Outcomes in Patients With B-cell Precursor Acute Lymphoblastic Leukemia Receiving Inotuzumab Ozogamicin Stratified by Cumulative Dose

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Objective

- Report outcomes of InO by total cumulative dose in adults with R/R B-ALL treated in Pfizer-sponsored clinical trials.

Conclusions

- Among responders, improved PFS/OS outcomes in patients from the ≤3.3 mg/m^2 group are attributed to a greater number of patients who proceeded to HSCT.
- The risk of post-HSCT SOS between dose groups appeared similar, but the incidence of post-HSCT mortality and NRM were lower in the ≤3.3 mg/m^2 group.
- Less myelosuppression was observed in the ≤3.3 mg/m^2 group.
- Future studies should investigate mitigation factors for SOS and transplant-related mortality as well as optimal InO dosing and combination strategies.

Background

- Inotuzumab ozogamicin (InO) is approved for adults with relapsed/refractory acute lymphoblastic leukemia (R/R B-ALL).[1,2]
- Based on the Phase 3 INO-VATE study, limiting InO to 2 cycles prior to hematopoietic stem cell transplantation (HSCT) is recommended to reduce risk of hepatic sinusoidal obstruction syndrome (SOS).[3,4]
- Evidence suggests that calicheamicin-antibody-drug conjugates injure liver sinusoidal endothelial cells leading to SOS.[5]
- A fractionated, lower dose of InO has been associated with lower risk of SOS in newly diagnosed ALL.[6]

Methods

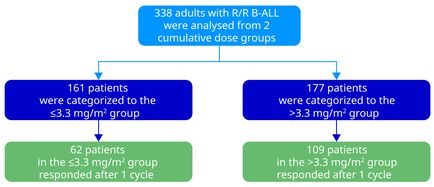
- Data from 3 previous studies were pooled for analysis:
  - In study B1931010 (NCT01363297) participants received InO at 0.8–1.8 mg/m^2/cycle in the Phase 1 portion of the study, and 1.6–1.8 mg/m^2/cycle in the Phase 2 portion[7]
  - In study B1931022 (NCT01564784) patients received InO at 1.5–1.8 mg/m^2/cycle[8]
  - In study B1931030 (NCT03677596) patients received InO at 0.9–1.2mg/m^2 or 1.5–1.8mg/m^2 per cycle[9].
- Patients were grouped based on total cumulative InO dose reflecting 2-cycle cut off:
  - ≤3.3 mg/m^2
  - >3.3 mg/m^2.
- This analysis assessed patients who achieved complete remission or remission with incomplete recovery (CR/CRi) after cycle 1 to remove non and poor responders.

Results

PATIENT POPULATION

- Data from 338 participants were analyzed (**Figure 1**).

Figure 1: Patient population



B-ALL=B-cell acute lymphoblastic leukemia; R/R=relapsed/refractory

- Baseline characteristics were generally similar between groups (**Table 1**).
- A high percentage of patients in the lower cumulative dose group proceeded to HSCT.
- Approximately half of patients received ursodiol as SOS prophylaxis.

Table 1: Baseline characteristics

	Patients who achieved CR/CRi	
Total cumulative dose	**≤3.3 mg/m^2**	**>3.3 mg/m^2**
N	62	109
Mean (SD)	2.5 (0.6)	5.7 (1.9)
Number of cycles		
1	15 (24)	0 (0)
2	40 (65)	15 (14)
3	7 (11)	37 (34)
≥ 4	0 (0)	57 (52)
Salvage status		
Salvage 1	32 (52)	67 (62)
Salvage ≥2	29 (47)	42 (39)
Prior HSCT	13 (21)	25 (23)
Proceeded to HSCT	46 (74)	50 (46)
Proceeded to 2nd HSCT	8 (13)	5 (5)
Received ursodiol as SOS prophylaxis	28 (45)	54 (50)

HSCT=hematopoietic stem cell transplantation; NRM=non-relapse mortality; SOS=sinusoidal obstruction syndrome

EFFICACY

- Sixty-two patients in the lower cumulative dose group, and 109 patients in the higher dose group achieved CR/CRi after 1 cycle (**Table 2**).

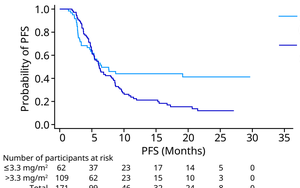
Table 2: Response data

Cycle 1 Responders	**≤3.3 mg/m^2 (n=62)**	**>3.3 mg/m^2 (n=109)**
CR/CRi overall, n (%)	62 (100)	109 (100)
Median time to remission, months (min, max)	0.85 (0.5, 2.3)	0.82 (0.5, 3.3)
MRD-negativity	46 (74)	98 (90)

CR=complete remission with incomplete hematologic recovery; MRD=minimum residual disease

- Median progression-free survival (PFS) was similar between dose groups (**Figure 2**).
- The estimate of PFS at 12 months was 44% for the lower dose group and 21% for the higher dose group.

Figure 2: Progression-free survival

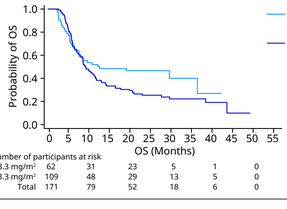


Number of participants at risk

≤3.3 mg/m^2	62	37	23	17	14	5	0
>3.3 mg/m^2	109	62	23	15	10	3	0
Total	171	99	46	32	24	8	0

- Median overall survival (OS) was longer in the 12 months in the lower cumulative dose (**Figure 3**).
- Estimates of overall survival at 12 months were 52% in the lower dose group and 38% in the higher dose group.

