



**pan-Canadian Oncology Drug Review
Submitter or Manufacturer Feedback on a
pCODR Expert Review Committee Initial
Recommendation**

Daratumumab (Darzalex) for Multiple Myeloma

December 1, 2016

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): DARZALEX™ (daratumumab)
Role in Review (Submitter and/or Manufacturer): Manufacturer/Submitter
Organization Providing Feedback: Janssen Inc.

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

- a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

_____ agrees _____ agrees in part x disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees, agrees in part or disagrees with the initial recommendation.

Janssen Inc disagrees with Initial pERC Recommendation for DARZALEX™ for the following reasons:

1) Feasibility of a Randomized Phase 3 Clinical Trial

- **The Clinical Guidance Panel (CGP) Report (pg. 7)** stated that “Prior to the results of MMY2002, a randomized control trial (RCT) of daratumumab vs. best supportive care (BSC) would have been possible as the clinical efficacy of the drug was unclear. However, **with the current results of the MMY2002 trial, and its clinical responses published on PI and IMiD refractory patients, a trial comparing daratumumab vs. BSC is not ethically feasible.** It is clear that PI and IMiD refractory patients have an accelerated mortality with no successful treatment options, making **daratumumab an essential agent in preventing end organ damage from myeloma, improving patient QoL, and maximizing PFS and OS.**”
- pERC concluded that due to the prevalence of the disease, a Phase 3 RCT would have been feasible. Janssen discussed the possibility of a RCT with clinical experts and Regulatory Agencies prior to the initiation of Study MMY2002. However, there was no agreement on the choice of the comparator and the idea of high-dose dexamethasone as one was rejected due to the toxicity profile. Furthermore, a clinical trial vs. other available treatment options (i.e. PIs and IMiDs) would have restricted the clinical trial population to those who are sensitive to these agents. The indication and the reimbursement ask are for patients who have failed a PI and an IMiD (regardless of the type of PI and IMiD) and thus have limited treatment options. As acknowledged by the CGP Report, a RCT would not be feasible now due to the demonstrated efficacy of daratumumab.

2) Propensity Score Matching (PSM) Analysis

- Janssen understands that it can be difficult to assess net clinical benefit from non-RCT data. In light of this as a Phase 3 study is not ethically feasible or possible following the results of GEN501/MMY2002, a PSM analysis was conducted as it is more rigorous in addressing the comparative efficacy vs. a naïve analysis.

- pERC concluded “that there were substantial limitations in the PSM analysis, including that some prognostically important variables were missing from matching, ..., and the groups were not balanced...” (pg. 2)
- To select the prognostic factors for matching, Janssen conducted a literature review and sought clinical expert opinion.
- Several studies have found that potential prognostic factors that are important in newly diagnosed multiple myeloma (MM), are not relevant in heavily pre-treated and highly refractory patients.
 - I. Turesson et al (1999) in a multivariate Cox analysis of 12 potential prognostic variables the authors found that the predictive value of some variables (beta-2M, W.H.O.-Performance Status) decreased significantly over time.¹
 - II. Liwing et al (2015) similarly found the prognostic factors changed over time:²
 - In **first line**, patient’s response rate, age, albumin, calcium, beta-2-microglobulin levels, type of treatment, International Staging System (ISS) and MM type were significant prognostic factors for OS.
 - For **second line, third line and fourth line**, OS multivariate cox-regression showed that **ONLY** response rate to the previous line and age were significant prognostic factors for OS.
- Therefore, factors such as ISS Stage and MM type were significant prognostic factors for response in first line, however, by fourth line these factors were not considered important.
- Clinical experts also agreed that prior lines of therapy and refractory status would be of greatest importance for this highly refractory population and therefore were included in the PSM. For completeness a number of other factors were included in the PSM: Age (continuous), gender (male/female), # prior lines of therapy (continuous), POM refractory (yes/no), CAR refractory (yes/no), BOR refractory (yes/no), LEN refractory (yes/no), albumin (continuous), and after matching, the DARA and IMF groups were well balanced (no statistically significant differences on matched parameters).
- pERC noted that the groups were not balanced in one parameter in Table 13 (pg. 44) of the Clinical Guidance Report, however, this table also indicates that the daratumumab group had statistically significantly more triple refractory (BOR+LEN+CAR) patients than the IMF cohort (p=0.04), and more quadruple refractory patients. Usmani et al 2015 demonstrated that patients who are triple and quadruple refractory have poorer OS outcomes than double refractory patients (Figure 1).³ Therefore, as there were more triple and quadruple refractory patients in the daratumumab arm, a bias in favor of daratumumab was highly unlikely.

