TAR421– Daratumumab for relapsed/refractory multiple myeloma, with 1 prior line of treatment

This assessment provides an estimate of the likely cost-effectiveness range of daratumumab for relapsed or refractory multiple myeloma, in both a subcutaneous (SC) formula, and an intra-venous (IV) formula.

A summary of the proposal is provided in the table below.

PROPOSAL OVERVIEW
Pharmaceutical Daratumumab (Darzalex) 5 mL vial containing 100 mg (IV) 20 mL vial containing 400 mg (IV) 15 mL vial containing 1800mg (SC)
Supplier Janssen
Proposed Indication Relapsed/refractory multiple myeloma, with 1 prior line of treatment
Dosing IV: 16 mg/kg administered intravenously until disease progression. SC: 1800mg flat dose, until disease progression. When used in combination with bortezomib and dexamethasone, daratumumab is given weekly for a total of 9 doses (weeks 1-9); every three weeks for a total of 5 doses (weeks 10-24) and then once every 4 weeks thereafter until disease progression.
Pharmaceutical Price s9(2)(b) 100mg vial (IV)* s9(2)(b)(ii); 1800mg vial (SC)** (Net)
CaTSoP PRIORITY **High, July CaTSoP 2021**
PHARConnect Reference **P001671 - Daratumumab - In combination with bortezomib and dexamethasone (DVd) for the treatment of patients with multiple myeloma who have received one prior line of myeloma therapy (1PL) (SC)** **P000337- Daratumumab (in combination with bortezomib & dexamethasone) - relapsed or refractory myeloma (IV)**

*Net price. Janssen daratumumab analysis, October 2021

** Net price, includes s9(2)(b)(ii);. Janssen daratumumab SC application, April 2021. Gross price: $8,305

Executive Summary

An application for the funding of daratumumab (IV) for relapsed/refractory MM was received from Janssen in November 2017, and for daratumumab (SC) in patients with at least one prior line of therapy in April 2021.

Multiple myeloma is a cell disorder characterised by proliferation of malignant plasma cells in the bone marrow. Multiple myeloma is a relapsing disease with shorter intervals of remission between each subsequent relapse. Five and 10-year overall survival of patients with multiple myeloma is ~50% and ~30%, respectively, with treatment. Agents which are funded in New Zealand for the treatment of multiple myeloma are bortezomib, and immunomodulatory agents, lenalidomide and thalidomide.

Review of Cost-Utility Analyses

A cost utility analysis (CUA) on daratumumab for people with relapsed or refractory multiple myeloma who have had one prior line of treatment was published by the National Institute for Health and Care Excellence (NICE) in April 2019, and recommended access for patients within the UK Cancer Drugs Fund. The incremental cost effectiveness ratio (ICER) was between £40,000 and £50,000 per QALY gained. s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2)(j)) s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2)(j)) s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2)(j)).

A CUA by the Pharmaceutical Benefits Advisory Committee (PBAC) assessed treatment with daratumumab, in combination with bortezomib and dexamethasone (DVd), for the second-line treatment of multiple myeloma. The ICER was between AUS$75,000 and AUS$105,000 per QALY gained. s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2)(j)) s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2)(j)) s9(2)(b)(ii));.

Summary of Pharmac Cost-Utility Analysis

A CUA was undertaken by Pharmac staff to estimate the cost-effectiveness of daratumumab for relapsed or refractory multiple myeloma. The economic model used data derived from the CASTOR trial which reported a longer median progression free survival (PFS) and overall survival (OS) time for patients treated with DVd, compared with bortezomib and dexamethasone alone.

The incremental QALYs gained per $1 million invested in daratumumab compared to a weighted comparator of bortezomib, cyclophosphamide and dexamethasone (CyBorD) and lenalidomide, for treating relapsed or refractory multiple myeloma with one prior line of treatment is estimated to be s9(2)(b)(ii)); s9(2)(ba)(i)); for the SC formula, s9(2)(b) for the IV formula. The difference between the cost utility associated with the two formulas reflects differences in cost only, as the efficacy is assumed to be the same. The results of the CUA were sensitive to convergence of daratumumab efficacy with the comparator efficacy, at 5-10 years in the

model (rather than 10-15), and variations in the proportion of patients assumed to be intolerant to bortezomib.

The 5-year net present value (NPV) to the Pharmaceutical Schedule of funding daratumumab SC and IV is estimated to be s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2) respectively, with costs of the first 12 months of s9(2)(b)(ii)); s9(2)(ba)(i)); respectively. Between 270 and 290 patients would be expected to receive treatment each year.

1. Proposal Overview

1.1 Summary

An application for the funding of daratumumab for relapsed or refractory multiple myeloma was received from Janssen in November 2017.

The application for daratumumab, bortezomib, and dexamethasone (DVd) (IV) was considered by CaTSoP and PTAC in 2018. They both deferred giving a recommendation until longer follow-up data became available. In October 2019 CaTSoP reviewed additional material from the supplier, including OS data from the CASTOR trial. While they agreed there was evidence of a significant benefit, they gave daratumumab a low priority due to the high cost. In July 2021 CaTSoP assessed the application from Janssen for the SC formula for daratumumab, giving it a high priority, as well as updating the recommendation for the IV formula to high for consistency.

The table below provides a summary of the patient population; intervention; comparator treatment; and main outcomes of treatment.

Table 1. PICO

PICO	
POPULATION	Multiple myeloma; patients with relapsed or refractory disease after one prior line of therapy (i.e., second line MM patients)
INTERVENTION	Daratumumab, bortezomib, and dexamethasone (DVd), cycles 1-8 Daratumumab monotherapy, cycles 9+
COMPARISON	Bortezomib, cyclophosphamide, and dexamethasone (CyBorD) Lenalidomide (if bortezomib intolerant)
OUTCOME	Improved PFS (HR of 0.22 vs Vd) and OS (HR of s9(2) vs Vd) in CASTOR trial

HR – hazard ratio; OS – overall survival; PFS – progression free survival; Vd – bortezomib and dexamethasone

1.2 Patient Population

"Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by proliferation of malignant plasma cells in the bone marrow accompanied by the secretion of monoclonal immunoglobulins. Multiple myeloma is thought to develop via a two-step model of progression. Firstly, an abnormal response to antigenic stimulation precipitates the development of a monoclonal gammopathy of undetermined clinical significantly [*sic*] (MGUS). Subsequent dysregulation stimulates clonal proliferation resulting in smouldering myeloma, in which there is clonal expansion without overt clinical symptoms. Once the clonal burden becomes substantial, dysfunctional plasma cells infiltrate bone and other organs causing direct damage, while the excessive production of monoclonal light chains causes indirect damage (symptomatic multiple myeloma).

