CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21174

MEDICAL REVIEW(S)

NDA MEDICAL REVIEW

NDA 21-174

MYLOTARG®

(GEMTUZUMAB OZOGAMICIN)

in Relapsed Acute Myelogenous Leukemia

Wyeth Ayerst Research

Submitted: October 29, 1999

Completed: April 18, 2000

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1. General Information

1.1. Title/Heading - Medical Officer's Review

1.1.1. NDA # 21-174

1.1.2. Submission (date) October 29, 1999

1.1.3. Review completed April 18, 2000

1.1.4. Drug name CMA 676

1.1.5. Generic name gemtuzumab ozogamycin

1.1.6. Proposed trade name: Mylotarg®

1.1.7. Chemical name (structure optional)

P67.6-NAc-gamma calicheamicin DMH AcBut conjugate

1.2. Sponsor

Wyeth Ayerst

1.3. Pharmacologic Category:

immunocongugate

1.4. Dosage Form(s) and Route(s) of Administration

Solution for intravenous injection

1.5. NDA Drug Classification

Standard

1.6. Important Related Drugs:

none

2. Material Reviewed

2.1. volume numbers which serve basis for this review)

NDA 21-174
Wyeth-Ayerst
Volumes 1,2 and 77-101

2.2. Other resources

Medline search of medical literature

Devita *et. al.*, Principles and Practice of Oncology, 5th Edition, New York, Lippincott 1997

2.3. Consultants

Ellin Berman, MD
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3. Chemistry/Manufacturing Controls

See chemistry review by Dr. Chen

4. Animal Pharmacology/Toxicology

There is no previous clinical pharmacokinetic information for gemtuzumab ozogamicin. Extrapolation of pharmacokinetic studies in animals is not thought to be predictive of clinical results because of the absence of CD33, which is presumed to be an important factor in elimination of the drug from plasma through binding and internalization into cells. However, a mass balance study of gemtuzumab ozogamicin in rats showed that cumulative excretion after 336 hours post dose accounted for 72% of the radioactivity. Cumulative recoveries (percent of dose) were 12.6% and 58.6% for urine and feces, respectively. Single intravenous (IV) doses of 2.5, 25, and 75 μg/kg of calicheamicin in dogs resulted in concentrations that were below the limit of detection. At 250 μg/kg doses, calicheamicin concentrations fell below 2.5 ng/mL within 6 hours of dose administration. Similar low concentrations of calicheamicin were observed in rats after doses of 10, 100, and 300 μg/kg.

5. Clinical Background

5.1. Proposed Indication

Treatment of relapsed CD 33 positive acute myeloid leukemia

5.2. Treatment of AML

Acute myeloid leukemia affects approximately 2.4 persons per 100,000 annually in the United States and occurs more commonly in adults than children, to a peak of 12.6 per 100,000 at age >65.[1] Chemotherapy is highly toxic, with a mortality rate of 3-30%, and requires 7 days of inpatient continuous infusion. Response rates for de novo AML are generally above 50% depending on prognostic characteristics, however most patients eventually relapse. Long-term survival is < 20% in all AML patients treated with chemotherapy and is somewhat better in a select subset of patients with good prognostic characteristics who are able to tolerate intensive postremission therapy.

The CD33 antigen is a 67 kd glycoprotein that functions as a sialic acid-dependent adhesion protein.[2] CD33 is expressed on leukemic myeloid colony-forming cells (CFC) and on about 90% of AML myeloblasts, including leukemic clonogenic precursors; however, it is not expressed on pluripotent hematopoietic stem cells and is absent from nonhematopoietic tissue.[3] *In vitro* studies showed rapid internalization of the antibody by the target cell. These properties make it possible to use antibodies against CD33 to specifically deliver agents to leukemia cells.[4]

Antibody therapy is ideally suited to treatment of hematologic malignancies because of the ready accessibility of neoplastic cells in the circulation. Monoclonal antibodies (MoAb's) have been manufactured against the CD33 epitope. Clinical studies have shown that radiolabeled anti-CD33 murine MoAbs localize to the bone marrow of patients with AML.[5] Three basic approaches have been used in the therapeutic use of monoclonal antibodies in hematologic malignancy.[6] In the first approach, the antibodies alone have been used to elicit an immune response to the malignant clone. Initial in vivo studies with an unmodified murine anti-CD33 antibody in patients with AML demonstrated that the antibody quickly bound to leukemia cells and that the antigen-antibody complex rapidly internalized following cell binding. However, when administered to patients with

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[1] Lowenburg B et.al: Acute Myeloid Leukemia, *New England Journal of Medicine*, 341:14, 1051-1061, 1999.

[2] Andrews RG, Myeloid-associated differentiation antigens on stem cells and their progeny identified by monoclonal antibodies. *Blood* 62:124, 1983.

[3] Dinndorf PA, et.al.: Expression of normal myeloid-associated antigens by acute leukemia cells. *Blood* 67:1048, 1986

[4] Bernstein ID et. al: Treatment of acute myeloid leukemia cells in vitro with a monoclonal antibody recognizing a myeloid differentiation antigen allows normal progenitor cells to be expressed. *J Clin Invest* 79:1153, 1987

[5] Van der Jagt RH, et.-al: Localization of radiolabeled antimyeloid antibodies in a human acute leukemia xeno-graft tumor model. *Cancer Res* 52:89, 1992

[6] Appelbaum FR: Antibody-targeted therapy for myeloid leukemia. *Semin Hematol* 1999 Oct;36(4 Suppl 6):2-8

overt leukemia, unmodified antibody resulted in only brief decreases in peripheral blast counts, not in sustained response.[7]

Radiolabeled antibodies have been explored as a stand-alone treatment or in the context of bone marrow transplantation.[8] In an effort to avoid toxicities to normal stem cells residing alongside leukemic cells in the marrow, studies have been performed to explore the use of 231Bi conjugated to an anti-CD33 monoclonal antibody. The short path length of this alpha-emitter could theoretically allow killing of the targeted leukemic cell without damage to normal neighbors. Of 12 patients with recurrent AML who received this drug, eight had reductions in marrow and peripheral blast counts. Complete remissions (CRs) have not been observed to date.
The third approach involved conjugating a toxin to the CD33 antibody, and this was the technique used in this study, in which a recombinant humanized anti-CD33 MoAb was linked to NAc-gamma calicheamicin (NAc-cal) and given to patients with relapsed AML.[9] The calicheamicins, small molecules with weights of approximately 1.5 kd, are potent antitumor antibiotics that were initially identified by their ability to damage DNA in screening tests. [10] They bind DNA in the minor groove and produce site-specific double strand break. They contain two "domains": the enediyne portion, which, on reductive activation, is responsible for DNA cleavage, and the aryltetrasaccharide tail, which anchors the whole molecule to the DNA minor groove. The aryltetrasaccharide moiety can efficiently inhibit the binding of transcription factors to a target DNA containing TCCT, generally considered to be the preferred canonical calicheamicin binding sequence. In this way, the drug can specifically interfere with DNA-related biological processes such as transcription and other biological events that depend on protein-DNA interactions. Calicheamicin can interfere with biological processes not simply by cleaving free DNA but also by displacing a DNA-binding protein through competition or modulation of DNA structure, according to recent research.[11] The antibody-calicheamicin complex is internalized, and it is believed that calicheamicin is cleaved from the gemtuzumab ozogamicin molecule within the cell. Some calicheamicin then binds to DNA, causing cell death. Studies in animals have demonstrated that unconjugated calicheamicin derivatives represent less than 4% of total derivatives in plasma, suggesting that calicheamicin remains linked to gemtuzumab ozogamicin in serum. [12]

5.3. Administrative History

Original IND[ ]for gemtuzumab ozogamicin was submitted on November 9, 1994 to the Division of Oncology Drug Products. The development of gemtuzumab ozogamicin was facilitated

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[7] Scheinberg DA: A phase I trial of monoclonal antibody M195 in acute myelogenous leukemia: Specific bone marrow targeting and internalization of radionuclide. *J Clin Oncol* 9:478, 1991

[8] . Appelbaum FR: The use of radiolabeled anti-CD33 antibody to augment marrow irradiation prior to marrow transplantation for acute myelogenous leukemia. *Transplantation* 54:829, 1992

[9] Sievers EL; Selective ablation of acute myeloid leukemia using antibody-targeted chemotherapy: a phase I study of an anti-CD33 calicheamicin immunoconjugate, *Blood* 1999 Jun 1;93(11):3678-84

[10] Zein N, Sinha AM, McGahren WJ, Ellestad GA: Calicheamicin gamma 1I: an antitumor antibiotic that cleaves double-stranded DNA site specifically. *Science* 240:1198, 1988

[11] Sissi C, et.al. Interaction of calicheamicin and its related carbohydrates with DNA-protein complexes, PNAS, Vol. 96, Issue 19, 10643-10648, September 14, 1999

[12] Wyeth-Ayerst Laboratories, NDA 21-174, Volume 103 p. 99

by the highly interactive relationship of the FDA and Wyeth-Ayerst. A number of meetings and teleconferences were held in which key aspects of the development program were discussed. The most significant of these interactions are summarized below:

An End-of-Phase I meeting was held on January 14, 1997. Sponsor's plan to support an NDA filing with one pivotal safety and efficacy study (Protocol 201) in 55 patients was deemed to be generally acceptable, assuming favorable results.

As a follow-up to the End-of-Phase I meeting, a teleconference was held on July 25, 1997 at the request of Wyeth-Ayerst to confirm the Division's acceptance of revisions to the pivotal 201 study relative to length of follow-up and the ability to measure the duration of gemtuzumab ozogamicin response. The Division acknowledged the difficulties in standardizing post remission therapy and establishing an appropriate length of follow-up in relapsed AML patients prior to additional therapy such as bone marrow transplantation. The Division agreed that the revisions to the protocol were acceptable and had addressed their concerns.

A meeting to discuss the interim analysis results from the pivotal 201-US study was held on September 16, 1998. The Division noted that morphologic remissions (MRs) could be used to support the primary complete remission (CR) endpoint if it was demonstrated in the NDA that MRs were functionally and clinically similar to CRs.

A Pre-NDA meeting specific to clinical issues was held on May 12, 1999. The Division agreed that the overall content and format of the NDA were acceptable. The Division also agreed that the patient numbers (104 patients in Phase 2) and data collection appeared sufficient for an NDA filing. The Division indicated that the proposal to include 28 day follow-up data on all 104 Phase H patients, and 6-month follow-up on 55 of the 104 Phase 2 patients, in the initial NDA submission was acceptable.

The Division also noted that Wyeth-Ayerst would need to clearly demonstrate the clinical benefit of the new response category of morphologic remission (MR) in order for MR to be used to support the primary endpoint of CR. The Division suggested that Wyeth-Ayerst use historical controls in the NDA as a comparison to support safety and efficacy claims in the NDA.

A Pre-NDA meeting specific to chemistry issues was held on June 2, 1999. The Division concurred with the proposal to designate hP67.6 antibody and activated N-Acetyl calichearnicin DMH as pivotal intermediates for the production of gemtuzumab ozogamicin. The Division also agreed with Wyeth-Ayerst's proposal to designate the bulk liquid conjugate as the active drug substance and lyophilized gemtuzumab ozogamicin as the drug product.

The amount of stability data to be included in the initial filing was agreed to by the Division. Because gemtuzumab ozogamicin is intended to treat a seriously ill population, and based on the biotechnology products guideline, the Division indicated that they would be flexible with respect to filing the NDA with less than 12 months real-time drug product stability data. The amount of stability data to be included in the original NDA was also outlined in a position paper submitted on September 15, 1999 (Serial No. 190).

5.4. *Relevant human experience*

See clinical studies section

5.5. *Related INDs and NDAs –*

none

5.6. *Foreign experience – see study # 202*

5.7. *Human Pharmacology, Pharmacokinetics, Pharmacodynamics: See PK review by Dr. Keiffer*

6. Description of Clinical Data Sources

6.1. *Patient Enumeration*

Table 1: Study Type and Design

Protocol #	Design	Accrual	Location(s)	Dates	Comments
0903A1-101	Phase I open label dose escalation	41	Seattle, WA Duarte, CA	4/95-5/98	MTD = 9 mg/m^2
0903A1-201	Phase II open label	59	Multicenter US/CA	5/97-ongoing	Pivotal trial
0903B1-202	Phase II open label	25	Multicenter Europe	4/98-ongoing	Relapse post BMT allowed
0903B1-203	Phase II open label	20	Multicenter US/Europe	12/97-ongoing	Elderly Pts
0903A1-102	Phase I	11	US	ongoing	Pediatric

6.2. *Extent of Exposure*

41 patients (including the patient who was enrolled and treated twice) received at least 1 dose of gemtuzumab ozogamicin ranging from 0.25 to 9 mg/m^2. Table 4 presents the numbers of patients receiving 1, 2, or 3 doses of gemtuzumab ozogamicin by dose group. For the 88 patients who received 2 or 3 doses, the number of days between the first and second dose ranged from 13 to 29 days, with a median of 16 days. The mean (+/- SD) number of days between the first and second dose was 17.9 (+/- 4.4).

