GEMTUZUMAB OZOGAMICIN

Summary for Presentation to the

FDA's ONCOLOGIC DIVISION ADVISORY COMMITTEE

WYETH-AYERST RESEARCH

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1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Table 1. ABBREVIATIONS

Abbreviation	Definition
AcBut	4-(4'-Acetylphenoxy)butanoic acid, a bifunctional linker
ALL	Acute lymphoid leukemia
ALT	Alanine aminotransferase (SGPT; serum glutamic pyruvic transaminase)
AML	Acute myeloid leukemia
AML-R	Relapsed AML trial conducted by Medical Research Council
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukemia
Ara-C	Cytarabine
AST	Aspartate aminotransferase (SGOT; serum glutamic oxaloacetic transaminase)
AUC	Area under the concentration time curve
BMT	Bone marrow transplantation
BUN	Blood urea nitrogen
BWH	Brigham and Women's Hospital
CFU-GEMM	Colony forming unit – granulocytic / erythrocytic / monocytic / megakaryocytic
CI	Confidence interval
CL	Total body clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	Complete remission
CRp	Complete remission with incomplete platelet recovery (previously termed MR)
CRF	Case report form
CSF	Colony stimulating factor
DIC	Disseminated intravascular coagulation
DMH	Dimethyl hydrazide
DPR	Data processing report
ECG	Electrocardiogram
FAB	French-American-British (group that developed classification of AML subtypes)
FDA	Food and Drug Administration
FLAG-IDA	Fludarabine-Ara-C-G-CSF-Idarubicin (combination chemotherapy regimen)
G6PD	Glucose-6-phosphate dehydrogenase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GO	Gemtuzumab ozogamicin
GVHD	Graft versus host disease
HiDAC	High-dose cytarabine
hP67.6	A recombinant humanized form of the murine monoclonal antibody mP67.6
HSCT	Hematopoietic stem cell transplantation; includes peripheral blood stem cell transplantation, bone marrow transplant, or umbilical cord blood transplant.
IDAC	Intermediate-dose cytarabine
IES	Integrated Efficacy Summary
IND	Investigational New Drug
ISS	Integrated Safety Summary
IV	Intravenous
LDH	Lactic acid dehydrogenase
LFT	Liver function tests
MDR	Multidrug resistance
MDS	Myelodysplastic syndrome

Table 1. ABBREVIATIONS

Abbreviation	Definition
MR	Morphologic remission (previous term for CRp)
MRC	Medical Research Council
MTD	Maximum tolerated dosage
NCI	National Cancer Institute
NDA	New Drug Application
NR	No remission
NTEL	No-toxicologic-effect level
OR	Overall remission (CR + CRp)
PSCT	Peripheral stem cell transplantation
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
SD	Standard deviation
TEAE(s)	Treatment-emergent adverse event(s)
$t_{1/2}$	Half-life associated with the terminal slope (λ_z)
t_{max}	Time to reach observed C_{max}
VOD	Veno-occlusive disease (hepatic)
$V_{\lambda z}$	Volume of distribution during terminal elimination phase
V_{ss}	Volume of distribution at steady-state
W-AR	Wyeth-Ayerst Research
WBC	White blood cell

Table 2.   GLOSSARY OF DEFINITIONS AND CONVENTIONS

Term	Definition
Blasts, blast cells	Undifferentiated hematopoietic precursor cells or leukemia cells
Bone marrow aspirate	Bone marrow cells removed by suction with a needle
Bone marrow biopsy	Bone marrow tissue removed en bloc
Bone marrow blast cell percentage	Percent of blast cells in the bone marrow—percent of marrow containing undifferentiated hematopoietic precursors or leukemia cells
Cellularity	Percent of bone marrow occupied by cells, as opposed to fat; can be described as aplastic, hypocellular, normocellular, or hypercellular
Dose-related terms	
Dose of gemtuzumab ozogamicin	A 2-hour intravenous (IV) infusion (0.25 up to 9 mg/m^2)
Dose period	The time from when 1 dose is given until the end of the subsequent 14- to 28-day follow-up
Course	One (1) course includes 2 to 3 doses of gemtuzumab ozogamicin
hP67.6 antibody	A recombinant humanized form of the murine monoclonal antibody mP67.6
MDR efflux	Functional measurement of multidrug resistance
Complete remission with incomplete platelet recovery	Same as complete remission except for incomplete platelet recovery (CRp is also referred to as MR)
Myelodysplastic syndrome	A clonal hematopoietic stem cell abnormality characterized by cytopenias and morphologic abnormalities of the bone marrow and peripheral blood
Part I	Study drug administration and 28-day follow-up
Part II	Six (6) month follow-up after part I
Part III	Poststudy 18-month follow-up after part II
Types of therapy	
Induction therapy	Intended to induce CR (absence of morphologic evidence of leukemia and recovery of peripheral blood counts)
Postremission therapy	Treatment after remission to prevent or delay relapse; drugs are administered at doses and schedules that are significantly myelosuppressive
Intensification of therapy	Use of higher doses of induction or postremission therapy to overcome resistance to chemotherapy
Palliative therapy	Low doses of chemotherapy used to alleviate symptoms, not cure the leukemia
Myeloablative therapy	Use of high doses of chemotherapy before bone marrow transplantation (to destroy leukemia cells and deplete all bone marrow)
Transplantation, bone marrow or peripheral stem cell	
Allogeneic	Transplantation from related or unrelated donor
Autologous	Transplantation from self (cells collected during remission)

Table 3. DEFINITIONS OF TREATMENT OUTCOME CATEGORIES

Term	Definition
Complete Remission (CR)	A patient was considered to be in CR if the following conditions were met: 1. Leukemic blasts were absent from the peripheral blood; 2. The percentage of blasts in the bone marrow was ≤ 5% as measured by morphology studies (either aspirate or bone marrow biopsy). An initial assessment was made by the investigator. An independent consultant reviewed the morphology from the bone marrow samples, and in the event of a discrepancy between the investigational site and the consultant, the consultant's opinion was used; 3. Peripheral counts reached the following levels: hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/µL, absolute neutrophil count ≥ 1,500/µL; and 4. The patient was red blood cell (RBC) and platelet-transfusion-independent (RBC transfusion independence required no RBC transfusions for 2 weeks, platelet transfusion independence required no platelet transfusions for at least 1 week).
Complete remission with incomplete platelet recovery (CRp; also referred to as MR)	A patient was considered to be in CRp if all the criteria for CR except platelet recovery were met. The following are the conditions for CRp: 1. Leukemic blasts are absent from the peripheral blood; 2. The percentage of blasts in the bone marrow is ≤ 5% as measured by morphology studies (either aspirate or bone marrow biopsy). An initial assessment was made by the investigator. An independent consultant reviewed the morphology from the bone marrow samples, and in the event of a discrepancy between the investigational site and the consultant, the consultant's opinion was used; 3. Peripheral counts reached the following levels: hemoglobin ≥ 9 g/dL and absolute neutrophil count ≥ 1,500/µL; 4. The patient was RBC and platelet-transfusion-independent (RBC transfusion independence required no RBC transfusions for 2 weeks, platelet transfusion independence required no platelet transfusions for at least 1 week).
No Remission (NR)	Patients were considered to be in NR if they did not meet all criteria for CR or CRp. They were: 1. Patients whose percentage of blasts in the bone marrow was > 5%; or, 2. Patients who had no leukemic blasts in the peripheral blood and ≤ 5% blasts in bone marrow (measured by aspirate or bone marrow biopsy) at the end of part I visit but did not meet other criteria for CR or CRp. These patients were followed up for response and adverse events.

2. INTRODUCTION AND OVERVIEW

Gemtuzumab ozogamicin is being developed as an antineoplastic agent to treat patients with relapsed acute myeloid leukemia (AML). It is the first antibody-targeted chemotherapy agent to demonstrate clinical efficacy.

Gemtuzumab ozogamicin has 3 components: a recombinant humanized antibody (hP67.6) directed against the CD33 antigen, a derivative of calicheamicin, and a linker connecting the antibody and the calicheamicin derivative. The calicheamicin component (N-acetyl gamma calicheamicin dimethyl hydrazide [DMH]) is a cytotoxic derivative of the calicheamicin family of antitumor antibiotics. The CD33 antigen is a cell surface protein expressed on the surface of the leukemic cell in more than 80% of patients with AML. The antigen is also expressed by immature myeloid cells, and megakaryocytes, and to a lesser degree by mature myeloid cells, but not by pluripotent stem cells. Gemtuzumab ozogamicin binds to the CD33 antigen on the surface of leukemic cells and other cells expressing CD33, and is then internalized. Once inside the cell, with increasing pH, calicheamicin is released from the antibody and is converted to a reactive intermediate that damages DNA, causing cell death.

Monoclonal antibodies are ideally suited for the treatment of AML because of the accessibility of leukemic cells in the blood, bone marrow, spleen, and lymph nodes. Moreover, because the leukemic cells of most AML patients express the CD33 antigen, a monoclonal antibody to CD33 offers a specifically targeted delivery vehicle for a cytotoxic agent in the CD33 positive patient population. Additionally, because the CD33 antigen is expressed only on cells within the hematopoietic system, an agent like gemtuzumab ozogamicin that is derived from a monoclonal antibody and targets CD33 expressing cells should have an improved safety profile compared with that of current agents.

Efficacy results reported in this document, based on the data from NDA 21-174 and the 3-month update report, were obtained from 3 open-label phase II clinical trials of gemtuzumab ozogamicin conducted by Wyeth-Ayerst Research (W-AR) in the United States, Canada, and Europe. The efficacy analysis was based on data from 142 patients enrolled in these studies as of 30 Apr 1999. All of the patients were being treated for AML in first relapse. Although these 3 studies remain open to gather additional safety and efficacy information, the cutoff date for inclusion of the data in this presentation was 28 Jul 1999. Efficacy data were available for 65, 40, and 37 patients in studies 201, 202, and 203,

respectively. The key efficacy parameters included remission status, relapse-free survival, progression-free survival, and overall survival.

Data from the 3 studies could be pooled because the studies had similar designs and the same dosage regimens of gemtuzumab ozogamicin. Although study 203 enrolled only an older population of patients ($\geq$ 60 years old), patients $\geq$ 60 years old could also be enrolled in studies 201 and 202. Two sets of pooled data were evaluated in the NDA: the data from studies 201 and 202 (201/202) were pooled and the data from all 3 studies were also pooled (201/202/203) to enable assessment of the effects of age on efficacy. The pooled data provide better estimates for the various efficacy parameters because of the increased number of patients. In this presentation we focus on the pooled data from the 3 phase II studies (n = 142). Analyses of data from the individual studies and from pooled studies 201/202, as well as from 201/202/203, were presented in the NDA and 3-month update, and the conclusions are consistent for the various sets of data.

In addition to the phase II studies, studies 101-US (adult phase I, completed) and 102-US (pediatric phase I, ongoing) included patients with relapsed and refractory AML; these studies were not designed to assess efficacy.

Although analysis of efficacy was not an objective of the phase I dose-escalating study (101), data were reviewed to monitor response to treatment. In addition to assessments of complete remission (CR), it was found that some of the patients with relapsed or refractory AML in this study had clearance of bone marrow blast cells with incomplete platelet recovery. The term "morphologic remission" (MR) was initially adopted to describe these responses; however, this term was subsequently changed to CRp, designating CR with incomplete platelet recovery. This category of response was included in the phase II protocols as a secondary efficacy endpoint. Originally, CRp did not include platelet transfusion independence as a criterion. After discussions with regulatory agencies, a more specific definition of CRp was developed for the phase II protocols.

To be classified as having a CRp, patients had to meet all the criteria for CR except recovery to 100,000 platelets/µL. The CRp patients had to have sufficient bone marrow recovery to be platelet transfusion independent. This is a clinically meaningful standard in that patients who are platelet transfusion independent are expected to be at a lower risk for bleeding than those who are not.

The emerging clinical profile of gemtuzumab ozogamicin indicates that CR and CRp patients are clinically comparable in terms of relapse-free survival, overall survival, rate of receiving hematopoietic stem cell transplants (HSCTs) after remission, and survival after HSCT. Therefore, an overall remission (OR) rate was also calculated (CR + CRp) for the efficacy assessments. Overall, the data support the conclusion that it was appropriate to base the efficacy evaluation of gemtuzumab ozogamicin in the treatment of AML in first relapse on OR rates. Treatment with gemtuzumab ozogamicin resulted in remission rates similar to those of comparable patient populations receiving conventional chemotherapy as reported in the literature (see section 7.3). The OR rate for the 142 patients in the phase II studies was 30%.

Gemtuzumab ozogamicin as a single agent produced an OR rate, duration of remission, survival, and HSCT outcome within the range of those reported for current available AML therapies. (A comparison of gemtuzumab ozogamicin and currently available AML therapies is discussed in section 7.)

The safety profile that emerged from these studies demonstrated a better adverse event profile for gemtuzumab ozogamicin than that reported in the literature for conventional combination therapy. Treatment with gemtuzumab ozogamicin was associated with a low incidence of severe mucositis, low incidence of severe infections, reduced need for hospitalization, mild and reversible nausea and vomiting, and no alopecia. In terms of myelosuppression and bleeding, the adverse event profile was similar to that of conventional combination regimens. Furthermore, treatment with gemtuzumab ozogamicin allows for outpatient administration.

The results from the studies performed to date indicate that gemtuzumab ozogamicin is safe and effective in the treatment of CD33 positive AML in first relapse.

2.1 Overview of Clinical Studies

2.1.1 Table of Studies
The principal sources of data for this report were the 3 open-label phase II studies (201, 202, and 203) being conducted in the United States, Canada, and Europe. These 3 multicenter studies were conducted at 52 sites. The important features of the phase II studies are summarized in Table 4. The table includes additional details of these studies such as the study design, dosages, duration of treatment, enrollment, and a brief summary of results. Details regarding the phase I studies are also shown in Table 4.

Table 4. CLINICAL STUDIES OF GEMTUZUMAB OZOGAMICIN (GO)[a]

Protocol No. Report No. Start/Stop Date Investigators (No. of study sites)	Study Design	Study Drug, Dose, Route, Duration	Batch No. Date Manufactured (Concentration)	Enrolled/ Safety/ Intent-to-Treat	Sex[b] Ethnic Origin[c] Age Range (yrs) (Mean)	Summary of Results
PHASE II STUDIES						
0903A1-201-US/CA 36635 5/97 – ongoing Multicenter (13 sites)	Phase II open-label, single-arm, 3-part, multidose, multicenter outpatient study with a 6- to 8-hour infusion observation period, to examine the effects of GO in patients with CD33 positive AML in first relapse.	GO, 9 mg/m^2 as a single 2-hour IV infusion per dose for 2 doses; certain patients eligible for a third dose.	R-1592-197 10 10 Oct 1996 (5 mg/vial) R2024-2 11 Nov 1996 (5 mg/vial) PSG2024-14 05 May 1997 (5 mg/vial)	65/65/65	32 M / 33 F 59W/1B/2A/3O 22 – 82 (53.5)	Eleven (11) patients had a CR and 10 had a CRp for an overall remission rate of 32%. Overall, CRs and CRps were found to be clinically comparable for efficacy, safety, and health outcome except that platelet recovery occurred more slowly in patients with CRps. GO demonstrated a tolerable safety profile with significant advantages over conventional chemotherapy drugs used to treat relapsed AML.
0903B1-202-EU 36634 4/98 - ongoing Multicenter (19 sites)	Phase II open-label, single-arm, 3-part, multidose, multicenter outpatient study with a 6- to 8-hour infusion observation period, to examine the effects of GO in patients with CD33 positive AML in first relapse.	GO, 9 mg/m^2 as a single 2-hour IV infusion per dose for 2 doses; certain patients eligible for a third dose.	1997B0191 10 Oct 1997 (5 mg/vial) R2024-2 11 Nov 1996 (5 mg/vial) PSG2024-14 05 May 1997 (5 mg/vial)	40/40/40	27 M / 13 F 39 W / 1 B 23 – 79 (56.6)	Eight (8) patients had a CR, and 5 had a CRp for an overall remission rate of 33%. Overall, CRs and CRps were found to be clinically comparable for efficacy, safety, and health outcome except that platelet recovery occurred more slowly in patients with CRp. GO demonstrated a tolerable safety profile with significant advantages over conventional chemotherapy drugs used to treat relapsed AML.

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Table 4. CLINICAL STUDIES OF GEMTUZUMAB OZOGAMICIN (GO)[a]

Protocol No. Report No. Start/Stop Date Investigators (No. of study sites)	Study Design	Study Drug, Dose, Route, Duration	Batch No. Date Manufactured (Concentration)	Enrolled/ Safety/ Intent-to-Treat	Sex[b] Ethnic Origin[c] Age Range (yrs) (Mean)	Summary of Results
0903B1-203-US/EU 36633 12/97 – ongoing Multicenter (12 EU sites, 8 US sites)	Phase II open-label, single-arm, 3-part, multidose, multicenter outpatient study with a 6- to 8-hour infusion observation period, to examine the effects of GO in older patients with CD33 positive AML in first relapse.	GO, 9 mg/m^2 as a single 2-hour IV infusion per dose for 2 doses; certain patients eligible for a third dose.	R1592-197 10 Oct 1996 (5 mg/vial) PSG2024-14 05 May 1997 (5 mg/vial) 1997B0191 10 Oct 1997 (5 mg/vial)	37/37/37	25 M / 12 F 35 W / 2 B 58 – 84 (68.5)	Four (4) patients had a CR and 4 had CRp for an overall remission rate of 22%.

Table 4. CLINICAL STUDIES OF GEMTUZUMAB OZOGAMICIN (GO)[a]

Protocol No. Report No. Start/Stop Date Investigators (No. of study sites)	Study Design	Study Drug, Dose, Route, Duration	Batch No. Date Manufactured (Concentration)	Enrolled/ Safety/ Intent-to-Treat	Sex[b] Ethnic Origin[c] Age Range (yrs) (Mean)	Summary of Results
PHASE I STUDIES						
0903A1-101-US D121-P1 30388 04/95 - 05/98 Appelbaum, Forman	Phase I, open-label, single-arm study to examine the effects of GO in adult patients with relapsed or refractory CD33 positive AML	GO; dose levels of 0.25, 0.5, 1, 2, 4, 5, 6, and 9 mg/m^2. Single 2-hour IV infusion per treatment dose; maximum of 3 doses.	B94-0082 (2.5 mg/vial); R2024-2 (5 mg/vial)	40/40/40[d]	20 M / 20 F 34 W / 4 A /3 O 23 - 73 (48.6)	Two (2) patients had a CR; 7 patients had clearance of blasts from bone marrow and blood but without full recovery of peripheral counts. The CRs were maintained for 140 and 214 days. GO was generally well tolerated with postinfusion fever and chills being the most common AE.
0903A1-102-US[e] Ongoing Multicenter	An ascending dose study of the safety of GO as single agent treatment of pediatric patients with refractory or relapsed AML	GO; 6, 9, and 12 mg/m^2 as a single 2-hour IV infusion per dose for up to 2 doses. Patients less than 3 years old receive doses based on a per kilogram dosage regimen.	R1592-197 (101096) (5 mg/vial) PSG2024-14 (050597) (5 mg/vial)	Ongoing 11 patients as of 30 Nov 1999	Ongoing 6 M / 5 F 2 – 16 (10.4)	Preliminary safety data only are available for these patients.

a: All 3 phase II studies remain open for enrollment.
b: Sex: M = Male, F = Female.
c: Ethnic origin: W = White, B = Black, A = Asian, O = Other.
d: Forty (40) patients were enrolled in the study and 1 was re-enrolled with a new patient number for a total of 41 patient treatments.
e: Study is ongoing.

2.1.2 Overall Study Design

Figure 1 shows an overview of the schedule in studies 201, 202, and 203. The phase II studies each consisted of 3 parts. Part I included a screening visit, 2 or 3 doses of gemtuzumab ozogamicin with at least 14 days but no more than 28 days between doses, and a 28-day follow-up after the last dose of study medication. Doses of gemtuzumab ozogamicin were only administered during part I of the studies.

In part II, all patients were followed for approximately 6 additional months and were evaluated monthly. Patients who had a CR or a CRp or who had clearance of blasts with gemtuzumab ozogamicin treatment were followed for efficacy and safety, and those patients who did not have clearance of the blasts in part I were followed in part II for safety only. Part III consisted of follow-up assessments of disease status and survival.

Figure 1. OVERALL STUDY DESIGN FOR GEMTUZUMAB OZOGAMICIN STUDIES 201/202/203.

PART I:
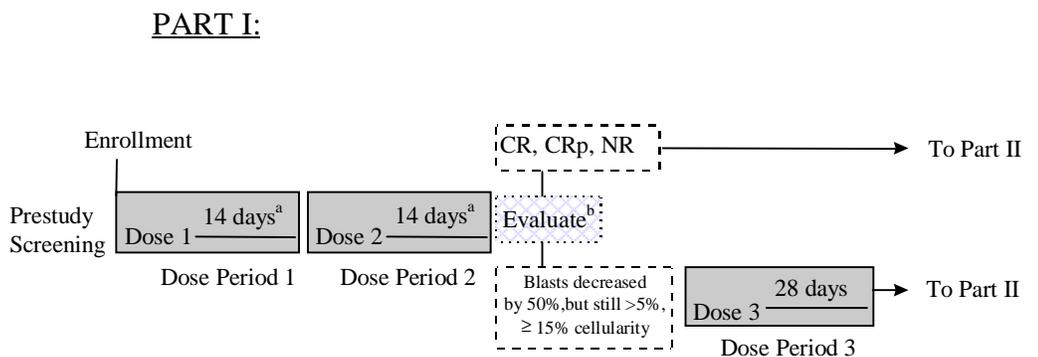
a: Patients were required to complete 28 days of evaluation after the last dose of gemtuzumab ozogamicin.
b: A bone marrow biopsy to evaluate cellularity was performed approximately 14 days after dose 2 on patients who were considered for a third dose.

PART II: Six (6) months follow-up for safety, disease status, and survival.
Response to HSCT and/or additional antileukemic therapy.
Monthly interim physical examination and CBC with differential for patients who were CR or CRp, or who did not meet all the criteria for CR or CRp, but had ≤ 5% bone marrow blasts.

Month 1   Month 2   Month 3   Month 4   Month 5   Month 6 → To Part III

PART III: Follow-up for disease status and survival. Telephone contact every 3 months for 18 months, then every 6 months until death or termination of the study by the sponsor.

2.1.3 Key Inclusion and Exclusion Criteria in Phase II Studies

All patients in the phase II studies had CD33 positive AML in first relapse as determined by the central flow cytometry laboratory. Table 5 shows the key inclusion criteria in the 3 phase II studies. In addition to meeting the criteria below, all patients were required to have > 5% leukemic blasts as determined by the central flow cytometry laboratory.

Table 5. KEY INCLUSION CRITERIA IN PHASE II STUDIES

Criteria	Study 201	Study 202	Study 203
CD33 positive AML in first relapse	Yes	Yes	Yes
Age, years	≥ 18	≥ 18	≥ 60
Duration of first remission, months	≥ 6	≥ 6	≥ 3
Prior HSCT	Not permitted	Permitted[a]	Not permitted
Eastern Cooperative Oncology Group performance status 0 - 2	Yes	Yes	Yes
Baseline serum creatinine	≤ 2.0 mg/dL (176.8 µmol/L)	≤ 2.0 mg/dL (176.8 µmol/L)	≤ 3.0 mg/dL (265.2 µmol/L)
Baseline serum total bilirubin	≤ 1.5 mg/dL (25.65 µmol/L)	≤ 1.5 mg/dL (25.65 µmol/L)	≤ 2.0 mg/dL (34.2 µmol/L)
No myelodysplastic syndrome (MDS)	Yes	Yes	Yes
No secondary AML	Yes	Yes	Yes

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

Studies 201 and 202 are nearly identical with the exception that study 202 was amended to allow the inclusion of patients with prior HSCT. Although this amendment was made to allow increased enrollment in study 202, only 5 of the 40 patients received prior HSCT.

Study 203 differs in some ways from studies 201 and 202 because the objective in study 203 was to evaluate the effects of gemtuzumab ozogamicin in older patients (≥ 60 years old). Patients in study 203 had to have a duration of first remission of at least 3 months, rather than at least 6 months because older patients as a group have shorter durations of first remission than younger patients. In study 203, 14 patients had < 6 months of first remission. Baseline serum creatinine and total bilirubin entry criteria in study 203 were higher than those in studies 201 and 202 to reflect the decrease in organ function commonly seen in older patients. However, all patients enrolled in study 203 met the creatinine criteria established for studies 201 and 202, and all except 2 patients enrolled in study 203 met the total bilirubin entry criteria established for studies 201 and 202.

2.2 Overview of Results

The following is an overview of results for the 142 patients discussed in this report:

Efficacy: The OR rate was 30% (42 of 142 patients). Twenty-three (23, 16%) patients had CRs and 19 (13%) had CRps. The CR and CRp patients were compared for all efficacy, safety, and health outcomes variables examined, and no differences were apparent except that hematologic recovery occurred more slowly in patients with CRps leading to an increased number of platelet and RBC transfusions in these patients (however, all CRp patients became platelet transfusion independent). Most importantly, the survival rates for patients with CR and CRp were essentially the same, and the 2 groups underwent similar post-gemtuzumab ozogamicin therapies with similar outcomes. Since patients with CR and CRp are clinically comparable, the OR rate of 30% after gemtuzumab ozogamicin will be used to express the remission rate.

The data demonstrate that gemtuzumab ozogamicin administered to patients with AML in first relapse has efficacy comparable with that of conventional AML therapies as determined by a review of published literature and institutional databases of patients with similar key prognostic factors. The median total days of hospitalization for the 142 gemtuzumab ozogamicin-treated patients was 24. There were 23 (16%) patients with 0 to 7 days of hospitalization; 5 (4%) of these patients had no hospitalization. These results represent an important advance when compared with the present conventional chemotherapy for patients with AML in relapse.

Safety: Gemtuzumab ozogamicin demonstrated a safety profile that compares favorably with safety profiles of conventional chemotherapy drugs used to treat AML in first relapse. The most common adverse event was a postinfusion symptom complex consisting of fever and chills. The adverse event profile largely reflected the specificity of gemtuzumab ozogamicin for the CD33 antigen. Severe myelosuppression was seen in virtually all patients. Gemtuzumab ozogamicin therapy is associated with a low incidence of clinically important drug-related mucositis, a low rate of severe infection, and an absence of alopecia.

Pharmacokinetics: Plasma was collected from all patients who participated in clinical studies to measure concentrations of both the hP67.6 antibody and calicheamicin. Clinical pharmacology studies were not performed in healthy volunteers because of the potential toxicity of gemtuzumab ozogamicin. Preclinical pharmacokinetic studies were not possible because of the absence of immunoreactive CD33 in all species except chimpanzees.

The pharmacokinetics of gemtuzumab ozogamicin are best represented by measurements of the hP67.6 antibody. After administration by IV infusion, the drug is completely absorbed and distributes to a relatively limited space. Slow elimination follows with a mean half-life of 67 hours. Apparently as a result of decreased leukemic blast cells, there is a significant increase in concentration after the second dose compared with that after the first. Although highly variable between individuals, changes in concentrations could not be linked to age, sex, weight, body surface area, or ethnicity.

Hospitalizations: Data on health outcomes were assessed in order to compare patients when treated with gemtuzumab ozogamicin therapy vs conventional chemotherapy. As reflected in the reduced need for hospitalization, the specificity and tolerability of gemtuzumab ozogamicin treatment was associated with important quality of life improvement over treatments with conventional chemotherapy.

3. STUDY POPULATION

3.1 Extent of Exposure

This section summarizes the numbers of patients who were treated with gemtuzumab ozogamicin. The section also includes exposure information on other medications that were required in the gemtuzumab ozogamicin studies.

3.1.1 Exposure to Gemtuzumab Ozogamicin

A total of 142 patients received at least 1 dose of 9 mg/m^2 gemtuzumab ozogamicin in the phase II trials. The numbers of patients exposed to 1 to 3 doses in these studies are shown in Table 6. A total of 5 patients in studies 201/202/203 received a third dose.

Table 6. PATIENTS RECEIVING 1, 2, OR 3 DOSES OF 9 mg/m^2 GEMTUZUMAB OZOGAMICIN

Total Doses	Number (%) (n = 142)
1	28 (20)
2	109 (77)
3	5 (4)

Of the 142 patients enrolled as of 30 Apr 1999, 4 received more than 1 course of gemtuzumab ozogamicin (ie, achieved remission after 1 or more doses, had a relapse, and then received additional doses). These patients are discussed in section 5.3.2.

3.1.2 Exposure to Other Medications Required by the Study

      Two (2) categories of medications were required by the protocol for the gemtuzumab ozogamicin studies 1) The use of hydroxyurea was required to reduce the peripheral WBC count to < 30,000/µL before gemtuzumab ozogamicin use if the initial WBC count was ≥ 30,000/µL and 2) Premedication with acetaminophen and an antihistamine was required for all patients.

3.2 Patient Characteristics and Disposition

      Patients participating in gemtuzumab ozogamicin clinical studies represented a cross-section of patients for the intended indication. Study inclusion and exclusion criteria were designed to ensure that patients too ill for treatment and those unlikely to respond to any therapy were not exposed to the risks of therapy. This section provides patient population demographics and baseline disease characteristics, details of prior chemotherapy, and patient disposition in the gemtuzumab ozogamicin studies.

3.2.1 Demographics

      The baseline demographic characteristics of patients in the phase II studies (Table 7) were similar to those of patients encountered in the general AML population. The phase II trials included adult patients with ages up to 84 years. Demographics by patient age and duration of first remission are presented for each study in Table 8.

Table 7. SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS[a]

Characteristic	Value (n = 142)
Age (years)	
Mean (SD)	58 (15)
Median	61
(Min – Max)	(22 - 84)
Sex, n (%)	
Female	58 (41)
Male	84 (59)
Ethnic origin, n (%)	
White	133 (94)
Black	4 (3)
Asian	2 (1)
Other	3 (2)
Height (cm), n	
Mean (SD)	171 (99)
(Min – Max)	(144 – 191)
Weight (kg), n	
Mean (SD)	79 (17)
(Min – Max)	(43 – 144)
Body surface area (m^2), n	
Mean (SD)	1.9 (0.2)[b]
(Min – Max)	(1.3 – 2.7)

a: Abbreviations: SD = standard deviation; Min = minimum; Max = maximum.

b: n = 141 for measurement of body surface area.

Table 8. PATIENT AGE AND DURATION OF FIRST REMISSION BY STUDY

Characteristic Statistic	Study 201	Study 202	Study 203	Studies 201/202/203
Age, years				
No. of patients	(n = 65)	(n = 40)	(n = 37)[a]	(n = 142)
Mean (SD)	53.5 (15.9)	56.6 (13.2)	68.5 (6.3)	58.3 (14.6)
Median	53.0	57.5	69.0	61.0
Min – Max	22 - 82	23 - 79	58 - 84	22 - 84
Duration of first remission (before gemtuzumab ozogamicin), months				
No. of patients	(n = 65)	(n = 40)	(n = 37)	(n = 142)
Mean (SD)	16.3 (14.1)	18.5 (21.9)	8.7 (5.9)	14.9 (15.7)
Median	12.0	11.3	7.0	11.1
Min – Max	6 - 95	5[b] - 117	2[c] - 35	2 - 117

a: Protocol violation in study 203: patient 20391-0001, who was 58 years old, was enrolled although study required age ≥ 60 years.

b: Protocol violation in study 202: patient 20276-0002 had a duration of first remission of 5 months, although study required ≥ 6 months.

c: Protocol violation in study 203: patient 203A2-0001 had a duration of first remission of 2 months although study required ≥ 3 months of first remission.

3.2.2 Prior Chemotherapy

Patients treated in the phase II trials with gemtuzumab ozogamicin all had AML in first relapse. Seventeen percent (17%) of patients required a second induction course to get into first CR. Nearly all (94%) patients had postremission therapy before gemtuzumab ozogamicin treatment. Table 9 summarizes the prior chemotherapy for patients in studies 201/202/203 by response category.