Multiple myeloma is an incurable relapsing and progressive disease, which returns more aggressively and has shorter periods of remission with each relapse.

The incidence of multiple myeloma is higher in Māori than non-Māori (7.6 per 100,000 vs 4.9 per 100,000), and the death rate due to multiple myeloma is higher for Māori than for non-Māori (3.4 per 100,000 vs 2.1 per 100,000).

The incidence of multiple myeloma is higher in Pacific peoples than in the non-Pacific, non-Māori population. The supplier has identified an incidence rate of 9.8 per 100,000 Pacific people, which is higher than the incidence for Māori.

According to data from the New Zealand Cancer Registry, there are no significant differences in the incidence of multiple myeloma by socioeconomic deprivation."(Carfilzomib 2019 PTAC paper)

These proposals are for people who have had one prior line of treatment only, as CaTSoP considered that this subgroup of relapsed or refractory multiple myeloma patients derived the most benefit from treatment with daratumumab.

1.3 Current Treatment in New Zealand

In April 2021, CaTSoP described a range of possible 2L treatment options as follows:

> *"The Subcommittee considered that the possible second-line treatment options consisted of bortezomib retreatment (as CyBorD/BTD) or bortezomib in combination with melphalan and prednisone (BMP) and that it was preferable to expose patients to new agents than retreating with bortezomib. Alternatively, patients would receive a thalidomide-based regimen, which would consist of cyclophosphamide, thalidomide and dexamethasone (CTD) or melphalan, prednisone and thalidomide (MPT), all for approximately six to 12 cycles. The Subcommittee noted that patients could be eligible for lenalidomide in combination with dexamethasone until progression if neuropathy prevents use of bortezomib and thalidomide-based regimens. The Subcommittee noted that in patients with relapsed/refractory multiple myeloma, if remission was for greater than two to three years, and the patient was transplant eligible, a second autologous stem cell transplant would be offered.*
>
> *The Subcommittee considered that the choice of second-line regimen would be determined by the duration of response to first-line treatment, toxicities experienced in the first-line, and patient-specific factors including the desire for oral therapy.*
>
> *The Subcommittee noted that once a patient progresses after second line therapy, if they had received an autologous stem cell transplant with lenalidomide maintenance there are no further options for this patient group. The Subcommittee noted that lenalidomide with dexamethasone with or without bortezomib was a third-line treatment option, only for transplant-ineligible patients who had not received lenalidomide maintenance post autologous stem cell transplant."*
>
> *"The Subcommittee considered that in the 2nd line setting patients would receive an alternative regimen to what was received in first line and that it would likely include bortezomib, unless not suitable or tolerated. The Subcommittee considered that these treatment options were suboptimal and noted the current applications for carfilzomib and daratumumab for patients with relapsed or refractory multiple myeloma for patients who had not previously received a transplant. The Subcommittee noted that only patients who*

had not had lenalidomide maintenance post ASCT would be eligible for lenalidomide in third line" CaTSoP, April 2021

1.4 Intervention

Daratumumab is to be taken in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. For IV, the supplier has indicated that in adults the recommended dose of daratumumab is 16 mg/kg body weight administered as an IV infusion. When taken as an SC injection, a flat dose of 1800mg per vial is used.

When used in combination with bortezomib and dexamethasone, daratumumab is given weekly for a total of nine doses (weeks 1-9); every three weeks for a total of five doses (weeks 10-24) and then once every four weeks thereafter until disease progression. From cycles nine onwards, daratumumab is taken as monotherapy.

2. Health Benefits

At its meeting in April 2018, CaTSoP reviewed the results of the CASTOR (Palumbo et al. N Engl J Med. 2016;375:754-66) and POLLUX (Dimopoulos et al. N Engl J Med. 2016;375:1319-1331) trials that were identified by the supplier as providing the primary evidence for the health benefits of daratumumab for the treatment of relapsed or refractory multiple myeloma .

The supplier later provided longer-term follow up data for the CASTOR (Spencer et al. Haematologica 2018;103:2079-2087) and POLLUX (Dimopoulos et al Haematologica 2018;103:2088-2096) trials. In July 2021, CaTSoP reviewed the longer term data of the SC daratumumab vs IV daratumumab. A summary of these trials is provided in Table 2 and Table 3 below.

2.1 Clinical Evidence

Table 2. Clinical evidence

Trial	Study Design	Patient Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
CASTOR	Phase 3, randomised, open-label	Patients with relapsed or refractory multiple myeloma who had received one or more previous lines of therapy.	N = 498	Bortezomib and dexamethasone alone vs in combination with daratumumab 16 mg per kg	Median follow-up of 7.4 months	Median PFS: not reached in daratumumab group vs 7.2 months in control (HR 0.39, <0.001) PFS at 12 months: 60.7% daratumumab vs 26.9% control. OR: 82.9% daratumumab vs 63.2% control (p<0.001)	SAE: 76.1% daratumumab vs 62.4% control.	Palumbo et al. N Engl J Med. 2016;375:754-66
Updated follow-up					Median follow-up of 19.4 months	Median PFS: 16.7 months daratumumab vs 7.1 months control (HR 0.39, p<0.0001)		Spencer et al. Haematologica.

