma:**

- Patients who have received at least one prior therapy. For use in combination with: 1) bortezomib and dexamethasone, 2) lenalidomide and dexamethasone, 3) carfilzomib and dexamethasone, or 4) SC formulation only: pomalidomide and dexamethasone (after at least one prior therapy including lenalidomide and a proteasome inhibitor; PI).
- Patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent. For use as: monotherapy.

**Previous PBAC consideration**

2.3 An application for the listing of DLd in the proposed population was considered, and not recommended for listing, by the PBAC at its meeting in March 2023. A summary of the key matters of concern from the PBAC March 2023 consideration, and how those issues were addressed in the resubmission, is presented in Table 2.

**Table 2: Summary of key matters of concern**

	<b>Matter of concern (March 2023, PBAC)</b>	<b>How the March 2025 resubmission addressed those concerns</b>
Proposed population and restriction	<p>The PBAC considered that the definition of transplant ineligibility was arbitrary and may change over time and that there was therefore a high risk that a large number of patients who were transplant eligible would receive DLd.</p> <p>Alternatively, the sponsor could seek a whole of myeloma listing which would enable access for a greater number of patients (paragraph 7.3, daratumumab PSD, March 2023).</p>	<p>Partially addressed. The March 2025 resubmission did not change the proposed listing; however, it proposed that an additional clinical criterion could be considered by the PBAC as follows:</p> <p>Patient must be 70 years of age or older, OR, Patient must be younger than 70 years of age AND have a Hematopoietic Cell Transplantation specific Comorbidity Index (HCT-CI) of 3 or more.</p> <p>The proposed additional criterion does not address the potential for daratumumab use prior to transplant, e.g. where a patient is classified “transplant ineligible” and receives PBS daratumumab but is later considered “eligible” for transplant.</p>

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	Matter of concern (March 2023, PBAC)	How the March 2025 resubmission addressed those concerns
		The resubmission did not comment on the suggestion of a whole of myeloma listing. The Pre-Sub-Committee-Response (PSCR) stated that a first line indication in TE patients is currently being assessed by the TGA. The sponsor will explore a potential PBS listing following an assessment of clinical need, applicability of the evidence to Australian clinical practice, maturity of the evidence and clinical and cost effectiveness.
Clinical effectiveness evidence, and clinical claim	The PBAC considered that the submission's claims that DLd was superior in terms of effectiveness and at worst non-inferior in terms of safety compared to BLd were highly uncertain and could not be supported as no comparative data were presented. (paragraph 7.13, daratumumab PSD, March 2023).	Partially addressed. The March 2025 resubmission maintained that DLd is superior to both Ld and BLd in terms of efficacy. The resubmission presented an adjusted ITC of PFS comparing DLd with BLd. An updated survival analysis of the MRDR comparing BLd vs Ld, from September 2024 was presented to support the claim that the clinical benefits of BLd are not different to Ld. <p>█ The resubmission did not provide an adjusted ITC for OS or validate that, in the absence of an ITC for OS, PFS is an appropriate surrogate outcome for OS in the TI NDMM population.</p> <p>For the MAIA trial, no new safety data, other than deaths, were presented in the March 2025 resubmission. A post-hoc analysis of safety in the SWOG s0777 trial by Durie et al 2022 where ≥ 65 years population was used as a proxy for transplant eligibility status was presented in the March 2025 resubmission.</p>
Treatment effect for BLd	The PBAC considered that the submission's claim that BLd was not superior to Ld was not supported (paragraph 7.5, daratumumab PSD, March 2023).	Partially addressed. The March 2025 resubmission maintained that PFS and OS outcomes for BLd are non-inferior to Ld in TI NDMM patients. The resubmission presented updated data from the MRDR to support this claim.
Economic comparison	The PBAC considered that the economic model should be revised to either present a (i) combined approach consisting of a cost-utility between DLd and Ld and a cost-minimisation approach between DLd and BLd, or (ii) re-specified base case which included a treatment effect for BLd, a time horizon of 15 years and revised OS extrapolations, a weighted comparison based on the MRDR (paragraph 7.15, daratumumab PSD, March 2023). The recommended weighting based on the MRDR data was 68% BLd use versus 32% Ld use (paragraph 7.6, daratumumab PSD, March 2023).	Partially addressed. The March 2025 resubmission updated the economic evaluation with TTD and OS data (median follow-up 89.3 months) and PFS (median follow-up of 64.5 month) from MAIA. The OS extrapolations were revised based on the final MAIA OS, and included a lifetime time horizon of 20 years in the updated economic evaluation. <p>The March 2025 resubmission did not include additional efficacy of BLd vs Ld in the base case, as advised by PBAC, and to reflect a BLd vs Ld weighting of 68% vs 32%. Instead, efficacy in the base case was limited to Ld.</p> <p>The resubmission did not present a cost-minimisation approach for DLd compared with BLd; nor did it present a re-specified base case.</p>

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	Matter of concern (March 2023, PBAC)	How the March 2025 resubmission addressed those concerns
Significant price reduction and cost of daratumumab per patient	Noting that a higher per patient cost in the first line was not supported by the evidence presented, the PBAC advised that a significant price reduction would be required for daratumumab to be equally cost effective in the first- and second line settings (paragraph 7.16, daratumumab PSD, March 2023).	Partially addressed. The resubmission proposed a [REDACTED]% reduction to the effective AEMP for daratumumab compared to that previously considered by the PBAC, and a [REDACTED]% reduction compared to the PBAC's cost-effective price of 2L daratumumab. The cost per patient remained approximately [REDACTED]% higher for the proposed 1L listing compared with the 2L listing.  Of note, the price of DLd in the resubmission is also reduced in comparison with the March 2023 submission, due to a price reduction for lenalidomide following expiry of its patent (multiple brands of lenalidomide are now PBS listed).
Financial estimates	The PBAC considered that the utilisation estimates were overestimated for the reasons outlined in paragraphs 6.67 to 6.70) (paragraph 7.17, daratumumab PSD, March 2023).	Partially addressed. The financial estimates model has been updated to reflect the PBAC's advice in March 2023 except for the changes in the use of drugs in third line setting.
Risk Share Arrangement	The PBAC considered that an RSA with clearly defined expenditure caps would be required to mitigate the risk of use outside the proposed patient population (paragraph 7.18, daratumumab PSD, March 2023).	A combined Risk Share Arrangement for daratumumab across the TI NDMM (DLd) and second line MM (DBd) populations is proposed accounting for the utilisation of DLd in the TI NDMM population, and DBd for second line MM.

Source: Table 1-7, p30-33 of the March 2025 resubmission

AEMP = approved ex-manufacturer price; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; MM = multiple myeloma; MRDR = Myeloma and Related Diseases Registry; MSAG = Myeloma Australia's Medical and Scientific Advisory Group; OS = Overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression-free survival; PSD = Public Summary Document; QALY = quality adjusted life year; RPBS = Repatriation Pharmaceutical Benefits Scheme; RSA = risk sharing agreement; SPA = special price arrangement; TI NDMM = transplant ineligible newly diagnosed multiple myeloma; TTD = time to discontinuation.

For more detail on PBAC's view, see section 7 PBAC outcome.

### 3 Requested listing

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
<b>Intravenous formulation</b>				
Daratumumab, intravenous infusion, liquid in vial, 100 mg; 400 mg	1920 mg	Initial: 15 Continuing: 5 Grandfathered: 7	Published: Public hospital: \$11,773.93 Private hospital: \$11,982.17 Effective: Public hospital: \$ [REDACTED] Private hospital: \$ [REDACTED]	DARZALEX® Janssen-Cilag Pty Ltd
<b>Subcutaneous formulation</b>				
Daratumumab, subcutaneous vial, 1800 mg	1800 mg	Initial: 15 Continuing: 5 Grandfathered: 7	Published price: General: \$7,172.88 EFC Related: \$7,010.28 Effective price: General: \$ [REDACTED] EFC Related: \$ [REDACTED]	DARZALEX® Janssen-Cilag Pty Ltd

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Category/ Program	IV – Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital) SC – Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT) SC – General Schedule (Code GE)
Prescriber type	Medical Practitioners
Condition	Multiple Myeloma
PBS indication	Untreated Multiple Myeloma
Treatment phase	Initial treatment as first line drug therapy for weeks 1 to 24
Restriction Level/ Method	Authority Required (telephone/online PBS Authorities system)
Clinical criteria	The condition must be newly diagnosed AND The condition must be confirmed by a histological diagnosis AND Patient must be ineligible for a primary stem cell transplantation AND The treatment must be in combination with and form part of triple combination therapy limited to: (i) this drug, (ii) lenalidomide, and (iii) dexamethasone AND Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib, elotuzumab, selinexor, thalidomide or pomalidomide AND Patient must be undergoing treatment with this drug, in one of the following situations: (i) for the first time, irrespective of whether the diagnosis has been re-classified (i.e. the diagnosis has changed between multiple myeloma/amyloidosis), (ii) changing the drug's form (intravenous/subcutaneous) within the first 9 weeks of treatment for the same PBS indication
Administrative advice	Special Pricing Arrangements apply
Treatment phase	Continuing treatment from week 25 onwards (administered once every four weeks)
Restriction Level/ Method	Authority Required – immediate, real-time assessment by Services Australia (online/telephone)
Clinical criteria	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND The treatment must be in combination with and form part of triple combination therapy limited to: (i) this drug, (ii) lenalidomide, and (iii) dexamethasone AND Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Administrative advice	Special Pricing Arrangements apply
Treatment phase	Grandfather treatment - Transitioning from non-PBS to PBS-subsidised supply
Restriction Level/ Method	Authority Required – immediate, real-time assessment by Services Australia (online/telephone)
Clinical criteria	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [listing date], AND Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug, which are: (i) The condition must be newly diagnosed, (ii) The condition must be confirmed by a histological diagnosis, (iii) Patient must be ineligible for a primary stem cell transplantation, (iv) Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib, elotuzumab, selinexor, thalidomide or pomalidomide.

	<p>(v) The treatment must be in combination with and form part of triple combination therapy limited to: (1) this drug, (2) lenalidomide, and (3) dexamethasone,</p> <p>(vi) Patient must be undergoing treatment with this drug, in one of the following situations:</p> <p>(1) for the first time, irrespective of whether the diagnosis has been re-classified (i.e. the diagnosis has changed between multiple myeloma/amyloidosis),</p> <p>(2) changing the drug's form (intravenous/subcutaneous) within the first 9 weeks of treatment for the same PBS indication,</p> <p>AND</p> <p>Patient must not have developed disease progression while receiving treatment with this drug for this condition.</p>
Administrative advice	Special Pricing Arrangements apply

Source: Table 1-11, p51 and Table 1-12, p56 of the March 2025 resubmission.

PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefit Scheme; SC = subcutaneous.

Blue shading indicates data previously seen by the PBAC.

- 3.1 As per the March 2023 submission, the resubmission requested the PBS listing of two formulations of daratumumab (i.e. intravenous [IV] and subcutaneous [SC]). Both formulations of daratumumab are currently PBS listed as a second-line treatment of MM for use in combination with bortezomib and dexamethasone (DBd). The resubmission also proposed a new PBS restriction for lenalidomide for use in combination with daratumumab and dexamethasone, should the proposed listing be recommended by the PBAC.
- 3.2 In March 2023, the PBAC considered that the definition of TI was arbitrary and may change over time, therefore there was a high risk that patients who were TE would receive DLd. The resubmission proposed criteria for daratumumab that were unchanged from the previous consideration and stated that defining transplant ineligibility further with more stringent criteria as proposed by the PBAC was not preferred based on advice from haematologists. The resubmission considered that the proposed PBS restriction for daratumumab was aligned with the current restriction for lenalidomide and dexamethasone (Ld) in TI NDMM in that it does not provide a definition (of TI), and therefore leaves the assessment of eligibility for stem cell transplantation to clinical judgement. The Pre-Sub-Committee Response (PSCR) also stated that the RSA proposed in the resubmission will mitigate any potential risk to Government from possible use outside the restriction, for example in TE patients.
- 3.3 The March 2025 resubmission proposed a 44.3% reduction to the effective AEMP for daratumumab compared to that previously considered by the PBAC.
- IV 100 mg vial: \$| requested, compared with \$|;
  - IV 400 mg vial: \$| requested, compared with \$|;
  - SC 1800 mg vial: \$| requested, compared with \$|.
- 3.4 The proposed AEMP for first-line daratumumab is 30.6% lower than the cost-effective AEMP for second line daratumumab.

- 3.5 The price of lenalidomide has also reduced by 34% since the March 2023 PBAC consideration due to price reductions following generic entry. A further statutory price reduction is due to occur on 1 April 2025.
- 3.6 In terms of cost per patient, in March 2023, the PBAC considered that a higher per patient cost in the first line (compared with second line) was not supported by the evidence presented. The submission had requested a modelled cost per patient for daratumumab in the first line setting that was more than double that accepted as being cost effective in the second line setting (paragraph 7.16, daratumumab public summary document [PSD], March 2023). The resubmission stated that at the requested price, the average cost of daratumumab per patient in the proposed first line listing (as DLd) was \$| and estimated this to be |% higher than use in the current second line listing (assumed to be \$|). The resubmission reported a mean time on 1L DLd as 48.4 months, compared with 32.8 months for 2L DBd.
- 3.7 The resubmission proposed that daratumumab would be restricted to once per lifetime use, and this was reflected in the financial estimates. The ESC considered that a criterion stating that the patient must only receive one course of daratumumab per lifetime for multiple myeloma should be added to the proposed restriction and should flow onto the second-line daratumumab listing.
- 3.8 The resubmission requested a grandfather restriction. The resubmission stated that < 500 patients will require transitioning to PBS-subsidised supply, after the anticipated commencement of an Early Access Program three months prior to PBS listing of DLd.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 The proposed population for treatment with DLd is TI NDMM. MM is a cytogenetically heterogeneous clonal plasma cell proliferative disorder characterised by an abnormal serum and/or urine immunoglobulin known as M-protein or free immunoglobulin light chain.
- 4.2 According to the Myeloma Australia's Medical and Scientific Advisory Group (MSAG) of Australia (MSAG 2022) clinical guidelines, patients' eligibility for transplant is assessed based on age, comorbidities and functional status. In general, the MSAG considers patients over 75 years of age to be ineligible for transplant (MSAG 2022, p20). However, patient eligibility can be subjective and can change following treatment (paragraph 7.5, lenalidomide PSD, August 2019). This assessment differs from the enrolment criteria for patients in the MAIA trial, which assessed transplant eligibility based on an age threshold of  $\geq 65$  years. This criterion impacts the adjusted indirect treatment comparison (ITC) between DLd and BLd, as it does not accurately reflect Australian clinical practice.
- 4.3 Daratumumab is a novel human monoclonal antibody that binds to and inhibits CD38, a transmembrane glycoprotein overexpressed in MM plasma cells. DBd was

recommended by the PBAC as a second-line treatment for patients with RRMM in July 2021.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 The March 2025 resubmission again nominated Ld and BLd as the comparators. The main arguments provided in support of this nomination were that these are the regimens most likely to be replaced in clinical practice. In March 2023, the PBAC considered that the nomination of both Ld and BLd as comparators was reasonable as: (i) both BLd and DLd are triple therapies and are therefore likely to be used in the same patients, and (ii) DLd is well tolerated and is therefore likely to replace some use of Ld in frailer patients (paragraph 7.2, daratumumab PSD, March 2023).
- 5.2 Currently, BLd is the most commonly used treatment for TI NDMM patients. The economic evaluation presented in the March 2025 resubmission implemented a weighted comparator approach for costs of treatment (68% BLd versus 32% Ld, based on MRDR data). In March 2023, the ESC considered that the weighting based on the MRDR data was reasonable (paragraph 5.2, daratumumab PSD, March 2023).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician stated that outcomes for older patients with NDMM have not improved relative to younger patients, that TI patients are less likely to receive second-line therapies, and that BLd does not deliver any additional benefits over Ld in terms of PFS or OS benefits in patients who do not receive a transplant. The clinician stated that in Australia (i) approximately 8-10% of patients aged > 70 will receive a transplant, and (ii) based on the MRDR data approximately 25% of patients aged less than 70 will not receive a transplant due to comorbidities. For patients who are TI, the registry data demonstrated that 25% will not receive second line therapy and 50% will not receive a third-line therapy.
- 6.2 The clinician also described the MAIA trial, noting that a large proportion (43.6%) of patients were aged over 75 years, that DLd resulted in a 33% reduction in the risk of death compared to Ld and that this OS benefit was consistent over all pre-specified subgroups. The clinician also noted that time to next treatment was substantially longer for DLd patients.

### ***Consumer comments***

- 6.3 The PBAC noted and welcomed the input from individuals (144), health care professionals (10) and organisations (3) via the Consumer Comments facility on the PBS website. The PBAC also recalled that it received input from individuals (100),

health care professionals (3) and organisations (3) associated with the March 2023 submission. The comments by health care professionals stated that first line daratumumab was the global standard of care and described a range of benefits of treatment with daratumumab including the improvement in PFS without additional toxicities. The comments from individuals described the highly positive response to daratumumab treatment, including improved rates of remission, few side effects and an improved quality of life. Individuals also described the need for more effective treatments, such as daratumumab, in the first line setting, and noted the prohibitive cost of daratumumab.

- 6.4 The PBAC noted that advice received from Myeloma Australia, Rare Cancers Australia and the Leukaemia Foundation. Myeloma Australia and the Leukaemia Foundation stated that daratumumab was associated with longer remission periods and was efficacious and well tolerated. Rare Cancers Australia stated that PBS listing of daratumumab would provide a more equitable and accessible treatment pathway for patients. All organisations described the need for additional treatment options for transplant ineligible patients with MM.
- 6.5 The PBAC recalled the March 2023 advice received from Myeloma Australia, MSAG and the Haematology Society of Australia and New Zealand (HSANZ) clarifying the likely use of daratumumab in clinical practice. The PBAC specifically noted the advice that the use of daratumumab may improve PFS, OS and quality of life and has a favourable side effect profile. The PBAC noted that this advice was generally supportive of the evidence provided in the submissions. The PBAC also recalled that in contrast to the submissions, MSAG differentiated between BLd and Ld in terms of efficacy, noting that BLd is highly effective at recommended doses, but noting that TI patients are frequently unable to tolerate the recommended doses which may compromise efficacy.

### ***Clinical trials***

- 6.6 The evidence in the March 2025 resubmission was from two open-label, phase 3, head-to-head randomised controlled trials (RCTs):
- Updated results of MAIA (March 2023 submission median follow-up = 64.5 months; March 2025 resubmission median follow-up = 89.3 months) comparing DLd to Ld in TI NDMM patients (DLd: n = 368, Ld: n = 369), and;
  - SWOG s0777 comparing BLd to Ld in patients with NDMM without an intent for immediate transplant (BLd: n = 242, Ld: n = 229). This evidence remained unchanged from March 2023 submission.
- 6.7 The approach to the evidence presented in the March 2025 resubmission, including the presentation of additional evidence beyond MAIA and SWOG s0777, to support the clinical claim is summarised in Table 3. Details of the trials presented are provided in Table 4.

**Table 3: Summary of the approach and additional evidence presented in the March 2025 resubmission**

Additional evidence presented in the resubmission	Approach taken in the resubmission
Updated results for OS (data cut-off: 30 November 2023) with a median follow-up of 89.6 months of the MAIA comparing DLd vs Ld.	Maintained the March 2023 submission claim that DLd is superior to Ld in terms of efficacy (paragraph 6.12).
A post-hoc analysis of efficacy and safety in the SWOG s0777 trial by Durie et al. (principal investigator of SWOG s0777) where $\geq 65$ years was used as a proxy for transplant eligibility status (Durie 2022).	Maintained the March 2023 submission claim that the $\geq 65$ years subpopulation is the most appropriate proxy for TI NDMM from SWOG s0777 (paragraph 6.28).
Updated survival analysis of the MRDR patients.	Maintained the March 2023 submission claim that PFS and OS for BLd are non-inferior to Ld in TI NDMM patients (paragraph 6.24).
An adjusted ITC of PFS where the principal investigator of SWOG s0777 compared DLd and BLd based on harmonised eligibility criteria and IPD from the MAIA and SWOG S0777 trials (Durie 2024)*	Maintained the March 2023 submission claim that DLd is superior to BLd in terms of efficacy (paragraph 6.25).
Observational study comparing DLd and BLd in a TI NDMM cohort treated in US clinical practice (Gordan 2024).	Maintained the March 2023 submission claim that DLd is superior to BLd in terms of efficacy (paragraph 6.33).

Source: Compiled during the evaluation using p128-155 of the March 2025 resubmission.

ASCT = autologous stem cell transplantation; BLd = bortezomib, lenalidomide, dexamethasone; DLd = daratumumab, lenalidomide, dexamethasone; ESC = Economics Sub Committee; IPD = individual patient data; ITC = indirect treatment comparison; Ld = lenalidomide, dexamethasone; MRDR = Myeloma and Related Diseases Registry; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PFS = progression free survival; PSD = Public Summary Document; TI NDMM = transplant ineligible, newly diagnosed multiple myeloma; US = United States of America.

\* Due to the difference in the population included in the trials (MAIA enrolled TI MM patients whereas SWOG s0777 enrolled patients without intent for immediate ASCT), the March 2025 resubmission presented an adjusted ITC of PFS for DLd versus BLd using IPD and a harmonised key inclusion/exclusion criteria to match MAIA TI NDMM population (median follow-up of 64.5 months) and SWOG s0777 (primary data cut of 55 months) to select the TI NDMM population (age  $\geq 65$  years as a proxy for transplant ineligibility) (Durie 2024). Following the application of harmonised inclusion/exclusion criteria, 727 patients from the MAIA (DLd, n = 363 [98.6% of the ITT]; Ld, n = 364 [98.7% of the ITT]) and 198 patients from the SWOG s0777 trial (BLd, n = 91 [37.6% of the ITT]; Ld, n = 107 [46.7% of the ITT]) were eligible for inclusion.

