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

PROTOCOL NO.: 3129K7-2001-WW (B1931007)

PROTOCOL TITLE: A Phase 2 Study of Inotuzumab Ozogamicin (CMC-544) in Subjects With Indolent Non-Hodgkin's Lymphoma (NHL) That Is Refractory to or Has Relapsed After Rituximab and Chemotherapy or Radioimmunotherapy

Study Centers: Twenty-five (25) centers; 10 in United States; 5 in Japan; 3 in Belgium; 2 in Hungary; 1 each in Germany, Hong Kong, Republic of Korea, the Netherlands, and Singapore took part in the study and enrolled subjects.

Study Initiation Date and Final Completion Date: 30 July 2009 to 27 June 2013

Phase of Development: Phase 2

Study Objectives:

Primary:

- To evaluate the antitumor activity of inotuzumab ozogamicin in subjects with indolent Non-Hodgkin's lymphoma (NHL) who had relapsed or were refractory to rituximab and chemotherapy, or anti cluster of differentiation (CD)-20 radioimmunotherapy (RIT), as measured by the overall response rate (ORR).

Secondary:

- To evaluate the safety and tolerability of inotuzumab ozogamicin in the treatment of subjects with indolent NHL;
- To evaluate complete response (CR) in subjects with indolent NHL after inotuzumab ozogamicin treatment;
- To evaluate progression free survival (PFS) in subjects with indolent NHL after inotuzumab ozogamicin treatment;
- To evaluate duration of response (DR) in subjects with indolent NHL after inotuzumab ozogamicin treatment;

- To evaluate overall survival (OS) in subjects with indolent lymphoma after inotuzumab ozogamicin treatment;

- To determine the ORR, CR, PFS, DR and OS in subjects with follicular NHL after inotuzumab ozogamicin treatment;

- To acquire data required for evaluation of the population pharmacokinetic (PK) profile of inotuzumab ozogamicin;

- To evaluate the concentration-effect relationship of cardiac QT measures.

METHODS

Study Design: This was a Phase 2, multicenter, single-arm, open-label study of inotuzumab ozogamicin administered intravenously (IV) to subjects with indolent NHL that was refractory to rituximab and chemotherapy or RIT. Subjects were given IV inotuzumab ozogamicin every 28 days for at least 4 cycles. The initial treatment was administered at the maximum tolerated dose (1.8 mg/m^2 every 4 weeks). After Cycle 1, the dose and/or the frequency could have been adjusted based on toxicities. Subjects who met the specified conditions and who, in the judgment of the Investigator, could have derived benefit from additional treatment, could have continued to receive additional cycles of test article, up to a maximum of 2 additional cycles after achievement of a CR or up to a maximum of 8 cycles in total, whichever occurred first. To receive additional cycles of test article beyond 4 cycles, subjects must have had evidence of response and must not have had any drug-related Grade 2 or greater non-hematologic toxicity (except for serum bilirubin which must have been within normal limits) on the day of dosing.

Subjects participated in the study for approximately 2 years. This included a 28 day screening period, up to approximately 32 weeks for administration of test article (up to a maximum of 8 cycles: 4 planned and up to 4 additional, if criteria were met), an end-of-treatment visit at least 4 weeks after the last dose of test article, and disease assessment and long-term follow-up periods for survival, through a maximum of 2 years after first dose.

This study was planned to be completed in approximately 3.5 years including the completion of follow-up phase.

The study flowchart is presented in Table 1 and the PK flowchart is presented in Table 2.

Table 1. Study Flowchart

Study Procedures	**Screening**	**Cycle 1**				**Cycle 2**				**Cycle 3, 5, 7**				**Cycle 4, 6, 8**				**EOT**[a]
Study Day for 4-Week Cycles	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**+28-56**
Study Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**
Informed consent	X																	
Inclusion/exclusion criteria	X																	
Histologic confirmation of indolent (follicular, marginal zone or SLL) B-cell lymphoma (accepted recognized classes documentation)	X																	
CD22 immunophenotyping of NHL (historical or prospective)	X																	
Demography	X																	
Medical history	X																	
Cancer history	X																	
FLIPI score	X																	
ECOG performance status	X	X				X				X				X				X
Complete physical examination	X																	X
Focused physical examination[b]		X				X				X				X				
BSA calculation		X				X				X				X				
B-symptom evaluation	X	X				X				X				X				X
β-HCG[c]	X	X				X				X				X				
HbsAg and anti-HCV	X																	
Immunoglobulin blood levels[d]	X																	X
Serum chemistry[e]	X	X[e]	X	X	X	X[e]	X	X	X	X[e]	X			X[e]	X			X
Hematology[f]	X	X[f]	X	X	X	X[f]	X	X	X	X[f]	X			X[f]	X			X
Coagulation[g]	X					X								X[g]				X
B-lymphocyte panel[h]		X[h]				X[h]								X[h]				X[h]
Complete urinalysis (including protein/creatinine ratio)[i]	X					X								X				X
Immune response/antibodies to inotuzumab ozogamicin		X[j]								X[j]								X[j]
Test article and pretreatment medications		X				X				X				X				
Vital signs[k]	X	X[k]				X[k]				X[k]				X[k]				X[k]
CT scan of chest, abdomen, pelvis (and neck if appropriate) and clinical disease assessments[l]	X[l]								X[l]								X[l]	X[l]
Bone marrow aspirate and biopsy[m]	X	To confirm a CR as indicated.																

Table 1. Study Flowchart

Study Procedures	**Screening**	**Cycle 1**				**Cycle 2**				**Cycle 3, 5, 7**				**Cycle 4, 6, 8**				**EOT**[a]
Study Day for 4-Week Cycles	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**+28-56**
Study Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**
LVEF assessment[n]	X																	
ECG: triplicate tracings for QTc analysis[o]	X	See PK flowchart																X
PK samples (blood and urine)	See PK flowchart																	
Adverse events[p]	X----------X																	
Concomitant treatment	X----------X																	

AEs = adverse events; ANC = absolute neutrophil count; β-HCG = beta human chorionic gonadotropin; BSA = body surface area; CD = cluster of differentiation; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FLIPI = Follicular Lymphoma International Prognostic Index; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IgA = immunoglobulin class A; IgG = immunoglobulin class G; IgM = immunoglobulin class M; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NHL = Non-Hodgkin's lymphoma; PK = pharmacokinetics; PR = partial response; PT = prothrombin time; PTT = partial thromboplastin time; QTc = corrected QT interval; SLL = small lymphocytic lymphoma.