Trial	Study Design	Patient Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
						OR: 83.8% daratumumab vs 63.2% control (p<0.001)		2018;103: 2079-2087
POLLUX Updated follow-up	Phase 3, randomised, open-label	Patients with relapsed or refractory multiple myeloma who had received one or more previous lines of therapy.	N = 569	Lenalidomide and dexamethasone alone vs in combination with daratumumab 16 mg per kg	Median follow-up of 13.5 months Median follow-up of 25.4 months	PFS at 12 months: 83.2% daratumumab vs 60.1% control ORR: 92.9% daratumumab vs 76.4% control (p<0.001) Median PFS: not reached in daratumumab group vs 17.5 months control. (HR 0.41, p<0.0001) ORR: 92.9% daratumumab vs 76.4% control (p<0.0001)	SAEs: 48.8% daratumumab vs 42.0% control.	Dimopoulos et al. N Engl J Med. 2016;375:1319-1331 Dimopoulos et al. Haematologica 2018;103:2088-2096

Table 3. COLUMBA trial data summary

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
COLUMBA	Multi-centre, open-label, non-inferiority, randomised	Patients aged ≥18 with relapsed or refractory multiple myeloma who received ≥3 previous lines of therapy including	N = 522	**1800 mg subcutaneous (SC) daratumumab monotherapy** co-	Median follow-up 7.5 months (IQR 6.5	Co-primary endpoints: **Overall response in 108/263 (41%) patients in the subcutaneous group**	Infusion-related reaction with SC daratumumab (33/260 [13%]) vs IV daratumumab (89/258 [34%]; odds	Mateos et al. Lancet Haematol. 2020;7:e370-e380

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
	(1:1) phase III trial	a proteasome inhibitor and immunomodulatory drug, or were double refractory to both a proteasome inhibitor and immunomodulatory drug and had ECOG performance status score ≤2 **Median ≤4 prior therapies in most patients** (66% subcutaneous, 68% intravenous); standard cytogenetic risk in 74% and 83%, respectively; more subcutaneous group patients had ECOG ≥1		formulated with 2000 U/mL recombinant human hyaluronidase PH20 vs 16 mg/kg intravenous (IV) daratumumab monotherapy Treatment given once weekly (cycles 1–2), every 2 weeks (cycles 3–6), and every 4 weeks thereafter with 28-day cycles continued until disease progression or toxicity	to 9.3) at data cut-ff Jan 2019.	**and 96/259 (37%) in the intravenous group (relative risk 1.11, 95% CI 0.89 to 1.37). Non-inferiority criteria met.** Overall responses consistent across pre-specified subgroups and in the subcutaneous group, were consistent in all bodyweight subgroups. **Maximum trough concentration** (C_{trough}; cycle 3, day 1 pre-dose): 149 subcutaneous group and 146 intravenous group patients evaluable for pharmacokinetics. Geometric means ratio for C_{trough} was 107.93% (90% CI 95.74 to 121.67) and the maximum C_{trough} was 593 µg/mL (SD 306) in the subcutaneous group and 522 µg/mL (226) in the intravenous	ratio 0.28, 95% CI 0.18 to 0.44, *P*<0.0001). Grade 3 infusion-related reactions in 4 (2%) SC and 14 (5%) IV. Most common grade 3 and 4 adverse events (AEs): anaemia (13% SC vs 14% IV), neutropenia (13% vs 8%, respectively) and thrombocytopenia (14% vs 14%, respectively). Pneumonia was the only serious AE in >2% of patients (7 [3%] SC and 11 [4%] IV). One treatment-related death in SC group (febrile neutropenia) and 4 IV group (sepsis [N=2], hepatitis B reactivation [N=1], and *Pneumocystis jirovecii* pneumonia [N=1]).	

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
						group. Non-inferiority criteria met.		
COLUMBA: bodyweight subgroup analysis	As above Bodyweight subgroup analysis (≤65 kg, >65 to 85 kg, and >85 kg) based on data from primary analysis.				As above	Flat dose subcutaneous daratumumab achieved adequate exposure for all body weight subgroups, as maximum C_{trough} (C3D1 predose) exceeded the 236 µg/mL threshold and was within the previously observed range for approved IV 16 mg/kg. Overall response rates in body weight subgroups for SC and IV suggest that the slightly lower exposure observed at higher body weights was not clinically relevant.	Incidence of grade 3/4 treatment-emergent AEs (TEAEs), grade 5 TEAEs, serious TEAEs, and infusion-related reactions similar across body weight subgroups. Increased incidence of any-grade TEAEs with decreasing body weight for SC; similar incidence of any grade TEAEs across IV body weight subgroups.	Mateos et al. Blood. 2019; 134 (Supplement_1): 1906
COLUMBA: updated results after longer follow-up	As above				Median follow-up 13.8 months.	**Overall response rate 43.7% subcutaneous vs 39.4% intravenous; comparable across all subgroups including body weight.**	Significantly lower rate of infusion-related reactions with subcutaneous daratumumab.	Usmani et al. Blood. 2019; 134 (Supplement_1): 1865

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
COLUMBA: Patient satisfaction	As above Collected data using a modified version of the Cancer Therapy Satisfaction Questionnaire (CTSQ) weekly (cycles 1-2) and monthly (cycles 3 +) intervals and at the end of treatment. Minimally important difference (MID) of 5.9 points.					Responses indicating positive perceptions of therapy were given by a numerically greater proportion of patients in the SC group than the IV group for most questions. At least 29% of patients had mean change from C1D8 in SWT domain score that met or exceeded the MID at every assessment time point (both groups).		Usmani et al. J Cancer Res Clin Oncol. 2021;147:619-631

2.2 Review of Clinical Evidence

The following is an excerpt from the July 2021 CaTSoP meeting record.

1.1. The Subcommittee **recommended** that subcutaneous daratumumab be funded with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

DARATUMUMAB SUBCUTANEOUS
Initial application – (relapsed/refractory multiple myeloma) only from a relevant specialist or other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received one prior line of therapy for multiple myeloma; and
3. Either:
   - 3.1. Both:
     - 3.1.1. In patients who received first-line bortezomib, patient's disease was not refractory to bortezomib (ie received >6 months response to first-line bortezomib) nor were they intolerant to bortezomib; and
     - 3.1.2. Daratumumab subcutaneous to be administered in combination with bortezomib and dexamethasone for weeks 1 through 24 and as a monotherapy from week 25 until disease progression.
   - 3.2. Both:
     - 3.2.1. In patients who received first-line bortezomib, patients disease was refractory to bortezomib in first line or they were intolerant to bortezomib
     - 3.2.2. Daratumumab to be administered in combination with dexamethasone

Renewal application - (relapsed/refractory multiple myeloma) only from a relevant specialist or other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. No evidence of disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

In making this recommendation, the Subcommittee:

- noted the evidence of a substantial progression-free survival benefit and overall survival benefit from the addition of daratumumab, irrespective of its formulation, to second-line bortezomib and dexamethasone treatment for patients who received one prior line of therapy for multiple myeloma
- considered that there was no evidence to suggest a difference in efficacy between intravenous and subcutaneous daratumumab
- considered the subcutaneous formulation would substantially reduce the health system's infusion resource impact compared with the high impact of intravenous treatments for relapsed/refractory multiple myeloma
- noted the high cost of subcutaneous daratumumab for this patient population
- noted that funding daratumumab for only those patients who are not refractory to or intolerant of bortezomib would result in a need for bortezomib-refractory/intolerant patients. The Subcommittee considered it reasonable to enable access to those bortezomib-refractory/intolerant patients in the funded group based on the likely efficacy of daratumumab for this patient group and the unmet need that would arise of daratumumab were funded for only bortezomib responsive patients.

