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GENERIC DRUG NAME / COMPOUND NUMBER: Inotuzumab ozogamicin (CMC-544) / PF-05208773

PROTOCOL NO.: 3129K5-2005-WW (B1931001)

PROTOCOL TITLE: An Open-Label, Single-Arm, Phase 2 Study of Inotuzumab Ozogamicin Plus Rituximab in Subjects With Relapsed/Refractory CD22-Positive Diffuse Large B-Cell Lymphoma, Eligible for Autologous Stem Cell Transplantation

Study Centers: In total, 24 centers took part in the study and enrolled subjects including 7 in France, 3 in the Republic of Korea, 11 in the United States, 1 in the United Kingdom, 1 in Singapore, and 1 in Germany.

Study Initiation and Final Completion Dates: 08 June 2009 to 31 October 2012

Phase of Development: Phase 2

Study Objectives:

Primary Objectives:

- To evaluate the efficacy and safety of inotuzumab ozogamicin in combination with rituximab as induction therapy prior to consolidation with high-dose chemotherapy (HD chemo) and autologous stem cell transplant (aSCT) in subjects with relapsed/refractory cluster of differentiation (CD)22-positive diffuse large B-cell lymphoma (DLBCL).

Secondary Objectives: To evaluate:

- The toxicities of inotuzumab ozogamicin plus rituximab;
- The efficacy of inotuzumab ozogamicin plus rituximab as measured by progression-free survival (PFS), complete response (CR), and overall survival (OS);
- The ability of inotuzumab ozogamicin plus rituximab to allow for successful peripheral blood stem cell (PBSC) mobilization and collection, as measured by mobilization-adjusted objective response rate (ORR) and the rate of successful PBSC collections;
- The efficacy of inotuzumab ozogamicin plus rituximab as induction therapy prior to consolidation with HD chemo and aSCT, as measured by transplantation rate and event-free survival (EFS);

- The population pharmacokinetic (PK) profile of inotuzumab ozogamicin.

METHODS

Study Design: This was a single-arm, open-label, Phase 2 clinical study evaluating the efficacy and safety of inotuzumab ozogamicin in combination with rituximab in subjects with relapsed/refractory CD22-positive DLBCL who were eligible for aSCT. Subjects were treated for 3 to 6 cycles of induction therapy (up to approximately 4.5 months) followed by consolidation therapy then entered the follow-up period.

Subjects received induction therapy every 21 days with inotuzumab ozogamicin + rituximab for a planned 3 cycles; subjects who had stable disease (SD) or a partial response (PR) after 3 cycles of induction therapy could receive up to 3 additional cycles of inotuzumab ozogamicin + rituximab if all study-specified dosing rules were met, and subjects with a CR after 3 cycles of induction therapy were permitted to have 1 additional cycle if all study-specified dosing rules were met.

PBSC mobilization with 1 of 3 permitted mobilization regimens could begin during Cycle 2 or later. Subjects who had a response (CR or PR) to induction therapy and from whom $\geq 2 \times 10^6$ CD34+ cells/kg were collected during mobilization received HD chemo and aSCT according to local practice 4 to 8 weeks after the last cycle of induction therapy. PK samples were collected at Cycles 1 and 3 of induction therapy.

Tumor and clinical disease measurements were obtained at Screening, approximately 2 to 3 weeks after 3 cycles of inotuzumab ozogamicin + rituximab (induction) therapy, at end-of-therapy (EOT), and approximately every 3 to 6 months during long-term follow-up visits (conducted up to 2 years until documentation of progressive disease or death). Assessments could also be performed as clinically indicated.

Responses were determined from objective measurements of tumor masses on computed tomography (CT or magnetic resonance imaging scans, clinical information (eg, liver and spleen size), results of B-symptoms evaluations, laboratory assessments (eg, bone marrow biopsies), and biochemical markers of disease activity (eg, lactate dehydrogenase concentrations), according to National Cancer Institute for International Response Criteria for non-Hodgkin's lymphoma (NHL).

Subjects without PD at EOT continued disease assessment approximately every 3 to 6 months for up to 2 years during long-term follow-up unless they withdrew consent, experienced disease progression, or began another anticancer therapy. All subjects were followed for survival for up to 2 years (Table 1).

Table 1. Study Flowchart

(Days Relative to Test Article Administration)	Screening	Induction Therapy (Cycles 1, 2 and 3)[a]			Evaluation	Consolidation Therapy[b]	EOT[c]	Long-Term Follow-Up[d]
	Days -30 to -3	Day -2 (Cycle 1 Only)	Day 1[e]	Day 2	Days 8 and 15[e]	Weeks 8 to 9	Week 10 to 14	Month 6	Months 9, 12, 18 and 24
Informed consent	X						HD Chemotherapy +aSCT		
Inclusion/exclusion criteria; demography	X								
CD20 and CD22 NHL immunophenotyping	X								
Medical and cancer history and treatment	X								
Complete physical examination	X					X		X	X
ECOG PS[f]	X					X		X	X
HBsAg and anti-HCV	X								
sIPI score[g]	X								
Evaluation of B symptoms and lymphoma[h]	X	X	X			X		X	X
β-HCG[i]	X	X	X			X			
Serum chemistry and hematology[j]	X	X	X		X	X		X	X
Coagulation profile[k]	X					X			
Complete urinalysis	X	X	X			X		X	
Urine protein/creatinine ratio[l]	X	X							
Immune response testing[m]		X							
Calculation of BSA		X	X						
Vital signs[n]	X			X		X		X	X
CT scan and clinical disease assessment[o]	X					X		X	X
Bone marrow aspirate/biopsy[p]	X					X		X	
LVEF by echocardiogram or MUGA	X								
ECGs[q]	X							X	
Adverse events[r]	X								
Prior and concomitant treatment	X								
PK									
Test-article administration		X	X	X					
PBSC mobilization[s]					X				
Survival status and other anticancer therapy									X