Table 2: NUMBER (%) OF PATIENTS VS. NUMBER OF DOSES AT 9 mg/m² GEMTUZUMAB OZOGAMICIN[a]

	Study 101	Studies 201/202/203
Total Doses	(n = 7)	(n = 104)
1	3 (43)	16 (15)
2	2 (29)	85 (82)
3	2 (29)	3 (3)

7. Clinical Studies

7.1. Phase 1 Trial:

7.1.1.1. Trial # 0903 A1 101

7.1.1.2. TITLE: A PHASE I STUDY OF RECOMBINANT ANTI-CD33 MONOCLONAL ANTIBODY (hP67.6 ANTIBODY)-CALICHEAMICIN DRUG CONJUGATE (hP67.6 CONJUGATE) AS TREATMENT FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML)

7.1.1.3. Objective/Rationale

1. To study the safety of gemtuzumab ozogamicin in terms of:
– Acute infusion related toxicities (ie, occurring within 6 hours of the start of the infusion of test drug).
– Hematologic toxicities.
– Nonhematolcgic toxicities.

2. To define the maximum tolerated dose (MTD) of gemtuzumab ozogamicin.

3. To study the pharmacokinetic properties of gemtuzumab ozogamicin.

7.1.1.4. Design

This trial was an open-label, single-arm, phase I dose escalation study to examine the effects of gemtuzumab ozogamicin given to patients with CD33-positive AML. It was conducted at two institutions in the United States.

7.1.1.5. Protocol

7.1.1.5.1. Population:

Men and women aged 16 to 70 years with CD33 positive (+) acute myeloid leukemia (AML) were eligible for entry in the study if they had failed to achieve remission or they had a relapse after remission. Patients with a relapse who had undergone marrow transplantation and in whom the transplant had engrafted were also eligible.

Forty (40) patients in 8 treatment groups were enrolled at the 2 investigational sites. Twenty-one (21) men and 20 women were enrolled. The mean age was 48.6 years. All patients had AML, and 22 (54%) had previously undergone a bone marrow transplant. Two (2) patients had a history of myelodysplastic syndrome.

7.1.1.5.2. Treatments:

Originally, 5 treatment groups were planned with 3 to a maximum of 6 patients each, at dose levels of 0.25, 0.5, 1, 2, and 4 mg/m^2 (expressed as dose of protein equivalent). In an attempt to reach the MTD, 3 additional treatment groups (5, 6, and 9 mg/m^2) were added during the conduct of the study. Patients received study drug as a single 2-hour IV infusion per dose for a maximum of 3 doses, with a minimum of 14 days between doses.

7.1.1.5.3. Safety endpoints:

Adverse events and toxicities were summarized by treatment group in 3 categories as follows:

a) acute and delayed infusion-related toxicities,

b) hematologic toxicities, and

c) nonhematologic toxicities.

7.1.1.5.4. Safety results:

This ascending dose trial in patients with relapsed and refractory AML evaluated the safety of dose levels of gemtuzumab ozogamicin from 0.25 to 9 mg/m^2. In addition to 7 patients who died within 30 days of receiving gemtuzumab ozogamicin (section 10.4.1), and 3 who were withdrawn for reasons related to safety (section 10.4.3), there were 39 hospitalizations or other serious adverse events reported.

Hospitalizations: The majority (21/28; 75%) of the hospitalizations were for fever and/or neutropenia. One patient died with marrow aplasia after 3 doses of CMA-676 at 6 mg/m^2. In subsequent studies, > 15% cellularity on bone marrow biopsy was required before the administration of a third dose of gemtuzumab ozogamicin to prevent prolonged myelosuppression. 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 hours

of the start of the gemtuzumab ozogamicin infusion and tended to be less frequent and less severe with subsequent doses. The most common delayed infusion-related events over all dose periods combined were fever (reported by 44% of patients), nausea (32%), chills (27%), leukopenia (22%), vomiting (12%), rash (12%), pain (10%), and thrombocytopenia. Nausea, vomiting, leukopenia, thrombocytopenia, and rash tended to occur more frequently at the higher dose levels.

Table 3 : common observed infusion-related toxicities

	ACUTE (6-HOUR)			DELAYED (24-HOUR)		
	GZ Treatment Group (mg/m^2)					
	5	6	9	5	6	9
Adverse Event	(n = 6)	(n = 8)	(n = 7)	(n = 6)	(n = 8)	(n = 7)
Any adverse event	6 (100)	5 (63)	4 (57)	6 (100)	6 (75)	7 (100)
Fever	4 (67)	4 (50)	3 (43)	4 (67)	2 (25)	4 (57)
Nausea	2 (33)	2 (25)	1 (14)	2 (33)	2 (25)	6 (86)
Chills	5 (83)	4 (50)	4 (57)	2 (33)	0	4 (57)
Leukopenia	-	-	-	3 (50)	2 (25)	1 (14)
Vomiting	2 (33)	0	1 (14)	1 (17)	2 (25)	2 (29)
Rash	-	-	-	3 (50)	1 (13)	1 (14)
Hypotension	1 (17)	1 (13)	1 (14)	-	-	-
Thrombocytopenia	-	-	-	0	2 (25)	0

Antibodies: Two patients exhibited evidence of development of antibodies to the calicheamicin - linker complex. One patient, after receiving 3 doses of gemtuzumab ozogamicin (1 mg/m^2), had a complete remission for 5½ months and was eligible for a second course of gemtuzumab ozogamicin after bone marrow relapse occurred. He received a second course of gemtuzumab ozogamicin in the 6 mg/m^2 treatment group. Approximately 5 minutes after the second dose of gemtuzumab ozogamicin was administered, the patient experienced mild shortness of breath and chest tightness lasting no more than 10 minutes. Treatment consisted of the administration of oxygen for a short period. Immune response studies documented a significant rise in titers of antibody to the calicheamicin linker complex. Thus, this patient appears to have had a respiratory syndrome associated with immune reaction to the gemtuzumab ozogamicin conjugate. One other patient developed antibodies to the calicheamicin-linker complex after a third dose of gemtuzumab ozogamicin, with no accompanying clinical signs reported.

Neutropenia: The duration of neutropenia may be related to dose level. Two (2) patients in this study had CR. One patient, who had CR in the 1 mg/m^2 dose group, had neutrophil count recovery to > 1,500/μL 4 days after receiving the third dose of gemtuzumab ozogamicin. Another patient, who had CR in the 4 mg/m^2 treatment group, had neutrophil count recovery to > 1,500/μL 35 days after receiving the third dose of gemtuzumab ozogamicin. These data, though scant, suggest a relationship between dose level and the duration of neutropenia. Prolonged neutropenia was observed in 2 patients. One (1) patient who received 3 doses of gemtuzumab ozogamicin at 9 mg/m^2 experienced grade 4 neutropenia for 6 weeks after the third dose was administered. An additional patient who received 2 doses of gemtuzumab ozogamicin at 9 mg/m^2 developed sepsis,

confirmed by blood culture, while neutropenic, and experienced grade 4 neutropenia and thrombocytopenia after that dose for a total of 7 weeks before dying from infection.

Thrombocytopenia: 10/40 patients were observed to exhibit grade 4 thrombocytopenia. 3 patients had thrombocytopenia at baseline. The duration of thrombocytopenia was several weeks, and was complicated by the presence of residual leukemia in some patients. The identification of several patients with blast clearance and persistent thrombocytopenia suggested that gemtuzumab ozogamicin is particularly toxic to megakaryocytes, and led to the proposal of a category of 'morphologic remission' with clearance of blasts but incomplete recovery of platelets.

Transaminases: 2 patients had grade 4 elevations of transaminases, and 9 patients had grade 3 elevations of transaminases. Most of these abnormalities were ascribed to concomitant medications and progression of disease.

Conclusions: Initially the MTD was not reached because drug-related events were often difficult to distinguish from disease-related events. The duration of myelosuppression encountered in 2 patients at 9 mg/m^2 was considered clinically important. 9 mg/m^2 of gemtuzumab ozogamicin was therefore chosen to be the appropriate safe dose for phase II clinical trials. Administration of more than two doses of CMA-676 may be associated with prolonged myelosuppression and possibly an increased risk of the development of antibodies to the linker complex.

7.1.1.6. Efficacy endpoint outcomes

Response rates: Two (2) of the 41 patient treatments resulted in objective CRs after 3 doses of CMA-676, one treated at 1mg/M^2 and one at 4 mg/M^2 . 7 additional patients treated with doses of 5, 6, and 9 mg/M^2 had clearance of leukemic blasts (<5%) from their blood and bone marrow without full recovery of peripheral counts. The term "morphologic remission" was adopted to describe the finding that some of the patients in this study had clearance of blast cells with incomplete platelet recovery. Because of the findings from study 101, MR was included in the phase II protocols as a secondary efficacy endpoint. Originally, MR was defined as clearance of leukemia from marrow, but after discussions with regulatory agencies, a more specific definition of MR was developed for the phase II protocols. MR was defined exactly the same as CR for all the parameters except platelets. To be classified as having a MR, patients had to meet all the criteria for CR except recovery to 100,000 platelets/µL. The MR patients had to have sufficient bone marrow recovery to be platelet transfusion independent.

Pharmacodynamics: Although evidence of efficacy was obtained at dose levels below 9 mg/m^2, at 9 mg/m^2 a high rate (4/7) of patients had blast clearance from the bone marrow. In addition, evaluation of the CD33 saturation data led to the conclusion that a dose level of 9 mg/m^2 would be effective in saturating CD33 sites in all patients regardless of leukemia burden. It is believed that gemtuzumab ozogamicin exerts its antineoplastic effect by binding to CD33 positive cells and then being internalized. Extensive saturation of CD33 binding sites is thus fundamental to effective therapy. In study 101, CD33 saturation was evaluated with doses of gemtuzumab ozogamicin ranging from 0.25 to 9 mg/m^2. Peripheral blood samples were collected at baseline, 3, and 6 hours

after the gemtuzumab ozogamicin infusion began and were analyzed to determine the percentage of CD33 sites on mononuclear cells that were saturated by gemtuzumab ozogamicin. There was variability in saturation when the area under the concentration time curve (AUC) was less than 100 mg h/L. CD33 site saturation increased with dose level. Patients who had experienced CRs or clearance of blasts all had maximum saturation of 70% and above during the first 6 hours after administration of the first dose of gemtuzumab ozogamicin. These data support the conclusion that one prerequisite for clinical response is the delivery of a sufficient dose of calicheamicin to the leukemic cells. These data also support the conclusion that a dose of 9 mg/m^2 of gemtuzumab ozogamicin can saturate CD33 sites.

Pharmacokinetics: Blood samples were collected throughout the 96-hour sampling period that followed initiation of gemtuzumab ozogamicin infusion. Only a limited assessment of the pharmacokinetic parameters in the lower- or higher-dose treatment groups could be made because of the limits of quantitation or because the sampling period was smaller than 3 times the estimated t½ There was no consistent accumulation between dose periods for any of the dose groups. In general, concentrations increased as gemtuzumab ozogamicin doses were escalated, but a definitive assessment of dose linearity could not be made because of the large inter-subject variability and the small numbers of patients in the treatment groups. The half life of the hP67.6 antibody was 69+/- 37 hours.

7.1.1.7. Conclusions of 101 study

Gemtuzumab ozogamicin administered as a single agent to patients with relapsed or refractory AML at dose levels of up to 9 mg/m^2 caused significant myelosuppression. Seven patients died within 30 days of study drug administration, six of these deaths were attributed to the disease progression and one to sepsis secondary to prolonged myelosupression. Greater than two doses resulted in prolonged myelosuppression in two patients. Safety data suggested 9mg/M^2 as the MTD, and CD33 receptor site saturation data further supported the choice of 9mg/M^2 as the appropriate dose for phase II studies. 7 patients had clearance of blasts and 2 patients had complete remissions at doses $\leq$9mg/M^2.

Two patients developed antibodies to the calicheamicin-linker complex, one with clinical symptoms. Remission was observed in two patients. The results of this study provided the safety and preliminary efficacy data to initiate phase II trials at a dose of 9 mg/m^2. The dosing interval of 14 days was based on the half-life of the antibody. A dose would be expected to be cleared from the body in 4 to 5 half lives, or approximately 12 to 15 days. Weekly administration might result in accumulation, whereas monthly administration might result in disease recurrence

7.2. *Phase 2 trials: THE EFFICACY AND SAFETY OF GEMTUZUMAB OZOGAMICIN AS SINGLE AGENT TREATMENT OF PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) IN FIRST RELAPSE*

7.2.1. Summary of clinical studies 201,202,203

Primary data from three phase II clinical studies was submitted in this NDA, which included 13 sites in the US, 2 in Canada, and 17 in Europe. A total of 154 patients were screened and 104 enrolled.

Reviewer comment: The submission of phase II studies rather than randomized controlled trials was agreed to by the FDA because the rarity of the disease would significantly limit accrual to a multi-arm trial.

7.2.1.1. **Objective/Rationale**

7.2.1.1.1. Primary:

- To assess efficacy in terms of the number of patients with acute myeloid leukemia (AML) who attained a complete remission (CR);
- to assess the safety of gemtuzumab ozogamicin.

7.2.1.1.2. Secondary:

- To assess the duration of CRs and morphologic remissions (MRs);
- To assess the pharmacokinetic (PK) properties of gemtuzumab ozogamicin;
- To assess possible predictors of response to gemtuzumab ozogamicin.

7.2.2. Design/ Methodology:

These were 3-part, open-label, single-arm, multidose studies.

