CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Daratumumab (Darzalex)+VMP for Multiple Myeloma

August 29, 2019

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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.
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1 ECONOMIC GUIDANCE IN BRIEF

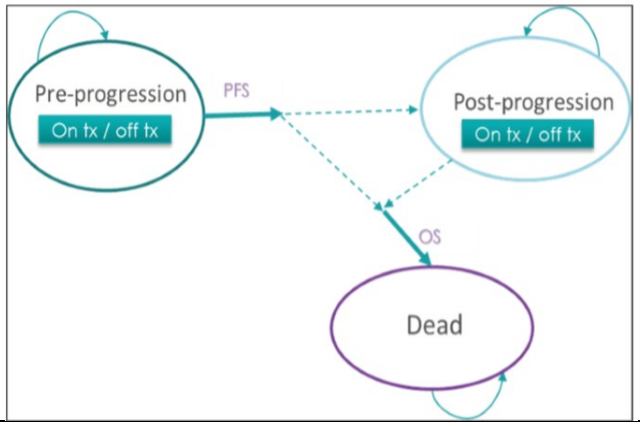
1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Janssen Inc. compared daratumumab in combination with bortezomib, melphalan and prednisone (DVMP) to bortezomib, melphalan and prednisone without daratumumab (VMP),for the treatment of patients with newly diagnosed multiple myeloma (NDMM) who are not suitable for autologous stem cell transplantation. The analysis also compared DVMP to lenalidomide and dexamethasone (Rd), and DVMP to cyclophosphamide, bortezomib, and dexamethasone (CyBorD). This matches the submitter's funding request.

Table 1. Submitted Economic Model Summary

Funding Request/Patient Population Modelled	Daratumumab in combination with VMP for the treatment of NDMM in patients who are ineligible for autologous stem-cell transplant (ASCT)
Type of Analysis	*Cost utility analysis (CUA) and Cost-effectiveness Analysis (CEA)*
Type of Model	*Partitioned-survival model*
Comparator	*Base case: VMP* *Additional comparators:* • *Cyclophosphamide+bortezomib+dexamethasone (CyborD)* • *Lenalidomide+dexamethasone (Rd)*
Year of costs	• *2018 Canadian dollars*
Time Horizon	*30 years (Lifetime)*
Perspective	*Canadian publicly-funded health system*
Cost of Daratumumab + VMP	DVMP Cost breakdown • Daratumumab costs $598.02 per 100 mg vial and 2,392.08 per 400mg vial • Bortezomib costs $1402.42 per 3.5mg vial • Melphalan costs $1.7372 per unit (50 unit pack, 2mg per unit) = $86.86 per pack • Prednisone costs $0.1735 per unit (100 unit pack, 50mg per unit) = $17.35 per pack, or $0.0220 per unit (100 unit pack, 5mg per unit)=$2.20 per pack 42-day cycle cost: • 1st 42-day cycle, total drug cost of DVMP is $43,939 • 2nd to 9th 42-day cycle, total drug cost of DVMP is $16,640 per cycle • 10th cycle until progression, average total drug cost of between $6,828 (1 daratumumab infusion), and $13,656 (2 daratumumab infusions) per 42-day cycle Calculated 28-day cycle cost • In first 42-day cycle average total cost of DVMP is $29,292.70 per 28-days

