

Report from the FDA**Approval Summary: Gemtuzumab Ozogamicin in Relapsed Acute Myeloid Leukemia**

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**Abstract**

**Purpose:** Gemtuzumab ozogamicin (Mylotarg; Wyeth Laboratories, Philadelphia, PA) consists of a semisynthetic derivative of calicheamicin, a cytotoxic antibiotic linked to a recombinant monoclonal antibody directed against the CD33 antigen present on leukemic myeloblasts in most patients with acute myeloid leukemia (AML). In this study, we review the preclinical and clinical profiles of this immun-conjugate and the regulatory review that led to marketing approval by the United States Food and Drug Administration.

**Experimental Design:** From the literature and manufacturer's data, we review the activity, tolerability, and pharmacokinetics of gemtuzumab ozogamicin in preclinical and Phase I studies and its activity, efficacy, and side effects in three Phase 2 trials of 142 patients with relapsed AML.

**Results:** In Phase I studies, the major toxicity was myelosuppression, especially neutropenia and thrombocytopenia, resulting from the expression of CD33 on myeloid progenitor cells. The Phase 2 dose was 9 mg/m<sup>2</sup> infused i.v. over 4 h, repeated on day 14. A minority of patients experienced acute infusion-related symptoms, usually transient and occasionally requiring hospitalization. The complete response (CR) rate with full recovery of hematopoiesis was 16%. A subset of patients [CRs with incomplete platelet recovery (CRps)] was identified with blast clearance and neutrophil recovery but incomplete platelet recovery. The duration of responses of CRps appeared to be similar to those of the CRs, although the numbers were small. The question of the equivalence of these response groups was a central issue in the review of this new drug application (NDA). After considerable discussion, the Oncology Drugs Advisory Committee recommended allowing inclusion of CRps resulting in an overall response rate in the Phase 2 studies of 30%. In the

subgroup of patients over 60 years of age, the overall response rate was 26%. Response duration was difficult to establish because of the high prevalence of postremission therapies. Tolerability and ease of administration may be improved compared with conventional chemotherapy, except for hepatotoxicity, with 31% of patients exhibiting abnormal liver enzymes. One patient died of liver failure in the Phase 2 trials.

**Conclusions:** Marketing approval of gemtuzumab ozogamicin was granted on May 17, 2000 by the United States Food and Drug Administration under the Accelerated Approval regulations. Gemtuzumab ozogamicin is indicated for the treatment of patients with CD33 positive AML in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy. The approved dose was 9 mg/m<sup>2</sup> i.v. over 4 h and repeated in 14 days. Completion of the ongoing studies of gemtuzumab ozogamicin in relapsed AML and initiation of randomized clinical trials comparing the effects of gemtuzumab ozogamicin in combination with conventional induction chemotherapy to conventional chemotherapy alone on survival are mandated to confirm clinical benefit under the accelerated approval Subpart H regulations. Postmarketing reports of fatal anaphylaxis, adult respiratory distress syndrome (ARDS), and hepatotoxicity, especially venoocclusive disease (VOD) in patients treated with gemtuzumab ozogamicin, with and without associated hematopoietic stem cell transplantation (HSCT), have required labeling revisions and the initiation of a registration surveillance program. Tumor lysis and ARDS have been reported in patients with leukocytes above 30,000/ml treated with gemtuzumab ozogamicin; therefore, the reduction of leukocyte counts to below 30,000/ml is recommended prior to treatment. Patients should be carefully monitored for acute hypersensitivity, hypoxia, and delayed hepatotoxicity following treatment with gemtuzumab ozogamicin.

**Introduction**

AML<sup>2</sup> is a disease characterized by the proliferation of clonal precursor myeloid cells with arrested differentiation. AML affects approximately 9000 people/year in the United States with a peak incidence in people 60–70 years of age. Conventional treatment with a combination of cytotoxic chemotherapeutic agents results in remission rates of up to 85%; however, many of these patients eventually relapse (1). Treatment of relapsed AML patients is considerably less successful,

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<sup>2</sup> The abbreviations used are: AML, acute myeloid leukemia; CR, complete response; CRp, CR with incomplete platelet recovery; OR, overall responder; AUC, area under the curve; RFS, relapse-free survival; HSCT, hematopoietic stem cell transplantation; VOD, venoocclusive disease; NCI, National Cancer Institute.