7.2.2.1. **Institutions**

Patients were enrolled at 13 investigational sites in the United States and Canada and 17 sites in Europe as of 31 Dec 1998

7.2.2.2. **Protocol**

7.2.2.2.1. Population, procedures

Main criteria for inclusion: Patients with CD33 positive AML in first relapse after at least 6 months of CR (3 months in study 203). Patients were required to have >5% blast cells identifiable by flow cytometry, of which a high percentage expressed CD33. For eligibility, CR was defined as the date bone marrow biopsies or aspirate specimens showed clearance of leukemic blasts. ≥3 months of CR was allowed in study 203.

Exclusion: Patients with secondary leukemia, FAB M3 promyelocytic leukemia, previous MDS, or history of prior chemotherapy for relapse were excluded. Patients with a history of previous hematopoetic stem cell transplant were allowed only in study 202.

Table 4: KEY INCLUSION AND EXCLUSION CRITERIA IN PHASE II STUDIES

Criteria	Study 201	Study 202	Study 203
Patients with AML in first relapse	Required	Required	Required
CD33-positive phenotype	Required	Required	Required
Minimum age, years	18	18	60
Duration of first remission, months	6	6	3
Prior HSCT	Not permitted	Permitted[a]	Not permitted
Baseline serum creatinine	≤ 2.0 mg/dL	≤2.0 mg/dL	≤ 3.0 mg/dL
Baseline serum total bilirubin	≤ 1.5 mg/dL	≤ 1.5 mg/dL	≤ 2.0 mg/dL

a. Originally not permitted, but protocol 202 was amended to allow HSCT.

7.2.3. Methodology:

(See Appendix 1 for study flow chart)

7.2.3.1. Prestudy Screening

All patients were screened within 1 week before administration of the first dose.

At screening, within 1 week before dose administration, the following were performed:

- Medical history - including history of past and present illness; full history of the course of AML with response to prior therapy, noting cytogenetic and molecular markers (if information is available) and current medical problems.

- Complete physical examination - including demographics (sex, birth date, ethnic origin), a physical examination with a review of systems, assessment of performance status, vital signs (sitting blood pressure, pulse, respiratory rate, and oral temperature), height and weight.

- Laboratory evaluation - including CBC with differential, blood chemistry, prothrombin time (PT) and partial thromboplastin time (PTT).Chest x-ray film -Posteroanterior and lateral. Electrocardiogram (ECG) - including rate, rhythm, complex and interval abnormalities, and other relevant abnormal findings. Beta-human chorionic gonadotropin - serum pregnancy test - for women of childbearing potential. Urinalysis – including specific gravity, pH, assessment of protein/albumin, glucose/sugar, ketones/acetone, hemoglobin/blood, microscopic examination

- Bone marrow aspirate and biopsy, and histochemical stains (myeloperoxidase, nonspecific esterase, and periodic acid Schiff stains). Immunophenotyping and confirmation of CD33+ AML/patient eligibility. Wright-Giemsa stained slides for morphologic evaluation of bone marrow aspirate (2 slides per specimen) were sent for review by an independent consultant for confirmation of AML. This was done in a blinded fashion. Eligibility at entry was based on the local pathologists' interpretation of the slides and a central laboratory conformation of CD33 positivity by flow cytometry, but response was based on the independent pathologists reading.

All studies were conducted on an outpatient basis with an initial study drug infusion observation period for each patient. Gemtuzumab ozogamicin (5 mg/vial); 9 mg/m^2 was administered as a single 2-hour intravenous (IV) infusion on day 1. The observation period began with the start of each infusion and continued for 8 hours during dose period 1. The infusion observation period was 6 hours for subsequent dose periods as long as no clinically significant infusion-related events occurred during dose period 1. In part I, (dose administration and evaluation) patients were eligible to receive a subsequent dose at least 14 days (but less than 28 days) from the previous infusicn, if the following conditions were met:

1. The patient had recovered from reversible non hematologic toxicities resulting from the first cycle,
2. There was no evidence of uncontrolled infection
3. There was no evidence of disease progression,
4. There was no evidence of antibody formation .

Investigators could delay the next dose beyond 14 days to allow the patient to recover from serious infections or other medically serious events. Delay beyond 28 days was not allowed because of concern that this interval would allow regrowth of leukemia cells, and extend the overall period of neutropenia experienced by patients.

Withdrawal from study: patients were withdrawn from the study if they were non evaluable or failed to show up for followup, and for disease progression, production of antibodies, and for serious adverse events.

Concomitant treatment:

All patients were premedicated with acetaminophen 650-1000g and benedryl 50 mg to decrease acute infusion-related symptoms.

Hydroxyurea 2g/day was administered to patients with white counts above 30,000 to decrease the likelihood of tumor lysis syndrome. This was discontinued 24 hours prior to treatment. Other cytotoxics and immunosuppressives were not allowed on protocol.

Growth factors and cytokines were not allowed. All other clinically indicated medications were allowed. Use of prophylactic antibiotics was not specified in the protocol.

Duration of treatment:

- Study part I - approximately 50 days (7 days screening; 2 doses with >14 and < 28 days between doses; 28-day follow-up after the last dose). Selected patients received an additional dose and follow-up dose period for a total of approximately 64 days in study part I.
- Study part II - approximately 6 months additional follow-up.
- Poststudy part III (patients completing study part II) - additional follow-up by telephone call every 3 months for 18 months; then patients were followed every 6 months until death.

Significant protocol amendments:

A total of 12 amendments were made to the 3 studies. The most significant amendments specified pretreatment medication to prevent infusion-related symptoms, allowed increased accrual, and allowed retreatment for subsequent relapse.

Initially a third dose of CMA 676 was allowed in patients who had not achieved a response after 2 doses, however, only 2 patients were treated with the extra dose and this option was discontinued due to prolonged myelosuppression and lack of efficacy. Study 202 was amended to allow prior hematopoetic stem cell transplant (HSCT).

7.2.3.2. Endpoints and objectives

The primary objectives of each study were

1. To assess efficacy in terms of the number of patients attaining CR.
2. To assess the safety of gemtuzumab ozogamicin.

The secondary objectives were

1. To assess the duration of CRs and MRs.

2. To assess the PK properties of gemtuzumab ozogamicin.

3. To assess possible predictors of response to gemtuzumab ozogamicin.

In addition, data were collected and presented regarding overall survival, health outcomes assessments, hematologic characteristics of response, and post-gemtuzumab ozogamicin treatments.

Criteria for evaluation/Efficacy assessment methods:

Study part I - primary endpoint: **CR** defined as

a) leukemic blasts absent from peripheral blood;
b) percentage of blasts in the bone marrow $\leq$ 5%;
c) peripheral levels of hemoglobin $\geq$9 g/dL, platelets $\geq$ 100,000/μL, absolute neutrophil count $\geq$ 1500/μL; and
d) the patient being red blood cell and platelet-transfusion independent.
e) The definition for **MR** was the same as that for CR except that platelets were not required to reach 100,000/μL. Patients who had no leukemic blasts in the peripheral blood and $\leq$ 5% blasts in bone marrow (measured by bone marrow aspirate or biopsy) at the end of part I visit but did not meet other criteria for CR or MR were eligible to achieve CR or MR status during part II.

Bone Marrow Aspirates: Bone marrow aspirates were to be obtained 7 days after each infusion. Biopsies and aspirates were obtained 28 days after the last infusion of study drug unless patients clearly experienced progression of AML. Bone marrow biopsy and aspirate slides were sent for evaluation by an independent consultant after being read by the local pathologist.

Study part II - secondary endpoint: duration of CR and MR were evaluated in part II for approximately 6 months.

Study part III: Responding patients had monthly physical examinations and CBC's for an additional six months. All patients were followed for an additional 18 months by telephone contact (every 3 months) regardless of remission/relapse status at the end of study part II.

Safety assessment methods:

Part I: Interim physical examinations were performed at least twice weekly for the first 2 weeks following each infusion, including assessment of performance status, vital signs and possible drug-related toxicities, and laboratory evaluations. Chest X-rays and electrocardiograms were obtained at entry and at the end of part 1. Antibodies against calicheamicin and against the hP67.6 conjugate were obtained at baseline, day 8, 22 and 43. Adverse events were assessed at each visit.

Part II: six month followup - Monthly interim physical examination, assessment of vital signs, performance status, status of disease, and monthly complete blood count with differential for patients who were CR or MR or who did not meet all the criteria for CR or MR, but had < 5% bone marrow blasts at the end of part I. Other patients had only status of disease evaluated monthly during part II.

Part III: overall patient status (duration of remission and survival). Responding patients had monthly physical examinations and CBC's for an additional six months.

Pharmacokinetic assessment methods: Plasma samples were to be collected at hour 0 (before dose administration) and 1, 2, 3, 4, and 6 hours after dose administration on each day of study drug administration, and then on days 3, 8 and 10 following each drug administration. A final sample was to be collected on day 28 of the last dose period. Plasma samples were assayed for hP67.6, unconjugated calicheamicin, and total calicheamicin. The PK parameters were assessed by using noncompartmental analysis methods for each dose period for every patient. The PK parameters included maximal or peak plasma or serum drug concentration (C_{max}), time to reach observed C_{max} (t_{max}) half-life associated with the terminal slope ($t_{1/2}$) terminal slope (λ_z) and area under the concentration time curve (AUC). In addition to these parameters, the AUC ratios of calicheamicin, both total and unconjugated, to hP67.6 was calculated. The PK parameters were summarized for each assayed species [hP67.6, unconjugated calicheamicin, and total calicheamicin] by dose period, and a statistical comparison was performed across the first and second dose periods.

7.2.3.3. Statistical considerations

Statistical methods: The study design used was a modification of the Simon Two-Stage Design. According to the Simon Two-Stage Design for this specific design, if 3 or fewer complete remissions (CRs) are observed during the first stage of the study the trial would be halted and the drug would be declared as ineffective. If the total number of CRs observed after completion of the second stage is fewer than 12, further development of the drug would not proceed.
The study design used is a modification of the Simon Two-Stage Design. The Phase 1 study identified a second class of remission, morphologic remission (MR) that appears to be very similar to CR except that platelets do not fully recover. Since the classification of gemtuzumab ozogamicin as a "good" or "poor" drug is very complicated, it cannot be made solely by determining whether a patient has obtained CR. Therefore, the design is modified so that the development of the drug would not automatically be halted if after the first stage there were 3 or fewer patients with complete remission. The Simon Two-Stage Design served as a guide, but the final decision to continue development beyond the first stage was a clinical decision based on the evaluation of the available efficacy and safety data.

Sample size requirements and stopping rules were based only on the complete remission rate and did not consider morphologic remission rate, safety profile of the test article etc. For this reason, the decision to continue the study beyond the interim analysis was not based solely on the complete remission rate, but rather resulted from an evaluation of the composite efficacy and safety information available at the time of the interim analysis. The results of the first stage of the

Simon Two-Stage Design served only as a guide to this decision making process. The statistical section of the protocol has been amended to clarify how the Simon Two-Stage Design was modified and used for this project.

Reviewer comment: the decision to continue the study was based on 2 CR's and 1 MR – by strict criteria of the CR being the primary endpoint, the study should have been terminated. The accrual for studies 201 and 203 was extended for unspecified reasons.

7.2.4. Results

7.2.4.1. Patient Disposition, comparability

Study 201 was a 3-part, open-label, single-arm, multidose study with patients enrolled at 11 investigational sites in the United States and Canada as of 31 Dec 1998. This study planned: a sufficient number of patients to allow for the assessment of 55 evaluable patients. Enrollment extended to an additional 55 patients by Amendment IV. Enrolled (as of 31 Dec 1998): 59; completed part I: 59; analyzed: 59 in this interim study report (data cutoff date 15 Mar 1999). The study remains open for enrollment, and final results will be summarized in a subsequent report.

Study 202 was similar in design except that prior BMT was allowed and was conducted at 17 sites in Europe. This study planned to allow for the evaluation of approximately 20 patients. For this interim report, 38 were screened; 25 were enrolled and 1 of these patients was treated with a second course of gemtuzumab ozogamicin for a total of 26 patient treatments. Twenty-three (23) completed the study and all 25 patients were included in the safety and efficacy analyses. Amendment IV of the protocol allowed for the enrollment of up to 150 patients and enrollment in the study is ongoing.

Study 203 was designed to determine efficacy in patients over 60 years old, and was carried out at 4 and 8 sites in the United States and Europe, respectively. This study planned: a sufficient number of patients to allow for the assessment of 55 evaluable patients. Enrolled (as of 31 Dec 1998): 20. One (1) of the patients was given a second course of gemtuzumab ozogamicin. Completed: 20. Analyzed: 20. Enrollment is ongoing.

