7.01 DARATUMUMAB, Solution concentrate for I.V. infusion, 100 mg in 5 mL, 400 mg in 20 mL, DARZALEX®, Janssen-Cilag Pty Ltd

1 Purpose of Application

1.1 The resubmission requested a Section 100 listing (Efficient Funding for Chemotherapy) for daratumumab in combination with bortezomib and dexamethasone (DBd) in patients with relapsed or refractory multiple myeloma (RRMM) who have received one prior therapy only (i.e. patients who have relapsed or are refractory following first-line treatment for newly diagnosed multiple myeloma, and hereafter referred to as second-line treatment – see Figure 1 below). Two previous submissions were rejected by the PBAC (November 2017 and March 2019) that sought listing of DBd in RRMM patients who had received at least one prior therapy. The March 2019 resubmission also requested daratumumab monotherapy for highly treatment experienced patients or patients who were refractory to at least three prior lines of therapy.

1.2 The November 2019 resubmission did not include a request to list daratumumab for use as monotherapy. The PBAC previously concluded that there was a high clinical need for daratumumab monotherapy, and that it was an important treatment option to provide equitable access for a small number of patients who had progressed to later stage RRMM (paragraph 7.15, Daratumumab Public Summary Document (PSD), March 2019). Furthermore, restricting the PBS listing of DBd to second-line patients only impedes equity of access for patients who are further along their treatment course for RRMM, given that the data from the CASTOR trial (as presented in the resubmission) demonstrated a benefit in these patients. The pre-PBAC response stated that daratumumab monotherapy will be supplied to eligible third and later-lines patients on a compassionate supply basis.

1.3 The resubmission presented a cost utility analysis comparing DBd with bortezomib plus dexamethasone (Bd). The key components of the clinical issue addressed by the resubmission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Multiple myeloma; patients with relapsed or refractory disease after one prior line of therapy (i.e., second line MM patients)
Intervention	Daratumumab is administered as an IV infusion at a dose of 16 mg/kg in combination with bortezomib-based therapies. Daratumumab is administered weekly for the first 3 cycles (3 week cycles), every three weeks for Cycles 4 to 8 (3 week cycles) and then once every 4 weeks from Cycle 9 onwards (4 week cycles) until disease progression or treatment-limiting toxicity.
Comparator	Main comparator: Placebo + bortezomib-based regimen. Secondary comparator: Carfilzomib + dexamethasone (Cd).
Outcomes	PFS, OS, ORR, MRD negative rates, AEs.
Clinical claim	In second line MM patients, DBd demonstrates superior comparative effectiveness compared with bortezomib-based regimens alone (Bd) as assessed by statistically and clinically significant improvements in PFS, OS and a significantly higher response rate. DBd is associated with additional AEs compared with Bd, and therefore has an inferior safety profile. However, these AEs remain manageable, do not require discontinuation of daratumumab, do not negatively impact quality of life and are largely consistent with treatment with bortezomib and as such clinicians are familiar with these and experienced in their management.

AE = adverse event; Bd = bortezomib-dexamethasone; Cd = carfilzomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; IV = intravenous; MM = multiple myeloma; MRD = minimal residual disease; ORR = overall response rates; OS = overall survival; PFS = progression free survival;
Source: Table 1.1, pp17-18 of the November 2019 resubmission. Table 1.2 p22 of the March 2019 resubmission.

2 Background

Registration status

2.1 Daratumumab was approved by the TGA on 17th July 2017 for use:

- 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;
- 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.

2.2 Daratumumab was approved by the TGA in September 2019 for use in combination with bortezomib, melphalan and prednisolone for the treatment of patients with newly diagnosed MM who are ineligible for ASCT.

Previous PBAC consideration

2.3 A summary of the matters of concern raised by the PBAC with respect to the March 2019 resubmission, and how they have been addressed in the November 2019 resubmission is provided in Table 2.

2.4 As distinct from the March 2019 resubmission, the November 2019 resubmission did not request listing of daratumumab for use in third and later lines as DBd, or for use as monotherapy as a fourth-line treatment in RRMM. The resubmission attributed its decision to exclude the request for these indications to the high cost to Government

and an apparent greater clinical benefit and clinician preference for using DBd earlier in treatment, in particular at second-line.

Table 2: Summary of outstanding matters of concern

Component	PBAC matters of concern arising from March 2019 PSD	How the November 2019 resubmission addresses it
Clinical evidence		
Requested listing	Preference to have DBd, DLd and daratumumab monotherapy listed (para 7.3 and 7.14).	Not addressed: proposed listing of DBd in second-line only; excluded daratumumab monotherapy; excluded DBd use beyond second-line. The pre-PBAC response stated that daratumumab monotherapy would be supplied to eligible third and later-line patients on a compassionate supply basis.
Indirect comparison of DBd to Cd	The differences between CASTOR and ENDEAVOR patient populations made the non-significant OS outcome difficult to interpret; no significant improvement in efficacy or reduction in toxicity over Cd was demonstrated (para 7.10).	Evidence presented to address PBAC concern: updated ITC between DBd and Cd for second-line subgroups for PFS and OS. The difference in OS in the second-line setting was not statistically significant.
Use of daratumumab as a subsequent therapy in the comparator arm, Bd	The methodology for adjustment of crossover was not based on any standardised method; lack of baseline data for patients who switched, thus it was not possible to evaluate the reliability of the method used (para 7.8).	Evidence presented to address PBAC concern: the resubmission provided baseline characteristics of the switching and non-switching patients in the Bd arm of the second-line subgroup. The resubmission used the inverse probability of censoring weights (IPCW) methodology to adjust the OS of Bd patients for the subsequent use of daratumumab.
Economic issues		
Population	Use of the ITT population, which more accurately reflected the proposed PBS population at the time of listing, should inform the base case model (para 7.12).	Partially addressed: Requested listing for second-line subgroup, IA5 data cut-off trial follow-up at 47 months (median follow-up 40.0 months); used in the economic analysis. The analysis in the second-line subgroup was not prospectively defined, not all of the relevant treatment-by subgroup interactions were presented by the resubmission, nor did the resubmission present a rationale to use the relative efficacy estimate from the subgroup in preference to that from the ITT population.
Time horizon	Proposed the use of a 10 year time horizon (para 7.12).	Not addressed: maintained 20-year time horizon and reiterated the previous justification and proposed a Managed Access Program to justify accepting a longer time-horizon.
ICER	Considered the ICER was high ($[redacted] in the pre-PBAC response and using a 15 year time horizon). Noted that the ICER for Cd (July 2017) was in the range of $[redacted]/QALY to $[redacted]/QALY (para 7.13).	Not addressed: The base case ICER was $[redacted]/QALY using a 20-year time horizon.
Financial issues		
Estimated financial implication	The opportunity cost of the requested listing was very high, with estimated cost of listing of $[redacted] million over six years with less than 10,000 initiating patients in DBd and daratumumab monotherapy (para 7.19, Mar 2019 Ratified Minutes). The estimated cost for second-line population presented in the pre-PBAC response in March 2019 was $[redacted][a] for [redacted] initiating patients.	Not addressed**:** The estimated total cost of listing DBd in second line was $[redacted] over six years, for approximately [redacted] initiating patients (i.e. a [redacted]% reduction).

Component	PBAC matters of concern arising from March 2019 PSD	How the November 2019 resubmission addresses it
Risk Sharing Arrangement	A clear, evaluable proposal based on total expenditure or number of cycles per patient was required to mitigate risks associated with the duration of therapy for continuing patients (para 7.19).	Partially addressed: A RSA which included the application of the MM Treatment Package, and [redacted], to address the risk for use of DBd beyond the requested restriction into later line settings (beyond second-line) was proposed.

Bd = bortezomib-dexamethasone; Cd = carfilzomib-dexamethasone; DBd = daratumumab- bortezomib-dexamethasone; DLd = daratumumab-lenalidomide-dexamethasone; IA4 = interim analysis 4; IA5 = interim analysis 5; ICER = incremental cost effectiveness ratio; ITC = indirect treatment comparison; ITT = intention to treat; MM = multiple myeloma; OS = overall survival; PFS = progression free survival; PSD = Public Summary Document; QALY = quality adjusted life years; RRMM = relapsed/refractory multiple myeloma; RSA = risk-sharing arrangement

a. Estimated during evaluation using the Excel workbook 'Daratumumab RRMM financial estimates model prePBAC_20180306' sheet 'Assumptions' by setting the daratumumab 3+line and daratumumab monotherapy uptake rates to 0%.

Source: Daratumumab March 2019 Public Summary Document and resubmission November 2019 – see right hand column in Table 4 for details.

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

3 Requested listing

3.1 The details of the proposed listing for daratumumab are summarised in Table 3.

Table 3: Details of proposed PBS listing

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	DPMA	Proprietary Name and Manufacturer
DARATUMUMAB VIAL, 400 mg and 100 mg	1920 mg	13 (initial) 5 (continuing)	Published: Public hospital: $[redacted] Private hospital: $[redacted] Effective: Public hospital: $[redacted] Private hospital: $[redacted]	DARZALEX® Janssen-Cilag Pty Ltd

3.2 The resubmission included an updated "Multiple Myeloma Treatment Package" consisting of a special pricing arrangement (SPA) for daratumumab and changes to the bortezomib listing as follows:

- Effective ex-manufacturer prices of $[redacted] per 400 mg vial and $[redacted] per 100 mg vial across the initial and continuing treatment periods (this is equal to a [redacted]% rebate on the published prices). The proposed effective price is [redacted]% [redacted] and is [redacted]% [redacted]. The resubmission claimed that this results in a [redacted]% [redacted], taking into account the balance of use between initial and continuing treatment.
- Simplified wording for the PBS listing of bortezomib, to "Treatment of multiple myeloma", in line with that applied to thalidomide.
- Reduction in the price of bortezomib:

[redacted]

[redacted]

3.3 The proposed listing criteria for daratumumab, as DBd, are summarised in Table 4.

Table 4: Proposed PBS listing criteria – daratumumab plus bortezomib plus dexamethasone

Category/Program:	Section 100 – Efficient Funding for Chemotherapy
PBS indication:	Multiple Myeloma
Treatment phase:	Initial and Continuing
Restriction:	Authority Required – In Writing (Initial) / Telephone (Continuing)
Clinical criteria:	Initial treatment: 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 one prior line of therapy AND Patient must not be receiving concomitant PBS-subsidised thalidomide or its analogues or carfilzomib AND Patient must not receive more than eight cycles of treatment under this restriction AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition Continuing treatment 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 AND Patient must not develop disease progression while receiving treatment with this drug for this condition AND Patient must not be receiving concomitant PBS-subsidised thalidomide or its analogues, bortezomib, or carfilzomib.

