CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Daratumumab (Darzalex) + Rd for Newly Diagnosed Multiple Myeloma

March 5, 2020

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1 ECONOMIC GUIDANCE IN BRIEF

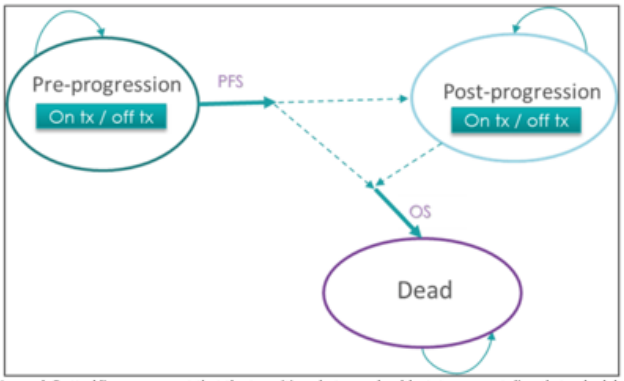
1.1 Submitted Economic Evaluation

The economic analysis **submitted to** pCODR by Janssen Pharmaceuticals compared the cost effectiveness of Daratumumab in combination with Lenalidomide (Revlimid) and Dexamethasone (DRd) to Lenalidomide and dexamethasone (Rd), cyclophosphamide, bortezomib, dexamethasone (CyBorD) and bortezomib (Velcade), melphalan, prednisone (VMP) for patients with newly-diagnosed Multiple Myeloma (NDMM) who were ineligible for Autologous Stem Cell Transplant. This population matches the submitter's funding request.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Daratumumab in combination with Lenalidomide and Dexamethasone for the treatment of patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplantation.
Type of Analysis	Cost-effectiveness (CEA) and Cost-utility analysis (CUA).
Type of Model	Partitioned survival model
Comparators	Lenalidomide and dexamethasone (RD) Cyclophosphamide, bortezomib, dexamethasone (CyBorD) Bortezomib, melphalan, prednisone (VMP)
Year of costs	2019 Canadian dollars
Time Horizon	30 years (Life time)
Perspective	Canadian publicly-funded health care system
Cost of DRd	Unit costs: Daratumumab: - $598.02 per 100 mg vial. - $2392.08 per 400 mg vial. Lenalidomide: - $424.00 (21-unit pack, 25 mg per unit, $8,904 per pack). Dexamethasone: -$0.3046 (100-unit pack, 4 mg per unit, $30.46 per pack). Cycle cost (28-day cycle): - Cycle 1 & 2: $34,786.98 - Cycle 3-6: $23,085.00 - Maintenance: $16,028.60 Calculated per day cost: - During Cycle 1 & 2: $1,242.39 - During Cycle 3-6: $824.46 - Maintenance: $572.45 Dosing/Administrations (28-day cycle): Daratumumab: - 16mg/kg, administered 4 times per cycle during cycle 1-2. - 16mg/kg administered 2 times per cycle during cycle 3-6. - 16mg/kg administered once per cycle afterwards until treatment discontinuation. Lenalidomide: - 25mg administered 21 times per cycle until progression.

