CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Daunorubicin and cytarabine (Vyxeos)

Indication: Treatment of adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

Recommendation: Reimburse with Conditions

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CADTH

DAUNORUBICIN AND CYTARABINE (VYXEOS — JAZZ PHARMACEUTICALS CANADA INC.)

Therapeutic Area: Acute Myeloid Leukemia

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that liposomal daunorubicin and cytarabine should be reimbursed for the treatment of adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from one open-label, phase III, randomized controlled trial (RCT), (Study 301, N = 309) in adult patients (60 to 75 years of age) with newly diagnosed t-AML or AML-MRC demonstrated that liposomal daunorubicin and cytarabine was associated with a statistically significant and clinically meaningful greater overall survival (OS) (median, 9.56 months; 95% confidence interval [CI], 6.60 to 11.86) compared with the control group, which consisted of conventional cytarabine and daunorubicin (7+3) (median, 5.95 months; 95% CI, 4.99 to 7.75). Further, treatment with liposomal daunorubicin and cytarabine lowered the risk of death by 31% compared with the control group (hazard ratio [HR]= 0.69; 95% CI, 0.52 to 0.90; 1-sided *P* = 0.003). At a 5-year follow-up, 18% of patients who received liposomal daunorubicin and cytarabine were alive compared with 8% of those who received 7+3, with median overall survival of 9.33 months and 5.95 months in the liposomal daunorubicin and cytarabine treatment group, and the 7+3 treatment group, respectively. Liposomal daunorubicin and cytarabine was also associated with a statistically significant higher remission rate (complete remission [CR] or CR with incomplete neutrophil or platelet recovery [CRi]) compared to 7+3 treatment group (74 patients [47.7%] in the liposomal daunorubicin and cytarabine treatment group and 52 patients (33.3%) in the 7+3 treatment group achieved a CR or CRi; OR = 1.77; 95% CI, 1.11 to 2.81; 1-sided *P* = 0.008). Prolonging life was a need identified as important to patients, and pERC concluded that this need was met with liposomal daunorubicin and cytarabine treatment. Patients also valued an outpatient treatment option that is accessible and closer to their home; however, the induction cycles of liposomal daunorubicin and cytarabine are administered in an inpatient setting. Other needs identified by patients were either unmet by liposomal daunorubicin and cytarabine or the evidence was not available, which include maintaining health-related quality of life (HRQoL).

Liposomal daunorubicin and cytarabine costs $7,774 per vial, and each vial contains 44 mg of daunorubicin and 100 mg of cytarabine. The recommended dose of liposomal daunorubicin and cytarabine is 100 units/m^2 (equivalent to 44 mg/m^2 of daunorubicin and 100 mg/m^2 of cytarabine) of body surface area resulting in a 28-day cycle cost of $46,642 for first induction, $31,094 for a second induction, and $31,094 for each consolidation. Using the sponsor submitted price for liposomal daunorubicin and cytarabine and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for liposomal daunorubicin and cytarabine was $110,283 per quality-adjusted life-year (QALY) compared with 7+3. At this ICER, liposomal daunorubicin and cytarabine is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adults with newly diagnosed t-AML or AML-MRC acute myeloid leukemia. A reduction in price of at least 68% is required for liposomal daunorubicin and cytarabine to be considered cost-effective at a $50,000 per QALY threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)	Patients enrolled in Study 301 were adults with newly diagnosed t-AML or AML-MRC
2. Patients must be deemed fit for intensive chemotherapy by the treating physician.	The clinical experts noted that patients who are considered to be fit enough for induction with existing chemotherapy regimens (e.g., 7+3 or combination of fludarabine, high dose cytarabine, granulocyte-colony stimulating factor, and idarubicin combination regimen [FLAG-IDA]) would likely be considered to be adequately fit for liposomal daunorubicin and cytarabine.
Renewal	
1. Initial reimbursement of liposomal daunorubicin and cytarabine should be limited to 2 cycles of induction therapy.	Patients enrolled in Study 301 were eligible to receive up to 2 cycles of inductions and up to 2 cycles of consolidations of liposomal daunorubicin and cytarabine. The product monograph notes that treatment with liposomal daunorubicin and cytarabine should be continued as long as the patient continues to benefit or until disease progression up to a maximum of 2 induction courses and up to a maximum of 2 consolidation courses.
2. Patients who achieve complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CRi) during induction cycles are eligible for reimbursement of up to an additional 2 cycles of consolidation therapy with liposomal daunorubicin and cytarabine.	In Study 301, patients who achieved CR or CRi after one or two induction cycles were eligible to receive up to two cycles of consolidation therapy. The clinical experts noted that a CR or CRi is the prerequisite to move forward with further cycles of consolidation chemotherapy.
Prescribing	
1. The induction cycles of liposomal daunorubicin and cytarabine should be administered in an in-patient setting and supervised by a hematologist with expertise in managing patients with acute leukemia.	The clinical experts noted that administration of induction therapies, including liposomal daunorubicin and cytarabine, is conducted under in-patient settings with close monitoring by specialists during and after infusion. Support from transfusion specialists may be required depending on patient status post-induction. In Study 301, during induction, patients were admitted to a hospital, and liposomal daunorubicin and cytarabine was administered as an inpatient.
2. The consolidation cycles of liposomal daunorubicin and cytarabine can be administered in an out-patient setting.	The clinical experts noted that consolidation therapy may be administered in outpatient settings. However, this varied between practices across Canada, depending on local capacity. In Study 301, during consolidation, approximately half of the patients in the liposomal daunorubicin and cytarabine treatment group were discharged and received their consolidation treatment in an outpatient infusion clinic.
3. Liposomal daunorubicin and cytarabine should not be used in combination with other anti-cancer therapy.	There is no evidence to demonstrate a benefit of liposomal daunorubicin and cytarabine in combination with other anti-cancer therapy for the treatment of adults with newly diagnosed t-AML or AML-MRC