Source: Table 1.7, p34 of the November 2019 resubmission.

3.4 Under the criteria for initial treatment, the November 2019 resubmission proposed restricting use to patients with progressive disease after one prior line of therapy. The treatment algorithm defines one line of prior therapy as any treatment received in the newly diagnosed setting – see Figure 1 below. The proposed wording does not restrict use to patients who have received one prior line of therapy only and the PBAC considered the clinical criterion should be 'no more than one prior line of therapy' in order to restrict use to the second-line setting.

3.5 The ESC were concerned that limiting use of DBd to the second-line setting would result in significant equity issues for RRMM patients who have already received two lines of therapy or who were refractory to bortezomib and who would have received daratumumab monotherapy. In the pre-PBAC response the sponsor stated that should DBd be listed as a second-line therapy, daratumumab monotherapy will be supplied on a compassionate basis to eligible third and later-line patients. The PBAC considered this would address the equity issue identified by the ESC.

3.6 The ESC noted that lines of therapy are difficult to define in MM as multiple regimens consisting of induction and maintenance therapy are used for patients undergoing stem cell transplants and there is a substantial risk of leakage with use in the first-line and third-line plus settings.

3.7 The resubmission requested the application of grandfathering criteria to patients receiving DBd prior to the commencement of PBS listed supply. The proposed detailed criteria were updated for consistency with those for newly commencing patients, with the addition of the following clinical criteria:

- Patient must not receive more than eight cycles of initial treatment in total, including supply under the PBS; AND
- Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to <date>.

3.8 The resubmission did not provide an estimate of the number of grandfathered patients expected and there was no provision for adjusting the duration of therapy for grandfathered patients in the financial estimates.

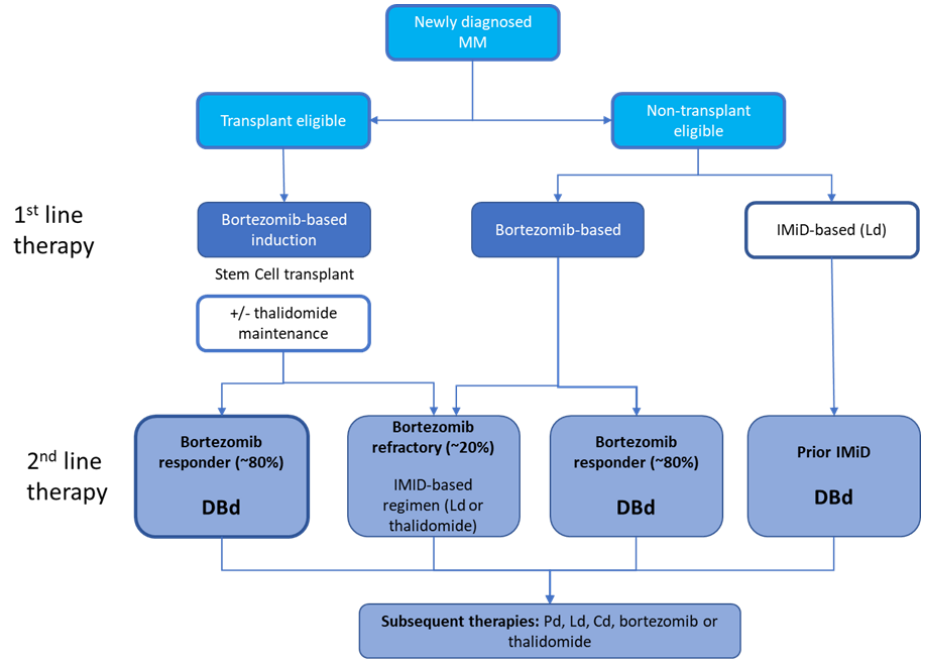
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Multiple myeloma (MM) is a cytogenetically heterogeneous clonal plasma cell proliferative disorder characterised by an abnormal serum and/or urine immunoglobulin. As MM 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 hyper viscosity of the blood.

4.2 The resubmission requested PBS listing of daratumumab in combination with bortezomib and dexamethasone (DBd) as a second-line treatment for patients with RRMM (i.e. after prior therapy in the newly diagnosed setting). The clinical algorithm presented by the resubmission in Figure 1 considered that DBd would substitute for Bd, Cd and Ld. However, the resubmission acknowledged that there was a possibility for leakage, with DBd being used in third and later-lines. The resubmission did not present cost-effectiveness or financial impact information that addressed the use of DBd beyond the second-line, or daratumumab as monotherapy for use in RRMM. The ESC noted the treatment algorithm did not include maintenance treatment with lenalidomide following a stem cell transplant (recommended at the July 2019 PBAC meeting) or combination therapy with lenalidomide and bortezomib in NDMM (recommended at the August 2019 PBAC meeting), and that both of these treatments should lead to fewer patients being treated with DBd in the second-line setting. The pre-PBAC response agreed that the lenalidomide listings would reduce the number of patients progressing from first-line to second-line therapy.

Figure 1: Proposed clinical management algorithm for DBd in the treatment of RRMM



Cd = carfilzomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; IMiD = immunomodulatory drug; Ld, = lenalidomide-dexamethasone; MM = multiple myeloma; Pd = pomalidomide-dexamethasone; RR = relapsed and/or refractory.
Source: Figure 1.1, p28 of the November 2019 resubmission.

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

5 Comparator

5.1 The resubmission nominated Bd as the main comparator for DBd. The resubmission noted that daratumumab is used as an add-on therapy and, if PBS listed, combination use of daratumumab with bortezomib (i.e. DBd) is most likely to replace bortezomib-based regimens without daratumumab. This was reasonable and was accepted by the PBAC at the November 2017 meeting (paragraph 7.4, Daratumumab PSD, November 2017) and at the March 2019 meeting (paragraph 7.4, Daratumumab PSD, March 2019).

5.2 The resubmission nominated carfilzomib plus dexamethasone (Cd), bortezomib plus cyclophosphamide plus dexamethasone (VCD) and lenalidomide plus dexamethasone (Ld) as secondary comparators. At its March 2019 meeting, the PBAC noted that no comparative data were provided for the comparison with Ld (paragraph 7.4, Daratumumab PSD, March 2019). The November 2019 resubmission presented an updated indirect comparison of DBd with Cd; no updated data were presented for the comparison with VCD and again, no data were presented to inform a comparison with Ld.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (89), health care professionals (7) and organisations (5) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with daratumumab including improved survival, an improved quality of life and fewer side effects.

6.3 The PBAC noted the advice received from (i) The Leukaemia Foundation, (ii) Myeloma Australia, (iii) Myeloma Australia's Medical and Scientific Group (MSAG), (iv) Rare Cancers Australia and (v) South East Myeloma Support Group, South Australia, which strongly supported the submission, outlining the clinical need for DBd in providing optimal management of myeloma and reiterating the patients' views.

Clinical trials

6.4 The resubmission was based on one head-to-head trial comparing DBd to Bd (CASTOR, N = 498). The resubmission presented updated longer-term data (interim analysis 5 (IA5) at 47.0 months, reflecting a median follow-up of 40 months) in addition to the IA4 (data cut-off at 31.2 months), as provided in the March 2019 submission, and the 120-day safety update (120dsu, data cut-off at 13.3 months), as provided in the November 2017 submission. The clinical claim was based on analyses of the second-line subgroup of patients. This was consistent with the updated proposed PBS restriction in the current resubmission.

6.5 The resubmission presented an update of the indirect comparison for the secondary comparator carfilzomib in second-line subgroup:

- DBd (CASTOR, n = 235) and Cd (ENDEAVOR, n = 464), with Bd as the common reference arm.

6.6 Details of the trials presented in the submission are provided in Table 5.

Table 5: 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.	
	Clinical study Report (CSR)	27 July 2016
	120-Day Safety Update	20 October 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	Journal of Clinical Oncology 2015; 33 (15 Suppl): TPS8609

Trial ID	Protocol title/ Publication title	Publication citation
	myeloma (MM): 54767414MMY3003 (Pollux) and 54767414MMY3004 (Castor).	
	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*
	Interim analysis 4	11 January 2018
	Spencer A, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR[a]	*Haematologica 2018; 103 doi:10.3324/haematol.2018.194118*
	Spencer A, et al. Daratumumab, bortezomib, and dexamethasone (DVD) versus bortezomib and dexamethasone (VD) in relapsed or refractory multiple myeloma (RRMM): Updated efficacy and safety analysis of castor	Blood 2017
	Iida S, Lentzsch S, et al. Safety and efficacy of daratumumab in combination with bortezomib and dexamethasone in Japanese patients with relapsed or refractory multiple myeloma.	International Journal of Haematology, 2017
	Lentzsch S, Quach H, et al. Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone for relapsed/refractory multiple myeloma (RRMM) patients: an update of overall survival in castor.	Blood 2017
	Lentzsch S, Weisel K, et al. Daratumumab, bortezomib and dexamethasone (DVD) vs bortezomib and dexamethasone (VD) in relapsed or refractory multiple myeloma (RRMM): Efficacy and safety update (CASTOR).	Haematological Oncology 2017
	Lentzsch S, Weisel K, et al. Daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): Efficacy and safety update (CASTOR).	Journal of clinical Oncology, 20 May 2017
	Mateos M, Spencer A, et al. Updated efficacy and safety analysis of daratumumab, bortezomib, and dexamethasone (DVD) versus bortezomib and dexamethasone (VD) for re-lapsed or refractory multiple myeloma (RRMM; CASTOR).	Haematologica 2017; 103 (S1) 30
	Weisel K, Lentzsch S, et al. Efficacy and safety of daratumumab, bortezomib and dexamethasone (DVD) versus bortezomib and dexamethasone (VD) in relapsed or refractory multiple myeloma (RRMM): Updated analysis of castor.	European Haematology Association 2017
	Interim analysis 5	
	Mateos MV, Sonneveld P, et al. Efficacy and Safety of daratumumab, bortezomib, and dexamethasone (D-Vd) versus bortezomib and dexamethasone (Vd) in first relapse patients with Multiple Myeloma (MM): Update of CASTOR.	Poster at 60th ASH: Dec 2018
	Avet-Loiseau H, San-Miguel J, et al. Evaluation of Sustained Minimal Residual Disease (MRD) Negativity in Relapsed/Refractory Multiple Myeloma (RRMM) Patients (Pts) Treated With Daratumumab in Combination With Lenalidomide Plus Dexamethasone (D-Rd) or Bortezomib Plus Dexamethasone (D-Vd): Analysis of POLLUX and CASTOR	Poster at 60th ASH: Dec 2018

a. This was identified during March 2019 evaluation. However, the median follow-up was 19.4 months, which is less than the most updated data (31.2 months) that was used in the resubmission.

