pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Gemtuzumab Ozogamicin (Mylotarg) for Acute Myeloid Leukemia

April 2, 2020

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

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 gemtuzumab ozogamicin (GO) for acute myeloid leukemia (AML). 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 regarding gemtuzumab ozogamicin for acute myeloid leukemia conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a reimbursement 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 Group Input on GO for AML, a summary of submitted Provincial Advisory Group Input on GO for AML, and a summary of submitted Registered Clinician Input on GO for AML, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The primary objective of the systematic review is to determine the efficacy and safety of GO in combination therapy with DA [daunorubicin and cytarabine (ARA-C)] compared to other therapies available in Canada for the treatment of adult with previously untreated CD33-positive acute AML, except acute promyelocytic leukemia. The original reimbursement request was for patients age 15 and above (pre-notice of compliance). The Sponsor amended their reimbursement request to align with the Health Canada approved indication that includes adult (18 years of age or older) patients. As a result, input from stakeholders (patient group, registered clinicians and PAG) may have reflected on the extension or request guidance on patients under 15 years of age. As well, the original systematic review protocol was reflective of patients age 15 and older. CD33 positivity as per the reimbursement request is defined as any blast CD33 expression (e.g. CD33 expression greater than 0%).[1]

According to the Product Monograph, a treatment course including GO in combination therapy consists of 1 induction cycle and 2 consolidation cycles:[2]

Induction: The recommended dose of GO is 3 mg/m^2/dose (up to a maximum of one 4.5 mg vial) infused over a 2-hour period on Days 1, 4, and 7 in combination with daunorubicin, 60 mg/m^2/day infused over 30 minutes on Day 1 to Day 3, and ARA-C 200 mg/m^2/day by continuous infusion on Day 1 to Day 7.[2]

Of note, for patients requiring a second induction cycle, GO should not be administered during the second induction cycle. For these patients, a combination of daunorubicin and ARA-C is administered during the second induction cycle, at the following recommended dosing: daunorubicin 35 mg/m^2/day on Days 1 and 2, and ARA-C 1 g/m^2 every 12 hours, on Day 1 to Day 3.[2]

Consolidation: For patients experiencing a complete remission (CR) following induction, defined as fewer than 5% blasts with no Auer rods in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts, transfusion

independence and resolution of any extramedullary disease, up to 2 consolidation courses of intravenous daunorubicin (60 mg/m^2 for 1 day [first course] or 2 days [second course]) in combination with intravenous ARA-C (1000 mg/m^2 per 12 hours, infused over 2 hours on Day 1 to Day 4) with intravenous GO (3 mg/m^2/dose infused over 2 hours up to a maximum dose of one 4.5 mg vial on Day 1) are recommended.[2]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomised open-label phase 3, superiority trial: Acute Leukemia French Association (ALFA)0701. ALFA 0701 was conducted in 26 haematology centres in France. Patients were randomized centrally via telephone in a 1:1 allocation ratio stratified by centre in block sizes of four. The trial included previously untreated patients aged 50–70 years with AML if they had normal cardiac function. Of note, expression of the CD33 antigen on leukemic blast cells was not required for study entry.

The objective of this trial was to assess the efficacy and safety of the standard 3+7 daunorubicin (days 1-3) and cytarabine (ARA-C; days 1-7) induction regimen (DA), with or without fractionated dosing of GO (3 mg/m^2 on days 1, 4, and 7). The primary endpoint was event-free survival (EFS). The secondary endpoints were rates of CR, overall survival (OS), relapse-free survival (RFS), and safety.[3] Patients were followed up for 3 years.

The trial randomized a total of 280 patients with median (IQR) age of 62.2 (58.5-66.3) years. Fifty percent (50%) were male. The study was powered at 80% to detect an increase in 2-year EFS of 15% (25% in control group; 40% on GO group; hazard ratio [HR] of 0.66) if 140 patients were enrolled and 184 events occurred for a type 1 error rate of 5%. Analyses was by intention-to-treat except if the patient withdrew consent. Cox proportional hazards methods were used to compute HRs and 95% confidence intervals (CI). Analyses were adjusted for imbalances of prognostic covariates and treatment centre effects. Sensitivity analyses were conducted to investigate protocol amendments.

Although the trial originally enrolled 280 patients, 2 patients were first excluded from each arm because they withdrew consent. The intention-to-treat (ITT) analysis included 278 patients (April 1, 2011 data cut-off).[4] Overall, 9 patients were excluded from the analyses as a result of the lack of documentation of informed consent (5 patients in the GO arm and 4 patients in the control arm). Therefore, the modified intent-to-treat (mITT) population (August 30, 2013) was comprised of 271 patients (GO arm, n=135; control arm, n=136).[5]

According to the sponsor, harmonized central CD33 expression was determined in 71.6% (of patients overall 194 out of 271; 100 patients from the GO arm and 94 patients from the control arm) and CD33 status was not available for 28.4% (n=77 out of 271) of patients. Overall, 99 patients in the GO arm and 93 patients in the control arm were documented CD33 positive.[1]

Among the mITT population (n=271), the distribution of cytogenetic risk was as follows: favourable (9 patients; 3%), intermediate (180 patients; 66%), adverse (57 patients; 21%) and not available (25 patients; 9.2%).

Overall the study was well conducted, with central randomization leading to appropriate allocation concealment. All clinical outcomes that could be reasonably expected and those planned for in the trial registry are reported. Quality of life was not reported. A blinded and independent review of the event-free survival endpoint was conducted. A total of 82/140 patients completed treatment in the GO arm and 89/140 in the control arm for a total of 171/140 (61.1%).[5] The analyses were appropriate, using a modified intention-to-treat approach. Some patients in the GO arm did not receive GO as planned, but there was no crossover. A total of six (6) patients in the control arm received GO after induction failure and 24 received it after relapse. Any potential crossover effects would bias the results against GO. Baseline differences and treatment centre effects were accounted for using adjusted analyses. Subgroup effects were tested using interaction terms. Further adjustments for protocol amendments were explored by stratified the data by whether patients were included before or after the amendment. Appropriate techniques were applied to control the overall Type I error rate after interim analyses. Analysis of secondary outcomes did not account for multiple testing. This study was funded by Wyeth (Pfizer).

Refer to Table 1.1 for highlights of key outcomes from the ALFA 0701 study.

Table 1.1: Highlights of Key Outcomes[3]

	ALFA 0701	
	GO (N=135)	**No GO (N=136)**
Primary Outcome: EFS ‡		
EFS (months) investigator assessed, median (95% CI)	**17.3 (13.4–30.0)**	**9.5 (8.1–12.0)**
HR (95% CI)*	0.56 (0.42–0.76)	
p-value	0.0002	
Primary Outcome: EFS ‡		
EFS (months) blinded independent review, median (95% CI)	**13.6 (9.0–19.2)**	**8.5(7.5–12.0)**
HR (95% CI)*	0.66 (0.49-0.89)	
p-value	0.006	
Secondary Outcome: OS‡		
OS (months), median	**27.5 (21.4-45.6)**	**21.8 (15.5-27.4)**
HR (95% CI)*	0.81 (0.60-1.09)	
p-value	0.16	
HRQoL	**NR**	**NR**
Difference (95% CI)	**NR**	**NR**
Harms Outcome, n (%)^	**GO (N=131)**	**No GO (N=137)**
Grade ≥3	**NR**	**NR**
AE (any grade)	**NR**	**NR**
TRAE (serious)	**80(61.1)**	**58 (42.3)**
WDAE	**41(31.3) †**	**10(7.3) †**

AE = adverse event, **CI** = confidence interval, **HR** = hazard ratio, HRQoL = health-related quality of life, **NR** = not reported, **SD** = standard deviation, **TRAE** = treatment-related adverse event, **WDAE** = withdrawal due to adverse event; EFS = event free survival; OS= overall survival; NE=not estimable

*HR < 1 favours GO

† Permanent drug discontinuation

‡ Efficacy Outcomes from final Analysis Data Cut-off April 30, 2013 (modified intention to treat population)

^ Harms Outcomes from final analysis Data Cut-off April 30, 2013 (as treated population)

1.2.2 Additional Evidence

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

Patient Group Input

Patients reported fatigue, fever, night sweats, dizziness and bruising and/or bleeding as symptoms of AML. Many respondents described the pathway to diagnosis as one that was not straight forward, and in a few cases took multiple visits to a physician before the diagnosis was made. Respondents reported mistaking their symptoms for a prolonged flu or cold or other ailments until receiving a diagnosis of AML. There were also comments regarding their difficulty of finally receiving a diagnosis, as patients had to go through multiple appointments and interactions with different physicians involved before receiving a diagnosis. A total of 16 patient respondents received front-line chemotherapy for AML, followed by high-dose chemotherapy (n=9), a stem cell or bone marrow transplant (n=9), radiation therapy (n=5), and maintenance therapy (n=1). The treatments respondents underwent resulted in side effects that impacted respondent's physical and mental health leading to a loss of independence. Respondents commented on their impacted motor functions and being dependent on others to care for themselves. Patients' main considerations for new treatments include fewer side effects, maintaining quality of life, and controlling disease. Of note, respondents commented on the importance of family and medical support; one patient commented that they had "no positive experiences" over the course of their treatment "except for staff."

One patient with AML had experience with GO and had accessed the treatment through a clinical trial. The treatment process was described as convenient as they were able to receive treatment at their local hospital. However, the patient was removed from the trial due to side effects; specifically, the patient experience thrombocytopenia that "slowed platelet recovery after each chemo session" resulting in their removal from the trial. The patient commented on the collaboration between their care team and their physician regarding the recommendation to be treated with GO.

Overall, patients with AML value having additional and effective treatment options, reduced side effects and improved quality of life and sense of independence.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Use of GO in combination with other treatments

Economic factors:

- Monitoring and supportive care for hepatotoxicity and hematological toxicities
- Additional resources (chemotherapy chair, pharmacy preparation and nursing)

Registered Clinician Input

One joint clinician input on behalf of six oncologists and two pharmacists from the Pediatric Oncology Group of Ontario (POGO), and three inputs from individual clinicians were provided for

this submission. A total of nine oncologists and two clinical pharmacists provided input on behalf of the provinces of Ontario, British Columbia and Alberta.

Current treatments for AML were stated to include FLAG-IDA, idarubicin, cytarabine, daunorubicin, and midostaurin. Clinicians from POGO stated that pediatric patients with AML currently do not have any provincially funded treatments. Unmet need was highlighted for both pediatric and adult patients, as outcomes for patients with AML are poor and gemtuzumab ozogamicin seems to show benefit. Inclusion and exclusion criteria of the pivotal trial were considered to be reflective of clinical practice. While not included in the funding request, one clinician suggested use of gemtuzumab ozogamicin be extended to patients with relapsed or refractory AML. Clinicians stated use of gemtuzumab ozogamicin in patients greater than 70 years of age would be reasonable. POGO and one individual clinician input identified the Children's Oncology Group trial AAML0531, which suggested benefit with gemtuzumab ozogamicin among pediatric AML patients. In general, the clinicians seemed not to support age as an eligibility criterion for gemtuzumab ozogamicin. For example, exclusion of patients less than 15 years or over 70 years was generally not supported. Clinicians expressed uncertainty extending the use of gemtuzumab ozogamicin to patients with t-AML, as they were not included in the ALFA-0701 trial; however, POGO suggested that gemtuzumab ozogamicin may be suitable for t-AML patients as they may have received significant doses of anthracycline in previous lines of therapy that may disqualify them from then receiving daunorubicin. All clinicians agreed that there is no data to support using gemtuzumab ozogamicin in combination with midostaurin and chemotherapy for newly diagnosed FLT3-mutated AML patients.

Benefit of gemtuzumab ozogamicin was suggested to be greatest for patients with low risk AML. However, all patients were stated to benefit from the treatment. As gemtuzumab ozogamicin would be added to an existing treatment combination, it would not replace any other treatments for AML patients in the front-line setting. Contraindications were stated to be patients with known hypersensitivity to the drug, cirrhosis, or other liver diseases. Cytogenetic testing is performed for AML patients as part of standard of care; as this test is already conducted for patients, no additional testing costs would be required. Clinicians stated that cytogenetic testing benefits their understanding of how to treat patients with AML. Although, concern was expressed regarding the availability of cytogenetic testing at different institutions, and the variable turnover time for results ranging from a few days to two or three weeks. Overall, clinicians seemed to endorse the funding of gemtuzumab ozogamicin, as AML patients have poor outcomes and current treatments are associated with potentially life-threatening toxicities for patients.

Summary of Supplemental Questions

PAG is seeking guidance on whether the addition of GO is appropriate for the following:

- Patients <15 or >70 years of age
- In combination with other treatments (e.g., FLAG-IDA, idarubicin, high dose cytarabine, or azacitidine)
- In combination with midostaurin along with combination chemotherapy for patients with newly diagnosed *FMS-Like Tyrosine Kinase 3* (FLT3)-mutated.

As a result, during development of the review protocol it was determined that randomized controlled trials that included patients under the age of 15 or GO in combination with other treatments (FLAG-IDA, idarubicin, high dose cytarabine, azacitidine, and midostaurin) would be relevant to the pCODR review of GO for AML.

GO in patients <18 or >70 years of age

One trial in children and adolescents showed improvements in EFS with GO compared to no GO (HR 0.83; 95% CI 0.70-0.99; p=0.04), but no improvements in DFS (0.82; 95% CI 0.67-1.02; p=0.7) OS (HR 0.91; 95% CI 0.74 to 1.13; p= 0.39) or remission (OR 0.76; 95% CI 0.79-1.08; p=0.3). This study compared GO + ARA-C + daunorubicin + Etoposide to ARA-C + daunorubicin + Etoposide.[6] Of note, etoposide is not included in the reimbursement request.

See section 7.1 for more information.

GO in combination with other treatments

GO was used in combination with cytarabine in one other trial.[7] The difference in OS at 3 years neared statistical significance, with 25% in the GO arm and 20% in the control arm for a HR of 0.87; 95% CI 0.76-1.00; p=0.05. CR was comparable at 3 years with 62% in the GO arm and 58% in the control arm for a OR of 0.84;95% CI 0.66-1.06; p=0.14.[7]

GO was used in combination with FLAG-IDA in one trial.[8] OS was comparable at 5 years with 43% in the GO arm and 41% in the control arm for a HR of 0.92;95% CI 0.79-1.08; p=0.3. In the MRC AML15 trial, CR was comparable at 5 years with 82% in the GO arm and 83% in the control arm for a OR of 1.04;95% CI 0.76-1.42; p=0.8.[8]

See section 7.1 for more information.

GO in combination with midostaurin along with combination chemotherapy for patients with newly diagnosed FLT3-mutated

No studies reported use of midostaurin in combination with GO.

One trial reported some benefits in remission rate among the FLT3-ITD HAR (internal tandem duplication high allelic ratio) adverse risk cohort.[6]

Two trials found no interaction between FLT3 status and outcomes.[7,8]

See section 7.1 for more information.

Summary of meta-analysis on the benefit of GO[9]

A meta-analysis of five randomized control trials was conducted by Hills et al. to determine whether patients experience benefit from treatment with gemtuzumab ozogamicin. Five trials were incorporated into the meta-analysis: MRC AML15, SWOG-0106, NCRI AML16, GOELAMS AML2006IR, ALFA-0701. In total, the five trials comprised of 3,325 randomized patients between 15 and 84 years of age. Both the MRC AML15 and ALFA-0701 trials showed that the effect of GO differed by cytogenetic group, whereby patients with favourable risk cytogenetics showed the greatest benefit from GO. Authors' analyses of GO benefit by cytogenetic risk showed meaningful absolute benefit of 20.7% (HR: 0.47; 95% CI 0.31-0.73) for favourable cytogenetic patients, and 5.7% (HR: 0.84, 95% CI 0.75-0.95) for intermediate cytogenetic patients. No evidence of benefit was observed in adverse(high) cytogenetic patients. Of note, the publication did not indicate that this subgroup analysis was prespecified.

See section 7.2 for more information.

Comparison with Other Literature

One ongoing trial was identified as possibly relevant in addressing PAG's request for guidance on GO in combination with other treatments. This is a randomized controlled Phase II/III open label trial with a factorial design. The trial is targeting recruitment of

1600 patients (60 years and above) with AML and High-Risk Myelodysplastic Syndrome. Arm A will receive DA chemotherapy with GO compared to CPX-351 (an agent not available in Canada). Arm B will receive Vosaroxin and Decitabine. Arm C will receive DA V FLAG-Ida V DAC. Arm D will compare small molecule or not. Arm E will receive CPX-351 (200 versus 300) and arm F will receive DA V IDAC. The primary outcomes are overall survival, complete remission, duration of remission, toxicity and supportive care requirements. The study is currently recruiting. The estimated completion data is October 2020.[10]

See Section 8 for more information.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence.

Table 1.2: Assessment of generalizability of evidence for GO for AML

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	**CD33 Status**	Patients were eligible for the ALFA 0701 trial regardless of CD33 status. The reimbursement request is solely for patients who are CD33 positive. According to the sponsor levels of CD33-positivity did not appear to impact on the treatment effect of GO, therefore they defined CD33 positivity as per the reimbursement request, as any blast CD33 expression (e.g. CD33 expression greater than 0%).[1]	Are the results of the ALFA 0701 trial applicable to only patients who are CD33 positive?	The vast majority of newly diagnosed AML patients will be CD33 positive and thus the requested indication for AML patients with CD33+ is acceptable. In Canada, CD33 testing is universal during standard of care diagnostic work-up for AML.
	Age	Patients eligible for the ALFA 0701 trial were age 50–70 years. The reimbursement request is for patients aged 18 and above.	Are the results of the ALFA 0701 trial applicable to patients aged 18 years above?	In general, there is no biological reason to believe that patients aged 50-70 will respond differently to those aged 18-49 years of age. The proportion of patients with "favourable" and "intermediate" risk cytogenetics (who appeared to derive the most clinical benefit from Gemtuzumab Ozogamicin), would be more frequent amongst

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				younger adults, making this an attractive therapeutic option for younger adults.
Intervention and Comparator	**Dose of Cytarabine**	In Canada, it is not common to give daunorubicin in consolidation phase. It is more common to give cytarabine alone, with a dose of cytarabine that would be different.	Are the results of the ALFA 0701 trial generalizable to the Canadian population given this difference in intervention?	There is no strong evidence that daunorubicin is required in any consolidation cycles. It is thus *unlikely* that Canadian Leukemia centers will follow the exact consolidation chemotherapy template followed in the ALFA trial. In Canada, high dose cytarabine (HIDAC) is commonly given as an outpatient regimen (as a single agent) in consolidation cycles. The CGP does not see this practice difference as an impediment to adopting GO into regular practice. The CGP foresees that GO in combination with single agent HIDAC consolidation therapy for 2 cycles would offer comparable outcomes. However, if a third cycle of HIDAC consolidation were to be given, CGP recommends that GO should not be included in this 3rd consolidation cycle, given the absence of data supporting the addition of GO beyond 1 cycle of induction and 2 cycles of consolidation chemotherapy.
Setting	**Country**	ALFA 0701 trial was conducted in France.	Are the results of the ALFA 0701 trial generalizable to the Canadian setting?	The ALFA 0701 trial results are generalizable to the Canadian setting. The disease (AML), the diagnostic work-up, and the standard of care therapy are very similar (if not identical) to Canada.

1.2.4 Interpretation

Burden of Illness and Need

In Canada, the age-adjusted incidence of AML is 4.1/100 000. In 2019, some 1675 new cases of AML are projected to occur in Canada. AML is diagnosed predominantly in adults, with a slight predominance in men, and a median age at diagnosis of 66 years. AML may be seen in children (age <15), albeit at a much lower incidence of 0.72 per 100 000, or approximately 40 new childhood cases per year in Canada.[11]

Overall, outcomes after diagnosis of AML are poor (5-year overall survival of 21%) but these outcomes are improving over time, and outcomes are considerably better amongst younger individuals. In addition, temporal improvements in outcome have been observed, and are primarily attributable to improvements in clinical supportive care (e.g. anti-microbials, blood transfusions) and the increasing application of allogeneic hematopoietic cell transplantation (HCT).

As noted by PAG, daunorubicin (or idarubicin) and cytarabine are used for remission induction, while high dose cytarabine (HIDAC) is used for consolidation in Canada. "FLAG-IDA" (fludarabine, idarubicin, high dose cytarabine) is a regimen available in some jurisdictions as a remission induction regimen. In most Canadian jurisdictions, midostaurin is funded in combination with standard cytarabine and daunorubicin (or idarubicin) induction and with cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FLT3-mutated AML. Although allogeneic HCT offers the potential of cure, HCT is a medically risky, resource intensive procedure that is only available to a proportion of AML patients. Despite these available therapies, there is a continued need for more effective treatment options given the high burden of illness, sub-optimal remission rates, and continued risk of relapse, even for those who achieve an initial complete remission.

Effectiveness

The evidence of the effectiveness of GO in the treatment untreated, de novo CD33-positive acute myeloid leukemia (AML), except acute promyelocytic leukemia is derived from a randomised open-label phase 3, superiority trial: ALFA 0701.[3]
The ALFA 0701 trial was conducted in 26 haematology centres in France. The trial included previously untreated patients aged 50–70 years with AML if they had normal cardiac function. Expression of the CD33 antigen on leukemic blast cells was not required for study entry. The objective of this trial was to assess the efficacy and safety of the standard 3+7 daunorubicin (daunorubicin; days 1-3) and cytarabine (ARA-C; days 1-7) induction regimen (DA), with or without fractionated dosing of GO (3 mg/m^2 on days 1, 4, and 7). A second remission induction course (2 days of daunorubicin 60 mg/m^2 per day, with HIDAC at a total dose of 6g/m^2, but without GO) was allowed if residual AML was noted on a day 15 bone marrow examination. Patients who achieved CR then received two further cycles of consolidation chemotherapy, consisting of 1 day of daunorubicin 60mg/m^2 and HIDAC, total dose 8 g/m^2 (1st cycle), followed by 2 days of daunorubicin 60mg/m^2 and HIDAC total dose 8 g/m^2, with or without a single dose of GO at 3 mg/m^2 on day 1 of each consolidation cycle, depending on initial randomization. Allogeneic HCT was allowed at any time point, at investigator discretion.

The primary endpoint of ALFA 0701 was event-free survival (EFS), defined as the time from randomization to relapse, death from any cause, or failure to achieve CR or CR with incomplete platelet recovery (CRp). Secondary endpoints were rates of CR, overall survival (OS), relapse-free survival (RFS), and safety. Patients were followed up for 3 years. The

trial randomized (using a 1:1 allocation ratio) a total of 280 patients with median (IQR) age of 62.2 (58.5-66.3) years. Fifty percent (50%) were men. The study was powered at 80% to detect an increase in 2-year EFS of 15% (25% in control group; 40% on GO group; hazard ratio [HR] of 0.66) if 140 patients were enrolled and 184 events occurred for a type 1 error rate of 5%. A blinded and independent review of the EFS endpoint was conducted.

ALFA 0701 showed that CR/CRp rates were not statistically different between the GO and standard arms (81.5% in the GO arm and 73.6% in the control arm). However, GO was associated with superior EFS (hazard ratio [HR] of 0.66; 95% CI0.49-0.89). There was no statistical improvement in overall survival (OS), with a HR of 0.81; 95% CI0.6-1.09. In subgroup analysis, the EFS benefit of GO was isolated to the patients with favourable or intermediate cytogenetic risk (HR: 0.46; 95% CI0.31–0.68; *P*<0.0001), as defined by the International System for Human Cytogenetic Nomenclature criteria. In contrast, the EFS of GO in patients with "adverse risk" cytogenetics was not apparent (HR: 1.11; 95% CI 0.63–1.95; *P*=0.72). This effect modification was similarly noted when two different AML genetic risk classification systems were applied (National Comprehensive Cancer Network [NCCN] and the European LeukemiaNet [ELN] systems). In another exploratory sub-group analysis, the EFS benefit of GO was noted even in FLT3 ITD mutated patients.

The results of ALFA0701 are supported by an individual patient data meta-analysis of this randomized controlled trial (RCT) combined with four other RCTs, all of which had examined the role of GO added to standard of care (SOC) therapy in untreated adult AML.[9] According to these combined data, the clinical benefit associated with GO appears to be isolated to those patients whose AML genetic risk group is of either "favourable" or "intermediate" in nature. Patients with genetically "adverse risk" AML do not experience clinical benefits from the addition of GO.

Safety

In the ALFA 0701 trial, GO was associated with excess rates of clinically significant hematological toxicity (delayed platelet recovery/persistent thrombocytopenia). Grade ≥3 hemorrhage was reported in 30 (22.9%) patients in the GO arm and 13 (9.5%) patients in the control arm. The median time to recovery of platelets was longer for patients in the GO arm than in the control arm for each treatment course. Additional analyses conducted to identify severe (grade 3 and 4) and persistent thrombocytopenia (i.e. platelet count $<50\times10^9$/L at 45 days after day 1 of the previous treatment phase in which a patient experienced CRp) showed that more patients had severe persistent thrombocytopenia in the GO arm (20.4%) than in the control arm (2.0%).

Grade $\geq$ 3 hepatotoxicity was more frequently associated with GO (13% GO versus 6% no GO); a total of six (4.6%) patients in the GO arm and 2 (1.5%) patients in the control arm experienced hepatic veno-occlusive disease (VOD; p=0.165).

The number of patients who died during the period from the time first dose of chemotherapy to 28 days after the last dose of study treatment was 6 (4.6%) in the GO arm and 5 (3.6%) in the control arm.

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a net clinical benefit to GO in the management of previously untreated, newly diagnosed adult individuals with AML who are

candidates for intensive, curative intent remission induction and consolidation therapy *and* who have genetically favourable risk, intermediate risk, or unknown risk AML using the International System for Human Cytogenetic Nomenclature, NCCN, or ELN classification systems.[12] The current and most widely used risk classification system is that of the ELN [2017]; [12] risk categories are as follows: favourable, Intermediate, adverse. The CGP recommendation using the ELN 2017 risk classification. This conclusion is based primarily on one RCT in adults with AML that demonstrated a clinically and statistically significant benefit in EFS for GO compared with SOC combination chemotherapy with daunorubicin and cytarabine in remission induction and consolidation cycles. This RCT is further supported by an individual patient data meta-analysis of this RCT combined with four other RCTs that examined the role of GO added to SOC therapy in untreated adult AML.[9] According to these data, the clinical benefit associated with GO is isolated to those patients whose AML genetic risk group is of either "favourable" or "intermediate" in nature, as compared to those patients with genetically "adverse risk" AML. In contrast, patients with genetically "adverse risk" AML do not experience clinical benefits from the addition of GO.

- Regarding safety, GO recipients experience more haemorrhage (as a result of a greater incidence and duration of thrombocytopenia) and hepatic VOD. However, the CGP does not feel that these toxicities substantially detract from the foreseeable net clinical benefit for patients with previously untreated, newly diagnosed individuals with AML who are candidates for intensive, curative intent remission induction and consolidation therapy *and* who have genetically favourable risk, intermediate risk, or unknown risk AML.

