PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Ibrutinib (Imbruvica) for Waldenström's Macroglobulinemia

November 3, 2016

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	IMBRUVICA®(ibrutinib) for the treatment of patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
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 agrees with the Clinical Guidance Panel conclusion that "there is a net clinical benefit to treatment with ibrutinib in patients with relapsed and refractory WM. This conclusion is based on the high response rate and long progression-free survival reported in a phase II study, supported by preliminary results from a phase three-arm trial reported in an abstract form (CGR,p.9)." "The Response rates and durations of response with ibrutinib were considered clinically meaningful. The activity in this heavily pre-treated population suggests that its unique mechanism of action translates into a true addition to the treatment armentarium" (CGR,p.9).

Janssen agrees with pERC that "the toxicity profile of ibrutinib, despite the high incidence of grade 3 or higher AEs, including neutropenia and thrombocytopenia, was reasonable and manageable" (pERC,p.6).

Janssen disagrees with the following component of the initial recommendation: "absence of clear advantage over available treatment options" (pERC,p.2) as this evaluation is inconsistent with the available evidence of ibrutinib in WM (Phase II single arm study - PCYC-1118E (Treon.2015) and PCYC-1127 substudy (arm C) (Dimopoulos.2015; Dimopoulos.2016)), and available evidence on relevant comparators reported in the initial recommendation (pERC, p.2 and p.4). Taking into consideration the following, Janssen believes that clear clinical benefit in terms of efficacy and safety is observed with ibrutinib in comparison to available therapies:

- **Ibrutinib efficacy profile favorably compares to available treatment options. In**

particular, compared with available chemo- and chemoimmuno-therapies, ibrutinib:

- Improves Overall Response Rate (ORR): patients receiving ibrutinib had an ORR (≥MR) of 90.5% and 90% in PCYC-1118E and in PCYC-1127 Arm C, respectively.These estimates exceed the upper range stated in the initial recommendation (85% with single agents and 83.3% with combo therapies) (pERC, p.4). In addition, ORR increased with longer ibrutinib treatment duration in both trials (from 87.3% to 90.5% in PCYC-1118E and 84% to 90% in arm C of PCYC-1127).

- **Prolongs Progression-Free Survival (PFS)**: estimated PFS among patients receiving ibrutinib is 69.1% at 2 years, and 93% at 1 year, in PCYC-1118E and in PCYC-1127 Arm C, respectively. Therefore, PFS with ibrutinib exceed the upper range expected with available agents by 8 months (median PFS of 12 to 16 months with relevant comparators stated in the recommendation) (pERC, p.4).

- **Ibrutinib safety profile favorably compares with available treatment options, with no treatment related IgM flare, neurotoxicity or infusion reactions reported with Ibrutinib.**

- ***IgM flare:*** WM patients with signs of hyperviscosity or patients with high IgM values are predisposed to serious and potentially life-threatening treatment related 'IgM flare', a transient increase of serum IgM immediately following initiation of rituximab treatment (Buske.2013). This flare or spike can lead to further hyperviscosity that can lead to serious complications (NCCN.2016; Treon.2004) like an increased risk of intracranial hemorrhage that requires acute management involving the use of urgent plasmapheresis (Treon.2009). In contrast, patients receiving ibrutinib have not reported IgM flare and most of the patients were able to discontinue required plasmapheresis following ibrutinib treatment, corroborating with the rapid decrease in serum IgM levels with ibrutinib treatment in PCYC-1118E and PCYC-1127 Arm C.