**Table 4: Trials and associated reports presented in the March 2025 resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
MAIA	SAN-MIGUEL, Jesus, et al. Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE.	Blood, The Journal of the American Society of Hematology, 2022, 139(4), pp.492-501.
	MATEOS, Maria-Victoria, et al. Switching to daratumumab SC from IV is safe and preferred by patients with multiple myeloma.	Journal of Oncology Pharmacy Practice, 2023, 29(5), pp.1172-1177.
	Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy (CSR of primary analysis, CSR of interim OS analysis [CCO as of Nov 2023], Protocol, SAP)	Nov 2023
	Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy (CSR of primary analysis, CSR of interim OS analysis [CCO as of Oct 2021], Protocol, SAP)	Oct 2021
	Facon, Thierry, et al. Daratumumab plus lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of MAIA	Leukemia, 2022, 36.4: 1066-1077.

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Trial ID	Protocol title/ Publication title	Publication citation
	Perrot, Aurore, et al. Health-related quality of life in transplant-ineligible patients with newly diagnosed multiple myeloma: findings from the phase III MAIA trial	Journal of Clinical Oncology, 2021, 39.3: 227.
	Usmani, Saad Z, et al. Efficacy of Daratumumab, Lenalidomide, and Dexamethasone in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma and Impaired Renal Function from the Phase 3 Maia Study Based on Lenalidomide Starting Dose	Blood, 2021, 138: 1646.
	Weisel, Facon, et al. Overall survival (OS) results with Daratumumab (DARA), Lenalidomide and Dexamethasone (D-Rd) Vs Lenalidomide and Dexamethasone (Rd) in transplant-ineligible newly diagnosed multiple myeloma (TIE-NDMM): Phase 3 MAIA study	Oncology Research and Treatment, 2021, 2022.2: 184-185
	Zweegman, S, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in transplant-ineligible newly diagnosed multiple myeloma (NDMM): frailty subgroup analysis of MAIA	2nd European Myeloma Network (EMN) Meeting; March 3-6. 2021.
	Perrot, Aurore, et al. Health-related quality of life in transplant-ineligible patients with newly diagnosed multiple myeloma: findings from the phase III MAIA trial	Journal of Clinical Oncology, 2021, 39.3: 227.
	Orlowski, Robert, et al. MM-155: Phase 3 MAIA Study: Overall Survival (OS) Results with Daratumumab, Lenalidomide, and Dexamethasone (D-Rd) vs Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (TIE-NDMM)	Clinical Lymphoma, Myeloma and Leukemia, 2021, 21: S424-S425.
	Moreau, Philippe, et al. OAB-001: Overall survival and progression-free survival by treatment duration with Daratumumab+ Lenalidomide/Dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: phase 3 MAIA study	Clinical Lymphoma, Myeloma and Leukemia, 2021, 21: S1.
	Facon, Thierry, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial	The Lancet Oncology, 2021, 22.11: 1582-1596.
	Kumar, Shaji K, et al. Updated analysis of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM): the phase 3 Maia study	Blood, 2020, 136: 24-26.
	Bahlis, Nizar, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant: updated analysis of MAIA	Blood, 2019, 134: 1875.
	Usmani, Saad Zafar, et al. Impact of age on efficacy and safety of daratumumab in combination with lenalidomide and dexamethasone (D-Rd) in patients (pts) with transplant-ineligible newly diagnosed multiple myeloma (NDMM): MAIA	2019
	Facon, Thierry, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma	New England Journal of Medicine, 2019, 380.22: 2104-2115.
	Facon, Thierry, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA)	Blood, 2018, 132.Supplement 1: LBA-2-LBA-2.
SWOG s0777	Durie, Brian GM, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT).	Blood cancer journal, 2020, 10.5: 1-11.

Trial ID	Protocol title/ Publication title	Publication citation
	European Medicines Agency Assessment Report (EPAR) – lenalidomide in combination with bortezomib and dexamethasone (new indication)	2017
	Durie, Brian GM, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial	The Lancet, 2017, 389.10068: 519-527.
	Durie, Brian, et al. Bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT): results of the randomized phase III trial SWOG S0777.	Blood, 2015, 126.23: 25.
MAIA and SWOG S0777	Durie BGM, Kumar SK, Ammann EM, Fu AZ, Kaila S, Lam A, Usmani SZ, Facon T. Adjusted Indirect Treatment Comparison of Progression-Free Survival with D-Rd and VRd Based on MAIA and SWOG S0777 Individual Patient-Level Data.	Adv Ther. 2024 May; 41(5):1923-1937

Source: Table 2-8, p80 of the March 2025 resubmission.

Blue shading indicates data previously seen by the PBAC.

6.8 The key features of the randomised trials are summarised in Table 5. The resubmission did not represent information on response, including minimal residual disease (MRD) negativity, for MAIA. This was reasonable on the basis that those data were not updated and the March 2023 PBAC meeting did not raise concerns regarding these outcomes.

**Table 5: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>DLd vs Ld</b>						
MAIA (ITT)	737	R, MC, OL 89.3 months	Low	TI NDMM	PFS, OS, TTP, CR rate, MRD negativity rate, PFS2, Time to next treatment, sCR rate, ORR, VGPR, Time to response, DOR, HRQoL.	PFS, OS, TTP, CR rate, Time to next treatment, HRQoL
<b>BLd vs Ld</b>						
SWOG s0777	523 (subgroup ≥ 65 years n = 202)	R, MC, OL 55 months	Low	Previously untreated MM without an intent for immediate transplant.	PFS, OS, ORR.	Not used

Source: Table 2-14, p100, Table 2-30, p133 of the March 2025 resubmission.

CR = complete response; DB = double blind; DOR = duration of response; HRQoL = health related quality of life; IMWG = International Myeloma Working Group; ITT = intention-to-treat; MC = multi-centre; MM = multiple myeloma; MRD = minimal residual disease; NR = not reported; ORR = overall response rate; OS = overall survival; OL = open label; PFS = progression-free survival; PFS2 = progression-free survival on next line of therapy; PR = partial response; R = randomised; sCR = stringent complete response; TI NDMM = transplant ineligible, newly diagnosed multiple myeloma; TTP = time to disease progression; TTR = time to response.

Blue shading indicates data previously seen by the PBAC.

## Comparative effectiveness

### MAIA: DLd versus Ld

6.9 A summary of the efficacy results for PFS and OS from the intention to treat (ITT) population in MAIA is presented in Table 6 with the corresponding Kaplan Meier curves presented in Figure 1. Significantly fewer progression or death events were observed in the DLd group than in the Ld group with a 45% reduction in the risk of progressive disease (PFS outcomes from MAIA reported in the March 2025 resubmission were the same as those reported in the March 2023 submission; HR = 0.55; 95% CI: 0.45, 0.67;  $p < 0.0001$ ) as the data at 55 months was the final analysis).

**Table 6: Results of overall survival and progression free survival (MAIA, ITT population)**

	DLd (N = 368)	Ld (N = 369)
Median follow-up (months)	64.5	
<b>PFS (data cut-off Oct 2021)</b>		
Number of events (%)	176 (47.8)	228 (61.8)
Number censored (%)	192 (52.2)	141 (38.2)
Median Kaplan-Meier estimate (months, 95% CI)	61.9 (54.8, NE)	34.4 (29.6, 39.2)
p-value <sup>a</sup>	<b>&lt; 0.0001</b>	
Hazard ratio (95% CI) <sup>b</sup>	<b>0.55 (0.45, 0.67)</b>	
<b>OS (data cut-off Nov 2021)</b>		
Number of events (%)	132 (35.9%)	176 (47.7%)
Number censored (%)	236 (64.1%)	193 (52.3%)
Median Kaplan-Meier estimate (months, 95% CI)	NE (73.72, NE)	65.54 (55.98, 75.66)
p-value <sup>a</sup>	0.0003	
Hazard ratio (95% CI) <sup>b</sup>	<b>0.66 (0.53, 0.83)</b>	
<b>OS (data cut-off Nov 2023)</b>		
Number of events (%)	175 (47.6%)	218 (59.1%)
Number censored (%)	193 (52.4%)	151 (40.9%)
Median Kaplan-Meier estimate (months, 95% CI)	90.25 (80.76, NE)	64.07 (55.98, 70.80)
p-value <sup>a</sup>	<b>0.0001</b>	
Hazard ratio (95% CI) <sup>b</sup>	<b>0.67 (0.55, 0.82)</b>	

Source: Table 2-19, p110 and Table 2.25, p142 of the resubmission.

CI = confidence interval; DLd = daratumumab, lenalidomide, dexamethasone; ITT = intention to treat; Ld = lenalidomide, dexamethasone; N = total participants in group; NE = not estimable; PFS = progression free survival; OS = overall survival.

<sup>a</sup> p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomised.

<sup>b</sup> Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomised. A hazard ratio <1 indicates an advantage for DLd.

Bold text indicates statistically significant results.

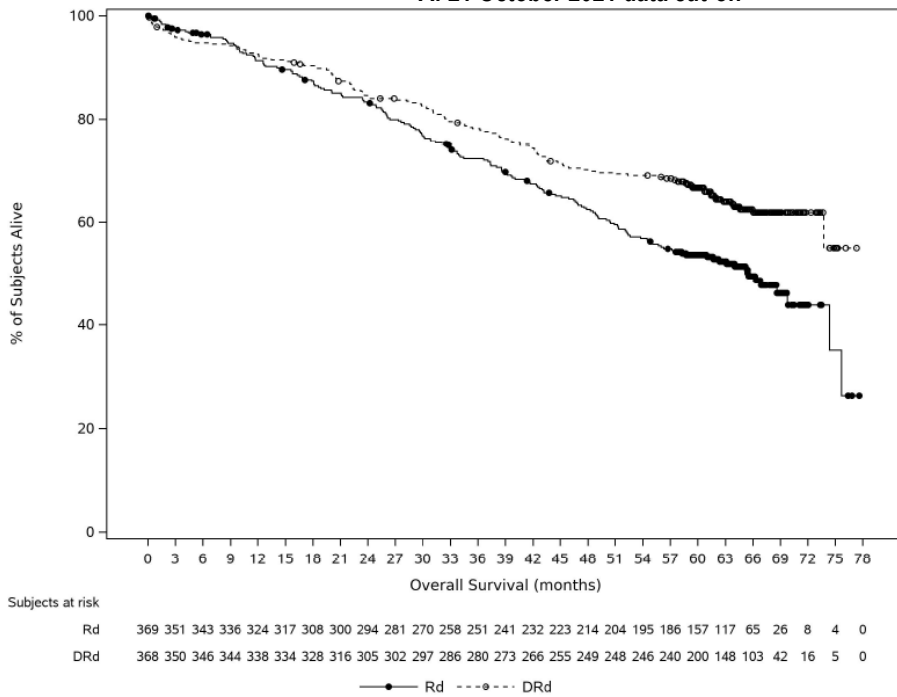
Blue shading indicates data previously seen by the PBAC.

6.10 After a median follow-up of 89.3 months, patients treated with DLd have statistically significantly longer OS than those treated with Ld, with a 33% reduction in the risk of death from any cause. The overall trend remains consistent compared to March 2023 submission, where the reduction in the risk of death was 34%.

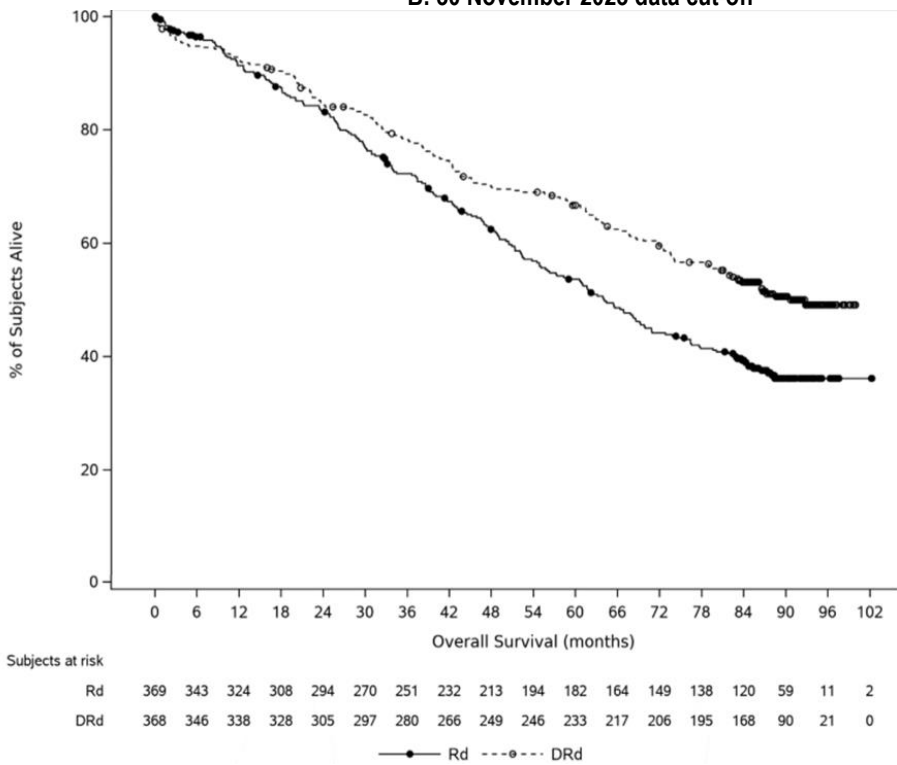
6.11 The difference in OS rates continued to increase from Oct 2021 (data considered by PBAC in the March 2023 meeting) to Nov 2023 with a clear separation after 2 years (24 months) favouring DLd over Ld (Figure 1). The more mature data (Nov 2023)

suggest a consistent continuation of the benefit up to approximately 90 months (Figure 1B).

Figure 1: Kaplan-Meier Curve of overall survival (MAIA, ITT population)  
A: 21 October 2021 data cut-off



B: 30 November 2023 data cut-off

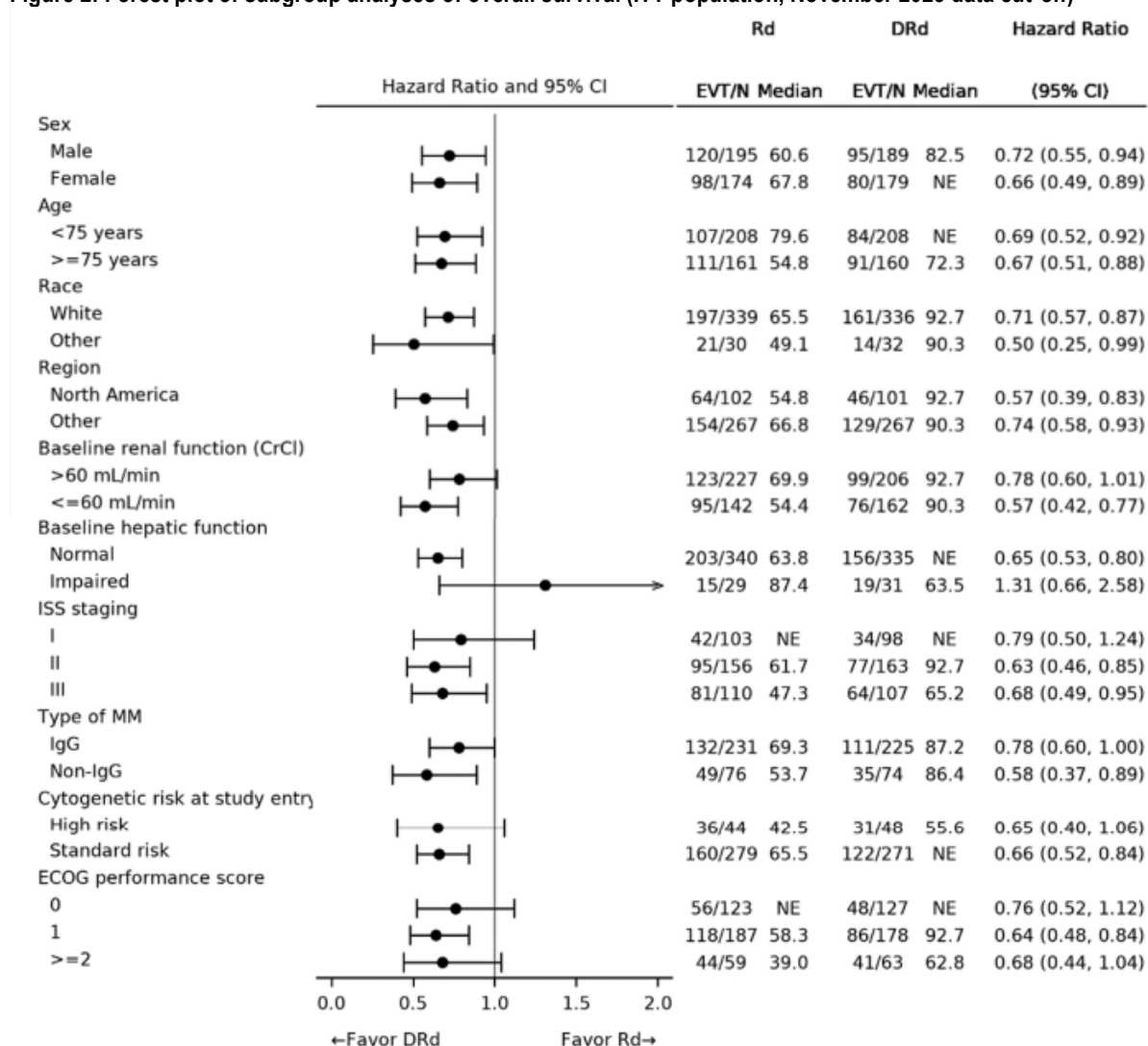


Source: Figure 2-7, p 112 of the March 2025 resubmission.

DRd = daratumumab-lenalidomide-dexamethasone; ITT = intention to treat; OS = overall survival; Rd = lenalidomide-dexamethasone.

- 6.12 During the March 2023 PBAC meeting, it was noted that OS results were not statistically significant in the subgroup of patients aged  $\geq 75$  years (HR = 0.75; 95% CI: 0.55, 1.02) (paragraph 6.13 daratumumab PSD, March 2023). The updated analysis presented in the March 2025 resubmission showed that the benefit of DLd compared with Ld was generally consistent across the prespecified relevant subgroups in the MAIA and in contrast to the previous submission, indicated a statistically significant difference in the subgroup of patients aged  $\geq 75$  years (HR = 0.67; 95% CI: 0.51, 0.88; see Figure 2). The PSCR stated that this analysis supported the claim that DLd will be effective in Australian clinical practice, in which most TI patients are aged 75 years or older.

Figure 2: Forest plot of subgroup analyses of overall survival (ITT population, November 2023 data cut-off)



Source: Figure 2-8, p112 of the March 2025 submission.

CI = confidence interval; CrCl = creatinine clearance.; DRd = daratumumab-lenalidomide-dexamethasone; ECOG = the Eastern Cooperative Oncology Group; EVT = event; IgG = Immunoglobulin G; ISS = international staging system; ITT = intention to treat; MM = multiple myeloma; MM = multiple myeloma; NE = not estimable; Rd = lenalidomide-dexamethasone.

Impaired baseline hepatic function includes mild (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5×ULN); moderate (1.5×ULN < total bilirubin ≤ 3×ULN); and severe (total bilirubin > 3×ULN).

High risk cytogenetics is defined as positive for any of t(4; 14), t(14; 16), and 17p deletion by FISH or karyotype.

6.13 The health-related quality of life (HRQoL) data in the March 2025 resubmission remained unchanged from the March 2023 submission. Overall, changes in both HRQoL instruments used in MAIA suggested an improvement in patients' quality of life for DLd and Ld compared to baseline scores, and those improvements did not decline over the follow-up period, noting that these results are susceptible to bias in this unblinded trial. The utility scores used in the economic model were sourced from the EQ-5D-5L as reported from MAIA.

**SWOG s0777 – BLd versus Ld**

- 6.14 The results of the SWOG s0777 trial (median follow up = 55 months) presented in the March 2025 resubmission remained unchanged from the March 2023 submission. The primary outcome data reported in SWOG s0777 are presented in Table 7 and the Kaplan Meier estimates are provided in Figure 3 and Figure 4. Age-based subgroup (i.e. < 65 years) analyses were not pre-specified or stratified in the original study design of SWOG s0777.
- 6.15 The ESC noted that the ITT analysis showed that BLd patients had significantly longer PFS (43 months in the BLd arm vs 30 months in the Ld arm) and OS (75 months in the BLd arm vs 64 months in the Ld arm) than those treated with Ld (see Figure 3, Figure 4 and Table 7).
- 6.16 The ESC considered the data do not support the resubmission’s claim that BLd and Ld are non-inferior in patients aged  $\geq 65$  years (as a proxy for transplant ineligibility). The ESC considered the data for the  $\geq 65$  year subgroup should be interpreted in the context of the interaction between age group and treatment and not in isolation, noting that the subgroup was not pre-specified and the study was not powered to assess efficacy in the  $\geq 65$  year subgroup. In this context, the ESC noted although the point estimates for the hazard ratios for both PFS and OS suggested the benefit of BLd over Ld was less in patients aged  $\geq 65$  years versus < 65 years, the difference was not statistically significant (i.e. the p-values for the tests for interaction were not < 0.05). Thus, the ESC considered the magnitude of the reduction in benefit, if any, of BLd versus Ld in patients  $\geq 65$  years was uncertain.
- 6.17 The authors of the SWOG s0777 study (Durie 2020), based on the analysis with a median of 84 months follow-up, similarly concluded ‘The benefits of VRd (i.e. BLd) are also evident in each of the three different age categories, showing a > 10-month median benefit across all age groups. Overall survival is also improved both above and below age 65 years’.

