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

PROTOCOL NO.: 3129K4-3301-WW (B1931006)

PROTOCOL TITLE: An Open-Label, Randomized, Phase 3 Study of Inotuzumab Ozogamicin (CMC-544) Administered in Combination With Rituximab Compared to a Defined Investigator's Choice Therapy in Subjects With Relapsed or Refractory, CD22-Positive, Follicular B-Cell Non-Hodgkin's Lymphoma

Study Centers: Twenty (20) centers; 8 in the United States (US); 3 in Spain; 2 each in Belgium, and India; 1 each in Canada, Hong Kong, Italy, Republic of Korea, and Mexico took part in the study and enrolled subjects.

Study Initiationand Final Completion Dates: 15 November 2007 to 07 April 2011

The study was terminated prematurely based on the determination that it was unlikely that the study would meet the estimated subject enrollment of approximately 978 subjects.

Phase of Development: Phase 3

Study Objectives:

Primary:

- To evaluate efficacy as measured by progression-free survival (PFS), with a goal of demonstrating the superiority of inotuzumab ozogamicin when administered in combination with rituximab (Rituxan/MabThera), compared with an active comparator arm.

Secondary:

- To evaluate the safety and tolerability of inotuzumab ozogamicin in combination with rituximab

- To evaluate the efficacy of inotuzumab ozogamicin in combination with rituximab using the following endpoints and analyses:

    - Objective response rate (ORR) (complete response [CR] + unconfirmed complete response [CRu] + partial response [PR])

    - Overall survival (OS).

- To evaluate the population pharmacokinetics (PK) of inotuzumab ozogamicin in combination with rituximab, and to evaluate factors affecting drug disposition

- QT assessment.

METHODS

Study Design: This was a 2-arm, randomized (1:1), open-label, Phase 3 trial designed to evaluate efficacy and safety of inotuzumab ozogamicin in combination with rituximab. Prior to randomization, subjects were stratified by: the number of prior regimens (1 or 2); the Investigator's choice of therapy; the region (Region 1: US, Canada, Western Europe and Australia; Region 2: Eastern Europe and Latin/South America; Region 3: rest of world).

Subjects in Arm 1 received inotuzumab ozogamicin in combination with Rituxan/MabThera. Subjects in Arm 2 received the Investigator's choice from 2 rituximab-containing regimens: rituximab in combination with cyclophosphamide, vincristine, and prednisone/prednisolone (R-CVP); or rituximab in combination with fludarabine, Novantrone (mitoxantrone), and dexamethasone (R-FND).

Prior to randomization, Investigators chose either R-CVP or R-FND for all subjects in order to stratify subjects across the 4 inotuzumab ozogamicin + rituximab and the Investigator's choice treatment groups (A-D). Those subjects that were randomized to the Investigator's choice treatment groups (ie, B or D) received the treatment that Investigators selected prior to randomization (ie, R-FND or R-CVP, respectively), otherwise subjects were randomized to 1 of 2 inotuzumab ozogamicin + rituximab treatment groups (A or C) and only received inotuzumab ozogamicin + rituximab. The "control arm" or "total Investigator's choice" referred to the number of subjects in both Investigator's choice groups (B + D = control arm).

The planned estimated total study duration (time to primary analysis) was 39 months (accrual time was to be approximately 25 months and disease assessment follow-up was to continue for all subjects up to 3 years until approximately 14 months after the last subject was randomized). Long-term follow-up for survival was for a minimum of 1-2 years and up to 5 years.

Study flowcharts can be found in Table 1, Table 2, Table 3, and Table 4.

Table 1. Study Flowchart for Arm 1 – Rituximab and Inotuzumab Ozogamicin

Study Procedures	Screening	Cycle 1			Cycle 2			Cycles 3, 5, 7		Cycles 4, 6, 8				EOT at 28-42 Days After the Last Dose of Therapy
		Day of Cycle												
		1	2	8, 15, 22	1	2	8, 15, 22	1	2	8	1	2	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	
Informed consent	X													
Inclusion/exclusion criteria	X													
CD20 and CD22 immunophenotyping	X													
Medical history/demographics	X													
Previous chemotherapy report	X													
Immune response/antibodies to rituximab (HAMA/HACA)[a]		X									X			X
Immune response/antibodies to inotuzumab ozogamicin[b]		X									X			X
ECOG and FLIPI	X													X
Complete physical examination[c]	X													X
Focused physical examination, ECOG and BSA[d]		X			X			X			X			
β-HCG[e]	X	X			X			X			X			X
Study drug administration (Rituxan/MabThera)[f]		X			X			X			X			
Study drug administration (inotuzumab ozogamicin)[g]			X			X			X			X		
Vital signs/observation period[h]			X			X			X			X		X
Postdose safety assessment[i]				X			X			X			X	
Complete chemistry panel/electrolytes[j]	X	X		X	X		X	X		X	X		X	X
CBC with differential[k]	X	X		X	X		X	X		X	X		X	X
HbsAg and anti-HCV	X													
Coagulation[l]	X				X						X			X

Table 1. Study Flowchart for Arm 1 – Rituximab and Inotuzumab Ozogamicin

Study Procedures	Screening	Cycle 1			Cycle 2			Cycles 3, 5, 7		Cycles 4, 6, 8				EOT at 28-42 Days After the Last Dose of Therapy
		Day of Cycle												
		1	2	8, 15, 22	1	2	8, 15, 22	1	2	8	1	2	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	
Electrocardiogram: North America and Western Europe (screening, Cycles 1-4, and EOT only)	X[m]		X[m]			X[m]			X[m]			X[m]		X
ECG: rest of world	X	As clinically indicated												X
LVEF assessment[n]	X	As clinically indicated												
CT scan of chest, abdomen, pelvis, (and neck, if appropriate); physical examination for clinical disease assesments[o]	X	To be performed every 6-12 weeks from first dose												X[o]
Complete urinalysis[p]	X				X						X			X
AEs/SAEs[q]	Monitored and recorded continuously													
Concomitant treatment	Monitored and recorded continuously													
IgA, IgG, IgM blood levels[r]	X	When clinically indicated												X
B/T lymphocyte panel[s]	X							X[s]						X
Bone marrow aspirate and/or biopsy[t]	X							As required to confirm a CR or CRu						
Pharmacokinetics[u]	(See Pharmacokinetic Flowchart)													

As communicated 16 January 2009, enrollment in this clinical trial was discontinued prematurely. Instructions for the management of study subjects who continued to take study drug as defined herein for use in this clinical trial were supplied to the Investigators, including the discontinuation of collection of all Health Outcome Questionnaires.

AE = adverse event; ANC = absolute neutrophil count; β-HCG = beta-human chorionic gonadotropin; BSA = body surface area; B\T = B cells\T cells; CBC = complete blood count; CD = cluster of differentiation; CR = complete response; CRu = unconfirmed complete response; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram, echocardiography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; exam = examination; HACA = human anti-chimeric antibody; HAMA = human anti-mouse antibody; Ig = immunoglobulin; FLIPI = Follicular Lymphoma International Prognostic Index; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; 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; PR = partial response; PT = prothrombin time; SAE = serious adverse event; WBC = white blood cell.

a. Antibodies against rituximab before rituximab administration. Antibodies against rituximab before Doses 1 and 4, and at the final visit.

b. Antibodies against inotuzumab ozogamicin before inotuzumab ozogamicin administration. Antibodies against inotuzumab ozogamicin only Doses 1 and 4,

Table 1. Study Flowchart for Arm 1 – Rituximab and Inotuzumab Ozogamicin

Study Procedures	Screening	Cycle 1			Cycle 2			Cycles 3, 5, 7		Cycles 4, 6, 8				EOT at 28-42 Days After the Last Dose of Therapy
		Day of Cycle												
		1	2	8, 15, 22	1	2	8, 15, 22	1	2	8	1	2	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	

and at the final visit.

c. Complete physical examination included vital signs, weight, liver and spleen assessments, and B-symptom evaluation. Height was obtained at Screening only.
d. Focused physical examinations (including vital signs, weight, liver and spleen assessments, and B-symptom evaluation), ECOG and BSA must have been done on the first day of dosing before administration, including clinical assessment of tumor masses if accessible.
e. For women of childbearing potential, serum β-HCG pregnancy test was performed at Screening and at the final visit. Urine β-HCG was done by dipstick and evaluated before the administration at every cycle. If the urine test was positive, results were confirmed with a serum β-HCG test. Serum β-HCG tests may have been done instead of urine β-HCG tests at all required visits.
f. Rituximab was administered according to the package insert, including all applicable premedication. For the purpose of this study, rituximab was administered according to the induction regimen outlined in the study only.
g. Pretreatment medications were administered to subjects receiving inotuzumab ozogamicin as specified in the study.
h. Vital signs were taken twice during the inotuzumab ozogamicin infusion period and followed up each hour for 2 hours (ie, a total of 3 hours for observation). Starting with Cycle 2, vital signs were measured and followed up to 2 hours in total for observation around the time of the inotuzumab ozogamicin infusion (twice during the 1 hour of infusion and once 1 hour after the infusion of inotuzumab ozogamicin).
i. Approximately 1 week to 10 days after administration at each cycle, to evaluate any AEs or other potential safety concerns.
j. Blood chemistry was done at Screening, and then weekly for the first 2 cycles. Thereafter within 3 days prior to Dose 1 of each cycle, and another assessment approximately 1 week to 10 days post administration. However, if laboratory parameters were elevated or if clinically indicated these were done until resolution or until levels returned to Baseline or ≤ NCI-CTCAE Grade 1.
k. CBC with a 5-part differential (including absolute lymphocyte and monocyte counts) was done at Screening and then weekly for the first 2 doses of study drug. Thereafter within 3 days prior to Dose 1 of each cycle, and another assessment approximately 1 week to 10 days after administration. In case of NCI-CTCAE Grade 4 hematologic toxicity (or if clinically indicated), the CBC was repeated approximately every 2 days until ANC ≥1000/μL, or platelets ≥75,000/μL. If WBC count was <500/μL no differential count was needed.
l. As measured by INR or PT.
m. Screening ECG was a single tracing for safety evaluation. For North America and Western Europe, the remaining ECGs were performed during Cycles 1 through 4 and EOT only. These ECGs were collected in triplicate, within approximately 2 minutes of each other. During Cycles 1 and 2: predose and immediately before the end of the infusion. During Cycles 3 and 4: predose, immediately before the end of the infusion, and 3 hours after the start of the infusion. At common times when pharmacokinetic samples were being collected the ECGs were taken before the pharmacokinetic draw. Please refer to Table 2 for details.
n. Measurement of ejection fraction by ECHO, MUGA scan or an equivalent methodology.