	Dexamethasone: - 40mg administered 4 times per cycle until progression.
Cost of Rd	Unit costs: Lenalidomide: - $424.00 (21-unit pack, 25 mg per unit, $8,904 per pack). Dexamethasone: -$0.3046 (100-unit pack, 4 mg per unit, $30.46 per pack). Cycle cost (28-day cycle): - All cycles: $8,914.97 Calculated per day cost: - All cycles: $318.38 Dosing/Administrations (28-day cycle): Lenalidomide: - 25mg administered 21 times per cycle until progression. Dexamethasone: - 40mg administered 4 times per cycle until progression
Cost of VMP	Unit costs: Bortezomib: - $1,402.42 per 3.5 mg vial. Melphalan: - $1.7614 per unit (50-unit pack, 2 mg per unit, $88.07 per pack). Prednisone: - $0.1735 (100-unit pack, 50 mg per unit, $17.35 per pack). - $0.0220 (100-unit pack, 5 mg per unit, $2.20 per pack). Cycle cost (42-day cycle): - Cycle 1: $ 7,266.04 - Cycle 2-9: $3,386.33 Calculated 28-day cycle cost: - During cycle 1: $ 4,844.027 - During cycle 2-9: $2,257.55 Calculated per day cost: - During cycle 1: $173.00 - During cycle 2-9: $80.63 Dosing/Administrations (42-day cycle): Bortezomib: - 1.3 mg/m^2 administered 8 times per cycle in cycle 1. - 1.3 mg/m^2 administered 4 times per cycle during cycles 2-9. Melphalan: - 9mg/m^2 administered 4 times per cycle during cycles 1-9. Prednisone: - 60mg/m^2 administered 4 times per cycle during cycles 1-9
Cost of CyBorD	Unit costs: Bortezomib: - $1,402.42 per 3.5 mg vial.

	Dexamethasone: -$0.3046 (100-unit pack, 4 mg per unit, $30.46 per pack) Cyclophosphamide: -$0.4740 (100-unit pack, 50 mg per unit, $47.40 per pack). <u>Cycle cost (28-day cycle)</u> - During cycles 1-9: $3908.94 <u>Calculated per day cost</u> - During cycles 1-9: $139.61 <u>Dosing/Administrations (28-day cycle):</u> Bortezomib: - 1.5 mg/m^2 administered 4 times per cycle during cycles 1-9. Dexamethasone: - 40 mg administered 4 times per cycle during cycles 1-9. Cyclophosphamide: - 300mg/m^2 administered 4 times per cycle during cycles 1-9.
Model Structure	The partitioned-survival model allocated a cohort of patients across three health states: pre-progression, post-progression, and death. At model start, the whole cohort is in the pre-progression health state. Over time the cohort transitions to either progression or to a death state. A proportion of the cohorts that are in the pre-progression or post-progression states can be receiving treatment while a proportion is assumed to be off treatment **Figure 5.1. Model structure**  Legend: Dotted lines represent that the transitions between health states are not directly tracked, but proportions of patients in each health state are calculated through the partition approach at each time point. KEY: OS = overall survival; PFS = progression-free survival; tx = treatment.
Key Data Sources	Parameters related to the efficacy of DRd and Rd were informed by the MAIA trial[1]. Relative efficacy for VMP was sourced from submitter's network meta-analysis. Efficacy of CyBorD was assumed to be the same as VMP[3]. Utility values were sourced from the MAIA trial. Adverse event (AE) frequency and resource utilization was sourced from the MAIA trial, previous trials, and clinical input[1].

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison in the economic submission is appropriate. The CGP noted that bortezomib, lenalidomide, and dexamethasone (VRd) and daratumumab, bortezomib, melphalan and prednisone (DVMP) would be a clinically relevant comparator. CADTH requested that the sponsor consider including a comparison to DVMP and VRd. However, the sponsor provided the following reasons for why it may not be appropriate to include as a comparator in the economic analysis:

- The randomized controlled trial (RCT) evaluating VRd and Rd for newly diagnosed multiple myeloma (SWOG-S0777) included both transplant eligible and transplant ineligible patients, 69% and 68%, respectively. As such, patients may have been an age or fitness that would deem them eligible to tolerate high dose chemotherapy required for ASCT. As such, the Sponsor noted that the lack of comparative trial data and important demographic difference between the patient populations enrolled in the phase III randomized controlled trials evaluating DRd and VRd resulting in an inappropriate comparison.
- The Sponsor did not include a comparison of DRd to D-VMP as patients would be best suited for one of the daratumumab-based combinations but not both. In addition, the Sponsor noted that DVMP is not currently used in Canadian Clinical practice.