a. EOT visit: occurred 28 to 56 days after the last dose of test article.
b. Where applicable to include liver and spleen assessments and clinical assessment of tumor masses (if accessible). Performed predose.
c. For women of childbearing potential, β-HCG serum pregnancy test was performed at Screening within 1 week of the first dose of test article. Urine β-HCG was done by dipstick and evaluated before each dose of test article. If the urine test was positive, the results were confirmed with serum β-HCG. Serum β-HCG may have been done directly instead of urine test before each dose of test article.
d. Immunoglobulins: IgG, IgA, IgM.
e. Serum chemistry: performed within 3 days before each dose of test article and as indicated above. Additional (unscheduled) assessments should have been done if laboratory values are abnormal (or if clinically indicated) and repeated until resolution, until return to baseline, or until NCI CTCAE Grade ≤1.
f. Hematology: performed within 3 days before each dose of test article and as indicated above. Additional (unscheduled) assessments should have been done in the case of NCI CTCAE Grade 4 hematologic toxicity (or if clinically indicated), and repeated twice a week or as clinically indicated until ANC ≥750/µL, or platelets ≥50,000/µL.
g. Coagulation: PT/INR, PTT, and fibrinogen. During test-article treatment period, performed predose Cycle 2 Day 1 and predose Cycle 4 Day 1 only.
h. B lymphocyte: performed Day 1 of Cycles 1, 2, 4, 6 & 8, and EOT only, (CD19 and/or CD20 and CD22).
i. A urinalysis and assessment of urine protein to creatinine ratio performed within 3 weeks prior to Day 1 of Cycles 2, 4, 6 & 8 did not need to be repeated. Twenty-four (24)-hour collection also performed as clinically indicated, in the event of urine protein to creatinine ratio >0.2.
j. Immune response: performed predose Cycle 1 Day 1, predose Cycle 3 Day 1 only, and EOT.
k. Vital signs: weight, height (screening only), respiratory rate, temperature, blood pressure, and pulse. On Day 1 of each cycle: collected predose, collected twice during the test article infusion period, and then followed-up each hour for 2 hours (Cycle 1) or for 1 hour after the infusion (all other cycles) (ie, total of 3 and 2 hours for observation, respectively).
l. CT scan and disease assessments: performed every other cycle, or approximately every 8 weeks from the first dose, but always within 5 weeks of the next dose (eg, screening; after Cycles 2, 4 and 6; and at the EOT). In addition, a confirmatory disease assessment with CT scan was performed at least 4 weeks after first documentation of tumor response (PR or CR). MRIs may have been used instead of CT scans, but the same method must have been used throughout the study. CT scan and disease assessment were required at EOT unless performed within the previous 6 weeks with no intervening test article administration.
m. Bone marrow aspirate and biopsy: as required for staging, preferably within 28 days of study start. Bone marrow biopsy was required in subjects who otherwise met the criteria for a CR unless the subject had an adequate bone marrow biopsy, which was negative for lymphoma and performed within 28 days before first dose of test article.
n. LVEF: ECHO or MUGA.

Table 1. Study Flowchart

Study Procedures	Screening	Cycle 1				Cycle 2				Cycle 3, 5, 7				Cycle 4, 6, 8				EOT[a]
Study Day for 4-Week Cycles	-28 to -1	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22	+28-56
Study Visit Window			±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2

o. ECG: To be collected for analysis by central vendor, as well as read and interpreted at the investigative site for subject eligibility and safety monitoring. The average of the 3 ECGs was used to assess eligibility and dosing criteria.

p. AEs: monitored throughout the study from the time the informed consent was signed and dated up to and including the EOT visit (28 to 56 days after the last dose of test article). Subjects who have evidence of study treatment -related adverse events at the EOT visit were followed until the toxicity had resolved or had been identified as irreversible (per Investigator judgment).

Table 2. Pharmacokinetics Flowchart

Cycle	**Screening**	**1**			**3**					**4**					**6**	**EOT**
Cycle Day	**-28 to -1**	**1**		**8**	**1**			**3**	**8**	**1**			**3**	**8**	**1**	**+28-56**
Time (hr) Relative to Test Article Administration	**0**	**0**	**1**	**168**	**0**	**1**	**3**	**48**	**168**	**0**	**1**	**3**	**48**	**168**	**0**	**0**
Test article administration		X			X					X					X	
PK sample collection[*]		X[a]	X[b]	X	X[a]	X[b]	X	X	X	X[a]	X[b]	X	X	X	X[a]	
Metabolite sample collection: urine[†]		X[a]				X[b]	X	X		X[a]					X[a]	
Metabolite sample collection: serum[†]		X[a]				X[b]	X	X		X[a]					X[a]	
ECG: for QTc analysis[c]	X	X[a]	X[b]		X[a]	X[b]	X	X	X	X[a]	X[b]	X	X	X	X[a]	X
Dose Day		**1**			**57[d]**					**85[d]**					**141[d]**	

[*] PK samples: whole blood was collected from all subjects to harvest 3 mL of serum (allocated as 1 mL each for inotuzumab ozogamicin, total calicheamicin, and free calicheamicin) collected in vials with no anticoagulant. Samples should have been taken as close to the designated time as possible, however acceptable windows were 3 hr ±0.5 hr; 48 hr ±4 hr and 168 hr ±12 hr.

[†] Metabolite samples: urine (25 mL) and serum samples (into 3 and 5 mL aliquots) were collected, at select sites in US only.

ECG = electrocardiogram; EOT = end-of-treatment; PK = pharmacokinetics; US = United States; QTc = corrected QT interval.

a. Collected before start of inotuzumab ozogamicin infusion.
b. Collected immediately before end of inotuzumab ozogamicin infusion.
c. ECG. Collected for analysis by central vendor, as well as read and interpreted at the investigative site for subject eligibility and safety monitoring. The average of the 3 ECGs was used to assess eligibility and dosing criteria. Collected in triplicate (within approximately 2 minutes of each other) before collection of each PK sample time point.
d. Approximate dose day: actual dose day to be a maximum of 56 days from start of prior cycle.