Table 1. Study Flowchart for Arm 1 – Rituximab and Inotuzumab Ozogamicin

Study Procedures	Screening	Cycle 1			Cycle 2			Cycles 3, 5, 7		Cycles 4, 6, 8				EOT at 28-42 Days After the Last Dose of Therapy
		Day of Cycle												
		1	2	8, 15, 22	1	2	8, 15, 22	1	2	8	1	2	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	

o. Every 6-12 weeks from first dose. MRIs were used instead of CT scans in cases of hypersensitivity to CT contrast media, but the same method was used throughout the study. Physical examination for assessment of B-symptoms and the presence/absence of new palpable lesions only. Not necessary at EOT visit if obtained within 4 weeks before. However if a PR or CR was observed then this was confirmed after 4 weeks by extending the EOT visit window if necessary.

p. Complete spot urinalysis (included assessment of urine protein to creatinine ratio) was completed at Screening, prior to every other cycle, and at the EOT visit. A urinalysis and assessment of urine protein to creatinine ratio performed within 3 weeks prior to Day 1 of Cycles 2, 4, 6, and 8 did not need to be repeated. If unavailable, spot protein and spot creatinine values were used to calculate the ratio. For a protein/creatinine ratio between >0.2 and ≤0.5, a 24-hour urine was collected to confirm the protein/creatinine ratio was ≤0.5. The complete urinalysis was taken at any time of day.

q. AEs were monitored throughout the study from the time the informed consent was signed and dated by the subject. In addition, all subjects were monitored for AEs, regardless of causality, for 28 to 42 days after the last dose of therapy. Subjects who had evidence of test-article-related AEs at the EOT visit were followed until the toxicity had resolved or been identified as irreversible (per judgment of the Investigator).

r. IgA, IgG (and subclasses IgG1, IgG2, IgG3, IgG4), and IgM were measured at Screening and at the EOT visit. During the study they were measured if clinically indicated.

s. Blood was collected to measure B/T lymphocyte panel at Screening or Baseline, before Dose 3 (Cycle 3 Day 1) and at the EOT visit.

t. To be performed at Screening if clinically indicated preferably within 28 days of the first dose of study treatment. A bone marrow biopsy and aspirate were required in subjects who otherwise met the criteria for a complete response or complete response unconfirmed with the exception of subjects who had an adequate bone marrow biopsy which was negative for lymphoma and performed within 28 days prior to the start of study treatment.

u. Pharmacokinetic samples were drawn during Cycles 1 through 4 only. For details regarding draw times, please refer Table 2.

Table 2. Pharmacokinetic Flow Chart (Arm 1 – Inotuzmab Ozogamicin/Rituximab Treatment Only)

Cycle	**1**				**2**				**3**					**4**					**EOT**
Cycle Day	**1**	**2**		**8**	**1**	**2**		**8**	**1**	**2**			**8**	**1**	**2**			**8**	**28**[a]
Time (h) Relative to Inotuzumab Ozogamicin Administration	**-24**	**0**	**1**	**168**	**-24**	**0**	**1**	**168**	**-24**	**0**	**1**	**3**	**168**	**-24**	**0**	**1**	**3**	**168**	**0**
Rituximab administration day	X				X				X					X					
Inotuzumab ozogamicin administration day		X				X				X					X				
PK of inotuzumab ozogamicin and calicheamicin in serum[b]		X[c]	X[d,e]	X		X[c]	X[d,e]	X		X[c]	X[d,e]	X[f,e]	X		X[c]	X[d,e]	X[f,e]	X	
ECG (North America and Western Europe only)[g]		X	X			X	X			X	X	X			X	X	X		X
Dose Day	**-1**	**1**			**29**				**57**					**85**					

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ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetics.

a. ECG measured at 28 to 42 days after the last dose of therapy.
b. PK samples: whole blood harvested 3 mL of serum (allocated as 1 mL each for inotuzumab ozogamicin, total calicheamicin, and free calicheamicin). Blood collected in red-top vials with no anticoagulant.
c. Sample was drawn before start of inotuzumab ozogamicin 1-hour infusion.
d. Sample was drawn immediately before end of inotuzumab ozogamicin infusion.
e. The 1-hour and 3-hour postdose PK samples were required only when collected in conjunction with central ECGs (ie, required in North America and Western Europe, optional in other regions).
f. Sample was drawn in close conjunction with the ECG assessments, where applicable.
g. For North America and Western Europe only. ECGs were collected in triplicate, within approximately 2 minutes of each other.

Table 3. Study Flow Chart for Arm 2 Option 1 – Rituximab – Cyclophosphamide, Vincristine, and Prednisone/Prednisolone (R-CVP)

Study Procedures	Screening	Cycle 1						Cycle 2						Cycles 3, 5, and 7						Cycles 4, 6, and 8						EOT (at 28-42 Days After the Last Dose of Therapy)
		Day of Cycle																								
		1	2	3	4	5	8 15	1	2	3	4	5	8 15	1	2	3	4	5	8	1	2	3	4	5	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	
Informed consent	X																									
Inclusion/exclusion criteria	X																									
CD20 and CD22 immunophenotyping	X																									
Medical history/ demographics	X																									
Previous chemotherapy report	X																									
ECOG and FLIPI	X																									X
Complete physical examination[a]	X																									X
Focused physical examination, ECOG and BSA[b]		X						X						X						X						
β-HCG[c]	X	X						X						X						X						X
Treatment with Rituximab[d]		X						X						X						X						
Treatment with cyclophosphamide[d]		X						X						X						X						
Treatment with vincristine[d]		X						X						X						X						
Treatment with prednisone/prednisolone[d]		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		
Vital signs[e]		X						X						X						X						X
Postdose safety assessment[f]							X						X						X						X	

Table 3. Study Flow Chart for Arm 2 Option 1 – Rituximab – Cyclophosphamide, Vincristine, and Prednisone/Prednisolone (R-CVP)

Study Procedures	Screening	Cycle 1						Cycle 2						Cycles 3, 5, and 7						Cycles 4, 6, and 8						EOT (at 28-42 Days After the Last Dose of Therapy)
		Day of Cycle																								
		1	2	3	4	5	8 15	1	2	3	4	5	8 15	1	2	3	4	5	8	1	2	3	4	5	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	
Complete chemistry panel/electrolytes[g]	X	X					X	X					X	X					X	X					X	X
CBC with differential[h]	X	X					X	X					X	X					X	X					X	X
Coagulation[i]	X							X												X						X
HbsAg and Anti-HCV	X																									
ECG[j]	X[j]	As clinically indicated																								X
LVEF assessment[k]	X	As clinically indicated																								
CT scan of chest, abdomen, pelvis, (and neck, if appropriate); clinical disease assessments[l]	X	Performed every 6-12 weeks from first dose																								X
Complete urinalysis[m]	X							X												X						X
AEs/SAEs[n]	Monitored and recorded continuously																									
Concomitant treatment	Monitored and recorded continuously																									
IgA, IgG, IgM blood levels[o]	X	When clinically indicated																								X
B/T lymphocyte panel[p]	X													X[p]												X
Bone marrow aspirate and/or biopsy[q]	X													As required to confirm a CR or CRu												

As communicated 16 January 2009, enrollment in this clinical trial was discontinued prematurely. Instructions for the management of study subjects who continued to take study drug as defined herein for use in this clinical trial were supplied to the Investigators, including the discontinuation of collection of all Health Outcome Questionnaires.
AE = adverse event; ANC = absolute neutrophil count; β-HCG = beta-human chorionic gonadotropin; BSA = body surface area; B\T = B cells\T cells; CBC = complete blood count; CD = cluster of differentiation; CR = complete response; CRu = unconfirmed complete response; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram, echocardiography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FLIPI = Follicular Lymphoma International Prognostic Index; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MRI = magnetic resonace imaging; MUGA = multigated acquisition; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PR = partial response;

Table 3. Study Flow Chart for Arm 2 Option 1 – Rituximab – Cyclophosphamide, Vincristine, and Prednisone/Prednisolone (R-CVP)

Study Procedures	Screening	Cycle 1						Cycle 2						Cycles 3, 5, and 7						Cycles 4, 6, and 8						EOT (at 28-42 Days After the Last Dose of Therapy)
		Day of Cycle																								
		1	2	3	4	5	8 15	1	2	3	4	5	8 15	1	2	3	4	5	8	1	2	3	4	5	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	

PT = prothrombin time; R-CVP = rituximab in combination with cyclophosphamide, vincristine, and prednisone/prednisolone; SAE = serious adverse event; WBC = white blood cell.

a. Complete physical examination included vital signs, weight, liver and spleen assessments, and B-symptom evaluation. Height was obtained at Screening only.
b. Focused physical examinations (including vital signs, weight, liver, spleen assessments and B-symptom evaluation), ECOG and BSA were performed on the first day of dosing before administration, including clinical assessment of tumor masses if accessible.
c. For women of childbearing potential, β-HCG serum pregnancy test was performed at Screening and at the final visit. Urine β-HCG was done by dipstick and evaluated before the administration at every cycle. If the urine test was positive, results were confirmed with a serum β-HCG test. Serum β-HCG tests were done instead of urine β-HCG tests at all required visits.
d. R-CVP was administered according to the package inserts, including all applicable premedications. For the purpose of this study, R-CVP was administered according to the regimen outlined in the study only.
e. Vital signs were taken once before and once after infusion.
f. Approximately 1 week to 10 days after administration at each cycle, to evaluate any AEs or other potential safety concerns.
g. Blood chemistry was done at Screening, and then weekly for the first 2 cycles. Thereafter within 3 days prior to Dose 1 of each cycle, and another assessment approximately 1 week to 10 days post administration. However, if laboratory parameters were elevated or if clinically indicated, these were done until resolution or until levels return to Baseline or ≤NCI-CTCAE Grade 1.
h. CBC with a 5-part differential (included absolute lymphocyte and monocyte counts) was done at Screening, and then weekly for the first 2 doses of administration. Thereafter within 3 days prior to Dose 1 of each cycle, and another assessment approximately 1 week to 10 days post administration. In case of NCI-CTCAE Grade 4 hematologic toxicity (or if clinically indicated), the CBC was repeated approximately every 2 days until ANC ≥1000/μL, or platelets ≥75,000/μL. If WBC count was <500/μL no differential count was needed.
i. As measured by INR or PT.
j. ECGs were performed during Screening, EOT and as clinically indicated.
k. Measurement of ejection fraction by ECHO, MUGA scan or an equivalent methodology
l. Every 6-12 weeks from first dose. MRIs were used instead of CT scans in cases of hypersensitivity to CT contrast media, but the same method was used throughout the study. Not necessary at EOT visit if obtained within 4 weeks before. However if a PR or CR was observed then this was confirmed after 4 weeks by extending the EOT visit window if necessary.
m. Complete spot urinalysis (included assessment of urine protein to creatinine ratio) was completed at Screening, prior to every other cycle, and at the EOT visit. A urinalysis and assessment of urine and protein to creatinine ratio performed within 3 weeks prior to Day 1 of Cycles 2, 4, 6, and 8 did not need to be repeated. If unavailable, spot protein and spot creatinine values were used to calculate the ratio. At Screening and EOT, for a protein/creatinine ratio between >0.2 and ≤0.5, a 24-hour urine was collected to confirm the protein/creatinine ratio was ≤0.5. The complete urinalysis was taken at any time of day.
n. AEs were monitored throughout the study from the time the informed consent was signed and dated by the subject. In addition, all subjects were monitored for AEs, regardless of causality, for 28 to 42 days after the last dose of therapy. Subjects who had evidence of test-article-related AEs at the EOT visit were followed until the toxicity

