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Letter to the Editor

Blinatumomab is associated with better post-transplant outcome than chemotherapy in children with high-risk first-relapse B-cell acute lymphoblastic leukemia irrespective of the conditioning regimen

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Author contributions
All authors were involved in data generation, data analysis, and review of the manuscript; they read and approved the manuscript and provided consent for publication.

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Clinical Trial: NCT02393859

Data sharing and availability: Qualified researchers may request data from Amgen clinical studies.

Total body irradiation (TBI) is a key component of many conditioning regimens administered prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in patients with acute lymphoblastic leukemia (ALL). A recent, large randomized clinical study—FORUM— including patients with a donor matched for $\geq$ 9/10 HLA loci demonstrated that children with high-risk/relapsed ALL who received TBI plus etoposide as conditioning regimen had a significantly improved 2-year probability of overall survival (OS; 0.91; 95% confidence interval [CI], 0.86–0.95; $P < 0.0001$) as compared with patients who received conditioning with chemotherapy (chemoconditioning; 0.75; 95% CI, 0.67–0.81) prior to alloHSCT.[1] Although effective, conditioning with TBI is associated with the risk of lifelong adverse effects, including impairment of growth, gonadal, thyroid and cognitive function, increased incidence of cataracts, and secondary malignancies.[2-4] Therefore, a novel approach aimed at providing an alternative to TBI-based conditioning is desirable.

Blinatumomab is a bispecific T-cell engager, which redirects CD3-positive T cells to engage and lyse CD19-positive target cells. A randomized, phase 3 trial (NCT02393859) demonstrated that treatment with one cycle of blinatumomab compared with standard intensive multidrug chemotherapy administered as the third consolidation course (HC3) prior to alloHSCT in pediatric high-risk first-relapse B-cell ALL (B-ALL) resulted in an improvement in event-free survival (EFS) and OS.[5, 6] In order to better dissect the contribution of immediate pre-transplant treatment with the role played by the conditioning regimen, we performed a post hoc analysis aimed at evaluating the outcome of children with high-risk first-relapse B-ALL from this phase 3 study who received either blinatumomab or chemotherapy (HC3) as the third consolidation course and for whom data on the type of conditioning regimen received (either TBI or chemoconditioning) prior to alloHSCT were available.

Details of the study design, patient eligibility, and treatment doses of blinatumomab and HC3 were previously reported.[5] High-risk first-relapse has been defined earlier.[7, 8] Patients who achieved/maintained second complete remission after treatment with either blinatumomab or HC3 were assigned to receive TBI or chemoconditioning before alloHSCT. Myeloablative conditioning prior to alloHSCT consisted of TBI (12 Gy in 6 fractions) plus 60 mg/kg etoposide [1.8 g/m2; maximum total dose 3.6 g]) or chemoconditioning including fludarabine (30 mg/m^2 once a day for 5 consecutive days) plus thiotepa (5 mg/kg twice a day for 1 day) and either treosulfan (14 g/m^2 once a day for 3 consecutive days) or busulfan.[1] Busulfan was dosed once, twice, or four times a day according to local guidelines, age, and body weight, usually with therapeutic drug monitoring and pharmacokinetic dose adjustment. Time-to-event end points were summarized using the Kaplan-Meier (KM) method. Transplant-emergent adverse events were assessed by the clinicians per good clinical practice guidelines and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Acute and chronic graft-versus-host disease (GVHD) was assessed at each visit and graded per description by Glucksberg et al.[9] The study protocol was approved by the institutional review boards or independent ethics committees of all participating institutions. A Cox regression model was employed for evaluating the effects of treatment with either blinatumomab or chemotherapy before alloHSCT and of conditioning regimen on patient's outcome.