The relevant issues identified by the CGP include:

- There is a net clinical benefit of the DRd combination in the treatment of patients with newly diagnosed, transplant ineligible myeloma
- The MAIA study demonstrated that DRd is a highly effective treatment regimen for transplant ineligible patients with myeloma. The 31% absolute improvement in progression-free survival after three years in the DRd arm was clinically meaningful.
- At the time of primary analysis, the follow up of 28.0 months in the MAIA trial was immature to determine the effectiveness of DRd with respect to overall survival.
- There are methodological concerns raised in the network meta-analysis that limit the conclusions that can be drawn from that assessment. These include the differences in the trials' definition of PFS, OS, the criteria used to define ORR and ≥CR, differences in the duration of follow-up and other trial characteristics such as dosing which may have affected the treatment effects observed in each trial.
- At the request of CADTH, the Sponsor provided a sensitivity analysis of the NMA which included VRd. The differences in the trial populations result in a violation of the similarity assumption of analysis and therefore represent a significant limitation in comparing efficacy outcomes of the SWOG-S0777 and MAIA trials.[3]

Summary of registered clinician input relevant to the economic analysis
Registered clinicians provided context on the need for therapies that can prolong the progression-free interval and the usefulness of DRd for patients with NDMM if made available. The clinicians provided input in support of the assumption that VMP and CyBorD had similar clinical effectiveness. However, based on the submitted clinicians' input, there were inconsistencies related to treatment sequencing and choice of combination therapies with daratumumab. The model was only able to consider a limited number of subsequent therapies that were mentioned by the clinicians.

Summary of patient input relevant to the economic analysis

There were 7 patients of the 214 who provided feedback which had experience with DRd as per the indication under review. Patients considered improvements to quality-of-life, increased

treatment options, and disease control as values important to them. The submitted economic model considered quality-of-life and disease control through outcomes such as survival and progression.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for DRd which are relevant to the economic analysis:

- The additional resources required for pre-medication, drug preparation, administration, and adverse event monitoring were highlighted as a potential barrier to implementation. The economic analysis incorporates drug preparation and administration, monitoring and adverse event-related costs.
- PAG outlined concerns regarding the incremental costs of drug wastage, specifically in centres where vial sharing would be difficult. The economic analysis contains a scenario analysis where drug wastage is considered.
- PAG highlighted the uncertainty regarding length-of-treatment. The economic analysis allowed for modification of treatment length estimates, including a treatment to progression scenario analysis, as well as a modification of the length of the progression-free interval estimates.
- The high cost of daratumumab, as an add-on therapy, was indicated as a barrier to implementation.

1.3 Submitted and EGP Reanalysis Estimates

The economic submission used a 30-year life-time horizon and used a discount rate of 1.5% to discount costs and effects. According to the submitted economic analysis when comparing DRd to Rd:

- The incremental cost of DRd was $905,935. The costs considered in the analysis include drug acquisition, administration, monitoring, adverse event management, terminal care, and cost of second-line and third-line treatments.
- The incremental clinical benefit of DRd was 6.11 additional life-years and a difference in quality-adjusted life years of 4.11. The clinical effect was based on progression-free survival and overall survival estimates as well as patient utilities.
- The submitter estimated the incremental cost-effectiveness ratio was $220,588/QALY.

According to the submitted economic analysis when comparing DRd to VMP:

- The incremental cost of DRd was $1,307,055. The costs considered in the analysis include drug acquisition, administration, monitoring, adverse event management, terminal care, and cost of second-line and third-line treatments.
- The incremental clinical benefit of DRd was 6.68 additional life-years and a difference in quality-adjusted life years of 4.50. The clinical effect was based on progression-free survival and overall survival estimates as well as patient utilities.
- The submitter estimated the incremental cost-effectiveness ratio was $230,210/QALY.

According to the submitted economic analysis when comparing DRd to CyBorD:

- The incremental cost of DRd was $1,025,168. The costs considered in the analysis include drug acquisition, administration, monitoring, adverse event management, terminal care, and cost of second-line and third-line treatments.
- The incremental clinical benefit of DRd was 6.68 additional life-years and a difference in quality-adjusted life years of 4.50. The clinical effect was based on progression-free survival and overall survival estimates as well as patient utilities.