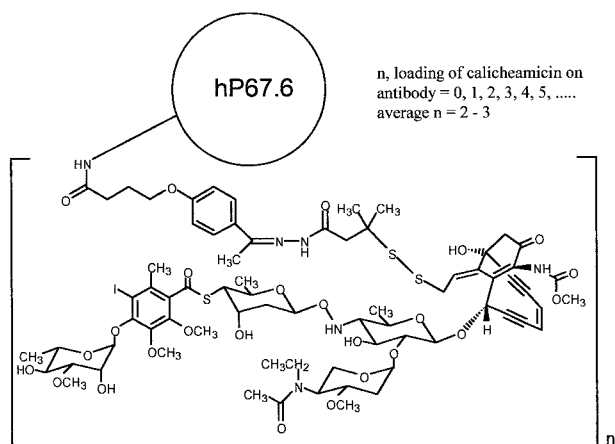


Fig. 1 Structure of gemtuzumab ozogamicin. HP67.6 represents the humanized monoclonal antibody directed against CD33. Calicheamicin is linked to the antibody in variable molar ratios; approximately 50% of the antibody is unconjugated.

especially in the elderly. Remission rates are generally reported to be 20–40% in patients over 65 years of age, compared with 40–50% in younger patients (2). Treatment of AML in the elderly has been particularly problematic, because the toxicity of standard induction chemotherapy is poorly tolerated in the older age group (3).

AML myeloblasts are immunophenotypically well characterized and accessible to circulating antibodies (4). CD33 is a  $M_r$  67,000 transmembrane cell surface glycoprotein receptor that is specific for myeloid cells. CD33 expression is down-regulated with maturation of the myeloid lineage, resulting in low-level expression on peripheral granulocytes and tissue macrophages (5). The CD33 antigen is expressed on approximately 90% of AML myeloblasts, including leukemic clonogenic precursors as well as normal myeloid precursor cells, but not on CD34+ pluripotent hematopoietic stem cells (6). *In vitro* studies have documented internalization of CD33 antibodies by the target cell (7). These properties enable the use of antibodies directed against CD33 in the treatment of myeloid leukemia (8).

Several approaches using antibodies to CD33 in the treatment of myeloid leukemia have been attempted, including the use of unconjugated so called “naked” antibodies, radioimmunoconjugates, and immunotoxin conjugates (9). The most clinically successful approach thus far has been with the antibody-directed cytotoxic agent gemtuzumab ozogamicin. This is a humanized anti-CD33 monoclonal antibody produced from a mammalian myeloma cell culture cell line covalently linked to a semisynthetic derivative of calicheamicin (Fig. 1). Calicheamicin  $\gamma_1^I$  is a potent cytotoxic enediyene antibiotic, originally isolated from *Micromonospora echinospora* ssp. *Calichensis*. This antibiotic is believed to be released inside the lysosomes of the myeloblast, binding to DNA in the minor groove and causing DNA double-strand breaks and ultimately cell death (10). About 50% of the antibody is linked to calicheamicin with an average loading of four to six molecules of calicheamicin/antibody. The remaining antibody is unconjugated.

**Preclinical Evaluation.** Gemtuzumab ozogamicin showed *in vitro* activity against the CD33-positive (CD33<sup>+</sup>) HL-60 human promyelocytic leukemia cell line and demonstrated selectivity for CD33<sup>+</sup> target cells relative to cells not expressing the CD33 antigen, thus causing significant reduction in growth in the HL-60 xenograft tumor model. When administered weekly for six doses, gemtuzumab ozogamicin was not lethal to rats up to 7.2 mg/m<sup>2</sup> and in monkeys up to 22 mg/m<sup>2</sup>. Marked changes in the histopathology of the testes, liver, and kidney were noted at these doses, as well as significant myelotoxicity. Free calicheamicin, as well as conjugated calicheamicin, was noted to cause liver toxicity in preclinical testing, and gemtuzumab ozogamicin was found to be preferentially distributed to the liver.

