**WYETH PHARMACEUTICALS INC., A SUBSIDIARY OF PFIZER INC**

# MYLOTARG® (gemtuzumab ozogamicin; PF-05208747)

**In combination with chemotherapy for the treatment of previously untreated de novo CD33-positive acute myeloid leukemia and as monotherapy for the treatment of CD33-positive acute myeloid leukemia in first relapse**

## FDA ONCOLOGIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

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# 1. EXECUTIVE SUMMARY

## 1.1. Introduction

Mylotarg (gemtuzumab ozogamicin [GO]) is an antibody-drug conjugate (ADC) composed of the cluster of differentiation (CD)33-directed monoclonal antibody covalently linked to the potent cytotoxic agent N-acetyl gamma calicheamicin.

Mylotarg received accelerated approval in the United States (US) in May 2000 and approval in Japan in 2005 as monotherapy for the treatment of patients with CD33-positive acute myeloid leukemia (AML) in first relapse. A Phase 3 study (Southwest Oncology Group [SWOG] S0106) evaluating Mylotarg in combination with chemotherapy in patients with previously untreated de novo AML was subsequently conducted from 2004 to 2009 to confirm the clinical benefit of Mylotarg in order to convert the accelerated approval to full approval. However, the SWOG S0106 study did not confirm the clinical benefit of Mylotarg, and fatal induction toxicity was significantly higher in the Mylotarg arm. Therefore, Pfizer voluntarily withdrew Mylotarg from the US market in October 2010. In addition, Mylotarg was associated with hepatic veno-occlusive disease (VOD), which has substantial morbidity and mortality. Nevertheless, Mylotarg has continued to be marketed for the treatment of patients with relapsed or refractory CD33-positive AML in Japan, hematologists have been requesting compassionate-use Mylotarg for their AML patients, and investigators have continued to evaluate Mylotarg in patients with AML.

The Mylotarg Biologics License Application (BLA) reflects the unique composition of the Mylotarg program. This BLA includes Pfizer-sponsored clinical studies from the initial New Drug Application (NDA), recent cooperative group studies designed and conducted by AML experts, an Individual Patient Data meta-analysis (MA) of 5 Phase 3 studies, and findings from exposure-response modeling.

Based on the availability of an expanded package of clinical data, Pfizer is currently seeking approval for Mylotarg for a new indication:

- In combination with standard chemotherapy for the treatment of previously untreated de novo CD33-positive AML:
  - For induction: The recommended dose of Mylotarg is 3 mg/m² (up to a maximum of 5 mg per dose), infused over a 2-hour period on Days 1, 4, and 7 in combination with daunorubicin (DNR) 60 mg/m²/day infused over 30 minutes on Days 1, 2, and 3 and cytarabine (AraC) 200 mg/m²/day by continuous infusion on Days 1 to 7.
  - For consolidation: For patients experiencing a complete remission (CR) following induction, defined as fewer than 5% blasts in a normocellular marrow and an absolute neutrophil count (ANC) of more than $1.0 \times 10^9$ cells/L with a platelet count of $100 \times 10^9$/L or more in the peripheral blood in the absence of transfusion, up to 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 1-4) with intravenous Mylotarg (3 mg/m$^2$/dose

infused over 2 hours up to a maximum dose of 5 mg/dose on Day 1) are recommended.

Pfizer is also seeking approval to re-introduce Mylotarg for the indication:

- As monotherapy for the treatment of CD33-positive AML patients in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy:
  - Using a Mylotarg dosing regimen of 9 mg/m² on Days 1 and 15 for patients without a prior hematopoietic stem cell transplant (HSCT) and who are not candidates for HSCT, or
  - Using a fractionated Mylotarg dosing regimen of 3 mg/m$^2$ on Days 1, 4, and 7 for patients who have received or may receive HSCT.

This briefing document presents a summary of the clinical data included in this BLA and provides compelling evidence to establish that Mylotarg has a favorable benefit/risk relationship for the treatment of CD33-positive AML, a serious, rapidly progressive, life-threatening disease for which there remains a high unmet medical need. As discussed with the Food and Drug Administration (FDA), the focus of this Oncologic Drugs Advisory Committee (ODAC) meeting will be on the benefit/risk assessment of Mylotarg as a treatment of patients with previously untreated de novo CD33-positive AML.

### 1.2. Rationale for Mylotarg Dosing Regimens

Initial clinical studies evaluated Mylotarg as monotherapy in patients with AML in first relapse utilizing a dosing regimen of 9 mg/m$^2$ on Days 1 and 15 (see Section 6.1.1). However, research studies suggested the possibility that lower doses might also be efficacious. These studies found that 90% saturation of CD33 on the surface of AML blasts by the anti-CD33 ADC was required for efficient killing of the blasts; that an estimated Mylotarg dose of 3 mg/m$^2$ was adequate to achieve 90% saturation, and that binding of the anti-CD33 ADC to CD33 antigen on cells resulted in internalization and re-expression of CD33, suggesting that repeated administration of Mylotarg would enhance the internalization process, increasing the intracellular accumulation of Mylotarg and its cytotoxic component. Based on this research, the Acute Leukemia French Association (ALFA) cooperative group hypothesized that lower fractionated doses of Mylotarg would be effective and better tolerated than the original 9 mg/m$^2$ x 2 dosing regimen, and conducted the Phase 2 MyloFrance 1 study to assess a regimen consisting of half the total dose of Mylotarg administered in 3 fractions (3 mg/m² on Days 1, 4, and 7) as monotherapy in adults with AML in first relapse. This study suggested that this lower dose fractionated regimen (3 doses of 3 mg/m$^2$ = 9 mg/m$^2$), delivered similar efficacy with an improved tolerability and safety profile compared to the original dosing regimen. The results of MyloFrance 1 prompted evaluation of this lower dose fractionated Mylotarg regimen in combination with chemotherapy in patients with AML in first relapse in the MyloFrance 2 study. The results of the MyloFrance 2 study led to further evaluation of this regimen of Mylotarg plus induction chemotherapy in the Phase 3 MyloFrance 3 (ALFA-0701) study in patients with previously untreated de novo AML.

Population pharmacokinetic (PK) modeling using data from the ALFA-0701 study predicted that the lower dose fractionated regimen would result in a maximum observed concentration ($C_{max}$) and a total area under the plasma concentration-time curve (AUC) for the monoclonal antibody of 24% and 25%, respectively, of the values for the original 9 mg/m$^2$ x 2 dosing regimen. Exposure-response modeling further predicted that receiving at least 2 doses of Mylotarg monotherapy would significantly increase the probability of remission compared to 1 dose, and supported the rationale for using a lower dose fractionated regimen of Mylotarg. The model also predicted that the 75% lower $C_{max}$ that would be seen with the lower dose fractionated regimen would reduce Mylotarg toxicity, resulting in a shorter duration of myelosuppression and an approximately 50% decreased risk of VOD. Thus, the model suggested that the lower dose fractionated regimen would provide similar efficacy and improve safety. The results of the MyloFrance 1 and ALFA-0701 studies, which used the lower dose fractionated regimen of Mylotarg in patients with relapsed AML and previously untreated AML, respectively, supported the predictions of the exposure-response modeling (see Section 4.2).

### 1.3. Mylotarg in Patients With Previously Untreated De Novo AML

Efficacy and safety data supporting the indication of Mylotarg in combination with standard induction chemotherapy for patients with previously untreated de novo AML are derived from the randomized Phase 3 ALFA-0701 study and an Individual Patient Data MA of over 3300 patients enrolled in 5 randomized clinical studies of similar design, including the ALFA-0701 and SWOG S0106 studies. The clinical trials included in the Individual Patient Data MA were selected on the basis of pre-specified criteria (see Section 5.1.3.1). Unlike most meta-analyses, the Individual Patient Data MA compiled and analyzed data from each patient enrolled in each study, not from the aggregate results of each study, making the analyses and conclusions robust.

ALFA-0701 was a randomized, open-label, Phase 3 study that compared the efficacy of a lower dose fractionated regimen of Mylotarg plus 3+7 DNR + AraC versus 3+7 DNR + AraC alone. The primary endpoint was event-free survival (EFS) using a pre-specified definition (see Section 5.1.2). Event-free survival was chosen by the ALFA cooperative group as the primary endpoint of this study because, in AML studies, it is a direct measure of clinically important benefit on its own (see Section 5.1.2.1). Secondary endpoints included relapse-free survival (RFS), a measure of response duration, overall survival (OS), overall response rate (ORR), and safety.

The ALFA-0701 study demonstrated that the lower dose fractionated regimen of Mylotarg + Chemotherapy resulted in a statistically significant and clinically meaningful improvement in investigator-assessed EFS (median EFS of 17.3 months versus 9.5 months; p=0.0002), subsequently confirmed by blinded independent review (median EFS of 13.6 months versus 8.5 months; p=0.0059), and RFS (median RFS of 28.0 months versus 11.4 months; p=0.0006), compared to Chemotherapy Alone. The ALFA-0701 study was underpowered for evaluating improvement in OS; nonetheless, a numerically superior, though not statistically significant, improvement in OS was observed (median OS of 27.5 months versus 21.8 months; hazard ratio [HR] 0.807, p=0.1646) (see Figure 9). Overall, analyses of both EFS and RFS by baseline characteristics were consistent with the overall results. Results of

an ad hoc analysis showed that patients in the Mylotarg + Chemotherapy arm experienced significantly longer time to subsequent anti-cancer therapy administered after induction failure or relapse compared to the Chemotherapy Alone arm (median time of 21.7 months [95% CI: 15.7-35.2] in the Mylotarg + Chemotherapy arm and 12.8 months [95% CI: 11.0-16.3] in the Chemotherapy Alone arm; HR 0.669; 95% CI: 0.492-0.910; p=0.0099 by log-rank test).

In the ALFA-0701 study, an emphasis was placed on the collection of treatment-emergent adverse events of special interest (AESIs) considered most important for understanding the safety profile of Mylotarg. The treatment-emergent AESIs in ALFA-0701 consisted of hemorrhage (all National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] grades), VOD, also known as sinusoidal obstruction syndrome (SOS) (all CTCAE grades), severe infections, and any other adverse event (AE) (regardless of the nature of the event) that led to the permanent discontinuation of either Mylotarg or chemotherapy before the completion of the study treatment phase. In the Mylotarg + Chemotherapy arm, 6 (4.6%) patients developed VOD, with 2 cases of fatal VOD reported. Two patients (1.5%) in the Chemotherapy Alone arm also developed VOD after receiving Mylotarg for compassionate use following HSCT. Veno-occlusive disease is discussed further in Section 5.2.2). A total of 67.2% of patients in the Mylotarg + Chemotherapy arm experienced serious adverse events (SAEs), regardless of causality, compared to 55.5% of patients in the Chemotherapy Alone arm. Deaths during the safety reporting period (ie, from first dose to 28 days after the last dose of study treatment) were reported in 6 patients (4.6%) in the Mylotarg + Chemotherapy arm and 5 patients (3.6%) in the Chemotherapy Alone arm.

An Individual Patient Data MA, conducted utilizing data from 5 randomized clinical studies of similar design, including the ALFA-0701 and SWOG S0106 studies, compared Mylotarg + Chemotherapy versus Chemotherapy Alone in the treatment of previously untreated patients with AML. In an Individual Patient Data MA, the raw individual patient level data for each study are obtained and used for analysis. This analysis stands in contrast to a traditional meta-analysis which aggregates published data across studies. A meta-analysis conducted on individual patient level data therefore has a number of potential statistical and clinical advantages over a meta-analysis of aggregate data (see Section 5.1.3.1). The Individual Patient Data MA was performed to evaluate the effect of adding Mylotarg to induction chemotherapy. The primary endpoint for the meta-analysis was OS. The secondary efficacy endpoints were EFS, complete remission rate (CRR), RFS, and ORR.

The Individual Patient Data MA included data from a total of each of 3331 patients; 1663 patients (49.9%) randomized to Mylotarg + Chemotherapy, and 1668 patients (50.1%) randomized to Chemotherapy Alone. Data were obtained from individual investigators and institutional sponsors of the 5 trials that met the criteria for inclusion (see Section 5.1.3.1_Ref48218115). Two of the 5 studies did not meet their primary endpoints. Median follow-up using reverse censoring methods ranged from 45.4 months in the ALFA-0701 study to 110.4 months in the AML15 study.

The Individual Patient Data MA allowed an evaluation to determine if the addition of Myotarg to chemotherapy statistically improved OS, and to determine if the positive trend in

OS improvement observed with Mylotarg in the ALFA-0701 study was more than a chance finding. Mylotarg + Chemotherapy provided a statistically significant improvement in OS versus Chemotherapy Alone (Peto odds ratio [OR] 0.91, 95% CI: 0.84-0.99, p=0.02), corresponding to a 9% reduction in the risk of death in the Mylotarg + Chemotherapy arm versus the Chemotherapy Alone arm, confirming the trend seen in the ALFA-0701 study. Overall, pooled median OS was 23.62 months in the Mylotarg + Chemotherapy arm versus 21.49 months in the Chemotherapy Alone arm. Mylotarg + Chemotherapy also significantly prolonged EFS and RFS compared to Chemotherapy Alone (Peto OR for EFS 0.85, 95% CI: 0.78-0.93, p=0.0002, median EFS durations of 9.63 months versus 7.59 months, respectively; Peto OR for RFS 0.84, 95% CI: 0.77-0.93, p=0.0004, median RFS durations of 18.10 months versus 14.49 months, respectively).

In the Individual Patient Data MA, AESIs were defined as Hepatotoxicity (Grade 3/4 aspartate aminotransferase [AST] elevation, Grade 3/4 alanine aminotransferase [ALT] elevation, Grade 3/4 bilirubin elevation, and Grade 3/4 VOD); Grade 3/4 Hemorrhage; Grade 3/4 Infection; and Myelosuppression (Grade 3/4 persistent neutropenia and Grade 3/4 persistent thrombocytopenia). In the Individual Patient Data MA, 75.2% of patients in the Mylotarg + Chemotherapy arm and 71.9% of patients in the Chemotherapy Alone arm experienced a Grade 3/4 AESI. Overall, incidence of Grade 3/4 VOD was 1.1% in patients randomized to Mylotarg + Chemotherapy and 0.1% in patients randomized to Chemotherapy Alone. Serious adverse events were experienced by 32.2% of patients in the Mylotarg + Chemotherapy arm and 26.4% of patients in the Chemotherapy Alone arm. A total of 109 deaths (6.6%) occurred within 30 days after randomization in patients randomized to the Mylotarg + Chemotherapy arm and 85 deaths (5.1%) occurred within 30 days in patients randomized to the Chemotherapy Alone arm. The safety profile of Mylotarg in combination with intensive chemotherapy observed in the Individual Patient Data MA was consistent with the known safety profiles of Mylotarg and the chemotherapeutic agents used in these studies and supports the use of low-dose fractionated Mylotarg in patients with previously untreated de novo CD33-positive AML.

### 1.4. Mylotarg in Patients With AML in First Relapse

Studies 201, 202, and 203 were single-arm studies in adult patients with CD33-positive AML in first relapse that supported the original accelerated approval of Mylotarg by the FDA in May 2000. These studies shared a similar design and used an identical Mylotarg dosing regimen of 9 mg/m$^2$ on Days 1 and 15. The primary objective of these studies was to assess the efficacy (based on the number of patients achieving CR or complete remission with incomplete platelet recovery [CRp]) and safety of Mylotarg monotherapy. Overall response rate was 35%, as measured by International Working Group (IWG) criteria. During these studies, it was noted that patients receiving Mylotarg had a high incidence of myelosuppression, manifested by delayed recovery time for neutrophil and platelet counts, and over time, hepatic VOD emerged.

The MyloFrance 1 study demonstrated clinical benefit of Mylotarg monotherapy using the lower dose fractionated regimen and the MyloFrance 2 study demonstrated clinical benefit of the lower dose fractionated regimen in combination with chemotherapy in patients with AML

in first relapse. Of note, in the MyloFrance 1 study, with the lower dose fractionated Mylotarg regimen, no VOD was observed, including in 7 patients who underwent HSCT.

### 1.5. Summary

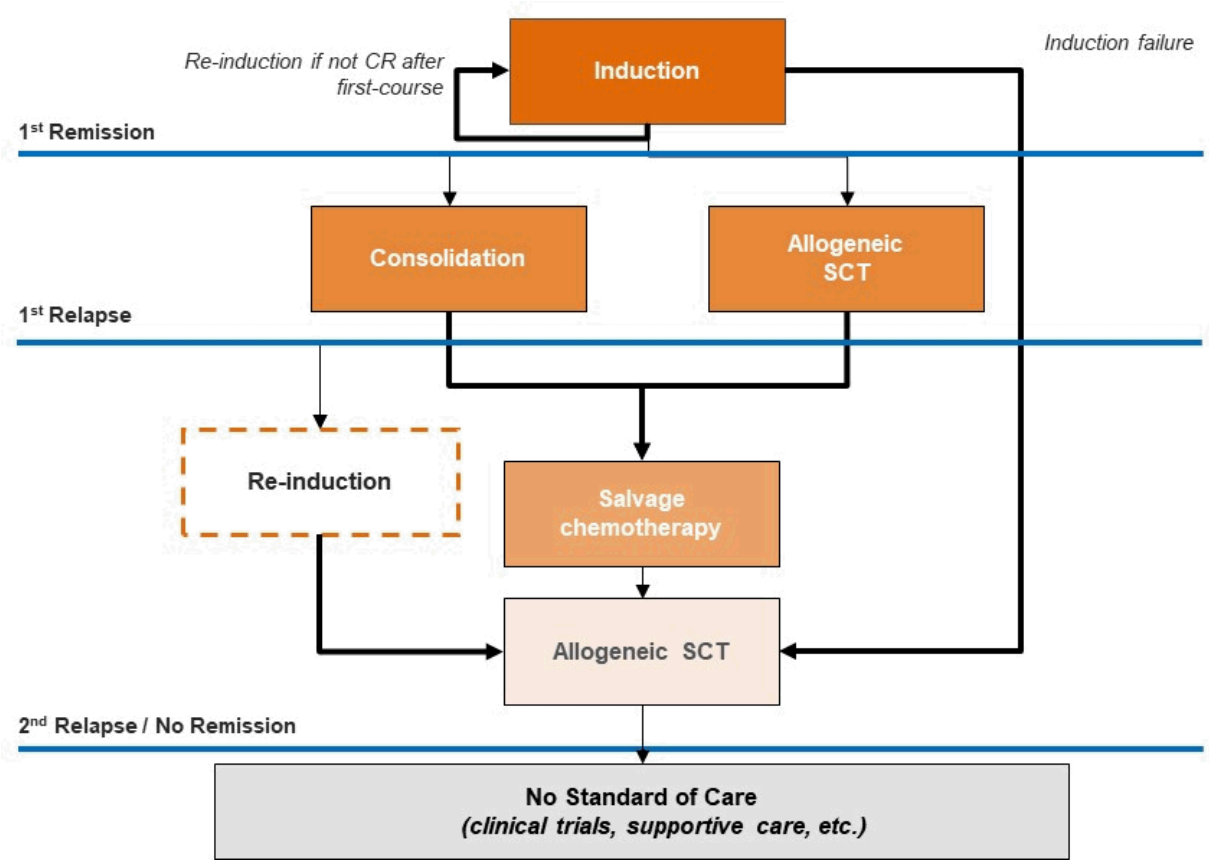
Based on an expanded package of clinical data from the original NDA, collaborations between Pfizer and AML investigators, including results of an Individual Patient Data MA, exposure-response modeling, and post-marketing experience from the US, Pfizer is submitting this BLA for consideration of full approval of Mylotarg for the treatment of patients with CD33-positive AML. The ALFA-0701 study and the Individual Patient Data MA provide data which support approval of Mylotarg for the treatment of patients with previously untreated de novo CD33-positive AML. Studies 201, 202, 203 and the MyloFrance 1 study provide data which support approval of Mylotarg for the treatment of patients with CD33-positive AML in first relapse. Collectively, the data included in the BLA indicate that Mylotarg has a favorable benefit/risk relationship for the treatment of patients with CD33-positive AML. The totality of evidence presents a compelling case for approval of Mylotarg for the treatment of patients with previously untreated de novo disease and of patients with CD33-positive AML in first relapse.

## 2. BACKGROUND AND TREATMENT LANDSCAPE

Acute myeloid leukemia is a serious, rapidly progressive, and life-threatening hematologic malignancy characterized by the clonal expansion of myeloblasts in the bone marrow, peripheral blood and other tissues. It is the most common acute leukemia in adults. In the United States (US), it is estimated that 21,380 people will be diagnosed with acute myeloid leukemia (AML) in 2017, and 10,590 will die from their disease.[1] The incidence of AML increases with age to 15-25 cases per 100,000 persons annually in individuals who are 70 years or older.[2] AML is a heterogeneous disease, with classification based on morphologic, cytogenetic, molecular, and immunophenotypic features, that along with baseline patient characteristics such as age and performance status (PS), influence outcomes and treatment recommendations.[3] Patients with the disease require attentive supportive care to treat conditions such as myelosuppression (thrombocytopenia, neutropenia, and/or anemia) that result both from the underlying leukemia and from adverse effects associated with chemotherapy.

While a complete remission (CR) can be expected in 60% to 85% of younger adults and 40% to 60% of older adults (defined as >60 years of age) with previously untreated AML, only 35% to 40% of patients ≤ 60 years of age and 5% to 15% of patients >60 years of age are cured, due to factors such as poor PS, various comorbidities, and treatment resistance.[4] Once remission is achieved, consolidation therapy is an important step in achieving a durable response. Options include additional intensive chemotherapy and non-intensive and low-dose chemotherapy regimens (monotherapy or combination). Hematopoietic stem cell transplant also remains an important modality for the prevention of relapse. Treatment of AML is thus comprised of induction chemotherapy and consolidation or post-remission therapy[4] (Figure 1).

**Figure 1. Schematic of Intensive AML Treatment**




Abbreviations: CR=complete remission; m=months; SCT=stem cell transplant.

With the exception of acute promyelocytic leukemia (APL), treatment regimens for AML have changed little in the last 40 years, with limited success in the clinical development of new treatment options.

For patients with previously untreated de novo AML, the initial intensive treatment is based on a backbone of cytarabine (AraC) plus an anthracycline, most commonly daunorubicin (DNR).[5] Complete remission rates for patients who are 50 years or younger treated with this regimen have consistently been in the range of 60% to 70% in most large cooperative group studies.[6, 7] However, patients >60 years of age with AML may have co-existing conditions that make it difficult for them to tolerate or make them ineligible for intensive therapy.[4] The induction death rate in AML patients is approximately 5%-7%.[8, 9, 10]

In patients with relapsed/refractory AML, a recent randomized controlled trial documented the poor outcomes and extremely short OS of approximately 3.5 months, confirming the dismal prognosis of these patients, regardless of treatment, and underscoring the fact that there is no effective standard of care for this disease.[11] Challenges in treating patients with relapsed AML include accurate assessment of the likelihood of achieving CR, selection of the salvage therapy that is most likely to be tolerated and succeed, and identification of patients for whom hematopoietic stem cell transplant (HSCT) is a viable option.[12] Currently, no curative therapy other than HSCT exists for patients with relapsed AML.

Thus, there is an urgent need for additional therapeutic options to treat broad populations of patients (as opposed to therapeutic options limited to subgroups based on molecular cytogenetics) with both previously untreated de novo and AML in first relapse. Newer agents are restricted to small subgroups of AML patients. One agent, midostaurin, an FMS-like tyrosine kinase 3 gene (FLT3) inhibitor, which targets the 30% to 40% of AML patients with FLT3 mutations, has recently been approved by the Food and Drug Administration (FDA) in combination with DNR + AraC for treatment of newly diagnosed AML that is FLT3 mutation-positive.[13] In contrast to midostaurin, Mylotarg targets the (cluster of differentiation) CD33 myeloid differentiation antigen which is expressed on the leukemic blasts of 85% to 90% of patients with AML.[14] Mylotarg therefore has the potential to benefit a wider proportion of patients with AML, including those whose tumors do not harbor FLT3 mutations.

