pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Daratumumab (Darzalex) for Multiple Myeloma

December 1, 2016

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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 cost-utility and cost-effectiveness analyses submitted to pCODR by Janssen Inc. compared daratumumab (DARA) to Canadian average current care as defined by Canadian clinical experts for patients with multiple myeloma (MM) who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who have failed or are intolerant to PI and IMiD. DARA is an intravenous (IV) medication while some medications in the current comparator are IV and some are taken orally. The pharmacoeconomic model was based on an indirect comparison. The effectiveness input parameters, the overall survival (OS) and progression free survival (PFS), and the cost input parameters of DARA came from the combined patient sample from GEN501/MMY2002 study with patients taking 16mg/kg dose of DARA (Table 1).[1] The estimates for the average current care came from a recent analysis using international chart review data *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)*. The relative efficacy of DARA compared with the average current care was obtained using propensity score matching.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Patients with MM who have received at least three prior lines of therapy including a PI and an IMiD or who have failed or are intolerant to PI and IMiD (modeled population is aligned with that of funding request)
Type of Analysis	CEA and CUA
Type of Model	Partitioned-survival
Comparator	Canadian average current care: patients receiving Pomalidomide/Dexamethasone (POM/DEX), Bortezomib/Dexamethasone/Cyclophosphamide (BOR/DEX/CYCLO), or High Dose Dexamethasone (HDD) – as defined by Canadian clinical experts
Year of costs	*Drug Costs – 2016, Physician Services – 2015, Laboratory Services – 2013; all costs inflated for 2016*
Time Horizon	10 years
Perspective	Government

Cost of Daratumumab	• $598.02 per 100mg/5mL vial, $2,392.08 per 400 mg/20mL vial • The intensity of IV injection is variable over time: 4 injections/month for the first two months; 2 injections/month from 3 to 6 months, and 1 injection/month from 7^{th} month • Of note, in response to the Submitter's feedback related to the cycle cost for daratumumab and how its cost attenuates with time, the EGP revised this bullet to include explicit detail on the cycle cost for daratumumab over time. The cost per cycle (28-day course) with 4 injections for the first two months would be $28,705 (or $7,176.25/week or $1,025.18/day), with 2 injections for months 3 to 6 would be $14,352 (or $3,588/week or $512.57/day), and 1 injection for month 7 would be $7,176.25 ($1,794.06/week or $256.29/day), using the average weight from MMY2002 study.
Cost of current average care	Using the average patient weight from MMY2002 study and 1.75m^2 body surface the 28-day cost of:

	• POM-DEX combination was calculated as $10,512 (2,628/week or 375.4/day); • BOR-DEX-CYCLO as $4,240 (1,060/week or $151.4/day); and • HDD as $37 ($9.25/week or $1.3/day).
Model Structure	A survival partition model was built with three health states that included 'pre-progression', 'post-progression' and 'death' states. All patients started from pre-progression and moved either to post-progression state or died; post-progression patients could move only to 'death' (absorbing) state. In the model, patients were receiving active treatment as long as they were in the pre-progression state. No other active treatment was assumed after progression.
Key Data Sources	DARA effectiveness estimates came from the integrated sample from MMY2002/GEN501 trials.[1] The efficacy estimate for current care came from an international chart review study with patients closely defined to target population. The relative efficacy of these two groups was obtained using propensity score matching. The frequency of adverse outcomes (AEs) came from the integrated study sample for DARA and from monographs for current care. Resource utilization for AEs came from surveying Canadian experts and respective unit costs mostly from Ontario administrative sources. The analysis also considered drug administration costs, costs of additional medications to prevent transfusion-related AEs, ongoing monitoring costs, palliative treatment and cost of terminal care. Utility estimates came from literature.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. However, the CGP considered that the patient population that already failed IMiD and PI therapy typically present with higher rates of end organ damage, immunosuppression, and poor hematopoetic reserve, and therefore, IMiD- or PI-based comparators for pharmacoeconomic analysis may underestimate the true economic costs of daratumumab, especially due to the observed survival benefit. The pooling of GEN501/MMY2002 study sample was considered appropriate.