Reimbursement Condition	Reason
Pricing	
1. Reduction in price	The ICER for liposomal daunorubicin and cytarabine is $110,283 per QALY when compared with 7+3. A price reduction of at least 68% would be required for liposomal daunorubicin and cytarabine to be able to achieve an ICER of $50,000 per QALY compared to 7+3, though this is likely underestimated.

Discussion Points

- pERC discussed that in Canada, a proportion of adult patients with t-AML or AML-MRC may be treated with a combination of fludarabine, high dose cytarabine, granulocyte-colony stimulating factor, and idarubicin combination regimen (FLAG-IDA) as an induction option and that patients with FLT3 mutations may be treated with 7+3 and midostaurin. However, there is no direct or indirect evidence comparing liposomal daunorubicin and cytarabine with FLAG-IDA or 7+3 in combination with midostaurin.

- Given that Study 301 enrolled only patients who were 60 to 75 years of age, the committee discussed that there is uncertainty whether results are generalizable to younger or older patients who may be eligible for treatment with liposomal daunorubicin and cytarabine. However, the clinical experts noted that age in itself is not an appropriate threshold to determine which patients would be eligible for induction therapy with liposomal daunorubicin and cytarabine, and that a patient's fitness would be a more appropriate indicator.

- pERC discussed that patients must be deemed fit for intensive chemotherapy by the treating physician in order to be eligible to receive induction therapy with liposomal daunorubicin and cytarabine. The clinical experts noted that patients considered to be fit enough for induction with existing chemotherapy regimens (e.g., 7+3 or FLAG-IDA) would likely be adequately fit for liposomal daunorubicin and cytarabine. The clinical experts indicated that there is no universal definition of fitness; however, age, comorbidities, performance status, and organ dysfunction are associated with AML treatment determination.

- pERC discussed the number of induction and consolidation cycles that should be eligible for reimbursement. The clinical experts noted that in clinical practice, patients receive up to 2 cycles of induction and up to 2 cycles of consolidation chemotherapy, and that it is rare that patients would receive more than two cycles of consolidation.

- In Study 301, the number of induction and consolidation cycles patients received depended on response (CR or CRi), which was confirmed by bone marrow assessment done on day 14 after each induction cycle. pERC discussed that bone marrow assessment across Canada varies in this regard, such that many centres do not routinely do a day 14 bone marrow aspirate. The clinical experts' input to pERC noted that in clinical practice, assessment of CR occurs between 28 and 35 days post-induction and includes the assessment of bone marrow, extramedullary disease, and complete blood count.

