CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Daratumumab (Darzalex) for Multiple Myeloma

October 5, 2017

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Janssen** compared daratumumab as a combination therapy (daratumumab with lenalidomide and dexamethasone (DRd) or daratumumab with bortezomib and dexamethasone (DVd) to standard of care for patients with relapsed or refractory multiple myeloma (RRMM) who have received at least one prior therapy.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Adults with RRMM who received at least one prior line of therapy, matching the two clinical trials (MMY3003 & MMY3004).
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned-survival.*
Comparator	*Standard of care based on Ontario reimbursement criteria that includes lenalidomide plus dexamethasone (Rd) or bortezomib plus dexamethasone (Vd).* *Patients previously treated with bortezomib was a subgroup of interest, and was considered in a scenario analysis.* *Following a request from pCODR, the submitter provided a network-metaanalysis to compare daratumumab to carfilzomib-based regimens.*
Year of costs	*2016*
Time Horizon	*30 years*
Perspective	*Canadian publicly funded health care system*
Treatment Regimens for Daratumumab	Daratumumab + Lenalidomide + Dexamethasone <u>Daratumumab</u> 16 mg/kg IV weekly (days 1, 8, 15, 22) for 8 weeks during cycles 1-2, q2wks (on days 1 and 15) for 16wks (cycles 3-6, and q4wks thereafter <u>Lenalidomide</u> 25mg orally on days 1-21 of each cycle if the creatinine clearance was >60mL/min (or a dose of 10mg daily if the creatinine clearance was 30-60mL/min) <u>Dexamethasone[2]</u> 40mg weekly split dose: 20mg prior to infusion as prophylaxis for IRR and 20mg the next day

	Daratumumab + Bortezomib + Dexamethasone Daratumumab 16 mg/kg IV weekly (days 1, 8, 15) during cycles 1-3, once q3wks (on day 1) during cycles 4-8, and once q4wks thereafter, until patient withdrawal, disease progression, or unacceptable toxicity Bortezomib 1.3 mg/m^2 SC on days 1, 4, 8, 11 of cycles 1-8 Dexamethasone[1] 20mg orally or IV on days 1,2,4,5 8,9,11,12 for a total dose of 160mg/cycle
Cost in Daratumumab + Lenalidomide + Dexamethasone Regimen Cost in Daratumumab + Bortezomib + Dexamethasone Regimen	$598.02 per 100mg vial and $2392.08 per 400mg vial ($5.9802/mg) POLLUX Trial: At the recommended dose of 16 mg/kg IV weekly (days 1, 8, 15, 22) for 8 weeks during cycles 1-2, q2wks (on days 1 and 15) for 16wks (cycles 3-6, and q4wks thereafter, daratumumab in the dar+len+dex regimen costs: Cycles 1 & 2 • Per day: $956.832 • Per 28-day course: $26 791.296 Cycles 3-6 • Per day: $478.416 • Per 28-day course: $13 395.648 Cycles Thereafter • Per day: $239.208 • Per 28-day course: $6697.824 CASTOR Trial: At the recommended dose of 16 mg/kg IV weekly (days 1, 8, 15) during cycles 1-3, once q3wks (on day 1) during cycles 4-8, and once q4wks thereafter, daratumumab in the dar+bor+dex regimen costs: Cycles 1-3 • Per day: $956.932 • Per 28-day course: $26 791.296 Cycles 4 -8 • Per day: $318.944 • Per 28-day course: $8930.430

	Cycles Thereafter • Per day: $239.208 • Per 28-day course: $6697.824
Cost of Lenalidomide	$ 424.00 per 25mg tablet Per day: $318.00 Per 28-day course: $8904.00
Cost of Bortezomib	$1402.42 per 3.5 mg vial Per day: $168.6720 Per 28-day course: $4,722.8160
Cost of Dexamethasone	$ 0.3046 per 4 mg tablet Per day: $0.4351 Per 28-day course: $12.1840
Cost of carfilzomib	$1,533.33 per single-use vial of 60 mg • 10-minute infusion on days 1, 2, 8, 9, 15, and 16 (starting dose, 20 mg/m2 on days 1 and 2 of cycle 1; target dose, 27 mg/m2 thereafter) during cycles 1 through 12 and on days 1, 2, 15, and 16 during cycles 13 through 18, after which carfilzomib was discontinued Cycle 1 • $ 229.63 per day and $6429.76 per 28 days (no wastage) Cycle 2-12 • $251.36 per day and $7037.98 per 28 days (no wastage) Cycle 13-18 • $167.57 per day and $4691.99 per 28 days (no wastage)
Model Structure	*A three-state model was used to follow patients from second-line treatment to death. Health states modeled are pre-progression (both on and off treatment), post-progression from initial therapy in economic model (both on and off treatment) and death.*
Key Data Sources	*POLLUX (MMY3003): DRd* *CASTOR (MMY3004): DVd* *Network meta-analysis performed by submitter at the request of pCODR*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is one of many appropriate comparators for this patient population.

