**5.05 DARATUMUMAB   
100 mg and 400 mg vial,   
Darzalex®, Janssen-Cilag Pty Ltd**

# Purpose of application

* 1. Section 100 listing (Efficient Funding for Chemotherapy) for daratumumab for treatment of relapsed or refractory multiple myeloma (RRMM). Daratumumab has not been considered by the PBAC previously.
  2. The submission presented cost utility analyses comparing daratumumab in combination with bortezomib and dexamethasone (DBd) and daratumumab in combination with lenalidomide and dexamethasone (DLd) with their respective comparator regimens (Bd and Ld).

**Table 1: Key components of the clinical issue addressed by the submission**

| Component | Description |
| --- | --- |
| Population | Multiple myeloma; patients with relapsed or refractory disease (RRMM) after at least one prior therapy. |
| Intervention | Daratumumab is administered as an IV infusion at a dose of 16 mg/kg in combination with either bortezomib or lenalidomide-based therapies.  Daratumumab in combination with bortezomib and dexamethasone (DBd): Daratumumab is administered weekly for the first 3 cycles (3 weekly cycle), every three weeks from cycles 4 to 8 (3 weekly cycle) and then once every 4 weeks from cycle 9 onwards (4 weekly cycle).  Daratumumab in combination with lenalidomide and dexamethasone (DLd): Daratumumab is administered weekly for the first 2 cycles (4 weekly cycle), every two weeks from cycles 3 to 6 (4 weekly cycle) and then once every 4 weeks from cycle 7 onwards (4 weekly cycle). |
| Comparator | Main comparator  For DBd: bortezomib-dexamethasone (Bd)  For DLd: lenalidomide-dexamethasone (Ld)  Supplementary comparator  For DBd: carfilzomib-dexamethasone (Cd)  For DLd: carfilzomib-lenalidomide-dexamethasone (CLd) |
| Outcomes | PFS, OS, ORR, MRD negativity rates |
| Clinical claim | Daratumumab in combination with bortezomib and dexamethasone: In patients with RRMM, DBd is more effective than Bd as assessed by statistically and clinically significant improvements in PFS, OS and a significantly higher ORR. DBd is associated with additional AEs compared with Bd, and therefore has an inferior safety profile. This was supported by the evidence.  Daratumumab in combination with lenalidomide and dexamethasone: In patients with RRMM, DLd is more effective than Ld as assessed by statistically and clinically significant improvements in PFS, OS and a significantly higher ORR. DLd is associated with additional AEs compared with Ld, and therefore has an inferior safety profile. This was supported by the evidence. |

Abbreviations: AE, adverse events; Bd, bortezomib- dexamethasone; Cd; carfilzomib- dexamethasone; CLd; carfilzomib- lenalidomide- dexamethasone; DBd; daratumumab-bortezomib-dexamethasone; DLd; daratumumab-lenalidomide-dexamethasone; Ld, lenalidomide-dexamethasone; MRD, minimal residual disease; ORR, overall response rates; OS, overall survival; PFS, progression free survival; RRMM, relapsed and/or refractory multiple myeloma.

Source: Table 1.2, p.15 Section 1 of the Submission.

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

# Requested listing

* 1. The submission proposed a “Multiple Myeloma Treatment Package” consisting of:
  + A special pricing arrangement (SPA) for daratumumab for the ''''''''' ''''''''''''''''''' '''''''''''''' ''''''' '''''''' ''' ''''''''''' '''''' '''''''' ''''''' ''' '''''''''''' '''''' '''''''''' resulting in a price which is '''''''''''% of the AEMP of daratumumab when used with bortezomib and ''''''% of the AEMP of daratumumab when used with lenalidomide.
  + Simplification of the wording for the PBS listing of bortezomib to “treatment of multiple myeloma”, in line with that applied to thalidomide.

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* 1. The PSCR (p4) accepted most restriction changes suggested by the Secretariat. Restriction wording that was changed in the PSCR has been indicated in italics for additions and strikethrough for deletions. The prescriber instructions and administrative advice have been excluded for brevity as they do not include any changes. The PSCR argued that the continuing restriction for DBd should allow daratumumab monotherapy, as this was consistent with the trial where patients only received 8 initial cycles of DBd combination therapy. The PSCR also argued that continuing treatment with Ld should not be required for the DLd continuing restriction to allow patients who experienced treatment toxicities to continue on daratumumab monotherapy.
  2. The submission proposed an amendment to the current PBS restrictions for bortezimib and lenalidomide to allow for use in combination with daratumumab in RRMM (see below).

**Daratumumab with bortezomib and dexamethasone**

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| **Name, Restriction,**  **Manner of administration and form** | | **Max. Amt** | **№.of**  **Rpts** | **Dispensed Price for Max. Amt** | **Proprietary Name and Manufacturer** | |
| DARATUMUMAB  VIAL, 400 mg and 100 mg | | 1920 mg | 13 (initial)  5 (continuing) | Public hospital: $'''''''''''''''''''''''''  Private hospital: $''''''''''''''''''''''' | DARZALEX® | Janssen Cilag Pty Ltd |
| Category / Program: | Section 100 – Efficient Funding for Chemotherapy | | | | | |
| PBS Indication: | Multiple Myeloma | | | | | |
| Treatment phase: | Initial and Continuing | | | | | |
| Restriction: | Authority required (Telephone) | | | | | |
| Clinical criteria: | Initial:  The condition must be confirmed by a histological diagnosis  AND  The treatment must be in combination with bortezomib and dexamethasone.  AND  Patient must have progressive disease after at least one prior therapy  AND  Patient must not be receiving concomitant PBS-subsidised lenalidomide, thalidomide, pomalidomide or carfilzomib.  AND  Patient must not receive more than eight cycles of treatment under this restriction  AND  Patient must not have previously received this drug for this condition  Continuing:  Patient must have previously received PBS-subsidised treatment with an authority prescription for this drug for this condition AND  The patient must have previously received PBS-subsidised treatment with this drug in combination with bortezomib and dexamethasone as initial treatment in the current course of treatment ~~The treatment must be in combination with bortezomib and dexamethasone,~~  AND  Patient must not develop disease progression while receiving treatment with this drug for this condition ~~Patient must not have progressive disease~~  AND  Patient must not be receiving concomitant PBS-subsidised bortezomib, lenalidomide, thalidomide, pomalidomide or carfilzomib. | | | | | |

**Daratumumab with lenalidomide and dexamethasone**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Name, Restriction,**  **Manner of administration and form** | | | **Max. Amt** | **№.of**  **Rpts** | **Dispensed Price for Max. Amt** | **Proprietary Name and Manufacturer** | |
| DARATUMUMAB  VIAL, 400 mg and 100mg | | | 1920 mg | 15 (initial)  5 (continuing) | Public hospital: $''''''''''''''''''''''  Private hospital: $''''''''''''''''''''''''' | DARZALEX® | Janssen Cilag Pty Ltd |
| Category / Program: | Section 100 – Efficient Funding for Chemotherapy | | | | | |
| PBS Indication: | Multiple Myeloma | | | | | |
| Treatment phase: | Initial and Continuing | | | | | |
| Restriction: | Authority required (Telephone) | | | | | |
| Clinical criteria: | Initial:  The condition must be confirmed by a histological diagnosis,  AND  The treatment must be in combination with lenalidomide and dexamethasone,  AND  Patient must have progressive disease after at least one prior therapy,  AND  Patient must not be receiving concomitant PBS-subsidised bortezomib, thalidomide, or pomalidomide or carfilzomib  AND  Patient must not receive more than six cycles of treatment under this restriction  AND  Patient must not have previously received this drug for this condition  Continuing:  Patient must have previously received PBS-subsidised treatment with an authority prescription for this drug for this condition,  AND  Patient must not develop disease progression while receiving treatment with this drug for this condition have progressive disease  AND  The treatment must be in combination with lenalidomide and dexamethasone or as monotherapy in patients who have developed treatment-limiting toxicity to lenalidomide  AND  Patient must not be receiving concomitant PBS-subsidised bortezomib, thalidomide, or pomalidomide or carfilzomib. | | | | | |

**Bortezomib**

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| **Name, Restriction,**  **Manner of administration and form** | | **Max. Amt** | **№.of**  **Rpts** | **Dispensed Price for Max. Amt** | **Proprietary Name and Manufacturer** | |
| BORTEZOMIB, IV, powder in vial; 1 mg, 3 mg and 3.5 mg | | 3000 mcg | 15 | Public hospital: $''''''''''''''''  Private hospital: $'''''''''''''''' | VELCADE ®, | Janssen‑Cilag Pty Ltd |
|  | | | | | | |
| Category / Program: | Section 100 – Efficient Funding for Chemotherapy | | | | | |
| PBS Indication: | Multiple Myeloma | | | | | |
| Restriction: | Streamlined | | | | | |
| Clinical criteria: | For the treatment of multiple myeloma. | | | | | |

**Lenalidomide**

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| --- | --- | --- | --- | --- | --- | --- |
| **Name, Restriction,**  **Manner of administration and form** | | **Max. Qty** | **№.of**  **Rpts** | **Dispensed Price for Max.Qty** | **Proprietary Name and Manufacturer** | |
| Lenalidomide, oral capsule 5 mg, 10 mg, 15 mg and 25 mg | | 21 | 0 | 5 mg Public hospital: $5,122.76  Private hospital: $5,169.78  10 mg Public hospital: $5,361.16  Private hospital: $5,408.18  15 mg Public hospital: $6,252.53  Private hospital: $6,299.55  25 mg Public hospital: $6,587.49  Private hospital: $6,634.51 | REVLIMID®, | Celgene Pty Ltd |
| Category / Program: | Section 100 – Highly Specialised Drugs | | | | | |
| PBS Indication: | Multiple Myeloma | | | | | |
| Restriction: | Authority Required – In Writing | | | | | |
| Clinical criteria: | Initial:  The condition must be confirmed by a histological diagnosis  AND  The treatment must be in combination with daratumumab and dexamethasone  AND  Patient must have progressive disease after at least one prior therapy  AND  Patient must not be receiving concomitant PBS-subsidised bortezomib, thalidomide or pomalidomide.  Continuing:  Patient must have previously received an authority prescription for this drug for this condition  AND  Patient must not have progressive disease  AND  The treatment must be in combination with daratumumab and dexamethasone or with dexamethasone only or as monotherapy in patients who have developed treatment-limiting toxicity to daratumumab  AND  Patient must not be receiving concomitant PBS-subsidised bortezomib, thalidomide or pomalidomide | | | | | |

* 1. Daratumumab is registered for use as a monotherapy “DARZALEX monotherapy is indicated for the treatment of patients with multiple myeloma 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”. However, this submission did not request PBS listing of daratumumab monotherapy.
  2. The ESC considered, given the potential benefit of daratumumab monotherapy for highly refractory patients,[[1]](#footnote-1) a listing these patients may be clinically appropriate, particularly in light of the difficulty in restricting use in this setting. The ESC noted the submission highlighted that the data supporting this indication is non-comparative and may not be of suitable quality or level of rigour for the PBAC to determine comparative efficacy, safety and cost‑effectiveness to the treatment daratumumab would replace in practice. The PBAC considered that there was a high clinical need, and clinician preference, in the patient population for whom daratumumab monotherapy would be appropriate, and that excluding such use may be inequitable. The PBAC also considered that in the case where monotherapy wasn’t listed, there would be a risk of use outside the requested indication into daratumumab monotherapy, particularly given that this would be an attractive option for patients who are refractory to other treatments or have treatment-related toxicities.
  3. The sponsor requested in its pre-PBAC response that the PBAC consider listing of the DBd regimen only.