Table 9.   SUMMARY OF PRIOR CHEMOTHERAPY: STUDIES 201/202/203

Group		-------------Response Category -----------------------			
Statistic	Total	CR	CRp	OR	NR
Second induction (%)	23/138 (17)	2/ 21 (10)	3/ 18 (17)	5/ 39 (13)	18/ 99 (18)
Postremission therapy[a] (%)	133/142 (94)	21/ 23 (91)	18/ 19 (95)	39/ 42 (93)	94/100 (94)
Cycles of postremission therapy[b]					
n	132	20	16	36	96
Mean (SD)	2.3 (1.5)	3.2 (2.4)	2 (1.2)	2.6 (2)	2.2 (1.3)
Median	2	2.5	2	2	2
Min – Max	0 - 11	0 - 11	0 - 4	0 - 11	0 - 7
HiDAC[c] (%)	96 /138 (70)	17 / 22 (77)	13 / 19 (68)	30 / 41 (73)	66 / 97 (68)

a: Determination was based on the medications collected on the prior chemotherapy CRF. Any chemotherapy medication that was started at least 20 days after first CR was considered postremission therapy.

b: For those 132 patients with data on the number of cycles of postremission therapy.

c: HiDAC = high dose cytarabine

3.2.3 French-American-British Subtype

The number of patients with each subtype was generally comparable across the phase II studies. Data on the FAB subtype of all patients measured at baseline and at relapse are summarized in Table 10.

Table 10.   NUMBER (%) PATIENTS WITH EACH FRENCH-AMERICAN-BRITISH SUBTYPE IN STUDIES 201/202/203

FAB Category[a]	Baseline	Relapse
M0-Undifferentiated	7 (5)	3 (2)
M1-Acute myeloid leukemia with minimal maturation	29 (20)	19 (13)
M2-Acute myeloid leukemia with maturation	49 (35)	36 (25)
M3-Acute promyelocytic leukemia	1 (< 1)	0
M4-Acute myelomonocytic leukemia	24 (17)	18 (13)
M4Eo-Acute myelomonocytic leukemia with eosinophilia	4 (3)	3 (2)
M5-Acute monocytic leukemia	15 (11)	10 (7)
M6-Acute erythroid leukemia	1 (< 1)	0
M7-Acute megakaryoblastic leukemia	1 (< 1)	1 (< 1)
Undetermined[b]	11 (8)	52 (37)

a: FAB = French-American-British classification

b: FAB subtypes were not available for all patients and were often not repeated at relapse.

Associations between FAB subtypes and adverse events were not evaluated.

3.2.4 Concomitant Medications

Concomitant medications with the exception of hematopoietic growth factors were permitted in all trials. Antileukemic therapies other than gemtuzumab ozogamicin were not permitted while patients were in part I of the phase II trials, except in cases where progression occurred during therapy with gemtuzumab ozogamicin. However, data were collected for patients completing their gemtuzumab ozogamicin administration and subsequently receiving additional antileukemic therapies.

3.2.5 Patient Disposition

A total of 124 patients entered the part II follow-up period of the phase II studies and 42 patients entered the poststudy (part III) period before the data cutoff date (Table 11).

Table 11.   SUMMARY OF PATIENT PARTICIPATION IN
GEMTUZUMAB OZOGAMICIN CLINICAL TRIALS

Study /Disposition	Number of patients
Part I	
Enrolled	142
Received dose 1	142
Received dose 2	114[a]
Received dose 3	5
Died in part I	18
Part II	
Entered 6-month follow-up	124[b]
Died in part II	54
Remain in part II	28
Part III	
Entered 18-month follow-up	42
Died in part III	14
Remain in part III	28

a: Nine (9) patients died before dose 2 and 19 patients only received 1 dose and then went into follow-up.

b: Includes 105 patients who survived after 2 doses (114 who had second dose minus 9 patients who died between the second dose and the end of part I) plus 19 patients who only received 1 dose and then went into the follow-up.

3.2.6 Discontinuations

Safety data were collected for all patients who received at least 1 dose of gemtuzumab ozogamicin. In the phase II trials, patients who failed to receive a second dose of gemtuzumab ozogamicin continued to be followed up for safety in part II of the study.

A summary tabulation of the number of patients who withdrew from studies 201/202/203 is presented by reason and treatment in Table 12.

Table 12. PATIENTS WHO WITHDREW FROM FURTHER TREATMENT DURING PART I (STUDIES 201/202/203)[a]

Reason	Number (%) (n = 142)
Any reason	40 (28)
Adverse reaction	6 (4)
Other medical event[b, c]	19[d] (13)
Unsatisfactory response - efficacy[b]	16 (11)

a: Includes patient deaths (see section 5.3.5).
b: One (1) patient (201B4-0001) had both "other medical event' and "unsatisfactory response – efficacy" listed as primary reasons for discontinuation from further treatment.
c: Two (2) patients (201B6-0001, and 201B6-0003) completed 2 doses and were candidates for receiving a third dose. However, they failed to meet the criteria for receiving dose 3 and are listed as discontinuations.
d: One (1) patient (20369-0002) completed 2 doses and was listed as a discontinuation because of leukemia progression at the end of part I.

The large majority of patients who withdrew did so because of disease progression. In these studies, "death" was not listed in the case report form (CRF) as a reason for discontinuation. A complete listing of deaths that occurred within 28 days of receiving gemtuzumab ozogamicin in studies 201/202/203 is presented in section 5.3.5.

4. EFFICACY

4.1 Summary of Results

The efficacy of gemtuzumab ozogamicin for the treatment of patients with AML in first relapse was evaluated in 3 phase II clinical studies. The efficacy results, based on data from 142 patients, demonstrated the following:

- Two categories of response designated as CR and CRp are comparable in their clinical outcomes. This justifies the use of an OR category to demonstrate the efficacy of gemtuzumab ozogamicin in patients with AML in first relapse.

- The OR rate for gemtuzumab ozogamicin was 30%, which is comparable with rates of remission after conventional therapy in trials with other agents that evaluated similar patient populations.

- Relapse-free survival and total survival are comparable with results from conventional therapy in similar patient populations.

4.2 Methods for Efficacy Assessments

4.2.1 Overview of Efficacy Endpoints

The efficacy assessments used in the gemtuzumab ozogamicin phase II studies are summarized in Table 13. The major efficacy assessments included rates of remission, relapse-free survival, and overall survival. The results are shown for various patient groups by remission status, ie, all patients, and those with CRs, CRps, ORs, and no remissions (NRs).

Table 13. EFFICACY ASSESSMENTS

Assessments	Subcategories of Assessments and/or Comments
Major efficacy endpoints	
Remission	Rates of remission: CR = primary endpoint. CRp and OR also evaluated
	Sensitivity analysis
	Time to remission from first dose
Relapse-free survival	Progression-free, from first dose of gemtuzumab ozogamicin
	Total duration, from maximum response (CR or CRp)
	Gemtuzumab ozogamicin relapse-free survival
	Gemtuzumab ozogamicin only relapse-free survival
Overall survival	Total survival duration, from first dose of gemtuzumab ozogamicin
	Landmark survival, from end of part I visit
Hematologic characteristics of response	
Time to clearance of bone marrow blast cells (≤5%)	Time from first dose of gemtuzumab ozogamicin, aspirates used
Bone marrow characteristics at final part I visit	% cellularity in bone marrow biopsy
	% blast cells in bone marrow aspirate and biopsy
Time to hematologic recovery[a]	Platelets, ANC, and hemoglobin recovery from final dose of gemtuzumab ozogamicin, and from first dose of gemtuzumab ozogamicin
Number of platelet transfusions[a]	During study part I
Number of RBC transfusions[a]	During study part I
Postremission therapy in second remission	
Number of patients receiving additional antileukemic therapy	HSCT and chemotherapy
Time to additional antileukemic therapy, from first dose of gemtuzumab ozogamicin	HSCT and chemotherapy
Post-HSCT survival	Relapse-free survival after HSCT
	Overall survival after HSCT
Hospitalization	
Hospitalizations during study part I[a]	Number of days of hospitalizations, number of hospitalizations, and time to hospitalizations

a: Data for time to hematologic recovery, number of platelet and RBC transfusions, and hospitalizations are presented only in sections 5.7.5, 5.7.6, and 5.7.7, respectively, with the safety data.

4.2.2 Criteria for Major Efficacy Endpoints

4.2.2.1 Remission Status

The remission status of the patients was initially evaluated at the final part I visit. All treatment decisions were based on pathology evaluations at the study site. The efficacy results in this report are based on pathology evaluations by an independent expert pathologist. The independent pathologist was blinded to the clinical data, to the identity of the patients, and to the sequence in time of each patient's slides.

4.2.2.2 Survival Estimates

Time-to-event data, such as duration of relapse-free survival and overall survival, were summarized by using Kaplan-Meier survival estimates or estimates from observed data. When there are sufficient data, Kaplan-Meier survival estimates are preferred because they are more precise in situations in which not all survival times are known exactly. The Kaplan-Meier estimates take into consideration events that have not occurred, whereas the observed estimates do not. Observed data were used when the number of patients was small and there were a large number of observations that were limited by the data cutoff period.

In some cases a median could not be calculated because of the large number of patients in the population that had not had the event being evaluated. In these cases, the median values are expressed as ">" (Kaplan-Meier estimates) or "≥" (observed data estimates). If the median could be calculated, the value was shown. In this document, references to "significance" refer to statistical significance at the α level of 0.05.

4.2.2.2.1 Relapse-Free Survival

Relapse-free survival (duration of remission) for patients in remission was evaluated in several ways and progression-free survival (event-free survival) was also evaluated. The dates used to calculate these parameters are shown in Table 14.

Table 14. MEASUREMENT DATES FOR PROGRESSION-FREE AND RELAPSE-FREE SURVIVAL

Relapse-Free Survival	From Date of	To Date of
Progression-free survival	First dose of gemtuzumab ozogamicin	Documentation of relapse, or death, followed until data cutoff
Total relapse-free survival	First documentation of maximum response (CR or CRp)	Documentation of relapse,[a] or death, followed until data cutoff
Gemtuzumab ozogamicin only relapse-free survival, for patients who never received additional antileukemic therapy (including HSCT)	First documentation of maximum response (CR or CRp)	Documentation of relapse, death, followed until data cutoff
Relapse-free survival after HSCT	HSCT (if patient was in remission on the date of HSCT)	Documentation of relapse, or death, followed until data cutoff

a: Date of relapse was the date of the pathology report or CBC showing leukemic blast recurrence in bone marrow or peripheral blood. If a patient missed a visit, it was assumed that the remission continued until the time when relapse was documented.

4.2.2.2.2 Overall Survival

Overall survival, regardless of remission or relapse status, was evaluated several ways (Table 15).

Table 15. MEASUREMENT DATES FOR OVERALL SURVIVAL

Type of Survival	From Date of	To Date of
Total survival	First dose of gemtuzumab ozogamicin	Death, or followed until data cutoff
Landmark survival	Final part I visit (approximately 28 days after the second or third dose of gemtuzumab ozogamicin)	Death, or followed until data cutoff
Survival after HSCT	HSCT	Death, or followed until data cutoff

4.3 Demographic and Other Baseline Characteristics Pertinent to Efficacy

Demographic characteristics for the 3 pooled study populations were shown in Tables 7 and 8. In addition, the baseline disease characteristics of patients based on their response to therapy are presented for the 3 pooled populations in Table 16.

CR and CRp patients were similar in age and had only a small difference in median duration of first remission (12.6 and 11.1 months, respectively). OR patients were slightly younger than NR patients (59.5 and 62.5 years, respectively), and OR patients had a slightly longer duration of first remission than NR patients (11.9 and 10.3 months, respectively).

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Table 16. BASELINE DISEASE CHARACTERISTICS FOR STUDIES 201/202/203

Characteristic	All Patients (n = 142)	CR (n = 23)	CRp (n = 19)	OR (n = 42)	NR (n = 100)
Age, years					
Mean (SD)	58.3 (14.6)	54.2 (17.1)	55.3 (15.4)	54.7 (16.1)	59.8 (13.7)
Median	61.0	60.0	59.0	59.5	62.5
Min – Max	22 - 84	22 - 77	26 - 75	22 - 77	24 - 84
Duration of first remission (before gemtuzumab ozogamicin), months					
Mean (SD)	14.9 (15.7)	15.7 (11.9)	12.1 (5.2)	14.1 (9.5)	15.3 (17.7)
Median	11.1	12.6	11.1	11.9	10.3
Min – Max	2 - 117	4 - 53	7 - 24	4 - 53	2 - 117
Postremission therapy (before gemtuzumab ozogamicin), n (%)					
No	9 (6)	2 (9)	1 (5)	3 (7)	6 (6)
Yes	133 (94)	21 (91)	18 (95)	39 (93)	94 (94)

Most patients (94%) had postremission therapy, indicating that they were treated aggressively (Table 16). There did not appear to be a relation between prior postremission therapy and response to gemtuzumab ozogamicin.

4.4 Efficacy Results for the Phase II Studies

4.4.1 Major Efficacy Endpoints

4.4.1.1 Remission

The data from 142 patients show that the remission rates with gemtuzumab ozogamicin were 32% in study 201, 33% in study 202, and 22% in study 203 (Table 17). The lower remission rate for the patients in study 203 was attributed to the older age and shorter duration of first remission of the patients in study 203 (see Table 8). The overall rate of remission in the 3 pooled studies was 30%.

Table 17. NUMBER (%) OF PATIENTS AND 95% CONFIDENCE INTERVAL (CI) BY REMISSION CATEGORY IN PHASE II STUDIES

Type of Remission	Study 201 (n = 65)	Study 202 (n = 40)	Study 203 (n = 37)	Studies 201/202/203 (n = 142)
CR, no. (%) of patients	11 (17)	8 (20)	4 (11)	23 (16)
95% CI	(9, 28)	(9, 36)	(3, 25)	(11, 23)
CRp, no. (%) of patients	10 (15)	5 (13)	4 (11)	19 (13)
95% CI	(8, 26)	(4, 27)	(3, 25)	(8, 20)
OR (CR + CRp), no. (%) of patients	21 (32)	13 (33)	8 (22)	42 (30)
95% CI	(21, 45)	(19, 49)	(10, 38)	(22, 38)

The median time to remission was 60 days for both patients with CRs (min – max, 38 - 239) and those with CRps (min – max, 43 - 150).

4.4.1.2 Relapse-Free Survival (Kaplan-Meier Estimates)

4.4.1.2.1 Total Relapse-Free Survival

Total relapse-free survival in the 3 pooled studies is shown in Figure 2. The median relapse-free survival was 216 days for the CR group and 132 days for the CRp group. The median relapse-free survival for the OR group was 203 days. As can be seen from the figure, the curves for the CR and CRp patient groups are similar. The differences between the CR and CRp groups were not statistically significant for relapse-free survival (p = 0.708).

Figure 2. TOTAL RELAPSE-FREE SURVIVAL FOR CRs AND CRps (MRs), 201/202/203.

LOGRANK P=0.708

Group	Total at Risk	Number at Risk/Number of Observed Events							
CR	23	14/9	11/1	3/4	1/0	1/0	1/0	0/0	8/0
MR	19	7/7	5/1	5/0	4/8	3/8	1/1	0/8	8/8
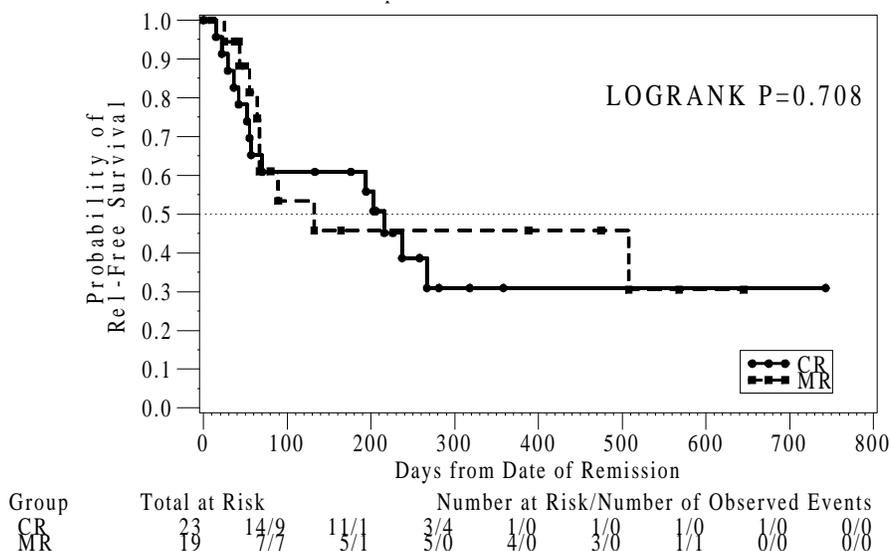
In the Kaplan-Meier graphs, the solid symbols not associated with a "step" represent observations limited by the data cutoff period. Patients who continued in the study beyond the upper limit of the x-axis are represented in the statistics below the graph, but are not shown graphically.
Rel-free survival = Relapse-free survival

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4.4.1.2.2 Relapse-Free Survival After Gemtuzumab Ozogamicin Only

Data were evaluated to determine relapse-free survival in patients who received gemtuzumab ozogamicin only and no other antileukemic treatment. Most patients who had second remissions with gemtuzumab ozogamicin received either an HSCT or other antileukemic therapy shortly after the remission and were excluded from this evaluation.

Of the 42 OR patients, 16 patients did not receive HSCT or additional antileukemic therapy up to the time of relapse or death (limited by the data cutoff date). For the OR patients, the median relapse-free survival was 132 days.

4.4.1.3 Overall Survival

As of the data cutoff date, 86 of the 142 patients in the 3 studies had died. Most of the deaths were attributable to progression of leukemia. The deaths are discussed in more detail in section 5.3.5.

4.4.1.3.1 Total Overall Survival

A Kaplan-Meier graph for total overall survival is shown in Figure 3. The median duration of total overall survival for the 142 patients in the 3 phase II studies was 177 days, based on Kaplan-Meier estimates. The probability of survival beyond 3, 6, and 12 months was 73%, 50%, and 31%, respectively.

Figure 3. TOTAL OVERALL SURVIVAL, ALL PATIENTS (201/202/203).

Group	Total at Risk	Number at Risk(Number of Observed Events)							
All	142	96 (42)	49 (28)	27 (9)	14 (5)	6 (2)	3 (0)	1 (0)	1 (0)
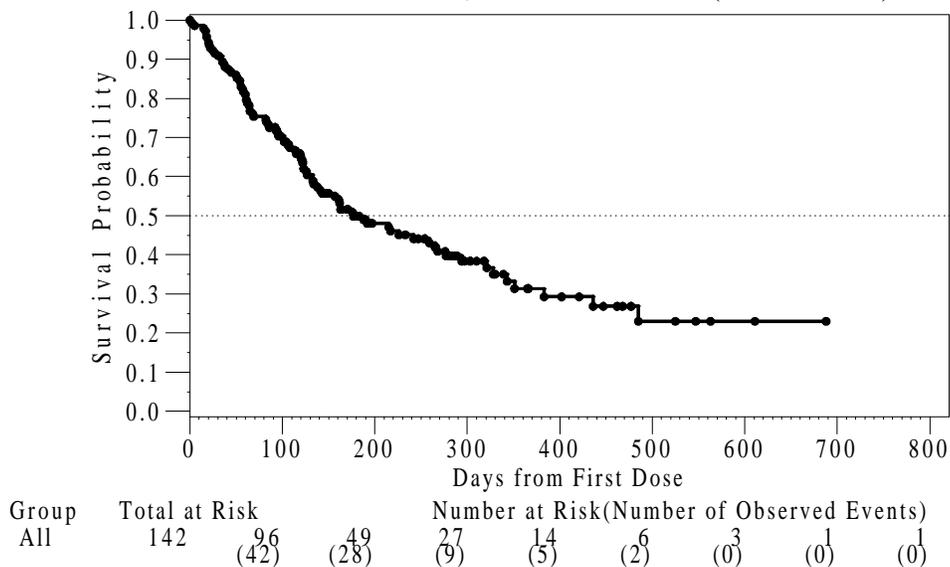
4.4.1.3.2 Landmark Survival (Kaplan-Meier Estimates)

A Kaplan-Meier graph for landmark survival in the 3 pooled studies is shown in Figure 4. As can be seen from the figure, the curves for the CR and CRp patient groups are similar.

Figure 4. LANDMARK SURVIVAL BY REMISSION STATUS, 201/202/203. (MR = CRp).

Group	Total at Risk	Number at Risk (Number of Observed Events)							
CR	23	20 (3)	17 (0)	5 (2)	3 (1)	2 (0)	1 (0)	1 (0)	0 (0)
MR	19	13 (1)	9 (3)	7 (1)	5 (1)	2 (0)	1 (0)	0 (0)	0 (0)
NR	63	26 (31)	14 (8)	5 (3)	2 (1)	0 (1)	0 (0)	0 (0)	0 (0)
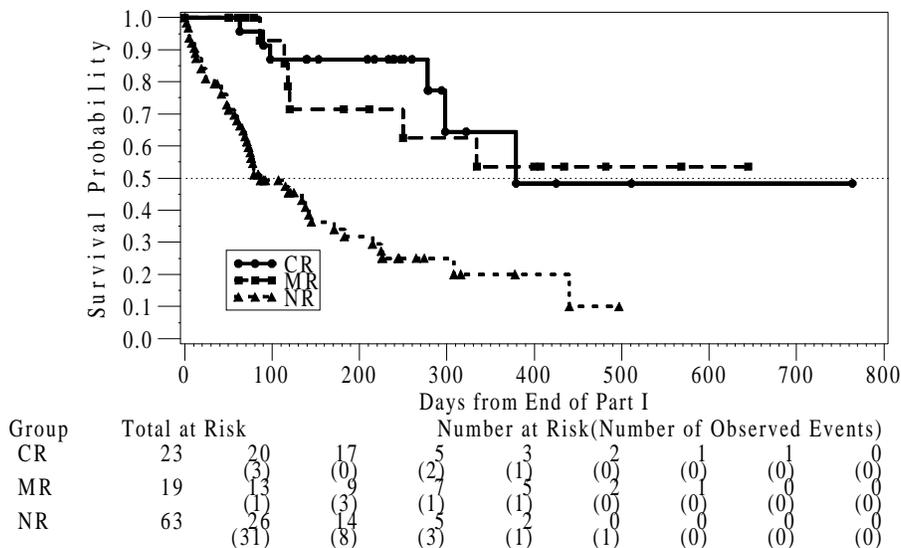
The median landmark survival values based on Kaplan-Meier estimates are summarized in Table 18. The median landmark survival was 379 days for the CR group. The CRp group had not reached the median as of the data cutoff date; the median landmark survival was more than 334 days for the CRp group. The OR median was more than 379 days. The NR patients had a median landmark survival of 87 days.

Table 18. LANDMARK SURVIVAL, KAPLAN-MEIER ESTIMATES (201/202/203)

Group	n	Kaplan-Meier Median (days)
All	105	225
CR	23	379
CRp	19	> 334
OR	42	> 379
NR	63	87

4.4.2 Hematologic Characteristics of Response

4.4.2.1 Time to Clearance of Blast Cells

Gemtuzumab ozogamicin produced a rapid clearance of aspirate bone marrow blast cells. For the 23 patients with CRs and 19 patients with CRps, the median time to blast cell clearance was 8 days after the last dose of gemtuzumab ozogamicin (medians are based on observed data, not Kaplan-Meier estimates).

4.4.2.2 Bone Marrow Characteristics at Final Part I Visit

The bone marrow cellularity data at the final part I visit (based on the independent pathologist's evaluation) show a median bone marrow cellularity of 50% for the OR patients (40% for CR patients and 50% for CRp patients), with values ranging from 5% to 70% (Table 19). These results suggest adequate marrow recovery at this point in the study for the CR and CRp patients.

Table 19. BONE MARROW CHARACTERISTICS AT FINAL PART I VISIT (201/202/203)

Variable, Statistic	All Patients	CR	CRp	OR	NR
Bone Marrow Aspirate					
n	94	19	19	38	56
Mean	34.2	0.7	1.1	0.9	56.8
SD	43.5	0.6	1.4	1.1	43.8
Median	2.0	1.0	1.0	1.0	75.0
Min - Max	0 - 100	0 - 2	0 - 5	0 - 5	0 - 100
95% CI	(12.5, 50)	(0.5, 1)	(0.5, 1.5)	(0.5, 1)	(50, 70)
95% CI for CRp-CR[a]	(-1, 1)				
Bone Marrow Biopsy					
n	81	22	18	40	41
Mean	13.7	0	0	0	27.1
SD	31.0	0	0	0	39.3
Median	0	0	0	0	0
Min - Max	0 - 100	0 - 0	0 - 0	0 - 0	0 - 100
95% CI	(0, 5)	(0, 0)	(0, 0)	(0, 0)	(5, 45)
95% CI for CRp-CR[a]	(0, 0)				
% Cellularity					
n	81	22	18	40	41
Mean	42.8	42.0	46.4	44.0	41.6
SD	18.2	13.9	15.7	14.7	21.3
Median	40	40	50	50	40
Min - Max	5 - 90	10 - 60	5 - 70	5 - 70	5 - 90
95% CI	(40, 45)	(35, 50)	(40, 55)	(40, 50)	(35, 50)
95% CI for CRp-CR[a]	(-5, 20)				

a: CI for the difference between CRp and CR.

The results from the bone marrow aspirate and biopsy samples taken at the final part I visit were used to categorize the remission status of patients. By definition, patients with CRs and CRps had to have ≤ 5% leukemic blast cells in the bone marrow. For the OR patients, the aspirate samples had from 0% to 5% blast cells and the biopsies all had 0% blast cells (Table 19).

4.4.2.3 Time to Hematologic Recovery (Platelets, ANC, and Hemoglobin)

Times to hematologic recovery are discussed in the safety section of this report (section 5.7.5).

4.4.2.4 Number of Platelet and RBC Transfusions

The number of platelet and RBC transfusions is discussed in the safety section of this report (section 5.7.6).

4.4.3 Postremission Therapy in Second Remission

4.4.3.1 Number of Patients Receiving Additional Antileukemic Therapy

Patients who were treated with gemtuzumab ozogamicin and then received additional treatment with another antileukemic therapy continued to be followed up. A higher percentage of patients who had CRs and CRps received HSCTs than did patients with NRs, thereby enhancing their likelihood of survival. Thirty-nine percent (39%) of patients with CRs and 37% of patients with CRps received HSCTs, whereas only 12% of the patients with NRs received HSCTs (Table 20). The difference between the OR and NR groups was statistically significant (Fisher's 2-sided exact test, $p = 0.002$).

Table 20. NUMBER (%) OF PATIENTS RECEIVING ADDITIONAL THERAPY AFTER
GEMTUZUMAB OZOGAMICIN, BY RESPONSE CATEGORY (201/202/203)

Group	Total Transplantations	Total Antileukemic Therapy Other Than Transplantations
All patients, n/total (%)	28/142 (20)	58/142 (41)
95% CI	(17, 31)	(31, 48)
CR, n/total (%)	9[a]/23 (39)	10/23 (43)
95% CI	(23, 66)	(23, 66)
CRp, n/total (%)	7/19 (37)	3/19 (16)
95% CI	(17, 64)	(4, 41)
OR, n/total (%)	16[a]/42 (38)	13/42 (31)
95% CI	(26, 58)	(18, 48)
NR, n/total (%)	12/100 (12)	45/100 (45)
95% CI	(9, 24)	(33, 53)

a: Includes 1 additional patient (201B0-0003) who had a relapse on 25 Jan 1999 and afterwards received a transplantation on 29 Mar 1999.

After gemtuzumab ozogamicin treatment, patients in the phase II studies were given a variety of additional antileukemic treatments with different dosage regimens. Preparative therapy for HSCT was not included as additional antileukemic therapy but was considered as part of HSCT. A summary of the number of patients who received additional antileukemic therapy in the pooled studies is also provided in Table 20.

The results show that 41% of patients received additional antileukemic therapy; this included 31% of OR patients (43% CR and 16% CRp) and 45% of the patients with NR. A 2-sided Fisher's exact test was used to compare CR and CRp with respect to the proportion of patients receiving other antileukemic therapy; there was no significant difference between these 2 remission groups (p = 0.093). The results from Table 20 indicate that the patients with and without remissions were being treated similarly with regard to the administration of additional antileukemic therapy other than HSCT.

4.4.3.2 Time to Additional Antileukemic Therapy

The Kaplan-Meier estimates of the median time to additional therapy (from the time of the first dose of gemtuzumab ozogamicin) were 106 days and 91 days for the CR and CRp patients, respectively, and 91 days for the overall group (OR patients). Among the NR patients, the median time to additional therapy was 69 days.

4.4.3.3 Survival After HSCT in Second Remission

The number of patients who had remissions and then HSCTs was relatively small; therefore, the observed data for relapse-free survival and overall survival after HSCT are presented below instead of data from Kaplan-Meier plots.

4.4.3.3.1 Relapse-Free Survival After HSCT (Observed Data)

Figure 5 shows the duration of relapse-free survival after HSCT for the patients with CRs and CRps in the 3 pooled studies (201/202/203.) Relapse-free survival after HSCT was similar for the CR and CRp patients.

Figure 5. SCATTERPLOT FOR DURATION OF RELAPSE-FREE SURVIVAL AFTER HSCT, 201/202/203. Open triangles represent patients who were in remission as of the cutoff date. Solid dots represent patients who relapsed or died. (MR = CRp).
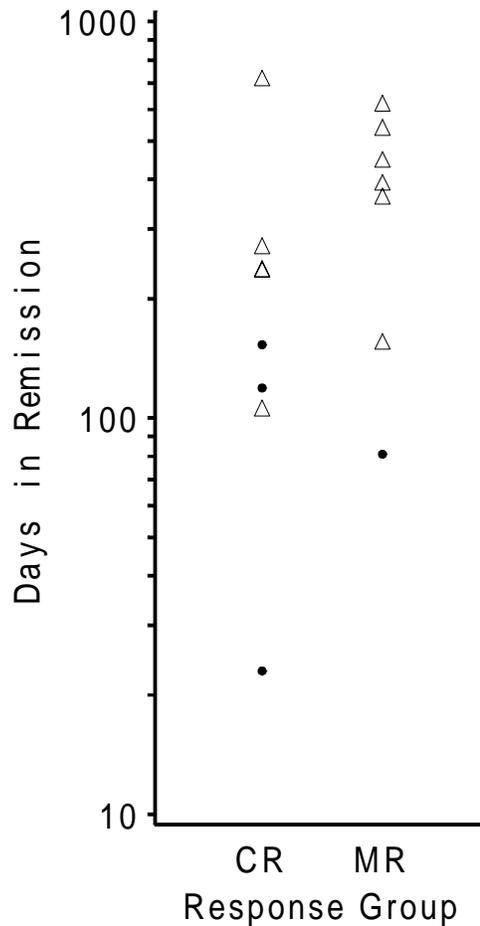
Of the 4 patients who died after HSCT, 3 (2 CRs and 1CRp) died due to disease progression, and 1 CR patient died of VOD 23 days after HSCT. The median number of days of post-HSCT relapse-free survival was at least 195 days for the 8 CR patients and at least 393 days for the 7 CRp patients who had HSCTs (Table 21). The duration of post-HSCT relapse-free survival ranged from 23 to 721 days in the CR patients and from 81 to 623 days in the CRp patients.

Table 21. RELAPSE-FREE SURVIVAL AFTER HSCT (201/202/203)

Remission Group	n	Median (days)[a]	Minimum (days)	Maximum (days)
CR	8[b]	≥ 195.0	23	721
CRp	7	≥ 393.0	81	623
OR	15	≥ 238.0	23	721

a: Medians are of the observed data and are not Kaplan-Meier estimates.
b: One (1) additional patient (201B0-0003) had a relapse on 25 Jan 1999 and afterwards received a transplantation on 29 Mar 1999.

