Inotuzumab Ozogamicin for Relapsed/Refractory Acute Lymphoblastic Leukemia in the INO-VATE Trial: CD22 Pharmacodynamics, Efficacy and Safety by Baseline CD22

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Supplementary Materials

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Laboratory Method for CD22 Molecules of Equivalent Soluble Fluorochrome (MESF) Assay

MESF values were calculated using QuantiBRITE PE Fluorescence Quantitation Kit (BD Biosciences, CA, USA). Each lot-specific QuantiBRITE PE tube contains a lyophilized pellet of beads conjugated with four known concentration levels of phycoerythrin (PE). The QuantiBRITE PE tubes were reconstituted and analyzed at the same instrument settings as sample of interest on a BD FACSCanto II flow cytometer. 10,000 PE bead events were collected and when displayed on PE-fluorescence histogram, four peaks are exhibited by fluorescence intensities, corresponding to the varying concentration levels of PE. With the fluorescent intensities of PE bead populations and values of PE molecules per bead (provided with kit), a calibration curve can be extrapolated that enables MFI values to be converted into PE molecules bound or MESF unit. Using this formula, MESF was calculated for CD22 on cells of B-cell acute lymphoblastic leukemia. At the time the study was performed, there were no data available correlating CD22 expression with clinical benefit from which a threshold defining positive versus negative could be established. No desirable established threshold was used. The percentage of CD22 positivity was quantified using the Fluorescence Minus One (FMO) control and reported as such; the characterization (positive or negative) of marker expression was assessed qualitatively by the overall expression shift.

Supplementary Table 1. Inotuzumab ozogamicin exposure

		CD22 MESF quartiles per central laboratory					CD22 positivity quartiles per local laboratory				
	Total	**Q1**	**Q2**	**Q3**	**Q4**	**Q2–4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q2–4**
	N=164	N=30	N=38	N=41	N=33	N=112	N=38	N=38	N=41	N=35	N=114
Dose reduction, n (%)											
0	143 (87.2)	24 (80.0)	34 (89.5)	35 (85.4)	29 (87.9)	98 (87.5)	34 (89.5)	33 (86.8)	34 (82.9)	30 (85.7)	97 (85.1)
≥1	21 (12.8)	6 (20.0)	4 (10.5)	6 (14.6)	4 (12.1)	14 (12.5)	4 (10.5)	5 (13.2)	7 (17.1)	5 (14.3)	17 (14.9)
Dose delay, n (%)											
0	91 (55.5)	14 (46.7)	17 (44.7)	22 (53.7)	23 (69.7)	62 (55.4)	20 (52.6)	22 (57.9)	23 (56.1)	18 (51.4)	63 (55.3)
≥1	73 (44.5)	16 (53.3)	21 (55.3)	19 (46.3)	10 (30.3)	50 (44.6)	18 (47.4)	16 (42.1)	18 (43.9)	17 (48.6)	51 (44.7)
Actual overall dose (mg/m^2)											
Mean (SD)	4.32 (2.31)	4.42 (2.21)	4.52 (1.98)	4.32 (2.22)	4.06 (2.44)	4.31 (2.20)	4.35 (2.08)	4.53 (2.54)	4.61 (2.44)	4.09 (2.10)	4.42 (2.36)
Median (range)	4.22 (0.78–9.59)	4.21 (1.33–9.16)	4.52 (0.82–9.18)	4.20 (0.79–9.29)	4.64 (0.78–9.59)	4.30 (0.78–9.59)	4.27 (0.82–9.59)	4.51 (0.81–9.46)	3.81 (0.78–9.59)	4.38 (0.79–9.09)	4.32 (0.78–9.59)
Actual dose intensity (mg/m^2/cycle)											
Mean (SD)	1.54 (0.32)	1.58 (0.28)	1.55 (0.28)	1.55 (0.32)	1.48 (0.37)	1.53 (0.32)	1.58 (0.27)	1.58 (0.33)	1.49 (0.33)	1.50 (0.31)	1.52 (0.32)
Median (range)	1.58 (0.77–2.06)	1.57 (1.06–2.06)	1.53 (0.81–2.03)	1.61 (0.77–1.99)	1.58 (0.78–1.91)	1.58 (0.77–2.03)	1.60 (0.82–1.94)	1.66 (0.80–2.06)	1.50 (0.77–2.01)	1.50 (0.79–1.99)	1.55 (0.77–2.06)

MESF, molecules of equivalent soluble fluorochrome; SD, standard deviation.

Supplementary Table 2. Overall and the most common TEAEs and SAEs leading to dose delays and dose reduction by CD22 expression (MESF quartiles) per central laboratory

	InO	SC	Total
Dose delays, n (%)*			
CD22 MESF Q1	N=30	N=33	N=63
Any AEs	14 (46.7)	7 (21.2)	21 (33.3)
Thrombocytopenia	6 (20.0)	1 (3.0)	7 (11.1)
Neutropenia	6 (20.0)	0	6 (9.5)
Any SAEs	4 (13.3)	3 (9.1)	7 (11.1)
Febrile neutropenia	1 (3.3)	1 (3.0)	2 (3.2)
Neutropenic sepsis	1 (3.3)	0	1 (1.6)
Pyrexia	1 (3.3)	0	1 (1.6)
Stomatitis	1 (3.3)	0	1 (1.6)
Sepsis	0	1 (3.0)	1 (1.6)
Thrombophlebitis	0	1 (3.0)	1 (1.6)
CD22 MESF Q2	N=38	N=27	N=65
Any AEs	20 (52.6)	6 (22.2)	26 (40.0)
Neutropenia	7 (18.4)	0	7 (10.8)
Febrile neutropenia	4 (10.5)	1 (3.7)	5 (7.7)
Thrombocytopenia	3 (7.9)	0	3 (4.6)
Any SAEs	8 (21.1)	1 (3.7)	9 (13.8)
Febrile neutropenia	2 (5.3)	1 (3.7)	3 (4.6)
CD22 MESF Q3	N=41	N=25	N=66
Any AEs	18 (43.9)	2 (8.0)	20 (30.3)
Neutropenia	9 (22.0)	0	9 (13.6)
Hyperbilirubinaemia	4 (9.8)	0	4 (6.1)
Alanine aminotransferase increased	2 (4.9)	0	2 (3.0)
Aspartate aminotransferase increased	2 (4.9)	0	2 (3.0)
Febrile neutropenia	2 (4.9)	0	2 (3.0)
Any SAEs	7 (17.1)	1 (4.0)	8 (12.1)
Febrile neutropenia	2 (4.9)	0	2 (3.0)
CD22 MESF Q4	N=33	N=32	N=65
Any AEs	13 (39.4)	1 (3.1)	14 (21.5)
Gamma-glutamyltransferase increased	5 (15.2)	0	5 (7.7)
Aspartate aminotransferase increased	4 (12.1)	0	4 (6.2)
Alanine aminotransferase increased	3 (9.1)	0	3 (4.6)
Thrombocytopenia	3 (9.1)	0	3 (4.6)
Blood alkaline phosphatase increased	2 (6.1)	0	2 (3.1)
Any SAEs	4 (12.1)	0	4 (6.2)
Septic shock	2 (6.1)	0	2 (3.1)
CD22 MESF Q2–4	N=112	N=84	N=196
Any AEs	51 (45.5)	9 (10.7)	60 (30.6)
Neutropenia	17 (15.2)	0	17 (8.7)
Febrile neutropenia	7 (6.3)	1 (1.2)	8 (4.1)
Aspartate aminotransferase increased	7 (6.3)	0	7 (3.6)
Gamma-glutamyltransferase increased	7 (6.3)	0	7 (3.6)
Thrombocytopenia	7 (6.3)	0	7 (3.6)
Alanine aminotransferase increased	5 (4.5)	1 (1.2)	6 (3.1)
Hyperbilirubinaemia	5 (4.5)	1 (1.2)	6 (3.1)
Blood alkaline phosphatase increased	3 (2.7)	0	3 (1.5)
Pneumonia	3 (2.7)	0	3 (1.5)

Pyrexia	2 (1.8)	1 (1.2)	3 (1.5)
Asthenia	2 (1.8)	0	2 (1.0)
Any SAEs	19 (17.0)	2 (2.4)	21 (10.7)
Febrile neutropenia	5 (4.5)	1 (1.2)	6 (3.1)
Pneumonia	3 (2.7)	0	3 (1.5)
Septic shock	2 (1.8)	0	2 (1.0)
Dose reduction, n (%)*			
CD22 MESF Q1	N=30	N=33	N=63
Any AEs	3 (10.0)	1 (3.0)	4 (6.3)
Neutropenia	2 (6.7)	0	2 (3.2)
Alanine aminotransferase increased	1 (3.3)	0	1 (1.6)
Platelet count decreased	1 (3.3)	0	1 (1.6)
Systemic infection	0	1 (3.0)	1 (1.6)
Any SAEs	0	0	0
CD22 MESF Q2	N=38	N=27	N=65
Any AEs	1 (2.6)	1 (3.7)	2 (3.1)
Thrombocytopenia	1 (2.6)	0	1 (1.5)
Headache	0	1 (3.7)	1 (1.5)
Pain in extremity	0	1 (3.7)	1 (1.5)
Any SAEs	0	0	0
CD22 MESF Q3	N=41	N=25	N=66
Any AEs	0	1 (4.0)	1 (1.5)
Sepsis	0	1 (4.0)	1 (1.5)
Any SAEs	0	1 (4.0)	1 (1.5)
Sepsis	0	1 (4.0)	1 (1.5)
CD22 MESF Q4	N=33	N=32	N=65
Any AEs	1 (3.0)	0	1 (1.5)
Aspartate aminotransferase increased	1 (3.0)	0	1 (1.5)
Any SAEs	0	0	0
CD22 MESF Q2–4	N=112	N=84	N=196
Any AEs	2 (1.8)	2 (2.4)	4 (2.0)
Aspartate aminotransferase increased	1 (0.9)	0	1 (0.5)
Thrombocytopenia	1 (0.9)	0	1 (0.5)
Headache	0	1 (1.2)	1 (0.5)
Pain in extremity	0	1 (1.2)	1 (0.5)
Sepsis	0	1 (1.2)	1 (0.5)
Any SAEs	0	1 (1.2)	1 (0.5)
Sepsis	0	1 (1.2)	1 (0.5)

* A patient may have more than 1 dose reductions and/or treatment delays.

