CADTH

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

Glasdegib (Daurismo) for Acute Myeloid Leukemia

January 8, 2021

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Daurismo in combination with low-dose cytarabine, for the treatment of newly diagnosed and previously untreated acute myeloid leukemia (AML) in adult patients, who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy.
Eligible Stakeholder Role	Manufacturer
Organization Providing Feedback	Pfizer Canada ULC

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

Pfizer respectfully believes that the clinical benefit glasdegib+LDAC provides to a high unmet need for elderly AML patients who are ineligible for intensive induction chemotherapy, was not fully appreciated by pERC. Particularly, we identified the following aspects:

1. pERC noted several limitations with this phase II trial which resulted in considerable uncertainty around the magnitude of the OS benefit (Clinical Benefit): Pivotal study B1371003 was a multi-center, randomized, controlled study prospectively powered to demonstrate an improvement in OS, with an appropriate number of patients to detect a magnitude of survival benefit that is considered clinically meaningful and statistically significant in this population. The primary endpoint of OS is considered the gold standard in assessing clinical benefit in an oncology trial. Study B1371003 met its prespecified primary endpoint of OS (HR 0.463 (95% CI: 0.299, 0.717; p=0.0002). A p-value of 0.0002 means that there is 0.02% probability for the null hypothesis to be correct. The data from the primary analysis were mature, with more than 80% of death events reported and a median follow-up time of >20 months. The survival benefits were also consistent across key subgroups and were not confounded by subsequent therapies, as evidenced below. Overall, the size, design and conduct of the trial was adequate to demonstrate a positive benefit:risk profile of glasdegib in this setting, and to support approval (NOC with no conditions) of glasdegib in a first-line indication with no need for a confirmatory phase 3 trial by Health Canada.
2. pERC suggested that given the availability of azacitidine, currently the most commonly used therapy for these patients in Canada, it is uncertain whether glasdegib+LDAC addresses an unmet need. (Clinical Benefit): The efficacy of azacitidine has not been demonstrated to be superior to LDAC as evidenced by two randomized head-to-head comparisons.[1,2] Azacitidine is not approved in Canada for AML patients with >30% blasts, which according to CGP represents approximately 70% of the total patients in this population and its use in this setting (and as a comparator) is therefore considered off-label, and not funded by many jurisdictions. LDAC remains a valid treatment option for elderly AML patients, and a valid comparator. The CGP noted that while azacitidine is currently the more commonly used treatment for elderly AML patients, there remains a need for LDAC-based AML treatment options in Canada. And recently, venetoclax+LDAC did not meet its primary survival endpoint and failed to demonstrate statistical OS benefits vs. LDAC alone at the planned primary analysis (mOS 7.2 vs. 4.1 months; HR= 0.75; 95%CI 0.52-1.07; p=0.11).[3] Therefore, Glasdegib+LDAC remains the only approved therapy that has demonstrated statistically significant OS benefits for these patients compared to LDAC alone, regardless of blast count. Finally, registered clinician input specified that glasdegib+LDAC would be a superior alternative to LDAC alone and would probably be preferred over azacitidine alone.
3. Although QoL was not measured (Clinical Benefit, Patient value), Glasdegib+LDAC aligns with patient values with patients experiencing more time without toxicity or progression relative to

LDAC alone. This suggests that glasdegib+LDAC patients experience longer quality-adjusted survival time (i.e., in "good health") and achieve higher rates of transfusion independence, resulting in improved quality of life.[4]

Given the high unmet medical need and limited treatment options, based on the fact that azacitidine failed to demonstrate clinical benefit in a significant proportion of the AML patient population with >30% blasts, Pfizer considers that the robust data provided support reimbursement of glasdegib+LDAC for the treatment of adult patients with newly diagnosed and previously untreated AML, who are 75 years or older or who are not eligible to receive intensive induction chemotherapy, and requests that pERC reconsider its initial recommendation.

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.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
3	Summary of pERC Deliberations	Para 2, Line 11-14, Line 18-23	*"Specifically, the Committee discussed that the magnitude of the treatment effect estimates observed […] to the target population in real-world clinical practice." […] "pERC also noted*
6	Key efficacy results	Para 2, Line 3-12	*that based on a one-sided level of significance of 0.10 and use of pre-specified 80% confidence intervals […] there are ongoing phase III trials in this setting."*
In Pfizer's opinion, the B1371003 study design has the robustness of an interim analysis of a Phase 3 study. Both the protocol and the statistical analysis plan specified that a total of 92 events out of 132 randomized patients would provide 80% power to detect a 60% improvement in OS, which translated to a hazard ratio of 0.625 for the glasdegib+LDAC arm vs. the LDAC arm, at 1-sided alpha of 0.10. As of the data cutoff date of January 2017, a total of 109 OS events were observed, and the primary analysis of OS demonstrated a statistically significant and clinically meaningful improvement in OS in the AML+MDS cohort with hazard ratio of 0.513 (95% CI: 0.343, 0.766) and 1-sided p-value of 0.0004. These results suggest that the assumption in the original study design might have been too conservative. If the study was designed as a Phase 3 study with targeted OS HR of 0.625 (i.e., a 60% improvement in OS, the same as the expected improvement for the randomized cohort specified in the study protocol and the SAP), then a total 180 events out of 266 patients randomized would provide 80% power at 1-sided alpha 0.025 with an interim analysis (IA) for both futility and efficacy when 109 events were observed. If exactly 109 OS events were observed at IA, the efficacy boundary would be crossed if the observed 1-sided p-value <0.002, which would lead to declaration of a positive readout at the IA. Given the reported primary analysis result (i.e., HR=0.513 and 1-sided p-value of 0.0004 with 109 events observed) of January 2017, this could have been the IA result for the hypothetical Phase 3 study. The observed p-value of 0.0004 would have crossed the efficacy boundary (i.e., 1-sided p-value < 0.002), which would lead to declaration of a positive readout at the IA. Therefore, the submission for a full approval could have been filed based on this IA result from a Phase 3 study.			