**Table 7: Progression free survival and overall survival in (SWOG s0777, ITT and subgroups)**

Primary Analysis Follow-up: 55 months						
PFS	ITT (n = 471)		Age < 65 years (n = 269)		Age ≥ 65 years (n = 202)	
	BLd (n = 242)	Ld (n = 229)	BLd (n = 149)	Ld (n = 120)	BLd (n = 93)	Ld (n = 109)
Number of events	137	166	NR	NR	NR	NR
Median (months)	43.0	30.0	55.4	36.6	33.1	25.8
p-value	p = 0.0037		NR		NR	
Hazard ratio (95% CI)	<b>0.71 (0.56, 0.91)</b>		<b>0.63 (0.46, 0.87)</b>		0.83 (0.60, 1.16)	
Test for interaction of Treatment and age, p = 0.237						
Adjusted hazard ratio (95% CI)	NE		<b>0.61 (0.45, 0.84)</b>		0.90 (0.65, 1.26)	
Test for interaction of Treatment and age, p = 0.093						
<b>OS</b>						
Number of events	76	100	NR	NR	NR	NR
Median (months)	75.0	64.0	NR	68.9	62.9	53.0
p-value	P = 0.025		-		-	
Hazard ratio (95% CI)	<b>0.71 (0.52, 0.96)</b>		<b>0.61 (0.39, 0.97)</b>		0.83 (0.55, 1.23) <sup>a</sup>	
Test for interaction of Treatment and age, p = 0.334						
Adjusted hazard ratio (95% CI)	NE		<b>0.62 (0.39, 0.99)</b>		0.88 (0.59, 1.31)	
Test for interaction of Treatment and age, p = 0.270						

Source: Table 2-30, p133 and Table 2.31, p136 of the March 2025 resubmission.

BLd = bortezomib, lenalidomide, dexamethasone; Ld = lenalidomide, dexamethasone; ITT = intention to treat; CI = confidence interval; NE = not estimated; NR = not reported; PFS = progression free survival; OS = overall survival.

<sup>a</sup> At a median follow-up of 84 months, Durie 2020 reported a HR = 0.77 (95% CI = 0.52, 1.14) for the subgroup ≥65 years.

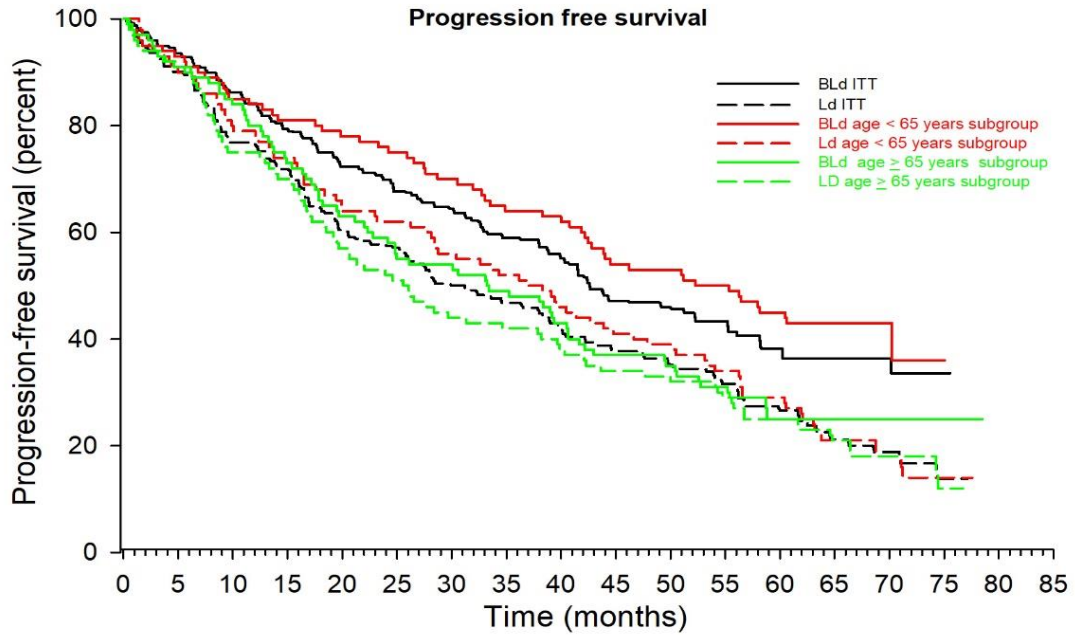
Median follow-up is 55 months, 54 months for BLd and 56 months (50–70) for the Ld group

Adjusted hazard ratio estimates reflect results from weighted Cox regression models where inverse-probability-of-treatment weighting was used to balance the BLd and Ld trial groups on the following measured baseline characteristics within each age subgroup (≥65, <65 years): age, sex, ISS stage, ECOG performance status score, haemoglobin (<10 g/dL, > = 10 g/dL), serum creatinine (<2 mg/dL, > = 2 mg/dL), cytogenetic risk by FISH test (high, intermediate, low, normal/missing/insufficient), and lactate dehydrogenase (<190 IU/L, > = 190 IU/L). Absolute standardised differences for all covariates were <0.1 with IPTW.

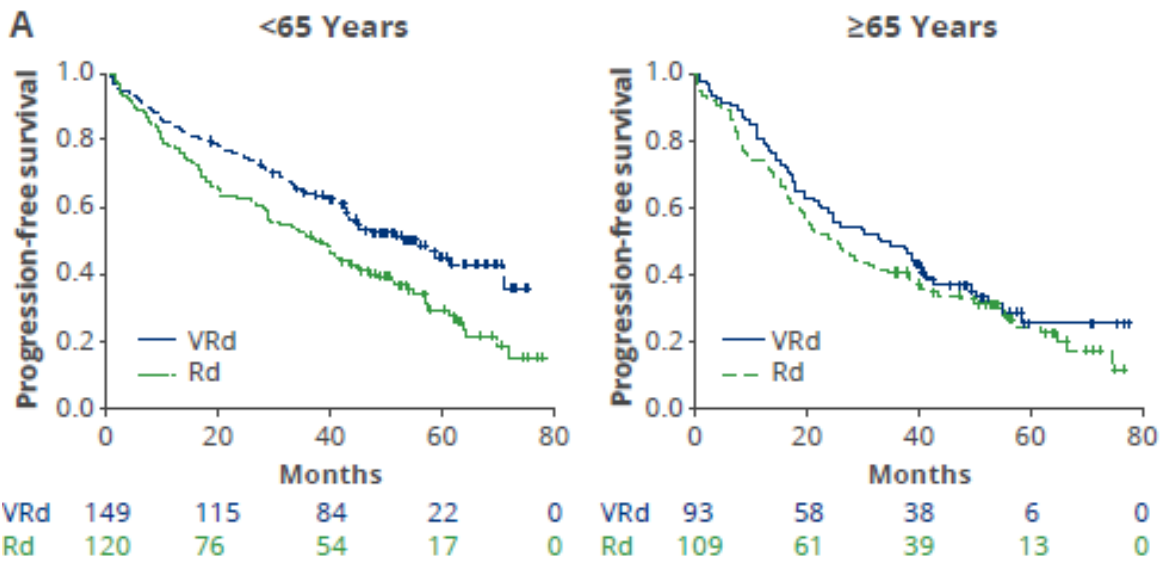
Bold text indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

Figure 3: Kaplan-Meier curves of progression-free survival (ITT and subgroups, central assessment)



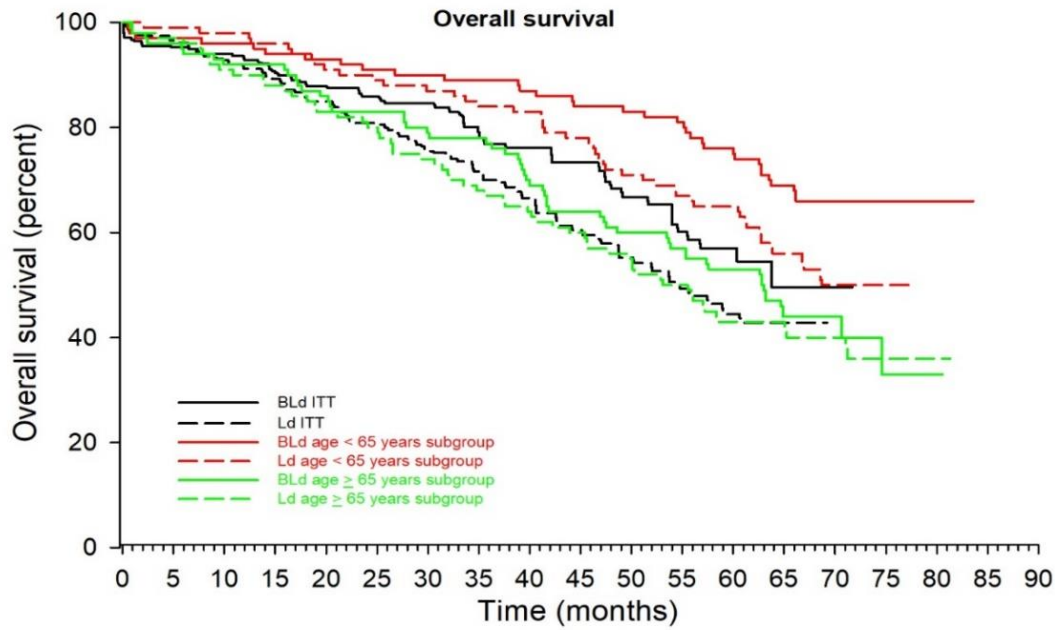
BLd <65yrs	149	139	129	122	111	100	89	73	57	42	22	15	7	0
Ld <65yrs	120	107	94	85	73	66	59	49	38	29	17	11	5	0
BLd ≥65yrs	93	82	70	62	55	49	46	35	27	16	6	3	1	0
Ld ≥65yrs	109	94	79	68	58	51	46	37	30	21	13	8	3	0
BLd ITT	242	221	199	184	166	149	135	108	84	58	28	18	8	
Ld ITT	229	201	173	153	131	117	105	86	68	50	30	19	8	



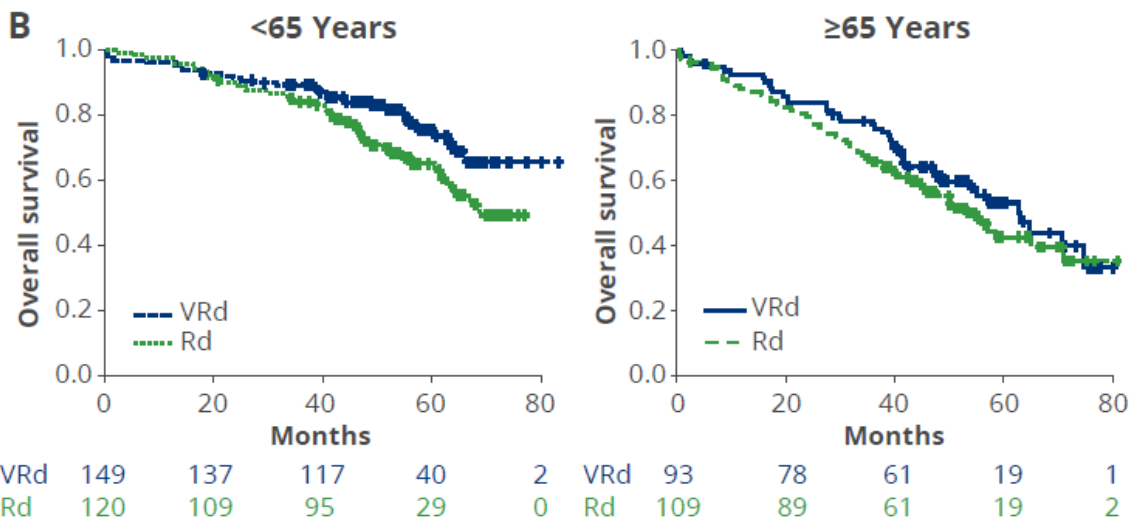
Source: Figure 2-12, p134 of the March 2025 resubmission.

BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; ITT = intent to treat; Ld = lenalidomide and dexamethasone; NE = not estimated; Rd = lenalidomide and dexamethasone; VRd = bortezomib, lenalidomide and dexamethasone.

Figure 4: Kaplan-Meier curves of overall survival (ITT and subgroups, central assessment) at a median follow up of 55 months



Bld <65yrs	149	146	144	144	136	127	124	102	85	66	40	28	13	2
Ld <65yrs	120	118	116	115	109	101	96	80	68	51	29	22	11	0
Bld ≥65yrs	93	89	83	79	75	72	72	58	47	34	19	9	2	1
Ld ≥65yrs	109	103	96	90	84	77	72	59	47	33	19	11	6	2
Bld ITT	242	235	227	223	211	199	196	160	132	100	59	37	15	0
Ld ITT	229	221	212	205	193	178	168	139	115	84	48	33	17	0



Source: Figure 2-13, p138 of the resubmission.

BLd = bortezomib, lenalidomide, dexamethasone; ITT = intention to treat; Ld = lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone.

### Survival analysis of the MRDR - BLd vs Ld

6.18 The March 2025 resubmission presented a survival analysis from the MRDR conducted in September 2024 for the outcomes of OS and PFS to support the claim that the clinical benefits of BLd are not different to Ld. The MRDR analysis (June 2022) presented in the March 2023 submission included 109 and 194 patients in the BLd and

Ld arms, respectively. This is increased to 361 and 320 patients in the BLd and Ld arms, respectively, included in MRDR analysis presented in the March 2025 resubmission.

- 6.19 The MRDR analysis defined patients as TI if they had not received an ASCT, did not have an ASCT planned, and had sufficient follow-up time to preclude an ASCT (i.e., diagnosed at least one year ago). A summary of baseline demographics and disease characteristics from the September 2024 MRDR analysis is presented in Table 8. In the survival analysis, the HR was adjusted for age, ISS, ECOG PS score and cytogenetic risk which are prognostic in MM. In line with the MSAG guidelines, age alone was not used to define transplant eligibility, and approximately 32% of recipients of ASCT were above 65 years old.
- 6.20 The analysis of the MRDR for TI NDMM patients presented in the March 2025 resubmission revealed demographic and clinical differences between the populations receiving Ld and BLd, particularly with respect to age, ECOG performance status, and cytogenetic risk profiles. The observed differences may indicate a divergence in treatment eligibility criteria or physician decision, with patients receiving the triplet therapy, BLd, likely representing a cohort with characteristics distinct from those receiving the doublet therapy, Ld, in the Australian clinical setting.

Table 8: Baseline demographics of TI NDMM patients in the MRDR efficacy analysis (September 2024)

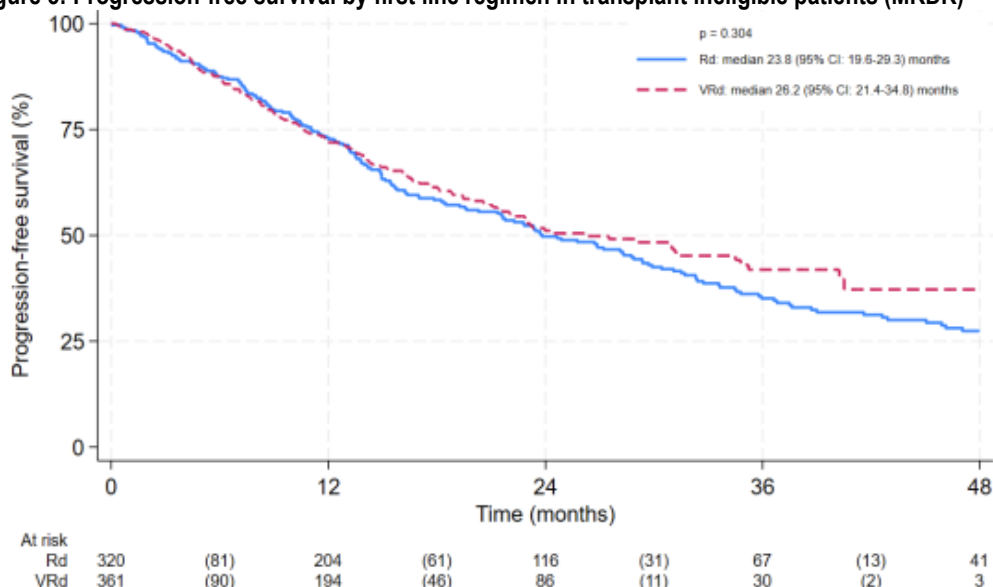
	BLd (n = 361)	Ld (n = 320)	p-value
Age, median (IQR)	72.8 (67.5; 76.6)	80.3 (76.1; 84.6)	<0.001
Age category			<0.001
< 65	63 (17.5%)	4 (1.2%)	
65 – 69	66 (18.3%)	13 (4.1%)	
70 – 74	104 (28.8%)	48 (15.0%)	
75 +	128 (35.5%)	255 (79.7%)	
Gender			0.41
N	359	319	
Male, n (%)	226 (63.0%)	191 (59.9%)	
Female, n (%)	133 (37.0%)	128 (40.1%)	
Weight (kg), median (IQR)	N = 324 79.0 (67.0, 93.0)	N = 248 74.0 (64.5, 86.0)	0.003
ECOG score, n (%)			0.090
N	247	220	
0	98 (39.7%)	66 (30.0%)	
1	102 (41.3%)	95 (43.2%)	
2	37 (15.0%)	42 (19.1%)	
3	8 (3.2%)	16 (7.3%)	
4	2 (0.8%)	1 (0.5%)	
ISS, n (%)			0.15
N	267	205	
I	75 (28.1%)	43 (21.0%)	
II	118 (44.2%)	93 (45.4%)	
III	74 (27.7%)	69 (33.7%)	
Cytogenetic risk			0.005
N	223	170	
Standard	167 (74.9%)	147 (86.5%)	
High	56 (25.1%)	23 (13.5%)	
FISH - Del(17p)	26 (11.7%)	15 (8.8%)	0.36
FISH - t(14;16)	9 (4.0%)	7 (4.1%)	0.97
FISH - t(4;14)	28 (12.6%)	4 (2.4%)	<0.001
Paraprotein type			0.86
N	340	307	
IgG	206 (60.6%)	183 (59.6%)	
IgA	66 (19.4%)	66 (21.5%)	
IgM	2 (0.6%)	2 (0.7%)	
IgD	3 (0.9%)	3 (1.0%)	
Light chain only Kappa	36 (10.6%)	30 (9.8%)	
Light chain only Lambda	24 (7.1%)	18 (5.9%)	
Non secretory MM	2 (0.6%)	1 (0.3%)	
Biclonal	1 (0.3%)	4 (1.3%)	
Paraprotein light chain, N			0.95
N	271	244	
Kappa	187 (69.0%)	169 (69.3%)	
Lambda	84 (31.0%)	75 (30.7%)	

Source: Table 2-36, p149 of the March 2025 resubmission.

BLd = bortezomib, lenalidomide and dexamethasone; ECOG = the Eastern Cooperative Oncology Group; FISH = fluorescent in situ hybridisation; IgA = Immunoglobulin A; IgD = Immunoglobulin D; IgG = Immunoglobulin G; IgM = Immunoglobulin M; IQR = interquartile range; ISS = International Staging System; Ld = lenalidomide and dexamethasone; MM = multiple myeloma; MRDR = Myeloma and Related Diseases Registry; TI NDMM = transplant ineligible newly diagnosed multiple myeloma.

6.21 The Kaplan Meier curves of PFS and OS by first line treatment regimen in TI NDMM patients from the analysis of the MRDR as of September 2024 are presented in Figure 5 and Figure 6 respectively.

Figure 5: Progression-free survival by first line regimen in transplant ineligible patients (MRDR)



Source: Figure 2-18, p153 of the March 2025 resubmission.

VRd = bortezomib, lenalidomide, dexamethasone, Rd = lenalidomide and dexamethasone; CI = confidence interval; PFS = progression free survival; MRDR = Myeloma and Related Diseases Registry.

The March 2025 resubmission did not provide an explanation for the numbers in brackets provided in this figure; they are assumed to correspond to the number of events observed between timepoints.

6.22 The results from the PFS analysis showed a similar trajectory for ASCT-ineligible patients treated with BLd and Ld. The median PFS of 26.2 (95% CI: 21.4, 34.8) months for BLd-treated patients was similar to the 23.8 (95% CI: 19.6, 29.3) months for Ld-treated patients. The unadjusted (HR = 0.89 (95% CI: 0.72, 1.11) and adjusted (HR = 0.90; 95% CI: 0.69, 1.16) results are presented in Table 9.