- The submitter estimated the incremental cost-effectiveness ratio was $227,571/QALY.

The factors driving the difference in costs between DRd and the comparators included drug acquisition cost, treatment duration and estimates of progression-free survival. Estimates of progression-free survival were extrapolated from MAIA trial results and the submitter's network meta-analysis.

The factors driving the difference in life-years and quality-adjusted life-years between DRd and the comparators were the estimates of progression-free survival and estimates of overall-survival. Estimates of progression-free survival and overall survival were extrapolated from MAIA trial results and the submitter's network meta-analysis.

The EGP used the submitted model to conduct probabilistic reanalyses (2,500 model runs). Section 1.4 provides detailed descriptions of the reanalyses conducted by the EGP. The EGP estimates differed substantially from those provided by the submitter. A comparison of the EGP reanalysis and the submitted model is provided in **Table 2.**

Table 2A. Submitted and EGP Estimates: DRd vs Rd

Estimates (range/point)	Submitted	EGP Reanalysis (lower bound)	EGP Reanalysis (Best estimate)	EGP Reanalysis (upper bound)
ΔE (LY)	6.1	5.04	2.12	1.00
Progression-free	3.36	3.27	3.92	3.92
Post-progression	2.75	1.77	-1.80	-2.92
ΔE (QALY)	4.11	3.43	1.65	0.96
Progression-free	2.38	2.32	2.78	2.78
Post-progression	1.72	1.11	-1.13	-1.83
ΔC ($)	$905,935	$904,224	$1,069,617	$1,260,781
ICER estimate ($/QALY)	$220,588	$263,555	$646,455	$1,315,950

Table 2B. Submitted and EGP Estimates: DRd vs VMP

Estimates (range/point)	Submitted	EGP Reanalysis (lower bound)	EGP Reanalysis (Best estimate)	EGP Reanalysis (upper bound)
ΔE (LY)	6.67	5.61	3.33	2.39
Progression-free	3.85	3.75	4.30	4.26
Post-progression	2.83	1.86	-0.97	-1.88
ΔE (QALY)	4.51	3.83	2.45	1.85
Progression-free	2.73	2.66	3.05	3.03
Post-progression	1.78	1.16	-0.60	-1.17
ΔC ($)	$1,025,169	$1,035,344	$1,232,785	$1,493,488
ICER estimate ($/QALY)	$230,210	$270,494	$503,170	$805,431

Table 2C. Submitted and EGP Estimates: DRd vs CyBorD

Estimates (range/point)	Submitted	EGP Reanalysis (lower bound)	EGP Re-analysis (Best estimate)	EGP Reanalysis (upper bound)
ΔE (LY)	6.51	5.61	3.33	2.39
Progression-free	3.85	3.75	4.30	4.26
Post-progression	2.83	1.86	-0.97	-1.88
ΔE (QALY)	4.51	3.83	2.45	1.85
Progression-free	2.73	2.66	3.05	3.03
Post-progression	1.78	1.16	-0.60	-1.17
ΔC ($)	$1,025,169	$1,023,457	$1,220,947	$1,481,659
ICER estimate ($/QALY)	$227,571	$267,388	$498,339	$799,051

The main assumptions and limitations with the submitted economic evaluation were:

The EGP in consultation with the CGP's input raised several concerns with the submitter's economic model. First, the overall survival estimates in the DRd arm of the economic model were deemed to be unlikely to be plausible given the large benefits occurring post-progression. In addition, based on CGP input, there were inconsistencies with post-progression OS benefit as those who progressed in the Rd, VMP, and CyBorD arm would have access to daratumumab combination therapies. The OS benefit associated with these second-line therapies was not considered. Clinicians also highlighted that daratumumab based therapies would be available upon progression for the non-DRd arms of the economic submission and that the selected overall-survival (OS) fits may be underestimating the effectiveness of these subsequent lines of therapy. Another concern was the large estimated time difference between the median duration of treatment and time to progression, which may not be realistic for all interventions in the economic model. Lastly, the gap between progression-free-survival (PFS) and OS in the DRd arm estimated by the model is unlikely to be plausible. The review team attempted to address these concerns in the EGP reanalysis.

