pan-Canadian Oncology Drug Review

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

Venetoclax (Venclexta) Chronic Lymphocytic Leukemia

March 2, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): VENCLEXTA (venetoclax)
Indication: in monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy, or patients with CLL without the 17p deletion who have received at least one prior therapy and for whom there are no other available treatment options.
Funding request: As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi)

Role in Review : Manufacturer

Organization Providing Feedback: AbbVie Corporation

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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**

AbbVie took notice of concerns in regards to Phase 2 non-comparative interim data and the uncertainty around outcomes such as overall survival and progression-free survival. However, after careful review of pERC recommendation and summary of deliberations, **AbbVie believes that pERC may not have fully appreciated the extent of the submitted evidence and may have misinterpreted several aspects of the submission:**

1. The CGP and pERC reported PFS in patients pre-treated with a BCRi to be less than 6 months. AbbVie notes that median OS reported in the literature for the same patient population ranges between 2 to 16 months.[1-4] The peer-reviewed manuscript[5] reports a median PFS (mPFS) of 24.7 months with venetoclax in patients pre-treated with ibrutinib. The Clinical Study Report (CSR) reported estimated 12-month PFS of 71%, 85.7% and 74.2% for the ibrutinib arm, idelalisib arm and expansion cohort, respectively. Median OS had not yet been reached after a median follow up of 18.5 months, 16.3 months and 7.9 months respectively. AbbVie believes this support the net clinical benefit of venetoclax in this difficult to treat patient population facing an extremely poor survival prognosis, and that pERC might have misinterpreted the extent of the clinical benefit venetoclax is providing.
2. The peer-reviewed manuscript (The Lancet Oncology)[5] was submitted as per pCODR's request following the checkpoint meeting process and it is AbbVie's understanding it was to be considered by pERC.
3. Venetoclax is the only CLL treatment with a prospective clinical study to support its use in CLL patients who have previously failed BCRi therapy, including those with del(17p)/TP53 mutation.[6-8] To AbbVie's knowledge, there are no planned studies (see clinicaltrial.gov) to compare venetoclax with standard of care in this patient population and even if one were to be conducted, it would take several years before any findings become available. Similarly, the final analysis of M14-032 will only be available in two years' time (2019).
4. Scores from the QoL instruments were misinterpreted by the CGP whereby decreasing scores represent an improvement of symptoms (e.g. less fatigue is an improvement) as opposed to GCP stated worsening of symptoms.[9] Although patient desire for treatments that improve QoL is noted in the recommendations, no mention of these results is made. Abbvie is concerned the CGP error led to further misunderstanding by pERC.
5. AbbVie believes too much emphasis might have been given to other factors, such as the health care resources associated with TLS management of high risk patients and the potential bias from the retrospective study submitted. We invite pERC to review the explanations provided below.

Considering the high unmet need and extremely poor prognosis in patients with CLL pre-treated with a BCRi, that venetoclax is the only product studied and indicated in Canada for these patients, that venetoclax is associated to a mPFS of 24.7 months (in patients pre-treated with ibrutinib) while these patients with PFS typically being < 6 months, the tolerable safety profile of venetoclax over alternative therapies, the clinically and statistically significant improvements of quality of life shown with venetoclax, the unlikelihood of any future RCT comparing venetoclax to standard of care in this patient population, and the compelling patient and clinician input submitted to pCODR, AbbVie respectfully requests pERC reconsider its initial recommendation and positively recommend the reimbursement of venetoclax for the treatment of patients with CLL who have received at least one prior therapy and who have failed a BCRi.

b)

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.**

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Page #	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
4	**Overall Clinical Benefit**	**Par #2; line 10**	**pERC reports: The M14-032 trial data are based on interim analysis of data that have not been peer-reviewed or published.**
The accepted peered-reviewed manuscript by The Lancet Oncology[5] for the M14-032 trial data pertaining to patients who received ibrutinib as their last prior BCRi was submitted to pCODR as part of the checkpoint meeting process. The patient population included in the manuscript is the most relevant for the Canadian patient population since in Canada, ibrutinib is primarily used in the majority of patients. Of note, each of the two arms of the M14-032 study was analyzed separately as pre-specified in the trial protocol.			
6	**Patient-reported outcome**	**Par #2**	**"Clinically meaningful worsening from baseline on a number of scales."**
There is a misinterpretation of the quality of life results for all 3 treatment arms (aggregate data) as described in Clinical Guidance Report Section 6.3.2.2 in the final paragraph of the Quality of Life section: Regarding fatigue scores from both the EORTC QLQ-CLL16 and EORTC QLQ-C30, negative scores on both fatigue scales represent an improvement as opposed to worsening. Regarding future health scores and social problems on the CLL16, negative scores also reflect improvement rather than worsening. Please refer to published results (abstract form) in the submission. [9]			
3	**Summary of pERC deliberation**	**Par #4, Line #9**	**"(…) due to limitations in the available non-randomized clinical evidence (…) and the absence of long-term data on the potential survival benefit gained in this setting (…) was challenging to determine the true ICER.**
AbbVie believes that the conducted cost-effectiveness re-analysis is inappropriate and outcomes are not informative to estimate the true incremental value of venetoclax. The approach chosen by the EGP for their 'lower' and 'upper' bound reanalysis is to ignore CADTH's current guidelines and revert to previous methods for analysis of uncertainty where extreme values for model parameters are considered deterministically (i.e., in this case upper and lower confidence intervals). This type of reanalysis, which does not reflect decisional uncertainty given available information but is instead based on a frequentist determination of confidence intervals, is highly inappropriate to add-on to a Bayesian analysis of uncertainty as recommended under CADTH's own guidelines.			

