5.07 SELINEXOR, Tablet 20 mg, Xpovio®, Antengene (Aus) Pty. Ltd.

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drug), Authority Required (STREAMLINED) listing for selinexor in combination with bortezomib and dexamethasone (SBd) for the treatment of relapsed and/or refractory multiple myeloma (RRMM).

1.2 Listing was requested based on a cost-utility analysis (CUA) versus bortezomib plus dexamethasone (Bd) as the main comparator. The submission also presented a cost-minimisation analysis (CMA) versus carfilzomib in combination with dexamethasone (Cd) as a secondary comparator. The key components of the clinical issues addressed by the submission are provided in Table 1.

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

Component	Description
Population	Adult patients with relapsed and/or refractory multiple myeloma who have received at least one prior therapy
Intervention	XPOVIO® (selinexor) in combination with bortezomib and dexamethasone (SBd)
Comparator	Main/direct comparator: bortezomib + dexamethasone (Bd) Secondary comparator: carfilzomib + dexamethasone (Cd)
Outcomes	PFS, Safety
Clinical claim	Primary claim: • In patients with multiple myeloma who have received at least one prior therapy, treatment with selinexor in combination with bortezomib and dexamethasone is more effective than Bd alone in extending progression free survival with a manageable safety profile. Secondary claims: • The clinical claim for superior efficacy and different safety of SBd compared with Bd is supported by the primary direct treatment comparison of SBd with Bd in BOSTON. • A secondary clinical claim for comparable effectiveness of SBd compared with Cd is supported by an indirect comparison of the results from BOSTON with those of ENDEAVOR.

Source: Table 1-1, p18 of the submission.
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC parallel process. At the time of PBAC consideration, only the Clinical Evaluation Report was available. The proposed TGA indication was:

'For use in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior line of therapy.'

2.2 SBd was approved by the FDA in December 2020 for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior therapy. SBd was not approved by the EMA for this indication at the time of PBAC consideration.

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Repeats	DPMQ	Proprietary Name and Manufacturer
SELINEXOR, TABLETS, 20 mg	16	2	Published price: Public $[redacted] Private $[redacted] Effective price: Public $[redacted] Private $[redacted]	XPOVIO® ANTENGENE Pty Ltd
SELINEXOR, TABLETS, 20 mg	20	2	Published price: Public $[redacted] Private $[redacted] Effective price: Public $[redacted] Private $[redacted]	XPOVIO® ANTENGENE Pty Ltd

Category/Program:	Section 100 – Highly Specialised Drugs Program
PBS indication:	Relapsed and/or refractory multiple myeloma
Treatment phase:	Initial treatment: Initial treatment following at least one prior line of drug therapy
Restriction:	☒Authority Required - STREAMLINED
Treatment criteria:	Initial treatment
Clinical criteria:	The condition must be confirmed by a histological diagnosis AND The treatment must be in combination with bortezomib and dexamethasone AND Patient must have progressive disease after at least one prior therapy AND Patient must not be receiving concomitant PBS-subsidised daratumumab, carfilzomib, pomalidomide, lenalidomide, or thalidomide or its analogues
Treatment criteria:	Continuing treatment
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with an authority prescription for this drug for this condition AND The treatment must be in combination with bortezomib and dexamethasone AND Patient must not have developed disease progression while receiving treatment with this drug for this condition AND Patient must not be receiving concomitant PBS-subsidised daratumumab, carfilzomib, pomalidomide lenalidomide, or thalidomide or its analogues

Source: Table 1-12, p43, Table 1-13, pp44-45, and Table 1-14, p45 of the submission.
DPMQ = dispensed price for maximum quantity; HSD = highly specialised drug; max = maximum; N/A = not applicable; qty = quantity.

3.1 The submission proposed restrictions for initial treatment, continuing treatment, and grandfathering with restriction level of Authority Required (STREAMLINED). The submission stated that the requested restriction level was based on the restriction granted to carfilzomib in July 2020 when the PBAC considered it would be appropriate to lower the restriction authority type to Authority Required (STREAMLINED) for all carfilzomib listings in RRMM to help improve patient access to MM treatment. The PBAC considered that an Authority Required (telephone/electronic) listing would be more appropriate, given selinexor is a new chemical entity and a first in class for which there is no prior experience on the PBS and given the potential safety concerns.

3.2 The submission claimed that the requested listing (pack size of 16 and 20 tablets with 2 repeats) would allow for a total of 3 treatment cycles equating to approximately 3 months of treatment. The proposed listing for initial and continuing treatment with the requested 2 repeats will not allow for a total of 3 treatment cycles at the recommended treatment of 100 mg per week for five weeks per cycle (allowing for approximately 2.5 cycles). The recommended dose will require 25 tablets (five tablets per week over five weeks), and therefore three cycles of treatment will require 75 tablets.

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

4 Population and disease

4.1 MM is a relatively uncommon cancer of the plasma cells, accounting for approximately 1-2% of all cancers, and approximately 17% of haematological malignancies. MM may remain asymptomatic until later stages of disease; however, several signs and symptoms may be clinically identifiable at diagnosis. Those with MM may also be at increased risk of infection due to immune dysfunction.

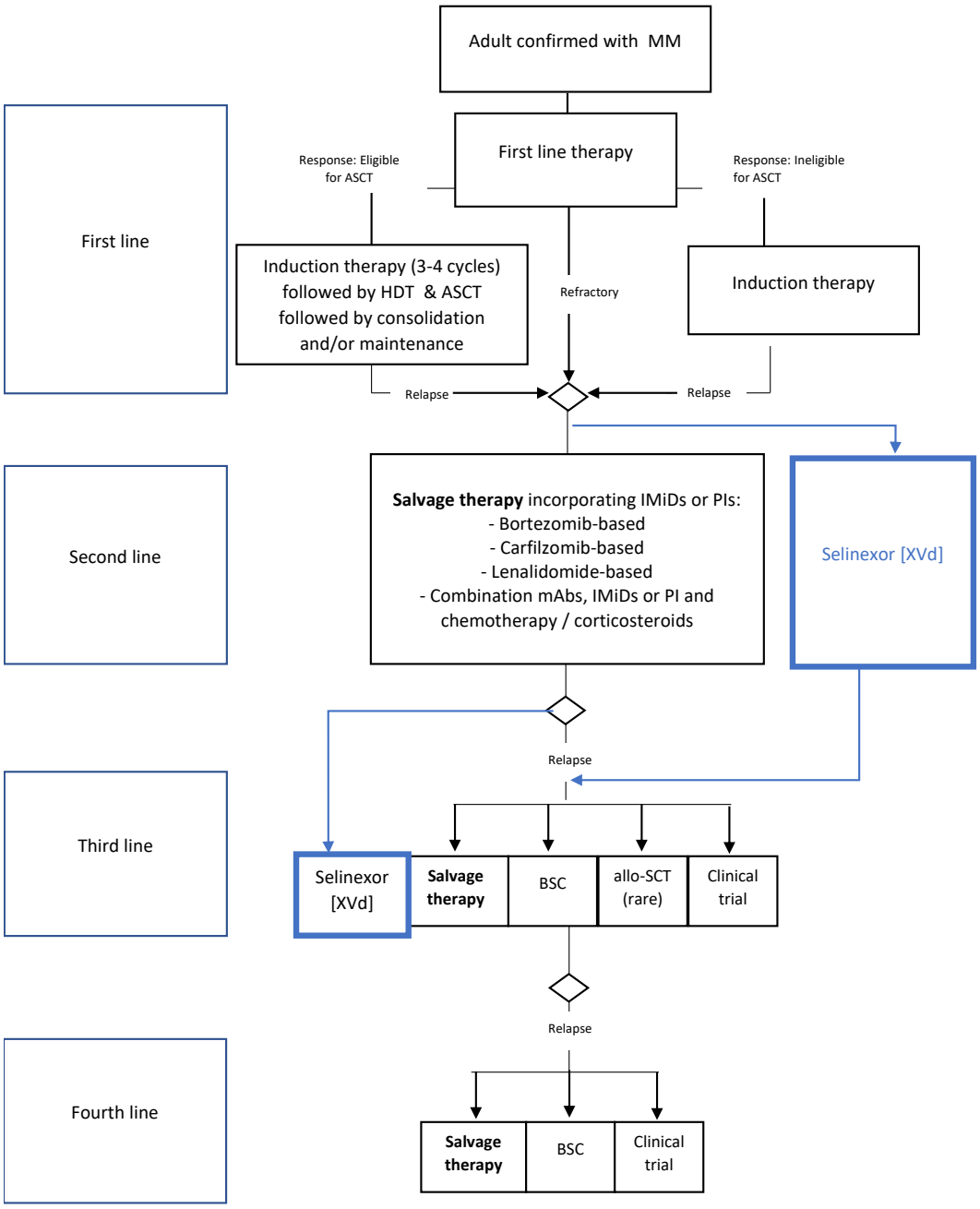
4.2 The clinical management algorithms presented in the submission were primarily based on recommendations by the Australian Medical Scientific Advisory Group (MSAG) MM clinical practice guidelines, which were updated in October 2019. The submission noted that these guidelines do not make specific recommendations for treatment regimens to be used in first and subsequent lines; rather, the guidelines provide recommendations for various protocols, with these being based on a specific 'backbone' agent, and state that the treatment should be catered to the specific need of the individual patient. The submission's proposed clinical algorithm is presented in Figure 1.

4.3 The proposed clinical algorithm placed SBd as a second or third line of therapy. The proposed clinical algorithm was mostly consistent with the proposed PBS restriction; the proposed Product Information; and the clinical evidence presented (although the clinical evidence presented by the submission was for the use of SBd after one to three prior therapies (second, third and fourth line of therapy)).The proposed clinical algorithm did not specifically include DBd as a second line therapy.

4.4 The place in therapy of SBd was unclear given its unfavourable safety profile. SBd might be reserved until later in the treatment algorithm (i.e. after daratumumab plus bortezomib and dexamethasone (DBd), Bd, Cd, and lenalidomide plus dexamethasone (Ld)) for patients without other treatment options.

4.5 The Pre-Sub-Committee Response (PSCR) stated that there was a high unmet clinical need for treatments for RRMM and that SBd was a treatment option for elderly and/or frail patients. The ESC noted that there were various PBS listed treatment options available for patients with RRMM including thalidomide, bortezomib, lenalidomide, carfilzomib, daratumumab and pomalidomide. In addition, the ESC considered that the use of SBd in elderly and/or frail patients would be low considering the high incidence of adverse events, particularly haematological events.

Figure 1: Proposed clinical management algorithm with introduction of SBd



Source: Figure 1-4, p41 of the Submission
allo-SCT = allogeneic stem cell transplant; ASCT = autologous stem cell transplant; BSC = best supportive care; HDT = High-dose therapy; IMiD = immunomodulator; mAb = monoclonal antibody; MM = multiple myeloma; PI = protease inhibitor.
Notes: The abbreviation of XVd referred to SBd (selinexor + bortezomib + dexamethasone).

4.6 Selinexor is an oral, first-in-class, potent, selective inhibitor of nuclear export (SINE) compound that specifically blocks Exportin-1 (XPO1). Inhibition of XPO1 leads, amongst other mechanisms, to the nuclear accumulation and activation of tumour suppressor proteins (TSPs), which then initiate apoptosis in cancer cells.

4.7 The rationale for combining selinexor with bortezomib and dexamethasone is based on non-clinical models of MM and other cancers, including in vitro and in vivo studies, which have shown that selinexor strongly synergises with PIs such as bortezomib and carfilzomib leading to inhibition of cell proliferation and induction of MM cell death.

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

5 Comparator

5.1 The submission nominated Bd as the main comparator and Cd as a secondary comparator.

5.2 Although the submission presented cost offsets due to reduced use of DBd in the second line setting, DBd was not nominated as a comparator and the submission did not present evidence of the comparative efficacy, safety or cost effectiveness of SBd relative to DBd. The submission also did not present any comparative evidence of SBd relative to Ld.

5.3 The ESC considered that SBd would most likely be used as a third or later line therapy and would replace and/or displace Cd, Ld, pomalidomide plus dexamethasone (Pd) and bortezomib based regimens including Bd.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor provided a hearing for this item. The clinician presented results from the BOSTON trial and discussed the natural history of the disease. The clinician described the benefits of SBd therapy, particularly in patients who are refractory to lenalidomide, have high risk cytogenetics or extramedullary disease. The clinician also described management of the potential adverse events associated with treatment. The PBAC considered that the hearing was informative as it provided a clinical perspective on the utilisation of SBd.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (18) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from the individuals described the ongoing need for new treatment options for the management of RRMM.

6.3 The PBAC noted the advice received from (i) Myeloma Australia, (ii) Rare Cancers Australia, and (iii) the Leukaemia Foundation which described the ongoing clinical need for new therapies, such as selinexor, for the treatment of RRMM. Myeloma Australia's MSAG cited results from the BOSTON trial and stated that SBd would provide a significant alternative for RRMM patients. The PBAC noted that this advice

was supportive of the evidence provided in the submission.

Clinical trials

6.4 The submission was based on one head-to-head randomised trial (Study KCP-330-023, referred to as 'BOSTON'; N = 402) comparing SBd to Bd in patients with MM who have received one to three prior therapies.

6.5 The submission presented a non-matched indirect treatment comparison (ITC) of SBd and Cd informed by two head-to-head randomised control trials: BOSTON and ENDEAVOR, comparing Cd with Bd (N = 929).

6.6 The PBAC has reviewed the ENDEAVOR study on previous occasions (carfilzomib, Public Summary Document (PSD), November 2016 and its resubmission in July 2017; daratumumab PSD, November 2017). Previously, the PBAC accepted the claim of superior comparative effectiveness for Cd over Bd based on a clinically meaningful overall survival (OS) advantage as shown by the updated clinical trial data in the July 2017 resubmission. Final progression free survival (PFS) data were from the prespecified interim analysis of ENDEAVOR, dated 10 November 2014.

6.7 Details of the two trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct trials (SBd versus Bd)		
BOSTON	KCP-330-023 A PHASE 3 RANDOMISED, CONTROLLED, OPEN-LABEL STUDY OF SBD (SBd) VERSUS BORTEZOMIB AND DEXAMETHASONE (Bd) IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM). Grosicki S, Simonova M, Spicka I, et al. Once-per-week SBd versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial.	May 2020 Lancet 2020 Nov; 14;396(10262):1563-1573.
Direct trials (Cd versus Bd)		
ENDEAVOR	Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): A randomised, phase 3, open-label, multicentre study. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Correction: Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an openlabel, randomised, phase 3 trial. Orlowski RZ, Moreau P, Niesvizky R, et al. Carfilzomib-Dexamethasone Versus Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups.	The Lancet Oncology 2016; 17(1): 27-38. The Lancet Oncology 2017; 18(10): 1327-1337. The Lancet Oncology. 18(10): e562. Clin Lymphoma Myeloma Leuk. 2019 Aug; 19(8):522-530.e1.