Limitations:

- **Lack of direct and indirect comparison of CyBorD with DRd**: There were no randomized control trial studies of CyBorD in the transplant-ineligible NDMM population to source an indirect comparison via the submitter's network meta-analysis. The economic model assumed that CyBorD had the same clinical efficacy of VMP relative to CyBorD. This was based on expert opinion, and two retrospective studies. The CGP did not object to this assumption.
- **Lack of direct comparison of VMP with DRd**: Given the lack of direct comparisons between VMP and DRd, the relative effectiveness of VMP to DRd was sourced from the submitter's network meta-analysis. The model assumed the effectiveness of VMP being relative to Rd. The choice of comparator (either DRd or Rd) to apply a relative effect had large impacts on estimates of VMP and CyBorD clinical-effectiveness.
- **Long-term extrapolation of short-term trial data**: The long-term estimates of PFS and OS for Rd and DRd were extrapolated from the MAIA trial. The MAIA trial had a median follow-up of 28 months and it is used by the economic model to extrapolate outcomes 30 years after diagnosis. The relative immaturity of the MAIA trial data results in large uncertainty on the long-term efficacy of DRd, and Rd.
- **Extrapolation of MAIA trial for survival post-progression**: Estimates of survival post-progression were based on extrapolated data from the MAIA trial data. Given the median

follow-up of 28 months, this is unlikely to accurately capture survival post-progression. The CGP highlighted that this may under-estimate the clinical efficacy of Rd, VMP and CyBorD as patients on these treatments would have access to daratumumab based therapies upon progression.

- **Exclusion of Daratumumab in combination with bortezomib, melphalan, and prednisone (DVMP) as a comparator:** CGP highlighted the relevance of DVMP as a comparator which the economic model did not include. The sponsor provided the reasoning that DVMP is not currently funded in Canada or currently established in clinical practice as the rationale for exclusion. The CGP noted that DVMP is likely to be a relevant comparator in the near future and many patients would be eligible for either DVMP or DRd. The exclusion of DVMP limited the generalizability of the economic model's findings to the Canadian setting.
- **Extrapolation of long-term efficacy outcomes:** The extrapolation of long-term efficacy outcomes for DRd, Rd were based on statistical measures of fit and graphical assessment. The economic submissions extrapolations resulted in long-term estimates of OS, PFS, that were deemed overly optimistic by the CGP.
- **Implementation:** the submitted model was implemented inefficiently and with a long run time that reduced the EGP's ability to fully explore uncertainty around effectiveness, costs, and cost-effectiveness estimates. Running 2,500 iteration analysis on a desktop computer with i5-8400 2.8GHz CPU with 8 GB of RAM took over 9 hours.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the economic model:

The EGP re-conducted several probabilistic scenario analyses modifying the following model parameters:

- **Statistics Canada general population mortality estimates:** The OS extrapolation estimates intersect with that of the general Canadian population. The Statistics Canada mortality hazard of the general population was increased by 49% to more accurately reflect the non-cancer mortality of the NDMM population.
- **Alternative extrapolation curves (OS):** Alternative parametric fitting curves for both the Rd and DRd arm were explored in order to guide the EGP's best estimate and upper bound estimate. The best-fitting curve (exponential) according to Bayesian Information Criterion (BIC) was selected for OS estimates of DRd. This modification resulted in a reduction in post-progression survival benefits in the DRd arm. Clinical input deemed the estimated OS of the exponential distribution to be more likely given the natural history of the disease. Rd, the EGP was considered the best-fitting curve (exponential) according to BIC to guide upper bound estimates. The exponential fit for the Rd resulted in an increase in post-progression survival benefits in the Rd arm.
- **Alternative extrapolation curves (PFS):** DRd, the EGP was considered an alternative parametric curve (Weibull) to model PFS. The Weibull distribution was the second-best fitting curve when judged using BIC. The more optimistic PFS reduced the portion of the effectiveness benefit of DRd that occurred post-progression.
- **Alternative extrapolation curves (TTTD)**: The EGP considered the time from treatment-to-progression to guide upper bound estimates. It considered an alternative parametric extrapolation for TTTD (Weibull) to address estimated gaps between treatment discontinuation and progression. According to BIC, the Weibull distribution was the second best-fitting curve for Rd and DRd respectively.