1.2. The Subcommittee **recommended** that intravenous daratumumab be funded with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

DARATUMUMAB INTRAVENOUS
Initial application – (relapsed/refractory multiple myeloma) only from a relevant specialist or other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received one prior line of therapy for multiple myeloma; and
3. Either:
   - 3.1. Both:
     - 3.1.1. In patients who received first-line bortezomib, patient's disease was not refractory to bortezomib (ie received >6 months response to first-line bortezomib) nor were they intolerant to bortezomib; and
     - 3.1.2. Daratumumab subcutaneous to be administered in combination with bortezomib and dexamethasone for weeks 1 through 24 and as a monotherapy from week 25 until disease progression.
   - 3.2. Both:
     - 3.2.1. In patients who received first-line bortezomib, patients disease was refractory to bortezomib in first line or they were intolerant to bortezomib
     - 3.2.2. Daratumumab to be administered in combination with dexamethasone

Renewal application - (relapsed/refractory multiple myeloma) only from a relevant specialist or other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. No evidence of disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

In making this recommendation, the Subcommittee:

- noted the evidence of a substantial progression-free survival benefit and overall survival benefit from the addition of daratumumab, irrespective of its formulation, to second-line bortezomib and dexamethasone treatment for patients who received one prior line of therapy for multiple myeloma
- considered the suitability of intravenous daratumumab was substantially improved due to an accelerated 90-minute infusion protocol, which has been used anecdotally in New Zealand, and that use of this rapid treatment regimen would substantially reduce the health system's infusion resource impact compared with the high impact of intravenous treatments for relapsed/refractory multiple myeloma
- noted the high cost of intravenous daratumumab for this patient population
- noted that only funding daratumumab for patients who are not refractory to or intolerant of bortezomib would result in an unmet need for bortezomib-refractory/intolerant patients. The Subcommittee considered it reasonable to enable access to those bortezomib-refractory/intolerant patients in the funded group based on the likely efficacy of daratumumab for this patient group and the unmet need that would arise of daratumumab were funded for only bortezomib responsive patients

3. Pharmac Cost-Utility Analysis

A CUA was undertaken to estimate the cost-effectiveness of daratumumab for relapsed or refractory multiple myeloma in patients with one prior line of treatment.

4.1 Scope of Analysis

The analysis was undertaken from the perspective of the funder, with regards to Pharmac's Factors for Consideration.

4.1.1 Target Population

The target population for this analysis was defined as patients with relapsed or refractory multiple myeloma , after one prior line of therapy.

4.1.2 Comparator

As discussed in section 1.3, there are currently no efficacious treatment options funded in NZ for second line treatment of this patient group, and patients tend to receive re-treatment with the same bortezomib regimen received at first line currently.

The comparator used in the analysis was a split comparator, with the majority of patients receiving a bortezomib, cyclophosphamide and dexamethasone regimen (CyBorD), and 19%[1] of patients receiving lenalidomide (the estimated proportion of patients who would not be able to receive bortezomib or thalidomide). In the sensitivity analysis, a proportion of 29% of people receiving lenalidomide was used instead, as this was the proportion of patients who have received lenalidomide as second line treatment for multiple myeloma in the last year of Pharmac medicine usage data. However due to variability in number of patients treated with lenalidomide across the last few years, Pharmac considered there to be a degree of uncertainty to this data. The comparator split proportions were not found to be impactful to the results of the CUA. In the intervention arm of the CUA, the proportion of patients who are intolerant to bortezomib have daratumumab with dexamethasone only.

A small proportion of patients are expected to be on a thalidomide regimen instead of bortezomib. Because patient numbers are expected to be low, the cost of a thalidomide-containing regimen is similar to bortezomib, and there is limited evidence relating to the relative efficacy of a thalidomide-containing comparator, Pharmac have excluded this comparator from the analysis. It is assumed that patients receiving this regimen would have a similar efficacy and cost to that of bortezomib-containing regimens.

4.2 Model Structure

A Markov model was constructed to model the different treatment strategies.

[1] Miguel et al. N Engl J Med. 2008;359:906-17 found that 19% of patients receiving bortezomib discontinued treatment due to adverse events.

4.2.1 Time Horizon

The time-horizon of the CUA was lifetime. Each Markov cycle was one week, to allow for treatment cycles of different lengths with the split intervention and split comparator.

All costs and benefits were discounted at 3.5%.

4.2.2 Model Structure

The Markov model included the following health states:

- Progression free disease (2L)
- Progression free disease (3L)
- Progressed disease
- Death

The cohort of patients in the CUA could enter one of three possible treatment paradigms, which included:

1) Transplant eligible, treated with CyBorD (comparator)/ Dvd (intervention) 2nd line
2) Transplant ineligible, treated with CyBorD (comparator)/ Dvd (intervention) 2nd line
3) Transplant ineligible, treated with lenalidomide (comparator)/ Dd (intervention) 2nd line

These are further described in Table 4.

Transplant eligible patients are defined as such based on their eligibility for transplant at diagnosis. As a result, patients considered 'transplant eligible' in the model, are people who have had an autologous stem cell transplant (SCT) already at first line and lenalidomide maintenance therapy subsequent to the SCT. These patients are separated from the others in the model because they are not eligible to receive lenalidomide treatment a second time. Hence, these patients move to the progressed disease health state, where they do not receive any active treatment, once they have progressed on the intervention/status quo second line treatment (CyBorD), as in Figure 1.