**Outcome Measures in AML**

The efficacy of AML treatments is measured in clinical studies by multiple parameters, including EFS, OS, RFS, disease-free survival (DFS), and ORR (including CR and CRp):

- Event-free survival (EFS) is defined as the time from date of randomization to the date of an event of induction failure, relapse, or death from any cause, whichever came first.
- Overall survival (OS) is defined as time from randomization to death from any cause.
- Relapse-free survival (RFS) is defined as the time from CR or CRp to relapse or death from any cause.
- Disease-free survival (DFS) is defined as the time from CR until relapse or death from any cause.
- Overall response rate (ORR) is defined as rate of CR + rate of CRp.
    - Complete remission (CR), defined as <5% AML blasts in normocellular marrow and >1000 neutrophils/µL and >100,000 platelets/µL in peripheral blood,[15] following treatment, is a recognized important clinical endpoint and is the first step in controlling the disease.
    - Complete remission with incomplete platelet recovery (CRp) allows patients to undergo HSCT while in remission, thus realizing better outcomes than patients who undergo HSCT after induction failure or while in disease relapse.[16, 17] CRp following treatment is associated with better prognosis than no remission (NR).[18, 19]

Hematologists consider that EFS assesses the benefit of AML therapy before the potentially confounding effect of subsequent therapies and so may provide a direct assessment of the clinical benefit of a therapy given during induction.[20, 21] The use of EFS as a primary endpoint for AML treatment efficacy is discussed in Section 5.1.2.1.

Analyses suggested that in ALFA-0701, there is a moderate positive correlation between EFS and OS. The observed level of correlation between EFS and OS is similar in magnitude to those of other published AML investigations.[20, 21, 22, 23] The correlation between EFS and OS,

including potential confounders which may decrease the correlation, is discussed in Section 5.1.4.

## 2.1. Regulatory History

Mylotarg has a unique regulatory history in that it has been previously approved by the FDA and subsequently voluntarily withdrawn from the market by the sponsor. Mylotarg was initially developed by Wyeth Pharmaceuticals Inc., now a subsidiary of Pfizer Inc. After the New Drug Application (NDA) review which included Oncologic Drugs Advisory Committee (ODAC) consultation, FDA granted Mylotarg accelerated approval in May 2000 as monotherapy 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 other cytotoxic chemotherapy.

In order to confirm the clinical benefit of Mylotarg and convert accelerated approval to full approval in the US, a post-approval clinical study (the S0106 study) was conducted by SWOG.[10] This study, initiated in August 2004, was a randomized 2-arm Phase 3 clinical study that evaluated the combination of Mylotarg (single unfractionated dose of 6 mg/m$^2$) and DNR (at a reduced dose of 45 mg/m²) plus AraC compared with DNR (60 mg/m²) plus AraC alone as induction and post-consolidation therapy in adult patients 18 to 60 years of age with previously untreated AML. The primary endpoints were CR rate and post-consolidation DFS. Following a pre-planned futility analysis showing that Mylotarg was unlikely to meet its primary endpoints, the study was closed to enrollment in August 2009. At the time enrollment was discontinued, 637 of the planned 684 patients had been enrolled (see Section 5.1.1). In addition, a US post-marketing registry Study 100847 (N = 482), conducted to primarily estimate the rate of veno-occlusive disease (VOD) and to identify risk factors for VOD, identified a final 9.1% incidence rate of VOD. Of the 143 patients in the study population who ever had a HSCT, 14.0% had VOD, compared with 7.2% in the 333 patients who were documented as never having undergone HSCT.

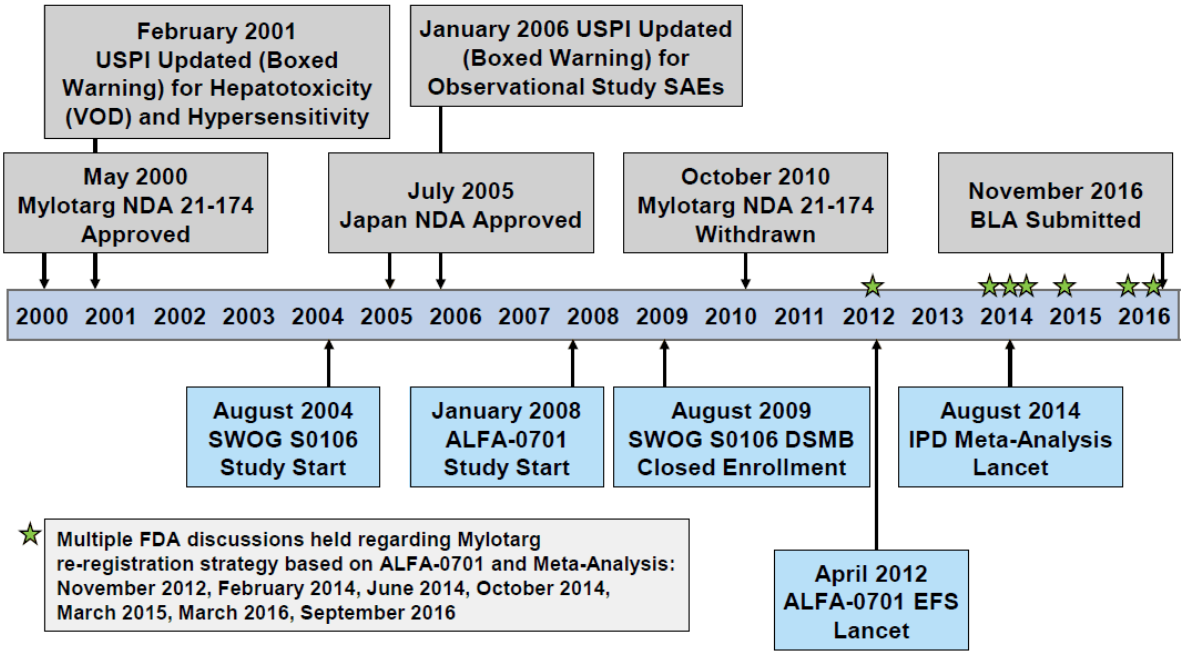
Following consultation with the FDA, on 25 October 2010, Pfizer voluntarily withdrew Mylotarg from the US market due to failure of this agreed-upon confirmatory trial.[24]

Mylotarg was approved in Japan on 25 July 2005 and continues to be used there for the treatment of patients with relapsed or refractory CD33-positive AML. At the time of the US NDA withdrawal, post-approval surveillance data from Japan were reviewed, and the clinical benefit/risk assessment was considered unchanged for patients in Japan eligible to receive Mylotarg. Approval was retained in Japan by conducting measures to ensure compliance with approved dosage and administration.

Pfizer has consulted with the FDA over the last 4 years in order to assemble an appropriate Biologics License Application (BLA) submission to enable the re-registration of Mylotarg. As part of this consultation, the FDA requested Pfizer to open an intermediate-size Expanded Access Protocol to help manage the multiple single-patient Investigational New Drug application requests.

Key regulatory and clinical milestones for Mylotarg are presented in Figure 2.

**Figure 2. Regulatory Timeline**




Abbreviations: ALFA=Acute Leukemia French Association; BLA=Biologics License Application; DSMB=Data Safety Monitoring Board; FDA=Food and Drug Administration; IPD=Individual Patient Data; NDA=New Drug Application; OS=overall survival; SAE=serious adverse event; SWOG=Southwest Oncology Group; USPI=United States Package Insert; VOD=veno-occlusive disease.

## 2.2. Mylotarg Clinical Trial Experience

Mylotarg has been evaluated in 19 completed clinical studies which are included in the current BLA (see Appendix 10.2).

In addition, there is also 1 ongoing Pfizer-sponsored study in the US which is not included in the BLA. The study is an Expanded Access Protocol B1761026 which was initiated in December 2014 and was designed to provide compassionate access to Mylotarg patients who have exhausted all other therapeutic options. As of 25 May 2017, Study B1761026 had enrolled 245 patients.

Efficacy and safety data supporting the indication of Mylotarg in combination with conventional induction chemotherapy for patients with previously untreated de novo CD33-positive AML are derived from the randomized Phase 3 ALFA-0701 study and an Individual Patient Data MA of over 3300 patients enrolled in 5 randomized clinical studies of similar design including ALFA-0701 and SWOG S0106 (Table 1). The clinical trials included in the Individual Patient Data MA were selected on the basis of pre-specified criteria (see Section 5.1.3.1).

**Table 1. Mylotarg Clinical Trial Experience in Previously Untreated AML**

| Study Name | Patient Population | Mylotarg Dosing | N |
|---|---|---|---|
| **Primary Study for BLA Submission** | | | |
| ALFA-0701 | 50-70 years | 3 mg/m$^2$ x 3 | 271 |
| **Supportive Studies** | | | |
| SWOG S0106 | 18-60 years | 6 mg/m$^2$ x 1 | 595 |
| MRC AML15 | <60 years | 3 mg/m$^2$ x 1 | 1099 |
| NCRI AML16 | >60 years | 3 mg/m$^2$ x 1 | 1115 |
| GOELAMS AML2006IR | ≤ 60 years | 6 mg/m$^2$ x 1 | 251 |

Abbreviations: ALFA=Acute Leukemia French Association; AML=acute myeloid leukemia; BLA=Biologics License Application; GOELAMS=Groupe Ouest Est d'Etude des Leucémies aiguës et Autres Maladies du Sang; MRC=Medical Research Council; N=number of patients; NCRI=National Cancer Research Institute; SWOG=Southwest Oncology Group.

Ten clinical studies provided efficacy and safety data using Mylotarg as monotherapy for patients with AML in first relapse: 3 Phase 2 studies (Studies 201, 202, and 203) that comprise the primary source of efficacy data, 7 supportive studies (Studies 101, 102, 103, 100374, 100863, and MyloFrance 1), including 1 observational study (100847) which provided supportive safety data (Appendix 10.3).

## 3. CLINICAL PHARMACOLOGY OF MYLOTARG

Mylotarg is an antibody-drug conjugate (ADC), composed of the antibody covalently linked to the potent cytotoxic agent N-acetyl gamma calicheamicin. The antibody targets the myeloid differentiation antigen CD33.

CD33 has been explored as an important therapeutic antigen in AML for over 25 years.[25, 26] Notably, CD33 is expressed on the leukemic blasts of a majority (85% to 90%) of patients with AML.[14] CD33 is a myeloid differentiation antigen which is highly expressed on normal multipotent myeloid precursors, unipotent colony-forming cells, and maturing granulocytes and monocytes. CD33 is not expressed on pluripotent hematopoietic stem cells.[27] It is internalized when bound by bivalent antibodies, rendering it an attractive antigen for therapeutic targeting of AML blasts.

The pharmacokinetic (PK) characteristics of Mylotarg are well established. Mylotarg is administered by intravenous (IV) infusion. When Mylotarg was administered using the original dosing regimen (9 mg/m$^2$ x 2 doses, 14 days apart), the observed mean maximum serum concentration ($C_{max}$) of the antibody following the first dose was 3.0 mg/L; $C_{max}$ increased to 3.6 mg/L after the second dose. The terminal phase half-life ($t_{1/2}$) for the antibody was 62 hours after the first dose and 90 hours after the second dose. The principal route of elimination of the antibody from plasma is hypothesized to be via the binding of the antibody to CD33 on CD33-bearing cells, followed by internalization into cells and subsequent intracellular breakdown. The observed differences in PK parameters following the first and second doses, respectively, support this hypothesis as the clearance of the antibody decreased following the second dose, consistent with a decrease in the number of circulating CD33-bearing cells. Pharmacokinetic data for Mylotarg following administration

using the lower dose fractionated regimen (3 mg/m$^2$ x 3) were not available, so modeling was used to simulate the PK data for this regimen (see Section 4.1).

### 3.1. Dose/Pharmacodynamic Relationships

In vitro data indicate that at least 90% of CD33 saturation is required for efficient killing of AML blasts.[28] The initial dose-escalation Study 101 (N = 40) in relapsed AML evaluated the pharmacodynamics (PD) (CD33 site saturation) of Mylotarg over a dose range of 0.25 to 9 mg/m$^2$. Based on these results, a dose of 3 mg/m$^2$ is estimated to produce 90% to 95% saturation of CD33.

## 4. PHARMACOKINETIC AND EXPOSURE-RESPONSE MODELING

### 4.1. Pharmacokinetic Modeling

Population PK modeling was used to simulate PK for patients with previously untreated de novo AML in the ALFA-0701 study, as PK data were not available for patients participating in that study. While the total dose of the lower fractionated regimen (3 doses of 3 mg/m$^2$ = 9 mg/m$^2$) used in ALFA-0701 was half that of the original dosing regimen (2 doses of 9 mg/m$^2$ = 18 mg/m$^2$) used in Studies 201/202/203, the PK model predicted that the $C_{max}$ and the area under the plasma concentration-time curve (AUC) for the antibody over the course of treatment using the lower dose fractionated regimen would be 24% and 25%, respectively, of the values for the original 9 mg/m$^2$ x 2 dosing regimen.

Plasma concentrations of the unconjugated cytotoxic agent, calicheamicin, were very low following dosing with Mylotarg, with an observed mean $C_{max}$ value of 5.8 ng/mL for the original 9 mg/m$^2$ x 2 dosing regimen. The observed low levels of calicheamicin in vivo are consistent with the demonstrated stability of Mylotarg. Levels of free calicheamicin in the drug product are maintained at ≤ 1 µg/mg protein.

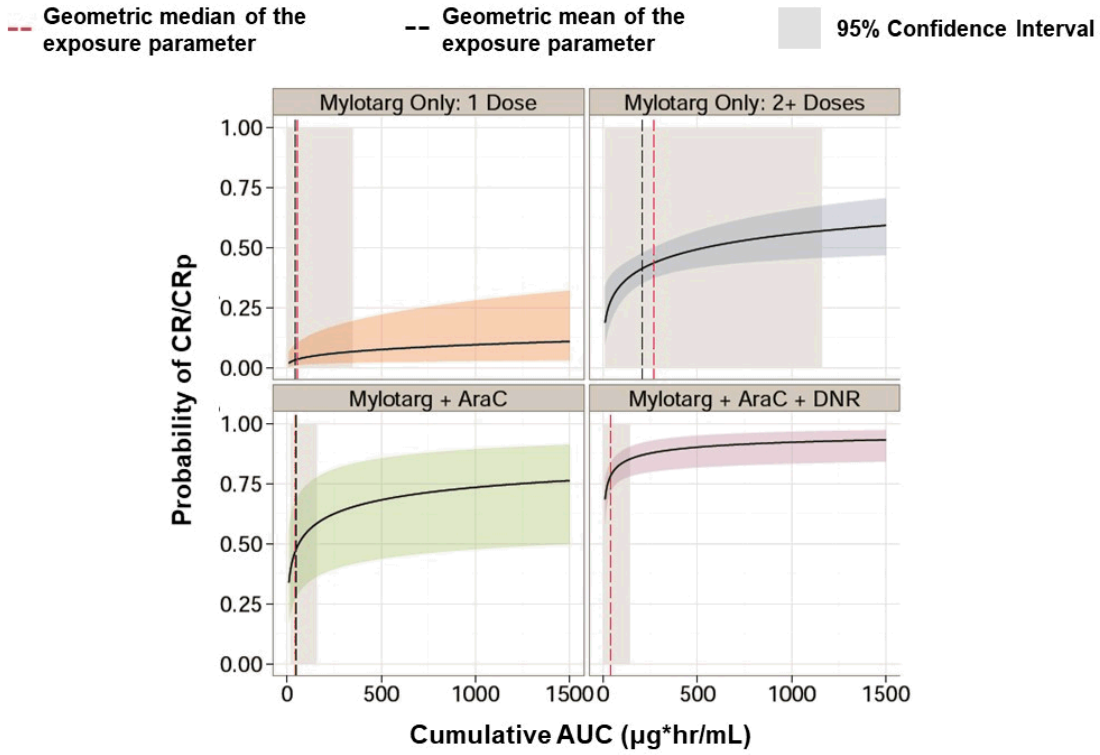
### 4.2. Exposure-Response Modeling

An exposure-response analysis in patients with AML was conducted using PK, PD, efficacy, and safety data from 8 prior studies (Studies 101, 102, 103, 201, 202, 203, 205, and 206), and simulated PK data from Study ALFA-0701. Mylotarg exposure correlated with both efficacy and safety outcomes, including VOD and myelosuppression, as presented below.

#### 4.2.1. Effect of Dose on Efficacy

A significant exposure-response relationship was found between cumulative antibody exposure and both ORR (CR+CRp, using International Working Group [IWG] criteria) and blast-free attainment. The model predicted that a single dose of Mylotarg would provide the lowest probability of remission. The addition of at least 1 subsequent dose of Mylotarg monotherapy significantly increased the probability of remission, with higher efficacy being achieved even at low exposure (Figure 3, top), and also significantly increased the probability of blast-free status (data not shown). The model also predicted that the addition of chemotherapy to Mylotarg further increased the probability of CR/CRp (Figure 3, bottom).

**Figure 3. Prediction Probabilities for the Final Model for CR/CRp Using Cumulative AUC**




Abbreviations: AraC=cytarabine; AUC=area under the antibody concentration-time curve; CR=complete remission; CRp=complete remission with incomplete platelet recovery; DNR=daunorubicin. The black and red dashed lines correspond to the geometric mean and median of the exposure parameter represented. The gray shaded area represents the 2.5% and 97.5% percentiles of the simulated cumulative AUCs from patients who received the specified dosing regimen.

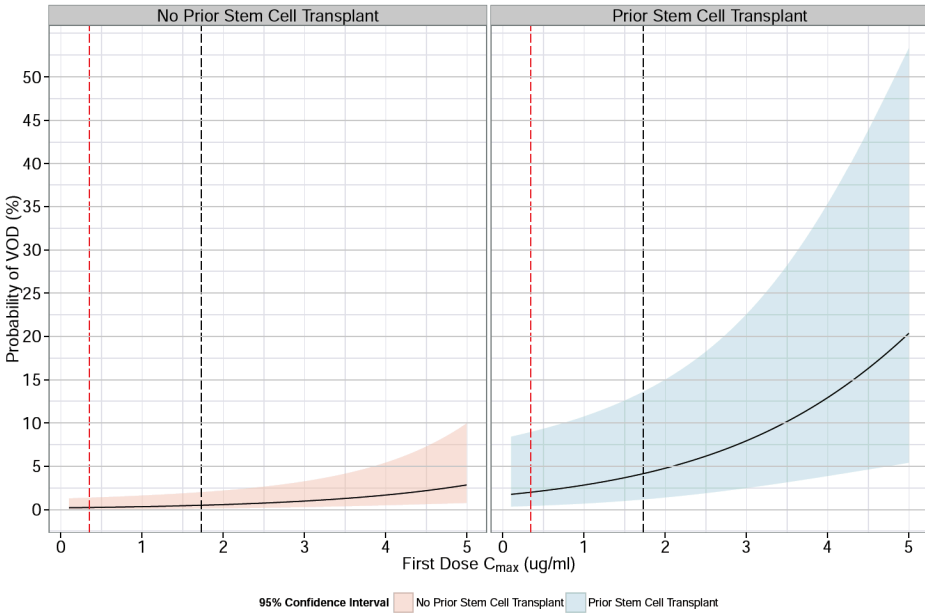
### 4.2.2. Effect of Dose on Hepatotoxicity and VOD

Exposure-response modeling has correlated Mylotarg exposure (antibody $C_{max}$) with development of hepatotoxicity and VOD. A significant positive exposure-response relationship was found between the antibody $C_{max}$ following the first dose of Mylotarg and elevated bilirubin, elevated AST, and hypoalbuminemia. The modeling also found a significant exposure-response relationship between the antibody $C_{max}$ following the first dose of Mylotarg and hepatic VOD occurring within 28 days after the last dose of Mylotarg. As noted in Section 4.1, the population PK model predicts that the lower dose fractionated regimen of 3 x 3 mg/m$^2$ reduces drug exposure as measured by both $C_{max}$ and AUC by approximately 75% relative to the initially approved 9 mg/m$^2$ x 2 dosing regimen. The exposure-response model predicts that the mean probability of developing VOD for the lower fractionated regimen is approximately half that expected with the original 9 mg/m$^2$ x 2 dosing regimen. Of note, the exposure-response model did not suggest any relationship between overall AUC and VOD occurring within 28 days of any Mylotarg dose.

In addition to the antibody $C_{max}$, the exposure-response model identified both baseline bone marrow blast level and prior HSCT as statistically significant predictors of VOD. A higher percentage of blasts in the bone marrow at baseline was negatively associated with

development of VOD (data not shown). For HSCT, the model predicted an approximately 50% lower mean probability of VOD with the lower dose fractionated Mylotarg regimen compared with the original 9 mg/m$^2$ x 2 Mylotarg dosing regimen, without (Figure 4, left side) or with (Figure 4, right side) prior HSCT. For patients with prior HSCT (Figure 4, right side), the model predicted a steeper slope of the exposure-response curve, wider confidence intervals, and a higher maximum probability of VOD. In the absence of prior HSCT (Figure 4, left side), the probabilities of VOD occurring within 28 days after Mylotarg dose were low for both the lower fractionated and original 9 mg/m$^2$ x 2 dosing regimens, and the differences between the rates would likely not be discernable.

**Figure 4. Plots of Logistic Regression Predictions for VOD in Relapsed AML**




Abbreviations: AML=acute myeloid leukemia; $C_{max}$=maximum serum concentration; VOD=veno-occlusive disease.
Note: Red vertical line is predicted antibody mean $C_{max}$ following the first dose of the 3 x 3 mg/m$^2$ lower dose fractionated Mylotarg regimen. The black and red dashed lines correspond to the geometric mean and median of the exposure parameter represented.

In addition to these analyses, additional analyses of risk factors for VOD across the Mylotarg clinical program (see Section 5.2 and Section 6.2) suggested higher starting dose levels (measured in mg/m$^2$) were associated with an increased risk of VOD. Those analyses included studies without antibody PK data, but since dose level tends to correlate with first $C_{max}$, the clinical analysis is consistent with the predictions of the exposure-response model.

### 4.2.3. Effect of Dose on Myelosuppression

Exposure-response modeling has also correlated Mylotarg exposure with myelosuppression. The model predicts an inverse relationship between concentrations of the antibody and neutrophil and platelet counts. Based on this model, a shorter duration of thrombocytopenia and neutropenia would be predicted for the lower dose fractionated regimen relative to the original 9 mg/m$^2$ x 2 dosing regimen.

### 4.2.4. Exposure-Response Model Summary

The exposure-response model predicted similar efficacy and improved safety with the lower dose fractionated regimen of Mylotarg, compared with the original 9 mg/m$^2$ x 2 dosing regimen, and provided an underlying rationale for the observed results in the clinical studies.

## 5. MYLOTARG IN PATIENTS WITH PREVIOUSLY UNTREATED AML

Several clinical studies have been conducted to evaluate the addition of Mylotarg to chemotherapy in the treatment of patients with previously untreated AML. The first study was SWOG S0106 that was conducted to confirm the clinical benefit of Mylotarg and convert accelerated approval to full approval in the US. Clinical benefit was not observed with the addition of Mylotarg to standard chemotherapy in that study (see Section 5.1.1 and Section 5.2.1). The ALFA-0701 study is the primary study in the current BLA, conducted using the lower dose fractionated Mylotarg regimen. The ALFA-0701 study demonstrated a clinically meaningful and statistically significant benefit in EFS, a direct measure of clinical benefit, when the lower dose fractionated Mylotarg regimen was added to chemotherapy (see Section 5.1.2 and Section 5.2.2) which, together with the results from the Individual Patient Data MA, confirmed the clinical benefit of Mylotarg in patients with CD33-positive AML. The results of these studies are summarized below. The ALFA-0701 and SWOG S0106 studies are compared and contrasted with respect to study design in Section 5.1.2.7_Ref482199778.