The EGP made the following changes to the submitted economic model:

Table 3A: Detailed Description of EGP Reanalysis – DRd vs Rd

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$905,935	4.11	6.11	$220,588	-
Lower bound					
Increase in general-population mortality by 49%	$904,224	3.43	5.04	$263,555	$42,967
Best case estimate of the above parameter	$904,224	3.43	5.04	$263,555	$42,967
Upper bound					
Increase in general-population mortality by 49%	$904,224	3.43	5.04	$263,555	$42,967
OS DRd Exponential	$905,812	3.45	5.06	$262,248	$41,660
PFS DRd Weibull	$905,074	4.20	6.11	$215,716	-$4,872
TTTD - Treat to progress	$1,064,565	4.11	6.11	$259,213	$38,625
OS Rd - Exponential	$896,900	1.73	2.33	$519,558	$298,970
Best case estimate of the above five parameters	$1,260,781	0.96	1.00	$1,315,950	$1,095,362
Best case estimate					
Increase in general-population mortality by 49%	$904,224	3.43	5.04	$263,555	$42,967
OS DRd Exponential	$905,812	3.45	5.06	$262,248	$41,660
PFS DRd Weibull	$905,074	4.20	6.11	$215,716	-$4,872
TTTD - Weibull	$1,030,309	4.11	6.11	$250,871	$30,283
Best case estimate of the above four parameters	$1,069,617	1.65	2.12	$646,455	$425,867

Based on 2500 iterations, the EGP's estimate of the ICER of DRd vs Rd is between $263,555/QALY and $1,315,950/QALY, with a best estimate of $646,455/QALY. The EGP noted that the best case estimate did not change with the correction made.

Table 3B: Detailed Description of EGP Reanalysis – DRd vs VMP

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$1,307,055	4.5	6.68	$230,210	-
Lower bound					
Increase in general-population mortality by 49%	$1,035,344	3.83	5.61	$270,494	$40,284
Best case estimate of above parameter	$1,035,344	3.83	5.61	$270,494	$40,284
Upper bound					

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Increase in general-population mortality by 49%	$1,035,344	3.83	5.61	$270,494	$40,284
OS DRd Exponential	$1,036,932	3.85	5.63	$269,198	$38,988
PFS DRd Weibull	$1,036,193	4.59	6.68	$225,574	-$4,636
TTTD - Treat to progression	$1,274,144	4.50	6.68	$282,840	$52,630
OS Rd - Exponential	$1,038,093	2.72	3.88	$381,188	$150,978
Best case estimate of above five parameters	$1,493,488	1.85	2.39	$805,431	$575,221
Best case estimate					
Increase in general-population mortality by 49%	$1,035,344	3.83	5.61	$270,494	$40,284
OS DRd Exponential	$1,036,932	3.85	5.63	$269,198	$38,988
PFS DRd Weibull	$1,036,193	4.59	6.68	$225,574	-$4,636
TTTD - Weibull	$1,175,796	4.50	6.68	$261,009	$30,799
Best case estimate of above four parameters	$1,232,785	2.45	3.33	$503,170	$272,960

Based on 2500 iterations, the EGP's estimate of the ICER of DRd vs VMP is between $270,494/QALY and $805,431/QALY, with a best estimate of $503,170/QALY. The EGP noted that the best case estimate did not change with the correction made.

