

**6.03 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[®],
Janssen-Cilag Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required (telephone/online) listing for the intravenous (IV) and subcutaneous (SC) 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 The submission stated that maximising the effectiveness of first-line therapy remains the best opportunity to optimise long term patient outcomes in patients with TI NDMM. This is in line with the recommendations of the Myeloma Australia's Medical and Scientific Advisory Group (MSAG) of Australia for this population (MSAG 2022).
- 1.3 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SoC), comprising lenalidomide in combination with dexamethasone (Ld) and bortezomib, lenalidomide and dexamethasone (BLd). The key components of the clinical issues addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

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 until 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	This submission nominates two comparators, as these are the regimens that will be most commonly replaced in clinical practice; <ul style="list-style-type: none"> • Lenalidomide in combination with dexamethasone (Ld); • Bortezomib, in combination with lenalidomide and dexamethasone (BLd)
Outcomes	Progression-free survival (PFS), overall survival (OS), overall response rate (ORR), minimal residual disease (MRD)-negativity, adverse events (AEs).
Clinical claim	Compared with Ld, DLd demonstrated statistically and clinically superior comparative efficacy based on PFS, OS and other secondary outcomes in the MAIA trial, including ORR and MRD-negativity. These outcomes are key goals of therapy in TI NDMM. Further, whilst the safety data were not adjusted for the longer exposure to DLd treatment and thus biased against DLd, DLd was associated with a higher incidence of grade 3 or 4 AEs and SAEs compared with Ld alone and therefore has an inferior safety profile. The profile of AEs observed with DLd is consistent with the known safety profiles of daratumumab and lenalidomide. Compared with BLd, given the claimed 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. 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.

Source: Table 1.1, p20 of the submission.

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; TI = transplant ineligible

2 Background

Registration status

2.1 Daratumumab, IV and SC formulations are 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: bortezomib and dexamethasone, or lenalidomide and dexamethasone.

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

2.2 Daratumumab was TGA approved in April 2020 (IV formulation) and September 2020 (SC formulation) for the indication corresponding to the proposed PBS listing, i.e. for use in combination with Ld for TI NDMM.

Previous PBAC consideration

2.3 DLd was considered by the PBAC in November 2017, for the treatment of relapsed and/or refractory MM (RRMM). This is the first consideration of DLd in the TI NDMM setting. Daratumumab IV in combination with bortezomib and dexamethasone (DBd) was considered by the PBAC in March 2019, November 2019 and July 2020, for the treatment of RRMM. Daratumumab SC in combination with bortezomib and dexamethasone was considered by the PBAC in July 2021 for the treatment of RRMM. Daratumumab SC in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) was considered by the PBAC in November 2021 and May 2022 for the treatment of Amyloid light-chain (AL) amyloidosis.

2.4 BLd was considered by the PBAC for TI NDMM at its August 2019 meeting.

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

3 Requested listing

Intravenous formulation				
Medicinal product pack	DPMA	Max. Amt	No. of Rpts	Available brands
Initial				
Daratumumab, intravenous infusion, liquid in vial, 400 mg Daratumumab, intravenous infusion, liquid in vial, 100 mg	Published: Public hospital: \$11,770.87 Private hospital: \$11,976.05 Effective: Public hospital: \$ [REDACTED] Private hospital: \$ [REDACTED]	1,920 mg	15	DARZALEX®
Continuing treatment from week 25 onwards (administered once every 4 weeks) ^a				
Daratumumab, intravenous infusion, liquid in vial, 400 mg Daratumumab, intravenous infusion, liquid in vial, 100 mg	Published: Public hospital: \$11,770.87 Private hospital: \$11,976.05 Effective: Public hospital: \$ [REDACTED] Private hospital: \$ [REDACTED]	1,920 mg	5	DARZALEX®
Subcutaneous formulation				
Medicinal product pack	DPMQ	Max. Qty	No. of Rpts	Available brands
Initial treatment from week 1 to 24				
Daratumumab, subcutaneous vial,	Published price:	1	15	DARZALEX®

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1800 mg	General: \$7,171.56 EFC Related: \$7,010.28 Effective price: General: \$ [REDACTED] EFC Related: \$ [REDACTED]			
Continuing treatment from week 25 onwards (administered once every 4 weeks) ^a				
Daratumumab, subcutaneous vial, 1800 mg	Published price: General: \$7,171.56 EFC Related: \$7,010.28 Effective price: General: \$ [REDACTED] EFC Related: \$ [REDACTED]	1	5	DARZALEX®
Requested restriction for initiating treatment phase				
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: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)				
Condition: Multiple myeloma				
Indication: Untreated Multiple Myeloma				
Treatment Phase: Initial treatment as first-line drug therapy for weeks 1 to 24				
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				
Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib, thalidomide or pomalidomide				
AND				
The treatment must be in combination with lenalidomide and dexamethasone				
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				
Requested restriction for continuing treatment phase				
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: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)				
Condition: Multiple myeloma				
Indication: Untreated Multiple Myeloma				
Treatment Phase: Continuing treatment from week 25 onwards (administered once every four weeks)				
Clinical criteria:				
Patient must have previously received PBS-subsidised treatment with this drug for this condition,				
AND				
The treatment must be in combination with lenalidomide and dexamethasone,				

AND
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Administrative Advice: Special Pricing Arrangements apply

Source: Table 1.17, p66 of the submission.

IV= intravenous; PBS= Pharmaceutical Benefit Scheme; SC= subcutaneous.

^a The submission requested the inclusion of a grandfather provision aligned with the PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug. The submission requested inclusion of a grandfathering restriction at the same requested prices but provided for 7 repeats.

- 3.1 The proposed dispensed price per maximum quantity/amount (DPMQ/DPMA) for each formulation (SC and IV) incorporated the applicable mark-ups and fees as of October 2022. The submission stated that the effective prices proposed in the submission and used in economic evaluation and financial impact analysis were the same as the effective prices for daratumumab in second-line multiple myeloma (MM). The ESC noted that the net-cost for daratumumab in second-line MM was achieved through a risk sharing arrangement (RSA) and was 1% lower than the effective prices. The proposed prices for first-line MM were therefore higher than that considered cost-effective for second-line MM.
- 3.2 The ESC considered that the criterion that a “Patient must be ineligible for a primary stem cell transplantation” was arbitrary and that there was a high risk that a number of patients who were transplant eligible would receive DLd. The ESC considered that a strong definition of transplant ineligibility which was applicable to the Australian population and a RSA would be required to help mitigate the risk. The ESC noted advice from the Myeloma and Related Diseases Registry (MRDR) prepared for the submission suggested that the mean age of first line treatment in patients who received ASCT was 61.1 years, compared with 74.5 years for patients who did not receive a stem cell transplant (MRDR Report September 2022, Table 1 and Table 3) and that the current MSAG guidelines (2022, p20) state that patients over the age of 75 are generally considered transplant ineligible.
- 3.3 The ESC noted that the MSAG guidelines 2022 (p11) state that “The traditional notion that patients aged above 65 years are ineligible for ASCT is no longer appropriate as it is clear that older patients who are biologically fit do benefit from intensive treatment.” With respect to eligibility for transplant, the ESC considered that individual assessment that considers the patient’s age, comorbidities, frailty and disability status is required. Clinical tools such as the haematopoietic stem cell transplant co-morbidity index (HCT-CI) may be useful to assess suitability for ASCT.
- 3.4 The submission requested a special pricing arrangement (SPA) for the supply of daratumumab (SC and IV formulations) for TI NDMM, which will be captured by a Deed of Agreement. The submission noted an RSA is in place for daratumumab in second-line MM (see paragraphs 6.65 and 6.66 for further details) and stated one was currently under assessment for daratumumab in amyloid light chain (primary) amyloidosis at time of submission. The PBS listing for light chain amyloidosis became effective on 1 Jan 2023.

- 3.5 The submission requested a grandfather provision aligned with the PBS-eligibility criteria applying to a non-grandfathered patient prior to commencing treatment with non-PBS daratumumab. The submission 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 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. The PBAC has seen multiple submissions across a variety of molecules and settings in MM since the early 2000s.
- 4.2 According to local 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 Public Summary Document (PSD), August 2019 PBAC meeting).
- 4.3 The proposed clinical algorithm incorporated DLd as a third treatment alternative to BLd and Ld for frail TI NDMM patients, and as a fourth treatment option for fit and intermediately fit TI NDMM patients where BLd, Ld and bortezomib in combination with cyclophosphamide and dexamethasone (BCd) are currently recommended. It is expected that if listed, DLd would decrease the use of daratumumab in combination with bortezomib and dexamethasone (DBd) in the second-line setting. Additionally, like the proposed comparators, Ld and BLd, DLd has a lenalidomide backbone, therefore, no impact on subsequent lines of treatment containing lenalidomide as the backbone therapy are expected from DLd being used first-line.
- 4.4 The pre-PBAC response noted that the TGA approved regimen for daratumumab in the transplant eligible population includes thalidomide, which has an unfavourable side effect profile. The pre-PBAC response noted that there was an ongoing trial for daratumumab in combination with BLd in the transplant eligible population, but that no data were yet reported.
- 4.5 Daratumumab is a novel human monoclonal antibody that binds to and inhibits CD38, a transmembrane glycoprotein overexpressed in MM plasma cells. Daratumumab as DBd was recommended by the PBAC for patients with RRMM as a second-line treatment in July 2021.

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

5 Comparator

- 5.1 The submission nominated Ld and BLd as the comparators arguing that these are the regimens most likely to be replaced in clinical practice. The submission included an analysis of PBS prescribing data from the Myeloma and Related Diseases Registry (MRDR) from June 2019 to June 2022 and presented data separately for the periods before and after the PBS listing of BLd in June 2020. The data showed that for the 12 - 24 month period post listing of BLd on the PBS, 50.7% of patients received BLd and 21.3% received Ld; for the period > 24 months post listing of BLd, the ESC noted that 38.0% of patients received BLd and 22.5% received Ld (MRDR Report September 2022, Table 5). The ESC considered that the nominated comparators were reasonable on the basis that: (1) they aligned with the treatment recommendations in the MSAG guidelines (2022); and (2) they are the two most commonly prescribed treatments for TI NDMM as per the analysis of the MRDR. The ESC also noted the high use of bortezomib in combination with cyclophosphamide and dexamethasone (BCd) in elderly TI patients in the poster by Zhao 2022¹ presented with the Pre-Subcommittee Response (PSCR). The ESC noted that BCd was used by up to 15.5% of TI patients on the MRDR (MRDR Report September 2022, Table 5), but considered as this regimen was recommended in the MSAG guidelines (2022) for patients who were unable to receive lenalidomide (e.g. those with severe renal impairment), that it was not a relevant comparator.
- 5.2 In the economic evaluation, the submission referred to the mix of BLd and Ld as the standard of care (SoC) comparator; however, it did not conduct a weighted comparison and instead utilised efficacy data for Ld only in the SOC arm. Although BLd might be considered a more relevant comparator, as DLd and BLd are triplet therapies, and are more likely to be used in the same patients (Ld is more likely to be used in patients unfit for triplet regimens), the PSCR stated that DLd is better tolerated than BLd and will be used in frail patients with TI NDMM who would have previously received Ld. Thus, the PSCR considered that DLd would replace both BLd and Ld if PBS listed. The ESC noted that use of BLd reflects the current MSAG guidelines (2022) which advise that a 'three drug combination, where feasible, is preferred to achieve the best response rate and consequently a long first remission'. Noting that Ld would be used in some frailer patients, the ESC considered that a weighted comparison best reflected current clinical practice. The ESC considered that the weighting based on the MRDR data and applied in the economic evaluation of 68% BLd versus 32% Ld would be reasonable (see paragraph 6.38).
- 5.3 The submission did not consider BLd-lite as a comparator. BLd-lite has a reduced dosing frequency of bortezomib (from twice-weekly to weekly) and a reduced dose of lenalidomide (from 25 mg to 15 mg). An analysis of the MRDR database indicated that

¹ Zhao S, et al (2022) Real world comparison of treatment outcomes for myeloma in elderly transplant ineligible population with RVd, Rd and VCd in frontline setting: Results from MRDR Australia and New Zealand.

of the TI NDMM patients analysed, only 12.0% received the recommended full dose of bortezomib as part of BLd (Table 1.8, p42 of the submission, MRDR Report September 2022, Table 4); the rest are described as having dose reductions, and/or less frequent dosing schedules of bortezomib and lenalidomide. The MSAG guidelines state that in the target population, BLd-lite achieves a similar cumulative dose compared to traditional BLd (due to fewer early treatment cessations). However, the evidence for BLd-lite in the TI NDMM setting is drawn from one single arm phase II study², and the MSAG note that as yet there are no phase III comparative data of its use relative to Ld (MSAG 2022). Use of BLd-lite compared to Ld or Bd is currently under investigation in an ongoing Australian trial, FRAIL-M).³ The ESC considered that BLd-lite is not commonly used and that patients are likely to achieve a similar cumulative dose of bortezomib and lenalidomide and therefore it does not need to be considered as a separate comparator. The ESC considered that the implications of BLd-lite would be minimal with respect to the clinical comparison of DLd with BLd.

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 discussed the therapies commonly used in Australian clinical practice, and how daratumumab would be used under the proposed listing. The clinician also addressed other matters such as attrition by line of treatment and the need for new and effective therapies in patients aged ≥ 75 years of age who were unlikely to receive a transplant, and the expected and manageable adverse event profile associated with daratumumab. The PBAC considered that the hearing was informative as it provided a clinical perspective on the Australian treatment algorithm and the range of potential therapeutic interventions, and the factors considered regarding eligibility for transplant.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (100), health care professionals (3) and organisations (3) via the Consumer Comments facility on the PBS website. The comments by health care professionals described a range of benefits of treatment with daratumumab including the improvement in progression free survival without additional toxicities. The comments from individuals described the need for more effective treatments, such as daratumumab, in the first line setting. The

² O'Donnell EK, et al., (2019), Updated Results of a Phase 2 Study of Modified Lenalidomide, Bortezomib, and Dexamethasone (RVd-lite) in Transplant-Ineligible Multiple Myeloma, *Blood*, Volume 134, Supplement 1, p 3178.

³ ANZCTR. Anzctr.org.au. 2022 [cited 2022 Dec 2]. Available from:

<https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12619001199101>.

comments also noted that daratumumab was associated with improved disease control, few side effects and an improved quality of life.