At 100 Days post-HSCT, 7 of 8 (88%) CR patients were alive, 6 of 7 (86%) CRp patients were alive, and 5 of 12 (42%) NR patients were alive. The CR patient who relapsed prior to HSCT was excluded from these calculations.

4.4.3.3.2 Overall Survival After HSCT (Observed Data)

Figure 6 shows the duration of overall survival after HSCT for the patients with CRs, CRps, and NRs in the 3 pooled studies (201/202/203.) The scatterplot demonstrates the similarity of the duration of survival after HSCT for the CR and CRp patients.

Figure 6. SCATTERPLOT OF SURVIVAL AFTER HSCT FOR PATIENTS WITH CR, CRp (MR), AND NR, 201/202/203. Open triangles represent patients who were alive as of the cutoff date. Solid dots represent patients who died.
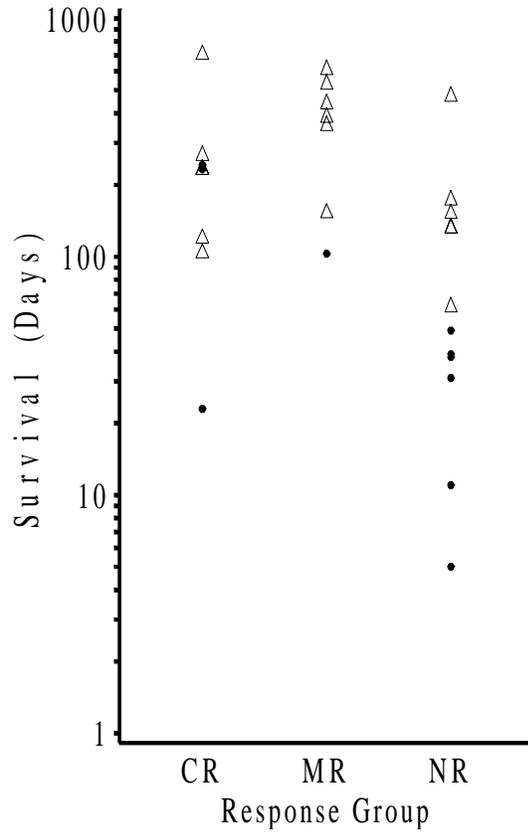
Survival after HSCT is summarized in Table 22. The median number of days of post-HSCT survival was at least 240.5 days among the OR patients (at least 237 days for CRs and at least 393 days for CRps). The maximum duration of survival after HSCT was 721 days for the OR patients. As of the data cutoff date, 4 (3 CRs and 1 CRp) of the patients who had remissions and received HSCTs had died (see section 4.4.3.3.1).

Table 22. OVERALL SURVIVAL AFTER HSCT (201/202/203)

Group	n	Median (days)[a]	Minimum (days)	Maximum (days)
All patients	28	$\geq$ 155.5	5	721
CR	9[b]	$\geq$ 237.0	23	721
CRp	7	$\geq$ 393.0	103	623
OR	16	$\geq$ 240.5	23	721
NR	12	$\geq$ 56.0	5	482

a: Medians are of the observed data and are not Kaplan-Meier estimates.
b: One (1) patient (201B0-0003) had a relapse on 25 Jan 1999 and
     afterwards received a transplantation on 29 Mar 1999.

Survival after HSCT was more limited for patients with NR than it was for the OR patients. Among the patients with NRs, the median number of days of survival after HSCT was at least 56 days, and the maximum duration of survival after HSCT was 482 days.

4.4.4 Hospitalizations

A summary of the number of days of hospitalizations, number of hospitalizations, and time to hospitalizations during part I of the studies is provided in the safety section of this update (section 5.7.7). The results are presented by remission status.

4.5 Evaluation of Major Efficacy Endpoints By Subgroups

Evaluations of efficacy assessments based on subsets by age group, sex, and ethnic origin are presented for the pooled data from all 3 phase II studies. The age categories were < 60 and $\geq$ 60 years old. For the category ethnic origin, most of the patients were white. The subset evaluations were done for the major efficacy endpoints.

4.5.1 Rates of Remission by Subgroups

Table 23 shows the rates of remission by age group, sex, ethnic origin (white), and duration of first remission (< 12 and $\geq$ 12 months) in the 3 pooled phase II studies.

For patients < 60 years old, the OR rate was 34%. Among patients $\geq$ 60 years old, the OR rate was 26%. The fact that the differences between the patients < 60 years old and $\geq$ 60 years old were small suggests that both younger and older patients with AML in first relapse respond to gemtuzumab ozogamicin therapy.

The rates of CR and CRp for women and men were similar; overall, 31% of the women and 29% of the men had remissions (Table 23).

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Table 23. RATES OF REMISSION IN POOLED PHASE II STUDIES (201/202/203)
BY SUBGROUPS: NUMBER (%) OF PATIENTS AND 95% CI

Category	Response Group	n/Total (%)	(95% CI)
Age < 60 years old	CR	11/62 (18)	(9, 30)
	CRp	10/62 (16)	(8, 28)
	OR	21/62 (34)	(22, 47)
Age ≥ 60 years old	CR	12/80 (15)	(8, 25)
	CRp	9/80 (11)	(5, 20)
	OR	21/80 (26)	(17, 37)
Women	CR	10/58 (17)	(9, 29)
	CRp	8/58 (14)	(6, 25)
	OR	18/58 (31)	(20, 45)
Men	CR	13/84 (15)	(9, 25)
	CRp	11/84 (13)	(7, 22)
	OR	24/84 (29)	(19, 39)
Ethnic origin, white	CR	23/133 (17)	(11, 25)
	CRp	19/133 (14)	(9, 21)
	OR	42/133 (32)	(24, 40)
Duration of first remission < 12 months	CR	10/80 (13)	(6, 22)
	CRp	12/80 (15)	(8, 25
	OR	22/80 (28)	(18, 39)
Duration of first remission ≥ 12 months	CR	13/62 (21)	(12, 33)
	CRp	7/62 (11)	(5, 22)
	OR	20/62 (32)	(21, 45)
Duration of first remission ≥ 6 months	CR	22/128 (17)	(11, 25)
	CRp	19/128 (15)	(5, 22)
	OR	41/128 (32)	(24, 41)

For the category ethnic origin, 94% of the patients were white and 6% were nonwhite (Table 23). All of the 42 patients who had CRs or CRps were white. None of the 9 nonwhite patients had remissions as of the data cutoff date. This difference may be due to the small size of the non-white patient population enrolled.

The rates of second remission with gemtuzumab ozogamicin were also evaluated by duration of first remission (Table 23). For patients who had a duration of first remission < 1 year, the OR rate was 28%. Among patients who had a duration of first remission ≥ 1 year, the OR rate was 32%. The fact that the overall differences were small suggests that relapsed

AML patients with a duration of first remission of < 1 year and ≥ 1 year have similar response rates with gemtuzumab ozogamicin.

4.5.2 Relapse-Free Survival by Subgroups (Kaplan-Meier Estimates)

Figures 7 through 10 show Kaplan-Meier graphs of relapse-free survival by age group, sex, ethnic origin (white), and duration of first remission (< 12 and ≥ 12 months). There were no statistically significant differences between the CR and CRp groups.

Figure 7. RELAPSE-FREE SURVIVAL BY AGE GROUP, PATIENTS < 60 YEARS OLD AND ≥ 60 YEARS OLD. (MR = CRp)

Age: < 60

LOGRANK P=0.698

Group	Total at Risk							
		Number at Risk(Number of Observed Events)						
CR	11	7 (4)	5 (0)	2 (1)	1 (0)	1 (0)	1 (0)	1 (0)	0 (0)
MR	10	6 (2)	5 (1)	5 (0)	4 (0)	3 (0)	1 (1)	0 (0)	0 (0)

Age: ≥ 60

LOGRANK P=0.4

Group	Total at Risk							
		Number at Risk(Number of Observed Events)						
CR	12	7 (5)	6 (1)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MR	9	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
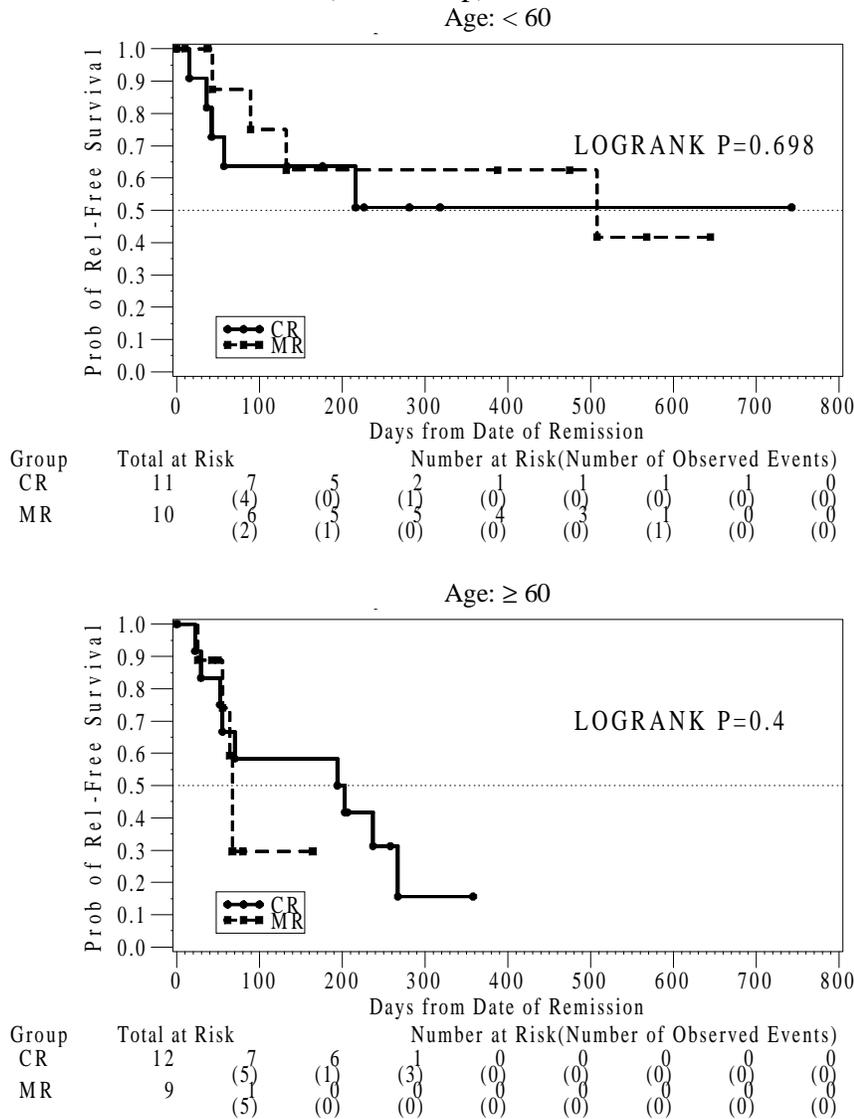
Figure 8. RELAPSE-FREE SURVIVAL BY SEX. (MR = CRp)

Sex: Female

LOGRANK P=0.411

Group	Total at Risk			Number at Risk(Number of Observed Events)					
CR	10	5	4	2	0	0	0	0	0
		(5)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
MR	8	4	3	3	2	2	0	0	0
		(2)	(1)	(0)	(0)	(0)	(1)	(0)	(0)

Sex: Male

LOGRANK P=0.948

Group	Total at Risk			Number at Risk(Number of Observed Events)					
CR	13	9	7	1	1	1	1	1	0
		(4)	(1)	(3)	(0)	(0)	(0)	(0)	(0)
MR	11	3	2	2	2	1	1	0	0
		(5)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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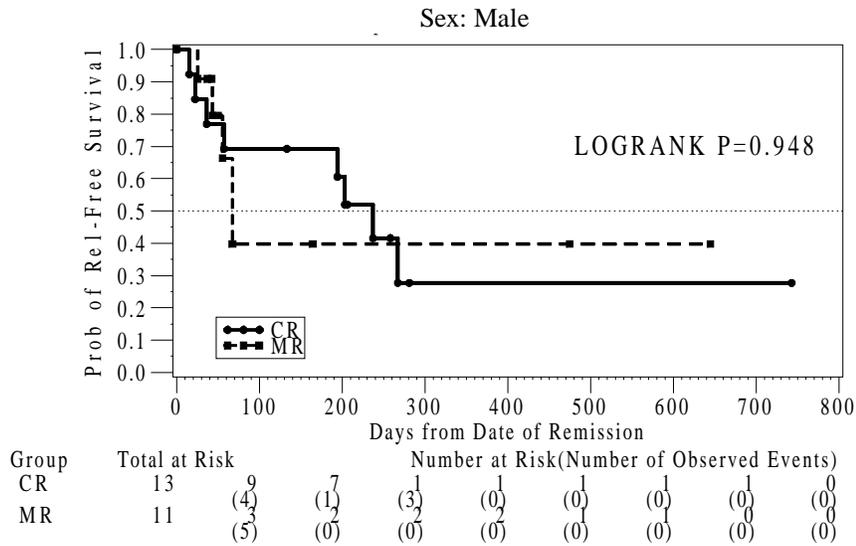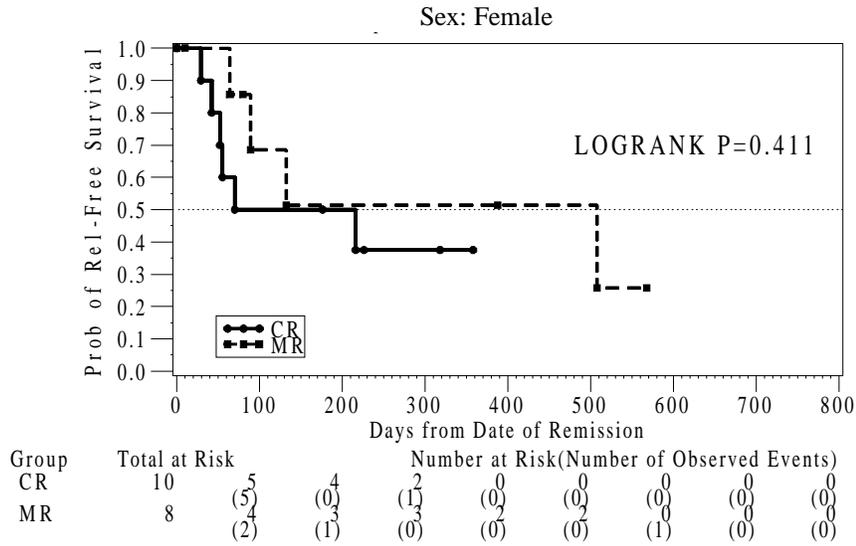
Figure 9. RELAPSE-FREE SURVIVAL BY ETHNIC ORIGIN, WHITE.
(MR = CRp)

Group	Total at Risk			Number at Risk(Number of Observed Events)					
CR	23	14	11	3	1	1	1	1	0
		(9)	(1)	(4)	(0)	(0)	(0)	(0)	(0)
MR	19	7	5	5	4	3	1	0	0
		(7)	(1)	(0)	(0)	(0)	(1)	(0)	(0)

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Figure 10. RELAPSE-FREE SURVIVAL FOR PATIENTS WHOSE DURATION OF FIRST REMISSION WAS < 12 MONTHS AND ≥ 12 MONTHS. (MR = CRp)

Duration of first remission: < 12 months

LOGRANK P=0.669

Group	Total at Risk	Number at Risk (Number of Observed Events)							
CR	10	6 (4)	5 (1)	1 (2)	1 (0)	1 (0)	1 (0)	1 (0)	0 (0)
MR	12	4 (6)	3 (0)	3 (0)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Duration of first remission: ≥ 12 months

LOGRANK P=0.578

Group	Total at Risk	Number at Risk (Number of Observed Events)							
CR	13	8 (5)	6 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MR	7	3 (1)	2 (1)	2 (0)	2 (0)	1 (0)	0 (0)	0 (0)	0 (0)
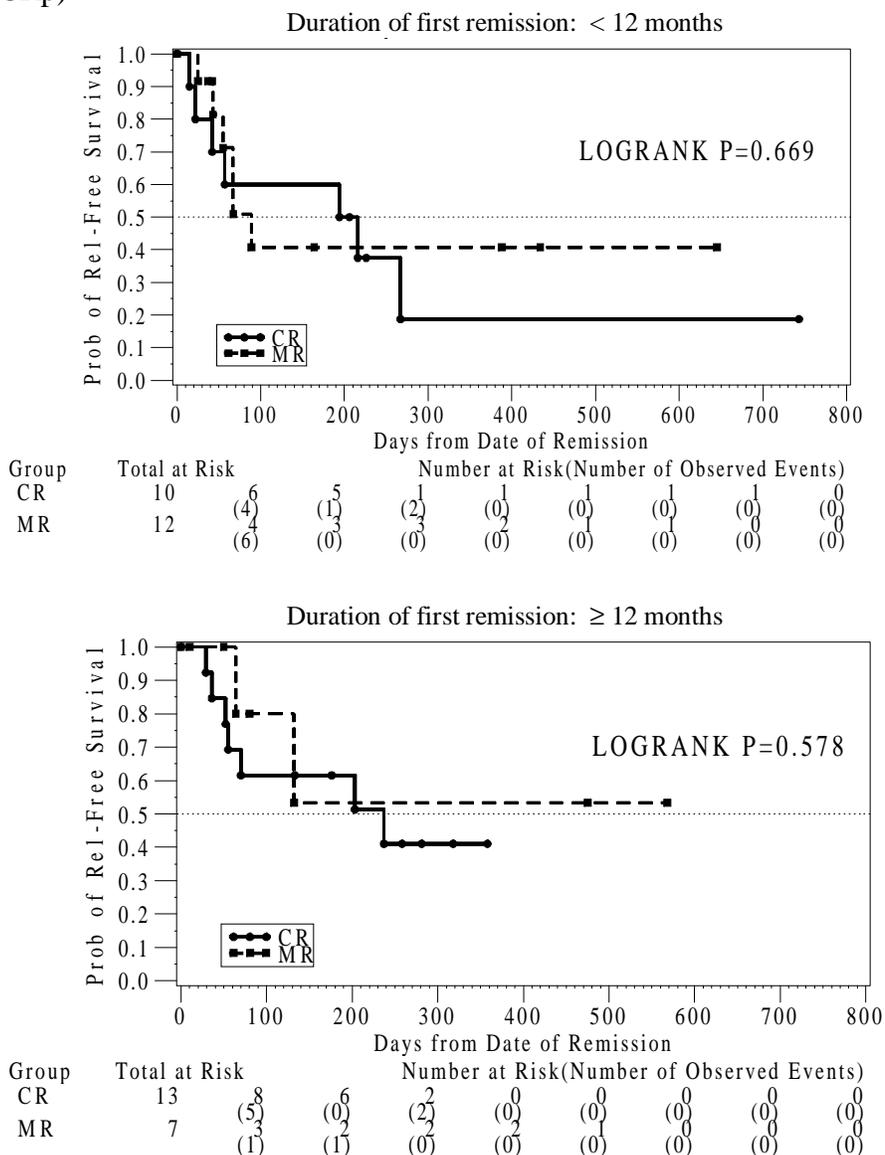
4.5.3 Overall Survival by Subgroups (Kaplan-Meier Estimates)

4.5.3.1 Total Overall Survival

Total overall survival for patients < 60 years old was similar to that for patients ≥ 60 year old (Figure 11). The median survival was 176 days for patients < 60 years old and was 188 days for those ≥ 60 years old. The differences in the total overall survival

distribution between the patients < 60 years old and those ≥ 60 years old were not significant (p = 0.399).

Figure 11. TOTAL OVERALL SURVIVAL, ALL PATIENTS IN 3 POOLED STUDIES BY AGE GROUP (< 60 YEARS AND ≥ 60 YEARS).

Group	Total at Risk			Number at Risk(Number of Observed Events)					
<60	62	43 (17)	25 (13)	12 (4)	8 (1)	5 (1)	3 (0)	1 (0)	1 (0)
>=60	80	53 (25)	24 (15)	15 (5)	6 (4)	1 (1)	0 (0)	0 (0)	0 (0)
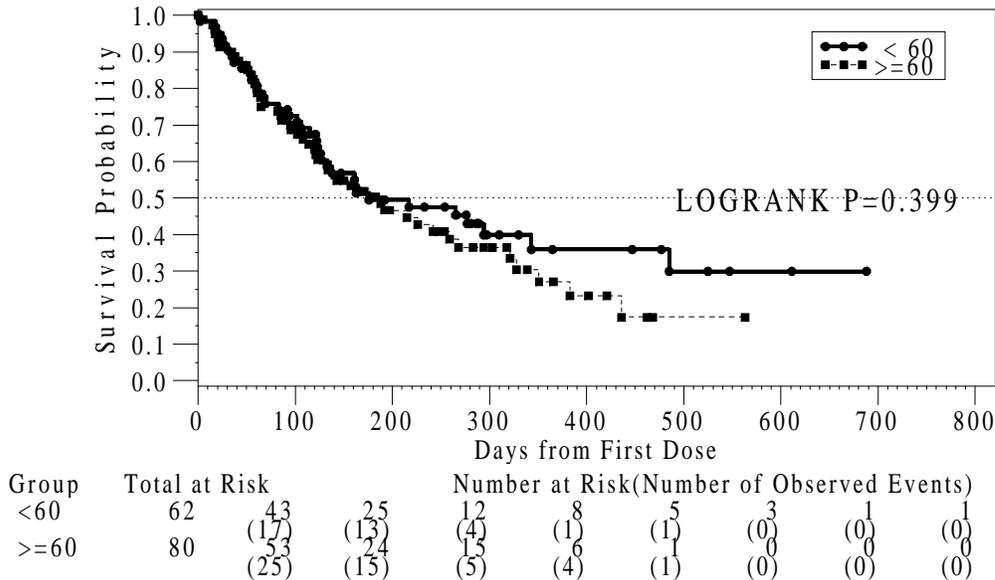
Total overall survival was similar for women and men (Figure 12).

Figure 12. TOTAL OVERALL SURVIVAL, ALL PATIENTS IN 3 POOLED STUDIES BY SEX.

Group	Total at Risk			Number at Risk(Number of Observed Events)					
F	58	39 (16)	20 (14)	13 (1)	5 (3)	1 (1)	1 (0)	0 (0)	0 (0)
M	84	57 (26)	29 (14)	14 (8)	5 (2)	1 (1)	2 (0)	1 (0)	0 (0)

46
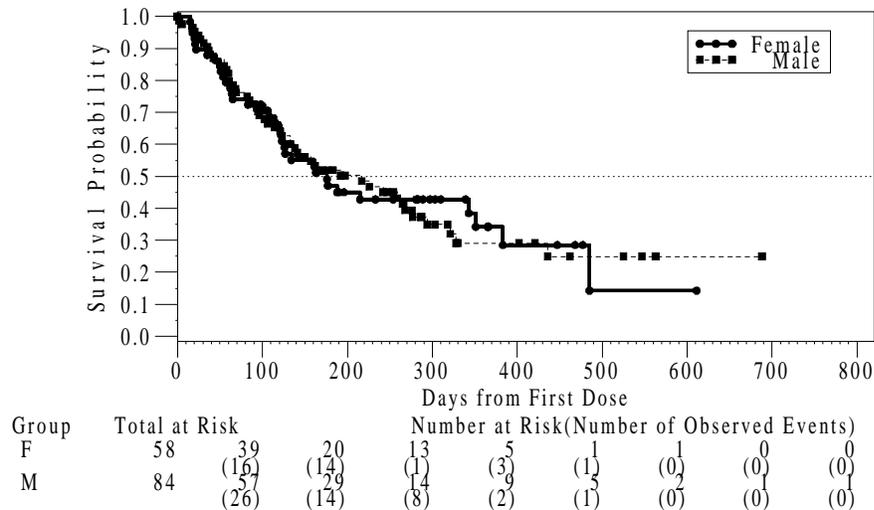
Total overall survival for all 142 patients who received gemtuzumab ozogamicin was also evaluated by duration of first remission (Figure 13). For patients who had a duration of first remission that was < 1 year, the median survival was 143 days (min - max, 15 - 808). Patients who had a duration of first remission that was ≥ 1 year had a median survival of 351 days (min - max, 2 - 611). There was a significant difference in the total overall survival distribution between the patients who had a duration of first remission that was < 1 year and those who had a duration of first remission that was ≥ 1 year (p = 0.011).

Figure 13. TOTAL OVERALL SURVIVAL, ALL PATIENTS IN 3 POOLED STUDIES BY DURATION OF FIRST REMISSION (< 1 YEAR AND ≥ 1 YEAR).

Group	Total at Risk	Number at Risk(Number of Observed Events)							
< 12	80	53 (25)	21 (22)	9 (6)	6 (2)	2 (1)	2 (0)	1 (0)	0 (0)
>=12	62	43 (17)	28 (6)	18 (3)	8 (3)	4 (1)	1 (0)	0 (0)	0 (0)
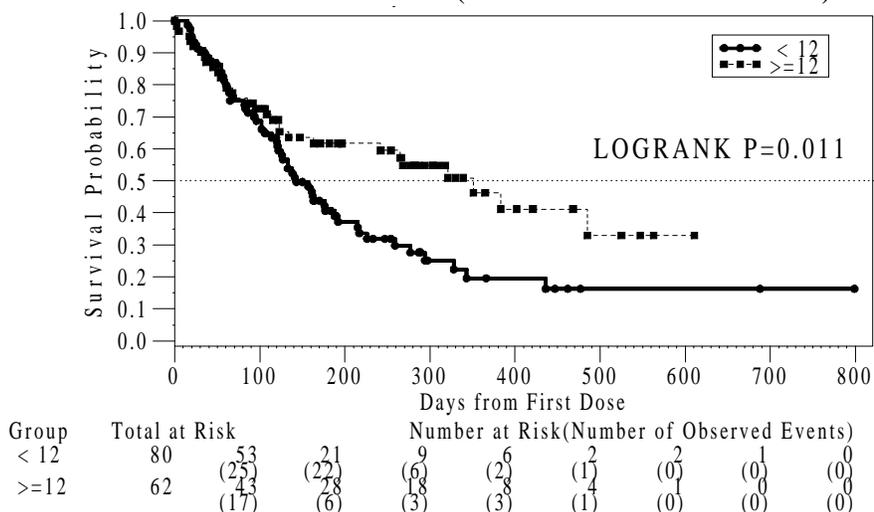
4.5.3.2 Landmark Survival by Subgroups

A Kaplan-Meier graph of landmark survival for all patients by age group is shown in Figure 14. The median survival was 250 days for patients < 60 years old and 145 days for the patients ≥ 60 years old. The differences in the landmark survival distribution between the patients < 60 years old and those ≥ 60 years old were not significant (p = 0.194).

Figure 14. LANDMARK SURVIVAL, ALL PATIENTS IN 3 POOLED STUDIES BY AGE GROUP (< 60 YEARS AND ≥ 60 YEARS).
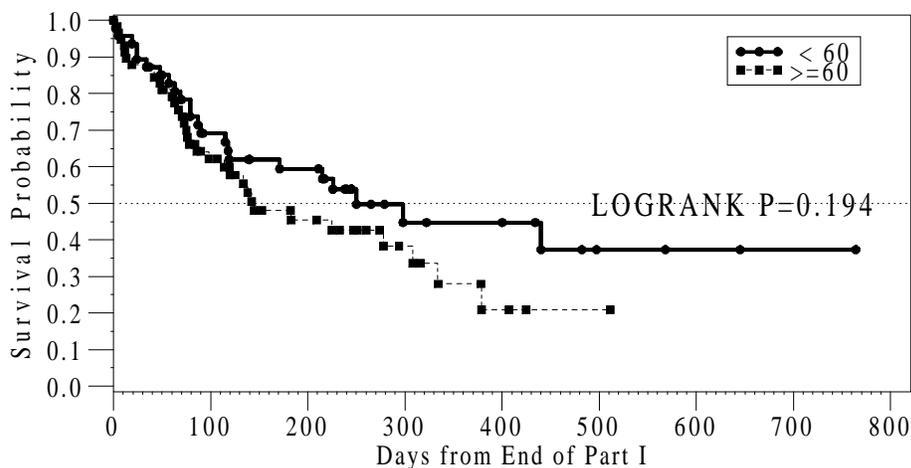
Group	Total at Risk		Number at Risk(Number of Observed Events)					
<60	47	29 (14)	23 (4)	9 (4)	7 (0)	3 (1)	2 (0)	1 (0)	0 (0)
>=60	58	30 (21)	17 (7)	8 (2)	3 (3)	1 (0)	0 (0)	0 (0)	0 (0)

A Kaplan-Meier graph of landmark survival for all patients by sex is shown in Figure 15. The median survival was 298 days for women and 215 days for men.

Figure 15. LANDMARK SURVIVAL, ALL PATIENTS IN 3 POOLED STUDIES BY SEX.
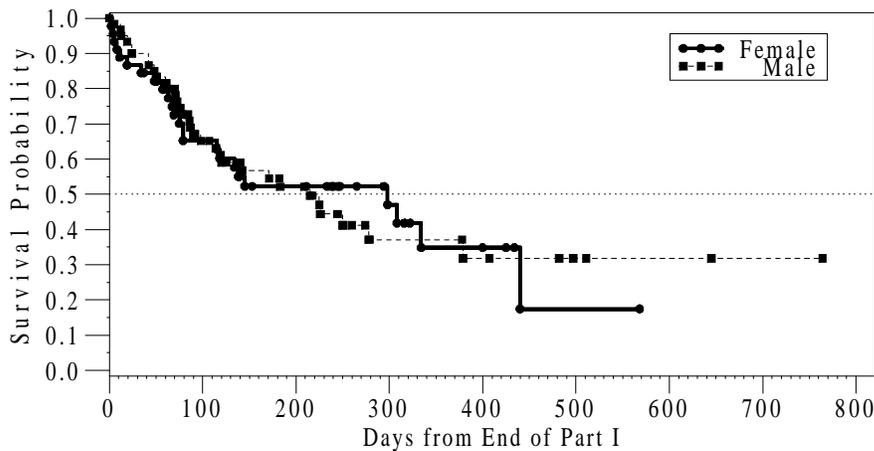
Group	Total at Risk		Number at Risk(Number of Observed Events)					
F	45	26 (15)	18 (5)	9 (1)	4 (2)	1 (1)	0 (0)	0 (0)	0 (0)
M	60	33 (20)	22 (6)	8 (5)	6 (1)	3 (0)	2 (0)	1 (0)	0 (0)

Landmark survival was also evaluated by duration of first remission (Figure 16). For patients who had a duration of first remission that was < 1 year, the median landmark survival was 134 days (min - max, 2 - 764). Patients who had a duration of first remission that was ≥ 1 year had a median survival of 440 days (min - max, 5 - 568). There was a significant difference in the landmark survival distribution between the patients who had a duration of first remission that was < 1 year and those who had a duration of first remission that was ≥ 1 year (p = 0.012).

Figure 16. LANDMARK SURVIVAL, ALL PATIENTS IN 3 POOLED STUDIES BY DURATION OF FIRST REMISSION (< 1 YEAR AND ≥ 1 YEAR).