Table 5: Number of subjects/patients

Study	Planned	Enrolled	Screened	Status	Maximum*
201	55	59*	88	open	110
202	20	25*	38	open	150
203	55	20	28	open	55

*enrollment increased by protocol amendment

The primary reason for screened patients not to be enrolled was insufficient expression of CD33 by flow cytometry. Other common reasons for exclusion were misdiagnosis (ALL), review of

pathological materials revealing the patients were not in relapse, and rapid progression of the disease:

Table 6:Reasons for Non Enrollment

Study	Not enrolled	Dim CD 33	Misdiagnosis	Other
201	29	14	3	12
202	18	10	1	7
203	8	4	3	1
Total	55	28	11	16

7.2.4.2. Demographics

A total of 104 patients were enrolled, 58% male, 92% Caucasian, with an age range of 22-84 and a mean age of 57. Protocol 203 had a higher mean age of 70 years (Table 7):

Table 7 : Demographic Data for Phase II studies

Study	*#*	*Male*	*Female*	*Race-white*	*Mean age*	*SD*	*Range*
201	59	30	29	54	52.7	15.8	22-81
202	25	18	7	24	57.4	12.1	30-79
203	20	12	8	18	70	7	60-84
All	104	60	44	96	57.1	15	22-84

The most common FAB subtypes accrued were M2, M1, M4 and M5. M3 was excluded because of the existence of effective treatment with the differentiating agent ATRA. This approximately reflects the reported incidence of AML in the population:

Table 8: FAB subtypes at initial presentation (M3 excluded)

Study	M0	M1	M2	M4	M4Eo	M5	M6,7	Unk.	Total
201	1	16	18	10	2	5	2	5	59
202	1	5	6	6	1	5		1	25
203	2	3	10	2		2		1	20
Total	4	24	34	18	3	12	2	7	104
AML*	5%	15%	25%	25%	5%	10%	15%		100%

*Reported incidence

Many patients in the study had unfavorable cytogenetics, which may reflect the tendency of this population to relapse. The two variables most closely correlated with response in relapsed AML are age and length of first remission, with older age and shorter remission carrying worse prognosis.

Table 9: Prognostic Characteristics at Relapse

Study		201	202	203	201/202/203
Accrual		59	25	20	104
Cytogenetics	favorable	1	2	0	3
	intermediate	24	10	10	44
	unfavorable	19	6	7	32
	Unknown	15	7	3	25
Prior Remission Duration	Mean (months)	16.7	21.3	8.9	16.4
	S.D.	14.7	27	7.6	17.9
	Range	6-95	5-117	3.3-34	3-117
Age	mean	52.7	57	70	57.1
	S.D.	15.8	12.1	7	15
	range	22-81	30-79	60-84	22-84

Reviewer comment: Most patients had unfavorable cytogenetics, probably reflecting the increased tendency of these patients to relapse. The decreased mean duration of prior remission in study 203 reflects the inclusion of patients with shorter duration of prior remissions in this study.

7.2.4.3. Efficacy endpoint outcomes

CRITERIA FOR EVALUATION:

Efficacy Assessment Methods:

Study part I: Efficacy was evaluated in terms of the number of patients who attained CR as the primary endpoint. CR was defined as

a) the absence of leukemic blasts from the peripheral blood,
b) the percentage of leukemic blasts in the bone marrow < 5%,
c) the recovery of peripheral blood counts to the following levels - hemoglobin _ 9 g/dL, platelets ≥ 100,000/μL, absolute neutrophil count ≥ 1500/μL; and
d) red blood cell and platelet-transfusion independence. Red blood cell transfusion independence required no red blood cell transfusions for 2 weeks. Platelet transfusion independence required no platelet transfusions for 1 week.

The definition of MR is the same as that for CR except that platelet counts are ≤100,000/μL and the patients are transfusion-independent for at least 10 days.

Study part II: The duration of CR or MR was evaluated as a secondarv endpoint. Duration was evaluated for approximately 6 months after the end of the part I evaluation visit.

Poststudy part III: Investigational sites continued to follow patients enrolled in part II every 3 months for 18 months. Additionally, patients were monitored every 6 months after the 18-month follow-up period until death or termination of the study. These data will be analyzed in a separate poststudy report.

7.2.4.4. Results of efficacy analysis

The rates of CR were consistent across the 3 individual studies, ranging from 15% to 19%. The rates of MR were similar for the patients in studies 201 (15%) and 202 (16%); however, the rate of MR for the older patients in study 203 was lower (5%). The OR rate (CR + MR) was 34% in study 201, 32% in study 202, and 20% of patients in study 203. The overall rate of remission in the 3 pooled studies was 31%, including both the MR and CR's as responders. Eligibility was initially based on the local site readings of bone marrow aspirates or biopsies. Final enrollment eligibility was based on the flow cytometry measurements done by the central laboratory that verified that these patients did have > 5% blast cells and qualified as relapsed AML patients. Enrollment was not required to be confirmed by the independent pathologist. The independent pathologist was blinded to the patients' clinical course, to the time of the bone marrow sample, and to whether it was a screening or posttreatment sample.

For 7 patients, there was a discrepancy between the bone marrow evaluations of screening bone marrow samples reviewed by the independent pathologist and the readings done by the local site. An analysis was conducted by the sponsor excluding the responders in this group to explore the potential impact of these patients on the OR rate,. Five (5) of the 7 patients had a CR or MR and 2 had NR. The OR rate decreased slightly to 28% when the 5 CR and MR patients were excluded from the remission category (Table 18). In these cases, the independent pathologist's opinion was that the blast cell percentage in the screening samples did not meet the criteria for relapsed AML. Because both the central flow cytometry laboratory and site readings classified these patients as having active leukemia, the sponsor has maintained the 5 responders in their efficacy analysis.

Reviewer Comment: Review of the data confirms the number and characterization of the responses. Minor inconsistencies between the local pathologist and the independent reviewing pathologist did not significantly alter the efficacy results.

Table 10: NUMBER (%) OF PATIENTS AND 95% CIs BY REMISSION CATEGORY IN PHASE II STUDIES

Type of Remission	Study 201[a] (n = 59)	Study 202 (n = 25)	Study 203 (n = 20)	201/202 (n = 84)	201/202/203 (n = 104)
CR					
No. (%) of patients 95% CIs	11 (19) (10, 31)	4 (16) (5, 36)	3 (15) (3, 38)	15 (18) (10, 28)	18 (17) (11, 26)
MR					
No. (%) of patients 95% CIs	9 (15) (7, 27)	4 (16) (5, 36)	1 (5) (0, 25)	13 (15) (9, 25)	14 (13) (8, 22)
OR (CR + MR)					
No. (%) of patients 95% CIs	20 (34) (22, 47)	8 (32) (15, 54)	4 (20) (6, 44)	28 (33) (23, 44)	32 (31) (22, 41)

a: Data from 1 patient (201-B2-0008) who had a bone marrow sample taken on day 20, rather than day 28, were also included in assessments.

If the MR's are included in the calculation of OR rates, a comparison with historical controls suggests that efficacy for gemtuzumab zogamycin is comparable to standard therapy in the higher risk patients, whose duration of first remission was < 1 year. The combined efficacy data for the three phase II studies showed an approximately 30% overall response rate, if the MR's are included, in patients whose first remission lasted less than one year. This is similar to the remission rates of 13-46% reported in several retrospective studies of patients whose remission lasted less than one year.

Patients whose first remission lasted greater than one year, who were able to tolerate chemotherapy, might have done somewhat better on standard induction therapy. In patients whose first remissions lasted over one year, remission rates were reported in the literature to be in the 50-60% range with standard induction therapy as compared with only 33% with the gemtuzumab zogamycin. (Table 11):

Table 11 : % PATIENTS WITH SECOND REMISSION vs DURATION OF FIRST REMISSION: RETROSPECTIVE REVIEWS WITH > 100 PATIENTS AND GEMTUZUMAB OZOGAMICIN IN PHASE II CLINICAL TRIALS

Author, Institution	Duration of First CR						
	< 1 Year				≥1 Year		
	Regimen	n	% CR's	95% CI	n	(%CR's)	CI
Rees,[13] MRC	DAT	251	13	8 - 18	234	(48)	42 - 55
Keating,[14] MD Anderson	various	105	19	12 - 28	82	(62)	51 - 73
Thalhammer,[15] Univ. of Vienna	various	121	33	25 - 42	47	(55)	40 - 70
Hiddemann,[16] German Coop. Group	DAT	87	46	35 - 57	49	(60)	44 - 73
Davis,[17] St. Bartholomew's	various	NA	33	NA	NA	(49)	NA
Gemtuzumab ozogamicin /Wyeth- Ayerst Research	GZ	56	14 (30)*	6 - 26 19-44	47	21 (32)*	11-36 19-47

MRC = Medical Research Council NA = Not Available * (CR+MR)
DAT = daunarubicin, cytarabine, 6 thioguanine

If the MR's are not included, the complete remission rate is only 17%, which is inferior to historical response rates. In an end of phase 1 meeting dated 9/16/98, the Division agreed to allowing inclusion of MR's in support of the primary endpoint of CR, but not to the inclusion of MR's in the primary endpoint.

The inclusion of patients with persistent thrombocytopenia but no evidence of residual leukemia under the category of complete responders runs counter to the conventions of leukemia therapy. According to NCI published guidelines, "because lengthy peripheral blood count depression can be due to chemotherapy or leukemia, complete remission status requires return of the blood counts to the values specified above. Nevertheless, particularly in studies of new agents or combinations, it is advisable to describe patients with hypocellular bone marrows but without evidence of leukemia separately, and not to include them as nonresponders."[18] Therefore it is

[13] Rees JKH,et. al.: Principle results of the medical research council's 8th actute myeloid leukaemia trial. Lancet 1986;236:1236-41.

[14] Keating MJ,et. al.: Response to salvage therapy and survival after relapse in acute myelogenous leukemia. J Clin Oncol 1989;7(8):1071-80.

[15] Thalhammer F,et. al. Duration of second complete remission in patients with acute myeloid leukemia treated with chemotherapy: A retrospective single-center study. Ann Hematol 1996;72:216-22.

[16] Hiddemann W, et. al. Definition of refractoriness against conventional chemotherapy in acute myeloid leukemia: A proposal based on the results of retreatment by thioguanine, cytosine, arabinoside, and daunoriubicin (TAD9) in 150 patients with relapse after standardized first line therapy. Leukemia 1990;4(3):184-8.

[17] Davis CL, Rohatiner AZS, Lim J, Whelan JS, Oza AM, Amess J, Love S, Stead E, Lister TA. The management of recurrent actue myelogenous leukaemia at a single centre over a fifteen-year period. Br J Haematol 1993;83:404-11.

[18] Cheson B et. al, Report on the National Cancer Institute-Sponsored Workshop on Definitions of Diagnosis and Response in Acute Myeloid Leukemia,Journal of Clinical Oncology 8:5, 813-819, 1990

recommended that this group of patients with persistent thrombocytopenia but who meet other criteria for remission be reported separately from the complete responders.

Reviewer comment: The phenomenon of post-remission thrombocytopenia following myeloablative chemotherapy with or without hematopoetic stem cell transplanation is well described.[19] The identification of several patients with apparent blast clearance and prolonged thrombocytopenia during phase I studies led the sponsor to initiate preclinical studies of the effects of mylotarg on megakaryocyte colony formation using samples of normal volunteers' bone marrow, in order to see if any risk factors for thrombocytopenia could be identified. Megakaryocyte colony formation was assayed in the presence of mylotarg and found to be variably suppressed. Gene chip expression studies were performed using RNA derived from normal donors, to see if any correlation between megakaryocyte colony formation suppression and variations in the glutathione pathway and multiple drug resistance genes could be found, however, only 5 samples were studied and no correlation was identified. No definitive conclusions were made regarding the etiology of the thrombocytopenia, however, it seems likely that the study drug caused a suppression of the megakaryocyte lineage and subsequent prolonged thrombocytopenia. CD 33 is known to be expressed on megakaryocytes and megakaryocyte precursors.[20]

Acute myeloid leukemia is more common in the elderly and the prognosis in elderly patients with AML is significantly worse than that observed in younger patients. Retrospective reviews have reported second remission rates of 14-44% in relapsed elderly patients with AML, and 33-54% in patients under 60. The 28% second remission rate observed in elderly patients treated with gemtuzumab zogamycin, is comparable to what is reported in the literature. Historically the younger patients have done somewhat better with conventional treatment (table 12):

Table 12: RETROSPECTIVE REVIEWS WITH > 100 PATIENTS AND GEMTUZUMAB OZOGAMICIN PHASE II CLINICAL TRIALS: % PATIENTS WITH SECOND REMISSIONS

Author, Institution	Total n	< 60 Years[a]			≥ 60 Years		
		n	(%)	CI[b]	n	(%)	CI[b]
Rees, MRC[c]	485	375	(33)	26-38	110	(19)	2 - 28
Keating, MD Anderson	187	208[d]	(36)	29-42	35	(14)	5 - 30
Hiddemann, German Coop. Group	136	104	(54)	44-64	32	(44)	26 - 62
Davis, St. Bartholomew's	126	NA	(40)	NA	NA	(40)	NA
Gemtuzumab ozogamicin	104	50	(34)*	21-49	54	(28)*	16 - 42

Note: see previous table for references * (CR+MR)

[19] Damon LE et. al. Post remission cytopenias following intense induciton chemotherapy for acute myeloid leukemia, Leukemia 8:4, 535-541, 1994

[20] Lazzari, L. *et al*, Interleukin-6 and interleukin-11 act synergistically with thrombopoietin and stem cell factor to modulate *ex vivo* expansion of human CD41+ and CD61+ megakaryocytic cells ° *Haematologica* 85:25-30 2000;

Reviewer comment: Despite the inherent hazards of subset analysis and using historical controls as comparators, the data seems to suggest that patients with remission durations over one year historically may have done somewhat better with conventional therapy compared with gemtuzumab zogamycin, whereas the elderly and those with shorter remission times seemed to do less poorly compared with those with more favorable prognostic characteristics when treated with gemtuzumab zogamycin. There are insufficient numbers to make any definitive conclusions regarding these groups.