TEAEs were defined as AEs that started on or after Cycle 1 Day 1 but within 42 days of the last dose and all treatment-related AEs thereafter. All SOS/VOD events within 2 years of randomization date regardless of causal attribution to study therapy were included. Medical Dictionary for Regulatory Activities (v19.1) coding dictionary is applied.

AE, adverse event; InO, inotuzumab ozogamicin; MESF, molecules of equivalent soluble fluorochrome; Q, quartile; SAE, serious AE; SC, standard of care chemotherapy; SOS, sinusoidal obstruction syndrome; TEAE, treatment-emergent AE; VOD, veno-occlusive disease.

Supplementary Table 3. Patient response to treatment in the ITT population by CD22 positivity per central laboratory

	InO	SC	Rate difference, % (97.5% CI)	*P* value
Baseline CD22 positivity ≥90%				
N	107	93		
CR/CRi, % (95% CI)	78.5 (69.5–85.9)	35.5 (25.8–46.1)	43.0 (28.8–57.3)	<0.0001
CR, % (95% CI)	42.1 (32.6–52.0)	16.1 (9.3–25.2)	25.9 (12.2–39.6)	<0.0001
CRi, % (95% CI)	36.4 (27.4–46.3)	19.4 (11.9–28.9)	17.1 (3.2–31.0)	0.0038
Baseline CD22 positivity <90%				
N	35	36		
CR/CRi, % (95% CI)	65.7 (47.8–80.9)	30.6 (16.3–48.1)	35.2 (10.3–60.0)	0.0015
CR, % (95% CI)	20.0 (8.4–36.9)	19.4 (8.2–36.0)	0.6 (−20.6–21.7)	0.4765
CRi, % (95% CI)	45.7 (28.8–63.4)	11.1 (3.1–26.1)	34.6 (12.4–56.8)	0.0012

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; InO, inotuzumab ozogamicin; ITT, intent to treat; SC, standard of care chemotherapy.

Supplementary Table 4. Efficacy measures by CD22 positivity quartile per local laboratory

	Q1	Q2	Q3	Q4	Q2–4
InO, n	38	38	41	35	114
SC, n	34	38	37	43	118
CR/CRi, n (%)					
InO*	31 (81.58)	26 (68.42)	30 (73.17)	27 (77.14)	83 (72.81)
SC*	14 (41.18)	14 (36.84)	10 (27.03)	9 (20.93)	33 (27.97)
P†	0.0002	0.0029	<0.0001	<0.0001	NE
MRD-negative among patients achieving CR/CRi, n (%)					
InO	27 (87.1)	18 (69.2)	20 (66.7)	21 (77.8)	59 (71.08)
SC	7 (50.0)	3 (21.4)	3 (30.0)	5 (55.6)	11 (33.33)
P†	0.0121	0.0048	0.0486	0.1930	NE
DoR, median (95% CI), months					
InO	5.9 (4.2–11.5)	4.0 (2.3–6.0)	5.4 (3.9–12.9)	5.2 (3.2–9.2)	4.9 (3.9–6.6)
SC	6.8 (0.8–9.2)	3.5 (0.7–6.9)	3.1 (0.3–8.0)	2.7 (0.2–4.8)	3.1 (1.6–4.9)
HR‡ (97.5% CI)	0.834 (0.325–2.139)	0.935 (0.414–2.110)	0.517 (0.189–1.416)	0.257 (0.094–0.702)	0.525 (0.312–0.882)
P‡	0.3320	0.4262	0.0677	0.0006	0.0023
PFS, median (95% CI), months					
InO	5.8 (3.9–9.4)	3.3 (2.6–4.8)	5.7 (2.9–7.1)	5.1 (3.4–8.0)	4.8 (3.4–5.7)
SC	2.3 (1.5–5.6)	2.0 (1.2–3.1)	1.7 (1.3–2.6)	1.4 (1.2–1.8)	1.6 (1.3–2.1)
HR‡ (97.5% CI)	0.493 (0.258–0.940)	0.745 (0.426–1.302)	0.393 (0.212–0.731)	0.261 (0.136–0.501)	0.436 (0.311–0.613)
P‡	0.0060	0.1168	0.0002	<0.0001	<0.0001
OS, median (95% CI), months					
InO	8.6 (5.6–16.5)	5.8 (3.9–9.4)	7.7 (5.6–13.4)	9.3 (5.0–13.3)	7.2 (5.7–9.4)
SC	12.2 (6.9–14.5)	8.0 (2.9–14.2)	5.3 (3.1–7.7)	5.5 (4.1–7.8)	5.6 (4.5–7.7)
HR‡ (97.5% CI)	0.801 (0.431–1.487)	1.051 (0.601–1.838)	0.515 (0.290–0.913)	0.624 (0.350–1.114)	0.713 (0.515–0.987)
P‡	0.2102	0.5792	0.0040	0.0325	0.0094

* Differences were not significant among quartiles in the InO (*P*=0.5906) or SC arm (*P*=0.2061); *P* values are from two-sided Chi-square test or Fisher's exact test (if any cell count is <5).

† *P* values are from one-sided Chi-square test or Fisher's exact test (if any cell count is < 5).

‡ HR, unstratified; *P* value, from 1-sided unstratified log-rank test.

CI, confidence interval; CR, complete remission; CRi, CR with incomplete hematologic recovery; DoR, duration of remission; HR, hazard ratio; InO, inotuzumab ozogamicin; MRD, minimal residual disease; NE, not estimated; OS, overall survival; PFS, progression-free survival; Q, quartile; SC, standard of care chemotherapy.

Supplementary Table 5. Percentage of leukemic blasts CD22-positive by response status

	INO-VATE				Phase 1/2 Study
	Responders*		Non-responders*		Responders*
	InO (N=24)	SC (N=14)	InO (N=43)	SC (N=112)	InO (N=24)
CD22 leukemic blasts, n (%)					
Baseline					
≥90%	15 (62.5)	13 (92.9)	23 (53.5)	60 (53.6)	19 (79.2)
≥70–<90	5 (20.8)	0	10 (23.3)	13 (11.6)	3 (12.5)
>0–<70	2 (8.3)	1 (7.1)	2 (4.7)	12 (10.7)	2 (8.3)
0	0	0	0	0	0
Not evaluable	1 (4.2)	0	1 (2.3)	4 (3.6)	0
Missing	1 (4.2)	0	7 (16.3)	23 (20.5)	0
EOT/Relapse†					
≥90%	1 (4.2)	4 (28.6)	2 (4.7)	12 (10.7)	3 (12.5)
≥70–<90	1 (4.2)	2 (14.3)	0	2 (1.8)	2 (8.3)
>0–<70	8 (33.3)	0	3 (7.0)	2 (1.8)	5 (20.8)
0	0	0	0	0	4 (16.7)
Not evaluable	2 (8.3)	0	1 (2.3)	2 (1.8)	0
Missing	12 (50.0)	8 (57.1)	37 (86.0)	94 (83.9)	10 (41.7)
CD22 expression as MESF					
Baseline	N=20	N=14	N=29	N=65	N=18
Median	3795.0	4641.5	4125.0	2963.0	178291.0
Range	853–10947	470–10226	442–26812	199–45371	145172–218104
EOT/Relapse	N=10	N=6	N=5	N=16	N=14
Median	275.5	3694.5	873.0	3242.5	119445.5
Range	74–4438	753–5027	234–3766	381–28748	0–190567

* Responders included patients who achieved CR or CRi but subsequently relapsed; non-responders included patients who did not achieve CR or CRi.

†Relapse only applicable for responders (i.e., patients who responded to treatment and subsequently relapsed).

CR, complete remission; CRi, complete remission with incomplete hematologic recovery; EOT, end of treatment; InO, inotuzumab ozogamicin; MESF, molecules of equivalent soluble fluorochrome; SC, standard of care.

Supplementary Table 6. Correlation between baseline CD22-positive leukemic blasts (%) level and cytogenetics in the ITT population per central laboratory

	CD22-positive leukemic blasts at baseline			
	≥90%	**<90%**	**Missing data**	***P****
Overall	**N=200**	**N=71**	**N=55**	
KMT2A−	130 (65.0)	36 (50.7)	11 (20.0)	0.0466
KMT2A missing	43 (21.5)	13 (18.3)	43 (78.2)	0.6132
Any KMT2A abnormality (KMT2A+)	27 (13.5)	22 (31.0)	1 (1.8)	0.0020
KMT2A rearrangements	7 (3.5)	12 (16.9)	0	0.0005
t(4;11)	3 (1.5)	11 (15.5)	0	<0.0001
Normal with metaphases analyzed ≥20	40 (20.0)	14 (19.7)	15 (27.3)	1.0000
Ph+	29 (14.5)	15 (21.1)	5 (9.1)	0.1951
Complex	35 (17.5)	10 (14.1)	5 (9.1)	0.5809
InO	N=107	N=35	N=22	
KMT2A−	69 (64.5)	18 (51.4)	3 (13.6)	0.2301
KMT2A missing	26 (24.3)	6 (17.1)	19 (86.4)	0.4870
Any KMT2A abnormality (KMT2A+)	12 (11.2)	11 (31.4)	0	0.0080
KMT2A rearrangements	4 (3.7)	7 (20.0)	0	0.0050
t(4;11)	0	6 (17.1)	0	0.0002
Normal with metaphases analyzed ≥20	24 (22.4)	6 (17.1)	5 (22.7)	0.6358
Ph+	14 (13.1)	6 (17.1)	2 (9.1)	0.5794
Complex	21 (19.6)	5 (14.3)	2 (9.1)	0.6173
SC	N=93	N=36	N=33	
KMT2A−	61 (65.6)	18 (50.0)	8 (24.2)	0.1119
KMT2A missing	17 (18.3)	7 (19.4)	24 (72.7)	1.0000
Any KMT2A abnormality (KMT2A+)	15 (16.1)	11 (30.6)	1 (3.0)	0.0869
KMT2A rearrangements	3 (3.2)	5 (13.9)	0	0.0381
t(4;11)	3 (3.2)	5 (13.9)	0	0.0381
Normal with metaphases analyzed ≥20	16 (17.2)	8 (22.2)	10 (30.3)	0.6145
Ph+	15 (16.1)	9 (25.0)	3 (9.1)	0.3129
Complex	14 (15.1)	5 (13.9)	3 (9.1)	1.0000

Values are n or n (%).