Furthermore, follow-up analyses using 95%CI were provided in this submission and were consistent with the results for the primary analyses 80%CI intervals. Finally, pERC has granted positive recommendations to submissions with lower levels of evidence (phase 2, non-comparative studies) within the context of high unmet clinical needs therefore, Pfizer believes that Glasdegib+LDAC should be treated in a similar manner considering that the B1371003 study was a comparative, randomized study that was prospectively designed and appropriately powered to assess improvement in the clinically relevant OS endpoint versus an established control. [5,6,7]			
3	Summary of pERC Deliberations	Para 2, Line 14-16	*"pERC also noted that the application of subsequent therapies after progression, which was higher in the glasdegib in combination with LDAC group than in the LDAC group, may have confounded OS results."*
Sensitivity analyses of OS were conducted in the AML patients of the ITT population by censoring the patients at the start date of their first subsequent therapy to assess the impact on OS due to subsequent therapies. The OS results based on the sensitivity analyses (i.e., HR=0.370 [95% CI: 0.214, 0639] for the AML patients, and HR= 0.431[95% CI:0.257,0.725] for ITT population) showed consistent results with the primary analyses in both populations.			
3 6	Summary of pERC Deliberations Key efficacy results	Para 2, Line 16-18 Para 2, line 11-12	*"pERC discussed that the results of the key secondary outcome of complete remission (CR), subgroup analyses, […] of multiple testing, which had not been adjusted for."*
Since this study was originally designed as a Phase 2 study, a gatekeeping testing procedure was applied to adjust for multiple statistical testing and ensure that the overall alpha level is controlled at or below 0.10. As for the various data cut-off dates, the primary readout date of January 2017 was specified in both the protocol and the SAP with the minimum number of OS events required. All the analyses based on the data at the subsequent cutoff dates (Oct 2018 and April 2019) are considered updated analyses with longer follow-up for efficacy and safety. All the updated analyses demonstrated continued benefits of Glasdegib + LDAC which were consistent with the primary readout.			
4	Summary of pERC Deliberations	Para 4, Line 1	*"pERC was unable to conclude that there is a net clinical benefit of glasdegib in combination with LDAC compared to LDAC alone […]"*
Glasdegib+LDAC is the first approved therapy in Canada that demonstrates clinically meaningful and statistically significant survival benefits, with a near doubling of median OS (8.3 months vs. 4.3 months), over LDAC alone in an area of high unmet medical need with limited treatment options. The CGP acknowledged that there is a net clinical benefit to the combination of glasdegib+LDAC and that it will be the preferred option to replace LDAC (CGP report p.21), and possibly even azacitidine monotherapy. This was further supported by the registered clinician inputs (CGP report p.35). Furthermore, within only 8 weeks, more than 20 patients were enrolled in the patient support program which further supports that glasdegib is anticipated to become an important in-home treatment option for AML patients, especially in the context of the COVID pandemic.			

References

1. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(4):562-569.

2. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with 30% blasts. Blood. 2015;126(3):291-299.

3. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Blood. 2020;135(24):2137-2145. doi:10.1182/blood.2020004856

4. Solem CT, Bell TJ, Kwon Y, Cappelleri JC, et al.. A quality-adjusted survival time without symptoms or toxicities analysis of glasdegib plus low-dose cytarabine versus low-dose cytarabine as initial therapy for acute myeloid leukemia in patients who are not considered candidates for intensive chemotherapy. Cancer. 2020 Jul 22;126(19):4315–21. doi: 10.1002/cncr.33072. Epub ahead of print. PMID: 32697335; PMCID: PMC7540307.

5. CADTH. Venclexta for Chronic Lymphocytic Leukemia - pERC final recommendation. March 2, 2018

6. CADTH. Blincyto for MRD-positive B-cell precursor ALL - pERC final recommendation. October 28, 2020

7. CADTH. Xalkori for ROS1-positive advanced Non-Small Cell Lung Cancer - pERC final recommendation. October 28, 2020