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

# Background

## Registration status

* 1. TGA status: Daratumumab was approved for registration on 17 July 2017. The approved indication is:
  + in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy; and
  + as monotherapy, for the treatment of patients with multiple myeloma 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 more detail on PBAC’s view, see section 7 PBAC outcome.*

# Population and disease

* 1. Multiple myeloma is a cytogenetically heterogeneous clonal plasma cell proliferative disorder characterised by an abnormal serum and/or urine immunoglobulin. As multiple myeloma progresses and patients relapse following initial treatment, the presence of subclonal populations of malignant plasma cells becomes increasingly prevalent. Typical clinical features include: bone disease (and bone loss) with skeletal pain, impaired renal function, anaemia, fatigue, hypercalcaemia, recurrent and/or persistent bacterial infection, and/or hyperviscosity of the blood.
  2. The submission requested listing of daratumumab, in combination with bortezomib or lenalidomide, as a second and later line treatment for progressive multiple myeloma, that is, the patient must have progressive disease after at least one prior therapy. The two clinical algorithms presented considered that DBd would substitute for Bd, and DLd would substitute for Ld. The clinical algorithms assumed that the majority of patients would switch the backbone class of therapy (between a proteasome inhibitor, such as bortezomib, and immunomodulatory agent, such as lenalidomide) in the relapsed/refractory setting. That is, if patients received Bd initially, most would use DLd in second line. The major change between the current and proposed algorithm is the addition of a third agent (daratumumab) after progression, also impacting on the subsequent choice of second line treatment. The submission stated, based on market research conducted with clinicians, that Bd is more commonly used first line and hence Ld therapy (or DLd) is more likely to be used in second line.
  3. The PBAC considered the proposal in the pre-PBAC response to list DBd only may influence the choice of the initial backbone therapy. The PBAC noted that Ld is currently the most commonly used second line therapy, and agreed that clinician preference would be to switch backbone therapy in the second line. The PBAC therefore considered that listing DBd only would result in a higher proportion of patients using the same backbone therapy in first and second line (i.e. Bd followed by DBd), and would potentially drive an increase in Ld use in first line, as well as increase the risk of use outside the current lenalidomide indication into transplant eligible patients.
  4. The PBAC agreed with the ESC that the choice of therapy for patients with RRMM was based on the consideration of a number of factors, including the therapies used in earlier treatment settings, the time from and response to initial therapy, patient comorbidities and the potential for toxicities, and preference for oral compared with injection/ infusion based therapies. It was noted that there are multiple potential treatments available for use in the second line setting. These are well described by the algorithms published by Nooka and Lonial 2016[[2]](#footnote-2), which better represent the complexity of treatment in this setting than those presented in the submission. The ESC also noted that contrary to the algorithm presented in the submission, transplant eligible patients in Australia are not able to access lenalidomide on the PBS.

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

# Comparator

* 1. The submission nominated two main comparators depending on the daratumumab combination:
  + For DBd the comparator is Bd; and
  + For DLd the comparator is Ld.
  1. During the evaluation, these comparators were considered appropriate. Both Bd and Ld are likely to be replaced by daratumumab based regimens.
  2. The ESC noted that both the Australian and International treatment guidelines present multiple options for treatment of RRMM as second line therapy. Whilst the nominated comparators of Bd and Ld are the two therapies used most commonly, they do not account for all second line therapy in patients with RRMM. The PBAC considered that there were other treatment options in the second line that were not addressed in the submission, such as Bd in combination with cyclophosphamide.
  3. The PBAC considered, in the context of the proposal in the pre-PBAC response to list DBd only, that Ld could also be considered a reasonable comparator for DBd.
  4. The submission nominated carfilzomib as a supplementary comparator; carfilzomib and dexamethasone (Cd) compared to DBd, and carfilzomib with lenalidomide and dexamethasone (CLd) compared to DLd. During the evaluation, this was considered an appropriate supplementary comparator. CLd and Cd were rejected at the November 2016 PBAC meeting. Cd was subsequently recommended for listing at the July 2017 meeting. The PBAC did not consider CLd at its July 2017 meeting (as it was not requested in the resubmission). The PBAC considered that Cd may also be a relevant comparator for DLd.

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

# Consideration of the evidence

## Sponsor hearing

* 1. The sponsor requested a hearing for this item. The sponsor presented clinical data that supported the consistency in treatment effect between both combination regimens. The sponsor also addressed the proposal in the pre-PBAC response to list DBd only, and reiterated that it was a valid clinical option for all patients, including using DBd after Bd in a prior line of therapy. The sponsor did not view listing daratumumab monotherapy as a way forward in isolation, particularly because daratumumab appears to have greatest effect when used in combination and early in treatment. The sponsor agreed that clinician preference was to switch the backbone therapy in the second line, and indicated that there was no currently no head-to-head clinical data available comparing DBd with Ld, which may be a relevant comparator in the event that only DBd was considered for PBS listing.

## Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (123), health care professionals (4) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with DBd or DLd, including improved survival, the potential to improve quality of life, and better tolerability.
  2. The PBAC noted the advice received from Myeloma Australia that reiterated the patients’ views that DBd and DLd have the potential to improve survival and quality of life.

## Clinical trials

* 1. The primary analysis presented in the submission was based on two head-to‑head randomised trials, one comparing DBd with Bd (CASTOR, n=498) and the other comparing DLd with Ld (POLLUX, n=569).
  2. The submission presented two indirect comparisons for the secondary comparator carfilzomib. The comparisons were:
* DBd (CASTOR, n=498) and Cd (ENDEAVOR, n=929), with Bd as the common reference arm; and
* DLd (POLLUX, n=569) and CLd (ASPIRE, n=792), with Ld as the common reference arm.
  1. Details of the daratumumab randomised trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| --- | --- | --- |
| **Direct randomised trials** | | |
| CASTOR  (NCT02136134) | MMY3004: Phase 3 Study Comparing Daratumumab, Bortezomib, and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Subjects with Relapsed or Refractory Multiple Myeloma. 120-Day Safety Update (20 October 2016). | 27 July 2016 |
|  | Palumbo, A., Chanan‑Khan, A., Weisel K., et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. | New England Journal of Medicine 2016; 375(8):754-66 |
|  | Palumbo, A., Chanan‑Khan, A., Weisel K., et al. Phase III randomised controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study. | Journal of Clinical Oncology 2016; 34, (suppl LBA4) |
|  | Weisel, K., Palumbo, A., Chanan-Khan, A., et al. Phase 3 randomised study of daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR. | Annals of Oncology 2016; 27 (Supplement 6): vi313–vi327 |
|  | Palumbo, A., Dimopoulos, MA., Reece, DE., et al. Twin randomised studies of daratumumab (DARA; D) plus standard of care (lenalidomide/dexamethasone or bortezomib/dexamethasone [DRd or DVd]) versus Rd or Vd alone in relapsed or refractory multiple myeloma (MM): 54767414MMY3003 (Pollux) and 54767414MMY3004 (Castor). | Journal of Clinical Oncology 2015; 33 (15 Suppl): TPS8609 |
|  | Mateos, M., Estell, J., et al. Efficacy of daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma based on prior lines of therapy: updated analysis of CASTOR | Blood 2016; 128 (22); 1150 |
|  | Avet-Loiseau, H., Casneuf, T., et al. Evaluation of minimal residual disease (MRD) in relapsed/refractory multiple myeloma (RRMM) patients treated with daratumumab in combination with lenalidomide plus dexamethasone or bortezomib plus dexamethasone. | Blood 2016; 128 (22), 246 |
|  | Chanan-Khan A., Lentzsch S., Quach H., et al. Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone alone for relapsed or refractory multiple myeloma based on prior treatment exposure: updated efficacy analysis of CASTOR. | Blood 2016; 128 (22), 3313 |
| POLLUX  (NCT02076009) | MMY3003. Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DLd) vs Lenalidomide and Dexamethasone (Ld) in Subjects With Relapsed or Refractory Multiple Myeloma. 120-Day Safety Update (20 October 2016). | 27 July 2016 |
|  | Dimopoulos M.A, Oriol A et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. | New England Journal of Medicine 2016; 375(14): 1319-1331 |
|  | Shah N.H, Dimopoulos M.A et al. An open-label, randomised, phase 3 study of daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): POLLUX. | Indian Journal of Hematology and Blood Transfusion 2016. 32 (pp S429) |
|  | Palumbo A, Dimopoulos M.A et al. Twin randomised studies of daratumumab (DARA; D) plus standard of care (lenalidomide/dexamethasone or bortezomib/dexamethasone [DRd or DVd]) versus Rd or Vd alone in relapsed or refractory multiple myeloma (MM): 54767414MMY3003 (Pollux) and 54767414MMY3004 (Castor). | Journal of Clinical Oncology 2015; 33 (15 Suppl): TPS8609 |
|  | Usmani S.Z, Meletios A et al. Efficacy of Daratumumab, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma Patients With 1 to 3 Prior Lines of Therapy: Updated Analysis of POLLUX. | Blood 2016; 128 (22), 1151 |
|  | Avet-Loiseau, H., Casneuf, T., et al. Evaluation of minimal residual disease (MRD) in relapsed/refractory multiple myeloma (RRMM) patients treated with daratumumab in combination with lenalidomide plus dexamethasone or bortezomib plus dexamethasone. | Blood 2016; 128 (22), 246 |

Source: Table 2.4, p.9 Section 2a of the submission; Table 2.4, p.8 Section 2b of the submission.

* 1. The key features of the direct randomised trials are summarised in the table below.

Table 3: Key features of the included evidence CASTOR and POLLUX

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **N** | **Design/ duration of follow-up** | **Risk of bias** | **Patient population** | **Outcomes** | **Use in modelled evaluation** |
| CASTOR | DBd: 251  Bd: 247  N: 498 | Phase 3, OL, AC, RCT, MC  CSR clinical cut-off: 7.4 mths  120-day safety update: 13.3 mths | Low | Received ≥ 1 previous lines of therapya | PFS, OS, ORR, MRD, PROs, safety | All outcomes used (MRD used to justify time horizon) except ORR. |
| POLLUX | DLd: 286  Ld: 283  N: 569 | Phase 3, OL, AC, RCT, MC  CSR clinical cut-off: 13.5 mths  120-day safety update: 17.3 mths | Low | Received ≥ 1 previous lines of therapya | PFS, OS, ORR, MRD, PROs, safety | All outcomes used (MRD used to justify time horizon) except ORR. |

Abbreviations: Bd, bortezomib-dexamethasone; CSR, clinical study report; DBd, daratumumab-bortezomib-dexamethasone; DLd, daratumumab-lenalidomide-dexamethasone; Ld, lenalidomide-dexamethasone; MC, multi-centre; MRD, minimal residual disease; OL, open label; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

Note: a. Documented MM and received ≥ 1 previous lines of therapy. At least a partial response to ≥ 1 previous therapies. Documented PD according to IMWG criteria during or after completion of last regimen.

Source: compiled during the evaluation.

* 1. CASTOR and POLLUX were open-label trials but had a low risk of bias as the outcomes were assessed using a computerised algorithm (PFS) or a definitive outcome (e.g. death).
  2. On the PBS up to 11 cycles of bortezomib is allowed subject to continuation rules (8 cycles to demonstrate response, then another 3 for responders). This differs from the CASTOR trial which allowed a maximum of 8 cycles of bortezomib therapy. Thus the incremental efficacy of DBd over Bd as estimated from the trial may be larger than expected with DBd use in the Australian setting. The PSCR referred to the DUSC multiple myeloma report, which showed that less than 20% of patients receive bortezomib beyond 8 cycles. On balance, the ESC considered that this difference was unlikely to result in clinically meaningful treatment differences between use of Bd in CASTOR and on the PBS.
  3. Across the CASTOR and POLLUX trials, there were differences in the baseline disease characteristics and prior therapies that may bias any comparison of treatment effects across the trials:
* The proportion of patients with International Staging System (ISS) low risk disease at baseline was approximately 39% in CASTOR and 50% in POLLUX, indicating a higher proportion of patients with better prognosis disease in the POLLUX trial.
* Prior use of therapy:
  + Prior use of the backbone therapy under investigation: A higher proportion of patients in CASTOR (66%) had received bortezomib previously, compared to POLLUX, where 18% of patients received prior lenalidomide.
  + Prior use of the other backbone therapy: 86% of patients in POLLUX (DLd vs. Ld) had received bortezomib previously, whereas 36-49% of patients in CASTOR (DBd vs. Bd) had received prior lenalidomide.
  + The median number of previous lines of therapy in CASTOR was 2 and in POLLUX was 1, suggesting that patients in CASTOR were more heavily pre-treated

## Comparative efficacy

* 1. The results for the primary outcome, PFS, are presented in Table 4 and Figures 1 (CASTOR) and 2 (POLLUX). The ESC noted that the median PFS was not reached in the daratumumab treatment groups, even with the longer-term follow-up, which indicates that the data are immature. The ESC considered that the data therefore may not accurately reflect the longer-term risks of progression associated with daratumumab based therapies. The PBAC considered the PFS may also not accurately reflect the mean duration of daratumumab use in practice.

