CADTH

CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

Glasdegib (DAURISMO)

(Pfizer Canada ULC)

Indication: 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.

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Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BID	Twice daily
BSC	Best supportive care
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CMH	Cochrane-Mantel-Haenszel
CNS	Central nervous system
CR	Complete remission or complete response
CRc	Cytogenetic complete response
CRF	Case report form
CRi	CR with incomplete blood count recovery
CRm	Molecular complete response
CSR	Clinical study report
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
EORTC QLC C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30
EQ-5D	EuroQol-5 Dimension
FAB	French, American, British
FDA	Food and Drug Administration
Hh	Hedgehog
HMA	Hypomethylating agent
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
IPSS	International Prognostic Scoring System
ITC	Indirect treatment comparison
ITD	Internal tandem duplication
IVRS	Interactive voice response system
LDAC	Low dose cytarabine

MDS	Myelodysplastic syndrome
MLFS	Morphologic leukemia-free state
MR	Minor response
MRD	Minimal residual disease
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NA	not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
OS	Overall survival
PF-04449913	glasdegib
PFS	Progression-free survival
PR	Partial remission or partial response
PRi	PR with incomplete blood count recovery
QD	Once daily
RAEB	Refractory anemia with excess blasts
RBC	Red blood cell
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	Standard of Care
Std	Standard deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding glasdegib [Daurismo] in combination with low-dose cytarabine for acute myeloid leukemia. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of glasdegib (Daurismo) in combination with low-dose cytarabine (LDAC) compared with LDAC in patients with 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.

Glasdegib is a potent and selective hedgehog pathway inhibitor, that acts by binding to the smoothened receptor. Glasdegib has been issues marketing authorization without conditions in combination with low-dose cytarabine (LDAC), for the treatment of newly diagnosed and previously untreated (AML in adult patients who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy. Note that the Health Canada indication aligns with the CADTH reimbursement criteria.

The recommended dose of glasdegib (Daurismo) is 100 mg administered orally once daily on days 1 to 28 in combination with cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of each 28-day cycle so long as there is no unacceptable toxicity or loss of disease control. Glasdegib should be continued until loss of clinical benefit. Patients without unacceptable toxicity, should be treated for a minimum of 6 cycles to allow time for clinical response.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The CADTH systematic review included one phase 2 study (BRIGHT 1003), that assessed the efficacy and safety of glasdegib for patients with newly diagnosed AML or high risk MDS; the focus of this review was a randomized cohort referred to as the “unfit” cohort.

Study Features

The BRIGHT 1003 study was a multicenter, multi-phase, open-label study with one phase 1b cohort and two phase 2 cohorts. The phase 1b cohort and one of the phase 2 cohorts did not meet the criteria for this review. In the phase 2 cohort that met the selection criteria for this review (unfit/ nonintensive cohort Arm A; N=132), patients with newly diagnosed AML (N=116) or high risk MDS (N=16) were randomized (2:1) to receive treatment with glasdegib plus LDAC or LDAC alone. These patients were considered unfit to receive intensive induction chemotherapy. This CADTH review will only present the efficacy and safety results from the phase II phase of the unfit/ nonintensive cohort. Treatment continued for up to 1 year (12 cycles) from start of therapy or until disease progression or relapse, patient refusal, or unacceptable toxicity (whichever occurred first). Patients who completed 12 months on study treatment, who demonstrated clinical benefit with manageable toxicity, and who were willing to continue receiving assigned treatment could be given the opportunity to do so upon agreement between investigator, sponsor and pending study drug availability.[5] All patients were to be followed up for 4 years after the first dose. The trial was conducted in Europe and North America at 48 sites including 2 sites in Canada, with most patient enrollment in Europe (70%) followed by USA (25%) and Canada (9%).

Key inclusion criteria included:

- Adults (≥ 55 years) with AML or RAEB-2 high-risk MDS who were newly diagnosed as per WHO 2008 Classification and previously untreated
- AML patients included de novo AML, AML evolving from MDS or other AHD and secondary AML (after previous cytotoxic therapy or radiation)
- For a diagnosis of high-risk MDS RAEB-2 the patient had to have 10-19% bone marrow blasts
- ECOG performance status 0-2
- Patients considered unfit for intensive chemotherapy if they met at least one of the following criteria: age ≥ 75 years, ECOG score of 2, Serum creatinine > 1.3 mg/dL or severe cardiac disease (e.g., LVEF < 45% by MUGA or echo).
- Newly diagnosed and previously untreated patients with AML or high-risk MDS, including those who may have had one prior regimen with a commercially available agent (e.g., azacitidine or decitabine) for their antecedent hematologic disease.
- Patients were not permitted to have had any prior therapy for AML

Glasdegib 100 mg once daily was administered orally in continuous 28-day cycles, starting on Day 1 of Cycle 1. In addition, LDAC was administered at a dose of 20 mg subcutaneously twice daily on Days 1 to 10 of the 28-day cycles. In the comparator group, LDAC was administered at a dose of 20 mg subcutaneously twice daily on Days 1 to 10 of the 28-day cycles.

The primary completion date of the study (January 2017) occurred after 109 deaths. The main publication by Cortes et al[1] and the Clinical Study Report[6] are based on the January 2017 data cut-off date, as were the FDA and Health Canada reviews of glasdegib + LDAC. At the final exploratory analysis data cut-off date (April 2019) 121 (91.7%) patients had died. There is no single report available that summarizes the data from the final data cut-off but there were data available from published abstracts and post-hoc analyses provided by the manufacturer (refer to Table 7 for a list of data cut-off dates).

The primary outcome was overall survival and the key secondary outcome was complete remission (CR). Other secondary efficacy outcomes included CR with incomplete blood count recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR), partial remission with incomplete blood count recovery (PRi), minor response (MR), stable disease (SD), cytogenetic complete response (CRc), and molecular complete response (CRm). Quality of life was not measured in the trial. Progression free survival was assessed in post-hoc analyses.

Study Population (unfit/nonintensive cohort)

The median age of enrolled patients was approximately 75 years; 71% of patients were male and almost all patients were white. All patients had ECOG score of 0,1 or 2. The majority of patients met 1 or 2 of the criteria used to determine that a patient was unfit for intensive induction chemotherapy. Approximately half of the unfit cohort had secondary AML. [redacted].[6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Baseline hematologic and bone marrow parameters were similar in the two treatment groups at baseline. European LeukemiaNet (ELN) 2010 risk classification showed that overall, 64% of patients had good or intermediate cytogenetic risk. There were more patients with good or intermediate cytogenetic risk in the glasdegib + LDAC group and more patients with adverse risk on the LDAC group. Ten percent of patients were FLT3 mutated. Numbers of patients with FLT3 and NPM1 mutations were similar across the treatment groups. No patient had a TP53 mutation. FAB classifications were approximately similar across treatment groups but half of all patients were missing FAB classification.

The demographic characteristics of patients with AML (N=116) was similar to the demographic characteristics of the overall unfit population (N=132).

Patient Disposition

As of the final data cut-off, the median (range) for treatment duration was 83 (3-1,575) days in the glasdegib + LDAC group and 40 (6-239) days in the LDAC group. The median follow-up for survival in the glasdegib + LDAC group and the LDAC group was 47.6 months and 48.1 months, respectively.[2] At study completion, five patients remained in follow up: 4 (4.5%) patients in the glasdegib + LDAC group and 1 (2.3%) patient in the LDAC group completed ≥4 years' follow-up.[2] At the last patient visit, 91.7% of patients were known to have died.[2]

Efficacy

A summary of the key efficacy results is presented in Table 1. Data are from the final analysis (data cut-off April 2019) unless otherwise noted.

Overall Survival (primary outcome)

The primary completion analysis (January 2017) showed that for the full trial population the median overall survival was longer in patients who were randomized to receive glasdegib + LDAC (8.8 months; 80%CI:6.9, 9.9) compared to patients who received LDAC (4.9 months (3.5, 6.0) and the difference was statistically significant (HR=0.513; 80%CI:0.394, 0.666; p=0.0004). Based on these results, the investigators noted that the trial had met its primary endpoint. The final analysis (Table 19) with updated exploratory data cut-off date of April 2019 and including all AML and MDS patients, suggested consistency with the earlier data cut. The median overall survival was longer in patients who were randomized to receive glasdegib + LDAC (8.8 months; 80%CI: 6.9, 9.9) compared to patients who received LDAC monotherapy (4.9 months; 80%CI: 3.5, 6.0) (HR=0.569; 80%CI: 0.441, 0.734). In addition, this report presents OS results for the AML population (excluding MDS patients N = 16), which aligns with the CADTH requested reimbursement criteria. These results were also presented in the FDA report in order to align with the FDA's labeled indication, which was for AML patients. Survival results in the AML population were consistent with survival estimates from the full trial population and the updated April 2019 results were similar to the January 2017 results.

Exploratory analyses of OS by cytogenetic risk (goo/intermediate versus poor) for the overall trial population (AML plus MDS patients) suggested that median survival was lower in patients with poor cytogenetic risk compared to patients with good/intermediate cytogenetic risk. In patients with good/intermediate cytogenetic risk, median overall survival for patients taking glasdegib + LDAC was 12.1 months (80%CI: 8.3; 14.4) and for patients taking LDAC it was 4.8 months (80%CI: 4.1; 6.0). In patients with poor cytogenetic risk, median overall survival for patients taking glasdegib + LDAC was 4.7 months (80%CI: 4.0; 7.4) and for patient taking LDAC it was 4.9 months (80%CI: 2.3; 6.4).

Response (secondary outcome)

In the full trial population (AML + MDS patients) a higher rate of CR was observed in patients taking glasdegib + LDAC (n = 15, 17.0%) compared to patients taking LDAC (n = 1, 2.3%). Exploratory subgroup analyses by cytogenetic risk profile suggested the rate of CR was higher in patients taking glasdegib + LDAC compared to patients taking LDAC in the subgroups of good/intermediate and poor cytogenetics, though the benefit of glasdegib + LDAC seemed more pronounced in the good/intermediate risk group.

Progression Free Survival (exploratory outcome)

[redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* The p-value should be regarded as nominal and the analyses as exploratory.

Patient reported outcomes were not assessed in the BRIGHT 1003 study.

Harms Results

The median duration of exposure to glasdegib + LDAC was approximately one month longer than patient exposure to LDAC alone but the adverse event data are not adjusted for differences in time of exposure to study drugs.

The most common adverse events of all grades in patients taking glasdegib + LDAC included anemia (47%), nausea (36%), febrile neutropenia (35%), decreased appetite (33%), and thrombocytopenia (32%). The most common adverse events of all grades in patients taking LDAC included anemia (42%), dyspnea (31%), pneumonia (28%), diarrhea (25%), and febrile neutropenia (25%). Patients taking glasdegib + LDAC and LDAC experienced adverse events of grade 3 (19 vs. 22%), grade 4 (43 vs. 31%), and grade 5 (32 vs. 44%), respectively.

There were 61 (81%) patients in the glasdegib + LDAC group and 28 (78%) patients in the LDAC alone group that experienced all-causality SAEs. The most frequently reported serious adverse events in the glasdegib + LDAC group included febrile neutropenia (21

[28%] patients), pneumonia (16 [21.3%] patients) and anemia (5 [7%] patients). The most frequently reported serious adverse events in the LDAC group were pneumonia (7 [19%] patients), febrile neutropenia (6 [17%] patients), sepsis (5 [14%] patients), and pancytopenia (2 [6%] patients).

Fewer patients discontinued study drug due to adverse events in the glasdegib + LDAC group (39%) compared to the LDAC group (47%).

Limitations

- Well conducted aspects of the BRIGHT 1003 study was that it had long follow up for patient survival (overall survival was the primary endpoint), included a stratified randomization procedure based on known prognostic factors to minimize potential imbalances between study groups, and allocation concealment was conducted through a centralized system.
- The BRIGHT 1003 study was designed as a Phase 2 study with sample size estimates based on a power of 80% and Type 1 error of 0.10. In many analyses, the hazard ratios for overall survival were presented with 80% confidence intervals indicating that the investigators were willing to accept a 20% chance of obtaining a false positive result. This was done according to the statistical analysis plan for the study. The willingness to accept a higher chance of achieving a false positive result is not uncommon in Phase 2 studies. However, there are drawbacks to this approach and there are numerous examples of phase 3 trials whose results did not support the phase 2 trial results. Phase 2 trials may not accurately predict harm and/or effectiveness for new medicines.[7,8] The primary objective of phase 2 (randomized or non-randomized) trials is to document the safety outcomes and investigate if the estimate of effect for a new drug is large enough to use it in confirmatory phase 3 trials. A subsequent Phase 3 study of glasdegib could serve to confirm the results of this Phase 2 trial. Data submitted to regulatory agencies and CADTH included post-hoc analyses using 95% confidence intervals which were consistent with the results for the 80%CI intervals.
- No multiplicity adjustments were made for either the multiple secondary endpoints or the multiple analyses at various data cut-off dates. This increases the probability of type 1 error and these results should be interpreted with caution.
- BRIGHT 1003 was an open label study and its investigators, patients and outcome assessors were aware of the assigned treatments. Investigators could potentially influence treatment duration and knowledge of assigned treatment may have influenced this aspect of the study. It is also possible that knowledge of treatment assignment affected both the threshold for reporting an adverse event and the assessment of the relationship to study treatment, biasing the assessment of adverse event causality against glasdegib.
- After study treatments were stopped, a greater proportion of patients received subsequent treatments for AML in the glasdegib + LDAC group compared to the LDAC monotherapy group during the follow-up period. This included a higher rate of chemotherapy in the glasdegib + LDAC group. This could have biased the survival and response results in favour of the glasdegib + LDAC group.
- BRIGHT 1003 compared the effect of glasdegib + LDAC with that of LDAC. The CGP noted that azacitidine is currently the most commonly used treatment in Canada in the present target population. Decitabine is currently rarely used in Canada in patients with newly diagnosed AML as it is not Health Canada approved for this indication and not funded in most jurisdictions. There was no evidence available of direct comparisons of glasdegib versus azacitidine. Since azacitidine is the most relevant comparator for some patients with AML unfit to receive intensive induction chemotherapy, this limits the ability to clearly define the place in therapy for glasdegib with respect to azacitidine in this setting. Of note, the submitter provided an indirect treatment comparison (ITC) report that included a comparison to azacitidine and a published ITC presented comparisons to azacitidine and decitabine (see section 7 for more details).
- Patient-reported quality of life outcomes were not assessed in the BRIGHT 1003 trial. Therefore, the direction and degree to which the study treatments could impact patients' quality of life are unknown.

Table 1: Highlights of Key Outcomes: BRIGHT 1003 Study

	AML + MDS patients (N = 132)	
	Glasdegib + LDAC (N=88)	**LDAC (N=44)**
Data cut-ff date	January 2017	
Median follow up	21.7 months	20.1 months
Primary Outcome: overall survival, median (80%CI), months	8.8 (6.9, 9.9)	4.9 (3.5, 6.0)
HR (80%CI); p-value	0.513 (0.394, 0.666), p=0.0004	
Deaths; n (%)	68 (77.3)	41 (93.2)
Response in AML patients n (%)	**N = 78**	**N = 38**
CR	14 (17.9)	1(2.6)
CRi	5 (6.4)	1 (2.6)
MLFS	2 (2.6)	0
PR	5 (6.4)	0
PRi	2 (2.6)	0
MR	4 (5.1)	4(10.5)
SD	13 (16.7)	9 (23.7)
Harms in AML patients, n (%)	**N=75**	**N=36**
Data cut-off date	April 2019	
Median follow up	47.6 months	48.1 months
AE (any grade)	75 (100.0)	36 (100.0)
Grade ≥3	67 (89.3)	34 (94.4)
Permanent discontinuation due to AE	29 (38.7)	17 (47.2)
SAE	61 (81.3)	28 (77.8)

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

The Leukemia & Lymphoma Society of Canada (LLSC) provided input on the glasdegib (Daurismo) for AML review. From the patient perspective, all patient respondents experienced the common symptoms of AML of fatigue, loss of appetite, and weight loss, and these were noted to disrupt daily life. Fatigue was reported to have the most impact on daily life, and 80% of patients noted that extreme fatigue had a “significant impact” on their daily lives. Fatigue was specified to disrupt activities, sleep patterns, and physical and emotional intimacy. Additionally, patients highlighted the lack of a social life attributed to AML as one patient noted that they experience social isolation due to a fear of catching an infection. All patient respondents had received treatment for AML; namely, 11 respondents received chemotherapy, 10 received high-dose chemotherapy, two received radiotherapy, 11 respondents received a stem cell or bone marrow transplant, one received immunotherapy, three received maintenance therapy, and one received two sets of consolidation therapy. Among these, the following were specified: daunorubicin, cytarabine, daunorubicin plus cytarabine (Vyxeos), venetoclax, azacitidine, busulfan, methotrexate, and cyclophosphamide. The most common side effects reported by patients included: fatigue, infections (e.g., viral and fungal), hair loss, neutropenia (low number of white blood cells), reduced movement/ inability to participate in physical activities, fever, and vomiting. The most serious side effect reported was a graft versus host reaction (GVH)— when the donor's immune cells attack the patient's normal cells. Another patient mentioned being unable to swallow and experiencing severe vomiting, which resulted in the patient receiving IV nutrition for several weeks in the hospital. Moreover, eight respondents had some form of infection or disease other than cancer, which was attributed to the deficiency of white

blood cells during treatment. In addition to the physical side effects, patients noted that treatments impacted their quality of life through a change in physical activity (e.g., gardening, exercise, etc.), the ability to work, anxiety levels, and social life (e.g., visiting other people or attending social functions).

Majority of patients reported (11/15) easy access to treatment; however, one patient reported having difficulty accessing treatment in BC (patient's province of residence) but was able to receive first-line treatment (high-dose chemotherapy: cytarabine with daunorubicin for induction and cytarabine for consolidation [two sets]) by connecting with a hematologist in another province (not specified), and another patient noted having difficulty finding transportation to receive treatment. Namely for elderly patients, it was highlighted that patients should be able to receive treatment based on their general state of health and not their age. Notably, none of the respondents had treatment experience with glasdegib; however, patients were asked if they would consider taking glasdegib and why they would be willing to tolerate the side effects. One patient would consider treatment with glasdegib if it meant choosing between life and death, and another patient would consider glasdegib if the positive results of glasdegib are as good or better than chemotherapy. Patients noted that doctor's recommendation, possible impact on the disease, and quality of life as the most important factors for patients and caregivers when deciding on a new cancer treatment. Overall, patients with AML value having access to treatments; accordingly, access should not be limited by a patients' financial status, geographic location (province of residence), or age; specifically, access to treatment should be based on a patients' general state of health rather than age. Further, patients seek treatments that are effective for symptom management, particularly fatigue as it has a significant impact on the daily lives of patients and treatments associated with reduced side effects; namely, infections, which also disrupt one's social life and keeps patients in their homes in fear of acquiring an infection.

Provincial Advisory Group (PAG) Input

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) and **one** Federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing with other therapies for AML

Economic factors:

- Additional safety monitoring

Registered Clinician Input

A total of two registered clinician inputs were provided for the review of glasdegib (Daurismo) in combination with LDAC, for the treatment of newly diagnosed and previously untreated AML in adult patients, who are ≥75 years of age or who are not eligible to receive intensive induction chemotherapy: one clinician provided input on behalf of Cancer Care Ontario (CCO) Hematology Drug Advisory Committee (DAC) and ten clinicians provided input on behalf of the Canadian Leukemia Study Group (CLSG)/Groupe Canadien d'Étude sur la Leucémie (GCEL). Both inputs mentioned the following treatment option for patients with newly diagnosed AML: induction chemotherapy (daunorubicin or idarubicin plus cytarabine in the form of standard 3+7 or Vyxeos liposomal therapy) followed by consolidation therapy (e.g., high-dose cytarabine monotherapy or high-dose cytarabine plus anthracycline) with the potential for transplant (e.g. hematopoietic stem cell transplant). Additionally, the CLSG clinicians noted that patients could receive a fludarabine-idarubicin-cytarabine regimen. Alternatively, patients who are ineligible for aforementioned regimens could receive best supportive care or less intensive chemotherapy regimens; azacitidine and LDAC were noted in both inputs while the CCO clinician additionally specified azacitidine plus venetoclax and the CLSG clinicians additionally specified decitabine. Moreover, the CLSG clinicians noted that some types of AML can be treated with targeted agents and the CCO clinician specified that patients with FLT3 mutations with newly diagnosed AML may be treated with standard induction 3+7 chemotherapy plus midostaurin. The CLSG clinicians stated that the most appropriate comparators for the current review would be LDAC or azacitidine. Compared to LDAC monotherapy, the CLSG clinicians highlighted that response rates (CR) and median OS were greater with glasdegib plus LDAC as demonstrated in the pivotal trial. Further, they highlighted that glasdegib plus LDAC is safe and well-tolerated and that contraindications to glasdegib plus LDAC are essentially the same as to LDAC alone, with the addition of known intolerance to glasdegib or another Hedgehog inhibitor. Accordingly, the CLSG clinicians specified that glasdegib plus LDAC would be a superior alternative to LDAC alone if the treatment under review becomes available for funding. The CCO and CLSG clinicians indicated that the trial criteria to identify patients not suitable for intensive chemotherapy were reasonable and reflective of clinical practice. The CCO clinician specified that the only patients who should not receive glasdegib align with the exclusions of the pivotal trial and there

should be no age restriction. Correspondingly, the CLSG clinicians stated they would specifically administer glasdegib plus LDAC in patients with one or more of the following: 1) difficulty in attending hospital visits for geographic or distance reasons, 2) standard risk cytogenetics, 3) prior treatment failure with a HMA Such as azacitidine or decitabine, and 4) intolerance to a HMA. For such patients, the CLSG clinicians stated that it is essential to have a LDAC-based treatment option in Canada. They specified that most of the patients receiving the treatment under review would be elderly and many elderly patients in Canada often live far from a cancer centre, and travel is difficult due to the distance and the requirement for an accompanying caregiver. Accordingly, when asked if it would be appropriate to implement a modified LDAC regimen to account for clinic opening hours; the CLSG clinicians (Canadian wide perspective) indicated that this practice would be appropriate. They specified that LDAC-based regimens offer the advantage of being delivered at home by homecare, a caregiver, or by the patient. Alternatively, azacitidine injections are not administered at home and the patient must attend a chemotherapy clinic for seven consecutive days. Thus, LDAC-based regimens can be much more favourable for the patient and caregiver while also sparing valuable hospital resources and increasing clinic capacity. Namely, the advantage of reducing the time needed to be in the hospital for the patient and caregiver is particularly favourable during the COVID-19 pandemic. The CCO clinician stated that patients usually inject themselves at home with pre-filled syringes in Ontario. Moreover, the CLSG clinicians highlighted that LDAC-based treatments may be effective for patients who have been treated with an HMA for an antecedent hematological disorder such as a myelodysplastic syndrome (MDS) that proceeded to AML despite HMA treatment. For such patients, treatment of their AML with an HMA-based regimen is considered medically futile.

Summary of Supplemental Questions

In the absence of direct evidence comparing glasdegib + LDAC to azacitidine in AML patients who are ineligible for intensive chemotherapy, the sponsor submitted ITCs to estimate the relative treatment effect in terms of OS between the two treatments. In order to perform the ITCs, two methodologies were used: 1) a base case using Bucher method, and 2) sensitivity analyses using simulated treatment comparisons (STC). Two scenarios of the STC were conducted: Scenario 1 adjusted for differences between trials while Scenario 2 adjusted for differences between trials and arms within trials. Separate analyses were conducted based on two subgroups of patients: 1) patients with a BMB count of 20-30%, and 2) patients with a BMB count of >30%. Two trials provided data for the azacitidine arm of the comparisons, one to each of the subgroups. The BRIGHT AML 1003 provided data for the glasdegib + LDAC arm. The results of the sponsor-provided ITC suggested no statistically significant difference and wide confidence intervals for the HRs of glasdegib + LDAC compared to azacitidine in the base case using Bucher method. For the sensitivity analyses using STC methods, results for the 20-30% subgroup showed no statistically significant differences between glasdegib + LDAC versus azacitidine. Results for the >30% subgroup demonstrated a statistically significant difference in favour of glasdegib + LDAC, however, the CIs were wide and the upper bound of the CI interval was near or at 1.00.

In addition, a published ITC[9] was identified which estimated the relative treatment effect for OS between glasdegib + LDAC and azacitidine and glasdegib + LDAC and decitabine. Several methods for modelling the data were investigated: unadjusted models, STC adjusted models, and propensity-score adjusted models. One trial each provided data for glasdegib + LDAC, azacitidine, and decitabine. Azacitidine and decitabine were each compared separately relative to glasdegib + LDAC. Results for glasdegib + LDAC compared to azacitidine demonstrated a statistically significant improvement for the OS HR for glasdegib + LDAC for all the models used (HR range: 0.412 to 0.514). Similarly, results for glasdegib + LDAC compared to decitabine demonstrated a statistically significant improvement for the OS HR for glasdegib + LDAC for all the models used (HR range: 0.482 to 0.565).

Due to severe limitations identified in the sponsor provided as well as the published ITCs, including concerns regarding the violation of the assumption of within-study randomization and heterogeneity across the study designs and populations, extreme caution must be used in interpreting the comparative efficacy estimates.

Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for glasdegib from BRIGHT 1003

Domain	Factor	Evidence[10-12]	Generalizability Question	CGP Assessment of Generalizability
Population	Myelodysplastic syndromes (MDS)	16 patients had MDS Glasdegib + LDAC: 10 patients LDAC: 6 patients	Are the results generalizable to patients with MDS?	The number of patients in the BRIGHT 1003 study with MDS was small (N=16). Given the different disease biology of MDS there is insufficient evidence to generalize the BRIGHT 1003 trial results to this patient group.
	Bone marrow blast count	For AML patients: **BMB > 30%:** Glasdegib+LDAC: n=51 LDAC group: n=25 **BMB 20 to 30%:** Glasdegib+LDAC: n=21 LDAC group: n=9	Is BMB an effect modifier? Are the results of the trial applicable to BMB counts of 20 to 30% and great than 30% in patients with ALM?	The CGP noted that bone marrow blast count in itself is not an established effect modifier. Post-hoc exploratory subgroup analyses for OS by bone marrow blast percentage (20-30% versus >30%) were conducted. Given the exploratory nature of these analyses no conclusions can be drawn from these results. The CGP noted that there is insufficient evidence to limit the use of glasdegib plus LDAC to specific subgroups by bone marrow blast percentage.
	CNS Metastases	Patients with controlled CNS leukemia were excluded.	Are the trial results generalizable to patients with controlled CNS leukemia?	CNS involvement would be an uncommon occurrence in the population for which glasdegib is indicated. LDAC will not cross the blood brain barrier. Therefore, the CGP noted that the combination of glasdegib + LDAC should not routinely be offered to patients with AML and CNS involvement.
Intervention	Dose and Schedule	100 mg once daily orally in continuous 28-day cycles, starting on Day 1 of Cycle 1, plus LDAC 20 mg subcutaneously twice daily on Days 1 to 10 of the 28-day cycles	Is the trial dosage generalizable to patients in Canadian clinical practice?	CGP noted that the dose administered in the trial aligns with the does that is recommended in the product monograph. The CGP agreed that this dose is applicable to Canadian clinical practice.

Domain	Factor	Evidence[10-12]	Generalizability Question	CGP Assessment of Generalizability
Outcomes	Assessment of Key Outcomes	Assessment of response was made using response criteria for MDS and AML as defined by the disease specific International Working Groups. Complete response / remission (CR) was defined as all of the following: Peripheral blood: ANC ≥ 1,000/μL, platelet count ≥ 100,000/μL, and adequate erythroid recovery so that RBC transfusions were not necessary (time frame not defined) Bone marrow: no Auer rods and < 5% blasts with spicules present No extramedullary leukemia	If the trial used a different method of assessment than that used in Canadian clinical practice, are the results of the trial applicable to the Canadian setting?	The CGP agreed that the criteria to assess response were fully applicable to Canadian clinical practice.
Ethnicity of Demographics/ Setting	Ethnicity of patients/Countries participating in the Trial	>95% of patients were white. Ethnicity was not reported. Sites in: Canada, USA, Germany, Poland, Spain, Italy. Population: USA: 25%, Canada: 9%, Europe 70%	Is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting. Are there any known difference in the practice patterns between Canada and other countries that the trial was conducted in?	The trial results are fully applicable to the Canadian landscape. The CGP does not expect a different treatment effect based on ethnicity or different disease management practices across countries.

Domain	Factor	Evidence[10-12]	Generalizability Question	CGP Assessment of Generalizability
	Supportive medications, procedures, or care	The most commonly used (in >40% of patients on the glasdegib + LDAC arm) concomitant medications were allopurinol, furosemide, paracetamol, levofloxacin, and ondansetron. Moderate or strong CYP3A4 inhibitors were used by 72 (63%) patients, with 50 (65%) patients in the glasdegib + LDAC group and 22 (58%) patients in the LDAC group. The most commonly used moderate or strong CYP3A4 inhibitors on the glasdegib + LDAC vs LDAC arms, respectively, were ciprofloxacin (33% vs 16%), fluconazole (30% vs 40%), posaconazole (17% vs 8%), and voriconazole (17% vs 8%).[4]	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	The supportive care interventions in the Bright 1003 trial are comparable to the supportive care medications that would be anticipated in a patient population being treated for AML with less intensive chemotherapy in Canada.

AML = acute myeloid leukemia; BID = twice daily; BM = bone marrow; CI = confidence interval; CNS = central nervous system; CR: complete remission; CRc = cytogenetic complete response; Cri = CR with incomplete blood count recovery; CRm = molecular CR; ECOG PS = eastern cooperative oncology group performance score; FAB = French, American, British; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; MLFS: morphologic leukemia-free state; PR: partial remission; PRi: PR with incomplete blood count recovery; MR: minor response; SD: stable disease; Std= standard deviation; ULN = upper limit of normal;

1.2.4 Interpretation

In Canada, the age adjusted incidence rate of AML is approximately 3.75 per 100,000. In 2017, there were 1,509 new cases of AML reported in Canada with a median age at diagnosis of 66 years, with just over a quarter of diagnoses in those over the age of 75.[13] Older patients with AML have few treatment options and are generally not eligible for intensive or curative intent chemotherapy because of comorbidities. There is no universal consensus regarding optimal management of older patients with AML who are not candidates for intensive therapy. Treatment options in Canada include best supportive or palliative care, azacitidine, LDAC, and enrollment on clinical trials. The most recent Canadian consensus guideline regarding management of older patients with AML who are not considered candidates for intensive chemotherapy,[14] recommends considering cytogenetic risk groups in treatment selection. For patients with adverse cytogenetics azacitidine is recommended and for patients with intermediate/favourable-risk cytogenetics LDAC, azacitidine, or decitabine are options. Decitabine is currently rarely used in Canada in patients with newly diagnosed AML as it is not Health Canada approved for this indication and not funded in most jurisdictions.

When azacitidine was compared to combined conventional care regimens (best supportive care, LDAC, intensive chemotherapy) in older AML or MDS patients with ≤30% bone marrow blasts, the majority of who were not candidates for intensive therapy, the group receiving azacitidine demonstrated a survival benefit (median OS: 24.5 versus 16 months; HR 0.47 (95% CI, 0.28-0.79).[15] When azacitidine was compared to conventional care regimens in older patients with newly diagnosed AML with blasts >30% azacitidine showed a trend towards prolonged median OS (6.5 versus 10.4 months). Compared with conventional care regimens, azacitidine showed improved median OS in patient with poor-risk cytogenetics (6.4 versus 3.2 months); however, in patients with intermediate risk cytogenetics, median OS did not differ between the two groups. In patients pre-selected to receive LDAC, OS was also similar between the LDAC and azacitidine groups.[16] In older AML patients not eligible for induction therapy LDAC was shown to be superior to best supportive care (OR, 0.60; 95% CI, 0.44–0.81; P = 0.0009). However, no remissions were observed in patients with poor cytogenetics.[17] Overall, there is no conclusive body of evidence to guide a universal consensus regarding the optimal management of the target population and there is inter-clinician variability in choosing the best treatment for each patient.

In Canada azacitidine is currently the most commonly used treatment in older patients with AML who are not considered candidates for intensive chemotherapy. The CGP estimates that approximately 30% of patients present with 20% to 30% bone blasts and approximately 70% of patients present with >30% bone marrow blasts at diagnosis. For patients with 20 to 30%bone marrow blasts and > 30% bone marrow blasts and poor cytogenetic risk the CGP anticipated that most clinicians prefer to use azacitidine as recommended by the Canadian consensus guideline. As well, the CGP estimated that azacitidine is currently the most commonly used treatment for patients with > 30% bone marrow blast and intermediate/favourable risk. The CGP agreed with the sponsor that LDAC is currently used by approximately 20-30% of elderly AML patients who are ineligible to receive intensive chemotherapy. The CGP noted that LDAC is mainly utilized in situations where patients are intolerant to azacitidine, patients have received hypomethylating agents (azacitidine, decitabine) for an antecedent hematological disorder and subsequently progressed to AML, or patients prefer to take treatment at home via self-administration, as azacitidine can only be provided in a hospital/ clinic setting. For patients with > 30% bone marrow blasts azacitidine is not Health Canada approved and way of access may be variable across provinces.

The CGP agreed that current treatment options for older patients who are not candidates for intensive chemotherapy are limited and that there is a need for more effective therapies that have less toxicities and offer longer remission, prevent relapse, and prolong survival.

In their feedback to the pERC Initial Recommendation the registered clinicians from CLSG suggested that glasdegib + LDAC addresses an unmet need as azacitidine is not available for a large proportion of patients because it is not approved by Health Canada for AML with >30% bone marrow blast. In response to the registered clinicians' feedback, CADTH review team noted that most jurisdictions are currently funding azacitidine for patients with AML with >30% bone marrow blast and those that are not, will likely move towards funding it. However, the CGP noted that although British Columbia (BC) is currently funding azacitidine for patients with >30% bone marrow blast, there are many smaller centres that do not deliver azacitidine (e.g., many parts of interior BC and most of Northern BC) due to practical and resource issues. A similar situation was reported for Manitoba, where the CGP noted that it is more challenging to provide azacitidine to patients who are in geographically isolated regions of the province. The CGP agreed that having an LDAC-based treatment option that is associated with improved survival would be beneficial for patients with AML living in these areas. It was noted that based on a recent review of treatment patterns in the BC population in older patients

(over 60 years of age) with AML, azacitidine was used in 14% of patients, LDAC in 9%, intensive treatment in 17% and best-supportive care/palliative care in 59% of patients. Older patients with AML represent a relatively vulnerable group with often significant barriers to accessing treatment and there is a large, unmet need for more effective treatments.