Of the 90 evaluable patients for whom data on the conditioning regimen administered were available, 51 received blinatumomab and 39 received HC3. Of the 51 patients treated with blinatumomab, 30 patients received TBI plus etoposide and 21 patients received chemoconditioning (5 of 21 patients received fludarabine+thiotepa+treosulfan; 16 of 21 received fludarabine+thiotepa+busulfan prior to alloHSCT). Among patients given HC3, 19 received TBI and 20 received chemoconditioning (16 patients received the busulfan-based regimen and the remaining 4 the treosulfan-based preparation), before alloHSCT. Patient demographics and baseline characteristics, including measurable residual disease (MRD), were well balanced between the blinatumomab and HC3 treatment groups prior to administration of TBI or chemoconditioning (**Table 1**). Fifty percent of patients treated with blinatumomab (25 of 51 patients) and 41% of patients

treated with HC3 (16 of 39 patients) received a transplant from matched donors with an HLA matching of ≥ 9/10, this representing the population of children eligible for the randomized trial conducted by the FORUM consortium. The remaining patients were eligible to be reported in the FORUM database. The median time elapsed between the last dose of blinatumomab and alloHSCT was 25 days (range, 8–67 days) and the median time between the last dose of HC3 and alloHSCT was 44 days (range, 20–107 days).

Two of 51 patients (4%) treated with blinatumomab experienced cytokine release syndrome. Cyclosporine and methotrexate were commonly administered for GVHD prophylaxis at investigator's discretion. The incidence of transplant-emergent adverse events in patients treated with blinatumomab was comparable with that of patients treated with HC3.[5] One patient each in the HC3 and blinatumomab group experienced graft failure.

The KM analysis of both OS and EFS showed that survival in patients treated with blinatumomab, regardless of subsequent treatment with TBI or chemoconditioning, was better compared with survival among patients treated with HC3 followed by TBI or chemoconditioning (**Figure 1A and 1B**). Twenty-four out of 39 (62%) patients given HC3 and 15 out of 51 (29%) blinatumomab-treated patients relapsed after transplantation. Treatment after relapse was heterogenous and included chemotherapy, Inotuzumab and chimeric antigen receptor (CAR)-modified T cells and allowed rescue of a proportion of patients: In detail, 8 out of the 24 HC3-treated patients (33%) who relapsed are alive, as well as 10 out of the 15 (66%) allocated to the blinatumomab arm. The KM estimates for EFS at 36 and 48 months after transplantation (35.5% [95% CI, 20.9%–50.4%] in both cases) indicated an increased probability of an event with HC3 when compared to patients treated with blinatumomab (63.8% [95% CI, 48.8%-75.4% at 36 months and 60.2% [95% CI, 44.4%-72.8%] at 48 months) irrespective of subsequent conditioning. Among patients treated with blinatumomab, EFS did not show a statistically significant difference between patients who received either TBI or chemoconditioning. **(Figure 1B)**.

The KM 100-day estimate of mortality after alloHSCT was 3.9% (95% CI, 1.0%–14.8%) in the blinatumomab arm and 5.1% (95% CI, 1.3%–19.0%) in the HC3 arm (**Table 2**). Among

patients treated with blinatumomab, the 2-year KM estimate for OS was numerically greater in patients who received conditioning with TBI (86.5%, 95%CI, 68.0–94.7%) than in patients who received chemoconditioning (75.2%; 95% CI, 50.3%–88.9%) (**Table 2**). The difference in favor of TBI persisted at the 4-year time-point after transplantation. Neither the pre-transplant treatment, nor the type of conditioning regimen used influenced the occurrence of acute or chronic GVHD (data not shown). Results from a multivariate Cox regression model for OS showed that pre-transplant treatment with blinatumomab was correlated with a statistically significant better outcome (Hazard ratio 0.33 [0.15–0.72]; p= 0.005), while the use of TBI did not reach a statistically significant value (data not shown).

Results from the current analysis demonstrate that children with high-risk first-relapse B-ALL receiving blinatumomab as the third consolidation course before alloHSCT had a better 2-year estimate of both OS and EFS as compared with patients who received HC3, irrespective of treatment with TBI plus etoposide or chemoconditioning. Persistence of MRD after induction with chemotherapy and prior to alloHSCT has been demonstrated to be predictive of recurrence of B-ALL.[7, 10-13] A recently published post hoc analysis of data from the randomized phase 3 study,[6] demonstrated that a higher proportion of patients with high-risk first-relapse B-ALL with MRD had undetectable disease after blinatumomab as the third consolidation course compared with patients treated with HC3. As patients included in the current analysis were drawn from the same phase 3 study, the deeper MRD remission (i.e. $< 10^{-4}$ leukemic blasts) observed with blinatumomab explains the numerically longer OS observed in patients treated with blinatumomab compared with patients treated with HC3, irrespective of subsequent conditioning. Although the best OS was observed in patients given blinatumomab followed by the TBI-containing regimen, this finding also suggests that blinatumomab consolidation (and the resulting lower leukemia burden even in the patients who were already MRD negative before the randomization) could render chemoconditioning a possible alternative in patients who are ineligible to receive TBI. In addition, the use of blinatumomab before alloHSCT can reduce the risk of pre-transplant bacterial/fungal colonization and tissue toxicity that can result into a higher risk of life-threatening or even fatal events after transplantation.