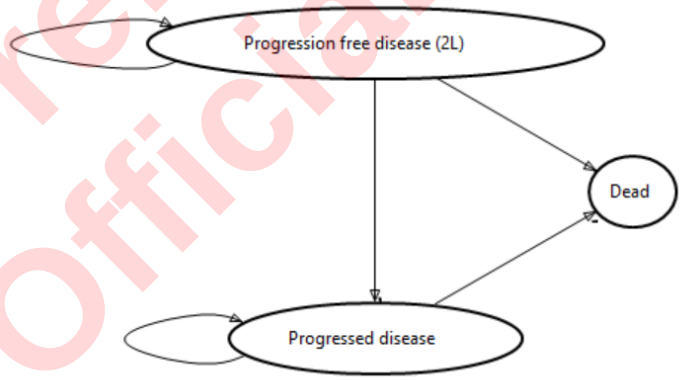

Figure 1. State transition diagram for patients who have had lenalidomide maintenance or 2nd line treatment

Patients who were transplant ineligible at baseline, and were treated with CyBorD retreatment (or the new intervention) second line will not have had lenalidomide maintenance therapy following auto-SCT. Hence, these patients will be eligible for lenalidomide once they have progressed on 2nd line treatment. This is represented in Figure 2, where an extra state is included relative to Figure 1, showing progression free disease on active third line treatment.

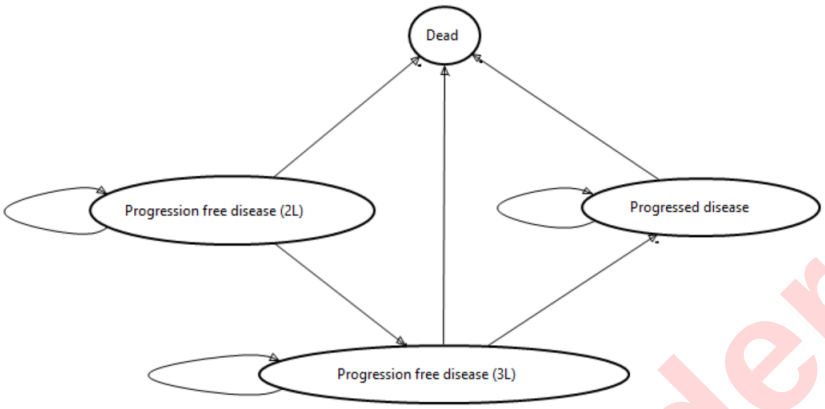

Figure 2. State transition diagram for patients who are eligible for lenalidomide as 3rd line treatment

Some transplant ineligible patients will have had lenalidomide as second line therapy, if they were unable to have bortezomib or thalidomide, so lenalidomide is the comparator for 2nd line treatment. Therefore, for these patients, the comparator arm of the Markov model resembles Figure 1, with lenalidomide as the second line treatment and no active third line treatment. For the intervention however, patients would be treated with Dd (bortezomib is excluded due to intolerance), and still be eligible for lenalidomide 3rd line, so in this arm of the mode, these patients fit the model in Figure 2.

Table 4. Summary of treatment paradigms in CUA

Line of treatment	**Intervention paradigm**			**Comparator paradigm**		
	1	***2***	***3***	***1***	***2***	***3***
1L include lenalidomide?	✓	×	×	✓	×	×
2L	DVd	DVd	Dd	CyBorD	CyBorD	Lenalidomide
3L	-	Lenalidomide	Lenalidomide	-	Lenalidomide	-

4.3 Transformation and Extrapolation of Clinical Evidence

This economic model uses data derived from the CASTOR trial, a phase 3 trial where patients were randomly assigned to receive bortezomib and dexamethasone alone (Vd, control group) or in combination with daratumumab (DVd, 16 mg per kilogram of body weight, IV). A subgroup analysis (Mateos et al. Clin Lymphoma Myeloma Leuk. 2020;20:509-518, n=235) included patients who had received only one prior line of therapy (1PL), and estimated the hazard ratio of PFS for DVd relative to Vd at 0.22 (Figure 3). Confidential data provided to Pharmac by the

supplier indicates an OS hazard ratio of s9(2) (corresponding K-M curves are shown in Figure 4) for DVd relative to Vd in the 1PL subgroup.

Pharmac staff note that the comparator in the CASTOR trial (Vd) differs slightly from the most prevalent comparator regimen in New Zealand, CyBorD. There is little literature on clinical difference between treatment with Vd, and the CyBorD regimen. However, a study by Figueiredo et al. Curr Oncol;2020:e81-e85. suggests the clinical efficacy is very similar. For the purpose of this model, and in the absence of head-to-head evidence for the efficacy of DVd vs CyBorD, Pharmac staff assume the efficacy of CyBorD is equivalent to Vd, as represented in the CASTOR trial.

The subgroup of patients on lenalidomide treatment (either 2L or 3L) was modelled using the lenalidomide data from Dimopoulos et al. N Engl J Med 2007; 357:2123-2132, a phase 3, randomised trial where patients received either lenalidomide plus dexamethasone, or placebo plus dexamethasone. Around 30% of these patients had exactly 1PL of treatment, with the remainder having at least 2 prior lines of treatment. While PFS was not measured separately in these subgroups, a response was reported in 66% of patients with 1PL and 58% of those with 2+ prior lines of treatment. With a higher response rate, the 1PL subgroup would likely have a higher PFS also, but the degree of which could not be measured. Pharmac staff considered that in the absence of further data in the 1PL subgroup, it was reasonable to apply the PFS identified in Figure 5 for both 2L and 3L lenalidomide treatments modelled. Pharmac staff note there is a risk for this group that the efficacy of lenalidomide may be underestimated.

Pharmac staff used CASTOR evidence to model the SC formula of daratumumab in the same way as the IV formula. This was considered an appropriate simplification, since recent COLUMBA trial (Mateos et al. Lancet Haematol. 2020;7:e370-e380) found the SC and IV-administered daratumumab to be therapeutically equivalent. The patients in the COLUMBA trial were treated with daratumumab monotherapy (rather than a combination with bortezomib or dexamethasone) and were multiply relapsed patients. Hence, given the comparable effect of the two formulae, Pharmac staff considered that the CASTOR 1PL subgroup better represented the target population and the proposed place of the medicines in the New Zealand treatment paradigm, for both the SC and IV models.

Data from the Kaplan-Meier curves were transformed into clinical parameter estimates by plot digitising PFS and OS curves. As seen in Figure 4, OS was captured for 48 months, however the median estimated from extrapolating this curve indicates that patients treated with daratumumab will survive to around 7 years. Because of this significant extrapolation of data, Pharmac staff have assumed that the mortality rate of patients on daratumumab will begin to converge with that of the comparator after 10 years in the model and will have completely converged at 15 years, as was assumed by PBAC (July 2020). In the sensitivity analysis, the convergence began at year 5 and ended at year 10.