- Patients younger than <18 or >70 years of age:

    - The CGP recognizes that the reimbursement request is for GO in combination with daunorubicin and cytarabine (ARA-C) for the treatment of patients age 18 years and above. The CGP recommends the use of GO for carefully selected patients >70 years of age on the condition that such patients be otherwise eligible for intensive remission induction chemotherapy with curative intent, with adequate baseline organ function, and in the absence of known adverse risk cytogenetic abnormalities. Although intensive chemotherapy would be given rarely to patients over 70, it is plausible that otherwise fit older patients would benefit from the addition of GO, provided if their baseline genetic risk group was not "adverse risk".

    - Patients with therapy-related AML (t-AML): the CGP recommends does not recommend GO in this sub-group. Reasons for this are as follows:
        - t-AML pts were not included in the RCT which forms the basis of the submission to CADTH. It is thus challenging to know whether similar benefits and risks will accrue to t-AML patients as compared to the standard AML patients.
        - Moreover, in patients who have received previous systemic chemotherapy, it would seem plausible that there is a heightened risk of hepatic VOD after GO exposure.

      Taken together, there does not seem to be sufficient rationale to recommend GO in t-AML patients even if they harbour favourable or intermediate risk cytogenetics/genetics.

    - Application of GO in combination with other induction regimens (e.g., FLAG-IDA, high dose cytarabine, or azacitidine): the CGP sees daunorubicin and idarubicin as interchangeable as the anthracycline drug that is used in

remission induction regimens; that is, the CGP recommends that cytarabine in combination with *either* daunorubicin or idarubicin be used. In contrast, the safety and efficacy of GO in combination with other induction regimens (e.g. FLAG-IDA, anthracycline combined with HIDAC, or azacytidine) is very limited. The CGP does not recommend that GO be added to other treatments for the management of untreated AML.

- GO for patients who are FLT3 positive:

    - GO in combination with midostaurin along with combination chemotherapy for patients with newly diagnosed FLT3-mutated AML: the safety and efficacy of GO in combination with midostaurin is unknown. The CGP does not recommend that GO be added to midostaurin for the management of untreated AML.

    - There is no specific preference for GO or midostaurin in this subgroup, as it plausible that either (but not both in combination) of these agents would result in clinical benefit for eligible patients. The CGP recommends that the decision to use one of either GO or midostaurin should be individualized, based on the available cytogenetic and molecular results that are available at the time of treatment initiation, intent to offer subsequent allogeneic HCT (in which case the risk of GO associated hepatic VOD may render GO an undesirable option), and patient preference.

- Patients with CD33-negative AML: Patients who are proven to be CD33-negative at time of diagnosis are unlikely to derive clinically meaningful benefit from the addition of GO, and the CGP recommends against the use of GO in this setting.

- For patients who progress/relapse on gemtuzumab ozogamicin, next line of therapy would depend on the clinical condition of the patient as well as their relevant cytogenetic and molecular data. There are several therapeutic avenues that could be followed ranging from novel targeted therapy, conventional intensive cytotoxic therapy, low dose chemotherapy or palliation with best-supportive care. However, re-challenge with a GO-based regimen would not be recommended based on the lack of data of the benefit of GO in the setting of patients with relapsed/refractory AML.

- In Canada, high dose cytarabine (HIDAC) consolidation is the current standard of care, and the CGP concludes that it is reasonable and safe to use gemtuzumab ozogamicin in combination with HIDAC consolidation for two cycles, as compared to the "doublet" cytarabine/daunorubicin consolidation regimen that was used in the ALFA 0701 trial.

- Time-limited basis for:
    - Patients who have already initiated or completed induction chemotherapy
    - Patients who have already initiated consolidation chemotherapy"

  The CGP recognize that this is a rare situation and assume that there may be a small benefit of GO for patients, and that an individualized discussion and decision would need to take place.

  Overall, the CGP concludes that there is a net clinical benefit to GO in the management of previously untreated, newly diagnosed individuals with CD33 positive AML who are candidates for intensive, curative intent remission induction and

consolidation therapy and who have cytogenetically favourable risk, intermediate risk, or unknown risk AML.

- The CGP noted the feedback on the initial pERC recommendation from PAG who requested additional clarification on the use of GO in combination with daunorubicin and cytarabine, and suggested updates to the recommendation. As a result, CGP supports the following as the revised wording to the recommendation: Gemtuzumab ozogamicin in combination with daunorubicin and cytarabine should consist of one induction cycle; if second induction is required, gemtuzumab ozogamicin should not be administered during the second induction cycle. For patients with complete remission following induction, gemtuzumab ozogamicin in combination with standard cytarabine consolidation or cytarabine and daunorubicin consolidation for up to two cycles is permitted.

- CGP also noted PAG's request for a statement from CGP on whether patients on midostaurin can be switched to gemtuzumab once the cytogenetic testing is available. At the time of the review, this request was not included in the initial input from PAG. As a result, it was not acknowledged by the CGP in the initial clinical guidance report. CGP believes that in patients with FLT3-mutated AML, either midostaurin (in all cytogenetic risk groups) or gemtuzumab (in favourable and intermediate risk groups) are likely to have clinical benefits for patients. However, it is unknown which one is preferred/superior. CGP notes that once midostaurin has been selected for a given patient, it would seem very unusual to switch to gemtuzumab at a later stage unless the patient was intolerant of midostaurin or had difficulty accessing midostaurin

- Lastly, CPG noted the feedback on the initial pERC recommendation from the sponsor who suggested alternative wording for the definition of unknown cytogenic status. In the absence of a definition of unknown cytogenetic status in the Study Protocol or Clinical Study Report, the CGP supports the suggested edits by the sponsor [i.e. In the event where their cytogenetic status is unknown (that is, because the test was unsuccessful) or when their cytogenetic test results are not yet available, gemtuzumab ozogamicin could be initiated at induction therapy. Patients are eligible to start consolidation therapy with gemtuzumab ozogamicin when their cytogenetic tests confirm that the cytogenetic status is favourable, intermediate, or unknown (because the test was unsuccessful)].

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR AML Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

AML is a malignancy of the hematopoietic system. AML is characterised by proliferation of immature white blood cells within the blood and bone marrow, suppression of normal hematopoiesis leading to bone marrow failure and eventual invasion of other organs and tissues. Left untreated, AML is a rapidly lethal condition.

In Canada, the age-adjusted incidence of leukemia overall is 16.4/100 000, with AML consisting of approximately 25% of these cases, giving an incidence of 4.1/100 000. In 2019, approximately 1675 new cases of AML are projected to occur in Canada. AML is diagnosed predominantly in adults, with a slight predominance in men, and a median age at diagnosis of 66 years. AML may be seen in children (age <15), albeit at a much lower incidence of 7.2 per million, or approximately 40 new cases per year in Canada.[11] In general, outcomes after diagnosis of AML are comparatively poor (5-year overall survival of 21%) but these outcomes are improving over time, and are considerably better amongst younger individuals.[11]

AML is clinically heterogeneous, with multiple different subtypes recognised by the World Health Organization (WHO).[13] One rare subtype of AML, acute promyelocytic leukemia is sufficiently distinct from a clinical, prognostic and therapeutic point of view that it will not be discussed in this summary of AML.

The majority of AML cases are of unknown cause. However, some AML cases evolve from preceding clonal hematological conditions such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN). AML may also arise as a complication of previous exposure to systemic DNA damaging agents such as radiation or chemotherapy given for an unrelated medical condition (therapy-related AML). A very small proportion of AML cases are familial, and these are predominantly seen in children.[13]

AML cells have a characteristic series of cell surface markers, permitting these malignant cells to be differentiated from normal blood cells and from other types of leukemia. Identification of these markers can be achieved using either special tissue stains (immunohistochemistry [IHC]) or by flow cytometry, both of which are readily available and standard diagnostic techniques at Canadian leukemia centers.[13] One cell surface marker, CD33, is offered as a standard flow cytometric test on all suspected cased of AML. CD33 is found on both normal and leukemic cells of myeloid lineage, but it is not found on hematopoietic stem cells or cells of lymphoid origin such as lymphocytes. Thus, the identification of CD33 allows AML cells to be differentiated from those of lymphoid or of other cell lineage. At diagnosis, CD33 is expressed in the majority (>90%) of cases of AML.[14]

In addition to its diagnostic significance in AML, the identification of CD33 has direct therapeutic significance, as it can be used as a target of AML specific treatment such as the anti-CD33 antibody-toxin conjugate GO (Mylotarg).[9,12]

The internationally accepted WHO AML classification system is based on clinical presentation combined with the microscopic and genetic characteristics of the AML cells.[13] The most important prognostic factors in AML consists of:

(i) Age at diagnosis (older patients faring less well).[12]

(ii) Genetic characteristics of the AML cells. Cytogenetic and molecular genetic testing permit the stratification of AML patients into "favourable risk", "adverse risk", and "intermediate/standard risk" groups.[12]

In addition to their prognostic importance, both age and genetic/cytogenetic features at diagnosis are pivotal guides to therapeutic decisions.[12,15]

One of the more recently recognized AML sub-types is based on the molecular signature of the leukemic cells: activating mutations of the *FLT3* gene occur in ~30% of newly diagnosed AML patients, and can be broadly categorised into those with internal tandem duplications (ITD), whose negative prognostic value is well established, and those with point mutations of the tyrosine kinase domain (TKD), where the negative prognostic implication is uncertain. Patients with *FLT3* ITD mutations experience higher relapse rates and poorer overall survival than *FLT3* negative patients. Patients with a quantitatively high allelic burden of *FLT3* ITD have an especially poor prognosis as compared to those without *FLT3* ITD mutations or those with a low *FLT3* ITD burden.[12]

2.2 Accepted Clinical Practice

Table 2.1 Patients with CD33+ AML who are eligible for intensive remission induction therapy

Line of Therapy	FLT3 unmutated/negative.	FLT3 mutated/positive.
1st-Line	Anthracycline (idarubicin or daunorubicin) x 3 days & infusional cytarabine x 7days ("7&3").	Anthracycline (idarubicin or daunorubicin) x 3 days & infusional cytarabine x 7 days ("7&3") PLUS midostaurin.
Consolidation chemotherapy	High-dose cytarabine (HIDAC) x 2-4 cycles (some centers may add an anthracycline to 1-2 cycles of consolidation, in addition to HIDAC). Patients with intermediate or adverse risk features eligible for allogeneic HCT in CR.	High-dose cytarabine (HIDAC) x 2-4 cycles plus midostaurin (some centers may add an anthracycline to 1-2 cycles of consolidation, in addition to HIDAC). Patients with intermediate or high-risk features eligible for allogeneic HCT in CR.
2nd-Line therapy (if refractory to 1st line)	Same as 1st line regimen. Alternative regimen: Fludarabine, idarubicin, high-dose cytarabine +/- filgrastim(GCSF) ["FLAG-IDA"]. Mitoxantrone, Etoposide, Cytarabine ["MEC"] If CR achieved, eligible for allogeneic HCT in CR.	Same as 1st line regimen, with Midostaurin. Alternative regimen: Fludarabine, idarubicin, high-dose cytarabine +/- filgrastim(GCSF) ["FLAG-IDA"] without Midostaurin. Mitoxantrone, Etoposide, Cytarabine ["MEC"] without Midostaurin If CR achieved, eligible for allogeneic HCT in CR.

Left untreated, AML is invariably lethal. Patients will succumb within days to weeks as a consequence of the effects of bone marrow failure (infection, anaemia, bleeding) or infiltration of vital organs by leukemia cells.

Supportive care remains the foundation of treatment for AML patients, including blood transfusions, treatment of opportunistic infections, and management of metabolic consequences such as tumour lysis syndrome. Without vigilant multi-disciplinary supportive care, attempts at intensive remission induction and curative systemic therapy are unlikely to be successful. As a consequence, patients who receive active therapy for their AML should be managed in an experienced leukemia referral centre that is capable of offering prompt and comprehensive multi-specialty care.[12,15]

Regarding AML-specific therapy, nationally accepted, peer-reviewed Canadian specific guidelines for the management of AML are not available. However, recent European and American guidelines have been widely adopted in Canada.[12,15] In addition, provincial guidelines such as Alberta Cancer Services' and Cancer Care Ontario's clinical practice guidelines are used within those respective provinces.[16,17]

The following general approaches to therapy are in use in Canada (see table 2.1): In predominantly younger adults (in general, younger than ~70 years old) with preserved baseline levels of fitness and functional status, the standard of care in Canada is dual chemotherapy remission induction with an anthracycline for 3 days (daunorubicin 60-90mg/m^2 or idarubicin 12mg/m^2) in combination with infusional cytarabine 100-200mg/m^2 by continuous infusion for 7 days ("7 & 3"). Using this approach, first complete remission (CR1) occurs in 50-80% of patients.[12]

If CR is achieved, and a curative outcome remains the objective, post-remission therapy most commonly consists of consolidation with high dose cytarabine ("HIDAC") for 2 to 4 cycles. As consolidation, HIDAC is usually use without and anthracycline. Approximately 60 to 70% of patients with "favourable risk" AML are cured in this fashion.[12] For patients without "favourable risk" biomarkers at diagnosis, outcomes after HIDAC consolidation alone are disappointing (cure rates of 10-40%, depending on other clinical variables).[7,8] Consequently, in the absence of "favourable risk" biomarkers, allogeneic hematopoietic cell transplantation (HCT) is offered as soon as possible, provided a suitable donor is identified. There are multiple, well established pediatric and adult centers across Canada that are capable of offering allogeneic HCT from related, unrelated/volunteer or umbilical cord blood donors.[18]

For patients with intermediate/standard risk or adverse risk AML, long-term survival after allogeneic HCT is approximately 50%.[12] However, despite the relative success of HCT for AML, this procedure is complex, arduous, and may be associated with substantial treatment related mortality, morbidity, and financial expense. Graft-versus-host-disease (GVHD) occurs in at least half of all allogeneic HCT recipients, and in some patients, this can lead to significant debility and reduction in quality of life. Moreover, HCT is not available to all HCT eligible patients for the following reasons: AML may relapse while awaiting HCT; patients may develop co-morbidities that prevent safe delivery of HCT; a suitable donor may not be located in a timely manner.

In patients with *FLT3* (ITD or TKD) mutations, the use of targeted, mutation specific interventions have recently become established. The addition of the *FLT3* inhibitor midostaurin to standard frontline and consolidation chemotherapy in *FLT3* mutated AML is associated with a reduction in relapse rates and improvement in overall survival. Midostaurin is now a widely adopted therapeutic tool in Canada.[19]

If a patient with AML is refractory to or relapses after intensive frontline therapy, the probability of achieving a second CR is lower than with 1st line therapy (i.e. probability of CR2 is 30-50%),

and the likelihood of a durable CR drops dramatically owing to a adverse risk of subsequent relapse.[7,8] The achievement and maintenance of CR1 represents the best chance of cure, and efforts to achieve a durable CR1 with safe therapy are of paramount importance.

The addition of the anti-CD33 monoclonal antibody-chemotherapy conjugate gemtuzumab ozogamicin (GO) to remission induction therapy may be associated with reduced rates of relapse and improved overall survival (OS) in adults with newly diagnosed AML.[9] At the time of this review, GO is not currently funded for therapeutic use in Canada. The adoption of frontline therapy with GO in combination with remission induction chemotherapy is the subject of this pCODR review.

2.3 Evidence-Based Considerations for a Funding Population

The evidence of the effectiveness of GO in the treatment untreated, de novo CD33-positive acute myeloid leukemia (AML), except acute promyelocytic leukemia is derived from a randomised open-label phase 3, superiority trial: ALFA 0701.[3]

The ALFA 0701 trial was conducted in 26 haematology centres in France. The trial included previously untreated patients aged 50–70 years with AML if they had normal cardiac function. Expression of the CD33 antigen on leukemic blast cells was not required for study entry. The objective of this trial was to assess the efficacy and safety of the standard 3+7 daunorubicin (daunorubicin; days 1-3) and cytarabine (ARA-C; days 1-7) induction regimen (DA), with or without fractionated dosing of GO (3 mg/m^2 on days 1, 4, and 7). A second remission induction course (2 days of daunorubicin 60 mg/m^2 per day, with HIDAC at a total dose of 6 g/m^2, but without GO) was allowed if residual AML was noted on a day 15 bone marrow examination. Patients who achieved CR then received two further cycles of consolidation chemotherapy, consisting of 1 day of daunorubicin 60 mg/m^2 and HIDAC, total dose 8 g/m^2 (1st cycle), followed by 2 days of daunorubicin 60 mg/m^2 and HIDAC total dose 8 g/m^2, with or without a single dose of GO at 3 mg/m^2 on day 1 of each consolidation cycle, depending on initial randomization. Allogeneic HCT was allowed at any time point, at investigator discretion.

The primary endpoint of ALFA 0701 was event-free survival (EFS), defined as the time from randomization to relapse, death from any cause, or failure to achieve CR or CR with incomplete platelet recovery (CRp). Secondary endpoints were rates of CR, overall survival (OS), relapse-free survival (RFS), and safety. Patients were followed up for 3 years. The trial randomized (using a 1:1 allocation ratio) a total of 280 patients with median (IQR) age of 62.2 (58.5-66.3) years. Fifty percent (50%) were men. The study was powered at 80% to detect an increase in 2-year EFS of 15% (25% in control group; 40% on GO group; HR of 0.66) if 140 patients were enrolled and 184 events occurred for a type 1 error rate of 5%. A blinded and independent review of the EFS endpoint was conducted.

ALFA 0701 showed that CR/CRp rates were not statistically different between the GO and control arms (81.5% in the GO arm and 73.6% in the control arm). However, GO was associated with superior EFS (HR of 0.66 [0.49-0.89]). There was no statistical improvement in overall survival (OS), with a HR of 0.81 (0.6-1.09). In subgroup analysis, the EFS benefit of GO was isolated to the patients with favorable or intermediate cytogenetic risk (HR: 0.46; 95% CI 0.31–0.68; *P*<0.0001), as defined by the International System for Human Cytogenetic Nomenclature criteria. In contrast, the EFS of GO in patients with “adverse risk” cytogenetics was not apparent (HR: 1.11; 95% CI 0.63–1.95; *P*=0.72). This effect modification was similarly noted when two different AML genetic risk classification systems were applied (National Comprehensive Cancer Network [NCCN] and the European LeukemiaNet [ELN] systems). In another exploratory sub-group analysis, the EFS benefit of GO was noted even in FLT3 ITD mutated patients.

The results of ALFA0701 are supported by an individual patient data meta-analysis of this RCT combined with four other RCTs, all of which had examined the role of GO added to SOC therapy in untreated adult AML.[9] According to these combined data, the clinical benefit associated with GO appears to be isolated to those patients whose AML genetic risk group is of either "favourable" or "intermediate" in nature. Patients with genetically "adverse risk" AML do not experience clinical benefits from the addition of GO.

Safety

In the ALFA 0701 trial, GO was associated with excess rates of clinically significant hematological toxicity (delayed platelet recovery/persistent thrombocytopenia). Grade ≥3 hemorrhage was reported in 30 (22.9%) patients in the GO arm and 13 (9.5%) patients in the control arm. The median time to recovery of platelets was longer for patients in the GO arm than in the control arm for each treatment course. Additional analyses conducted to identify severe (grade 3 and 4) and persistent thrombocytopenia (i.e. platelet count $<50\times10^9$/L at 45 days after day 1 of the previous treatment phase in which a patient experienced CRp) showed that more patients had severe persistent thrombocytopenia in the GO arm (20.4%) than in the control arm (2.0%). Grade ≥ 3 hepatotoxicity was more frequently associated with GO (13% GO versus 6% no GO); six (4.6%) patients in the GO arm and 2 (1.5%) patients in the control arm experienced hepatic veno-occlusive disease (VOD; p=0.165). The number of patients who died during the period from the time first dose of chemotherapy to 28 days after the last dose of study treatment was 6 (4.6%) in the GO arm and 5 (3.6%) in the control arm.

In this trial, the CR, OS, EFS, and TRM rates in the standard of care arm would be in keeping with expected rates associated with intensive therapy for older adult AML; thus, these results are reflective of the outcomes of regular clinical practice in Canada for older (50-70 years) and even younger (<50 years) adults.

Several academic Canadian centres participated in a similar RCT that evaluated the role of GO for newly diagnosed adults with AML, albeit with GO administered at a higher dose (6 mg/m^2 as a single dose on day of the remission induction cycle).[20] This North American intergroup study demonstrated excess treatment-related mortality in the GO arm.

The ALFA 0701 trial utilized GO in two major stages of treatment: (i) remission induction and (ii) consolidation therapy. As the trial did not incorporate a factorial design, it is not possible to know whether the survival benefits associated with GO were attributable to its use in stage (i) or (ii) of therapy or a combination of these stages.

According to the ALFA 0701 trial, the eligible patient population for GO would be adults with newly diagnosed, untreated AML and who are otherwise eligible for remission induction with 7&3. If used, GO would be administered in both the remission induction and consolidation phases, but would be discontinued if and when allogeneic HCT is administered.

The ALFA 0701 trial studied patients restricted to the age group 50-70. This chosen age group years is likely to be an arbitrary one without pharmacological, physiological, or leukemia-related justification. The inclusion of both younger and older patients is supported by British (age range 15-84), North American (age range 18-60) and French (age range 18-60) trials that evaluated the role of upfront GO in AML, albeit using a GO dosing schedule that was different to that of the ALFA 0701 trial.[7,8,20,21]

7&3 remission induction therapy, with or without GO, is administered as an in-patient at an acute leukemia referral centre, with adequate haematology, oncology, critical care, infectious disease, blood transfusion, nursing, pharmacy, and psychosocial supports. In Canada,

consolidation chemotherapy with HIDAC is usually offered as an outpatient, and this would likely remain the case if GO were added to the consolidation regimen.

During the diagnostic work-up of suspected AML, the expression of CD33 on the leukemia cells in the blood or bone marrow should be reported qualitatively (positive or negative) as part of a standard panel of cell surface markers. The CGP expects that all Canadian leukemia centres already offer this as in-house testing.

2.4 Other Patient Populations in Whom the Drug May Be Used

1. Relapsed AML.

   It is foreseeable that for patients with AML in relapse who are GO naïve, prescribers may want to use GO with second line remission induction chemotherapy, or as GO monotherapy. However, the evidence to support this is considerably less robust than using GO in combination with systemic chemotherapy in the first-line setting.

2. *FLT3* mutated AML.

   Midostaurin is licensed and funded for use across Canada for adults up to with FLT3 mutated ("positive") AML in combination with 7&3 remission induction and consolidation. This represents an overlapping (~30%) group of AML patients who derive may benefit from the addition of GO to 7&3 remission induction and consolidation. In a retrospective sub-group analysis of the ALFA 0701 trial, FLT3 ITD positive patients experienced an overall survival benefit from the addition of GO (HR in *FLT3* ITD patients 0.3, 95% CI 0.1-0.97, compared to H.R. 0.82, 95% CI 0.5-1.37 in *FLT3* ITD negative patients), likely because AML patients with FLT3 ITD mutations exuberantly express CD33, the target antigen of GO.

   It is unknown whether, in FLT3 mutated, CD33 positive patients, either GO or midostaurin represents the preferred frontline therapy. Moreover, there is no evidence that GO and midostaurin can be safely combined, however tempting this may be.

   The results of FLT3 testing may be delayed for up to a week from the initial AML diagnosis; for CD33 positive patients in whom the FLT3 genotype is unknown at the time of treatment initiation, it would be reasonable to offer GO based on its foreseeable clinical benefits, even if the patient were later found to be FLT3 mutated. For FLT3 positive CD33 positive patients, prescribers will need to individualise their decision to use one of either GO or midostaurin as frontline therapy.

3. Pediatric AML:

   The CGP foresees that in pediatric patients (under 18 years old) with newly diagnosed CD33 positive AML, prescribers may wish to apply GO in combination with remission induction chemotherapy. The safety and efficacy of GO in the paediatric setting, at a single dose of 3 mg/m^2 on day 6 of remission induction and on day 6 of the second cycle of consolidation, was examined in the COG AML0531 trial. This randomized controlled trial, which recruited 1070 patients and closed in 2010, showed improved EFS due to reduced relapse incidence in GO treated patients. However, the Health Canada indication for GO is for patients 18 years and older. As such, the CGP has not focused on the use of GO in patients younger than 18 years of age.

4. Older/frailer AML patients.

It is foreseeable that in older (>70 years) and/or less fit patients with newly diagnosed AML who are ineligible for 7&3 remission induction, prescribers may want to apply GO in combination *lower dose* systemic chemotherapy (e.g. low dose cytarabine [LDAC] or azacytidine [AZA]), or even as GO monotherapy. However, the efficacy of GO in these settings is not established. Further study about GO's role in this patient population is recommended. However, the CGP recognizes that a small proportion of older (>70 years) patients who with excellent organ function and functional status are likely to tolerate and respond to 7&3 remission induction therapy (with or without GO) in a comparable manner to younger adults.

5. Patients with secondary AML(sAML), therapy-related AML(tAML), and adverse risk cytogenetics at diagnosis.

5. 1. The presence of sAML and tAML were exclusion criteria for the ALFA0701 trial.[4] Thus, it is not known whether such patients would derive similar benefits from GO; more data are needed in these AML sub-groups. It is thus challenging to know whether similar benefits and risks will accrue to t-AML patients as compared to the standard AML patients. Moreover, in patients who have received previous systemic chemotherapy, it would seem plausible that there is a heightened risk of hepatic VOD after GO exposure.

Taken together, there does not seem to be sufficient rationale to recommend GO in t-AML patients even if they harbour favourable or intermediate risk cytogenetics/genetic.

5. 2. Although included in the ALFA0701 trial, patients with adverse risk baseline genetics did not experience a survival benefit from GO in an exploratory sub-group analysis,[4] as well as in a subsequent meta-analysis of multiple GO RCTs in adults with AML.[9] If cytogenetic risk stratification is possible prior to treatment initiation, the CGP recommends against the adoption of GO for those patients with known adverse risk cytogenetic characteristics. However, the CGP recognises that that for the majority of AML patients, baseline cytogenetic results will not be available at the time of initial AML-directed treatment.

6. Patients with pre-existing liver disease.

GO may result in serious hepatotoxicity, especially hepatic VOD. VOD may lead to a life-threating multi-organ failure syndrome. Within the ALFA 0701 trial, the potential of VOD was acknowledged within the clinical design, such that eligibility criteria were restricted to those with well-preserved liver function, as measured by serum bilirubin and liver enzyme tests. The CGP recommends that the incorporation of GO into an AML regimen should adhere, as much as possible, to the baseline organ function criteria outlined within ALFA 0701 trial, and that vigilant attention be paid to hepatic function during and after GO administration. The CGP recommends prophylactic strategies against VOD, including the use of urso-deoxycholic acid (ursodiol), an oral agent that is readily available at Canadian hospitals. Further, if VOD is strongly suspected or confirmed, management with intravenous defibrotide, a drug that is licensed in Canada for use in hepatic VOD, should be considered.[22]

3 SUMMARY OF PATIENT GROUP INPUT

One patient group, the Leukemia and Lymphoma Society of Canada (LLSC) provided input on GO (Mylotarg) for patients aged 15 years and above with previously untreated, de novo CD33-positive AML, except acute promyelocytic leukemia.