Source: Table 2.4, p.9 Section 2a of the November 2017 submission (information not presented in the resubmission); Table 2.5, p12 Section 2 of the March 2019 resubmission. Compiled during evaluation.

6.7 The key features of CASTOR are summarised in Table 6.

Table 6: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Direct randomised trial (DBd)						
CASTOR	DBd: 251 Bd: 247 Total: 498	Phase 3, OL, AC, RCT, MC 120-day safety update: 13.3 months Interim analysis 4: 31.2 months Interim analysis 5: 40.0 months (median)	Low	Received ≥ 1 previous lines of therapy[a]	PFS, OS, ORR, MRD, PROs, safety	PFS, OS, PROs, Safety

AC = active-controlled; Bd = bortezomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; MC = multi-centre; MRD = minimal residual disease; mths = months; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; RCT = randomised controlled trial

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

b. Risk of confounding, selection and performance bias was high whilst risk of bias due to detection, attrition, reporting and misclassification was low.

Source: compiled during the evaluation.

Comparative effectiveness

ITT population

6.8 The resubmission presented both OS and PFS results from the IA5 data cut-off (only OS data from IA5 was presented in the March 2019 Pre-Sub-Committee Response (PSCR)), which provided an additional 8.8 months of data compared with the IA4 (as reported in March 2019 resubmission). The results from the updated data continued to demonstrate significant improvements in PFS and OS for DBd compared to Bd; see Table 7.

6.9 The ESC noted that the PFS results using the updated were consistent with those previously considered by the PBAC for the ITT population (IA4 data cut-off: HR = 0.32; 95% CI: 0.25, 0.40; p<0.0001; and IA5 data cut-off: HR = 0.31; 95% CI: 0.25, 0.40; p<0.0001). At both data cut-offs, the difference in median PFS was 9.6 months in favour of DBd. The ESC considered that the data for PFS demonstrated a clear benefit for DBd over Bd.

6.10 Similarly, the ESC noted that the OS results using the updated data were consistent with those previously considered by the PBAC for the ITT population. The [redacted] in OS may be partially due to patients in the Bd arm crossing over to receive daratumumab monotherapy treatment. While median OS was [redacted]. The ESC noted that the data for OS demonstrated a [redacted] improved survival for DBd compared to Bd, but considered that due to the crossover design of the trial which allowed patients in the Bd arm to switch to daratumumab treatment, OS data beyond the 120-day safety update (HR = 0.63; 95% CI: 0.42, 0.96) did not accurately reflect the difference between the arms.

Table 7: Results of overall survival and progression free survival in the CASTOR (ITT population, IA5 data cut-off)

	DBd n/N (%)	DBd Median time to event, months (95% CI)	Bd n/N (%)	Bd Median time to event, months (95% CI)	Difference in median, months	P value (log rank test)	Hazard ratio (95% CI)
March 2019 resubmission: IA4[a,b]							
PFS	172/251 (68.5%)	16.7 (13.14, 19.38)	204/247 (82.6%)	7.1 (6.21, 7.66)	9.6	**p<0.0001**	**0.32 (0.25, 0.40)**
OS	[redacted]/251 ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]/247 ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]	[redacted][c]	([redacted], [redacted])
November 2019 resubmission: IA5[d]							
PFS	NR	16.7	NR	7.1	9.6	**p< 0.0001**	**0.31 (0.25, 0.40)**
OS	[redacted]/251 ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]/247 ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]	p=[redacted]	([redacted], [redacted])

Bd = bortezomib-dexamethasone; CI = confidence interval; DBd = daratumumab-bortezomib- dexamethasone; IA4 = interim analysis 4; IA5 = interim-analysis 5; ITT = intention to treat; NE = not evaluable; NR = not reported; OS = overall survival; PFS = progression free survival
Note: Bold indicates a statistically significant difference.
a. Median follow-up for CASTOR is 31.2 months.
b. PFS measured by computerised algorithm.
c. p-value was verified from source during evaluation.
d. Median follow-up for CASTOR is 40.0 months.
Source: Table 2.10, p.22, Table 2.11, p.24, Table 2.13, p.27, Table 2.19, p.40 Section 2 of the March 2019 resubmission; Table 2.14, p.29 Section 2 CASTOR IA4 data TEFPFS01 TEFPFS01_1PL_PRIMID_MAF, TEFPFS01_1PL_PRLENA_2_MAF, Janssen internal analyses, Submission Figures Excel file, Appendix 4 of the resubmission *and compiled during the evaluation.* Table 2.8, p52 and Table 2.9, p53 of the November 2019 resubmission.

6.11 The November 2019 resubmission stated that results for overall response and minimal residual disease negativity in the IA5 data cut-off for the ITT population remained unchanged from the March 2019 resubmission (IA4 data cut-off).

Second-line subgroup analyses

6.12 The PFS and OS results for the second-line subgroup and complement are presented in Table 8 with the Kaplan Meier plots presented in Figure 2 and Figure 3. These outcomes were statistically significantly different in favour of DBd for both PFS (HR = 0.22; 95% CI: 0.15, 0.32; p<0.0001) and OS (HR = [redacted]; 95% CI: [redacted], [redacted]; p = [redacted]); noting that the outcome for OS was not adjusted for crossover.

6.13 The main difference between the ITT and second-line subgroup in terms of baseline characteristics was the shorter time from MM diagnosis to randomisation; 3.6 years in the second-line subgroup and 4.7 or 4.8 years for DBd and Bd respectively in the ITT analysis. There was also a higher proportion of patients refractory to lenalidomide in the ITT population (DBd =24%; and Bd = 33%) compared to the second-line group (DBd = 5%; and Bd = 16%).

6.14 The second-line subgroup analysis was not predefined; however, randomisation of the trial participants was stratified by the number of prior lines of treatment (1 versus 2 or 3 versus >3). The resubmission presented results of the relative effect (hazard ratios) for PFS and OS, comparing the second-line subgroup to its complement (third- and further-lines (3+Lines)). The resubmission did not present an absolute treatment effect for the subgroup analyses. The PSCR presented Figure 4 below to demonstrate that patients treated with DBd in the second-line setting remain alive and progression free for substantially longer that patients who use DBd in the third and later-line settings. At 42 months the proportion of patients remaining progression free when treated in the second-line setting was 28.7%, compared to [redacted]% of patients being

treated in the third and later-line setting; the rates of OS were [redacted]% and [redacted]% respectively.

6.15 The resubmission did not present a biological rationale for the greater clinical effect of DBd relative to Bd in the second-line subgroup compared with later line use. The PSCR stated that it is well accepted that MM becomes more difficult to treat, response rates reduce and the duration of remission and survival shortens at each subsequent relapse. In addition, the greater benefit seen in the second-line setting was likely due to the mechanism of action of daratumumab with the efficacy of daratumumab being dependent of the strength of the patients' immune system. Given the increasing dysregulation and compromised nature of the immune system with every relapse, the anti-tumour activity of daratumumab is likely to be stronger when given earlier in a patient's disease course. The ESC considered that this reasoning was biologically plausible, noting that daratumumab would still be beneficial to patients receiving it in later-lines.

Table 8: Results of OS and PFS in the second-line subgroup and complement from CASTOR (IA5 data cut-off)

	DBd n/N (%)	DBd Median time to event, months (95% CI)	Bd n/N (%)	Bd Median time to event, months (95% CI)	Difference in median, months	P value (log rank test)	Hazard ratio (95% CI)
ITT population							
PFS	NR	16.7	NR	7.1	9.6	**p< 0.0001**	**0.31 (0.25, 0.40)**
OS	[redacted]/251 ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]/247 ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]	p=[redacted]	([redacted], [redacted])
Second-line subgroup							
PFS	NR	27.0	NR	7.6	19.1	**<0.0001**	**0.22 (0.15, 0.32)**
OS	[redacted]/122 ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]/113 ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]	p=[redacted]	([redacted], [redacted])
3L+ therapy subgroup (complement)							
PFS	NR	NR	NR	NR	NR	[redacted]	([redacted], [redacted])
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	p=[redacted]	([redacted], [redacted])

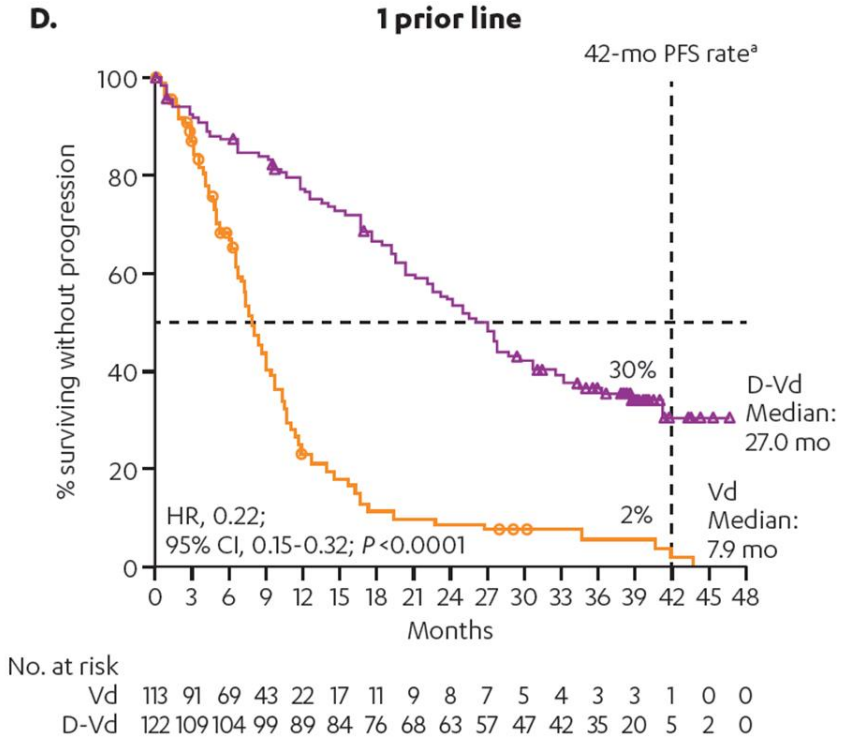
3L+ = third or later line of therapy; Bd = bortezomib-dexamethasone; CI = confidence interval; DBd = daratumumab-bortezomib-dexamethasone; IA5 = interim analysis 5; NE = not evaluable; ITT = intention to treat; NR = not reported; PFS = progression free survival; OS = overall survival

Note: Bold indicates a statistically significant difference.

