pan-Canadian Oncology Drug Review

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

Ofatumumab (Arzerra) for Chronic Lymphocytic Leukemia

January 29, 2015

3. Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): Arzerra (ofatumumab) for 1L CLL
Role in Review (Submitter and/or Manufacturer): Submitter and manufacturer
Organization Providing Feedback: GlaxoSmithKline

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

GSK disagrees with the initial recommendation for the following reasons:

1. **The clinical value of Arzerra (ofatumumab) was not evaluated versus the standard of care (SOC).**
   - The current standard of care and therefore appropriate comparator for the first-line treatment of CLL in patients for whom fludarabine is inappropriate ("less fit") is chlorambucil monotherapy. Bendamustine monotherapy is also approved and widely funded for this patient population.
     - Bendamustine (Treanda) received a positive recommendation in 2013 by pCODR for the same patient population as requested for Arzerra (first line treatment of CLL in patients for whom fludarabine-based therapy is inappropriate). The pERC decision on January 17, 2013, was that chlorambucil monotherapy was the appropriate comparator (SOC). R-Chl was not included as a comparator in that pCODR review, and the lack of comparative data for Bendamustine vs R-Chl was not seen as a weakness in the submission.
     - There has been no indication that the use of R-Chl has increased to any notable degree since Feb 2013, when pERC noted that "patients who are not candidates for fludarabine are frequently treated with chlorambucil but there is a need for more effective treatment options in this population"(*pCODR final recommendation pg.2, Bendamustine for 1L CLL who are inappropriate for FCR, Feb.2013*).
   - Clinicians from across the country who attended a GSK advisory board meeting in Nov.2013 also provided consensus that chlorambucil monotherapy was standard of care, and, in somewhat fitter patients, bendamustine monotherapy was also utilized.
     - This clinical opinion is substantiated by the survey conducted by the Leukemia and Lymphoma Society of Canada (LLSC), where patients reported no use of R-Chl in first line treatment of CLL (*pCODR Clinical Guidance Report pg.20, Arzerra)*.
   - Rituximab-chlorambucil (R-Chl) is considered a valid clinical comparator, however, it is not considered SOC.
     - Rituximab in combination with chlorambucil may be used in clinical practice in the less fit CLL population, however, this combination is not approved by Health Canada as a safe and effective treatment regimen for any patient population, nor is it readily available to the majority of Canadians. Hematologists and oncology pharmacists across the country have validated that R-Chl is not used in BC or NB, is rarely used in Ontario (restricted to patients who do not rely on public drug funding and in centres which infuse non-funded agents), and is available only on a case by case basis in AB, SK and MN.

- In contradiction to the importance that pERC has put on R-Chl as a clinical comparator, feedback from the Provincial Advisory group states, "From a PAG perspective, chlorambucil monotherapy would be the treatment option for previously untreated CLL in patients where fludarabine-based chemotherapy is not suitable" (*pCODR Clinical Guidance Report, pg.13, Arzerra*).

- The value of Arzerra should be evaluated compared to standard of care (chlorambucil monotherapy) and not discounted for the lack of data comparing to all clinical comparators, especially comparators that pERC suspects are broadly used off-label and are not equally accessible to all patients across the country.

2. The pERC recommendation eliminates patient and physician choice for the management of 1L CLL.

- There is a need for more effective and available treatment options for 1L CLL patients who are inappropriate for fludarabine based treatments;
    - Although tolerable and broadly available to patients, chlorambucil monotherapy is limited in efficacy.
    - Bendamustine (Treanda) monotherapy is a valid treatment option, however, tolerability challenges have limited this to the "fitter" of the fludarabine-inappropriate patients. Additionally, it is unclear how the efficacy and safety of bendamustine compares to Arzerra + Chl, given the invalidity of an indirect treatment comparison.
    - R-Chl is a clinically relevant treatment option, however, it is only available in a few jurisdictions, is not approved by Health Canada, and it is unclear how the efficacy of R-Chl compares to Arzerra + Chl.
    - Obinutuzumab(Gazyva) obtained Health Canada approval in November 2014, however, it is still under review with pCODR, and it is unclear how the efficacy and safety of Gazyva + Chl compares to Arzerra + Chl, given the invalidity of an indirect treatment comparison.
- Since Arzerra + Chl, bendamustine, obinutuzumab + Chl and R-Chl cannot be compared in terms of efficacy or safety, physicians and patients should have the choice of therapies to optimize treatment for each individual.
    - Patient advocacy groups (CLL PAG and LLSC) both indicated the high importance of having choices in CLL treatment (*pCODR Clinical Guidance Report pg.17, Arzerra)*.
    - Given the heterogeneous nature of CLL, physicians want access to a variety of treatments in order to better suit the holistic needs of each individual patient, finding a balance between tolerability and efficacy.

3. Interpretation of the clinical value of Arzerra is inconsistent with previous pCODR/pERC assessments of benefit for similar patient populations (1L CLL).

Assessment of clinical value should be consistent across pCODR submissions, and should take into consideration the totality of evidence to support the use of the treatment for the group of patients

- pERC's assessment of an improvement in median PFS benefit of 9.3 months as "modest" is subjective and inconsistent with other clinical experts in Canada and globally.
    - The improvement in PFS, as assessed by an independent review committee (IRC), was statistically significant. The addition of Arzerra to chlorambucil resulted in a 71% improvement in PFS compared to chlorambucil alone, an acknowledged SOC.