Number of Subjects (Planned and Analyzed): Eighty (80) subjects were planned to be enrolled in the study. A total of 119 subjects were screened. A total of 81 subjects were enrolled; 40 in the United States; 24 in Japan; 4 each in Belgium, Germany, and Hungary; 2 in Singapore; 1 each in Hong Kong, Republic of Korea, and the Netherlands.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were expected to meet the following criteria: subjects who were previously diagnosed with CD22-positive, indolent NHL (defined as follicular, marginal zone, or small lymphocytic lymphoma) that had progressed after ≥2 prior systemic therapies; previous anti-cancer treatment given which contained rituximab and chemotherapy, or anti-CD20 RIT (subjects must have exhibited no response or have progressed within 6 months from the completion of the most recent rituximab or rituximab containing therapy or within 12 months of the completion of RIT); measurable disease with at least 1 lymph node or tumor mass >1.0 cm in the greatest transverse diameter and the product of the diameters ≥2.25 cm^2 as measured by computed tomography (CT) or magnetic resonance imaging (MRI).

Exclusion Criteria: Candidate for potentially curative therapies, subject with history of, or suggestive of, veno-occlusive disease or sinusoidal obstruction syndrome, prior allogeneic hematopoietic stem cell transplant (HSCT), autologous HSCT within the last 6 months before receiving test article, clinical evidence of transformation to a more aggressive subtype of lymphoma or Grade 3b follicular lymphoma, symptomatic central nervous system NHL, any evidence of serious active infection, primary effusion lymphoma, left ventricular ejection fraction more than Grade 1, previous myocardial infarction or pulmonary hypertension within the past 6 months, history of clinically significant ventricular arrhythmia, prolonged QTc, or unexplained, syncope, QTcF >470 msec, major surgery, not related to debulking surgical procedures, within 28 days before the first dose of test article, have received any chemotherapy, cancer immunosuppressive therapy, growth factors (except erythropoietin), or investigational drugs/devices within 28 days before administration of the first dose of test article, prior treatment with inotuzumab ozogamicin, subjects with intolerance to or who have had a severe allergic or anaphylactic reaction to any humanized monoclonal antibodies, administration of a live vaccine within 6 weeks of the first dose of test article, concurrent active malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix, known system vasculitides, primary or secondary immunodeficiency, current or chronic hepatitis B or C infection, known seropositivity for human immunodeficiency virus, history of chronic liver disease or suspected alcohol abuse, pregnant or breastfeeding women, any uncontrolled medical condition, and any major illness/condition/abnormal laboratory finding that in the Investigator's judgment would increase the risk associated with the subject's participation in the study were ineligible to participate in the study.

Study Treatment: Inotuzumab ozogamicin was reconstituted with sterile water and administered IV in 50 mL of 0.9 % sodium chloride over approximately 1 hour (±10 minutes), unless the subject required temporary interruption of test article administration. If the administration of inotuzumab ozogamicin had to be interrupted, the infusion could be restarted, but the administration had to be completed by 4 hours of the start of infusion and within 8 hours from reconstitution of the test article and as long as the prescribed dose was infused over 1 hour (±10 minutes).

The initial treatment dosage was 1.8 mg/m^2 every 28 days. After Cycle 1, dose and frequency could have been adjusted based on toxicities. Subjects received a planned minimum of 4 cycles of treatment.

Efficacy Endpoints: The primary efficacy endpoint was the confirmed ORR at the time of the final analyses, which was to be conducted after all indolent NHL subjects had completed disease follow-up.

Secondary efficacy endpoints included:

- PFS, CR, OS and DR in subjects with indolent NHL;
- ORR, CR, PFS, DR and OS in subjects with follicular NHL.

Safety Evaluations: Safety evaluations included clinical monitoring, adverse events (AEs), safety laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, and medical history.

Statistical Methods: The intent-to-treat (ITT) population included all subjects who were enrolled into the study. The primary analysis was carried out using the ITT population.

The per-protocol (PP) population included all subjects who were enrolled and received at least 1 dose of inotuzumab ozogamicin, had at least 1 index lesion that was ≥1 cm in 2 perpendicular dimensions, and whose product of diameters was >2.25 cm^2 and whose assessment was within (before) 28 days of first dose of study treatment, had no major protocol violations, and had at least 1 valid post-baseline assessment. All subjects who received at least 1 dose of study medication were included in the safety population.

Clinical activity was assessed using the primary endpoint of ORR in all indolent subjects.

Primary and secondary efficacy endpoints were analyzed based on the ITT and PP populations; however, the efficacy analyses based on the ITT population were considered as the primary analysis.

The primary analysis was estimation (number of responses/N) of ORR (including CR and partial response [PR]) and an exact confidence interval (CI) approach for the estimate.

The secondary time-to-event efficacy endpoints, such as PFS and OS, were summarized using the Kaplan-Meier method. Other secondary efficacy endpoints of categorical variables were presented using estimates and exact confidence intervals. Missing data in the primary analysis were imputed by assuming that all subjects not exhibiting response were non-responders. Subgroup analyses, such as those restricted to follicular NHL subjects, were also conducted using similar methodologies. For the time-to-event endpoints, the primary missing data handling method was censoring.

Descriptive statistics were used to summarize safety data.

RESULTS

Subject Disposition and Demography: A summary of subject disposition and reasons for discontinuation from the study and from the treatment phase is provided in Table 3.

Table 3. Summary of Subject Disposition and Reasons for Discontinuation From Study and From Treatment Phase

Conclusion Status / Reason	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72) n (%)	NHL Type (Marginal Zone) (N=4) n (%)	NHL Type (Small Lymphocytic) (N=5) n (%)	Total (N=81) n (%)
Screened: 119				
Enrolled: 81				
Number of cycles completed				
Cycle 1	72 (100.0)	4 (100.0)	5 (100.0)	81 (100.0)
Cycle 2	64 (88.9)	3 (75.0)	3 (60.0)	70 (86.4)
Cycle 3	45 (62.5)	2 (50.0)	1 (20.0)	48 (59.3)
Cycle 4	35 (48.6)	2 (50.0)	1 (20.0)	38 (46.9)
Cycle 5	18 (25.0)	2 (50.0)	1 (20.0)	21 (25.9)
Cycle 6	9 (12.5)	2 (50.0)	1 (20.0)	12 (14.8)
Cycle 7	5 (6.9)	0	0	5 (6.2)
Cycle 8	5 (6.9)	0	0	5 (6.2)
Treatment phase				
Phase completed	13 (18.1)	0	0	13 (16.0)
Discontinued from treatment phase	59 (81.9)	4 (100.0)	5 (100.0)	68 (84.0)
Disease progression	8 (11.1)	1 (25.0)	3 (60.0)	12 (14.8)
AEs[a]	43 (59.7)	0	1 (20.0)	44 (54.3)
Death	0	0	1 (20.0)	1 (1.2)
Investigator request	3 (4.2)	1 (25.0)	0	4 (4.9)
Subject request	2 (2.8)	2 (50.0)	0	4 (4.9)
Symptomatic deterioration	1 (1.4)	0	0	1 (1.2)
Other	2 (2.8)	0	0	2 (2.5)
Long-term follow-up				
Entered into long-term follow-up	69 (95.8)	3 (75.0)	5 (100.0)	77 (95.1)
Study				
Study completed	49 (68.1)	1 (25.0)	0	50 (61.7)
Discontinued from study	23 (31.9)	3 (75.0)	5 (100.0)	31 (38.3)
Lost to follow-up	3 (4.2)	0	1 (20.0)	4 (4.9)
Death	16 (22.2)	2 (50.0)	4 (80.0)	22 (27.2)
Subject request	3 (4.2)	1 (25.0)	0	4 (4.9)
Other	1 (1.4)	0	0	1 (1.2)