A limitation of this analysis is that the generalizability of the findings to routine clinical practice could be limited by the sample size evaluated and the post hoc nature of the analysis. The ongoing FORUM-study with more than 1700 registered ALL children will provide a clearer picture on the benefit of using blinatumomab before alloHSCT in the real word.[1]

Overall, this analysis demonstrates that blinatumomab as the third consolidation course improved OS and EFS post alloHSCT in pediatric high-risk first-relapse B-ALL irrespective of the conditioning therapy employed (TBI or chemoconditioning) prior to alloHSCT as compared with patients treated with HC3. Further prospective studies are needed to evaluate if TBI could be substituted with chemoconditioning in patients with high-risk first-relapse B-ALL who are treated with blinatumomab and who become MRD-negative before transplantation.

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Table 1. Patient demographics and characteristics

	Total body irradiation		Chemoconditioning		Overall	
	HC3 (N = 19)	Blinatumomab (N = 30)	HC3 (N = 20)	Blinatumomab (N = 21)	HC3 (N = 39)	Blinatumomab (N = 51)
Age						
Median (range), years	6.0 (3–16)	6.0 (3–17)	5.0 (1–17)	5.0 (1–17)	5.0 (1–17)	6.0 (1–17)
Distribution, n (%)						
1–9 years	13 (68.4)	21 (70.0)	16 (80.0)	15 (71.4)	29 (74.4)	36 (70.6)
10–18 years	6 (31.6)	9 (30.0)	4 (20.0)	6 (28.6)	10 (25.6)	15 (29.4)
Sex, n (%)						
Male	6 (31.6)	14 (46.7)	7 (35.0)	13 (61.9)	13 (33.3)	27 (52.9)
Stem cell source, n (%)						
Peripheral blood	4 (21.1)	13 (43.3)	7 (35.0)	8 (38.1)	11 (28.2)	21 (41.2)
Bone marrow	14[a] (73.7)	14 (46.7)	11[a] (55.0)	12[a] (57.1)	25[a] (64.1)	26[a] (51.0)
Cord blood	2 (10.5)	3 (10.0)	3 (15.0)	2 (9.5)	5 (12.8)	5 (9.8)
Donor type, n (%)						
Matched sibling	4 (21.1)	6 (20.0)	6 (30.0)	6 (28.6)	10 (25.6)	12 (23.5)
HLA loci matching ≥ 9/10	3 (75.0)	6 (100.0)	4 (66.7)	4 (66.7)	7 (70.0)	10 (83.3)
HLA loci matching 10/10	3 (75.0)	6 (100.0)	4 (66.7)	4 (66.7)	7 (70.0)	10 (83.3)
Matched unrelated donor	7 (36.8)	12 (40.0)	5 (25.0)	6 (28.6)	12 (30.8)	18 (35.3)
HLA loci matching ≥ 9/10	6 (85.7)	10 (83.3)	3 (60.0)	5 (83.3)	9 (75.0)	15 (83.3)
HLA loci matching 10/10	2 (28.6)	5 (41.7)	2 (40.0)	4 (66.7)	4 (33.3)	9 (50.0)
Haploidentical parental donor[b]	4[c] (21.1)	9 (30.0)	9 (45.0)	6[d] (28.6)	13[c] (33.3)	15[d] (29.4)
Mismatched sibling	0 (0.0)	0 (0.0)	1 (5.0)	1 (4.8)	1 (2.6)	1 (2.0)
Mismatched unrelated donor	4 (21.1)	3 (10.0)	2 (10.0)	5 (23.8)	6 (15.4)	8 (15.7)

[a]One patient received stem cells from peripheral blood in addition to bone marrow.