Group	Total at Risk	Number at Risk(Number of Observed Events)							
< 12	57	29 (22)	15 (10)	7 (4)	4 (1)	2 (0)	2 (0)	1 (0)	0 (0)
>=12	48	30 (13)	25 (1)	10 (2)	6 (2)	2 (1)	0 (0)	0 (0)	0 (0)
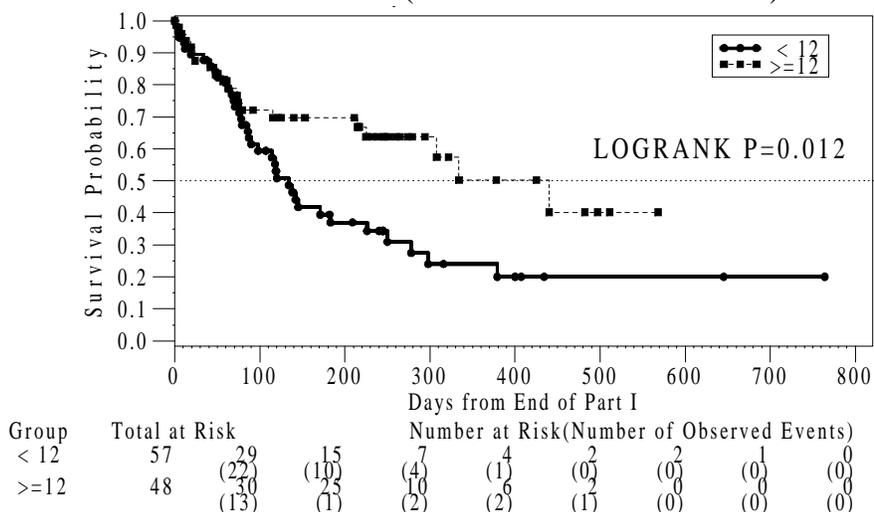
4.6 Summary and Conclusions of Efficacy Results

4.6.1 CRp Clinically Comparable With CR

The emerging clinical profile indicates that CRps are clinically comparable with CRs, thereby justifying the use of OR (CR + CRp) for gemtuzumab ozogamicin efficacy assessments. By definition, to be classified as having a CRp, patients had to meet all the criteria for CR except recovery to 100,000 platelets/μL. This single difference in criteria did not appear to produce any clinically meaningful differences in the clinical outcome of CR and CRp patients.

The patients with CRp were clinically comparable with CR patients in relapse-free survival and landmark survival. The median total relapse-free survival based on the Kaplan-Meier estimate was 216 days for the CR group and 132 days for the CRp group.

The differences between the CR and CRp groups were not statistically significant. The median landmark survival was 379 days for the CR group and more than 334 days for the CRp group. In contrast, the NR patients had a median landmark survival of 87 days.

Patients with CRs and CRps were treated similarly as measured by the rates of administration of HSCT and additional antileukemic therapy after gemtuzumab ozogamicin treatment. Nine (9, 39%) of the 23 CR patients and 7 (37%) of the 19 CRp patients received HSCT. Also, 10 (43%) of the CR patients and 3 (16%) of the CRp patients received additional antileukemic therapy; the difference between the CR and CRp groups was not statistically significant.

Based on the observed data, relapse-free survival and overall survival after HSCT were similar for patients with CRs and those with CRps. The median number of days of post-HSCT relapse-free survival was at least 195 days for the 8 CR patients and at least 393 days for the 7 CRp patients who had HSCTs (Table 21). The duration of post-HSCT relapse-free survival ranged from 23 to 721 days for the CR patients and from 81 to 623 days for the CRp patients. For overall post-HSCT survival, the median was at least 237 days for the patients with CRs and was at least 393 days for the patients with CRps. However, for the 12 NR patients who received HSCTs, the median post-HSCT survival was at least 56 days.

4.6.2 Overall Efficacy Results

As discussed in the previous section, the efficacy assessments indicated that the clinical profiles of patients with CRs and those with CRps were clinically comparable, thereby justifying the use of OR (CR + CRp) for gemtuzumab ozogamicin efficacy assessments. The OR rate for gemtuzumab ozogamicin was 30%. This remission rate is comparable with rates after conventional therapy in trials with other agents in similar patient populations (see section 7.3).

The 2 known prognostic factors for AML in first relapse, duration of first remission and age, were considered when evaluating the responses of patients to gemtuzumab ozogamicin. The median duration of first remission for all patients was 11.1 months. The rates of second remission (OR) were 28% and 32% for patients who had durations of first remission of < 1 year and ≥ 1 year, respectively. The fact that the differences were small suggests that response rates with gemtuzumab ozogamicin for relapsed AML patients with a

duration of first remission of < 1 year were similar to those for patients with a duration of first remission ≥ 1 year.

The median age was 61 years in the gemtuzumab ozogamicin studies. The OR rate in the 62 patients < 60 years old was 34%, while the OR rate in the 80 patients ≥ 60 years old was 26%. AML patients ≥ 60 years old are a distinct subset of AML patients. They have lower response rates to conventional antileukemic therapies; these lower response rates are associated with decreased survival rates. Thus the observation of only a modestly lower remission rate in older patients is clinically important in that it suggests that gemtuzumab ozogamicin is a useful agent in this population.

The median relapse-free survival was 203 days. Based on the observed data for the OR patients, the median number of days of post-HSCT relapse-free survival was at least 238 days.

Total overall survival for all 142 patients in the 3 phase II studies was evaluated by using Kaplan-Meier estimates. The median duration of total overall survival for the 142 patients was 177 days. The probability of survival beyond 3, 6, and 12 months was 73%, 50%, and 31%, respectively.

5. SAFETY

5.1 Organization of the Safety Sections

The key features of the safety sections are:

1. Combined data from studies 201, 202, and 203 are presented.

2. There is an emphasis on clinically important adverse events, including infusion-related adverse events, mucositis, myelosuppression, bleeding, infection, liver function abnormalities, and tumor lysis syndrome.

3. There is emphasis on laboratory parameters that are suspected to be affected by gemtuzumab ozogamicin, eg, hematologic variables (ANC, WBC counts, and platelet counts), liver function, and other parameters relevant to the particular patient population.

4. A separate safety analysis by treatment outcome is provided.

5.2 Summary of Safety Findings

Information is provided on the demographics of the patient population, the exposure to gemtuzumab ozogamicin, the frequency and type of treatment-emergent adverse events (TEAEs), serious adverse events and deaths, discontinuations, laboratory test results, and vital signs. The safety data were also examined to determine if there were any age- or sex-related changes in the safety profile of gemtuzumab ozogamicin.

Safety data from the 3 open-label phase II studies demonstrate the following:

- The safety profile of gemtuzumab ozogamicin is comparable in CR and CRp patients.
  Although CRp patients had slower platelet recovery and required more platelet and RBC transfusions than CR patients (sections 5.7.5 and 5.7.6), they became transfusion-independent like the CRs, and there were no clinically meaningful differences in safety data including bleeding.
- The safety profile is similar to that of conventional chemotherapies (section 7.4) 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 because of both short outpatient infusion and decreased need for in-hospital supportive care.

Only mild and reversible nausea and vomiting.

No alopecia.

- 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 and without clinical sequelae.

- Transient and reversible liver function test abnormalities occurred with moderate incidence.

- There were no unexpected adverse events in patients who received HSCT after gemtuzumab ozogamicin therapy.

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

5.3 Adverse Events

All adverse events were reported for part I of studies 201/202/203. During part II, only serious adverse events were reported. The severity of the adverse events was determined by using the NCI toxicity rating scale (version 1). Patients who discontinued treatment during part I continued to be followed for safety for 28 days after their last dose of gemtuzumab ozogamicin. Adverse events reported during this 28-day period were included in the database.

5.3.1 Treatment-Emergent Adverse Events

Table 24 shows common treatment-emergent adverse events (TEAEs) occurring in at least 10% of patients during part I of studies 201/202/203, for patients who received at least 1 dose of gemtuzumab ozogamicin.

Table 24. COMMONLY REPORTED (≥ 10%) TEAEs DURING PART I:
NUMBER (%) OF PATIENTS

Body System Adverse Event[a]	(n = 142)
Body as a whole	
Abdominal pain	52 (37)
Asthenia	63 (44)
Back pain	22 (15)
Chest pain	12 (8)
Chills	104 (73)
Fever	121 (85)
Headache	50 (35)
Infection	11 (8)
Neutropenic fever	30 (21)
Pain	30 (21)
Sepsis	36 (25)
Cardiovascular system	
Hemorrhage	14 (10)
Hypertension	29 (20)
Hypotension	28 (20)
Tachycardia	15 (11)
Digestive system	
Anorexia	41 (29)
Constipation	36 (25)
Diarrhea	54 (38)
Dyspepsia	16 (11)
Gum hemorrhage	13 (9)
Liver function tests abnormal	35 (25)
Nausea	100 (70)
Stomatitis	45 (32)
Vomiting	89 (63)
Hemic and lymphatic system	
Anemia	35 (25)
Ecchymosis	18 (13)
Leukopenia	76 (54)
Petechiae	28 (20)
Thrombocytopenia	84 (59)
Metabolic and nutritional	
Bilirubinemia	22 (15)
Hypokalemia	44 (31)
Hypomagnesemia	14 (10)
Hypophosphatemia	13 (9)
Lactic dehydrogenase increased	19 (13)
Peripheral edema	23 (16)
Nervous system	
Depression	13 (9)
Dizziness	22 (15)
Insomnia	22 (15)
Respiratory system	
Cough increased	28 (20)
Dyspnea	46 (32)
Epistaxis	44 (31)
Pharyngitis	20 (14)
Pleural effusion	10 (7)
Pneumonia	14 (10)

Table 24. COMMONLY REPORTED (≥ 10%) TEAEs DURING PART I:
NUMBER (%) OF PATIENTS

Body System Adverse Event[a]	(n = 142)
Pulmonary physical finding	16 (11)
Rhinitis	14 (10)
Skin and appendages	
Herpes simplex	31 (22)
Rash	31 (22)
Study event assoc. w. misc. factors	
Local reaction to procedure	35 (25)
Urogenital system	
Hematuria	14 (10)
Vaginal hemorrhage	7 (12)

a: Percentages for sex-specific adverse events are based on the number of patients of
     the relevant sex.

The most common TEAEs reported during part I for the 142 patients in studies
201/202/203 were fever (85%), chills (73%), nausea (70%), vomiting (63%),
thrombocytopenia (59%), leukopenia (54%), asthenia (44%), diarrhea (38%), abdominal
pain (37%), headache (35%), stomatitis (32%), dyspnea (32%), epistaxis (31%), and
hypokalemia (31%). The hematologic TEAEs were common and expected because of the
targeting of hematopoietic precursor cells.

The TEAEs reported here reflect those that occurred in part I after administration of
gemtuzumab ozogamicin. Table 25 presents the most common TEAEs (≥ 30%) in part I of
the phase II studies as reported during dose period 1 and dose period 2.

Table 25. MOST COMMONLY REPORTED (≥ 30%) TEAEs IN DOSE PERIODS 1 AND 2 OF
STUDIES 201/202/203[a]: NUMBER (%) OF PATIENTS

Adverse Event	Dose Period 1 (n = 142)	Dose Period 2 (n = 114)
Fever	109 (77)	75 (66)
Nausea	95 (67)	54 (47)
Chills	91 (64)	65 (57)
Vomiting	81 (57)	38 (33)
Thrombocytopenia	80 (56)	27 (24)
Leukopenia	73 (51)	30 (26)
Asthenia	50 (35)	31 (27)
Headache	46 (32)	19 (17)
Diarrhea	41 (29)	22 (19)
Abdominal pain	32 (23)	27 (24)
Hypokalemia	30 (21)	20 (18)
Stomatitis	29 (20)	21 (18)
Dyspnea	26 (18)	28 (25)
Epistaxis	26 (18)	27 (24)

a: These TEAEs were reported for ≥ 30% of the patients in part I of studies 201/202/203.

The frequency of TEAEs in studies 201/202/203 tended to decrease between dose 1 and dose 2, or remained at the same level. The decrease in the frequency of TEAEs reflects the lower incidence of postinfusion syndrome in subsequent doses. This may reflect lower disease burden or tachyphylaxis to gemtuzumab ozogamicin.

5.3.2 Adverse Events in Relation to the Number of Courses of Treatment

Four (4) patients have received more than 1 course of gemtuzumab ozogamicin (ie, had remission after 1 or more doses, had a relapse, and then received additional doses) before 30 Apr 1999. The patients received the second courses at 5, 10, 10.5, and 11 months after the first doses. Patient 20274-0001 had a CRp after 2 doses of gemtuzumab ozogamicin and was re-treated with 2 additional doses as patient 20274-0201. Patient 20361-0002 had CR after 2 doses of gemtuzumab ozogamicin. The CR lasted for 6½ months and the patient had a relapse. The patient was re-treated with 2 additional doses of gemtuzumab ozogamicin as patient 20361-0202 and again had a CR. Patient 201A9-0002 received additional treatment with gemtuzumab ozogamicin as patient 201A9-0201 but only preliminary information was available at the time of the data cutoff. One (1) additional patient (201B1-0003) was retreated on 29 Mar 1999 as patient 201B1-0201. This patient died on 07 Apr 1999.

The 4 patients receiving repeat courses of gemtuzumab ozogamicin in the phase II studies tolerated a second course as well as they tolerated the first course. Only 4 severe (grade 3 or grade 4) TEAEs were reported. Patient 20274-0001 experienced grade 3 herpes

simplex after dose 1 of the first course of treatment. Patient 20361-0002 experienced grade 4 thrombocytopenia after dose 1 and severe constipation after dose 2 of the first course of treatment. After dose 1 of the second course of treatment this patient (as patient 20361-0202) experienced grade 4 thrombocytopenic purpura.

5.3.3 Severity of Adverse Events

The severity of the adverse events was determined by using the NCI toxicity rating scale. Events with a severity of grade 1 or grade 2 were considered as mild or moderate, easily manageable events; grade 3 or grade 4 events were considered to be severe or life-threatening and these were selected for further analysis. All TEAEs of grade 3 or grade 4 severity that occurred in part I of studies 201/202/203 are presented in Table 26.

Table 26. TEAEs OF NCI GRADE 3 OR 4 SEVERITY IN PART I OF STUDIES
201/202/203[a]: NUMBER (%) OF PATIENTS

Body System Adverse Event[b]	Grades 3 - 4 (n = 142)	Grades 1 – 4[c] (n = 142)
Any adverse event	129 (91)	142 (100)
Body as a whole		
Abdominal pain	4 (3)	52 (37)
Abscess	2 (1)	4 (3)
Asthenia	10 (7)	63 (44)
Back pain	2 (1)	22 (15)
Cellulitis	2 (1)	7 (5)
Chills	18 (13)	104 (73)
Face edema	1 (<1)	7 (5)
Fever	21 (15)	121 (85)
Generalized edema	1 (<1)	5 (4)
Halitosis	1 (<1)	1 (<1)
Headache	5 (4)	50 (35)
Infection	2 (1)	11 (8)
Lab test abnormal	1 (<1)	4 (3)
Neck pain	1 (<1)	7 (5)
Neutropenic fever	10 (7)	30 (21)
Non-specified drug reaction	2 (1)	10 (7)
Pain	5 (4)	30 (21)
Retroperitoneal hemorrhage	1 (<1)	1 (<1)
Sepsis	23 (16)	36 (25)
Tumor lysis syndrome	3 (2)	4 (3)
Cardiovascular system		
Atrial fibrillation	1 (<1)	4 (3)
Bradycardia	1 (<1)	2 (1)
Cerebral hemorrhage	3 (2)	3 (2)
Congestive heart failure	4 (3)	4 (3)
Cyanosis	1 (<1)	2 (1)
Hypertension	13 (9)	29 (20)
Hypotension	11 (8)	28 (20)
Intracranial hemorrhage	3 (2)	3 (2)
Left heart failure	1 (<1)	1 (<1)
Shock	3 (2)	3 (2)
Tachycardia	1 (<1)	15 (11)
Tachycardia sinus	1 (<1)	2 (1)
Digestive system		
Anorexia	2 (1)	41 (29)
Bloody diarrhea	1 (<1)	2 (1)
Cheilitis	1 (<1)	5 (4)
Colitis	1 (<1)	1 (<1)
Constipation	2 (1)	36 (25)
Diarrhea	3 (2)	54 (38)
Esophagitis	2 (1)	4 (3)
Gastrointestinal disorder	1 (<1)	3 (2)
Gastrointestinal physical finding	1 (<1)	1 (<1)
Hematemesis	1 (<1)	6 (4)
Liver damage	3 (2)	3 (2)
Liver function tests abnormal[d]	11 (8)	35 (25)
Melena	1 (<1)	6 (4)

Table 26. TEAEs OF NCI GRADE 3 OR 4 SEVERITY IN PART I OF STUDIES
201/202/203[a]: NUMBER (%) OF PATIENTS

Body System Adverse Event[b]	Grades 3 - 4 (n = 142)	Grades 1 – 4[c] (n = 142)
Nausea	13 (9)	100 (70)
Stomatitis	5 (4)	45 (32)
Vomiting	5 (4)	89 (63)
Hemic and lymphatic system		
Agranulocytosis	4 (3)	4 (3)
Anemia	22 (15)	35 (25)
Aplastic anemia	2 (1)	2 (1)
Coagulation disorder	1 (<1)	3 (2)
Disseminated intravascular coagulation	3 (2)	7 (5)
Ecchymosis	1 (<1)	18 (13)
Hypochromic anemia	6 (4)	7 (5)
Leukocytosis	1 (<1)	2 (1)
Leukopenia	75 (53)	76 (54)
Lymphadenopathy	2 (1)	4 (3)
Pancytopenia	4 (3)	6 (4)
Petechiae	1 (<1)	28 (20)
Purpura	1 (<1)	3 (2)
Thrombocytopenia	82 (58)	84 (59)
Metabolic and nutritional		
Acidosis	2 (1)	2 (1)
Alkaline phosphatase increased	2 (1)	11 (8)
Bilirubinemia	11 (8)	22 (15)
BUN increased	1 (<1)	3 (2)
Cachexia	1 (<1)	1 (<1)
Creatinine increased	1 (<1)	11 (8)
Edema	1 (<1)	12 (8)
Hyperglycemia	6 (4)	13 (9)
Hyperkalemia	1 (<1)	4 (3)
Hyperuricemia	1 (<1)	3 (2)
Hypokalemia	4 (3)	44 (31)
Hypophosphatemia	3 (2)	13 (9)
Lactic dehydrogenase increased	6 (4)	19 (13)
Peripheral edema	1 (<1)	23 (16)
Weight gain	1 (<1)	6 (4)
Musculoskeletal system		
Arthralgia	1 (<1)	12 (8)
Bone pain	2 (1)	7 (5)
Myalgia	2 (1)	10 (7)
Tenosynovitis	1 (<1)	1 (<1)
Nervous system		
Agitation	2 (1)	5 (4)
Anxiety	1 (<1)	11 (8)
CNS depression	1 (<1)	1 (<1)
Coma	1 (<1)	1 (<1)
Confusion	2 (1)	8 (6)
Convulsion	2 (1)	2 (1)
Depression	2 (1)	13 (9)
Dizziness	1 (<1)	22 (15)
Facial paralysis	1 (<1)	1 (<1)
Hallucinations	1 (<1)	1 (<1)
Hypertonia	2 (1)	4 (3)

Table 26. TEAEs OF NCI GRADE 3 OR 4 SEVERITY IN PART I OF STUDIES
201/202/203[a]: NUMBER (%) OF PATIENTS

Body System Adverse Event[b]	Grades 3 - 4 (n = 142)	Grades 1 – 4[c] (n = 142)
Paresis	1 (<1)	1 (<1)
Somnolence	3 (2)	10 (7)
Stupor	3 (2)	3 (2)
Subdural hematoma	1 (<1)	1 (<1)
Thinking abnormal	1 (<1)	2 (1)
Respiratory system		
Dyspnea	13 (9)	46 (32)
Epistaxis	4 (3)	44 (31)
Hyperventilation	1 (<1)	2 (1)
Hypoxia	3 (2)	8 (6)
Laryngitis	1 (<1)	1 (<1)
Lung disorder	2 (1)	5 (4)
Lung edema	2 (1)	4 (3)
Pharyngitis	1 (<1)	20 (14)
Pneumonia	10 (7)	14 (10)
Respiratory failure	4 (3)	4 (3)
Skin and appendages		
Herpes simplex	3 (2)	31 (22)
Pruritus	1 (<1)	12 (8)
Rash[d]	1 (<1)	30 (21)
Skin necrosis	1 (<1)	1 (<1)
Special senses		
Eye disorder	1 (<1)	2 (1)
Pupillary disorder	1 (<1)	1 (<1)
Study event assoc. w. misc. factors		
Local reaction to procedure	6 (4)	35 (25)
Urogenital system		
Acute kidney failure	3 (2)	3 (2)
Anuria	1 (<1)	1 (<1)
Hematuria	2 (1)	14 (10)
Kidney pain	1 (<1)	1 (<1)
Oliguria	1 (<1)	1 (<1)
Urinary tract disorder	1 (<1)	1 (<1)
Urinary tract infection	1 (<1)	6 (4)

a: NCI toxicity is regarded as the maximum intensity reported for the adverse events. Severity grades (mild, moderate, or severe) were merged to NCI toxicity grades (1, 2, or 3, respectively).

b: Percentages for sex-specific adverse events are based on the number of patients of the relevant sex.

c: The grades 1 – 4 column includes adverse events of any severity.

d: One (1) patient had rash listed as NCI severity 0 and was not included in the table.

The most commonly reported severe (grade 3 and grade 4) TEAEs in part I for the 142 patients in studies 201/202/203 were thrombocytopenia (58%), leukopenia (53%), sepsis (16%), anemia (15%), fever (15%), and chills (13%). The adverse events that occurred during follow-up, which are not included here, generally reflect other treatments administered to AML patients or progressive disease.

Specific comparisons of severe (grade 3 or grade 4) adverse events were made to published reports of other therapies in relapsed AML; these comparisons showed that patients treated with gemtuzumab ozogamicin have a lower incidence of severe mucositis, a low incidence of severe infections, and a shorter duration of hospitalizations than those treated with conventional chemotherapy.

5.3.4 Analysis of Specific Adverse Events

Adverse events associated with the infusion-related symptom complex, mucositis, myelosuppression, bleeding, infection, liver function abnormalities, and tumor lysis syndrome are discussed below.

5.3.4.1 Infusion-Related Symptom Complex

A summary of the severe infusion-related events for studies 201/202/203 is presented in Table 27. These events all occurred on the same day as gemtuzumab ozogamicin infusion.

Table 27. INFUSION-RELATED TEAEs OF NCI GRADE 3 OR 4 SEVERITY[a]:
NUMBER (%) OF PATIENTS

Body System Adverse Event[c]	Grades 3 – 4 (n = 142)	Grades 1 – 4[b] (n = 142)
Any adverse event		
Any adverse event	55 (39)	127 (89)
Body as a whole		
Chills	15 (11)	88 (62)
Fever	10 (7)	87 (61)
Headache	1 (<1)	17 (12)
Neutropenic fever	2 (1)	8 (6)
Pain	1 (<1)	4 (3)
Sepsis	1 (<1)	3 (2)
Cardiovascular system		
Hypertension	4 (3)	9 (6)
Hypotension	5 (4)	15 (11)
Intracranial hemorrhage	1 (<1)	1 (<1)
Digestive system		
Liver function tests abnormal	1 (<1)	3 (2)
Nausea	1 (<1)	54 (38)
Vomiting	1 (<1)	45 (32)
Hemic and lymphatic system		
Anemia	2 (1)	4 (3)
Disseminated intravascular coagulation	1 (<1)	1 (<1)
Leukopenia	8 (6)	12 (8)
Pancytopenia	1 (<1)	1 (<1)
Thrombocytopenia	17 (12)	19 (13)
Metabolic and nutritional		
Bilirubinemia	1 (<1)	1 (<1)
Edema	1 (<1)	2 (1)
Hyperglycemia	3 (2)	3 (2)
Hypophosphatemia	1 (<1)	1 (<1)
Musculoskeletal system		
Bone pain	2 (1)	3 (2)
Myalgia	1 (<1)	3 (2)
Respiratory system		
Dyspnea	2 (1)	6 (4)
Hypoxia	3 (2)	8 (6)

a: NCI toxicity is regarded as the maximum intensity reported for the adverse events. Severity grades (mild, moderate, or severe) were merged to NCI toxicity grades (1, 2, or 3, respectively).
b: The grades 1 – 4 column includes adverse events of any severity.
c: TEAEs occurring the day of gemtuzumab ozogamicin administration. Percentages for sex-specific adverse events are based on the number of patients of the relevant sex.

The most common severe (grade 3 and grade 4) infusion-related TEAEs reported for the 142 patients in studies 201/202/203 were thrombocytopenia (12%), chills (11%), fever (7%), leukopenia (6%), and hypotension (4%). Leukopenia and thrombocytopenia were expected because of the direct action of gemtuzumab ozogamicin on CD33 positive hematopoietic cells.

The infusion-related symptom complex is a recognized occurrence in patients treated with gemtuzumab ozogamicin. Fever and chills were commonly reported despite prophylactic treatment with acetaminophen and antihistamines. The incidence of severe hypotension was approximately 4% (5/142 patients had grade 3 or grade 4 hypotension); these patients received IV fluid support, and occasionally IV vasopressor support, which led to the resolution of hypotension in all cases.

There were 2 reports of severe dyspnea in the 142 patients included in part I of these studies. Both cases of dyspnea occurred within 4 hours after dose administration and lasted less than 1 hour.

Table 28 presents the most common ($\geq 5\%$) infusion-related TEAEs reported for doses 1 and 2.

Table 28. COMMONLY REPORTED ($\geq 5\%$) INFUSION-RELATED TEAEs OF NCI GRADE 3 OR 4 SEVERITY BY DOSE[a] (STUDIES 201/202/203): NUMBER (%) OF PATIENTS

Adverse Event	----- Dose 1 (n = 142) -----		----- Dose 2 (n = 114) -----	
	Grades 3 - 4	Grades $1 - 4$[b]	Grades 3 - 4	Grades 1 - 4[b]
Any infusion-related adverse event	48 (33)	123 (87)	14 (12)	75 (66)
Chills	12 (8)	78 (55)	7 (6)	46 (40)
Fever	8 (6)	71 (50)	2 (2)	44 (39)
Thrombocytopenia	12 (8)	14 (10)	5 (4)	5 (4)

a: Events occurring the day of gemtuzumab ozogamicin administration.
    These TEAEs were reported for $\geq 5\%$ of the patients in studies 201/202/203.
    NCI toxicity is regarded as the maximum intensity reported for the adverse events. Severity grades (mild, moderate, or severe) were merged to NCI toxicity grades (1, 2, or 3, respectively).
b: The grades $1 - 4$ columns include TEAEs of any severity.

There were fewer incidents of chills and fever after the second dose than after the first dose.

5.3.4.2 Mucositis

An evaluation of the occurrence of events of mucositis in patients enrolled in studies 201/202/203 was performed. The criteria for this evaluation included any adverse events with a verbatim term of mucositis, stomatitis, ulcerative stomatitis, oral ulcer(s), or mouth pain. In addition, all events coding to mucositis, oral (secondary to herpes simplex virus) stomatitis, ulcerative stomatitis, mouth ulceration, and pain were reviewed for events that may have been missed by the verbatim terms. Any events that could have indicated the

presence of mucositis (such as mouth sores, oral lesions, oral pain, or blood blisters) were assumed to represent an event of mucositis.

There were 50 patients with TEAEs that met the criteria for mucositis during part I of studies 201/202/203 (Table 29). Five (5) of these patients experienced severe mucositis (3 patients with grade 3, and 2 with grade 4), and details are provided below.

Table 29. MUCOSITIS-RELATED TEAEs OF NCI GRADE 3 OR 4 SEVERITY[a] IN PART I (STUDIES 201/202/203) (n = 142): NUMBER (%) OF PATIENTS

Adverse Event	Grades 3 - 4	Grades 1 – 4[b]
Any mucositis-related adverse event	5 (4)	50 (35)
Body as a whole		
Pain	0	3 (2)
Digestive system		
Mouth ulceration	0	4 (3)
Stomatitis	5 (4)	45 (32)

a: NCI toxicity is regarded as the maximum intensity reported for the adverse events. Severity grades (mild, moderate, or severe) were merged to NCI toxicity grades (1, 2, or 3, respectively). Events with missing NCI toxicity are not tabulated.

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

Gemtuzumab ozogamicin therapy is associated with a lower incidence of clinically severe mucositis than that of conventional chemotherapies (see Table 55 in section 7.4.1).

Patient 201A9-0010 developed grade 3 mucositis 23 days after her first dose of gemtuzumab ozogamicin. The investigator judged this event to be not related to gemtuzumab ozogamicin. The mucositis occurred 13 days after the patient received other antileukemic therapy of mitoxantrone and etoposide and persisted until her death. Patient 201E5-0001 developed grade 3 mucositis 14 days after receiving gemtuzumab ozogamicin. With local oral treatment, the mucositis resolved within nine days. In the opinion of the investigator, there was a possible relationship to gemtuzumab ozogamicin.

In patient 20361-0001, grade 4 stomatitis started on study day 15 and lasted for 10 days. In the opinion of the investigator, this event was related to the administration of gemtuzumab ozogamicin. Patient 20372-0002 experienced grade 1 stomatitis on day 6 (which lasted for 2 days) before increasing to grade 3 (for 2 days) and then to grade 4 (for 17 days). Patient 20372-0002 also experienced severe herpes simplex on the lips beginning on day 8 and lasting for 15 days. The investigator considered the stomatitis to be possibly related to the administration of gemtuzumab ozogamicin. Patient 203A9-0002 developed grade 3 stomatitis 7 days after receiving the second dose of gemtuzumab ozogamicin. It

resolved 7 days later. In the opinion of the investigator, this event was not related to the administration of gemtuzumab ozogamicin.

The mucositis events in the remaining patients were mild or moderate in severity (grade 1 or grade 2).

5.3.4.3 Myelosuppression

Myelosuppression is a common complication of both conventional chemotherapy and targeted therapy with gemtuzumab ozogamicin. Although pluripotent stem cells are CD33 negative, some hematopoietic precursor cells are CD33 positive and are therefore targeted by gemtuzumab ozogamicin. A summary of the reported cases of grade 3 and grade 4 myelosuppression for part I of the pooled phase II studies is presented in Table 30.

Table 30. MYELOSUPPRESSION OF NCI GRADE 3 OR 4[a] SEVERITY DURING PART I: NUMBER (%) OF PATIENTS

Body System[b] Adverse Event	Grades 3 - 4 (n = 142)	Grades 1 – 4[c] (n = 142)
Any myelosuppression adverse event	102 (72)	105 (74)
Agranulocytosis	4 (3)	4 (3)
Anemia	22 (15)	35 (25)
Aplastic anemia	2 (1)	2 (1)
Hypochromic anemia	6 (4)	7 (5)
Leukopenia	75 (53)	76 (54)
Pancytopenia	4 (3)	6 (4)
Thrombocytopenia	82 (58)	84 (59)

a: NCI toxicity is regarded as the maximum intensity reported for the adverse events. Severity grades (mild, moderate, severe) were merged to NCI toxicity grades (1, 2, or 3, respectively).
b: Body system totals are not necessarily the sum of the individual adverse events since a patient may report 2 or more different adverse events in the same body system.
c: Grades 1 – 4 body system totals include adverse events of any severity.

The observed incidence of severe myelosuppression was not in excess of that expected based on a review of the literature presented in section 7.4.1.

5.3.4.4 Bleeding

A summary of the reported cases of severe bleeding for the pooled phase II studies of gemtuzumab ozogamicin is presented in Table 31.

Table 31. BLEEDING OF NCI GRADE 3 OR 4[a] SEVERITY DURING PART I:
NUMBER (%) OF PATIENTS

Adverse Event	Grades 3 - 4 (n = 142)	Grades 1 – 4[b] (n = 142)
Any bleeding adverse event	21 (15)	95 (67)
Bloody diarrhea	1 (< 1)	2 (1)
Cerebral hemorrhage	3 (2)	3 (2)
DIC	3 (2)	7 (5)
Ecchymosis	1 (< 1)	18 (13)
Epistaxis	4 (3)	44 (31)
Hematemesis	1 (< 1)	6 (4)
Hematuria	2 (1)	14 (10)
Intracranial hemorrhage	3 (2)	3 (2)
Petechiae	1 (< 1)	28 (20)
Purpura	1 (< 1)	3 (2)
Retroperitoneal hemorrhage	1 (< 1)	1 (< 1)
Subdural hematoma	1 (< 1)	1 (< 1)

a: NCI toxicity is regarded as the maximum intensity reported for the adverse events. Severity grades (mild, moderate, severe) were merged to NCI toxicity grades (1, 2, or 3, respectively).
b: Grades 1 – 4 body system totals include adverse events of any severity.