AEs = adverse events; ANC = absolute neutrophil count; aSCT = autologous stem cell transplant; β-HCG = beta human chorionic gonadotropin; BSA = body surface area; CD = cluster of differentiation; CT = computed tomography; CR = complete response; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ELISA = enzyme linked immunosorbent assay; EOT = end-of-treatment; G-CSF = granulocyte colony-stimulating factor; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HD chemo = high-dose chemotherapy; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NHL = Non-Hodgkin lymphoma;

Table 1. Study Flowchart

PBSC = peripheral blood stem cells, PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; SAEs = serious adverse events; SD = standard deviation; sIPI = secondary International Prognostic Index; VS = vital signs; WBC = white blood cell.

a. Twenty-one (21) day cycles of inotuzumab ozogamicin (1.8 mg/m^2, Day 2 [capped at BSA 2.2 m^2]) plus rituximab (375 mg/m^2, Day 1 [and Cycle 1 Day -2]); up to 6 total cycles were permitted if study-specified criteria were met. Study procedures for additional cycles were the same except PK/ECGs were not done.
b. Consolidation therapy was scheduled 4 to 8 weeks after the last cycle of induction therapy.
c. EOT was approximately 3 months (±14 days) after the completion of consolidation therapy, or 42 to 63 days after last dose of study therapy for subjects who did not undergo consolidation therapy.
d. Subjects without PD were followed for at least survival status for up to 2 years. Long-term follow-up visits were every 3 to 6 months beginning approximately 3 months after the EOT visit and included assessment of disease, vital signs (VS), labs, and ECOG PS.
e. Study visit window ±2 for Days 1, 8 and 15 of all cycles.
f. ECOG PS ≤2 required for study eligibility.
g. sIPI score >1 or persistent disease/relapsed disease (<12 months after start of the most recent prior therapy) required for study eligibility.
h. Predose evaluation of B symptom and lymphoma included liver and spleen assessments and clinical assessment of tumor masses (if accessible).
i. Women of childbearing potential had β-HCG serum pregnancy testing at Screening. Urine β-HCG was evaluated before each dose of test article and at the Evaluation visit. If the urine test was positive, results were confirmed with a serum β-HCG, or serum β-HCG could be done initially.
j. Serum chemistry and hematology were required within 3 days before each dose of test article and as indicated. Additional unscheduled chemistry assessments were done if laboratory values were abnormal (or as clinically indicated) and repeated until resolution, return to baseline, or until NCI CTCAE Grade ≤1. Additional (unscheduled) hematology assessments were done in the case of NCI CTCAE Grade 4 hematologic toxicity (or as clinically indicated), and repeated twice a week or as clinically indicated until ANC was ≥1000/μL or platelets were ≥75,000/μL. If WBC count was <500/μL, differential was not required.
k. PT/INR, PTT, and fibrinogen.
l. Urine protein/creatinine ratio required during screening and prior to Cycle 4 (if planned); 24-hour collection was optional as clinically indicated.
m. Immune response testing included ELISA for anti-rituximab and anti-inotuzumab ozogamicin antibodies and was required during Cycle 1 only before test article administration.
n. Vital signs included height (screening only), weight, temperature, blood pressure, and pulse. On Day 2, VS were done predose, twice during test article infusion, and hourly for 2 hours during Cycle 1 (3 hours of observation) and at 1 hour after infusion for all other cycles (2 hours of observation).
o. Disease was assessed by CT scans or MRIs, but the same method was used throughout the study. PET scan was required to confirm SD at first response assessment and was recommended at subsequent response assessments when SD was noted.
p. Bone marrow aspirate and/or biopsy were optional before study start but were required in subjects who otherwise met the criteria for a CR unless an adequate bone marrow biopsy had been negative for lymphoma within 28 days before first dose of test article.
q. Triplicate ECGs (3 consecutive ECGs approximately 2 minutes apart) were read and interpreted locally for subject eligibility and safety monitoring. The average of the 3 ECGs was used to assess eligibility. Copies of ECGs were also sent to a central vendor for analysis.
r. AEs were collected from the signing of informed consent through the EOT visit (subjects who did not undergo consolidation treatment) or until consolidation therapy. SAEs were collected from the signing of informed consent until the EOT visit for all subjects. Subjects with evidence of test article related AEs and SAEs were followed until the event or its sequelae resolved or stabilized at a level acceptable to the Investigator and the Sponsor concurred with that assessment.
s. Subcutaneous G-CSF treatment (5 to 15 μg/kg/day) alone or in combination with plerixafor injection (Mozobil) or with 1 of 2 study-defined chemotherapy regimens until collection by apheresis of ≥2.0 × 10^6 CD34+ cells/kg.

Number of Subjects (Planned and Analyzed): It was planned to enroll about 60 subjects. Eighty-five (85) subjects were screened, 63 subjects were enrolled and included in the intent-to-treat (ITT) and safety populations, and 53 subjects were included in the per-protocol (PP) population.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Male and female subjects aged ≥18 years (≥20 years in Japan);
- CD20/CD22-positive DLBCL that had relapsed after 1 or 2 prior therapies; 1 prior therapy must have included anthracyclines and 1 must have included rituximab in combination with chemotherapy;
- Relapsed/disease progression within 12 months after start of prior therapy and/or secondary International Prognostic Index (sIPI) score >1;
- Eligible for aSCT.

Exclusion Criteria:

- Prior allogeneic hematopoietic stem cell transplant;
- Within 6 months prior to test article: autologous transplant, treatment with anti-CD22 antibodies, radio-immunotherapy;
- Veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS), chronic liver disease, systemic vasculitides, current or chronic hepatitis B or C infection.