### 5.1. Efficacy in Patients With Previously Untreated AML

#### 5.1.1. Study SWOG S0106

The SWOG S0106 study was conducted to confirm the clinical benefit of Mylotarg and convert accelerated approval to full approval in the US. The objective of this study was to evaluate the effect of the addition of Mylotarg to induction and post-consolidation therapy in adult patients <61 years with previously untreated de novo AML.[10] A total of 295 patients received Mylotarg (single dose of 6 mg/m$^2$) + modified induction chemotherapy (DNR 45 mg/m² based on contemporaneous maximum tolerated dose [MTD] information plus AraC) in the Mylotarg + Chemotherapy arm, and 300 patients received standard induction therapy (DNR 60 mg/m² to ensure adequate anthracycline intensity plus AraC) in the Chemotherapy Alone arm. Patients who achieved CR were eligible to receive 3 courses of consolidation therapy of AraC. After completing consolidation therapy, patients who continued to meet the criteria for consolidation therapy were re-randomized to additional post-consolidation therapy with Mylotarg (5 mg/m$^2$, 3 doses at least 28 days apart) or to observation. The primary endpoints were CR rate for induction therapy and DFS from randomization for post-consolidation therapy.

In the induction phase, no clinical benefit was observed with the addition of Mylotarg to standard chemotherapy (Table 2).

**Table 2. Treatment Outcomes After Induction Chemotherapy – SWOG S0106**

| Outcome | Mylotarg + Chemotherapy (N = 295) % (95% CI) | Chemotherapy Alone (N = 300) % (95% CI) | p-value |
|---|---|---|---|
| CR | 69 (63-74) | 70 (64-75) | 0.59 |
| CR or CRi | 76 (69-79) | 74 (69-79) | 0.36 |
| Resistant Disease | 15 (12-20) | 20 (16-25) | 0.065 |
| OS at 5 years | 46 (40-52) | 50 (44-56) | 0.85 |
| RFS at 5 years | 43 (36-50) | 42 (35-49) | 0.40 |

Abbreviations: CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete blood count recovery; N=total number of patients in the treatment arm; OS=overall survival; RFS=relapse-free survival; SWOG=Southwest Oncology Group.

In the post-consolidation phase, Mylotarg did not significantly prolong DFS overall (hazard ratio [HR] 1.48; 95% CI: 0.99-2.22; p=0.97) or in any cytogenetic risk subgroup.[10]

A review of the results of SWOG S0106 suggested several factors that may have contributed to the negative outcome. Patients in the Mylotarg + Chemotherapy arm received what is now known to be a suboptimal dose of DNR of 45 mg/m² as compared with patients in the Chemotherapy Alone arm who were given DNR at 60 mg/m². The lower dose of DNR in the Mylotarg + Chemotherapy arm has been shown to be inferior to that of higher doses and may have confounded the interpretation of the comparison of results across treatment arms.[29] In addition, the single dose of Mylotarg of 6 mg/m$^2$ administered on Day 4 was different from both the unfractionated and lower dose fractionated regimens administered in other clinical trials, and may not have conferred the clinical benefit seen in those other trials. So, while Mylotarg may have partially compensated for an inferior dose of DNR, it did not improve RFS, DFS, or OS when compared with the standard dose of DNR.

### 5.1.2. ALFA-0701 Study

#### 5.1.2.1. Study Objectives and Design

ALFA-0701 was a randomized, open-label, Phase 3 study designed to compare the efficacy and safety of a lower dose fractionated regimen of Mylotarg plus 3+7 DNR+AraC versus 3+7 DNR+AraC alone. Patients were randomized (1:1) to induction treatment and could have also received a second induction course with DNR + AraC alone or a salvage induction course including idarubicin + AraC without being considered to have experienced induction failure. Patients with CR or CRp then received consolidation therapy with 2 courses of treatment including DNR + AraC with or without Mylotarg according to their initial randomization (see Appendix 10.4). The results of the ALFA-0701 study were published in 2012.[30]

Following publication of the study results, Pfizer and Centre Hospitalier de Versailles (CHV) signed a "data acquisition agreement" stating that Pfizer was acquiring from CHV the exclusive rights to the ALFA-0701 study data. All available study data were transferred from CHV to Pfizer.

To address current regulatory standards and in consultation with the FDA, Pfizer completed a rigorous review of the study data over a 5-year period. Most of the sites, including the high enrolling sites, participating in the ALFA-0701 study were audited to assess the quality of study monitoring and conduct. In addition, key data, including adverse events of special interest (AESIs) and all relevant laboratory data were retrospectively collected more than 4 years following the original data cutoff date. All of these new data added to the initial data transferred to Pfizer were re-assembled into a new database with a data cutoff date of 30 April 2013.

The primary endpoint was EFS, defined as the time from randomization to the date of an event of induction failure (lack of CR/CRp), relapse, or death due to any cause, whichever came first. Event-free survival was calculated independent of post-remission therapy (ie, HSCT); in addition, a sensitivity analysis was performed, with data censored at the last assessment before any HSCT. The EFS as the pre-specified endpoint was determined by investigator assessment and subsequently retrospectively re-analyzed by blinded independent review.

The secondary endpoints included CR and CRp rates (ORR), OS, RFS (time from CR or CRp to relapse or death), and safety.

#### 5.1.2.2. Appropriateness of EFS as the Primary Efficacy Endpoint in AML Studies

Event-free survival assesses the clinical benefit of AML therapy before the potentially confounding effect of subsequent therapies. In clinical trials evaluating AML therapies, many factors can impact the detection of a statistically significant OS benefit. First, AML is a relatively rare disease and enrollment of patients in large enough numbers to adequately power a study for OS is a major challenge. Second, long follow-up durations are required, during which clinical practice patterns change and may affect OS in ways extraneous to the treatment effect. Third, most AML patients are older and have a higher probability of death than younger patients (5-year survival rates are 6.7% in patients 65 years of age and over, and 45.2% in patients under 65 years of age, respectively).[31] Thus, deaths unrelated to leukemia in older patients can potentially confound interpretation of overall survival data. Finally, and with particular relevance to the study of post-remission maintenance AML therapy, such patients may receive salvage therapies post relapse. Post-relapse salvage therapies are far from standardized and may have different mortality risks, and thus any observed differences in OS might result from such therapies rather than from the randomized intervention.[21]

In addition, EFS, unlike OS, is not influenced by therapy given after failure to attain, or relapse from, remission, and so may provide a more direct assessment of the benefit of a therapy given during induction. As there are risks associated with both subsequent chemotherapy as part of post-remission treatment and with recurrent AML, there is a benefit to prolonging EFS in patients with AML that delays relapse and the toxicities that follow. In addition, patients in remission during the period of EFS plausibly have a better quality of life (QOL) consequent to a reduced frequency of transfusions, less time spent in hospital for treatment of infections, and a more hopeful view of their future.[20]

### 5.1.2.3. Study Population

Overall, the baseline characteristics of the study population in the ALFA-0701 study reflected those of the AML patient population intended for treatment in clinical practice (Table 3). Patients with APL or secondary AML were excluded. A total of 271 patients were included in the modified intent-to-treat (mITT) population (135 in the Mylotarg + Chemotherapy arm and 136 in the Chemotherapy Alone arm), which comprised all patients who were randomized, unless consent was withdrawn prior to start of treatment. All patients were analyzed according to their initial randomization.

**Table 3. Demographic and Baseline Characteristics (mITT Population) – ALFA-0701**

| | Mylotarg + Chemotherapy (N = 135) | Chemotherapy Alone (N = 136) |
|---|---|---|
| Gender, n (%) | | |
| Male | 74 (54.8) | 60 (44.1) |
| Female | 61 (45.2) | 76 (55.9) |
| Age (years), n (%) | | |
| <60 | 38 (28.1) | 52 (38.2) |
| ≥ 60 | 97 (71.9) | 84 (61.8) |
| Mean (Std Dev) | 62.1 (5.02) | 60.8 (5.39) |
| Median (Range) | 62.0 (50-70) | 61.0 (50-70) |
| CD33 expression (positivity), n (%) | | |
| N | 100 | 94 |
| <30% | 17 (12.6) | 20 (14.7) |
| ≥ 30% | 83 (61.5) | 74 (54.4) |
| <70% | 37 (27.4) | 31 (22.8) |
| ≥ 70% | 63 (46.7) | 63 (46.3) |

Abbreviations: ALFA=Acute Leukemia French Association: CD=cluster of differentiation; mITT=modified intent-to-treat; n=number of patients in each category; N=total number of patients in the treatment arm; Std Dev=standard deviation.

Of these 271 patients, 98.9% received study treatment, and 93.9% patients in the Mylotarg + Chemotherapy arm received all 3 fractionated doses of Mylotarg during induction therapy. More patients in the Chemotherapy Alone arm required a second induction course compared with the Mylotarg + Chemotherapy arm (25.0% versus 14.1%), and the proportion of patients who received a salvage course was the same in both treatment arms (3.7%). Similar numbers (%) of patients in both treatment arms received the first consolidation course: 97 (71.9%) patients in the Mylotarg + Chemotherapy arm (including 6 [4.4%] patients who did not receive Mylotarg) and 97 (71.3%) patients in the Chemotherapy Alone arm. The number (%) of patients receiving a second consolidation course was also similar between the 2 treatment arms: 82 (60.7%) patients in the Mylotarg + Chemotherapy arm (including 18 [13.3%] patients who did not receive Mylotarg) and 89 (65.4%) patients in the Chemotherapy Alone arm. Overall, 64 (47.4%) patients in the Mylotarg + Chemotherapy arm and 89 (65.4%) patients in the Chemotherapy Alone arm completed treatment as defined per protocol (Table 4).

**Table 4. Patient Treatment Summary (All Patients) – ALFA-0701**

| | Mylotarg + Chemotherapy (N = 135) n (%) | Chemotherapy Alone (N = 136) n (%) |
|---|---|---|
| Randomized to study treatment | 135 | 136 |
| Treated (as randomized to treatment) | 134 (99.3) | 134 (98.5) |
| Received first induction course | 134 (99.3) | 134 (98.5) |
| With Mylotarg | 131 (97.0) | NA |
| Without Mylotarg | 3 (2.2) | NA |
| Received second induction course | 19 (14.1) | 34 (25.0) |
| Received salvage course | 5 (3.7) | 5 (3.7) |
| Received Consolidation 1 course | 97 (71.9) | 97 (71.3) |
| With Mylotarg | 91 (67.4) | NA |
| Without Mylotarg | 6 (4.4) | NA |
| Received Consolidation 2 course | 82 (60.7) | 89 (65.4) |
| With Mylotarg | 64 (47.4) | NA |
| Without Mylotarg | 18 (13.3) | NA |
| Completed treatment[a] | 64 (47.4) | 89 (65.4) |

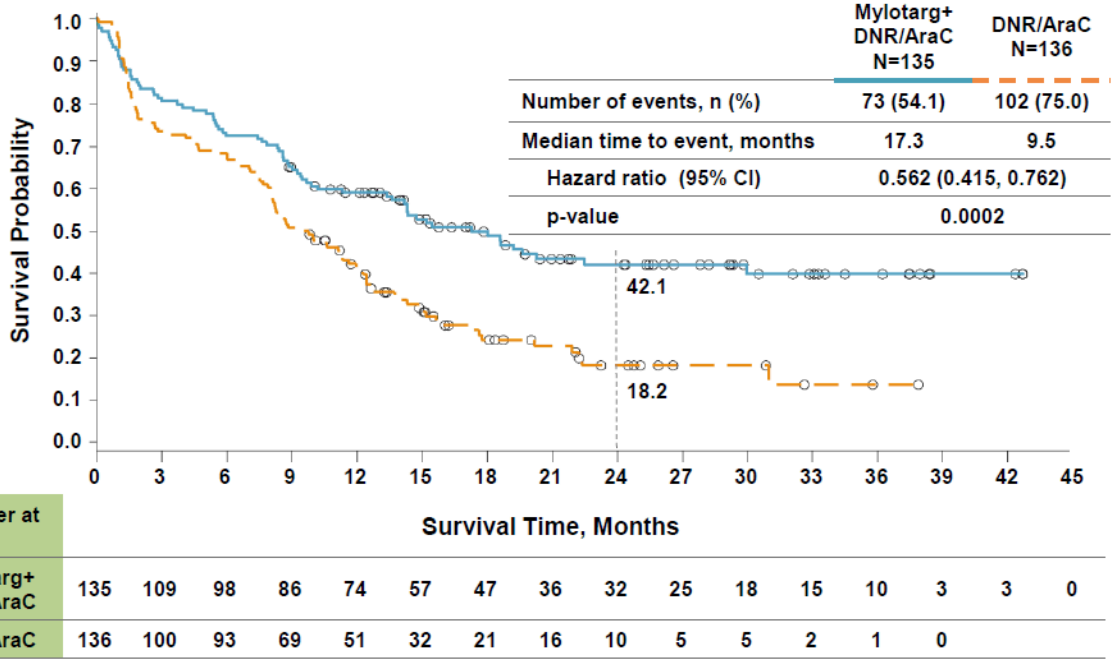
Received a course defined as received at least one of the treatments, but did not require all treatments to be received and was determined per treatment phase dosing records.
Abbreviations: ALFA=Acute Leukemia French Association; NA=not applicable; n=number of patients in each category; N=total number of patients in the treatment arm.
a. For Mylotarg + Chemotherapy arm, completed both Mylotarg and chemotherapy treatments per disposition case report form. For Chemotherapy Alone arm, completed chemotherapy treatment per disposition case report form.

### 5.1.2.4. Primary Efficacy Endpoint (Event-Free Survival by Investigator Assessment)

The ALFA-0701 study met its primary objective of demonstrating that the lower dose fractionated Mylotarg regimen of 3 mg/m$^2$ x 3 in combination with standard induction chemotherapy resulted in a statistically significant and clinically meaningful improvement in EFS in patients with previously untreated de novo AML (Figure 5) in the mITT population. Median EFS was 17.3 months (95% CI: 13.4-30.0) in the Mylotarg + Chemotherapy arm versus 9.5 months (95% CI: 8.1-12.0) in the Chemotherapy Alone arm; HR 0.562 (95% CI: 0.415-0.762; 2-sided log-rank p=0.0002 by log-rank test). These results corresponded to a 44% reduction in the risk of EFS events for patients in the Mylotarg + Chemotherapy arm compared to the Chemotherapy Alone arm. All 3 elements of EFS (induction failure, relapse, and death) were observed to be lower in the Mylotarg arm. Event-free survival was achieved by more patients in the Mylotarg + Chemotherapy arm at Year 2 and Year 3 than by patients in the Chemotherapy Alone arm: 42.1% (95% CI: 32.9-51.0) versus 18.2% (95% CI: 11.1-26.7) at Year 2 and 39.8% (95% CI: 30.2-49.3) versus 13.6% (95% CI: 5.8-24.8) at Year 3.

Events defining EFS, per investigator assessment, as of the data cutoff date of 01 August 2011, were reported in 54.1% of patients in the Mylotarg + Chemotherapy arm and 75.0% of patients in the Chemotherapy Alone arm (Table 5).

**Figure 5. Kaplan-Meier Plot of Event-Free Survival (mITT Population) – ALFA-0701 (Data Cutoff Date 01 August 2011)**




Note: Data are not censored for HSCT.
Abbreviations: ALFA=Acute Leukemia French Association; CI: confidence interval: DNR/AraC=daunorubicin+cytarabine; HSCT=hematopoietic stem cell transplant; mITT=modified intent-to-treat; N=total number of patients in the treatment arm

**Table 5. Primary Event-Free Survival Endpoint (mITT Population) – ALFA-0701**

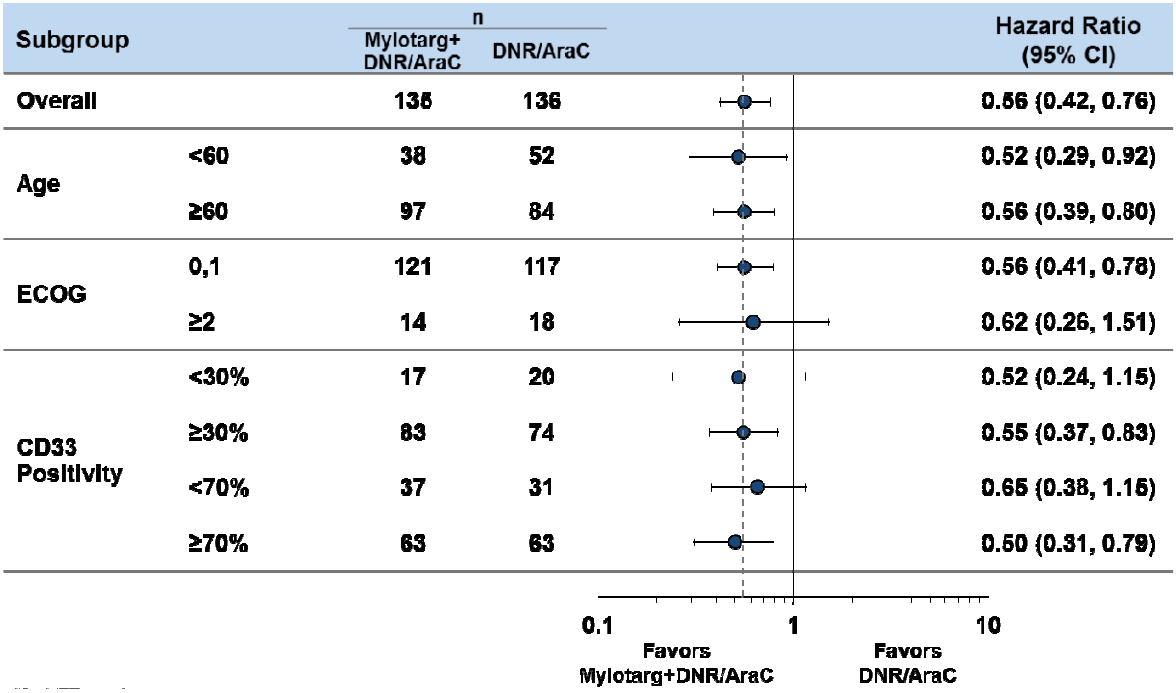
| | Mylotarg + Chemotherapy (N = 135) | Chemotherapy Alone (N = 136) |
|---|---|---|
| Number of events, n (%) | 73 (54.1) | 102 (75.0) |
| Induction failure | 17 (12.6) | 29 (21.3) |
| Relapse | 44 (32.6) | 58 (42.6) |
| Death | 12 (8.9) | 15 (11.0) |
| Number of censored patients, n (%) | 62 (45.9) | 34 (25.0) |
| Reason for censoring, n (%) | | |
| Event-free at cutoff date | 62 (45.9) | 34 (25.0) |
| KM estimate of median time to event (months) [95% CI][a] | 17.3 [13.4, 30.0] | 9.5 [8.1, 12.0] |
| Probability of being event-free at 2 years [95% CI][b,c] | 42.1 [32.9, 51.0] | 18.2 [11.1, 26.7] |
| Probability of being event-free at 3 years [95% CI][b,c] | 39.8 [30.2, 49.3] | 13.6 [5.8, 24.8] |

Cutoff date 01 August 2011.
Abbreviations: ALFA=Acute Leukemia French Association; CI=confidence interval; KM=Kaplan-Meier; mITT=modified intent-to-treat; n=number of patients in each category; N=total number of patients in the treatment arm.

a. Based on the Brookmeyer and Crowley Method with log-log transformation.
b. Estimated from the KM curve.
c. Calculated from the product-limit method/Calculated from the log[-log(x-<year,month> survival probability)] using a normal approximation and back transformation.

Results for EFS were similar when analyzed by subgroup (Figure 6).

**Figure 6. Forest Plot of Event-Free Survival by Investigator Assessment by Subgroup (mITT Population) – ALFA-0701**




Data cutoff date 01 August 2011.
Abbreviations: ALFA=Acute Leukemia French Association; AraC=cytarabine; CI=confidence interval; CD=cluster of differentiation; DNR=daunorubicin; ECOG=Eastern Cooperative Oncology Group; mITT=modified intent-to-treat; n=number of patients in each category; N=total number of patients in the treatment arm

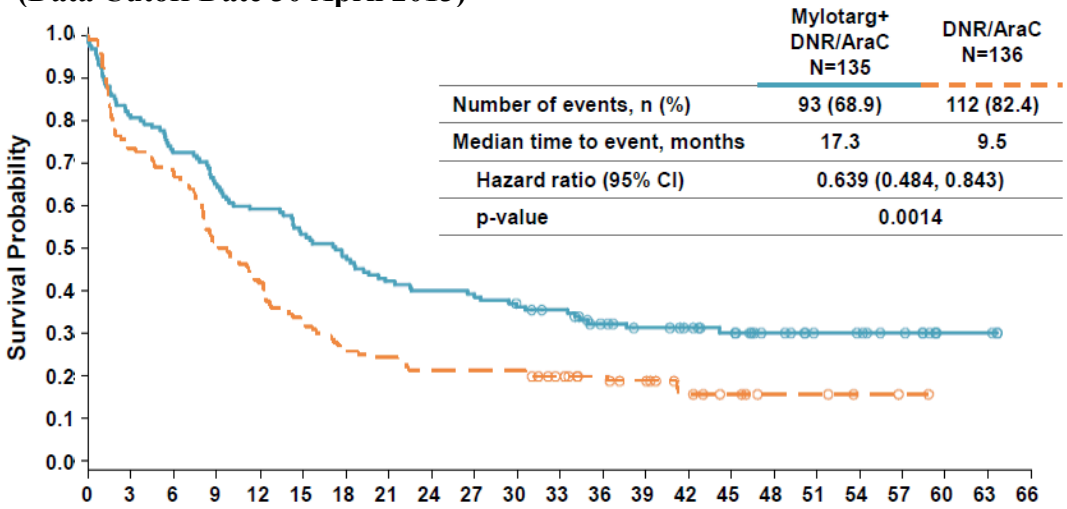
Patient risk can be assessed using standard cytogenetics or using criteria that incorporate molecular abnormalities in addition to standard cytogenetics, such as those included in the European Leukemia Network (ELN) 2010 guidelines.[32] One important practical consideration affecting treatment decisions is whether cytogenetic results are available to the treating physician before treatment needs to be initiated; these results may not be available for up to 2 weeks.

While the study met its primary endpoint for the entire mITT population, the efficacy benefit of the addition of Mylotarg to chemotherapy was more apparent in the ALFA-0701 study in patients with favorable/intermediate cytogenetic risk AML than in patients with adverse/poor cytogenetic risk AML. For patients with favorable/intermediate cytogenetic risk AML at baseline, EFS was longer for patients in the Mylotarg + Chemotherapy arm compared to the Chemotherapy Alone arm (HR 0.460 [95% CI: 0.313-0.676)]; p<0.0001 by log rank test). This advantage in EFS in the Mylotarg + Chemotherapy arm was not apparent for patients with poor cytogenetic risk AML at baseline (HR 1.111 [95% CI: 0.633-1.949]; p=0.7151 by log-rank test). However, the addition of Mylotarg to the backbone chemotherapy did not appear to negatively impact the outcome of patients with poor cytogenetic risk AML. This is

an important consideration in treatment decisions, especially if cytogenetic results are not available before treatment needs to begin.

The EFS for patients in the ALFA-0701 study followed over a longer duration (data cutoff date 30 April 2013) is shown in Figure 7. Median EFS was 17.3 months (95% CI: 13.4-21.4) in the Mylotarg + Chemotherapy arm versus 9.5 months (95% CI: 8.1-12.2) in the Chemotherapy Alone arm; HR 0.639 (95% CI: 0.484-0.843; 2-sided p=0.0014 by log-rank test).