The observed incidence of severe bleeding for gemtuzumab ozogamicin-treated patients was not in excess of that expected for AML patients in first relapse with conventional therapy (see Table 55 in section 7.4.1).

5.3.4.5 Infection

A summary of the reported cases of severe infection for part I of studies 201/202/203 is presented in Table 32.

Table 32. INFECTIONS OF NCI GRADE 3 OR 4[a] SEVERITY DURING PART I: NUMBER (%) OF PATIENTS

Adverse Event	Grades 3 - 4 (n = 142)	Grades 1 - 4[b] (n = 142)
Any infection adverse event	40 (28)	115 (81)
Cellulitis	2 (1)	7 (5)
Esophagitis	2 (1)	4 (3)
Gastrointestinal disorder	1 (<1)	3 (2)
Herpes simplex	3 (2)	31 (22)
Infection	2 (1)	11 (8)
Laryngitis	1 (<1)	1 (<1)
Lymphadenopathy	2 (1)	4 (3)
Pneumonia	10 (7)	14 (10)
Sepsis	23 (16)	36 (25)
Shock	3 (2)	3 (2)
Stomatitis	5 (3)	45 (32)
Urinary tract infection	1 (<1)	6 (4)

a: NCI toxicity is regarded as the maximum intensity reported for the adverse events. Severity grades (mild, moderate, severe) were merged to NCI toxicity grades (1, 2, or 3, respectively).
b: Grades 1 – 4 body system totals include adverse events of any severity.

Infection was not in excess of that expected based on literature review and was lower than that reported in most publications (see Table 55 in section 7.4.1).

5.3.4.6 Liver Function Abnormalities

Liver function abnormalities are common in AML patients undergoing cancer therapy. These abnormalities may be attributed to many factors, including the presence of the disease or a direct effect of the therapy. Abnormal LFTs were not consistently reported as TEAEs by the investigators but these results were collected and are reported. A summary of the reported cases of liver function abnormality TEAEs for part I of studies 201/202/203 is presented in Table 33.

Table 33. LIVER FUNCTION ABNORMALITIES OF NCI GRADE 3 OR 4[a] SEVERITY IN PART I: NUMBER (%) OF PATIENTS

Adverse Event	Grades 3 - 4 (n = 142)	Grades 1 – 4[b] (n = 142)
Any liver function adverse event	23 (16)	60 (42)
Alkaline phosphatase increased	2 (1)	11 (8)
Bilirubinemia	11 (8)	22 (15)
Lactic dehydrogenase increased	6 (4)	19 (13)
Liver damage	3 (2)	3 (2)
Liver function tests abnormal	11 (7)	35 (25)

a: NCI toxicity is regarded as the maximum intensity reported for the adverse events. Severity grades (mild, moderate, severe) were merged to NCI toxicity grades (1, 2, or 3, respectively).

b: Grades 1 – 4 body system totals include adverse events of any severity.

In part I, 16% (23/142) of the patients in studies 201/202/203 experienced grade 3 or grade 4 liver function abnormalities. This represented 38% (23/60) of all of the liver function-related TEAEs. These abnormal values are generally transient and reversible.

The observed incidence of severe liver function abnormalities was not in excess of that expected based on a review of the literature presented in section 7.4.1. The majority of observed events were transient, reversible, and required no medical intervention.

5.3.4.7 Tumor Lysis Syndrome

Only 4 of 142 patients (3%) reported tumor lysis syndrome as a TEAE. The TEAE was considered to be severe in 3 of the 4 patients. Patient 201B0-0001, a 36-year-old man, experienced grade 3 tumor lysis syndrome that started 13 days after dose 1 and persisted for 13 days. This TEAE was not considered to be related to the administration of gemtuzumab ozogamicin by the investigator. The second patient (20292-0001), a 58-year-old man, experienced grade 3 tumor lysis syndrome that started 2 days after the administration of dose 1 and persisted for 5 days. This TEAE was considered by the investigator to be probably related to the administration of gemtuzumab ozogamicin. This patient did not have high levels of potassium, phosphate, or uric acid. A third patient experienced grade 1 tumor lysis syndrome and is not discussed here.

Patient 20292-0004 experienced grade 3 tumor lysis syndrome after the first dose of gemtuzumab ozogamicin. The tumor lysis syndrome event was reported as an IND Safety Report. This patient developed tumor lysis syndrome one day after being mistakenly administered the first dose of gemtuzumab ozogamicin in less than one hour instead of the recommended 2-hour administration. The patient experienced acute renal failure with

anuria (without hyperuricemia), liver failure, cholestasis, and disseminated intravascular coagulation. Patient was treated in the intensive care unit for 5 days and the tumor lysis syndrome resolved.

5.3.5 Deaths and Serious Adverse Events

Serious adverse events reported for this patient population is not unexpected, given the seriousness of the underlying disease process in patients with AML in first relapse.

A list of patients who died during part I of the phase II studies with cause of death is presented in Table 34. Many of these deaths were because of progression of AML. In addition, 54 patients died during the 6-month follow-up period in studies 201/202/203.

Table 34. SUMMARY OF DEATHS THAT OCCURRED DURING PART I OF STUDIES 201/202/203

Dose Patient	Age (y) / Sex	Day[a]	Cause of Death
Dose 1			
201A9-0008	49 / M	2	Left frontoparietal intraparenchymal hemorrhage
20274-0007	69 / M	5	Cerebral hemorrhage
20354-0002	61 / F	15	Intracerebral bleed
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, increase of creatinemia, renal failure, acute pulmonary edema.
201B4-0001	64 / F	22	Disease progression
Dose 2			
20365-0001	70 / F	17	Intracerebral hemorrhage because of 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
20277-0007	66 / M	38	Disease progression
20357-0004	60 / M	42	Leukemia progression
20354-0001	69 / M	55	Disease progression (AML)

a: Day relative to the start of the study.

Patients with de novo AML have a treatment-related mortality rate of 5% to 10%.[1] For AML patients in first relapse the treatment-associated death rate is 10% to 30%.[1] In

studies 201/202/203 with gemtuzumab ozogamicin, the part I mortality rate was 13% (18/142). The part I mortality rate was 12.9% (8/62) for patients who were < 60 years old, and 12.5% (10/80) for patients who were ≥ 60 years old.

5.4 Clinical Laboratory Evaluations

Laboratory determinations were performed to monitor the effects of gemtuzumab ozogamicin on specific laboratory parameters that may have indicated the occurrence of adverse events. Patients were followed closely with frequent hematology and clinical chemistry profiles for 28 days after study drug infusion in part I of the study. All laboratory tests with values that became abnormal after drug administration were repeated until the values returned to normal or were no longer clinically important.

Laboratory values of clinical importance were those that were classified as being of severity grade 3 or 4. These values are defined in Table 35.

Table 35. LABORATORY TEST CRITERIA[a] OF CLINICAL IMPORTANCE

| Category | -------- Severity -------- | |
Test	Grade 3	Grade 4
Hematology		
Hemoglobin (g/dL)	6.5 - 7.9	< 6.5
Lymphocytes, absolute (10^3/µL)	0.5 - 0.9	< 0.5
Total neutrophils, absolute (10^3/µL)	0.5 - 0.9	< 0.5
Partial thromboplastin time (sec)	2.34 - 3.00 x N	> 3.00 x N
Platelet count (10^3/µL)	25.0 - 49.9	< 25.0
Prothrombin time (sec)	1.51 - 2.00 x N	> 2.00 x N
WBC (10^3/µL)	1.0 - 1.9	< 1.0
Clinical Chemistry		
Alkaline phosphatase (units)	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Calcium (mg/dL)	6.1 - 6.9 or, 12.6 – 13.5	≤ 6.0 or ≥ 13.5
Creatinine (mg/dL)	> 3.0 - 6.0 x ULN	> 6.0 x UL
Glucose (mg/dL)	30 – 39 or 251 - 500	< 30 or > 500 or ketoacidosis
AST (units)	≥ 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT (units)	≥ 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin (mg/dL)	> 1.5 - 3.0 x ULN	> 3.0 x ULN

a: N = normal; ULN = upper limit of normal range.

When a patient was identified as having laboratory data meeting 1 of these criteria, the test result was considered clinically important. Each of these values was medically evaluated in the context of a patient's complete laboratory results, and vital signs. In addition, all adverse event records, any other pertinent sections of the CRF, and all

correspondence related to the patient were considered. Investigators were instructed to enter laboratory abnormalities as adverse events in the adverse event section of the CRF.

5.4.1 Hematologic Laboratory Abnormalities

This section reviews findings by laboratory parameter for clinically important hematologic abnormalities. The expression of CD33 on hematopoietic precursors was anticipated to result in hematopoietic toxicity following gemtuzumab ozogamicin therapy. Although the target-specific mechanism of action for gemtuzumab ozogamicin is unique, this toxicity is also seen with conventional chemotherapy. A summary of hematologic laboratory abnormalities of grade 3 or grade 4 severity in part I of studies 201/202/203 is presented in Table 36.

Table 36. HEMATOLOGY TEST RESULTS OF CLINICAL IMPORTANCE IN PART I: NUMBER (%) OF PATIENTS

| Test | ---------- Studies 201/202/203 (n = 142) ---------- | | |
	Grade 3	Grade 4	Total
Hemoglobin	62/141 (44)	4/141 (3)	66/141 (47)
Lymphocytes	26/140 (19)	104/140 (74)	130/140 (93)
Partial thromboplastin time	1/ 79 (1)	0	1/ 79 (1)
Platelet count	6/141 (4)	133/141 (94)	139/141 (99)
Prothrombin time	0	2/ 47 (4)	2/ 47 (4)
Total neutrophils, absolute ($10^3/\mu$L)	1/140 (< 1)	136/140 (97)	137/140 (98)
WBC	9/141 (6)	127/141 (90)	136/141 (96)

5.4.2 Nonhematologic Laboratory Abnormalities

A summary of the nonhematologic laboratory abnormalities of grade 3 or grade 4 severity in part I of studies 201/202/203 is presented in Table 37.

Table 37. NONHEMATOLOGIC LABORATORY TEST RESULTS OF CLINICAL IMPORTANCE IN PART I: NUMBER (%) OF PATIENTS

| Test | -------- Studies 201/202/203 (n = 142) --------------- | | |
	Grade 3	Grade 4	Total
Alkaline phosphatase	5/141 (4)	0	5/141 (4)
Calcium	11/141 (8)	6/141 (4)	17/141 (12)
Creatinine	2/141 (1)	0	2/141 (1)
Glucose	16/140 (11)	1/140 (< 1)	17/140 (12)
AST	20/141 (14)	4/141 (3)	24/141 (17)
ALT	10/141 (7)	2/141 (1)	12/141 (9)
Total bilirubin	23/141 (16)	10/141 (7)	33/141 (23)

The most common abnormal laboratory results during part I were transitory LFT values: 23% (33/141) of patients showed severe elevations in bilirubin. LFT elevations are common in AML patients, especially in those receiving conventional chemotherapy (see section 7.4.1). The abnormal LFTs were generally grade 2 (not shown) or grade 3 in severity with 7% (10/141) of patients having grade 4 elevations in bilirubin. A total of 45 patients (32%) had at least 1 grade 3 or grade 4 hepatic (AST, ALT, or total bilirubin) laboratory test abnormality during part I. These abnormal values were generally transient and reversible. The pattern shows that liver functions generally rose within 2 days of treatment, and then fell within a week to 10 days and generally returned to normal.

5.5 Immunogenicity and Vital Signs

The immunogenic potential of gemtuzumab ozogamicin was examined in study 101 and in studies 201/202/203.

In study 101, a total of 40 patients were tested for development of antibodies to gemtuzumab ozogamicin; the results of only 2 were positive. One (1) patient (10132-0007 experienced a CR at 1 mg/m^2 and received a second course of gemtuzumab ozogamicin at 6 mg/m^2 as patient 10132-0107 at the time of next relapse) developed antibodies to the calicheamicin/linker portion of gemtuzumab ozogamicin, but not to the antibody portion 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 (10132-0002) developed these antibodies after the third dose of 0.25 mg/m^2 gemtuzumab ozogamicin.

None of the 142 patients in the phase II studies had any antibody responses or clinical evidence of immune response. Four (4) patients received a second course and did not develop anti-gemtuzumab ozogamicin antibodies.

No predetermined vital signs safety limits (ranges) were specified in the protocols. However, vital sign data were screened to identify changes of potential clinical importance. Each of these values was medically evaluated in the context of a patient's complete laboratory results, other vital signs, and ECG data. In addition, adverse event records, other pertinent sections of the CRF, and correspondence related to the patient were considered. No consistent changes in vital signs were noted after gemtuzumab ozogamicin administration.

5.6 Analysis of Safety by Demography and Special Populations

5.6.1 Effect of Age

Approximately 50% of AML patients were ≥ 60 years old and this age group represents a distinct challenge in AML therapy. There are patient and disease factors that result in a poorer prognosis in these patients; these include an increased frequency of poor-risk cytogenetic abnormalities, and an increased treatment mortality rate. However, there were no pharmacokinetic differences to suggest that the gemtuzumab ozogamicin dose needs to be altered in patients ≥ 60 years old. The most common (≥ 5%) TEAEs for patients < 60 years of age and those ≥ 60 years of age are summarized in Table 38 and are similar for the 2 age groups.

Table 38.COMMON ($\geq$ 5%)[a] TEAEs REPORTED FOR PATIENTS < 60 AND $\geq$ 60 YEARS OF AGE IN PART I: NUMBER (%) OF PATIENTS

Body System Adverse Event[b]	Age < 60 (n = 62)	Age $\geq$ 60 (n = 80)
Body as a whole		
Abdomen enlarged	4 (6)	9 (11)
Abdominal pain	29 (47)	23 (29)
Accidental injury	3 (5)	5 (6)
Ascites	3 (5)	5 (6)
Asthenia	27 (44)	36 (45)
Back pain	8 (13)	14 (18)
Cellulitis	3 (5)	4 (5)
Chest pain	8 (13)	4 (5)
Chest pain substernal	3 (5)	1 (1)
Chills	51 (82)	53 (66)
Face edema	4 (6)	3 (4)
Fever	57 (92)	64 (80)
Generalized edema	2 (3)	3 (4)
Headache	29 (47)	21 (26)
Infection	4 (6)	7 (9)
Neck pain	3 (5)	4 (5)
Neutropenic fever	14 (23)	16 (20)
Non-specified drug reaction	5 (8)	5 (6)
Pain	10 (16)	20 (25)
Sepsis	17 (27)	19 (24)
Tumor lysis syndrome	3 (5)	1 (1)
Cardiovascular system		
Atrial fibrillation	1 (2)	3 (4)
Congestive heart failure	1 (2)	3 (4)
Hemorrhage	8 (13)	6 (8)
Hypertension	13 (21)	16 (20)
Hypervolemia	3 (5)	3 (4)
Hypotension	15 (24)	13 (16)
Syncope	3 (5)	2 (3)
Tachycardia	7 (11)	8 (10)
Thrombosis	6 (10)	1 (1)
Vasodilatation	6 (10)	2 (3)
Digestive system		
Anorexia	16 (26)	25 (31)
Cheilitis	1 (2)	4 (5)
Constipation	14 (23)	22 (28)
Diarrhea	24 (39)	30 (38)
Dry mouth	2 (3)	7 (9)
Dyspepsia	7 (11)	9 (11)
Esophagitis	3 (5)	1 (1)
Flatulence	2 (3)	4 (5)
Glossitis	5 (8)	2 (3)
Gum hemorrhage	9 (15)	4 (5)
Hematemesis	5 (8)	1 (1)
Liver function tests abnormal	18 (29)	17 (21)
Melena	1 (2)	5 (6)
Mouth ulceration	0	4 (5)

Table 38.COMMON (≥ 5%)[a] TEAEs REPORTED FOR PATIENTS < 60 AND ≥ 60 YEARS OF AGE IN PART I: NUMBER (%) OF PATIENTS

Body System Adverse Event[b]	Age < 60 (n = 62)	Age ≥ 60 (n = 80)
Nausea	49 (79)	51 (64)
Oral moniliasis	5 (8)	7 (9)
Rectal hemorrhage	2 (3)	4 (5)
Stomatitis	25 (40)	20 (25)
Stools abnormal	2 (3)	5 (6)
Vomiting	45 (73)	44 (55)
Hemic and lymphatic system		
Agranulocytosis	4 (6)	0
Anemia	15 (24)	20 (25)
Disseminated intravascular coagulation	5 (8)	2 (3)
Ecchymosis	6 (10)	12 (15)
Hypochromic anemia	5 (8)	2 (3)
Leukopenia	37 (60)	39 (49)
Lymphadenopathy	1 (2)	3 (4)
Pancytopenia	5 (8)	1 (1)
Petechiae	11 (18)	17 (21)
Thrombocytopenia	40 (65)	44 (55)
Metabolic and nutritional		
Alkaline phosphatase increased	2 (3)	9 (11)
Bilirubinemia	9 (15)	13 (16)
Creatinine increased	4 (6)	7 (9)
Dehydration	4 (6)	4 (5)
Edema	6 (10)	6 (8)
Hyperglycemia	5 (8)	8 (10)
Hypocalcemia	4 (6)	4 (5)
Hypokalemia	20 (32)	24 (30)
Hypomagnesemia	11 (18)	3 (4)
Hypophosphatemia	7 (11)	6 (8)
Lactic dehydrogenase increased	5 (8)	14 (18)
Peripheral edema	6 (10)	17 (21)
Weight gain	3 (5)	4 (5)
Weight loss	5 (8)	5 (6)
Musculoskeletal system		
Arthralgia	4 (6)	8 (10)
Bone pain	5 (8)	2 (3)
Myalgia	10 (16)	0
Nervous system		
Agitation	4 (6)	1 (1)
Anxiety	4 (6)	7 (9)
Confusion	4 (6)	4 (5)
Depression	5 (8)	8 (10)
Dizziness	13 (21)	9 (11)
Insomnia	8 (13)	14 (18)
Somnolence	5 (8)	5 (6)
Respiratory system		
Asthma	4 (6)	1 (1)
Cough increased	13 (21)	15 (19)
Dyspnea	17 (27)	29 (36)
Epistaxis	21 (34)	23 (29)
Hemoptysis	3 (5)	3 (4)

Table 38. COMMON (≥ 5%)[a] TEAEs REPORTED FOR PATIENTS < 60 AND ≥ 60 YEARS OF AGE IN PART I: NUMBER (%) OF PATIENTS

Body System Adverse Event[b]	Age < 60 (n = 62)	Age ≥ 60 (n = 80)
Hypoxia	5 (8)	3 (4)
Lung disorder	1 (2)	4 (5)
Lung edema	1 (2)	3 (4)
Pharyngitis	9 (15)	11 (14)
Pleural effusion	4 (6)	6 (8)
Pneumonia	6 (10)	8 (10)
Pulmonary physical finding	6 (10)	10 (13)
Respiratory failure	3 (5)	1 (1)
Rhinitis	6 (10)	8 (10)
Skin and appendages		
Acne	2 (3)	4 (5)
Herpes simplex	19 (31)	12 (15)
Maculopapular rash	1 (2)	4 (5)
Pruritus	7 (11)	5 (6)
Rash	13 (21)	18 (23)
Skin disorder	4 (6)	4 (5)
Sweating	4 (6)	3 (4)
Special senses		
Abnormal vision	2 (3)	3 (4)
Conjunctivitis	1 (2)	4 (5)
Eye hemorrhage	3 (5)	2 (3)
Study event assoc. w. misc. factors		
Local reaction to procedure	15 (24)	20 (25)
Urogenital system		
Acute kidney failure	3 (5)	0
Hematuria	6 (10)	8 (10)
Menorrhagia	3 (10)	0
Metrorrhagia	4 (14)	0
Urinary incontinence	1 (2)	4 (5)
Urinary retention	0	4 (5)
Urinary tract infection	4 (6)	2 (3)
Vaginal hemorrhage	5 (17)	2 (7)

a: ≥ 5% limit specifies the minimum percentage threshold from at least one column as a criteria for an event to be displayed in the table.
b: Percentages for sex-specific adverse events are based on the number of patients of the relevant sex.

5.6.2 Effect of Sex

The most common TEAEs (≥ 5%) for female and male patients were similar except for sex-specific adverse events, and are summarized in Table 39.

Table 39. COMMON TEAEs (≥ 5%)[a] REPORTED FOR FEMALE AND MALE PATIENTS IN PART I: NUMBER (%) OF PATIENTS

Body System Adverse Event[b]	Female (n = 58)	Male (n = 84)
Body as a whole		
Abdomen enlarged	4 (7)	9 (11)
Abdominal pain	23 (40)	29 (35)
Accidental injury	4 (7)	4 (5)
Ascites	3 (5)	5 (6)
Asthenia	26 (45)	37 (44)
Back pain	9 (16)	13 (15)
Cellulitis	4 (7)	3 (4)
Chest pain	6 (10)	6 (7)
Chest pain substernal	3 (5)	1 (1)
Chills	43 (74)	61 (73)
Face edema	3 (5)	4 (5)
Fever	50 (86)	71 (85)
Flu syndrome	2 (3)	0
Generalized edema	1 (2)	4 (5)
Headache	28 (48)	22 (26)
Infection	5 (9)	6 (7)
Injection site reaction	3 (5)	0
Malaise	2 (3)	2 (2)
Neck pain	3 (5)	4 (5)
Neutropenic fever	12 (21)	18 (21)
Non-specified drug reaction	5 (9)	5 (6)
Pain	15 (26)	15 (18)
Sepsis	18 (31)	18 (21)
Cardiovascular system		
Atrial fibrillation	1 (2)	3 (4)
Congestive heart failure	4 (7)	0
Cyanosis	2 (3)	0
Hemorrhage	4 (7)	10 (12)
Hypertension	9 (16)	20 (24)
Hypervolemia	1 (2)	5 (6)
Hypotension	13 (22)	15 (18)
Shock	2 (3)	1 (1)
Syncope	3 (5)	2 (2)
Tachycardia	2 (3)	13 (15)
Thrombosis	4 (7)	3 (4)
Vasodilatation	5 (9)	3 (4)
Digestive system		
Anorexia	16 (28)	25 (30)
Cheilitis	3 (5)	2 (2)
Constipation	19 (33)	17 (20)
Diarrhea	24 (41)	30 (36)
Dry mouth	4 (7)	5 (6)
Dyspepsia	8 (14)	8 (10)
Flatulence	2 (3)	4 (5)
Gingivitis	2 (3)	3 (4)
Glossitis	5 (9)	2 (2)
Gum hemorrhage	5 (9)	8 (10)

Table 39. COMMON TEAEs (≥ 5%)[a] REPORTED FOR FEMALE AND MALE PATIENTS IN PART I: NUMBER (%) OF PATIENTS

Body System Adverse Event[b]	Female (n = 58)	Male (n = 84)
Hematemesis	0	6 (7)
Liver function tests abnormal	13 (22)	22 (26)
Melena	4 (7)	2 (2)
Nausea	50 (86)	50 (60)
Oral moniliasis	6 (10)	6 (7)
Rectal hemorrhage	1 (2)	5 (6)
Stomatitis	15 (26)	30 (36)
Stools abnormal	2 (3)	5 (6)
Vomiting	45 (78)	44 (52)
Hemic and lymphatic system		
Agranulocytosis	3 (5)	1 (1)
Anemia	16 (28)	19 (23)
Coagulation disorder	0	3 (4)
Disseminated intravascular coagulation	4 (7)	3 (4)
Ecchymosis	11 (19)	7 (8)
Hypochromic anemia	2 (3)	5 (6)
Leukopenia	30 (52)	46 (55)
Lymphadenopathy	0	4 (5)
Pancytopenia	1 (2)	5 (6)
Petechiae	10 (17)	18 (21)
Thrombocytopenia	37 (64)	47 (56)
Metabolic and nutritional		
Alkaline phosphatase increased	4 (7)	7 (8)
Bilirubinemia	7 (12)	15 (18)
Creatinine increased	4 (7)	7 (8)
Dehydration	6 (10)	2 (2)
Edema	3 (5)	9 (11)
Hyperglycemia	4 (7)	9 (11)
Hyperuricemia	0	3 (4)
Hypocalcemia	3 (5)	5 (6)
Hypokalemia	21 (36)	23 (27)
Hypomagnesemia	9 (16)	5 (6)
Hyponatremia	2 (3)	0
Hypophosphatemia	5 (9)	8 (10)
Lactic dehydrogenase increased	7 (12)	12 (14)
Peripheral edema	10 (17)	13 (15)
Weight gain	3 (5)	4 (5)
Weight loss	2 (3)	8 (10)
Musculoskeletal system		
Arthralgia	4 (7)	8 (10)
Bone pain	4 (7)	3 (4)
Myalgia	5 (9)	5 (6)
Nervous system		
Agitation	3 (5)	2 (2)
Anxiety	8 (14)	3 (4)
Confusion	2 (3)	6 (7)
Depression	8 (14)	5 (6)
Dizziness	13 (22)	9 (11)
Insomnia	13 (22)	9 (11)
Somnolence	2 (3)	8 (10)

Table 39. COMMON TEAEs (≥ 5%)[a] REPORTED FOR FEMALE AND MALE PATIENTS IN
PART I: NUMBER (%) OF PATIENTS

Body System Adverse Event[b]	Female (n = 58)	Male (n = 84)
Respiratory system		
Asthma	2 (3)	3 (4)
Cough increased	7 (12)	21 (25)
Dyspnea	15 (26)	31 (37)
Epistaxis	18 (31)	26 (31)
Hemoptysis	2 (3)	4 (5)
Hypoxia	5 (9)	3 (4)
Lung disorder	3 (5)	2 (2)
Pharyngitis	5 (9)	15 (18)
Pleural effusion	4 (7)	6 (7)
Pneumonia	2 (3)	12 (14)
Pulmonary physical finding	5 (9)	11 (13)
Rhinitis	6 (10)	8 (10)
Sinusitis	2 (3)	1 (1)
Upper respiratory infection	2 (3)	0
Skin and appendages		
Acne	3 (5)	3 (4)
Dry skin	2 (3)	0
Herpes simplex	12 (21)	19 (23)
Maculopapular rash	1 (2)	4 (5)
Pruritus	6 (10)	6 (7)
Rash	15 (26)	16 (19)
Skin disorder	2 (3)	6 (7)
Sweating	3 (5)	4 (5)
Special senses		
Abnormal vision	3 (5)	2 (2)
Conjunctivitis	1 (2)	4 (5)
Eye disorder	2 (3)	0
Eye hemorrhage	1 (2)	4 (5)
Study event assoc. w. misc. factors		
Local reaction to procedure	17 (29)	18 (21)
Urogenital system		
Dysuria	2 (3)	1 (1)
Hematuria	4 (7)	10 (12)
Kidney function abnormal	1 (2)	4 (5)
Menorrhagia	3 (5)	0
Metrorrhagia	4 (7)	0
Urinary incontinence	2 (3)	3 (4)
Urinary retention	3 (5)	1 (1)
Urinary tract infection	5 (9)	1 (1)
Vaginal hemorrhage	7 (12)	0

a: ≥ 5% limit specifies the minimum percentage threshold from at least one column as a criterion for an event to be displayed in the table.
b: Percentages for sex-specific adverse events are based on the number of patients of the relevant sex.

5.6.3 Effect of Ethnic Origin

Because the vast majority (94%) of patients enrolled in gemtuzumab ozogamicin clinical trials have been white, an analysis of safety by ethnicity would not be conclusive.

5.6.4 Effect of Hepatic or Renal Insufficiency

Patients with hepatic or renal impairment (bilirubin > 1.5 mg/dL; creatinine > 2.0 mg/dL) were excluded from participation in studies 201 and 202. In study 203, the allowable limits that defined impairment were increased (bilirubin > 2.0 mg/dL; creatinine > 3.0 mg/dL). All patients enrolled in study 203 met the creatinine criteria established for studies 201 and 202. There were two patients entered into study 203 with bilirubin values above 1.5 mg/dL (patients 20388-001 and 20394-001). Neither of these patients developed grade 3 or 4 elevations of hepatic enzymes or bilirubin after gemtuzumab ozogamicin administration. With the data presently available, the effect of gemtuzumab ozogamicin in patients with hepatic or renal impairment cannot be determined.

5.7 Analysis of Safety by Treatment Outcome

For the efficacy endpoints evaluated, the results showed that the outcomes after gemtuzumab ozogamicin treatment were comparable for the patients with CRs and CRps. These included the second CR rate, duration of second CR (relapse-free survival), survival, and survival after HSCT. To further compare the CRp and CR patients, the TEAE profiles of the treatment outcome groups were compared.

5.7.1 Treatment-Emergent Adverse Events

All 4 treatment outcome groups of patients were compared in terms of their adverse event profile. The results of the clinical safety comparison are presented in the following sections. A summary of all common TEAEs in part I (based on an incidence of $\geq 5\%$ of the 142 patients) is presented by treatment outcome category in Table 40.