Source: Table 2-3, pp53-56 of the submission.
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; N/A = not applicable; OS = overall survival; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone.

6.8 The key features of the trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
SBd vs. Bd						
BOSTON[1, 2, 3]	402	R, OL, phase 3, 2-arm, global, active comparator-controlled, multicentre study	Low	Patients with RRMM who had 1-3 prior treatments	Primary: PFS Secondary: ORR, ≥VGPR, PN, OS, DOR, TTNT, safety and tolerability.	PFS, OS and TTNT used in the CUA
Cd vs. Bd						
ENDEAVOR[3]	929	R, OL, phase 3, multicentre study	Low	Patients with RRMM who had 1-3 prior treatments	Primary: PFS Secondary: OS, ORR, DOR, incidence of Grade ≥ 2 PN, safety.	Formed part of CMA

Source: Source: Table 2-37, p103 of the submission.
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CMA = cost minimisation analysis; CUA = cost utility analysis; DOR = duration of response; IMWG = International Myeloma Working Group; IRC = Independent Review Committee; ITC = indirect treatment comparison; OL = open-label; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PN = peripheral neuropathy; R = randomised; RRMM = relapsed and/or refractory multiple myeloma; SBd = selinexor + bortezomib + dexamethasone; TTNT = time to next treatment; VGPR = very good partial response.
1. Crossover from the Bd arm to a treatment that included selinexor was allowed at the point of IRC-confirmed objective disease progression per the IMWG criteria for patients in the Bd arm.
2. Used for direct comparison of SBd versus Bd (primary comparator).
3. Used for ITC of SBd versus Cd (secondary comparator).

6.9 The overall risk of bias in BOSTON and ENDEAVOR was considered low. The potential sources of bias included:

- the open-label nature of both trials. This meant that the assessment of subjective outcomes such as treatment-related adverse events might have been biased. However, the PBAC previously noted that the assessment of PFS in ENDEAVOR was blinded and was based on objective measures of response (paragraph 7.5, carfilzomib PSD, November 2016). The same consideration of the extent of bias is likely to be applicable to the conduct and evidence from BOSTON;
- that both trials included a high proportion of patients who had failed prior bortezomib therapy (BOSTON: 69.4%; ENDEAVOR: 54%);
- that a high proportion of patients (59% in SBd arm versus 40% in Bd arm) in the BOSTON trial were censored (primarily due to treatment discontinuation) at the time of data cut-off for the primary analysis of PFS; and
- that 11 patients (5.6%) in SBd arm and 5 patients (2.5%) in Bd arm of the BOSTON trial discontinued the study without confirmed progressive disease, and no specific reason for their withdrawal was reported.

6.10 The eligibility criteria were similar for both trials with both recruiting RRMM patients who had received one to three prior therapies.

6.11 Baseline demographic, disease, and clinical characteristics in BOSTON were balanced across the two treatment arms. Similarly, baseline characteristics of the ENDEAVOR

population were also generally balanced between treatment arms. Differences between the trials which may impact the transitivity of the trials included:

- that patients in BOSTON were slightly older, appeared to have more advanced/severe disease compared to ENDEAVOR, with a greater proportion of patients (67%) with higher stages of revised international staging system (R-ISS; stage II and III) disease and higher average Eastern Cooperative Oncology Group (ECOG) performance status;
- the time difference between the trials of five years. The submission stated that this partly explained the fact that patients in BOSTON had more advanced disease and were exposed to a wider range of prior therapies (5 prior unique therapies compared with 3 in ENDEAVOR); and
- that the bortezomib dosing regimen differed between the trials. In BOSTON bortezomib was administered twice weekly for the first eight cycles and once per week thereafter, whereas in ENDEAVOR it was administered twice weekly for the entire treatment duration.

6.12 Within BOSTON, seventy-four (36%) patients crossed over to SBd from Bd following progression. The submission presented a switch-adjusted hazard ratio based on the two-stage estimation method (TSEM) comparing OS for SBd versus Bd. The adjusted OS forms the basis of the economic model comparing SBd and Bd.

Comparative effectiveness

BOSTON (SBd versus Bd)

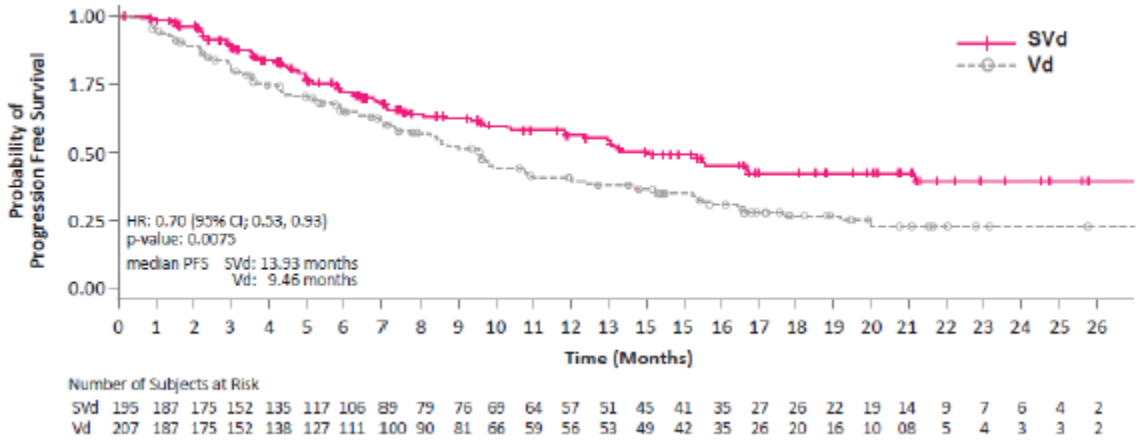
6.13 The median PFS was 13.9 months in the SBd arm and 9.4 months in the Bd arm (HR = 0.70; 95% CI: 0.53, 0.93). The submission noted that this represents an increase in median PFS of more than 4.4 months and a 30% reduction in the risk of progressed disease or death (see Table 4 and Figure 2).

Table 4: Progression free survival by treatment arm (ITT population)

	SBd arm (N=195)	Bd arm (N=207)
Median progression-free survival, months	13.9	9.5
95% CI	11.73, NE	8.11, 10.78
Stratified log-rank test [a] one-sided p-value	**0.0075**	
Hazard ratio [a,b] (95% CI)	**0.70 (0.53, 0.93)**	

Source: Table 2-15, p72 of the submission.
Bd = bortezomib + dexamethasone; CI = confidence interval; ITT = intent to treat; IRC = independent review committee; NE = not estimable; PD = progressive disease; SBd = selinexor + bortezomib + dexamethasone.
Notes: **Bold** indicates a statistically significant difference.
Progression-free survival is calculated from date of randomisation until the first date of IRC-confirmed PD per International Myeloma Working Group response criteria, or death due to any cause, whichever occurs first.
a. Stratified for prior proteasome inhibitor therapies, number of prior anti-MM regimens and R-ISS Stage at study entry.
b. Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties.

Figure 2: Kaplan-Meier curve of PFS by treatment arm (ITT population)



Source: Figure 2-6, p73 of the submission.
CI = confidence interval; HR = hazard ratio; ITT = intent to treat; PFS = progression free survival.
Notes: The abbreviation of SVd referred to SBd (selinexor + bortezomib + dexamethasone); The abbreviation of Vd referred to Bd (bortezomib + dexamethasone).

6.14 At the time of the data cut-off for the primary analysis of PFS, 115 patients (59%) in the SBd arm and 83 patients (40%) in the Bd arm were censored (primarily due to treatment discontinuation). When treatment discontinuation for any reason was counted as a PFS event there was no significant difference between treatment arms, noting that the result was numerically in favour of Bd (the median PFS in the SBd arm was 6.70 months and 6.97 months in the Bd arm).

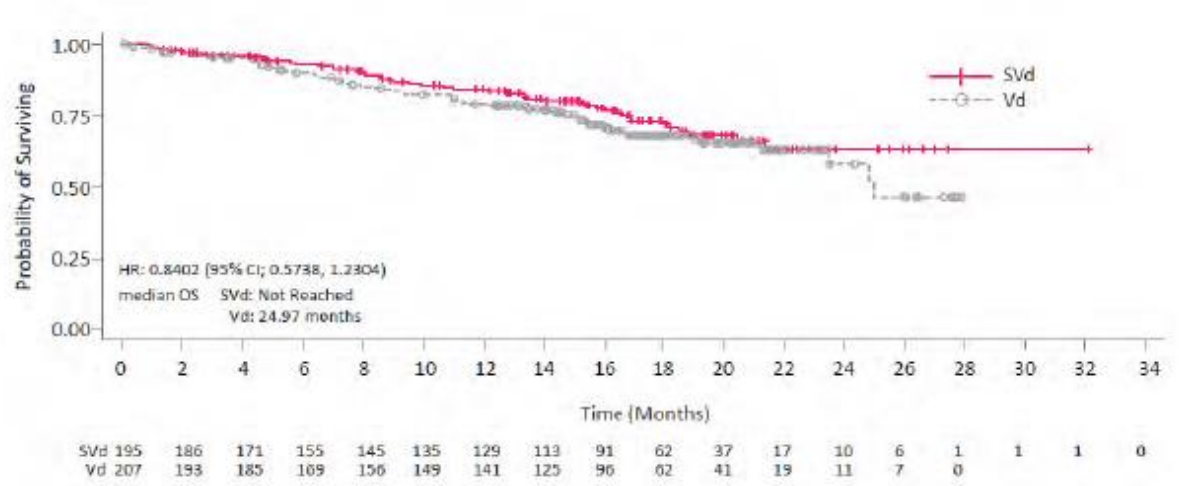
6.15 The ESC noted that the OS data were immature with median OS not reached for the SBd arm (median follow-up of 17.3 months); the median OS for patients in Bd arm was 24.97 months (median follow-up of 17.5 months; see Table 5 and Figure 3). The difference in OS was not statistically significant between the two trial arms (HR = 0.84; 95% CI: 0.57, 1.23). The PSCR stated that the BOSTON trial was not powered to show a difference in OS.

Table 5: OS by treatment arm (ITT population)

	SBd arm (N=195)	Bd arm (N=207)
Death, n (%)	47 (24.1)	62 (30.0)
Patients censored, n (%)	148 (75.9)	145 (70.0)
Median follow-up time, months (95% CI)	17.28 (16.56, 18.27)	17.51 (17.08, 18.23)
Median OS, months (95% CI)	NE (NE, NE)	24.97 (23.49, NE)
Stratified log-rank test[a]		
One sided p-value	0.1852	
Hazard ratio [a,b], (95% CI)	0.84 (0.57, 1.23)	

Source: Table 2-18, p77 of the submission.
Bd = bortezomib + dexamethasone; CI = confidence interval; ITT = intention to treat; MM = multiple myeloma; NE = not evaluable; OS = overall survival; PI = proteasome inhibitors; R-ISS = Revised International Staging System; SBd = selinexor + bortezomib + dexamethasone
Notes: OS is calculated from date of randomisation to date of death. Patients without events were censored at the date of study discontinuation or date of last participating visit, whichever occurred first.
a. Stratified for prior PI therapies, number of prior anti-MM regimens and R-ISS Stage at screening.
b. Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties.

Figure 3: Kaplan-Meier curve of OS by treatment arm (ITT population)



Source: Figure 2-9, p77 of the submission.
Bd = bortezomib + dexamethasone; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; OS = overall survival; SBd = selinexor + bortezomib + dexamethasone.
Notes: The abbreviation of SVd referred to SBd (selinexor + bortezomib + dexamethasone). The abbreviation of Vd referred to Bd (bortezomib + dexamethasone).

6.16 Patients in the BOSTON trial were permitted to crossover from the Bd treatment arm to SBd treatment at the point of independent review committee (IRC) confirmed objective disease progression.

6.17 The submission presented a switch-adjusted OS estimate between SBd and Bd based on the TSEM (HR = 0.77; 95% CI: 0.52, 1.14).

6.18 Although the submission did not justify selection of the TSEM approach, the PSCR presented some rationale for why the inverse probability of censoring weight (IPCW) and the rank preserving structural failure time model (RPSFTM) were not chosen. The ESC noted that the neither the submission, nor the PSCR, presented results using alternative methods as required in the PBAC Guidelines 2016, v5.0. The ESC also noted that results based on the IPCW method, with weights trimmed at the 99th percentile, were presented in the BOSTON Clinical Study Report (CSR; HR = 0.86; 95% CI: 0.53, 1.40). The CSR also stated that the artificial censoring of death when deaths are, in fact, known to have occurred favoured the TSEM over the IPCW method for crossover adjustment in the present context.

6.19 Table 6 demonstrates that overall response rate (ORR) was significantly higher in the SBd arm (76.4%) than in the Bd arm (62.3%) (OR = 1.96; 95% CI: 1.3, 3.1).

Table 6: ORR by treatment arm (ITT population)

	SBd arm (N=195)	Bd arm (N=207)
ORR, n (%)[a]	149 (76.4)	129 (62.3)
Exact 95% CI	69.8, 82.2	55.3, 68.9
RR (95% CI)	**1.23 (1.07, 1.40)**	
Cochran-Mantel-Haenszel Test (SBd vs. Bd)[b]		
OR (95% CI)	**1.96 (1.26, 3.05)**	
One-sided p-value	**0.0012**	
Breslow-Day Test for homogeneity		
p-value	0.2430	

Source: Table 2-17, p76 of the submission.
Bd = bortezomib + dexamethasone; CI = confidence interval; ITT = intention to treat; IRC = Independent Review Committee; OR = odds ratio; ORR = overall response rate; RR = risk ratio; SBd = selinexor + bortezomib + dexamethasone.
Notes: **Bold** indicates a statistically significant difference.
a. ORR is the proportion of patients who achieve a partial response or better, before IRC-confirmed PD or initiating a new MM treatment or crossover.
b. Analysis using Cochran-Mantel-Haenszel test stratified by prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at screening.

6.20 BOSTON assessed data on health-related quality of life (HRQoL) as an exploratory endpoint using the EQ-5D-5L and the EORTC QLQ-C30 instruments. Model-based change from baseline to Day 106 on patients reported symptoms showed statistically significant difference in levels of sensory, pain, and autonomic neuropathy symptoms between treatment arms.

ENDEAVOR (Cd versus Bd)

6.21 The median PFS was 18.7 months in the Cd arm versus 9.4 months in Bd arm (HR = 0.53; 95% CI: 0.44, 0.65) at a median follow of 11.9 months in the Cd arm and 11.1 months in the Bd arm (see Table 7).