LLSC obtained information via a survey conducted in both English and French. The English survey was made available to respondents between July 24, 2019 and August 18, 2019, while the French survey was made available between July 29, 2019 and August 18, 2019. The survey was posted using Survey Monkey, distributed through social media channels and by email, and was targeted to patients and families who were diagnosed with AML, and who may have had experience with gemtuzumab ozogamicin. A total of 25 responses were obtained via LLSC's survey, one of whom reported having experience with gemtuzumab ozogamicin. LLSC removed one response obtained via the French survey from their analysis as the response was incomplete. Therefore, the analysis conducted and reported by LLSC incorporates 24 responses, 19 patients with AML or in remission from AML and five immediate family members of patients with AML. Patients varied in age ranging between 23 years of age to 84 years of age. The average age of diagnosis of patients with AML was reported to be 49.3 years. All respondents were Canadian. Table 3.1 provides a geographic breakdown of where in Canada respondents were providing input from.

Table 3.1: Breakdown of Survey Respondents by Geographic Location in Canada

Province	N
Alberta	8
Ontario	4
Nova Scotia	4
British Columbia	3
Newfoundland	2
New Brunswick	1
Saskatchewan	1
Manitoba	1

Patients reported fatigue, fever, night sweats, dizziness and bruising and/or bleeding as symptoms of AML. Many respondents described the pathway to diagnosis as one that was not straight forward, and in a few cases took multiple visits to a physician before the diagnosis was made. Respondents reported mistaking their symptoms for a prolonged flu or cold or other ailments until receiving a diagnosis of AML. There were also comments regarding their difficulty of finally receiving a diagnosis, as patients had to go through multiple appointments and interactions with different physicians involved before receiving a diagnosis. A total of 16 patient respondents received front-line chemotherapy for AML, followed by high-dose chemotherapy (n=9), a stem cell or bone marrow transplant (n=9), radiation therapy (n=5), and maintenance therapy (n=1). The treatments respondents underwent resulted in side effects that impacted respondent's physical and mental health leading to a loss of independence. Respondents commented on their impacted motor functions and being dependent on others to care for themselves. Patients' main considerations for new treatments include fewer side effects, maintaining quality of life, and controlling disease. Of note, respondents commented on the importance of family and medical support; one patient commented that they had *"no positive experiences*" over the course of their treatment *"except for staff."*

One patient with AML had experience with gemtuzumab ozogamicin and had accessed the treatment through a clinical trial. The treatment process was described as convenient as they were able to receive treatment at their local hospital. However, the patient was removed from the trial due to side effects; specifically, the patient experience thrombocytopenia that *"slowed platelet recovery after each chemo session"* resulting in their removal from the trial. The patient commented on the collaboration between their care team and their physician regarding the recommendation to be treated with gemtuzumab ozogamicin.

Overall, patients with AML value having additional and effective treatment options, reduced side effects and improved quality of life and sense of independence.

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 groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Acute Myeloid Leukemia

Prior to diagnosis, LLSC reported the following symptoms experienced by patients: fatigue, fever and/or night sweats, dizziness/light headedness, bruising and/or bleeding, and rashes/skin changes. LLSC also reported the following symptoms experienced by patients: shortness of breath (n=2), swollen/painful gums (n=2), chest pain, throat abscesses, and flu-like symptoms.

According to LLSC, respondents described experiencing difficulty obtaining a diagnosis, undergoing multiple appointments with physicians before receiving a diagnosis. Until finally receiving a diagnosis of AML, respondents believed they were suffering from a lingering flu or cold or other ailments. *"I had a head cold I could not shake for a month and weight gain was an issue. We were testing my thyroid 5 months prior with the weight gain then I was to go back in to get a second look. As I was sick for 5 days thinking I had pneumonia and was very short of breath to the point I felt really out of shape even walking. I went in for a chest x-ray and decided to do my thyroid test at the same time… I got lucky it was found on that test. I was shipped via ambulance to Edmonton where a Bone marrow test was completed."*

3.1.2 Patients' Experiences with Current Therapy for Acute Myeloid Leukemia

Table 3.2 indicates treatments reported by respondents that they received to treat their AML in the front-line, where many patients reported receiving chemotherapy. Many challenges experienced during frontline treatment included hospitalization, developing side effects, impact on family, and loss of independence. Loss of independence impacted respondent's ability to care for themselves, engage in activities, and conduct basic motor functions. Some quotes from respondents provided by LLSC are included below:

- *"I was very sick obviously and hospitalized a long time. I had to do the induction treatment twice. I developed grade 4 graph versus host disease which was terrible."*
- *"Stress on family especially wife and adult children. Extreme dependence on family because unable to walk unaided or go to bathroom, shower etc. Staff unable to provide level of care required."*
- *"Completely debilitating disease and treatment. Frequent infections. Side effects from chemo and antibiotics. Had life threatening skin rash requiring IGG and long*

term prednisone. Had blood clot related to IV. PICC line didn't work. Hickman catheter got infected. Needed 3. No positive experiences except for staff."

- *"I lost the ability to use my arms and legs and had to learn over again. I was very sick for a long period of time and I had lung scarring which effected my ability to exercise."*

Table 3.2: Previous Treatments Reported by Respondents

Treatment	N
Front-line chemotherapy	16
High-dose chemotherapy	9
Stem cell/bone marrow transplant	9
Radiation therapy	5
Maintenance therapy	1

According to LLSC, the following is a list of physical side effects due to treatments reported by patients from most extreme to side effects with little to no impact: neutropenia/low white blood cell counts, reduced movement/ability to take part in physical activities, hair loss, nausea, fevers, pain, vomiting, organ damage, eye sight issues, neuropathic pain, and constipation. Emotional and quality-of-life related side effects due to treatments from those resulting in extremely large impact to side effects that have little to no impact on respondents were reported to be: changes to physical activity, anxiety, mental health and overall happiness, eating challenges, social development, and educational development.

LLSC also provided input emphasising the importance of support systems, such as the medical staff available to patients, and how this impacted their disease and treatment experience. *"Positives- Edmonton and Calgary hospitals were amazing, Staff listened to my symptoms, isolation made it easier to cope, Staff support was amazing, Processes were explained in depth, family was supported, tests were always one step ahead alleviating concerns."*

When asked about what patients and caregivers would expect in new treatments for front-line therapies, LLSC stated reduced side effects as being mentioned by most of the respondents. Specifically, one patient commented hoping for a treatment that did not result in hair loss. The following were listed in order of most to least important to consider when deciding about a new cancer treatment: quality of life, possible impact on disease, physician recommendation, closeness of home, outpatient treatment, and religious considerations. When asked why respondents would be willing to tolerate side effects of a drug, one respondent stated, *"Any bit of hope for a cure or treatment that extends a loved one's life. That would be reason enough to tolerate side-effects of any drug."*

3.1.3 Impact of Acute Myeloid Leukemia and Current Therapy on Caregivers

One respondent emphasized the emotional toll the illness and treatments took on their family: *"A mandated family mental health meeting after treatment to assist family in knowing where the patient is at and things that may come up. Cancer, menopause and my anxiety after even with mental health for myself destroyed my family."* One spouse commented that some side effects experienced by their wife were reduced as a result of their treatment. However, other side effects emerged, as well as stress and fear related to the cancer. *"Treatment reduced most of the bone pain. Soon my wife had a reduction in*

night sweats, reduction in fatigue. Down side was she was constantly immobilized due to her condition and treatment. She felt emotionally trapped by fear, pain, worry and more."

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences to Date with Gemtuzumab Ozogamicin

One patient with AML reported having experience with GO. The patient obtained gemtuzumab ozogamicin via a clinical trial and experienced no difficulty in accessing the drug. LLSC commented that the patient had access to GO through their local hospital. The patient commented on the collective decision involved in going forward with treatment with GO, as their care team and treating physician were involved in making the recommendation.

Persistent thrombocytopenia was mentioned as a side effect experienced as a result of gemtuzumab ozogamicin; due to this side effect the patient was removed from the clinical study. *"Slowed platelet recovery after each chemo session so I was removed from the trial."*

3.3 Additional Information

None.

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 pCODR website (www.cadth.ca/pcodr). 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) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Use of gemtuzumab ozogamicin in combination with other treatments

Economic factors:

- Monitoring and supportive care for hepatotoxicity and hematological toxicities
- Additional resources (chemotherapy chair, pharmacy preparation and nursing)

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that daunorubicin (or idarubicin) and cytarabine are used for induction and high dose cytarabine is used for consolidation for acute myeloid leukemia (AML). The comparator in the ALFA-0701 trial was anthracycline and cytarabine in both the induction and consolidation phases. As cytarabine consolidation is the current standard of care, PAG is seeking information on gemtuzumab ozogamicin in combination with and comparing to high dose cytarabine consolidation.

FLAG-IDA is also available in some jurisdictions. In some jurisdictions, midostaurin is funded in combination with standard cytarabine and daunorubicin (or idarubicin) induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FLT3-mutated AML. As some patients in the ALFA-0701 trial were FLT3-ITD status positive, for patients with FLT3-mutated AML, PAG is seeking comparative information on gemtuzumab ozogamicin compared with midostaurin (both with combination chemotherapy).

4.2 Eligible Patient Population

PAG is seeking guidance on whether the addition of gemtuzumab ozogamicin is appropriate for the following:

- Patients <15 or >70 years of age
- Patients with therapy-related AML (t-AML)
- In combination with other treatments (e.g., FLAG-IDA, idarubicin, high dose cytarabine, or azacitidine)
- In combination with midostaurin along with combination chemotherapy for patients with newly diagnosed FLT3-mutated AML
- Patients with CD33-negative AML

If recommended for reimbursement, PAG noted that the following groups of patients would need to be addressed on a time-limited basis:

- Patients who have already initiated or completed induction chemotherapy
- Patients who have already initiated consolidation chemotherapy

There is a potential for indication creep to patients who are not receiving induction chemotherapy. PAG is seeking information on the use of gemtuzumab ozogamicin in patients who are undergoing re-induction and consolidation, recognizing this may be out of scope of the current review of gemtuzumab ozogamicin for previously untreated, de novo CD33-positive AML. There is also a potential for indication creep of gemtuzumab ozogamicin, particularly for older patients in the relapsed setting as a single agent for CD33-positive AML.

4.3 Implementation Factors

The recommended dose of gemtuzumab ozogamicin is 3 mg/m^2 (up to a maximum dose of one 4.5 mg vial), the maximum one vial is an enabler to implementation and there would be minimal wastage.

Gemtuzumab ozogamicin is an intravenous drug that is an add-on to current induction and consolidation treatment with intravenous chemotherapy.

PAG noted that gemtuzumab ozogamicin is administered by intravenous infusion over two hours and would be administered in hospital and in the clinic setting, since induction is administered as an inpatient and consolidation chemotherapy may be administered as an inpatient. Consolidation chemotherapy, for adults, is administered as an outpatient This would be a barrier as there would be additional chemotherapy chair utilization, increased pharmacy preparation time and increased nursing resources. Additional chair time for infusion and monitoring may be an issue, especially when given the same day as high dose cytarabine which is a three hour infusion. PAG also noted light exposure must be minimized during drug preparation. Monitoring and supportive care resources would be required for hepatotoxicity and hematological toxicities. Defibrotide is not available in all jurisdictions in the event of veno-occlusive disease (VOD).

PAG noted given the complexity of AML, gemtuzumab ozogamicin will likely only be administered in treatment centres where clinicians with experience with AML practice.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on:

- For patients with FLT3 positive mutation AML, whether there is a preference for gemtuzumab ozogamicin or midostaurin, or if patients should receive both?
- What treatment options would be available to patients upon progression on gemtuzumab ozogamicin?

4.5 Companion Diagnostic Testing

CD33 positivity and cytogenetics testing is completed in all jurisdictions.

4.6 Additional Information

None identified.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One joint clinician input on behalf of six oncologists and two pharmacists from the Pediatric Oncology Group of Ontario (POGO), and three inputs from individual clinicians were provided for this submission. A total of nine oncologists and two clinical pharmacists provided input on behalf of the provinces of Ontario, British Columbia and Alberta.

Current treatments for AML were stated to include FLAG-IDA, idarubicin, cytarabine, daunorubicin, and midostaurin. Clinicians from POGO stated that pediatric patients with AML currently do not have any provincially funded treatments. Unmet need was highlighted for both pediatric and adult patients, as outcomes for patients with AML are poor and gemtuzumab ozogamicin seems to show benefit. Inclusion and exclusion criteria of the pivotal trial were considered to be reflective of clinical practice. While not included in the funding request, one clinician suggested use of gemtuzumab ozogamicin be extended to patients with relapsed or refractory AML. Clinicians stated use of gemtuzumab ozogamicin in patients greater than 70 years of age would be reasonable. POGO and one individual clinician input identified the Children's Oncology Group trial AAML0531, which suggested benefit with gemtuzumab ozogamicin among pediatric AML patients. In general, the clinicians seemed not to support age as an eligibility criterion for gemtuzumab ozogamicin. For example, exclusion of patients less than 15 years or over 70 years was generally not supported. Clinicians expressed uncertainty extending the use of gemtuzumab ozogamicin to patients with t-AML, as they were not included in the ALFA-0701 trial; however, POGO suggested that gemtuzumab ozogamicin may be suitable for t-AML patients as they may have received significant doses of anthracycline in previous lines of therapy that may disqualify them from then receiving daunorubicin. All clinicians agreed that there is no data to support using gemtuzumab ozogamicin in combination with midostaurin and chemotherapy for newly diagnosed FLT3-mutated AML patients.

Benefit of gemtuzumab ozogamicin was suggested to be greatest for patients with low risk AML. However, all patients were stated to benefit from the treatment. As gemtuzumab ozogamicin would be added to an existing treatment combination, it would not replace any other treatments for AML patients in the front-line setting. Contraindications were stated to be patients with known hypersensitivity to the drug, cirrhosis, or other liver diseases. Cytogenetic testing is performed for AML patients as part of standard of care; as this test is already conducted for patients, no additional testing costs would be required. Clinicians stated that cytogenetic testing benefits their understanding of how to treat patients with AML. Although, concern was expressed regarding the availability of cytogenetic testing at different institutions, and the variable turnover time for results ranging from a few days to two or three weeks. Overall, clinicians seemed to endorse the funding of gemtuzumab ozogamicin, as AML patients have poor outcomes and current treatments are associated with potentially life-threatening toxicities for patients.

Please see below for a summary of specific input received from the registered clinicians. References to evidence in this clinician input summary were provided in the original clinician inputs and included in the summary below.

5.1 Current Treatments for Acute Myeloid Leukemia

Two individual clinician inputs acknowledged the treatments listed by CADTH for AML which were: daunorubicin and cytarabine for induction and high dose cytarabine for consolidation. An individual input identified FLAG-IDA as an available treatment in Alberta; however, FLAG-IDA is not used in induction. Standard therapy in Alberta was stated to be idarubicin and cytarabine in induction, with high dose cytarabine in consolidation. In British Columbia, another individual clinician identified standard treatment for fit, newly diagnosed patients with AML as being 7+3 (daunorubicin-cytarabine) chemotherapy, with daunorubicin and cytarabine induction and cytarabine-based consolidation. For patients with FLT3-mutated AML, midostaurin was also stated to be available to

patients in some jurisdictions. Two individual inputs stated that, as gemtuzumab ozogamicin is given in conjunction with standard therapy, there is no specific comparator.

POGO identified the lack of standard treatment available to pediatric patients with AML in Ontario. Currently, there are no treatments publicly funded provincially for pediatric patients with AML in Ontario.

5.2 Eligible Patient Population

Unmet need was highlighted in this population for both adult and pediatric patients. POGO highlighted the unsatisfactory outcomes for pediatric patients with AML, and the improved upfront outcomes that gemtuzumab ozogamicin results in for these patients. Traditionally, pediatric patients are treated with a three-drug induction consisting of cytarabine, daunorubicin and etoposide (ADE). When gemtuzumab ozogamicin is added to the three-drug combination, clinicians from POGO referred to the AAML0531 Trial showing improved event free survival (EFS) in pediatric patients.

The three individual clinician inputs agreed that the inclusion and exclusion criteria of the trial were reasonable and applicable to clinical practice. One clinician stated that they would use gemtuzumab ozogamicin in conjunction with intense chemotherapy in patients with intermediate or favourable risk karyotypes, based on the findings of a meta-analysis by Hills et al. 2014 of five RCTs on adults which showed that benefit was limited to these groups. In addition, this clinician stated there was evidence for use of gemtuzumab ozogamicin in patients with relapsed and refractory AML; although, the clinician acknowledged that this patient group was not included in the funding request. Another citation referring to a retrospective study by Hospital et al. 2014 where patients with core binding factor AML received re-induction with gemtuzumab had improved disease free and overall survival after transplant; this clinician suggested that gemtuzumab ozogamicin seems to have the greatest benefit for patients with core binding factor AML who had favourable karyotypes. In general, another individual clinician stated that they would not use gemtuzumab ozogamicin in unreported combinations without the support of evidence.

5.2.1 *In clinical practice, is there evidence to extend the use of gemtuzumab ozogamicin to (provided all other eligibility criteria are met):*

5.2.1.1 *Patients <15 or >70 years of age*

The individual clinician inputs acknowledged their uncertainty with extending the use of gemtuzumab ozogamicin to patients less than 15 years of age as they do not treat pediatric patients. However, an ongoing study targeting pediatric patients was identified by one input; while the specific trial was not named, another individual input as well as POGO referred to the randomized phase III Children's Oncology Group (COG) trial AAML0531 which suggested an EFS benefit with upfront gemtuzumab ozogamicin in pediatric AML. Based on the phase III trial, POGO suggested the extension of all eligibility criteria for gemtuzumab ozogamicin to children with CD33-positive, non-acute promyelocytic leukemia and AML. Current inclusion and exclusion criteria do not include the majority of pediatric patients. POGO provided references to the AAML0531 and AAML03P1 COG Trials supporting the safety of gemtuzumab ozogamicin in pediatric patients including infants. Based on the provided evidence from the two COG trials, POGO suggested that a lower age limit not be included in the final recommendation for this drug.

All three individual clinician inputs agreed that extending the use of gemtuzumab ozogamicin to adults over 70 years of age would be reasonable. One clinician stated that the study criteria fit many patients in their practice. Also, this clinician would not typically treat someone over the age of 70 induction chemotherapy. Another clinician stated that there is no biologic reason that a fit older patient with AML would not also benefit from gemtuzumab ozogamicin. In general, this clinician did

not support the concept of using age as a determinant for treatment eligibility in AML, so long as the fitness and genetics of the patient were considered. However, the clinician acknowledged that age was used as a criterion for patient selection in previous trials, including the ALFA 0701 study.

5.2.1.2 *Patients with therapy-related AML (t-AML)*

While POGO stated that gemtuzumab ozogamicin may be suitable for patients with t-AML, two of the individual clinician inputs were uncertain about extending treatment use for this population. The individual clinicians highlighted that t-AML patients were not included in the ALFA-0701 trial, therefore there is not a strong rationale to support the use of gemtuzumab ozogamicin in this population. One individual input suggested that use of liposomal product (Vyxeos) for use in patients with t-AML as it would be a better fit. POGO identified the use of significant doses of anthracycline in previous lines of therapy that t-AML patients may have received which may disqualify patients from being candidates to receive daunorubicin usually associated with AML therapy. POGO suggested that t-AML patients could be treated with therapy similar to the AAML0531 trial.

5.2.1.3 *In combination with other treatments (e.g., FLAG-IDA, idarubicin, high dose cytarabine, or azacytidine)*

One clinician stated that gemtuzumab ozogamicin should be given with 3+7; this clinician was wary of extending the use of gemtuzumab ozogamicin to other combinations listed. Another clinician stated there was some evidence, referencing trial NCT00801489, for using gemtuzumab ozogamicin with FLAG in the upfront setting in core binding factor AML; the clinician identified a phase II single arm study reporting a favourable three-year overall survival (OS) of 78%, similar to that reported with 7+3 and gemtuzumab ozogamicin in this group of patients. While the single arm phase II trial makes it difficult to compare the efficacy of gemtuzumab ozogamicin in conjunction with FLAG, the clinician stated that it would be reasonable to use this drug combination in centres that use FLAG upfront as induction, particularly in the core binding factor group.

POGO referred to the AAML0531 trial for pediatric patients, which combined gemtuzumab ozogamicin with ADE in induction, and mitoxantrone and high dose cytarabine in intensification. POGO suggested that gemtuzumab ozogamicin be continued in intensification for patients that achieve an acceptable response in induction therapy, and that gemtuzumab ozogamicin in combination with mitoxantrone and high dose cytarabine may be beneficial to patients with refractory AML post their first induction as salvage therapy.

5.2.1.4 *In combination with midostaurin along with combination chemotherapy for patients with newly diagnosed FLT3-mutated AML*

All inputs expressed uncertainty about using gemtuzumab ozogamicin in combination with midostaurin along with combination chemotherapy for patients with newly diagnosed FLT3-mutated AML. As there is no data to currently support use of gemtuzumab ozogamicin with this combination, clinicians agreed that use of gemtuzumab ozogamicin in this manner would be based on pure speculation. The possible toxicities of using gemtuzumab ozogamicin with midostaurin are not well known. One input stated that over 50% of AML patients have an intermediate risk karyotype and that FLT3 mutations are common; however, at the time induction therapy is started, the genetic risks of the patient are unknown, as most Canadian centres have a turn-around time of three to seven days. Therefore, if gemtuzumab ozogamicin is approved and funded, patients may receive both gemtuzumab ozogamicin and midostaurin at least during the initial induction period. However, as

neither gemtuzumab ozogamicin and midostaurin are given concurrently, the potential for toxicity and drug interactions may be lessened.

POGO provided evidence by Tarlock et al. 2017 based on the AAML0531 Trial which identified the benefit that gemtuzumab ozogamicin showed in pediatric FLT3-mutated patients with AML, and the promising activity that FLT-3 inhibition has shown in pediatric AML, mainly with sorafenib. However, POGO also acknowledged the lack of evidence to support the safety of adding gemtuzumab ozogamicin and an FLT-3 inhibitor, such as midostaurin, to the treatment of pediatric FLT-3 mutated AML.

5.3 Relevance to Clinical Practice

All submitted clinician inputs, except for one individual clinician input, reported having experience with using gemtuzumab ozogamicin. The individual clinicians agreed that gemtuzumab ozogamicin seems to be most beneficial for patients with low risk AML (favourable and intermediate risk karyotypes); however, noted that all patients may benefit. Intermediate risk patients, particularly those with normal karyotypes, were stated to have the highest incidence of FLT3 mutations; a clinician suggested that some of these patients also appear to benefit from treatment with gemtuzumab ozogamicin. A meta-analysis from the ALFA0701 study was referenced, as it was stated to show improved EFS, OS and relapse free survival among patients with FLT3 mutations who received gemtuzumab ozogamicin. In addition, a subset analysis from the Children's Oncology Group Trial suggested that use of gemtuzumab ozogamicin is associated with lower relapse incidence. One clinician stated they would use gemtuzumab ozogamicin in combination with front-line intensive induction and consolidation. Specifically, another clinician stated they would use gemtuzumab ozogamicin with an anthracycline and low dose cytarabine. The clinician also stated that they would not use gemtuzumab ozogamicin in patients who are FLT3 positive as they would have already received an FLT3 inhibitor, which is a combination that has not yet been studied or reported.

Gemtuzumab ozogamicin would not replace other treatments in the front-line setting as it is being added to an existing combination. Gemtuzumab ozogamicin was stated to be contraindicated in patients with known hypersensitivity reaction to the drug, cirrhosis, or other clinically significant liver diseases given the risk of veno-occlusive disease. Patients with liver disease were stated generally not to be treated with intensive induction. While more efficacious and better tolerated than other available treatments, one clinician stated that gemtuzumab ozogamicin may result in greater hematotoxicity. Another clinician stated that at the doses studied, toxicity to the drug combination does not seem to be excessive.

POGO stated that gemtuzumab ozogamicin has been used in pediatric centres in Ontario through clinical trials in upfront AML, and off-label/compassionate use in relapsed and refractory AML. POGO referred to data between 2008 and 2017 from their own POGONIS Childhood Cancer Database which showed that an average of 19 patients (range: 14-23) are diagnosed with and treated for non- acute promyelocytic leukemia AML in pediatric cancer programs per year. POGO stated that many of these patients would be CD33-positive, making them potential candidates for gemtuzumab ozogamicin to be used as upfront therapy. Early studies had suggested that use of gemtuzumab ozogamicin led to significant risk of sinusoidal obstruction syndrome (SOS), particularly for patients moving onto subsequent stem cell transplant. However, through the collective experience of POGO and in the AAML0531 trial, POGO found that the risk of SOS in patients does not seem to increase, regardless of transplant status. Some patients that experience relapse may be salvaged through additional therapy and a stem cell transplant; however, POGO stated that outcomes for relapsed AML patients continues to be poor. Relapsed AML patients would also be a higher risk for subsequent late effects

of treatment; therefore, POGO highlighted the importance of avoiding relapse in patients after first-line treatment.

5.4 Sequencing and Priority of Treatments with Gemtuzumab Ozogamicin

5.4.1 *For patients with FLT3 positive mutation AML, what clinical scenarios would gemtuzumab ozogamicin or midostaurin be the preferred treatment option for newly diagnosed FLT3-mutated AML, or is there evidence to support the use of both gemtuzumab ozogamicin or midostaurin?*

One clinician noted that this combination is being studied. POGO also acknowledged that current data may suggest benefit with the use of both gemtuzumab ozogamicin and FLT3 inhibition in pediatric AML. However, all clinician inputs acknowledged the lack of currently available evidence to support the use of both gemtuzumab ozogamicin and midostaurin in combination; efficacy and safety of induction and consolidation regimens including both gemtuzumab ozogamicin and midostaurin are currently unknown. Therefore, clinicians will most likely not use the combination of gemtuzumab ozogamicin and midostaurin at this point.

5.4.2 *What clinical scenarios would gemtuzumab ozogamicin or chemotherapy alone be the preferred treatment option?*

One clinician input stated that there would be very few cases where single agent chemotherapy would be used. Another stated they would prefer to use single agent chemotherapy in cases with adverse risk karyotypes. This clinician speculated that CPX-351 (cytarabine and daunorubicin) may be available to treat patients with adverse risk karyotypes, for example, World Health Organization (WHO) categories AML with myelodysplasia related changes and therapy related AML.

In general, clinicians also did not support the use of single agent gemtuzumab ozogamicin in the front-line setting. Use of gemtuzumab ozogamicin combined with chemotherapy would be the favourable approach. However, one clinician did identify presence of some evidence for use of single agent gemtuzumab ozogamicin in the relapsed and refractory setting. One clinician stated the combination treatment would be preferred, except in cases where patients present with cirrhosis. The clinician stated that it would be unusual for a patient to progress while on treatment. POGO acknowledged that primary treatment would have to be modified for patients with t-AML as they may not be suitable for further anthracycline exposure. Patients with recurrent CD33 positive AML may benefit from single-agent gemtuzumab ozogamicin at the time of recurrence. In addition, the treatment of choice for a subset of high-risk patients would be an allogenic stem cell transplant following gemtuzumab ozogamicin-containing induction therapy.

One clinician stated that evidence exists potentially showing benefit among patients with mixed-linkage (MLL)-rearranged leukemia (11q23) based on post-hoc analyses from pediatric clinical studies. In adults, MLL-rearranged leukemia is generally considered an adverse risk change (except for t(9;11)). The clinician was uncertain whether gemtuzumab ozogamicin would benefit MLL-rearranged leukemia patients, however they stated that it may be possible.