- 6.3 The PBAC noted the advice received from Myeloma Australia, Myeloma Australia's Medical and Scientific Advisory Group (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 progression free survival, overall survival 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 submission. Two of the organisations (Myeloma Australia, and MSAG) differentiated between BLd and Ld in terms of efficacy, noting that BLd is highly effective at recommended doses, and noting that patients in the transplant ineligible group are frequently unable to tolerate the recommended doses which may compromise efficacy.

Clinical trials

- 6.4 The submission was based on 2 open-label, phase 3, head-to-head randomised controlled trials (RCTs):
- MAIA 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).
- 6.5 Both trials enrolled adult patients with NDMM with a presence of CRAB (calcium elevation, renal insufficiency, anaemia and bone abnormalities) and measurable disease. Randomisation in MAIA was stratified by International Staging System (ISS) (I vs II vs III), region (North America vs Other), and age (<75 vs ≥75) whereas SWOG s0777 stratified based on ISS stage (I, II, or III) and intent to transplant (yes vs no). MAIA enrolled patients that were not considered eligible for transplant (determined by age ≥ 65, or < 65 years with presence of important comorbid conditions, for example unstable angina or congestive heart failure), and SWOG s0777 enrolled patients without intent for immediate transplant (either based on the patients' decision, or due to transplant ineligibility). The submission stated that SWOG s0777 enrolled a broader population that included patients who were potentially candidates for transplant and therefore, an ITC informed by the data from the ITT populations of MAIA and SWOG s0777 would be biased against DLd (discussed in paragraph 6.21). The submission presented the results of a subgroup of patients ≥ 65 years of age from SWOG s0777, which it claimed more accurately represented the target population. However, the choice of a subgroup of patients from SWOG s0777 to improve comparability with MAIA does not overcome the issue that patients included in MAIA might have also been eligible for transplant. Transplant eligibility within the Australian setting is determined by various factors, including age, comorbidities, frailty and disabilities. In this regard, the MSAG guidelines (2022) state: "The traditional notion that patients aged above 65 years are ineligible for transplant is no longer appropriate

as it is clear that older patients who are biologically fit do benefit from intensive treatment. In assessing eligibility for transplant (generally in patients aged up to 70 years), individual assessment that takes into consideration the patient's age, comorbidities, frailty and disability is required". Therefore, some patients aged ≥ 65 years within MAIA may have also been considered eligible for transplant in local clinical practice. The PSCR maintained that MAIA was applicable to the Australian TI NDMM setting and noted that of the 322 patients who received a subsequent therapy in MAIA, only 9 received a stem cell transplant (2.8%). The PSCR also maintained that the submission's approach which utilised a cut-off of 65 years to identify a subgroup of patients from SWOG s0777, provided an appropriate comparison because it captured a "vastly" TI population. Based on analysis of the PBS 10% sample, the PSCR suggested that 91.2% of TI NDMM patients were aged over 65 years, and the remaining 8.8% were aged 36-65 years (PSCR Figure 1). The ESC considered that the 'no transplant' subgroup in the Durie 2020 analysis best reflected the TI NDMM Australian population as these patients did not receive a transplant (see paragraph 6.17).

- 6.6 In reviewing the application for BLd in August 2019, the PBAC noted that SWOG s0777 did not specifically restrict recruitment to patients considered ineligible for transplant and that a number of patients received high dose chemotherapy/transplant as the first subsequent antimyeloma therapy. However, in 2019 the PBAC considered this to be consistent with clinical practice as a patient's suitability for a transplant can change following treatment (paragraph 2.9, lenalidomide PSD, August 2019 PBAC meeting).
- 6.7 The submission provided an unpublished subgroup analysis of the ≥ 65 year age group of patients in SWOG s0777 using data provided by the NCTN/NCORP Data Archive. The median follow-up time from that subgroup (55 months) aligned with that from the Durie et al 2017 publication (previously considered by the PBAC in August 2019). However, a more recent publication by Durie et al. in 2020 provided in the submission had a median follow-up of 84 months and presented results for the ITT, the subgroup of patients ≥ 65 years, and for that subgroup of patients who did not go on to receive a transplant. A comparison of results of the submission's analysis after 55 months of follow-up and the Durie et al. 2020 analysis after 84 months of follow-up is presented in paragraph 6.18.
- 6.8 The submission considered an ITC between DLd and BLd was not required, because a statistically significant difference was not demonstrated between BLd and Ld in the ≥ 65 year-old subgroup from SWOG s0777. This claim was poorly justified and is discussed in paragraph 6.22.
- 6.9 A listing of the trials presented in the submission is provided in Table 2.

Table 2: Trials and associated reports presented in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
MAIA	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	<i>Leukemia</i> , 2022, 36.4: 1066-1077.
	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	<i>Journal of Clinical Oncology</i> , 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	<i>Blood</i> , 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	<i>Oncology Research and Treatment</i> , 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	<i>2nd European Myeloma Network (EMN) Meeting</i> ; 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	<i>Journal of Clinical Oncology</i> , 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)	<i>Clinical Lymphoma, Myeloma and Leukemia</i> , 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	<i>Clinical Lymphoma, Myeloma and Leukemia</i> , 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	<i>The Lancet Oncology</i> , 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	<i>Blood</i> , 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	<i>Blood</i> , 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	<i>New England Journal of Medicine</i> , 2019, 380.22: 2104-2115.

Trial ID	Protocol title/ Publication title	Publication citation
	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)	<i>Blood</i> , 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).	<i>Blood cancer journal</i> , 2020, 10.5: 1-11.
	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	<i>The Lancet</i> , 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.	<i>Blood</i> , 2015, 126.23: 25.

Source: Table 2.7, p85 of the submission.

6.10 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
DLd vs Ld						
MAIA (ITT)	737	R, MC, OL 64.5 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
BLd vs Ld						
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 2.23, p131, Table 2.24, p134 of the submission. Text from p134-136 of the submission.

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.

Comparative effectiveness

MAIA: DLd versus Ld

6.11 A summary of the efficacy results for PFS and OS from the ITT population in MAIA is presented in Table 4 with the corresponding Kaplan Meier (KM) curves presented in Figure 1 and Figure 2. After a median follow-up of 64.5 months, significantly fewer deaths were observed in the DLd group (132/368; 35.9%) than in the Ld group

(176/369; 47.7%) (HR = 0.66; 95% CI: 0.53, 0.83; p < 0.0003) with a 45% reduction in the risk of progressive disease (HR = 0.55; 95% CI: 0.45, 0.67; p < 0.0001).

Table 4: Results of overall survival and progression free survival (MAIA, ITT population).

	DLd (N= 368)	Ld (N= 369)
Median follow-up (months)	64.5	
PFS		
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 ^a	< 0.0001	
Hazard ratio (95% CI) ^b	0.55 (0.45, 0.67)	
OS		
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 ^a	0.0003	
Hazard ratio (95% CI) ^b	0.66 (0.53, 0.83)	

Source: Table 2.27, p146 and Table 2.25, p142 of the submission.

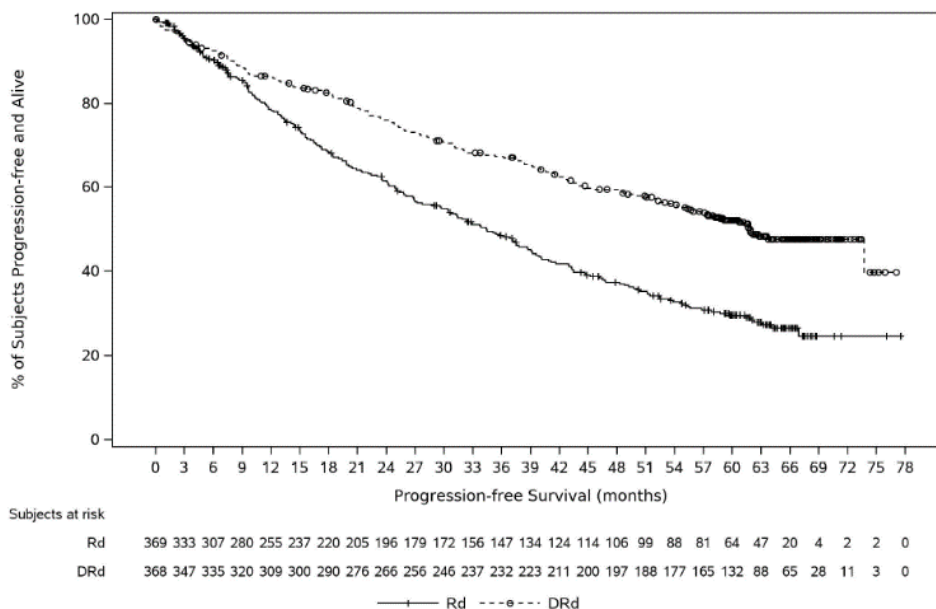
CI= confidence interval; DLd= daratumumab, lenalidomide, dexamethasone; ITT= intention to treat; Ld= lenalidomide, dexamethasone; N= total participants in group; NE= not estimable; PFS= progression free survival; OS= overall survival.

^a 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.

^b 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.

Figure 1: Kaplan-Meier curves for progression free survival (MAIA ITT population).



Source: Figure 2.5, p143 of the submission.

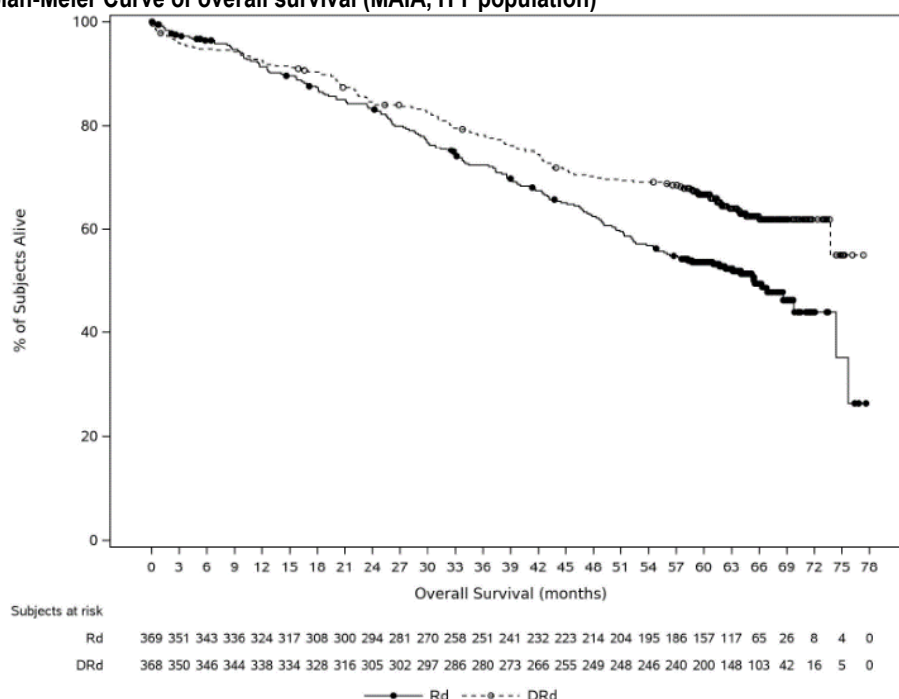
DLd= daratumumab, lenalidomide, dexamethasone; ITT= intention to treat; Rd= lenalidomide, dexamethasone.

6.12 For PFS, the superior treatment effect for DLd over Ld was consistent across subgroups, including age ≥ 75 years, with the exception of patients with impaired hepatic function at baseline (HR = 0.99; 95% CI: 0.51, 1.91) for whom there was no

significant treatment effect. However, the submission noted that the interpretation of the result for patients with impaired hepatic function was limited by the small sample size (31 and 29 patients in the DLd and Ld arms, respectively) and differences in cytogenetic risk categories between arms at study entry (20.0% of patients with hepatic impairment in the DLd arm had high-risk cytogenetic features compared with 7.4% in the Ld arm; p31 of the CSR 2022).

- 6.13 Although results of the subgroup analyses presented in the submission of OS indicated that the treatment effect of DLd for patients ≥ 75 years was not statistically significant when compared to Ld after a median follow up of 64.5 (HR = 0.75; 95% CI: 0.55, 1.02), the pre-PBAC presented results from Kumar et al (2022) which were statistically significant for this population at a median follow up of 73.6 months (HR = 0.67; 95% CI: 0.50, 0.90)⁴. Other subgroup analyses showed generally consistent results for OS with the ITT population. However, similar to PFS, when OS among the subgroup of patients with impaired hepatic function at baseline was analysed, the treatment effect for DLd was not statistically significantly different from Ld, noting the small patient numbers and wide confidence intervals (HR = 1.23; 95% CI: 0.57, 2.63).

Figure 2: Kaplan-Meier Curve of overall survival (MAIA, ITT population)



Source: Figure 2.7, p147 of the submission.

DRd= daratumumab, lenalidomide, dexamethasone; ITT= intention to treat; Rd= lenalidomide, dexamethasone.

⁴ Kumar et al. (2022). Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of the Phase 3 MAIA Study. ASH conference, December 2022.

6.14 The overall response rate (ORR) after a median follow-up of 64.5 months was statistically significantly higher in patients treated with DLd compared with Ld (92.9% vs 81.6%; OR = 3.00; 95% CI: 1.85, 4.86; $p < 0.0001$; see Table 5). ORRs were consistent across the analysed subgroups (including age)⁵ and the ITT population, with the exception of ECOG performance score ≥ 2 , where the OR favoured Ld but was not statistically significant (OR = 0.78; 95% CI: 0.31, 1.96). This has implications for the anticipated benefit from PBS listing of DLd, compared with Ld, given that a higher proportion of TI NDMM patients in Australia are of ECOG ≥ 2 compared to those in MAIA (MRDR: ECOG ≥ 2 = 27.8%; ITT population in MAIA: ECOG ≥ 2 = 16.6%).

Table 5: Overall response rate (MAIA, ITT population).

	DLd (N= 368)	Ld (N= 369)	Odds Ratio (95% CI)^a	P-value^b
Response category, % (95% CI)				
Stringent complete response (sCR)	35.6 (30.7, 40.7)	15.7 (12.2, 19.8)	2.98 (2.09, 4.24)	<0.0001
Complete response (CR)	15.5 (11.9, 19.6)	14.4 (10.9, 18.4)	NR	NR
Very good partial response (VGPR)	30.4 (25.8, 35.4)	26.8 (22.4, 31.7)	NR	NR
Partial response (PR)	11.4 (8.4, 15.1)	24.7 (20.3, 29.4)	NR	NR
Stable disease (SD)	3.0 (1.5, 5.3)	14.9 (11.4, 19.0)	NR	NR
Progressive disease (PD)	0.3 (0.0, 1.5)	0 (NE, NE)	NR	NR
Not evaluable (NE)	3.8 (2.1, 6.3)	3.5 (1.9, 5.9)	NR	NR
Overall response rate (sCR+CR+VGPR+PR)	92.9 (89.8, 95.3)	81.6 (77.2, 85.4)	3.00 (1.85, 4.86)	<0.0001
VGPR or better (sCR + CR + VGPR)	81.5 (77.2, 85.4)	56.9 (51.7, 62.0)	3.40 (2.42, 4.77)	<0.0001
CR or better (sCR + CR)	51.1 (45.9, 56.3)	30.1 (25.4, 35.0)	2.44 (1.80, 3.30)	<0.0001

Source: Table 2.29, p 149 of the submission.