Table 4: Results of progression free survival across the studies

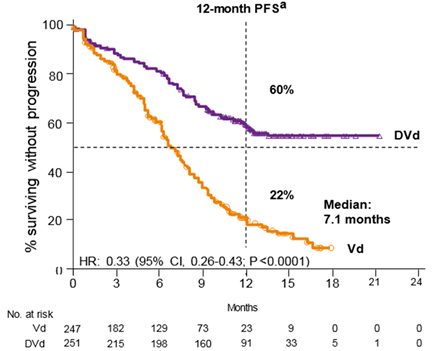
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **CASTOR** | **DBd, N=251** | | **Bd, N=247** | | **Median difference** | **P value (log rank test)** | **Hazard ratio (95% CI)** |
| **n/N with event (%)** | **Median, months (95% CI)** | **n/N with event (%)** | **Median, months**  **(95% CI)** |
| Initial follow-up: Computer Algorithma,c | 67 (26.7) | NE  (12.25. NE) | 122 (49.4) | 7.16  (6.21, 7.85) | NE | P<0.0001 | 0.39  (0.28, 0.53) |
| Initial follow-up: Investigator Assessed a,d | '''''' ''''''''''''''' | '''''''''''' ''''''''''''''''' '''''''''' | '''''''''' '''''''''''''' | '''''''''''  '''''''''''''' ''''''''''''' | '''''''''' | '''''''''''''''''''' | '''''''''''  '''''''''''''' ''''''''''''' |
| Subsequent follow-up: Computer Algorithmb,c | 100 (39.8) | NE  (12.6, NE) | 177 (71.7) | 7.1  (6.2, 7.7) | NE | P<0.0001 | 0.33  (0.26, 0.43) |
| **POLLUX** | **DLd, N=286** | | **Ld, N=283** | | **Median difference, months** | **P value (log rank test)** | **Hazard ratio (95% CI)** |
| **n/N with event (%)** | **Median, months (95% CI)** | **n/N with event (%)** | **Median, months**  **(95% CI)** |
| Initial follow-up: Computer Algorithma,c | 53 (18.5) | NE  (NE, NE) | 116 (41.0) | 18.43 (13.86, NE) | NE | P<0.0001 | 0.37  (0.27, 0.52) |
| Initial follow-up: Investigator Assessed a,d | '''''' '''''''''''''' | '''''''  ''''''''''' '''''''''' | '''''''''' ''''''''''''''' | ''''''''''''' ''''''''''''''''' '''''''' | '''''''' | '''''''''''''''''''''' | '''''''''''  ''''''''''''''' '''''''''''' |
| Subsequent follow-up: Computer Algorithmb,c | 66 (23.1) | NE  (NE, NE) | 135 (47.7) | 17.5  (13.9, NE) | NE | P<0.0001 | 0.37  (0.28, 0.50) |

Abbreviations: Bd, bortezomib-dexamethasone; CI, confidence interval; DBd, daratumumab-bortezomib-dexamethasone; DLd, daratumumab-lenalidomide-dexamethasone; Ld, lenalidomide-dexamethasone; n, number of participants reporting data; N, total participants in group; NE, not evaluable.

Note: a median follow-up for CASTOR is 7.4 months and POLLUX is 13.5 months; b median follow-up for CASTOR is 13.3 months and POLLUX is 17.3 months; c. PFS measured by computerised algorithm.; d. PFS measured by investigator assessed. ;

Source: Table 2.26 and Table 2.27, p.52 and p.56 Section 2a of the Submission; Table 2.27 and Table 2.28, p.50 and p.54 Section 2b of the Submission; CASTOR CSR Table 15, p.74; POLLUX CSR, Table 16, p.70 and compiled during the evaluation.

Figure 1: Kaplan-Meier Curve of PFS (ITT population, computerised algorithm), CASTOR



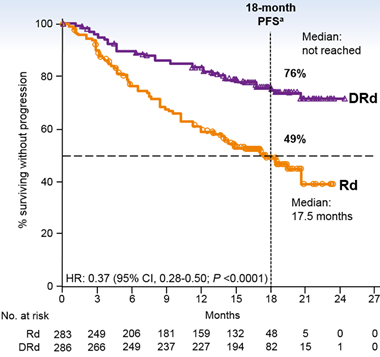
Abbreviations: CI, confidence intervals; DVd, daratumumab-bortezomib-dexamethasone; HR, hazard ratio; PFS, progression free survival.

Note: Median follow-up for CASTOR is 13.2 months. a Kaplan-Meier estimate

Source: Figure 2.4, p.53 Section 2a of the submission.

* 1. For the CASTOR trial subgroup analyses based on prior use of bortezomib were presented. Bortezomib was previously used in 65-66% of patients. The HR for PFS was '''''''' (95% CI: ''''''''' '''''''') for those who had not received prior bortezomib treatment and was ''''''''' (95% CI: ''''''''' ''''''''') for those who had received prior bortezomib. The PBAC noted that while the improvement in PFS for patient who had previous bortezomib was statistically significant, based on the point estimates, DBd was less effective in these patients. The PBAC considered that this may be relevant in the context of the proposal to list DBd only, as patients previously treated with bortezomib would not have the option to change the backbone therapy.

Figure 2: Kaplan-Meier Curve of PFS (ITT population, computerised algorithm), POLLUX



Abbreviations: CI, confidence intervals; DRd, daratumumab-lenalidomide-dexamethasone; HR, hazard ratio; PFS, progression free survival; Rd, lenalidomide-dexamethasone;

Note: Median follow-up for POLLUX is 17.3 months. a Kaplan-Meier estimate

Source: Figure 2.3, p.51 Section 2b of the submission.

* 1. The results for OS at the 120-Day Safety Update (longer-term follow-up) are presented in Table 5, with the Kaplan-Meier plots for CASTOR in Figure 3 and POLLUX in Figure 4. The median OS had not been reached at the longer-term follow-up in any arm across the two trials. The PBAC agreed with the ESC that the data are immature and may not accurately reflect the longer-term benefits associated with daratumumab based therapies.

Table 5: Results of overall survival across the studies

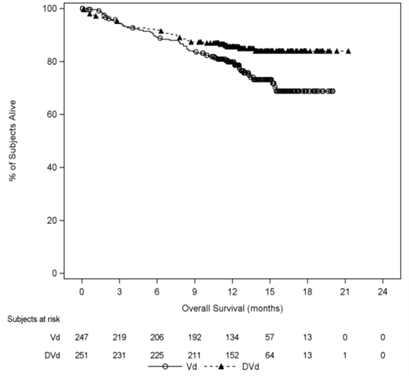
|  | **n/N with event (%)** | **Median (95% CI), months** | **n/N with event (%)** | **Median (95% CI), month** | **Median difference, months** | **P value (log rank test)** | **Hazard ratio (95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **CASTOR** | **DBd** | | **Bd** | |  |  |  |
|  | 37/251 (14.7) | NE (NE,NE) | 58/247 (23.5) | NE (NE, NE) | NE | P=0.029 | 0.63 (0.42,0.96) |
| **POLLUX** | **DLd** | | **Ld** | |  |  |  |
|  | 40/286 (14.0) | NE (NE,NE) | 56/283 (19.8) | NE (NE, NE) | NE | P=0.027 | 0.63 (0.42,0.95) |

Abbreviations: CI, confidence interval; n, number of participants reporting data; N, total participants in group; NE, not evaluable.

Note: Median follow-up in CASTOR is 13.0 months and POLLUX is 17.3 months

Source: Table 2.28, p.58 Section 2a of the submission; Table 2.29, p.56 Section 2b of the submission.

Figure 3: Kaplan-Meier curve of overall survival (ITT population), CASTOR

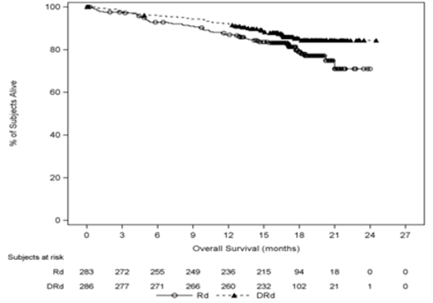


Abbreviations: DVd, daratumumab-bortezomib-dexamethasone; ITT, intent-to-treat; Vd, bortezomib-dexamethasone.

Note: median follow-up for CASTOR is 13.2 months.

Source: Figure 2.6, p.58 Section 2a of the submission.

Figure 4: Kaplan-Meier curve of overall survival (ITT population), POLLUX



Abbreviations: D, daratumumab; d, dexamethasone; ITT, intent-to-treat; R, lenalidomide

Note: median follow-up for POLLUX is 17.3 months.

Source: Figure 2.5, p.56 Section 2b of the submission.

* 1. The results for the overall response rate are presented in Table 6, and Minimal Residual Disease (MRD) negativity in Table 7. Daratumumab in combination with either Bd or Ld was associated with a statistically significant improvement in the overall response rate, and was associated with more patients achieving MRD negativity (at all sensitivity levels). The submission argued that there is some evidence that overall survival is improved in patients who achieve MRD negativity. However, no claim of a survival gain on the basis of gains in MRD negativity was made in the submission or included in its economic evaluation.

Table 6: Results of overall responses (computerised algorithm) across the studies (response evaluable population)

| **Trial ID** | **n/N with event (%)** | **n/N with event (%)** | **OR (95% CI), p-valuea** | **Risk difference (95% CI)** |
| --- | --- | --- | --- | --- |
| **CASTOR** | **DBd** | **Bd** |  |  |
| ORR | 202/240 (84) | 147/234 (63) | '''''''''' '''''''''''''' '''''''''''', p<0.0001 | ''''''''''''' ''''''''''''''' '''''''''''''''' |
| **POLLUX** | **DLd** | **Ld** |  |  |
| ORR | '''''''''''''''''''''' '''''''''' | ''''''''''''''''''''' ''''''''' | '''''''''' '''''''''''''' ''''''''''''''' '''''''''''''''''''' | '''''''''''''' '''''''''''''''' ''''''''''''''' |

Abbreviations: Bd, bortezomib and dexamethasone; DBd, daratumumab, bortezomib, and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; CI, confidence interval; Ld, lenalidomide and dexamethasone; n, number of participants with event; N, total participants in group; NR, not reported; OR, odds ratio; ORR, overall response rate

Note: Median follow-up in CASTOR is 13.0 months and POLLUX is 17.3 months. ORR is stringent complete response + complete response + very good partial response + partial response

a. The OR and p-value for the longer-term follow-up data was calculated by the sponsor and not adjusted by stratification factors as done in the primary analysis of ORR.

Source: Table 2.34, p.71 Section 2a of the submission; Table 2.3.5, p.70 Section 2b of the submission. Risk difference calculated during the evaluation.