	• 2nd to 9th 42-day cycle, average total cost of DVMP is $11,093.40 per 28-day cycle • 10th cycle until progression, total drug cost of DVMP is $6,828 per 28-day cycle (one daratumumab infusion per 4-week period [28-days]) •
Cost of Comparators	VMP Cost breakdown: • Bortezomib costs $1402.42 per 3.5mg vial • Melphalan costs $1.7372 per unit (50 unit pack, 2mg per unit) = $86.86 per pack • Prednisone costs $0.1735 per unit (100 unit pack, 50mg per unit) = $17.35 per pack, or $0.0220 per unit (100 unit pack, 5mg per unit)=$2.20 per pack 42-day cycle cost: • 1st 42 day cycle, total drug cost of VMP is $7,031 • 2nd to 9th 42 day cycle, total drug cost of VMP is $3,278 per cycle • 9th+ cycle until progression, total drug cost of VMP is $0 per cycle* Calculated 28-day cycle cost: • In first 42-day cycle, average total drug cost of VMP is $4,687.66 per 28-days • 2nd to 9th cycle, average total drug cost of VMP is $2,185.07 • 9th cycle until progression, average total drug cost of VMP is $0 per 28-days* CyBorD Cost breakdown: • Bortezomib costs $1402.42 per 3.5mg vial • Cyclophosphamide costs $0.4740 per unit (100 unit pack, 50mg per unit) • Dexamethasone costs $0.3046 per unit (100 unit pack, 4mg per unit) • Per 28 day cycle, at the doses included in the model, CyBorD costs $4,055 Rd Cost breakdown: • Lenalidomide costs $424.00 per unit (21 unit pack, 25mg per unit) • Dexamethasone costs $0.3046 per unit (100 unit pack, 4mg per unit) • Per 28-day cycle at the doses included in the model, Rd costs $8,916

	*VMP was given up to 9 cycles in DVMP and VMP regimens, therefore the cost of VMP beyond 9 cycles is $0
Model Structure	*The partitioned-survival model was comprised of 3 health states (alive pre-progression, alive post-progression, and dead), and a cycle length of one week was used. It was assumed that any survival benefit could be extrapolated beyond the follow-up period and be adequately captured using parametric survival models. Expected (mean) values for costs and effects were obtained from probabilistic analysis.* 
Key Data Sources	*The ALCYONE trial was used for efficacy and safety data for the comparison of DVMP with VMP. The model assumed that efficacy for CyBorD was the same as the efficacy for VMP in the ALCYONE trial. PFS for Rd was based on the FIRST trial and OS was based on a network meta-analysis. Safety outcomes were based on published trials for these regimens. Utility values used in the base case were derived from an analysis of EQ-5D-5L data from ALCYONE during the pre- and post-progression periods.*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison (DVMP vs VMP) is appropriate but VMP is less commonly used in Canada. The Clinical Guidance Panel considered that DVMP vs Rd or DVMP vs CyBorD may be a more clinically relevant comparator. The submitter did include these comparisons in the main economic analysis.

- Relevant issues identified included:
    - There is a net clinical benefit derived from the addition of daratumumab to the standard of care control group for newly diagnosed non-transplant eligible patients with multiple myeloma. This is based on a well-conducted sufficiently powered trial with no significant identifiable methodological weaknesses that clearly shows a 50% reduction in risk of progression or death.
    - The toxicity profile of the daratumumab arm was similar to the control arm with the exception of a 25% increase in infusion reactions (grade 3-4 infusion reactions occurred in 5% of patients in the daratumumab group) and an increase in infections and pneumonia

- 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

The clinicians providing input reported an unmet need in transplant ineligible multiple myeloma patients to improve the initial therapy and PFS, and that daratumumab in combination with VMP would be useful for patients if made available. However, based on the 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.

The review team noted the feedback on pERC's initial recommendation from the registered clinician that red cell typing will need to be considered if daratumumab + VMP is to be implemented. The EGP noted that the cost of red cell typing was not included in the model, however, it was noted by the CGP that the cost would not likely be significant. The CGP also agreed that red cell typing was a logistical consideration and that it is currently being done, given the approvals for daratumumab in the relapsed setting.

Summary of patient input relevant to the economic analysis
None of the patients recruited for patient input had received DVMP. Patients recruited either had experience with VMP or CyBorD as first-line treatment.

The submitted economic model did consider three factors that were important and relevant to patients: survival, quality of life and adverse events.

