FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting
July 11, 2017

BLA 761060
Mylotarg (gemtuzumab ozogamicin)
Applicant: Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the Mylotarg BLA to this Advisory Committee in order to gain the Committee's insights and opinions regarding the effectiveness and safety of the proposed drug product for the proposed oncologic indications. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
Cmax	Maximal concentration
CR	Complete remission
CRp	CR with incomplete platelet recovery
DA	Daunorubicin/cytarabine (7+3)
DFS	Disease-free survival
EFS	Event-free survival
GO	Gemtuzumab ozogamicin
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
IPD	Individual patient-level data
IRC	Independent Review Committee
OR	Odds ratio
OS	Overall survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PLT	Platelets
PMR	Postmarketing requirement
RFS	Relapse-free survival
RR	Relapsed or refractory
SAE	Serious adverse event
SMQ	Standardized MedDRA query
VOD	Veno-occlusive disease

1. INTRODUCTION

1.1 Proposed Indication

The applicant is seeking approval of Mylotarg (gemtuzumab ozogamicin, GO), a CD33-directed antibody-drug conjugate for the 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 (AML)."

1.2 Purpose of the Meeting

The purpose of this Advisory Committee meeting is two-fold: to discuss whether the fractionated low-dose GO regimen in combination with daunorubicin and cytarabine (DA; also known as 7+3) provides an acceptable safety profile, and to discuss whether EFS is an acceptable endpoint on which to base a determination of efficacy of GO in combination with DA treatment of patients with newly-diagnosed CD33-positive AML.

GO was granted accelerated approval on May 17, 2000, as a single agent (see Table 1) for the treatment of patients with CD33-positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy. Myelosuppression and infusion-related reactions were identified as the major safety concerns at the time of approval. In the postmarketing period, fatal hepatotoxicity and veno-occlusive disease (VOD) were added as boxed warnings, highlighting an especially increased risk of VOD in patients who received GO either before or after hematopoietic stem cell transplantation (HSCT).

Table 1: Comparison of GO Regimens

	Original Approval 2000	**SWOG S0106** [a]	**ALFA-0701** [a]
Induction	GO 9 mg/m^2 IV x 2 doses 14 days apart	D 45 mg/m^2/day on days 1-3 A 100 mg/m^2/day on days 1-7 GO 6 mg/m^2 on day 4	D 60 mg/m^2/day on days 1-3 A 200 mg/m^2/day on days 1-7 GO 3 mg/m2 on days 1, 4, 7
Consolidation	-	A 3 g/m^2 BID on days 1, 3, 5	D 60 mg/m^2/day on day 1(-2)[b] A 1 g/m^2 BID on days 1-4 GO 3 mg/m2 on day 1
Maintenance	-	GO 5 mg/m^2 x 3 doses 28 days apart	-

Abbreviations: A, cytarabine; D, daunorubicin; GO, gemtuzumab ozagamicin
[a]Patients randomized to the control arm did not receive GO. There was a rerandomization for maintenance in S0106
[b]Daunorubicin given on days 1-2 in consolidation cycle 2 only

As the subpart H postmarketing requirement (PMR), Wyeth was required to confirm clinical benefit in a randomized controlled trial of gemtuzumab ozogamicin, daunorubicin and cytarabine versus daunorubicin and cytarabine as induction therapy in patients with de novo CD33-positive acute myeloid leukemia. Wyeth identified the SWOG study S0106 as the study to fulfill the PMR. S0106 was a randomized trial comparing DA with or without GO 6 mg/m^2 (see Table 1) for treatment of patients ≤60 years old with newly-diagnosed AML. The primary endpoint was CR rate post induction and disease-free survival (DFS) post consolidation. There were 637 patients randomized. The study showed no improvement in CR, DFS or OS with the addition of GO. There was a higher rate of fatal induction toxicities in the GO arm (5.8% vs 1.3%). FDA concluded that clinical benefit was not confirmed and that there was a potential safety issue due to the increase in early deaths. Wyeth withdrew GO from marketing (notice of withdrawal published November 28, 2011).

Results of subsequent trials suggested that a lower dose of GO could be combined safely with DA. Wyeth has now submitted the results of ALFA-701 to support its marketing application. ALFA-701 was a randomized trial comparing DA with or without GO 3 mg/m^2 days 1, 4 and 7 (see Table 1) for treatment of patients 50-70 years old with newly-diagnosed AML. The primary endpoint was event-free survival (EFS). There were 271 patients randomized. The analysis of EFS showed a statistically significant improvement with a hazard ratio (HR) of 0.56 (95% CI 0.42, 0.76; p<0.001), but analysis of the secondary endpoint OS did not show statistically significant improvement (HR 0.81; 95% CI, 0.60, 1.09; p=0.16). The results from ALFA-0701 demonstrated the superiority of GO 3 mg/ m^2/dose + DA versus DA in the sensitivity analyses using different definitions of EFS and in a time-to-event endpoint that only considered relapse and death as events. There was no significant difference in 30-day mortality between the GO and no GO arms (3.8% vs 2.2%, respectively), but the patients treated with GO had a higher rate of hemorrhage and a prolonged time to recovery of platelets.

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. 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). Note that an R^2 close to 1 indicate 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.

Wyeth also provided a meta-analysis for OS in the subgroup of 5 randomized GO studies with patient-level data. In this meta-analysis, HR was 0.91 (95% CR 0.84, 0.99) with an estimated 2.1 months increase in OS. FDA does not generally accept retrospective meta-analyses of OS as the primary evidence to establish clinical benefit.

The meta-analysis for safety outcomes in the subgroup of 5 randomized GO studies with patient-level data confirmed the increased risk of hemorrhage, hepatotoxicity and VOD in patients treated with GO, although there was a trend for the effect to be dose-related.

The committee discussion will assist the FDA in determining whether the safety outcomes in ALFA-701 and the meta-analysis allay the previous safety concerns about use of GO in combination with DA. FDA also seeks input from the advisory committee regarding whether there are alternative statistical approaches better suited to assess the surrogacy of EFS for OS specifically for patients with AML, or whether EFS represents a clinical benefit in itself for patients with newly diagnosed AML.

2. REGULATORY BACKGROUND

GO was developed under IND 046635 which was received by FDA on November 10, 1994. The first marketing application for GO (NDA 021174) was received on October 29, 1999. Orphan designation was granted on November 24, 1999. The marketing application was discussed by ODAC on March 20, 2000. GO (Mylotarg) received accelerated approval on May 17, 2000, contingent on fulfilling the post-marketing requirement of a randomized trial to confirm clinical benefit. GO was also discussed at ODAC meetings on March 13, 2003, and November 8, 2005; the subject of these meetings was delays in PMR fulfillment for products which had received accelerated approval.

Wyeth notified FDA that their PMR study did not confirm the clinical benefit of GO, and on May 21, 2010, FDA requested that Wyeth withdraw GO from marketing and establish an expanded access protocol. Wyeth voluntarily withdrew GO from marketing, and the NDA was formally withdrawn on October 25, 2010. An expanded access protocol was submitted April 10, 2013.

On eight occasions between 2012 and 2016, FDA and Wyeth discussed or corresponded about additional emerging data on the efficacy of GO and the information that would be required for submission of a new marketing application. BLA 761060 was received November 2, 2016.

3. CLINICAL IMPACT OF MYLOTARG DOSE AND SCHEDULE

3.1 Pharmacokinetics of GO

In the review of pharmacokinetics (PK) for the prior marketing application for Mylotarg (Kieffer, et al. 2000), FDA confirmed the Applicant's findings that for hP67.6 (the anti-CD33 antibody), total and unconjugated calicheamicin, a) exposure increased more than dose-proportional, b) there was 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 observed between dosing periods. Table 2 shows the key PK parameters for hP67.6 in dose periods 1 and 2 from the initial Phase 1 study 0903A1-101-US.

Table 2: Mean hP67.6 Cmax and AUCinf by GO Dose

	Cmax (ng/mL)[a]		AUCinf (ng h/mL)[a]	
GO Dose (mg/m^2)	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
0.25	15	14	82	125
0.5	28	43	468	1273
1	50	103	943	1740
2	411	370	11110	11610
4	611	847	10970	20100
5	1325	1673	29980	43400
6	2219	3660	69300	138200
9	2870	3968	80430	204700

Source: Applicant's Summary of Clinical Pharmacology Table 9
[a]Mean values for cohorts of 1-7 subjects each in Study 0903A1-101-US

Although the data suggest that there might be a substantial decrease in exposure for the GO dose of 3 mg/m^2 in comparison to doses of 6 or 9 mg/m^2, there were no actual PK studies performed in patients treated with GO 3 mg/m^2 on days 1, 4 and 7. To address this, the Applicant utilized their population PK model to simulate exposure for the fractionated GO regimen. Table 3 shows the results for the AUC and Cmax at first dose and the full course for GO 9 mg/m^2 and the fractionated GO regimen.

Table 3: Simulated Cmax and AUCinf by GO Dose

	GO Dose 1		Full GO Course	
	9 mg/m^2	**3 mg/m^2**	**9 mg/m^2 d 1 and 15**	**3 mg/m^2 d 1, 4, 7**
hP67.6				
AUC (ng h/mL)	49400 (43200, 56500)	5740 (5140, 6410)	208000 (197000, 221000)	51400 (47700, 55300)
Cmax (ng/mL)	1730 (1630, 1840)	383 (364, 402)	2620 (2530, 2710)	632 (612, 654)
Calicheamicin[b]				
AUC (ng h/mL)	151 (144, 157)	30.5 (29.5, 31.5)	343 (327, 359)	181 (172, 190)
Cmax (ng/mL)	3.7 (3.6, 3.9)	1.3 (1.2, 1.3)	3.9 (3.7, 4.0)	1.5 (1.4, 1.6)

Source: Applicant's Summary of Clinical Pharmacology Tables 24-27
[a]Geometric mean (95% CI)
[b]Unconjugated

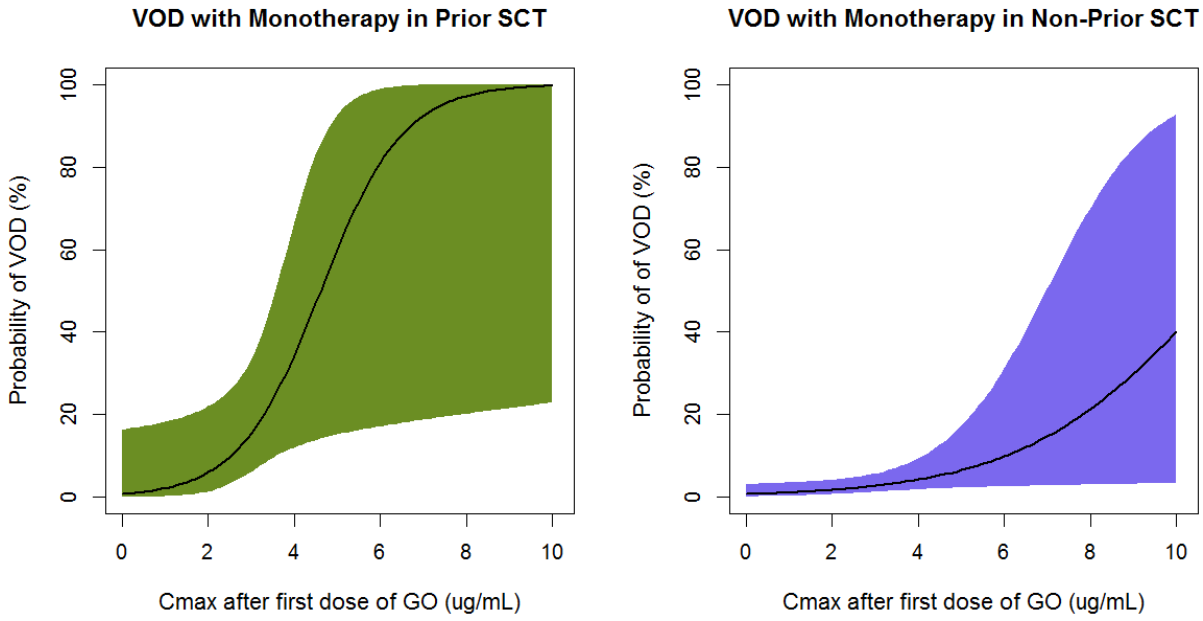
The simulations also suggest that the fractionated GO regimen 3 mg/m^2 on days 1, 4 and 7 would have a reduced Cmax and exposure at the first dose and over the full course. Based on a few observed data with lower doses, Cmax and AUC tend to decrease as dose decreased, but it is hard to make a clear prediction with too few data (< 5 subjects for lower than 5 mg doses). There are several points to consider when the Applicant's simulated values are interpreted. The population PK model did not appear to characterize observed concentration data well enough to be utilized for simulation exercises, especially for the random effects for time-dependent clearance. The model tends to underpredict the concentrations of hP67.6. Nonetheless, the Applicant's predicted median with confidence intervals could not reflect the actual variability in

concentrations with the untested dose without prediction intervals, especially when inter-subject variability is large (82.5% for linear clearance and 173% for time-dependent clearance variable).

3.2 Exposure-Response Relationships

To understand whether the apparent dose-response for VOD is associated with exposure of GO, FDA conducted exposure-response analysis for VOD using logistic regression. The analysis data for VOD include a total of 358 patients from three Phase 2 studies (Study 101, Study 102, Study 103) and the pivotal studies (Study 201, Study 202, Study 203). As Figure 1 shows, there is a relationship between Cmax after the first dose of GO and the probability of having VOD in patients either with or without prior HSCT. The results suggest that the reduction in Cmax that results from fractionated dosing will reduce the incidence of VOD.

Figure 1: Exposure-Response Relationships between Cmax After the First Dose of GO and VOD in Patients with Prior HSCT and Non-prior HSCT



Source: FDA analysis

FDA also conducted an exposure-response analysis for complete remission. Because the complete remission data were available only from the three pivotal studies, the analysis data include a total of 269 patients from Study 201, Study 202, and Study 203. From univariate logistic regression analyses, complete remission did not show a significant relationship with any of the exposure measures, such as AUC after the first dose, Cmax after the first dose, and overall AUC. However, the baseline platelet counts (p=0.00214), the baseline bone marrow blasts ($p=1.86 \times 10^{-05}$), and the baseline P-gp expression (p=0.00113) were significant predictors for complete remission. The pharmacodynamics analysis suggested that CD33 will be adequately occupied in vivo at GO doses of 2 mg/m^2 and above. Therefore, it is reasonable to project that

the lower dose fractionated regimen will provide benefit of reducing VOD without compromising efficacy benefit.

3.3 Clinical Assessment

3.3.1 Clinical Assessment Strategy

FDA analyzed and compared efficacy and safety for various unfractionated and fractionated doses and schedules of GO when used as monotherapy for treatment of patients with relapsed or refractory (R/R) AML. The review was based primarily on studies 0903B1-201-US/CA (201), 0903B1-202-EU (202), 0903B1-203-US/EU (203), and MyloFrance 1 (Taksin, et al. 2007) which included patients with AML in first relapse. 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 Appendix 1 Table 21, and are identified as using the unfractionated (0.25-9 mg/m^2 x 2-3 doses 14 days apart) or fractionated (3 mg/m^2 x 3 doses 3 days apart) dosing schedules.

The Applicant performed a literature search on GO monotherapy in patients with R/R AML. Their methods included searches of OVID MEDLINE (1946-7/1/2015), OVID MEDLINE In-Process, BIOSIS Previews (1969-2015, week 31), Embase Daily Alerts (5/4/2015-7/1/2015), and Embase (1974-7/1/2015) using terms "cma-676," "mylotarg," "gemtuzumab ozogamicin," or "gemtuzumab." Published papers and meeting abstracts of studies must have fulfilled all of the following criteria: "GO administered as a single agent in patients with relapsed or refractory AML, studies reported the endpoints of CR/CRp, and enrolled and treated at least 10 patients. Review articles, preclinical studies, meta-analyses, case reports, and papers focusing on APL only were excluded from the literature review." Thirteen studies were identified that matched their criteria.

FDA further refined the literature review performed by the Applicant in order to compare the safety and 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.

Appendix 1 Table 21 lists the six additional publications that FDA considered in the review Trials are identified as evaluating unfractionated or fractionated GO regimens. In 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.

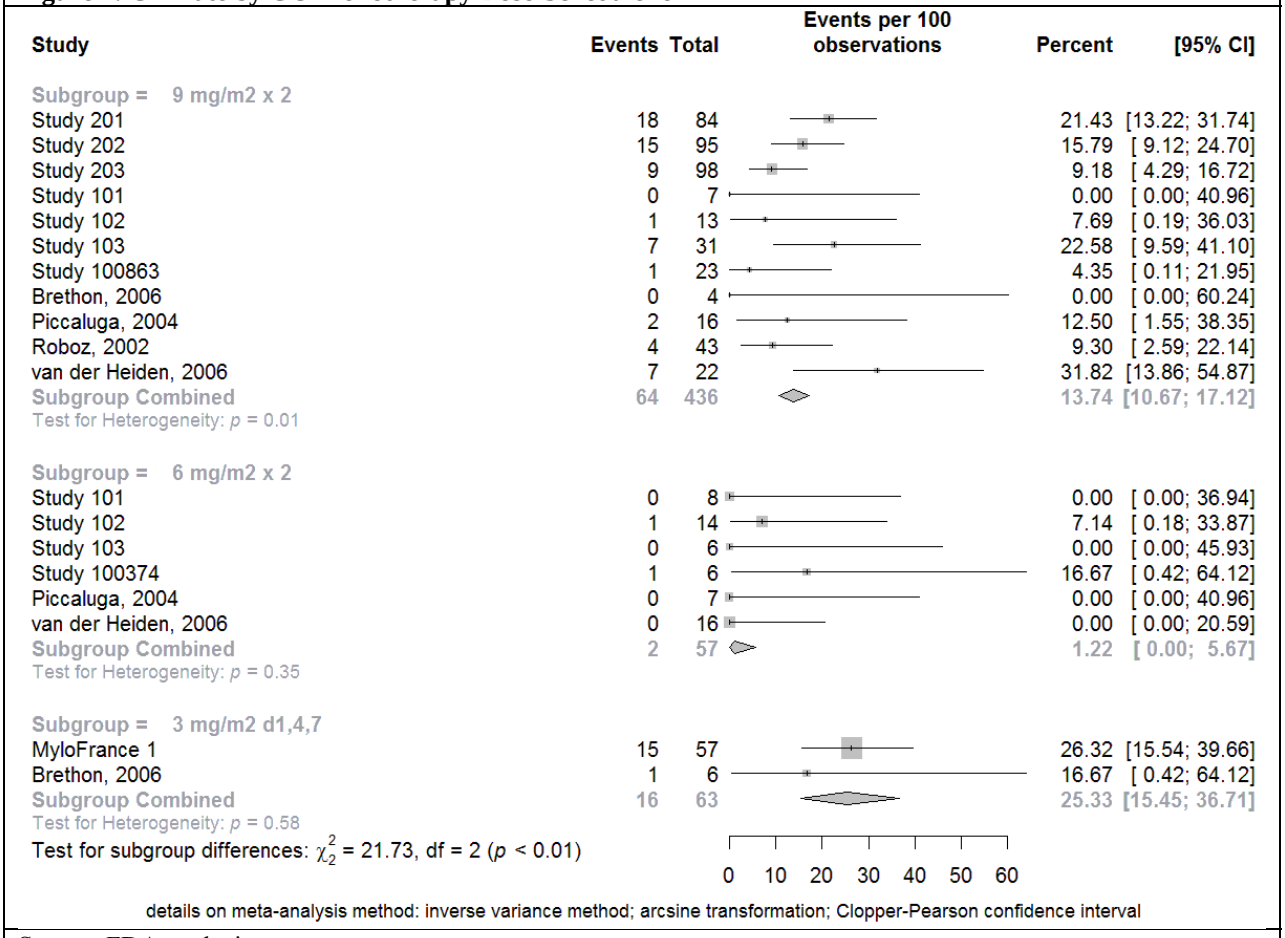
FDA acknowledges the caveat that comparisons of outcomes across trials may be problematic. As such, these analyses are considered only exploratory.

3.3.2 Impact of Monotherapy Dose on Efficacy

To assess the impact of dose and schedule on efficacy, FDA 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 201-203, MyloFrance-1, and the publications listed in Appendix 1 Table 21 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 2 lists that 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.

Figure 2: CR Rate by GO Monotherapy Dose-Schedule for RR AML



Source: FDA analysis
Abbreviations: CI, confidence interval; d, day; df, degrees of freedom.

3.3.3 Impact of Monotherapy Dose on Safety

The safety of the unfractionated and fractionated dosing regimens was primarily evaluated based on studies 201-203 and MyloFrance 1, respectively. Supportive safety data was derived from an analysis of safety from all studies listed in Appendix 1 Table 21. FDA focused the analysis on the 6 and 9 mg/m^2 unfractionated regimens and the 3 mg/m^2 fractionated regimen.

Early Mortality

FDA assessed early mortality rates among the different dosing schedules of GO for RR AML. Literature studies were included if induction death rates were available from the text or by personal communication. Table 4 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 4: Early Mortality by GO Monotherapy Dose-Schedule for RR AML

Dose regimen	Individual Studies	Deaths N (%, 95% CI)
9 mg/m^2 x 2* (N=410)		**70 (17%, 14-21%)**
	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)		**5 (12%, 5-27%)**
	101 (N=8)	2 (25%)
	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%)

Abbreviations: CI, confidence interval; N, number.
Sources: FDA analysis
*Note that 201-203, 101, Piccaluga et al and Roboz et al allowed for up to 3 doses of GO. Deaths reported through day 43 for Studies 101 - 203 and Study 100863, "during the treatment period" in Piccaluga 2004 and as "early deaths" in Roboz 2002.

Table 5 shows the causes of death within 43 days after the first 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 5: Causes of Early Mortality by GO Monotherapy Dose-Schedule for RR 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%)	7 (14%)	5 (22%)	3 (11%)	-	4 (7%)
Persistent AML	19 (7%)	4 (8%)	1 (4%)	1 (4%)	-	2 (4%)
Infection	14 (5%)	1 (2%)	2 (9%)	1 (4%)	-	-
Sepsis or septic shock	8 (3%)	-	1 (4%)	1 (4%)	-	-
Pneumonia	6 (2%)	-	1 (4%)	-	-	-
Hemorrhage	11 (4%)	-	-	-	-	-
Intracranial	10 (4%)	-	-	-	-	-
Retroperitoneal	1 (<1%)	-	-	-	-	-
Cerebral Infarction	-	1 (2%)	-	-	-	-
VOD	3 (1%)	-	1 (4%)	-	-	-
Respiratory failure	1 (<1%)	1 (2%)	-	1 (4%)	-	-
Multiple organ failure	1 (<1%)	-	1 (4%)	-	-	-
Acute renal failure	1 (<1%)	-	-	-	-	-
Unknown	1 (<1%)	-	-	-	-	2 (4%)†

Sources: FDA analysis
Abbreviations: d, day; N, number; VOD, veno-occlusive disease.
* Note that 201-203 and 101 allowed for up to 3 doses of GO.
†One patient had an early death before day 15 and another died at day 27 during treatment-induced bone marrow hypoplasia with no persistent leukemia.

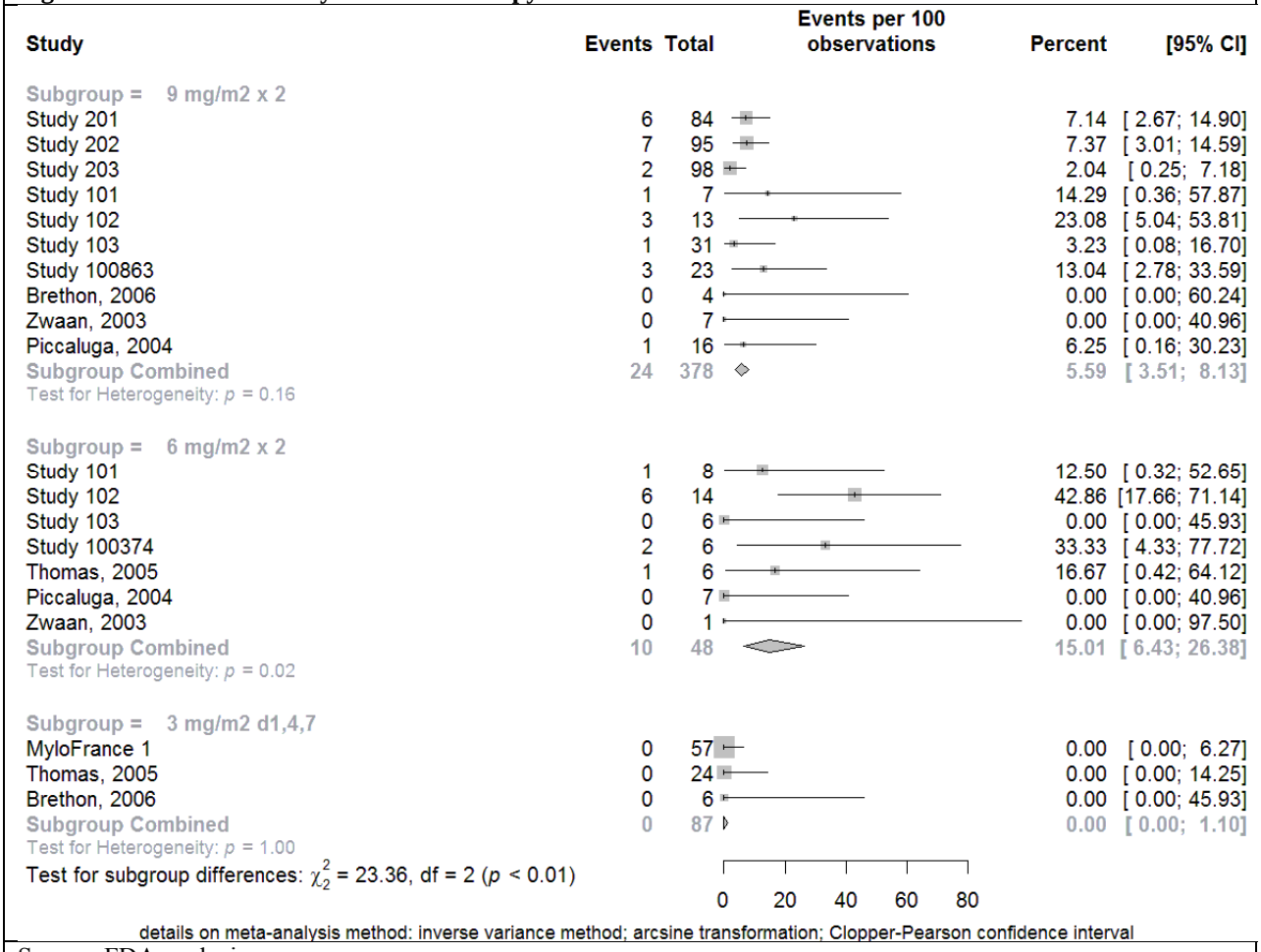
Hepatotoxicity and VOD

Given the substantial toxicity and high mortality rate associated with hepatic VOD, FDA's review focused heavily on hepatotoxicity and VOD. In addition to analyzing VOD across studies 201-203 and MyloFrance-1, FDA performed a meta-analysis using the GO monotherapy studies listed Appendix 1 Table 21 with available data.

For the studies listed in Table 5 above the rates of Grades 3-4 hepatotoxicity were 13% - 27% 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 3 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 the 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 is similar to 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%).

Figure 3: VOD Incidence by GO Monotherapy Dose-Schedule for RR AML



Source: FDA analysis
Abbreviations: CI, confidence interval; 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/m^2 (n=13) had a 0% incidence. This suggests a higher risk of VOD with higher unfractionated doses of GO in AML patients post-HSCT.

The Applicant performed a logistic regression analysis to assess the effects of several variables on the risk of developing VOD, including age, gender, total dose, therapy indicator, baseline ALT, AST, and bilirubin, type of HSCT, HSCT indicator (follow-up), time of HSCT relative to GO dose, and exposure to busulfan/cyclophosphamide. However, aside from HSCT itself, none of the other variables were found to be independently associated with VOD.

Of the patients who developed VOD on Studies 201-203 (5%), it is notable that the majority died as a consequence (4% fatal VOD). The incidence of VOD and fatal VOD among the 31 patients undergoing allogeneic HSCT post-GO on studies 201-203 was 23% and 19%, respectively. Only 3 patients on these trials 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.

In terms of pre- or post-transplant safety of GO using the 3 mg/m^2 fractionated schedule, there are little data, but no safety signals to date. On MyloFrance-1, 7 patients underwent 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 on to allogeneic HSCT post-GO (1 was the second HSCT). None of these 3 patients developed VOD either.

Prolonged Cytopenias

FDA analyzed the time to neutrophil and platelet count recovery for both unfractionated and fractionated GO regimens (Table 6). Data were available only for Studies 201-203 and MyloFrance 1. Time to count recovery was not specifically reported for CR patients in the MyloFrance 1 paper. Therefore, count recovery data only for combined CR+CRp responders is provided in the table below (98/277 patients for studies 201-203 and 19/57 patients for MyloFrance 1). It appears that recovery of neutrophils and platelets is shorter with the fractionated regimen of GO.

Table 6: Time to Hematopoietic Recovery with GO Monotherapy

	Median time in days (range)	
Parameter	**9 mg/m^2 x 2 201-203 (N=98)**	**3 mg/m^2 d1,4,7* MyloFrance-1 (N=19)**
ANC > 0.5 Gi/L	42 (16-100)	23
Platelets > 50 Gi/L	51 (15-528)†	20

Source: FDA analysis; data shown for patients who achieved CR or CRp
Abbreviations: ANC, absolute neutrophil count; d, days; N, number.
*Ranges not reported.
†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).

Time to neutrophil recovery for patients with CR on Studies 201-203 was similar to that for those with CR+CRp, with median time to ANC > 0.5 Gi/L of 41 days (range 16-85 days). As expected, median time to platelet recovery > 50 Gi/L for patients with CR was shorter at 40 days (range 17-104 days). Even when assessing count recovery only in patients with full CR responses, the fractionated schedule appeared to cause substantially less prolonged cytopenias.

It is notable that STudies 201-203 and MyloFrance-1 required transfusion independence for CRp responses. Furthermore, MyloFrance-1 required that platelets be greater than 20 Gi/L to qualify. Despite the requirement for transfusion independence on Studies 201-203 for CRp, this independence was not required to be sustained, and multiple patients still needed intermittent transfusions. Twenty-two of 56 patients with CRp on 201-203 never recovered their platelets above 50 Gi/L, and 4 of 56 with CRp never recovered platelets above 25 Gi/L.

The clinical consequences of the prolonged cytopenias appeared to impact the risk of hemorrhage more than that of infection. For the studies listed in Table 5 above, the rates of Grades 3-4 hemorrhage were 8% - 48% for the 9 mg/m^2 GO regimen, 17%-18% for the GO 6 mg/m^2 regimen, and 7% with the 3 mg/m^2 fractionated regimen. The rates of Grades 3-4 infection overlapped substantially, being 14% - 52% for the 9 mg/m^2 GO regimen, 21% - 33% for the GO 6 mg/m^2 regimen, and 39% with the 3 mg/m^2 fractionated regimen.

3.3.4 Dose Selection Studies for GO+DA

Study 0903B1-206-AU/EU/US included a small dose-escalation portion to identify the maximal tolerable dose of GO in combination with DA. GO doses of only 6 or 9 mg/m^2 were tested in this study, so the results are not applicable to the Applicant's proposed dose of 3 mg/m^2 on days 1, 4 and 7.

The NCRI AML17 trial was a randomized study comparing GO 3 mg/m^2 vs 6 mg/m^2 on day 1 in combination with intensive induction chemotherapy for first-line treatment of patients with AML or high-risk MDS (Burnett, et al. 2016). The accrued population included 788 patients of median age 50 years (range, 0-81 years), and 95% of the patients had AML rather than MDS. Interpretation of the study is somewhat confounded by the inclusion of multiple chemotherapy regimens and multiple additional rerandomizations for consolidation, but the investigators reported that in comparison to GO 6 mg/m^2, the patients treated with GO 3 mg/m^2 had a higher CR rate (82% vs 76%), lower 30-day mortality (3% vs 7%), less grade 3-4 ALT elevation (7% vs 17%), less VOD (0.5% vs 5.6%), more rapid recovery of platelets (29 vs 31 days), and fewer platelet transfusions (mean 12.2 vs 16.1 units). There was no significant difference between the study arms for the endpoints of overall survival or relapse-free survival.

3.4 Summary of Issues for Dose Selection

- GO 6 mg/m^2 was found to be too toxic when used in combination with DA. The Applicant proposes to recommend the lower and fractionated GO dose of 3 mg/m^2 days 1, 4 and 7 in combination with DA for induction.
- Population PK analyses suggest that an increased Cmax after the first GO dose is associated with an increased risk of VOD, but there was no relationship between GO PK and CR.
- In the cross-study analysis of clinical outcomes for patients with RR AML treated with GO monotherapy, in comparison to the regimens using GO 6 or 9 mg/m^2, studies using GO 3 mg/m^2 reported less early mortality, less hepatotoxicity, less VOD, more rapid platelet recovery and less hemorrhage without an apparent decrease in the CR rate.
- The Applicant's suggestion that the GO regimen of 3 mg/m^2 days 1, 4 and 7 would be less toxic than GO 6 mg/m^2 in combination with DA is supported indirectly by the available data, but in the absence of a dose-ranging or randomized trial comparing the lower-dose regimens (i.e., 3 mg/m^2 day 1 only vs days 1, 4 and 7), it is not clear that GO 3 mg/m^2 days 1, 4 and 7 would provide optimal safety and efficacy.

4. MYLOTARG COMBINATION THERAPY - CLINICAL TRIALS USED IN THE REVIEW OF EFFICACY AND SAFETY

The FDA review of efficacy of the combination regimen was based on data and analyses submitted by Wyeth for ALFA-701 (the pivotal trial), 5 studies of GO in the IPD meta-analysis of patient-level data, and FDA's review of the literature. The clinical studies are described in detail in Wyeth's briefing document. The sections below provide a brief overview for reference.

4.1 ALFA-701

The pivotal trial ALFA-0701 was a multi-center (France only), open-label, 1:1 randomized Phase 3 trial of GO plus DA vs DA alone for induction and consolidation therapy in patients 50-70 years old with untreated de novo AML. CD33-positivity was not required for eligibility for the trial. Treatment consisted of induction followed by two cycles of consolidation (see Table 1 above), and follow-up extended through 2 years from randomization. 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 relapse or death, starting from the date of randomization. The key secondary objectives included evaluation of rate of CR and CRp (CR with incomplete platelet recovery to >100 Gi/L). CR was defined as no circulating blasts, marrow blast cells < 5%, Hgb > 9g/dL, platelets >100 Gi/L, neutrophils > 1 Gi/L, and transfusion independence. Cumulative response rate, relapse-free survival, overall survival, and the safety profile of the combination were also examined.

Safety data were collected originally using a predefined checklist of Grade 3 and 4 AEs developed by the trial sponsor, Versailles Hospital Centre (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/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., induction failure 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.

ALFA-0701 enrolled 280 patients; 9 patients were excluded from analysis 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. CD33 expression data was available for 194 patients, and none had a CD33 percentage of zero. FDA noted that the demographic characteristics in the two treatment arms were well-balanced with respect to age, performance status and baseline disease characteristics. A slightly higher proportion of males were randomized to the GO arm than the control arm (55% vs 44%). Data on race were not collected in this study.

4.2 Studies in the Patient-Level Meta-Analysis

The meta-analysis included the ALFA-0701 and 4 additional randomized trials investigating GO with different dosages in intensive induction regimens for treatment of patients with newly-diagnosed AML. The eligible patients varied in age, although no pediatric study was included. The doses of GO used in induction included 6 mg/m^2 x 1, 3 mg/m^2 x 3 and 3 mg/m^2 x 1. Table 7 provides a summary of the 5 studies.

Table 7: Trials Used in the Applicant's Individual Data Meta-Analysis

Study (enrollment)	Population	Design Induction therapy	GO Dose	Endpoint primary (secondary)	Sample size (GO/no GO)	Cutoff Date for Analysis (median follow-up[a])
ALFA-0701 (2008-2010)	Patients aged 50 to 70 years with untreated de novo AML	Phase 3, 2-arm, randomized, open-label GO + DA (3+7)	3 mg/m^2 D 1,4, 7	EFS (CR, CRp, RFS, OS, toxicity)	271 (135/136)	April 2013 (45.4 months)
S0106 (2004-2009)	Adult patients <56 years old with untreated de novo AML	Phase 3, 2-arm, randomized, open-label GO + DA (3+7) + growth factor	6 mg/m^2 D 4	DFS, CRR (CRi, PR, RD, OS, RFS, toxicity)	595 (295/300)	June 2015 (66.2 months)
AML15 (2002-2006)	Adult patients <60 years old with untreated de novo or secondary AML	Phase 3, 6-arm, randomized, open-label GO + DA or ADE or FLAG-Ida	3 mg/m^2 D 1	OS, CRR (RD, RFS, CIR, CIDCR, toxicity)	1099 (548/551)	August 2015 (110.5 months)
AML16 (2006-2010)	Adult patients >60 years old with untreated de novo or secondary AML, or high risk MDS	Phase 3, 4-arm, randomized, open-label GO + DA or DClo	3 mg/m^2 D 1	OS (CR, CRi, RFS, RR, DCR1, toxicity)	1115 (559/556)	August 2015 (69.1 months)
AML2006IR (2007-2010)	Patients aged 18 to 60 years with untreated de novo AML	Phase 3, 2-arm, randomized, open-label GO + DA (3+7)	6 mg/m^2 D 4	EFS (OS, CIR, CIDND, CR, toxicity)	251 (126/125)	June 2015 (66.2 months)

Source: Applicant IPD Meta-Analysis Report, Tables 1 and 6

Abbreviations: ADE=daunorubicin, cytarabine, and etoposide, ALFA=Acute Leukemia French Association, AML=acute myeloid leukemia, CIDCR=Cumulative incidence of death in first remission, CIDND=Cumulative incidence of death not attributable to disease, CIR=Cumulative incidence of relapse, CR=Complete remission, CRi=CR with incomplete blood count recovery, CRp=CR with incomplete platelet recovery, CRR=Complete remission rate, D=Day, DA=Daunorubicin plus cytarabine, DClo= Daunorubicin plus clofarabine, DCR1=Death in first CR, DFS=disease-free survival, EFS=event-free survival, FLAG-Ida=fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin, GO= Gemtuzumab ozogamicin, MDS=myelodysplastic syndromes, No GO=chemotherapy alone treatment arms, OS=overall survival, PR=Partial remission, RD=Resistant disease, RFS=Relapse-free survival, RR=Relapse rate.

[a] Calculated by reverse Kaplan-Meier method

5. MYLOTARG COMBINATION THERAPY - EFFICACY

5.1 Trial ALFA-0701 Efficacy Results

The primary endpoint for trial ALFA-0701 was event-free survival (EFS). Pre-specified secondary endpoints included overall survival (OS), relapse-free survival (RFS), and response rate of true complete remission (true CR) or complete remission with incomplete platelet recovery (CRp). 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. The trial had 271 patients signed a consent and randomized. Efficacy analyses were performed in those patients.

The cut-off date for EFS and RFS analyses was 01 August 2011. For the primary OS analysis, the cutoff date was 30 April 2013, in order 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.

5.1.1 Results of Event-Free Survival

EFS was defined as the time from the date of randomization to the date of induction failure, relapse, or death due to any cause. For the primary analysis, the date of induction failure was defined to be the date of evaluation of bone marrow response after the last induction cycle if a response (true 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.

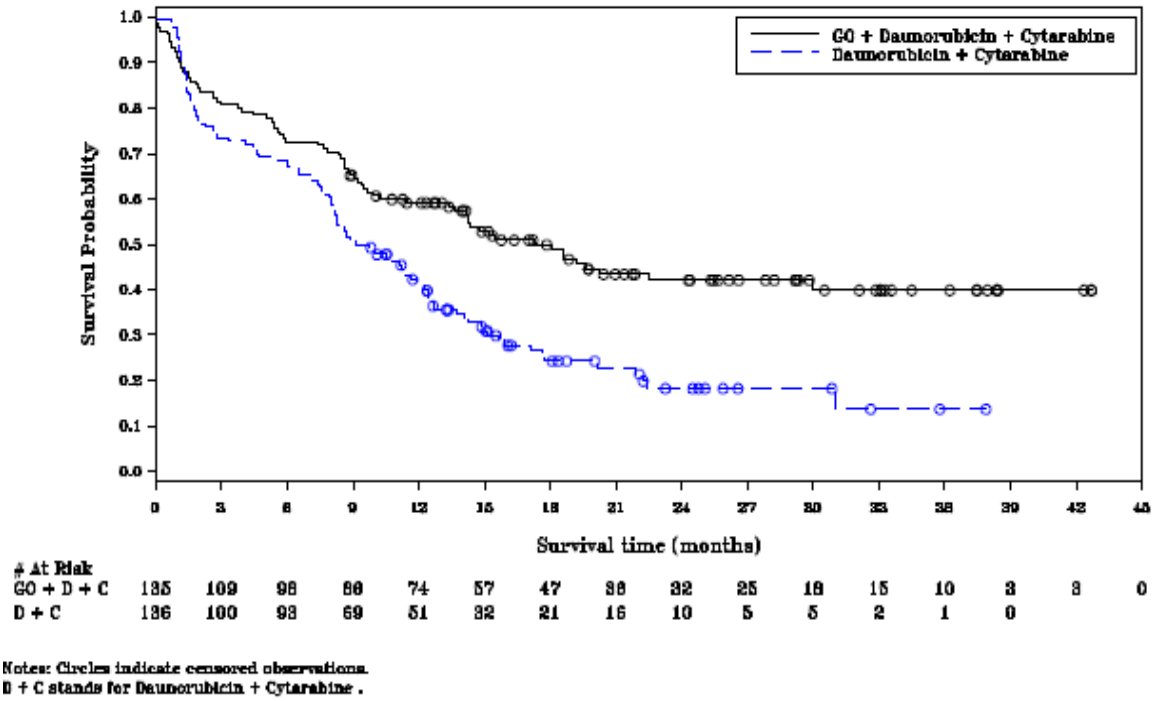
The primary analysis results are shown in Table 8 and Figure 4. The difference in 3-year EFS rate was 26.2%, and the difference in median EFS was 7.8 months favoring the GO+DA arm. Twenty-one percent more censoring occurred in the GO+DA arm, all censored because of event-free at data cut-off. EFS was not censored for occurrence of transplants in the primary analysis.

Table 8: Event-free Survival by Investigator

	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.

Figure 4: Kaplan-Meier Plot of Event-free Survival by Investigator Assessment



Notes: Circles indicate censored observations.
D + C stands for Daunorubicin + Cytarabine .

Table 9 summarizes results of applicant's sensitivity analyses by alternative EFS definitions. 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 independent reviews. 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 9: Event-free Survival Sensitivity Analyses by Alternative Definitions

	Hazard ratio[a]	95% CI of hazard ratio
Primary: investigator, IF date=date of post-induction assessment	0.56	[0.42, 0.76]
Alt 1: investigator, IF date=date of randomization	0.56	[0.41, 0.75]
Alt 2: investigator, HSCT censored	0.59	[0.43, 0.81]
Alt 3: investigator, IF date=randomization, HSCT censored	0.58	[0.43, 0.80]
Alt 4: investigator, salvage therapy classified as an IF event	0.60	[0.45, 0.81]
Alt 5: investigator, events of relapse and death only	0.60	[0.44, 0.81]
Alt 6: IRC, IF date=date of post-induction assessment	0.66	[0.49, 0.89]
Alt 7: IRC, HSCT censored	0.71	[0.52, 0.96]

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

Note that EFS Alt 5 in Table 9 only counts relapse and death as events. Without counting not achieving CR as an event, this endpoint appears in harmony with the endpoint of PFS (time to objective tumor progression or death) in other diseases.

5.1.2 Results of Overall Survival

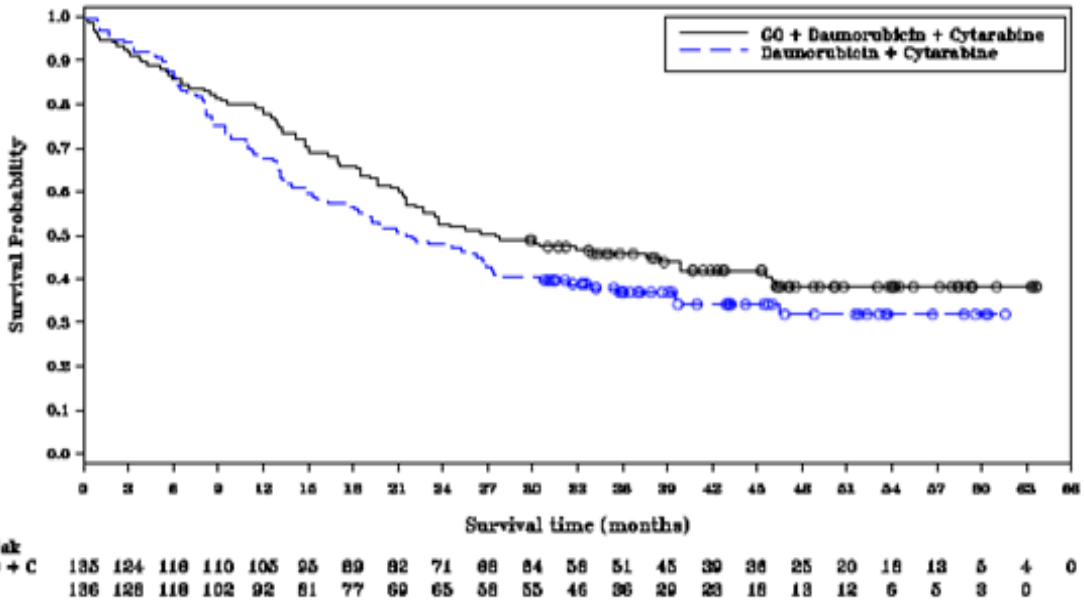
OS was defined as time from the date of randomization to the date of death due to any cause. The primary analysis of OS was based on 168 deaths occurred prior to the survival final analysis data cut-off date of 30 April 2013. The result did not reach statistical significance at a level of 2-sided p-value of 0.05. There were 5 percent fewer deaths reported in the GO+DA arm compared to the DA arm. The difference between treatment arms in median OS was 5.7 months.

Table 10: 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.

Figure 5: Kaplan-Meier Plot of Overall Survival



Notes: Circles indicate censored observations.
D + C stands for Daunorubicin + Cytarabine.

5.1.3 Results of Relapse-Free Survival and Response Rate

Investigators determined that a majority of patients in both treatment arms achieved a response of CR or CRp following induction (81.5% versus 73.5% for GO+DA versus DA, p=0.146). The true CR rate was very similar in the treatment arms (70.4% versus 69.9% for GO+DA versus DA, p=1.000). RFS derived from investigator assessment was longer for patients in the GO+DA arm, with a median RFS estimated at 28.0 months for the GO+DA arm versus 11.4 months for the DA arm (HR=0.53, p=0.001). The p-values for these analyses were not adjusted for multiplicity.

5.1.4 Subgroup Results of Event-Free Survival and Overall Survival

Results of subgroup analyses for EFS and OS by age, sex, and baseline characteristics are shown in Table 11. In general, the results in subgroups were comparable with the overall result, except for the subgroup of patients with unfavorable cytogenetic risk at baseline.

Table 11: 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]
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]
CD33 expression					
<30%	37	17	20	0.52 [0.24, 1.15]	0.87 [0.39, 1.95]
>=30%	157	83	74	0.55 [0.37, 0.83]	0.77 [0.52, 1.15]
Cytogenetics					
Favorable/Intermediate	189	94	95	0.46 [0.31, 0.68]	0.75 [0.51, 1.09]
unfavorable	57	27	30	1.11 [0.63, 1.95]	1.55 [0.88, 2.75]
Risk per NCCN					
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]

Table 11: Event-free Survival and Overall Survival by Subgroups

Subgroup	N			EFS HR [95% CI]	OS HR [95% CI]
	Total	GO+DA	DA		
FLT3 ITD					
Positive	32	16	16	0.33 [0.13, 0.83]	0.40 [0.16, 1.00]
Negative	107	56	51	0.51 [0.30, 0.87]	0.93 [0.54, 1.60]
NPM1					
Positive	68	35	33	0.39 [0.20, 0.74]	0.56 [0.28, 1.10]
Negative	70	37	33	0.58 [0.30, 1.12]	1.05 [0.54, 2.02]

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, NCCN=National Comprehensive Cancer Network, FLT3_ITD=internal tandem duplication of the FMS-like tyrosine kinase 3 gene, NPM1=nucleophosmin-1 gene, CI=confidence interval, L=liter

5.2 EFS as a Surrogate Endpoint of OS

5.2.1 Applicant Analyses

The primary endpoint of trial ALFA-0701 was EFS instead of OS. In order to establish EFS as a surrogate endpoint for OS, the applicant performed individual patient data as well as aggregate data meta-analyses to support the surrogacy of EFS for OS based on correlation between these two endpoints.

The applicant's individual patient data meta-analysis used data from 5 clinical trials, and the aggregate data meta-analysis used summary data from 33 publications, in patients with untreated AML. The 5 individual trials are summarized in Appendix 1. In the individual patient data meta-analysis, EFS was defined as time from randomization to induction failure, relapse, or death due to any cause. Induction failure was defined as failure to achieve a CR (including true CR, CRp, or CR with incomplete blood count recovery [CRi]) within 60 days of randomization. For patients with induction failure, the date of induction failure was the randomization date. In the aggregate data meta-analysis, EFS was defined according to the source publication. OS was defined as time from randomization to death due to any cause.

The definition of EFS in the individual patient data meta-analysis was different from the one used in trial ALFA-0701 EFS primary analysis, in which the determination of induction failure was not limited to the first 60 days from randomization and the date of induction failure was the date of post-induction assessment.

Correlation between EFS and OS was estimated on an individual level by Kendall's tau rank correlation coefficient as the degree of concordance between rankings of individual EFS and OS values, and on a trial level by R^2 from linear regressions of treatment effects on EFS and OS as assessed in terms of hazard ratios. For individual data meta-analysis, the applicant applied bivariate copulas including Hougaard, Clayton, and Plackett copulas (Hougaard, 1986; Clayton, 1978; and Plackett, 1965) to simultaneously model the individual distributions and treatment

effects. For aggregate data meta-analysis, because individual data were not available, Kendall's tau at individual level was not estimated.

Table 12 shows the estimated correlation between EFS and OS from the individual data and aggregate data meta-analyses. Among the estimates from application of copulas, Table 12 shows only the estimates by Hougaard copula, as the estimates by other two copulas were similar. These estimates did not suggest a strong correlation between EFS and OS. In addition, the confidence interval for R-square covering the whole range of R-square from 0 to 1 indicated lack of precision in the estimation of R-square from only 5 trials in the fitting of regressions.

Table 12: Estimated Individual Level and Trial Level Correlations between EFS and OS

Data	Correlation parameter	Estimate	[95% CI]
Individual data (5 trials)	Kendall tau	0.51	[0.39, 0.63]
	By Hougaard copula	0.48	[0.47, 0.50]
	R-square, un-weighted	0.70	[0.35, 1.00]
	By Hougaard copula	0.62	[0.09, 1.14]
	R-square, weighted*	0.61	[0.20, 1.00]
	By Hougaard copula	0.45	[0.00, 1.00]
Aggregate data (33 trials)	R-square, un-weighted	0.45	[0.21, 0.68]
	R-square, weighted*	0.46	[0.23, 0.70]

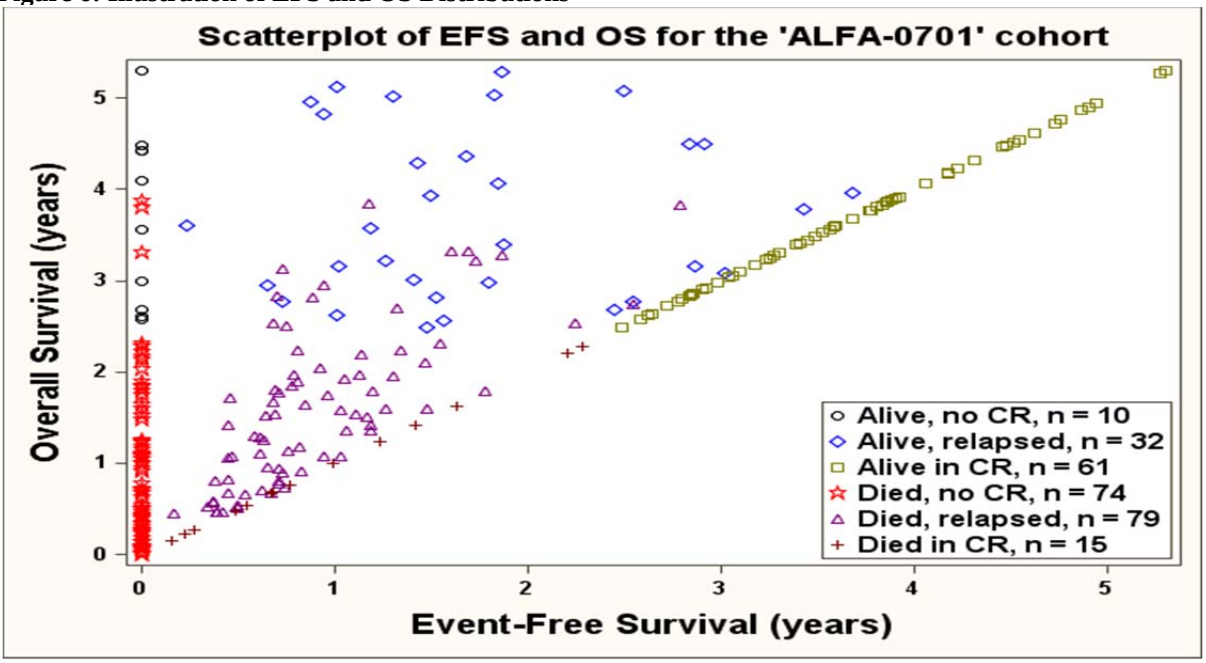
* Estimated from linear regression weighted by trial sample size; CI=confidence interval

5.2.2 FDA Assessment

The Agency currently does not have a statistical guideline on surrogate endpoint validation. In recent practice, correlation-based approaches are primarily applied for statistical validation. The validation would be required at both the individual level and at the trial level, because a valid surrogate endpoint should correlate with the clinically-significant endpoint in individual patients, and the treatment impact on surrogate endpoint should correlate with treatment impact on the clinically-significant endpoint. There is no consensus of which R-square values are sufficient to assume adequate surrogacy, but values of between 0.85 and 0.95 are often discussed (Sargent et al., 2005; Michiels et al., 2009; Oba et al., 2013; Mauguen et al., 2013). A threshold for individual level correlation has not been proposed, but a Kendall's tau of 0.75 or greater is usually indicated as a strong correlation in common practices.

The applicant's meta-analyses suggested at best a moderate correlation between EFS and OS. The moderate correlation was expected as a result of EFS not being predicative of OS; particularly, in patients who did not achieve a CR. As illustrated by the scatter plot of EFS versus OS for the pivotal trial ALFA-0701 in Figure 6, EFS and OS were the same in patients who either died in CR or were still alive in CR; EFS was not totally predictive of OS in patients who achieved a CR but had relapsed; and EFS was totally un-predictive of OS in patients who did not achieve a CR because EFS was the same for this group of patients but OS ranged over several years. The phenomenon was also observed in the other 4 trials, as shown in Appendix 2.

Figure 6: Illustration of EFS and OS Distributions



It is possible that the wide range of survival in patients who had an induction failure or relapse may reflect the effect from a salvage therapy, including a hematopoietic stem cell transplant (HSCT). There was a high proportion of patients without achieving a CR or relapsed from CR in each of the 5 trials. The individual trial summary (Table 13) suggest the transplantation rate varied form one trial to another, but across all trials, the median survival was longer in patients who received HSCT versus the ones who did not.

Table 13: Individual Trial Summary on EFS and OS Events, Survival by Transplantation Status, and Individual-Level Correlation between EFS and OS

Trial	ALFA-0701		S0106		AML15		AML16		AML2006IR	
Patient N.	271		595		1099		1115		251	
Enrollment	2008-2010		2004-2009		2002-2006		2006-2010		2007-2010	
OS events	168	62.0%	305	51.3%	696	63.3%	966	86.6%	119	47.4%
EFS events	210	77.5%	406	68.2%	814	74.1%	1032	92.6%	149	59.4%
No CR	84	31.0%	192	32.3%	324	29.5%	513	46.0%	52	20.7%
Alive	10	3.7%	55	9.2%	54	4.9%	30	2.7%	12	4.8%
Died	74	27.3%	137	23.0%	270	24.6%	483	43.3%	40	15.9%
Relapsed	111	41.0%	173	29.1%	366	33.3%	447	40.1%	71	28.3%
Alive	32	11.8%	46	7.7%	64	5.8%	36	3.2%	18	7.2%
Died	79	29.2%	127	21.3%	302	27.5%	411	36.9%	53	21.1%
Not Relapsed	76	28.0%	230	38.7%	409	37.2%	155	13.9%	128	51.0%
Alive	61	22.5%	189	31.8%	285	25.9%	83	7.4%	102	40.6%
Died	15	5.5%	41	6.9%	124	11.3%	72	6.5%	26	10.4%

Trial	ALFA-0701		S0106		AML15		AML16		AML2006IR	
Survival in months	n	median	n	median	n	median	n	median	n	median
No CR	84	12.0	305	12.2	324	9.9	513	6.1	52	12.1
Received HSCT	18	20.1	60	38.2	98	22.8	48	22.7	15	63.9
No HSCT	66	8.6	245	8.5	226	4.7	465	5.2	37	9.3
Relapsed	111	23.4	173	23.9	366	26.9	447	18.7	71	23.0
Received HSCT	41	30.4	6	NR	194	42.1	68	28.3	31	28.9
No HSCT	70	20.1	167	23.8	172	15.9	379	17.1	40	20.9
Not relapsed	76	NR	230	NR	409	NR	155	NR	128	NR
Received HSCT	26	NR	7	NR	121	NR	41	22.8	87	NR
No HSCT	50	NR	223	NR	288	NR	114	NR	41	NR
Hazard ratio[1], OS	0.81		1.09		0.93		0.87		0.86	
Hazard ratio[1], EFS	0.67		0.95		0.89		0.86		0.82	
Kendall's tau[2]	0.51		0.42		0.53		0.48		0.49	

EFS=event-free survival, OS=overall survival, CR=complete remission within 60 days since treatment randomization, HSCT=hematopoietic stem cell transplant, GO=gemtuzumab ozogamicin, NR=not reached
[1] Hazard ratio for GO over No GO from Cox proportional hazards model
[2] Calculated using the cenken function from R-package NADA library

The assessment presented earlier suggests the correlation between EFS and OS was lower by the lack of predictability of survival in patients who did not achieve a CR, for whom a transplant might have been given as a salvage therapy. To evaluate the impact from considering not achieving a CR as an event and from the use of transplantations, the correlation parameters were estimated by alternative definitions of EFS (Table 14). Definition 1 is the primary definition of EFS in applicant's individual data meta-analysis, which considers not achieving a CR within 60 days of treatment as an event. Definition 2 is the primary definition of EFS in the pivotal trial, which considers not achieving a CR during induction as an event. Definition 3 is different from Definition 2 for having the date of induction failure to be the date of randomization to avoid the impact from different duration of induction treatment between individuals. Definition 4 is having EFS time censored at the time of transplantation, and Definition 5 is considering only true CR as a treatment success (i.e., CRp or CRi is considered as a treatment failure). Definition 6 is considering events of relapse or death only; not achieving a CR is not an event in this definition.

Results suggest none of the EFS definitions that consider failure to attain CR as an event are able to demonstrate both a strong correlation between individual EFS and OS times and a strong correlation between hazard ratios for treatment effects on EFS and OS. Definition 6, which considers only events of relapse or death, is the only one suggests a correlation of around 0.75 or higher on both individual level and trial level correlations.

For definitions 4 and 5, a high trial level correlation is estimated but the individual level correlation is moderate. The lower individual level correlation between EFS and OS estimated by these definitions can be explained by the fact that more EFS times have been truncated in these definitions. And the higher trial level correlation can be explained by bigger estimated hazard ratios for EFS due to the time truncations (for example, trial ALFA-0701 estimated a

hazard ratio of 0.67 for EFS under definition 1, but estimated a hazard ratio of 0.77 and 0.85 under definitions 4 and 5, respectively).

Note that the confidence intervals for R-square are wide because the estimation is based on only 5 trials. There are 33 trials used in applicant's aggregate data meta-analysis, but R-square estimates by various definitions of EFS cannot be derived from those trials without individual data. Also note that R-square estimates by application of copulas are not reported due to a concern about robustness of results (for example, the estimated R-square for EFS considering only true CR during induction is >0.8 by applications of Clayton and Plackett copulas, but is <0.5 by Hougaard copula, with a confidence interval covering 0 to 1).

It may be important to know that the EFS as defined in definition 6 is different from the relapse-free survival. It is not only calculated in patients who achieved a CR but in all patients, and it is not calculated from the time of complete remission but from the time of randomization.

Table 14: Estimates of Correlations between EFS and OS by Alternative EFS Definitions

EFS	Definition	Kendall's tau [95% CI][5]		R-square[2] [95% CI][5]	
		model free[3]	copula model[4]	not weighted[6]	weighted[6]
1	Events: induction failure (IF), relapse, or death; IF = did not achieve a CR by Day 60 IF date=date of randomization	0.51 [0.39, 0.63]	0.49 [0.47, 0.50]	0.71 [0.37, 1.05]	0.63 [0.22, 1.03]
2	Events: induction failure (IF), relapse, or death; IF = did not achieve a CR during induction IF date=date of end of induction	0.61 [0.46, 0.75]	0.72 [0.71, 0.73]	0.71 [0.37, 1.05]	0.73 [0.42, 1.05]
3	Events: induction failure (IF), relapse, or death; IF = did not achieve a CR during induction IF date=date of randomization	0.57 [0.43, 0.71]	0.55 [0.53, 0.56]	0.68 [0.32, 1.04]	0.70 [0.35, 1.05]
4	Events: induction failure (IF), relapse, or death; IF = did not achieve a CR during induction IF date=date of randomization; HSCT censored[1]	0.42 [0.32, 0.52]	0.52 [0.50, 0.54]	0.86 [0.69, 1.04]	0.82 [0.61, 1.04]
5	Events: induction failure (IF), relapse, or death; IF = did not achieve a CR during induction IF date=date of randomization; True CR only	0.53 [0.40, 0.66]	0.52 [0.50, 0.53	0.86 [0.67, 1.04]	0.90 [0.78, 1.03]
6	Events: relapse or death only	0.74 [0.56, 0.92]	0.84 [0.83, 0.85]	0.75 [0.44, 1.05]	0.78 [0.51, 1.05]

HSCT=hematopoietic stem cell transplantation, CI=confidence interval

[1] When EFS is censored at HSCT, correlation is calculated with OS censored at HSCT

[2] R-square estimated from linear regressions of hazard ratio for OS versus estimated hazard ratio for EFS, on a natural log scale, without application of copulas

[3] Kendall's tau estimated from R software NADA package, without application of copulas

[4] reported estimates are based on Hougaard copula, estimates by Clayton or Plackett copulas are similar

[5] Approximate normal CI: for Kendall's tau, calculation is based on conversion from p-value to standard error (Altman, 2011); for R-square, calculation is based on Olkin and Finn's approximation for standard error (Olkin and Finn, 1995)

[6] weighted by trial sample size

Note: there were 7 patients whose EFS was undefined by definition 2, because information on the end of induction date was not available in those patients

5.3 Meta-analysis of GO for Overall Survival

In addition to the meta-analyses for EFS as a surrogate endpoint of OS, the applicant conducted a meta-analysis to evaluate the effect of GO on overall survival when added to standard intensive first-line induction chemotherapy in adult patients with AML. The same 5 individual clinical trials, including two studies that were designed to demonstrate OS benefit as the primary objective in GO, used in the individual data meta-analysis of EFS was used for this meta-analysis of OS. The meta-analysis is retrospectively conducted, while the statistical analysis plan was submitted to the FDA and reviewed by the FDA prior to conducting the meta-analysis.

The effect of GO on overall survival was estimated using the method of Peto (Yusuf et al., 1985), which was based on quantities required for the calculation of the log-rank test. The overall treatment effect is often expressed as Peto's odds ratio, but is the same as hazard ratio stratified by trials because the log-rank test is the same as the Mantel-Haenszel test when stratified by event time (Rothman and Greenland, 1998, p. 294).

OS results for the meta-analysis and by individual trials are shown in Table 15. The meta-analysis suggested an improvement in survival from the addition of GO, with an estimated hazard ratio of 0.91 (95% CI, 0.84, 0.99) and an estimated 2.1 months increase in median survival. However, the individual trial results were not all consistent with the meta-analysis result. Although a test for heterogeneity was not statistically significant, the number of trials may be too small for making a conclusion.

Table 15: Overall Survival Result for the Meta-analysis and for the Individual Trials

Trial (enrollment)	N	Age, year	GO dose	Overall Survival				HR	[95% CI]
				Death rate (%)		Median (months)			
				GO	No-GO	GO	No-GO		
Meta-analysis	3,331	18-70	various	66.2	69.1	23.6	21.5	0.91	[0.84, 0.99]
AML 15 (2002-2006)	1,099	< 60	3 mg/m^2 D1	61.9	64.8	34.4	27.5	0.93	[0.80, 1.08]
AML 16 (2006-2010)	1,115	> 60	3 mg/m^2 D1	84.4	88.8	14.0	12.0	0.87	[0.77, 0.99]
ALFA-0701 (2008-2010)	271	50-70	3 mg/m^2 D 1, 4, 7	59.3	64.7	27.5	21.8	0.81	[0.60, 1.09]
AML2006IR (2007-2010)	251	18-60	6 mg/m^2 D 4	44.4	50.4	NR	67.4	0.86	[0.60, 1.23]
S0106 (2004-2009)	595	< 56	6 mg/m^2 D 4	52.2	30.3	43.6	61.0	1.09	[0.87, 1.36]

GO = gemtuzumab Ozogamicin, HR = hazard ratio, CI = confidence interval, N = number of patients in analysis

Subgroup analyses conducted by the applicant suggested the addition of GO may not improve overall survival in all patients. The death rate was higher in the GO group for patients aged 40-49 years compared to the No Go group (55.4% versus 48.8% for GO versus No GO, hazard ratio 1.21). For patients with adverse cytogenetic risk, the death rate was high at 90% or above, with or without the addition of GO as part of their treatment.

5.4 Summary of Efficacy Results and Issues

The results from ALFA-0701, the pivotal trial, demonstrated the superiority of GO 3mg/m^2/dose + DA versus DA in the primary analysis of EFS as well as in the sensitivity analyses using different definitions of EFS. The pivotal trial also demonstrated superiority of GO+DA over DA in RFS. However, the primary analyses of OS and CR/CRp rate, the key secondary endpoints in the pivotal trial, did not show statistical significance. In fact, the true CR rate was very similar between the treatment arms (70.4% versus 69.9% for GO+DA versus DA).

We noted that EFS is not likely a good surrogate endpoint for OS when failure to attain CR is considered as an event. A definition of EFS considering only events of relapse or death, which was used for a sensitivity analysis in the pivotal trial, was able to suggest a good correlation between EFS and OS at both individual level and trial level based on individual data from 5 randomized clinical trials in patients with previously untreated AML. The level of evidence for this observation could be strengthened if individual data from more studies were available. Although the applicant has provided information on EFS and OS from 33 studies, analyses by alternative definitions of EFS could not be performed without individual data.

We do recognize the fact that EFS is not confounded by the use of salvage therapy following induction failure, and that the correlation with OS will increase with a lower percent of induction failures.

The following are some issues identified:

- Treatment effect on OS has not been clearly established
  - OS result in the pivotal trial was not statistically significant.
  - OS meta-analysis was based on data from 5 trials. Results were not all consistent from those trials. In addition, subgroup analyses suggested the addition of GO may not be beneficial to patients of adverse cytogenetic risk or of certain age.
- EFS is a debatable surrogate for OS
  - The pivotal trial was highly positive for EFS but not for OS.
  - Correlation between EFS and OS is impacted by patients not achieving CR during induction. It is unlikely that the correlation between EFS and OS will be high enough to establish statistical validity for EFS as surrogate endpoint for OS as long as failure to attain CR is an event.

6. MYLOTARG COMBINATION THERAPY - SAFETY

The analysis of safety of GO in combination with DA utilized the data collected retrospectively for ALFA-0701 (see Section 4.1 regarding the limitations of the retrospective data collection), the applicant-submitted IPD meta-analysis (including ALFA-0701 and 4 other randomized trials of GO), and a survey of other randomized trials of GO + chemotherapy in the published literature (Appendix 4 Table 23). FDA's approach focused on early mortality, hepatotoxicity, hemorrhage and prolonged cytopenias.

6.1 ALFA-701 - Treatment-Emergent Adverse Events

Of the 271 patients randomized in ALFA-701, 268 patients proceeded to treatment. Permanent discontinuation due to any AE occurred in 27% of patients in the GO arm compared to 4% in the control arm. Of the patients discontinuing treatment, the proportion discontinuing due to AEs was higher in the GO arm (31% vs 7%). The AEs that primarily account for this difference were thrombocytopenia (15% vs 0%) and hepatobiliary disorders (6% vs <1%).

Some patients randomized to the GO arm did not receive GO during induction, consolidation 1 or consolidation 2. Of the 35 patients who discontinued GO due to an adverse event, 14 patients continued treatment with DA. Twelve discontinued GO due to thrombocytopenia, and two discontinued GO due to Grade 2-3 hepatotoxicity (laboratory abnormalities only). Table 16 shows the numbers of patients by randomized arm and as-treated by phase of the regimen ("As-Treated" indicates received GO). The FDA analysis of common treatment-emergent adverse events was based on the as-treated population. Table 22 in Appendix 3 lists all AEs reported for the entire study period according to treatment during induction.

Table 16: ALFA-701 - Randomized vs As-Treated Subjects

	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

Table 17 shows the adverse events reported during the induction period in decreasing order of risk difference with or without GO as treated. The adverse events occurring most commonly with GO were due to bleeding. VOD was also greater in the GO + DA group (3% vs 0).

Table 17: ALFA-701 - Adverse Events in Induction

	GO + DA (N = 131)		DA (N = 137)		
Preferred Term	**Number of patients**	**Proportion (%)**	**Number of patients**	**Proportion (%)**	**Risk Difference**
Epistaxis	62	47	43	31	16
Purpura	29	22	17	12	10
Blood blister	18	14	7	5	9
Mouth hemorrhage	16	12	5	4	9
Petechiae	25	19	16	12	7
Hemoptysis	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
Hematuria	19	15	13	9	5
Catheter site hematoma	10	8	4	3	5
Melena	5	4	0	0	4
Post procedural hemorrhage	8	6	4	3	3
Conjunctival hemorrhage	6	5	2	1	3
Veno-occlusive liver disease	4	3	0	0	3

Source: FDA analysis

Table 18 shows the adverse events reported during the first consolidation period in decreasing order of risk difference with or without GO as treated. The adverse events occurring most commonly with GO were due to bleeding or infection. The trends were similar for adverse events during the second consolidation period (data not shown).