CI= confidence interval; DLd= daratumumab, lenalidomide, dexamethasone; Ld= lenalidomide, dexamethasone; NE= not estimable; NR= not reported.

^a Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥ 75 years) as randomized. An odds ratio > 1 indicates an advantage for DLd.

^b P-value from the Cochran Mantel-Haenszel Chi-Squared test.

Response was assessed by computerised algorithm, based on International Uniform Response Criteria Consensus Recommendations. Percentages are calculated with the number of patients in each group as the denominator.

Bold text indicates statistically significant results.

6.15 The submission reported that functional status and well-being in MAIA were assessed by the EORTC-QLQ-C30 and the EQ-5D-5L. In both treatment groups, the compliance rates at baseline exceeded 90% and were greater than 70% during the treatment phase through cycle 60. The EORTC-QLQ-C30 global health status score demonstrated a statistically significant difference at one timepoint, Cycle 12, with a least squared mean difference of 0.05 (95% CI: 0.01, 0.09; $p = 0.0178$) favouring DLd over Ld however the difference in global health status at cycle 12 was not sustained over time. All other measurements from Cycle 3 to Cycle 66 were non-significant but numerically favoured the DLd group, with most differences ranging from 0.01 to 0.03. Similarly, a statistically significant difference in utility values between groups measured through the EQ-5D-5L was only observed at Cycle 42 (LS mean change: DLd = 0.11; 95% CI:

⁵ Subgroup analyses included sex, age, race, region, renal function, hepatic function, ISS staging, type of MM (IgG or Non-IgG), cytogenetic risk, and ECOG performance score (Table TEFRESPO1A, p 226, MAIA Oct21 CSR)

0.09, 0.14, Ld = 0.06; 95% CI: 0.03, 0.10; p = 0.0178). No minimum clinically important difference (MCID) for the EQ-5D-5L was stated in the submission, however the mean change in scores between baseline and treatment endpoint (0.07 [-0.00, 0.14]) was smaller than the minimum clinically important differences published for EQ-5D-5L in the literature, which range from 0.072 to 0.101⁶.

- 6.16 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 evaluation were sourced from the EQ-5D-5L as reported from MAIA. The submission applied utility values based on disease progression states (progression free or progressed) which were independent of the treatment received; this was reasonable.

SWOG s0777 results

- 6.17 The primary outcome data reported in SWOG s0777 are presented in Table 6 and the KM estimates are provided in Figure 3 and Figure 4. The adjusted HR estimates are from weighted Cox regression models, adjusted for age, sex, ISS stage, ECOG PS and various baseline laboratory values, as described in the notes to Table 6. Similarly, Durie 2020 used a stratified Cox proportional-hazard model according to the factors used for randomisation (ISS (I, II, or III) and intent to transplant [yes vs no]). All presented HRs are adjusted by these factors unless otherwise stated. The ESC considered that the 'no transplant' subgroup in the Durie 2020 analysis best reflected the TI NDMM Australian population as these patients did not receive a transplant. In these patients, BLd demonstrated a statistically significant improvement over Ld for both PFS and OS (Table 6), unlike the subgroup of patients aged ≥ 65 years that the submission proposed was most relevant.
- 6.18 After a median follow-up of 55 months, BLd achieved a statistically significant improvement in PFS compared with Ld in patients < 65 years (HR = 0.61; 95% CI: 0.45, 0.84; p < 0.05). However, BLd did not result in a statistically significant improvement in PFS compared with Ld in patients aged ≥ 65 years (HR = 0.90; 95% CI: 0.65, 1.26; p > 0.05). The ESC noted that for the 'no transplant' subgroup reported in Durie 2020, BLd demonstrated a statistically significant improvement over Ld after 84 months follow-up (HR = 0.74; 95% CI: 0.55, 0.98). Results for PFS were not reported for the 84-month (Durie 2020) follow-up for patients aged ≥ 65 years).
- 6.19 At the median follow-up of 55-months, BLd resulted in a statistically significant improvement of OS in patients < 65 years of age (HR = 0.62; 95% CI: 0.39, 0.99; p < 0.05) compared to Ld but did not result in a statistically significant difference in patients ≥ 65 years (HR = 0.88; 95% CI: 0.59, 1.31; p > 0.05). The ESC noted that there was a

⁶ Henry, EB, Barry, LE, Hobbins, AP, McClure, NS & O'Neill, C 2020, 'Estimation of an Instrument-Defined Minimally Important Difference in EQ-5D-5L Index Scores Based on Scoring Algorithms Derived Using the EQ-VT Version 2 Valuation Protocols', Value Health, vol. 23, no. 7, Jul, pp. 936-944.

statistically significant improvement in BLd over Ld in the ‘no transplant subgroup after 84-months follow-up (HR = 0.63; 95% CI: 0.45, 0.89) and a numerical improvement in the HR based on the 84-month follow-up in the ≥ 65 subgroup (HR = 0.77; 95% CI: 0.52, 1.14). The ITT analysis showed that BLd patients had significantly longer OS than those treated with Ld (HR = 0.71; 95% CI: 0.52, 0.96; see Table 6, Figure 3 and Figure 4).

Table 6: Progression free survival and overall survival in (SWOG s0777, ITT and subgroups).

	Primary Analysis Follow-up: 55 months						Extended follow-up: 84 months (Durie 2020)			
	ITT (n= 471)		Age < 65 years (n= 269)		Age ≥ 65 years (n= 202)		Age ≥ 65 years (n= 197)		“No Transplant” (n= 299)	
	BLd	Ld	BLd	Ld	BLd	Ld	BLd	Ld	BLd	Ld
N	242	229	149	120	93	109	91	106	157	142
PFS										
Number of events	137	166	NR	NR	NR	NR	NR	NR	105	111
Median (months)	43.0	30.0	55.4	36.6	33.1	25.8	NR	NR	NR	NR
p-value	p= 0.0037		NR		NR		NR		NR	
Hazard ratio (95% CI)	0.71 (0.56, 0.91)		0.63 (0.46, 0.87)		0.83 (0.60, 1.16)		NR		NR	
Test for interaction of Treatment and age, p= 0.237							NR		NR	
Adjusted hazard ratio (95% CI)	NE		0.61 (0.45, 0.84)		0.90 (0.65, 1.26)		NR		0.74 (0.55, 0.98)	
Test for interaction of Treatment and age, p= 0.093							NR		NR	
OS										
Number of events	76	100	NR	NR	NR	NR	54	68	72	86
Median (months)	75.0	64.0	NR	68.9	62.9	53.0	65	56	NR	NR
p-value	P= 0.025		-		-		p=0.168		NR	
Hazard ratio (95% CI)	0.71 (0.52, 0.96)		0.61 (0.39, 0.97)		0.83 (0.55, 1.23) ^a		NR		NR	
Test for interaction of Treatment and age, p= 0.334							NR		NR	
Adjusted hazard ratio (95% CI)	NE		0.62 (0.39, 0.99)		0.88 (0.59, 1.31)		0.77 (0.52, 1.14)		0.63 (0.45, 0.89)	
Test for interaction of Treatment and age, p= 0.270							NR		NR	

Source: Table 2.49, p183 and Table 2.50, p186 of the submission. Durie 2020.

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.

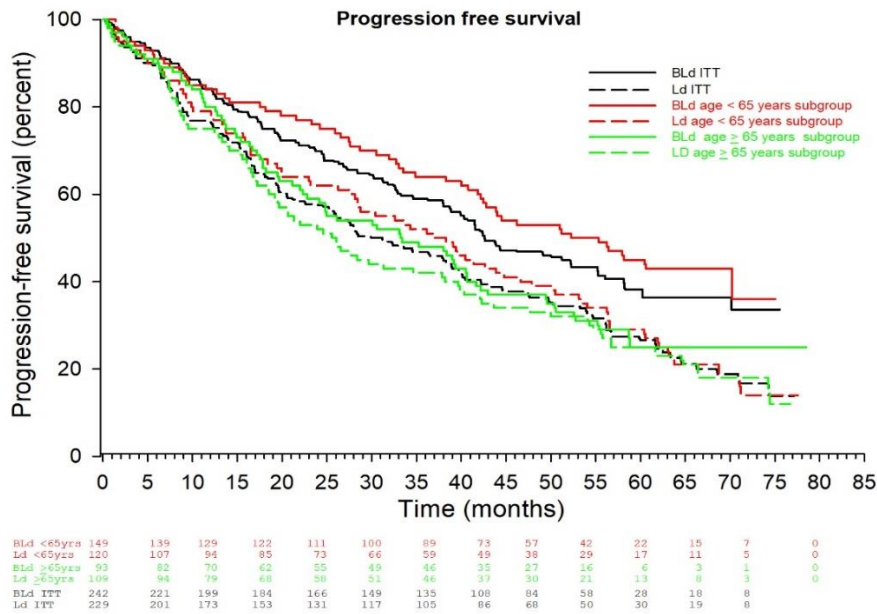
^a At a median follow-up of 84 months, Durie 2020 reported a HR=0.77 (95% CI= 0.52, 1.14) for the subgroup ≥65 years.

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 inverse-probability-of-treatment weighting (IPTW).

Bold text indicates statistically significant results.

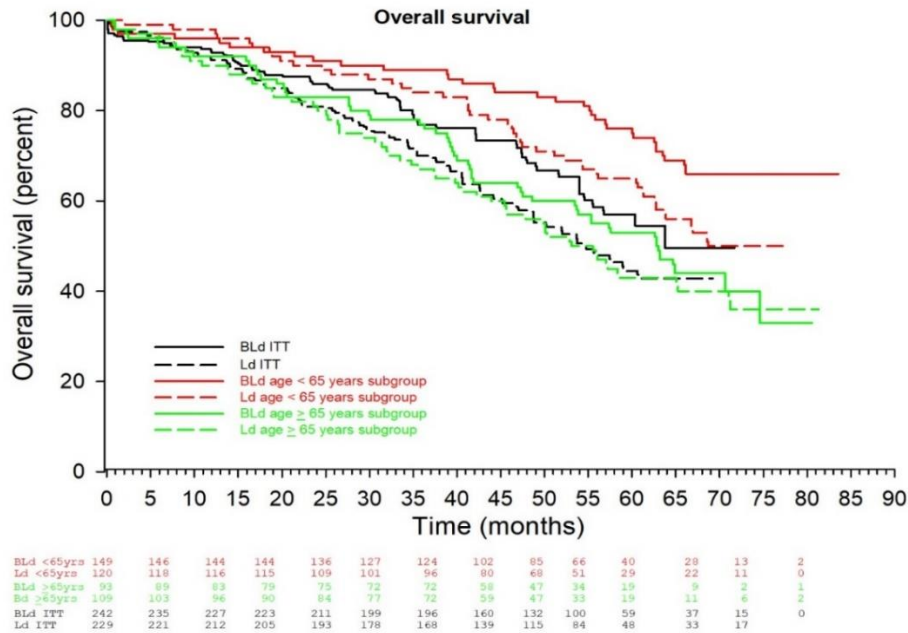
Figure 3: Kaplan-Meier curves of progression free survival (SWOG s0777, ITT and subgroups, primary analysis follow-up 55 months)



Source: Figure 2.14, p184 of the submission.

BLd= bortezomib, lenalidomide, dexamethasone; Ld= lenalidomide, dexamethasone; ITT= intention to treat; CI= confidence interval.

Figure 4: Kaplan-Meier curves of overall survival (SWOG s0777, ITT and subgroups, primary analysis follow-up 55 months).



Source: Figure 2.15, p187 of the submission.

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

6.20 In the ITT population, the overall response rate (CR + VGPR + PR) was higher in patients treated with BLd compared to Ld (81.5% vs 71.5%). More patients treated with BLd achieved a complete response (CR) compared with those treated with Ld (15.7% vs

8.4%). Consistent with the difference reported in the ITT population, patients in the subgroup aged ≥ 65 years receiving Bld had a higher ORR than those treated with Ld.

Table 7: Overall response rate (SWOG s0777, ITT and subgroups, primary analysis follow-up 55 months)

	ITT				Age < 65 years		Age ≥ 65 years	
	Bld (N=242)	Ld (N=229)	OR (95% CI) ^a	P- value ^b	Bld (N=149)	Ld (N=120)	Bld (N=93)	Ld (N=109)
Data missing	26 (10.7%)	15 (6.6%)	-	-	14 (9.4%)	9 (7.5%)	12 (12.9%)	6 (5.5%)
Response category, n (%)								
CR	34 (15.7%)	18 (8.4%)	2.03 (1.11, 3.72)	0.02	14.0%	11.0%	19.0%	6.0%
VGPR	60 (27.8%)	50 (23.4%)	1.26 (0.82, 1.95)	NR	25.0%	23.0%	32.0%	23.0%
PR	82 (38.0%)	85 (39.7%)	0.93 (0.63, 1.37)	NR	43.0%	34.0%	29.0%	47.0%
SD	34 (15.7%)	52 (24.3%)	0.58 (0.36, 0.94)	NR	NE	NE	NE	NE
PD or death	6 (2.8%)	9 (4.2%)	0.65 (0.23, 1.86)	NR	NE	NE	NE	NE
ORR (CR+VGPR+PR)	176 (81.5%)	153 (71.5%)	1.75 (1.11, 2.76)	NR	82.0%	68.0%	80.0%	76.0%
VGPR or better (CR + VGPR)	94 (43.5%)	68 (31.8%)	1.65 (1.11, 2.45)	NR	39.0%	34.0%	51.0%	29.0%
CR or better	34 (15.7%)	18 (8.4%)	2.03 (1.11, 3.72)	NR	14.0%	11.0%	19.0%	6.0%

Source: Table 2.51, p189 of the submission.

CI=confidence interval; CR=complete response; DLd=daratumumab, lenalidomide, dexamethasone; Ld=lenalidomide, dexamethasone; NE=not estimable; OR= odds ratio; ORR = overall response rate; PD= progressive diseases; PR= partial response; SD= stable diseases; VGPR= very good partial response.

a ORs were estimated for the ITT population based on assessable patients (Durie 2017). The submission did not provide the OR for subgroups.

b The statistical analysis used to derive the p-value was not reported by Durie 2017.