Furthermore, in their feedback to the pERC Initial Recommendation the registered clinicians from CLSG suggested that a proportion of patients (>20%) have already failed azacitidine for MDS before proceeding to AML. These patients would not be able to receive azacitidine for their AML. In response to the registered clinicians' feedback the CGP noted that whereas the proposed estimate of 20% appeared a little high, a significant proportion of patients with higher risk MDS treated with azacitidine will transform to AML eventually. This is a relatively commonly encountered group of patients in clinical practice with no effective treatment options if patients are not eligible for intensive treatment.

A recent phase 3, multicenter, double-blind, RCT[18] in AML patients not candidates for intensive therapy compared the combination of azacitidine and venetoclax to azacitidine alone showing a significant survival benefit to the combination treatment in this population. The CGP noted that this trial evaluated a new alternative treatment compared to the currently most commonly used therapy, azacitidine.

Effectiveness

A recently published randomized multicenter phase II study, the Bright AML 1003 study, meant to test the role of a hedgehog inhibitor (glasdegib) in AML or high risk myelodysplastic syndrome (MDS)[1]. It accrued patients ≥55 with newly diagnosed untreated AML or high risk MDS (RAEB-2 WHO 2016) who were not suitable for intensive chemotherapy (age ≥75, serum creatinine ≥ 115 uM, left ventricular ejection fraction<45% or ECOG performance status ≥2). Patients with acute promyelocytic leukemia, t(9;22), uncontrolled central nervous system disease or prior treatment with a hedgehog inhibitor or other investigational agent for an antecedent hematological malignancy were excluded.

Patients were randomized (2:1) to receive glasdegib + LDAC or LDAC. Glasdegib was administered at a dose of 100 mg daily. LDAC 20 mg was administered subcutaneously twice daily for 10 days every 28 days. Patients remained on treatment until disease progression, unacceptable toxicity or patient refusal. The protocol specified treatment duration was up to 12 months, but investigators could elect to continue longer until loss of clinical benefit. The primary objective was OS. Secondary objectives included clinical efficacy endpoints, safety and tolerability, pharmacokinetic and effect on QTc. The study had 80% power to detect a 60% improvement in OS at a one-sided significance level of 0.1.

132 patients were randomized to receive either glasdegib + LDAC (N = 88) or LDAC (N = 44). Over half of patients were ≥75. The median range of cycles of glasdegib + LDAC was 3 (1-35) and for LDAC 2 (1-9). Median follow up for OS was 21.7 months with glasdegib + LDAC and 20.1 months with LDAC at the primary completion date. The median OS for the glasdegib + LDAC group was 8.8 months and for the LDAC group was 4.9 months (HR 0.51, 80% CI 0.39-0.67). In patients with AML median OS was 8.3 months with glasdegib + LDAC vs 4.3 months with LDAC. According to exploratory subgroup analyses in patients with good/intermediate risk cytogenetics, glasdegib + LDAC compared with LDAC had a median OS of 12.2 versus 4.8 months (HR 0.43; 80% CI, 0.300, 0.609). For patients with poor risk cytogenetics median OS comparing the glasdegib+ LDAC and LDAC groups was 4.7 months and 4.9 months (HR 0.63; 80%CI, 0.430, 0.934). The proportion of deaths in the glasdegib + LDAC group were 68/88 and the proportion of deaths in the LDAC group was 41/44. 15 patients (17%) in the glasdegib+ LDAC group achieved complete remission (CR) in contrast to 1 patient (2.3%) in the LDAC arm. In the glasdegib + LDAC group median duration of response was 9.9 months for patients achieving CR. CGP noted that achieving a complete or partial remission is a useful clinical endpoint to determine that there is treatment effect.

Safety

Treatment emergent adverse events (TEAEs) of all grades were reported in 85 (100%) and 41 (100%) of patients in the glasdegib + LDAC and LDAC groups, respectively. The most commonly reported all grade TEAEs included anemia (45.2%), febrile neutropenia (35.7%), nausea (35.7%), and decreased appetite (3.6%) in the glasdegib + LDAC group and anemia (41.5%), thrombocytopenia (26.8%), dyspnea (26.8%), and febrile neutropenia (24.4%). While slightly more grade 3-4 TEAEs occurred in the glasdegib + LDAC group compared with the LDAC group (64.3 versus 56.1%) more grade 5 AEs were reported in the LDAC group compared with the glasdegib + LDAC group (41.5% versus 28.6%). TEAEs (Grade 3-4) of interest associated with the glasdegib + LDAC group were pneumonia (16.7%) and sepsis (6%). The most frequently reported grade 5 TEAEs in the glasdegib + LDAC and LDAC groups was

pneumonia (7.1% versus 7.3%, respectively). 30/84 patients in the glasdegib + LDAC group permanently discontinued study treatment due to AEs whereas 19/41 patients in the LDAC arm permanently discontinued study treatment due to AEs. QTc>480 ms was reported in 9 patients treated with glasdegib + LDAC with 2 patients temporarily discontinuing treatment and 5 patients treated with LDAC alone had QTc prolongation>480 ms. The CGP agreed that overall glasdegib + LDAC had a manageable toxicity profile.

The CGP noted that patient-reported quality of life outcomes have not been measured in the BRIGHT 1003 trial. Therefore, the direction and degree to which glasdegib + LDAC compared with LDAC could impact patients' quality of life is unknown.

In their feedback on the pERC Initial Recommendation, the registered clinicians from CLSG suggested that despite the absence of quality of life data from the BRIGHT 1003 trial, the benefit seen with glasdegib + LDAC extends to improve quality of life. It was noted that according to their clinical experience improvements in quality of life can be seen in patients who have complete responses as well as in a subset of patients not achieving complete response. According to the registered clinicians, improvements in cytopenia as well as transfusion independence are associated with improvements in quality of life (fewer infections, fewer hospital admissions, fewer clinic/transfusion unit visits, decreased travel time, etc.) and were observed in patients who received glasdegib + LDAC and did not achieve a complete response in a post-hoc analysis of the BRIGHT 1003 study by Cortes et al. (2020)[19]. The CADTH Methods Team noted that Cortes et al. (2020) was not included in the CADTH systematic review, as it was a post-hoc analysis and did not contain outcomes of interest as prespecified by the CADTH Methods Team's review protocol. In response to the sponsor's feedback the CGP strongly agreed that complete response, improved cytopenia, and transfusion independence are associated with improvements in quality of life. Furthermore, the CGP noted that the doubling of median OS with glasdegib + LDAC compared with LDAC, is in itself an important and meaningful outcome for older patients and more important than the absence of patient-reported quality of life data. Furthermore, the CGP highlighted the requirement for glasdegib + LDAC needing to show a QoL benefit (when there is a clear OS benefit) may be inconsistently applied by pERC/CADTH compared to other recently reviewed AML drugs primarily used in younger patients such as gemtuzumab ozogamicin[20] and gilteritinib[21] where there was also a relatively modest OS benefit. Overall, the CGP noted that they disagreed with the pERC Initial Recommendation regarding being unable to conclude that there was a net clinical benefit of glasdegib + LDAC compared with LDAC.

Comparative therapies considered

Currently, only indirect comparisons can be made between glasdegib + LDAC versus azacitidine as no trial to date has directly compared these drugs. The sponsor undertook an indirect treatment comparison (ITC) of glasdegib + LDAC versus azacitidine through a systematic review methodology (see section 7 for a summary and critical appraisal of the ITCs). The systematic review inclusions included adults ≥ 18 with AML or high risk MDS not eligible for intensive therapy. Randomized controlled trials and systematic reviews or metanalyses were included. Three trials met the sponsors inclusion and exclusion criteria. The three trials included the Bright AML 1003 trial[1] as well as Fenaux 2010[15] and Dombret 2015.[16]

The CGP noted that results of the sponsor-provided ITC suggested no statistically significant difference and wide confidence intervals for the HRs of glasdegib + LDAC compared to azacitidine in the base case using Bucher method. For the sensitivity analyses using simulated treatment comparisons (STC) methods, results for the 20-30% subgroup showed no statistically significant differences between glasdegib + LDAC versus azacitidine. Results for the >30% subgroup demonstrated a statistically significant difference in favour of glasdegib + LDAC, however, the CIs were wide and the upper bound of the CI interval was near or at 1.00. In addition, a published ITC[9] comparing glasdegib + LDAC and azacitidine and glasdegib + LDAC and decitabine was identified by the CADTH review team. However, the CGP agreed with the CADTH Methods Team, that due to severe limitations identified in the sponsor provided as well as the published ITCs, extreme caution must be used in interpreting the comparative efficacy estimates. Given the absence of a direct comparison between glasdegib + LDAC versus azacitidine, there is no robust evidence to ascertain which of the treatments (i.e., glasdegib + LDAC or azacitidine) has superior efficacy. Therefore, the CGP concluded that patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.

In their feedback on the pERC Initial Recommendation, the registered clinicians from CLSG suggested that patients in the BRIGHT 1003 study were of considerably higher risk clinically than were the patients in comparative studies (MRC AML14, AZA-MDS-001, AZA-AML-001, Viale-A, and Viale-C). It was suggested that the treatment effect seen with glasdegib plus LDAC in the BRIGHT 1003 study was better than would be expected in this higher risk population. In response to the registered clinician's feedback, the CGP agreed that the BRIGHT 1003 study enrolled a high-risk group of patients that was ineligible for intensive treatment with an expected poor prognosis. The CGP was uncertain if the population enrolled in the BRIGHT 1003 study was higher risk than the studies

mentioned by the registered clinicians. The CGP noted that the inclusion and exclusion criteria of the BRIGHT 1003 trial are similar to the Viale-A and Viale-C trials and patient characteristics in these studies were similar. However, the CGP noted that the population in the BRIGHT 1003 study may have been higher risk than patients in the AZA-001 and MDS-001 trials, which had slightly lower age cut-offs and reported better results than what is observed in clinical practice in the BC population with azacitidine. However, the CGP cautioned against making indirect cross-trial comparisons regarding the level of risk observed in different trial populations.

In their feedback on the pERC Initial Recommendation, the registered clinicians from CLSG suggested that although there are no direct comparisons of glasdegib + LDAC versus azacitidine, indirect comparisons do not support the notion that azacitidine is preferable over glasdegib + LDAC (rather the opposite conclusion is suggested) referring to a recent abstract[22] from the 25th European Hematology Association Annual Congress. In response to the registered clinicians feedback the CADTH Methods Team noted that the ITC referred to by the registered clinicians in the previously mentioned abstract[22] has been considered in its full form for the present submission and has been summarized and critically appraised in this CADTH Clinical Guidance Report in section 7.1. Given the serious limitations identified and the high level of uncertainty reflected in the CIs, results of the analyses were interpreted with extreme caution.

1.3 Conclusions

The clinical guidance panel concluded that there is a net clinical benefit to the combination of glasdegib + LDAC in comparison with LDAC alone in adult patients with newly diagnosed and previously untreated AML, who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy. This conclusion is based on evidence from one randomized phase II trial that demonstrated a clinically meaningful and statistically significant benefit in OS and an acceptable adverse event profile. The CGP agreed that OS is a clinically meaningful endpoint in this incurable disease setting. Upon relapse after glasdegib + LDAC, treatment options are limited with generally shorter survival times. Additionally, the improvements in OS observed with glasdegib + LDAC are important in this patient population as clinically older patients who are ineligible to receive intensity chemotherapy have poorer treatment outcomes and shorter survival times than patients who are eligible for intensive chemotherapy.

In making this recommendation, the Clinical Guidance Panel considered:

- The CGP noted that patients under the age of 55 are rare in this setting. However, if these patients are not candidates for intensive chemotherapy, then it would be reasonable to generalize the treatment effect of glasdegib + LDAC to this patient population.
- An exploratory subgroup analysis of OS by cytogenetic risk suggested that patients with good/ intermediate risk derive more benefit with glasdegib + LDAC compared with LDAC than patients with poor risk. However, interpretation of this analysis is limited by the relatively small number of patients in the subgroups and exploratory nature of the analyses. While the CGP anticipated that clinicians may prefer to use hypomethylating agents such as azacitidine or decitabine in patients with poor cytogenetic risk, the CGP noted that there is insufficient evidence to inform the use of glasdegib + LDAC in specific cytogenetic subgroups of AML.
- In their feedback on the pERC Initial Recommendation, the registered clinicians from CLSG suggested that the BRIGHT 1003 study showed that glasdegib + LDAC is more effective in poor risk cytogenetic patients than LDAC alone, suggesting that it would be possible to expand glasdegib + LDAC to patients with higher cytogenetic risk. In response to the feedback, the CGP anticipated that, if glasdegib + LDAC were available, most centers would likely prefer to use it in patients with intermediate rather than poor cytogenetic risk. According to exploratory subgroup analyses the rate of CR was higher with glasdegib + LDAC than LDAC alone in patients with poor risk cytogenetics (36% versus 19%), however, the median OS was similar between the two groups (4.7 months versus 4.9 months for glasdegib + LDAC and LDAC, respectively). The CGP reiterated that there is insufficient evidence to inform the use of glasdegib + LDAC in specific cytogenetic subgroups of AML.
- Currently approved treatment options in Canada for adult patients with AML who are not candidates for intensive induction therapy include supportive or palliative care or LDAC in patients who lack adverse cytogenetic findings; or azacytidine for all other patients. The Bright AML 1003 randomized phase II trial clearly indicates the superiority of glasdegib + LDAC versus LDAC in older patients with AML who are not candidates for intensive chemotherapy. Based on the CGP clinical opinion, it is reasonable to anticipate that if glasdegib plus LDAC becomes available for the requested target population, it will be the preferred option to replace LDAC, because of its prolonged OS and manageable toxicity profile. However, as noted

previously, given the absence of a robust comparative data between glasdegib + LDAC versus azacytidine, it remains uncertain if glasdegib + LDAC or azacitidine has superior efficacy.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
The standard of care options for newly diagnosed AML patients who are not eligible for intensive induction chemotherapy, include less intensive chemotherapy regimens (e.g. low-dose cytarabine (LDAC), azacitidine, or decitabine) or best supportive care. Of those, azacytidine is the most frequently used therapy in Canada. The comparator in the BRIGHT AML 1003 study was low-dose cytarabine. • PAG is seeking comparative data on glasdegib plus LDAC versus low-intensity chemotherapy regimens	• Currently, only indirect comparisons can be made between glasdegib plus LDAC and azacitidine as no trial to date has directly compared these drugs. Refer to Section 7 for summaries and critical appraisals of a Sponsor-submitted and published indirect treatment comparison (ITC). The CGP noted that results of the sponsor-provided ITC suggested no statistically significant difference and wide confidence intervals for the OS HRs of glasdegib + LDAC compared to azacitidine in the base case using Bucher method. For the sensitivity analyses using simulated treatment comparisons (STC) methods, results for the 20-30% blasts subgroup showed no statistically significant differences for OS between glasdegib + LDAC and azacitidine. Results for the >30% blasts subgroup demonstrated a statistically significant difference in favour of glasdegib + LDAC, however, the CIs were wide and the upper bound of the CI interval was near or at 1.00. Results for the published ITC suggested that results for glasdegib + LDAC compared to azacitidine demonstrated a statistically significant improvement for the OS HR for glasdegib + LDAC (HR range: 0.412 to 0.514). However, the CGP agreed with the CADTH Methods Team, that due to severe limitations identified in the ITCs extreme caution must be used in interpreting the comparative efficacy estimates. Given the absence of a direct comparison, there is no robust evidence to ascertain which of the agents (i.e., glasdegib plus LDAC or azacitidine) has superior efficacy. Therefore, the CGP concluded that patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.
Eligible Patient Population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with glasdegib + LDAC: • Patients who have experienced disease progression on intensive chemotherapy (and are not candidates for further intensive chemotherapy). • Patients with therapy-related AML	• The CGP noted that patients who had experienced disease progression on intensive chemotherapy were not eligible for the BRIGHT 1003 trial. The CGP did not support generalizing the trial results to these patients. • The CGP noted that therapy-related AML is not expected to be an independent risk factor for a worse prognosis, but patients with therapy-related AML tend to have unfavourable risk

PAG Implementation Questions	CGP Response
	cytogenetics. Some patients with therapy-related AML were included in the BRIGHT 1003 study (8% and 3% of patients in the glasdegib + LDAC and LDAC groups, respectively), therefore there is some evidence to warrant generalizing these results to therapy-related AML.
• Patients younger than 55 (age cut-off in trial).	• The CGP noted that patients under the age of 55 are rare in this setting. However, if these patients are not candidates for intensive chemotherapy, then it would be reasonable to generalize the treatment effect of glasdegib + LDAC to this patient population.
• Patients with an ECOG performance status greater than 2.	• The CGP noted that patients with ECOG PS greater than 2 were not eligible for the trial. The CGP did not support generalizing the trial result to patients with ECOG 2 or greater. This would be a group of patients who may not be able to self administer LDAC and there is insufficient evidence on the treatment effect of glasdegib + LDAC in patients with ECOG PS of greater than 2.
• Patients with various cytogenetic risk profiles (low, intermediate, high).	• The CGP noted that prespecified but exploratory subgroup analyses of OS by cytogenetic risk in the BRIGHT 1003 trial suggested that patients with good/ intermediate risk derive more benefit with glasdegib plus LDAC compared with LDAC than patients with poor risk. However, interpretation of these analyses is limited by the relatively small number of patients in the subgroups and exploratory nature of the analyses. While CGP anticipated that clinicians may prefer to use a hypomethylating agent such as azacitidine in patients with poor cytogenetic risk, the CGP noted that there is insufficient evidence to limit the use of glasdegib plus LDAC to specific cytogenetic subgroups of AML.
PAG noted that the Health Canada product monograph mentions adverse changes in growing bone and teeth in animal studies. Consequently, there are concerns regarding the safety of glasdegib in the pediatric population.	The CGP agreed that in general drugs that affect development and growth in the pediatric population are used with caution. CGP noted that in the event that glasdegib plus LDAC would be suggested for the pediatric population, these concerns would have to be closely examined.
If recommended for reimbursement, patients currently on low-dose cytarabine or other low-dose chemotherapies such as azacytidine would need to be addressed on a time-limited basis.	The CGP anticipated that glasdegib + LDAC will replace LDAC therapy in clinical practice, based on the BRIGHT 1003 results, which demonstrated a statistically significant OS benefit in the glasdegib + LDAC compared with the LDAC group. The CGP noted that it would be reasonable to offer glasdegib + LDAC to patients currently on LDAC therapy on a time-limited basis. However, the CGP noted that there is insufficient evidence to ascertain the treatment effect of glasdegib + LDAC in patients who have started treatment with azacitidine or decitabine. Furthermore, the CGP noted that there is currently no robust evidence to ascertain which of the agents (i.e., glasdegib + LDAC, azacitidine, or decitabine) has superior efficacy. For these reasons the CGP does not support offering glasdegib + LDAC on a time-limited basis in patients who are currently on azacytidine or other low-dose chemotherapies such as decitabine.
PAG is concerned with potential indication creep to patients who progressed or had inadequate response on low dose	As patients who progressed or had inadequate response on low dose chemotherapy were excluded from the trial, there are no

PAG Implementation Questions	CGP Response
chemotherapy or who relapsed after treatment.	data to support the generalizability of treatment benefit with glasdegib plus LDAC in this patient population.
Patients with MDS—also studied in the BRIGHT AML 1003 trial—may also be subjects of non-indicated use. MDS patients with a higher blast count (e.g., 20-30%) that may meet some definitions of AML may be more likely to use this drug, should it be reimbursed.	The CGP noted that MDS with blasts between 20-30% no longer exists as a diagnostic category. The WHO Classification of Tumors of hematopoietic and lymphoid tissue 2017 defines an AML as having blasts ≥20%. AML with t(8;21), inv(16) and t(16;16) are considered AML regardless of blast count.
Are the criteria used in the trial to identify patients not suitable for intensive chemotherapy reflective of the criteria used for the patients seen in Canadian clinical practice?	The CGP noted that the criteria in the BRIGHT AML 1003 trial used to identify patients not suitable for intensive chemotherapy included at least one of the following: Age ≥ 75 years ECOG of 2 Serum creatinine > 1.3 mg/dL Severe cardiac disease (e.g., left ventricular ejection fraction [LVEF] < 45% by multi-gated acquisition or echocardiography at screening The CGP agreed that these criteria seemed reasonable and are fully applicable to Canadian clinical practice. It was noted that there is some inter-clinician variability in identifying patients that are not suitable for intensive chemotherapy.
Implementation Factors	
• PAG seeks clarification on the definition of “clinical benefit” to help identify criteria for treatment discontinuation.	The CGP considered the BRIGHT AML 1003 study design that specified that treatment with glasdegib + LDAC continued for up to 1 year until disease progression or relapse, patient refusal or unacceptable toxicity, whichever comes first. Patients who completed the maximum number of cycles on study treatment, demonstrated **clinical benefit** with manageable toxicity, and were willing to continue receiving the assigned treatment were given the opportunity to do. Furthermore, the CGP noted that the product monograph recommended that treatment with glasdegib + LDAC is to be continued in the absence of unacceptable toxicity or loss of disease control. Treatment should be continued as long as the patient is deriving clinical benefit. In the BRIGHT AML 1003 study clinical benefit was defined as stable disease or better as per the treating investigator. The CGP noted that the definition for clinical benefit used in the BRIGHT 1003 trial is reasonable and applicable to Canadian clinical practice. The CGP noted that in clinical practice clinicians use the following parameters to assess clinical benefit: decreased transfusion requirements, increased constitutional wellness, and normalization of the complete blood count. The CGP noted that patients who have achieved complete remission would also continue on glasdegib + LDAC as long as clinical benefit is derived.
• PAG also seeks any recommendations regarding dose reduction due to toxicity.	• CGP agreed with the recommendations regarding dose reduction as per the product monograph.
PAG commented that glasdegib is metabolized primarily by CYP3A4, which may be affected by a number of other drugs. PAG also noted that co-administration of glasdegib with	CGP noted that the following monitoring would be reasonable as a precaution for patients receiving glasdegib + LDAC:

PAG Implementation Questions	CGP Response
specific drugs may increase the risk of QT prolongation. Therefore, PAG would like information on any additional monitoring or precautions to be recommended for patients receiving this drug.	Electrocardiograms measures taken at baseline and once per cycle up to approximately 3 cycles to ensure QT is not prolonged. Any moderate/strong CYP3A4 inhibitors received by patients should be monitored.
It was noted that low dose cytarabine needs to be administered twice daily and that some treatment rooms are not open for 12 hours. PAG is seeking guidance on administration of cytarabine at intervals of less than 12 hours. Moreover, cytarabine is cytotoxic and hazardous, and may not be able to be administered in patient's home; the patient may need to visit a treatment room for ten consecutive days. For treatment rooms that are not open on weekends and holidays, PAG would like clarity on whether it is acceptable to add the days missed to the following week, similar to azacitidine. Would it be appropriate to implement a modified low-dose cytarabine regimen to account for clinic opening hours?	The CGP noted that currently the syringes for LDAC are commonly prepared by the hospital pharmacy and dispensed to the patient to administer at home. However, CGP acknowledged that the National Association of Pharmacy Regulatory Authorities (NAPRA) has issued standards that may affect how LDAC is administer. The CGP noted that pharmacies in respective jurisdictions will likely have to address this issue upon implementation of reimbursement of glasdegib plus LDAC.
PAG remarked that vismodegib, another oral hedgehog pathway inhibitor, is controlled by a distribution program. Because glasdegib is in the same class, PAG would like to know if there will be a similar program in which pharmacies will need to complete checklists with patients prior to each dispensation.	The CGP noted that glasdegib is only available through a control distribution program called the DAURISMO Pregnancy Prevention Program (DPPP). Under this program, only prescribers and pharmacies registered with the program are able to prescribe and dispense the product, respectively. In addition, glasdegib can only be dispensed to patients who are registered and meet all the conditions of the DPPP.
Sequencing and Priority of Treatment	
PAG is seeking guidance on the appropriate place in therapy of glasdegib and overall sequencing of all treatments available for AML. In particular, PAG would need information on the following aspects: Using glasdegib + LDAC after treatment failure with low-dose chemotherapy. Use of other therapies after failure of glasdegib + LDAC.	The CGP noted that a small number of patients (n=24) in the BRIGHT 1003 study were enrolled onto the study after treatment with azacitidine or decitabine for MDS. Outcomes were not reported for these patients after treatment with glasdegib + LDAC. There is insufficient evidence to make strong recommendations about treatment of glasdegib + LDAC after treatment with other low-dose chemotherapies for AML. Similarly, optimal treatment after failure of glasdegib + LDAC is unknown.
What treatments would be given to patients upon progression of glasdegib + LDAC?	The CGP anticipates that upon progression on glasdegib + LDAC that other important treatment options could include: hypomethylating agents such as azacitidine, best supportive care or a clinical trial if available.
Additional Information	
PAG identified an ongoing phase III RCT, BRIGHT AML 1019, studying glasdegib in the context of both intensive and non-intensive therapies, that may provide further evidence for use in the broader AML population, in line with the funding request and provisional indication.	Upon request, the sponsor noted that based on a preplanned efficacy and futility analysis, the independent Data Monitoring Committee (DMC) of the Phase 3 BRIGHT AML 1019 Non-Intensive cohort established that glasdegib + azacitidine will unlikely demonstrate a statistically significant improvement in overall survival (primary endpoint). Following the recommendation of the independent DMC, the Sponsor agreed to stop the Non-Intensive cohort of the Phase 3 clinical trial BRIGHT AML 1019. It was further noted that the cohort that evaluates glasdegib in combination with intensive chemotherapy (cytarabine and daunorubicin) for the treatment of adult patients with previously untreated AML, is ongoing.

PAG = Provincial Advisory Group, CGP = Clinical Guidance Panel

2 Background Clinical Information

2.1 Description of the Condition

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults and is an aggressive hematological malignancy that presents with signs or symptoms of bone marrow failure (fatigue, dyspnea, bleeding, bruising or infection), organ infiltration, central nervous system and systemic complaints (chiefly fevers, fatigue, night sweats). Presentation is variable and while patients often present to hospital acutely ill, some patients present with mild symptoms (fatigue) and abnormal CBC. The diagnosis of AML is confirmed by bone marrow histology and ancillary tests such as cytogenetics and molecular testing.

In Canada, the age adjusted incidence of AML is approximately 3.75/10. In 2017 there were 1,509 new cases of AML reported in Canada with a median age at diagnosis of 66 years. AML incidence increases with age with just over a quarter of diagnoses in those over the age of 75. AML is uncommon in children with an age adjusted incidence of 7.2/10.[13] The most recent mortality statistics indicate that 1,184 Canadians died from AML in 2017.[23] The 5-year expected survival after diagnosis for AML in the United States is 28% and in Canada is 21%.[24,25] Older people have a lower response rate to treatment. With treatment, approximately 20% of people over the age of 60 are expected to survive 2 years.[26] There is a need for new therapy options that offer less toxicity and more durable responses.

AML represents a heterogeneous group of disorders with similar clinical presentations but variable prognosis. AML is classified according to the World Health Organization (WHO) Classification of Tumors of the Hematopoietic and Lymphoid Tissues.[27] The WHO classification is a combined clinicopathological and molecular genetic classification.

AML is classified into four main disease subtypes by the WHO classification system: AML with recurrent genetic abnormalities (11% of cases), AML with myelodysplasia-related features (6% of cases), therapy-related AML (2% of cases) and AML, not otherwise specified (81% of cases).[28] One subtype of AML, Acute Promyelocytic Leukemia (currently classified as acute promyelocytic leukemia with t(15;17)(q24.1;q21.2);PML-RARA in the World Health Organization classification system), is sufficiently distinct from a prognostic and therapeutic perspective that it will not be further discussed in this background section. Commonly associated mutations in AML include mutations in FMS-Like Tyrosine Kinase 3 (FLT3) FLT3 gene and mutations in Nucleophosmin 1 (NPM1) both of which are found in approximately 30% of AML patients. The prognosis of patients with AML is influenced by several factors including age at diagnosis and cytogenetics. Prognosis may also be affected by site of treatment as tertiary /quaternary centres are often more experienced and offer more comprehensive supportive care. AML patients are stratified into those with favorable, intermediate and adverse risk primarily mediated by the molecular genetic profile of the AML.[29]

Generally, 20% blasts in the marrow or blood is required for a diagnosis of AML, however, a diagnosis of AML may be made with <20% blasts with the following cytogenetic abnormalities: t(15;17), t(8;21), t(16;16), inv(16).[30,31] The role of bone marrow blast levels in guiding treatment strategy (e.g. drug selection, duration of therapy) and its significance as a prognostic factor is emerging.[32,33] Recent research suggests it is one of many factors that influence survival but the role of bone marrow blast percentage has not been clearly established in treatment paradigms for older patients with AML.[33] In the Canadian 2017 guidelines, bone marrow blast percentage between 20-30% is an indication to use azacitidine based on a previous study[15] but there are no recommendations in the guideline for using blast percentage to guide other treatment options.[16]

2.2 Accepted Clinical Practice

Left untreated, AML is uniformly fatal with survival ranging from weeks to months. The backbone of successful therapy remains intensive multidisciplinary supportive care including transfusion support, antimicrobial prophylaxis and management of tumor lysis syndrome.

While there are no overarching national Canadian guidelines on the management of AML, several international guidelines harmonize with practice in Canada.[29,30,34] In younger fit patients, initial induction remission involves combination chemotherapy (7 days of cytarabine and 3 days of anthracycline therapy [7+3]). In younger fit patients the goal of remission induction therapy is to achieve a complete remission (CR1). A risk adapted approach is utilized to optimize the likelihood of a curative outcome.

Patients with AML are usually assigned to a genetic risk group to determine optimal post-remission therapy; for example many centres use the favourable, intermediate, or adverse genetic abnormalities as described in the 2017 ELN recommendations.[29,35] Risk stratification is important for determining the optimal therapy.[14] For those with favourable risk, post remission therapy involves up to 3 or 4 cycles of high dose cytarabine (HIDAC) consolidation with or without anthracycline depending on local practice. Approximately 60% of patients are cured in this fashion.[29,30,34] For patients with intermediate and adverse risk, AML results with HIDAC consolidation are unsatisfactory, consequently in younger fit patients allogeneic transplantation is pursued as a consolidation strategy in CR1. Allogeneic transplantation for AML in CR1 is associated with a probability of long-term survival of 50%, however, the procedure is associated with a high risk of morbidity and mortality.[36]

The approach to treatment of AML in older adults (60 years or older) differs from treatment of younger adults. Older patients are less likely to be offered intensive treatment, suffer more treatment-related toxicity, generally have poorer risk disease with increased secondary AML and fewer favourable risk cases and are expected to have inferior clinical outcomes. The goals of treatment in medically frail patients are to prolong life, alleviate symptoms, and/or improve quality of life. An evaluation of the fitness of patients to receive intensive induction chemotherapy for AML includes age at diagnosis, ECOG status, comorbid conditions, activities of daily living, physical performance tests and cognition. There is no consensus as to what degree of comorbidity constitutes an absolute contraindication to intensive induction therapy.[14]

There is variability between centres in Canada in the treatment of patients who are not candidates for intensive therapy (remission induction, allogeneic stem cell transplant) because of advanced age or frailty.[14] In Canadian clinical practice, available treatment options for newly diagnosed AML patients who are not eligible for intensive induction chemotherapy include less intensive chemotherapy regimens (e.g. LDAC, azacitidine, decitabine) or best supportive care. Treatment with a lower intensity regimen is not expected to achieve cure of AML. These agents are typically given continuously until disease progression to obtain the optimal therapeutic response. In some elderly frail patients, supportive care (palliative care) may be offered as an alternative approach to drug treatment.

In Canada, azacitidine has Health Canada approval for adult patients who are not eligible for hematopoietic stem cell transplantation with AML with 20-30% blasts and multi lineage dysplasia, according to World Health Organization (WHO) classification, based on a phase III trial[15] in patients with intermediate-2- and high-risk MDS. Since then, emerging evidence suggests activity of azacitidine in a broader patient population.[14,16] According to the revised Canadian Consensus Guidelines (2017)[14] for older patients who are not considered suitable for inducting therapy, frontline azacitidine is (1) the standard treatment for patients with 20 to 30% bone marrow blasts with myelodysplasia-related changes, (2) the preferred frontline treatment for patients with adverse-risk cytogenetics, and (3) one treatment options among LDAC and decitabine for patients with favorable-risk cytogenetics.[14]

Azacitidine is currently the most frequently used therapy in newly diagnosed AML in Canada. It is currently available under the Health Canada approved indication as well as for patients with >30% marrow blasts, either via patient access programs or more rarely through provincial reimbursement.[37]

LDAC has Health Canada approval for the treatment of AML.[38] LDAC is currently used across Canada in approximately 20-30% of elderly AML patients who are not medically fit for induction therapy.[37] According to the revised Canadian Consensus Guidelines (2017) for older patients who are not considered suitable for inducting therapy LDAC is currently recommended as a possible frontline option for patients with intermediate/ favorable risk cytogenetics with >30% bone marrow blasts.[14] Decitabine is currently Health Canada approved for patients with de novo or secondary MDS.[39] According to the revised Canadian Consensus Guidelines (2017) for older patients who are not considered suitable for induction therapy decitabine is currently recommended as a possible frontline options (other recommended options include azacitidine or LDAC) for patients with intermediate/ favorable risk cytogenetics with >30% bone marrow blasts.[14]

3 Summary of Patient Advocacy Group Input

The Leukemia & Lymphoma Society of Canada (LLSC) provided input on the glasdegib (Daurismo) for AML review and their input is summarized below. Namely, the funding request under review is glasdegib in combination with low-dose cytarabine, for the treatment of newly diagnosed and previously untreated AML in adult patients, who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy. The LLSC provided data from an online survey that was created by LLSC on March 2, 2020 in English and French. The survey was posted online through Survey Monkey and distributed through various social media channels and directly by email. The survey asked for the opinions of people diagnosed with AML and their families whether they had experience with glasdegib or not. There was a total of 18 responses; however, responses of three respondents were not included in the input due to the diagnosis not being specified and the lack of response for majority of the survey questions. Therefore, 15 patient responses were included in the input provided by LLSC. Most respondents were in the age range of 55 to 64 (n=4); however, the age ranged from 25 to 84 among all respondents. Additionally, all patients were Canadian with most patients reporting Ontario as their province of residence (n=6). Of note, none of the respondents received glasdegib for treatment of AML. Table 4 summarizes the age and Canadian province of residence of patient respondents.