Table 18: ALFA-701 - Adverse Events in Consolidation 1

	GO + DA (N = 91)		DA (N = 103)		
Preferred Term	**Number of patients**	**Proportion (%)**	**Number of patients**	**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 bacteremia	4	4	0	0	4
Hematuria	4	4	1	1	3
Mouth hemorrhage	4	4	1	1	3
Pneumonia	3	3	0	0	3
Hematoma	7	8	5	5	3

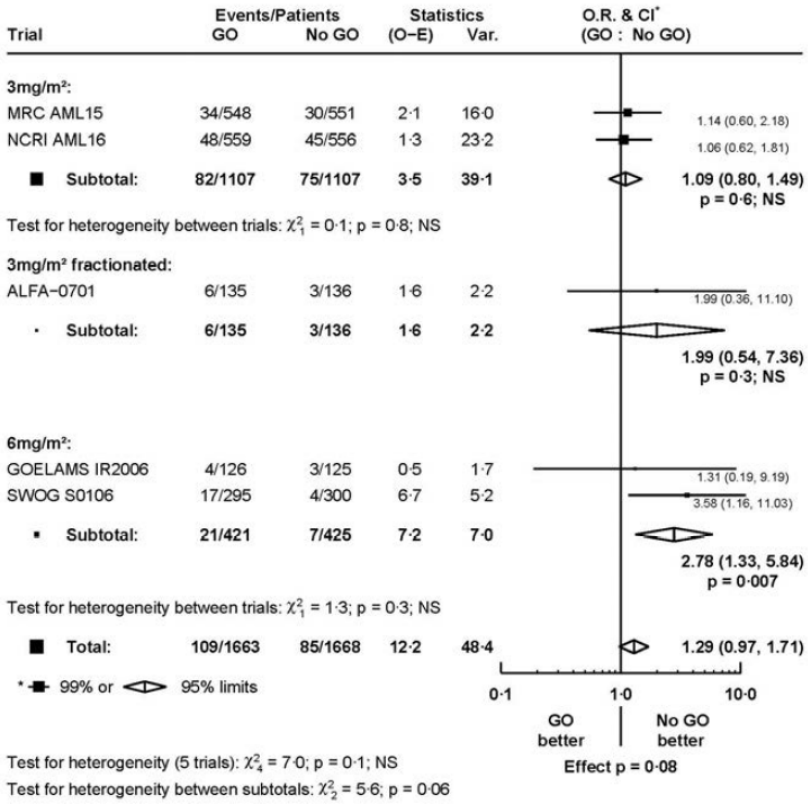
Source: FDA analysis

6.2 Early Mortality

Death by day 30 of induction was reported for 5 (3.8%) patients treated with GO + DA vs 3 (2.2%) of those who received DA alone. Four patients treated with GO had treatment-related deaths in the 30-day window (3 cases of hemorrhage and 1 fatal VOD) compared to one patient on DA (sepsis while in bone marrow aplasia following second induction).

The applicant also provided an analysis of early mortality in the randomized population for ALFA-701 and for all trials in the IPD meta-analysis. In ALFA-701, 30-day mortality was similar between the two treatment arms with 5 (3.8%) patients in the GO + DA arm and 3 (2.2%) patients in the DA arm dying within 30 days of the first study treatment. There was no apparent correlation between age and 30-day mortality, but the range of ages of subject in ALFA-701 was limited by the eligibility criteria. Figure 7 shows the 30-day mortality by trial in the IPD meta-analysis. FDA observed that there was a trend for reduction in the imbalance in early mortality with a decrease in dose of GO. This trend persisted when results from published data was considered as well (Appendix 5 Figure 11).

Figure 7: IPD Meta-Analysis - 30-Day Mortality



Source: Applicant's Summary of Clinical Safety Figure 2

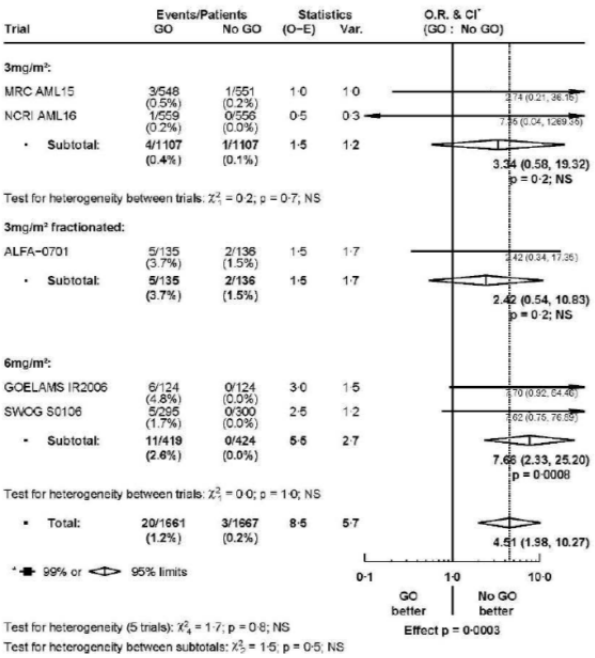
6.3 Hepatotoxicity and VOD

Eight patients in ALFA-0701 developed VOD. Six were randomized to the GO + DA arm; three cases were fatal and two were determined to be treatment-related. The remaining 2 patients were randomized to the DA arm but received GO treatment after relapse and subsequently developed VOD. Seven of the 8 patients developed VOD without HSCT, and one developed VOD 25 days after HSCT.

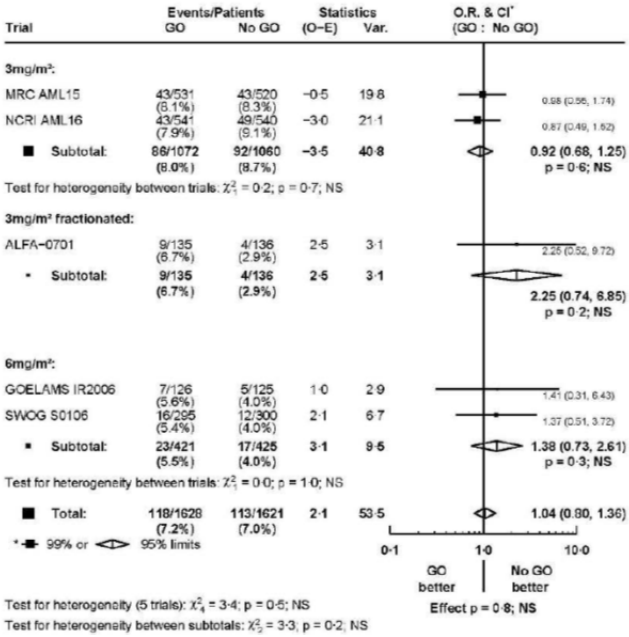
Figure 8 shows VOD and hepatotoxicity by trial in the IPD meta-analysis. FDA observed that there was a trend for reduction in the imbalance in VOD with a decrease in dose of GO. This trend persisted when results from published data was considered as well (Appendix 5 Figure 12). A similar trend was seen for grade 3-4 elevations of bilirubin (Figure 8b) and AST (Figure 8c) during induction, but less so for ALT (Figure 8d) during induction.

Figure 8: IPD Meta-Analysis - VOD and Hepatotoxicity

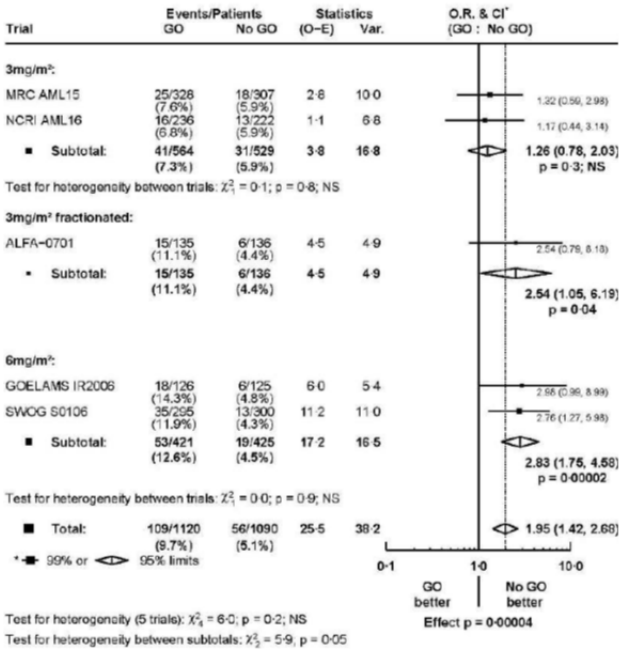
(a) VOD (All safety period; all sources)



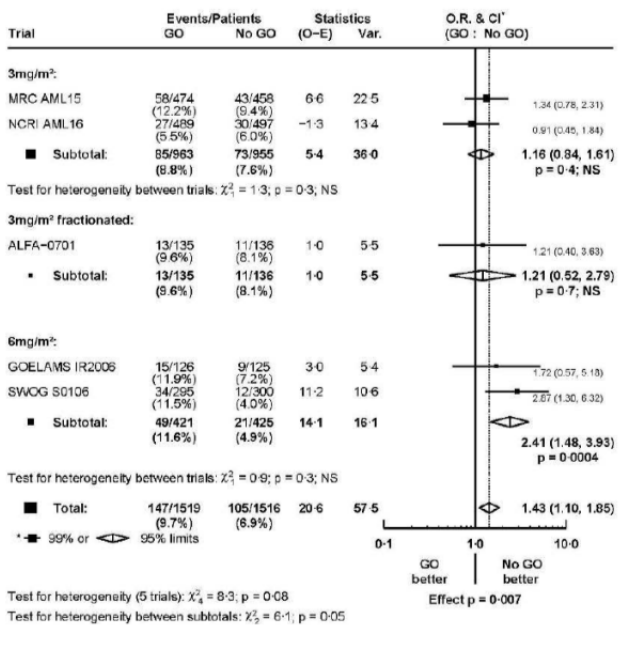
(b) Grade 3-4 bilirubin elevations (Induction)



(c) Grade 3-4 AST elevations (Induction)



(c) Grade 3-4 ALT elevations (Induction)



Source: Applicant's IPD meta-analysis report Figures 343, 420, 447 and 474.

6.4 Hemorrhage

Overall and during each phase of treatment, the incidence of hemorrhage events was greater for those patients treated with GO + DA than with DA alone as treated in ALFA-701 (Table 19). Grade ≥ 3 hemorrhage also occurred more frequently in patients treated with GO (23% vs 7% in Induction 1, 13% vs 2% in Consolidation 1, and 6% vs <1% in consolidation 2). Fatal treatment-related hemorrhage was reported for four patients on GO + DA vs none on DA alone.

Table 19: ALFA-701 - Hemorrhage Events[a]

	DA + GO		DA	
Phase of Regimen	**Number of patients**	**Proportion (%)**	**Number of patients**	**Proportion (%)**
Induction	114 / 131	87	97 / 137	71
Consolidation 1	55 / 91	60	35 / 103	26
Consolidation 2	40 / 64	63	46 / 107	43
Any Phases	119 / 131	91	107 / 137	78

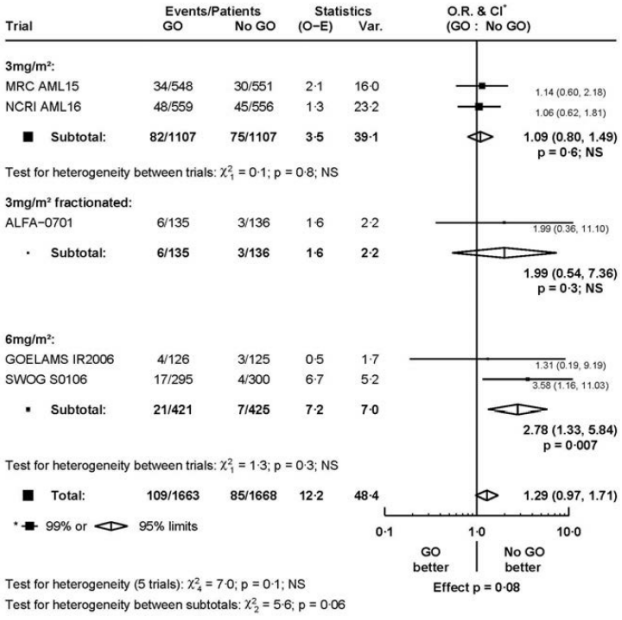
Source: FDA analysis
[a] Based on SMQ Hemorrhages (excluding laboratory terms)

Figure 9 shows Grade 3-4 hemorrhage by trial in the IPD meta-analysis. FDA observed that there was a trend for reduction in the imbalance in hemorrhage during induction with a decrease

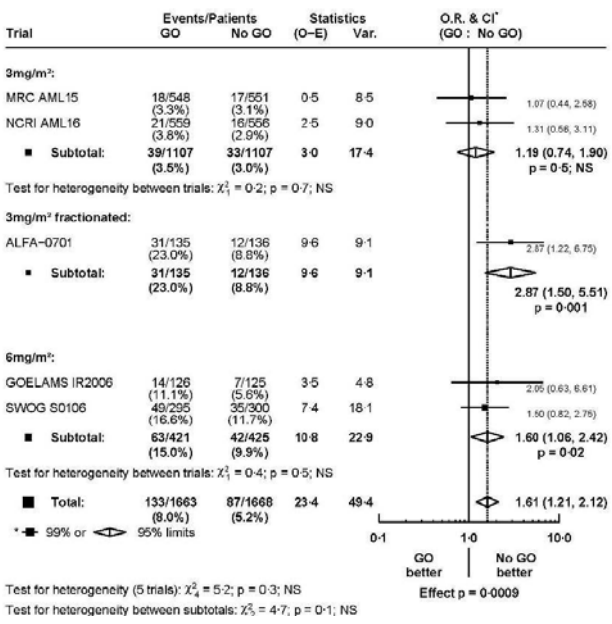
in dose of GO, but the correlation was less so for the entire safety period. This trend for increasing hemorrhage events with increasing GO dose was also seen when results from published data was considered as well (Appendix 5 Figure 13).

Figure 9: IPD Meta-Analysis - Grade 3-4 Hemorrhage

(a) Induction; all sources



b) All-safety period; all sources



Source: Applicant's IPD meta-analysis report Figures 181 and 183

6.5 Prolonged Cytopenias

Overall and during each phase of treatment, the time to recovery of platelet counts was greater for those patients on GO + DA arm vs DA as treated in ALFA-701 (Table 20); however, the time to recovery of neutrophil counts was similar in both groups.

