CCR Drug Updates

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FDA Approval: Gemtuzumab Ozogamicin for the Treatment of Adults with Newly Diagnosed CD33-Positive Acute Myeloid Leukemia

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Abstract

On September 1, 2017, the FDA granted approval for gemtuzumab ozogamicin (Mylotarg; Pfizer Inc.) in combination with daunorubicin and cytarabine and as a monotherapy for the treatment of adult patients with newly diagnosed CD33-positive acute myeloid leukemia (AML). Gemtuzumab ozogamicin is a CD33-targeted antibody–drug conjugate joined to calicheamicin. Approval of gemtuzumab ozogamicin combination treatment was based on a randomized trial of 271 patients with newly diagnosed AML treated with daunorubicin and cytarabine with or without 3 mg/m^2 fractionated gemtuzumab ozogamicin, which resulted in an event-free survival (EFS) of 13.6 months for gemtuzumab ozogamicin + daunorubicin and cytarabine and 8.8 months for daunorubicin and cytarabine alone [HR = 0.68 (95% confidence interval (CI), 0.51–0.91)]. Hemorrhage, prolonged thrombocytopenia, and veno-occlusive disease were serious toxicities that were more common in patients treated with gemtuzumab ozogamicin + daunorubicin and cytarabine. Approval of gemtuzumab ozogamicin monotherapy was based on a randomized trial of 237 patients with newly diagnosed AML treated without curative intent. Median overall survival (OS) was 4.9 months with gemtuzumab ozogamicin versus 3.6 months on best supportive care [HR = 0.69 (95% CI, 0.53–0.90)]. Adverse events were similar on both arms. Postapproval, several studies are required including evaluation of fractionated gemtuzumab ozogamicin pharmacokinetics, safety of combination gemtuzumab ozogamicin in the pediatric population, immunogenicity, and the effects of gemtuzumab ozogamicin on platelet function. *Clin Cancer Res; 24(14); 3242–6. ©2018 AACR.*

Introduction

Combination chemotherapies with or without hematopoietic stem cell transplantation (HSCT) are the standard of care for patients with newly diagnosed acute myeloid leukemia (AML). For patients who can tolerate intensive therapy, induction with 7 days of cytarabine and 3 days of an anthracycline followed by high-dose cytarabine consolidation has been used for decades. Current 5-year survival rates for patients with newly diagnosed AML who receive intensive therapy are 30% to 40% (1). Improvements in HSCT and supportive care have decreased treatment-related mortality, but relapse continues to be the most significant cause of treatment failure. There remains a strong need for new treatments for patients with newly diagnosed AML.

Gemtuzumab ozogamicin is an antibody–drug conjugate comprised of a CD33-directed humanized mAb linked covalently to the cytotoxic agent N-acetyl gamma calicheamicin. The antibody portion binds the CD33 antigen present on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage. Following internalization, calicheamicin is released and binds to DNA, resulting in DNA double-strand breaks and subsequent cell death. In nonclinical studies, gemtuzumab ozogamicin was hepatotoxic, nephrotoxic, and myelotoxic in rats and monkeys at doses of $\geq$7.2 mg/m^2 and was embryotoxic and reprotoxic at approximately similar human clinical exposure after repeat doses of 3 mg/m^2. *In vitro*, calicheamicin was mutagenic and clastogenic.

Gemtuzumab ozogamicin was granted accelerated approval on May 17, 2000, as monotherapy for the treatment of patients $\geq$60 years of age with CD33-positive AML in first relapse who were not considered candidates for cytotoxic chemotherapy. Approval was based on the response rate from three pooled single-arm trials in patients with first relapse of AML. The approved regimen was two doses of gemtuzumab ozogamicin 9 mg/m^2 14 days apart. As part of the original approval, Wyeth was required to confirm clinical benefit. SWOG S0106, the confirmatory trial, evaluated the addition of gemtuzumab ozogamicin 6 mg/m^2 on day 4 in a randomized fashion to standard daunorubicin and cytarabine for the treatment of patients with newly diagnosed AML. S0106 was terminated early when an interim analysis showed increased deaths in induction (6% vs. 1% in the control arm) and lack of improvement in complete response rate, disease-free survival, or overall survival (OS) with the addition of gemtuzumab

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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ozogamicin. Gemtuzumab ozogamicin was withdrawn from the U.S. market in 2010.