**Figure 7. Kaplan-Meier Plot of Event-Free Survival (mITT Population) – ALFA-0701 (Data Cutoff Date 30 April 2013)**




| Number at Risk | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mylotarg+ DNR/AraC | 135 | 109 | 98 | 88 | 80 | 72 | 65 | 57 | 54 | 53 | 48 | 45 | 36 | 32 | 29 | 25 | 19 | 14 | 13 | 10 | 3 | 3 | 0 |
| DNR/AraC | 136 | 100 | 93 | 69 | 57 | 44 | 35 | 33 | 29 | 29 | 29 | 23 | 19 | 16 | 10 | 7 | 4 | 4 | 2 | 1 | 0 | | |

Censoring date is date of last disease assessment.
Abbreviations: ALFA=Acute Leukemia French Association; CI=confidence interval; DNR/AraC=daunorubicin+cytarabine; mITT=modified intent-to-treat; N=total number of patients in the treatment arm

Event-free survival was also assessed retrospectively by blinded independent hematologists, using complete blood count (CBC) and bone marrow aspirate (BMA) data, to provide a verifiable and objective assessment of each patient's disease status. This blinded independent review of EFS supported the EFS results by investigator assessment (median EFS was 13.6 months ([95% CI: 9.0-19.2] in the Mylotarg + Chemotherapy arm and 8.5 months [95% CI: 7.5-12.0] in the Chemotherapy Alone arm; [HR 0.661; 95% CI: 0.491-0.891; p=0.0059 by log-rank test]). These results correspond to a 34% reduction in the risk of an EFS event for patients in the Mylotarg + Chemotherapy arm compared to the Chemotherapy Alone arm. Multiple sensitivity analyses, eg, censoring at HSCT, also demonstrated the robustness of the EFS results.

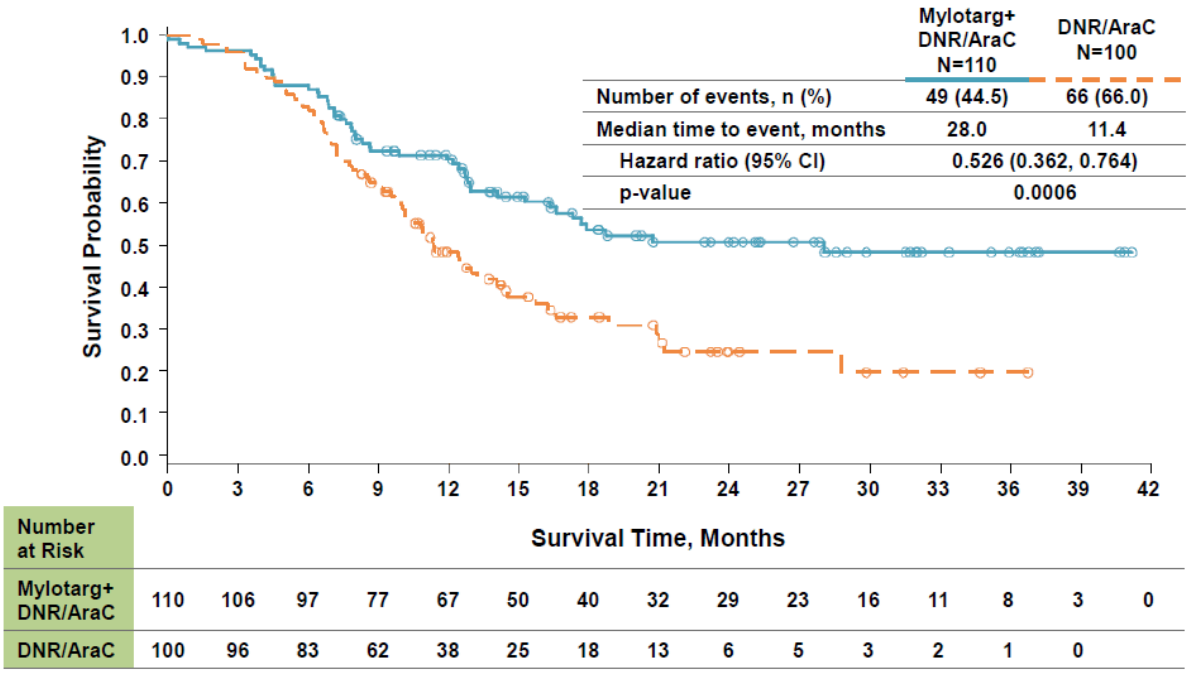
A significant prolongation of EFS is considered by hematologists to represent clinical benefit for patients, in part, by delaying the inconvenience and toxicities associated with subsequent therapy, and the morbidities that accompany recurrent AML. Results of an ad hoc analysis

supported this premise and showed that patients in the Mylotarg + Chemotherapy arm experienced significantly longer time to subsequent anti-cancer therapy administered after induction failure or relapse, compared to the Chemotherapy Alone arm (median time of 21.7 months [95% CI: 15.7-35.2] in the Mylotarg + Chemotherapy arm and 12.8 months [95% CI: 11.0-16.3] in the Chemotherapy Alone arm; HR 0.669 [95% CI: 0.492-0.910]; p=0.0099 by log-rank test).

#### 5.1.2.5. Secondary Efficacy Endpoints (Relapse-Free Survival, Overall Survival, Overall Response Rate)

Relapse-free survival is an important measure of the duration of the response from time of CR or CRp. The RFS (the time from CR or CRp to relapse or death) per investigator assessment was significantly longer for patients in the Mylotarg + Chemotherapy arm than in the Chemotherapy arm, with a median RFS of 28.0 months (95% CI: 16.3-not estimable [NE]) versus 11.4 months (95% CI: 10.0-14.4); HR 0.526 (95% CI: 0.362-0.764); p=0.0006 by log-rank test (Figure 8).

**Figure 8. Kaplan-Meier Plot of Relapse-Free Survival (mITT Population)– ALFA-0701 (Data Cutoff Date 01 August 2011)**

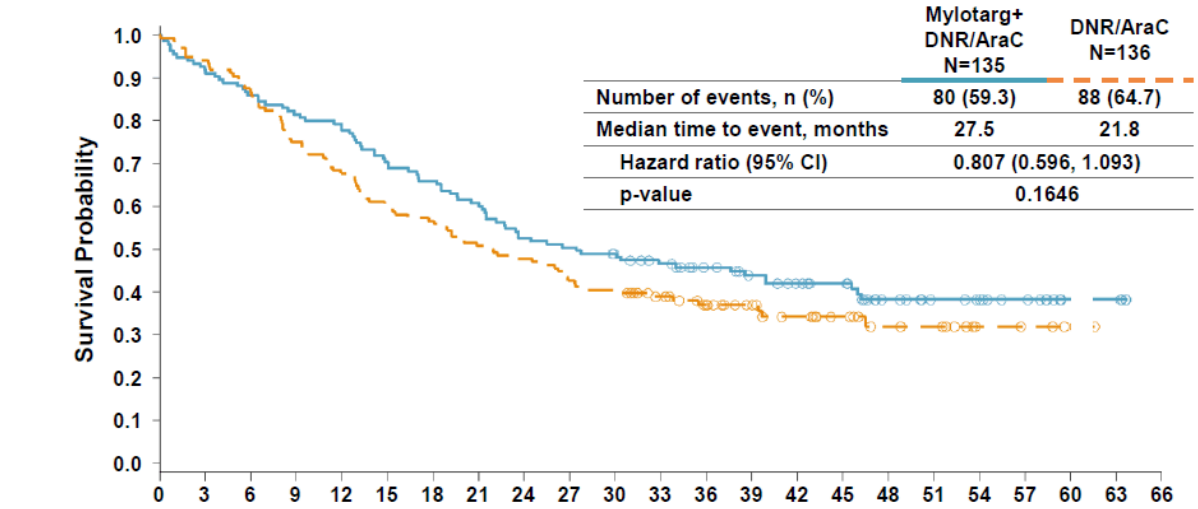



Abbreviations: ALFA=Acute Leukemia French Association; CI=confidence interval; DNR/AraC=daunorubicin+cytarabine; N=total number of patients in the treatment arm; mITT=modified intent-to-treat

A total of 80 patients (59.3%) in the Mylotarg + Chemotherapy arm and 88 patients (64.7%) in the Chemotherapy Alone arm died prior to the later data cutoff date of 30 April 2013. The OS was longer in the Mylotarg + Chemotherapy arm than in the Chemotherapy Alone arm; however, this comparison did not reach statistical significance (Figure 9). The median OS was 27.5 months (95% CI: 21.4-45.6) versus 21.8 months (95% CI: 15.5-27.4); HR 0.807

(95% CI: 0.596-1.093); 2-sided log-rank p=0.1646. Of note, the ALFA-0701 study was underpowered to detect a statistically significant improvement in OS (powered to detect HR ≤ 0.66).

**Figure 9. Kaplan-Meier Plot of Overall Survival (mITT Population) – ALFA-0701 (Data Cutoff Date 30 April 2013)**

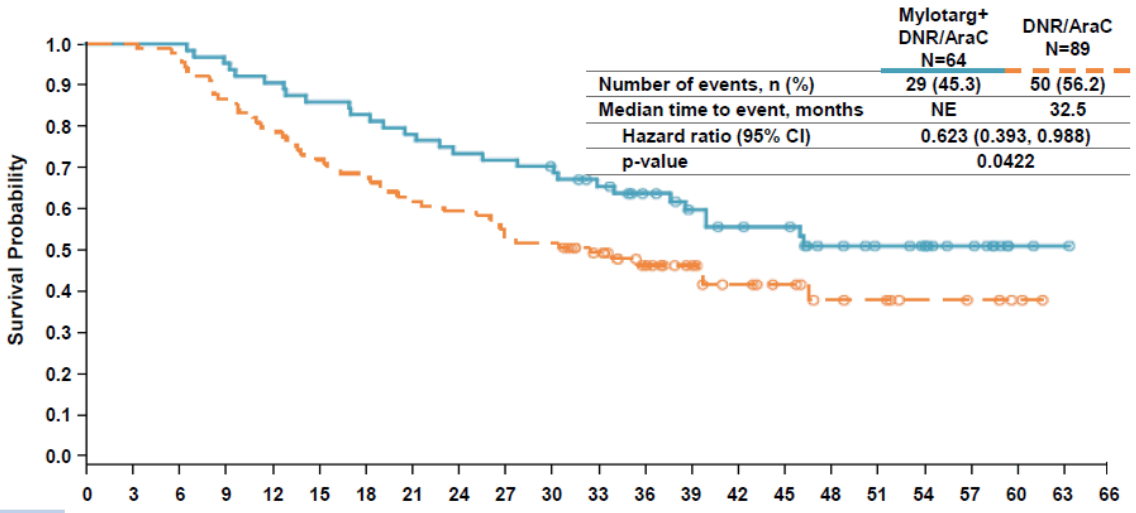



| Number at Risk | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mylotarg+ DNR/AraC | 135 | 124 | 116 | 110 | 105 | 95 | 89 | 82 | 71 | 68 | 64 | 58 | 51 | 45 | 39 | 36 | 25 | 20 | 18 | 13 | 5 | 4 | 0 |
| DNR/AraC | 136 | 128 | 118 | 102 | 92 | 81 | 77 | 69 | 65 | 58 | 55 | 46 | 36 | 29 | 23 | 18 | 13 | 12 | 6 | 5 | 3 | 0 | |

Note: No adjustment was made for imbalances in subsequent therapy between the treatment arms, including subsequent off-protocol treatment with Mylotarg.
Abbreviations: ALFA=Acute Leukemia French Association; CI=confidence interval; DNR/AraC=daunorubicin+cytarabine; mITT=modified intent-to-treat; N=total number of patients in the treatment arm.

The OS results may have been confounded by a number of factors which may have diluted the EFS benefit (see Section 5.1.2.1). For example, 22.1% of patients in the Chemotherapy Alone arm subsequently received Mylotarg as a component of follow-up therapy as part of the compassionate use program. There were also imbalances in subsequent AML therapy between the 2 treatment arms, with 71.1% of patients in the Mylotarg + Chemotherapy arm versus 80.1% of patients in the Chemotherapy Alone arm receiving other AML therapy, and 23.7% of patients in the Mylotarg + Chemotherapy arm versus 39.0% of patients in the Chemotherapy Alone arm undergoing HSCT. Some patients in the Mylotarg arm completing consolidation chemotherapy did not complete the Mylotarg component of their therapy. Patients in the Mylotarg + Chemotherapy arm who completed all study medication had significant improvement in OS when compared to patients in the Chemotherapy Alone arm who completed all study medication (Figure 10).

**Figure 10. Kaplan-Meier Plot of Overall Survival For Patients Who Completed Treatment (As-Treated Population) – ALFA-0701 (Data Cutoff Date 30 April 2013)**




| Number at Risk | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mylotarg+ DNR/AraC | 64 | 64 | 64 | 61 | 58 | 55 | 53 | 50 | 47 | 46 | 44 | 39 | 34 | 29 | 26 | 25 | 19 | 16 | 14 | 9 | 2 | 1 | 0 |
| DNR/AraC | 89 | 89 | 87 | 77 | 70 | 64 | 61 | 55 | 53 | 47 | 46 | 38 | 28 | 22 | 16 | 13 | 9 | 8 | 5 | 4 | 2 | 0 | |

Abbreviations: ALFA=Acute Leukemia French Association; CI=confidence interval; DNR/AraC=daunorubicin+cytarabine; N=total number of patients in the treatment arm; NE=not estimable.
Cutoff date for analysis was 30 April 2013; censoring indicated by circles.

The ORR (CR + CRp) by investigator assessment was not significantly different between patients in the Mylotarg + Chemotherapy arm (81.5%) and in those in the Chemotherapy Alone arm (73.5%) (risk difference of 7.95 [95% CI: -3.79-19.85] with p=0.1457 using Fisher's exact test). While the rate of CR was similar in the 2 arms (70.4% and 69.9%, respectively), there was a significantly higher rate of CRp in the Mylotarg + Chemotherapy arm (11.1% versus 3.7%, with a risk difference of 7.43 [95% CI: -4.52, 19.13], p=0.0211).

Although the number of minimal residual disease (MRD)-evaluable patients was small (39 patients in the Mylotarg + Chemotherapy arm and 37 patients in the Chemotherapy Alone arm), a higher percentage of patients achieving a response had no evidence of MRD as assessed by nucleophosmin-1 gene (NPM1) mutational status in the Mylotarg + Chemotherapy arm compared to the Chemotherapy Alone arm at Month 1 (29.7% and 6.3%), Month 3 (45.9% and 18.8%), and Month 6 (56.8% and 34.4%), respectively. Conversely, fewer patients in the Mylotarg + Chemotherapy arm than in the Chemotherapy Alone arm who achieved CR/CRp had NPM1mut-positive AML cells at Month 1 (54.1% versus 81.3%), Month 3 (13.5% versus 40.6%), and Month 6 (5.4% versus 21.9%).

Overall, analyses of both EFS and RFS by baseline characteristics (including age; Eastern Cooperative Oncology Group [ECOG] PS status; and FLT3-internal tandem duplication, NPM1, and Wilms' tumor suppressor gene [WT1] status) were consistent with the overall

results for these subgroups, and baseline characteristics did not appear to have an impact on the Mylotarg treatment outcome.

#### 5.1.2.6. Efficacy Conclusions from the ALFA-0701 Study

Mylotarg administered as a lower dose fractionated regimen in combination with standard intensive induction chemotherapy resulted in a statistically significant and clinically meaningful improvement in EFS, the primary endpoint of the ALFA-0701 study, and RFS, compared to chemotherapy alone. In addition, there was a trend towards improvement in OS over chemotherapy alone. These data demonstrate the clinical benefit of the addition of a lower dose fractionated Mylotarg regimen to standard intensive induction chemotherapy and confirm the clinical benefit originally established in the first-relapse AML treatment setting.

#### 5.1.2.7. Differences in Design and Outcome Between the ALFA-0701 and SWOG S0106 Studies

There were some key differences in design between the ALFA-0701 and SWOG S0106 studies that may have contributed to the different results observed in the 2 studies:

- The DNR dose in SWOG S0106 was unbalanced between treatment arms with a lower, less efficacious dose in the Mylotarg + Chemotherapy arm. Patients in the Mylotarg + Chemotherapy arm were administered lower doses of DNR at 45 mg/m² as compared to patients in the Chemotherapy Alone arm, who were given DNR at 60 mg/m². It is now known that 45 mg/m$^2$ of DNR is inferior to 60 mg/m$^2$ of DNR.[29]. The ALFA-0701 study assigned doses of DNR at 60 mg/m² to patients in both treatment arms of the study.
- The SWOG S0106 study used only a single unfractionated 6 mg/m$^2$ dose of Mylotarg on Day 4, while the ALFA-0701 study used lower fractionated dosing of 3 mg/m² of Mylotarg on Days 1, 4, and 7. Exposure-response modeling showed that administering more than 1 dose of Mylotarg produces superior efficacy to a single dose, independent of exposure (see Section 4.2.1).
- The SWOG S0106 study design included post-consolidation re-randomization of patients to Mylotarg or observation, whereas patients in the ALFA-0701 study received Mylotarg during consolidation therapy according to their initial randomization. The re-randomization for post-consolidation therapy in the SWOG S0106 study may have diluted any difference in the primary endpoint of post-consolidation DFS between the treatment arms.

### 5.1.3. Individual Patient Data Meta-Analysis

#### 5.1.3.1. Objectives and Design

Based on their positive experience with different doses and schedules of Mylotarg added to chemotherapy in the first-line de novo AML treatment setting, Dr. Robert K. Hills of Cardiff University in collaboration with the lead investigators of the other cooperative studies performed an Individual Patient Data MA that was comprised of patients enrolled in 5 Phase 3 studies that satisfied the following criteria:

- Patients were to have newly diagnosed AML (either de novo or secondary) or high-risk myelodysplastic syndrome (MDS). Studies that enrolled only patients with APL were excluded.
- Study patients had to be age 15 years or older.
- An unconfounded comparison of Mylotarg in Course 1 of induction chemotherapy (ie, Mylotarg + Chemotherapy versus Chemotherapy Alone); studies in which Mylotarg was used in place of part of a chemotherapy regimen, before chemotherapy, or only in consolidation were excluded.
- Study treatment had to be intensive induction chemotherapy, designed to induce CR in patients; studies involving less intensive regimens such as low-dose cytarabine (AraC) were excluded.

The 5 studies which met these criteria were ALFA-0701, SWOG S0106, Medical Research Council (MRC) AML15, National Cancer Research Institute (NCRI) AML16, and Groupe Ouest Est d'Etude des Leucémies aiguës et Autres Maladies du Sang (GOELAMS) AML2006IR. Two of the 5 studies did not meet their primary endpoints. The Individual Patient Data MA was independently conducted by Dr. Hills and his co-investigators without Pfizer support, and was published in Lancet.[33]

In an Individual Patient Data MA, the raw individual patient level data for each study are obtained and used for analysis. This analysis is in contrast to a traditional meta-analysis which aggregates published data across studies. A meta-analysis conducted on individual patient level data thus has a number of potential statistical and clinical advantages over a meta-analysis of aggregate data. These advantages include application of consistent eligibility criteria across the studies, inclusion of unpublished results or updated study data with up-to-date follow-up information, standardization of statistical analysis across the studies, calculation of endpoints (eg, EFS) not initially determined, and assessment of differential treatment effects for specific subgroups of patients (eg, cytogenetic risk subgroups).

Following the initial analysis by Dr. Hills, Pfizer began a collaboration with Dr. Hills to perform a repeat analysis using updated individual patient data with longer follow-up and additional analyses. A confirmatory literature review was conducted by Pfizer covering the period up to July 2015, without identifying any additional eligible studies. The statistical analysis plan for the repeat Individual Patient Data MA was reviewed and commented on by the FDA. Potential biases within studies and across studies (eg, selection, performance, detection, attrition, and reporting bias) were assessed retrospectively by Pfizer, utilizing tools identified by the Cochrane Collaboration, and as such, there was generally determined to be a low risk of bias. The data presented are from the repeated Individual Patient Data MA, performed as a collaboration between Dr. Hills and his associates and Pfizer.

This meta-analysis included individual patient level data from a total of 3331 patients: 1663 patients (49.9%) randomized to Mylotarg (3 mg/m² single dose, 3×3 mg/m² fractionated dosing regimen, or 6 mg/m² single dose) + Chemotherapy, and 1668 patients (50.1%) randomized to Chemotherapy Alone. An overview of the 5 studies is presented in Table 6.

Median follow-up using reverse censoring methods ranged from 45.4 months in the ALFA-0701 study to 110.4 months in the AML15 study.

The primary endpoint for the Individual Patient Data MA was OS, defined as the time from date of randomization to date of death due to any cause. The secondary efficacy endpoints were EFS, complete remission rate (CRR), RFS, and ORR.

**Table 6. Studies Included in the Individual Patient Data Meta-Analysis**

| Study Name | Trial Endpoints: Primary (Secondary) | Study Population | Induction Therapy | | Enroll-ment | No. of Patients Randomized (Mylotarg/ Control) | Median Follow-up in Current Analysis[a] (months) |
|---|---|---|---|---|---|---|---|
| | | | Chemotherapy | Mylotarg[b] | | Current Analysis | |
| MRC AML15 | OS and CR, CRi (RD, RFS, CIR, CIDCR, toxicity) | AML, de novo or secondary, APL[c] | DA (3+10, 3+8) or ADE (3+10+5, 3+8+5) or FLAG-Ida | 3 mg/m² Day 1 | 2002-2006 | 1099 (548/551) | 110.45 |
| NCRI AML16 | OS (CR, CRi, RFS, RR, DCR1, toxicity) | AML, de novo, secondary, or high risk MDS | DA (3+10, 3+8) or DClo (D 1, 3, 5/ clofarabine D 1-5) | 3 mg/m² Day 1 | 2006-2010 | 1115 (559/556) | 69.06 |
| ALFA-0701 | EFS (CR, CRp, RFS, OS, toxicity) | de novo AML | DA (3+7) | 3 mg/m² D 1,4,7 (≤5 mg/ dose) | 2008-2010 | 271 (135/136) | 45.44 |
| GOELAMS AML2006IR | EFS at 3 years (OS, CIR, and CIDND at 3 years, CR, toxicity) | de novo AML, intermediate cytogenetics | DA (3+7) | 6 mg/m² Day 4 | 2007-2010 | 251 (126/125) | 66.2 |
| SWOG S0106 | DFS, CR (CRi, PR, RD, OS, RFS, toxicity) | de novo AML | DA (3+7) + growth factor | 6 mg/m² Day 4 | 2004-2009 | 595 (295/300) | 66.23 |

Abbreviations: ADE=daunorubicin, cytarabine, and etoposide; ADE 3+10+5 or 3+8+5=DNR Days 1, 3, 5, AraC Days 1-10 or Days 1-8, etoposide Days 1-5; ALFA=Acute Leukemia French Association; AML=acute myeloid leukemia; APL=acute promyelocytic leukemia; CIDCR=cumulative incidence of death in first response; 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; D=Day; DA=daunorubicin plus cytarabine; DA 3+7, 3+8 or 3+10=DNR Days 1-3 or Days 1, 3, 5 and AraC Days 1-7, 1-8 or 1-10; 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; GOELAMS=Groupe Ouest Est d'Etude des Leucémies aiguës et Autres Maladies du Sang, MDS=myelodysplastic syndrome; MRC=Medical Research Council; NCRI=National Cancer Research Institute; OS=overall survival; No.=Number; PR=Partial remission; RD=resistant disease; RFS=relapse-free survival; RR=relapse rate; SWOG=Southwest Oncology Group.

a. Calculated by reverse Kaplan-Meier method.
b. Mylotarg dose administered in combination with chemotherapy.
c. APL patients were not included in the meta-analysis.

### 5.1.3.2. Primary Efficacy Endpoint: Overall Survival

Across studies, despite differences in Mylotarg dosing regimens, Mylotarg in combination with standard intensive first-line induction chemotherapy in adult patients with untreated AML provided a clinically meaningful and statistically significant improvement versus chemotherapy alone in the primary efficacy endpoint of OS (Peto OR 0.91, 95% CI: 0.84-0.99, p=0.02, 2-sided stratified log-rank test), corresponding to a 9% reduction in risk of death in the Mylotarg + Chemotherapy arm (N = 1663) versus the Chemotherapy Alone arm (N = 1668) (Table 7 and Figure 11). Overall, pooled median OS was 23.62 months (95% CI: 21.22-27.33 months) in the Mylotarg + Chemotherapy arm and 21.49 months (95% CI: 19.42-23.20 months) in the Chemotherapy Alone arm.