AE = adverse event; N = total number of subjects; n = number of subjects in each group; NHL=Non-Hodgkin's lymphoma.

a. A total of 44 subjects had an AE leading to treatment discontinuation. Of the other 24 subjects who were discontinued from the treatment phase, 3 subjects had an AE leading to treatment discontinuation listed as a secondary reason for treatment discontinuation (thrombocytopenia, neutropenia, and disease progression).

A summary of analysis populations is provided in Table 4.

Table 4. Analysis Populations

Analysis Population	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72) n (%)	NHL Type (Marginal Zone) (N=4) n (%)	NHL Type (Small Lymphocytic) (N=5) n (%)	Total (N=81) n (%)
Safety	72 (100.0)	4 (100.0)	5 (100.0)	81 (100.0)
ITT	72 (100.0)	4 (100.0)	5 (100.0)	81 (100.0)
PP	67 (93.1)	3 (75.0)	4 (80.0)	74 (91.4)

ITT = intent-to-treat; N = total number of subjects; n = number of subjects in each group; NHL = Non-Hodgkin's lymphoma; PP = per protocol.

A summary of demographic and other baseline characteristics is provided in Table 5.

Table 5. Summary of Demographic and Baseline Characteristics (Safety Population)

Characteristic	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total (N=81)
Age (years)				
Mean (SD)	60.53 (10.22)	70.75 (13.50)	65.20 (9.96)	61.32 (10.51)
Median	62.00	74.50	67.00	63.00
(Minimum-maximum)	(29.00-84.00)	(52.00-82.00)	(55.00-77.00)	(29.00-84.00)
Age range, n (%)				
18≤ age <65	44 (61.1)	1 (25.0)	2 (40.0)	47 (58.0)
Age ≥65	28 (38.9)	3 (75.0)	3 (60.0)	34 (42.0)
Gender, n (%)				
Female	35 (48.6)	2 (50.0)	0	37 (45.7)
Male	37 (51.4)	2 (50.0)	5 (100.0)	44 (54.3)
Race, n (%)				
Asian	27 (37.5)	1 (25.0)	0	28 (34.6)
Black or African American	3 (4.2)	0	0	3 (3.7)
White	42 (58.3)	3 (75.0)	5 (100.0)	50 (61.7)
Other	0	0	0	0
ECOG performance at Baseline[a], n (%)				
0	51 (70.8)	1 (25.0)	4 (80.0)	56 (69.1)
1	20 (27.8)	2 (50.0)	1 (20.0)	23 (28.4)
2	1 (1.4)	1 (25.0)	0	2 (2.5)
Body mass index (kg/m^2)[b]				
Mean (SD)	25.59 (5.42)	25.85 (3.89)	26.50 (4.26)	25.66 (5.26)
Median	25.00	26.95	27.10	25.30
(Minimum-maximum)	(14.40-46.60)	(20.60-28.90)	(19.60-31.30)	(14.40-46.60)

ECOG = Eastern Cooperative Oncology Group; N = total number of subjects; n = number of subjects in each group; NHL = Non-Hodgkin's lymphoma; SD = standard deviation.

a. Baseline ECOG performance score was taken from the visit closest to Cycle 1/Day 1.

b. Body mass index – weight (kg)/height (m)^2.

Efficacy Results: A summary of ORR and CR for the ITT population is provided in Table 6.

Table 6. Summary of Best Overall Response (ITT Population)

	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total (N=81)
Number (%) of subjects with CR or PR	51 (70.8)	2 (50.0)	1 (20.0)	54 (66.7)
95% CI for rate	(58.93, 80.95)	(6.76, 93.24)	(0.51, 71.64)	(55.32, 76.76)
80% CI for rate	(62.89, 77.87)	(14.26, 85.74)	(2.09, 58.39)	(59.08, 73.61)
Number (%) of subjects with CR	25 (34.7)	0	0	25 (30.9)
95% CI for rate	(23.88, 46.86)	(0, NE)	(0, NE)	(21.07, 42.11)
80% CI for rate	(27.25, 42.86)	(0, NE)	(0, NE)	(24.10, 38.37)

Subjects were categorized according to the best response during the study.
CI = confidence interval; CR = complete response; ITT = intent-to-treat; N = number of subjects; NE = not estimable; NHL = Non-Hodgkin's lymphoma; PR = partial response.

The summary of DR is provided in Table 7.

Table 7. Summary of Duration of Response (ITT Population)

	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total (N=81)
Subjects with event, n (%)	20 (39.2)	2 (100.0)	1 (100.0)	23 (42.6)
Subjects censored[a], n (%)	31 (60.8)	0	0	31 (57.4)
Median DR (months) (95% CI)	24.8 (12.9, NE)	8.4 (2.0, 14.8)	0.7 (NE, NE)	24.8 (10.9, NE)
6 month probability of maintaining a response (95% CI)	0.85 (0.71, 0.92)	0.50 (0.01, 0.91)	0.00 (0, NE)	0.82 (0.68, 0.90)
12 month probability of maintaining a response (95% CI)	0.67 (0.51, 0.79)	0.50 (0.01, 0.91)	0.00 (0, NE)	0.65 (0.50, 0.77)
24 month probability of maintaining a response (95% CI)	0.57 (0.40, 0.70)	0.00 (0, NE)	0.00 (0, NE)	0.53 (0.38, 0.66)

CIs were based on Brookmeyer and Crowley method.
CI = confidence interval; DR = duration of response; ITT = intent-to-treat; N = total number of subjects; n = number of subjects in each group; NE = not estimable; NHL = Non-Hodgkin's lymphoma.
a. Censored = no progressive disease or death yet after best tumor response (complete response or partial response).