Study Treatment: Subjects received inotuzumab ozogamicin + rituximab every 21 days (1 cycle) for a planned minimum of 3 cycles. Up to 3 additional cycles, for a maximum of 6 total cycles, were permitted if study-specific conditions were met.

The starting dose of inotuzumab ozogamicin was 1.8 mg/m^2 (capped at body surface area of 2.2 m^2). Intravenous inotuzumab ozogamicin was reconstituted with sterile water and administered in 50 mL of 0.9% sodium chloride over 1 hour ± 10 minutes. Dose reductions were permitted.

The rituximab dose was 375 mg/m^2. Rituximab was administered per local prescribing information, clinical judgment, and in accordance with local standards of care. Rituximab dose reductions were not recommended.

Efficacy and Safety Endpoints:

Primary:

- ORR: CR + PR (confirmed or unconfirmed) after 3 cycles of inotuzumab ozogamicin plus rituximab therapy;
- Safety as measured by the incidence of adverse events (AEs) and laboratory abnormalities.

Secondary:

- PFS, 6 months and 2 years after inotuzumab ozogamicin plus rituximab therapy. Events were: death from any cause without progression, relapse after CR, progression during and after treatment, and initiation of a new treatment for the lymphoma excluding treatments and procedures for consolidation therapy in this study;
- Mobilization-adjusted ORR: CR + PR in subjects who had successful granulocyte colony-stimulating factor (G-CSF) mobilization of PBSC ($\geq 2.0 \times 10^6$ CD34+ cells/kg collected) after 3 cycles of inotuzumab ozogamicin plus rituximab therapy;
- Rate of successful G-CSF mobilization of PBSC, defined as: $\geq 2.0 \times 10^6$ CD34+ cells/kg collected after 3 cycles of inotuzumab ozogamicin plus rituximab therapy;
- Transplantation rate;
- EFS after aSCT. Events were: death from any cause without progression, relapse after CR, progression during and after treatment, and initiation of a new treatment for the lymphoma;
- CR;
- OS;
- The population PK profile of inotuzumab ozogamicin.

Safety Evaluations: Safety evaluations included assessment of AEs and serious AEs (SAEs), assignment of toxicity grades, deaths, laboratory evaluations, vital signs, physical examinations, and 12-lead electrocardiograms.

Statistical Methods: The ITT population included all subjects who were enrolled in the study. The PP population included all enrolled subjects who had no major study violations with a complete baseline assessment and at least 1 complete post-baseline tumor assessment. The safety analysis population included all subjects who received at least 1 dose of test article (either inotuzumab ozogamicin or rituximab).

This study was intended to estimate the clinical activity of inotuzumab ozogamicin in combination with rituximab in subjects with relapsed/refractory DLBCL. Efficacy analyses

based on the ITT population were considered primary, and analyses based on the PP population were considered supportive results. The ORR was estimated as the number of subjects with a CR or PR/number of subjects in the ITT population, and an exact confidence interval (CI) was generated. Time-to-event endpoints were summarized using the Kaplan-Meier method. Median survival time or survival rate at a specific time was estimated, and the corresponding 95% CI was generated based on the Brookmeyer and Crowley CI for median survival time with Greenwood formula log-log transformation. Rates for categorical endpoints were estimated and 95% exact CIs were generated based on a binomial distribution. Kaplan-Meier curves, median survival time (and the 95% CI), and survival rates at 6 months, 1 year, and 2 years after the combination therapy (and the 95% CIs) were generated.

Successful G-CSF mobilization of PBSC was defined as $\geq 2 \times 10^6$ CD34+ cells/kg collected after 3 cycles of inotuzumab ozogamicin plus rituximab therapy, and the mobilization-adjusted ORR was defined as CRs + PRs in subjects who had successful G-CSF mobilization after 3 cycles of inotuzumab ozogamicin plus rituximab therapy. The transplantation rate was defined as the proportion of subjects who underwent aSCT, and EFS after aSCT was defined as the time from the start of consolidation therapy to death from any cause without progression, relapse, progression during and after treatment, or initiation of a new treatment for the lymphoma.

Safety endpoints were summarized using descriptive statistics on the basis of the safety population.

No formal PK analysis was planned. The measures were included as part of a separate formal population PK analysis.

RESULTS

Subject Disposition and Demography: Eighty-five (85) subjects were screened. As shown in Table 2, 63 subjects were enrolled and 23 subjects (36.5%) completed the treatment phase (induction therapy). All 63 enrolled subjects were included in the ITT population and safety population, and 53 subjects (84.1%) were included in the PP population. A total of 40 (63.5%) subjects discontinued during the treatment phase; due to disease progression (29 [46.0%] subjects), AEs (5 [7.9%] subjects), death (1 [1.6%] subject), Investigator request (2 [3.2%] subjects), subject request (2 [3.2%] subjects) and protocol violation (1 [1.6%] subject).

Table 2. Subject Disposition

	Number of Subjects (%)
Total enrolled ('randomized')	63 (100)
Began treatment phase	63 (100)
Completed treatment phase	23 (36.5)
Discontinued treatment phase	40 (63.5)
Completed the study	21 (33.3)
Discontinued the study	42 (66.7)
Began long-term follow-up	51 (81.0)
Completed long-term follow-up	32 (50.8)
Discontinued long term follow-up	19 (30.2)

Table 3 presents the demographic characteristics of the subjects.

Table 3. Demographic and Baseline Characteristics (ITT Population)

Age (years)	
Mean (SD)	57.7 (12.92)
Median (range)	60.0 (19.0-75.0)
Sex (number, %)	
Female	16 (25.4)
Male	47 (74.6)
Race (number, %)	
Asian	7 (11.1)
Black or African American	1 (1.6)
White	50 (79.4)
Other	5 (7.9)
ECOG PS (number, %)[a]	
0	27 (42.9)
1	34 (54.0)
2	2 (3.2)

ECOG PS = Eastern Cooperative Oncology Group performance status.

a. ECOG PS 0 = fully active, able to carry on all predisease performance without restriction (Karnofsky 90-100).
ECOG PS 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework, office work (Karnofsky 70-80).
ECOG PS 2 = ambulatory and capable of self-care, but unable to carry out any work activities; up and about >50% of waking hours (Karnofsky 50-60).
ECOG PS 3 = capable of only limited self-care; confined to bed or chair >50% of waking hours (Karnofsky 30-40).
ECOG PS 4 = completely; cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10-20).