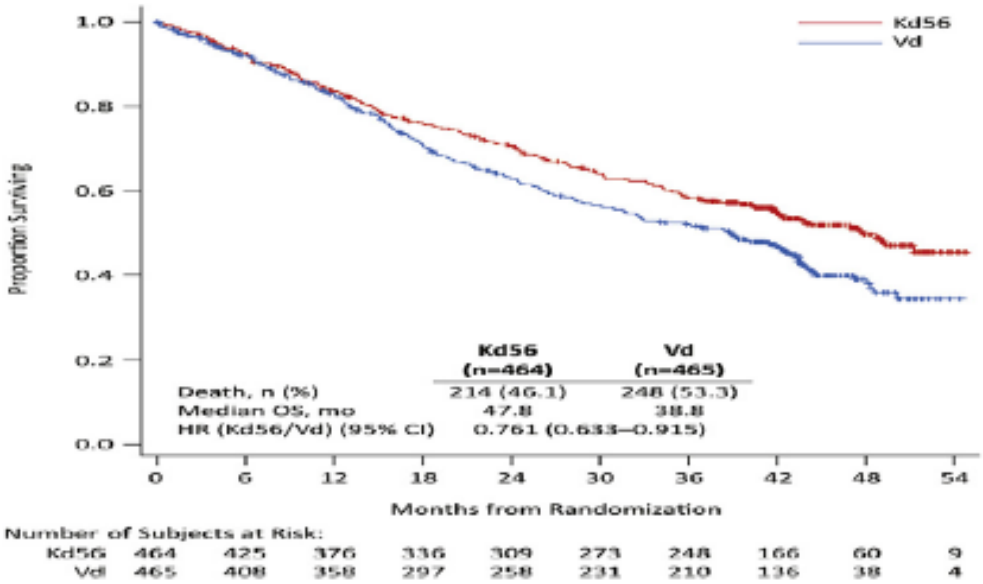
Table 7: Results of PFS in ENDEAVOR

	Patients with event, n/N (%)	Median, months (95% CI)	Difference in median, months	P value (log rank test)	HR (95% CI)
Cd	171/464 (36.9%)	18.7 (15.6, NE)	9.3	**< 0.0001**	**0.53 (0.44, 0.65)**
Bd	243/465 (52.3%)	9.4 (8.4, 10.4)			

Source: Table 2-21, p83 of the submission.
Bd = bortezomib + dexamethasone; CI = confidence interval; Cd = carfilzomib + dexamethasone; HR = hazard ratio; NE = not estimable; PFS = progression free survival
Note: **Bold** indicates a statistically significant difference.

6.22 Final OS data from the 19 July 2017 data cut-off (Orlowski et al, 2019) found that there were 214 (46.1%) patients alive in the Cd arm and 168 (36.1%) in the Bd arm at a median follow-up of 44.3 months in the Cd arm and 43.7 months in the Bd arm (see Figure 4). The median OS for the ITT population was 9.0 months longer for Cd (47.8 months) than Bd (38.8 months), resulting in an HR = 0.76 (95% CI: 0.63, 0.92).

Figure 4: Kaplan Meier curve of OS (ITT)



Source: Figure 2-15, p86 of the submission.
CI = confidence interval; Cd56 = carfilzomib + dexamethasone; OS = overall survival.
Notes: Kd56 referred to Cd (carfilzomib + dexamethasone). Vd referred to Bd (bortezomib + dexamethasone).

ITC – SBd versus Cd

6.23 The submission presented an ITC comparing SBd with Cd for the efficacy outcome of PFS only.

6.24 The submission stated that the eligibility criteria were similar for both trials with the key similarity being the recruitment of RRMM patients who have received one to three prior therapies.

6.25 The submission noted that various factors were identified in the trial populations that may have impacted on the comparability of BOSTON and ENDEAVOR, including the varying degree of disease and patient heterogeneity (see paragraph 6.11). However, the submission stated that the assumption of similar effectiveness of SBd compared with Cd remained plausible. The ESC noted the differences in the trial populations, the difference in the timing of the trials and the transitivity issues between the trials.

6.26 The key results of the ITC for PFS between SBd and Cd, using Bd as a common comparator, are presented in Table 8.

Table 8: Results of the ITC of SBd vs Cd for PFS

Trial ID	Comparison	Basis of comparison	Median PFS, months	Direct HR (95% CI)	Indirect estimate of effects HR (95%CI)[a]
BOSTON [b]	SBd versus Bd	ITT	SBd: 13.9 Bd: 9.5	0.70 (0.53,0.93)	1.27 (0.91, 1.77); p=0.15
ENDEAVOR [c]	Cd versus Bd	ITT	Cd: 18.7 Bd: 9.4	0.55 (0.46, 0.65)	

Source: Table 2-39, pp105-106 of the submission.
Bd = bortezomib + dexamethasone; CI = confidence interval; Cd = carfilzomib + dexamethasone; ITT = intention to treat; ITC = indirect treatment comparison; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone.
a. Calculated during evaluation as the submission did not present a statistical measure of the indirect estimate of effects.
b. Median follow-up time was 17.3 months in the SBd arm and 17.5 months in the Bd arm.
c. Median follow-up time was 11.9 months in the Cd arm and 11.1 months in the Bd arm.

6.27 The submission stated that PFS rates for the SBd and Cd regimen were similar, with the HR point estimates in the respective trials favouring Cd over Bd compared to SBd over Bd. The submission stated that this may be reflective of the potential confounders identified in the patient populations which could benefit the Cd treatment effect. The ESC noted that a large difference in median PFS was observed between SBd (13.9 months) and Cd (18.7 months); whereas, results were similar between the Bd arms (9.5 months versus 9.4 months) at the presented median times to follow-up (17.5 months in the Bd arm of BOSTON compared to 11.1 months in the Bd arm of ENDEAVOR).

6.28 Although the submission did not present a statistical measure of the indirect estimate of effects, this was calculated during the evaluation. There was no statistical difference between SBd and Cd in terms of PFS (HR = 1.27, 95% CI: 0.91, 1.77). Although this result should be interpreted with caution given the underlying issues of transitivity and the absence of a non-inferiority margin, the ESC noted that the point estimate suggested SBd was inferior to Cd with respect to PFS.

6.29 Overall, and noting the transitivity issues between the trials, the ESC considered that it was difficult to conclude that SBd and Cd had a comparable efficacy.

6.30 The PSCR presented the results of the measure of the indirect estimate of effects using the Bucher method and the OS data for SBd (adjusted for treatment switching using the TSEM) and Cd (HR = 1.01; 95% CI: 0.66, 1.56). The ESC considered that the results would be confounded by transitivity issues and noted that the analysis relied upon the cross-over adjusted result which was inadequately justified in the submission. In addition, the ESC noted that Cd demonstrated a statistically significant benefit in OS compared to Bd in the ENDEAVOR trial, whereas SBd in the BOSTON trial did not.

Comparative harms

BOSTON (SBd versus Bd)

6.31 The submission stated that the proportion of patients experiencing a treatment emergent adverse event (TEAE) was comparable between the SBd arm (99.5%) and the Bd arm (97.1%). The differences in serious adverse events (SAEs; 51.8% vs 37.7%);

Grade 3/4 TEAEs (79.0% vs 55.9%); and TEAEs leading to either dose modification (88.7% vs 76.5%), reduction (72.3% vs 51.0%), or interruption (85.6% vs 68.1%), were nominally statistically significant in terms of risk ratio and risk difference with lower event rates in the Bd arm.

Table 9: Summary of TEAEs (safety population)

Patients with at least one, n (%)	SBd arm (N=195)	Bd arm (N=204)	RD (95% CI)[d]	RR (95% CI)[d]
TEAE	194 (99.5)	198 (97.1)	0.02 (0.00, 0.05)	1.03 (1.00, 1.05)
Grade 3/4 TEAE[a]	154 (79.0)	114 (55.9)	0.23 (0.14, 0.32)	1.41 (1.23, 1.63)
Grade 4 TEAE[a]	34 (17.4)	22 (10.8)	0.07 (0.00, 0.14)	1.62 (0.98, 2.66)
SAE	101 (51.8)	77 (37.7)	0.14 (0.04, 0.24)	1.37 (1.10, 1.71)
TEAE leading to dose modification in study treatment[c]	173 (88.7)	156 (76.5)	0.12 (0.05, 0.20)	1.16 (1.06, 1.27)
TEAE leading to dose reduction in study treatment	141 (72.3)	104 (51.0)	0.21 (0.12, 0.31)	1.42 (1.21, 1.66)
TEAE leading to dose interruption in study treatment	167 (85.6)	139 (68.1)	0.18 (0.09, 0.26)	1.26 (1.13, 1.40)
TEAE leading to study treatment discontinuation	41 (21.0)	32 (15.7)	0.05 (-0.02, 0.13)	1.34 (0.88, 2.04)
TEAE leading to death	12 (6.2)	11 (5.4)	0.01 (-0.04, 0.05)	1.14 (0.52, 2.53)

Source: Table 2-25, p89 of the submission.

Bd = bortezomib + dexamethasone; CI = confidence interval; RD = risk difference; RR = relative risk; SBd = selinexor + bortezomib + dexamethasone; SAE = serious adverse event; TEAE = treatment emergent adverse events.

a. Based on maximum severity grade of each patient.

b. The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.

c. Study treatment is selinexor with bortezomib and dexamethasone for the SBd arm and bortezomib with dexamethasone for the Bd arm.

d. RD and RR were calculated during the evaluation.

6.32 A summary of TEAEs occurring in ≥ 10% of patients in both treatment arms is presented in Table 10 and shows that thrombocytopenia, fatigue, nausea, anaemia, decreased appetite, weight decreased, cataract, asthenia, and vomiting occurred statistically significantly more in the SBd arm compared to the Bd arm, while peripheral neuropathy (PN) occurred statistically significantly more in the Bd arm. The submission stated that these adverse events are consistent with the known safety profile of selinexor alone or in combination with other therapies and that no new TEAEs were reported on the SBd arm. The difference in PN is likely due to the difference in bortezomib exposure between the two treatment arms (once weekly bortezomib in the SBd arm compared with twice weekly bortezomib for the Bd arm) and is consistent with the mostly sensory nature of bortezomib-induced PN.

Table 10: TEAEs occurring in ≥10% of patients in either treatment arm (safety population)

MedDRA preferred term, n (%)	SBd arm (N=195)	Bd arm (N=204)	RD (95% CI)[a]	RR (95% CI)[a]
Patients with ≥1 TEAE	194 (99.5)	198 (97.1)	0.02 (0.00, 0.05)	1.03 (1.00, 1.05)
Thrombocytopenia	117 (60.0)	55 (27.0)	0.33 (0.24, 0.42)	2.23 (1.73, 2.87)
Peripheral neuropathy	63 (32.3)	96 (47.1)	-0.15 (-0.24, -0.05)	0.69 (0.53, 0.88)
Fatigue	82 (42.1)	37 (18.1)	0.24 (0.15, 0.33)	2.32 (1.66, 3.24)
Nausea	98 (50.3)	20 (9.8)	0.41 (0.32, 0.49)	5.13 (3.30, 7.95)
Anaemia	71 (36.4)	47 (23.0)	0.13 (0.05, 0.22)	1.58 (1.16, 2.16)
Decreased appetite	69 (35.4)	11 (5.4)	0.30 (0.23, 0.37)	6.56 (3.58, 12.02)
Weight decreased	51 (26.2)	25 (12.3)	0.14 (0.06, 0.22)	2.13 (1.38, 3.30)
Asthenia	48 (24.6)	27 (13.2)	0.11 (0.04, 0.19)	1.86 (1.21, 2.86)
Cataract	42 (21.5)	13 (6.4)	0.15 (0.09, 0.22)	3.38 (1.87, 6.10)
Vomiting	40 (20.5)	9 (4.4)	0.16 (0.10, 0.22)	4.65 (2.32, 9.33)
Neutropenia	29 (14.9)	12 (5.9)	0.09 (0.03, 0.15)	2.53 (1.33, 4.81)
Nasopharyngitis	23 (11.8)	10 (4.9)	0.07 (0.02, 0.12)	2.41 (1.18, 4.92)
Dizziness	24 (12.3)	8 (3.9)	0.08 (0.03, 0.14)	3.14 (1.44, 6.82)

Source: Table 2-26, p90 of the submission.

Bd = bortezomib + dexamethasone; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; RD = risk difference; RR = relative risk; SBd = selinexor + bortezomib + dexamethasone; TEAE = treatment emergent adverse events.

Note: For patients who crossed over, adverse events that occurred after the crossover were not included. This table uses MedDRA version 22.0. Preferred Terms are recoded to aggregate medically similar preferred terms.

a. RD and RR were calculated during the evaluation.

6.33 The occurrence of Grade ≥3 TEAEs is presented in Table 11 and shows nominally statistically significantly more thrombocytopenia (39.5% versus 17.2%), fatigue (13.3% versus 1.0%), neutropenia (8.7% versus 3.4%), nausea (7.7% versus 0.0%), cataract (8.7% versus 1.5%), and diarrhoea (6.2% versus 0.5%) for SBd compared with Bd.

Table 11: Treatment-emergent Grade 3 or higher adverse events occurring in ≥5% of patients in either treatment arm (safety population)

MedDRA preferred term, n (%)	SBd arm (N=195)	Bd arm (N=204)	RD (95% CI)[a]	RR (95% CI)[a]
Patients with ≥1 Grade 3+ TEAE	166 (85.1)	125 (61.3)	0.24 (0.16, 0.32)	1.39 (1.23, 1.57)
Thrombocytopenia	77 (39.5)	35 (17.2)	0.22 (0.14, 0.31)	2.30 (1.63, 3.26)
Fatigue	26 (13.3)	2 (1.0)	0.12 (0.07, 0.17)	13.60 (3.27, 56.53)
Peripheral neuropathy	9 (4.6)	18 (8.8)	-0.04 (-0.09, 0.01)	0.52 (0.24, 1.14)
Neutropenia	17 (8.7)	7 (3.4)	0.05 (0.01, 0.10)	2.54 (1.08, 5.99)
Cataract	17 (8.7)	3 (1.5)	0.07 (0.03, 0.12)	5.93 (1.76, 19.91)
Nausea	15 (7.7)	0	0.08 (0.04, 0.11)	NE
Diarrhoea	12 (6.2)	1 (0.5)	0.06 (0.02, 0.09)	12.55 (1.65, 95.64)

Source: Table 2-27, p91 of the submission.
Bd = bortezomib + dexamethasone; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; NE = not estimable; RD = risk difference; RR = relative risk; SBd = selinexor + bortezomib + dexamethasone; TEAE = treatment emergent adverse events.
a. RD and RR were calculated during the evaluation.