Table 3. Study Flow Chart for Arm 2 Option 1 – Rituximab – Cyclophosphamide, Vincristine, and Prednisone/Prednisolone (R-CVP)

Study Procedures	Screening	Cycle 1						Cycle 2						Cycles 3, 5, and 7						Cycles 4, 6, and 8						EOT (at 28-42 Days After the Last Dose of Therapy)
		Day of Cycle																								
		1	2	3	4	5	8 15	1	2	3	4	5	8 15	1	2	3	4	5	8	1	2	3	4	5	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	

had resolved or been identified as irreversible (per judgment of the investigator).

o. IgA, IgG (and subclasses IgG1, IgG2, IgG3, IgG4), and IgM were measured at Screening and at the EOT visit. During the study they were measured if clinically indicated.

p. Blood was collected to measure B/T lymphocyte panel at Screening or Baseline, before Dose 3 (Cycle 3 Day 1) and at the EOT visit.

q. Performed at Screening if clinically indicated, preferably within 28 days of the first dose of study treatment. A bone marrow biopsy and aspirate were required in subjects who otherwise met the criteria for a complete response or complete response unconfirmed with the exception of subjects who had an adequate bone marrow biopsy which was negative for lymphoma and performed within 28 days prior to the start.

Table 4. Study Flow Chart for Arm 2 Option 2 – Rituximab – Fludarabine, Mitoxantrone and Dexamethasone (R-FND)

Study Procedures	Screening	Cycle 1						Cycle 2						Cycles 3, 5, and 7						Cycles 4, 6, and 8						EOT (at 28-42 Days After the Last Dose of Therapy)
		Day of Cycle																								
		1	2	3	4	5	8 15	1	2	3	4	5	8 15	1	2	3	4	5	8	1	2	3	4	5	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	
Informed consent	X																									
Inclusion/exclusion criteria	X																									
CD20 and CD22 immunophenotyping	X																									
Medical history/ demographics	X																									
Previous chemotherapy report	X																									
ECOG and FLIPI	X																									X
Complete physical examination[a]	X																									X
Focused physical examination, ECOG and BSA[b]		X						X						X						X						
β-HCG[c]	X	X						X						X						X						X
Treatment with Rituximab[d]		X						X						X						X						
Treatment with fludarabine[d]			X	X	X				X	X	X				X	X	X				X	X	X			
Treatment with mitoxantrone[d]			X						X						X						X					
Treatment with dexamethasone[d]		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		
Vital signs[e]		X	X	X	X			X	X	X	X			X	X	X	X			X	X	X	X			X
Postdose safety assessment[f]							X						X						X					X		
Complete chemistry panel/electrolytes[g]	X	X					X	X					X	X					X	X					X	X
CBC with	X	X					X	X					X	X					X	X					X	X

Table 4. Study Flow Chart for Arm 2 Option 2 – Rituximab – Fludarabine, Mitoxantrone and Dexamethasone (R-FND)

Study Procedures	Screening	Cycle 1						Cycle 2						Cycles 3, 5, and 7						Cycles 4, 6, and 8						EOT (at 28-42 Days After the Last Dose of Therapy)
		Day of Cycle																								
		1	2	3	4	5	8 15	1	2	3	4	5	8 15	1	2	3	4	5	8	1	2	3	4	5	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	
differential[h]																										
Coagulation[i]	X							X												X						X
HbsAg and Anti-HCV	X																									
ECG[j]	X	As clinically indicated																								X
LVEF assessment[k]	X	As clinically indicated																								
CT scan of chest, abdomen, pelvis, (and neck, if appropriate); clinical disease assessments[l]	X	Performed every 6-12 weeks from first dose																								X[l]
Complete urinalysis[m]	X							X												X						X
AEs/SAEs[n]	Monitored and recorded continuously																									
Concomitant treatment	Monitored and recorded continuously																									
IgA, IgG, IgM blood levels[o]	X	When clinically indicated																								X
B/T lymphocyte panel[p]	X													X[p]												X
Bone marrow aspirate and/or biopsy[q]	X													As required to confirm a CR or CRu												

As communicated 16 January 2009, enrollment in this clinical trial was discontinued prematurely. Instructions for the management of study subjects who continued to take study drug as defined herein for use in this clinical trial were supplied to the Investigators, including the discontinuation of collection of all Health Outcome Questionnaires.

AE = adverse event; ANC = absolute neutrophil count; β-HCG = beta-human chorionic gonadotropin; BSA = body surface area; B\T = B cells\T cells; CBC = complete blood count; CD = cluster of differentiation; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram, echocardiography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FLIPI = Follicular Lymphoma International Prognostic Index; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MRI = magnetic resonace imaging; MUGA = multigated acquisition; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PR = partial response; PT = prothrombin time; R-FND = rituximab in

Table 4. Study Flow Chart for Arm 2 Option 2 – Rituximab – Fludarabine, Mitoxantrone and Dexamethasone (R-FND)

Study Procedures	Screening	Cycle 1						Cycle 2						Cycles 3, 5, and 7						Cycles 4, 6, and 8						EOT (at 28-42 Days After the Last Dose of Therapy)
		Day of Cycle																								
		1	2	3	4	5	8 15	1	2	3	4	5	8 15	1	2	3	4	5	8	1	2	3	4	5	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	

combination with fludarabine, Novantrone (mitoxantrone), and dexamethasone; SAE = serious adverse event; WBC = white blood cell.

a. Complete physical examination included vital signs, weight, liver and spleen assessments, and B-symptom evaluation. Height was obtained at Screening only.
b. Focused physical examinations (included vital signs, weight, liver, spleen assessments, and B-symptom evaluation), ECOG and BSA were done on the first day of dosing before administration, including clinical assessment of tumor masses if accessible.
c. For women of childbearing potential, β-HCG serum pregnancy test was performed at Screening and at the final visit. Urine β-HCG was done by dipstick and evaluated before the administration at every cycle. If the urine test was positive, results were confirmed with a serum β-HCG test. Serum β-HCG tests were done instead of urine β-HCG tests at all required visits.
d. R-FND was administered according to the package inserts, including all applicable premedications. For the purpose of this study, R-FND was administered according to the regimen outlined in this study only.
e. Vital signs were taken once before and once after infusion.
f. Approximately 1 week to 10 days after administration at each cycle, to evaluate any AEs or other potential safety concerns.
g. Blood chemistry was done at Screening, and then weekly for the first 2 cycles. Thereafter within 3 days prior to Dose 1 of each cycle, and another assessment approximately 1 week to 10 days post administration. However, if laboratory parameters were elevated or if clinically indicated, these were done until resolution or until levels return to Baseline or ≤ NCI-CTCAE Grade 1.
h. CBC with a 5-part differential (included absolute lymphocyte and monocyte counts) was done at Screening, and then weekly for the first 2 doses of administration. Thereafter within 3 days prior to Dose 1 of each cycle, and another assessment approximately 1 week to 10 days post administration. In case of NCI-CTCAE Grade 4 hematologic toxicity (or if clinically indicated), the CBC was repeated approximately every 2 days until ANC ≥1000/μL, or platelets ≥75,000/μL. If WBC count was <500/μL no differential count was needed.
i. As measured by INR or PT.
j. ECGs were performed during Screening, EOT and as clinically indicated.
k. Measurement of ejection fraction by ECHO, MUGA scan or an equivalent methodology.
l. Every 6-12 weeks from first dose. MRIs were used instead of CT scans in cases of hypersensitivity to CT contrast media, but the same method was used throughout the study. Not necessary at EOT visit if obtained within 4 weeks before. However if a PR or CR was observed then this was confirmed after 4 weeks by extending the EOT visit window if necessary.
m. Complete spot urinalysis including assessment of urine protein to creatinine ratio was completed at Screening, prior to every other cycle, and at the EOT visit. A urinalysis and assessment of urine and protein to creatinine ratio performed within 3 weeks prior to Day 1 of Cycles 2, 4, 6, and 8 did not need to be repeated. If unavailable, spot protein and spot creatinine values were used to calculate the ratio. At Screening and EOT, for a protein/creatinine ratio between > 0.2 and ≤ 0.5, a 24-hour urine was collected to confirm the protein/creatinine ratio was ≤0.5. The complete urinalysis was taken at any time of day.
n. AEs were monitored throughout the study from the time the informed consent was signed and dated by the subject. In addition, all subjects were monitored for AEs, regardless of causality, for 28 to 42 days after the last dose of therapy. Subjects who had evidence of test-article-related AEs at the EOT visit were followed until the toxicity had resolved or been identified as irreversible (per judgment of the Investigator).
o. IgA, IgG (and subclasses IgG1, IgG2, IgG3, IgG4), and IgM were measured at Screening and at the EOT visit. During the study they were measured if clinically indicated.
p. Blood was collected to measure B/T lymphocyte panel at Screening or Baseline, before Dose 3 (Cycle 3 Day 1) and at the EOT visit.
q. Performed at Screening if clinically indicated, preferably within 28 days of the first dose of study treatment. A bone marrow biopsy and aspirate were required in subjects

Table 4. Study Flow Chart for Arm 2 Option 2 – Rituximab – Fludarabine, Mitoxantrone and Dexamethasone (R-FND)

Study Procedures	Screening	Cycle 1						Cycle 2						Cycles 3, 5, and 7						Cycles 4, 6, and 8						EOT (at 28-42 Days After the Last Dose of Therapy)
		Day of Cycle																								
		1	2	3	4	5	8 15	1	2	3	4	5	8 15	1	2	3	4	5	8	1	2	3	4	5	8	
Study Visit Window (Days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	

who otherwise met the criteria for a complete response or complete response unconfirmed with the exception of subjects who had an adequate bone marrow biopsy which was negative for lymphoma and performed within 28 days prior to the start of study treatment.