Figure 3: Overall survival

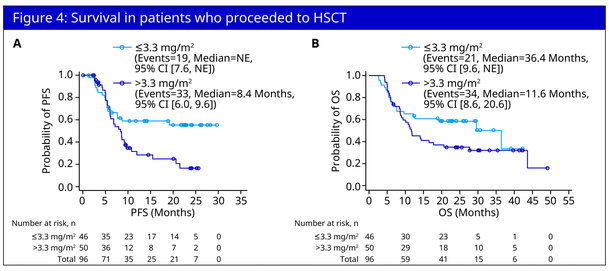


Number of participants at risk

≤3.3 mg/m^2	62	31	23	5	1	0	
>3.3 mg/m^2	109	48	29	13	5	0	
Total	171	79	52	18	6	0	

- In patients who proceeded to HSCT, median PFS was not evaluable in the lower cumulative dose group compared with 8.4 months in the higher dose group (**Figure 4A**).
- Median OS was longer in the lower cumulative dose group (**Figure 4B**).

Figure 4: Survival in patients who proceeded to HSCT



Number at risk, n

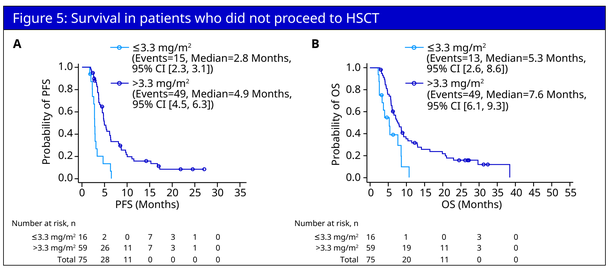
≤3.3 mg/m^2	46	35	23	17	14	5	0
>3.3 mg/m^2	50	36	12	8	7	2	0
Total	96	71	35	25	21	7	0

Number at risk, n

≤3.3 mg/m^2	46	30	23	5	1	0	
>3.3 mg/m^2	50	29	18	10	5	0	
Total	96	59	41	15	6	0	

- In patients who did not proceed to HSCT, median PFS (**Figure 5A**) and OS (**Figure 5B**) were both shorter in the lower cumulative dose group.

Figure 5: Survival in patients who did not proceed to HSCT



Number at risk, n

≤3.3 mg/m^2	16	2	0	7	3	1	0
>3.3 mg/m^2	59	26	11	7	3	1	0
Total	75	28	11	0	0	0	0

Number at risk, n

≤3.3 mg/m^2	16	1	0	3	0		
>3.3 mg/m^2	59	19	11	3	0		
Total	75	20	11	0	0		

SAFETY

- The most common cause of death was disease progression (**Table 3**).
- Study drug toxicity and SOS as a cause of death were uncommon, although it appeared moderately higher in the >3.3 dose group.

Table 3: Deaths

Cycle 1 responders	**≤3.3 mg/m^2 (n=62)**	**>3.3 mg/m^2 (n=109)**
Summary of OS, n (%)		
Deaths	34 (55)	83 (76)
Cause of death		
AE not related to study drug	5 (8)	9 (8)
Disease progression	14 (23)	41 (38)
Study drug toxicity	2 (3)	7 (6)
SOS	1 (2)	3 (3)
Transplant complication	1 (2)	1 (1)
Other or unknown	12 (19)	25 (23)

AE=adverse event; OS=overall survival, SOS=sinusoidal obstruction syndrome

- Grade ≥3 hematologic TEAEs were more common in the higher cumulative dose group (**Table 4**)
- Grade ≥3 hepatic TEAEs, specifically SOS, were similar between dose groups.

Table 4: Adverse events

Grade ≥3 TEAEs in Cycle 1 Responders	**≤3.3 mg/m^2 (n=62)**	**>3.3 mg/m^2 (n=109)**
Patients reporting blood and lymphatic system disorders	29 (47)	87 (80)
Anemia	8 (13)	23 (21)
Febrile neutropenia	10 (16)	29 (27)
Leukopenia	7 (11)	22 (20)
Lymphopenia	3 (5)	15 (14)
Neutropenia	14 (23)	55 (51)
Thrombocytopenia	14 (23)	45 (41)
Patients reporting hepatobiliary disorders	8 (13)	12 (11)
SOS	8 (13)	12 (11)

SOS=sinusoidal obstruction syndrome

- In patients who proceeded to stem cell transplant, post-HSCT mortality and non-relapse mortality were less common in the lower dose group (**Table 5**).
- The risk of any grade post-HSCT SOS between dose groups was similar.

Table 5: Post-HSCT outcome

Cycle 1 Responders	**≤3.3 mg/m^2 (n=62)**	**>3.3 mg/m^2 (n=109)**
Proceeded to HSCT, n (%)	46 (74)	50 (46)
Post-HSCT mortality, n (%)	18 (39)	31 (62)
Post-HSCT NRM, n (%)	13 (28)	22 (44)
Any grade post-HSCT SOS, n (%)	11 (24)	12 (24)
Grade 3–4 post-HSCT SOS, n (%)	7 (15)	9 (18)

HSCT=hematopoietic stem cell transplantation; NRM=non-relapse mortality; SOS=sinusoidal obstruction syndrome

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