- Other relevant issues identified included:
  - The uncertainty in the OS and PFS estimates received from the propensity score matching may be greater than the confidence intervals due to absence of important prognostic factors from matching and other potential unknown confounders.
  - It was unclear whether the results of the two studies reviewed, apply equally to patients who are double-refractory and to patients who are refractory to three or more lines of therapy. As per the Economic Guidance Panel's (EGP) request, the submitter presented the results of economic evaluation separately for i) only patients with 3 or more prior lines of therapy; ii) for patients who were double refractory to PI and IMiD; iii) for patients in the MMY2002 study. This, however, was only possible for a naïve sample and not using propensity score matching, due to the timeframe the request was made. The OS and PFS estimates were not largely different from the base case analysis

with the pooled patient population. While the cost-effectiveness ratio (ICER) for the base case was $92,589/QALY for the matched group ($89,670/QALY for naïve comparison), it was $100,740/QALY when limiting to those with 3 or more lines of therapy and $108,751/QALY when limiting to double refractory group.

Summary of patient input relevant to the economic analysis
Patients considered the side effect profile, availability and effect on quality of life of medications to treat MM to be important. They considered the side effects of DARA tolerable and commented on improved quality of life after treatment. The side effects of DARA were considered in economic analysis; however, estimates of quality of life did not come from the patients taking DARA but from a different study. Patients mentioned that although DARA infusion takes time, the frequency of the infusions decreases significantly over time, up to once monthly. The economic evaluation did not consider any patient costs (e.g., travel time and costs) since the analysis was done from the government perspective (as per pCODR guidelines).

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

- The prevalent population that will be eligible to receive DARA is unknown. The EGP noted that the source used by the submitter for budget impact analysis may not be representative of the eligible population, and this is a limitation to the current analysis.
- PAG noted that additional resources may be needed for pre-medication, drug preparation, administration time (including nurse chair time and pharmacist time) and monitoring for side effects. All these resource utilisation and costs have been considered in economic evaluation.
- The other factor was regarding the drug wastage in cases when vial sharing is impossible. The submitter considered potential drug wastage in base case analysis, and tested the effect of assuming no wastage in scenario analysis.
- PAG also noted that the unknown and variable treatment duration can be important for economic analysis. For the economic report, the submitter used the integrated GEN501/MMY2002 trial sample as a source for DARA efficacy; in the propensity score matched sample the median PFS (similar to median treatment duration) was 3.87 months (1.61-8.32) after a median follow-up of 20.7 months.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians commented on the following factors relevant to the economic analysis:

- In terms of eligible patient population for DARA, they noted that it is possible that not all patients who reach fourth line treatment may receive it as they may be too sick for that, some may prefer not to receive and some may not be able to travel to chemotherapy clinics for infusions. In submitter's budget impact analysis, all potential eligible patients (as per assumed market shares) received DARA which could overestimate the budget impact if approving funding for DARA.
- Some clinicians believed that DARA could be used with other current MM treatments or it may possibly replace pomalidomide or reduce its use. Pomalidomide was considered as one of the comparators in the PE report and the decrease of its use was considered in the submitter's budget impact analysis.
- Clinicians noted that a testing of erythroid phenotype may be needed for patients on DARA in case they require red blood cell transfusion. This was not considered in the economic analysis; however, for all patients on DARA the submitter considered the costs of red blood cell transfusion (once per treatment duration) and Epoetin alfa (once weekly).

1.3 Submitted and EGP Reanalysis Estimates

Two errors (related to the median survival time of 20.1 months and selection of distribution) were noted in the report and therefore have been corrected. These errors, however, have little impact on the EGP's initial reanalysis estimates.

Table 2. Submitted and EGP Estimates

Estimates	Submitted	EGP Reanalysis
ICER estimate ($/QALY), range/point	92,589	$101,465/QALY
ΔE (QALY), range/point	0.845	0.712 - not estimable
ΔE (LY), range/point	1.232	1.232 - not estimable
ΔC ($), range/point	78,233	78,233 - not estimable

The base case analysis resulted in 2.26 total life years on DARA and 1.028 years on average current care and a difference of 1.232 years (Table 2). This corresponded to 1.537 quality-adjusted life years (QALYs) on DARA and 0.692 QALYs on current care (ΔQALY = 0.845). The total healthcare cost was $126,879 on DARA and $48,646 on current care. The resulted ICER was $92,589/QALY. Increased post-progression survival by DARA contributed to 75% of total QALY gain while increased DARA costs contributed to 91% of increased costs.

