Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY APPENDIX

Inotuzumab Ozogamicin Versus Standard Care for Acute Lymphoblastic Leukemia

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Additional Methods

a. Eligibility Criteria

Patients with peripheral absolute lymphoblast count ≥10,000/μL were excluded (hydroxyurea and/or steroids/vincristine treatment within 2 weeks of randomization was allowed to reduce circulating blasts). Patients with lymphoblastic lymphoma were included provided they satisfied all eligibility criteria; patients with Burkitt lymphoma were excluded. Patients had an Eastern Cooperative Oncology Group performance status ≤2; adequate hepatic function (total serum bilirubin ≤1.5 × upper limit of normal [ULN; except for documented Gilbert syndrome; ≤2 × ULN for hepatic abnormalities considered tumor-related]; alanine aminotransferase and aspartate aminotransferase ≤2.5 × ULN); serum creatinine ≤1.5 × ULN or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 mL/min; unresponsive to prior treatment with ≥1 second/third generation TKIs and standard induction chemotherapy (patients with Ph+ ALL only); no isolated testicular or central nervous system (CNS) extramedullary relapse, active CNS leukemia or mixed phenotype ALL; no chemotherapy <2 weeks before randomization (except to reduce the circulating lymphoblast count or palliation [steroids, hydroxycarbamide, or vincristine]; for maintenance therapy [mercaptopurine, methotrexate, vincristine, thioguanine, and/or TKIs]; no monoclonal antibody treatment <6 weeks before randomization (≥2 weeks before randomization for rituximab); no allogeneic hematopoietic stem cell transplantation (HSCT) ≤4 months before randomization.

b. Recommended Dose Modifications

For each arm, treatment was delayed unless patients demonstrated the following: no evidence of progressive disease; recovery to grade 1 or baseline from treatment-related, nonhematologic AEs (except alopecia); adequate hepatic and renal function (as defined for study eligibility except ≤2 × ULN for creatinine clearance); adequate bone marrow function (for patients with pretreatment absolute neutrophil count [ANC] ≥1000/μL and platelet count ≥50,000/μL, ANC and platelet count must be equal to ≥1000/μL and ≥50,000/μL, respectively; patients with baseline ANC <1000/μL and/or platelet count <50,000/μL must recover at least to levels obtained for the prior cycle, or the most recent bone marrow assessment must demonstrate stable or improved disease and ANC and platelet count are believed to be low due to disease); average Fridericia QTc interval of ≤470 ms (confirmed before cycles 1, 2 and 4 only). For patients not meeting the above criteria, administration of InO could be delayed for ≤28 days; however, any further delay due to a treatment-related toxicity resulted in permanent treatment discontinuation. Treatment cycle 1 could be extended to 28 days for patients in CR or CRi, or to allow for recovery from toxicity. Dose delays due to treatment-related AEs lasting >7 days resulted in omission of the next dose within the treatment cycle, but patients were still eligible to receive subsequent planned doses if there were at least 6 days between doses. For patients in the InO arm whose treatment was delayed ≥14 days due to a treatment-related toxicity, InO treatment was resumed upon adequate recovery, with a 25% dose reduction to 0.375 mg/m^2 for 1 subsequent cycle; patients requiring further dose reduction received 2 rather than 3 InO doses in subsequent cycles.

c. Hematologic Remission Assessed by the Endpoint Adjudication Committee

Complete response was defined as the disappearance of leukemia as indicated by <5% marrow blasts and the absence of peripheral blasts, with recovery of hematopoiesis defined by ANC ≥1000/μL and platelets ≥100,000/μL. C1 extramedullary disease status is required; patients were considered to have C1 extramedullary disease status if the following criteria were met:

1. Complete disappearance of all measurable and nonmeasurable extramedullary disease with the exception of lesions for which the following had to be true: For patients with at least 1 measurable lesion, all nodal masses >1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤1.5 cm in GTD; all nodal masses ≥1 and ≤1.5 cm in GTD at baseline must have regressed to <1 cm GTD or they must have been reduced by 75% in sum of products of greatest diameters.