Median follow-up of CASTOR is 40.0 months.

Source: Table 2.12, p59 and Table 2.13, p62 of the November 2019 resubmission.

Figure 2: Kaplan-Meier Curve of PFS in the second-line subgroup of CASTOR (IA5, computerised algorithm)



Abbreviations: CI = confidence interval; DVd = daratumumab-bortezomib-dexamethasone; HR = hazard ratio; IA5 = interim analysis 5; mo = months; PFS = progression free survival; Vd = bortezomib-dexamethasone
Note: Median follow-up for is 40.0 months
Source: Figure 2.3, p.25 Section 2 of the resubmission.

Figure 3: Kaplan-Meier curve of OS in the second-line subgroup of CASTOR (IA5 data)

DVd = daratumumab-bortezomib-dexamethasone; IA5 = interim analysis 5; OS = overall survival; Vd = bortezomib-dexamethasone
Note: Median follow-up is 40.0 months.
Source: Figure 2.6, p62 of the November 2019 resubmission.

Figure 4: Kaplan-Meier curves for PFS and OS for DBd in second and third or later line patients

DBd = daratumumab-bortezomib-dexamethasone; OS = overall survival; PFS = progression free survival
Source: Figure 3, p6 of the PSCR

6.16 The resubmission presented a crossover adjusted analysis of OS to account for the [redacted]% of patients who switched to DBd from the Bd arm in the second-line subgroup. The resubmission used the inverse probability of censoring weights (IPCW) method and based its analysis on the CASTOR IA5 data cut-off, using an individual patient data set with baseline and time dependent covariates included in the analysis. The ESC considered that use of the IPCW method was more appropriate than the non-standardised method used in the March 2019 resubmission (i.e. using data from the 120 day update to inform OS in the Bd arm of the model). The adjustment for crossover improved the hazard ratio in favour of DBd although the 95% confidence intervals for the unadjusted and adjusted analyses overlapped; Table 9. Appropriately, the economic evaluation applied both the adjusted and unadjusted values, with the base case applying the adjusted OS.

Table 9: Comparison of OS unadjusted and adjusted (IPCW) hazard ratios in second-line therapy subgroup (IA5)

Method	HR (95% CI)
Second-line therapy (unadjusted)	[redacted] ([redacted]; [redacted])
Second-line therapy (adjusted: IPCW)	[redacted] ([redacted]; [redacted])

CI = confidence interval; HR = hazard ratio; IA5 = interim analysis 5; IPCW = inverse probability of censored weights; OS = overall survival
Note: The estimate for the HR for OS in second-line (unadjusted) differs from the estimate presented in the clinical results for second-line subgroup in IA5 data cut-off.
Source: Table 2.18, p76 of the November 2019 resubmission.

Supplementary comparator (Cd)

6.17 The updated indirect comparison between DBd (CASTOR) and Cd (ENDEAVOR) was based on the second-line subgroups from both trials. The randomisation in both trials was stratified by the number of previous lines of treatment. The median follow-up in ENDEAVOR for the PFS analysis was 19.4 months for the Bd arm and 17.7 months in

the Cd arm; for the OS analysis it was 37.5 months in the Cd arm and 36.9 months in the Bd arm. The median duration of follow-up from CASTOR was 40 months.

6.18 The indirect treatment comparison demonstrated that there was a statistically significant difference in PFS in favour of DBd (HR = 0.49; 95% CI: 0.30, 0.80).

6.19 The second-line subgroup analyses demonstrated that there was a clinically significant trend towards superior OS for DBd compared with Cd (HR = [redacted]; 95% CI: [redacted], [redacted]). The comparison remained clinically significant when incorporating the resubmission's analysis that accounted for crossover in the Bd arm of CASTOR (HR = [redacted]; 95% CI: [redacted], [redacted]).

6.20 Potential transitivity issues included:

- differences in disease stage (more patients in CASTOR had ISS stage II disease; whereas more patients in ENDEAVOR had ISS stage III disease and a high cytogenic risk status); and
- the ENDEAVOR trial allowing treatment with bortezomib until disease progression compared with a maximum of 8 cycles in CASTOR.

Comparative harms

6.21 The November 2019 resubmission stated that the safety profile of daratumumab was unchanged between the IA4 and IA5 data cut-offs in the ITT population (see Table 10). The resubmission did not present a safety analysis for the second-line subgroup.

Table 10: Summary of key adverse events in the trials (ITT population)

Trial ID: CASTOR	DBd, n/N (%)	Bd, n/N (%)	Risk Difference (95% CI)	Relative risk (95% CI)
November 2017 submission: 120dsu				
Any AE, n (%)	240/243 (98.8%)	226/237 (95.4%)	**3.41 (0.39, 6.42)**	1.04 (1.00, 1.07)
Grade 3 and 4 AEs	193/243 (79.4%)	149/237 (62.9%)	**16.55 (8.58, 24.53)**	1.26 (1.12, 1.42)
Any serious AE, n (%)	118/243 (48.6%)	81/237 (34.2%)	**14.38 (5.67, 23.10)**	1.42 (1.14, 1.77)
≥1 AE related to discontinuation of all study treatment, n (%)	22/243 (9.1%)	22/237 (9.3%)	-0.23 (-5.39, 4.93)	0.98 (0.56, 1.71)
Total number of deaths within 30 days of last dose, n (%)	14/243 (5.8%)	13/237 (5.5%)	0.28 (-3.85, 4.40)	1.05 (0.50, 2.19)
March 2019 resubmission: IA4				
Any AE, n (%)	241/243 (99.2%)	226/237 (95.4%)	**3.82 (0.91, 6.73)**	**1.04 (1.01, 1.07)**
Grade 3 or 4 AE, n (%)	199/243 (81.9%)	149/237 (62.9%)	**19.02 (11.20, 26.85)**	**1.30 (1.16, 1.46)**
Any serious AE, n (%)	127/243 (52.3%)	81/237 (34.2%)	**18.09 (9.37, 26.80)**	**1.53 (1.23, 1.89)**
Any AE leading to discontinuation of study treatment, n (%)	23/243 (9.5%)	22/237 (9.3%)	0.18 (-5.03, 5.40)	1.02 (0.58, 1.78)
Grade 3 or 4 AE, n (%)	15/243 (6.2%)	11 (4.6%)	1.53 (-2.51, 5.57)	1.30 (1.16, 1.46)
Deaths	15/243 (6.2%)	14 (5.9%)	0.27 (-4.0, 4.53)	1.04 (0.52, 2.12)

120dsu = 120-day safety update; AE = adverse event; Bd = bortezomib-dexamethasone; CI = confidence interval; DBd = daratumumab-bortezomib-dexamethasone; IA4 = interim analysis 4; ITT = intention to treat

Note: Risk difference > 0 favours Bd over DBd. Bold indicates a statistically significant difference.

Source: Table 2.44, p. 92 Section 2a of the November 2017 submission (information not presented in the resubmission); Table 2.28, p. 59 Section 2 of the March 2019 resubmission.

6.22 The November 2019 resubmission provided updated data for the occurrence of the most common all grade AEs (≥ 20% of patients) for DBd and Bd in the ITT population (thrombocytopenia: 60% vs 44%; anaemia 29% vs 32%; neutropenia 20% vs 10%; and lymphopenia 13% vs 4%). The most common Grade 3+ AEs (≥ 5% of patients) in the ITT population were thrombocytopenia (DBd, 46% vs Bd, 33%); anaemia (16% vs 16%);

neutropenia (14% vs 5%); and lymphopenia (10% vs 3%). Overall, treatment with DBd was associated with more AEs than Bd. In the March 2019 assessment, the PBAC considered the clinical claim of inferior safety of DBd was reasonable (paragraph 7.9, Daratumumab PSD, March 2019).

Supplementary comparator (Cd)

6.23 The November 2019 resubmission did not update the comparison of safety with Cd, referring to the comparison presented in the March 2019 resubmission. The March 2019 resubmission claimed that the indirect comparison comparing AEs for DBd and Cd demonstrated non-inferior safety with an overlapping, but different and manageable, profile of AEs. In its March 2019 assessment, the PBAC considered the clinical claim of non-inferior safety of DBd to Cd was partially supported by the data (paragraph 6.38, Daratumumab PSD, March 2019).

Benefits/harms

6.24 A summary of the comparative benefits and harms for DBd vs Bd in the ITT population is presented in Table 11. A summary of the available information on the benefits and harms for the second-line subgroup, the focus of the resubmission, is presented in Table 12.

Table 11: Summary of comparative benefits and harms for DBd vs Bd (ITT population)

Benefits (IA5 data cut-off)						
	DBd	**Bd**	**Absolute difference**			**HR (95% CI)**
Progression events						
Number of events, n/N (%)	NR	NR	-			**0.31 (0.25, 0.40)**
Median, months (95% CI)	16.7	7.1	9.6 months			
Not progressed at 42 months, %	22%	1%	21%			
Deaths						
Number of events, n/N (%)	[redacted]/251 ([redacted]%)	[redacted]/247 ([redacted]%)	[redacted]			[redacted] ([redacted], [redacted])
Median, months (95% CI)	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])	[redacted]			
Alive at 42 months, %	[redacted]%	[redacted]%	[redacted]%			
Harms (IA4 data cut-off)						
	DBd, n/N	**Bd, n/N**	**RR (95% CI)**	**Event rate/100 patients[a]**		**RD (95% CI)**
				DBd	**Bd**	
Any AE	241/243	226/237	**1.04 (1.01, 1.07)**	99.2	95.4	**3.82 (0.91, 6.73)**
Grade 3 or 4 AE	199/243	149/237	**1.30 (1.16, 1.46)**	81.9	62.9	**19.02 (11.20, 26.85)**
Any serious AE	127/243	81/237	**1.53 (1.23, 1.89)**	52.2	34.2	**18.09 (9.37, 26.80)**
Discontinuation of study treatment due to AE	23/243	22/237	1.02 (0.58, 1.78)	9.5	9.1	0.18 (-5.03, 5.40)

AE = adverse event; Bd = bortezomib-dexamethasone; CI = confidence interval; DBd = daratumumab-bortezomib-dexamethasone; HR = hazard ratio; IA4 = interim analysis 4; IA5 = interim analysis 5; ITT = intention to treat; NE = not estimable; NR = not reported RD = risk difference; RR = risk ratio

Note: Bold indicates a statistically significant difference.

a. Median follow-up for CASTOR IA5 data cut-off is 40.0 months.