Table 20: ALFA-701 - Time to Hematopoietic Recovery

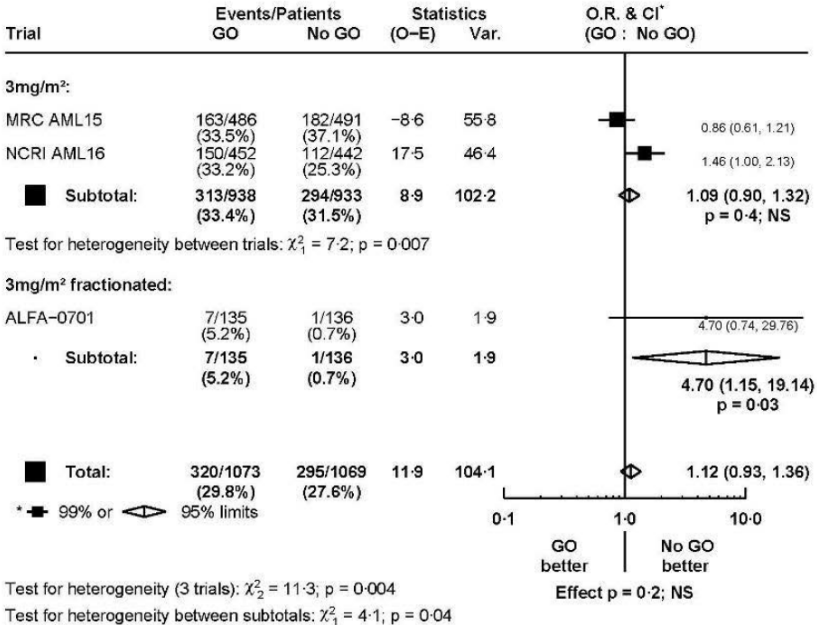
	Median Time to			
	ANC > 0.5 Gi/L	**ANC > 1.0 Gi/L**	**PLT >50 Gi/L**	**PLT > 100 Gi/L**
Induction				
GO + DA	24 days	25 days	33 days	34 days
DA	23 days	25 days	29 days	29 days
Consolidation 1				
GO + DA	21 days	24 days	32 days	34 days
DA	22 days	24 days	26 days	27 days
Consolidation 2				
GO + DA	22 days	27 days	37 days	42 days
DA	23 days	26 days	30 days	34 days

Source: FDA analysis
Abbreviations: ANC, absolute neutrophil count; PLT, platelet count

The protocol defined the event "Persistent Thrombocytopenia" in patients experiencing CR/CRp whose platelets were < 50 Gi/L at 45 days after Day 1 of the treatment phase. In the GO + DA arm, 20% of patients met this definition of persistent thrombocytopenia compared to 2% in the DA arm.

Figure 10 shows persistent Grade 3-4 thrombocytopenia by trial in the IPD meta-analysis. FDA observed that there was a trend for reduction in the imbalance in thrombocytopenia during induction with a decrease in dose of GO.

Figure 10: IPD Meta-Analysis - Persistent Grade 3-4 Thrombocytopenia



Source: Applicant's IPD meta-analysis report Figure 690

6.6 Summary of Safety Results and Issues

- The safety analysis is limited by the retrospective nature of the collection of adverse events.
- The adverse event terms reported in ALFA-701 that occurred most commonly (≥10%) in patients treated with GO + DA were epistaxis, thrombocytopenia, purpura, hematoma, device related infection, petechiae, blood blister, catheter site hemorrhage, hematuria, gingival bleeding, mouth hemorrhage, hemoptysis, bronchopulmonary aspergillosis, device related sepsis, bacterial sepsis and septic shock.
- The adverse events that occurred more frequently with GO + DA vs DA in ALFA-0701 were due to bleeding or infection, and differences in the adverse event rates occurred during each phase of treatment (induction, consolidation 1 and consolidation 2).

- Overall, 30-day mortality is not significantly different between the GO + DA arm vs the DA arm (3.8% vs 2.2%) in ALFA-701. The disparity in 30-day mortality in ALFA-701 is lower than that reported for S0106 (5.8% vs 1.3%), suggesting that the fractionated lower dose of GO is safer.
- VOD occurred was reported for 6 (4.6%) patients treated with GO in the main part of ALFA-701, and 2 additional patients from the DA arm developed VOD after receiving GO as treatment for relapse.
- In ALFA-701, hemorrhage events occurred more frequently with GO + DA than with DA during induction (87% vs 71%), consolidation 1 (60% vs 26%) and consolidation 2 (63% vs 43%).
- Platelet recovery appeared to be delayed in patients on ALFA-701 treated with GO + DA vs DA alone. A delay in recovery to later than day 45 was reported for 20% of patients on GO + DA vs 2% on DA alone. GO did not appear to impact time to recovery of neutrophils.
- The IPD meta-analysis showed a trend for lesser disparity in 30-day mortality, VOD, Grade 3-4 hemorrhage, and persistent Grade 3-4 thrombocytopenia with decreasing GO dose. The lowest risks appeared to occur with trials combining only a single dose of GO 3 mg/m^2 with chemotherapy.
- The additional data from the published literature was consistent with the clinical trial safety findings.
- The mechanism of prolonged thrombocytopenia is unclear.

7. CONCLUSIONS

The Applicant proposes to recommend GO 3 mg/m^2 days 1, 4 and 7 in combination with DA as first line treatment of patients with CD33-positive AML. FDA's exposure-response analysis of monotherapy data suggested that a lower Cmax would be associated with less risk of VOD, but there are no PK data for the proposed fractionated GO regimen specifically. Nonetheless, in cross-study analysis of clinical outcomes for patients with RR AML treated with single-agent GO, in comparison to the regimens using GO 6 or 9 mg/m^2 x 1- 2 doses 14 days apart, patients treated with GO 3 mg/m^2 days 1, 4 and 7 had less early mortality, less hepatotoxicity, less VOD, more rapid platelet recovery and less hemorrhage without an apparent decrease in the CR rate.

In ALFA-701, a randomized comparison of DA with or without GO 3 mg/m^2 days 1, 4 and 7, FDA's review showed that the addition of GO results in more bleeding and infection events, and there was a delay in platelet recovery, but there was no difference between the study arms for early mortality. The results of the IPD meta-analysis of safety outcomes across 5 randomized trials of various doses of GO in combination with induction chemotherapy were consistent with the expectation that the lower GO dose of 3 mg/m^2 days 1, 4 and 7 had less toxicity than GO 6 mg/m^2 day 4 as was used in S0106 previously. VOD, however, still occurred and was reported for 4.6% of patients treated with GO in ALFA-701. Consequently, although the proposed

regimen has less toxicity, whether the safety profile is acceptable remains a concern for discussion.

With regard to efficacy, ALFA-701 demonstrated a treatment effect of GO by EFS (HR 0.56; 95% CI 0.42, 0.76), but no statistically significant impact on OS. FDA generally requires for approval that a new drug for first-line treatment of AML with curative intent demonstrates a survival benefit. Moreover, the applicant's surrogacy analysis failed to provide strong evidence that EFS is a surrogate of OS for patients being treated for AML. 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. FDA therefore seeks ODAC's advice on alternative approaches to assess surrogacy when such confounding factors are present. FDA is also open to hearing ODAC's opinion on whether EFS itself, as a measure of CR with durability, is an alternative to OS as a clinical benefit.

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9. APPENDICES

Appendix 1. Clinical Studies of GO Monotherapy

Table 21: Clinical Studies of GO Monotherapy

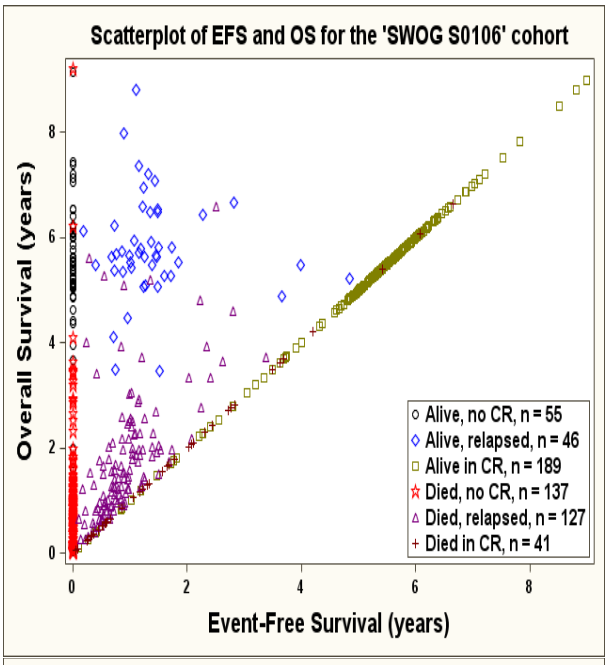
Study/Reference	Design	Population	Primary Endpoint(s)
Unfractionated			
Study 201	Single-arm, open-label Phase 2 trial • GO 9 mg/m^2 x 2-3, 14-28d apart	Adults with CD33+ AML in first relapse after CR ≥ 6 months - 84 patients	CR rate
Study 202	Single-arm, open-label Phase 2 trial • GO 9 mg/m^2 x 2-3, 14-28d apart	Adults with CD33+ AML in first relapse after CR ≥ 6 months - 95 patients	CR rate
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

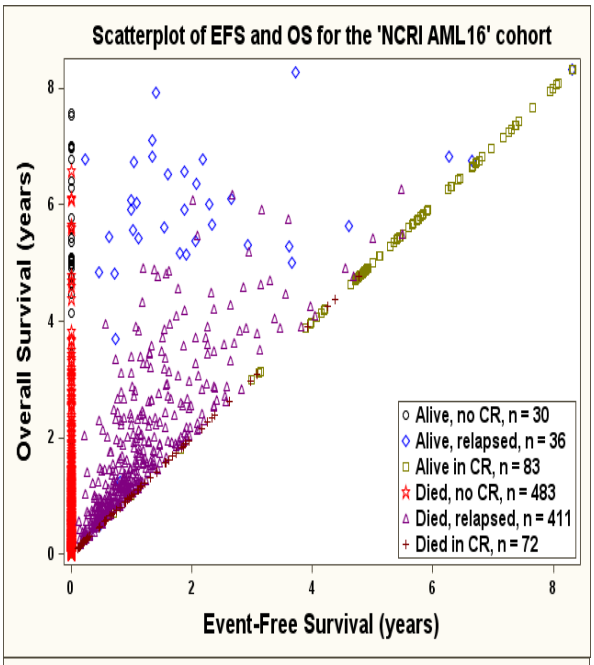
Table 21: Clinical Studies of GO Monotherapy

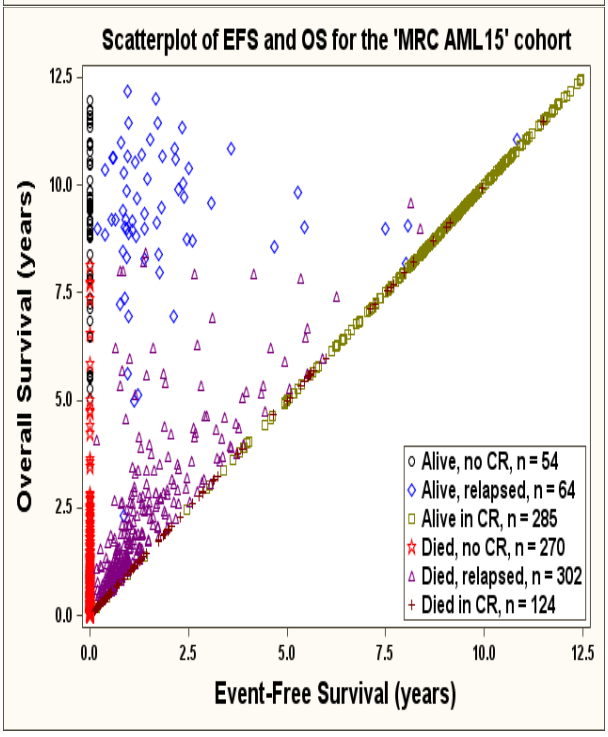
Study/Reference	Design	Population	Primary Endpoint(s)
Piccaluga 2004	Prospective, single-arm, open-label trial • GO 9 mg/m^2 x 2-3 q14-28d (n=16) or • GO 6 mg/m^2 x 2-3, q14-28d (n=7) or • GO 1.5 mg/m^2 x 2-3, q14-28d (n=1)	Adults with CD33+ R/R AML - 24 patients	CR+CRp rate
van der Heiden 2006	Retrospective, 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			
Taksin 2007	Single-arm, open-label Phase 2 trial • Induction: GO 3 mg/m^2 d 1, 4, 7 • Consolidation: cytarabine 3 g/m^2 q12h d1-3 (1 g/m^2 patients >55 y or CrCl >50 mL/min)	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

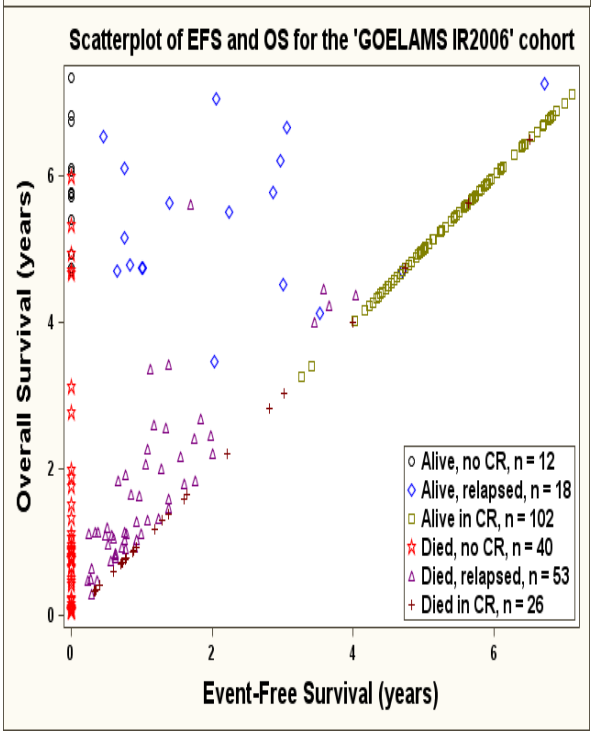
Source: FDA analysis
Abbreviations: AML, acute myeloid leukemia; CD, cluster of differentiation; CR, complete remission; CrCl, creatinine clearance; CRp, complete remission with incomplete platelet recovery; d, days; GO, gemtuzumab ozogamicin; h, hours; HSCT, hematopoietic stem cell transplantation; R/R, relapsed and/or refractory. CML-BC, chronic myeloid leukemia in blast crisis; RAEB-T, refractory anemia with excess blasts in transformation; d, days