Table 40. COMMON (≥ 5%)[a] TEAEs BY TREATMENT OUTCOME CATEGORY IN PART I
(STUDIES 201/202/203): NUMBER (%) OF PATIENTS

Body System[b] Adverse Event	TOTAL (n = 142)	CR (n = 23)	CRp (n = 19)	OR (n = 42)	NR (n = 100)
Body as a whole					
Abdomen enlarged	13 (9)	1 (4)	2 (11)	3 (7)	10 (10)
Abdominal pain	52 (37)	6 (26)	10 (53)	16 (38)	36 (36)
Accidental injury	8 (6)	1 (4)	0	1 (2)	7 (7)
Ascites	8 (6)	0	4 (21)	4 (10)	4 (4)
Asthenia	63 (44)	10 (43)	10 (53)	20 (48)	43 (43)
Back pain	22 (15)	3 (13)	3 (16)	6 (14)	16 (16)
Cellulitis	7 (5)	1 (4)	1 (5)	2 (5)	5 (5)
Chest pain	12 (8)	2 (9)	2 (11)	4 (10)	8 (8)
Chills	104 (73)	14 (61)	12 (63)	26 (62)	78 (78)
Face edema	7 (5)	1 (4)	1 (5)	2 (5)	5 (5)
Fever	121 (85)	19 (83)	17 (89)	36 (86)	85 (85)
Headache	50 (35)	10 (43)	5 (26)	15 (36)	35 (35)
Infection	11 (8)	3 (13)	1 (5)	4 (10)	7 (7)
Neck pain	7 (5)	0	1 (5)	1 (2)	6 (6)
Neutropenic fever	30 (21)	4 (17)	6 (32)	10 (24)	20 (20)
Non-specified drug reaction	10 (7)	1 (4)	2 (11)	3 (7)	7 (7)
Pain	30 (21)	6 (26)	6 (32)	12 (29)	18 (18)
Sepsis	36 (25)	7 (30)	4 (21)	11 (26)	25 (25)
Cardiovascular system					
Hemorrhage	14 (10)	0	2 (11)	2 (5)	12 (12)
Hypertension	29 (20)	2 (9)	4 (21)	6 (14)	23 (23)
Hypotension	28 (20)	4 (17)	5 (26)	9 (21)	19 (19)
Tachycardia	15 (11)	4 (17)	1 (5)	5 (12)	10 (10)
Thrombosis	7 (5)	0	1 (5)	1 (2)	6 (6)
Vasodilatation	8 (6)	2 (9)	0	2 (5)	6 (6)
Digestive system					
Anorexia	41 (29)	3 (13)	5 (26)	8 (19)	33 (33)
Constipation	36 (25)	6 (26)	5 (26)	11 (26)	25 (25)
Diarrhea	54 (38)	5 (22)	8 (42)	13 (31)	41 (41)
Dry mouth	9 (6)	0	2 (11)	2 (5)	7 (7)
Dyspepsia	16 (11)	3 (13)	3 (16)	6 (14)	10 (10)
Glossitis	7 (5)	0	2 (11)	2 (5)	5 (5)
Gum hemorrhage	13 (9)	2 (9)	2 (11)	4 (10)	9 (9)
Liver function tests abnormal	35 (25)	5 (22)	2 (11)	7 (17)	28 (28)
Nausea	100 (70)	19 (83)	16 (84)	35 (83)	65 (65)
Oral moniliasis	12 (8)	2 (9)	1 (5)	3 (7)	9 (9)
Stomatitis	45 (32)	6 (26)	6 (32)	12 (29)	33 (33)
Stools abnormal	7 (5)	3 (13)	2 (11)	5 (12)	2 (2)
Vomiting	89 (63)	16 (70)	10 (53)	26 (62)	63 (63)
Hemic and lymphatic system					
Anemia	35 (25)	6 (26)	2 (11)	8 (19)	27 (27)
DIC	7 (5)	0	1 (5)	1 (2)	6 (6)
Ecchymosis	18 (13)	1 (4)	2 (11)	3 (7)	15 (15)
Hypochromic anemia	7 (5)	1 (4)	1 (5)	2 (5)	5 (5)

Table 40. COMMON (≥ 5%)[a] TEAEs BY TREATMENT OUTCOME CATEGORY IN PART I
(STUDIES 201/202/203): NUMBER (%) OF PATIENTS

Body System[b] Adverse Event	TOTAL (n = 142)	CR (n = 23)	CRp (n = 19)	OR (n = 42)	NR (n = 100)
Leukopenia	76 (54)	15 (65)	10 (53)	25 (60)	51 (51)
Petechiae	28 (20)	2 (9)	6 (32)	8 (19)	20 (20)
Thrombocytopenia	84 (59)	17 (74)	9 (47)	26 (62)	58 (58)
Metabolic and nutritional					
Alkaline phosphatase increased	11 (8)	0	1 (5)	1 (2)	10 (10)
Bilirubinemia	22 (15)	3 (13)	1 (5)	4 (10)	18 (18)
Creatinine increased	11 (8)	1 (4)	2 (11)	3 (7)	8 (8)
Dehydration	8 (6)	0	2 (11)	2 (5)	6 (6)
Edema	12 (8)	1 (4)	2 (11)	3 (7)	9 (9)
Hyperglycemia	13 (9)	1 (4)	2 (11)	3 (7)	10 (10)
Hypocalcemia	8 (6)	3 (13)	1 (5)	4 (10)	4 (4)
Hypokalemia	44 (31)	4 (17)	5 (26)	9 (21)	35 (35)
Hypomagnesemia	14 (10)	1 (4)	1 (5)	2 (5)	12 (12)
Hypophosphatemia	13 (9)	3 (13)	0	3 (7)	10 (10)
Lactic dehydrogenase increased	19 (13)	1 (4)	3 (16)	4 (10)	15 (15)
Peripheral edema	23 (16)	2 (9)	4 (21)	6 (14)	17 (17)
Weight gain	7 (5)	1 (4)	2 (11)	3 (7)	4 (4)
Weight loss	10 (7)	2 (9)	1 (5)	3 (7)	7 (7)
Musculoskeletal system					
Arthralgia	12 (8)	4 (17)	1 (5)	5 (12)	7 (7)
Bone pain	7 (5)	0	2 (11)	2 (5)	5 (5)
Myalgia	10 (7)	2 (9)	2 (11)	4 (10)	6 (6)
Nervous system					
Anxiety	11 (8)	3 (13)	1 (5)	4 (10)	7 (7)
Confusion	8 (6)	0	0	0	8 (8)
Depression	13 (9)	4 (17)	0	4 (10)	9 (9)
Dizziness	22 (15)	3 (13)	5 (26)	8 (19)	14 (14)
Insomnia	22 (15)	5 (22)	3 (16)	8 (19)	14 (14)
Somnolence	10 (7)	2 (9)	0	2 (5)	8 (8)
Respiratory system					
Cough increased	28 (20)	3 (13)	4 (21)	7 (17)	21 (21)
Dyspnea	46 (32)	4 (17)	6 (32)	10 (24)	36 (36)
Epistaxis	44 (31)	4 (17)	7 (37)	11 (26)	33 (33)
Hypoxia	8 (6)	1 (4)	1 (5)	2 (5)	6 (6)
Pharyngitis	20 (14)	3 (13)	3 (16)	6 (14)	14 (14)
Pleural effusion	10 (7)	0	3 (16)	3 (7)	7 (7)
Pneumonia	14 (10)	2 (9)	0	2 (5)	12 (12)
Pulmonary physical finding	16 (11)	3 (13)	1 (5)	4 (10)	12 (12)
Rhinitis	14 (10)	1 (4)	2 (11)	3 (7)	11 (11)
Skin and appendages					
Herpes simplex	31 (22)	5 (22)	8 (42)	13 (31)	18 (18)
Pruritus	12 (8)	2 (9)	0	2 (5)	10 (10)
Rash	31 (22)	8 (35)	5 (26)	13 (31)	18 (18)
Skin disorder	8 (6)	0	2 (11)	2 (5)	6 (6)
Sweating	7 (5)	1 (4)	0	1 (2)	6 (6)
Urogenital system					
Hematuria	14 (10)	0	2 (11)	2 (5)	12 (12)

Table 40. COMMON (≥ 5%)[a] TEAEs BY TREATMENT OUTCOME CATEGORY IN PART I
(STUDIES 201/202/203): NUMBER (%) OF PATIENTS

Body System[b] Adverse Event	TOTAL (n = 142)	CR (n = 23)	CRp (n = 19)	OR (n = 42)	NR (n = 100)
Menorrhagia	3 (5)	0	1 (13)	1 (6)	2 (5)
Metrorrhagia	4 (7)	1 (10)	1 (13)	2 (11)	2 (5)
Vaginal hemorrhage	7 (12)	1 (10)	0	1 (6)	6 (15)
Study event assoc. w. misc. Factors					
Local reaction to procedure	35 (25)	5 (22)	7 (37)	12 (29)	23 (23)

a: ≥ 5% limit specifies the minimum percentage threshold from at least one column as a criteria for an event to be displayed in the table.
b: Percentages for sex-specific adverse events are based on the number of patients of the relevant sex.

The TEAEs that occurred in ≥ 25% of each treatment outcome population were identified and the distribution compared across the treatment outcomes. Nine (9) TEAEs were common in all groups: fever (85%), chills (73%), nausea (70%), vomiting (63%), thrombocytopenia (59%), leukopenia (54%), asthenia (44%), headache (35%), and stomatitis (32%).

None of these differences in TEAEs by treatment outcome category during part I of studies 201/202/203 were considered to be clinically important. Specifically, the CR and CRp categories were comparable in their adverse event profile.

5.7.2 Bleeding

The number of patients reported to have common bleeding-related TEAEs (based on an incidence of ≥ 5% of patients) in part I of studies 201/202/203 is presented by treatment outcome in Table 41.

Table 41. 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 =142)	CR (n =23)	CRp (n = 19)	OR (n = 42)	NR (n = 100)
Disseminated intravascular coagulation	7 (5)	0	1 (5)	1 (2)	6 (6)
Ecchymosis	18 (13)	1 (4)	2 (11)	3 (7)	15 (15)
Epistaxis	44 (31)	4 (17)	7 (37)	11 (26)	33 (33)
Gum hemorrhage	13 (9)	2 (9)	2 (11)	4 (10)	9 (9)
Hematuria	14 (10)	0	2 (11)	2 (5)	12 (12)
Hemorrhage	14 (10)	0	2 (11)	2 (5)	12 (12)
Menorrhagia	3 (5)	0	1 (13)	1 (6)	2 (5)
Metrorrhagia	4 (7)	1 (10)	1 (13)	2 (11)	2 (5)
Petechiae	28 (20)	2 (9)	6 (32)	8 (19)	20 (20)
Vaginal hemorrhage	7 (12)	1 (10)	0	1 (6)	6 (15)

a: ≥ 5% limit specifies the minimum percentage from the total of 142 patients.
b: Percentages for sex-specific adverse events are based on the number of patients of the relevant sex.

There were no statistically significant or clinically important differences in bleeding by treatment outcome category during part I of studies 201/202/203; specifically, the CR and CRp categories were comparable in their adverse event profiles.

5.7.3 Infection

The number of patients reported to have common infection-related TEAEs (based on an incidence of ≥ 5% of the 104 patients) in part I of studies 201/202/203 by treatment outcome is presented in Table 42.

Table 42. COMMON (≥ 5%)[a] INFECTION TEAEs IN PART 1 BY TREATMENT OUTCOME CATEGORY (STUDIES 201/202/203): NUMBER (%) OF PATIENTS

Infection Adverse Event[b]	Total (n =142)	CR (n =23)	CRp (n = 19)	OR (n = 42)	NR (n = 100)
Cellulitis	7 (5)	1 (4)	1 (5)	2 (5)	5 (5)
Cough increased	28 (20)	3 (13)	4 (21)	7 (17)	21 (21)
Glossitis	7 (5)	0	2 (11)	2 (5)	5 (5)
Herpes simplex	31 (22)	5 (22)	8 (42)	13 (31)	18 (18)
Infection	11 (8)	3 (13)	1 (5)	4 (10)	7 (7)
Injection site reaction	3 (2)	0	1 (5)	1 (2)	2 (2)
Mouth ulceration	4 (3)	2 (9)	0	2 (5)	2 (2)
Oral moniliasis	12 (8)	2 (9)	1 (5)	3 (7)	9 (9)
Pneumonia	14 (10)	2 (9)	0	2 (5)	12 (12)
Rhinitis	14 (10)	1 (4)	2 (11)	3 (7)	11 (11)
Sepsis	36 (25)	7 (30)	4 (21)	11 (26)	25 (25)
Stomatitis	45 (32)	6 (26)	6 (32)	12 (29)	33 (33)

a: ≥ 5% limit specifies the minimum percentage from the total of 142 patients.
b: Percentages for sex-specific adverse events are based on the number of patients of the
     relevant sex.

There were no clinically important differences in infection by treatment outcome category during part I of studies 201/202/203; specifically, the CR and CRp categories were comparable in their adverse event profiles.

5.7.4 Post-Hematopoietic Stem Cell Transplantation Events

5.7.4.1 Transplantation

In the phase II studies, patients who received therapy with gemtuzumab ozogamicin could receive postremission therapy if they had remission, or could receive additional antileukemic therapy if they failed to have remission. This included both HSCT and non-HSCT approaches. Twenty-eight (28) patients received HSCT and 58 patients received additional anti-leukemia chemotherapy. Table 43 presents summaries of survival and treatment outcomes for patients who received HSCT after treatment with gemtuzumab ozogamicin.

Table 43.   SUMMARY OF SURVIVAL AND TREATMENT OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION PATIENTS

Category Cell Source	n	-------- Survival --------		-----GO Treatment Outcome -----		
		30 Day	100 Day	CR	CRp	NR
Autologous	8	8	8	5	1	2
BM	2	2	2	1	0	1
PBSC	6	6	6	4	1	1
Allogeneic	20	17	12	4	6	10
BM	9	7	5	2	2	5
PBSC	11	10	7	2	4	5
Total	28	25	20	9[a]	7	12
BM	11	9	7	3	2	6
PBSC	17	16	13	6	5	6

a: One (1) patient (201B0-0003) had a relapse 25 Jan 1999 and afterwards received a transplantation on 29 Mar 1999.

The Kaplan-Meier estimate of survival after HSCT for the 16 patients in the OR group is 0.9375 for both 30 and 100 days. The value is the same because there were no additional deaths between 30 and 100 days. A summary of TEAEs following HSCT is presented in section 5.7.4.2.

5.7.4.2 Treatment-Emergent Adverse Events

The patients who received HSCT were followed up for the incidence of infections, bleeding, veno-occlusive disease (VOD), graft versus host disease (GVHD), other serious events and survival. The results of TEAEs following HSCT are summarized in Table 44.

Table 44. TEAEs[a] AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION BY TREATMENT
OUTCOME CATEGORY: FOLLOW-UP (STUDIES 201/202/203): NUMBER (%) OF PATIENTS

Body System[b] Adverse Event	Total (n = 28)	CR (n = 9)	CRp (n = 7)	OR (n = 16)	NR (n = 12)
Any adverse event	19 (68)	6 (67)	6 (86)	12 (75)	7 (58)
Body as a whole					
Asthenia	1 (4)	0	0	0	1 (8)
Fever	4 (14)	2 (22)	0	2 (13)	2 (17)
Headache	1 (4)	1 (11)	0	1 (6)	0
Immune system disorder	5 (18)	1 (11)	2 (29)	3 (19)	2 (17)
Infection	2 (7)	1 (11)	1 (14)	2 (13)	0
Malaise	1 (4)	1 (11)	0	1 (6)	0
Moniliasis	1 (4)	0	0	0	1 (8)
Neutropenic fever	2 (7)	1 (11)	0	1 (6)	1 (8)
Pain	1 (4)	1 (11)	0	1 (6)	0
Sepsis	5 (18)	4 (44)	0	4 (25)	1 (8)
Cardiovascular system					
Atrial flutter	1 (4)	0	0	0	1 (8)
Bradycardia	1 (4)	1 (11)	0	1 (6)	0
Cerebral ischemia	1 (4)	1 (11)	0	1 (6)	0
Cerebrovascular accident	1 (4)	0	0	0	1 (8)
Hypertension	2 (7)	1 (11)	0	1 (6)	1 (8)
Hypervolemia	1 (4)	0	1 (14)	1 (6)	0
Hypotension	1 (4)	1 (11)	0	1 (6)	0
Shock	1 (4)	0	0	0	1 (8)
Digestive system					
Diarrhea	1 (4)	0	1 (14)	1 (6)	0
Gastrointestinal hemorrhage	2 (7)	0	1 (14)	1 (6)	1 (8)
Hepatic failure	1 (4)	0	0	0	1 (8)
Liver function tests abnormal	3 (11)	0	1 (14)	1 (6)	2 (17)
Stomach ulcer hemorrhage	1 (4)	1 (11)	0	1 (6)	0
Stomatitis	2 (7)	0	1 (14)	1 (6)	1 (8)
Venoocclusive liver disease	2 (7)	1 (11)	0	1 (6)	1 (8)
Hemic and lymphatic system					
Coagulation disorder	1 (4)	0	0	0	1 (8)
Marrow depression	1 (4)	0	0	0	1 (8)
Metabolic and nutritional					
Bilirubinemia	2 (7)	0	2 (29)	2 (13)	0
Hyperglycemia	1 (4)	1 (11)	0	1 (6)	0
Hypomagnesemia	2 (7)	0	2 (29)	2 (13)	0
Peripheral edema	1 (4)	0	1 (14)	1 (6)	0
Musculoskeletal system					
Osteoporosis	1 (4)	0	0	0	1 (8)
Nervous system					
Convulsion	1 (4)	0	0	0	1 (8)
Encephalopathy	2 (7)	1 (11)	0	1 (6)	1 (8)
Hypesthesia	1 (4)	1 (11)	0	1 (6)	0
Respiratory system					
Atelectasis	1 (4)	1 (11)	0	1 (6)	0
Lung edema	1 (4)	1 (11)	0	1 (6)	0
Pharyngitis	1 (4)	1 (11)	0	1 (6)	0
Pneumonia	1 (4)	0	0	0	1 (8)
Respiratory failure	1 (4)	0	0	0	1 (8)
Skin and appendages					
Herpes simplex	1 (4)	1 (11)	0	1 (6)	0

Table 44. TEAEs[a] AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION BY TREATMENT OUTCOME CATEGORY: FOLLOW-UP (STUDIES 201/202/203): NUMBER (%) OF PATIENTS

Body System[b] Adverse Event	Total (n = 28)	CR (n = 9)	CRp (n = 7)	OR (n = 16)	NR (n = 12)
Rash	2 (7)	1 (11)	0	1 (6)	1 (8)
Special senses					
Dry eyes	1 (4)	0	0	0	1 (8)
Urogenital system					
Hemorrhagic cystitis	2 (7)	1 (11)	1 (14)	2 (13)	0
Kidney failure	2 (7)	1 (11)	0	1 (6)	1 (8)
Kidney function abnormal	1 (4)	0	0	0	1 (8)
Testis disorder	1 (8)	0	1 (33)	1 (11)	0
Study event assoc. w. misc. factors					
Local reaction to procedure	1 (4)	0	1 (14)	1 (6)	0

a: TEAE were defined using pre-HSCT status as baseline.

b: Body system totals are not necessarily the sum of the individual adverse events since a patient may report 2 or more different adverse events in the same body system. Percentages for sex-specific adverse events are based on the number of patients of the relevant sex.

The CR and CRp categories were comparable in their adverse event profile, including bleeding and infection. No meaningful differences in these TEAE were observed among the treatment outcome groups; however, the small number of patients precludes definitive statements.

Of the 28 patients who received HSCT, 2 patients (201B3-0003, 201B3-0010) developed VOD and died 22 and 37 days after transplantation. One (1) other patient (201B3-0007) who died on the day of his transplantation has VOD listed as the cause of death. VOD is a known complication of high-dose chemotherapy and HSCT. One (1) patient (20280-0001) developed GVHD (listed as immune system disorder in DPR) and died 38 days after receiving HSCT.

5.7.4.3 Bleeding

A total of 6 patients reported bleeding TEAEs after they received HSCT. The TEAEs are presented by response category in Table 45. Because of the small number of patients reported to have bleeding, no clinically meaningful comparisons can be made among treatment outcome groups.

Table 45. NUMBER (%) OF PATIENTS REPORTING BLEEDING TREATMENT-EMERGENT ADVERSE EVENTS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION BY TREATMENT OUTCOME CATEGORY: FOLLOW-UP (STUDIES 201/202/203)

Adverse Event	Total (n = 28)	CR (n = 9)	CRp (n = 7)	OR (n = 16)	NR (n = 12)
Any bleeding adverse event	5[a] (18)	2 (22)	2 (29)	4 (25)	1 (8)
Gastrointestinal hemorrhage	2 (7)	0	1 (14)	1 (6)	1 (8)
Hemorrhagic cystitis	2 (7)	1 (11)	1 (14)	2 (13)	0
Stomach ulcer hemorrhage	1 (4)	1 (11)	0	1 (6)	0

a: One (1) additional patient (20277-0004) had cerebellar bleeding after an allogenic HSCT. This adverse event was coded as cerebrovascular accident under the cardiovascular body system, which was not included in the list of COSTART terms for the bleeding subcategory.

5.7.4.4 Infection

The number and percentage of patients reporting infections after HSCT by treatment outcome category is presented in Table 46. Infections are expected because of immunosuppression associated with both HSCT and AML. The incidence of infections reported in Table 46 is lower than that presented in section 5.3.4.5 and most likely reflects the collection of only serious adverse events. Because of the small numbers of patients reported to have infections, no clinically meaningful comparisons can be made among treatment outcome groups.

Table 46. NUMBER (%) OF PATIENTS REPORTING INFECTION TREATMENT-EMERGENT ADVERSE EVENTS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION BY TREATMENT OUTCOME CATEGORY: FOLLOW-UP (STUDIES 201/202/203)

Body System Adverse Event	Total (n = 28)	CR (n = 9)	CRp (n = 7)	OR (n = 16)	NR (n = 12)
Any infection adverse event	10 (36)	4 (44)	2 (29)	6 (38)	4 (33)
Herpes simplex	1 (4)	1 (11)	0	1 (6)	0
Infection	2 (7)	1 (11)	1 (14)	2 (13)	0
Pneumonia	1 (4)	0	0	0	1 (8)
Sepsis	5 (18)	4 (44)	0	4 (25)	1 (8)
Shock	1 (4)	0	0	0	1 (8)
Stomatitis	2 (7)	0	1 (14)	1 (6)	1 (8)

5.7.5 Hematopoietic Recovery (Platelet, ANC, Hemoglobin)

The method for calculating recovery of platelets and absolute neutrophil count (ANC) has not been commonly specified in published reports. When specified, however, it is defined as recovery from the start of chemotherapy. Consequently, for this report, recovery of these parameters was assessed from the first dose.

A comparison of patients who had CRs and those who had CRps shows a slower recovery of platelets for the CRp patients, as expected from the criteria used to define these populations. By definition, CRp patients had to meet the same criteria for remission that CR patients did except for platelet recovery to 100,000 platelets/µL. Despite the slower recovery of platelets in the CRp patients, these patients became platelet transfusion independent and were otherwise clinically comparable with patients with CRs.

The time to recovery of platelet counts by remission status, measured from the time of administration of the first dose of gemtuzumab ozogamicin is shown in Table 47. The data presented are for the patients whose platelet counts recovered to the target levels.

Table 47. TIME TO PLATELET RECOVERY (DAYS) FROM FIRST DOSE OF GEMTUZUMAB OZOGAMICIN (STUDIES 201/202/203)

Parameter Statistic	All Patients	CR	CRp	OR	NR
Total no. patients	(n = 142)	(n = 23)	(n = 19)	(n = 42)	(n = 100)
Platelets ≥ 25,000/µL					
n	71	23	17	40	31
Median	35.0	34.0	48.0	38.5	29.0
Min - Max	8 – 119	17 - 71	16 - 91	16 - 91	8 - 119
Platelets ≥ 50,000/µL					
n	53	23	13	36	17
Median	40.0	38.0	56.0	41.5	36.0
Min - Max	16 - 155	17 - 71	16 - 86	16 - 86	16 - 155
Platelets ≥ 75,000/µL					
n	39	23	8	31	8
Median	41.0	41.0	61.0	43.0	26.5
Min – Max	16 - 142	19 - 71	16 - 142	16 - 142	17 - 74
Platelets ≥ 100,000/µL					
n	30	23	1	24	6
Median	44.0	50.0	26.0	50.0	29.0
Min - Max	17 - 173	21 - 173	26 - 26	21 - 173	17 - 33

All patients with a CR or a CRp had to have ANC recovery to ≥ 1,500/µL by definition. The time to recovery of ANC by remission status, measured from the time of administration of the first dose of gemtuzumab ozogamicin, is shown in Table 48. The data presented are for the patients whose ANC recovered to the target levels.

Table 48. TIME TO RECOVERY OF ANC FROM FIRST DOSE OF GEMTUZUMAB
OZOGAMICIN (STUDIES 201/202/203)

Parameter Statistic	All Patients	CR	CRp	OR	NR
Total no. of patients	(n = 142)	(n = 23)	(n = 19)	(n = 42)	(n = 100)
ANC ≥ 500/μL					
n	77	23	19	42	35
Median	42.0	41.0	40.0	40.5	44.0
Min - Max	12 - 105	16 - 85	18 - 84	16 - 85	12 - 105
ANC ≥ 1,000/μL					
n	67	23	19	42	25
Median	44.0	43.0	44.0	43.0	45.0
Min - Max	12 - 105	16 - 85	30 - 85	16 – 85	12 - 105
ANC ≥ 1,500/μL					
n	61	23	19	42	19
Median	48.0	45.0	54.0	49.0	47.0
Min - Max	12 - 177	30 - 85	30 - 150	30 - 150	12 – 177

By definition, all patients classified as a CR or a CRp had to have recovery of hemoglobin to ≥ 9 g/dL, independent of RBC transfusions. The median time to hemoglobin recovery was 11 days for the CR patients and 37 days for the CRp patients. Among patients with NR, only 32% had hemoglobin recovery to ≥ 9 g/dL.

5.7.6 Platelet and RBC Transfusions

RBC and platelet transfusions were analyzed as the number of transfusion events during part I. The number of platelet and RBC transfusions over the entire course of part I, by response status and study population is shown in Table 49.

Table 49. PLATELET AND RBC TRANSFUSIONS DURING STUDY PART I
(STUDIES 201/202/203)

Parameter Statistic	All Patients	CR	CRp	OR	NR
No. of platelet transfusions					
Total no. patients	(n = 142)	(n = 23)	(n = 19)	(n = 42)	(n = 100)
Mean (SD)	14.0 (23)	5.4 (6)	14.8 (12)	9.7 (10)	15.8 (27)
Median	11.0	4.0	12.0	6.0	12.5
95% CI	(10, 13)	(2.5, 7)	(9, 18.5)	(5.5, 11)	(11, 15)
95% CI for CRp-CR	(4, 12)[a]				
No. of RBC transfusions					
Total no. patients	(n = 142)	(n = 23)	(n = 19)	(n = 42)	(n = 100)
Mean (SD)	8.2 (26)	2.6 (2)	6.2 (5)	4.2 (4)	9.9 (31)
Median	4.0	2.0	5.0	3.5	5.0
95% CI	(4, 5)	(1.5, 3.5)	(4, 7.5)	(3, 5)	(4.5, 6)
95% CI for CRp-CR	(1, 5)[a]				

a: Significant difference between CR and CRp.

Patients who had CRs received fewer platelet transfusions (median of 4.0) than those who had CRps or NRs (medians of 12 and 12.5, respectively). The difference in the median number of platelet transfusions between the CR and CRp groups was statistically significant.

The patients who had CRs also received fewer RBC transfusions (median of 2.0) than patients with CRps or NRs (both medians 5.0). The difference in the median number of RBC transfusions between the CR and CRp groups was statistically significant.

5.7.7 Hospitalizations
The median number of days of hospitalization among all of the 142 patients in the phase II studies was 24 days (Figure 17 and Table 50). For patients who had a CR, the median number of days of hospitalization was 18 days, for CRps it was 13 days, and for NRs 26.5 days. However, the median data included patients who died during part I of the study (within 28 days of the last dose of gemtuzumab ozogamicin) who may have had hospitalization shortened by their deaths.

Figure 17. BOX PLOT OF DURATION OF HOSPITALIZATION BY RESPONSE GROUP FOR HOSPITALIZATIONS OCCURRING IN PART I (STUDIES 201/202/203), ALL PATIENTS

Statistical Report <E03A01 07JAN00>
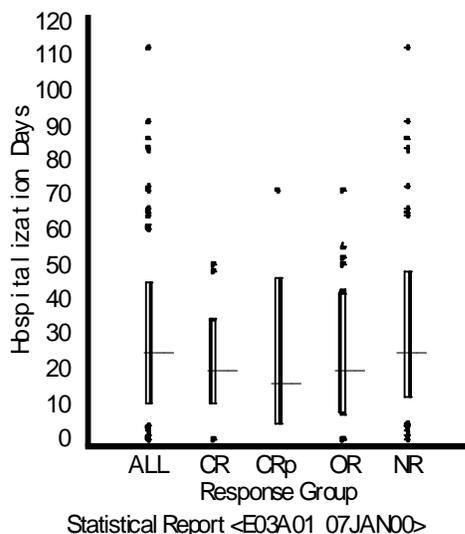
The number of days of hospitalizations, number of times patients were hospitalized, and time to hospitalizations during part I of the studies are summarized in Table 50 by remission status. The incidence and number of days of hospitalizations were similar for CR and CRp patients.

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Table 50. SUMMARY OF PATIENT HOSPITALIZATIONS DURING STUDY PART I,
ALL PATIENTS (STUDIES 201/202/203)

Statistic	All Patients (n = 142)	CR (n = 23)	CRp (n = 19)	OR (n = 42)	NR (n = 100)
Number of hospitalizations					
Median no. hospitalizations	1.5	2	2	2	1
No. of hospitalizations[a]					
0	5	2	2	4	1
1	66	8	7	15	51
2	44	9	5	14	30
> 2	27	4	5	9	18
Number of days of hospitalization					
Median no. days	24	18	13	17.5	26.5
Min - Max	0 - 133	0 - 50	0 - 71	0 - 71	0 - 133
No. hospitalization days[b]					
0	5	2	2	4	1
1 to 7	21	3	6	9	12
8 to 14	21	4	2	6	15
> 14	95	14	9	23	72
Time to first hospitalization					
Median no. days	1	1	1	1	1
Min - Max	1 - 50	1 - 50	1 - 43	1 - 50	1 - 50

a: Number of patients hospitalized 0, 1, 2, > 2 times.
b: Number of patients hospitalized for 0, 1 - 7, 8 - 14, and > 14 days.

A large percentage of patients had brief hospitalizations; 26 (18%) of the 142 gemtuzumab ozogamicin-treated patients had 0 to 7 days of hospitalization during part I of the phase II trials. Five (5, 4%) of these patients had no days of hospitalization, and 21 (15%) of these patients had 1 to 7 days of hospitalization. In addition, 21 (15%) were hospitalized for 8 to 14 days.

None of the publications in the literature that were reviewed reported having patients with no days of hospitalization (see section 7.5.1). In published reports of health outcomes of current therapy of AML, the median number of days in the hospital varied from 29 to 38.[2,3] These results indicate that patients who had CRs and CRps in the gemtuzumab ozogamicin studies had fewer days of hospitalization than patients treated with conventional chemotherapy.

An analysis of hospitalizations was also done without patients who died during part I. When patients who died during part I are excluded, the overall median number of days of hospitalization was 27 days in part I of studies 201/202/203. The median number of days of hospitalization was 18 days for patients who had CRs and 13 for those who had CRps, whereas it was 33 days for the patients without remissions.

5.8 Other Categories of Safety Information

5.8.1 Drug-Drug Interaction

There have been no formal studies of the interaction of gemtuzumab ozogamicin with concomitant medications.

5.8.2 Concomitant Medications

AML patients in relapse receive a variety of medications for the management of their disease. Examination of the clinical records from these studies did not indicate any association between treatment with gemtuzumab ozogamicin and specific adverse events following the use of concomitant medications, or any marked change in the efficacy or safety of the concomitant medications themselves.

5.8.3 Progress Report on Ongoing Phase II Studies

In serious and unexpected adverse events occurring in the patient population enrolled by 30 Apr 1999 and reported between 29 Jul 1999 and 30 Nov 1999, none indicated a new category of adverse events or a change in frequency from that observed earlier in clinical trials with gemtuzumab ozogamicin.

Studies 201, 202, and 203 are ongoing and remain open to enroll additional patients and to obtain additional safety and efficacy information. Between 30 Apr 1999 and 30 Nov 1999, an additional 11, 36, and 40 patients were enrolled in studies 201, 202, and 203, respectively. The overall safety profile remains unchanged with low rates of severe mucositis and low rates of severe infections. There were 3 cases of VOD reported in these patients. Of these 3 cases, 2 occurred after 1 dose and 1 occurred after 2 doses. One (1) case of VOD (patient 20277-0011) resolved and follow-up is ongoing for the other 2 cases (patients 20274-0010 and 20293-0003). The databases for these studies are not complete and in many instances only incomplete information is available from the investigator.

Six (6) additional patients (201B2-0206, 201B2-0212, 20285-0201, 20289-0202, 20361-0302, and 20370-0202) received more than 1 course of gemtuzumab ozogamicin. Patient 20361-0302 (previously reported as 20361-0002) received 3 courses of gemtuzumab ozogamicin.

All patients continued to be examined for the development of antibodies to gemtuzumab ozogamicin; none of the patients to date in the pediatric or phase II studies developed antibodies to gemtuzumab ozogamicin.

5.9 Safety Conclusions

Data from 3 phase II studies demonstrate the safety of gemtuzumab ozogamicin in the treatment of AML in first relapse.

Specifically, the safety data support the following conclusions:

- The adverse event profile of gemtuzumab ozogamicin is similar to that of conventional chemotherapies in terms of myelosuppression and bleeding but offers a safety advantage in terms of:
  1. Low incidence of severe mucositis.
  2. Low incidence of severe infections.
  3. Reduced median number of days of hospitalization because of both short outpatient infusion and decreased need for in-hospital supportive care.
  4. Generally mild and reversible nausea and vomiting.
  5. No alopecia.
- The safety profile of gemtuzumab ozogamicin is comparable in CR and CRp patients.

  Although CRp patients had slower platelet recovery and required more platelet and RBC transfusions than CR patients, they became transfusion-independent like the CRs, and there were no clinically meaningful differences in safety parameters, including bleeding.
- 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 and without clinical sequelae.
- Transient and reversible liver function test abnormalities occurred with moderate incidence.
- In patients who received HSCT after gemtuzumab ozogamicin therapy, there were no unexpected adverse events.
- No patients developed an immune response to gemtuzumab ozogamicin in the phase II studies.