Table 4: Summary of Patient Respondent Demographics

Patient Respondent Demographics			
Age Range	**Number of Patient Respondents**	**Canadian Province of Residence**	**Number of Patient Respondents**
25-34	3	Alberta	3
35-44	1	British Columbia (BC)	4
45-54	2	Manitoba	1
55-64	4	Ontario	6
65-74	3	Quebec	1
75-84	2		

From the patient perspective, all patient respondents experienced the common symptoms of AML of fatigue, loss of appetite, and weight loss, and these were noted to disrupt daily life. Namely, fatigue was reported to have the most impact on daily life, and 80% of patients noted that extreme fatigue had a “significant impact” on their daily lives. Fatigue was specified to disrupt activities, sleep patterns, and physical and emotional intimacy. Additionally, patients highlighted the lack of a social life attributed to AML as one patient noted that they experience social isolation due to a fear of catching an infection. All patient respondents had received treatment for AML; namely, 11 respondents received chemotherapy, 10 received high-dose chemotherapy, two received radiotherapy, 11 respondents received a stem cell or bone marrow transplant, one received immunotherapy, three received maintenance therapy, and one received two sets of consolidation therapy. Among these, the following were specified: daunorubicin, cytarabine, daunorubicin plus cytarabine (Vyxeos), venetoclax, azacitidine, busulfan, methotrexate, and cyclophosphamide. The most common side effects reported by patients included: fatigue, infections (e.g., viral and fungal), hair loss, neutropenia (low number of white blood cells), reduced movement/ inability to participate in physical activities, fever, and vomiting. The most serious side effect reported was a graft versus host reaction (GVH)— when the donor's immune cells attack the patient's normal cells. Another patient mentioned being unable to swallow and experiencing severe vomiting, which resulted in the patient receiving IV nutrition for several weeks in the hospital. Moreover, eight respondents had some form of infection or disease other than cancer, which was attributed to the deficiency of white blood cells during treatment. In addition to the physical side effects, patients noted that treatments impacted their quality of life through a change in physical activity (e.g., gardening, exercise, etc.), the ability to work, anxiety levels, and social life (e.g., visiting other people or attending social functions).

Majority of patients reported (11/15) easy access to treatment; however, one patient reported having difficulty accessing treatment in BC (patient’s province of residence) but was able to receive first-line treatment (high-dose chemotherapy: cytarabine with daunorubicin for induction and cytarabine for consolidation [two sets]) by connecting with a hematologist in another province (not specified), and another patient noted having difficulty finding transportation to receive treatment. Namely for elderly patients, it was highlighted that patients should be able to receive treatment based on their general state of health and not their age. Notably, none of the respondents had treatment experience with glasdegib; however, patients were asked if they would consider taking glasdegib and

why they would be willing to tolerate the side effects. One patient would consider treatment with glasdegib if it meant choosing between life and death, and another patient would consider glasdegib if the positive results of glasdegib are as good or better than chemotherapy. Patients noted that doctor's recommendation, possible impact on the disease, and quality of life as the most important factors for patients and caregivers when deciding on a new cancer treatment. Overall, patients with AML value having access to treatments; accordingly, access should not be limited by a patients' financial status, geographic location (province of residence), or age; specifically, access to treatment should be based on a patients' general state of health rather than age. Further, patients seek treatments that are effective for symptom management, particularly fatigue as it has a significant impact on the daily lives of patients and treatments associated with reduced side effects; namely, infections, which also disrupt one's social life and keeps patients in their homes in fear of acquiring an infection.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient group.

3.1 Condition and Current Therapy Information

3.1.1 Patients' Experiences

All patients were diagnosed as adults between 2015 and 2019. Overall, all patients reported that their diagnosis had resulted in many disruptions in their daily lives. The following symptoms were reported to disrupt daily lives, listed in order of importance: fatigue, loss of appetite and weight, fever/ night sweats, skin rashes/ skin changes, pain, nausea and/ or vomiting, dizziness, vision changes, constipation, and headache. Notably, all respondents experienced common AML symptoms such as fatigue, loss of appetite, and weight loss. Further, each respondent ranked all their symptoms on a scale from 1 to 7; fatigue was reported to have the most impact on daily life. Namely, 12 respondents (80% of patients surveyed) noted that extreme fatigue had a "significant impact" on their daily lives. Fatigue was specified to disrupt activities, sleep patterns, and physical and emotional intimacy. Additionally, patients highlighted how the disease disrupted one's social life. Namely, the following patient quotations demonstrate the impact of fatigue on daily life and the interference of one's social life:

- "*ability to work has been diminished, fatigue impacts time I can spend with family drastically*"
- "*daily routine affected. Fatigue prevented me from gardening and also exercise*"
- "*kind of social isolation due to fear of catching infection*"
- "*it keeps me in the apartment too much*."

3.1.2 Patients' Experiences with Current Therapy

All patient respondents had received treatment for AML; namely, 11 respondents received chemotherapy, 10 received high-dose chemotherapy, two received radiotherapy, 11 respondents received a stem cell or bone marrow transplant, one received immunotherapy, three received maintenance therapy and one received two sets of consolidation therapy. Among these, the following were specified: daunorubicin, cytarabine, daunorubicin plus cytarabine (Vyxeos), venetoclax, azacitidine, busulfan, methotrexate, and cyclophosphamide.

The most common side effects reported by patients included: fatigue, infections (e.g., viral and fungal), hair loss, neutropenia (low number of white blood cells), reduced movement/ inability to participate in physical activities, fever, and vomiting. The most serious side effect reported was a GVH reaction; namely, GVH disease develops when the donor's immune cells attack the patient's normal cells. This disease can be mild, moderate or severe, and even life threatening. Another respondent mentioned being unable to swallow and experiencing severe vomiting, which resulted in the patient receiving IV nutrition for several weeks in the hospital. Moreover, eight respondents had some form of infection or disease other than cancer, which was attributed to the deficiency of white blood cells during treatment that can lead to infections by bacteria normally present in the environment, on the skin, in the nose and mouth, on the gums, or the colon (infection risk is higher when white blood cell count is low). In addition to the physical side effects, patients noted that treatments impacted their quality of life through a change in physical activity (e.g., gardening, exercise, etc.), the ability to work, anxiety levels, and social life (e.g., visiting other people or attending social functions). Notably, the following patient quotations reflect aforementioned changes:

- "*I was very active and social before treatment. I have lost the urge to work out and have been keeping myself away from large crowds as my numbers are still not high. As well as not having all my vaccinations this offers other problems in the way of socializing*"
- *"you cannot do the things you once did. Life is on hold during the whole treatment procedure"*
- *"need to stay isolated due to low immune system, can't participate in normal activities"*
- *"I had to live away from home during treatment, which was financially challenging"*
- *"long months off work and feeling useless and burden to the family and society."*

Patients were asked if they had difficulty accessing their treatments; 11 respondents indicated that they had easy access to treatment options. However, one respondent noted having difficulty finding transportation to treatment centres. Additionally, a second patient reported having difficulty accessing treatment in BC, her province of residence, as the clinician in BC refused to treat her; however, she was able to receive first-line treatment (high-dose chemotherapy: cytarabine with daunorubicin for induction and cytarabine for consolidation [two sets]) by connecting with a hematologist in another province (not specified). In her own words, "*as they felt I was too old to have a positive outcome. Thankfully in another province I was able to connect with a hematologist who felt it was worth a try. That was just over three years ago and for now I'm still in remission. If I relapse and desire further treatment I will have to permanently relocate to the province I received first line treatment*." Further, it was highlighted that elderly patients should be able to access treatment based on their general state of health and not their age. In one patient's own words, "*I think that elderly patients (over 65) should receive treatment according to their general state of health and not their age. I am sad that there are people in this province who are going to bed tonight with a 'death sentence' and not knowing that there could be treatment in another province*."

3.1.3 Impact on Caregivers

None to report, there were no caregiver respondents to the survey.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Respondents were asked what the most important factors are for patients and caregivers when deciding on a new cancer treatment; the top three answers were: doctor's recommendation (10 respondents), possible impact on the disease (9 respondents), and quality of life (9 respondents). Additionally, the LLSC highlighted the importance for patients to know that they have treatment options, as reflected in one patient's own words, "*I would feel more comfortable if I knew what my options were for future treatment if my cancer came back*."

3.2.2 Patient Experiences to Date

None of the respondents had treatment experience with glasdegib; however, respondents were asked if they would consider taking glasdegib and why they would be willing to tolerate the side effects, one respondent stated, "*would consider this if it meant a choice between life and death*." Another respondent stated, "*it would depend on whether the positive results were as good or better than the chemo treatment*."

3.3 Companion Diagnostic Testing

None to report.

3.4 Additional Information

None to report.

4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) and **one** Federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:
- Sequencing with other therapies for AML

Economic factors:
- Additional safety monitoring

Please see below for more details.

4.1 Currently Funded Treatments

The standard of care for newly diagnosed AML patients who are not eligible for intensive induction chemotherapy, options include less intensive chemotherapy regimens (e.g. LDAC, azacitidine, decitabine) or best supportive care. Of those, azacytidine is the most frequently used therapy in Canada. The comparator in the BRIGHT AML 1003 study was LDAC.

PAG is seeking comparative data on glasdegib plus LDAC versus low-intensity chemotherapy regimens.

4.2 Eligible Patient Population

The funding request of glasdegib is in combination with LDAC, 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.

PAG is seeking clarity on whether the following patients would be eligible for treatment with glasdegib:
- Patients who progressed on chemotherapy.
- Patients with therapy-related AML.
- Patients younger than 55 (age cut-off in trial).
- Patient with an ECOG performance status greater than 2.
- Patients with various cytogenetic risk profiles (low, intermediate, high).

PAG noted that the draft product monograph mentions adverse changes in growing bone and teeth in animal studies. Consequently, there are concerns regarding the safety of glasdegib in the pediatric population.

If recommended for reimbursement, patients currently on LDAC or other low-dose chemotherapies such as azacytidine would need to be addressed on a time-limited basis.

PAG is concerned with potential indication creep to patients who progressed or had inadequate response on low dose chemotherapy or who relapsed after treatment. Patients with MDS—also studied in the BRIGHT AML 1003 trial—may also be subjects of non-indicated use. MDS patients with a higher blast count (e.g., 20-30%) that may meet some definitions of AML may be more likely to use this drug, should it be reimbursed.

4.3 Implementation Factors

The recommended dose of glasdegib is 100 mg taken orally once daily on days 1 to 28 in combination with cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of each 28-day cycle in the absence of unacceptable toxicity or loss of disease control, as long as the patient is deriving clinical benefit. Glasdegib is available in oral tablets of 25 mg and 100 mg, which facilitates dose adjustments, minimizes drug wastage, and is thus an enabler to implementation. PAG seeks clarification on the definition of "clinical benefit" to help identify criteria for treatment discontinuation. PAG also seeks any recommendations regarding dose reduction due to toxicity.

PAG commented that glasdegib is metabolized primarily by CYP3A4, which may be affected by a number of other drugs. PAG also noted that co-administration of glasdegib with specific drugs may increase the risk of QT prolongation. Therefore, PAG would like information on any additional monitoring or precautions to be recommended for patients receiving this drug.

PAG noted that glasdegib would be an additional therapy as it does not replace chemotherapy. Extra pharmacy resources for dispensing and monitoring would be required, as patients would otherwise be on subcutaneous or intravenous chemotherapy alone. It was noted that low dose cytarabine needs to be administered twice daily and that some treatment rooms are not open for 12 hours. PAG is seeking guidance on administration of cytarabine at intervals of less than 12 hours. Moreover, cytarabine is cytotoxic and hazardous, and may not be able to be administered in patient's home; the patient may need to visit a treatment room for ten consecutive days. For treatment rooms that are not open on weekends and holidays, PAG would like clarity on whether it is acceptable to add the days missed to the following week, similar to azacitidine. It was noted that a ten-day treatment with LDAC would entail additional resources to monitor side effects.

PAG remarked that vismodegib, another oral hedgehog pathway inhibitor, is controlled by a distribution program. Because glasdegib is in the same class, PAG would like to know if there will be a similar program in which pharmacies will need to complete checklists with patients prior to each dispensation.

PAG noted that glasdegib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation and that once daily dosing (with or without food) would be convenient for patients.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate place in therapy of glasdegib and overall sequencing of all treatments available for AML. In particular, PAG would need information on the following aspects:

- Using glasdegib/LDAC after treatment failure with low-dose chemotherapy.
- Use of other therapies after failure of glasdegib/LDAC.

4.5 Companion Diagnostic Testing

None needed.

4.6 Additional Information

PAG identified an ongoing phase III RCT, BRIGHT AML 1019, studying glasdegib in the context of both intensive and non-intensive therapies, that may provide further evidence for use in the broader AML population, in line with the funding request and provisional indication.

5 Summary of Registered Clinician Input

A total of two registered clinician inputs were provided for the review of glasdegib (Daurismo) in combination with LDAC, for the treatment of newly diagnosed and previously untreated AML in adult patients, who are ≥75 years of age or who are not eligible to receive intensive induction chemotherapy: one clinician provided input on behalf of Cancer Care Ontario (CCO) Hematology Drug Advisory Committee (DAC) and ten clinicians provided input on behalf of the Canadian Leukemia Study Group (CLSG)/Groupe Canadien d'Étude sur la Leucémie (GCEL). Both inputs mentioned the following treatment option for patients with newly diagnosed AML: induction chemotherapy (daunorubicin or idarubicin plus cytarabine in the form of standard 3+7 or Vyxeos liposomal therapy) followed by consolidation therapy (e.g., high-dose cytarabine monotherapy or high-dose cytarabine plus anthracycline) with the potential for transplant (e.g. hematopoietic stem cell transplant). Additionally, the CLSG clinicians noted that patients could receive a fludarabine-idarubicin-cytarabine regimen. Alternatively, patients who are ineligible for aforementioned regimens could receive best supportive care or less intensive chemotherapy regimens; azacitidine and LDAC were noted in both inputs while the CCO clinician additionally specified azacitidine plus venetoclax and the CLSG clinicians additionally specified decitabine. Moreover, the CLSG clinicians noted that some types of AML can be treated with targeted agents and the CCO clinician specified that patients with FLT3 mutations with newly diagnosed AML may be treated with standard induction 3+7 chemotherapy plus midostaurin. The CLSG clinicians stated that the most appropriate comparators for the current review would be LDAC or azacitidine. Compared to LDAC monotherapy, the CLSG clinicians highlighted that response rates (CR) and median OS were greater with glasdegib plus LDAC as demonstrated in the pivotal trial. Further, they highlighted that glasdegib plus LDAC is safe and well-tolerated and that contraindications to glasdegib plus LDAC are essentially the same as to LDAC alone, with the addition of known intolerance to glasdegib or another Hedgehog inhibitor. Accordingly, the CLSG clinicians specified that glasdegib plus LDAC would be a superior alternative to LDAC alone if the treatment under review becomes available for funding. The CCO and CLSG clinicians indicated that the trial criteria to identify patients not suitable for intensive chemotherapy were reasonable and reflective of clinical practice. The CCO clinician specified that the only patients who should not receive glasdegib align with the exclusions of the pivotal trial and there should be no age restriction. Correspondingly, the CLSG clinicians stated they would specifically administer glasdegib plus LDAC in patients with one or more of the following: 1) difficulty in attending hospital visits for geographic or distance reasons, 2) standard risk cytogenetics, 3) prior treatment failure with a HMA such as azacitidine or decitabine, and 4) intolerance to a HMA. For such patients, the CLSG clinicians stated that it is essential to have a LDAC-based treatment option in Canada. They specified that most of the patients receiving the treatment under review would be elderly and many elderly patients in Canada often live far from a cancer centre, and travel is difficult due to the distance and the requirement for an accompanying caregiver. Accordingly, when asked if it would be appropriate to implement a modified LDAC regimen to account for clinic opening hours; the CLSG clinicians (Canadian wide perspective) indicated that this practice would be appropriate. They specified that LDAC-based regimens offer the advantage of being delivered at home by homecare, a caregiver, or by the patient. Alternatively, azacitidine injections are not administered at home and the patient must attend a chemotherapy clinic for seven consecutive days. Thus, LDAC-based regimens can be much more favourable for the patient and caregiver while also sparing valuable hospital resources and increasing clinic capacity. Namely, the advantage of reducing the time needed to be in the hospital for the patient and caregiver is particularly favourable during the COVID-19 pandemic. The CCO clinician stated that patients usually inject themselves at home with pre-filled syringes in Ontario. Moreover, the CLSG clinicians highlighted that LDAC-based treatments may be effective for patients who have been treated with an HMA for an antecedent hematological disorder such as a MDS that proceeded to AML despite HMA treatment. For such patients, treatment of their AML with an HMA-based regimen is considered medically futile.

Regarding AML patients with an identified mutation, the CCO clinician stated that the only targeted regimen presently available in the first-line setting is 3+7 induction chemotherapy plus midostaurin; however, patients with an identified mutation would likely not receive this treatment. The CLSG clinicians stated that the glasdegib plus LDAC combination is largely "mutation" agnostic. Further commenting that there may be an inferior response in patients bearing an IDH2 mutation; however, the patient numbers are small to inform this. Additionally, they highlighted that targeted agents are not yet approved in Canada for up-front treatment in patients who are not eligible for intensive therapies. Nevertheless, they noted there is some clinical trial evidence that the combination of LDAC plus venetoclax is particularly effective in AML patients bearing the NPM1 mutation; however, venetoclax is not approved in Canada for this indication. The CCO clinician stated that palliative care and hydroxyurea would be available for most patients upon progression of glasdegib plus LDAC. If patients had an identified mutation such as IDH2 they may be able to receive a targeted-agent through compassionate access. Additionally, they highlighted that gilteritinib may be an option for patients with a FLT3 mutation and noted that FLT3 mutation status can change. The CLSG clinicians stated that assuming patients are still considered

ineligible for intensive chemotherapy upon progression of glasdegib plus LDAC, subsequent treatment may include azacitidine monotherapy, azacitidine plus venetoclax, a targeted agent if appropriate (e.g., FLT3 inhibitor or IDH inhibitor), enrollment in a clinical trial (for receipt of a therapeutic agent to treat relapsed AML), or supportive care. If the patient is eligible for intensive treatment at the time of glasdegib plus LDAC failure then salvage chemotherapy or enrollment into a clinical trial to receive a therapeutic agent to treat relapsed AML could be considered. The CLSG clinicians stated there is no evidence that specific subtypes of AML or subgroups of patients should not receive glasdegib. In contrast to LDAC monotherapy, glasdegib plus LDAC exhibits efficacy in good/intermediate and poor risk cytogenetics cases. Regarding comparative data that would inform selection of azacitidine or glasdegib plus LDAC as the preferred regimen; the CLSG clinicians and CCO clinician were unsure if direct comparisons (head to head) presently exist. However, the CCO clinician highlighted the doubling of the survival rate for the glasdegib cohort in the pivotal trial and stated that glasdegib would probably be preferred over azacitidine alone. Regarding evidence to inform whether glasdegib plus LDAC could be used as an additional line of therapy in patients who have experienced disease progression on intensive chemotherapy; the CCO clinician stated there is no evidence at this time and the CLSG clinicians were also unaware. However, the CLSG clinicians noted this would not be an unreasonable treatment option in patients who have progressed on intensive therapy and for patients whom another non-intensive strategy including azacitidine-based, targeted drug, or clinical trial approaches are not options.

Please see below for details from the clinician inputs.

5.1 Current Treatment(s)

For patients with newly diagnosed AML, current treatment options include the following:

- induction chemotherapy (daunorubicin or idarubicin plus cytarabine) followed by consolidation therapy with the potential for transplant
  - The CCO clinician specified that induction chemotherapy could be administered in the form of Vyxeos liposomal induction chemotherapy (daunorubicin plus cytarabine) or standard induction 3+7 chemotherapy
  - CLSG clinicians specified that patients could receive intensive induction chemotherapy (daunorubicin or idarubicin plus cytarabine) followed by consolidation therapy (e.g., high-dose cytarabine monotherapy or high-dose cytarabine plus anthracycline) with the potential to receive hematopoietic stem cell transplant.
- fludarabine-idarubicin-cytarabine regimen (specified by CLSG clinicians)
- less intensive chemotherapy regimens
  - CCO and CLSG clinicians specified azacitidine and LDAC
  - CCO clinician additionally specified azacitidine plus venetoclax
  - CLSG clinicians additionally specified decitabine
- best supportive care.

For newly diagnosed AML patients with targetable mutations, current treatment options include the following:

- targeted agents (CLSG clinicians)
- standard induction 3+7 chemotherapy plus midostaurin specifically for patients with FLT3 mutations.

Further, the CLSG clinicians stated that the most appropriate comparators for the current review would be LDAC or azacitidine.

5.2 Eligible Patient Population

The CCO clinician stated that this treatment should be for patients defined by the study eligibility criteria (patients not eligible for standard induction treatment); further, there should be no age restriction.

In general, the CLSG clinicians noted that patients receiving the treatment under review would have untreated AML and would not be candidates for intensive chemotherapy; notably, most of these patients would be elderly. Further, they specified that they would particularly administer glasdegib plus LDAC in patients with one or more of the following:

- difficulty in attending hospital visits for geographic or distance reasons
- standard risk cytogenetics
- prior treatment failure with a HMA such as azacitidine or decitabine
- intolerance to a HMA.

Namely, they highlighted that LDAC can be administered at home whereas administration of HMAs require travel to the cancer centre. This is favourable in Canada where elderly patients often live far from a cancer centre, and travel is difficult due to distance and the requirement for an accompanying caregiver. Overall, they stated that it is essential to have a LDAC-based treatment option in Canada for such patients.

5.2.1 Are the criteria used in the trial to identify patients not suitable for intensive chemotherapy reflective of the criteria used for your patients?

The CCO clinician stated that the trial criteria (to identify patients not suitable for intensive chemotherapy) seem reasonable and the CLSG clinicians indicated that the trial criteria are reflective of the criteria used for their patients.

5.3 Relevance to Clinical Practice

The CCO clinician reported that they had no experience administering the treatment under review. They noted that they would follow the same inclusion criteria as the pivotal trial (i.e. administer glasdegib plus LDAC to patients not suitable for induction chemotherapy). Further, they are unsure how glasdegib plus LDAC compares to venetoclax plus azacitidine; namely, venetoclax is not approved in Canada for this indication.

The CLSG clinicians indicated that they had experience administering the treatment under review. As stated above, they would administer the treatment under review to patients with untreated AML and who are not candidates for intensive chemotherapy. Further, they specified that they would particularly administer glasdegib plus LDAC in patients with one or more of the following factors: 1) difficulty in attending hospital visits for geographic or distance reasons, 2) standard risk cytogenetics, 3) prior treatment failure with a HMA such as azacitidine or decitabine, and 4) intolerance to a HMA. Compared to LDAC monotherapy, the CLSG clinicians highlighted that response rates (CR) and median OS were greater with the glasdegib plus LDAC combination as demonstrated in the pivotal trial. Namely, they reported that the response rates (CR rates; 17% vs. 2.3%; $p<0.05$) were considerably higher and median OS was considerably longer (8.8 months vs. 4.9 months; HR=0.51; $p= 0.0004$) with glasdegib plus LDAC compared to LDAC monotherapy. Moreover, glasdegib plus LDAC is safe and well tolerated. Additionally, they noted that contraindications to glasdegib plus LDAC are essentially the same as LDAC alone with the addition of known intolerance to glasdegib or another Hedgehog inhibitor.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The CLSG clinicians stated that sequencing is less of an issue because the glasdegib plus LDAC combination would be administered in patients with untreated AML. They highlighted LDAC-based treatments may be effective for patients who have been treated with a HMA for an AHD such as a MDS that proceeded to AML despite HMA treatment. For such patients, treatment of their AML with a HMA-based regimen is considered medically futile. Moreover, they specified that glasdegib plus LDAC would be a superior alternative to LDAC alone if the treatment under review becomes available for funding.

5.4.1 What would be the preferred sequencing of therapies for patients with an identified mutation?

The CCO clinician stated that the only targeted regimen presently available in the first-line setting for patients with AML is 3+7 chemotherapy plus midostaurin; however, patients with an identified mutation would likely not receive this treatment. The CLSG clinicians stated that the glasdegib plus LDAC combination is largely "mutation" agnostic. Further commenting that there may be an inferior response in patients bearing an IDH2 mutation; however, the patient numbers are small to inform this. Additionally, they highlighted that targeted agents are not yet approved in Canada for up-front treatment in patients who are not eligible for intensive therapies. Accordingly, the CLSG clinicians stated the preferred sequencing is moot; however, patients may prefer to be enrolled into a clinical trial to receive an up-front targeted agent. Namely, there is some clinical trial evidence that the combination of LDAC plus venetoclax is particularly effective in AML patients bearing the NPM1 mutation; however, venetoclax is not approved in Canada for this indication.

5.4.2 Is there any evidence that specific subtypes of AML (e.g., based on cytogenetics, therapy-related AML) or subgroups of patients should not receive glasdegib?

The CCO clinician stated that the only patients who should not receive glasdegib are those that align with the exclusions of the pivotal trial. The CLSG clinicians stated there is no evidence that specific subtypes of AML or subgroups of patients should not receive glasdegib. In contrast to LDAC monotherapy, glasdegib plus LDAC exhibits efficacy in good/intermediate and poor risk cytogenetics cases.

5.4.3 What treatments would be given to patients upon progression of glasdegib+LDAC?

The CCO clinician stated that palliative care and hydroxyurea would be available for most patients upon progression of glasdegib plus LDAC. If patients had an identified mutation such as IDH2 they may be able to receive a targeted-agent through compassionate access. Additionally, they highlighted that gilteritinib may be an option for patients with a FLT3 mutation and noted that FLT3 mutation status can change. The CLSG clinicians stated that assuming patients are still considered ineligible for intensive chemotherapy, subsequent treatment may include azacitidine monotherapy, azacitidine plus venetoclax, a targeted agent if appropriate (e.g., FLT3 inhibitor or IDH inhibitor), enrollment in a clinical trial (for receipt of a therapeutic agent to treat relapsed AML), or supportive care. If the patient is eligible for intensive treatment at the time of glasdegib plus LDAC failure then salvage chemotherapy or enrollment into a clinical trial to receive a therapeutic agent to treat relapsed AML could be considered.

5.4.4 Is there any comparative data that would inform selection of either azacitidine or glasdegib+LDAC as the preferred regimen?

The CCO clinician was unsure if there are any head to head comparisons at the present moment. However, they highlighted the doubling of the survival rate for the glasdegib cohort in the pivotal trial and stated that glasdegib would probably be preferred over azacitidine alone. The CLSG clinicians were unaware of a direct comparison of azacitidine with the LDAC/glasdegib combination; they noted that comparisons among studies may not be statistically sound and may be highly speculative.

5.4.5 Is there any evidence to inform whether glasdegib plus low-dose cytarabine could be used as an additional line of therapy in patients who have experienced disease progression on intensive?

The CCO clinician stated that there is no evidence at this time and the CLSG clinicians were unaware of any evidence to inform whether glasdegib plus LDAC could be used as an additional line of therapy in patients who have experienced disease progression on intensive chemotherapy. However, they noted this would not be an unreasonable treatment option in patients who have progressed on intensive therapy and for patients whom another non-intensive strategy including azacitidine-based, targeted drug, or clinical trial approaches are not options.

5.5 Companion Diagnostic Testing

The CCO clinician stated that no companion diagnostic test is required. The CLSG clinicians noted that there is no specific additional companion diagnostic testing needed for this combination. They specified that these patients would require the routine up-front testing (e.g., cytogenetics and molecular studies) that all newly diagnosed AML patients should undergo.

5.6 Implementation Questions

5.6.1 Would it be appropriate to implement a modified low-dose cytarabine regimen to account for clinic opening hours?

The CCO clinician stated that patients usually inject pre-filled syringes at home; thus, this implementation question is not relevant for Ontario. The CLSG clinicians believe that administering a modified LDAC regimen would be appropriate to account for clinic opening hours. They specified that a LDAC-based regimen offers the advantage that LDAC can be delivered at home by homecare, a caregiver, or by the patient; alternatively, azacitidine injections are not administered at home and the patient must attend a chemotherapy clinic for seven consecutive days. Thus, LDAC-based regimens can be much more favourable for the patient and caregiver while also sparing valuable hospital resources and increasing clinic capacity. Namely, the advantage of reducing the time needed to be in the hospital for the patient and caregiver is particularly favourable during the COVID-19 pandemic.

5.7 Additional Information

None to report.

6 Systematic Review

6.1 Objectives

The primary objective of this systematic review is to evaluate the safety and efficacy of glasdegib in combination with LDAC, 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.

Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 5 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 5: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, non-randomized studies with a control group and single group studies will be considered	Newly diagnosed and previously untreated acute myeloid leukemia (AML) adult patients, who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy Subgroups of interest: Cytogenetic subtype (high/low risk); Age (<75 years or >75 years); Blast % (high/low); FLT3 mutation (yes/no)	Glasdegib in combination with low-dose cytarabine	Cytarabine alone; azacitidine; decitabine; no treatment	• **Overall Survival** • **Progression Free Survival** • **Response rates** • **Complete remission** • **HRQoL** • **SAE, WDAE, AE**

AE= adverse events; AML= acute myeloid leukemia; HRQoL= health related quality of life; RCT = randomized controlled trial; SAE= serious adverse event; WDAE= withdrawals due to adverse events;

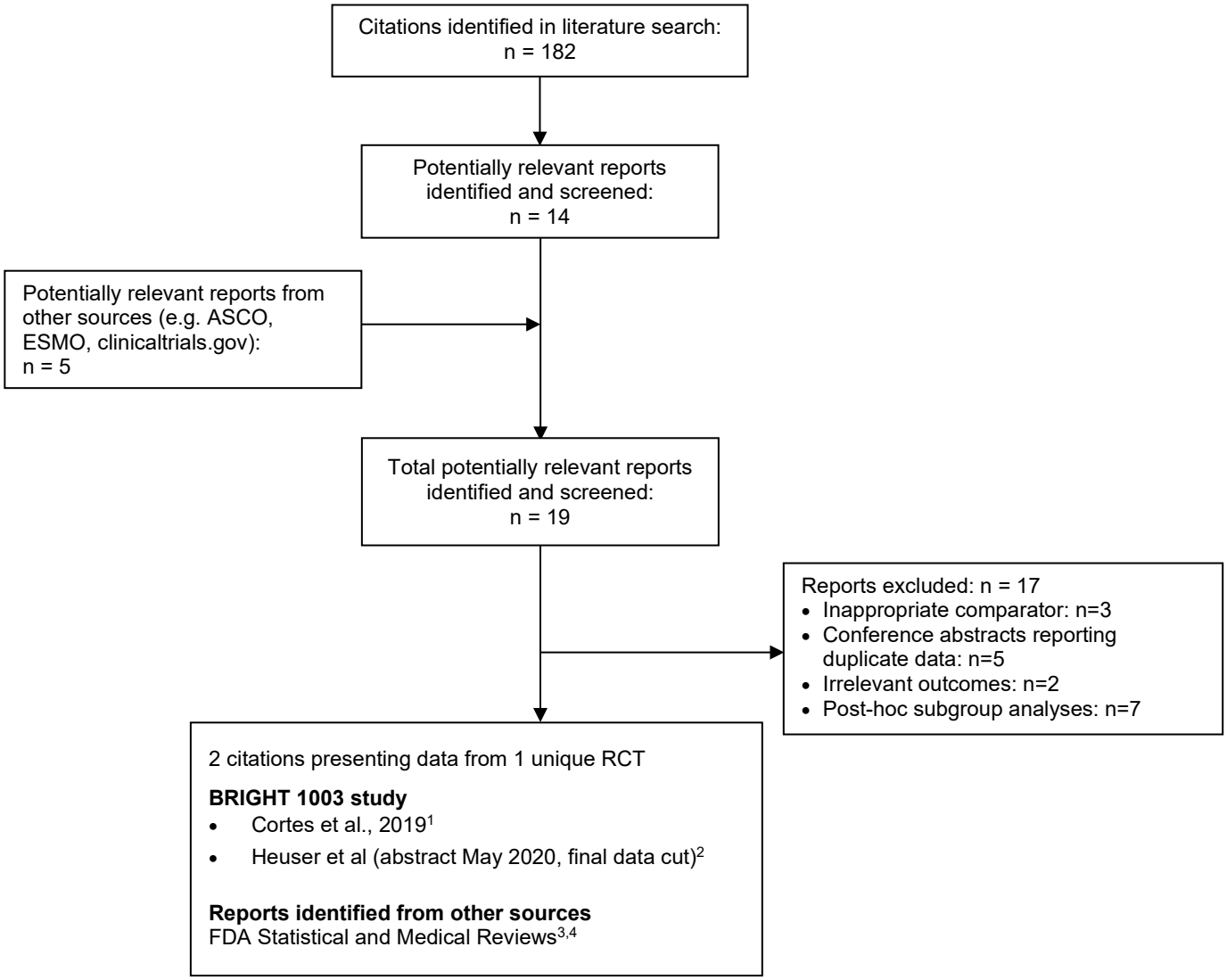
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.3 Results

6.3.1 Literature Search Results

Of the 16 potentially relevant reports identified, one trial, reported in 2 citations was included in the CADTH systematic review.[1,2] Fourteen reports were excluded because they had an inappropriate comparator,[40-42] or were conference abstracts reporting duplicate data,[43-48] irrelevant outcomes,[49,50] or post-hoc subgroup analyses[51-54] from the included study.

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to the BRIGHT 1003 study were also obtained through requests to the Sponsor by CADTH[5,6,55]

6.3.2 Summary of Included Studies

One cohort of one study met the selection criteria of this review. The BRIGHT 1003 study was a multicenter, multi-phase, open-label study with one phase 1b cohort and two phase 2 cohorts. In the phase 2 cohort that met the selection criteria for this review, patients with AML or high risk MDS were randomized (2:1) to receive treatment with glasdegib plus LDAC or LDAC alone. Relevant information on trial characteristics is summarized in Table 6.