Subsequent trials have tested lower doses of gemtuzumab ozogamicin in patients with newly diagnosed AML. The clinical pharmacology of gemtuzumab ozogamicin has been reviewed in detail previously (2). In pharmacokinetics studies, gemtuzumab ozogamicin exposure increased more than dose proportionate with increasing doses of gemtuzumab ozogamicin. The exposure–response analyses showed an association between C_{max} after the first dose of gemtuzumab ozogamicin and the probability of developing veno-occlusive disease (VOD), but no relationship between C_{max} or AUC and complete remission. In addition, saturation of a high percentage of CD33 antigens is believed to be required for maximum delivery of calicheamicin to leukemic blast cells; in the pharmacodynamics assessment, CD33 appeared to be saturated with gemtuzumab ozogamicin doses above 2 mg/m^2. Therefore, there were several theoretical advantages for using lower doses of gemtuzumab ozogamicin. Herein, we summarize the review of the new information and rationale for the FDA's 2017 approval of gemtuzumab ozogamicin for the treatment of adults with newly diagnosed CD33-positive AML based on the results of studies ALFA-0701 and AML19 using lower doses of gemtuzumab ozogamicin. Gemtuzumab ozogamicin was also approved for relapsed/refractory AML, which is discussed in a separate review (3).

Gemtuzumab Ozogamicin + Chemotherapy for Treatment of Newly Diagnosed AML

ALFA-0701 (NCT00927498) was a randomized phase III trial of daunorubicin and cytarabine with or without gemtuzumab ozogamicin for the treatment of adults age 50 to 70 years with newly diagnosed *de novo* AML. Patients were randomized (1:1) to receive induction therapy consisting of daunorubicin (60 mg/m^2 on days 1–3) and cytarabine (200 mg/m^2 on days 1–7) with or without gemtuzumab ozogamicin 3 mg/m^2 (up to maximum of one vial) on days 1, 4, and 7. Patients who did not achieve a response after first induction could receive a second induction with daunorubicin and cytarabine alone. Patients with response received consolidation therapy with two courses of treatment including daunorubicin (60 mg/m^2 on day 1, consolidation 1; 60 mg/m^2 on days 1 and 2, consolidation 2) and cytarabine (1 g/m^2 every 12 hours on days 1–4) with or without gemtuzumab ozogamicin 3 mg/m^2 on day 1 per their initial randomization. The primary efficacy endpoint was event-free survival (EFS), with a key secondary endpoint of OS. A sample size of 280 patients was planned to test a 3-year EFS rate assuming an EFS of 40% in the experimental arm versus 25% in the control arm (corresponding HR = 0.66) at a two-sided type I error rate of 0.05 and 80% power.

Disposition and demographics

ALFA-0701 originally enrolled 280 patients; 9 patients were excluded from the analyses for lack of documentation of informed consent (gemtuzumab ozogamicin arm: 5, control arm: 4). The modified intent-to-treat (ITT) analysis population therefore comprised 271 patients, with 135 patients in the gemtuzumab ozogamicin arm and 136 patients in the control arm. The demographics and disease characteristics of the study population are shown in Table 1. These baseline characteristics were balanced between treatment arms except for gender, as a higher percentage of males were enrolled in the gemtuzumab ozogamicin arm than in the control arm. Data on race were not collected in the trial. CD33 expression on AML blasts by flow cytometry was available for 72% of patients; although the level of expression was variable, no patients assessed lacked expression of CD33.

Table 1. ALFA-0701—patient characteristics and outcomes

	GO + DA *n* = 135	DA *n* = 136
Demographics		
Age		
Median	62 yrs	60 yrs
Range	50–70 yrs	50–70 yrs
Sex		
Female	61 (45)	76 (56)
Male	74 (55)	60 (44)
ECOG status		
0–1	121 (90)	117 (86)
2–3	14 (10)	18 (13)
Unknown	0	1 (<1)
Disease characteristics		
Disease status		
Newly-diagnosed *de novo* AML	135 (100)	136 (100)
Cytogenetics		
Favorable	3 (2)	6 (4)
Intermediate	91 (67)	89 (65)
Poor	27 (20)	30 (22)
Unknown	14 (10)	11 (8)
CD33$^+$		
<30%	17 (13)	20 (15)
30%–70%	20 (15)	11 (8)
>70%	63 (47)	63 (46)
Unknown	35 (26)	42 (31)
Efficacy outcomes		
Median EFS based on CR/CRp	17.3 mos	9.5 mos
$EFS_{CR/CRp}$ HR (95% CI)	0.56 (0.42–0.76)	
	$P < 0.001$	
Median EFS based on CR	13.6 mos	8.8 mos
EFS_{CR} HR (95% CI)	0.68 (0.51–0.91)	
Median OS	27.5 mos	21.8 mos
OS HR (95% CI)	0.81 (0.60–1.09)	

Abbreviations: CI, confidence interval; CR, complete remission; CRp, complete remission without platelet recovery; DA, daunorubicin and cytarabine; ECOG, Eastern Cooperative Oncology Group; GO, gemtuzumab ozogamicin; mos, months; yrs, years.

Assessment of efficacy

Efficacy was established based on EFS, measured from the date of randomization until induction failure (IF), relapse, or death by any cause (Table 1). Per protocol, IF was defined as failure to achieve complete remission (CR) or CR without platelet recovery (CRp) in induction, with date of IF defined as date of marrow evaluation after the last course of induction. Median EFS was 17.3 months in the gemtuzumab ozogamicin arm versus 9.5 months in the control arm [HR = 0.56 (95% confidence interval (CI), 0.42–0.76)]. OS did not differ between arms. The EFS results in subgroups were comparable with the overall results except for the subgroup of 51 patients with adverse risk cytogenetics [HR = 1.11 (95% CI, 0.63–1.95)].

The FDA performed an exploratory analysis of EFS restricting the definition of IF to failure to achieve CR in induction and using the date of randomization as the date of IF. Applying this definition, median EFS was 13.6 months for gemtuzumab ozogamicin + daunorubicin and cytarabine and 8.8 months

Table 2. ALFA-0701—selected grade ≥3 higher adverse reactions

	GO + DA	DA
Induction		
Infection[a]	61/131 (47%)	53/137 (39%)
Hemorrhage[a]	24/131 (18%)	12/137 (9%)
Veno-occlusive liver disease[a]	3/131 (2%)	0
Prolonged thrombocytopenia[b]	19/101 (19%)	7/97 (7%)
Prolonged neutropenia[b]	3/106 (3%)	0/101 (0%)
Consolidation 1		
Infection[a]	50/91 (55%)	43/103 (42%)
Hemorrhage[a]	5/91 (5%)	0
Veno-occlusive liver disease[a]	0	0
Prolonged thrombocytopenia[b]	21/87 (24%)	6/91 (7%)
Prolonged neutropenia[b]	3/88 (3%)	1/97 (1%)
Consolidation 2		
Infection[a]	32/64 (50%)	54/107 (50%)
Hemorrhage[a]	4/64 (6%)	0
Veno-occlusive liver disease[a]	0	0
Prolonged thrombocytopenia[b]	22/62 (35%)	25/103 (24%)
Prolonged neutropenia[b]	1/62 (2%)	2/105 (2%)

Abbreviations: DA, daunorubicin and cytarabine; GO, gemtuzumab ozogamicin.
[a]Grouped term consisting of multiple preferred terms. See Supplementary Table S4.
[b]Platelets less than 50 Gi/L or neutrophils less than 0.5 Gi/L lasting past cycle day 42 in the absence of active leukemia.

for daunorubicin and cytarabine alone [HR = 0.68 (95% CI, 0.51–0.91)].