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 + VMP which are relevant to the economic analysis:

- Drug wastage: PAG has concerns that there would be incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult. Wastage was not included in the submitter's base case model.
- Additional resources are needed to monitor for infusion reaction: PAG has concerns that additional resources will be required for pre-medication, drug preparation, administration time and monitoring for multiple severe adverse effects including infusion reactions. The model included an associated inpatient hospital cost.
- Unknown and variable treatment duration: As treatment may be continued until progression, the unknown duration of treatment is a barrier to implementation and to plan the resources needed to deliver and fund the drug. The submitter's model allowed the user to select from different options for the treatment duration assumption including "treat to progression".
- The dosing of daratumumab may prove difficult for patients that need to travel long distances to and from cancer centres.

1.3 Submitted and EGP Reanalysis Estimates

According to the economic analysis that was submitted by Janssen Inc, when:

DVMP vs VMP:

- The extra cost of DVMP is $564,674 (ΔC). Costs considered in the analysis included drugs, disease management, and adverse events.

- The extra clinical effect of DVMP is 3.89 quality-adjusted life years and 5.36 life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, incidence of adverse events, and utilities.
- The submitter estimated that the incremental cost-effectiveness ratio was $145,207 per QALY over a 30-year time horizon.

DVMP vs Rd:

- The extra cost of DVMP is $494,197 (ΔC). Costs considered in the analysis included drugs, disease management, and adverse events.
- The extra clinical effect of DVMP is 3.18 quality-adjusted life years and 4.41 life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, incidence of adverse events, and utilities.
- The submitter estimated that the incremental cost-effectiveness ratio was $155,180 per QALY over a 30-year time horizon.

DVMP vs CyBorD:

- The extra cost of DVMP is $560,646 (ΔC). Costs considered in the analysis included drugs, disease management, and adverse events.
- The extra clinical effect of DVMP is 3.89 quality-adjusted life years and 5.36 life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, incidence of adverse events, and utilities.
- The submitter estimated that the incremental cost-effectiveness ratio was $144,171 per QALY over a 30-year time horizon.

The EGP used the model submitted by Janssen Inc and performed reanalyses. Detailed tables reporting the results of the EGP Reanalysis are provided in Section 1.4. The EGP estimates differed from the submitted estimates. Comparison between the submitted model and EGP reanalysis results was provided in **Table 2**.

Table 2A. Submitted and EGP Estimates: DVMP vs VMP

Estimates (range/point)	Submitted	EGP Reanalysis (Lower bound)	EGP Reanalysis (Upper bound)
ΔE (LY)	5.36	2.14	0.92
Progression-free	5.20	2.70	2.70
Post-progression	0.16	-0.56	-1.78
ΔE (QALY)	3.89	1.56	0.71
Progression-free	3.78	1.96	1.96
Post-progression	0.12	-0.39	-1.25
ΔC ($)	$564,674.72	$267,309.73	$274,785.05
ICER estimate ($/QALY)	$145,207.02	$170,859.48	$389,092.12

Table 2B. Submitted and EGP Estimates: DVMP vs CyBorD

Estimates (range/point)	Submitted	EGP Reanalysis (Lower bound)*
ΔE (LY)	5.36	2.14
Progression-free	5.2	2.70
Post-progression	0.16	-0.56

ΔE (QALY)	3.89	1.56
Progression-free	3.78	1.96
Post-progression	0.12	-0.39
ΔC ($)	$560,646.29	$269,397.84
ICER estimate ($/QALY)	$144,171.36	$172,194.16

*Note: Unable to estimate upper bound due to uncertainty.

Table 2C. Submitted and EGP Estimates: DVMP vs Rd

Estimates (range/point)	Submitted	EGP Reanalysis (Lower bound)*
ΔE (LY)	4.41	1.33
Progression-free	3.67	1.36
Post-progression	0.74	-0.03
ΔE (QALY)	3.18	0.97
Progression-free	2.66	0.98
Post-progression	0.53	-0.02
ΔC ($)	$494,197.35	$235,273.89
ICER estimate ($/QALY)	$155,180.08	$243,804.19

*Note: Unable to estimate upper bound due to uncertainty.