Source: Table 2.8, p52 and Table 2.9, p53 of the November 2019 resubmission. Table 2.28, p. 59 Section 2 of the March 2019 resubmission. The absolute difference, event rate and RR were calculated during the evaluation.

6.25 On the basis of the direct evidence presented in CASTOR for the ITT population, for every 100 patients treated with DBd rather than Bd:

- Approximately 21 fewer patients would have progressed at 42 months after the start of treatment.
- Approximately [redacted] patients would be alive at 42 months after the start of treatment.
- Approximately 4 additional patients would have an AE over a median duration of exposure of 31.2 months.
- Approximately 19 additional patients would have a Grade 3 or 4 AE over a median duration of exposure of 31.2 months.
- Approximately [redacted] additional patients would have a serious AE over a median duration of exposure of 31.2 months.

Table 12: Summary of comparative benefits and harms for DBd vs Bd (second-line subgroup)

Benefits (IA5 data cut-off)[a]				
Event:	**DBd**	**Bd**	**Absolute difference**	**HR (95% CI)**
Progression events				
Number of events, n/N (%)	NR	NR	-	**0.22 (0.15, 0.32)**
Median, months (95% CI)	27.0	7.9	19.1 months	
Not progressed at 42 months, %	30%	2%	28%	
Deaths*				
Number of events, n/N (%)	[redacted]/122 (28.7%)	[redacted]/113 (45.1%)	-	**[redacted] ([redacted], [redacted])**
Median, months (95% CI)	[redacted] ([redacted], [redacted])	[redacted] ([redacted], NE)	NE	
Alive at 42 months, %	[redacted]%	[redacted]%	[redacted]%	

AE = adverse event; Bd = bortezomib-dexamethasone; CI = confidence interval; DBd = daratumumab-bortezomib-dexamethasone; HR = hazard ratio; IA5 = interim analysis 5; NE = not estimable; NR = not reported

Note: Bold indicates a statistically significant difference.

* Results are not adjusted for crossover

a. Median follow-up for CASTOR IA5 data cut-off is 40.0 months.

Source: Table 2.12, p59 and Table 2.13, p62 of the November 2019 resubmission. The absolute difference was calculated during the evaluation.

6.26 On the basis of the direct evidence presented in CASTOR for patients in the second-line setting, for every 100 patients treated with DBd rather than Bd:

- Approximately 28 fewer patients would have progressed at 42 months after the start of treatment.
- Approximately [redacted] additional patients would be alive at 42 months after the start of treatment. The additional number of patients alive at 42 months may be more than [redacted], as the results presented above were not adjusted to account for patients in the Bd arm receiving daratumumab post-progression.

6.27 Based on the estimates provided in the resubmission, approximately [redacted] patients would initiate second-line treatment over the first 5 years. After 42 months (3.5 years) of DBd treatment, it would be expected that there would be an additional [redacted] ([redacted] x [redacted]) patients free of progression and an additional [redacted] ([redacted] x [redacted]) patients alive.

Clinical claim

Main comparator DBd vs. Bd

6.28 The resubmission claimed that DBd was superior in terms of efficacy compared to Bd as a second-line treatment for RRMM patients.

6.29 The resubmission claimed that DBd was inferior in terms of safety compared to Bd based on the ITT population. The resubmission assumed that the safety profile of DBd in the second-line subgroup would be consistent with that in the ITT population. The PBAC has previously considered that the claim of inferior safety was reasonable for the ITT population (paragraph 7.9, Daratumumab PSD, March 2019).

6.30 The ESC considered that the proposed clinical claims were reasonable in the context of the evidence presented and were consistent with the requested listing. However, the evidence demonstrated that DBd, when used as a later-line therapy (i.e. third-line and beyond) also results in a clinical benefit. The ESC were concerned that restricting use to the second-line setting would thus represent an impediment to equity of access across the broader RRMM population. The PBAC considered that the compassionate supply of daratumumab for eligible patients requiring third or later-line therapy would address the equity issue identified by the ESC.

6.31 The PBAC considered the claim that DBd was superior to Bd in terms of efficacy in the second-line subgroup was reasonable.

6.32 The PBAC considered the claim that DBd was inferior to Bd in terms of safety in the second-line subgroup was reasonable.

Supplementary comparators

6.33 The resubmission claimed that DBd was superior to Cd in terms of PFS, with a strong and consistent clinically significant trend towards superior OS in the second-line subgroup. The ESC considered that this claim was partially supported by the evidence presented, subject to the potential issues of transitivity associated with differences in the disease severity and exposure to bortezomib. The PBAC previously considered that the claim that DBd was superior compared to Cd in the ITT population in terms of PFS was supported by the data. The PBAC previously considered that DBd demonstrated a trend towards superior OS compared to Cd. However, the PBAC remained concerned that there was no statistically significant OS benefit (paragraph 6.38, Daratumumab PSD, March 2019). The PBAC considered that the same conclusion applied to the comparison in the second-line subgroup.

6.34 The resubmission did not present an indirect comparison of safety between DBd and Cd in the second-line subgroups. The resubmission referred to the ITT population claim presented in the March 2019 resubmission of non-inferior safety for DBd compared to Cd, with overlapping but different and manageable adverse events. The PBAC previously considered that this was partially supported by the data (paragraph 6.38, Daratumumab PSD, March 2019).

Economic analysis

6.35 The resubmission presented a cost-utility analysis of DBd compared to Bd relying on the second-line subgroup from CASTOR as the base-case. The structure of the economic model is summarised in Table 13.

Table 13: Summary of model structure and rationale

Component	Summary
Time horizon	Time horizon of 20 years versus IA5 trial follow-up 47 months (median follow-up 40.0 months) in CASTOR
Outcomes	LYG and QALYs

Component	Summary
Methods used to generate results	Partitioned survival model, incorporating a cohort expected value analysis.
Health states	Three: progression free, progressive disease and death.
Cycle length	1 month.
Extrapolation approach (area under the curve)	The time points (months) from which the extrapolations began were based on when fewer than 20% of patients remained at risk, as follows: • DBd: PFS at 38.7 months, OS at 41.2 months, TTD at 39.1 months. • Bd: PFS at 11.9 months, OS at 40.3 months, TTD at 5.4 months. The functional forms applied for the extrapolations were as follows: • PFS to PD using a Weibull. • Survival to death using a generalised gamma. • TTD for DBd using exponential; for Bd using Weibull. In the March 2019 resubmission the exponential function was used for OS extrapolation.

Bd = bortezomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; IA5 = interim analysis 5; LYG = life years gained; OS = overall survival; PD = progressive disease; PFS = progression free survival; QALY = quality adjusted life year; TTD = time to treatment discontinuation
Source: Table 3.1.1, p85 of the November 2019 resubmission

6.36 A major change to the economic model compared to the previous submissions was the use of the generalised gamma function in place of the exponential function for the extrapolation of the OS curve. The PBAC previously noted that "using the second-line subgroup, [redacted]% ([redacted]%) of DBd patients were modelled to be alive at 20 years (15 years) and considered that this was clinically implausible" (paragraph 7.11, Daratumumab minutes, March 2019). Fitting the generalised gamma extrapolation to the OS Kaplan-Meier curves (updated to use the IA5 data cut-off) predicted that [redacted]% ([redacted]%) of DBd patients and [redacted]% ([redacted]%) of Bd patients will be alive at 20 years (15 years). The estimated survival using the exponential (best-fit) function at 20 years (15 years) were [redacted]% ([redacted]%) for DBd patients and [redacted]% ([redacted]%) for Bd patients. Traces for the model results are presented in Figure 5.

Figure 5: Markov traces for the CASTOR (DBd vs. Bd) model in second-line patients

[redacted]

Abbreviations: Bd = bortezomib-dexamethasone; DBd = daratumumab- bortezomib-dexamethasone; PFS = progression free survival
Note: Model time horizon 20 years (240 months)

Source: Figure 3.6, p102 of the November 2019 resubmission.

6.37 The ESC noted that the resubmission increased the time horizon from 15 years in the March 2019 pre-PBAC response to 20 years. The ESC considered that this was inadequately supported given:

- the PBAC previously stated in November 2017 and March 2019 that a 10 year time horizon would result in greater confidence in establishing cost effectiveness, noting that a 10 year horizon was presented in the July 2017 consideration of carfilzomib in the RRMM setting (paragraph 7.10, Daratumumab PSD, November 2017 and paragraph 7.12, Daratumumab PSD, March 2019);
- a publication from Rajkumar 2016[1] which stated that median survival for patients with newly diagnosed multiple myeloma was 6 to 7 years; and
- that the mean age of the second-line subgroup from the CASTOR trial was approximately 63.5 years, which the ESC considered aligned with the age of the Australian RRMM population. The ESC noted that when considering the age of the Australian RRMM population, application of a 20 year time horizon resulted in implausible survival estimates for second-line patients relative to the average life expectancy of Australians. The pre-PBAC response stated that the 20 year time horizon accounted for the tail in the survival curve.

6.38 The ESC also noted recent data from Nandakumar, et al., 2019[2] which suggested that median OS for patients with MM is improving. The ESC noted that the median OS for patients diagnosed between 2004 and 2007 was 3.9 years and for those diagnosed between 2008 and 2012 it was 6.3 years. For patients diagnosed between 2013 and 2017 median OS was yet to be reported.

6.39 The ESC considered that although median OS for patients with newly diagnosed multiple myeloma was likely to be improving, DBd was being considered as a second-line treatment and therefore, survival estimates would be reduced. Overall, the ESC considered that a time horizon of 20 years was not supported by the available data.