A summary of PFS is provided in Table 8.

Table 8. Summary of Progression Free Survival (ITT Population)

	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total (N=81)
6 month PFS				
Subjects with events prior to 6 months, n	21	1	5	27
Subjects censored[a], n	7	1	0	8
KM 6 month estimate (95% CI)	69.3 (56.8,78.8)	75.0 (12.8, 96.1)	0.0 (0.0, NE)	65.1 53.3, 74.6)
12 month PFS				
Subjects with events prior to 12 months, n	29	2	5	36
Subjects censored[a], n	9	1	0	10
KM 12 month estimate (95% CI)	56.3 (43.4,67.3)	37.5 (1.1, 80.8)	0.0 (0.0, NE)	52.0 (40.0, 62.7)
24 month PFS				
Subjects with events prior to 24 months, n	35	3	5	43
Subjects censored[a], n	19	1	0	20
KM 24 month estimate (95% CI)	46.1 (33.5,57.8)	0.0 (0.0, NE)	0.0 (0.0, NE)	41.3 (29.8, 52.5)
Median PFS (months) (95% CI)	14.7 (11.0, NE)	8.8 (3.6, 17.0)	2.4 (1.7, 5.8)	12.7 (8.9, 26.9)

CI = confidence interval; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects; n = number of subjects in each group; NE = not estimable; NHL = Non-Hodgkin's lymphoma; PFS = progression-free survival.
a. Censored = no progressive disease or death recorded but followed for <6, 12, 24 months.

A summary of OS is provided in Table 9.

Table 9. Summary of Overall Survival (ITT Population)

	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total (N=81)
Subjects with event, n (%)	16 (22.2)	2 (50.0)	4 (80.0)	22 (27.2)
Subjects censored[a], n (%)	56 (77.8)	2 (50.0)	1 (20.0)	59 (72.8)
Median OS (months) (95% CI)	NE (NE, NE)	11.4 (3.6, NE)	14.6 (2.4, 16.6)	NE (26.6, NE)
6 month OS (95% CI)	0.91 (0.82, 0.96)	0.75 (0.13, 0.96)	0.60 (0.13, 0.88)	0.89 (0.79, 0.94)
12 month OS (95% CI)	0.83 (0.72, 0.90)	0.38 (0.01, 0.81)	0.60 (0.13, 0.88)	0.80 (0.69, 0.87)
24 month OS (95% CI)	0.78 (0.67, 0.86)	0.38 (0.01, 0.81)	0.00 (0, NE)	0.73 (0.61, 0.81)

CIs were based on Brookmeyer and Crowley method.
Subjects who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.
CI = confidence interval; ITT = intent-to-treat; N = total number of subjects; n = number of subjects in each group; NE = not estimable; NHL = Non-Hodgkin's lymphoma; OS = overall survival.
a. Censored = no death recorded.

Safety Results: The number (%) of subjects reporting all-causality treatment-emergent AEs (TEAEs) is provided in Table 10.

Table 10. Treatment-Emergent Non-Serious Adverse Events by System Organ Class, and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5%

Number of Subjects With AEs by: System Organ Class MedDRA (v16.0) Preferred Term	Inotuzumab Ozogamicin 1.8 mg/m^2 NHL Type (Follicular) n (%)	NHL Type (Marginal Zone) n (%)	NHL Type (Small Lymphocytic) n (%)
Number (%) of subjects			
Evaluable for AEs	72	4	5
With AEs	69 (95.8)	4 (100.0)	5 (100.0)
Blood and lymphatic system disorders			
Anaemia	12 (16.7)	0	0
Leukopenia	26 (36.1)	2 (50.0)	1 (20.0)
Lymphopenia	25 (34.7)	2 (50.0)	1 (20.0)
Neutropenia	40 (55.6)	1 (25.0)	4 (80.0)
Thrombocytopenia	55 (76.4)	3 (75.0)	2 (40.0)
Cardiac disorders			
Atrial fibrillation	2 (2.8)	0	1 (20.0)
Cardiac failure	0	0	1 (20.0)
Ear and labyrinth disorders			
Vertigo	0	1 (25.0)	0
Eye disorders			
Visual impairment	1 (1.4)	0	1 (20.0)
Gastrointestinal disorders			
Abdominal distension	6 (8.3)	0	1 (20.0)
Abdominal pain	8 (11.1)	1 (25.0)	1 (20.0)
Abdominal pain lower	1 (1.4)	1 (25.0)	0
Abdominal pain upper	6 (8.3)	1 (25.0)	0
Constipation	12 (16.7)	1 (25.0)	1 (20.0)
Diarrhoea	8 (11.1)	0	0
Dry mouth	1 (1.4)	0	1 (20.0)
Dyspepsia	2 (2.8)	0	1 (20.0)
Gastrooesophageal reflux disease	3 (4.2)	0	1 (20.0)
Haemorrhoids	0	0	1 (20.0)
Nausea	35 (48.6)	2 (50.0)	1 (20.0)
Oesophagitis	0	1 (25.0)	0
Stomatitis	4 (5.6)	0	0
Vomiting	14 (19.4)	0	1 (20.0)
General disorders and administration site conditions			
Chills	6 (8.3)	0	0
Early satiety	0	0	1 (20.0)
Fatigue	34 (47.2)	3 (75.0)	2 (40.0)
Oedema peripheral	7 (9.7)	0	0
Pyrexia	14 (19.4)	1 (25.0)	0
Hepatobiliary disorders			
Hyperbilirubinaemia	11 (15.3)	1 (25.0)	0
Infections and infestations			
Genital infection fungal	0	0	1 (20.0)
Nasopharyngitis	8 (11.1)	0	0
Oral candidiasis	0	0	1 (20.0)
Pneumonia	2 (2.8)	1 (25.0)	0
Sinusitis	5 (6.9)	1 (25.0)	0
Upper respiratory tract infection	9 (12.5)	1 (25.0)	0

Table 10. Treatment-Emergent Non-Serious Adverse Events by System Organ Class, and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5%