5.4.3 *What treatment options would be available to patients upon progression on gemtuzumab ozogamicin?*

Upon progression on gemtuzumab ozogamicin, treatment options available to patients were stated to include those that are already currently available, such as salvage chemotherapy, allogenic stem cell transplant. Another individual clinician input agreed, stating that at the time of relapse they

would likely not use gemtuzumab ozogamicin again, but a salvage combination chemotherapy regimen, such as FLAG-IDA and then hematopoietic stem cell transplant if they are eligible, or a hypomethylating agent, such as azacitidine if they are not eligible for intensive chemotherapy. POGO also agreed, stating that patients with progressive/recurrent/refractory AML would be treated with alternative chemotherapy (i.e., fludarabine, cytarabine, filgrastim (FLAG)) with the hopes of obtaining remission and subsequent allogenic stem cell transplant. Palliative measures were also stated to be suitable. However, one clinician pointed out that multiagent re-induction regimens, such as FLAG, or a combination of methotrexate, epirubicin and cisplatin (MEC) are not generally used for patients who progress on front-line treatment, including gemtuzumab ozogamicin. Patients who respond are generally targeted to undergo transplant if eligible.

5.5 Companion Diagnostic Testing

The clinician inputs agreed that, while a specific companion diagnostic test is not required, CD33-positive AML can be confirmed by cytogenetic testing. Cytogenetic testing is performed as a standard of care for AML patients; thus, no additional diagnostic costs would be required. Specifically, POGO stated that all pediatric oncology centres in Ontario perform routine flow cytometry. The results of cytogenetic testing were stated by one clinician to be helpful when considering when to add gemtuzumab ozogamicin to standard induction. However, two individual clinician inputs acknowledged the difference in availability of the test between difference centres, and the concern around turnaround time for results; turnaround time was stated to vary between difference centres from a few days to multiple weeks. One clinician expressed concern about the availability and turnaround time for cytogenetic testing, as this test may be used a discriminating factor when deciding to treat a patient with gemtuzumab ozogamicin.

5.6 Additional Information

POGO highlighted the intensive nature of treatments for patients with AML, as they are associated with substantial life-threatening toxicities, including infections. POGO also highlighted that therapy and subsequent supportive care for pediatric patients occurs in hospital. Funding for gemtuzumab ozogamicin would occur in an inpatient setting. The Cancer Care Ontario New Drug Funding Program (NDFP) traditionally focuses on only outpatient therapies; however, POGO strongly endorsed that gemtuzumab ozogamicin be funded for patients on a per case basis via the NDFP, despite its inpatient administration.

An individual clinician input reiterated that there is strong evidence to support the use of gemtuzumab ozogamicin in AML in the font-line setting in patients with favourable or intermediate and adverse risk karyotypes; the clinician suggested reimbursing the drug for this patient group.

6 SYSTEMATIC REVIEW

6.1 Objective

The primary objective is to determine the efficacy and safety of gemtuzumab ozogamicin (GO) in combination therapy with daunorubicin and cytarabine (DA) compared to other therapies available in Canada for the treatment of patients aged 15 and above with previously untreated acute myeloid leukemia (AML), except acute promyelocytic leukemia. It is worth noting that the objective of the systematic review was based on the original reimbursement request which was then amended to align with the Health Canada approved indication that included adult patients (aged ≥ 18 years) only.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

Table 6.0 Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
• Published or unpublished RCTs • In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of GO in combination therapy with DA should be included	Patients aged 15 and above with previously untreated acute AML, except acute promyelocytic leukemia <u>Subgroups of interest:</u> • Patients with adverse-risk cytogenetics, low risk cytogenetics, and intermediate risk cytogenetics • Patients who have already initiated or completed induction chemotherapy • Patients who have already initiated consolidation chemotherapy • Patients with t-AML • Patients with FLT3-mutations (and who are CD33 positive) • Pediatric populations (15-17 years of age) • De novo CD33 positive vs. CD33 negative	GO (3 mg/m^2)†IV in combination therapy with DA	Daunorubicin + high or standard dose Cytarabine Idarubicin + high or standard dose Cytarabine FLAG-IDA+ standard dose Cytarabine MEC (as first line induction) DAE (Daunorubicin cytarabine with etoposide)** Midostaurin Azacitidine	<u>Efficacy:</u> • EFS • DFS • OS • CRR <u>Patient reported outcome:</u> • HRQOL <u>Safety:</u> • AE • SAE • WDAE <u>Adverse events of special interest:</u> • Neutropenia • Hemorrhage • Hepatotoxicity • Infusion related reactions • QT-interval prolongation • Embryo-foetal toxicity • Thrombocytopenia • Veno-occlusive disease • Other cardiac toxicity

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
AE: Adverse events; AML: Acute Myeloid Leukemia; CRR: Complete remission rate; DA: Daunorubicin + cytarabine; DFS: Disease free survival; EFS: Event Free survival; FLAG-IDA: fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (G-CSF); GO: Gemtuzumab ozogamicin; HRQoL: Health-Related Quality of life; OS: Overall survival; RCT: Randomized Control Trial SAE: Serious adverse events; t-AML: therapy-related AML WDAE: Withdrawal due to adverse events;				

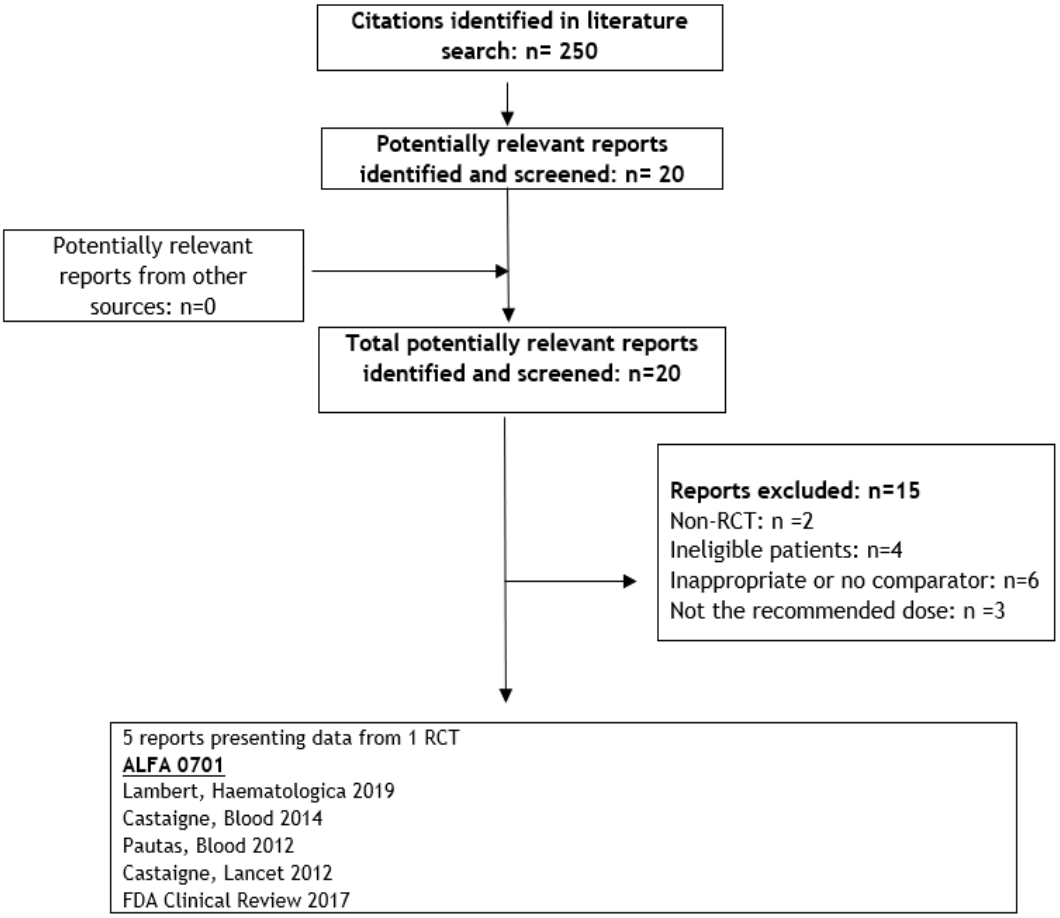
† *Other dosages will be considered*
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*
***Not available in Canada*

6.3 Results

6.3.1 Literature Search Results

Of the 250 potentially relevant reports identified, 1 study (5 reports): the Acute Leukemia French Association (ALFA) -0701 study,[3-5,23,24] was included in the pCODR systematic review, and 12 studies (15 reports) were excluded. Studies were excluded because they were non-randomised comparisons,[25,26] included ineligible patients,[6,27-31] used inappropriate comparators[7,8,32,33] or did not use the recommended dose of GO.[20,34,35]

Figure 6.1. QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to ALFA 0701 were also obtained through requests to the sponsor by CADTH.[1,36]

6.3.2 Summary of the Included Study

One phase III, open-label randomized trial comparing GO in combination with daunorubicin and cytarabine to daunorubicin and cytarabine in patients aged 50-70 years with de novo AML was identified based on the primary objective of the systematic review.

6.3.2.1 Detailed Trial Characteristics

Table 6.1: Summary of Trial Characteristics of the Included Study

Trial Design Characteristics	Key Inclusion / Exclusion Criteria	Intervention & Comparator	Trial Outcomes
ALFA 0701 (Castaigne 2012; Lambert 2019)[3,4]			
• **Phase:** III • **Blinding:** open label • **Randomization method:** a computer-generated sequence • Randomization ratio: 1:1 • **Randomized (n):** 280 • Treated (n):271 • Centres (n): 26 • Countries (n): France • Date – patient enrolment: January 2008 -November 2010 • Date – data cut-off: August 1, 2011 • Date – final analysis: April 30, 2013 • **Funding:** Wyeth (Pfizer)	Inclusion: Previously untreated patients aged 50–70 years, with AML were eligible if they had normal cardiac function. Exclusion: Previous myeloproliferative or myelodysplastic syndrome or exposure to chemotherapy or radiotherapy. CNS involvement in acute myeloid leukaemia, severe uncontrolled infection, and liver (serum aminotransferase concentrations ≥2·5 upper limit of normal [ULN], serum bilirubin ≥2 ULN) or renal (serum creatinine ≥2·5 ULN) dysfunction.	Intervention: Intravenous GO (3 mg/m² [maximum dose 5 mg] infused over 2 h on days 1, 4, and 7; after premedication with methylprednisolone + A 3+7 induction course of intravenous daunorubicin (60 mg/m² on days 1 to 3) and intravenous cytarabine (200 mg/m² as continuous infusion for 7 days). Patients in complete remission or complete remission with incomplete recovery were given two consolidation courses of intravenous daunorubicin (60 mg/m² for 1 day [first course] or 2 days [second course]) in combination with intravenous cytarabine (1000 mg/m² per 12 h, infused over 2 h on days 1–4), with intravenous GO (3 mg/m² on day 1) Comparator: Patients were given a 3+7 induction course of intravenous daunorubicin (60 mg/m² on days 1 to 3) and intravenous cytarabine (200 mg/m² as continuous infusion for 7 days) Patients in complete remission or complete remission with incomplete recovery were given two consolidation courses of intravenous daunorubicin (60 mg/m² for 1 day [first course] or 2 days [second course]) in combination with intravenous cytarabine (1000 mg/m² per 12 h, infused over 2 h on days 1–4), without GO.	Primary: • EFS Secondary: • CRR • OS • RFS

CIR= Cumulative Incidence of Relapse, CR= Complete Remission, CRi: Complete remission with incomplete recovery CRR=Complete Remission Rate, EFS =Event Free Survival, ORR: Overall Remission Rate, Overall Survival= OS, RFS=Remission Free Survival,

a) Trial

One trial met the inclusion criteria. The Acute Leukemia French Association (ALFA)-0701 trial was a randomised open-label phase 3, superiority trial conducted in 26 haematology centres in France. Patients were randomized centrally via telephone in a 1:1 allocation ratio stratified by centre in block sizes of four. Expression of the CD33 antigen on leukemic blast cells was not required for study entry. Cytogenetic analyses were conducted centrally and reported as favourable, intermediate, and adverse based on the International System for Human Cytogenetic Nomenclature criteria. Screening for other relevant mutations was also done centrally: nucleophosmin gene (NPM1), FMS-like tyrosine kinase 3 gene (FLT3) internal tandem duplication (ITD), and CCAAT/enhancer-binding protein alpha gene (CEBPA). Favorable genotypes were defined as normal karyotype and NPM1 mutation without FLT3-ITD or a normal karyotype and CEBPA mutation.

The primary endpoint was event-free survival (EFS). The secondary endpoints were rates of complete remission (CR), overall survival (OS), relapse-free survival (RFS), and safety.[3] The study was powered at 80% to detect an increase in 2-year EFS of 15% (25% in control group; 40% on GO group; hazard ratio [HR] of 0.66) if 140 patients were enrolled and 184 events occurred for a type 1 error rate of 5%. Analyses were by intention-to treat except if the patient withdrew consent. Cox proportional hazards methods were used to compute HRs and 95% confidence intervals (CI). Analyses were adjusted for imbalances of prognostic covariates and treatment centre effects. Sensitivity analyses were conducted to investigate protocol amendments.

There were four protocol amendments (See Table 6.2 below). Of note, the protocol was amended once on December 2009 (Amendment 4) to stop the use of GO during consolidation in patients with a platelet count of less than $100x10^9$/ L by day 45 after initiation of chemotherapy. A total of 178 patients were treated prior to Amendment 4 and 90 patients were treated after Amendment 4.

Four unplanned interim analyses were conducted: 2 were requested by the Agence Francaise de la Sécurité Sanitaire des Produits de Santé (AFSSAPS), one for a conference abstract (ASH 2011) and the last prior to the Lancet paper at the cut-off date of August 1, 2011 using intention to threat analysis.[4] The latter included 278 patients out of 280 randomized (140 to GO; 140 to control). Two patients withdrew consent after randomization. At the time of this analysis, 131 deaths had occurred.[1]

The findings reported here are from the final analyses at cut-off date April 30, 2013 using a modified intention to treat (mITT) analysis (except where indicated). The mITT population was defined as "all patients who were randomized, unless consent was withdrawn before treatment initiation."[3] Participant data were analysed in the arm to which they were randomized irrespective of if they received the intervention.[3] The mITT population included 271 patients (135 in the GO arm and 136 in the control arm). Data from 9 patients (5 in the GO arm; 4 in the control arm) were excluded because no signed copy of the consent form was available in the file. At the time of the April 30, 2013 data-cut-off date, 168 deaths had occurred (80/135 [59.3%] in the GO arm and 88/136[64.7%] in the control arm).[1]

Table 6.2 List of ALFA 0701 Protocol Amendments[5]

Amendment Number	Date of Amendment	Brief Description of the Changes	Primary Reason for the Amendment
1	22 Oct 2007	Addition of recommendation around consolidation course (complete laboratory tests to be performed before each consolidation course and GO should not be administered in case of liver abnormalities). Addition of recommendations around GO infusion in case of hyperleukocytic leukemia.	Changes resulting from discussions with the French regulatory agency.
2	18 Feb 2008	Addition of eligibility criteria (biological specimen for molecular biology/AML arising from known myelodysplastic syndromes documented by myelogram and diagnosed more than 6 months earlier). Additional clarity on Day 15 BMA. Addition of biological sampling for residual disease assessment. Conditions for re-induction course were modified (trigger for re-induction course was revised from Day 15 BMA blasts >10% to Day 15 BMA blasts >5%, and DNR dosing was modified from 60 to 35 mg/m^2/day). Addition of guidelines for allogeneic transplant	Changes resulting from discussions with study investigators.
3	25 May 2009	Addition of the salvage course. Additional clarity on bone marrow transplant with respect to last dose of GO.	Changes resulting from discussions with study investigators.
4	21 Dec 2009	Addition of recommendations around management of persistent Thrombocytopenia: GO to be discontinued ig platelets did not recover to at least 100,000/µL 14 days at the latest after the planned date of next treatment course.	Changes resulting from safety signal observed during the course of the study.

Source: FDA Clinical Review[5]

Some protocol deviations occurred but did not lead to exclusion of patients from the efficacy analyses. A total of thirteen (13) patients had eligibility criteria deviations (abnormal cardiac or hepatic function); 5 patients had a positive HIV/HBV/HCV serology at the time of study entry (2 in the GO arm; 3 in the control arm); 3 randomized patients did not receive treatment (2 in the GO arm; 1 in the control arm).[5]

There were GO dosing errors in 25 patients (19 received GO on an incorrect schedule and 6 received GO at a dose above the maximum 5mg). DA dosing errors were underdosing (11 in GO arm; 12 in control arm), overdosing (8 in GO arm; 6 in control arm) and temporary interruptions (11 in GO arm; 6 in control arm). See Table 6.3.

Table 6.3 ALFA 0701 –Protocol Deviations – ITT Population[5]

	GO + DA N = 140	DA N = 140
Eligibility Criteria		
• ICF not available	5 (4%)	4 (3%)
• Cardiac function not WNL	3 (2%)	4 (3%)
• Inadequate hepatic or renal function	2 (1%)	6 (4%)
• Serology positive for HIV, HBV, or HCV	2 (1%)	3 (2%)
Treatment allocation		
• Treatment not received	4[a] (3%)	0 (0%)
GO dosing error		
• Dosing schedule incorrect	19 (14%)	-
• GO dose >5mg maximum	6 (4%)	-
Chemotherapy dosing error		
• DA underdosed (<10%)	11 (8%)	12 (9%)
• DA overdosed (>10%)	8 (6%)	6 (4%)
• DA temporarily interrupted	11 (8%)	6 (4%)

Abbreviations: WNL – within normal limits; HBV – hepatitis B virus; HCV – hepatitis C virus; HIV – human immunodeficiency virus;
[a] 3/4 patients did not receive GO but did receive DA
Source: FDA Analysis

Source: FDA Clinical Review[5]

b) Populations

The trial randomized a total of 280 patients with median (IQR) age of 62.2 (58.5-66.3). Two patients withdrew consent. The following baseline characteristics reflect the ITT population (n=278; which excludes the two patients that withdrew consent): 50% of patients were male. The majority had an Eastern Cooperative Oncology Group (ECOG) status of 1 (140 patients; 50%) or 0 (104 patients; 37%). The rest had ECOG status of 2 (30 patients; 11%) or 3 (2 patients; <1%). ECOG status was unavailable for 2 (<1%) patients.[3,4,8] The distribution of cytogenetic risk was as follows n=278): favourable (9 patients; 3%), intermediate (182 patients; 65%), adverse (58 patients; 21%) and not available (29; patients 10%). Among the mITT population (n=271), the distribution of cytogenetic risk was as follows: favourable (9 patients; 3%), intermediate (180 patients; 66%), adverse (57 patients; 21%) and not available (25 patients; 9.2%).

A total of ninety three patients (33%) had the NPM1 mutation, 49 patients (18%) were FLT3-ITD positive and 18 patients (6%) had the CEBPA mutation. A total of forty-eight patients (17%) had a favorable genotype.

CD33 expression was not required for enrollment in this trial. Although results are presented for different thresholds, CD33 positivity was considered as any expression (i.e., >0% of positive blasts). According to the sponsor, harmonized central CD33 expression was determined in 71.6% of patients overall (194 out of 271; 100 patients from the GO arm and 94 patients from the control arm), and CD33 status was not available for 28.4% (77 out of 271) of patients. Overall, 99/100 patients in the GO arm and 93/94 patients in the control arm were documented CD33 positive.[1] The distribution of CD33 expression (percentage of leukemic blasts that were CD33-positive using 30% and 70% cut-offs) were as follows: <30% (37 patients; 13.7%), ≥ 30% (157 patients; 57.9%) and <70% (68/25.1%), ≥70% (126 patients; 46.5%).[3,4,23] See Table 6.4 and Table 6.5.

A total of 21 out of 135 (15.6%) patients in the GO arm, and 22 out of 136 (16.2%) patients in the control arm, were documented FLT3-ITD positive. FLT3-ITD status was unknown for a total of 14 patients (5.2%). Of the 21 FLT3-ITD positive patients in the GO arm, 12 were CD33 positive and 9 had an unknown CD33 expression status. Of the 22 FLT3-ITD positive patients in the control arm, 17 were CD33 positive and 5 had an unknown CD33 expression status (Table 6.6). [1]

There are no efficacy or safety data available on the combined CD33+/FLT3-ITD+ status.[1]

Table 6.4 ALFA 0701 Baseline Characteristics in Patients – ITT Population[4]

	Control group	Gemtuzumab ozogamicin group	All patients
Patients	139	139	278
Age (years)			
Median (IQR)	61·7 (57·4–65·6)	62·8 (59·3–66·8)	62·2 (58·5–66·3)
≥60	86 (62%)	100 (72%)	186 (67%)
Men	61 (44%)	77 (55%)	138 (50%)
ECOG performance status			
0	54 (39%)	50 (36%)	104 (37%)
1	65 (47%)	75 (54%)	140 (50%)
2	17 (12%)	13 (9%)	30 (11%)
3	1 (<1%)	1 (<1%)	2 (<1%)
Not available	2 (1%)	0	2 (<1%)
White blood cell count (x10^9 per L; median, IQR)	5·0 (1·9–26·7)	6·9 (2·3–30·4)	5·9 (2·1–29·1)
Platelet count (x10^9 per L; median, IQR)	67·5 (36·3–125·5)	66·0 (36·5–118·5)	67·0 (36·0–122·0)
Percentage of CD33-expressing cells (median, IQR)	88% (57–96)	92% (67–97)	90% (63–97)
Cytogenetics			
Favourable	6 (4%)	3 (2%)	9 (3%)
Intermediate*	91 (65%)	91 (65%)	182 (65%)
Unfavourable	30 (22%)	28 (20%)	58 (21%)
Not available	12 (9%)	17 (12%)	29 (10%)
NPM1 status			
Mutated	48 (35%)	45 (32%)	93 (33%)
Wild type	90 (65%)	91 (65%)	181 (65%)
Not available	1 (<1%)	3 (2%)	4 (1%)
FLT3-ITD status			
Positive	27 (19%)	22 (16%)	49 (18%)
Negative	111 (80%)	115 (83%)	226 (81%)
Not available	1 (<1%)	2 (1%)	3 (1%)
CEBPA status			
Mutated	8 (6%)	10 (7%)	18 (6%)
Wild type	119 (86%)	110 (79%)	229 (82%)
Not available	12 (9%)	19 (14%)	31 (11%)
Genotype (appendix)			
Favourable	24 (17%)	24 (17%)	48 (17%)
Unfavourable	101 (73%)	95 (68%)	196 (71%)
Not available	14 (10%)	20 (14%)	34 (12%)

Data are number or number (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. *Including 72 normal karyotypes in the control group and 70 in the gemtuzumab ozogamicin group.

Table 1: **Baseline characteristics of patients**

Source: Castaigne et al. Lancet. 2012;379(9825):1508-1516.[4] Copyright 2012. Reprinted with permission from Elsevier.

Table 6.5 ALFA 0701 Baseline Characteristics in Patients – mITT Population[3]

SUPPLEMENTAL TABLES

Table S1. Baseline Patient Characteristics (mITT Population)

	GO (n=135)	Control (n=136)	Total (N=271)
Age, y			
Median (range)	62 (50–70)	61 (50-70)	62 (50–70)
≥60, n (%)	97 (71.9)	84 (61.8)	181 (66.8)
Men, n (%)	74 (54.8)	60 (44.1)	134 (49.4)
ECOG performance status, n (%)			
0–1	121 (89.6)	117 (86.0)	238 (87.8)
≥2	14 (10.4)	18 (13.2)	32 (11.8)
Not available	0	1 (0.7)	1 (0.4)
White blood cell count ($x10^9$/L) categories, n (%)			
<30	108 (80.0)	114 (83.8)	222 (81.9)
≥30	26 (19.3)	21 (15.4)	47 (17.3)
CD33 expression (positivity)			
N	100	94	194
<30%, n (%)	17 (12.6)	20 (14.7)	37 (13.7)
≥30%, n (%)	83 (61.5)	74 (54.4)	157 (57.9)
<70%, n (%)	37 (27.4)	31 (22.8)	68 (25.1)
≥70%, n (%)	63 (46.7)	63 (46.3)	126 (46.5)
Cytogenetics, n (%)*			
Favorable	3 (2.2)	6 (4.4)	9 (3.3)
Intermediate	91 (67.4)	89 (65.4)	180 (66.4)
Unfavorable	27 (20.0)	30 (22.1)	57 (21.0)
Not available	14 (10.4)	11 (8.1)	25 (9.2)
Genotype*			
Favorable risk	27 (20.0)	24 (17.6)	51 (18.8)
Unfavorable risk	44 (32.6)	40 (29.4)	84 (31.0)
Not available	64 (47.4)	72 (52.9)	136 (50.2)

Control, daunorubicin + cytarabine; D+A, daunorubicin + cytarabine; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent to treat; GO, gemtuzumab ozogamicin plus D+A.

*As classified by Centre Hospitalier de Versailles.

Source: Lambert et al., 2019.[3] Copyright 2019 Ferrata Storti Foundation. Reprinted in accordance with CC BY-NC 4.0.

Table 6.6. Summary of CD33 Positivity and FLT3-ITD (without regard to karyotype status) at Baseline (mITT Population)[1]

	GO + Daunorubicin + Cytarabine (N=135)	Daunorubicin + Cytarabine (N=136)	Total (N=271)
CD33 expression (%) >0 / FLT3-ITD positive	**12 (8.9)**	**17 (12.5)**	**29 (10.7)**
CD33 expression (%) >0 / FLT3-ITD negative	84 (62.2)	68 (50.0)	152 (56.1)
CD33 expression (%) >0 / FLT3-ITD unknown	3 (2.2)	8 (5.9)	11 (4.1)
CD33 expression (%) =0 / FLT3-ITD negative	1 (0.7)	1 (0.7)	2 (0.7)
CD33 expression (%) unknown / FLT3-ITD positive	**9 (6.7)**	**5 (3.7)**	**14 (5.2)**
CD33 expression (%) unknown / FLT3-ITD negative	24 (17.8)	36 (26.5)	60 (22.1)
CD33 expression (%) unknown / FLT3-ITD unknown	2 (1.5)	1 (0.7)	60 (1.1)

FLT3-ITD status regardless of karyotype status.
CD33 positivity on AML blasts by flow cytometry harmonized from local laboratory results rounded to the nearest whole percent.
Source: Pfizer response to pCODR checkpoint meeting questions[1]

c) Interventions

In the ALFA 0701 trial, patients in the intervention group received intravenous GO (3 mg/m^2 [maximum dose 5 mg] infused over 2 h on days 1, 4, and 7); after premedication with methylprednisolone and a 3+7 induction course of intravenous daunorubicin (60 mg/m^2 on days 1 to 3) and intravenous cytarabine (200 mg/m^2 as continuous infusion for 7 days).
Bone marrow aspirates were taken on day 15 and if there were more than 10% persistent leukemic blasts a second induction course was given with intravenous daunorubicin (60 mg/m^2 per day for 2 days and intravenous cytarabine (1000 mg/m^2 per 12 h, infused over 2 h for 3 days), followed by daily granulocyte colony-stimulating factor (lenograstim 263 µg, intravenously) until neutrophil recovery.