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

- A major limitation of the model however is the fact that it is based on an indirect comparison; i.e., the active treatment DARA has not been compared with the modeled current care in a randomized clinical trial setting. The evidence on DARA came from combining two open-label, single arm studies while the evidence on current comparator came from the chart review data using IMF database.
- A propensity score matching (PSM) was applied to create comparable groups and obtain comparative effectiveness estimates for OS and PFS. However, prognostically important variables such as beta-2 microglobulin (and subsequently International Staging System for MM), performance status, cytogenetics, and immunoglobulin subtype, and time from diagnosis were not considered. There were more double and triple refractory patients in the DARA sample than in the IMF sample. The EGP felt that at the same time, when looking at active treatments at the time of enrollment, the IMF group appeared to be heavily treated with experimental agents (e.g. on new active or multiple treatment combinations) beyond what is assumed to be 'current average Canadian standard'. This, however, was somewhat contradictory to the large post-progression survival benefit in the DARA group compared to average current care. What treatment patients in the current care group received after progression remains unclear. Overall, the EGP found the justification for this reported survival benefit after progression to be weak and not convincing. Considering all these limitations, and the small sample size, the evidence generated from the PS matching has high uncertainty and should be interpreted with caution.
- Furthermore, when extrapolating beyond the trial duration the submitter did not consider the underlying all-cause mortality for survivors justifying it by the fact that less than 1% of patients survived beyond 10 years based on extrapolation. This is however highly uncertain given the fact that the 1% estimate is based on heavily extrapolated data (the median follow-up time of the integrated DARA sample was 20.7 months).
- The submitter conducted a literature review to identify utility values for the model, as utilities were not captured in patient samples used for OS and PFS estimates. The pre-progression utility estimate (0.81) was taken from the study by van Agthoven et al[2]

conducted in the Netherlands among previously untreated patients with stage II/III multiple myeloma at 6 months after intensive chemotherapy. The post-progression utility (0.644) was taken from the same study reflecting the utility of patients in an "in an undefined state" (not in remission) following intentionally curative primary therapy. From the published source it is unclear however if these numbers represent mean or median utilities.[2] In addition, the transfer of utility estimates from one jurisdiction to another increases the uncertainty of the final cost-effectiveness outcomes.

- In the model, costs of care after progression considered only routine monitoring costs but not costs of any other subsequent active treatment. In response to checkpoint questions, the submitter presented the type of treatments used in DARA group post-progression. Similar information was not available for the comparator group. The submitter commented that the observed overall survival benefit of DARA may be partially explained by the fact that DARA may enhance patient's response to subsequent treatments. This only highlights the need of modelling this cost into the model. The EGP felt that the model provided was not flexible enough for the EGP to build scenarios around the cost of subsequent treatments.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the economic model:

- Follow-up duration: considering the relatively short duration of follow-up data from GEN501/MMY2002 which was 20.7 months against the model's time horizon which was 10 years (using extrapolation of clinical data), we tested the effect of limiting the model's time horizon to 20.7 months (Table 3). The ICER increased significantly to $241,695 (because the shorter time horizon generated a much smaller difference in effectiveness).
- Efficacy period: to test the effect of extrapolation on ICER, we set a conservative estimate to OS assuming no difference in effect (OS HR=1) after model's efficacy period (which was 35 months as per maximum the follow-up duration available for current care). This scenario resulted in an ICER of $122,221/QALY.
- Utility values: The base utility value for progression-free state in the submitted model is higher than what was reported or used in past studies. For example, a cross sectional study among 402 UK multiple myeloma patients using EQ-5D instrument reported that the average utility on 1st line treatment was 0.63, 2nd line treatment (treatment after 1st relapse) was 0.67, in 1st time active treatment-free remission 0.72 and later stage (after 2nd remission) 0.63.[3] The utility values for responsive disease, stable disease and progressed disease received from the MM003 study (that compared POM plus low-dose dexamethasone versus high-dose dexamethasone for patients with relapsed and refractory multiple myeloma) were 0.75, 0.65 and 0.61 respectively.[4] The utility values from these two studies were also used for a recent health technology assessment by the Institute for Clinical and Economic Review on treatment options for relapsed or refractory multiple myeloma.[5] The baseline mean utility in the expanded access study (MMY3010) was used.[6] Using this as the utility value for pre-progression state resulted in ICER of $101,465/QALY. Using pre- progression utility of 0.65 and post-progression utility of 0.61 resulted in an ICER of $101,589/QALY.
- Costs: We tested the effect changing DARA cost to 5, 10, and 15% lower and higher from the cost proposed by submitter.