Table 9: Results of Cox model for PFS and OS in transplant ineligible patients (MRDR; September 2024)

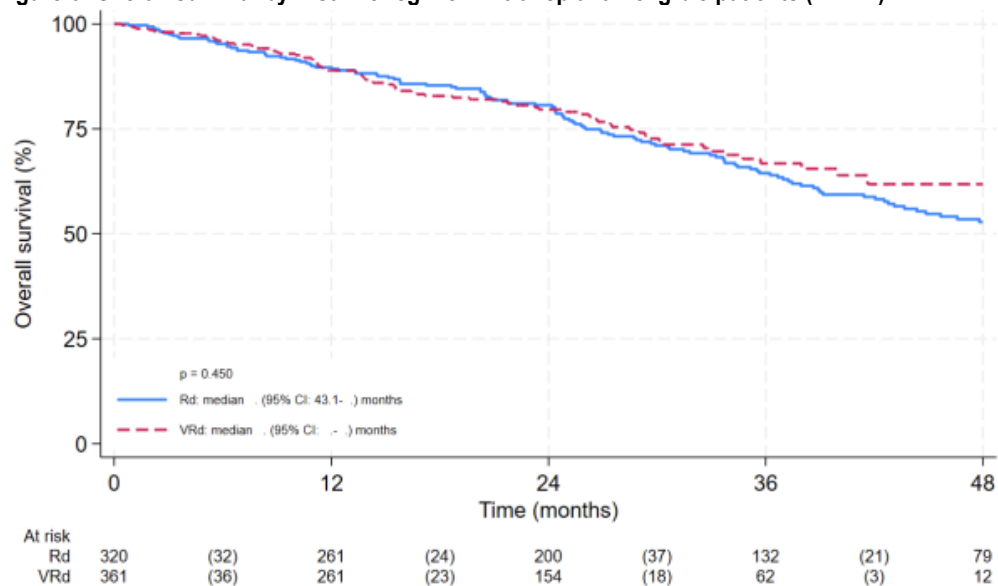
	Hazard ratio (95% CI)	Adjusted <sup>a</sup> hazard ratio (95% CI)
<b>PFS: BLd vs Ld</b>	0.89 (0.72, 1.11) p = 0.304	0.90 (0.69, 1.16) p = 0.400
<b>OS: BLd vs Ld</b>	0.89 (0.67, 1.20) p = 0.450	0.97 (0.68, 1.40) p = 0.877

Source: Table 2-37, p152 and Table 2-38, p154 of the March 2025 resubmission.

BLd = bortezomib, lenalidomide and dexamethasone; CI = confidence interval; Ld = lenalidomide and dexamethasone; MRDR = Myeloma and Related Diseases Registry; PFS = progression free survival; OS = overall survival.

<sup>a</sup> Hazard ratio adjusted for age, ISS, ECOG and cytogenetic risk

Figure 6: Overall survival by first line regimen in transplant ineligible patients (MRDR)



Source: Figure 2-18, p 153 of the March 2025 resubmission.

MRDR = Myeloma and Related Diseases Registry; Rd = lenalidomide and dexamethasone; VRd = bortezomib, lenalidomide and dexamethasone.

The March 2025 resubmission did not provide an explanation for the numbers in brackets provided in this figure; they were assumed to correspond to the number of events observed between timepoints.

6.23 The Kaplan-Meier curves for OS and PFS only extend to 48 months, which prevents an assessment of late divergence or convergence in the survival curves and potentially masks important trends in long-term efficacy. However, there is an imbalance in patients remaining at 48 months (3 vs 41 for PFS and 12 vs 79 for OS in the BLd and Ld arms, respectively), which compromises the reliability of long-term survival estimates.

6.24 The evaluation stated that the March 2025 resubmission's conclusion that there is no difference in terms of PFS and OS between BLd and Ld based on the non-significant HR of PFS = 0.90 (95% CI: 0.69, 1.16) and OS = 0.97 (95% CI: 0.68, 1.40) in the MRDR analysis should be interpreted with caution as there is a potential for bias in patient selection as patients in the MRDR were not randomised to receive BLd or Ld.

#### Indirect treatment comparison – DLd vs BLd

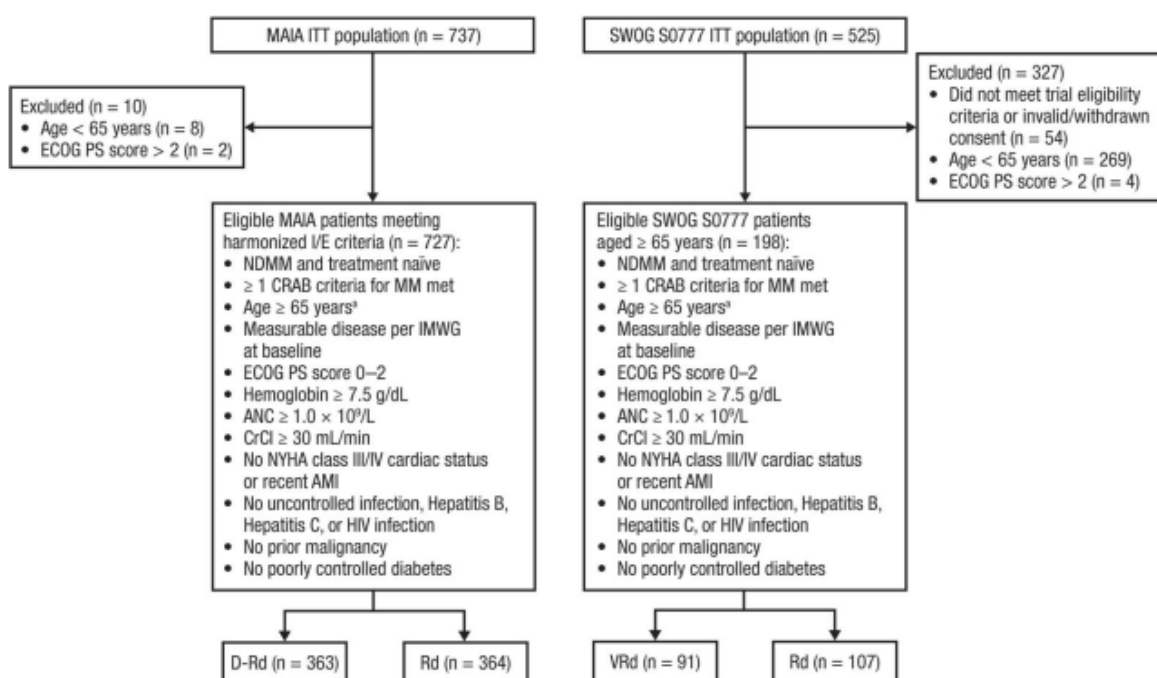
6.25 The March 2023 submission stated that in the subgroup of patients aged  $\geq 65$  years, the comparison between BLd and Ld demonstrated no statistically significant differences in terms of PFS and OS (see paragraph 6.15). Therefore, the submission concluded that BLd and Ld were equivalent in terms of efficacy and asserted that the results from MAIA (DLd versus Ld) were a reasonable proxy for the comparison between DLd and BLd (from SWOG s0777). The PBAC did not agree with the March 2023 submission's claim that Ld was a proxy for BLd (paragraph 7.10, daratumumab PSD, March 2023).

6.26 In response to the PBAC's concern, the March 2025 resubmission presented an adjusted indirect treatment comparison (ITC) of PFS for DLd versus BLd in TI NDMM patients using individual patient data from MAIA (median follow-up of 64.5 months)

and SWOG s0777 (primary data cut of 55 months) to support the superiority claim of DLd over BLd (Durie 2024). The March 2025 resubmission did not provide a rationale for the omission of more mature data from the SWOG s0777 trial (Durie 2020, data cut 84 months) in conducting the adjusted ITC nor did it provide results of the adjusted ITC for OS. The 55-month follow-up results indicate a diminished benefit of the BLd regimen over Ld for patients aged 65 years or older, with a HR of 0.88 (95% CI: 0.59, 1.31;  $p > 0.05$ ), compared to the 84 months follow-up HR of 0.77 (95% CI: 0.52, 1.14). Due to the difference in the population included in the trials (MAIA enrolled TI MM patients whereas SWOG s0777 enrolled patients without intent for immediate ASCT), the adjusted ITC harmonised key inclusion/exclusion criteria of MAIA and SWOG s0777 (i.e., it applied the same criteria across the trials, see Figure 4) to select what the resubmission considered was the TI NDMM population (using age  $\geq 65$  years as a proxy for transplant ineligibility, Figure 7).

- 6.27 Following the application of harmonised inclusion/exclusion criteria, 727 patients from MAIA (DLd,  $n = 363$  (98.6%); Ld,  $n = 364$  (98.7%)) and 198 patients from the SWOG s0777 (BLd,  $n = 91$  (37.6%); Ld,  $n = 107$  (46.7%)) were included in the analysis (Figure 7). The most common reason patients were excluded was age  $< 65$  years (MAIA,  $n = 8$  (1.1%); SWOG s0777,  $n = 269$  (51.2%)). The unadjusted ITC conducted during the March 2023 evaluation comparing MAIA ITT versus SWOG s0777 in patients  $> 65$  years included a similar number of patients from the SWOG s0777 trial, with 93 patients in the BLd arm and 109 patients in the Ld arm (Table 8, f daratumumab PSD, March 2023).
- 6.28 The application of matching eligibility criteria led to a noticeable reduction in the number of SWOG s0777 patients eligible for inclusion in the ITC (SWOG s0777: primary,  $n = 525$ ; ITC,  $n = 198$ ). Additionally, as noted previously by the PBAC (paragraph 7.7, daratumumab PSD, March 2023), stem cell transplant is feasible in some patients aged  $\geq 65$ ; thus, the use of this proxy as an upper age limit for eligibility is an important limitation and does not reflect Australian clinical practice. Data from the MRDR reveals that a significant proportion (31.5%) of Australian NDMM patients who underwent autologous stem cell transplantation (ASCT) were 65 years of age or older. Therefore, the ESC considered that the population used for the adjusted ITC may not accurately represent the Australian clinical setting, and the applicability of the findings to the local patient population remains uncertain.

Figure 7: Selection of eligible patients from MAIA and SWOG s0777 trials



Source: Figure 2-15, p144 of the March 2025 submission and Figure 1 of Durie 2024

AMI = acute myocardial infarction; ANC = absolute neutrophil count; CRAB = calcium elevation, renal insufficiency, anaemia; CrCl = creatinine clearance; DRd = daratumumab in combination with lenalidomide and dexamethasone; ECOG PS = eastern cooperative oncology group performance status; HIV = human immunodeficiency virus; IMWG = international myeloma working group; ITC = indirect treatment comparison; ITT = intention to treat; MM = multiple myeloma; NDMM = newly diagnosed multiple myeloma; NYHA = New York heart association; Rd = lenalidomide; VRd = bortezomib in combination with lenalidomide and dexamethasone.

6.29 Propensity-score weighting was used to balance the two trial populations on key baseline characteristics. Baseline covariate balance after propensity-score weighting was assessed using standardised differences, with an absolute standardised difference > 0.1 considered a meaningful imbalance. Multiple imputation was used to assign missing baseline covariate values and address the missing baseline covariate data before the application of propensity-score weighting. Durie 2024 reported that the baseline patient characteristics were balanced across treatment arms within each trial and across trials (absolute standardised mean differences < 0.1 for all covariates) following multiple imputation and propensity-score weighting, see Table 10. However, data were missing for two baseline covariates in the SWOG S0777 trial, cytogenetic risk and lactate dehydrogenase (LDH), with high missingness (BLd, 40.7%; Ld, 36.4%) for cytogenetic risk. Cytogenetic risk is a prognostic factor in multiple myeloma and its absence could lead to unmeasured confounding, potentially biasing the treatment effect estimates in the ITC. However, the subgroup analysis conducted in Durie 2024 restricted to patients with known high cytogenetic risk was consistent with results in the overall TI NDMM population. The March 2025 resubmission did not provide the distributions of factors for patients before the weighting and multiple imputation procedures were applied. This limited the ability to assess the direction and magnitude of potential shifts in important prognostic factors, such as ISS stage. However, the

subgroup analysis conducted in Durie 2024 which was restricted to patients with known high cytogenetic risk was consistent with the results in the overall TI NDMM study population (Durie 2024).

**Table 10: Baseline patient characteristics after multiple imputation and propensity-score weighting in the MAIA and SWOG trials**

Covariate	MAIA (64.5 month*)			SWOG s0777 (55 month*)		
	DLd (N = 363)	Ld (N = 364)	Standardised difference <sup>a</sup>	BLd (N = 91)	Ld (N = 107)	Standardised difference <sup>a</sup>
Age (Years), n (%)						
Mean (SD)	72.75 (4.77)	72.65 (4.81)	0.021	72.69 (5.36)	72.65 (5.13)	0.009
Gender, %						
Female	40.4	41.9	- 0.031	39.0	39.8	- 0.017
ISS disease stage %						
I	20.2	20.6	- 0.010	20.1	19.7	0.010
II	44.0	45.3	- 0.026	44.5	44.8	- 0.006
III	35.8	34.1	0.036	35.4	35.5	- 0.002
ECOG PS score, %						
0	42.5	40.9	0.032	40.1	40.1	0.001
1	48.9	50.4	- 0.030	51.2	51.0	0.004
≥ 2	8.6	8.7	- 0.003	8.7	8.9	- 0.009
Haemoglobin < 10 g/dL, %	31.0	30.4	0.013	31.9	32.1	- 0.004
eGFR <60 mL/min/1.73m <sup>2</sup> , %	47.3	47.0	0.005	47.2	46.9	0.007
LDH>190 U/L, %	38.6	39.9	- 0.027	39.4	39.0	0.009
High cytogenetic risk <sup>b</sup> , %	18.1	19.1	- 0.024	16.4	16.6	- 0.005

Source: Table 2-34, p145 of the March 2025 submission and Table 1 of Durie 2024.

BLd = bortezomib, lenalidomide and dexamethasone; DLd = daratumumab, lenalidomide and dexamethasone; ECOG PS = Eastern Cooperative Oncology Group performance status; eGFR = estimated glomerular filtration rate; ISS = international staging system; Ld = lenalidomide and dexamethasone; LDH = lactate dehydrogenase; SD = standard deviation.

\*Refers to data cut-off length

<sup>a</sup> Standardised mean differences shown in the table reflect the magnitude of the difference in baseline covariate means across trial arms within each trial. Cross-trial standardized mean differences for the MAIA versus SWOG S0777 trials, not shown in the table, were 0.1 for all baseline covariate

<sup>b</sup> High cytogenetic risk was defined in the MAIA and SWOG S0777 trials as the presence of C 1 high-risk cytogenetic abnormality (del17p, t[14;16], or t[4;14])

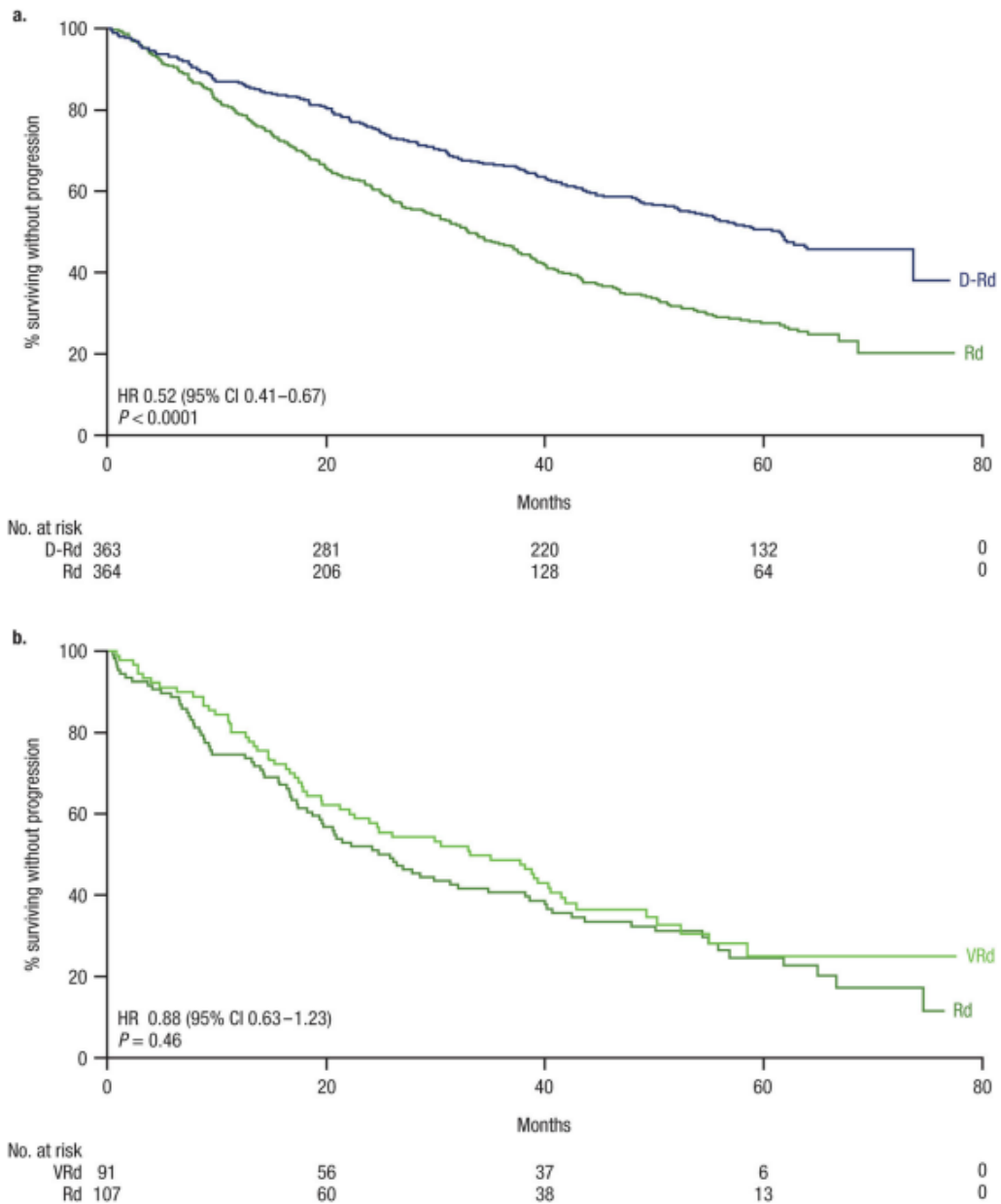
6.30 The March 2025 resubmission presented an updated MRDR analysis of survival in patients receiving BLd and Ld. Patients in the MRDR analysis had a cytogenetic risk stratification slightly more favourable (15.6% of patients categorised as high-risk), compared to the ITC cohort (16.6% to 19.1% as high risk). Furthermore, the MRDR population demonstrated a higher proportion of patients with impaired functional status, with 27.8% exhibiting an ECOG score of ≥ 2, in contrast to only 8.6% to 8.9% of patients in the ITC cohort. Therefore, the population used in the adjusted ITC is likely not representative of Australian patients.

### PFS results

6.31 The Kaplan Meier curves for PFS for MAIA and SWOG s0777 after harmonisation of the eligibility criteria and propensity-score weighting are presented in Figure 8. The results of the adjusted ITC of DLd versus BLd for PFS are presented in Table 11. Patients

treated with DLd had a 41% reduction in the risk of disease progression compared with BLd treatment (HR = 0.59; 95% CI: 0.39-90; p = 0.01). A sensitivity analysis in which harmonised inclusion/exclusion criteria were applied to both trial populations without propensity-score weighting showed that patients treated with DLd had a 35% reduction in the risk of disease progression compared with BLd (HR = 0.65; 95% CI: 0.44, 0.95; p = 0.03). The propensity-weighted analysis is considered the primary analysis due to its methodological advantages in addressing potential confounding and bias.

Figure 8: PFS Kaplan Meier plots after harmonised inclusion/exclusion criteria and propensity-score weighting for patients in the (a) MAIA DLd vs Ld and (b) SWOG s0777 trial (BLd vs Ld)



Source: Figure 2-16, p133 of the March 2025 resubmission and Figure 2 of Durie 2024

BLd = bortezomib plus lenalidomide and dexamethasone; CI = confidence interval; DLd = daratumumab plus lenalidomide and dexamethasone; DR-d = bortezomib plus lenalidomide and dexamethasone; HR = hazard ratio; Ld = lenalidomide and dexamethasone; Rd = lenalidomide and dexamethasone; VRd = bortezomib plus lenalidomide and dexamethasone.

HRs for PFS reflect comparisons after application of harmonized inclusion/exclusion criteria and propensity-score weighting.

**Table 11: Indirect treatment comparisons of PFS**

	Direct within-study treatment comparisons		ITC
	MAIA DLd vs MAIA Ld (HR)	SWOG BLd vs SWOG Ld (HR)	MAIA DLd vs SWOG BLd (HR)
Primary analysis: Adjusted (aligned I/E criteria and propensity-score weighted)	<b>0.52 (95% CI: 0.41, 0.67)</b> p <0.0001	0.88 (95% CI: 0.63, 1.23) p = 0.46	<b>0.59 (95% CI: 0.39, 0.90)</b> p = 0.01
Sensitivity analysis: Aligned I/E criteria but no propensity-score weighting	<b>0.54 (0.45, 0.66)</b> p <0.0001	0.84 (95% CI 0.60, 1.17) p = 0.31	<b>0.65 (95% CI: 0.44, 0.95)</b> p = 0.03

Source: Table 2-35, p147 of the March 2025 resubmission and Table 2 of Durie 2024.

BLd = bortezomib lenalidomide and dexamethasone; CI = confidence interval; DLd = daratumumab lenalidomide and dexamethasone; HR = hazard ratio; I/E = inclusion/exclusion; ITC = indirect treatment comparison; Ld = lenalidomide and dexamethasone; PFS = progression-free survival.

a High cytogenetic risk was defined in the MAIA and SWOG S0777 trials as the presence of C 1 high-risk cytogenetic abnormality (del17p, t[14;16], or t[4;14]). Note that the high cytogenetic risk subgroup analysis was based on small sample sizes (MAIA, n = 91; SWOG S0777, n = 17).

Bold text indicates statistically significant results

6.32 The results of the adjusted ITC for PFS comparing MAIA DLd vs SWOG s0777 BLd presented in the March 2025 resubmission (HR = 0.59; 95% CI 0.39, 0.90) were aligned with the results from the unadjusted ITC for PFS comparing MAIA ITT population vs SWOG s0777 > 65 population presented in the March 2023 PBAC meeting (HR = 0.61; 0.42, 0.90; see Table 12). The resubmission did not provide the results of the adjusted ITC for OS or validate that, in the absence of an ITC for OS, that PFS is an appropriate surrogate outcome for OS in the TI NDMM population.