Table 7: Results of MRD negative rate at 10-4, 10-5, 10-6 sensitivity levels across the studies (ITT population)

| **Trial ID** | **n/N with event (%)** | **n/N with event (%)** | **OR (95% CI), p-value** | **Risk difference (95% CI)** |
| --- | --- | --- | --- | --- |
| **CASTOR** | **DBd** | **Bd** |  |  |
| MRD (10-4) | 46/251 (18.3) | 9/247 (3.6) | 5.1 (NR, NR), p<0.0001 | ''''''''''''''' ''''''''''''''' '''''''''''''' |
| MRD (10-5) | 26/251 (10.4) | 6/247 (2.4) | 4.3 (NR, NR), p<0.005 | ''''''''''' ''''''''''''''' ''''''''''''''' |
| MRD (10-6) | 11/251 (4.4) | 2/247 (0.8) | 5.5 (NR, NR), p<0.05 | ''''''''''' ''''''''''''' '''''''''''''' |
| **POLLUX** | **DLd** | **Ld** |  |  |
| MRD (10-4) | 91/286 (31.8) | 25/283 (8.8) | 3.6 (NR, NR), p<0.0001 | '''''''''''' '''''''''''''''''' ''''''''''''''' |
| MRD (10-5) | 71/286 (24.8) | 16/283 (5.7) | 4.4 (NR, NR), p<0.0001 | ''''''''''''' '''''''''''''''' '''''''''''''' |
| MRD (10-6) | 34/286 (11.9) | 7/283 (2.5) | 4.8 (NR, NR), p<0.0001 | '''''''''''' ''''''''''''''' '''''''''''''''' |

Abbreviations: Bd, bortezomib and dexamethasone; DBd, daratumumab, bortezomib, and dexamethasone; DLd, daratumumab, lenalidomide and dexamethasone; CI, confidence interval; Ld, lenalidomide and dexamethasone; MRD, minimal residual disease; n, number of participants with event; N, total participants in group; NR, not reported; OR, odds ratio.

Note: Median follow-up in CASTOR is 13.0 months and POLLUX is 17.3 months. For patients without MRD result it was assumed they did not achieve a negative result.

Source: Table 2.40, p.79 Section 2a of the submission; Table 2.4.1, p.79 Section 2b of the submission. Risk difference calculated during the evaluation.

* 1. The ESC noted that the sponsor requested patients who experience toxicity to Bd or Ld after commencement of daratumumab combination therapy be allowed to continue on daratumumab monotherapy. However, it is unclear what affect this would have on the effectiveness of the proposed treatment. The submission stated that '''''''% of patients in the DLd arm received daratumumab monotherapy after the 120 day safety update. Information on the number of patients in the DBd arm of CASTOR that moved to daratumumab monotherapy before completing 8 cycles of DBd was not provided.
  2. The supplementary indirect comparison of DBd vs. Cd using Bd as the common comparator included the CASTOR (DBd vs. Bd) and ENDEAVOR (Cd vs. Bd) trials. In the ENDEAVOR trial median PFS was 18.7 months in the Cd group and 9.4 months in the Bd group (HR 0.53, 95% CI: 0.44-0.65), with a median duration of follow-up of 11.9 months and 11.1 months, respectively. The HR for the indirect treatment comparison of DBd and Cd for PFS was '''''''' (95% CI: '''''''' ''''' '''''''''), with median follow-up in CASTOR of 13.0 months. In ENDEAVOR, median OS survival was not reached for Cd and was 24.3 months for Bd and the HR was 0.79 (95% CI: 0.58-1.08). The HR for the indirect treatment comparison of DBd and Cd for OS resulted in a HR was ''''''''' (95% CI: ''''''''' ''''' '''''''''), with median follow-up in CASTOR of 13.3 months.
  3. The indirect comparisons were potentially confounded by a number of factors:
  + more patients in CASTOR were ISS stage II (moderate risk) compared to ENDEAVOR, which may favour Cd;
  + More patients in CASTOR had been previously treated with Bd compared with those in ENDEAVOR. This may favour DBd because patients who have previously responded to bortezomib may be more likely to respond to repeat bortezomib if an additional agent is added;
  + The higher rate of progression in CASTOR vs ENDEAVOR; and
  + CASTOR only permitted 8 cycles of Bd, whereas ENDEAVOR permitted treatment until disease progression, which may favour Cd.

The ESC noted that due to confounding factors, this comparison should be interpreted with caution. The PBAC considered that it may be more informative for an indirect comparison to be performed on the Bd naïve subgroup of patients of each trial.

## Comparative harms

* 1. A summary of the key safety outcomes from the 120-Day Safety Updates for CASTOR and POLLUX is presented in Table 8.

Table 8: Summary of key adverse events in the direct randomised trials

|  |  |  |  |
| --- | --- | --- | --- |
| **Trial ID** | **n with event/N (%)** | **n with event/N (%)** | **RD (95% CI)** |
| **CASTOR (120-Day safety update)** | **DBd, N=243** | **Bd, N=237** |  |
| Any AE, n (%) | ''''''''' '''''''''''' | '''''''''' '''''''''''''' | **''''''''''''' '''''''''''''' '''''''''''''''** |
| Grade 3 and 4 AEs | '''''''' ''''''''''''''' | '''''''''' ''''''''''''''' | **''''''''''''''' ''''''''''''' ''''''''''''''''** |
| Any serious AE, n (%) | ''''''''' '''''''''''''''' | ''''' ''''''''''''''' | **'''''''''''''''' '''''''''''''' '''''''''''''''** |
| ≥1 AE related to discontinuation of all study treatment, n (%) | '''''' '''''''''' | '''''' '''''''''''' | ''''''''''''''' ''''''''''''''''''' ''''''''''''''''' |
| Total no. deaths within 30 days of last dose, n (%) | '''''' ''''''''''' | '''''' ''''''''''' | '''''''''''''''' '''''''''''''''''' '''''''''''''''' |
| **POLLUX (120-Day safety update)** | **DLd, N=318** | **Ld, N=281** |  |
| Any AE, n (%) | '''''''''' ''''''''''''''' | '''''''' ''''''''''''' | '''''''''''''''' ''''''''''''''''''''' '''''''''''''''' |
| Grade 3 or 4 AEs | ''''''''' '''''''''''''' | ''''''''' ''''''''''''''' | **'''''''''''''' '''''''''''''''' '''''''''''''''''** |
| Any serious AE, n (%) | ''''''''' ''''''''''''' | ''''''''' ''''''''''''''' | **''''''''''''' ''''''''''''''' ''''''''''''''''** |
| ≥1 AE related to discontinuation of all study treatment, n (%) | ''''' '''''''''''' | ''''' '''''''''''' | '''''''''''''''''' '''''''''''''''''' '''''''''''''''' |
| Total no. deaths within 30 days of last dose, n (%) | ''''''' ''''''''''' | '''''' ''''''''''' | '''''''''''''''' '''''''''''''''''''''' ''''''''''''''''''' |

Abbreviations: AE, adverse event; Bd, bortezomib-dexamethasone; CI, confidence intervals; DBd, daratumumab-bortezomib-dexamethasone; DLd, daratumumab- lenalidomide-dexamethasone; RD, risk difference

Note: ''' ''''''''' '''''''''''''''''''''' ''' '''' '''''''''''''''''' '''''''' ''''' '''''' ''''''''''' '''''''''' ''''' '''''''''. Median follow-up in CASTOR is 13.0 months and POLLUX is 17.3 months.

Source: Table 2.44, p. 92 Section 2a of the submission and Table 2.45, p.92 Section 2b of the submission.

* 1. Both DBd and DLd resulted in a higher proportion of grade 3 and 4 adverse events compared to Bd and Ld, respectively.
  2. In CASTOR, the grade 3 or 4 adverse events that occurred more often in DBd treated patients included lymphopenia, neutropenia, thrombocytopenia, hypertension and infusion site reactions.
  3. In POLLUX, the grade 3 or 4 adverse events that occurred more often in DLd treated patients included neutropenia, infections and infestations, and infusion site reactions.
  4. In the ENDEAVOR trial, Cd resulted in more grade 3 or 4 adverse events compared to Bd (RR 1.09, 95% CI: 1.01 to 1.19). DBd also resulted in more (RR 1.26, 95% CI: 1.12 to 1.42) grade 3 or 4 adverse events compared to Bd in the CASTOR trial. The indirect treatment comparison of DBd and Cd for grade 3 or 4 adverse events resulted in a RR of ''''''''' (95% CI: '''''''''' ''''''''').
  5. The PBAC considered that the occurrence of toxicities in these trials was consistent with that commonly seen by haematologists in the treatment of patients with RRMM, and that they could be appropriately managed in the clinical setting.

## Benefits and harms

* 1. A summary of the comparative benefits and harms for DBd versus Bd and DLd versus Ld is presented in the table below.

Table 9: Summary of comparative benefits and harms for DBd vs. Bd and DLd vs. Ld

| Benefits | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Event** | | | **Proposed drug** | | | **Main comparator** | | **Absolute Difference (%)** | | **HR (95% CI)** |
| **CASTOR (DBd vs. Bd)\*** | | |  | | |  | |  | |  |
| Progressed, n (%) | | | 100/251 (39.8) | | | 177/247 (71.7) | | 32.4 | | 0.33 (0.26, 0.43) |
| Dead, n (%) | | | 37/251 (14.7) | | | 58/247 (23.5) | | 8.8 | | 0.63 (0.42, 0.96) |
| **POLLUX (DLd vs. Ld)\*** | | |  | | |  | |  | |  |
| Progressed, n (%) | | | 66/251 (23.1) | | | 135/283 (47.7) | | 24.6 | | 0.37 (0.28, 0.50) |
| Dead, n (%) | | | 40/286 (14.0) | | | 56/283 (19.8) | | 5.8 | | 0.63 (0.42, 0.95) |
| **Harms** | | | | | | | | | | |
|  | **Proposed drug** | | | **Main comparator** | **RR**  **(95% CI)** | | **Events/100 patients\*** | | | **RD**  **(95% CI)** |
| **Proposed drug** | | **Main comparator** |
| **Any AE** | | | | | | | | | | |
| CASTOR (DBd vs. Bd) | | ''''''''''''''''''''' | | '''''''''''''''''''' | '''''''''' ''''''''''''''' ''''''''''''' | | ''''''''''' | | '''''''''' | '''''''''''''''' ''''''''''''''''''' '''''''''''''''''' |
| POLLUX (DLd vs. Ld) | | '''''''''''''''''''' | | ''''''''''''''''''' | '''''''''' '''''''''''''''''''''''' | | '''''''''' | | '''''''''' | '''''''''''''' ''''''''''''''''''''' ''''''''''''''''''' |
| **Grade 3 and 4 AE** | | | | | | | | | | |
| CASTOR (DBd vs. Bd) | | ''''''''''''''''' | | ''''''''''''''''''''' | ''''''''''' '''''''''''''' '''''''''''''' | | '''''''''''' | | ''''''''''' | '''''''''''''''''' '''''''''''''''''''' ''''''''''''''''''' |
| POLLUX (DLd vs. Ld) | | ''''''''''''''''''' | | '''''''''''''''''' | '''''''''' ''''''''''''' ''''''''''''' | | '''''''''' | | '''''''''' | ''''''''''''''' ''''''''''''''''' ''''''''''''''''''' |
| **Any Serious AE** | | | | | | | | | | |
| CASTOR (DBd vs. Bd) | '''''''''''''''''' | | | ''''''''''''''' | ''''''''''' ''''''''''''''''''''''' | | '''''''''' | | '''''''''''' | ''''''''''''''''''' '''''''''''''''''' ''''''''''''''''''''' |
| POLLUX (DLd vs. Ld) | '''''''''''''''''''' | | | ''''''''''''''''''' | ''''''''''' ''''''''''''''' '''''''''''''' | | '''''''''' | | '''''''''' | '''''''''''''' ''''''''''''''''''' '''''''''''''''''''''' |

\* Median follow-up for CASTOR is 13.3 months and POLLUX is 17.3 months Abbreviations: PBO, placebo; RD, risk difference; RR, risk ratio. There were 35 DLd patients added from single arm daratumumab study (GEN503)

Source: Table 2.27, p.56 Section 2a of the Submission; Table 2.28, p.54 Section 2b of the Submission; Table 3.2, p.8 Section 3 of the submission. Table 2.28, p.58 Section 2a of the submission; Table 2.29, p.56 Section 2b of the submission. The risk difference and relative risk were calculated during the evaluation.