Number of Subjects With AEs by: System Organ Class MedDRA (v16.0) Preferred Term	Inotuzumab Ozogamicin 1.8 mg/m^2 NHL Type (Follicular) n (%)	NHL Type (Marginal Zone) n (%)	NHL Type (Small Lymphocytic) n (%)
Urinary tract infection	5 (6.9)	0	0
Injury, poisoning and procedural complications			
Arthropod bite	0	0	1 (20.0)
Investigations			
Alanine aminotransferase increased	16 (22.2)	0	0
Aspartate aminotransferase increased	32 (44.4)	2 (50.0)	1 (20.0)
Blood alkaline phosphatase increased	21 (29.2)	1 (25.0)	0
Blood chloride increased	0	0	1 (20.0)
Blood creatinine increased	5 (6.9)	0	1 (20.0)
Blood lactate dehydrogenase increased	5 (6.9)	1 (25.0)	0
Blood magnesium decreased	0	0	1 (20.0)
Blood potassium decreased	0	0	1 (20.0)
Blood urea increased	0	0	1 (20.0)
Gamma-glutamyltransferase increased	21 (29.2)	0	0
Lymphocyte count increased	0	0	1 (20.0)
Monocyte count increased	2 (2.8)	1 (25.0)	0
Protein urine present	0	0	2 (40.0)
Metabolism and nutrition disorders			
Decreased appetite	20 (27.8)	2 (50.0)	1 (20.0)
Hyperglycaemia	9 (12.5)	1 (25.0)	1 (20.0)
Hyperuricaemia	2 (2.8)	0	1 (20.0)
Hypoalbuminaemia	10 (13.9)	1 (25.0)	0
Hypocalcaemia	5 (6.9)	1 (25.0)	0
Hypoglycaemia	2 (2.8)	1 (25.0)	0
Hypokalaemia	8 (11.1)	0	0
Hypomagnesaemia	4 (5.6)	0	0
Hyponatraemia	4 (5.6)	1 (25.0)	0
Hypophosphataemia	9 (12.5)	0	0
Hypoproteinaemia	0	0	1 (20.0)
Musculoskeletal and connective tissue disorders			
Arthralgia	9 (12.5)	0	1 (20.0)
Back pain	4 (5.6)	0	0
Neck pain	1 (1.4)	1 (25.0)	0
Pain in extremity	2 (2.8)	0	1 (20.0)
Nervous system disorders			
Dizziness	4 (5.6)	0	1 (20.0)
Dysgeusia	5 (6.9)	0	0
Headache	12 (16.7)	1 (25.0)	0
Somnolence	0	0	1 (20.0)
Psychiatric disorders			
Delirium	0	0	1 (20.0)
Insomnia	8 (11.1)	0	0
Renal and urinary disorders			
Dysuria	4 (5.6)	0	0
Proteinuria	1 (1.4)	1 (25.0)	0
Respiratory, thoracic and mediastinal disorders			
Cough	12 (16.7)	1 (25.0)	1 (20.0)

Table 10. Treatment-Emergent Non-Serious Adverse Events by System Organ Class, and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5%

Number of Subjects With AEs by: System Organ Class MedDRA (v16.0) Preferred Term	Inotuzumab Ozogamicin 1.8 mg/m^2 NHL Type (Follicular) n (%)	NHL Type (Marginal Zone) n (%)	NHL Type (Small Lymphocytic) n (%)
Dyspnoea	5 (6.9)	1 (25.0)	2 (40.0)
Epistaxis	6 (8.3)	0	0
Productive cough	1 (1.4)	0	1 (20.0)
Skin and subcutaneous tissue disorders			
Hyperhidrosis	0	0	1 (20.0)
Petechiae	4 (5.6)	0	0
Rash	9 (12.5)	0	0

Subjects were only counted once per treatment for each row.
Includes data up to 56 days after last dose of study drug.
MedDRA (v16.0) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in specific category; NHL = Non-Hodgkin's lymphoma; v = version.

The number (%) of subjects reporting treatment-related TEAEs (serious and non-serious) is provided in Table 11.

Table 11. Number (%) of Subjects Reporting Treatment-Related Treatment-Emergent Adverse Events (Serious and Non-Serious) in Descending Order of Frequency for Adverse Events Occurring in ≥10% of All Subjects (Safety Population)

System Organ Class Preferred Term n (%)	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total[a] (N=81)
Any adverse event	68 (94.4)	4 (100.0)	3 (60.0)	75 (92.6)
Blood and lymphatic system disorders	59 (81.9)	3 (75.0)	3 (60.0)	65 (80.2)
Thrombocytopenia	54 (75.0)	3 (75.0)	2 (40.0)	59 (72.8)
Neutropenia	40 (55.6)	1 (25.0)	3 (60.0)	44 (54.3)
Leukopenia	24 (33.3)	1 (25.0)	1 (20.0)	26 (32.1)
Lymphopenia	19 (26.4)	2 (50.0)	0	21 (25.9)
Gastrointestinal disorders	45 (62.5)	3 (75.0)	1 (20.0)	49 (60.5)
Nausea	33 (45.8)	3 (75.0)	1 (20.0)	37 (45.7)
Vomiting	12 (16.7)	0	1 (20.0)	13 (16.0)
Constipation	9 (12.5)	1 (25.0)	0	10 (12.3)
General disorders and administration site conditions	36 (50.0)	4 (100.0)	1 (20.0)	41 (50.6)
Fatigue	28 (38.9)	3 (75.0)	1 (20.0)	32 (39.5)
Pyrexia	10 (13.9)	1 (25.0)	0	11 (13.6)
Investigations	37 (51.4)	2 (50.0)	0	39 (48.1)
Aspartate aminotransferase increased	27 (37.5)	2 (50.0)	0	29 (35.8)
Blood alkaline phosphatase increased	19 (26.4)	1 (25.0)	0	20 (24.7)
Gammaglutamyl transferase increased	20 (27.8)	0	0	20 (24.7)
Alanine aminotransferase increased	13 (18.1)	0	0	13 (16.0)
Metabolism and nutrition disorders	24 (33.3)	2 (50.0)	1 (20.0)	27 (33.3)
Decreased appetite	14 (19.4)	2 (50.0)	1 (20.0)	17 (21.0)
Hepatobiliary disorders	14 (19.4)	1 (25.0)	0	15 (18.5)
Hyperbilirubinemia	9 (12.5)	1 (25.0)	0	10 (12.3)
Nervous system disorders	13 (18.1)	1 (25.0)	0	14 (17.3)
Headache	9 (12.5)	1 (25.0)	0	10 (12.3)
Infections and infestations	8 (11.1)	2 (50.0)	1 (20.0)	11 (13.6)
Skin and subcutaneous tissue disorders	10 (13.9)	0	0	10 (12.3)

Non-serious adverse events and serious adverse events are not separated out in the table.
Classifications of adverse events were based on MedDRA v16.0.
MedDRA = Medical Dictionary for Drug Regulatory Activities; N = total number of subjects; n = number of subjects in each group; NHL = Non-Hodgkin's lymphoma; v = version.

a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have had reported ≥2 different AEs within the higher-level category.