- ***Neurotoxicity:*** Peripheral neuropathy is a key morbidity associated with the disease due to the high production of IgM (Treon.2009). Peripheral neuropathy, is reported in as many as 47% of WM patients and can cause permanent weakness and even paralysis (Levine.2006). Peripheral neuropathy may be exacerbated following use of available treatments such as bortezomib and rituximab. Dose-limiting related neuropathy has been reported with bortezomib based therapies and can further increase the risk for permanent nerve damage and lifelong debilitation in WM patients (Chen.2007). Moreover, rituximab can often cause a flare in serum IgM levels that can potentiate symptoms of peripheral neuropathy in WM patients (Treon.2009; Dimopoulos.2014)**.** In contrast, patients receiving ibrutinib have not reported treatment related neurotoxicity (PCYC-1118E and PCYC-1127 Arm C). In addition, some patients receiving ibrutinib reported subjective improvements in peripheral sensory neuropathy (PCYC-1118E), corroborating with the rapid decrease in serum IgM levels with ibrutinib treatment.

- ***Major infusion reactions:*** WM patients are particularly susceptible to severe rate-related infusion reactions with rituximab (Dimopoulos.2014, Dimopoulos.2002). This could impact the tolerability of R-based therapies. In contrast, as an oral therapy, ibrutinib is not associated with infusion reactions.

***Janssen agrees with the pERC evaluations that in the two studies of ibrutinib, there was a "lack of complete responses with ibrutinib" (pERC, p.2)*; however, Complete Responses (CRs) are exceedingly rare with single agents and very rare in combination therapies:**

- In fact, when considering studies of single agents listed in the table "summary of selected WM studies" (CGR,p.45): CRs were reported in 0% of patients treated with rituximab (TN + R/R patients), fludarabine (R/R patients) or bortezomib (TN+R/R patients) and only 2% of patients treated with cladribine (R/R patients) (Dimopoulos.2002,Gertz.2004,Treon.2005,Leblond. 2001, Chen.2007,Treon.2007, Dimopoulos.1995).

- When taking into account studies for the Bendamustine + Rituximab (BR) combination in R/R WM: CRs were reported in 0-7% of patients (Treon.2011; Tedeschi.2015) (CGR, p.46).

Janssen agrees with the following component of the initial recommendation that "treatment options with demonstrated benefit over available treatment options in terms of symptom control, improvement in quality of life and longer remission rates are a continued need for patients" (pERC, p.2).

Janssen believes that there is a high unmet need in the management of patients with R/R WM. In fact, there are very few options for patients who have received at least 2 prior therapies including R-based treatment who are not eligible for further chemo-immunotherapy. This population would include patients who had a suboptimal response to R-based regimens (for example: BR, CVP-R or CHOP-R) or those who are considered too frail.

Per the evidence provided as part of our submission to pCODR, Ibrutinib is established as a highly effective treatment option with manageable safety profile. Ibrutinib is indicated for all patients with WM, including the patient population targeted in the submission "patients with WM who have received at least one prior therapy" as well as heavily pretreated patients who are refractory to R-based regimens and are not eligible for further chemo-immunotherapy (Treon.2015; Dimopoulos.2016).

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.

____	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?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

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
3	Summary of pERC deliberations	Paragraph 1, Line 14	Janssen suggests that based on the information provided to pCODR re. quality of life data reported in Arm C (non-disclosable information), there is: "**alignment of quality of life data from Arm C of the PCYC-1127 trial, which indicated [redacted] in quality of life compared with the experiences patients reported through the patient group input indicating improvements in quality of life."**

3.3 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	Paragraph 1, Line 3	**"combined total of 94 patients"** instead of **"combined total of 91 patients"**
7	Patient-Based values	Paragraph 1, line 1	
5	Overall clinical benefit	Paragraph 4, line 10	The MRR was defined in Dimopoulos et al. 2015 and Dimopoulos et al. 2016 as **"(≥PR)"**
5	Overall clinical benefit	Paragraph 6, line 5	In reference to the CGR, this statement was amended to **"the pCODR review team requested data on completion rates and minimally important differences for these data. These data were requested but made non disclosable until publication of the data."** Suggest to replace with the CGR statement.
6	Overall clinical benefit	Paragraph 2, line 2	**"Grade 3 or 4 adverse events (AE's) were experienced in 50% (n=31) of the patients in the study"**

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.