2. No new lesions.

3. Spleen and other previously enlarged organs must have regressed in size and must not be palpable.

4. All disease must be assessed using the same technique as at baseline.

CRi was defined as CR except with ANC <1000/μL and/or platelets <100,000/μL.

d. Definitions of Duration of Remission, Overall Survival and Progression-Free Survival

For patients with CR/CRi, remission duration was defined as the duration from remission to progressive disease (objective progression, relapse, treatment discontinuation due to health deterioration) or death. Overall survival was defined as the time from randomization to death due to any cause, censored at the last known alive date; progression-free survival was defined as the time from randomization to the earliest of disease progression (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), starting new induction therapy or poststudy SCT without achieving CR/CRi, or death due to any cause, censored at the last valid disease assessment. In addition, subjects with documentation of an event after an unacceptably long interval (>28 weeks if there was post-baseline disease assessment, or >12 weeks if there was no post-baseline assessment) since the previous disease assessment were censored at the time of the previous assessment (date of randomization if no post-baseline assessment).

e. Definition and Confirmation of Veno-occlusive Disease

Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) was assessed and diagnosed by the investigators and evaluated according to previously defined clinical criteria and required the occurrence of 2 or more of the following events: hyperbilirubinemia (>34 μmol/L or >2 mg/dL), ascites or sudden weight gain (>2.5% of baseline body weight), and painful hepatomegaly. Diagnosis also required no other explanation for these signs and symptoms (eg, septicemia, cyclosporine toxicity, heart failure, hepatitis). An external, blinded, independent Hepatic Events Adjudication Board

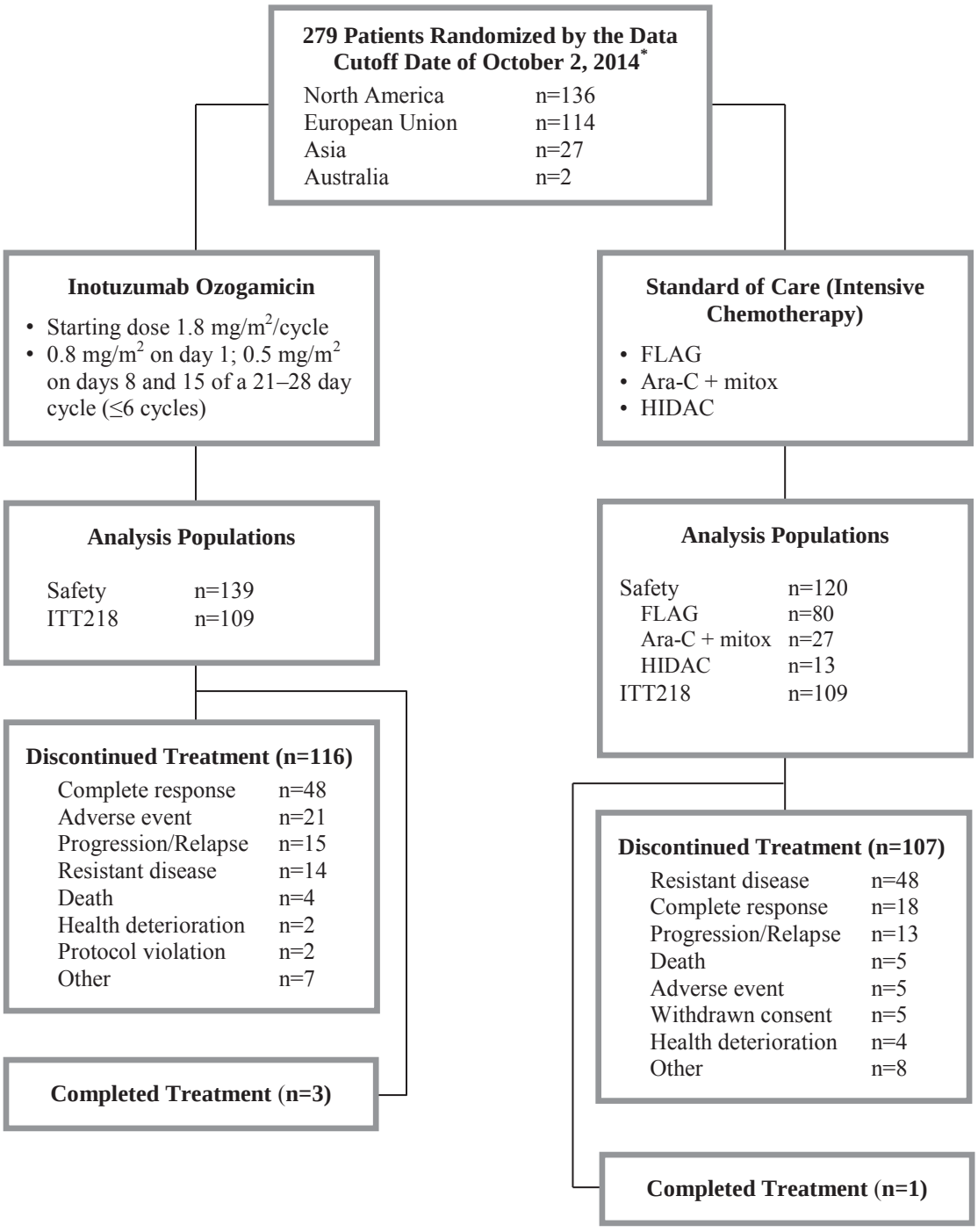
(HEAB), also reviewed all significant hepatic events, including all potential cases of VOD/SOS. The findings of the HEAB will be presented in a separate manuscript.