**Table 12: Unadjusted indirect treatment comparison of MAIA and SWOG s0777 by subgroups.**

Population	DLd vs BLd via Ld PFS-HR (95% CI)	DLd vs BLd via Ld OS-HR (95% CI)
MAIA ITT vs SWOG s0777 ITT	0.77 (0.57, 1.06)	0.93 (0.64, 1.36)
MAIA ITT vs SWOG s0777 > 65	<b>0.61 (0.42, 0.90)</b>	0.75 (0.47, 1.19)
MAIA ITT vs SWOG s0777 "No transplant"	0.75 (0.53, 1.06)	1.04 (0.7, 1.56)

Source: Table 9, p23 of daratumumab PSD, March 2023 PBAC meeting.

BLd = bortezomib, lenalidomide, dexamethasone; CI = confidence interval; DLd = daratumumab, lenalidomide, dexamethasone; HR = hazard ratio; ITT = intention to treat; Ld = lenalidomide, dexamethasone; PFS = progression free survival; OS = overall survival.

Blue shading indicates data previously seen by the PBAC.

Bold text indicates statistically significant results

6.33 Additionally, the March 2025 resubmission presented the results of an observational study comparing the outcomes for DLd and BLd in a TI NDMM cohort treated in US clinical practice (Gordan 2024). Gordan 2024 reported that patients treated with DLd had a statistically significant lower risk of progression or death compared to BLd (adjusted HR = 0.35, 95% CI 0.17; 0.73). Despite efforts in Gordan 2024 to balance patient characteristics using inverse probability of treatment weightings (IPTW), the risk of residual confounding from unmeasured factors remains. The lack of detailed treatment information, such as drug administration frequency and subsequent therapies, may limit the ability to fully account for differences in treatment regimens and their potential impact on the observed outcomes.

## Comparative harms

6.34 The March 2025 resubmission stated that no new safety data, other than deaths, were reported in the final analysis of MAIA (November 2023; Table 13). A summary of the comparative harms for DLd versus Ld from MAIA after a median follow-up of 64.5 months is presented in Table 14.

**Table 13: Incidence of death and cause of death in MAIA (safety population set)**

	Oct 21	Oct 21	Nov 23	Nov 23
	DLd, n (%)	Ld, n (%)	DLd, n (%)	Ld, n (%)
Analysis set: safety	364	365	364	365
Total number of patients who died during study, n (%)	130 (35.7%)	176 (48.2%)	173 (47.5%)	218 (59.7%)
Primary cause of death, n (%)				
Adverse event	41 (11.3%)	38 (10.4%)	44 (12.1%)	40 (11.0%)
At least one related <sup>a</sup>	14 (3.8%)	10 (2.7%)	14 (3.8%)	10 (2.7%)
Adverse event(s) unrelated	27 (7.4%)	28 (7.7%)	28 (7.7%)	29 (7.9%)
COVID-19	2 (0.5%)	0	2 (0.5%)	0
Progressive disease	56 (15.4%)	68 (18.6%)	76 (20.9%)	88 (24.1%)
Unknown	0	0	0	0
Other	33 (9.1%)	69 (18.9%)	53 (14.6%)	90 (24.7%)
COVID-19	1 (0.3%)	4 (1.1%)	5 (1.4%)	6 (1.6%)
Total number of patients who died within 30 days of last study treatment dose, n (%)				
	31 (8.5%)	33 (9.0%)	31 (8.5%)	35 (9.6%)
Primary cause of death, n (%)				
Adverse event	29 (8.0%)	31 (8.5%)	29 (8.0%)	32 (8.8%)
At least one related <sup>a</sup>	11 (3.0%)	10 (2.7%)	11 (3.0%)	10 (2.7%)
Adverse event(s) unrelated	18 (4.9%)	21 (5.8%)	18 (4.9%)	22 (6.0%)
COVID-19	2 (0.5%)	0	2 (0.5%)	0
Progressive disease	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Unknown	0	0	0	0
Other	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.5%)
COVID-19	0	0	0	0

Source: Table 2-29, p 127 of the March 2025 resubmission.

Ld = lenalidomide-dexamethasone, DLd = daratumumab-lenalidomide-dexamethasone.

<sup>a</sup> Includes adverse events that were related to at least 1 of the 3 components of study treatment: daratumumab, lenalidomide or dexamethasone.

Blue shading indicates data previously seen by the PBAC.

Table 14: Summary of key adverse events in MAIA, safety population (cut-off date 21 October 2021)

MAIA	DLd n with event (%)	Ld n with event (%)	RR (95% CI) <sup>c</sup>	RD (95% CI) <sup>c</sup>
Safety analysis set	364	365	-	-
<b>Summary of TEAEs</b>				
Any TEAE	364 (100)	363 (99)	1.01 (1, 1.02)	0.01 (0, 0.01)
At least one related <sup>a</sup>	362 (99)	347 (95)	1.05 (1.02, 1.08)	0.04 (0.02, 0.07)
Grade 3	197 (54)	203 (56)	0.97 (0.85, 1.11)	-0.01 (-0.09, 0.06)
Grade 4	118 (32)	89 (24)	1.33 (1.05, 1.68)	0.08 (0.02, 0.15)
Grade 5	36 (10)	34 (9)	1.06 (0.68, 1.66)	0.01 (-0.04, 0.05)
Any serious TEAE	287 (79)	259 (71)	1.11 (1.02, 1.21)	0.08 (0.02, 0.14)
TEAE leading to discontinuation of lenalidomide	134 (37)	89 (24)	1.51 (1.21, 1.89)	0.12 (0.06, 0.19)
TEAE leading to discontinuation of dexamethasone	145 (40)	132 (36)	1.1 (0.91, 1.32)	0.04 (-0.03, 0.11)
TEAE leading to discontinuation of daratumumab	53 (15)	NA	NA	NA
TEAE leading to discontinuation of study treatment <sup>b</sup>	53 (15)	87 (24)	0.61 (0.45, 0.83)	-0.09 (-0.15, -0.04)
<b>Most commonly reported (&gt;5%) toxicity Grade 3 or 4 TEAEs</b>				
Patients with toxicity grade 3 or 4 TEAEs	349 (96)	324 (89)	1.08 (1.04, 1.13)	0.07 (0.03, 0.11)
Neutropenia	197 (54)	135 (37)	1.46 (1.24, 1.72)	0.17 (0.1, 0.24)
Leukopenia	42 (12)	23 (6)	1.83 (1.12, 2.98)	0.05 (0.01, 0.09)
Hypertension	32 (9)	16 (4)	2.01 (1.12, 3.6)	0.04 (0.01, 0.08)
Lymphopenia	60 (16)	41 (11)	1.47 (1.02, 2.13)	0.05 (0, 0.1)
<b>Common (≥2%) treatment-emergent SAEs.</b>				
Patient with >1 TESAEs	287 (79)	259 (71)	1.11 (1.02, 1.21)	0.08 (0.02, 0.14)
Pneumonia	68 (19)	39 (11)	1.75 (1.21, 2.52)	0.08 (0.03, 0.13)
Sepsis	11 (3)	10 (3)	1.1 (0.47, 2.56)	0 (-0.02, 0.03)

Source: Table 2-27 p124, Table 2-28 p125 of the March 2025 resubmission.

CI = confidence interval; DLd = daratumumab, lenalidomide, dexamethasone; Ld = lenalidomide, dexamethasone; n = number of participants reporting data; N = total participants in group; NA = not applicable; RD = risk difference; RR = relative risk; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

<sup>a</sup> TEAEs related to at least 1 of the 3 components of study treatment: lenalidomide, dexamethasone or daratumumab.

<sup>b</sup> Includes those patients indicated as having discontinued study treatment due to an adverse event on the end of treatment CRF page.

Adverse events are reported using MedDRA version 23.0. Percentages are calculated with the number of patients in each group as denominator. Dexamethasone is for "dexamethasone or equivalent".

<sup>c</sup> This analysis was not powered to detect statistical differences in the occurrence of safety events; apparent differences shown in relative measures of effect are exploratory only.

Blue shading indicates data previously seen by the PBAC.

6.35 Almost all patients in the DLd and Ld treatment groups experienced one or more treatment emergent adverse events (TEAEs) (100.0% vs 99.5%). Although more patients in the DLd treatment group experienced any serious TEAE compared with those treated with Ld (78.8% vs 71.0%), fewer patients in the DLd treatment group discontinued all study treatment due to a TEAE compared with the Ld group (14.6% vs 23.8%). However, this proportion should be interpreted carefully as it was defined as patients discontinuing all components of treatment, and the total number of patients discontinuing at least one component of treatment was higher for DLd than Ld (see "TEAE leading to discontinuation" in Table 14).

- 6.36 A summary of the TEAEs (any grade and Grade 3 or more) from SWOG s0777, with a median follow-up of 55 months, as presented by the resubmission is provided in Table 15. BLd was associated with a higher incidence of musculoskeletal or soft tissue, neurological, gastrointestinal adverse events than Ld in the subgroup of patients aged  $\geq 65$  years. BLd was also associated with more treatment discontinuations due to toxicity.

Table 15: TEAEs by CTC toxicity category in SWOG s0777 (ITT and subgroups, safety analysis set at a median follow-up of 55 months)

SWOG s0777	BLd n with event (%)	Ld n with event (%)	RR (95% CI) <sup>a</sup>	RD (95% CI) <sup>a</sup>
Safety analysis set	241 (100)	226 (100)	NA	NA
Number of patients with 1 or more any grade TEAE	241 (100)	226 (100)	1 (1, 1)	0 (0, 0)
- Lymphatics	123 (51)	96 (42)	1.2 (0.99, 1.46)	0.09 (0, 0.18)
- Ocular or visual	82 (34)	58 (26)	1.33 (1, 1.77)	0.08 (0, 0.17)
- Neurology	213 (88)	184 (81)	1.09 (1.01, 1.18)	0.07 (0, 0.13)
- Gastrointestinal	213 (88)	184 (81)	1.09 (1.01, 1.18)	0.07 (0, 0.13)
Number of patients with 1 or more Grade 3 or higher TEAE	215 (89)	189 (84)	1.07 (1, 1.15)	0.06 (-0.01, 0.12)
- Neurology	90 (37)	44 (19)	1.92 (1.41, 2.62)	0.18 (0.1, 0.26)
- Pain	57 (24)	36 (16)	1.48 (1.02, 2.15)	0.08 (0.01, 0.15)
- Gastrointestinal	64 (27)	29 (13)	2.07 (1.39, 3.09)	0.14 (0.07, 0.21)
<b>SWOG s0777 Age &lt;65 years</b>				
Safety analysis set	149 (100)	119 (100)	NA	NA
Number of patients with 1 or more any grade TEAE	149 (100)	119 (100)	1 (1, 1)	0 (0, 0)
- Neurology	126 (85)	83 (70)	1.21 (1.06, 1.39)	0.15 (0.05, 0.25)
Number of patients with 1 or more Grade 3 or higher TEAE	129 (87)	94 (79)	1.1 (0.98, 1.23)	0.08 (-0.02, 0.17)
- Neurology	49 (33)	15 (13)	2.61 (1.54, 4.42)	0.2 (0.11, 0.3)
- Pain	35 (23)	13 (11)	2.15 (1.19, 3.88)	0.13 (0.04, 0.21)
- Gastrointestinal	32 (21)	13 (11)	1.97 (1.08, 3.58)	0.11 (0.02, 0.19)
- Treatment discontinuation - toxicity	43 (29)	21 (18)	1.64 (1.03, 2.61)	0.11 (0.01, 0.21)
<b>SWOG s0777 Age ≥65 years</b>				
Safety analysis set	92 (100)	107 (100)	NA	NA
Number of patients with 1 or more any grade TEAE	92 (100)	107 (100)	1 (1, 1)	0 (0, 0)
- Musculoskeletal or soft tissue	51 (55)	44 (41)	1.35 (1.01, 1.81)	0.14 (0.01, 0.28)
Number of patients with 1 or more Grade 3 or higher TEAE	86 (93)	95 (89)	1.05 (0.96, 1.14)	0.05 (-0.03, 0.13)
- Neurology	41 (45)	29 (27)	1.64 (1.12, 2.41)	0.17 (0.04, 0.31)
- Gastrointestinal	32 (35)	16 (15)	2.33 (1.37, 3.96)	0.2 (0.08, 0.32)
- Musculoskeletal or soft tissue	24 (26)	15 (14)	1.86 (1.04, 3.33)	0.12 (0.01, 0.23)
- Renal or genitourinary	3 (3)	14 (13)	0.25 (0.07, 0.84)	-0.1 (-0.17, -0.02)
- Treatment discontinuation - toxicity	43 (47)	28 (26)	1.79 (1.22, 2.63)	0.21 (0.07, 0.34)

Source: Table 2-32, p141-143 of the March 2025 resubmission.

BLd = bortezomib, lenalidomide, dexamethasone; CTC = common terminology criteria; Ld = lenalidomide, dexamethasone; NA = not applicable; RD = risk difference; RR = risk ratio; TEAE = treatment emergent adverse event.

<sup>a</sup> This analysis was not powered to detect statistical differences in the occurrence of safety events; apparent differences shown in relative measures of effect are exploratory only.

Blue shading indicates data previously seen by the PBAC.

## Benefits/harms

6.37 A summary of the comparative benefits and harms for DLd versus Ld, based on data from the MAIA, is presented in Table 16. The ESC considered that the comparative benefit of DLd versus BLd was expected to be less than that for DLd versus Ld, but the magnitude of the reduction was uncertain based on the available clinical evidence.

Table 16: Summary of comparative benefits and harms for DLd and Ld.

Benefits						
Progression free survival (median duration of follow-up 64.5 months)						
Event	DLd	Ld	Absolute Difference	HR (95% CI)		
Progressed, n (%)	176 (47.8%)	228 (61.8%)	-	<b>0.55 (0.45, 0.67)</b> <b>P = 0.0001</b>		
Median PFS, months (95% CI)	61.9 (54.8, NE)	34.4 (29.6, 39.2)	27.5			
% not progressed at 12-month (95% CI)	86.5 (82.5, 89.6)	78.1 (73.3, 82.1)	8.4			
% not progressed at 24-month (95% CI)	76.3 (71.5, 80.4)	61.1 (55.6, 66.1)	15.2			
% not progressed at 36-month (95% CI)	67.4 (62.2, 72.0)	47.2 (41.6, 52.5)	20.2			
% not progressed at 48-month (95% CI)	59.4 (54.1, 64.4)	36.3 (31.0, 41.6)	23.1			
% not progressed at 60-month (95% CI)	51.8 (46.3, 57.0)	28.0 (23.0, 33.1)	23.8			
Overall survival (median duration of follow-up 89.3 months)						
Deaths, n/N (%)	175 (47.6%)	218 (59.1%)	-	<b>0.67 (0.55, 0.82)</b> <b>P = 0.0001</b>		
Median OS, months (95% CI)	90.25 (80.76, NE)	64.07 (55.98, 70.80)	26.18			
% Alive at 12-month (95% CI)	92.6 (89.4, 94.9)	91.3 (87.9, 93.8)	1.3			
% Alive at 24-month (95% CI)	84.3 (80.2, 87.7)	83.4 (79.1, 86.9)	0.9			
% Alive at 36-month (95% CI)	78.2 (73.6, 82.1)	72.3 (67.3, 76.6)	5.9			
% Alive at 48-month (95% CI)	69.8 (64.8, 74.3)	62.4 (57.1, 67.3)	7.4			
% Alive at 60-month (95% CI)	66.6 (61.5, 71.2)	53.6 (48.2, 58.7)	13			
% Alive at 72-month (95% CI)	59.5 (54.3, 64.4)	44.2 (38.9, 49.3)	15.3			
% Alive at 84-month (95% CI)	53.1 (47.8, 58.2)	39.3 (34.1, 44.5)	13.8			
Harms						
	DLd n/N	Ld n/N	RR (95% CI)	Event rate/100 patients (DLd)	Event rate/100 patients (Ld)	RD (95% CI)
Any TEAE at least one related						
MAIA	362/364	347/365	1.05 (1.02, 1.08)	99	95	0.04 (0.02, 0.07)
Any serious TEAE						
MAIA	287/364	259/365	1.11 (1.02, 1.21)	79	71	0.08 (0.02, 0.14)
TEAE leading to discontinuation of study treatment						
MAIA	53/364	87/365	0.61 (0.45, 0.83)	15	24	-0.09 (-0.15, -0.04)
Patient with >1 TESAEs						
MAIA	287/364	259/365	1.11 (1.02, 1.21)	79	71	0.08 (0.02, 0.14)
Pneumonia						
MAIA	68/364	39/365	1.75 (1.21, 2.52)	19	11	0.08 (0.03, 0.13)
Patients with toxicity grade 3 or 4 TEAEs						
MAIA	349/364	324/365	1.08 (1.04, 1.13)	96	89	0.07 (0.03, 0.11)
Leukopenia						
MAIA	42/364	23/365	1.83 (1.12, 2.98)	12	6	0.05 (0.01, 0.09)

Source: Table 2.26, p144, Table 2.27, p146, Table 2.45, p174 and Table 2.44, p173 of the March 2025 resubmission.

CI = confidence interval; DLd = daratumumab, lenalidomide, dexamethasone; Ld = lenalidomide, dexamethasone; n = number of participants reporting data; N = total participants in group; NE = not estimable; OS = overall survival; PFS = progression free survival; RD = risk difference; RR = relative risk; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Blue shading indicates data previously seen by the PBAC.

- 6.38 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with DLd in comparison with Ld, after 60 months:
- Approximately 24 additional patients will remain progression-free.
  - Approximately 13 additional patients will remain alive.
  - Approximately 4 additional patients would have a treatment emergent adverse event.
  - Approximately 8 additional patients would have a serious treatment emergent adverse event.
  - Approximately 9 fewer patients would discontinue all study treatment due treatment emergent adverse event over.
  - Approximately 8 additional patients would have more than one treatment emergent serious adverse event.
  - Approximately 8 additional patients would be diagnosed with pneumonia (an infection of the lungs) rated as serious.
  - Approximately 7 additional patients would have a grade 3 or 4 toxicity treatment emergent adverse event.
  - Approximately 5 additional patients would be diagnosed with leukopenia (a decrease in the white blood cell count) grade 3 or 4.

### ***Clinical claim***

- 6.39 The March 2025 resubmission described DLd as superior in terms of effectiveness and inferior in terms of safety compared to Ld. The ESC considered that these claims were adequately supported by the evidence presented, noting that the PBAC had previously accepted these claims in March 2023 (paragraph 6.33, daratumumab PSD, March 2023).
- 6.40 The resubmission described DLd as superior in terms of effectiveness compared to BLd. The superiority claim of DLd over BLd relied on an adjusted ITC of PFS. The ITC used matched eligibility criteria to align with those used in MAIA, which relied on an age threshold of 65 years or older as the determinant of transplant ineligibility. However, in Australian clinical practice, the assessment of transplant eligibility considers a combination of factors such as age, comorbidities, and functional status. Furthermore, data from the MRDR reveals that a significant proportion (31.5%) of Australian NDMM patients who underwent ASCT were 65 years of age or older. Therefore, the adjusted ITC may not accurately represent the outcomes that would be expected in the Australian clinical setting, and the applicability of these findings to the local patient population remains uncertain.
- 6.41 Additionally, adjusted ITC results for OS were not presented, so the relative effectiveness of DLd and BLd for this endpoint is unknown. Results from an

unadjusted, anchored ITC conducted during the March 2023 evaluation did not demonstrate a statistically significant difference between DLd and BLd for OS (Table 12).

- 6.42 On balance, the ESC considered that DLd was superior in terms of PFS and OS compared to BLd. However, the ESC considered that the magnitude of benefit associated with DLd over BLd in TI NDMM was uncertain.
- 6.43 The March 2025 resubmission described DLd as at worst non-inferior to BLd in terms of safety. The ESC, noting that BLd had a higher incidence of a number of adverse events compared to Ld (see paragraph 6.36), considered that this claim was adequately supported by the evidence presented.
- 6.44 The PBAC considered that the claim that DLd was superior in terms of comparative effectiveness compared to Ld and BLd was reasonable; however, the magnitude of benefit associated with DLd over BLd was uncertain.
- 6.45 The PBAC considered that the claim that DLd was inferior in terms of comparative safety compared to Ld was reasonable. The PBAC considered that the claim that DLd was non-inferior in terms of comparative safety compared to BLd was also reasonable.

### ***Economic analysis***

- 6.46 The March 2025 resubmission presented a stepped economic evaluation and modelled cost-utility analysis based on evidence from a direct randomised trial (MAIA), i.e. DLd versus Ld, as the resubmission assumed BLd was non-inferior to Ld. A summary of the key components of the economic evaluation is presented in Table 17. The approach remained largely the same as that in March 2023.

**Table 17: Key components of the economic evaluation**

Component	Description
Population	Patients with TI NDMM
Intervention	DLd (administered until disease progression or unacceptable toxicity)
Comparator	SoC, involving administration of an Ld or BLd regimen, based on a weighting of 32% and 68%, respectively for costs only. BLd was assumed to be non-inferior to Ld in terms of effectiveness. Ld is administered until disease progression or unacceptable toxicity but bortezomib in BLd is administered for up to 8 x 21-day cycles.
Type of analysis	Cost-utility analysis, cost-effectiveness analysis
Outcomes	Quality-adjusted life-years gained Life-years gained
Time horizon	20 years
Discounting	5% per annum (applied to both costs and outcomes)
Method used to generate results	Partitioned survival analysis
Health states	Progression-free survival Progressed disease Dead
Cycle length	28 days
Source of effectiveness inputs	MAIA clinical trial data (& extrapolations of these data)
Resource use and costs	Where possible, unit costs have been sourced in accordance with the recommendations of the PBAC Manual of Resource Items and their Associated Costs
Software	Microsoft Office 365 Excel

Source: Table 3-1, p170 of the March 2025 resubmission.