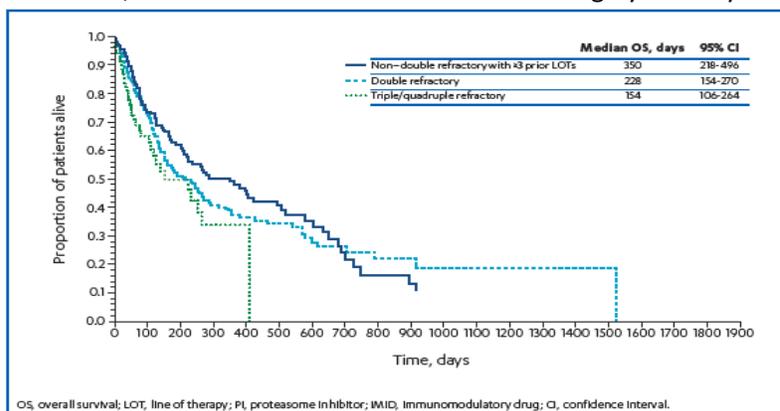


Figure 1: Median OS for double, triple and quadruple refractory multiple myeloma patients

In addition to the PSM, Janssen has incorporated several analyses to help address the uncertainty:

- Sensitivity analyses were performed with the PSM. These included alternate matching methodologies and varied caliper width. The range of HRs for these analyses were consistent with the base case.
- Additionally, a naïve analysis was performed vs. pomalidomide (POM)/dexamethasone. The baseline patient characteristics and the corresponding reimbursement ask for daratumumab, represent a more treatment refractory population vs. the POM clinical study. ISS staging and time since diagnosis are summarized below (Table 1). Please note that the ISS stage 3 in the daratumumab study was 38% vs. 31% for POM/dex. Also, daratumumab patients had reached a median of 5 prior lines in a shorter time since diagnosis which may be

indicative of more aggressive disease. Despite the imbalance of baseline characteristics in favour of POM/dex in this analysis, the median OS for daratumumab is 18.6 months vs. 12.7 months for POM/dex.^{4,5}

Table 1. Baseline Characteristics of Interest for Daratumumab vs. Pomalidomide/dex (Naïve Analysis)

| Baseline Characteristic | Daratumumab (MMY2002, n=106) | Pomalidomide (MM-003, n=302) |
|---------------------------------------|------------------------------|------------------------------|
| ISS Stage 1 | 26 (25%) | 197 (65%) |
| ISS Stage 2 | 40 (38%) | |
| ISS Stage 3 | 40 (38%) | 93 (31%) |
| Missing ISS Stage | N/A | 12 (4%) |
| Median Time Since Diagnosis (Years) | 4.8 | 5.3 |
| Time Since Diagnosis (Range in Years) | 1.1 – 23.8 | 0.6 – 30.0 |

- A match adjusted indirect comparison (MAIC) of the daratumumab clinical trials (GEN501/MMY2002) vs. POM/dex (MM-003) has been conducted. The MAIC-adjusted OS HR was 0.56 (95% CI 0.38; 0.83) in favour of daratumumab when all available baseline characteristics were matched. When patients with prior POM exposure were excluded from the daratumumab dataset to compare similar patient populations, the OS HR improved to 0.33 (95% CI 0.17; 0.66) in favour of daratumumab.⁶
- As discussed in the pCODR submission, Table 2 demonstrates that the median OS observed by daratumumab in GEN501/MMY2002 in patients who have received at least 3 prior lines or those who are refractory to both a PI and an IMiD, has never been observed in this patient population.

Taken in totality, these analyses demonstrate the most important prognostic factors for heavily pretreated multiple myeloma patients were accounted for and the OS results demonstrated by daratumumab in this patient population are greater than that observed by any other agent or regimen in multiple myeloma. Thus, we believe that the net clinical benefit of daratumumab vs. available treatment options has been demonstrated.

Table 2. Overall Survival of Daratumumab vs. Different International Cohorts (naïve comparison)

| Study | Median OS |
|--|-------------|
| Daratumumab (Integrated GEN501/MMY2002 results; n=148) ⁴ | 20.1 months |
| International Myeloma Foundation Cohort (Kumar 2016; n=543) ⁷ | 13 months |
| US Real World Cohort (Usmani 2015; n=662) ³ | 8 months |
| Kumar 2012 (n=286) ⁸ | 9 months |

3) PFS/OS Relationship

- “pERC noted that the majority of the clinical benefit derived in the model submitted by the manufacturer occurred in the post-progression state. In other words, accepting the model would require an assumption that patients derived the majority of the benefit of the treatment after they had stopped receiving the treatment. pERC agreed with the EGP and CGP that the clinical plausibility of this assumption was difficult to accept.”
- It is not uncommon for drugs to exert survival benefit after the patient stops taking the drug. For example, in the pomalidomide MM-003 study, the median PFS is 4 months and the OS is 12.7 months.⁵ Thus, it is accepted that patients do derive some clinical benefit after they stop taking a drug.
- The difference with daratumumab that leads to the prolonged OS is hypothesized to be due to the immunological mechanism of action. Data suggest that the immunological activity of daratumumab may contribute to deeper clinical responses and enhanced survival. The following observations support this:⁴