KMT2A by central laboratory FISH analysis (KMT2A ≥1%), except for t(4;11), which was assessed locally by karyotyping. Ph+ status by central laboratory FISH analysis (*BCR ABL* ≥7%) or local laboratory results or medical history (if both central FISH or local results missing).

*2-sided *P*-value from Fisher's exact test that was used to compare rates between CD22 ≥90% and CD22 <90% subgroups, patients with missing baseline CD22 data were excluded from the calculation.

FISH, fluorescence *in situ* hybridization; InO, inotuzumab ozogamicin; ITT, intent to treat; KMT2A, histone-lysine N-methyltransferase 2A; Ph+, Philadelphia chromosome–positive; SC, standard of care chemotherapy.

Supplementary Table 7. Correlation between baseline CD22 Expression (MESF) per central laboratory and cytogenetics - ITT population

	N	MESF		*P* value*
		Mean (SD)	Median (range)	
Normal cytogenetics				
InO	30	4538.1 (3223.0)	3903.5 (971.0–17100.0)	NA
SC	24	3541.3 (3349.2)	1847.0 (118.0–11920.0)	NA
Total	54	4095.1 (3286.6)	3586.5 (118.0–17100.0)	NA
KMT2A Rearrangement				
InO	11	1878.9 (1344.8)	1327.0 (442.0–5236.0)	0.0120
SC	8	1482.0 (1698.0)	608.0 (119.0–5122.0)	0.1080
Total	19	1711.8 (1471.9)	1289.0 (119.0–5236.0)	0.0033
KMT2A t(4;11)				
InO	6	992.8 (586.1)	1048.0 (259.0–1833.0)	0.0120
SC	8	2060.9 (2492.5)	608.0 (119.0–6603.0)	0.2617
Total	14	1603.1 (1943.7)	762.0 (119.0–6603.0)	0.0086

KMT2A Rearrangements by central laboratory break-apart FISH analysis (KMT2A ≥1%); t(4;11) assessed locally by karyotyping displayed separately.

**P* value based on pairwise comparison of t(4;11) versus normal cytogenetics, KMT2A+/ Rearrangement versus normal cytogenetics.

FISH, fluorescence *in situ* hybridization; InO, inotuzumab ozogamicin; ITT, intent to treat; KMT2A, histone-lysine N-methyltransferase 2A; SC, standard of care chemotherapy; SD, standard deviation.

Supplementary Table 8. Overall survival by level of CD22 expression and cytogenetics status in the ITT population

	N	Number of deaths	Overall survival in months, median (95% CI)	Unstratified HR (97.5% CI)*	*P* value†
CD22-positive ≥90% with normal cytogenetics					
InO	24	14	8.7 (7.1–NE)		
SC	16	15	4.5 (2.0–9.4)		
				0.308 (0.130–0.729)	0.0006
CD22-positive <90% with normal cytogenetics					
InO	6	5	6.5 (4.8–NE)		
SC	8	6	12.2 (1.6–27.8)		
				1.310 (0.301–5.701)	0.6601
CD22-positive ≥90% with KMT2A-					
InO	69	50	8.6 (6.0–13.3)		
SC	61	51	6.8 (4.6–9.1)		
				0.639 (0.407–1.002)	0.0121
CD22-positive <90% with KMT2A-					
InO	18	17	5.2 (3.0–8.6)		
SC	18	14	12.2 (1.6–18.8)		
				1.704 (0.734–3.955)	0.9246
CD22-positive ≥90% with KMT2A+/Rearrangement					
InO	4	4	5.5 (2.2–10.3)		
SC	3	3	6.0 (5.5–22.0)		
				1.852 (0.260–13.198)	0.7624
CD22-positive <90% with KMT2A+/Rearrangement					
InO	7	7	5.8 (2.2–7.4)		
SC	5	5	2.5 (1.0–14.5)		
				1.494 (0.304–7.341)	0.7151

* Cox proportional hazards model was used.

† One-sided unstratified log rank test.

InO, inotuzumab ozogamicin; ITT, intent to treat; KMT2A, histone-lysine N-methyltransferase 2A; NE, not evaluable; OS, overall survival; SC, standard of care chemotherapy.

Supplementary Table 9. Selected ≥grade 3 treatment-emergent adverse events by CD22 positivity quartiles per local laboratory

	CD22 positivity quartile							
	Q1		Q2		Q3		Q4	
TEAEs, n (%)	InO N=38	SC N=31	InO N=38	SC N=34	InO N=41	SC N=31	InO N=35	SC N=37
Any AEs	34 (89.5)	30 (96.8)	33 (86.8)	34 (100)	40 (97.6)	31 (100)	32 (91.4)	34 (91.9)
Neutropenia	20 (52.6)	16 (51.6)	18 (47.4)	19 (55.9)	16 (39.0)	11 (35.5)	17 (48.6)	15 (40.5)
Thrombocytopenia	13 (34.2)	17 (54.8)	17 (44.7)	23 (67.6)	19 (46.3)	17 (54.8)	11 (31.4)	24 (64.9)
Leukopenia	10 (26.3)	9 (29.0)	12 (31.6)	18 (52.9)	12 (29.3)	10 (32.3)	7 (20.0)	14 (37.8)
Lymphopenia	7 (18.4)	7 (22.6)	8 (21.1)	10 (29.4)	6 (14.6)	9 (29.0)	3 (8.6)	7 (18.9)
Febrile neutropenia	6 (15.8)	16 (51.6)	11 (28.9)	16 (47.1)	12 (29.3)	18 (58.1)	12 (34.3)	23 (62.2)
Infection	8 (21.1)	15 (48.4)	10 (26.3)	23 (67.6)	15 (36.6)	17 (54.8)	11 (31.4)	19 (51.4)
Hyperbilirubinemia	2 (5.3)	2 (6.5)	3 (7.9)	3 (8.8)	1 (2.4)	2 (6.5)	4 (11.4)	2 (5.4)
SOS/VOD	5 (13.2)	0	3 (7.9)	0	3 (7.3)	0	6 (17.1)	3 (8.1)
Grade 3	2 (5.3)	0	1 (2.6)	0	2 (4.9)	0	2 (5.7)	3 (8.1)
Grade 4	0	0	2 (5.3)	0	1 (2.4)	0	2 (5.7)	0
Grade 5	3 (7.9)	0	0	0	0	0	2 (5.7)	0

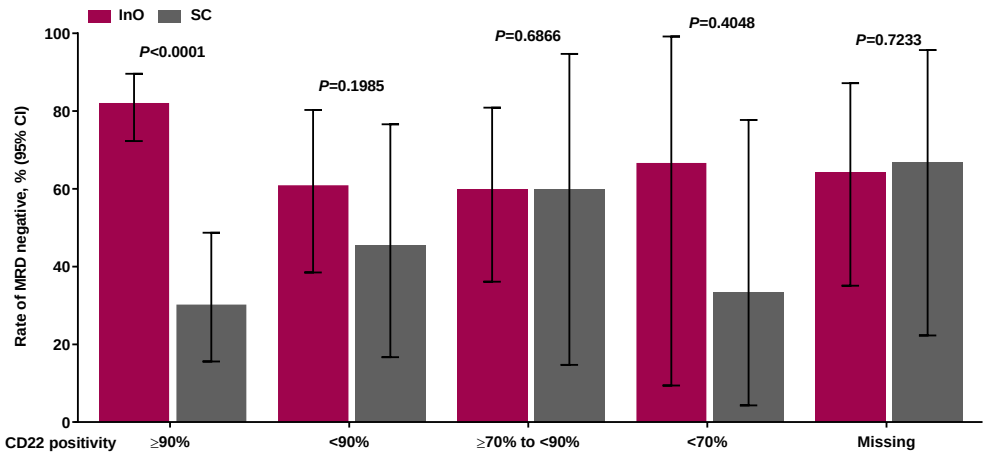
TEAEs were defined as AEs that commence on or after Cycle 1 Day 1 but within 42 days of last dose and all treatment-related AEs thereafter. All SOS/VOD events within 2 years of randomization were included regardless of causality. MedDRA (v19.1) coding dictionary was applied. AEs were graded according to the NCI CTCAE, version 3.0.

*No Grade 5 neutropenia, thrombocytopenia, or febrile neutropenia occurred.

AE, adverse event; InO, inotuzumab ozogamicin; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; Q, quartile; TEAE, treatment-emergent adverse event; SOS/VOD, sinusoidal obstruction syndrome/veno-occlusive disease.