- Patient groups' input to CADTH highlighted that patients need a treatment that would maintain their HRQoL. HRQoL was not measured in Study 301, therefore pERC was unable to draw any conclusions pertaining to the potential benefit of liposomal daunorubicin and cytarabine on HRQoL.

- The committee noted that a sizeable majority of predicted incremental clinical benefit (QALYs) were predicted to occur after patients had experienced relapse. While CADTH noted that this apparent bias is often seen in models of this type, pERC noted that the size of the implied benefit was larger than normal, and larger than the evidence from Study 301 supports. Neither pERC nor CADTH could estimate the extent to which this was due to model structure, an increase in survival for patients receiving transplant, or some other factor. Consequently, the ICER and the required price reduction are likely underestimated.

- The committee discussed the substantial difference in budget impact when considering the inclusion of the cost of liposomal daunorubicin and cytarabine when administered in the inpatient setting. CADTH's base case estimate for the budget impact assessment excluded costs of liposomal daunorubicin and cytarabine when administered on an inpatient basis; however, input from the provincial advisory group (PAG) indicated that if liposomal daunorubicin and cytarabine is listed, most jurisdictions are

likely to cover the costs of these drugs through their current cancer funding programs. A scenario analysis that is inclusive of in-patient costs estimates a three-year budget impact of $34,304,171.

- The sponsor's pharmacoeconomic model did not include FLAG-IDA as a comparator. Consequently, the cost-effectiveness of liposomal daunorubicin and cytarabine compared to FLAG-IDA is unknown.

Background

Liposomal daunorubicin and cytarabine has a Health Canada indication for the treatment of adults with newly diagnosed t-AML or AML-MRC. Liposomal daunorubicin and cytarabine is a combination of daunorubicin and cytarabine in a 1:5 molar ratio encapsulated in liposomes for intravenous administration. Cytarabine is a cytidine analog that interferes with DNA synthesis and daunorubicin is anthracycline antibiotic which intercalates between DNA base pairs and interferes with DNA repair. Liposomal daunorubicin and cytarabine is available as an intravenous infusion, with each vial contains 44 mg of daunorubicin and 100 mg of cytarabine. The Health Canada–approved dose for induction is daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 administered intravenously over 90 minutes on days 1, 3, and 5 as the first course of induction therapy, and on days 1 and 3 as subsequent course of induction therapy, if needed. For consolidation, the recommended dosing schedule of liposomal daunorubicin and cytarabine is daunorubicin 29 mg/m^2 and cytarabine 65 mg/m2 administered intravenously over 90 minutes on days 1 and 3 as subsequent courses of consolidation therapy, if needed.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of one phase III randomized controlled trial in patients who were 60 to 75 years of age with newly diagnosed t-AML or AML-MRC,
- Patients' perspectives gathered by one patient group, the Leukemia and Lymphoma Society of Canada (LLSC),
- Input from public drug plans and cancer agencies that participate in the CADTH review process,
- Three clinical specialists with expertise diagnosing and treating patients with t-AML or AML-MRC,
- Input from two clinician groups, including the Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-CCO's DAC) and The Canadian Leukemia Study Group (CLSG), and
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Patient input was provided by the Leukemia and Lymphoma Society of Canada (LLSC) through an English and French language online survey from December 7, 2020 through January 24, 2021. Patients were asked to describe their experiences with treatment for AML. In total, 29 individuals responded, all of whom identified as patients and all of whom live in Canada. No breakdown was provided on the proportions of patients with AML-MRC or t-AML.

Patients reported how AML symptoms varied from losing the ability to work, impacting social lives and relationships, fatigue, numbness and a large number of detrimental effects on their health. Many respondents indicated that they felt physically and socially isolated and those who had completed therapy identified a concern about relapse.

Patients listed physician recommendation as being the most important factor when deciding on new treatments which was followed by possible impact on disease, quality of life, closeness to home, and outpatient treatment.

In general, respondents would like new therapies that have fewer side effects, were more holistic, would help maintain their remission, were covered through drug plans, and were accessible closer to their home. Patients were also interested in having more information on emerging therapies and being able to access all possible treatments in the future.