- Interpretation of PFS improvement as "modest" is in contrast to unanimous feedback obtained by Canadian hematologists at a GSK Advisory Board meeting in November 2013 and to international HTA assessment bodies (NICE).
- Independent review of the Arzerra clinical safety and efficacy data by Health Canada led to an approval of the use of Arzerra in combination with chlorambucil in the patient population for whom GSK has sought pCODR recommendation.
- Although R-Chl should not be considered standard of care in this patient population, it can be considered a clinical comparator. To this end, the median PFS benefit demonstrated by the addition of rituxumab to chlorambucil demonstrated in the CLL11 trial was only 4.9 months (16.3 months with R-Chl vs. 11.1 months with chlorambucil alone; hazard ratio, 0.44; 95% CI, 0.34 to 0.57; P<0.001).

- Overall survival results are immature and should not be considered "lacking" as the true OS assessment is pending. The COMPLEMENT 1 study was not powered to show a difference in overall survival (OS) at the time of the PFS assessment. While the OS assessment of Arzerra + Chl versus Chl is immature and did not reach statistical significance, the point estimate for OS favours the combination. A subsequent analysis will be done at 5 years.
    - A statistically significant OS advantage was also not observed for bendamustine at the time of its positive recommendation by pCODR, despite significant improvements in both PFS and overall response.
- The fact that QOL did not deteriorate with the addition of Arzerra, despite the occurrence of infusion related reactions or neutropenia, is a positive sign of the relative risk/benefit of Arzerra. Throughout the study and during follow-up, HRQOL was similar between the two arms of the study except in two scales: physical functioning favoured chlorambucil, and financial difficulties favoured the combination arm.
    - Clinical endpoints that are relevant to QOL and expressed patient need do not appear to have been adequately considered by pERC
        - Patients have indicated that extending the duration of time between treatments is very important to them. Specifically, "they are willing to tolerate side effects that are manageable with medication and are short term especially if the treatment results in a longer remission" (*pCODR Clinical Guidance Report pg.21, Arzerra).*
        - Time to next treatment (TTNT) provides an indicator in this regard. In the COMPLEMENT-1 study, TTNT improved significantly with the addition of ofatumumab. The median TTNT was 39.8 months in the ofatumumab plus chlorambucil arm, compared with 24.7 months in the chlorambucil monotherapy arm (HR, 0.49; 95% CI, 0.36-0.67; $P < 0.001$).
- Assessment of clinical value should be consistent across pCODR submissions for a similar patient population in terms of data expectations
    - The data sets for the submission of Arzerra + Chl and Bendamustine monotherapy to pCODR included data that demonstrated statistically significant improvements in PFS,

statistically significant improvements in overall response rates, no statistically significant OS due to immature datasets, and did not demonstrate improvements in quality of life.

- In spite of these similarities, pERC assessment of clinical value were very different;
  - In the case of Bendamustine, pERC concluded that there was a net clinical benefit associated with bendamustine in this setting and patient population", (*pCODR final recommendation pg.2, Bendamustine for FCR-inapprop. 1L CLL, Feb.2013*).
  - In the case of Arzerra, pERC questioned the net clinical benefit (*pCODR initial rec. pg.2, Arzerra*)

4. Clinical data needs were not communicated throughout the pCODR review process, rendering the initial recommendation unreasonable and unfair.

pCODR is required to ensure that its conduct and its decisions are rendered in a fair and transparent way.

- GSK responded fully to all of the inquiries made by pCODR during the review process. At no time during the review process did pCODR make any inquiries, or raise any issue or concern about the significance of Arzerra's clinical value (ex. "modest PFS improvement", R-CHL, no QOL improvement, acceptability of chlorambucil as the appropriate comparator, lack of statistically significant OS improvement due to data immaturity, and the impact of the delay in publishing the study manuscript). GSK is forced to question why such fundamental concerns were not raised by the clinical reviewers until the time of initial recommendation.
- For example, pCODR cites the lack of publication of the data as creating ambiguity over the role of GSK in the conduct of the trial. Quite simply, taking such a decision in this manner is procedurally unfair. Indeed, the inherent unfairness is only augmented by the fact that the pCODR review process specifically mandates an active consultation process with the submitter prior to the publication of an initial recommendation. In this case, no consultation occurred regarding pCODR's apparent concerns about this issue, despite the fact that pCODR had multiple opportunities to do so. At the time of submission, GSK advised pCODR that publication would not occur before Q4 2014. pCODR raised no concerns at that time. During the review, GSK advised pCODR that publication would be delayed. pCODR raised no concerns at that time. The inherent unfairness and unreasonableness of taking such a decision in this way is further exacerbated by the fact that publication is not a prerequisite for submission or review and, in any event, even if it was, publication is imminent. Had the weight of the publication upon the initial recommendation been communicated to GSK, it could have and would have worked to mitigate this risk.
  - If the initial recommendation stands, patients will be the ones who will suffer most. That is why compliance with the principles of procedural fairness is so essential here. Decisions simply cannot be taken in the manner outlined above and be considered procedurally fair.

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. Recommendation does not require reconsideration by pERC.	__x__	Do not support conversion to final recommendation. 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

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments