CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761060Orig1s000
761060Orig2s000

CLINICAL REVIEW(S)

CROSS-DISCIPLINE TEAM LEADER MEMO

Application Number	**BLA 761060**
Submission Type	Original-1 and Original-2
Applicant	Wyeth Pharmaceuticals Inc.
Submission Date	November 2, 2016
Trade Name	Mylotarg
Proper Name	Gemtuzumab ozogamicin
CDTL	Donna Przepiorka, MD, PhD

The CDTL review is incorporated into the combined Division Director Summary Review for Regulatory Action and Cross-Discipline Team Leader Review. The recommended regulatory action is regular approval for Original-1 and Original-2.

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/s/

DONNA PRZEPIORKA
08/12/2017

CLINICAL REVIEW

Application Type	Original
Application Number(s)	BLA 761060, Ori-1
Priority or Standard	Standard
Submit Date(s)	November 2, 2016
Received Date(s)	November 2, 2016
PDUFA Goal Date	September 2, 2017
Division / Office	DHP/CDER/OHOP
Reviewer Name(s)	Emily Jen, M.D., Ph.D.
Review Completion Date	July 28, 2017
Established Name	Gemtuzumab ozogamicin
(Proposed) Trade Name	Mylotarg
Therapeutic Class	Antineoplastic
Applicant	Wyeth (a subsidiary of Pfizer)
Formulation(s)	Intravenous injection, lyophilized power (5mg)
Dosing Regimen	• *Induction:* GO 3 mg/m^2 up to a maximum dose of 5 mg, infused over a 2-hour period on Days 1, 4, and 7 in combination with DNR 60 mg/m^2/day infused over 30 minutes on Days 1, 2, and 3 and AraC 200 mg/m^2/day by continuous infusion on Days 1-7. • *Consolidation:* For patients experiencing a complete remission (CR) following induction, 2 consolidation courses of intravenous DNR (60 mg/m^2 for 1 day [first course] or 2 days [second course]) in combination with intravenous AraC (1000 mg/m^2 per 12 hours, infused over 2 hours on Days 1 through 4) with intravenous GO (3 mg/m^2 up to a maximum dose of 5 mg on Day 1).
Indication(s)	In combination with daunorubicin and cytarabine for the treatment of patients with newly-diagnosed, CD33-positive de novo acute myeloid leukemia.

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Table 1. List of Abbreviations

ADC	Antibody-drug conjugate
ALFA	Acute Leukemia French Association
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukemia
AraC	Cytarabine
AST	Aspartate aminotransferase
CBC	Complete blood count
CBF	Core binding factor
CFR	Code of Federal Regulations
CHV	Centre Hospitalier de Versailles
CI	Confidence interval
CLS	Capillary leak syndrome
CML	Chronic myelogenous leukemia
COD	Cause of death
COG	Children's Oncology Group
CR	Complete response
CRF	Case report form
CRi	CR with incomplete count recovery
CRp	CR with incomplete platelet recovery to >100,000/mm^3
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DA	Daunorubicin + cytarabine
DNR	Daunorubicin
eCTD	Electronic common technical document
EFS	Event-free survival
ELN	European Leukemia Net
FAB	French-American-British
GCP	Good Clinical Practice
GIMEMA	Gruppo Italiano Malattie EMatologiche dell'Adulto
GO	Gemtuzumab ozogamicin
GOELAMS	Groupe Ouest Est des Leucémies Aiguës et Maladies du San
GVHD	Graft versus host disease
Hgb	Hemoglobin
HiDAC	High dose AraC
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
ICH	International Conference on Harmonization
IF	Induction failure

IPD	Individual patient data
IRC	Independent review committee
IRR	Infusion-related reaction
LDAC	Low dose AraC
MDS	Myelodysplastic syndrome
MPN	Myeloproliferative neoplasm
MRC	Medical Research Counsel
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
OR	Odds ratio
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PRBC	Packed red blood cells
PRO	Patient reported outcome
SAE	Serious adverse event
SOS	Sinusoidal obstruction syndrome
SPR	Study progress report
SUAE	Serious unexpected adverse event
SWOG	Southwest Oncology Group
TEAE	Treatment-emergent adverse event
TRM	Treatment-related mortality
VOD	Veno-occlusive disease

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends regular approval of gemtuzumab ozogamicin under 21 CFR 601 in combination with daunorubicin and cytarabine for the treatment of patients with newly-diagnosed CD33-positive acute myeloid leukemia. Approval is supported by the results of ALFA-0701 in which treatment with GO in combination with daunorubicin and cytarabine (DA) showed a clinically meaningful EFS benefit with a hazard ratio of 0.68 (95% CI 0.51, 0.91). The median EFS for GO+DA was 17.3 months compared with 9.5 months for DA.

1.2 Risk Benefit Assessment

Table 2. Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In the United States, it is estimated that 21,380 people will be diagnosed with AML in 2017, and 10,590 will die from their disease. • AML is universally fatal without treatment, with a median survival of approximately two months.	• AML is a fatal disease.
Unmet Medical Need	• Intensive chemotherapy regimens, with or without HSCT, currently yield 5-year survival rates of ~30-40% in adults. • Pediatric chemotherapy regimens are generally much more intensive, but only yield a 5-year survival rate of 60%.	• Current standard of care regimens are insufficient, and more effective therapies are needed.
Clinical Benefit	• ALFA-0701 was an open-label randomized trial of gemtuzumab ozogamicin plus daunorubicin and cytarabine for patients between 50-70 years old with newly-diagnosed AML (n=271). - Median EFS with GO was 17.3 months compared with 9.5% in the DA arm with HR 0.68 (95% CI 0.51, 0.91). • AAML0531 was an open-label randomized trial of gemtuzumab ozogamicin plus standard intensive chemotherapy for children with newly-diagnosed AML (n=1022). - 3-year EFS with GO was 53% vs 47% in the DA arm with HR 0.83 (95% CI 0.70, 0.99).	• GO treatment using a fractionated dosing regimen in combination with DA in adults and a single dose (x2) in combination with standard five-course induction in children was active in the treatment of newly-diagnosed AML.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risks	• VOD and hemorrhage are potential fatal adverse reactions. • Thrombocytopenia and hepatotoxicity were the most common adverse events that resulted in drug discontinuation. • Other serious reactions included infections, prolonged platelet recovery time, and elevated liver enzymes. • Other common (>10%) reactions were related to bleeding or infection. • Infusion-related reactions are a known risk with ADCs but were rare in these studies.	• The overall safety profile is acceptable for patients newly-diagnosed AML.
Risk Management	• Serious or life-threatening toxicities were avoided by close monitoring, premedication prior to GO, and stopping guidelines in the protocol.	• To minimize risks, labeling should include instructions for steroid premedication, monitoring, and stopping GO for toxicities.

Background:

There were 19,950 new cases of AML and 10,430 deaths from AML in the United States in 2016, and those numbers are expected to rise this year. AML occurs in all age groups and is universally fatal without treatment, having a median survival of approximately two months. Intensive chemotherapy regimens, with or without HSCT, are the standard of care and currently yield 5-year survival rates of around 30-40% in adults. Pediatric chemotherapy regimens are generally much more intensive, but only yield a 5-year survival rate of 60%. AML is difficult to treat, and there remains a need for more effective therapies for this disease.

Gemtuzumab ozogamicin was previously granted accelerated approval in 2000 as a monotherapy at a dose of 9 mg/m^2 x 2 doses in patients with relapsed AML. The confirmatory trial SWOG S0106 used GO 6 mg/m^2 in combination with daunorubicin and cytarabine, but the trial was terminated early after an interim analysis showed increased deaths in induction and lack of improvement in complete response rate in the GO arm. GO was subsequently withdrawn from the US market in 2010. Based on data from studies conducted in the interim, a fractionated schedule of 3 mg/m^2 GO in combination with DA appeared to address the safety concerns seen with the prior dose regimens.

Basis of the application:

GO is an antibody-drug conjugate that binds the CD33 antigen present on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, forming a complex which is then internalized. Upon internalization, the calicheamicin is released and binds to DNA, resulting in DNA double strand breaks and subsequent cell death.

This application is based on the results of pivotal trial ALFA-0701, a phase III randomized trial of 3 mg/m^2 GO fractionated schedule plus DA vs DA alone in patients with newly-diagnosed AML. There were 271 patients were randomized, and the primary efficacy endpoint was EFS.

Efficacy:

Fractionated GO in combination with DA showed a clinically meaningful EFS benefit with an improvement in median EFS of 7.8 months with GO+DA over the control arm. The hazard ratio (HR) for EFS as defined by FDA was 0.68 (95% CI 0.51, 0.91). However, a corresponding OS benefit was not seen, and in the meta-analysis, EFS was not found to have a strong correlation with OS. This analysis may have been confounded, in part, by active salvage therapies including stem cell transplantation. In consultation with ODAC, it was accepted that EFS itself represents a clear benefit for patients and is a reasonable endpoint for new therapies for the treatment of patients with newly-diagnosed AML.

No PROs were collected in this trial.

Safety:

From a safety perspective, there remains a risk of VOD with an incidence of 5% with GO+DA. Patients treated with GO also had prolonged platelet recovery time and more high-grade hemorrhages. But, the difference in early mortality with GO+DA vs DA alone is small (4% vs 2%), and the disparity in 30-day mortality between treatment arms in ALFA-0701 is lower than that reported for SWOG S0106 (2% vs 6%) suggesting that the lower dose of GO in the fractionated schedule is safer with regards to early mortality.

Special Populations:

- Adverse cytogenetic risk: Data in ALFA-0701 and across the published literature show no benefit in patients with adverse risk cytogenetics. However, cytogenetics data may not be available at the time of treatment initiation, and safety data for GO combinations with chemotherapy do not indicate that these patients are at significantly higher risk for toxicity. Restricting the indication by cytogenetic risk category would require that all patients delay treatment until that information is obtainable. This may be an unacceptable risk for most patients. Therefore, the label should be clear with regards to the lack of evidence in this subset; however, the decision regarding the use of GO in these patients should be left to the discretion of the treating physician to be assessed on an individual patient basis.

- Pediatrics: COG AAML0531 was a phase III randomized trial of GO single dose 3 mg/m^2 in combination with intensive chemotherapy for untreated AML in children between 1 month and 29 years old. There were 1022 patients randomized, and the primary endpoints were EFS and OS. Event-free survival with GO was significantly better than without GO with a HR 0.83 (95% CI 0.70-0.99). Also, relapse was reduced significantly with the use of GO; however this did not translate into a statistically significant improvement in overall survival. These efficacy findings are consistent with adult trials. The safety profile in children treated with GO is also similar to that seen in adults,

and the incidences, as well as the disparities between treatment arms, for VOD, hemorrhage, and prolonged thrombocytopenia were all lower than those seen in ALFA-0701.

Overall Benefit-Risk Assessment:

Current standard of care frontline treatment of AML consists of intensive chemotherapy with or without HSCT and results in 30-40% overall survival in adults and 60% OS in children. The fractionated 3 mg/m^2 dose schedule in combination with DA studied in ALFA-0701 resulted in a clinically-meaningful improvement in EFS of 7.8 months over DA with an HR of 0.68 (95% CI 0.51, 0.91).

From a safety standpoint, the disparity in early mortality between treatment arms is lower than previously seen with GO 6 mg/m^2 in SWOG S0106, suggesting the lower fractionated dosing schedule is safer in combination with DA. However, there remains a risk for VOD (5% with GO+DA) and high-grade hemorrhage in the setting of prolonged thrombocytopenia. These risks were moderated in part by close monitoring and implementation of hematologic criteria for permanent discontinuation of GO.

Although single-dose GO 3 mg/m^2 indirectly appears safer than fractionated dosing with regards to VOD, hepatotoxicity, hemorrhage, and thrombocytopenia in the meta-analysis, the efficacy data are not clear for single-dose GO in adults, and there are no dose-finding studies that directly compare the 2 schedules. Therefore, given the available safety and efficacy data, the benefit:risk is positive for the combination of fractionated GO 3 mg/m^2 days 1, 4, and 7 of induction and day 1 of consolidation 1 and 2 plus DA for adult patients with newly-diagnosed CD33-positive AML.

Additionally, a large pediatric randomized trial of 1022 patients found that treatment with single-dose 3 mg/m^2 GO in induction 1 and intensification 2 in combination with standard 5-course chemotherapy also resulted in improvement in EFS. The safety profile in children treated with GO is similar to that seen in adults, and there are adequate data to support extending the indication to children using the single-dose GO regimen studied in COG AAML0531.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The safety concerns with Mylotarg are well documented, and providers who treat patients with AML should be familiar with the risks and importance of patient monitoring in the setting of treatment for AML. Therefore, FDA determined that a REMS is not necessary for Mylotarg.

1.4 Recommendations for Postmarket Requirements and Commitments

No post-marketing requirements or commitments are recommended for this indication.

2 Introduction and Regulatory Background

2.1 Product Information

Drug Established Name:	Gemtuzumab ozogamicin (GO)
Trade Name:	Mylotarg
Prior Names:	PF-0520874, CMA-676
Dosage Forms:	Intravenous injection - lyophilized powder 5mg
Chemical Class:	Recombinant antibody-drug conjugate
Therapeutic Class:	Antineoplastic
Pharmacologic Class:	Antibody-drug conjugate
Mechanism of Action:	The antibody portion binds the CD33 antigen present on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, forming a complex which is then internalized. Upon internalization, the calicheamicin is released and binds to DNA, resulting in DNA double strand breaks and subsequent cell death.
Proposed Indication:	Combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia
Proposed Dose Schedule:	• *Induction:* GO 3 mg/m^2 up to a maximum dose of 5 mg, infused over a 2-hour period on Days 1, 4, and 7 in combination with DNR 60 mg/m^2/day infused over 30 minutes on Days 1, 2, and 3 and AraC 200 mg/m^2/day by continuous infusion on Days 1-7. • *Consolidation:* For patients experiencing a complete remission (CR) following induction, 2 consolidation courses of intravenous DNR (60 mg/m^2 for 1 day [first course] or 2 days [second course]) in combination with intravenous AraC (1000 mg/m^2 per 12 hours, infused over 2 hours on Days 1 through 4) with intravenous GO (3 mg/m^2 up to a maximum dose of 5 mg on Day 1).

2.2 Table of Currently Available Treatments for Proposed Indication

Combination chemotherapy regimens with or without hematopoietic stem cell transplantation (HSCT) are the standard of care for patients with newly-diagnosed AML. A list of chemotherapy agents with FDA approval for the treatment of AML is provided in Table 3. For patients who are able to tolerate

intensive therapy, standard frontline treatment typically involves induction with 7 days of cytarabine and 3 days of an anthracycline, or what is commonly referred to as the "7+3" regimen, followed by high-dose cytarabine consolidation. This treatment regimen was shown to be effective in adults in the 1970s. Current 5-year survival rates for patients who receive intensive therapy are around 30-40% (Dombret, 2016). Standard of care treatment of AML in pediatrics is built upon the 7+3 backbone, but has been intensified with the addition of etoposide in induction and other chemotherapies in later phases of treatment. The current 5-year survival rate is 60% in children (Rubnitz, 2012).

Improvements in HSCT and supportive care have decreased mortality. However, over the past several decades, successes in the treatment of AML have only modestly improved. With recent advances in the understanding of AML biology and genetics, it has become clear that AML is a biologically heterogeneous disease, and targeted treatments for specific AML subgroups are being explored. There remains a strong need for new treatments for patients with AML.

Table 3. Approved Agents with Indication(s) Relevant to the Treatment of de novo AML

Agent	Excerpted Indication
Cyclophosphamide	Treatment of acute myelogenous and monocytic leukemia. Although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs.
Cytarabine	In combination with other approved anti-cancer drugs for remission induction in acute non-lymphocytic leukemia of adults and pediatric patients
Daunorubicin	In combination with other approved anticancer drugs, for remission induction in acute non-lymphocytic leukemia of adults
Doxorubicin	Has been used successfully to produce regression in disseminated neoplastic conditions including acute myeloblastic leukemia.
Idarubicin	In combination with other approved anti-leukemic drugs, for the treatment of acute myeloid leukemia in adults. This includes FAB classifications M1 through M7.
Midostaurin	In combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly-diagnosed acute myeloid leukemia (AML) who are FLT3 mutation positive, as detected by an FDA approved test.
Mitoxantrone	In combination with other approved drugs, in the initial therapy of acute nonlymphocytic leukemia in adults. This category includes myelogenous, promyelocytic, monocytic and erythroid acute leukemias.
Thioguanine	For remission induction and remission consolidation treatment of acute nonlymphocytic leukemias... Reliance upon thioguanine alone is seldom justified for initial remission induction of acute non-lymphocytic leukemias because combination chemotherapy including thioguanine results in more frequent remission induction and longer duration of remission than thioguanine alone.
Vincristine	Indicated in acute leukemia

2.3 Availability of Proposed Active Ingredient in the United States

Currently, gemtuzumab ozogamicin is only available in the Unites States through clinical trials and Pfizer's expanded access protocol.

2.4 Important Safety Issues With Consideration to Related Drugs

- There are no currently approved ADCs for the treatment of AML. GO is the first CD33-targeted ADC.

- Antibody related toxicities - immunomodulatory monoclonal antibodies may cause infusion and hypersensitivity reactions, including allergic reactions, pseudoallergic reactions (IgE-independent reactions), and cytokine release syndrome (CRS). Other known adverse events related to directed-antibody therapies include neutropenia, infection, and tumor lysis syndrome.

- Anti-CD33 agents –
  - Lintuzumab (SGN-33) is an immunoconjugate monoclonal antibody directed against CD33 which has orphan designation for the treatment of AML and MDS. In a randomized trial of lintuzumab + LDAC vs LDAC, a majority of TEAEs that were higher in the lintuzumab arm were thought to be related to infusion-related reactions to lintuzumab. There was no apparent clinical difference in incidence of Grade ≥3 TEAEs between study arms (Sekeres, 2013).

  - Vadastuximab talirine (SGN-CD33A) is an ADC directed against CD33 conjugated to a pyrrolobenzodiazepine dimer (DNA binding agent) which has orphan designation for the treatment of AML. In December 2016, FDA briefly placed several early-stage clinical trials on hold due to a concern for increased fatal VOD. In June 2017, after a review of unblinded data, Seattle Genetics terminated its Phase 3 trial in frontline AML due to a higher rate of deaths including fatal infection in the experimental arm. Based on available data, the safety issues did not appear to be related to hepatotoxicity. (Seattle Genetics Press Release 6/19/2017: http://investor.seattlegenetics.com/phoenix.zhtml?c=124860&p=irol-newsArticle_Print&ID=2281531)

- Calicheamicin – Inotuzumab ozogamicin is a calicheamicin-conjugated monoclonal antibody that targets CD22 cells on lymphoblasts in acute lymphoblastic leukemia (ALL). The adverse drug reactions known to be associated with inotuzumab include veno-occlusive disease (VOD), infusion-related reactions, myelosuppression, and delayed platelet recovery. These were taken into consideration in the evaluation of this application.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The key US regulatory activities related to this submission are as follows:

11/10/1994	Original IND 46635 for CMA-676 submitted
10/29/1999	Original NDA 21174 submitted
11/24/1999	Orphan designation – treatment of CD33-positive acute myeloid leukemia.
5/17/2000	Accelerated approval granted for the treatment of patients ≥ 60 years old with AML in first relapse who are not otherwise candidates for cytotoxic chemotherapy based on a 30% overall response rate. The approved dose is 9 mg/m^2 for 2 doses 14 days apart. The post marketing requirement to confirm benefit was a randomized trial comparing daunorubicin and cytarabine with or without Mylotarg as induction therapy in patients with de novo CD33-positive acute myeloid leukemia.
2004	Confirmatory trial SWOG S0106 initiated.
2009	SWOG S0106 terminated early by DSMB. Interim analysis showed lack of improvement in CR rate in the Mylotarg arm and an increase in deaths during induction.
5/21/2010	FDA proposes to withdraw approval of Mylotarg because the confirmatory trial failed to verify the clinical benefit for Mylotarg.
10/25/2010	Sponsor voluntarily withdraws Mylotarg. Continued use is limited by the sponsor to single patient INDs only. The drug remains approved in Japan and is denied approval in the EU.
2012-2016	On eight occasions between 2012 and 2016, FDA and Wyeth discussed or corresponded about additional emerging data on the efficacy of GO, the negative OS analysis of ALFA-0701, the need for an analysis of EFS/OS correlation, and the information that would be required for submission of a new marketing application.
4/10/2013	Expanded access protocol submitted
11/2/2016	BLA 761060 submitted

2.6 Other Relevant Background Information

The prognosis of AML is influenced both by patient-specific and disease-specific factors. Age is the most important patient-specific risk factor, with older patients having lower rates of complete remission and shorter disease-free survival. Poor performance status (often related to comorbidities), history of prior exposure to cytotoxic agents or radiation therapy, and history of prior MDS or myeloproliferative neoplasms are also adverse clinical predictors.

Cytogenetics remain the strongest disease-related prognostic factor in AML. Patients who fall in the intermediate cytogenetic risk category represent the largest and most heterogeneous group of patients. For patients with cytogenetically normal AML, prognosis may be directed by the mutational status of genes such as NPM1, FLT3 and CEBPA. Guidelines such as ELN and NCCN attempt to incorporate these molecular changes into risk categories. However, a growing number of recurrent mutations in additional genes have recently been identified for which the prognostic effect yet has to be determined.

2.7 Compliance with the Pediatric Research Equity Act

Gemtuzumab ozogamicin has orphan designation for treatment of CD33-positive acute myeloid leukemia and is therefore exempt from the requirements for a pediatric assessment under the Pediatric Research Equity Act.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA 761060 was received on 11/2/2016. The submission was provided in accordance with the International Conference on Harmonization (ICH) Electronic Common Technical Document (eCTD). Data for the pivotal ALFA-0701 trial were provided using CDISC standard ADaM and SDTM datasets. Data for the supporting IPD Meta-Analysis were provided in Legacy format. The application was filed on 1/1/2017. Additional amendments used for this review are listed in Table 4 below.

Table 4. BLA Submission and Amendments

SDN	Received	Category	Subcategory
1	11/02/16	Original	BLA
6	12/16/16	Clinical	Response to Information Request
11	1/27/17	Clinical	Response to Information Request
16	2/28/17	Clinical	Response to Information Request
26	3/27/17	Clinical	Response to Information Request
30	5/2/17	Clinical	Response to Information Request
38	6/16/17	Clinical	Response to Information Request
39	6/19/17	Clinical	Response to Information Request
40	6/26/17	Clinical	Response to Information Request
43	7/7/17	Clinical	Response to Information Request
48	7/27/17	Clinical	Response to Information Request

3.2 Compliance with Good Clinical Practices

The pivotal trial ALFA-0701 and 3 of the other 4 studies in the IPD meta-analysis submitted by the applicant were conducted solely outside the US. In compliance with 21 CFR 312.120, a list of foreign clinical trials was submitted. All protocols and/or clinical study reports stated that they were conducted in compliance with Good Clinical Practice (GCP). A list of study sites and investigators for ALFA-0701 was also provided. In compliance with 21 CFR 314.106, a statement regarding the applicability of foreign data to US medical practice and population was submitted on 12/16/16 in response to an information request (SDN 6).

FDA's Office of Scientific Investigations conducted audits at 4 clinical sites for the pivotal trial ALFA-0701. An audit was also conducted of the Applicant to verify that all required study documents, including foreign clinical trial info were available. The sites requested for inspection enrolled the largest

numbers of subjects with efficacy results at or above those for the study as a whole. They were chosen for the potential that the overall trial outcome was driven by results at these centers.

Three clinical investigation sites were classified as No Action Indicated (NAI) and one site (19) had Form 483 issued for: Investigational records were not retained for a period of two years following the approval of a drug's marketing application, specifically:

- Source documents were missing for two subjects (b) (6) Only the signed Informed Consent and computer printed hospitalization reports were present.
- The signed Informed Consent was missing for one subject (b) (6).
- Myelograms were missing for one subject (b) (6).

Both Pfizer and Centre Hospitalier de Versailles (CHV) sponsors were inspected and classified as NAIs. No data integrity issues were identified.

Reviewer comment: Patient (b) (6) was censored from the study due to lack of consent form and is not included in the datasets or analyses provided by the applicant. The remaining issues were taken into consideration as protocol deviations.

3.3 Financial Disclosures

The applicant submitted financial disclosure information from some of the principal investigators and sub-investigators from ALFA-0701. Because ALFA-0701 was not conducted under an IND, no financial disclosure was collected at the beginning of the study. Financial disclosure forms were collected retrospectively. For several investigators including the PIs of 6/27 sites, this information was not available as they had left the site before the documents could be collected and did not respond to requests from the applicant. All financial disclosures totaled less than $20,000 each except for the PI from Site (b) (6) who reported more than $83,000 income from consulting.

Reviewer comment: The hazard ratio for Site (b) (6) is poor (0.95). Additionally, Pfizer asserts that the consultant agreements (b) (6) with and payments to this PI occurred after the data for the primary efficacy endpoint (EFS) were collected (b) (6) and publicly presented at ASH (12/2011). Moreover, a retrospective data collection was performed, and efficacy data were reviewed in a blinded manner by an Independent Review Committee. These analyses are included in the submission and confirm the primary EFS analysis. Therefore, the financial conflicts of interest do not appear to compromise the integrity of the trial data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were several post-manufacturing changes since Mylotarg was approved in 2000. All of them through 2007 have been approved as post-marketing supplements to NDA 21-174/S-036.

One recent change, [redacted], was discovered in 2014 using more sensitive analytical methods. Wyeth found an increase in the levels of [redacted] starting around 2005. They did a retrospective analysis of pre-change lots and could find trace levels [redacted]%) in a few of the lots, but coinciding with the manufacturing changes in lots manufactured between 2005 and 2011, the levels were higher and have remained consistent. These [redacted] do not appear to affect binding to CD33 or add new conjugation sites in a way that affects the overall cytotoxicity of the product.

The Manufacturing and Clinical Pharmacology Reviewers confirmed that [redacted] is unlikely to impact clinical efficacy, given that lots containing the higher levels were used commercially and clinically. The reviewed data is considered applicable to current drug product. Approval was recommended.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

See clinical review of Ori-2.

4.4 Clinical Pharmacology

Office of Clinical Pharmacology reviewed the application and determined that there was sufficient evidence to support approval of GO 3 mg/m^2 (on Days 1, 4, and 7) in combination with DNR/AraC for de novo AML with a PMR/PMC to evaluate the efficacy and safety of 3 mg/m^2 dose as a monotherapy.

4.4.1 Mechanism of Action

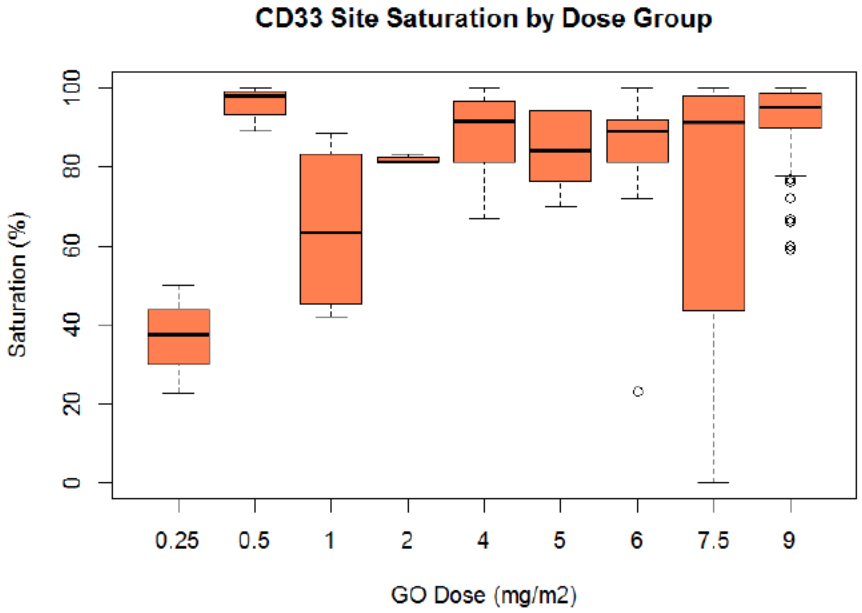
The antibody portion of GO binds the CD33 antigen present on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, forming a complex which is then internalized. Upon internalization, the calicheamicin is released and binds to DNA, resulting in DNA double strand breaks and subsequent cell death.

4.4.2 Pharmacokinetics

FDA's review of pharmacokinetics data from the prior application for Mylotarg confirmed the Applicant's finding that a. exposure to antibody and calicheamicin increased more than dose-proportional, b. there was an accumulation with multiple doses of GO (increases in Cmax and AUC were observed in Dose Period 2 compared to Dose Period 1 when multiple doses were administered 14 days apart), and c. corresponding decreases in clearance and volume of distribution were seen between dosing periods. However, no PK studies were performed in patients treated with fractionated GO either as a monotherapy or in combination with DA in ALFA-0701.

Saturation of a high percentage of CD33 antigens is believed to be required for maximum delivery of calicheamicin to leukemic blast cells. The relationship between dose and CD33 site saturation is shown in Figure 1, and it appears that CD33 antigen is saturated with GO doses of 2 mg/m^2 and above.

Figure 1 – CD33 Site Saturation Following Single Dose of GO at Doses Ranging from 0.25 mg/m^2 to 9 mg/m^2



Source: FDA Clinical Pharmacology Review

Exposure-response analyses of monotherapy GO dosing showed a relationship between Cmax after the 1st dose of GO and the probability of developing VOD. Therefore, a reduction in Cmax resulting from fractionated dosing may decrease the incidence of VOD.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5. Table of Studies/Clinical Trials

Trial Name	Trial Design	Population and number of patients (GO/No GO)	Primary Endpoint
Pivotal Study			
ALFA-0701	Randomized 1:1, open-label, Phase 3 trial • GO: 3 mg/m^2/dose (max dose 5mg) D1, 4, 7 plus Chemotherapy: 1) DNR: 60 mg/m^2/d D1-3 2) AraC: 200 mg/m^2/d D1-7 • Chemotherapy without GO	Adults 50-70 years old with previously untreated de novo AML - Efficacy n=271(135/136) - Safety n=268 (131/137)	EFS

Supporting Studies - Efficacy and Safety			
IPD Meta-Analysis (includes ALFA-0701 and the following 4 studies)			
	Randomized studies of GO added to intensive chemotherapy during induction	Patients ≥ 15 years old with newly-diagnosed AML and MDS - n=3331 (1663/1668)	
MRC AML15	Randomized, open-label, Phase 3 trial of GO added to induction and/or consolidation chemotherapy • GO: 3 mg/m^2 D1 of Course 1 plus Chemotherapy: 1) ADE 2) DNR: 50 mg/m^2 D1, 3, 5 AraC: 100 mg/m^2/q12h D1-10 3) FLAG-IDA • Chemotherapy without GO • Patients in remission randomized to no treatment or GO + MACE or high dose AraC consolidation	Adults <60 years old with previously untreated de novo AML or secondary AML, APL - n=1113 (557/556)	OS and ORR (CR + CRi)
NCRI AML16	Randomized, open-label, Phase 2-3 trial of GO added to standard induction chemotherapy • GO: 3 mg/m^2 D1 plus Chemotherapy: 1) DNR: 50 mg/m^2/d D1, 3, 5 AraC: 100 mg/m^2/q12h D1-10 2) DNR: 50 mg/m^2/d D1, 3, 5 Clofarabine 20 mg/m^2/d D1-5 • Chemotherapy without GO	Adults <60 years old with previously untreated de novo or secondary AML or high-risk MDS - n=1115 (559/556)	OS
SWOG S0106	Randomized, open-label, Phase 3 trial of GO added to standard induction followed by post-consolidation randomization to 3 additional doses of GO or no additional therapy • GO: 6 mg/m^2 D4 plus Chemotherapy: DNR: 45 mg/m^2/d D1, 2, 3 AraC: 100 mg/m^2/d CI D1-10 • Chemotherapy without GO	Adults 18-60 years of age with previously untreated de novo non-M3 AML - n=595 (295/300)	DFS, CR

GOELAMS AML2006IR	Randomized, open-label, Phase 3 trial of GO added to standard induction and consolidation chemotherapy • GO: 6 mg/m^2 D4 plus Chemotherapy: DNR: 60 mg/m^2/d D1, 2, 3 AraC: 200 mg/m^2/d D1-10 Chemotherapy without GO	Adults ≤60 years of age with newly-diagnosed intermediate-risk cytogenetics CD33-positive AML - n=251 (126/125)	EFS at 3 years
COG AAML0531, Gamis, 2014	Randomized, open-label, Phase 3 trial of GO added to standard pediatric chemotherapy • GO: 3 mg/m^2 D6 of induction I and D7 of intensification II Chemotherapy: Pediatric SOC (DA backbone) – See Table 32 for full pediatric regimen • Chemotherapy without GO	Children and young adults age 0-29 years with newly-diagnosed AML - n=1022 (511/511)	EFS and OS

Abbreviations: AraC – cytarabine; CR – complete response; DFS – disease-free survival; DNR – daunorubicin; EFS – event-free survival; FLAG-IDA - fludarabine/ cytarabine/filgrastim/idarubicin; MACE - amsacrine, cytarabine, etoposide; ORR – overall response rate (CR+CRp); OS – overall survival; SOC – standard of care

5.2 Review Strategy

The key materials used for the review of efficacy and safety include:

- BLA 761060
- Relevant published literature
- Relevant information in the public domain

The review of efficacy was based primarily on ALFA-0701 and supported as follows:

- Efficacy data from the IPD meta-analysis were used to demonstrate overall survival of GO in combination with chemotherapy (exploratory analysis only).
- Efficacy data from the IPD meta-analysis and literature were used to demonstrate preservation of efficacy despite the use of lower GO doses.
- Efficacy data from the Applicant's surrogacy meta-analysis were used to analyze the surrogacy of EFS for OS in AML.
- Efficacy data from COG AAML0531 Fall 2013 Study Progress Report (SPR) and Gamis, 2014 were used to demonstrate EFS benefit with GO in combination with pediatric standard of care chemotherapy and to extend the indication to include children with newly-diagnosed CD33-positive AML.

The review of safety was based on data from all 6 trials of GO in combination with chemotherapy listed in Table 5. Emphasis was placed on safety data from ALFA-0701 and was supported as follows:

- Safety data from the IPD meta-analysis and literature were used to support the analysis of GO dose selection in combination with chemotherapy.
- Safety data from the IPD meta-analysis and safety events reported in the literature were used to look for potential safety signals.
- Safety data from COG AAML0531 SPR and Gamis, 2014 were used to support the analysis of safety with GO in combination with chemotherapy in the pediatric population.

Statistical analyses by the clinical reviewer were performed using JMP 12 (SAS Institute, Inc., Cary, NC), and MedDRA Adverse Events Diagnostic (MAED) (Clinical Trials & Surveys Corporation, Owings Mills, MD) was used to assess for safety signals. For the primary efficacy analysis provided by the statistician in Section 6.1, see the statistician's review for a description of the methodology used. Unless stated otherwise, all other p-values are unadjusted for multiplicity and should be interpreted with caution.

Limitations of data:

1. Retrospective data collection in ALFA-0701

Study ALFA-0701, sponsored by Centre Hospitalier de Versailles (CHV) and conducted by the ALFA, was not prospectively performed for regulatory purposes and did not follow the standards of clinical trials conducted by pharmaceutical companies. Therefore, Pfizer decided in agreement with the study Sponsor (CHV) to perform a retrospective data collection in order to address the potential gaps and to complete the initial database.

Safety data were collected originally using a predefined checklist of Grade 3 and 4 AEs developed by CHV, for use during conduct of the trial. Grade 1 and 2 adverse events were not recorded. In order to address this deficiency, the applicant (via independent contract research organization) performed a retrospective collection of adverse events of specific interest (AESI) to capture all grades of hemorrhage and VOD, severe (Grade >2) infections, and any other adverse event that led to early permanent discontinuation of GO or chemotherapy. These data were collected from screening to 28 days after the last dose of study drugs, except for VOD which was collected until patient death or up to the retrospective data collection cutoff date. AEs leading to dose reduction or treatment interruption were not gathered. Additionally, although SAEs were reported for all patients in the trial, CHV did not assess relatedness for SAEs in patients in the control arm. Therefore the applicant (via independent review committee) reviewed and adjudicated all reported SAEs individually to ensure SAEs in both treatment arms were assessed for treatment relatedness.

As part of the applicant's retrospective data collection, all data involved in efficacy measurements (laboratory, blood, and bone marrow aspirate results) from screening until death or 28 days after induction failure (IF)/relapse were collected. An IRC completed a retrospective, blinded, independent review of each event included in the determination of the primary efficacy endpoint of the study (i.e., IF status, dates of response and relapse) in order to exclude the possibility of bias introduced into the investigator assessment of EFS. Both investigator assessments and independent review assessments are included in the application. The initial plan for retrospective data collection and for analyses of safety

and efficacy was submitted to the FDA prior to data transfer to the applicant and execution of any analyses.

2. IPD Meta-Analysis

The ALLTOX dataset provided for the IPD meta-analysis contains only prespecified composite Grade 3 and 4 broad adverse events. Therefore a more detailed safety analysis is not possible.

3. COG trial AAML0531

The primary data from AAML0531 were not submitted with this BLA. However, this trial currently represents the largest body of information on the use of GO in combination with chemotherapy in the pediatric AML population. COG's Fall 2013 Study Progress Report was submitted to the BLA at the request of the FDA, and efficacy and safety results from the Journal of Clinical Oncology publication Gamis, 2014 were included in the review of this application. However, independent confirmation of results by FDA was not possible.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Pivotal trial: ALFA-0701

Multicentre, randomized, phase 3 study of fractionated doses of the monoclonal antibody Gemtuzumab Ozogamicin (Mylotarg) in addition to Daunorubicin + Cytarabine for induction and consolidation therapy in patients with Acute Myeloid Leukemia (AML) aged 50-70 years

Sponsor: Centre Hospitalier de Versailles
Coordinating Investigator: Sylvie Castaigne

ALFA-0701 Design

ALFA-0701 was a multi-center (France only), open-label, randomized Phase 3 trial of GO plus DNR/AraC vs DNR/AraC alone for induction and consolidation therapy in patients 50-70 years old with untreated, de novo AML. There was no CD33 requirement for eligibility. Treatment consisted of GO 3 mg/m^2 days 1, 4, and 7 of induction and day 1 of consolidation 1 and 2 in combination with standard DA, and follow up extended through 2 years from date of last inclusion (randomization date of the last patient recruited in the study – November 9, 2010).

ALFA-0701 Objectives

The primary objective of the protocol was to evaluate the efficacy of adding GO to standard chemotherapy in patients 50-70 years old with AML. The primary endpoint for this objective was EFS, defined as the occurrence of an event, including induction failure, relapse, or death, starting from the date of randomization.

The secondary objectives included evaluation of overall survival, rate of CR and CRp (CR with incomplete platelet recovery). CR was defined as no circulating blasts, % of marrow blast cells <5%, Hgb >9g/dL, platelets >100,000/mm^3, neutrophils > 1000/mm^3, and transfusion independence. Cumulative response rate, length of remission, and safety profile were also examined along with correlation between MDR proteins, cytogenetic risk categories, FLT3, MLL, CEBPa, NPM gene mutation or overexpression and disease response, and correlation between level of residual disease measured by WT1 or NPM1 transcripts and the length of remission.

ALFA-0701 Key Eligibility

- Morphologically documented AML
- Age ≥50 and ≤70 years
- No prior therapies for AML
- ECOG performance status 0-3
- Cardiac function by scintigraphy or echocardiography within normal limits
- Able to sign informed consent

- No AML3, MPN, MDS, or secondary AML
- No CNS disease
- No uncontrolled infection
- No Creatinine ≥2.5x normal; ALT or AST ≥2.5x normal; total bilirubin ≥2x normal
- No pregnant women

ALFA-0701 Treatment Plan

Prior to administering gemtuzumab ozogamicin:

- Premedication with Polaramine (dexchlorpheniramine), ± solumedrol 1mg/kg 1 hour before infusion (repeat if needed)
- Mylotarg should not be given if leukocytes >30,000/mm^3 – leukoreduction should be performed with hydroxyurea, then begin cytarabine on day -2 (through day 5) before starting DNR and GO according to the usual regimen.

Gemtuzumab ozogamicin dose – 3 mg/m^2 GO was given IV over 2 hours on days 1, 4, and 7 of induction and day 1 of consolidation 1 and consolidation 2 (see Table 6 for DA doses).

Table 6. ALFA-0701 – Treatment Plan

Treatment Course	GO	Daunorubicin	Cytarabine
Induction	3 mg/m^2/dose (up to a maximum of 5 mg/dose) on Days 1,4, and 7	60 mg/m^2/day on Days 1-3	200 mg/m^2/day on Days 1-7

Second induction (if required)[a]	**No GO in second induction**	35 mg/m²/day IV (30 min), Days 1 and 2.	1 g/m²/12 hours by continuous infusion, from Days 1-3.
Salvage (if required)[b]	**No GO in salvage**	Idarubicin: 12 mg/m^2 Days 1 and 2	1g/m^2 twice daily Days 1-4
Consolidation Course 1[c]	3 mg/m^2/dose (up to a maximum of 5 mg/dose) on Day 1	60 mg/m^2/day on Day 1	1 g/m^2/12 hours on Days 1-4
Consolidation Course 2[c]	3 mg/m^2/dose (up to a maximum of 5 mg/dose) on Day 1	60 mg/m^2/day on Days 1-2	1 g/m^2/every 12 hours on Days 1-4

a. Second Induction: D15 after the start of induction (or D22) – only patients with >5% blast cells in a moderately rich or normal marrow (if in doubt, a second myelogram will be repeated in one week)
b. Salvage course after induction: patients who did not receive second induction and who did not achieve CR after induction (i.e. patients with ECOG < 3, CrClearance > 30 mL/min)
c. Consolidation: all patients who achieve CR or CRp at the end of induction or induction II who have adequate liver function may continue on to consolidation 2 weeks after hematologic recovery from the previous cycle

Protocol Guidelines for Allogeneic Transplantation

For patients enrolled in the trial who achieve remission, consider allogeneic transplantation according to performance status, age, molecular and cytogenetic risk category (Table 7) and the existence or not of a related donor.

- Favourable and Intermediate-1 risk categories: no transplant in first complete remission
- Intermediate-2 and Unfavourable risk categories: transplantation with related donor or 10/10 MUD (type of conditioning at the discretion of transplant center)
- Allow an interval of 2 months between the last dose of Mylotarg and transplantation

Table 7. CHV Risk Categories for Consideration of Transplantation

Risk	Criteria
Favourable	CBF
Intermediate-1	NPM1+ and FLT3wt* CEBPA + and FLT3wt*
Intermediate-2	Others
Unfavourable	• -5/5q-, -7/7q-, • complex karyotype (>3 abnormalities) • abnormalities 11q23 except t(9;11), • 3q26 • t(6;9) • FLT3-ITD+ and NPMwt* • MLL-PTD+ • EVI1+

*wt: wild type

Source: ALFA-0701 Protocol Version 5 (31/12/2009), Section 6.5, p18 – the Applicant refers to this as "CHV defined" risk

Additional non-standard SAE definition

In the specific context of this protocol, any thrombocytopenia meeting all of the following criteria will be deemed to be persistent thrombocytopenia and must be reported as a serious adverse event to the sponsor within the regulatory deadlines:

- Grade 3 or 4 thrombocytopenia (<50 000/mm3)
- Patients treated and in remission after induction (CR or CRp), including additional course or salvage course
- Not resolved at the planned start of the next treatment phase (or 45 days after D1 of consolidation 2 where applicable).

Interruptions for toxicity and permanent discontinuation of GO

- GO should be interrupted in patients experiencing dyspnea or clinically significant hypotension.
- In case of persistent thrombocytopenia < 100,000/mm3 on the scheduled date of the first or second consolidation (i.e., 2 weeks after haematological recovery from the previous cycle): repeat CBC at D7 and D14. As soon as the thrombocytopenia is corrected (7 or 14 days after scheduled date): administer consolidation as specified in protocol.
- *If thrombocytopenia is not corrected by the latest at D14 after the scheduled date of the cycle:
  - Moderate thrombocytopenia (platelets ≥50,000/mm^3 and <100,000/mm^3) - give consolidation with DNR and AraC but **without GO**.
  - Persistent thrombocytopenia (platelets <50,000/mm^3) – do not give consolidation specified in protocol (patients withdrawn from study)
- If liver function tests are abnormal, the consolidation cycle will not be postponed, but only DA will be given.

Reviewer comment: There are no instructions in the protocol for holding, stopping, or dose reducing chemotherapy for toxicity. Additionally, prior to Protocol Version 5 (12/31/09), there were no instructions for holding/stopping GO due to thrombocytopenia.

After the 4th amendment, GO was permanently discontinued for persistent moderate thrombocytopenia (platelets ≥50,000/mm^3 and <100,000/mm^3) lasting 14 or more days after the scheduled date of the next cycle. No specific guidelines were given regarding holding or stopping chemotherapy with the exception of the following: " if thrombocytopenia <50,000/mm^3 persists for more than 14 days, do not administer consolidation as specified in the protocol, check myelogram, and discuss continuation of therapy on an individual basis with study coordinator." See reviewer comment below under Key Revisions.

Schedule of Assessments

Clinical and hematologic response was assessed after 2 weeks of induction to determine need for second induction course, before each consolidation course, 1-2 months after hematologic recovery from second consolidation, and every 3 months afterwards for 2 years. Follow-up visits continued every 6 months thereafter. All laboratory evaluations were performed locally.

Table 8. ALFA-0701 – Schedule of Assessments

	Pretreatment evaluation	Induction + possible second induction course	Consolidation	Follow-up after end of treatment
History	X			
Clinical examination	X	X [2]	X [2]	X
Chest x-ray	X	X [3]	X [3]	X
ECG	X			
Cardiac function evaluation	X			X
Biological characteristics of blast cells 1	X			
Creatinine clearance	X			X
HIV, hepatitis A, B, C serologies	X			
Protein electrophoresis	X			
LDH	X			
CBC	X	X [4]	X [4]	X
Serum electrolytes	X	X [4]	X [4]	X
Serum creatinine	X	X [4]	X [4]	
Blood glucose	X	X [4]	X [4]	
CRP		X [5]	X [5]	
Phosphoremia	X	X [5]	X [5]	
Calcemia	X	X [5]	X [5]	
Liver function tests	X	X [5]	X [5]	X
PT, APTT	X	X [5]	X [5]	
Uricemia	X			
Cholesterol	X			
Triglycerides	X			
Fibrinogen	X			
Myelogram	X	X [6] (D15)	X [6] (M1, M3)	X (M6)
Residual disease	X		X (M1, M3)	X (M6)
Centralized sample	X [7] (M0)		X [7] (M1, M3)	X [7] (M6)
Sample for MDR status	X			

[1] : blood morphology and bone marrow aspiration, immunophenotype including CD33, cytogenetic study (bone marrow) +/- FISH, MDR status, molecular status of FLT3, NPM, MLL, CEBPa, WT1 genes
[2] : daily
[3] : once a week
[4] : three times a week
[5] : twice a week
[6] : D15 after start of treatment to determine need for second induction course; at haematological recovery or just before start of first consolidation to confirm remission, or at D40 in absence of haematological recovery.
[7] : Sample banks and study of residual disease: At diagnosis (M0), Before consolidation No. 1 (M1), Before consolidation No. 2 (M3), at first follow-up visit (M6), then every 3 months.

Source: ALFA-0701 Protocol Version 5 (31/12/2009), Section 5.3.4, p16

The immunophenotype of blast cells for the presence or absence of CD33 was assessed at baseline by local laboratories. Results were collected centrally and the percentage of CD33-positive blast cells was determined based on a threshold set for lymphocytes. In addition, mean fluorescence intensity (MFI) of blast cells and of lymphocytes (latter presumed to be CD33-negative) was determined and a CD33 MFI ratio calculated (MFI CD33 on blasts/MFI CD33 on lymphocytes).

ALFA-0701 Statistical Analysis Plan

All FDA analyses are based on Wyeth's statistical analysis plan which is described below. Version 1.1 (dated 3/22/13) was the approved version after FDA review. There were 2 subsequent minor amendments which did not affect analysis of the primary endpoint.

Endpoint:
The primary endpoint was event-free survival (EFS) and overall survival (OS) was a key secondary endpoint. The primary comparison between treatment arms for these endpoints was based on un-stratified log-rank test and Cox proportional hazards model. Two-sided confidence interval for median time to events was estimated using the Brookmeyer-Crowley method with log-log transformation. Neither EFS nor OS was censored at the time of HSCT in the primary analysis.

Analysis population:
The primary analysis population for evaluation of efficacy endpoints was the modified intent-to-treat (mITT) population of 271 patients (see reviewer comment), who signed consent and were randomized. They were analyzed according to the treatment arm assigned at randomization. Transplanted patients were not excluded from the analysis.

Sample size:
A sample size of 280 patients was planned based on EFS, to test a 3-year EFS rate of 40% in the experimental arm versus 25% in the control arm (corresponding hazard ratio = 0.66) with 184 events at 2-sided type I error rate of 0.05 and 80% power.

Time for primary analysis of primary endpoint/ method for primary and secondary sensitivity analyses
The date of 01 August 2011 was chosen by ALFA to be the analysis cut-off date for EFS when the study was close to reaching the number of targeted number of events. The applicant kept the same cut-off date for EFS analysis when they inherited data from ALFA and the last follow-up date for all patients was set to this reference date.

Four unplanned interim analyses were performed by CHV. 2 were requested by the Agence Francaise de la Sécurité Sanitaire des Produits de Santé (AFSSAPS), 1 for preparation for abstract submission to ASH 2011 and the final prior to the Lancet publication (Castaigne, 2012). To account for these IAs, the Lan-DeMets alpha spending approach with an O'Brien-Fleming efficacy boundary will be used to retrospectively control the overall Type I error rate.

Sensitivity analyses for timing of disease assessments were conducted to assess the imbalance in the disease assessment schedule between the 2 arms, using the following time to-event variables:

- Time from randomization to the first induction disease assessment
- Time from randomization to the last induction disease assessment
- Time from randomization to the first consolidation disease assessment
- Time from randomization to the last consolidation disease assessment
- Time from randomization to the first follow-up visit after the end of treatment

· Time from the last disease assessment prior to the disease assessment documenting relapse to relapse

For each analysis, patients who did not have such an event were excluded. Disease assessments were based on investigator assessments from the CHV CRF. Analyses used the Kaplan-Meier method and 2-sided log rank test.

Timing and method for secondary endpoints

The study was initially not powered for OS. The applicant, before acquiring data from ALFA, set 4/30/2013 as the cut-off date for OS analysis in order to have sufficient number of death events to test the null hypothesis of no treatment difference versus superiority of the experimental arm with the same hazard ratio of 0.66 as for the EFS.

Reviewer comment: ALFA-0701 originally enrolled 280 patients; 9 patients were excluded from the analyses due to lack of documentation of informed consent (5 in the GO arm and 4 in the control arm). The modified ITT analysis population therefore comprised 271 patients.

Key Revisions

The initial version of ALFA-0701 (Version 1) was never implemented or submitted. Protocol version 2 (finalized October 22, 2007) was the first version approved by regulatory authorities and the central ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Saint-Germain-en-Laye, France).

Table 9. ALFA-0701 – List of Protocol Amendments

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: WS936568 (ALFA-0701) Clinical Study Report, Section 9.8.1 Table 4, page 59

Reviewer Comment: The final protocol revision is dated Dec 31, 2009 (not Dec 21). 178 patients were treated prior to Amendment 4. 90 patients were treated after Amendment 4. See section 7.3.4.3 for an analysis of thrombocytopenia and hemorrhage in patients treated before and after Amendment 4.

5.3.2 Protocols Supporting Efficacy

5.3.2.1 Individual Patient Database (IPD) Meta-Analysis

The Applicant submitted an IPD Meta-Analysis to support the pivotal trial. All randomized trials of GO plus induction chemotherapy available as of 05/01/2013 were examined for the following criteria: 1. unconfounded comparison of GO in Course 1 of induction chemotherapy (i.e. GO plus chemotherapy vs chemotherapy alone), 2. patients with newly-diagnosed AML (de novo or secondary) or high-risk MDS (trials enrolling only patients with APL were excluded), 3. intensive induction chemotherapy, and 4. patients had to be over 15 years old. Five trials (including ALFA-0701) were selected. Individual investigators and institutional sponsors were contacted to request IPD for baseline characteristics, trial treatment, efficacy, and safety. Demographics data included baseline disease characteristics, FLT3,

NPM1 status, karyotype, cytogenetic group, CD33 status (determined according to each trial's approach), and CD33% positive, if collected. Efficacy variables included CR, best response, date of remission (CR/CRp/CRi), relapse, SCT, and survival status. Because each cooperative group collected safety data according to its own procedures, only high level common element Grade 3-4 data were collected. These included early mortality (30 and 60-day), composite nausea/vomiting/diarrhea, oral mucosal toxicity, hemorrhage, cardiac toxicity, neurologic toxicity, VOD, infection, hepatic laboratory elevations, persistent neutropenia and persistent thrombocytopenia (Grade 3-4 lasting 45 days after start of study treatment for period). The primary comparison was GO plus chemotherapy versus chemotherapy alone (No GO) in all patients. The primary endpoint was OS, defined as date of death minus date of randomization for patients who had died, and date last known alive minus date of randomization for all other patients. EFS was a key secondary endpoint, with induction failure defined as no CR1 within 60 days of randomization and event of day 0. Data were provided to Dr. Robert K. Hills (Cardiff University) to perform the meta-analysis. The individual trials are described below. Results are discussed in Sections 6 and 7.

5.3.2.1.1 MRC AML15 – An open-label, randomized trial to evaluate the addition of GO to induction and/or consolidation chemotherapy in untreated younger adult patients with AML.
AML15 was a multi-center, open-label, randomized trial evaluating the addition of GO to induction and/or consolidation chemotherapy in newly-diagnosed, untreated patients with AML. Eligible patients were <60 years old with untreated de novo or secondary AML as defined by WHO classification, or >60 years old if eligible for intensive therapy. Patients randomized to treatment with GO received a single dose of GO 3 mg/m^2 on day 1 of induction Course 1 in combination with one of the following three induction schedules: 1) daunorubicin and cytarabine; 2) cytarabine, daunorubicin, and etoposide; or 3) fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin. Induction course 2 consisted of only chemotherapy. Patients who achieved remission after induction (course 1 or course 2) underwent a second randomization to GO in consolidation course 3 in combination with amsacrine, cytarabine, and etoposide or high-dose cytarabine. Marrow examinations were performed at diagnosis and at 18-21 days after the end of Course 1 and Course 2 (if not in CR after Course 1). SUAEs are defined by NCI-CTC grade and dose modifications are provided, but the schedule of safety evaluations was not described in the protocol. The primary end points were overall survival and overall response rate. 1113 patients were enrolled.

5.3.2.1.2 NCRI AML16 – A programme of development for older patients with acute myeloid leukemia and high risk myelodysplastic syndrome.

AML16 was a multi-center, open-label, randomized trial evaluating the addition of GO to induction chemotherapy in newly-diagnosed, untreated patients with AML or high-risk MDS. Eligible patients were >60 years old (or those <60 not considered fit for AML15) with de novo or secondary AML as defined by WHO classification or high-risk MDS (defined as >10% marrow blasts). Patients with blast transformation of CML or APL were excluded. Patients randomized to treatment with GO received a single dose of GO 3 mg/m^2 on day 1 of induction in combination with either the standard DA regimen or daunorubicin/clofarabine (DClo). Patients achieving CR or PR after one course received a second course of chemotherapy alone; those achieving CR after the second course were subsequently randomized to additional 1-2 courses of chemotherapy. Marrow examination was performed at diagnosis, at the end of induction 1, and at the end of induction 2. The schedule of safety evaluations

was not described in the protocol. The primary endpoint was overall survival. 1115 patients were enrolled.

5.3.2.1.3 SWOG S0106 – A Phase III study of the addition of gemtuzumab ozogamicin induction therapy versus standard induction with daunomycin and cytosine arabinoside followed by consolidation and subsequent randomization to post-consolidation therapy with gemtuzumab ozogamicin or no additional therapy for patients under age 56 with previously untreated de novo acute myeloid leukemia (AML)

SWOG S0106 was a randomized trial evaluating the addition of GO to DA in induction, followed by HiDaC consolidation, and a second randomization to GO post-consolidation vs no therapy in patients with newly-diagnosed de novo AML. Eligible patients were between 18 and 56 years old with untreated de novo AML defined as ≥20% bone marrow blasts and clinical disease or translocations consistent with AML. Patients with blast percentages between 20-30% with features consistent with myelodysplasia required a follow-up marrow. Patients with M3 AML, blastic transformation of CML, or preexisting myelodysplasia or secondary leukemia were excluded. Patients randomized to treatment with GO received a single dose of GO 6 mg/m^2 on day 4 of induction in combination with daunomycin 45 mg/m^2 and cytarabine 100 mg/m^2/day, Chemotherapy was given on the standard 7+3 schedule; however, the daunomycin dose is lower than the standard 7+3 dose (60 mg/m^2). For all patients, induction was followed by standard HiDaC consolidation. Patients in CR after consolidation were eligible for re-randomization to post-consolidation treatment with GO 5 mg/m^2 x 3 doses at least 28 days apart vs no treatment. Marrow examination was performed at diagnosis, day 14 of induction (and day 19 if ≥5% blasts on day 14), and before and after consolidation. For patients randomized to GO post-consolidation, an additional marrow was performed in week 9. Safety evaluations were conducted daily days 1-10, days 14, 17, 21, and 24 of induction, and weekly during consolidation. 595 patients were enrolled.

5.3.2.1.4 GOELAMS AML2006IR – Randomised open-label mutlicentre phase III study testing the efficacy of gemtuzumab ozogamicin in combination with intensive chemotherapy in 18 to 60-year-old patients suffering from acute myeloblastic leukaemia (AML) wither intermediary cytogenetics

AML2006IR was a randomized, open-label, Phase 3 trial assessing the addition of GO to the standard 7+3 DA induction regimen in patients with previously untreated AML. Eligible patients were between 18 and 60 years old with untreated de novo AML (≥20% blasts in bone marrow) and "intermediary cytogenetics" defined as normal karyotype or karyotypes with other abnormalities excluding the favorable and adverse groups, and "whose expression of CD33 antigen on the blast has been defined according to the method described in Annex 11." Patients with secondary AML, unclassifiable or M3 AML, or blast transformation of MPN or MDS were excluded. Patients randomized to treatment with GO received a single dose of GO 6 mg/m^2 on day 4 of induction in combination with standard DA followed by DA mini-consolidation. Marrow examination was performed at diagnosis and routinely on day 15 of induction, on leaving the aplastic phase (neutrophils ≥1 G/L, platelets ≥100 G/L) to assess response to treatment, or a routine bone marrow between D45 and D62 in the event of persistent aplasia, and after induction 2 if not in CR after induction 1. Safety evaluations were conducted daily during

treatment, 3 times a week until leaving the aplastic phase, then twice weekly until full hematologic recovery. The primary end point was event-free survival (EFS) at 3 years estimated using the Kaplan Meier method in patients who are ineligible for standard allotransplantation. 254 patients were enrolled.

5.3.2.2 COG AAML0531

The applicant did not request inclusion of the pediatric population in the newly-diagnosed indication, and the primary data from AAML0531 were not submitted with this BLA. However, this trial currently represents the largest body of information on the use of GO in combination with chemotherapy in the pediatric AML population. COG's Fall 2013 Study Progress Report was submitted to the BLA at the request of the FDA, and efficacy and safety results from the publication (Gamis, 2014) were also evaluated for this application. AAML0531 was an adequate and well-controlled, IRB-approved clinical trial meeting the requirements of 21 CFR 314.126 and Good Clinical Practice.

AAML0531 was a prospective phase III randomized trial of gemtuzumab ozogamicin combined with conventional chemotherapy for de novo AML in children, adolescents, and young adults. Eligible patients were ≥1 month up to <30 years old with previously untreated primary AML (≥20% blasts in bone marrow or <20% blasts with karyotypic abnormality characteristic of de novo AML *(t(8;21)(q22;q22), inv(16)(p13q22)* or *t(16;16)(p13;q22*) or *11q23* abnormalities) or unequivocal presence of megakaryoblasts). Patients with M3 AML, JMML, secondary/treatment related AML, or known bone marrow failure syndromes were excluded. Patients randomized to treatment with GO received a single dose of GO 3 mg/m^2 on day 6 of induction 1 in combination with ADE. All patients received induction 2 (ADE only). After induction 2, patients with <5% bone marrow blasts proceeded to Intensification 1. High and intermediate risk patients without an appropriate SCT donor and all low risk patients received additional Intensification 2 therapy with MA ± one dose GO 3 mg/m^2 on day 7 (according to initial randomization), followed by Intensification 3. Marrow examination was performed at diagnosis, 18-25 days after the last day of therapy on Induction 1, Induction 2, and Intensification 1, or later if adequate hematologic recovery had not yet occurred. Safety evaluations were conducted daily during treatment and prior to each course of therapy. The primary endpoint was EFS. 1022 patients were randomized. Results are discussed in Sections 6 and 7. See Table 32 for the full treatment regimen.

5.3.3 Protocols Supporting Safety

See description of the IPD meta-analysis and AAML0531 above.

6 Review of Efficacy

Efficacy Summary

ALFA-0701

The pivotal trial ALFA-0701 enrolled 271 adults between the ages of 50-70 years old with newly-diagnosed AML. 135 were randomized to treatment with GO 3 mg/m^2 days 1, 4, and 7 of induction and day 1 of consolidation 1 and 2 in combination with DA. 136 patients were randomized to treatment with DA alone. The primary endpoint was EFS with induction failure defined as not achieving CR or CRp and the date of IF being the date of bone marrow assessment after last cycle of induction.

The appropriate endpoint for patients with newly-diagnosed AML treated with curative intent is CR. Therefore, FDA's definition of EFS specified induction failure as failure to achieve CR (i.e. CRp was considered IF) and defined the date of IF as the date of randomization. The results of the per protocol primary analysis are described in Section 6.1.5, but the EFS result in the benefit:risk analysis in section 1, in this summary, and in the label will use FDA defined EFS.

The key results from the review of efficacy showed:

- In ALFA-0701, fractionated GO in combination with DA showed a clinically meaningful EFS benefit. Median EFS was 17.3 months for GO+DA and 9.5 months for DA with a HR 0.68 (95% CI 0.51, 0.91).

- OS benefit was not statistically significant in ALFA-0701 (HR 0.81 (0.60, 1.09)), and GO had only a marginal effect on OS in the exploratory IPD Meta-Analysis (HR of 0.91 (95% CI 0.84, 0.99)).

- There was no difference in CR with a rate of 70% in both arms.

- A higher proportion of patients in the GO arm had unplanned hospitalizations (including re-admission or prolongation of planned hospitalizations due to adverse events) compared with patients in the control arm.

- Although the median PRBC transfusions required was the same in both arms (14), patients in the GO arm required more than twice as many platelet transfusions as patients in the control arm, both overall (23 transfusions vs 11), and in each treatment phase.

- Data from ALFA-0701, the IPD Meta-Analysis, and literature clearly showed that only patients who were CD33-positive derived benefit from GO. However, there are no data to support a specific cut-off value. Therefore, for the purposes of this application, FDA defined CD33-positivity as any level >0.

- There is a lack of data in ALFA-0701, the IPD Meta-Analysis, and any other randomized trial of GO in the literature to support benefit with the addition of GO in patients with adverse risk cytogenetics.

However, cytogenetics data may not be available at the time of treatment initiation, and safety data for GO combinations with chemotherapy do not indicate that these patients are at significantly higher risk for toxicity. Restricting the indication by cytogenetic risk category would require that all patients delay treatment until that information is obtainable. This may be an unacceptable risk for most patients. Therefore, the label should be clear with regards to the lack of evidence in this subset; however, the decision regarding the use of GO in these patients should be left to the discretion of the treating physician to be assessed on an individual patient basis.

- EFS did not have a strong correlation with OS. However, the analysis may have been confounded by the treatment failure component of EFS, since salvage options for such patients, including HSCT, may confer longer than expected survival.

- More patients in the control arm of ALFA-0701 received HSCT both in CR1 and as salvage after relapse.

AAML0531

AAML0531 randomized 1022 pediatric patients to GO + best standard chemotherapy vs chemotherapy alone. The primary endpoints were EFS and OS, with induction failure defined as failure to achieve CR and IF date being the date of study entry. Efficacy data were examined from the AAML0531 publication, Gamis, 2014.

- EFS benefit was seen 53.1% of patients treated with GO compared with 46.9% without GO at 3 years (HR 0.83, 95% CI, 0.70-0.99, p=0.04).

- Similarly to the adult trials, there was no corresponding OS benefit. The EFS benefit is thought to be largely due to a significant reduction in relapse risk (3 years: 32.8% vs 41.3%; HR 0.73; 95% CI 0.58-0.91, p=0 .006).

- Subset analyses in this pediatric trial also failed to show benefit for patients with adverse cytogenetic risk or low CD33 expression (bottom quartile by MFI).

- These data support a finding of efficacy with GO in children with newly-diagnosed CD33-positive AML.

6.1 GO combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients with newly-diagnosed, de novo CD33-positive acute myeloid leukemia

6.1.1 Methods

Newly-diagnosed adults with AML

The efficacy of GO + DA for this indication was based on the primary analysis of ALFA-0701 supported by data from the IPD Meta-Analysis. The details of the protocol design for ALFA-0701 were

described in Section 5.3.1, and the meta-analysis was described in Section 5.3.2. FDA adjudicated all major efficacy findings.

For pivotal trial ALFA-0701, eligible patients had ≥20% blasts in the marrow or had AML diagnosis supported by FAB classification, other cell lineages in the bone marrow aspirate, and/or cytogenetic molecular results consistent with AML. The GO dose and schedule studied was 3 mg/m^2 days 1, 4, and 7 of induction and day 1 of consolidation 1 and 2. The primary efficacy endpoint was EFS with induction failure defined as failure to achieve CR or CRp and the date of IF being the date of bone marrow assessment after last cycle of induction.

Reviewer Comment:

The per protocol analysis of EFS in ALFA-0701 included No CR/CRp in the definition of induction failure and set the event time as day of bone marrow assessment after the last cycle of induction. CRp is not a valid endpoint for patients with newly-diagnosed AML treated with curative intent. The primary analysis is presented per protocol in Section 6.1.5. However, FDA conducted a separate analysis defining IF as No CR and the date of event as the date of randomization. This analysis is presented after the primary analysis in 6.1.5 and is the analysis that will be used for benefit:risk determination.

Review Issue:

The applicant is seeking approval based on EFS advantage alone.

1. Endpoints for Assessment of Clinical Benefit in AML

In 2007, FDA held a joint workshop with the American Society of Hematology (ASH) and concluded that other possible surrogate endpoints including CRp and other variants of CR, minimal residual disease, and quality of life measures all require further validation (Appelbaum, 2007). The FDA May 2007 Guidance for Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics states that the established endpoint of clinical benefit in leukemia is durable complete response, where CR is associated with increased survival and decreased infection, bleeding, blood product support.

Idarubicin was granted regular approval in 1999 for the treatment of AML in adults based on durable complete response (CR). The submission included data from four prospective randomized studies, and in addition to significant improvement in CR rate, the results also showed improvement in overall survival (OS).

Recently, regular approval of midostaurin in combination with chemotherapy for the treatment of newly-diagnosed FLT3 mutation-positive AML was based on the results of a single randomized, double-blind, placebo-controlled study that demonstrated an overall survival advantage in patients who received midostaurin in addition to standard chemotherapy compared with those who did not (HR 0.77, p = 0.016).

2. EFS/OS Correlation in AML

Because FDA usually uses OS as the endpoint to confirm clinical benefit for treatment of AML, Wyeth performed analyses to determine if EFS was a surrogate of OS. The results of these analyses are discussed in Section 6.1.11 and in the statistical review of the application, but briefly, EFS was not found to have strong correlation with OS. The surrogacy analysis, however, may have been confounded by the treatment failure component of EFS, since salvage options for such patients, including HSCT, may confer longer than expected survival. Therefore, the lack of correlation between EFS and OS is not unexpected.

3. EFS as an endpoint for newly-diagnosed AML

From a clinical standpoint, overall survival clearly represents a benefit. Durable complete response is also beneficial for the patient, and event-free survival reflects durable CR and survival. For patients in remission, benefits to prolonging EFS include delaying the toxicities related with further therapies and possibly reduced time in the hospital for transfusions or treatment of adverse events. In addition, FDA has accepted progression-free survival for drug approvals in other diseases with similar circumstances.

Newly-diagnosed children with AML

The efficacy of GO + chemotherapy for the treatment of pediatric patients with newly-diagnosed AML was evaluated based on the results of pediatric COG trial AAML0531. The primary data from AAML0531 were not submitted by the applicant; therefore, the analysis is based on the AAML0531 Fall 2013 Study Progress Report and the literature report (Gamis, 2014). The efficacy results are discussed in Section 6.1.11.3.

6.1.2 Demographics

ALFA-0701 Demographics

ALFA-0701 was conducted exclusively in France. The applicant provided a statement which describes the consistency of the treatment plan and supportive care with US medical practices, as well as the results of population modeling analysis reports (PMARs) examining the impact of race on the pharmacokinetics of GO including data from 8 Wyeth sponsored studies. Of note, race data were not collected in ALFA-0701. The applicant's exposure-response analysis found that race was not a covariate that significantly impacted the safety or efficacy of GO.

The demographic characteristics in the two treatment arms were well-balanced with respect to age, performance status and baseline disease characteristics. Slightly more males were randomized to the GO arm than to the control arm (55% vs 44%).

Table 10. ALFA-0701 – Patient Demographics and Disease Characteristics – mITT population

	GO + DA N = 135 n (%)	DA N = 136 n (%)
Sex		
Female	61 (45)	76 (56)
Male	74 (55)	60 (44)
Age (Years)		
Median	62	60
Range	50-70	50-70
ECOG status		
0	48 (35)	52 (38)
1	73 (54)	65 (48)
2	13 (10)	17 (13)
3	1 (<1)	1 (<1)
Unknown	0	1 (<1)
Cytogenetics		
Favorable	3 (2)	6 (4)
Intermediate	91 (67)	89 (65)
Poor	27 (20)	30 (22)
Unknown	14 (10)	11 (8)
ELN 2010		
Favorable	27 (20)	26 (19)
Intermediate I	40 (30)	48 (35)
Intermediate II	19 (14)	17 (13)
Adverse	37 (27)	36 (26)
Unknown	12 (9)	9 (7)
NCCN		
Favorable	27 (20)	24 (18)
Intermediate	53 (39)	56 (41)
Poor	43 (32)	46 (34)
Unknown	12 (9)	10 (7)
CD33+ (%)		
<30	17 (13)	20 (15)
30-70	20 (15)	11 (8)
>70	63 (47)	63 (46)
Unknown	35 (26)	42 (31)
Median baseline WBC $10^3/mm^3$ (range)	5.8 (0.5-151)	4.1 (0.4-180.5)

Source: FDA Analysis

IPD Meta-Analysis Demographics

The demographics and disease-characteristics of patients in the IPD Meta-Analysis are presented below. Due to the nature of the meta-analysis data and differences in timing of GO treatment, the ITT

population and the as-treated population were not able to be straightforwardly differentiated. Therefore, efficacy and safety analyses were performed on the same population.

Table 11. IPD Meta-Analysis – Patient Demographics

	MRC AML15 n (%)	NCRI AML16 n (%)	ALFA-0701 n (%)	GOELAMS AML2006IR n (%)	SWOG S0106 n (%)	All Trials n (%)
Number of patients	1099	1115	271	251	595	3331
Treatment arm						
• GO	548 (50)	559 (50)	135 (50)	126 (50)	295 (50)	1663 (50)
• No GO	551 (50)	556 (50)	136 (50)	125 (50)	300 (50)	1668 (50)
Median age (range)	49 (15-71)	67 (51-84)	62 (50-70)	50 (18-60)	47 (18-60)	58 (15-84)
Sex						
• Male	514 (47)	444 (40)	137 (51)	108 (43)	282 (47)	1485 (45)
• Female	585 (53)	671 (60)	134 (49)	143 (57)	313 (53)	1846 (55)
Performance status						
• 0	790 (72)	679 (61)	100 (37)	118 (47)	235 (40)	1922 (58)
• 1	262 (24)	375 (34)	138 (51)	119 (47)	283 (48)	1177 (35)
• 2	29 (3)	36 (3)	30 (11)	8 (3)	53 (9)	156 (5)
• ≥3	18 (1)	25 (2)	2 (1)	2 (1)	21 (3)	68 (2)
• Unknown	0	0	1 (<1)	4 (2)	3 (<1)	8 (<1)

Source: FDA Analysis

Table 12. IPD Meta-Analysis – Patient Disease Characteristics

	MRC AML15 n (%)	NCRI AML16 n (%)	ALFA-0701 n (%)	GOELAMS AML2006IR n (%)	SWOG S0106 n (%)	All Trials n (%)
Number of patients	1099	1115	271	251	595	3331
Type of AML						
• de novo	1011 (92)	805 (72)	271 (100)	251 (100)	595 (100)	2933 (88)
• Secondary	88 (8)	197 (18)	0	0	0	285 (9)
• HR-MDS	0	113 (10)	0	0	0	113 (3)
Cytogenetic risk group						
• Favorable	133 (12)	33 (3)	9 (3)	1 (<1)	72 (12)	248 (7)
• Intermediate	565 (51)	580 (52)	176 (65)	223 (89)	283 (48)	1827 (55)
• Adverse	196 (18)	264 (24)	53 (20)	0	67 (11)	580 (17)
• Unknown	205 (19)	238 (21)	33 (12)	27 (11)	173 (29)	676 (20)

ELN Risk Group						
• Favorable	183 (17)	59 (5)	58 (21)	59 (24)	112 (19)	471 (14)
• Intermediate I	138 (12)	93 (8)	85 (31)	106 (42)	95 (16)	517 (16)
• Intermediate II	170 (15)	164 (15)	36 (13)	55 (22)	84 (14)	509 (15)
• Adverse	193 (18)	261 (23)	54 (20)	0	73 (12)	581 (17)
• Unknown	415 (38)	538 (48)	38 (14)	31 (12)	231 (39)	1253 (38)
CD33 expression						
• <30%	127 (12)	239 (21)	37 (14)	28 (11)	0	431 (13)
• ≥30%	423 (39)	517 (46)	157 (58)	220 (88)	0	1317 (40)
• <70%	243 (22)	442 (40)	68 (25)	71 (28)	0	824 (25)
• ≥70%	307 (28)	314 (28)	126 (47)	177 (71)	0	924 (28)
• Unknown	549 (50)	359 (32)	77 (28)	3 (1)	595 (100)	1583 (48)

Source: FDA Analysis

6.1.3 ALFA-0701 Subject Disposition

The first patient was enrolled on 1/10/2008. The last patient was enrolled 11/9/2010. The cut-off date for EFS analysis was 8/1/2011. The study was not initially powered for OS, but the decision was made to use a cut-off date of 4/30/2013 for OS analysis. The cut-off for all retrospective data collection was 11/1/2013.

ALFA-0701 originally enrolled 280 patients; 9 patients were excluded from the analyses due to lack of documentation of informed consent (5 in the GO arm and 4 in the control arm). The modified ITT analysis population therefore comprised 271 patients.

A total of 64 patients (46%) completed GO treatment in the GO arm. Completion of chemotherapy was similar between arms with 82 (59%) of patients in the GO arm and 89 (64%) patients in the control arm completing treatment. The most common reasons for permanent discontinuation of GO were adverse events (30%) and resistant disease (12%). The most common reason for treatment discontinuation in the control arm was resistant disease (21%).

Table 13. ALFA-0701 – Patient Disposition – ITT Population

	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

Drug Exposure

There were no GO or chemotherapy dose reductions defined in ALFA-0701.

Of patients randomized to the GO arm, 3 (2%) patients in induction, 6 (4%) patients in consolidation 1, and 18 (13%) patients in consolidation 2 did not receive GO but continued treatment with DA.

"The percentage of patients in the GO arm who received DNR and AraC were 100% each during induction, 73.3% and 74.0% during consolidation 1, and 62.6% each during consolidation 2, respectively. Of these patients in the GO arm, the expected prescribed dose of DNR as described in the protocol were delivered during induction, consolidation 1, and consolidation 2 to 95.4%, 95.8%, and 96.3% patients, respectively, with the expected prescribed dose of AraC delivered to 96.2%, 86.6%, and 87.8% patients, respectively." *Source: Applicant's response to IR, SDN 48 Received 7/27/17.*

"The percentage of patients in the control arm who received DNR and AraC were 98.5% and 100% during induction 70.8% each during consolidation 1, and 65.0% each during consolidation 2, respectively. Of these patients in the control arm, targeted doses of DNR were delivered during induction, consolidation 1, and consolidation 2 to 92.6%, 97.9%, and 95.5% patients, respectively, with targeted doses of AraC delivered to 92.0%, 90.7%, and 86.5% patients, respectively. Thus, the majority of patients received the expected prescribed doses of chemotherapy." *Source: Applicant's response to IR, SDN 48 Received 7/27/17.*

Reviewer comment: These proportions provided by the applicant appear to have been calculated using the as-treated population as the denominator. However, all patients who received chemotherapy in either arm in each phase received >80% of the planned doses.

6.1.4 ALFA-0701 Protocol Deviations

Only data on major protocol deviations pertaining to eligibility criteria and dosing or randomization errors were collected. 9 patients (5 in the GO arm and 4 in the control arm) did not have a copy of the ICF available and were excluded from the data transfer to Wyeth and are not included in any analyses. The remaining 271 patients were used by FDA for analysis of the primary endpoint.

Other eligibility criteria deviations included 13 patients with abnormal cardiac or hepatic function at the time of study entry, and 5 patients with positive HIV/HBV/HCV serology at the time of study entry. These patients were included in both efficacy and safety analyses.

3 patients randomized were not treated (2 control and 1 GO; Patient 333 – Eligibility protocol violation: esophageal cancer, Patient (b) (6) – death, and Patient (b) (6) – Eligibility protocol violation: hepatitis B). These patients were included in the efficacy analyses but not the safety analyses.

In order to confirm eligibility, FDA reviewed all patients for baseline bone marrow blast levels ≥20%, and requested further justification for the inclusion of 6 patients who did not meet this criteria. Those patients had AML diagnosis supported by FAB classification, other cell lineages in BMA, and/or cytogenetic molecular results consistent with AML.

The most common GO dosing errors included 19 patients receiving GO on an incorrect schedule (most commonly days 1, 3, and 7) and 6 patients who received a GO dose above the maximum 5mg dose. The most common chemotherapy dosing errors were under or overdosing and temporarily discontinuing DA.

Table 14. ALFA-0701 – Protocol Deviations – ITT population

	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

6.1.5 Analysis of Primary Endpoint(s)

ALFA-0701 Primary Analysis

The primary endpoint for ALFA-0701 was event-free survival, defined as the occurrence of an event including induction failure, relapse, or death, starting from the date of randomization. For the per protocol primary analysis, the date of IF was defined to be the date of evaluation of bone marrow response after the last induction cycle if a response (CR or CRp) by investigator assessment had not been achieved. EFS was censored at the date of the last disease assessment prior to data cut-off for patients who were event-free.

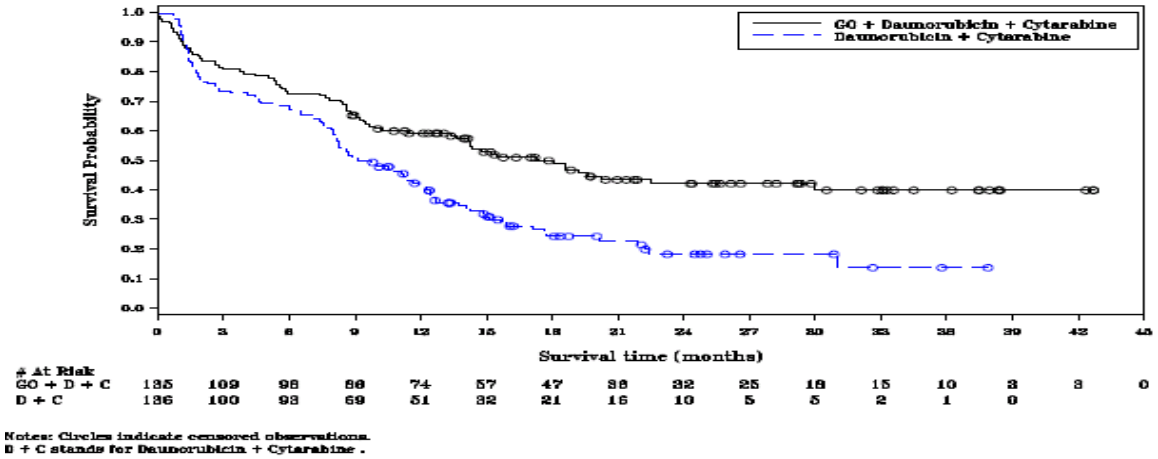
The primary analysis results, based on data at the cut-off date of 8/1/ 2011, are shown in Table 15 and Figure 2. The difference in 3-year EFS rate was 26.2%, and the difference in median EFS was 7.8 months favoring the GO arm. Twenty-one percent more censoring occurred in the GO arm, all because of event-free at data cut-off. EFS was not censored for occurrence of transplantation in the primary analysis.

Table 15. ALFA-0701 – Event-free Survival by Investigator Assessment

	GO + DA N = 135	DA N = 136
EFS events, n (%)	73 (54.1)	102 (75.0)
Induction failure	17 (12.6)	29 (21.3)
Relapse	44 (32.6)	58 (42.6)
Death	12 (8.9)	15 (11.0)
EFS censored, n (%)	62 (45.9)	34 (25.0)
3-year event-free probability, % [95% CI]	39.8 [30.2, 49.3]	13.6 [5.8, 24.8]
Median time to event, months[1] [95% CI]	17.3 [13.4, 30.0]	9.5 [8.1, 12.0]
Hazard ratio[2] [95% CI]	0.56 [0.42, 0.76]	
p-value[3]	< 0.001	

EFS=event-free survival; GO=gemtuzumab ozogamicin; DA = daunorubicin plus cytarabine; CI = confidence interval. [1] Kaplan-Meier estimates. [2] Hazard ratio for GO+DA vs. DA from Cox proportional hazards model. [3] 2-sided p-value from log-rank test.
Source: FDA Statistical Review

Figure 2. ALFA-0701 – Kaplan-Meier Plot of Event-free Survival by Investigator Assessment



Source: FDA Statistical Review

FDA Defined EFS Analysis

CR and CRp (or CRi) are not equivalent clinical endpoints. Patients who achieve only CRp/CRi have poorer prognoses compared with those who achieve CR. The appropriate endpoint for patients with newly-diagnosed AML treated with curative intent is CR. Therefore, FDA's definition of EFS specified induction failure as failure to achieve CR (i.e. CRp was considered IF) and defined the date of IF as the date of randomization. The ALFA-0701 EFS result according to the FDA definition resulted in the same median EFS of 17.3 months for GO+DA and 9.5 months for DA with a higher HR 0.68 (95% CI 0.51, 0.91).

ALFA-0701 Sensitivity Analyses

Table 16 summarizes results of applicant's sensitivity analyses by alternative EFS definitions (all exclude CRp in the definition of IF). These alternative definitions were revised from the primary definition using alternative induction failure date, alternative censoring status for occurrence of transplants, and alternative events. In addition, some analyses were repeated using the assessments from retrospective reviews by an independent review committee. Although the results from independent review analyses were not as significant as the ones from investigator assessments, none of the sensitivity analyses contradicted to the primary analysis.

Table 16. ALFA-0701 – Event-free Survival Sensitivity Analyses by Alternative Definitions

	GO+DA versus DA		
	Hazard ratio[a]	95% CI of hazard ratio	p-value[b]
Primary: investigator, IF date=date of post-induction assessment	0.56	[0.42, 0.76]	<0.001
Alt 1: investigator, IF date=date of randomization	0.56	[0.41, 0.75]	<0.001
Alt 2: investigator, HSCT censored	0.59	[0.43, 0.81]	0.001
Alt 3: investigator, IF date=randomization, HSCT censored	0.58	[0.43, 0.80]	0.001

	GO+DA versus DA		
	Hazard ratio[a]	95% CI of hazard ratio	p-value[b]
Alt 4: investigator, salvage therapy classified as an IF event	0.60	[0.45, 0.81]	0.001
Alt 5: investigator, events of relapse and death only	0.60	[0.44, 0.81]	0.001
Alt 6: IRC, IF date=date of post-induction assessment	0.66	[0.49, 0.89]	0.006
Alt 7: IRC, HSCT censored	0.71	[0.52, 0.96]	0.026

IF=induction failure, defined as not achieving CR/CRp during the induction period; IRC=independent review committee; HSCT=hematopoietic stem cell transplantation; CI=confidence interval; GO=gemtuzumab ozogamicin; DA=daunorubicin+cytarabine
[a] Estimated using Cox proportional hazards model. [b] 2-sided nominal p-value from the log-rank test.
Source: FDA Statistical Review

Supportive data from IPD Meta-Analysis

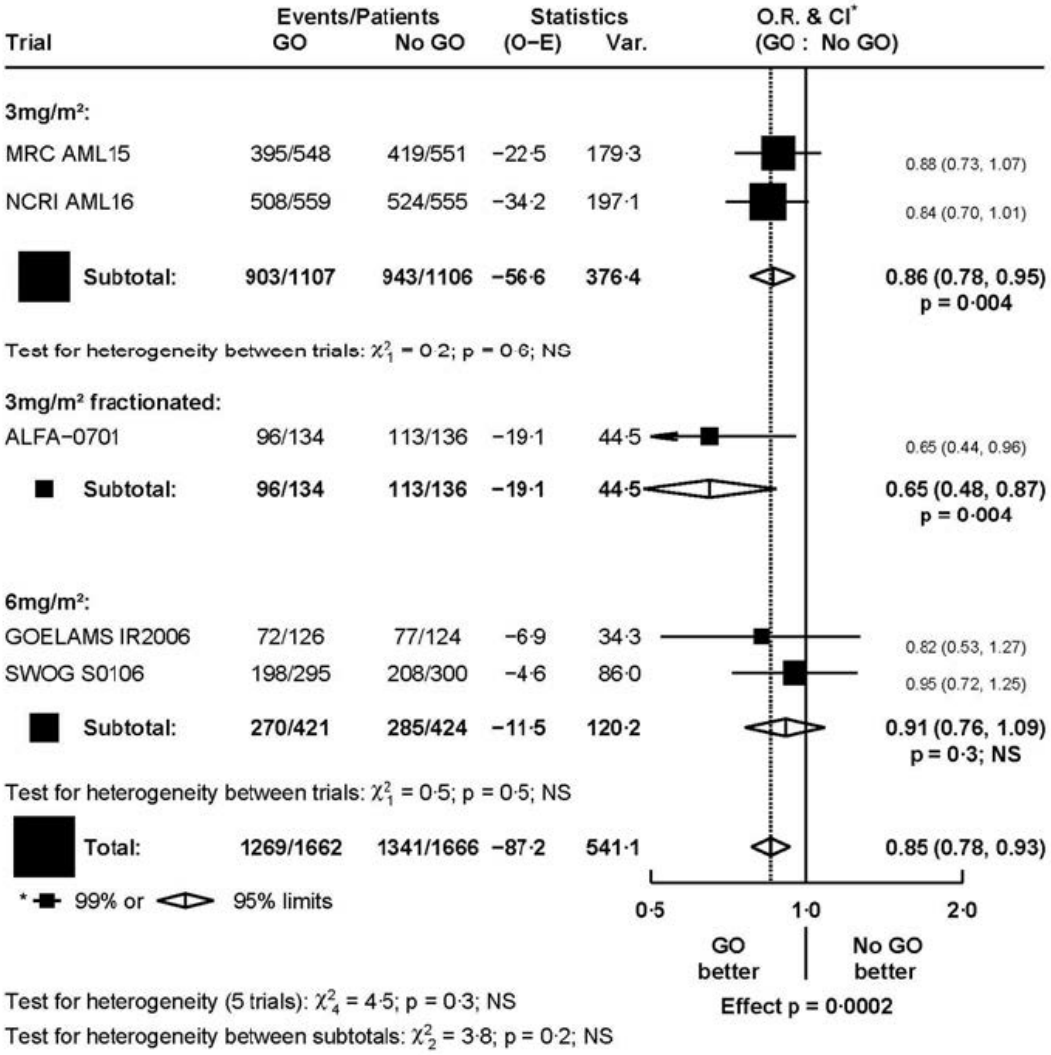
EFS in the IPD Meta-Analysis used failure to achieve a first Overall Response (CR/CRi or CR/CRp) in the first 60 days after randomization as the definition of induction failure, with the date of IF being the date of randomization. Table 17 shows the individual trial EFS hazard ratios. FDA did not pool the data due to heterogeneity between trials. Although the GO dose varied among the trials and CRi/CRp was included in the EFS definition, overall, the data support an EFS benefit in patients who received GO compared with those treated with chemotherapy only. The applicant's evaluation of EFS odds ratio by trial and dose is shown in Figure 3.

Table 17. IPD Meta-Analysis – Individual Trial Summary of Event-Free Survival

Trial	ALFA-0701	S0106	AML15	AML16	AML2006IR
Number of patients	271	595	1099	1115	251
EFS events, n (%)	210 77.5%	406 68.2%	814 74.1%	1032 92.6%	149 59.4%
Hazard ratio[1]	0.67	0.95	0.89	0.86	0.82

Source: FDA Statistical Review
[1] Hazard ratio for GO over No GO from Cox proportional hazards model

Figure 3. IPD Meta-Analysis – Event-free survival



Source: Applicant submitted IPD-Meta Analysis CSR Figure 17.

6.1.6 Analysis of Key Secondary Endpoints(s)

ALFA-0701 – Overall Survival

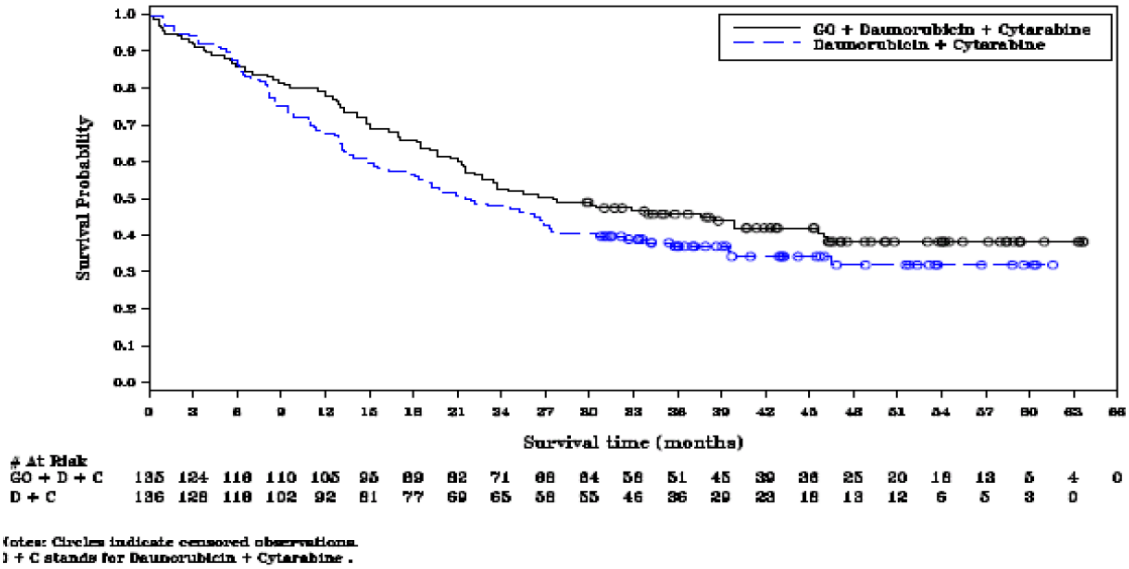
OS was defined as time from the date of randomization to the date of death due to any cause. The primary analysis of OS was based on 168 deaths occurred prior to the survival final analysis data cut-off date of 30 April 2013. The result did not reach statistical significance at a level of 2-sided p-value of 0.05. There were 5 percent fewer deaths reported in the GO arm compared to the control arm. The estimated median survival was 21.8 months in the control arm and was 27.5 months in the GO arm.

Table 18. ALFA-0701 – Overall Survival

	GO + DA N = 135	DA N = 136
OS events, n (%)	80 (59.3)	88 (64.7)
Censored, n (%)	55 (40.7)	48 (35.3)
3-year survival probability, % [95% CI]	45.7 [37.2, 53.9]	37.0 [28.8, 45.1]
Median time to event, months[1][95% CI]	27.5 [21.4, 45.6]	21.8 [15.5, 27.4]
Hazard ratio [95% CI]	0.81 [0.60, 1.09]	
p-value	0.165	

OS=overall survival; GO=gemtuzumab ozogamicin; DA=daunorubicin plus cytarabine; CI=confidence interval. [1] Kaplan-Meier estimates. [2] Hazard ratio for GO+DA vs. DA from Cox proportional hazards model. [3] 2-sided p-value from log-rank test.
Source: FDA Statistical Review

Figure 4. ALFA-0701 – Kaplan-Meier Plot of Overall Survival



Source: FDA Statistical Review

Supportive data from IPD Meta-Analysis:

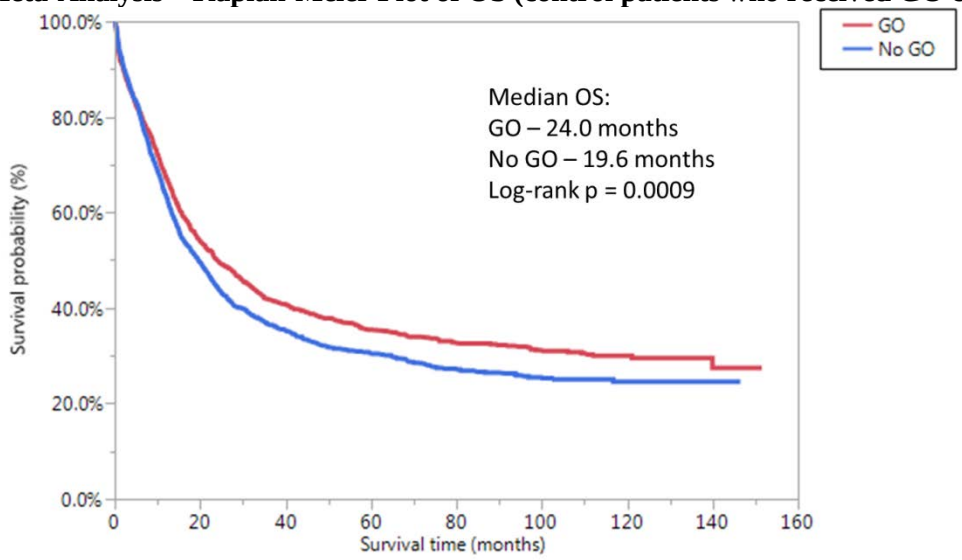
Wyeth provided a meta-analysis for OS in 5 randomized GO studies with patient-level data (including ALFA-0701). FDA does not generally accept retrospective meta-analysis of OS as the primary evidence to establish clinical benefit. Therefore, the applicant's IPD meta-analysis is considered exploratory.

In this meta-analysis, there was a marginal effect with an estimated OS HR of 0.91 (95% CI 0.84, 0.99) and an estimated 2.1 months increase in OS. However, there were important differences between the 5 trials in age (a known prognostic factor for survival) and GO dosing.

Possible Confounding in IPD Meta-Analysis:

Patients in AML15 were re-randomized to GO vs No GO in consolidation. 20% of patients enrolled in the control arm received GO in consolidation. Patients in SWOG S0106 were re-randomized to GO vs no treatment in maintenance. 14% of patients enrolled in the control arm received GO in maintenance. FDA analysis censoring these patients resulted in a slightly larger effect on median OS.

Figure 5. IPD Meta-Analysis – Kaplan-Meier Plot of OS (control patients who received GO censored)



Source: FDA Analysis

6.1.7 Other Endpoints in ALFA-0701

6.1.7.1 Complete Response and Relapse-free survival

Multiplicity was not adjusted for the secondary endpoints discussed below.

By investigator assessment, the CR rate was very similar in the treatment arms (70.4% versus 69.9% for GO+DA versus DA, p=1.00). Independent reviewers assessed only composite CR/CRp. RFS derived from investigator assessment was longer for patients in the GO arm, with a median RFS estimated at 28.0 months for the GO arm versus 11.4 months for the control arm (HR 0.53, p=0.001).

Efficacy results from randomized trials of GO plus chemotherapy in the literature review can be found in Appendix 1, Table 56.

6.1.7.2 Unplanned hospitalizations

A higher proportion of patients in the GO arm had unplanned hospitalizations (including re-admission or prolongation of planned hospitalizations due to adverse events) compared with patients in the control

arm. This difference was observed overall and in both induction and consolidation 1 (Table 19). The length of hospital stay was similar between arms. There was no difference in the proportion of patients with unplanned ICU admissions or in their median length of ICU stay.

Table 19. ALFA-0701 – Unplanned Hospitalizations – As-treated population

	GO + DA	DA
Induction	N=131	N=137
General Hospitalization		
• Patients with at least 1, n (%)	26 (20%)	19 (14%)
• Median number of hospitalizations (range)	1	1
• Median time in hospital in days (range)	8 (2-76)	9 (2-37)
ICU hospitalization, n (%)		
• Patients with at least 1, n (%)	12 (9%)	11 (8%)
• Median number of ICU hospitalizations (range)	1 (1-2)	1 (1-2)
• Median time in ICU in days (range)	5 (2-42)	3 (1-38)
Consolidation 1	N=91	N=103
General Hospitalization		
• Patients with at least 1, n (%)	18 (20%)	4 (4%)
• Median number of hospitalizations (range)	1 (1-3)	1
• Median time in hospital in days (range)	9 (2-37)	8 (5-14)
ICU hospitalization, n (%)		
• Patients with at least 1, n (%)	5 (5%)	1 (<1%)
• Median number of ICU hospitalizations (range)	1 (1-2)	1
• Median time in ICU in days (range)	4 (2-7)	30
Consolidation 2	N=64	N=107
General Hospitalization		
• Patients with at least 1, n (%)	3 (5%)	9 (8%)
• Median number of hospitalizations (range)	1	1
• Median time in hospital in days (range)	15 (15-20)	14 (8-30)
ICU hospitalization, n (%)		
• Patients with at least 1, n (%)	4 (6%)	8 (7%)
• Median number of ICU hospitalizations (range)	1	1
• Median time in ICU in days (range)	6 (2-27)	6 (2-29)
Any Phase	N=131	N=137
General Hospitalization		
• Patients with at least 1, n (%)	44 (34%)	33 (24%)
• Median number of hospitalizations (range)	1 (1-2)	1 (1-2)
• Median time in hospital in days (range)	12 (2-76)	10 (2-37)
ICU hospitalization, n (%)		
• Patients with at least 1, n (%)	23 (18%)	23 (17%)
• Median number of ICU hospitalizations (range)	1 (1-2)	1 (1-2)
• Median time in ICU in days (range)	4 (2-42)	4 (1-53)

Source: FDA Analysis

6.1.7.3 Transfusions

Overall, 99% of patients in both arms required at least 1 PRBC transfusion during any phase of treatment. The two arms were evenly matched with a similar median number of transfusions per patient (14). See Appendix 2, Table 57 for the analysis by treatment phase.

In contrast, although 99% of patients in both arms also required at least 1 platelet transfusion, the median number of platelet transfusions in the GO arm was more than twice that of the control arm, both overall (23 transfusions vs 11), and in each treatment phase.

Table 20. ALFA-0701 – Platelet Transfusions by Treatment Phase – As-treated population

	GO + DA	DA
Induction	N=131	N=137
• Patients receiving at least 1 transfusion, n (%)	130 (99)	134 (98)
• Median transfusions per patient (range)	11 (1-43)	5 (1-31)
Consolidation 1	N=91	N=103
• Patients receiving at least 1 transfusion, n (%)	89 (98)	100 (97)
• Median transfusions per patient (range)	7 (2-22)	2 (1-13)
Consolidation 2	N=64	N=107
• Patients receiving at least 1 transfusion, n (%)	62 (97)	105 (98)
• Median transfusions per patient (range)	7 (3-16)	4 (1-16)
Any Phase	N=131	N=137
• Patients receiving at least 1 transfusion, n (%)	130 (99)	136 (99)
• Median transfusions per patient (range)	23 (1-61)	11 (1-42)

Source: FDA Analysis

6.1.8 Subpopulations

Results of subgroup analyses for EFS and OS by age, sex, and baseline characteristics are shown in Table 21. In general, the results in subgroups were comparable with the overall results. Results for subgroup analysis by CD33 expression, cytogenetic risk, and ELN/NCCN risk categories are discussed separately later in this section.

Table 21. ALFA-0701 – Event-free Survival and Overall Survival by Subgroups

Subgroup	N			EFS HR [95% CI]	OS HR [95% CI]
	Total	GO+DA	DA		
Overall	271	135	136	0.56 [0.42, 0.76]	0.81 [0.60, 1.09]
Age (year)					
<60	90	38	52	0.52 [0.29, 0.92]	0.61 [0.34, 1.12]
≥60	181	97	84	0.56 [0.39, 0.80]	0.85 [0.59, 1.21]

Subgroup	N			EFS HR [95% CI]	OS HR [95% CI]
	Total	GO+DA	DA		
Sex					
Male	134	74	60	0.57 [0.38, 0.88]	0.82 [0.54, 1.25]
Female	137	61	76	0.55 [0.36, 0.85]	0.77 [0.49, 1.20]
WBC count (10^9/L)					
<30	222	108	114	0.52 [0.37, 0.74]	0.81 [0.58, 1.15]
≥30	47	26	21	0.67 [0.35, 1.31]	0.67 [0.34, 1.31]
ECOG					
0,1	238	121	117	0.56 [0.41, 0.78]	0.82 [0.59, 1.14]
≥2	32	14	18	0.62 [0.26, 1.51]	0.78 [0.33, 1.84]

EFS=event-free survival, OS=overall survival, HR=hazard ratio, GO=gemtuzumab ozogamicin, DA=daunorubicin plus cytarabine, WBC=white blood cells, ECOG=European Cooperative Oncology Group, L=liter
Source: FDA Statistical Review

6.1.8.1 CD33 Expression

In ALFA-0701, 194 patients (72%) had %CD33 expression data, and no patients had a value of zero. FDA's analysis of efficacy in ALFA-0701 by CD33 expression showed that, although the EFS benefit was most significant for patients with ≥70% expression, all groups derived some degree of benefit. There was no consistent relationship between CD33 expression and OS in this trial.

Table 22. ALFA-0701 – Efficacy by CD33 Expression

CD33 Expression	Treatment Arm	N	CR		EFS			OS		
			No. of responders (%)	Diff. (%)	No. of events (%)	Median in month	HR (95% CI)	No of events (%)	Median in month	HR (95% CI)
No value available	GO + DA	35	24 (69)	-5.2	19 (54)	18.0	0.59 (0.33, 1.05)	20 (57)	38.6	0.81 (0.45, 1.45)
	DA	42	31 (74)		31 (74)	11.8		26 (62)	27.5	
< 30%	GO + DA	17	14 (82)	32.4	11 (65)	14.3	0.52 (0.24, 1.15)	11 (65)	22.2	0.87 (0.39, 1.95)
	DA	20	10 (50)		15 (75)	6.5		13 (65)	24.1	
>=30% to <70%	GO + DA	20	10 (50)	-13.6	13 (65)	14.3	0.83 (0.34, 2.01)	15 (75)	20.6	0.99 (0.41, 2.37)
	DA	11	7 (64)		8 (73)	11.3		8 (73)	25.2	
> 70%	GO + DA	63	47 (75)	0.6	30 (48)	NR	0.50 (0.31, 0.79)	34 (54)	34.0	0.71 (0.45, 1.12)
	DA	63	47 (75)		48 (76)	8.7		41 (65)	18.9	

Source: FDA Statistical Review

Independently, Olombel, et al (Blood 2016) performed a similar analysis of ALFA-0701 and found that prolonged EFS and RFS with GO administration were observed in high-$CD33^+$ (defined as CD33 ≥70%) patients only, with hazard ratios of 0.56 (p=0.005) and 0.47 (p=0.002) respectively. The 70% cut-off was chosen because the MFI ratio remained relatively low in patients until there were 70% $CD33^+$ blasts. They therefore concluded that "a $CD33^+$ expression level as high as 70% or more (observed... in 65% of patients and 64% of those with nonadverse cytogenetics [in this study]) appeared to be necessary to allow a beneficial response to GO."

Although CD33 analysis in ALFA-0701 was a retrospective subset analysis, the results of large trials published in the literature support the general hypothesis that CD33 expression correlates with response to GO.

Khan, et al looked at 393 adult patients treated on the NCRI AML16 and AML17 trials. 244 patients received GO + chemotherapy (142 – GO 3 mg/m^2, 102 – 6 mg/m^2), and 149 received chemotherapy alone. The results showed no significant interaction between GO and CD33 quartiles on overall survival using either CD33% or MFI. However, there was a significant interaction between GO and %CD33-positive blasts and relapse rate. Patients in the bottom quartile (CD33 <37%) had significantly greater relapse risk when given GO (HR 2.41; CI 1.27-4.56) while patients with CD33 >98% had reduced relapse risk (HR 0.63, CI 0.35-1.12). This relationship was not observed with blast CD33-MFI (bottom quartile cut-off of 3.52).

In pediatric patients, Pollard, et al performed a prospective analysis of CD33 expression by MFI in 825 patients with de novo AML enrolled in AAML0531. They found that patients in the bottom quartile (median MFI 34.62, range 2.68-67.00) derived no relapse-free, event-free or overall survival benefit from the addition of GO to conventional chemotherapy, whereas patients in the composite upper 3 quartiles had a significant improvement in clinical outcome with the addition of GO (relapse risk 32% vs 49%, EFS 53% vs 41%). These findings were consistent when disease risk groups in combination with CD33 expression were taken into account; i.e. there was no disease risk group (including CBF-AML) in the bottom CD33 quartile that derived any benefit with the addition of GO.

Reviewer comments: GO is a CD33-targeted therapy. Although some smaller early studies failed to find a predictive role for CD33 expression, the majority of recent large randomized trials demonstrate a correlation between CD33 expression and response to GO. However, the cut-offs used for these determinations vary widely between trials. All patients in ALFA-0701 who had a CD33 level in the dataset had a level greater than 0. FDA's analysis showed that, although patients with >70% CD33 expression had the most significant improvement in EFS, all groups appeared to derive some degree of benefit.

The other two studies referenced above simply divided the study population into quartiles and found that patients in the bottom quartile did not derive benefit. The publication from Khan, et al, also describes poor agreement between their centrally analyzed %CD33 positivity data and those acquired by local laboratories for the same samples. Therefore, while data clearly show that only patients who

are CD33-positive derive benefit from GO, there are no data to support a specific cut-off value, and we will define CD33-positivity as any level >0.

6.1.8.2 Cytogenetics

Because cytogenetics is the strongest disease-specific prognostic factor in AML, FDA examined the efficacy results by cytogenetic risk category to determine whether patients in all categories derived benefit from the addition of GO.

ALFA-0701 – Efficacy by Cytogenetic Risk Category

In the pivotal trial, patients with favorable cytogenetic risk had significant improvement in EFS when treated with GO + DA compared with DA alone. This advantage in EFS with the addition of GO was not seen in patients with adverse cytogenetic risk at baseline.

Table 23. AFLA-0701 – EFS and OS by Cytogenetic Risk Category

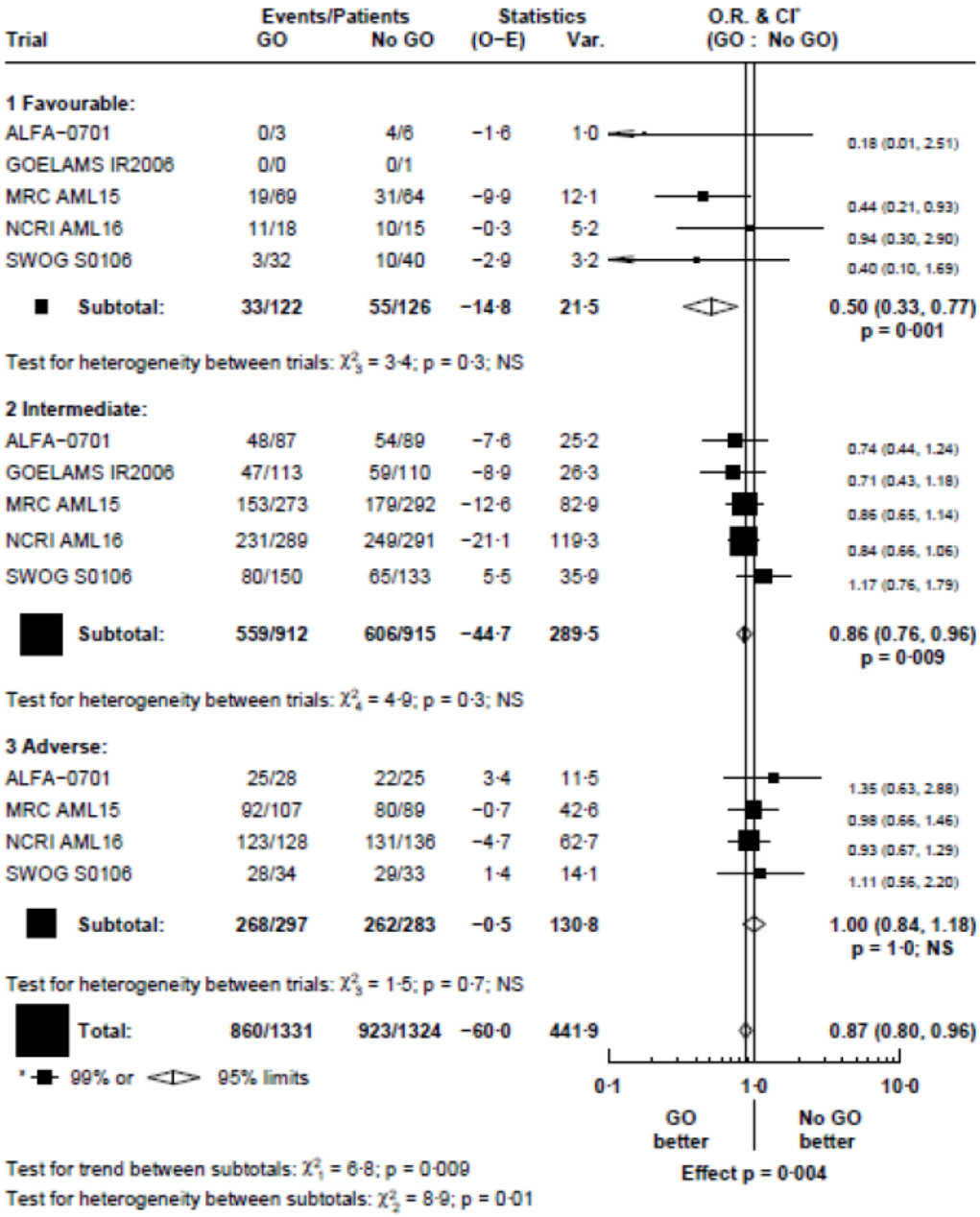
	N			EFS HR	OS HR
	Total	GO+DA	DA	[95% CI]	[95% CI]
Favorable/Intermediate	189	94	95	0.46 [0.31, 0.68]	0.75 [0.51, 1.09]
Adverse	57	27	30	1.11 [0.63, 1.95]	1.55 [0.88, 2.75]

Source: FDA Statistical Review

IPD Meta-Analysis – Overall Survival by Cytogenetic Risk Category

Figure 6 shows the Applicant-submitted forest plot for OS by cytogenetic risk category for studies included in the IPD Meta-Analysis. These data support the finding of a trend towards OS benefit for patients with favorable and intermediate risk cytogenetics and no benefit in patients with adverse risk cytogenetics.

Figure 6. IPD Meta-Analysis – OS by Cytogenetic Risk Category



Source: Applicant submitted IPD-Meta Analysis CSR Efficacy Figure 27.

Literature Review of GO and Cytogenetic Risk

Several other meta-analyses of randomized trials of GO plus chemotherapy have been published. In addition to the five trials above, Loke, et al looked at GIMEMA AML17 and COG AAML0531 and also found no OS benefit for patients with adverse cytogenetics. Additional analyses of other trials in the

FDA literature review (see Table 36) consistently concluded that benefit is mainly seen in the favorable cytogenetics group, with a trend towards benefit with intermediate risk cytogenetics, and lack of benefit in patients with adverse risk cytogenetics.

6.1.8.3 Adverse Cytogenetics and CD33 Status

In order to look more closely at the patients who would be eligible for treatment under the proposed indication, FDA performed a separate analysis of patients with adverse cytogenetic risk by CD33 level both in ALFA-0701 (Table 24) and in the IPD Meta-Analysis (Table 25). Figure 7 shows overall survival of patients with adverse risk cytogenetics and CD33 ≥30% or CD33 ≥ 70% in the IPD Meta-Analysis. Neither CD33 cutoff yielded a population that benefitted from GO.

Table 24. ALFA-0701 – Efficacy in Patients with Adverse Cytogenetics by CD33 level

	CR		EFS		OS	
	GO + DA	DA	GO + DA	DA	GO + DA	DA
CD33 < 30% - N	5	4	5	4	5	4
• n	5	1	4	3	4	2
• Odds ratio (95% CI)	Not estimable		0.54 (0.12, 2.50)		3.62 (0.62, 21.04)	
CD33 30-< 70% - N	6	1	6	1	6	1
• n	3	1	5	0	5	0
• Odds ratio (95% CI)	Not estimable		Not estimable		Not estimable	
CD33 ≥70% - N	12	15	12	15	12	15
• n	3	8	10	13	11	12
• Odds ratio (95% CI)	0.29 (0.04, 1.92)		1.51 (0.66, 3.48)		1.75 (0.77, 4.00)	

Source: FDA Analysis and Applicant Submitted IR response SDN 43

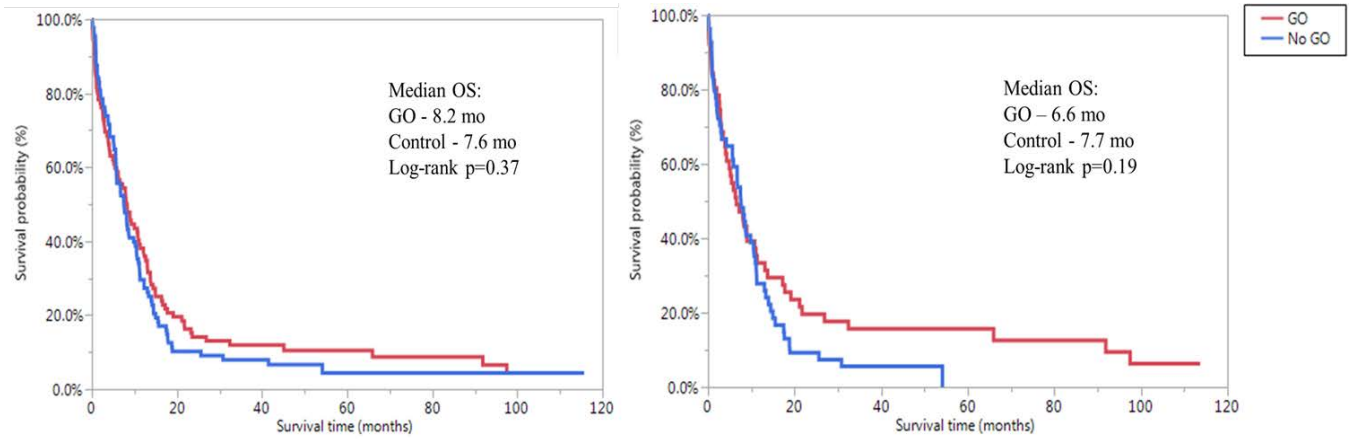
Table 25. IPD Meta-Analysis – Efficacy in Patients with Adverse Cytogenetics by CD33 level

	CR		EFS		OS	
	GO + DA	DA	GO + DA	DA	GO + DA	DA
CD33 < 30% - N	43	42	43	42	43	42
• n	24	25	39	41	39	39
• Odds ratio (95% CI)	1.23 (0.52, 2.90)		0.74 (0.44, 1.26)		1.27 (0.81, 2.01)	
CD33 30-< 70% - N	53	43	53	43	53	43
• n	28	17	51	41	50	40
• Odds ratio (95% CI)	0.58 (0.26. 1.32)		0.82 (0.49, 1.38)		0.97 (0.63, 1.49)	
CD33 ≥70% - N	69	69	69	69	69	69
• n	36	32	61	68	60	65
• Odds ratio (95% CI)	0.85 (0.43, 1.70)		0.73 (0.47, 1.14)		0.84 (0.58, 1.20)	

Source: FDA Analysis and Applicant Submitted IR response SDN 43

Figure 7. IPD Meta-Analysis – Overall Survival in Patients With Adverse Cytogenetics by CD33-Positivity

a. CD33 ≥ 30% **b. CD33 ≥ 70%**



Source: FDA Analysis

Reviewer Comments: As demonstrated above, for the subgroup of patients with adverse cytogenetic risk, benefit of GO treatment was not observed in either EFS or OS. When CD33 expression was taken into account, the number of patients in each category was very small. In the patients in the IPD meta-analysis, those with the lowest CD33 expression (<30%) failed to derive even CR benefit. There was minimal difference in median OS in patients with at least 30% CD33 expression (Figure 7a.) and median OS was actually worse with GO in this subset using the ≥70% CD33 cut-off (Figure 7b). However, these are retrospective subset analyses performed on a very small proportion of patients, and can be considered only as exploratory, hypothesis-generating analyses.

Nevertheless, the hypothesis that patients with adverse cytogenetics fail to derive benefit from GO is supported by the published literature (Loke, 2014; Burnett, 2011; Li, 2014; Kharfan-Dabaja, 2013). The risks involved with GO treatment may outweigh the lack of benefit in patients with adverse cytogenetics. But, while the oncology field may be moving towards precision medicine, from a real-world perspective, cytogenetic data may not be available at the time of treatment initiation. Additionally, the safety data for GO+DA do not support an increased risk of harm in these patients. Restricting the indication by cytogenetic risk category would require that all patients delay treatment until that information is obtainable. This may be an unacceptable risk for many patients. Therefore, the label should be clear with regards to the lack of evidence in this subset; however, the decision regarding the use of GO in these patients should be left to the discretion of the treating physician to be assessed on an individual patient basis.

6.1.8.4 ELN 2010 and NCCN Risk Categories

Where data were available, FDA looked at efficacy in ALFA-0701 based on ELN 2010 and NCCN risk criteria. Patients with favorable or intermediate risk classification derived EFS benefit with a trend

towards OS benefit. However, for patients with NCCN or ELN poor risk classification, EFS and OS were not longer for patients in the GO arm.

Table 26. ALFA-0701 – EFS and OS by ELN 2010 Risk Criteria

	N			EFS HR	OS HR
	Total	GO+DA	DA	[95% CI]	[95% CI]
Favorable	53	27	26	0.38 [0.17, 0.85]	0.62 [0.26, 1.47]
Intermediate	124	59	65	0.52 [0.33, 0.83]	0.78 [0.50, 1.23]
Poor/Adverse	73	37	36	0.72 [0.43, 1.21]	1.12 [0.68, 1.87]

Source: FDA Statistical Review

Table 27. ALFA-0701 – EFS and OS by NCCN Risk Criteria

	N			EFS HR	OS HR
	Total	GO+DA	DA	[95% CI]	[95% CI]
Favorable	51	27	24	0.37 [0.16, 0.83]	0.63 [0.26, 1.52]
Intermediate	109	53	56	0.53 [0.32, 0.87]	0.95 [0.59, 1.53]
Poor/Adverse	89	43	46	0.74 [0.46, 1.19]	0.92 [0.57, 1.48]

Source: FDA Statistical Review

Data from the IPD Meta-Analysis ELN subgroup analyses are similar with favorable risk patients seeing the most significant benefit, both in EFS and OS. Intermediate risk patients had a trend towards benefit, and adverse risk patients derived no EFS or OS benefit. There were no data available on NCCN risk in the meta-analysis.

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

GO Dose Selection

GO originally received regular approval as a monotherapy for the treatment of patients with relapsed AML at a dose of 9 mg/m^2 x 2 doses. The confirmatory trial SWOG S0106 used GO 6 mg/m^2 in combination with DA as treatment for patients with newly-diagnosed AML, but was terminated early after an interim analysis showed increased deaths in induction and lack of improvement in complete response rate in the GO arm. GO was subsequently withdrawn from the US market in 2010. The Applicant proposes that a lower and fractionated GO dose of 3 mg/m^2 days 1, 4 and 7 in combination with DA for induction may address the safety concerns seen with previous dose regimen.

Clinical pharmacology data suggest that GO doses above 2 mg/m^2 are sufficient to saturate CD33 and are unlikely to result in substantial loss of efficacy. Population PK analyses suggest that an increased Cmax after the first GO dose is associated with an increased risk of VOD. (For details of these analyses, see the Clinical Pharmacology review in Section 4.4). Thus, the proposed fractionated dose and schedule may reduce the risk of VOD without substantial loss of efficacy. However, these tentative

conclusions are based on simulated data, as no PK data were collected for the pivotal trial ALFA-0701.

To assess the impact of dose and schedule on safety, FDA performed a meta-analysis analyzing VOD rates reported in the literature across studies of GO used as a monotherapy for the treatment of patients with relapsed/refractory AML at 6 or 9 mg/m^2 unfractionated regimens or the 3 mg/m^2 fractionated regimen. Details of this meta-analysis can be found in the clinical review for GO monotherapy (Ori-2). Although the number of patients treated with fractionated GO in the relapsed/refractory setting is small, of the patients described in Table 28 receiving fractionated GO monotherapy, no patients developed VOD. Additionally, the meta-analysis data appear to show that the complete response rate is no worse using the fractionated GO schedule than with the unfractionated 6 or 9 mg/m2 GO regimens in the relapsed/refractory AML population (Table 29). Given these findings, FDA concluded that the 3 mg/m^2 dose fractionated GO schedule is reasonable to study.

Table 28. FDA Meta-Analysis –VOD Rate by GO Monotherapy Dose in Patients with Relapsed/Refractory AML

GO dose	N	VOD incidence (95% CI)
9 mg/m^2 x 2 (10 studies combined)	378	5.6% (3.5, 8.1)
6 mg/m^2 x 2 (7 studies combined)	48	15.0% (6.4, 26.4)
3 mg/m^2 d1, 4, 7 (3 studies combined)	87	0% (0.0, 1.1)

Source: FDA Analysis

Table 29. FDA Meta-Analysis – CR Rate by GO Monotherapy Dose in Patients with Relapsed/Refractory AML

GO dose	N	CR (95% CI)
9 mg/m^2 x 2 (11 studies combined)	436	13.7% (10.7, 17.1)
6 mg/m^2 x 2 (6 studies combined)	57	1.2% (0.0, 5.7)
3 mg/m^2 d1, 4, 7 (2 studies combined)	63	25.3% (15.5, 36.7)

Source: FDA Analysis

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

See review of EFS in Section 6.1.5. There are no data available on retreatment or tolerance effects.

6.1.11 Additional Efficacy Issues/Analyses

6.1.11.1 EFS surrogacy for OS

In a trial-level analysis of 33 randomized studies in untreated patients with de novo AML, the trial-level weighted R^2 was only 0.46 (95% CI 0.23, 0.70). An R^2 close to 1 indicates a strong trial-level surrogacy. In the subgroup of 5 randomized GO studies for which patient-level data were available, the weighted R^2 through a copula model was 0.45 (95% CI 0.00, 1.00) and was 0.61 (95% CI 0.20, 1.00) without application of a copula model. For this patient-level analysis, EFS was clearly not predictive of OS, particularly for patients who did not achieve CR. Further details of these analyses are discussed in the statistical review of this application.

The surrogacy of EFS for OS may be influenced in part by active salvage therapies including stem cell transplantation; therefore, the lack of correlation between EFS and OS is not unexpected.

6.1.11.2 Transplant in ALFA-0701

A greater proportion of patients in the control arm of ALFA-0701 received an HSCT both overall and in CR1, as induction failure salvage, and after relapse (Table 30). As a whole, patients who received a transplant had better survival than those who did not (Table 31). Therefore, it is possible that active salvage with HSCT affected the overall survival results and may have given an advantage to the control arm.

Table 30. ALFA-0701 – Hematopoietic Stem Cell Transplantation Rates

	CR	CRp	No CR/CRp	All
All study patients	**190**	**20**	**61**	**271**
Patients received HSCT, n (%)	69 (36.3)	5 (25.0)	11 (18.0)	85 (31.4)
Status at HSCT				
Before relapse	36 (18.9)	3 (15.0)	0	39 (14.4)
After relapse	33 (17.4)	2 (10.0)	0	35 (12.9)
After induction failure	0	0	11 (18.0)	11 (4.1)
Median time to HSCT, days				
From randomization	256	202	168	214
From relapse/Induction failure	168	767	106	156
Patients in the GO+DA arm	**95**	**15**	**25**	**135**
Patients received HSCT, n (%)	27 (28.4)	3 (20.0)	2 (8.0)	32 (23.7)
Status at HSCT				
Before relapse	15 (15.8)	2 (13.3)	0	17 (12.6)
After relapse	12 (12.6)	1 (6.7)	0	13 (9.6)
After induction failure	0	0	2 (8.0)	2 (1.5)
Median time to HSCT, days				
From randomization	256	202	159	230
From relapse/Induction failure	164	190	94	160

Patients in the DA arm	95	5	36	136
Patients received HSCT, n (%)	42 (44.2)	2 (40.0)	9 (25.0)	53 (39.0)
Status at HSCT				
Before relapse	21 (22.1)	1 (20.0)	0	22 (16.2)
After relapse	21 (22.1)	1 (20.0)	0	22 (16.2)
After induction failure	0	0	9 (25.0)	9 (6.6)
Median time to HSCT, days				
From randomization	279	804	168	202
From relapse/Induction failure	172	1344	128	156

Note: summary based on applicant data for study report (data cutoff: 01Aug2011, responses considering CR/CRp as determined by investigators during induction)
Source: FDA Statistical Review

Table 31. ALFA-0701 – Overall Survival Sensitivity Analyses with Consideration of Transplantation

OS Analysis	Description	HR (95% CI)	p-value
1	OS primary analysis	0.81 (0.60, 1.09)	0.165
2	OS censored at HSCT	0.81 (0.56, 1.15)	0.238
3	OS with HSCT as a time-varying covariate	0.85 (0.63, 1.16)	0.308
4	OS with HSCT (yes or no) as a covariate	0.74 (0.54, 1.01)	0.062
5*	OS in patients who didn't receive HSCT	0.68 (0.48, 0.97)	0.033
6*	Post-HSCT survival in patients who received HSCT	0.97 (0.53, 1.75)	0.908

HSCT: hematopoietic stem cell transplantation; OS: overall survival
HR: hazard ratio estimated from Cox proportional hazards model for experimental arm versus control arm
p-value: 2-sided nominal p-value from log-rank test, stratified by HSCT (yes/no) in analysis 4, un-stratified in others
* Not an ITT analysis (in other words, analysis was not performed in all the randomized patients)
Source – FDA Statistical Review. Analyses were performed based on study report data cut-off 30April2013 for OS.

6.1.11.3 Efficacy in COG AAML0531

The efficacy data presented in this section are from Gamis, 2014 unless otherwise noted.

For AAML0531, eligible patients had ≥20% blasts in the marrow or had AML diagnosis supported by FAB classification, other cell lineages in BMA, and/or cytogenetic molecular results consistent with AML. The GO dose and schedule studied was 3 mg/m^2 day 6 of induction 1 and day 7 of intensification 2. The full treatment plan is listed in Table 32. The primary efficacy endpoints were EFS and OS from study entry. Induction failure was defined as not achieving CR by the end of induction 2 and the date of IF was the date of study entry.

Table 32. AAML0531 – Therapeutic Regimen

Table 1. COG AAML0531 Therapeutic Regimen

Course and Agent	Dose	Days
IND1		
Cytarabine	100 mg/m^2/dose twice per day IV	1 to 10
Daunomycin	50 mg/m^2/dose IV	1, 3, 5
Etoposide	100 mg/m^2/dose IV	1 to 5
Gemtuzumab, arm B only	3 mg/m^2/dose IV over 2 hours	6
IND2		
Cytarabine	100 mg/m^2/dose twice per day IV	1 to 8
Daunomycin	50 mg/m^2/dose IV	1, 3, 5
Etoposide	100 mg/m^2/dose IV	1 to 5
INT1		
Cytarabine	1,000 mg/m^2/dose twice per day IV	1 to 5
Etoposide	150 mg/m^2/dose IV	1 to 5
For patients not undergoing stem-cell transplantation		
INT2		
Mitoxantrone	12 mg/m^2/dose IV	3 to 6
Cytarabine	1,000 mg/m^2/dose twice per day IV	1 to 4
Gemtuzumab, arm B only	3 mg/m^2/dose IV over 2 hours	7
INT3		
Cytarabine	3,000 mg/m^2/dose twice per day IV	1, 2, 8, 9
Escherichia coli L-asparaginase	6,000 mg/m^2/dose IM	2, 9
For patients receiving matched family-donor stem-cell transplantation		
Busulfan, 16 total doses	Age and weight based	−9
< 10 kg or > 4 years old	0.8 mg/kg/dose once every 6 hours IV	
> 10 kg and < 4 years old	1 mg/kg/dose every 6 hours IV	
All patients	Adjusted AUC based on first dose	−8 to −6
Cyclophosphamide	50 mg/kg/dose IV once per day	−5 to −2

Abbreviations: AUC, area under the concentration-time curve; COG, Children's Oncology Group; IM, intramuscular; IND1, induction course; INT, intensification course; IV, intravenous.

Source: Gamis, 2014. Table 1.

The trial was well balanced with respect to demographics and baseline disease characteristics (Table 33). Completion of treatment was similar between arms (Table 34), and there were no significant differences between arms in the reasons for treatment discontinuation.

Table 33. AAML0531 – Demographics

Eligible patients	No GO N=517 n (%)	GO N=511 n (%)
Sex		
Female	247 (48%)	267 (52%)
Male	264 (52%)	244 (48%)
Age (Years)		
Median	9.5	9.9
Range	0.003-29.8	0.02-29.4
Cytogenetics		
t(8;21)*	69 (14%)	68 (13%)
Inv16, t (16;16)*	52 (10%)	57 (11%)
-7^	16 (3%)	9 (2%)
-5/5q^	10 (2%)	4 (<1%)
Median baseline WBC $10^3/mm^3$ (range)	24.3 0.2-526	23.6 0.4-827.2
Risk Group Assignment		
Low	121 (24%)	125 (25%)
Intermediate	302 (59%)	305 (60%)
High	88 (17%)	81 (16%)

Source: Gamis, 2014, Condensed from Table 2.
* Low risk factors
^ High risk factors

Table 34. AAML0531 – Patient Disposition

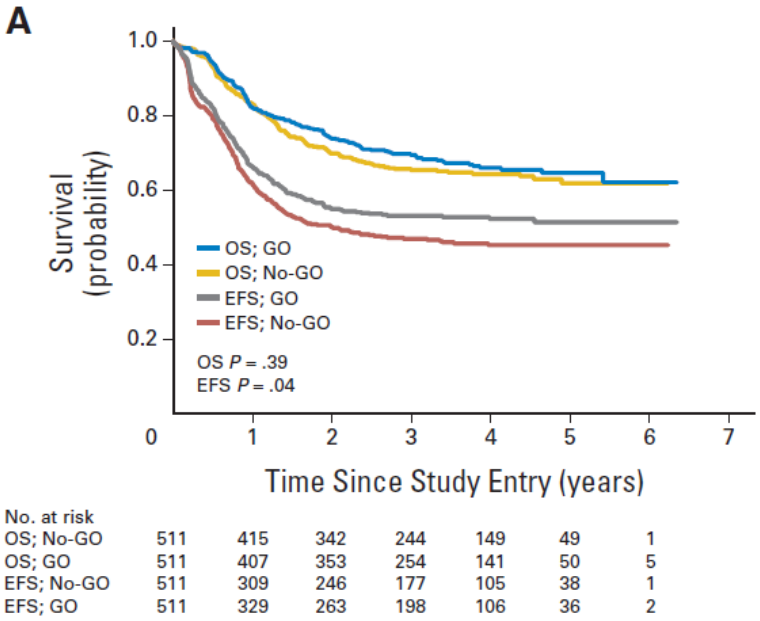
Cumulative Reasons for Not Completing All Therapy	Control Arm (No. of Patients)	GO Arm (No. of Patients)	*P*
Total enrolled	511	511	
Total completing all therapy	327	334	.65
Total of those not completing all therapy	184	177	
Reasons for not completing all therapy			
Elective withdrawal	42	41	.94
Withdrawal because of toxicity	43	45	.65
Toxic mortality	16	20	.41
Refractory disease/relapsed before therapy completion	82	71	.39
Lost to follow-up	1	0	1.00

Abbreviation: GO, gemtuzumab-ozogamicin arm.
Source: Gamis, 2014. Table A2.

Primary Endpoints

There were 1,022 evaluable patients enrolled. Similarly to ALFA-0701, addition of GO improved significantly EFS (3 years: 53.1% vs 46.9%, HR 0.83, 95% CI 0.70-0.99, p=0.04) but not OS (3 years: 69.4% vs 65.4%, HR 0.91, 95% CI 0.74-1.13, p=0.39). Median EFS in the GO arm was not reached and was 24.3 months in the No GO arm. Median OS was not reached in either arm.

Figure 8. AAML0531 – EFS and OS from Study Entry



Source: Gamis, 2014. Figure 2a.

Secondary Endpoints

Although CR was not improved (88% vs 85%; p= 0.15), posthoc analyses found that relapse risk (RR) was reduced significantly among GO recipients overall (3 years: 32.8% vs 41.3%, HR 0.73, 95% CI 0.58-0.91, p =0.006) and disease-free survival was better among GO recipients (3 years: 60.6% vs 54.7%, HR 0.82, 95% CI 0.67-1.02, p=0.07).

Subset analyses

Univariate risk factor analysis of cytogenetic risk group and institutional risk group are shown in Table 35. No benefit in EFS or OS was detected in either cytogenetic high risk or institutional high risk patients when analyzed from study entry. Note that institutional risk categories do not directly correspond with regularly used adult ELN or NCCN risk guidelines, but are commonly used to make treatment decisions in COG trials.

The institutional risk categories were defined as follows:

- Low risk (LR) was defined by the presence of t(8;21)(q22;q22), inv(16)(p13.1q22), or t(16;16)(p13.1;q22).
- High risk (HR) was defined by presence of monosomy 7, monosomy 5/5q deletion, or persistent disease (PD) at the end of IND1 (bone marrow blasts >15% by morphology). *FLT-3* internal tandem duplication high allelic ratio (>0.4;FLT3-ITD HAR) was also a marker of HR disease.

- Cytogenetics outweighed response in risk classification, whereas *FLT3*-ITD HAR outweighed favorable cytogenetics

Table 35. AAML0531 – Univariate Risk Factor Analysis by Risk Group

		EFS From Study Entry			OS From Study Entry		
Characteristic	No. of Patients	HR	95% CI	*P*	HR	95% CI	*P*
Cytogenetic risk group							
Intermediate	702	1			1		
Low, t(8;21) or inv(16)	244	0.46	0.36 to 0.59	**< .001**	0.38	0.27 to 0.53	**< .001**
High, mono5/del5q or mono7	35	1.32	0.88 to 2.00	.19	1.88	1.22 to 2.91	**.004**
Institutional risk group							
Intermediate	607	1			1		
Low	246	0.53	0.42 to 0.68	**< .001**	0.40	0.29 to 0.56	**< .001**
High	169	1.95	1.58 to 2.41	**< .001**	1.67	1.30 to 2.15	**< .001**

Source: Gamis, 2014. Table A4.

Reviewer Comments: Addition of GO 3 mg/m^2 yielded an EFS benefit of 53.1% vs 46.9% without GO at 3 years (HR 0.83, 95% CI 0.70- 0.99, P=0.04). There was no corresponding OS benefit, and the EFS benefit is thought to be largely due to a significant reduction in relapse risk. This data supports a finding of efficacy with GO in children.

7 Review of Safety

Safety Summary

ALFA-0701

The safety dataset included 131 patients treated with fractionated GO + DA and 137 patients treated with DA alone. The demographics of the group was representative of the intended population; although ALFA-0701 enrolled patients between 50-70 years old, trials included in the supportive IPD Meta-Analysis allowed for safety analyses across a broader age range (including patients between the ages of 15 and 90 years old). However, it is important to note that the safety analysis was limited by the retrospective nature of the collection of adverse events. The study population was examined for early mortality, treatment-related deaths, serious adverse events, adverse events of special interest, common adverse events, and common laboratory tests. There were no QT data available, and only baseline ECGs were collected.

The key results from the review of safety showed:

- 30-day mortality was not significantly different between the GO + DA arm vs the DA arm (4% vs 2%). Importantly, the disparity in early mortality between treatment arms was lower in ALFA-0701 than in SWOG S0106 with odds ratios of 1.99 and 3.58, respectively. This suggests that the 3 mg/m^2 fractionated GO schedule is safer with regards to early mortality.

- Overall, incidence of treatment-related mortality was low, but remained higher in the GO arm (6% vs 2%). In the GO arm, these deaths were predominantly due to hemorrhage and VOD. In the control arm, all TRM was related to sepsis.

- Treatment discontinuation due to adverse event was higher in the GO arm (31% vs 7%). The adverse events that primarily accounted for this difference were thrombocytopenia (15% vs 0%) and hepatobiliary disorders (6% vs <1%).

- The most common adverse events occurring more frequently with GO + DA vs DA were due to bleeding or infection, and differences in rates occurred during each phase of treatment.

- There remains a risk for VOD which occurred in 5% of patients randomized to GO+DA vs 0% in patients who did not receive GO. There were 3 fatal cases of VOD. 7 of 8 patients developed VOD without prior transplantation.

- Hemorrhage events occurred more frequently with GO + DA than with DA during all phases of treatment. ALFA-0701 had a higher overall risk difference for Grade 3 and higher hemorrhage (in any phase) than other protocols in the meta-analysis or literature review, with a risk difference of 13.4% with GO+DA over DA alone.

- Platelet recovery appeared to be delayed in patients treated with GO + DA vs DA alone.

- The laboratory shifts to Grade≥3 that were higher in the GO arm were AST and bilirubin elevations, hypophosphatemia, hypokalemia, and hyponatremia.

- The results of the IPD meta-analysis were consistent with the expectation that the lower GO dose and fractionated schedule had less toxicity than GO 6 mg/m^2 used in S0106 previously.

AAML0531

The study population in AAML0531 comprised 511 patients treated with GO plus best current chemotherapy vs 511 patients treated with chemotherapy alone. The COG AAML0531 SPR and the Gamis, 2014 publication were examined for early mortality, treatment-related deaths, serious adverse events, and adverse events of special interest.

Overall, the safety profile of AAML0531 was comparable to that seen in adults.

- Early mortality was lower than in adult trials and was evenly distributed between arms (2.3% in the GO arm vs 2.2% in the control arm). Deaths were due to multi-organ failure, hemorrhage, infection, and disease.

- TRM was higher in the GO arm, but the disparity between arms was slightly lower than in ALFA-0701 (2.7% risk difference in AAML0531 compared with 3.9% risk difference in ALFA-0701).

- Rates of Grade ≥3 infection were similar between arms but accounted for at least part of the increase in TRM in the GO arm during later cycles of therapy.

- Incidence and severity of VOD were lower than in ALFA-0701 and was similar in both treatment arms. There were no VOD-related fatalities. However, in contrast to the adult data, a higher percentage of VOD occurred with transplantation, likely related in part to the use of busulfan in the transplant preparative regimen.

- Incidence of hemorrhage remained higher in the GO arm compared with the control, but the overall incidence was lower than in ALFA-0701.

- The disparity between arms in time to platelet recovery is significantly lower than was seen in ALFA-0701.

- Time to neutrophil recovery was delayed in a greater proportion of patients in the GO arm during intensification 2 (12.0% vs 6.3%).

These data appear adequate to extend the indication to include children with newly-diagnosed CD33-positive AML using the dose schedule from AAML0531 (3 mg/m^2 single doses in induction 1 and intensification 2).

See clinical review of Ori-2. for an analysis of the safety of GO as a monotherapy.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

FDA's safety analysis for this indication included examination of all patients in ALFA-0701, data from the applicant-submitted IPD meta-analysis (including ALFA-0701 and 4 other randomized trials), and a survey of other randomized trials of GO + chemotherapy in the literature.

Literature searches were performed using the terms "Mylotarg," "gemtuzumab ozogamicin," or "gemtuzumab." Published papers that included randomized studies of GO in combination with chemotherapy in the front-line AML setting were included. Four randomized trials not included in the Applicant's IPD meta-analysis were identified (Table 36). These studies covered a range of GO doses and patient age groups. Given the historical safety concerns with GO and their potential relationship to GO dose and patient age, FDA included these four studies in the analysis of safety.

The results from the respective publications were analyzed for early mortality, VOD, and high-grade hemorrhage (where results were available) as well as any other significant reported toxicities.

Table 36. Literature Review – Randomized Trials of GO + Chemotherapy for AML

Study	# of patients	Median age (range)	Induction GO dose	Concurrent Chemotherapies	Primary Endpoint
Gamis, 2014: COG AAML0531	1070	9.7 (3 mo-29.8 y)	3 mg/m^2 x 1 (d1)	Pediatric SOC (DA+)[a]	OS, EFS
Burnett, 2013: AML14/16	495	75 (54-90)	5 mg/m^2 x 1 (d1)	Low dose AraC	OS
Brunnberg, 2012	1019	68 (60-83)	6 mg/m^2 (d1), 4 mg/m^2 (d8)	7+GO vs 7+3	EFS
Amadori, 2013: AML17	472	67 (61-75)	6 mg/m^2 x 2 (d1, 15)	GO pretreatment, mitoxantrone, AraC, etoposide	OS

Source: FDA literature analysis
[a] See Table 32 for full AAML0531 treatment regimen.

Pediatric data from AAML0531 were also evaluated separately and safety outcomes from that trial are discussed in Section 7.6.3.

7.1.2 Categorization of Adverse Events

For ALFA-0701, while occurrence of infectious toxicity, Grade 3 or 4 TEAEs of Haemorrhage, VOD, and reason for study discontinuation were assessed by the Sponsor (CHV), all adverse events in the both the Applicant's and FDA's analyses were derived from data captured during the retrospective data collection described in Section 5.2 unless otherwise noted. Each investigator term was recorded and coded using Medical Dictionary for Regulatory Activities (MedDRA) (v18.0). Severity of TEAEs was assessed by Common Terminology Criteria for Adverse Events (CTCAE), v3.0. Severity of all TEAEs, except Infections, was graded using Grades 1 through 5. For Infections, the retrospective data collection captured only severe (Grade ≥3) infections.

FDA compared the verbatim adverse event description with the MedDRA preferred term for all adverse events reported on ALFA-0701 and did not identify any irregularities. The applicant did not group preferred terms in their analysis with the exception of Veno-occlusive liver disease and veno-occlusive disease. FDA grouped terms can be found in Section 9.4. Standard MedDRA Query (SMQ) analysis was performed using MAED, and no additional safety signals were identified beyond those discussed below.

All trials included in the IPD Meta-Analysis assessed severity of TEAEs using CTCAE v3.0. However, the datasets submitted contain data only for predefined composite Grade 3-4 AEs. Therefore, verification of the coding of adverse events is not possible. AAML0531 was graded using CTCAE v4.0; however, the datasets are not available for FDA review.

7.1.3 Pooling of Data Across Studies/Clinical Trials

ALFA-0701 was the only trial that studied the 3 mg/m^2 GO fractionated dose schedule in combination with DA. Therefore, it was evaluated separately for safety. Data from the IPD meta-analysis and literature review were used to examine the effect of GO dose on the various safety signals.

7.2 Adequacy of Safety Assessments

As described in Section 5.2, there are some potential limitations to the available safety data in this application. ALFA-0701 was not prospectively performed for regulatory purposes, and only predefined Grade 3 and 4 adverse events were recorded. Therefore, the applicant performed a retrospective collection of adverse events of special interest, capturing all grades of hemorrhage and VOD, severe infections, and any other adverse event that led to early permanent discontinuation of GO or chemotherapy. All safety analyses done by FDA have been conducted on this dataset of retrospectively collected AEs.

Additionally, for the IPD meta-analysis, safety data are available only for a limited list of prespecified Grade 3-4 events. Therefore, a more detailed analysis is not possible.

The datasets from AAML0531 were not submitted with this application. The review of this trial is based on COG's Fall 2013 Study Progress Report and Gamis, 2014.

7.2.1 Overall Exposure

70% of patients in the GO arm received at least 80% of the planned GO doses.

Table 37. ALFA-0701 – GO Fractionated Dose Exposure

Completed treatment	GO + DA N=131 n (%)
Induction (GO days 1, 4, 7)	131 (100%)
Consolidation 1 (GO day 1)	91 (70%)
Consolidation 2 (GO day 1)	64 (49%)

Source: FDA Analysis

Although ALFA-0701 randomized patients 1:1 between the GO and control arms, some patients randomized to the GO arm did not receive GO in each phase of treatment. This resulted in an as-treated population that changed unpredictably with each cycle. The as-treated patient numbers detailed in Table 38 are the ones used in FDA's analysis of safety, and all adverse events of special interest and patient deaths were independently adjudicated by FDA. Therefore, there may be differences in the numbers presented by FDA and those presented by the applicant.

Table 38. ALFA-0701 – As-Treated Population

	Phase of Regimen		
	Induction	Consolidation 1	Consolidation 2
Randomized			
GO + DA	135	97	82
DA	136	97	89
As-Treated			
GO + DA	131	91	64
DA	137	103	107

Source: FDA Analysis

The demographics of the safety population do not differ significantly from those of the mITT population described in Section 6.1.2, Table 10 and are adequately consistent with those of the intended population.

7.2.2 Explorations for Dose Response

No randomized trials directly comparing the fractionated GO dose to other dose regimens were performed. Indirect comparisons of adverse events of special interest by GO dose in studies of GO included in the IPD meta-analysis and FDA's review of the literature are described in the major safety results below.

7.2.3 Special Animal and/or In Vitro Testing

There were no issues raised by the preclinical reviewers that warranted any additional safety studies.

7.2.4 Routine Clinical Testing

The schedule of safety monitoring for ALFA-0701 was described in Section 5.3.1, and where available for the protocols in the IPD Meta-Analysis in Section 5.3.2. The frequency of monitoring in the pivotal trial was considered adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Results of human pharmacokinetics and pharmacodynamics relevant to safety of GO monotherapy were summarized in Section 4.4. No PK/PD studies were performed on the fractionated GO dose schedule used in ALFA-0701.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Antibody related toxicities include infusion-related reactions (IRR). Because all patients in ALFA-0701 were premedicated prior to receiving GO, there were minimal infusion reactions reported in the study. Only 1 patient in the GO arm was reported to have capillary leak syndrome.

In addition to IRR, known adverse events related to CD33-targeted antibodies include neutropenia, infection, and tumor lysis syndrome.

- Neutropenia is discussed in Section 7.3.4.3 but was not significantly different between treatment arms.
- The incidence of Grade ≥3 infection in ALFA-0701 was also balanced between arms (78% of patients in the GO arm and 77% in the control arm).
- Tumor lysis syndrome was rare in ALFA-0701, occurring in only two patients (both in the GO arm).

Inotuzumab ozogamicin is a calicheamicin-conjugated monoclonal antibody targeting CD22. The adverse drug reactions known to be associated with inotuzumab include veno-occlusive disease (VOD), myelosuppression, and delayed platelet recovery. These were taken into consideration in the evaluation of this application, and occurrence of these adverse events with GO are discussed below.

7.3 Major Safety Results

7.3.1 Deaths

The leading causes of death in both treatment arms were disease progression, septic shock, and infection.

Table 39. ALFA-0701 – Summary of Overall Deaths – As-treated population

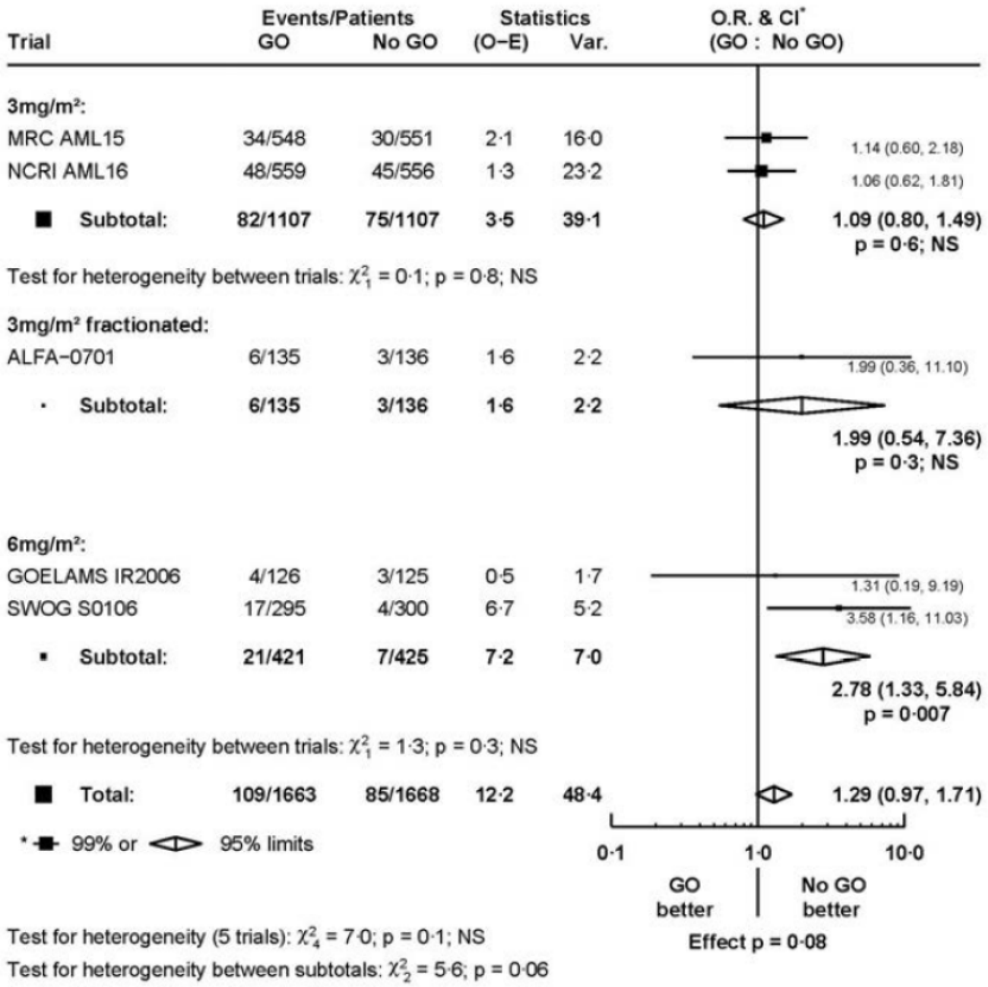
	GO+DA N=131 n (%)	DA N=137 n (%)	Total N=268 n (%)
Overall Number of Deaths	80 (61.1)	90 (65.7)	170 (63.4)
Mechanism(s) of death*			
• Disease progression or relapse	50 (38.2)	62 (45.3)	112 (41.2)
• Septic shock	18 (13.7)	13 (9.5)	31 (11.6)
• Infection	14 (10.7)	19 (13.9)	33 (12.3)
• GVHD	4 (3.1)	7 (5.1)	11 (4.1)
• Liver toxicity	4 (3.1)	1 (0.7)	5 (1.9)
• Hemorrhage	10 (7.6)	7 (5.1)	17 (6.3)
• Other^	23 (17.6)	31 (22.6)	54 (20.1)

Source: FDA analysis
*More than 1 mechanism of death could have been selected per patient; therefore column totals may be higher than total number of deaths.
^ Other includes all mechanisms not included in predefined categories (e.g. cardiac failure, respiratory distress, multi-organ failure)

7.3.1.1 Early mortality

In ALFA-0701, early mortality (defined as death within the first 30 days of treatment) occurred in 4% of patients in the GO arm compared with 2% of patients in the control arm. Of the 5 deaths occurring in the GO arm, 4 were determined to be treatment-related: 2 patients died of CNS hemorrhage, 1 of hemorrhagic shock, and 1 died of VOD. In the control arm, there were 3 deaths overall, including one treatment-related death, which was due to sepsis in the setting of bone marrow aplasia.

Figure 9. IPD Meta-Analysis – 30-Day Mortality



Source: Applicant-submitted Summary of Clinical Safety Figure 2

In this figure provided by the applicant, the IPD meta-analysis supports a trend towards a reduction in the odds ratio for early mortality with reduced doses of GO. This trend persisted when results from published data were considered (See Appendix 3, Figure 10). In particular, the disparity in 30-day mortality between treatment arms in ALFA-0701 is lower than in the confirmatory trial SWOG S0106 with odds ratios of 1.99 and 3.58, respectively. This suggests that the 3 mg/m^2 fractionated GO schedule is safer with regards to early mortality.

7.3.1.2 Fatal treatment-related adverse events

Treatment-related deaths were identified based on relationship of fatal SAEs classified by Wyeth as related to any study treatment based on the SAE report, Grade 5 events (or infection events indicating the patient withdrew from the study) considered related to any study treatment or deaths classified as

study treatment toxicity. The most common fatal adverse events were hemorrhage, sepsis, and VOD/liver toxicity.

FDA independently adjudicated all deaths in ALFA-0701. There were 8 deaths in the GO arm considered by FDA to be at least possibly related to treatment. Three cases were due to VOD and four cases were hemorrhage-related. In the control arm, only 3 deaths were considered by FDA to be at least possibly related to treatment. All 3 of these deaths were due to infection/sepsis.

Table 40. ALFA-0701 – Treatment-Related Deaths as Adjudicated by FDA and Applicant

			FDA Adjudication		Applicant Adjudication	
Treatment Arm	**Patient ID**	**Day of Death**	**FDA Root COD**	**Related**	**Applicant COD**	**Related**
GO+DA	(b) (6)	34	Suspected cardiac cause	Related	Suspected cardiac cause (COD unknown despite autopsy)	Related (unable to rule out)
GO+DA		428	VOD	Related	Liver toxicity	Not related
GO+DA		14	Mixed shock w/ hemorrhagic shock	Related	Progressive disease, Sepsis. Hemorrhage	Not related Related Related
GO+DA		177	VOD	Related	VOD	Related
GO+DA		19	CNS hemorrhage	Related	Hemorrhage	Related
GO+DA		21	VOD	Related	VOD	Related
GO+DA		7	CNS hemorrhage	Related	Hemorrhage	Related
GO+DA		56	CNS hemorrhage	Related	Acute subdural hematoma and thrombocytopenia	Related
DA		1081	Infection	Not related	Infection, Thrombocytopenia	Not related Related
DA		182	Infection	Related	Septic shock, Candida sepsis	Related
DA		246	Progressive disease	Not related	Progressive disease, Multiple organ failure, Thrombocytopenia	Not related Not related Related
DA		28	Infection	Related	Sepsis, cardiopulmonary failure	Related
DA		101	Infection	Related	Sepsis, *Candida tropicalis* and *Staphylococcus epidermidis* septicemia	Related

Source: FDA Analysis

Descriptions from CRFs are provided below for cases in which the FDA adjudication disagreed with the applicant's with regards to root COD, relatedness to treatment, and/or classification as a treatment-related fatality.

Patient (b) (6) was a 64 year old woman randomized to the GO arm with normal baseline LFTs who developed Grade 4 VOD 2 days after starting HSCT conditioning with fludarabine and busulfan. She completed conditioning and received her transplant prior to starting treatment with defibrotide. This was followed by 3 days of clinical and laboratory deterioration. Her defibrotide dose was increased, and after 10 days of treatment there was an improvement in liver abnormalities lasting 48-72 hours (lab values not provided). She then experienced cholestatic injury with hepatocellular injury and respiratory distress leading to death. The applicant considered this a non-treatment-related fatality because her liver abnormalities temporarily improved; however, 48-72 hours of improving labs do not exclude VOD as a contributory factor in this patient's death.

Patient (b) (6) was a 65 year old woman randomized to the GO arm who experienced a fall with Grade 3 hematoma on day 12 of induction. She was aplastic with a platelet count was 21,000/mm^3, and she subsequently developed Grade 3 hemorrhage with progression to hemorrhagic shock necessitating multiple PRBC transfusions as well as platelets and FFP. Ultimately, she died of multi-organ failure induced by sepsis (unclear origin) and hemorrhagic shock. Although the applicant CSR lists this patient's primary COD as "progressive disease," there is no evidence of this from her laboratory values or CRF narrative. In fact, the narrative states that the patient died "due to progressive disease (haemorrhage, septic shock and multi-organ failure)." This description of "progressive disease" appears to refer to the evolution of hemorrhagic and septic shock to multi-organ failure, not to progression of her AML.

Patient (b) (6) was a 53 year old man randomized to the DA arm who died of infection 990 days after the last dose of study treatment (assessed as unrelated to treatment). His narrative states that his platelet count remained low (20,000/mm^3) "at the time of last contact" which was more than 2 years prior to his death. There is no indication that low platelets contributed to his death.

Patient (b) (6) was a 65 year old man randomized to the DA arm who died of progressive disease and multi-organ failure. Platelet counts reported in the CFR were all above 100,000/mm^3 range for the 5 months prior to his death, and he has no recorded lab values to suggest that he was thrombocytopenic at time of death or that low platelets could have contributed to his death.

Reviewer Comment: The incidence of treatment-related mortality was higher (6%) in the GO arm compared with the control (2%). However, overall in ALFA-0701, TRM was low. The fatalities that were more common with GO were due to VOD and hemorrhage, whereas all TRM in the DA arm were due to infection. VOD and hemorrhage should be prominently addressed in the label.

7.3.2 Serious Adverse Events

CHV Predefined TEAEs

CHV predefined Grade 3-4 TEAEs observed with a higher incidence (>5% difference) in the GO arm compared with the control arm included hemorrhage (90% vs 78%), mucosal toxicity (16% vs 6%), pain (15% vs 4%), and composite of nausea, vomiting, and diarrhea (17% vs 10%). No further details are available regarding the components of these general terms.

ALFA-0701 Retrospective Data Collection SAEs

67% of patients treated with GO had an SAE compared with 56% of patients treated with DA. The distribution of SAEs by System Organ Class is shown in Table 41.

Table 41. ALFA-0701 – Serious Adverse Events by MedDRA SOC – As-treated population

	GO + DA N = 131		DA N = 137		
System Organ Class	**Number of subjects**	**Proportion (%)**	**Number of subjects**	**Proportion (%)**	**Risk difference**
Any Class	**88**	**67**	**76**	**56**	**11**
Blood and lymphatic system disorders	52	40	19	14	26
Skin and subcutaneous tissue disorders	69	53	45	33	20
Respiratory, thoracic and mediastinal disorders	88	67	66	48	19
Gastrointestinal disorders	63	48	44	32	16
Eye disorders	17	13	4	3	10
Renal and urinary disorders	31	24	19	14	10
Vascular disorders	41	31	31	23	9
Hepatobiliary disorders	19	15	8	6	9
General disorders and administration site conditions	50	38	44	32	6
Injury, poisoning and procedural complications	21	16	17	12	4
Nervous system disorders	8	6	4	3	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	5	2	1	3
Metabolism and nutrition disorders	4	3	0	0	3

Source: FDA Analysis

61% of patients in the GO arm were reported to have had a treatment-related SAE compared with 42% of patients in the control arm. The most common treatment-related SAEs that were higher in the GO arm (>3% risk difference) were thrombocytopenia (24% vs 4%), febrile bone marrow aplasia (9% vs 5%), bacterial sepsis (7% vs 0%), acute kidney injury (4% vs 0%), VOD (4% vs 0%), and hepatocellular injury (3% vs 0%). A more detailed discussion of significant adverse events is found in Section 7.3.4.

IPD Meta-analysis

Safety data from the studies in the IPD-meta-analysis were available only for Grade 3-4 adverse events of specific predefined high level terms. Given the limitations of the available data it was not possible to perform a more in depth safety analysis.

In general, the safety findings from the meta-analysis appear similar to the results from ALFA-0701. The proportion of patients experiencing any SAE was higher in the GO arm (32% vs 26%). Specific categories of AE that were higher in the GO arm included Grade ≥3 VOD (1.1% vs 0%) and Grade ≥3

hemorrhage (7% vs 4%). Composite nausea/vomiting/diarrhea and "neurologic" AEs were also noted to be higher in the GO arm.

For two of the five studies, there was a second randomization to GO. In AML15, 20% of patients in the control arm were randomized to GO consolidation. In SWOG S0106, 14% of patients in the control arm were randomized to GO maintenance. Due to the concern for confounding, FDA performed an analysis censored at induction (Table 42). Our analysis confirmed higher rates of any Grade 3-4 AE, Grade ≥3 hemorrhage, and Grade ≥3 VOD in the GO arm compared to the control.

Table 42. IPD Meta-Analysis – Safety Events Censored after Induction

Outcome	GO (%)	No GO (%)	OR	95% CI low	95% CI high	p
Any Grade 3-4 AE	1121 (67.4)	1043 (62.5)	1.24	1.07	1.43	<0.01
Grade 3-4 VOD	15 (0.9)	0 (0)	31.38	1.88	524.85	0.01
Grade 3-4 Hemorrhage	108 (6.5)	60 (3.6)	1.86	1.35	2.57	<0.01
Grade 3-4 Neurologic	45 (2.7)	29 (1.7)	1.57	0.98	2.52	0.06
Grade 3-4 N/V/D	329 (20.1)	292 (17.8)	1.16	0.97	1.38	0.1
Grade 3-4 Infection	474 (30.8)	448 (29.0)	1.09	0.93	1.27	0.27

Source: FDA analysis

7.3.3 Dropouts and/or Discontinuations

Overall, more TEAEs associated with permanent discontinuation of study drug were reported in the GO arm than in the control arm: 41 (31%) patients versus 10 (7%) patients, respectively in the as-treated population. TEAEs in the GO arm which primarily account for this difference were thrombocytopenia in 20 (15%) patients versus no patients in the control arm, and hepatotoxicity disorders in 9 (7%) patients (including 4 patients with VOD) in the GO arm versus 1 (<1%) patient in the control arm.

Of the 41 patients who discontinued GO due to an adverse event, 16 continued treatment with DA. 12 of those patients discontinued GO due to thrombocytopenia. 1 patient discontinued GO due to VOD, 1 due to hepatocellular injury, and 2 patients discontinued GO due to Grade 2-3 hepatotoxicity (laboratory elevations only).

3 other patients discontinued GO at the discretion of the primary investigator and continued on DA alone. 1 patient had persistence of CR, 1 had a planned transplant and received consolidation 2 without GO, and 1 was eligible per protocol but did not receive GO in consolidation 2.

7.3.4 Significant Adverse Events

Given the historical clinical experience with GO monotherapy and the potential adverse events for similar drugs in the drug class described in Section 7.2.6, detailed analyses were performed on several adverse events of special interest (AESI). Rates of infection were similar between arms, and infusion reactions and tumor lysis syndrome were rare. Events that were higher in the GO arm included VOD, hemorrhage, and prolonged thrombocytopenia.

7.3.4.1 Veno-Occlusive Disease

In ALFA-0701, 6 patients (4.6%) in the GO arm developed VOD, and 3 cases were fatal. Additionally, 2 patients in the control arm developed VOD after receiving compassionate use GO for relapsed disease. Across the studies included in the meta-analysis there were 19 patients (1.1%) treated with GO who developed VOD compared with no patients who did not receive GO, and there was a trend towards reduction in the imbalance in VOD between treatment arms with the 3 mg/m^2 single dose of GO (See Appendix 3, Figure 11).

It is important to note that in their analysis of VOD incidence in both ALFA-0701 and in the meta-analysis, the applicant included the two patients in ALFA-0701 who were randomized to the control arm but developed VOD after receiving GO compassionate use in their reports. However, no patients in these trials developed VOD without first receiving GO.

The pediatric trial AAML0531 included treatment with more intense chemotherapy and busulfan-containing HSCT preparative regimen. In this trial, patients in the control arm also developed VOD; however AAML0531 had the lowest disparity in VOD incidence between arms (3.5% with GO vs 2.5% with control) (Source: COG AAML0531 SPR) of all trials examined.

VOD Timing in Relationship to Transplant

In ALFA-0701, 7 of 8 patients developed VOD without prior transplant. One of those 7 patients went on to develop VOD a second time a few days following transplant, and the remaining patient developed VOD 25 days after transplant. In the IPD meta-analysis, 15 of the 18 total reported cases of Grade 3-4 VOD occurred during induction.

In contrast, in children enrolled on AAML0531 who received much higher intensity chemotherapy as well as a transplant preparative regimen including busulfan, 71% (22/31) of patients who developed VOD did so during stem cell transplantation. Of the remaining VOD events, 5 occurred in Induction 1, 1 in Intensification 1 and 2, and 4 in Intensification 3. (Source: AAML0531 SPR)

Reviewer comment: Although the FDA meta-analysis discussed in Section 6.1.8 seemed to show a decrease in VOD incidence (zero) using 3 mg/m^2 fractionated GO as a monotherapy, the incidence of VOD with 3 mg/m^2 fractionated GO in combination with DA is in fact similar to the VOD incidence seen with the 9 mg/m^2 GO monotherapy dose (See Table 28).

With regards to the timing of VOD in relation to transplantation, in the adult trials, VOD with GO appears to be independent of transplantation with most events occurring without prior transplant. However, with the higher intensity chemotherapy regimen in combination with busulfan HSCT prep used in children, a majority of VOD events were associated with transplantation.

Non-VOD hepatotoxicity TEAEs

23 patients experienced non-VOD hepatotoxicity events, 15 in the GO arm and 8 in the control arm. These events were not graded using CTCAE grading criteria, but 13 patients in the GO arm and 8 patients in the control arm had events labeled "serious." Recovery of hepatotoxicity TEAEs was reported for 13 patients in the GO arm and all of the 8 patients in the control arm. In the GO arm, 1 patient did not recover (drug-induced liver injury due to voriconazole) and 1 patient died from hepatotoxicity and Grade 5 VOD (the two events were coded separately with the same start date).

7.3.4.2 Hemorrhage

Hemorrhage occurred at a higher rate in patients treated with GO both overall and in each phase of treatment. Grade 3 or higher hemorrhage was also more frequent in patients treated with GO compared with patients treated with DA alone (Table 43). Of note, ALFA-0701 had a higher overall risk difference for Grade 3 and higher hemorrhage (in any phase) than all other trials in the meta-analysis or literature review, with a risk difference of 13.4% with GO + DA over DA alone (See Appendix 3, Figure 12).

Table 43. ALFA-0701 – Hemorrhage Events by Treatment Phase – As-treated population

	GO + DA n (%)	DA n (%)
Induction	N=131	N=137
Any Grade Hemorrhage	110 (84)	90 (66)
Grade 3+ Hemorrhage	24 (18)	12 (9)
Consolidation 1	N=91	N=103
Any Grade Hemorrhage	55 (60)	35 (34)
Grade 3+ Hemorrhage	5 (5)	0 (0)
Consolidation 2	N=64	N=107
Any Grade Hemorrhage	40 (63)	46 (43)
Grade 3+ Hemorrhage	4 (6)	0 (0)
Any Phase	N=131	N=137
Any Grade Hemorrhage	119 (91)	108 (79)
Grade 3+ Hemorrhage	30 (23)	13 (9)

Source: FDA analysis – Hemorrhage SMQ narrow excluding lab terms
*Note: the same patient may have had hemorrhage events in several phases of treatment resulting in an "Any Phase" total that differs from the sum of each arm.

Treatment-related Grade ≥4 hemorrhage events occurred only in the GO arm. Grade 4 events with GO included gastrointestinal hemorrhage, hemorrhage, and 2 patients with pulmonary alveolar hemorrhage.

Fatal treatment-related hemorrhage was reported in 4 patients in the GO arm compared with none in patients treated with DA alone. Three of those events were CNS hemorrhages (cerebral hematoma, intracranial hematoma, subdural hematoma) and one was due in part to hemorrhagic shock subsequent to hemorrhage after a fall. One patient in the control arm had a non-treatment related Grade 5 cerebral hemorrhage attributed to disease progression; the event occurred on day 2 of induction in the setting of hyperleukocytosis (WBC >100,000/mm^3), rapid disease progression, and DIC.

A higher proportion of patients in the GO arm who had a hemorrhage event had a corresponding platelet count of <20,000/mm^3 within 3 days prior to the event. This suggests that prolonged thrombocytopenia due to treatment with GO may be a significant contributing factor to the development of hemorrhage in these patients.

Table 44. ALFA-0701 – Hemorrhage Events and Corresponding Platelet Counts

	GO + DA	DA
Patients with Any Grade Hemorrhage – n	119	108
Platelet count within 3 days prior to onset – n (%)		
• <20,000/mm^3	105 (88)	76 (70)
• ≥20,000/mm^3	14 (12)	30 (28)
• Unknown	0 (0)	2 (2)
Patients with Grade ≥ 3 Hemorrhage – n	30	13
Platelet count within 3 days prior to onset – n (%)		
• <20,000/mm^3	22 (73)	6 (46)
• ≥20,000/mm^3	8 (27)	7 (54)
• Unknown	0 (0)	0 (0)

Source: Applicant response to IR, SDN 40

7.3.4.3 Myelosuppression

Anemia

Anemia was an expected adverse event with both GO and DA and was not significantly different between arms. As discussed in Section 6.1.7.3, PRBC transfusion requirements were the same with a median number of transfusions of 14 in both arms.

Neutropenia

Neutropenia was an expected adverse event with both GO and DA. Time to neutrophil recovery was similar between arms in all phases of treatment (Table 45).

Table 45. ALFA-0701 – Neutrophil Recovery

	Median time to ANC > 0.5 Gi/mm^3 Days (25-75 percentile)		Median time to ANC > 1.0 Gi/mm^3 Days (25-75 percentile)	
	GO+DA	DA	GO+DA	DA
Induction	24 (22-28)	23 (20-26)	25 (23-28)	25 (22-29)
Consolidation 1	21 (18-26)	22 (19-25)	24 (19-33)	24 (20-28)
Consolidation 2	22 (17-27)	23 (17-26)	27 (21-34)	26 (21-33)

Source: FDA Analysis

Thrombocytopenia

Although >98% of patients in both arms experienced Grade 4 thrombocytopenia, the median times to recovery of platelets, both overall and in each phase of treatment, were longer for patients in the GO arm than in the control arm. Correspondingly, as discussed in Section 6.1.6.3, patients in the GO arm required significantly more platelet transfusions. Furthermore, a delay in time to platelet recovery (>100,000/mm^3) of greater than 45 days was reported in a larger percentage of patients in the GO arm in each phase of treatment. Per protocol, such delays would result in permanent discontinuation of GO.

In Table 46, of the patients with prolonged thrombocytopenia reported in the control arm, 2/6 patients in Consolidation 1 and 8/28 patients in Consolidation 2 had been treated with GO in the previous cycle and had GO permanently discontinued due to prolonged thrombocytopenia. This suggests that the effect may be cumulative. The mechanism of this prolonged thrombocytopenia is unclear, but the meta-analysis shows a trend for reduced imbalance in thrombocytopenia with reduced GO dose.

Table 46. ALFA-0701 – Platelet Recovery and Prolonged Thrombocytopenia

	Median time to Plt > 100,000 cells/mm^3 Days (25-75 percentile)		Prolonged thrombocytopenia* n (%)	
	GO+DA	DA	GO+DA	DA
Induction	34 (27-41)	29 (26-35)	24 (18%)	12 (9%)
Consolidation 1	34 (27-44)	27 (23-35)	22 (24%)	6 (6%)
Consolidation 2	42 (30-59)	34 (27-47)	24 (38%)	28 (26%)

Source: FDA Analysis
*Prolonged thrombocytopenia = time to platelet recovery (>100,000 cells/mm^3) > 45 days

Comparison of patients treated before and after Amendment 4

ALFA-0701 protocol Amendment 4 permanently discontinued GO for persistent moderate thrombocytopenia (platelets ≥50,000/mm^3 and <100,000/mm^3) lasting 14 or more days after the scheduled date of the next cycle. If platelets <50,000/mm^3 persisted for more than 14 days, both GO and DA were to be discontinued.

19 patients treated prior to Amendment 4 continued treatment with GO + DA or DA alone who would have otherwise discontinued all treatment. Of the patients who failed to recover platelets >50,000/mm^3 by day 45 (and therefore should discontinue all treatment per protocol), a smaller proportion treated after Amendment 4 had Grade ≥3 hemorrhage compared with those treated before (16% vs 21%) (Table 48).

Table 47. ALFA-0701 – Treatment of Patients with Prolonged Platelet Recovery Before and After Amendment 4

	Before Amendment 4		After Amendment 4	
Patients treated	N=178		N=90	
Patients without platelet recovery >50,000/mm^3 by day 45	47		19	
	GO + DA	DA	GO + DA	DA
Induction	15	8	4	2
Outcome:				
• Continued GO	9	-	1	-
• Continued DA only	1	3	2	2
• Discontinued both	5[a]	5[a]	1[b]	-
Consolidation 1	14	2	4	1
Outcome:				
• Continued GO	6	-	1	-
• Continued DA only	3	2[d]	2	1
• Discontinued both	5[c]	-	1	-
Consolidation 2	10	13[e]	5	8

Source: FDA Analysis
[a] 7/10 discontinued treatment due to resistant disease, 1 in the GO arm discontinued due to thrombocytopenia
[b] This patient discontinued treatment due to a subdural hematoma.
[c] 4/5 discontinued both drugs due to thrombocytopenia
[d] 1 previously treated with GO
[e] 4 previously treated with GO

Table 48. Patients With Hemorrhage Events Before and After ALFA-0701 Amendment 4

	Before Amendment 4	After Amendment 4
All patients	N=178	N=90
Any grade Hemorrhage[a]	148 (83%)	79 (88%)
Grade ≥3	29 (16%)	14 (16%)
Patients with platelet recovery to >100,000/mm^3 >45 days	N=65	N=25
Any grade Hemorrhage[a]	59 (91%)	24 (96%)
Grade ≥3	15 (23%)	6 (24%)

Patients with platelet recovery to >50,000/mm^3 >45 days	N=47	N=19
Any grade Hemorrhage[a]	44 (94%)	19 (100%)
Grade ≥3	10 (21%)	3 (16%)

Source: FDA Analysis
a. Hemorrhage Narrow SMQ excl labs

7.3.5 Submission Specific Primary Safety Concerns

See above.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 49 shows ALFA-0701 adverse events occurring during induction in order of risk difference of GO compared with the control arm. Adverse events that were higher in the GO arm were due primarily to bleeding and to a lesser extent infection. VOD was also greater in the GO arm (3% vs 0%). These differences in rates occurred during each phase of treatment. Tables for adverse events in consolidation 1 and 2 may be found in Appendix 3, Table 58 and Table 59.

Table 49. ALFA-0701 – Adverse Events in Induction

	GO + DA (N = 131)		DA (N = 137)		
Preferred Term	**Number of subjects**	**Proportion (%)**	**Number of subjects**	**Proportion (%)**	**Risk Difference**
Epistaxis	62	47	43	31	16
Purpura	29	22	17	12	10
Blood blister	18	14	7	5	9
Mouth haemorrhage	16	12	5	4	9
Petechiae	25	19	16	12	7
Haemoptysis	16	12	7	5	7
Device related infection	24	18	16	12	7
Gingival bleeding	19	15	12	9	6
Thrombocytopenia	7	5	0	0	5
Haematuria	19	15	13	9	5
Catheter site haematoma	10	8	4	3	5
Melaena	5	4	0	0	4
Post procedural haemorrhage	8	6	4	3	3
Conjunctival haemorrhage	6	5	2	1	3
Venoocclusive liver disease	4	3	0	0	3

Source: FDA analysis

7.4.2 Laboratory Findings

As seen in Table 50, in ALFA-0701, Grade 3-4 alkaline phosphatase, bilirubin, and AST elevations were more common in the GO arm compared with the control arm. ALT elevations were not significantly higher with GO.

There were 8 potential Hy's law cases – 5 cases in the GO arm and 3 in the control arm. In the GO arm, 1 patient died of VOD and 1 died of sepsis/ progressive disease. In the control arm, 1 patient recovered after discontinuation of chemotherapy. The remaining 5/8 patients had resolution of their abnormal liver tests without discontinuation of treatment.

The meta-analysis data show a trend for decreased imbalance in Grade 3-4 bilirubin and AST elevations with decreasing GO dose.

Table 50. ALFA-0701 – Laboratory Values of Interest: Shifts in Subjects with Baseline Grade ≤2 Values

	GO + DA		DA	
Laboratory Abnormality	**Subjects (n) with Baseline Gr ≤2**	**Progressed to Gr ≥3 at least once (n, %)**	**Subjects (n) with Baseline Gr ≤2**	**Progressed to Gr ≥3 at least once (n, %)**
Neutropenia	47	47 (100%)	46	46 (100%)
Thrombocytopenia	86	86 (100%)	101	101 (100%)
Anemia	108	100 (93%)	119	114 (96%)
Alkaline phosphatase increased	130	16 (12%)	130	4 (3%)
AST increased	127	15 (12%)	133	9 (7%)
ALT increased	125	14 (11%)	133	23 (17%)
Hyperbilirubinemia	120	8 (7%)	128	5 (4%)

Source: FDA Analysis
Abbreviations: ALT – alanine aminotransferase; AST – aspartate aminotransferase

Other Grade 3-4 laboratory shifts by arm are summarized in Table 51, and include any abnormality that occurred in ≥5% of patients in the GO arm. Other than the toxicities listed below and the hepatotoxicites described above in Table 50, no other laboratory shifts occurred more frequently on the GO arm than on the control arm.

Table 51. ALFA-0701 – Other Laboratory Values: Shifts in Subjects with Baseline Grade ≤2 Values

	GO + DA		DA	
Laboratory Abnormality	**Subjects (n) with Baseline Gr ≤2**	**Progressed to Gr ≥3 at least once (n, %)**	**Subjects (n) with Baseline Gr ≤2**	**Progressed to Gr ≥3 at least once (n, %)**
Hypophosphatemia	117	75 (64%)	128	53 (41%)
Hypokalemia	127	74 (58%)	133	44 (33%)
Hyponatremia	129	57 (44%)	134	37 (28%)

Hyperglycemia	104	20 (19%)	116	25 (22%)
Hypocalcemia	124	10 (8%)	132	14 (11%)
Hypoalbuminemia	60	4 (7%)	71	9 (13%)

Source: FDA Analysis

7.4.3 Vital Signs

Vital sign data were not included in the retrospective data collection and are not present in the submitted datasets.

Reviewer comment: See clinical review of GO monotherapy (Ori-2) for a discussion of the vital sign data with GO monotherapy. There were no significant vital sign instabilities noted at the time of the original review, and GO removal from the market was not related to vital sign concerns. This does not change the risk:benefit analysis for this indication.

7.4.4 Electrocardiograms (ECGs)

There are no QTc data in this submission. Baseline ECGs and baseline and follow-up left ventricular ejection fraction results from echocardiograms were provided, where available, in Listing 16.2.8.4 of the ALFA-0701 CSR. The difference between treatment arms in incidence of Grade 3 left ventricular ejection systolic dysfunction reported in the echocardiogram results was small (2% with GO + DA vs 4% with DA). Post-baseline left ventricular ejection fraction results were missing from 79 (60.3%) patients in the GO arm and 78 (56.9%) patients in the control arm.

The proportion of patients with cardiac-related AEs was not significantly different (Table 52).

Table 52. ALFA-0701 – Cardiac Adverse Events

	GO + DA		DA		
Preferred Term	**N**	**(%)**	**N**	**(%)**	**P-value**
Total	5	(3)	8	(5)	0.57
Acute coronary syndrome	1	(0)	.	.	.
Aortic valve disease	1	(0)	.	.	.
Arrhythmia	1	(0)	.	.	.
Atrial fibrillation	.	.	2	(1)	.
Cardiac disorder	.	.	1	(0)	.
Cardiac failure	.	.	1	(0)	.
Cardiopulmonary failure	.	.	1	(0)	.
Left ventricular dysfunction	.	.	1	(0)	.
Left ventricular fail	1	(0)	1	(0)	1.00
Tachycardia	.	.	1	(0)	.
Ventricular hypokinesis	1	(0)	.	.	.

Source: FDA Analysis

7.4.5 Special Safety Studies/Clinical Trials

Key Safety Outcomes in Other Published Trials

Together with the results from studies included in the meta-analysis, it was noted that the risks for early mortality and VOD appeared to be lower with the 3 mg/m^2 dose of GO compared to fractionated or higher doses in combination with chemotherapy. With regards to high-grade hemorrhage in GO + chemotherapy, the risk appears to increase as the GO dose increases. However, fractionated GO dosing in ALFA-0701 resulted in a higher risk of Grade ≥3 hemorrhage than reported with any other combination dose or with monotherapy GO dosing. See Appendix 3, Figure 10, Figure 11, and Figure 12.

7.4.6 Immunogenicity

There were no immunogenicity studies performed in ALFA-0701. See clinical review for Ori-2 for data from studies of GO monotherapy.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As discussed in the sections above, no dose finding studies including the fractionated GO dose schedule have been performed. However, a comparison of the studies included in the IPD meta-analysis and literature review appears to show a trend for decreased imbalance between GO and No GO arms for toxicities including early mortality, VOD, hemorrhage, and hepatotoxicity.

Taken together, these data indirectly support the Applicant's suggestion that the GO regimen of 3 mg/m^2 days 1, 4 and 7 may be less toxic than GO 6 mg/m^2 in combination with DA. However, there are no dose-ranging trials comparing the lower-dose regimens (i.e., 3 mg/m^2 day 1 only vs days 1, 4 and 7); therefore, it is not clear that GO 3 mg/m^2 days 1, 4 and 7 would provide optimal safety.

7.5.2 Time Dependency for Adverse Events

All adverse events of special interest in ALFA-0701 occurred during all phases of treatment.

7.5.3 Drug-Demographic Interactions

There are insufficient data in the submission for this indication to determine drug-demographic interactions. See clinical review for Ori-2.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There are no data regarding human carcinogenicity in ALFA-0701. See clinical review for Ori-2.

7.6.2 Human Reproduction and Pregnancy Data

There are no human reproduction and pregnancy data available for this indication. See clinical review for Ori-2.

7.6.3 Pediatrics and Assessment of Effects on Growth

There are no data on the effects of GO on growth in this submission.

The following is a discussion of the safety of GO plus chemotherapy from AAML0531. All findings presented below are from Gamis, 2014 or AAML0531 Fall 2013 Study Progress Report (SPR) (data reported by COG but submitted by the applicant at FDA's request), whichever had more comprehensive information available for the toxicity being described.

Early Mortality
Induction death was 2.3% with GO vs 2.2% in the chemotherapy only arm (Gamis, 2014). Neither the publication nor the SPR break these deaths down by treatment arm. According to the table of "Deaths on treatment or within 30 days of being off protocol therapy" on SPR page 45, in Induction 1, 7 patients died of multi-organ failure, 4 died of hemorrhage, 3 died of infection, 2 died of disease, and 3 died of other/unknown causes.

Treatment-related mortality
Cumulative TRM from enrollment through last follow-up without relapse or induction failure was higher in GO recipients with 5-year TRM with GO of 8.6% ± 2.5% vs No GO 5.9%±2.1%. This difference was primarily accounted for by low risk patients during Intensification 2 and 3 who had infections before neutrophil recovery (GO 8 patients, No GO 2 patients). See Table 54 (Gamis, 2014).

Infection
According to the data in the SPR, the incidence of Grade ≥3 infection is similar between arms in all phases of treatment. Given the limitations of the data available at the time of review, it is not possible to break down this information further. However, as discussed above, in the subset of patients with low risk disease who were neutropenic in intensification 2 and 3, there were more infection-related deaths in patients treated with GO.

VOD and hepatotoxicity

As previously discussed in section 7.3.4.1, data from the SPR show that the incidence of VOD overall in AAML0531 was low, occurring in 3.5% of patients in the GO arm compared with 2.5% in the control. In contrast to the adult trials which had no VOD in the chemotherapy only arms, the higher intensity chemotherapy and busulfan transplant preparative regimen given in this trial resulted in some patients in the control arm developing VOD.

Also, in contrast to the adult trials where VOD was seen predominantly during induction, 71% (22/31) of patients who developed VOD did so during stem cell transplantation. However, the seriousness of VOD was lower compared with cases seen in adults, and there were no cases of fatal VOD. Life-threatening VOD overall (0.6%), during HSCT (5/158 pts during HSCT), and chemotherapy (1/1022 pts) were evenly distributed between the arms.

According to the SPR, Grade 3-5 toxicity rates between the two arms were comparable using data compiled through March 31, 2010. Overall, hepatic grade 3-5 toxicities included ALT 19%, bilirubin 10%, and VOD 1%. Between arms, only ALT was slightly more prevalent (No GO 4%, GO 9%).

Platelet and Neutrophil Recovery Time

The disparity between treatment arms for time to platelet recovery in AAML0531 is much lower than that seen in ALFA-0701. As expected, the time to recovery of both neutrophil and platelet counts increased with further courses of treatment, with a significant increase in time to count recovery in the last two courses (Table 54). Posthoc analysis to examine causes for TRM differences found a higher proportion of GO patients during Intensification 2 with prolonged (>59 days) neutrophil recovery times (12.0% vs 6.3%; p=0.01) (Gamis, 2014).

Hemorrhage

Given the data presented in 7.3.4.2 regarding the risk of hemorrhage in ALFA-0701, incidence of hemorrhage was of interest in the review of this trial. Data from AAML0531 SPR Section III (Tables of adverse events by treatment phase) were evaluated for hemorrhage events and are presented below in Table 53.

While the risk difference is much lower than in ALFA-0701, it is interesting to note that the highest disparity in Grade ≥3 hemorrhage events between treatment arms occurred during phases of treatment in which GO was given. There were a total of 6 fatal hemorrhages reported in the SPR (p45-47), 4 in induction 1 (2 CNS hemorrhage, 2 pulmonary hemorrhage), 1 in induction 2 (fatal hemorrhage in the setting of disease progression), and 1 in intensification 2 (CNS hemorrhage). The treatment arms for those patients are not provided (although those who died of CNS hemorrhage can be extrapolated to have been in the GO arm from Table 53 below).

Table 53. AAML0531 – Hemorrhage Grade ≥3 Events

	Any Grade ≥3 Hemorrhage		Grade ≥3 Intracranial Hemorrhage	
	GO n (%)	No GO n (%)	GO n	No GO n
Induction 1*	31 (6)	16 (3)	6	1
Induction 2	13 (3)	12 (2)	0	1
Intensification 1	3 (<1)	1 (<1)	0	0
Intensification 2*	23 (5)	9 (2)	2	0
Intensification 3	2 (<1)	1 (<1)	0	0

Source: AAML0531 Fall 2103 SPR – data combined from Section III
*GO given in Induction 1 and Intensification 2

Table 54. AAML0531 – Toxicities by Course and Arm

AAML0531 – Toxicities by Course and Arm

Arm	IND1		IND2		INT1		INT2		INT3		SCT	
	No-GO (n = 511)	GO (n = 511)	No-GO (n = 474)	GO (n = 477)	No-GO (n = 417)	GO (n = 434)	No-GO (n = 302)	GO (n = 324)	No-GO (n = 259)	GO (n = 255)	No-GO (n = 75)	GO (n = 82)
Overall nonhematologic toxicity												
Any grade ≥ 3 toxicity												
No. of patients	389	388	305	311	312	317	261	284	216	217	61	71
%	76	76	64	65	75	73	86	88	83	85	81	87
Hematologic recovery*												
Median time to plts > 50,000, days	26	28	24	25	25	26	38	41	42	44	40	45
No. of patients with plts never > 50,000	103	104	75	79	73	62	98	115	78	67	13	14
Median time to ANC > 500, days	30	30	28	28	27	28	37	38	40	39	30	31
No. of patients who needed > 59 days for ANC recovery	1	0	1	0	0	0	19†	39†	9	11	3	1
No. of patients whose ANC was never > 500‡	125	121	78	70	62	49	42	53	47	44	6	6
Infection incidence, No. of patients												
Documented infection	178	182	175	169	206	209	209	224	173	173	41	46
Neutropenic fever	158	163	103	117	97	93	68	77	47	62	14	15
Therapy dose reduced, No. of patients	6	11	10	6	4	6	8	15	10	4	5	5
Toxic mortality during therapy												
Nonleukemic death, No. of patients	9	9	2	2	0	2	5	7	3	7	3	2
Course day of death												
Median	8	10	13, 25	12, 24	—	16, 21	53	59	18	30	50	53, 124
Range	1-56	0-28					14-93	9-88	15-19	17-41	49-60	
LR nonleukemic death, No. of patients	0	3	1	0	0	1	2	4	0	4	NA	NA
LR course day of death												
Median	—	19	13	—	—	21	63, 93	70	—	33	—	—
Range		0-20						59-88		17-42		

Abbreviations: ANC, absolute neutrophil count; GO, received gemtuzumab-ozogamicin; IND, induction course; INT, intensification course; LR, low risk; NA, not applicable; No-GO, did not receive gemtuzumab-ozogamicin (control arm); plts, platelets; SCT, stem-cell transplantation (matched-family and alternative donor).
*Hematologic recovery values do not include those patients who died during their respective courses.
†P = .01.
‡If ANC was never > 500, patient proceeded to next course before ANC recovery.

Source: Gamis, et al. 2014

Reviewer comment: Overall, the safety profile of AAML0531 is very similar to that of ALFA-0701. AAML0531 was a much larger trial. Early mortality was low. VOD, hepatotoxicity, and hemorrhage were present and higher in the GO arm than the control arm, but all were less common and had lower disparity between arms than in ALFA-0701. These data appear adequate to extend the indication to include children with newly-diagnosed CD33-positive AML.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no abuse potential for this product.

7.7 Additional Submissions / Safety Issues

Hyperleukocytosis

The protocol for ALFA-0701 included instructions for delaying the start of GO in patients with hyperleukocytosis (defined as WBC ≥30,000/mm^3). In response to an information request, the applicant identified 12 patients who may have been treated according to the protocol, but stated that "The limited scope of data collected during retrospective data collection in Study ALFA-0701 does not allow for identification of patients with hyperleukocytosis at study entry and whether or not they received additional treatment to reduce the WBC count on top of the study treatment modification recommended in the protocol."

FDA review of the submitted datasets found 27 patients in the GO arm who met the definition for hyperleukocytosis. Fewer than half of those patients may have been treated per protocol. There were no statistically significant differences in AEs between those treated per protocol and those who received GO on the regular schedule. One patient not treated per protocol developed tumor lysis syndrome (WBC >100); however, in the entire study only 2 patients had TLS (the other patient did not have hyperleukocytosis). There were no treatment-related deaths during induction in any of these patients. One patient not treated per protocol died on day 2 of induction due to progressive disease. (b) (4)

Table 55. ALFA-0701 – Hyperleukocytosis in the GO arm

Hyperleukocytosis treatment	Per protocol N = 12	Unknown N = 15
Median WBC (range)	62.9 (30-107.4)	44.5 (21.3-180.3)
Induction deaths	0	1
Induction failure	2	2
Tumor lysis syndrome	0	1

Source: FDA Analysis

8 Postmarket Experience

The pharmacovigilence review was not complete at the time of this review.

9 Appendices

Appendix 1. Randomized Clinical Studies of GO Combinations in AML

Table 56. Efficacy Results from Randomized Trials of GO Plus Chemotherapy for Newly-diagnosed AML

Study	# of patients	Median age (range)	Induction GO dose	Concurrent chemotherapy	CR (%) GO vs No GO OR, 95% CI	EFS/RFS (%) GO vs No GO HR, 95% CI	OS (%) GO vs No GO HR, 95% CI
***MRC AML15**	1113	49 (15-71)	3 mg/m^2 x 1 (d1)	DA, ADE, FLAG-Ida	82 vs 83 1.04 (0.76, 1.42) p = 0.8	5y RFS 39 vs 35 0.87 (0.73-1.02) p = 0.09	5y OS 43 vs 41 0.92 (0.79-1.08) p = 0.3
NCRI AML16	1115	67 (51-84)	3 mg/m^2 x 1 (d1)	DA, Dclof	62 vs 58 0.84 (0.66, 1.06) p = 0.04	3y RFS 21 vs 16 0.84 (0.71, 0.99) p = 0.04	3y OS 25 vs 20 0.87 (0.76-1.00) p = 0.5
Gamis, 2014: COG AAML0531	1070	9.7 (3mo-29.8y)	3 mg/m^2 x 1 (d1)	Pediatric SOC (DA+)	88 vs 85 0.76 (0.53-1.09) p = 0.14	3y EFS 52 vs 47 0.83 (0.70-0.99) p = 0.04	3y OS 69 vs 65 0.91 (0.74-1.13) p = 0.39
ALFA-0701	271	62 (50-70)	3 mg/m^2 x 3 (d1, 4, 7) Fractionated	DA	70 vs 70 0.98 (0.58, 1.64) p = 0.93	3y EFS 40 vs 14 0.56 (0.42-0.76) p = <0.001	3y OS 46 vs 37 0.81 (0.60-1.09) p = 0.16
Burnett, 2013: AML14/16	495	75 (54-90)	5 mg/m^2 x 1 (d1)	Low dose AraC	21 vs 11 0.46 (0.29-0.75) p = 0.002	12 mo RFS 31 vs 40 1.11 (0.73-1.67) p = 0.6	12 mo OS 55 vs 62 1.31 (0.86-2.01) p = 0.2
***SWOG S0106**	595	47 (18-60)	6 mg/m^2 x 1 (d4)	DA	69 vs 70 1.06 (0.75-1.50) p = 0.75	5y RFS 43 vs 42 0.97 (0.75-1.26) p = 0.40	5y OS 46 vs 50 1.13 (0.90-1.42) p = 0.59
GOELAMS AML 2006 IR	254	50 (18-60)	6 mg/m^2 x 1 (d4)	DA	92 vs 87 0.60 (0.26-1.34) p = 0.22	3y EFS 51 vs 33 HR not given	3y OS 53 vs 46 HR not given
Brunnberg, 2012	1019	68 (60-83)	6 mg/m^2 (d1), 4 mg/m^2 (d8)	7+GO vs 7+3	54 vs 55 1.03 (0.50-2.15) p = 0.93	% not given Median 5mo vs 2mo p = 0.40	% not given Median 10mo vs 9mo p = 0.84
Amadori, 2013: AML17	472	67 (61-75)	6 mg/m^2 x 2 (d1, 15)	GO pretx, MEC	36 vs 41 1.21 (0.84-1.76) p = 0.30	EFS 9 vs 7 1.08 (0.89-1.30) p = 0.36	5y OS 11 vs 14 1.20 (0.99-1.45) p = 0.07

Source: Applicant's ALFA-0701 CSR, IPD Meta-Analysis Report, FDA literature analysis

*SWOG S0106 – 2nd randomization to GO maintenance, AML15 – 2nd randomization to GO consolidation
Abbreviations: AraC, cytarabine; CI, confidence interval; DA, daunorubicin/cytarabine, ADE, cytarabine/ daunorubicin/etoposide; Dclof, daunorubicin/clofarabine; EFS, event-free survival; FLAG-Ida, fludarabine/ cytarabine/filgrastim/idarubicin; GO, gemtuzumab ozogamicin; HR, hazard ratio; MEC, mitoxantrone/etoposide/ cytarabine; OR, odds ratio; pretx, pretreatment; RFS, relapse-free survival; SOC, standard of care

Appendix 2. Additional Efficacy Evaluations.

Table 57. ALFA-0701 – PRBC Transfusions by Treatment Phase – As-treated population

	GO + DA	DA
Induction	N=131	N=137
• Patients receiving at least 1 transfusion, n (%)	130 (99)	134 (98)
• Median transfusions per patient (range)	8 (2-32)	6 (2-17)
Consolidation 1	N=91	N=103
• Patients receiving at least 1 transfusion, n (%)	87 (96)	102 (99)
• Median transfusions per patient (range)	4 (1-9)	4 (1-10)
Consolidation 2	N=64	N=107
• Patients receiving at least 1 transfusion, n (%)	60 (94)	97 (91)
• Median transfusions per patient (range)	4 (1-10)	4 (2-10)
Any Phase	N=131	N=137
• Patients receiving at least 1 transfusion, n (%)	130 (99)	135 (99)
• Median transfusions per patient (range)	14 (5-44)	14 (3-39)

Source: FDA Analysis

Appendix 3. Additional Safety Evaluations

Table 58. ALFA-0701 – Adverse Events in Consolidation 1

	GO + DA (N = 91)		DA (N = 103)		
Preferred Term	**Number of subjects**	**Proportion (%)**	**Number of subjects**	**Proportion (%)**	**Risk difference**
Epistaxis	33	36	10	10	27
Blood blister	12	13	3	3	10
Bacterial sepsis	8	9	0	0	9
Thrombocytopenia	10	11	3	3	8
Gingival bleeding	7	8	0	0	8
Petechiae	12	13	7	7	6
Device related sepsis	8	9	3	3	6
Purpura	7	8	2	2	6
Septic shock	5	5	1	1	5
Streptococcal sepsis	5	5	1	1	5
Escherichia bacteraemia	4	4	0	0	4
Haematuria	4	4	1	1	3
Mouth haemorrhage	4	4	1	1	3
Pneumonia	3	3	0	0	3

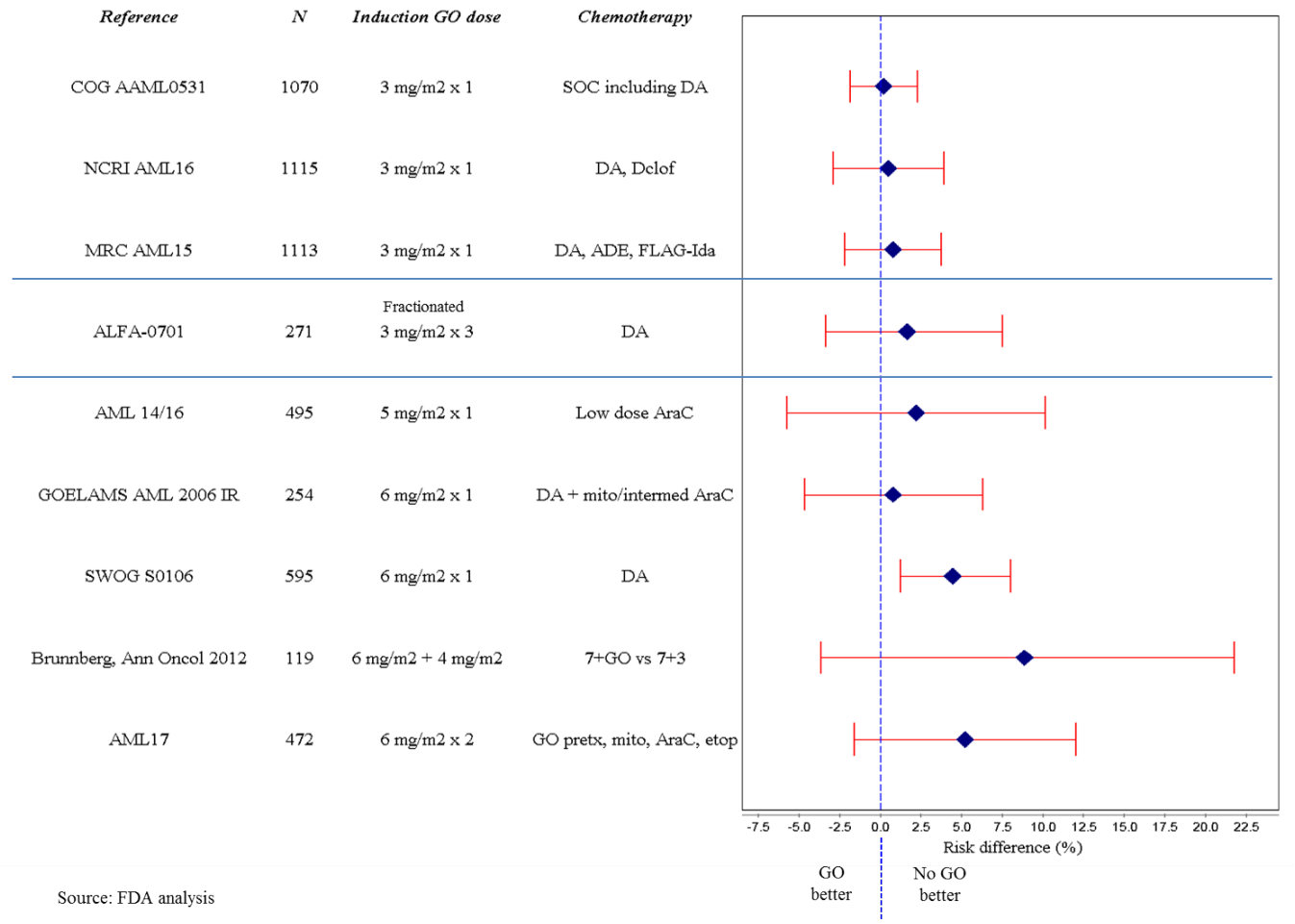
Source: FDA Analysis

Table 59. ALFA-0701 – Adverse Events in Consolidation 2

	GO + DA (N = 64)		DA (N = 107)		
Preferred Term	**Number of subjects**	**Proportion (%)**	**Number of subjects**	**Proportion (%)**	**Risk difference**
Epistaxis	26	41	17	16	25
Gingival bleeding	7	11	0	0	11
Escherichia sepsis	4	6	0	0	6
Catheter site haemorrhage	6	9	4	4	6
Conjunctival haemorrhage	3	5	1	1	4
Aspergillus infection	2	3	0	0	3
Clostridium difficile colitis	2	3	0	0	3
Enterococcal sepsis	2	3	0	0	3
Haematuria	2	3	0	0	3

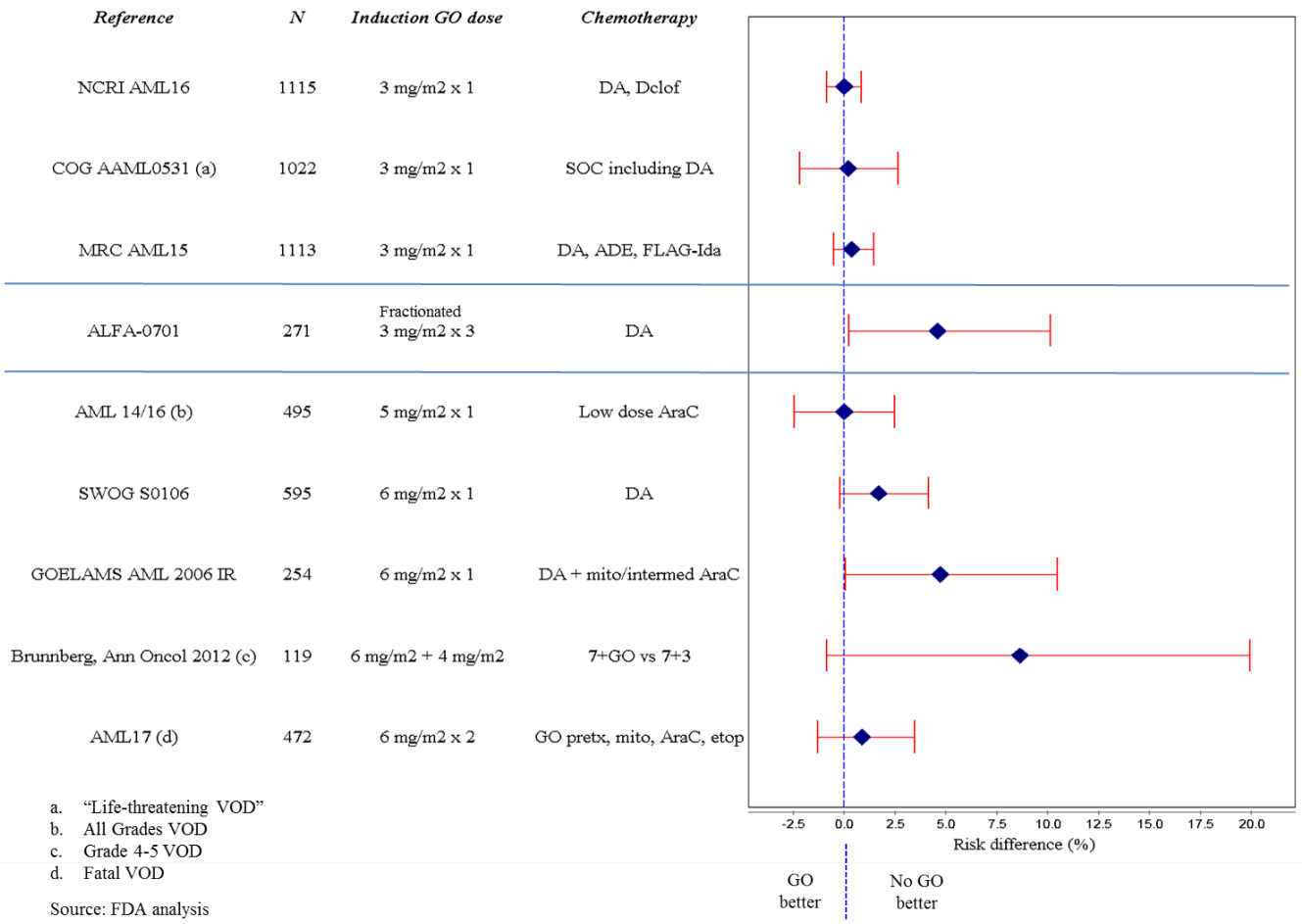
Source: FDA Analysis

Figure 10. GO Combination Therapy – Early Mortality



Source: FDA analysis

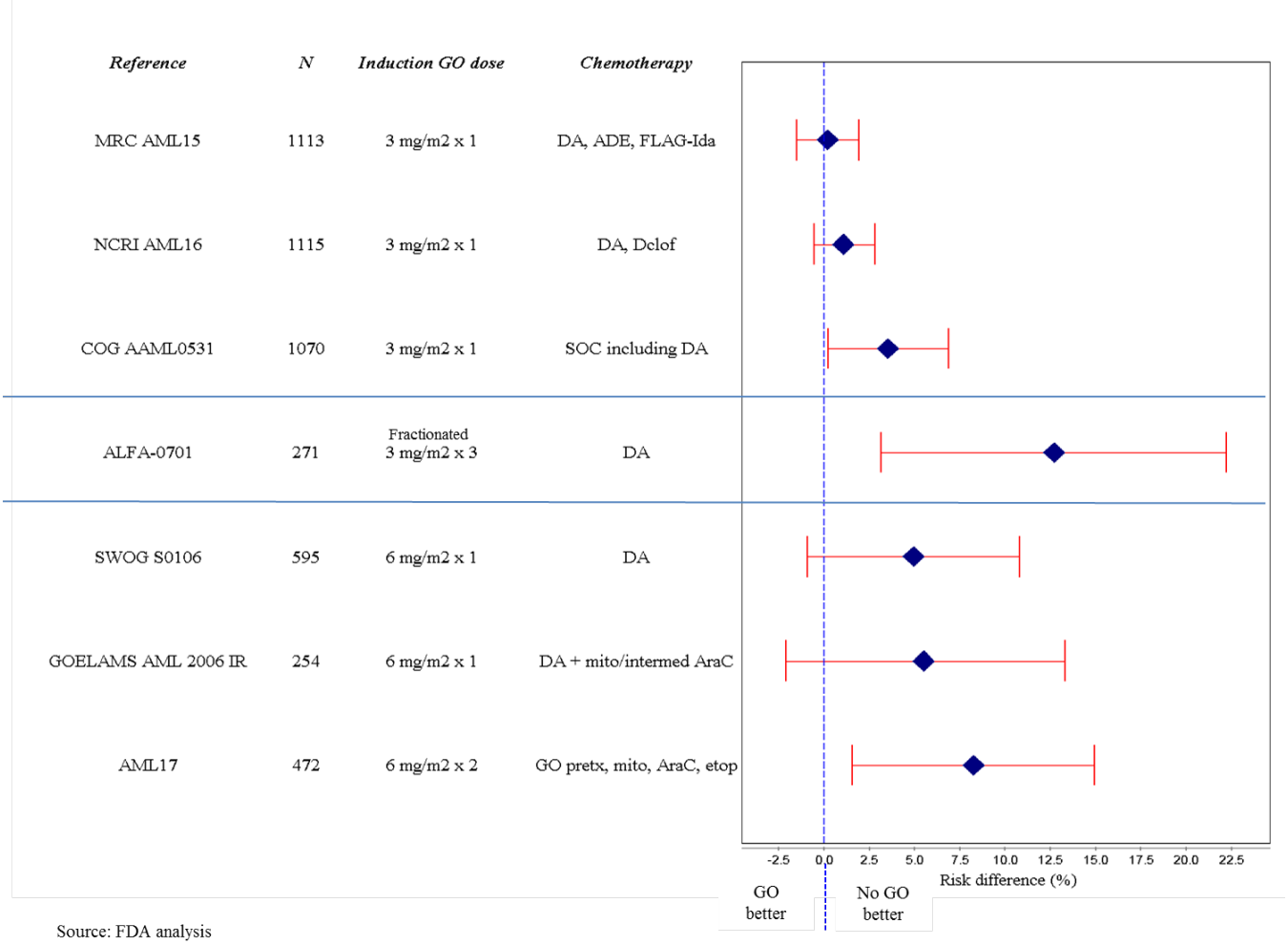
Figure 11. GO Combination Therapy – VOD Grade ≥3



a. "Life-threatening VOD"
b. All Grades VOD
c. Grade 4-5 VOD
d. Fatal VOD

Source: FDA analysis

Figure 12. GO Combination Therapy – Hemorrhage Grade ≥3



Source: FDA analysis

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9.2 Labeling Recommendations

- Boxed Warning –
  - Add boxed warning for Hemorrhage.
- 1. Indication –
  - Remove the word "adult" from the GO combination indication.
- 2. Dosage and administration –
  - Add standardized guidelines regarding premedication prior to administering GO.
  - Remove (b) (4).
  - Include guidelines for holding or stopping GO for both hematologic and non-hematologic toxicities.
- 5. Warnings and Precautions –
  - Revise (b) (4) for hemorrhage.
- 6.1 Clinical Trials Experience –
  - Include information regarding GO discontinuation due to adverse events.
  - Include information on fatal adverse events.
  - Revise the adverse reaction table to show only Grade 3-4 reactions and separate the incidence by treatment phase. (b) (4)
  - Provide a table of common adverse reactions seen with GO.
  - Provide laboratory abnormality data as a shift table.
  - Include safety data from AAML0531.
- 14.1 Clinical Studies –
  - Add EFS analysis by FDA definition of EFS (induction failure = No CR, date of induction failure = date of randomization).
  - Remove (b) (4) as they are not pertinent to the label.
  - Remove (b) (4) and should not be included in the label.
  - Describe the lack of data supporting efficacy in patients with adverse cytogenetics.
  - Add a description of AAML0531.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting for this application was held on July 11, 2017. Acknowledging the lack of surrogacy of EFS for OS, FDA requested a discussion of the utility of EFS as a stand-alone endpoint in newly-diagnosed AML. The voting question for the committee was "Do the results of ALFA-0701 demonstrate a favorable risk:benefit for gemtuzumab ozogamicin 3 mg/m2 days 1, 4 and 7 added to DA for patients with newly-diagnosed CD33-positive AML?"

The committee unanimously voiced agreement on the use of EFS as an endpoint in newly-diagnosed AML. The final vote regarding the positive risk:benefit in ALFA-0701 was 6 votes Yes, 1 vote No. The committee member voting No voiced concerns regarding the inclusion of patients with adverse risk cytogenetics in the indication given the risks of the treatment and the lack of data supporting benefit in

this subset of patients; however, he agreed that for patients with favorable/ intermediate risk the evidence was sufficient to support a favorable risk:benefit.

9.4 Grouped Terms Used in the Safety Review

Hemorrhage intracranial	Cerebral hematoma, Intracranial hematoma, Subdural hematoma, Cerebral hemorrhage
Hepatotoxicity (except VOD)	Hepatocellular injury, Hepatotoxicity, Cholestasis, Cholestatic liver injury, Hepatitis cholestatic, Mixed liver injury, Cholecystitis, Cholecystitis acute, Liver function test abnormal, Liver Disorder, Drug-induced liver injury, Hepatic cirrhosis
VOD	Veno-occlusive liver disease, Veno-occlusive disease

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EMILY Y JEN
07/29/2017

DONNA PRZEPIORKA
07/29/2017

CLINICAL REVIEW

Application Type	Original
Application Number(s)	BLA 761060, Ori-2
Priority or Standard	Standard
Submit Date(s)	11/2/2016
Received Date(s)	11/2/2016
PDUFA Goal Date	9/2/2017
Division / Office	Division of Hematology Products / Office of Hematology and Oncology Products
Reviewer Name(s)	Kelly Norsworthy, MD
Review Completion Date	7/28/2017
Established Name	Gemtuzumab ozogamicin
(Proposed) Trade Name	Mylotarg
Therapeutic Class	Antineoplastic
Applicant	Pfizer
Formulation(s)	Injection, lyophilized (5 mg) (b) (4)
Dosing Regimen	a) 3 mg/m^2 days 1, 4, and 7; b) 6 mg/m^2 day 1, 3 mg/m^2 day 8, followed by 2 mg/m^2 day 1 every 4 weeks for up to 8 additional doses
Indication(s)	As a single agent for treatment of adult and pediatric patients with CD33-positive acute myeloid leukemia
Intended Population(s)	CD33-positive acute myeloid leukemia

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Abbreviations

AC	advisory committee
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALFA	Acute Leukemia French Association
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase
ATU	authorization for use
BLA	biologics license application
BM	bone marrow
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSC	best supportive care
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHV	Centre Hospitalier de Versailles
CI	confidence interval (95%, unless otherwise specified)
CLL	chronic lymphocytic leukemia
CMC	chemistry, manufacturing, and controls
CML-BC	chronic myeloid leukemia in blast crisis
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CrCl	creatinine clearance
CRi	complete response with incomplete count recovery
CRF	case report form
CRO	contract research organization
CRp	complete remission with incomplete platelet recovery
CRT	clinical review template
CSR	clinical study report
CSS	controlled substance staff
CTCAE	common terminology criteria for adverse events
DFS	disease-free survival

DLT	dose limiting toxicity
DMC	data monitoring committee
EAP	expanded access protocol
ECG	electrocardiogram
ECOG	Easter Cooperative Oncology Group
eCTD	electronic common technical document
EFS	event-free survival
ETASU	elements to assure safe use
EU	European Union
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FLT3-ITD	Fms-like tyrosine kinase 3 internal tandem duplication
GCP	good clinical practice
GO	gemtuzumab ozogamicin
GRMP	good review management practice
GVHD	graft versus host disease
HiDAC	high dose cytarabine
HSCT	hematopoietic stem cell transplantation
ICH	International Conference on Harmonization
IND	Investigational New Drug
IPSS	International Prognostic Scoring System
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IT	intrathecal
ITT	intent to treat
IV	intravenous
IWG	International Working Group
LFT	liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodysplastic syndrome
mITT	modified intent to treat
MTD	maximal tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	new drug application
NME	new molecular entity
NR	not reported
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology

OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PS	performance status
PSUR	Periodic Safety Update report
PT	preferred term
RAEB-T	refractory anemia with excess blasts in transformation
REMS	risk evaluation and mitigation strategy
RFS	relapse-free survival
R/R	relapsed and/or refractory
SAE	serious adverse event
SAP	statistical analysis plan
SCE	summary of clinical efficacy
SGE	special government employee
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment emergent adverse event
ULN	upper limit of normal
VOD	veno-occlusive disease
WHO	World Health Organization

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends regular approval of gemtuzumab ozogamicin (GO) under 21 CFR 601 for the treatment of adult and pediatric patients with CD33-positive acute myeloid leukemia (AML). Approval in the relapsed/refractory (R/R) setting is supported by the results of MyloFrance 1 in which 26% (95% confidence interval [CI], 16% - 40%) of patients with AML in first relapse achieved complete remission (CR) with one cycle of treatment with single-agent Mylotarg per the fractionated schedule of 3 mg/m^2 days 1, 4, and 7, and the response was durable, with median relapse-free survival (RFS) 11.6 months. Efficacy in the setting of refractory or subsequently relapsed AML was determined based on supporting studies and the literature showing meaningful, albeit lower, remission rates in different relapse populations. Extension to the pediatric population was based on evidence of similar efficacy and toxicity in supporting studies and the literature. (b) (4) Approval in the newly-diagnosed setting is supported by the results of AML-19, given an improvement in median overall survival (OS) of 4.9 months on the GO arm using 6 mg/m^2 GO on day 1, 3 mg/m^2 on day 8, and 2 mg/m^2 monthly for up to 8 infusions compared to 3.6 months on the best supportive care (BSC) arm (HR 0.69, 95% CI 0.53 – 0.90). The efficacy of GO in comparison to available therapy has been confirmed based on the upfront combination trial ALFA-0701, which will be addressed in the review for Ori-1.

1.2 Risk Benefit Assessment

Table 1: Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Survival at 5 years is ~10% for patients with first relapse of AML and even lower following a subsequent relapse • Cure rates for adults 65 years of age and older with newly-diagnosed AML are < 10%	R/R AML and newly-diagnosed AML in older adults are fatal conditions
Unmet Medical Need	• Remission rates using current available therapy are low; 10-20% with low intensity single agents and 30-70% with intensive regimens	There is a need for an effective agent for treatment of R/R AML and newly diagnosed AML in older patients
Clinical Benefit	• MyloFrance 1 was an open-label single-arm trial of GO for patients with first relapse of AML (n=57) - CR rate was 26% (95% CI, 16%-40%) - Median RFS was 11.6 months • 201-203 were open-label single-arm studies of GO for patients with first relapse of AML (n=277) - CR rate was 15% (95% CI, 11%-20%)	GO using the fractionated, unfractionated, and upfront monotherapy dosing regimens was active in the treatment of AML across disease stages

	- Median RFS was 7.4 months • FDA meta-analysis of single arm trials showed CR rate 14% (95% CI, 11-17%) with 9 mg/m^2 unfractionated GO (N=436) and CR rate 25% (95% CI 15-37%) with 3 mg/m^2 fractionated dosing (n=63) - R/R AML trials using 9 mg/m^2, excluding those limited to first relapse, showed CR rate 14% - R/R AML trials using 3 mg/m^2, excluding those limited to first relapse, showed CR rate 17% and CR+CRp rate 29-33% • AML-19 was a randomized, open-label trial of GO versus BSC for patients with newly diagnosed AML unsuitable for intensive chemotherapy (n=237) - Median OS 4.9 (95% CI 4.2-6.8) months GO versus 3.6 (95% CI 2.6-4.2) months BSC arm (HR 0.69, 95% CI 0.53-0.90) - CR rate GO arm 15% (95% CI 9-23%)	
Risks	• VOD is a potential fatal adverse reaction, with higher incidence using the 9 mg/m^2 unfractionated regimen, especially pre- or post-HSCT - No cases of VOD reported to date with fractionated or AML-19 dosing regimens • Hemorrhage is a potential fatal adverse reaction, with higher incidence using the 9 mg/m^2 unfractionated regimen • Early deaths with the 9 mg/m^2 unfractionated regimen were 16% across studies (95% CI 13-20%) compared to 9% (95% CI 4-18%) with the fractionated regimen • Other serious reactions included infusion reactions, infections, myelosuppression, and elevated liver enzymes - Time to count recovery was shorter with fractionated dosing - Hepatotoxicity was reduced with fractionated and AML-19 dosing • Other common (>10%) reactions included fever, chills, nausea, and vomiting • Treatment required inpatient administration on MyloFrance 1 and AML-19	The overall short-term safety profile of the unfractionated and upfront monotherapy GO doses are acceptable for patients with AML
Risk Management	• No evidence to support prophylactic measures for VOD, such as use of defibrotide • Serious or life-threatening toxicities may have been avoided by inpatient monitoring on MyloFrance 1 for the duration of therapy and period of aplasia and on AML-19 until completion of induction • Fatal hemorrhages with the unfractionated 9 mg/m^2 regimen occurred at a median platelet count of 18 (range 4-60) and transfusion thresholds are unknown • Minimal data exists regarding post-baseline coagulation parameters and their possible contribution to hemorrhagic events • Infusion reactions were reduced, but not eliminated, with the use of methyprednisolone prophylaxis	To minimize risks, labeling should include instructions for monitoring and steroid premedication.

Background: AML in first relapse is difficult to treat. Prognosis varies based on factors such as duration of first CR, Fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) status, cytogenetic risk, age, and prior hematopoietic stem cell transplantation (HSCT). Based on the European Prognostic Index score, OS at 5 years ranges from 46% in the most favorable to 4% in the poorest risk group (Breems, Van Putten et al. 2005). Of 667 patients age 15 to 60 years in first relapse following intensive induction, 1-year and 5-year OS were 29% and 11%, respectively, with the majority of patients receiving intensive salvage chemotherapy. In patients who were able to achieve a second CR and undergo allogeneic HSCT, 5-year OS ranged from 26% for poor risk to 88% for favorable risk patients. Refractory- or multiply-relapsed patients have an even poorer prognosis. A study by Roboz *et al* randomized adults with AML who relapsed or were refractory after 2 or 3 prior regimens to the investigational drug elacytarabine versus investigator's choice, including intensive, non-intensive, and supportive care options (69% received intensive therapy) and OS was under 10% at 2 years on the control arm, with median OS 3.3 months (95% CI 2.9-4.4 months).

The current standard of care is intensive combination chemotherapy in patients who can tolerate it. Using intensive regimens in R/R AML, CR rates range from around 30-70% depending on the regimen and patient population (Thol, Schlenk et al. 2015). Generally, older patients, those with shorter previous remissions, more prior relapses, and relapse after HSCT have lower CR rates. Amongst patients treated with low-intensity regimens, including hypomethylating agents and low-dose cytarabine, CR rates in the relapsed setting are in the range of 10-20% (Sarkozy, Gardin et al. 2013, Itzykson, Thepot et al. 2015).

Newly-diagnosed AML in older patients is similarly difficult to treat. Cure rates for adults ≥ 65 years old with AML are < 10% (Walter and Estey 2015), with perhaps recent improvements to roughly 20% in adults ≥ 60 years old with shorter follow-up (Burnett, Wetzler et al. 2011). Co-morbidities and advanced age often prevent the successful administration of intensive chemotherapy, which likely contributes to the poor outcomes. Even when intensive therapy is possible, CR rates are lower than with younger patients, in the range of 30-60% (Estey 2000, Appelbaum, Gundacker et al. 2006, Ossenkoppele and Lowenberg 2015). The use of less intensive therapies, such as hypomethylating agents and low-dose cytarabine results in CR rates of 18-20% and median OS of roughly 4-10 months (Burnett, Milligan et al. 2007, Dombret, Seymour et al. 2015).

Clinical Development Program: GO is an antibody-drug conjugate composed of a CD33-directed monoclonal antibody covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. GO exerts its effect through binding the CD33 antigen on the surface of myeloid leukemic blasts, formation of a complex that is internalized, and then release of calicheamicin inside the lysosome, leading to DNA double-strand breaks and cell death.

The clinical development program for the relapsed AML indication consisted of three phase 1 protocols in relapsed and refractory patients (Protocol 101 in adults, Protocol 102 in pediatrics, and Protocol 103 in Japanese patients) and three phase 2 protocols in patients with CD33-positive AML in first relapse (Protocols 201 and 202 in adult patients, and Protocol 203 in patients ≥ 60 years). Two phase 4 single agent trials were conducted in the R/R setting to study GO in patients post-transplant (Study 100374) and with the use of corticosteroid prophylaxis (Study 100863). A prospective observational cohort study (Study 100847) was conducted to assess the safety of GO in routine practice.

The dose-schedule used in the trials 201-203 was 9 mg/m^2 for 2 or 3 doses, 14 to 28 days apart. The dose was selected based on safety and pharmacodynamic (PD) analyses from Study 101. Protocols 201-203 were single-arm, open-label trials of single-agent GO. The primary efficacy endpoint was CR rate following 2-3 doses of GO, and the objective was to test the hypothesis that the remission rate was ≥ 30%.

An investigator-sponsored trial, MyloFrance 1, studied fractionated dosing of GO at 3 mg/m^2 days 1, 4, and 7 based on data to support enhanced internalization of the drug complex and a hypothesis that it may be better tolerated. Another investigator-sponsored trial, AML-19, studied a unique monotherapy dose of 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8, followed by 2 mg/m^2 monthly for up to 8 additional doses versus best supportive care in older patients considered unsuitable for intensive chemotherapy after their phase 2 trial showed promising results with this new regimen.

The results submitted to support the relapsed AML indication in this application were from the final analysis of all enrolled patients on studies 201-203. MyloFrance 1 and AML-19 were submitted as supportive data.

Efficacy:

Relapsed AML

Fractionated dosing

MyloFrance 1 enrolled 57 patients with CD33-positive *de novo* AML in first relapse. The study included 29 males and 28 females. The median age was 64 (range, 22-80) years, and 35 of the patients were ≥ 60 years old. No patients had a prior HSCT.

In the analysis of the primary endpoint, the rate of CR+CRp was 33% (95% CI, 22-47%). Thus, their primary objective to demonstrate that CR+CRp was > 30% was met. Results for the primary endpoint were essentially consistent across the subpopulations tested.

The secondary endpoints of CR and RFS were used to inform the regulatory decision-making process. CR was achieved by 15 (26%) patients (95% CI, 16-40%). This compares favorably to other single agent non-intensive options in the first relapse setting, including azacitidine at 10% (95% CI 5-16%) (Itzykson, Thepot et al. 2015) and LDAC at 17% (95% CI 7-30%) (Sarkozy, Gardin et al. 2013).

Due to the competing risk of death in remission, RFS was used as the measure of duration of response. For the patients who achieved CR, the median RFS was 11.6 months, so it was concluded that the responses were reasonably durable.

Unfractionated dosing

Studies 201-203 enrolled 277 patients with CD33-positive *de novo* AML in first relapse. The studies included 151 males and 126 females. The median age was 61 (range, 20-87) years, and 157 of the patients were ≥ 60 years old. Twenty-eight (10%) patients underwent a prior HSCT, with the majority (9%) being autologous.

In the analysis of the primary endpoint, the rate of CR was 15% (95% CI, 11-20%). Thus, their primary objective to achieve a CR rate of ≥30% was not met. Results for the primary endpoint were essentially consistent across the subpopulations tested.

The Applicant proposed to use the secondary endpoint of ORR (CR+CRp) of 35% (95% CI 30-41%) to support the clinical benefit of GO. However, they did not submit independent data to validate the prognostic value of CRp, so this result was not considered further.

The secondary endpoint of RFS was used as the measure of duration of response. For the patients who achieved CR, the median RFS was 7.4 (95% CI 5.6-8.7) months. It was concluded that the CR duration was reasonably durable.

FDA meta-analysis

The FDA's meta-analysis showed that the overall CR rate with fractionated 3 mg/m^2 dosing was 25% (95% CI 15-37%) and with unfractionated 9 mg/m^2 dosing was 14% (95% CI 11-17%). Thus, it was concluded that the CR rates with fractionated dose GO are at least as good or better than with the unfractionated dose regimens.

The meta-analysis also examined CR rates in R/R AML trials, excluding those limited to first relapse. Results showed that CR rate was 14% using 9 mg/m^2 unfractionated dosing and 17% using fractionated dosing. Data for the fractionated dosing was quite limited, but supported by CR+CRp rates of 29-33% in 2 additional studies that did not report CR results. This data suggests activity in R/R AML, not limited to the first relapse setting.

Newly-diagnosed AML

AML-19 enrolled 237 patients with newly-diagnosed AML who were more than 60 years old and not "eligible" for intensive chemotherapy. Patients were randomized (1:1) to receive GO or BSC. The study included 130 males (57 GO, 73 BSC) and 107 females (61 GO, 46 BSC). The median age was 77 years on both arms (range 62-88 GO, 66-88 BSC). Seventy-three patients (39 GO, 34 BSC) had secondary AML. Twenty-four patients (10 GO, 14 BSC) had <20% CD33 expression.

In the analysis of the primary endpoint, median OS was 4.9 (95% CI 4.2-6.8) months on the GO arm versus 3.6 (95% CI 2.6-4.2) months on the BSC arm (HR 0.69, 95% CI 0.53-0.90). Thus, their primary objective to demonstrate superior OS on the treatment arm was met. Exploratory subgroup analyses showed that patients with < 20% CD33 expression had a HR for OS of 1.5 (95% CI 0.7-3.6), patients with adverse cytogenetics had a HR of 1.1 (95% CI 0.7-1.8) and men had a HR 0.9 (95% CI 0.6-1.3). CD33 expression and sex were significant treatment-by-covariate interactions and cytogenetic profile was of borderline significance. It was concluded that this therapy is unlikely to be beneficial in patients with no CD33 expression, with efficacy in adverse risk cytogenetics and men being less clear.

Safety:

Relapsed AML

Fractionated dosing

The safety data set included 57 patients with AML in first relapse. All patients completed the planned induction therapy of 3 mg/m^2 on days 1, 4, and 7. Two deaths that occurred before day 43 of therapy were considered at least possibly related to GO. Both were sudden deaths at home. All-cause mortality before day 43 was 7% (95% CI 2-17%) and this was not greater than expected based on historical controls (14-17%) (Karanes, Kopecky et al. 1999, Cortes, Goldberg et al. 2015, Itzykson, Thepot et al. 2015).

The most common (>20%) TEAEs were pyrexia, nausea, vomiting, constipation, bleeding, mucositis, and elevated AST. Hyperbilirubinemia was reported in 7%. A grade 3 TEAE (no grade 4 TEAEs) occurred in 56% of patients, the most common (>5%) nonhematological events being infection, pyrexia, rash, bleeding, and pneumonia. There were no cases of grade 3 hepatotoxicity and no cases of VOD.

Patients achieving an overall response had a median time to ANC >500/μL of 23 days and a median time to platelets >50,000/μL of 20 days from the first dose of GO.

Unfractionated dosing

The safety data set included 936 patients with AML or MDS, including 277 adults from studies 201-203 with first relapse of AML treated with GO at the proposed dose-schedule. The majority of patients (76%) received the planned 2 or more doses of GO.

On studies 201-203, 32 deaths that occurred within 28 days after the last dose of GO were considered at least possibly related to GO. Most were due to infection or hemorrhage, but there were 3 deaths due to VOD. The all-cause early mortality for the 277 patients on studies 201-203 was 18% (95% CI 14-23%), near the upper end of historical controls (14-17%) (Karanes, Kopecky et al. 1999, Cortes, Goldberg et al. 2015, Itzykson, Thepot et al. 2015).

In the first relapse patients on studies 201-203, GO was interrupted by 2% and discontinued prematurely by 14% due to an AE. The most common reasons for withdrawal were cerebral hemorrhage, multi-organ failure, pneumonia, sepsis, and VOD. The SOCs with the highest rates of patients with SAEs were Blood and lymphatic system disorders and General disorders and administration site conditions.

The most common (>20%) TEAEs were fever, chills, nausea, vomiting, thrombocytopenia, headache, diarrhea, fatigue, epistaxis, decreased appetite, constipation, hypokalemia, neutropenia, anemia, dyspnea, and leukopenia. Hyperbilirubinemia was reported for 8%.

Grade 3-4 TEAEs occurred in 96% of patients, the most common (>5%) nonhematological events being pyrexia, nausea, vomiting, chills, AST increased, diarrhea, hypotension, headache, febrile neutropenia, ALT increased, dyspnea, hypertension, epistaxis, blood LDH increased, sepsis, hyperbilirubinemia, hyperglycemia, pneumonia, alkaline phosphatase increased, and decreased appetite.

VOD occurred in 5% of patients in the first relapse subgroup, with fatal VOD occurring in 4%. In patients with no HSCT, VOD occurred in 2 (1%) of patients, both being fatal. The incidence of VOD and fatal VOD in the 31 patients undergoing an allogeneic HSCT post-GO was 23% and 19%, respectively.

Laboratory abnormalities were common, but where shifts could be assessed, nonhematological grade ≥3 abnormalities that occurred in > 10% included increased AST and bilirubin. There were 12 patients considered to be at least potential Hy's law cases and VOD developed in 4/12 (33%).

Patients achieving an overall response had a median time to ANC >500/μL of 42 days and a median time to platelets >50,000/μL of 51 days from the first dose of GO.

FDA meta-analysis

Based on a review of the available data by dose in the submitted datasets and our literature search, FDA determined that early mortality within 28 days after the last dose of GO appeared to be reduced in patients treated with the 3 mg/m^2 fractionated regimen at 9% (95% CI 4-18%) compared to 16% (13-20%) using the 9 mg/m^2 unfractionated dose regimen. Furthermore, treatment-related causes of death were lower at 4% with the fractionated regimen, compared to 10% with the 9 mg/m^2 unfractionated regimen, due to more cases of fatal infection, hemorrhage, and VOD.

Furthermore, grade 3-4 hepatotoxicity and VOD were lower with the fractionated dosing. In fact, there have been no cases of VOD reported to date with the fractionated dose regimen. However, to date, only 19 patients from available reports underwent HSCT before or after GO. It was concluded that the fractionated dose regimen is safer with respect to hepatotoxicity and VOD, but further data are required for confirmation.

Newly-diagnosed AML

The safety population included 111 newly-diagnosed AML patients randomized to the GO arm and 114 patients randomized to the BSC care arm on AML-19. The majority of patients (94%) received the planned 2 doses of GO during induction, 53% received at least one post-induction infusion at 2 mg/m^2, and 8% received the entire treatment program of 10 infusions.

Eight deaths during induction were considered treatment-related. Most were due to infection, but there was one death each due to hemorrhage, renal failure, and cardiac failure. The all-cause 30- and 60-day mortality for all 111 patients the GO arm was 11% and 18%, respectively. All-cause 30- and 60-day mortality were higher in the 114 patients treated on the BSC arm at 14% and 30%, respectively.

The most common (>20%) TEAEs on the GO arm were infection, bleeding, fatigue, liver dysfunction, and cardiac dysfunction. TEAEs on the control arm were similar, with the most common (>20%) TEAEs being infection, bleeding, fatigue, liver dysfunction, cardiac dysfunction and febrile neutropenia.

Grade ≥3 TEAEs occurred in 61% of patients on the GO arm and 68% on the BSC arm, with the most common (>5%) nonhematological events on the GO arm being infection, febrile neutropenia, bleeding, fatigue, liver dysfunction, and cardiac dysfunction. Grade ≥ 3 TEAEs on the BSC arm were similar, with the most common (>5%) being the same, with the addition of metabolic dysfunction (6%). Death due to any AE occurred in 17% of patients on the GO arm and 20% of patients on the BSC arm. There were no cases of VOD.

Special Populations: A combined analysis of 125 pediatric patients with R/R AML revealed comparable CR and CR+CRp rates to the adult population. The safety profile of the unfractionated GO regimen in pediatric patients with R/R AML was comparable to

that seen in the adults, with the exception of a higher incidence of VOD. Overall, there was a 31% incidence of VOD and a 3% incidence of fatal VOD on study 102. For children going on to allogeneic HSCT post-GO, the VOD rate was 54% and fatal VOD was 8%. Limited data suggest that the fractionated dose monotherapy regimen is better tolerated in children, with no reported cases of VOD. However, further data are required for confirmation in the post-marketing setting.

Overall Benefit-Risk Assessment: Although the current standard of care for treatment of AML in the upfront and R/R settings is combination chemotherapy, the results with this approach may not be suitable for all patients, particularly those who are older, have co-morbid conditions, impaired performance status, or previously failed to respond to similar agents. Thus, effective treatments that are not cross-resistant based on mechanism of action could potentially benefit these patients. In MyloFrance 1, the CR rate was 26%, which is better than with any other non-intensive single agent therapy, and the responses were durable (median RFS 11.6 months). On AML-19, median OS was improved by 1.3 months compared to BSC, with 1 year OS improved by 14.6% (24.3% on the GO arm versus 9.7% on the BSC arm). Furthermore, the ALFA-0701 randomized trial supported the clinical benefit of GO in the front-line intensive setting. Taken together, the available data provides a strong basis for regular approval.

The safety review revealed significant nonhematological risks, including fatal events. The risks were moderated in part by inpatient monitoring and steroid prophylaxis, a strategy that would be needed for safe use of the drug in practice. Furthermore, the lower doses of GO used on MyloFrance 1 and AML-19 appeared to be better tolerated by patients compared to the 9 mg/m^2 unfractionated dose regimen, with less hemorrhage, hepatotoxicity, and no cases of VOD. With the approval of these lower dose regimens, the current measure of clinical benefit from treatment with GO outweighs the expected risks for patients with CD33-positive AML.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

FDA determined that a REMS is not necessary for Mylotarg to ensure that the benefits outweigh the risks. Safety concerns with Mylotarg are well documented, and healthcare providers who treat AML should be familiar with the risks and importance of patient monitoring in the setting of treatment for AML.

1.4 Recommendations for Postmarket Requirements and Commitments

PMR: Dose-Schedule Toxicity and Pharmacokinetics Trial

Preliminary data indicates that the incidence of hepatic adverse events, VOD, and hemorrhage may be less in patients treated with the fractionated dosing schedule of

GO. However, the numbers are small and so the safety of this dosing schedule is not well characterized.

Therefore, the Applicant will conduct a single arm trial in adult and pediatric patients receiving GO at a dose of 3 mg/m^2 up to a maximum dose of 5 mg on days 1, 4, and 7 to identify and characterize the adverse events and pharmacokinetics (PK) of this regimen. The Applicant should propose a trial with this safety objective. The primary objective is to evaluate the incidence of hepatic adverse events, VOD, and hemorrhage.

The protocol should study 1) patients with prior allogeneic HSCT and 2) patients intended to proceed with allogeneic HSCT post-GO. The study must include a minimum number of patients to determine that VOD incidence does not exceed 10% and that fatal VOD does not exceed 4%. Specific details regarding the interpretation of changes in hepatic function and the incidence of VOD should be pre-specified and outlined in the SAP. In addition to analyzing overall hepatic AEs, SAEs, incidence of VOD, and fatal VOD, we ask that you analyze, at a minimum, the association with prior HSCT (with allogeneic and autologous HSCTs considered separately), subsequent HSCT (with allogeneic and autologous HSCTs considered separately), length of time between HSCT and GO administration (whether before or after), effect of myeloablative versus reduced intensity conditioning regimens, and effect of baseline hepatic dysfunction.

Regarding hemorrhage, the study should evaluate the incidence of overall hemorrhagic AEs, SAEs, and fatal hemorrhage. The study must include a minimum number of patients to determine that fatal hemorrhage does not exceed 4%. Given uncertainties with regards to the bleeding risks with GO, we ask that you institute specific transfusion thresholds for your study and monitor CBC, PT/INR, aPTT, and fibrinogen frequently until 4 weeks following the last dose of GO. Grade ≥ 3 bleeding events should trigger an analysis of these coagulation parameters.

2 Introduction and Regulatory Background

2.1 Product Information

Drug Established Name: Gemtuzumab ozogamicin

Proposed Trade Name: Mylotarg

Prior Names: CMA 676

Dosage Forms: Injection, lyophilized (5 mg) [(b) (4)] containing [(b) (4)]% sodium phosphate, [(b) (4)]% sucrose, [(b) (4)]% sodium chloride, and [(b) (4)]% dextran 40

Chemical Class:	Recombinant protein conjugated to calicheamicin
Therapeutic Class:	Anti-neoplastic
Pharmacologic Class:	Antibody-drug conjugate (ADC)
Mechanism of Action:	Mylotarg binds to the CD33 antigen found on the surface of myeloid leukemic blasts and immature normal cells of the myelomonocytic lineage, forming a complex that is internalized, leading to release of the calicheamicin derivative inside the myeloid cell, which then binds to DNA resulting in DNA double-strand breaks and cell death
Proposed Indication:	Treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy
Proposed Dose-Schedule:	9 mg/m^2, infused over a 2-hour period, with the recommended treatment course of 2 doses total, administered 14 days between the doses 3 mg/m^2, infused over a 2-hour period, with the recommended treatment course of 3 doses total administered 3 days between the doses

2.2 Tables of Currently Available Treatments for Proposed Indications

A number of agents have approvals for treatment of AML. Others are approved only for palliation. Agents with approval(s) relevant to treatment of AML are listed in Table 2.

Table 2: Approved Agents with Indication(s) Relevant to Treatment of Relapsed AML

Agent	Excerpted Indication
Azacitidine	Indicated for myelodysplastic syndrome (MDS), including refractory anemia with excess blasts in transformation (i.e., 20-30% blasts), which is now classified as AML per contemporary classification systems
Cyclophosphamide	Indicated for the treatment of leukemias
Cytarabine	Indicated in combination with other approved anticancer drugs for induction in acute non-lymphocytic leukemia of adults and children
Daunorubicin	Indicated in combination with other approved anticancer drugs for remission induction in acute non-lymphocytic leukemia of adults
Decitabine	Indicated for myelodysplastic syndrome (MDS), including refractory anemia with excess blasts in transformation (i.e., 20-30% blasts),

	which is now classified as AML per contemporary classification systems
Dexamethasone	For the palliative management of leukemias and lymphomas
Doxorubicin	Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions, including acute myeloblastic leukemia
Idarubicin	Indicated in combination with other approved anti-leukemic drugs for the treatment of AML in adults
Methylprednisolone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Mitoxantrone	Indicated in combination with other approved drug(s) in the initial therapy of acute non-lymphocytic leukemia in adults
Prednisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Thioguanine	Indicated for remission induction and remission consolidation treatment of acute non-lymphocytic leukemias, with higher remission rates in combination with other chemotherapy agents
Vincristine	Indicated in acute leukemia

Historically, the response to single agent salvage therapy is poor. Thus, most treatments for R/R AML include combination chemotherapy. When using such intensive salvage chemotherapy, CR rates range from 40-60% for patients with an initial CR duration of 1 year or longer and 10-15% for patients with a shorter CR duration (Thol, Schlenk et al. 2015).

In older patients or others who are not expected to tolerate intensive combination chemotherapy, hypomethylating agents are often tried. One retrospective analysis in 130 patients older than age 50 with refractory or first relapsed AML demonstrated a CR rate of 10% with azacitidine, with an additional 7% of patients achieving CRi (Itzykson, Thepot et al. 2015). Median OS was 8.4 months. A retrospective trial in 8 pediatric patients with refractory or relapsed (relapse 1-5) AML achieved a CR rate of 12.5% with decitabine, with an additional 25% of patients achieving CRp (n=1) or CRi (n=1) (Phillips, Davies et al. 2013).

In addition to duration of initial CR, factors associated with outcome of AML at first relapse include cytogenetics at diagnosis, age at first relapse, and occurrence of relapse after HSCT (Breems, Van Putten et al. 2005). Depending on the combination of such prognostic factors, the CR rate with salvage therapy varied from 34% to 85%, with the majority patients being treated with intensive therapy and/or transplantation. Across the entire cohort, 5-year OS was only 11% (4% to 46% depending on risk group). All prognostic groups fared better if they were able to proceed with HSCT. Thus, there remains a clear need for new treatments for patients with R/R AML.

Newly-diagnosed AML in older patients is similarly difficult to cure, with long term survival rates for adults ≥ 65 years old with AML being < 10% (Walter and Estey 2015). Co-morbidities and advanced age often prevent the administration of intensive

chemotherapy, which likely contributes to the poor outcomes. But even when intensive therapy is possible, CR rates are lower than with younger patients, in the range of 30-60% (Estey 2000, Appelbaum, Gundacker et al. 2006, Ossenkoppele and Lowenberg 2015). Use of less intensive therapies, such as azacitidine and low-dose cytarabine, result in CR rates of 18-20% and median OS of roughly 4-10 months (Burnett, Milligan et al. 2007, Dombret, Seymour et al. 2015). Thus, there remains a need for new treatments for older and otherwise co-morbid patients with newly-diagnosed AML.

2.3 Availability of Proposed Active Ingredient in the United States

GO is currently not marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

GO is a first-in-class CD33 targeted ADC. Calicheamicin, the payload, is a DNA intercalator that can cause double strand breaks. There are some related classes of biologics on which to base class-specific safety concerns.

- There are no approved agents that target CD33, but there are several monoclonal antibodies that target CD19, CD20, and CD30. These agents carry warnings for infusion reactions, hematologic toxicities, serious infections, tumor lysis syndrome, and hepatotoxicity.

- There are no approved products using calicheamicin, but other intercalating agents include the anthracyclines, such as daunorubicin and doxorubicin. These agents carry warnings for myocardial toxicity, myelosuppression, hemorrhage, and infection.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The key US presubmission regulatory activities for this submission are as follows:

- Original IND 46635 for CMA-676 was submitted on 11/9/1994
- Original NDA 21174 submitted 10/29/1999
- Orphan designation granted for the treatment of CD33-positive AML on 11/24/1999.
- Accelerated approval granted for the treatment of patients ≥ 60 years old with AML in first relapse who are not otherwise candidates for cytotoxic chemotherapy on 5/17/2000. Approval was based on a roughly 30% overall response rate. The approved dose was 9 mg/m^2 for 2 doses 14 days apart. The post marketing requirement was a randomized trial comparing daunorubicin and cytarabine with or without Mylotarg as induction therapy in patients with *de novo* CD33-positive AML.
- SWOG S0106 was initiated in 2004.

- SWOG S0106 was terminated early by the DSMB in 2009. An interim analysis showed a lack of improvement in the CR rate in the Mylotarg arm in addition to an increase in deaths during induction.
- FDA proposed to withdraw approval of Mylotarg since the confirmatory trial failed to verify the clinical benefit for Mylotarg on 5/21/2010
- The sponsor voluntarily withdrew Mylotarg on 10/25/2010. Continued use was limited by the sponsor to single patient INDs only. The drug remained approved in Japan and was denied approval in the European Union (EU).
- FDA asked the sponsor to clarify its plans for development of Mylotarg and to use an intermediate size expanded access protocol (EAP) on 7/13/2012.
- Type C meeting held on 11/8/2012 regarding plans to use the final OS analysis of ALFA-0701 (MyloFrance 3) to support an NDA for treatment of *de novo* AML in patients age 50-70 years. FDA indicated that an improvement in OS is required for approval.
- Draft EAP was submitted on 4/10/2013 and was later withdrawn.
- Type C meeting held on 2/13/2014 to discuss negative OS analysis of ALFA-0701.
- Draft EAP resubmitted on 6/5/2014.
- Teleconference held on 6/10/2014 to discuss accelerated approval based on the EFS analysis from ALFA-0701.
- Type C meeting held on 10/14/2014 to discuss BLA clinical content and format.
- CMC PBLA meeting held on 11/21/2014 to discuss Module 3 contents.
- FDA made the determination that Mylotarg is a biologic on 1/22/2015.
- Pre-BLA meeting held on 3/19/2015 to discuss BLA contents.
- Proprietary name Mylotarg conditionally approved on 5/12/2015.
- Pre-BLA meeting held on 3/14/2016 to provide an update on BLA contents.
- Fast Track Designation requested on 5/11/2016.
- Teleconference on 5/13/2016 was held to discuss the Fast Track application – sponsor notified that confirmatory trials using OS as endpoint would be expected for this application.
- Fast Track Designation request withdrawn on 5/23/2016.
- Pre-BLA meeting held on 8/30/2016 to discuss whether their data could support a marketing application for indications in both newly-diagnosed and relapsed AML.

2.6 Other Relevant Background Information

FDA has commonly used durable CR as the endpoint for accelerated approval of new agents for treatment of acute leukemia. CR without platelet recovery (CRp) was taken into consideration in the initial accelerated approval of Mylotarg for AML in 2000 (Bross, Beitz et al. 2001), but subsequent studies failed to confirm its prognostic value. Retrospective data has indicated that patients who achieve CR responses have less MRD and lower levels of MRD compared to patients achieving CRp or CRi responses (Chen, Xie et al. 2015). Furthermore, the CRp and CRi responses were associated with higher rates of relapse and death.

It is acknowledged that when patients proceed to consolidation therapy shortly after induction, one cannot determine whether incomplete restoration of blood counts is due to persistent subclinical disease or resulted from interruption of count recovery for administration of the next course of therapy.

2.7 Compliance with Pediatric Research Equity Act

GO has orphan designation for treatment of CD33-positive AML and is therefore exempt from the requirements for a pediatric assessment under the Pediatric Research Equity Act.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA761060 was received on 11/2/2016 as an electronic submission in CTD format. The contents of the clinical module were reviewable, and the application was filed on 1/1/2017. Additional amendments used for this review are listed in Table 3.

Table 3: BLA Submission and Amendments

SDN	Received	Category	Subcategory
1	11/2/2016	Original	BLA
2	11/7/2016	Clinical	Response To Information Request
5	12/6/2016	Clinical	Response To Information Request
6	12/16/2016	Clinical	Response To Information Request
11	1/27/2017	Clinical	Response To Information Request
13	2/15/2017	Clinical	Response To Information Request
17	3/2/2017	Clinical	120 Day Safety Update
18	3/6/2017	Clinical	Response To Information Request
20	3/13/2017	Clinical	Response to Information Request
21	3/17/2017	Clinical	Response to Information Request
23	3/20/2017	Clinical	Response to Information Request
24	3/20/2017	Clinical	Response to filing communication
25	3/24/2017	Clinical	Response to Information Request
31	5/4/2017	Clinical	Response to Information Request
32	5/5/2017	Clinical	Response to Information Request
41	6/30/2017	Clinical	Response to Information Request
42	6/30/2017	Clinical	Response to Information Request
43	7/7/2017	Clinical	Response to Information Request

3.2 Compliance with Good Clinical Practices

All protocols and/or clinical study reports stated that they were conducted in compliance with Good Clinical Practice (GCP). Audits were conducted at 2 clinical sites for Protocol 201 at the time of the original Mylotarg NDA submission:

1. Richard Larson, The University of Chicago Medical Center, Chicago, IL – 15 enrolled (15 audited)
2. Eric Sievers, Fred Hutchinson Cancer Research Center, Seattle, WA – 15 enrolled (11 audited)

Although minor violations in the protocol were reported, DSI concluded in their reviews dated April 7th and 14th 2000, respectively, that the data were acceptable in support of NDA 21-174.

3.3 Financial Disclosures

Certifications declaring absence of financial conflict of interest were obtained for 67% of the 899 investigators in company sponsored Wyeth studies (including clinical studies 101, 102, 103, 201, 202, 203, 205, 207, 100374, 100847, and 100863). Certifications were obtained by Pfizer for 45% of the 1,202 investigators in non-company sponsored trials, which included MyloFrance 1 for the monotherapy indication.

No investigators were full-time or part-time employees of the sponsor of the covered studies. Due diligence activities were required for 950 of the 2,101 clinical investigators. Of this total, due diligence is provided for 297 of 899 investigators in the sponsored trials, primarily as a result of the retrospective recreation of incomplete financial disclosure documentation transferred to Pfizer and the difficulty in finding and receiving updated financial disclosure information from investigators years after study completion. Due diligence was also provided for 653 of 1,202 investigators from non-company sponsored trials, again due to the retrospective nature of the research and financial disclosure form collection, which took place after many of the studies had concluded.

Nine of 2,101 clinical investigators listed in the study reports had financial information to disclose. Two were involved in company sponsored trials and 7 were involved in non-company sponsored trials. The Sponsor included information regarding efforts to eliminate bias for each of the studies, including regular visits, data monitoring, clinical data validation, and discrepancy resolution.

Per information submitted with the original NDA 21-174, [redacted] (b) (6), subinvestigator in study [redacted] (b) (6), was to receive a royalty from the sale of GO when it was marketed. However, Pfizer was not able to obtain a completed Financial Disclosure Form from him for this application, despite acting with

due diligence. His involvement in the phase (b) (6) clinical studies was minimal. The (b) (6) was to also receive royalties from the sale of GO.

The data submitted are acceptable for analysis, given no evidence to suggest bias.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

4.1.1 Manufacturing

GO is a recombinant, humanized IgG_4 monoclonal antibody conjugated to the cytotoxic agent N-acetyl gamma calicheamicin. The ADC binds to the CD33 antigen expressed on the surface of leukemic cells. The protein has a molecular weight of 151,520 to 153,185 Da. During the course of the clinical trials, changes were made to the manufacturing process. Patients treated on the pivotal and supportive protocols received GO produced using older methods and specifications. Of note, (b) (4) was recently detected, with analyses showing trace levels as early as 1999, a shift to higher levels in 2005, and consistent levels since 2006.

The Manufacturing and Clinical Pharmacology Reviewers confirmed that the new manufacturing processes yield comparable product, and thus, the reviewed data is considered applicable to current drug product. Approval was recommended.

4.1.2 Immunogenicity

Immunogenicity assays have not been updated since the original methods were validated in 1998. They were reviewed as part of the original NDA and were not reviewed with this BLA given that they would not meet the current recommendations of either the 2009 or more recent 2016 Draft Guidance "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products." However, data from phase 1 and 2 trials showed a low incidence of anti-drug antibodies (ADA) (<1%). (b) (4) The immunogenicity reviewer recommended approval.

4.2 Clinical Microbiology

This section is not applicable.

4.3 Preclinical Pharmacology/Toxicology

4.3.1 General Toxicology

Single dose toxicology was assessed in 5 studies using mice, rats, and non-human primates. Repeat dose studies were assessed in 4 studies using rats, rabbits, and non-human primates. There were twenty other toxicity studies. The review focused on two fertility and early embryonic toxicology studies in rats. There were no major review issues and the toxicology reviewer recommended approval.

4.3.2 Genotoxicity and Carcinogenicity

No genetic toxicology or carcinogenicity studies were submitted for review.

4.3.3 Reproductive and Developmental Toxicology

The Preclinical Pharmacology/Toxicology reviewer found that GO decreases male rats fertility, with effects on spermatogonia and spermatocytes consistent with calicheamicin producing double-stranded DNA breakage. Similar findings were observed in repeat-dose toxicology studies in rats.

There were no GO effects in female rats on copulation and fertility index, but there were effects on maternal birth weight and early embryonic development. The Preclinical Pharmacology/Toxicology reviewer recommended approval with labeling stating that Mylotarg can cause embryo-fetal harm when administered to a pregnant woman.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

GO is a recombinant, humanized IgG_4 monoclonal antibody conjugated to the cytotoxic agent N-acetyl gamma calicheamicin. The ADC binds to the CD33 antigen found on the surface of myeloid leukemic blasts and immature normal cells of the myelomonocytic lineage, forming a complex that is internalized, leading to release of the calicheamicin derivative inside the myeloid cell, which then binds to DNA resulting in double-strand breaks and cell death.

4.4.2 Pharmacodynamics

The pharmacodynamics (PD) effect observed in the patient population included target antigen saturation of CD33 with GO doses of 2 mg/m^2 or above. The exposure-efficacy relationship for CR was relatively flat for any exposure measures including Cmax after first dose, AUC after first dose, and average AUC.

4.4.3 Pharmacokinetics

The volume of distribution of GO was 21.4 L, and the elimination half-life of hP67.6 was approximately 31 hours following the first dose of 9 mg/m^2 and 45 hours after the second dose. PK of unconjugated calicheamicin was not well characterized since plasma concentrations of unconjugated calicheamicin were low and could only be measured for a short time after the end of the infusion. Urinary and fecal excretion in humans was not evaluated, but in rats about 59% and 13% were found in feces and urine, respectively. Mild or moderate renal impairment did not appear to affect the PK of GO. Also, mild hepatic impairment did not appear to affect the PK of GO. The impact of severe renal/hepatic impairment on the PK of GO was not evaluated.

Of note, the exposure of hP67.6 increased more than proportionally as GO dose increased. Cmax after first dose and AUC following 2 mg/m^2 were significant lower than those with 9 mg/m^2. The risk for VOD increased as Cmax after the first dose of GO increased. After adjusting for prior stem cell transplantation, the effect of Cmax on the risk of VOD was still significant.

The Clinical Pharmacology reviewer agreed with pharmacological basis for the recommended dose-schedule with regard to the fractionated dosing of 3 mg/m^2 based on the exposure-response relationships for safety and efficacy.

In response to a Clinical IR, the Applicant performed an analysis of simulated total hP67.6 antibody exposure and unconjugated calicheamicin exposure (AUC and Cmax) for the GO dose-schedule of 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8. Changing the regimen from 9 mg/m^2 on days 1 and 16 to 6 mg/m^2 day 1 and 3 mg/m^2 day 8 resulted in approximately 64% reduction in overall AUC and 56% reduction in overall Cmax of hP67.6.

4.5 Interdisciplinary Review Team (IRT)

A throughout QT study was not conducted. Thus, there was no IRT review for this Application. FDA informed the Applicant at the pre-BLA meeting in August 2016 that “A dedicated study should be performed before BLA or post-marketing based on benefit/risk evaluation.”

4.6 Pharmacovigilance

The DRISK reviewer assessed the safety data from the clinical trials and determined that a REMS is not necessary for Mylotarg to ensure that the benefits outweigh the risks. This was based on safety concerns with Mylotarg being well documented and the assumption that healthcare providers who treat AML should be familiar with the risks and importance of patient monitoring.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Clinical Trials

Trials / Status	Design	Population	Primary Endpoint(s)
	Pivotal Studies		
0903B1-201-US/CA ***(Completed)***	Single-arm, open-label Phase 2 trial • GO 9 mg/m^2 x 2-3 14-28d apart	Adults with CD33+ AML in first relapse after CR ≥ 6 months - 84 patients	CR rate
0903B1-202-EU ***(Completed)***	Single-arm, open-label Phase 2 trial • GO 9 mg/m^2 x 2-3 14-28d apart	Adults with CD33+ AML in first relapse after CR ≥ 6 months - 95 patients	CR rate
0903B1-203-US/EU ***(Completed)***	Single-arm, open-label Phase 2 trial • GO 9 mg/m^2 x 2-3 14-28d apart	Adults ≥ 60 with CD33+ AML in first relapse after CR ≥ 3 months - 98 patients	CR rate
MyloFrance 1 - WS1591694 ***(Completed)***	Single-arm, open-label Phase 2 trial Induction: GO 3 mg/m^2 d 1, 4, and 7 Consolidation: AraC 3 g/m^2 q12h d1-3 (1 g/m^2 for patients >55 y or CrCl >50 mL/min)	Adults with CD33+ AML in first relapse after CR ≥3, ≤18 months - 57 patients	CR+CRp
AML 19 – EORTC/ GIMEMA 06031 ***(Completed)***	Prospective, open-label, randomized trial with a sequential phase 2-3 design • GO 6 mg/m^2 d1, 3 mg/m^2 d8 (n=118) *or* • BSC (n=119)	Untreated AML age >75, 61-75 with PS>2, or unwilling to receive intensive therapy - 237 total patients randomized	OS
	Supporting Studies – Efficacy and Safety		
0903A1-101-US ***(Completed)***	Single-arm, open-label Phase 1 dose-escalation trial • GO 0.25-9 mg/m^2 x 3 doses ≥14d apart	Adults with R/R CD33+ AML - 41 patients	Safety
0903A1-102-US ***(Completed)***	Single-arm, open-label Phase 1 dose-escalation trial • GO 6-9 mg/m^2 up to 2 doses ≥14d	Pediatric patients with R/R CD33+ AML - 29 patients	CR/CRp rate

	apart (< 3 years, per kg dosing used)		
0903A1-103-JA ***(Completed)***	Single-arm, open-label Phase 1-2 dose-escalation trial **Ph 1:** GO 6-9 mg/m^2 x 2 doses ≥14d apart **Ph 2:** GO 9 mg/m^2 x 2 doses ≥14d apart	Adults with R/R CD33+ AML - Ph1: 20 patients - Ph2: 20 patients	CR/CRp rate
0903X-100374 ***(Completed)***	Single-arm, open-label Phase 4 dose-escalation trial • GO 2-6 mg/m^2 x 2 doses ≥14d apart • Optional consolidation up to 4 doses for patients with CR or CRp ≥4 weeks	Adults with relapsed CD33+ AML post HSCT - 37 patients	CR/CRp rate
0903X-100863 ***(Completed)***	Single-arm, open-label Phase 4 trial • GO 9 mg/m^2 x 2 doses d 1 and 15 • Studied steroid prophylaxis (methylprednisolone or dexamethasone)	Adults with R/R CD33+ AML - 23 patients	Safety
	Supporting Studies – Safety		
0903X-100847-US ***(Completed)***	Prospective observational study • GO per treating physician or clinical study	Patients for whom the treating physician determined GO was appropriate - 461 patients	Safety
0903B1-207-US/EU ***(Completed)***	Two-arm, open-label Phase 2 trial Arm A: GO 9 mg/m^2 x 1 dose Arm B: GO 9 mg/m^2 x 2 ≥14 d apart Consolidation: for responders, up to 3 cycles GO 6 mg/m^2 x 1 28-42d apart	Adults with MDS and IPSS ≥1.5 - 26 patients	OS, quality of life
B1761026 ***(Ongoing)***	Single arm, open-label EAP	Age ≥ 3 months with R/R CD33+ AML or MDS with no other available therapies	Safety
0903B1-205-US/EU/AU ***(Completed)***	Single-arm, open-label Phase 1/2 trial • GO 6 mg/m^2 day 1, 4 mg/m^2 day 8 (step 1a) • All other dose schedules included cytarabine	Adults with R/R CD33+ AML (step 1a) - 3 patients	CR/CRp rate

5.2 Review Strategy

The key materials used for the review of efficacy and safety include:

- BLA 761060
- MyloFrance 1 data obtained from Professor Castaigne (e-mail: SCASTAIGNE@ch-versailles.fr) and the study sponsor, the Centre Hospitalier de Versailles (CHV)
- Relevant published literature

- Relevant information in the public domain

Protocols 201, 202, 203, and the investigator sponsored trials MyloFrance 1 and AML 19 were used for the analysis of efficacy. Protocols 201, 202, and 203 were analyzed separately and in aggregate given the similarity between the trials. The details of each protocol are listed below.

Of note, the primary data for studies MyloFrance 1 and AML-19 were not provided by the Applicant. Thus, the literature reports for MyloFrance 1 (Taksin, Legrand et al. 2007) and AML-19 (Amadori, Suciu et al. 2016) were used in the assessment of efficacy and safety. MyloFrance 1 was sponsored by the CHV and investigators were from the Acute Leukemia French Association (ALFA). The primary data was obtained from Professor Castaigne and the CHV to supplement and confirm the results of this trial.

The protocols for both studies MyloFrance 1 and AML-19 were submitted to the BLA. I performed a detailed review of both protocols and confirmed that they were adequate and well-controlled, meeting the requirements of 21 CFR 314.126 and GCP.

Table 5: Determination of Adequate and Well-Controlled Status

	MyloFrance 1	AML-19
Study	Prospective	Prospective
Patients	57 patients with relapsed AML	237 patients with untreated AML
IRB-approved protocol	Yes	Yes
Objectives	Yes	Yes
Valid design for comparison to a control	Comparison to historical control	Comparison to control arm
Appropriate selection of subjects	Yes	Yes
Treatment is unbiased	Yes	Yes
Bias in study conduct is minimized	Yes	Yes
Endpoint is defined and reliable	Yes	Yes
Analysis is statistically adequate	Yes	Yes
Test article is characterized	Yes	Yes

Source: FDA analysis

Data from all 13 protocols listed in Table 4 were used for the analysis of safety. The patients treated on these protocols received GO produced using older methods and specifications. Of note, [redacted] (b) (4) was recently detected, with analyses showing trace levels as early as 1999, a shift to higher levels in 2005, and consistent levels since 2006. Since the Manufacturing and Clinical Pharmacology Reviewers confirmed that the new manufacturing processes yield comparable product, the reviewed data is considered applicable to current drug product and pooling of data obtained from trials over time was considered acceptable.

Statistical analyses by the clinical reviewer were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC), and MedDRA Adverse Events Diagnostic (MAED) (Clinical Trials & Surveys Corporation, Owings Mills, MD) was used to assess for safety signals.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol 0903B1-201-US/CA (Protocol 201)

A study of the efficacy and safety of CMA-676 as a single agent treatment of patients with acute myeloid leukemia (AML) in first relapse

Protocol 201 Design

Protocol 201 was a single-arm, open-label, multicenter outpatient trial of GO in adults with CD33-positive AML in first relapse, which took place in the United States and Canada. The treatment consisted of induction with Mylotarg, with initial follow-up until month 6, and telephone follow-up every 3-6 months until death or termination of the study by the Sponsor. The primary endpoint was CR rate. A Simon two-stage design was utilized, with a plan to evaluate up to 55 patients. However, they later allowed for enrollment of up to an additional 55 patients.

Protocol 201 Objectives

The primary objective of the protocol was to evaluate the efficacy (CR) and safety of Mylotarg. The primary efficacy endpoint for this objective was CR rate. CR was defined as absence of peripheral blood blasts, ≤5% blasts in the marrow morphologically, hemoglobin ≥9 g/dL, platelets ≥100,000/µL, ANC ≥ 1,500/µL, and absence of need for transfusion of platelets and red blood cells.

The secondary objectives were to evaluate the duration of CRs and morphologic remissions, PK studies, and to assess possible predictors of response to Mylotarg. Morphologic remissions were defined as CR, except that platelet counts did not reach the level defined by CR (essentially CRp).

Protocol 201 Key Eligibility

1. CD33-positive *de novo* AML in first relapse following at least 6 months of CR (starting from the date of the bone marrow specimen in CR). Patients were required to have AML blast cells ≥ 5% of nucleated cells in bone marrow aspirates and ≥ 80% of the leukemic blasts had to have CD33 expression > 4 times that of baseline (as measured by the background fluorescence on that patient's unstained cells).
2. Age ≥ 18 years
3. Performance status 0 to 2 (ECOG)
4. Serum creatinine ≤ 2 mg/dL
5. Serum total bilirubin ≤ 1.5 mg/dL
6. A signed, informed consent
7. Negative pregnancy tests during the week prior to treatment
8. No myelodysplasia prior to AML
9. No AML secondary to exposure to chemotherapy or toxins
10. No prior allogeneic HSCT
11. No peripheral WBC ≥30,000/μL at the time of initial drug administration. Patients may be pre-treated with hydroxyurea, but it must be discontinued 24 hours prior to GO administration.
12. No treatment with chemotherapy for relapse except Hydroxyurea
13. No cerebral or meningeal leukemia
14. No pregnant women or breastfeeding mothers
15. No previous treatment with anti-CD33 antibody
16. No uncontrolled infection
17. No other malignancy at time of entry into the study
18. No serious cardiac or lung disorder
19. No HIV
20. No use of a studied medicinal product during the 4 weeks prior to entry in the study
21. No patients unable to have a bone marrow aspirate

Protocol 201 Treatment Plan

Premedication – Acetaminophen 650-1000 mg orally and diphenhydramine 50 mg orally 1-2 hours prior. Additional doses of acetaminophen 650-1000 mg would be administered every 4 hours as needed following the initial pre-treatment dose.

Mylotarg – Treatment was given at 9 mg/m^2 as a single IV infusion over approximately 2 hours per dose for 2 doses.

- Part I of study: about 50 days, including 7 days screening, 2 doses GO 14-28 days apart, and 28 days follow-up after the last dose of GO.

- Infusion observation period began with the start of each infusion and continued for 8 hours during dose 1 and 6 hours for subsequent doses as long as no infusion-related events occurred during dose 1.
- Use of a central IV line was preferred for administration of GO, but not required.
- Dose calculation did not change between dose periods 1 and 2 regardless of weight change.
- Patients were eligible to receive dose 2 provided that they recovered from reversible non-hematologic toxicities from the previous treatment dose, there was no evidence of uncontrolled infection, no evidence of disease progression, no evidence of significant formation of antibodies reactive with calicheamicin or the hP67.6 antibody, and the patient had to be at least 14 days, but no more than 28 days from the previous infusion. 14 day dosing schedule preferred. Delays beyond 17 days required notation in the case report form (CRF).
- An earlier version of the protocol allowed for a third dose of Mylotarg if the patient did not achieve a CR or morphologic remission, satisfied criteria in the previous bullet, demonstrated > 50% decrease in BM blast percent from the screening aspirate, and their BM biopsy demonstrated ≥15% cellularity.
- Part II of study: initial follow-up of about 6 additional months.
- Patients who attained CR or morphologic remission were not to be offered consolidation therapy, or any other anti-leukemic therapy, for at least 30 days after they entered remission.
- After 30 days, patients in CR would receive no further therapy, allogeneic HSCT, autologous HSCT, or one cycle of mitoxantrone 10 mg/m^2 x 5 days and VP-16 100 mg/m^2 x 5 days.
- Selected patients with an initial CR or CRp lasting at least a month were able to be treated with GO (2 doses) following a second or subsequent relapse. They had to meet the initial eligibility criteria, with the exception of treatment with prior anti-CD33 antibody and no prior transplantation (i.e. they allowed for re-treatment after a post-transplant relapse).
- Part III of study: patients who completed part II were considered completed in the study, but those patients continued to be followed up by telephone communication in this post-study phase for an additional 18 months. In addition, the follow-up was maintained on a 6 month basis until death or termination of study by the Sponsor.

Protocol 201 Schedule of Assessments

Study Schedule Visit	Screening	Baseline ~~Cycle~~Dose 1			Study Period ~~Cycle~~Dose 2*										End of Study Period	
Study Week		1			2			3			4		5		6	7
Study Day (approximate)	-7 to 1	1			8			15			22		29		36	43**
Medical History	X															
Complete Physical Exam[a]	X															X
CBC with Differential[d]	X	X[b]	X	X	X	X	X	X[b]	X	X	X	X	X	X		X
Blood Chemistry	X	X[b]	X	X	X	X	X	X[b]	X	X	X	X	X	X		X
PT, PTT	X															X
Chest X-ray	X															X
ECG	X	X[b]														X
β-HCG	X[e]															
Urinalysis	X															X
Bone Marrow Aspirate	X[f]				X						X					X[g]
Bone Marrow Biopsy	X[f]										~~X~~[f]					X[g]
Plasma Samples for PK		X[b,c]	X		X	X		X[b,c]	X		X	X				X
Whole Blood for CD33 Saturation		X[b,c]						X[b,c]								
Ab Against CMA-676[h]		X[b]			X						X					X
Pretreatment Medications		X[i]						X[i]								
Study Drug Administration		X						X*								
Interim Physical Exams [a, j]		X[b,c]	X		X	X		X[b,c]	X		X	X		X		
Monitor Study Events		X			X			X			X			X	X	X

Following Each Infusion															
Study Days 1, 15[a]															
Hours	0	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	7[c]	8[c]
Minutes	0	15	30	45	60	90	120	150	180	210	240	300	360	420	480
Vital Signs[d]	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Plasma Samples	X[e]				X		X		X		X		X		
CD33 Site Saturation Blood Samples	X								X				X		
Study Drug Administration	X----------														X

STUDY FLOW CHART PART II - RESPONDERS

Study Schedule Visit						Final
Study Week	11	15	19	23	27	31
Study Day (approximate)	71	99	127	155	183	211
Interim Physical Examination[a]	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X
CBC with Differential[c]	X	X	X	X	X	X
Survival status*	X	X	X	X	X	X

STUDY FLOW CHART PART II- NONRESPONDERS

Study Schedule Visit						Final
Study Week	11	15	19	23	27	31
Study Day (approximate)	71	99	127	155	183	211
Survival status*	X	X	X	X	X	X

The schedule of efficacy and safety assessments is shown above. Safety laboratory tests were performed at the local laboratories. CBC and CMPs were performed three times weekly for either 2 weeks following infusion of GO or until recovery of granulocytes and platelets to ≥1500/μL and ≥100,000/μL, respectively.

Screening bone marrow aspirate was sent to [redacted] (b) (4) for confirmation of CD33+ AML. Details of flow cytometric testing were not included. Bone marrow was checked at screening, 7 days following each infusion, and 28 days following the last infusion of study drug (on approximately days 8, 22, and 43).

In addition to the investigational site, aliquots were sent to [redacted] (b) (4) laboratory at [redacted] (b) (4) and an independent consultant, who reviewed morphology from the bone marrow samples in a blinded fashion. There was to be no direct communication between personnel at the investigational sites and the independent contractor with regard to the status of patients enrolled in the study. Analyses of CD33 site saturation and PK/immune analyses (evaluation of antibodies against calicheamicin and hP67.6 antibody) were sent out to [redacted] (b) (4) and Wyeth-Ayerst in Pearl River, respectively.

Patients were monitored for safety and antibody response for 28 days after the last dose of GO. For patients who failed treatment and were treated with other regimens, collection of subsequent BM specimens was not required.

For patients who went to HSCT, the type of transplant, date, date of platelet recovery > 20,000/μL without transfusion, neutrophil recovery ≥500/μL, status at approximately 100 days (including CBC, remission and survival status), date of relapse or death including cause of death, and occurrence of clinically serious hemorrhage, infection, GVHD, VOD, or other serious unusual toxicities after HSCT. For patients receiving additional chemotherapy in part II of the study, the names of drugs and dates received were collected, as well as response to the additional therapy, and the occurrence of the same clinically serious toxicities monitored post-HSCT mentioned above (except GVHD).

Protocol 201 Statistical Analysis Plan

The primary endpoint of the protocol was the proportion of patients who achieved a CR. The endpoint was initially evaluated approximately 28 days after the final dose of GO. Patients not achieving CR by this date, but with no peripheral blasts and no more than 5% aspirate or biopsy blasts were followed into the 6-month follow-up period to determine whether remission occurred. The sample size was based on estimates of the response probability of an ineffective drug being 0.15 and the response probability of an effective drug being 0.30. Calculations were made at the 0.10 level of significance with power of 90%. They utilized a Simon 2-stage design, for which the first stage consisted of 23 patients and the sample size required for the entire study was 55. In order to obtain further safety information, they allowed for enrollment of up to 55 additional patients.

Their primary analysis was based on the intent-to-treat population (i.e. all patients receiving at least one dose of GO), consisting of patients enrolled on or before the enrollment cutoff of 12/31/1998. As secondary analyses, the primary endpoint and most important endpoints would be re-analyzed for 1) the originally planned number of patients, 2) excluding non-evaluable patients (i.e. the evaluable patient analysis), and 3) including patients who did not meet criteria for remission, but who were considered as successfully treated (referred to as “responders,” essentially CRi).

Analysis of secondary endpoints included rate of CRp, RFS (total and post-HSCT), OS (total, landmark, and post-HSCT), and platelet and ANC recovery after the final dose. Other endpoints included time to remission, CD33 site saturation, the time to clearance of blasts, time to additional therapy, % cellularity, and % blast cells. They additionally analyzed health outcomes, such as hospital admissions, duration of hospital stay, time to hospital admission, number of days on antibiotics, and number of transfusions. Survival endpoints were estimated using Kaplan-Meier survival estimates and calculating median survival and/or probability of patients surviving to 3, 6, and 12 months.

Safety analyses were descriptive and severity was based on NCI Common Toxicity Criteria (version 2).

Patients discontinuing for reasons other than disease progression, production of antibodies to GO, or an AE were replaced. Evaluable patients met eligibility criteria, completed 2-3 doses of GO, or discontinued due to disease progression, production of antibodies to GO, or an AE.

Key Revisions to Protocol 201

The initial version of Protocol 201 was finalized on 2/26/1997. There were 5 amendments. The following revisions were considered major:

Amendment IV 12/10/1998	Added requirement for additional data on follow-up for patients undergoing HSCT after GO. Provided for continued enrollment beyond 55 evaluable patients.
Amendment V: 10/1/1999	Modified the Simon 2-stage design such that the development of the drug would not be automatically halted if after the first stage there were 3 or fewer CRs. This was done based on observation of CRp responses in phase I studies using Mylotarg. This decision would inflate the original type I error if there were only 2-3 CRs. They also eliminated the 3rd dose of Mylotarg.

5.3.2 Protocol 0903B1-202-EU (Protocol 202)

A study of the efficacy and safety of CMA-676 as single agent treatment of patients with acute myeloid leukemia (AML) in first relapse

Protocol 202 Design

Protocol 202 was a European single-arm, open-label, multicenter outpatient trial of GO in adults with CD33-positive AML in first relapse. The treatment consisted of induction with Mylotarg, with initial follow-up until month 6, and telephone follow-up every 3-6 months until death or termination of the study by the Sponsor. The primary endpoint was CR rate. There was no formal hypothesis testing and they planned for pooling of their results with Study 201. Sample size was based on practical, rather than statistical needs to provide safety data and limited efficacy data in Europe. They originally planned to enroll enough patients to allow for assessment of approximately 20 evaluable patients. However, an amendment allowed for continued enrollment of up to 130 additional patients. They ultimately enrolled 95 total patients to this trial.

Protocol 202 Objectives

The primary objective of the protocol was to evaluate the efficacy (CR) and safety of GO. The primary efficacy endpoint for this objective was CR rate. CR was defined as absence of peripheral blood blasts, ≤5% blasts in the marrow morphologically,

hemoglobin ≥9 g/dL, platelets ≥100,000/μL, ANC ≥ 1,500/μL, and absence of need for transfusion of platelets and red blood cells.

The secondary objectives were to evaluate the duration of CRs and morphologic remissions, PK studies, and to assess possible predictors of response to Mylotarg. Morphologic remissions were defined as CR, except that platelet counts did not reach the level defined by CR (i.e. CRp).

Protocol 202 Key Eligibility

1. CD33-positive *de novo* AML in first relapse following at least 6 months of CR (starting from the date of the bone marrow specimen in CR), including patients who had autologous or allogeneic HSCT if they previously engrafted. Patients were required to have AML blast cells > 5% of nucleated cells in bone marrow aspirates and ≥ 80% of the leukemic blasts had to have CD33 expression > 4 times that of baseline (as measured by the background fluorescence on that patient's unstained cells).
2. Age ≥ 18 years
3. Performance status 0 to 2 (ECOG)
4. Serum creatinine ≤ 2 mg/dL
5. Serum total bilirubin ≤ 1.5 mg/dL
6. A signed, informed consent
7. Negative pregnancy tests during the week prior to treatment. Male and female patients of child-bearing potential must use an acceptable and effective method of contraception throughout the study.
8. No myelodysplasia prior to AML.
9. No AML secondary to exposure to chemotherapy or toxins.
10. No peripheral WBC ≥30,000/μL at the time of initial drug administration. Patients may be pre-treated with hydroxyurea, but it must be discontinued 24 hours prior to GO administration.
11. No treatment with chemotherapy for relapse except Hydroxyurea.
12. No cerebral or meningeal leukemia.
13. No pregnant women or breastfeeding mothers.
14. No previous treatment with anti-CD33 antibody.
15. No uncontrolled infection.
16. No other malignancy at time of entry into the study.
17. No serious cardiac or lung disorder.
18. No HIV.
19. No use of an investigational agent during the 4 weeks prior to entry in the study.
20. No patients unable to have a bone marrow aspirate.

Protocol 202 Treatment Plan

Premedication – Acetaminophen 650-1000 mg orally and diphenhydramine 50 mg orally 1-2 hours prior. Additional doses of acetaminophen 650-1000 mg would be administered every 4 hours as needed following the initial pre-treatment dose.

Mylotarg – Treatment was given at 9 mg/m^2 as a single IV infusion over approximately 2 hours per dose for 2 doses.

- Part I of study: about 50 days, including 7 days screening, 2 doses GO 14-28 days apart, and 28 days follow-up after the last dose of GO.
- Infusion observation period began with the start of each infusion and continued for 8 hours during dose 1 and 6 hours for subsequent doses as long as no infusion-related events occurred during dose 1.
- Dose calculation did not change between dose periods 1 and 2 regardless of weight change.
- Patients were eligible to receive dose 2 provided that they recovered from reversible non-hematologic toxicities from the previous treatment dose, there was no evidence of uncontrolled infection, no evidence of disease progression, no evidence of significant formation of antibodies reactive with calicheamicin or the hP67.6 antibody, and the patient had to be at least 14 days, but no more than 28 days from the previous infusion.
- An earlier version of the protocol allowed for a third dose of Mylotarg if the patient did not achieve a CR or CRp, satisfied criteria in the previous bullet, demonstrated > 50% decrease in BM blast percent from the screening aspirate, and their BM biopsy demonstrated ≥15% cellularity.
- Part II of study: initial follow-up of about 6 additional months.
- Patients who attained CR or CRp were not to be offered consolidation therapy, or any other anti-leukemic therapy, for at least 30 days after they entered remission.
- After 30 days, patients in CR or CRp would receive no further therapy, allogeneic HSCT, autologous HSCT, or one cycle of mitoxantrone 10 mg/m^2 x 5 days and VP-16 100 mg/m^2 x 5 days.
- Selected patients with an initial CR or CRp lasting at least a month were able to be treated with GO (2 doses) following a second or subsequent relapse. They had to meet the initial eligibility criteria, with the exception of treatment with prior anti-CD33 antibody, bilirubin and creatinine values (instead bilirubin needed to be ≤ 2 mg/dL and creatinine needed to be ≤ 3 mg/dL).
- Part III of study: patients who completed part II were considered completed in the study, but those patients continued to be followed up by telephone communication in this post-study phase for an additional 18 months. In addition, the follow-up was maintained on a 6 month basis until death or termination of study by the Sponsor.

Protocol 202 Schedule of Assessments

The schedule of assessments is essentially the same as Study 201, provided in section 5.3.1 above, with the exception that both responders and non-responders were followed monthly for 6 months on this protocol. Safety laboratory tests were performed at the local laboratories. CBC and CMPs were performed three times weekly for either 2 weeks following infusion of GO or until recovery of granulocytes and platelets to ≥1500/μL and ≥100,000/μL, respectively.

Screening bone marrow aspirate was sent to the EU central laboratory for confirmation of CD33+ AML. Details of flow cytometric testing were not included. Bone marrow was checked at screening, 7 days following each infusion, and 28 days following the last infusion of study drug (on approximately days 8, 22, and 43).

In addition to the investigational site, aliquots were sent to the EU central laboratory for research tests and an independent consultant, who reviewed morphology from the bone marrow samples in a blinded fashion. There was to be no direct communication between personnel at the investigational sites and the independent contractor with regard to the status of patients enrolled in the study. Analyses of CD33 site saturation/immune analyses (evaluation of antibodies against calicheamicin and hP67.6 antibody) and PK were sent out to the EU central laboratory and Wyeth-Ayerst in Pearl River, respectively.

Patients were monitored for safety and antibody response for 28 days after the last dose of GO. All hospitalizations suspected to be drug related adverse events or which were prolonged because of drug related events were reported.

For patients who went to HSCT, the type of transplant, date, date of platelet recovery > 20,000/μL without transfusion, neutrophil recovery > 500/μL, status at approximately 100 days (including CBC, remission and survival status), date of relapse or death including cause of death, and occurrence of clinically serious hemorrhage, infection, GVHD, VOD, or other serious unusual toxicities after HSCT. For patients receiving additional chemotherapy in part II of the study, the names of drugs and dates received were collected, as well as response to the additional therapy, and the occurrence of the same clinically serious toxicities monitored post-HSCT mentioned above (except GVHD).

Protocol 202 Statistical Analysis Plan

The primary endpoint of the protocol was the proportion of patients who achieved a CR. The endpoint was initially evaluated approximately 28 days after the final dose of GO. Patients not achieving CR by this date, but with no peripheral blasts and no more than 5% aspirate or biopsy blasts were followed into the 6-month follow-up period to determine whether remission occurred. Maximum response was used for the analysis. No formal significance testing was carried out.

Sample size was based upon practical, not statistical, needs to provide safety data and limited efficacy data in Europe. They originally planned to enroll enough patients to allow for assessment of approximately 20 evaluable patients. However, an amendment allowed for continued enrollment of up to 130 additional patients.

Remission status was summarized as the proportion of patients achieving CR, CRp, overall response, or no response. A 95% CI for the true proportion of patients was calculated for each response using the method of Clopper and Pearson. Data from the study was to be eventually pooled with Study 201 and an analysis of the pooled data was to form the basis of an Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS).

Their primary analysis was based on the intent-to-treat population (i.e. all patients receiving at least one dose of GO), consisting of patients enrolled on or before the enrollment cutoff of 11/15/2000. In order to assess the effect of GO, patients who attained CR or CRp were not offered consolidation therapy, or any other antileukemic therapy, for at least 30 days after achieving remission. Remission status was not assessed after the date of HSCT or other antileukemic therapy.

Analysis of secondary endpoints included rate of CRp, overall response, RFS, OS, and platelet and ANC recovery from the time of the first dose of GO. Other endpoints included CD33 site saturation, time to first hospitalization, number of days on antibiotics, number of transfusions, and time to additional therapy. Survival endpoints were estimated using Kaplan-Meier survival estimates and calculating median survival and/or probability of patients surviving to 12 months using the method of Clopper and Pearson.

Safety analyses were descriptive and severity was based on NCI Common Toxicity Criteria (version 1.0).

Patients discontinuing for reasons other than disease progression, production of antibodies to GO, or an AE were replaced. Evaluable patients met eligibility criteria, completed 2-3 doses of GO, or discontinued due to disease progression, production of antibodies to GO, or an AE.

Key Revisions to Protocol 202

The initial version of Protocol 201 was finalized on 4/4/1997. There were 4 amendments. The most significant changes were pretreatment medication to prevent infusion-related symptoms, allowance of prior HSCT, increased accrual of up to an additional 130 patients, the ability to re-treat for a subsequent relapse, and removal of the third dose of GO due to prolonged myelosuppression and lack of efficacy. The final amendment IV was finalized on 10/1/1999.

5.3.3 Protocol 0903B1-203-US/EU (Protocol 203)

A study of the safety and efficacy of CMA-676 in treatment of elderly patients with acute myeloid leukemia (AML) in first relapse

Protocol 203 Design

Protocol 203 was a single-arm, open-label, multicenter outpatient trial of GO in elderly patients (≥ 60 years) with CD33-positive AML in first relapse. The study was conducted at sites in the US and Europe. The treatment consisted of induction with Mylotarg, initial follow-up until month 6, and telephone follow-up every 3-6 months until death or termination of the study by the Sponsor. The primary endpoint was CR rate. A Simon two-stage design was utilized, with a plan to evaluate up to 55 patients. However, they later allowed for enrollment of up to an additional 55 patients.

Protocol 203 Objectives

The primary objective of the protocol was to evaluate the efficacy (CR) and safety of GO in elderly patients with AML in first relapse. The primary efficacy endpoint for this objective was CR rate. CR was defined as absence of peripheral blood blasts, ≤5% blasts in the marrow morphologically, hemoglobin ≥9 g/dL, platelets ≥100,000/μL, ANC ≥ 1,500/μL, and absence of need for transfusion of platelets and red blood cells.

The secondary objectives were to evaluate the duration of CRs and morphologic remissions, assess the PK properties, and assess possible predictors of response to GO. Morphologic remissions were defined as CR, except that platelet counts did not reach the level defined by CR (i.e. CRp). The definition of CRp includes transfusion independence.

Protocol 203 Key Eligibility

1. CD33-positive *de novo* AML in first relapse following at least 3 months of CR (starting from the date of the bone marrow specimen in CR). Patients were required to have AML blast cells ≥ 5% of nucleated cells in bone marrow aspirates and ≥ 80% of the leukemic blasts had to have CD33 expression > 4 times that of baseline (as measured by the background fluorescence on that patient's unstained cells).
2. Age ≥ 60 years
3. Recovery from reversible toxicities due to previous antineoplastic therapy (except alopecia).
4. Performance status 0 to 2 (ECOG)
5. Serum creatinine ≤ 3 mg/dL.
6. Serum total bilirubin ≤ 2 mg/dL
7. A signed, informed consent
8. No myelodysplasia prior to AML.

9. No AML secondary to exposure to chemotherapy or toxins.
10. No history of bone marrow and peripheral blood HSCT.
11. No peripheral WBC ≥30,000/μL at the time of initial drug administration. Patients may be pre-treated with hydroxyurea, but it must be discontinued 24 hours prior to GO administration.
12. No treatment with chemotherapy for relapse except Hydroxyurea.
13. No cerebral or meningeal leukemia.
14. No previous treatment with anti-CD33 antibody.
15. No uncontrolled, life-threatening infections.
16. No other malignancy at time of entry into the study.
17. No uncontrolled pulmonary or cardiac disease.
18. No HIV.
19. No use of an investigational agent during the 4 weeks prior to entry in the study.
20. No patients unable to have a bone marrow aspirate.

Protocol 203 Treatment Plan

Premedication – Acetaminophen 650-1000 mg orally and diphenhydramine 50 mg orally 1-2 hours prior. Additional doses of acetaminophen 650-1000 mg would be administered every 4 hours as needed following the initial pre-treatment dose.

Mylotarg – Treatment was given at 9 mg/m^2 as a single IV infusion over approximately 2 hours per dose for 2 doses.

- Part I of study: about 50 days, including 7 days screening, 2 doses GO 14-28 days apart, and 28 days follow-up after the last dose of GO.
- Infusion observation period began with the start of each infusion and continued for 8 hours during dose 1 and 6 hours for subsequent doses as long as no infusion-related events occurred during dose 1.
- Dose calculation did not change between dose periods 1 and 2 regardless of weight change.
- Patients were eligible to receive dose 2 provided that they recovered from reversible non-hematologic toxicities from the previous treatment dose, there was no evidence of uncontrolled infection, no evidence of disease progression, no evidence of significant formation of antibodies reactive with calicheamicin or the hP67.6 antibody, and the patient had to be at least 14 days, but no more than 28 days from the previous infusion.
- An earlier version of the protocol allowed for a third dose of Mylotarg if the patient did not achieve a CR or CRp, satisfied criteria in the previous bullet, demonstrated > 50% decrease in BM blast percent from the screening aspirate, and their BM biopsy demonstrated ≥15% cellularity.
- Part II of study: initial follow-up of about 6 additional months.
- Patients who attained CR or CRp were not to be offered consolidation therapy, or any other anti-leukemic therapy, for at least 30 days after they entered remission.

- After 30 days, patients in CR or CRp would receive no further therapy, allogeneic HSCT, autologous HSCT, or one cycle of mitoxantrone 10 mg/m^2 x 5 days and VP-16 100 mg/m^2 x 5 days.
- Selected patients with an initial CR or CRp lasting at least a month were able to be treated with GO (2 doses) following a second or subsequent relapse. They had to meet the initial eligibility criteria, with the exception of treatment with prior anti-CD33 antibody.
- Part III of study: patients who completed part II were considered completed in the study, but those patients continued to be followed up by telephone communication in this post-study phase for an additional 18 months. In addition, the follow-up was maintained on a 6 month basis until death or termination of study by the Sponsor.

Protocol 203 Schedule of Assessments

The schedule of assessments is essentially the same as Study 201, provided in section 5.3.1 above, with the exception that both responders and non-responders were followed monthly for 6 months on this protocol. Safety laboratory tests were performed at the local laboratories. CBC and CMPs were performed three times weekly for either 2 weeks following infusion of GO or until recovery of granulocytes and platelets to ≥1500/μL and ≥100,000/μL, respectively.

Screening bone marrow aspirate was sent to (b) (4) for confirmation of CD33+ AML. Bone marrow was checked at screening, 7 days following each infusion, and 28 days following the last infusion of study drug (on approximately days 8, 22, and 43).

In addition to the investigational site, an aliquot was sent to (b) (4) laboratory at (b) (4) for research tests. An independent consultant reviewed morphology from bone marrow samples in a blinded fashion. There was to be no direct communication between personnel at the investigational sites and the independent contractor with regard to the status of patients enrolled in the study. Analyses of CD33 site saturation and PK/immune analyses (evaluation of antibodies against calicheamicin and hP67.6 antibody) were sent out to (b) (4) and Wyeth-Ayerst in Pearl River, respectively.

Patients were monitored for safety and antibody response for 28 days after the last dose of GO. All hospitalizations and reasons for hospitalization were to be reported. Of note, patients not eligible to receive dose 2 were to undergo procedures outlined in schedule of assessments for weeks 3 through 7. The procedures outlined for day 43 would be obtained 28 days after the last dose of GO.

For patients who went to HSCT, the type of transplant, date, date of platelet recovery > 20,000/μL without transfusion, neutrophil recovery > 500/μL, status at approximately 100 days (including CBC, remission and survival status), date of relapse or death including cause of death, and occurrence of clinically serious hemorrhage, infection,

GVHD, VOD, or other serious unusual toxicities after HSCT. For patients receiving additional chemotherapy in part II of the study, the names of drugs and dates received were collected, as well as response to the additional therapy, and the occurrence of the same clinically serious toxicities monitored post-HSCT mentioned above (except GVHD).

Protocol 203 Statistical Analysis Plan

The primary endpoint of the protocol was the proportion of patients who achieved a CR. The endpoint was initially evaluated approximately 28 days after the final dose of GO. Patients not achieving CR by this date, but with no peripheral blasts and no more than 5% aspirate or biopsy blasts were followed into the 6-month follow-up period to determine whether remission occurred.

Sample size estimates were based on the response probability of an ineffective drug being defined as 0.15 and the response probability of an effective drug being 0.30. Calculations were made at the 0.10 significance level with power 90%. They originally planned to enroll a sufficient number of patients to allow for assessment of up to 55 evaluable patients. In the first stage, 23 patients would be evaluated and, depending on the safety and CR rate in these patients, a decision would be made regarding continuation of the study. An amendment allowed for continued enrollment of up to an additional 55 patients.

A later protocol amendment modified the Simon 2-stage design such that the development of the drug would not be automatically halted if after the first stage there were 3 or fewer CRs. This was done based on observation of CRp responses in phase I studies using Mylotarg. This decision would inflate the original type I error if there were only 2-3 CRs.

Remission status was summarized as the proportion of patients achieving CR, CRp, overall response, or no response. A 95% CI for the true proportion of patients was calculated for each response using the method of Clopper and Pearson. CIs were adjusted to account for the interim analysis at the end of the first stage.

Their primary analysis was based on the intent-to-treat population (i.e. all patients receiving at least one dose of GO), consisting of patients enrolled on or before the enrollment cutoff of 12/31/1998. In order to assess the effect of GO, patients who attained CR or CRp were not offered consolidation therapy, or any other antileukemic therapy, for at least 30 days after achieving remission. Remission status was not assessed after the date of HSCT or other antileukemic therapy.

Analysis of secondary endpoints included rate of CRp, overall response, RFS, OS, and platelet and ANC recovery from the time of the first dose of GO. Other endpoints included time to remission, CD33 site saturation, time to first hospitalization, number of

days on antibiotics, number of transfusions, and time to additional therapy. Survival endpoints were estimated using Kaplan-Meier survival estimates.

Safety analyses were descriptive and severity was based on NCI Common Toxicity Criteria (version 1.0).

Patients discontinuing for reasons other than disease progression, production of antibodies to GO, or an AE were replaced. Evaluable patients met eligibility criteria, completed 2-3 doses of GO, or discontinued due to disease progression, production of antibodies to GO, or an AE.

Key Revisions to Protocol 203

The initial version of Protocol 203 was finalized on 10/9/1997. There were 4 amendments. The most significant changes were pretreatment medication to prevent infusion-related symptoms, accrual of up to an additional 55 patients, modification of the statistical section to describe changes to the Simon 2-stage design in light of the many CRp responses, the ability to re-treat for a subsequent relapse, and removal of the third dose of GO due to prolonged myelosuppression. The final amendment IV was finalized on 10/1/1999.

5.3.4 Protocol MyloFrance 1 (WS1591694)

A multi-centre, non-randomised, open-label, phase II study to evaluate the efficacy and safety of the monoclonal antibody gemtuzumab ozogamicin (Mylotarg®) with fractionated doses in adult patients with acute myeloblastic anaemia (AML) in relapse

Protocol MyloFrance 1 Design

Protocol MyloFrance 1 was a single-arm, open-label inpatient trial of the fractionated dosing regimen of GO in adults with CD33-positive *de novo* AML in first relapse. The treatment consisted of induction with Mylotarg and consolidation with HiDAC, with laboratory follow-up until month 6, and long-term follow-up every 3 months until death. The primary endpoint was ORR (CR+CRp).

Protocol MyloFrance 1 Objectives

The primary objective of the protocol was to evaluate the efficacy (ORR, CR, CRp, OS, RFS) and safety of fractionated doses of Mylotarg. The primary efficacy endpoint for this objective was CR+CRp within 43 days. CR was defined as absence of blood blasts and absence of clinical tumor, <5% blasts in the marrow, hemoglobin > 9 g/dL, platelets >100,000/mm^3, white blood cells > 1,000/mm^3 and absence of need for transfusion of

platelets and red blood cells. CRp was defined as absence of blood blasts and absence of clinical tumor, <5% blasts in the marrow, hemoglobin > 9 g/dL, platelets >20,000/mm^3, white blood cells > 1,000/mm^3 and absence of need for transfusion of platelets and red blood cells.

The secondary objectives were to evaluate the duration of CR and PK studies of Mylotarg with fractionated doses.

Protocol MyloFrance 1 Key Eligibility

1. CD33-positive *de novo* AML (CD33 positive in > 80% cells) in a first early relapse with duration of first CR at least 3 months and less than 18 months, starting from the date of the bone marrow smear in CR.
2. Age > 18 years
3. Performance status 0 to 2 (ECOG)
4. Serum creatinine < 2 mg/dL
5. Transaminases < 2 N and serum bilirubin < 2 N
6. A signed, informed consent
7. Negative pregnancy tests during the week prior to treatment
8. No myelodysplasia prior to AML
9. No refractory AML
10. No acute promyelocytic leukemia (APL)
11. No prior autologous or allogeneic HSCT
12. No treatment with chemotherapy for relapse except Hydroxyurea
13. No proposed allograft transplantation or autologous HSCT during the 3 months following treatment with Mylotarg
14. No history of serious liver disease (including hepatitis)
15. No cerebral or meningeal leukemia
16. No pregnant women or breastfeeding mothers
17. No previous treatment with anti-CD33 antibody
18. No uncontrolled infection
19. No other malignancy at time of entry into the study
20. No serious cardiac or lung disorder
21. No HIV
22. No use of a studied medicinal product during the 4 weeks prior to entry in the study
23. No patients unable to have a bone marrow aspirate

Protocol MyloFrance 1 Treatment Plan

Premedication – 20 mg Solumedrol one half hour before the infusion of Mylotarg.

Mylotarg – Treatment was given at 3 mg/m^2 on days 1, 4, and 7 as an IV infusion administered over 2 hours.

- The protocol required that patients be monitored during the infusion and during 4 hours after the infusion, given the possibility of an infusion reaction.
- The protocol stated that since ampules of Mylotarg are 5 mg and the dose is 3 mg/m^2/day, doctors were asked to not exceed 5 mg/day total dose.
- Treatment was discontinued if elevation of transaminases was > 5 times normal and/or factor V < 50% when checked on days 3, 6, and 9.
- Responding patients, in the absence of signs of hepatic toxicity, were eligible to receive consolidation HiDAC at 3 g/m^2/12 hours on days 1-3 in patients <55 with creatinine clearance >50 mL/min or 1 g/m^2/12 hours on days 1-3 in patients >55 or <55 with creatinine clearance <50 mL/min.
- Eligible patients could receive autologous or allogeneic transplantation within 4 months after treatment with Mylotarg. It was recommended to delay HSCT by at least 90 days following Mylotarg treatment.

Protocol MyloFrance 1 Schedule of Assessments

		Treatment period																
	screening	day																Final[3]
Day		1	3	4	6	7	9	11	15	18	21	24	28	31	35			43
Informed consent	X																	
Medical history	X																	
Clinical examination	X	X		X		X			X			X			X			X
Bone marrow smear	X								X		X							X
Immuno-phenotype (CD33)	X																	X
FAB Type	X																	X
Karyotype	X																	X
CBC[2]	X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Biochemistry[3]	X	X[1]	X		X		X		X		X		X		X	X	X	X
Coagulation tests	X	X[1]	X		X		X		X		X		X		X	X	X	X
Chest X-ray	X					X					X		X					X
ECG	X																	X
FEV	X																	X
βhCG	X																	
Freezing of blasts	X																	
MDR, FLT3 MLL markers	X																	X
Infusion of Mylotarg®		X		X		X												
Adverse reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

The schedule of efficacy and safety assessments is shown above. Bone marrow was checked on day 15 and again following count recovery or on day 43 at the latest.

Reviewer comments: It is not clear from the protocol, but appears that safety laboratory tests were performed at the local laboratories. Furthermore, it is not clear whether local readings of marrow aspirates were used to determine eligibility and response. Lastly, the details of flow cytometric testing were not included.

Protocol MyloFrance 1 Statistical Analysis Plan

The primary endpoint of the protocol was the proportion of patients who achieved a CR or CRp within 43 days of therapy. The study was designed to test sequentially if the ORR with Mylotarg was <15% (null hypothesis) or >30% (alternative hypothesis). They considered 15% to represent the observed ORR with reference treatments in the literature (but did not provide specific references). With a type 1 error of 5% and type 2 error beta 15% (power of 85%), with two-sided tests, they planned to enroll 87 patients. They used a closed sequential rule for stopping (triangular test), so that it the ORR with Mylotarg was > 30%, the conclusion of the trial would be obtained on average with a sample size reduced by about 1/3 compared to the fixed number (n=58).

The analysis was performed whenever a group of 10 patients was evaluated and consisted of determining the total number of objective responses observed since the start of the trial. At the second interim analysis, based on the first 26 patients (performed June 2005), the trial was stopped because the upper boundary was crossed and thus they concluded that Mylotarg was beneficial. Their final analysis was based on 57 patients. This was an ITT analysis, including 7 patients with protocol violations (5 had first CR longer than 18 months, one had IT chemotherapy a few days prior to treatment, and one had secondary AML).

There was no description in the protocol of how they handled early dropouts. However, the paper notes that results represent 57 patients enrolled and that all 57 patients received the three doses of Mylotarg. Response rates were calculated from the total 57 patients. There was no description of the statistical analysis of secondary endpoints, including OS and RFS, in the protocol. However, the paper defines OS from first GO administration and RFS from first documentation of CR or CRp to the date of relapse or death before relapse. They said that they analyzed survival data with Kaplan-Meier estimates, with comparison based on log-rank tests. P-values were two-sided, with 0.05 or less denoting significance.

Safety analyses were descriptive and severity was based on NCI Common Toxicity Criteria (version 2).

Key Revisions to Protocol MyloFrance 1

The Sponsor submitted version 2 of the protocol dated January 20, 2004. Data on other amendments is not available.

5.3.5 Protocol AML-19 (EORTC / GIMEMA 0631)

Gemtuzumab Ozogamicin (GO) monotherapy versus standard supportive care for previously untreated AML in elderly patients who are not eligible for intensive chemotherapy: a randomized phase II/III trial (AML-19) of the EORTC-LG and GIMEMA-ALWP

Protocol AML-19 Design

Protocol AML-19 was a randomized, open-label, multi-center European trial with a sequential phase II-III design that investigated 2 induction regimens of GO in the phase II component, along with BSC as the control arm, and chose the regimen with the most favorable therapeutic index to be evaluated in phase III testing against BSC in elderly adults with *de novo* AML. The treatment arms consisted of GO induction and continuation therapy (if no disease progression), with laboratory follow-up for the first year, and long-term follow-up every 3 months until death. The primary endpoint for phase III was OS. The final OS analysis was to be performed after approximately 1 year of follow-up after closure of the study.

Protocol AML-19 Objectives

The primary objective of phase III was to prospectively compare, in terms of OS, the efficacy and toxicity of GO monotherapy (best induction regimen, selected after phase II, followed by a maximum of 8 four-weekly pulses of low dose GO as continuation therapy) versus standard supportive care. The primary efficacy endpoint for this objective was OS.

The secondary endpoints for phase III were to evaluate the rate of complete remission (CR+CRp) by the end of induction and by the end of the continuation therapy, for patients in GO arm, DFS for patients who reached CR or CRp, PFS (defined from randomization for patients in the GO arm until the date of first progression, first relapse for patients who reached CR/CRp, or death), and toxicity, including time to hematological recovery.

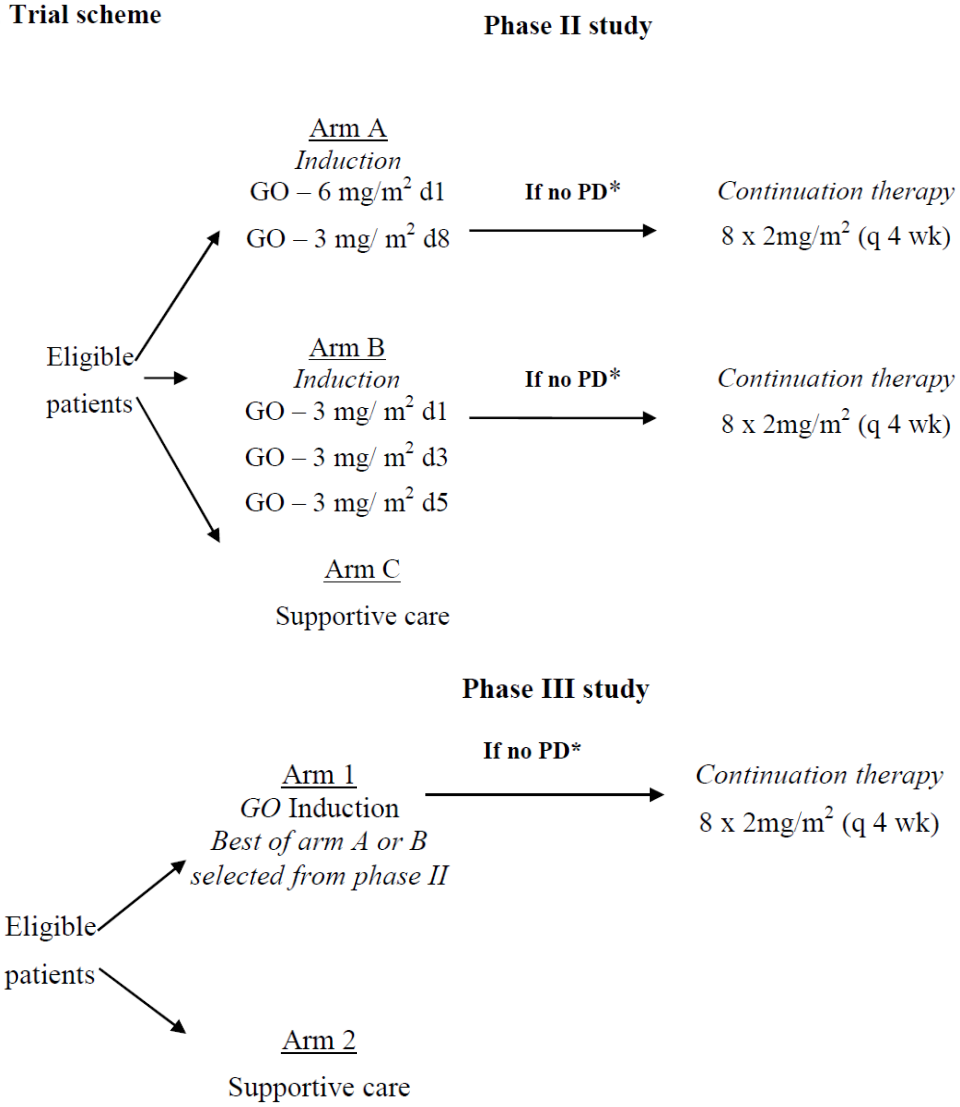
CR was defined as BM < 5% blasts, cellularity ≥ 20% with maturation of all cell lines, absence of Auer rods and extramedullary leukemia, blood smear without leukemic blasts, hemoglobin ≥ 9 g/dL, ANC ≥ 1.5 x 10^9/L, and platelets ≥ 100 x 10^9/L. CRp was essentially a CR except that the platelet count does not reach the level defined by CR. However, they should be red blood cell and platelet transfusion independent. PR required all criteria for CR/CRp, except that the marrow would contain 5-10% blasts, or <5% blasts in the presence of Auer rods. “No change” responses did not meet criteria for CR/CRp/PR, but progressive disease could not be established. PD during induction was defined as >5% leukemic blasts in the peripheral blood or ≥ 25% increase over baseline in the number of circulating blasts, irrespective of BM status, or extramedullary leukemia (diagnosis based on tissue histology or cytology). PD during continuation was defined for different initial responses in the protocol.

Protocol AML-19 Key Eligibility

1. Age ≥ 61 years and not eligible for intensive chemotherapy, defined as a) age > 75 years or b) age 61-75 and WHO PS > 2 and/or unwilling to receive intensive chemotherapy
2. AML diagnosed according to the WHO criteria, i.e. BM blasts ≥ 20%
3. All FAB subtypes except M3 (APL)
4. Previously untreated (except ≤ 14 days hydroxyurea and/or corticosteroids) primary or secondary AML (including AML after MDS)
5. No blast crisis of chronic myeloid leukemia
6. No AML supervening after other myeloproliferative diseases
7. WBC at randomization should be < 30 x 10^9/L (may have been after a maximum of 14 days hydroxyurea)
8. No concomitant malignant disease
9. No active CNS leukemia
10. No active uncontrolled infection
11. Adequate renal and liver function, i.e. creatinine and bilirubin ≤ 1.5 x ULN
12. No serious cardiac or lung disorder.
13. Absence of severe concomitant neurological and psychiatric disease.
14. No history of alcohol abuse.
15. Absence of psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration.
16. No HIV.
17. A signed, informed consent
18. It was mandatory to perform immunophenotyping prior to randomization; in particular, determination of CD33-positivity (use of peripheral blasts was allowed).

Protocol AML-19 Treatment Plan

Fig 1. **Trial scheme**



Premedication: 50 mg methylprednisolone immediately prior to the infusion of GO.

Arm A induction: GO was given at 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8 (total dose 9 mg/m^2), as 2-hour IV infusions.

Arm B induction: GO was given at 3 mg/m^2 on days 1, 3 and 5 (total dose 9 mg/m^2), as 2-hour IV infusions.

Continuation therapy: GO 2 mg/m^2 every 4 weeks x 8 doses, as 2-hour IV infusions.

- It was recommended that patients be hospitalized until completion of the induction regimen. Patients would not be discharged following the last GO infusion until they were free of clinically significant study drug effects, as judged by the investigator.
- Investigators were encouraged to give GO early in the morning in order to closely monitor possible drug related side effects.
- Subsequent doses were administered provided the following:
    - Patient recovered (to CTCAE grade 0, 1 or 2) from non-hematological toxicities resulting from the previous infusion
    - No evidence of ascites
    - No evidence uncontrolled infection
    - No evidence disease progression
    - Delay of no more than 2 days allowed between sequential infusions (omit scheduled dose if delay > 2 days occurs)
    - Patients with evidence disease progression at any time during GO induction will be discontinued from protocol treatment
- No dose modifications were allowed.
- Patients with no evidence of disease progression after GO induction (CR, CRp, PR, no change) and fulfilling the following criteria should proceed ideally within 2 weeks from assessment of response to continuation therapy:
    - Absence of severe cardiac, pulmonary, neurologic or metabolic disease
    - Absence of ascites
    - Absence of uncontrolled infection
    - Absence of renal and liver abnormalities, i.e. creatinine and bilirubin ≤ 1.5 x ULN
    - Patient recovered (to CTCAE grade 0 or 1) from non-hematologic toxicities resulting from the last administration of the induction treatment
- Criteria for delaying continuation therapy:
    - Patients with a hypoplastic BM for whom response cannot be assessed
    - Presence of severe cardiac, pulmonary, neurologic or metabolic disease
    - Presence of ascites
    - Presence of uncontrolled infection
    - Presence of renal and liver abnormalities, i.e. creatinine and bilirubin > 1.5 x ULN
    - No recovery (to CTCAE grade 0 or 1) from non-hematologic toxicities resulting from the last administration of the induction treatment
- Criteria for not starting continuation therapy:
    - Lack of CR, CRp, PR, no change after GO induction
    - Delay of more than 3 months from last GO infusion
- Continuation therapy will be performed on an outpatient basis, whenever possible.
- Patients may continue on continuation therapy providing that they continue to meet criteria (above) and do not experience relapse/disease progression.
- No more than 8 weeks are allowed between 2 sequential infusions.

- Patients with documented CR/CRp at the end of continuation therapy will receive no further treatment. For patients with PR or no change at the end of continuation, further treatment is left to the discretion of the investigator.
- Supportive therapy was provided for all patients as medically indicated (e.g. blood, fluids, antimicrobials, etc.):
    - Guidelines provided for management and prophylaxis of tumor lysis syndrome
    - Prophylactic platelet transfusions per (Gmur, Burger et al. 1991):
        - < 5 x 10^9/L in patients without fever or bleeding manifestations
        - < 10 x 10^9/L in patients with fever or bleeding manifestations
        - < 20 x 10^9/L in patients with coagulation disorders, on heparin, or with anatomical lesions
    - Empiric broad spectrum antibiotics for patients with fever
    - Decontamination of the gastrointestinal tract recommended for prophylaxis of infection during the period of pancytopenia
    - Use of myeloid growth factors not allowed unless the patient is experiencing life-threatening infections due to neutropenia

Guidelines for supportive care arm:

- Standard supportive care, as above.
- Palliative (low dose) hydroxyurea recommended for white blood count > 20 x 10^9/L, for organ pain and dysfunction due to leukemia infiltration, or when general conditions deteriorate as the presumed result of progressive leukemia.
- Patients whose leukemic cells are proliferating rapidly should respond to a daily oral dose of 2-4 g. When the targeted response is achieved, a maintenance dose of 0.5-2g/day may be sufficient.
- Other low dose cytostatics (i.e. 6-thioguanine, 6-mercaptopurine) are allowed, according to local policy, for palliative purposes.

Protocol AML-19 Schedule of Assessments

Examination / Timeline	Before trt start	During induction	Continuation	Follow-up
Physical examination	X	Daily during hopitalisation/ 3 times per week as outpatients	Every 4 weeks	Every month first year Every 3 months thereafter
BM sample	X	Day +36	4 weeks after course 3,6,8	Whenever PD is suspected
•Morphology	X	Day + 36	4 weeks after course 3,6,8	At relapse
•Cytogenetics	X			
•Immunophenotype	X			
Blood counts and WBC differential	X	3 times/week	Every 4 weeks	Every month for the first year and every 3 months thereafter
Biochemistry	X	3 times/week	Every 4 weeks	Whenever necessary
Chest X-Ray	X	Whenever considered necessary		
Ultrasound abdomen	X	Whenever considered necessary		
ECG	X	Whenever considered necessary		
Microbiological investigation	Whenever considered necessary			
Adverse events /Toxicity	X	X	X	Whenever necessary

It is not clear from the protocol, but appears that safety laboratory tests were performed at the local laboratories. Complete blood counts, chemistries, uric acid, coagulation profile, and liver function tests (LFTs) were checked at least 3 times per week during induction therapy. During continuation therapy, labs were checked every 4 weeks, or more often as clinically indicated.

Bone marrow aspirate was checked on day 36 for assessment of response. If the marrow was hypoplastic, a repeated BM would be performed at 7-10 day intervals for evaluation of response. Patients with a persistently hypoplastic BM 3 months after the last infusion of GO will be deemed to have failed treatment (regeneration failure) and will be taken off protocol. BM morphology will be checked during continuation therapy 4 weeks after courses 3, 6 and 8 (last course). In the case of a try tap, a BM biopsy will be obtained. Labs and BM will also be checked when a patient goes off-protocol.

Clinical assessment and blood counts continued every month for the first year after the patient went off-protocol and every 3 months thereafter until death. Whenever disease progression was suspected, a completed clinical and hematological work-up (including BM evaluation) was to be done.

For the BSC care arm, clinical assessment and blood cell counts were to be done as often as clinically indicated and at least every 4 weeks.

The protocol called for external review of histology (b) (4) or), cytogenetics (b) (4)), and immunology (b) (4) Italian sites

had all samples sent to [redacted] (b) (4). Flow cytometric testing was performed using an extended panel of anti-myeloid (CD13, CD14, CD33, CD34) and anti-lymphoid (B-lineage and T-lineage markers) monoclonal antibodies.

Protocol AML-19 Statistical Analysis Plan

Randomization was stratified by the following factors:

- Age (61-75 vs 76-80 years vs ≥ 81 years)
- CD33 positivity of BM blasts (<20% vs 20-80% vs > 80% vs unknown)
- Initial WBC (< 30 vs ≥ 30 x 10^9/L), before eventual hydroxyurea administration
- WHO PS (0-1 vs 2 vs 3-4)
- Institution

The aim of phase II was to screen in parallel 2 schedules of GO (Arm A and B) in two-thirds of patients and the remaining one-third was randomized to receive BSC. At the end of phase II, the most feasible arm (largest rate of reaching continuation treatment) was selected to proceed to phase III. 75 patients were to be randomized, 25 in each arm. Using a Fleming 1-stage design, with null hypothesis disease non-progression rate of ≤ 35% versus alternative hypothesis that disease non-progression was ≥ 60% with alpha 0.10 and beta 0.10, if ≥ 12 patients reach the continuation step, then that arm would be considered feasible and thus selected to be the treatment arm of the phase III study. This criterion was met for Arm A.

The primary endpoint of the phase III protocol was OS, defined as survival from the date of randomization until death. Patients were censored at the moment of last visit/contact. Based on their previous phase 2 protocol EORTC/GIMEMA 06993 AML-15B, they expected a 1-year survival of 15% in the experimental group and 5% in the control group. Thus, they aimed to randomize a total of 234 patients. The final analysis would be performed after approximately 1 year of follow-up, after closure of the study, when the number of required deaths was reported (i.e. 210 deaths in total).

They performed an ITT analysis, including all randomized patients. Curves were generated with the Kaplan-Meier technique. The logrank 2-sided test would be used for comparison of treatment outcome. Cox proportional hazards model was used to determine the independent prognostic importance of several factors, particularly of the stratification factors (except center), and of the treatment group, and to obtain hazard ratios and the corresponding 95% CIs. If the overall difference between the treatment groups appeared significant ($p<0.05$), possible treatment prognostic factor interactions would be determined for exploratory purposes.

Safety analyses were descriptive and severity was based on NCI Common Toxicity Criteria (version 3).

There were no interim analyses. There was no independent data monitoring committee. Efficacy results would not be presented at Group meetings before the trial was closed to recruitment and the appropriate number of cases were evaluable for the principal endpoint.

Key Revisions to Protocol AML-19

The Sponsor sent us version 1.1 of the protocol dated November 18, 2004 and we are not aware of any other amendments.

5.3.6 Protocols Supporting Efficacy

5.3.6.1 **Protocol 0903A1-101-US (Protocol 101) – A phase I study of recombinant anti-CD33 monoclonal antibody (hP67.6 antibody)-calicheamicin drug conjugate (hP67.6 conjugate) as treatment for patients with acute myeloid leukemia (AML)**

Protocol 101 was an open-label, single-arm, phase 1 dose escalation study to evaluate the safety and PK properties of GO. Eligible patients were ages 16 and above with relapsed or refractory CD33-positive AML, including patients who received a prior HSCT, provided they had engrafted. GO was administered to treatment groups at dose levels of 0.25, 0.5, 1, 2, 4, 5, 6, and 9 mg/m^2 infusions over 2 hours following acetaminophen and diphenhydramine pre-medication. Retreatment with up to 2 additional infusions of GO at the same dose level was allowed if infusion-related and nonhematologic toxicities from the previous dose were no more than grade 3, no patient at the previous or same dose level experienced grade 4 non-AML related toxicity, no patient had severe hypoplasia of > 6 weeks duration not due to recurrent or persistent leukemia, the patient recovered from all toxicities from the previous infusion of GO, there was no disease progression, no evidence of significant antibody formation reactive with calicheamicin or protein, and at least 14 days elapsed since the patient's previous infusion. Bone marrows were performed on days 1 and 7 of each dose and then on day 28 after the last dose. Safety evaluations were performed 3 times a week or daily if indicated while on therapy. The primary endpoint was safety. The study opened in April 1995 and was completed in May 1998. 40 patients were enrolled in the study and 1 patient re-enrolled for a second course for a total of 41 patient treatments. Results of the analyses are discussed in Sections 6.1.8, 7.3.1, 7.3.4, 7.4.1, and 7.5.1.

5.3.6.2 **Protocol 0903A1-102-US (Protocol 102) – An ascending-dose study of the safety of gemtuzumab ozogamicin as single-agent treatment of pediatric patients with refractory or relapsed acute myelogenous leukemia: final report**

Protocol 102 was a multi-center, open-label, single-arm, phase 1 dose escalation study to evaluate the safety, efficacy, and PK properties of GO in children. Eligible patients were age ≤ 17 years with relapsed or refractory CD33-positive AML, including patients who received a prior HSCT. GO was administered at dose levels of 6, 7.5, or 9 mg/m^2

per dose (patients < 3 years old received 0.2 mg/kg, 0.25 mg/kg, or 0.3 mg/kg, respectively) over 2 hours following acetaminophen and diphenhydramine pre-medication. During the conduct of the protocol, the 7.5 mg/m^2 dose level was added based on dose limiting toxicity (DLT) at the 9 mg/m^2 dose. Retreatment with up to one additional infusion of GO at the same dose level was allowed if the patient recovered from reversible non-hematologic toxicities resulting from the previous infusion, NCI grade 3-4 hepatic enzyme elevations and bilirubin resolved to grade 1-2, there was no evidence of uncontrolled infection, no evidence of disease progression, and at least 14 days, but not more than 28 days elapsed from the patient's previous infusion. Bone marrows were performed 7 days after each drug administration and 28 days after the last dose of GO. Safety evaluations were performed 3 times a week while on therapy, 28 days following the last dose of GO, and then monthly for 6 months for responders. The primary efficacy endpoint was the number of patients attaining a CR or CRp. The study opened in March 1999 and was completed in March 2002. 29 patients were enrolled in the study. Results of the analyses are discussed in Sections 6.1.8, 6.1.10.1, and 7.5.1.

5.3.6.3 **Protocol 0903A1-103-JA (Protocol 103) – Phase I/II clinical study with CMA-676 in the treatment of patients with acute myeloid leukemia (AML) (General Multi-Center Clinical Study)**

Protocol 103 was a multi-center, open-label, single-arm, phase 1/2 study to evaluate the safety, efficacy, and PK of GO in Japanese patients with R/R AML. Eligible patients were age 18 to 70 years with relapsed or refractory CD33-positive AML, including patients who received a prior HSCT if they had recovery of bone marrow function. GO was administered at dose levels of 6, 7.5, or 9 mg/m^2 per dose over 2 hours following acetaminophen and diphenhydramine pre-medication. During the conduct of the protocol, the 7.5 mg/m^2 dose level was added based on a death due to pulmonary hemorrhage at the 9 mg/m^2 dose. Retreatment with up to one additional infusion of GO at the same dose level was allowed if the patient recovered from non-hematologic toxicities resulting from the previous infusion, there was no evidence of uncontrolled infection, no evidence of disease progression, no evidence of antibody formation against calicheamicin or hP67.6, and at least 14 days, but not more than 28 days elapsed from the patient's previous infusion (was acceptable for more than 28 days to have elapsed in the phase 1 portion and there were added restrictions regarding allowance of the second dose). Bone marrows were performed 7 days after each drug administration and 28 days after the last dose of GO. Safety evaluations were performed 2-3 times a week while on therapy, 28 days following the last dose of GO, and then monthly for 6 months. The primary efficacy endpoint was the number of patients attaining a CR and CRp. The study opened in September 1999 and was completed in August 2004. 40 patients were enrolled in the study, 20 in phase 1 and 20 in phase 2. Results of the analyses are discussed in Section 6.1.8, 7.3.1, 7.3.4, 7.4.1, and 7.5.1.

5.3.6.4 **Protocol 0903X-100374 (Protocol 100374) – A dose finding study of the safety of gemtuzumab ozogamicin (Mylotarg™) as single agent treatment of patients with relapsed acute myelogenous leukemia after autologous or allogeneic hematopoietic stem cell transplant (HSCT)**

Protocol 100374 was a phase 4, multi-center, open-label, single-arm, dose finding study to evaluate the safety and efficacy of GO in relapsed CD33+ AML patients who received HSCT. Eligible patients were individuals of any age with relapsed CD33-positive (based on local laboratory criteria) AML ≥ 60 days after autologous or allogeneic HSCT. GO was administered at dose levels of 2, 4, or 6 mg/m^2 over 2 hours. Retreatment with up to one additional infusion of GO at the same dose level was allowed if the patient recovered from non-hematologic toxicities resulting from the previous infusion, there was no evidence of uncontrolled infection, no evidence of disease progression, and at least 14 days, but not more than 28 days elapsed from the patient's previous infusion. Bone marrows were performed 7 days after each drug administration and 28 days after the last dose of GO. Safety evaluations were performed 3 times a week while on therapy, 28 days following the last dose of GO, and then monthly for 6 months for responders. The primary efficacy endpoint was the number of patients attaining a CR or CRp. The study opened in March 2000 and was completed in October 2003. 37 patients were enrolled in the study. Results of the analyses are discussed in Sections 6.1.8, 6.1.10.1, 7.4.5, and 7.5.1.

5.3.6.5 **Protocol 0903X-100863 (Protocol 100863) – A phase IV study of corticosteroids as prophylaxis for infusion-related adverse events to Mylotarg® in patients with acute myelogenous leukemia (AML)**

Protocol 100863 was a phase 4, multi-center, open-label, single-arm study to evaluate the effect of corticosteroids on the frequency and severity of Mylotarg infusion-related adverse events. Eligible patients were ≥ 18 years with R/R CD33-positive AML. GO was administered at the previously approved dose of 9 mg/m^2 over 2 hours with diphenhydramine 50 mg oral pre-medication 1 hour prior and methylprednisolone 50 mg IV (or dexamethasone 10 mg orally) 30 minutes prior and 4 hours after completion of the infusion. Up to one additional infusion of GO was administered at the same dose level 14 days after the first dose, with delay of up to 28 days for resolution of toxicities. If patients experienced no grade 3-4 infusion related AEs with the first dose, they repeated the same prophylactic regimen for dose 2. If they did experience a grade 3-4 infusion-related AE with the first dose, they did not receive corticosteroid prophylaxis with dose 2, but received acetaminophen 650 mg orally 1 hour prior to infusion. A bone marrow was performed 28 days after the last dose of GO. Safety laboratory tests were done per the investigator's discretion and then 28 days following the last dose of GO. The primary efficacy endpoint was the number of patients attaining a CR and CRp at one-month post treatment. The study opened in April 2002 and was completed in March 2004. 23 patients were enrolled in the study, which was closed early due to low

enrollment rate. Results of the analyses are discussed in Section 6.1.8, 7.3.1, 7.3.4, 7.4.1, and 7.5.1.

5.3.7 Protocols Supporting Safety

5.3.7.1 **Protocol 0903X-100847-US (Protocol 100847) – Prospective observational study of Mylotarg® (gemtuzumab ozogamicin) in usual care**

Protocol 100847 was a prospective, observational study to evaluate the safety of Mylotarg therapy in routine practice, whether in community-based, academic, or hospital-based infusion clinics in the United States. Eligible patients were those for whom the treating physician determined Mylotarg to be appropriate. GO was administered as per the treating physician. A bone marrow was performed 28 days after the last dose of GO. Weekly follow-up response and safety assessment were requested as part of the study, from initial therapy for 6 weeks after the first dose or 4 weeks after the last dose, whichever was later. In the case of hepatic events, hypersensitivity reactions such as anaphylaxis, pulmonary events, or renal failure, follow-up was requested on a monthly basis until resolution of the AEs or death. Occurrence of HSCT, evidence of VOD not previously reported, and date/cause of death if deceased were collected for all patients at 6 months following the final Mylotarg dose. The primary endpoint was safety, including the rate of VOD, SAEs, and non-serious AEs of special interest (i.e. hepatic, hypersensitivity, infusion-related, pulmonary, and renal events). The study opened in October 2001 and was completed in July 2006. Of 512 patients enrolled in the study, 482 were analyzed in the clinical study report (CSR). 21 patients from this observational study were being treated on either study 100863 or 100374, and thus, only 461 patients on this trial were not represented elsewhere in the application. Safety results are described in Sections 7.3.1 and 7.4.5.

5.3.7.2 **Protocol 0903B1-207-US/EU (Protocol 207) – A randomized study of the safety and efficacy of 2 dose schedules of gemtuzumab ozogamicin in patients with intermediate-2 or high-risk myelodysplastic syndromes**

Protocol 207 was a multicenter, parallel-arm, open-label study of patients with intermediate-2 or high-risk MDS who were randomized 1:1 to either 1 dose of GO or 2 doses of GO 14 days apart. Eligible patients were ≥ 18 years of age with MDS with an International Prognostic Scoring System score ≥ 1.5, without prior HSCT. GO was administered at 9 mg/m^2 as a single IV infusion over approximately 2 hours following acetaminophen and diphenhydramine pre-medication. If patients had evidence of response, up to 3 additional cycles of GO 6 mg/m2 as a single dose 28 to 42 days apart could have been given as postremission therapy. A bone marrow was performed at the end of induction. Safety laboratory tests were performed 3 times weekly during induction. The primary endpoints were OS and quality of life, measured using the Functional Assessment of Cancer Therapy questionnaire. The study opened in January 2001 and was terminated prematurely in October 2002 after 26 patients had been

enrolled. Only one patient experienced hematologic improvement in the erythroid and neutrophil lineages per the International Working Group (IWG). Safety results are described in Sections 7.3 and 7.4.

5.3.7.3 **Protocol B1761026 – Gemtuzumab ozogamicin (Mylotarg®) expanded access protocol for treatment of patients in the United States with relapsed/refractory acute myelogenous leukemia who may benefit from treatment and have no access to other comparable/alternative therapy**

Protocol B1761026 is an ongoing EAP allowing compassionate access to GO for patients with no other reasonable treatment options, including clinical trials. Eligible patients are ≥ 3 months and have R/R AML, APL, or MDS expressing CD33 (according to the investigator's own institutional standards that define positive expression) with no other comparable or satisfactory alternative therapy available. Following prophylactic diphenhydramine, acetaminophen, and/or methylprednisolone 1 hour before administration, GO was administered as per one of several treatment regimens. Monotherapy options include doses ≤ 9 mg/m^2 on days 1 and 15 of a 28-day treatment cycle with up to 2 cycles administered or fractionated doses of 3 mg/m^2 (maximum 5 mg per dose) on days 1, 4, and 7. For APL, ≤ 9 mg/m^2 on days 1 and 15 of a 28-day cycle is recommended, for a total of 2 cycles in the absence of a CR. For APL only, they allow for a total of 5 post-remission treatment cycles of single agent GO at a dose of ≤ 9 mg/m^2 on day 1 of each 28 day post-remission cycle, provided complete hematologic recovery. Combination options are listed, but will not be addressed in this review. Finally, investigators can use alternative GO treatment regimens if based on published clinical trial data, pending approval of the Sponsor. Bone marrows and safety laboratory tests are performed at the discretion of the investigator, but standard labs should be collected within 7 days of GO, at a minimum. AEs are to be reported until 60 days after the last dose of GO or on initiation of any subsequent anticancer treatment. There is no formal primary endpoint, but safety is monitored, collected, and reported. The study opened in October 2014 and is ongoing. An amendment increased enrollment to 250 patients, and as of November 2016, 188 patients had enrolled. The 120 day safety update included an analysis of the 188 patients. Safety results are described in Section 7.7.

5.3.7.4 **Protocol 0903B1-205-US/EU/AU (Protocol 205) – A dose ranging study of the safety and efficacy of gemtuzumab ozogamicin (GO) given in combination with cytarabine in relapsed or refractory patients and older de novo patients with acute myeloid leukemia**

Protocol 205 was a phase 1/2, multi-center, open-label, single-arm study to determine the MTD and examine the effects of GO given with cytarabine in adults with R/R or de novo CD33+ AML. For phase 1, which included the single agent step 1a, eligible patients were ≥ 18 years with R/R CD33-positive (based on local laboratory criteria) AML. For the single agent step 1a, GO was administered at 6 mg/m^2 over 2 hours on

day 1 and 4 mg/m^2 on day 8, with either methylprednisolone 50 mg IV/PO or acetaminophen and diphenhydramine 1-2 hours prior. Step 1a was added in a protocol amendment to test the safety of the day 1 and 8 dosing schedule, given that the originally planned GO dosing on days 1 and 15 in combination with cytarabine resulted in prolonged marrow suppression. Subsequent steps included this day 1 and 8 schedule in combination with cytarabine. A bone marrow was performed on approximately day 15 and at the end of induction therapy (around day 36 or on hematologic recovery). Safety laboratory tests were done 3 times weekly during induction. The primary efficacy endpoint was the number of patients attaining a CR and CRp at the end of induction therapy. The study opened in August 2000 and was completed in April 2003. Only 3 patients were enrolled in the single agent step 1a. Results of the analyses are discussed in Sections 7.3 and 7.4.

5.3.8 Analysis of the Literature

The Applicant provided a literature review of GO administered as a single agent in patients with relapsed or refractory AML or APL. Their methods are described in section 2.7.3.1.4.5 of their Summary of Clinical Efficacy (SCE) for the first relapse indication and in module 1.11.3 in their response to question 3. They also identified GO monotherapy trials in the upfront setting in their SCE for the untreated indication (section 2.7.3.2.3.1). An additional two trials of single agent GO for upfront therapy of elderly CD33+ AML patients (Amadori, Suciu et al. 2005, Nabhan, Rundhaugen et al. 2005) and an updated report by Piccaluga *et al* was identified by this reviewer. All studies from the literature considered as informative for the monotherapy indication are included in Table 6 below.

Table 6: Supportive studies from the literature

Trials / Status	Design	Population	Primary Endpoint(s)
Published studies			
Roboz (Roboz, Knovich et al. 2002)	Prospective, single-arm, open-label trial • GO 9 mg/m^2 d1, 15	Adults with CD33+ R/R or untreated AML, CML-BC, or RAEB-T - 43 patients	CR/CRp rate
Zwaan (Zwaan, Reinhardt et al. 2003)	Retrospective, single-arm, open-label trial • GO 4-9 mg/m^2 x1-3	Children with CD33+ (>20% positivity) R/R AML - 15 patients	CR/CRp rate
Piccaluga (Piccaluga, Martinelli et al. 2004)	Prospective, single-arm, open-label trial • GO 9 mg/m^2 x 2-3 q14-28d (n=16) *or* • GO 6 mg/m^2 x 2-3, q14-28d (n=7) *or* • GO 1.5 mg/m^2 x 2-3, q14-28d (n=1)	Adults with CD33+ R/R AML - 24 patients	CR/CRp rate
Reinhardt (Reinhardt, Diekamp et al. 2004)	Retrospective, single-arm, open-label trial • GO 1.8-9 mg/m^2 x 1-2, q14d	Children with R/R AML - 12 patients	CR rate

Lo-Coco (Lo-Coco, Cimino et al. 2004)	Prospective, single-arm, open-label trial • GO 6 mg/m^2 x 2-3, q14d	Adults with molecularly relapsed APL - 16 patients	Molecular remission
Nabhan (Nabhan, Rundhaugen et al. 2005)	Prospective, single-arm, open-label trial • GO 9 mg/m^2 d1, 15	Adults > 65 years with untreated AML - 12 patients	CR rate
Brethon (Brethon, Auvrignon et al. 2006)	Retrospective, open-label trial • GO 6-9 mg/m^2 x 1-2 q14-28d (n=5) *or* • GO 3 mg/m^2 d1, 4, 7 (n=6)	Children with CD33+ (>20% positivity) R/R AML - 11 patients	CR/CRp rate
Yamaguchi (Yamaguchi, Usui et al. 2009)	Retrospective, open-label trial • GO 6-9 mg/m^2 x2 q14-28d	Adults with R/R AML - 10 patients	CR rate
Zwaan (Zwaan, Reinhardt et al. 2010)	Prospective, single-arm, open-label trial • GO 7.5 mg/m^2 x2 q14d *or* • If age <3 years, GO 0.25 mg/kg x2 q14d	Children with CD33+ (>20% positivity) R/R AML - 30 patients	CR/CRp rate
Amadori (Amadori, Suciu et al. 2010)	Prospective, open-label, randomized trial with a sequential phase 2-3 design • GO 3 mg/m^2 d1, 3, 5 (n=29) *or* • GO 6 mg/m^2 d1, 3 mg/m^2 d8 (n=27) *or* • BSC (n=28)	Untreated AML age >75, 61-75 with PS>2, or unwilling to receive intensive therapy - 56 patients randomized to GO arms	Rate of disease non-progression
Amadori (Amadori, Suciu et al. 2005)	Prospective, single-arm, open-label trial • GO 9 mg/m^2 d1, 15	Untreated AML age >75, 61-75 with PS 2 - 40 patients	CR/CRp rate
van der Heiden (van der Heiden, Jedema et al. 2006)	Retrospective, open-label trial • GO 6-9 mg/m^2 x1-3	Adults with untreated or R/R AML - 38 patients	CR/CRp rate
Studies in abstract form			
Thomas (Thomas, Le et al. 2005)	Open-label trial • GO 6 mg/m^2 d1, 15 (n=6) *or* • GO 3 mg/m^2 d1, 4, 7 (n=24)	Adults with R/R AML - 30 patients	CR/CRp rate
Reinhardt (Reinhardt, Zwaan et al. 2010)	Open-label trial • GO 7.5 mg/m^2 d1, 15	Children with R/R AML - 28 patients	ORR (CR+CRp+PR)
Takeshita (Takeshita, Ono et al. 2011)	Post-marketing surveillance study • GO doses not reported	Patients with R/R AML - 25 patients with R/R APL - 503 patients with R/R AML	CR/CRp rate
Yahagi (Yahagi, Usui et al. 2012)	Retrospective, open-label trial • GO 9 mg/m^2 x 2 q14-28d (n=11) *or* • GO 3 mg/m^2 d1,3,5 x 2 q14-28d (n=9)	Adults with R/R AML - 20 patients	CR/CRp rate

6 Review of Efficacy

Efficacy Summary

Unfractionated regimen

The clinical development of Mylotarg was initiated in the 1990s, with the pivotal Protocols 201-203 leading to the initial accelerated approval of Mylotarg in 2000. Multiple post-marketing and investigator-initiated trials have been conducted in the interim, leading to the current application. The Applicant submitted final data from Protocols 201-203 to support the 9 mg/m^2 dose of Mylotarg, as per the initial indication in patients ≥ 60 years old with AML in first relapse who are not otherwise candidates for cytotoxic chemotherapy. This dose was originally supported by the phase 1 Study 101 given a lack of DLTs, 4 of 7 patients experiencing marrow blast clearance, and CD33 saturation in all patients regardless of leukemia burden at this dose. However, high maximum peripheral CD33 saturation was also observed at dose levels of 2 mg/m^2 and above, and CR was achieved in patients at the 1 and 4 mg/m^2 dose levels.

Studies 201-203 were single-arm, open-label studies of single-agent Mylotarg. The primary efficacy endpoint was CR rate following 2-3 doses of Mylotarg per the unfractionated (every 14 day) regimen. Studies 201 and 203 tested the hypothesis that the remission rate was > 30%. Studies 201-203 accrued 277 adults. Analyses showed:

- CR was achieved by 42 (15%) of patients (95% CI 11-20%). Per the initial statistical analysis plan for studies 201 and 203, these should have been negative studies.
- The results for the primary endpoint were consistent across subpopulations.
- Median RFS was 7.4 (95% CI, 5.6-8.7) months.

Further data to support the effectiveness of the unfractionated dose of Mylotarg came from the phase 1 Studies 101-103, the post-marketing Studies 100374 and 100863, and studies listed in Table 6 from the literature. CR rates from these studies varied from 0-32%. Excluding Studies 201-203, the CR rate across R/R-AML trials at the 9 mg/m^2 dose was 14% (95% CI, 9-20%).

Fractionated regimen

The Applicant included the publication from the investigator-initiated trial MyloFrance 1 in this submission, which used the fractionated 3 mg/m^2 dosing of Mylotarg in a similar first relapsed AML patient population. This dose was based on observations from phase 2 studies of continuous renewed expression of CD33 after exposure to Mylotarg, leading to the hypothesis that repeated administrations may enhance internalization and intracellular accumulation of the drug. Thus, the authors fractionated the dose of 9

mg/m^2 in attempt to enhance safety without impacting efficacy (Taksin, Legrand et al. 2007).

MyloFrance 1 was a single-arm, open-label study of single-agent Mylotarg, using sequential analyses according to a triangular test and adhering to a closed sequential rule for stopping. The primary efficacy endpoint was CR+CRp rate within 43 days following 3 doses of Mylotarg on days 1, 4, and 7. The objective MyloFrance 1 was to test the hypothesis that the CR+CRp rate was > 30%. MyloFrance 1 accrued 57 adults. Analyses showed:

- CR+CRp was achieved by 19 (33%) of patients (95% CI 22-47%). MyloFrance 1 was concluded to be a positive study.
- CR was achieved by 15 (26%) of patients (95% CI 16-40%).
- Results for the primary endpoint were consistent across subpopulations tested.
- Median RFS was 11.0 months for patients achieving a CR+CRp and 11.6 months for patients achieving a CR.

Further data to support the effectiveness of the fractionated dose of Mylotarg came from the studies listed in Table 6 from the literature, which used this dose regimen. CR+CRp rates from these studies varied from 21-33%. CR rates ranged from 17-21% (Brethon, Auvrignon et al. 2006, Amadori, Suciu et al. 2010). Excluding the upfront Amadori trial, CR rates in a R/R setting were 17% and CR+CRp 29-33%.

Newly-diagnosed regimen

AML-19 used a unique dose and schedule of Mylotarg at 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8, followed by up to 8 monthly infusions of 2 mg/m^2 in older patients with newly-diagnosed AML. This dose was developed based on the observation of excess toxicity and minimal efficacy on a previous EORTC trial (AML-15B) using the unfractionated dose and schedule of Mylotarg in elderly patients with newly-diagnosed AML (Amadori, Suciu et al. 2005). The authors aimed to investigate fractionated lower doses of GO monotherapy in older patients with newly-diagnosed AML (Amadori, Suciu et al. 2016).

AML-19 was a randomized, open-label, multi-center European trial with a sequential phase 2-3 design that investigated two induction regimens of GO (6 mg/m^2 day 1 and 3 mg/m^2 day 8 versus 3 mg/m^2 days 1, 3, and 5) in the phase 2 component, along with BSC as the control arm, and chose the regimen with the most favorable therapeutic index to be evaluated in phase 3 against BSC in elderly adults with newly-diagnosed AML. They used a Fleming 1-stage design, with hypothesis that the disease non-progression was ≥ 60%. This was met for the 6 mg/m^2 day 1 and 3 mg/m^2 day 8 regimen. The primary efficacy endpoint for phase 3 was OS. AML-19 accrued 237 adults to phase 3, with 118 patients on the GO arm and 119 on BSC arm. Analyses showed:

- Median OS was 4.9 (95% CI 4.2-6.8) months on the GO arm and 3.6 (95% CI 2.6-4.2) months on the BSC arm with HR 0.69 (95% CI 0.53-0.90; p=0.005). AML-19 was concluded to be a positive study.
- The results for the primary endpoint were consistent across most subpopulations, but CD33 expression and sex were significant treatment-by-covariate interactions
    - Females appeared to benefit more from GO (HR 0.5 women vs 0.9 for men)
    - Patients with higher CD33 expression appeared to benefit more from GO, with no demonstrable benefit at expression levels < 20% (HR 0.49 CD33 > 80%, 0.75 CD33 20-80%, and 1.52 CD33 <20%).
- CR+CRi rate was achieved by 30 (27%) of patients (95% CI 19-36%).
- CR was achieved by 17 (15%) of patients (95% CI 9-23%).
- Median RFS was 5.3 (95% CI 3.1-8.0) months for patients achieving a CR+CRi.

There are no further data to support this exact dose and schedule of GO. However, the early phase studies 101 and 102, the post-marketing study 100374, and studies from the literature in Table 6 showed CR+CRp responses ranging from 0-33% using doses of 1-6 mg/m^2 every 14 days per an unfractionated regimen (full data not shown).

6.1 Indication

6.1.1 Methods

The review of efficacy of Mylotarg for the monotherapy indication was primarily based on the analysis of Studies 201, 202, 203, MyloFrance 1, and AML-19. The details of the protocol designs were described in Sections 5.3.1 through 5.3.5. Eligible patients for Studies 201 to 203 and MyloFrance 1 included adults with a first relapse of CD33-positive (≥ 80% expression) AML. Eligible patients for AML-19 included elderly adults who were deemed ineligible for intensive induction therapy based on age > 75 or age 61-70, PS > 2, and/or refusal of intensive chemotherapy.

The primary endpoint of the pivotal trials 201, 202, and 203 was CR. Durable CR is the endpoint established as reasonably likely to predict clinical benefit for patients with acute leukemia (Appelbaum, Rosenblum et al. 2007). The composite endpoint for MyloFrance 1 included CRp, which required transfusion independence.

The primary data for studies MyloFrance 1 and AML-19 were not provided by the Applicant. Thus, the literature reports for MyloFrance 1 (Taksin, Legrand et al. 2007) and AML-19 (Amadori, Suciu et al. 2016) were used in the assessment of efficacy. MyloFrance 1 was sponsored by the CHV and investigators were from ALFA. The primary data was obtained from Professor Castaigne and the CHV to supplement our investigation of the results of this trial.

In order to compare results with the unfractionated versus fractionated dose and schedule of GO, assessment of efficacy across all available data was performed, including dose finding trials, phase 4 trials, and reports from the literature. Lastly, I reviewed results from 2 reports of GO monotherapy in APL from the literature.

Review Comments:

- ***Although durable CR is the endpoint established as reasonably likely to predict clinical benefit for patients with acute leukemia (Appelbaum, Rosenblum et al. 2007), the composite endpoint for MyloFrance 1 included CRp. ORR is a reasonable endpoint for exploratory early phase trials, but its prognostic value is unclear. The analysis of the primary endpoint for MyloFrance 1 was used as planned to determine that it was a positive trial, but this endpoint alone would not be sufficient for regulatory decision making. It is notable, however, that the definition of CRp across trials required transfusion independence.***

- ***It is noteworthy that the pivotal trials (201-203) initially used criteria based on recommendations of a 1988 NCI sponsored workshop (Cheson, Cassileth et al. 1990). However, since the IWG guidelines were introduced in 2003 (Cheson, Bennett et al. 2003), efficacy in the pivotal studies was re-evaluated by the Applicant using these newer criteria. The FDA review focused on the more contemporary guidelines of the IWG, as opposed to the "per protocol (PP)" analysis. However, this was not possible for the supportive trials (101-103, 100374, and 100863) and so these were based on PP definitions.***

- ***The protocol eligibility criteria for the pivotal trials and MyloFrance 1 differed slightly, in that MyloFrance 1 allowed for patients in earlier first relapse (at least 3 months and up to 18 months in CR1), compared to studies 201 and 202, which required first relapse of 6 months or greater, with no upper limit (except protocol 203, which called for ≥ 3 months). All of these patients have a relatively poor prognosis with conventional therapy, but patients with earlier relapse are expected to have lower remission rates and worse prognosis (Thol, Schlenk et al. 2015). Thus, this variation could complicate interpretation of the results.***

6.1.2 Demographics

The demographics and baseline characteristics of the analysis population are shown in Table 7.

Table 7: Characteristics of the Analysis Populations

Variable	201/202/203	MyloFrance 1[a]	AML-19[b] GO	vs	BSC

Number	277	57	118	119
Median age (range)	61 (20-87)	64 (22-80)	77 (62-88)	77 (66-88)
Age ≥60 years	157 (57%)	35 (61%)	118 (100%)	119 (100%)
ECOG PS				
0-2	277 (100%)	57 (100%)	110 (93%)	110 (92%)
>2	0	0	8 (7%)	9 (8%)
Male	151 (55%)	29 (51%)	57 (48%)	73 (61%)
Female	126 (45%)	28 (49%)	61 (52%)	46 (39%)
White	264 (95%)	NR	NR	NR
Black	6 (2%)	NR	NR	NR
Asian	2 (1%)	NR	NR	NR
Other	5 (2%)	NR	NR	NR
Missing	0	NR	NR	NR
US	119 (43%)	0	0	0
Europe	151 (55%)	57 (100%)	118 (100%)	119 (100%)
Canada	7 (3%)	0	0	0
Missing	0	0	0	0
Prior therapies	1	1	0	0
Prior HSCT				
Total	28 (10%)	0	0	0
Allogeneic	3 (1%)	0	0	0
Autologous	25 (9%)	0	0	0
Duration of CR1				
Median	11 mos	10 mos	N/A	N/A
Cytogenetics				
Known	216/277	56/57	92/118	77/119
Favorable	12 (4%)	0	*	*
Intermediate	159 (57%)	44 (77%)	59 (50%)	45 (38%)
Poor risk	45 (16%)	12 (21%)	33 (28%)	32 (27%)
De novo				
Yes	277 (100%)	56 (98%)	79 (67%)	85 (71%)
No	0	1 (2%)	39 (33%)	34 (29%)
CD33+				
<20%	0	0	10 (9%)	14 (12%)
20-80%	4 (1%)	0	58 (49%)	58 (49%)
>80%	260 (94%)	57 (100%)	48 (41%)	47 (40%)
Unknown	13 (5%)	0	2 (2%)	0
GO regimen				
9 mg/m^2 x 2-3	277 (100%)	0	0	0
3 mg/m^2 d1,4,7	0	57 (100%)	0	0
6 mg/m^2 d1, 3 d8	0	0	118 (100%)	0

[a]From (Taksin, Legrand et al. 2007) and CHV dataset
[b]From (Amadori, Suciu et al. 2016)
Source studies 201-203: Analysis dataset
*Favorable and intermediate risk cytogenetics combined in AML-19 publication.

Review Comments: Neither MyloFrance 1 nor AML-19 reported on race. The median age reported for the first relapse trials (201-203 and MF1) is similar to that of AML in the general population of 67 years (Howlader N 2015). The median age on AML-19 was a decade older than this on both the treatment and control arms.

Furthermore, 7-8% of patients had ECOG PS > 2. It is notable that there is a slight female preponderance on the GO arm of AML-19, which is atypical for an AML population.

Median duration of CR1 was well matched on pivotal trials 201-203 and MyloFrance 1. Note that cytogenetics were slightly poorer risk on MyloFrance 1 compared to the pivotal trials. There was only 1 secondary AML patient on MyloFrance 1, which constituted a protocol violation.

The only pivotal study allowing prior HSCT was study 202 and most patients underwent autologous transplantation, which varies from current practice.

On AML-19, there were 22% of patients with missing cytogenetic data on the GO arm versus 35% with missing data on the BSC arm. Considering the data that we have, 59/92 (64%) on the GO arm had low/intermediate risk cytogenetics versus 45/77 (58%) on the BSC arm. 33/92 (36%) on the GO arm and 32/77 (42%) on the BSC arm had poor risk cytogenetics. Therefore, the arms were relatively well balanced in terms of cytogenetics, within the limitations of the missing data. Furthermore, de novo versus secondary and % CD33 positivity were well balanced between the arms.

6.1.3 Subject Disposition

Treatment Intensity

Studies 201-203

The study start and completion dates for the trials 201-203 are as follows:

- 201 - 5/12/1997 to 2/28/2002
- 202 - 4/23/1998 to 2/28/2002
- 203 - 12/1997 to 2/2002

A median of 2 doses (range, 1-7) of GO were administered. Those who received beyond 2 doses were either enrolled prior to elimination of the third dose from the protocols and/or were treated with additional courses of GO following a second or subsequent relapse (after an initial CR or CRp). Table 8 provides a summary of the treatment intensity. Twenty-four percent of patients were only able to receive the first dose of GO.

MyloFrance 1

The study start and completion dates for MyloFrance 1 are not known. However, we have the following information from the CHV data, protocol, and publication:

- The first patient enrolled on 12/11/2003
- Version 2 of the protocol was dated 1/20/2004
- The second interim analysis was conducted in 6/2005, at which time the trial was stopped due to the upper boundary being crossed (Taksin, Legrand et al. 2007)
- The last patient was enrolled on 8/2/2005

All 57 patients treated on MyloFrance 1 received 3 doses of Mylotarg per protocol.

AML-19

The study start and completion dates for AML-19 are as follows:

- Phase 2 – 11/2004 to 12/2006
- Phase 3 – 9/2007 to 5/2/2013

GO therapy was started in 111 patients and 104 (94%) received the 2 planned induction doses. Fifty-nine (53%) received at least 1 post-induction dose, per the planned continuation therapy. However, only 9 (8%) received all 10 continuation doses. The median number of GO doses was 3 (range, 1-10).

Table 8: Gemtuzumab Ozogamicin Treatment Intensity

Doses	201/202/203 (N=277)	MyloFrance 1[a] (N=57)	AML-19 GO arm[b] (N=111)
1	67 (24%)	0	7 (6%)
2	183 (66%)	0	104 (94%)
≥3	27 (10%)	57 (100%)	59 (53%)*

[a]From (Taksin, Legrand et al. 2007)
[b]From (Amadori, Suciu et al. 2016)
Source studies 201-203: Analysis dataset
*59 (53%) patients received ≥ 1 post-induction infusion at 2 mg/m^2

Reviewer comment: It is notable that disposition data from Wyeth trials was not consistently reported. For some studies, CSR algorithms were not available, so it was unclear how CSR summaries of disposition/termination were derived. Therefore, this data should be interpreted cautiously.

Disposition

Studies 201-203

The 34% of patients who dropped out early did so primarily due to an adverse event (14%) or the primary disease (12%). Only 2 patients discontinued early to go to HSCT. However, 19% ultimately underwent HSCT after GO therapy (11% allogeneic and 8% autologous). Table 9 shows the disposition of the 277 patients treated on 201-203 at the

end of the treatment period. When including discontinuations beyond the treatment period, 49 (18%) of patients discontinued from the study due to AEs, of which 11% were considered related to the study drug.

MyloFrance 1

Disposition data was not presented in the MyloFrance 1 publication and was not available in the CHV datasets obtained by FDA. However, we know that 18 of 19 patients who achieved a CR or CRp received additional treatment with HiDAC and there were no deaths after the consolidation courses. Seven (12%) of patients ultimately underwent HSCT after GO therapy (5% allogeneic and 7% autologous) (Taksin, Legrand et al. 2007).

AML-19

The majority (90%) of patients on the GO arm ultimately discontinued therapy on the trial, mostly due to the primary disease (50%) or an AE (17%). Even more patients (96%) discontinued treatment on the BSC arm, primarily due to the underlying AML (67%) or an AE (20%). Table 9 shows the disposition of patients on both arms.

Table 9: Disposition of Patients on Pivotal Trials

	201/202/203 (N=277)	MyloFrance 1[a] (N=57)	AML-19[b] GO (N=111)	AML-19[b] vs BSC (N=114)
Completed therapy*	210 (76%)	57 (100%)	9 (8%)	N/A
Discontinued early†	94 (34%)	NR	100 (90%)	110 (96%)
Reason				
Primary disease	34 (12%)	.	56 (50%)	76 (67%)
HSCT	2 (1%)	.	NR	NR
Adverse event	40 (14%)	.	19 (17%)	23 (20%)
Lost to follow-up	2 (1%)	.	2 (2%)	4 (4%)
Protocol violation	1 (0.4%)	.	9 (8%)	0
Other	1 (0.4%)	.	16 (14%)	11 (10%)

[a]From (Taksin, Legrand et al. 2007).
[b]From (Amadori, Suciu et al. 2016).
Source studies 201-203: Analysis dataset
*3 doses fractionated, ≥ 2 doses unfractionated, 10 doses AML-19 (including post-induction therapy)
†Less than 28 days following the last dose of GO (part 1 of studies 201-203) and prior to completion of protocol therapy on AML-19.

Protocol Deviations

Studies 201-203

A total of 111 protocol deviations were reported for the 277 patients on studies 201-203. Table 10 lists the number of deviations by broad criterion. The most common deviations

were treatment errors (28%), including a prolonged infusion time beyond 135 minutes, a shortened infusion time < 105 minutes, and administration of the second dose of GO outside of the 14-28 day window. Furthermore, 11% of patients were ineligible by labs, most commonly due to WBC ≥ 30,000/μL, bilirubin above 1.5 mg/dL, and creatinine ≥ 2 mg/dL. Four patients did not meet the protocol definition of CD33 positivity (≥80% leukemic blasts with expression ≥ 4 times background fluorescence), but all of these patients had > 50% expression of CD33 and were included in the efficacy analysis. Most of the 3% of patients ineligible by history had an ECOG PS > 2. One patient on study 203 (b) (6) was less than 60 years of age (58 years old). This patient did not achieve remission and ultimately died of PD. She was included in the efficacy analysis. There was no missing data for the efficacy endpoint on the pivotal trials 201-203.

In order to confirm eligibility, FDA reviewed documentation and labs to ensure that they were consistent with the established definition of relapse, specifically ≥ 5% blasts in the marrow, circulating blasts in the peripheral blood, or extramedullary disease. All patients met these criteria at baseline.

MyloFrance 1

From the MyloFrance 1 publication (Taksin, Legrand et al. 2007), we know that 7 patients (12%) did not meet the inclusion criteria. However, the total breadth of protocol violations is not known. Of the 7 patients, 5 had first remission duration longer than 18 months – one at 22 months, three at 23 months, and one at 108 months. One patient had neurologic symptoms without meningeal blast cell involvement, but received intrathecal chemotherapy a few days before treatment with GO, and one patient had secondary AML. All patients were included in the efficacy analysis per the ITT principle.

AML-19

From the AML-19 publication (Amadori, Suciu et al. 2016), we know that 1 patient was never treated with GO due to a protocol violation and that another 9 patients ultimately discontinued GO due to protocol violations. However, we do not know the details of these violations, nor do we know the full breadth of violations on the trial.

Table 10: Protocol Deviations on Pivotal Trials

	201/202/203 (N=277)	MyloFrance 1[a] (N=57)	AML-19[b] GO (N=111)	AML-19[b] vs BSC (N=114)
Patients with deviation	111 (40%)	≥7 (≥12%)	≥10 (≥9%)	NR
Deviations by criterion				
Treatment error	77 (28%)	NR	NR	NR
Ineligible by labs	30 (11%)	0	NR	NR
Ineligible by history	8 (3%)	7 (12%)	NR	NR

[a]From (Taksin, Legrand et al. 2007).

[b]From (Amadori, Suciu et al. 2016).
Source studies 201-203: CSRs.

6.1.4 Analysis of Primary Endpoint(s)

Complete Remission

CR rate was the primary endpoint on studies 201-203, CR+CRp rate was the primary endpoint on MyloFrance 1, and OS was the primary endpoint on AML-19. CR rate data is provided side-by-side for all studies in Table 11 below for comparison purposes.

Studies 201-203

The primary endpoint for pivotal studies 201-203 was CR rate, with the endpoint initially evaluated about 28 days after the final dose of GO. Patients not achieving CR by this date, but with no peripheral blasts and ≤ 5% bone marrow blasts were followed into the 6-month follow-up period to determine whether remission occurred. The Sponsor provided results by per-protocol (PP) CR criteria and the more contemporary IWG CR criteria. This review focused on the IWG results from the pivotal trials.

The CR rate was 21% for study 201, 16% for study 202, and 9% for study 203 (PP CR rates were slightly lower at 18%, 14%, and 8%, respectively). As shown in Table 11, the CR rate for the pooled trials was 15% (PP was 13%). Per the statistical analysis plans, studies 201 and 203 were technically negative given CR rates < 30%, whereas study 202 had no formal planned significance testing. Studies 201 and 203 utilized Simon 2-stage designs, in which the first stage required > 3 CRs out of 23 patients. Protocol amendments were required to allow continuation of the trials if there were only 2 or 3 CRs, given the observation of CRp responses in phase 1 trials.

Reviewer comments: Eight patients had their CR status affected by the change from PP to IWG criteria:

- ***$CRp^{PP} \rightarrow CR^{IWG}$ (n=4): Recovered counts after HSCT (n=2), recovered counts after consolidation therapy (n=1), and ANC 1-1.5x10^9 on date of platelet recovery (n=1)***
- ***$NR^{PP} \rightarrow CR^{IWG}$ (n=3): Recovered counts while undergoing transplantation conditioning following a morphologic remission (n=1), blasts evaluated less than 28 days after the last dose (n=1), and 2% blasts in the peripheral blood (n=1)***
- ***$CR^{PP} \rightarrow CRp^{IWG}$ (n=1)***

The majority of changes in remission status (n=23) were due to a re-classification from NR^{PP} to CRp^{IWG}. Many of these were due to ANC 1-1.5x10^9 or failure to reach transfusion independence per the PP criteria (n=10). 8/10 patients who failed to

meet transfusion independence per protocol had a transfusion independent period of 1 week or greater. The remaining 2 patients had ongoing intermittent transfusions, but had no transfusions for a few days around the date of the CRp determination. Thus, 10/56 (18%) of the total CRp responses on the pivotal trials were not truly transfusion independent for a sustained period of time.

MyloFrance 1

The primary endpoint for MyloFrance 1 was CR+CRp by 43 days of therapy with Mylotarg. The results of the published analysis are summarized in Table 11 below (Taksin, Legrand et al. 2007). Response rates were confirmed with the primary data provided by the CHV. The lower bound of the 95% CI was greater than 15%, so this is a positive study according to the statistical analysis plan in the MyloFrance 1 protocol.

AML-19

CR+CRp rate was a secondary endpoint on AML-19. Table 11 demonstrates the results of this endpoint.

Table 11: Analysis of the Primary Efficacy Endpoint

			AML-19[b]		
	201/202/203 (N=277)	MyloFrance 1[a] (N=57)	GO (N=111)	vs	BSC (N=114)
CR n (%)	42 (15%)	15 (26%)	17 (15%)		N/A
(95% CI*)	(11%-20%)	(16%-40%)	(9%-23%)		
Median RFS for CR	7.4 mos	11.6 mos	NR		
(95% CI)	(5.6-8.7 mos)	NR	NR		
CR+CRp n (%)	98 (35%)	19 (33%)	30 (27%)**		N/A
(95% CI*)	(30%-41%)	(22%-47%)	(19%-36%)		
Median RFS for CR+CRp	5.0 mos	11.0 mos	5.3 mos**		
(95% CI)	(4.2-6.7 mos)	NR	(3.1-8.0 mos)		
CRp n (%)	56 (20%)	4/57 (7%)	13 (12%)**		N/A
(95% CI*)	(16%-25%)	(2%-18%)	(7%-20%)		
Median RFS for CRp	4.2 mos	8.6 mos	NR		
(95% CI)	(2.9-4.8 mos)	NR	NR		

[a]From (Taksin, Legrand et al. 2007) and CHV dataset
[b]From (Amadori, Suciu et al. 2016).
Source studies 201-203: Reviewer analysis of ISE data
*Calculated using the exact Clopper-Pearson method
**CRi responses reported in paper (not CRp)

Reviewer comments: With the limitations of a smaller sample size, it is notable that the CR rate with the fractionated dosing regimen is greater than that seen on each of studies 201, 202, and 203. However, ORR (CR+CRp) is roughly equivalent

across the pivotal studies and MyloFrance 1. This indicates a similar effect on the leukemia, but less thrombocytopenia with the fractionated dosing regimen. One cannot conclude that CRp alone is useful and certainly not preferable to a CR response.

Induction responses on AML-19 were CR 8% and CR+CRi 24%. Table 11 lists best responses with further follow-up/GO treatment. Of note, CRi responses required transfusion independence (personal communication with Prof. Amadori).

The CR rate for single-agent GO is favorable compared to non-intensive therapy options for AML, including hypomethylating agents and low-dose cytarabine. This is true for both the relapsed and upfront settings, but with more comparable results in the upfront setting.

When considering the higher RFS on MyloFrance 1 compared to studies 201-203, it is important to keep in mind the difference in consolidation therapies. MyloFrance 1 utilized a cycle of HiDAC for consolidation and studies 201-203 utilized a cycle of mitoxantrone and etoposide. Patients on either trial were eligible for HSCT as well, which could affect long-term outcomes. Furthermore, the RFS data is exploratory in the context of the single arm trials, but is favorable when compared to other therapies in the first relapse setting.

Overall Survival

Reviewer comments: OS was the primary endpoint on AML-19. OS data is provided side-by-side for all studies in Table 12 below for comparison purposes.

Studies 201-203

OS was a secondary endpoint on studies 201-203 and was not the subject of hypothesis testing. OS results are shown in Table 12 and Figure 1 below. Pivotal studies OS, CR versus CRp patients. Median OS was 12.9 (95% CI 10.8-18.8) months in patients achieving CR versus 9.6 (95% CI 6.7-10.7) months in patients achieving CRp (P=0.01, log rank test comparison).

MyloFrance 1

OS was a secondary endpoint on MyloFrance 1 and was not the subject of hypothesis testing. OS results are shown in Table 12 and Figure 1 below. Roughly the same proportion of patients achieving CR and CRp died from leukemia (p=0.96) (Taksin, Legrand et al. 2007). However, median OS was not specifically reported for those with CR and/or CRp responses. Given the lack of follow-up information in the datasets provided by the CHV, we were unable to verify median OS.

AML-19

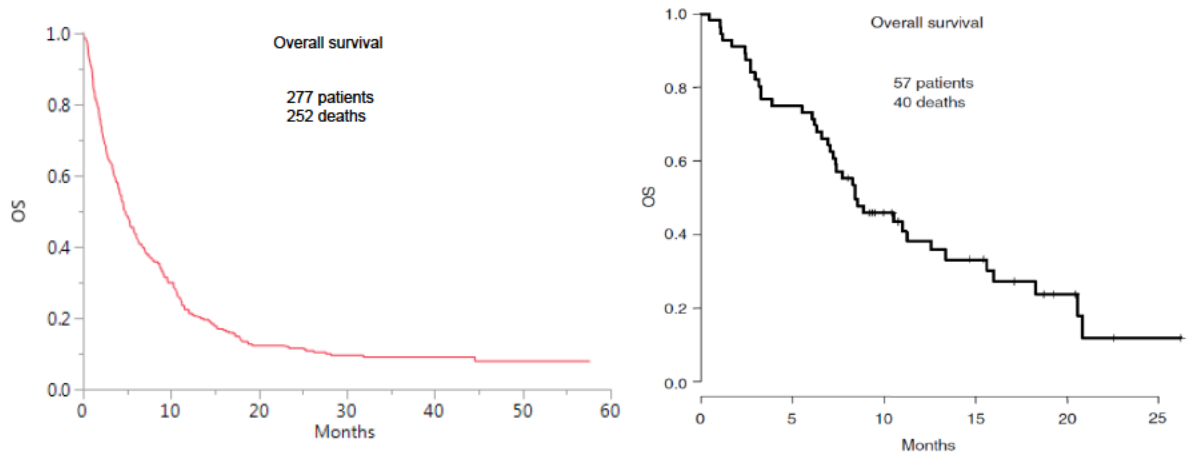
The primary endpoint for AML-19 was OS and a statistically significant survival advantage was demonstrated compared to BSC (Table 12 and Figure 1). One-year OS was 24% with GO and 10% with BSC. In patients with CR or CRi responses, median OS was 8.2 (95% CI 5.4-12.8) months and those with PR or SD lasting longer than 30 days had median OS 5.8 months (95% CI 2.9-9.9 months) (Amadori, Suciu et al. 2016).

Table 12: Analysis of Overall Survival Across Studies

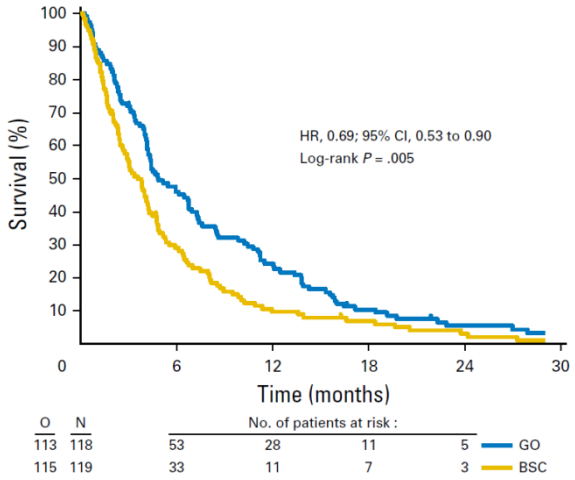
	201/202/203 (N=277)	MyloFrance 1[a] (N=57)	AML-19[b] GO (N=111)	vs	AML-19[b] BSC (N=114)
Median OS (95% CI)	4.9 mos (4.2-5.9 mos)	8.4 mos NR	4.9 mos (4.2-6.8 mos)		3.6 mos (2.6-4.2 mos)

[a]From (Taksin, Legrand et al. 2007)
[b]From (Amadori, Suciu et al. 2016).
Source studies 201-203: SCE

Figure 1: Overall Survival Studies 201-203 (a), MyloFrance 1a (b), and AML-19b (c)



(a) (b)



(c)

[a]From (Taksin, Legrand et al. 2007)
[b]From (Amadori, Suciu et al. 2016).
Source studies 201-203: Reviewer analysis of ISE data

Reviewer comment: Median OS on studies 201-203 was lower, but it is important to consider that these studies took place several years earlier and 10% patients had a prior HSCT. It is notable, however, when comparing OS curves from the unfractionated dose Studies 201-203 (Figure 1a) and MyloFrance 1 (Figure 1b) that a higher proportion of early deaths occurred on the former. Regardless, this median OS is roughly comparable to that seen with other conventional therapies in a first relapse setting (Karanes, Kopecky et al. 1999, Sarkozy, Gardin et al. 2013, Cortes, Goldberg et al. 2015).

OS on MyloFrance 1 was 8.4 months, which compares favorably with other therapies studied in a similar patient population (Faderl, Wetzler et al. 2012, Itzykson, Thepot et al. 2015). However, the OS data are exploratory in the context of a single arm trial and without formal hypothesis testing. Again, 18 of the 19 patients who achieved a CR or CRp on this study received additional treatment with HiDAC and this may have contributed to ultimate outcomes. It is interesting that roughly the same proportion of patients achieving CR and CRp on MyloFrance 1 died from leukemia, although numbers were small (Taksin, Legrand et al. 2007).

On AML-19, there was a clear separation of the Kaplan-Meier curves when comparing single agent GO with BSC (Figure 1c) and this reached statistical significance. Although most patients on both arms ultimately died, deaths were significantly delayed with GO therapy.

6.1.5 Analysis of Secondary Endpoints(s)

Studies 201-203

The secondary endpoints for studies 201-203 included RFS, OS, and platelet and ANC recovery after the final dose of GO. RFS was addressed in section 6.1.4, in support of the primary endpoint of CR rate. OS for studies 201-203 was also addressed above in section 6.1.4, in order to provide comparison to AML-19. Time to count recovery is addressed in the safety review, section 7.4.2.

MyloFrance 1

For MyloFrance 1, RFS and OS were secondary endpoints. RFS was addressed in section 6.1.4, in support of the primary endpoint of CR+CRp rate. OS for MyloFrance 1 was also addressed above in section 6.1.4, in order to provide comparison to AML-19.

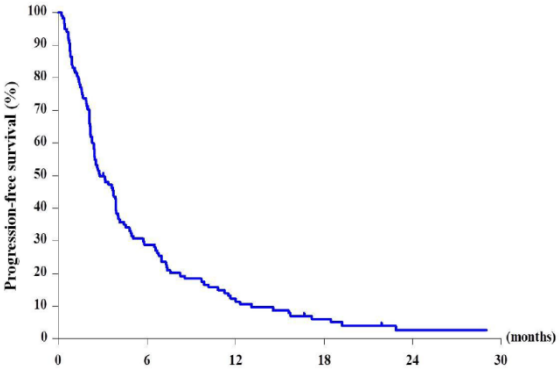
AML-19

AML-19 secondary endpoints included CR+CRp, DFS (defined as RFS) for patients who achieved CR+CRp, PFS, and time to count recovery. CR data for AML-19 was addressed above in section 6.1.4, in order to provide comparison to CR rates on the relapsed pivotal studies. RFS was also addressed in section 6.1.4, in support of the primary endpoints on the relapsed trials (and for AML-19 as a comparison).

PFS on AML-19 was defined akin to EFS, from randomization until the date of first progression, first relapse for patients who reached CR/CRp, or death. Median PFS on AML-19 for the entire 118 patients randomly assigned to the GO arm was 2.8 months (95% CI, 2.4 to 3.8 months). See Figure 2 below.

Reviewer comment: Note that compared to the AZA-001 study (Dombret, Seymour et al. 2015), PFS on AML-19 was much lower (6.7 months with azacitidine on AZA-001). However, the definition of PFS in the AZA-001 paper was vague and we do not know how they defined treatment failure.

Figure 2: Progression/Event-Free Survival on AML-19



Source: (Amadori, Suciu et al. 2016)

Reviewer comment: Note that none of the secondary endpoints addressed in this section were the subject of hypothesis testing. (b) (4)

6.1.6 Other Endpoints

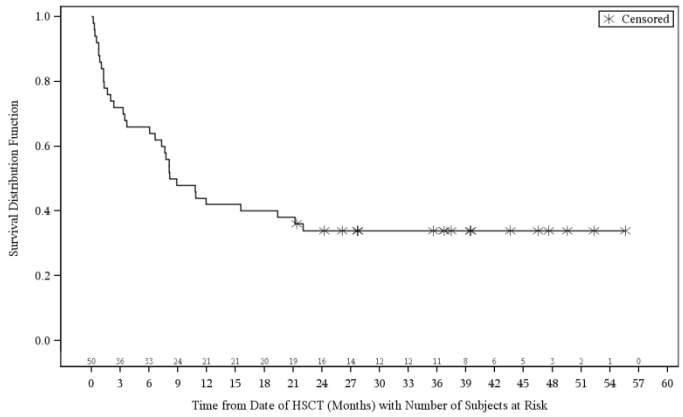
Studies 201-203

Additional endpoints reported by the applicant for studies 201-203 included post-HSCT RFS and post-HSCT survival for the 52 (19%) of patients who underwent allogeneic or autologous HSCT post-GO.

- Median RFS post-HSCT was 9.3 months in the 28 (10%) patients from the pooled studies who underwent HSCT after achieving a CR or CRp with GO (Figure 3)
  - Median RFS post-HSCT was 5.8 months for patients who achieved CR (n=15)
  - Median RFS post-HSCT was 11.4 months for patients who achieved CRp (n=13)
- Median OS post-HSCT was 8.5 months for patients who underwent HSCT post-GO
  - Median OS post-HSCT was 11.9 months for patients who experienced CR or CRp
  - Median OS post-HSCT was 9.5 months for patients who achieved CR
  - Median OS post-HSCT was 15.6 months for patients who achieved CRp
  - Median OS post-HSCT was 6.1 months for patients with no response

Reviewer comment: The post-HSCT survival curve indicates that if patients make it to HSCT post-GO therapy, over 30% of patients experienced prolonged survival.

Figure 3: Post-HSCT survival in studies 201-203



MyloFrance 1

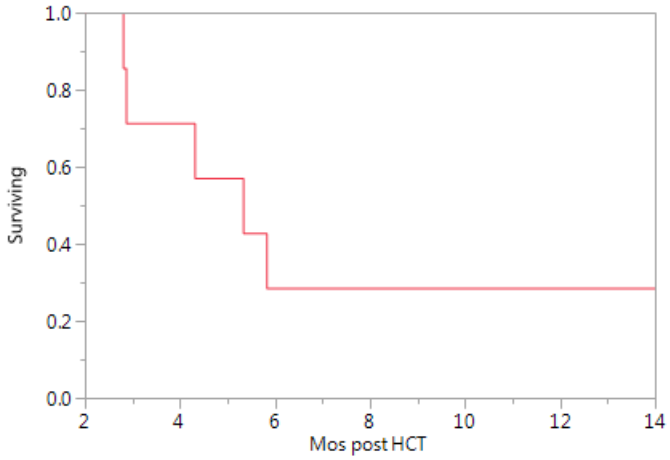
Post-HSCT RFS and OS were not included as endpoints on the MyloFrance 1 study. Only 7 patients (12%) from MyloFrance 1 underwent HSCT post-GO (Taksin, Legrand et al. 2007). We have the following information from the manuscript:

- Three patients received an allogeneic transplantation (2 non-responders, 1 CR)
    - One patient relapsed 2 months after transplantation, one died 5 months post-transplant, and one was alive in CR at 14 months
- Four patients received an autologous transplantation (1 CRp patient, 3 CR patients)
    - Three patients relapsed after 4, 9, and 9 months and one is alive in CR 12 months after transplantation

The following additional information was determined from FDA's analysis of the data received by CHV:

- Median OS post-HSCT was 5.3 months for the 7 patients who underwent HSCT post-GO (Figure 4)
- Median OS post-HSCT was not reached for the 4 patients who achieved CR
- Median OS post-HSCT was 5.3 months for the 3 patients with no response

Figure 4: Post-HSCT survival on MyloFrance 1



Source: FDA analysis

Reviewer comment: The median post-HSCT OS on MyloFrance 1 was roughly comparable to that seen on the pivotal trials 201-203. However, the patient numbers were much smaller and the follow-up much shorter.

Although not pre-specified in the MyloFrance 1 protocol, the paper reported on cumulative incidence of relapse at 1 year, which was 57% (Taksin, Legrand et al. 2007).

Taksin *et al* also reported on results from MDR studies, which were available for 40 patients. The mean *D*-value for Pgp function from 14 patients with CR or CRp was 0.10±0.09, compared with 0.37±0.21 (p=0.0001) in 26 samples from non-responders. Median *D*-values for MRP1 function from the 14 patients with CR or CRp was 0.15±0.14 compared with 0.35±0.20 (p=0.004) in 26 samples from non-responders.

AML-19

The AML-19 publication does not mention any patients receiving HSCT post-GO. Furthermore, there was no analysis of cumulative incidence of relapse, Pgp or MRP1 function.

6.1.7 Subpopulations

Studies 201-203

There was no significant difference in CR, CRp, or OR rates with GO by age (< or ≥ 60), sex, race, duration of first remission, or cytogenetics (Table 13 shows a subset of these analyses). However, there was a numerical trend towards a higher ORR for patients with longer first remission duration.

There were only 4 patients who did not meet the inclusion criteria of ≥ 80% leukemic blasts with expression > 4 times background fluorescence, and of these patients, ORR was 50%. All of these 4 patients had over 50% expression of CD33.

MyloFrance 1

The MyloFrance 1 paper reported no significant difference in remission rates across all subpopulations examined. Furthermore, the CHV data analyzed by FDA did not show an effect of sex on response rates. However, there was a numerical trend towards a higher ORR for patients with intermediate vs poor risk cytogenetics, older age, and longer first remission duration (see Table 13). All results were verified by FDA using the CHV data, with the exception of duration of first remission, since that data was not provided.

CD33 positivity in > 80% of cells was required for entry on MyloFrance 1 and there is no data in the publication or datasets provided about protocol violations and/or responses in patients with < 80% CD33 expression.

AML19

Overall Response Rate

There was a significantly higher ORR in patients with favorable and intermediate risk cytogenetics compared to those with poor risk cytogenetics at 36% versus 7%, respectively (see Table 13). All patients were over the age of 60 and response rates were not significantly different by age. However, there was a numerical trend towards an increase in response rate by age. Patients 61-75 years of age had ORR 13% (95% CI 4-27%), patients 76-80 had ORR 34% (95% CI 20-50%), and patients ≥ 81 had ORR 37% (95% CI 19-58%).

Other subgroup analyses reported by Amadori *et al* (Amadori, Suciu et al. 2016) included sex, performance status, type of disease, WBC count, and CD33 status:

- Females had a trend toward higher ORRs at 34% (95% CI 22-48%) versus 19% with males (95% CI 9-32%)
- Patients with a higher WHO performance status tended to have higher ORRs with ORR 23% (95% CI 13-34%) for 0-1, 34% (95% CI 19-53%) for 2, and 38% (9-76%) for > 2
- *De novo* versus secondary disease and WBC < 30 x 10^9 or ≥ 30 x 10^9 did not result in different ORRs
- Higher levels of CD33 expression trended toward higher response rates with ORR 11% (95% CI 0.3-48%) for expression < 20%, 26% (95% CI 15-40%) for 20-80% expression, and 33% (95% CI 20-48%) for > 80% expression

Table 13: Subpopulation Analysis of Overall Response Rate Across Studies

	201/202/203 (N=277)	MyloFrance 1[a] (N=57)	AML-19[b] GO (N=111) vs BSC (N=114)	
ORR by cytogenetic risk (95% CI)*				
Favorable	33% (4-78%)	-	**	
Intermediate	41% (32-51%)	35% (21-51%)	36% (23-50%)	N/A
Poor	33% (22-46%)	25% (5-57%)	7% (1-22%)	
ORR by age (95% CI)*				
Age ≥60 years	35% (28-43%)	40% (24-58%)	15% (9-23%)	N/A
Age <60 years	36% (27-45%)	23% (8-45%)	-	
ORR by CR1 duration (95% CI)*				
<12 mos	30% (23-38%)	25% (11-43%)	N/A	N/A
>12 mos	43% (34-53%)	44% (24-65%)		

[a]From (Taksin, Legrand et al. 2007)
[b]From (Amadori, Suciu et al. 2016).
Source studies 201-203: SCE
*Calculated using the exact Clopper-Pearson method
**Favorable and intermediate risk cytogenetics combined in AML-19 publication.

Reviewer comments: Results are relatively consistent across subgroups, importantly cytogenetics, age, and duration of first CR. One exception is that AML-19 showed a significantly higher CR rate in patients with low or intermediate risk cytogenetics. It is unknown how the numbers compare between low and intermediate risk patients since both groups were combined in the publication. Furthermore, the results should be interpreted with caution since cytogenetic data was missing for 22% of patients on the GO arm.

Slightly lower CD33 expression in the 4 patients with protocol violations on studies 201-203 did not seem to affect outcomes. There were 2 CRp responses and 2 NR responses in these patients. It is difficult to make anything of the lack of CR responses in this small number of patients. It is unknown if any protocol violations occurred on MyloFrance 1 and whether lower CD33 expression could have affected the results. On AML-19, there did seem to be a clear trend towards increased ORRs with higher CD33 expression.

Overall Survival

Given that AML-19 had a primary endpoint of OS, Amadori *et al* performed an exploratory subgroup analysis on this endpoint with various baseline characteristics (Amadori, Suciu et al. 2016). Hazard ratios and interaction tests were calculated with a

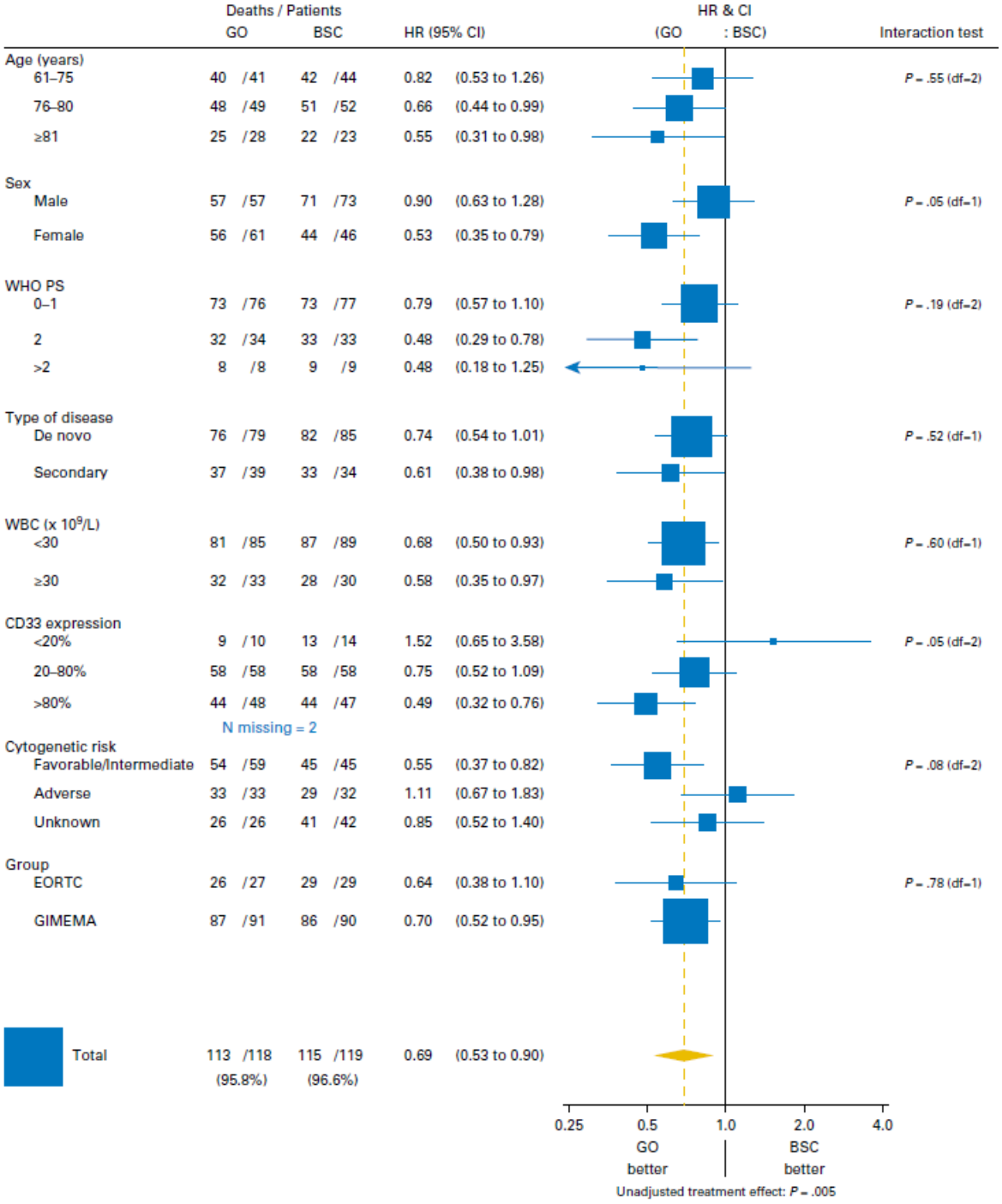
bivariate Cox model. CD33 expression and sex were significant treatment-by-covariate interactions. The interaction between treatment and cytogenetic profile was of borderline significance (Figure 5).

Reviewer comments: Similar to the trend with ORR, there was a significant effect of CD33 expression level on OS with GO therapy. Although the numbers are small for patients with < 20% CD33, it is concerning that the HR is 1.52. Patients with > 80% CD33 expression appeared to experience the greatest benefit with GO, whereas those with 20-80% expression had a somewhat lesser benefit compared to the BSC arm.

Also similar to the ORR results, patients with adverse risk cytogenetics did not appear to receive benefit from GO in terms of OS, but this was not statistically significant in this exploratory analysis. It is unknown whether patients with adverse risk cytogenetics were enriched for patients with less CD33 expression. Furthermore, the missing cytogenetic data in 22% of patients on the GO arm and 35% of patients on the BSC arm complicates interpretation of these results.

Lastly, there was a significant effect of female sex on improved OS with GO. The HR for men was still < 1, however. It is unclear why this would be the case, but it is notable that there were slightly more women than men on the GO arm in this trial, which is atypical for an AML population.

Figure 5: Overall Survival Subgroup Analysis AML-19



Source: (Amadori, Suciu et al. 2016)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant indicated that the 9 mg/m^2 dose for adults was based on a significant exposure-response relationship between hP67.6 antibody cumulative exposure and ORR (Module 2.7.2 Summary of Clinical Pharmacology Studies Section 3.11). However, CD33 was saturated at GO doses > 2 mg/m^2. And furthermore, the Clinical Pharmacology reviewer determined that the exposure-efficacy relationship is very low for CR responses (P=0.6). Thus, it is expected that the 3 mg/m^2 fractionated dosing regimen should not lead to a significant loss in efficacy. However, we do not have formal PK studies with this dosing regimen.

We analyzed and compared efficacy for various unfractionated and fractionated doses and schedules of GO when used as monotherapy for treatment of patients with R/R-AML. The review was based primarily on studies 201-203 and MyloFrance 1 (Taksin, et al. 2007). In addition, results from dose-escalation and postmarketing studies in patients with R/R-AML helped to inform the review. The clinical trials reviewed are displayed in Table 4 and used unfractionated (0.25-9 mg/m2 x 2-3 doses 14 days apart) or fractionated (3 mg/m2 x 3 doses 3 days apart) dosing schedules. All studies in Table 4 with R/R-AML patients for which response data was available were included, with the exception of study 205 since it contained only 3 patients treated with monotherapy.

Based on the literature review performed by the Applicant (see section 5.3.8), we further refined the literature review in order to compare the efficacy of GO by dose and regimen, specifically focusing on the unfractionated dosing regimens of 6 mg/m^2 x 2, 9 mg/m^2 x 2, and the fractionated dosing regimen of 3 mg/m^2 days 1, 4, and 7. Seven studies identified by the Applicant were excluded in our analysis given lack of information on CR rate or VOD incidence, failure to distinguish safety and efficacy by dose, use of a different dosing regimen, inclusion of patients treated on MyloFrance 1, or inclusion of patients treated on Study 103. Table 14 lists all of the studies from both the application and literature review used in this analysis by dose and regimen. It should be noted that two studies (Brethon, et al. 2006; Thomas, et al. 2005) investigated both unfractionated and fractionated schedules and therefore are included under both categories.

Table 14: Clinical Studies of GO Monotherapy for Dose and Schedule Analysis

Study/Reference	Design	Population	Primary Endpoint(s)
Unfractionated			
Study 201	Single-arm, open-label Phase 2 trial • GO 9 mg/m^2 x 2-3, 14-28d apart	Adults with CD33+ AML in first relapse after CR ≥ 6 months - 84 patients	CR rate
Study 202	Single-arm, open-label Phase 2 trial • GO 9 mg/m^2 x 2-3, 14-28d apart	Adults with CD33+ AML in first relapse after CR ≥ 6 months	CR rate

Study/Reference	Design	Population	Primary Endpoint(s)
		- 95 patients	
Study 203	Single-arm, open-label Phase 2 trial • GO 9 mg/m^2 x 2-3, 14-28d apart	Adults ≥ 60 years with CD33+ AML in first relapse after CR ≥ 3 months - 98 patients	CR rate
Study 101	Single-arm, open-label Phase 1 dose-escalation trial • GO 0.25-9 mg/m^2 x 3, ≥14d apart	Adults with R/R CD33+ AML - 41 patients	Safety
Study 102	Single-arm, open-label Phase 1 dose-escalation trial • GO 6-9 mg/m^2 x1-2 doses, ≥14d apart (< 3 years, per kg dosing)	Pediatric patients with R/R CD33+ AML - 29 patients	CR+CRp rate
Study 103	Single-arm, open-label Phase 1-2 dose-escalation trial GO 6-9 mg/m^2 x 2, ≥14d apart	Japanese adults with R/R CD33+ AML - 40 patients	CR+CRp rate
Study 100374	Single-arm, open-label Phase 4 dose-escalation trial • GO 2-6 mg/m^2 x 2, ≥14d apart • Consolidation: up to 4 doses GO	Adults with relapsed CD33+ AML post HSCT - 37 patients	CR+CRp rate
Study 100863	Single-arm, open-label Phase 4 trial • GO 9 mg/m^2 x 2, 14d apart • Studied steroid prophylaxis	Adults with R/R CD33+ AML - 23 patients	Safety
Roboz 2002	Prospective, single-arm, open-label trial • GO 9 mg/m^2 x 2, 14d apart	Adults with CD33+ R/R or untreated AML, CML-BC, or RAEB-T - 43 patients	CR+CRp rate
Zwaan 2003	Retrospective, single-arm, open-label trial • GO 4-9 mg/m^2 x1-3	Children with CD33+ R/R AML - 15 patients	CR+CRp rate
Piccaluga 2004	Prospective, single-arm, open-label trial • GO 9 mg/m^2 x 2-3 q14-28d (n=16) or • GO 6 mg/m^2 x 2-3, q14-28d (n=7) or • GO 1.5 mg/m^2 x 2-3, q14-28d (n=1)	Adults with CD33+ R/R AML - 24 patients	CR+CRp rate
van der Heiden 2006	Retrospective, open-label trial • GO 6-9 mg/m2 x1-3	Adults with untreated or R/R AML - 38 patients	CR+CRp rate
Brethon 2006	Retrospective, open-label trial • GO 7.5-9 mg/m^2 x 1-2,14-28d apart	Children with CD33+ R/R AML - 5 patients (unfractionated)	CR+CRp rate
Thomas 2005	Open-label trial • GO 6 mg/m^2 x2, 14d apart	Adults with R/R AML - 6 patients (unfractionated)	CR+CRp rate

Fractionated GO 3 mg/m^2 d 1, 4, 7

Study/Reference	Design	Population	Primary Endpoint(s)
Taksin 2007	Single-arm, open-label Phase 2 trial • GO 3 mg/m^2 d 1, 4, 7	Adults with CD33+ AML in first relapse after CR ≥3, ≤18 months - 57 patients	CR+CRp rate
Brethon 2006	Retrospective, open-label trial • GO 3 mg/m^2 d1, 4, 7	Children with CD33+ R/R AML - 6 patients (fractionated)	CR+CRp rate
Thomas 2005	Open-label trial • GO 3 mg/m^2 d1, 4, 7	Adults with R/R AML - 24 patients (fractionated)	CR+CRp rate

Source: FDA analysis

We acknowledge the caveat that comparisons of outcomes across trials may be problematic, and as such, these analyses are considered only exploratory.

To assess the impact of dose and schedule on efficacy, we performed an analysis of CR across studies using the 6 or 9 mg/m^2 unfractionated regimens or the 3 mg/m^2 fractionated regimen. The analysis included studies listed in Table 14 using these specific doses and schedules. Two studies from the literature (Thomas, et al. 2005; Zwaan, et al. 2003) were excluded since they reported CR+CRp but not CR alone.

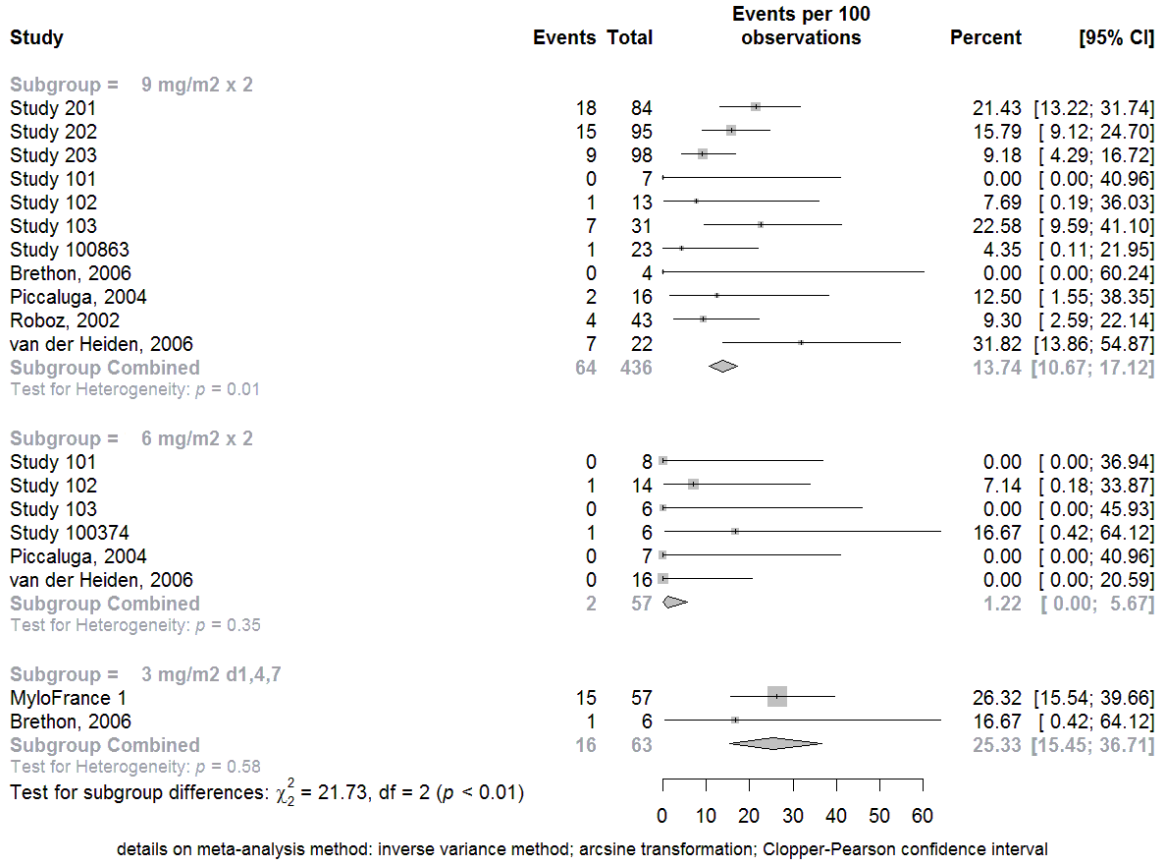
Figure 6 lists the CR rates by study. The results suggest that the CR rate is no worse using GO 3 mg/m^2 days 1, 4 and 7 in comparison to doses of 6 mg/m^2 or 9 mg/m^2. A separate analysis of all available unfractionated CR data in patients with R/R-AML combined across trials from Table 4 and Table 6 (excluding study 205) showed similar results with a CR rate of 10% out of 1082 total patients (data not shown).