Clinician input

Input from clinical experts consulted by CADTH

The clinical experts consulted by CADTH for this review described how patients in this population are high-risk individuals with high unmet needs. Existing induction and consolidation therapies were described by the experts as not meeting the needs of all patients, resulting in many individuals not achieving remission and thus ineligible for hematopoietic stem-cell transplantation (HSCT). The drug under review is intended to act at the same step of the clinical pathway for patients with AML-MRC or t-AML who are fit enough for induction therapy. Survival, as well as response to induction therapy, was highlighted as a key outcome of interest. Complete response or complete response with incomplete hematological remission are influential on decisions for subsequent HSCT, which reported by the experts to confer a survival benefit.

Clinician group input

Two clinician groups provided input to this review, the Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-CCO's DAC) and The Canadian Leukemia Study Group (CLSG). Broadly, there was good concordance between the clinical experts consulted by CADTH for this review and clinician group input regarding patient populations of interest, their unmet need, and the outcomes of importance in this population. The clinician groups identified that the proposed product would act in a similar role and replace existing 7+3 therapy.

Drug program input

The drug program had questions surrounding alternative therapies, as only evidence of liposomal daunorubicin and cytarabine relative to 7+3 was identified, whereas in practice FLAG-IDA is also utilized in Canadian settings. No data were identified, and clinical experts were uncertain as to the relative effects of liposomal daunorubicin and cytarabine versus FLAG-IDA. The Provincial Advisory Group (PAG) inquired about the efficacy of azacitidine ± venetoclax compared with liposomal daunorubicin and cytarabine. The clinical experts indicated that azacytidine ± venetoclax is reserved for patients who are not candidates for induction therapy, and patients who are treated with azacitidine ± venetoclax are different patient populations than those who are treated with 7 + 3, FLAG-IDA, or liposomal daunorubicin and cytarabine. The PAG also inquired about eligible population, the clinical experts indicated that the criteria used to enroll patients in Study 301 were representative of patients identified in practice, and that for patients with an ECOG of >2, if the ECOG status was assessed to be related to their AML status, patients would be considered for treatment in this context with an available induction regimen, patients younger than 60 would be considered for treatment with liposomal daunorubicin and cytarabine, while patients older than 75 would be considered if they were appropriately fit, although it was highlighted that this may not be common in practice. For patients with myeloproliferative neoplasms (MPN) or combined myelodysplastic disorder (MDS)/MPN, it was noted that these patients, with the exception of a small proportion of patients with CMMoL, were not included within Study 301 and therefore, it is uncertain how such patients would respond to liposomal daunorubicin and cytarabine. For patients with active CNS leukemia, it was noted that patients would most likely be considered for treatment with liposomal daunorubicin and cytarabine. For patients with favourable cytogenetics, patients would still be treated with 7+3 if they were candidates for induction therapy and would also be considered for treatment with liposomal daunorubicin and cytarabine. Some patients with favorable cytogenetics are treated with 7+3 for induction followed by high dose cytarabine with or without gemtuzumab. For patients being treated in combination with other therapies (e.g., midostaurin) it was highlighted that this could occur off-label. Gemtuzumab was not considered to be a likely candidate for combination therapy. The PAG also inquired whether liposomal daunorubicin and cytarabine be used off-label, for example, in patients with other AML subtypes and other lines of therapy. The clinical experts noted it was unlikely that liposomal daunorubicin and cytarabine would be utilized in other AML subtypes. Receiving liposomal daunorubicin and cytarabine in another line of therapy was considered to be very unlikely. The PAG inquired whether patients who are currently on 7+3 or FLAG-IDA be switched over to liposomal daunorubicin and cytarabine, the clinical experts noted that this switch is unlikely in the majority of cases. For a small number of patients this may be relevant during the window for which compassionate use ends and approval (if provided) is given. No specific cut-off point was identified.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

One study, Study 301, was identified and included in the review. Study 301 was a phase III randomized controlled, multicentre, open-label, therapy controlled clinical trial which recruited 309 patients across 39 centers, 4 of which were based in Canada. Patients included those with newly diagnosed t-AML or AML-MRC aged between 60 to 75 years. Patients were randomly assigned to either liposomal daunorubicin and cytarabine (N = 153) or 7+3 (N = 156).