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

- Lack of direct comparative effectiveness estimates for some clinically relevant comparators: There were no head-to-head clinical trials comparing DVMP to CyBorD or DVMP to Rd included in this review. The submitted economic model made the following assumptions:
    - **Efficacy of CyBorD** – Direct evidence was not available; therefore, efficacy of CyBorD was assumed to be equivalent to that of VMP. This was based on expert opinion and a recent publication by the Myeloma Canada Research Network comparing bortezomib-containing regimens for the treatment of ASCT-ineligible patients in a real-world Canadian setting. The CGP felt that although VMP and CyBorD are different drug combinations and have different dosing, their clinical efficacy is similar.
    - **Efficacy of Rd** – Direct evidence was not available. Therefore PFS for Rd was extrapolated directly from the FIRST trial, a phase III trial comparing Rd with melphalan, prednisone and thalidomide (MPT) in ASCT-ineligible patients with NDMM. The submitter noted that while an indirect treatment comparison was possible for Rd and DVMP, the method for extrapolating long-term PFS for DVMP resulted in an inflection point and it would not be appropriate to do the same for Rd when applying the hazard ratio. OS for Rd was estimated using network meta-analysis (NMA) which was considered appropriate by the submitter because an inflection point was not observed. TTTD for Rd was estimated based on median treatment duration in FIRST.
    - The uncertainty generated from the CyBorD efficacy assumption (i.e. efficacy equivalent to VMP, hazard ratio = 1) was not incorporated in the economic model, therefore there remains considerable uncertainty in relative efficacy between DVMP versus CyBorD.
- **Extrapolation of overall survival using short term data** - The median follow-up in the ALCYONE trial was relatively short (median follow-up of 27.8 months), with insufficient long term follow up. Thus, the overall survival data are immature.
- **Extrapolation of efficacy data** - The median follow-up in the ALCYONE trial was relatively short (median follow-up of 27.9 months). Extrapolation of PFS, OS and treatment duration was estimated using Kaplan-Meier data, parametric distributions or a combination of both for 30 years. Accepting the extrapolation in the economic model assumes that the RCT data are sufficiently representative for long-term extrapolation.

- **Subsequent therapies** - The subsequent therapies accounted for in the model and the proportion of patients receiving each therapy were based on clinician input and may not reflect current clinical practice Figure 12 shows the proportion of patients receiving subsequent therapies in the submitter's model, and Table 10 shows the proportions based on input from the CGP.
- **Dosing** - The doses used in the ALCYONE trial for DVMP and VMP may not reflect what is used in real-world Canadian clinical practice. In addition, the dose of Rd and CyBorD used in the model may not represent most clinical practices in Canada.
- **Utilities** - Quality-of-life data were collected in the ALCYONE trial, however, most patients contributing to the post-progression utility were likely in post-progression for a relatively short time and had not yet proceeded to third or later lines of therapy. Therefore, the post-progression utility may not accurately reflect patients in real life.
- Inefficient implementation – The submitted model was implemented inefficiently. Running a 1,000 iterations analysis on a desktop equipped with i7 CPU@ 3.60GhZ with 16GB memory took over 4 hours. This greatly limited EGP ability to investigate all the uncertainty associated with the model.
- **Wastage** - The submitted model assumed vial sharing and therefore wastage was not included.