1. *In MMY2002/GEN501, patients achieved deep responses with daratumumab treatment, including CRs and sCRs, which arose over time after initial PRs and VGPRs.*

- II. *A survival benefit was observed even in those patients that achieved MR or SD (median OS = 18.5 months in these patients); which is remarkable as these patients do not typically respond with this magnitude.*
- III. *Re-sensitization of the myeloma clone to previous therapy.*
- IV. *Immunomodulatory effects mediated by T-cell activation and expansion. Similar observations have been reported for other immuno-oncology drugs such as the checkpoint inhibitors.*

4) Patient population

- “PAG noted that when data becomes available to use daratumumab in earlier lines or in combination, there may be pressure from clinicians and patients to use daratumumab outside of the current funding request and review scope.” “pERC agreed with PAG that daratumumab would be add-on therapy, and not a replacement therapy.” (pg 8)
- The reimbursement scope submitted by Janssen is for single-agent daratumumab use in heavily pretreated patients. Appropriate utilization should be managed through reimbursement criteria at the provincial level. Heavily pretreated multiple myeloma patients with limited treatment options should not be penalized for potential scenarios outside the reimbursement ask.

5) Price

- “...[the Committee] noted the extremely high cost of daratumumab, and that it was one of the most expensive drugs ever considered by the Committee, based on drug cost alone.” (pg. 3) “The cost per cycle (28-day course) with four injections would be \$27,705 (or \$7,176.25/week or \$1,025.18/day) using the average weight from the MMY2002 study. pERC noted that this is one of the most expensive drugs it has ever considered.” (pg. 7)
- Janssen is clarifying that pERC has quoted the initial drug cost for daratumumab during cycles 1-2 and these statements do not acknowledge that the cycle cost for daratumumab attenuates with time. In fact, starting cycle 7, the cycle cost for daratumumab is \$7,176.25/cycle. This cycle cost is lower than the cost of pomalidomide (at \$10,500/cycle), and the cycle costs for pomalidomide do not decrease with time. We recommend that the wording be changed to “the cost per 28-day cycle for the first two cycles is \$27,705, cycles 4-6 is \$14,353 and cycles ≥ 7 is \$7,176.”

References:

1. Turesson I et al. Prognostic evaluation in multiple myeloma: an analysis of the impact of new prognostic factors. *Br J Haematol*. 1999. 106(4):1005-12.
2. Liwing J et al. Is a deep response the key to successful treatment of multiple myeloma? Presented at EHA 2015 (Abs. #P291). Available at: <http://learningcenter.ehaweb.org/eha/2015/20th/100540/johan.liwing.is.a.deep.response.the.key.to.successful.treatment.of.multiple.html>
3. Usmani S, et al. Analysis of overall survival in multiple myeloma patients with 3 lines of therapy including a PI and an IMiD, or double refractory to a PI and an IMiD using real world data. European Hematology Association (EHA) - 20th Congress(abstract # E1256) Vienna, June 12, 2015.
4. Usmani SZ et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. *Blood* 2016; Published online <http://www.bloodjournal.org/content/bloodjournal/early/2016/05/23/blood-2016-03-705210.full.pdf?sso-checked=true>.
5. San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol*. Oct 2013;14(11):1055-1066.
6. Van Sanden S et al. Comparative efficacy of daratumumab monotherapy and pomalidomide plus low dose dexamethasone (POMA+LoDex) in the treatment of multiple myeloma: a matching adjusted indirect comparison (MAIC). 19th Annual European ISPOR 2016; Vienna, Austria, 29 October – 2 November, 2016.
7. Kumar S et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: A multicenter IMWG study. Abstract accepted at the 58th American Society of Hematology Conference; San Diego, California, USA, December 3-6, 2106.
8. Kumar S et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib. A multicenter international myeloma working group study. *Leukemia* 2012; 26(1): 149-57.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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.

| | |
|--|--|
| <p><input type="checkbox"/> Support conversion to final recommendation. Recommendation does not require reconsideration by pERC.</p> | <p><input checked="" type="checkbox"/> Do not support conversion to final recommendation. Recommendation should be reconsidered by pERC.</p> |
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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?

| Page Number | Section Title | Paragraph, Line Number | Comments and Suggested Changes to Improve Clarity |
|-------------|---------------|------------------------|---|
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3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

| Page Number | Section Title | Paragraph, Line Number | Comments related to Submitter or Manufacturer-Provided Information |
|-------------|---------------|------------------------|--|
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3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

| Page Number | Section Title | Paragraph, Line Number | Additional Comments |
|-------------|---------------|------------------------|---------------------|
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About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an “early conversion” of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

- a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.
- b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.
- c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)
- d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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 Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.
- e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½” by 11” paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

- f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.
- g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.
- h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.
- i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.