The primary outcome was overall survival, and secondary end points included response, event-free survival (EFS), remission duration and proportions of patients achieving HSCT. Response was defined as patients who achieved a CR or CRi during the treatment phase, where CR was defined as bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 10^9/L (1000/µL); platelet count >100 x 10^9/L (100,000/µL); independence from red cell transfusions, and Cri was defined as all CR criteria except for residual neutropenia (<1.0 x 10^9/L [1000/µL]) or thrombocytopenia (<100 x 10^9/L [100,000/µL]). Event-free survival was defined as the time from study randomization to the date of induction treatment failure (persistent disease), relapse from CR or CRi or death from any cause, whichever came first. Remission duration was measured from the date of achievement of remission (CR or CRi) until the date of relapse or death from any cause. All outcomes which had formal statistical assessments were conducted utilizing a one-sided 0.025 hypothesis testing cut-off alpha value.

Patients within this study had a mean age of 67.7 years (SD = 4.14), were predominantly male (61%), and the most common AML subtype included was AML-MRC with prior hypomethylating agent exposure (34%). Seventy-two patients (50.3%) in the liposomal daunorubicin and cytarabine treatment group and 83 patients (56.8%) in the 7+3 treatment group had unfavourable cytogenetic risk, while 64 patients (44.8%) in the liposomal daunorubicin and cytarabine treatment group and 58 patients (39.7%) in the 7+3 treatment group had intermediate cytogenetic risk. The median duration of follow-up was similar between treatment arms with a median follow-up time of 20.5 months for patients treated with liposomal daunorubicin and cytarabine and a median follow-up time of 21.22 months for patients treated with 7+3.

Efficacy Results

The primary outcome, overall survival, was assessed in 153 patients who were randomized to liposomal daunorubicin and cytarabine treatment group and 156 patients who were randomized to 7+3 treatment group (ITT Population). The median overall survival in the liposomal daunorubicin and cytarabine treatment group was 9.56 months (95% confidence interval [CI], 6.60 to 11.86), and in the 7+3 treatment group, it was 5.95 months (95% CI, 4.99 to 7.75). In the 153 patients assigned to the liposomal daunorubicin and cytarabine treatment group, there were 104 events, and in the 156 patients assigned to the 7+3 treatment group, there were 132 events. The liposomal daunorubicin and cytarabine treatment group was associated with a statistically significant improvement in overall survival when compared to patients who received 7+3 (hazard ratio [HR] = 0.69; 95% CI, 0.52 to 0.90; 1-sided log-rank test P = 0.003). At a 5-year follow-up, 18% of patients who received liposomal daunorubicin and cytarabine were alive versus 8% who received 7+3, with median overall survival of 9.33 months and 5.95 months in the liposomal daunorubicin and cytarabine treatment group the 7+3 treatment group, respectively, resulting in a HR of 0.70 (0.55-0.91) in favour of liposomal daunorubicin and cytarabine treatment group.[7] However, results from the 5-year follow-up are considered descriptive and should be interpreted with caution.

The median EFS was higher in the liposomal daunorubicin and cytarabine treatment group (2.53 months, 95% CI, 2.07 to 4.99) than in the 7+3 treatment group (1.31 months, 95% CI, 1.08, 1.64), resulting in a statistically significant hazard ratio of 0.74 (95% CI, 0.58 to 0.96; 1-sided log-rank test P = 0.011).

For response rates, 73 (47.7%) patients in the liposomal daunorubicin and cytarabine treatment group achieved a CR or CRi, as opposed to 52 (33.3%) patients in the 7+3 treatment group. The liposomal daunorubicin and cytarabine treatment group was associated with a statistically significant higher response compared to the 7+3 treatment group (OR = 1.77; 95% CI, 1.11 to 2.81; 1-sided P = 0.008).

No statistically significant difference was observed in remission duration between patients in the liposomal daunorubicin and cytarabine treatment group compared with the 7+3 treatment group. The median remission duration in the liposomal daunorubicin and cytarabine treatment group was 6.93 months (95% CI, 4.60 to 9.23) compared to of 6.11 months (95% CI, 3.45 to 8.71) in the 7+3 treatment group (HR = 0.77; 95% CI, 0.47 to 1.26; 1-sided log-rank test P = 0.147).

The percentage of patients receiving an HSCT in the liposomal daunorubicin and cytarabine treatment group was 34%, as opposed to 25% in the 7+3 treatment group. No statistically significant difference was reported for the proportion of patients receiving HSCT when liposomal daunorubicin and cytarabine treatment group compared with the 7+3 treatment group (OR = 1.54, 95% CI, 0.92 to 2.56; 1-sided P = 0.049).