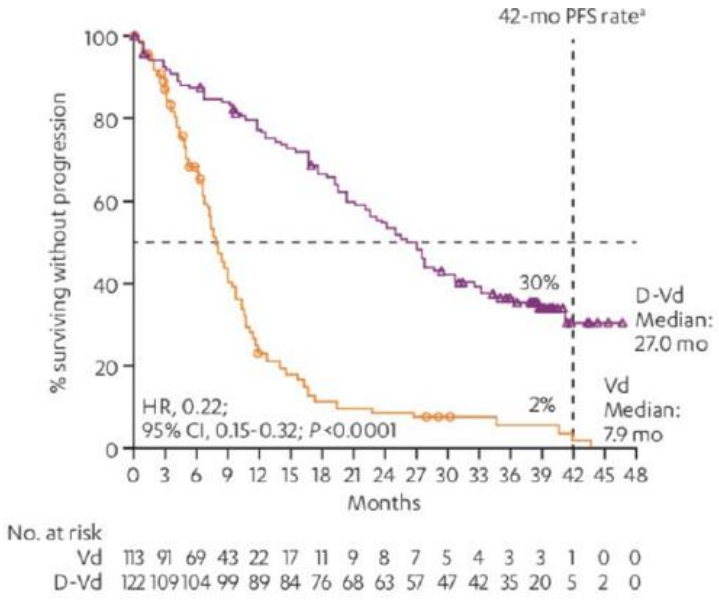

Figure 3. CASTOR PFS for population with only 1 prior line of therapy

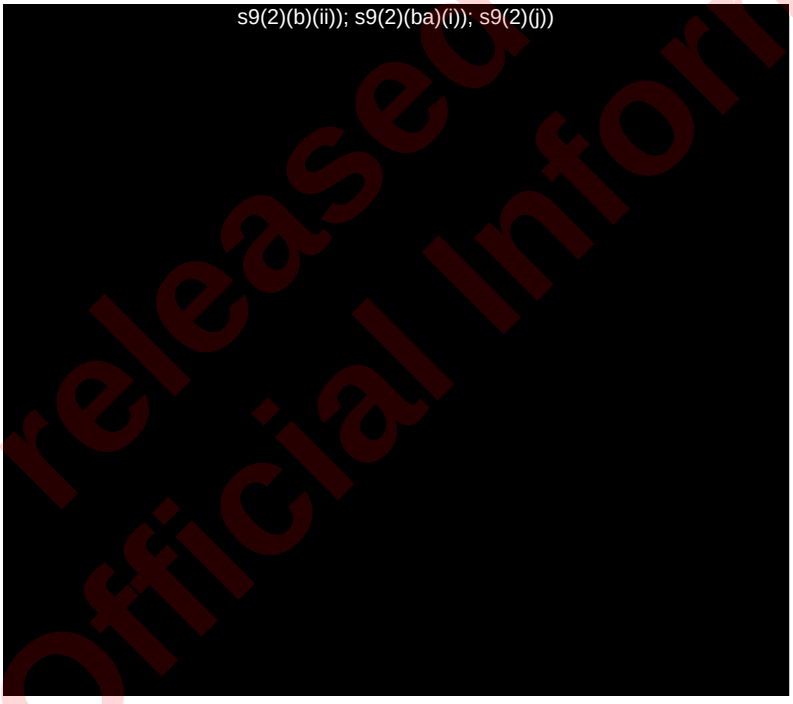

Figure 4. CASTOR OS for population with only 1 prior line of therapy, [confidential, Pharmac data on file from supplier]

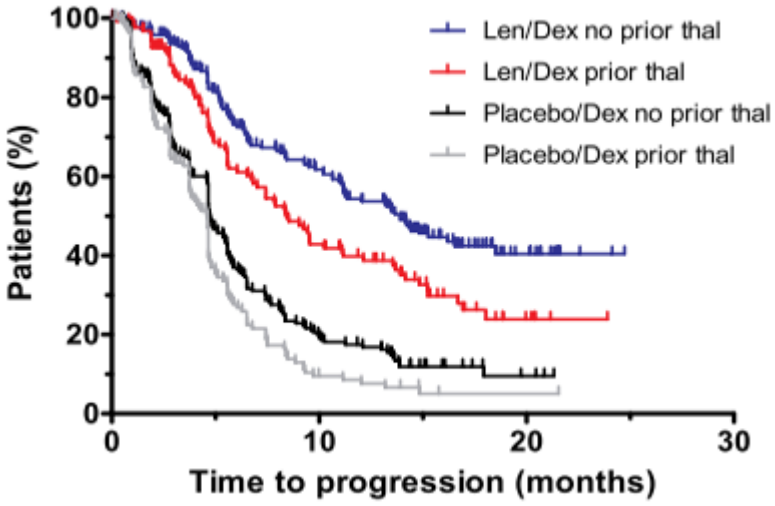

Figure 5. PFS of patients treated with lenalidomide plus dexamethasone

Duration of treatment

In CASTOR, the duration of treatment was not identified for the 1PL subgroup. The ITT median duration of treatment was 13.4 months, 80% of the median PFS found in the ITT population (16.7 months). Pharmac assumed that time on treatment was 80% of the median PFS in the 1PL subgroup PFS also. Similarly, median time on treatment represented 73% of the median PFS in the ITT population for the comparator. This was applied in the same way to the 1PL subgroup for the comparator.

Stem cell transplants

In CASTOR, 1.6% and 0.4% of patients in the DVd and comparator arms respectively had a subsequent autologous SCT. Pharmac staff applied these rates to determine a weighted cost of second auto SCT in each treatment arm in the base case of the model, however, it is uncertain if these rates are representative of the NZ context. In the sensitivity analysis, Pharmac applied no SCT cost to either arm of the model.

4.4 Health-Related Quality of Life

The health-related quality of life (HRQoL) utility weights for 2L and 3L treatment were taken from the NICE TA657 paper assessing carfilzomib in relapsed or refractory multiple myeloma patients. NICE mapped EORTC QLQ-C30 data from ENDEAVOR for Carfilzomib plus dexamethasone (Cd) versus Vd to EQ-5D utility values. While in the post progression treatment phase, NICE estimated Cd and Vd to have equal utility values (0.638), they assumed a HRQoL benefit was associated with treatment with carfilzomib relative to Vd (0.741 vs 0.714 on Vd). Pharmac staff considered it reasonable to apply the Vd utility value (0.714) to both DVd and comparator 2L treatment states in the base-case, as there is no evidence of a HRQoL benefit for daratumumab. However, a utility benefit equal to that found with carfilzomib relative to Vd was tested in a sensitivity analysis.