Pharmacokinetic studies were conducted in rats and monkeys after administration of single and repeated i.v. doses of gemtuzumab ozogamicin. The major excretion pathways appeared to be biliary, and plasma concentrations of the unconjugated calicheamicin derivatives were generally below the assay limits. Reproductive toxicology suggests the potential for adverse human effects on fertility, dysmorphogenesis, and fetal growth. Gemtuzumab ozogamicin was clastogenic in an *in vivo* mouse micronucleus assay, as expected from the induction of DNA damage by calicheamicin.

**Phase I Trials.** A single Phase I trial evaluated the dose range, safety, and pharmacokinetics of gemtuzumab ozogamicin in men and women 16 to 70 years of age with CD33 positive AML who had failed to achieve remission or had a relapse after remission. A dosing interval of 2 weeks was selected because of the relatively long half-life of the drug (over 3 days; see “Pharmacokinetics” section). Initially, three biweekly doses were studied, but this led to profound and persistent myelosuppression. Subsequently, two doses were used in the Phase 2 trials, and the dose was not adjusted for high blast counts. The dose-limiting toxicity was neutropenia, and persistent thrombocytopenia occurred in half of the patients. The most common acute infusion-related clinical adverse event was a postinfusion symptom complex consisting of fever and chills. This symptom complex generally occurred within 6 h after infusion and tended to be less frequent and severe with subsequent doses. The most common delayed infusion-related events overall in dose periods were fever (44% of patients), nausea (32%), chills (27%), leukopenia (22%), vomiting (12%), rash (12%), and pain (10%).

**Activity.** Two of the 41 patients treated in the Phase I trials experienced objective CRs after three doses of gemtuzumab ozogamicin, one treated at 1 mg/m<sup>2</sup> and one at 4 mg/m<sup>2</sup>. Seven additional patients treated with doses of 5, 6, and 9 mg/m<sup>2</sup> had clearance of leukemic blasts (<5%) from their blood and bone marrow but without full recovery of peripheral leukocyte or platelet counts. The phenomenon of postremission thrombocytopenia after myeloablative chemotherapy with or without HSCT has been described previously (11). Persistent thrombocytopenia could not be ascribed to binding of megakaryocytes by gemtuzumab ozogamicin, because CD33 is found on less than 20% of megakaryocytes (12). Studies of the toxicity of gemtuzumab ozogamicin on normal human bone marrow samples revealed variable suppression of megakaryocyte colony formation in different samples.

NCI consensus criteria for complete remission in AML

Table 1 Prognostic characteristics at entry of 142 patients with CD33 positive AML in first relapse treated with gemtuzumab ozogamicin<sup>a</sup>

	Study 201	Study 202	Study 203	Study 201/202/203
Accrual	65	40	37	142
Prior remission duration (mo)				
Mean $\pm$ SD	16 $\pm$ 14	19 $\pm$ 22	8.7 $\pm$ 6	14.9 $\pm$ 16
Minimum	6	6	3	
Mean age $\pm$ SD	53.5 $\pm$ 16	56.6 $\pm$ 13	68.5 $\pm$ 6.3	58 $\pm$ 15
Minimum age	18	18	60	
Prior HSCT	0	5	0	

<sup>a</sup> Study 202 allowed previous HSCT, and study 203 excluded patients under 60 years of age.

included the absence of peripheral blasts, <5% residual marrow blasts, an absolute neutrophil count of at least 1500/ $\mu$ l, and achievement of platelet counts above 100,000/ $\mu$ l. A 1990 NCI-sponsored workshop on definitions of diagnosis and response in AML concluded that patients with prolonged cytopenias but no marrow evidence of leukemia should be described separately and "not considered to be nonresponders" (13). The identification of patients with apparent blast clearance but persistent thrombocytopenia in the Phase I study led to the proposal of a new category of responses termed "CRps," with clearance of blasts but incomplete platelet recovery. The combination of CRs and CRps, termed "overall responders" (ORs) was a secondary end point of the Phase 2 trials, whereas CR remained the primary end point.

**Pharmacokinetics.** *In vitro* metabolism studies performed indicate that numerous metabolites of gemtuzumab ozogamicin are formed. The biotransformation pathways identified in liver microsomes were oxygenation and demethylation, whereas the acetylation of calicheamicin and its derivatives are the major pathways in cytosol. Animal studies indicate that gemtuzumab ozogamicin undergoes hepatobiliary elimination; however, the route of elimination has not been studied in humans. The pharmacokinetics of gemtuzumab ozogamicin was characterized by separate assays of the antibody portion of the conjugate as well as calicheamicin (total and unconjugated) in plasma. The elimination half-life of the antibody was highly variable after i.v. administration of the 9 mg/m<sup>2</sup> dose and ranged from 67  $\pm$  37 h to 88  $\pm$  58 h from dose period 1 to dose period 2. Corresponding AUCs were 132  $\pm$  136 and 243  $\pm$  198 mg  $\cdot$  h/liter for dose periods 1 and 2, respectively. Because approximately 50% of the antibodies are not linked to the calicheamicin derivative, the reliability of the antibody to characterize the pharmacokinetics of gemtuzumab ozogamicin may be questioned. Total calicheamicin elimination half-life and AUC were 39  $\pm$  25 h and 2.1  $\pm$  1.8 mg/h/liter, respectively, after the first dose period of gemtuzumab ozogamicin administration, and both were increased in the second dose period (63  $\pm$  63 h and 4.7  $\pm$  4.1 mg/h/liter, respectively).

Clearance of both antibody and unconjugated calicheamicin consistently decreased during subsequent dose periods, and half-life, C<sub>max</sub>, and AUC were increased, independent of the technique of measurement. Although this observation may reflect a decrease in tumor burden in subsequent courses, no definite correlation of increased clearance with increased peripheral blast count was observed. On the basis of the occurrence of dose-limiting myelosuppression and saturation of

CD33-binding sites, the recommended Phase 2 dose was 9 mg/m<sup>2</sup> i.v. over 2 h for two doses.

#### Phase 2 Trials in Patients with AML in First Relapse.

Three open-label single arm studies (Trials 201, 202, and 203) were performed in patients with AML in first relapse (Table 1). This study design was deemed acceptable for registration on the basis of the sponsor's assertion that relapsed AML represented an unmet medical need and the drug showed clinical promise in Phase I trials. Patients with secondary leukemia, promyelocytic leukemia (FAB M3), previous myelodysplasia, or history of prior chemotherapy for relapse were excluded. The most common subtypes accrued were M2, M1, M4, and M5 and reflected reported natural distribution of FAB subtypes. A total of 142 patients were enrolled, 59% male and 94% Caucasian, with an age range of 22–84 and a mean age of 58. One study (203) excluded patients under 60 years of age and had a higher mean age of 69 years. Patients were required to have >5% blast cells identifiable by flow cytometry, of which a "high percentage" expressed CD33, as confirmed by a central laboratory. Remission status was defined from the date bone marrow biopsies or aspirate specimens were obtained. An independent pathologist blinded to patients' clinical status reviewed marrow pathology.

All of the patients were premedicated with 650–1000 mg of acetaminophen and 50 mg of diphenhydramine p.o. Entry criteria required pretreatment with hydroxyurea if the total WBCs exceeded 30,000/ $\mu$ l to reduce the risk of tumor lysis syndrome in patients with high leukocyte counts. One hundred forty-two patients received at least one 9 mg/m<sup>2</sup> dose of gemtuzumab ozogamicin, 109 patients (77%) received two doses, and 5 patients (4%) received three doses. The use of growth factors was prohibited except for patients experiencing life-threatening infections because of prolonged neutropenia.

**Activity.** The primary end point of CR, defined as transfusion independence, absence of peripheral blasts,  $\leq$ 5% residual marrow blasts, hemoglobin  $\geq$  9 g/dl, an absolute neutrophil count of  $\geq$  1500/ $\mu$ l, and a platelet count of 100,000/ $\mu$ l, was achieved in 16% of patients (Table 2). With the inclusion of "CRps," the total number of responders was 42, for an OR rate of 30%. The RFS of all of the relapsed AML patients in the gemtuzumab ozogamicin trials who attained a remission was 6.8 months: 7.2 months for the CR group and 4.4 months for the CRps. The survival of patients in the CR and CRp categories appeared similar (Fig. 2), although the numbers were inadequate to derive any definitive conclusions regarding the comparability of these groups. Although preliminary evidence suggests that the CRs and CRps experience improved survival compared with