6.3.2.1 Detailed Trial Characteristics

Table 6: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: BRIGHT 1003 (unfit/non-intensive cohort)[1] NCT01546038[56] Characteristics: Phase 2 multicentre, open-label, randomized (2:1 ratio) trial, superiority design N= 132 randomized (88 glasdegib + LDAC; 44 LDAC). n=116 with AML and n=16 with MDS **Randomization stratified by:** Cytogenetic risk (good/intermediate risk, poor risk) **Setting:** 48 sites in 6 countries (Canada, USA, Germany, Poland, Spain, Italy) Overall study dates: July 2012 to May 2019 Unfit cohort enrollment: [redacted][6] **Data cut-off dates:** April 2016 (pre-specified when a total of 92 OS events are observed) January 2017 (pre-specified*; primary completion date) October 2018 (updated exploratory analysis) April 2019 (final exploratory analysis) Study completion date: May 2019. **Funding**: Pfizer	Key inclusion criteria for patients enrolled in Phase 2 unfit/non-intensive group: Adult (≥ 55 years) patients with AML or RAEB-2 high-risk MDS who were newly diagnosed as per WHO 2008 Classification and previously untreated AML patients included de novo AML, AML evolving from MDS or other AHD and secondary AML (after previous cytotoxic therapy or radiation) For a diagnosis of high-risk MDS RAEB-2 the patient had to have 10-19% bone marrow blasts ECOG performance status 0-2 Patients considered unfit for intensive chemotherapy were age ≥ 75 years, ECOG score of 2, Serum creatinine > 1.3 mg/dL or severe cardiac disease (e.g., LVEF < 45% by MUGA or echo) Key exclusion criteria: APL patients with t(15;17) or patients with a t(9;22) cytogenetic translocation, hyperleukocytosis, patients refractory to platelet or packed red cell transfusions, active malignancy with exception of basal cell carcinoma or non-melanoma skin cancer. Patients were not permitted to have had any prior therapy for AML. However, patients were allowed to have one prior regimen with a commercially available agent (e.g., azacitidine or decitabine) for their antecedent hematologic disease.5	Phase 2 unfit/non-intensive population: Oral glasdegib 100 mg once daily continuous starting Day 1 of a 28-day cycle plus SC cytarabine 20 mg twice daily on Days 1 to 10 of a 28-day cycle SC cytarabine 20 mg twice daily on Days 1 to 10 of a 28-day cycle (LDAC) Treatment continued for up to 1 year (12 cycles) from start of therapy or until disease progression or relapse, patient refusal, or unacceptable toxicity (whichever occurred first). Investigators could elect to continue treatment beyond 12 months if patients demonstrated clinical benefit with manageable toxicity.[5]	Primary:OS Secondary:CR In AML patients: CRi, MLFS, PR, PRi, MR, SD, CRc, CRm Harms: Adverse events, serious adverse events, withdrawal due to adverse events, QTc interval

AHD = antecedent hematologic disease; AML = acute myeloid leukemia; CR = complete response or complete remission; CRc = cytogenetic complete response; CRi = CR with incomplete blood count recovery; CRm = molecular complete response; ECOG = Eastern Cooperative Oncology Group; LDAC = low-dose cytarabine; LVEF = left ventricular ejection fraction; MDS = myelodysplastic syndrome; MLFS = morphologic leukemia-free state; OL = open-label; OS = overall survival; PR = partial remission; PRi = partial remission with incomplete blood count recovery; RAEB = refractory anemia with excess blasts; SC = subcutaneous; WHO = World Health Organization

*Upon request the Sponsor indicated that the January 2017 data cut was pre-specified as per statistical analyses plan, however, further details were not provided in this submission.[55]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Source: Pfizer Clinical Summary,[5] Clinical Study Report BRIGHT 1003,[6] FDA Statistical and Medical Reviews[3,4] Cortes et al.[1]

a) Trial

The BRIGHT 1003 trial was designed in two phases—the first phase 1b portion evaluated the safety and dosing of glasdegib as a component of three first-line combination chemotherapy regimens (LDAC, decitabine, or cytarabine/daunorubicin, N=52, Figure 2). Phase 1b evaluated 2 doses of glasdegib (100 mg and 200 mg) and established the maximal tolerated dose and the recommended dose for phase 2. Following determination of the dose, the glasdegib plus decitabine combination was not further evaluated. A main reason for not completing the glasdegib plus decitabine expansion cohort was that single-agent decitabine is currently not approved in the US for patients with AML unfit to receive intensive chemotherapy.[57] [redacted].[6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

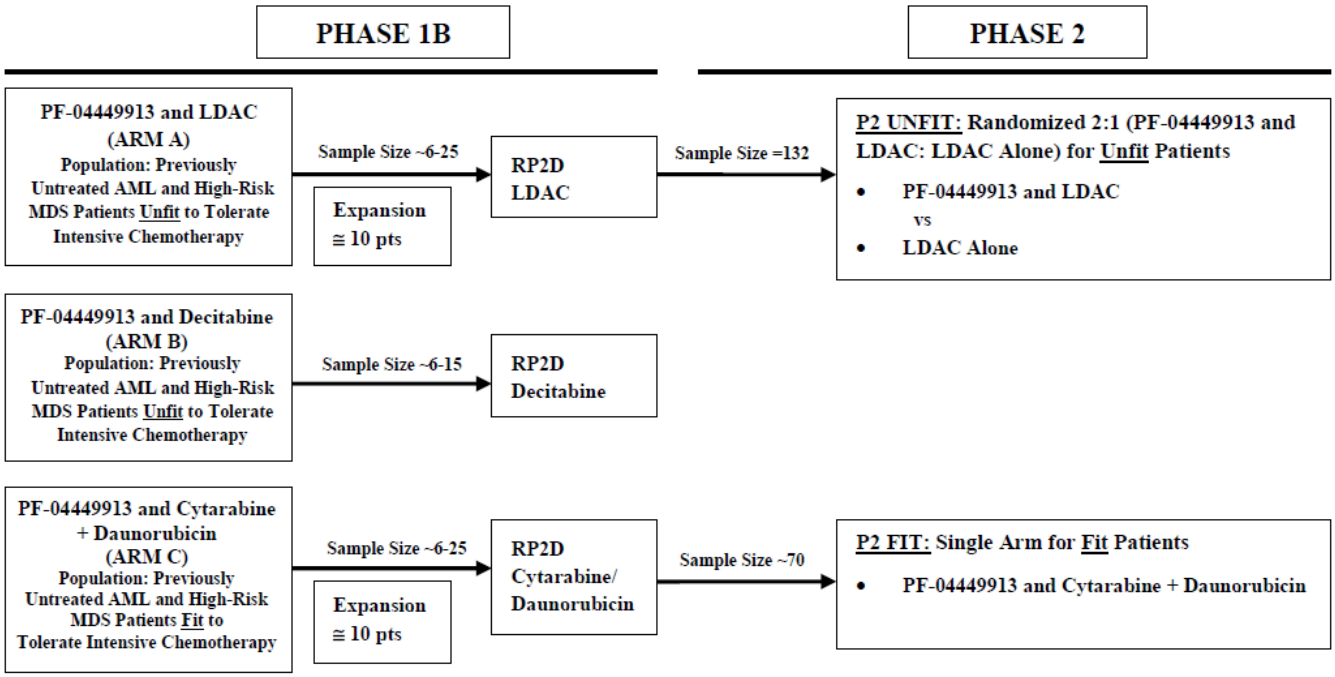
The phase 2 portion followed phase 1b and had 2 objectives: 1) to assess the efficacy and safety of the combination of glasdegib and cytarabine/daunorubicin in the fit/intensive patient population (N=71) and 2) to evaluate glasdegib in combination with LDAC in the unfit/non-intensive patient population (N=132). This latter population is the focus of this review.

For the unfit/non-intensive population, 132 previously untreated patients with AML or high-risk MDS were randomized using an interactive voice response system (IVRS) 2:1 to glasdegib plus LDAC (n=88) or LDAC alone (n=44). Randomization was stratified by cytogenetic risk factor (good/intermediate or poor). Patients were to be followed up for 4 years after the first dose.

[redacted].[6]*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

The trial was conducted in Europe and North America at 48 sites including 2 sites in Canada. The majority of patients were enrolled in European sites (70%) followed by USA (25% and Canada (9%).

Figure 2: BRIGHT 1003 – Study Design



AML=acute myeloid leukemia; LDAC=low dose Ara-C; MDS=myelodysplastic syndrome; PF-04449913= glasdegib; P2 FIT=Phase 2 single group component in fit patients; P2 UNFIT=Phase 2 randomized component in unfit patients; pts=patients; RP2D=recommended Phase 2 dose;

Source: FDA Statistical Review[3]

Statistical Analysis Plan Summary

Primary Analyses: "*The primary endpoint of OS will be analysed and displayed graphically for each arm separately using the Kaplan-Meier method on the Full Analysis Set. A stratified log-rank test (one-sided α=10%) will be used to compare OS between the two treatment arms. The hazard ratio and its 80% CI will be estimated. The estimate of survival probabilities at 6 and 12 months and their 80% CI (using log-log transformation and back-transformation) will be provided for each arm separately. The median event time for each treatment arm and corresponding two-sided 80% CI will be provided for OS. In addition, the median OS and its two-sided 80% CI will be provided for the poor and good/intermediate prognosis stratum according to IVRS within each treatment arm separately.*"[5]

Secondary Analyses: "*An unstratified log-rank test (one-sided, α=10%) and Cox regression model will be used as secondary analyses of the primary endpoint of OS. A Cox regression model will be used to explore the potential influence of the stratification factor according to IVRS and to CRF as secondary analysis (prognosis: poor vs good/intermediate) on the primary endpoint of OS. Sensitivity analyses of the primary endpoint of OS may be provided by censoring patients upon receiving transplant.*"[5]

"The point estimate and 80% CI (using normal approximation) of the proportion of patients with CR based on derived response will be summarized by treatment arm using the Full Analysis Set. The point estimate and 80% exact CI of the proportion of patients with CR will also be provided for the poor and good/intermediate prognosis stratum within each treatment arm separately. A Pearson χ2 test (unstratified) and Cochran-Mantel-Haenszel (CMH) test stratified by prognosis (poor vs good/intermediate) according to IVRS and to CRF as secondary analysis will be used to compare CR rate between the two treatment arms. Sensitivity analyses of the above based on investigator- reported response will also be provided."[5]

"Specifically, for AML patients, the following binary efficacy endpoints (with 80% exact CI) will be summarized in frequency tables, CRi, CR/CRi, proportion of patients achieving Morphologic Leukemia-Free State (MLFS), Partial Remission (PR), Partial Remission with incomplete blood count recovery (PRi), Minor Response (MR), Stable Disease (SD), Cytogenetic Complete Response, and Molecular Complete Response. Cytogenetic Complete Response (CRc) and Molecular Complete Response (CRm) will be investigator -reported only."[5]

"For MDS patients, the following binary efficacy endpoints will be summarized in frequency tables, proportion of patients achieving CR, CRi (derived only), marrow CR, Partial Remission (PR), Stable Disease (SD), and Partial or Complete Cytogenetic Response. Partial or Complete Cytogenetic Response will be investigator-reported only."[5]

Exploratory Analyses: "*For Clinical Benefit the point estimate and 80% CI using normal approximation of the proportion of patients achieving Clinical Benefit based on investigator response will be summarized. Additional exploratory analyses of the efficacy endpoints above based on patient baseline characteristics, including but not limited to the ones listed below, may be performed for each treatment arm separately to inform future clinical investigation."*[5]

"Where possible, the AML-specific efficacy endpoints may be analyzed in an exploratory fashion on favorable/intermediate /unfavorable cytogenetics;

Where possible, the MDS-specific efficacy endpoints may be analyzed in an exploratory fashion on the following subsets:

- *Good/intermediate/poor cytogenetics; IPSS (intermediate-1 or score 0.5-1, intermediate-2 or score 1.5-2, high or score ≥2.5, and indeterminate or unknown);*
- *Whether patients have received prior hypo-methylating agents"*[5]

Interim Analysis: One futility interim analysis is planned when 46 OS events have been observed. The rho(1) spending function is used as the beta-spending function. If exactly 46 OS events are observed at the interim analysis, the futility boundary will be crossed if the observed HR>0.92. The stopping probability is 61% if HR=1 and 10% if HR=0.625, respectively. The futility boundary will be calculated accordingly using the chosen spending function and number of observed OS events.[5]

Final Analysis: The final analysis will occur when a total of 92 OS events are observed. At the final analysis, an observed HR of 0.76 or below (i.e., observed nominal alpha ≤ 0.1) will reject the null hypothesis of HR=1.[5]

Sample Size: For the sample size estimation, investigators estimated that the historical median OS for LDAC was 5 months and the expected median OS for glasdegib + LDAC was 8 months, resulting in an expected HR of 0.625. Based on 2:1 randomization, a

planned accrual period of about 13 months, a follow-up period of approximately 6 months, a 1-sided log-rank test with alpha=0.1 (type I error) and one futility analysis when 46 OS events were observed (50% information, rho(1) beta spending function), a total of 92 OS events would provide 80% power to detect this difference between the two groups. The required sample size was 132 patients (88 in the LDAC + glasdegib group and 44 in the LDAC group). Patients were randomized 2:1 by a centrally administered system and were stratified at time of randomization based on prognosis (poor versus good/intermediate prognosis base on cytogenetic risk).[1,5]

Assessment of response was made using response criteria for MDS and AML derived and defined by the disease specific International Working Groups and WHO Guidelines. Disease response assessments were reported by investigators as well as derived by the sponsor.[6] The primary analyses for efficacy endpoints would be based on derived response, and the secondary analyses based on investigator-assessed data. The interim analyses were based on investigator's assessments. No data were imputed for missing data.[5]

No multiplicity adjustments were made for the multiple secondary endpoints, subgroup analyses (e.g. overall survival and response), post-hoc analyses (e.g. progression free survival), or multiple analysis timepoints.[6]

In their feedback on the pERC Initial Recommendation, the sponsor stated that a gatekeeping testing procedure was applied to adjust for multiple statistical testing. The CADTH Methods Team reiterated that the Clinical Study Report (section 11.4.2.5) for the BRIGHT 1003 study stated that "No multiplicity adjustment was made" for multiple comparisons or multiplicity.

In their feedback on the pERC Initial Recommendation, the sponsor stated that the BRIGHT 1003 study had the "robustness of an interim analysis of a Phase 3 study" and described retrospective power analyses of hypothetical scenarios. In response to the sponsor's feedback, the CADTH Methods Team did not agree with the retrospective application of power analyses to predict what may have happened when in fact the study has already been completed. Power calculations are helpful for estimating probabilities and are forward-looking (Jiroutek and Turner, 2018)[58]. Retrospective power analyses could at best be used to inform power calculations for a subsequent study. The CADTH Methods Team acknowledged this feedback but noted this did not impact their review as well as interpretation of the results from the BRIGHT 1003 study.

Table 7 summarizes the key data cut-off dates in the BRIGHT 1003 study. The pre-specified data cut-off date (April 2016) was performed after 92 deaths had occurred. Updated analyses at the primary completion date (January 2017) were reported after 109 deaths had occurred. The main publication by Cortes et al[1] and Clinical Study Report[6] is based on this time point. The Health Canada and the FDA reviews of glasdegib were also based on the January 2017 data cut-off date. The final exploratory analysis (data cut-off date of April 2019) occurred 2 years later and 121 patients had died by this time point. There is no report available that summarizes the data from the final data cut-off. The final analyses were derived from a number of sources including the manufacturer's Clinical Summary, post-hoc unpublished analyses provided to CADTH by the Sponsor and one conference abstract.[2,5,59]

Table 7: Data cut-off dates for the BRIGHT 1003 study

Data Cut-off Date	Total number of primary outcome events (deaths)	Median Follow up time for survival, months	Analysis Label	Data Sources
April 2016	96 actual (92 planned)	Not reported	Pre-specified data cut	Health Canada Reviewer Report[60]
January 2017	109 (AML + MDS) 94 (AML)	Glasdegib + LDAC: 21.7 LDAC: 20.1	Primary Completion date	Clinical Study Report (Pfizer)[6] Cortes et al[1] FDA Clinical and Statistical Review[3,4]
October 2018	104 (AML)	Glasdegib + LDAC: 43.4 LDAC: 42.0	Updated Analysis. Exploratory. European regulatory requirement.	Papayannidis et al (abstract June 2019)[43]
April 2019	121 (AML + MDS) 106 (AML)	Glasdegib + LDAC: 47.6 LDAC: 48.1	Final Analysis Exploratory	Clinical Summary (Pfizer)[5] Post hoc analyses (Pfizer)[5]

				Heuser et al (abstract May 2020)[2]

AML = acute myeloid leukemia; LDAC = low dose Ara-c; MDS = myelodysplastic syndrome;

Note: This report focuses on data emerging from the primary completion date of January 2017 and the final updated April 2019 analyses. For the earliest April 2016 data cut-off date only limited information was available from submission materials,[5] which suggested similar results to the January 2017 and April 2019 data cuts; no results were presented in this report for the April 2016 data cut. The October 2018 data are from a single abstract whose results were similar to the results reported for the January 2017 and April 2019 data cut-off dates; results for the October 2018 data cut have not been presented in this report. Upon request the Sponsor indicated that the January 2017 data cut was pre-specified as per statistical analyses plan,[55] however, further details were not provided in this submission.

Protocol amendments

The original protocol was dated October 2011 and there were five amendments to the protocol. Key amendments are listed below and there were no major changes to response criteria or inclusion/exclusion.[4,5]

- Amendment 1 (effective May 15, 2012) added a requirement for bone marrow slides to be available for central review.
- Amendment 2 (effective November 1, 2012) Added requirement for safety and efficacy review of study results by an internal review committee. Added a restriction of enrollment to patients ≥ 55 years in the phase 2 randomized cohort.
- Amendment 3 (effective March 26, 2014) Independent bone marrow pathology review was removed.
- Amendment 4 (effective April 20, 2015). Removed requirement for bone marrow biopsies, if this evaluation is not performed as standard of care (the requirement for bone marrow aspirates remains unchanged).
- Amendment 5 (effective February 8, 2016) removed phase 2 secondary endpoints cumulative incidence of relapse, relapse free survival, event free survival, cumulative incidence of death, and hematologic improvement (MDS patients only). Added requirement for survival follow-up for randomized patients that did not start treatment. Added monitoring of potential cardiovascular symptoms and guidance on the use of moderate/strong CYP3A4/5 inhibitors or drugs with a known risk of Torsades de Pointes as concomitant therapy.

Major Protocol deviations

As of the January 2017 data cut-off date, there were 1,272 protocol deviations reported for 111 AML patients. The majority (1,212 deviations, 95%) were classified by the sponsor as minor deviations. Major protocol deviations occurred in 20 (39%) in the glasdegib + LDAC group and 20 (53%) in the LDAC group. A total of 21 patients (18%) had major deviations in safety reporting; the majority due to delayed SAE reporting. Fourteen (18%) patients taking glasdegib + LDAC and 6 (16%) taking LDAC had a major deviation in randomization. These occurred because they were not stratified correctly at randomization in the interactive voice response system. This was investigated by the FDA statistical reviewer who concluded that this did not have a significant impact on the overall survival results.[3,4] Protocol deviations did not appear to be a likely source of bias in the study.[3,4]

Analysis Populations

The full analysis set included all randomized patients of the phase 2 portion. The full analysis set was used for efficacy analyses. The safety analysis set for each drug combination included all enrolled patients who received at least one dose of any study medication.

Study Endpoints

Primary Endpoint:

- Overall survival, defined as the time from randomization to the date of death from any cause.

Secondary Endpoints:

- The key secondary efficacy outcome for the unfit/non-intensive population was complete remission/response (CR).
- For patients with AML: CR with incomplete blood count recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR), partial remission with incomplete blood count recovery (PRi), minor response (MR), stable disease (SD), cytogenetic complete response (CRc), and molecular complete response (CRm).
- For patients with MDS: Marrow CR, PR, SD, partial or complete cytogenetic response.
- Type, incidence, severity, seriousness of adverse events, including QTc interval.
- Pharmacodynamic biomarkers
- Pharmacokinetic parameters of glasdegib

Health-related quality of life was not measured in the trial.

Response Assessments:

Response as assessed based on response criteria for MDS (Cheson et al. 2006)[61] and AML (Cheson et al. 2003) [62] as defined by the disease specific International Working Groups.[4]

Complete response / remission (CR) was defined as all the following:

- Peripheral blood: Absolute neutrophil count (ANC) ≥ 1,000/µL, platelet count ≥ 100,000/µL, and adequate erythroid recovery so that red blood cell (RBC) transfusions were not necessary (time frame not defined)
- Bone marrow: no Auer rods and < 5% blasts with spicules present
- No extramedullary leukemia

Complete response with incomplete blood count recovery (CRi) was defined as: < 5% blasts in the bone marrow, no extramedullary disease, but either ANC < 1000/µL or platelets < 100,000/µL.

Morphologic leukemia-free state was defined as: < 5% blasts in the bone marrow with spicules and no Auer rods, flow cytometry negative, no extramedullary disease, but ANC < 1000/µL and platelets < 100,000/µL.

Partial remission (PR) was defined as: ANC ≥ 1,000/µL, platelet count ≥ 100,000/µL, but the bone marrow may contain 5-25% blasts, if decreased by ≥ 50% from baseline. Blasts could be ≤ 5% if Auer rods present. [3,4]

For further detailed on response assessment for patients with AML see Table 8 and Table 9.

Bone Marrows:

[redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 8: AML – Hematologic Responses to Treatment

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Table 9: AML – Cytogenetic Response to Treatment

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

b) Populations

Eligibility

Eligible patients included newly diagnosed and previously untreated patients with AML or high-risk MDS, including those who may have had one prior regimen with a commercially available agent (e.g., azacitidine or decitabine) for their antecedent hematologic disease. Patients were not permitted to have had any prior therapy for AML. Key inclusion and exclusion criteria are listed below:[5]

Key Inclusion Criteria:

1. Patients with AML or RAEB-2 high-risk MDS:
   - Newly diagnosed according to the WHO 2008 classification and previously untreated.
   - Eligible patients with MDS, as well as eligible patients with AML arising from an AHD or MDS, may have had 1 prior regimen with commercially available agent(s) (e.g., azacitidine or decitabine) for the treatment of their prior hematologic disease.

- The patients may not have had any prior therapy for their AML.
- AML patients included those with *de novo* AML, AML evolving from MDS or other AHD, and AML after previous cytotoxic therapy or radiation (secondary AML).

2. AML Diagnosis
   - Bone marrow blast count of 20% or more
   - For AML defined by cytogenetic aberrations t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia, the proportion of bone marrow blasts could be <20%.
   - According to AML-FAB classification M6a (erythroid leukemia), ≥20% of non-erythroid cells in the bone marrow had to be leukemic blasts, and ≥50% of the cells had to be erythroid precursors.
   - For AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes, but not abnormal monocytes, were counted as blast equivalents.
3. High-risk MDS RAEB 2 diagnosis with 10-19% bone marrow blasts.
4. ≥55 years old for patients enrolled in Phase 2 unfit/non-intensive group.
5. ECOG PS 0, 1, or 2.
6. Adequate organ function
7. Concomitant treatments
   - Unless specified, all anti-cancer treatments were discontinued >2 weeks prior to study entry.
   - For control of rapidly progressing leukemia, hydroxyurea or leukopheresis could be used, before and for up to 1 week after, the first dose of glasdegib.
   - Patients with controlled CNS leukemia (documented by two consecutive assessments of zero blast count in CSF), and who were still receiving intra-thecal therapy at study entry, were considered eligible and continued to receive intra-thecal therapy.

Key Exclusion Criteria:

1. Diagnosis
   - Patients with APL with t(15;17) or patients with a t(9:22) cytogenetic translocation for any component of the study.
   - Hyperleukocytosis: Patients with leukocytes ≥ 30 × 109 /L at study entry. These patients may either have been treated with hydroxyurea or received leukopheresis treatment, according to routine practice and enrolled in the study when the leukocyte count < 30 × 109 /L.
   - Patients with active malignancy, except basal cell carcinoma, NMSC, and cervical carcinoma in-situ. Other prior or concurrent malignancies were considered on a case-by-case basis
2. Patients known to be refractory to platelet or packed red cell transfusions
3. In the previous six months: Myocardial infarction, Congenital long QT syndrome, TdP, clinically significant ventricular arrhythmias, QTcF interval > 470 milliseconds.
4. Patients with known, active uncontrolled CNS leukemia.
5. Patients with known HIV or AIDS-related illness, or active hepatitis B or C infection or with an active, life threatening or clinically significant uncontrolled systemic infection.
6. Patients with known, malabsorption syndrome
7. Patients undergoing major surgery or radiation within 4 weeks of study start.
8. Prior treatment with: a hedgehog inhibitor at any time, an investigational agent for the treatment of an antecedent hematological disorder, patients with a primary diagnosis of antecedent hematological disorder, or cytarabine
9. Use of concurrent treatment with any investigational or approved oncology agent, herbal preparation, or strong CYP3A4/5 inducers.

Definition of 'unfit for intensive chemotherapy'

Patients with at least one of the following criteria were considered unfit for intensive chemotherapy and were eligible for participation in the phase 2 unfit/non-intensive population:

- Age ≥ 75 years
- ECOG of 2
- Serum creatinine > 1.3 mg/dL
- Severe cardiac disease (e.g., left ventricular ejection fraction [LVEF] < 45% by multi-gated acquisition or echocardiography at screening

Baseline Characteristics

The demographic and other baseline characteristics are summarized in Table 10, Table 11, Table 12, and Table 13. The baseline characteristics of the overall population (AML + MDS) were similar to the AML population.

Demographic Characteristics: The total study population included 116 patients with AML and 16 patients with high risk MDS. Demographic and baseline characteristics were similar between treatment groups in terms of age and baseline cytogenetic risk. Most patients were white, and ethnicity was not reported. Median age was 76 years (range: 58-92 years). There were more men than women in both treatment groups and a higher proportion of male patients were randomized to the glasdegib + LDAC group compared to the LDAC group. All patients had ECOG score of 0-2 (except for 1 untreated patient in the glasdegib + LDAC group without data). In the glasdegib + LDAC group, 20/88 patients had body mass index > 30kg/m^2 compared to 15/44 (34%) in the LDAC group.[55] Of the patients with AML (N=115), 30% were enrolled in North American sites and 70% were enrolled in European sites. Examination of the regional distribution showed an imbalance in the proportion of patients randomized to glasdegib + LDAC (North America 35%; Europe 65%) versus LDAC alone (North America 18%; Europe 82%).[4] There were 9 (9%) patients in Canada enrolled in the study.[4]

Criteria that were used to qualify for the 'unfit/non-intensive' inclusion category are summarized in Table 11. The majority of patients met 1 or 2 of the criteria. The proportion of patients who met ≥2 criteria was higher in the glasdegib + LDAC group (70%) compared to the LDAC group (50%).

Disease Characteristics: Approximately half of the population had secondary AML. [redacted].[6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Baseline hematologic and bone marrow parameters were similar in the two treatment groups at baseline. ELN 2010 risk classification showed that overall, 64% of patients had good or intermediate cytogenetic risk. There were more patients with good or intermediate cytogenetic risk in the glasdegib + LDAC group and more patients with adverse risk on the LDAC group. Ten percent of patients in a subgroup of patients who had baseline mutational analysis (N=88) were FLT3 mutated. Numbers of patients with FLT3 and NPM1 mutations were similar across the treatment groups. No patient had a TP53 mutation. FAB classifications were approximately similar across treatment groups but half of all patients were missing FAB classification. In patients with AML at baseline, 30 (26%) patients had bone marrow blasts 20%-30% and 76 (65%) patients had bone marrow blasts >30%.[37]

Table 10: Summary of Baseline Characteristics in BRIGHT 1003 Phase 2 unfit/nonintensive cohort

	Glasdegib 100 mg+LDAC	LDAC Alone
Number of patients	**88**	**44**
Gender		
Female	19	18
Male	69	26
Age (years), n (%):		
<18	0	0
18-44	0	0
45-64	2 (2.3)	1 (2.3)
≥65	86 (97.7)	43 (97.7)
Mean (std)	76.2 (6.2)	74.5 (4.9)
Median	77.0	75.0
Range	63-92	58-83
Race:		
White	85 (96.6)	44 (100.0)
Black	1 (1.1)	0
Asian	2 (2.3)	0
Weight (kg):		
Mean (std)	79.1 (13.6)	77.7 (14.2)
Range	50.1-119.6	52.2-118.0
Body Mass Index[a] (kg/m^2):		
Mean (std)	27.4 (4.2)	28.2 (5.5)
Range	17.5-41.9	20.0-48.2
ECOG performance status		
0	11 (12.5)	3 (6.8)
1	29 (33.0)	18 (40.9)
2	47 (53.4)	23 (52.3)
3	0	0
4	0	0
Not reported[b]	1 (1.1)	0
Cytogenetic risk[c], n (%)		
Good/intermediate cytogenetic risk	52 (59.1)	25 (56.8)
Poor cytogenetic risk	36 (40.9)	19 (43.2)
Prognostic risk factors for AML, n (%)	N=78	N=38
Favorable	5 (6.4)	3 (7.9)
Intermediate-I	27 (34.6)	11 (28.9)
Intermediate-II	21 (26.9)	8 (21.1)
Adverse	25 (32.1)	16 (42.1)
Prognostic factors for MDS, n (%)	N=10	N=6
Good risk	3 (30.0)	2 (33.3)
Intermediate risk	1 (10.0)	3 (50.0)
Poor risk	6 (60.0)	1 (16.7)
MDS IPSS score, n (%)	N=10	N=6
0.5-1 (Intermediate-1)	0	2 (33.3)
1.5-2 (Intermediate-2)	4 (40.0)	4 (66.7)
≥2.5 (High)	6 (60.0)	0

AML=acute myeloid leukemia; CRF=case report form; ECOG=Eastern Cooperative Oncology Group; IPSS=International Prognostic Scoring System; IVRS=Interactive Voice Response System; LDAC=low dose Ara-C; MDS=myelodysplastic syndrome; N=number of patients evaluable for the parameter; n=number of patients in the category; std=standard deviation

a. Body mass index was calculated as weight (kg)/(height [cm] × 0.01)

b. Patient 10022012 was randomized to the glasdegib 100 mg+LDAC arm but did not receive any study treatments

c. Based on IVRS;

Note: For AML, good/intermediate cytogenetic risk=favorable, intermediate-I and intermediate-II risk groups; poor cytogenetic risk=adverse risk group. For MDS, good/intermediate cytogenetic risk=good and intermediate risk groups; poor cytogenetic risk=poor risk group.