3.3 Additional Comments About the Initial Recommendation Document

Page #	Section Title	Par #, Line Number	Additional Comments
1	**pERC Recomendation**	**Par #1; line 10**	**pERC reports: (…)considerable uncertainty in the magnitude(…)based on immature interim analysis (…) such as OS and PFS.**

1. The peer-reviewed manuscript of the efficacy of venetoclax in patients who were refractory to or relapsed during or after ibrutinib therapy[5] reported a median follow-up of 14 months for all patients, 19 months for the main cohort and 12 months for the expansion cohort. The results showed a median PFS of 24.7 months (95% CI 19.2-not reached) and an estimated 12 month PFS of 75% (95% CI 64-83).
2. In the CSR of the M14-032 trial submitted to pCODR, median time on venetoclax was 18.5 months for the ibrutinib arm, 16.3 months for the idelalisib arm and 7.9 months for the expansion cohort. Median PFS had not been reached in either cohorts and was estimated at 71%, 85.7% and 74.2% respectively after 12 months. AbbVie believes these results show a net clinical benefit in this patient population who have a poor prognosis with PFS typically being < 6 months as noted by the CGP and pERC, and median OS reported in the literature of 2 to 16 months [1-4].
3. pERC mentioned the absence of mature OS as a factor precluding them to conclude on the positive clinical benefit of venetoclax. However, PFS in the presence of immature OS has been used as an acceptable outcome for net clinical benefit in previous positive pERC recommendations, including idelalisib (Aug 2015), ibrutinib (March 2015) and first-line bendamustine (Nov 2012), where alternatives have high toxicity and limited effectiveness. With estimated OS at 12 months in the ibrutinib pre-treated cohort of 91% (83-95) and median OS not reached (27.8-not reached)[5], the anticipated benefit of venetoclax on OS of one to two-year reported by the CGP is not

only based on clinical opinion but also supported by the M14-032 data submitted and the Mato et al. (2017) retrospective study.

4. As recognized by pERC in its correspondence of July 24 2017 when granting venetoclax a priority review, there is a significant need for effective treatment options in this setting "*in this heavily pre-treated population, median overall survival was not reached at 11.8 months of follow up period, a finding which the panel considered to be very promising.*" As reported by pERC, the prognosis for patients resistant or intolerant to available TKi is very poor and these patients have no reasonable treatment options remaining. To our knowledge, venetoclax is the only CLL treatment with a prospective clinical study (M14-032) that addresses this high unmet medical need.
5. AbbVie believes all currently available evidence establishes venetoclax as the most effective agent available for the treatment of such patients and supports a conclusion that there is a net overall clinical benefit from the use of venetoclax in the treatment of symptomatic CLL patients resistant to at least one BCRi.

5	**Key efficacy results**	**Par #2; Line 10**	**pERC reports: (…) although ORRs were high, a small number of patients experienced complete responses while the majority of patients who responsed experienced partial responses**

In patients who have failed ibrutinib, the ORR rate from venetoclax was 65% (95% CI: 53-74) including a 9% CR/CRi. The median duration of response was not reached (95% CI: 17.6 – not reached)[5]. Given poor overall survival reported in the literature included in the submission (median OS of 2 to 16 months)[1-4] in this heavily pre-treated population and the meaningfulness of achieving a more-than-50% response in last line therapy for patients, this evidence speaks to the clinical benefit of venetoclax. AbbVie also notes that pERC provided a positive recommendation to agents in earlier lines of therapy despite the absence of either median PFS, median OS and very low or absent CR rates (e.g. ibrutinib and idelalisib).

2	**Summary of pERC Deliberations**	**Par #; Line 1**	**pERC reports: (…) CGP indicated that a RCT is unlikely to be conducted in this setting (…). pERC (…) agreed that it would have been feasible to conduct a RCT vs available treatment options.**

'pERC noted that it has accepted evidence from non-comparative studies in previous submissions for reasons that are context (drug and disease) specific.' AbbVie believes that the current venetoclax submission should be treated similarly: Considering the strong activity showed by venetoclax monotherapy in refractory CLL at the time, the absence of effective therapy indicated for the treatment of CLL patients who have failed a BCRi, the smaller target population this represents, and that there are no other prospective clinical trial data to establish the standard of care in this setting, study M14-032 was designed as a phase 2 non-comparative trial. VENCLEXTA is the only CLL treatment with a prospective clinical study to support its use in CLL patients who have previously failed BCRi therapy, including those without del(17p)/TP53 mutation. [6-8] To AbbVie's knowledge, there are no planned studies (see clinicaltrial.gov) to compare venetoclax with standard of care in this patient population and even if one were to be conducted, it would take several years before any findings become available. Similarly, the final analysis of M14-032 will only be available in two years' time (2019). AbbVie also wants to reiterate that such a study would be difficult to conduct given the lack of consensus on treatment options for these patients. Finally, as recognized by pERC when granting venetoclax the status of priority review, there is a high unmet need for effective treatment options in this patient population.