**Table 2** Response rates vs. age in Phase 2 studies of 142 patients with CD33 positive AML in first relapse treated with gemtuzumab ozogamicin

Type of remission	201/202/203 (n = 142)	<60 yr (n = 62)	≥60 yr (n = 80)
<b>CR</b>			
No. (%) of patients	23 (16)	11/62 (18)	12/80 (15)
95% CIs <sup>a</sup>	(11, 23)	(9, 30)	(8, 25)
<b>CRp</b>			
No. (%) of patients	19 (13)	10/62 (16)	9/80 (11)
95% CIs	(8, 20)	(8, 28)	(5, 20)
<b>OR (CR + CRp)</b>			
No. (%) of patients	42 (30)	21/62 (34)	21/80 (26)
95% CIs	(22, 38)	(22, 47)	(17, 37)

<sup>a</sup> CI, confidence interval.

nonresponders, comparisons between responders and nonresponders tend to be problematic. The comparability of the CRs and CRps remains to be established by further clinical experience. In the absence of a concurrent control group, it was not possible to derive any definite conclusions regarding the relative efficacy of gemtuzumab ozogamicin as compared with conventional cytotoxic induction chemotherapy.

The two variables most consistently correlated with response in relapsed AML are patients' age and length of first remission: older age and shorter remission duration are associated with an inferior prognosis. The mean age was 61 years in the gemtuzumab ozogamicin studies. The OR rate in the 62 patients <60 years of age was 34%, whereas the OR rate in the 80 patients ≥60 years old was 26% (Table 2). However, patients over 60 years of age had a much shorter RFS of 2.3 months *versus* 17 months for patients <60 years of age. Remission rates were 28% and 32% for patients with durations of first remission <1 year and ≥1 year, respectively.

Forty-five percent (19 of 42) of patients who achieved remission were prescribed additional antileukemic therapy, including HSCT. Therefore, it is not possible to make any definite conclusions regarding the duration of response of gemtuzumab ozogamicin in patients with relapsed AML because the type of postremission consolidation therapy is known to affect long-term survival (14). Of the 42 patients who achieved remission, 15 went on to HSCT, 4 received other postremission treatments, and 23 had no further therapy. Median RFS of patients who attained a remission and subsequently received a HSCT was not reached. Among patients who did not receive further therapy, the median RFS was 2.1 months.

**Tolerability.** The three Phase 2 trials in 142 patients with AML in first relapse suggest a safety profile of gemtuzumab ozogamicin distinct from standard induction chemotherapy. Most patients tolerated the infusions without significant complications; 5 of 142 patients were treated without hospitalization. An infusion-related symptom complex of fever, chills, and hypotension occurred commonly in patients treated with gemtuzumab ozogamicin despite prophylactic treatment with acetaminophen and antihistamine. This symptom complex may be related to cytokine release and appeared to be less common during the second dose. One third of patients reported a grade 3–4 infusion-related adverse event. The incidence of grade 3 or 4 hypotension was 5% and generally resolved after i.v. fluid

support (and in one case vasopressors). Three patients were reported with grade 3–4 hypoxia, which eventually resolved after treatment with oxygen. Two patients in the Phase I studies exhibited evidence of development of antibodies after receiving more than two doses of gemtuzumab ozogamicin: one patient developed antibodies after receiving a third dose of gemtuzumab ozogamicin and was asymptomatic, and the other developed antibodies during a second course of therapy and had a transient episode of dyspnea after infusion. Development of antibodies was not reported in the Phase 2 studies. Four cases of tumor lysis syndrome were reported; one was fatal. Prevention of tumor lysis syndrome with supportive measures including hydration, allopurinol, and leukoreduction with hydroxyurea or leukapheresis is recommended in patients with leukocytosis.

