CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Sponsor)

Isatuximab (Sarclisa) for Multiple Myeloma

April 1, 2021

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Isatuximab (SARCLISA) for Multiple Myeloma
Eligible Stakeholder Role	Sponsor/Manufacturer
Organization Providing Feedback	Sanofi Genzyme

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

3.1 Comments on the Initial Recommendation

a) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the initial recommendation:

☐ Agrees ☒ Agrees in part ☐ Disagrees

OVERALL CLINICAL BENEFIT

Sanofi Genzyme (SGZ) agrees with pERC's initial recommendation supporting the use of isatuximab with pomalidomide/dexamethasone (IsaPd) for the treatment of patients with relapsed or refractory multiple myeloma (RRMM). SGZ agrees with Registered Clinician Input that "IsaPd is an ideal therapy for patients with significant unmet need" (CGR, pg 16) and suggests this be noted within the Initial Recommendation.

PATIENT BASED VALUES

SGZ agrees that treatment with isatuximab aligns with important patient values. SGZ would like to note that treatment with isatuximab would help ensure that patients are able to enroll in ongoing clinical trials, which increasingly require prior anti-CD38 exposure.

ECONOMIC EVALUATION

SGZ respectfully disagrees with the Economic Guidance Panel (EGP) re-analysis estimates and price reduction recommendations within the Economic Guidance Report (EGR) and the pERC Initial Recommendation. Specifically, SGZ disagrees with the EGP's overall survival (OS) projection for IsaPd. **The selection of the Weibull (U) curve for IsaPd results in a clinically implausible crossing of OS between the treatment arms around 4 years. For this reason, use of Weibull (U) for IsaPd OS curve should be eliminated from consideration and alternative curves should be used.**

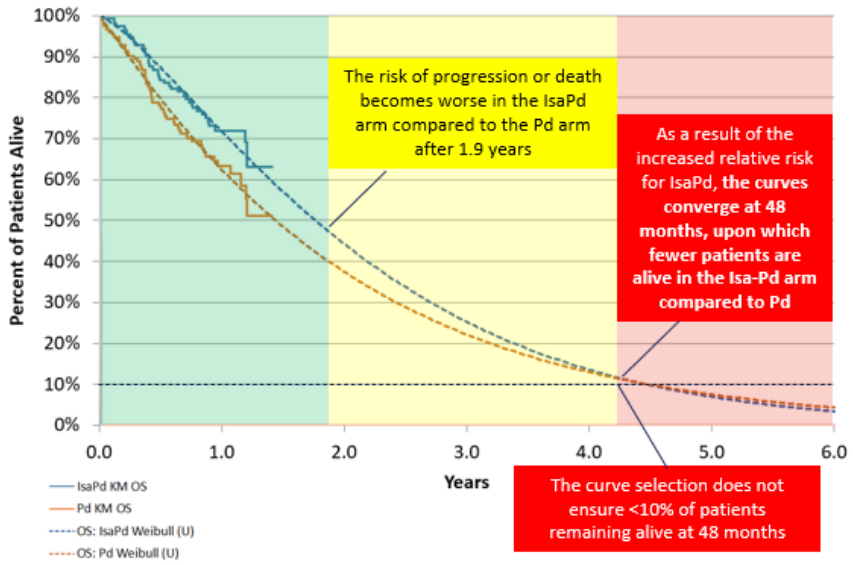

Figure 1: EGP re-analysis of long-term OS for IsaPd (blue dashed line) vs Pd (orange dashed line) In the EGP re-analysis, the IsaPd curve was altered to the Weibull (U) parametric model. EGP re-analysis predicts IsaPd will result in an accelerated hazard for death after 1.9 years and become worse over time compared to Pd, despite Pd being used in both arms. The re-analysis results in the curves converging at 48 months and a loss of 0.11 QALYs in the post-progression (PPS) health state for patients being treated with IsaPd.

Although SGZ acknowledges the re-analysis aimed to address uncertainty around long term OS and ensure a realistic % of patients remain alive, SGZ identified inadvertent effects from changing the OS curve for IsaPd:

- In the EGP reanalysis, the mortality risk in the IsaPd arm becomes greater than that for pomalidomide/dexamethasone (Pd) alone after 1.9 years, despite the use of Pd in both arms:
  - Based on trial data, IsaPd results in a 31% reduction in the risk of death compared to Pd
  - However, in the re-analysis, the risk of dying becomes higher in the IsaPd arm after 1.9 years compared to the Pd arm (e.g. the IsaPd survival curve falls at a faster rate compared to Pd).
- In the EGP reanalysis, survival in the IsaPd arm is lower than in the Pd arm after approximately 4 years:
  - Based on our trial, estimated probability of survival at 12 months was 72% and 63% in the IsaPd and Pd groups (CGR, pg 74).
  - However, in the re-analysis, the OS curves converge after ~48 months and OS is lower for the IsaPd arm compared to the Pd arm after this point.

SGZ disagrees with the EGP that IsaPd will become worse than Pd for the following reasons:

1 Does not align with the clinical HTA assessment in CGR or initial positive funding recommendation

SGZ was not able to find evidence from the clinical assessment by the CGR that OS among patients receiving IsaPd will become worse over time compared to Pd.

2 Is not supported by our clinical trial results

Evidence submitted to CADTH from the ICARIA-MM trial does not provide any support that the mortality rate for IsaPd would become worse over time and that the OS curves for IsaPd and Pd would converge. Rather, results of the trial suggest that IsaPd results in improvements not only in OS but also depth of response, a prognostic indicator for sustained survival:

- IsaPd demonstrated a strong trend in OS by reducing the mortality risk by 31% compared to Pd patients (see figure 2), despite extensive use of novel agents post-progression in the Pd arm.
  - As noted in the CGR (pg 69): "A higher proportion of patients randomized to Pd received subsequent therapy" (39.0% IsaPd vs. 54.2% Pd including 45 patients receiving daratumumab in Pd arm).
  - CGR noted that "the higher % of patients receiving subsequent treatment would also be expected to favour the Pd group and underestimate the OS benefit associated with the experimental group."
  - SGZ would also like to note that the novel treatments used post-progression in the Pd comparator arm in the ICARIA-MM trial are not accessible in Canada (e.g. patients progressing on Pd cannot use an anti-CD38). SGZ agrees with EGP that Pd OS curve may be optimistic from a purely Canadian context.
  - Despite these limitations that bias the results in favour of Pd for OS in the ICARIA-MM trial, IsaPd demonstrated a strong trend in improving OS.
- Deeper responses, as measured by minimal-residual disease negativity (MRD-), have been shown to result in improved OS outcomes in the literature. IsaPd results in deeper responses, with 5.2% of patients achieving MRD- status (compared to 0% in Pd arm). All MRD- patients were progression-free at the end of follow-up. HCPs suggest MRD- as a prognostic indicator for prolonged OS benefit. (Munshi, 2020)
- SGZ believes OS benefit and MRD- achievement inform EGP's selection for an appropriate model to extrapolate OS and ensure curves not converge and mortality hazard for IsaPd remain $\leqslant$ than Pd.

3 Is inconsistent with Registered Clinician Input in the CGR

EGP re-analysis suggests the addition of isatuximab to a Pd backbone will worsen survival outcomes compared to treatment with a Pd doublet backbone alone. It additionally suggests patients in the IsaPd arm may be rescued using Pd alone.

- However, HCP feedback in the CGR confirmed the use of a triplet therapy to be superior to a doublet: "Both clinician groups prefer to treat with an antibody triplet such as IsaPd…. In general, clinicians felt that triplet therapy is superior to doublets for RRMM patients. CMRG clinicians felt that IsaPd would be preferred over Pd- or Kd-based therapy… (which also have) a higher rate of discontinuation due to

TEAEs." (CGR, pg 40). Clinicians have also confirmed that Pd is viewed as a backbone and almost never used as a doublet.

- Clinicians have also highlighted evidence supporting an "anti-CD38 class effect" whereby treatment with an anti-CD38 result in long-term OS prolongation and a visible 'tail', as noted in long-term OS data for other anti-CD38s, even among patients who have progressed. (Usmani, 2020).
- SGZ believes this evidence be used in the consideration for a more optimistic OS model for IsaPd.

4 Is inconsistent with past HTA reviews by EGP for other MM products, including anti-CD38s

In previous HTA assessments of MM products, the EGP re-analysis has not considered an accelerated risk of mortality for the study drug. Precedence from prior EGP re-analysis for anti-CD38 treatments (e.g. daratumumab) provide more clinically plausible survival projections:

- In the daratumumab monotherapy review (at least three prior lines of therapy), the EGP re-analysis modified the OS HR post follow-up period to 1, thus ensuring that the risk of death be equal to but never worse than the comparator, despite the use of daratumumab as a monotherapy.
- In the DRd vs Rd review (RRMM who received at least one prior line of therapy), the EGP assumed a treatment effect of up to 48 months (4x duration of follow-up), thereby assuming an ongoing treatment effect for up to 34.7 months beyond median follow-up.
- In both cases, the EGP did not assume a higher mortality risk for the anti-CD38 treatment compared to the comparator arm. SGZ requests the EGP apply a similar approach for modelling OS for IsaPd.

5 Other HTA bodies (e.g. NICE) have accepted the log-normal distribution to model OS for IsaPd. based on OS improvement, MRD- achievement and feedback from ICARIA-MM investigators. (NICE. 2020)

6 Violates proportional hazard assumption and leads to a loss in post-progression survival (PPS) despite the use of Pd in both arms

There was no evidence from the trial that the hazards for OS with IsaPd would ever converge much less exceed those of Pd, which should also ensure we see no loss of post-progression survival benefit for IsaPd. Analyses of Schoenfeld residuals for OS during the trial provide no evidence of non-proportionality of hazards and thus do not support a projection in which the hazards of death are greater for IsaPd vs. PD.

The assumption that IsaPd will become worse over time compared to treatment with Pd leads to a negligible survival advantage attributable to IsaPd and a very high incremental cost-effectiveness ratio (ICER). Given the limitations of the EGP re-analyses as described above, SGZ suggest consideration of several analyses using alternative approaches for modeling IsaPd OS which address EGP concerns around OS uncertainty (~10% of patients alive within 5 years) but ensure clinical plausibility (curves shouldn't converge & no PPS loss).

Sponsor Proposed Re-analysis 1: Sponsor's base-case OS curve for IsaPd*, CADTH OS curve for Pd, and CADTH re-analysis 2-5

First, SGZ suggests consideration of an analysis in which distributions for OS for IsaPd are those used in the SGZ base-case--i.e., the unrestricted (U) lognormal distribution for IsaPd OS, with all other parameters consistent with those in the EGP re-analyses 1-5 (including use Weibull (U) for Pd). [result: $166,116/QALY gained]

Sponsor proposed re-analysis 2: Sponsor Proposed re-analysis 1 & shorter time horizon

Since SGZ is aligned to the EGP concerns around long-term survival uncertainty, SGZ suggests consideration of an analyses in which the same assumptions are employed as the sponsor's proposed re-analysis 1, but the time horizons limited to 10 years. [result: $224,818/QALY gained].

Sponsor proposed re-analysis 3: Proportional hazard model using Weibull restricted models

To further address uncertainty around OS, SGZ suggests consideration of a scenario with implementation of EGP re-analyses 2-5 and using the Weibull restricted (R) distributions for both IsaPd and Pd, yielding a

probabilistic ICER of $483,898/QALY gained. SGZ believes this analysis is reasonable for CADTH's consideration for several reasons:

a) For Pd, the Weibull (R) distribution yields projections of OS similar to the Weibull (U) distribution, with **OS at 48 months below 10%** as suggested by the clinical experts consulted by the EGP.
b) For IsaPd, the Weibull (R) is **more conservative than the lognormal (U) distribution** used in the SGZ original base case and therefore addresses the EGPs concern around uncertainty in SGZ OS projections.
c) The visual fit ensures clinical plausibility since by **demonstrating that the curves do not converge**
d) Finally, use of the Weibull (R) distributions for both arms yields projections of the difference in PPS that are not negative, which is consistent with expectations, assuming that there is no compelling evidence of detrimental carry-over effects of IsaPd after treatment discontinuation.

Sponsor Proposed Re-analysis 4: Sponsor Proposed Re-analysis 3 w/ shorter time horizon

To address uncertainty associated with the above analyses, SGZ suggests shortening time horizon Sponsor's proposed analysis 4, but the time horizon is limited to 10, yielding corresponding probabilistic ICERs of $499,186 per QALY gained.

Analysis		Parameter			Result			Clinical Plausability Check		
SGZ Analysis	EGP Re-Analyses*	IsaPd OS	Pd OS	Time Horizon (y)	Δcost, $	ΔQALY	ICUR (QALY), $	Pd OS @ 60 Months[1]	OS Converges?[2]	ΔPPS LYs[3]
EGP Re-Analysis*										
	1 to 5	Weibull (U)	Weibull (U)	20	188,480	0.13	1,416,676	13.0%	Yes	-0.18
SGZ Suggested Alternative Analyses										
1	2 to 5	Lognormal (U)	Weibull (U)	20	209,198	1.26	166,116	12.96%	No	1.60
2	2 to 5	Lognormal (U)	Weibull (U)	10	192,972	0.86	224,818	12.96%	No	0.98
3	2 to 5	Weibull (R)	Weibull (R)	20	191,845	0.40	483,898	9.67%	No	0.24
4	2 to 5	Weibull (R)	Weibull (R)	10	190,351	0.38	499,186	9.67%	No	0.21