6.34 The ESC noted the high number of haematological adverse events associated with SBd and that thrombopoietin receptor agonists were used to mitigate thrombocytopaenia in 35 patients (18%) in the SBd arm, compared to 2 (1%) in the Bd arm.

ENDEAVOR (Cd versus Bd)

6.35 Overall, 457 (98.7%) patients in the Cd arm and 451 (98.9%) patients in the Bd arm experienced an adverse event (see Table 12). Results were nominally statistically significantly different for Grade 3/4 and any SAE in favour of Bd. Previously PBAC considered that the overall safety profile of carfilzomib was inferior to bortezomib (paragraph 7.5, carfilzomib PSD, July 2017).

Table 12: Summary of adverse events (safety population)

	Cd (N=463)	Bd (N=456)	RD (95% CI)[a]	RR (95% CI)[a]
Any AE	457 (98.7)	451 (98.9)	0.00 (-0.02, 0.01)	1.00 (0.98, 1.01)
Grade 3 and 4 AEs	379 (81.9)	324 (71.1)	0.11 (0.05, 0.16)	1.15 (1.07, 1.24)
Any serious AE	279 (60.3)	183 (40.1)	0.20 (0.14, 0.27)	1.50 (1.31, 1.72)
Any Adverse Event Leading to carfilzomib or bortezomib dose reduction	138 (29.8)	226 (49.6)	-0.20 (-0.26, -0.14)	0.60 (0.51, 0.71)
Any AE leading to discontinuation of study treatment	137 (29.6)	121 (26.5)	0.03 (-0.03, 0.09)	1.12 (0.91, 1.37)
Any adverse event leading to death	32 (6.9)	22 (4.8)	0.02 (-0.01, 0.05)	1.43 (0.85, 2.43)

Source: Table 2-31, p98 of the submission.
AE = adverse event; Bd = bortezomib + dexamethasone; Cd= carfilzomib + dexamethasone; CI = confidence interval; NE = not estimable; RD = risk difference; RR = relative risk.
a. RD and RR were calculated during the evaluation.

ITC – SBd versus Cd

6.36 Although the submission presented measures of the relative effect between SBd and Cd with respect to safety outcomes (see Table 13), these did not account for the indirect nature of the evidence and were constructed based on the comparison of data from single arms extracted from the respective trials. Accordingly, the measure of comparative effect (risk ratio) as presented by the submission was confounded by

underlying transitivity issues and the lack of a common reference and should be interpreted with caution.

6.37 A comparison of Grade 3-4 adverse events between SBd and Cd was presented. The submission stated that SBd and Cd have different adverse event profiles with gastrointestinal events related to SBd being largely manageable with dose modifications and supportive therapy and SBd resulting in significantly lower rates of cardiac and renal failure compared to Cd. SBd was associated with higher rates of thrombocytopenia and neutropenia compared to Cd.

Table 13: Comparison of adverse events for SBd and Cd

Grade 3-4 AEs, n (%)	SBd (N = 195)	Cd (N = 463)	RR (95% CI)
Hypertension	8 (4.1)	69 (14.9)	0.28 (0.14, 0.56)
Dyspnoea	1 (0.5)	29 (6.3)	0.08 (0.01, 0.60)
Cardiac failure (SMQN)	1 (0.5)	28 (6.0)	0.09 (0.01, 0.62)
Acute renal failure (SMQN)	3 (1.5)	27 (5.8)	0.26 (0.08, 0.86)
Hematopoietic thrombocytopenia (SMQN)	77 (39.5)	58 (12.5)	3.15 (2.34, 4.24)
Neutropenia (PT)	17 (8.7)	12 (2.6)	3.36 (1.64, 6.91)

Source: Table 2-40, pp106-107 of the submission.
AE = adverse events; Bd = bortezomib + dexamethasone; CI = confidence interval; Cd = carfilzomib + dexamethasone; PT = preferred term; RR = risk ratio; SMQN = Standardised Medical Dictionary for Regulatory Activities Query; SBd = selinexor + bortezomib + dexamethasone.

Benefits/harms

6.38 A summary of comparative benefits and harms for SBd versus Bd is presented in Table 14.

Table 14: Summary of comparative benefits and harms for SBd versus Bd (ITT population)

Benefits						
Progression free survival[a]						
Event	**SBd**	**Bd**	**Absolute Difference**			**HR (95% CI)**
Progressed, n (%)	80/195 (41.0%)	124/207 (59.9%)	-			**0.70 (0.53, 0.93)**
Median PFS, months (95% CI)	13.9 (11.7, NE)	9.5 (8.11, 10.78)	4.4			**p = 0.0075**
Overall survival[b]						
Deaths, n/N (%)	47/195 (24.1%)	62/207 (30.0%)	-			0.84 (0.57, 1.23)
Median OS, months (95% CI)	NE (NE, NE)	24.97 (23.97, NE)	NE			p = 0.1852
Harms						
	SBd	**Bd**	**RR (95% CI)**	**Event rate/100 patients[c]**		**RD (95% CI)**
				SBd	**Bd**	
Treatment emergent adverse events (at least one Grade 3+)						
BOSTON	166/195	125/204	**1.39 (1.23, 1.57)**	85.1	61.3	**0.24 (0.16, 0.32)**
Treatment emergent SAEs (at least one)						
BOSTON	101/195	77/204	**1.37 (1.10, 1.71)**	51.8	37.7	**0.14 (0.04, 0.24)**
Thrombocytopenia (Grade 3+)						
BOSTON	77/195	35/204	2.30 (1.63, 3.26)	39.5	17.2	0.22 (0.14, 0.31)
Neutropenia (Grade 3+)						
BOSTON	17/195	7/204	2.54 (1.08, 5.99)	8.7	3.4	0.05 (0.01, 0.10)
Cataract (Grade 3+)						
BOSTON	17/195	3/204	5.93 (1.76, 19.91)	8.7	1.5	0.07 (0.03, 0.12)

Source: Table 2-15, p72, Table 2-18, p77, Table 2-25, p89, Table 2-27, p91, Table 2-24, p88, and Table 2-29, p93, Table 2-30, p93 of the submission.

Bd = bortezomib + dexamethasone; CI = confidence interval; HR = hazard ratio; NE = not estimable; PN = peripheral neuropathy; RD = risk difference; RR = risk ratio; SAE= serious adverse event; SBd = selinexor + bortezomib + dexamethasone; TEAE = treatment emergent adverse event.

Notes: **Bold** indicates statistically significant results. Only grade 3-4 adverse events with statistically significant difference were presented.

a. Median duration of follow up was 13.2 and 16.5 months for SBd and Bd respectively.

b. Median duration of follow up was 17.28 and 17.51 months for SBd and Bd respectively.

c. Median duration of study treatment was 30.0 weeks in the SBd arm and 32.0 weeks in the Bd arm, and the mean treatment durations were 40.0 and 38.3 weeks, respectively.

6.39 On the basis of the direct evidence presented in BOSTON, after approximately 30 weeks treatment, for every 100 patients treated with SBd in comparison with Bd:

- Approximately 24 additional patients would have treatment emergent adverse events (Grade 3+).
- Approximately 14 additional patients would have treatment emergent serious adverse events.
- Approximately 22 additional patients would have thrombocytopenia (low platelet count detectable by testing).
- Approximately 5 additional patients would have neutropenia (low white cell count detectable by testing).
- Approximately 7 additional patients would have cataract.

6.40 A summary of the benefits and harms was not presented for SBd versus Cd, given the non-inferiority nature of the claim.

Clinical claim

6.41 The submission described SBd as superior in terms of effectiveness compared to Bd. The ESC considered that SBd may demonstrate a small improvement in PFS (HR = 0.70; 95% CI: 0.53, 0.93); however, the claim of superior efficacy was not supported in terms of OS (HR = 0.84; 95% CI: 0.57, 1.23), noting that the data for OS was immature.

6.42 The PBAC considered that the claim that SBd demonstrated superior comparative effectiveness compared to Bd was reasonable in terms of PFS but was not adequately supported by the data in terms of OS.

6.43 The submission described SBd as different, with a manageable safety profile, compared to Bd. This claim was not reasonable as the data from BOSTON showed that SBd was associated with statistically significantly more SAEs, Grade 3/4 TEAEs and TEAEs resulting in dose modification, reduction or interruption compared to Bd. Overall, the ESC considered that SBd has an inferior safety profile to Bd.

6.44 The PBAC considered that the claim that SBd demonstrated a different but manageable safety profile compared to Bd was not adequately supported by the data.

6.45 On the basis of the ITC, the submission claimed that SBd was non-inferior in terms of efficacy and had a comparable but different safety profile compared to Cd. The ITC was based on the assumption that the trials (BOSTON and ENDEAVOR) were comparable; however, there were a number of transitivity issues between the trials (patient baseline disposition, period of conduct, differences in comparator regimen). Moreover, the submission did not present a measure of the relative treatment effect (one estimated by the evaluation found a numerical difference that favoured Cd, but which was not statistically significant).

6.46 The absence of a statistically significant difference in PFS (albeit indirect) between SBd and Cd does not adequately establish non-inferiority; this would have required that the confidence limits of the difference in treatment effect did not include an *a priori* stated clinically meaningful difference favouring the comparator (PBAC Guidelines, v5.0, 2016). Given the submission did not estimate the difference in treatment effect and did not include a stated clinically meaningful difference, the ESC considered that the clinical efficacy claim with respect to Cd could not be supported. The ESC also noted a statistically significant improvement in OS has been demonstrated for Cd, but not for SBd, versus Bd.

6.47 The PBAC considered that the claim that SBd was non-inferior compared to Cd in terms of effectiveness was not adequately supported by the data.

6.48 In terms of comparative safety of SBd versus Cd, the ESC considered that the claim of comparable but different safety profile could not be supported given the non-interpretable measure of comparative effect (which was based on the comparison of data from single arms), lack of common reference, and the underlying transitivity issues.

6.49 The PBAC considered that the claim that SBd demonstrated a comparable but different safety profile compared to Cd was not adequately supported by the data.

Economic analysis

6.50 The submission presented a CUA comparing SBd and Bd and a CMA comparing SBd and Cd.

CUA – SBd versus Bd

6.51 The key components and assumptions of the CUA are presented in Table 15. The CUA was presented based on the clinical evidence from BOSTON, which relied on the difference in PFS (13.9 months SBd vs 9.46 months Bd; HR = 0.70; 95% CI: 0.53, 0.93). Although the clinical evidence for OS was immature and not statistically significant (HR = 0.84; 95% CI: 0.57, 1.23) an OS benefit for SBd was modelled.

Table 15: Key components of the economic evaluation (CUA)

Component	Description
Treatments	SBd vs Bd
Time horizon	15 years
Outcomes	Incremental cost per QALY gained
Method used to generate results	Partitioned survival model incorporating a cohort expected value analysis
Health states	Three: progression free (PF), progressive disease (PD) and death
Cycle length	1 week
Allocation of health states	Derived from time to event analyses (OS [a], PFS and TTD/TOT) from BOSTON
Extrapolation approach (area under the curve)	The time points (months) from which the extrapolations began, were based on the median follow-up in each treatment arm of BOSTON: SBd: OS – 17.28 months; PFS – 13.17 months; TTD – 13.17 months [b] Bd: OS – 17.51 months; PFS – 16.53 months; TTD – 16.53 months [b] The parametric survival functions applied for the extrapolations were as follows: PFS to PD – Dependent log-normal model with treatment as a covariate. Survival to death – Dependent exponential model with treatment as a covariate. TTD – Independently fit log-normal (SBd) and log-logistic (Bd)
Health related quality of life	Health state utility values based on ENDEAVOR – PF (0.741) and PD (0.665). AE associated disutilites were based on BOSTON

Source: Table 3-1, pp123-4 of the submission; developed during the evaluation

AE = adverse event; Bd = bortezomib + dexamethasone; CUA = cost utility analysis; OS = overall survival; PD = progressive disease; PF = progression free; PFS = progression free survival; QALY = quality adjusted life year; TOT = time on treatment; TTD = time to treatment discontinuation; SBd = selinexor + bortezomib + dexamethasone

a. OS adjusted for treatment crossover using the two-stage estimation method

b. As median follow-up for time to treatment discontinuation was not reported in BOSTON, the model assumes that the follow-up was the same as for progression-free survival.

6.52 The time horizon of the economic model was 15 years in the base case. However, the transition probabilities that inform the model were derived from BOSTON with an approximate median follow-up for OS of 17 months (i.e. less than 10% of the overall time horizon applied in the model). Extensive extrapolation of the time horizon (to 15 years) led to a high degree of uncertainty with respect to the model outputs. The ESC considered that a time horizon consistent with the PBAC submission for Cd of 10-years would have been more appropriate.

6.53 The model assumed that patients had RRMM after at least one prior therapy with similar characteristics as patients in BOSTON. The model population reflected the proposed PBS population. The economic model also incorporated costs associated with terminal care.

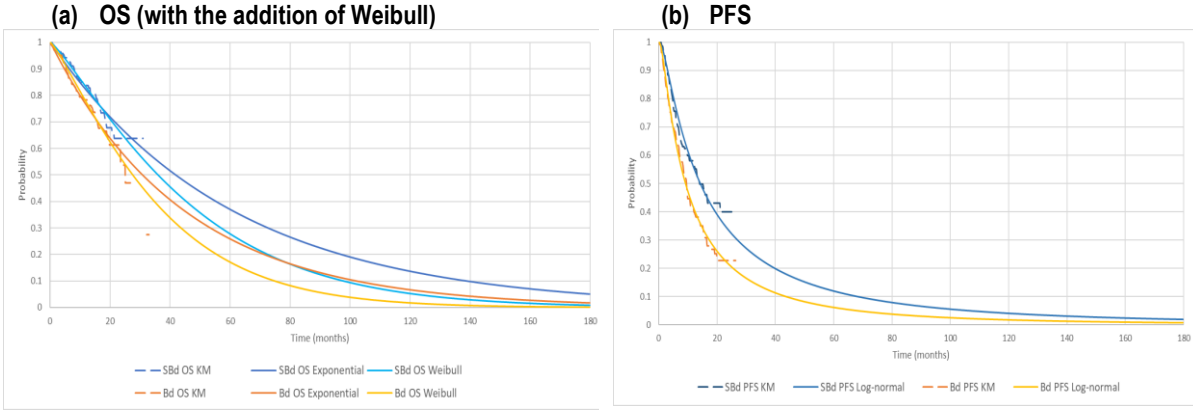
6.54 Applicability issues with respect to the economic evidence included that:

- the model did not apply utility values collected from the BOSTON trial, rather it applied values from ENDEAVOR. BOSTON-collected values were included as alternative utility profiles in a scenario analysis; and
- health resource utilisation with respect to routine care was estimated based on a health technology assessment by the National Institute for Health and Care Excellence (NICE) of pomalidomide for RRMM. It is anticipated that the pomalidomide population would be more heavily pre-treated with more advanced disease (as they required more lines of therapy to be eligible for pomalidomide); therefore, their health resource needs were likely to be different to the BOSTON trial population.