Health related quality of life was not assessed in Study 301.

Harms Results

All patients included in Study 301 experienced at least 1 adverse event (AE). Similarly, serious adverse events (SAEs) were comparatively common across the trial, with 59% of patients in the liposomal daunorubicin and cytarabine treatment group experiencing a SAE compared to 43% of patients in the 7+3 treatment group. The nature of SAEs were relatively consistent between treatment arms, although sepsis was noted at twice the frequency in the liposomal daunorubicin and cytarabine treatment group (7.8%) when compared to the 7+3 treatment group (3.3%).

Most harms of special interest were relatively evenly distributed between treatment arms, with the proportions of patients experiencing an event varying depending on the event of interest. For ICU admission, a greater proportion of patients who received 7+3 were admitted to ICU (25.2%) when compared to patients who received liposomal daunorubicin and cytarabine (18.3%). In contrast, the duration of ICU stay was longer for patients who received liposomal daunorubicin and cytarabine (mean ICU stay duration was 8.2 days, SD = 9.69) when compared to patients who received 7+3 (mean ICU stay duration was 6.9 days, SD = 4.85), although the median duration of ICU was the same (6 days) between treatment arms.

Critical Appraisal

A dynamic balancing randomization algorithm was used in Study 301 to ensure that the assignment of treatments is balanced across all the stratification factors. However, because it was an open-label trial, patients were aware of the treatment allocation following randomization. Therefore, the evaluation of adverse events may be biased by treatment knowledge.

Overall, no differences between treatment arms in Study 301 were noted with regards to drop-out rates. The statistical analyses identified were pre-specified and powered adequately. Many outcomes identified as being significant to patient and clinician groups were reported within the study, and outcomes utilized were similar to those used in other clinical trials and close to criteria routinely used in practice across Canada. The patient population recruited was considered to be representative of high-risk Canadian patients, and the associated response to conventional therapy (7+3) for efficacy and safety outcomes was noted by clinical experts to be similar to what is observed in practice. It is important to note that as the trial population only recruited patients who were 60 to 75 years of age, hence there is uncertainty whether results from Study 301 are generalizable for younger or older patients who may be eligible for treatment with liposomal daunorubicin and cytarabine.

An important limitation of these findings is the lack of health-related quality of life (HRQoL) assessment. This was noted to be an important outcome by the patient and clinician groups who provided input to CADTH on this submission; hence the effect of liposomal daunorubicin and cytarabine on HRQoL is uncertain. Similarly, measurable residual disease (MRD) was noted to be an informative measure in determining post-transplantation survival; however, MRD was not captured in Study 301. As such, assessment of comparative efficacy of liposomal daunorubicin and cytarabine relative to 7+3 is not possible for these outcomes.

Indirect Comparisons

No indirect comparison was performed for this review. A feasibility assessment was provided by the sponsor. Using a non-systematic literature review process, the sponsor did not identify any studies which would be appropriate to analyze using indirect treatment comparison methods. Studies varied with regard to patient inclusion and exclusion criteria, and treatments provided were non-overlapping. An important limitation of this feasibility assessment is the non-systematic nature of the evidence identification process,

