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ORIGINAL RESEARCH

Matching-Adjusted Indirect Comparison of Blinatumomab vs. Inotuzumab Ozogamicin for Adults with Relapsed/Refractory Acute Lymphoblastic Leukemia

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ABSTRACT

Introduction: In the absence of head-to-head trials, this analysis aimed to provide a fair indirect comparison of the efficacy between blinatumomab and inotuzumab ozogamicin (InO), two treatments for adult patients with relapsed or refractory acute lymphoblastic leukemia (R/R ALL) who received no more than one prior salvage therapy, by adjusting for cross-trial differences.

Methods: Patient-level data from the Phase 3 blinatumomab trial TOWER and published aggregated data from the Phase 3 InO trial INO-VATE-ALL were used to conduct matching-adjusted indirect comparisons. Patients with 2+ prior salvage therapies from TOWER were excluded because such patients were not included in INO-VATE-ALL. To ensure balance in the remaining patients, baseline characteristics for the TOWER patients were weighted to match the average baseline characteristics in INO-VATE-ALL, including sex, age, race, performance status, bone marrow blast, previous salvage therapy, previous allogeneic transplantation, complete remission with complete hematologic recovery (CR) to most recent induction therapy, and duration of first remission. Overall survival (OS), including median and restricted mean survival time (RMST) at 12 and 20.7 months, and CR were estimated and compared.

Results: A total of 310 patients in TOWER were included (blinatumomab, $n = 203$; standard of care chemotherapy, $n = 107$). After matching the listed baseline characteristics, the median OS was 9.3 months for blinatumomab and 7.7 months for InO (weighted log-rank test $p = 0.4$). The relative RMST at 12 months was 1.6 months longer for blinatumomab than for InO [95% CI (0.1, 3.2); $p = 0.04$]; at 20.7 months the RMST was not significantly different. The CR rates were similar [anchor-based difference = − 2.8%, 95% CI (− 17.5%, 11.9%); $p = 0.71$].

Conclusions: After adjusting for cross-trial differences, blinatumomab demonstrated a similar CR rate and potential OS benefit versus InO among adult patients with R/R ALL who received no more than one prior salvage

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therapy. Further studies are suggested to confirm this finding.
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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a rare but aggressive type of leukemia characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs [1]. Approximately 20% of ALL cases are in adults (aged ≥ 18 years) [2]. In Europe, the overall prevalence of ALL was approximately 1 in 10,000 people in 2014 [3].

Current treatments for ALL include chemotherapy, often with the intent of hematopoietic stem cell transplant (HSCT). There are usually three phases to chemotherapy: induction, consolidation, and maintenance. More than 80% of adults with ALL achieve complete remission with intensive induction chemotherapy [2, 4–8]. Patients who fail to respond to induction therapy are considered to have refractory ALL. More than half of the patients who initially responded will ultimately relapse [2, 4–8], i.e., leukemia cells reappear in the bone marrow or peripheral blood after attaining complete remission. The prognosis of relapsed or refractory (R/R) ALL for adult patients is very poor, with a median overall survival (OS) of 3–6 months [9]. For patients receiving first-line salvage chemotherapy, 49% were alive after 6 months, 26% at 1 year, and just 11% at 3 years [9].

Blinatumomab and inotuzumab ozogamicin (InO) are two recently approved treatment options recommended by the latest National Comprehensive Cancer Network guidelines for adult patients with R/R ALL [10]. Blinatumomab is a bi-specific T cell engager antibody that targets the CD19 antigen present on B cells. It received full approval for the treatment of Philadelphia-chromosome-negative (Ph−) precursor B cell R/R ALL by the United States Food and Drug Administration (FDA) in July 2017 (accelerated approval was granted in 2014) [11], and by the European Medicines Agency in November 2015 (conditional approval) [12]. A Phase III trial (TOWER) compared blinatumomab with standard of care (SOC) chemotherapy among patients with Ph− R/R B-cell ALL [13–16], and reported that the median OS was significantly higher for patients receiving blinatumomab (7.7 months) versus SOC chemotherapy (4.0 months), with a hazard ratio (HR) of 0.71 and a 95% confidence interval (CI) of 0.55–0.93 ($p = 0.01$). Furthermore, 33.6% of patients receiving blinatumomab achieved complete remission with full hematologic recovery (CR) within 12 weeks after the initiation, compared with 15.7% of patients receiving SOC chemotherapy ($p < 0.001$).