**Table 7. Overall Survival – Individual Patient Data Meta-Analysis**

| | Mylotarg + Chemotherapy n/N (%) | Chemotherapy Alone n/N (%) | Peto Odds Ratio (CI) | p-value[a] |
|---|---|---|---|---|
| **3 mg/m$^2$ x 1 dose** | | | | |
| MRC AML15 | 339/548 (61.9) | 357/551 (64.8) | 0.93 (0.76, 1.13)* | -- |
| NCRI AML16 | 472/559 (84.4) | 494/556 (88.8) | 0.87 (0.74, 1.03)* | -- |
| Subtotal | 811/1107 (73.3) | 851/1107 (76.9) | 0.89 (0.81, 0.98)† | -- |
| **3 mg/m$^2$ fractionated** | | | | |
| ALFA-0701 | 80/135 (59.3) | 88/136 (64.7) | 0.81 (0.54, 1.20)* | |
| Subtotal | 80/135 (59.3) | 88/136 (64.7) | 0.81 (0.59, 1.09)† | -- |
| **6 mg/m$^2$ x 1 dose** | | | | |
| GOELAMS IR2006 | 56/126 (44.4) | 63/125 (50.4) | 0.86 (0.54, 1.38)* | -- |
| SWOG S0106 | 154/295 (52.2) | 151/300 (50.3) | 1.09 (0.81, 1.46)* | -- |
| Subtotal | 210/421 (49.9) | 214/425 (50.4) | 1.02 (0.84, 1.23)† | -- |
| **Total** | 1101/1663 (66.2) | 1153/1668 (69.1) | 0.91 (0.84, 0.99)† | 0.02 |

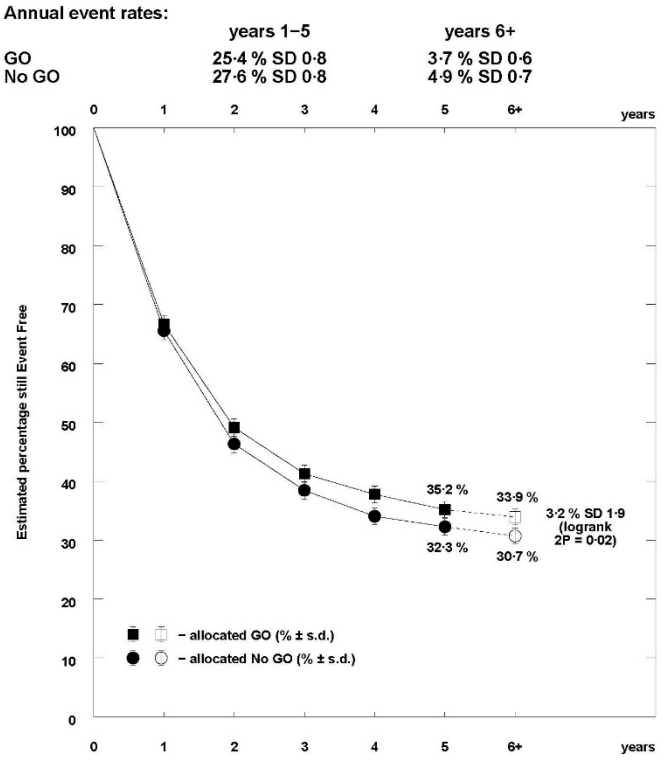
* 99% CI

† 95% CI

Abbreviations: ALFA=Acute Leukemia French Association; AML=acute myeloid leukemia; CI=Confidence interval; GOELAMS=Groupe Ouest Est d'Etude des Leucémies aiguës et Autres Maladies du Sang; MRC=Medical Research Council; n=number of events; N=total number of patients in the treatment arm; NCRI=National Cancer Research Institute; SWOG=Southwest Oncology Group.

a. p-value from 2-sided stratified log-rank test.

**Figure 11. Overall Survival for Mylotarg + Chemotherapy Versus Chemotherapy Alone – Individual Patient Data Meta-Analysis**




| Events/person-years | | | | | | |
|---|---|---|---|---|---|---|
| All patients | | | | | | |
| GO | 546/1346 | 287/939 | 131/742 | 57/623 | 38/527 | 42/1123 |
| No GO | 569/1348 | 314/905 | 127/689 | 68/568 | 25/485 | 50/1025 |

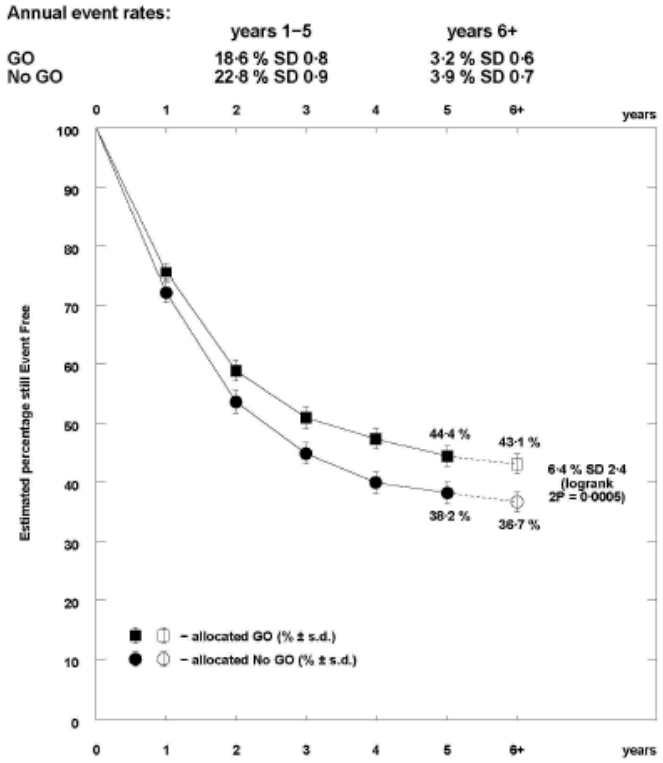
Abbreviations: GO=gemtuzumab ozogamicin (Mylotarg); No GO=patients randomized to chemotherapy alone without Mylotarg; SD=standard deviation.

## Efficacy in Subpopulations

Within the Individual Patient Data MA, subgroup analyses of OS stratified by age, sex, type of induction chemotherapy, FLT3 mutation status, and NPM1 mutation status were consistent with the primary analysis.

Subgroup analysis of OS stratified by Medical Research Council (MRC) cytogenetic risk classification found that OS in the Mylotarg + Chemotherapy arm was significantly prolonged compared to the Chemotherapy Alone arm in patients in the combined favorable or intermediate cytogenetic risk groups (OR 0.82, 95% CI: 0.73-0.92, p=0.0005) (Figure 12). When the favorable and intermediate cytogenetic risk groups were analyzed separately,[34] OS was significantly prolonged in the Mylotarg + Chemotherapy arm compared to the Chemotherapy Alone arm in each group (p=0.001 and p=0.009, respectively).

**Figure 12. Overall Survival for Mylotarg + Chemotherapy Versus Chemotherapy Alone for Favorable/Intermediate Cytogenetic Risk Patients – Individual Patient Data Meta-Analysis**




| Events/person-years | | | | | | |
|---|---|---|---|---|---|---|
| All patients | | | | | | |
| Mylotarg | 249/899 | 170/682 | 82/560 | 36/482 | 27/413 | 28/886 |
| No Mylotarg | 292/881 | 188/632 | 88/495 | 48/412 | 15/353 | 30/767 |

Abbreviations: GO=gemtuzumab ozogamicin (Mylotarg); No GO=patients randomized to chemotherapy alone without Mylotarg; SD=standard deviation.

A subgroup analysis stratified by percent leukemic blasts expressing CD33 (<30% versus ≥ 30%, and <70% versus ≥ 70%) was conducted. No study had eligibility criteria requiring a minimum percent of leukemic blasts expressing CD33. The SWOG S0106 study did not evaluate CD33 expression on patients' leukemic blasts, so data from the SWOG S0106 study patients were excluded from this subgroup analysis. Thus, CD33 expression data were available for 52.5% of patients included in the Individual Patient Data MA. In these patients, the percent of leukemic blasts expressing CD33 was high, with only 12.9% and 24.7% of evaluable patients having leukemic blasts that were <30% and <70% CD33-positive, respectively.

The effect on OS of the addition of Mylotarg to chemotherapy when stratified by percent CD33-positive leukemic blasts was consistent with the primary analysis: Peto OR 0.85 (95% CI: 0.76-0.95; p=0.004) for the <30% versus ≥30% comparison and 0.85 (95% CI: 0.76-0.95; p=0.005) for the <70% versus ≥70% comparison. No difference in response was observed between the categories of percent CD33 positivity for OS.

### 5.1.3.3. Secondary Efficacy Endpoints

Event-free survival is an efficacy endpoint indicative of clinically important benefit to AML patients. Mylotarg + Chemotherapy significantly prolonged EFS compared to Chemotherapy Alone (Peto OR 0.85, 95% CI: 0.78-0.93, p=0.0002, 2-sided stratified log-rank test). This result corresponded to a 15% reduction in risk of EFS events (death, relapse, or induction failure) for the Mylotarg + Chemotherapy arm. The median EFS durations for Mylotarg + Chemotherapy and the Chemotherapy Alone arms were 9.63 months (95% CI: 8.84-10.68 months) and 7.59 months (95% CI: 6.54-8.57 months), respectively.

Mylotarg + Chemotherapy significantly prolonged RFS compared to Chemotherapy Alone (Peto OR 0.84, 95% CI: 0.77-0.93, p=0.0004, 2-sided stratified log-rank test) corresponding to a 16% reduction in risk of RFS (death or relapse) in the Mylotarg + Chemotherapy arm. The median RFS was 18.10 months (95% CI: 16.20-20.67 months) in the Mylotarg + Chemotherapy arm and 14.49 months (95% CI: 13.44-16.10 months) in the Chemotherapy Alone arm.

The CRR did not differ significantly between the Mylotarg + Chemotherapy and the Chemotherapy Alone arms. In the Mylotarg + Chemotherapy arm, 1189 patients (71.5%) achieved a CR compared to 1166 patients (70.0%) in the Chemotherapy Alone arm. Mylotarg treatment did not significantly increase the odds of achieving CR (OR 0.93, 95% CI: 0.80-1.08, p=0.3).

The ORR did not differ significantly between the Mylotarg + Chemotherapy and the Chemotherapy Alone arms. In the Mylotarg + Chemotherapy arm, 1308 patients (78.7%) achieved an ORR compared with 1285 patients (77.1%) in the Chemotherapy Alone arm. However, in patients achieving a response, Mylotarg + Chemotherapy significantly prolonged OS compared to Chemotherapy Alone (OR 0.87, 95% CI: 0.79-0.96, p=0.005).

### 5.1.3.4. Efficacy Conclusions from the Individual Patient Data MA

The Individual Patient Data MA of the 5 randomized controlled studies demonstrated a statistically significant clinical benefit of Mylotarg + Chemotherapy versus Chemotherapy Alone in OS, EFS, and RFS. In the case of OS, the large sample size in the Individual Patient Data MA allowed the demonstration of a statistically significant result which confirmed the trend favoring Mylotarg + Chemotherapy over Chemotherapy Alone that was observed in the ALFA-0701 study. OS results were also consistent with the primary analysis when stratified by subgroups (age, sex, type of induction chemotherapy, CD33 positivity, FLT3 mutation status, or NPM1 mutation status). In addition, the Individual Patient Data MA examined different subsets within the studies and found consistent results, allowing similar conclusions to be drawn across the studies. The one exception in the consistency of the subgroup analyses was for the adverse cytogenetic risk group where the addition of Mylotarg to chemotherapy did not statistically prolong OS, but importantly, also had no detrimental effect on OS.

### 5.1.4. Correlation Between EFS and OS

During the current BLA review, the FDA requested that Pfizer conduct an analysis to evaluate statistically whether EFS, the primary endpoint in the ALFA-0701 study, could be considered a surrogate for OS by assessing individual and study level correlations. Two approaches were employed, the first using individual patient data and the second using summary data from the literature.

Individual Level Correlation

In the first approach, evaluations were conducted excluding and including the ALFA-0701 study using data from the Individual Patient Data MA with 3 types of statistical copula models (Hougaard, Clayton, and Plackett) with a study-specific baseline Weibull hazard.[35, 36, 37, 38] The results were similar among these 3 statistical models. Individual-level correlation as measured by Spearman's ρ was as high as 0.68, both excluding and including the ALFA-0701 study, and indicated a moderate positive correlation between EFS and OS. Additionally, individual level correlation was estimated for each trial, and the correlations were similar to the estimates for the other trials as well as to the combined estimates.

Study Level Correlation

Study-level correlation, using the first approach in these Mylotarg studies, with treatment effects estimated by the copula models and Cox proportional hazards model in weighted regression as measured by the Pearson correlation coefficient, $R^2$, was as high as 0.61. Based on this analysis, in the context of Mylotarg specifically in combination with intensive induction chemotherapy in previously untreated AML, EFS has a moderate correlation with OS, demonstrating a positive relationship between EFS and OS.

In the second approach, evaluations were conducted using all relevant randomized clinical studies of Mylotarg and other agents in patients with previously untreated de novo AML. Further evaluation of study level correlation was assessed in 33 randomized clinical studies in patients with de novo AML receiving first-line induction therapy, in which the experimental treatment was given during induction and which had data for both OS and EFS. These results indicated a positive relationship between EFS and OS, and the observed study level correlation ($R^2$) ranged from approximately 0.45 to 0.50.

**Summary of Individual Level and Study Level Correlations**

These analyses suggested that there is a moderate positive correlation between EFS and OS. The observed level of correlation between EFS and OS is similar in magnitude to those of other published AML investigations.[20, 21, 22, 23] However, in AML, the finding of only a moderate positive correlation between EFS and OS results, at least in part, from the efficacy of rescue therapies and consequent ability to prolong OS after events have occurred.[39]

At the FDA's request, the statistical evaluation of correlation between EFS and OS was repeated with an alternative ad hoc EFS definition that considered (1) only CR (and not CRp/complete remission with incomplete blood count recovery [CRi]) as a treatment success

and (2) the entire induction treatment period (as opposed to within 60 days of randomization used in the Individual Patient Data MA EFS definition). Individual-level correlations were similar among the 3 copula models and were consistent with the correlation based on the original pre-specified EFS definition.

Event-free survival, like OS, is defined for all patients, not just the subset of patients who achieve a CR. As long as patients who do not achieve a CR or relapse can be salvaged (including by HSCT) or live long enough to receive several salvage therapies, the correlation between EFS and OS in AML will remain modest.[20]

## 5.2. Safety in Patients With Previously Untreated AML

### 5.2.1. SWOG S0106 Study

In the SWOG S0106 study[10] where 295 patients received Mylotarg (6 mg/m$^2$) + Chemotherapy (DNR + AraC) and 300 patients received Chemotherapy Alone, the rate of fatal induction toxicity was significantly higher in the Mylotarg + Chemotherapy arm than in the Chemotherapy Alone arm (5.5% versus 1.4%; p=0.0062). The fatal induction toxicity rate in the Mylotarg + Chemotherapy arm was 5.5% versus 1.4% in the Chemotherapy Alone arm. The induction death rate in the Mylotarg + Chemotherapy arm, but not the Chemotherapy Alone arm, was similar to that seen in contemporaneous large Phase 3 trials with a similar population.[8, 9, 10] The most common fatal events included infections and hemorrhages. Six patients in the Mylotarg + Chemotherapy arm died due to hemorrhage: 4 due to central nervous system hemorrhage and 2 due to lung hemorrhage. The fatal induction toxicities in the Mylotarg + Chemotherapy arm were not characterized by an increased number of patients with abnormal liver function tests (LFTs) or VOD. The rate of VOD in this study was 1.7% in the Mylotarg + Chemotherapy arm and 0% in the Chemotherapy Alone arm. The rate of Grade 4 or fatal nonhematologic induction toxicity was also higher in the Mylotarg + Chemotherapy than in the Chemotherapy Alone arm (21% versus 12%). It is now known that a Mylotarg dose of 6 mg/m$^2$ is too high a dose to be combined with chemotherapy due to $C_{max}$-driven adverse events (AEs) and overlapping AE profiles between Mylotarg and chemotherapy.

### 5.2.2. ALFA-0701 Study

In the ALFA-0701 study, 131 patients received Mylotarg + Chemotherapy and 137 patients received Chemotherapy Alone. The treatment-emergent AESIs in ALFA-0701 consisted of hemorrhage (all Common Terminology Criteria for Adverse Events [CTCAE] grades), VOD (all CTCAE grades), severe infections, and any other AE (regardless of the nature of the event) that led to the permanent discontinuation of either Mylotarg or chemotherapy before the completion of the study treatment phase. Of note, AEs leading to dose reduction or temporary discontinuation were not collected. Pfizer also reviewed and adjudicated each reported serious adverse event (SAE) individually to ensure all SAEs in both treatment arms were uniformly assessed for study treatment relatedness. All SAE analyses reference only the Pfizer global safety database.

In the ALFA-0701 study, in which the lower dose fractionated Mylotarg regimen was used, the AESIs by System Organ Class (SOC) in the Mylotarg + Chemotherapy arm and in the

Chemotherapy Alone arm were compared. The AESIs which occurred with a higher incidence in the Mylotarg + Chemotherapy arm than in the Chemotherapy Alone arm included Grade ≥ 1 Haemorrhage (90.1% versus 78.1%) and Grade ≥ 1 VOD (4.6% versus 1.5%). In contrast, the AESI of Grade ≥ 3 Infection had similar incidences in the 2 treatment arms (77.9% versus 77.4%) (Table 8). Although the rates of hemorrhage in ALFA-0701 for both the Mylotarg + Chemotherapy arm and the Chemotherapy Alone arm were higher than the rate (67.1%) in the Mylotarg monotherapy AML in first relapse studies (Studies 201, 202, 203), suggesting a contribution of the concomitant chemotherapy, the rate was also higher in the Mylotarg + Chemotherapy arm relative to the Chemotherapy Alone arm in ALFA-0701. The rates of infection were similar between the Mylotarg + Chemotherapy and Chemotherapy Alone arms.

**Table 8. Adverse Events of Special Interest by MedDRA SOC and PT (As-Treated Population) – ALFA-0701**

| System Organ Class<br>Preferred Term | Mylotarg + Chemotherapy (N = 131) | | Chemotherapy Alone (N = 137) | |
|---|---|---|---|---|
| | All Grades % | Grade 3/4 % | All Grades % | Grade 3/4 % |
| Infections and infestations | | | | |
| Infection[a] | 77.9[b] | 76.3 | 77.4[b] | 74.5 |
| Vascular disorders | | | | |
| Haemorrhage[c] | 90.1 | 20.6 | 78.1 | 8.8 |
| Hepatobiliary disorders | | | | |
| Veno-occlusive liver disease[d] | 4.6 | 2.3 | 1.5 | 1.5 |

Abbreviations: ALFA=Acute Leukemia French Association; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients in the treatment arm; NEC=not elsewhere classified; PT=preferred term; SOC=System Organ Class.

a. Infection included all primary SOC of "Infections and infestations" or any of the following High Level Terms: Bacterial lower respiratory tract infections, Fungal lower respiratory tract infections, Lower respiratory tract infections NEC, Respiratory tract infections NEC, Viral lower respiratory tract infections.
b. Only significant infections were collected and all were considered severe (Grade ≥3).
c. Haemorrhage included any reported PT terms within the Haemorrhage terms (excl. laboratory terms) (standardized MedDRA query [SMQ]) narrow.
d. Veno-occlusive liver disease includes the following reported PTs: Veno-occlusive disease and Veno-occlusive liver disease.

Of the AEs that have been identified with the use of Mylotarg, 2 AEs have emerged to be of special interest, myelosuppression and VOD.

Myelosuppression (Including Neutropenia and Thrombocytopenia)

In AML, bone marrow infiltration by leukemic blasts invariably causes leukopenia, anemia, and thrombocytopenia; thus, AML itself causes myelosuppression. Chemotherapy regimens used to treat AML also produce myelosuppression.[40]

In the ALFA-0701 study, the median times to recovery of platelet counts to 50,000/mm$^3$ were 34.0, 32.0, and 36.5 days in the Mylotarg + Chemotherapy arm in the Induction, Consolidation 1, and Consolidation 2 periods, respectively, and were a few days longer for the corresponding periods in the Chemotherapy Alone arm. Median times to recovery of neutrophil counts to 500/mm$^3$ were similar between the 2 treatment arms (Table 9).

**Table 9. Time to Recovery of Platelets and Neutrophils (As-Treated Population) – ALFA-0701**

| | Mylotarg + Chemotherapy | | | Chemotherapy Alone | | |
|---|---|---|---|---|---|---|
| | Ind N = 131 | Con 1 N = 97 | Con 2 N = 82 | Ind N = 137 | Con 1 N = 97 | Con 2 N = 89 |
| **Platelets** | | | | | | |
| Patients recovered to 50,000/mm$^3$, % | 83.2 | 94.8 | 97.6 | 86.1 | 88.7 | 95.5 |
| Median time to recovery (days)[a] | 34.0 | 32.0 | 36.5 | 29.0 | 27.0 | 30.0 |
| Patients recovered to 100,000/mm$^3$, % | 75.6 | 73.2 | 85.4 | 81.0 | 82.5 | 92.1 |
| Median time to recovery (days)[a] | 35.0 | 35.0 | 43.0 | 30.0 | 28.0 | 32.0 |
| **Neutrophils** | | | | | | |
| Patients recovered to 500/mm$^3$, % | 92.4 | 96.9 | 97.6 | 91.2 | 96.9 | 98.9 |
| Median time to recovery (days)[a] | 25.0 | 21.0 | 22.0 | 24.0 | 22.0 | 22.0 |
| Patients recovered to 1000/mm$^3$, % | 90.1 | 93.8 | 96.3 | 87.6 | 91.8 | 98.9 |
| Median time to recovery (days)[a] | 25.0 | 25.0 | 27.0 | 25.0 | 24.0 | 26.0 |

Abbreviations: ALFA=Acute Leukemia French Association; KM=Kaplan-Meier; Con=Consolidation; Ind=Induction; N=number of patients in each treatment stage within each treatment arm.
a. KM estimate based on the Brookmeyer and Crowley Method.

Veno-Occlusive Disease

Hepatic VOD, also known as sinusoidal obstruction syndrome (SOS), is a syndrome characterized by increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase (ALP), rapid weight gain, ascites, painful hepatomegaly, and jaundice. VOD ranges in severity from a mild, reversible disease to a severe syndrome associated with multi-organ failure and death.[41] Its most common risk factor is the administration of myeloablative conditioning therapy for HSCT. A review of 135 studies of >50 patients undergoing HSCT between 1979 and October 2007 reported that the mean incidence of VOD was 13.7% (95% CI: 13.3%-14.1%).[41]

In the ALFA-0701 study conducted in patients with previously untreated de novo AML who were treated with the lower dose fractionated regimen, 6 (4.6%) patients in the Mylotarg + Chemotherapy arm developed VOD, with 2 cases of fatal VOD reported (Table 10). Two patients (1.5%) in the Chemotherapy Alone arm also developed VOD. Both of these patients were reported to have received Mylotarg during the follow-up phase of the study as part of the compassionate-use program after having experienced relapse before developing VOD. Neither one of these AEs of VOD resulted in death.

**Table 10. Incidence of VOD in Patients Receiving Mylotarg (As-Treated Population) – ALFA-0701**

| | Mylotarg+ Chemotherapy | Chemotherapy Alone |
|---|---|---|
| N | 131 | 137 |
| VOD, n (%) | 6 (4.6) | 2 (1.5) |
| Fatal VOD, n (%) | 2 (1.5) | 0 |
| Patients with HSCT, n (%) | 31 (23.7) | 53 (38.7) |
| HSCT before Mylotarg, N | 0 | 0 |
| HSCT after Mylotarg, N | 31 | 53 |
| Incidence of VOD, n (%) | 3 (9.7) | 2 (3.8) |
| Incidence of fatal VOD, n (%) | 0 | 0 |
| Patients without HSCT, n (%) | 100 (76.3) | 84 (61.3) |
| Incidence of VOD, n (%) | 3 (3.0) | 0 |
| Incidence of fatal VOD, n (%) | 2 (2.0) | 0 |

Abbreviations: ALFA=Acute Leukemia French Association; HSCT=hematopoietic stem cell transplant; n=number of patients in each category; N=total number of patients in the treatment arm; VOD=veno-occlusive disease.