Assessment of safety

Safety in ALFA-0701 was assessed in 131 patients treated with gemtuzumab ozogamicin + daunorubicin and cytarabine and 137 patients treated with daunorubicin and cytarabine alone. Wyeth performed a retrospective collection of adverse events of special interest, capturing all grades of hemorrhage and VOD, severe infections, and any other adverse event that led to early permanent discontinuation of gemtuzumab ozogamicin or chemotherapy. Overall findings by treatment phase are presented in Supplementary Tables S1–S3. Early mortality was slightly higher in the gemtuzumab ozogamicin arm (4% vs. 2%); treatment-related deaths were due predominantly to hemorrhage and VOD in the gemtuzumab ozogamicin arm and to infections in the control arm. Six patients (5%) in the gemtuzumab ozogamicin arm developed VOD during treatment or follow-up, and 3 cases were fatal; 2 patients in the control arm developed VOD after receiving gemtuzumab ozogamicin for relapsed AML. Infection, bleeding, and prolonged thrombocytopenia were more common in the gemtuzumab ozogamicin arm, especially during induction and consolidation 1 (Table 2).

The safety assessment was supported by a meta-analysis of patient-level data from ALFA-0701 (4) and four other randomized trials (5–8) of various doses of gemtuzumab ozogamicin in combination with different chemotherapy regimens for treatment of newly-diagnosed AML (Supplementary Table S5), as well as a comprehensive review of the literature. The results of the meta-analyses (Table 3) showed an overall trend for decreased imbalance between treatment arms in early mortality, VOD, transaminase elevation, and bleeding with decreasing doses of gemtuzumab ozogamicin. These findings were consistent with the expectation that the lower gemtuzumab ozogamicin dose and fractionated schedule had less toxicity than gemtuzumab ozogamicin 6 mg/m^2 used in S0106.

Gemtuzumab Ozogamicin Monotherapy for Treatment of Newly Diagnosed AML

AML19 (NCT00091234) was a randomized, open-label, multicenter phase II/III trial of gemtuzumab ozogamicin monotherapy. Eligible patients had newly diagnosed AML (*de novo* or secondary) and were age >75 years or age 61 to 75 years with a World Health Organization performance status >2 and/or unwilling to receive intensive chemotherapy. In the phase III portion, the patients were randomized 1:1 to gemtuzumab ozogamicin monotherapy or best supportive care (BSC) and stratified by age, CD33 positivity, initial white blood cell count, performance status, and institution. Treatment in the gemtuzumab ozogamicin induction arm consisted of 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8. Patients without evidence of disease progression or significant toxicities after induction could receive continuation therapy with up to eight courses of gemtuzumab ozogamicin 2 mg/m^2 on day 1 every 4 weeks. Patients on the BSC arm received standard supportive care measures and hydroxyurea or other antimetabolites (e.g., 6-mercaptopurine) for palliative purposes.

A total of 237 patients, 118 on the gemtuzumab ozogamicin arm and 119 on the BSC arm, were included in the ITT population. Baseline demographics were well-balanced, apart from more females and favorable/intermediate cytogenetics on the gemtuzumab ozogamicin arm (Table 4). The median number of gemtuzumab ozogamicin doses per patient was three (range, 1–10). Fifty-nine (53%) patients received at least one postinduction dose of gemtuzumab ozogamicin, but only 9 (8%) received all 10 planned infusions.

Table 3. Summary of meta-analyses of clinical outcomes by gemtuzumab ozogamicin regimen for treatment of newly-diagnosed AML in combination with chemotherapy

	Gemtuzumab ozogamicin regimen used with chemotherapy induction[a]		
	6 mg/m^2 day 4	3 mg/m^2 days 1, 4, and 7	3 mg/m^2 day 1
Number of studies	2	1	2
Safety outcomes			
OR day-30 mortality (95% CI)	2.78 (1.33–5.84)	1.99 (0.54–7.36)	1.09 (0.80–1.49)
OR grade 3–4 VOD (95% CI)	7.66 (2.33–25.20)	2.42 (0.54–10.83)	3.34 (0.58–19.32)
OR grade 3–4 AST[b] (95% CI)	2.83 (1.75–4.58)	2.54 (1.05–6.19)	1.26 (0.78–2.03)
OR grade 3–4 ALT[b] (95% CI)	2.41 (1.48–3.93)	1.21 (0.52–2.79)	1.16 (0.84–1.61)
OR grade 3–4 hemorrhage[b] (95% CI)	2.03 (1.27–3.26)	2.46 (1.22–4.96)	1.44 (0.85–2.45)
Efficacy outcomes			
HR[c] OS (95% CI)	1.02 (0.84–1.23)	0.81 (0.59–1.09)	0.89 (0.81–0.98)
HR[c] EFS (95% CI)	0.91 (0.76–1.09)	0.65 (0.48–0.87)	0.86 (0.78–0.95)

[a]See Supplementary Table S5 for details of the trials used in the meta-analysis.
[b]Limited to induction period.
[c]HR estimated using the method of Peto (14).