InO is a humanized anti-CD22 antibody conjugated to calicheamicin (a potent cytotoxic antibiotic), which received FDA approval for adult R/R B-cell precursor ALL in August 2017 [17]. In the Phase III trial INO-VATE-ALL, the CR rate in the intention-to-treat population was 33.5% in the InO arm compared to 16.0% in the SOC chemotherapy arm [14]. There was not a statistically significant improvement in the median OS for InO compared to the chosen chemotherapy regimen. The median OS as of January 5, 2017 was 7.7 (95% CI 6.0–9.2) months for InO versus 6.2 (4.7–8.3) months for SOC chemotherapy patients, with a HR of 0.75 (97.5% CI 0.57–0.99; $p = 0.04$, above the prespecified two-sided significance level boundary of $p = 0.0208$) [16, 18].

Currently, there are no randomized head-to-head trials that have compared the effects of blinatumomab versus InO. These two Phase III trials have substantial differences in design and patient characteristics, which make direct comparisons of treatment efficacy challenging. For example, TOWER included patients with more than one previous salvage therapy while INO-VATE-ALL did not. In addition, higher proportions of patients in the TOWER population had ≥ 50% blasts in the bone marrow and had previous HSCT compared to the INO-VATE-ALL population. Based on the literature, all of these three disease characteristics are important

factors impacting patients' outcomes [8, 19, 20]. Therefore, conclusions based on a naïve comparison without adjusting for patient characteristics differences between trials would be biased and can be misleading. Additionally, the two trials assessed complete remission differently. CR, complete remission with partial hematologic recovery (CRh) and complete remission with incomplete hematologic recovery (CRi) were assessed as key secondary efficacy endpoints in TOWER, but only CR and CRi were assessed in INO-VATE-ALL.

Matching-adjusted indirect comparison (MAIC) is a credible and widely-used method for comparing outcomes of interventions in the absence of head-to-head trials, and uses individual patient data from trial(s) of one treatment to match the baseline summary statistics reported from trial(s) of a comparator [21]. After matching, treatment outcomes are compared across balanced trial populations using an approach similar to propensity score weighting. It is one of the population-adjusted indirect comparison approaches recognized by the United Kingdom's National Institute for Health and Care Excellence and is well accepted across various health technology assessment (HTA) bodies [22, 23]. To adjust for heterogeneity in enrollment criteria and baseline characteristics between the trial populations and to provide a fair comparison between blinatumomab and InO, this analysis used MAIC to indirectly compare efficacy (OS and CR) between these therapies for R/R ALL. Simulated treatment comparison, another approach to adjust for observed baseline differences between trials, was not used in the analysis because that approach may introduce bias for nonlinear outcomes.

METHODS

Data Sources

Patient-level data from the blinatumomab and SOC arms of the Phase III trial TOWER were used in the current analyses. TOWER was a multicenter, randomized, open-label study that enrolled 405 adult patients with Ph− primary R/R precursor B-cell ALL (untreated first relapse with first remission duration < 12 months, untreated second or greater relapse, or relapse at any time after allogeneic HSCT) [11]. Patients were randomized at a 2:1 ratio to receive blinatumomab or SOC chemotherapy regimens. Patients in the blinatumomab arm received two induction cycles, with up to three consolidation cycles and up to 12 months of maintenance, if patients achieved a bone marrow response ($\leq$ 5% bone marrow blasts) or CR/CRh/CRi.

Aggregated data for the InO and SOC arms of the Phase III trial INO-VATE-ALL as of January 5, 2017 were extracted from the literature [14, 16, 18]. INO-VATE-ALL was a randomized, open-label study of InO compared to SOC chemotherapy in adult patients with R/R CD22-positive ALL. The trial enrolled 326 patients who were randomized at a 1:1 ratio to receive InO or SOC chemotherapy. Patients in the InO arm could receive up to 6 cycles with no maintenance phase.

As this was a post hoc analysis of previously published data, no institutional board review was required. This analysis followed the principles of the Declaration of Helsinki.

Sample Selection

The study populations of the INO-VATE-ALL and TOWER trials were adults (aged $\geq$ 18 years) with R/R ALL, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2, and without any active central nervous system or isolated extramedullary disease. However, the INO-VATE-ALL trial additionally required patients to have received no more than one prior salvage therapy, while the TOWER trial did not. Therefore, to prevent confounding of the outcome comparisons and have a fair comparison, patients with more than one prior salvage therapy were excluded from the TOWER population, so that only patients with no more than one prior salvage therapy were included in the analysis.

Efficacy Outcomes

Outcomes examined in the current analysis included OS and the percent of patients achieving CR. OS information in INO-VATE-ALL was extracted from the published Kaplan–Meier curves using digitization software (Engauge; open source, http://digitizer.sourceforge.net/). Based on the extracted survival curves and reported numbers of events and patients at risk at various time points, pseudo-patient-level data of death and time to death were generated using the approach described by Guyot et al. [24]. The restricted mean survival time (RMST) was estimated and compared (at 12 and 20.7 months) to assess the cumulative treatment effect without imposing the proportional hazards (PH) assumption. The latter time period (20.7 months) was the earliest time point among the ends of follow-up periods for all four arms [i.e., blinatumomab, InO, and SOC chemotherapy (TOWER and INO-VATE-ALL)].