Bold indicates statistically significant difference.

Efficacy claim based on transitivity of results

6.21 The submission argued that an ITC between the ITT populations of MAIA and SWOG s0777 would be biased against daratumumab, as SWOG s0777 enrolled patients who may have been physiologically eligible for SCT whilst MAIA did not. To overcome this transitivity issue, the submission claimed that the age ≥ 65 subgroup of SWOG s0777 more accurately captured those patients who are transplant ineligible. The submission claimed that since a statistically significant difference was not demonstrated between Bld and Ld in the age ≥ 65 subgroup of SWOG s0777 for either PFS or OS, the efficacy of Bld in the TI NDMM population was reasonably represented by the efficacy of Ld in the ≥ 65 subgroup in MAIA. Therefore, the submission argued that an anchored ITC of results from MAIA and SWOG s0777 (DLd versus Bld using Ld as an anchor) was not required, and instead the results of MAIA alone (DLd versus Ld) were a reasonable proxy for a comparison of DLd versus Bld. To further support this argument, the PSCR presented a poster of Australian and New Zealand real-world data from the MRDR

(Zhao et al, 2022)⁷ which concluded that there were no differences in PFS and OS between BLd, Ld or BCd. The ESC noted that this information was in the form of a non-peer reviewed, retrospective study and that the BLd and Ld arms were unbalanced in terms of size (BLd = 102 patients, Ld = 232 patients), follow-up (BLd = 11.3 months, Ld = approximately 28 months) and ECOG status (ECOG 0-1: BLd = 78.8%, Ld = 69.7%). In addition, the ESC noted that the reported hazard ratio for OS comparing Ld to BLd favoured BLd (HR = 1.22; 95% CI: 0.61, 2.44) and that the confidence interval was wide (i.e. patients treated with Ld may have more than twice the rate of death compared with patients treated with BLd).

6.22 The ESC considered that the submission's claim that the results for Ld serve as a reasonable proxy for BLd, and, by transitivity, that the results from MAIA show that DLd is superior to Ld and therefore BLd, was not supported by the evidence because:

- Using age (over 65 years) as the only basis to determine transplant eligibility in order to form a comparison with the results from MAIA may not be reasonable as age alone is not the only criterion applied in deciding on suitability for transplant (discussed in paragraph 6.5).
- That SWOG s0777 was unable to demonstrate a statistically significant difference in the ≥ 65 years of age subgroup of patients does not necessarily establish non-inferiority of BLd versus Ld, unless the study was appropriately powered to detect a difference in this population; while the OS HR favoured BLd over Ld, the confidence intervals were wide (HR=0.77; 95%CI 0.52, 1.14; two-sided p=0.17).
- The longer-term follow-up of SWOG s0777 (Durie et. al. 2020) provided efficacy data on the subpopulation which did not go on to have a transplant (distinct from the population for which there was no intent to transplant, and likely to resemble more closely the TI NDMM population) and found BLd was statistically significantly superior to Ld in terms of PFS (HR= 0.74; 95% CI: 0.55, 0.98; p= 0.03) and OS (HR= 0.63; 95% CI: 0.45, 0.89).
- BLd was listed on the PBS on the basis of a CUA compared to Ld, where the PBAC noted that BLd is clinically superior to Ld (paragraph 7.5, lenalidomide PSD, August 2019 PBAC meeting). The pre-PBAC response stated that the conclusion that BLd was superior to Ld was in the broad NDMM setting, which included both transplant eligible and ineligible patients. The pre-PBAC response stated that there was an increasing body of evidence demonstrating that the efficacy of BLd and Ld was similar in the TI NDMM setting.

6.23 When the populations of MAIA and SWOG s0777 were compared, it was noted that patients in MAIA were older, the proportion of males and Caucasians was higher, a higher proportion of patients were in ISS III and had worse cytogenetics (see Table 8).

⁷ Zhao S, et al (2022) Real world comparison of treatment outcomes for myeloma in elderly transplant ineligible population with RVd, Rd and VCd in frontline setting: Results from MRDR Australia and New Zealand.

Despite these differences, an ITC using Ld as an anchor might be informative with respect to the comparative treatment effect between DLd and BLd.

Table 8: Baseline demographic and disease characteristics that may affect transitivity

	MAIA – ITT		SWOG s0777 – ITT		SWOG s0777: age < 65 subgroup		SWOG s0777: age ≥ 65 subgroup	
	DLd (N= 368)	Ld (N= 369)	BLd (N= 263)	Ld (N= 260)	BLd (N= 149)	Ld (N= 120)	BLd (N= 93)	Ld (N= 109)
Age								
Mean, years (SD)	74.0 (5.4)	74.2 (5.7)	NR	NR	56.1 (7.3)	55.2 (7.1)	73.2 (5.6)	72.2 (5.2)
Median	73.0	74.0	63.0	63.0	NR	NR	NR	NR
Range	(45; 89)	(50; 90)	(35; 85)	(28; 87)	NR	NR	NR	NR
≥ 65 years, %	98.9%	98.9%	38%	48%	0%	0%	100%	100%
Sex, n (%)								
Male, %	51.4%	52.8%	62.4%	52.7%	63%	50%	63%	57%
Race, %								
White	91.3%	91.9%	79.8%	79.6%	NR	NR	NR	NR
Black or African American	3.3%	4.3%	Non-Caucasian: 17.5%; Unknown: 2.7%	Non-Caucasian: 18.1%; Unknown: 2.3%	NR	NR	NR	NR
Asian	0.8%	0.5%			NR	NR	NR	NR
Others, unknown or not reported	4.6%	3.3%			NR	NR	NR	NR
Baseline ECOG score, n (%)								
0	127 (34.5%)	123 (33.3%)	106 (40.3%)	101 (38.8%)	42%	37%	39%	39%
1	178 (48.4%)	187 (50.7%)	128 (48.7%)	120 (46.2%)	45%	45%	53%	49%
≥2	63 (17.1%)	59 (16.0%)	29 (11.0%)	39 (15.0%)	13%	18%	9%	13%
Baseline ISS stage, n (%)								
I	98 (26.6%)	103 (27.9%)	78 (29.7%)	75 (28.8%)	34%	33%	22%	17%
II	163 (44.3%)	156 (42.3%)	99 (37.6%)	98 (37.7%)	36%	32%	42%	49%
III	107 (29.1%)	110 (29.8%)	86 (32.7%)	87 (33.5%)	30%	35%	37%	34%
Cytogenetic risk								
N	319	323	240	243	149	120	93	109
Standard	271 (85.0%)	279 (86.4%)	210 (87.5%)	207 (85.2%)	90%	91%	92%	90%
High	48 (15.0%)	44 (13.6%)	30 (12.5%)	36 (14.8%)	10%	9%	8%	10%

Source: Table 2.13, p110 of the submission, Table 2.14, p112 of the submission

BLd= bortezomib, lenalidomide, dexamethasone; BSA= body surface area; DLd= daratumumab, lenalidomide, dexamethasone; ECOG= the Eastern Cooperative Oncology Group; ISS = International Staging System; Ld= lenalidomide, dexamethasone; NR = not reported; SD= standard deviation.

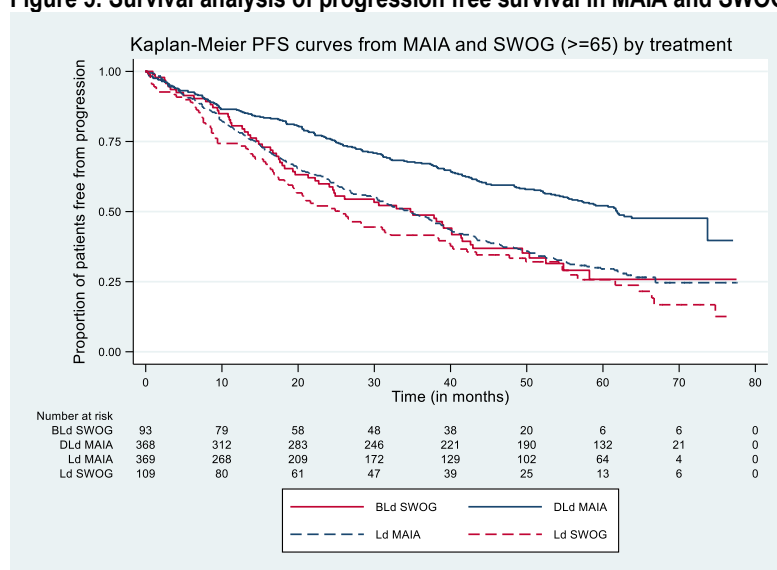
Indirect comparison conducted during the evaluation (DLd vs BLd)

6.24 A survival analysis was conducted during the evaluation to compare PFS and OS across the treatment groups for the ≥ 65 years of age subgroup from SWOG s0777 and from MAIA. Figures provided in the PSCR are presented below. The purpose of this analysis was to assess the comparability of the common reference group Ld by overlaying the outcome curves from the respective studies; a difference in Ld outcomes would support the submission's assertion that it would be inappropriate to conduct an ITC due to differences in the underlying patient populations.

6.25 The submission was concerned that an ITC would be unfairly biased against DLd due to SWOG s0777 enrolling a potentially healthier population. If this were the case, it

would be anticipated that the Ld arm in MAIA would be below that of the Ld arm in SWOG s0777, indicating poorer outcomes. Contrary to the submission's concern, the results of the survival analysis (Figure 5 and Figure 6) show that the Ld arm in MAIA is not below that of the Ld arm of the ≥ 65 years subgroup in SWOG s0777, in terms of PFS and OS. These results should be interpreted with caution because: SWOG s0777 was not powered to detect differences by age; and, because of the difference in inclusion criteria between the trials affects the extent to which they reflect the same population with respect to transplant eligibility and potentially their applicability to Australian clinical practice (which generally relies on more than age to determine transplant eligibility).

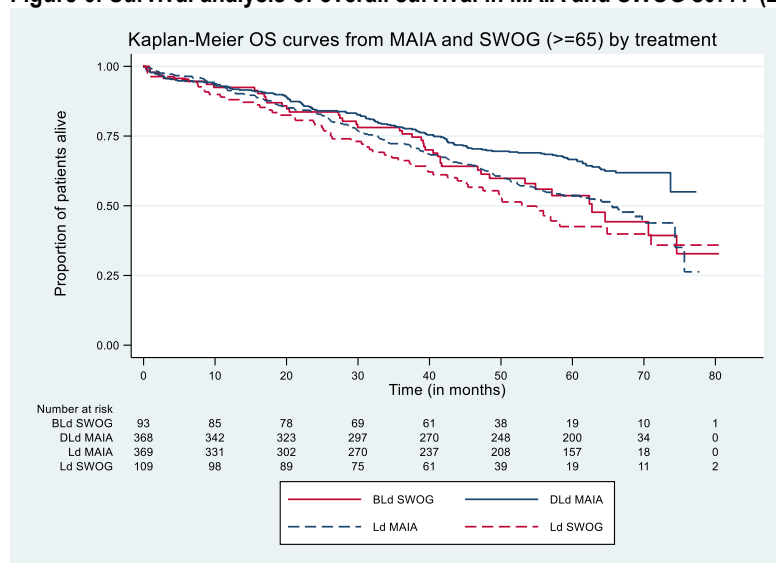
Figure 5: Survival analysis of progression free survival in MAIA and SWOG s0777 (≥ 65 years of age subgroup).



Source: Figure 3, p6 of the PSCR

BLd= bortezomib, lenalidomide, dexamethasone; DLd= daratumumab, lenalidomide, dexamethasone; Ld= lenalidomide, dexamethasone; PFS= progression free survival.

Figure 6: Survival analysis of overall survival in MAIA and SWOG s0777 (≥ 65 years of age subgroup).



Source: Figure 3, p6 of the PSCR

BLd= bortezomib, lenalidomide, dexamethasone; DLd= daratumumab, lenalidomide, dexamethasone; Ld= lenalidomide, dexamethasone; OS= overall survival.

6.26 During the evaluation, an anchored ITC was conducted comparing the ITT population of MAIA with the ITT, ≥ 65 years and the “No transplant” population in SWOG s0777 (as reported in Durie 2020, see paragraph 6.22), noting the potential for issues of transitivity across MAIA and SWOG s0777. The results of the ITC of DLd vs BLd (via an Ld common comparator) showed that, with the exception of PFS for MAIA-ITT compared with ≥ 65 years in SWOG s0777, a significant difference could not be demonstrated between DLd and BLd for PFS or OS, as shown in Table 9. The ESC considered that the comparison most applicable to the proposed PBS population was the comparison of MAIA ITT vs SWOG s0777 "No transplant" group and noted this did not demonstrate DLd to be superior to BLd, indeed the point estimate of the ITC of OS favoured BLd (HR=1.04; 95% CI: 0.70, 1.56).

Table 9: Indirect treatment comparison of MAIA (ITT) and subgroups of SWOG s0777.

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	0.61 (0.42, 0.90)	0.75 (0.47, 1.19)
MAIA ITT vs SWOG s0777 "No transplant"	0.75 (0.53, 1.06)	1.04 (0.70, 1.56)

Source: Table 2.27, p146, Table 2.25, p142, Table 2.49, p184, Table 2.50, p186 of the submission and figure 4b of Durie 2020.

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.

Assessment of differences between the trial setting and the Australian setting after listing

6.27 Australian patients with MM in the MRDR had similar demographic characteristics compared to those enrolled in MAIA, but some differences in terms of disease stage and health status were observed, mainly:

- Transplant eligibility criteria: Patients in the MRDR were presumably assessed according to local clinical guidelines where age, disabilities, frailty and

comorbidities are used to assess eligibility to transplant. In contrast, MAIA patients were primarily defined as transplant ineligible based on age alone (patients 65 and over were considered TI, while those under 65 may have been classified as TI in the presence of specific comorbidities). Thus, a proportion of patients in MAIA, particularly of those over 65 years of age, may have been considered transplant eligible in Australian practice. Therefore, it is expected that if listed, DLd may be used to treat Australian patients who are frailer with more comorbidities compared to MAIA patients.

- ECOG score: MRDR patients had higher (worse) ECOG scores compared with the ITT population in MAIA (MRDR-ECOG ≥ 2 = 27.8% and MAIA-ECOG ≥ 2 = 16.6%).
- MM type: A higher proportion of patients in the MRDR had light chain MM (one of the most common types of MM), associated with poorer prognosis when compared to the immunoglobulin (Ig) G or IgA variant (MRDR= 19.4% and MAIA= 11.4%).
- ISS stage: More patients in the MRDR were ISS stage III compared to those included in MAIA (MRDR= 39.6%, MAIA= 29.4%).