Efficacy Results:

Primary:

As shown in Table 4, the ORR after 3 cycles of combination therapy was 28.6% (95% CI: 17.9, 41.4), and 8 subjects (12.7%; 95% CI: 5.7, 23.5) had a CR after 3 cycles.

Table 4. Objective Response Rate (ITT Population)

Subjects with a confirmed or unconfirmed CR or PR	18
ORR (95% CI)	28.6% (17.89, 41.35)
Subjects with a confirmed or unconfirmed CR	8
CR rate (95% CI)	12.7% (5.65, 23.50)

Subjects were categorized according to response after 3 cycles of combination therapy.
Where applicable, excluded responses after start date of chemoprimed G-CSF mobilization and/or excluded responses after the earliest start date of consolidation therapy.
CI = confidence interval; CR = complete response; G-CSF = granulocyte colony stimulating factor; ITT = intent-to-treat; ORR = objective response rate; PR = partial response.

Secondary:

Progression-Free Survival:

Median PFS in the ITT population was 3.0 months (95% CI: 2.2, 6.3). PFS was 39.1% (95% CI: 26.9, 51.1) at 6 months, 28.9% (95% CI: 18.1, 40.6) at 1 year, and 25.3% (95% CI: 15.1, 36.8) at 2 years (Table 5).

Median PFS and PFS rates were similar in the PP population.

Rates of Successful G-CSF Mobilization of PBSC and Transplantation:

Thirty-two (32) subjects received G-CSF based treatment for PBSC mobilization. Of these, 18 subjects (28.6%; 95% CI: 17.89, 41.35) had successful collection of PBSC ($\geq 2.0 \times 10^6$ CD34+ cells/kg). Collections for these 18 subjects ranged from 2.1×10^6 to 7.1×10^6 cells/kg. Mobilization regimens for the 18 subjects with successful PBSC collections were as follows: 9 subjects received G-CSF alone, 8 subjects received G-CSF + plerixafor, and 1 subject received chemoprimed G-CSF treatment.

Of the 14 subjects with unsuccessful PBSC collections, collection was attempted for 10 subjects, including 2 subjects for whom CD34+ cell collection was not reported, and collection was not attempted for 4 subjects. Eight (8) of the 14 subjects with unsuccessful PBSC collection received G-CSF alone, 3 received chemoprimed G-CSF treatment, 2 subjects received G-CSF + plerixafor, and 1 subject received chemoprimed G-CSF + plerixafor.

High-dose transplant preparatory regimens used for the 18 subjects who underwent aSCT included BEAM (busulfan, etoposide, cytarabine, and melphalan) for 16 subjects, BEAC (carmustine, cyclophosphamide, cytarabine, and etoposide) for 1 subject, and busulfan, etoposide, and melphalan for 1 subject. For these 18 subjects, HD chemo started between 25 and 89 days from the last dose of inotuzumab + rituximab induction therapy. Among these 18 subjects, 5 subjects did not meet study criteria to undergo aSCT: 4 subjects did not have a response to R-INO (SD reported for each), and 1 subject did not have $\geq 2 \times 10^6$ CD34+ cells/kg collected.

Table 5. Summary of Progression Free Survival (ITT Population)

No. of Subjects	6 Months PFS			1 Year PFS			2 Years PFS			Median PFS (Months)	95 % CI	
	% PFS	95 % CI		% PFS	95 % CI		% PFS	95 % CI			Lower	Upper
		Lower	Upper		Lower	Upper		Lower	Upper			
63	39.1	26.9	51.1	28.9	18.1	40.6	25.3	15.1	36.8	3.0	2.2	6.3

PFS is defined as time from date of randomization to the earliest date of progression, death or start of new anti-cancer therapy, or censored at date of last tumor assessment.
Treatment: Rituximab 375 mg/m^2 + inotuzumab ozogamicin 1.8 mg/m^2.
CI = confidence interval; ITT = intent-to-treat; No. = number; PFS = progression free survival.

Mobilization-Adjusted Response Rate:

The mobilization-adjusted ORR, which represents responders (CR + PR) who had successful mobilization of PBSC (≥2 × 10^6 CD34+ cells/kg collected), was 17.5% in the ITT population (Table 6). The percentage of subjects with both CR and PR after 3 cycles of treatment and successful mobilization was 15.9% (95% CI: 7.88, 27.26).

Table 6. Summary of Objective Response Rate Modified by Successful Stem Cell Mobilization (ITT Population)

	n[a]	ORR (%)	95 % CI
Responders[b] (CR + PR) who had successful mobilization of PBSC	11	17.5	9.05, 29.10

Number of responders = subjects with a confirmed CR/PR + subjects with an unconfirmed CR/PR. Where applicable, excludes responses after the start of chemoprimed G-CSF mobilization and/or after the earliest start date of consolidation therapy.
CD = cluster of differentiation; CI = confidence interval; CR = complete response; G-CSF = granulocyte colony stimulating factor; ITT = intent-to-treat; n = number of subjects in specific category; ORR = objective response rate (CR + PR); PBSC = peripheral blood stem cell; PR = partial response.

a. One (1) additional subject should have been included as a responder who had successful mobilization of PBSC. The subject, with PR after 3 cycles, underwent apheresis twice: 1 × 10^6 cells/kg and 1.1 × 10^6 cells/kg were harvested for the first and second collections, respectively. Only the first collection with an outcome of 'unsuccessful' was reported; the second collection, with a result of 'successful', should have been reported since ≥2 × 10^6 cells/kg were collected across both attempts. Inclusion of this subject results in mobilization-adjusted ORR of 19.0%, and a mobilization-adjusted ORR after 3 cycles of 17.5%.
b. Subjects who had successful mobilization of PBSC (≥2 × 10^6 CD34+ cells/kg collected).