Other outcomes [e.g., HSCT, CRi/CRh, progression-free survival (PFS), duration of remission (DOR)] were not included in the analysis. HSCT is driven by multiple factors beyond the treatments, such as the availability of appropriate donors. Without being able to adjust for those factors or having a head-to-head controlled study, the HSCT rate was not comparable between the blinatumomab and InO populations.

In addition to $< 5\%$ bone marrow blasts and no evidence of disease, patients who achieved CRi in TOWER were required to have platelets $> 100{,}000/\mu l$ or absolute neutrophil count (ANC) $> 1000/\mu l$, while no such requirements on platelets and ANC were applied to the definition of CRi in INO-VATE-ALL. It was not feasible to expand the definition of CRi in TOWER to match the broader definition in INO-VATE-ALL, therefore this outcome was not compared in this analysis. CRh was also not compared in the analysis because it was not reported in INO-VATE-ALL. From a clinical perspective, CR is more important than CRi or CRh, as it represents more meaningful and persistent recovery. Patients who achieve CRi or CRh but not CR (i.e., do not have a full recovery of peripheral blood counts) may experience symptoms related to incomplete hematological recovery, and lack of complete hematological recovery may suggest the presence of submicroscopic cancerous blast cells. This is referred to as minimal residual disease (1 or more cancerous cells in 10,000 normal cells), and is predictive of relapse.

Event-free survival (EFS) in TOWER was not compared to DOR or PFS in INO-VATE-ALL in this analysis. EFS and DOR were assessed among different populations. EFS was assessed among patients who achieved CR, CRi, or CRh in TOWER, while DOR was reported only among patients who achieved CR or CRi in INO-VATE-ALL. The events for EFS and PFS were defined differently. For EFS, the events included hematological or extramedullary relapse after achieving CR/CRh/CRi, or death. For PFS, the events included disease progression (i.e., objective progression, relapse from CR/CRi, or treatment discontinuation due to global deterioration of health status), starting new induction therapy or post-study stem cell transplant without achieving CR/CRi, or death. It was not feasible to recreate DOR or PFS curves for TOWER using the definitions reported in the INO-VATE-ALL publications due to the different CRi definitions. Additionally, treatment discontinuation due to health deterioration, one of the end points for DOR and PFS in INO-VATE-ALL, was not recorded in TOWER.

Statistical Analyses

MAIC methodology was used to compare outcomes among adult patients with R/R ALL receiving blinatumomab versus InO who received no more than one prior salvage therapy. Baseline characteristics for patients in TOWER were weighted to match the average baseline characteristics reported in INO-VATE-ALL, including sex, age, race, ECOG performance status, bone marrow blast levels, previous salvage therapy, previous allogeneic transplantation, CR to most recent induction therapy, and duration of first remission. These baseline characteristics were selected based on their availability in both trials, and their

potential to be treatment effect modifiers based on the results from subgroup analyses in TOWER and INO-VATE-ALL.

The individual patient weights were estimated with a logistic regression model using the method of moments [25, 26]. The weighted outcomes in TOWER were statistically compared to the observed outcomes in INO-VATE-ALL in the balanced trial populations. Both non-anchor-based (i.e., comparing active treatment arms without accounting for the common SOC arm) and anchor-based (i.e., comparing active treatment arms relative to the common SOC arm) approaches were used in this analysis. CR rates were compared using Chi squared tests before matching and Wald tests after matching, and reported with 95% CI. OS curves were compared using unweighted and weighted log-rank tests. Hazard ratios were assessed using unweighted and weighted Cox PH models, and the PH assumption was tested. RMSTs were compared using Wald tests and reported with 95% CI. Statistical significance was set at $p < 0.05$.

RESULTS

Ninety patients were excluded from the TOWER population due to having more than one previous salvage therapy. In addition, 5 patients had missing baseline characteristics and were also excluded from the analysis. A total of 203 patients receiving blinatumomab and 107 patients receiving SOC chemotherapy were included from TOWER, with inclusion of 164 patients receiving InO and 162 receiving SOC chemotherapy from INO-VATE-ALL.

The baseline characteristics of each patient population are summarized in Table 1. Before matching, the TOWER population (blinatumomab arm) was younger (43% vs. 33% younger than 35 years old, respectively), included fewer Asians (7% vs. 19%), more Whites (85% vs. 68%), more patients with previous salvage therapies (44% vs. 32%), more patients with previous HSCT (29% vs. 18%), and had higher bone marrow blasts (74% vs. 67% with $\geq$ 50% blasts) compared to the INO-VATE-ALL population (InO arm). After applying weights to the baseline characteristics of patients enrolled in TOWER, the summary statistics of their adjusted baseline characteristics matched those of the INO-VATE-ALL population.