6.28 The poorer health state, worse severity of the disease and the greater prevalence of light chain MM (associated with poorer outcomes) in the Australian population, may result in a diminished treatment effect for DLd, if listed, compared to that reported in MAIA. A subgroup analysis in MAIA showed statistically significant results for PFS in ISS stage III but non-significant results in OS when ISS stage and ECOG performance status were analysed, and no subgroup analyses were conducted in MAIA to test the treatment effect associated with light chain MM type subgroups.

Comparative harms

6.29 A summary of the comparative harms for DLd vs Ld from MAIA after a median follow-up of 64.5 months is presented in Table 10. 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 the treatment and the total number of patients discontinuing at least one component of the treatment was higher for DLd than Ld (see “TEAE leading to discontinuation” in Table 10).

Table 10: 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) ^d	RD (95% CI) ^d
Safety analysis set	364	365	-	-
Summary of TEAEs				
Any TEAE	364 (100)	363 (99)	1.01 (1, 1.02)	0.01 (0, 0.01)
At least one related ^a	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 ^c	53 (15)	87 (24)	0.61 (0.45, 0.83)	-0.09 (-0.15, -0.04)
Most commonly reported (>5%) toxicity Grade 3 or 4 TEAEs				
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)
Common (≥2%) treatment-emergent SAEs.				
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 2.42, p167, Table 2.44, p173 and Table 2.45, p174 of the submission.

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.

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

^b COVID-19 associated AEs are based on events coded to a COVID-19 MedDRA preferred term, including COVID-19, COVID-19 pneumonia, suspected COVID-19, asymptomatic COVID-19 and SARS-COV-2 test positive.

^c 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".

^d Calculated during the evaluation. 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.

6.30 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 submission is provided in Table 11. Overall, the incidence of any grade TEAEs in the subgroup of patients aged ≥ 65 years was the same between the two groups.

Table 11: 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) ^a	RD (95% CI) ^a
Safety analysis set	241 (100)	226 (100)	NA	NA
Number of patients with 1 or more any 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)
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	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)
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)
SWOG s0777 Age <65 years				
Safety analysis set	149 (100)	119 (100)	NA	NA
Number of patients with 1 or more any 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)
SWOG s0777 Age ≥65 years				
Safety analysis set	92 (100)	107 (100)	NA	NA
Number of patients with 1 or more any 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 2.52, p191 of the submission.

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.

^a Calculated during the evaluation. 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.

Benefits/harms

6.31 A summary of the comparative benefits and harms for DLd versus Ld, based on data from the MAIA trial, is presented in Table 12.

Table 12: 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%)	-	0.55 (0.45, 0.67) P = 0.0001	
Median PFS, months (95% CI)	61.9 (54.8, NE)		34.4 (29.6, 39.2)	27.5		
% progression free at 12-month (95% CI)	86.5 (82.5, 89.6)		78.1 (73.3, 82.1)	8.4		
% progression free at 24-month (95% CI)	76.3 (71.5, 80.4)		61.1 (55.6, 66.1)	15.2		
% progression free at 36-month (95% CI)	67.4 (62.2, 72.0)		47.2 (41.6, 52.5)	20.2		
% progression free at 48-month (95% CI)	59.4 (54.1, 64.4)		36.3 (31.0, 41.6)	23.1		
% progression free 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 64.5 months)						
Deaths, n/N (%)	132 (35.9%)		176 (47.7%)	-	0.66 (0.53, 0.83) P = 0.0003	
Median OS, months (95% CI)	NE (73.72, NE)		65.54 (55.98, 75.66)	NE		
% 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		
Harms						
	DLd n/N	Ld n/N	RR (95% CI) ^a	Event rate/100 patients (DLd)	Event rate/100 patients (Ld)	RD (95% CI) ^a
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 submission.

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.

^a Calculated during the evaluation. 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.

6.32 On the basis of direct evidence presented by the submission, for every 100 patients treated with DLd in comparison with Ld, after 48 months:

- Approximately 23 additional patients will remain progression-free.
- Approximately 7 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 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

- 6.33 The submission described DLd as superior in terms of effectiveness and inferior in terms of safety compared to Ld. The PBAC agreed with ESC and considered that these claims were adequately supported.
- 6.34 The submission described DLd as superior in terms of effectiveness and at worst non-inferior in terms of safety compared to BLd. The ESC considered that the claim of superior efficacy was not supported as this relied on the treatment effects of Ld being non-inferior to BLd which was not supported by the evidence provided. The ESC considered that this justification was unreasonable as the absence of a statistically significant difference does not establish equivalent efficacy of BLd and Ld. The ESC noted that the PBAC has previously concluded that BLd is superior to Ld (paragraph 7.5, lenalidomide PSD, August 2019). In addition, results from an unadjusted, anchored ITC conducted during the evaluation did not demonstrate a statistically significant difference between DLd and BLd for the relevant ITT analyses or nominated subgroup comparisons. The PBAC considered that the claims of that DLd was superior in terms of efficacy and non-inferior in terms of safety compared to BLd were not adequately supported by the data.

Economic analysis

- 6.35 The submission presented a stepped economic evaluation, including a cost-utility analysis (CUA) based on the results from MAIA. A summary of the key components of the economic evaluation is presented in Table 13.

Table 13: 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 (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)
Perspective	Health care system perspective
Method used to generate results	Partitioned survival analysis model
Health states	Progression-free survival; Progressed disease; Time-to-treatment discontinuation ^a Dead
Cycle length	One month
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, p20 of the submission.

BLd = bortezomib, lenalidomide and dexamethasone; DLd = daratumumab, lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone; NDMM = newly diagnosed multiple myeloma; PBAC = Pharmaceutical Benefits Advisory Committee; SoC = standard of care; TI = transplant ineligible

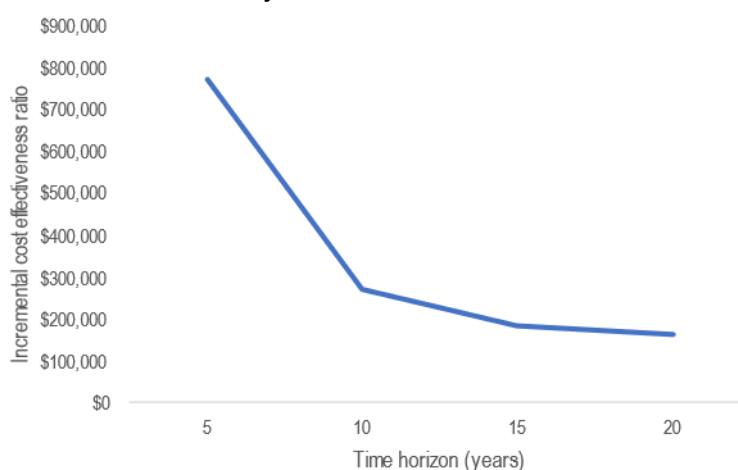
a. Noted during evaluation.

- 6.36 Daratumumab (in DLd) in the model comprised use of both the IV and SC formulations given that the submission requests listing of both the IV and SC forms. The submission stated that the price of the IV and SC formulations of daratumumab in the model was the same as their prices for treatment of RRMM (in DBd). However, the ESC noted that the submission's economic model assumed the net cost of daratumumab to be 1% lower than the effective price when daratumumab was used in the post-progression health state (consistent with the agreed RSA), but did not assume the same when daratumumab was used in the proposed first line population (nil reduction was assumed). As such, the submission applied a higher price for daratumumab in the proposed first line setting compared with that considered by the PBAC to be cost-effective for daratumumab in RRMM (see paragraph 3.1).
- 6.37 The price of SC daratumumab was derived from a cost-minimisation approach with the IV formulation at the recommended equi-effective doses of 1,800 mg daratumumab SC to 1,200 mg daratumumab IV (paragraph 7.3, daratumumab PSD, July 2021 PBAC meeting). In the model, the estimate of cost per dose of IV daratumumab was based on the distribution of patient weight in the DLd arm of MAIA resulting in use of 1,250 mg per IV administration. Based on this the submission estimated the use of 1.49 x 100 mg vials and 2.75 x 400 mg vials to achieve the dose of 1,250 mg per IV administration. For SC daratumumab, a flat-dose as used in MAIA of 1,800 mg per administration irrespective of weight was used in the model. The dose of 1,250 mg estimated for IV administration in this submission was slightly higher than of IV daratumumab in RRMM of 1,200 mg. This results in a cost per administration of

- IV that is higher than SC; the submission has not proposed a new price for the SC formulation based on the increased use of the IV formulation in this setting (i.e., it is maintaining the established relativity of 1,800 mg SC = 1,200 mg IV).
- 6.38 SoC in the model comprised BLd and Ld, weighted according to the proportion of use of each regimen in patients with TI NDMM in the MRDR, of 68% for BLd and 32% for Ld. Efficacy for SoC was informed by the Ld arm in MAIA. As noted in the clinical claim section, while the clinical evidence supported the claim of superiority for DLd compared with Ld - and hence a cost-effectiveness analysis for this comparison - it does not support the superiority of DLd compared with BLd. The model assumed that Ld was a proxy for BLd and did not include any BLd specific efficacy data, relying solely on the efficacy data from the Ld arm of MAIA to inform the outcomes for SoC. The ESC considered that this was not appropriate. In addition, BLd was listed on the PBS on the basis of a CUA compared to Ld, where the PBAC noted that BLd is clinically superior to Ld (paragraph 7.5, lenalidomide PSD, August 2019 PBAC meeting). In contrast, the costs applied included those associated with Ld, and the more expensive costs of BLd. The combined effect of including outcomes for Ld only, but costs for both Ld and BLd biased the comparative economic analysis in favour of DLd.
- 6.39 At its July 2021 meeting the PBAC considered an application for selinexor in RRMM which presented a weighted economic evaluation, comprising a cost-utility analysis (comparing selinexor plus bortezomib and dexamethasone with bortezomib and dexamethasone) and cost-minimisation analysis (comparing selinexor plus bortezomib and dexamethasone with carfilzomib and dexamethasone). In making its recommendation, "the PBAC considered that the weighted approach was not appropriate in the absence of a defined patient population receiving either comparator" (paragraph 7.12, selinexor PSD, July 2021 PBAC meeting). In this case, the ESC considered that a weighted approach to estimating the cost-effectiveness of DLd in TI NDMM, may be applicable given that it may be reasonable to define patient populations based of the proportions that receive triplet (i.e., BLd) or doublet (i.e., Ld) regimens. The ESC noted that the available clinical evidence may support a combined analysis approach comprising a cost-effectiveness analysis for the comparison of DLd with Ld and a cost-minimisation approach for the comparison of DLd with BLd.
- 6.40 The ESC considered that the time horizon of 20 years was overly long given the population entering the model had an average age of 74 years. In its consideration of BLd for treatment of TI NDMM, the PBAC preferred a time horizon of 15 years (paragraph 7.9, lenalidomide PSD, August 2019 PBAC meeting). Furthermore, patients entering the BLd economic model were younger than the population entering the DLd model (63 years vs 74 years respectively). A summary of the ICER per QALY gained when the time horizon was varied is presented in Figure 7. The PSCR noted that as a 15 year time horizon was accepted by the PBAC for DBd in the second line setting, it would be reasonable to expect a longer time horizon in the first line setting, and thus, a time horizon of 20 years was appropriate. The ESC noted however, that the average age of patients entering the DBd model was 63.5 years (paragraph 6.37,

Daratumumab PSD, November 2019 PBAC meeting) compared to 74 years in the DLd model. The ESC considered that a 15 year time horizon would be reasonable for the TI NDMM Australian population. The pre-PBAC response stated that DLd resulted in significant improvements in OS and that a 20 year time horizon was required to appropriately capture the expected survival of patients treated with DLd, noting that approximately 15% of patients were modelled to remain alive at 15 years.

Figure 7: Incremental cost effectiveness ratio by time horizon

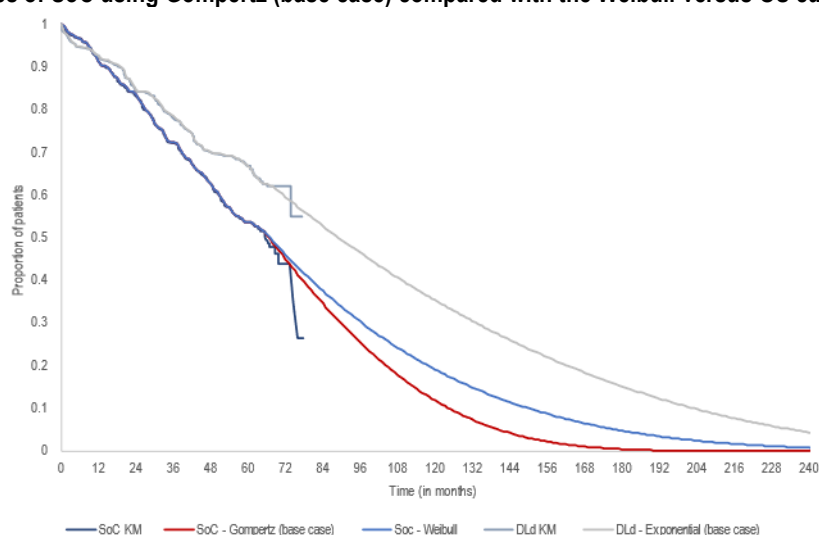


Source: Compiled during the evaluation using the information from the economic model of the submission.