4	**Studies included**	**Par #; Line 3**	**pERC reports: (…) this evidence has not been confirmed by results from comparative trials.**

The Mato et al. (2017) study provides insights into the effectiveness and toxicity of venetoclax in a large unselected generalizable cohort of CLL patients (n=683) failing BCRi therapy. The strength of this study is the consistent and systematic clinically rich data collected across multiple academic centers and the use of IWCLL criteria in effectiveness assessment; in-line with the criteria used in the M14-032 clinical trial. Using the IWCLL criteria, the ORR (74%) observed in this study was consistent with the ORR reported for Arm A (ibrutinib failures ORR 72%) and arm B (idelalisib failures ORR 67%) in the M14-032 trial. These study findings indicate that the efficacy observed among venetoclax users in the M14-032 study can be achieved in CLL patients in practice. Overall, despite from a potential for selection bias or retrospective data collection, this study provides information on a broader non-trial patient population complementing the clinical trial data. AbbVie notes that Mato et al. (2017) also supports the CGP/pERC assessment of PFS outcome associated to alternative therapies post-BCRi of less than 6 months.

3	**Summary of pERC Deliberations**	**Par #5; Line 2-4**	**pERC reports: (…) continued risk for TLS (…) would need to be assessed and treated in hospital (…) this monitoring would require additional health care resources.**

AbbVie believes pERC may have misunderstood the level of additional health care resources needed to address TLS risk associated with venetoclax. Despite observations of highly proliferative disease in patients with relapsed CLL upon discontinuation of ibrutinib, venetoclax was not associated with an increased risk of TLS when recommended dose ramp-up, prophylaxis, and monitoring were applied.[5]CGP reports (Section 2.3): Referring to the need to screen for TLS risk prior to therapy, including regular standard blood tests and imaging assessments (usually CT scanning): "*Although CT scanning is not ordinarily required for initial assessment and primary management of patients with*

CLL, it is a standard evaluation for management of patients in need of treatment of recurrent leukemia and, therefore, will not require extra resources beyond standard of care".

REFERENCES (ALL FOUND IN AbbVIE SUBMISSTION TO PCODR)

1. Mato AR, Nabhan C, Barr PM, Ujjani CS, Hill BT, Lamanna N *et al.* Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience. *Blood* 2016. doi: 10.1182/blood-2016-05-716977

2. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncology* 2015; **1**(1)**:** 80-87. doi: 10.1001/jamaoncol.2014.218

3. Jain P, Thompson PA, Keating M, Estrov Z, Ferrajoli A, Jain N *et al.* Long-term outcomes for patients with chronic lymphocytic leukemia who discontinue ibrutinib. *Cancer* 2017; **123**(12)**:** 2268-2273. e-pub ahead of print 2017/02/09; doi: 10.1002/cncr.30596

4. Jain P, Keating M, Wierda W, Estrov Z, Ferrajoli A, Jain N *et al.* Outcomes of patients with chronic lymphocytic leukemia (CLL) after discontinuing ibrutinib. *Blood* 2015; **125**(13)**:** 2062-2067. doi: 10.1182/blood-2014-09-603670

5. Jones JA, Mato AR, Wierda WG, Davids MS, Choi M, Cheson BD *et al.* Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *The Lancet Oncology*. doi: 10.1016/S1470-2045(17)30909-9

6. Jones J, Mato AR, Coutre S, Wierda W, Choi MY, Davids MS *et al.* Preliminary Results of a Phase 2, Open-Label Study of Venetoclax (ABT-199 / GDC-0199) Monotherapy in Patients with Chronic Lymphocytic Leukemia Relapsed after or Refractory to Ibrutinib or Idelalisib Therapy. *ASH* 2015.

7. Coutre SE, Wierda WG, Choi MY, Davids MS, Cheson BD, Furman RR *et al.* Venetoclax Is Active In CLL Patients Who Have Relapsed After Or Are Refractory To Ibrutinib Or Idelalisib. *EHA Abstracts* 2016**:** 616581.

8. Abbvie. M14-032: A Phase 2 Open-Label Study of the Efficacy and Safety of Venetoclax (ABT-199/GDC-0199) in Chronic Lymphocytic Leukemia Subjects with Relapse or Refractory to B-Cell Receptor Signaling Pathway Inhibitor Therapy. *Clinical Study Protocol* 2015.

9. Wierda W. SK, Potluri J. et al. Impact of Venetoclax on the Quality of Life of CLL Patients Relapsed/Refractory to B-Cell Receptor (BCR) Signaling Pathway Inhibitor Treatment. *Abstract presented at the 22nd Congress of the European Hematology Association, Madrid, Spain, June 22-25, 2017* 2017.