Source: Clinical Study Report for BRIGHT 1003[6]

Table 11: Summary of Patients Meeting "unfit" Criteria at Baseline

	Glasdegib 100 mg+LDAC	LDAC
Number of patients	**88**	**44**
Criteria for non-intensive, n (%)		
≥75 years old	53 (60.2)	24 (54.5)
ECOG of 2	47 (53.4)	23 (52.3)
Serum creatinine >1.3 mg/dL	19 (21.6)	5 (11.4)
Severe cardiac disease[a]	58 (65.9)	21 (47.7)
Number of criteria met, n (%)		
1	26 (29.5)	22 (50.0)
2	38 (43.2)	16 (36.4)
3	21 (23.9)	5 (11.4)
4	3 (3.4)	1 (2.3)

[a] Patients may have had multiple applicable terms for severe cardiac disease

ECOG=Eastern Cooperative Oncology Group; LDAC=low dose Ara-C;

Source: Clinical Study Report BRIGHT 1003,[6] FDA Statistical Reviews[3]

Table 12: Baseline hematologic and bone marrow parameters

	Glasdegib 100 mg+LDAC	LDAC Alone
Number of patients	**84**	**41**
Parameters (units)	**Median (range)**	**Median (range)**
White blood cell ($10^3/mm^3$)	2.3 (0.6 - 64.0)	3.6 (1.1 - 45.2)
Hemoglobin (g/dL)	9.1 (6.4 - 14.0)	9.2 (6.0 - 14.6)
Platelets ($10^3/mm^3$)	47.0 (5.0 - 587.0)	38.0 (7.0 - 398.0)
Peripheral blood blasts (%)	6.6 (0.0 - 91.0)	13.5 (0.0 - 83.0)
Bone marrow blasts (%)	40.0 (7.5 - 100.0)	38.5 (10.5 - 95.0)

LDAC=low dose Ara-C;

Note: Safety Analysis Set

Source: Clinical Study Report BRIGHT 1003[6]

Table 13: Baseline AML-related disease characteristics

	Glasdegib+LDAC (n=77)	LDAC (n=38)	Total (n=115)
Clinical onset of AML			
De novo[1]	39 (51%)	18 (47%)	57 (50%)
MDS-related	28 (36%)	15 (39%)	43 (37%)
Myeloproliferative neoplasm-related	5 (6%)	4 (11%)	9 (8%)
Therapy-related	6 (8%)	1 (3%)	7 (6%)
ELN risk			
Favorable	5 (6%)	3 (8%)	8 (7%)
Intermediate-I	27 (35%)	11 (29%)	38 (33%)
Intermediate-II	20 (26%)	8 (21%)	28 (24%)
Adverse	25 (32%)	16 (42%)	41 (36%)
Stratification factors (CRF)			
Good/intermediate cytogenetic risk	52 (68%)	22 (58%)	74 (64%)
Poor cytogenetic risk	25 (32%)	16 (42%)	41 (36%)
FLT3 mutated	7 (9%)	4 (11%)	11 (10%)
NPM1 mutated	7 (9%)	2 (5%)	9 (8%)
Leukemia classification (FAB subtype)			
M0 – Undifferentiated AML	6 (8%)	1 (3%)	7 (6%)
M1 – AML without maturation	9 (13%)	4 (11%)	13 (12%)
M2 – AML with maturation	13 (18%)	5 (14%)	18 (17%)
M4 – Acute myelomonocytic leukemia	6 (8%)	4 (11%)	10 (9%)
M5 – Acute monocytic leukemia	2 (3%)	2 (6%)	4 (4%)
M6 – Acute erythroid leukemia	1 (1%)	1 (3%)	2 (2%)
M7 – Acute megakaryoblastic leukemia	0	0	0
Missing	35 (49%)	19 (53%)	54 (50%)

AML = acute myeloid leukemia; CRF = case record form; ELN = European LeukemiaNet; FAB = French, American British; MDS = myelodysplastic syndrome;

1 Includes a patient that the Applicant coded as secondary AML, given that this patient just had a monoclonal gammopathy of undetermined significance

Source: FDA Clinical Review[4]

c) Interventions

Intervention and Comparator

In the phase 2 unfit/non-intensive population, glasdegib 100 mg once daily was administered orally in continuous 28-day cycles, starting on Day 1 of Cycle 1. In addition, LDAC was administered at a dose of 20 mg subcutaneously twice daily on Days 1 to 10 of the 28-day cycles. Glasdegib was given in the morning at approximately the same time as the first dose of LDAC. Glasdegib tablets were to be swallowed whole and not chewed. Study treatment could continue for up to 1 year (12 cycles) from start of therapy or until disease progression or relapse, patient refusal, or unacceptable toxicity (whichever occurred first). In the comparator group, LDAC was administered at a dose of 20 mg subcutaneously twice daily on Days 1 to 10 of the 28-day cycles. LDAC could be self-administered by the patient at home or administered in the clinic by study staff.[4]

Patients who completed 12 months on study treatment, who demonstrated clinical benefit with manageable toxicity, and who were willing to continue receiving assigned treatment could be given the opportunity to do so upon agreement between investigator, sponsor and pending study drug availability.[63] Fourteen patients in the glasdegib + LDAC group continued treatment beyond 12 months. No patients in the LDAC group continued study treatment for more than one year.[55] The duration of therapy was calculated as (last dosing date – Cycle 1 Day 1+1 day), where the last dosing date is the last non-0 mg dose date and it excluded days when total dose administered was 0 mg.[63]

As of the April 2019 data cut-off, the median (range) for treatment duration was 83 (3-1575) days in the glasdegib + LDAC group and 40 (6-239) days in the LDAC group (Table 16). At study completion, five patients remained in follow up: 4 (4.5%) patients in the glasdegib + LDAC group and 1 (2.3%) patient in the LDAC group completed ≥4 years' follow-up.[2] At the last patient visit, 91.7% of patients were known to have died.[2]

Dose delays, reductions or modifications: In the event of study treatment related toxicity, dosing could be delayed and/or dose reduced. Below are some of the key criteria:[4]

- Doses of glasdegib that were held or missed during any cycle due to glasdegib-related toxicities were not made up (e.g. cycles would not be prolonged beyond the 28th calendar day).
- Glasdegib could be dose reduced during any cycle.
- No dose reductions were permitted in cycle 1 for any of the backbone chemotherapeutic agents.
- After cycle 1, if a toxicity was attributed to the backbone chemotherapy and not to glasdegib, chemotherapeutics could be delayed or reduced, while glasdegib dosing could be continued.
- Missed doses of backbone chemotherapy could be made up if the investigator considered it appropriate according to standard practice.
- Cycles could be extended to a maximum of 56 days for non-hematologic toxicity, or to a maximum of 70 days if due to hematologic toxicity. Glasdegib dosing could continue if observed toxicity was not deemed related to glasdegib.
- If a treatment interruption continued beyond day 28 of the cycle for any agent, then the day when full treatment (all agents in the combination) was restarted would be counted as day 1 of the next cycle for all agents.
- In a subsequent cycle, dose reductions were based on the worst toxicity in the previous cycle.
- A study treatment related continuous treatment interruption or delay of >28 days for non-hematologic toxicity or >42 days for prolonged myelosuppression defined as ANC<500/µL or platelet count <10 x109/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia, would result in permanent discontinuation from treatment, unless the patient demonstrated clinical benefit as agreed by the Investigator and Sponsor.

Sixty-five (77%) patients had dose interruptions and 14 (17%) patients had dose reductions in the glasdegib + LDAC group compared to zero patients in the LDAC group (Table 14). All dose reductions were due to adverse events. Dose interruptions were due to various reasons including adverse events, compliance, patient scheduling problems or physician decision.[63]

Table 14: Treatment duration and dose exposure for all cycles (January 2017 data cut-off)

Number of patients	Glasdegib 100 mg+LDAC 84		LDAC Alone 41
Exposure drug name	**Glasdegib**	**LDAC**	**LDAC**
Treatment duration (days), n	84		41
Mean (median)	189.4 (83.0)		66.4 (47.0)
Treatment exposure (days), n	84	Not calculated	Not calculated
Median (range)	75.5 (3, 954)		
Average dose per cycle (mg/day), n	84	84	41
Mean (std)	83.1 (19.71)	36.9 (5.92)	38.4 (3.51)
Median (range)	90.3 (19, 101)	40.0 (8, 40)	40.0 (24, 40)
Number (%) of patients with			
Dose reduction	14 (16.7)	13 (15.5)	0
Temporary dose delay	3 (3.6)	3 (3.6)	0
Dose interruption	65 (77.4)	None	None
Relative dose intensity (%), n	84	84	41
Mean (std)	89.0 (19.69)	95.5 (15.19)	96.1 (8.77)
Median (range)	92.3 (19, 181)	100.0 (20, 154)	100.0 (60, 100)

LDAC=low dose Ara-C; std=standard deviation;

Notes: LDAC was given at a dose of 20 mg (not adjusted for the patient's weight) subcutaneously twice daily (morning and evening; approximately 12 hours apart) on Days 1-10 days of the 28-day cycles. The treatment duration (in days) was calculated as (the last dosing date - Cycle 1/Day 1 + 1 day), where the last dosing date was the last non-zero dose date and it included missed doses on unknown dates. Treatment exposure (in days) of glasdegib was calculated as (the last dosing date - Cycle 1/Day 1 + 1 day), where the last dosing date was the last non-zero dose date and it excluded days with total dose administered of 0 mg. A cycle delay was defined as ≥8 weeks apart between cycles (from Day 1 of the previous cycle). A dose reduction was defined as a day when the prescribed dose was less than the previously prescribed dose for any reason with the exception that a day with total dose administered of 0 mg was not considered a dose reduction. A dose interruption/missed dose was defined as a planned dosing day with 0 mg total dose administered. Average dose per cycle = actual total dose in this cycle (exclude 0 mg and dose missed on unknown days) / actual dosing days in this cycle (include 0 mg and dose missed on unknown days)

Source: Clinical Study Report BRIGHT 1003[6]

Table 15: Duration of study treatments (AML and MDS patients, January 2017 data cut-off)

	PF-04449913 100 mg + LDAC (II)	LDAC Alone (II)
Number of Subjects	84	41
Duration Category (Days)		
<=1	0	0
2-7	3	2
8-14	4	11
15-28	10	0
29-60	17	10
61-90	11	6
>=91	39	12
Median Duration	83.0	47.0
Mean Duration	189.4	66.4
Range	3-972	6-239

LDAC = low dose Ara-c; PF-04449913 = glasdegib

Source: Clinical Study Report BRIGHT 1003[6]

Table 16: Duration of study treatments (AML patients, April 2019 data cut-off)

	PF-04449913 100 mg + LDAC (II)	LDAC Alone (II)
Number of Subjects	75	36
Duration Category (Days)		
<=1	0	0
2-7	3	2
8-14	4	10
15-28	8	0
29-60	15	10
61-90	11	4
>=91	34	10
Median Duration	83.0	40.5
Mean Duration	221.6	61.6
Range	3-1575	6-239

LDAC = low dose Ara-c; PF-04449913 = glasdegib

Source: Pfizer data output BRIGHT 1003[5]

Concomitant Treatment

Concomitant treatment considered necessary for the patient's wellbeing could be given at the discretion of the treating physician. Concomitant administration of glasdegib with moderate/strong CYP3A4/5 inhibitors and inducers or drugs with a known risk of torsades de pointes was not recommended due to the potential for a drug-drug interaction to prolong the QTc interval.

[redacted].[6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* The use of concomitant CYP3A4 inhibitors and inducers was of particular interest because CYP3A4 plays a major role in glasdegib metabolism.[64] Moderate or strong CYP3A4 inhibitors were used in 72 (63%) of patients, with 50 (65%) patients on the glasdegib + LDAC group and 22 (58%) patients on the LDAC group.[4] The most frequently used moderate or strong CYP3A4 inhibitors on the glasdegib + LDAC versus LDAC groups, respectively, were ciprofloxacin (33% versus 16%), fluconazole (30% versus 40%), posaconazole (17% versus 8%), and voriconazole (17% versus 8%).

Hematopoietic growth factor use during therapy was generally balanced across both treatment groups.[4] Filgrastim, lenograstim, or granulocyte colony stimulator factor were used in 6 (8%) of patients on the glasdegib + LDAC group and 4 (11%) of patients on the LDAC group. Darbepoetin alfa, epoetin alfa, or erythropoietin were used by 2 (3%) patients on the glasdegib + LDAC group and one patient (3%) on the LDAC group.

Study follow up and alternative drug use after study drug discontinuation

After discontinuation of study treatment, post-treatment survival status was collected every month for the first two months and thereafter every 2 months until death.[63] Patients were followed for 4 years after the first dose. Survival data (including date and cause of death) and, where possible, subsequent anticancer therapies or hematopoietic stem cell transplantation (HSCT), whether the patient remains in remission, or if relapsed and the date of relapse, were measured. Adverse event information and concomitant medications were also collected for the first month post-treatment.

Patients received subsequent therapies including chemotherapy (40% in the glasdegib + LDAC group and 34% in the LDAC group). One (1.3%) patient in the glasdegib + LDAC group went on to receive a stem cell transplant and 2 (2.7%) patients in the glasdegib +

LDAC group received subsequent investigational treatments for AML (Table 17).[63] Chemotherapy treatments received by patients after study drug discontinuation included a variety of agents, notably cytarabine, decitabine, and azacitidine.

Table 17: Patients receiving follow-up systemic therapies (January 2017 data cut-off)

Systemic therapy	Glasdegib + LDAC N=84	LDAC N=41
Transplant	**1(1)**	**0**
Chemotherapy	**34(40)**	**14(34)**
Biologic	**0**	**0**
Tyrosine kinase inhibitor	**0**	**0**
Investigational agent	**2(2)**	**0**
Other	**0**	**1(2)**

Source: Clinical Study Report BRIGHT 1003[6]

d) Patient Disposition

As of the January 2017 data cut-off, 132 patients had been randomized, 125 received treatment and 7 never received treatment. Four patients remained on therapy in the glasdegib + LDAC treatment group (Table 18). The most common reason for discontinuing study treatment was insufficient clinical response (i.e. disease progression); 37 [44%] and 15 [37%] patients in the glasdegib + LDAC and LDAC groups, respectively). Fewer patients discontinued treatment because of adverse events in the glasdegib + LDAC group (21 [25%]) compared to the LDAC group (12 [29%]). Fewer patients discontinued study medication because of death in the glasdegib + LDAC group (10 [12%]) compare to the LDAC group (11 [27%]). Two patients in the glasdegib + LDAC group discontinued therapy to receive hematopoietic stem cell transplantation or donor lymphocyte infusion, whereas no patients in the LDAC group proceeded to transplantation.[4]

As of the January 2017 data cut-off, the median follow-up time for survival was 21.7 months in the glasdegib + LDAC group and 20.1 months in the LDAC group.[6] Sixteen patients (18%) were being followed up in the glasdegib + LDAC group and 1 (2%) patient was being followed up in the LDAC group at the January 2017 data cut-off date.

As of the April 2019 data cut-off, the median follow-up for survival in the glasdegib + LDAC group and the LDAC group was 47.6 months and 48.1 months, respectively.[2] Four patients (5%) were being followed up in the glasdegib + LDAC group and 1 (2%) patient was being followed up in the LDAC group at the April 2019 data cutoff.

Table 18: Patient disposition (January 2017 data cut-off) Phase 2 Unfit/Non-intensive Population

Number (%) of patients		Glasdegib 100 mg+LDAC	LDAC Alone
Screened	132		
Assigned to study treatment		88	44
Treated		84	41
Treatment completed		0	0
Treatment discontinued		80 (95.2)	41 (100.0)
Patient died		10 (11.9)	11 (26.8)
Global deterioration of health status		3 (3.6)	1 (2.4)
Insufficient clinical response		37 (44.0)	15 (36.6)
Other		3 (3.6)	0
Protocol violation		1 (1.2)	0
Patient refused continued treatment for reason other than AE		5 (6.0)	2 (4.9)
AEs - relation to study treatments[a] not defined		13 (15.5)	10 (24.4)
AEs - related to study treatments[a]		8 (9.5)	2 (4.9)
Treatment ongoing at cutoff date		4 (4.8)	0
Study completed		0	0
Study discontinued		72 (81.8)	43 (97.7)
Patient died		68 (77.3)	41 (93.2)
Lost to follow-up		1 (1.1)	0
Patient refused further follow-up		3 (3.4)	2 (4.5)
Study ongoing at cutoff date		16 (18.2)	1 (2.3)

AE=adverse event; LDAC= low dose Ara-C

Source: FDA Statistical Review[3]

e) Limitations/Sources of Bias

- Well conducted aspects of the BRIGHT 1003 study was that it had long follow up for patient survival (overall survival was the primary endpoint), included a stratified randomization procedure based on known prognostic factors to minimize potential imbalances between study groups, and allocation concealment was conducted through a centralized system.
- The BRIGHT 1003 study was designed as a Phase 2 study with sample size estimates based on a power of 80% and Type 1 error of 0.10. In many analyses, the hazard ratios for overall survival were presented with 80% confidence intervals indicating that the investigators were willing to accept a 20% chance of obtaining a false positive result. This was done according to the statistical analysis plan for the study. The willingness to accept a higher chance of achieving a false positive result is not uncommon in Phase 2 studies. However, there are drawbacks to this approach and there are numerous examples of phase 3 trials whose results did not support the phase 2 trial results. Phase 2 trials may not accurately predict harm and/or effectiveness for new medicines.[7,8] The primary objective of phase 2 (randomized or non-randomized) trials is to document the safety outcomes and investigate if the estimate of effect for a new drug is large enough to use it in confirmatory phase 3 trials. A subsequent Phase 3 study of glasdegib could serve to confirm the results of this Phase 2 trial. Data submitted to regulatory agencies and CADTH included post-hoc analyses using 95% confidence intervals which were consistent with the results for the 80%CI intervals.
- In their feedback on the pERC Initial Recommendation, the sponsor stated that the results of the 95% confidence intervals were consistent with the results of the 80% intervals in the study. In response to the sponsor's feedback, the CADTH Methods Team reiterated that the results for the 80% confidence interval were consistent with the results for the 95% confidence interval. The CADTH Methods Team noted that post-hoc analyses using 95% confidence intervals were included in analyses performed and reviewed by the FDA, which noted that the OS results for the patient population including AML plus MDS patients and AML patients only, were statistically significant using the 95% confidence intervals.
- No multiplicity adjustments were made for either the multiple secondary endpoints or the multiple analyses at various data cut-off dates. This increases the probability of type 1 error and these results should be interpreted with caution.

- BRIGHT 1003 was an open label study and its investigators, patients and outcome assessors were aware of the assigned treatments. The primary outcome of overall survival and objective outcomes (e.g. laboratory values) are less susceptible to the biases of open label trials, however, the awareness of treatment status could have affected study procedures, reporting and evaluation of other outcomes. For example, for patients in the glasdegib + LDAC group, median treatment duration was twice as long as the median treatment duration in the LDAC alone group (83 days versus 40 days). Investigators could influence treatment duration and knowledge of assigned treatment may have influenced this aspect of the study. Assessment of response and adverse event reporting may also have been influenced by a knowledge of treatment assignment. [redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*
- It is possible that knowledge of treatment assignment affected both the threshold for reporting an adverse event and the assessment of the relationship to study treatment, biasing the assessment of adverse event causality against glasdegib.
- After study treatments were stopped, a greater proportion of patients received subsequent treatments for AML in the glasdegib + LDAC group compared to the LDAC monotherapy group during the follow-up period. This included a higher rate of chemotherapy in the glasdegib + LDAC group. This could have biased the survival and response results in favour of the glasdegib + LDAC group.
  - In their feedback on the pERC Initial Recommendation, the sponsor noted that the survival data in the BRIGHT 1003 study were not confounded by subsequent therapies. The sponsor stated that they performed a post-hoc analysis in which patients were censored if they received treatments for AML after discontinuing the study treatment. The sponsor reports that the overall survival results were similar to the primary analyses. In response to the sponsor's feedback, the CADTH Methods Team reiterated that patients received subsequent therapies including chemotherapy (40% in the glasdegib + LDAC group and 34% in the LDAC group). One (1.3%) patient in the glasdegib + LDAC group went on to receive a stem cell transplant and 2 (2.7%) patients in the glasdegib + LDAC group received subsequent investigational treatments for AML (see Table 17).[63] Chemotherapy treatments received by patients after study drug discontinuation included a variety of agents, notably cytarabine, decitabine, and azacitidine. The CADTH Methods Team acknowledges that an analysis in which patients were censored if they received treatment for AML after discontinuing the study treatment is a helpful analysis to understand the impact of subsequent therapies, but is unable to comment on the validity of the results because details regarding the methods used, the censoring rates, and when the censoring occurred, were not provided.
- There are no universally accepted criteria to determine fitness to receive induction chemotherapy; however, the CGP agreed that the criteria used to determine fitness to receive induction chemotherapy in the BRIGHT 1003 study were reasonable and are reflective of criteria used by clinicians in Canada.
- BRIGHT 1003 compared the effect of glasdegib + LDAC with that of LDAC. The CGP noted that azacitidine is currently the most commonly used treatment in Canada in the present target population. Decitabine is currently rarely used in Canada in patients with newly diagnosed AML as it is not Health Canada approved for this indication and not funded in most jurisdictions. There was no evidence available of direct comparisons of glasdegib versus azacitidine. Since azacitidine is the most relevant comparator for some patients with AML unfit to receive intensive induction chemotherapy, this limits the ability to clearly define the place in therapy for glasdegib with respect to azacitidine in this setting. Of note, the submitter provided an indirect treatment comparison (ITC) report that included a comparison to azacitidine, and a published ITC presented comparisons to azacitidine and decitabine (see section 7 for more details).
- The exposure to the study drugs differed between the two treatment groups. The adverse event data were not adjusted for exposure to the study drug and this confounds the ability to compare adverse event rates between the treatment groups. Rates of adverse events related to the study drugs may have appeared higher in the glasdegib + LDAC group because patients were exposed to the study drugs for a longer period of time relative to the LDAC monotherapy group.
- Patient-reported quality of life outcomes were not assessed in the BRIGTH 1003 trial. Therefore, the direction and degree to which the study treatments could impact patients' quality of life are unknown.

Detailed Outcome Data and Summary of Outcomes

Results for efficacy outcomes focus on the data emerging from the January 2017 (primary completion date) and April 2019 (final exploratory data cut) analyses. The data from the updated exploratory October 2018 data cut were presented in a single abstract with similar results as reported for January 2017 and April 2019. October 2018 data were therefore not reported in this section. Data are presented for the full trial population (AML + MDS patients) and the AML populations.

Efficacy Outcomes

Overall Survival (primary outcome)

Overall Survival – January 2017 data cut (primary completion date)

The median duration of follow-up was 21.7 months for the glasdegib + LDAC group and 20.1 months for the LDAC group.[1] There were 68 deaths (77.3%) and 41 deaths (93.2%) in the glasdegib + LDAC and LDAC groups, respectively.[1] [redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

The median OS was longer in patients who were randomized to receive glasdegib + LDAC (8.8 months, 80%CI: 6.9, 9.9) compared to patients who received LDAC (4.9 months, 80%CI: 3.5, 6.0) and the difference was statistically significant (HR=0.513; 80%CI: 0.394, 0.666; p=0.0004) (Table 19, Figure 3). Based on these results, the investigators noted that the BRIGHT 1003 study had met its primary endpoint in the overall trial population (patients with AML and high-risk MDS). Additional analyses for the AML patients also showed consistent results with the overall trial population (Table 20). At the January 2017 data cut-off, 94 AML patients had died. OS results were consistent in additional post-hoc analyses using 95% CIs.

Overall Survival – April 2019 data cut (final exploratory date cut)

At the final data cu-off date median duration of follow-up in the glasdegib + LDAC and the LDAC groups was 47.6 months and 48.1 months, respectively.[2] The OS results at the final exploratory data cut-off date were consistent with the OS results at the primary data cut-off date. The OS analyses including AML and MDS patients, suggested that the median OS was longer in patients who were randomized to receive glasdegib + LDAC (8.8 months; 80%CI: 6.9, 9.9) compared to patients who received LDAC (4.9 months; 80%CI: 3.5, 6.0) with a hazard ratio of HR=0.569 (80%CI: 0.441, 0.734; p=0.0020) (Table 19). Additional analyses for the AML patients also showed consistent results with the overall trial population (Table 20, Figure 4). At the April 2019 data cut-off, 106 AML patients had died. OS results were consistent in additional post-hoc analyses using 95% CIs.

Table 19: Overall survival (AML+MDS patients) – January 2017 and April 2019 data cuts

	Patients with AML/MDS (N=132) January 2017 data cut-off		Patients with AML/MDS (N=132) April 2019 data cut-off	
	Glasdegib + LDAC	LDAC	Glasdegib + LDAC	LDAC
Number of patients randomized	88	44	88	44
Kaplan-Meier estimate of median time to event (months)				
Median OS (80% CI)	8.8 (6.9, 9.9)	4.9 (3.5, 6.0)	8.8 (6.9, 9.9)	4.9 (3.5, 6.0)
Hazard Ratio[a] (80% CI) [p-value[b]]	0.513 (0.394, 0.666) [0.0004]		0.569 (0.441, 0.734) [0.0020]	
Median OS (95% CI)	8.8 (5.0, 11.7)	4.9 (2.9, 6.5)	8.8 (5.0, 11.7)	4.9 (2.9, 6.5)
Hazard Ratio[a] (95% CI) [p-value[b]]	0.513 (0.343, 0.766) [0.0004]		0.569 (0.385, 0.840) [0.0020]	

AML = acute myeloid leukemia; CI=confidence interval; LDAC=low dose cytarabine; NE=not estimable; OS = overall survival

[a] Based on the Cox Proportional hazards model stratified by prognosis stratum

[b] 1-sided p-value from the stratified log-rank test.

Source: Clinical Study Report BRIGHT 1003,[6] Clinical Summary[5] Pfizer additional information provided to pCODR[65]

Table 20: Overall survival (AML patients) - January 2017 and April 2019 data cuts

	Patients with AML (N=116) January, 2017 data cut-off		Patients with AML (N=116) April 2019 data cut-off	
	Glasdegib + LDAC	LDAC	Glasdegib + LDAC	LDAC
Number of patients randomized	78	38	78	38

	Patients with AML (N=116) January, 2017 data cut-off		Patients with AML (N=116) April 2019 data cut-off	
Deaths; n (%)	59 (75.6)	35 (92.1)	71 (91.0)	35 (92.1)
Number of patients censored, n (%)	19 (24.4)	3 (7.9)	7 (9.0)	3 (7.9)
Survival Probability at month 6 (95%CI)	59.7(47.7,69.9)	33.4(18.8,48.7)	NR	NR
Survival Probability at month 12 (95%CI)	39.4(28.3,50.3)	8.4(2.2,20.1)	NR	NR
Reason for censorship, n (%)				
Patients remained in follow-up	15 (19.2)	1 (2.6)	2 (2.6)	0 (0)
Patients no longer being followed for survival	4 (5.1)	2 (5.3)	5 (6.4)	3 (7.9)
Kaplan-Meier estimate of median time to event (months)				
Median OS (80% CI)	8.3 (6.6, 9.5)	4.3 (2.9, 4.9)	8.3 (6.6, 9.5)	4.3 (2.9, 4.9)
Hazard Ratio[a] (80% CI) [p-value[b]]	0.463 (0.348, 0.616) [0.0002]		0.529 (0.401; 0.697) [0.0013]	
Median OS (95% CI)	8.3 (4.7, 12.2)	4.3 (1.9, 5.7)	8.3(4.7, 12.2)	4.3(1.9, 5.7)
Hazard Ratio[a] (95% CI) [p-value[b]]	0.463 (0.299, 0.717) [0.0002]		0.529 (0.347, 0.807) [0.0013]	

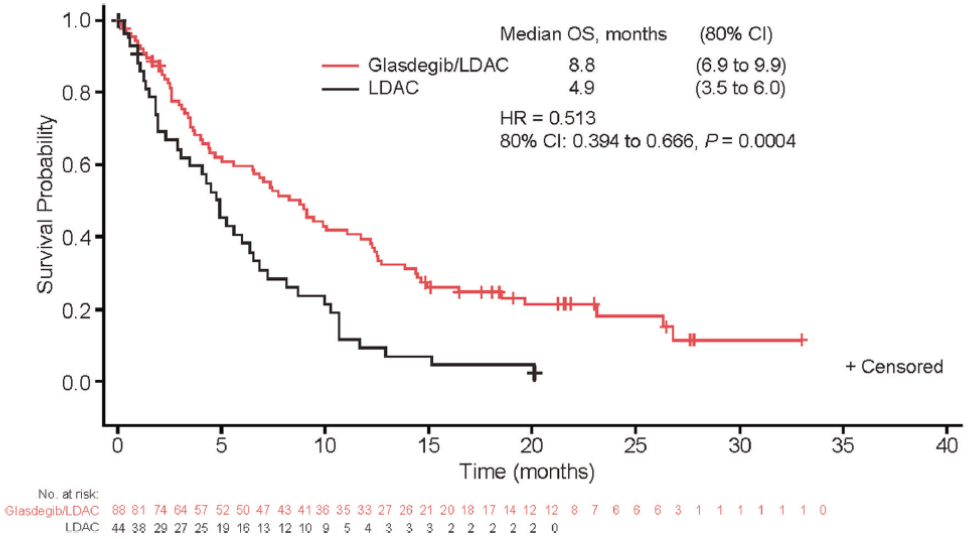
AML = acute myeloid leukemia; CI=confidence interval; LDAC=low dose cytarabine; NE=not estimable; NR= not reported; OS = overall survival

[a] Based on the Cox Proportional hazards model stratified by prognosis stratum

[b] 1-sided p-value from the stratified log-rank test.

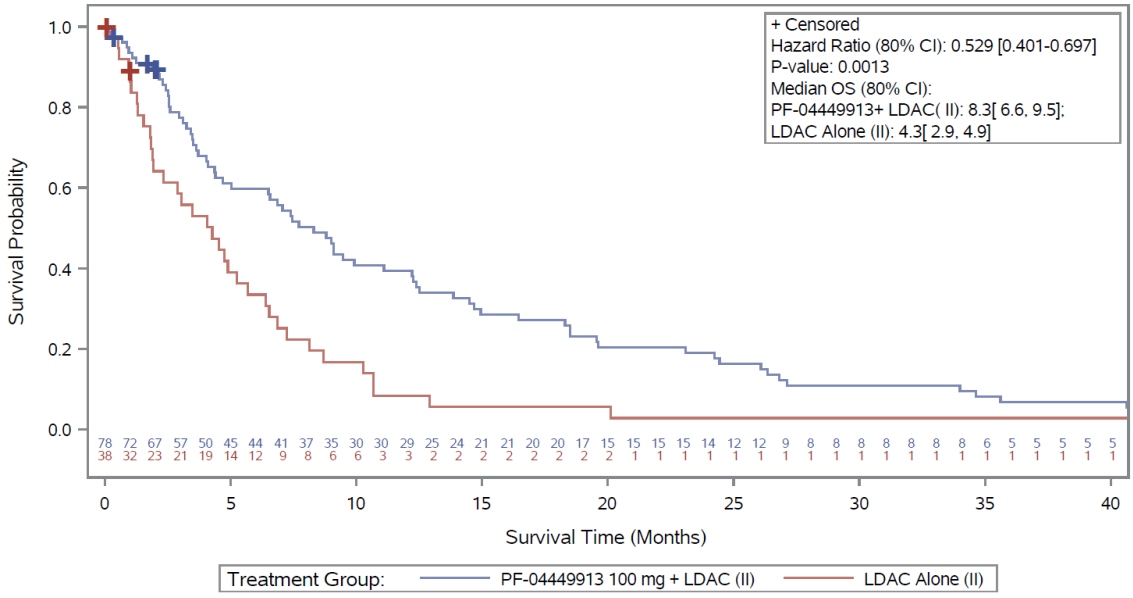
Source: Clinical Study Report BRIGHT 1003,[6] Clinical Summary[5] Pfizer additional information provided to CADTH,[65] Heuser et al.[2]

Figure 3: Overall Survival (AML and MDS patients, January 2017 data cut-off)



Source: Reproduced from Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2019;33(2):379-389. Fig 2. Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/

Figure 4: Overall Survival (AML patients, April 2019 data cut-off)



Source: Post hoc analyses (Pfizer),[5]

Pre-specified exploratory subgroup analyses for OS by cytogenetic risk

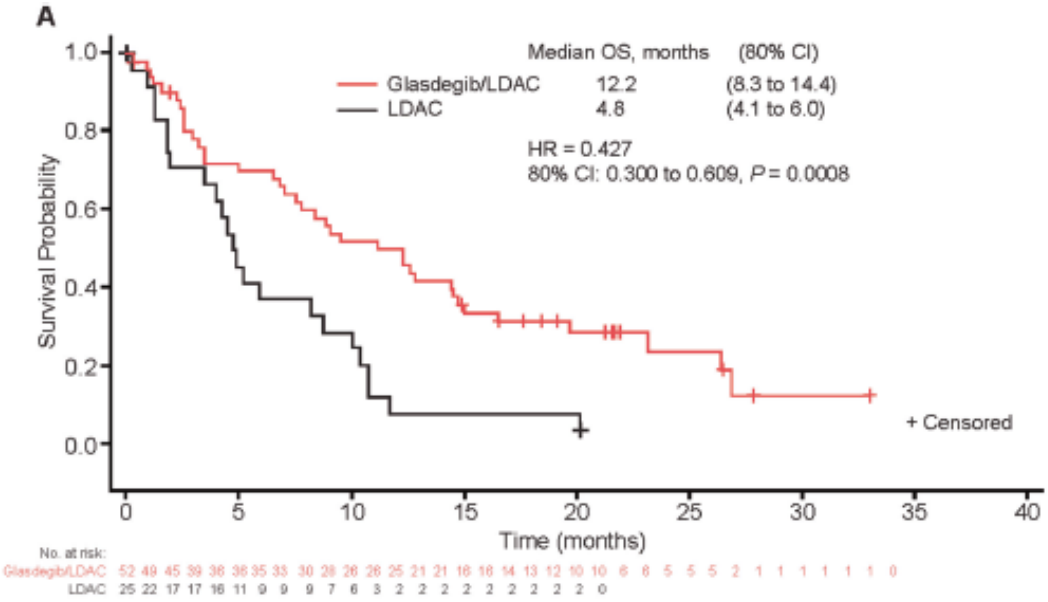
Overall trial population (AML + MDS patients) – January 2017

Table 21 summarizes analyses of OS by cytogenetic risk (goo/intermediate versus poor) for the overall trial population (AML plus MDS patients). Median survival was lower in the patients with poor cytogenetic risk compared to patients with good/intermediate cytogenetic risk. In patients with good/intermediate cytogenetic risk, median OS for patients taking glasdegib + LDAC was 12.1 months (80%CI: 8.3; 14.4) and for patients taking LDAC it was 4.8 months (80%CI: 4.1; 6.0). In patients with poor cytogenetic risk, median OS for patients taking glasdegib + LDAC was 4.7 months (80%CI: 4.0; 7.4) and for patient taking LDAC it was 4.9 months (80%CI: 2.3; 6.4). The hazard ratios for the comparison of glasdegib + LDAC versus LDAC in the group with good/intermediate cytogenetic risk was HR=0.427 compared to the group with poor cytogenetic risk (HR=0.633).[1] No 95% confidence intervals were reported for these analyses of overall survival by cytogenetic risk. These subgroup analyses were not adjusted for multiplicity and p-values should be regarded as nominal only. See Figure 5 and Figure 6 of OS in patients with good/intermediate cytogenetic risk and poor cytogenetic risk.

Table 21: Overall survival (AML + MDS) by cytogenetic risk – Jan. 2017 data

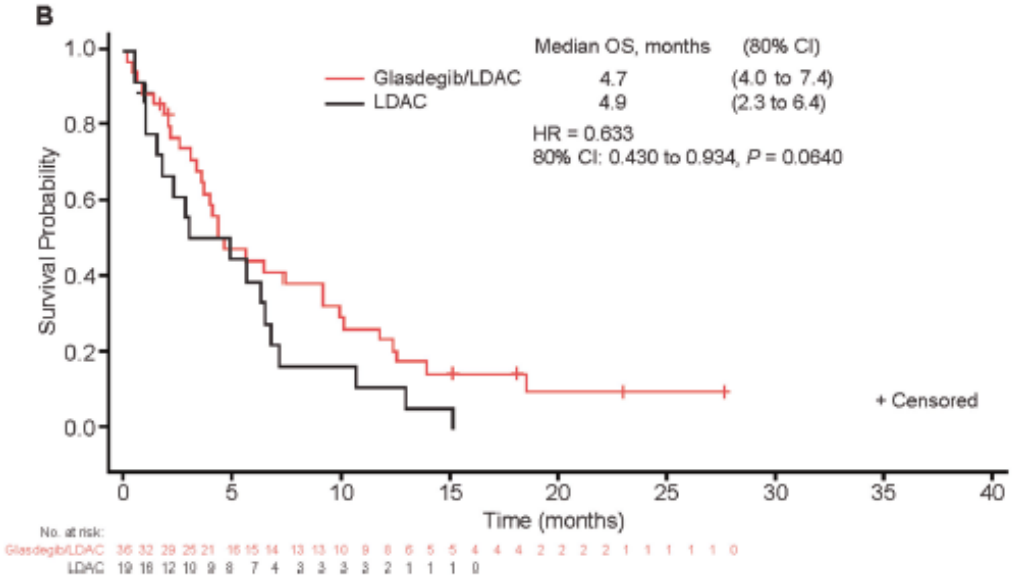
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Figure 5: Overall Survival (AML + MDS) - good/intermediate cytogenetic risk – Jan. 2017 data



Source: Reproduced from Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2019;33(2):379-389. Fig 3. Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/

Figure 6: Overall Survival (AML + MDS) - poor cytogenetic risk – Jan. 2017 data



Source: Reproduced from Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2019;33(2):379-389. Fig 3. Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/

AML patients – OS by cytogenetic risk - April 2019 data cut

Table 22 summarizes additional analyses of OS by cytogenetic risk (good/intermediate versus poor) in the AML population at the April 2019 data cut. Results were available for the January 2017 and April 2019 data cuts. Results for the AML population were overall consistent at both data cuts as well as with the overall trial population. At the final data cut (April 2019) median survival was lower in the patients with poor cytogenetic risk compared to patients with good/intermediate cytogenetic risk. In patients with good/intermediate cytogenetic risk, median overall survival for patients taking glasdegib + LDAC was 11.1 months (80%CI: 7.7; 14.5) and for patients taking LDAC it was 4.4 months (80%CI: 1.9; 5.3). In patients with poor cytogenetic risk, median overall survival for patients taking glasdegib + LDAC was 4.4 months (80%CI: 3.7; 6.5) and for patient taking LDAC it was 3.1 months (80%CI: 1.8; 5.7). The hazard ratios for the comparison of glasdegib + LDAC versus LDAC were similar in the group with good/intermediate cytogenetic risk (HR=0.529) compared to the group with poor cytogenetic risk (HR=0.528). No 95% confidence intervals were reported for these analyses of overall survival by cytogenetic risk. These subgroup analyses were not adjusted for multiplicity and p-values should be regarded as nominal only. See Figure 7 and Figure 8 of OS in AML patients with good/intermediate cytogenetic risk and poor cytogenetic risk.