- 6.41 The KM data from MAIA were applied in the model for OS, PFS, and TTD of DLd and SoC up to the time point representing median follow-up (approximately 66 months). The submission then applied parametric functions to these outcomes after the period for which KM data were available (post 66 months). Based on visual inspection of the plot of the Schoenfeld residuals and log-log plot hazards, the submission found the proportional hazards assumption for OS between DLd and SoC (Ld) to be violated, which it claimed supported the use of independent parametric functions for OS. The submission stated that the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were used to decide which distribution models best fit the data for the purposes of extrapolation beyond 66 months (out to month 240). This resulted in the application of the exponential function to the OS curve in the DLd arm and the Gompertz function to the OS curve in the SoC arm. The exponential function was applied to the PFS and TTD curves for both the DLd and SoC arms. The ESC considered that the application of the exponential function to the PFS and TTD curves in both the DLd and SoC arms appeared reasonable.
- 6.42 The application of the Gompertz function to the OS curve in the SOC arm resulted in the most pessimistic estimate of survival for SoC. Compared to the DLd arm (exponential function), the ESC noted that the decline in OS in the Ld arm over the extrapolation period (i.e., beyond the median point of follow-up in MAIA, 66 months) appeared to occur at an accelerated rate, converging to zero at approximately month 180 (see Figure 8). In addition, this rapid rate of decline in OS during the extrapolation period for the Ld arm results in the OS curve converging with the PFS curve at

approximately 144 months (see Figure 9) which was not adequately justified by the submission. The application of the Weibull function (see Figure 8 ; next best fit in terms of AIC and BIC) appeared to provide a more consistent rate of decline in OS between the Kaplan Meier data and the extrapolated portion. The PSCR reiterated that the Gompertz function was the best statistical fit to the Ld Kaplan Meier data. The ESC noted that although the use of fit statistics helped to inform the choice of appropriate parametric curves to fit the data during the trial time, it does not necessarily indicate that the curves are appropriate beyond the trial duration. In addition, there was very little difference in the fit statistics for the Gompertz function (AIC: 829.21; BIC: 837.03) as compared with the Weibull function (AIC: 830.92; BIC: 838.74), and the selection of the Gompertz function could not be justified on this basis alone. The corresponding fit statistics for the Exponential function were (AIC: 837.05; BIC: 840.96). The ESC noted the sensitivity of the ICER to changing the extrapolation assumptions (see Table 18).

Figure 8: OS curves of SoC using Gompertz (base case) compared with the Weibull versus OS curve of DLd

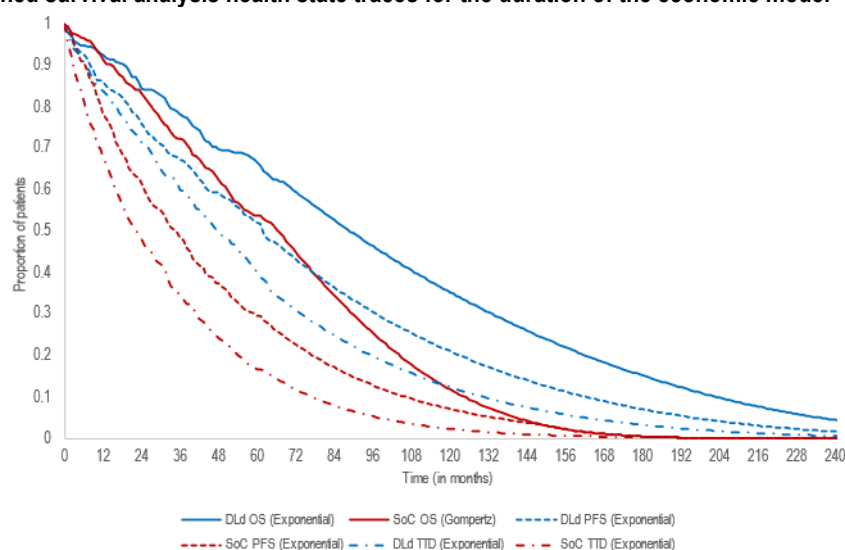


Source: Compiled during the evaluation using the information from the economic model of the submission.

DLd = daratumumab, lenalidomide and dexamethasone; KM = Kaplan Meier; PFS = progression free survival; OS = overall survival; SoC = standard of care; TTD = time-to-treatment discontinuation

6.43 Traces for the predicted time to event outcomes of OS, PFS and TTD for the DLd and SoC arms are presented in Figure 9. The OS curves included background mortalities from the Australian population. No external data were used in the validation of the predicted outcomes from the model. The ESC noted that the application of the exponential function to OS in the DLd arm resulted in 4.4% of patients predicted to be alive at the end of the 20 year time horizon. Noting the age of patients entering the model (74 years), whereas all patients in the SOC arm had died by approximately 15 years. Overall, the ESC considered that the application of independent parametric functions to model OS resulted in the extrapolated curves diverging at an unreasonably accelerated rate for the SOC arm in comparison with the DLd arm (Figure 9).

Figure 9: Partitioned survival analysis health state traces for the duration of the economic model

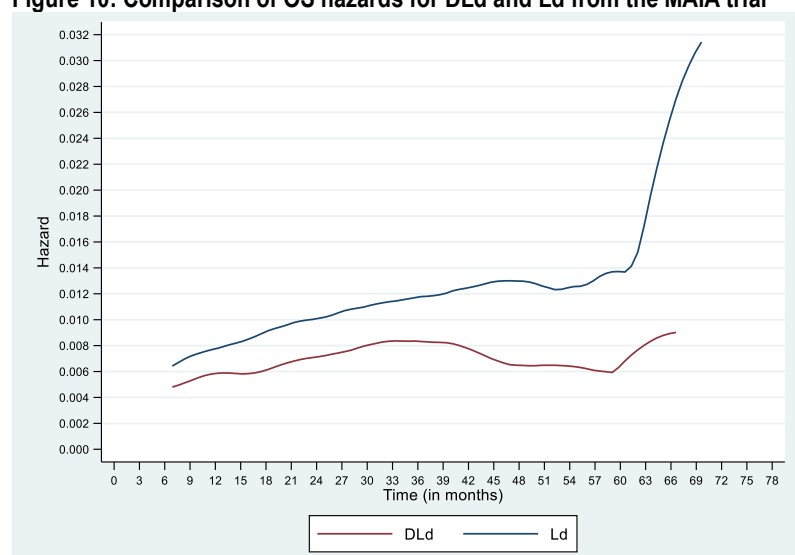


Source: Compiled during the evaluation using the information from the economic model of the submission.

DLd = daratumumab, lenalidomide and dexamethasone; PFS = progression free survival; OS = overall survival; SoC = standard of care; TTD = time-to-treatment discontinuation

6.44 When considering BLd, the PBAC stated a preference for convergence of the PFS and OS curves from Year 10 to 15 (paragraph 7.9, lenalidomide PSD, August 2019 PBAC meeting). No convergence was applied in the proposed DLd model. The PSCR presented Figure 10 below which demonstrated that the hazards for mortality were not showing signs of convergence. Therefore, the PSCR stated that there was no evidence to support a forced convergence of the OS curves. The ESC considered that given that (i) the hazards for mortality beyond the trial period were unknown, and (ii) the length of the extrapolated period (up to 20 years) relative to the trial data (66 months), the application of conservative modelling approaches would be reasonable. The pre-PBAC response maintained that a forced convergence of the OS curves would not be appropriate.

Figure 10: Comparison of OS hazards for DLd and Ld from the MAIA trial



Source: Figure 4, p6 of the PSCR

DLd = daratumumab, lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone; OS = overall survival

6.45 Overall, the ESC considered that the predicted outcomes for OS in the model were not adequately justified. The ESC noted the sensitivity of the ICER to the optimistic assumptions used in the submission and considered that a more conservative approach to modelling OS would be reasonable.

6.46 The submission assumed that the post-progression treatments following DLd and SoC would be Bd and DBd, respectively. This was not consistent with the variety of post-progression treatments used in MAIA (see Table 14).

Table 14: Use of subsequent therapies in each arm of the MAIA trial*

Drug	DLd (N=128)	Ld (N=194)
Bortezomib	71.1%	76.3%
Daratumumab	14.1%	48.5%
Carfilzomib	17.2%	21.1%
Pomalidomide	46.1%	35.6%
Lenalidomide	25.8%	21.1%

Source: Table TSISAT01 of the MAIA CSR

DLd = daratumumab, lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone

* The percentages sum to > 100% as the majority of therapies are used in combination regimens

6.47 The ESC noted that issues regarding the estimation of post-progression costs applied in the submission included:

- Given that other drugs were used post-progression following DLd in MAIA which are more expensive than Bd meant that the use of Bd only in the economic model underestimated post-progression costs for DLd.
- The model assumed that all progressing SoC patients received DBd. This may not be appropriate as it was provided to only 48.5% of Ld patients in MAIA. Including DBd costs for all progressing SoC patients, without similarly adjusting efficacy to assume that all progressing patients were receiving daratumumab second-line

results in a disconnect between the trial evidence for outcomes from MAIA and the costs applied in the model.

- The submission estimated the duration of subsequent treatment of DBd (30.7 months discounted) and Bd (8.9 months discounted) from the economic model used in the November 2019 daratumumab submission for DBd as a second-line treatment for RRMM. This results in a disconnect in the overall time considered in the model in that it incorporates longer time on a post-progression treatment for the SoC group compared with DLd. This might not be clinically reasonable given that the model estimated that SoC will have lower OS than DLd patients. Also, this is not reasonable given that patients in this submission are older and likely to have a shorter duration of treatment on DBd compared to those in the DBd submission. Given the submission adopted a partitioned survival model (PSM), time on second-line treatments should be less than the area between the PFS and OS curves. Use of data external to the PSM results in time on second-line treatment that is not clinically plausible, and favours DLd given that more patients progressed in the Ld arm compared with the DLd arm. The ESC noted that the estimated durations of subsequent treatment from the PSM were 17.2 months (discounted) for DLd and 17.3 months (discounted) for Ld.
- 6.48 The combined effect of the approaches adopted in the submission result in post-progression costs that were overestimated for SoC and underestimated for DLd (discounted post-progression costs per patient of \$ for patients in the SoC arm and of \$23,570 for patients in the DLd arm).
- 6.49 The PSCR provided a revised economic analysis which used a different approach to calculate the post progression costs. Revised average durations of subsequent therapy (272 days (8.9 months) in the DLd arm and 301 days (9.8 months) in the SOC arm) were derived from the patient-level data from MAIA. The derived proportion of use of each of the regimens (see Table 15) was based on the proportions of patients who received the most commonly used subsequent therapies from MAIA (summarised in Table 14). Costs associated with subsequent therapies (\$39,952 for the DLd arm and \$73,863 for the SOC arm) were then attributed to 72.7% of progressors in the DLd arm and 85.1% of progressors in the SOC arm. The ESC noted that these changes to post progression costs increased the base case ICER from \$155,000 to < \$255,000 to \$155,000 to < \$255,000 per QALY gained. Although the PSCR did not justify the basis for the assumed distribution of combined regimens applied, the ESC considered that this revised analysis was likely to be more realistic than what was presented in the submission.

Table 15: Derived proportion of use of subsequent therapies*

Regimen	DLd (N=128)	Ld (N=194)
DBd	0.00%	48.45%
PBd	46.09%	27.84%
Bd	25.00%	0.00%
Pd	0.00%	7.73%
Cd	17.19%	21.13%
Ld	25.78%	21.13%

Source: Table 3, p6 of the PSCR

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; DLd = daratumumab, lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone; PBd = pomalidomide, bortezomib and dexamethasone; Pd = pomalidomide and dexamethasone

* Assumptions applied (i) patients can only have a course of daratumumab once per lifetime; (ii) all use of daratumumab in the 2L scenario would be in combination with bortezomib (DBd); (iii) remaining bortezomib would be used in combination with pomalidomide (PBd); (iv) any bortezomib remaining allocation to DBd and PBd that was assumed to be used as Bd; (v) if any pomalidomide was left, it was assumed to be used as Pd (vi) carfilzomib was assumed to be given as part of a Cd regimen; and (vii) lenalidomide was assumed to be used as Ld.

6.50 The submission applied the EQ-5D-5L HRQoL data from MAIA in the economic model. The data suggest a higher utility value in the pre-progression state (0.699) compared to the progressed state (0.631). The use of health utility values in the economic model that were directly derived from MAIA appears reasonable. The submission applied these values irrespective of treatment received. The values applied indicate a moderate disutility associated with progression (0.068), approximately 10% of the observed pre-progression utility value (arguably within the minimal important difference for this scale).

6.51 A summary of the key drivers of the model is provided in the Table 16.

Table 16: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$█ ¹ /QALY gained
Time horizon	The submission applied a time horizon of 20 years.	Moderate, favours DLd. Use of 15 years increased the ICER to \$█ ¹ /QALY gained.
Extrapolation	No convergence of OS, PFS, and TTD for DLd	High, favours DLd. Application of convergence from year 10 increased the ICER to \$█ ¹ /QALY gained.
	Application of the Gompertz distribution to the SoC OS Kaplan Meier curve	High, favours DLd Use of the Weibull increased the ICER to \$█ ¹ /QALY gained.
Post-progression costs	High post-progression costs for SoC were applied based on the DBd in RRMM submission population	High, favours DLd Adjusting the post-progression time on treatment ^a increased the ICER to \$█ ¹ /QALY gained.

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

DLd = daratumumab with lenalidomide 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

^a adjust post-progression cost of SoC with a factor of 56.4% which is a ratio of (discounted) mean post-progression time in the economic model of SoC (17.3 months) to (discounted) time-on-treatment with DBd (30.7 months).

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

6.52 A summary of the results of the stepped economic analysis is presented in Table 17. The results of the revised base case presented in the PSCR is also presented which applies the updated subsequent therapy costs as described above (see paragraph

6.49). These results were based on the effective price for daratumumab (without RSA adjustment), bortezomib and assumed effective price for lenalidomide (50% of the published price). The pre-PBAC response presented an updated base case in which the revised costs for lenalidomide, following PBS listing of a generic brand, were included.

Table 17: Results of the base-case modelled economic evaluation

	DLd	SoC	Increment
Step 1: trial-based analysis			
Costs	\$█	\$86,986	\$█
LYs	4.362	4.070	0.292
Incremental cost per LY gained			\$█ ¹
Step 2: analysis extrapolated to a lifetime time horizon, cost of second-line therapy and discounting applied			
Costs	\$█	\$208,088	\$█
LYs	6.443	4.805	1.638
Incremental cost per LY gained			\$█ ²
Step 3: application of utility weights			
Costs	\$█	\$208,088	\$█
QALYs	4.408	3.261	1.148
Incremental cost per QALY gained			\$█ ³
PSCR revised base case with changes to second-line therapies			
Costs	\$█	\$153,408	\$█
LYs	6.443	4.805	1.638
QALYs	4.408	3.261	1.148
Incremental cost per LY gained			\$█ ³
Incremental cost per QALY gained			\$█ ³
Pre-PBAC revised base case with updated costs of lenalidomide included			
Costs	\$█	\$137,832	\$█
QALYs	4.408	3.261	1.148
Incremental cost per QALY gained			\$█ ³

Source: Table 3.14, p244 and Table 3.15, p246 of the submission and compiled during the evaluation using the information from the economic model of the submission

DLd = daratumumab with lenalidomide and dexamethasone; LY = life-year; QALY = quality-adjusted life-year; SOC = standard of care

The redacted values correspond to the following ranges:

¹ \$755,000 to < \$855,000

² \$115,000 to < \$135,000

³ \$155,000 to < \$255,000

6.53 The results of key univariate and multivariate sensitivity analyses (based on the submission's base case) are summarised in Table 18. This included a threshold analysis conducted during the evaluation which investigates the price reduction required to achieve an ICER equivalent to the level preferred by the PBAC of less than \$75,000/QALY (paragraph 6.1, daratumumab, PSD, July 2020 PBAC meeting).