* 1. On the basis of the direct evidence presented in the CASTOR trial, for every 100 patients treated with DBd over a median follow-up of 13.3 months:
  + 32 fewer would have progressed than if treated with Bd.
  + 9 fewer would have died than if treated with Bd.
  + '''''' additional patients would have a Grade 3 or 4 adverse event than if treated with Bd.
  1. On the basis of the direct evidence presented in the POLLUX trial, for every 100 patients treated with DLd over a median follow-up of 17.3 months:
  + 25 fewer would have progressed than if treated with Ld.
  + 6 fewer would have died than if treated with Ld.
  + ''' additional patients would have a Grade 3 or 4 adverse event than if treated with Ld.

## Interpretation of clinical evidence

* 1. The PBAC considered that the submission’s claim of superior efficacy of DBd over Bd was supported by the data statistically, although the data are immature and may not reflect the differences between the treatment arms in the longer term. The PBAC noted there is no plateau on the PFS curve, and thus risk of progression and death from myeloma will likely remain continuous.
  2. The PBAC considered that the submission’s claim of inferior safety of DBd over Bd was supported by the data. However the PBAC noted that the similar and relatively low discontinuation rates in both arms of the trial suggested that the toxicity was manageable.
  3. The PBAC considered that the submission’s claim that DBd was superior compared to Cd in terms of effectiveness and non‑inferior in terms of safety was uncertain due to the potential biases and confounding factors between the trials used in the indirect comparison.
  4. The PBAC considered that the submission’s claim of superior efficacy of DLd over Ld was supported by the data statistically, although the data are immature and may not reflect the differences between treatment arms in the longer term. The PBAC noted there is no plateau on the PFS curve, and thus risk of progression and death from myeloma will likely remain continuous.
  5. The PBAC considered that the submission’s claim of inferior safety of DLd over Ld was supported by the data. However the PBAC noted that the similar and relatively low discontinuation rates in both arms of the trial suggested that the toxicity was manageable.
  6. In order to recommend DBd or DLd at a higher price than Cd, the PBAC would need to be satisfied that DBd or DLd provide, for some patients, a significant improvement in efficacy or reduction in toxicity over Cd. The PBAC did not consider that this had been adequately established by the data presented in the submission.
  7. The ESC was of the view that although the results from both CASTOR and POLLUX supported the claim of superiority over the nominated comparators, both studies were based on immature data, which may not accurately reflect the longer-term comparative risks of progression or death associated with daratumumab based therapies. The PBAC considered that although the data supported the claim of superiority of DBd and DLd over Bd and Ld respectively, the immaturity of the data and lack of demonstrated survival benefit compared to other relevant therapies meant that the magnitude of the incremental benefit was highly uncertain.
  8. The ESC also noted that there are no data on the efficacy of existing doublet or monotherapies for RRMM after DBd or DLd. The impact on overall outcomes of the introduction of a triplet therapy (DBd) earlier in the sequence of treatments for RRMM is therefore unknown. The PBAC considered there was additional uncertainty regarding the incremental benefit of adding to daratumumab to Bd with no comparison provided with cyclophosphamide and Bd, which is another commonly used regimen.

## Economic analysis

* 1. The submission presented two cost-utility analyses: DBd vs Bd (based on the CASTOR trial); and DLd vs Ld (based on the POLLUX trial). The two economic models were structurally identical with different inputs. A summary of the model structure and rationale is presented in Table 10.

Table 10: Summary of model structure and rationale

| **Component** | **Summary** |
| --- | --- |
| Time horizon | Lifetime horizon (20 years) in the model base case versus 20 months in CASTOR and 24 months in POLLUX. |
| Outcomes | LYG and QALYs. |
| Methods used to generate results | Partitioned survival model, incorporating a cohort expected value analysis. |
| Health states | Three: progression free, progressive disease and death. |
| Utilities | CASTOR and POLLUX for baseline, on-treatment and progression free health states. For progressed disease, a utility value (0.61) was used from the pomalidomide trial MM-003, PSD November 2014. The submission did not use the within trial values for PD as these were based on a small sample size. Within trial values for PD were used in sensitivity analyses. |
| Cycle length | 1 month. |
| Transition probabilities | Partitioned survival model with patients in the progressed (alive) health state estimated as the residual of PFS and OS.  During the trial time horizon: Based on Kaplan-Meier (KM) time to event estimates of time to progression and time to death as measured in the CASTOR and POLLUX trials. Because the KM estimates become unstable as the number of patients at risk reduces, these estimates were used only up to the time point at which there were at least 20% of the patients remaining in the risk set. The PBAC noted that this may favour daratumumab, and that it may be more appropriate to use the KM estimates to median follow-up.  Beyond the trial time horizon: Transition probabilities beyond the trial time horizon were based on a parametric extrapolation of the trial time to event data. The choice of parametric function was based on statistical goodness of fit tests (Akaike information criterion [AIC] and Bayesian information criterion [BIC]) and the clinical plausibility (which relied on visual inspection to choose the extrapolated curve with the “leanest” tail; implying the curve that results in the lowest prolonged surviving cohort).  The time points (months) from which extrapolations began were as follows:  For DBd vs Bd:  • DBd = PFS 13.9, OS 13.8, TTD 13.8 months.  • Bd = PFS 10.7, OS 15.2, TTD 5.3 months.  For DLd vs Ld:  • DLd = PFS 18.7, OS 17.5; TTD 19.1 months.  • Ld = PFS 18.0, OS 18.5, TTD 17.9 months.  A range of different functional forms was used to extrapolate the same outcomes (e.g. PFS) across the different treatment regimens as follows:  DBd vs Bd:  • PFS to PD = Weibull  • Survival to death = Exponential  • TTD = DBd Exponential; Bd Weibull  DLd vs Ld:  • PFS to PD = Exponential  • Survival to death = Weibull  • TTD = DLd Exponential, Ld Exponential  The ESC considered that the use of these different functional forms was not justified in the submission. |

Abbreviations: Bd, bortezomib-dexamethasone; DBd, daratumumab-bortezomib-dexamethasone; DLd, daratumumab-lenalidomide-dexamethasone; Ld, lenalidomide-dexamethasone; KM, Kaplan-Meier; OS, overall survival; PD, progressive disease; PFS, progression free survival; QALYs, Quality Adjusted Life Year, TTD, time to treatment discontinuation;

Source: Table 3.1, p.6 Section 3 of the submission.

* 1. The ESC noted that the model applied a 20 year time horizon, which was considerably longer than the 10 year time horizon applied for carfilzomib. The PBAC previously considered that applying a 15 year time horizon to the carfilzomib economic analysis “was not reasonable, given the patients’ age… applying a 10 year time horizon would be more appropriate” (p.19, carfilzomib PSD November 2016). The ESC considered that the same rationale would apply in the context of modelling the cost-effectiveness of the daratumumab based regimens, and that the use of a 10 year time horizon, as compared with the 20 year horizon presented in the submission, would better reflect the natural history of the disease and be consistent with the consideration of the evidence for carfilzomib. The pre‑PBAC response (p2) claimed that consistency with the carfilzomib model was not a valid rationale for a 10 year time horizon given that DBd and DLd demonstrate superior efficacy to carfilzomib. However, the PBAC considered that as a survival benefit for DBd or DLd over Cd had not been demonstrated, this was an insufficient justification for a longer time horizon. The PBAC further considered that while some patients may be alive beyond 10 years and possibly 15 years, extrapolation of immature trial data to 20 years substantially increases the uncertainty with the cost effectiveness estimates (refer to Table 15 below). It was considered that the greatest confidence in establishing cost effectiveness will be derived by limiting the time horizon to 10 years.
  2. The economic evaluation for DBd vs Bd included a maximum of 8 cycles of treatment with Bd only and may not reflect utilisation on the PBS. The ESC noted the PSCR argued that there would be no difference in clinical outcomes between the use of Bd in CASTOR and on the PBS because <20% of PBS patients received 11 cycles of Bd. The PBAC agreed with the ESC that the difference in the number of cycles was unlikely to result in a substantial difference in clinical outcomes, but would also potentially reduce the costs associated with Bd in the economic model. The PBAC considered that the overall impact of assuming a maximum of 8 cycles of Bd was unclear.
  3. The key drivers of the model for DBd vs. Bd are presented in Table 11.

Table 11: Key drivers of the model in DBd vs Bd

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| Extent of extrapolation of PFS/OS | Treatment effect continued beyond median follow-up of 13.3 months for up to 20 years. | High, favours DBd |
| '''''''''''''''''''''' ''''''''''''''''''''''' ''''''' ''''''''''''''''''''''''''''''''''' | '''''''''''''''''''''' '''' '''''''''''''''' '''''' ''''''''' ''''''''''''' '''' '''''''''''''''''''''''''''''''''' '''''''''''''''''''' '''''' '''''''''' ''''''''' '''''''' '''''' ''''''' '''''''''''''''''''' ''''' ''' ''''''''''' ''''''''''''''''''''''' ''''''''''''''''''''''' '''' ''''''' '''''''''' '''''''' '''''''''''''' ''''''''''''''''' ''''''''''' '''''''''''''''''''''' ''''' ''''''''''''''''''''' '''''''''''' ''''''' | High |
| Discounting | Annual rate of 5% | High |
| Time horizon | Model adopts a 20-year time horizon, which it supports with data from the PBS/Australia Cancer Database to support patient longevity in this indication. | High, favours DBd |

Source: compiled during the evaluation Excel spreadsheet ‘RR MM – Model DBd vs Bd’

* 1. The key drivers of the model for DLd vs. Ld are presented in Table 12.