[b]Haploidentical father or mother or both.

[c]Three patients received stem cells from a second source in addition to a haploidentical donor, 1 patient received stem cells from a matched unrelated donor, 1 patient received stem cells from a mismatched unrelated donor, and 1 patient received transplant from a matched sibling.

[d]One patient received transplant from mismatched sibling and one patient received transplant from mismatched unrelated donor.

HC3, third consolidation course with chemotherapy; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation.

Table 2. Overall survival following allogeneic hematopoietic stem cell transplant in patients with high-risk first-relapse B-cell acute lymphoblastic leukemia who received blinatumomab or chemotherapy as the third consolidation course and subsequent myeloablative total body irradiation or chemoconditioning, respectively

	TBI		Chemoconditioning		Overall	
	HC3 (N = 19)	Blinatumomab (N = 30)	HC3 (N = 20)	Blinatumomab (N = 21)	HC3 (N = 39)	Blinatumomab (N = 51)
Mortality following alloHSCT						
KM estimate at 100 days, (%)	5.3	3.3	5.0	4.8	5.1	3.9
(95% CI)	(0.8–31.9)	(0.5–21.4)	(0.7–30.5)	(0.7–29.3)	(1.3–19.0)	(1.0–14.8)
Patient status at last follow-up						
Dead	10 (52.6)	4 (13.3)	10 (50.0)	6 (28.6)	20 (51.3)	10 (19.6)
Alive	9 (47.4)	26 (86.7)	10 (50.0)	15 (71.4)	19 (48.7)	41 (80.4)
Overall survival (KM), days						
Median	1558	NE	NE	NE	1558	NE
(95% CI)	(267.0–NE)	(NE–NE)	(220.0–NE)	(1379.0–NE)	(431.0–NE)	(NE–NE)
Range	22.0 to 1558.0	63.0 to 492.0	78.0 to 727.0	67.0 to 1379.0	22.0 to 1558.0	63.0 to 1379.0
KM estimate, %						
At 24 months	52.1	86.5	50.0	75.2	50.9	82.0
(95% CI)	(28.0–71.6)	(68.0–94.7)	(27.1–69.2)	(50.3–88.9)	(34.4–65.3)	(68.3–90.2)
At 48 months	52.1	86.5	50.0	66.8	50.9	77.9
(95% CI)	(28.0–71.6)	(68.0–94.7)	(27.1–69.2)	(39.1–84.1)	(34.4–65.3)	(61.8–87.9)

alloHSCT, allogeneic hematopoietic stem cell transplant; B-ALL, B-cell acute lymphoblastic leukemia; CI, confidence interval; HC3, third consolidation course with chemotherapy; KM, Kaplan-Meier; NE, not estimable; TBI, total body irradiation.