BLd = bortezomib, lenalidomide and dexamethasone; DLd = daratumumab, lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone; TI = transplant ineligible; NDMM = newly diagnosed multiple myeloma; SoC = standard of care.

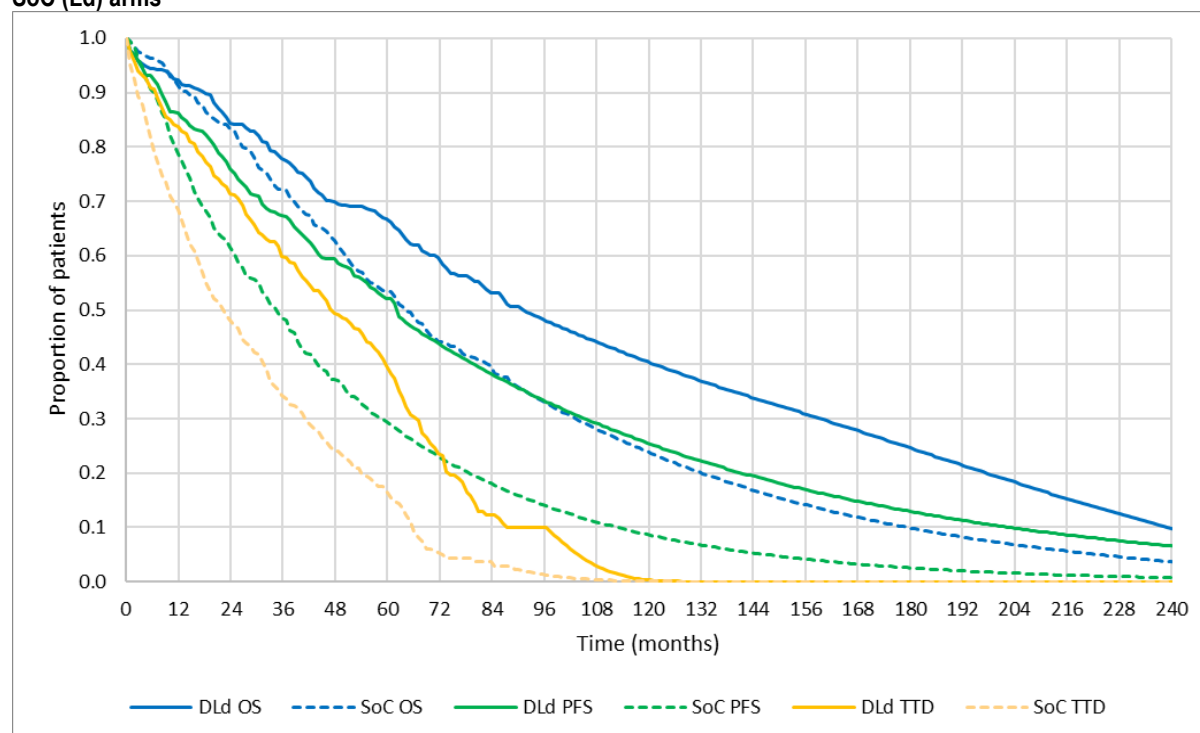
Blue shading indicates data previously seen by the PBAC.

6.47 In reviewing the March 2023 submission, the PBAC considered that the economic model should be revised to either present a (i) combined analysis approach consisting of a cost-utility analysis for the comparison between DLd and Ld and a cost-minimisation approach for the comparison between DLd and BLd, or (ii) re-specified base case which included a treatment effect for BLd, a time horizon of 15 years and revised OS extrapolations (paragraph 7.15, daratumumab PSD, March 2023). The ESC noted that the March 2025 resubmission presented a cost-utility analysis without including the treatment effect for BLd in the base case (the resubmission applied a weighting of 32% Ld use and 68% BLd use, based on the MRDR data, for costs of therapy only), and retaining a time horizon of 20 years, as per the March 2023 submission. The March 2025 resubmission justified the exclusion of efficacy for BLd in the model base case by restating the claim of non-inferiority between BLd and Ld. The resubmission stated the use of a 20-year time horizon was justified given that more mature evidence from MAIA (compared with the 2023 submission) reduced the uncertainty of the long-term clinical benefit and cost-effectiveness. The PSCR stated that as the PBAC has accepted that DLd is superior to Ld, DLd extends survival beyond Ld, and therefore truncating the time horizon to 15 years is not appropriate and will not capture the full extent of survival benefit for DLd versus SoC. The PSCR also stated that while the average age of the MAIA population was 74 years, 21% of the study population were less than 70 years of age (1.1% < 65 years of age, 19.9% between 65 and 69 years of age) and therefore the lifetime time-horizon of 20 years was

appropriate. The ESC considered that the time horizon of 20 years was long given the average age of the population in the model was 74 years. Further, the ESC noted that the majority of patients in the Australian setting would be older than those in the MAIA trial. In addition, the ESC did not accept the claim that BLd was non-inferior to Ld.

- 6.48 Parametric functions used to extrapolate PFS in the March 2025 resubmission remained the same as those in March 2023 submission (i.e., exponential for both arms). In March 2023, the ESC considered that the application of the exponential function to the PFS curves in both the DLd and SoC arms appeared reasonable (paragraph 6.41, daratumumab PSD, March 2023). The point of truncation of the Kaplan Meier estimates were changed slightly to reflect the point at which 20% of the trial cohort remained progression free.
- 6.49 In March 2023, the PBAC considered that the choice of parametric functions applied to the OS Kaplan Meier curves resulted in the extrapolated curves diverging at an unreasonably accelerated rate for the SoC arm in comparison to the DLd arm, and thus revised OS extrapolations were required (paragraphs 7.14 and 7.15, daratumumab PSD, March 2023). The March 2025 resubmission revised the parametric function for OS in SoC arm. For the DLd and SoC arms of the model, exponential (same as the March 2023 submission) and Weibull (Gompertz was applied in March 2023) parametric functions were chosen as the best fit by sum of AIC/BIC respectively. The choice of extrapolations adopted in the March 2025 resubmission reduced the divergence of OS curves compared with the March 2023 submission, thus the increment between the curves was reduced.
- 6.50 For the SoC arm, the Weibull and gamma functions had the best fit by sum of AIC/BIC. The resubmission stated that the Weibull function was selected due to better visual fit to the Kaplan Meier data (the gamma function sits below the Kaplan Meier-data from 12 months until the data cut-off, whereas the Weibull intersects the KM-curve at multiple points). During the evaluation it was observed that visually both Weibull and gamma functions fit the Kaplan Meier curve well, and it was difficult to support the resubmission's statement that the Weibull function was the best visual fit to the Kaplan Meier data. Visually, both the Weibull and gamma extrapolations overlapped up until 115 months after which the gamma function sits above the Weibull function. Use of the Weibull function in the base case slightly favours DLd. Use of Gamma parametric function instead of Weibull increases the ICER by 1%.
- 6.51 Similar to the extrapolation of PFS, the clinical trial-based Kaplan Meier estimates for OS were used until there were less than 20% of the trial cohort remaining alive in the at-risk set.
- 6.52 The traces for the predicted time to event outcomes of OS and PFS for DLd and SoC are presented in Figure 9. The OS curves include the background mortalities from the Australian population. No external data were used by the resubmission in the validation of the predicted outcomes from the model.

Figure 9: Partitioned survival analysis health state trace for the duration of the economic model in both the DLd and SoC (Ld) arms



Source: Compiled during the evaluation using the information from the economic model of the March 2025 resubmission. DLd = daratumumab, lenalidomide and dexamethasone; Ld = lenalidomide, dexamethasone; KM = Kaplan Meier; PFS = progression free survival; OS = overall survival; SoC = standard of care; TTD = time-to-treatment discontinuation

6.53 Time to treatment-discontinuation (TTD) curves were used to model the duration of treatment. The analysis of TTD was separate from the overall time frame of the partitioned survival model (PSM). The TTD and OS curves were informed by updated data (median follow-up of 89.3 months) whereas the PFS data were from the March 2023 submission (median follow-up of 64.5 months) as the PFS data was already mature. TTD traces are shown in Figure 9. In contrast to the March 2023 submission, the TTD traces for both the DLd and SoC (Ld) arms are not aligned with the respective PFS curves, in that the TTD curves appear to fall more sharply after 60 months compared with the PFS curves. The approach adopted by the resubmission likely underestimated time on treatment and costs for both DLd and SoC patients. The PSCR stated that the approach utilised the most mature data, thereby reducing uncertainty.

6.54 The March 2023 submission assumed that second line treatments after treatment with DLd or SoC are Bd and DBd, respectively. However, this was not consistent with post-progression treatments used in the MAIA trial (paragraph 6.46, daratumumab PSD, March 2023), nor in current clinical practice in Australia. The March 2025 resubmission revised the costs in the post-progression state by including a mix of subsequent therapies after progression on DLd or SoC. The mix of therapies was based on those used in the MAIA trial and the 10% PBS sample of treatments available for second line

- MM. The ESC considered that the mix of therapies was more likely to reflect expected Australian clinical practice.
- 6.55 The March 2025 resubmission estimated the duration of second line treatments based on the TTD for DBd as second line treatment for RRMM (paragraph 6.35, daratumumab PSD, November 2019). Given the resubmission adopted a PSM, time on second line treatments should exist in the area between PFS and OS. However, the introduction into the analysis of TTD from the DBd model results in a disconnect in the overall time considered in the model in that it incorporates longer time on a second line treatment for SoC compared with DLd. This might not be clinically reasonable given that the model estimates that SoC will have lower OS than DLd patients. The approach adopted by the resubmission likely overestimated time on treatment and costs for SoC patients and underestimated those costs for DLd patients and had a bias in favour of the proposed listing. Per patient discounted costs of post-progression treatments estimated by the resubmission were \$23,163 and \$85,405 for DLd and SoC arms respectively. The ESC considered that the difference in post-progression costs was unrealistic and biased the economic analysis in favour of daratumumab.
- 6.56 The PSCR acknowledged that it was inappropriate that the model estimated a time on subsequent therapy that exceeded the time in post progression state (i.e. OS – PFS), particularly for DBd after SoC. The PSCR presented a revised modelling approach for subsequent therapy so that the average time on subsequent therapy did not exceed the average time in the post progression phase. The duration of subsequent therapy was equal to either the duration accepted by PBAC as being cost-effective or the mean time in the progressed disease state, whichever was shortest. For regimens with a fixed duration or which have an equi-effective dosage duration, once the maximum number of treatment days had passed, a zero cost was applied. The revised approach for modelling the cost of subsequent therapy increased the base case ICER from \$45,000 to < \$55,000 per QALY to \$55,000 to < \$75,000 per QALY. The ESC noted that the revised economic model resulted in decreased per patient discounted costs for post-progression treatment of \$20,729 (from \$23,163) and \$76,259 (from \$85,405) for the DLd and SOC arms respectively. The ESC noted that the difference in costs across the arms remained high and the assumptions regarding post progression treatments remained a model driver.
- 6.57 Although the March 2023 submission did not include end-of-life costs, the March 2025 resubmission included costs of \$60,019, which favoured DLd as within the model time horizon fewer patients in the DLd arm of the economic model died. Removal of end-of-life costs increased the ICER by 1%.
- 6.58 The ESC noted that the March 2025 resubmission appropriately updated the utility values for pre-progression and post-progression states using the Australian values

(Norman et al. 2023<sup>1</sup>). UK tariffs were applied in the March 2023 submission. While the Australian tariffs are higher than UK tariffs, the difference in utility between states was only slightly reduced (0.001).

6.59 A summary of the key drivers of the model is provided in the Table 18. The largest single impact on the ICER in the March 2025 resubmission, relative to the March 2023 submission, is the reduction in the proposed price of daratumumab, and the lower PBS prices for lenalidomide.

**Table 18: Key drivers of the model**

Description	Method/Value	Impact Base case: \$ <sup>1</sup> /QALY gained
Price of daratumumab	The resubmission reduced the price of daratumumab by █████% and updated the prices of lenalidomide	High, favours DLd. Use of price of daratumumab and lenalidomide as per March 2023 submission increased the ICER to \$█████ <sup>2</sup> /QALY gained.
Post-progression costs	High post-progression costs for SoC were applied based on the use of DBd	High, favours DLd. Adjusting the post-progression time on treatment <sup>a</sup> increased the ICER to \$█████ <sup>3</sup> /QALY gained. The ESC noted that a relatively small change in post-progression costs had a relatively large impact on the ICER.
Efficacy of BLd	Efficacy of BLd was not included	Moderate to high, favours DLd. Including the efficacy of BLd the ICER increased in a range of \$█████ <sup>4</sup> /QALY gained (using age adjusted MRDR data) to \$█████ <sup>3</sup> /QALY gained (using age unadjusted SWOG data)
Time horizon	The resubmission applied a time horizon of 20 years.	Moderate, favours DLd. Use of 15 years increased the ICER to \$█████ <sup>4</sup> /QALY gained.
Percentage of BLd	Ld vs BLd: 32% vs 68%	Low, favours DLd. Considering 100% Ld cost the ICER increased to \$█████ <sup>4</sup> /QALY gained (results reflect the resubmission's assumption that efficacy of BLd was equal to Ld).

Source: Compiled during the evaluation using the information from the economic model of the resubmission.

DLd = daratumumab with lenalidomide and dexamethasone; DBd = daratumumab with bortezomib and dexamethasone; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life-year; SoC = standard of care; TTD = time-to-treatment discontinuation

<sup>a</sup> Adjust post-progression cost of SoC with a factor of 85.5% which is a ratio of (discounted) mean post-progression time in the economic model of SoC (26.26 months) to (discounted) time-on-treatment with DBd (30.7 months). Adjust post-progression cost of DLd with a factor of 220% which is a ratio of (discounted) mean post-progression time in the economic model of DLd (19.69 months) to (discounted) time-on-treatment with Bd (8.9 months).

The redacted values correspond to the following ranges:

<sup>1</sup> \$45,000 to < \$55,000

<sup>2</sup> \$155,000 to < \$255,000

<sup>3</sup> \$75,000 to < \$95,000

<sup>4</sup> \$75,000 to < \$95,000

<sup>1</sup> Norman et al., (2023), The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia, *PharmacoEconomics*, 41:427–438.

6.60 A summary of the results of the stepped economic analysis is presented in Table 19.

**Table 19: Stepped costs, outcomes and cost-effectiveness results of the economic evaluation**

	Costs			Health outcomes			ICER
	DLd	SoC	Increment	DLd	SoC	Increment	
Step 1: trial-based analysis	\$█	\$45,178	\$█	5.454 LYs	4.892 LYs	0.562 LYs	\$█ <sup>1</sup> /LY
Step 2: analysis extrapolated to a lifetime time horizon, cost of 2L therapy and discounting applied	\$█	\$172,436	\$█	6.896 LYs	5.475 LYs	1.421 LYs	\$█ <sup>2</sup> /LY
Step 3: application of utility weights	\$█	\$172,436	\$█	5.652 QALYs	4.433 QALYs	1.219 QALYs	\$█ <sup>2</sup> /QALY
Updated PSCR analysis, with different assumptions for subsequent therapy and April 2025 statutory price reductions for lenalidomide and bortezomib	\$█	\$160,842	\$█	5.652 QALYs	4.4333 QALYs	1.219 QALYs	\$█ <sup>3</sup> /QALY
<b>March 2023 submission</b>							
Step 1: trial-based analysis	\$█	\$86,986	\$█	4.362 LYs	4.070 LYs	0.292 LYs	\$█ <sup>4</sup> /LY
Step 2: analysis extrapolated to a lifetime time horizon, cost of 2L therapy and discounting applied	\$█	\$208,088	\$█	6.443 LYs	4.805 LYs	1.638 LYs	\$█ <sup>5</sup> /LY
Step 3: application of utility weights	\$█	\$208,088	\$█	4.408 QALYs	3.261 QALYs	1.148 QALYs	\$█ <sup>6</sup> /QALY

Source: Table 3-14, p244; compiled during the evaluation using the information from the economic model of the March 2025 resubmission. 2L = second line; DLd = daratumumab with lenalidomide and dexamethasone; ICER = incremental cost-effectiveness ratio; LY = life-year; p.a. = per annum; QALY = quality-adjusted life-year; SoC = standard of care  
Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

- <sup>1</sup> \$255,000 to < \$355,000
- <sup>2</sup> \$45,000 to < \$55,000
- <sup>3</sup> \$55,000 to < \$75,000
- <sup>4</sup> \$755,000 to < \$855,000
- <sup>5</sup> \$115,000 to < \$135,000
- <sup>6</sup> \$155,000 to < \$255,000

6.61 Compared to the previous submission in March 2023, the ICER in the March 2025 resubmission was reduced by █%, mainly due to the reduction in the price of daratumumab and reduced price for lenalidomide. The estimate of incremental QALYs was slightly higher in the current model (1.219) compared with the March 2023 submission (1.148). The March 2025 resubmission did not incorporate the PBAC's previous advice regarding inclusion of a treatment effect for BLd and a time horizon of 15 years (paragraph 7.15, daratumumab PSD, March 2023).

6.62 The results of key univariate and multivariate sensitivity analyses, based on the model from the resubmission (i.e. not the updated PSCR model), are summarised in Table 20.

Table 20: Sensitivity analyses

	Scenario	Incremental costs	Incremental QALY	ICER	% change
	<b>Base case</b>	\$█	1.219	\$█ <sup>1</sup>	-
A	0% discounting rate (base case 5.00%)	\$█	1.968	\$█ <sup>2</sup>	█%
B	3.5% discounting rate (base case 5.00%)	\$█	1.397	\$█ <sup>1</sup>	█%
C	15-year time horizon (base case 20-year)	\$█	1.026	\$█ <sup>3</sup>	█%
D	Gamma function for OS of SoC (base case Weibull)	\$█	1.174	\$█ <sup>3</sup>	█%
E	Cost of BLd 0% vs Ld 100% in SoC (base case 68% vs 32%)	\$█	1.219	\$█ <sup>3</sup>	█%
F	Post-progression costs for SoC arm based on mean time spent in post-progression state from the economic model <sup>a</sup> (base case based on DBd model)	\$█	1.219	\$█ <sup>4</sup>	█%
G	No end-of-life costs (base case: assumed end-of-life costs)	\$█	1.219	\$█ <sup>3</sup>	█%
H	HR for treatment effect of BLd vs Ld (base case OS HR: 1.0, PFS HR: 1.0)				
I	Durie 2022 SWOG s0777 age 65+ subgroup unadjusted analyses (OS HR: 0.83, PFS HR 0.83)	\$█	0.868	\$█ <sup>4</sup>	█%
J	Durie 2022 SWOG s0777 age 65+ subgroup adjusted analyses (OS HR: 0.88, PFS HR: 0.90)	\$█	0.982	\$█ <sup>3</sup>	█%
K	MRDR unadjusted for age analyses (OS HR: 0.89, PFS HR: 0.89)	\$█	1.001	\$█ <sup>3</sup>	█%
L	MRDR adjusted for age analyses (OS HR: 0.97, PFS HR: 0.90)	\$█	1.152	\$█ <sup>3</sup>	█%
M	Subsequent therapy costs removed	\$█	1.219	\$█ <sup>5</sup>	█%
N	PSCR revised base case with different assumptions for subsequent therapy duration	\$█	1.219	\$█ <sup>3</sup>	█%
	<b>Multivariate analyses</b>				
	C + I	\$█	0.717	\$█ <sup>4</sup>	█%
	C + J	\$█	0.817	\$█ <sup>4</sup>	█%
	C + K	\$█	0.833	\$█ <sup>4</sup>	█%
	C + L	\$█	0.966	\$█ <sup>3</sup>	█%

Source: Table 3.16, pp247-248 of the March 2025 resubmission; Compiled during the evaluation using the information from the economic model  
 BLd = bortezomib, lenalidomide and dexamethasone; DLd = daratumumab with lenalidomide and dexamethasone; ICER = incremental cost-effectiveness ratio; Ld = lenalidomide and dexamethasone; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life-year; SoC = standard of care

<sup>a</sup> Adjust post-progression cost of SoC with a factor of 85.5% which is a ratio of (discounted) mean post-progression time in the economic model of SoC (26.26 months) to (discounted) time-on-treatment with DBd (30.7 months). Adjust post-progression cost of DLd with a factor of 220% which is a ratio of (discounted) mean post-progression time in the economic model of DLd (19.69 months) to (discounted) time-on-treatment with Bd (8.9 months).

The redacted values correspond to the following ranges:

- <sup>1</sup> \$45,000 to < \$55,000
- <sup>2</sup> \$35,000 to < \$45,000
- <sup>3</sup> \$55,000 to < \$75,000
- <sup>4</sup> \$75,000 to < \$95,000
- <sup>5</sup> \$95,000 to < \$115,000

6.63 The ESC, noting that according to guidelines patients in Australia were generally considered TI when they were over 75 years of age, considered that a time horizon of 15 years was appropriate. The ESC also noted that although the magnitude of treatment effect of DLd compared to BLd was uncertain, it was likely to be less than that of DLd compared to Ld. Therefore, the assumption in the model that the treatment effect of BLd was equal to Ld biased the model in favour of daratumumab. The ESC noted that when the treatment effect of BLd was varied, the ICER ranged from \$55,000 to < \$75,000 per QALY to \$75,000 to < \$95,000 per QALY. The ESC noted that

these analyses incorporated the costs of subsequent therapies as per the resubmission’s base case which overestimated the cost of subsequent therapies for Ld arm and hence underestimated the ICER. The ESC noted correcting these costs were likely to substantially further increase the ICER.