6.40 The PBAC agreed with the ESC and considered that a time horizon of 20 years was not supported by the available data. However, the PBAC noted the recent data which suggested that the median OS for patients with MM was improving and considered that a 10 year time horizon might be too short to capture the OS for some patients treated in the second-line setting. The PBAC considered that a 15 year time horizon could be reasonable if the extrapolation of the OS curves appropriately represented the expected survival estimates, rather than if the 20 year time horizon curves were simply truncated at 15 years. The PBAC considered that the generalised gamma

[1] Rajkumar V. Multiple myeloma: 2016 update on diagnosis, risk stratification, and management. American Journal of Haematology. 2016; 91(7): 719-734.
[2] Nandakumar B, et al. Continued improvement in survival in multiple myeloma (MM) including high-risk patients. Presented at: American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2019; Chicago, Illinois. Suppl Abstract 8039.

extrapolation to the OS Kaplan Meier curves which resulted in [redacted]% of DBd patients alive at 15 years overestimated survival.

6.41 The resubmission updated the utility values in the baseline and progression free states based on individual patient data from the CASTOR trial in the second-line subgroup.

6.42 A summary of the key drivers of the model is shown in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact Base: $[redacted]*
Extrapolation function of OS	Base-case was based on a generalised gamma extrapolation of OS KM data. It was not the best fit extrapolation according to AIC and BIC; it was considered conservative by the resubmission. A supplementary analysis used exponential function (AIC and BIC best-fit) for OS extrapolation.	High ICER (exponential function): $[redacted] ICER (trial based): $[redacted] The ESC considered the extent of extrapolation introduced considerable uncertainty in the estimated ICER.
Time horizon	Model adopted a 20-year time horizon, which it supported with updated IA5 data cut-off outcomes for second-line subgroup. The ESC considered that the use of a 20-year time horizon was inappropriate.	High, favours DBd ICER (10 years): $[redacted]
Adjustment for crossover	Base case was based on IPCW adjustment for crossover of the Bd treatment arm. The ESC considered that this was reasonable. The PBAC previously stated that scenario analysis with and without adjustment for crossover would be appropriate (para 7.13, Daratumumab PSD, March 2019).	Moderate, favours DBd ICER (no crossover): $[redacted]

AIC = Akaike information criterion; Bd = bortezomib-dexamethasone; BIC = Bayesian information criterion; DBd = daratumumab-bortezomib-dexamethasone; IA5= interim analysis 5; ICER = incremental cost-effectiveness ratio; IPCW = inverse probability of censoring weights; KM = Kaplan Meier; OS = overall survival

* ICERs updated in the ESC Advice based on changes made in the PSCR

Source: Table 3.15-16, p.68-69 and 72-73, Table 3.19, p.79 Section 3 of the resubmission and Section 3 IA5 2L MM Economic Model DBd vs Bd_PSCR

6.43 A stepped economic evaluation was presented (see Table 15) for the second-line subgroup. Step 1 was a within trial analysis (with 47 months follow-up), Step 2 extrapolated the time horizon to 20 years with OS extrapolated using an exponential (AIC/BIC best-fit) function, and Step 3 extrapolated OS using a generalised gamma function (which the submission considered conservative). In addition, Step 2 and Step 3 presented analyses for OS with the Bd arm adjusted and unadjusted for crossover as requested by the PBAC in March 2019 (paragraph 7.13, Daratumumab PSD, March 2019). All analyses were for the second-line subgroup and it was not possible to respecify the model to estimate the cost-effectiveness in the ITT population.

6.44 The base case ICER included the "Multiple Myeloma Treatment Package" – see paragraph 3.2. Removal of the "Multiple Myeloma Treatment Package" resulted in an ICER of $105,000 - $200,000 per QALY. The ESC noted if the price reduction for bortezomib was removed the base case ICER increased from $75,000 - $105,000 to $75,000 - $105,000 per QALY.

6.45 The ICERs presented below were calculated using the published prices of lenalidomide, pomalidomide and carfilzomib, which were included as subsequent therapies.

Table 15: Results of the stepped economic evaluation – second-line subgroup (MMTP prices for daratumumab and bortezomib; published priced for lenalidomide, pomalidomide and carfilzomib)

Data	Costs			QALY			ICER
	DBd	Bd	Incr.	DBd	Bd	Incr.	
Step 1: Trial based (47 months)							
Part A	$ [redacted]	$ [redacted]	$ [redacted]	[redacted]	[redacted]	[redacted]	$ [redacted]
Step 2: Extrapolated to 20-year time horizon (OS exponential - best fit)							
Part A (not adj.)	$ [redacted]	$ [redacted]	$ [redacted]	[redacted]	[redacted]	[redacted]	$ [redacted]
Part B (adj. for crossover)	$ [redacted]	$ [redacted]	$ [redacted]	[redacted]	[redacted]	[redacted]	$ [redacted]
PSCR updated ICER[b]	$ [redacted]	$ [redacted]	$ [redacted]	[redacted]	[redacted]	[redacted]	$ [redacted]
Step 3: Extrapolated to 20-year time horizon (OS generalised gamma extrapolation - conservative)							
Part A (not adj.)	$ [redacted]	$ [redacted]	$ [redacted]	[redacted]	[redacted]	[redacted]	$ [redacted]
Part B (adj. for crossover)	$ [redacted]	$ [redacted]	$ [redacted]	[redacted]	[redacted]	[redacted]	$ [redacted]
PSCR updated ICER[b]	$ [redacted][c]	$ [redacted][c]	$ [redacted][c]	[redacted]	[redacted]	[redacted]	$ [redacted][c]
March 2019 pre-PBAC response (IA4, 2nd-line subgroup, 15 year time horizon)	$ [redacted]	$ [redacted]	$ [redacted]	[redacted]	[redacted]	[redacted]	$ [redacted]

adj. = adjusted; Bd = bortezomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; ICER= incremental cost-effectiveness ratio; Incr = incremental; OS = overall survival; MMTP = Multiple Myeloma Treatment Package; QALY= quality adjusted life year

a. The updated ICER was estimated during evaluation with updated PBS and MBS fees and prices for 1 July 2019.

b. Updated to include 1 July 2019 fee and mark-up changes, plus a 10% statutory price reduction which was incurred by bortezomib in June 2018 which was mistakenly not included in the 'bortezomib when daratumumab is available' scenario.

c. The MBS costs relating to the administration of bortezomib were excluded from the PSCR-provided analyses.

Source: Table 3.6, p107, Table 3.7, p108 and Table 3.8, p109, of the November 2019 resubmission; Table 13, Daratumumab Ratified Minutes, March 2019 and p3 of the PSCR

6.46 The ESC noted that the ICER presented in the resubmission was approximately equal to that presented in the March 2019 pre-PBAC response which utilised a 15 year time horizon.

6.47 The ICER was sensitive to the choice of OS extrapolation function and adjustment for crossover.

6.48 The impact of the time horizon on the ICER when the generalised gamma (i.e. step 3) and exponential (i.e. step 2) functions were used to extrapolate the OS curve is presented in Figure 6. A time horizon of 15 years resulted in ICERs of $75,000/QALY - $105,000/QALY using the generalised gamma OS curve and $75,000/QALY - $105,000/QALY using the exponential OS curve. A time horizon of 10 years, as previously recommended by the PBAC, resulted in ICERs of $105,000/QALY - $200,000/QALY using the generalised gamma OS curve and $105,000/QALY – $200,000/QALY using the exponential OS curve.

Figure 6: ICER and time horizon, DBd vs Bd (second-line subgroup, adjusted for crossover)

Abbreviations: Bd = bortezomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year
Note: Base case (generalised gamma function) in second-line subgroup over 20-year horizon, ICER was $ per QALY gained. ICER at 20-year time horizon with exponential function was $.
Source: compiled during the evaluation and Excel spreadsheet 'Section 3 IA5 2L MM Economic Model DBd vs Bd', sheet 'Inputs' cells [B16 & B40] and 'Results IA5 1PL IPWC adjusted'.

6.49 The resubmission proposed a Managed Access Program (MAP) as a means of addressing the immature OS data and the resulting uncertainty in the magnitude of the survival benefit for DBd (paragraph 6.34, Daratumumab PSD, March 2019). The final data collection for CASTOR is scheduled for January 2021[3], with the resubmission stating that final results should be available in the first half of 2022. The proposed MAP applied a % confidence limit around the current extrapolated OS in the DBd arm of the economic model, with the final CASTOR result being compared to these (± %) thresholds. In the event that the final DBd OS data were consistently below the lower % threshold (defined in the submission as the median OS being below months), then the time horizon would be truncated to 15 years and the ; if the data were anywhere above the % lower threshold the .

6.50 The structure of the MAP would require the PBAC to accept that the final median OS for DBd would be less than months (the median OS in the economic model was months), before the . This would represent

[3] National Institute for Health and Care Excellence. Cancer drugs fund – data collection arrangement: Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (ID974. Available from: www.nice.org.uk/guidance/ta573/documents/committee-papers-4

a gain of approximately [redacted] months over the current known median survival for Bd patients (47.01 months as per CASTOR; see Table 8) in the second-line setting.

6.51 The proposed operation of the MAP is such that in the event the lower [redacted]% confidence limit did apply, it would result in truncating only the model time horizon; the resubmission stated that the model would not be re-defined (i.e. the extrapolations would not be re-estimated with the additional data, rather the functions as presented in this submission would be truncated at 15 years). The evaluation considered that a more reasonable approach would be to re-estimate the extrapolation functions incorporating the final CASTOR Kaplan Meier data and resulting shortened time-horizon.

6.52 The PSCR stated that the final OS analysis was expected to provide data with a median duration of follow-up of approximately [redacted] months ([redacted] years). Further, at the conclusion of the MAP, it was anticipated that [redacted]% of the QALYs for DBd and [redacted]% of the QALYs for Bd in the economic model will be based on trial data, providing certainty in the magnitude of benefit and cost-effectiveness of DBd.

6.53 The ESC and PBAC considered that the proposed MAP did not address the immature OS data or the uncertainty in the magnitude of the survival benefit of DBd as the final analysis of the CASTOR trial would not accurately reflect the difference in OS between the DBd and Bd arms due to the provision in the trial which allowed patients who received Bd to switch to daratumumab treatment. The ESC noted that if the OS with DBd was less than [redacted] months, and therefore the model time horizon was reduced to 15 years, [redacted] from [redacted]% to [redacted]% to maintain the ICER at $75,000/QALY - $105,000/QALY. The ESC considered that this was a [redacted] given the associated large reduction in incremental overall survival (median difference reduced from approximately [redacted] months to [redacted] months).