Patients in complete remission or complete remission with incomplete recovery were given two consolidation courses of intravenous daunorubicin (60 mg/m^2 for 1 day [first course] or 2 days [second course]) in combination with intravenous cytarabine (1000 mg/m^2 per 12 h, infused over 2 h on days 1–4), with intravenous GO (3 mg/m^2 on day 1). In the control group the treatment was the same except for the absence of GO.[3,4]

No GO or chemotherapy dose reductions were defined.[5]

In the GO arm 3 patients in induction, 6 patients first consolidation therapy and 18 patients in second consolidation therapy did not receive GO but continued treatment with DA.[5]

Of the 280 patients randomized, 134 patients completed induction. A total of ninety-seven patients received first consolidation therapy and 89 received second consolidation therapy.

"*All patients who received chemotherapy in either arm in each phase received >80% of the planned doses.*"[5]

According to the sponsor, "the median overall duration of study treatment, from first dose until last dose of study treatment (including recovery periods without treatment) was 12.1 weeks (range, 0.6 to 22.1 weeks) in the GO arm and 11.7 weeks (range, 0.3 to 19.0 weeks) in the control arm."[1]

Concomitant medication taken during the trial are categorised as anti-infectious, liver toxicity and cardiac toxicity treatments. Selected concomitant medication (using the as-treated population) are outlined in the Table 6.7 below:

Table 6.7 Selected Concomitant Medication (As-Treated Population)[36]

WHO Drug Classification Drug Name	GO + Daunorubicin + Cytarabine (N=131)	Daunorubicin + Cytarabine (N=137)
Anti-Infectious Treatment		
All Other Therapeutic Products		
Cilastatin	1 (0.8)	1 (0.7)
Antibacterials for Systemic Use		
Amikacin	42 (32.1)	43 (31.4)
Amoxi-Clavulanico	1 (0.8)	2 (1.5)
Amoxicillin	3 (2.3)	4 (2.9)
Aztreonam	2 (1.5)	3 (2.2)
Bactrim	2 (1.5)	4 (2.9)
Carbapenems	0	1 (0.7)
Cefazolin	0	1 (0.7)
Cefepime	9 (6.9)	6 (4.4)
Cefotaxime	0	2 (1.5)
Cefoxitin	0	1 (0.7)
Ceftazidime	20 (15.3)	19 (13.9)
Ceftriaxone	12 (9.2)	4 (2.9)
Ciprofloxacin	10 (7.6)	17 (12.4)
Claventin /00973701/	3 (2.3)	2 (1.5)
Clindamycin	0	1 (0.7)
Cloxacillan	1 (0.8)	0
Colistin	1 (0.8)	1 (0.7)
Doripenem	0	1 (0.7)
Erythromycin	1 (0.8)	0
Fosfomycin	2 (1.5)	0
Fusidic Acid	1 (0.8)	0
Gentamicin	21 (16.0)	9 (6.6)
Imipenem	0	1 (0.7)
Levofloxacin	0	3 (2.2)
Linezolid	6 (4.6)	6 (4.4)
Metropenem	2 (1.5)	0
Metronidazole	9 (6.9)	3 (2.2)
Ofloxacin	2 (1.5)	6 (4.4)
Ornidazole	0	2 (1.5)
Oxacillin	1 (0.8)	1 (0.7)
Pip/Tazo	55 (42.0)	49 (35.8)
Piperacillin	8 (6.1)	1 (0.7)
Primaxin	39 (29.8)	42 (30.7)
Spiramycin	1 (0.8)	1 (0.7)
Sulfamethoxazole	1 (0.8)	0
Teicoplanin	9 (6.9)	19 (13.9)
Ticarcillin	1 (0.8)	0
Tobramycin	8 (6.1)	3 (2.2)
Vancomycin	61 (46.6)	63 (46.0)

Table 6.7 Selected Concomitant Medication (As-Treated Population) – con't

Table 7. Selected Concomitant Medications (As-Treated Population) – con't

WHO Drug Classification Drug Name	GO + Daunorubicin + Cytarabine (N=131)	Daunorubicin + Cytarabine (N=137)
Anti-Infectious Treatment (con't)		
Antimycobacterials		
Rifampicin	0	1 (0.7)
Antimycotics for Systemic Use		
Amphotericin B	14 (10.7)	7 (5.1)
Caspofungin	14 (10.7)	12 (8.8)
Fluconazole	4 (3.1)	2 (1.5)
Flucytosine	1 (0.8)	0
Voriconazole	13 (9.9)	10 (7.3)
Antivirals for Systemic Use		
Aciclovir	2 (1.5)	1 (0.7)
Oseltamir	0	1 (0.7)
Ribavirin	0	1 (0.7)
Liver Toxicity Treatment		
Antithrombotic Agents		
Defibrotide	2 (1.5)	1 (0.7)
Bile and Liver Therapy		
Ursodeoxycholic Acid	0	1 (0.7)
Drugs for Functional Gastrointestinal Disorders		
Trimebutine	1 (0.8)	0
Cardiac Toxicity Treatment		
Agents Acting on the Renin-Angiotensin System		
Bi Predonium	2 (1.5)	0
Co-Diovan	1 (0.8)	1 (0.7)
Irbesartan	1 (0.8)	0
Perindopril	1 (0.8)	2 (1.5)
Ramipril	6 (4.6)	6 (4.4)
Valsartan	1 (0.8)	1 (0.7)
Zaneril	0	1 (0.7)
Antithrombotic Agents		
Clopidogrel	1 (0.8)	0
Heparin	1 (0.8)	2 (1.5)
Beta Blocking Agents		
Atenolol	1 (0.8)	1 (0.7)
Bisoprolol	3 (2.3)	5 (3.6)
Carvedilol	0	1 (0.7)
Calcium Channel Blockers		
Amlodipine	9 (6.9)	11 (8.0)
Lercanidipine	0	1 (0.7)
Nicardipine	31 (23.7)	24 (17.5)

Table 6.7 Selected Concomitant Medication (As-Treated Population) -con't

Table 7. Selected Concomitant Medications (As-Treated Population) – con't

WHO Drug Classification Drug Name	GO + Daunorubicin + Cytarabine (N=131)	Daunorubicin + Cytarabine (N=137)
Cardiac Toxicity Treatment (con't)		
Cardiac Therapy		
Amiodarone	4 (3.1)	6 (4.4)
Digoxin	1 (0.8)	3 (2.2)
Dobutamine	2 (1.5)	2 (1.5)
Epinephrine	1 (0.8)	1 (0.7)
Flecainide	0	1 (0.7)
Isosorbide dinitrate	2 (1.5)	1 (0.7)
Norepinephrine	3 (2.3)	3 (2.2)
Trimetazidine	0	1 (0.7)
Diuretics		
Furosemide	19 (14.5)	18 (13.1)
Hydrochlorothiazide	1 (0.8)	0
Spironolactone	2 (1.5)	3 (2.2)
Lipid Modifying Agents		
Rosuvastatin	0	1 (0.7)
Ophthalmologicals		
Isosorbide	0	1 (0.7)

Source: Table 14.4.2.5.1

Per the retrospective data collection, only G-CSF, corticosteroids, IV antibiotics, and any new treatments for cardiac and liver conditions were collected and reported.
WHODrug v2015Q2 applied.
Abbreviations: G-CSF=granulocyte colony-stimulating factor; GO=gemtuzumab ozogamicin; IV=intravenous; N=number of patients; Q=quarter; v=version; WHO=World Health Organization.

Source: Clinical Study Report ALFA-0701[36]

In the post-study period 96 patients in the GO arm and 109 in the control arm had at least one follow-up therapy. A total of two in the GO arm and 30 in the control arm received GO as part of follow-up therapy, while 32 (23.7%) in the GO arm and 53 (39.0%) in the control arm received hematopoietic stem cell transplantation (HSCT). See Table 6.8 and 6.9 below.

Table 6.8 Post-study treatment (mITT population)[3]

	GO n=135	Control n=136
Patients with ≥1 follow-up therapy, n (%)	96 (71.1)	109 (80.1)
Patients receiving GO as a component of follow-up therapy, n (%)	2 (1.5)	30 (22.1)
Patients with HSCT, n (%)	32 (23.7)	53 (39.0)
Timing of HSCT, n (%)		
In first remission for responder patients	17 (12.6)	22 (16.2)
After induction failure	2 (1.5)	9 (6.6)
After relapse	13 (9.6)	22 (16.2)

Data are number (n) (%) unless otherwise indicated. Control: 3+7 daunorubicin + cytarabine (DA); GO: gemtuzumab ozogamicin + 3+7 DA; HSCT: hematopoietic stem cell transplant; mITT: modified intent to treat.

Source: Lambert et al., 2019.[3] Copyright 2019 Ferrata Storti Foundation. Reprinted in accordance with CC BY-NC 4.0.

Further details on the number of follow up regimens and treatments are outlined in Table 6.9.

Table 6.9 Follow-up Therapy (for Acute Myeloid Leukemia) (mITT Population)

	GO + Daunorubicin + Cytarabine (N=135)	Daunorubicin + Cytarabine (N=136)	Total (N=271)
	n (%)	n (%)	n (%)
Patients with at least 1 follow-up therapy	**96 (71.1)**	**109 (80.1)**	**205 (75.6)**
Patients receiving GO as a component of follow-up therapy	**2 (1.5)**	**30 (22.1)**	**32 (11.8)**
Number of follow-up regimens[a]			
1	38 (28.1)	35 (25.7)	73 (26.9)
2	26 (19.3)	35 (25.7)	61 (22.5)
3	21 (15.6)	19 (14.0)	40 (14.8)
>3	11 (8.1)	20 (14.7)	31 (11.4)
Number of follow-up induction regimens[b]			
1	56 (41.5)	61 (44.9)	117 (43.2)
2	13 (9.6)	17 (12.5)	30 (11.1)
3	5 (3.7)	9 (6.6)	14 (5.2)
>3	3 (2.2)	3 (2.2)	6 (2.2)
Number of follow-up consolidation regimens[c]			
1	42 (31.1)	35 (25.7)	77 (28.4)
2	20 (14.8)	24 (17.6)	44 (16.2)
3	2 (1.5)	7 (5.1)	9 (3.3)
>3	1 (0.7)	4 (2.9)	5 (1.8)
Follow-up therapy (>10%)[d]			
Cytarabine	65 (48.1)	77 (56.6)	142 (52.4)
Fludarabine	33 (24.4)	47 (34.6)	80 (29.5)
Azacitidine	25 (18.5)	36 (26.5)	61 (22.5)
Idarubicin	24 (17.8)	31 (22.8)	55 (20.3)
Busulfan	16 (11.9)	36 (26.5)	52 (19.2)
Amsacrine	18 (13.3)	22 (16.2)	40 (14.8)
Gemtuzumab ozogamicin	2 (1.5)	30 (22.1)	32 (11.8)
Etoposide	13 (9.6)	15 (11.0)	28 (10.3)

Source: Table 14.4.6.4
Data collected as part of retrospective data collection.
Abbreviations: CR=complete response; GO=gemtuzumab ozogamicin; HSCT=hematopoietic stem cell transplant; mITT=modified intent-to-treat; N=number of patients; n=number of patients; Q=quarter; v=version; WHO=World Health Organization.

a. Follow-up regimen included HSCT conditioning regimen.
b. As per CRF completion guidelines (Section 16.1.2), follow-up induction regimen was any regimen given before CR.
c. As per CRF completion guidelines, follow-up consolidation regimen was any regimen given while patient in CR.
d. WHODrug v2015Q2 applied.

Source: Clinical Study Report ALFA-0701[36]

d) Patient Disposition

The median (IQR) follow up was 14.8 months (9.3-23.8), overall; and 20.0 months (14.5-30.5) among survivors.

In the GO arm, 64/140 patients (46%) completed GO treatment. The most common cause of permanent discontinuation in the GO arm was adverse events (42/140; 30%) followed by resistant disease (17/140[12%]). The most common cause of permanent discontinuation in the control arm was resistant disease (19/140; 14%) followed by adverse events (8/140; 6%).

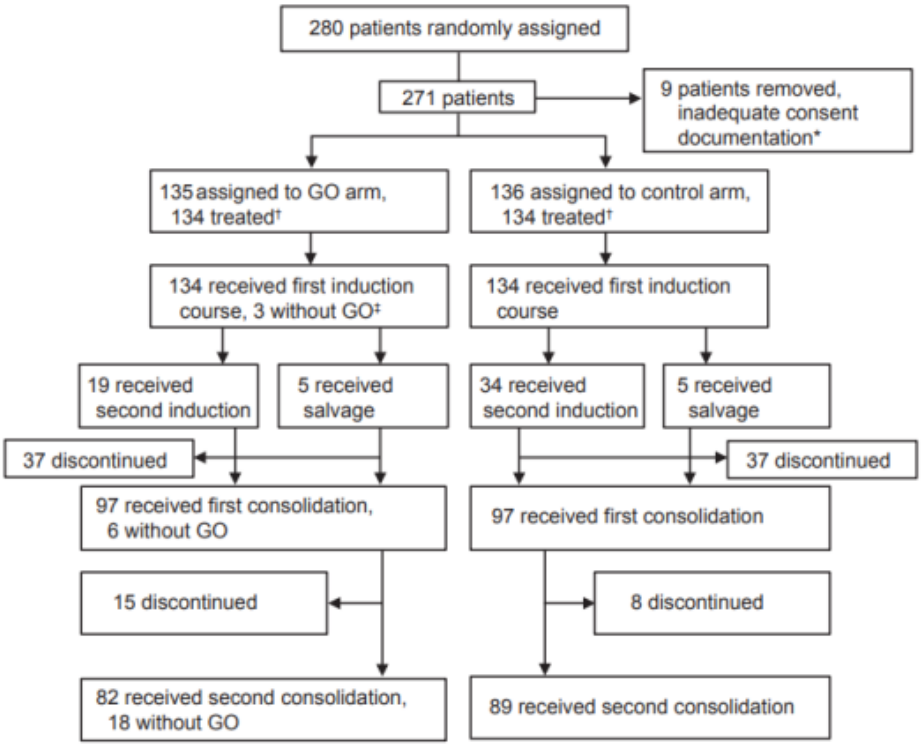
The CONSORT flow diagram is shown below in Figure 6.2 as well as the patient disposition in Table 6.10.

Figure 6.2 ALFA 0701 CONSORT Diagram[3]

Patients in the control arm were administered standard 3+7 D+A induction chemotherapy. In the GO arm, patients were administered GO via a 3 × 3 mg/m^2 (not exceeding one 5-mg vial per dose) fractionated dosing regimen plus standard D+A chemotherapy. Patients randomized to the GO arm received 1 additional dose of GO 3 mg/m^2 in each of 2 consolidation courses of D+A.

D+A, daunorubicin + cytarabine; GO, gemtuzumab ozogamicin plus D+A.

*Noted at the time of data transfer (April 30, 2013).
†3 patients not treated (GO arm, n=1; control arm, n=2); reasons were death or eligibility violation because of esophageal cancer or hepatitis B.
‡Reasons for not receiving GO during induction were either abnormal liver function, eligibility criteria not met, or death.



Source: Lambert et al., 2019.[3] Copyright 2019 Ferrata Storti Foundation. Reprinted in accordance with CC BY-NC 4.0.

Table 6.10 ALFA 0701 Patient Disposition – ITT Population[5]

	GO + DA N=140 n (%)		DA N=140 n (%)
Completed treatment	GO	DA	DA
Induction	131[a, b, c] (94%)	134[a, b] (96%)	134[a, b] (96%)
Consolidation 1	91[d] (65%)	97 (69%)	97 (69%)
Consolidation 2	64[e] (46%)	82 (59%)	89 (64%)
Discontinued treatment	GO	DA	DA
Adverse Event	42 (30%)	27 (19%)	8 (6%)
Death (all causality)	7 (5%)	7 (5%)	5 (4%)
Other	6 (4%)	2 (1%)	4 (3%)
Protocol violation	2 (1%)	1 (1%)	2 (1%)
Resistant disease/ Relapse	17 (12%)	19 (14%)	29 (21%)
Started new treatment	3 (2%)	3 (2%)	3 (2%)
Symptomatic deterioration	1 (1%)	1 (1%)	0 (0%)

Source: FDA Analysis

a. 9 patients were randomized who did not have a copy of the ICF available were not included in the datasets or analyses (5 patients in GO arm, 4 in control arm)
b. 3 patients not treated (2 patients in control arm, 1 in GO arm) due to 1. eligibility protocol violation – esophageal cancer, 2. death, 3. eligibility protocol violation – Hepatitis B
c. 3 patients did not receive GO in induction due to 1. abnormal liver function, 2. unknown – eligibility criteria not met (1403), 3. death
d. 6 patients did not receive GO in C1 but received DA
e. 18 patients did not receive GO in C2 but received DA

Source: FDA Clinical Review[5]

e) Limitations/Sources of Bias

Overall the study was well conducted, with central randomization leading to appropriate allocation concealment. All clinical outcomes that could be reasonably expected and those planned for in the trial registry are reported. Quality of life was not reported. The study was open label, but knowledge of treatment is unlikely to influence the efficacy outcomes given that the primary outcome is objective and an independent blinded review of the event-free survival endpoint was conducted. However, the possibility of reporting bias (e.g., for subjective adverse events) should be noted. A total of 82/140 patients completed treatment in the GO arm and 89/140 in the control arm for a total of 171/140 (61.1%).[5] The analyses were appropriate, using a modified intention-to-treat approach. Some patients it the GO arm did not receive GO as planned, but there was no crossover. A total of six patients in the control arm received GO after induction failure and 24 received it after relapse. Any potential crossover effects would bias the results against GO. Baseline differences and treatment centre effects were accounted for using adjusted analyses. Subgroup effects were tested using interaction terms. Further adjustments for protocol amendments were explored by stratified the data by whether patients were included before or after the amendment. "Estimates of treatment effect were not greatly affected when the analysis was stratified for the period of inclusion in relation to protocol amendment (data not shown)."[4] The Lan-DeMets alpha spending approach with an O'Brien-Fleming efficacy boundary was applied control the overall Type I error rate after interim analyses. However, the analysis of secondary outcomes did not account for multiple testing; therefore, these analyses are considered

exploratory. Multiple testing can increase the probability of type 1 error and, therefore, lead to false positive conclusions. This study was funded by Wyeth (Pfizer).

Table 6.11: Select quality characteristics of included study of gemtuzumab ozogamicin in patients with acute myeloid lymphoma

Study	ALFA 0701 (Castaigne 2012, Lambert 2019)
Treatment vs. Comparator	GO + daunorubicin + ARA-C versus daunorubicin + ARA-C
Primary outcome	Response rate
Required sample size	140
Sample size	280
Randomization method	Central randomization (1:1 ratio) and telephone allocation using a randomization sequence developed in R software. Randomization was done in block sizes of 4 and stratified by centre.
Allocation concealment	Allocation was done remotely/centrally by telephone
Blinding	No
ITT Analysis	Yes (modified intention to treat: all patients who were randomized, unless consent was withdrawn before the start of treatment)
Final analysis	April 30, 2013
Early termination	No
Ethics Approval	Saint-Germain en Laye ethics committee in France and the institutional review board of the French Regulatory Agency
GO =gemtuzumab ozogamicin, ARA-C=cytarabine, DA= Daunorubicin/cytarabine, FLAD-Ida = fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (G-CSF)	

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The results reported here are based on the final analysis results, cut off date April 30, 2013, unless otherwise stated. See Table 6.12, Table 6.13, Figure 6.3 and Figure 6.4.

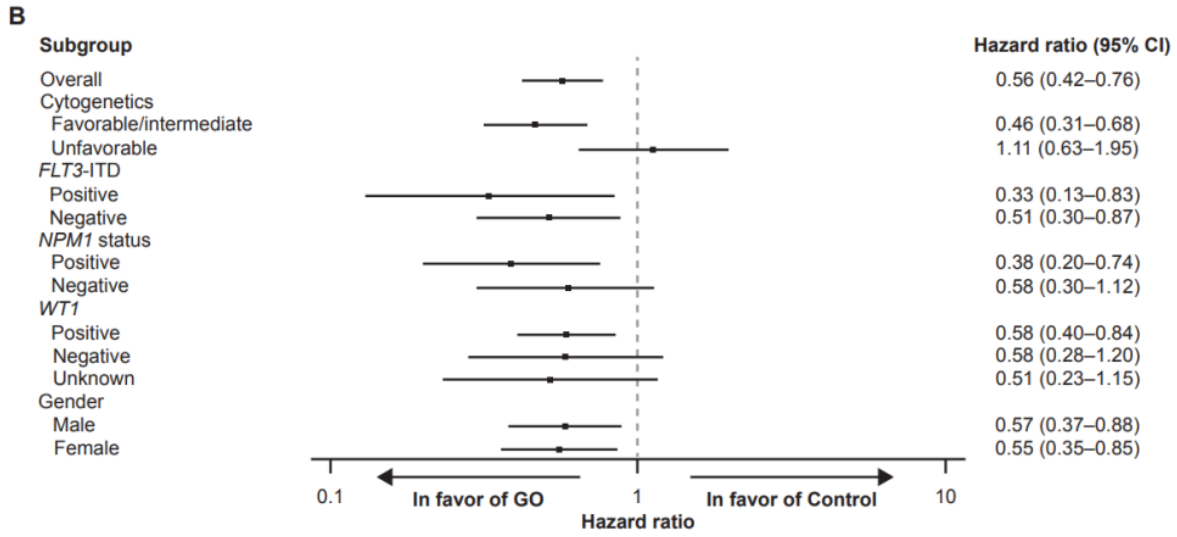
Efficacy Outcomes

Primary Outcome:

Event Free Survival (EFS): Median (EFS at 2 years was longer in the GO group and estimated at 40.8%; 95% CI 32.8–50.8) in the GO group versus 17.1% (10.8–27.1) in the control group for a hazard ratio of 0.58; 95% CI 0.43-0.78; p=0.0003).[4] This corresponds to a clinically relevant increase of 23.7% EFS (the prespecified target was 15%).[4] At 3 years, EFS was longer in the GO group (17.3 months; 95 % CI 13.4-30.0) than the control group (9.5 months; 95% CI 8.1-12.0) for a hazard ratio of 0.56 (95% CI 0.42-0.72; p=0.0002).[3] These results were statistically significant. In subgroup analyses (at 2 years with the mITT population), for patients with favourable or intermediate cytogenetics, EFS was longer in the GO arm (HR 0.46; 95% CI 0.31-0.68; p <0.0001) but not for patients with adverse cytogenetics (HR 1.11; 95% CI 0.63-1.95; p=0.72).[3] Even though the subgroups were prespecified, and conducted appropriately, the trial was not sufficiently powered to detect a subgroup treatment effect. This is apparent in the wide and overlapping

confidence intervals. However, there is preliminary is evidence in favour of a difference in magnitude of effect across cytogenetic subgroups but not a difference in direction of effect.

Figure 6.3 EFS subgroup analyses (A) and (B) – by investigator assessment at August 1, 2011, cut off (mITT population)[3]



Source: Lambert et al., 2019.[3] Copyright 2019 Ferrata Storti Foundation. Reprinted in accordance with CC BY-NC 4.0.

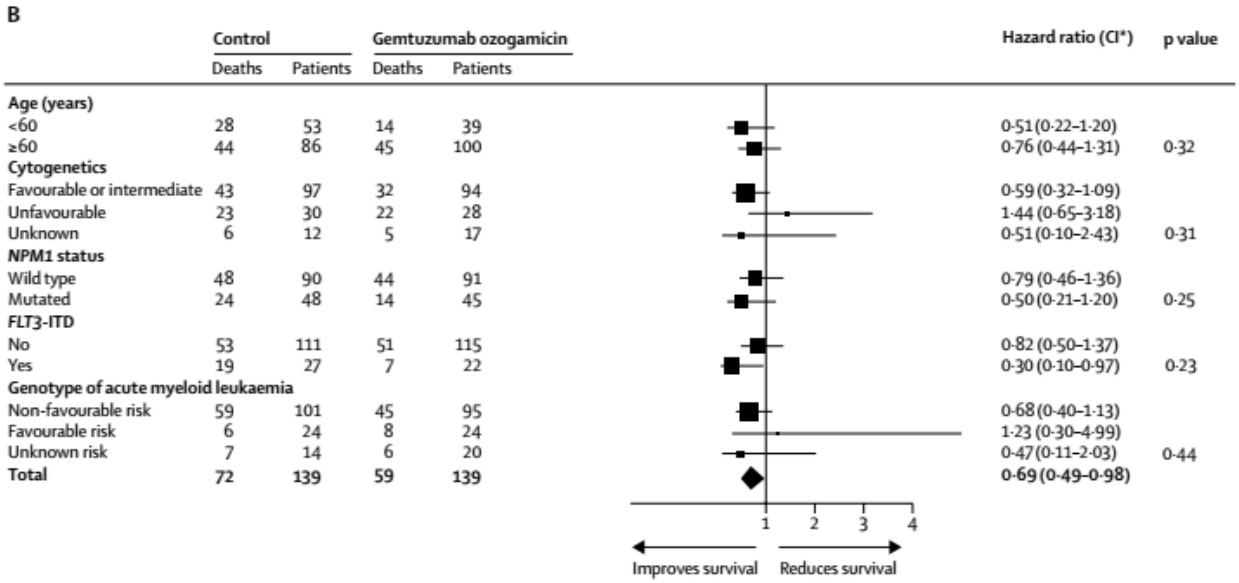
Secondary Outcomes:

Disease Free Survival (DSF): DSF was not reported in the ALFA 701 study.

Overall survival (OS): Median OS at 2 years was longer in the GO group, estimated at 15.6 months; 95% CI 11.7-22 versus 9.7 months ;95% CI 8.0-11.9 in the control group for a hazard ratio of 0.69; 95% CI 0.49-0.98.[4] At 3 years, the difference in OS was not statistically significant, with median of 27.5 months;95% CI 21.4-45.6 in the GO arm and 21.8 months (95% CI15.5-27.4) for a hazard ratio of 0.81; 95% CI 0.60-1.09; p=0.16.[3]

At 2 years in the ITT population, there was no difference in OS between arms for the patients with favourable or intermediate (HR 0.59; 95% CI 0.32-1.09), adverse (HR 1.44; 95% CI 0.65-3.18) or unknown risk cytogenetics (HR 0.51; 95% CI 0.10-2.43).[4]

Figure 6.4. Forest plot of subgroup analyses[4]



Source: Castaigne et al. Lancet. 2012;379(9825):1508-1516.[4] Copyright 2012. Reprinted with permission from Elsevier.

Complete Remission (Response Rate)

At 2 years in the ITT population (August 1, 2011 data cut-off), there was no difference in complete remissions rated, with 113/139 (81%) in the GO arm and 104/139 (75%) in the control arm, for an odds ratio (OR) of 1.46; 95% CI 0.20-2.59; p=0.25.[4]

Overall response rate by investigator assessment (using mITT population, data cut-off April 30, 2013) was 81% (110 out of 135; 95% CI 73.9-87.6) in the GO arm and 73.5% (110 out of 136; 95% CI 65.3–80.7) in the control arm. Complete remission rates were similar (70.4% versus 69.9%), while complete remission with incomplete platelet recovery was 11.1% in the GO arm compared to 3.7% in the control arm.[3]

Quality of Life

No studies reported quality of life outcomes.