6. HUMAN PHARMACODYNAMICS AND PHARMACOKINETICS

6.1 Pharmacodynamics

There are 3 aspects to the dose of gemtuzumab ozogamicin: the amount of medication administered with each dose, the time interval between doses, and the number of doses administered. Each of these will be considered to explain how the recommended dose schedule was determined.

Amount – It is believed that gemtuzumab ozogamicin reaches its site of action in the leukemic cell by binding to CD33 positive cells and subsequent internalization of the drug-receptor complex. Extensive saturation of potential binding sites is thus fundamental to effective therapy. As shown in Figure 18, there is variability in saturation when the area under the concentration time curve (AUC) is less than 100 mg.h/L. The dose that can be reasonably expected to produce an AUC of at least 100 mg.h/L is 9 mg/m^2 of gemtuzumab ozogamicin. Thus it was concluded that 9 mg/m^2 was the best dose to give for optimal saturation.

Time Interval Between Doses – The half-life ($t_{1/2}$) of hP67.6 is 67 ± 37 hours. A dose would be expected to be completely cleared from the body in 4 to 5 half-lives, which is approximately 11 to 14 days. A dose interval of 2 weeks would therefore be expected to allow complete elimination before receiving another dose.

Number of Doses – The phase I clinical trial used 3 doses of medication; however, 3 doses resulted in an unacceptable level of toxicity. One (1) patient had profound, long-lasting myelosuppression. Consequently, a treatment course of 2 doses was adopted for the phase II studies.

In conclusion, data have been presented that justify the amount of gemtuzumab ozogamicin administered in each dose, the time interval between doses, and the number of doses in a treatment regimen, supportive of the conclusion that 9 mg/m^2 administered twice, 2 weeks apart, would be the optimal dose to study in clinical trials.

6.2 Pharmacokinetics

The pharmacokinetics of gemtuzumab ozogamicin have been well described. Every patient who was treated had samples collected for the measurement of hP67.6, calicheamicin and unbound calicheamicin. Assay problems and instability of samples meant that

calicheamicin concentrations, both total and unconjugated, were available only for patients in phase II studies.

The concentrations of hP67.6 were measured with an enzyme-linked immunosorbent assay. Adequate stability of the samples was demonstrated.

After administration of the recommended 9 mg/m^2 dose of gemtuzumab ozogamicin, the pharmacokinetic parameters (mean ± SD) of hP67.6 following the first dose were as follows: peak plasma concentration (C_{max}), 3.09 ± 2.27 mg/L; AUC, 132 ± 136 mg·h/L; $t_{1/2}$, 66.5 ± 36.8 h; and clearance (CL), 0.353 ± 0.551 L/h. Accumulation of gemtuzumab ozogamicin is not expected with a 14-day period between doses, based on the half-life. Increased concentrations observed after the second dose are believed to be due to a reduced tumor burden, by decreasing the number of blast cells and decreasing the clearance by CD33 positive blast cells.

The volume of distribution is 20.6 ± 20.2 L, suggesting that gemtuzumab ozogamicin does not extensively distribute into the peripheral compartment. This value is consistent with those estimated from biodistribution studies reported in the literature that used various radiolabeled anti-CD33 antibodies. Metabolic studies give additional support to the known hydrolytic release of a specific calicheamicin derivative from gemtuzumab ozogamicin. Many metabolites of this derivative were found after in vitro incubation in liver microsomes and cytosol, and in HL-60 promyelocytic leukemia cells. The formation of NAc-epsilon calicheamicin and its derivatives appears to be the major metabolic pathway in vivo.

Although there is large interindividual variability, differences in pharmacokinetic parameters because of age, sex, weight, body surface area, or ethnicity were not observed. Also, no relationship was found between plasma concentration and either response or adverse experiences at the recommended dose.

Drug interaction studies were not part of the clinical program. Standard pretreatment was not administered in several patients. Their hP67.6 concentrations were similar to those of patients receiving pretreatment with acetaminophen and antihistamines.

Preliminary pharmacokinetic data are also available from 5 children with AML who received 6 mg/m^2 of gemtuzumab ozogamicin. The pharmacokinetic parameters of hP67.6 in children (mean ± SD) following the first dose were: C_{max} 1.42 ± 0.92 mg/L, AUC 48.5 ±

43.0 mg·h/L, $t_{1/2}$ 51.6 ± 25.0 hr, CL 0.296 ± 0.248 L/h (0.254 ± 0.211 L/h/m^2) and V 16.3 ± 10.7 L (13.1 ± 7.8 L/m^2).

The concentrations of calicheamicin decrease in a parallel fashion to those of hP67.6 as may be seen in Figure 19.   The ratio of total calicheamicin AUC to hP67.6 AUC was 2.02% for the first dose period and 2.46% for the second dose period, consistent with the molar ratio within gemtuzumab ozogamicin.

Figure 18. PERIPHERAL SATURATION OF CD33 VERSUS HP67.6 AUC FOLLOWING A DOSE OF BETWEEN 0.25 AND 9 mg/m^2 OF GEMTUZUMAB OZOGAMICIN.
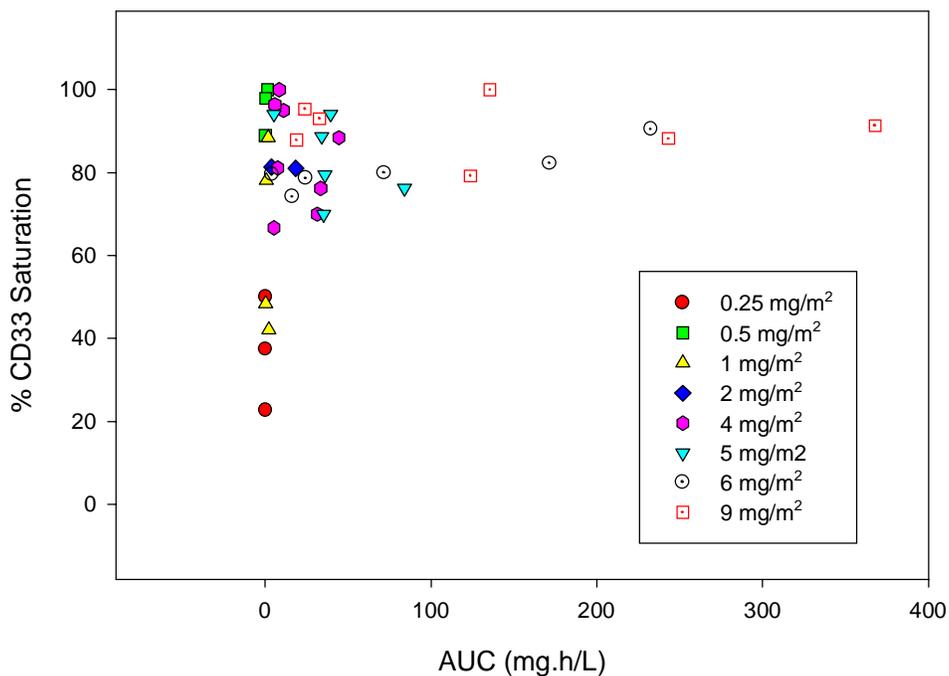
Figure 19. MEAN AND STANDARD DEVIATION OF HP67.6, TOTAL
CALICHEAMICIN, AND UNCONJUGATED CALICHEAMICIN VERSUS TIME
FOLLOWING DOSES OF 9 mg/m^2 OF GEMTUZUMAB OZOGAMICIN.
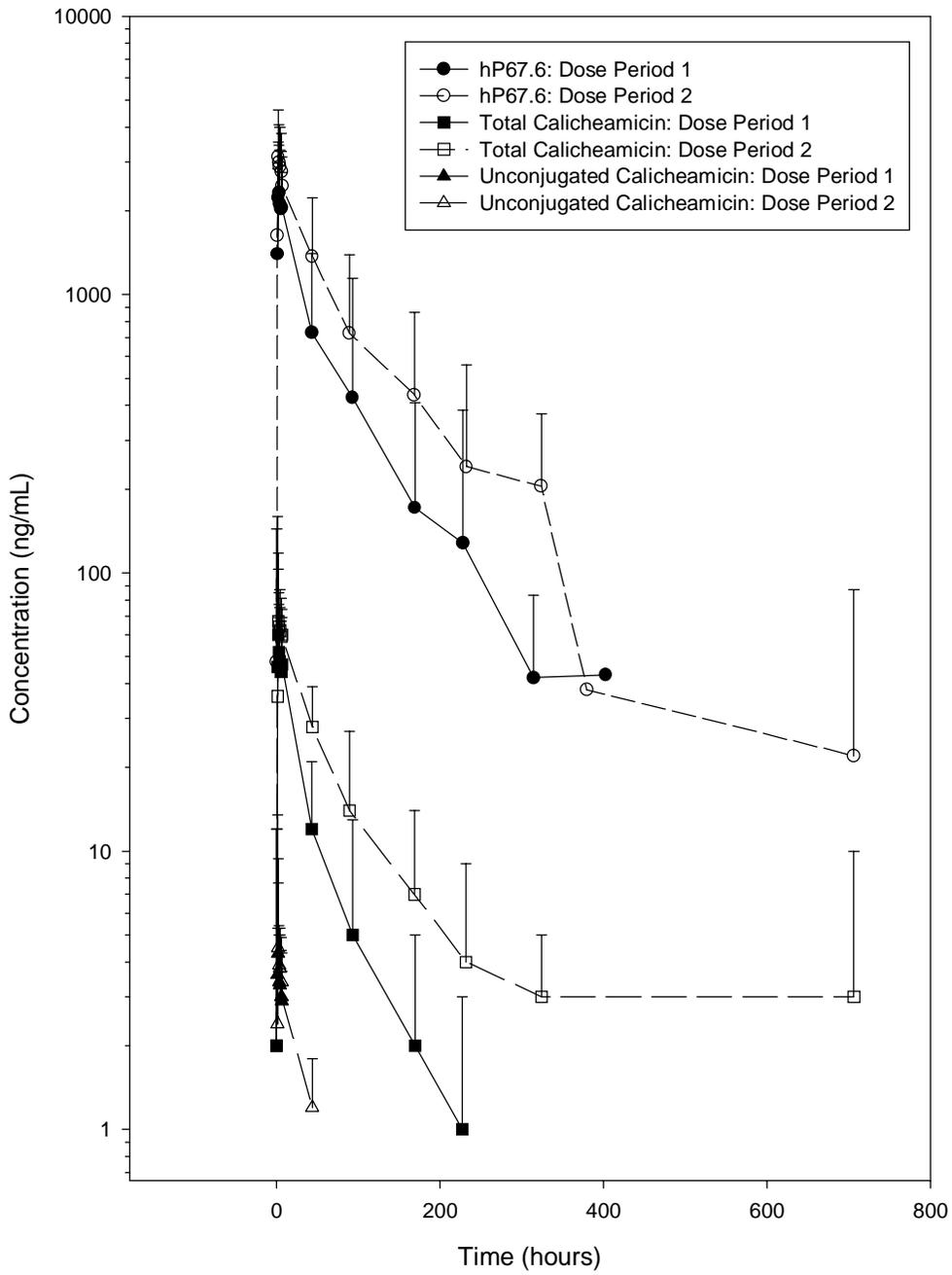
7. LITERATURE AND INSTITUTIONAL DATABASE REVIEW

7.1 Introduction and Overview

In response to a request by the FDA, the efficacy and safety of gemtuzumab ozogamicin in patients with AML in first relapse were compared with those of available combination therapies by using data from the medical literature and from institutional databases. This was necessary because there are several practical difficulties in conducting randomized comparative studies with relapsed AML patients. The number of patients with relapsed AML is limited, there are no conventional regimens specifically approved for treatment of relapsed AML, and a placebo-controlled design is not an option for ethical reasons. For these reasons, W-AR did not include a comparison treatment in the studies of gemtuzumab ozogamicin.

7.1.1 Sources of Data for Comparison

The data collection efforts included 1) a comprehensive search of the medical literature and selection of papers reporting studies in patient populations with AML in first relapse and with stated prognostic factors, and 2) evaluation of data from several institutional/cooperative group databases on AML patients in first relapse. The efficacy and safety data from these efforts were compared with corresponding data from gemtuzumab ozogamicin clinical studies, although no statistical comparisons were made with the efficacy data. A summary of the results is provided here.

A Medline search was performed for publications including patients with relapsed AML published after 1979. From this search, 524 abstracts were identified and screened, 104 papers were reviewed, and 22 papers were selected that provided sufficient information on important prognostic factors for patients with AML in first relapse. Excluded were articles that reported on fewer than 20 patients, had undefined durations of first CR, or included primarily pediatric patients. The studies reported in the selected papers involved a total of 1,903 patients. The extent of overlap among the patient populations in the published literature is unknown. According to the literature, the 2 most important factors in predicting response to therapy for patients with AML in first relapse are a patient's age and duration of first remission. Because of this, patients in each of the data collection efforts described above were chosen only if their age and duration of first remission were available.

The institutional databases included information on 2,193 patients with AML in first relapse. The extent of overlap between the patient populations from the published literature and the databases is unknown. The institutional databases used to obtain supplemental

information about the treatment of AML patients in first relapse included databases from the MD Anderson Cancer Center in Houston, Texas, the University of Vienna, Austria, and the Medical Research Council (MRC), University of Birmingham, United Kingdom. The data obtained from these medical centers were not quality assured, or monitored, and the analyses were exploratory in nature. A chart review was also done at Brigham and Women's Hospital (BWH) to obtain hospitalization data for patients being treated for AML in first relapse.

The MD Anderson Cancer Center has a database with information on over 300 patients with AML, including 200 patients in first relapse treated over the past 20 years. The database was reviewed for patients who had remissions but whose platelets failed to recover to 100,000/μL to determine the incidence of CRp as defined in the gemtuzumab ozogamicin studies. In addition, the remission rates and survival of 59 patients in gemtuzumab ozogamicin study 201 were compared with the remission rates of 121 patients treated with HiDAC at the MD Anderson Cancer Center. The patients were matched for age, duration of first CR, and cytogenetic risk category.

The Austrian database has detailed information on 170 patients with AML in first relapse with adequate follow-up data for analysis. Of the 170 patients, 119 received chemotherapy for relapsed AML and 51 received only supportive/palliative therapy. These data were analyzed for correlation between duration of first CR and age with second CR rate, duration of second CR, and survival. In addition, this database was reviewed for the time to recovery of ANC and platelets, and outcome of HSCT.

The largest database of patients with AML in first relapse that was available to us was the MRC database. This database has data from 5,307 de novo AML patients treated in 3 successive trials during the past decade; 1,696 of these patients had relapsed as of 01 Jul 1999. These data were also analyzed for correlation between duration of first CR and age with second CR rate, duration of second CR, and survival. In addition, a subset of this database including 175 patients with AML in first relapse was reviewed for the time to recovery of ANC and platelets, specific adverse events, and outcome of HSCT.

7.1.2 Efficacy Endpoints
The primary efficacy endpoints obtained from the publications reviewed were the second CR rate, duration of second CR, overall survival, and outcome of patients who received an HSCT in second CR. Various definitions of CR were used in the published

reports and most often they were not completely consistent with, for instance, the Cancer and Leukemia Group B criteria previously published. The validity of comparisons of remission rates between published reports and the gemtuzumab ozogamicin trials depends critically on the definition of CR used.

7.2 Results of Literature Review of Current Relapsed AML Therapies

The literature review demonstrated that there was a wide range of remission rates and survival for patients with AML in first relapse treated with conventional therapies. In prospective trials of single-agent therapies for AML in first relapse, the remission rates varied from 8% to 40%, and in prospective trials of combination therapies for AML in first relapse, from 14% to 89%. These remission rates were significantly influenced by age and duration of first remission of the patients enrolled. Median duration of second CRs generally varied from 3 to 12 months for responders. However, the median duration of survival for nonresponders was only approximately 2 months. Despite the occurrence of remissions in patients with AML in first relapse, only 5% to 10% of patients have long-term disease-free survival with chemotherapy in the absence of HSCT.

Multivariate analyses performed in the publications consistently showed that duration of first CR was an important predictor of response to therapy for AML in first relapse. Age was often, but not universally, found to be a predictor of the response rate to chemotherapy. No other factor, including type of treatment regimen or identification of a specific cytogenetic abnormality, reliably predicted response to treatment.

In addition, as a group, these studies reported limited survival rates and high treatment mortality rates in AML patients in first relapse when compared with de novo AML patients. Relatively little insight was obtained regarding the incidence of CRp in publications in the medical literature. Based on the limited data available, it is deduced to be less than 5%. Also, conventional chemotherapy appears to be associated with a high incidence of clinically important mucositis, infection, and hospitalization when compared with gemtuzumab ozogamicin.

7.3 Efficacy Comparison of Gemtuzumab Ozogamicin and Conventional Chemotherapy

7.3.1 Literature Review

This section compares the key efficacy results from the gemtuzumab ozogamicin clinical trials with data obtained from the literature review. When pretreatment factors were

considered, patients with AML in first relapse treated with conventional therapies and those treated with gemtuzumab ozogamicin had comparable remission rates and survival.

7.3.1.1 Remission Rate

The heterogeneity of the CR rates for the various therapies reviewed can be largely explained by considering 2 key prognostic factors, duration of first CR and age. When adjusted for pretreatment prognostic factors, the OR rate for patients treated with gemtuzumab ozogamicin was within the range of results reported with current available combination therapies. To compare therapies, 95% CIs for the second CR rates in the subgroups of patients treated for AML in first relapse were calculated. Table 51 shows second CR rates from randomized phase III trials reported in the literature. In addition, Table 52 shows second CR rates for retrospective studies with 100 or more patients, and less than 100 patients. In the study by Thomas et al., patients had a median age of 47, and, despite the high reported remission rates, had median survivals of 8.5 and 10 months in the 2 arms. In Figure 20, the CR rates for the reports in the literature review are shown, along with the OR rate in patients treated with gemtuzumab ozogamicin.

Table 51. SECOND CR RATES IN RANDOMIZED PHASE III TRIALS AND IN GEMTUZUMAB OZOGAMICIN STUDIES[a]

Institution/Group	Therapy	Second CR Rate[b] % Patients (95% CI)
German Cooperative Group (Kern et al, 1998[4])	HiDAC versus IDAC plus mitoxantrone	47 (39 - 56)
(Thomas et al, 1999[5])	Etoposide + mitoxantrone + cytarabine Versus	81 (64 - 92)
	Etoposide + mitoxantrone + cytarabine + GM-CSF	89 (74 - 97)
Southeastern Cancer Group (Vogler et al, 1994[6])	HiDAC + etoposide versus	45 (30 - 61)
	HiDAC	40 (26 - 56)
Kohseisho Leukemia Group (Ohno et al, 1994[7])	Cytarabine + mitoxantrone + etoposide + filgrastim versus	54 (33 - 74)
	Cytarabine + mitoxantrone + etoposide	42 (23 - 63)
W-AR	Gemtuzumab ozogamicin	30 (22 - 38)

a: Abbreviations: HiDAC = high-dose cytarabine, IDAC = intermediate-dose cytarabine, GM-CSF = granulocyte-macrophage colony-stimulating factor.

b. The heterogeneity of the AML patient population involved is reflected in the wide range of remission rates reported. The published reports generally did not include older patients (median age in published reports was 45 to 50 years). The median age in the gemtuzumab ozogamicin studies was 61 years and included patients up to 80 years of age.

Table 52. NUMBER (%) OF PATIENTS WITH SECOND REMISSION
RETROSPECTIVE REVIEWS WITH ≥ 100 PATIENTS AND GEMTUZUMAB OZOGAMICIN PHASE II CLINICAL TRIALS

| Author, Institution | Total, n | Duration of First CR | | | | | Age | | | |
| | | < 1 Year | | ≥ 1 Year | | | < 60 Years[a] | | ≥ 60 Years | |
		n (%)	95% CI	n (%)	95% CI		n (%)	95% CI	n (%)	95% CI
Rees,[8] MRC	485	251 (13)	8 - 18	234 (48)	42 - 55		375 (33)	26 - 38	110 (19)	2 - 28
Keating,[9] MD Anderson	187	105 (19)	12 - 28	82 (62)	51 - 73		208[b] (36)	29 - 42	35 (14)	5 - 30
Thalhammer,[10] Univ. of Vienna	168	121 (33)	25 - 42	47 (55)	40 - 70		NA[c]	NA	NA	NA
Hiddemann,[11] German Coop. Group	136	87 (46)	35 - 57	49 (60)	44 - 73		104 (54)	44 - 64	32 (44)	26 - 62
Davis,[12] St. Bartholomew's	126	NA (33)	NA	NA (49)	NA		NA (40)	NA	NA (40)	NA
Gemtuzumab ozogamicin, W-AR[d]	142	80 (28)	18 - 39	62 (32)	21 - 45		62 (34)	22 - 47	80 (26)	17 - 37

a: MD Anderson cohort age stratified < 65 and ≥ 65 years.
b: Subgroups by age include relapsed and refractory AML patients.
c: NA = not available.
d: OR rate, not CR rate, used for gemtuzumab ozogamicin data.

| Author, Institution | Total, n | Duration of First CR | | | | Age | | | |
| | | < 1 Year | | ≥ 1 Year | | < 60 Years[a] | | ≥ 60 Years | |
		n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Angelov,[13] Toronto Hospital	51	22 (32)	14 – 55	29 (72)	53 – 87	35[a] (69)	51 - 83	20 (35)	15 - 59
Peterson,[2] Univ. Minnesota	35	NA[b]	NA	NA	NA	NA	NA	NA	NA
MacCallum,[14] St. Bartholomew's	25	NA	NA	NA	NA	19 (63)	38 - 84	6 (67)	22 - 96
Letendre,[15] Mayo Clinic	24	17 (29)	10 - 56	7 (57)	18 – 90	20 (40)	19 - 64	4 (25)	1 - 81
Rassam,[16] UK Multicentre Group	22	NA (54)	NA	NA (33)	NA	NA	NA	NA	NA
Gemtuzumab ozogamicin program/W-AR[c]	142	80 (28)	18 - 39	62 (32)	21 - 45	62 (34)	22-47	80 (26)	17 - 37

a: Number of patients with age < or ≥ 60 includes relapsed and refractory patients.

b: NA = not available.

c: OR rate for gemtuzumab ozogamicin data.

Figure 20. COMPARISON OF REMISSION RATES FROM LITERATURE AND
OVERALL REMISSION RATE WITH GEMTUZUMAB OZOGAMICIN.
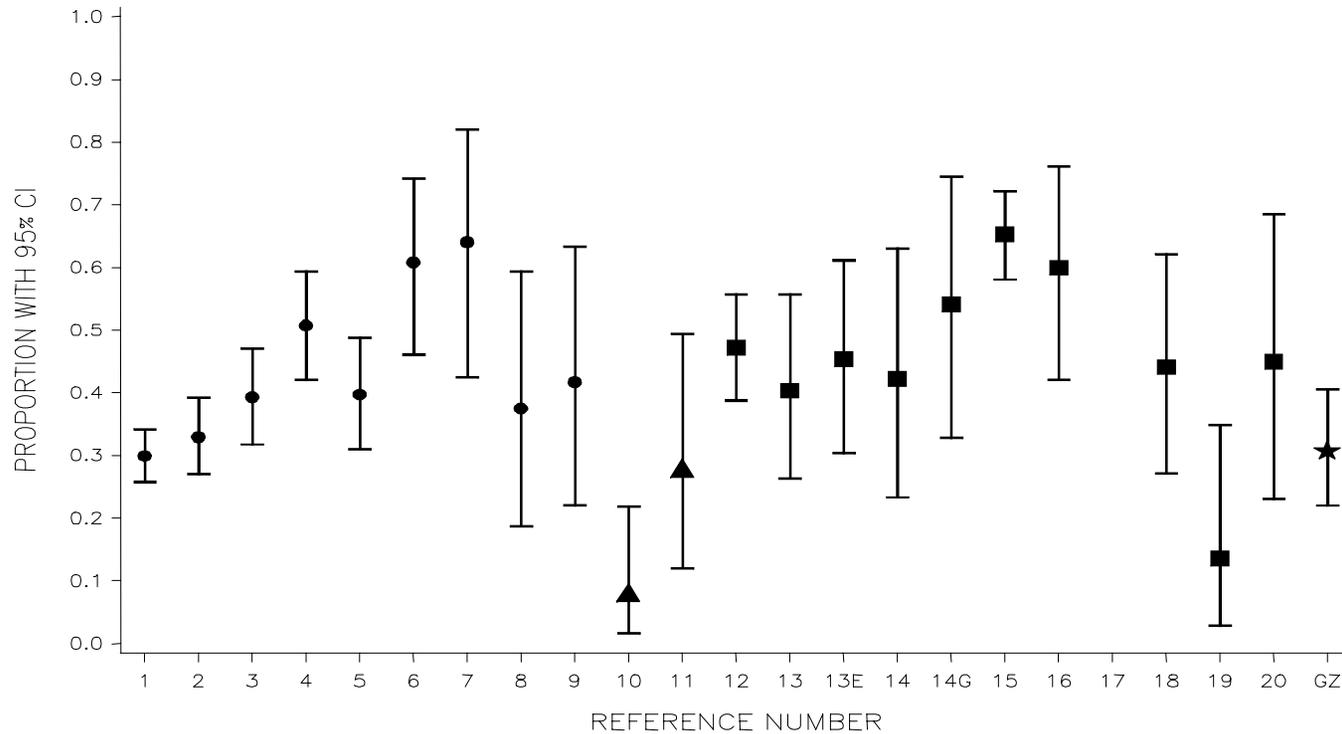
● RETROSPECTIVE   ▲ SINGLE-AGENT   ■ COMBINATION THERAPY   ★ GEMTUZUMAB OZOGAMICIN

Key to the authors by figure reference numbers:

1 = Rees,[8] 2 = Keating,[9] 3 = Thalhammer,[10] 4 = Hiddemann,[11] 5 = Davis,[12] 6 = Angelov,[13] 7 = MacCallum,[14] 8 = Letendre,[15] 9 = Rassam,[16]

10 = Welborn,[17] 11 = Harousseau,[18] 12 = Kern,[4] 13 = Vogler[6] (13 without etoposide, 13E with etoposide), 14 = Ohno[7] (14 without

filgrastim, 14G with filgrastim), 15 = Archimbaud[19] (results for a subset of these patients were reported by Thomas et al.[5]),

16 = Harousseau,[20] 17 = Peterson,[3] 18 = Estey,[21] 19 = Kornblau,[22] 20 = Ho[23]

Several factors should be considered when comparing remission rates between gemtuzumab ozogamicin and conventional therapies. Many of the studies with conventional therapies had patients with better pretreatment prognoses. For example, the Archimbaud[19] trial limited participation of older patients, and most of the patients in the Hiddemann[11] and the MacCallum[14] trials were less than 60 years old. The trial by Angelov et al[13] had a cohort with a median duration of first CR of 18 months.

In addition, it is important to compare remission rates based on similar criteria. In Figure 20, the OR rate of 30% (from the primary analysis) was used for gemtuzumab ozogamicin. However, 14 of the 20 publications shown in the figure had definitions of CR different from the CR definition in the gemtuzumab ozogamicin studies. Most of the trials defined CR as requiring marrow with < 5% leukemic blast cells, WBC > 1,000/μL, and platelets > 100,000/μL, but hemoglobin levels were not specified.

Many of the trials provided sufficient data to allow subgroup analysis based on duration of first CR and age. The results of comparing gemtuzumab ozogamicin data with data from these subgroups demonstrated that gemtuzumab ozogamicin as a single agent produced a remission rate in the range of currently available treatment options. Subgroup analyses by duration of first CR and age demonstrated that no therapy was clearly superior. Gemtuzumab ozogamicin had efficacy comparable with conventional therapy for these subgroups.

The following figures show remission rates and 95% CIs from the literature and from the gemtuzumab ozogamicin trials. Figure 21 and Figure 22 show second remission rates by duration of first CR (< 12 months and ≥ 12 months) and Figure 23 and Figure 24 show second remission rates by age (< and ≥ 60 years of age). The comparative cohorts from the gemtuzumab ozogamicin trials were included.

Figure 21 shows second remission rates reported in publications and in the gemtuzumab ozogamicin trials for patients who had a duration of first remission of < 12 months.

Figure 21. COMPARISON OF OVERALL REMISSION RATES FROM LITERATURE
WITH GEMTUZUMAB OZOGAMICIN,
DURATION OF FIRST REMISSION < 12 MONTHS[a,b]

● RETROSPECTIVE, ■ COMBINATION THERAPY, ★ GEMTUZUMAB OZOGAMICIN
a: The data without CIs appear as closed circles (figure references 5 and 9).
b: Figure references 10 to 17 are included in the display although they did not have data for this
figure.
Key to the authors by figure reference numbers:
1 = Rees,[8] 2 = Keating,[9] 3 = Thalhammer,[10] 4 = Hiddemann,[11] 5 = Davis,[12] 6 = Angelov,[13]
7 = MacCallum,[14] 8 = Letendre,[15] 9 = Rassam,[16] 10 = Welborn,[17] 11 = Harousseau,[18] 12 = Kern,[4] 13
= Vogler[6] (13 without etoposide, 13E with etoposide), 14 = Ohno[7] (14 without filgrastim, 14G with
filgrastim), 15 = Archimbaud,[19] 16 = Harousseau,[20] 17 = Peterson,[3] 18 = Estey,[21] 19 = Kornblau,[22]
20 = Ho[23]

Considering the subgroup with duration of first CR less than 12 months (n = 80), the
second remission rate of 28% for gemtuzumab ozogamicin-treated patients is comparable
with that of second remission rates reported in the literature. References 8, 9, 18 and 19 in
Figure 21 comprised fewer than 20 patients each, limiting the power of these observations.

Figure 22 shows second remission rates reported in publications and in the
gemtuzumab ozogamicin trials for patients who had a duration of first remission of
≥ 12 months.

Figure 22. COMPARISON OF OVERALL REMISSION RATES FROM LITERATURE
WITH GEMTUZUMAB OZOGAMICIN,
DURATION OF FIRST REMISSION ≥ 12 MONTHS[a,b]

● RETROSPECTIVE, ■ COMBINATION THERAPY, ★ GEMTUZUMAB OZOGAMICIN
a: The data without CIs appear as closed circles (figure references 5 and 9).
b: Figure references 10 to 17 are included in the display although they did not have data for this figure.
Key to the authors by figure reference numbers:
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7 = MacCallum,[14] 8 = Letendre,[15] 9 = Rassam,[16] 10 = Welborn,[17] 11 = Harousseau,[18] 12 = Kern,[4] 13
= Vogler[6] (13 without etoposide, 13E with etoposide), 14 = Ohno[7] (14 without filgrastim, 14G with
filgrastim), 15 = Archimbaud,[19] 16 = Harousseau,[20] 17 = Peterson,[2] 18 = Estey,[21] 19 = Kornblau,[22]
20 = Ho[23]

The remission rate was 32% for gemtuzumab ozogamicin-treated patients who had a duration of first CR of 12 or more months (n = 62). In Figure 22, the trials notably different from the gemtuzumab ozogamicin trials were the retrospective review by Keating et al[9] and prospective studies by Angelov et al[13] and Estey et al.[21] As stated previously, Keating et al[9] included only a small percentage of patients (14%) more than 65 years old compared with the gemtuzumab ozogamicin studies, in which 40% of the patients were 65 or more years old. In addition, both Keating et al[9] and Estey et al[21] used definitions of CR that only required an ANC > 1,000/μL and did not include hemoglobin in the response criteria. The trial by Angelov et al[13] included a distinctly different patient population with a long median

duration of first CR (18 months). Also, the CR definition only required that patients have a normocellular marrow with < 5% blast cells. Lastly, the data point for figure reference 18[21] in Figure 22 is based on a remission rate for 9 of 10 patients treated with fludarabine and cytarabine for AML in first relapse. Subsequent reports from the MD Anderson Cancer Center did not identify this or any other regimen as predictive of second CR.[24,25] Thus, the high remission rate in a small subgroup of patients may be explained by these non-treatment considerations.