- Relevant issues identified included:
    - There is net clinical benefit derived from the addition of daratumumab to standard therapy for patients with relapsed or refractory multiple myeloma. This is based on the results of two well-conducted randomized, non-blinded studies demonstrating clinically and statistically significant improvements in progression-free and overall survival.
    - Daratumumab does not substantially increase toxicity, which is a high priority for patients with this disease.
    - There are methodological concerns raised in the network meta-analysis that limit the conclusions that can be drawn from that assessment.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered the comparators included in the submitted base case (lenalidomide and bortezomib) as current standard of care. Clinicians considered that the patient population that will be eligible for either daratumumab plus lenalidomide plus dexamethasone or daratumumab plus bortezomib plus dexamethasone to range from 5% to 90%. Registered clinicians supported the low toxicity of daratumumab and improvements in survival. The majority of these factors were incorporated into the EGR. The relative impact of each regimen was not considered, as two separate economic models were submitted.

Summary of patient input relevant to the economic analysis
Patients considered the expectation of treatment to prolong their lives, disease control and fewer side effects as important factors relevant to the treatment under review. The administration of daratumumab was also considered an important factor. These factors were considered in the economic model, though the societal impact of the administration time of daratumumab is not included as the submitted economic model is from the perspective of the government payer.

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 daratumumab which are relevant to the economic analysis:

- Drug wastage. There was the assumption of vial sharing the base case. Vial sharing may be difficult in smaller centres.
- Unknown and variable treatment duration, as daratumumab is continued until progression. This is a barrier to implementation as planning resources to deliver and fund the drug is unknown.
- The incorporation of daratumumab triplet regimens into clinical practice.
- The high cost of daratumumab, as an add-on therapy, is a barrier to implementation.
- The dosing of daratumumab may prove difficult for patients that need to travel far to and from cancer centres. It should be noted that the administration schedule for daratumumab plus lenalidomide is different than for daratumumab plus bortezomib.

1.3 Submitted and EGP Reanalysis Estimates

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

- The duration of treatment effect is unknown, though unlikely to remain for the entire time horizon. This parameter had a significant impact on results.
- *Though the funding request is similar, there are two economic models, with two distinct populations. The submitter stated that they could not pool these populations due to differences in the clinical trial populations (MMY3003 & MMY3004). In clinical reality however, the two regimens under consideration for funding would be funded for these population in proportions that are not all or nothing. Not assessing the relative contribution of each of these regimens to the population under consideration is a limitation.*
- *The modeling of overall survival and the resulting shape of the overall survival curve does not reflect clinical reality.*
- *There are relatively large gains in the post-progression health state, including large incremental gains between the treatments under consideration. Incremental gains in the post-progression state do not reflect clinical practice.*
- *The mediation duration of follow-up in the two clinical trials is relatively short compared to the extrapolation to the time horizon of 30 years. Accepting the extrapolation in the economic model assumes that the RCT data is sufficiently representative for long-term extrapolation.*
- *The network meta-analysis provided by the submitter at the request of pCODR does not explicitly state that effect modifiers were adjusted for between patient populations considered in each treatment network (Rd of Vd-based). Due to the lack of adjustment and the potential for significant bias in the results, the results of the network meta-analysis were not considered for reanalysis of the comparators of KRd or Kd.*

1.4 Detailed Highlights of the EGP Reanalysis

A. DRd vs Rd

Table 2. Submitted and EGP Reanalysis Estimates for DRd vs Rd

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	3.67	4.65	0.85
Progression-free	2.38	2.89	1.42
Post-progression	1.29	1.75	-0.57
ΔE (QALY)	2.97	3.76	0.71
Progression-free	1.96	2.38	1.16
Post-progression	1.02	1.39	-0.45
ΔC ($)	$539,113	$622,746	$422,874
ICER estimate ($/QALY)	$181,212	$165,496	$594,144

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

- Time horizon: 20 years. The submitted time horizon of 30 years does not align with clinical plausibility of patients with relapsed or refractory multiple myeloma or with previous submissions. When examining the overall survival of the submitted base case, it is unlikely that 4.7% of the population would still be alive at 30 years, given age at

diagnosis and other clinical factors. The EGP aligned this review with other reviews in relapsed/refractor MM and chose a time horizon of 20 years.