Bleeding is a common and potentially serious complication of the treatment of AML, most often secondary to thrombocytopenia. Bleeding varied in severity from petechiae and mild epistaxis to fatal hemorrhage (Table 3). One patient died of a retroperitoneal hemorrhage, one patient who was treated with a preexisting coagulopathy developed a fatal intracerebral hemorrhage within 5 h of treatment, and another patient with thrombocytopenia developed an intracranial hemorrhage 1 day after treatment. Three patients died of cerebral hemorrhage >30 days from the last dose of gemtuzumab ozogamicin. Patients with CRps required more platelet and probably more packed RBC transfusions before the attainment of transfusion independence. The overall incidence of severe bleeding appeared to be similar in the CR and CRp groups.

Calicheamicin caused liver toxicity in preclinical studies, and gemtuzumab ozogamicin is associated with clinical hepatotoxicity. In the Phase 2 clinical trials, 45 patients had at least one grade 3 or 4 hepatic function abnormality, 33 patients (23%) showed severe (grade 3–4) bilirubin elevations, and 12 patients exhibited elevations of both transaminases and bilirubin. Most liver toxicity was transient and reversible; however, one patient in study 201 exhibited persistent jaundice and ascites for several weeks after treatment and eventually died of hepatic failure. Hepatotoxicity may be more common in patients who have undergone HSCT: of 27 patients who received HSCT, 3 developed clinical hepatic VOD and died 22, 30, and 37 days after transplantation. One patient with a history of VOD who relapsed after transplant was treated with gemtuzumab ozogamicin and died after an episode of severe liver toxicity.

In the absence of randomized studies, definitive conclusions regarding relative toxicities of gemtuzumab ozogamicin and conventional cytotoxic induction chemotherapy cannot be made. However, the rates of hematological toxicity, bleeding, and treatment-related mortality reported in relapsed AML patients treated with gemtuzumab ozogamicin appeared to be similar to those rates reported in studies with conventional chemotherapy (Table 4). Mucositis and infections may be decreased, whereas significant hepatotoxicity may be more common, particularly in association with previous or subsequent HSCT.

**Basis for Approval.** Under the accelerated approval NDA regulations (21 CFR 314.500, Subpart H), drugs for serious or life-threatening illnesses may be approved on the basis of an improvement in a surrogate end point that is "reasonably likely" to predict clinical benefit. The clinical data from the

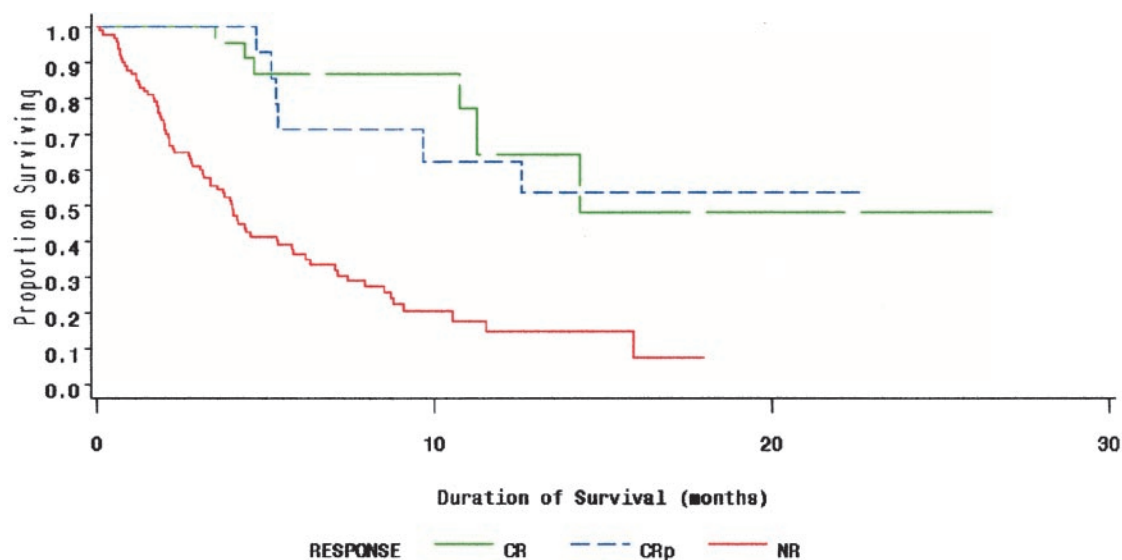


Fig. 2 Kaplan-Meier survival by remission status of 142 patients treated with gemtuzumab ozogamicin. CR ( $n = 23$ ) and CRp ( $n = 19$ ) survivals appear similar, but numbers are too small for definitive conclusions.