Table 4. AML19—patient characteristics and outcomes

	Monotherapy GO $n = 118$	BSC $n = 119$
Demographics		
Age		
Median	77 yrs	77 yrs
Range	(62–88 yrs)	(66–88 yrs)
Sex		
Male	57 (48%)	73 (61%)
Female	61 (52%)	46 (39%)
WHO status		
0–2	110 (93%)	110 (92%)
>2	8 (7%)	9 (8%)
Disease characteristics		
Disease status		
Newly diagnosed *de novo* AML	79 (67%)	85 (71%)
Newly diagnosed secondary AML	39 (33%)	34 (29%)
Cytogenetics		
Favorable/intermediate	59 (50%)	45 (38%)
Poor	33 (28%)	32 (27%)
Unknown	26 (22%)	42 (35%)
$CD33^+$		
<20%	10 (9%)	14 (12%)
20%–80%	58 (49%)	58 (49%)
>90%	48 (41%)	47 (40%)
Unknown	2 (2%)	0
Efficacy outcomes		
Median OS	4.9 mos	3.6 mos
OS HR (95% CI)	0.69 (0.53–0.90) $P = 0.005$	

Abbreviation: GO, gemtuzumab ozogamicin; mos, months; yrs, years.

The primary endpoint was OS. There was a significant improvement in median OS with gemtuzumab ozogamicin [HR = 0.69 (95% CI, 0.53–0.90)], although the difference was modest at 1.3 months (Table 4). The investigators reported that subgroup analyses of OS showed comparable results across subpopulations except that the treatment effect was not evident in patients with CD33 positivity < 20% [HR 1.52 (95% CI, 0.65–3.58)] and in patients with adverse cytogenetics [HR 1.11 (95% CI, 0.67–1.93)].

All-cause 60-day mortality following gemtuzumab ozogamicin versus BSC was 18% versus 30%, respectively. On the gemtuzumab ozogamicin arm, fatal adverse reactions during induction were due to infection ($n = 5$), hemorrhage, renal failure, or cardiac failure (1 each). Treatment-emergent adverse events (TEAE) were similar between the gemtuzumab ozogamicin and BSC arms (Table 5). There were no cases of VOD.

Regulatory Insights

ALFA-0701 provided the major body of evidence to support approval of gemtuzumab ozogamicin for treatment of adults with newly diagnosed CD33-positive AML. For this indication, the FDA generally uses OS as the basis for approval (9). In ALFA-0701, there was no OS benefit. In addition, the meta-analyses of patient-level and trial-level data showed that EFS did not have a strong correlation with OS (10). Use of active salvage therapies, including stem cell transplantation, which prolonged OS in patients with treatment failure, was identified as a potential confounding factor in these analyses. Thus, EFS is not a surrogate for OS. However, because durable CR is a desired outcome for patients with AML, and EFS reflects durable CR and survival, the FDA concluded that EFS itself is considered a clinical benefit for patients with newly diagnosed AML if defined in a way that accurately reflects achievement of CR and meaningful durability of CR, as discussed below.

Table 5. AML19—common (>5%) grade ≥3 adverse reactions

	Monotherapy GO $n = 111$	BSC $n = 114$
Infection	39%	34%
Febrile neutropenia	18%	25%
Bleeding	14%	12%
Fatigue	13%	22%
Liver dysfunction	4%	4%
Cardiac dysfunction	7%	11%

Abbreviation: GO, gemtuzumab ozogamicin.