1.4 Detailed Highlights of the EGP Reanalysis

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

The EGP re-conducted several probabilistic scenario analyses. The EGP considered the following important factors after consulting with the CGP:

- **Time horizon**: The time horizon was shortened to 10 years from the 30 years that was used in the submitter's base case. The time horizon was shortened to address the uncertainty in survival estimates based on extrapolation of short-term trial data (27.8 months) and to reflect the clinical opinion of the CGP.
- **Subsequent therapies**: The subsequent therapies accounted for in the model and the proportion of patients receiving each therapy were modified (See Table 10) to reflect the clinical opinion of the CGP.
- **Cost of bortezomib:** The EGP felt that the cost of bortezomib accounted for in the model was overestimated. A 50% reduction in the cost of bortezomib was used in the reanalysis.
- **Extrapolation options:** Alternative parametric fitting curves were explored by the EGP for both DVMP and VMP arms to guide the derivation of the upper bound estimates. The second-best fitting parametric curve for VMP overall survival (Exponential) was selected based on reported AIC and BIC by EGP after consultation with CGP. The alternate curve choice demonstrated better overall survival than the best-fitting curve (Gompertz) for VMP, therefore leading to a smaller difference in effectiveness between DVMP and VMP than with the submitter's model.
- **Wastage:** Wastage was not included in the submitter's base case model and it was assumed that vial sharing occurred. The EGP felt that a more appropriate assumption would be to include wastage in the reanalysis.

Summary Tables – EGP Reanalysis

Based on 1,000 iterations, the EGP's best estimate of the ICER of DVMP vs VMP is between a lower bound of $170,859/QALY and upper bound of $389,092/QALY. See Table 3A.

Table 3A. Detailed Description of EGP Reanalysis: DVMP vs VMP

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$564,674.72	3.89 QALYs	5.36 LYs	$145,207	--
[LOWER BOUND]					
Time horizon – 10 years	$289,017	1.56	2.14	$184,734	$39,527
Subsequent therapies – Table 10	$516,320	3.89	5.36	$132,815	-$12,392
Cost of bortezomib (50% of price)	$557,803	3.89	5.36	$143,489	-$1,718
Wastage	$588,455	3.89	5.36	151,376	$6,169
Best case estimate of above 4 parameters	$267,310	1.56 QALYs	2.14 LYs	$170,859	$25,652
[UPPER BOUND]					
Time horizon – 10 years	$289,017	1.56	2.14	$184,734	$39,527
Subsequent therapies – Table 10	$516,320	3.89	5.36	$132,815	-$12,392
Cost of bortezomib (50% of price)	$557,803	3.89	5.36	$143,489	-$1,718
Alternative parametric fitting VMP OS curves - Exponential	$558,379	1.79	2.38	$311,436	$166,228
Wastage	$588,455	3.89	5.36	$151,376	$6,169
Best case estimate of above 5 parameters	$274,785	0.71 QALYs	0.92 LYs	$389,092	$243,885

Based on 1,000 iterations, the EGP's best estimate of the ICER of DVMP vs CyBorD is between a lower bound of $172,194/QALY and upper bound of unknown. Due to the uncertainty generated from the CyBorD efficacy assumption, EGP was not able to estimate the upper bound of the ICER. See Table 3B.

Table 3B. Detailed Description of EGP Reanalysis: DVMP vs CyBorD

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	560,646.29	3.89	5.36	$144,171	--
[LOWER BOUND					
Time horizon – 10 years	$285,730	1.56	2.14	$182,634	$38,463
Subsequent therapies – Table 10	$516,320	3.89	5.36	$132,815	-$11,356
Cost of bortezomib (50% of price)	$556,418	3.89	5.36	$143,133	-$1,038
Wastage	$592,311	3.89	5.36	$152,368	$8,197

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Best case estimate of above 4 parameters	$269,398	1.56 QALYs	2.14 LYs	$172,194	$28,023

Based on 1,000 iterations, the EGP's best estimate of the ICER between DVMP vs Rd is between a lower bound of $243,804/QALY and upper bound of unknown. Due to the uncertainty generated from the OS extrapolation and ITC, EGP was not able to estimate the upper bound of the ICER. See Table 3C.