f. Details of Statistical Analyses

The sample size was calculated to adequately assess differences in CR/CRi and overall survival independently by splitting the 1-sided alpha of 0.025 evenly between the 2 primary endpoints. With 218 patients and 1-sided alpha of 0.0125, the study had ≥88.5% power to detect a difference in CR/CRi probabilities of 61% in the inotuzumab ozogamicin arm versus 37% in the standard care arm; with 248 overall survival events and 1-sided alpha of 0.0125, the study had 80% power to detect a difference in overall survival (median of 6.45 months in the inotuzumab ozogamicin arm and 4.30 months in the standard arm; hazard ratio [HR], 0.67). All reported *P* values are 2-sided.

Two prespecified interim analyses of overall survival for futility (first interim analysis) and efficacy and futility (second interim analysis) were performed when approximately 25% and ≥60% of the required 248 overall survival events, respectively, occurred. At both interim analyses, the External Data Monitoring Committee recommended the study be continued as planned. The final overall survival analysis was prespecified to occur after 248 events. The actual *P*-value boundaries for efficacy and futility were derived using the interpolated spending function, and were based on the actual number of overall survival events at the interim and final analyses. To account for decreases in alpha due to the 2 interim analyses, the significance level to detect a difference in the primary endpoint was adjusted to 0.0208. Progression-free survival was analyzed concurrently with the final overall survival analysis; both were stratified by randomization stratification factors.

Figure S1. Patient Disposition.

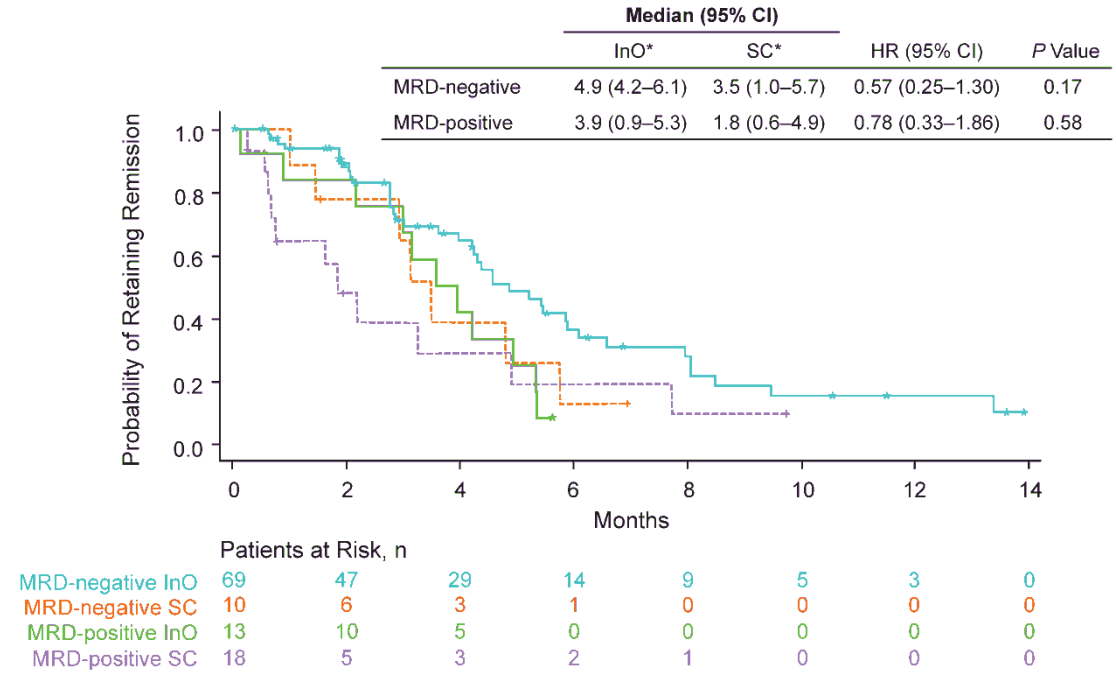


Ara-C=cytarabine; FLAG=fludarabine/

Ara-C/granulocyte-colony stimulating factor; HIDAC=high-dose Ara-C; ITT=intent-to-treat; Mitox=mitoxantrone. The ITT218 population includes the first 218 patients