Table 18: Sensitivity analyses (submission base case and PSCR base case)

Scenario	Incremental QALY	Incremental costs	ICER	% change to ICER
Base case	1.15	\$ [redacted]	\$ [redacted] ¹	
0% discounting rate (base case 5.00%)	1.83	\$ [redacted]	\$ [redacted] ²	-28%
3.5% discounting rate (base case 5.00%)	1.31	\$ [redacted]	\$ [redacted] ³	-9%
15-year time horizon (base case 20-year)	1.02	\$ [redacted]	\$ [redacted] ¹	+11%
Weibull function for OS of SoC (base case Gompertz)	0.92	\$ [redacted]	\$ [redacted] ¹	+25%
Convergence of OS, PFS, and TTD from Year 10 (base case no convergence)	0.92	\$ [redacted]	\$ [redacted] ¹	+26%
Cost of BLd 0% vs Ld 100% in SoC (base case 68% vs 32%)	1.15	\$ [redacted]	\$ [redacted] ¹	+6%
Post-progression costs for SoC arm based on mean time spent in post-progression state from the economic model ^a (base case based on DBd model)	1.15	\$ [redacted]	\$ [redacted] ¹	+27%
Post-progression costs for SoC arm based on the proportion of daratumumab received in MAIA i.e. 48.5% (base case = 100%)	1.15	\$ [redacted]	\$ [redacted] ¹	+32%
[redacted] % rebate for daratumumab (in DLd) (base case 0%)	1.15	\$ [redacted]	\$ [redacted] ²	-25%
[redacted] % rebate for daratumumab (in DLd) (base case 0%)	1.15	\$ [redacted]	\$ [redacted] ⁴	-43%
[redacted] % rebate for daratumumab (in DLd) ^b (base case 0%)	1.15	\$ [redacted]	\$ [redacted] ⁴	-50%
[redacted] % for lenalidomide generic (base case no reduction)	1.15	\$ [redacted]	\$ [redacted] ³	-7%
Multivariate analysis:				
15-year time horizon + [redacted] % rebate for daratumumab (in DLd) + Convergence from year 10 + 0% use of BLd in SoC + Adjust post-progression cost for SoC with mean post - progression time from the economic model.	0.88	\$ [redacted]	\$ [redacted] ¹	+41%
15-year time horizon + Convergence from year 10 + 0% use of BLd in SoC + Adjust post-progression cost for SoC with mean post-progression time from the economic model + Post progression costs for SoC arm based on the proportion of daratumumab received in MAIA i.e. 48.5% + Weibull for OS of SoC	0.68	\$ [redacted]	\$ [redacted] ⁵	154%
PSCR revised base case with changes to 2L therapies	1.148	\$ [redacted]	\$ [redacted]¹	-
Price reduction to reflect ICER <\$75,000/QALY 72.4% rebate for daratumumab (in DLd) (base case 0%)	1.15	\$ [redacted]	\$ [redacted] ⁶	-67%
Cost of BLd 0% vs Ld 100% in SoC (base case 68% vs 32%)	1.15	\$ [redacted]	\$ [redacted] ¹	+4%
15-year time horizon (base case 20-year)	1.02	\$ [redacted]	\$ [redacted] ¹	+11%
Weibull function for OS of SoC (base case Gompertz)	0.92	\$ [redacted]	\$ [redacted] ⁷	+25%
Exponential function for OS of SoC (base case Gompertz)	0.75	\$ [redacted]	\$ [redacted] ⁷	+53%
Convergence of OS, PFS, and TTD from Year 10 ^c (base case no convergence)	0.92	\$ [redacted]	\$ [redacted] ⁷	+26%

Source: Table 3.16, pp247-248 of the submission; 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

^a adjust post-progression cost of SoC with a factor of 56.4% which is a ratio of (discounted) mean post-progression time in the economic model of SoC (17.3 months) to (discounted) time-on-treatment with DBd (30.7 months)

^b threshold analysis setting ICER to be at level preferred by the PBAC of less than \$75,000/QALY (para 6.1, daratumumab, PSD July 2020 PBAC meeting)

^c method for applying convergence as shown in Table 3.9.1 of the commentary

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$115,000 to < \$135,000

³ \$135,000 to < \$155,000

⁴ \$75,000 to < \$95,000

⁵ \$355,000 to < \$455,000

⁶ \$55,000 to < \$75,000

⁷ \$255,000 to < \$355,000

- 6.54 The ESC noted the proposed cost per patient for daratumumab in the first line setting was more than double that accepted as cost-effective in the second line setting (approximately \$⁸ versus \$⁹; discounted⁹) which was inconsistent with the smaller benefit modelled for first line treatment (1.148 QALYs versus 1.36 QALYs¹⁰, discounted). The ESC noted the smaller modelled benefit in the first line setting likely reflected the relative benefit being smaller (PFS HR=0.55 for DLd vs Ld versus HR=0.22 for DBd versus Bd¹¹, OS HR=0.66 and HR=0.55¹², respectively) and patients progressing on first line treatment having access to effective second line treatments.
- 6.55 Overall, the ESC considered that the revised base case presented in the PSCR which updated the subsequent therapy costs remained highly optimistic. The ESC considered that there were two potential options for the Sponsor to consider:
1. A combined analysis approach comprising of a cost-effectiveness analysis for the comparison of DLd with Ld and a cost-minimisation approach for the comparison of DLd with BLd (see paragraph 6.39); or
 2. A re-specified base case which included a treatment effect for BLd, a time horizon of 15 years and revised assumptions around the OS extrapolations (see paragraphs 6.42 and 6.43). The ESC considered that a substantial price reduction would be required to achieve a cost-effective ICER.

Drug cost/patient/course

- 6.56 A summary of the drug cost per patient of DLd and SoC is presented in Table 19.

⁸ From PSCR model (Revised economic model - Daratumumab 1L TI NDMM Economic model_Nov 2022.xlsx).

⁹ From July 2020 submission economic model (Attachment 1 - IA5 2L MM Economic Model DBd vs Bd.xlsx).

¹⁰ Table 4, daratumumab PBAC PSD, July 2020

¹¹ Table 8, daratumumab PBAC PSD, November 2019

¹² Table 8, daratumumab PBAC PSD, November 2019

Table 19: Drug cost per patient for proposed and comparator drugs

	DLd			SoC		
	Trial	Model	Financial estimates	Trial	Model	Financial estimates
Mean dose intensity (%)	<u>DLd</u> D: 95.8 L: 73.6 d: 78.4	<u>DLd</u> D: 97.9 L: 67.7 d: 74.1	<u>DLd</u> D: 97.2 L: 67.7 d: 74.1	<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 d: 79.6 <u>BLd</u> B: 79.9 L: 80.1 d: 79.6
Mean duration (months)	42	60	60	28	33	33
Cost/patient/month	D: Month 1-2 = \$ Month 3-6 = \$ Month 7+ = \$ L: \$3,222 ^a d: \$7			L: \$3,222 ^a d: \$7	<u>Ld</u> L: \$3,222 ^a d: \$7 <u>BLd</u> B: Month 1-6 = \$2,694 L: \$3,222 ^a d: \$7	<u>Ld</u> L: \$6,445 ^b d: \$7 <u>BLd</u> B: Month 1-6 = \$2,694 L: \$6,445 ^b d: \$7
Cost/patient/course ^c	\$	\$	\$	\$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

^a assumed effective price (50% of the published price)

^b the submission used the published price of lenalidomide in the financial estimate.

^c 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.

Estimated PBS usage & financial implications

6.57 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the financial implications. A summary of the key inputs used in the estimation is presented in Table 20.

Table 20: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident patients	1,574 in Yr 1 increased to 1,848 in Yr 6. A total of 17% increase or 3.3% annually. Projected based on DUSC 2014 to 2019 data requested by the sponsor (BLd TI, Ld TI, and thalidomide)	Likely overestimate. The total growth of incident patients projected over the 6 years (17%) is higher than a previous estimate for a similar setting in MM seen by the PBAC (11%; paragraph 5.37, daratumumab, PBAC minute, July 2020). The PSCR stated that the growth rate in the second-line setting was not comparable as it was informed by all patients with NDMM, not just those with TI NDMM.
Grandfather patients	< 500 patients. Internal data from the submission.	Inadequate details were provided in the submission as to whether these patients will meet the proposed PBS criteria, noting that the expanded access program into which these patients would be recruited has not yet commenced.
Uptake rate	Assumed 75% in Yr 1 increasing to 85% in Yr 2, and 90% in Yr 3 to Yr 6. 89.6% over 6 years.	The ESC considered that uptake of DLd was likely to be high.
Persistence	Yr 1: 91%, Yr 2: 77%, Yr 3: 65%, Yr 4: 53%, Yr 5: 42%, Yr 6: 32%. The economic model (TTD)	-
Number of scripts	1 st Yr of treatment: 16 scripts (initial) + 7 scripts (continuing), from 2 nd year of treatment: 13 per year. As per PI	-
Compliance	95.6% (IV), 98.7% (SC). Dose intensity from MAIA	-
Price of daratumumab	IV 100 mg vial: \$ [REDACTED] IV 400 mg vial: \$ [REDACTED] SC 1,800 mg vial: \$ [REDACTED]	Reflects proposed prices.
Offsets	<u>Reduction in the use of existing treatment regimens in TI NDMM patients</u> ^b : BLd: -55.0% (0.3%) Ld: -23.9% (3.3%) Bd: -3.4% (6.0%) BCd: -4.6% (3.4%) Total: -89.6% (13.1%). Projected from the MRDR report for TI NDMM	Likely overestimated change in use of the current options. Doublet treatment is likely to remain an option for those not fit for triplet treatment.
	<u>Reduction in the use of DBd in second-line MM:</u> Yr 1 of 55 initial patients, increased to 77 initial patients and 856 continuing patients in Yr 6. Projected DLd progressed patients	Likely underestimate. The submission only estimated offsets for those who progress following first line DLd, rather than considering those who would have been treated with second line daratumumab if they had not been treated with DLd in the first-line setting.
	<u>Increase in use of lenalidomide and dexamethasone when used as DLd:</u> based on increase in DLd use	Slight increase in the net use of lenalidomide and dexamethasone after listing of DLd was reasonable.

Source: Table 4.2, pp256-257; Table 4.3, p258; Table 4.6, p260; Table 4.11, p265 of the submission; Compiled during the evaluation using the information from the financial model.

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

^b % in parentheses show the anticipated market share after listing of DLd.

6.58 The ESC considered that the submission overestimated the number of patients treated with DLd, as:

- The submission applied an annual growth rate of 3.3% for the projected incident patients based on 2014 to 2019 data for the use of first-line treatments for TI NDMM obtained from the DUSC. This exceeds the annual growth of the Australian population (e.g. at 0.9% for 2021 reported by the Australian Bureau of Statistics; ABS). The 3.3% growth results in an extra 274 incident patients (a 17% increase) up to Year 6. Previously, the PBAC has seen an estimate of 11% for growth in the incident MM patient population over the 6-year forward estimates period (para 5.37, daratumumab, PBAC PSD July 2020). Using this growth rate would have resulted in an increase of 173 patients over the 6 years. The PSCR stated that an exponential function was applied to the PBS 10% data, and as it was the best statistical fit it was appropriate for determining the 3.3% growth. The ESC noted that no statistics were provided to justify the choice of the exponential function. The PSCR also stated that the growth rate in the second-line setting was not comparable as it was informed by all patients with NDMM, not just those with TI NDMM. The ESC considered that although this argument was reasonable there was no justification as to why the growth rate in the TI NDMM population should exceed that of NDMM.
- The commentary considered the assumed uptake of DLd (almost 90% by Year 6; 86.9% on average over the 6 years) likely to be overestimated, as some patients would not be fit enough/eligible for triplet treatment. In considering the submission to list DBd, the PBAC advised a 50% uptake rate for DBd in the second line setting for Year 1 was reasonable (para 5.25, daratumumab, PBAC PSD July 2020). In addition, according to the MRDR data, 37% of TI NDMM patients still receive Ld or Bd, despite the availability of triplet BLd treatment on the PBS. The PSCR stated that uptake is expected to be high, noting that the MSAG Guidelines (2022) state that “maximising the effectiveness of first-line therapy remains the best opportunity to optimise long term patient outcomes”. The ESC agreed that uptake of DLd was likely to be high.
- The submission included < 500 grandfathered patients in Year 1. The inclusion of these patients was not adequately justified given that the access program from which grandfathered patients has not yet commenced.
- The submission appeared to underestimate the reduction in use of DBd in second-line treatment. The submission estimated offsets based on the proportion of patients who progressed following first line DLd of 9% (e.g. Year 1), rather than considering the proportion who would have progressed to second-line daratumumab if they did not receive DLd in the first-line setting of 42% (e.g. Year 1; based on SoC of the economic model). This might result in up to 33% underestimate in the reduction of use for DBd. The PSCR disagreed with the concern raised by the evaluation, maintaining that the approach used in the

submission was appropriate. The ESC agreed with the evaluation that the reduction in use of DBd in second-line treatment had been 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. The submission estimated a reduction in daratumumab scripts in second line use between 500 to < 5,000 (in year 1) and 20,000 to < 30,000 (in year 6; Submission Table 4.10), which appeared low in comparison to the estimated number of daratumumab scripts for the proposed listing in first line use (20,000 to < 30,000 in year 1 to 90,000 to < 100,000 in year 6; Submission Table 4.10). Although duration of treatment is expected to be longer in the first line setting, it appeared the submission did not take account of additional patients that would no longer be eligible for DBd in second line, including patients that received DLd and did not progress to second line (but in the absence of DLd would have received DBd in second line).

- The submission did not estimate changes in the use of other medicines in the second and third-line settings. Since the submission anticipated that patients receiving DLd will remain on treatment longer (compared to those receiving current first-line options), it was argued that there would be further reductions in the use of second and third-line treatments not captured within the submission over the 6-year time frame of the financial estimates. However, the ESC considered this was not accurate, because there may be a change in patterns of use of therapies currently used in later line settings after DBd, both in terms of mix of therapies and timing which may both impact costs. The ESC considered that medicines currently used in lines after DBd may be used one line earlier on average, because DBd will not be applicable for patients that received DLd in first line, and similar flow on impacts to later lines. In addition, there may be a change to timing, where patients may remain in first line treatment for a longer period on average (due to extended treatment duration for DLd compared with SOC). This may lead to a reduction in use of other treatments over the 6 year forecast period, which was not estimated by the submission.