Event-Free Survival:

Median EFS could not be calculated in the ITT population. Only subjects in the ITT population who had transplantation (n=18) were included in the evaluation of EFS, and 11 subjects were censored (Table 7). Results were similar in the PP population.

Table 7. Summary of Event Free Survival After aSCT (ITT Population)

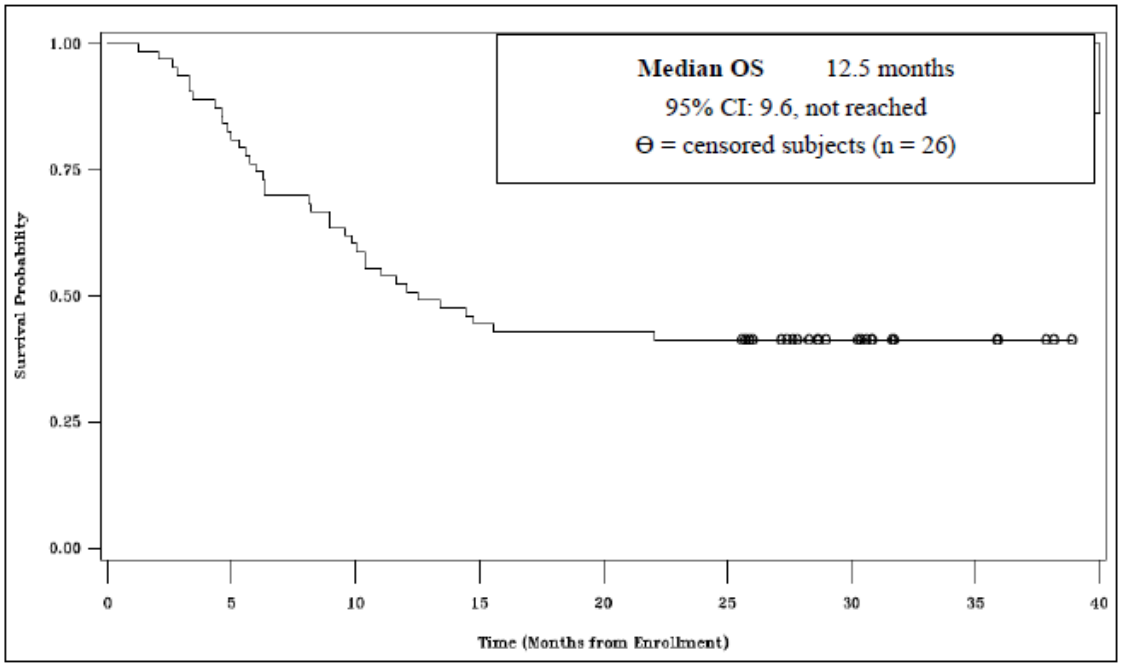
Number of Subjects	Censored	Median EFS	95% Confidence Interval	
			Lower	Upper
18	11	-	4.1	-

EFS is defined as time from date of transplant to the earliest date of progression, death or start of new anti-cancer therapy, or censored at date of last tumor assessment.
Only subjects who had transplant were included.
Treatment: Rituximab 375 mg/m^2 + inotuzumab ozogamicin 1.8 mg/m^2.
aSCT = autologous stem cell transplant; EFS = event free survival; ITT = intent-to-treat.

Overall Survival:

Median OS was 12.5 months in the ITT population as shown in Figure 1. In the PP population (n=53), median OS was slightly longer (13.4 months).

Figure 1. Kaplan-Meier Plot of Overall Survival (ITT Population)



CI = confidence interval; ITT = intent-to-treat; OS = overall survival; n = number of subjects.

Safety Results:

Serious Adverse Events and Adverse Events:

Treatment-emergent non-serious AEs (TEAEs) all causalities and treatment-related having a frequency rate >5% are presented in Table 8 and Table 9.

Treatment-emergent all causalities and treatment-related SAEs are presented in Table 10 and Table 11. Data in Table 10 and Table 11 can include SAEs post consolidation therapy (HD chemo + aSCT) (see Table 1 [footnote r] for non-serious AEs and SAEs reporting requirements).

Table 8. Treatment-Emergent Non-Serious Adverse Events by System Organ Class, and Preferred Term (All Causality) for Events Having a Frequency Rate >5%