Table 12: Key drivers of the model in DLd vs. Ld

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| Extent of extrapolation of PFS/OS | Treatment effect continued beyond median follow-up of 17.3 months for up to 20 years; | High, favours DLd |
| '''''''''''''''''''''' ''''''''''''''''''''''' '''''' '''''''''''''''''''''''''''''''''' | '''''''''''''''''''''' '''' '''''''''''''''' '''''' '''''''' ''''''''''''' ''' '''''''''''''''' ''''''''''''''''''''''''''''''''''' ''''''''''''''''''' ''''''' '''''''''' '''''''' '''''' ''''''''''''''''' ''''' ''' ''''''''''''''' '''''''''''''''''''''''' '''''''''''''''''''''' '''' '''''''' '''''''''' '''''''' '''''''''''''''' ''''''''''''''' '''''''''''' ''''''''''''''''''''' '''' '''''''''''''''''''' ''''''''''' ''''''' | High |
| Discounting | Annual rate of 5%. | High |
| ''''''''''''''''''''''''''''' '''''''''' ''''''''''''''''''''''' | '''''''''' ''''''''''''''''''''''''' '''''''''''''''' ''''''''''' ''''''''''''''''''''' '''''''''' ''''''' ''''''''''''''''''''' ''''''''''''''''''''''''' ''''''''''' '''''' '''''''''' '''''''' '''''''''''''''''''''''''''''''''''''''' | High, favours DLd |
| Time horizon | Model adopts a 20 year time horizon, which it supports with data from the PBS/ACD to support patient longevity in this indication. | High, favours DLd |

Source: compiled during the evaluation Excel spreadsheet ‘RR MM – Model DLd vs Ld’

* 1. Two stepped economic evaluations were presented.
  + Step 1 was a trial-based economic evaluation;
  + Step 2 extrapolated to a lifetime horizon and included ''''''''''''' '''''' '''''''''''''''''' ''''' ''''''''''''''''''''''''''''', ''' ''''''''' '''''''''''''''''' '''''' '''''''''''''''''''', and a ''''''''''''''''''''''''' '''''''''''''''' '''' ''''''' ''''''''' '''' '''''''''''''''''''''';
  + Step 3 represents the proportional use of daratumumab combination therapy in a world where it is reimbursed compared to when it is not (based on commissioned market research), which the PSCR argued was intended to illustrate the impact of the “Multiple Myeloma Treatment Package” offered in the submission '''''' '''''' ''''''''' '''' ''''''''''''''''''''''' both in combination with daratumumab and alone.
  1. The ESC considered that the presentation of a proportional uptake analysis (Step 3) in the submission was not an appropriate approach to the assessment of cost‑effectiveness, which is the comparison of an intervention (DBd or DLd) and its appropriate comparator (Bd or Ld, respectively) for a given cohort. The PBAC agreed with the ESC that a more appropriate comparison would be the assessment of cost‑effectiveness based on 100% use of the alternatives (DBd vs Bd and DLd vs Ld).
  2. The ESC noted that both Step 2 and Step 3 (base case) also included the impact of proposed '''''''''''''' for daratumumab, the proposed ''''''''' '''''''''''''''''''' '''''' ''''''''''''''''''''', and the '''''''''''''''' '''''''''''''' ''''''''' ''''''''''''''''' ''''' ''''''''''''''''''''''. The PBAC noted that the pre-PBAC response indicated that the ''''''''' '''''''''''''''''' ''''''''''''''' '''''' ''''''''''''''''''''''' would remain if only DBd were to be listed, and therefore considered inclusion of the ''''''''''''' '''''''' '''''''''' ''''''''''''''''' for daratumumab and bortezomib, respectively, may be reasonable as both of these are supplied by the sponsor. However, the PBAC noted that the ''''''''' ''''''''''''''''''' ''''' ''''''''''''''''''''''''' '''''''' '''''' ''''''''''''''''''' ''''''' '''''''''' ''''''' ''''' '''''''''''''''''''''' '''''''' therefore agreed with the ESC that ''''''' ''''''''' ''''''''''''''''''' '''''' ''''''''''''''''''''''''' should not be included in the economic analysis.
  3. The PBAC therefore considered that the most appropriate approach for the base case analysis would be to use Step 2 without the ''''''''' ''''''''''''''''''' '''''' ''''''''''''''''''''''. The ESC also advised that the modelled changes should be provided as individual steps, rather than bundled together in Step 2.
  4. The results of the stepped economic evaluation are presented in Tables 13‑14. These estimates include corrections provided in the PSCR that ensured that treatment exposure did not exceed PFS, and that the correct dose intensity was used for Ld in the DLd model. While the impact of these changes was verified, they did not address the structural and parameter uncertainties in the cost-effectiveness analysis as identified by the ESC. Accordingly, the robustness of the model estimates was assessed based on changes from Step 2 as contained in the submission.

Table 13: Results of the stepped economic evaluation, DBd vs. Bd

| **Step** | **Costs** | | | **QALYs** | | | **Cost per QALY gained** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **DBd** | **Bd** | **Incr** | **DBd** | **Bd** | **Incr** |
| Step 1: CASTOR transformed to QALY (20-month follow-up) | '''''''''''''''''''' | ''''''''''''''''''''' | ''''''''''''''''''' | '''''''''' | '''''''''' | '''''''''' | ''''''''''''''''''''' |
| Step 2: Step 1 extrapolated to lifetime horizon | '''''''''''''''''''' | ''''''''''''''''''''' | ''''''''''''''''''''''' | '''''''''''' | ''''''''''' | '''''''''' | ''''''''''''''''''''' |
| Step 2: PSCR revised to reflect minimum of time on treatment and PFS | ''''''' | '''''''' | ''''''''''''''''''''' | '''''''' | '''''''' | '''''''''' | '''''''''''''''''' |

Abbreviations: Bd, bortezomib-dexamethasone; DBd; daratumumab-bortezomib-dexamethasone; ICER, incremental cost-effectiveness ratio; Incr, incremental; NR, not reported; QALY, quality adjusted life year;

Source: Table 3.21-4, p.67, 69, 75 and 76 Section 3 of the submission.

Table 14: Results of the stepped economic evaluation, DLd vs. Ld

| **Step** | **Costs** | | | **QALYs** | | | **Cost per QALY gained** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **DLd** | **Ld** | **Incr** | **DLd** | **Ld** | **Incr** |
| Step 1: POLLUX transformed to QALY (24-month follow-up) | '''''''''''''''''''' | ''''''''''''''''''''' | ''''''''''''''''''''' | '''''''''' | '''''''''' | '''''''''' | ''''''''''''''''''''''''''' |
| Step 2: Step 1 extrapolated to lifetime horizon | '''''''''''''''''''''' | ''''''''''''''''''''''' | '''''''''''''''''''''''' | ''''''''''' | '''''''''''' | '''''''''' | '''''''''''''''''''''''' |
| Step 2: PSCR revised to reflect minimum of time on treatment and PFS and correct lenalidomide dose intensity | ''''''' | '''''''' | ''''''''''''''''''''' | '''''''' | '''''''' | '''''''''' | ''''''''''''''''''''''' |

Abbreviations: DLd; daratumumab-lenalidomide- dexamethasone; ICER, incremental cost-effectiveness ratio; Incr, incremental; Ld, lenalidomide-dexamethasone; NR, not reported; QALY, quality adjusted life year;

Source: Table 3.21-4, p.67, 69, 75 and 76 Section 3 of the submission.

* 1. The total QALY gains for both regimens were similar (DBd and Bd vs. Bd = 1.14; DLd and Ld vs. Ld = 1.06. However, the health states contributing to the total incremental QALY gains were different:
  + The proportion of QALYs gained from the PFS state for DBd and Bd was '''''% and '''''%, respectively, indicating that for the DBd vs Bd model the majority of QALYs are gained from the progressed disease (alive) state.
  + Conversely, in the DLd vs. Ld model QALY gains were mainly from the PFS health state (''''''% for DLd and '''''% for Ld). However, the economic model for DLd vs. Ld resulted in a total incremental QALY loss '''''''''''') for patients in progressive disease. This is an artefact of progressive disease being estimated as the residual of PFS and death.
  1. The ESC considered that it lacked biological plausibility that such a large difference by health state between two daratumumab-based regimens might exist, even though some differences existed in the characteristics of patients included in CASTOR and POLLUX. The ESC considered that the apparent differences may be an artefact of the different extrapolation forms applied, rather than reflecting a true difference between the different backbone therapies.
  2. Although the overall QALY gains were similar across the regimens there was considerable difference in the magnitude of the cost per QALY gained between the two daratumumab regimens because the incremental cost of daratumumab treatment was much higher in the DLd economic model. This is was due to:
  + more patients being treated with DLd remained in the progression free health state, and thus on treatment, compared to DBd;
  + lenalidomide being used in combination with daratumumab throughout treatment, whereas bortezomib is only used in combination with daratumumab for 8 cycles;
  + the cost of bortezomib with the proposed price reduction was lower than lenalidomide; and,
  + the rate of monthly treatment discontinuations was higher for DBd (4.6%), compared to DLd (1.9%).
  1. The economic models applied different functional forms for the extrapolation of events across the trials and treatment groups for the same outcome (PFS and OS). Applying the same functional forms for the extrapolations across arms had a moderate impact on the ICER. The ESC considered that the PSCR did not adequately justify the application of different extrapolation methods.
  2. Traces for the modelled results for OS and PFS, and the source Kaplan‑Meier estimates are presented in Figure 5. The comparison of the KM component of each curve to the extrapolated period shows that the majority of the benefit estimated for daratumumab based regimens was obtained from the extrapolated data. For OS, approximately 24 months of data were trial based and this represented approximately 10% of the overall modelled time-horizon (240 months).

Figure 5: Modelled OS and PFS and Kaplan-Meier estimates (DBd vs. Bd above and DLd vs. Ld below)





Abbreviations: Bd, bortezomib-dexamethasone; DBd; daratumumab-bortezomib-dexamethasone; DLd; daratumumab-lenalidomide-dexamethasone; KM, Kaplan-Meier; Ld, lenalidomide-dexamethasone.

Source: Figure 18, p.61 Section 3 of the submission.

* 1. The majority of QALY gains were from the extrapolation period (see Table 15). Approximately ('''''% for DBd and '''''% for DLd) were accrued in the extrapolation period. The PBAC considered that this gave rise to considerable uncertainty in the model.

Table 15: QALY gains from health state split between Kaplan-Meier period and extrapolation

| **Comparison** | **KM period (months)** | **KM gains** | | **Extrapolation gains** | | **Total** |
| --- | --- | --- | --- | --- | --- | --- |
|  | **QALY** | **% of total QALYs** | **QALY** | **% of total QALYs** |  |
| **DBd vs. Bd** |  |  |  |  |  |  |
| DBd | 13.9 | ''''''''''' | '''''''''''' | '''''''''' | '''''''''' | '''''''''''' |
| Bd | 10.7 | '''''''''' | ''''''''''' | ''''''''''' | '''''''''' | '''''''''' |
| Increment |  |  |  |  |  | ''''''''''' |
| **DLd vs. Ld** |  |  |  |  |  |  |
| DLd | 18.66 | ''''''''''' | '''''''''' | '''''''''' | '''''''''''' | '''''''''' |
| Ld | 17.47 | '''''''''''' | ''''''''''' | '''''''''' | '''''''''''' | '''''''''' |
| Increment |  |  |  |  |  | ''''''''''' |

Abbreviations: Bd, bortezomib-dexamethasone; DBd, daratumumab-bortezomib-dexamethasone; DLd, daratumumab-lenalidomide-dexamethasone; Ld, lenalidomide-dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival; QALY, quality adjusted life year

Note: Analysis performed setting daratumumab uptake to 100% in both economic models (Step 2). Extrapolations were implemented from the time point at which there are less than 20% of the patients remaining in the risk set until 244 months (20 years).

Source: Excel spreadsheet "RR MM - Model DBd vs Bd" using sheets 'DBd LY calc' and 'Bd LY calc D not available' and "RR MM - Model DLd vs Ld" using sheets 'DLd LY calc' and 'Ld LY calc D not available'.

* 1. Selected univariate sensitivity analyses specified by the submission and additional analyses specified during the evaluation are presented in Tables 16-17. These have been conducted using Step 2 (100% daratumumab uptake) as the most appropriate base case analysis.