Although numbers are small, progression free survival and relapse free survival seem comparable between the CR's and the MR's altough the MR's may have a slightly shorter RFS (Table 14):

Table 13: SUMMARY OF PROGRESSION-FREE SURVIVAL[a] AND RELAPSE-FREE SURVIVAL[b] (201/202/203)

Remission Group	n	Median (Months)[c]	Minimum (days)	Maximum (days)
Progression-free survival				
CR	18	9.6	83	673
MR	14	7.1	95	553
OR	32	9.5	83	673
Relapse-free survival				
CR	18	7.2	15	608
MR	14	4.4	21	510
OR	32	6.8	15	608

a: Survival measured from day of first dose
b: Duration of remission measured as relapse-free survival starting from the time CR or MR was achieved.
c: Medians are of the observed data and are not Kaplan-Meier estimates.

The sponsor has clamed that the MR group is clinically indistinguishable from the CR group in terms of RFS and PFS, and therefore that the MR group should be included in the calculation of OR.

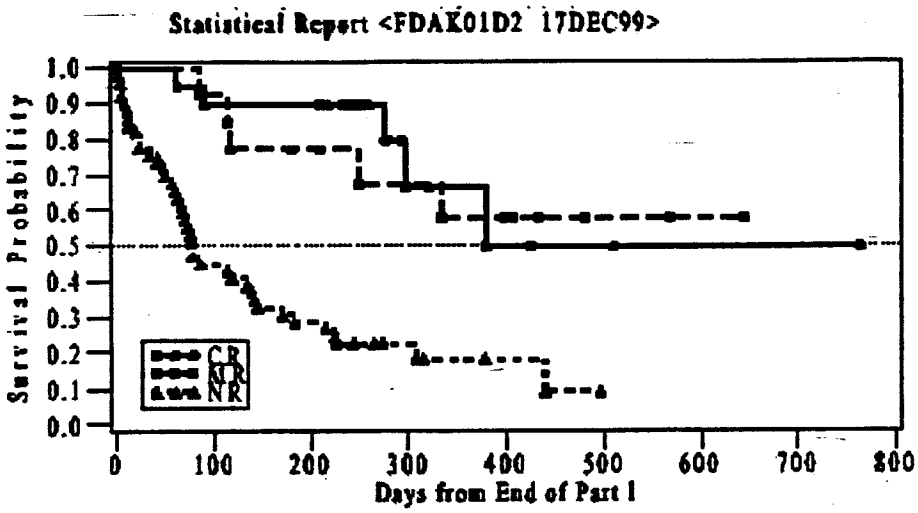
Reviewer comment: The numbers are far too small to derive any conclusions regarding the comparability of these groups, however the MR group had somewhat shorter median survivals. There are too few patients to conclude if there are any meaningful differences in PFS and RFS between the MR and CR groups. The duration of second remission observed with gemtuzumab zogamycin is comparable to that reported in the literature with conventional therapy. Overall survival rates are similar in the MR and CR groups and worse in the NR groups (Table 14):

Table 14:SUMMARY OF LANDMARK SURVIVAL (201/202/203)

Group	n	Median* (days)	Minimum (days)	Maximum (days)
All patients	105	225	2	629
CR	18	379	63	629
MR	14	> 334	47	510
OR	32	> 379	47	629
NR	49	87	2	362

* Kaplan Meier Median, updated

Figure 1: Landmark Survival by Remission Status



(Kaplan-Meier survival data from V. 1 p125 of sponsor's safety update)

One potential confounder for response duration is the therapy received by patients following attainment of remission. 60% of all patients and 72% of patients who achieved remission were given some kind of additional antileukemic therapy making it difficult to isolate the contribution of gemtuzumab zogamycin to the durations of response (Table 15):

Table 15: NUMBER (%) OF PATIENTS RECEIVING ADDITIONAL THERAPY AFTER GEMTUZUMAB OZOGAMICIN

Therapy	Transplantations	Other antileukemic therapy
All patients, n/total (%) 95% CI	21/104 (20) (13, 29)	41/104 (39) (30, 49)
CR, n/total (%) 95% CI	6/18 (33) (13, 59)	7/18 (39) (17, 64)
MR, n/total (%) 95% CI	7/14 (50) (23, 77)	2/14 (14) (2, 43)
OR, n/total (%) 95% CI	13/32 (41) (24, 59)	9/32 (28) (14, 47)
NR, n/total (%) 95% CI	8/72 (11) (5, 21)	32/72 (44) (33, 57)

21 patients went on to receive some kind of hematopoetic stem cell transplant. 3 patients received an autologous transplant and 18 patients received an allogeneic transplant (Table 16):

Table 16: SUMMARY OF SURVIVAL AND TREATMENT OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION PATIENTS

		Survival		Treatment Outcome (after treatment with GZ)		
Cell Source	n	30 Day	100 Day	CR	MR	NR
Autologous	3	3	2	2	1	0
BM	1	1	1	1	0	0
PBSC	2	2	1	1	1	0
Allogeneic	18	14	11	4	6	8
BM	8	5	4	2	2	4
PBSC	10	9	7	2	4	4
Total	21	17	13	6	7	8
BM	9	6	5	3	2	4
PBSC	12	11	8	3	5	4

The effect of the type of post remission therapy on survival is difficult to estimate. Recent studies in the literature suggest that autologous stem cell transplantation may not contribute a significant survival advantage to patients in first remission compared with high dose cytarabine or allogeneic transplants.[21] Patients who attained complete remissions following treatment with gemtuzumab

[21] Cassileth PA, Harrington DP, Appelbaum FR, Lazarus HM, Rowe JM, Paietta E, Willman C, Hurd DD, Bennett JM, Blume KG, Head DR, Wiernik PH. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Eng J Med* 1998;339(23):1649-56.

ozogamicin, seemed to do equally well whether or not they received a transplant, however patients who achieved a MR may have done somewhat better with a transplant, although the numbers are too small for meaningful comparisons (Table 17):

Table 17: RELAPSE-FREE SURVIVAL

Remission Group	n	Median (months)	Minimum (days)	Maximum (days)
CR	18	≥4.3	15	608
MR	14	≥2.6	21	510
OR	32	≥4.1	15	608
AFTER HSCT				
CR	6	≥ 4.3	23	586
MR	7	≥ 8.6	21	488
OR	13	≥ 5.1	21	586

Medians of the observed data, not Kaplan Meier estimates.

Patients who went on to receive a transplant after attaining a remission survived a median total of at least 7.4 months (Table18):

Table 18: OVERALL SURVIVAL AFTER HSCT (201/202/203)

Remission Group	n	Median (months)	Minimum (days)	Maximum (days)
All patients	21	≥ 3.4	5	586
CR	6	≥ 5.6	23	586
MR	7	≥ 8.6	21	488
OR	13	≥ 7.4	21	586
NR	8	1.3	5	347

Medians are of the observed data and are not Kaplan-Meier estimates.

A multivariate analysis was used to try to determine predictors for response. The presence of CD 13 and CD56 were found to decrease the likelihood of a response, as did a low baseline hemoglobin. Increase in CD33 expression mildly decreased the risk of death, as did an increse in the duration of prior remission. Presence of peripheral blasts and CD34 markers were strongly predictive of shorter survival (Table 19):

Table 19:RESULTS OF MULTIVARIATE EXPLORATORY ANALYSIS FOR PROGNOSTIC FACTORS

Analysis Variable	Wald Chi-Square p-Value	Odds Ratio[a]
OR versus NR[b]		
CD13	0.005	0.03
MDR Efflux	0.009	0.97
Hemoglobin	0.015	1.71
CD56	0.026	0.08
Landmark Survival	Wald Chi-Square p-Value	Risk Ratio for Death
Quantitative CD33 expression	0.002	0.98
Duration of 1st remission	0.013	0.92
Peripheral blood blasts	0.029	4.2
CD34	0.035	2.75

a: For CD13, CD56, and CD34, the ratios are for positive baseline values versus negative baseline values. For the other baseline values, the odds ratios and risk ratios are per unit increase in that prognostic variable.
b: The variables listed are those that were significant at the 0.05 level.

Conclusions: In the combined NDA studies, approximately 18% of patients treated with gemtuzumab ozogamicin attained a complete remission, according to traditional criteria. Another 15% of patients achieved clearance of blasts but never regained normal platelet counts, and this group was termed "morphologic remission." RFS and OS seem to be similar for the two groups, suggesting that the thrombocytopenia seen in the MR group is not indicative of residual leukemia. In addition, the survival of MRs following HSCT does not appear to be inferior to that of CR's following HSCT. Patient numbers however are too small to make any definitive conclusions regarding the similarity between these MR's and CR's. Some preclinical data suggests that the thrombocytopenia is a result of marrow toxicity of the study drug. If MR's are included in the analysis of overall response rates, gemtuzimab ozogamicin appears to be comparable to conventional treatment in terms of remission rates except in those patients with relatively good prognosis whose duration of first remission exceeds one year. In the latter group, conventional therapy may be more efficacious. The duration of remission achieved with gemtuzimab ozogamicin appears to be similar to that which is reported in the literature in those relapsed AML patients who do achieve a second remission.

7.2.5. Safety comparisons

Safety Assessment Methods:

Study part I: Evaluation included a physical examination, assessment of performance status, vital signs and possible drug-related toxicities, laboratory evaluations, chest X-ray film, electrocardiogram (ECG), and diagnostic tests for antibodies against calicheamicin and against the

hP67.6 conjugate. In addition, all adverse events were documented in the adverse event record of the patient's case report form.

Study part II: All patients were followed for evaluation of serious adverse events associated with administration of further chemotherapy. In addition, responding patients had monthly interim physical examination, assessment of vital signs and performance status, and monthly complete blood count (CBC) with differential.

Poststudy part III: The overall patient status, including the duration of remission and survival was evaluated.

7.2.5.1. Safety results:

Since efficacy has not been demonstrated to be significantly improved over conventional therapy, the sponsor is applying for accelerated approval on the basis of improved safety profile. Specifically, the sponsor claims

1. *Outpatient administration is feasible and safe. As with other antibody-based therapies, a mild infusion-related symptom complex was observed in most patients. These events were usually brief in duration without clinical sequelae.*

The infusion-related symptom complex is a recognized occurrence in patients treated with gemtuzumab ozogamicin. The etiology is unclear but may be related to cytokine release and appears to be somewhat less common during the second dose. . Fever and chills were commonly reported despite prophylactic treatment with acetaminophen and antihistamine. One third of patients reported a grade 3-4 infusion – related adverse event. The incidence of severe hypotension was approximately 5% (5/104 patients had Grade 3 or Grade 4 hypotension) and these patients required intravenous fluid support and in one case dopamine. Hypotension resolved in all patients. 3 patients reported grade 3-4 hypoxia, which resolved spontaneously, and was treated with oxygen (Table 20):

Table 20: NUMBER (%) OF PATIENTS REPORTED TO HAVE THE MOST COMMON NCI GRADE 3 OR 4 SEVERITY INFUSION-RELATED TREATMENT-EMERGENT ADVERSE EVENTS BY DOSE[a] (STUDIES 201/202/203)

	Dose 1 (n = 104)		Dose 2 (n = 88)	
Adverse Event	Grades 3 - 4	Grades 1 – 4[b]	Grades 3 - 4	Grades 1 - 4
Any infusion-related adverse event	35 (34)	87 (84)	8 (9)	61 (69)
Chills	12 (12)	58 (56)	6 (7)	37 (42)
Fever	6 (6)	52 (50)	2 (2)	35 (40)
Hypotension	5 (5)	11 (11)	0	2 (2)
Leukopenia	5 (5)	6 (6)	2 (2)	3 (3)
Thrombocytopenia	5 (5)	6 (6)	1 (1)	5 (6)

a: Events occurring the day of gemtuzumab ozogamicin administration. These TEAEs were reported for ≥ 5% of the patients in studies 201/202/203. Severity grades (mild, moderate, or severe) were merged to NCI toxicity grades (1, 2, or 3, respectively).

b: The Grades 1 – 4 columns include adverse events of any severity.

The primary reason for discontinuation was unsatisfactory response – lack of efficacy. 7 patients died prior to receiving a second dose of gemtuzumab zogamycin because of disease progression (Table 21):

Table 21: NO. PATIENTS (%) WHO DISCONTINUED FROM STUDY PART I – SUMMARY OF PRIMARY REASONS FOR DISCONTINUATION

Reason for Discontinuation	Number of patients
Adverse event	3
Unsatisfactory response – efficacy[a]	10
Other medical event (death in part I)[b]	7
Other medical event (HSCT)	1

7 patients had 2 primary reasons for discontinuation (unsatisfactory response and death), and are counted under both categories.

Reviewer comment: the administration of gemtuzumab zogamycin is probably safe in the outpatient setting, since most adverse events occurred within 4 hours of administration. It is considerably more convenient that conventional AML induction which requires 7 days of continuous inpatient intravenous infusion of cytotoxic medication. Discontinuations due to adverse reactions were uncommon. However, the infusion center needs to be prepared to recognize and treat infusion-related hypoxic or hypotensive episodes.

