CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Registered Clinician Input on a Drug Review

Daratumumab (Darzalex) for Multiple Myeloma

December 1, 2016

Feedback on pERC Initial Recommendation

Name of the drug indication(s):	Daratumumab (Darzalex®) For the treatment of patients with multiple myeloma who 1) have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD); OR 2) have failed or are intolerant to a PI and who have failed or are intolerant to an IMiD
Name of registered clinician(s):	Myeloma Canada Research Network
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**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

1. Comments on the Initial Recommendation

a) Please indicate if the registered clinician(s) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part X disagree

The Canadian myeloma expert physicians, who comprise the MCRN, respectfully disagree with the conclusion that there is a lack of evidence that daratumumab has a net clinical benefit in the above setting, and, therefore, reimbursement is not recommended.

Since myeloma is not curable, improvements in the outcome of patients depends on the introduction of new drugs—ideally with novel mechanisms of action—alone or in combination- that can be used as another line of therapy when the current treatment loses its effectiveness. Myeloma patients in Canada now currently receive at least 3 or 4 lines of therapy, often more if clinical trials are available. As a simplistic overview, in Canada, funded first-line therapy is based on fixed duration combinations of bortezomib (often with alkylating agents such as cyclophosphamide and steroids +/- stem cell transplantation), second-line therapy on lenalidomide and third-line on pomalidomide, with specific options individualized based on a number of factors. In many jurisdictions, bortezomib may be used again for retreatment in combinations such as CyBorD. [However it is important to note that, in Ontario, bortezomib is NOT provided for retreatment and this gap limits options for effective therapy for relapse in a significant number of Canadian patients.] When the 3 key PI and IMiD agents have lost effectiveness, there is no standard reimbursed drug/regimen available.

The MMY2002 and GEN501 studies, in advanced disease after a median of 5 and 4 prior treatment lines, respectively, demonstrated that 26.3% and 30.85% of patients, respectively, responded to daratumumab. The MCRN physicians feel that response rates are appropriate end points in trials involving such advanced disease, and note that remissions in myeloma patients are associated with a marked

decrease in skeletal events, transfusion requirements and renal failure - hence a decrease in utilization of health resources. The reported response rates are unprecedented in patients who are so-called "triple-refractory" and have failed bortezomib, lenalidomide and pomalidomide, like an increasing number of our own patients. Moreover, carfilzomib is increasingly used in Canada both via compassionate access programs that were initiated after Health Canada approval, and via clinical trials, so the findings in MMY2002 and GEN501 that "quadruple refractory patients" (refractory to bortezomib, lenalidomide, pomalidomide and carfilzomib) have remission rates of 26.3% and 40.0%, respectively, have increasing relevance. Responding patients in these trials also have a meaningful duration of remission. Although the mechanism of the relatively prolonged overall survival of a median of 17.5 months in MMY2002 and not yet reached in GEN501 is not clear, one could argue that the data is consistent for this novel immune agent and, regardless of the lack of explanation, is simply good for our patients. Given these findings, it would be very difficult to perform a phase 3 trial comparing daratumumab with best supportive care, as patients would likely decline participation and opt for a clinical trial that insures delivery of another potentially efficacious agent.

b) Notwithstanding the feedback provided in part a) above, please indicate if the registered clinician(s) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____	Support conversion to final recommendation.	X	Do not support conversion to final recommendation.
	Recommendation does not require reconsideration by pERC.		Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

No comments

2. Comments Related to the Registered Clinician(s) Input

No comments

3. Additional comments about the initial recommendation document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
3	**Summary of pERC deliberations**	**Para 3**	It is noted that daratumumab would be an add-on therapy and not a replacement therapy, that would increase the budget impact. The MCRN acknowledges the challenges of funding expensive new cancer drugs, but would like to point out that, for patients with this incurable disease, having

			another effective line of "add-on" therapy -and one that is not chemotherapy *per se* but a monoclonal antibody with mainly infusion side effects with the first dose - is an important step forward. Also in that paragraph, it is noted that the infusions times and administration schedule for daratumumab is very intensive and would affect the budget impact. The clinicians would like to comment that, as familiarity with the drug increases, there are measures now available to mitigate this impact to some extent, such as split dosing with administration on 2 days for the long first infusion.
8	**Adoption Feasibility**	**Para 5**	It is noted that interference with blood compatibility testing would contribute to the need for additional downstream resources. Our clinical experience has indicated that this issue seems to be minor, as major ABO testing is not impacted and one simply needs to notify the blood bank in advance of use of this agent.

About Completing This Template

- The following template form should be used by the registered clinician(s) to submit input at the beginning of a drug review. Please note that there is a separate template for providing feedback on an initial recommendation.

- The clinician(s) **must be registered with the pCODR program** to provide input. (See https://www.cadth.ca/pcodr/registration for information on eligibility and registration.)

- The registered clinician(s) must also complete the *pCODR Clinician Conflict of Interest Declarations Template* when providing input at the beginning of a drug review (see Appendix A of this document). While CADTH encourages collaboration among registered clinicians and that feedback submitted for a specific drug or indication be made jointly, each registered clinician must complete their own separate *pCODR Clinician Conflict of Interest Declarations Template*.

- Please ensure that the input is in English, and that it is succinct and clear. Please use a minimum 11-point font and do not exceed six (6) typed, 8 ½″ by 11″ pages. If a submission exceeds six pages, only the first six will be considered.

- The registered clinician(s) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the registered clinician(s) should not feel restricted by the space allotted on the form and can expand the tables in the template as required. The categories and questions outlined are only examples, to guide identification of relevant clinical factors for pERC's consideration. Please note that comments may be attributed to a specific individual clinician and that registered clinicians who submit input will be identified as a contributor to the specific input. CADTH's pCODR program maintains the discretion to remove any information that may be out of scope of the review.

- It is important to note that scientific published references are not required, as pCODR has access to current scientific literature through the manufacturer's submission, tumour groups, and a rigorous, independent literature search.

- The registered clinician(s) must be submitted by the **deadline date** for this drug, posted on the pCODR section of the CADTH website under *Find a Review* so that it can be available in time to be fully used in the pCODR review process. If more than one submission is made by the same registered clinician(s), only the first submission will be considered.

- In addition to its use in the pCODR process, the information provided in this submission may be shared with the provincial and territorial ministries of health and Provincial cancer agencies that participate in pCODR, to use in their decision-making.

Should you have any questions about completing this form, please email submissions@pcodr.ca