Number of Subjects (Planned and Analyzed): A total of 978 subjects were planned and in total 29 subjects were randomized to study treatment in the study. The number percentage of subjects randomized by region and treatment arm is presented in Table 5.

Table 5. Number (%) of Subjects Randomized by Region and Treatment Arm Intent-to-Treat Population

	Treatment		
	Inotuzumab Ozogamicin + Rituximab (N=15)	**Investigator's Choice (N=14)**	**Total (N=29)**
United States, Canada, Western Europe, and Australia	10 (66.7)	8 (57.1)	18 (62.1)
Eastern Europe and Latin/South America	2 (13.3)	3 (21.4)	5 (17.2)
Rest of the World[a]	3 (20.0)	3 (21.4)	6 (20.7)

N = number of subjects.
a. Rest of the World = Hong Kong, Korea, and India.

Diagnosis and Main Criteria for Inclusion: Subjects with a diagnosis of cluster of differentiation (CD) 20 and CD22-positive, follicular lymphoma, who received 1 or 2 prior regimens, at least 1 of which contained administration of rituximab (ie, either as a single agent or in combination). Subjects also had prior CD20 and CD22-immunophenotyping of tumors to document B-cell non-Hodgkin's lymphoma (NHL), an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, a life expectancy ≥12 weeks, and at least 1 measurable disease lesion that was ≥1.5 cm × 1.5 cm by computed tomography (CT) or magnetic resonance imaging (MRI).

Excluded from the study were subjects with a prior allogeneic hematopoietic stem cell transplant (HSCT); with clinical evidence of transformation to a more aggressive subtype of lymphoma or Grade 3B follicular lymphoma; prior treatment with anti-CD22 antibodies; or any previous radio-immunotherapy within 6 months before the administration of the first dose of study drug.

Study Treatment:

Arm 1: Inotuzumab Ozogamicin and Rituximab

Subjects received rituximab intravenous (IV) at a dose level of 375 mg/m^2 on Day 1 of each cycle followed by inotuzumab ozogamicin administered IV at a dose level of 1.8 mg/m^2 on Day 2. Dosing was capped at a body surface area (BSA) of 2.2 m^2. The sequence was repeated every 28 days.

Arm 2: R-CVP

Subjects received rituximab IV at a dose of 375 mg/m^2 on Day 1 (maximum BSA of 2.2 m^2), IV cyclophosphamide at a dose of 750 mg/m^2 on Day 1, IV vincristine at a dose of 1.4 mg/m^2 (not to exceed 2 mg) on Day 1, and oral prednisone/prednisolone at a dose of 40 mg/m^2 on Days 1 through 5. This sequence was repeated every 21 days.

Arm 2: R-FND

Subjects received rituximab IV at a dose of 375 mg/m^2 on Day 1, IV mitoxantrone 10 mg/m^2 on Day 2, IV fludarabine 25 mg/m^2 on Days 2 through 4, and oral dexamethasone 20 mg/day on Days 1 through 5. This sequence was repeated every 21 days.

Efficacy Endpoints:

The primary efficacy variable PFS was defined as the interval from the date of randomization until the earlier date of progression or death from any cause, censored at the last tumor evaluation date.

Secondary endpoints were to evaluate the efficacy of inotuzumab ozogamicin in combination with rituximab relative to an active comparator arm using the following endpoints and analyses: ORR (CR + CRu + PR) and OS. Survival was recorded from the date of randomization until the time of death, censored at the last date known alive. In addition, the population PK of inotuzumab ozogamicin in combination with rituximab was evaluated.

Safety Evaluations: Safety and tolerability of inotuzumab ozogamicin in combination with rituximab, defined as the nature, incidence, and severity of adverse events (AEs), changes in laboratory test results over time, the evaluation of the population PK of inotuzumab ozogamicin in combination with rituximab, the evaluation of factors affecting drug disposition, the assessments of impact on QT interval, and vital signs monitoring were evaluated.

Statistical Methods:

Safety Population: All subjects who received at least 1 dose of a study drug (either inotuzumab ozogamicin administrated in combination with rituximab or Investigator's choice). This subject population excluded only subjects who never received any study drug.

Intent-to-Treat (ITT) Population: The ITT population included all subjects who were randomized into the study.

Evaluable Population: All subjects who met all of the following criteria:

- Randomized and received at least 1 dose of a study drug
- Remained in the treatment phase of the study for at least 6 weeks, unless early discontinuation due to disease progression or death
- No major protocol violations. Major violations included failure to satisfy major entry criteria (CD22 positive NHL confirmation, prior rituximab containing therapies, a lymph node or tumor mass ≥1.5 cm ×1.5 cm by CT, signed Informed Consent Form) or taking any other anticancer therapies during the active treatment and disease follow-up of the study
- A baseline tumor assessment and at least 1 postbaseline tumor assessment.

Since this study was terminated early, the planned statistical analyses were not performed. Only descriptive summaries and subject listings were created.

RESULTS

Subject Disposition and Demography: Overall, 29 subjects were randomized to study treatment, 15 subjects to the inotuzumab ozogamicin + rituximab treatment arm and 14 subjects to the control arm (ie, R-CVP + R-FND; Table 6).

Table 6. Subject Disposition by Treatment Arm (ITT Population)

No. of Subjects (%)	Treatment Arm		Total (N=29)
	Inotuzumab Ozogamicin + Rituximab (N=15)	Control (R-CVP + R-FND) (N=14)	
Randomized	15 (100)	14 (100)	29 (100)
Treated	15 (100)	13 (92.9)	28 (96.6)
Completed treatment	7 (46.7)	7 (50.0)	14 (48.3)
Did not complete treatment	8 (53.3)	6 (42.9)	14 (48.3)
Entered follow-up	7 (46.7)	7 (50.0)	14 (48.3)
Completed follow-up	7 (46.7)	5 (35.7)	12 (41.4)
Lost to follow-up	0	0	0
Died	0	2 (14.3)	2 (6.9)
Subject populations			
ITT	15	14	29
Safety	15	13	28
Evaluable for efficacy	13	12	25

One subject was randomized but withdrew from the study before receiving Investigator choice medication. Subjects were stratified according to the Investigator choice regimen that was used if randomized to receive Investigator choice therapy.
ITT = intent-to-treat; N = number of subjects; No. = number; R-CVP = rituximab in combination with cyclophosphamide, vincristine, and prednisone/prednisolone; R-FND = rituximab in combination with fludarabine, Novantrone (mitoxantrone), and dexamethasone.

A summary of subject disposition summarized by Investigators' R-CVP and R-FND pre-randomization selections and by the actual randomization treatment assignments to the 4 treatment groups (A-D) is presented in Table 7. All treatment groups had similar percentages of subjects who were randomized, treated, completed treatment, and entered the follow-up period.

Table 7. Subject Disposition by Pre-Randomization Selections, Treatment Group, and by Treatment Arm (ITT Population)

Pre-Randomization R-CVP or R-FND Selections	R-CVP		R-FND		Total (Treatment Arms)	
Assigned Treatment Groups (A-D): No. of Subjects (%)	A Inotuzumab Ozogamicin + Rituximab (N=7)	B R-CVP (N=6)	C Inotuzumab Ozogamicin + Rituximab (N=8)	D R-FND (N=8)	A + C Inotuzumab Ozogamicin + Rituximab (N=15)	B + D Control (N=14)
Randomized	7 (100)	6 (100)	8 (100)	8 (100)	15 (100)	14 (100)
Treated	7 (100)	6 (100)	8 (100)	7 (87.5)	15 (100)	13 (92.9)
Completed treatment	3 (42.9)	3 (50.0)	4 (50.0)	4 (50.0)	7 (46.7)	7 (50.0)
Did not complete treatment	4 (57.1)	3 (50.0)	4 (50.0)	3 (37.5)	8 (53.3)	6 (42.9)
Entered follow-up	3 (42.9)	3 (50.0)	4 (50.0)	4 (50.0)	7 (46.7)	7 (50.0)
Completed follow-up	3 (42.9)	1 (16.7)	4 (50.0)	4 (50.0)	7 (46.7)	5 (35.7)
Lost to follow-up	0	0	0	0	0	0
Died	0	2 (33.3)	0	0	0	2 (14.3)

Subjects were stratified according to the Investigator choice regimen that would be used if randomized to receive Investigator choice therapy.
ITT = intent-to-treat; No. = number; N = number of subjects; R-CVP = rituximab in combination with cyclophosphamide, vincristine, and prednisone/prednisolone; R-FND = rituximab in combination with fludarabine, Novantrone (mitoxantrone), and dexamethasone.

Baseline characteristics and demographics are summarized in Table 8.

Table 8. Subject Demographics and Baseline Characteristics by Treatment Arm (ITT Population)

Parameter	Treatment Arm		Total (N=29)
	Inotuzumab Ozogamicin + Rituximab (N=15)	Control (R-CVP + R-FND) (N=14)	
Sex, n (%)			
Male	6 (40.0)	8 (57.1)	14 (48.3)
Female	9 (60.0)	6 (42.9)	15 (51.7)
Age (years)			
n	15	14	29
Mean (SD)	62.3 (11.4)	60.9 (12.4)	61.7 (11.7)
Range	44-79	35-83	35-83
Race, n (%)			
Asian	3 (20.0)	3 (21.4)	6 (20.7)
Black or African American	1 (6.7)	0	1 (3.4)
White	10 (66.7)	11 (78.6)	21 (72.4)
Other	1 (6.7)	0	1 (3.4)
ECOG performance status, n (%)			
0	9 (60.0)	9 (64.3)	18 (62.1)
1	6 (40.0)	5 (35.7)	11 (37.9)
FLIPI Score, n (%)			
0	1 (6.7)	0	1 (3.4)
1	1 (6.7)	0	1 (3.4)
2	4 (26.7)	6 (42.9)	10 (34.5)
3	5 (33.3)	6 (42.9)	11 (37.9)
4	2 (13.3)	2 (14.3)	4 (13.8)
5	1 (6.7)	0	1 (3.4)
Missing	1 (6.7)	0	1 (3.4)

ECOG = Eastern Cooperative Oncology Group; FLIPI = Follicular Lymphoma International Prognostic Index; ITT = intent-to-treat; No. = number; N = number of subjects; n = number of subjects meeting prespecified criteria; R-CVP = rituximab in combination with cyclophosphamide, vincristine, and prednisone/prednisolone; R-FND = rituximab in combination with fludarabine, Novantrone (mitoxantrone), and dexamethasone; SD = standard deviation.