- Discounting: In order to align with the recently published guidelines of CADTH, the EGP used 1.5% to discount both costs and effects.
- Treatment effect: Median duration of follow-up was 17.3 months, however in the submitted base case, the duration of treatment effect is prolonged throughout the model. In order to explore the uncertainty of duration of extrapolating short-term data over the period of a lifetime of a patient, treatment effect was truncated at 4 years to explore a clinically defensible upper bound. The CGP confirmed that there is little likelihood that beyond progression on daratumumab, the sustained treatment effect would impact overall survival until 179 months. However, in the absence of data, the EGP is unable to confirm when the duration of treatment effect would cease. **Figure 17** demonstrates the effect on overall survival of truncating the treatment effect at 4 years.

Table 3. EGP Reanalysis Estimates for DRd vs Rd

	ΔC	ΔE QALYs	**ICUR (QALY)**	
Baseline	$539,113	2.98	**$181,212**	-----
EGP's Reanalysis for the Best Case Estimate – Lower Bound				
Description of Reanalysis	ΔC	ΔE QALYs	**ICUR (QALY)**	Δ from baseline submitted ICER
Time horizon – 20 years	$535,212	2.78	**$192,555**	$11,343
Discount rates of costs and effects: 1.5%	$631,332	4.20	**$150,311**	-$30,901
Lower bound best case estimate – modification of all above parameters	$622,746	3.76	**$165,496**	
EGP's Reanalysis for the Best Case Estimate – Upper Bound				
Time horizon – 20 years	$535,212	2.78	**$192,555**	$11,343
Discount rates of costs and effects: 1.5%	$631,332	4.20	**$150,311**	-$30,901
Duration of treatment effect – 4 years	$391,518	0.63	**$623,955**	$442,743
Upper bound best case estimate – modification of all above parameters	$422,874	0.71	**$594,144**	$412,932

B. DVd vs Vd

Table 4. Submitted and EGP Reanalysis Estimates for DVd vs Vd

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	1.76	2.81	1.13
Progression-free	1.19	1.31	1.08
Post-progression	0.56	0.88	0.05
ΔE (QALY)	1.38	1.72	0.91
Progression-free	0.96	1.06	0.88

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
Post-progression	0.06	0.66	0.04
ΔC ($)	$178,779	$189,690	$178,583
ICER estimate ($/QALY)	$128,839	$110,273	$195,399

The EGP made the following changes to the economic model:

- Time horizon: 20 years. The submitted time horizon of 30 years does not align with clinical plausibility of patients with relapsed or refractory multiple myeloma or with previous submissions. When examining the overall survival of the submitted base case, it is unlikely that 4.7% of the population would still be alive at 30 years, given age at diagnosis and other clinical factors. The EGP aligned this review with other reviews in relapsed/refractor MM and chose a time horizon of 20 years.
- Discounting: In order to align with the recently published guidelines of CADTH, the EGP used 1.5% to discount both costs and effects.
- Treatment effect: Median duration of follow-up was 13.3 months, however in the submitted base case, the duration of treatment effect is prolonged throughout the model. In order to explore the uncertainty of duration of extrapolating short-term data over the period of a lifetime of a patient, treatment effect was truncated at 4 years to explore a clinically defensible upper bound. The CGP confirmed that there is little likelihood that beyond progression on daratumumab, the sustained treatment effect would impact overall survival until 179 months. However, in the absence of data, the EGP is unable to confirm when the duration of treatment effect would cease. **Figure 17** demonstrates the effect on overall survival of truncating the treatment effect at 4 years.

Table 5. EGP Reanalysis Estimates for DVd vs Vd

	ΔC	ΔE QALYs	**ICUR (QALY)**	
Baseline	$178,779	1.39 QALYs	**$128,839**	-----
EGP's Reanalysis for the Best Case Estimate – Lower Bound				
Description of Reanalysis	ΔC	ΔE QALYs	**ICUR (QALY)**	Δ from baseline submitted ICER
Time horizon – 20 years	$178,482	1.33	**$134,592**	$6,113
Discount rates of costs and effects: 1.5%	$190,351	1.86	**$102,493**	$-26,346
Lower bound best case estimate – modification of all above parameters	$189,690	1.72	**$110,273**	-$18,566
EGP's Reanalysis for the Best Case Estimate – Upper Bound				
Time horizon – 20 years	$178,482	1.33	**$134,592**	$6,113
Discount rates of costs and effects: 1.5%	$190,351	1.86	**$102,493**	$-26,346
Duration of treatment effect – 4 years	$170,459	0.77	**$219,950**	$91,111
Upper bound best case estimate – modification of all above parameters	$178,583	0.91	**$195,399**	$66,560