### Drug cost per patient

6.64 A summary of the drug cost per patient of DLd and SoC is presented in Table 21.

**Table 21: Drug cost per patient for proposed and comparator drugs**

	DLd			SoC		
	Trial	Model	Financial estimates <sup>a</sup>	Trial	Model	Financial estimates <sup>a</sup>
Mean dose intensity (%)	<u>DLd</u> D: 95.8 L: 73.6 d: 78.4	<u>DLd</u> D: 98.7 L: 67.7 d: 74.1	<u>DLd</u> D: 98.7 L: 67.7	<u>Ld</u> L: 83.5 d: 82.6	<u>Ld</u> L: 80.1 d: 79.6 <u>BLd</u> B: 79.9 L: 80.1 d: 79.6	<u>Ld</u> L: 80.1 <u>BLd</u> L: 80.1
Mean duration (months)	42 <sup>c</sup>	48.4	48.4	28 <sup>c</sup>	30	30
Cost/patient/month		D: Month 1-2 = \$ Month 3-6 = \$ Month 7+ = \$ L: \$1,742 d: \$26		L: \$1,742 d: \$26	<u>Ld</u> L: \$1,742 d: \$26 <u>BLd</u> B: Month 1- 6 = \$849 L: \$1,742 d: \$26	<u>Ld</u> L: \$1,742 <u>BLd</u> L: \$1,742
Cost/patient/course <sup>b</sup>	\$	\$	\$	\$41,345	Ld: \$42,498 BLd: \$47,593	Ld: \$41,866 BLd: \$41,866
<b>March 2023 Submission</b>						
Cost/patient/course	\$	\$	\$	\$75,492	Ld: \$85,351 BLd: \$98,266	Ld: \$170,545 BLd: \$98,266

Source: Compiled during the evaluation using the information from the economic model; Table 8, p41 of Attachment 2.5 MAIA CSR (primary analysis for actual dose in MAIA)

B = bortezomib; BLd = bortezomib, lenalidomide and dexamethasone; d = dexamethasone; DLd = daratumumab with lenalidomide and dexamethasone; L = lenalidomide; Ld = lenalidomide and dexamethasone; NA = not applicable; SoC = standard of care

<sup>a</sup> Financial estimates in the March 2025 resubmission for did not include costs of bortezomib or dexamethasone.

<sup>b</sup> The estimates shown are derived by multiplying the mean dose (expressed as proportion i.e. 0.958) by the cost per patient per month (based on a full month of treatment) by the mean duration of treatment in months.

<sup>c</sup> Table TS1EXP02, p485 of the Attachment 2.6 provided with the March 2025 resubmission.

Blue shading indicates data previously seen by the PBAC.

6.65 The financial estimates presented in the resubmission did not include the costs of bortezomib and dexamethasone. Hence the cost per patient per course in the financial estimates are lower compared to the modelled analysis.

### Estimated PBS usage & financial implications

6.66 This resubmission was not considered by DUSC. The March 2025 resubmission applied an epidemiological approach to the financial estimates. The methods for estimating the utilisation and financial implications to Government remain largely unchanged

from the March 2023 submission. The sources of data and methods applied by the resubmission to derive the financial estimates are summarised in Table 22.

**Table 22: Key inputs for financial estimates**

Parameter	Value applied and source	Comment	
Incident patients	1,548 in Yr 1 increased to 1,719 in Yr 6. To estimate the number of incident TI NDMM patients over the forecast period (i.e., years 2025 to 2030), the DUSC data in 2019 for TI NDMM patients were used and an annual growth rate of 2.12% per annum was applied.  The PBAC noted the market was defined as patients treated with the following regimens: BLd, Ld, Bd, BCd.	The growth rate of 2.12% is aligned with that previously accepted by the PBAC at the July 2020 PBAC meeting for second line DBd which was 11% over the 6-year forward estimates period (equating to 2.12% per annum) for NDMM patients. The ESC considered that this was reasonable.	
Grandfather patients	█ <sup>1</sup> patients. Internal data.	Inadequate details were provided in the resubmission as to whether these patients will meet the proposed PBS criteria. Further, the access program is yet to commence.	
Uptake rate	Assumed 65% in Yr 1 increasing to 80% in Yr 4 to Yr 6.	Market share over a period of six years was reduced from 87% in the March 2023 submission to 75% in the March 2025 resubmission. The PBAC noted that the uptake would be different across the 4 drug regimens (BLd, Ld, Bd, BCd), and considered the overall uptake to be too high.	
Persistence	Yr 1: 90.1%, Yr 2: 76.2%, Yr 3: 63.2%, Yr 4: 52.1%, Yr 5: 41.6%, Yr 6: 25%. The economic model (TTD curve of DLd reflecting use in the MAIA trial).	Consistent with economic model	
Number of scripts per patient	1 <sup>st</sup> Yr of treatment: 16 scripts (initial) + 7 scripts (continuing), from 2 <sup>nd</sup> year of treatment: 13 per year. As per PI	Consistent with the PI	
Compliance	95.6% (IV), 98.7% (SC). Dose intensity from MAIA	Consistent with trial.	
Price of daratumumab	IV 100 mg vial: \$ █ IV 400 mg vial: \$ █ SC 1,800 mg vial: \$ █	Reduced by █% compared to March 2023 submission.	
Offsets	Reduction in the use of existing treatment regimens in TI NDMM patients, average over 6 years:	The March 2025 resubmission assumed that in TI NDMM patients DLd would primarily replace BLd and Ld. It was assumed that in Year 1, DLd would replace 94% ((50.5-2.8)/50.5) of BLd use, and that for years 2-6 DLd would replace 100% of the BLd use. It was assumed that in Year 1, DLd would replace 70% ((23.5-7)/23.5) of Ld increasing to 80% by Year 6 (30-6)/30. The PBAC considered the assumed replacement for both BLd and Ld was too high, particularly noting for Ld, the age of the TI population and the inferior safety of DLd compared to Ld.	
	Assumption from MM clinical community.		
	Reduction in the use of DBd in second line MM: Yr 1: 40; Yr 2: 148; Yr 3: 265; Yr 4: 359; Yr 5: 440; Yr 6: 515 Projected DLd progressed patients	The resubmission estimated offsets for those who progress following first line DLd, grandfathered patients and daratumumab naïve patients who are eligible for second line DBd. Use in the second line setting included patients	

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Parameter	Value applied and source	Comment
		progressing from other first line therapies.
	Increase in use of lenalidomide when used as DLd: based on increase in DLd use	-
	Reduction in the use of lenalidomide in existing treatments in TI NDMM (Lenalidomide as BLd and Ld) Based on the change in market share pre and post listing of DLd	-
	Reduction in use of second line treatments other than DBd Based on the change in market share pre and post listing of DLd for Lenalidomide as (Ld and ELd), Carfilzomib (as Kd), Pomalidomide (as PBd), Elotuzumab (as ELd)	The resubmission did not estimate the cost offsets due to bortezomib, dexamethasone and cyclophosphamide (BCd) citing the small extent of replacement and the very low of cost of bortezomib. This results in underestimation of cost offsets.

Source: Compiled during the evaluation using the information from the financial model and Tabl4 4-1, p223; Table 4-4, p232; Table 4-15, p246.

BCd = Bortezomib, cyclophosphamide and dexamethasone; Bd = bortezomib and dexamethasone; BLd = bortezomib, lenalidomide and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; DLd = daratumumab, lenalidomide and dexamethasone; DUSC = Drug Utilisation Sub Committee; IV = intravenous; Ld = lenalidomide and dexamethasone; MM = multiple myeloma; MRDR = Myeloma and Related Diseases Registry; NDMM = newly diagnosed multiple myeloma; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PI = product information; RRMM = relapsed/refractory multiple myeloma; SC = subcutaneous; SoC = standard of care; TI = transplant ineligible; TTD = time-to-treatment discontinuation; Yr = Year

Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

1 < 500

- 6.67 The PBAC previously noted that the assumed annual growth rate of 3.3% for the projected incident patients in the March 2023 submission was not adequately justified and that the growth rate in the TI NDMM population exceeded that of NDMM (paragraph 6.58, daratumumab PSD, March 2023). Following the PBAC advice, the March 2025 resubmission projected a 2.12% annual increase in incident patients. It was estimated that there will be 500 to < 5,000 incident TI NDMM patients in Year 1, increasing to 500 to < 5,000 in Year 6 of the forecast period. This results in 11% growth in TI NDMM patients over the 6 years of the forward estimates, which aligns with the estimate of 11% for growth in the incident MM patient population the PBAC has previously accepted (paragraph 5.37, daratumumab PSD, July 2020).
- 6.68 The uptake rate of DLd in the March 2023 submission (90% by Year 6; 86.9% on average over the 6 years) was considered to be an overestimate by the ESC as some patients would not be fit enough/eligible for triplet treatment (paragraph 6.58, daratumumab PSD, March 2023). The March 2025 resubmission revised the uptake rates to 65% in Year 1, increasing to 80% in Year 6.
- 6.69 The estimated cost of daratumumab to PBS/RPBS provided in the March 2025 resubmission represents a reduction from that in the March 2023 submission, arising due to two primary sources: a reduction in the estimated number of scripts dispensed (due to the assumed lower number of patients eligible for treatment); and a lower proposed published price.
- 6.70 At its March 2023 meeting, the PBAC considered that the reduction in use of DBd in second line MM was underestimated because the submission incorrectly modelled the reduction based on the assumed efficacy of DLd in the entire population, regardless of

the proportion assumed to receive DLd rather than SoC (paragraph 6.58, daratumumab PDS, March 2023). In the March 2025 resubmission, the change in the second line therapies was modelled by estimating the current (i.e. before listing of DLd) and proposed (i.e. after listing of DLd) second line MM market and taking the difference in market share for the regimens.

6.71 The March 2025 resubmission revised the cost offsets due to the reduction in DBd and other second line regimens. However, no cost offsets were estimated due to the change in use of third line regimens. The impact of this was uncertain as the listing of daratumumab in first line (as DLd) may increase costs in that treatment pathway if more expensive therapies are pushed to later lines and may increase the number of patients who go on to later lines of therapy.

6.72 A summary of the estimated use and financial implications of daratumumab is presented in Table 23.

**Table 23: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Initiating patients treated	1	1	1	1	1	1
Continuing patients treated	-	1	1	1	1	1
Total treated patients	1	1	1	1	1	2
Scripts dispensed	3	4	5	6	7	8
<b>Estimated financial implications of daratumumab (effective price for daratumumab)</b>						
Cost to PBS/RPBS less copayments	\$ 9	\$ 10	\$ 11	\$ 11	\$ 11	\$ 11
<b>Estimated financial implications for affected medicines</b>						
Cost offsets to PBS/RPBS less copayments	-\$ 12	-\$ 12	-\$ 12	-\$ 12	-\$ 12	-\$ 12
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$ 9	\$ 13	\$ 10	\$ 14	\$ 11	\$ 11
Net cost to MBS/Services Australia	\$ 15	\$ 15	\$ 15	\$ 15	\$ 15	\$ 15
<b>Net cost to PBS/RPBS/MBS/Services Australia</b>	<b>\$ 9</b>	<b>\$ 13</b>	<b>\$ 10</b>	<b>\$ 14</b>	<b>\$ 11</b>	<b>\$ 11</b>
<b>March 2023 submission</b>						
Net cost to PBS/RPBS	\$ 11	\$ 11	\$ 11	\$ 16	\$ 16	\$ 16
Net cost to MBS/Services Australia	\$ 15	\$ 15	\$ 15	\$ 15	\$ 15	\$ 15
<b>Net cost to PBS/RPBS/MBS/Services Australia</b>	<b>\$ 11</b>	<b>\$ 11</b>	<b>\$ 11</b>	<b>\$ 16</b>	<b>\$ 16</b>	<b>\$ 16</b>

Source: Table 4.3, p258; Table 4.8, p261; Table 4.17, p274; Table 4.22, p281 of the March 2025 resubmission.

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme  
Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

- <sup>1</sup> 500 to < 5,000
- <sup>2</sup> 5,000 to < 10,000
- <sup>3</sup> 20,000 to < 30,000
- <sup>4</sup> 30,000 to < 40,000
- <sup>5</sup> 50,000 to < 60,000
- <sup>6</sup> 60,000 to < 70,000
- <sup>7</sup> 70,000 to < 80,000
- <sup>8</sup> 80,000 to < 90,000
- <sup>9</sup> \$50 million to < \$60 million

<sup>10</sup> \$80 million to < \$90 million

<sup>11</sup> \$100 million to < \$200 million

<sup>12</sup> net cost saving

<sup>13</sup> \$60 million to < \$70 million

<sup>14</sup> \$90 million to < \$100 million

<sup>15</sup> \$0 to < \$10 million

<sup>16</sup> \$200 million to < \$300 million

6.73 The net cost to the PBS/RPBS of listing daratumumab was estimated to be \$100 million to < \$200 million in Year 6, and total \$500 million to < \$600 million over the first 6 years of listing (using the published prices of carfilzomib and elotuzumab in the second-line cost offsets).

### **Quality Use of Medicines**

6.74 The discussion of the quality use of medicines has not changed since the March 2023 submission. The March 2025 resubmission, like the March 2023 submission described education and resources to be provided by focusing on key quality use of medication discussion points, including promoting awareness of TI NDMM, its signs and symptoms for diagnosis; identifying the appropriate patients for daratumumab used in combination with lenalidomide and dexamethasone; and promoting appropriate dosing and administration of daratumumab as per the recommendations in the PI.

### **Financial Management – Risk Sharing Arrangements**

6.75 In March 2023, the PBAC considered that the definition of TI was arbitrary and may change over time, such that there is a high risk of a large number of patients who are TE receiving DLd (paragraph 7.3, daratumumab PSD, March 2023). Further, the PBAC advised that a risk-sharing arrangement (RSA) with clearly defined expenditure caps would be required to mitigate the risk of use outside the proposed patient population. If the proposed listing of daratumumab (as DLd) in TI NDMM is recommended, the PBAC noted that it may be appropriate to modify the existing RSA to reflect not only a potential decline in use of second line daratumumab in TI patients (noting that TE patients with relapsed/refractory MM would still be eligible for DBd in the second line setting), and to ensure that the price of daratumumab in the second line setting is cost effective (paragraph 6.67, daratumumab PSD, March 2023).

6.76 To address the concerns of the PBAC from their March 2023 consideration, the March 2025 resubmission proposed a combined RSA for daratumumab across the TI NDMM and second line MM settings.

6.77 The resubmission stated that in the scenario where DLd is PBS listed in TI NDMM, the sponsor would agree to reduce the price of daratumumab (as DBd) in second line MM to reflect the cost-effective price as determined previously by the PBAC, which will be achieved through an SPA alone (i.e. an AEMP of \$| per 1,200 mg IV or 1,800 mg SC, in contrast to current arrangements in which the AEMP is \$| per 1,200 mg or 1,800 mg and it is required that the expenditure caps are exceeded by at least |% to achieve the cost-effective price for daratumumab).

6.78 Based on the proposed effective DPMQs, the proposed subsidisation cap values for the combined daratumumab RSA proposed by the resubmission are presented in Table 24. In the combined RSA, the expenditure caps for second-line daratumumab were proposed to be increased above the agreed level for Year 5 of the current deed (\$); see Table 24). The ESC considered that this was not appropriate and the current second-line expenditure caps should be reduced to account for the expected reduced use of DBd with the listing of DLd for NDMM. Further, current second-line expenditure caps, which as noted above, are set % lower than expected usage to attain a cost-effective price, are only being exceeded by an average of % per year when the effective AEMP of daratumumab is \$ (see paragraph 6.79 and Table 25). On this basis, ESC noted there is a rationale to further reduce the current second-line expenditure caps.

**Table 24: Proposed subsidisation caps for daratumumab (as DLd & DBd)**

Cost to PBS/RPBS	Year 1	Year 2	Year 3	Year 4	Year 5
1L daratumumab	\$	\$	\$	\$	\$
2L daratumumab	\$	\$	\$	\$	\$
<b>Total cap value</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>

Source: Table 4-46, p 281 of the resubmission

Bd = daratumumab, bortezomib and dexamethasone; DLd = daratumumab, lenalidomide and dexamethasone

a Daratumumab second-line offsets only, AEMP of daratumumab assumed to be \$, based on proposal in resubmission to reduce AEMP of daratumumab from \$

### Current second-line daratumumab RSA

6.79 The subsidisation caps in the current second line RSA were set below the level of projected expenditure, reducing the cost of daratumumab for the PBS/RPBS by an average % over 5 years. As noted in the resubmission the required level of use to achieve the % breach of caps had not been observed in Years 1 to 3 of the Deed.

**Table 25: Current RSA for daratumumab in RRMM (financial estimates underpinning the RSA)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5
	Jan 21 - Dec 21	Jan 22 - Dec 22	Jan 23 - Dec 23	Jan 24 - Dec 24	Jan 25 - Dec 25	-
<b>Reimbursement above subsidisation caps:</b>						
Value of subsidisation caps	\$	\$	\$	\$	\$	\$
Commonwealth payments	\$	\$	\$*	\$*	-	-
% cap exceeded	%	%	%	%	-	-

Source: Provided by the Department during the evaluation (provided 29 November 2024).

RRMM = relapsed and/or refractory multiple myeloma; RSA = risk-sharing arrangement

\* These are draft amounts and are subject to change

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

7.1 The PBAC recommended daratumumab for use in combination with lenalidomide and dexamethasone (DLd) for the treatment of transplant ineligible, newly diagnosed multiple myeloma (TI NDMM) on the basis that it should be available only under special arrangements under the Section 100 Program (Efficient Funding of

Chemotherapy) listing for the intravenous formulation (public and private hospitals) and subcutaneous formulation (related benefits) and as a General Schedule listing for the subcutaneous formulation. The PBAC considered that DLd was superior in terms of effectiveness to the nominated comparators, lenalidomide plus dexamethasone (Ld) and bortezomib plus lenalidomide and dexamethasone (BLd) but considered that the magnitude of the benefit over BLd remained uncertain. In terms of the economic analysis, the PBAC considered that DLd could be considered cost effective with a price reduction. The PBAC considered that the revised estimated financial impact of listing DLd was overestimated and considered that a risk sharing arrangement (RSA) that included the use of daratumumab both in the first line (newly diagnosed) and second line settings would be required. The PBAC noted that the RSA should account for the expected reduced use of second line daratumumab as a result of the first line listing.

- 7.2 The PBAC is satisfied that daratumumab provides, for some patients, a significant improvement in efficacy over Ld and BLd.
- 7.3 The PBAC acknowledged the strong consumer support for daratumumab which described the benefits of first line treatment with DLd and highlighted the ongoing need for new and effective therapies for the treatment of multiple myeloma. The PBAC considered that the input from individuals, health care professionals and organisations provided valuable insights about the experience of individuals diagnosed with multiple myeloma, and the desire for improved treatment outcomes.
- 7.4 In terms of the proposed restriction, the PBAC agreed with the resubmission and considered that daratumumab should be limited to once per lifetime use. The PBAC advised that a criterion stating that the patient must only receive treatment with daratumumab once per lifetime for multiple myeloma should be added to the proposed restriction and flow onto the second-line daratumumab listing. The PBAC recommended that, similar to the other multiple myeloma listings on the PBS, prescriber instructions to document details of histological diagnosis and diagnostic reports in the patient's medical records should be added. The PBAC also recommended 15 repeats for the initial grandfather restriction as the number of doses provided prior to PBS listing can vary. The PBAC considered that the proposed lenalidomide restriction was appropriate.
- 7.5 The PBAC again considered that the nominated comparators, Ld and BLd, were reasonable.
- 7.6 The PBAC noted that the comparison between DLd and Ld was again based on the MAIA trial. The PBAC recalled that in terms of progression free survival (PFS), DLd was associated with a statistically significant improvement (HR = 0.55; 95% CI: 0.45, 0.67). The PBAC noted that updated overall survival (OS) data were presented, and that DLd continued to result in a statistically significant improvement over Ld (HR = 0.67; 95% CI: 0.55, 0.82). The PBAC recalled that it had previously noted that although the incidence of treatment emergent adverse events (TEAEs) was similar for patients receiving DLd and Ld, DLd was associated with more serious adverse events.

- 7.7 Overall, the PBAC again considered that DLd was superior in terms of effectiveness and inferior in terms of safety compared to Ld.
- 7.8 The PBAC recalled that in March 2023 it has considered that the submission's claim that Ld was a proxy for BLd was not supported (paragraph 7.10, daratumumab PSD, March 2023); however, the resubmission again claimed that Ld was a reasonable proxy for BLd in terms of efficacy, i.e. it was claimed that the addition of bortezomib had no effect on the efficacy of Ld. The PBAC noted that this was again based primarily on the fact that there were no statistically significant differences in PFS or OS between BLd or Ld in the subgroup of patients aged  $\geq 65$  in the SWOG s0777 trial (see Table 7), with additional data presented from a survival analysis from the Myeloma and Related Diseases Registry (MRDR).
- 7.9 The PBAC considered that the SWOG s0777 trial data did not support the resubmission's claim that BLd and Ld are non-inferior in patients aged  $\geq 65$  years (as a proxy for transplant ineligibility). The PBAC reiterated that the subgroup of patients aged  $\geq 65$  years was not pre-specified or stratified in the original study design, and that although the point estimates for the hazard ratios for both PFS and OS suggested the benefit of BLd over Ld was less in patients aged  $\geq 65$  years versus  $< 65$  years, the difference was not statistically significant (i.e. the p-values for the tests for interaction were not  $< 0.05$ ). Thus, the PBAC agreed with ESC and considered the magnitude of the reduction in benefit, if any, of BLd versus Ld in patients  $\geq 65$  years was uncertain. The PBAC noted that although the survival analysis from the MRDR data resulted in no statistically significant differences between BLd and Ld in terms of PFS and OS, the analyses were uncertain as patients were not randomised and there were differences in terms of age, ECOG performance status and cytogenetic risk profiles between the patients receiving the treatments.
- 7.10 The resubmission presented an adjusted indirect treatment comparison of PFS between DLd and BLd in TI NDMM using individual patient data from the MAIA and SWOG s0777 trials. The PBAC noted that DLd was associated with a statistically significant improvement in PFS over BLd (HR = 0.59; 95% CI: 0.39, 0.90). The PBAC noted that, to account for fundamental differences in the patient populations enrolled in the two trials, the analysis excluded patients from the SWOG s0777 trial that were not matched with those of the MAIA trial and then performed propensity-score weighting to balance the two trial populations on key baseline characteristics. The PBAC considered that these adjustments introduced uncertainty, especially as the analysis only included 198 of 525 (38%) patients randomised in the SWOG s0777 trial. The PBAC also noted that an indirect comparison of OS results was not presented.
- 7.11 Overall, the PBAC considered that DLd was superior compared to BLd in terms of PFS, but that the magnitude of benefit, though likely to be less than the benefit compared to Ld, was uncertain. The PBAC considered that the relative effectiveness of DLd and BLd for OS was also uncertain as an adjusted indirect treatment comparison was not presented for this outcome.