randomized and is the primary population for the CR/CRi analysis. The safety population includes all randomized patients who received ≥1 dose of study drug by October 2, 2014. Patients who completed treatment received the maximum number of doses allowed per protocol. An additional 47 patients were randomized after this cut-off date for a total of 326 patients; these 47 patients were included in the survival analysis based on the ITT population of 326 patients. The prespecified requirement for >248 events to trigger the final overall survival analysis was achieved on March 8, 2016 when 252 events were observed.

Figure S2. Duration of Remission by Minimal Residual Disease Status.



HR=hazard ratio; InO=inotuzumab ozogamicin; MRD=minimal residual disease; SC=standard of care.

*Among patients achieving CR/CRi per investigator's assessment.

P values are from a 2-sided, unstratified log-rank test; HRs and corresponding 95% CIs are from unstratified Cox proportional hazard regression.

Table S1. All-Cause and Treatment-Related Treatment-Emergent Adverse Events

	InO (n=139)				SC (n=120)			
	All-Cause		Treatment-Related		All-Cause		Treatment-Related	
	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Any AE,*† n (%)	136 (98)	126 (91)	119 (86)	96 (69)	119 (99)	114 (95)	109 (91)	93 (78)
Thrombocytopenia	62 (45)	51 (37)	40 (29)	28 (20)	73 (61)	71 (59)	57 (48)	56 (47)
Neutropenia	67 (48)	64 (46)	50 (36)	47 (34)	53 (44)	50 (42)	46 (38)	43 (36)
Anemia	42 (30)	26 (19)	25 (18)	15 (11)	64 (53)	48 (40)	46 (38)	35 (29)
Nausea	44 (32)	3 (2)	21 (15)	0	56 (47)	0	41 (34)	0
Febrile neutropenia	37 (27)	33 (24)	22 (16)	20 (14)	62 (52)	59 (49)	51 (43)	48 (40)
Pyrexia	37 (27)	5 (4)	15 (11)	2 (1)	51 (43)	6 (5)	30 (25)	3 (3)
Leukopenia	38 (27)	35 (25)	23 (17)	21 (15)	47 (39)	47 (39)	31 (26)	31 (26)
Diarrhea	25 (18)	1 (1)	8 (6)	0	48 (40)	1 (1)	27 (23)	1 (1)
Headache	39 (28)	2 (1)	13 (9)	1 (1)	33 (28)	0	9 (8)	0
Lymphopenia	24 (17)	22 (16)	15 (11)	15 (11)	34 (28)	34 (28)	22 (18)	22 (18)
Vomiting	24 (17)	1 (1)	10 (7)	0	28 (23)	0	19 (16)	0
Constipation	23 (17)	0	9 (7)	0	28 (33)	0	9 (8)	0
Fatigue	31 (22)	4 (3)	13 (9)	2 (1)	17 (14)	2 (2)	12 (10)	1 (1)
Hypokalemia	23 (17)	10 (7)	7 (5)	3 (2)	23 (19)	3 (3)	11 (9)	2 (2)
AST increased	28 (20)	7 (5)	13 (9)	1 (1)	12 (10)	4 (3)	5 (4)	1 (1)
Insomnia	21 (15)	0	6 (4)	0	18 (15)	0	2 (2)	0
Abdominal pain	19 (14)	3 (2)	5 (4)	1 (1)	20 (17)	1 (1)	11 (9)	1 (1)
Rash	13 (9)	0	4 (3)	0	23 (19)	0	13 (11)	0
Cough	15 (11)	0	0	0	21 (18)	1 (1)	4 (3)	0
GGT increased	24 (17)	12 (9)	16 (12)	6 (4)	9 (8)	5 (4)	1 (1)	1 (1)
Hyperbilirubinemia	21 (15)	5 (4)	10 (7)	4 (3)	12 (10)	4 (3)	6 (5)	3 (3)
Epistaxis	21 (15)	1 (1)	5 (4)	1 (1)	11 (9)	2 (2)	3 (3)	0