Appendix 2. Scatter Plots of EFS versus OS - Individual Historical Trials









Appendix 3. ALFA-701 Common Adverse Events

Table 22: ALFA-701 - Common Adverse Events

	DA + GO (N = 131)		DA (N = 137)	
PT	**Number of patients**	**Proportion (%)**	**Number of patients**	**Proportion (%)**
Epistaxis	82	63	50	37
Thrombocytopenia	37	28	6	4
Purpura	35	27	20	15
Haematoma	33	25	24	18
Device related infection	32	24	33	24
Petechiae	30	23	23	17
Blood blister	29	22	11	8
Catheter site haemorrhage	29	22	28	20
Haematuria	25	19	14	10
Gingival bleeding	23	18	12	9
Mouth haemorrhage	21	16	6	4
Haemoptysis	19	15	13	9
Bronchopulmonary aspergillosis	14	11	11	8
Device related sepsis	14	11	15	11
Bacterial sepsis	13	10	4	3
Septic shock	13	10	12	9
Febrile bone marrow aplasia	12	9	8	6
Conjunctival haemorrhage	11	8	3	2
Catheter site haematoma	11	8	7	5
Sepsis	10	8	7	5
Staphylococcal sepsis	10	8	16	12
Post procedural haemorrhage	9	7	4	3
Streptococcal sepsis	9	7	4	3
Rectal haemorrhage	9	7	9	7
Melaena	7	5	0	0
Haematemesis	7	5	3	2
Puncture site haemorrhage	7	5	3	2
Escherichia sepsis	7	5	5	4
Pneumonia	7	5	7	5
Venoocclusive liver disease	6	5	0	0
Enterococcal sepsis	6	5	1	1
Acute kidney injury	6	5	4	3
Escherichia bacteraemia	6	5	4	3
Haemorrhage	6	5	6	4
Haematochezia	6	5	8	6

Source: FDA analysis

Appendix 4. Randomized Clinical Studies of GO Combinations

Table 23: Efficacy Results from Randomized Trials of GO in Combination with Chemotherapy

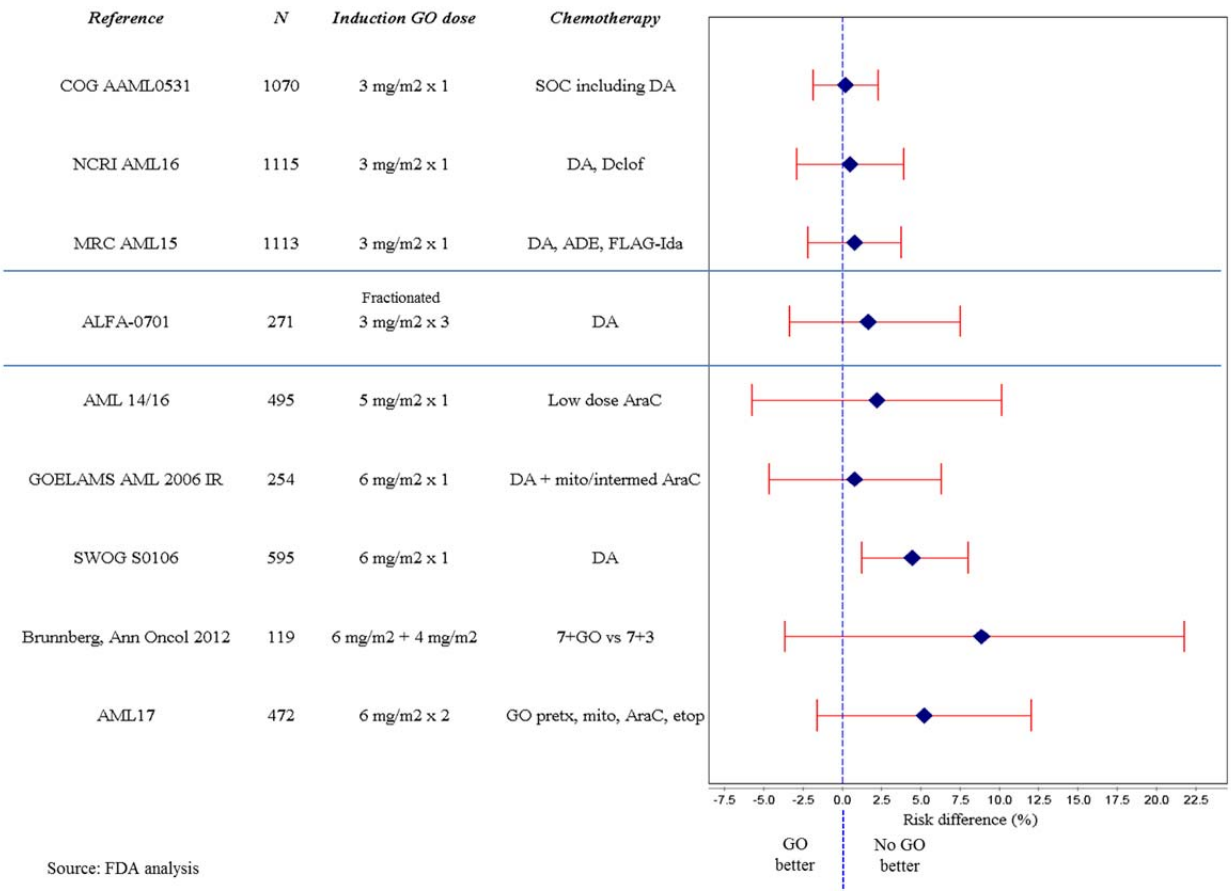
Study	# of patients	Median age (range)	Induction GO dose	Combined drugs	CR (%) GO vs No GO OR, 95% CI	EFS/RFS (%) GO vs No GO HR, 95% CI	OS (%) GO vs No GO HR, 95% CI
***MRC AML15**	1113	49 (0-71)	3mg/m² x 1 (d1)	DA, ADE, FLAG-Ida	82 vs 83 1.04 (0.76, 1.42) p = 0.8	5y RFS 39 vs 35 0.87 (0.73-1.02) p = 0.09	5y OS 43 vs 41 0.92 (0.79-1.08) p = 0.3
NCRI AML16	1115	67 (51-84)	3mg/m² 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, et al 2014: COG AAML0531	1070	9.7 (3mo-29.8y)	3mg/m² 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)	3mg/m² 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, et al 2013: AML14/16	495	75 (54-90)	5mg/m² 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)	6mg/m² 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)	6mg/m² 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, et al 2012	1019	68 (60-83)	6mg/m² (d1), 4mg/m² (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, et al 2013: AML17	472	67 (61-75)	6mg/m² x 2 (d1, 15)	GO pretx, mito, AraC, etop	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 ALFA-0701 CSR, IPD Meta-Analysis Report, FDA literature analysis

*SWOG S0106 – 14% of patients in control arm randomized to GO maintenance, AML15 – 20% of patients in control arm randomized to GO consolidation

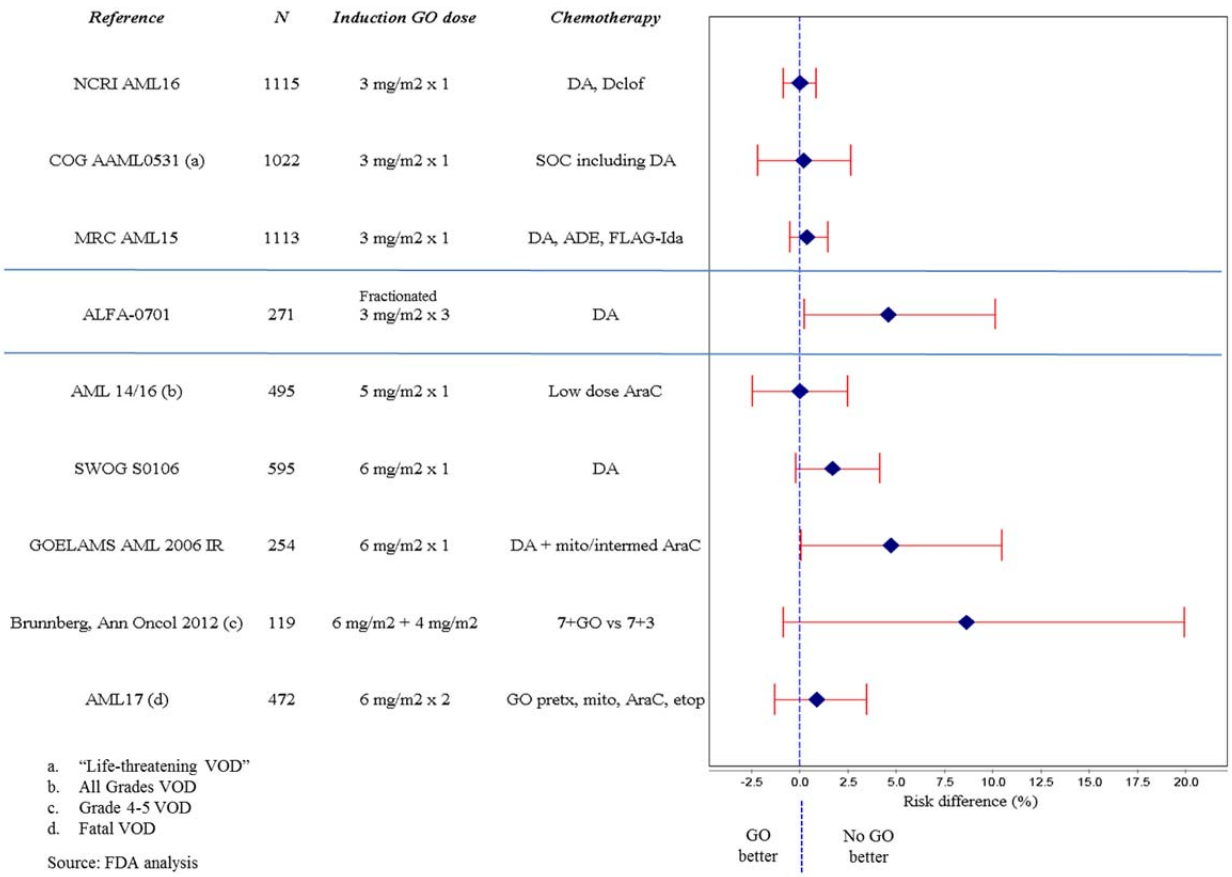
Appendix 5. Safety Outcome Forest Plots

Figure 11: GO Combination Therapy - Early Mortality



Source: FDA analysis

Figure 12: GO Combination Therapy - VOD

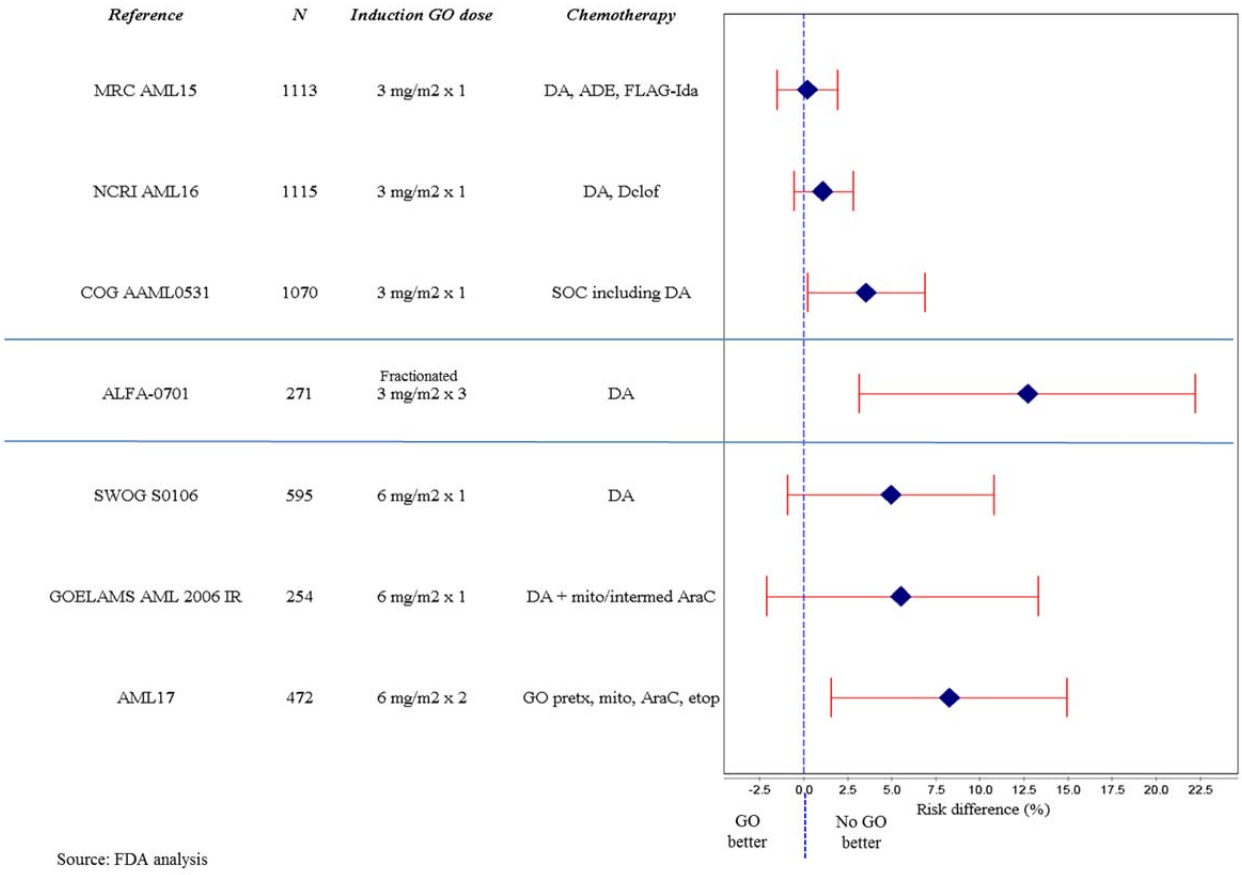


a. "Life-threatening VOD"
b. All Grades VOD
c. Grade 4-5 VOD
d. Fatal VOD

Source: FDA analysis

Source: FDA analysis

Figure 13: GO Combination Therapy - Grade 3-4 Hemorrhage



Source: FDA analysis