Table 16: Results of univariate sensitivity analyses, DBd vs. Bd

| Parameter | Base case | Value | Incr cost | Incr QALY | ICER |
| --- | --- | --- | --- | --- | --- |
| Base case, Step 2 | - | - | ''''''''''''''''''''''' | '''''''''' | ''''''''''''''''''''''' |
| Time horizon | 20 years | 15 years | ''''''''''''''''''''''' | '''''''''' | '''''''''''''''''''' |
| Time horizon | 20 years | 10 years | '''''''''''''''''''''''' | ''''''''''' | '''''''''''''''''''''' |
| Time horizon | 20 years | 5 years | ''''''''''''''''''''' | '''''''''' | ''''''''''''''''''''''' |
| Discounting | 5% | 3.5% | '''''''''''''''''''''' | ''''''''''' | ''''''''''''''''''''' |
| Discounting | 5% | 0% | ''''''''''''''''''''''' | '''''''''''' | ''''''''''''''''''''' |
| Progressive-disease health state utility | 0.61 | 0.642 (CASTOR) | ''''''''''''''''''''''' | '''''''''' | ''''''''''''''''' |
| Time point from which to start extrapolation | 20% remaining at riska | Median follow-upa | '''''''''''''''''''''''' | '''''''''' | ''''''''''''''''''''' |
| End of life hospitalisation cost | $9,138 | $0 | '''''''''''''''''''' | ''''''''''' | '''''''''''''''''''''' |
| PFS extrapolation | Weibull | Exponential | ''''''''''''''''''''' | '''''''''''' | ''''''''''''''''''''' |
| OS extrapolation | Exponential | Weibull | ''''''''''''''''''''''' | '''''''''' | ''''''''''''''''' |
| Effective price bortezomib (without discount) | Price per 3 mg vial $691.62 | Effective price per 3 mg vial $1,123.18 | '''''''''''''''''''''''' | ''''''''''' | ''''''''''''''''''''' |
| Cycles of bortezomib | 8 | 11 | '''''''''''''''''''' | ''''''''''' | ''''''''''''''''''' |
| ''''''''''''''''''''''' ''''''''''''''''''''' '''''' '''''''''''''''''''''''''''''''''' | ''''''''''' '''' | '''' | ''''''''''''''''''''''' | '''''''''' | '''''''''''''''''''' |
| In a scenario where carfilzomib is reimbursed  Uptake in Year 2 and subsequent years  (Uptake in step 2) | CASTOR: p = 100% | CASTOR: p = 69.48% | ''''''''''''''''''''' | ''''''''''' | ''''''''''''''''''' |

Note: a. 20% remaining at risk: CASTOR: DBd 5.67 and Bd 15.28 months. Median follow-up: CASTOR: 13.3 months,

Source: Table 3.24, p.76 and Table 3.25, p.79 Section 3 of the submission

The redacted table shows ICERs in the range of $75,000/QALY to more than $200,000/QALY.

Table 17: Results of univariate sensitivity analyses, DLd vs. Ld

| Parameter | Base case | Value | Incr cost | Incr QALY | ICER |
| --- | --- | --- | --- | --- | --- |
| Base case, Step 2 | - | - | '''''''''''''''''''''' | '''''''''''' | ''''''''''''''''''''''' |
| Time horizon | 20 years | 15 years | ''''''''''''''''''''''' | '''''''''' | '''''''''''''''''''' |
| Time horizon | 20 years | 10 years | '''''''''''''''''''''''' | ''''''''''' | '''''''''''''''''''''' |
| Time horizon | 20 years | 5 years | ''''''''''''''''''''''' | '''''''''' | ''''''''''''''''''''' |
| Discounting | 5% | 3.5% | '''''''''''''''''''''''' | ''''''''''' | ''''''''''''''''''''''' |
| Discounting | 5% | 0% | '''''''''''''''''''''' | '''''''''' | '''''''''''''''''''''''' |
| Progressive-disease health state utility | 0.61 | 0.591 (POLLUX) | ''''''''''''''''''''''' | '''''''''' | '''''''''''''''''''' |
| Time point from which to start extrapolation | 20% remaining at riska | Median follow-upa | '''''''''''''''''''''''' | ''''''''''' | '''''''''''''''''''''''' |
| End of life hospitalisation cost | $9,138 | $0 | ''''''''''''''''''''''' | '''''''''''' | ''''''''''''''''''''''' |
| PFS extrapolation | Exponential | Weibull | '''''''''''''''''''''' | '''''''''' | '''''''''''''''''''''''' |
| OS extrapolation | Weibull | Exponential | ''''''''''''''''''''''' | '''''''''' | '''''''''''''''''''' |
| Flow-on discount for lenalidomide from bortezomib | Public: $1,626.04 and Private: $1,648.05. | Public: $3,280.99 and Private: $3,303.00. | ''''''''''''''''''''''' | ''''''''''' | ''''''''''''''''''''''' |
| '''''''''''''''''''' ''''''''''''''''''''''' '''''' '''''''''''''''''''''''''''''''''' | '''''''''' '''' | '''' | '''''''''''''''''''''''' | '''''''''' | '''''''''''''''''''' |
| In a scenario where carfilzomib is reimbursed  Uptake in Year 2 and subsequent years  (Uptake in step 2) | POLLUX: p =100% | POLLUX: p =82.88% | ''''''''''''''''''''' | ''''''''''' | ''''''''''''''''''''''' |
| 10 year time horizon and removal of LEN price reduction (published price) | 20 years, lenalidomide price reduction | 10 years, lenalidomide published price | ''''''''''''''''''''' | '''''''''' | ''''''''''''''''''''''' |

Note: a. 20% remaining at risk: POLLUX: DLd 19.4 and Ld 19.2 months. Median follow-up: POLLUX: 17.3 months.

Source: Table 3.24, p.76 and Table 3.25, p.79 Section 3 of the submission

The redacted table shows ICERs in the range of more than $200,000/QALY.

* 1. The inclusion of a '''''''''''' '''''' ''''''' ''''''''''' ''''''''''''''''''''''''''' '''''''''''''''' for both models reduced the ICER. Without the '''''''''''''''' '''''''''''''''' the ICER for DBd vs Bd would be $105,000/QALY - $200,000/QALY gained and for DLd vs. Ld would be more than $200,000/QALY gained over the modelled 20 year time-horizon. The PBAC noted ''''''''''''''' '''''' '''''''''' '''''''''''''''' does not address the major uncertainty associated with daratumuab use which is the mean duration of use.
  2. Overall, the PBAC agreed with the ESC that the ICERs estimated for daratumumab for both combinations were very high and highly uncertain, reflecting the immaturity of the clinical data, the approaches to the data extrapolation and the model time horizon. Adopting the preferred time horizon (10 years), and restricting the analysis to Step 2 (which assumes bortezomib priced reductions are fully realised), the resulting ICER was $105,000/QALY - $200,000/QALY gained for DBd vs. Bd. Adopting the preferred time horizon (10 years), restricting the analysis to Step 2, and using the lenalidomide published price resulted in an ICER of more than $200,000/QALY gained for DLd vs. Ld.
  3. The PBAC recalled that it recently recommended Cd on the basis of superior efficacy compared to Bd, and that Cd may be a relevant comparator for both DBd and DLd (in the absence of CLd being listed). Although this submission did not adequately demonstrate a survival benefit for DBd over Cd, and did not present data for DLd vs Cd, the PBAC considered an economic analysis including Cd may be informative.

## Drug cost/patient/year

* 1. The average cost of daratumumab in the DBd regimen ('''''''''''''''''''' ''''''''''''''') for the first year is $''''''''''''''. This is based on the effective price of $''''''''''''''''' (for 3 vials per infusion, weighted across public + private hospitals) and 18 infusions over 12 months.
  2. The average cost of daratumumab in the DLd regimen (''''''''''''''''''' ''''''''''''') for the first year is $''''''''''''''''. This is based on the effective price of $'''''''''''''''' (for 3 vials per infusion, weighted across public + private hospitals) and 22 infusions over 12 months.

## Estimated PBS usage & financial implications

* 1. This submission was not considered by DUSC. The submission used a mixed epidemiological and market share approach to estimate the utilisation and financial impact of listing daratumumab.
  2. The submission estimated prevalent and incident MM populations from AIHW data (ACIM and Cancer in Australia, respectively). The submission then applied the estimated proportion of RRMM incident and RRMM prevalent patients using the 10% PBS sample. The PSCR provided further information that clarified that treatments used as the basis of this 10% sample were likely to be representative of the range of therapies used in MM and argued that this was therefore a reasonable basis upon which to estimate the number of RRMM patients eligible for daratumumab based therapies.
  3. The submission noted that the market research conducted among clinicians indicated that as Bd is more commonly used in first line, Ld therapy (or DLd) is more likely to be used in second line. This difference in uptake has been incorporated into the financial estimates. The PBAC noted that if DBd only were listed, this would likely also influence the utilisation of Ld and Bd in the first line setting. The PBAC also considered that this indicated there was likely to be strong clinician preference for both daratumumab combination regimens to be available, to enable switching of backbone therapies.
  4. The estimated use and financial implications of listing daratumumab are presented in Table 18.
  5. The use of bortezomib, lenalidomide, dexamethasone and AE treatments as estimated in the submission included use as part of the daratumumab regimen (the world with daratumumab) and use substituted for by the daratumumab regimen (the world without daratumumab). Only the net difference in the use of those therapies contributed to the financial impact of listing daratumumab.

Table 18: Estimated use and financial implications

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated extent of use** | | | | | |  |
| Patients receiving DBd | '''''''''' | '''''''''' | ''''''''' | ''''''''' | '''''''''' | '''''''''' |
| Patients receiving DLd | '''''''''' | ''''''''' | ''''''''' | '''''''''' | '''''''''' | ''''''''' |
| Number of daratumumab scripts dispensed for DBd a | ''''''''''''' | ''''''''''''''' | ''''''''''''''''' | '''''''''''''''' | '''''''''''''''' | '''''''''''''''' |
| Number of daratumumab scripts dispensed for DLd a | ''''''''''''''''' | '''''''''''''''' | ''''''''''''''''' | '''''''''''''''' | ''''''''''''''' | ''''''''''''''''' |
| **Estimated financial implications of daratumumab at dispensed price** | | | | | |  |
| Cost to PBS/RPBS less copayments DBd | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''' |
| Cost to PBS/RPBS less copayments DLd | ''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''''' |
| Total cost to PBS/RPBS less co-payments of daratumumab | '''''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''''' |
| **Estimated financial implications for other medicines (bortezomib, lenalidomide, dexamethasone, pegfilgrastim, hydrochlorothiazide) (effective prices)** | | | | | |  |
| Cost to PBS/RPBS less co-payments – daratumumab listed | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''''' |
| Cost to PBS/RPBS less co-payments – daratumumab not listed | ''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''''' |
| Cost to PBS/RPBS less co-payments – daratumumab not listed, net change | '''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''' |
| **Net financial implications no copayments (effective prices)** | | | | | |  |
| Net cost to PBS | '''''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''' |
| Net cost to RPBS | '''''''''''''''''''''''' | ''''''''''''''''''''''''' | '''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' |
| Net cost to MBS | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | '''''''''''''''''''''''''' | ''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''' |
| Net cost to PBS/RPBS/MBS | **'''''''''''''''''''''''''''''** | **'''''''''''''''''''''''''''** | **''''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **''''''''''''''''''''''''''''** | **''''''''''''''''''''''''''** |

Note: a Assuming 14 scripts for initiating patients (over 6 months) and 12 scripts per year for continuing patients. Year 1 consisted only 6 months (14 scripts), Year 2 onwards consisted of 12 months and included initiating and continuing patients, with each subsequent year accumulating continuing patients from previous Years as estimated by the submission.

Source: Table 4.1.3-4.1.6, p.14-18 and Table 4.1.15, p.35 Section 4 of the submission and sheet ‘4.2 Use and cost of dara’ in Excel Spreadsheet ‘Daratumumab\_RRMM\_Section\_4’ of the submission. Drug costs were included for the treatment of adverse events including pegfilgrastim for treatment of neutropenia and hydrochlorothiazide for hypertension (for DBd only). The proportions of utilisation for these drugs were based on those used in the economic models which were derived from the appropriate trials.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to Government would be more than $100 million per year.