Table 3C: Detailed Description of EGP Reanalysis - DRd vs CyBorD

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$1,025,168	4.50	6.68	$ 227,571	-
Lower bound					
Increase in general-population mortality by 49%	$1,023,457	3.83	5.61	$267,388	$39,817
Best case estimate of above parameter	$1,023,457	3.83	5.61	$267,388	$39,817
Upper bound					
Increase in general-population mortality by 49%	$1,023,457	3.83	5.61	$267,388	$39,817
OS DRd Exponential	$1,025,045	3.85	5.63	$266,112	$38,541
PFS DRd Weibull	$1,024,307	4.59	6.68	$222,987	-$4,584
TTTD - Treat to progress	$1,262,258	4.50	6.68	$280,202	$52,631
OS Rd - Exponential	$1,026,267	2.72	3.88	$376,846	$149,275
Best case estimate of above five parameters	$1,481,659	1.85	2.39	$799,051	$571,480
Best case estimate					
Increase in general-population mortality by 49%	$1,023,457	3.83	5.61	$267,388	$39,817
OS DRd Exponential	$1,025,045	3.85	5.63	$266,112	$38,541

PFS DRd Weibull	$1,024,307	4.59	6.68	$222,987	-$4,584
TTTD - Weibull	$1,163,910	4.50	6.68	$258,370	$149,275
Best case estimate of above four parameters	$1,220,947	2.45	3.33	$498,339	$270,768

Based on 2,500 iterations, the EGP's estimate of the ICER of DRd vs CyBorD is between $267,388/QALY and $799,051/QALY, with a best estimate of $498,339 /QALY. The EGP noted that the best case estimate did not change with the correction made.

Furthermore, the EGP conducted price reduction scenarios to assess the impact of a change of daratumumab price on the ICER. The sponsor provided feedback on the pERC Initial Recommendation noting that a price reduction of the overall DRd regimen price should be conducted. The sponsor noted that the DRd regimen is driven by the cost of daratumumab and of lenalidomide, highlighting that over the median duration of therapy extrapolated for DRd in the reanalysis, the cost of lenalidomide exceeds that of daratumumab. In response to the sponsor's feedback, the EGP noted that in the price reduction scenarios, the drug acquisition cost of daratumumab was reduced while keeping constant the drug acquisition cost of other drugs and administration costs for the DRd regimen. This approach is consistent with the appraisal of the sponsor's reimbursement request for the submitted product under review. From these analyses, it can be concluded that an ICER around $100,000 QALY could not be achieved even with a price reduction of 95%. The EGP noted that this is most likely due to the high cost of treatment of daratumumab and the inclusion of daratumumab in other regimens (Rd, VMP and CyBorD) in subsequent lines of treatment, which reduces the comparator arm cost.
The limited effect of price reduction on the ICER of daratumumab is caused by the fact that daratumumab is also used as second-line treatment for Rd, VMP, and CyBorD. While a reduction in the price of daratumumab reduces first-line treatment costs for DRd, it also reduces subsequent line treatment for Rd, VMP, and CyBorD. In the PE model, daratumumab is not available for DRd patients at second-line.

1.5 Evaluation of Submitted Budget Impact Analysis

The budget impact analysis (BIA) estimated the overall and net budget impact to Canadian public drug programs of funding DRd for the treatment of ASCT-ineligible NDMM patients via provincial cancer agencies. The two scenarios considered were 1) a listing scenario in which DRd is funded and widely adopted reducing the market share of Rd, CyBorD and VMP and 2) a reference case in which DRd is not funded. The BIA includes Canadian and provincial/territorial summary of results.[2]

The factors that most influence the budget impact analysis include the proportion of ASCT-ineligible patients, the DRd market capture and the generic price of lenalidomide.