6.55 The results of the Kaplan Meier outcomes for time to treatment discontinuation (TTD), PFS and OS (TSEM adjusted for treatment crossover) and the parametric function used in the economic model for each outcome, are presented in Figure 5. The use of the cross-over adjusted hazard ratio for OS was not justified in the submission. Although a sensitivity analysis based on the unadjusted OS hazard ratio was presented, the ESC noted that an analysis using the results of the IPCW method was not presented in the submission.

Figure 5: Traces of comparative outcomes of SBd and Bd from the model (a) OS (with the addition of Weibull) and (b) PFS

(a) OS (with the addition of Weibull) **(b) PFS**



Source: developed during evaluation using results in Excel workbook PBAC_March 2021_XPOVIO Selinexor_RRMM_XVd_Section 3 CUA Workbook_Final.xlsm
Bd = bortezomib + dexamethasone; KM = Kaplan-Meier, PFS = progression free survival; OS = overall survival; SBd = selinexor + bortezomib + dexamethasone; TSEM = two-stage estimation method; TTD = time to treatment discontinuation
Note: OS is adjusted for treatment crossover using the TSEM.

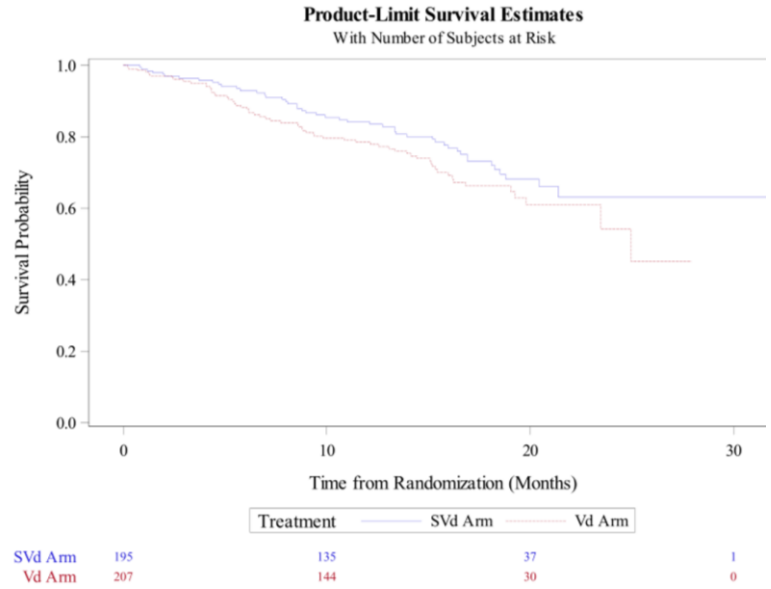
6.56 An informed choice of best parametric fit based on visual inspection was unreliable within this context due to extensive extrapolation (15-year time horizon) based on

immature Kaplan-Meier data. For the TTD of Bd, the Kaplan-Meier curve appears to plateau quicker than the parametric model estimates, with the extrapolation curves for SBd sitting below the observed data and the curves for Bd sitting above the observed data. The ESC noted that this resulted in a modelled mean TTD for SBd of 12.73 months versus 14.37 months for Bd which was inconsistent with the clinical claim that SBd was superior to Bd in terms of efficacy. The pre-PBAC response stated that the median TTD in BOSTON for SBd and Bd was 7.10 months (95% CI: 6.44, 8.54) and 7.95 months (95% CI: 6.80, 9.23) respectively, with modelled median TTDs of 7.13 months and 8.05 months respectively. In addition, a more durable response in PFS was observed for SBd (median = 13.93 months, change compared to TTD = 6.83 months) following cessation of treatment compared to Bd (median = 9.46 months, change compared to TTD = 1.51 months), which was not incongruent with the clinical claim of superior efficacy. Additionally, the pre-PBAC response noted that the longer modelled TTD for Bd was likely due to the decreasing hazard of discontinuation observed in the tail of the TTD Kaplan-Meier curve relative to SBd.

6.57 Within the context of relatively short follow-up for the OS data and thus limitation in the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics, the exponential model was the best fit in terms of BIC, but the sixth best fit as to AIC; whereas, the Weibull distribution was the best fit in terms of AIC and the third best fit as to BIC. Furthermore, noting that the clinical data was not statistically significant for OS, the ESC considered it was highly unlikely that the survival advantage of SBd based on the exponential distribution would extend beyond the 15-year time horizon. To that end, the choice of Weibull may be more appropriate as the OS appears to converge over the 15-year time horizon (see Figure 5).

6.58 The ESC noted that the assumption of constant proportional hazards resulted in the majority of the extrapolation models predicting differences in OS at 15 years (only use of the Gompertz model resulted in OS curves that completely converged). The ESC considered that the assumption of constant proportional hazards was difficult to justify based on the observed OS data and the short time follow-up for the trial (median follow-up = 17 months).

Figure 6: OS using the TSEM (ITT population)



Source: Figure 3-4 p144 of the submission.
ITT = intent to treat; OS = overall survival; SVd = selinexor + bortezomib + dexamethasone; TSEM = two-stage estimation method; Vd = bortezomib + dexamethasone

6.59 The trial-collected utility values were not applied in the base case, as the submission considered that the small difference between the health states (progression free = 0.8; progressive disease = 0.78) did not capture the true expected detriment of progressive disease for RRMM. The submission further stated that compared to published utility for progressive disease in RRMM (ENDEAVOR: 0.665, ASPIRE: 0.637 and TOURMALINE-MM1: 0.616), HRQoL for progressive disease in BOSTON appeared to be overestimated. The submission did not justify why the values obtained from BOSTON were overestimated and hence, not reflective of the HRQoL impact of treatment with SBd.

6.60 The submission utilised the health state values from ENDEAVOR (progression free = 0.741; progressive disease = 0.665) to form the base case in the economic model. The utility value for progression free of 0.741 for Cd was calculated in a subgroup of patients from ENDEAVOR (with one prior therapy and no prior bortezomib) which was not consistent with the ITT population of ENDEAVOR nor BOSTON.

6.61 BOSTON patient-data analyses were utilised in the application of utility decrements for AEs (anaemia -0.0558, fatigue -0.1003, peripheral neuropathy -0.0582 and thrombocytopenia -0.0319). A disutility value was not applied to all Grade ≥ 3 adverse events associated with SBd. The inconsistency in the source of utility values (in terms of populations and instruments applied) confounds the interpretation of utility values applied.

6.62 Costs associated with Grade ≥ 3 adverse events for SBd and Bd were applied as a one-time cost during the first cycle of the economic model. This likely underestimated the

costs associated with the management of adverse events as it did not account for a particular patient experiencing the same event more than once within the follow-up period and assumed resolution of the Grade ≥ 3 event within the same model cycle in which it occurred. Furthermore the submission did not include costs associated with Grade ≥ 3 pneumonia (13.8% SBd vs 11.8% Bd), asthenia (8.2% SBd vs 4.4% Bd) and hypophosphataemia (5.1% SBd vs 1.5% Bd), thus likely to result in an under-estimation of costs associated with the management of SBd adverse events.

6.63 The model did not consider subsequent treatment costs associated with either arm despite 35% of the patients in the SBd arm, 32% of patients who did not crossover to SBd in the Bd arm, and 49% of patients who crossed over from Bd to SBd receiving subsequent anti-myeloma therapy. The omission of subsequent therapy limits the applicability of the economic model to the Australian clinical setting, where patients are very likely to receive subsequent therapy beyond SBd.

6.64 The dose frequency, dose intensity, and time on treatment were informed by the data from BOSTON for both SBd and Bd treatment arms. The dose intensities presented in the economic model were 80% for selinexor, 89.6% for bortezomib and 90.6% for dexamethasone in the SBd arm, and 99.0% for bortezomib and 94.5% for dexamethasone in the Bd arm. The dose intensity for selinexor appears low relative to the Bd backbone. The ESC considered that the lower dose intensity for selinexor represented the high rate of adverse events associated with SBd and the required dose modifications (i.e. dose reductions and interruptions).

6.65 A summary of the key drivers of the model is presented in Table 16.

Table 16: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1] per QALY
Time horizon	15 years	Moderate, favours SBd. Reduction in the time horizon to 10 years increased the ICER to $[redacted][2] per QALY.
Treatment crossover	Treatment crossover for OS was adjusted using TSEM	High, favours SBd. No adjustment for crossover increased the ICER to $[redacted][3] per QALY.
Extrapolation	Parametric models for extrapolation were selected based on AIC, BIC, and visual inspection. External validity of OS was based on published estimates and plausibility.	High, favours SBd. Assumption of no OS gain with SBd over Bd increased the ICER to $[redacted][4] per QALY.
Utility values	ENDEAVOR trial utility values.	Moderate, favours Bd. Utility values from BOSTON decreased the ICER to $[redacted][1] per QALY.

Source: compiled during the evaluation using results in Excel workbook PBAC_March 2021_XPOVIO Selinexor_RRMM_XVd_Section 3 CUA Workbook_Final.xlsm

AIC = Akaike Information Criterion; BIC = Bayesian information criterion; ICER = incremental cost effectiveness ratio; OS = overall survival; QALY = quality adjusted life year; SBd = selinexor + bortezomib + dexamethasone; TSEM = two-stage estimation method

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *$75,000 to < $95,000*

[3] *$95,000 to < $115,000*

[4] *$155,000 to < $255,000*

6.66 The results from the economic evaluation are summarised in Table 17. In the base-case, treatment with SBd resulted in estimated incremental costs of $35,000 to < $45,000, incremental life years of 0.806 and incremental quality adjusted life years (QALYs) of 0.581, compared with treatment with Bd, resulting in an ICER of $45,000 to < $55,000 per life year gained and of $75,000 to < $95,000per QALY gained.

Table 17: Economic model base-case results for SBd vs Bd in the treatment of RRMM

Result	SBd	Bd	Incremental
Total LYs	3.89	3.09	0.806
Total QALYs	2.74	2.16	0.581
Total costs	$ [redacted]	$82,770	$ [redacted]
Incremental cost-effectiveness ratios			
Cost per LY gained			$ [redacted] [1]
Cost per QALY gained			**$** [redacted] [2]

Source: Table 3-17 of the submission

AEMP = approved ex-manufacturer price; Bd = bortezomib + dexamethasone; DPMQ = dispensed price for maximum quantity; LY = life year; QALY = quality adjusted life year; SBd = selinexor + bortezomib + dexamethasone

Note: Prices were updated based on the DPMQ of selinexor (rather than the use of AEMP for consistency with other comparator drugs) and MBS item cost updates.

The redacted values correspond to the following ranges:

[1] $45,000 to < $55,000

[2] $75,000 to < $95,000

6.67 The life years gained in the economic analysis (15-year time horizon = 0.806 years; 10-year = 0.671 years) were significantly longer than those resulting from the economic analysis for Cd versus Bd (10-year time horizon = 0.329 years; Table 14, carfilzomib PSD, July 2017). Thus, in the context of a claim of non-inferiority in comparison with Cd and immature OS data, a survival advantage of more than double that of Cd does not appear to be clinically plausible. The PSCR stated that the OS estimates for Cd and Bd from which the comparison of life years gained between SBd and Cd were drawn were based on an earlier data cut of the ENDEAVOR trial (HR = 0.79; 95% CI: 0.65, 0.96) and were underestimated. The PSCR stated that use of the later data cut (HR = 0.76; 95% CI: 0.63, 0.92) would result in a survival advantage for Cd over Bd which would be similar to that currently estimated for SBd vs Bd. The ESC noted that the PSCR did not provide a quantitative analysis for this claim. Furthermore, the ESC noted that Cd resulted in a statistically significant improvement in OS compared to Bd at both data cuts.

6.68 The results of the key sensitivity analyses are summarised in Table 18.

Table 18: Results of sensitivity analyses

Scenario	Base-case value	Scenario analysis value	Incremental costs	Incremental outcomes	ICER
Base case [a]			**$** [redacted]	**0.581**	**$** [redacted] [1]
Time horizon	15 years	5 years	$ [redacted]	0.270	$ [redacted] [2]
		10 years	$ [redacted]	0.488	$ [redacted] [1]
		20 years	$ [redacted]	0.614	$ [redacted] [3]
OS	With TSEM adjustment for treatment crossover	No adjustment [b]	$ [redacted]	0.431	$ [redacted] [4]
OS extrapolation	OS advantage with SBd	No OS gain for SBd	$ [redacted]	0.215	$ [redacted] [5]
	Dependent exponential model	Dependent Weibull	$ [redacted]	0.480	$ [redacted] [1]
	No OS convergence	Convergence at 5 years	$ [redacted]	0.448	$ [redacted] [4]
PFS extrapolation	No PFS convergence	Convergence at 5 years	$ [redacted]	0.579	$ [redacted] [1]
TTD extrapolation	Independent log-normal (SBd) and independent log-logistic (Bd) models	Independent log-logistic (SBd)	$ [redacted]	0.581	$ [redacted] [1]
		Independent log-normal (Bd)	$ [redacted]	0.581	$ [redacted] [1]
Extrapolation start point (OS, PFS, TTD)	Median follow-up	From start	$ [redacted]	0.599	$ [redacted] [1]
		From 10% patients at risk [c]	$ [redacted]	0.484	$ [redacted] [4]
		From 20% patients at risk [c]	$ [redacted]	0.529	$ [redacted] [1]
Utility values	ENDEAVOR trial utility values	TOURMALINE-MM1 BoR adjusted [d]	$ [redacted]	0.579	$ [redacted] [1]
		BOSTON trial values	$ [redacted]	0.639	$ [redacted] [3]
Time horizon (10 years), dependent Weibull for OS			$ [redacted]	0.444	$ [redacted] [4]
Time horizon (10 years), dependent Weibull for OS (no adjustment)			$ [redacted]	0.318	$ [redacted] [2]
Time horizon (10 years), dependent Weibull for OS and BOSTON utility values			$ [redacted]	0.482	$ [redacted] [1]

Source: Table 3-22 of the submission; and developed during the evaluation

The redacted values correspond to the following ranges:

[1] $75,000 to < $95,000

[2] $135,000 to < $155,000

[3] $55,000 to < $75,000

[4] $95,000 to < $115,000

[5] $155,000 to < $255,000

Bd = bortezomib + dexamethasone BOR = best overall response; ICER = incremental cost effectiveness ratio; HR = hazard ratio; OS = overall survival; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone; TTD = time to treatment discontinuation; TSEM= two-stage estimation method

a. The base case scenario presented in the scenario analysis in Table 3-22 of the submission was slightly different (incremental outcomes = 0.582, incremental cost = $[redacted] and ICER = $[redacted] [3]) to that presented in Section 3A.8. Results from Section 3A.8 reflected the excel model.

b. The cost calculations between the submission and the evaluation varied, the submission estimated the ICER as $[redacted] *[1]* per QALY, and incremental outcome as 0.479 whilst calculations during the evaluation are presented in the table. These results were based on selecting "none" in cell C9 worksheet 'Survival'

c. The cost calculated between the submission and the evaluation varied, the submission estimated the ICER as $[redacted] *[1]* per QALY and incremental outcome as 0.484 for 10% risk and ICER $[redacted] *[1]* per QALY and incremental outcome as 0.471 for 20% risk whilst calculations during the evaluation are presented in the table. These results were based on selecting "10% patients left at risk" and "20% patients left at risk" respectively in cell C8 worksheet 'Survival'

d. Utility type was also changed to 'treatment-specific' during the validation process, as health state specific utilities were not available. Calculations varied slightly potential based on the calculation differences in base case, which were suspected to have been carried through the sensitivity analyses cautions.