Among the individual dose-ranging studies, there was not a clear dose response relationship. In Study 101, there was 1 CR out of 4 patients treated with the 1 mg/m^2 dose, none with 2 mg/m^2 dose, 1 CR out of 6 treated at the 4 mg/m^2 dose, and none at doses of 5, 6, or 9 mg/m^2. The pediatric study 102 showed 1 CR each at the 6, 7.5, and 9 mg/m^2 doses. The post-transplant study 100374 showed 1 response each in the 2, 4, and 6 mg/m^2 cohorts. The only exception to the apparent lack of dose response was the Japanese study 103, which only had CR responses in patients treated with 9 mg/m^2 and none at 6 or 7.5 mg/m^2.

Aside from MyloFrance 1 and the Brethon *et al* (Brethon, Auvrignon et al. 2006) paper included in Figure 6 below, two additional studies listed in Table 6 with CR+CRp data provide supportive evidence for the fractionated regimen in patients with R/R-AML. The retrospective trial by Thomas *et al* (Thomas, Le et al. 2005) showed equivalent CR+CRp rates at 7/24 (29%) treated with 3 mg/m^2 days 1, 4, and 7 and 2/6 (33%) treated with 6 mg/m^2 unfractionated dosing. The Yahagi *et al* (Yahagi, Usui et al. 2012) retrospective study similarly showed equivalent CR+CRp rates at 3/9 (33%) with 3 mg/m^2 fractionated dosing and 3/11 (27%) with 9 mg/m^2 unfractionated dosing. An additional study in untreated older patients with AML (phase 2 of AML-19) also

investigated a fractionated dose of 3 mg/m^2 days 1, 3, and 5 and showed a CR rate of 6/29 (21%).

Figure 6: CR Rate by GO Monotherapy Dose-Schedule for R/R-AML



Source: FDA analysis
Abbreviations: d, day; df, degrees of freedom.

Reviewer comments: The above forest plot demonstrates overall higher CR rates with the fractionated dose regimens. This should be interpreted with caution since the numbers are much smaller. However, it is clear that CR rates are at least as good with fractionated dosing as they are with the unfractionated dosing regimens.

Also clear from the plot is that CR rates were generally higher in the first relapse trials 201-203. Excluding 201-203, the CR rate across trials at the 9 mg/m^2 unfractionated dose was 13.8%, which is not far off from the 15% CR rate across 201-203. However, the Japanese dose-ranging study 103, which had a higher CR rate, mostly included patients with only 1 prior therapy. Furthermore, the van der Heiden paper included some newly-diagnosed patients, which could have led to

the higher CR rate of 32%. The remainder of the studies included more heavily pre-treated patient populations. Thus, excluding studies 201-203, 103, and van der Heiden, the CR rate at the 9 mg/m^2 dose was 8%.

As for the fractionated dosing regimen in a more heavily pre-treated patient population, the Brethon paper indicates a favorable CR rate of 17%, although this was only 1 of 6 pediatric patients. It is reassuring to see the results of the Thomas (Thomas, Le et al. 2005) and Yahagi (Yahagi, Usui et al. 2012) retrospective studies, which showed favorable ORRs of 29% and 33%, respectively, in patients with R/R-AML. On the Thomas study, patients had a median of 2 prior therapies (Thomas, Le et al. 2005).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Since the duration of treatment was short, and only 20 patients were retreated, there is insufficient data for a meaningful analysis of tolerance of effect. However, it is notable that 2 (10%) of the 20 patients on the pivotal trials who received more than one course of GO for a subsequent relapse achieved a CR and 4 (20%) experienced a CRp. We do not have any data on re-treatment effect with the doses used on either MyloFrance 1 or AML-19.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Historical Control Data

The Applicant provided data on alternative options for patients with relapsed or refractory AML. Intensive options in the NCCN guidelines, many of which contain cytarabine as a backbone, result in remission rates ranging from 13% to 66%. In terms of non-intensive therapies, options include low-dose cytarabine and hypomethylating agents. The CR rates for these regimens range from 10% to 17% (Sarkozy, Gardin et al. 2013, Itzykson, Thepot et al. 2015). CR+CRi rate was 17% with azacitidine (Itzykson, Thepot et al. 2015).

Reviewer comment: The historical control using azacitidine in the relapsed setting supports the assumption used in the design of MyloFrance 1 that CR+CRp rate would be around 15% for the patient population treated with non-intensive therapy. Studies 201-203 were designed to exclude a CR rate of 15%, which was not achieved. However, CR+CRp rate met this criterion.

6.1.10.1 Efficacy Results from Other Protocols

Protocol 102 was a small dose-ranging study in pediatric patients with R/R-AML. Details of the protocol design were described in Section 5.3.6. The study enrolled and treated 29 patients with a median age of 12 (range 1-16) years. Dose levels included 6, 7.5,

and 9 mg/m^2. Patients had a median of 2 or more prior therapies, but none had a prior HSCT. CR rate was 10% (95% CI 3-28%) and CR+CRp rate was 14% (95% CI 5-33%). CR rate at 6 mg/m^2 was 1/14 (7%), at 7.5 mg/m^2 was 1/2 (50%), and at 9 mg/m^2 was 1/13 (8%).

Pediatric data from the literature are partially reported in Section 6.1.9 above. Considering all pediatric patients, including 29 patients on study 102 and 96 patients on the pediatric trials listed in Table 6, 125 pediatric patients have been treated with R/R AML. Some studies reported on CR rate, while others only reported on CR+CRp rate. Of those with CR rate, reported, there were 4/52 (8%) patients with CR. Of those with CR+CRp rate reported, there were 23/97 (24%) patients with CR+CRp.

The only pediatric trial that looked at the fractionated dose regimen was Brethon *et al* (Brethon, Auvrignon et al. 2006), which was a small retrospective trial including 6 patients treated with fractionated dose GO at 3 mg/m^2 on days 1, 4, and 7. One of 6 (17%) patients achieved a CR and 2/6 (33%) achieved a CR+CRp.

Reviewer comments: Protocol 102 provides evidence of similar efficacy in a pediatric patient population with R/R-AML compared to that seen with adults using unfractionated doses of Mylotarg. The lower doses of Mylotarg did not seem to affect efficacy in the pediatric patients.

Combining all available pediatric data from the submission and the literature, the CR rate of 8% in patients with R/R AML is similar to that seen with the heavily pre-treated R/R adult patients. Looking only at the fractionated doses, the efficacy in this population with 4 refractory relapse patients, one de novo refractory patient, and a patient with second relapse post-HSCT was not much lower than that seen in the first relapse population in adults. Furthermore, there is no biological reason to expect a different response rate with GO in pediatric versus adult patients with AML. Thus supports extension of the indication to the pediatric population.

Protocol 100374 was a post-marketing dose-escalation trial in patients with prior HSCT. Details of the protocol design were described in Section 5.3.6. The study enrolled and treated 37 patients with a median age of 50 (range 4-71) years. Dose levels included 2, 4, and 6 mg/m^2. 73% of patients had a prior allogeneic HSCT and 27% had a prior autologous HSCT. CR rate was 8% (95% CI 2-23%) and CR+CRp rate was 19% (95% CI 9-36%). CR rate at 2 mg/m^2 was 1/13 (8%), at 4 mg/m^2 was 1/18 (6%), and at 6 mg/m^2 was 1/6 (17%).

Reviewer comments: Protocol 100374 provides evidence of similar efficacy in a post-transplant patient population compared to that seen with adults with R/R-AML using unfractionated doses of Mylotarg. The lower doses of Mylotarg did not seem to affect efficacy in these patients, but the sample sizes were quite small.

Takeshita *et al* (Takeshita, Ono et al. 2011) reported on the results of a large post-marketing surveillance study in Japan, which included 25 patients with R/R-APL. Doses of GO were not provided. CR rate was 48% (95% CI 28-69%) and CR+CRp rate was 56% (95% CI 35-76%). Duration of CR1 and number of relapses influenced CR rates, but use of prior arsenic and age did not. Two-year OS and RFS were 63% and 71%, respectively.

Reviewer comments: This retrospective data indicates substantial efficacy in patients with APL, a disease which is characterized by bright CD33-positivity.

Lo Coco *et al* (Lo-Coco, Cimino et al. 2004) reported on the results of a prospective, single-arm, open-label trial using GO 6 mg/m^2 x 2-3 every 14 days in 16 adults with molecularly relapsed APL. Molecular remission rate was 88% (95% CI 60-98%). Of note, GO was administered again in 2 patients with relapse and both obtained a new MR. Two-year OS was 74% and 2-year molecular RFS was 43%.

Reviewer comments: This data indicates substantial efficacy in patients with molecular relapse of APL.

Nabhan *et al* (Nabhan, Rundhaugen et al. 2005) reported the results of a prospective, single-arm, open-label trial using GO 9 mg/m^2 days 1 and 15 in 12 adults over 65 years of age with untreated AML. The median age was 75 (range 66-79). 58% of patients received 2 or more doses of GO. The CR rate was 25% (95% CI 7-57%) and there were no CRp responses.

Reviewer comments: This small trial provides supportive data to AML-19 for the efficacy of GO monotherapy in the upfront setting in patients who are not eligible for intensive chemotherapy.

7 Review of Safety

Safety Summary

The safety data set included 936 patients with AML or MDS treated with various doses and schedules of GO. The proposed dose-schedule of GO monotherapy in the relapsed setting is up to 2 doses of 9 mg/m^2, 14 days apart (unfractionated dosing), versus a fractionated schedule of 3 mg/m^2 on days 1, 4, and 7. For the upfront indication, the dose-schedule of GO is 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8, followed by up to 8 monthly infusions of 2 mg/m^2.

Relapsed/refractory monotherapy indication

Unfractionated dosing: The 277 patients with CD33+ AML in first relapse treated on pivotal trials 201-203 were referred to as the "first relapsed" subgroup (see Table 15). 61 patients with CD33+ R/R-AML (not limited to first relapse) treated with 9 mg/m^2 dosing from studies 101, 103, and 100863 were referred to as the "R/R AML" subgroup. Furthermore, safety was analyzed for 37 patients treated on the phase 4 post-HSCT trial 100374 and 29 children on study 102. Available safety data, specifically regarding the incidence of VOD, was supplemented by the literature studies listed in Table 6.

Studies 201-203 include information on deaths, SAEs, adverse events of interest, common adverse events, common laboratory tests, and changes in vital signs. A thorough QT study was not conducted, but the application included a summary of available ECG data.

Out of 936 patients in the monotherapy safety database, there were 206 (22%) early deaths within 28 days of the last dose of GO. 155 (17%) of patients died within 30 days of the first dose. Causality in terms of treatment-related deaths was not systematically collected. Most TEAEs resulting in deaths were due to infections, cytopenias, disease progression, and respiratory disorders.

In studies 201-203, there were 252 (91%) deaths observed. There were 51 (18%) early deaths on or before day 43 of therapy (within 28 days of the last dose). 29 (10%) of patients died within 30 days of the first dose. At least 63% of the total deaths were considered to be related to active primary malignancy. All-cause TEAEs with outcome recorded as death were reported in 70 patients (25%) across the pivotal trials (25, 25, and 20 patients from studies 201, 202, and 203, respectively). Causality in terms of treatment-related was not systematically collected. Most TEAEs resulting in deaths were due to infections, cytopenias, and respiratory disorders. Other key safety results showed the following:

- Infectious deaths occurred in 5% of patients within 28 days after the last dose of GO
- Grade 3-4 TEAEs in > 1% patients included pyrexia (51%), infections (40%), nausea (39%), bleeding (28%), increased AST (15%), diarrhea (15%), hypotension (14%), headache (12%), stomatitis (12%), ALT increased (11%), dyspnea (11%), pneumonia (9%), hyperbilirubinemia (8%), VOD (5%), edema (4%), rash (4%), mucositis (3%)
- All grade hyperbilirubinemia was seen in 22 (8%) of patients
- There were 12 patients considered at least potential Hy's law cases and VOD was seen in 4/12 (33%)
- All grade elevations in AST or ALT were observed in 52 (19%) and 37 (13%) of patients, respectively
- There were 15 (5%) cases of VOD and 10 (4%) were fatal
    - In patients with no HSCT, VOD occurred in 2 (1%) of patients, both fatal

    - Incidence of VOD and fatal VOD in 31 patients undergoing an allogeneic HSCT post-GO was 23% and 19%, respectively
- CR and CRp patients had a median time to ANC >500/μL 42 days from the first dose of GO
- CR and CRp patients had median time to platelets >50,000/μL of 51 days

Fractionated dosing: To support the fractionated dose schedule, safety data from MyloFrance 1 in CD33+ AML patients in first relapse was analyzed based on the published report (Taksin, Legrand et al. 2007) and supplemented by data provided by the CHV. This is referred to as the "MF1" subgroup. Available safety data, specifically regarding the incidence of VOD, was supplemented by the literature studies listed in Table 6.

Of the 57 patients in MyloFrance 1, there were 40 (70%) deaths observed. There were 4 early deaths (7%) before day 43 of therapy. There was one death before the day 15 bone marrow evaluation, one at day 27 during treatment-induced bone marrow hypoplasia with no persistent leukemia, and two on days 23 and 30 with persistent leukemia. Other key safety results showed the following:

- No infectious deaths occurred
- Grade 3 TEAEs in > 1% patients included sepsis (32%), fever (16%), rash (11%), pneumonia (7%), bleeding (7%), mucositis (4%), diarrhea (2%), headaches (2%), and edema (2%)
- No grade 4 toxicity was observed
- Grade 1 or 2 hyperbilirubinemia was reported in 4 (7%) patients
- Grade 1 or 2 elevations in AST or ALT were observed in 23 (40%) and 9 (16%) patients, respectively
- No episodes of VOD occurred
- CR and CRp patients had median time to ANC >500/μL 23 days from the first dose of GO
- CR and CRp patients had median time to platelets >50,000/μL of 20 days

Comparison of fractionated dosing (3 mg/m^2 days 1, 4, and 7) with unfractionated dosing of GO (at doses of 6 or 9 mg/m^2 every 14 days), using all available data in relapsed AML patients revealed the following observations:

- Early mortality lower across studies with lower doses of GO (9% overall using 3 mg/m^2 fractionated dosing, 10% using 6 mg/m^2 unfractionated, and 16% using 9 mg/m^2 unfractionated dosing)
- Treatment-related causes of death appeared to be reduced in patients treated with the 3 mg/m^2 fractionated regimen
- Grade 3-4 hemorrhage 7% on MyloFrance 1 versus 8-48% across studies using 6 and 9 mg/m^2 unfractionated doses of GO (28% on Studies 201-203)

- Grade 3-4 hepatotoxicity was not seen on Study MyloFrance 1 using the fractionated dose regimen, compared to rates up to 29% on studies 201-203
- No cases of VOD reported across all fractionated dose trials to date compared to 6% and 15% incidence across trials using 9 mg/m^2 and 6 mg/m^2 unfractionated dose regimens, respectively
    - Fatal VOD 4% on Studies 201-203 and 5% on the post-transplant Study 100374
    - Incidence of VOD with unfractionated dosing higher when administered pre- or post-HSCT
    - No cases of VOD out of 19 patients reported to date receiving fractionated doses of GO pre- or post-HSCT
- Time to neutrophil and platelet recovery on MyloFrance 1 substantially shorter than studies 201-203

Regarding a broader subset of R/R AML patients, the safety profile was similar in the R/R AML subgroup, although with a slightly higher incidence of VOD of 8% (only 2% fatal). Retrospective studies by Thomas *et al* (Thomas, Le et al. 2005) and Brethon *et al* (Brethon, Auvrignon et al. 2006) indicate a comparable safety profile in R/R patients with AML treated with fractionated doses of GO (i.e. not limited to the first relapse setting) without any cases of VOD.

Regarding pediatric use, the safety profile of unfractionated doses of GO in pediatric patients with relapsed or refractory AML was comparable to that seen in adults, with the exception that VOD was much more common on study 102, with an incidence of 31% overall. However, fatal VOD was only 3%. The retrospective pediatric trial by Brethon *et al* (Brethon, Auvrignon et al. 2006) indicated that fractionated doses of GO may be better tolerated in children, with none of the 6 patients treated with this dosing regimen developing VOD.

Lastly, regarding patients with AML who are post-HSCT, the safety of unfractionated doses of GO in these patients has not been established. DLTs occurred at all dose levels for the allogeneic HSCT group in Study 100374 and VOD incidence was 14% overall. There is little data on safety pre- or post- HSCT with the fractionated dosing regimen, but there are no safety signals to date. Out of 19 documented patients with a prior or subsequent HSCT with respect to treatment with fractionated dose GO, there were no cases of VOD.

Newly-diagnosed monotherapy indication

Upfront monotherapy dosing: Safety data from 111 older patients planned for non-intensive therapy treated with GO on AML-19 was analyzed, based on the published report (Amadori, Suciu et al. 2016). This is referred to as the “AML19” subgroup.

Of 118 patients randomized to GO on AML-19, there were 113 (96%) deaths observed versus 115/119 (97%) on the BSC arm. The all-cause 30-day mortality was 11% in the GO arm versus 13.5% in the BSC arm. 60-day mortality was 18% in the GO arm versus 30% in the BSC arm. Of 111 patients who were treated with GO, 8 (7%) experienced early deaths that were deemed treatment-related (infection, n=5; hemorrhage, n=1; renal failure, n=1; and cardiac failure, n=1). Deaths due to any AE over the course of the trial were 17% on the GO arm versus 20% on the BSC arm. Other key safety results showed the following:

- Grade ≥ 3 TEAEs in > 5% patients were comparable between the GO and BSC arms, including infection (GO 35% vs BSC 34%), febrile neutropenia (18% vs 24%), bleeding (13% vs 12%), fatigue (12% vs 21%), liver toxicity (7% vs 6%), cardiac toxicity (6% vs 14%), metabolic toxicities (4% vs 6%), and renal toxicity (4% vs 4%)
- No episodes of VOD occurred

Overdosage due to preparation or administration errors was not reported across the data submitted.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety for this BLA was based on all available safety data from the 13 protocols summarized in Section 5.1. The ISS data set was used for the safety analyses, along with the publication and data supplied by the CHV for MyloFrance 1 (Taksin, Legrand et al. 2007) and the publication for AML-19 (Amadori, Suciu et al. 2016).

7.1.2 Categorization of Adverse Events

Adverse events were reported down to the verbatim term for the unfractionated data. The adverse events were coded using MedDRA version 18.0. Terms that referred directly to relapse, persistence or progression of the primary AML were excluded from the analyses. Where indicated in the tables or text, some adverse events are presented as grouped terms as defined in Appendix 9.4. Treatment-emergent adverse events (TEAE) excluded events that started and ended before the start of study drug. For some analyses, where described in the text, TEAE were limited to those occurring only 28 days after the last dose of GO.

For MyloFrance 1, adverse events were reported as per the publication (Taksin, Legrand et al. 2007) and supported by the CHV data. The CHV data included selected AEs and it is unclear which coding system was used. It appears that grouped terms were used. The dataset included the following AEs: nausea vomiting, fever, infections,

diarrhea, pain, headache, tachycardia, bleeding, mucositis, rash, hypotension, hypothermia, constipation, leg edema, lung edema, dizziness, dyspnea, hemorrhoids, stomach pain, pneumonia, dementia, deafness, fatigue, renal failure, and dyskinesia. Additional data on incidence of fever and chills, nausea and vomiting, and infections were available for days 1-7 of therapy.

For AML-19, AEs were reported as per the publication (Amadori, Suciu et al. 2016). Their CRFs listed AEs per CTCAE v3.0. It is unclear which coding system was used, but it appears that grouped terms were used. The paper reported on infection, febrile neutropenia, bleeding, fatigue, liver, cardiac, metabolic, and renal for both treatment arms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Given identical dosing schemas for the Studies 201, 202, and 203, the safety profile of unfractionated GO for adults with first relapse of AML was developed using pooled data for subjects in these protocols (see Table 15).

Patients from studies 101, 103, and 100863 treated with the unfractionated dose of 9 mg/m^2 were pooled to analyze safety in a R/R patient population that was not limited to first relapse ("R/R AML" subgroup).

Data from studies MyloFrance 1 and AML-19 were reported separately.

Table 15: Pooling of safety data

Pool	Studies
Unfractionated	
First relapse	201, 202, 203
R/R AML	101, 103, 100863 (9 mg/m^2 doses only)
Total Treated*	101, 102, 103, 201, 202, 203, 205, 207, 100374, 100847, 100863
Fractionated	
MF1	MyloFrance 1
Upfront monotherapy	
AML19	AML-19

Key safety analyses were performed across dosing regimens of GO monotherapy in the relapsed AML setting, specifically focusing on the unfractionated regimens of 9 mg/m^2 x 2, 6 mg/m^2 x 2, and the fractionated dosing regimen of 3 mg/m^2 days 1, 4, and 7. We used available data from studies in the application (Table 4) and the literature (Table 6) in order to pool a larger group of patients together by these dosing regimens. Studies were excluded from our analysis when they lacked information on VOD incidence, failed

to distinguish safety by dose, used a different dosing regimen, or included patients treated on other protocols.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Detailed safety data were available for 936 patients with AML or MDS treated with various doses and schedules of GO. The demographics of these 936 patients are shown in Table 16. The Applicant's proposed dose-schedules of GO monotherapy in the relapsed setting are 1) up to 2 unfractionated doses of 9 mg/m^2, 14 days apart and 2) a fractionated schedule of 3 mg/m^2 on days 1, 4, and 7. The proposed dose-schedule of GO monotherapy in the newly-diagnosed setting is 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8, followed by up to 8 monthly infusions of 2 mg/m^2. The demographics for the patients in the first relapse subgroup treated with unfractionated dosing, the MyloFrance-1 patients in first relapse treated with fractionated dosing, the R/R AML subgroup treated with 9 mg/m^2 unfractionated dosing, and the AML-19 newly-diagnosed patients are shown in Table 16.

Table 16: Demographics of the Safety Population

		Subgroups				Total
		First relapse (N=277)	MF1 (N=57)	R/R AML (N=61)	AML19 (N=111)*	Treated† (N=936)
Age						
	Median (range)	61 (20-87)	64 (22-80)	59 (18-80)	NR	60 (3-90)
Age Group	< 18 years	0	0	0	0	28 (3%)
	18 - <60 years	120 (43%)	22 (39%)	37 (61%)	0	407 (43%)
	≥60 years	157 (57%)	35 (61%)	24 (39%)	111 (100%)	501 (54%)
Gender						
	Male	151 (55%)	29 (51%)	39 (64%)	NR	539 (58%)
	Female	126 (45%)	28 (49%)	22 (36%)	NR	397 (42%)
Race						
	White	264 (95%)	NR	28 (46%)	NR	798 (85%)
	Black	6 (2%)	NR	1 (2%)	NR	46 (5%)
	Asian	2 (1%)	NR	1 (2%)	NR	18 (2%)
	Other	5 (2%)	NR	0	NR	34 (4%)
	Missing	0	NR	31 (51%)	NR	40 (4%)
Site						
	Canada	7 (3%)	0	0	0	7 (1%)
	Europe	151 (55%)	57 (100%)	0	111 (100%)	161 (17%)
	US	119 (43%)	0	30 (49%)	0	728 (78%)
	Missing	0	0	31 (51%)	0	40 (4%)
Diagnosis						

	AML	277 (100%)	57 (100%)	61 (100%)	111 (100%)	449 (48%)
	MDS	0	0	0	0	26 (3%)
	Unknown‡	0	0	0	0	461 (49%)
GO Regimen	9 mg/m^2 unfractionated	277 (100%)	0	61 (100%)	0	377 (40%)
	3 mg/m^2 fractionated	0	57 (100%)	0	0	0
	6 d1, 3 mg/m^2 d8	0	0	0	111 (100%)	0
	Other	0	0	0	0	98 (10%)
	Unknown‡	0	0	0	0	461 (49%)

Sources: MyloFrance 1 paper (Taksin, Legrand et al. 2007) supplemented by CHV data, AML-19 paper (Amadori, Suciu et al. 2016), and FDA analysis
*Full demographics only reported for the ITT population in the paper. See Section 6.1.2 for this data.
†Total treated excludes MF1 and AML19 patients.
‡GO administered per investigator discretion on the observational study 100847.

7.2.2 Explorations for Dose Response

Ten starting doses of GO were tested in prospective company-sponsored clinical trials, MyloFrance 1, and AML-19. In addition, 461 patients from the observational study 100847 used unknown doses per investigator discretion. Table 17 shows the numbers of patients starting therapy at each of the doses. Out of 1,104 total patients, the majority of patients for whom we know the dose started treatment at 9 mg/m^2 (34%), 6 mg/m^2 (13%), or 3 mg/m^2 (5%). Results of the formal dose-escalation trials are discussed in section 7.5.1.

Table 17: GO Starting Doses Across Trials*

Dose	N	%
0.25 mg/m^2/dose	4	0.4%
0.5 mg/m^2/dose	3	0.3%
1 mg/m^2/dose	3	0.3%
2 mg/m^2/dose	16	1%
3 mg/m^2/dose	57	5%
4 mg/m^2/dose	24	2%
5 mg/m^2/dose	6	0.5%
6 mg/m^2/dose	148	13%
7.5 mg/m^2/dose	5	0.5%
9 mg/m^2/dose	377	34%
Unknown	461	42%

Source: FDA analysis
*Includes all unfractionated trials, MyloFrance1, and AML-19

For the unfractionated dosing schemas, GO was administered as a 2-hour IV infusion for 2-3 doses at least 14 days, but no more than 28 days from the previous infusion. However, later protocol amendments eliminated the option for a third dose. The second (or third) doses would only be given if certain criteria were met, such as recovery from

toxicity and absence of disease progression. The majority of patients received the intended 2 or more doses of GO (544/936 patients, 58%).

For the fractionated dosing schema, GO was administered as a 2-hour IV infusion days 1, 4, and 7. The second and third doses would only be given if transaminases were ≤ 5 times normal and factor V ≥ 50% when checked on days 3 and 6. All patients received the intended 3 doses of GO (57/57 patients, 100%).

For the newly-diagnosed dosing schedule of 6 mg/m^2 day 1 and 3 mg/m^2 day 8, GO was administered as 2-hour IV infusions. The second dose would only be given if certain criteria were met, such as recovery from toxicity and absence of disease progression, with a delay of no more than 2 days between sequential infusions. The majority of patients received the intended 2 doses of GO induction (104/111 patients, 94%).

Table 18 below shows an integrated analysis of cumulative GO exposure across all trials, with the exception of study 100847 (doses not available). Overall, the majority of patients received 2 or more doses of GO (705/1104, 64%).

Table 18: Cumulative GO Exposure in Safety Population

Dose	1 dose	2 doses	≥3 doses
Any Dose	**399**	**536**	**169**
0.25 mg/m^2/dose	3	0	1
0.5 mg/m^2/dose	0	2	1
1 mg/m^2/dose	2	0	1
2 mg/m^2/dose	6	8	2
3 mg/m^2/dose	0	0	57
4 mg/m^2/dose	12	10	2
5 mg/m^2/dose	3	0	3
6 mg/m^2/dose	12	74	62
7.5 mg/m^2/dose	2	3	0
9 mg/m^2/dose	106	240	31

Source: FDA analysis, (Taksin, Legrand et al. 2007, Amadori, Suciu et al. 2016)

Reviewer comment: Table 18 suggests that the 9 mg/m^2 fractionated dose of Mylotarg was more difficult for patients to tolerate, as 106/377 (28%) patients treated at this dose received only the first dose. Compare this to the 3 mg/m^2 dose where all patients received 3 doses and the 6 mg/m^2 dose where 92% of patients received 2 or more doses.

The maximum number of doses to be administered varied by protocol, but was ultimately capped at 2 doses in later studies. For subgroups used in the safety analyses, the number of patients by number of doses administered is shown in Table 19.

Table 19: Number of Patients by Doses Administered

Doses	Subgroups				Total
	First relapse (N=277)	MF1 (N=57)	R/R AML (N=61)	AML19 (N=111)	Treated* (N=936)
1	67 (24%)	0	15 (25%)	7 (6%)	392 (42%)
2	183 (66%)	0	43 (70%)	104 (94%)	491 (52%)
≥3	27 (10%)	57 (100%)	3 (5%)	N/A†	53 (6%)

Sources: MyloFrance 1 paper (Taksin, Legrand et al. 2007), AML-19 paper (Amadori, Suciu et al. 2016), and FDA analysis
*Total treated excludes MF1 and AML19 patients.
†Post-induction therapy was considered separately.

On AML-19, a total of 59 patients (53%) received at least one post-induction infusion at 2 mg/m^2. Nine (8%) received the entire treatment program of 10 infusions. The median number of GO infusions administered was 3 (range 1-10) (Amadori, Suciu et al. 2016).

7.2.3 Special Animal and/or In Vitro Testing

Results of preclinical studies relevant to safety were summarized in Section 4.3. There were no issues raised by the preclinical reviewers of the *in vivo* preclinical testing that warranted clinical monitoring beyond that used routinely in the development of recombinant proteins and oncolytic therapies.

7.2.4 Routine Clinical Testing

The schedule of safety evaluations for each protocol was described in Section 5.3. The frequency of monitoring was considered adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Results of the studies of human PK and PD relevant to safety were summarized in Section 4.4. Issues identified included an increased risk of VOD with increases in Cmax after the first dose of GO. The role of anti-biologic antibodies on safety is discussed in Section 7.4.6.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant noted 6 important identified risks: myelosuppression (including neutropenia and thrombocytopenia), infection, bleeding/hemorrhage, hepatotoxicity (including VOD), infusion-related reactions (including anaphylaxis), and tumor lysis syndrome. Furthermore, they noted 4 potential identified risks: neurotoxicity, renal toxicity, reproductive and developmental toxicity, and second primary malignancy.

The Applicant did not provide specific search strategies for each identified risk. However, they stated that the AEs relevant to these safety topics were analyzed in

aggregate using clustered TEAEs derived from search criteria comprising preferred terms, standardized MedDRA queries, and high level terms. The same clustered TEAEs were used by this reviewer and are included in Appendix 9.4.

7.3 Major Safety Results

7.3.1 Deaths

Unfractionated dosing

For the assessment of deaths, the applicant reviewed deaths within 30 days of the first dose of study treatment and up to 28 days after the last dose of GO. They summarized TEAEs from the clinical trials database with an outcome of death by MedDRA SOC and PT for individual studies and pooled monotherapy studies. SAEs from the safety database with an outcome of fatal were summarized by MedDRA SOC and PT for individual studies and pooled monotherapy trials. Causes of treatment-related deaths were not systematically collected across all studies, but were collected for Studies 201, 202, and 203.

All treated

Out of all 936 patients in the monotherapy safety database, there were 206 (22%) early deaths within 28 days of the last dose of GO. 155 (17%) of patients died within 30 days of the first dose. All deaths are unknown since not all trials tracked for OS.

All-cause TEAEs with outcome recorded as death were reported in 90 of 377 patients (24%) treated with the 9 mg/m^2 dose across the monotherapy trials and in 157 of 461 patients (34%) in the GO per investigator discretion Study 100847. Again, causality in terms of treatment-related deaths was not systematically collected. Most TEAEs resulting in deaths were due to infections (7-10%), cytopenias (3-8%), disease progression (1-9%), and respiratory disorders (5-6%).

SAEs with outcome reported as death were reported in 535 patients (57%) across all GO monotherapy studies, 209/377 patients (55%) in the GO 9 mg/m^2 group, and in 301/461 patients (65%) in the GO per investigator discretion group. Across all dose levels, the most frequently reported SAEs with outcome resulting in death were disease progression (23%), infections (15%), and neoplasm/AML (12%).

First relapse subgroup

In studies 201-203, there were 252 (91%) deaths observed (see Table 20 below). Per the Cause of Death dataset submitted by the Applicant in response to an IR, at least 63% of the total deaths were considered to be related to active primary malignancy.

There were 51 (18%) early deaths on or before day 43 of therapy, i.e. within 28 days of the last dose (Table 20). Early deaths were equivalent in younger and older patients, with 22 (18%) of 120 patients < 60 years of age and 29 (18%) of 157 patients ≥ 60 years of age experiencing early deaths. 29 (10%) of patients died within 30 days of the first dose. All-cause TEAEs with outcome recorded as death were reported in 70 patients (25%) across the pivotal trials (25, 25, and 20 patients on studies 201, 202, and 203, respectively). Again, causality in terms of treatment-related was not systematically collected. Most TEAEs resulting in deaths were due to infections (12%), cytopenias (9%), and respiratory disorders (7%).

R/R AML subgroup

Given that OS was not an efficacy endpoint on studies 101, 103, and 100863, we do not have all death data available for these 61 patients. Of the 35 deaths we know about, 12 (34%) were considered leukemia-related. Early death results were similar to those seen on studies 201-203 (Table 20). Of the 10 early deaths, infections accounted for 3 (5% of the population).

MyloFrance 1

Of the 57 patients on MyloFrance 1, there were 40 (70%) deaths observed (see Table 20). There were 4 early deaths (7%) before day 43 of therapy. The CHV data was used to supplement the death data reported in the publication. There were 2 sudden deaths at home, one on day 14 before the day 15 marrow evaluation and one on day 27 during treatment-induced bone marrow hypoplasia with no persistent leukemia. The other 2 deaths on days 23 and 30 of therapy were related to persistent leukemia. Among the 19 patients in remission, 11 relapsed and 9 died from leukemia: 7 of the 15 who achieved CR and 2 of the 4 with CRp (Taksin, Legrand et al. 2007).

AML-19

Of 118 patients randomized to GO on AML-19, there were 113 (96%) deaths observed versus 115/119 (97%) on the BSC arm. The all-cause 30-day mortality was 11% in the GO arm versus 13.5% in the BSC arm. 60-day mortality was 18% in the GO arm versus 30% in the BSC arm. Of 111 patients who were treated with GO, 8 (7%) experienced early deaths that were deemed treatment-related (infection, n=5; hemorrhage, n=1; renal failure, n=1; and cardiac failure, n=1). Deaths due to any AE over the course of the trial were 17% on the GO arm versus 20% on the BSC arm (Amadori, Suciu et al. 2016).

Table 20: Deaths

Study Day	Subgroups				Total
	First relapse (N=277)	MF1 (N=57)	R/R AML (N=61)	AML19 (N=111)	Treated* (N=936)
Within 30 days of 1st dose	29 (10%)	4 (7%)	7 (11%)	13 (11%)	155 (17%)
Within 28 days of last dose	51 (18%)	4 (7%)	10 (16%)	Unknown	206 (22%)
All deaths	252 (91%)	40 (70%)	Unknown	113 (96%)	Unknown

Sources: ISS, FDA analysis, MyloFrance 1 paper (Taksin, Legrand et al. 2007), and AML-19 paper (Amadori, Suciu et al. 2016)
*Total treated excludes MF1 and AML19 patients.
†Included R/R patients treated at all dose levels for this analysis, per the Integrated Summary of Safety.

Unfractionated dosing

FDA reviewed narratives for studies 201-203 to confirm the cause of death for patients meeting narrative criteria (n=135, out of 252 total deaths). FDA considered the cause of death to be the primary malignancy when supported by a high burden of disease in the marrow or peripheral blood by blast count or flow cytometry, imaging report, or description of other objective evidence. In response to an information request, the applicant provided additional data as well as their adjudication of proximate cause of death in a Cause of Death dataset, which was used to supplement the narratives. Of the 135 patient narratives, I confirmed that 70 (52%) deaths were due to the primary malignancy. There were 50 deaths (37%) considered by FDA to be at least possibly related to treatment with GO, and our assessment was mostly in line with that of the Applicant (Table 21).

Table 21: Deaths suspected by FDA as related to GO

Patient ID	Day of death	FDA COD	Adjudication Reported by Applicant	
			Applicant COD	Related
Study 201				
(b) (6)	2	Cerebral hemorrhage	Cerebral hemorrhage	Study Drug
	58	Subdural hematoma	Subdural hematoma	Study Drug
	13*	Cerebral hemorrhage	Cerebral hemorrhage	Study Drug
	35	Retroperitoneal bleed	Multisystem organ failure	Study Drug
	15	Fungemia/sepsis	Fungemia/sepsis	Study Drug
	39	Pneumonia	Lung infection	Study Drug
	53	Enterococcal sepsis	Enterococcal sepsis	Study Drug
	8*	Sepsis	Sepsis	Study Drug
	9*	Unknown	Unknown	Unknown
	105	VOD	VOD	Study Drug
	53	VOD	VOD	Study Drug
	121	VOD	VOD	Study Drug
	140	VOD	Hepatic failure	Study Drug
	9*	VOD	VOD	Study Drug
	14*	VOD	VOD	Study Drug
	83	VOD	VOD	Study Drug

Study 202				
(b) (6)	32	Cerebral hemorrhage	Cerebral hemorrhage	Study Drug
	7	Cerebral hemorrhage	Cerebral hemorrhage	Study Drug
	35	Cerebral hemorrhage	Cerebral hemorrhage	Study Drug
	5	Cerebral hemorrhage	Cerebral hemorrhage	Study Drug
	75	Infectious meningitis	Infectious meningitis	Study Drug
	13	Septic shock	Septic shock	Study Drug
	64	Fungal pneumonia	Fungal pneumonia	Study Drug
	19	Pneumonia	Pneumonia	Study Drug
	30	Fungal infection	Fungal infection	Study Drug
	36	Pneumonia	Pneumonia	Study Drug
	24	Respiratory failure/cerebral hemorrhage	Respiratory failure/cerebral hemorrhage	Study Drug
	42*	ARDS	ARDS	Study Drug
	68	ARDS/Pneumonia	ARDS/Pneumonia	Study Drug
	51	ARDS/Aspergillosis	ARDS/Aspergillosis	Study Drug
	28	Multiple organ failure	Multiple organ failure	Study Drug
	16	VOD/multiple organ failure	VOD/multiple organ failure	Study Drug
	139	VOD	VOD	Study Drug
Study 203				
(b) (6)	14	Cerebral hemorrhage	Cerebral hemorrhage	Study Drug
	16	Cerebral hemorrhage	Cerebral hemorrhage	Study Drug
	84	Cerebral hemorrhage	Disease progression	AML
	20*	Subdural hematoma	Disease progression	AML
	54	Pneumonia	Pneumonia	Study Drug
	130	Sepsis	Disease progression	AML
	44	Sepsis	Sepsis	Study Drug
	32	Sepsis	Sepsis	Study Drug
	73	Acute cholecystitis	Disease progression	AML
	11	Pneumonia	Respiratory distress	Study Drug
	26	Pneumonia	Pneumonia	Study Drug
	40	Sepsis/respiratory failure	Sepsis/respiratory failure	Study Drug
	41	Sepsis/respiratory failure	Toxic shock syndrome	Study Drug
	2	Sepsis/multiple organ failure	Septic shock	Study Drug
	21	Respiratory failure	Respiratory failure	Study Drug
	16	Acute renal failure	Acute renal failure	Study Drug
	16	VOD	Unknown	Unknown

Sources: CSRs for studies 201, 202, and 203, and COD dataset
*Following 3rd dose of GO after disease relapse

Reviewer comments: With the limitation of smaller sample size, the induction mortality rate using fractionated dose GO (MyloFrance 1), in a similar first relapse patient population to Studies 201-203, appeared to be much lower. Furthermore, the R/R AML population had a similar induction mortality rate of 16% using 9 mg/m² GO. The total treated population, which included only unfractionated doses, was even higher at 22%.

From studies 201-203, we can see that most deaths were related to infection and bleeding, which makes intuitive sense given unfractionated GO's propensity to cause prolonged cytopenias, particularly thrombocytopenia. VOD was another major cause of treatment-related death. In contrast, MyloFrance 1 reported no infectious or hemorrhagic deaths (although these cannot be completely ruled out for the 2 sudden deaths at home) and no cases of VOD.

AML-19 had a similar 30-day mortality rate to the unfractionated dose studies, but it included an older, more co-morbid patient population. Furthermore, the control arm on AML-19 showed that 30 and 60-day mortality were lower on the GO arm than the BSC arm.

Overall, the high incidence of fatal bleeding on studies 201-203 justifies a warning for hemorrhage, including fatal intracranial hemorrhage, in the PI. The fractionated/lower doses appear to decrease this risk, but it is unlikely to be completely eliminated.

7.3.2 Nonfatal Serious Adverse Events

Unfractionated dosing

An SAE occurring within 28 days after the last dose of GO was reported for 667 (71%) of the 936 total treated patients, including 226/277 (82%) of the first relapse subgroup and 34/61 (56%) of the R/R AML subgroup. The distribution of SAEs by SOC is shown in Table 22.

Table 22: Serious Adverse Events within 28 Days of Follow-Up

System Organ Class	Subgroups				Total Treated (N=936)	
	First relapse (N=277)		R/R AML (N=61)			
	n	%	n	%	n	%
Any Class	**226**	**82%**	**34**	**56%**	**667**	**71%**
Blood and lymphatic system disorders	215	78%	24	39%	514	55%
General disorders and administration site conditions	194	70%	17	28%	534	57%
Infections and infestations	105	38%	17	28%	298	32%
Gastrointestinal disorders	86	31%	8	13%	223	24%
Respiratory, thoracic and mediastinal disorders	47	17%	11	18%	201	22%
Investigations	36	13%	22	36%	339	36%
Vascular disorders	35	13%	3	5%	91	10%
Nervous system disorders	29	11%	1	2%	62	7%
Metabolism and nutrition disorders	24	9%	1	2%	58	6%
Hepatobiliary disorders	21	8%	3	5%	90	10%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18	7%	1	2%	41	4%
Cardiac disorders	13	5%	5	8%	80	9%
Musculoskeletal and connective tissue disorders	12	4%	1	2%	20	2%

Renal and urinary disorders	10	4%	6	10%	67	7%
Skin and subcutaneous tissue disorders	10	4%	0	0%	18	2%
Eye disorders	5	2%	0	0%	9	1%
Injury, poisoning and procedural complications	5	2%	4	7%	100	11%
Immune system disorders	3	1%	1	2%	18	2%
Congenital, familial and genetic disorders	2	1%	0	0%	3	0.3%
Psychiatric disorders	2	1%	2	3%	14	2%
Reproductive system and breast disorders	2	1%	0	0%	4	0.4%
Endocrine disorders	1	0.4%	0	0%	1	0.1%
Surgical and medical procedures	1	0.4%	0	0%	3	0.3%

Sources: FDA analysis
*Occurred between start of therapy and 28 days after last GO dose

Reviewer comments: It is notable that the R/R-AML population and the all-treated population had more SAEs in the Investigations category, many of which were due to liver PTs. This may be due to a higher propensity for liver toxicity in a more highly pretreated population. There was also slightly more renal and urinary SAEs with the R/R and all-treated populations. Injury, poisoning and procedural complications occurred more in the all-treated patients, with 7 total cases of intracranial hemorrhage (1 traumatic). The remainder of the SAEs were roughly equivalent across the unfractionated populations.

Out of the 936 all-treated patients, there were 757 (81%) SAEs occurring on treatment or within 30 days of follow-up. A related SAE was reported for 205 (74%) of subjects in the first relapse subgroup, 27 (44%) in the R/R-AML subgroup, and 522 (56%) in the total treated population. For the first relapse subgroup, the most common (>2%) related SAEs were pyrexia (42%), neutropenia (32%), thrombocytopenia (14%), sepsis (11%), chills (8%), febrile neutropenia (7%), nausea (6%), pneumonia (6%), vomiting (6%), hypotension (5%), pancytopenia (5%), leukopenia (4%), anemia (4%), infection (3%), and liver disorder (3%).

MyloFrance 1

We do not have available SAE data from MyloFrance 1.

AML-19

Per Amadori *et al*, the rates of serious adverse events were similar in the GO and BSC groups (Amadori, Suciu et al. 2016). However, we do not have the primary data to perform this analysis.

7.3.3 Dropouts and/or Discontinuations

Unfractionated dosing

Overall, 97 (10%) treated patients had a dose interruption or permanent discontinuation, including 59 (21%) patients in the first relapse subgroup. The percentages of patients with either an interruption or a permanent discontinuation due to an adverse event are shown in Table 23.

Table 23: Treatment Interruptions or Withdrawals due to Adverse Event

	Subgroups		Total
	First relapse (N=277)	R/R AML (N=61)	Treated (N=936)
Interruption	6 (2%)	0 (0%)	6 (1%)
Withdrawal	40 (14%)	2 (3%)	71 (6%)
Either	46 (17%)	2 (3%)	77 (8%)

Source: FDA analysis
*Occurred between start of therapy and 28 days after last GO dose

The most common TEAEs resulting in treatment interruption or permanent discontinuation are shown in Table 24 in decreasing order in the first relapse and R/R-AML subgroups. The table includes only those events that occurred in >1% of patients in either subgroup. There were no AEs resulting in interruption in >1% of patients, and thus, the table only includes AEs leading to withdrawal.

Table 24: TEAEs Resulting in Withdrawal*

	Subgroups			
Preferred Term	First relapse (N=277)		R/R AML (N=61)	
	n	%	n	%
Cerebral haemorrhage	6	2.2%	0	0%
Multi-organ failure	4	1.4%	0	0%
Pneumonia	3	1.1%	0	0%
Sepsis	3	1.1%	0	0%
Septic shock	3	1.1%	0	0%
VOD	3	1.1%	0	0%
Abdominal pain	0	0%	1	1.6%
Atrial fibrillation	0	0%	1	1.6%
Chills	0	0%	1	1.6%
Metabolic acidosis	0	0%	1	1.6%
Pyrexia	0	0%	1	1.6%
Respiratory distress	0	0%	1	1.6%

Source: FDA analysis
*Occurred between start of therapy and 28 days after last GO dose

Cerebral hemorrhage, organ failure, and infection were the most common TEAEs leading to treatment withdrawal. Treatment interruptions were uncommon since the therapy only consisted of 2-3 doses of drug. However, reasons for interruptions were increased bilirubin, abnormal hepatic function, dyspnea, dyspepsia, hypertension, hypotension, and pyrexia (occurring in one patient each).

MyloFrance 1

All 57 patients on the MyloFrance 1 study completed 3 fractionated doses of GO. There was no data on dose interruptions in the publication or the datasets received from the CHV.

AML-19

Out of 111 patients on the GO arm, 104 (94%) received the full induction course of 2 infusions and 59 (53%) received at least one post-induction infusion. Only 9 (8%) received the entire treatment program of 10 infusions.

Out of 111 patients on the GO arm, 100 (90%) discontinued therapy, mostly due to the primary disease (n=56, 50%) or an AE (n=19, 17%). Even more patients (110/114, 96%) discontinued treatment on the BSC arm, primarily due to the underlying AML (n=76, 67%) or an AE (n=23, 20%).

Reviewer comments: Considering all of the discontinuation data, it is concerning that with the unfractionated regimen, hemorrhage, infection, organ failure, and VOD prevented patients from completing GO therapy. This is in contrast to the MyloFrance 1 data where all patients completed 3 doses of fractionated GO. For AML-19, all but 6% completed induction and discontinuation rates overall were favorable on the GO arm compared to the BSC arm. However, we do not have data on the types of AEs for which patients withdrew from both arms.

7.3.4 Significant Adverse Events

Unfractionated dosing

The applicant reported the incidence of adverse events for identified risks, which I will hereafter refer to as adverse events of special interest (AESI). The search strategies used for each of these AESIs are listed in Appendix 9.4. For the purposes of this analysis, we investigated the first relapse and R/R-AML populations. The results are summarized in Table 25. Grade 3-4 AESIs are also compared alongside MyloFrance 1 and AML-19 in Table 26.

Table 25: Adverse Events of Special Interest

	Any Grade		Grade 3-4	
AESI	First relapse (N=277)	R/R AML (N=61)	First relapse (N=277)	R/R AML (N=61)
Myelosuppression	202 (73%)	55 (90%)	190 (69%)	55 (90%)
Infection	189 (68%)	42 (69%)	117 (42%)	16 (26%)
Hemorrhage	186 (67%)	47 (77%)	77 (28%)	14 (23%)
VOD	15 (5%)	5 (8%)	12 (4%)	1 (2%)
Hepatotoxicity	104 (38%)	43 (70%)	79 (29%)	10 (16%)
Infusion reactions	218 (79%)	40 (66%)	140 (51%)	17 (28%)
TLS	7 (3%)	0	5 (2%)	0

Source: FDA analysis and ISS

Infusion reactions were common on studies 201-203, with chills being the most frequent manifestation (60%). The administration of corticosteroids prior to GO on the post-marketing Study 100863 appeared to lessen, but not completely eliminate, infusion-related events. In this study of 23 patients, included in the R/R AML subgroup, any infusion-related event was seen in 39% of patients and severe infusion-related AEs were seen in 13% of patients.

AESIs were relatively well-matched in the first relapse versus R/R-AML subgroups. However, myelosuppression was more common in the R/R-AML subgroup. Hepatotoxicity of all-grades was more common in the R/R-AML subgroup, but grade 3-4 hepatotoxicity was greater in the first relapse subgroup. Infusion reactions were less in the R/R-AML subgroup, likely due to the inclusion of Study 100863, the post-marketing steroid prophylaxis study. TLS was uncommon overall, but was not seen at all in the R/R subgroup, likely due to more resistant tumors in these patients and thus less of a propensity to lyse.

Reviewer comments: Note that the rate of grades 3-4 VOD was likely underestimated in the table above given that many events in the VOD database did not have grades assigned. See Section 7.5.1 for a more detailed evaluation of VOD across doses and schedules of GO.

MyloFrance 1

The grade 3-4 AESIs from MyloFrance 1 are summarized in Table 26 below. Myelosuppression was not reported in the MyloFrance 1 paper and hematologic AEs were not included in the provided CHV dataset, aside from time to count recovery.

Per the CHV data, all-grade infections, including pneumonias, were seen in 56% of patients and grade 3 infections were seen in 39%.

All-grade bleeding events were seen in 23% of patients and grade 3 bleeding was seen in 7%.

Hyperbilirubinemia was seen in 7%, AST elevations were seen in 40%, and ALT elevations were seen in 16% of patients. However, there was no grade 3-4 hepatotoxicity reported. Furthermore, there were no episodes of VOD.

MyloFrance 1 did not report any grade 3-4 infusion-related events, but 16% of patients were noted to have grade 3 fever and 2% had grade 3 tachycardia at some point during induction. This was confirmed with the CHV data. No cases of TLS were reported in either the manuscript or the CHV data.

AML-19

Grade 3-4 AESIs from AML-19 are summarized in Table 26 below. While myelosuppression was not reported in detail in the manuscript, they state that pancytopenia was universally seen during GO induction (Amadori, Suciu et al. 2016).

All-grade infections were 44% on the GO arm versus 42% on the BSC arm. Grade ≥ 3 infections were also well-balanced at 35% vs 34%.

All-grade bleeding was seen in 25% on the GO arm versus 30% on the BSC arm and ≥ grade 3 bleeding was seen in 13% versus 12%, respectively.

Liver toxicity was seen in 51% of GO-treated patients versus 46% of BSC patients and ≥ grade 3 hepatotoxicity was 7% vs 6 %, respectively. There were no episodes of VOD on the GO arm.

Table 26: Grade 3-4 Adverse Events of Special Interest Across Regimens

			Subgroups		
AESI	First relapse (N=277)	MF1 (N=57)	R/R AML (N=61)	AML19-GO* (N=111)	AML19-BSC* (N=114)
Myelosuppression	190 (69%)	NR	55 (90%)	NR	NR
Infection	117 (42%)	22 (39%)	16 (26%)	35%	34%
Hemorrhage	77 (28%)	4 (7%)	14 (23%)	13%	12%
VOD	12 (4%)	0	1 (2%)	0	NR
Hepatotoxicity	79 (29%)	0	10 (16%)	7%	6%
Infusion reactions	140 (51%)	NR	17 (28%)	NR	NR
TLS	5 (2%)	NR	0	NR	NR

Abbreviations: NR, not reported
Sources: ISS, FDA analysis, MyloFrance 1 paper (Taksin, Legrand et al. 2007), CHV data, and AML-19 paper (Amadori, Suciu et al. 2016)
*Paper reported on grade ≥ 3 AEs, so unclear if some may have been grade 5

Reviewer comments: It is notable that infections were roughly equal across the first relapse setting and across arms on AML-19. Hemorrhage, however, was substantially higher in the unfractionated dose studies. Furthermore, VOD was

not seen on either MyloFrance 1 or AML-19. Hepatotoxicity was also much lower on these studies.

Given the high rate of grade 3-4 hepatotoxicity seen with the unfractionated doses, I agree with the need for a warning in labeling addressing the risk of hepatotoxicity, even if we do not approve these doses.

7.3.5 Submission Specific Primary Safety Concerns

AESIs are reviewed in Section 7.3.4 above and in more detail per dose in section 7.5.1 below.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Unfractionated dosing

Common TEAEs were assessed through 28 days after the last dose of GO for the company-sponsored trials, all of which used unfractionated doses of GO. The numbers of patients with a TEAE are shown in Table 27 by SOC in decreasing order of incidence in the different subgroups.

Table 27: TEAE Within 28 Days of Follow-Up by SOC

System Organ Class	Subgroups				Total Treated (N=936)	
	First relapse (N=277)		R/R AML (N=61)			
	n	%	n	%	n	%
General disorders and administration site conditions	265	96%	60	98%	692	74%
Gastrointestinal disorders	259	94%	56	92%	556	59%
Blood and lymphatic system disorders	202	73%	31	51%	485	52%
Infections and infestations	189	68%	42	69%	437	47%
Respiratory, thoracic and mediastinal disorders	177	64%	43	71%	413	44%
Investigations	170	61%	54	89%	506	54%
Metabolism and nutrition disorders	164	59%	54	89%	340	36%
Nervous system disorders	150	54%	34	56%	299	32%
Skin and subcutaneous tissue disorders	139	50%	41	67%	278	30%
Vascular disorders	125	45%	30	49%	290	31%
Musculoskeletal and connective tissue disorders	108	39%	28	46%	202	22%
Psychiatric disorders	94	34%	17	28%	155	17%
Cardiac disorders	71	26%	26	43%	185	20%
Injury, poisoning and procedural complications	70	25%	9	15%	119	13%
Renal and urinary disorders	62	22%	21	34%	157	17%
Eye disorders	42	15%	3	5%	79	8%
Hepatobiliary disorders	37	13%	4	7%	107	11%
Reproductive system and breast disorders	27	10%	6	10%	40	4%

Ear and labyrinth disorders	19	7%	3	5%	31	3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9	3%	2	3%	64	7%
Immune system disorders	8	3%	6	10%	38	4%
Congenital, familial and genetic disorders	1	0.4%	0	0%	2	0.2%
Endocrine disorders	1	0.4%	1	2%	2	0.2%
Surgical and medical procedures	1	0.4%	0	0%	3	0.3%

Sources: FDA analysis
*Occurred between start of therapy and 28 days after last GO dose

Integrated analysis of TEAEs

A TEAE was reported in 276 (99.6%) of patients in the first relapse subgroup. The numbers of patients with common (≥10%) TEAE are shown in Table 28 by PT in decreasing order of incidence in the first relapse subgroup. The results are compared alongside those from MyloFrance 1 and AML-19.

Table 28: TEAEs Within 28 Days of Follow-Up by PT

	First relapse (N=277)		MF1 (N=57)		R/R AML (N=61)		AML19-GO (N=111)		AML19-BSC (N=114)	
Preferred Term*	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Pyrexia	225	81%	45	79%	44	72%	NR	NR	NR	NR
Nausea†	197	71%	12	21%	51	84%	NR	NR	NR	NR
Chills	188	68%	NR	NR	41	67%	NR	NR	NR	NR
Vomiting	168	61%	12	21%	36	59%	NR	NR	NR	NR
Thrombocytopenia	125	45%	NR	NR	30	49%	111	100%	NR	NR
Headache	106	38%	11	19%	23	38%	NR	NR	NR	NR
Diarrhea	94	34%	7	12%	22	36%	NR	NR	NR	NR
Fatigue	79	29%	3	5%	17	28%	51	46%	69	61%
Epistaxis/"bleeding"	79	29%	13	23%	19	31%	28	25%	34	30%
Decreased appetite	75	27%	NR	NR	42	69%	NR	NR	NR	NR
Constipation	70	25%	12	21%	16	26%	NR	NR	NR	NR
Hypokalemia/"metabolic"	68	25%	NR	NR	18	30%	18	16%	17	15%
Neutropenia	67	24%	NR	NR	17	28%	111	100%	NR	NR
Anemia	66	24%	NR	NR	29	48%	111	100%	NR	NR
Dyspnea	65	23%	2	4%	13	21%	NR	NR	NR	NR
Leukopenia	63	23%	NR	NR	1	2%	111	100%	NR	NR
Hypotension	55	20%	1	2%	15	25%	NR	NR	NR	NR
Febrile neutropenia	53	19%	NR	NR	19	31%	20	18%	27	24%
AST increased/"Liver"	52	19%	23	40%	31	51%	57	51%	52	46%
Cough	51	18%	NR	NR	14	23%	NR	NR	NR	NR
Petechiae	49	18%	NR	NR	16	26%	NR	NR	NR	NR
Abdominal pain	47	17%	7	12%	13	21%	NR	NR	NR	NR
Blood LDH increased	46	17%	NR	NR	31	51%	NR	NR	NR	NR
Oral herpes	46	17%	NR	NR	3	5%	NR	NR	NR	NR
Hypertension	44	16%	NR	NR	9	15%	NR	NR	NR	NR
Peripheral edema	40	14%	4	7%	8	13%	NR	NR	NR	NR
Back pain‡	39	14%	8	14%	7	12%	NR	NR	NR	NR
ALT increased	37	13%	9	16%	25	41%	NR	NR	NR	NR
Rash	37	13%	9	16%	9	15%	NR	NR	NR	NR

Dizziness	35	13%	2	4%	11	18%	NR	NR	NR	NR
Asthenia	34	12%	NR	NR	9	15%	NR	NR	NR	NR
Insomnia	34	12%	NR	NR	3	5%	NR	NR	NR	NR
Mucosal inflammation	31	11%	12	21%	8	13%	NR	NR	NR	NR
Abdominal pain upper	31	11%	NR	NR	5	8%	NR	NR	NR	NR
Hyperglycemia	30	11%	NR	NR	27	44%	NR	NR	NR	NR
Tachycardia/"cardiac"	30	11%	4	7%	21	34%	31	28%	37	33%
Depression	28	10%	NR	NR	8	13%	NR	NR	NR	NR
Hypocalemia	28	10%	NR	NR	8	13%	NR	NR	NR	NR
Sepsis/"infection"	26	9%	24	42%	19	31%	49	44%	48	42%
Bilirubin increased	22	8%	4	7%	9	15%	NR	NR	NR	NR

Abbreviations: NR, not reported
Sources: FDA analysis, MyloFrance 1 paper (Taksin, Legrand et al. 2007), CHV data, and AML-19 paper (Amadori, Suciu et al. 2016)
*Items in quotes were reported in the AML-19 publication
†Nausea and vomiting were combined in the CHV dataset for MyloFrance 1
‡CHV data provided here is for "pain"

Gastrointestinal side effects were much lower on the MyloFrance 1 study with rates of nausea being 21% versus 71% on the first relapse studies 201-203. Headache, abdominal pain, diarrhea, dyspnea, peripheral edema, dizziness, and fatigue were also much less common. All grades of bleeding were also less on MyloFrance 1 at 23% versus 29-31% with the unfractionated first relapse and R/R-AML subgroups. AML-19 showed a similar bleeding rate of 25%, which compared favorably to the control arm at 30%.

Hypotension was also less common on MyloFrance 1 at 2% versus 20-25% with the unfractionated regimen. This may be related to the steroid prophylaxis given to all patients on MyloFrance 1.

Febrile neutropenia was roughly equivalent across the trials at rates that are actually lower than what you would expect for AML therapies.

All-grade liver toxicities and infections were roughly equivalent across trials. However, infections are much higher than what is listed here for the unfractionated subgroups since only the sepsis PT was listed.

All-grade mucosal inflammation was more common on MyloFrance 1 at 21% vs 11-13% with the unfractionated doses.

In the R/R-AML setting, increased LDH, AST, ALT, bilirubin, decreased appetite, and tachycardia were more common than in the first relapse setting, as might be expected.

AML-19, in general, had TEAEs well-matched between the GO and BSC arms. Fatigue was actually less on the GO arm, as were bleeding and febrile neutropenia.

A TEAE with grade ≥3 was reported in 267 (96%) of patients in the first relapse subgroup. The numbers of patients with common (>5%) grade ≥ 3 TEAEs are shown in Table 29 by PT in decreasing order of incidence in the first relapse subgroup.

Table 29: Grade 3-4 TEAEs Within 28 Days of Follow-Up

	First relapse (N=277)		MF1 (N=57)		R/R AML (N=61)		AML19-GO (N=111)		AML19-BSC (N=114)	
Preferred Term*	n	%	n	%	n	%	n	%	n	%
Pyrexia	141	51%	9	16%	10	16%	NR	NR	NR	NR
Thrombocytopenia	124	45%	NR	NR	30	49%	NR	NR	NR	NR
Nausea†	109	39%	0	0%	9	15%	NR	NR	NR	NR
Vomiting	93	34%	0	0%	4	7%	NR	NR	NR	NR
Neutropenia	64	23%	NR	NR	17	28%	NR	NR	NR	NR
Leukopenia	63	23%	NR	NR	29	48%	NR	NR	NR	NR
Anemia	59	21%	NR	NR	24	39%	NR	NR	NR	NR
Chills	48	17%	NR	NR	2	3%	NR	NR	NR	NR
AST increased/"Liver"	41	15%	0	0%	6	10%	8	7%	7	6%
Diarrhea	41	15%	1	2%	0	0%	NR	NR	NR	NR
Hypotension	40	14%	0	0%	2	3%	NR	NR	NR	NR
Headache	34	12%	1	2%	2	3%	NR	NR	NR	NR
Febrile neutropenia	32	12%	NR	NR	14	23%	20	18%	27	24%
ALT increased	31	11%	0	0%	5	8%	NR	NR	NR	NR
Dyspnea	30	11%	0	0%	3	5%	NR	NR	NR	NR
Hypertension	25	9%	NR	NR	2	3%	NR	NR	NR	NR
Epistaxis/"bleeding"	23	8%	4	7%	5	8%	14	13%	14	12%
Blood LDH increased	20	7%	NR	NR	1	2%	NR	NR	NR	NR
Sepsis/"infection"	20	7%	18	32%	1	2%	39	35%	39	34%
Bilirubin increased	19	7%	0	0%	1	2%	NR	NR	NR	NR
Hyperglycemia	19	7%	NR	NR	7	12%	NR	NR	NR	NR
Pneumonia	19	7%	4	7%	2	3%	NR	NR	NR	NR
Alk phos increased	17	6%	NR	NR	1	2%	NR	NR	NR	NR
Decreased appetite	17	6%	NR	NR	8	13%	NR	NR	NR	NR
Constipation	14	5%	1	2%	0	0%	NR	NR	NR	NR
Granulocytopenia	14	5%	NR	NR	2	3%	NR	NR	NR	NR
Rash	10	4%	6	11%	1	2%	NR	NR	NR	NR
Lymphocyte count decr	4	1%	NR	NR	16	26%	NR	NR	NR	NR
Pancytopenia	8	3%	NR	NR	6	10%	NR	NR	NR	NR
Fatigue	12	4%	0	0%	5	8%	13	12%	24	21%
Hypokalemia/"metabolic"	13	5%	NR	NR	5	8%	4	4%	7	6%
Disease progression	0	0%	NR	NR	4	7%	NR	NR	NR	NR
Tachycardia/"cardiac"	10	4%	1	2%	2	3%	7	6%	16	14%

Abbreviations: NR, not reported
Sources: FDA analysis, MyloFrance 1 paper (Taksin, Legrand et al. 2007), CHV data, and AML-19 paper (Amadori, Suciu et al. 2016)
*Items in quotes were reported in the AML-19 publication
†Nausea and vomiting were combined in the CHV dataset for MyloFrance 1

The data on grade 3-4 TEAEs demonstrates that pyrexia and hypotension were less common on MyloFrance 1 and the R/R-AML subgroups, which may reflect the steroid pre-medication and less infusion reactions. Furthermore, there were less grade 3-4

chills in the R/R-AML subgroup, which contained the steroid pre-medication study 100863.

Compared to the unfractionated regimens, MyloFrance 1 had significantly less grade 3-4 dyspnea, fatigue, nausea, vomiting, and liver toxicity. Epistaxis/bleeding appears equivalent, but it is actually much higher with the unfractionated regimens since only the epistaxis PT is reported here for those subgroups (see AESIs in Section 7.3.4 and below for more accurate information on hemorrhage). The data is also skewed here for infection – see Section 7.3.4.

Interestingly, MyloFrance 1 had a higher incidence of grade 3-4 rashes (all grade 3).

Compared to the first relapse subgroup, the R/R-AML subgroup had more grade 3-4 febrile neutropenia, decreased appetite, and increased fatigue, as may be expected in a more highly pre-treated population.

The GO and BSC arms were again well matched with regards to grade 3-4 toxicities, with exceptions that febrile neutropenia, fatigue, and cardiac side effects were lower on the GO arm.

Hemorrhage

In order to delve further into the details of the bleeding risks with Mylotarg, I reviewed the precise PTs for hemorrhage TEAEs in the first relapse subgroup. Table 30 includes the bleeding PTs in decreasing order of total incidence for studies 201-203.