Table 3 Patients reporting severe NCI grade 3–4 treatment related adverse events by age (incidence  $\geq 5\%$ )

The incidence of NCI grade 3 or 4 grade 3–4 treatment-related events appeared similar in the subgroup of patients  $\geq 60$  years of age, compared with the overall incidence of adverse events.

Adverse event	All Patients ( $n = 142$ )	Age $\geq 60$ ( $n = 80$ )
Body as a whole		
Neutropenic fever	10 (7)	4 (5)
Sepsis	23 (16)	12 (16)
Cardiovascular system		
Hypertension	13 (9)	9 (11)
Hypotension	11 (8)	6 (8)
Respiratory system		
Dyspnea	13 (9)	10 (13)
Pneumonia	10 (7)	5 (6)
NCI Grade 3–4 laboratory abnormalities		
Hematological		
Hemoglobin	66/141 (47)	36/80 (45)
Absolute neutrophils	137/140 (98)	78/79 (99)
Platelets	139/141 (99)	79/80 (99)
Nonhematological		
Creatinine	2/141 (1)	0/80 (0)
Total bilirubin	33/141 (23)	18/80 (23)
AST	24/141 (17)	12/80 (15)

gemtuzumab ozogamicin studies were presented at the March 14, 2000 public meeting of the Oncology Drugs Advisory Committee. The committee concluded that there was evidence to suggest that CRps were comparable with CRs; therefore, the combined OR rate could be used as evidence of efficacy. The Oncology Drugs Advisory Committee reached a consensus that this drug provided a useful therapeutic option in patients over 60 years of age with relapsed AML who would not be candidates for standard cytotoxic chemotherapy. The combined OR rate was believed to represent a surrogate likely to predict clinical benefit.

The agency accepted the committee's recommendation, and gemtuzumab ozogamicin was given accelerated marketing approval on May 17, 2000, about 7 months after submission of the NDA and 6.5 years after the original investigational new drug application (IND) was filed. Gemtuzumab ozogamicin is indicated for use in patients with CD33 positive AML in first relapse who are 60 years of age or older and are not candidates for cytotoxic chemotherapy. The recommended dose was 9 mg/m<sup>2</sup> i.v. over 4 h and repeated in 14 days.

Under the accelerated approval Phase 4 regulations, the sponsor is required to complete the original studies in relapsed AML. In the absence of randomized trials, the response rates cannot be compared directly with standard induction chemotherapy. Until further clinical experience is available, gemtuzumab ozogamicin should not be used for treatment of AML in younger patients and those who are candidates for standard induction chemotherapy except in the context of clinical trials. Additional studies are mandated under Subpart H to confirm the clinical benefit of gemtuzumab ozogamicin in randomized, controlled trials evaluating the effects on survival of adding gemtuzumab ozogamicin to conventional cytotoxic chemotherapy in patients with *de novo* AML. Additional studies are ongoing to evaluate the safety and efficacy of gemtuzumab ozogamicin in the context of HSCT.

**Postmarketing Data.** Subsequent to the approval of this drug, a large number of spontaneous reports of severe adverse events in patients receiving gemtuzumab ozogamicin prompted an early review of postmarketing safety data. Reports collected during the first 6 months after approval were grouped into the most commonly reported severe adverse events: hypersensitivity reactions, pulmonary toxicity, and hepatotoxicity.