All-causality serious AEs (SAEs) are presented in Table 12.

Table 12. Treatment-Emergent Serious Adverse Events by System Organ Class, and Preferred Term (All Causality)

Number of Subjects With AEs by: System Organ Class MedDRA (v16.0) Preferred Term	Inotuzumab Ozogamicin 1.8 mg/m^2 NHL Type (Follicular) n (%)	NHL Type (Marginal Zone) n (%)	NHL Type (Small Lymphocytic) n (%)
Number (%) of subjects			
Evaluable for AEs	72	4	5
With AEs	12 (16.7)	2 (50.0)	1 (20.0)
Gastrointestinal disorders	6 (8.3)	1 (25.0)	0
Abdominal distension	1 (1.4)	0	0
Abdominal pain upper	1 (1.4)	0	0
Ascites	1 (1.4)	0	0
Constipation	1 (1.4)	0	0
Dyspepsia	1 (1.4)	0	0
Intestinal obstruction	1 (1.4)	0	0
Nausea	0	1 (25.0)	0
General disorders and administration site conditions	2 (2.8)	1 (25.0)	1 (20.0)
Fatigue	0	1 (25.0)	0
Pyrexia	2 (2.8)	0	1 (20.0)
Hepatobiliary disorders	2 (2.8)	0	0
Budd-Chiari syndrome	1 (1.4)	0	0
Cholelithiasis	1 (1.4)	0	0
Hepatic function abnormal	1 (1.4)	0	0
Hyperbilirubinaemia	1 (1.4)	0	0
Infections and infestations	5 (6.9)	1 (25.0)	1 (20.0)
Catheter site infection	1 (1.4)	0	0
Peritonitis	1 (1.4)	0	0
Pneumonia	2 (2.8)	1 (25.0)	1 (20.0)
Sepsis	2 (2.8)	0	0
Staphylococcal bacteraemia	1 (1.4)	0	0
Metabolism and nutrition disorders	0	1 (25.0)	0
Decreased appetite	0	1 (25.0)	0
Musculoskeletal and connective tissue disorders	1 (1.4)	0	0
Arthralgia	1 (1.4)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (25.0)	0
Non-Hodgkin's lymphoma	0	1 (25.0)	0
Nervous system disorders	1 (1.4)	0	0
Syncope	1 (1.4)	0	0
Renal and urinary disorders	2 (2.8)	0	0
Hydronephrosis	1 (1.4)	0	0
Urinary retention	1 (1.4)	0	0
Respiratory, thoracic and mediastinal disorders	2 (2.8)	0	1 (20.0)
Chronic obstructive pulmonary disease	1 (1.4)	0	0
Epistaxis	1 (1.4)	0	0
Pneumonia aspiration	0	0	1 (20.0)

Subjects were only counted once per treatment for each row.
Includes data up to 56 days after last dose of study drug.
MedDRA (v16.0) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in specific category; NHL = Non-Hodgkin's lymphoma; v = version.

A summary of the number (%) of subjects reporting treatment-related SAEs in descending order of frequency is provided in Table 13.

Table 13. Number of Subjects Reporting Treatment-Related Serious Adverse Events in Descending Order of Frequency (Safety Population)

System Organ Class Preferred Term n (%)	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total[a] (N=81)
Any SAE	7 (9.7)	2 (50.0)	1 (20.0)	10 (12.3)
Infections and infestations	2 (2.8)	1 (25.0)	1 (20.0)	4 (4.9)
Pneumonia	2 (2.8)	1 (25.0)	1 (20.0)	4 (4.9)
General disorders and administration site conditions	2 (2.8)	1 (25.0)	0	3 (3.7)
Pyrexia	0	1 (25.0)	0	1 (1.2)
Fatigue	2 (2.8)	0	0	2 (2.5)
Gastrointestinal disorders	1 (1.4)	1 (25.0)	0	2 (2.5)
Ascites	1 (1.4)	0	0	1 (1.2)
Nausea	0	1 (25.0)	0	1 (1.2)
Hepatobiliary disorders	2 (2.8)	0	0	2 (2.5)
Budd-Chiari syndrome	1 (1.4)	0	0	1 (1.2)
Hepatic function abnormal	1 (1.4)	0	0	1 (1.2)
Hyperbilirubinaemia	1 (1.4)	0	0	1 (1.2)
Respiratory, thoracic and mediastinal disorders	2 (2.8)	0	0	2 (2.5)
Chronic obstructive pulmonary disease	1 (1.4)	0	0	1 (1.2)
Epistaxis	1 (1.4)	0	0	1 (1.2)
Metabolism and nutrition disorders	0	1 (25.0)	0	1 (1.2)
Decreased appetite	0	1 (25.0)	0	1 (1.2)

Classifications of AEs were based on MedDRA v 16.0.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in each group; n = number of subjects in specific category; NHL = Non-Hodgkin's lymphoma; SAE = serious adverse event; v = version.
a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have been reported ≥2 different AEs within the higher-level category.

A summary of the number (%) of subjects reporting AEs leading to treatment discontinuation is provided in Table 14.