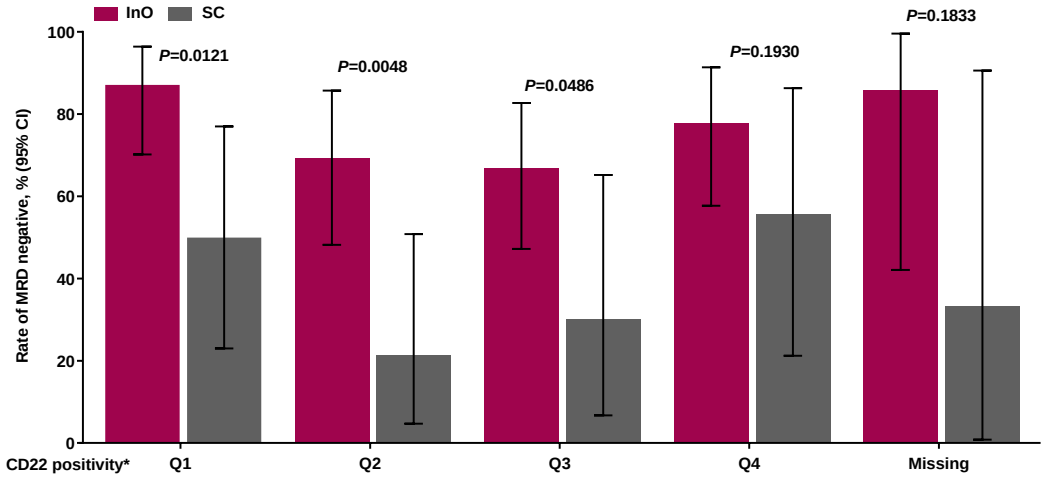
Supplementary Figure 1. Rate of MRD negativity in responding patients

S1A. By central laboratory CD22 positivity



CD22 positivity	≥90%	<90%	≥70% to <90%	<70%	Missing
Responding patients / Total number of patients					
InO	84/107	23/35	20/30	3/5	14/22
SC	33/85	11/32	5/15	6/17	6/26
MRD negative, n (%)					
InO	69 (82.1)	14 (60.9)	12 (60.0)	2 (66.7)	9 (64.3)
SC	10 (30.3)	5 (45.5)	3 (60.0)	2 (33.3)	4 (66.7)

S1B. By CD22 positivity quartile per local laboratory

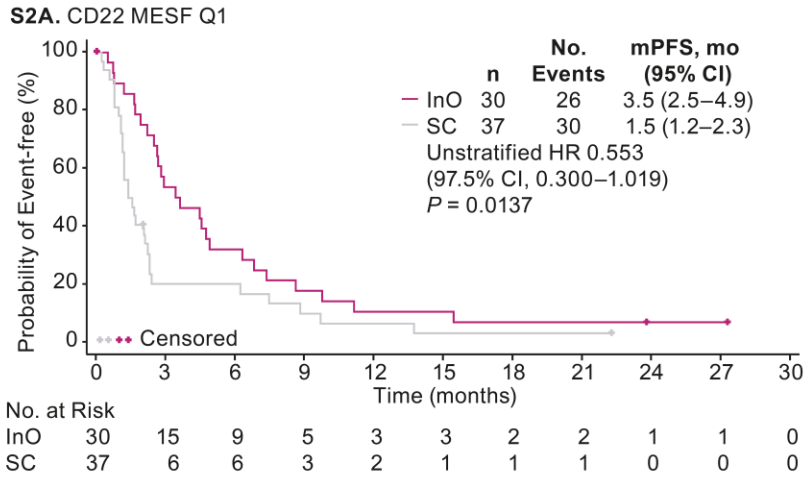


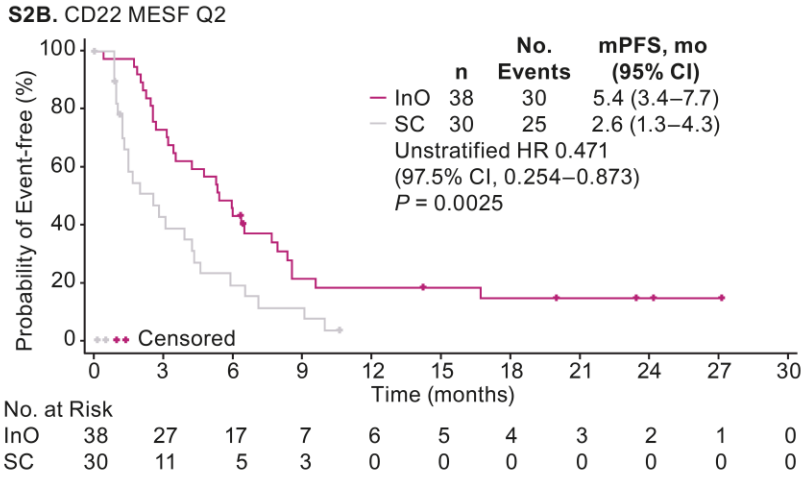
CD22 positivity*	Q1	Q2	Q3	Q4	Missing
Responding patients / Total number of patients					
InO	31/38	26/38	30/41	27/35	7/12
SC	14/31	14/34	10/31	9/37	3/10
MRD negative, n (%)					
InO	27 (87.1)	18 (69.2)	20 (66.7)	21 (77.8)	6 (85.7)
SC	7 (50.0)	3 (21.4)	3 (30.0)	5 (55.6)	1 (33.3)

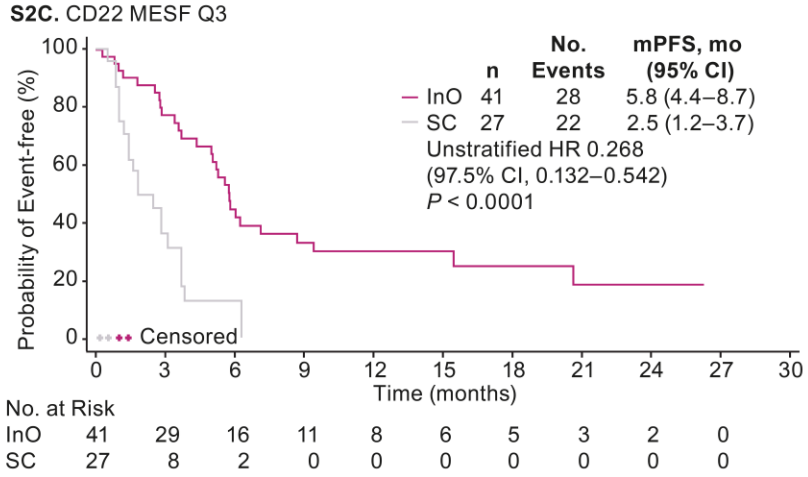
* CD22 positivity quartile per local laboratory.

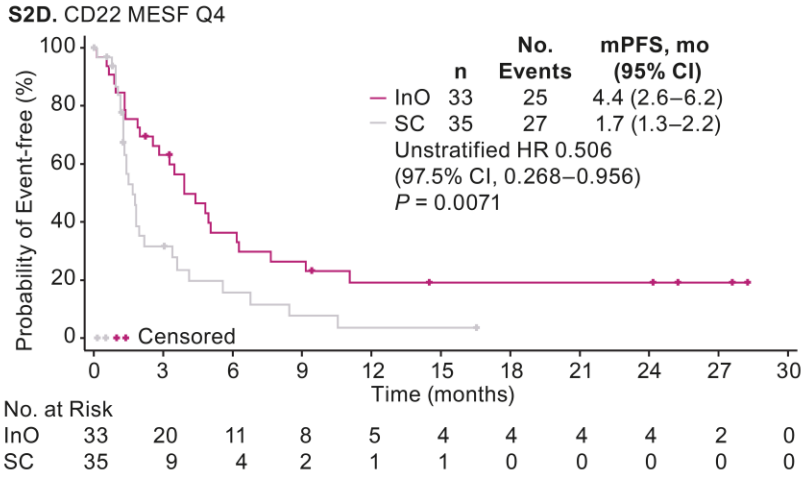
One-sided *P* value for MRD-negative was based on the test conducted on the MRD-negative rates between the two treatment groups. Minimum MRD% <0.01% was defined as MRD-negative.

Supplementary Figure 2. PFS by CD22 expression as assessed by central laboratory MESF and CD22 positivity, and local laboratory CD22 positivity quartile

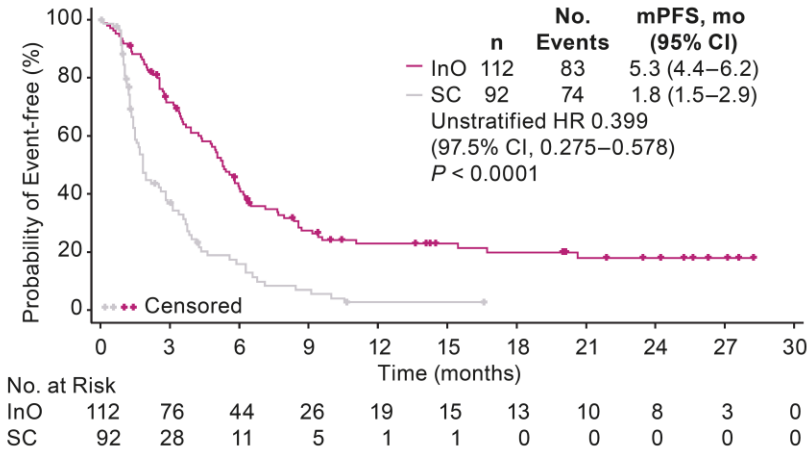








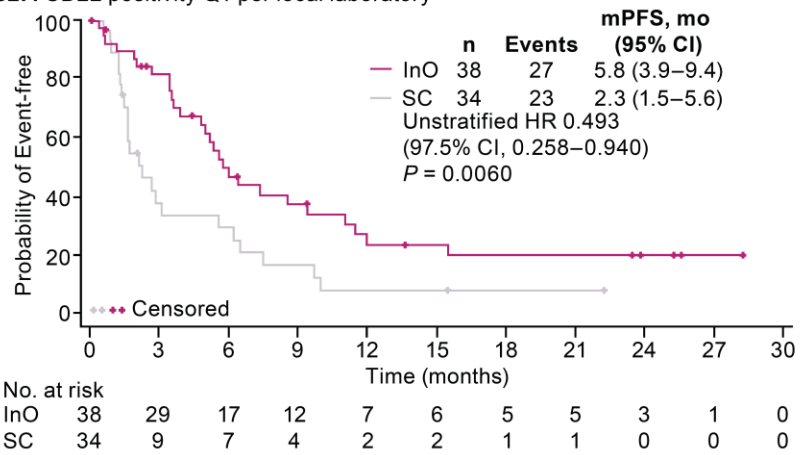
S2E. CD22 MESF Q2–4



No. at Risk

InO	112	76	44	26	19	15	13	10	8	3	0
SC	92	28	11	5	1	1	0	0	0	0	0

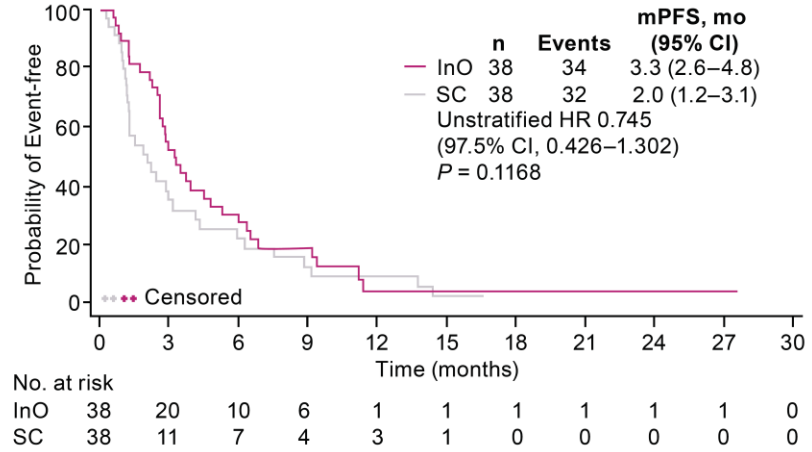
S2F. CD22 positivity Q1 per local laboratory