Severe hypersensitivity was defined as a life-threatening reaction with onset temporally related to drug administration, during or a short time after infusion, involving at least two of the following organ systems: respiratory, skin, and cardiovascular

Table 4 Safety and efficacy in published studies of relapsed AML, compared with the 142 relapsed AML patients treated with gemtuzumab ozogamicin

Treatment-related adverse events (measurement)	Regimen			
	G-O <sup>a</sup> n = 142	FLAG <sup>b</sup> n = 38	HIDAC-M <sup>c</sup> n = 90	DEM <sup>d</sup> n = 57
Median time from first dose to platelets $\geq 100,000/\mu\text{l}$ (days)	50.0	28	50	NR
Median time to ANC $>500/\mu\text{l}$ (days)	40.5	21	40	34
Grade 3–4 infections (%)	28	44	55	83
Grade 3–4 abnormal transaminases (%)	17	8	10	26
Grade 3–4 bleeding (%)	15	NR	10	21
Grade 3–4 nausea or vomiting (%)	11	NR	20	27
Grade 3–4 CNS bleeding (%)	4	3	NR	NR
Grade 3–4 mucositis (%)	4	10	9	23
Treatment mortality rate (%)	13	10	16	32
CR rate	16	55	44	30

<sup>a</sup> G-O, gemtuzumab ozogamicin; FLAG, fludarabine, cytarabine, granulocyte colony-stimulating factor; HIDAC-M, cytarabine 1 g/m<sup>2</sup> q12 × 4d + mitoxantrone 12 mg/m<sup>2</sup> × 4d diazepam, etoposide, mitoxantrone; NR, not reported. CR rate as defined by NCI workshop criteria; reference 12.

<sup>b</sup> Montillo Mirto *et al.*, Ref 20.

<sup>c</sup> Kern *et al.*, Ref 21.

<sup>d</sup> Lee *et al.*, Ref 22.

systems. Nine cases of severe hypersensitivity reactions were reported after treatment with gemtuzumab ozogamicin, four of them fatal. Eight reported the onset during or after the patients' first gemtuzumab ozogamicin exposure, and one began immediately after the beginning of the second infusion. Most reactions occurred during infusion or within 2 h after infusion. Fevers, rigors, chills, diaphoresis, and "anaphylactoid type" reactions have been reported (15) in patients receiving monoclonal antibodies associated with binding to high levels of circulating cells; direct cytokine release is postulated to be the cause.

Eight patients were identified who experienced pulmonary events immediately after or within 24 h of the gemtuzumab ozogamicin 2-h infusion, of whom six had initial leukocyte counts above 60,000/ $\mu\text{l}$ . Five were described as adult respiratory distress syndrome, and three were reported as "pulmonary edema." Five deaths were reported in these patients. Although pulmonary leukostasis has a similar clinical presentation and occurs in about half of the patients presenting with blast counts above 100,000/ $\mu\text{l}$  (16), the temporal association of these events with drug administration suggests a drug reaction. Acute pulmonary events including adult respiratory distress syndrome have been described (17, 18) with the use of unconjugated therapeutic antineoplastic monoclonal antibodies, including rituximab and trastuzumab, and may be associated with pulmonary neoplastic involvement. Reduction in peripheral blast counts to below 30,000/ $\mu\text{l}$  with hydroxyurea or leukapheresis should be considered before gemtuzumab ozogamicin administration.

Calicheamicin as well as gemtuzumab ozogamicin are both known to cause hepatotoxicity in preclinical models. As of April 30, 2000, 11 of 271 (4%) patients treated in the Phase 2 studies and 6 of 120 (5%) patients treated by individual physicians developed VOD. Since marketing approval, five spontaneous reports of liver failure were reported in patients treated with gemtuzumab ozogamicin, two with prior histories of HSCT, and one with a history of concomitant INH administration. Three deaths were reported, one in a patient with prior HSCT (19). Of

27 patients in the original NDA studies who subsequently underwent HSCT, 3 developed fatal VOD (11%).

VOD has been reported after treatment with gemtuzumab ozogamicin in patients who subsequently receive HSCT, as well as in patients without a previous history of HSCT (23). On the basis of these reports, the Division of Oncology Drug Products has initiated revisions of the product label to include warnings regarding the risk of hypersensitivity reactions, pulmonary events, and hepatic toxicity, as well as a recommendation to reduce leukocyte counts below 30,000/ $\mu\text{l}$  prior to treatment. A registration program has been initiated and further studies are ongoing to ascertain more precisely the risk of adverse events following treatment with gemtuzumab ozogamicin.

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## Approval Summary: Gemtuzumab Ozogamicin in Relapsed Acute Myeloid Leukemia

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