Number of Subjects With AEs by: System Organ Class MedDRA (v14.1) Preferred Term	Treatment: Rituximab 375 mg/m^2 + Inotuzumab Ozogamicin 1.8 mg/m^2 n (%)
Number (%) of subjects	
Evaluable for AEs	63
With AEs	63 (100)
Blood and lymphatic system disorders	
Anaemia	9 (14.3)
Febrile neutropenia	4 (6.3)
Leukopenia	15 (23.8)
Lymphopenia	25 (39.7)
Neutropenia	22 (34.9)
Thrombocytopenia	43 (68.3)
Gastrointestinal disorders	
Abdominal pain	11 (17.5)
Constipation	16 (25.4)
Diarrhoea	18 (28.6)
Dyspepsia	5 (7.9)
Flatulence	4 (6.3)
Nausea	32 (50.8)
Vomiting	16 (25.4)
General disorders and administration site conditions	
Chills	7 (11.1)
Fatigue	26 (41.3)
Mucosal inflammation	7 (11.1)
Oedema peripheral	8 (12.7)
Pain	6 (9.5)
Pyrexia	21 (33.3)
Hepatobiliary disorders	
Hyperbilirubinaemia	8 (12.7)
Infections and infestations	
Upper respiratory tract infection	4 (6.3)
Investigations	
Alanine aminotransferase increased	9 (14.3)
Aspartate aminotransferase increased	27 (42.9)
Blood alkaline phosphatase increased	15 (23.8)
Blood lactate dehydrogenase increased	7 (11.1)
Metabolism and nutrition disorders	
Decreased appetite	9 (14.3)
Hyperglycaemia	5 (7.9)
Hypoalbuminaemia	5 (7.9)
Hypocalcaemia	5 (7.9)
Hypokalaemia	13 (20.6)
Hypophosphataemia	10 (15.9)
Musculoskeletal and connective tissue disorders	
Arthralgia	5 (7.9)
Back pain	6 (9.5)
Myalgia	4 (6.3)
Nervous system disorders	
Dizziness	7 (11.1)
Headache	14 (22.2)
Lethargy	6 (9.5)
Psychiatric disorders	
Insomnia	8 (12.7)
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	7 (11.1)

Table 8. Treatment-Emergent Non-Serious Adverse Events by System Organ Class, and Preferred Term (All Causality) for Events Having a Frequency Rate >5%

Number of Subjects With AEs by: System Organ Class MedDRA (v14.1) Preferred Term	Treatment: Rituximab 375 mg/m^2 + Inotuzumab Ozogamicin 1.8 mg/m^2 n (%)
Skin and subcutaneous tissue disorders	
Rash	4 (6.3)
Vascular disorders	
Flushing	4 (6.3)

Subjects were only counted once per treatment for each row.
Includes data up to 140 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in specific category; v = version.

Table 9. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (Treatment-Related) for Events Having a Frequency Rate >5%

Number of Subjects With AEs by: System Organ Class MedDRA (v14.1) Preferred Term	Treatment: Rituximab 375 mg/m^2 + Inotuzumab Ozogamicin 1.8 mg/m^2 n (%)
Number (%) of subjects	
Evaluable for AEs	63
With AEs	58 (92.1)
Blood and lymphatic system disorders	
Anaemia	5 (7.9)
Leukopenia	14 (22.2)
Lymphopenia	18 (28.6)
Neutropenia	18 (28.6)
Thrombocytopenia	42 (66.7)
Gastrointestinal disorders	
Constipation	6 (9.5)
Diarrhoea	8 (12.7)
Nausea	25 (39.7)
Vomiting	12 (19.0)
General disorders and administration site conditions	
Chills	6 (9.5)
Fatigue	21 (33.3)
Mucosal inflammation	5 (7.9)
Pyrexia	11 (17.5)
Hepatobiliary disorders	
Hyperbilirubinaemia	6 (9.5)
Investigations	
Alanine aminotransferase increased	8 (12.7)
Aspartate aminotransferase increased	22 (34.9)
Blood alkaline phosphatase increased	11 (17.5)
Blood lactate dehydrogenase increased	6 (9.5)
Metabolism and nutrition disorders	
Decreased appetite	4 (6.3)
Hypophosphataemia	6 (9.5)
Nervous system disorders	
Headache	4 (6.3)
Lethargy	5 (7.9)

Subjects were only counted once per treatment for each row.
Includes data up to 140 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in specific category; v = version.

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class, and Preferred Term (All Causality), Inclusive of Events Occurring After Consolidation Therapy (HD Chemo + aSCT)

Number of Subjects With AEs by: System Organ Class MedDRA (v14.1) Preferred Term	Treatment: Rituximab 375 mg/m^2 + Inotuzumab Ozogamicin 1.8 mg/m^2 n (%)
Number (%) of subjects	
Evaluable for AEs	63
With AEs	29 (46.0)
Blood and lymphatic system disorders	11 (17.5)
Anaemia	1 (1.6)
Febrile bone marrow aplasia	2 (3.2)
Febrile neutropenia	2 (3.2)
Neutropenia	2 (3.2)
Thrombocytopenia	8 (12.7)
Congenital, familial and genetic disorders	2 (3.2)
Aplasia	2 (3.2)
Gastrointestinal disorders	5 (7.9)
Abdominal pain	1 (1.6)
Ascites	1 (1.6)
Melaena	1 (1.6)
Nausea	2 (3.2)
General disorders and administration site conditions	6 (9.5)
General physical health deterioration	2 (3.2)
Multi-organ disorder	1 (1.6)
Multi-organ failure	1 (1.6)
Oedema	1 (1.6)
Pyrexia	1 (1.6)
Hepatobiliary disorders	4 (6.3)
Hepatitis	1 (1.6)
Hyperbilirubinaemia	1 (1.6)
Venoocclusive liver disease	2 (3.2)
Infections and infestations	11 (17.5)
Bronchopneumonia	1 (1.6)
Candidiasis	1 (1.6)
Cellulitis	1 (1.6)
Device related infection	2 (3.2)
Enterobacter infection	1 (1.6)
Enterobacter pneumonia	1 (1.6)
Klebsiella bacteraemia	1 (1.6)
Lower respiratory tract infection	1 (1.6)
Neutropenic sepsis	1 (1.6)
Pneumonia	1 (1.6)
Sepsis	2 (3.2)
Staphylococcal infection	1 (1.6)
Streptococcal sepsis	1 (1.6)
Urinary tract infection enterococcal	1 (1.6)
Investigations	2 (3.2)
Blood creatinine increased	1 (1.6)
Platelet count decreased	1 (1.6)
Metabolism and nutrition disorders	2 (3.2)
Decreased appetite	1 (1.6)
Hypercalcaemia	1 (1.6)

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class, and Preferred Term (All Causality), Inclusive of Events Occurring After Consolidation Therapy (HD Chemo + aSCT)