Harms Outcomes

The frequencies of key harm outcomes are summarized in Table 6.12. In the as-treated population(defined as all patients who received ar least one dose of study treatment), treatment related deaths were more frequent in the GO arm (8 patients; 6.1%) compared to the control arm (3 patients; 2.2%).[5] Serious adverse events (SAE) were more frequent in the GO arm (88; patients 67.2%) compared to the control arm (76 patients; 55.5%). Withdrawals due to adverse events (WDAE) were more frequent in the GO arm (41 patients; 31.3%) compared to control (10 patients; 7.3%). The frequency of neutopoenia was similar in the GO (129 patients; 97.7%)and control arms (135 patients; 98.5%). Hemorrhage was more frequent in the the in GO arm (12 patients; 9.0%) compared to the control arm (4 patients; 3.0%). Hepatotoxicity was higher in the the GO arm (18 patients; 13.0%) compared to the control arm (9 patients; 6.0%). Thrombocytopoenia was more frequent in the GO arm (34 patients; 26%) compared to the control arm (6 patients; 4.4%). Veno-

occlusive events only occurred in the GO arm (5 patients; 3.8%). Cardiac events were comparable in both groups (11patients [8.0%] in the GO arm vs 9 patients [6.0%] in the control arm).

Clinically relevant laboratory abnormalities in the as-treated population are outlined in Table 6.13.

Table 6.12 Highlights of Key Outcomes[3,4]

ALFA 0701 (Castaigne 2012; Lambert 2019)		
Efficacy Outcomes from Final Analysis Data Cut-off April 30, 2013 (modified intention to treat population)	**GO (N=135)**	**No Go (N= 136)**
3-year EFS	**18.0 (9.4-NE)**	**12.2 (8.1-15.6)**
HR (95% CI)	0.66 (0.49-0.89)	
p-value	0.006	
DFS		
HR (95% CI)	NR	
p-value	**NR**	
3-year OS	**27.5 (21.4-45.6)**	**21.8 (15.5-27.4)**
HR (95% CI)	0.81 (0.6-1.09)	
p-value	**0.16**	
3-year CR		
N (%)	110 (81.5)	100 (73.5)
OR (95% CI)	**1.58 (0.86-2.96) ****	
p-value	**0.146****	
HRQoL		
Difference (95% CI)	**NR**	**NR**
Harms Outcomes from Final Analysis Data Cut-off April 30, 2013 (As treated population)	**GO (N=131)**	**No Go (N=137)**
Any Grade AE	**NR**	**NR**
Grade 3-4 AE	**NR**	**NR**
SAE	**88 (67.2)**	**76 (55.5)**
WDAE	**41(31.3) †**	**10(7.3) †**
TRAE (serious)	**80(61.1)**	**58 (42.3)**
Neutropoenia	**129 (97.7)**	**135 (98.5)**
Infusion related	**NR**	**NR**
QT prolongation	**NR**	**NR**
Embryo-foetal	**NR**	**NR**
Thrombocytopenia	**34 (26.0)**	**6 (4.4)**
Veno-occlusive	**5(3.8)**	**0(0.0)**
Other cardiac	**NR**	**NR**
Efficacy Outcomes from Interim Analysis Data Cut-Off: August 1, 2011	**GO (N=139)**	**No Go (N= 139)**
2-year EFS		
HR (95% CI)	0.58 (0.43-0.78)	
p-value	0.0003	
2-year OS		
HR (95% CI)	**0.69 (0.49-0.98)**	
p-value	**0.0368**	
2-year CR		
N (%)	104 (75)	113 (81)
OR (95% CI)	1.46 (0.82-2.59)	

Harms Outcomes from interim Analysis Data Cut-Off: August 1, 2011	GO (N=139)	No Go (N=139)
Hemorrhage¥	**12 (9.0)**	**4 (3.0)**
Hepatotoxicity¥	**18 (13.0)**	**9 (6.0)**
AE = adverse event, **CI** = confidence interval, **HR** = hazard ratio, HRQoL = health-related quality of life, **NR** = not reported, **OR** = odds ratio, **WDAE** = withdrawal due to adverse event, **EFS**=Event Free Survival, DFS=Disease Free Survival, **OS**=Overall Survival, **CR**=Complete Remission; ¥Grades 3and 4; † Permanent drug discontinuation; *HR/OR < 1 favours GO; **Computed from data		

Table 6.13 Clinically Relevant Laboratory Abnormalities (As-Treated Population*)[3]

Laboratory Abnormality	GO			Control		
	n	All Grades, %	Grade 3/4, %	n	All Grades, %	Grade 3/4, %
Hematologic						
Hemoglobin decreased	130	100	86.2	136	100	89.7
Lymphocytes (absolute) decreased	129	98.5	90.7	135	97.8	89.6
Neutrophils decreased	129	97.7	96.1	135	98.5	97.0
Platelets decreased	131	100	100	136	100	100
WBC count decreased	131	100	100	136	99.3	99.3
Nonhematologic						
ALT increased	129	78.3	10.9	134	81.3	15.7
ALP increased	128	79.7	13.3	132	68.9	5.3
AST increased	129	89.2	14.0	134	73.9	9.0
Blood bilirubin increased	126	51.6	7.1	132	50.8	3.8
Hyperglycemia	125	92.0	19.2	135	91.1	17.8
Hyperuricemia	117	32.5	2.6	123	28.5	0

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; control, daunorubicin + cytarabine; D+A, daunorubicin + cytarabine; GO, gemtuzumab ozogamicin plus D+A; WBC, white blood cell.

*Defined as all patients who received at least 1 dose of study medication and reported according to whether or not GO was received.

Source: Lambert et al., 2019.[3] Copyright 2019 Ferrata Storti Foundation. Reprinted in accordance with CC BY-NC 4.0.

Figure 6.5 ALFA 0701 Event-free Survival (EFS) (investigator-assessed)[3]

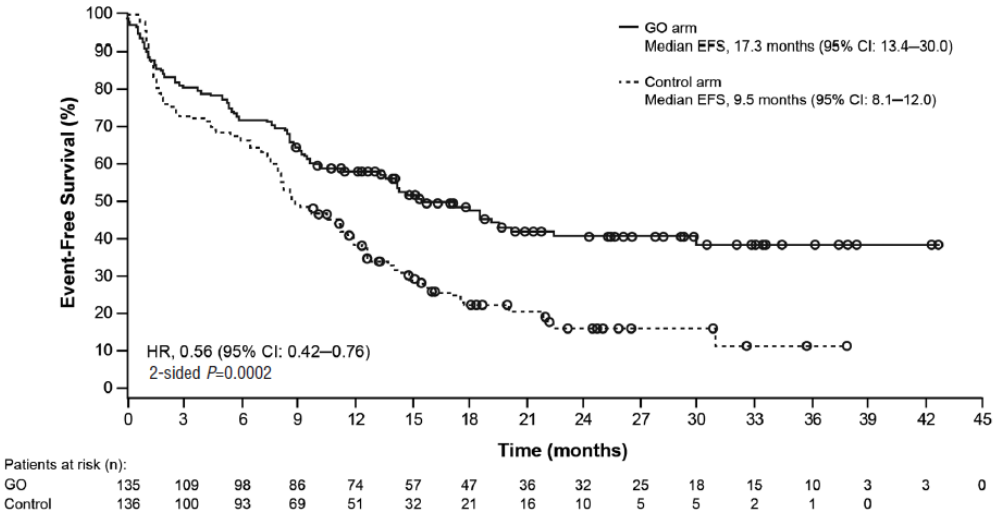


Figure 2. Event-free survival (EFS) (investigator-assessed). Control: daunorubicin + cytarabine (D+A); GO: gemtuzumab ozogamicin plus D+A; EFS: event-free survival; HR: hazard ratio; CI: Confidence Interval; n: number.

Source: Lambert et al., 2019.[3] Copyright 2019 Ferrata Storti Foundation. Reprinted in accordance with CC BY-NC 4.0.

Figure 6.6 ALFA 0701 Overall Survival

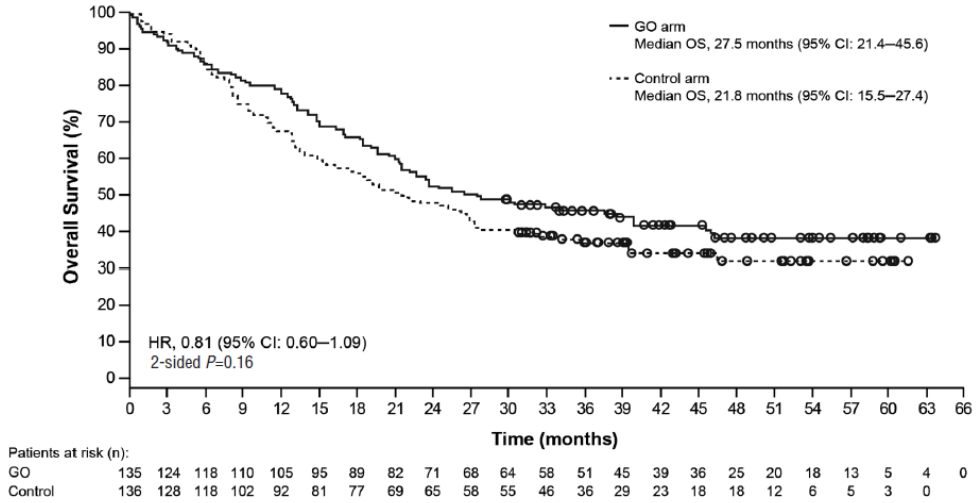


Figure 1. Overall survival. Control: daunorubicin + cytarabine (D+A); GO: gemtuzumab ozogamicin plus D+A; OS: overall survival; HR: hazard ratio; CI: Confidence Interval; n: number.

Source: Lambert et al., 2019.[3] Copyright 2019 Ferrata Storti Foundation. Reprinted in accordance with CC BY-NC 4.0.

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

PAG is seeking guidance on whether the addition of gemtuzumab ozogamicin is appropriate for the following:

- Patients <15 or >70 years of age
- In combination with other treatments (e.g., FLAG-IDA, idarubicin, high dose cytarabine, or azacitidine)
- In combination with midostaurin along with combination chemotherapy for patients with newly diagnosed FLT3-mutated.

As a result, during development of the review protocol it was determined that randomized controlled trials that included patients under the age of 15 or GO in combination with other treatments (FLAG-IDA, idarubicin, high dose cytarabine, azacitidine, and midostaurin) would be relevant to the pCODR review of GO for AML.

7.1 *Patients aged less than 15 or greater than 70; GO combined with other treatments and in combination with midostaurin for new diagnosed FLT3 mutated patients*

7.1.1 *Objective*

PAG requested guidance on the use of GO in younger and older patients, in combination with other treatments and in combination with midostaurin for patients with FLT3-mutation.

7.1.2 *Findings*

The Methods Team identified three studies that included some of these data.[6-8] The AAML053 and AML15 trials include people aged <15 and the AML16 trial included people aged >70.[6,8] The AAML053 and AML 16 trials used GO in combination with cytarabine. The AML15 trial used GO in combination with FLAG-IDA.[8] All three trials reported on FLT3 status. No studies reported on the use of midostaurin.

7.1.3 *Summary*

The three phase III, open-label randomized trials were identified as literature to support the information requested by PAG. See Table 7.1.

6.4.1.1 Detailed Trial Characteristics

Table 7.1 Summary of Trial Characteristics of the Included Studies

Trial Design Characteristics	Key Inclusion / Exclusion Criteria	Intervention & Comparator	Trial Outcomes
AAML0531 (Gamis 2014)[6]			
• **Phase:** III • **Blinding:** Open label • **Randomization method:** blocked, block sizes of 4 • **Randomization ratio:** 1:1 • **Randomized (n):** 1022 • **Treated (n): 1085** • **Centres (n):** 181 • **Countries (n):** 6; USA, Canada, Australia, New	Inclusion: Patients 1 month to 29.99 years, who had previously untreated primary AML Exclusion: Prior chemotherapy (except intrathecal cytarabine), acute promyelocytic leukemia [t(15;17)], juvenile myelomonocytic leukemia,	Intervention: GO (each dose 3 mg/m2) administered once on day 6 of induction course 1 (IND1) and once on day 7 of intensification course 2. This is given in addition to standard therapy. Comparator:	Primary: • EFS at 3 Years • OS at 3 Years Secondary: • Remission Induction Rate After 2

Trial Design Characteristics	Key Inclusion / Exclusion Criteria	Intervention & Comparator	Trial Outcomes
Zealand, Puerto Rico, Switzerland. • **Date – patient enrolment:** Aug 2006 – Jun 2010 • **Date – final analysis:** Mar 31, 2013 • **Funding:** Chair's Grant No. U10 CA98543-08 and Statistics and Data Center Grant No. CA98413-08 of the Children's Oncology Group (COG) from the National Cancer Institute, National Institutes of Health	bone marrow failure syndromes, or secondary AML	Standard therapy alone (No-GO) with cytarabine (ARA-C), daunorubicin and etoposide.	Courses of Induction Therapy. • DFS • Mortality • Time to Marrow Recovery
AML15 (Burnett 2011)[8]			
• **Phase:** III • **Blinding:** open label • Randomization method: random assignment • **Randomization ratio:** 1:1 • **Randomized (n):** 1113 (induction) and 948 (consolidation) 2061 total • Treated (n): 1113 (induction); 948 (consolidation) • **Centres (n):** 145 • **Countries (n):** 3; UK, Denmark, New Zealand • **Date – patient enrolment:** Jul 2002 – Mar 2009 • Date – data cut-off: January 1, 2009 • Date – final analysis: January 1, 2009 • **Funding:** United Kingdom Medical Research Council Grant No. G9901427	Inclusion: Age < 60 Exclusion: Patients without Acute promyelocytic leukemia	Intervention: GO as part of induction therapy (daunorubicin and cytarabine; cytarabine, daunorubicin, and etoposide; or fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin) and as part of consolidation therapy (amsacrine, cytarabine, and etoposide or high-dose cytarabine) Comparator: No GO as part of induction therapy (daunorubicin and cytarabine; cytarabine, daunorubicin, and etoposide; or fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin) and as part of consolidation therapy (amsacrine, cytarabine, and etoposide or high-dose cytarabine)	Primary: • CRR Secondary: • OS • RFS
AML16 (Burnett 2012)[7]			
• Phase: III • Blinding: Open label • **Randomization method:** stratified • Randomization ratio: 1:1 • **Randomized (n):** 1115 • **Treated (n):** 1115 • **Centres (n):** 149 • **Countries (n):** 2; UK & Denmark • **Date – patient enrolment:** Dec 4 2006 – Jul 2 2010 • Date – data cut-off: July 1, 2011 • **Date – final analysis:** July 1, 2011 • **Funding:** Genzyme (SANOFI) and Cancer Research UK	Inclusion: Generally age > 60 years, who did not have blast transformation of chronic myeloid leukemia or acute promyelocytic leukemia, serum creatinine within local normal limits, liver function tests (bilirubin and transaminases) had to be within twice the local upper limit of normal Patients with de novo or secondary AML or high-risk myelodysplastic syndrome, defined as 10% marrow blasts. Exclusion:	Intervention: Patients were randomly assigned between two courses of chemotherapy comprising daunorubicin/ARA-C or daunorubicin/clofarabine. To be eligible for random assignment, patients were required to have serum creatinine within local normal limits. In addition, patients were randomly assigned to receive GO 3 mg/m2 or not on day 1 of the first course of chemotherapy Comparator: No GO	Primary: OS Secondary: • RFS • CR • CRi • ORR • 30- and 60-day mortality • 3-year OS and RFS • 3-year OS from CR • 3-year CIR • Resource usage

Trial Design Characteristics	Key Inclusion / Exclusion Criteria	Intervention & Comparator	Trial Outcomes
	< 60 years, patients who withdrew consent before treatment. Blast transformation of chronic myeloid leukemia or acute promyelocytic leukemia.		
EFS =Event Free Survival, Overall Survival= OS, RFS=Remission Free Survival, CRR=Complete Remission Rate, CR= Complete Remission, CIR= Cumulative Incidence of Relapse; CRi: Complete remission with incomplete recovery, ORR: Overall Remission Rate			

f) Populations

The three included trials randomized a total of 3250 patients. One of the studies focused on the elderly with median (range) of 67 years (56-84). [8] One study included children, adolescents and young adults with median age (range) 9.7 years (0-29.8),[6] and the last one included people of all ages, with median age (range) of 47.5 years (1-69.5).[7]

None of the studies included people with treatment-related acute myeloid leukemia.

All studies included patients with different levels of cytogenetic risk. In the AAML0531 study 246 (24.1%) were at low cytogenetic risk (t[8;21] or Inv16, t[16;16]) and 39 (3.9%) were at high cytogenetic risk (7 or 5/5q-t).[6] In the MRC AML15 study the cytogenetic risk was as follows: favourable (331 patients; 19.3%); intermediate (1218 patients; 70.9%); adverse (167 patients; 9.7%).[5] In the MRC AML 16 study the distribution of cytogenetic risk was as follows: favourable (33 patients; 2.9%), intermediate (629 patients; 56.4%); adverse (204 patients; 18.3%).

Two studies reported CD33 mutations status. In the MRC AML15 study, 66 (6.9%) were negative (<20% of blasts positive) and 723 (76.3%) were positive (>20% of blasts positive).[8] In the MRC AML 16 study it was as follows: negative (112 patients; 10.1%); positive (775 patients; 69.5%); unknown (228 patients; 20.4%).[8,32]

With regards to FLT3 status, in the AAML053 trial, 63 patients (9.7%) had a high FLT3-ITD allelic ratio (>0.4) of which 38 (11.7%) were in the GO arm and 25 (7.7%) were in the control arm.[6] In the MRC AML15 trial, 48 out of 556 patients (8.6%) and 66 out of 557 patients (11.8%) had mutant FLT3-ITD status in the GO arm and control arms at induction respectively. At consolidation, 22 out of 473 patients (4.6%) and 32 out of475 patients (6.7%) had mutant FLT3-ITD status in the GO arm and control arms respectively.[8] In the MRC AML 16 trial, 56 out of 1115 patients (5.0%) had a mutant FLT3-ITD status of which 30 out of 559 patients (5.3%) were in the GO arm and 26 out of 556 patients (4.6%) were in the control arm.[7]

g) Interventions

All the studies used GO at 3 mg/m^2. Two of them used it in the induction and consolidation phases of treatment[6,8] and one used it only in the induction phase.[7]

In the AAML0531 trial, patients randomized to GO received GO (each dose 3 mg/m^2) administered once on day 6 of induction course 1 (IND1) and once on day 7 of intensification course 2. Chemotherapy cytoreduction preceded GO administration to maximize CD33 target saturation. Patients received intrathecal (IT) cytarabine (ARA-C) at diagnosis or on day 1 of treatment or twice a week for up to six doses. They also receive an infusion of ARA-C on days 1-10; a 6-hr infusion of daunorubicin on days 1, 3, & 5; a 4-hr infusion of etoposide on days 1-5;

and a 2-hr infusion of GO on day 6. In the control group, the treatment was the same, but without GO.[6]

In the MRC AML15 trial, patients received GO 3 mg/m^2 on day 1 with fludarabine 30 mg/m^2 IV days 2-6 inclusive, cytosine arabinoside 2 g/m^2 over 4h starting after fludarabine on days 2-6, G-CSF (lenograstim 263 µg (1 vial) SC daily (days 1-7) or GO 3 mg/m^2 on day 1 with daunorubicin 50 mg/m^2 (days 1,3,5); cytarabine 100 mg/m^2 (days 1-10) every 12h compared to daunorubicin 50 mg/m^2 (days 1,3,5); cytarabine 100 mg/m^2 (days 1-10) every 12h; etoposide 100 mg/m^2 (days 1-5).[8]

In the MRC AML 16 trial,[7] patients were randomized to receive induction chemotherapy with either daunorubicin/ARA-C or daunorubicin/clofarabine, with or without GO 3 mg/m^2 on day 1 of course one of therapy.

h) Limitations/Sources of Bias

The studies were generally well conducted, with some concerns. All three were randomized. One used block randomization[6] and the other used stratified randomization.[7] Details on allocation concealment were not reported in two trials.[7,8] None of them were blinded, but blinding is unlikely to affect outcomes in this context. Attrition was high (>20%) in one study.[6] All relevant outcomes were reported and data were analysed using the intention to treat principle.

Table 7.2: Select quality characteristics of included studies of gemtuzumab ozogamicin in patients with acute myeloid lymphoma

Study	AAML0531 (Gamis 2014)	AML15 (Burnett 2011)	AML16 (Burnett 2012)
Treatment vs. Comparator	GO + ARA-C + daunorubicin +Etoposide versus ARA-C + daunorubicin +Etoposide	GO +DA (FLAG-Ida) versus ADE	GO + daunorubicin +ARA-C (clofarabine) versus daunorubicin +ARA-C (clofarabine)
Primary outcome	3-year EFS 3-year OS	CRR	OS
Required sample size	1000	3000 (target)	800
Sample size	1022	1113	1115
Randomization method	Block	NR	Stratified
Allocation concealment	Yes	NR	NR
Blinding	No	No	No
ITT Analysis	Yes	Yes	Yes
Final analysis	Mar 31, 2013	January 1, 2009	August 2012
Early termination	No	No	No
Ethics Approval	National Cancer Institute's central institutional review board	NR	Wales Multicenter Research Ethics Committee
GO =gemtuzumab ozogamicin, ARA-C=cytarabine, DA= Daunorubicin/cytarabine, FLAD-Ida = fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (G-CSF), ADE = cytarabine, daunorubicin and etoposide			

i) Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

See table 7.3.

Event Free Survival:

In the AAML0531 trial, EFS was better in the GO group at 3 years (53.1%) compared to the control group (46.9%) for a HR of 0.83; 95% CI 0.70-0.99; p=0.04.[6] The MRC AML15 and MRC AML16 trials did not report EFS.[7,8]

Disease Free Survival:

In the AAML0531 trial, DFS was comparable in the GO group at 3 years (60.6%) compared to the control group (54.7%) for a HR of 0.82; 95% CI 0.67-1.02; p=0.7.[6] The MRC AML15 and MRC AML16 trials did not report EFS.[7,8]

Overall survival:

In the AAML053 trial, OS was comparable at 3 years with 69.4% in the GO arm versus 65.4% in the control arm for a HR of 0.91; 95% CI 0.74 to 1.13; p= 0.39.[6]

In the MRC AML15 trial, OS was comparable at 5 years with 43% in the GO arm and 41% in the control arm for a HR of 0.92;95% CI 0.79-1.08; p=0.3.[8]

In the MRC AML 16 trial, the difference in OS at 3 years neared statistical significance, with 25% in the GO arm and 20% in the control arm for a HR of 0.87;95% 0.76-1.00; p=0.05.[7]

Complete Remission:

In the AAML053 trial, CR was comparable at 3 years with 88.3% in the GO arm and 85.1% in the control arm for a OR of 0.76; 95% CI 0.79-1.08; p=0.3.[6]

In the MRC AML15 trial, CR was comparable at 5 years with 82% in the GO arm and 83% in the control arm for a OR of 1.04; 95% CI 0.76-1.42; p=0.8.[8]

In the MRC AML 16 trial, CR was comparable at 3 years with 62% in the GO arm and 58% in the control arm for a OR of 0.84;95% CI 0.66-1.06; p=0.14.[7]

Harms

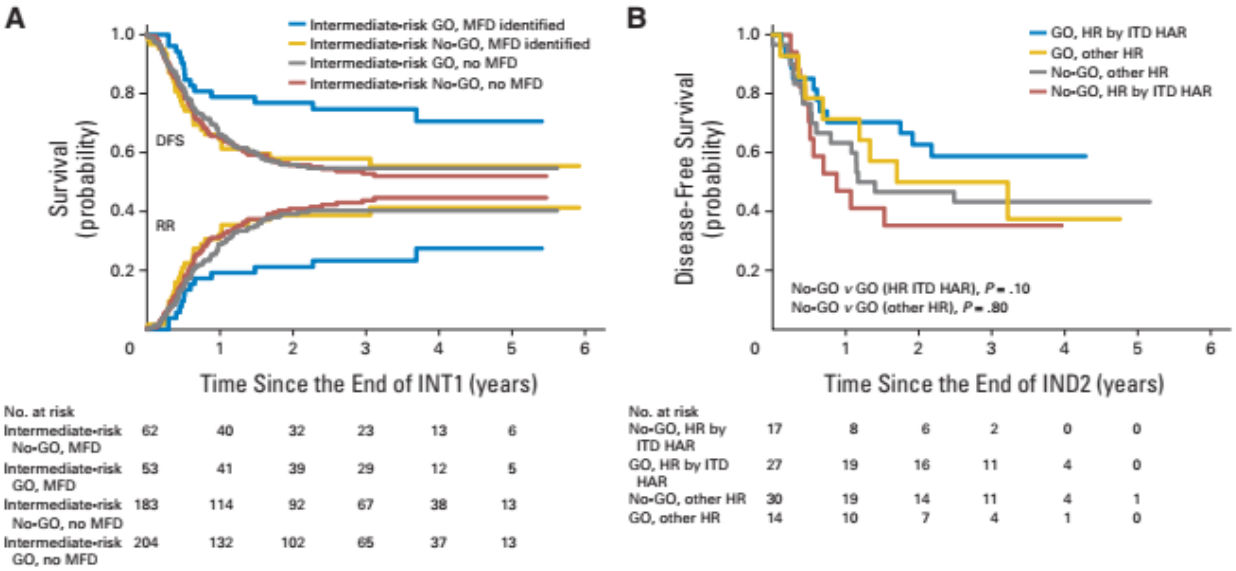
In the AAML0531 trial, SAEs in the GO arm (16/3.1%) were comparable to the control group (20/3.9%). WDAEs were also comparable (43/8.9% in the GO arm; 45/8.8% in the control arm).[6]

In the AML 16 trial cardiac AEs were comparable in the GO and control arms (7% vs 7%).[7] See table 7.3.

FLT3 status:

The AAML0531 trial reported some benefits in remission rate among the FLT3-ITD HAR (internal tandem duplication high allelic ratio) adverse risk cohort: "in HR patients, the FLT3-ITD HAR cohort was the only one to benefit from GO".[6] See Figure 7.1 below.

Figure 7.1 Outcome by study arm in patients who underwent stem-cell transplantation



Source: Gamis et al. J Clin Oncol 2014, 32(27):3021-3032.[6] Reprinted with permission. © 2014 American Society of Clinical Oncology. All rights reserved.