Table 22: Overall survival by cytogenetic risk (AML population, April 2019 data cut-off)

	Patients with AML (n= 70) Good or Intermediate cytogenetic risk		Patients with AML (n=46) Poor cytogenetic risk	
	Glasdegib + LDAC	**LDAC**	**Glasdegib + LDAC**	**LDAC**
Number of patients randomized (%)	49 (100)	21 (100)	29 (100)	17 (100)
Deaths, n (%)	45 (91.8)	19 (90.5)	26 (89.7)	16 (94.1)
Number of patients censored, n (%)	4 (8.2)	2 (9.5)	3 (10.3)	1 (5.9)
Reason for censorship, n (%)				
Patient remains in follow-up	1 (2.0)	0 (0)	1 (3.4)	0 (0)
Patient no longer being followed up for survival	3 (6.1)	2 (9.5)	2 (6.9)	1 (5.9)
Survival probability, % (80% CI)				
At Month 6	70.4 (60.9; 78.0)	35.0 (21.8; 48.5)	41.2 (29.0; 52.9)	31.5 (17.6; 46.5)
At Month 12	49.1 (39.4; 58.0)	10.0 (3.5; 20.5)	22.5 (13.1; 33.4)	6.3 (1.3; 17.1)
Kaplan-Meier estimates of time to event (months) (80% CI)				
25%	3.5 (2.6; 6.9)	1.9 (1.3; 3.5)	2.6 (2.1; 3.6)	1.5 (0.6; 2.3)
50%	11.1 (7.7; 14.5)	4.4 (1.9; 5.3)	4.4 (3.7; 6.5)	3.1 (1.8; 5.7)
75%	24.4 (18.5; 26.8)	9.5 (5.3; 10.7)	9.9 (7.4; 13.9)	6.5 (4.9; 7.2)
Hazard Ratio[a] (80% CI) [p-value[b]]	0.529 (0.370; 0.758); P = 0.0105		0.528 (80% CI: 0.343; 0.813); P = 0.0269	

AML = acute myeloid leukemia; CI=confidence interval; LDAC=low dose cytarabine

[a] Based on the Cox Proportional hazards model.

[b.] 1-sided p-value from the unstratified log-rank test.

Data cut-off: April 2019

Source: Pfizer Clinical Summary[5]

Figure 7: Overall Survival - Good or Intermediate Cytogenetic Risk - AML Population – April 2019 data

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Figure 8: Overall Survival - Poor Cytogenetic Risk - AML Population – April 2019 data

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

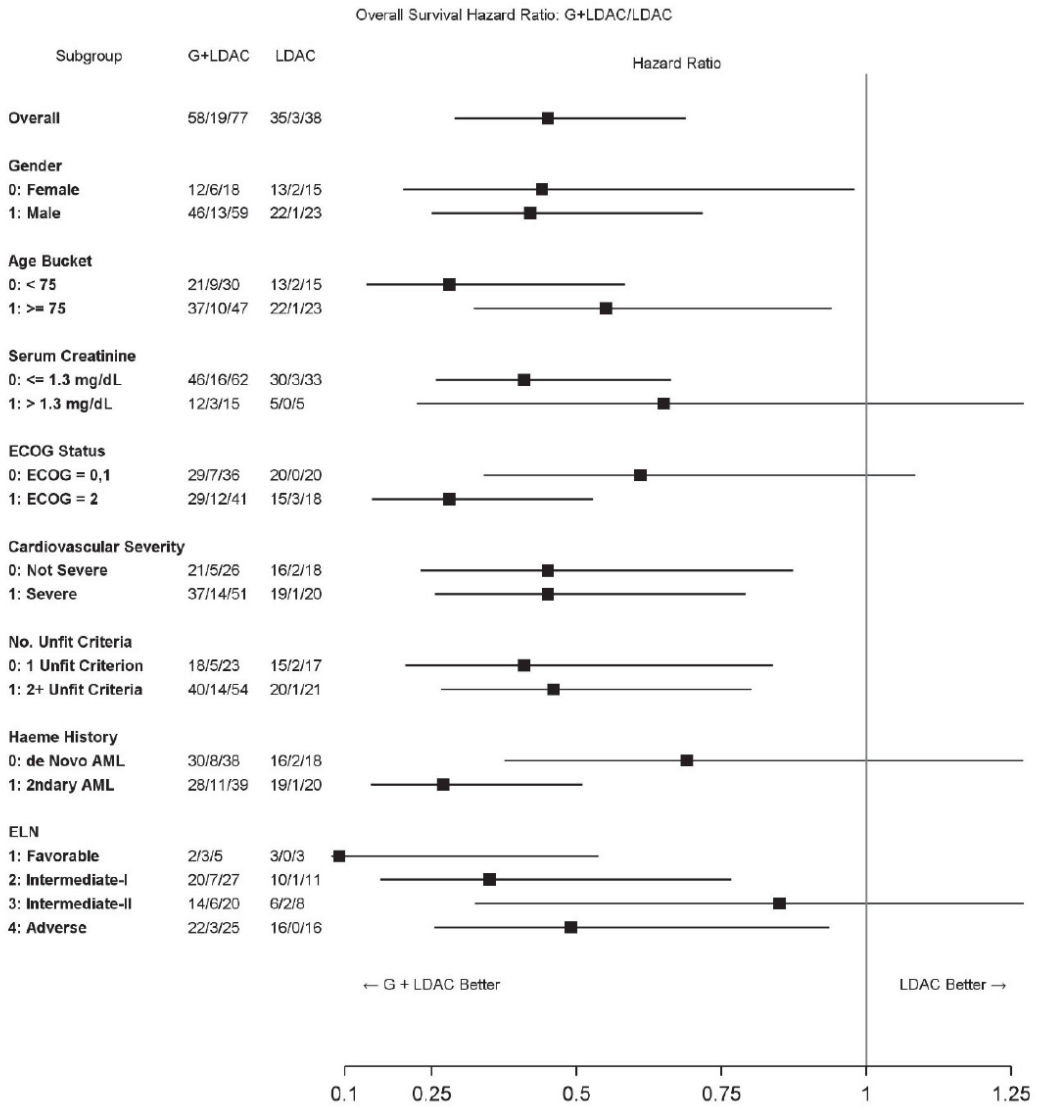
Data cut-off: April 2019.

Source: Pfizer Clinical Summary[5]

Additional exploratory OS subgroup analyses – January 2017 data cut

Figure 9 summarizes post-hoc analyses of overall survival by potential prognostic demographic and disease factors. Factors investigated included gender, age, creatinine level, ECOG status, cardiovascular disease severity, number of criteria to qualify for unfit to receive intensive induction chemotherapy, primary or secondary AML and ELN classification. Results suggested more favourable results from glasdegib + LDAC compared with LDAC in younger patients, lower serum creatinine, ECOG 2, secondary AML, and favorable/ intermediate-I risk AML. However, it is important to note that these subgroup analyses were exploratory and hypotheses generating only.

Figure 9: Overall Survival by subgroups (AML population, January 2017 data cut-off)



G= glasdegib; ECOG = European cooperative oncology group; ELN = European LeukemiaNet; LDAC = low dose Ara-c;

Note: Values in treatment columns have the format a/b/c, where a= number of events, b= number censored and c= total number of patients;

Source: FDA Clinical Review[4]

Post hoc analyses for OS by bone marrow blast percentage

The sponsor provided a post hoc analysis of OS by blast % for AML patients. In patients with blasts 20-30%, median overall survival for patients taking glasdegib + LDAC was 10.7 months (95%CI: 5.0, 19.5) and was 4.5 months (95%CI: 0.5, 6.5) in patients taking LDAC (HR=0.172; 95%CI: 0.061-0.484, p<0.0001). These post hoc analyses were exploratory only and p-values should be regarded as nominal only.

In their feedback on the pERC Initial Recommendation, the sponsor noted that the BRIGHT 1003 study met its primary endpoint, the data were mature, and survival benefits were consistent across subgroups. In response to the submitter's feedback the CADTH Methods Team agreed that the study met its primary prespecified endpoint and that the overall survival results were consistent for

the January 2017 and April 2019 data-cut off dates in the populations that included only AML as well as AML plus MDS patients (see Tables 19, 20 in the CADTH Clinical Guidance Report). Further, the pCODR Methods Team agrees that the data were mature. The study had adequate follow-up of sufficient duration to assess overall survival.

The CADTH Methods Team considers that subgroup analyses of overall survival presented by the manufacturer (Figure 9, pCODR Clinical Guidance Report) are useful observations for generating hypotheses but not appropriate for confirming the efficacy of glasdegib + LDAC in any specific subpopulation.

Response Rates/Complete Remission (secondary outcome)

This section summarizes the response data from the primary completion date (January 2017) and the final analysis (April 2019). Response data are summarized for the full trial population (AML + MDS patients) and for AML patients only. The data were similar between data cut-off dates and populations.

Key secondary outcome: Complete remission – (AML + MDS patients) – January 2017 data cut (primary completion date)

In the full trial population (AML + MDS patients) a higher rate of CR was observed in patients taking glasdegib + LDAC (n = 15, 17.0%) compared to patients taking LDAC (n = 1, 2.3%) (see Table 23). Exploratory subgroup analyses by cytogenetic risk profile suggested the rate of CR was higher in patients taking glasdegib + LDAC compared to patients taking LDAC in the subgroups of good/intermediate and poor cytogenetics, though the benefit of glasdegib + LDAC seemed more pronounced in the good/intermediate risk group. Due to small patient numbers and the exploratory nature of the analyses the results by cytogenetic risk groups should be interpreted with caution.

In the glasdegib + LDAC group median (range) duration of response was 9.9 (0.03–28.8) months for patients with CR and 6.5 (0.03–28.8) months for patients with either CR, CRi, or MLFS.[1]

At the updated April 2019 data cut CR was reported for the AML population (excluding MDS patients).

Table 23: Investigator reported CR – full trial population (AML + MDS patients) – January 2017 data cut

	Glasdegib 100 mg +LDAC, $N = 88$	LDAC, $N = 44$
Patients with CR, *n* (%)	15 (17.0)	1 (2.3)
80% CI[a]	11.9–22.2	0.0–5.2
Cytogenetic risk		
Good/intermediate	52	25
Patients with CR, *n* (%)	10 (19.2)	0 (0.0)
80% exact CI[b]	12.3–28.1	0.0–8.8
Poor cytogenetic risk	36	19
Patients with CR, *n* (%)	5 (13.9)	1 (5.3)
80% exact CI[b]	6.9–24.2	0.6–19.0
Combination versus LDAC		
Pearson Chi-square test for all enrolled patients (unstratified)		
P value		0.0142
CMH test for all enrolled patients stratified by cytogenetics[c]		
Odds ratio (80% CI)		5.03 (1.59–15.88)
P value		0.0152

CI confidence interval, *CMH* Cochran–Mantel–Haenszel, *CR* complete remission, *IVRS* interactive voice response system, *LDAC* low-dose cytarabine

[a]Using normal approximation

[b]Using exact method based on binomial distribution

[c]Good/intermediate and poor cytogenetic risk based on IVRS

Source: Reproduced from Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2019;33(2):379-389.Table 2. Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/

Additional response-related data – (AML population) – January 2017 data cut (primary completion date)

Best overall response and other response outcomes of interests (CR/CRi, disease modifying response, and clinically beneficial response) for patients with AML are summarized in Table 24. Results were consistent with the results for the full trial population (AML + MDS patients). A higher rate of complete remission was observed in patients taking glasdegib + LDAC (n=14, 17.9%) compared to patients taking LDAC (n=1, 2.6%) at the primary completion date.

Prespecified exploratory subgroup analysis reported overall response by cytogenetic risk classification in AML patients. The rate of CR was numerically higher in patients taking glasdegib + LDAC compared to patients taking LDAC in the subgroups with good/intermediate risk (10/49; 20.4% versus 0/21; 0%) and poor risk cytogenetics (4/29; 13.8% vs 1/17; 5.9%).

Exploratory analyses of response rates by mutation frequency in a subgroup of patients who had baseline mutational analysis (N=88) at the January 2017 data cut showed that, in the glasdegib + LDAC group, clinical responses were reported in all mutations except KRAS. The most commonly mutated genes in patients taking glasdegib + LDAC and who responded were RUNX1, IDH1 and TET2 (10/21 [47.6%], 5/21 [23.8%] and 7/21 [33.3%] responding patients, respectively). There were no significant correlations between mutational status of any of the individual 12 reported genes and clinical response.[6]

Response rates in the subgroup of patients with MDS (N=16)

[redacted].[6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 24: Best overall response (AML population, January 2017 data cut-off)- Investigator-assessed

	Glasdegib + LDAC (n=78)			LDAC alone (n=38)		
	N	(%)	80% CI[a]	N	(%)	80% CI
Objective response (disease status)						
CR	14	17.9	12.4, 24.8	1	2.6	0.3, 9.9
CRi	5	6.4	3.2, 11.6	1	2.6	0.3, 9.9
MLFS	2	2.6	0.7, 6.7	0	0.0	0.0, 5.9
PR	5	6.4	3.2, 11.6	0	0.0	0.0, 5.9
PRi	2	2.6	0.7, 6.7	0	0.0	0.0, 5.9
MR	4	5.1	2.3, 10.0	4	10.5	4.7, 19.9
SD	13	16.7	11.3, 23.4	9	23.7	14.8, 34.8
Indeterminate	0	0.0	0.0, 2.9	0	0.0	0.0, 5.9
Cytogenetic response						
CRc	8	10.3	6.1, 16.1	0	0.0	0.0, 5.9
Molecular response						
CRm	12	15.4	10.3, 21.9	1	2.6	0.3, 9.9
Objective disease progression						
Treatment failure	9	11.5	7.1, 17.6	7	18.4	10.6, 29.0
Resistant disease	8	10.3	6.1, 16.1	7	18.4	10.6, 29.0
Aplasia	0	0.0	0.0, 2.9	0	0.0	0.0, 5.9
Indeterminate cause	1	1.3	0.1, 4.9	0	0.0	0.0, 5.9
Relapse	0	0.0	0.0, 2.9	0	0.0	0.0, 5.9
Not evaluable	24	30.8	23.9, 38.4	16	42.1	31.1, 53.8
Further endpoints of interest[b]						
CR/CRi	19	24.4	18.1, 30.6	2	5.3	0.6, 9.9
Disease modifying response	26	33.3	26.5, 40.2	2	5.3	0.6, 9.9
Clinically beneficial response	28	35.9	28.9, 42.9	2	5.3	0.6, 9.9

[a:] Using exact method based on binomial distribution.

[b]The CI for further endpoints are 95% CI using normal approximation

Indeterminate = not evaluable (i.e. dry tap or insufficient sample), or unable to be determined (i.e. unfit patient per Am 2 with increase in BM blasts during first 3 cycles but treatment continued per protocol). Not evaluable defined as patients not assessed for response.

BM = bone marrow; CI = confidence interval; CR: complete remission; CRc = cytogenetic complete response; Cri = CR with incomplete blood count recovery; CRm = molecular CR; LDAC = low-dose cytarabine; MLFS: morphologic leukemia-free state; PR: partial remission; PRi: PR with incomplete blood count recovery; MR: minor response; SD: stable disease

Disease Modifying Response = CR, CRi, MLFS, and PR; Clinically Beneficial Response = CR, CRi, MLFS, PR, and PRi

Data cut-off date: January 3, 2017

Source: Pfizer Clinical Summary[5]

Other response-related data (AML population) – April 2019 data cut (final exploratory data cut)

Best overall response and other response outcomes of interests (CR/CRi, disease modifying response, and clinically beneficial response) for patients with AML are summarized in Table 25. Results for the AML population were similar between the January 2017 and April 2019 data cuts. A higher rate of CR was observed in patients taking glasdegib + LDAC (n=15, 19.2%) compared to patients taking LDAC (n=1, 2.6%) at the final analysis using the April 2019 data cut-off date. When rates of CR and CRi were combined (CR+CRi), patients taking glasdegib + LDAC had a higher CR+CRi remission rate (n=19, 24.4%) compared to patients taking LDAC (n=2, 5.3%).

Table 25: Best overall response (AML population, April 2019 data cut-off)- Investigator-assessed

	Glasdegib + LDAC (n=78)			LDAC alone (n=38)		
	N	(%)	80% CI[a]	N	(%)	80% CI
Objective response (disease status)						
CR	15	19.2	13.5; 26.2	1	2.6	0.3; 9.9
CRi	4	5.1	2.3; 10.0	1	2.6	0.3; 9.9
MLFS	2	2.6	0.7; 6.7	0	0	0.0; 5.9
PR	5	6.4	3.2; 11.6	0	0	0.0; 5.9
PRi	2	2.6	0.7; 6.7	0	0	0.0; 5.9
MR	4	5.1	2.3; 10.0	4	10.5	4.7; 19.9
SD	14	17.9	12.4; 24.8	9	23.7	14.8; 34.8
Indeterminate	0	0	0.0; 2.9	0	0	0.0; 5.9
Cytogenetic response						
CRc	9	11.5	7.1; 17.6	0	0	0.0; 5.9
Molecular response						
CRm	13	16.7	11.3; 23.4	1	2.6	0.3; 9.9
Objective disease progression						
Treatment failure	9	11.5	7.1; 17.6	7	18.4	10.6; 29.0
Resistant disease	8	10.3	6.1; 16.1	7	18.4	10.6; 29.0
Aplasia	0	0	0.0; 2.9	0	0	0.0; 5.9
Indeterminate cause	1	1.3	0.1; 4.9	0	0	0.0; 5.9
Relapse	0	0	0.0; 2.9	0	0	0.0; 5.9
Not evaluable	23	29.5	22.7; 37.1	16	42.1	31.1; 53.8
Further endpoints of interest[b]						
CR/CRi	19	24.4	18.1; 30.6	2	5.3	0.6; 9.9
Disease modifying response	26	33.3	26.5; 40.2	2	5.3	0.6; 9.9
Clinically beneficial response	28	35.9	28.9; 42.9	2	5.3	0.6; 9.9
Cytogenetic subgroup analysis, patients with CR:						
Good/intermediate cytogenetic risk, n/N	11/49	22.4	14.8/31.9	0/21	0	0; 10.4
Poor cytogenetic risk, n/N	4/29	13.8	6.2;25.7	1/17	5.9	0.6; 21.0

BM = bone marrow; CI = confidence interval; CR: complete remission; CRc = cytogenetic complete response; Cri = CR with incomplete blood count recovery; CRm = molecular CR; LDAC = low-dose cytarabine; MLFS: morphologic leukemia-free state; PR: partial remission; PRi: PR with incomplete blood count recovery; MR: minor response; SD: stable disease

Note: Disease Modifying Response = CR, CRi, MLFS, and PR; Clinically Beneficial Response = CR, CRi, MLFS, PR, and PRi

[a] Using exact method based on binomial distribution.

[b]The confidence interval for these endpoints are 95% CI using normal approximation

Data cut-off date: April, 2019

Source: Pfizer Clinical Summary[5]

Exploratory outcome PFS

Post hoc analyses of Progression Free Survival

[redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* The p-value should be regarded as nominal and the analyses as exploratory.

Table 26: Progression free survival (AML patients, April 2019 data cut-off)

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Health-related Quality of Life

Health-related quality of life was not measured in the BRIGHT 1003 trial.

In their feedback on the pERC Initial Recommendation, the sponsor noted that quality of life was not measured in the trial but suggests that treatment with glasdegib + LDAC is associated with longer 'quality-adjusted survival time' based on a post-hoc analysis of the data from the BRIGHT 1003 study (Solem et al., 2020)[66].In response to the sponsor's feedback the CADTH Methods Team reiterated that patient-reported quality of life data were not collected in the BRIGHT 1003 study. "Quality-adjusted survival time" referred to by the Sponsor is not a measure of patient-reported quality of life. Solem et al. (2020)[66] was a post-hoc analysis and did not contain outcomes of interest as prespecified by the CADTH Methods Team's review protocol. Therefore, Solem et al. (2020)[66] was not included in the CADTH systematic review. Solem et al. (2020)[66] assessed quality-adjusted survival time according to the quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) method. [67,68] Survival time in the BRIGHT 1003 study was partitioned into 3 health states. Times in each state were calculated for the 2 treatment groups. Utilities were assigned for each health state. Utility-adjusted times were summed up to produce "Quality-adjusted survival time." The CADTH Methods Team noted that the study was not designed to measure the patients' quality of life status in the 3 specified states and therefore there is uncertainty in the generated estimates. Another source of uncertainty is the selection of the utility values assigned to each health state, which were not prespecified and have a significant impact on the results. Furthermore, four of eight authors of the Solem et al, (2020) publication are employees of the sponsor and three authors were employees of a company which received funds from the sponsor to conduct the analysis.

Harms

Adverse Events

This section presents the adverse events analyses for the longest follow-up time at the final data cut-off date April 2019. Results for adverse events at the final data cut-off date were consistent with results observed at the January 2017 data cut-off date (primary study completion date). The adverse event analysis was performed by the sponsor for patients with AML and excluded 16 patients with MDS.

As of the final April 2019 data cut-off, the median (range) treatment duration was 83 (3-1575) days in the glasdegib + LDAC group and 40 (6-239) days in the LDAC group.[5]

All patients with AML experienced at least one adverse event, 80% of all patients experienced a serious adverse event, and the rates of serious adverse events were 81% in patients glasdegib + LDAC and 78% in patients who received LDAC (Table 27). Patients experienced similar rates of grade 3 or 4 adverse events (89% versus 94% in patients taking glasdegib + LDAC versus LDAC, respectively). The rate of grade 5 adverse events was lower in patients taking glasdegib + LDAC (32%) compared to patients taking LDAC alone (44%). Fewer patients discontinued study drug due to adverse events in the glasdegib + LDAC group (39%) compared to the LDAC group (47%). There were 445 adverse events that were deemed to be treatment related occurring in 60 (80%) patients taking glasdegib + LDAC compared to 66 events in 19 (53%) patients taking LDAC monotherapy.

The most common adverse events of all grades in patients taking glasdegib + LDAC included anemia (47%), nausea (36%), febrile neutropenia (35%), decreased appetite (33%) and thrombocytopenia (32%) (Table 28). The most common adverse events of all grades in patients taking LDAC included anemia (42%), dyspnea (31%), pneumonia (28%), diarrhea (25%) and febrile neutropenia (25%) (Table 29). Adverse events with grade 3, 4 or 5 were experienced by 19%, 43% and 32% of patients taking glasdegib + LDAC and by 22%, 31% and 44% of patients taking LDAC, respectively.

[redacted].[5]*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Serious Adverse Events

There were 61 (81%) patients in the glasdegib plus LDAC group and 28 (78%) patients in the LDAC alone group that experienced all-causality SAEs (Table 30, Table 31). The most frequently reported serious adverse events in the glasdegib + LDAC group included febrile neutropenia (21 [28%] patients), pneumonia (16 [21.3%] patients), and anemia (5 [7%] patients). The most frequently reported serious adverse events in the LDAC group were pneumonia (7 [19%] patients), febrile neutropenia (6 [17%] patients), sepsis (5 [14%] patients), and pancytopenia (2 [6%] patients).

Adverse events of Interest

Adverse events (typically associated with Hedgehog pathway inhibitors) occurring within the first 30 days of study treatment

Incidence of adverse effects typically associated with Hedgehog pathway inhibitors, and that occurred within the first 90 days of study treatment in the AML and MDS populations, included (glasdegib + LDAC versus LDAC):[64] musculoskeletal pain (30 [35%] versus 17 [41%]), muscle spasms (15 [18%] versus 5 [12%]), dysgeusia (21 [25%] versus 2 [5%]), fatigue (36 [43%] versus 32 [78%]), weight decreased (11 [13%] versus 5 [12%]), nausea (29 [35%] versus 12 [29%], vomiting (18 [21%] versus 10 [24%]), diarrhea (18 [21%] versus 22 [54%]) and renal insufficiency (19 [23%] versus 10 [24%]).

Withdrawals Due to Adverse Events

Fewer patients discontinued study treatments due to adverse events in the glasdegib + LDAC group (29 [39%] patients) compared to the LDAC group (17 [47%] patients). The most common reasons for permanent discontinuation of glasdegib + LDAC treatment included pneumonia (4 [5%] patients), febrile neutropenia (2 [3%] patients), and nausea (2 [3%] patients). The most common reasons for permanent discontinuation in the LDAC group included febrile neutropenia (2 [6%] patients) and sepsis (2 [6%] patients).

One person permanently discontinued from study treatment in the glasdegib + LDAC group because of QT prolongation and no patients discontinued for this reason in the LDAC group.[5]

Deaths

[redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 27: Adverse Event Summary (AML patients)

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Table 28: Adverse events occurring in ≥10% of patients: Glasdegib + LDAC Group, N=75

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Table 29: Adverse events occurring in ≥10% of patients: LDAC Group, N=36

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Table 30: Serious Adverse Events occurring in ≥2 patients: Glasdegib + LDAC Group, N=75

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Table 31: Serious Adverse Events occurring in ≥2 patients: LDAC Group, N=36

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Table 32: Permanent discontinuations due to adverse events in ≥2 patients: Glasdegib + LDAC Group, N=75

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	2	(2.7)	4	(5.3)	10	(13.3)	8	(10.7)	5	(6.7)	0	(0.0)	29	(38.7)
Pneumonia	0	(0.0)	0	(0.0)	1	(1.3)	3	(4.0)	0	(0.0)	0	(0.0)	4	(5.3)
Disease progression	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.7)	0	(0.0)	2	(2.7)
Febrile neutropenia	0	(0.0)	0	(0.0)	2	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.7)
Nausea	1	(1.3)	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.7)
Sudden death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.7)	0	(0.0)	2	(2.7)

AE = adverse event

Source: Pfizer post-hoc analysis[5]

Table 33: Permanent discontinuations due to adverse events in ≥2 patients: LDAC Group, N=36

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	1	(2.8)	1	(2.8)	6	(16.7)	6	(16.7)	3	(8.3)	0	(0.0)	17	(47.2)
Febrile neutropenia	0	(0.0)	0	(0.0)	1	(2.8)	1	(2.8)	0	(0.0)	0	(0.0)	2	(5.6)
Sepsis	0	(0.0)	0	(0.0)	0	(0.0)	2	(5.6)	0	(0.0)	0	(0.0)	2	(5.6)

AE = adverse event

Source: Pfizer post-hoc analysis[5]

6.4 Ongoing Trials

There were six ongoing trials identified as potentially relevant to this review. The inclusion criteria for these studies may have included patients who would meet the criteria the CADTH systematic review, however, none of the trials focused exclusively on the relevant population (age ≥75 years or who are not eligible to receive intensive induction chemotherapy.).

Table 34: Potentially relevant ongoing trials of glasdegib in AML

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT04231851[5] Non randomized, open label, single group N=30 Start: February 2020 End: December 2020 Sponsor: Pfizer	Previously Untreated Patients with Acute Myelogenous Leukemia with MDS Related Changes or Therapy-related Acute Myeloid Leukemia Criteria: ≥ 18 years with previously untreated therapy-related AML or AML with myelodysplastic changes as per WHO, ECOG PS 0-2, adequate organ function,	Intervention(s): Induction: CPX-351 44 mg/m^2/100 mg/m^2 IV on Days 1, 3 and 5 and glasdegib 100 mg QD Days 6-28; Re-induction: CPX-351 29 mg/m2/65 mg/m^2 IV on Days 1 and 3 and glasdegib 100 mg QD Days 4-28; Consolidation: CPX-351 29 mg/m^2/65 mg/m^2 on Days 1 and 3 and glasdegib 100 mg QD Days 4-28; Maintenance: glasdegib 100 mg QD for up to one year Comparator(s): NA	Outcomes: **Primary:** EFS at 6 months; **Secondary:** Safety (Grade 3-5 AEs), ORR, DOR, OS, time to normal hematopoiesis, proportion of pts who go on to receive allogenic HSCT
NCT03416179[5] BRIGHT AML1019 Randomized, double blind, parallel group N=720 Start: April 2018 End: March 2025 Sponsor: Pfizer	Patients with Previously Untreated Acute Myeloid Leukemia Criteria: ≥ 18 years with untreated AML as per WHO criteria, adequate organ function and all anti-cancer treatments DC 2 weeks from study entry	*Intervention*: Intensive study: Glasdegib + '7 + 3' induction with daunorubicin and cytarabine and consolidation with single agent cytarabine and if required, HSCT and Non-intensive study: Glasdegib + azacitidine *Comparators*: Intensive study: Matched placebo + '7 +3' induction as above and Non-intensive study: Matched placebo + azacitidine	**Primary:** OS; **Secondary:** Fatigue score by the MDASI-AML/MDS questionnaire, CR, DOR, TTR, EFS, PROs, and safety outcomes
NCT04051996[5] RCT, parallel group, Phase 2, single blinded N=46 Start: September 2019 End: September 2022 Sponsor: Pfizer	Population: Older Patients with Poor-risk Acute Myeloid Leukemia Who Are Unfit for or Refuse Intensive Chemotherapy Criteria: > 18 years with morphologically confirmed AML as per WHO criteria with poor cytogenetic risk or molecular abnormalities (excluding FLT3-mutated AML), ECOG PS 0-2, adequate renal and liver function	Intervention: Glasdegib 100 mg daily with decitabine 20 mg/m^2 on a 5-day schedule per 28-day cycle Comparator: Glasdegib 100 mg daily with decitabine 20 mg/m^2 on a 10-day schedule per 28-day cycle	**Primary:** CR/Cri as per 2017 ELN criteria; **Secondary:** OS, EFS, RFS, time to CR/Cri, duration of CR/Cri, BM mutational clearance
NCT02367456[5] BRIGHT 1012	Population: previously untreated higher-risk MDS, acute myeloid leukemia, or chronic myelomonocytic leukemia	Intervention(s): Glasdegib 100 mg QD continuously in 28-day cycles + azacitidine 75 mg/m^2	Outcomes: **Primary:** CR for MDS, CR for AML, AEs,

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Nonrandomized, phase 1b, open label N=73 Start: April 2015 End: January 2021 Sponsor: Pfizer	Criteria: ≥ 18 yrs with previously untreated MDS, AML, or CMML according to WHO criteria, MDS pts must have intermediate, high-risk, or very high-risk disease according to revised IPSS 2012 and clinical indication for treatment with azacitidine for MDS or AML	Comparator: none	**Secondary:** Response rate, hematologic improvement by IWG criteria, marrow CR, cytogenetic response, SD, PK, OS and many others
NCT04093505[5] Randomized, phase 3, quadruple blind factorial assignment N=252 Start: March 2020 End: March 2024 Sponsor: University Hospital Heidelberg	Older Patients with Newly Diagnosed AML Criteria: ≥ 60 years with newly diagnosed AML according to WHO criteria with genetic and immunophenotypic assessment, no prior chemotherapy for leukemia except hydroxyurea, ECOG PS 0-2	Intervention(s): Induction: Gemtuzumab ozogamicin 3 mg/m^2 on Days 1, 4, 7 or on Day 1 and Consolidation and Maintenance: Glasdegib 100 mg on Days 4-27 Comparator(s): Gemtuzumab ozogamicin 3 mg/m^2 on Days 1, 4, 7 or on Day 1 and Consolidation and Maintenance: Placebo on Days 4-27	Outcomes: **Primary:** MRD negativity; **Secondary:** EFS
NCT03226418[5] Non-randomized, open label, phase 2 N=75 Start: July 2017 End: December 2024 Sponsor: University of Nebraska, National Cancer Institute	Acute Myeloid Leukemia in Older Patients Criteria: ≥ 60 yrs with newly diagnosed AML or AML equivalent such as myeloid sarcoma, MDS in transformation to AML, or high-grade treatment-related myeloid neoplasm, Karnofsky PS ≥ 60%.	Intervention(s): Intensive induction: cytarabine Days 1-7 and idarubicin on Days 1-3 (7 + 3), or liposome-encapsulated daunorubicin-cytarabine IV on Days 1, 3 and 5. Gemtuzumab or midostaurin are added to 7 + 3 as per SoC and Intensive Consolidation for patients who go into remission: cytarabine BID on Days 1, 3 and 5 repeated every 4 weeks for 2-4 courses and patients who received the liposome-encapsulated regimen receive liposome-encapsulated daunorubicin-cytarabine on Days 1 and 3 and repeated every 5-8 weeks for 2 courses in the absence of disease progression or unacceptable toxicity. OR Low-Intensity induction: ventoclax + azaciditine or decitabine or other SoC low -intensity therapy such as azacitidine or decitabine alone in combination with midostaurin	**Primary:** CR and mortality; **Secondary:** CR and mortality in subsets (intensive and non-intensive), baseline functional status, symptom burden, mortality at 90 days, QoL (EORTC QLQ-C30), and neurocognitive status by MOCA randomized, parallel-group, interventional trial

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
		or low-dose cytarabine in combination with glasdegib Comparator(s): NA	

AE = adverse event; AML = acute myeloid leukemia; BID = twice daily; BM = bone marrow; CMML = chronic myelomonocytic leukemia; CR = complete response; CRc = cytogenetic complete response; CRi = complete response with incomplete blood count recovery; CRm = molecular complete response; DB = double blind; DC = discontinuation; DOR = duration of response; ECOG = European Cooperative Oncology Group; EFS = event-free survival; ELN = European LeukemiaNet; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HSCT = hematopoietic stem cell transplantation ; IWG = International Working Group; IV = intravenous; MDASI = MD Anderson Symptom Inventory; MDS = myelodysplastic syndrome; MOCA = Montreal Cognitive Assessment; MRD = minimal residual disease; NA = not applicable; OL = open-label; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PK=pharmacokinetic; PR = partial response; PRi = partial response with incomplete blood count recovery; PS = performance score; Pts = patients; QD = once daily; QoL = quality of life; RFS = relapse-free survival; SD=stable disease; SoC = standard of care; TTR = time to response; WHO = World Health Organization

7 Supplemental Questions

The following supplemental question was identified during development of the review protocol as relevant to the CADTH review of glasdegib + LDAC, for the treatment of newly diagnosed and previously untreated AML in adult patients, who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy:

- Summary and critical appraisal of sponsor-submitted indirect treatment comparisons (ITCs) comparing glasdegib + LDAC to azacitidine in AML patients who are ineligible for intensive chemotherapy.
- Summary and critical appraisal of a published ITC comparing glasdegib + LDAC to azacitidine and to decitabine in adult patients with previously untreated AML.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary and critical appraisal of sponsor-submitted ITCs comparing glasdegib + LDAC to azacitidine in AML patients who are ineligible for intensive chemotherapy.