Number of Subjects With AEs by: System Organ Class MedDRA (v14.1) Preferred Term	Treatment: Rituximab 375 mg/m^2 + Inotuzumab Ozogamicin 1.8 mg/m^2 n (%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (3.2)
Adenocarcinoma	1 (1.6)
Non-Hodgkin's lymphoma	1 (1.6)
Nervous system disorders	1 (1.6)
Encephalopathy	1 (1.6)
Psychiatric disorders	1 (1.6)
Delirium	1 (1.6)
Renal and urinary disorders	3 (4.8)
Renal failure	2 (3.2)
Renal failure acute	1 (1.6)
Respiratory, thoracic and mediastinal disorders	3 (4.8)
Chronic obstructive pulmonary disease	1 (1.6)
Pleural effusion	1 (1.6)
Respiratory failure	1 (1.6)
Vascular disorders	1 (1.6)
Hypotension	1 (1.6)

Subjects are only counted once per treatment for each row.
Includes data up to 140 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
AEs = adverse events; aSCT = autologous stem cell transplant; HD chemo = high-dose chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

Table 11. Treatment-Emergent Serious Adverse Events by System Organ Class, and Preferred Term (Treatment-Related), Inclusive of Events Occurring After Consolidation Therapy (HD Chemo + aSCT)

Number of Subjects With AEs by: System Organ Class MedDRA (v14.1) Preferred Term	Treatment: Rituximab 375 mg/m^2 + Inotuzumab Ozogamicin 1.8 mg/m^2 n (%)
Number (%) of subjects	
Evaluable for AEs	63
With AEs	11 (17.5)
Blood and lymphatic system disorders	4 (6.3)
Thrombocytopenia	4 (6.3)
Gastrointestinal disorders	1 (1.6)
Nausea	1 (1.6)
Hepatobiliary disorders	4 (6.3)
Hepatitis	1 (1.6)
Hyperbilirubinaemia	1 (1.6)
Venoocclusive liver disease	2 (3.2)
Infections and infestations	1 (1.6)
Lower respiratory tract infection	1 (1.6)
Investigations	1 (1.6)
Platelet count decreased	1 (1.6)

Subjects are only counted once per treatment for each row.
Includes data up to 140 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
AEs = adverse events; aSCT = autologous stem cell transplant; HD chemo = high-dose chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

SAEs during inotuzumab ozogamicin + rituximab induction therapy, prior to consolidation therapy (HD chemo +aSCT), are summarized in Table 12. Overall, 34.9% of subjects had SAEs during rituximab + inotuzumab ozogamicin induction treatment. SAEs reported in >1 subject included thrombocytopenia (6 subjects, 9.5%), neutropenia (2 subjects, 3.2%), febrile bone marrow aplasia (2 subjects, 3.2%), device-related infection (2 subjects, 3.2%), general physical health deterioration (2 subjects, 3.2%), and aplasia (2 subjects, 3.2%). In total, 8 subjects (12.7%) had SAEs in the SOC of Infections and Infestations.

Table 12. Subjects With Serious Adverse Events Prior to Consolidation Therapy (Safety Population) (n, %)

Any serious adverse event prior to consolidation therapy	22 (34.9)
Blood and lymphatic system disorders	8 (12.7)
Thrombocytopenia	6 (9.5)
Neutropenia	2 (3.2)
Febrile bone marrow aplasia	2 (3.2)
Anemia	1 (1.6)
Infections and infestations	8 (12.7)
Device related infection	2 (3.2)
Abdominal wall abscess	1 (1.6)
Bronchopneumonia	1 (1.6)
Candidiasis	1 (1.6)
Cellulitis	1 (1.6)
Lower respiratory tract infection	1 (1.6)
Neutropenic sepsis	1 (1.6)
Sepsis	1 (1.6)
Streptococcal sepsis	1 (1.6)
General disorders and administration site conditions	5 (7.9)
General physical health deterioration	2 (3.2)
Multi-organ failure	1 (1.6)
Oedema	1 (1.6)
Pyrexia	1 (1.6)
Gastrointestinal disorders	4 (6.3)
Abdominal pain	1 (1.6)
Ascites	1 (1.6)
Melaena	1 (1.6)
Nausea	1 (1.6)
Congenital, familial and genetic disorders	2 (3.2)
Aplasia	2 (3.2)
Investigations	2 (3.2)
Blood creatinine increased	1 (1.6)
Platelet count decreased	1 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (3.2)
Adenocarcinoma	1 (1.6)
Non-Hodgkin's lymphoma	1 (1.6)
Respiratory, thoracic and mediastinal disorders	2 (3.2)
Chronic obstructive pulmonary disease	1 (1.6)
Pulmonary embolism	1 (1.6)
Metabolism and nutrition disorders	1 (1.6)
Hypercalcaemia	1 (1.6)
Nervous system disorders	1 (1.6)
Encephalopathy	1 (1.6)
Renal and urinary disorders	1 (1.6)
Renal failure	1 (1.6)

Classifications of AEs are based on the Medical Dictionary for Regulatory Activities.
Totals at a higher level were not necessarily the sum of those at the lower levels since a subject could report ≥2 different AEs within the higher level category.
Table includes AEs from subjects who did and did not receive consolidation treatment.
For subjects who received consolidation treatment, AEs reported after the earliest start date of HD chemo consolidation therapy were excluded.
AEs = adverse events; HD chemo = high-dose chemotherapy; n = number of subjects.

Deaths: Thirty-seven (37) subjects (58.7%) died, 29 due to disease progression, 2 related to study treatment, and 6 due to other causes (Table 13). One (1) subject died within 30 days of the last dose of study treatment; this death was attributed to disease progression.
Four (4) subjects died within 90 days of the first dose of study treatment; all 4 deaths were attributed to disease progression.