Table 30: Hemorrhage TEAEs Within 28 Days of Follow-Up on Studies 201-203

	First relapse (N=277)				
Preferred Term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Total n(%)**
Any TEAEs	60 (22%)	50 (18%)	65 (24%)	11 (4%)	186 (67%)
Epistaxis	39 (14%)	17 (6%)	22 (8%)	1 (0.4%)	79 (29%)
Petechiae	26 (9%)	12 (4%)	11 (4%)	0	49 (18%)
Gingival bleeding	11 (4%)	3 (1%)	7 (3%)	1 (0.4%)	22 (8%)
Hematuria	6 (2%)	4 (1%)	10 (4%)	1 (0.4%)	21 (8%)
Mouth haemorrhage	14 (5%)	3 (1%)	4 (1%)	0	21 (8%)
Ecchymosis	13 (5%)	1 (0.4%)	4 (1%)	0	18 (7%)
Vaginal haemorrhage	10 (4%)	5 (2%)	0	0	15 (%)
Haemoptysis	9 (3%)	2 (1%)	3 (1%)	0	14 (5%)
Hematemesis	3 (1%)	6 (2%)	4 (1%)	0	13 (5%)
Melaena	1 (0.4%)	9 (3%)	3 (1%)	0	13 (5%)
Haematoma	5 (2%)	3 (1%)	4 (1%)	0	12 (4%)
Contusion	9 (3%)	2 (1%)	0	0	11 (4%)
Catheter site haemorrhage	8 (3%)	1 (0.4%)	1 (0.4%)	0	10 (4%)
Occult blood positive	5 (2%)	2 (1%)	2 (1%)	0	9 (3%)

Cerebral haemorrhage	0	0	6 (2%)	2 (1%)	8 (3%)
Disseminated intravascular coagulation	1 (0.4%)	3 (1%)	4 (1%)	0	8 (3%)
Purpura	5 (2%)	1 (0.4%)	1 (0.4%)	0	7 (3%)
Rectal haemorrhage	1 (0.4%)	3 (1%)	3 (1%)	0	7 (3%)
Gastrointestinal haemorrhage	1 (0.4%)	5 (2%)	0	0	6 (2%)
Post procedural haemorrhage	3 (1%)	2 (1%)	0	1 (0.4%)	6 (2%)
Blood urine present	4 (1%)	1 (0.4%)	0	0	5 (2%)
Haematochezia	3 (1%)	1 (0.4%)	1 (0.4%)	0	5 (2%)
Haemorrhage	1 (0.4%)	1 (0.4%)	3 (1%)	0	5 (2%)
Haemorrhoidal haemorrhage	3 (1%)	0	2 (1%)	0	5 (2%)
Diarrhoea haemorrhagic	1 (0.4%)	0	0	3 (1%)	4 (1%)
Eye haemorrhage	3 (1%)	1 (0.4%)	0	0	4 (1%)
Memorrhagia	0	2 (1%)	2 (1%)	0	4 (1%)
Retinal haemorrhage	1 (0.4%)	2 (1%)	1 (0.4%)	0	4 (1%)
Tongue haemorrhage	4 (1%)	0	0	0	4 (1%)
Catheter site hematoma	2 (1%)	0	1 (0.4%)	0	3 (1%)
Conjunctival haemorrhage	0	3 (1%)	0	0	3 (1%)
Metrorrhagia	2 (1%)	0	0	1 (0.4%)	3 (1%)
Scleral haemorrhage	2 (1%)	1 (0.4%)	0	0	3 (1%)
Subdural haematoma	0	2 (1%)	1 (0.4%)	0	3 (1%)
Anal haemorrhage	0	0	2 (1%)	0	2 (1%)
Ear haemorrhage	2 (1%)	0	0	0	2 (1%)
Eyelid hematoma	2 (1%)	0	0	0	2 (1%)
Increased tendency to bruise	1 (0.4%)	0	1 (0.4%)	0	2 (1%)
Post procedural haematoma	2 (1%)	0	0	0	2 (1%)
Pulmonary alveolar haemorrhage	0	0	2 (1%)	0	2 (1%)
Traumatic haematoma	1 (0.4%)	1 (0.4%)	0	0	2 (1%)
Blood blister	0	0	1 (0.4%)	0	1 (0.4%)
Central nervous system haemorrhage	0	0	1 (0.4%)	0	1 (0.4%)
Gastric haemorrhage	0	1 (0.4%)	0	0	1 (0.4%)
Haemarthrosis	1 (0.4%)	0	0	0	1 (0.4%)
Haemorrhage intracranial	0	0	1 (0.4%)	0	1 (0.4%)
Lip haemorrhage	1 (0.4%)	0	0	0	1 (0.4%)
Mallory-Weiss syndrome	0	1 (0.4%)	0	0	1 (0.4%)
Procedural haemorrhage	1 (0.4%)	0	0	0	1 (0.4%)
Puncture site haemorrhage	1 (0.4%)	0	0	0	1 (0.4%)
Retroperitoneal haematoma	0	0	0	1 (0.4%)	1 (0.4%)
Subarachnoid haemorrhage	1 (0.4%)	0	0	0	1 (0.4%)
Thrombocytopenic purpura	0	0	0	1 (0.4%)	1 (0.4%)
Tooth socket haemorrhage	1 (0.4%)	0	0	0	1 (0.4%)
Ulcer haemorrhage	1 (0.4%)	0	0	0	1 (0.4%)
Upper gastrointestinal haemorrhage	0	1 (0.4%)	0	0	1 (0.4%)
Vessel puncture site bruise	1 (0.4%)	0	0	0	1 (0.4%)

Sources: ISS, FDA analysis
*Occurred between start of therapy and 28 days after last GO dose

The most common bleeding TEAEs were epistaxis, petechiae, gingival bleeding, hematuria, and mouth haemorrhage. More concerning, though less common, were hemoptysis, gastrointestinal bleeding, and cerebral hemorrhages.

From Section 7.3.4, Table 26, we know that hemorrhage risks are higher with the unfractionated regimens, but we do not have the patient-level data to know the specific bleeding events seen on MyloFrance 1 and AML-19. We can, however, say that MyloFrance 1 did not have any grade 4 bleeding TEAEs and AML-19 had balanced grade 3-4 bleeding TEAEs between the GO and BSC arms.

Infusion-Related Reactions

I reviewed the precise PTs for infusion-related TEAEs occurring within 24 hours of GO in the first relapse subgroup. Table 31 includes the infusion-related PTs in decreasing order of total incidence for studies 201-203.

Table 31: Infusion-related TEAEs Within 24 Hours on Studies 201-203

	First relapse (N=277)				
Preferred Term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Total n(%)**
Any TEAEs	19 (7%)	59 (21%)	137 (50%)	3 (1%)	218 (79%)
Chills	51 (18%)	72 (26%)	44 (16%)	0	167 (60%)
Pyrexia	8 (3%)	54 (20%)	98 (35%)	2 (1%)	162 (59%)
Hypotension	3 (1%)	5 (2%)	27 (10%)	1 (0.4%)	36 (13%)
Tachycardia	9 (3%)	3 (1%)	4 (1%)	0	16 (6%)
Dyspnea	3 (1%)	2 (1%)	5 (2%)	0	10 (4%)
Dizziness	5 (2%)	2 (1%)	0	0	7 (3%)
Hyperhidrosis	4 (1%)	2 (1%)	1 (0.4%)	0	7 (3%)
Flushing	5 (2%)	0	0	0	5 (2%)
Rash	2 (1%)	2 (1%)	1 (0.4%)	0	5 (2%)
Bronchospasm	0	1 (0.4%)	2 (1%)	0	3 (1%)
Infusion related reaction	0	1 (0.4%)	1 (0.4%)	0	2 (1%)
Urticaria	2 (1%)	0	0	0	2 (1%)
Catheter site rash	1 (0.4%)	0	0	0	1 (0.4%)
Dermatitis exfoliative	0	1 (0.4%)	0	0	1 (0.4%)
Drug hypersensitivity	0	0	1 (0.4%)	0	1 (0.4%)
Eczema	1 (0.4%)	0	0	0	1 (0.4%)
Eye swelling	1 (0.4%)	0	0	0	1 (0.4%)
Hot flush	1 (0.4%)	0	0	0	1 (0.4%)
Hypersensitivity	0	1 (0.4%)	0	0	1 (0.4%)
Periorbital edema	1 (0.4%)	0	0	0	1 (0.4%)
Rash erythematous	1 (0.4%)	0	0	0	1 (0.4%)
Red man syndrome	1 (0.4%)	0	0	0	1 (0.4%)
Wheezing	1 (0.4%)	0	0	0	1 (0.4%)

Sources: ISS, FDA analysis

The most common infusion-related TEAEs within 24 hours were chills, pyrexia, hypotension, and tachycardia. Of note, none were fatal on these studies or any of the supportive studies.

On Study 100863, the post-marketing study investigating steroid prophylaxis prior to GO in patients with R/R-AML, severe infusion events occurred in 3/16 (19%) of patients who received steroid prophylaxis. Thus, steroid prophylaxis decreases, but does not eliminate, the risk.

While we do not have detailed infusion-related TEAE data from MyloFrance 1 or AML-19, the CHV data for MyloFrance 1 included some early safety information on days 1-7, including fevers and chills. On day 1, 33% of patients experienced fever and chills and 5% had grade 3 fever and chills. The incidence of fever and chills went down to 12% and 7% on infusion days 4 and 7, respectively. On day 4, there were no grade 3 fever/chills and on day 7 there were only grade 1 events. Furthermore, as per Table 29 above, there was less grade 3-4 hypotension seen on MyloFrance 1 compared to studies 201-203. Thus, infusion-related reactions appeared to be better controlled with the fractionated dosing regimen and use of methylprednisolone prophylaxis.

Reviewer comments: Given the high incidence of infusion-related reactions on studies 201-203, as well as frequent febrile episodes on day 1 of MyloFrance 1, I agree with the Sponsor to include a warning in the PI for hypersensitivity reactions and to recommend premedication with steroids.

Infections

To evaluate the causes of infection, the applicant conducted an analysis using the SOC Infection and infestations. In the 277 patients with first relapse of AML treated with GO, the incidence of TEAE with infection was 68%; the TEAE was grade 3-4 in 42%, and 29% were considered related. Fatal infection TEAEs occurred in 12%. The most common infection TEAEs were oral herpes (17%), pneumonia (10%), sepsis (9%), and device related infections (5%). An infection TEAE considered opportunistic occurred in 5%, an included fungal pneumonia, fungal sinusitis, cytomegalovirus infection, Herpes zoster, and respiratory syncytial virus infection.

Reviewer comments: The patients on studies 201-203 had several risk factors for infection, including neutropenia from active AML, immunodeficiency from prior chemotherapy and/or HSCT, and indwelling devices. In addition, Mylotarg is expected to deplete normal myeloid cells, resulting in neutropenia. Consequently, high rates of infections, including opportunistic infections, are to be expected. The range of infection TEAEs reported by the Applicant are consistent with this expectation.

Veno-Occlusive Disease

Given the substantial toxicity and high mortality rate associated with hepatic VOD, FDA's review focused heavily on this adverse event.

The Applicant performed a logistic regression analysis to assess several variables with the risk of developing VOD, including age, gender, dose, number of doses, baseline ALT, AST, and bilirubin, hepatic impairment at baseline (moderate/severe versus none/mild), type of HSCT, HSCT indicator (prior and follow-up), time of HSCT relative to GO dose, and exposure to busulfan/cyclophosphamide. However, only HSCT before or after GO and moderate/severe hepatic impairment at baseline were independently associated with VOD:

- Patients who received an HSCT prior to GO were 2.6 times more likely (95% CI: 1.448-4.769) to develop VOD compared to patients without prior HSCT
- Patients who received an HSCT following GO were 2.9 times more likely (95% CI: 1.502-5.636) to develop VOD compared to those without HSCT following GO
- Patients who had moderate/severe hepatic impairment at baseline were 8.7 times more likely (95% CI: 1.879-39.862) to develop VOD compared to those with none/mild hepatic impairment at baseline

Of the patients who developed VOD on studies 201-203 (5%), it is notable that the majority died as a consequence (4% fatal VOD). In patients with no history of HSCT, VOD occurred in 2 patients (1%), with fatal VOD reported in both patients.

The incidence of VOD and fatal VOD among the 31 patients undergoing an allogeneic HSCT post-GO on studies 201-203 was 23% and 19%, respectively. Only 3 patients on studies 201-203 received an allogeneic HSCT pre-GO and none of these patients experienced VOD. Of the 21 patients who underwent an auto-HSCT post-GO, 5% developed VOD and 0 cases were fatal. Of 25 patients who received an auto-HSCT pre-GO, 20% and 8% developed VOD and fatal VOD, respectively, after GO. Table 32 includes a summary of VOD data across trials.

Table 32: Incidence of VOD and Relationship to HSCT

	Subgroups					
	First relapse (N=277)	**MF1 (N=57)**	**R/RAML (N=61)**	**AML19-GO (N=111)**	**AML19-BSC (N=114)**	**Total treated (N=936)**
VOD	**5%**	**0%**	**8%**	**0%**	NR	**8%**
Fatal VOD	**4%**	**0%**	**2%**	**0%**	NR	**3%**
Auto pre-GO (n, %)	25 (9%)	0	.	0	0	.
VOD	**5/25 (20%)**		.			.
Fatal VOD	**2/25 (8%)**		.			.
Allo pre-GO (n, %)	3 (1%)	0	.	0	0	.
VOD	**0**		.			.
Fatal VOD	**0**		.			.
Auto post-GO (n, %)	21 (8%)	4 (7%)	.	0	0	.
VOD	**1/21 (5%)**	**0**	.			.

Fatal VOD	**0**	**0**	.			.
Allo post-GO (n, %)	31 (11%)	3 (5%)	.	0	0	.
VOD	**7/31 (23%)**	**0**	.			.
Fatal VOD	**6/31 (19%)**	**0**	.			.

Source: FDA analysis

Reviewer comments: It is remarkable that there were no cases of VOD on studies MyloFrance 1 and AML-19, whereas the incidence of VOD on studies using unfractionated dosing regimens were consistently ≥5% (the only exceptions being the 3 patients on study 205 step 1a and the MDS Study 207). However, the limitation is that 52 patients on studies 201-203 underwent HSCT post-GO, whereas only 7 patients on MyloFrance 1 underwent a HSCT post-GO. Thus, it is unclear what the incidence of VOD will be in the post-marketing setting with the use of 3 mg/m^2 fractionated doses.

Given the lack of significant data with the fractionated doses pre- or post-HSCT, the Sponsor should track the incidence and risks factors for VOD with this new dosing regimen in the post-marketing setting. I agree with inclusion of VOD as a warning in the PI.

In terms of timing of transplantation relative to GO dose, the Sponsor's analysis indicated that there was no effect on the incidence of VOD. However, an early report indicated that transplantation less than or equal to 3.5 months following GO led to higher rates of VOD (Wadleigh, Richardson et al. 2003). Perhaps for this reason, the MyloFrance 1 investigators proposed to delay HSCT by at least 90 days following Mylotarg treatment.

The following data regarding timing is listed below for studies 201-203:

- Auto-HSCT median 354 (range 129-3417) days pre-GO
  - VOD patients, median 260 (range 206-1639) days pre-GO
  - Fatal VOD patients, median 950 (range 260-1639) days pre-GO
- Allo-HSCT median 281 days pre-GO (range 218-490)
  - No cases of VOD in these patients
- Auto-HSCT median 144 days post-GO (range 43-281)
  - VOD patient had HSCT 93 days post-GO
- Allo-HSCT median 84 days post-GO (range 31-304)
  - VOD patients, median 83 days (range 38-102) post-GO
  - Fatal VOD patients, median 78 days post-GO (range 38-102)

In contrast, the mean time between GO infusion and HSCT on MyloFrance 1 was 152 days (range, 112-220 days).

Reviewer comments: This data indicates that the enhanced risk for VOD post-GO persists even after a long interim since a prior autologous HSCT. There were only 3 patients on studies 201-203 with a prior allogeneic HSCT and none developed VOD, so it is unclear if the same pattern exists for those patients.

The one patient on studies 201-203 who developed VOD following an autologous HSCT had their transplantation more than 3 months post-GO. Of 31 patients who underwent allogenic HSCT post-GO, the 7 who developed VOD had their transplantation after a median of just under 3 months and some had the transplantation as early as 38 days post-GO. In contrast, on MyloFrance 1, the mean time to HSCT was 152 days and the lower end of the range was 112 days post-GO. Thus, it is highly possible that the short interval between GO and the allo-HSCTs on studies 201-203 increased the likelihood of developing VOD.

In terms of time to onset, the 15 patients on studies 201-203 with VOD developed the syndrome a median of 12 days (range 3-107 days) following the last dose of GO. For those who underwent HSCT and developed VOD, the median time from HSCT to onset of VOD was 23 days (range 4-1646 days).

Further analyses of VOD by dose are included in Section 7.5.1 below.

7.4.2 Laboratory Findings

For the standard clinical laboratory test results, the applicant focused on a pooled analysis from studies 201, 202, and 203. However, evaluations were also performed from the dose-finding studies of GO monotherapy and for all GO monotherapy studies. The denominator for percentages was the number of patients treated in the group with at least 1 post-baseline assessment of the lab test. Chemistry parameters were presented according to worst grade on study, summarized by number and percent of patients for each grade.

MyloFrance 1 reported on limited laboratory data in the manuscript and the CHV datasets only include the time to count recovery dataset. Comparisons are provided to studies 201-203 below, when possible. AML-19 does not include laboratory data.

The applicant drew several conclusions from their analysis of laboratory data from studies 201-203 (ISS Sections 2.1.5.4.3, 2.1.5.4.6, 3.4, and 7.3.4.2.1). These included:

Blood counts

- Grade ≥ 3 decreases in ANC and platelets were almost universal, whereas as grade 3 decreases in hemoglobin were seen in about half of patients.
- Only 1 case of grade ≥ 2 PT/INR elevation.
- Six (4%) cases of grade ≥ 2 aPTT elevation, including 2 (1%) grade 3 cases.

- Median time to platelet recovery to 100,000/μL for patients achieving an IWG-defined CR was 50 days (95% CI 43-64).
- Median time to platelet recovery to 50,000/μL for patients achieving IWG-defined CR was 40 days (95% CI 32-43) and for patients achieving CR+CRp was 54 days (95% CI 43-66) (Table 33).
    - 17/42 (40%) of CR responders required > 42 days to recover platelets above 50,000/μL
    - 6/42 (14%) of CR responders required > 42 days to recover platelets above 25,000/μL
    - 22/56 (39%) of CRp responders never recovered platelets above 50,000/μL
    - 4/56 (7%) of CRp responders never recovered platelets above 25,000/μL
- Median time to ANC recovery to 500 x 10^6/L was 41 days (95% CI 36-43) for IWG-defined CR patients and 42 days (95% CI 37-43) for CR+CRp patients.
- Median time to ANC recovery to 1000 x 10^6/L was 44 days (95% CI 41-50) for IWG-defined CR patients and 45 days (95% CI 43-50) for CR+CRp patients.
- There were no significant differences in time to count recovery by age.

Table 33: Time to Hematopoietic Recovery with GO

Parameter	Median time in days (range)	
	9 mg/m² x 2 **201-203 (N=98)**	***3 mg/m² d1,4,7*** **MyloFrance-1 (N=19)**
ANC > 500/μL	42 (16-100)	23 (10-38)
Platelets > 50,000/μL	54 (15-528)†	20 (0-43)‡

Source: FDA analysis, CHV data; data shown for patients who achieved CR or CRp
Abbreviations: ANC, absolute neutrophil count; d, days; N, number.
†Given failure to achieve the target platelet level, 22 patients were censored at the date of last laboratory evaluation prior to HSCT, other anti-leukemic therapy, or death (whichever came first).
‡ Given failure to achieve the target platelet level, 1 patient was censored on day 43.

It appears that recovery of neutrophils and platelets is shorter with the fractionated regimen of GO. Even when compared to the time to count recovery for full CR responses on studies 201-203, the fractionated schedule appears to cause substantially less prolonged cytopenias.

While we do not have the time to count recovery data for the phase 3 portion of AML-19, the publication reporting the phase 2 portion of AML-19 included median times to neutrophil and platelet recovery for the 6 of 27 patients with a CR+CRp response treated with 6 mg/m^2 day 1 and 3 mg/m^2 day 8 (Amadori, Suciu et al. 2010). The median time to neutrophil recovery ≥ 500/μL was 24 days (range 1-41) and the median time to platelet recovery ≥ 50,000/μL was 26 days (range 1-50+).

Reviewer comments: It is striking how much more quickly the neutrophil and platelet counts recovered on MyloFrance 1 with the fractionated dosing regimen. Only 1 of 19 (5%) patients on MyloFrance 1 with a CR+CRp response failed to recover their platelets above 50,000 by day 43, as opposed to studies 201-203 where 22 of 98 (22%) responding patients failed to recover their platelets. This likely played a big role in the decreased induction deaths and hemorrhage seen with the fractionated dose and schedule.

Although we do not have the full data from AML-19, the preliminary phase 2 count recovery data are similarly favorable. It is expected that this older population (median age 78) would have slightly longer count recovery compared to the younger patients on MyloFrance 1 and studies 201-203. The recovery times were in fact slightly longer than on MyloFrance 1, but compared to studies 201-203, the median times to recovery were much shorter.

Given the high incidence of hemorrhagic TEAEs, including 13/277 (5%) deaths due to hemorrhage, 12 due to intracranial hemorrhage, I reviewed the laboratory abnormalities in the 12 patients with hemorrhage being the primary cause of death (one was due to respiratory failure and cerebral haemorrhage). I focused on coagulation parameters and platelet levels to see if they could have contributed to the fatal AEs (Table 34). PT/INR is excluded from the table due to only one patient with this information, who had a normal post-baseline INR.

Median platelet count at time of fatal hemorrhage was 18 (range 4-60). Only two patients experienced their fatal bleed with a platelet count of less than 10.

Table 34: Platelets and coagulation labs in patients with fatal hemorrhage on studies 201-203

Patient ID	Preferred term	Day of GO*	Plt		PTT		Fibrinogen	
			Base	Post	Base	Post	Base	Post
(b) (6)	Cerebral haemorrhage	2	51	**19**	.	.	.	**66**
	Subdural hematoma	37	27	21	21	**50**	.	.
	Cerebral hemorrhage	148	82	**32**	32	27	.	.
	Cerebral hemorrhage	4	25	17	30	32	.	.
	Cerebral haemorrhage	24	38	**12**	32	.	.	.
	Cerebral haemorrhage	35	36	**4**	20	.	.	.
	Cerebral haemorrhage	5	23	13	31	36	.	402
	Cerebral haemorrhage	31	36	60	30	.	.	.
	Cerebral haemorrhage	15	13	6	33	**42**	.	.
	Cerebral haemorrhage	17	27	**15**	27	33	.	.
	Subdural hematoma	145	31	**19**	29	.	.	.
	Retroperitoneal haemorrhage	31	81	**33**	29	.	.	.

Source: FDA analysis
*Day of GO therapy on which the AE began. Post-baseline lab tests are listed for this date.

Reviewer comments: The fact that the fatal hemorrhages occurred at relatively modest platelet counts may indicate a need for enhanced vigilance for count

monitoring and perhaps a higher transfusion threshold than standard practice. The risk appears to be lower with the fractionated regimen, but given that two sudden deaths occurred at home on MyloFrance 1, it is impossible to know if fatal hemorrhage was the cause there as well. Thus, the PI should include a warning for hemorrhage, including fatal intracranial hemorrhage and should include guidance to investigators on how they might mitigate this risk.

Of note, one patient had a low fibrinogen at the time of fatal cerebral hemorrhage, but this was only one of 2 patients with post-baseline fibrinogen levels available for all patients in studies 201-203. DIC was only reported in 3 patients on these studies. It is unclear if hypofibrinogenemia could have correlated with the other bleeding events, since the level of bleeding seems out of proportion to the level of thrombocytopenia.

Chemistries

- Most frequent grade ≥ 3 abnormalities were hypophosphatemia (42%), hypokalemia (35%), and hyponatremia (17%).
- Grade ≥ 3 creatinine elevations in 4% of patients.
- Grade ≥ 3 hyperglycemia in 12%.
- Grade ≥ 3 hypocalcemia in 12%.

Liver function tests

- AST post-baseline elevations in 86%
  - Grade 3-4 elevations in 17% (3% grade 4)
- ALT post-baseline elevations in 66%
  - Grade 3-4 elevations in 10% (2% grade 4)
- Alkaline phosphatase post-baseline elevations in 63%
  - Grade 3-4 elevations in 5% (0% grade 4)
- Bilirubin post-baseline elevations in 63%
  - Grade 3-4 elevations in 12% (3% grade 4)
- No major differences based on age, but trend toward less LFT elevations for older patients

Hy's Law cases

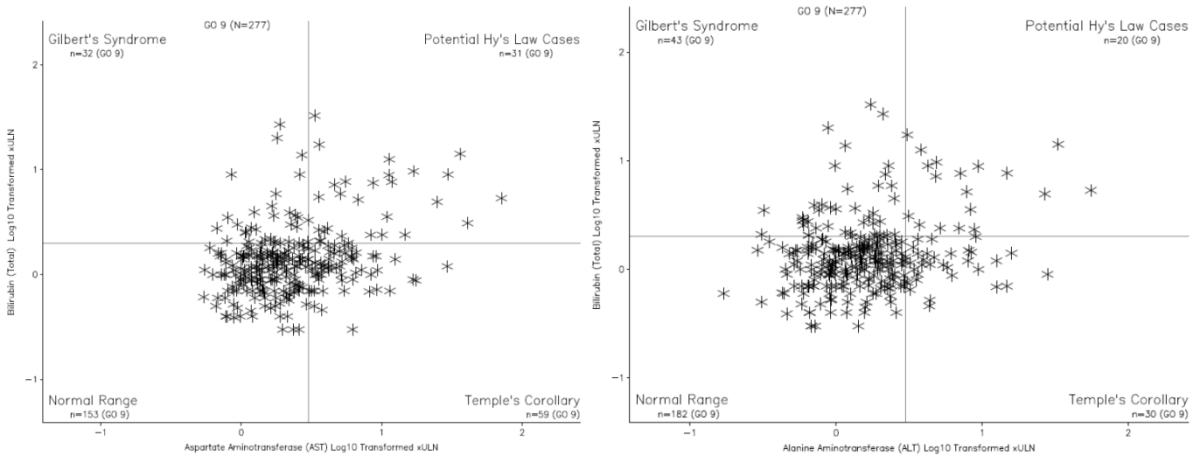
Potential cases of drug-induced liver injury (potential Hy's Law cases) were defined as AST and/or ALT ≥ 3 x ULN and concurrent total bilirubin ≥ 2 x ULN in the absence of other causes of liver injury.

<u>First relapse subgroup</u>

- 30 cases met criteria for Hy's Law (see Figure 7 below).
  - VOD was associated with the lab result abnormalities in 6/30 (20%)

- 3 patients did not have concurrent abnormalities or alkaline phosphatase elevation was ≥ 2 x ULN
- Drug-induced liver injury was ruled out in 15 cases based on plausible alternative causes
  - I reviewed all narratives and Applicant's assessments were sound
  - Alternative causes included progressive disease, sepsis, and VOD
- 12 patients were considered at least potential Hy's law cases
  - VOD was seen in 4/12 (33%)
  - Confounders included concomitant fluconazole, acetaminophen, sepsis, and progressive disease

Figure 7: AST/ALT versus total bilirubin during treatment period for studies 201-203.



Source: M 5.3.5.3 Integrated Summary of Safety Figures 18 and 19.

<u>Dose-finding studies (101-103, 100374, and 205 1a)</u>

9 mg/m^2 doses:

- Similar decreases in blood counts to the first relapse trials, except for slightly more grade 3 hemoglobin decreases at 68%.
- Of the 37 patients with post-baseline fibrinogen levels available, 4 patients (11%) had a ≥ grade 2 fibrinogen decrement (3 grade 2, 1 grade 3).
- Only 1 case of grade ≥ 2 PT elevation.
- Four (24%) had grade ≥ 2 aPTT elevations, including 1 grade 3 elevation.
- Similar chemistry and LFT abnormalities to pivotal trials

All doses:

- No clear dose response for myelosuppression
- No clear dose effect on LFTs, but no grade 3-4 bilirubin elevations in patients receiving ≤ 1 mg/m^2 doses

All monotherapy studies

- Similar decreases in blood counts to pivotal trials, except for less neutropenia due to this information not being collected on the observational trial 100847.
- Similar chemistry and LFT abnormalities to pivotal trials.

Reviewer comments: Post-baseline fibrinogen levels were checked more frequently in the dose-finding trials. It is concerning that 11% of patients with post-baseline fibrinogen levels available were decreased to ≥ grade 2. It is unclear if this is related to increased rates of DIC in this more highly pre-treated patient population or whether it is related to a drug effect.

7.4.3 Vital Signs

In studies 201-203, vital signs were collected up to 8 hours following administration of GO. Blood pressure and heart rate within 24 hours after GO administration are shown below in Table 35.

Table 35: Vital signs within 24 hours of GO

Vital Sign Limit		First relapse N=277 n (%)
Systolic BP (mmHg)		
	< 90	38 (13.7)
	>170	38 (13.7)
Diastolic BP (mmHg)		
	≤65	226 (81.6)
	≥105	16 (5.8)
Pulse Rate (BPM)		
	<60	52 (18.8)
	>140	11 (4.0)
Temperature (°C) >40		20 (7.2)
Respiration Rate (RESP/MIN)*		
	<8	0
	>30	8 (10.7)

Source: ISS data

The vital signs seen within 24 hours reflect the infusion-related TEAEs seen on studies 201-203. While fever was common (59% patients), temperatures above 40 were seen in <10% of patients. When considering all monotherapy data (N=936), a temperature > 40

was seen in only 3% of patients within 24 hours of dosing, but less intensive recording of vital signs was required on many of the other studies.

While we do not have detailed vital sign data from MyloFrance 1, we have data from the CHV showing that the median number of days with a temperature > 38.5 °C was 2 (range 0-32) days. Note that there was missing data on 4 of the 57 patients.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed on 8 GO monotherapy studies and post-baseline ECGs were obtained on 6 studies. There is limited data on QTc prolongation given the age of the studies. However, the following was available:

- Post-baseline ECGs were performed on 166/277 patients on studies 201-203
- 63/166 (38%) of post-baseline ECGs were abnormal
    - Only 2/63 (3%) of the abnormal post-baseline ECGs had prolonged QT
        - One case on study day 31 (second dose GO given day 19) – this patient had no baseline ECG
        - Other case was on study day 53 (second dose GO day 22) – again no baseline ECG

Given that the half-life of GO is 3.8 days, the majority of GO should have been eliminated by the time the 2 patients experienced prolonged QT.

I reviewed the cardiac TEAEs on the pivotal trials and the most common were tachycardia (11%), followed by bradycardia (3%), atrial fibrillation, arrhythmia, cardiac congestive failure, and sinus tachycardia (all 2%). Grade ≥3 cardiac TEAEs included tachycardia (4%), arrhythmia (1%), and cardiac failure congestive (1%).

Although the data is very limited, there is no clear data to suggest a QT-prolonging effect of Mylotarg.

7.4.5 Special Safety Studies/Clinical Trials

Post-transplant Study 100374

Study 100374 was a post-marketing study investigating the safety and efficacy of GO in relapsed CD33+ AML patients who received HSCT. The study enrolled 37 total patients. Dosing started at 2 mg/m^2 (n=13) in an unfractionated schedule 14 days apart and escalated to 4 (n=18) and then 6 mg/m^2 (n=6). 27 patients had a prior allogeneic HSCT and 10 had a prior autologous HSCT.

DLTs were observed at all dose levels for patients post-allogeneic HSCT. One of the 2 patients with a prior allogeneic HSCT treated at the 6 mg/m^2 dose level experienced a

DLT of grade 4 liver disorder ending in death. This exceeded the MTD per the protocol. Two of 12 allogeneic HSCT patients on the 4 mg/m^2 cohort experienced a DLT – grade 4 VOD ending in death and grade 3 bilirubin elevations that did not resolve. Given that these events were observed after the first 6 patients, 4 mg/m^2 was concluded to be the MTD. One of 13 post-allogeneic HSCT patients treated at 2 mg/m^2 experienced a DLT of grade 3 hepatic toxicity that resolved.

In the post-autologous HSCT group, there were no DLTs. The 6 mg/m^2 was the maximum administered dose to these patients, but since only 4 patients were enrolled at this dose level, there was not an adequate minimum sample size (n=6) to exclude the possibility that this dose level did not exceed the MTD.

The incidence of VOD on this study was 14% overall with fatal VOD seen in 5%. The incidence of VOD increased with dose level, with 0% at 2 mg/m^2, 17% at 4 mg/m^2, and 33% and 6 mg/m^2. Both of the fatal cases of VOD occurred at the 4 mg/m^2 dose.

Reviewer comments: Although this study was not completed and had limitations with regards to retrospective determination of DLTs, it is clear that even the lower doses per the unfractionated schedule were quite toxic to patients with a prior allogeneic HSCT.

Observational Study 100847

Study 100847 was a post-marketing observational study to evaluate the safety of Mylotarg therapy in routine practice in the United States. 21 patients from this observational study were being treated on either study 100863 or 100374, and thus, only 461 patients on this trial were not represented elsewhere in the application. This study is included in the “All treated” patient population in the above sections. However, the VOD incidence is worth highlighting here given that this study represented a “real-life” patient population.

On Study 100847, VOD was seen in 41 (9%) patients. Fatal VOD occurred in 2%. 12% of patients on this study had a prior allogeneic HSCT and 6% had a prior autologous HSCT. 14% of patients received a HSCT following GO, including 11% allogeneic and 3% autologous. The following was noted with regards to VOD incidence and HSCT:

- Allogeneic HSCT post-GO: 14% VOD, 4% fatal
- Autologous HSCT post-GO: 7% VOD, 0% fatal
- Allogeneic HSCT pre-GO: 13% VOD, 2% fatal
- Autologous HSCT pre-GO: 18% VOD, 4% fatal

7.4.6 Immunogenicity

The immunogenicity of GO was examined in Study 101 and Studies 201-203. The incidence of anti-drug antibodies was low at <1%. Patients in studies 201-203 did not develop antibodies to hP67.6 or NAc-gamma calicheamicin DMH. Only 2 patients on Study 101 developed anti-product antibodies.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose escalation studies

Protocols 101-103 were dose escalation studies, 101 in US adults, 102 in pediatrics, and 103 in Japanese adults. Treatment consisted of Mylotarg every 14 days for 2-3 doses with doses ranging from 0.25 mg/m^2-9mg/m^2 on Study 101 and 6-9 mg/m^2 on Studies 102 and 103. Protocol details were included in Section 5.3.6. The transplant study 100374 was also a dose escalation study and is described in Section 7.4.5 above.

Study 101 enrolled 41 patients with R/R AML ages 23 to 73. The dose was not escalated beyond 9 mg/m^2, even though no DLTs were recorded, due to the observation of myelosuppression. TEAEs on this study were similar to that seen on studies 201-203 and it appeared that grade 3-4 myelosuppression, febrile neutropenia, infections, liver toxicity, and VOD increased with rising doses.

Study 102 enrolled 29 pediatric patients with R/R AML ages 1 to 16 years. A DLT was observed at 9 mg/m^2. Thus, an amendment added a 7.5 mg/m^2 dose level, but only 2 patients were evaluated at this level as the trial closed early due to lack of enrollment. TEAEs were similar to studies 201-203, but hepatotoxicity and VOD were much more common. Almost all patients had transient and reversible elevations in LFTs and VOD was seen in 9 (31%) patients. However, fatal VOD was only 3%. Of note, 48% of patients on this trial underwent a HSCT post-GO. Seven (54%) of the 13 patients who underwent an allogeneic HSCT post-GO developed VOD.

Reviewer comments: Given that a DLT occurred at the 9 mg/m^2 dose level and the study only recruited 2 patients to the 7.5 mg/m^2, there is no clearly established safe pediatric unfractionated monotherapy dose.

Study 103 enrolled a total of 40 Japanese patients with R/R AML ages 28-68. In the phase 1 portion, there was 1 DLT of grade 4 pulmonary hemorrhage at the 9 mg/m^2 dose level. Thus, a 7.5 mg/m^2 dose was investigated in 3 patients. Ultimately, the 9

mg/m^2 dose was pursued in the phase 2 portion of the trial. TEAEs were similar to studies 201-203 with no clear dose response for AEs. However, VOD was only seen at the 9 mg/m^2 dose level in 1 patient.

Early mortality by dose

Aside from the analysis of the dose escalation studies, FDA performed a series of broader analyses across studies and the literature, focusing on the 6 and 9 mg/m^2 unfractionated regimens and the 3 mg/m^2 fractionated regimen in R/R-AML.

First, we analyzed early mortality among the different dosing schedules of GO, given indications that the fractionated regimen in MyloFrance 1 resulted in less early mortality than on studies 201-203. Literature studies were included if induction death rates were available from the text or by personal communication. Table 36 shows the early mortality rates pooled by dose regimen and for the individual studies. The point estimates suggest a relationship between dose and early mortality, but the smaller sample size for the lower doses may make the point estimates less reliable.

Table 36. Day 28 Mortality by GO Monotherapy Dose-Schedule for R/R-AML

Dose regimen	Individual Studies	Deaths within 28 days follow-up N (%, 95% CI)
9 mg/m^2 x 2* (N=410)		**67 (16%, 13-20%)**
	201 (N=84)	16 (19%)
	202 (N=95)	14 (15%)
	203 (N=98)	21 (21%)
	101 (N=7)	1 (14%)
	102 (N=13)	2 (15%)
	103 (N=31)	4 (13%)
	100863 (N=23)	5 (22%)
	Piccaluga, 2004 (N=16)	1 (6%)
	Roboz, 2002 (N=43)	6 (14%)
6 mg/m^2 x 2* (N=41)		**4 (10%, 3-24%)**
	101 (N=8)	1 (13%)
	102 (N=14)	1 (7%)
	103 (N=6)	0 (0%)
	100374 (N=6)	0 (0%)
	Piccaluga, 2004 (N=7)	2 (29%)
3 mg/m^2 d1,4,7 (N=81)		**7 (9%, 4-18%)**
	MyloFrance 1 (N=57)	4 (7%)
	Thomas, 2005 (N=24)	3 (13%)

Sources: FDA analysis

*Note that 201-203, 101, Piccaluga et al and Roboz et al allowed for up to 3 doses of GO.

Table 37 shows the causes of death within 28 days after the last dose of GO in studies where data are available. Although persistent leukemia is a major cause of early mortality in all of the trials, the results do not suggest that the risk of treatment failure was worse using the 3 mg/m^2 fractionated regimen than with the higher doses. Treatment-related causes of death appear to be reduced in patients treated with the 3 mg/m^2 fractionated regimen.

Table 37: Causes of Early Mortality by GO Monotherapy Dose-Schedule for R/R-AML

Cause of death	9 mg/m^2 x 2*			6 mg/m^2 x 2*		3 mg/m^2 d1,4,7
	201-203 (N=277)	101-103 (N=51)	100863 (N=23)	101-103 (N=28)	100374 (N=6)	MyloFrance 1 (N=57)
All causes	51 (18%)	5 (10%)	4 (17%)	2 (7%)	0	4 (7%)
Persistent AML	19 (7%)	4 (8%)	1 (4%)	1 (4%)	0	2 (4%)
Infection	14 (5%)	0	1 (4%)	1 (4%)	0	0
Sepsis/septic shock	8 (3%)		0	1 (4%)		
Pneumonia	6 (2%)		1 (4%)	0		
Hemorrhage	11 (4%)	0	0	0	0	-
Intracranial	10 (4%)					
Retroperitoneal	1 (0.4%)					
VOD	3 (1%)	0	1 (4%)	0	0	0
Respiratory failure	1 (0.4%)	1 (2%)	0	0	0	-
Multi-organ failure	1 (0.4%)	0	1 (4%)	0	0	-
Acute renal failure	1 (0.4%)	0	0	0	0	-
Unknown	1 (0.4%)	0	0	0	0	2 (4%)†

Sources: FDA analysis
* Note that 201-203 and 101 allowed for up to 3 doses of GO.
†Two sudden deaths at home, one on day 14 before the day 15 marrow evaluation and one on day 27 during treatment-induced bone marrow hypoplasia with no persistent leukemia

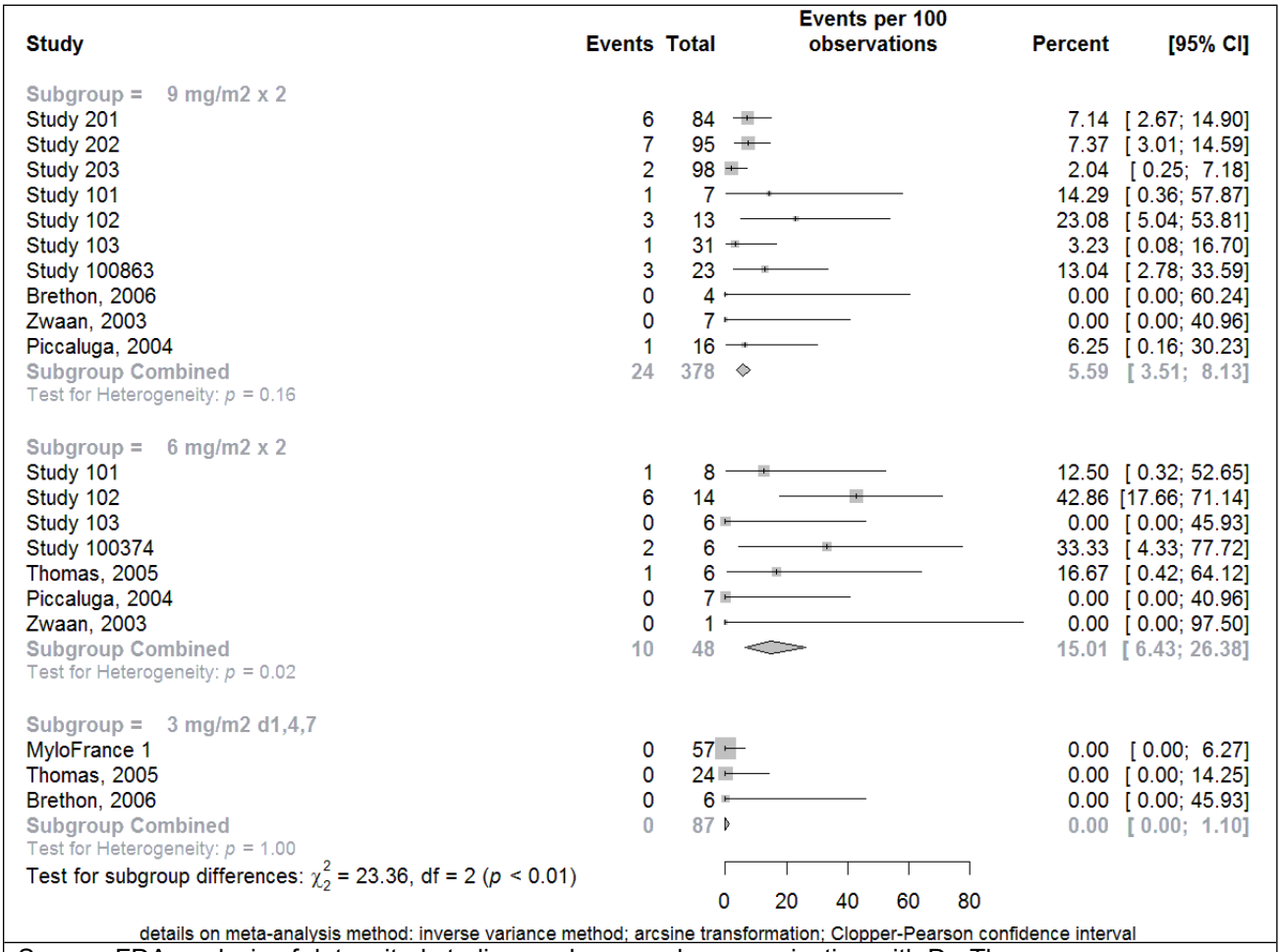
Hepatotoxicity and VOD by dose

In addition to analyzing VOD across studies 201-203 and MyloFrance-1, FDA performed a meta-analysis using the GO monotherapy studies listed in Table 4 and Table 6 with available data.

For the studies listed in Table 37 above, the rates of Grades 3-4 hepatotoxicity were 13% - 29% for the 9 mg/m^2 GO regimen, 4% - 17% for the GO 6 mg/m^2 regimen, and 0% with the 3 mg/m^2 fractionated regimen. There was a clear trend for a reduction in hepatotoxicity with the fractionated schedule.

Figure 8 shows the incidence of VOD by dosing regimen of Mylotarg. It is notable that there were 0 cases of VOD in the fractionated dose studies. Across the unfractionated studies, VOD incidence ranged from 0% to as high as 43%. The highest rate came from the pediatric dose escalation trial Study 102, on which almost half of patients underwent a HSCT post-GO. The overall incidence of VOD across the 9 and 6 mg/m^2 unfractionated studies was 6% (95% CI 4-8%) and 15% (95% CI 6-26%), respectively. This supports the incidence of VOD seen in the large US post-marketing observational study 100847, which showed a VOD incidence of 9% (95% CI 7-12%) (Tallman, McDonald et al. 2013).

Figure 8: VOD Incidence by GO Monotherapy Dose-Schedule for R/R-AML



Source: FDA analysis of data, cited studies, and personal communication with Dr. Thomas
Abbreviations: d, day; df, degrees of freedom.

Study 100374, which evaluated GO in patients with AML relapsed post-HSCT, showed a high incidence of VOD of 33% at the dose of 6 mg/m^2 (n=6). Patients on that trial who received 4 mg/m^2 (n=18) had a 17% incidence of VOD, and those who received 2

mg/m2 (n=13) had a 0% incidence. This suggests a higher risk of VOD with higher unfractionated doses of GO in AML patients post-HSCT.

As mentioned in Section 7.4.1 above, there is less data on pre- or post-transplant safety of GO using the fractionated schedule on MyloFrance 1. When combined with the studies from the literature, there is still little data, but no safety signals to date. On MyloFrance-1, 7 patients received a HSCT post-GO (3 allogeneic, 4 autologous) and none developed VOD. From the retrospective pediatric study (Brethon, et al. 2006), 2 patients treated with fractionated dosing had a prior allogeneic HSCT and 2 went onto an allogeneic HSCT post-GO (1 was the second HSCT). None of these 3 patients developed VOD either. From the retrospective adult study (Thomas, Le et al. 2005), 6 patients treated with the fractionated dosing had a prior HSCT (4 allogeneic, 2 autologous) and 3 went onto an allogeneic HSCT post-GO (personal communication with Dr. Thomas). None of these 9 patients developed VOD either (personal communication with Dr. Thomas).

Reviewer comments: Although there is less data on patients receiving HSCT before or after the fractionated dosing regimen, it is remarkable that there have been no cases to date out of 19 total patients reported to have had a transplantation before or after fractionated doses of GO. Given that the incidence of VOD with a HSCT before or after GO (allogeneic and autologous combined) is in the range of 16-19%, one would expect to have seen at least 1 of 19 patients develop VOD. This, combined with the reduced grade 3-4 liver toxicity, supports 3 mg/m^2 x 3 as a safer dosing regimen of GO, particularly for patients with prior or future plans for HSCT.

7.5.2 Time Dependency for Adverse Events

Given that most patients received only 2 doses of therapy, a meaningful analysis of the safety of long-term use could not be performed with the data available. However, it is notable that 7 of the 20 patients on trials 201-203 who received more than one course of GO for a subsequent relapse died soon after, possibly related to treatment (see Section 7.3.1). This may reflect their poorly responsive and refractory disease, however.

7.5.3 Drug-Demographic Interactions

The Applicant evaluated drug-demographic interactions by age, gender, race/ethnic origin, renal, and hepatic impairment. There were no clinically meaningful differences by age < 60 or ≥ 60 years, including early mortality (17% for patients < 60 and 20% for those ≥ 60). For gender, there were slightly more female patients who experienced nausea and vomiting, but otherwise TEAEs were quite similar.

Regarding ethnicity, most patients across the GO monotherapy studies were white, making comparisons difficult. However, TEAEs appeared to be similar across races. Furthermore, the Japanese study 103 demonstrated a similar toxicity profile to the US and European studies.

Analyses were not possible for renal impairment given that studies excluded patients with baseline renal dysfunction. Furthermore, GO has not been studied in patients with moderate or severe hepatic impairment and with bilirubin > 2 mg/dL.

7.5.4 Drug-Disease Interactions

The Applicant did not perform an analysis of AEs by disease intrinsic factors for the GO monotherapy studies.

7.5.5 Drug-Drug Interactions

There were no clinical studies of drug-drug interactions submitted.

7.6 Additional Safety Evaluations

Studies 201-203 administered GO to patients on an outpatient basis. However, all patients were hospitalized at least once during therapy. Hospitalization data was collected and showed the following results, per the ISS dataset:

- 171 patients (62%) were hospitalized at least once due to an AE
  - 114 (41%) were hospitalized once
  - 98 (35%) were hospitalized twice
  - 43 (16%) were hospitalized 3 times
  - 11 (4%) were hospitalized 4 times
  - 4 (1%) were hospitalized 5 times
  - No significant difference in hospitalizations by age group
- 5 patients (2%) were hospitalized for “chemotherapy administration” or ”medication infusion” or ”treatment”
- 168 (61%) were hospitalized for observation
- 4 (1%) were hospitalized for relapse

On MyloFrance 1, all patients were hospitalized for the duration of therapy and the period of aplasia (personal communication, Dr. Castaigne). For AML-19, it was recommended that patients be hospitalized until completion of the induction regimen. Patients would not be discharged following the last GO infusion until they were free of clinically significant study drug effects, as judged by the investigator.

Reviewer comments: It is unclear whether the required hospitalizations for MyloFrance 1 and AML-19 contributed to their more favorable safety outcomes.

7.6.1 Human Carcinogenicity

From the All treated safety database of 936 patients treated with unfractionated doses of GO, there was one case of lung neoplasm, one testicular neoplasm, and one uterine leiomyoma.

Reviewer comments: A potential relationship of the neoplasms to treatment with Mylotarg is doubtful.

7.6.2 Human Reproduction and Pregnancy Data

There is no experience on the effects of Mylotarg in patients who are pregnant or nursing.

7.6.3 Pediatrics and Assessment of Effects on Growth

See Section 7.5.1 for a description of the pediatric study 102. Additional studies from the literature include the retrospective study by Brethon *et al* (Brethon, Auvrignon et al. 2006) in 11 children with R/R AML, the retrospective study by Reinhardt *et al* (Reinhardt, Diekamp et al. 2004) in 12 children with R/R AML, the prospective study by Reinhardt *et al* (Reinhardt, Zwaan et al. 2010) in 28 children with R/R AML, and the prospective studies by Zwaan *et al* (Zwaan, Reinhardt et al. 2003, Zwaan, Reinhardt et al. 2010) in 15 and 30 children with R/R AML, respectively.

Across trials, 125 children have been treated with GO monotherapy. The median age on study 102 was 12 (range 1-16) years. The median ages from the literature ranged from 2-10 years, with minimum age 0.2 to maximum age 21 years. We do not have data on effects on growth.

As reported in section 7.5.1, there is no established safe unfractionated dose of GO in pediatric patients based on study 102. TEAEs on study 102 were similar to studies 201-203, but hepatotoxicity and VOD were much more common (VOD 31%).

From the literature review, Brethon reported no VOD events with doses ranging from 3 mg/m^2 fractionated doses (n=6) to 6-9 mg/m^2 unfractionated doses (n=5). Rates of grade 3-4 infection, febrile neutropenia, and liver toxicity were lower (18% each) than with unfractionated doses of GO in the adult population. The Reinhardt retrospective trial showed an 8% incidence of VOD with unfractionated GO at doses of 1.8-9 mg/m^2 (Reinhardt, Diekamp et al. 2004). The prospective trial with a dose of 7.5 mg/m^2 x 2 resulted in an 18% incidence of VOD, with 7% being fatal (Reinhardt, Zwaan et al. 2010). The retrospective Zwaan trial using unfractionated doses of 6-9 mg/m^2 had a VOD incidence of 7% (Zwaan, Reinhardt et al. 2003), but the prospective trial using 7.5

mg/m^2 unfractionated dosing showed no cases of VOD (Zwaan, Reinhardt et al. 2010). All but one of the 9 patients who were transplanted on the latter trial received defibrotide prophylaxis during the transplantation.

Reviewer comments: The additional safety data from the literature indicates that the fractionated dosing regimen used by Brethon et al may have been better tolerated than the unfractionated regimens.

Although neither of the 2 patients treated with 7.5 mg/m^2 GO on study 102 developed VOD, this dose still carries a notable risk of VOD in children, as evidenced by the literature reports. However, the one trial by Zwaan et al suggests that defibrotide prophylaxis may be effective. Or, perhaps the lower incidence of VOD on this study was related to less patients proceeding to transplantation post-GO (30% vs 56% on Reinhardt et al 2010).

Given a similar toxicity profile of GO in pediatric patients, extension of the indication could be considered. It is clear that the higher unfractionated doses carry a high risk of VOD in children. To date, there is limited information on the safety profile of 3 mg/m^2 in children, but the one retrospective study in 6 children showed no cases of VOD and lower rates of grade 3-4 infection, febrile neutropenia, and liver toxicity than seen in adults. There is no biological rationale to expect that a different toxicity profile would be seen with the fractionated dose regimen in children. Further data could be obtained in the PMR.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose with GO have been reported. No mortality was observed at doses that exceeded the recommended dose.

7.7 Additional Submissions / Safety Issues

A summary from the 120 day safety update, with data on 188 patients from the ongoing EAP B1761026 was provided. Of the 188 patients, 181 (96%) had AML, 3 (2%) had APL, and 4 (2%) had MDS. Ninety-two patients were treated with monotherapy. Of the monotherapy patients, the mean age was 49 and range was 0-94 years. 78 (84%) were white, 8 (9%) were black, 1 (1%) was Asian, and 5 (5%) were other.

SAEs were combined between monotherapy and combination regimens. The most frequently reported all-cause SAEs (>19%) by PT were disease progression (24%), AML (21%), and febrile neutropenia (20%). The most frequently reported treatment-related SAEs were febrile neutropenia, septic shock, and decreased WBC count.

There was 1 case of suspected VOD in a 26 year old man, which resulted in death. He experienced sepsis and bilirubin elevation starting on day 13. GO monotherapy 9 mg/m^2

was administered as one dose and then permanently discontinued as a result of the AEs. The patient died on day 22 due to sepsis/possible VOD within rising bilirubin and disease progression. Other medications included acyclovir, cefalexin, and fluconazole.

Other fatal treatment-related SAEs, occurring in one patient each, included tumor lysis syndrome (day 14), cardiac arrest (day 18), AKI (day 17), multiple organ dysfunction syndrome (day 20), CVA (day 6), DIC (day 6), and sepsis (day 10).

There were a total of 55 cases with a fatal outcome reported, with the most common cause of death (n=33) being AML/disease progression. Other events included sepsis/septic shock (n=7), multiple organ dysfunction syndrome (n=5), respiratory failure (n=4), cardiogenic shock/arrest (n=2), cardiac failure (n=1), cardio-respiratory arrest (n=1), tumor lysis syndrome (n=1), AKI (n=1), CVA (n=1), and DIC (n=1). Of 5 patients with multiple organ dysfunction syndrome, 1 patient had an elevated bilirubin at the time of death, 1 had hepatitis/acute hepatic insufficiency, 1 had serious acute sinusitis and died of disease progression, and the remaining 2 patients had “multi-organ failure” in the context of disease progression.

In addition to EAP data, the safety updated included a safety line-listing to update their last PSUR from May 2016 to November 2016, capturing post-marketing cases reported to the Applicant. 118 cases were received reporting 215 events. The majority (n=108) were from clinical studies and the remaining 10 were from spontaneous sources. The majority were from the US (57%). A total of 35 cases (30%) were associated with a fatal outcome. Some were reported with the EAP data. Fatal events included disease progression (n=17), infections including sepsis (n=5), renal failure (n=2), respiratory failure (n=2), dyspnea (n=1), stridor (n=1), HLH (n=1), DIC (n=1), cardiac failure (n=1), multiple organ dysfunction syndrome (n=1), CVA (n=1). The most frequently reported events were febrile neutropenia (16%), disease progression (10%), AML (9%), WBC decreased (8%), neoplasm progression (5%), respiratory failure, pyrexia, and sepsis (each 4%). There was one event of VOD.

These findings are consistent with the known safety profile of GO and that of AML in general in a heavily pre-treated population.

8 Postmarket Experience

GO received accelerated approval in May 2000 in the US for the treatment of patients with CD33-positive AML in first relapse, who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy. Following the US approval, GO was approved in 14 additional countries. After voluntary withdrawal of the US NDA in October 2010, GO registration was withdrawn from all countries except Japan where it

continues to be marketed for the treatment of patients with relapsed or refractory CD33-positive AML.

The Applicant estimates a worldwide commercial Mylotarg exposure of (b) (4) patients from the second quarter of 2000 through the second quarter of 2016. Of these patients, (b) (4) were in the US, (b) (4) were in Japan, and (b) (4) were in other areas. They estimate that (b) (4) patients received GO through single patient compassionate use. In terms of Pfizer managed programs, they estimate (b) (4) patients received GO in the US EAP, (b) (4) through the France temporary authorization for use (ATU) and (b) (4) patients through the France Nominative ATU.

FDA performed an analysis on the FDA Adverse Event Reporting System (FAERs) data for Mylotarg reported between January 2010 through May 2017. This data was run through MAED to identify AE signals. Out of 2,740 preferred term (PT) events, the most common are listed in Table 38 below.

Table 38: Common PTs FAERs data (≥20 events)

Preferred Term	Events (N=2740)
Sepsis	75 (3%)
Febrile neutropenia	72 (3%)
Thrombocytopenia	59 (2%)
Pyrexia	51 (2%)
VOD	45 (2%)
Pneumonia	43 (2%)
Neutropenia	42 (2%)
AML	41 (1%)
Multiple organ dysfunction syndrome	41 (1%)
Bone marrow failure	39 (1%)
Disease progression	36 (1%)
ALT increased	33 (1%)
Septic shock	33 (1%)
AKI	28 (1%)
Pancytopenia	28 (1%)
Hypotension	25 (1%)
Infection	22 (1%)
Platelet count decreased	22 (1%)
Diarrhea	21 (1%)
Neutropenic sepsis	21 (1%)
Renal failure	20 (1%)
Respiratory failure	20 (1%)

Source: FDA analysis, FAERs data.

Other signals included cardiac disorders with this SOC reported in 138 events. Most were related to arrhythmias (n=53) and coronary artery disorders (n=17). Cardiac PTs included cardiac failure (n=18), cardiac arrest (n=10), atrial fibrillation (n=9), myocardial infarction (n=8), pericarditis (n=8), tachycardia (n=8), mitral valve incompetence (n=5),

ventricular fibrillation (n=5), acute cardiac failure (n=4), cardio-respiratory arrest (n=4), QT prolongation (n=4), left ventricular dysfunction (n=4), myocardial ischemia (n=4), acute myocardial infarction (n=3), cardiac failure congestive (n=3), ejection fraction decreased (n=3), myocarditis (n=3), pericardial effusion (n=3), cardiac tamponade (n=2), cardiogenic shock (n=2), cardiomyopathy (n=2), myocardial necrosis marker increased (n=2), troponin I increased (n=2), ventricular tachycardia (n=2), atrial flutter (n=1), ECG abnormal (n=1), and ECG repolarization abnormality (n=1).

Other notable PTs included immune thrombocytopenic purpura (n=4), thrombotic microangiopathy (n=4), intravascular hemolysis (n=1), and HLH (n=1).

Reviewer comments: The significance of the cardiac PTs is unclear. Certainly the relapsed AML population has a variety of risk factors for cardiac disease, including prior anthracycline exposure, transplantation, concomitant medications, infections, active leukemia, advanced age, and others. On AML-19, for example, the rate of cardiac AEs of any grade was 28% on the GO arm and 33% on the BSC arm. Grade 3-4 cardiac AEs was 6% on the GO arm and 14% on the BSC arm. This suggests that GO is not cardiotoxic itself, at least with the upfront monotherapy dosing regimen, in a newly-diagnosed elderly population. However, there remains some concern on the cardiac AEs, especially since there was no formal characterization of QT risks in the clinical development program.

The small number of immune-related events and hemolysis, including ITP, TMA, intravascular hemolysis, and HLH are of unclear significance. It is unclear whether this could be related to ADAs. However, the incidence was sufficiently low that it could reflect the background prevalence in the population.

A review of SMQs revealed a total of 7752 broad events and 4029 narrow events. The most common (≥ 100 events) are listed in Table 39 below.

Table 39: Common Broad SMQs FAERs data (≥100 events)

SMQ	Events	
	Broad (N=7752)	Narrow (N=4029)
Drug reaction with eosinophilia and systemic symptoms syndrome	734 (9%)	0
Haematopoietic cytopenias	390 (5%)	343 (9%)
Agranulocytosis	333 (4%)	192 (5%)
Hepatic disorders	197 (3%)	180 (4%)
Haemorrhages	159 (2%)	142 (4%)
Systemic lupus erythematosus	155 (2%)	0
Shock	146 (2%)	70 (2%)
Neuroleptic malignant syndrome	125 (2%)	0
Embolic and thrombotic events	123 (2%)	123 (3%)
Anaphylactic reaction	121 (2%)	1 (0.02%)
Malignancies	115 (1%)	115 (3%)
Cardiomyopathy	104 (1%)	13 (0.3%)

Tumor lysis syndrome	104 (1%)	3 (0.07%)
GI nonspecific inflammation and dysfunctional conditions	103 (1%)	93 (2%)
Hypersensitivity	102 (1%)	36 (1%)

Source: FDA analysis, FAERs data.

Under the broad SMQ search, there were 36 events reported for Torsade de pointes/QT prolongation. Under the narrow search, there were 6 such events. There were 56 events under the broad SMQ of cardiac failure and 46 under the narrow SMQ. Cardiac arrhythmias were seen in 71 cases per the broad SMQ and 36 per the narrow SMQ. Seven were reported to be ventricular tachyarrhythmias. Although cardiomyopathy broad SMQ resulted in 104 events, the narrow SMQ revealed only 13 events. There were 19 events of ischemic heart disease on the narrow search (21 broad).

Of the 123 embolic and thrombotic events, 77 were venous, 27 were unspecified or mixed arterial and venous, and 19 were arterial.

A signal on the broad SMQ analysis was pancreatitis seen in 83 cases, although there were only 3 on the narrow search (3 PTs reported).

There were 55 events of Guillain-Barre syndrome per the broad SMQ and none in the narrow SMQ. No PTs reported this syndrome.

Reviewer comments: The SMQ searches helped to further characterize the incidence of cardiac AEs. They also indicated that arterial and venous thrombotic events have occurred. Considering the numbers, this is unlikely to be disproportionately high in the patient population, many of whom have co-morbidities and indwelling catheters. However, this should be followed closely in the post-marketing setting.

We sent an IR asking the Applicant to review the cumulative postmarketing data and submit an analysis of the following unlabeled events from all sources, including post-marketing data and clinical trials.

- Blood: thrombotic microangiopathy
- Cardiac: cardiac failure, atrial fibrillation, myocardial infarction, torsade de pointes
- Gastrointestinal: neutropenic colitis, pancreatitis, acute pancreatitis
- Hepatobiliary: Budd-Chiari syndrome
- Immune: graft versus host disease, acute graft versus host disease
- Infections: Pneumocystis jirovecii pneumonia, pulmonary mycosis, Stenotrophomonas infection
- Renal: cystitis haemorrhagic, renal failure, acute kidney injury
- Respiratory: pulmonary veno-occlusive disease, interstitial lung disease
- Vascular: capillary leak syndrome

The full analysis of the above AEs was not received in time for inclusion in this review. At this time, the FAERs data does not indicate that additional risks need to be added to the PI. However, the cardiac signals, including arrhythmias, support the need for QT evaluation in a PMR.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The following are recommendations for GO labeling based on this review:

- Include Boxed Warnings for a) hepatotoxicity, including severe or fatal VOD, b) severe or fatal hypersensitivity reactions, and c) hemorrhage, including fatal intracranial hemorrhage.
- Recommend hospitalization for close monitoring during induction therapy.
- Describe the recommended premedications.
- Include instructions for dose interruption and discontinuation for patients who develop hepatotoxicity or other severe or life-threatening reactions.
- Include instructions for monitoring of complete blood counts prior to each dose of Mylotarg and monitoring of signs and symptoms of bleeding/hemorrhage during treatment with Mylotarg.

9.3 Advisory Committee Meeting

The advisory committee meeting did not address the monotherapy indication.

9.4 Grouped Terms Use in the Safety Review

Grouped Term	MedDRA Terms
Hepatotoxicity	Cholestasis and jaundice of hepatic origin (SMQ narrow); Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ narrow); Hepatitis, noninfectious (SMQ narrow); Liver related

	investigations, signs and symptoms (SMQ narrow and broad); and Preferred Terms of Venoocclusive liver disease, Venoocclusive disease, Hepatic vein occlusion, Hepatic vein thrombosis, Portal vein thrombosis, Portal vein occlusion, and Budd-Chiari syndrome
Hemorrhage	Haemorrhage terms (excl laboratory terms) (SMQ narrow)
Infections	Infections and Infestations (SOC); HLTs of Bacterial lower respiratory tract infections, Fungal lower respiratory tract infections, Lower respiratory tract infections NEC, Respiratory tract infections NEC, and Viral lower respiratory tract infections
Infusion reactions (from start of infusion to within 24 hours of end of infusion)	Anaphylactic reaction (SMQ narrow); Angioedema (SMQ narrow); Hypersensitivity (SMQ narrow); and Preferred Terms of Cytokine release syndrome, Infusion related reaction, Chills, Dizziness, Dyspnoea, Feeling hot, Flushing, Hot flush, Hyperhidrosis, Hypotension, Pyrexia, Tachycardia, and Wheezing
Myelosuppression	Haematopoietic thrombocytopenia (SMQ narrow and broad); Haematopoietic leukopenia (SMQ narrow); Haematopoietic erythropenia (SMQ narrow and broad); Haematopoietic cytopenia affecting more than one type of blood cell (SMQ narrow)
Tumor lysis syndrome	Tumour lysis syndrome (SMQ narrow)

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/s/

KELLY J NORSWORTHY
07/28/2017

DONNA PRZEPIORKA
07/28/2017