In the MRC AML15 trial, they found no interaction between treatment and FLT3 mutation status:" In this trial, we found no interaction between treatment and FLT3 mutation status."[8]

In the MRC AML 16 trial, no mutations were predictive of response to GO: "the more common mutations involving NPM1andFLT3 are independently prognostic in older patients but were not predictive of response to GO therapy".[7]

Table 7. 3 Highlights of Key Outcomes

	AAML0531		MRC AML15		MRC AML 16	
	GO (N=511)	No Go (N= 511)	GO (N=557)	No Go (N=556)	GO (N=556)	No Go (N=559)
EFS						
HR (95% CI)	0.83 (0.70-0.99)		**NR**		**NR**	
p-value	0.04		**NR**		**NR**	
DFS						
HR (95% CI)	0.82 (0.67-1.02)		**NR**		**NR**	
p-value	0.07		**NR**		**NR**	
OS						
HR (95% CI)	0.92 (0.79-1.08)		0.92 (0.79-1.08)		**0.87 (0.79-1.00)**	
p-value	0.3		0.16		**0.05**	
CR						
N (%)	451 (88.3)	435 (85.1)	457 (82)	461 (83)	345 (62)	324 (58)

	AAML0531		MRC AML15		MRC AML 16	
OR (95% CI)	0.76 (0.52-1.11)		1.04 (0.76-1.42)		0.84 (0.66-1.06)	
p-value	0.15		0.8		0.14	
HRQoL						
Difference (95% CI)	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Harms Outcome, n (%)	**GO (N=511)**	**No Go (N= 511)**	**GO (N=557)**	**No Go (N=556)**	**GO (N=556)**	**No Go (N=559)**
AE	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
SAE	**16(3.1) [¥]**	**20(3.9) [¥]**	**NR**	**NR**	**NR**	**NR**
WDAE	**43 (8.4)**	**45 (8.8)**	**NR**	**NR**	**NR**	**NR**
Neutropoenia	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Hemorrhage	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Hepatotoxicity	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Infusion related	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
QT prolongation	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Embryo-foetal	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Thrombocytopenia	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Veno-occlusive	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Other cardiac	**NR**	**NR**	**NR**	**NR**	**7%**	7%

AE = adverse event, **CI** = confidence interval, **HR** = hazard ratio, HRQoL = health-related quality of life, **NR** = not reported, **OR** = odds ratio, **WDAE** = withdrawal due to adverse event, **EFS**=Event Free Survival, DFS=Disease Free Survival, **OS**=Overall Survival, **CR**=Complete Remission, Remission Free Survival

[¥]Toxic mortality and deaths; † Permanent drug discontinuation; *HR/OR < 1 favours GO

7.2 *Summary of meta-analysis*

7.2.1 *Objective*

The CGP concluded that there is a net clinical benefit to GO in the management of previously untreated, newly diagnosed adult individuals with AML who are candidates for intensive, curative intent remission induction and consolidation therapy and who have genetically favourable risk, intermediate risk, or unknown risk AML using the International System for Human Cytogenetic Nomenclature, NCCN, or ELN classification systems.[12] The current and most widely used risk classification system is that of the ELN [2017]; risk categories are as follows: favourable, Intermediate, adverse. The CGP recommendation using the ELN 2017 risk classification. The CGP noted that the results of ALFA0701 are supported by an individual patient data meta-analysis of this RCT combined with four other RCTs,[9] all of which had examined the role of GO added to SOC therapy in untreated adult AML and stated that according to these combined data, the clinical benefit associated with GO appears to be isolated to those patients whose AML genetic risk group is of either "favourable" or "intermediate" in nature. As a result, this meta-analysis is summarized in

this section: a meta-analysis of five randomized control trials was conducted by Hills et al.[9] to determine whether patients experience benefit from treatment with gemtuzumab ozogamicin.

Methods:

Hills et al. conducted a literature search using PubMed to identify relevant trials available as of May 1, 2013. [9] Eligibility criteria of the chosen trials were as follows:

- An unconfounded comparison of GO in course 1 induction chemotherapy (i.e., chemotherapy plus GO vs. chemotherapy), excluding trials where GO was used in place of part of a chemotherapy regimen, before chemotherapy, or only in consolidation.
- Patients with a newly diagnosed AML (either de novo or secondary) or adverse risk MDS, excluding acute promyelocytic leukemia.
- Patients had to be aged 15 or older.
- An intensive induction chemotherapy regimen designed to induce complete remission in patients. Trials involving less intensive regimens such as low-dose ARA-C were excluded.

Authors contacted all collaborative groups who had run such a trial, and requested data on baseline characteristics, including age, sex, chemotherapy given, cytogenetics, and FLT-3 ITD and NPM1 mutation status, together with dates of entry, first complete remission, transplant, death and relapse. Endpoints were defined according to Revised International Working Group Criteria, with the exception that peripheral count recovery was not required for complete remission.

An individual patient data (IPD) meta-analysis of five trials in patients 15 and above receiving GO combined with standard induction chemotherapy was assessed. Data were analyzed using an assumption free (or fixed-effect) methodology. Comparisons were made within trial, and observed minus expected (o-e), V statistics obtained for each trial (or each stratum within each trial). The overall (o-e), V (and hence effect size and confidence intervals), were calculated as the sum over all trials. The log rank test was used for analysis of time-to-event outcomes. Significance was set at $p<0.05$ in all cases.

7.2.2 *Findings[9]*

Five trials were incorporated into the meta-analysis: MRC AML15, SWOG-0106, NCRI AML16, GOELAMS AML2006IR, ALFA-0701 (refer to Table 7.4). In total, the five trials comprised of 3,325 randomized patients between 15 and 84 years of age (median 58 years), 55% (1842 out of 3325 patients) of whom were male, 88% (2927 out of 3325 patients) of whom had de novo disease, 9% (285 patients) who had secondary MDS and 3% (113 patients) who had adverse risk MDS. Regarding eligibility criteria of the included trials, only trials MRC AML15 and NCRI AML16 included secondary AML patients, and only trial AML16 included adverse risk MDS. Median follow-up was 60.8 months (IQR 40.6–82.8). In the entire cohort, the remission rate was 78% (2589 out of 3324 patients) with a median survival of 22.5 months and pooled 5-year survival of 34% (total 2108 deaths). All trials were

open-label, centrally randomized and had OS as a primary endpoint. The authors reported that due to this there was a low risk of bias.

Table 7.4 Details of Trials Included in the Meta-Analysis[9]

	Dates of recruitment	Number of patients	Eligibility criteria	Median age of patients in years (range)	Cytogenetic grouping by MRC[14] classification*	Chemotherapy given	Dose and dosing schedule of gemtuzumab ozogamicin	Median follow-up for survival	Time of last follow-up (original publication)	Time of last follow-up (data for meta-analysis)
MRC AML15[†]	2002–06	1099	AML, either de novo or secondary; mostly aged <60 years	50 (15–71)	Favourable n=133 (15%); intermediate n=565 (63%); adverse n=196 (22%); unknown n=205	DA (3+10 then 3+8), ADE (3+10+5 then 3+8+5), or FLAG-Ida	3 mg/m² on day 1 of chemotherapy	86·0 months (IQR 76·6–99·4)	January, 2009	March, 2013
SWOG S0106[7]	2004–09	595	De-novo AML; aged 18–60 years	47 (18–60)	Favourable n=72 (17%); intermediate n=283 (67%); adverse n=67 (16%); unknown n=173	DA (3+7) plus G-CSF or GM-CSF	6 mg/m² on day 4 of chemotherapy	55·2 months (IQR 46·0–66·3)	February, 2013	June, 2013
NCRI AML16[4]	2006–10	1115	AML, either de novo or secondary, or high-risk myelodysplastic syndrome; mostly aged ≥60 years	67 (51–84)	Favourable n=33 (4%); intermediate n=576 (66%); adverse n=264 (30%); unknown n=242	DA (3+10 then 3+8) or daunorubicin (days 1, 3, and 5) plus clofarabine (days 1–5)	3 mg/m² on day 1 of chemotherapy	45·5 months (IQR 34·3–57·6)	July, 2011	March, 2013
GOELAMS AML 2006 IR[8]	2007–10	238	De-novo AML, aged 18–60 years	50·5 (18–60)	Favourable n=0; intermediate n=224 (100%); adverse n=0; unknown n=14	DA (3+7)	6 mg/m² on day 4 of chemotherapy	39·3 months (IQR 29·1–44·4)	–	January, 2013
ALFA-0701[15]	2008–10	278	De-novo AML; aged 50–70 years	62 (50–70)	Favourable n=9 (4%); intermediate n=179 (73%); adverse n=57 (23%); unknown n=33	DA (3+7)	3 mg/m² on days 1, 4, and 7 of chemo-therapy, up to 5 mg per dose	24·1 months (IQR 15·7–32·8)	August, 2011	August, 2011

AML=acute myeloid leukaemia. DA=daunorubicin plus cytarabine. ADE=daunorubicin, cytarabine, and etoposide. FLAG-Ida=fludarabine, cytarabine, G-CSF, and idarubicin. G-CSF=granulocyte colony-stimulating factor. GM-CSF=granulocyte-macrophage colony-stimulating factor. *Percentages exclude those with unknown cytogenetic characteristics. †14 patients in AML15 aged younger than 15 years were excluded from this meta-analysis.

Table: Trials included in the meta-analysis

Source: Hills et al. Lancet Oncol. 2014 Aug;15(9):986-996.[9] Copyright 2014. Reprinted with permission from Elsevier.

A variety of induction schedules were used in the trials with most patients were treated with an anthracycline plus ARA-C combination. GO was given to patients at varying doses, including 3 mg/m^2 on day 1 in two trials (MRC AML15, NCRI AML16), 6 mg/m^2 on day 4 in two trials (GEOLAMS AML2006IR and SWOG-0106), and 3 mg/m^2 (capped at 5mg per dose) on days 1, 4, 7 in one trial (ALFA-0701). Due to the varying GO administration schedules in the five trials, analyses were stratified by GO schedule. Chemotherapy schedule was another stratification variable to see if effect of GO varied by induction regimen.

No significant effect of GO on complete remission rate (OR: 0.91; 95% CI 0.77-1.07, p=0.3) was shown, with no heterogeneity by trial or GO administration schedule (Table 7.5). The authors reported a trend for higher 30-day mortality with some evidence of heterogeneity between different dosing regimens of GO, however these results were not statistically significant. Greater early mortality was observed among patients given GO at 6 mg/m^2 (p-value for heterogeneity 6 mg vs 3 mg, p=0.03); results of the SWOG-0106 study differed from all the other trials (p=0.01). When the SWOG-0106 study was excluded, the results for 30-day mortality continued not to be statistically significant; the authors concluded that there was no evidence of harm for the remaining 2,728 out of 3,325 patients.

The addition of GO to induction chemotherapy resulted in significantly reduced relapse (HR: 0.81; 95% CI 0.73-0.90, p=0.001). The effect of reduced relapse was greatest in the French ALFA-0701 trial; the other four trials exhibited heterogeneity, however when these four trials were combined

there was also a significant reduction in relapse (HR: 0.84; 95% CI 0.75-0.93, p=0.001). There were no significant differences in deaths in remission among all of the trials; there was a significant benefit in the ALFA-0701 trial, with some heterogeneity (p=0.03), however there was no evidence in any of the trials that deaths in remission increased as a result of the addition of GO. There was significant improvement in relapse free survival (HR: 0.84; 95% CI 0.76-0.92, p=0.0003); the largest effect was observed in the ALFA-0701 trial, although the remaining four trials also showed significant improvement in RFS (HR: 0.87; 95% CI 0.79-0.96, p=0.005).

Table 7.5: Meta-analysis results for overall response rate, 30-day mortality, relapse, death in complete remission, relapse free survival, survival from remission and overall survival [9]

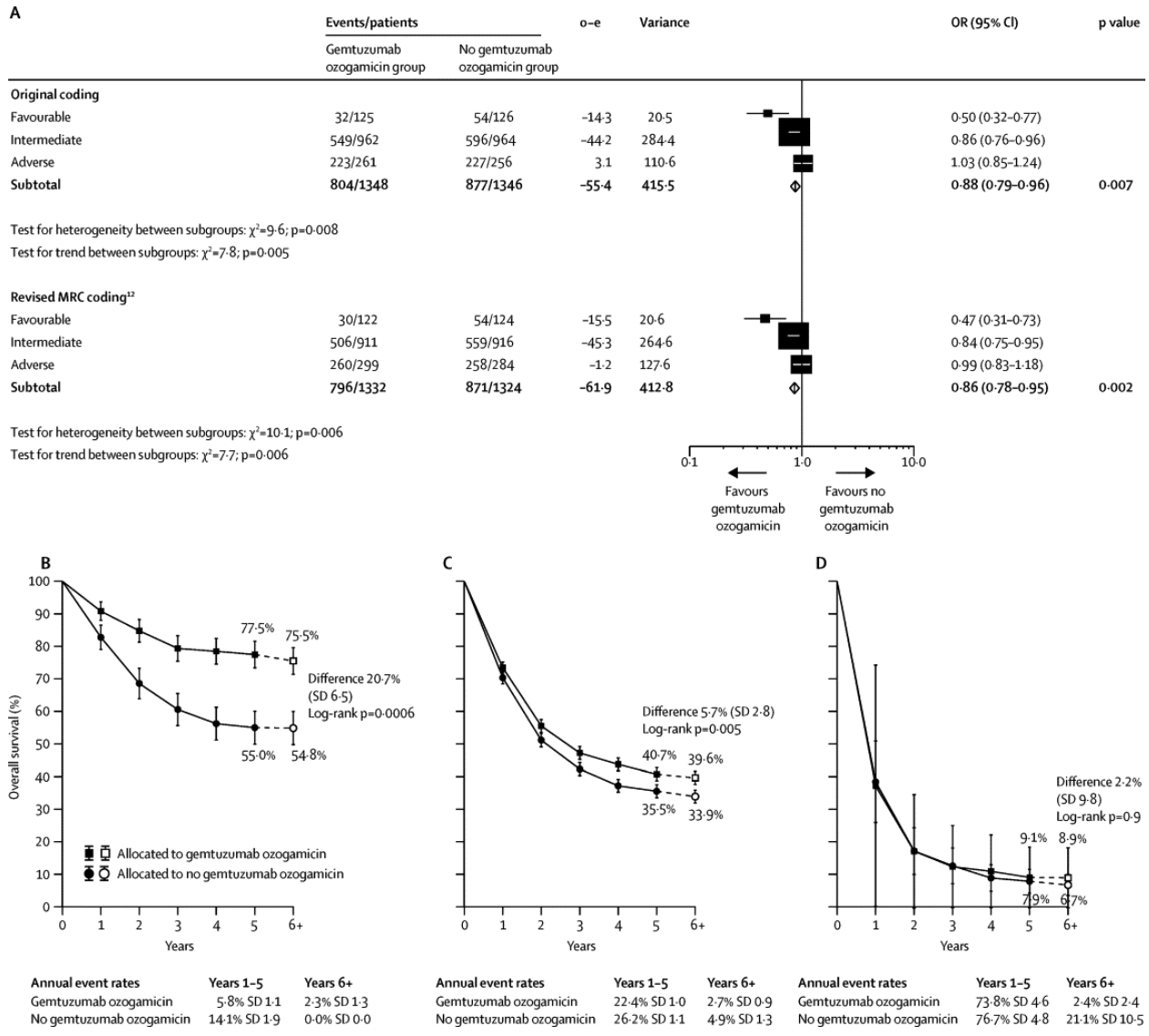
	OR (CI)						
Dose schedule	**ORR (CR+CRi)**	**30-day mortality**	**Relapse**	**Death in complete remission**	**Relapse free survival**	**Survival from remission**	**Overall survival**
3 mg/m^2 single dose	0.96 (0.79, 1.18)	1.09 (0.80, 1.49)	0.82 (0.73, 0.93)*	1.00 (0.78, 1.30)	0.86 (0.77, 0.96)*	0.84 (0.75, 0.95)*	0.89 (0.81, 0.98)*
3 mg/m^2 fractioned	0.69 (0.39, 1.21)	1.75 (0.54, 5.70)	0.55 (0.38, 0.81)*	0.24 (0.07, 0.85)*	0.51 (0.36, 0.74)*	0.61 (0.38, 0.95)*	0.69 (0.49, 0.98)*
6 mg/m^2	0.85 (0.61, 1.20)	2.79 (1.33, 5.87)	0.88 (0.69, 1.13)	1.04 (0.65, 1.66)	0.91 (0.74, 1.14)	0.97 (0.76, 1.24)	1.01 (0.83, 1.23)
Total	0.91 (0.77, 1.07)	1.28 (0.97, 1.70)	0.81 (0.73, 0.90)*	0.97 (0.77, 1.21)	0.84 (0.76, 0.92)*	0.85 (0.77, 0.94)*	0.90 (0.82, 0.98)*

Abbreviations: OR=odds ratio; CI=confidence interval; ORR=overall response rate; CR=complete response; CRi=complete response with incomplete hematologic recovery
[a] log rank test
* indicating statistical significance

Based on the reduction of relapse, there was also significant improvement in survival from remission (HR: 0.85; 95% CI 0.77-0.94, p=0.002). The addition of GO to induction chemotherapy led to significant improvement in OS (HR: 0.90; 95% CI 0.82-0.98, p=0.01). The authors noted no significant heterogeneity by dosing regimen or by trial, with the overall absolute improvement being 4% at 5 years. Authors conducted exploratory stratified analyses to identify whether baseline features impacted the benefit of GO. Analyses were stratified by age, sex, diagnosis and induction chemotherapy; the authors noted no evidence of interaction. It was suggested in the ALFA-0701 trial that patients with FLT3 mutations showed greater benefit from GO, however in the overall analysis this was not observed. The authors also assessed for differences in benefit among NPM1c patients, due to the associated increase in CD33 expression, however this was also not observed.

Both the MRC AML15 and ALFA-0701 trials showed that the effect of GO differed by cytogenetic group, whereby patients with favourable risk cytogenetics showed the greatest benefit from GO. Authors' analyses of GO benefit by cytogenetic risk showed meaningful absolute benefit of 20.7% (HR: 0.47; 95% CI 0.31-0.73) for favourable cytogenetic patients, and 5.7% (HR: 0.84; 95% CI 0.75-0.95) for intermediate cytogenetic patients. No evidence of benefit was observed in adverse cytogenetic patients (refer to Figure 7.2).

Figure 7.2 Overall survival stratified by cytogenetic characteristics[9]



(A) Overall survival stratified by cytogenetic characteristics; the size of the boxes is proportional to the amount of data contained in each data line. (B) Absolute survival for patients with favourable cytogenetic characteristics. (C) Absolute survival for patients with intermediate cytogenetic characteristics. (D) Absolute survival for patients with adverse cytogenetic characteristics. Patients with insufficient karyotype data or fewer than 20 metaphases are classified as unknown and excluded from the stratified analysis. Error bars show SDs. Dashed lines and white boxes represent projections beyond 5 years. o-e=observed minus expected events. MRC=Medical Research Council

Source: Hills et al. Lancet Oncol. 2014 Aug;15(9):986-996.[9] Copyright 2014. Reprinted with permission from Elsevier.

The authors conducted sensitivity analyses, as almost one quarter (785/3,325) of patients underwent stem cell transplant; the sensitivity analyses censored these patients. Results for OS were similar

(HR: 0.88; 95% CI 0.80-0.97, p=0.01). Among transplanted patients (n=785), those given GO were reported to have no overall dis-benefit from transplant.

Critiques of the Meta-Analysis

- Authors clearly identified the purpose of the meta-analysis and outlined their research questions. Authors conducted a literature search to identify relevant and current literature; a list of eligibility criteria were provided for screening literature retrieved through the systematic review.
- This meta-analysis included individual patient data, had updated data for all trials included, except for the ALFA-0701 trial where follow-up data were not available de to contractual arrangements with the supplying company.
- Of the trials retrieved from the literature search, authors identified and contacted all groups associated with the trials and obtained baseline data for patients. All five groups of the trials provided the requested most up-to-date information.
- The authors outlined the definitions to be used for the assessment of endpoints.
- Comparisons were made within trials, and stratified analyses were conducted to investigate interactions between baseline characteristics and treatment effectiveness.
- The authors declared having received no funding for conducting this meta-analysis, eliminating the potential for reporting bias.
- One journal database, PubMed, was used as a source of literature retrieval. It is unclear how many results were screened from the literature search and whether results were screened by multiple screeners.
- Of the patients analyzed in the meta-analysis, 20% (667/3325) of patients did not have cytogenetic data. Missing data from these patients may affect the validity of conclusions made by authors regarding the cytogenetic status of patients and the benefit they may receive from GO. However, the trials included in the meta-analysis supported the superior benefit of GO among patients with favourable risk cytogenetics. Of note, the publication did not indicate that this subgroup analysis was prespecified.

7.2.3 *Summary*

In conclusion, the meta-analysis demonstrated improved OS with the addition of GO to induction chemotherapy. The authors concluded that GO has a role in the treatment of patients with AML. While no statistically significant differences in early mortality were observed at different dosing schedules for GO, the authors observed trends towards greater mortality among patients who received GO at 6 mg/m^2 compared to patients who received it at 3 mg/m^2. The SWOG-0106 trial was reported to show slightly excess early mortality among patients compared to the other four trials included in the author's analysis; this was reported to be due to the untypically low rate in the control group. The improved survival was stated to be a result of reduction in relapse rather than an improved rate of remission, suggesting that the "quality" of remission was improved. The lower dose of 3 mg/m^2 was suggested to provide similar benefit as the larger 6 mg/m^2 dose based on the fact that the increased early mortality observed in the SWOG-0106 trial, which used the higher dose, was not replicated in other trials using a lower dose of GO. In addition, the lower dose may avoid excess early mortality. A fractioned versus single-dose schedule GO may also better reduce relapse based on results from the ALFA-0701 trial. The authors suggested that future research could focus on the optimal dosing schedule and whether fractioned dosing schedules provides significant advantages

over a single dose given on day 1. The authors made note of the NCRI AML16 trial, where minimal residual disease (MRD) detection in the remission marrow was available among a minority of patients (n=186); the data did not show a difference in the "quality" of remission between arms when assessed by flow cytometry at a 10^4 detection level.

Cytogenetics of patients was the only factor to interact with treatment of GO. Patients with favourable and intermediate cytogenetic risk showed the greatest survival benefit, while patients with adverse cytogenetic risk did not show such benefit. The authors suggested that eligibility of patients should be rapidly determined to optimise the use of GO, such that GO should be provided to patients with favourable or intermediate cytogenetic risk but avoided for patients with adverse cytogenetic risk. Adoption of rapid and routine diagnostic testing was stated to identify between 50% and 80% of patients with adverse cytogenetic risk within the MRC 2009 classification.

8 Comparison with Other Literature

One ongoing trial was identified as possibility relevant. This is a randomized controlled Phase II/III open label trial with a factorial design. The trial is targeting 1600 older patients with acute myeloid leukaemia and high-risk myelodysplastic syndrome. Arm A will receive DA chemotherapy with GO compared to CPX-351 (not available in Canada). Arm B will receive Vosaroxin and Decitabine. Arm C will receive DA versus FLAG-Ida versus DA plus Cladribine (DAC). Arm D will compare small molecule or not. Arm E will receive CPX-351 (200 versus 300) and arm F will receive DA V IDAC. The primary outcomes are overall survival, complete remission, duration of remission, toxicity and supportive care requirements. The study is currently recruiting. The estimated completion data is October 2020.

Table 8.1: Ongoing trials of gemtuzumab ozogamicin in patients with previously untreated acute myeloid leukemia[10]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT02272478 (AML 18) A randomized controlled Phase II/III trial with a factorial design including five randomized comparisons of which 1 includes GO Characteristics (Phase of study, blinding, placebo, randomization method, randomization ratio) Estimated enrollment 1600 (unclear how many will be in GO randomization) Country: UK Study start date: October 2014 Primary completion date: October 2019 Estimated completion date: October 2020 Funding: Cancer Research UK	<u>Key Inclusion Criteria:</u> Acute myeloid leukaemia, except Acute Promyelocytic Leukaemia <u>Age 60+</u> Serum creatinine ≤ 1.5 × ULN <u>On contraception</u> ECOG Performance Status of 0-2 <u>For the GO comparison</u> Patients not known to have adverse risk cytogenetics <u>Key Exclusion Criteria:</u> <u>Previous cytotoxic chemotherapy for AML</u> They are in blast transformation of chronic myeloid leukaemia They have a concurrent active malignancy excluding basal cell carcinoma They are pregnant or lactating They have Acute Promyelocytic Leukaemia Known infection with human immunodeficiency virus Patients with prior cumulative anthracycline exposure (from prior treatment of a non AML cancer) of greater than 300 mg/m^2	Intervention: DA chemotherapy with GO delivered at 3 mg/m^2 on day 1 of chemotherapy Control: CPX-351 on days 1, 3 and 5.*	<u>Primary:</u> 1. Overall survival [Time Frame: 1 year] 2. Complete remission achievement and reasons for failure (for induction questions) [Time Frame: 1 month] 3. Duration of remission, relapse rates and deaths in first CR [Time Frame: 1 month] 4. Toxicity, both haematological and non-haematological [Time Frame: 1 month] 5. Supportive care requirements (and other aspects of health economics) [Time Frame: 6 months] <u>Secondary:</u> 1. The relevance of the presence of a cytogenetic abnormality in the bone marrow of patients in morphological remission [Time Frame: At study end] 2. The relevance of molecular characteristics and response to treatment [Time Frame: 1 month] 3. To store diagnostic tissue for future research in the AML Tissue Bank [Time Frame: 6 years]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	daunorubicin (or equivalent). History of myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within 3 months before entry Specific for GO arm Pre-existing liver impairment with known cirrhosis Total bilirubin > 1.5 x the ULN AST > 2.5 x ULN ALT > 2.5 x ULN		

Abbreviations: AML = acute myeloid leukemia; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; DA = daunorubicin and cytarabine; GO = Gemtuzumab Ozogamicin; ULN = Upper limit of normal

* Currently not available in Canada.

9 ABOUT THIS DOCUMENT

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

pCODR 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 pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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.