Efficacy Results: Three subjects (20%) in the inotuzumab ozogamicin + rituximab treatment arm died or experienced disease progression compared with 9 subjects (64.3%) in the control arm (Table 9). PFS rates at 6, 12, and 24 months for the inotuzumab ozogamicin + rituximab and control arms were 93.3% versus (vs) 90.9%, 86.2% vs 54.5%, and 73.8% vs 27.3%, respectively.

Table 9. Summary of Progression-Free Survival by Pre-Randomization Selections, Treatment Group, and by Treatment Arm (ITT Population; Investigator's Assessment)

Pre-Randomization R-CVP or R-FND Selections	R-CVP		R-FND		Total (Treatment Arms)	
Assigned Treatment Groups (A-D)	**A**	**B**	**C**	**D**	**A + C**	**B + D**
	Inotuzumab Ozogamicin + Rituximab (N=7)	**R-CVP (N=6)**	**Inotuzumab Ozogamicin + Rituximab (N=8)**	**R-FND (N=8)**	**Inotuzumab Ozogamicin + Rituximab (N=15)**	**Control (N=14)**
Number of subjects with postbaseline tumor assessment (n, %)	7 (100)	6 (100)	8 (100)	7 (87.5)	15 (100)	13 (92.9)
Number of subjects with PD or who died (n, %)	2 (28.6)	5 (83.3)	1 (12.5)	4 (50.0)	3 (20.0)	9 (64.3)
Number of censored subjects (n, %)	5 (71.4)	1 (16.7)	7 (87.5)	4 (50.0)	12 (80.0)	5 (35.7)
Median PFS in months (95% CI)[a]	NE (7.4, NE)	7.9 (4.5, 28.4)	NE (NE, NE)	19.3 (16.4, NE)	NE (22.2, NE)	16.4 (7.9, 28.4)
6 month PFS rate (95% CI)	85.7 (59.8, 100.0)	80.0 (44.9, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	93.3 (80.7, 100.0)	90.9 (73.9, 100.0)
12 month PFS rate (95% CI)	68.6 (32.1, 100.0)	20.0 (0.0, 55.1)	100.0 (100.0, 100.0)	83.3 (53.5, 100.0)	86.2 (68.3, 100.0)	54.5 (25.1, 84.0)
24 month PFS rate (95% CI)	68.6 (32.1, 100.0)	20.0 (0.0, 55.1)	83.3 (53.5, 100.0)	33.3 (0.0, 71.1)	73.8 (46.8, 100.0)	27.3 (1.0, 53.6)
p-Value[b]					0.0358	
Hazard ratio (95% CI)[c]					0.19 (0.04, 1.02)	

Subjects were stratified according to the investigator choice regimen that would be used if randomized to receive investigator choice therapy.
CI = confidence interval; ITT = intent-to-treat; N = number of subjects; n = number of subjects meeting prespecified criteria; NE = not estimable; PD = progressive disease; PFS = progression-free survival; R-CVP = rituximab in combination with cyclophosphamide, vincristine, and prednisone/prednisolone; R-FND = rituximab in combination with fludarabine, Novantrone (mitoxantrone), and dexamethasone.

a. Kaplan-Meier method used to estimate PFS median time and associated 95% CI.
b. PFS curve of the inotuzumab ozogamicin + rituximab was compared to that of the control arm using a score test at a 2-sided 5% significance level on a stratified Cox proportional hazard regression model in which treatment arm was the only covariate and the strata are the variables over which subjects were stratified prior to randomization.
c. The hazard ratio compared the relative risk of developing disease progression or death in the treatment arms inotuzumab ozogamicin + rituximab vs control.

The best overall and objective responses are summarized by treatment arm in Table 10.

Table 10. Investigator Assessment Overall Best Response and Objective Response Rate by Treatment Arm (ITT Population)

No. of Subjects (%)	Totals for Treatment Arms	
	A + C	B + D
	Inotuzumab Ozogamicin + Rituximab (N=15)	Control (N=14)
Best overall response		
CR	6 (40.0)	1 (7.1)
CRu[a]	0	0
PR	8 (53.3)	8 (57.1)
SD[b]	0	4 (28.6)
PD	1 (6.7)	0
Nonevaluable[c]	0	1 (7.1)
Objective response rate		
Number of subjects with CR, CRu, or PR (n, %)	14 (93.3)	9 (64.3)
95% CI for rate	(68.1,99.8)	(35.1,87.2)
p-Value[d]	0.0801	

CI = confidence interval; CR = complete response; CRu = complete response, unconfirmed; ITT = intent-to-treat; No. = number; N = number of subjects; n = number of subjects meeting prespecified criteria; PD = progressive disease; PR = partial response; SD = stable disease.

a. CRu was defined as: a) a residual lymph node mass >1.5 cm in greatest tranverse diameter that has regressed >75% in the product diameter. Individual nodes that were previously confluent must have regressed >75% in their product diameters. b) Indeterminate bone marrow (ie, increased number or size of lymphoid aggregates without cytologic or architectural atypia).
b. Stable disease must be sustained for at least 4 weeks.
c. Nonevaluable subject did not have tumor assessments.
d. Comparison of treatment arms (inotuzumab ozogamicin + rituximab and control) based on the Fisher's Exact test.

OS results for each of the 4 treatment groups can be found in Table 11.

Table 11. Summary of Overall Survival by Pre-Randomization Selections, Treatment Group, and by Treatment Arm (ITT Population

Pre-Randomization R-CVP or R-FND Selections	R-CVP		R-FND		Total (Treatment Arms)	
Assigned Treatment Groups (A-D)	A	B	C	D	A + C	B + D
	Inotuzumab Ozogamicin + Rituximab (N=7)	R-CVP (N=6)	Inotuzumab Ozogamicin + Rituximab (N=8)	R-FND (N=8)	Inotuzumab Ozogamicin + Rituximab (N=15)	Control (N=14)
Number of subjects who died (n, %)	2 (28.6)	4 (66.7)	0	0	2 (13.3)	4 (28.6)
Number of censored subjects (n, %)	5 (71.4)	2 (33.3)	8 (100)	8 (100)	13 (86.7)	10 (71.4)
6 month OS (95% CI)	100.0 (100.0, 100.0)	83.3 (53.5, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0,100.0)	92.3 (77.8, 100.0)
12 month OS (95% CI)	71.4 (38.0, 100.0)	66.7 (28.9, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	86.7 (69.5, 100.0)	83.9 (63.4, 100.0)
24 month OS (95% CI)	71.4 (38.0, 100.0)	33.3 (0.0, 71.1)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	86.7 (69.5, 100.0)	67.1 (40.7, 93.6)
p-Value[a]					0.1727	
Hazard ratio (95% CI)[b]					0.30 (0.05, 1.81)	

Subjects were stratified according to the Investigator choice regimen that would be used if randomized to receive Investigator choice therapy.
CI = confidence interval; ITT = intent-to-treat; N = number of subjects; n = number of subjects meeting prespecified criteria; OS = overall survival; R-CVP = rituximab in combination with cyclophosphamide, vincristine, and prednisone/prednisolone; R-FND = rituximab in combination with fludarabine, Novantrone (mitoxantrone), and dexamethasone.

a. OS curve of the inotuzumab ozogamicin + rituximab was compared to that of the control arm using a score test at a 2-sided 5% significance level on a stratified Cox proportional hazard regression model in which treatment arm was the only covariate and the strata were the variables over which subjects were stratified prior to randomization.
b. The hazard ratio compared the relative risk of death in the treatment arms inotuzumab ozogamicin + rituximab versus control.

Given the limited number of subjects who provided PK samples and the sparse sampling schedule, noncompartmental analysis and Electrocardiogram correlation to PK measures and study-specific population PK analyses were not performed.

The decision about termination of the study was not prompted by the identification of safety signals or concerns with inotuzumab ozogamicin in this study or other active studies. The decision followed from a recent evaluation of the enrollment status, in which it was determined that it was unlikely this study would meet the estimated enrollment of approximately 978 subjects.

Safety Results: Treatment-emergent AEs (TEAEs) by treatment arms (all causalities, all cycles) of total subjects are summarized in Table 12. The most frequent TEAEs observed overall were neutropenia, thrombocytopenia, cough, and nausea.