Serious Adverse Events in Study ALFA-0701

A total of 67.2% of patients in the Mylotarg + Chemotherapy arm experienced SAEs, regardless of causality, compared to 55.5% of patients in the Chemotherapy Alone arm (Table 11). The most frequently reported (>10% of patients) SAEs in the ALFA-0701 study were thrombocytopenia and bronchopulmonary aspergillosis.

**Table 11 Treatment-Emergent SAEs (≥ 2% of Patients in Either Treatment Arm) by MedDRA PT (As-Treated Population) – ALFA-0701**

| Preferred Term | Mylotarg+ Chemotherapy (N = 131) | | Chemotherapy Alone (N = 137) | |
|---|---|---|---|---|
| | All-Causality SAEs n (%) | Related SAEs n (%) | All-Causality SAEs n (%) | Related SAEs n (%) |
| Any Serious TEAE | 88 (67.2) | 80 (61.1) | 76 (55.5) | 58 (42.3) |
| Thrombocytopenia | 34 (26.0) | 32 (24.4) | 6 (4.4) | 5 (3.6) |
| Bronchopulmonary aspergillosis | 14 (10.7) | 13 (9.9) | 10 (7.3) | 10 (7.3) |
| Febrile bone marrow aplasia | 12 (9.2) | 12 (9.2) | 8 (5.8) | 7 (5.1) |
| Septic shock | 12 (9.2) | 9 (6.9) | 9 (6.6) | 7 (5.1) |
| Bacterial sepsis | 7 (5.3) | 6 (4.6) | 0 | 0 |
| Acute kidney injury | 6 (4.6) | 3 (2.3) | 4 (2.9) | 0 |
| Acute myeloid leukaemia | 5 (3.8) | 0 | 0 | 0 |
| Acute respiratory distress syndrome | 5 (3.8) | 3 (2.3) | 3 (2.2) | 2 (1.5) |
| Escherichia sepsis | 5 (3.8) | 3 (2.3) | 1 (0.7) | 1 (0.7) |
| Pneumonia | 5 (3.8) | 4 (3.1) | 6 (4.4) | 4 (2.9) |
| Sepsis | 5 (3.8) | 5 (3.8) | 4 (2.9) | 4 (2.9) |
| Veno-occlusive liver disease | 5 (3.8) | 4 (3.1) | 0 | 0 |
| Hepatocellular injury | 4 (3.1) | 4 (3.1) | 2 (1.5) | 0 |
| Cholestatic liver injury | 3 (2.3) | 3 (2.3) | 2 (1.5) | 1 (0.7) |
| Disease progression | 3 (2.3) | 0 | 0 | 0 |
| Enterococcal sepsis | 3 (2.3) | 3 (2.3) | 0 | 0 |
| Febrile neutropenia | 3 (2.3) | 1 (0.8) | 1 (0.7) | 1 (0.7) |
| Mucosal inflammation | 3 (2.3) | 3 (2.3) | 1 (0.7) | 1 (0.7) |
| Staphylococcal sepsis | 2 (1.5) | 2 (1.5) | 5 (3.6) | 5 (3.6) |
| Toxic skin eruption | 1 (0.8) | 1 (0.8) | 3 (2.2) | 3 (2.2) |

A patient with multiple occurrences of the same treatment-emergent SAE at the preferred term level is only counted once in each row.
Related SAEs are designated as such by the company (Pfizer) and were considered as study drug related if any one of the study drugs was assessed as related.
Argus data summarized.
MedDRA version 18.0 for ALFA-0701.
Abbreviations: ALFA=Acute Leukemia French Association; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with at least 1 event for the given serious TEAE; N=total number of patients in the treatment arm; PT=preferred term; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Deaths in Study ALFA-0701

In the ALFA-0701 study, deaths during the safety reporting period (ie, from first dose to 28 days after the last dose of study treatment) were reported in 6 patients (4.6%) in the Mylotarg + Chemotherapy arm and 5 patients (3.6%) in the Chemotherapy Alone arm. While the number (%) of patients who died was numerically higher in the Mylotarg + Chemotherapy arm than in the Chemotherapy Alone arm at 28 days following the last dose of study treatment, the number (%) of patients who died was similar at 60 days after the first dose of study treatment (7 patients [5.3%] in the Mylotarg + Chemotherapy arm versus 7 patients [5.1%] in the Chemotherapy Alone arm). The reasons for death (regardless of causality) on study included hemorrhage, infection, and VOD/liver toxicity (1 case after the induction course and 1 case after the first consolidation course)[30] (Table 12).

**Table 12. Deaths Within 28 Days of Last Dose of Study Treatment (As-Treated Population) – ALFA-0701**

| | Mylotarg + Chemotherapy (N = 131) n (%) | Chemotherapy Alone (N = 137) n (%) |
|---|---|---|
| **Death within 28 days after last dose** | 6 (4.6) | 5 (3.6) |
| **Cause of death** | | |
| Disease progression or relapse | 2 (1.5) | 2 (1.5) |
| Septic shock | 2 (1.5) | 2 (1.5) |
| Infection | 0 | 1 (0.7) |
| Liver toxicity | 1 (0.8) | 0 |
| Haemorrhage | 3 (2.3) | 1 (0.7) |
| Other[a] | 2 (1.5) | 3 (2.2) |

More than 1 mechanism of death on the relevant CRF could have been selected; therefore, row totals could be larger than the total number of deaths.
Last dose of study treatment was determined from the Mylotarg, daunorubicin, cytarabine dosing records and also included idarubicin (a component of salvage therapy).
Abbreviations: ALFA=Acute Leukemia French Association; CRF=case report form; n=number of patients with at least 1 event in the category; N=total number of patients in the treatment arm.

a. Among the 5 the patients reported under the "Other" mechanism of death, 3 died because of multiple mechanism of deaths including Haemorrhage, Infection or Septic Shock, 1 patient died of unknown causes where a cardiac cause was suspected, and the fifth patient died of cardiorespiratory arrest.

In total, 12 patients (4.5%) had treatment-related deaths, including all patients who died because of events reported at any time during the study, either in the clinical or safety databases as of the OS analysis reference date of 30 April 2013, and assessed as related to the study drug: 7 patients (5.3%) in the Mylotarg + Chemotherapy arm and 5 patients (3.6%) in the Chemotherapy Alone arm. These 12 patients included 8 patients whose primary cause of death was assessed as study treatment toxicity by the investigator; 3 patients whose primary cause of death was assessed by the investigator as being related to disease progression, but had ongoing events considered related to the study drug at the time of death; and 1 patient whose cause of death was unknown (despite autopsy), but relatedness to the study drug could not be excluded.

### 5.2.3. Individual Patient Data Meta-Analysis

The safety data from the Individual Patient Data MA included AESIs that were predefined based on similarities in the prospectively collected AEs across the 5 studies (Table 13). In the Individual Patient Data MA, the treatment-emergent adverse events (TEAEs) of special interest were Grade 3/4 TEAEs (as defined by CTCAE version 3.0) in the following categories were collected and analyzed: oral toxicity/mucositis, haemorrhage, cardiac toxicity, neurological toxicity, VOD, infection, AST elevation, ALT elevation, bilirubin elevation, persistent neutropenia, persistent thrombocytopenia, and a composite AE consisting of nausea/vomiting/diarrhea. Deaths within 30 days following randomization were also analyzed.

The AE data from the ALFA-0701 study are supported by the AE data from the 5 randomized clinical studies in the Individual Patient Data MA. In the Individual Patient

Data MA, 75.2% of patients in the Mylotarg + Chemotherapy arm and 71.9% of patients in the Chemotherapy Alone arm experienced a Grade 3/4 AESI.

The overall incidence of Grade 3/4 VOD in the Individual Patient Data MA was 1.1% in patients randomized to Mylotarg + Chemotherapy and 0.1% in patients randomized to Chemotherapy Alone (Table 13). Two patients with VOD were identified in the Mylotarg + Chemotherapy arms in the MRC AML15 and NCRI AML16 studies (0.2%), while 1.7% to 4.8% of patients had VOD in the other 3 studies.

**Table 13. Overview of Safety – Individual Patient Data Meta-Analysis**

| | Mylotarg + Chemotherapy N = 1663 | | Chemotherapy Alone N = 1668 | |
|---|---|---|---|---|
| | n (%) | N* | n (%) | N* |
| Any AESI toxicity type Grade 3/4** | 1251 (75.2) | 1663 | 1199 (71.9) | 1668 |
| Hepatotoxicity | | | | |
| ALT Grade 3/4 | 185 (12.1) | 1528 | 155 (10.1) | 1533 |
| AST Grade 3/4 | 136 (12.0) | 1135 | 88 (7.9) | 1114 |
| Bilirubin Grade 3/4 | 144 (8.8) | 1630 | 137 (8.4) | 1630 |
| VOD Grade 3/4 | 18 (1.1) | 1661 | 2 (0.1) | 1667 |
| Hemorrhage Grade 3/4 | 114 (6.9) | 1663 | 67 (4.0) | 1668 |
| Infection Grade 3/4 | 486 (31.6) | 1537 | 505 (32.7) | 1543 |
| Myelosuppression | | | | |
| Persistent neutropenia Grade 3/4 | 228 (23.6) | 965 | 247 (25.7) | 960 |
| Persistent thrombocytopenia Grade 3/4 | 433 (40.3) | 1075 | 393 (36.7) | 1070 |

*Number of patients included in the analysis varied between studies as safety endpoints data were not available for all patients in all studies
**This row provides the number (incidence) of patients in each treatment arm who experienced at least 1 Grade 3/4 AESI.
Abbreviations: AESI=adverse event of special interest; ALT=alanine aminotransferase; AST=aspartate aminotransferase; n=number of patients in each category; N=total number of patients in the treatment arm; SAE=serious adverse event; VOD=veno-occlusive disease.

In the Individual Patient Data MA, 32.2% of patients in the Mylotarg + Chemotherapy arm and 26.4% of patients in the Chemotherapy Alone arm experienced an SAE.

A total of 109 deaths (6.6%) occurred within 30 days after randomization in 1663 patients randomized to the Mylotarg + Chemotherapy arm, and 85 deaths (5.1%) occurred within 30 days in 1668 patients randomized to the Chemotherapy Alone arm (Table 14). The OR for 30-day mortality in the Mylotarg + Chemotherapy arm was higher relative to the Chemotherapy Alone arm, but not statistically different with an OR 1.29 (95% CI: 0.97-1.71). The 30-day mortality associated with Mylotarg administered at 6 mg/m$^2$ + Chemotherapy relative to Chemotherapy Alone (OR 2.78 [95% CI: 1.33-5.84]) was higher than Mylotarg administered at 3 mg/m$^2$ + Chemotherapy relative to Chemotherapy Alone (OR 1.13 95% CI: 0.83-1.53).

**Table 14. 30-Day Mortality – Individual Patient Data Meta-Analysis**

| | Mylotarg + Chemotherapy n/N (%) | Chemotherapy Alone n/N (%) | Odds Ratio (CI) |
|---|---|---|---|
| **3 mg/m$^2$** | | | |
| MRC AML15 | 34/548 (6.2) | 30/551 (5.4) | 1.14 (0.60, 2.18) |
| NCRI AML16 | 48/559 (8.6) | 45/556 (8.1) | 1.06 (0.62, 1.81) |
| Subtotal | 82/1107 (7.4) | 75/1107 (6.8) | 1.09 (0.80, 1.49) |
| **3 mg/m$^2$ fractionated** | | | |
| ALFA-0701 | 6/135 (4.4) | 3/136 (2.2) | 1.99 (0.54, 7.36) |
| **6 mg/m$^2$** | | | |
| GOELAMS IR2006 | 4/126 (3.2) | 3/125 (2.4) | 1.31 (0.19, 9.19) |
| SWOG S0106 | 17/295 (5.8) | 4/300 (1.3) | 3.58 (1.16, 11.03) |
| Subtotal | 21/421 (5.0) | 7/425 (1.6) | 2.78 (1.33, 5.84) |
| **Total** | 109/1663 (6.6) | 85/1668 (5.1) | 1.29 (0.97, 1.71) |

Abbreviations: ALFA=Acute Leukemia French Association; AML=acute myeloid leukemia; CI=Confidence interval; GOELAMS=Groupe Ouest Est d'Etude des Leucémies aiguës et Autres Maladies du Sang; MRC=Medical Research Council; n=number of patients in each category; N=total number of patients in the treatment arm; NCRI=National Cancer Research Institute; SWOG=Southwest Oncology Group.

## 6. MYLOTARG IN PATIENTS WITH RELAPSED AML

Subsequent to the approval of Mylotarg and the identification of post-approval safety concerns, cooperative group studies were conducted to explore alternative dosing regimens that maintain efficacy and improve tolerability. The MyloFrance 1 study,[42] conducted by the Acute Leukemia French Association (ALFA) cooperative group, provided evidence that a lower dose fractionated regimen (3 mg/m$^2$ on Days 1, 4, and 7) produced similar efficacy to that seen in Studies 201, 202, and 203 with improved safety/tolerability. Efficacy and safety data from MyloFrance 1 are provided in Section 6.1.3 and Section 6.2.4, respectively.

### 6.1. Efficacy in Patients With Relapsed AML

#### 6.1.1. Studies 201, 202, and 203

Studies 201, 202, and 203 were single-arm Phase 2 studies in adult patients with CD33-positive AML in first relapse. The 3 studies had similar design and used an identical 9 mg/m$^2$ x 2 dosing regimen (Mylotarg 9 mg/m$^2$ given on Days 1 and 15 [total dose of 18 mg/m$^2$]). The primary objective of the studies was to assess the ORR (number [%] of patients achieving CR or CRp subsequently re-analyzed according to IWG criteria [CR$^{IWG}$ or CRp$^{IWG}$]) and safety of Mylotarg monotherapy. Secondary objectives included assessments of CR and CRp duration, hematologic characteristics of response, and PK parameters. Overall survival was measured as a secondary endpoint.

In the 3 studies, a total of 277 patients were treated with Mylotarg. The ORR$^{IWG}$ was 35%, with 15% of patients achieving CR$^{IWG}$ and 20% of patients achieving CRp$^{IWG}$ (Table 15). In terms of durability of response, the median RFS duration was 5.0 months for patients with ORR$^{IWG}$. Median RFS$^{IWG}$ was 7.4 months for patients who achieved CR$^{IWG}$ and 4.2 months for patients who achieved CRp$^{IWG}$ (log rank p=0.0222).

**Table 15. IWG-Defined Remission Rates in Pooled Studies 201/202/203**

| Remission Category | n/N (%) | 95% CI |
|---|---|---|
| $CR^{IWG}$ | 42/277 (15) | 11-20 |
| $CRp^{IWG}$ | 56/277 (20) | 16-25 |
| $ORR^{IWG}$ | 98/277 (35) | 30-41 |

95% CIs were calculated using the exact Clopper-Pearson method.
Abbreviations: CI=confidence interval; $CR^{IWG}$=complete remission (IWG-defined criteria); $CRp^{IWG}$=complete remission with incomplete platelet recovery (IWG-defined criteria); IWG=International Working Group; n=number of patients in remission category; N=total number of patients; $ORR^{IWG}$=overall response rate (IWG-defined criteria).

These response rates were higher than the 21%-23% rates recently published in a randomized controlled trial comparing various agents administered as monotherapy to patients with relapsed/refractory AML.[11]

Median OS durations were 4.9 months overall and 11.1 months for patients experiencing $ORR^{IWG}$. These results demonstrated an improvement over those seen with low-dose AraC, which had been reported to induce responses in 15% to 20% of patients with median survival times of 5 to 6 months.[4]

### 6.1.2. Rationale for Lower Dose Fractionated Regimen

Pharmacodynamic analysis (CD33 site saturation) of Mylotarg indicated that an estimated dose of 3 mg/m$^2$ resulted in 90% to 95% saturation of CD33 (see Section 3.1). In vitro data indicated that at least 90% of CD33 saturation is required for efficient killing of AML blasts.[28] In vivo and in vitro studies showed internalization and re-expression of the CD33 antigen after binding of anti-CD33 antibodies,[43] leading to the hypothesis that repeated administration of lower doses of Mylotarg (eg, 3 mg/m$^2$ on Days 1, 4, and 7) may enhance the internalization process and thus the intracellular accumulation and activity of the drug.[44]

Based on this early research, the ALFA cooperative group conducted 2 pilot Phase 2 studies, MyloFrance 1 (with Mylotarg monotherapy)[42] and MyloFrance 2 (with Mylotarg in combination with chemotherapy), to assess a lower dose fractionated regimen of Mylotarg (3 mg/m² [maximum dose 5 mg] on Days 1, 4, and 7) in adults with relapsed AML. These 2 studies showed that Mylotarg administered in low, fractionated doses demonstrated a similar efficacy as the original 9 mg/m$^2$ x 2 dosing regimen, with an improved tolerability and safety profile in the relapsed AML treatment setting (Section 6.1.3), and provided impetus to use this lower dose fractionated regimen in combination with induction chemotherapy for patients with previously untreated de novo AML in the ALFA-0701 study (see Section 5.1.2).

### 6.1.3. MyloFrance 1

MyloFrance 1 was a prospective, multicenter, single-arm, Phase 2 study that evaluated the efficacy and safety of lower fractionated doses of Mylotarg monotherapy administered IV as a 2-hour infusion on Days 1, 4, and 7 in adult patients with AML in first relapse, with durations of first response from 3 to 18 months.[42] Of the 57 treated patients, 19 patients (33.3%) achieved a response (CR or CRp) by Day 43, including 26.3% who had CR and

7.0% who had CRp (Table 16). Of the 19 patients in CR or CRp, 18 subsequently received AraC consolidation per study protocol. These results are comparable to those seen in the original Mylotarg studies (201, 202, and 203).

**Table 16. Efficacy Outcomes – MyloFrance 1**

| Main Efficacy Outcome | |
|---|---|
| Early deaths (before Day 43), n/N (%) | 4/57 (7.0) |
| CR/CRp, n/N (%) | 19/57 (33.3) |
| CR, n/N (%) | 15/57 (26.3) |
| CRp, n/N (%) | 4/57 (7.0) |
| Median OS | 8.4 months |
| Median RFS | 11.0 months |

Abbreviations: CR=complete remission; CRp=complete remission with incomplete platelet recovery; N=total number of patients in study; n=number of patients with outcome; OS=overall survival; RFS=relapse-free survival.

MyloFrance 2 showed that the combination of lower fractionated Mylotarg doses with DNR plus AraC was active and tolerable in 20 patients with AML in first relapse and prompted the investigation of a lower dose fractionated Mylotarg regimen in combination with chemotherapy in the ALFA-0701 study in patients with previously untreated de novo AML (see Section 5.1.2).[45]

### 6.2. Safety in Patients With Relapsed AML

The safety profile of Mylotarg given as the original 9 mg/m$^2$ x 2 dosing regimen in relapsed AML was established in the 3 Phase 2 studies (Studies 201, 202, and 203; N = 277) which shared similar study objectives and designs. The current BLA submission also incorporates data from 8 additional studies conducted by Wyeth, including 5 dose-finding studies (N = 149), 2 post-marketing studies (N = 505), and 1 MDS study (N = 26). Limited safety data from MyloFrance 1 are presented in Section 6.2.4.

#### 6.2.1. Studies 201, 202, and 203

Overall, in the 3 Phase 2 studies (201, 202, and 203), 99.6% of patients experienced 1 or more TEAEs, as shown in Table 17. The most frequently reported TEAEs included adverse events that are common in patients with AML and in those undergoing chemotherapy.

**Table 17. Summary of TEAEs – Studies 201/202/203**

| | Mylotarg 9 mg/m$^2$ (N = 277) | |
|---|---|---|
| | **All Causality n (%)** | **Treatment-Related n (%)** |
| Number (%) of patients | | |
| Patients with TEAEs | 276 (99.6) | 274 (98.9) |
| Patients with Grade 3 or 4 TEAEs | 267 (96.4) | 250 (90.3) |
| Patients with Grade 5 TEAEs | 43 (15.5) | 22 (7.9) |
| Patients who discontinued study treatment due to TEAEs | 40 (14.4) | 24 (8.7) |
| Patients with TEAEs leading to dose reduction | 1 (0.4) | 0 |
| Patients with TEAEs leading to temporary discontinuation | 6 (2.2) | 5 (1.8) |

Abbreviations: n=number of patients with finding in each category; N=total number of patients; TEAE=treatment-emergent adverse event.

### 6.2.2. Myelosuppression (Including Neutropenia and Thrombocytopenia) With Mylotarg Monotherapy

In the 3 Phase 2 relapsed AML studies (201, 202, 203) using the original 9 mg/m$^2$ x 2 dosing regimen of Mylotarg, the median time to recovery of platelet counts to 50,000/mm$^3$ was 80.0 days overall (51.0 days in responders) and median time to recovery of neutrophil counts to 500×10$^6$/L was 45.0 days overall (40.5 days in responders) (Table 18).

**Table 18. Time to Recovery of Platelets and Neutrophils – Studies 201/202/203**

| | Mylotarg 9 mg/m$^2$x 2 (N = 277) | |
|---|---|---|
| | **ORR** | **Overall** |
| **Platelets** | | |
| Patients recovered to 50,000/mm$^3$, % | 22.4 | 35.0 |
| Median time to recovery (days)[a] | 51.0 | 80.0 |
| Patients recovered to 100,000/mm$^3$, % | 14.8 | 19.5 |
| Median time to recovery (days)[a] | 99.0 | NE |
| **Neutrophils** | | |
| Patients recovered to 500×10$^6$/L, % | 26.0 | 57.0 |
| Median time to recovery (days)[a] | 40.5 | 45.0 |
| Patients recovered to 1000×10$^6$/L, % | 26.0 | 48.4 |
| Median time to recovery (days)[a] | 43.5 | 52.0 |

Abbreviation: N=total number of patients; NE=not estimable; ORR=overall response rate.
a. Based on the Brookmeyer and Crowley Method with log(-log) transformation.

### 6.2.3. Veno-Occlusive Disease With Mylotarg Monotherapy

In the 3 trials of Mylotarg employing the original 9 mg/m$^2$ x 2 dosing regimen in relapsed AML (Studies 201, 202 and 203), the incidence of VOD was 5.4%, with fatal VOD reported in 3.6% of patients. The incidence of VOD was also investigated in a larger pool of 936 patients who participated in the Mylotarg monotherapy studies included in the BLA submission. In these 936 patients, there was a higher incidence of patients with VOD

(8.2%), with fatal VOD occurring in 2.4% of the patients. The pooled data included the Phase 4 usual care Study 100847, in which 44 of 482 patients (9.1%) developed VOD and 9 patients (1.9%) developed fatal VOD (Table 19). The incidence of VOD was highest in patients who underwent HSCT, either before or after treatment with Mylotarg (Table 19). Although patients enrolled in Studies 201, 202 and 203 were considered ineligible for standard cytotoxic chemotherapy, a number of patients underwent HSCT either prior to study entry or following treatment with Mylotarg. In these 3 studies, 77 (27.8%) of 277 patients underwent HSCT, with an incidence of VOD of 18.5% when HSCT occurred prior to Mylotarg therapy, and 16.0% when HSCT occurred following Mylotarg therapy. The analogous incidences of VOD in the pooled relapsed or refractory AML study dataset, in which 291 (31.2%) of 936 patients underwent HSCT, were 14.7% and 19.0%, respectively.