No. at risk

InO	38	29	17	12	7	6	5	5	3	1	0
SC	34	9	7	4	2	2	1	1	0	0	0

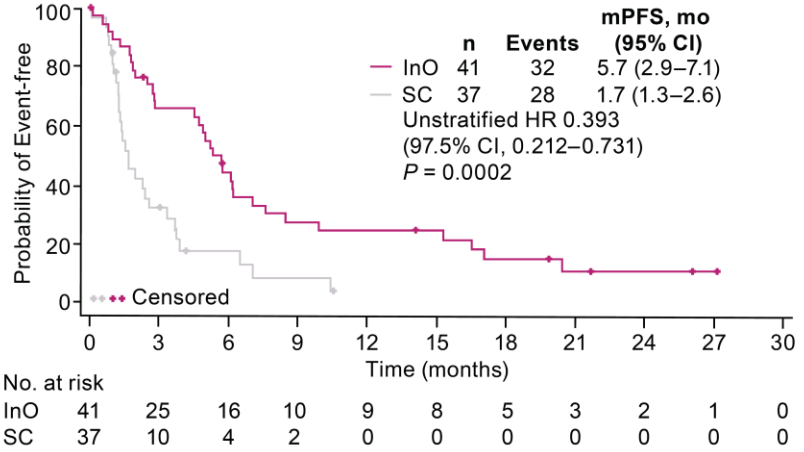
S2G. CD22 positivity Q2 per local laboratory



No. at risk

InO	38	20	10	6	1	1	1	1	1	1	0
SC	38	11	7	4	3	1	0	0	0	0	0

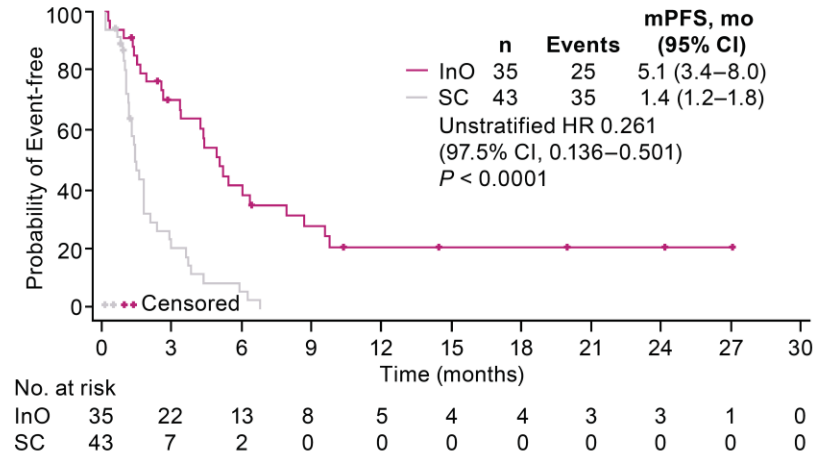
S2H. CD22 positivity Q3 per local laboratory



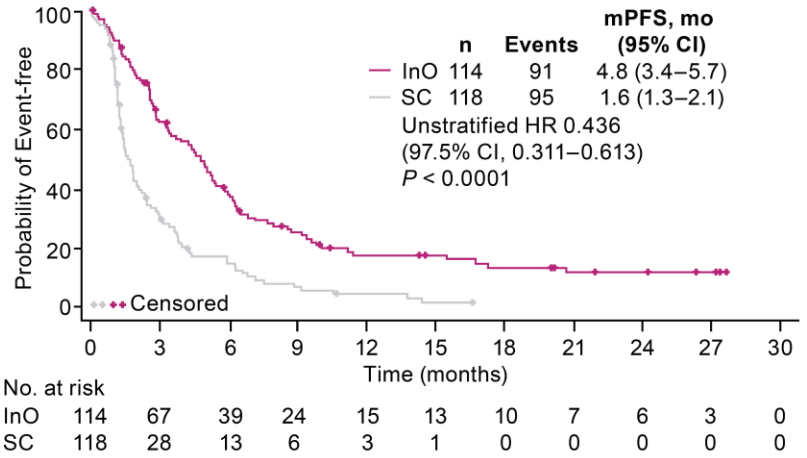
No. at risk

InO	41	25	16	10	9	8	5	3	2	1	0
SC	37	10	4	2	0	0	0	0	0	0	0

S2I. CD22 positivity Q4 per local laboratory

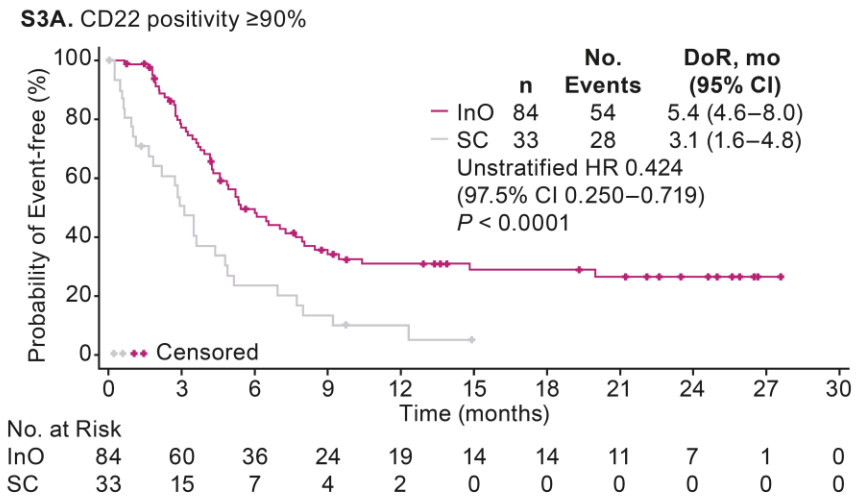


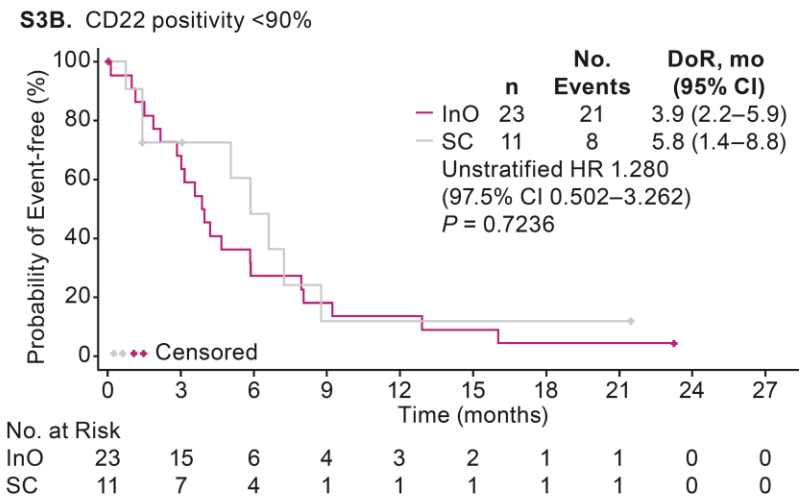
S2J. CD22 positivity Q2–4 per local laboratory

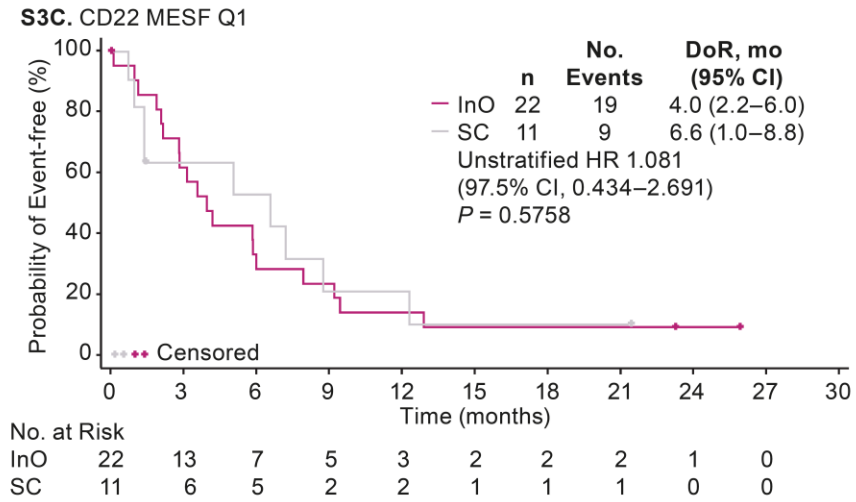


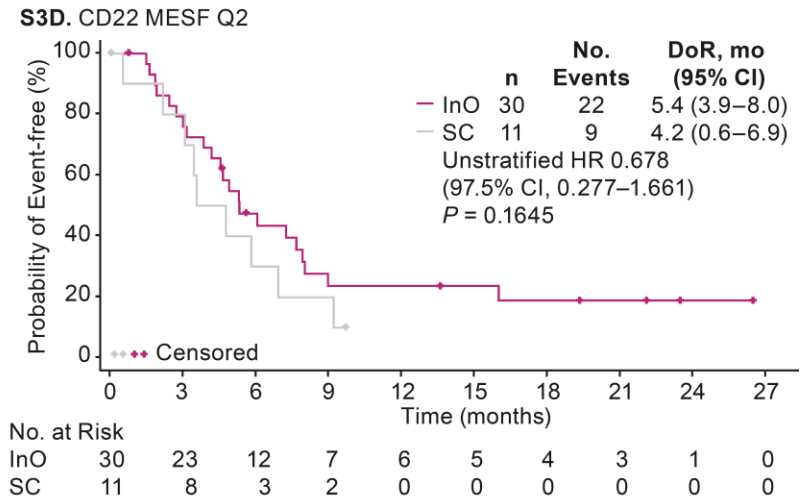
CI, confidence interval; HR, hazard ratio; InO, inotuzumab ozogamicin; mPFS; median PFS; OS, overall survival; PFS, progression-free survival; Q, quartile; SC, standard of care chemotherapy.

Supplementary Figure 3. Duration of remission by CD22 expression as assessed by MESF and CD22 positivity

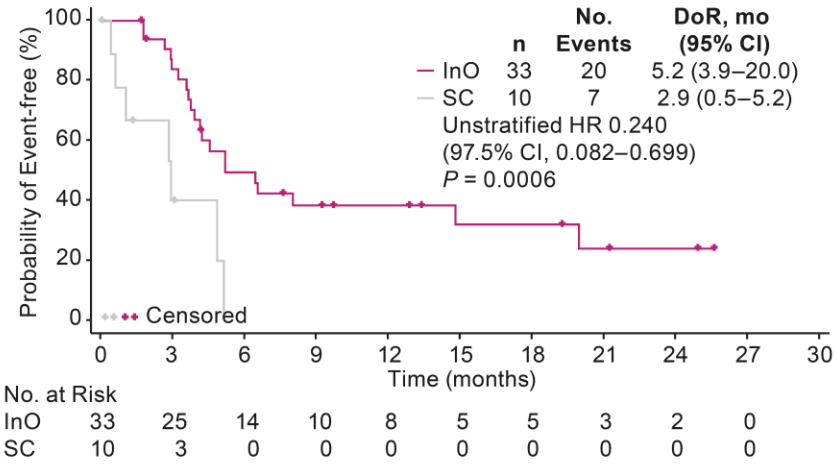








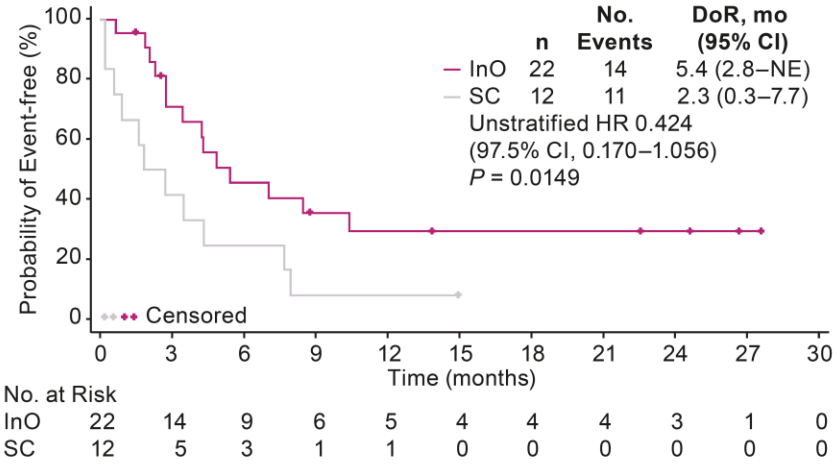
S3E. CD22 MESF Q3



No. at Risk

InO	33	25	14	10	8	5	5	3	2	0
SC	10	3	0	0	0	0	0	0	0	0

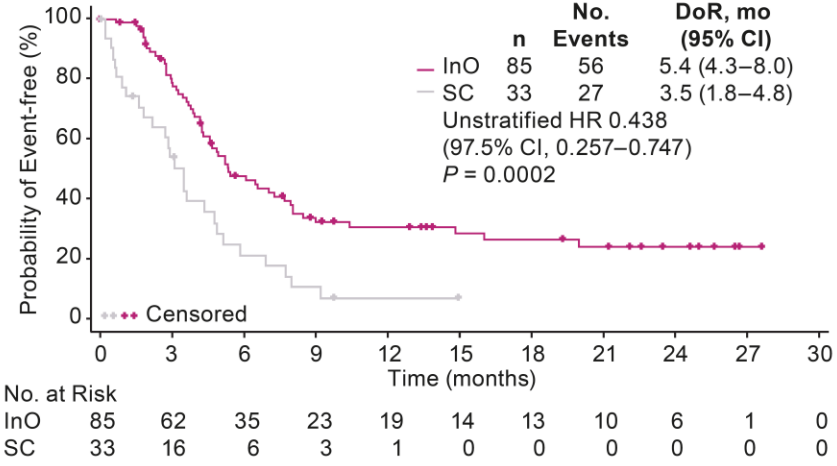
S3F. CD22 MESF Q4



No. at Risk

InO	22	14	9	6	5	4	4	4	3	1	0
SC	12	5	3	1	1	0	0	0	0	0	0

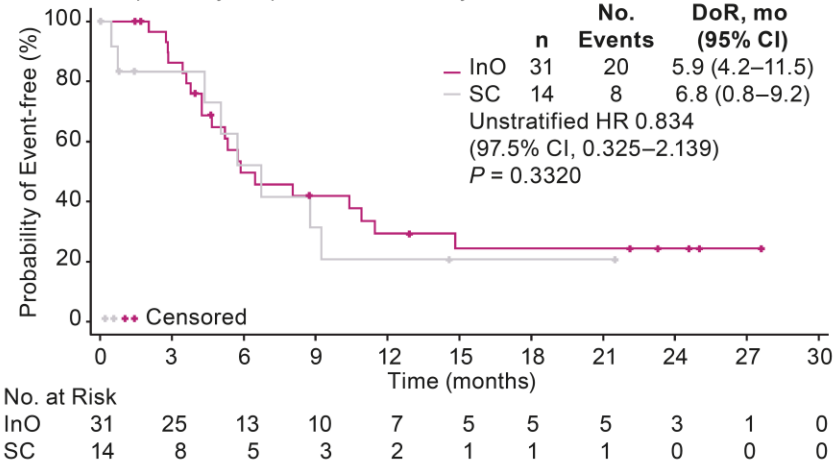
S3G. CD22 MESF Q2–4



No. at Risk

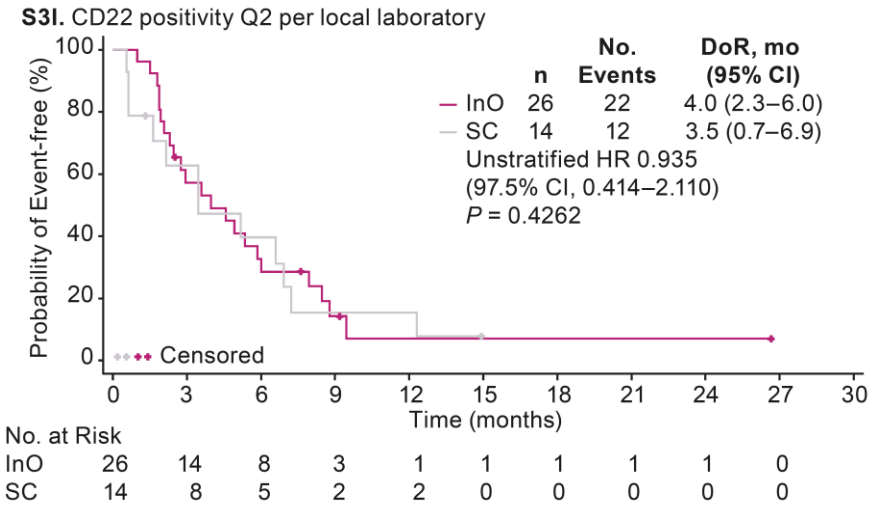
InO	85	62	35	23	19	14	13	10	6	1	0
SC	33	16	6	3	1	0	0	0	0	0	0

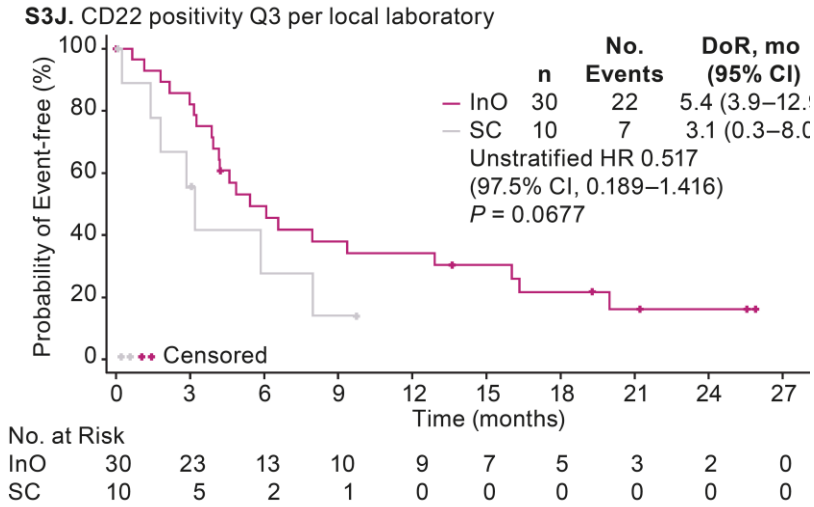
S3H. CD22 positivity Q1 per local laboratory