In Figure 23 and Figure 24, the CR rate for publications that stratified remission rates by the patient's age (< or ≥ 60 years old) were compared with the OR rate of patients treated with gemtuzumab ozogamicin.

Figure 23. COMPARISON OF OVERALL REMISSION RATES FROM LITERATURE WITH GEMTUZUMAB OZOGAMICIN, AGE < 60 YEARS[a,b]

● RETROSPECTIVE, ■ COMBINATION THERAPY, ★ GEMTUZUMAB OZOGAMICIN
a: The data without CIs appear as closed circles (figure references 5 and 9).
b: Figure references 10 to 17 are included in the display although they did not have data for this figure.
Key to the authors by figure reference numbers:
1 = Rees,[8] 2 = Keating,[9] 3 = Thalhammer,[10] 4 = Hiddemann,[11] 5 = Davis,[12] 6 = Angelov,[13] 7 = MacCallum,[14] 8 = Letendre,[15] 9 = Rassam,[16] 10 = Welborn,[17] 11 = Harousseau,[18] 12 = Kern,[4] 13 = Vogler[6] (13 without etoposide, 13E with etoposide), 14 = Ohno[7] (14 without filgrastim, 14G with filgrastim), 15 = Archimbaud,[19] 16 = Harousseau,[20] 17 = Peterson,[2] 18 = Estey,[21] 19 = Kornblau,[22] 20 = Ho[23]

The remission rate for gemtuzumab ozogamicin-treated patients younger than 60 years of age (n = 62) was 34%. The trials notably different from the gemtuzumab ozogamicin trials have been discussed above. Considering the important differences in patient demographics between these trials and the gemtuzumab ozogamicin trials, the results appear to be comparable.

Figure 24. COMPARISON OF OVERALL REMISSION RATES FROM
LITERATURE WITH GEMTUZUMAB OZOGAMICIN, AGE ≥ 60 YEARS[a,b]

● RETROSPECTIVE, ■ COMBINATION THERAPY, ★ GEMTUZUMAB OZOGAMICIN
a: The data without CIs appear as closed circles (figure references 5 and 9).
b: Figure references 10 to 17 are included in the display although they did not have data for this figure.
Key to the authors by figure reference numbers:
1 = Rees,[8] 2 = Keating,[9] 3 = Thalhammer,[10] 4 = Hiddemann,[11] 5 = Davis,[12] 6 = Angelov,[13]
7 = MacCallum,[14] 8 = Letendre,[15] 9 = Rassam,[16] 10 = Welborn,[17] 11 = Harousseau,[18] 12 = Kern,[4] 13
= Vogler[6] (13 without etoposide, 13E with etoposide), 14 = Ohno[7] (14 without filgrastim, 14G with
filgrastim), 15 = Archimbaud,[19] 16 = Harousseau,[20] 17 = Peterson,[2] 18 = Estey,[21] 19 = Kornblau,[22]
20 = Ho[23]

The remission rate for gemtuzumab ozogamicin-treated patients 60 years of age or
older (n = 80) was 26%. All of the CR rates reported in the literature for patients 60 or more
years old were comparable with the remission rate obtained for this subgroup of patients in
the gemtuzumab ozogamicin trials. No specific treatment emerged as the treatment of
choice when considered by this criterion alone (age).

The variability in the published remission rates has been accounted for by
considering the heterogeneity of the populations treated as well as the data considerations
for retrospective or small trials. Subgroup analyses by duration of first CR and age

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demonstrated that no therapy is clearly superior. Gemtuzumab ozogamicin has efficacy comparable with that reported for conventional therapies for these subgroups.

7.3.1.2 Duration of Second Remission

Duration of second CR in AML was closely related to survival, which as stated previously, was limited. In the publications reviewed, conventional chemotherapy rarely resulted in prolonged disease-free survival. The goal of therapy was to achieve a remission that allowed for the application of further curative therapies, primarily, HSCT. The duration of second CRs ranged from 3 to 7.5 months in the retrospective studies and was generally from 3 to 12 months in the prospective studies, although in 1 report second CR was as high as 25 months.[6] In the latter report by Vogler,[6] the 25-month duration of second CR was not statistically different from the 12-month duration of second CR observed in the comparator arm.

As of the data cutoff dates, the median total relapse-free survival for those in the gemtuzumab ozogamicin studies who had a second remission was 203 days (6.8 months) based on the Kaplan-Meier estimate. The observed data show that the minimum total relapse-free survival was 10 days (0.3 months) and the maximum was 743 days (24.8 months).

7.3.1.3 Survival

The ultimate goal of therapy for AML in first relapse is cure of leukemia. While this continues to be a difficult clinical challenge, a new therapy in AML must at least be comparable in survival with available therapies. In the published reports, overall survival and survival of responders and nonresponders were measured. Survival data were not reported for subgroups stratified by pretreatment prognostic factors. Many of the trials included patients with refractory AML and survival data were not stratified for relapsed and refractory patients. However, the ranges of survival in trials that included or excluded refractory AML patients often overlapped. Survival of patients treated with gemtuzumab ozogamicin was within the range of survival reported for patients treated with conventional chemotherapy. Table 53 shows landmark survival in the gemtuzumab ozogamicin-treated patients and overall survival from published reports. In the gemtuzumab ozogamicin trials, the median landmark survival was at least 12.6 months in patients with remissions (the median has not been reached because data were limited by the cutoff date).

Table 53. SURVIVAL IN POPULATIONS DISCUSSED IN LITERATURE AND
IN PATIENTS WHO RECEIVED GEMTUZUMAB OZOGAMICIN

Statistic	Literature Review Populations[a]		Gemtuzumab Ozogamicin Clinical Studies[b]
	Retrospective	Prospective	
No. of patients	798	159	105
Median overall survival, months	3 - 8	4 - 10	7.5
Median survival of responders, months	12	3 - 12	> 12.6[c]
Median survival of nonresponders, months	1 - 2	2.5	2.9

a: Several of the trials summarized in this table included refractory and relapsed
    AML patients in their cohorts. Duration is given as an individual number when
    only 1 publication contributed relevant information and as a range when multiple
    survival statistics are available.
b: From landmark analysis (section 4.4.1.3.2, Table 18).
c: The median cannot be calculated until enough time has elapsed for more data on
    patient deaths to be obtained.

7.3.1.4 Survival After HSCT

The ability of patients who receive gemtuzumab ozogamicin to tolerate HSCT is
within the range reported in the literature for other studies, although there were limitations to
the papers in the literature. None presented an intent-to-treat analysis, and older patients or
those with documented infections were excluded. There was also great heterogeneity in the
treatment strategies adopted, and few details were provided on the types of HSCT.

Table 54 shows short-term mortality and assessments of survival after HSCT in
patients who had remissions after being treated with gemtuzumab ozogamicin and in
patients treated with conventional therapies. In the gemtuzumab ozogamicin studies,
survival data were based on 15 patients who had remissions and then went on to HSCT.
Because of the small patient numbers, comparison with currently available therapies is
limited. No stratification of HSCT outcome by age or duration of first CR was available for
comparison with gemtuzumab ozogamicin-treated patients.

Table 54. SURVIVAL AFTER HSCT, LITERATURE REPORTS VERSUS
GEMTUZUMAB OZOGAMICIN

Statistic	Literature Review Populations		Gemtuzumab Ozogamicin Clinical Studies
	Retrospective	Prospective	
No. of transplantations	46	37	15[a]
Death rate during HSCT aplasia % (min, max)	28% (20 - 36)	NA	27% (4 of 15)
Long-term[b] survivors after HSCT % (min, max)	41% (9 - 59)	33% (29 - 35)	73%[c]

a: Patients who had CR and CRp.
b: Long-term is defined in the text below.
c: Because of data cutoff, the duration of follow-up in gemtuzumab ozogamicin-treated
    patients is presently less than reported in the literature. The range of follow-up was
    approximately 1 to 24 months, with a median of approximately 8 months.

Eleven (11; 73%) of the 15 gemtuzumab ozogamicin-treated patients survived after
HSCT; the median post-HSCT survival was at least 240.5 days (approximately 8 months).
The minimum post-HSCT survival was 23 days and the maximum was 721 days. These
patients had a shorter median follow-up than is generally reported in the literature. The
follow-up after HSCT in the published reports varied and was 2 to 5 years for Rees et al,[8]
> 5 years for Keating et al,[9] 1 to 3 years for Davis et al,[12] 1 to 4 years for MacCallum et al,[14]
and a median of 2 years for Archimbaud et al.[19] There is no evidence that survival after
HSCT is compromised by gemtuzumab ozogamicin therapy, as the short-term mortality is
no greater than that in the comparison population.

7.3.2 Database Reviews

7.3.2.1 MD Anderson Cancer Center (Efficacy)

The retrospective review of data from patients treated with conventional therapies at
the MD Anderson Cancer Center indicated that 10 (5%) of 200 patients with AML in first
relapse had clearance of bone marrow and peripheral blood blasts, but recovery of platelet
counts to levels between 30,000/µL and 100,000/µL. This observation supports the
impression from the literature review that with conventional cytotoxic chemotherapy, the
percentage of patients who match the criteria for CRp defined in the gemtuzumab
ozogamicin clinical trials is low. Thus, to include such patients with those who achieve CR
would not substantially alter the conclusions of the comparative review presented in this
document.

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In a second assessment, 59 patients treated with gemtuzumab ozogamicin in study 201 were matched with 121 patients treated at first relapse with HiDAC alone or in combination at the MD Anderson Cancer Center. This preliminary analysis compared both the CR rate and OR rate for the matched pairs. Matching was based on duration of first CR, age, and cytogenetic risk category. Of the gemtuzumab ozogamicin-treated patients, 70% had HiDAC exposure before first relapse, suggesting that HiDAC may not have been an effective treatment for the patients enrolled in the gemtuzumab ozogamicin trials.

When the OR rate for gemtuzumab ozogamicin-treated patients was compared with the remission rate for HiDAC-treated patients, the chance of remission varied with duration of first CR. For patients with a first CR < 12 months, gemtuzumab ozogamicin was more likely to induce a remission. For patients with first CR > 12 months, HiDAC therapy was more likely to result in a remission. Nevertheless, there was no difference in survival between patients treated with HiDAC and those receiving gemtuzumab ozogamicin. Note that this analysis is preliminary and reflects only 59 patients in the gemtuzumab ozogamicin database.

7.3.2.2 University of Vienna Database (Efficacy)
The University of Vienna AML database was used to explore the efficacy endpoints reported in a retrospective publication by Dr. Thalhammer et al.[26] This cohort included 51 patients treated palliatively for whom survival data were available. The effect of age, duration of first CR, and prior HiDAC exposure on second CR rate, duration of remission, and survival were evaluated. The incidence of CRp was also examined.

The findings of this database review were that the gemtuzumab ozogamicin second CR rate was similar to that reported by Thallhammer et al.[26] The second CR rate varied with the duration of first CR and age, but not with prior HiDAC exposure. Median overall survival of treated patients was 7.9 months but was as high as 16 months in patients with a first CR > 12 months. Long-term disease-free survival was only observed for patients with first CR > 12 months. The median overall survival of patients treated palliatively (n = 50/170) was 2 months. The incidence of CRp was 3% (n = 1/35), consistent with the estimate from the MD Anderson database.

7.3.2.3 Medical Research Council Database (Efficacy)
The MRC in the United Kingdom has treated 5,431 patients with de novo AML in successive clinical trials. They identified 1,696 patients who had relapsed as of 01 Jul 1999.

The median duration of first CR in this group of patients was 9.8 months (min - max, 0.3 - 80.4 months). The median age at diagnosis of their AML patients in first relapse was 45 years (min - max, 0 - 91). Using a definition of CR that required only the absence of leukemia blasts in a recovery marrow that demonstrated evidence of trilineage recovery, the overall second CR rate in treated patients was 49% (600/1,221). The disease-free survival for patients from second CR was 42% at 1 year and 29% at 2 years. Survival from the time of relapse was 32% at 1 year and 16% at 2 years. Subgroup analysis by age and duration of first CR revealed that greater age and shorter duration of first CR correlated with a decrease in the second CR rate, disease-free survival, and overall survival. Among the total group of 1,696 patients, 22% were treated with palliative intent and only 15.9% survived greater than 6 months.

In a subgroup analysis of 175 patients treated with cytarabine, daunorubicin, and etoposide in the relapsed AML trial (AML-R), the second CR rate was 44% (n = 77/175). The median age and duration of first CR were similar to those of the entire relapsed cohort.

7.4 Safety Comparison of Gemtuzumab Ozogamicin and Conventional Chemotherapy

7.4.1 Literature Review
The safety data demonstrate an improved safety profile for patients treated with gemtuzumab ozogamicin in comparison with that for conventional chemotherapy. Therapy with gemtuzumab ozogamicin is comparable with conventional therapies for many adverse events, and more favorable with respect to severe (grade 3 to grade 4) mucositis, severe infections, and hospitalizations. (Hospitalizations are discussed briefly in this section and in more detail in section 7.5.)

Table 55 summarizes the comparisons between gemtuzumab ozogamicin and conventional chemotherapy for important safety endpoints. The incidences and durations of adverse events from the publications reviewed are presented as ranges. Although several of the reviewed publications included patients with refractory and relapsed AML, the incidence of adverse events in the trials that included or excluded refractory AML patients was similar.

Table 55. COMPARISON OF SAFETY RESULTS REPORTED IN LITERATURE[a] WITH RESULTS
FROM GEMTUZUMAB OZOGAMICIN STUDIES

Adverse event/measurement	Gemtuzumab Ozogamicin[b]	Range of Literature Values
Median time to platelets $\geq 100,000/\mu L$ (days)	50[c]	34 - 43
Median time to ANC $\geq 500/\mu L$ (days)	42[d]	23 - 40
Grade 3 or grade 4 infections (%)	28	29 - 65.2
Grade 3 or grade 4 abnormal LFTs (%)	32[e]	2 - 34
Grade 3 or grade 4 bleeding (%)	15[f]	9 - 25
Grade 3 or grade 4 nausea or vomiting (%)	13[g]	3 - 30
CNS bleeding (%)	4.9	4 – 11[h]
Grade 3 or grade 4 mucositis (%)	4	3 - 27
Median duration of hospitalization (days)	24	38[j]
Induction death rate (%)[j]	13	3 - 27

a: Several publications included relapsed and refractory AML patients.
b: Reported for part I of gemtuzumab ozogamicin trials.
c: Platelet recovery calculated from first dose of gemtuzumab ozogamicin, for CR patients only.
d: Median time to ANC > 500/µL for all 142 gemtuzumab ozogamicin-treated patients, from first dose of
     gemtuzumab ozogamicin. For the OR patients, the median was 40.5 days. Many published reports did
     not state how recovery from myelosuppression was defined.
e: Transient and reversible in all but 1 patient who developed liver failure secondary to progression of
     leukemia.
f: If petechial bleeding and epistaxis are excluded, the grade 3 or grade 4 bleeding incidence is 11%.
g: 4% vomiting and 9% nausea.
h: Only reported in 2 studies.
i: Only reported in 1 study.
j: Treatment mortality was defined for the gemtuzumab ozogamicin studies as death that occurred during
     part I of the studies. In published literature, it was defined as death occurring during the period of
     neutropenia after chemotherapy administration.

The literature indicates that conventional chemotherapy for patients with AML in
first relapse often requires inpatient treatment for drug administration and management of
serious systemic complications of therapy. These adverse events include mucositis,
neutropenic fevers, infections, abnormal LFTs, and nausea and vomiting, among others.
Hospitalization rates have rarely been reported, but hospitalization is generally regarded as
universal in this population of patients. In addition, treatment mortality rates during the
period of neutropenia are significant with chemotherapy. Also, as alopecia is virtually
universal with conventional therapy, it is not generally reported.

For patients with AML in first relapse, the major clinical advantages that were
achieved with gemtuzumab ozogamicin therapy were reductions in severe mucositis, severe
infections, and in the number of days of hospitalization. The rate of severe mucositis varied
from 3% to 27% with conventional chemotherapy; the ranges overlapped in trials that
included or excluded refractory AML patients. The highest mucositis rates were seen in
trials employing combination regimens. Only 4% of patients with AML in first relapse

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treated with gemtuzumab ozogamicin had severe (grade 3 or grade 4) drug-related mucositis.

Another key benefit of therapy with gemtuzumab ozogamicin is a reduced rate of severe infections. Most likely, the reduced infection rate results from the reduction in severe mucositis. The observed reduction in the median number of days of hospitalization correlates with the reduction in mucositis and infections.

The incidence of CNS bleeding was 4.9% for patients treated with gemtuzumab ozogamicin, which was consistent with the published rates (4% to 11%).

The incidence of abnormal LFTs in the gemtuzumab ozogamicin studies was within the range reported in the literature for trials that included and excluded patients with refractory AML. Although the incidence of any grade 3 or grade 4 abnormal LFT was 32% for gemtuzumab ozogamicin-treated patients, these abnormalities were generally transient and reversible.

The duration of myelosuppression is an important safety concern with chemotherapy for AML in first relapse. Many publications did not state how the time to recovery of platelets and ANC were calculated. When stated, recovery was generally calculated from the first dose of chemotherapy. In addition, the populations included in the time to recovery analyses were not uniformly defined in the literature; in some cases recovery was assessed for the entire cohort while in others, it was assessed only for patients who had remissions.

The median time to recovery of platelet count to $\geq 100,000/\mu L$ was 34 to 43 days in the literature, and was 50 days in gemtuzumab ozogamicin-treated CR patients (from the first dose of gemtuzumab ozogamicin). There was delayed platelet recovery for CRp patients in the gemtuzumab ozogamicin studies. For instance, recovery of platelets to $25,000/\mu L$, while platelet transfusion independent, required a median of 34 days for CR patients and 48 days for CRp patients.

In the literature, the median time to an ANC $\geq 500/\mu L$ was reported to be 23 to 40 days in the absence of growth factors. Among all the gemtuzumab ozogamicin-treated patients whose ANC recovered to $\geq 500/\mu L$, the median time to ANC recovery from the first dose of gemtuzumab ozogamicin was 42 days.

The incidence of severe nausea and vomiting for gemtuzumab ozogamicin treated patients was 9% and 4%, respectively. These rates are within the range of those reported in the literature for available therapies (3% to 30%).

The early death rate during the period of neutropenia following chemotherapy administration varied from 3% to 27% with conventional therapies in the studies reviewed and was 13% during part I of the trials in patients treated with gemtuzumab ozogamicin. Thus, the early death rate during gemtuzumab ozogamicin therapy was comparable to that of conventional therapies in the literature.

Alopecia was absent for patients who received targeted therapy with gemtuzumab ozogamicin, a marked difference from conventional chemotherapy.

7.4.2 Database Review- MRC

Safety information was also available from the MRC database. In a subset of 175 patients treated in the AML-R trial, the most common grade 3 or 4 adverse events were alopecia (52%), nausea and vomiting (22%), mucositis (20%), diarrhea (12%), and elevations of bilirubin (8%) and hepatic transaminases (5%). The median time to recovery of ANC to > 1,000/μL was 34 days and to recovery of platelets to 100,000/μL was 54 days. Patients were hospitalized for a median of 31 days.

7.5 Hospitalization, Comparison of Gemtuzumab Ozogamicin and Other Data

7.5.1 Hospitalization Comparison, Literature Review

To compare the duration of hospitalization during part I of the gemtuzumab ozogamicin trials with reports in the literature, the literature review was broadened to include data from trials with de novo AML patients. Because AML patients in first relapse have a worse prognosis than de novo AML patients, it was expected that this comparison would not be biased in favor of gemtuzumab ozogamicin. However, AML patients in first relapse have a higher treatment mortality rate, which could result in a shorter duration of hospitalization but not reflect a favorable treatment outcome. Thus, comparisons between the published reports and studies of gemtuzumab ozogamicin-treated patients were performed including and excluding patients who died in part I (first 56 days) of the gemtuzumab ozogamicin phase II trials.

Data on hospitalizations for gemtuzumab ozogamicin-treated patients and for de novo and relapsed AML patients reported in the literature are shown in Table 56. In some

trials patients were randomized to receive colony stimulating factor (CSF); the data from these trials are presented for the subgroups of patients who did and did not receive CSFs. In the gemtuzumab ozogamicin studies, CSFs were not recommended and few patients received them.

Table 56: DURATION OF HOSPITALIZATION IN PUBLISHED REPORTS OF AML THERAPY

Study	No. of Patients in Study	All patients/ by Receipt of G-CSF	Median Number of Hospital Days	Range of Hospital Days (Min-Max)	Treatment Mortality (%)
Relapsed AML- Gemtuzumab Ozogamicin					
Gemtuzumab ozogamicin	142	All Patients	24	(0 - 133)	13[a]
Gemtuzumab ozogamicin, excluding patients who died in part I	124	All Patients	27	(0 - 133)	--
Relapsed or Refractory AML- Literature					
Montillo M, et al [1](1998)	38	All patients	31	(17 - 61)	11
Peterson BA, et al [2](1981)	35	All patients	38	(NA)	17
De Novo AML- Literature					
Bennett CL, et al[27] (1999)[b]	88	All patients	37.7	(NA)	NA
		+CSF	32.5		
Godwin JR, et al[28] (1998)[b]	207	- CSF	29	(3 - 104)	25
		+ CSF	29	(4 - 155)	
Heil G, et al[29] (1997)[b]	521	All patients	32	(2 - 104)	NA
		+ CSF	29	(2 - 104)	
Rowe JM, et al[30] (1995)[b]	98	All patients	37	(NA)	NA
		+ CSF	36	(NA)	
Uyl-de Groot CA, et al[31] (1998)[b]	109	All patients	35.5	(3 - 63)	
		+ CSF	35	(3 - 69)	
Boubdallah R, et al[32] (1999)	51	Patients hospitalized for induction (32 of 51)	14.5	NA	16
Lowenberg B, et al[33] (1998)	489	All patients	31	NA	18
Pierri I, et al[34] (1999)	21	All patients	22	NA	14

a: For the gemtuzumab ozogamicin studies, treatment-related mortality was measured as the death rate during part I of the study.

b: Trials randomly assigning patients to colony stimulating factors.

As can be seen, gemtuzumab ozogamicin-treated patients had fewer median days in the hospital during part I when compared with corresponding data from these published trials. The results cannot be explained by early deaths in part I of the gemtuzumab ozogamicin phase II studies for several reasons. First, treatment mortality rates during the period of neutropenia following chemotherapy administration were comparable in the gemtuzumab ozogamicin studies and in the trials that reported mortality rates (Table 55). Secondly, the median number of days in the hospital for gemtuzumab ozogamicin-treated

patients did not change substantially by inclusion or exclusion of patients with part I treatment mortality (24 vs.27 days, respectively). Lastly, the publications listed in Table 56 did not exclude patients who died in their analyses.

The study by Boubdallah et al[32] examined primarily older, de novo AML patients treated with oral idarubicin as outpatients, which represents a departure from conventional therapy. Only 32 of 51 (63%) patients were hospitalized for the initial induction. This regimen produced a low second CR rate of 15%. The 32 patients receiving inpatient treatment were hospitalized for a median of 14.5 days; the infrequent hospitalizations reflected less intensive therapy. In the other studies, there was no evidence of patients receiving outpatient treatment.

Among gemtuzumab ozogamicin-treated patients, there was a difference in median number of days in the hospital between patients treated at North American hospitals and at European hospitals. The median number of hospital days in part I for the 76 patients treated at North American centers was 18.5 days, whereas for the 66 patients treated at European centers it was 33 days. This may reflect demographic differences in these patients or differences in clinical practice between North America and Europe.

An important aspect of the hospitalization data for patients treated with gemtuzumab ozogamicin in the phase II trials is the high rate of patients hospitalized for 7 days or less. As reported in the literature, it was universal for patients who received therapy for relapsed AML to require hospitalization (none of the minimum number of days in the hospital from the literature reports includes zero). In contrast, 26 (18%) of the 142 gemtuzumab ozogamicin-treated patients had 0 to 7 days of hospitalization during part I of the phase II trials. Five (5, 4%) of these patients had no days of hospitalization, and 21 (15%) of these patients had 1 to 7 days of hospitalization. This indicates a clinically significant improvement over currently available therapies.

7.5.2 Hospitalization Comparison, Brigham and Women's Hospital Database

In order to gain additional insight into the duration of hospitalization for patients with AML in first relapse, an exploratory analysis was performed with the data available as of the NDA cutoff date. For this analysis, 104 patients in the gemtuzumab ozogamicin trials were compared with 22 patients treated for AML in first relapse during the 1990s at BWH. The BWH cohort was comparable in important demographic features with the gemtuzumab ozogamicin-treated patients. In the BWH cohort, the median duration of first CR was 8.5 months, the median age was 62 years, 50% of the patients were male, and 86% were white. In the 104 gemtuzumab ozogamicin-treated patients, the median duration of first CR was 11.2 months, the median age was 60 years, 58% were male, and 92% were white. Of note, 36% of patients in the BWH cohort had prior myelodysplastic syndrome (MDS), but a history of MDS was an exclusion criterion in gemtuzumab ozogamicin trials. The impact of these differences on the duration of hospitalization for treatment of relapsed AML is unknown.

Table 57 compares the median number of days of hospitalization for patients treated with gemtuzumab ozogamicin with the corresponding number of hospital days for patients treated with conventional therapies at BWH. To determine any bias resulting from patients who died in the gemtuzumab ozogamicin trials, data including and excluding patients who died in part I are presented. The median number of days of hospitalization was shorter for gemtuzumab ozogamicin-treated patients. The percentage of patients treated with gemtuzumab ozogamicin who were hospitalized for less than 1 week or for less than 2 weeks was also lower when compared with the BWH cohort.

Table 57. TOTAL DAYS OF HOSPITALIZATION DURING TREATMENT OF RELAPSED AML: A COMPARISON OF CONVENTIONAL TREATMENTS WITH GEMTUZUMAB OZOGAMICIN CLINICAL TRIALS

Statistic	Gemtuzumab Ozogamicin All Patients (n = 142)	Gemtuzumab Ozogamicin Excluding Part I Deaths (n = 124)	Conventional Chemotherapy for AML at BWH (n = 22)
Median no. days of hospitalization (min-max)	24 (0 - 133)	27 (0 - 133)	31 (12-85)
Mean (SD) no. of days of hospitalization	30 (± 25)	32 (± 26)	34 (± 14)
Number (%) of patients hospitalized for 0 to 7 days	26 (18)	23 (19)	0 (0)
Number (%) of patients hospitalized for 0 to 14 days	47 (33)	38 (31)	1 (5)
Number (%) of patients with treatment mortality[a]	18 (13)	--	1 (5)

a: Treatment mortality was defined for the gemtuzumab ozogamicin studies as death that occurred during part I of the studies. In published literature, it was defined as death occurring during the period of neutropenia after chemotherapy administration.

7.6 Conclusions of Comparisons of Gemtuzumab Ozogamicin With Literature and Institutional Databases

7.6.1 Efficacy Results

With conventional therapy, remission consists almost entirely of CR, and the response that we observed as CRp is seldom observed. Our literature review showed that the incidence of CRp was < 5% with conventional therapy. Patients treated with gemtuzumab ozogamicin have a higher incidence of remission with incomplete platelet recovery (CRp). This may be because of effects on CD33 positive platelet precursors or decreased bone marrow reserves. However, the clinical outcomes of CR and CRp patients after gemtuzumab ozogamicin therapy are comparable. Thus, the comparison of OR (CR + CRp) rate for gemtuzumab ozogamicin with CR rate for conventional therapy is appropriate.

Gemtuzumab ozogamicin as a single agent produced an OR rate (30%), duration of remission, survival, and HSCT outcome within the range of those reported for currently available AML therapies. These conclusions were based on evaluation of the relevant medical literature. The comparisons were done with consideration of recognized pretreatment prognostic factors for patients with relapsed AML, when available. The

comparative assessments of survival and outcome of HSCT were restricted by limited reporting in the publications reviewed.

The purpose of obtaining additional information from institutional databases was to gain additional insights into the treatment results of AML patients in first relapse. Published reports of treatment results for AML patients in first relapse may be biased because of the small population sizes, exclusion of high-risk AML patients, or from a publication bias to report results of positive trials. For instance, none of the publications meeting the criteria for evaluation had a median age > 56 years. The median age in the gemtuzumab ozogamicin phase II studies was 61 years. In addition, specific analyses were performed to gain insight into the incidence of CRp, the outcome of second remission patients who receive HSCT therapy, and the outcome of treatment in subgroups of AML patients based on duration of first CR and age.

These exploratory analyses validated the conclusions from the detailed review of the literature on AML patients in first relapse. The second CR rates from the institutional databases were generally lower than those reported in smaller studies of selected therapies in the literature review. This most likely reflects the consideration of all patients at an institution with AML in first relapse, rather than a subgroup selected and treated in a particular trial.

Consistent with previous observations from the literature review, duration of first CR and age were again noted to be pretreatment prognostic factors that affected treatment outcome in AML patients in first relapse. The incidence of CRp in the databases was < 5%, confirming the impression from published reports that this is not a common outcome of therapy for AML in first relapse. The outcome of HSCT was as poorly defined in institutional databases as in published reports of patients with AML in first relapse.

7.6.2 Safety Results

The adverse event profile of gemtuzumab ozogamicin was similar to that of conventional chemotherapies in terms of myelosuppression and bleeding, but offers a safety advantage in terms of a lower incidence of severe mucositis and severe infections. With gemtuzumab ozogamicin, there is only mild and reversible nausea and vomiting and no alopecia. Transient and reversible liver function test abnormalities occurred with moderate incidence. In patients who received HSCT after gemtuzumab ozogamicin therapy, there were no unexpected adverse events. In addition, patients treated with gemtuzumab

ozogamicin had a reduced median number of days of hospitalization because of both a short outpatient infusion and a decreased need for in-hospital supportive care.

The incidence of adverse events reported in the MRC database was consistent with those reported in the published literature. The MRC reported the median time to recovery of platelets to > 100,000/μL to be 54 days, which is similar to that in the phase II gemtuzumab ozogamicin trials.

7.6.3 Hospitalizations

When compared with both the medical literature and an institutional database, the median number of days of hospitalization for patients with AML in first relapse treated with gemtuzumab ozogamicin was reduced. The median duration of hospitalization for gemtuzumab ozogamicin-treated patients was shorter than the majority reported in the literature. Comparisons with cohorts of de novo AML patients treated with CSFs do not alter this conclusion and treatment mortality does not explain these results. When compared with published literature and with a hospital database, a higher percentage of gemtuzumab ozogamicin-treated patients did not require hospitalization or were hospitalized for 7 days or less.

8. OVERALL CONCLUSIONS

Data presented in this report demonstrate the efficacy and safety of gemtuzumab ozogamicin in the treatment of patients with AML in first relapse. Gemtuzumab ozogamicin, as a single-agent therapy, produced clinically meaningful efficacy results comparable to those with conventional AML therapy as demonstrated by remission rate, relapse-free survival, overall survival, and survival after HSCT.

The CR and CRp patients were compared for all efficacy, safety, and health outcomes variables examined, and no differences were apparent except that hematologic recovery occurred more slowly in patients with CRps (however, all CRps were platelet transfusion independent). Most importantly, the survival rates for patients with CR and those with CRp were essentially the same, and the 2 groups underwent similar therapies after gemtuzumab ozogamicin with similar outcomes.

Gemtuzumab ozogamicin, the first antibody-targeted chemotherapy agent, has an acceptable adverse event profile consistent with its targeted nature. Gemtuzumab ozogamicin therapy is associated with a lower incidence of clinically severe mucositis, a low rate of infections, and a lower median number of days of hospitalization compared with conventional therapy for AML patients in first relapse.

None of the 142 patients in the phase II studies had any antibody responses or clinical evidence of immune response. Four (4) patients received a second course of gemtuzumab ozogamicin therapy and did not develop antibodies to gemtuzumab ozogamicin.

Gemtuzumab ozogamicin is an effective and safe single-agent therapy for treatment of patients with relapsed AML.

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