Drug cost/patient/course

6.54 The cost per patient per course is presented Table 16. Taking into account the anticipated mean duration of treatment, as reported from CASTOR ([redacted]months), for the second-line subgroup, the cost of the DBd regimen per patient per course of treatment in RRMM was $[redacted]. This was based on an average effective price of $[redacted] in the eight initial cycles (in which the patient received daratumumab, bortezomib and dexamethasone) and $[redacted] in the [redacted] continuing cycles (in which the patient received daratumumab and dexamethasone), weighted across public and private hospitals and with the application of the proposed "MM Treatment Package". Applying the mean duration of treatment from the economic model resulted in a higher cost per patient per course for DBd of $[redacted].

6.55 The resubmission applied a patient flow model in order to estimate the financial implications of listing DBd. Due to the operation and structure of that model it was not possible to extract, on a consistent basis, the cost per course of treatment with DBd or Bd as applied in the financial estimates. However, based on the unit prices and

durations of therapies applied, there is no reason to expect that those estimates would differ from those arising from the within trial or CUA estimates.

Table 16: Drug cost per patient for proposed (with MM Treatment package) and comparator drugs

	DBd		Bd	
	Within trial analysis	**CUA**	**Within trial analysis**	**CUA**
Mean dose/injection	Dara: 1,161 mg Bort: 1.92 mg Dex: 4 mg	Dara: 1,161 mg Bort: 1.92 mg Dex: 4 mg	Bort: 2.05 mg Dex: 4 mg	Bort: 2.05 mg Dex: 4 mg
Mean duration	[redacted] months	[redacted] months	[redacted] months	[redacted] months
Median duration	[redacted] months	[redacted] months	[redacted] months	[redacted] months
Cost/patient/cycle	Initial (DBd): $[redacted] Cont (Dd): $[redacted]	Initial (DBd): $[redacted] Cont (Dd): $[redacted]	(Bd) $[redacted]	(Bd) $[redacted]
Cost/patient/course	$[redacted][a]	$[redacted][b]	$[redacted][c]	$[redacted][d]

Bd = bortezomib-dexamethasone; Bort = bortezomib; Cont = continuing; CUA = cost utility analysis; Dara = daratumumab; DBd = daratumumab-bortezomib-dexamethasone; Dd = daratumumab-dexamethasone; Dex = dexamethasone; MMTP = Multiple Myeloma Treatment Package; SPA = Special Pricing Arrangement;

Source: Compiled during evaluation. MMTP prices were used in estimating DBd costs, current SPA prices were used in estimating Bd cost.

Note:

a. The cost/patient/course was based on mean duration of [redacted] months ([redacted] weeks) which included [redacted] initial cycles and [redacted] continuing cycles with daratumumab, [redacted] cycles of bortezomib, and [redacted] initial cycles and [redacted] continuing cycles of dexamethasone.

b. The cost/patient/course was based on mean duration of [redacted] months ([redacted] weeks) which included [redacted] initial cycles and [redacted] continuing cycles with daratumumab, [redacted] cycles of bortezomib, and [redacted] initial cycles and [redacted] continuing cycles of dexamethasone.

c. The cost/patient/course was based on mean duration of [redacted] months ([redacted] weeks) which included [redacted] cycles of bortezomib, and [redacted] cycles of dexamethasone.

d. The cost/patient/course was based on mean duration of [redacted] months ([redacted] weeks) which included [redacted] cycles of bortezomib, and [redacted] cycles of dexamethasone.

Estimated PBS usage & financial implications

6.56 This resubmission was not considered by DUSC.

6.57 The estimated use and financial implications of listing daratumumab as DBd are presented in Table 17.

6.58 A mixed epidemiological and market share approach was used to estimate the utilisation and financial impact of listing DBd in the second-line population. The estimated patient and prescription numbers for the DBd second-line population are the same as those presented in the pre-PBAC response to the March 2019 resubmission. The resubmission did not consider potential DBd use in later-lines or the potential use of daratumumab as monotherapy. In addition, the resubmission did not provide an estimate of the number of grandfathered patients expected and there was no provision for adjusting the duration of therapy for grandfathered patients.

6.59 The March 2019 resubmission used PBS data to estimate the population eligible for DBd in the second-line setting. The pre-PBAC response stated that the number of second-line patients initiating DBd may be overestimated given the recent recommendations of lenalidomide plus bortezomib and dexamethasone in newly diagnosed MM patients and of lenalidomide as maintenance therapy post ASCT. The pre-PBAC response stated that the listing of lenalidomide in the first-line setting will pro-long PFS compared to current standard of care, resulting in fewer patients progressing to second-line treatments.

Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of initiating patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of daratumumab (published price)						
Cost of daratumumab	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications of daratumumab (effective price)						
Cost of daratumumab	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
March 2019 estimates (pre-PBAC response)						
Estimated extent of use (DBd in 2nd-line and beyond + daratumumab monotherapy)						
Number of initiating patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBd, 2nd + line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of daratumumab (published price)						
Cost of daratumumab	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications of daratumumab (effective price)						
Cost of daratumumab	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

a. Assuming 2.5 prescriptions/month for DBd in the initial period and 1.1 prescriptions/month in the continuing period

Source: Table 4.17, p136 of the November 2019 resubmission with costs updated to reflect PBS fee and mark-up changes as of 1 July 2019 as per the PSCR.

6.60 The total cost to the PBS/RPBS of listing daratumumab for use as a second-line treatment, using the effective price of daratumumab less co-payments, was estimated at more than $100 million over the first six years of listing for approximately less than 10,000 initiating patients. The ESC noted that in the pre-PBAC response to the March 2019 resubmission the total cost of daratumumab was estimated at more than $100 million for approximately less than 10,000 initiating patients. The ESC considered that the opportunity cost of the requested listing remained very high.

6.61 The ESC noted that the number of initiating patients in the November 2019 resubmission (i.e. for second line only) in Year 1 was [redacted]% of that estimated for second and later-line therapy in the March 2019 pre-PBAC response (i.e. [redacted]/[redacted]). The ESC considered that the number of initiating second-line patients might be overestimated when compared to the proportion of second line patients in the CASTOR trial (47.2% = 235/498).

6.62 The ESC also noted the number of initiating patients (less than 10,000 in Year 1, approximately less than 10,000 in Years 4 to 6, Table 17) seemed high in comparison to the number of patients estimated to be treated with DBd as a second-line treatment in England. Specifically, based on an incidence of 5,540 MM patients in

England in 2015, the estimated number of patients treated with second-line DBd was 865 in Year 1 and 2,017 in subsequent years[4]. The incidence of MM in Australia in 2015 was 1,885[5], which was forecasted to be less than 10,000 in the first year of daratumumab's listing. Assuming the same proportion of patients are treated with DBd in Australia as in England, the expected number of initiating patients would be 294 in Year 1 (865 x 1,885/5,540) and 686 in subsequent years (2,017 x 1,885/5,540). The pre-PBAC response stated that the comparison between Australia and England does not take into account potential differences in the incidence rate, reporting of diagnoses, gender and/or age structure and treatment availability between the two countries. In addition, the estimated uptake in Year 1 of 30% in the UK was substantially underestimated (actual uptake was 58%). Carfilzomib was PBS listed on 1 January 2018 and in 2018 there were 839 patients treated with Cd (based on analyses undertaken by the DUSC Secretariat). This is lower than predicted for DBd, despite Cd being listed for use in RRMM as a second or later-line treatment. The pre-PBAC response stated that the uptake of DBd will be greater than of Cd due to superior efficacy.

6.63 The PBAC considered that the number of DBd initiating patients was overestimated. The PBAC noted that the total number of patients initiating on PBS listed RRMM therapies (i.e. bortezomib, lenalidomide, pomalidomide, carfilzomib and thalidomide, as it has a line agnostic listing has been declining (2016: 1,243 initiating RRMM patients; 2017: 1,163 patients; and 2018: 1,127 patients). The PBAC therefore considered that the resubmissions assumption that less than 10,000 patients would initiate DBd in Year 1 was high relative to the 2018 RRMM patient count. The PBAC considered that any RRMM population growth assumption should be applied to the 2018 patient total (1,127) and that although DBd uptake would be high (the resubmission assumed [redacted]% to [redacted]%), it would likely be graduated, starting at 50% in Year 1 and up to 90% over the forward estimates. The PBAC considered it was appropriate to include continuing patients, and that for each yearly initiating cohort, the time to treatment discontinuation derived from the Kaplan-Meier estimates in the economic model should be applied.

6.64 The resubmission assumed that there would be cost offsets, primarily due to the assumed reduction of Cd use in the second-line setting. The resubmission assumed that DBd would replace Cd in the second-line setting, with the PSCR stating that any displaced Cd use was likely to be incurred beyond the six-year forward estimates. The ESC considered that this overestimated the total cost-offsets as the median duration of DBd therapy in the second-line subgroup was 24 months and therefore use of displaced Cd was likely to occur within the six year forward estimates for a large proportion of patients (including those who would be grandfathered). The pre-PBAC response stated that real world data demonstrates that PFS and treatment duration shortens with each line of therapy[6]. In addition, the pre-PBAC response stated that the recent recommendations of lenalidomide in the first-line setting would reduce

[4] https://www.nice.org.uk/guidance/ta573/documents/committee-papers-4
[5] https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/acim-books
[6] Yong K, et al. Multiple myeloma: patient outcomes in real-world practice. British Journal of Haematology. 2016;175:252-264.

lenalidomide use in the relapsed setting. Therefore, in the relapsed setting DBd may offset less lenalidomide and more Cd and pomalidomide.

6.65 Univariate sensitivity analyses were conducted during the evaluation to test the potential impact if DBd was used as third and later-lines of therapy, as well as monotherapy (based on uptake rates used in the March 2019 resubmission). The results are presented in Table 18.

Table 18: Univariate sensitivity analysis for estimated cost to PBS/RPBS (MMTP prices used for daratumumab and bortezomib)

Scenarios	Year 1 2019	Year 2 2020	Year 3 2021	Year 4 2022	Year 5 2023	Year 6 2024
Base-case	$	$	$	$	$	$
Including DBd 3+ lines therapy[a]	$	$	$	$	$	$
Including D mono[a]	$	$	$	$	$	$
Including 3+ lines and D mono	$	$	$	$	$	$

3+ lines = third- and later-lines of therapy; D mono = daratumumab monotherapy; dara = daratumumab; DBd = daratumumab-bortezomib-dexamethasone; MM = multiple myeloma; SA = sensitivity analysis

a. Proportions for 3+ lines of therapy and daratumumab monotherapy as per March 2019 resubmission

Source: Calculated during evaluation of the November 2019 resubmission. Calculations were performed in updated Excel workbook 'Daratumumab RRMM financial estimates model prePBAC_20180306xlsx' from pre-PBAC response (March 2019 resubmission) using fees and costs from November 2019 resubmission.