Table 12. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for Non-Serious Adverse Events - Safety Population

System Organ Class[a] Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Any adverse event	15 (100)	13 (100)	28 (100)
Blood and lymphatic system disorders	11 (73.3)	12 (92.3)	23 (82.1)
Anaemia	2 (13.3)	7 (53.8)	9 (32.1)
Febrile neutropenia	0	1 (7.7)	1 (3.6)
Hypercoagulation	0	1 (7.7)	1 (3.6)
Leukocytosis	2 (13.3)	0	2 (7.1)
Leukopenia	2 (13.3)	5 (38.5)	7 (25.0)
Lymph node pain	1 (6.7)	0	1 (3.6)
Lymphopenia	2 (13.3)	2 (15.4)	4 (14.3)
Monocytosis	1 (6.7)	0	1 (3.6)
Neutropenia	5 (33.3)	11 (84.6)	16 (57.1)
Thrombocytopenia	8 (53.3)	7 (53.8)	15 (53.6)
Cardiac disorders	3 (20.0)	2 (15.4)	5 (17.9)
Atrial fibrillation	0	1 (7.7)	1 (3.6)
Extrasystoles	1 (6.7)	0	1 (3.6)
Palpitations	2 (13.3)	1 (7.7)	3 (10.7)
Supraventricular extrasystoles	1 (6.7)	0	1 (3.6)
Supraventricular tachycardia	1 (6.7)	0	1 (3.6)
Ear and labyrinth disorders	0	1 (7.7)	1 (3.6)
Ear pain	0	1 (7.7)	1 (3.6)
Eye disorders	1 (6.7)	0	1 (3.6)
Eye disorder	1 (6.7)	0	1 (3.6)
Gastrointestinal disorders	8 (53.3)	10 (76.9)	18 (64.3)
Abdominal discomfort	1 (6.7)	0	1 (3.6)
Abdominal pain	5 (33.3)	0	5 (17.9)
Abdominal pain lower	0	1 (7.7)	1 (3.6)
Abdominal pain upper	1 (6.7)	0	1 (3.6)
Aphthous stomatitis	0	1 (7.7)	1 (3.6)
Constipation	3 (20.0)	2 (15.4)	5 (17.9)
Diarrhoea	2 (13.3)	5 (38.5)	7 (25.0)
Dry mouth	1 (6.7)	0	1 (3.6)
Dyspepsia	1 (6.7)	2 (15.4)	3 (10.7)
Dysphagia	0	1 (7.7)	1 (3.6)
Gastric ulcer	0	1 (7.7)	1 (3.6)
Gastritis	0	1 (7.7)	1 (3.6)
Gastrooesophageal reflux disease	1 (6.7)	0	1 (3.6)
Mouth ulceration	1 (6.7)	0	1 (3.6)
Nausea	4 (26.7)	7 (53.8)	11 (39.3)
Oesophagitis	1 (6.7)	0	1 (3.6)
Oral pain	1 (6.7)	0	1 (3.6)
Stomatitis	1 (6.7)	1 (7.7)	2 (7.1)
Vomiting	2 (13.3)	1 (7.7)	3 (10.7)
General disorders and administration site conditions	13 (86.7)	8 (61.5)	21 (75.0)
Asthenia	2 (13.3)	0	2 (7.1)
Chest pain	1 (6.7)	0	1 (3.6)
Chills	3 (20.0)	0	3 (10.7)

Table 12. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for Non-Serious Adverse Events - Safety Population

System Organ Class[a] Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Fatigue	6 (40.0)	3 (23.1)	9 (32.1)
Feeling cold	1 (6.7)	0	1 (3.6)
Generalised oedema	1 (6.7)	0	1 (3.6)
Influenza like illness	1 (6.7)	0	1 (3.6)
Malaise	0	1 (7.7)	1 (3.6)
Mucosal inflammation	0	1 (7.7)	1 (3.6)
Oedema	1 (6.7)	0	1 (3.6)
Oedema peripheral	1 (6.7)	1 (7.7)	2 (7.1)
Pain	1 (6.7)	2 (15.4)	3 (10.7)
Pyrexia	6 (40.0)	3 (23.1)	9 (32.1)
Thirst	1 (6.7)	0	1 (3.6)
Hepatobiliary disorders	4 (26.7)	3 (23.1)	7 (25.0)
Hyperbilirubinaemia	4 (26.7)	3 (23.1)	7 (25.0)
Infections and infestations	7 (46.7)	6 (46.2)	13 (46.4)
Bronchitis	1 (6.7)	0	1 (3.6)
Cystitis	1 (6.7)	0	1 (3.6)
Device related infection	0	1 (7.7)	1 (3.6)
Ear infection	0	1 (7.7)	1 (3.6)
Folliculitis	0	1 (7.7)	1 (3.6)
Fungal infection	0	1 (7.7)	1 (3.6)
Herpes zoster	0	1 (7.7)	1 (3.6)
Influenza	1 (6.7)	2 (15.4)	3 (10.7)
Localised infection	1 (6.7)	0	1 (3.6)
Nasopharyngitis	1 (6.7)	2 (15.4)	3 (10.7)
Pharyngotonsillitis	1 (6.7)	0	1 (3.6)
Pneumonia	1 (6.7)	1 (7.7)	2 (7.1)
Rhinitis	0	1 (7.7)	1 (3.6)
Sinusitis	0	1 (7.7)	1 (3.6)
Upper respiratory tract infection	0	2 (15.4)	2 (7.1)
Urinary tract infection	1 (6.7)	0	1 (3.6)
Vulvovaginal mycotic infection	0	1 (7.7)	1 (3.6)
Injury, poisoning and procedural complications	2 (13.3)	1 (7.7)	3 (10.7)
Excoriation	1 (6.7)	0	1 (3.6)
Fall	1 (6.7)	0	1 (3.6)
Infusion related reaction	0	1 (7.7)	1 (3.6)
Procedural pain	1 (6.7)	0	1 (3.6)
Investigations	7 (46.7)	7 (53.8)	14 (50.0)
Activated partial thromboplastin time prolonged	0	1 (7.7)	1 (3.6)
Alanine aminotransferase increased	4 (26.7)	2 (15.4)	6 (21.4)
Aspartate aminotransferase increased	6 (40.0)	2 (15.4)	8 (28.6)
Bilirubin conjugated increased	1 (6.7)	0	1 (3.6)
Blood albumin decreased	2 (13.3)	2 (15.4)	4 (14.3)
Blood albumin increased	1 (6.7)	0	1 (3.6)
Blood alkaline phosphatase increased	5 (33.3)	2 (15.4)	7 (25.0)
Blood amylase increased	1 (6.7)	0	1 (3.6)

Table 12. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for Non-Serious Adverse Events - Safety Population

System Organ Class[a] Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Blood bicarbonate decreased	1 (6.7)	0	1 (3.6)
Blood bicarbonate increased	1 (6.7)	0	1 (3.6)
Blood calcium decreased	1 (6.7)	2 (15.4)	3 (10.7)
Blood chloride decreased	1 (6.7)	0	1 (3.6)
Blood chloride increased	1 (6.7)	0	1 (3.6)
Blood creatinine decreased	1 (6.7)	0	1 (3.6)
Blood glucose increased	1 (6.7)	3 (23.1)	4 (14.3)
Blood lactate dehydrogenase decreased	2 (13.3)	1 (7.7)	3 (10.7)
Blood lactate dehydrogenase increased	3 (20.0)	1 (7.7)	4 (14.3)
Blood phosphorus decreased	0	1 (7.7)	1 (3.6)
Blood phosphorus increased	2 (13.3)	3 (23.1)	5 (17.9)
Blood potassium decreased	0	3 (23.1)	3 (10.7)
Blood sodium decreased	1 (6.7)	2 (15.4)	3 (10.7)
Blood sodium increased	1 (6.7)	0	1 (3.6)
Blood urea decreased	2 (13.3)	0	2 (7.1)
Blood urea increased	2 (13.3)	2 (15.4)	4 (14.3)
Blood uric acid decreased	1 (6.7)	0	1 (3.6)
Blood uric acid increased	0	1 (7.7)	1 (3.6)
Gamma-glutamyltransferase increased	3 (20.0)	0	3 (10.7)
Haemoglobin decreased	1 (6.7)	1 (7.7)	2 (7.1)
Lymphocyte count decreased	1 (6.7)	0	1 (3.6)
Neutrophil count	0	1 (7.7)	1 (3.6)
Neutrophil count decreased	0	1 (7.7)	1 (3.6)
PCO2 decreased	1 (6.7)	0	1 (3.6)
PCO2 increased	1 (6.7)	0	1 (3.6)
Protein total decreased	2 (13.3)	1 (7.7)	3 (10.7)
Red blood cell count decreased	1 (6.7)	0	1 (3.6)
Urine output decreased	1 (6.7)	1 (7.7)	2 (7.1)
White blood cell count decreased	0	1 (7.7)	1 (3.6)
Metabolism and nutrition disorders	9 (60.0)	7 (53.8)	16 (57.1)
Acidosis	0	1 (7.7)	1 (3.6)
Decreased appetite	4 (26.7)	3 (23.1)	7 (25.0)
Dehydration	1 (6.7)	0	1 (3.6)
Fluid overload	0	1 (7.7)	1 (3.6)
Hyperglycaemia	1 (6.7)	1 (7.7)	2 (7.1)
Hypoalbuminaemia	0	1 (7.7)	1 (3.6)
Hypocalcaemia	2 (13.3)	1 (7.7)	3 (10.7)
Hypochloraemia	0	1 (7.7)	1 (3.6)
Hypokalaemia	5 (33.3)	4 (30.8)	9 (32.1)
Hypomagnesaemia	0	1 (7.7)	1 (3.6)
Hyponatraemia	1 (6.7)	0	1 (3.6)
Hypoproteinaemia	0	1 (7.7)	1 (3.6)
Hypouricaemia	1 (6.7)	0	1 (3.6)
Musculoskeletal and connective tissue disorders	5 (33.3)	5 (38.5)	10 (35.7)
Arthralgia	0	2 (15.4)	2 (7.1)

Table 12. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for Non-Serious Adverse Events - Safety Population