6.69 Overall, the sensitivity analyses demonstrated that the ICER was sensitive to the time horizon, TSEM adjustment for treatment crossover, the choice of parametric function chosen for extrapolation and the survival advantage of SBd over Bd. The submission considered that the Weibull distribution appeared to underestimate mean survival according to the published literature and expert clinical opinion. The rationale for these considerations was not presented within the submission. The choice of the Weibull function for OS extrapolation over a 10-year time horizon and no adjustment for treatment crossover increased the ICER to $135,000 to < $155,000per QALY.

6.70 The ESC considered that the economic model should be revised to better estimate any likely OS gain by using (i) a 10 year time horizon; (ii) the unadjusted OS results from BOSTON or results from an appropriately justified adjusted analysis; and (iii) the fitting of independent survival curves for OS that predicted more realistic long-term survival effects. Additional revisions would be required relating to the resource use including improved modelling of TTD and costing of subsequent therapies and adverse events.

CMA – SBd versus Cd

6.71 The key components and assumptions of the CMA are presented in Table 19. The CMA was presented based on the naïve ITC between the SBd arm of BOSTON and the Cd arm of ENDEAVOR. As the claim of non-inferiority between SBd and Cd was not supported, the ESC considered that the CMA was not informative.

Table 19: Key components and assumptions of the economic evaluation (CMA)

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence from a naïve ITC, effectiveness is assumed to be comparable
Therapeutic claim: safety	Based on evidence from a naïve ITC, safety is assumed to be comparable
Evidence base	A naive ITC comparing SBd and Cd using data from the BOSTON and ENDEAVOR trials.
Equi-effective doses	SBd per 35-day cycle – selinexor 100 mg D1,8,15,22,29; bortezomib 1.3 mg/m^2 D1,8,15,22, dexamethasone 20 mg D1,2,8,9,15,16,22,23,29,30 is equi-effective to Cd (twice weekly – model base case; Cd 56/20 mg/m^2) [a] per 28-day cycle: Cycle 1 - carfilzomib 20 mg/m^2 D1,2, 56 mg/m^2 D8,9,15,16; dexamethasone 20 mg D1,2,8,9,15,16,22,23 Cycles 2+ - carfilzomib 56 mg/m^2 D1,2,8,9,15,16; dexamethasone 20 mg D1,2,8,9,15,16,22,23
Other costs or cost offsets	Adverse effect-related costs, leading to an incremental cost savings result

Source: Table 3-23 p173 of the submission

Cd = carfilzomib + dexamethasone; CMA = cost minimisation analysis; D = day; ITC = indirect treatment comparison; SBd = selinexor + bortezomib + dexamethasone

a. The base case assumed the use of Cd twice weekly only, a sensitivity analysis which assumed 100% weekly Cd (70/20 mg/m^2) is presented in Table 22.

6.72 The equi-effective doses for SBd and Cd were estimated based on the key clinical trials (BOSTON and ENDEAVOR) and PIs for selinexor and carfilzomib. The base case assumed the use of Cd twice weekly regimen only as per the ENDEAVOR trial. The PBAC considered that it would be appropriate to apply the effective approved ex-manufacturer price (AEMP) of carfilzomib which corresponded to this regimen. The

submission stated that the dose intensity for Cd in ENDEAVOR was 87% and the median duration of treatment was 9.18 months; however, this could not be verified based on the reference provided in the submission. A sensitivity analysis was conducted during the evaluation which applied a dose intensity of 91.0% for Cd and a treatment duration of 48.0 weeks (i.e. 12 cycles), consistent with the CMAs presented in the submissions for ixazomib and elotuzumab which were considered at the November 2020 PBAC Meeting (paragraph 6.41; elotuzumab PSD, November 2020; and paragraph 6.48; ixazomib PSD, November 2020).

6.73 The duration of treatment with SBd was made equivalent to that of Cd (9.18 months of treatment, i.e. 7.98 cycles of SBd and 9.98 cycles of Cd) within the CMA. This may not have been reasonable when considered in terms of the shorter median PFS observed for SBd in BOSTON (13.9 months) compared with that observed for Cd in ENDEAVOR (18.7 months) and reflected the uncertainties associated with the non-inferiority claim.

6.74 Administration costs were included to account for the variance in administration between SBd and Cd. Costs resulting from differences in safety and toxicity management were calculated separately by the submission but not incorporated within the CMA. The ESC considered that adverse event costs, particularly those related to haematological events (e.g. thrombopoietin receptor agonists, platelet monitoring and platelet transfusions) should be incorporated into the CMA. The submission did not include concomitant medication costs as they were considered to be negligible. All patients in ENDEAVOR received antiviral and proton pump inhibitor therapies.

6.75 Although the base case assumed the use of Cd twice weekly regimen only, a sensitivity analysis that assumed 100% once weekly Cd use had lower administration and drug costs, was conducted during the evaluation (see Table 22).

6.76 The submission presented a CMA based on the published AEMP Cd (see Table 20 and Table 21). This was appropriate if the basis of the non-inferiority claim was accepted.

6.77 The total cost of the Cd regimen over 9.98 cycles, based on the estimated equi-effective dose, was estimated to be $118,572.99.

Table 20: Results of the cost-minimisation analysis (Cd)

Row	Parameter	Input	Source/calculation
Carfilzomib			
A	AEMP 10 mg vial	$211.49	PBS item 11229B, 11230C, 12243J, 12244K
B	AEMP 30 mg vial	$634.47	
C	AEMP 60 mg vial	$1,268.94	
D	DI, %	87.0%	ENDEAVOR trial [a]
E	IV infusion	$111.40	MBS item 13950
F	Total cost/dose (initial)	$845.96	(A + B)
G	Total cost/dose (continuing)	$1,903.41	(B + C)
Dexamethasone			
H	AEMP	$4.84	PBS item 2507Y
I	DI, %	90.6%	ENDEAVOR trial [a]
J	Cost/dose	$0.73	Calculated [b]
Cd – drug acquisition cost			
K	Total cost for initial cycle	$9,311.41	(2 x F) + (4 x G) + (8 x J)
L	Total cost per continuing cycle	$11,426.31	(6 x G) + (8 x J)
M	Median duration of therapy, cycles	9.98	As per submission [c]
Total cost per cycle			
N	Cycle 1	$9,979.81	K + (6 x E)
O	Cycle 2+	$12,094.71	L + (6 x E)
P	**Total Cost of Cd**	**$118,572.99**	**N + [(M-1) x O)]**

Source: using results in Excel workbook PBAC_March 2021_XPOVIO Selinexor_RRMM_XVd_Section 3 CMA vs Kd_Final

AEMP = approved ex-manufacturer price; Cd = carfilzomib + dexamethasone; DI = dose intensity; MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme

a. This could not be verified based on the reference provided in the submission.

b. Calculated by the submission as the actual dose (20 mg x 90.6%) ÷ 4 mg tablets x $[redacted] per tablet.

c. The duration of treatment with SBd was made equivalent to that of Cd (279.4 days = 7.98 SBd cycles and 9.98 Cd cycles) in the CMA.

6.78 Based on the estimated costs of Cd, the AEMP of selinexor 20 mg x 20 tablets was $[redacted].

Table 21: Results of the cost-minimisation analysis (SBd)

Row	Parameter	Input	Source/calculation
Bortezomib			
A	AEMP	$691.62	PBS item 12219D, 12227M
B	DI, %	89.6%	BOSTON trial [a]
C	Cost/dose	$691.62	Calculated
D	Doses per cycle	4	BOSTON trial
Dexamethasone			
E	AEMP	$4.84	PBS item 2507Y
F	DI, %	90.6%	BOSTON trial [a]
G	Cost/dose	$0.73	Calculated [b]
H	Doses per cycle	10	BOSTON trial
Selinexor			
I	AEMP	$[redacted]	
J	DI, %	80.0%	BOSTON trial [a]
K	Cost/dose	$[redacted]	Calculated [c]
L	Doses per cycle	5	BOSTON trial
SBd – drug acquisition cost			
J	Total cost per cycle	$[redacted]	(C x D) + (G x H) + (K X L)
K	Median duration of therapy, cycles	7.98	As per submission [d]
L	**Total Cost of SBd**	**$[redacted]**	**J x K; Row P of Table 20**

Source: developed during the evaluation, using results in Excel workbook PBAC_March 2021_XPOVIO Selinexor_RRMM_XVd_Section 3 CMA vs Kd_Final

AEMP = approved ex-manufacturer price; DI = dose intensity; PBS = Pharmaceutical Benefits Scheme; SBd = selinexor + bortezomib + dexamethasone

a. See section 3A.6 for the discussion of BOSTON dose intensity

b. Calculated by the submission as the actual dose (20 mg x 90.6%) ÷ 4 mg tablets x $[redacted] per tablet.

c. Calculated by the submission as the actual dose (100 mg x 80.0%) ÷ 20 mg tablets x $[redacted] per tablet.

d. The duration of treatment with SBd was made equivalent to that of Cd (279.4 days = 7.98 SBd cycles and 9.98 Cd cycles) within the CMA.

6.79 The results of the key sensitivity analyses are summarised in Table 22. The ESC noted that the selinexor AEMP was sensitive to weekly Cd use and the dose intensity of selinexor.

Table 22: Sensitivity analyses selinexor AEMP

	Base case value	Scenario analysis value	Total cost of Cd	Total cost of Bd [a]	Total cost of selinexor [b]	Selinexor AEMP estimation
Base case			**$118,572.99**	**$22,142.76**	**$[redacted]**	**$[redacted]**
Cd utilisation	100% Cd twice weekly	100% Cd weekly	$77,673.08	$22,142.76	$[redacted]	$[redacted]
DI and median DOT	DI: C = 87.0%, d = 90.6% DOT: Cd = 9.18 months	DI: Cd = 91.0% DOT: Cd = 48.0 weeks/ 12 cycles [c]	$143,021.89	$22,142.76	$[redacted]	$[redacted]
	DI: S = 80% DOT: SBd = 9.18 months	DOT: SBd = 12.73 months/11.07 cycles [d]	$118,572.99	$30,705.84	$[redacted]	$[redacted]
		DI: S = 100%	$118,572.99	$22,142.76	$[redacted]	$[redacted]

Source: calculated during evaluation, Table 3-36 of the submission

AEMP = approved ex-manufacturer price; Bd = bortezomib + dexamethasone; C = carfilzomib; Cd = carfilzomib + dexamethasone; d = dexamethasone; DI = dose intensity; DOT = duration of treatment; S = selinexor

a. As part of SBd backbone

b. Calculated as the total cost of Cd minus the total cost of Bd.

c. Consistent with the ENDEAVOR evidence presented in the CMA submission for ixazomib and elotuzumab considered at the November 2020 PBAC Meeting (paragraph 6.41; Elotuzumab PSD, November 2020; and paragraph 6.48; Ixazomib PSD, November 2020)

d. Consistent with the duration of therapy for SBd presented in the CUA.

6.80 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with SBd would be no more than the cost per patient of Cd. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapy, and also accounts for any difference in the mean duration of treatment. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

Economic Evaluation Summary

6.81 The submission presented the requested AEMPs for selinexor 20 x 20 mg and 16 x 20 mg based on a weighted price, combining the price applied in the CUA with that resulting from the CMA. The weights were derived from the relative replacement of patients on Bd (64.28%) or Cd (35.72%) as derived from the financial estimates which were not sufficiently justified. The results of the weighted AEMP calculations are presented in Table 23.

Table 23: Calculation of weighted cost-effective ex-manufacturer price of selinexor

Analysis/ comparator	Presentation	AEMP	Relative estimated replacement of comparator
CUA: Bd	Selinexor 20 x 20 mg tablets	$ [redacted]	64.28%
CMA: Cd	Selinexor 20 x 20 mg tablets	$ [redacted]	35.72%
CUA: Bd	Selinexor 16 x 20 mg tablets	$ [redacted]	64.28%
CMA: Cd	Selinexor 16 x 20 mg tablets	$ [redacted]	35.72%
Weighted cost-effective price (AEMP)			
	Selinexor 20 x 20 mg tablets	$ [redacted]	
	Selinexor 16 x 20 mg tablets	$ [redacted]	

Source: Table 3-38, 191 of the submission
AEMP = approved ex-manufacturer price; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone

6.82 The ESC noted that the incremental benefits of SBd vs Bd should be comparable to that of Cd vs Bd based on the non-inferiority claim of SBd with Cd, and as Cd was listed on the basis of a CUA comparing Cd with Bd (Table 11, carfilzomib, PSD, July 2017). Therefore, prior to the price reduction of Bd (in January 2021) the cost of SBd based on the CUA and CMA should have been similar, and the price reduction of Bd should have resulted in a lower price based on CUA. However, the selinexor AEMPs based on the CMA were more than double those based on the CUA. This was only partly explained by the longer survival advantage claimed in the SBd CUA (and thus a lower price) compared to the economic analysis for Cd. Furthermore, in the absence of a defined patient population receiving either comparator (i.e. Bd or Cd), a weighted comparator may not be justified.

Drug cost/patient/course

6.83 Table 24 presents a summary of the drug cost per patient for SBd and its comparators Bd and Cd. The average time on SBd treatment based on the CMA and the CUA were different (7.98 cycles and 11.07 cycles respectively). These results in a

drug/cost/patient/course for SBd of $[redacted] based on the CMA and $[redacted] based on the CUA. Furthermore, the duration of therapy based on BOSTON was lower for both SBd and Bd arms compared to the economic and financial estimates.