* 1. The financial estimates are uncertain for the following reasons:
  + The cost of bortezomib and lenalidomide was underestimated due to:
    - including a maximum of 8 cycles of treatment with Bd only. The ESC noted that the assumption of only 8 cycles of Bd (as compared with the 11 cycles permitted on the PBS) impacted on the financial estimates but was unlikely to have a substantial impact on the clinical outcomes.
    - the assumption that there would be a ''''''''''''''' ''''''''' '''''''''''''''''' '''' '''''''''''''''''''''''''''' '''''''' '''''''' ''''''''''' '''''''' '''''''''''''''' '''' '''''''' ''''''''' ''''''''''''''''''' '''''''' ''''''''''''''''' '''''' ''''''''''''''''' '''''''''' ''''' '''''''''''''''''''''' ''''''''''''''''''''' '''''''''''''''''''' ''''''' ''''''''''''''' '''''''''''''' '''' '''''' ''''''''''''''''''''' '''''''''''''''
  + The estimate of the prevalent RRMM population is based on a projection. The submission presented a scenario analysis that increased the prevalent population from '''''''''' to ''''''''''' patients. The increased patient numbers were based on using an older age segment (60+ instead of 50+) in the AIHW dataset. The older age segment corresponded to a higher growth rate of 16% instead of 12.1% over the 5-year period (2012-2017) applied to the projections. If the population of patients using these treatments on the PBS is older than the group used in the growth projections, the sensitivity analysis suggests that it is likely that utilisation has been underestimated.
  + Discontinuation of daratumumab was based on the time to treatment discontinuation (TTD) extrapolations conducted in the economic model. These extrapolations were based on short-term trial data and may not reflect the typical duration of daratumumab therapy for these patients. Longer time on therapy with daratumumab would increase the cost to Government.
  + Although an increase in bortezomib use as a result of use in combination with daratumumab was included in the estimates, the submission did not account for an increase in utilisation or duration of use of bortezomib in Bd regimens as a result of streamlining the restriction.
  1. The PBAC noted that the estimated financial impact indicated a very high opportunity cost for the proposed listings, for which the incremental cost‑effectiveness ratio was too high and uncertain.

## Quality use of medicines

* 1. The submission provided examples of educational resources for patients, carers, physicians and nurses as evidence of its approach to QUM. These explain the complex dosing and administration requirements including the duration of the first infusion (7 hours); need for blood typing patients prior to the first infusion and potential and management of infusion related reactions.

## Financial management – risk sharing arrangements

* 1. The sponsor proposed a special pricing arrangement, which was intended to '''''''''''' '''''' '''''''' ''''' '''''' '''''''' ''' '''''''' '' '''''''''''''''''''''''''''''' '''''''''''''''' ''''''''' '''' ''''''''''''''''''''''''' '''''''''' ''''''''''''''''''' '''''''' ''''''''''''''''''''''''' '''''''''''''''''''''. The '''''''''''''''''''' ''''''''''''' '''''''' '''''''''''% of the AEMP of daratumumab when used with bortezomib and '''''% of the AEMP of daratumumab when used with lenalidomide. The PSCR claimed therefore, that a cap on total expenditure or number of cycles was not required. Moreover, the PSCR noted that the proposed SPA would not apply to use by Grandfathered patients. The PBAC did not agree with the PSCR and considered that the duration of daratumumab treatment was a key area of uncertainty in relation to these listings. The PBAC agreed with the ESC ''''''''' ''''''''''''''' '''''' ''''''''''''' '''' '''''''''' '''''''''''''''''''' ''''''''' results in no coverage of the risk associated with uncertainties around the duration of therapy for continuing treatment, the number of patients continuing treatment, the replacement of comparator regimens in ongoing treatment, use of daratumumab monotherapy, or exposure the number of grandfathered patients. The PBAC therefore advised that a risk sharing arrangement based on total expenditure or number of cycles would be required for these listings.

Table 19: Estimated use and financial implications with MM Treatment Package

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| Net implications with co-payments removed (with MM Treatment Package) | | | | | |  |
| PBS | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''' |
| RPBS | ''''''''''''''''''''''''' | '''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' |
| MBS | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | ''''''''''''''''''''''''' | '''''''''''''''''''''''''' |
| **Total financial implications for the health budget** | **'''''''''''''''''''''''** | **''''''''''''''''''''''''''''** | **'''''''''''''''''''''''''''** | **''''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **''''''''''''''''''''''''''''** |
| **Cost offset by MM Treatment Package** | **'''''''''''''''''''''''''''** | **'''''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **'''''''''''''''''''''''''** | **'''''''''''''''''''''''''''''** | **'''''''''''''''''''''''''''** |
| Net implications with MM Treatment Package by regimens | | | |  |  |  |
| For DBd or Bd | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' |
| For DLd or Ld | ''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''' |
| **Total financial implications for the health budget** | **'''''''''''''''''''''''** | **'''''''''''''''''''''''''** | **''''''''''''''''''''''''''** | **'''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **'''''''''''''''''''''''''''''** |

Abbreviations: DBd; daratumumab-bortezomib-dexamethasone; DLd; daratumumab-lenalidomide-dexamethasone; MM, multiple myeloma.

Source: Table 4.1.15, p.35 Section 4 of the submission.

The redacted table shows that at year 5, the estimated net cost to Government would be more than $100 million per year.

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

# PBAC Outcome

* 1. The PBAC did not recommend the listing of daratumumab for use in combination with bortezomib and dexamethasone (DBd) or lenalidomide and dexamethasone (DLd) in relapsed or refractory multiple myeloma (RRMM) due to the very high and uncertain incremental cost-effectiveness ratios, and a preference to have both combinations of therapies available for RRMM patients, as well as monotherapy for patients no longer suitable for treatment with bortezomib or lenalidomide.
  2. The PBAC considered that the clinical place in therapy as proposed in the submission (in combination with bortezomib or lenalidomide) was appropriate based on the available evidence. In addition, the PBAC considered there is a high clinical need for patients who are refractory to both bortezomib and lenalidomide, and noted that daratumumab is TGA registered as a monotherapy for these patients. The PBAC considered that it would be inequitable to make DBd and/or DLd combination treatment available through the PBS to relapsed patients without also making daratumumab monotherapy available for refractory patients. The PBAC also noted that in the absence of a daratumumab monotherapy listing, the risk of use outside the combination therapy indication would be higher.
  3. The PBAC noted '''''' ''''''''''''''''' ''''''''''''''''''' ''''''''''''''''' ''' '''''''''' ''''''''''''''''' ''''''''''''''''''' ''''' '''''' ''''''''' '''''''. The PBAC noted the incremental efficacy with the addition of daratumumab to bortezomib or lenalidomide was similar, ''''''' '''''''''''''''''''' '''''''' ''''''' '''''''''''''''''' ''''' '''''''' '''''''' ''''''''''''' '''''''''''' '''''' ''''''' '''''''''''''' ''''''''''''''''''' '''''''''''''''''''. Information was presented in the submission which indicated the majority of patients are treated with bortezomib and dexamethasone (Bd) first-line, and then switch the backbone therapy in the second‑line, generally to lenalidomide and dexamethasone (Ld). Thus the availability of DBd only for refractory patients would result in patients previously treated with Bd switching to DBd, and although DBd is effective in patients previously treated with Bd it appears to be less effective than in patients not previously treated with bortezomib. The availability of DBd only would also potentially drive an increase in Ld use in first line, as well as increase the risk of use outside the current lenalidomide indication into transplant eligible patients. Thus, whilst the PBAC noted that a treatment sequence with DBd may be clinically appropriate, it considered that the preferred approach would be to not limit clinician choice to this combination.
  4. The PBAC accepted that the proposed comparators were reasonable. However, the PBAC also considered that other potentially relevant comparators, such as Bd with cyclophosphamide, were not considered. Further, the PBAC noted that Ld was listed on a cost-minimisation basis to Bd, and that Cd was considered superior to Bd. On this basis, Cd was also considered a relevant comparator.
  5. The PBAC noted the submission was based on two randomised trials with a low risk of bias (CASTOR comparing DBd and Bd and POLLUX comparing DLd and Ld). The risk of progression or death was significantly reduced by 67% and 63%, respectively, with the addition of daratumumab to bortezomib or lenalidomide. The risk of death was significantly reduced by 37% with the addition of daratumumab to either backbone therapy. The PBAC further noted the addition of daratumumab resulted in high response rates, and deep responses as demonstrated by the proportion of patients achieving minimal residual disease (MRD) negativity.
  6. The PBAC considered that the data presented in the submission supported the claim of superior efficacy for DBd compared to Bd, and DLd compared to Ld. However, the PBAC also noted that median PFS had not been reached for DBd or DLd, and that median OS had not been reached in any arm. The PBAC therefore considered that although superior efficacy was supported, the magnitude of the incremental benefit was uncertain due to the immaturity of the data.
  7. The PBAC considered that the data presented in the submission supported the claim of inferior safety. The PBAC considered the low and similar rates of discontinuation across the treatment arms in both trials suggest daratumumab has a manageable side effect profile.
  8. The PBAC noted that although the indirect comparison of DBd to Cd suggested DBd may be superior in terms of PFS, but not OS, the indirect comparison was affected by a number of potential confounding factors. The PBAC was of the view that it would be more informative for an indirect comparison to be performed on the Bd naïve subgroup of patients of each trial.
  9. The PBAC agreed with the ESC that ‘step 3’ of the economic model was not an appropriate approach to the economic analysis, and that the economic analysis should assess the incremental cost effectiveness on the basis on 100% use of the alternatives. The PBAC also agreed with the ESC that the ''''''''''' ''''''''''''''''' '''''' '''''''''''''''''''''''' should not be included in the economic analysis '''' ''''''' '''''''''' '''''''''''''''''' '''''' ''''''''''''''''''''''''' ''''''' ''''''' '''''''''''''''' ''''''' ''''''''''' ''''''' ''''' ''''''''''''''''''''''.
  10. The PBAC noted that a substantial proportion of the modelled gain in QALYs was from the extrapolated period ('''''% for DBd and '''''% for DLd). The PBAC considered that this resulted in the incremental cost effectiveness ratios (ICERs) being highly uncertain. In order to reduce the uncertainty the PBAC considered it appropriate to use a shorter (10 year) model time horizon. The PBAC recalled a 10 year time horizon was applied in the carfilzomib PBAC submission. The PBAC considered that while some patients may be alive beyond 10 years and possibly 15 years, it was noted that extrapolation of immature trial data to 20 years substantially increases the uncertainty with the cost effectiveness estimates and that greater confidence in establishing cost effectiveness will be derived by limiting the time horizon to 10 years.
  11. The PBAC agreed with the ESC that the ICERs estimated for daratumumab for both combinations were highly uncertain, reflecting the immaturity of the clinical data, the approaches to the data extrapolation and the model time horizon. With a 10 year time horizon and restricting the analysis to Step 2 (which assumes ''''''''''''''''''''''' '''''''''''' ''''''''''''''''''' are fully realised), the resulting ICER was $105,000/QALY - $200,000/QALY for DBd vs Bd. With a 10 year time horizon, restricting the analysis to Step 2, and using the ''''''''''''''''''''''''' '''''''''''''''''' '''''''''', the resulting ICER was more than $200,000/QALY for DLd vs Ld. The PBAC considered that in the context of the sensitivity of the model to key variables, and the immaturity of the data that the estimated ICERs were uncertain, and too high.
  12. The PBAC also noted that the opportunity cost of the requested listing was very high, and considered that this was particularly problematic given the high and uncertain ICERs. The PBAC also noted that in the situation where only DBd was listed, the utilisation of Bd and Ld in prior lines of therapy would likely change.
  13. The PBAC considered that any future resubmission should be a major submission.
  14. The PBAC noted that this submission is eligible for an Independent Review.

**Outcome**

Rejected

# Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

# Sponsor’s Comment

The sponsor had no comment.

1. *Usmani SZ, Weiss BM, Plesner T, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood 2016; 128:37-44.*

   *Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med 2015; 373:1207-19.*

   *Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet 2016; 387:1551-60.*

   *Usmani SZ, Diels J, Ito T, Mehra M, Khan I, Lam A. Daratumumab monotherapy compared with historical control data in heavily pretreated and highly refractory patients with multiple myeloma: An adjusted treatment comparison. Am J Hematol 2017; 92:E146-e152.* [↑](#footnote-ref-1)
2. *Nooka, Ajay K., and Sagar Lonial. "Novel combination treatments in multiple myeloma." Oncology, May 2016, p. 451. Academic OneFile, Accessed 4 Oct. 2017.* [↑](#footnote-ref-2)