2. *The safety profile of gemtuzumab ozogamicin is comparable to that for conventional chemotherapies in terms of myelosuppression and bleeding but offers a safety advantage in terms of:*

- *Low incidence of severe mucositis*
- *Low incidence of severe infections*
- *Reduced median number of days of hospitalization due to both short outpatient infusion and decreased need for in-hospital supportive care.*
- *Only mild and reversible nausea and vomiting*

- *No alopecia*
- *Transient and reversible liver function test abnormalities occurred with moderate incidence*

Although the administration of gemtuzumab zogamycin is more convenient, the degree of myelosuppression achieved is comparable to that of conventional induction therapy. The risk of significant bleeding appears comparable to that of conventional therapy. Although only one study reported hospitalization rates in the setting of relapsed AML, there are several studies of hospitalization rates in patients with *de novo* AML attempting to show an effect of colony stimulating factors on hospitalization days.[22 23 24] These studies reported hospitalization rates in the range of 29-43 days. Overall hospitalization days appeared to be markedly reduced in the gemtuzumab group compared with historic controls. 5 patients (4 responders and 1 nonresponder) were treated without the necessity for any days in hospital, and 20 patients (11 responders and 9 nonresponders) required ≤ 7 days of hospitalization. Conventional induction requires 7 days of inpatient continuous infusion which accounts for some of the observed differences in hospitalization days. (Table 22):

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[22] Bennett, CL, Stinson, TJ, Tallman, MS, Stadtmauer, EA, Marsh, RW, Friedenberg, W, et al. Economic analysis of a randomized placebo-controlled phase III study of granulocyte macrophage colony stimulating factor in adult patients (>50 to 70 years of age) with acute myelogenous leukemia. Eastern Cooperative Oncology Group (E1490). Annals of Oncology, 1999;10(2):177-82.

[23] Godwin, JE, Kopecky, KJ, Head, DR, Willman, CL, Leith, CP, Hynes, HE, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031). Blood, 1998 May;91(10):3607-3615.

[24] Heil, G, Hoelzer, D, Sanz, MA, Lechner, K, Liu Yin, JA, Papa, G, et al. A randomized, double-blind placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. Blood, 1997;90:4710.

Table 22:COMPARISON OF SAFETY RESULTS REPORTED IN RELAPSED/REFRACTORY AML WITH RESULTS FOR PATIENTS WHO RECEIVED GEMTUZUMAB OZOGAMICIN

Source	GZ	FLAG[25]	HIDAC-M[26]	DEM[27]
Adverse event (measurement)		N=38	N=90	N=57
Median time to platelets > 100,000/μL (days)	31.5[c]	28	50	NR
Median time to ANC > 500/μL (days)	22	21	40	34
Grade 3-4 Infections (%)	26	44	55	83
Grade 3-4 abnormal LFTs (%)	31[e]	8	10	26
Grade 3-4 Bleeding (%)	14	NR	10	21
Grade 3-4 Nausea or Vomiting (%)	14	NR	20	27
CNS bleeding (%)	4	3	NR	NR
Grade 3-4 Mucositis (%)	2	10	9	23
Median duration of hospitalization (days)	20	31	NR	NR
Treatment mortality rate (%)[j]	13	10	16	32
Complete response rate	17	55	44	30

Mucositis appears somewhat decreased compared with historic controls, however this is not a dramatic decrease, and a recent review of the treatment of relapsed and refractory AML reports only 0% and 6% grade 3-4 stomatitis with HIDAC (3 g/m^2) and HIDA plus mitoxantrone 10 mg/M^2 respectively[28]. Although the hospitalization and infection rates appear to be somewhat decreased, the incidence of hepatic dysfunction appears to be increased in the gemtuzumab group over that reported with conventional chemotherapy. 32 patients had at least one grade 3 or 4 hepatic function abnormality during part 1, and 25 (24%) of patients showed severe (grade 3-4) elevations in bilirubin (Table 23):

[25] Montillo et. al. FLAG for the treatment of poor risk AML, *American Journal of Hematology*, 58: 105-109,1998

[26] HIDAC-M = cytarabine 1g/M^2 q12 x 4d + mitoxantrone 12 mg/ M^2 x 4d (see Kern W, *et al*: Superiority of high-dose over intermediate-dose cytosine arabinoside in the treatment of patients with high-risk acute myeloid leukemia: results of an age-adjusted prospective randomized comparison. *Leukemia* 1998;12:1049-55)

[27] DEM = diaziquone + etoposide + Mitoxantrone (see Lee, EJ *et al*, An evaluation of combinations of diaziquone, etoposide and mitoxantrone in the treatment of adults with relapsed or refractory acute myeloid leukemia, *Leukemia*, 12: 139-143, 1998)

[28] Karenes C. et. al. A phase 3 comparison of HIDA vs. HIDAC plus mitoxantrone in the treatment of relapsed or refractory AML. *Leukemia Research*, 23, 787-794, 1999.

Table 23: NUMBER (%) OF PATIENTS WITH NON-HEMATOLOGIC LABORATORY TEST RESULTS OF CLINICAL IMPORTANCE IN PART 1

	Studies 201/202/203 (n = 104)		
Test	Grade 3	Grade 4	Total
Alkaline phosphatase	4/103 (4)	0	4/103 (4)
Calcium	10/103 (10)	5/103 (5)	15/103 (15)
Creatinine	1/103 (<1)	0	1/103 (<1)
Glucose	10/102 (10)	1/102 (<1)	11/102 (11)
AST	11/103 (11)	3/103 (3)	14/103 (14)
ALT	4/103 (4)	1/103 (<1)	5/103 (5)
Total bilirubin	18/103 (17)	7/103 (7)	25/103 (24)

Reviewer comment: Although it is sometimes difficult to ascribe the etiology of liver dysfuntion in relapsed AML patients, it appears that this drug exhibits definite hepatotoxicity. 13 patients exhibited elevations of both transaminases and bilirubin, a marker for potentially significant hepatotoxicity. Calicheamicin was noted to cause liver toxicity in preclinical testing, and it is likely that this is the etiology of the hepatic toxicity seen in these studies. In the clinical trials, most of the toxicity was transient and reversible, however one patient on study 201 exhibited persistent jaundice and ascites for several weeks following treatment. Of the 21 patients who received HSCT, 4 developed VOD and died 22, 30, 48, and 392 days after transplantation. In addition, one patient with a history of VOD who relapsed following transplant was treated on a compassionate IND died following an episode of severe liver toxicity

3. *Although MR patients had slower platelet recovery and required more platelet transfusions than CR patients, the overall safety profile of gemtuzumab ozogamicin is comparable in CR and morphologic remission (MR) patients . The MR patients become transfusion-independent like the CRs, and there were no clinically meaningful differences in safety parameters including bleeding.*

Patients with MR's who by definition were more thrombocytopenic than CR patients required significantly more platelet transfusions prior to being declared MRs. There was a trend toward increased packed red blood cell requirements in the MR patients prior to the attainment of transfusion independence, as compared with the CR's. The CR and MR groups were therefore clinically distinguishable on the basis of platelet requirements, however the MR's exhibited a trend toward fewer packed red blood cell requirements than nonresponders (Table 24):

Table 24: NUMBER OF RED BLOOD CELL AND PLATELET TRANSFUSIONS[a] (STUDIES 201/202/203)

Parameter Statistic	Total (n = 104)	CR (n = 18)	MR (n = 14)	OR (n = 32)	NR (n = 72)
Number of red blood cell transfusions					
Mean (SD)	8.6 (26)	3.0 (3)	6.7 (7)	4.6 (5)	10.3 (31)
Median	5.0	1.5	4.5	3.0	5.5
Approx 95% CI[b]	(4, 6)	(1, 4.5)	(2.5, 12)	(2.5, 5.5)	(4.5, 6.5)
95% CI for MR-CR	(-1, 4)				
Number of platelet transfusions					
Mean (SD)	16.7 (29)	5.3 (5)	15.8 (12)	9.9 (10)	19.7 (33)
Median	11.0	4.5	11.0	7.5	13.0
Approx 95% CI	(10, 14.5)	(2.5, 7.5)	(8.5, 23)	(5.5, 12)	(11.5, 17)
95% CI for MR-CR	(2, 17)				

a: All transfusions occurring in part I of the phase II studies.
b: Non-parametric confidence intervals.
CR = complete remission; MR = morphologic remission;
OR = overall remission rate (CR + MR); NR = no remission.

Bleeding is a common and potentially serious complication of AML, most often due to thrombocytopenia. Sometimes bleeding is exacerbated by a coagulopathy especially DIC, although the protocol excluded M3 AML which is most commonly associated with DIC. Bleeding varied in severity from petechiae and mild epistaxis to fatal hemorrhages. One patient died of retroperitoneal hemorrhage, one patient who was treated with a preexisting coagulopathy (DIC) developed a fatal intracerebral hemorrhage within 5 hours of treatment, and another patient who was thrombocytopenic developed an intracranial hemorrhage 1 day after treatment. The numbers are too small to derive any conclusions regarding these adverse events. 3 patients died of cerebral hemorrhage >30 days from the last dose of study medication; it was not clear that these events were related to the study medication. The overall incidence of bleeding as an adverse event appeared to be similar in the CR and MR group and increased in nonresponders (Table 25):

Table 25: NUMBER (%) OF PATIENTS REPORTING ≥ 5%[a] BLEEDING TREATMENT-EMERGENT ADVERSE EVENTS IN PART I BY TREATMENT OUTCOME CATEGORY (STUDIES 201/202/203)

Bleeding Adverse Event[b]	Total (n = 104)	CR (n = 18)	MR (n = 14)	OR (n = 32)	NR (n = 72)
Ecchymosis	15 (14)	1 (6)	1 (7)	2 (6)	13 (18)
Epistaxis	32 (31)	4 (22)	4 (29)	8 (25)	24 (33)
Gum hemorrhage	12 (12)	2 (11)	1 (7)	3 (9)	9 (13)
Hematemesis	6 (6)	0	0	0	6 (8)
Hematuria	10 (10)	0	2 (14)	2 (6)	8 (11)
Hemoptysis	5 (5)	0	1 (7)	1 (3)	4 (6)
Hemorrhage	11 (11)	0	0	0	11 (15)
Menorrhagia	2 (5)	0	1 (14)	1 (7)	1 (3)
Metrorrhagia	4 (9)	1 (14)	1 (14)	2 (14)	2 (7)
Petechiae	22 (21)	1 (6)	3 (21)	4 (13)	18 (25)
Rectal hemorrhage	6 (6)	0	1 (7)	1 (3)	5 (7)
Vaginal hemorrhage	5 (11)	1 (14)	0	1 (7)	4 (13)

a: ≥ 5% limit specifies the minimum percentage from the total of 104 patients.
b: Percentages of sex-specific adverse events are based on the number of patients of the relevant sex.
CR = complete remission; MR = morphologic remission; OR = overall remission rate (CR + MR);
NR = no remission.

4. *No patients developed an immune response to gemtuzumab ozogamicin in the phase II studies*

During the phase I trials, 40 patients were tested for the formation of antibodies to gemtuzumab ozogamicin; and 2 were positive. One (1) patient experienced a CR at 1 mg/m^2 and subsequently received a second course of gemtuzumab ozogamicin at 6 mg/m^2 at the time of next relapse). This patient developed antibodies to the calicheamicin/linker portion of gemtuzumab ozogamicin, and had transient shortness of breath that was associated with immune reaction to the gemtuzumab ozogamicin conjugate. Antibody formation to the calicheamicin/linker portion appeared to be dose independent, as the second patient developed these antibodies after the third dose of 0.25 mg/m^2 gemtuzumab ozogamicin.

In the phase II studies, patients were screened for antibodies directed against the calicheamicin/linker portion of gemtuzumab ozogamicin and to the antibody portion. In 104 patients and 196 doses, none of the patients studied had any antibody responses or clinical evidence of immune response. This included samples after 1 , 2 or 3 doses. Four (4) patients received a second course (4 doses total) of gemtuzumab ozogamicin therapy and did not develop anti-gemtuzumab ozogamicin antibodies. No patients in either phase 1 or phase 2 studies developed antibodies against P67.6.

CBER reviewer's comment: The HAHA assay is appropriately designed to detect antibodies against the F(ab')$_2$ portion of P67.6. A minor flaw is that it cannot detect anti-allotype antibodies directed against the heavy chain constant region where most allotypic differences lie. Clinical

experience with humanized antibodies is limited. For the most part however, if antibodies are detected, they tend to be directed to the V region and not constant regions. We recommend that Wyeth-Ayerst continue to monitor for HAHA, especially since they plan to use gemtuzumab ozogamicin as a part of post-remission therapy that would allow the administration of multiple doses. An assay has also been developed and validated to detect antibodies against N-acetyl-gamma calicheamicin DMH AcBut. The design of this assay parallels that of the HAHA assay. **Current wording regarding immunogenicity of gemtuzumab ozogamicin in the package insert is reasonable. Division of Monoclonal Antibodies, CBER may be able to suggest additional wording based on the experience with other licensed humanized mAbs.**

7.2.5.1.1. Pharmacokinetic/ Pharmacodynamic Results:

The highest concentration of hP67.6 and calicheamicin were observed shortly after the end of the 2 hour infusion for most patients. The pharmacokinetic profile showed extreme variabilty. Some of the variability observed may be due to changes in antigen burden in patients, formulation, or inability of the assay methodology to distinguish between naked antibody, conjugated antibody, and antibody fragments. (See Dr. Kieffer's PK review).