Key limitations to the BIA model were the assumed market share of Rd and VMP in the listing scenario. These parameters were modified and explored by the EGP resulting in a 6% over-estimation of the net-budget impact.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for DRd when compared to Rd is:

- Lower bound ΔC = $904,224
- Upper bound ΔC = $1,260,781
- Best estimate ΔC = $1,069,617
- The main factors that influence ΔC are the cost of DRd, the cost of subsequent therapies for Rd, and the extrapolated estimates of PFS and TTTD for both the DRd and Rd arms.

- Lower bound ΔE = 3.43
- Upper bound ΔE = 0.96
- Best estimate ΔE =1.65
- The main factors that influence estimates of ΔE are the long-term extrapolated estimates of OS in the DRd and Rd arms and the predicted general population mortality rates.
- These ranges produced an ICER between $263,555/QALY and $1,315,950/QALY, with a best estimate of $646,455/QALY.
- A price reduction as high as 95% could not achieve an ICUR of around $100,000 per QALY
- The substantial uncertainty in the long-term efficacy estimates of DRd is the main contributor to the wide range between the lower bound and upper bound estimate of the ICER.

The EGP's best estimate of ΔC and ΔE for DRd when compared to VMP is:

- Lower bound ΔC = $1,035,344
- Upper bound ΔC = $1,493,488
- Best estimate ΔC = $1,232,785
- The main factors that influence ΔC are the cost of DRd, the cost of subsequent therapies for VMP patients, and the extrapolated estimates of PFS and TTTD for DRd and VMP.
- Lower bound ΔE = 3.83
- Upper bound ΔE = 1.85
- Best estimate ΔE =2.45
- The main factors that influence estimates of ΔE are the long-term extrapolated estimates of OS in the DRd and VMP arms and the predicted general population mortality rates.
- These ranges produced an ICER between $270,494/QALY and $805,431/QALY, with a best estimate of $503,170/QALY.
- A price reduction as high as 95% could not achieve an ICUR of around $100,000 per QALY
- The substantial uncertainty in the long-term efficacy estimates of DRd is the main contributor to the wide range between the lower bound and upper bound estimate of the ICER.

The EGP's best estimate of ΔC and ΔE for DRd when compared to CyBorD is:

- Lower bound ΔC = $1,023,457
- Upper bound ΔC = $1,481,659
- Best estimate ΔC = $1,220,947
- The main factors that influence ΔC are the cost of DRd, the cost of subsequent therapies for CyBorD patients, and the extrapolated estimates of PFS and TTTD for DRd and CyBorD.
- Lower bound ΔE = 3.83
- Upper bound ΔE = 1.85
- Best estimate ΔE =2.45
- The main factors that influence estimates of ΔE are the long-term extrapolated estimates of OS in the DRd and CyBorD arms and the predicted general population mortality rates.
- These ranges produced an ICER between $267,388/QALY and $799,051/QALY, with a best estimate of $498,339/QALY.
- A price reduction as high as 95% could not achieve an ICUR of around $100,000 per QALYThe substantial uncertainty in the long-term efficacy estimates of DRd is the main contributor to the wide range between the lower bound and upper bound estimate of the ICER.

Overall conclusions of the submitted model:

The economic model structure and methods employed are appropriate. The data inputs for the clinical effectiveness of DRd and Rd were sourced from a trial with a relatively short follow up. This generated substantial uncertainty in the assessment of the longer term clinical effectiveness of DRd and Rd. The data to inform the effectiveness of VMP was sourced from a network meta-analysis rather than a direct comparison. There was no data to inform a direct or indirect comparison of CyBorD to DRd; the effectiveness of CyBorD was assumed to be the same as VMP.

The limited follow-up of the MAIA and the large uncertainty surrounding long-term efficacy of DRd and Rd limited the EGP's ability to provide a narrow range of ICERs.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Myeloma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of daratumumab (Darzalex) in combination with lenalidomide + dexamethasone for newly diagnoses multiple myeloma. A full assessment of the clinical evidence of [drug name and indication] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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