7.1.1 Objective

The objective of this section is to summarize and critically appraise the methods and findings of the sponsor-submitted ITCs comparing glasdegib + LDAC to azacitidine in AML patients who are ineligible for intensive chemotherapy.

7.1.2 Findings

Methods

Systematic review

The primary objective of the sponsor submitted ITCs was to estimate the relative treatment effect of glasdegib + LDAC versus AZA for AML patients who are ineligible for intensive chemotherapy, using the Bucher NMA methodology as the base case, as well as an anchored STC approach as a sensitivity analysis to adjust for differences in the baseline patient characteristics between trials. The ITCs were based on a systematic literature review (SLR) performed to identify studies comparing glasdegib + LDAC to azacitidine or decitabine. MEDLINE (including MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations), EMBASE, and the Cochrane collaboration were searched for RCTs published from 2000 using the OVID platform, with an initial search in December 2016 and the most recent search performed in June 2020. The following conference abstracts were searched from January 2016 to June 2020: European Society for Medical Oncology, American Society of Haematology, and American Society of Clinical Oncology. Published guidelines and recommendations for HCC from the following sources were also consulted: British Committee for Standards in Haematology, Cancer Care Ontario, European LeukemiaNet, European Society for Medical Oncology, National Cancer Institute, and National Cancer Comprehensive Network. Additionally, FDA/EMA Prescribing information were reviewed and information from RCTs was considered in absence of published evidence and the ClinicalTrials.gov website was searched to retrieve a list of ongoing trials in AML.

Articles that met the eligibility criteria described in Table 35 were considered for inclusion in the SLR. Titles and abstracts of all literature identified by the search were screened for eligibility, followed by full-text article screening. All screening was performed by two independent reviewers, and a third reviewer was consulted to resolve discrepancies if necessary.

Table 35: Inclusion Criteria for the Systematic Literature Review

Criteria	Inclusion Criteria	Exclusion Criteria
Population	• Adults (≥18 years) • Newly diagnosed with AML or high risk MDS • Not eligible for intensive chemotherapy	• Non-human • Refractory / relapsed AML • AML treated with intensive chemotherapy
Interventions and Comparators	• Glasdegib • Azacitidine • Decitabine • Low dose cytarabine • Hydroxycarbamide • 6-mercaptopurine • Etoposide • Best supportive care	• Studies not including any therapies of interest • Stem cell transplantation studies • Surgery studies • Radiotherapy studies • Different dose or schedule comparison study
Outcomes	• OS • DFS • EFS • DOR • Rate of completed response • Duration of treatment • Adverse events: serious, leading to discontinuation • Duration of adverse events • Treatment Interruptions or modifications due to adverse events • Discontinuation • HRQoL	• Studies not including at least one of the outcomes listed in the Inclusion Criteria • Studies with failed outcomes
Study Design	• RCTs • Systematic reviews and meta-analysis (to be used for checking only)	• Non-human/pre-clinical studies • Reviews/Editorials • Non-randomized and single arm studies • Notes/Comments/Letters • Retrospective studies • Observational studies • Uncontrolled studies • Phase I trials • Studies with fewer than 10 patients per arm • Case series • Case reports
Restrictions	• Published in the English or German language • Year limitation: 2000-current	• Published in a non-English, non-German language

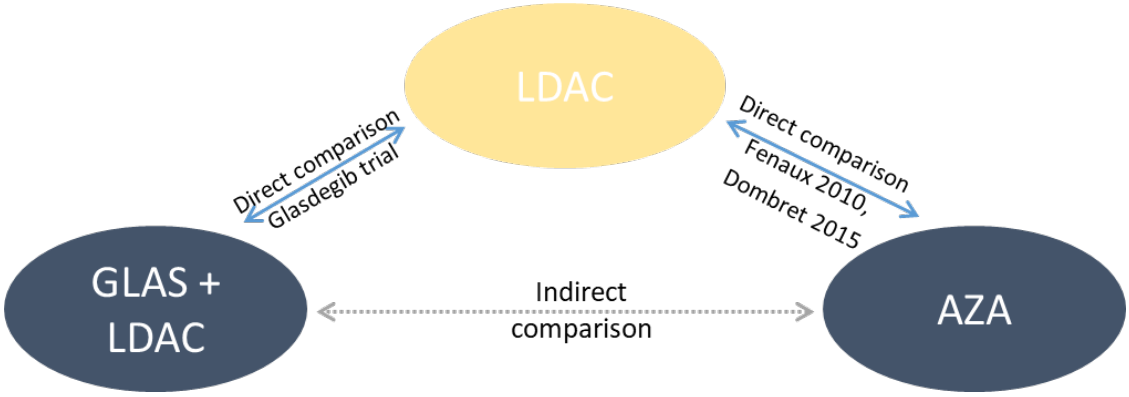
AE = adverse events; AML = acute myeloid leukemia; DFS = disease-free survival; DOR = duration of response; EFS = event-free survival; HRQoL = health-related quality of life; MDS = myelodysplastic syndrome; OS = overall survival; RCT = randomized controlled trial.

Indirect Treatment Comparisons

For inclusion in the ITCs, studies identified from the SLR were limited to glasdegib and azacitidine, the population was limited to studies or subgroups involving patients with AML, and the outcome of interest was limited to OS. No rationale was provided as to why the analyses were limited to these interventions and outcomes.

Separate ITCs were conducted for each of the identified studies by bone marrow blast (BMB) counts. The subgroups were selected as a post-hoc decision based on the patient populations reported in the azacitidine trials.[37] The results of the SLR are further described below, but briefly, three trials met the inclusion criteria for the ITCs: one trial of glasdegib (BRIGHT AML 1003) and two trials of azacitidine which both reported data by BMB counts (Fenaux et al., 2010:[15] 20-30%; Dombret et al. 2015:[16] >30%). Individual patient data (IPD) were available for the glasdegib trial only, while the two azacitidine trials provided aggregate level data. An overview of the evidence network for the comparisons, which used LDAC as the common comparator is displayed in Figure 10.

Figure 10: Overview of the Evidence Network



AZA = azacitidine; GLAS = glasdegib; LDAC = low-dose cytarabine.

In order to perform the ITCs, two methodologies were used: 1) a base case using the Bucher method, and 2) sensitivity analyses using simulated treatment comparisons (STC). Simulated treatment comparison was selected over matching adjusted indirect treatment comparison (MAIC) as the methodology for the adjusted ITC given the limited sample sizes of the included studies and the ability of STC to retain the full dataset as opposed to MAIC which would reduce the effective sample size.

The Bucher method was conducted as the base case analysis using a frequentist NMAs using Cox regression models. Published HRs from the two azacitidine trials were used and calculated HRs from the BMB count subgroups of the glasdegib trial were used to compare OS using the netmeta statistical software in the R package.

The STCs were performed as sensitivity analyses to adjust for imbalances in baseline characteristics between the trials. For the STC, guidance outlined by the National Institute for Health and Care Excellence Decision Support Unit (NICE DSU)[5] was followed. Baseline characteristics that were common to the index and comparator trial were identified (see Table 37 and Table 38 for variables assessed for each subgroup), and those that appeared to be imbalanced were assessed statistically as potential effect modifiers (further described below in the Results section). As well, baseline characteristics used as the stratification factors in the glasdegib trial were also regarded as effect modifiers in the STC analysis. To determine if any of the common baseline characteristics were effect modifiers, a Cox regression analyses were performed with models that included treatment, one of the commonly reported baseline characteristics, and an interaction term between treatment and the baseline characteristic that was being evaluated as a potential effect modifier. Baseline characteristics with statistically significant interactions suggested a statistical effect modification. Given the small sample size in the glasdegib trial (n=30 for 20-30% BMB subgroup and n=80 for >30% BMB subgroup), a P-value of 0.2 was used as the threshold for statistical significance for the interaction term. The remaining common baseline characteristics that were not identified as effect modifiers were then considered as potential prognostic variables, and ones that could improve the model fit (i.e. by lowering the Akaike information criterion (AIC)/ Bayesian information criterion (BIC)) were included in the final model.

The following parametric distributions were considered: exponential, Weibull, Gompertz, log-logistic, lognormal, and generalized gamma. The best fitting distribution was selection based on the model fit statistics (AIC/BIC) and on visual inspection. The final model with the selected distribution was used to provide the adjusted HRs for glasdegib + LDAC versus LDAC after correcting the imbalances in the selected baseline characteristics between the trials. A Bucher ITC was then conducted using the STC adjusted HR of glasdegib + LDAC versus LDAC and the reported HR of azacitidine versus LDAC.

There was a difference noted in the proportion of high-risk cytogenetics between the treatment arms in the Fenaux et al. trial (analyses for 20-30% BMB); therefore two STC scenarios were conducted: Scenario 1 which corrected the imbalances in baseline effect modifiers over the trials, and Scenario 2 which also attempted to correct for the imbalances in baseline effect modifiers both over the trials and across the treatment arms of the trials. These two sensitivity analyses were also conducted for the analyses with the Dombret et. al trial (analyses for the >30% subgroup). In Scenario 1, the mean % of patients with poor cytogenetics in azacitidine

was subtracted from the STC regression model. In Scenario 2, the mean % of patients with poor cytogenetics in the azacitidine group of the azacitidine trial was subtracted from the STC regression model for patients receiving glasdegib + LDAC (of the glasdegib trial), and the mean % of patients with poor cytogenetics in the LDAC group of the azacitidine trial was subtracted from the STC regression model for patients receiving LDAC (of the glasdegib trial).

Results

Systematic review

The SLR identified 2814 citations based on the database, of which 1414 were selected for abstract review and then 99 were selected for full text review. From these, 26 records representing 22 original studies were selected for data extraction. Three studies met inclusion criteria for the ITC. The Fenaux et. al 2010 trial represented a subset of patients from the full trial (NCT00071799). Data from the one publication (Cortes et. al 2016) was not included as the publication was associated with the current submission under review, for which IPD data was available. The Clinical Study Report (CSR) of the BRIGHT AML 1003 trial reported outcomes with 80% CIs, however 95% CIs were calculated from the IPD and used throughout the ITC analyses. Details of the included trials is displayed in Table 36.

Table 36: Population Descriptions of Included Publications

Study	Interventions	Trial Design	Trial Inclusion Criteria	Population included in ITC
BRIGHT AML 1003 (Cortes et. al, 2016)	GLAS+LDAC LDAC	Phase II, international, multicenter, randomized, controlled, open-label.	age ≥75 years ECOG PS 0 to 2 Serum creatinine >1.3 mg/dL Severe cardiac disease (LVEF <45%)	Previously untreated AML patients who are unfit for intensive chemotherapy
Fenaux et. al 2010	AZA LDAC	Phase III, international, multicenter, randomized, controlled, parallel-group trial	age ≥ 18 years ECOG PS 0 to 2 estimated life expectancy ≥ 3 months	The subgroup of AML patients met WHO criteria with ≥ 20% BM or peripheral blasts based on central BM review
Dombret et. al 2015	AZA LDAC	Phase III, international, multicenter, randomized, controlled, open-label, parallel-group trial.	age ≥ 65 years newly diagnosed and histologically confirmed de novo or secondary AML >30% BM blasts ineligible for HSCT intermediate- or poor-risk cytogenetics ECOG PS 0 to 2 WBC ≤15 X 3 10^9/L	Older patients with newly diagnosed AML with >30% blasts

AML = Acute myeloid leukaemia; AZA = azacitidine; BM = bone marrow; ECOG PS = Eastern Cooperative Oncology Group performance status; GLAS = glasdegib; HSCT = Hematopoietic stem cell transplantation; LDAC = Low-dose cytarabine; MDS = Myelodysplastic syndrome; WHO = World Health Organization.

Data Sources: Sponsor Submitted ITC Report, Sponsor Submitted SLR Report, Dombret et. al 2015,[16] Fenaux et. al 2010,[15] BRIGHT AML1003

Determination of inputs for the STC

a) 20-30% BMB subgroup

Baseline characteristics that were reported in both the glasdegib trial and Fenaux et al. trial are displayed in Table 37. BMB was excluded as a potential variable as the analyses were already a subgroup by BMB, and the median BMB between the trials was similar. While transfusion dependence was reported as a characteristic, it was excluded as a potential variable due to difference in the definition between the trials. Imbalances were found between the median age, gender (% male), and cytogenetic risk (% poor cytogenetics) and therefore these were further investigated as potential effect modifiers. None of the interaction terms with the investigated characteristics were significant (the interaction with age was not tested as only seven patients had age < 70, which had all been treated with glasdegib). As the variable for poor cytogenetic risk was included as a stratification variable in the BRIGHT AML

trial, it was included in the model even though the p-value of the interaction was non-significant (p = 0.27) Therefore, the base case model included treatment, poor cytogenetics and an interaction term between poor cytogenetics and treatment as covariates.

Table 37: Variables available for inclusion: 20-30% BMB subgroup

Variable	Glasdegib Trial (20-30% BMB)		AZA trial (20-30% BMB)		Effect Modifier Assessment			
	glasdegib + LDAC (n=21)	LDAC (n=9)	AZA (n=14)	LDAC (n=20)	Covariate interpretation	P-value of the interaction	Stratification factor in BRIGHT AML 1003?	Inclusion in model?
Age (median), years	74	74	69	71	age70=1 if age<70	n/a[b]	No	No
Male, %	71.43	66.67	92.9	75	binary variable	0.47	No	No
ECOG 0-1, %	100.0	100.0	100.0	100.0[a]	n/a	n/a	n/a	n/a
Poor cytogenetics, %	33.33	66.67	35.7	5	binary variable	0.27	Yes	Yes

AZA = azacitidine; BMB = bone marrow blasts; ECOG = Eastern Cooperative Oncology Group; LDAC = low-dose cytarabine; n/a = not applicable.
Notes:

[a] After excluding 1 patient with a missing ECOG score.
[b] Among 30 patients with 20-30% BMB, there were 7 patients with age 70=1. All the 7 patients were treated with glasdegib. No patient with age<70 was treated with LDAC. Therefore, the interaction term was omitted in the regression.

Data Source: Sponsor Submitted ITC Report

The remaining common baseline characteristics were then tested as prognostic variables to determine whether they could improve the model fit. The addition of any of the remaining variables did not improve the base case model, and therefore the base case model was selected for the analysis. The Weibull distribution was then selected as the best fitting model based on fit statistics and visual inspection.

b) >30% BMB subgroup

Baselines characteristics that were reported in both the glasdegib trial and Dombret et al. trial are displayed in Table 38. Imbalances were found between all the baseline characteristics (except for median age), and therefore these were all further investigated as potential effect modifiers. The interaction terms with the investigated characteristics were significant for de novo AML % (p-value = 0.05), median BMB (p-value = 0.17), median ANC * 10^9/L (p-value = 0.20). As the variable for poor cytogenetic risk was included as a stratification variable in the BRIGHT AML trial, it was included in the model even though the p-value of the interaction was non-significant (p = 0.99).Therefore, the base case model included treatment, de novo AML, BMB count, ANC, poor cytogenetics, and the interaction terms of these variables and treatment as covariates.

Table 38: Variables available for inclusion: >30% BMB subgroup

Variable	Glasdegib Trial (>30% BMB)		AZA trial (>30% BMB)		Effect Modifier Assessment			
	glasdegib + LDAC (n=53)	LDAC (n=27)	AZA (n=241)	LDAC (n=158)	Covariate tested (interpretation)	P-value of the interaction	Stratification factor in BRIGHT AML 1003?	Inclusion in model?
Age (median), years	77	76	75	75	n/a	n/a	n/a	n/a
Male, %	77.36	55.56	57.7	59.5	binary variable	0.27	No	No
De novo AML	58.49	51.85	79.7	85.4	binary variable	0.05	No	**Yes**
BMB (median)	0.58	0.60	0.70	0.74	BM72=1 if BM<0.72[a]	0.17	No	**Yes**
ECOG 0-1, %	49.06	55.56	77.2	77.9	binary variable	0.33	No	No
Poor cytogenetics, %	41.51	33.33	35.3	34.2	binary variable	0.99	Yes	**Yes**
WBC * 10^9/L (median)	2.2	4.2	3.1	2.3	WBC28=1 if WBC<2.8[a]	0.45	No	No
ANC * 10^9/L (median)	0.3	0.8	0.3	0.3	ANC03=1 if ANC<0.3[a]	0.20	No	**Yes**
Hgb * g/dL (median)	8.9	9.3	9.5	9.3	HGB94=1 if hgb<9.4[a]	0.62	No	No
Platelets * 10^9/L (median)	47	30	52	54	Platelet53=1 if platelet<53[a]	0.40	No	No

AML = acute myeloid leukaemia; ANC = absolute neutrophil count; AZA = azacitidine; BMB = bone marrow blasts; ECOG = Eastern Cooperative Oncology Group; dL = decilitre; Hgb = haemoglobin; LDAC = low-dose cytarabine; n/a = not applicable; WBC - white blood cell.
Notes:
[a] The weighted mean of the AZA trial.

Data Source: Sponsor Submitted ITC Report

The remaining variables were then tested as prognostic variables to determine whether they could improve the model fit. The addition of any of the remaining variables did not improve the base case model (the addition of HGB94 led to an AIC decrease and BIC increase, which the report authors regarded as minor), and therefore the base case model was selected for the analysis. The exponential distribution was then selected as the best fitting model based on fit statistics and visual inspection.

ITC Results

The HR inputs for the analyses and the corresponding HR results of the analyses are presented in Table 39.

Base case analyses (Bucher NMA): In the 20-30% BMB subgroup, the results demonstrated no statistically significant difference in OS between glasdegib + LDAC and azacitidine (HR, 95% CI: 0.46, 0.10 to 2.14). Similarly, no statistically significant difference for OS was observed in the 30% BMB subgroup (HR, 95% CI: 0.69, 0.39 to 1.20).

Sensitivity analyses (STC): For the 20-30% BMB subgroup, none of the resulting HRs suggested a statistically significant difference between the treatments on OS. For the >30% BMB subgroup, results from the STC adjusted by trial demonstrated a statistically significant difference in favour of glasdegib + LDAC (HR, 95% CI: 0.48, 0.23 to 0.97) as did the STC adjusted by arm (HR, 95% CI: 0.48, 0.24 to 1.00). The results of these STC analyses were just at the point of statistical significance (i.e. the upper bound of the CI interval was near or at 1.00).

Table 39: ITC results

ITC Method	20-30% BMB Subgroup			>30% BMB Subgroup		
	Glasdegib + LDAC versus LDAC (inputs) HR (95% CI)	AZA versus LDAC (inputs) HR (95% CI)	Glasdegib + LDAC versus AZA (outputs) HR (95% CI)	Glasdegib + LDAC versus LDAC (inputs) HR (95% CI)	AZA versus LDAC (inputs) HR (95% CI)	Glasdegib + LDAC versus AZA (outputs) HR (95% CI)
Bucher NMA	0.17 (0.06 to 0.48)	0.37 (0.12 to 1.13)	0.46 (0.10 to 2.14)	0.62 (0.38 to 1.02)	0.90 (0.70 to 1.16)	0.69 (0.39 to 1.20)
STC (adjusted by trial)	0.11 (0.03 to 0.41)	0.37 (0.12 to 1.13)	0.31 (0.06 to 1.69)	0.42 (0.22 to 0.84)	0.90 (0.70 to 1.16)	**0.48 (0.23 to 0.97)**
STC (adjusted by arm)	0.14 (0.03 to 0.53)	0.37 (0.12 to 1.13)	0.36 (0.06 to 2.15)	0.42 (0.22 to 0.86)	0.90 (0.70 to 1.16)	**0.48 (0.24 to 1.00)**

AZA = azacitidine; BMB = bone marrow blasts; CI = confidence interval; HR = hazards ratio; ITC = indirect treatment comparison; LDAC = low-dose cytarabine; NMA = network meta-analysis; STC = simulated treatment comparisons.

Data Source: Sponsor Submitted ITC Report

Critical Appraisal

The sponsor submitted ITCs were critically appraised according to recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons and Network Meta-Analyses for the Bucher analyses and the NICE DSU Population-Adjusted TSD for the STC analyses.

SLR:
The ITCs were based on a SLR that identified studies according to prespecified inclusion criteria. The literature search appeared comprehensive. The search was last updated in June of 2020, and therefore the most recent published literature was likely included. Additionally, there was no list of studies excluded at the full-text stage provided, and therefore it was not possible to assess whether potentially eligible studies may have been excluded. The report did however include a list of studies that were included in the SLR but then excluded from the ITC, along with the justification for exclusion. No quality appraisal or risk of bias assessments of the included studies was provided, and therefore it is not clear how the quality/risk of bias may have affected the results or interpretation of the individual included trials.

An inclusion criterion of the SLR was a patient population that was not eligible for intensive chemotherapy. While the BRIGHT AML 1003 trial specified that patients must be ineligible for intensive chemotherapy, it was not clear how this inclusion criterion was described for the purpose of the ITCs, and whether the ineligibility for intensive chemotherapy was similarly described in the other included trials.

*Bucher methodology (details of the quality appraisal are provi*ded in *Table 40*):
The trials included in the ITCs formed a connected network which was anchored on LDAC. Some limitations of the ITC methodology should be considered. Limited details were provided for the actual between treatment comparison methodology performed in the Bucher analyses.

Several sources of clinical heterogeneity were noted, and some potential effect modifiers and prognostic factors were identified prior to comparing the studies. The analyses were conducted for two subgroups based on the BMB counts (20-30% BMB and >30% BMB), which would have reduced the heterogeneity in this factor. However, it should be noted that in the azacitidine arm of the Fenaux et. al trial (the trial which provided data for the 20-30% BMB count analyses), the range for BMB count was stated as being 20-34%,[15] which exceeded the 30% cut-off. The small sample size available for this subgroup also resulted in a large amount of uncertainty with wide confidence intervals.

In both the Fenaux et. al trial and the Dombret et. al trial, patients were randomly assigned to azacitidine or to one of three conventional care regimens (CCR).[15] The CCR, which could be best supportive care, LDAC, or intensive chemotherapy, was

selected by investigators prior to randomization based on several clinical risk factors. Therefore, the comparator arm in both azacitidine trials was not solely LDAC, and the analyses used in this ITC represent a subset of patients in the comparator arm. Furthermore, while the patients were randomly assigned in the trial to either azacitidine or to CCR, the treatment in the CCR arm was not randomly assigned, potentially leading to imbalances when a subset (i.e. LDAC receiving patients only) are analyzed. In the Dombret et. al trial, randomization was stratified by the preselected CCR, however this stratification did not appear to have been performed in the Fenaux et. al trial. Within-study randomization may not have been preserved due to the analysis of subsets of the trials (including the glasdegib trial), resulting in imbalances in baseline characteristics between treatment arms of each trial.

STCs:

Overall, the methodology for the STCs was described thoroughly. The report provided details on the methodology used to identify and balance variables using the STC. The report authors did consider several models for estimating the comparative effectiveness of the trials after adjustment with STC. Models with the incorporation of several potential prognostic factors and various distributions were considered. The AIC and BIC of each of the models was reported, and the rationale for the model selection was appropriate.

Several limitations of the STCs were identified. As previously noted, within-study randomization may not have been preserved due to the analysis of subsets of the trials which violates an assumption necessary for the STC analysis. Additionally, although the report stated that the baseline factors identified for STC adjustments were determined according to guidelines form the NICE DSU, several methodological concerns were noted. While they selected variables that were imbalanced, which is appropriate for STC, they used internal data to statistically identify effect modifiers, which is inconsistent with the recommendations. Specifically, NICE recommends using external quantitative evidence, expert opinion, or systematic review to identify effect modification. Additionally, given the small sample sizes the interaction terms would likely have limited statistical power. The small sample sizes/subgroups also likely led to the large imbalances of baseline characteristics identified.

The report stated that imbalances in baseline characteristics between the trials were corrected using STC estimated HRs. Factors such as the trial design (e.g. open-label or double-blind), phase of the trial (i.e. BRIGHT AML 1003 as a phase II trial and both azacitidine trials as phase III trials), inclusion/exclusion criteria (e.g. age cut-offs for inclusion and length of life expectancy), and differences in the definition of some characteristics (i.e. transfusion dependence) can not be adjusted for using STC. These characteristics, other potentially relevant characteristics which were not identified, and characteristics that were only reported in one of the trials, could still have remained unbalanced in the STC analyses. The report did not state whether clinical experts were consulted to identify any other potential effect modifiers and prognostic factors or to establish whether the variables that were included were clinically plausible. No information was provided on the treatment exposure of patients in any of the trials. Additionally, the length of follow-up was not reported (however this may be a minor concern due to the short survival in this group of patients).

Generalizability:

Overall, several factors limit the generalizability of the results to the Canadian context. The reimbursement request for this submission is for patients who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy. The analyses presented for the ITCs were not specifically for patients who are age ≥75 years, and it was unclear how the specification for ineligible to receive intensive induction chemotherapy was defined and matched between the trials. The treatment analyzed as the comparator (azacitidine) is the approved treatment in Canada for these patients, and therefore the comparisons are relevant. The analyses were performed by BMB subgroups, and no comparisons for the overall population were provided. The NMA did not consider decitabine, which has been investigated in this patient group, however this treatment is not currently approved for use in Canada in the target population. Outcomes related to other relevant efficacy outcomes (e.g. PFS and response rates), safety, and HRQoL were not included in the analyses, and therefore no conclusions can be drawn comparing the treatment for these outcomes. Additionally, no conclusions can be made for other relevant subgroups identified previously by the CGP of this review (i.e. cytogenetic subtype and FLT3 mutations) as these subgroups were not analyzed in the ITC.

Table 40: Appraisal of the Bucher ITC using ISPOR criteria

ISPOR Questions	Details and Comments
1. Is the population relevant?	The reimbursement request for this submission is for patients who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy. The analyses presented for the ITCs were not specifically for patients who are age ≥75 years, and it was unclear how the specification for ineligible to receive intensive induction chemotherapy was defined and matched between the trials.
2. Are any critical interventions missing?	The ITC did not consider decitabine, which has been investigated in this patient group, however, this treatment is currently rarely used in Canada in patients with newly diagnosed AML as it is not Health Canada approved for this indication and not funded in most jurisdictions.
3. Are any relevant outcomes missing?	The report only included analyses for the efficacy outcome of overall survival. Outcomes related to other relevant efficacy outcomes, safety, and HRQoL were not included in the analyses.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Overall, several factors limit the generalizability of the results to the Canadian context. The reimbursement request for this submission is for patients who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy. The analyses presented for the ITCs were not specifically for patients who are age ≥75 years, and it was unclear how the specification for ineligible to receive intensive induction chemotherapy was defined and matched between the trials.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	The search was last updated in June of 2020, and therefore the most recent published literature was likely included. However, there was no list of studies excluded at the full-text stage provided, and therefore it was not possible to assess whether potentially eligible studies may have been excluded.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The included trials formed a connected network.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The quality of the publications and risk of bias were not reported.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Only studies reporting the outcome of OS were included. Therefore, there was selective reporting of outcomes, and the report did not provide a rationale for this selection.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Several sources of clinical heterogeneity were noted, and some potential effect modifiers and prognostic factors were identified prior to comparing the studies.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	While unadjusted Bucher ITC comparisons were performed, analyses were also performed that adjusted some of the imbalances in covariates using the STC methodology, allowing for comparability of selected baseline factors. However, factors such as the phase of the trial (i.e. BRIGHT AML 1003 as a phase II trial and both azacitidine trials as phase III trials), inclusion/exclusion criteria, and differences in the definition of some characteristics (i.e. transfusion dependence) can not be adjusted for using STC. These characteristics, other potentially unidentified relevant characteristics, and characteristics that were only reported in one of the trials could still have remained unbalanced in the STC analyses. Furthermore, the report did not state whether clinical

ISPOR Questions	Details and Comments
	experts were consulted to identify any other potential effect modifiers and prognostic factors.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Subgroups from the trials were included from the trials, and it did not appear that methods were used to preserve within-study randomization
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	There were no closed loops in the network. Consistency could not be assessed.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	There were no closed loops in the network. Consistency could not be assessed.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	The authors performed separate analyses based on BMB count which minimized heterogeneity for this characteristic. While analyses were also performed that adjusted some of the imbalances in covariates using the STC methodology, the analyses by BMB subgroup violates assumptions of STC (within-study randomization).
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Not applicable.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	The authors performed separate analyses based on BMB count which minimized heterogeneity for this characteristic. While analyses were also performed that adjusted some of the imbalances in covariates using the STC methodology, the analyses by BMB subgroup violates assumptions of STC (within-study randomization).
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Graphical representation of the networks and the number of trials per arm were provided for both outcomes analyzed.
19. Are the individual study results reported?	Individual study results were reported.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	There were no closed loops and only indirect comparisons were possible in the analyses.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	All pairwise point estimates and CIs were provided.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Not applicable.
23. Is the impact of important patient characteristics on treatment effects reported?	Some potential treatment effect modifiers were identified prior to performing the analyses. STC methodology was performed and both adjusted and unadjusted results were included in the report. Therefore, the impact of these patient characteristics was demonstrated.
24. Are the conclusions fair and balanced?	The conclusions in the report did not reflect the lack of statistic significance demonstrated from the analyses and the high level of uncertainty reflected in the confidence intervals. While the HRs reported were in the direction of favouring glasdegib + LDAC, these results were not statistically significant, and the confidence intervals were large. Some limitations of the ITCs were recognized and reported.

ISPOR Questions	Details and Comments
25. Were there any potential conflicts of interest?	No conflict of interest information was reported; however, the ITC/NMA was commissioned by the sponsor.
26. If yes, were steps taken to address these?	No

7.1.3 Summary

In the absence of direct evidence comparing glasdegib + LDAC to azacitidine in AML patients who are ineligible for intensive chemotherapy, the sponsor submitted ITCs to estimate the relative treatment effect in terms of OS between the two treatments. In order to perform the ITCs, two methodologies were used: 1) a base case using Bucher method, and 2) sensitivity analyses using STC. Two scenarios of the STC were conducted: Scenario 1 adjusted for differences between trials while Scenario 2 adjusted for differences between trials and arms within trials. Separate analyses were conducted based on two subgroups of patients: 1) patients with a BMB count of 20-30%, and 2) patients with a BMB count of >30%. Two trials provided data for the azacitidine arm of the comparisons, one to each of the subgroups. The BRIGHT AML 1003 provided data for the glasdegib + LDAC arm.

Results of the base case analyses demonstrated no statistically significant difference and wide confidence intervals for the HRs of glasdegib + LDAC compared to azacitidine for both BMB subgroup. For the sensitivity analyses using STC, results for the 20-30% subgroup showed no statistically significant differences in any of the analyses between glasdegib + LDAC and azacitidine. Results for the >30% subgroup sensitivity analyses demonstrated a statistically significant difference in favour of glasdegib + LDAC for both scenarios, however the CIs were wide, with the upper bound of the CI interval was near or at 1.00.

The analyses presented for the ITCs were not specifically for patients who are age ≥75 years, and it was unclear how the specification for ineligible to receive intensive induction chemotherapy was defined and matched between the trials. The treatment analyzed as the comparator (azacitidine) is the approved treatment in Canada for these patients, and therefore the comparisons are relevant. The analyses were performed by BMB subgroups, and no comparisons for the overall population were provided. Outcomes related to other relevant efficacy outcomes (e.g. PFS and response rates), safety, and HRQoL were not analyzed, and therefore no conclusions can be drawn comparing the treatment for these outcomes.

Overall, the base case analyses demonstrated no difference between treatments. Although a small difference was noted in the STC adjusted analyses for the 20-30% BMB subgroup, these analyses were sensitivity analyses. The key limitations to the STCs were the violation of the assumptions of within-study randomization, and the potential for characteristics that could not be adjusted for, other potentially relevant characteristics which were not identified, and characteristics that were only reported in one of the trials could still have remained unbalanced in the STC analyses. The report did not state whether clinical experts were consulted to identify any other potential effect modifiers and prognostic factors. Given the serious limitations identified and the high level of uncertainty reflected in the CIs, results of the analyses should be interpreted with extreme caution.

7.2 Summary and critical appraisal of published ITC comparing glasdegib + LDAC to azacitidine and to decitabine in adult patients with previously untreated AML.

7.2.1 Objective

The objective of this section is to summarize and critically appraise the methods and findings of a published ITC comparing glasdegib + LDAC to azacitidine and to decitabine in adult patients with previously untreated AML.