**Table 19. Incidence of VOD for Patients Receiving Mylotarg – Relapsed/Refractory AML**

| | Relapsed/Refractory AML | | |
|---|---|---|---|
| | **Studies 201/202/203 Mylotarg Dose 9 mg/m$^2$ Days 1 & 15** | **Study 100847[a] Mylotarg Dose Per Treating Physician** | **All Mylotarg Monotherapy Studies** |
| N | 277 | 482 | 936 |
| VOD, n (%) | 15 (5.4) | 44 (9.1) | 77 (8.2) |
| Fatal VOD, n (%) | 10 (3.6) | 9 (1.9) | 22 (2.4) |
| HSCT before Mylotarg, N | 27 | 88 | 170 |
| Incidence of VOD, n (%) | 5 (18.5) | 12 (13.6) | 25 (14.7) |
| Incidence of fatal VOD, n (%) | 2 (7.4) | 3 (3.4) | 7 (4.1) |
| HSCT after Mylotarg, N | 50 | 55 | 121 |
| Incidence of VOD, n (%) | 8 (16.0) | 8 (14.5) | 23 (19.0) |
| Incidence of fatal VOD, n (%) | 6 (12.0) | 2 (3.6) | 9 (7.4) |
| No HSCT, N | 200 | 339 | 601 |
| Incidence of VOD, n (%) | 2 (1.0) | 24 (7.1) | 28 (4.7) |
| Incidence of fatal VOD, n (%) | 2 (1.0) | 4 (1.2) | 6 (1.0) |

Abbreviations: AML=acute myeloid leukemia; HSCT=hematopoietic stem cell transplant; n=number of patients in category; N=total number of patients; SOS=sinusoidal obstruction syndrome; VOD=veno-occlusive disease.

a. In Study 100847, where a primary study objective was to estimate the incidence of hepatic VOD in the post-approval clinical setting, the data collection and assessment of VOD included an expert panel's determination of VOD/SOS (including diagnostic certainty and severity). The adjudicated VODs were included in the analysis for this study.

Risk Factors for VOD in Patients with Relapsed/Refractory AML

The potential association of key variables with the risk of developing VOD (both VOD observed at any time following exposure to Mylotarg and VOD within 28 days of any dose of Mylotarg) was assessed by logistic regression. The analysis included adult patients treated with Mylotarg monotherapy from all relapsed/refractory AML studies except dose-finding Study 103, and had data for all key variables. The covariates evaluated in this analysis were age, sex, starting dose of Mylotarg (mg/m$^2$), total dose of Mylotarg (in mg), number of Mylotarg doses, baseline ALT, baseline AST, baseline bilirubin, hepatic impairment baseline

(categorized into 2 categories moderate/severe and none/mild) and indicator of HSCT (prior and follow-up).

For patients with data for the covariates listed above (N = 669), the covariates of HSCT prior to study entry, HSCT following Mylotarg treatment, and moderate/severe hepatic impairment at baseline were associated with a statistically significantly increased risk for development of VOD at any time following exposure to Mylotarg. Patients who had received an HSCT prior to Mylotarg exposure were 2.6 times more likely (95% CI: 1.448-4.769] to develop VOD compared to patients without HSCT prior to Mylotarg treatment; patients who had received an HSCT following Mylotarg treatment were 2.9 times more likely (95% CI: 1.502-5.636) to develop VOD compared to patients without HSCT following Mylotarg treatment; and 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 patients without moderate/severe hepatic impairment at baseline.

For patients with all the covariates listed above plus the additional covariates of HSCT within 60 days of Mylotarg dose, and any exposure to busulfan, cyclophosphamide, and radiation (N = 614), the factors of HSCT prior to study entry, hepatic impairment at baseline, and starting dose level ($mg/m^2$) were associated with a statistically significant increased risk for VOD within 28 days of any Mylotarg dose. Patients who had received an HSCT prior to Mylotarg exposure were 3.5 times more likely (95% CI: 1.692-7.049) to develop VOD compared to patients without HSCT prior to Mylotarg treatment, and patients who had moderate/severe hepatic impairment at baseline were 9.2 times more likely (95% CI: 1.805-46.512) to develop VOD compared to patients without moderate/severe hepatic impairment at baseline. For each increase of 1 $mg/m^2$ in starting dose level, the risk of VOD increased by 1.3 times.

Additional analyses of VOD were conducted in patients who had undergone HSCT (N = 119). In addition to all the covariates mentioned above, the timing of HSCT relative to the Mylotarg dose was also considered. Exposure to radiation was identified as having statistically significant increased risk for development of VOD. Patients with HSCT who had exposure to radiation were 3.2 times more likely (95% CI: 1.105-9.305]) to develop VOD compared to patients without exposure to radiation.

Serious Adverse Events

Overall, 93.1% of patients in the relapsed AML Studies 201/202/203 experienced SAEs, regardless of causality. The most frequently reported SAEs (>20% of patients) were Pyrexia, Neutropenia, Thrombocytopenia, and Sepsis.

In the 3 relapsed AML studies (201/202/203), 29 patients (10.5%) died within 30 days after their first dose of Mylotarg, and 51 patients (18.4%) died while on treatment or within 28 days after their last dose of Mylotarg. The most frequently reported all causality Grade 5 AE SOCs were Infections and Infestations (21 patients, 7.6%), Nervous System Disorders (9 patients, 3.2%) and Respiratory, Thoracic and Mediastinal Disorders (5 patients, 1.8%). Of the 43 patients that had a Grade 5 TEAE leading to death, 22 patients experienced Grade 5 TEAEs that were considered related to Mylotarg by the investigator. The most frequently

reported treatment-related Grade 5 AE SOCs were Infections and Infestations (11 patients, 4.0%) and Nervous System Disorders (7 patients, 2.5%).

### 6.2.4. MyloFrance 1

The MyloFrance 1 study provided initial evidence that Mylotarg administered in a lower dose fractionated regimen could reduce the duration of cytopenia compared with the original 9 mg/m$^2$ x 2 dosing regimen in patients with AML in first relapse.[42] In the 19 patients who achieved a response in the MyloFrance 1 study, the median times to recovery of neutrophil count to 500/mm$^3$ and of platelet count to 50,000/mm$^3$ occurred at 23 and 20 days, respectively, which were approximately half the median times to recovery observed in Studies 201/202/203 (40.5 days and 51 days, respectively). Thus, MyloFrance 1 provides support of the exposure response modeling in that lower fractionated dosing of Mylotarg in patients with AML in first relapse reduces the duration of cytopenia compared to the original 9 mg/m$^2$ x 2 dosing.

Grade 3 TEAEs and their respective incidences that occurred in >1% patients in the MyloFrance 1 study included sepsis (31.5%), fever (15.8%), rash (10.5%), pneumonia (7.0%), bleeding (7.0%), mucositis (3.5%), and diarrhea, headaches, tachycardia, and edema (1.8% each). No Grade 4 toxicity was observed in the MyloFrance 1 study. No infectious deaths occurred.

Grade 1 or 2 hyperbilirubinemia (1.5 to 3 × upper limit of normal [ULN]) was reported in 4 patients. Grade 1 or 2 elevations of AST or ALT levels (> ULN to 5 × ULN) were observed in 23 patients and 9 patients, respectively. No episodes of VOD occurred.

Seven patients received HSCT after Mylotarg treatment. Three patients received an allogeneic bone marrow transplant (BMT) (2 NR, 1 CR): 1 patient relapsed 2 months after transplant, 1 patient died 5 months after transplant, and 1 patient remained alive in CR 14 months after transplant. Four patients (1 CRp, 3 CR) were treated with autologous BMT: 3 patients relapsed after 4, 9, and 9 months. One patient remained alive in CR 12 months after transplant. None of these patients developed VOD.

Deaths before Day 43 occurred in 4 of the 57 patients (7%) and 2 of these patients died with resistant disease.

## 7. RATIONALE FOR PROPOSED DOSING REGIMENS

In order to find an optimal dosing regimen that maintained efficacy and reduced Mylotarg toxicity, Pfizer has reviewed previous PK/PD studies, supported the AML community to generate new data, and conducted exposure-response modeling to explore the PK/efficacy and PK/safety relationships of Mylotarg. Pharmacokinetic/PD study data indicated that a dose of 3 mg/m$^2$ is sufficient to saturate 90%-95% of CD33 on the surface of AML blasts. Exposure-response modeling conducted by Pfizer supported the hypothesis that repeated administration of lower fractionated doses (3 mg/m$^2$) of Mylotarg would enhance leukemic cell internalization of CD33-Mylotarg complexes, thereby increasing the intracellular concentration of calicheamicin, the cytotoxic moiety of Mylotarg, and improving efficacy. The model also predicted that the lower dose fractionated regimen would result in lower

cumulative exposure relative to the original 9 mg/m$^2$ x 2 dosing regimen, leading to an improved safety profile.

### 7.1. Rationale for Proposed Dosing Regimen in Patients With Previously Untreated De Novo CD33-Positive AML

Exposure-response modeling predicted that Mylotarg administered as a lower dose fractionated regimen of 3 mg/m$^2$ on Days 1, 4, and 7 in combination with AraC and DNR for previously untreated de novo CD33-positive AML would produce sufficient exposure for efficacy (as defined by 90% to 95% saturation of CD33 on leukemic blast cells), but with a lower $C_{max}$, which in turn would reduce certain AEs (eg, VOD, bilirubin elevation, AST elevation) compared to the original 9 mg/m$^2$ x 2 dosing regimen. Since some of the same AEs, such as myelosuppression, are associated with Mylotarg as well as chemotherapeutic agents, the reduced dose of Mylotarg was expected to help improve the overall safety profile when used in combination with chemotherapy. Thus, the exposure-response model supported the use of the lower dose fractionated regimen of Mylotarg at 3 mg/m$^2$ in combination with chemotherapy. Consistent with the dosing regimen used in the ALFA-0701 study, capping each dose at 5 mg is also recommended.

Based on the results from the exposure-response model and the results of the ALFA-0701 study, and the Individual Patient Data MA, the following dosing regimens of Mylotarg in combination with DNR + AraC for the treatment of patients with previously untreated de novo CD33-positive AML are recommended:

- Induction: The recommended dose of Mylotarg is 3 mg/m² 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/m²/day infused over 30 minutes on Days 1, 2, and 3 and AraC 200 mg/m²/day by continuous infusion on Days 1 to 7.
- Consolidation: For patients experiencing a CR following induction, defined as fewer than 5% blasts in a normocellular marrow and an absolute neutrophil count (ANC) of more than $1.0 \times 10^9$ cells/L with a platelet count of $100 \times 10^9$/L or more in the peripheral blood in the absence of transfusion, up to 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 1-4) with intravenous Mylotarg (3 mg/m$^2$/dose infused over 2 hours up to a maximum dose of 5 mg/dose on Day 1) are recommended.

### 7.2. Rationale for Proposed Dosing Regimen in Patients With CD33-Positive AML in First Relapse

The initially approved Mylotarg dosing regimen of 9 mg/m$^2$ on Days 1 and 15 of the induction phase in patients with CD33-positive AML in first relapse was established based on the data from Study 101, where dose escalation was stopped at the 9 mg/m$^2$ dose level due to increased myelosuppression. The exposure-response modeling (see Section 4.2) showed a significant exposure-response relationship between cumulative exposure to Mylotarg and both ORR (CR+CRp, using IWG criteria) and attainment of blast-free status. The model also predicted that 2 doses of Mylotarg as monotherapy significantly increased the probability of

remission (Figure 3) and blast-free status (data not shown) compared with a single dose of Mylotarg. However, as was observed in Study 101, the administration of more than 2 doses of Mylotarg at 9 mg/m$^2$ was associated with prolonged myelosuppression. The 14-day interval between doses was selected on the basis of near-total clearance of the antibody within this time period.

The indication for Mylotarg monotherapy for the treatment of CD33-positive AML in first relapse is supported by data from 277 patients with relapsed AML in the single-arm, Phase 2 Studies 201, 202, and 203 submitted as part of the original NDA. These studies were conducted with the original Mylotarg monotherapy dosing regimen of 9 mg/m$^2$ administered on Days 1 and 15 during the induction phase. The clinical benefit observed in these studies supported its accelerated approval in May 2000. Data from 57 patients with relapsed AML in the MyloFrance 1 study, conducted with the lower dose fractionated Mylotarg monotherapy regimen of 3 mg/m$^2$ on Days 1, 4, and 7, were supportive of the results observed in Studies 201, 202, and 203.

Overall, the data support use of the following Mylotarg dosing regimen for the treatment of patients with CD33-positive AML in first relapse:

- The recommended dose of Mylotarg used as monotherapy for the treatment of CD33-positive AML in first relapse is 9 mg/m$^2$, infused IV over a 2-hour period, with up to 2 doses administered 14 to 28 days apart.

### 7.2.1. Dosing Regimen Adjustment for Patients With CD33-Positive AML in First Relapse who Undergo HSCT

While the dose of 9 mg/m$^2$ x 2 has a favorable benefit/risk relationship for patients with CD33-positive AML in first relapse, new approaches to dosing regimens were investigated in order to improve tolerability. Lower fractionated dosing of Mylotarg appeared to retain efficacy and improve safety, particularly in patients who underwent HSCT, which was shown to be a significant predictor of VOD in the exposure-response model (Figure 4). This conclusion was supported by the results of the MyloFrance 1 study (see Section 6.2.4). Similar efficacy and better safety results were observed compared with the results of the primary Phase 2 studies that used the original 9 mg/m$^2$ x 2 dosing regimen (Studies 201/202/203).

Therefore, based on this information and to minimize the risk of VOD, Pfizer proposes to incorporate the lower dose fractionated Mylotarg regimen of 3 mg/m$^2$ (up to a maximum of 5 mg) infused over a 2-hour period on Days 1, 4, and 7, into the proposed Mylotarg product label for disease in first relapse as an alternative dosing option for the subset of patients with relapsed CD33-positive AML who have a history of HSCT or may undergo HSCT subsequent to Mylotarg therapy. This dosing regimen would provide a balance between safety and efficacy in patients who may be at a higher risk of VOD:

- The recommended dose of Mylotarg used as monotherapy for the treatment of CD33-positive AML in first relapse is 3 mg/m$^2$ Mylotarg on Days 1, 4, and 7 for patients who have received or may receive HSCT.

# 8. DISCUSSION

Following withdrawal of Mylotarg from the US, continued research by AML investigators and international cooperative groups has supported the concept of Mylotarg as a valued and viable initial treatment for patients with either previously untreated de novo CD33-positive AML or CD33-positive AML in first relapse. For patients with previously untreated de novo disease, the unmet medical need is high, but for patients in first relapse, the therapeutic need is dire, and demand for Mylotarg has continued based on increasing expanded access program and compassionate-use requests. Studies have been conducted by cooperative groups to evaluate new Mylotarg dosing regimens in order to improve both safety and efficacy for these patients. The new Mylotarg dosing regimens have reduced early mortality and VOD, particularly in the setting of HSCT. In addition, better understanding of VOD and new treatment strategies have mitigated VOD risk, as have improvements in patient selection and conditioning regimens for HSCT.[46] The results of these studies are presented in the current BLA.

## 8.1. Advantages of the Lower Dose Fractionated Regimen of Mylotarg

With over 20 years of clinical study and post-marketing experience, Mylotarg has a well-characterized safety profile that has led to an enhanced understanding of risks associated with Mylotarg therapy. In particular, myelosuppression and VOD, especially in association with HSCT, have been identified as well-defined risks of Mylotarg treatment. While Mylotarg 9 mg/m$^2$ x 2 continues to have a favorable benefit/risk relationship for the treatment of patients with relapsed CD33-positive AML, a lower dose fractionated Mylotarg regimen of 3×3 mg/m$^2$ (up to a maximum of 5 mg per dose) appears to have an improved safety profile with respect to VOD and hematologic toxicities. Exposure-response modeling revealed that the risk of VOD is related to $C_{max}$ after the first dose of Mylotarg, and that the risk is increased when patients both undergo HSCT and receive Mylotarg. To reduce the risk of VOD, this lower dose fractionated Mylotarg regimen is recommended in combination with chemotherapy in previously untreated de novo CD33-positive AML, and for patients with relapsed CD33-positive AML who have a history of HSCT or may undergo HSCT following Mylotarg therapy. In this last population, this proposed dosing regimen provides a balance between safety and efficacy in these patients who are more susceptible to developing VOD.

## 8.2. Benefit/Risk Assessment of the Lower Dose Fractionated Mylotarg Regimen in Previously Untreated De Novo CD33-Positive AML

The ALFA-0701 study demonstrated that the lower dose fractionated regimen of Mylotarg in combination with chemotherapy resulted in a clinically meaningful and statistically significant improvement in EFS by investigator assessment (confirmed by blinded independent review) and RFS, with a trend towards improved OS that was not adjusted for imbalances in subsequent therapy between the treatment arms, including patients in the control arm subsequently receiving Mylotarg. Event-free survival was chosen by the ALFA cooperative group as the primary endpoint of this study because, in AML studies, it is a direct measure of clinically important benefit on its own and has a moderate positive correlation with OS.

These results are reinforced by the results of the Individual Patient Data MA of 5 randomized controlled studies in previously untreated AML. Using data gathered and updated from >3300 patients, this Individual Patient Data MA showed that the addition of Mylotarg to chemotherapy resulted in a significant improvement in OS and confirmed the positive trend in OS observed in the ALFA-0701 study, as well as significant improvements in EFS and RFS.

Safety data from patients with previously untreated CD33-positive AML showed that Mylotarg can be administered safely for this indication, as adverse effects were acceptable and generally manageable. The lower fractionated dosing of Mylotarg recommended for this indication reduced the incidence of VOD and duration of myelosuppression, without increasing the 30-day mortality rates relative to chemotherapy alone.

### 8.3. Benefit/Risk Assessment of Mylotarg Dosing for the Treatment of CD33-Positive AML in First Relapse

Most patients with AML eventually experience relapse. Relapsed/refractory AML has a dismal prognosis and currently available treatment options are generally ineffective.[11] A recent large, international, randomized clinical trial investigated the efficacy of elacytarabine, a novel elaidic acid ester of cytarabine, versus the investigator's choice of 1 of 7 commonly used AML salvage regimens, including high-dose cytarabine, multi-agent chemotherapy, hypomethylating agents, hydroxyurea, and supportive care. Neither elacytarabine nor any of the 7 alternative treatment regimens provided clinically meaningful benefit to these patients. OS in both study arms and for all treatments was extremely poor. The investigators concluded that there was a desperate unmet medical need for this patient population. [11]

Extensive experience with Mylotarg in the relapsed CD33-positive AML treatment setting has been accumulated and has resulted in improved understanding of how to best use Mylotarg to treat these patients whose medical need remains unmet.

Mylotarg monotherapy (9 mg/m$^2$) was originally approved in the US in May 2000 under an accelerated approval mechanism on the basis of results from Studies 201, 202, and 203 which demonstrated clinical benefit in patients with CD33-positive AML in first relapse as measured by ORR, and was subsequently approved for this indication in Japan in 2005. The SWOG S0106 study was conducted to evaluate the combination of Mylotarg and chemotherapy in patients with previously untreated de novo AML but did not confirm the clinical benefit of Mylotarg, leading to the voluntary withdrawal of Mylotarg by Pfizer in the US. Despite the withdrawal, Mylotarg has continued to be used to treat patients with CD33-positive AML in first relapse in Japan since 2005 and in response to ongoing demand, has been supplied for compassionate use in many other countries around the world, including the US.

## 9. OVERALL CONCLUSION

Collectively, the data included in the BLA indicate that Mylotarg has a favorable benefit/risk relationship for the treatment of CD33-positive AML, a serious, rapidly progressive, life-threatening disease for which there remains a high unmet medical need. The totality of evidence presents a compelling case for the re-introduction of Mylotarg for a new indication in combination with chemotherapy for the treatment of patients with previously untreated de novo CD33-positive AML and the original indication as monotherapy in patients with CD33-positive AML in first relapse.

# 10. APPENDICES

## 10.1. Abbreviations and Definitions

| Term | Definition |
|---|---|
| ADC | antibody-drug conjugate |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALFA | Acute Leukemia French Association |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| ANC | absolute neutrophil count |
| APL | acute promyelocytic leukemia |
| AraC | cytarabine |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration-time curve |
| BLA | Biologics License Application |
| BMA | bone marrow aspirate |
| BMT | bone marrow transplant |
| CBC | complete blood count |
| CD | cluster of differentiation |
| CHV | Centre Hospitalier de Versailles |
| CI | confidence interval |
| CIDCR | cumulative incidence of death in complete response |
| CIDND | cumulative incidence of death not attributable to disease |
| CIR | cumulative incidence of relapse |
| $C_{max}$ | maximum observed concentration |
| CR | complete remission |
| CRi | complete remission with incomplete blood count recovery |
| CRp | complete remission with incomplete platelet recovery |
| CRR | complete remission rate |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DA | daunorubicin and cytarabine (AraC) |
| DFS | disease-free survival |
| DNR | daunorubicin |
| ECOG | Eastern Cooperative Oncology Group |
| EFS | event-free survival |
| ELN | European Leukemia Network |
| EU | European Union |
| FDA | Food and Drug Administration |
| FLAG-Ida | fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin |
| FLT3 | FMS-like tyrosine kinase 3 gene |
| GO | gemtuzumab ozogamicin (Mylotarg) |
| GOELAMS | Groupe Ouest Est d'Etude des Leucémies aiguës et Autres Maladies du Sang |
| HR | hazard ratio |
| HSCT | hematopoietic stem cell transplant |
| IPD | Individual Patient Data |
| IV | intravenous |
| IWG | International Working Group |
| LFT | liver function test |
| MA | meta-analysis |
| MDS | myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent-to-treat |

| Term | Definition |
|---|---|
| MRC | Medical Research Council |
| MRD | minimal residual disease |
| MTD | maximum tolerated dose |
| n | number of patients in each category |
| N | total number of patients in the treatment arm |
| NCI | National Cancer Institute |
| NCRI | National Cancer Research Institute |
| NDA | New Drug Application |
| NE | not estimable |
| NEC | not elsewhere classified |
| NPM1 | Nucleophosmin-1 gene |
| NR | no remission |
| ODAC | Oncologic Drugs Advisory Committee |
| OR | odds ratio |
| ORR | overall response rate |
| OS | overall survival |
| PD | pharmacodynamics(s) |
| PK | pharmacokinetic(s) |
| PR | partial remission |
| PS | performance status |
| PT | preferred term |
| QOL | quality of life |
| RFS | relapse-free survival |
| SAE | serious adverse event |
| SCT | stem cell transplant |
| SMQ | standardized MedDRA query |
| SOC | System Organ Class |
| SOS | sinusoidal obstruction syndrome |
| SWOG | Southwest Oncology Group |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| US | United States |
| USPI | United States Package Insert |
| VOD | veno-occlusive disease |
| WT1 | Wilms' tumor suppressor gene |