A utility value of 0.5 was applied to the progressed state with no treatment. This was reported by Weisel et al. (2015) in a study which investigated the effects of pomalidomide with dexamethasone on HRQoL in patients with multiply relapsed or refractory multiple myeloma.

Table 5. Utility Values

Health State	Annual Utility	Source
2nd line treatment	0.714	NICE TA657, Table 19.
3rd line treatment	0.638	NICE TA657, Table 19.
Progressed disease	0.5	Weisel et al. Clin Lymphoma Myeloma Leuk. 2015;15:519-30, Figure 4.

4.5 Costs

4.5.1 Pharmaceutical Cost

Daratumumab IV

Daratumumab is to be taken in combination with bortezomib and dexamethasone. The recommended dose of daratumumab IV is 16mg/kg body weight administered as an intravenous infusion. One vial contains 100mg daratumumab, and at an average bodyweight of 80kg the required dose is 1280mg, requiring 13 vials. At a net cost of s9(2)(b)(ii); vial, the cost per dose is s9(2)(b). When used in combination with bortezomib and dexamethasone, daratumumab (IV or SC) is given weekly for a total of 9 doses (weeks 1-9); every three weeks for a total of 5 doses (weeks 10-24) and then once every 4 weeks there-after until disease progression. The estimated duration of treatment is 80% of the median PFS (see section 4.3), which calculates to 22 months. This represents approximately 31 doses, amounting to a cost of s9(2)(b)(ii); per patient treated.

Daratumumab SC

Subcutaneous daratumumab is given at a dose of 1800mg. The gross cost per 1800mg single use vial is $8,305. The supplier included in their own model a s9(2)(b)(ii);, which they stated does not constitute a formal commercial offer. Pharmac has used this informal net price as a proxy, as it indicates the supplier is willing to come to a similar agreement with Pharmac should this proposal be progressed. This brings the net cost per vial/dose to s9(2)(b). Using the same treatment duration as for daratumumab IV (based on the assumption of comparable efficacy), the median treatment cost per patient is estimated to be s9(2)(b)(ii);.

Bortezomib

Bortezomib, either in combination with daratumumab, or as part of the CyBorD regimen, is taken at a dose of 1.3mg/m^2, four times per 21 day cycle, according to EviQ - Multiple myeloma - CyBorD twice weekly. One mg via ECP costs $31.20[2]. Bortezomib is to be taken with daratumumab for the first 8 cycles, after which daratumumab is used as a monotherapy only. The median PFS of Vd in CASTOR was 8 months. The duration of treatment is estimated to be 73% of this (5.8 months, section 4.3). This is also equivalent to 8 cycles, bringing the total cost of bortezomib in both regimens to $2,500.

Cyclophosphamide

Cyclophosphamide is to be taken at 300mg/m^2 once per week. The schedule price is $145 per 50 x 50mg tablets. Pharmac staff estimate that the majority of patients require 12 tablets, bringing the weekly dose to $35. At 8 x 28-day cycles, this is a cost of ~$300 per patient treated.

Lenalidomide (2L and 3L)

Lenalidomide is to be taken as one 25mg tablet every day for 21 days in a 28 day cycle. While the gross price per pack is $7627[2] per 21 tablets, lenalidomide is subject to s9(2)(b) rebate. The median time to progression for patients on lenalidomide treatment is

[2] Pharmac schedule. https://www.pharmac.govt.nz/wwwtrs/ScheduleOnline.php

approximately 14 months (~15 28-day cycles). This brings the median cost of a patient on lenalidomide treatment s9(2)(b)(ii);.

Dexamethasone is taken as part of all regimens, and the cost is negligible.

Table 6. Pharmaceutical Cost

Regimen	DVd			CyBorD		Rd
Pharmaceutical	**Daratumumab IV**	**Daratumumab SC**	**Bortezomib**	**Cyclophosphamide**	**Bortezomib**	**Lenalidomide**
Form, strength and pack size	100mg vial	1800mg vial	Inj 1 mg for ECP	50mg tablets (50 per pack)	Inj 1 mg for ECP	25mg (21 tablets per pack)
Net price per pack*	s9(2)(b)	s9(2)(b)	$31.20[3]	$145[3]	$31.20[3]	s9(2)(b)
Price per dose	s9(2)(b)	s9(2)(b)	$78[5]	$35	$78[5]	s9(2)(b)
Cost per treatment course	s9(2)(b)	s9(2)(b)	$2,500	$300	$2,500	s9(2)(b)

[1] Janssen daratumumab analysis, October 2021.
[2] Janssen daratumumab SC application, April 2021. Including estimated s9(2)(b)(ii);
[3] Schedule price
[4] Celgene Revlimid agreement November 2019
[5] Based on average BSA = 1.92

4.5.3 Health Sector Costs

Adverse events

The most common adverse events associated with DVd versus Vd, which occurred at different rates between treatments, were thrombocytopenia (46% vs. 33%), neutropenia (14% vs 5%) and lymphophenia (10% vs 3%).[3] The costs for these are taken from the DRG costs found in the Pharmac cost spreadsheet, as shown in Table 7, and applied once, to the proportion of patients stated above.

Table 7. Adverse events

Hospitalisations	Cost	Source of cost
Thrombocytopenia	$3,624	DRG Q62 coagulation disorders - average of values for 'coagulation disorders' and 'coagulation disorders same day' as no information found about the split between these two. Sourced from CUA cost spreadsheet.
Neutropenia	$4,538	D70, D72.8, D72.9 - white blood cell disorders and agranulocytosis codes - map to Q60A-C
Lymphophenia	$4,538	D70, D72.8, D72.9 - white blood cell disorders and agranulocytosis codes - map to Q60A-C

Outpatient costs

Daratumumab IV has significant infusion times, at 7 hours for the first infusion, 5 hours for the second, and 4 hours for subsequent infusions. Infusions are costed at $120 per hour plus $35 of specialist time per infusion, as per the cost spreadsheet. Daratumumab SC and bortezomib

[3] Mateos et al. Clin Lymphoma Myeloma Leuk. 2020;20(8):509-518.

are required to be administered in an outpatient clinic. Pharmac staff assume 30 mins of bed and nurse time will be required in total for a subcutaneous treatment administration, regardless of whether one (daratumumab or bortezomib) or two (both) SC injections are required.