Table 3C. Detailed Description of EGP Reanalysis: DVMP vs Rd

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$494,197.35	3.18	4.41	$155,180	--
[LOWER BOUND, if applicable]					
Time horizon – 10 years	$228,328	0.97	1.33	$236,607	$81,427
Subsequent therapies – Table 10	$478,691	3.16	4.37	$151,639	-$3,541
Cost of bortezomib (50% of price)	$478,933	3.16	4.37	$151,716	-$3,464
Wastage	$534,111	3.16	4.37	$169,152	$13,972
Best case estimate of above 4 parameters	$235,274	0.97 QALYs	1.33 LYs	$243,804	$88,624

The Submitter provided feedback on pERC's Initial Recommendation disagreeing with the EGP's reanalysis. Specifically, the Submitter did not agree with the use of a 10-year time horizon in the reanalysis and noted that there have been previous pCODR submissions for multiple myeloma in which the EGP assumed a 20-year time horizon. The EGP, however, maintains their reanalysis estimates for the lower bound and upper bound ICER estimates. The EGP did consider that there have been previous pCODR submissions for multiple myeloma in which the EGP used a 20 year time-horizon in their reanalysis. Both the EGP and CGP acknowledged that some patients receiving DVMP may live up to or longer than 10 years. However, given the relatively short follow-up in the ALCYONE trial (median follow-up of 27.8 months), with insufficient long term follow up data, both the CGP and EGP concluded that a time horizon of 10 years was appropriate. The EGP conducted additional sensitivity analyses on the final EGP reanalysis (EGP's best case estimate) for pERC to better understand the impact of the time horizon.

Table 3D. Sequential Analysis of Lower Bound for All Comparators

Name	Costs	QALYs	Incremental Costs (vs Referent)	Incremental QALYs (vs Referent)	ICER (vs Referent)	Incremental Costs (Sequential)	Incremental QALYs (Sequential)	ICER (Sequential)	Dominated (Sequential)
CyBorD	$358,809.74	3.08	$0.00	0.00					
VMP	$360,897.85	3.08	$2,088.11	0.00	Dominated	$2,088.11	0.00		Dominated by CyBorD
Rd	$392,933.69	3.68	$34,123.95	0.60	$56,921.75	$32,035.84	0.60	$53,393.06	
DVMP	$628,207.58	4.64	$269,397.84	1.56	$172,194.16	$235,273.89	0.97	$242,550.40	

Note: A sequential analysis was only completed for the EGP's lower bound reanalysis estimate. The EGP's upper bound reanalysis for the comparison between DVMP and CyBorD and DVMP and Rd would be infinite, therefore a sequential analysis was not performed.

1.5 Evaluation of Submitted Budget Impact Analysis

The BIA estimated the overall and net budget impact to the Ontario Public Drug Programs (OPDP) of funding DVMP through the CCO New Drug Funding Program (NDFP) for 3 years. The base analysis is for Ontario and the user may switch between jurisdictions or select "All jurisdictions" for a Canadian perspective. The other jurisdictions included were: Quebec, Manitoba, Saskatchewan, Alberta, British Columbia, Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, and the Yukon.

The factors that most influence the budget impact analysis include population size, wastage cost, subsequent treatment cost, and market share. It is difficult to determine how accurate the eligible population and market share are at this point in time. However, these parameters were able to be modified and a range of values were explored by the EGP.

Key limitations of the BIA model were the inability to evaluate the impact of the 3rd line therapies as in the CEA model. The BIA only accounted for first-line and second-line therapies.

The Submitter provided feedback on pERC's initial recommendation disagreeing with the EGP's statement that a key limitation of the budget impact analaysis model was the inability to evaluate the impact of the third-line therapies. The Submitter stated that treatment times in the reference scenario and new treatment scenario were long enough such that patients would not progress to a third-line treatment within the 3-year time horizon, and that the inclusion of third-line therapies would increase the downstream cost of comparator regimens and decrease the overall incremental budget impact of funding daratumumab in the first-line setting. After consultation with the CGP, it was noted that patients who relapse early may be able to begin 3rd line therapy within the 3-year time horizon. However, the EGP was unable to conduct an analysis on the impact of 3rd line therapies, which may potentially create a smaller or larger overall budget impact.