7.3. Significant/Potentially Significant Events

7.3.1. Deaths

7.3.1.1. Phase I trials

Seven (7) patients died during the study or within 30 days of their last dose of gemtuzumab ozogamicin. These patients are shown in Table 10.4.1A. Other deaths are shown in Table 10.4.1B. The treatment relationship of these deaths was assessed inconsistently by the investigators. The majority of the deaths were the result of the underlying disease progression in this patient population. However, 2 patients died from infection. Another patient had prolonged neutropenia and a patient had sepsis, both leading to death. Both of these events were judged probably treatment related by the investigator.

7.3.1.2. Phase 2 trials

14 patients died within 30 days of receiving gemtuzumab ozogamicin . The most common reason for treatment related death was disease progression (6 patients). Three patients died as a result of cerebral bleeding and 3 patients died from multisystem organ failure. Two patients died from sepsis (Table 26).

Table 26: SUMMARY OF DEATHS THAT OCCURRED IN PART I OF STUDIES 201/202/203

Dose Patient	Age (y) / Sex	Day[a]	Cause of Death
Dose 1			
201A9-0008	49 / M	2	L Frontoparietal intraparenchymal hemorrhage.
20363-0001	62 / F	18	Disease progression (AML).
201B2-0002	24 / M	18	Sepsis.
201B0-0001	36 / M	20	Multisystem deterioration
20378-0002	80 / F	20	Disease progression.
20372-0001	84 / F	21	Hyperkalemia, bradycardia, hypotension, renal failure, acute pulmonary edema
201B4-0001	64 / F	22	Disease progression.
Dose 2			
20365-0001	70 / F	17	Intracerebral hemorrhage due to thrombocytopenia.
20278-0002	48 / M	25	Frontal lobe bleeding.
201A9-0001	44 / M	27	Neutropenic fever. Progression of leukemia.
201A9-0004	45 / M	31	Sepsis secondary to disease progression.
201B1-0004	24 / F	35	Multisystem organ failure.
20276-0001	53 / M	37	Respiratory failure.
20357-0004	60 / M	42	Leukemia progression.

a: Day relative to the start of the study.

The overall treatment-related mortality rate was 13%, as compared with 10-30% reported in previously cited studies of relapsed AML. Mortality was primarily related to disease progression.

7.3.2. Other Serious Adverse events

96 patients experienced grade 3-4 events, and 17 patients experienced serious and unexpected events. 4 of these events were judged probably related to the drug, and 12 possibly related in the opinion of the investigator. Most of these events were related to progression of the disease, however there was one patient who experienced persistent hyperbilirubinemia which may have been related to the study drug (Table 27):

Table 27:PATIENTS EXPERIENCING SERIOUS AND UNEXPECTED ADVERSE EVENTS (STUDIES 201/202/203)

"probably related" to the study drug, (in the opinion of the investigator)			
Age / Sex	Primary Event	Other conditions	Outcome
24 / M	severe lower back pain,	hypophosphatemia, hyperkalemia, bradycardia	Resolved
60 / F	neutropenic fever	diabetes insipidus	Resolved
43 / F	Fever	cyanosis, hypoxia, rigors,	Resolved
67 / M	nose bleeding, fever;	bone marrow aplasia > 8 weeks	Resolved
"Possibly Related" to the study drug, in the opinion of the investigator			
65 / M	hip pain and neutropenia;	fungal infection	Died
51 / M	neutropenic fever and joint pain	tenosynovitis	Resolved
81 / F	Rectal bleeding and vaginal bleeding		Resolved
74 / M	ascites, jaundice	Hyperbilirubinemia, hepatosplenomegaly	Persistent
75 / M	diffuse fluid retention, R pleural effusion, and ascites		Resolved
72 / F	seizures		Resolved
36 / F	Hospitalization for neutropenic fever and	L orbital cellulitis	Resolved
66 / M	hemoptysis and epistaxis; fever	bleeding from the bone marrow aspirate site	Resolved
75 / M	exacerbation of DIC, bone pain	aplasia	Resolved
75 / M	Hypertension crisis and	fever	Resolved
70 / F	Intracerebral hemorrhage		Died
69 / F	allergic reaction, hypotension	exacerbation of pre-existing DIC	Resolved

7.4. Overview of Safety

Gemtuzumab ozogamicin offers improved convenience of administration compared with conventional chemotherapy for relapsed AML. Hospitalization days and rates of severe infection, and mucositis, appear to be decreased compared to that reported in the literature for conventional chemotherapy. Nausea, vomiting bleeding and myelosuppression appear to be comparable to historical controls, however elevation in transaminases and bilirubin appears to be more frequent than that reported in the literature.

7.4.1. Overdosage exposure

No cases of overdose with MYLOTARG were reported in clinical experience. Single doses higher than 9 mg/m^2 in adults were not tested.

7.4.2. Drug-Demographic Interactions

Effect of Age

Patients ≥ 60 years comprise approximately 50% of AML patients and represent a distinct challenge in AML therapy. There are patient and disease factors that result in a poor outcome in these patients. Of note, there were no pharmacokinetic differences to suggest that gemtuzumab ozogamicin dosing needs to be altered in patients ≥ 60 years old. The most common TEAEs (those reported by ≥ 30% of patients) in patients ≥ 60 years of age were: fever, chills, nausea, vomiting, thrombocytopenia, leukopenia, asthenia, diarrhea, abdominal pain, headache, stomatitis, dyspnea, anorexia, hypokalemia, and epistaxis. The following TEAEs were identified as being reported more commonly for patients < 60 than those ≥ 60 years of age: abdominal pain, headache, myalgia, chills, hypomagnesemia, herpes simplex, gum hemorrhage, and stomatitis. Similarly, some TEAEs were identified as being reported more commonly for patients ≥ 60 than for those < 60 years of age. These TEAEs were peripheral edema, back pain, pain, dry mouth, anemia, lactic dehydrogenase increased, insomnia, and constipation. There were considered to be no clinically important differences in TEAEs between the two age groups of patients. Bilirubin had statistically significant and clinically important patterns of change in patients ≥ 60 years old only. In addition, AST, which did have statistically significant and clinically important patterns of change in the phase II patients as a whole, had consistent changes between dose periods 1 and 2 for patients ≥ 60 years old but not for patients < 60 years old. ALT had statistically significant and patterns of change only in patients ≥ 60 years old. These data suggest that changes in some laboratory parameters associated with hepatic dysfunction were more consistently observed in patients ≥60 years old than in those < 60 years old.

Reviewer comment: These findings should be considered for inclusion in labeling.

Effect of sex

The following TEAEs were identified as being reported more commonly for female than for male patients: headache, dehydration, and ecchymosis. Similarly, some TEAEs were identified as being reported more commonly for male than for female patients. These TEAEs were cough increased, pharyngitis, tachycardia, AST increased, hypertension, diarrhea, hyperbilirubinemia, dyspnea, herpes simplex, hematemesis, petechiae, pneumonia, hematuria, hemorrhage, hypervolemia, edema, and arthralgia. There were considered to be no clinically important differences in TEAEs between the female and male patients.

Effect of Ethnic Origin

Because the vast majority of patients enrolled in gemtuzumab ozogamicin clinical trials have been white, an analysis of safety or efficacy by ethnicity would not be meaningful.

7.4.3. Drug-Disease Interactions

The extreme variability in t ½ was postulated as possibly related to the total body load of CD33 positive blasts, however, this has yet to be confirmed.

7.4.4. Drug-Drug Interactions

None known

7.4.5. Withdrawal Phenomena/Abuse Potential

None known

7.4.6. Human Reproduction Data

See pharmacologic review

8. Conclusions

Gemtuzumab ozogamicin, an innovative anti CD33 monoclonal antibody conjugated to calicheamicin, showed modest efficacy in the treatment of CD 33 positive relapsed acute myeloid leukemia in these clinical trials. A significant portion of patients achieved clearance of blasts but exhibited prolonged thrombocytopenia following treatment. These patients initially required significantly more platelet transfusions and showed a trend towards more red cell transfusions, however they eventually attained transfusion independence. Remission durations in the patients with persistent thrombocytopenia appeared comparable to those patients whose platelets recover above 100,000 and have a comparable overall survival after subsequent hematopoetic stem cell transplant. These patients therefore appear to have sustained a clinically meaningful response. Comparison with historical controls suggests that patients with the favorable prognostic characteristic of longer duration of first remission who are able to tolerate conventional re induction chemotherapy, may have a somewhat greater chance of attaining remission with conventional treatment.

Improved ease of administration, reduced severe mucositis and infection rates appear to decrease hospitalization rates and may allow some patients to achieve a remission without the necessity of hospitalization. Elevations of hepatic transaminases, with or without hyperbilirubinemia, are generally transient but sometimes persist. Five patients who have gone on to transplant have developed fatal VOD.

Accelerated approval of a new agent for use in the treatment of relapsed acute myeloid leukemia may be based on the demonstration of improved safety and comparable efficacy to conventional chemotherapy.

9. Oncologic Drugs Advisory Committee Meeting Summary

This application was considered at the March 17, 2000 meeting of the ODAC. The following background information and accompanying questions were presented to the Committee for discussion and vote after the presentations of the sponsor and the FDA. The ODAC vote is recorded with each question.

9.1. Accelerated Approval

Drugs for serious or life-threatening illnesses may be approved on the basis of an improvement in a surrogate endpoint under the Accelerated Approval regulations (21 CFR 314.500, Subpart H). To be eligible for accelerated approval, the treatment must represent a therapeutic gain. It must be expected to "provide meaningful therapeutic benefit to patients over existing treatments e.g. ability to treat patients unresponsive to, or intolerent of, available therapy or improved patient response over available therapy." In this application, demonstration of improved safety with at least similar efficacy compared to existing treatments, would be the basis for a recommendation for marketing approval under subpart H.

Under subpart H, approval can be based on a surrogate endpoint that is reasonably likely to predict clinical benefit. For hematologic malignancies, durable complete remissions have been considered as adequate evidence of clinical benefit. In this case, however, the duration of responses is difficult to measure because of subsequent antileukemic therapies, including hematopoetic stem cell transplantation. Therefore, complete responses in this application are viewed as surrogate endpoints.

9.2. Efficacy:

Three single treatment arm phase 2 studies and one phase 1 study in patients with relapsed Acute Myeloid Leukemia (AML) were submitted in the NDA. The original submission contained safety and efficacy data on 104 patients. Data on additional 38 patients was submitted in late January, and an efficacy update was received on February 25.

Table 28:Response rates in Studies 201/202/203

Type of Remission	Original data (n = 104)	Updated data (n = 142)
CR		
No (%) of patients	*19 (18)*	23 (16)
95% CIs	*(11, 27)*	(11, 23)
CR_p		
No (%) of patients	*13 (13)*	19 (13)
95% CIs	*(7, 20)*	(8, 20)
OR ($CR + CR_p$)		
No (%) of patients	*32 (31)*	42 (30)
95% CIs	*(22, 41)*	(22, 38)

Clinical trials of salvage therapy have traditionally reported complete responses according to criteria that have included a return of platelet counts to above 100K. The sponsor has identified a significant proportion of potentially responding patients, termed Morphologic Responses or CRp's) who achieve clearance of blasts but do not achieve platelet counts above 100K. This effect is postulated to derive from the toxicity of gemtuzumab ozogamicin on megakaryocyte precursors, and the sponsor believes that CR_p's should be considered equivalent to CR's. A way to examine this question is to compare the disease course in CR and CR_p patients. Although the Kaplan Meier landmark survival curves for the CR and CRp patients appeared similar, with a median survival of 7.2 months for both groups, median relapse free survival appears slightly decreased the CRp patients in our calculations based on updated survival data:

Table 29:Kaplan-Meier estimates of median Relapse Free survival

Remission Group	*N*	*# failures*	*Median Relapse Free Survival (months)*
CR	19	11	7.8
CR_p	13	8	4.4
OR	32	19	7.2

However, this difference does not approach statistical significance and it is not possible to demonstrate either statistical equivalence or difference given the small numbers in each group.

1. Is there sufficient evidence to conclude that CR'_{ps} (morphologic responses) are comparable to complete responses and should be considered CR's in terms of efficacy outcomes?

YES – 7 NO – 5 Abstain – 1

Although the majority of the Committee felt that CR_ps should be considered comparable to CRs, there was concern that there was insufficient evidence for this claim, and that there was no significant difference between the two groups because they are doing equally poorly.

The sponsor has stated that the efficacy of gemtuzumab ozogamicin is comparable to that of conventional antileukemic salvage therapy, but the complete response rate of 16% reported in the updated gemtuzumab ozogamicin trials is somewhat lower than that reported in recent reviews of salvage regimens in relapsed AML. Only by including the group of patients who achieved a "Morphologic Response" (CRp) under overall response rates does the response rate approach those reported in the literature. The results of some recent trials in relapsed and refractory AML are displayed below. Note that all comparisons are with reports in the literature, and that these trials are not controlled for prognostic features (Table 3):

Table 30: Response rates in relapsed AML by regimen

Source	GOz N=142	FLAG[29] N=38	HIDAC-M[30] N=90	DEM[31] N=57
Median Age	61	41	50	54
% Complete response (% overall response)	16 (30)	55 (NR)	44 (50)	30 (32)

NR= not reported

2. Does the Committee agree that the efficacy of this product can be satisfactorily judged on the basis of the OR rate (CR+CRp) and compared with CR's reported in the literature?