C. Daratumumab, Lenalidomide & dexamethasone (DRd) vs Carfilzomib, Lenalidomide, & Dexamethasone (Krd)

The network meta-analysis was conducted without adjusting for any treatment effect modifiers between the patient populations included. This lack of adjustment renders it difficult to conclude on the results. Therefore, due to this uncertainty within the NMA, the EGP is unable to present reanalysis estimates for DRd vs KRd.

D. Daratumumab, Bortezomib, & Dexamethasone (DVd) vs Carfilzomib & Dexamethasone (Kd)

The network meta-analysis was conducted without adjusting for any treatment effect modifiers between the patient populations included. This lack of adjustment renders it difficult to conclude on the results. Therefore, due to this uncertainty within the NMA, the EGP is unable to present reanalysis estimates for DVd vs Kd.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis for the Rd-market include:

- *The percent of MM patients who require at least 1 prior therapy.*
- *The market share of daratumumab.*
- *The average annual growth of patient population.*

The factors that most influence the budget impact analysis for the Vd-market include:

- *The percent of MM patients who require at least 1 prior therapy.*
- *The market share of daratumumab.*
- *The average annual growth of patient population.*

Key limitations of the BIA model include the lack of consideration of the impact of both regimens being approved in a given market.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for daratumumab plus lenalidomide plus dexamethasone when compared to lenalidomide plus dexamethasone is:

- Between $165,496/QALY and $594,144/ QALY
- Within this range, the best estimate depends on the duration of the treatment effect. If you believe the duration of the treatment effect is around 4 years, the best estimate would be near the upper bound. If you believe the duration of the treatment effect is longer, the best estimate is towards the lower bound.
- The extra cost of daratumumab plus lenalidomide and dexamethasone (in the Rd network) is between $422,874 and $622,746 (ΔC). *The factors that most influence ΔC include the truncation of treatment effect, treatment duration and the cost of daratumumab.*
- The extra clinical effect of daratumumab (in the Rd network) is between 0.71 and 3.76 (ΔE). *The factors that most influence ΔE include the time horizon and the truncation of the treatment effect.*

The EGP's best estimate of ΔC and ΔE for daratumumab plus bortezomib plus dexamethasone when compared to bortezomib plusl dexamethasone is:

- Between $110,273/QALY and $195,399/QALY
- Within this range, the best estimate depends on the duration of treatment effect. If you believe the duration of the treatment effect is around 4 years, the best estimate would be near the upper bound. If you believe the duration of the treatment effect is longer, the best estimate is towards the lower bound.
- The extra cost of daratumumab (in the Vd network) is between $178,583 andn $189,690. *The main factors that influence ΔC include the inclusion of patients previous treated with bortezomib, the truncation of the treatment effect and treatment duration.*
- The extra clinical effect of daratumumab (in the Vd network) is between 0.91 and 1.72 (ΔE). *The main factors that influence ΔE include the inclusion of patients previously treated with bortezomib and the truncation of the treatment effect.*

The EGP was unable to provide a best estimate for Daratumumab, Lenalidomide & dexamethasone (DRd) vs Carfilzomib, Lenalidomide, & Dexamethasone (Krd)

The EGP was unable to provide a best estimate for Daratumumab, Bortezomib, & Dexamethasone (DVd) vs Carfilzomib & Dexamethasone (Kd.)

Overall conclusions of the submitted model:

- *The submitted model structure was adequate, though unconventional, given the modeling of the constant mortality rate from PFS.*
- *It is difficult to estimate the overall ICER for this patient population given the two separate models for the two separate treatment regimens. In clinical reality, each treatment regimen would contribute to a proportion of the eligible population.*
- *As daratumumab is part of a triplet regimen, changing the price of any of the agents used in combination with daratumumab would impact the ICER. For example, a reduction in price of lenalidomide would decrease the ICER.*
- *The network meta-analysis is of low quality and given the large uncertainty in the results, was not able to be used to conduct reanalysis of the submitted models (DRd vs KRd and DVd vs Kd).*

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 Lymphoma & 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) for 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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