1.6 Conclusions

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

- Lower bound ΔC = $267,310
- Upper bound ΔC = $274,785
- Lower bound ΔE = 1.56
- Upper bound ΔE = 0.71
    - These ranges produced an ICER between $170,859/QALY and $389,092/QALY
- This large range of ICERs provided by the EGP reflects a large amount of uncertainty present in the incremental benefit against the VMP.
- Within this range, the best estimate would likely be close to the lower bound.

- The extra cost of DVMP is between $267,310 and $274,785. The main factor that influences the change in cost of the best estimate is the shortened time horizon (from 30 years to 10 years). Other cost drivers in the model include the cost of DVMP and VMP and the choice of subsequent therapies.
- The extra clinical effect of DVMP is between 1.56 and 0.71 QALYs. The main factor that influences ΔE is the extrapolation model used for the OS; and a shortened time horizon (from 30 years to 10 years). Another minor effect driver in the model is the choice of utility value.

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

- Lower bound ΔC = $269,398
- Upper bound ΔC = Unknown
- Lower bound ΔE = 1.56

- Upper bound ΔE = Unknown
    - These ranges produced an ICER between $172,194/QALY and Unknown
- Due to the uncertainty generated from the CyBorD efficacy assumption, EGP was not able to estimate the upper bound of the ICER.

- The extra cost of DVMP (lower bound) is $269,398. The main factor that influences the change in cost of the best estimate is the shortened time horizon (from 30 years to 10 years). Other cost drivers in the model include the cost of DVMP and CyBorD and the choice of subsequent therapies.
- The extra clinical effect of DVMP (lower bound) is 1.56 QALYs. The main factor that influences ΔE is the extrapolation model used for the OS; and a shortened time horizon (from 30 years to 10 years). Another minor effect driver in the model is the choice of utility value.

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

- Lower bound ΔC = $235,274
- Upper bound ΔC = Unknown
- Lower bound ΔE = 0.97
- Upper bound ΔE = Unknown
    - These ranges produced an ICER between $243,804/QALY and Unknown
- Due to the uncertainty generated from the Rd efficacy assumption, EGP was not able to estimate the upper bound of the ICER.

- The extra cost of DVMP (lower bound) is $235,274. The main factor that influences the change in cost of the best estimate is the shortened time horizon (from 30 years to 10 years). Other cost drivers in the model include the cost of DVMP and Rd and the choice of subsequent therapies.
- The extra clinical effect of DVMP (lower bound) is 0.97 QALYs. The main factor that influences ΔE is the extrapolation model used for the OS and a shortened time horizon (from 30 years to 10 years). Another minor effect driver in the model is the choice of utility value.

Overall conclusions of the submitted model:

- **Model Structure**
    - The economic model structure and the parametric extrapolation are appropriate, however, the model did not consider the uncertainty generated from the indirect treatment comparison for selected treatment comparators (CyBorD and Rd).
- **Data Inputs**
    - Extrapolating 27.8 months OS to 30 years creates a great deal of uncertainty.
    - There are no comparative effectiveness trials between the commonly used treatment regimens (DVMP vs CyBorD or DVMP vs Rd). The effectiveness data used in the economic model were based on indirect treatment comparisons and efficacy assumptions.
- **Patient Input**
    - The factors relevant to patients were taken into consideration in the economic model.
- **Overall**
    - Overall, the model structure and the parametric extrapolation methodology are appropriate; however, given the lack of long-term OS data, comparative effectiveness estimates in selected treatment and the inability to evaluate the uncertainty from the indirect treatment comparison, it was very difficult for the EGP to estimate the ICER.

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 Multiple 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 in combination with bortezomib, melphalan, and prednisone (DVMP)for the treatment of patients with newly diagnosed 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 information redacted from this publicly available Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

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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