Table 14. Number (%) of Subjects Reporting Adverse Events Leading to Treatment Discontinuation in Descending Order of the Incidences (Safety Population)

System Organ Class Preferred Term n (%)	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total[a] (N=81)
Any AE[b]	45 (62.5)	1 (25.0)	1 (20.0)	47 (58.0)
Blood and lymphatic system disorders	32 (44.4)	0	1 (20.0)	33 (40.7)
Thrombocytopenia	29 (40.3)	0	1 (20.0)	30 (37.0)
Neutropenia	9 (12.5)	0	0	9 (11.1)
Leukopenia	1 (1.4)	0	0	1 (1.2)
Investigations	10 (13.9)	0	0	10 (12.3)
GGT increased	6 (8.3)	0	0	6 (7.4)
AST increased	2 (2.8)	0	0	2 (2.5)
Blood alkaline phosphatase increased	2 (2.8)	0	0	2 (2.5)
ALT increased	1 (1.4)	0	0	1 (1.2)
Hepatobiliary disorders	6 (8.3)	0	0	6 (7.4)
Hyperbilirubinemia	4 (5.6)	0	0	4 (4.9)
Budd-Chiari syndrome	1 (1.4)	0	0	1 (1.2)
Hepatic function abnormal	1 (1.4)	0	0	1 (1.2)
Liver disorder	1 (1.4)	0	0	1 (1.2)
Infections and infestations	3 (4.2)	0	0	3 (3.7)
Sepsis	2 (2.8)	0	0	2 (2.5)
Peritonitis	1 (1.4)	0	0	1 (1.2)
Pneumonia	1 (1.4)	0	0	1 (1.2)
Gastrointestinal disorders	1 (1.4)	0	0	1 (1.2)
Intestinal obstruction	1 (1.4)	0	0	1 (1.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (25.0)	0	1 (1.2)
NHL	0	1 (25.0)	0	1 (1.2)
Renal and urinary disorders	1 (1.4)	0	0	1 (1.2)
Hydronephrosis	1 (1.4)	0	0	1 (1.2)

Classifications of AEs were based on MedDRA v16.0.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects in each group; NHL = Non-Hodgkin's lymphoma; v = version.

a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different AEs within the higher-level category.
b. A total of 44 subjects had an AE leading to treatment discontinuation listed as a primary reason for treatment discontinuation. Of the other 24 subjects who were discontinued from the treatment phase, 3 subjects had an AE leading to treatment discontinuation listed as a secondary reason for treatment discontinuation (thrombocytopenia, neutropenia, and disease progression).

Dose Reductions or Temporary Discontinuations due to Adverse Events: A total of 39 (48.1%) subjects had an AE leading to dose delay. The most common (>2 subjects) AEs leading to dose delay included neutropenia (21 [25.9%] subjects) and thrombocytopenia (20 [24.7%] subjects).

A total of 27 (33.3%) subjects had an AE leading to dose reduction. The most common (>2 subjects) AEs leading to dose reduction included thrombocytopenia (19 [23.5%] subjects) and neutropenia (9 [11.1%] subjects).

No subject died within 30 days of the last dose of study drug.

A summary of deaths is provided in Table 15. A summary of deaths ≤90 days after the first dose is provided in Table 16.

Table 15. Summary of Deaths (Safety Population)

	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total (N=81)
Number of all deaths, n (%)	16 (22.2)	2 (50.0)	4 (80.0)	22 (27.2)
Categorization of death, n (%)				
Disease progression	12 (16.7)	2 (50.0)	2 (40.0)	16 (19.8)
Other	4 (5.6)[a]	0	2 (40.0)[b]	6 (7.4)

N = total number of subjects; n = number of subjects in each group; NHL = Non-Hodgkin's lymphoma.
a. Other included severe sepsis/septic shock in 1 subject; adenovirus in 1 subject; Budd-Chiari syndrome secondary to hyperbilirubinemia in 1 subject; bacterial peritonitis, sepsis of urinary origin, and acute kidney insufficiency in 1 subject.
b. Other included complications of stem cell transplant and aspiration pneumonia.

Table 16. Summary of Deaths ≤90 Days After the First Dose (Safety Population)

	Inotuzumab Ozogamicin 1.8 mg/m^2			
	NHL Type (Follicular) (N=72)	NHL Type (Marginal Zone) (N=4)	NHL Type (Small Lymphocytic) (N=5)	Total (N=81)
Number of all deaths, n (%)	1 (1.4)	0	1 (20.0)	2 (2.5)
Categorization of death, n (%)				
Disease progression	1 (1.4)	0	0	1 (1.2)
Other	0	0	1 (20.0)[a]	1 (1.2)

N = total number of subjects; n = number of subjects in each group; NHL = Non-Hodgkin's lymphoma.
a. Other was aspiration pneumonia.

A total of 70 (86.4%) subjects had a Grade 3/4 laboratory test result while on study therapy. The most common (>10%) Grade 3/4 laboratory test results were low platelets (59.3% of subjects), lymphopenia (40.7% of subjects), neutrophil count decreased (33.3% of subjects), low white blood cells count (14.8% of subjects), and high gamma-glutamyl transferase; (12.3% of subjects). There were no subjects with vital signs of potential clinical importance at the End-of treatment. There were no subjects with diastolic or systolic blood pressure values of potential clinical importance. There were occurrences of temperature <35°C (13 instances) and respiration rate <10 breaths/min (2 instances) on-therapy. There was 1 occurrence of temperature <35°C during long-term follow-up. Overall, there were small changes from Baseline in ECG parameters. The maximum mean change from Baseline in corrected QT interval, Fridericia's correction (QTcF) interval was 23.5 msec. No subject had a QTcF interval of >500 msec. One (1) subject had an increase from Baseline in QTcF interval of ≥60 msec.

CONCLUSIONS: In subjects with indolent NHL who had relapsed or were refractory to rituximab and chemotherapy, or anti-CD20 RIT:

- Inotuzumab ozogamicin had anti-tumor activity as the ORR was 66.7% (95% CI: 55.32%, 76.76%). The CR was 30.9%, the median PFS was 12.7 months, the median DR was 24.8 months, estimated probability of 6 month survival was 0.89, estimated probability of 12 month survival was 0.80, and estimated probability of 24 month survival was 0.73 in subjects with indolent NHL after inotuzumab ozogamicin treatment.

- Inotuzumab ozogamicin was associated with hematologic, gastrointestinal, and hepatic toxicities in the treatment of subjects with indolent NHL. The majority of subjects were able to receive at least 3 cycles of therapy as 59.3% and 46.9% of subjects received 3 and 4 cycles of treatment, respectively; however, 58.0% of subjects discontinued the study due to an AE, mostly due to laboratory abnormalities that did not recover to National Cancer Institute Common Terminology Criteria for Adverse Events Grade ≤1 within the 28-day dose delay window allowed per study. The most common laboratory abnormalities leading to discontinuation were thrombocytopenia, neutropenia, and abnormalities of liver function tests.

- As significant anti-tumor activity was seen with a limited number of cycles, an additional study would be required to determine whether an alternative dosing regimen such as lower doses or allowing more time between doses would allow for improved efficacy or lower toxicity.