- 7.12 In terms of safety, the PBAC considered that DLd was likely non-inferior compared to BLd.
- 7.13 The PBAC noted that the incremental cost-effective ratio (ICER) presented in the PSCR was \$55,000 to < \$75,000 per quality adjusted life year (QALY), using indicative April 2025 prices for lenalidomide and bortezomib, and that the key outstanding matters for consideration were (i) model time horizon, (ii) efficacy of BLd relative to Ld, and (iii) post-progression treatment costs.
- 7.14 The PBAC recalled that in March 2023 it had considered that a 15-year time horizon would be appropriate but noted that the revised model presented in the current resubmission applied a 20-year time horizon. The PBAC accepted the 20-year time horizon as reasonable in the context of the revised OS extrapolations (exponential for the DLd arm and Weibull for the comparator arm) which were based on the updated OS data which had a median follow up of 89.3 months (as compared to 64.5 months in the previous submission).
- 7.15 The PBAC considered that with the addition of bortezomib, i.e. BLd, the efficacy of Ld should be assumed to be increased, although noted that there was not a reliable estimate of the incremental benefit. The PBAC noted, based on the analyses included in Table 20, that the ICER increased by |% to |% depending on the data and analyses used to estimate the incremental benefit of BLd over Ld.
- 7.16 The PBAC noted the costs for post progression treatments were estimated to be substantially lower for DLd compared with Ld/BLd (\$20,729 versus \$76,259, respectively) and that the model was sensitive to changes in these costs. The PBAC considered the difference in post progression costs across the arms was likely overestimated, resulting in the ICER being underestimated.
- 7.17 Overall, given the uncertainties noted, the PBAC did not consider daratumumab to be cost effective at the price proposed in the resubmission.
- 7.18 The PBAC noted that the cost per patient for daratumumab in the first-line setting was estimated to be |% higher than that for use in the second-line setting (see paragraph 3.7), and that a price reduction of |% for daratumumab in the first line setting would result in the cost per patient across both settings being approximately equal. The PBAC noted that a |% price reduction for daratumumab for the first-line setting reduced the ICER from \$55,000 to < \$75,000 per QALY to \$45,000 to < \$55,000 per QALY. The PBAC considered that daratumumab could be considered cost-effective based on this reduced ICER, noting that it was lower than that previously accepted for daratumumab in the second-line setting, but was associated with the uncertainties noted above.
- 7.19 The PBAC noted that the financial estimates for DLd were structurally similar to those considered in March 2023. The PBAC noted that the resubmission again assumed that there would be < 500 grandfathered patients in Year 1. The PBAC, noting that the patient access program had not commenced, considered that inclusion of these patients was not appropriate given these patients would be captured in the incident

patient population.

- 7.20 The PBAC considered that the utilisation estimates remained overestimated. The PBAC noted that the market was defined based on patients treated with BLd, Ld, bortezomib plus dexamethasone (Bd) or bortezomib plus cyclophosphamide and dexamethasone (BCd). The PBAC noted uptake was assumed to be primarily due to replacement of BLd and Ld, and considered that the assumed uptake from these regimens was too high. Specifically, the PBAC considered that (i) uptake from DLd should be less than 100% in Year 2 onwards; and (ii) uptake from Ld would likely be substantially less than assumed (70% in Year 1 increasing to 80% by Year 6). The PBAC noted as TI patients in Australia were generally over 75 years of age and as the safety of DLd is inferior compared to Ld that, therefore, a significant proportion of patients currently treated with dual oral therapy may not be fit enough to receive triple therapy.
- 7.21 The PBAC reaffirmed its March 2023 advice that a RSA would be required to mitigate the risk of use outside the proposed patient population. The PBAC considered the resubmission's proposal for combined subsidisation caps of first and second line daratumumab usage, and with a reduced price for daratumumab in the second line setting to the intended cost-effective price, was reasonable.
- 7.22 The PBAC considered that the first-line utilisation estimates used to inform the RSA expenditure caps should be revised as outlined in paragraph 7.18. The PBAC considered that the second-line utilisation estimates should appropriately account for the actual use of daratumumab being less than expected when the second-line RSA was agreed. Further, the PBAC considered that daratumumab second-line utilisation should be reduced in line with its expected reduced use following the listing of DLd for NDMM.
- 7.23 The PBAC noted the large number of treatments listed on the PBS for the treatment of multiple myeloma. The PBAC recommended that the Department undertake a utilisation analysis to understand the treatment pathways and duration of treatment for PBS-listed therapies for multiple myeloma.
- 7.24 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for daratumumab:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies, on the basis of the results of the MAIA trial;
  - b) The treatment is expected to address a high and urgent unmet clinical need;
  - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 7.25 The PBAC advised that this submission would not meet the criteria for an Independent

Review as it received a positive PBAC recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item:

**Daratumumab:**

**Initial (week 0-24)**

MEDICINAL PRODUCT medicinal product pack	PBS item code	Maximum Amount	No. of Rpts
DARATUMUMAB Injection	New (Public) New (Private)	1920 mg	15
<b>Available brands</b>			
Darzalex daratumumab 100 mg/5 ml injection, 5 mL vial			
Darzalex daratumumab 400 mg/20 mg injection, 20 mL vial			
<b>Restriction Summary/ Treatment of Concept:</b>			
<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Public/Private hospital			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate, real-time assessment by Services Australia (telephone/online PBS Authorities system)			
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Indication:</b> Untreated Multiple Myeloma			
<b>Treatment Phase:</b> Initial treatment as first-line drug therapy from week 0 to week 24			
<b>Clinical criteria:</b>			
The condition must be newly diagnosed			
<b>AND</b>			
<b>Clinical criteria:</b>			
The condition must be confirmed by a histological diagnosis			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must be ineligible for a primary stem cell transplantation			
<b>AND</b>			
<b>Clinical criteria:</b>			
The treatment must form part of triple combination therapy limited only to: (i) this drug, (ii) lenalidomide, and (iii) dexamethasone,			
<b>AND</b>			
<b>Clinical criteria:</b>			

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	Patient must not be receiving concomitant PBS-subsidised treatment with bortezomib, carfilzomib, elotuzumab, pomalidomide, selinexor or thalidomide.
	<b>Treatment criteria:</b>
	Patient must be undergoing PBS-subsidised treatment with this drug once per lifetime. Meaning, patient must access this drug in one of the following situations: (i) for the first time, irrespective of whether the diagnosis has been re-classified (i.e. the diagnosis has changed between multiple myeloma/amyloidosis), or irrespective if the disease staging has been changed (i.e. disease has changed from untreated multiple myeloma to relapsed or refractory multiple myeloma) (ii) changing the drug's form (intravenous/subcutaneous) within the first 9 weeks of treatment for the same PBS indication.
	<p><b>Prescriber instructions:</b></p> <p>Details of the histological diagnosis of multiple myeloma, record of ineligibility for stem cell transplant and confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records:</p> <p>(a) the level of serum monoclonal protein; or  (b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or  (c) the serum level of free kappa and lambda light chains; or  (d) bone marrow aspirate or trephine; or  (e) if present, the size and location of lytic bone lesions (not including compression fractures); or  (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or  (g) if present, the level of hypercalcaemia, corrected for albumin concentration.</p> <p>As these parameters must be used to determine response, results for either (a) or (b) or (c) should be documented for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) must be documented in the patient's medical records.</p> <p>Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be documented in the patient's medical records</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DARATUMUMAB					
daratumumab 1.8 g/15 injection, 15 mL vial	New (EFC – Related Benefit) New (Gen. Schedule)	1	1	15	Darzalex SC

**Restriction Summary/ Treatment of Concept:**

	<p><b>Category / Program:</b></p> <p><input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT)  <input checked="" type="checkbox"/> General Schedule (Code GE)</p> <p><b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners</p> <p><b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate, real-time assessment by Services Australia (telephone/online PBS Authorities system)</p>
	<p><b>Administrative Advice:</b>  Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p>
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>PBS Indication:</b> Untreated Multiple myeloma

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	<b>Treatment Phase:</b> Initial treatment as first-line drug therapy for from week 0 to week 24
	<b>Clinical criteria:</b>
	The condition must be newly diagnosed
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must be confirmed by a histological diagnosis
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must be ineligible for a primary stem cell transplantation
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must form part of triple combination therapy limited only to: (i) this drug, (ii) lenalidomide, and (iii) dexamethasone,
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not be receiving concomitant PBS-subsidised treatment with bortezomib, carfilzomib, elotuzumab, pomalidomide, selinexor or thalidomide.
	<b>Treatment criteria:</b>
	Patient must be undergoing PBS-subsidised treatment with this drug once per lifetime. Meaning, patient must access this drug in one of the following situations: (i) for the first time, irrespective of whether the diagnosis has been re-classified (i.e. the diagnosis has changed between multiple myeloma/amyloidosis), or irrespective if the disease staging has been changed (i.e. disease has changed from untreated multiple myeloma to relapsed or refractory multiple myeloma) (ii) changing the drug's form (intravenous/subcutaneous) within the first 9 weeks of treatment for the same PBS indication.
	<b>Prescriber instructions:</b> Details of the histological diagnosis of multiple myeloma, record of ineligibility for stem cell transplant and confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records: (a) the level of serum monoclonal protein; or (b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or (c) the serum level of free kappa and lambda light chains; or (d) bone marrow aspirate or trephine; or (e) if present, the size and location of lytic bone lesions (not including compression fractures); or (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or (g) if present, the level of hypercalcaemia, corrected for albumin concentration.  As these parameters must be used to determine response, results for either (a) or (b) or (c) should be documented for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) must be documented in the patient's medical records. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be documented in the patient's medical records

**Continuing (week 25 onwards)**

MEDICINAL PRODUCT medicinal product pack	PBS item code	Maximum Amount	No. of Rpts
DARATUMUMAB Injection	New (Public) New (Private)	1920 mg	5
<b>Available brands</b>			
Darzalex daratumumab 100 mg/5 ml injection, 5 mL vial			
Darzalex daratumumab 400 mg/20 mg injection, 20 mL vial			
<b>Restriction Summary / Treatment of Concept:</b>			
<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Public/Private hospital			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate, real-time assessment by Services Australia (telephone/online PBS Authorities system)			
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Indication:</b> Untreated Multiple myeloma			
<b>Treatment Phase:</b> Continuing treatment as first line drug therapy from week 25 onwards (administered once every four weeks)			
<b>Clinical criteria:</b>			
Patient must have previously received PBS-subsidised treatment with this drug for this condition			
<b>AND</b>			
<b>Clinical criteria:</b>			
The treatment must form part of triple combination therapy limited only to: (i) this drug, (ii) lenalidomide, and (iii) dexamethasone			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must not be receiving concomitant PBS-subsidised treatment with bortezomib, carfilzomib, elotuzumab, pomalidomide, selinexor or thalidomide.			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must not have developed disease progression while receiving treatment with this drug for this condition			
<b>Prescriber instructions:</b> Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or			

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(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
<b>Prescriber instructions:</b> Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DARATUMUMAB					
daratumumab 1.8 g/15 injection, 15 mL vial	New (EFC – Related Benefit) New (Gen. Schedule)	1	1	5	Darzalex SC

**Restriction Summary/ Treatment of Concept:**

	<p><b>Category / Program:</b>  <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT)  <input checked="" type="checkbox"/> General Schedule (Code GE)</p> <p><b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners</p> <p><b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate, real-time assessment by Services Australia (telephone/online PBS Authorities system)</p>
	<p><b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p>
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Indication:</b> Untreated Multiple myeloma
	<b>Treatment Phase:</b> Continuing treatment as first line drug therapy from week 25 onwards (administered once every four weeks)
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must form part of triple combination therapy limited only to: (i) this drug, (ii) lenalidomide, and (iii) dexamethasone,
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not be receiving concomitant PBS-subsidised treatment with bortezomib, carfilzomib, elotuzumab, pomalidomide, selinexor or thalidomide.
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	<b>Prescriber instructions:</b> Progressive disease is defined as at least 1 of the following:

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	(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
	<b>Prescriber instructions:</b> Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.

### Grandfather

MEDICINAL PRODUCT medicinal product pack	PBS item code	Maximum Amount	No. of Rpts
DARATUMUMAB Injection	New (Public) New (Private)	1920 mg	15
<b>Available brands</b>			
Darzalex daratumumab 100 mg/5 ml injection, 5 mL vial			
Darzalex daratumumab 400 mg/20 mg injection, 20 mL vial			
<b>Restriction Summary / Treatment of Concept:</b>			
<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Public/Private hospital			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate, real-time assessment by Services Australia (telephone/online PBS Authorities system)			
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>PBS Indication:</b> Untreated Multiple myeloma			
<b>Treatment Phase:</b> Transitioning from non-PBS to PBS-subsided treatment - Grandfather arrangements			
<b>Clinical criteria:</b>			
Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date]			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug, which are: (a) the condition was newly diagnosed, (b) the condition was confirmed by a histological diagnosis, (c) the patient was/is ineligible for a stem cell transplant, (d) the treatment is being given as triple combination therapy limited only to (i) this drug, (ii) lenalidomide, (iii) dexamethasone, (e) patient is not receiving concomitant PBS-subsidised treatment with bortezomib, carfilzomib, elotuzumab, pomalidomide, selinexor or thalidomide.			

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	<b>Treatment criteria:</b>
	Patient must be undergoing PBS-subsidised treatment with this drug once per lifetime. Meaning, patient must access this drug in one of the following situations: (i) for the first time, irrespective of whether the diagnosis has been re-classified (i.e. the diagnosis has changed between multiple myeloma/amyloidosis), or irrespective if the disease staging has been changed (i.e. disease has changed from untreated multiple myeloma to relapsed or refractory multiple myeloma) (ii) changing the drug's form (intravenous/subcutaneous) within the first 9 weeks of treatment for the same PBS indication.
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	<p><b>Prescriber instructions:</b>  Details of the histological diagnosis of multiple myeloma, record of ineligibility for stem cell transplant and confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records:</p> <ul style="list-style-type: none"> <li>(a) the level of serum monoclonal protein; or</li> <li>(b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or</li> <li>(c) the serum level of free kappa and lambda light chains; or</li> <li>(d) bone marrow aspirate or trephine; or</li> <li>(e) if present, the size and location of lytic bone lesions (not including compression fractures); or</li> <li>(f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or</li> <li>(g) if present, the level of hypercalcaemia, corrected for albumin concentration.</li> </ul> <p>As these parameters must be used to determine response, results for either (a) or (b) or (c) should be documented for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) must be documented in the patient's medical records. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be documented in the patient's medical records</p>
	<p><b>Prescriber instructions:</b>  Progressive disease is defined as at least 1 of the following:</p> <ul style="list-style-type: none"> <li>(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or</li> <li>(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or</li> <li>(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or</li> <li>(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or</li> <li>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or</li> <li>(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or</li> <li>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</li> </ul>
	<p><b>Prescriber instructions:</b>  Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p>
	<p><b>Administrative advice:</b>  Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.</p>
	<p><b>Administrative advice:</b>  This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</p>

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DARATUMUMAB					
daratumumab 1.8 g/15 injection, 15 mL vial	New (EFC – Related Benefit) New (Gen. Schedule)	1	1	7	Darzalex SC
<b>Restriction Summary/ Treatment of Concept:</b>					
	<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT) <input checked="" type="checkbox"/> General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate, real-time assessment by Services Australia (telephone/online PBS Authorities system)				
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).				
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.				
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.				
	<b>PBS Indication:</b> Untreated Multiple myeloma				
	<b>Treatment Phase:</b> Transitioning from non-PBS to PBS-subsided treatment - Grandfather arrangements				
	<b>Clinical criteria:</b>				
	Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date]				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug, which are: (a) the condition was newly diagnosed, (b) the condition was confirmed by a histological diagnosis, (c) the patient was/is ineligible for a stem cell transplant, (d) the treatment is being given as triple combination therapy limited only to (i) this drug, (ii) lenalidomide, (iii) dexamethasone, (e) patient is not receiving concomitant PBS-subsidised treatment with bortezomib, carfilzomib, elotuzumab, pomalidomide, selinexor or thalidomide.				
	<b>Treatment criteria:</b>				
	Patient must be undergoing PBS-subsidised treatment with this drug once per lifetime. Meaning, patient must access this drug in one of the following situations: (i) for the first time, irrespective of whether the diagnosis has been re-classified (i.e. the diagnosis has changed between multiple myeloma/amyloidosis), or irrespective if the disease staging has been changed (i.e. disease has changed from untreated multiple myeloma to relapsed or refractory multiple myeloma) (ii) changing the drug's form (intravenous/subcutaneous) within the first 9 weeks of treatment for the same PBS indication.				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	Patient must not have developed disease progression while receiving treatment with this drug for this condition				
	<b>Prescriber instructions:</b> Details of the histological diagnosis of multiple myeloma, record of ineligibility for prior stem cell transplant and confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records: (a) the level of serum monoclonal protein; or (b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or (c) the serum level of free kappa and lambda light chains; or				

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	<p>(d) bone marrow aspirate or trephine; or                  (e) if present, the size and location of lytic bone lesions (not including compression fractures); or                  (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or                  (g) if present, the level of hypercalcaemia, corrected for albumin concentration.</p> <p>As these parameters must be used to determine response, results for either (a) or (b) or (c) should be documented for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) must be documented in the patient's medical records. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be documented in the patient's medical records</p>
	<p><b>Prescriber instructions:</b>                  Progressive disease is defined as at least 1 of the following:                  (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or                  (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or                  (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or                  (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or                  (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or                  (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or                  (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</p>
	<p><b>Prescriber instructions:</b>                  Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p>
	<p><b>Administrative advice:</b>                  Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.</p>
	<p><b>Administrative advice:</b>                  This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</p>

8.2 Add new item:

**Lenalidomide:**

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
LENALIDOMIDE					
lenalidomide 25 mg capsule, 21 lenalidomide 20 mg capsule, 21 lenalidomide 15 mg capsule, 21 lenalidomide 10 mg capsule, 21 Lenalidomide 5 mg capsule, 21	New (HSD Public) New (HSD Private)	1	21	2	Various brands
<b>Restriction Summary / Treatment of Concept:</b>					

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<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program - Public/Private hospital	
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners	
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate, real-time assessment by Services Australia (telephone/online PBS Authorities system)	
<b>Authority type:</b> <input checked="" type="checkbox"/> Complex Authority Required (CAR)	
	<b>Caution:</b> This drug is a category X drug and must not be given to pregnant women. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out.
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
	<b>Administrative Advice:</b> Patients receiving lenalidomide under the PBS listing must be registered in the risk management program relevant for the brand of lenalidomide being prescribed and dispensed: Revlimid - i-access program; Cipla Lenalidomide - Pregnancy Prevention Program; Lenalidomide Dr.Reddy's - Reddy-2-Assist Controlled Access Program; Lenalide - Juno ConnectedTM; Lenalidomide Sandoz - MyCheckPoint Pregnancy Prevention Program; Lenalidomide Teva - Pregnancy Prevention Program; Lenalidomide Viatrix - Viatrix Care.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>PBS Indication:</b> Untreated Multiple myeloma	
<b>Treatment Phase:</b> Triple combination therapy consisting of daratumumab, lenalidomide and dexamethasone	
<b>Treatment criteria:</b>	
Patient must be undergoing concurrent treatment with daratumumab obtained through the PBS for the treatment of transplant ineligible, newly diagnosed multiple myeloma.	
<b>AND</b>	
<b>Treatment criteria:</b>	
Patient must not be undergoing simultaneous treatment with this drug obtained under another PBS listing.	

8.3 Flow-on to daratumumab existing listings for relapsed and/or refractory multiple myeloma:

- Amend the treatment criterion (concept ID: 29637) that currently exists in daratumumab listings for relapsed and/or refractory multiple myeloma, (item codes: 12683M, 12746W, 12228N, 12230Q) to ensure that PBS subsidised treatment with daratumumab is limited to once per lifetime.

<i>Patient must be undergoing PBS-subsidised treatment with this drug once per lifetime. Meaning, patient must access this drug in one of the following situations: (i) for the first time, irrespective of whether the diagnosis has been re-classified (i.e. the diagnosis has changed between multiple myeloma/amyloidosis), or irrespective if the disease staging has been changed (i.e. disease has changed from untreated multiple myeloma to relapsed or refractory multiple myeloma) (ii) changing the drug's form (intravenous/subcutaneous) within the first 9 weeks of treatment for the same PBS indication.</i>	
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***These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

The sponsor had no comment