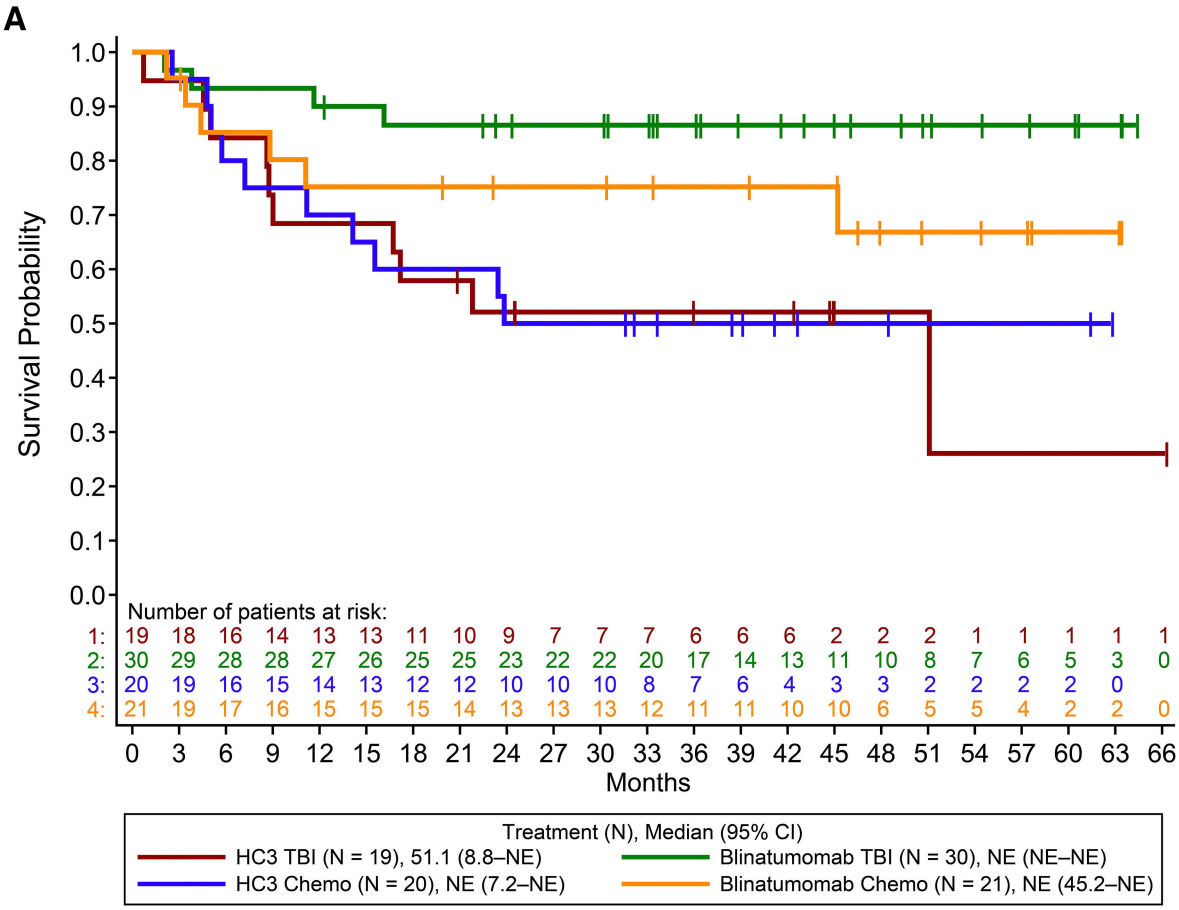
Figure 1. Kaplan-Meier analysis for survival outcomes following allogeneic hematopoietic stem cell transplant in patients with high-risk first-relapse B-cell acute lymphoblastic leukemia who received blinatumomab versus chemotherapy as the third consolidation course and subsequently received either total body irradiation or chemotherapy as conditioning regimen. A. Overall survival, and B. Event-free survival