## 10.2. Overview of the Clinical Studies Included in the BLA

| Study Name | Study Design | Study Population | Efficacy Population[GO/No GO] (Safety Population [GO/No GO]) | Induction Treatment |
|---|---|---|---|---|
| **Studies with GO in Combination with Chemotherapy** | | | | |
| ***Pivotal Phase 3 Study*** | | | | |
| Study ALFA-0701 (MyloFrance 3, WS936568) | Phase 3, open-label, randomized 1:1 study to assess benefit and toxicity of adding fractionated GO to standard induction chemotherapy. | Adults 50-70 years of age with previously untreated de novo AML | 271 [135/136] (268 [131/137]) | GO: 3 mg/m² (maximum dose 5 mg) D1, 4, 7.<br>Chemotherapy: DNR 60 mg/m²/d D1-3; AraC 200 mg/m²/d D1-7<br>vs<br>Chemotherapy without GO |
| ***Individual Phase 3 Studies Included in the IPD Meta-Analysis***[a] | | | | |
| Study SWOG S0106 (WS936510) | Phase 3, open-label, randomized study to assess the benefit of adding GO to standard induction therapy, followed by a post-consolidation randomization to receive either 3 additional doses of GO or no additional therapy. | Adults 18-60 years of age with previously untreated de novo non-M3 AML | 595 [295/300] (595 [295/300]) | GO: 6 mg/m$^2$ D4<br>Chemotherapy:<br>DNR 45 mg/m²/d D1, 2, 3;<br>AraC 100 mg/m²/d CI D1-7;<br>vs<br>Chemotherapy without GO |
| Study MRC AML15 (WS1974568) | Phase 3, open-label, randomized study to assess the benefit of adding GO to induction and/or consolidation chemotherapy. | Adults <60 years of age with previously untreated de novo AML or secondary AML, APL[d] | 1099 [548/551] (1099 [548/551]) | GO: 3 mg/m$^2$ D1 of Course 1 plus<br>Chemotherapy:<br>1) ADE<br>2) DNR 50 mg/m² D1, 3, 5<br>AraC 100 mg/m²/q12h, D1-10<br>3) FLAG-IDA<br>vs<br>Chemotherapy without GO |
| Study NCRI AML16 (WS936667) | Phase 2/3, open label, randomized study to assess the benefit of adding GO to standard induction chemotherapy. | Adults >60 years of age with previously untreated de novo or secondary AML or high-risk MDS | 1115 [559/556] (1115 [559/556]) | GO: 3 mg/m$^2$ D1<br>Chemotherapy:<br>1) DNR 50 mg/m²/d D1, 3, 5<br>AraC 100 mg/m²/q12h, D1-10<br>2) DNR 50 mg/m²/d D1, 3, 5<br>clofarabine 20 mg/m²/d D1-5;<br>+GO 3 mg/m² D1<br>vs<br>Chemotherapy without GO |
| Study GOELAMS AML2006IR (WS936554) | Phase 3, open label, randomized study to assess the benefit of adding GO to standard induction and consolidation chemotherapy. | Patients ≤60 years of age with newly diagnosed intermediate-risk cytogenetics CD33-positive AML | 251 [126/125] (251 [126/125]) | GO: 6 mg/m$^2$ D4<br>Chemotherapy:<br>DNR 60 mg/m² D1-3<br>AraC 200 mg/m²/d D1-7<br>vs<br>Chemotherapy without GO |
| ***Other Studies*** | | | | |
| 0903B1-205-US/EU/AU (Study 205) | Phase 1/2, open label, single-arm, multicenter study to assess the safety and efficacy of GO given in combination with AraC. | Phase 1: Adults ≥18 years of age with relapsed or refractory AML or patients ≥60 years of age with untreated de novo CD33-positive AML | Phase 1: N/A[b] (21) | Phase 1:<br>GO:<br>1) 6 mg/m$^2$ D1, 15<br>1a) 6 mg/m$^2$ D1 and 4 mg/m$^2$ D8<br>2a) 6 mg/m$^2$ D1 and 4 mg/m$^2$ D8<br>3a) 9 mg/m$^2$ D1 and 6 mg/m$^2$ D8<br><br>Chemotherapy:<br>(1, 2a and 3a): AraC 100 mg/m$^2$ D1-7 |
| | | Phase 2: Adults ≥60 years of age with untreated de novo CD33-positive AML | Phase 2: 21 (21) with 17 patients from Phase 2 and 4 patients from Step 2a of Phase 1 | Phase 2: GO dose schedule as in Step 2a from Phase 1 plus Chemotherapy |

| Study Name | Study Design | Study Population | Efficacy Population[GO/No GO] (Safety Population [GO/No GO]) | Induction Treatment |
|---|---|---|---|---|
| 0903B1-206-US/EU/AU (Study 206) | Phase 1/2, open-label, single-arm, multicenter study to assess safety and efficacy of GO given in combination with AraC and DNR. | Phase I: Adults ≥18 and <60 years of age with de novo AML or adults ≥60 years of age with relapsed or refractory AML | Phase 1: N/A[a] (22) | Phase 1: GO:6 or 9 mg/m$^2$ D4<br><br>Chemotherapy: DNR 45 mg/m$^2$ D1-3<br>AraC 100 or 200 mg/m$^2$/d D1-7 |
| | | Phase 2: Adults ≥18 and <60 years of age with de novo AML | Phase 2: 53 (53) with 49 from Phase 2 and 4 patients from regimen a of Phase 1 | Phase 2: GO:6 mg/m$^2$ D4<br>Chemotherapy: DNR 45 mg/m$^2$ D1-3<br>AraC 100 mg/m$^2$/d D1-7 |
| MyloFrance 2 (WS936540) | Phase 1/2, open label study to determine optimal doses of DNR and Ara-C to be combined with fractionated doses of GO. | Adult 50-70 years of age with AML in first relapse | 20 (20) | GO: 3 mg/m2 D1, 4, 7<br>Chemotherapy: 3+7 DA at 45/100 or 60/100 or 60/200 mg/m$^2$ |
| **Studies with Single-Agent GO** | | | | |
| ***Pivotal Phase 2 Studies*** | | | | |
| 0903B1-201-US/CA (Study 201) | Phase 2, open-label, single-arm, 3-part, multidose, multicenter, study to examine the effects of GO in patients with CD33-positive AML in first relapse. | Adults with CD33-positive AML in first relapse | 84 (84) | GO: 9 mg/m$^2$ for 2 or 3 doses 14 days apart |
| 0903B1-202-EU (Study 202) | Phase 2, open-label, single-arm, 3-part, multidose, multicenter, study to examine the effects of GO in patients with CD33-positive AML in first relapse. | Adults with CD33-positive AML in first relapse | 95 (95) | GO: 9 mg/m$^2$ for 2 or 3 doses 14 days apart |
| 0903B1-203-US/EU (Study 203) | Phase 2, open-label, single-arm, 3-part, multidose, multicenter, study to examine the effects of GO in patients with CD33-positive AML in first relapse. | Adults ≥60 yrs with CD33-positive AML in first relapse | 98 (98) | GO: 9 mg/m$^2$ for 2 or 3 doses 14 days apart |
| ***Other Studies*** | | | | |
| 0903A1-101-US (Study 101) | Phase 1, single-arm, dose escalation study to examine the safety and PK of GO. | Adults with relapsed or refractory CD33-positive AML | 40 (40) | GO: 0.25, 0.5, 1, 2, 4, 5, 6, and 9 mg/m$^2$ (>14 days apart); maximum of 3 doses. |
| 0903A1-102-US (Study 102) | Phase 1, 2 part, single-arm, open-label dose-escalation study to assess safety, efficacy, and PK of GO in pediatric patients. | Children (≤17 yrs) with refractory or relapsed CD33-positive AML | 29 (29) | GO: 6, 7.5, and 9 mg/m$^2$ for up to 2 doses. For patients <3 years of age, per kilogram dosing was used. |
| 0903A1-103-JP (Study 103) | Phase 1/2, single-arm, open-label study in Japanese patients to study safety, efficacy, PK, and to confirm the tolerance of GO at 9 mg/m$^2$. | Japanese adults 18 to 70 yrs with relapsed or refractory CD33-positive AML in first relapse | Phase 1: 20 (20)<br><br>Phase 2: 20 (20) | Phase 1: GO: 6, 7.5, and 9 mg/m$^2$ for up to 2 doses<br><br>Phase 2: GO: 9 mg/m$^2$ for up to 2 doses |
| 0903X-100374 (Study 100374) | Phase 4, single-arm, dose-finding study to assess safety of GO as single-agent treatment of patients with relapsed AML who have received prior HSCT. | Patients with relapsed AML after autologous or allogeneic HSCT | 37: Allogeneic HSCT: 27, Autologous HSCT: 10 (37) | Phase 1: 2, 4, and 6 mg/m$^2$ GO; up to 2 doses<br><br>Phase 2: GO: up to an additional 4 doses |

| Study Name | Study Design | Study Population | Efficacy Population[GO/No GO] (Safety Population [GO/No GO]) | Induction Treatment |
|---|---|---|---|---|
| 0903X-100863 (Study 100863) | Phase 4, single-arm multicenter study to assess efficacy of corticosteroids prophylaxis on frequency and severity of GO infusion-related AEs and to evaluate the effect of corticosteroids on GO efficacy after 1 month of treatment. | Adults ≥18 yrs with CD33-positive AML, resistant or relapsed | 23 (23) | GO: 2 to 9 mg/m$^2$×2 doses (Day 1 and Day 15) |
| 0903X-100847 (Study 100847) | Phase 4, single arm, prospective observational study to primarily estimate the rate of VOD and to identify risk factors for VOD and to collect safety data in routine clinical practice. | Patients with CD33-positive AML in first relapse | 512 enrolled[b](482) | GO, IV, as per the treating physician or clinical study. |
| MyloFrance 1[c] | Phase 2, single-arm, prospective, multicenter study to assess the safety and efficacy of fractionated doses of GO. | Adult ≥18 years of age with CD33-positive AML in first untreated relapse with a duration of CR1 3-18 months | 57 (57) | GO: 3 mg/m$^2$ IV Days 1, 4, 7 |
| **Study with Single-Agent GO in Patients With MDS** | | | | |
| 0903B1-207-US/EU (Study 207) | Phase 2, single arm, multidose study to assess total survival and QOL after GO treatment. | Adults >18 years of age with intermediate or high-risk MDS | 26[b](26) | GO: 9 mg/m$^2$ Arm A: 1 dose; Arm B: 2 doses |

Abbreviations: AE=adverse event; ADE=cytarabine (AraC)/daunorubicin/etoposide; ALFA=Acute Leukemia French Association; AML=acute myeloid leukemia; AraC=cytarabine; APL=acute promyelocytic leukemia; AU=Australia; CA=Canada; D or d=day; DA=daunorubicin and cytarabine; DNR=daunorubicin; EU=European Union; FLAG-IDA=fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO=gemtuzumab ozogamicin (Mylotarg); GOELAMS=Groupe Ouest Est d'Etude des Leucémies aiguës et Autres Maladies du Sang; HSCT=hematopoietic stem cell transplantation; IPD=individual patient data; JP=Japan; IV=intravenous; MDS=myelodysplastic syndrome; MRC=Medical Research Council; N/A=not applicable; NCRI=National Cancer Research Institute; PK=pharmacokinetics; SWOG=Southwest Oncology Group; US=United States; VOD=veno-occlusive disease.

a. Study ALFA-0701 presented in previous row was also included in the meta-analysis.
b. No efficacy data were collected.
c. Study MyloFrance 1 was a dose-finding study to evaluate the safety and efficacy of the fractionated dosing regimen of GO in patients with AML in first relapse.
d. APL patients were not included in the meta-analysis.

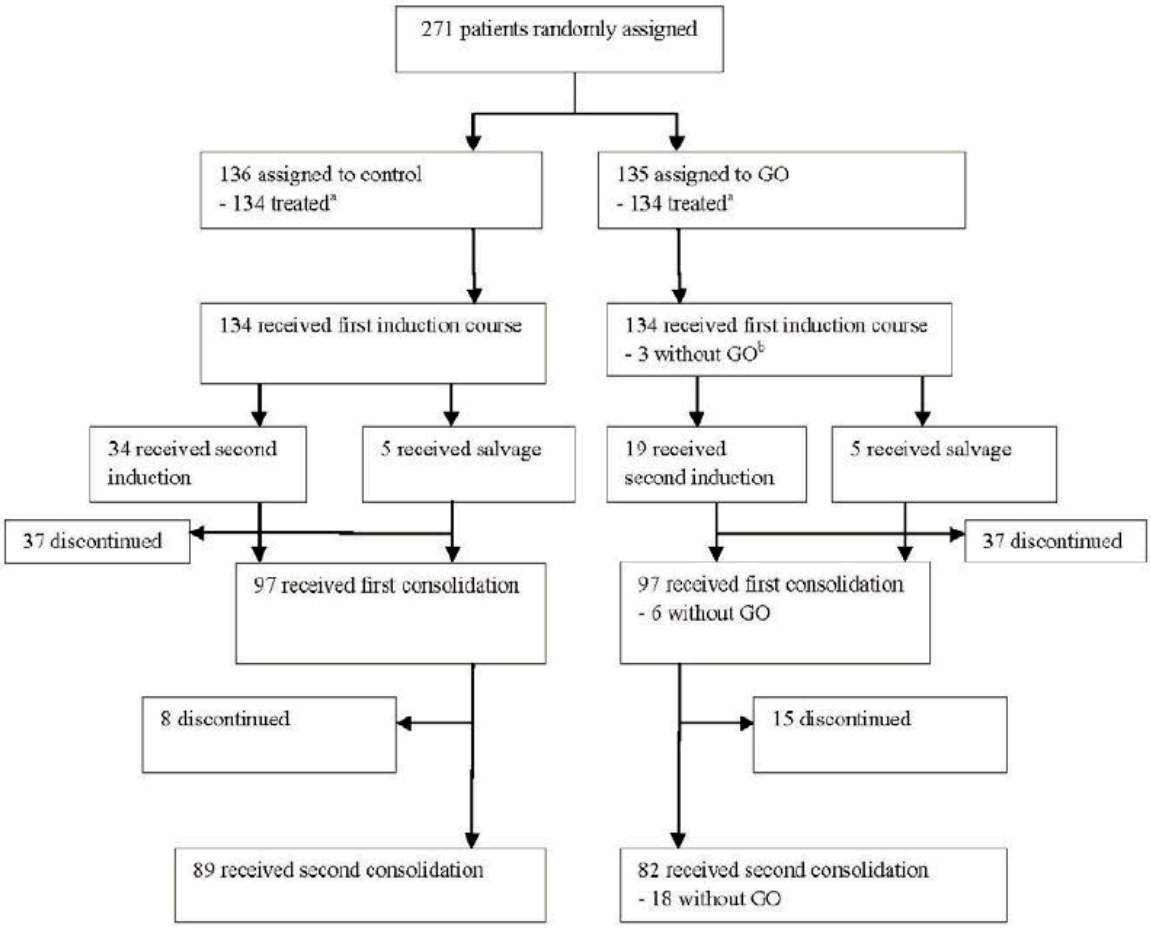
## 10.3. Mylotarg Clinical Trial Experience in Relapsed/Refractory AML

| Study Name | Design | Mylotarg Dosing | N |
|---|---|---|---|
| **Primary Studies for BLA Submission** | | | |
| 201/202/203 | Efficacy/Safety | 9 mg/m$^2$ x 2 or 3[a] | 277 |
| **Supportive Studies** | | | |
| 101 | Dose Finding | 0.25 to 9 mg/m$^2$ | 40 |
| 102 | Dose Finding | 6 to 9 mg/m$^2$ | 29 |
| 103 | Dose Finding | 6 to 9 mg/m$^2$ | 40 |
| 100374 | Post HSCT | 2 to 6 mg/m$^2$ | 37 |
| 100847 | Prospective Observational | Routine Practice | 482 |
| 100863 | Premedication[b] | 2 to 9 mg/m$^2$ x 2 | 23 |
| MyloFrance 1 | Fractionated | 3 mg/m$^2$ x 3 | 57 |

Studies 101, 102, 100374, 100847, and 100863 were conducted in the US. Study 103 was conducted in Japan. Study 201 was conducted in the US and Canada. Study 202 was conducted in the EU. Study 203 was conducted in the US and EU.
Abbreviations: AML=acute myeloid leukemia; BLA=Biologics License Application; EU=European Union; HSCT=hematopoietic stem cell transplant; N=number of patients; US=United States.

a. The third dose was removed by protocol amendment.
b. Evaluation of corticosteroid pretreatment on Mylotarg efficacy and tolerability.

## 10.4. Patient Treatment Summary – ALFA-0701




As shown above, patients were randomly assigned in a 1:1 ratio to receive standard induction therapy with DNR + AraC without (control arm) or with Mylotarg (GO arm).

A second course of induction therapy with DNR + AraC without Mylotarg regardless of the randomization arm may have been given if more than 5% (or 10% depending on the protocol amendment) leukemic blasts persisted in the bone marrow. Patients who did not receive the second course of induction therapy and did not achieve a CR after the first induction course could receive a salvage course of idarubicin + AraC as long as the patient had an ECOG PS <3 and creatinine clearance >30 mL/min.

Patients who did not respond to induction therapy (including salvage course) discontinued study treatment.

Patients with a CR or CRp received consolidation therapy with 2 courses of treatment including DNR + AraC with or without Mylotarg according to their initial randomization. Patients who achieved remission were also eligible for allogeneic transplant.

Abbreviation: GO=gemtuzumab ozogamicin.

a. 3 patients not treated (2 control and 1 GO; Patient 333 [Eligibility protocol violation: esophageal cancer];Patient 702 [death], and Patient 1308 [Eligibility protocol violation: hepatitis B]).
b. Reasons for not receiving GO during induction (Patient 903 [abnormal liver function], Patient 1403[unknown – eligibility criteria not met], and Patient 2202 [patient died]).

## 10.5. References

[1] American Cancer Society. Cancer Facts & Figures 2017. Atlanta. American Cancer Society; 2017. Available: https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html.

[2] Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, based on November 2015 SEER data submission, posted to the SEER web site. Available: http://seer.cancer.gov/csr/1975_2013/ . Apr 2016.

[3] Legrand O, Perrot JY, Baudard M, et al. The immunophenotype of 177 adults with acute myeloid leukemia: Proposal of a prognostic score. Blood 2000;96(3):870-7.

[4] Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med 2015;373(12):1136-52.

[5] Yates JW, Wallace HJ Jr, Ellison RR, et al. Cytosine arbinoside (NSC 63878) and daunorubicin (NSC-83142) therapy in acute nonlymphocytic leukemia. Cancer Chemother Rep 1973;57(4):485-8.

[6] **I**damycin [Prescribing Information] Pfizer Inc. New York, NY; December 2014. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050661s014lbl.pdf. Accessed April 24, 2017.

[7] Novantrone [Prescribing Information] EMD Soreno Inc. March 2012. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019297s035lbl.pdf Accessed April 24, 2017.

[8] Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med. 2009;361(13):1249-59.

[9] Deangelo DJ, Liu D, Stone R, et al. Preliminary report of a phase 2 study of gemtuzumab ozogamicin in combination with cytarabine and daunorubicin in patients, <60 years of age with de novo acute myeloid leukemia. In: Proceedings from the American Society of Clinical Oncology; May 31-June 3, 2003; Chicago, IL. Abstract 2325.

[10] Petersdorf SH, Kopecky KJ, Slovak M, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy

in younger patients with acute myeloid leukemia. Blood 2013;121(24):4854-60.

[11] Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. J Clin Oncol 2014;32(18):1919-26.

[12] Mangan JK, Luger SM. Salvage therapy for relapsed or refractory acute myeloid leukemia. Ther Adv Hematol 2011;2(2):73-82.

[13] FDA News Release. FDA approves new combination treatment for acute myeloid leukemia. Available: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm555778.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. 28 Apr 2017.

[14] Ehninger A, Kramer M, Rollig C, et al. Distribution and levels of cell surface expression of CD33 and CD123 in acute myeloid leukemia. Blood Cancer J 2014;4:e218.

[15] Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21(24):4642-9.

[16] Magenau J, Couriel DR. Hematopoietic stem cell transplantation for acute myeloid leukemia: To whom, when, and how. Curr Oncol Rep 2013;15(5):436-44.

[17] Walter RB, Buckley SA, Pagel JM, et al. Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission. Blood 2013;122(10):1813-21.

[18] Walter RB, Kantarjian HM, Huang X, et al. Effect of complete remission and responses less than complete remission on survival in acute myeloid leukemia: a combined Eastern Cooperative Oncology Group, Southwest Oncology Group, and M.D. Anderson Cancer Center study. J Clin Oncol 2010;28(10):1766-71.

[19] Shah SS, Kantarjian HM, Ravandi F, et al. Survival outcomes in relapsed/refractory acute myeloid leukemia patients who achieve less than-complete response after salvage therapy. Blood 2013;122(21):2654.

[20] Othus M, van Putten W, Lowenberg B, et al. Relationship between event-free survival and overall survival in acute myeloid leukemia: a report from SWOG, HOVON/SAKK, and MRC/NCRI. Haematologica 2016;101(7):e284-6.

[21] Buyse M, Michiels S, Squifflet P, et al. Leukemia-free survival as a surrogate end point for overall survival in the evaluation of maintenance therapy for patients with acute myeloid leukemia in complete remission. Haematologica 2011;96(8):1106-12.

[22] Luskin MR, Lee J-W, Fernandez HF, et al. Results of the ECOG E1900 trial in younger adults with AML using an event free survival endpoint are concordant with results based on overall survival: potential for a surrogate endpoint to facilitate rapid approval of therapies in AML. Blood 2014;124(21):2599.

[23] Schlenk RF, Dohner H, Dohner K, et al. event-free survival is a surrogate for overall survival in patients treated for acute myeloid leukemia. Blood 2015;126(23):3744.

[24] Food and Drug Administration. HHS. Wyeth Pharmaceuticals, Inc.; Withdrawal of approval of a New Drug Application for MYLOTARG. Fed Regist 2011;76(228):72955.

[25] Campos L, Guyotat D, Archimbaud E, et al. Surface marker expression in adult acute myeloid leukaemia: correlations with initial characteristics, morphology and response to therapy. Br J Haematol 1989;72(2):161-6.

[26] Drexler HG, Minowada J. The use of monoclonal antibodies for the identification and classification of acute myeloid leukemias. Leuk Res 1986;10(3):279-90.

[27] Laszlo GS, Estey EH, Walter RB. The past and future of CD33 as therapeutic target in acute myeloid leukemia. Blood Rev 2014;28(4):143-53.

[28] van der Velden VH, van Dogen JJ. Effectiveness of gemtuzumab ozogamicin treatment: cellular and systemic determinants. Eur J Hosp Pharm Sci 2006;1781:20.

[29] Gasiorowski RE, Clark GJ, Bradstock K, et al. Antibody therapy for acute myeloid leukaemia. Br J Haematol 2014;164(4):481-95.

[30] Castaigne S, Pautas C, Terré C, et al. Acute Leukemia French Association. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012;379(9825):1508-16.

[31] National Cancer Institute. SEER Survival Data. Available: https://seer.cancer.gov/csr/1975_2014/results_merged/topic_survival.pdf. Accessed 23 May 2017.

[32] Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010;115(3):453-74.

[33] Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol 2014;15(9):986-96.

[34] Orozco JJ, Appelbaum FR. Unfavorable, complex, and monosomal karyotypes: the most challenging forms of acute myeloid leukemia. Oncology (Williston Park) 2012;26(8):706-12.

[35] Burzykowski T, Molenberghs G, Buyse M, et al. Validation of surrogate end points in multiple randomized clinical trials with failure time end points. J R Stat Soc Ser C (Applied Statistics) 2001;50(4):405-22.

[36] Burzykowski T, Cortinas Abrahantes J. Validation in the case of two failure-time endpoints. In: Burzykowski T, Molenberghs G, Buyse M, eds: The Evaluation of Surrogate Endpoints. New York, NY, Springer; 2005:163-94.

[37] Buyse M, Molenberghs G, Burzykowski T, et al. The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics 2000;1(1):49-67.

[38] Buyse M, Molenberghs G, Paoletti X, et al. Statistical evaluation of surrogate endpoints with examples from cancer clinical trials. Biom J 2016;58(1):104-32.

[39] Estey E, Othus M, Lee SJ, et al. New drug approvals in acute myeloid leukemia: what's the best end point? Leukemia 2016;30(3):521-5.

[40] Barreto JN, McCullough KB, Ice LL, et al. Antineoplastic agents and the associated myelosuppressive effects: a review. J Pharm Pract 2014;27(5):440-6.

[41] Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant 2010;16(2):157–68.

[42] Taksin AL, Legrand O, Raffoux E, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: A prospective study of the ALFA group. Leukemia 2007;21(1):66-71.

[43] van Der Velden VH, te Marvelde JG, Hoogeveen PG, et al. Targeting of the CD33-calicheamicin immunoconjugate Mylotarg (CMA-676) in acute myeloid leukemia: in vivo and in vitro saturation and internalization by leukemic and normal myeloid cells. Blood 2001;97(10):3197–204.

[44] van der Velden VH, Boeckx N, Jedema I, et al. High CD33-antigen loads in peripheral blood limit the efficacy of gemtuzumab ozogamicin (Mylotarg) treatment in acute myeloid leukemia patients. Leukemia 2004;18(5):983-8.

[45] Farhat H, Reman O, Raffoux E, et al. Fractionated doses of gemtuzumab ozogamicin with escalated doses of daunorubicin and cytarabine as first acute myeloid leukemia salvage in patients aged 50-70-year old: A phase 1/2 study of the acute leukemia French association. Am J Hematol 2012;87(1):62-5.

[46] Johnson DB, Savani BN. How can we reduce hepatic veno-occlusive disease-related deaths after allogeneic stem cell transplantation? Exp Hematol 2012;40(7):513-7.