Table 24: Drug cost per patient for proposed and comparator drugs (AEMP)

	SBd			Bd			Cd (twice weekly regimen) [a]		
	Trial dose and duration	**CUA/CMA**	**Financial estimates**	**Trial dose and duration**	**CUA**	**Financial estimates**	**Trial dose and duration**	**CMA**	**Financial estimates**
Frequency/ cycle [c]	Cycle 1+ (35 day cycles): Sel: 100 mg PO (Days 1,8,15,22,29) Bort: 1.3 mg/m^2 SC (Days 1,8,15, 22) Dex: 20 mg PO (Days 1,2,8,9,15,16,22,23,29,30)			Cycles 1 – 8 (21 day cycles): Bort: 1.3 mg/m^2 SC (Days 1,4,8,11) Dex: 20 mg PO (Days 1,2,4,5,8,9, 11,12) Cycles 9+ (35 day cycles): Bort: 1.3 mg/m^2 SC (Days 1,8,15,22) Dex: 20 mg PO (Days 1,2,8,9,15,16, 22,23,29,30)			Cycle 1 (28 day cycle): Carf: 20 mg/m^2 (Days 1,2); 56 mg/m^2 IV (Days ,9,15,16) Dex: 20 mg PO/IV (Days 1,2,8,9,15,16,22 ,23) Cycle 2+ (28 day cycles): Carf: 56 mg/m^2 IV (Days 1,2,8,9,15, 16) Dex: 20 mg PO/IV (Days 1,2,8,9,15,16,22,23)		
Dose intensity	S: 80.0% B: 89.4% d: 90.6%	S: 80.0% B: 89.6% d: 90.6%	S: 80.0% B: 89.6% d: 90.6%	B: 99.0% [b] d: 94.5% [b]	B: 99.0% d: 94.5%	B: 99.0% d: 90.6%	C: 87.0% [e,f] d: NR [e]	C: 87.0% d: 90.6%	C: 87.0% d: 90.6%
Duration of therapy (cycles)	6.67 [g]	CMA: 7.98 CUA: 11.07	11.07 [h]	10.86 [g]	15.7	15.7 [i]	9.18 [e]	9.98	9.18
Average cost per patient [c,d]	Total: $[redacted] S: $[redacted] B: $13,082 d: $49	CMA Total: $[redacted] S: $[redacted] B: $15,686 d: $58 CUA Total: $[redacted] S: $[redacted] B: $21,760 d: $81	Total: $[redacted] S: $[redacted] B: $21,760 d: $81	Total: $23,653 B: $23,587 d: $66	Total: $34,194 B: $34,099 d: $96	Total: $34,190 B: $34,099 d: $92	Total: $103,912 C: $103,859 d: $54	Total: $112,968 C: $112,909 d: $58	Total: $38,372 B: $38,269 d: $103

Source: Developed during the evaluation from using results in Excel workbook PBAC_March 2021_XPOVIO Selinexor_RRMM_XVd_Section 3 CUA Workbook_Final.xlsm; Excel workbook PBAC_March 2021_XPOVIO Selinexor_RRMM_XVd_Section 3 CMA vs Kd_Final; PBAC_March 2021_XPOVIO Selinexor_RRMM_XVd_Section 4 Workbook_Final; p105 BOSTON CSR

B or Bort = bortezomib; Bd = bortezomib + dexamethasone; C or Carf = carfilzomib; Cd = carfilzomib + dexamethasone; CMA = cost minimisation analysis; CUA = cost utility analysis; d or Dex= dexamethasone; IV = intravenous; PO = oral; S or Sel = selinexor; SC = subcutaneous; SBd = selinexor + bortezomib + dexamethasone

a. For simplicity the dose of Cd was assumes to be 56 mg/m^2 for the entire regimen

b. Submission stated those used in the CUA were consistent with the trial however, the median dose intensity of Bd in BOSTON could not be verified

c. SBd = 35 day cycle; Bd = 21 day cycle C1-8 then 35-days C9 onwards; Cd = 28 day cycle. For simplicity, the cost of Bd was considered to be the same of each cycle (4 x bortezomib doses and 8 x dexamethasone doses, as the additional 2 x dexamethasone doses from cycle 9 onwards was considered to have minimal impact on costs).

d. Doses based on a BSA of 1.83 m^2

e. The dose intensity of carfilzomib and the median duration of therapy were as per the submission. These could not be verified during the evaluation based on the reference provided in the submission.

f. For the purposes of calculating costs, the dose intensity was considered to be consistent with those of the CMA and financial estimates at 90.6%

g. The mean duration of study treatment was reported as 40.0 weeks in SBd and 38.3 weeks in Bd (p105, BOSTON CSR).
h. The financial worksheet calculated 55.35 weeks
i. The financial worksheet calculated 62.48 week

Estimated PBS usage & financial implications

6.84 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the financial implications. However, the submission based the financial estimates on the impact of the PBS listing of DBd on the projected treatment landscape and then estimated change in utilisation of medicines on the PBS (and associated financial impact to Government) following the proposed listing of SBd. Thus, a market share approach may have been more appropriate to estimate market size. An overview of the data sources and assumptions used to populate the financial estimates is provided in Table 25.

Table 25: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible Population		
Prevalence of MM	Year 1: 6,295 to Year 6: 6,791 (AIHW, 2017)	Prevalent patients could also be forecasted based on actual counts of patients supplied PBS listed MM medications.
Prevalent of MM in second or third treatment (= total patients eligible for selinexor)	Year 1: 3,763 to Year 6: 4,059 Submission calculated the proportion of patient receiving active treatment based on the PBS 10% dataset and adjusted for an increase in TTNT based on the availability of DBd.	The calculation of estimated patients receiving active treatment was reasonable. However, adjustment for prolonged TTNT with DBd appeared to be speculatory.
Total patients	Year 1: [redacted] [a,1] to Year 6: [redacted] [2]	The submission anticipated SBd would replace rather than displace comparators. Replacement rates were not well justified.
Treatment utilisation		
Uptake rate (second and third line)	Year 1: [redacted]% to Year 6: [redacted]%	DUSC considered that the uptake rates were high given the toxicity and uncertain efficacy associated with SBd. In addition, DUSC noted that there were uncertainties between the uptake rates and those electing treatment, both of which were unjustified and unverifiable.
Treatment duration (months)	12.83 months SBd 14.37 months Bd Based on the economic model in Section 3	The value for SBd used in the financial estimates was 12.73 months which is consistent with the evaluator's calculation. The duration of treatment for SBd < Bd which favoured SBd with respect to the cost-offsets The DUSC considered that treatment duration for SBd be based on treatment exposure from the BOSTON trial.
Scripts dispensed	Year 1: [redacted] [2] to Year 6: [redacted] [3]	The submission assumed a higher proportion of patients receiving the 16 – pack (51.57%) compared to the 20 – pack (48.43%) despite the 20 – pack being sufficient for 1 month supply. This was based on a relatively low (80%) dose intensity for selinexor in BOSTON. However, whether this is consistent in clinical practice is unknown.

Parameter	Value applied and source	Comment
Costs		
Proposed medicine	Published: 20 x 20 mg: $[redacted]; 16 x 20 mg: $[redacted] Effective: 20 x 20 mg: $[redacted]; 16 x 20 mg: $[redacted] Requested price, AEMP	The effective AEMP prices proposed in Section 3 of the submission were slightly different: 20 x 20 mg tablets – $[redacted]; 16 x 20 mg tablets – $[redacted]
Other medicine included in therapy	Bortezomib (1,3 and 3.5 mg) - Published: $806.89 Bortezomib 12219D, 12227M, AEMP Dexamethasone (4 mg) – Published: $4.84 Dexamethasone 2507Y - AEMP	Bd as part of SBd
Comparator	Daratumumab (100 mg and 400 mg) - Published: $2,336.76 (multiple PBS item numbers) AEMP Carfilzomib (10, 30, 60 mg) - Published: $1,268.94 (PBS items 11230C, 12243J, 12243J, 12244K), AEMP Bortezomib (1,3 and 3.5 mg) - Published: $806.89 (PBS items 12219D, 12227M), AEMP Dexamethasone (4 mg) - Published: $4.84 (PBS item 2507Y), AEMP	As part of comparators: Bd – assumed replacement rate 70% Yr 1 up to 95% in Yr 6 (5% incremental increase per year), Cd – assumed replacement rate 35% Yr 1 up to 60% Yr 6 (5% incremental increase per year) DBd – assumed replacement rate 5% Yr 1 up to 7.5% Yr 6 (0.5% incremental increase per year)
AE Management (PBS)	Filgrastim (300 mcg) – Published: $154.80 (PBS items 5742F, 6291D, 5742F, 6291D), AEMP	Attributed to neutropenia
AE Management (MBS)	$85.95 (MBS item 13706) $140.95 (MBS item 13750) $38.75 (MBS item 23) $613.30 (MBS item 42698)	Attributed to the incremental AE resulting in the substitution of SBd with Bd or Cd

Source: Table 4-6, p200; 4-7 pp200-1; 4-8, p202; 4-9, p203; 4-10, p204 of the submission

AE = adverse event; AEMP = approved ex-manufacturer price; AIHW = Australian Institute of health and welfare; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; DBd = daratumumab + bortezomib + dexamethasone; MM = multiple myeloma; PBS = Pharmaceutical Benefits Schedule; RPBS = Repatriation Schedule of Pharmaceutical Benefits; SBd = selinexor + bortezomib + dexamethasone; TTNT = time to next treatment; Yr = year

a. This number included [redacted][1] Grandfathered Patients

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

[3] 5,000 to < 10,000

6.85 Following the listing of daratumumab on the PBS in January 2021for use as combination DBd in second line RRMM, the submission expected that the current treatment algorithm would reflect increasing uptake and use of DBd in the second line setting compared to other currently available treatments. Although this was consistent with expected use of DBd, the submission assumed that SBd would replace 5.0% of DBd in Year 1, increasing to 7.5% in Year 6. This was inconsistent with the information presented in the submission as DBd was not nominated as a comparator, and no comparative clinical or economic evidence for SBd compared with DBd was presented. The PSCR stated that SBd would replace DBd in older and frailer patients. Advice received by DUSC suggested that SBd would specifically be avoided in these

populations due to adverse events associated with selinexor. As noted in paragraph 5.3, it was expected that SBd would most likely be used as a third or later line therapy.

6.86 Despite a 20 mg x 20-pack being sufficient for a month's supply of selinexor (100 mg weekly) the submission estimated a lower proportion of patients (48.43%) would receive the 20-pack compared to the 16-pack. This was based on the 80% dose intensity of selinexor in BOSTON. However, the transferability of this relatively low dose intensity in clinical practice is unknown. Furthermore, DUSC considered it was unclear as to when a 16-pack would be prescribed over the 20-pack, given that the proposed restriction for the 16-pack and the 20-pack are the same, and at a dose intensity of 80%, the 20-pack would provide a full cycle's requirement of selinexor.

6.87 The submission considered that the proportion of patients receiving active treatment for MM was 94.6%, and the proportion of patients on first, second- and third-line therapy at any time was 36.82%, 31.96%, and 31.22% respectively. The submission did not provide the PBS 10% dataset this was based on, for verification.

6.88 The submission estimated that the time to next treatment (TTNT) would be prolonged due to the listing of DBd in the second line setting, and the effect of treatment persistence was applied to patients who were estimated to receive DBd. The additional time had the effect of increasing the relative share of patients receiving second line therapy compared to those receiving third or later line therapy, which was estimated by the addition and subtraction of continuing DBd patients to the treated second and third line MM populations in each subsequent year, respectively and vice-versa for discontinuing DBd patients. The TTNT for DBd could not be verified during the evaluation. However, according to the reference provided by the submission the TTNT at median follow-up of 26.9 months was 25.4 months for the DBd group (Daratumumab in combination with bortezomib for treating RRMM ID974, NICE Single Technology Appraisal). Thus, a shorter TTNT is likely to decrease the adjustment (increased TTNT with DBd) in the second line setting and increase the adjustment for third line in Years 5 and 6.

6.89 A summary of the estimated use and financial implications for the proposed listing of SBd for the treatment of RRMM on the PBS is presented in Table 26.

Table 26: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted] a,1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 2
Number of scripts dispensed [b] – selinexor	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 3	[redacted] 3
Estimated financial implications of selinexor (Effective Price)						
Cost to PBS/RPBS less copayments	$[redacted] 4	$[redacted] 4	$[redacted] 5	$[redacted] 5	$[redacted] 5	$[redacted] 6
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments – Total	-$[redacted] 7	-$[redacted] 8	-$[redacted] 4	-$[redacted] 4	-$[redacted] 5	-$[redacted] 9
Cost to PBS/RPBS less copayments - daratumumab	-$[redacted] 7	-$[redacted] 8	-$[redacted] 8	-$[redacted] 4	-$[redacted] 5	-$[redacted] 5
Cost to PBS/RPBS less copayments – carfilzomib [c]	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7	-$[redacted] 8
Cost to PBS/RPBS less copayments – bortezomib	$[redacted] 7	$[redacted] 7	$[redacted] 7	$[redacted] 7	$[redacted] 7	$[redacted] 7
Cost to PBS/RPBS less copayments – dexamethasone	-$[redacted] 7	-$[redacted] 7	$[redacted] 7	$[redacted] 7	$[redacted] 7	$[redacted] 7
Cost to PBS/RPBS less copayments – filgrastim	$[redacted] 7	$[redacted] 7	$[redacted] 7	$[redacted] 7	$[redacted] 7	$[redacted] 7
Net financial implications						
Net cost to PBS/RPBS	$[redacted] 8	$[redacted] 8	$[redacted] 8	$[redacted] 7	-$[redacted] 7	$[redacted] 7
Net cost to MBS	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7
Net cost to PBS/RPBS/MBS	**$**[redacted] 8	**$**[redacted] 8	**$**[redacted] 7	**$**[redacted] 7	**-$**[redacted] 7	**$**[redacted] 7

Source: Table 4-8, 4-9,4-15, 4-16,4-24 pp202,203,209,210-212,216-217 of the submission.

a. This number included [redacted] 1 Grandfathered Patients

b. Assuming [redacted] months of treatment per patient (and [redacted] months for Grandfathered patients), based on the economic model (CUA) in Section 3.

c. The submission base case assumed 100% patients received the twice-weekly dosing.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *5,000 to < 10,000*

[4] *$20 million to < $30 million*

[5] *$30 million to < $40 million*

[6] *$50 million to < $60 million*

[7] *$0 to < $10 million*

[8] *$10 million to < $20 million*

[9] *$40 million to < $50 million*

6.90 The total cost to the PBS/RPBS of listing selinexor was estimated to be $0 to < $10 million in Year 6, and a total of $40 million to < $50 million in the first six years of listing.

6.91 DUSC noted that the assumed cost offsets for daratumumab over six years represented $100 million to < $200 million, which was unreasonable as DBd was not nominated as a comparator in the submission. In addition, DUSC noted that the current utilisation of Cd indicates increasing use of the once-weekly dosing schedule over the twice-weekly schedule, which represented 100% of the Cd use in the submission. Use of the once-weekly Cd dosing schedule would considerably reduce the total six-year cost offset for carfilzomib.