System Organ Class[a] Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Back pain	2 (13.3)	0	2 (7.1)
Bone pain	0	2 (15.4)	2 (7.1)
Flank pain	0	1 (7.7)	1 (3.6)
Groin pain	1 (6.7)	1 (7.7)	2 (7.1)
Mobility decreased	1 (6.7)	0	1 (3.6)
Musculoskeletal chest pain	1 (6.7)	1 (7.7)	2 (7.1)
Myalgia	2 (13.3)	0	2 (7.1)
Pain in jaw	0	1 (7.7)	1 (3.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (6.7)	0	1 (3.6)
Cancer pain	1 (6.7)	0	1 (3.6)
Nervous system disorders	6 (40.0)	6 (46.2)	12 (42.9)
Dizziness	0	1 (7.7)	1 (3.6)
Dysgeusia	0	2 (15.4)	2 (7.1)
Headache	6 (40.0)	2 (15.4)	8 (28.6)
Memory impairment	1 (6.7)	0	1 (3.6)
Neuropathy peripheral	0	2 (15.4)	2 (7.1)
Paraesthesia	1 (6.7)	0	1 (3.6)
Peripheral sensory neuropathy	3 (20.0)	1 (7.7)	4 (14.3)
Psychomotor hyperactivity	0	1 (7.7)	1 (3.6)
Psychiatric disorders	1 (6.7)	3 (23.1)	4 (14.3)
Insomnia	1 (6.7)	3 (23.1)	4 (14.3)
Renal and urinary disorders	4 (26.7)	1 (7.7)	5 (17.9)
Chromaturia	1 (6.7)	0	1 (3.6)
Dysuria	1 (6.7)	0	1 (3.6)
Haematuria	2 (13.3)	0	2 (7.1)
Micturition urgency	1 (6.7)	0	1 (3.6)
Pollakiuria	1 (6.7)	0	1 (3.6)
Proteinuria	1 (6.7)	0	1 (3.6)
Renal failure	0	1 (7.7)	1 (3.6)
Reproductive system and breast disorders	1 (6.7)	0	1 (3.6)
Epididymitis	1 (6.7)	0	1 (3.6)
Respiratory, thoracic and mediastinal disorders	11 (73.3)	7 (53.8)	18 (64.3)
Cough	7 (46.7)	5 (38.5)	12 (42.9)
Dyspnoea	2 (13.3)	3 (23.1)	5 (17.9)
Dyspnoea exertional	1 (6.7)	0	1 (3.6)
Epistaxis	4 (26.7)	0	4 (14.3)
Haemoptysis	1 (6.7)	0	1 (3.6)
Oropharyngeal pain	1 (6.7)	1 (7.7)	2 (7.1)
Paranasal sinus hypersecretion	1 (6.7)	1 (7.7)	2 (7.1)
Productive cough	1 (6.7)	2 (15.4)	3 (10.7)
Rhinorrhoea	0	1 (7.7)	1 (3.6)
Sinus congestion	1 (6.7)	1 (7.7)	2 (7.1)
Skin and subcutaneous tissue disorders	5 (33.3)	4 (30.8)	9 (32.1)
Alopecia	0	2 (15.4)	2 (7.1)
Hyperhidrosis	0	1 (7.7)	1 (3.6)

Table 12. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for Non-Serious Adverse Events - Safety Population

System Organ Class[a] Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Night sweats	1 (6.7)	0	1 (3.6)
Pigmentation disorder	0	1 (7.7)	1 (3.6)
Pruritus	1 (6.7)	0	1 (3.6)
Rash	1 (6.7)	0	1 (3.6)
Rash macular	1 (6.7)	0	1 (3.6)
Skin lesion	2 (13.3)	0	2 (7.1)
Vascular disorders	3 (20.0)	2 (15.4)	5 (17.9)
Hot flush	1 (6.7)	0	1 (3.6)
Hypertension	2 (13.3)	0	2 (7.1)
Hypotension	0	1 (7.7)	1 (3.6)
Subclavian vein thrombosis	0	1 (7.7)	1 (3.6)

Classification of adverse events are based in the Medical Dictionary for Regulatory Activities (MedDRA).
Treatment-emergent was up to 42 days post last dose used.
n = number of subjects.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report ≥2 different adverse events within the higher level category.

The number of subjects reporting treatment-related AEs is presented in Table 13. The most frequent treatment-related AEs overall were neutropenia, thrombocytopenia, increased aspartate aminotransferase levels, and nausea.

Table 13. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (Non-Serious and Serious) - Safety Population

System Organ Class Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Any adverse event	14 (93.3)	12 (92.3)	26 (92.9)
Blood and lymphatic system disorders	10 (66.7)	11 (84.6)	21 (75.0)
Anaemia	2 (13.3)	5 (38.5)	7 (25.0)
Febrile neutropenia	0	3 (23.1)	3 (10.7)
Leukocytosis	1 (6.7)	0	1 (3.6)
Leukopenia	2 (13.3)	5 (38.5)	7 (25.0)
Lymphopenia	2 (13.3)	1 (7.7)	3 (10.7)
Monocytosis	1 (6.7)	0	1 (3.6)
Neutropenia	5 (33.3)	10 (76.9)	15 (53.6)
Thrombocytopenia	8 (53.3)	6 (46.2)	14 (50.0)
Cardiac disorders	2 (13.3)	0	2 (7.1)
Extrasystoles	1 (6.7)	0	1 (3.6)
Palpitations	1 (6.7)	0	1 (3.6)
Supraventricular tachycardia	1 (6.7)	0	1 (3.6)
Gastrointestinal disorders	5 (33.3)	5 (38.5)	10 (35.7)
Abdominal pain	4 (26.7)	0	4 (14.3)
Constipation	1 (6.7)	1 (7.7)	2 (7.1)
Diarrhoea	1 (6.7)	1 (7.7)	2 (7.1)
Dry mouth	1 (6.7)	0	1 (3.6)
Dyspepsia	1 (6.7)	2 (15.4)	3 (10.7)
Gastrooesophageal reflux disease	1 (6.7)	0	1 (3.6)
Mouth ulceration	1 (6.7)	0	1 (3.6)
Nausea	4 (26.7)	4 (30.8)	8 (28.6)
Stomatitis	1 (6.7)	1 (7.7)	2 (7.1)
Vomiting	1 (6.7)	1 (7.7)	2 (7.1)
General disorders and administration site conditions	6 (40.0)	4 (30.8)	10 (35.7)
Chills	3 (20.0)	0	3 (10.7)
Fatigue	3 (20.0)	3 (23.1)	6 (21.4)
Feeling cold	1 (6.7)	0	1 (3.6)
Mucosal inflammation	0	1 (7.7)	1 (3.6)
Oedema peripheral	1 (6.7)	0	1 (3.6)
Pyrexia	2 (13.3)	1 (7.7)	3 (10.7)
Thirst	1 (6.7)	0	1 (3.6)
Hepatobiliary disorders	4 (26.7)	1 (7.7)	5 (17.9)
Hyperbilirubinaemia	3 (20.0)	1 (7.7)	4 (14.3)
Venoocclusive liver disease	1 (6.7)	0	1 (3.6)
Infections and infestations	1 (6.7)	3 (23.1)	4 (14.3)
Influenza	0	1 (7.7)	1 (3.6)
Nasopharyngitis	1 (6.7)	0	1 (3.6)
Pneumonia	0	2 (15.4)	2 (7.1)
Rhinitis	0	1 (7.7)	1 (3.6)
Injury, poisoning and procedural complications	0	1 (7.7)	1 (3.6)
Infusion related reaction	0	1 (7.7)	1 (3.6)
Investigations	7 (46.7)	5 (38.5)	12 (42.9)
Activated partial thromboplastin time prolonged	0	1 (7.7)	1 (3.6)
Alanine aminotransferase increased	4 (26.7)	2 (15.4)	6 (21.4)
Aspartate aminotransferase increased	6 (40.0)	2 (15.4)	8 (28.6)

Table 13. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (Non-Serious and Serious) - Safety Population

System Organ Class Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Bilirubin conjugated increased	1 (6.7)	0	1 (3.6)
Blood albumin decreased	1 (6.7)	2 (15.4)	3 (10.7)
Blood albumin increased	1 (6.7)	0	1 (3.6)
Blood alkaline phosphatase increased	5 (33.3)	2 (15.4)	7 (25.0)
Blood amylase increased	1 (6.7)	0	1 (3.6)
Blood calcium decreased	1 (6.7)	2 (15.4)	3 (10.7)
Blood chloride decreased	1 (6.7)	0	1 (3.6)
Blood creatinine decreased	1 (6.7)	0	1 (3.6)
Blood lactate dehydrogenase decreased	2 (13.3)	1 (7.7)	3 (10.7)
Blood lactate dehydrogenase increased	3 (20.0)	1 (7.7)	4 (14.3)
Blood phosphorus decreased	0	1 (7.7)	1 (3.6)
Blood phosphorus increased	2 (13.3)	3 (23.1)	5 (17.9)
Blood potassium decreased	0	2 (15.4)	2 (7.1)
Blood sodium decreased	1 (6.7)	2 (15.4)	3 (10.7)
Blood sodium increased	1 (6.7)	0	1 (3.6)
Blood urea increased	1 (6.7)	2 (15.4)	3 (10.7)
Gamma-glutamyltransferase increased	3 (20.0)	0	3 (10.7)
Haemoglobin decreased	1 (6.7)	0	1 (3.6)
Lipase increased	1 (6.7)	0	1 (3.6)
Lymphocyte count decreased	1 (6.7)	0	1 (3.6)
Neutrophil count	0	1 (7.7)	1 (3.6)
Neutrophil count decreased	0	1 (7.7)	1 (3.6)
Protein total decreased	2 (13.3)	1 (7.7)	3 (10.7)
Red blood cell count decreased	1 (6.7)	0	1 (3.6)
Urine output decreased	0	1 (7.7)	1 (3.6)
White blood cell count decreased	0	1 (7.7)	1 (3.6)
Metabolism and nutrition disorders	7 (46.7)	5 (38.5)	12 (42.9)
Acidosis	0	1 (7.7)	1 (3.6)
Decreased appetite	4 (26.7)	2 (15.4)	6 (21.4)
Dehydration	1 (6.7)	0	1 (3.6)
Hypocalcaemia	2 (13.3)	1 (7.7)	3 (10.7)
Hypokalaemia	2 (13.3)	1 (7.7)	3 (10.7)
Hyponatraemia	1 (6.7)	0	1 (3.6)
Hypouricaemia	1 (6.7)	0	1 (3.6)
Musculoskeletal and connective tissue disorders	2 (13.3)	0	2 (7.1)
Myalgia	2 (13.3)	0	2 (7.1)
Nervous system disorders	5 (33.3)	3 (23.1)	8 (28.6)
Dysgeusia	0	2 (15.4)	2 (7.1)
Headache	5 (33.3)	0	5 (17.9)
Memory impairment	1 (6.7)	0	1 (3.6)
Neuropathy peripheral	0	2 (15.4)	2 (7.1)
Paraesthesia	1 (6.7)	0	1 (3.6)
Peripheral sensory neuropathy	3 (20.0)	1 (7.7)	4 (14.3)
Psychomotor hyperactivity	0	1 (7.7)	1 (3.6)
Psychiatric disorders	1 (6.7)	1 (7.7)	2 (7.1)
Insomnia	1 (6.7)	1 (7.7)	2 (7.1)
Renal and urinary disorders	2 (13.3)	0	2 (7.1)

Table 13. Number (%) of Subjects Reporting Drug Related Treatment-Emergent Adverse Events (Non-Serious and Serious) - Safety Population

System Organ Class Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Chromaturia	1 (6.7)	0	1 (3.6)
Micturition urgency	1 (6.7)	0	1 (3.6)
Respiratory, thoracic and mediastinal disorders	6 (40.0)	3 (23.1)	9 (32.1)
Cough	2 (13.3)	2 (15.4)	4 (14.3)
Dyspnoea	2 (13.3)	2 (15.4)	4 (14.3)
Epistaxis	4 (26.7)	0	4 (14.3)
Lung infiltration	1 (6.7)	0	1 (3.6)
Oropharyngeal pain	1 (6.7)	1 (7.7)	2 (7.1)
Paranasal sinus hypersecretion	0	1 (7.7)	1 (3.6)
Sinus congestion	0	1 (7.7)	1 (3.6)
Skin and subcutaneous tissue disorders	2 (13.3)	4 (30.8)	6 (21.4)
Alopecia	0	2 (15.4)	2 (7.1)
Hyperhidrosis	0	1 (7.7)	1 (3.6)
Pigmentation disorder	0	1 (7.7)	1 (3.6)
Pruritus	1 (6.7)	0	1 (3.6)
Rash	1 (6.7)	0	1 (3.6)
Skin lesion	1 (6.7)	0	1 (3.6)
Vascular disorders	3 (20.0)	1 (7.7)	4 (14.3)
Hot flush	1 (6.7)	0	1 (3.6)
Hypertension	2 (13.3)	0	2 (7.1)
Hypotension	0	1 (7.7)	1 (3.6)

Non-SAEs and SAEs results are not seperated out.
System organ class totals are not necessarily the sum of the individual preferred terms since a subject may report ≥2 different preferred terms in the same system organ class.
AE = adverse event; n = number of subjects; SAE = serious adverse event.