Table 3. EGP Reanalysis Estimates

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC, $	ΔE, QALYs	ΔE, LYs	ICUR, ($/QALY)	Δ from baseline submitted ICER
Base case scenario	**78,233**	**0.845**	**1.232**	**92,589**	--
Limiting efficacy in OS to 35 months (maximum follow up in the average current care)	77,492	0.624	0.904	122,221	+29,632
Limiting time horizon to median follow-up of integrated GEN501/MMY2002 sample: 20.7 months	70,000	0.290	0.378	241,695	+149,106
Pre-progression utility (mean) as per expanded access study (MMY3010)	78,233	0.771	1.232	101,465	+8,876
Pre-progression utility=0.65 and post-progression utility=0.61	78,233	0.770	1.232	101,589	+9,000
DARA cost decreased by 5%	73,053	0.845	1.232	86,459	-6,130
DARA cost decreased by 10%	67,873	0.845	1.232	80,328	-12,261
DARA cost decreased by 15 %	62,693	0.845	1.232	74,198	-18,391
DARA cost increased by 5%	83,413	0.845	1.232	98,720	6,131
DARA cost increased by 10%	88,593	0.845	1.232	104,850	12,261
DARA cost increased by 15%	93,773	0.845	1.232	110,981	18,392
EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE, QALYs	ΔE, LYs	ICUR	Δ from baseline
Baseline (Submitter's best case)	**78,233**	**0.845**	**1.232**	**92,589**	--
LOWER BOUND					
Pre-progression utility (mean) as per expanded access study (MMY3010)	78,233	0.771	1.232	101,465	+8,876
Best case estimate of above parameters	78,233	0.771	1.232	101,465	+8,876
UPPER BOUND – NOT ESTIMABLE					

Overall, the ICER is difficult to estimate because of high level of uncertainty of the comparative effectiveness data: the upper boundary of ICER was not estimable while there is a high level of uncertainty with the estimated lower bound of $101,465/QALY. In their feedback, the patient advocacy group noted that one would assume that with an ICER of $92,589/QALY, there is a patient population for which daratumumab would be cost-effective and warrant it being reimbursed under predetermined conditions. The EGP would like to clarify that $92,589/QALY is the Submitter's base case and reiterate that ICER is difficult to estimate because of high level of uncertainty of the comparative effectiveness data.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include body weight (increasing budget impact with increasing weight) and price of POM (decreasing budget impact of DARA with increasing cost of POM).

A key limitation of the budget impact model was not having accurate data for estimating the number and proportion of MM population potentially eligible for DARA. This was not further modified or tested by the EGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for DARA when compared to average current care in Canada is:

- Between $101,465/QALY and unknown.
- Given the limitations of the data used to obtain the comparative effectiveness information, it is difficult to provide a best estimate or range for the ICER (or ΔC and ΔE).
- The EGP's confidence in the lower bound of $101,465/QALY is also low.

Overall conclusions of the submitted model:

- The lack of head to head comparative data between DARA and current standard of care, the weak clinical justification of the post-progression survival benefit and the use of propensity score matching without considering several important clinical factors limit the level of confidence in the submitted economic model and economic evaluation report.
- If one ignores the level of evidence and uncertainty around the comparative effectiveness estimate, then the lower end of the ICER would be $101,465/QALY. However, the confidence in the lower bound remains low.
- Given the limitations of the data, the EGP cannot estimate the upper boundary of the ICER. Information from direct comparative trials with longer follow-up data is still warranted.

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 daratumumab (Darzalex) for multiple myeloma 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*.

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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