Financial Management – Risk Sharing Arrangements

6.66 The sponsor stated that it recognised that the PBAC may consider that there is a risk for use of DBd beyond the requested restriction into later line settings (outside the requested listing). The ESC considered that use outside of the requested listing was likely in terms of the later line settings. The ESC also considered that the use of DBd in the second-line setting could be inflated by use in newly diagnosed patients who were considered to be suitable for DBd therapy. The ESC noted the cost-effectiveness of DBd in these settings was unknown.

6.67 The resubmission proposed an RSA with of annual subsidisation caps based on the total cost of DBd to the PBS/RPBS:

- : the number of daratumumab prescriptions expected to be used as DBd for second-line MM patients, which reflects the requested PBS listing of daratumumab in the current resubmission. was equal to the estimated prescription numbers in the November 2019 resubmission and the March 2019 pre-PBAC response for second-line treatment setting.
- : the number of daratumumab prescriptions expected to be used as DBd in third and later lines (i.e. outside the requested listing), but not including any daratumumab monotherapy use. The ESC noticed that although the number of DBd prescriptions (and patients) for second-line therapy matched those estimated in Table 17 (and the March 2019 resubmission), the number of prescriptions for third or later-line therapy did not match those presented in the March 2019 resubmission; the RSA estimated that there would be an additional 726 third or later-line prescriptions – see Table 19. The PSCR stated that as patients

cannot receive daratumumab monotherapy, more third or later-line patients would receive DBd.

Table 19: Number of 2nd and 3+ line daratumumab prescriptions in proposed RSA and March 2019 resubmission

	Year 1	Year 2	Year 3	Year 4	Year 5
2nd line (Nov 2019 and March 2019)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3+ line (Nov 2019)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3+ line (March 2019)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RSA = Risk Sharing Arrangement
Source: Table 4.4, p126 of the Nov 2019 resubmission

6.68 The resubmission proposed reimbursing the Commonwealth Government [redacted]% of the Commonwealth Payment (i.e., Commonwealth Expenditure less SPA rebate) for expenditure between [redacted] and [redacted]. Above [redacted], which reflects the use of DBd beyond that expected by all RRMM patients, the resubmission proposed reimbursing the Commonwealth Government [redacted]% of the Commonwealth Payment.

6.69 The ESC considered that as a cost-effectiveness analysis was not presented for patients using DBd in the later line setting, a subsidisation cap based on the number of second-line patients, beyond which [redacted] rebates would be applied, would be more reasonable.

6.70 The PBAC noted that the pre-PBAC response stated that daratumumab would be offered to all eligible prevalent daratumumab naïve patients as a third and later-line treatment on a compassionate basis.

Table 20: Estimated use and financial implications with Risk Sharing Arrangement (MM Treatment Package prices)

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Number of DBd prescriptions						
A. Second-line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. Third or later lines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsidisation caps – number of prescriptions						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsidisation caps – value						
[redacted] ($)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
[redacted] ($)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Actual estimated cost to PBS/RPBS (i.e. if [redacted]% rebate applied for use between [redacted] and [redacted])						
[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

DBd = daratumumab + bortezomib + dexamethasone; [redacted]; [redacted]; MM = multiple myeloma
Note: The prescription numbers for third and later lines were not verified during evaluation, however they were similar to the script numbers presented in March 2019 resubmission, pre-PBAC response.
Source: Table 4.19, p138 of the November 2019 resubmission with costs updated to reflect PBS fee and mark-up changes as of 1 July 2019 as per the PSCR.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for daratumumab, in combination with

bortezomib and dexamethasone (DBd), as a second-line treatment in patients with relapsed and/or refractory multiple myeloma (RRMM). The PBAC considered that there were important clinical benefits associated with DBd therapy, but requested revisions to the economic model, the estimated financial implications and the proposed Risk Sharing Arrangement (RSA).

7.2 The PBAC noted the large number of consumer comments that described a range of benefits associated with DBd treatment including improved survival, improved quality of life and fewer side effects compared to currently available treatments.

7.3 The PBAC considered that the proposed clinical place in therapy as a second-line treatment only was reasonable provided the sponsor supplied daratumumab to eligible patients in the third and later-line setting on a compassionate basis. The PBAC considered that the availability of daratumumab to all RRMM patients addressed concerns regarding equity of access.

7.4 The PBAC noted that bortezomib in combination with dexamethasone (Bd) was again appropriately nominated as the primary comparator, and carfilzomib plus dexamethasone (Cd) and bortezomib plus cyclophosphamide and dexamethasone (VCd) and lenalidomide plus dexamethasone (Ld) as secondary comparators.

7.5 The PBAC noted that updated data from the Interim Analysis 5 (IA5) data cut (median follow-up = 40 months) of the CASTOR trial were presented for all outcomes.

7.6 The PBAC noted that the resubmission was based on a subgroup of patients from the CASTOR trial who received DBd or Bd as second-line treatment only. The PBAC noted that the second-line subgroup was consistent with the proposed PBS restriction.

7.7 The PBAC considered that the evidence presented in the resubmission supported a claim of superior efficacy in the second-line subgroup for DBd over Bd in terms of both PFS (HR = 0.22; 95% CI: 0.15, 0.32) and OS (HR = [redacted]; 95% CI: [redacted], [redacted]). Noting that the hazard ratio for OS was likely confounded by cross-over, the PBAC considered that the cross-over adjusted analysis, which was adjusted using the inverse probability of censoring weights, was appropriate (HR = [redacted]; (95% CI: [redacted], [redacted]).

7.8 The PBAC considered that the claim that DBd had inferior safety compared to Bd remained reasonable.

7.9 The PBAC noted that the resubmission presented an updated indirect comparison between DBd (CASTOR trial) and the supplementary comparator Cd (ENDEAVOR trial) based on the second-line subgroups from each trial. The indirect comparison demonstrated a statistically significant difference in PFS in favour or DBd (HR = 0.49; 95% CI: 0.30, 0.80) and a trend towards superior OS, particularly when the CASTOR data were adjusted for cross-over (HR = [redacted]; 95% CI: [redacted], [redacted]). The PBAC noted that an indirect comparison of safety was not updated in the resubmission, but recalled that it had previously considered the claim of non-inferior safety of DBd to Cd was partially supported by the data.

7.10 The PBAC noted that no data were provided for the other supplementary comparators.

7.11 The PBAC noted that the use of the second-line subgroup to inform the economic analysis reflected the proposed PBS population and the clinical data presented.

7.12 The PBAC noted that the time horizon in the model had been extended from 15 years, in the March 2019 pre-PBAC response, to 20 years in the resubmission, despite the PBAC previously requesting a 10 year time horizon, as per that which was accepted in 2017 for carfilzomib in the RRMM setting. The PBAC noted recent data which suggested that the median OS for patients with MM was improving. The PBAC considered that a 15 year time horizon could be reasonable for patients treated in the second-line setting, but only if the extrapolation of the OS curves appropriately represented the expected survival estimates, rather than if the curves were simply truncated at 15 years. The PBAC considered that the generalised gamma extrapolation to the OS Kaplan Meier curves which was applied in the resubmission and which resulted in [redacted]% of DBd patients alive at 15 years overestimated survival.

7.13 The PBAC considered that the incremental cost effectiveness ratio (ICER) for DBd as a second-line treatment, using the generalised gamma function, a 15 year time horizon, adjusted for crossover and using the published priced of lenalidomide, pomalidomide and carfilzomib, of $75,000 - $105,000 per quality adjusted life year (QALY) was high. The PBAC reiterated that it would consider an ICER within the range of $45,000/QALY to $75,000/QALY appropriate, as this is what was previously accepted in consideration of Cd (July 2017).

7.14 The PBAC noted that the estimated patient and prescription numbers for the DBd second-line population in the resubmission were the same as those presented in the pre-PBAC response to the March 2019 submission. The PBAC, noting (i) the pre-PBAC response which stated that the number of patients initiating DBd might have been overestimated considering the recent PBAC recommendations for lenalidomide in the newly diagnosed setting; and (ii) recent PBS data suggesting that the total number of patients accessing second-line treatment options in 2018 was 1,127 and that 839 patients were treated with carfilzomib in 2018 as a second or later-line treatment, considered that the estimates for the number of patients initiating DBd second-line treatment (less than 10,000 in Year 1 and approximately less than 10,000 in Years 4 to 6) were overestimated.

7.15 The PBAC considered that although likely to be high, the assumed uptake rates of DBd ([redacted]% in Year 1 and [redacted]% in Year 6) should be amended to 50% in Year 1, increasing to 90% over the forward estimates. The PBAC considered it was appropriate to include continuing patients, and that for each yearly initiating cohort, the time to treatment discontinuation derived from the Kaplan-Meier estimates in the economic model should be applied.

7.16 The PBAC considered that the opportunity cost of daratumumab to the PBS/RPBS of more than $100 million over the first six years for approximately less than 10,000 initiating patients remained very high.

7.17 The PBAC noted that the resubmission proposed a RSA which consisted of [redacted] beyond which [redacted]% and [redacted]% rebates would apply. The PBAC considered that due to the compassionate supply offer proposed in the pre-PBAC response the risk of leakage into the third and later-line settings would be reduced. In addition, the PBAC noted that the cost effectiveness of daratumumab treatment in the third and later-line setting was unknown. The PBAC considered that a single subsidisation cap beyond which a higher rebate would apply would be appropriate.

Noting that there is a RSA in place for carfilzomib, the PBAC considered that it might be appropriate for daratumumab to join the existing cap, which would be expanded, so that the second-line carfilzomib cost offsets were realised. The PBAC, noting that the patient numbers in the resubmission were overestimated, recommended that the subsidisation cap be calculated based on recent PBS data of the number of patients accessing second-line treatment options and the uptake rates proposed in paragraph 7.15.

7.18 The PBAC considered that the Managed Access Program (MAP) as proposed did not adequately address the uncertainties with the economic model.

7.19 The PBAC advised that any future resubmission should address the outstanding issues with the economic model and the resulting uncertainty in the ICER. In addition, a resubmission should provide updated financial estimates with additional information around the estimated cost offsets, including any reduction in the costs of other medicines, and provide an updated RSA proposal.

Outcome:
Deferred

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.