All causality and treatment-related serious AEs (SAEs) by treatment arm are summarized in Table 14 and Table 15 respectively.

Table 14. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for Serious Adverse Events - Safety Population

System Organ Class[a] Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Any adverse event	6 (40.0)	6 (46.2)	12 (42.9)
Blood and lymphatic system disorders	0	5 (38.5)	5 (17.9)
Febrile neutropenia	0	3 (23.1)	3 (10.7)
Leukopenia	0	1 (7.7)	1 (3.6)
Neutropenia	0	2 (15.4)	2 (7.1)
Thrombocytopenia	0	1 (7.7)	1 (3.6)
Gastrointestinal disorders	1 (6.7)	0	1 (3.6)
Abdominal pain	1 (6.7)	0	1 (3.6)
General disorders and administration site conditions	1 (6.7)	2 (15.4)	3 (10.7)
Asthenia	0	1 (7.7)	1 (3.6)
Chills	1 (6.7)	0	1 (3.6)
Pyrexia	0	1 (7.7)	1 (3.6)
Hepatobiliary disorders	1 (6.7)	0	1 (3.6)
Venoocclusive liver disease	1 (6.7)	0	1 (3.6)
Infections and infestations	3 (20.0)	4 (30.8)	7 (25.0)
Cellulitis	1 (6.7)	0	1 (3.6)
Lower respiratory tract infection	0	1 (7.7)	1 (3.6)
Pneumonia	0	2 (15.4)	2 (7.1)
Pneumonia cryptococcal	1 (6.7)	0	1 (3.6)
Sepsis	1 (6.7)	1 (7.7)	2 (7.1)
Viral infection	0	1 (7.7)	1 (3.6)
Investigations	2 (13.3)	0	2 (7.1)
Blood creatinine increased	1 (6.7)	0	1 (3.6)
Gamma-glutamyltransferase increased	1 (6.7)	0	1 (3.6)
Lipase increased	1 (6.7)	0	1 (3.6)
Respiratory, thoracic and mediastinal disorders	1 (6.7)	2 (15.4)	3 (10.7)
Cough	0	1 (7.7)	1 (3.6)
Lung infiltration	1 (6.7)	0	1 (3.6)
Respiratory failure	0	1 (7.7)	1 (3.6)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Treatment-emergent was up to 42 days post last dose used.
n = number of subjects.

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report ≥ 2 different adverse events within the higher level category.

Table 15. Number (%) of Subjects Reporting Adverse Events of Drug Related Serious Adverse Events - Safety Population

System Organ Class Preferred Term	Treatment		
	Inotuzumab Ozogamicin + Rituximab n=15	Investigators Choice n=13	Total n=28
Any adverse event	4 (26.7)	6 (46.2)	10 (35.7)
Blood and lymphatic system disorders	0	5 (38.5)	5 (17.9)
Febrile neutropenia	0	3 (23.1)	3 (10.7)
Leukopenia	0	1 (7.7)	1 (3.6)
Neutropenia	0	2 (15.4)	2 (7.1)
Thrombocytopenia	0	1 (7.7)	1 (3.6)
General disorders and administration site conditions	0	1 (7.7)	1 (3.6)
Pyrexia	0	1 (7.7)	1 (3.6)
Hepatobiliary disorders	2 (13.3)	0	2 (7.1)
Hyperbilirubinaemia	1 (6.7)	0	1 (3.6)
Venoocclusive liver disease	1 (6.7)	0	1 (3.6)
Infections and infestations	0	3 (23.1)	3 (10.7)
Pneumonia	0	3 (23.1)	3 (10.7)
Investigations	1 (6.7)	0	1 (3.6)
Gamma-glutamyltransferase increased	1 (6.7)	0	1 (3.6)
Lipase increased	1 (6.7)	0	1 (3.6)
Respiratory, thoracic and mediastinal disorders	1 (6.7)	1 (7.7)	2 (7.1)
Cough	0	1 (7.7)	1 (3.6)
Diffuse alveolar damage	1 (6.7)	0	1 (3.6)
Hypoxia	1 (6.7)	0	1 (3.6)
Lung infiltration	1 (6.7)	0	1 (3.6)
Organising pneumonia	1 (6.7)	0	1 (3.6)
Respiratory failure	1 (6.7)	0	1 (3.6)

Drug related SAEs were not limited to treatment-emergent SAEs.
Treatment emergent was up to 42 days post last dose used.
System organ class totals are not necessarily the sum of the individual preferred terms since a subject may report ≥ 2 different preferred terms in the same system organ class.
n = number of subjects; SAEs = serious adverse events.

Five subjects (33.3%), all in the inotuzumab ozogamicin + rituximab treatment group discontinued treatment due to AEs during the study (3 due to SAEs) and all events leading to discontinuation were considered related to study treatment. No subjects in the control arm discontinued treatment due to AEs. All 5 subjects who discontinued treatment due to an AE are listed in Table 16.

Table 16. Discontinuations From Treatment due to Adverse Events (Safety Population)

Treatment Arm	Serial No.	AE Leading to D/C From Treatment	AE Grade[a]/ Outcome	Related to Study Drugs	SAE
Inotuzumab ozogamicin + rituximab	1	Neutropenia	2/Resolved	Yes	No
Inotuzumab ozogamicin + rituximab	2	Gamma-glutamyltransferase increased	3/Persisted	Yes	Yes
Inotuzumab ozogamicin + rituximab	3	Hyperbilirubinaemia	3/Resolved	Yes	Yes
		Hyperbilirubinaemia	2/Resolved	Yes	Yes
Inotuzumab ozogamicin + rituximab	4	Pyrexia	1/Persisted	Yes	No
Inotuzumab ozogamicin + rituximab	5	Venoocclusive liver disease	3/Resolved	Yes	Yes

Medical Dictionary for Regulatory Activities (MedDRA v14.0) coding dictionary applied.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; D/C = discontinuation; NA = not available; No. = number; SAE = serious adverse event; v = version.
a. Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1= mild AE; Grade 2= moderate AE; Grade 3= severe AE; Grade 4= life-threatening or disabling AE; Grade 5= death related to AE.

A total of 6 deaths were reported (Table 17), 5 occurred >30 days from the last dose of treatment and 1 occurred within 30 days of the last dose date. Of the 6 deaths, 4 occurred in the control arm and 2 occurred in the inotuzumab ozogamicin + rituximab treatment arm. One death was due to disease progression, 3 deaths were attributed to other reasons (ie, multiorgan failure and respiratory failure), and 2 deaths were attributed to the study medication/test article (ie, 1 respiratory failure and 1 pneumonia).

One subject in the inotuzumab ozogamicin + rituximab treatment arm died due to underlying disease progression, not attributed to test article. Three subjects in the control arm died due to other reasons.

Table 17. Summary of Mortalities (ITT Population)

No. of Subjects (%) MedDRA Preferred Term	Treatment Arms		Total (N=29)
	Inotuzumab Ozogamicin + Rituximab (N=15)	Control (N=14)	
Total number of deaths	2 (13.3)	4 (28.6)	6 (20.7)
Disease progression	1 (6.7)	0	1 (3.4)
Other[a]	0	3 (21.4)	3 (10.3)
Protocol related	0	0	0
Test article[b]	1 (6.7)	1 (7.1)	2 (6.9)

Medical Dictionary for Regulatory Activities (MedDRA v14.0) coding dictionary applied.
AE = adverse event; ITT = intent-to-treat; N = number of subjects; No. = number; v = version.
a. Two subjects died due to respiratory failure and 1 due to multiorgan failure.
b. Death attributed to an AE related to test article.

Electrocardiograms: Slight increases in mean Bazett's corrected QT interval (QTcB) and Fridericia's corrected QT interval (QTcF) were observed during treatment. Two subjects experienced Grade 1, and 3 subjects experienced Grade 2 prolonged QTcB intervals. Three subjects experienced Grade 1 prolonged QTcF intervals. No subjects had a QT or corrected

QT interval >500 msec. In addition, no ventricular arrhythmias were noted and no QTcF prolongations ≥Grade 3 were observed.

CONCLUSIONS:

- This study was terminated early and the resultant small sample size and short follow-up period may have led to an overestimation of the PFS effect. Inotuzumab ozogamicin + rituximab prolonged the PFS of subjects with relapsed or refractory, CD22 positive, follicular B-Cell non-Hodgkin's lymphoma. PFS rates of subjects taking inotuzumab ozogamicin + rituximab at 6, 12, and 24 months compared with control-treated subjects were 93.3% vs 90.9%, 86.2% vs 54.5%, and 73.8% vs 27.3%, respectively. The median PFS of subjects taking inotuzumab ozogamicin + rituximab was not estimable. The median PFS of subjects in the control arm was 16.4 (95% confidence interval = [7.9, 28.4]) months. The hazard ratio was 0.19 (95% CI = [0.04, 1.02]) with a p-value=0.036. No significant difference in OS was observed.

- Both treatment arms were associated with acceptable but distinct safety profiles.

- Conclusions were limited by the small number of subjects enrolled in this study and due to early study termination.