ALT increased	19 (14)	4 (3)	10 (7)	1 (1)	13 (11)	4 (3)	5 (4)	0
Hypotension	11 (8)	0	3 (2)	0	20 (17)	5 (4)	4 (3)	1 (1)
Appetite decreased	13 (9)	2 (1)	6 (4)	2 (1)	16 (13)	3 (3)	12 (10)	2 (2)
Chills	14 (10)	0	6 (4)	0	14 (12)	0	8 (7)	0
Pain in extremity	12 (9)	0	0	0	15 (13)	1 (1)	4 (3)	1 (1)
Dizziness	12 (9)	0	3 (2)	0	13 (11)	0	4 (3)	0
Asthenia	13 (9)	3 (2)	5 (4)	2 (1)	12 (10)	2 (2)	5 (4)	0
Peripheral edema	12 (9)	1 (1)	1 (1)	0	12 (10)	0	3 (3)	0
Dyspnea	7 (5)	1 (1)	1 (1)	0	16 (13)	2 (2)	4 (3)	0
ALP increased	16 (12)	2 (1)	8 (6)	1 (1)	7 (6)	1 (1)	4 (3)	1 (1)
Hypocalcemia	11 (8)	2 (1)	2 (1)	1 (1)	12 (10)	3 (3)	3 (3)	1 (1)
Mucosal inflammation	5 (4)	1 (1)	3 (2)	1 (1)	15 (13)	3 (3)	11 (9)	2 (2)
Tachycardia	6 (4)	0	1 (1)	0	12 (10)	1 (1)	2 (2)	0
VOD	15 (11)	13 (9)	13 (9)	11 (8)	1 (1)	1 (1)	0	0
Lipase increased	14 (10)	6 (4)	10 (7)	4 (3)	0	0	0	0

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase; InO=inotuzumab ozogamicin; SC=standard of care; VOD=veno-occlusive disease.

*Data represent the safety population (data cutoff date of October 2, 2014); adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

†All-cause AEs with ≥10% incidence occurring in either arm in the safety population (any treatment cycle) in descending order of total frequency across arms.

Table S2. Association of Patient Characteristics at Baseline and at SCT with VOD Occurrence in Patients Receiving InO

Characteristic	Estimate	*P* Value	Odds Ratio (95% CI)
Univariate analysis			
Age (≥55 y [n=12] vs <55 y [n=36])	0.92	0.23	2.5 (0.6−11.1)
ECOG performance status (2 [n=5] vs <2 [n=43)	−0.06	0.96	0.94 (0.1−9.5)
Duration* (continuous [n=48])	0.00	0.81	1.0 (1.0−1.0)
Dual vs single alkylator conditioning (n=9 vs n=34)	1.79	0.04	6.0 (1.1−32.1)
Busulfan containing conditioning regimen (yes [n=9] vs no [n=39])	1.48	0.07	4.4 (0.9−21.3)
Type of SCT (myeloablative [n=33] vs nonmyeloablative [n=15])	0.07	0.92	1.1 (0.2−4.9)
SCT donor (alternative [n=32] vs matched related [n=15])	1.70	0.13	5.5 (0.6−48.0)
Prior SCT (yes [n=7] vs no [n=41])	1.29	0.14	3.6 (0.7−20.0)
Number of treatment cycles received (continuous [n=48])	0.06	0.86	1.1 (0.6−2.0)
Salvage status (≥2 [n=11] vs 1 [n=36])	1.05	0.17	2.9 (0.6−12.9)
Liver function test abnormalities† (yes [n=24] vs no [n=24])	−0.51	0.48	0.6 (0.1−2.5)
History of liver disease/hepatitis (yes [n=16] vs no [n=32])	0.90	0.22	2.5 (0.6−10.2)
Multivariate analysis			
Dual vs single alkylator conditioning (n=8 vs n=33)	1.72	0.04	5.6 (1.0−30.1)

ECOG=Eastern Cooperative Oncology Group; InO=inotuzumab ozogamicin; SCT=stem cell transplant; TBI=total body irradiation; VOD=veno-occlusive disease.

The second level is the reference level for interpretation of odds ratios for categorical factors.

*Time from last dose of study treatment to first date of conditioning.

†Includes alanine/aspartate aminotransferase and bilirubin elevations.