7.2.2 Findings

Methods

Systematic review

The ITCs were based on a SLR which identified studies comparing glasdegib + LDAC to azacitidine or decitabine (among other comparators). MEDLINE (including MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations), EMBASE, and the Cochrane collaboration were searched for articles published from 2000 using the OVID platform. The inclusion criteria for the SLR were identical to those from the sponsor-submitted ITC. No further details for screening methodology were provided.

Indirect Treatment Comparisons

For inclusion in the ITCs, studies identified from the SLR were limited to published trials of glasdegib, azacitidine, or decitabine, the population was limited to a patient population with previously untreated high-risk AML, and the outcome of interest was limited to OS. The rationale given in the publication for evaluating only OS was that this was a key relevant patient outcome and it was the primary endpoint in the included trials. To be included in the analyses, trials must have had sufficient reporting on patient eligibility and AML disease characteristics across studies and to be able to inform of potential prognostic factors and effect modifiers. No further details were provided as to what constituted 'sufficient reporting'.

In addition to the trial provided for the submission under review of glasdegib + LDAC (BRIGHT AML 1003), two studies met inclusion criteria for the STCs: 1) Dombret et al. 2015, which compared azacitidine to LDAC, and 2) Kantarjian et al. 2012, which compared decitabine to LDAC. LDAC was determined as the common comparator between the glasdegib + LDAC trial and the other two treatments (azacitidine or decitabine). These trials are further described under *Results*.

When possible, the authors extracted data from subgroups of the included studies that were relevant to the ITC, however only aggregate data for a wider population was available in some cases, as described next. While BRIGHT AML 1003 included patients with AML and patients with MDS, the IPD data used in the ITCs were restricted to those of the AML patients. Dombret et al. 2015 had multiple comparator arms, and the available data for baseline characteristics included patients receiving best supportive care, LDAC or intensive chemotherapy (i.e. the characteristics were not just for patients who received LDAC). The published OS HRs from this trial were however for the comparison of patients in the azacitidine arm to the subgroup of patients who received LDAC. Kantarjian et al. 2012 also had multiple comparator arms, however, baseline characteristics were presented for the decitabine and LDAC arms. The published OS HRs from this trial compared decitabine to LDAC receiving patients pooled with patients who received best supportive care (i.e. the OS HR was not just for patients who received LDAC).

Separate comparisons were conducted for each of the treatments compared to glasdegib + LDAC (i.e., glasdegib + LDAC versus azacitidine; glasdegib + LDAC versus decitabine). Unadjusted ITCs and STCs using IPD from the glasdegib trial were performed. The analyses were performed based on guidance from the NICE DSU TSD 18.[5] The analyses were conducted in Microsoft Excel 2016 and Stata. The approach to conduct the analyses used the steps detailed next and displayed in Table 41.

Criterion 1 - Variable selection. Four criteria had to be met for a baseline variable to be used in the model for covariate adjustment: 1) availability in studies being compared, 2) demonstration of an imbalance between the studies at baseline, 3) potentially being an effect modifier, and, 4) potentially having an impact on the results for estimating the OS HR for glasdegib + LDAC versus LDAC. Reduced stepwise models were also explored that retained variables which met at least one of the following stepwise criteria: 1) the presence of a statistically significant covariate from both the full and reduced models, 2) identification as an effect modifier in at least one of the trials, or 3) having been used as a stratification factor in one of the three trials. The stepwise variables could be different for the analyses comparing glasdegib + LDAC versus azacitidine and the analyses comparing glasdegib + LDAC versus decitabine.

Criterion 2 - Model exploration and comparison of functional forms. Both the full models and the reduced models were explored to determine the optimal regression model using Cox regression estimation to compare with parametric modelling of proportional hazards (PHs) and non-proportional accelerated failure time (AFT) models. The appropriateness of using a Cox regression model was determined based on visual inspection of the log-cumulative hazards plots and using the Schoenfeld global test of proportionality. Unadjusted Cox regression models contained only treatment as a covariate. Model fit statistics were compared between all the resulting models in order to inform the selection of the optimal stepwise and full adjustment models. To estimate the

HRs at the median OS in the AFT models, the hazard rates within each trial arm were constructed from the difference in the natural log of the survival between each month. These hazard rates were then summed and divided between trial arms to estimate the HR for each month.

Criterion 3 and 4 – Visual inspection and prediction validation. Continuous survival outcomes were then estimated with each of the models and compared to the original trial KM estimates. Post-regression predictions were performed to estimate the average survival, median OS, and extended OS for both treatment arms. OS HRs estimated all the models were also compared. The survival curves were visually compared to the original trial KM curves, and each model's HR was plotted over 20 months (with the rationale being that this was the maximum duration of survival in the LDAC treatment group of the glasdegib + LDAC trial).

Survival curve graphs for each of the treatment arms of the glasdegib trial were modeled using two approaches (with the rationale provided for conducting the second approach as being to improve the visual fit of the parametric survival curves to the KM curves) : 1) parametric STC models were generated using the IPD from the BLAST AML 1003 trial of the AML patients, and 2) parametric STC models were generated using the IPD from the BLAST AML 1003 trial which was propensity weighted for trial-level cytogenetic risk (a stratification factor during randomization in the trial). No further details were provided for the methodology for the propensity scoring.

Table 41: Multi-stepped Criteria to Conduct and Evaluate Simulated Treatment Comparisons

Criteria	Parameters	Interpretation
Criterion 1– Variable Selection	Effect modification testing with Cox regression Step-wise process for variable selection	Models to adjust for variables that demonstrate potential effect modification or are prognostic factors
Criterion 2 – Comparison of Functional Forms	Proportional hazards assumption testing Statistical fit measures AIC/BIC, Chi2, log-likelihood and treatment effect (e.g. hazard ratio)	Proportionality testing to determine if AFT or proportional hazards models should be used
Criterion 3 – Visual Inspection	Comparison of survival curves from AFT and PH models to the Kaplan-Meier graphs Graphing hazard ratios over time for the functional forms, Kaplan-Meier and Cox models	Comparability of the survival curves and hazard ratios over time to the original Kaplan-Meier and Cox model graphs
Criterion 4 – Prediction validation	Survival time (mean, median), survival difference between arms, predicted hazard ratios Comparing the covariate-adjusted estimates	Comparability of the covariate-adjusted predictions to the original trial population using the different functional forms

AFT, Accelerated Failure Time; AIC, Akaike's information criterion; BIC, Bayesian information criterion; Chi2, Chi-Squared

Data Source: Reproduced from: Tremblay, G. Westley, T. et al. Overall survival of glasdegib in combination with low-dose cytarabine, azacitidine, and decitabine among adult patients with previously untreated AML: comparative effectiveness using simulated treatment comparisons. *Clinicoeconomics and Outcomes Research*. 2019:11 pages: 551-565; Figure 2, p. 555. Creative Commons License CC BY-NC 3.0: https://creativecommons.org/licenses/by-nc/3.0/

Once a model was selected based on the previously described steps, simulated estimates were obtained for the covariate-adjusted survival curves, survival times, and OS HRs, which were then compared to the original IPD estimates from the BLAST AML 1003 trial. The ITCs were then performed using the Bucher method with 95% CIs. First ITCs were performed using unadjusted OS HRs

from the publications. Second, OS HRs generated with Cox multivariate regression model generated using IPD for glasdegib + LDAC versus LDAC were compared to published OS HRs from the other treatments. Third, OS HRs generated using the optimal full and stepwise models for glasdegib + LDAC versus LDAC were compared (individually) to published OS HRs from the other treatments.

Results

Systematic review

The SLR identified 2841 citations based on the database, of which 1414 were selected for abstract review and then 99 were selected for full text review. From these, 24 records representing 21 original studies were selected for data extraction. One trial (Fenaux et. al 2010) was excluded as there was a lack of reporting on mutual patient baseline characteristics for the AML subgroup, the trial population was significantly younger, and the AML subgroup was small (n = 34). Another trial (Seymour et. al 2010) was excluded as the reported results were for a combined population of MDS and CMML patients. Three studies met final inclusion criteria. Details of the included trials is displayed in Table 42.

Table 42: Population Descriptions of Included Publications

Study	Interventions	Trial Design	Trial Inclusion Criteria	Population included in ITC
BRIGHT AML 1003 (Cortes et. al, 2016)	GLAS+LDAC LDAC	Phase II, international, multicenter, randomized, controlled, open-label.	age ≥75 years ECOG PS 0-2 Serum creatinine >1.3 mg/dL Severe cardiac disease (LVEF <45%)	Previously untreated AML patients who are unfit for intensive chemotherapy
Dombret et. al 2015	AZA LDAC	Phase III, international, multicenter, randomized, controlled, open-label, parallel-group trial.	age ≥ 65 years newly diagnosed and histologically confirmed de novo or secondary AML >30% BM blasts ineligible for HSCT intermediate- or poor-risk cytogenetics ECOG PS 0 to 2 WBC ≤15 X 3 10^9/L	Older patients with newly diagnosed AML with >30% blasts
Kantarjian et. al 2015	AZA LDAC	Phase III, international, multicenter, randomized, controlled, open-label trial.	Age ≥65 poor- or intermediate-risk cytogenetics, ECOG PS of 0 to 2, WBC 40,000/mm, bilirubin 1.5xULN, AST or ALT 2.5xULN, CrCl 40 mL/min, and life expectancy 12 weeks	Previously untreated, newly diagnosed de novo or secondary AML (>=20% blasts)

AML = Acute myeloid leukemia; AZA = azacitidine; BM = bone marrow; ECOG PS = Eastern Cooperative Oncology Group performance status; GLAS = glasdegib; HSCT = Hematopoietic stem cell transplantation; LDAC = Low-dose cytarabine; MDS = Myelodysplastic syndrome; WHO = World Health Organization.
Data Sources: Tremblay et al. 2019,[69] Dombret et. al 2015,[16] Kantarjian et. al 2015[70]

Baseline characteristics from the three included trials are summarized in Table 43. Median age ranged from 73 to 77 years, percentage of male patients ranged from 59.5% to 75.6%, percentage of patients with de novo AML ranged from 47.4% to 85.4%, percentage of patients with secondary AML ranged from 14.6% to 51.3%, median haemoglobin ranged from 9.1 to 9.5 g/dL, percentage of patients with an ECOG PS of 0-1 ranged from 47.4% to 77.9%, percentage of patients with BMB >50% ranged from 39.8% to 81.0%, and percentage of patients with poor cytogenetic risk ranged from 32.1% to 42.1%. Differences were noted in the dosing for LDAC between trials. In the BRIGHT AML 1003 trial (Cortes 2016; glasdegib + LDAC trial), LDAC was given subcutaneously at 20 mg twice daily on days 1 to 10 of each 28-day cycle. In the Dombret et. al trial (trial of azacitidine), LDAC was given at 20 mg twice daily for 10 days per 28-day cycle for ≥4 cycles (route of administration not provided). In the Kanrajian et. al trial (trial of decitabine), LDAC was given subcutaneously at 20 mg/m^2 once daily for 10 consecutive days every four weeks.

Table 43: Baseline Characteristics of Selected Studies

Reference	Intervention	N	Median Age	Male, n (%)	De novo, n (%)/Secondary, n (%)	Median hemoglobin, g/dL (range)	ECOG PS 0/1, n (%)	Bone Marrow Blasts >50% n (%)	Cytogenetic risk (poor), n (%)
Cortes 2016 (Individual Patient Data)[8]	GLAS + LDAC: GLAS 100 mg orally, once daily + LDAC 20 mg SC twice daily, days 1–10 of each 28-day cycle	78	77	69 (75.6)	38 (48.7)/40 (51.3)	9.1 (6.4–14.0)	37 (47.4)	31 (39.8)	25 (32.1)
	LDAC: 20 mg SC twice daily, days 1–10 of each 28-day cycle	38	76	23 (60.5)	18 (47.4)/20 (52.6)	9.3 (6.0–14.6)	20 (52.6)	18 (47.4)	16 (42.1)
Dombret 2015[5]	AZA: 75 mg/m^2 SC per day for 7 consecutive days per 28-day cycle for ≥6 cycles	241	75	139 (57.7)	192 (79.7)/49 (20.3)	9.5 (5.0–13.4)	186 (77.2)	173 (71.8)	85 (35.3)
	LDAC: 20 mg twice daily for 10 days per 28-day cycle for ≥4 cycles	158	75	94 (59.5)	135 (85.4)/23 (14.6)	9.3 (5.6–14.4)	123 (77.9)	128 (81.0)	54 (34.2)
Kantarjian 2012[6]	DEC: 20 mg/m^2 once daily for 5 consecutive days every 4 weeks	242	73	137 (56.6)	155 (64.0)/87 (36)	9.3 (5.2–15.0)	184 (76.0)	105 (43.4)	87 (36.1)
	LDAC: LDAC 20 mg/m^2 SC once daily for 10 consecutive days every 4 weeks	215	73	131 (60.9)	140 (65.1)/73 (34.0)	9.4 (5.0–12.6)	164 (76.3)	90 (41.9)	79 (36.9)

Abbreviations: AZA, azacitidine; DEC, decitabine; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GLAS, glasdegib; LDAC, low-dose cytarabine; SC, subcutaneously.

Data Source: Reproduced from: Tremblay, G. Westley, T. et al. Overall survival of glasdegib in combination with low-dose cytarabine, azacitidine, and decitabine among adult patients with previously untreated AML: comparative effectiveness using simulated treatment comparisons. *Clinicoeconomics and Outcomes Research*. 2019:11 pages: 551-565; Table 1, p. 554. Creative Commons License CC BY-NC 3.0: https://creativecommons.org/licenses/by-nc/3.0/

Model Selection Results

The baseline characteristics included in the full covariate models for the glasdegib + LDAC versus azacitidine comparisons were age, sex, AML type (de novo or secondary), proportion of bone marrow blasts >50%, ECOG PS, cytogenetic risk, and hemoglobin level. All stepwise models included age, sex, and poor cytogenetic risk (Table 44 for provided rationale).

Table 44: Variable Selection for Glasdegib + LDAC versus Azacitidine

Full Model Results			Statistical Evidence	Justification for Inclusion in Stepwise Models
Included Baseline Characteristics	GLAS + LDAC (IPD)	AZA (Dombret 2015)	GLAS + LDAC versus LDAC IPD Cox *p*-value	
Mean age at baseline	75.9	75.0	0.54	Included due to significant treatment effect for subgroup age <75 years but not age ≥75 years in Dombret 2015
Sex, male	70.7%	58.4%	0.41	Included due to significant treatment effect for females but not males in Dombret 2015, prognostic in the literature, large imbalance between trials
AML type, de novo	48.3%	82.0%	0.52	Excluded for lack of significance in GLAS + LDAC versus LDAC IPD regression and no subgroup analysis in Dombret 2015
Bone marrow blasts >50%	47.9%	75.4%	0.52	Excluded for lack of significance in GLAS + LDAC versus LDAC IPD regression and lack of significance in Dombret 2015
ECOG PS 0 or 1 versus 2	49.1%	77.4%	0.91	Excluded for lack of significance in GLAS + LDAC versus LDAC IPD regression and no subgroup analysis in Dombret 2015
Cytogenetic risk: poor versus good/ intermediate	39.6%	34.8%	-	Included due to being a stratification factor in both trial protocols
Median baseline hemoglobin level (g/dL)	9.2	9.4	0.59	Excluded for lack of significance in GLAS + LDAC versus LDAC IPD regression and no subgroup analysis in Dombret 2015

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; DSU, Decision Support Unit; ECOG PS, Eastern Cooperative Oncology Group performance status; GLAS, glasdegib; IPD, individual patient-level data; LDAC, low-dose cytarabine.

Data Source: Reproduced from: Tremblay, G. Westley, T. et al. Overall survival of glasdegib in combination with low-dose cytarabine, azacitidine, and decitabine among adult patients with previously untreated AML: comparative effectiveness using simulated treatment comparisons. *Clinicoeconomics and Outcomes Research.* 2019:11 pages: 551-565; Table 2, p. 557. Creative Commons License CC BY-NC 3.0: https://creativecommons.org/licenses/by-nc/3.0/

The baseline characteristics included in the full covariate models for the glasdegib + LDAC versus decitabine comparisons were age, sex, AML type (de novo or secondary), proportion of bone marrow blasts >50%, ECOG PS, cytogenetic risk, and hemoglobin level. All stepwise models included age, AML type, proportion of bone marrow blasts <50%, ECOG PS, and cytogenetic risk (Table 45 for provided rationale).

Table 45: Variable Selection for Glasdegib + LDAC versus Decitabine

Full Model Results			Statistical Evidence	Justification for Inclusion in Stepwise Models
Included Baseline Characteristics	GLAS + LDAC (IPD)	DEC (Kantarjian 2012)	GLAS IPD Cox *p*-value	
Mean age at baseline	75.9	73.0	0.54	Included due to significant treatment effect for only subgroup age ≥ 75 years in Kantarjian 2012, potentially prognostic as advised by clinical expertise
Sex, male	70.7%	58.%	0.41	Excluded for lack of subgroup analysis in Kantarjian 2012
AML type, de novo	48.3%	64.6%	0.52	Significant treatment effect for de novo but not secondary AML in Kantarjian 2012, large imbalance between trials
Bone marrow blasts >50%	47.9%	42.7%	0.52	Included due to significant treatment effect for subgroup >30% in Kantarjian 2012, large imbalance between trials
ECOG PS 0 or 1 versus 2	49.1%	76.2%	0.91	Included due to significant treatment effect for subgroup ECOG =2 in Kantarjian 2012, large imbalance between trials
Cytogenetic risk: poor versus good/ intermediate	39.6%	36.3%	-	Included due to being a stratification factor in both trial protocols
Median hemoglobin at baseline	9.2	9.3	0.59	Excluded for lack of significance in GLAS + LDAC versus LDAC IPD regression and no subgroup analysis in Kantarjian 2012

Abbreviations: AML, acute myeloid leukemia; DEC, decitabine; DSU, Decision Support Unit; ECOG PS, Eastern Cooperative Oncology Group performance status; GLAS, glasdegib; LDAC, low-dose cytarabine.

Data Source: Reproduced from: Tremblay, G. Westley, T. et al. Overall survival of glasdegib in combination with low-dose cytarabine, azacitidine, and decitabine among adult patients with previously untreated AML: comparative effectiveness using simulated treatment comparisons. *Clinicoeconomics and Outcomes Research*. 2019:11 pages: 551-565; Table 5, p. 563. Creative Commons License CC BY-NC 3.0: https://creativecommons.org/licenses/by-nc/3.0/

For both the glasdegib+ LDAC versus azacitidine analysis and the glasdegib + LDAC versus decitabine analysis, no statistically significant deviation from the PH assumption was demonstrated for either the full or stepwise Cox models. The AIC and BICs were similar for the full and stepwise Cox models. Significance for at least one of the included variables in the OS HR regressions were demonstrated from the Chi-square tests for the log likelihood for all full and stepwise model parametrizations. Final models were selected based on the previously described methodology. For the DSU guided approach, the exponential model was selected for both the stepwise and full covariate modelling. For the weighted-STC approach using propensity-scores, the Weibull distribution was selected for stepwise modelling and the exponential model was selected for full covariate modelling. All models demonstrated a survival advantage for glasdegib + LDAC compared to LDAC.

ITC Results

All models selected to compare glasdegib + LDAC versus azacitidine demonstrated a statistically significant OS improvement for glasdegib + LDAC (HR range: 0.412 to 0.514). Similarly, all models selected to compare glasdegib + LDAC versus decitabine demonstrated a statistically significant OS improvement for glasdegib + LDAC (HR range: 0.482 to 0.565).

Critical Appraisal of ITCs

The published ITCs were critically appraised according to recommendations of the ISPOR Task Force on ITCs and NMAs and the NICE DSU Population-Adjusted TSD. Details of the appraisal are provided in Table 46.

The ITCs were based on a SLR that identified studies according to prespecified inclusion criteria. The literature search appeared comprehensive. It was unclear when the most recent search was performed. Additionally, there was no list of studies excluded at the

full-text stage provided, and therefore it was not possible to assess whether potentially eligible studies may have been excluded. Although some rationale was provided, it was not clear why the Fenaux et. al trial, which was included in the Section 7.1 analyses, did not meet the inclusion criteria for these analyses. No quality appraisal or risk of bias assessments of the included studies was provided, and therefore it is not clear how the quality/risk of bias may have affected the results.

An inclusion criterion of the SLR was a patient population that was not eligible for intensive chemotherapy. While the BRIGHT AML 1003 trial specified that patients must be ineligible for intensive chemotherapy, it was not clear how this inclusion criterion was described, and whether the ineligibility for intensive chemotherapy was similarly described in the other included trials.

The trials included in the ITCs formed a connected network which was anchored on LDAC only indirect evidence was available. The authors did consider several models for estimating the comparative effectiveness of the trials. Models with the incorporation of several potential prognostic factors and various distributions were considered, however, no a priori approach was selected. A base case was not stated, and it was not described whether additional modeling approaches would be considered as the sensitivity analyses. The approaches taken appear to be data driven and extend beyond what is recommended by the NICE document for STC (e.g. they have used other approaches such as the propensity-score weighting in addition to the NICE recommended approach).

Limitations to the methodology were identified. As subgroups of the trials were extracted for inclusion in the analyses, within-study randomization may not have been preserved which violates an assumption necessary for the STC analysis. Furthermore, while the report provided methodology used to identify and balance variables using the STC, it was not clear how a variable was identified as a potential effect modifier, as having the potential to impact the results for estimating the OS HR for glasdegib + LDAC versus LDAC, or for being considered as a statistically significant covariate from both the full and reduced models. Therefore, the appropriateness of the covariate selection is questionable. Additionally, although the report stated that the baseline factors identified for STC adjustments were determined according to guidelines form the NICE DSU, several methodological concerns were noted. While they selected variables that were imbalanced, which is appropriate for STC, they used internal data to statistically identify effect modifiers, which is inconsistent with the recommendations. Specifically, NICE recommends using external quantitative evidence, expert opinion, or systematic review to identify effect modification

Several sources of clinical heterogeneity were noted, and some potential effect modifiers and prognostic factors were identified prior to comparing the studies. While unadjusted comparisons were performed, analyses were also performed that adjusted some of the imbalances in covariates using the STC methodology as well as propensity-score weighting, allowing for comparability of these baseline factors. However, it appeared as though the decision to perform propensity-score weighting was a post-hoc decision based on the lack of visual fit of the non-weighted models. Additionally, the three treatments were not compared in a network, and therefore the comparative effectiveness of all three treatments remains unknown. Different baseline characteristics were available for adjustments between the glasdegib + LDAC trial versus the azacitidine trial and the glasdegib + LDAC trial and the decitabine trial, and only pairwise comparisons were performed.

The report stated that imbalances in baseline characteristics between the trials were corrected using STC estimated HRs. However, factors such as the phase of the trial (i.e. BRIGHT AML 1003 as a phase II trial and the azacitidine and decitabine trials as phase III trials), inclusion/exclusion criteria, and differences in LDAC dosing can not be adjusted for using STC. These characteristics, other potentially relevant characteristics which were not identified, and characteristics that were only reported in one of the trials, could still have remained unbalanced in the adjusted analyses. The report did not state whether clinical experts were consulted to identify any other potential effect modifiers and prognostic factors or to establish whether the variables that were included were clinically plausible. No information was provided on the treatment exposure of patients in any of the trials. Additionally, the length of follow-up was not reported (however this may be a minor concern due to the short survival in this group of patients). The publication also noted that summary statistics for some of the covariates in the Kantarjian and Dombret trials were only available as medians, and therefore a weighted mean between the comparator trial arms (divided by total patients) had to be estimated. The accuracy of the calculated mean for the subset of patients included in these analyses compared to the actual mean is unknown. The small sample sizes/subgroups also likely led to the large imbalances of baseline characteristics identified and contributed to the large amount of uncertainty and wide confidence intervals in the resulting HRs.

In both the Dombret et. al trial and the Kantarjian et. al trial, patients were randomly assigned to investigational treatment (azacitidine or decitabine, respectively) or to a CCR. The regimen, which could be best supportive care, LDAC, or intensive chemotherapy (for

Dombret et. al only), was selected by investigators/patients prior to randomization based on several clinical risk factors. Therefore, the comparator arm in both these trials was not solely LDAC, and the analyses used in this ITC represent a subset of patients in the comparator arm (LDAC subset; n = 158 from Dombret et. al, n = 215 from Kantarjian et al.). Furthermore, while the patients were randomly assigned in the trial to either investigational treatment or to a CCR, the treatment in the CCR arm was not randomly assigned, potentially leading to imbalances when a subset (i.e. LDAC receiving patients only) are analyzed. In the Dombret et. al trial, randomization was stratified by the preselected CCR, however this stratification did not appear to have been performed in the Kantarjian et. al trial. Within-study randomization may not have been preserved due to the analysis of subsets of the trials (including the glasdegib trial), resulting in imbalances in baseline characteristics between treatment arms of each trial.

Overall, several factors limit the generalizability of the results to the Canadian context. The reimbursement request for this submission is for patients who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy. The analyses presented for the ITCs were not specifically for patients who are age ≥75 years, and it was unclear how the specification for ineligible to receive intensive induction chemotherapy was defined and matched between the trials. One of the treatments analyzed as the comparator (azacitidine) is the approved treatment in Canada for these patients, and therefore the comparisons are relevant. The ITCs also included decitabine, which has been investigated in this patient group, however this treatment is currently rarely used in Canada in patients with newly diagnosed AML as it is not Health Canada approved for this indication and not funded in most jurisdictions. Outcomes related to other relevant efficacy outcomes (e.g. PFS and response rates), safety, and HRQoL were not included in the analyses and therefore no conclusions can be drawn comparing the treatment for these outcomes. Additionally, no conclusions can be made for other relevant subgroups identified previously by the CGP of this submission (i.e. cytogenetic subtype and FLT3 mutations) as these subgroups were not analyzed in the ITC.

Table 46: Appraisal of the ITCs using ISPOR criteria

ISPOR Questions	Details and Comments
1. Is the population relevant?	The reimbursement request for this submission is for patients who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy. The analyses presented for the ITCs were not specifically for patients who are age ≥75 years, and it was unclear how the specification for ineligible to receive intensive induction chemotherapy was defined and matched between the trials.
2. Are any critical interventions missing?	One of the treatments analyzed as the comparator (azacitidine) is the approved treatment in Canada for these patients, and therefore the comparisons are relevant. The ITCs also included decitabine, which has been investigated in this patient group, however this treatment is currently rarely used in Canada in patients with newly diagnosed AML as it is not Health Canada approved for this indication and not funded in most jurisdictions.
3. Are any relevant outcomes missing?	The report only included analyses for the efficacy outcome of OS. Outcomes related to other relevant efficacy outcomes, safety, and HRQoL were not included in the analyses.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Overall, several factors limit the generalizability of the results to the Canadian context. The reimbursement request for this submission is for patients who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy. The analyses presented for the ITCs were not specifically for patients who are age ≥75 years, and it was unclear how the specification for ineligible to receive intensive induction chemotherapy was defined and matched between the trials.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	The ITCs were based on a SLR that identified studies according to prespecified inclusion criteria. The literature search appeared comprehensive. It was unclear when the most recent search was performed. Additionally, there was no list of studies excluded at the full-text stage provided, and therefore it was not possible to assess whether potentially eligible studies may have been excluded. Although some rationale was provided, it was not clear why the Fenaux et. al trial, which was included in the Section 7.1 analyses, did not meet the inclusion criteria for these analyses.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The included trials formed a connected network; however, only indirect evidence was available.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The quality of the publications and risk of bias were not reported.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Only studies reporting the outcome of OS were included. Therefore, there was selective reporting of outcomes, and the report did not provide a rationale for this selection.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Several sources of clinical heterogeneity were noted, and some potential effect modifiers and prognostic factors were identified prior to comparing the studies.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	While unadjusted comparisons were performed, analyses were also performed that adjusted some of the imbalances in covariates using the STC methodology as well as propensity-score weighting, allowing for comparability of these baseline factors. However, factors such as the phase of the trial (i.e. BRIGHT AML 1003 as a phase II trial and the azacitidine and glasdegib trials as phase III trials), inclusion/exclusion criteria, and LDAC dosing can not be adjusted for using STC. These characteristics, other potentially unidentified relevant characteristics, and characteristics that were only reported in one of the trials

ISPOR Questions	Details and Comments
	could still have remained unbalanced in the adjusted analyses. Furthermore, the report did not state whether clinical experts were consulted to identify any other potential effect modifiers and prognostic factors.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Subgroups from the trials were included from the trials, and it did not appear that methods were used to preserve within-study randomization.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	There were no closed loops in the network. Consistency could not be assessed.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	There were no closed loops in the network. Consistency could not be assessed.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	While unadjusted comparisons were performed, analyses were also performed that adjusted some of the imbalances in covariates using the STC methodology and propensity score-weighting, allowing for comparability of these baseline factors. However, the use of subgroups from trials violates the within-study randomization assumption of STC.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Not applicable.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	While unadjusted comparisons were performed, analyses were also performed that adjusted some of the imbalances in covariates using the STC methodology propensity score-weighting, allowing for comparability of these baseline factors.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Graphical representation of the networks and the number of trials per arm was provided.
19. Are the individual study results reported?	Individual study results were reported.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	There were no closed loops and only indirect comparisons were possible in the analyses.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	All pairwise point estimates and CIs were provided.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Not applicable.
23. Is the impact of important patient characteristics on treatment effects reported?	Some potential treatment effect modifiers were identified prior to performing the analyses. STC methodology was performed and both adjusted and unadjusted results were included in the report. Therefore, the impact of these patient characteristics was demonstrated.
24. Are the conclusions fair and balanced?	The conclusions in the report did not reflect the high level of uncertainty reflected in the confidence intervals and did not comment on the use of multiple

ISPOR Questions	Details and Comments
	models, some of which were not following the DSU guidance. Limitations to the modeling were stated.
25. Were there any potential conflicts of interest?	Several authors from the publication declared being employees or receiving payments from Pfizer, the sponsor of glasdegib.
26. If yes, were steps taken to address these?	No

7.2.3 Summary

In the absence of direct evidence comparing glasdegib + LDAC to other relevant treatments in AML patients who are ineligible for intensive chemotherapy, a published ITC was identified which estimated the relative treatment effect for OS between glasdegib + LDAC and azacitidine and glasdegib + LDAC and decitabine. Several methods for modelling the data were investigated: unadjusted models, STC adjusted models, and propensity-score adjusted models. One trial each provided data for glasdegib + LDAC, azacitidine, and decitabine. Azacitidine and decitabine were each compared separately relative to glasdegib + LDAC.

Results for glasdegib + LDAC compared to azacitidine demonstrated a statistically significant improvement for the OS HR for glasdegib + LDAC for all the models used (HR range: 0.412 to 0.514). Similarly, results for glasdegib + LDAC compared to decitabine demonstrated a statistically significant improvement for the OS HR for glasdegib + LDAC for all the models used (HR range: 0.482 to 0.565). The small sample sizes/subgroups likely led to large imbalances of baseline characteristics identified and contributed to the large amount of uncertainty and wide confidence intervals in the resulting HRs.

The analyses presented for the ITCs were not specifically for patients who are age ≥75 years, and it was unclear how the specification for ineligible to receive intensive induction chemotherapy was defined and matched between the trials. One of the treatments analyzed as the comparator (azacitidine) is the approved treatment in Canada for these patients, and therefore the comparisons are relevant. The ITCs also included decitabine, which has been investigated in this patient group, however this treatment is currently rarely used in Canada in patients with newly diagnosed AML as it is not Health Canada approved for this indication and not funded in most jurisdictions. Outcomes related to other relevant efficacy outcomes (e.g. PFS and response rates), safety, and HRQoL were not analyzed, and therefore no conclusions can be drawn comparing the treatment for these outcomes.

The key limitations to the STCs were the violation of the assumptions of within-study randomization, and the potential for characteristics that could not be adjusted for, other potentially relevant characteristics which were not identified, and characteristics that were only reported in one of the trials could still have remained unbalanced in the STC analyses. The report did not state whether clinical experts were consulted to identify any other potential effect modifiers and prognostic factors. Given the serious limitations identified in STC methodology and the high level of uncertainty reflected in the CIs, results of the analyses should be interpreted with extreme caution.

8 Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Leukemia Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on glasdegib [Daurismo] in combination with low-dose cytarabine for acute myeloid leukemia. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials April 2020, Embase 1974 to 2020 May 20, Ovid

MEDLINE(R) ALL 1946 to May 20, 2020

#	Searches	Results
1	(Daurismo* or glasdegib* or PF-04449913 or PF04449913 or PF-4449913 or PF4449913 or TH2EV99S4Z or K67DMO5H9 or 4Y7R3PBO4V or 5H2T9QGD7G).ti,ab,ot,kf,kw,hw,rn,nm.	441
2	1 use cctr	56
3	1 use medall	61
4	limit 3 to english language	59
5	*glasdegib/	74
6	(Daurismo* or glasdegib* or PF-04449913 or PF04449913 or PF-4449913 or PF4449913).ti,ab,kw,dq.	289
7	5 or 6	290
8	7 use oemezd	174
9	limit 8 to english language	173
10	9 and conference abstract.pt.	73
11	limit 10 to yr="2015 -Current"	54
12	9 not conference abstract.pt.	100
13	2 or 4 or 12	215
14	remove duplicates from 13	155
15	11 or 14	209

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Results
#5	Search: **#3 AND #4** Filters: **English**	5
#4	Search: **publisher[sb]** Filters: **English**	394,109
#3	Search: **#1 OR #2** Filters: **English**	59
#2	Search: **Daurismo*[tiab] OR glasdegib*[tiab] OR PF-04449913[tiab] OR PF04449913[tiab] OR PF-4449913[tiab] OR PF4449913[tiab] OR TH2EV99S4Z[rn] OR K67DMO5H9[rn] OR 4Y7R3PBO4V[rn] OR 5H2T9QGD7G[rn]** Filters: **English**	58
#1	Search: **Glasdegib[supplementary concept]** Filters: **English**	22

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

The European Clinical Trial Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: Daurismo/glasdegib and acute myeloid leukemia (AML)

Select international agencies including:

US Food and Drug Administration (FDA)

https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Daurismo/glasdegib and acute myeloid leukemia (AML)

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Daurismo/glasdegib and acute myeloid leukemia (AML)–last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[71]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were daurismo (glasdegib).

No filters were applied to limit retrieval by study type. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of October 1, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[72] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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