which was not described in sufficient detail to formally assess. As such, there is uncertainty as to whether all appropriate evidence has been identified for indirect comparisons.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (initiated with a decision tree)
Target population	Adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
Treatment	Liposomal daunorubicin and cytarabine
Submitted drug price	Daunorubicin (44 mg/100mL) and cytarabine (100 mg/100mL) liposome: $77.74 per 100 mL vial
Cost per course	The recommended dose of liposomal daunorubicin and cytarabine is 100 units/m2 of body surface area resulting in a 28-day cycle cost of $46,642 for first induction, $31,094 for a second induction, and $31,094 for each consolidation.
Comparator	7+3 (conventional 7 days of cytarabine plus 3 days of daunorubicin)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	15 years
Key data source	Study 301
Submitted results	ICER = $85,832 per QALY (incremental costs: $76,418, incremental QALYs: 0.89)
Key limitations	• Relevant comparators including a combination of fludarabine, high dose cytarabine, granulocyte-colony stimulating factor (G-CSF), and idarubicin (FLAG-IDA), or 7+3 + midostaurin for patients with a FLT-3 mutation, were not included in the sponsor's model. The cost-effectiveness of liposomal daunorubicin and cytarabine relative to these comparators is unknown. • Comparative clinical effectiveness was subject to uncertainty from multiple sources. In addition to structural uncertainty contributed by the modeling approach used, the sponsor used parametric survival curves to extrapolate the trial data over the time horizon of the model using separate curves for liposomal daunorubicin and cytarabine and 7+3 for each clinical pathway (i.e., by response and transplant status). The use of multiple overall survival and event-free survival curves increased the overall uncertainty of the model. • The sponsor assumed a greater disutility from induction and consolidation with 7+3 compared with liposomal daunorubicin and cytarabine, and a post-transplant remission health state value that assumed no complications. These assumptions do not align with feedback from clinical experts consulted by CADTH for this review and may overestimate the incremental benefit of liposomal daunorubicin and cytarabine. • The sponsor assumed that 70% of patients receiving consolidation therapy with liposomal daunorubicin and cytarabine would receive it in an outpatient setting compared to 40% of patients receiving 7+3. This difference in outpatient consolidation is not expected to occur in clinical practice. • Literature-based estimates suggest mortality is higher for patients' post-transplant. The sponsor assumed that patients receiving HSCT would experience the same background mortality as that of the general population, which overestimates the benefit post-transplant. • The sponsor's model was based on the characteristics of the patient population included in Study 301 which included patients 60 to 75 years of age. The cost-effectiveness of liposomal daunorubicin and cytarabine in patients <60 years of age or >75 years of age who are otherwise eligible for treatment is unknown.
CADTH reanalysis results	• CADTH reanalysis included: alternate assumptions for the parametric OS curves used in the model; changes to the health state utility value for post-HSCT remission; changes to the disutility associated with an induction and consolidation cycle of liposomal daunorubicin and

Component	Description
	cytarabine; reduced the percentage of patients anticipated to receive outpatient consolidation for liposomal daunorubicin and cytarabine; and increased the risk of post-HSCT mortality. CADTH was unable to address uncertainty associated with the omission of relevant treatment comparators and the appropriateness of the modeled patient population (i.e., lack of inclusion of patients aged <60 years of age or >75 years). • In the sequential analysis, liposomal daunorubicin and cytarabine was associated with an ICER of $110,283 per QALY compared to 7+3 (incremental cost, $84,730; incremental QALYs, 0.77) • Liposomal daunorubicin and cytarabine had a 0.2% chance of being cost effective at a cost-effectiveness threshold of $50,000 per QALY. A price reduction of at least 68% is needed for liposomal daunorubicin and cytarabine to be cost-effective compared to 7+3 at a cost-effectiveness threshold of $50,000 per QALY. • Cost-effectiveness was particularly sensitive to the choice of parametric survival curves.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the use of Quebec drug prices for comparator agents, the exclusion of relevant comparators, underestimate of the incidence of AML in Canada, underestimate of the market share assumed for years 2 and 3, the inclusion of drug costs administered in hospital, and assuming different percentages of patients would receive outpatient consolidation therapy for liposomal daunorubicin and cytarabine.

CADTHs reanalysis included revisions to the incidence of AML in Canada, assumed market share, percentage of patients receiving outpatient therapy and the exclusion of in-hospital drug costs.

The sponsor's results suggested the introduction of liposomal daunorubicin and cytarabine would lead to a budget impact of $4,408,784 in year 1, $6,252,389 in year 2, and $8,141,761 in year 3 with a year budgetary impact of $18,802,933. The CADTH reanalysis found the estimated a budget impact to be $355,685 in year 1, $828,692 in year 2, $1,167,732 in year 3. After 3 years since entering the market, the total anticipated budget impact of liposomal daunorubicin and cytarabine is $2,352,109. The results of the CADTH reanalysis were primarily driven by the exclusion of in-hospital drug costs. CADTH conducted a scenario analysis in which inpatient drug costs were included, which resulted in a 3-year budget impact of $34,304,171.

pERC Members

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

June 10, 2021 Meeting

Regrets

None

Conflicts of Interest

None

CADTH

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