In ALFA-0701, the definition of EFS considered IF as failure to achieve CR or CRp, with the event date as the date of evaluation of bone marrow response after the last induction cycle. However, studies have shown that CR and CRp [or complete remission with incomplete hematologic recovery (CRi)] are not equivalent measures of cytotoxic drug activity in AML. Patients who achieve only CRp/CRi have inferior prognosis and long-term survival compared with those who achieve CR (11). Whether this is also true for treatment with targeted therapies has not been established; lacking further evidence, CR and CRp/CRi cannot be considered equivalent endpoints for regulatory decision-making. For patients with newly diagnosed AML treated with curative intent, achieving only CRp/CRi is considered treatment failure. In the FDA's exploratory analysis of EFS in ALFA-0701, limiting the definition of induction response to only CR and using the date of randomization as the event date (Table 1), the HR remained nominally significant, albeit with a smaller difference in median EFS between treatment arms than with per-protocol EFS definition (4.8- vs. 7.8-month difference).

This modest improvement in EFS in ALFA-0701 must be weighed against the toxicities of gemtuzumab ozogamicin. As shown in Table 3, the lower dose fractionated regimen of gemtuzumab ozogamicin in ALFA-0701 was indeed associated with a lower odds ratio (OR) for early mortality and liver toxicity than the higher dose used in the failed SWOG S0106 trial. Nevertheless, the incidences of infection, bleeding, VOD, and prolonged thrombocytopenia were still increased with the lower dose fractionated regimen of gemtuzumab ozogamicin in comparison with standard chemotherapy alone (Table 2). With appropriate mitigation strategies in place, these risks were considered outweighed by the potential benefit of gemtuzumab ozogamicin when added to standard chemotherapy. Whether alternative gemtuzumab ozogamicin regimens, such as a single 3-mg/m^2 dose, are safer than and still as effective as the lower fractionated regimen when used with standard chemotherapy remains to be determined in randomized clinical trials.

Subgroup analyses of efficacy in ALFA-0701 provided two findings of interest. First, patients with adverse risk cytogenetics did not appear to derive EFS benefit from the addition of gemtuzumab ozogamicin (EFS HR = 1.11). This was considered a true finding based on biological plausibility; adverse cytogenetics in AML correlate with expression of p-glycoprotein, a factor associated with lower response to gemtuzumab ozogamicin (12, 13). Hence, this observation is described in a warning in the gemtuzumab ozogamicin prescribing information. Second, the FDA's analysis showed that, although patients with >70% CD33 expression had the most significant improvement in EFS, all CD33 subgroups appeared to derive some degree of benefit. Therefore,

the indication for patients with CD33-positive AML was approved without qualifiers.

In AML19, there was a 1.3-month median OS advantage for gemtuzumab ozogamicin over BSC. As the toxicities did not differ substantially between treatment arms, it was concluded that the potential benefit of gemtuzumab ozogamicin outweighs the risks. Although gemtuzumab ozogamicin monotherapy is not curative, the monotherapy regimen represents an option for patients who desire even a short survival benefit but are unwilling to accept the risks of intensive chemotherapy. Such decisions are considered within the purview of the practice of medicine and cannot be limited by age alone. Taken together, the results of ALFA-0701 and AML19 provide treatment options for adults with newly diagnosed *de novo* or secondary CD33-positive AML. No data were submitted for the FDA to assess safety and efficacy of gemtuzumab ozogamicin in combination with chemotherapy for the treatment of pediatric patients with newly diagnosed AML.

Conclusions

In ALFA-0701, gemtuzumab ozogamicin 3 mg/m^2 on days 1, 4, and 7 in combination with daunorubicin and cytarabine resulted in an improvement in EFS over daunorubicin and cytarabine alone [HR = 0.68 (95% CI, 0.51–0.91)] for patients with newly diagnosed CD33-positive *de novo* AML except in patients with adverse cytogenetic risk. In AML19, patients with newly diagnosed CD33-positive AML treated without curative intent derived an OS improvement of 6 weeks over BSC using gemtuzumab ozogamicin monotherapy 6 mg/m^2 on day 1 and 3 mg/m^2 on day 4 [HR = 0.69 (95% CI, 0.53–0.90)]. Overall, ALFA-0701 and AML19 confirmed the clinical benefit of gemtuzumab ozogamicin in adult patients with newly diagnosed CD33-positive AML. The available data suggest that the safety concerns that resulted in withdrawal of gemtuzumab ozogamicin from the U.S. market are ameliorated with the lower dose and fractionated gemtuzumab ozogamicin regimens.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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