Table 13. Summary of Deaths (Safety Population)

Characteristics	Rituximab 375 mg/m^2 + Inotuzumab Ozogamicin 1.8 mg/m^2 n=63
Number of all deaths	37 (58.7)
Categorization of death	
Disease progression	29 (46.0)
Study related	2 (3.2)
Other	6 (9.5)

Discontinuations and Dose reductions due to Adverse Events: Six (6) subjects (9.5%) experienced AEs leading to treatment discontinuation prior to consolidation therapy:
4 subjects discontinued due to AEs of thrombocytopenia, 1 subject due to neutropenia, and 1 subject due to NHL (Table 14). Seven (7) subjects (11.1%) required dose reductions due to AEs (5 events of thrombocytopenia, 3 events of neutropenia, and 1 event of increased gamma-glutamyl transferase (Table 15).

Table 14. Number (%) of Subjects With Adverse Events Prior to Consolidation Therapy Leading to Study Drug Treatment Discontinuation (Safety Population)

System Organ Class[a] Preferred Term	Rituximab 375 mg/m^2 + Inotuzumab Ozogamicin 1.8 mg/m^2 n=63
Any adverse event	6 (9.5)
Blood and lymphatic system disorders	5 (7.9)
Thrombocytopenia	4 (6.3)
Neutropenia	1 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (1.6)
Non-Hodgkin's lymphoma	1 (1.6)

Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities.
Includes adverse events from subjects who have never received consolidation treatment.
n = number of subjects.
a. Totals at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

Table 15. Number (%) of Subjects With Adverse Events Leading to Dose Reduction (Safety Population)

System Organ Class[a] Preferred Term	Rituximab 375 mg/m^2 + Inotuzumab Ozogamicin 1.8 mg/m^2 n=63
Any adverse event	7 (11.1)
Blood and lymphatic system disorders	6 (9.5)
Thrombocytopenia	5 (7.9)
Neutropenia	3 (4.8)
Investigations	1 (1.6)
Gamma-glutamyl transferase increased	1 (1.6)

Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities.
n = number of subjects.
a. Totals at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

Laboratory Test Abnormalities: During induction treatment with rituximab + inotuzumab, 58 of 63 subjects (92.1%) had a Grade 3/4 laboratory test abnormality of potential clinical importance (PCI). Hematologic abnormalities were the most common: 38/63 (60.3%) had a Grade 3/4 lymphopenia, 36/63 (57.1%) subjects had a Grade 3/4 low platelet count, 22/63 (34.9%) had a Grade 3/4 low neutrophil count, 8/63 (12.7%) had a Grade 3/4 low leukocytes. Other than Grade 3/4 abnormalities of hyperglycemia and hypokalemia, which were both reported in 6/63 (9.5%) subjects, all other Grade 3/4 laboratory test abnormalities of PCI were limited to 3 or fewer subjects.

Ten (10) of 45 subjects who did not undergo consolidation therapy had laboratory results reported for long-term follow-up, and 6 of the 10 (60.0%) had Grade 3/4 abnormalities.

Three (3) of 9 subjects (33.3%) had Grade 3/4 lymphopenia, 3/10 (30.0%) had low platelet count, 2/7 (28.6%) subjects had Grade 3/4 hyperglycemia, 2/9 (22.2%) had Grade 3/4 hypokalemia, 2/9 (22.2%) had Grade 3/4 high blood bilirubin, 2/9 (22.2%) had Grade 3/4 low neutrophil count, 2/10 (20.0%) had Grade 3/4 low leukocytes, and 1/9 (11.1%) had Grade 3/4 high alkaline phosphatase. Due to the nature of the disease and study treatment administrations, these results were not unexpected.

Vital Signs: No subjects had vital signs abnormalities of PCI during treatment or long-term follow-up.

Electrocardiograms: QTc interval data available pre- and post-inotuzumab ozogamicin dosing was available for only 2 subjects. Two (2) subjects showed slight increases (≤20 msec) in Fridericia's corrected QT interval (QTcF). None of the 7 subjects with available data showed a QTcF >500 msec at any timepoint.

CONCLUSION: This study demonstrated that the combination of inotuzumab + rituximab shows activity in high-risk subject populations. Response to prior therapy (particularly the time to tumor progression or treatment failure) appeared to be an important prognostic factor for tumor response, PFS, and OS (data not shown). Successful PBSC mobilization and high-dose therapy (HDT)-aSCT following inotuzumab+rituximab induction therapy is

possible. Most subjects were mobilized with G-CSF alone or with G-CSF and plerixafor, though several subjects were not able to have ≥2.0 × 10^6 CD34+ cells/kg collected. Subjects able to achieve a response followed by aSCT had a better overall outcome based on PFS and OS compared to subjects not proceeding to aSCT (data not shown).

The safety profile of inotuzumab + rituximab therapy was similar to the previously reported safety profile of inotuzumab ozogamicin. Furthermore, many of the AEs reported, such as hematologic and gastrointestinal AEs, can also be seen with standard chemotherapy.

All subjects experienced at least 1 TEAE during inotuzumab + rituximab treatment; the most common TEAEs were hematologic abnormalities (thrombocytopenia, lymphopenia, and neutropenia), gastrointestinal disorders (nausea, diarrhea, vomiting), hepatic abnormalities (increased aspartate aminotransferase levels), and fatigue and pyrexia. Other than hematologic toxicities, most TEAEs were Grade 1/2.

There were no cases of hepatic VOD/SOS during inotuzumab + rituximab treatment. Two (2) subjects had SAEs of hepatic VOD/SOS following HD chemo + aSCT. Other significant toxicities observed after initiation of HDT-aSCT included infections, and 3 subjects had engraftment failure following consolidation with HD chemo + aSCT.

Due to a change in development strategy for inotuzumab ozogamicin in NHL, PK data presentation for this study was limited to generation of listings of the final bioanalytical results.