YES – 2 NO – 10 Abstain – 1

The Committee felt that there are some important differences between the current study and the historical controls. The literature reports were on clinical patients who were not often in clinical studies and so had worse prognostic standards, and only two of the literature studies would have included patients designated in the current study as CR_ps. In addition, it was pointed out that most studies in the literature do not enroll elderly patients.

3. Does the committee agree that the efficacy of this product in relapsed AML has been shown to be comparable to that of conventional salvage regimens?

YES – 3 NO – 10 Abstain – 0

References

[29] Montillo et. al. FLAG for the treatment of poor risk AML, *American Journal of Hematology*, 58: 105-109,1998

[30] HIDAC-M = cytarabine 1g/M^2 q12 x 4d + mitoxantrone 12 mg/ M^2 x 4d (see Kern W, *et al*:. Superiority of high-dose over intermediate-dose cytosine arabinoside in the treatment of patients with high-risk acute myeloid leukemia: results of an age-adjusted prospective randomized comparison. *Leukemia* 1998;12:1049-55)

[31] DEM = Diaziquone + Etoposide + Mitoxantrone (see Lee, EJ *et al*, An evaluation of combinations of diaziquone, etoposide and mitoxantrone in the treatment of adults with relapsed or refractory acute myeloid leukemia, *Leukemia*, 12: 139-143, 1998)

9.3. Safety:

Table 31: Adverse events by treatment regimen

Adverse event (measurement)	GOz N=104	FLAG N=38	HIDAC-M N=90	DEM N=57
Median time to platelets > 100,000/μL (days)	31.5[c]	28	50	NR
Median time to ANC > 500/μL (days)	22	21	40	34
Grade 3-4 Infections (%)	26	44	55	83
Grade 3-4 abnormal LFTs (%)	31	8	10	26
Grade 3-4 Bleeding (%)	14	NR	10	21
Grade 3-4 Nausea or Vomiting (%)	14	NR	20	27
CNS bleeding (%)	4	3	NR	NR
Grade 3-4 Mucositis (%)	2	10	9	23
Median duration of hospitalization (days)	20	31	NR	NR
Treatment mortality rate (%)	13	10	16	32

Ease of administration, fewer days in the hospital, and some toxicities such as severe mucositis and infection appear to be improved in patients treated with gemtuzumab ozogamicin compared with literature reports of conventional salvage regimens. The incidence of liver toxicity, however, appears to be increased over that reported with conventional salvage therapy. Grade 3-4 hyperbilirubinemia was reported in 24% of patients in the trials and elevated transaminases associated with hyperbilirubinemia have been reported in 13 patients in the phase 2 trials. Four patients (one CR and 3 nonresponders) previously treated with gemtuzumab ozogamicin have developed fatal VOD following allogeneic transplantation, and one patient with a history of VOD who relapsed following transplant developed fatal VOD following treatment on a single patient IND.

4. Does the Committee agree that there is sufficient evidence to support a claim of improved safety over conventional salvage chemotherapy regimens?

YES – 8 NO – 3 Abstain – 2

9.4. Approvability:

5. Does the Committee believe that there is sufficient evidence of improved safety and comparable efficacy in patients with relapsed acute myeloid leukemia to support approval of gemtuzumab ozogamicin under the Accelerated Approval regulations? Do you recommend Accelerated Approval?

YES – 4 NO – 7 Abstain – 2

6. If Accelerated Approval is recommended, the applicant would be required to perform post marketing studies to verify and describe the clinical benefit associated with the use of the product. What studies should be performed?

No vote was taken on this question, as the Committee voted against Accelerated Approval in Question 5.

Table 32: Response rates vs. Duration of first Remission

Author, Institution	Duration of First CR						
	< 1 Year				≥1 Year		
	Regimen	n	% CR's	95% CI	n	(%CR's)	CI
Rees,[32] MRC	DAT	251	13	8 - 18	234	(48)	42 - 55
Keating,[33]	various	105	19	12 - 28	82	(62)	51 - 73
Thalhammer,[34]	various	121	33	25 - 42	47	(55)	40 - 70
Hiddemann,[35]	DAT	87	46	35 - 57	49	(60)	44 - 73
Davis,[36] St. Bartholomew's	various	NA	33	NA	NA	(49)	NA
Gemtuzumab ozogamicin /Wyeth- Ayerst Research	GZ	56	14 (30)*	6 - 26 19-44	47	21 (32)*	11-36 19-47

MRC = Medical Research Council NA = Not Available * ($CR+CR_p$)
DAT = daunarubicin, cytarabine, 6 thioguanine

Table 33: Response rates vs. age

Author, Institution	Total n	< 60 Years[a]			≥ 60 Years		
		n	(%)	CI[b]	n	(%)	CI[b]
Rees, MRC[c]	485	375	(33)	26-38	110	(19)	2 - 28
Keating, MD Anderson	187	208[d]	(36)	29-42	35	(14)	5 - 30
Hiddemann,	136	104	(54)	44-64	32	(44)	26 - 62
St. Bartholomew's	126	NA	(40)	NA	NA	(40)	NA
Gemtuzumab ozogamicin	104	50	(34)*	21-49	54	(28)*	16 - 42

* ($CR+CR_p$)

[32] Rees JKH,et. al.: Principle results of the medical research council's 8th actute myeloid leukaemia trial. *Lancet* 1986;236:1236-41.
[33] Keating MJ,et. al. . Response to salvage therapy and survival after relapse in acute myelogenous leukemia. *J Clin Oncol* 1989;7(8):1071-80.
[34] Thalhammer F,et. al. Duration of second complete remission in patients with acute myeloid leukemia treated with chemotherapy: A retrospective single-center study. *Ann Hematol* 1996;72:216-22.
[35] Hiddemann W, et. al. Definition of refractoriness against conventional chemotherapy in acute myeloid leukemia: A proposal based on the results of retreatment by thioguanine, cytosine, arabinoside, and daunoriubicin (TAD9) in 150 patients with relapse after standardized first line therapy. *Leukemia* 1990;4(3):184-8.
[36] Davis CL, et. al. The management of recurrent actue myelogenous leukaemia at a single centre over a fifteen-year period. *Br J Haematol* 1993;83:404-11.

7. (REWORDED) If the answer to question 5 is no, does the Committee agree that sufficient evidence of improved safety and *acceptable* efficacy has been demonstrated in a subgroup of patients *(60 years of age or older)* with relapsed acute leukemia to support approval?

YES – 11 NO – 2 Abstain – 0

The Committee indicated that the efficacy demonstrated by gemtuzumab ozogamicin in these studies was at the low end of the range of standard therapy. There was some improvement in toxicity, particularly in the lower frequency and severity of mucositis. In the elderly subgroup, treatment options are very limited and a less toxic option would be useful, if efficacy is acceptable.

10. Recommendations

10.1. Accelerated Approval,

Based on the data provided in the applications, s-NDA 21-174, the following regulatory action is recommended: Product labeling has been revised in accordance with these recommendations. **Gemtuzumab ozogamicin should be approved under the accelerated approval regulations (21 CFR 314.500, Subpart H) for the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older.**

The ODAC expressed that, in the elderly subgroup, treatment options are very limited and a less toxic option would be useful. This indication is more restricted than that proposed by the sponsor which would have included "patients younger than 60 years with CD33 positive acute myeloid leukemia in first relapse who are unable to tolerate conventional chemotherapy" because there were no data on this subpopulation in the trials.

10.2. Phase 4 Commitments

The sponsor will be asked to agree to the following post-approval studies to verify and describe the clinical benefit of Gemtuzumab ozogamicin under 21 CFR 314.510 (Subpart H).

1) A randomized controlled trial of gemtuzumab ozogamicin, daunorubicin and cytarabine versus daunorubicin and cytarabine as induction therapy in patients with de novo CD33-positive acute myeloid leukemia. This trial should be designed to demonstrate a 20% superiority in response rates.

2) The appropriate phase 1 trials will be performed to determine dosages and ensure that the toxicities observed with the dose combinations in the above trial are acceptable, and appropriate pharmacokinetic parameters will be measured to determine any potentially significant drug-drug interactions.

3) If a 3 drug regimen cannot be designed with acceptable toxicity, then a study of equivalent efficacy in gemtuzumab ozogamicin and cytarabine versus daunorubicin and cytarabine in patients over 60 years of age should be initiated.

4) A thorough evaluation of toxicity, both hematologic and non-hematologic, in patients undergoing subsequent postremission therapy such as hematopoietic stem cell transplantation or consolidation chemotherapy cytarabine should be performed.

5) Long-term follow-up for relapse, toxicity, and survival following such procedures as well as for those patients who receive no further therapy should be performed.

/S/	April 18, 2000	/S/	4/18/00
Peter F., Bross, M.D.	Date	Julie Beitz, M.D.	Date

CC: Orig NDA
Division file, HFD-150

11. Appendices

11.1. Appendix 1: Study Flow Chart for Part 1:

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

a: Patients were eligible to receive dose 2 provided the following conditions were met before each dose: the patient had recovered from reversible nonhematologic toxicities resulting from the previous doses; there was no evidence of disease progression; there was no evidence of significant formation of antibodies reactive with calicheamicin or protein; at least 14 days, but not more than 28 days, had passed since the previous infusion. In the event that patients were not eligible for subsequent doses and were withdrawn from the study, procedures outlined for the time frame from dose 2 to the end of part I evaluation visit were to be followed beginning with the corresponding day in the dose period. For selected patients possibly eligible for an additional dose, study procedures were to be followed as for doses 1 and 2.

b: End of part I evaluation (day 43 if the patient received 2 doses OR 28 days following the last dose of study medication). All patients were to enter part II and be evaluated approximately monthly to document survival status and antileukemic therapy. In addition, all patients with no leukemic blasts in the peripheral blood and ≤ 5% blasts in the bone marrow (measured by bone marrow aspirate or biopsy) at the end of part I visit were to have monthly interim physical examinations (including vital signs and performance status), as well as monthly CBC with differential. All patients receiving HSCT or additional antileukemic therapy in part II were to have information collected regarding responses to these therapies.

c: Including performance status. : CBCs were to be performed Monday, Wednesday and Friday (or on alternate days in a similar pattern) for the first 2 weeks after infusion of GZ or until recovery of granulocytes and platelets, to ≥1500/μL and ≥ 100,000/μL respectively, whichever came first. Additional CBCs were to be performed as clinically indicated.

c: Including performance status.

d: CBCs were to be performed Monday, Wednesday and Friday (or on alternate days in a similar pattern) for the first 2 weeks after infusion of GZ or until recovery of granulocytes and platelets, to ≥ 1500/μL and ≥ 100,000/μL respectively, whichever came first. Additional CBCs were to be performed as clinically indicated.

Before dose administration.

Bone marrow aspirate/biopsy was performed to confirm diagnosis of CD33 positive AML. Slides for morphologic uation of bone marrow aspirate and biopsy were sent for review by an independent consultant. Histochemical stains were oe performed by each investigational site on prestudy specimens only. An aliquot of bone marrow aspirate was to be sent for immunophenotyping by ; an aliquot of bone marrow aspirate was also to be provided for analysis of leukemic cell MDR efflux and in vitro sensitivity to gemtuzumab ozogamicin (Dr. Bernstein's lab Bone marrow biopsies obtained within 14 days before dose administration were acceptable. Bone marrow biopsy was required on patients who were to receive a third cycle of gemtuzumab ozogamicin.

h: For patients who discontinued dose administration and did not receive 2 doses of gemtuzumab ozogamicin, there was no need to obtain the final bone marrow biopsy.

i: See study drug infusion/PK flowchart for schedule for obtaining vital signs and blood samples during the study drug infusion observation period. (Vital signs included blood pressure, heart rate, respiratory rate, and oral temperature except where otherwise noted on the study drug infusion/PK flowchart.)

j: Subsequent dose administration could NOT proceed until verification was provided by W-AR regarding the absence of significant formation of antibodies against calicheamicin and hP67.6 antibody.

k: Patients were pretreated with acetaminophen and diphenhydramine approximately 1 hour before study drug administration; 2 additional doses of acetaminophen were administered; 1 at approximately 4 hours, and the other at approximately 8 hours, after the initial pretreatment dose.

l: At least twice weekly for the first 2 weeks after infusion of study drug; including assessment of performance status and vital signs at each interim physical examination.

Abbreviations: MDR = multiple-drug resistances

11.2. *Appendix 2: Audits, Financial Disclosures*

11.2.1. DSI audits were completed in the following sites:

[ ]

Scientific audit has been completed and although minor violations in protocol were reported, DSI has concluded that "the data from all sites appear acceptable for use in support of pending NDA 21-174."

11.2.2. Financial Disclosure Statements:

11.2.2.1. Certifications declaring absence of financial conflict of interest were obtained for [ ] investigators in the 4 clinical studies (101, 201, 202, and 203).

11.2.2.2. [ ]

There is no evidence to suggest that the results of these studies was biased in any way by financial interests of any of the investigators.

NDA-21-174
Mylotarg (gemtuzumab ozogamicin) for injection

Safety Update Review

Included in Medical Officer review dated April18, 2000.