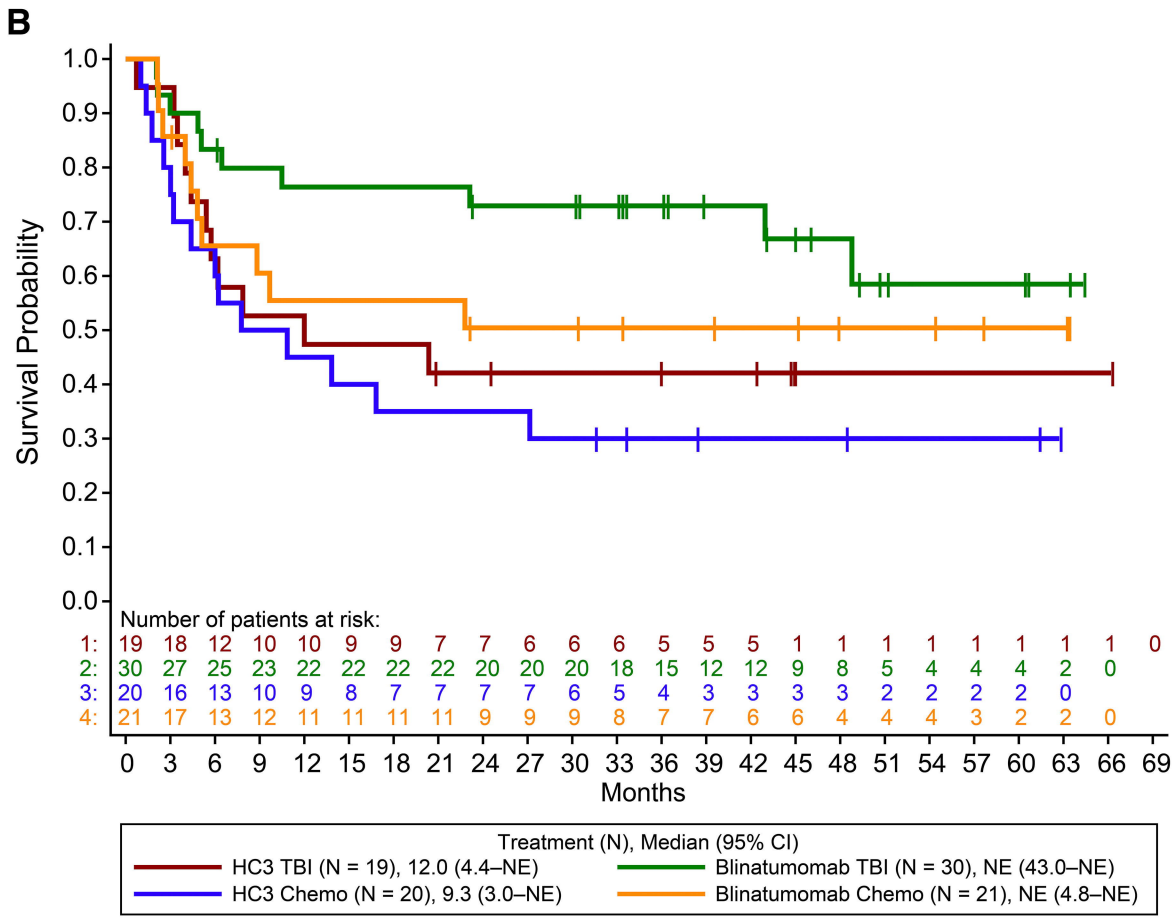
A

Censor indicated by |.
Log-rank *P* value for all 4 subgroups in Figure 1A was 0.0147.
alloHSCT, allogeneic hematopoietic stem cell transplant; B-ALL, B cell acute lymphoblastic leukemia; chemo, chemotherapy; CI, confidence interval; HC3, third consolidation course of chemotherapy; N, number of patients included in the analysis; NE, not estimable; TBI, total body irradiation.

B

Censor indicated by |.
Log-rank *P* value for all 4 subgroups in Figure 1B was 0.0568.
alloHSCT, allogeneic hematopoietic stem cell transplant; B-ALL, B cell acute lymphoblastic leukemia; chemo, chemotherapy; CI, confidence interval; EFS, event-free survival; HC3, third consolidation course of chemotherapy; N, number of patients included in the analysis; NE, not estimable; TBI, total body irradiation.


A
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Number of patients at risk:
1: 19 18 16 14 13 13 11 10 9 7 7 7 6 6 6 2 2 2 1 1 1 1 1
2: 30 29 28 28 27 26 25 25 23 22 22 20 17 14 13 11 10 8 7 6 5 3 0
3: 20 19 16 15 14 13 12 12 10 10 10 8 7 6 4 3 3 2 2 2 2 0
4: 21 19 17 16 15 15 15 14 13 13 13 12 11 11 10 10 6 5 5 4 2 2 0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63 66
Months
Treatment (N), Median (95% CI)
HC3 TBI (N = 19), 51.1 (8.8–NE)
Blinatumomab TBI (N = 30), NE (NE–NE)
HC3 Chemo (N = 20), NE (7.2–NE)
Blinatumomab Chemo (N = 21), NE (45.2–NE)


B
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Number of patients at risk:
1: 19 18 12 10 10 9 9 7 7 6 6 6 5 5 5 1 1 1 1 1 1 1 1 0
2: 30 27 25 23 22 22 22 22 20 20 20 18 15 12 12 9 8 5 4 4 4 2 0
3: 20 16 13 10 9 8 7 7 7 7 6 5 4 3 3 3 3 2 2 2 2 0
4: 21 17 13 12 11 11 11 11 9 9 9 8 7 7 6 6 4 4 4 3 2 2 0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63 66 69
Months
Treatment (N), Median (95% CI)
HC3 TBI (N = 19), 12.0 (4.4–NE)
Blinatumomab TBI (N = 30), NE (43.0–NE)
HC3 Chemo (N = 20), 9.3 (3.0–NE)
Blinatumomab Chemo (N = 21), NE (4.8–NE)