No. at Risk

InO	31	25	13	10	7	5	5	5	3	1	0
SC	14	8	5	3	2	1	1	1	0	0	0



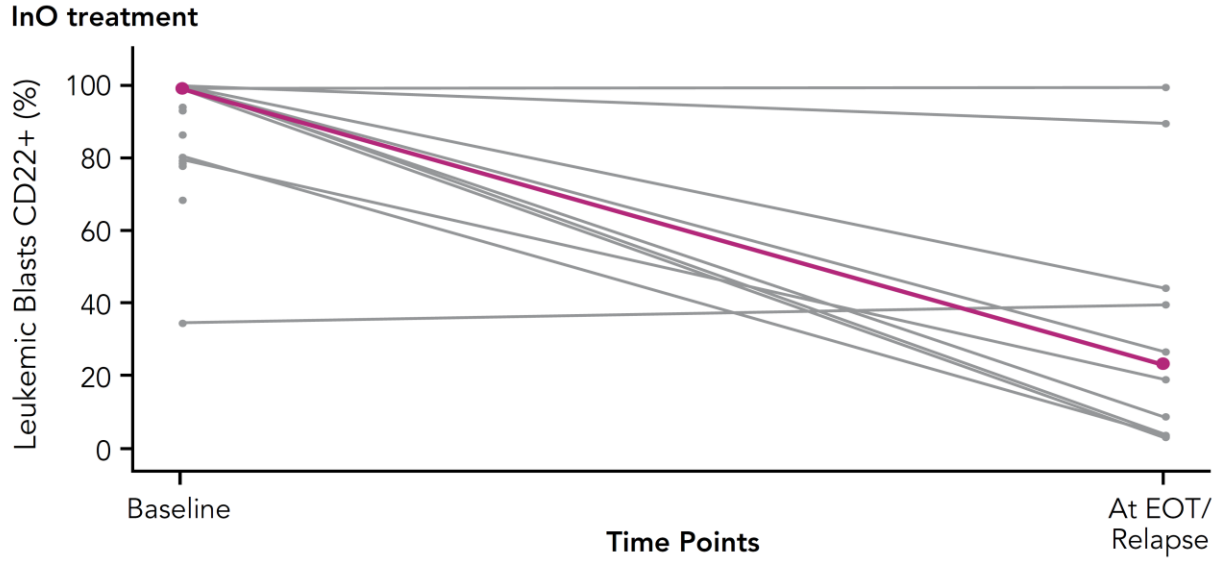


Median DoR (95% CI) in months is shown in each panel.

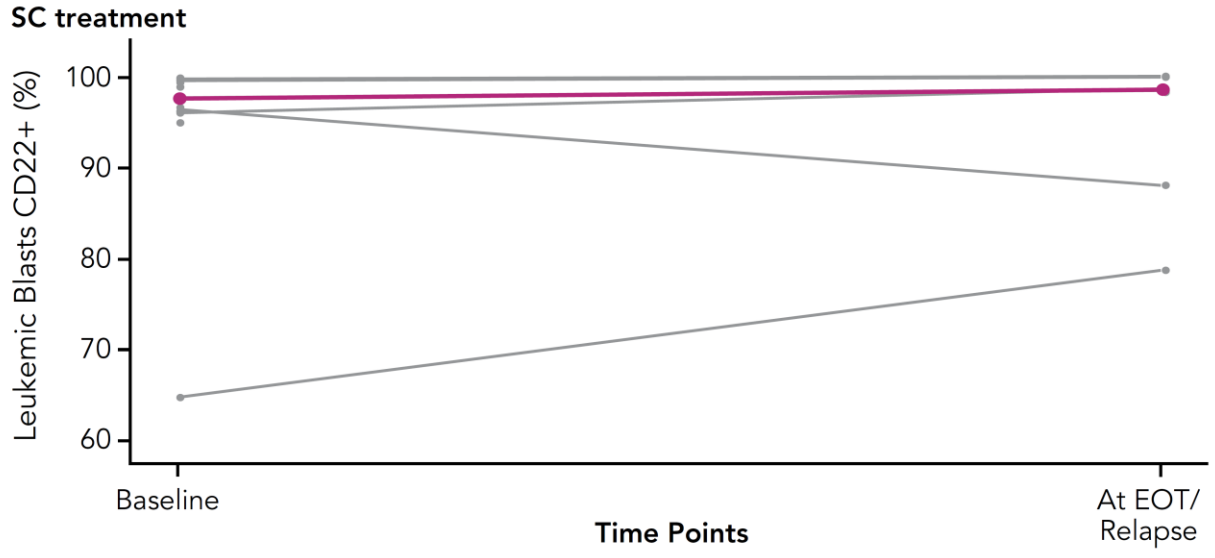
CI, confidence interval; DoR, duration of remission; HR, hazard ratio; InO, inotuzumab ozogamicin; Q, quartile; SC, standard of care chemotherapy.

Supplementary Figure 4. CD22 positivity and CD22 expression in individual responders (CR/CRi) who subsequently relapsed at baseline and EOT/relapse.

S4A. CD22 positivity

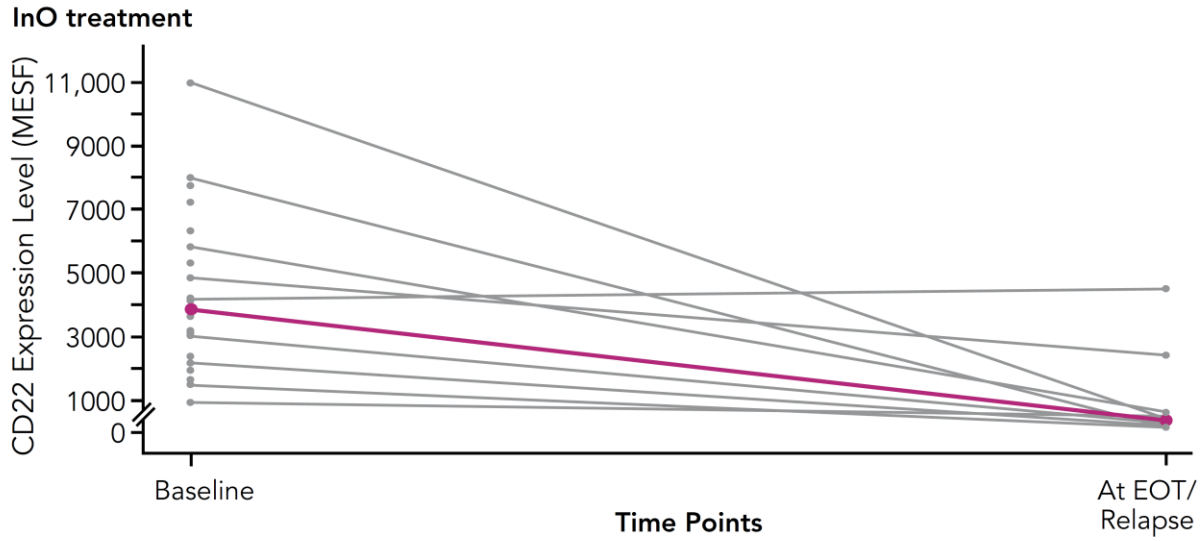


n	22	10
Mean	90.09	33.37
SD	15.803	35.224
Median	98.78	22.53
Min	34.1	2.6
Max	99.9	98.9

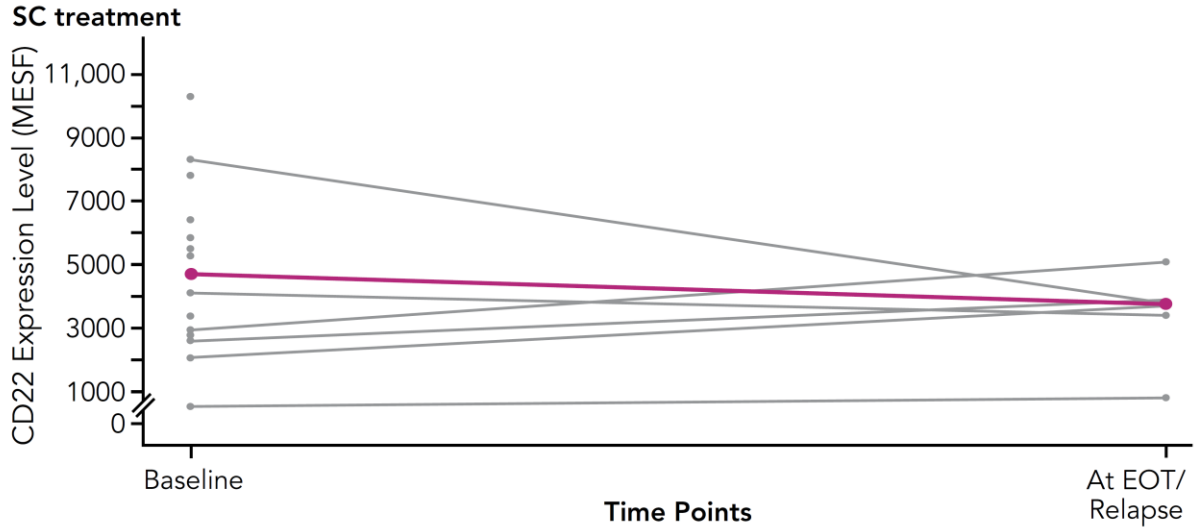


n	14	6
Mean	95.57	93.92
SD	9.067	8.786
Median	97.56	98.55
Min	64.6	78.6
Max	100.0	100.0

S4B. CD22 MESF



n	20	10
Mean	4332.50	864.80
SD	2640.007	1428.330
Median	3795.00	275.50
Min	853.00	74.00
Max	10,947.00	4438.00