6.59 A summary of the estimated use and financial implications of DLd is presented in Table 21.

Table 21: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Initiating patients treated	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Continuing patients treated	-	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Scripts dispensed: initial	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Scripts dispensed: continuing	■ ³	■ ²	■ ⁴	■ ⁵	■ ⁶	■ ⁷
Scripts dispensed: total	■ ²	■ ⁸	■ ⁶	■ ⁷	■ ⁹	■ ¹⁰
Estimated financial implications of daratumumab						
Cost to PBS/RPBS less copayments (\$)	■ ¹¹	■ ¹¹	■ ¹²	■ ¹²	■ ¹³	■ ¹³
Estimated financial implications for affected medicines						
Cost to PBS/RPBS less copayments (\$)	■ ¹⁴	■ ¹⁴	■ ¹⁴	■ ¹⁴	■ ¹⁴	■ ¹⁴
Net financial implications						
Net cost to PBS/RPBS (\$)	■ ¹¹	■ ¹¹	■ ¹¹	■ ¹²	■ ¹²	■ ¹²
Net cost to MBS (\$)	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵
Net cost to PBS/RPBS/MBS (\$)	■ ¹¹	■ ¹¹	■ ¹¹	■ ¹²	■ ¹²	■ ¹²

MBS fees include fees for parenteral administration (MBS item 13950) and blood typing (MBS item 65090) which is required before patients commence daratumumab.

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

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² 20,000 to < 30,000
- ³ 5,000 to < 10,000
- ⁴ 30,000 to < 40,000
- ⁵ 50,000 to < 60,000
- ⁶ 60,000 to < 70,000
- ⁷ 70,000 to < 80,000
- ⁸ 40,000 to < 50,000
- ⁹ 80,000 to < 90,000
- ¹⁰ 90,000 to < 100,000
- ¹¹ \$100 million to < \$200 million
- ¹² \$200 million to < \$300 million
- ¹³ \$300 million to < \$400 million
- ¹⁴ net cost saving
- ¹⁵ \$0 to < \$10 million

6.60 The net cost to the PBS/RPBS of listing DLd was estimated to be \$200 million to < \$300 million in Year 6, and total > \$1 billion over the first 6 years of listing. With the inclusion of MBS fees, the net cost to PBS/RPBS/MBS was estimated to be \$200 million to < \$300 million in Year 6, and total > \$1 billion over the first 6 years of listing.

6.61 The submission estimated the change in MBS items associated with the administration of daratumumab (Item 13950) for both IV and SC. This was not appropriate given the administration cost should be applied to IV only. The submission also estimated the cost of blood type testing (Item 65090) as the daratumumab PI suggests that blood typing be undertaken in all patients initiating daratumumab prior to the first infusion/injection. This was appropriate.

- 6.62 The ESC considered that the submission appeared to have underestimated the reduction in use of subsequent therapies and overestimated the cost of daratumumab in the first line setting due to the application of the high assumed growth rate of the TI NDMM population and uncertainties with the number of grandfathered patients. Overall, the net increase in cost to the PBS/RPBS of daratumumab appeared to be overestimated.
- 6.63 Further, the ESC noted that the utilisation estimates were significantly higher than those presented for the same proposed population for lenalidomide (as BLd) in August 2019.

Quality Use of Medicines

- 6.64 The 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

- 6.65 There is a current RSA for daratumumab (as DBd) in the second line RRMM setting. A new RSA for daratumumab in TI NDMM has not been proposed in the submission. However, the submission stated that the sponsor is amenable to an RSA for daratumumab in TI NDMM after the evaluation of the financial estimates.
- 6.66 A summary of the current RSA for daratumumab for RRMM is presented in Table 22. The current RSA for daratumumab consists of a rebate of █% for any year where utilisation of daratumumab exceeds the expenditure cap in that year. The expenditure caps were set at an average of █% lower than the estimated financial impact of DBd over the five year period █ (refer Table 22). █. Based on actual data for Year 1 (2021), the expenditure cap was exceeded by █% (Commonwealth Payment was \$█) and in Year 2 (2022) it was exceeded by █% (Commonwealth Payment was \$█).

Table 22: Current RSA for daratumumab in RRMM (financial estimates underpinning the RSA)

	2021	2022	2023	2024	2025	Year 1-5
Reimbursement above subsidisation caps: █%						
Value of subsidisation caps	\$█	\$█	\$█	\$█	\$█	\$█
Cost of daratumumab for PBS/RPBS						
Commonwealth Payment	\$█	\$█	\$█	\$█	\$█	\$█
RSA reimbursement	\$█	\$█	\$█	\$█	\$█	\$█
Net cost of daratumumab for the PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Change in budget impact with the RSA	-█%	-█%	-█%	-█%	-█%	-█%

Source: Provided by the ESC during the evaluation

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; RRMM = relapsed and/or refractory multiple myeloma; RSA = risk-sharing arrangement

- 6.67 It is likely that listing daratumumab in the first-line setting will result in a substantial reduction of its use in the second-line setting such that further thresholds in the RSA are unlikely to be reached, although the decrease in second-line use may occur progressively over time reflecting the time taken for patients to progress from first line to second line treatment (refer discussion on treatment patterns in paragraph 6.58, page 42). If the proposed listing of daratumumab in the first-line setting is recommended, it may be appropriate to modify the existing RSA to reflect not only a potential decline in use of second-line daratumumab in transplant ineligible patients (noting that transplant eligible patients with RRMM would still be eligible for DBd in the second-line setting), but to ensure that the price of daratumumab in the second-line setting is cost effective. The ESC considered it may be necessary to revise the estimates for second line accordingly, to ensure that the PBAC advice leading to the PBS listing of daratumumab in the second-line setting is appropriately applied (average █% reduction over the duration of the estimates).
- 6.68 There is the potential for the use of DLd beyond the proposed restriction, i.e., in patients who are transplant eligible. The PBAC has previously considered that patients' eligibility for transplant can be subjective, and that eligibility can change following treatment (para 7.4, lenalidomide PSD, August 2019). The submission did not quantify the extent to which such use might occur. The PSCR stated that there was a relatively low risk of leakage into the transplant eligible population, as this population is more likely to receive additional lines of therapy compared with the transplant ineligible population, and thus would have the option to receive daratumumab in the second line. The ESC noted that this explanation contradicted the MSAG guideline (2022) advice presented in the PSCR in relation to the high uptake rate, which was that “maximising the effectiveness of first-line therapy remains the best opportunity to optimise long term patient outcomes”.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend daratumumab, for use in combination with lenalidomide and dexamethasone (DLd) for the treatment of patients with transplant ineligible (TI) newly diagnosed multiple myeloma (NDMM). The PBAC noted the benefits of treatment with DLd compared with lenalidomide plus dexamethasone (Ld) and the strong consumer support for this item but considered there were numerous issues that had not been addressed in the submission. These included, but were not limited to, the definition of the proposed patient population, concerns regarding the assumed efficacy of the proposed comparators, the unreasonably high and uncertain incremental cost-effectiveness ratio (ICER) and the very high and uncertain estimated financial impact estimates. The PBAC considered that a substantial price reduction would be required to ensure daratumumab was cost-effective and that a risk sharing arrangement (RSA) would be required to mitigate the high likelihood of use in the transplant eligible population, especially given that a patient's eligibility for

transplantation may change over time based on many factors, including the alternative treatments available.

- 7.2 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 for this incurable disease.
- 7.3 The PBAC noted that the submission proposed that DLd would be used in patients with NDMM who were ineligible for a primary stem cell transplant (SCT). 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. The PBAC advised that the proposed restriction should be amended to include more stringent criteria to limit use to the TI NDMM population, or alternatively the sponsor could seek a whole of myeloma listing which would enable access for a greater number of patients.
- 7.4 The PBAC noted that the submission nominated Ld and bortezomib in combination with Ld (BLd) as comparators. 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 replace some use of Ld in frailer patients.
- 7.5 The PBAC noted that the submission claimed that Ld was a reasonable proxy for BLd in terms of efficacy based on the fact that there were no statistically significant differences in PFS or OS between BLd or Ld in the subgroup of patients aged ≥ 65 in the SWOG s0777 trial (see paragraphs 6.21 and 7.10). The PBAC recalled that it had previously considered that BLd was superior to Ld (paragraph 7.5, lenalidomide PSD, August 2019 PBAC meeting) and considered that the submission's claim was not supported for the reasons outlined in paragraph 6.22.
- 7.6 Thus, the PBAC considered that a weighted comparison between Ld and BLd would best reflect current clinical practice, and advised that basing the weighting on data from the Myeloma and Related Diseases Registry (MRDR; i.e. 68% BLd use versus 32% Ld use), would be appropriate.
- 7.7 The PBAC noted that the submission was based on two randomised controlled trials, MAIA, which compared DLd to Ld in TI NDMM patients, and SWOG s0777, which compared BLd to Ld in patients with NDMM without an intent for immediate transplant. The PBAC noted that MAIA enrolled patients who were not considered eligible for transplant, determined by age (≥ 65 years or < 65 with presence of comorbid conditions). As SWOG s0777 enrolled patients who were potentially candidates for transplant, the submission presented results for a subgroup of patients who were ≥ 65 years of age. The PBAC considered that the evidence may not reflect

Australian clinical practice as some of the patients included in the analyses (i.e. the intention to treat (ITT) population from MAIA and the subgroup from SWOG s0777) could potentially be candidates for transplant as patients in Australia¹³.

- 7.8 The comparison between DLd and Ld was based on the results of MAIA. The PBAC noted that DLd was associated with statistically significant improvements in progression free survival (PFS; HR = 0.55; 95% CI: 0.45, 0.67), overall survival (OS; HR = 0.66; 95% CI: 0.53, 0.83) and overall response rate (ORR; OR = 3.00; 95% CI: 1.85, 4.86) in the ITT population. The PBAC noted that although the incidence of adverse events was fairly similar for patients receiving DLd and Ld, DLd was associated with more serious adverse events.
- 7.9 Overall, the PBAC considered that the submission's claims that DLd was superior in terms of effectiveness and inferior in terms of safety compared to Ld were reasonable.
- 7.10 The PBAC noted that instead of presenting indirect treatment comparisons (ITCs) between DLd and BLd using Ld as the common comparator, the submission only presented the results of the comparisons between BLd and Ld from SWOG s0777. As the comparison between BLd and Ld for the subgroup of patients aged ≥ 65 years demonstrated no statistically significant differences in terms of PFS (HR = 0.90; 95% CI: 0.65, 1.26) and OS (HR = 0.88; 95% CI: 0.59, 1.31) after a median follow up of 55 months, the submission concluded that BLd and Ld were equivalent in terms of efficacy. Thus, the submission stated that an ITC between DLd and BLd was not required and the results from MAIA (DLd versus Ld) were a reasonable proxy for the comparison between DLd and BLd. As noted in paragraph 7.5, the PBAC did not consider that the submission's claim that Ld was a proxy for BLd was reasonable.
- 7.11 The PBAC noted that the results of an unadjusted, unanchored ITC comparing DLd with BLd conducted by the evaluators (see Table 9) using the DLd arm from MAIA and the BLd arm of the ≥ 65 years subgroup from SWOG s0777. Although there were potential issues of transitivity due to differences in patient baseline and disease characteristics, the results demonstrated that DLd was not statistically different compared to BLd in terms of OS.
- 7.12 The PBAC noted that the submission did not present a comparison of safety between DLd and BLd.
- 7.13 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. The PBAC noted that BLd is the most commonly used treatment based on MRDR data (see

¹³ MSAG Guidelines 2022, p11 state: The traditional notion that patients aged above 65 years are ineligible for transplant is no longer appropriate as it is clear that older patients who are biologically fit do benefit from intensive treatment. In assessing eligibility for transplant (generally in patients aged up to 70 years), individual assessment that takes into consideration the patient's age, comorbidities, frailty and disability is required.

paragraph 7.6).

- 7.14 The submission presented a cost utility analysis based on the results of the MAIA trial. The PBAC noted that the base case ICER in the submission was \$155,000 to < \$255,000 per quality adjusted life year (QALY), which was increased to \$155,000 to < \$255,000 per QALY in the pre-PBAC response when subsequent treatment costs were updated and the generic price of lenalidomide was included. The PBAC noted that the ICER was substantially higher than (i) generally accepted by the PBAC for similar conditions, and (ii) previously accepted for the listing of daratumumab plus bortezomib and dexamethasone (DBd) in relapsed and/or refractory MM, and likely optimistic. The PBAC considered that there were numerous issues associated with the economic model, including:
- No BLd specific efficacy data were included as efficacy in the comparator arm was informed by the Ld arm of the MAIA trial only based on the assumption that Ld was a reasonable proxy for BLd. As noted above, this assumption was not accepted by the PBAC;
 - The time horizon of 20 years was long given the average age of patients entering the model was 74 years;
 - The choice of parametric functions applied to the OS Kaplan Meier curves resulted in the extrapolated curves diverging at an unreasonably accelerated rate. The PBAC noted that 4.4% of patients in the DLd arm were alive at the end of the 20 year time horizon, whereas all patients in the comparator arm had died by approximately 15 years; and
 - Convergence of the OS curves was not applied.
- 7.15 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. For both options, the PBAC considered that a weighted comparison based on the MRDR data would be appropriate (see paragraph 7.6).
- 7.16 The PBAC noted that the modelled cost per patient for daratumumab in the first line setting was more than double that accepted as being cost effective in the second line setting. 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.
- 7.17 The PBAC, noting that the estimated financial impact of listing DLd on the PBS/RPBS exceeded > \$1 billion over the first 6 years of listing, considered that the utilisation estimates were overestimated for the reasons outlined in paragraph 6.58. The PBAC considered that the estimated cost was very high, particularly considering the high

and uncertain ICER and the clinical evidence which did not demonstrate that DLd was superior to BLd in terms of efficacy.

- 7.18 The PBAC noted that the submission did not present a RSA despite a high risk of daratumumab being used in patients who were transplant eligible. The PBAC considered that a RSA with clearly defined expenditure caps would be required to mitigate the risk of use outside the proposed patient population
- 7.19 The PBAC considered a resubmission for daratumumab should address the numerous issues highlighted in this PSD. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 7.20 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 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.

9 Sponsor's Comment

The sponsor had no comment.