6.92 The submission included the cost of filgrastim to account for costs associated with Grade 3-4 neutropenia during SBd treatment. This was calculated as the difference in adverse event incidence between SBd (8.7%) and Bd (3.4%) from BOSTON and Cd (2.6%) from ENDEAVOR. The incremental difference in the occurrence of neutropenia based on DBd replacement was not presented by the submission. PBS costs associated with other adverse events (such as propranolol for ischaemic heart disease and cardiac failure; iron infusion for anaemia, and anti-emetics for nausea) were not considered in the financial estimates. However, as these are not high cost drugs, it is unlikely that the financial estimates were impacted greatly by their omission. DUSC noted that the cost of ophthalmic review was not included in the estimates, despite being mandatory in the BOSTON trial.

6.93 The submission acknowledged uncertainties associated with the prevalence rate of MM, proportion of patients receiving once weekly Cd, treatment duration of SBd, compliance of treatment with SBd, uptake of SBd among eligible patients and the substitution rate of SBd versus Cd or DBd. Overall, the financial estimates appear to be sensitive to the proportion of patients receiving Cd once weekly, and the duration of SBd therapy. Uncertainties in the TTNT for DBd resulted in a higher net cost to the Government in Years 5 and 6 (difference of $10 million to < $20 million and $0 to < $10 million respectively). The results of these sensitivity analyses and those conducted during the evaluation are presented in Table 27.

Table 27: Results of sensitivity analyses (Net Impact PBS/RPBS/MBS Effective price of selinexor and Published price for comparators)

Scenario	Year 1 (2021)	Year 2	Year 3	Year 4	Year 5	Year 6
Base case	$ [redacted][1]	$ [redacted][1]	$ [redacted][2]	$ [redacted][2]	-$ [redacted][2]	$ [redacted][2]
100% receiving once-weekly Cd	$ [redacted][2]	$ [redacted][2]	$ [redacted][2]	-$ [redacted][2]	-$ [redacted][2]	-$ [redacted][1]
SBd substitution rate vs DBd low (2.5-5% vs 5-7.5%) [c]	$ [redacted][1]	$ [redacted][1]	$ [redacted][1]	$ [redacted][1]	$ [redacted][2]	$ [redacted][1]
SBd substitution rate vs DBd high (7.5-10% vs 5-7.5%) [d]	$ [redacted][1]	$ [redacted][2]	$ [redacted][2]	-$ [redacted][2]	-$ [redacted][2]	-$ [redacted][2]
TTNT for DBd of 25.4 months (base case – 33 months)	$ [redacted][1]	$ [redacted][1]	$ [redacted][2]	$ [redacted][2]	$ [redacted][2]	$ [redacted][2]
Selinexor 100% dose intensity and provision of 20-pack only (base case – 80% dose intensity; 48.4% 20-pack and 51.57% 16-pack)	$ [redacted][1]	$ [redacted][1]	$ [redacted][1]	$ [redacted][1]	$ [redacted][2]	$ [redacted][1]

Source: Table 4-25, pp219-222 of the submission and Developed during the evaluation using Section 4 worksheet
Cd = carfilzomib + dexamethasone; DBd = daratumumab + bortezomib + dexamethasone; PBS = Pharmaceutical Benefits Schedule; MBS = Medicare Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits; TTNT = time to next treatment
Note: Prices are corrected - the submission included calculation errors in the sensitivity analyses where the PBS/RPBS cost of selinexor and MBS items were double counted.
The redacted values correspond to the following ranges:
[1] $10 million to < $20 million
[2] $0 to < $10 million

6.94 The submission estimated < 500 RRMM patients receiving compassionate access and eligible for PBS funded treatment through the grandfather restriction. For these patients it was assumed that patients had received an average of 6 months treatment

at the PBS listing of SBd and thus a duration of therapy of 6.73 months (i.e. 6 months subtracted from the estimated PBS treatment duration), consistent with a total of 11.07 cycles. These patients were appropriately incorporated into the financial estimates presented by the submission.

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

Quality use of medicines

6.95 The submission did not provide discussion of quality use of medicines. DUSC expressed concern that the quality use of medicines issues for this first in class medication with significant toxicities was not addressed in the submission. DUSC considered that as the sponsor has knowledge of both trial data and overseas use, this should form a comprehensive training and education program such that practitioners are well-equipped to handle selinexor's adverse event profile.

6.96 The pre-PBAC response indicated that the sponsor was preparing a multi-stakeholder quality use of medicines approach for haematologists, nurses, pharmacists and patients to ensure minimisation of adverse events and optimised treatment.

7 PBAC Outcome

7.1 The PBAC did not recommend selinexor, in combination with bortezomib and dexamethasone (SBd), for the treatment of relapsed and/or refractory multiple myeloma (RRMM). The PBAC noted that SBd provided, for some patients, an improvement in progression free survival (PFS) compared to the primary comparator bortezomib plus dexamethasone (Bd) but noted that the data for overall survival (OS) were immature and difficult to interpret. The PBAC considered that the economic model overestimated the benefits of SBd treatment compared to Bd, resulting in an incremental cost effectiveness ratio (ICER) that was underestimated. The PBAC considered that the indirect treatment comparisons (ITCs) presented between SBd and the secondary comparator Cd, did not adequately support non-inferiority and hence, the cost minimisation analysis (CMA) between SBd and Cd was not informative. The PBAC considered that the utilisation estimates for SBd were overestimated, particularly given the toxicity associated with SBd treatment, and that the financial impact estimates were underestimated due to the application of unlikely substitution assumptions.

7.2 The PBAC noted the consumer comments describing the ongoing clinical need for therapies for the treatment of RRMM. The PBAC noted the comments provided in sponsor hearing that highlighted that SBd was an immunomodulatory drug free regimen that demonstrated some benefit in patients with a 17p deletion or extramedullary disease.

7.3 The PBAC noted that the submission nominated Bd as the primary comparator and carfilzomib plus dexamethasone (Cd) as a secondary comparator. The PBAC noted that the clinical algorithm presented in the submission placed SBd as a second or third line therapy; however, the PBAC considered that, as daratumumab in combination with bortezomib and dexamethasone (DBd) was available on the PBS as a second line treatment only, SBd would likely be used as a third or later line treatment. The PBAC considered that SBd was most likely to replace and/or displace Cd, lenalidomide plus dexamethasone, pomalidomide plus dexamethasone and some bortezomib-based regimens including Bd.

7.4 The PBAC noted that the submission was based on one head-to-head randomised controlled trial comparing SBd to Bd (BOSTON) and ITCs for PFS and safety between SBd and Cd that were informed by the BOSTON and ENDEAVOR (comparing Cd with Bd) trials.

7.5 The PBAC noted that the BOSTON trial demonstrated that SBd (median PFS = 13.9 months) compared to Bd (median PFS = 9.4 months) resulted in a statistically significant improvement in PFS (HR = 0.70; 95% CI: 0.53, 0.93).

7.6 The PBAC noted that the OS data were immature, with median OS not reached for the SBd arm (HR = 0.84; 95% CI: 0.57, 1.23). The PBAC noted that the submission also presented OS data adjusted for crossover using the two-stage estimation method (TSEM) to account for the 36% of patients in the Bd arm who received either SBd or selinexor plus dexamethasone (Sd) following independent review committee confirmed objective disease progression (HR = 0.77; 95% CI: 0.52, 1.14). The PBAC noted that the submission did not adequately justify use of the TSEM and did not present results using alternative methods of adjustment as per the PBAC Guidelines 2016, v5.0, and therefore, the appropriateness of the adjustment could not be assessed.

7.7 In terms of safety, the PBAC noted that compared to Bd, SBd was associated with more serious adverse events, Grade 3 and 4 treatment emergent adverse events and treatment emergent adverse events resulting in dose modification, reduction or interruption. The PBAC particularly noted that the high incidence of haematological and gastrointestinal adverse events associated with SBd.

7.8 Overall, the PBAC considered that the submission's claim that SBd was superior compared to Bd in terms of PFS was reasonable but noted that in terms of OS, the claim of superior efficacy could not be supported due to the immaturity of the data from the BOSTON trial. The PBAC considered that SBd was inferior compared to Bd in terms of safety.

7.9 The PBAC noted that although the eligibility criteria of the BOSTON and ENDEAVOR trials were generally similar, there were differences that might have impacted the transitivity of the trials including differences in the baseline disease characteristics of patients, differences in the time at which the trials were conducted and differences in the maturity of the data. The PBAC noted that the PFS hazard ratio point estimate favoured Cd over Bd (HR = 0.55; 95% CI: 0.46, 0.65) compared to SBd over Bd (HR = 0.70; 95% CI: 0.53, 0.93). In addition, the PBAC noted the large difference in median PFS between the SBd (13.9 months) and Cd (18.7 months) arms; whereas the results were similar in the Bd common comparator arms (9.5 months in the Bd arm of BOSTON compared to 9.4 months in the Bd arm of ENDEAVOR).

7.10 The submission presented a comparison between the SBd arm of BOSTON and the Cd arm of ENDEAVOR for Grade 3-4 adverse events which indicated that SBd and Cd had differing adverse event profiles. The PBAC, noting that SBd was associated with higher rates of haematological events compared to Cd; whereas, Cd was associated with higher rates of cardiac and renal failure, considered that the comparison was difficult to interpret due to the transitivity issues between the trials and the absence of data presented for the Bd common reference arms.

7.11 The PBAC considered that the claim that SBd was non-inferior compared to Cd in terms of efficacy was not supported given the numerically superior PFS results for Cd versus Bd and the lack of a significant gain in OS for SBd versus Bd. The PBAC considered that the claim that SBd had a comparable but different safety profile compared to Cd was not supported due to the non-interpretable measure of comparative effect, which was based on single arm data extracted from the BOSTON and ENDEAVOR trials and the underlying transitivity issues.

7.12 The PBAC noted that the submission presented a CUA comparing SBd to Bd and a CMA comparing SBd to Cd, and then calculated a weighted cost effective price for selinexor. The PBAC considered that the weighted approach was not appropriate in the absence of a defined patient population receiving either comparator (Bd or Cd). Additionally, the PBAC noted that inconsistencies in the CUA and CMA price for selinexor, particularly when considered in relation to the prior PBAC decision relating to Cd versus Bd.

7.13 The PBAC noted that the CUA comparing SBd to Bd resulted in an ICER of $75,000 to < $95,000per quality adjusted life year (QALY). The PBAC considered that the ICER was likely underestimated as, despite not demonstrating an OS advantage in the BOSTON trial, the model estimated a relatively large gain in OS for SBd over Bd, with a difference in OS assumed for the entire 15 year time horizon. The PBAC noted that extrapolating the trial data using an exponential distribution resulted in 0.806 life years gained over a time horizon of 15 years and 0.671 years over a time horizon of 10 years. The PBAC recalled that this was considerably larger than the survival gain of 0.329 years over a 10 year time horizon estimated for Cd versus Bd in July 2017, and the PBAC further noted for Cd compared to Bd that a statistically significant improvement in OS was demonstrated. The PBAC considered that the economic

model should conservatively estimate any survival advantage for SBd due to the lack of demonstrated OS benefit in the clinical trial.

7.14 The PBAC noted other concerns with the economic model including:

- the application of the unjustified TSEM adjusted OS data. The PBAC considered that application of the unadjusted results from BOSTON would be more appropriate in the absence of a reliable adjustment;
- the application of a 15-year time horizon. The PBAC considered that a time horizon of no longer than 10 years, which was consistent with that applied in the July 2017 submission for Cd, would be reasonable, particularly considering that SBd would most likely be used in the third and later line settings;
- that utility values from ENDEAVOR were applied for the progression free and progressed disease states, whereas disutility values from BOSTON were applied for some, but not all, Grade ≥ 3 adverse events associated with SBd. The PBAC considered that utility values should be sourced from a consistent source and disutilities should be applied to all Grade ≥ 3 adverse events with a meaningful increase in the number of events with the addition of selinexor; and
- that the model did not consider subsequent treatment costs associated with either arm despite 35% of patient in the SBd arm, 32% of patients who did not crossover to SBd in the Bd arm and 49% of patients who crossed over from Bd to SBd receiving subsequent therapy. The PBAC considered that subsequent treatment costs should be applied to both arms as a proportion of patients in the Australian setting are likely to receive therapy beyond SBd and Bd.

7.15 The PBAC considered that the CMA between SBd and Cd was not informative as non-inferiority was not adequately supported. Noting that the claim that SBd had a comparable but different safety profile to Cd was not supported, the PBAC considered that the CMA should incorporate adverse event costs, particularly haematological events related to SBd use. In addition, the PBAC noted that within the CMA the duration of treatment of SBd was made equivalent to that of Cd (9.18 months of treatment, i.e. 7.98 SBd cycles and 9.98 Cd cycles). The PBAC considered that this was not reasonable, and that it highlighted the uncertainties associated with the non-inferiority claim.

7.16 The PBAC also noted that the durations of SBd treatment applied in the CMA and CUA differed considerably (7.98 cycles and 11.07 cycles respectively) and were considerably higher than that observed in the BOSTON trial (6.67 cycles). The PBAC considered that this highlighted uncertainty within both economic analyses.

7.17 The PBAC considered that the utilisation estimates for SBd were overestimated. The PBAC noted that the distinction between the uptake rate applied and the rate of patients electing treatment was unclear but considered that, due to the toxicity associated with selinexor and the uncertain efficacy, utilisation would be lower than assumed in the submission.

7.18 The PBAC also considered that the financial impact estimates were underestimated. The PBAC considered that the submission inappropriately assumed that SBd would replace some DBd use in the second line setting resulting in cost offsets which would not be realised in clinical practice. In addition, the PBAC considered the assumption that 100% of Cd patients would receive twice-weekly dosing was not reasonable.

7.19 The PBAC noted that the submission did not propose a Risk Sharing Arrangement.

7.20 The PBAC considered that any future resubmission for selinexor should present:

- a revised economic model which is more conservative in its assumptions as outlined in paragraph 7.13 and 7.14; and
- revised utilisation and financial impact estimates which include more conservative estimates in terms of uptake and assumed cost offsets.

7.21 The resubmission may be lodged at any future standard due date for PBAC submission using the standard re-entry pathway.

7.22 The PBAC advised that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

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

9 Sponsor's Comment

Antengene is committed to working with the PBAC to secure equitable access to selinexor in a triplet regimen for both patients and physicians in relapsed/refractory multiple myeloma. We wish to thank and acknowledge the contribution of clinicians, patients, and advocacy groups in supporting this submission.

For paragraph 4.3 of the PSD, the sponsor wishes to clarify that the proposed clinical algorithm did not specifically include DBd as a second line therapy as it was yet to be PBS listed at the time of the submission.