Pharmacy distribution fee

Pharmacy net distribution fees of 3% and 4% are applied to the cost of cyclophosphamide and lenalidomide respectively as they are distributed in the community.

Monitoring costs

Monitoring unit costs are as found in the Pharmac cost spreadsheet. Serum electrophoresis is the cost of an alkaline test as this was the midpoint of three different serum electrophoresis tests; urea/electrolyte/creatinine is the sum of testing costs for each of these tests separately; a dummy cost of $30 was used for serum light chain test, in the absence of data and noting the immateriality of this cost. The frequency of events are from the 2015 supplier model for pomalidomide for relapsed or refractory multiple myeloma. The yearly total for a patient in the stable or progressive disease state is $4,896 and $5,310, respectively. These are applied as weekly costs in the model.

Table 8. Monitoring costs

	Cost ($)	Stable disease	Progressive disease
		Number / year	Number / year
Haematologist consultation	350	12	12
Complete blood count	8.55	10.7	20.1
Urea/electrolyte / creatinine	12.14	9.7	17.3
Serum electrophoresis	60.53	6.7	9.6
Serum light chain	30	2.7	4.9

4.6 Cost-Effectiveness Results

Daratumumab SC

The incremental cost is estimated to be s9(2)(b)(ii); with a QALY gain of 1.68. The estimated base case cost utility, in QALYs per $1 million, is s9(2)(b)(ii); (cost per QALY of s9(2)(b)(ii);). This is shown in the table below.

Table 9. Daratumumab SC Cost-Effectiveness Results

	Daratumumab SC	Comparator	Incremental
QALYs	4.20	2.52	1.68
Cost	s9(2)(b)	s9(2)(b)	s9(2)(b)
QALYs per $1m			s9(2)(b)

Daratumumab IV

The incremental cost is estimated to be s9(2)(b)(ii); with a QALY gain of 1.68. The estimated QALYs per $1million is s9(2)(b)(ii); (cost per QALY of s9(2)(b)(ii);). This is shown in the table below.

Table 10. Daratumumab IV Cost-Effectiveness Results

	Daratumumab IV	**Comparator**	**Incremental**
QALYs	4.20	2.52	1.68
Cost	s9(2)(b)(ii);	s9(2)(b)	s9(2)(b)(ii);
QALYs per $1m			s9(2)(b)(ii);

4.7 Sensitivity Analysis

Table 11. Daratumumab SC Sensitivity analysis

	ICER	QALYs per mill
Base case	s9(2)(b)(ii));	s
Converge efficacy of daratumumab to that of the comparator over 5-10 years	s9(2)(b)(ii));	s
Proportion intolerant to bortezomib 29%	s9(2)(b)(ii));	s
Proportion intolerant to bortezomib 19% (intervention) and 29%(comparator)	s9(2)(b)(ii));	s
No SCTs for any patients	s9(2)(b)(ii));	s
1/3 of the SCTs are allogenic rather than autologous	s9(2)(b)(ii));	s
Progression HR low (-SE)	s9(2)(b)(ii));	s
Progression HR high (+SE)	s9(2)(b)(ii));	s
Utility benefit for daratumumab (PFS utility 0.741 rather than 0.714)	s9(2)(b)(ii));	s

SE: standard error

Table 12. Daratumumab IV Sensitivity analysis

	ICER	QALYs per mill
Base case	s9(2)(b)(ii));	s
Converge efficacy of daratumumab to that of the comparator over 5-10 years	s9(2)(b)(ii));	s
Proportion intolerant to bortezomib 29%	s9(2)(b)(ii));	s
Proportion intolerant to bortezomib 19% (intervention) and 29%(comparator)	s9(2)(b)(ii));	s
No SCTs for any patients	s9(2)(b)(ii));	s
1/3 of the SCTs are allogenic rather than autologous	s9(2)(b)(ii));	s
Progression HR low (-SE)	s9(2)(b)(ii));	s
Progression HR high (+SE	s9(2)(b)(ii));	s
Utility benefit for daratumumab (PFS utility 0.741 rather than 0.714)	s9(2)(b)(ii));	s

Both Daratumumab SC and IV results are not very sensitive to changes in model parameters, due to the high cost of treatment. The parameters that made the most impact was the convergence of daratumumab efficacy from 5-10 years (rather than 10-15), and variations in the proportion of patients who are intolerant to bortezomib.

4.8 Summary of Overall Cost-Effectiveness

As outlined above, the base-case QALYs per $1m estimate are s9(2)(b) for CS and IV respectively. Taking into account the results of the sensitivity analysis, the likely ranges are

estimated to be s9(2)(b)(ii); for SC and IV respectively. This range captures a convergence in survival between treatments, and alternative proportions of patients who are intolerant to bortezomib.

5. Budget Impact Analysis

The 5-year net present value (NPV) to the Pharmaceutical Schedule of funding daratumumab SC and IV is estimated to be s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2) respectively, with costs of the first 12 months of s9(2)(b)(ii)); s9(2)(ba)(i)); , respectively. This is outlined in Table 13 and Table 14Table 14 below. The 5-year NPVs to DHBs are estimated to be s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2). All costs are discounted at a rate of 8%.

The BIAs take into account the subsequent lenalidomide treatment that some patients will receive as 3rd line treatment, infusion costs (for daratumumab IV), outpatient costs for subcutaneous injections, and the longer period of monitoring costs accumulated via longer survival on daratumumab. The pharmaceutical cost of daratumumab is only minimally offset by the comparator regimen costs.

Table 13. Daratumumab SC Net Budget Impact to DHBs

	Year 1	Year 2	Year 3	Year 4	Year 5	5-Year NPV
Incident patient numbers	268	273	279	285	291	-
Pharmaceutical Budget	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));
Other DHB Costs	$650,000	$720,000	$950,000	$1,270,000	$1,630,000	4,340,000
Total net budget impact to DHBs	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));

Table 14. Daratumumab IV Net Budget Impact to DHBs

	Year 1	Year 2	Year 3	Year 4	Year 5	5-Year NPV
Incident patient numbers	268	273	279	285	291	-
Pharmaceutical Budget	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));
Other DHB Costs	$1,580,000	$2,450,000	$3,280,000	$4,050,000	$4,770,000	13,380,000
Total net budget impact to DHBs	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));	s9(2)(b)(ii));