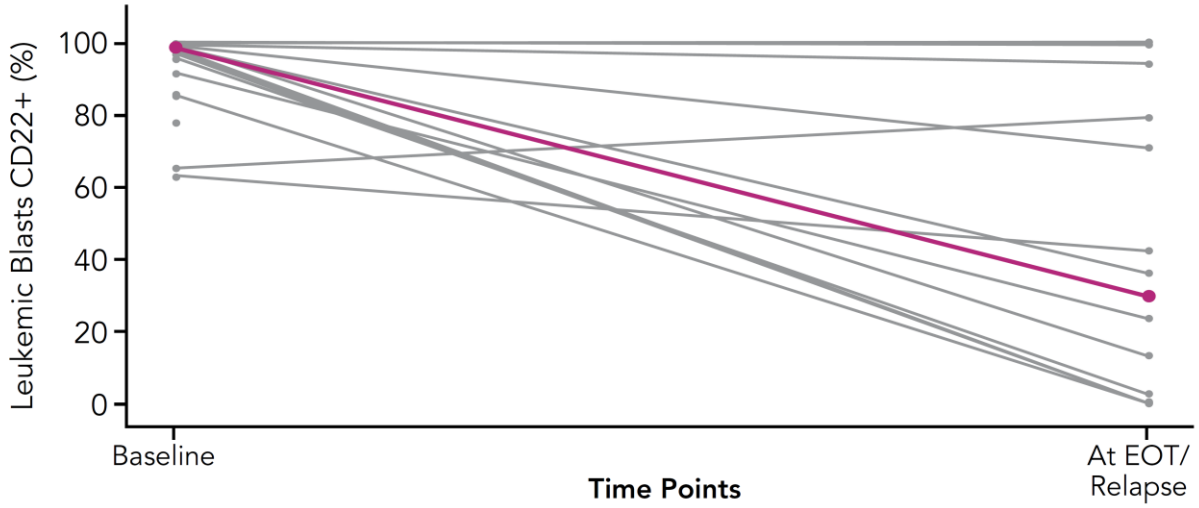
n	14	6
Mean	4789.07	3392.17
SD	2724.459	1415.937
Median	4641.50	3694.50
Min	470.0	753.00
Max	10,226.00	5027.00

Median is represented by solid red. Individual patient profiles are shown in gray.

CR/CRi, complete remission/complete remission with incomplete hematologic recovery; EOT, end of treatment; InO, inotuzumab ozogamicin; max, maximum; MESF, molecules of equivalent soluble fluorochrome; min, minimum; SC, standard of care; SD, standard deviation.

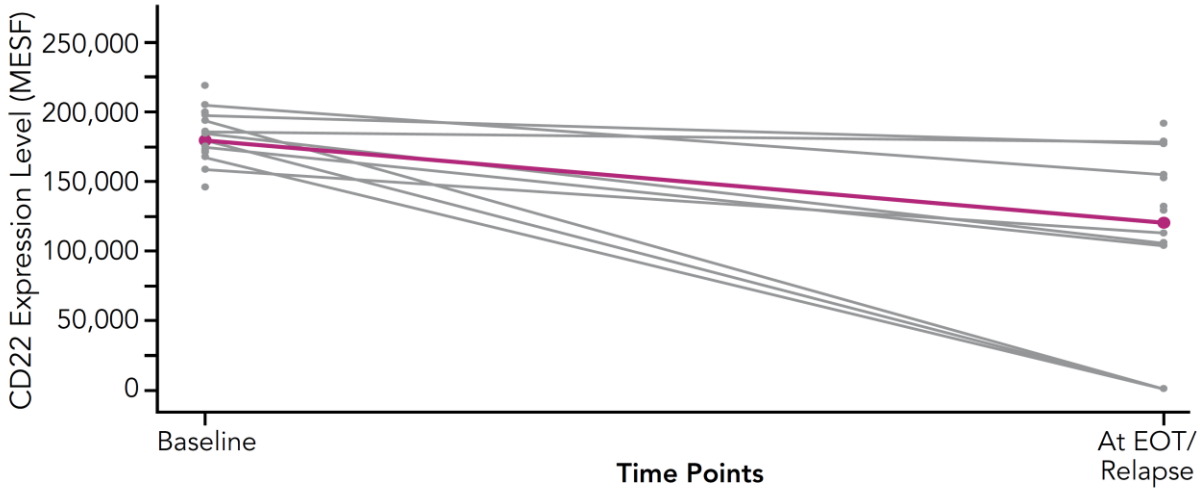
Supplementary Figure 5. CD22 positivity and CD22 expression in individual responders (CR/CRi) who subsequently relapsed at baseline and EOT/relapse for the B1931010 (NCT01363297) phase 1/2 study.

S5A. CD22 positivity



n	24	14
Mean	93.43	39.96
SD	10.601	40.513
Median	98.50	29.50
Min	63.1	0.0
Max	100.0	99.9

S5B. CD22 MESF



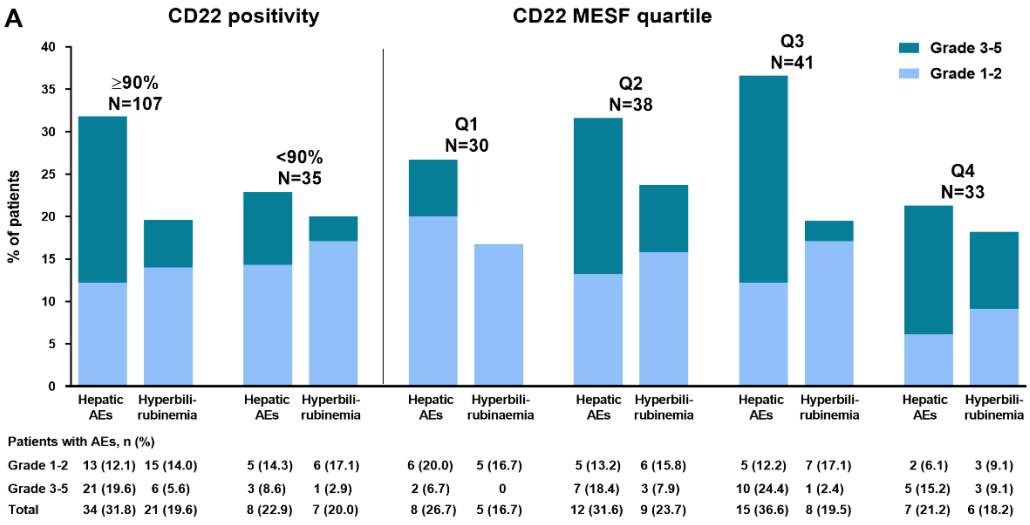
n	18	14
Mean	179,934.7	101,855.3
SD	17,355.81	71,931.65
Median	178,291.0	119,445.5
Min	145,172.0	0.0
Max	218,104.0	190,567.0

Median is represented by solid red. Individual patient profiles are shown in gray.

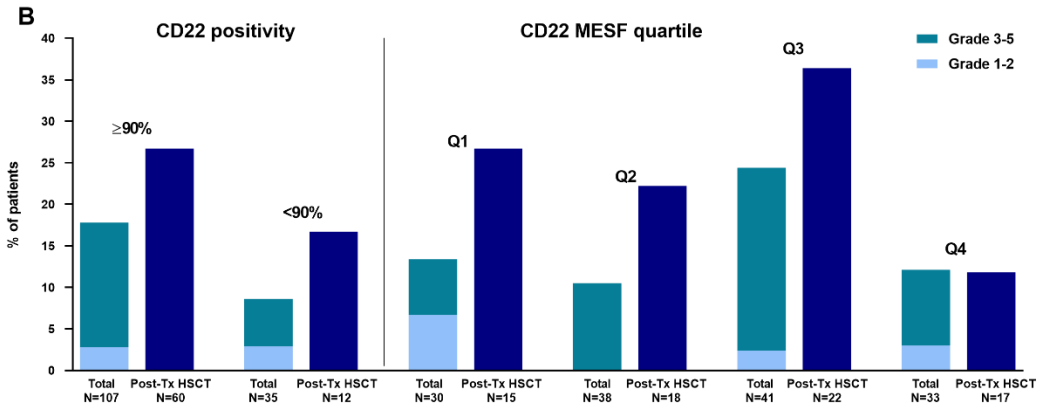
CR/CRi, complete remission/complete remission with incomplete hematologic recovery; EOT, end of treatment; InO, inotuzumab ozogamicin; max, maximum; MESF, molecules of equivalent soluble fluorochrome; min, minimum; SC, standard of care; SD, standard deviation.

Supplementary Figure 6. Selected treatment-emergent clustered hepatotoxicity* in patients administered InO by CD22 positivity and CD22 MESF quartile

S6A. Selected all-causality TEAEs. **S6B**. All-causality SOS/VOD



Patients with AEs, n (%)	≥90%		<90%		Q1		Q2		Q3		Q4	
Grade 1-2	13 (12.1)	15 (14.0)	5 (14.3)	6 (17.1)	6 (20.0)	5 (16.7)	5 (13.2)	6 (15.8)	5 (12.2)	7 (17.1)	2 (6.1)	3 (9.1)
Grade 3-5	21 (19.6)	6 (5.6)	3 (8.6)	1 (2.9)	2 (6.7)	0	7 (18.4)	3 (7.9)	10 (24.4)	1 (2.4)	5 (15.2)	3 (9.1)
Total	34 (31.8)	21 (19.6)	8 (22.9)	7 (20.0)	8 (26.7)	5 (16.7)	12 (31.6)	9 (23.7)	15 (36.6)	8 (19.5)	7 (21.2)	6 (18.2)



Patients with SOS/VOD*, n (%)	≥90%	<90%	Q1	Q2	Q3	Q4
Grade 1-2	3 (2.8)	1 (2.9)	2 (6.7)	0	1 (2.4)	1 (3.0)
Grade 3-5	16 (15.0)	2 (5.7)	2 (6.7)	4 (10.5)	9 (22.0)	3 (9.1)
Total	19 (17.8)	3 (8.6)	4 (13.3)	4 (10.5)	10 (24.4)	4 (12.1)
Patients with SOS/VOD following post-Tx HSCT, n (%)						
Total	16 (26.7)	2 (16.7)	4 (26.7)	4 (22.2)	8 (36.4)	2 (11.8)

* Clustered hepatotoxicity included hyperbilirubinaemia and SOS/VOD. All SOS/VOD events within 2 years of randomization date regardless of causal attribution to study therapy are included.

AE, adverse event; HSCT, hematopoietic stem cell transplant; InO, inotuzumab ozogamicin; MESF, molecules of equivalent soluble fluorochrome; Q, quartile; SOS/VOD, sinusoidal obstruction syndrome/veno-occlusive disease; TEAE, treatment-emergent AE.