The Leukemia Clinical Guidance Panel is comprised of three clinicians. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** July 2019**, Embase** 1974 to 2019 August 29**, Ovid MEDLINE(R) ALL** 1946 to August 29, 2019
Search Strategy:

#	Searches	Results
1	(gemtuzumab* or Mylotarg* or CMA 676 or CMA676 or CDP 771 or CDP771 or 93NS566KF7 or 8GZG754X6M).ti,ab,ot,kf,kw,hw,nm,rn.	4522
2	exp Daunorubicin/ or (daunorubicin* or daunarubicin* or daunomycin* or daunamycin* or rubomycin* or Dauno-Rubidomycine* or daunoblastin* or cerubidin* or dannomycin* or dauno rubidomycin* or daunobin* or daunoblastin* or daunorrubicin* or daunorubidomycin* or daunorubimycin* or daunoxome* or daurorumicin* or duarorubicin* or duanomycin* or duanorubicin* or FI 6339 or FI6339 or maxidauno* or "NDC 0082 4155" or "NDC 00824155" or NDC0082 4155 or NDC00824155 or NSC 82 151 or NSC 82151 or NSC82151 or RP 13057 or RP13057 or rubidiomycin* or rubidomycin* or rubidomycin* or rubilem* or rubomycin* or trixilem* or acetyladriamycin* or AI3-52942 or AI352942 or BRN 1445583 or BRN1445583 or CCRIS 914 or CCRIS914 or EINECS 244-069-7 or EINECS244-069-7 or HSDB 5095 or HSDB5095 or Leukaemomycin C or NCI-C04693 or NCIC04693 or NSC 83142 or NSC83142 or "RCRA waste no. U059" or ZS7284E0ZP).ti,ab,ot,kf,kw,hw,nm,rn.	99348
3	Carubicin/ or (carubicin* or carminomycin* or carminomycin* or carminomitsin* or demehtyldaunorubicin* or karminomycin* or karminomicin* or demethyldaunomycin* or rubeomycin* or "NSC 180 024" or NSC 180024 or NSC180024 or "NSC180 024" or CCRIS 961 or CCRIS961 or CCRIS 6185 or CCRIS6185 or E7437K3983).ti,ab,ot,kf,kw,hw,nm,rn.	1075
4	exp Doxorubicin/ or (doxorubicin* or farmiblastina or ribodoxo* or rubex* or adriamycin* or adriblast* or adriablast* or adriacin* or adriamicin* or adrimedac* or adrim* or adrimedac* or adrubicin* or amminac* or doxo-cell* or doxolem* or doxotec* or myocet* or onkodox* or caelyx* or caelix* or doxil* or carcinocin* or dexorubicin* or dox sl* or doxolem* or doxor* or evacet* or ifadox* or lipodox* or rubex* or rubidox* or sarcodoxome* or tic d 99 or rastocin* or resmycin* or myocet* or CCRIS 739 or CCRIS739 or EINECS 245-495-6 or EINECS245-495-6 or FI106 or FI 106 or HSDB 3070 or HSCB3070 or NCI-C01514 or NCIC01514 or NDC 38242-874 or NDC38242-874 or NSC 123127 or NSC123127 or MCC465 or MCC 465 or RP 25253 or RP25253 or 80168379AG).ti,ab,ot,kf,kw,hw,nm,rn.	274684
5	Epirubicin/ or (epirubicin* or EPI cell or epicell or epilem* or farmorubicin* or farmorrubicin* or ellence* or pharmorubicin* or pidorubicin* or ridorubicin* or epi-dx* or epiadriamycin* or	39199

	epidoxorubicin* or binarin* or epidoxo* or epidx* or epiham* or epifil* or IMI 28 or IMI28 or NSC-256942 or NSC256942 or BRN 1445813 or BRN1445813 or CCRIS 2261 or CCRIS2261 or 3Z8479ZZ5X).ti,ab,ot,kf,kw,hw,nm,rn.	
6	Idarubicin/ or (idarubicin* or damycin* or idamycin* or idaralem* or zavedos* or IMI 30 or IMI30 or NSC 256439 or NSC256439 or CCRIS 5083 or CCRIS5083 or IMI 30 or IMI30 or ZRP63D75JW).ti,ab,ot,kf,kw,hw,nm,rn.	13444
7	exp Nogalamycin/ or (Nogalamycin* or nogalamicin* or NSC 70845 or NSC70845 or U 15167 or U15167 or L059DCD6IP).ti,ab,ot,kf,kw,hw,nm,rn.	709
8	Menogaril/ or (menogaril* or menogarol* or Tomosar* or 7-omen or tut 7 or tut7 or NSC 269148 or NSC269148 or CCRIS 8607 or CCRIS8607 or "U 52 047" or U 52047 or U52047 or 8JSV4O30HQ).ti,ab,ot,kf,kw,hw,nm,rn.	485
9	or/2-8	327932
10	exp Cytarabine/ or (cytarabin* or arabino* or aracytidine* or Cytosar* or Ara C or AraC or aracytine* or Cytonal* or alcysten* or alexan* or arabatin* or arabitin* or aracytin* or citaravin* or citarabin* or cyclocide or cylocide or cytarabin* or citarabide* or cytarbin* or cytarin* or cytidine or cytoarabin* or cytosa* or cytosin* or cytovis* or depocyt* or udicil* or DTC 101 or DTC101 or iretin* or laracit* or novumtrax* or tarabine* or Arafcyt* or Erpalfa* or Spongocytidine* or NSC-287459 or NSC287459 or NSC 63878 or NSC63878 or U-19,920 or U-19920 or U19920 or U 1992 A or U 19920A or U1992A or U1992 A or AC-1075 or AC1075 or AI3-52329 or AI352329OR or CHX 3311 or CHX3311 or MK8242 or MK 8242 or NCI-C04728 or NCIC04728 or 04079A1RDZ).ti,ab,ot,kf,kw,hw,nm,rn.	240534
11	Ancitabine/ or (Ancitabine* or Cyclo* or anhydrocytidine* or CCRIS 2757 or CCRIS2757 or NSC 145 688 or NSC145 688 or NSC145688 or U 33 624A or U33 624A or U33624A or DO2D32W0VC).ti,ab,ot,kf,kw,hw,nm,rn.	1137334
12	or/10-11	1344913
13	1 and 9 and 12	1468
14	13 use medall	110
15	13 use cctr	77
16	*Gemtuzumab ozogamicin/ or *Gemtuzumab/ or (gemtuzumab* or Mylotarg* or CMA 676 or CMA676 or CDP 771 or CDP771).ti,ab,kw,dq.	2073
17	*Daunorubicin/ or (daunorubicin* or daunarubicin* or daunomycin* or daunamycin* or rubomycin* or Dauno-Rubidomycine* or daunoblastin* or cerubidin* or dannomycin* or dauno rubidomycin* or daunobin* or daunoblastin* or daunorrubicin* or daunorubidomycin* or daunorubimycin* or daunoxome* or daurorumicin* or duarorubicin* or duanomycin* or duanorubicin* or FI 6339 or	23294

	FI6339 or maxidauno* or "NDC 0082 4155" or "NDC 00824155" or NDC0082 4155 or NDC00824155 or NSC 82 151 or NSC 82151 or NSC82151 or RP 13057 or RP13057 or rubidiomycin* or rubidomycin* or rubidomycin* or rubilem* or rubomycin* or trixilem* or acetyladriamycin* or AI3-52942 or AI352942 or BRN 1445583 or BRN1445583 or CCRIS 914 or CCRIS914 or EINECS 244-069-7 or EINECS244-069-7 or HSDB 5095 or HSDB5095 or Leukaemomycin C or NCI-C04693 or NCIC04693 or NSC 83142 or NSC83142 or "RCRA waste no. U059").ti,ab,kw,dq.	
18	Daunorubicin derivative/	399
19	*Carubicin/ or (carubicin* or carminomycin* or carminomycin* or carminomitsin* or demehtyldaunorubicin* or karminomycin* or karminomicin* or demethyldaunomycin* or rubeomycin* or "NSC 180 024" or NSC 180024 or NSC180024 or "NSC180 024" or CCRIS 961 or CCRIS961 or CCRIS 6185 or CCRIS6185).ti,ab,kw,dq.	932
20	*Doxorubicin/ or (doxorubicin* or farmiblastina or ribodoxo* or rubex* or adriamycin* or adriblast* or adriablast* or adriacin* or adriamicin* or adrimedac* or adrim* or adrimedac* or adrubicin* or amminac* or doxo-cell* or doxolem* or doxotec* or myocet* or onkodox* or caelyx* or caelix* or doxil* or carcinocin* or dexorubicin* or dox sl* or doxolem* or doxor* or evacet* or ifadox* or lipodox* or rubex* or rubidox* or sarcodoxome* or tic d 99 or rastocin* or resmycin* or myocet* or CCRIS 739 or CCRIS739 or EINECS 245-495-6 or EINECS245-495-6 or FI106 or FI 106 or HSDB 3070 or HSCB3070 or NCI-C01514 or NCIC01514 or NDC 38242-874 or NDC38242-874 or NSC 123127 or NSC123127 or MCC465 or MCC 465 or RP 25253 or RP25253).ti,ab,kw,dq.	162717
21	*Epirubicin/ or (epirubicin* or EPI cell or epicell or epilem* or farmorubicin* or farmorrubicin* or ellence* or pharmorubicin* or pidorubicin* or ridorubicin* or epi-dx* or epiadriamycin* or epidoxorubicin* or binarin* or epidoxo* or epidx* or epiham* or epifil* or IMI 28 or IMI28 or NSC-256942 or NSC256942 or BRN 1445813 or BRN1445813 or CCRIS 2261 or CCRIS2261).ti,ab,kw,dq.	19331
22	*Idarubicin/ or (idarubicin* or damycin* or idamycin* or idaralem* or zavedos* or IMI 30 or IMI30 or NSC 256439 or NSC256439 or CCRIS 5083 or CCRIS5083 or IMI 30 or IMI30).ti,ab,kw,dq.	5896
23	*Nogalamycin/ or (Nogalamycin* or nogalamicin* or NSC 70845 or NSC70845 or U 15167 or U15167).ti,ab,kw,dq.	552
24	*Menogaril/ or (menogaril* or menogarol* or Tomosar* or 7-omen or tut 7 or tut7 or NSC 269148 or NSC269148 or CCRIS 8607 or CCRIS8607 or "U 52 047" or U 52047 or U52047).ti,ab,kw,dq.	349
25	or/17-24	198269
26	*Cytarabine/ or Cytarabine derivative/ or (cytarabin* or arabino* or aracytidine* or Cytosar* or Ara C or AraC or aracytine* or Cytonal* or alcysten* or alexan* or arabatin* or arabitin* or aracytin* or	155654

	citaravin* or citarabin* or cyclocide or cylocide or cytarabin* or citarabide* or cytarbin* or cytarin* or cytidine or cytoarabin* or cytosa* or cytosin* or cytovis* or depocyt* or udicil* or DTC 101 or DTC101 or iretin* or laracit* or novumtrax* or tarabine* or Arafcyt* or Erpalfa* or Spongocytidine* or NSC-287459 or NSC287459 or NSC 63878 or NSC63878 or U-19,920 or U-19920 or U19920 or U 1992 A or U 19920A or U1992A or U1992 A or AC-1075 or AC1075 or AI3-52329 or AI352329OR or CHX 3311 or CHX3311 or MK8242 or MK 8242 or NCI-C04728 or NCIC04728).ti,ab,kw,dq.	
27	*Ancitabine/ or (Ancitabine* or Cyclo* or anhydrocytidine* or CCRIS 2757 or CCRIS2757 or NSC 145 688 or NSC145 688 or NSC145688 or U 33 624A or U33 624A or U33624A).ti,ab,kw,dq.	710737
28	or/26-27	858485
29	16 and 25 and 28	353
30	*Cytarabine plus daunorubicin/ or (Vyxeos* or CPX 351 or CPX351).ti,ab,kw,dq.	429
31	16 and 30	76
32	29 or 31	394
33	32 use oemezd	239
34	33 not conference abstract.pt.	120
35	14 or 15 or 34	307
36	remove duplicates from 35	201
37	33 and conference abstract.pt.	119
38	limit 37 to yr="2014 -Current"	48
39	36 or 38	249
40	limit 39 to english language	215

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#16	Search **#14 AND publisher[sb]**	1
#15	Search **#2 AND #10 AND #13** Filters: **English**	99
#14	Search **#2 AND #10 AND #13**	105
#13	Search **#11 OR #12**	111163
#12	Search **Ancitabine[mh] OR Ancitabine*[tiab] OR Cyclo*[tiab] OR anhydrocytidine*[tiab] OR CCRIS 2757[tiab] OR CCRIS2757[tiab] OR NSC 145 688[tiab] OR NSC145 688[tiab] OR NSC145688[tiab] OR U 33 624A[tiab] OR U33 624A[tiab] OR U33624A[tiab] OR DO2D32W0VC[rn]**	38636
#11	Search **Cytarabine[mh] OR cytarabin*[tiab] OR arabino*[tiab] OR aracytidine*[tiab] OR Cytosar*[tiab] OR Ara C[tiab] OR AraC[tiab] OR**	72904

Search	Query	Items found
	aracytine*[tiab] OR Cytonal*[tiab] OR alcysten*[tiab] OR alexan*[tiab] OR arabatin*[tiab] OR arabitin*[tiab] OR aracytin*[tiab] OR citaravin*[tiab] OR citarabin*[tiab] OR cyclocide[tiab] OR cylocide[tiab] OR cytarabin*[tiab] OR citarabide*[tiab] OR cytarbin*[tiab] OR cytarin*[tiab] OR cytidine[tiab] OR cytoarabin*[tiab] OR cytosa*[tiab] OR cytosin*[tiab] OR cytovis*[tiab] OR depocyt*[tiab] OR udicil*[tiab] OR DTC 101[tiab] OR DTC101[tiab] OR iretin*[tiab] OR laracit*[tiab] OR novumtrax*[tiab] OR tarabine*[tiab] OR Arafcyt*[tiab] OR Erpalfa*[tiab] OR Spongocytidine*[tiab] OR NSC-287459[tiab] OR NSC287459[tiab] OR NSC 63878[tiab] OR NSC63878[tiab] OR U-19,920[tiab] OR U-19920[tiab] OR U19920[tiab] OR U 1992 A[tiab] OR U 19920A[tiab] OR U1992A[tiab] OR U1992 A[tiab] OR AC-1075[tiab] OR AC1075[tiab] OR AI3-52329[tiab] OR AI352329OR[tiab] OR CHX 3311[tiab] OR CHX3311[tiab] OR MK8242[tiab] OR MK 8242[tiab] OR NCI-C04728[tiab] OR NCIC04728[tiab] OR 04079A1RDZ[rn]	
#10	Search **#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9**	112379
#9	Search **Menogaril[mh] OR menogaril*[tiab] OR menogarol*[tiab] OR Tomosar*[tiab] OR 7-omen[tiab] OR tut 7[tiab] OR tut7[tiab] OR NSC 269148[tiab] OR NSC269148[tiab] OR CCRIS 8607[tiab] OR CCRIS8607[tiab] OR U 52 047[tiab] OR U 52047[tiab] OR U52047[tiab] OR 8JSV4O30HQ[rn]**	145
#8	Search **Nogalamycin[mh] OR Nogalamycin*[tiab] OR nogalamicin*[tiab] OR NSC 70845[tiab] OR NSC70845[tiab] OR U 15167[tiab] OR U15167[tiab] OR L059DCD6IP[rn]**	310
#7	Search **Idarubicin[mh] OR idarubicin*[tiab] OR damycin*[tiab] OR idamycin*[tiab] OR idaralem*[tiab] OR zavedos*[tiab] OR IMI 30[tiab] OR IMI30[tiab] OR NSC 256439[tiab] OR NSC256439[tiab] OR CCRIS 5083[tiab] OR CCRIS5083[tiab] OR IMI 30[tiab] OR IMI30[tiab] OR ZRP63D75JW[rn]**	2244
#6	Search **Epirubicin[mh] OR epirubicin*[tiab] OR EPI cell[tiab] OR epicell[tiab] OR epilem*[tiab] OR farmorubicin*[tiab] OR farmorrubicin*[tiab] OR ellence*[tiab] OR pharmorubicin*[tiab] OR pidorubicin*[tiab] OR ridorubicin*[tiab] OR epi-dx*[tiab] OR epiadriamycin*[tiab] OR epidoxorubicin*[tiab] OR binarin*[tiab] OR epidoxo*[tiab] OR epidx*[tiab] OR epiham*[tiab] OR epifil*[tiab] OR IMI 28[tiab] OR IMI28[tiab] OR NSC-256942[tiab] OR NSC256942[tiab] OR BRN 1445813[tiab] OR BRN1445813[tiab] OR CCRIS 2261[tiab] OR CCRIS2261[tiab] OR 3Z8479ZZ5X[rn]**	7471
#5	Search **Doxorubicin[mh] OR doxorubicin*[tiab] OR farmiblastina[tiab] OR ribodoxo*[tiab] OR rubex*[tiab] OR adriamycin*[tiab] OR adriblast*[tiab] OR adriablast*[tiab] OR adriacin*[tiab] OR adriamicin*[tiab] OR adrimedac*[tiab] OR adrim*[tiab] OR adrimedac*[tiab] OR adrubicin*[tiab] OR amminac*[tiab] OR doxo-cell*[tiab] OR doxolem*[tiab] OR doxotec*[tiab] OR myocet*[tiab] OR onkodox*[tiab] OR caelyx*[tiab] OR caelix*[tiab] OR doxil*[tiab] OR carcinocin*[tiab] OR dexorubicin*[tiab] OR dox sl*[tiab] OR doxolem*[tiab] OR doxor*[tiab] OR evacet*[tiab] OR ifadox*[tiab] OR lipodox*[tiab] OR rubex*[tiab] OR rubidox*[tiab] OR sarcodoxome*[tiab] OR tic d 99[tiab] OR rastocin*[tiab] OR resmycin*[tiab] OR myocet*[tiab] OR CCRIS 739[tiab] OR CCRIS739[tiab] OR EINECS 245-495-6[tiab] OR EINECS245-495-6[tiab] OR FI106[tiab] OR FI 106[tiab] OR HSDB 3070[tiab] OR HSCB3070[tiab] OR NCI-C01514[tiab] OR NCIC01514[tiab] OR NDC 38242-874[tiab] OR NDC38242-874[tiab] OR NSC 123127[tiab] OR NSC123127[tiab] OR MCC465[tiab] OR MCC 465[tiab] OR RP 25253[tiab] OR RP25253[tiab] OR 80168379AG[rn]**	70866
#4	Search **Carubicin[mh] OR carubicin*[tiab] OR carminomycin*[tiab] OR carminomycin*[tiab] OR carminomitsin*[tiab] OR demehtyldaunorubicin*[tiab] OR karminomycin*[tiab] OR karminomicin*[tiab] OR demethyldaunomycin*[tiab] OR rubeomycin*[tiab] OR NSC 180 024[tiab] OR NSC 180024[tiab] OR NSC180024[tiab] OR NSC180 024[tiab] OR CCRIS**	27082

Search	Query	Items found
	961[tiab] OR CCRIS961[tiab] OR CCRIS 6185[tiab] OR CCRIS6185[tiab] OR E7437K3983[rn]	
#3	Search **Daunorubicin[mh] OR daunorubicin*[tiab] OR daunarubicin*[tiab] OR daunomycin*[tiab] OR daunamycin*[tiab] OR rubomycin*[tiab] OR Dauno-Rubidomycine*[tiab] OR daunoblastin*[tiab] OR cerubidin*[tiab] OR dannomycin*[tiab] OR dauno rubidomycin*[tiab] OR daunobin*[tiab] OR daunoblastin*[tiab] OR daunorrubicin*[tiab] OR daunorubidomycin*[tiab] OR daunorubimycin*[tiab] OR daunoxome*[tiab] OR daurorumicin*[tiab] OR duarorubicin*[tiab] OR duanomycin*[tiab] OR duanorubicin*[tiab] OR FI 6339[tiab] OR FI6339[tiab] OR maxidauno*[tiab] OR NDC 0082 4155[tiab] OR NDC 00824155 [tiab] OR NDC0082 4155[tiab] OR NDC00824155[tiab] OR NSC 82 151[tiab] OR NSC 82151[tiab] OR NSC82151[tiab] OR RP 13057[tiab] OR RP13057[tiab] OR rubidiomycin*[tiab] OR rubidomycin*[tiab] OR rubidomycin*[tiab] OR rubilem*[tiab] OR rubomycin*[tiab] OR trixilem*[tiab] OR acetyladriamycin*[tiab] OR AI3-52942[tiab] OR AI352942[tiab] OR BRN 1445583[tiab] OR BRN1445583[tiab] OR CCRIS 914[tiab] OR CCRIS914[tiab] OR EINECS 244-069-7[tiab] OR EINECS244-069-7[tiab] OR HSDB 5095[tiab] OR HSDB5095[tiab] OR Leukaemomycin C[tiab] OR NCI-C04693[tiab] OR NCIC04693[tiab] OR NSC 83142[tiab] OR NSC83142[tiab] OR "RCRA waste no. U059"[tiab] OR ZS7284E0ZP[rn]**	64712
#2	Search **Gemtuzumab[supplementary concept] or gemtuzumab*[tiab] OR Mylotarg*[tiab] OR CMA 676[tiab] OR CMA676[tiab] OR CDP 771[tiab] OR CDP771[tiab] OR 93NS566KF7[rn] OR 8GZG754X6M[rn]**	734

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/

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

   Search: Mylotarg, gemtuzumab, 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: Mylotarg, gemtuzumab, 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: Mylotarg, gemtuzumab, 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).

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 gemtuzumab/Mylotarg, daunorubicin and cytarabine.

No filters were applied to limit retrieval by publication types. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of December 19, 2019.

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).[37] 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 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 the 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.

REFERENCES

1. Pfizer response to pCODR checkpoint meeting questions on gemtuzumab ozogamicin (Mylotarg) for acute myeloid leukemia. Kirkland (QC): Pfizer Canada; 2019.
2. [Pr]Mylotarg® (gemtuzumab ozogamicin): lyophilized powder for solution for intravenous infusion, 4.5 mg single-use vial [product monograph]. Kirkland (QC): Pfizer Canada; 2019: https://pdf.hres.ca/dpd_pm/00054128.PDF. Accessed 2019 Dec 6.
3. Lambert J, Pautas C, Terre C, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. *Haematologica*. 2019;104(1):113-119.
4. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet*. 2012;379(9825):1508-1516.
5. Center for Drug Evaluation and Research. Clinical review(s). Mylotarg (gemtuzumab ozogamicin) powder for solution for infusion. Company: Wyeth Pharmaceuticals. Application No.:761060. Approval date: 09/01/2017. *(FDA approval package)*. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2017: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761060Orig1s000Orig1Orig2s000MedR.pdf . Accessed 2019 Nov 19.
6. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. *J Clin Oncol*. 2014;32(27):3021-3032.
7. Burnett AK, Russell NH, Hills RK, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. *J Clin Oncol*. 2012;30(32):3924-3931.
8. Burnett AK, Hills RK, Milligan D, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *J Clin Oncol*. 2011;29(4):369-377.
9. Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol*. 2014;15(9):986-996.
10. Cardiff University. NCT02272478: Trial to test the effects of adding 1 of 2 new treatment agents to commonly used chemotherapy combinations (AML18). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/NCT02272478. Accessed 2019 Dec 6.
11. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2019. Toronto (ON): Canadian Cancer Society; 2019: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2019-EN.pdf?la=en. Accessed 2019 Dec 6.
12. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
13. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
14. Buckley SA, Walter RB. Antigen-specific immunotherapies for acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program*. 2015;2015:584-595.
15. Tallman MS, Wang ES, Altman JK, et al. Acute Myeloid Leukemia, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019;17(6):721-749.
16. Acute myeloid leukemia. *Clinical practice guideline*. Edmonton (AB): Alberta Health Services; 2019: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lyhe006-aml.pdf. Accessed 2019 Dec 6.
17. Schuh AC, Fletcher GG, Leber B, Sabloff M, Systemic Treatment Disease Site Group. Systemic treatment of acute myeloid leukemia (AML). *Guideline 12-9*. Toronto (ON): Cancer Care Ontario; 2016: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/28266. Accessed 2019 Dec 6.
18. Cell Therapy Transplant Canada. https://www.cbmtg.org/default.aspx Accessed 2019 Dec 6.

19. Midostaurin (Rydapt) acute myeloid leukemia. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/rydapt-acute-myeloid-leukemia-details. Accessed 2019 Dec 6.
20. Petersdorf SH, Kopecky KJ, Slovak M, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. *Blood*. 2013;121(24):4854-4860.
21. Delaunay J, Recher C, Pigneux A, et al. Addition of gemtuzumab ozogamycin to chemotherapy improves event-free survival but not overall survival of AML patients with intermediate cytogenetics not eligible for allogeneic transplantation: results of the GOELAMS AML 2006 IR study [abstract]. *Blood*. 2011;118(21):79. Presented at American Society of Hematology Annual Meeting; Dec 2011; San Diego, CA.
22. Regulatory Decision Summary for Defitelio. Ottawa (ON): Health Canada; 2019: https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00270. Accessed 2019 Dec 6.
23. Castaigne S, Pautas C, Terré C, et al. Final analysis of the ALFA 0701 study [abstract]. *Blood*. 2014;124(21):376. Presented at American Society of Hematology Annual Meeting; Dec 2014; San Francisco, CA.
24. Pautas C, Raffoux E, Lambert J, et al. Outcomes following hematopoietic stem cell transplantation in patients treated with chemotherapy with or without gemtuzumab ozogamicin for acute myeloid leukemia [abstract]. *Blood*. 2018;132(Suppl 1):28. Presented at American Society of Hematology Annual Meeting; Dec 2018, San Diego, CA.
25. O'Hear C, Inaba H, Pounds S, et al. Gemtuzumab ozogamicin can reduce minimal residual disease in patients with childhood acute myeloid leukemia. *Cancer*. 2013;119(22):4036-4043.
26. Rubnitz JE, Inaba H, Dahl G, et al. Minimal residual disease-directed therapy for childhood acute myeloid leukaemia: results of the AML02 multicentre trial. *Lancet Oncol*. 2010;11(6):543-552.
27. Sung L, Aplenc R, Alonzo TA, et al. Severe toxicities during pediatric acute myeloid leukemia chemotherapy: a report from the children's oncology group [abstract]. *Blood*. 2010;116(21):Presented at American Society of Hematology Annual Meeting; Dec 2010; Orlando, FL.
28. Gamis AS, Alonzo TA, Gerbing RB, et al. Remission rates in childhood Acute Myeloid Leukemia (AML) utilizing a dose-intensive induction regimen with or without Gemtuzumab Ozogamicin (GO): initial results from the children's oncology group phase III Trial, AAML0531 [abstract]. *Blood*. 2010;116(21):Presented at American Society of Hematology Annual Meeting; Dec 2010; Orlando, FL.
29. Farhat H, Reman O, Raffoux E, et al. Fractionated doses of gemtuzumab ozogamicin with escalated doses of daunorubicin and cytarabine as first acute myeloid leukemia salvage in patients aged 50-70-year old: a phase 1/2 study of the acute leukemia French association. *Am J Hematol*. 2012;87(1):62-65.
30. Cooper TM, Franklin J, Gerbing RB, et al. AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia: a report from the Children's Oncology Group. *Cancer*. 2012;118(3):761-769.
31. Gibson B, Houlton AE, Baruchel A, et al. Intensified dosing of gemtuzumab ozogamicin can be safely combined with induction chemotherapy in children with acute myeloid leukaemia (AML) and high risk myelodysplasia (MDS) [abstract]. *Blood*. 2018;132(Suppl 1):Presented at American Society of Hematology Annual Meeting; Dec 2018, San Diego, CA.
32. Burnett AK, Russell NH, Kell J, et al. A comparison of daunorubicin/ara-c (DA) versus daunorubicin/clofarabine (DCLO) and two versus three courses of total treatment for older patients with aml and high risk MDS: results of the UK NCRI AML16 trial [abstract]. *Blood*. 2012;120(21): Presented at American Society of Hematology; Dec 2012; Atlanta, GA.
33. Fernandez HF, Sun Z, Litzow MR, et al. Autologous transplantation gives encouraging results for young adults with favorable-risk acute myeloid leukemia, but is not improved with gemtuzumab ozogamicin. *Blood*. 2011;117(20):5306-5313.
34. Brunnberg U, Mohr M, Noppeney R, et al. Induction therapy of AML with ara-C plus daunorubicin versus ara-C plus gemtuzumab ozogamicin: a randomized phase II trial in elderly patients. *Ann Oncol*. 2012;23(4):990-996.
35. Amadori S, Suciu S, Stasi R, et al. Sequential combination of gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed acute myeloid leukemia: results of a

randomized phase III trial by the EORTC and GIMEMA consortium (AML-17). *J Clin Oncol*. 2013;31(35):4424-4430.
36. Clinical Study Report ALFA-0701. Multicenter, randomized, phase 3 study of fractionated doses of the monoclonal antibody [drug conjugate] gemtuzumab ozogamicin (Mylotarg) in addition to daunorubicin + cytarabine for induction and consolidation therapy in patients with acute myeloid leukemia (AML) aged 50 to 70 years [Internal sponsor's report]. New York (NY): Pfizer; 2016.
37. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2019 Nov 5.