*Note - SGZ was unanble to replicate the probabilistic ICUR for the CADTH reanalysis ($1,555,947 per QALY gained) using the SGZ model and the description of the reanalyses provided by EGP. The deterministic ICUR using the SGZ model and the EGP description of their re-anayses was $1,553,609 per QALY gained.
[1]To ensure that a clinically plausible number of patients remain alive at the 5-year landmark
[2]To ensure that the IsaPd and Pd curves to not converge
[3]To ensure that the survival distributions to not result in a loss in post-progression survival gain in the IsaPd arm

Taken as a whole, even using the EGP analyses 2-5, the relatively conservative Weibull (R) distributions for OS for IsaPd and Pd and the conservative time horizon of 5-years, the ICER for IsaPd versus Pd is still far below that suggested in the EGP revised analyses 1-5.

ADOPTION FEASIBILITY

Sanofi strong believes that an error may have been made in modifying the BIA model for removing IsaPd use as a second-line treatment, which is driving an overestimation of the budget impact. A detailed summary regarding this potential error was provided to CADTH in advance of the initial recommendation being posted. When considering all of the changes used to derive the CADTH base case, SGZ estimated a 3-year budget impact of approximately $15M.

**Note: The OS model selection for the manufacturer base-case analysis (IsaPd: Log-normal; Pd: Exponential) have been discussed extensively and validated using clinical data, expert elicitation, diagnostic plots, best statistical fit using AIC/BIC criteria (as acknowledged by EGP), and visual inspection. Please refer to pg. 47 – 50 of submitted PE report for more information.*

b) Please provide editorial feedback on the initial recommendation to aid in clarity. 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

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the stakeholder would support this initial recommendation proceeding to final recommendation ("early conversion"), which would occur two business days after the end of the feedback deadline date.

☐ Support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.

☒ Do not support conversion to final recommendation.
Recommendation should be reconsidered by pERC.

If the eligible stakeholder does not support conversion to a final recommendation, please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the stakeholder 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.
Additionally, if the eligible stakeholder supports early conversion to a final recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, the criteria for early conversion will be deemed to have not been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

CADTH

Template for Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

1 About Stakeholder Feedback

CADTH invites eligible stakeholders to provide feedback and comments on the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) initial recommendation.

As part of the CADTH's pan-Canadian Oncology Drug Review (pCODR) process, pERC makes an initial recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. The initial recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 business days within which to provide their feedback on the initial recommendation. It should be noted that the initial recommendation may or may not change following a review of the feedback from stakeholders.

CADTH welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

a) Application of Early Conversion

The stakeholder feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the initial recommendation?**
   All eligible stakeholders are requested to indicate whether they agree, agree in part, or disagree with the initial recommendation, and to provide a rationale for their response. Please note that if a stakeholder agrees, agrees in part or disagrees with the initial recommendation, they can still support the recommendation proceeding to a final recommendation (i.e. early conversion).
2. **Does the stakeholder support the recommendation proceeding to a final recommendation ("early conversion")?**
   An efficient review process is one of the key guiding principles for CADTH's pCODR process. If all eligible stakeholders support the initial recommendation proceeding to a final recommendation and that the criteria for early conversion as set out in the *Procedures for the CADTH Pan-Canadian Oncology Drug Review* are met, the final recommendation will be posted on the CADTH website two business days after the end of the feedback deadline date. This is called an "early conversion" of an initial recommendation to a final recommendation.
   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), the criteria for early conversion will be deemed to have **not** been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. Please note that if any one of the eligible stakeholders does not support the initial recommendation proceeding to a final recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the initial recommendation.

b) Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the initial recommendation. If the feedback can be addressed editorially this will done by the CADTH staff, in consultation with pERC, and may not require reconsideration at a subsequent pERC meeting.

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

2 Instructions for Providing Feedback

- The following stakeholders are eligible to submit feedback on the initial recommendation:
  - The sponsor and/or the manufacturer of the drug under review;
  - Patient groups who have provided input on the drug submission;
  - Registered clinician(s) who have provided input on the drug submission; and
  - CADTH's Provincial Advisory Group (PAG)
- 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.
- The template for providing stakeholder is located in section 3 of this document.
- The template must be completed in English. The stakeholder 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.
- Feedback on the initial recommendation should not exceed three 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 provided to the pERC for their consideration.
- 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, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.
- References may be provided separately; however, these cannot be related to new evidence.
- CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback must be disclosable and will be posted on the CADTH website.
- The template must be filed with CADTH as a Microsoft Word document by the posted deadline.
- If you have any questions about the feedback process, please e-mail requests@cadth.ca