In the comparison of OS between patients receiving blinatumomab versus InO, the median OS for blinatumomab increased from 8.4 (95% CI 6.4, 10.8) months before matching to 9.3 (7.5, 14.3) months after matching, and both were higher than the median OS for InO [7.7 (95% CI 6.3, 9.2) months] (Table 2). The OS curves for patients receiving blinatumomab, InO, and SOC chemotherapy (INO-VATE-ALL and TOWER) before and after matching are shown in Fig. 1; no statistically significant difference (p value from the log-rank tests) was found between the OS curves for blinatumomab versus InO before ($p = 0.8$) or after matching ($p = 0.4$). The PH assumption between blinatumomab and InO was not met according to the test for independence between scaled Schoenfeld residuals and time.

Comparisons of RMST among the patient populations were conducted at 12 months (Table 3) and 20.7 months (Table 4). At 12 months, the RMST for blinatumomab increased from 7.42 (95% CI 6.78, 8.06) months before matching to 7.77 (7.02, 8.53) months after matching. While anchored to the SOC chemotherapy arms, the RMST for blinatumomab was higher than that for InO both before [difference (95% CI) 1.02 (− 0.41, 2.44) months] and after [1.62 (0.06, 3.19) months] matching, and the difference in after-matching anchored RMST was statistically significant ($p = 0.04$). Similarly, at 20.7 months, the RMST for blinatumomab also increased after matching, from 10.25 (95% CI 9.05, 11.45) months to 10.97 (9.47, 12.47) months. In addition, the unanchored and anchored RMST for blinatumomab were higher than those for InO, both before [unanchored difference (95% CI) 0.21 (− 1.42, 1.83) months; anchored difference: 1.15 (− 1.38, 3.67) months] and after matching [unanchored difference: 0.87 (− 0.99, 2.73) months; anchored difference: 2.35 (− 0.47, 5.17) months; all $p > 0.05$].

In the comparison of CR between patients receiving blinatumomab versus InO, without considering the SOC arms, a higher percentage

Table 1 Baseline characteristics

	Before matching		After matching			
	Blinatumomab ***n*** **= 203 (%)**	**SOC (TOWER)** ***n*** **= 107 (%)**	**Blinatumomab** ***n*** **= 203 (%)**	**SOC (TOWER)** ***n*** **= 107 (%)**	**InO** ***n*** **= 164 (%)**	**SOC (INO-VATE-ALL)** ***n*** **= 162 (%)**
Sex						
Female	41.4%	43.0%	44.5%	37.0%	44.5%	37.0%
Male	58.6	57.0	55.5	63.0	55.5	63.0
Age < median age in INO-VATE-ALL[a]	56.7	55.1	50.0	50.0	50.0	50.0
Age < 35 years	42.9	37.4	32.9	31.5	32.9	31.5
Race						
White	84.7	84.1	68.3	74.1	68.3	74.1
Black	2.0	2.8	2.4	1.9	2.4	1.9
Asian	7.4	7.5	18.9	14.8	18.9	14.8
Other	5.9	5.6	10.4	9.3	10.4	9.3
ECOG status						
0	39.4	40.2	37.8	37.9	37.8	37.9
1	47.8	44.9	49.4	49.7	49.4	49.7
2	12.8	15.0	12.8	12.4	12.8	12.4
Bone marrow blasts						
< 50%	26.1	23.4	32.7	29.8	32.7%	29.8
≥ 50%	73.9	76.6	67.3	70.2	67.3	70.2
Previous salvage therapy	44.3	40.2	31.5	35.4	31.5	35.4
Previous HSCT	28.6	29.9	17.7	19.8	17.7	19.8
Complete remission to most recent prior induction therapy	68.5	62.6	73.8	68.5	73.8	68.5
Duration of first remission < 12 months	45.8	36.4	58.5	65.4	58.5	65.4

ECOG Eastern Cooperative Oncology Group, *HSCT* hematopoietic stem cell transplantation, *InO* inotuzumab ozogamicin, *SOC* standard of care chemotherapy

[a] In the INO-VATE-ALL trial, the median ages were 46.5 years for the InO arm and 47.5 years for the SOC chemotherapy arm

of patients treated with blinatumomab achieved CR (37.4%) compared to the patients treated with InO (33.5%) before matching [difference (95% CI): 3.9% (− 5.9%, 13.7%); $p = 0.437$)] (Table 5). After matching, the CR rate for blinatumomab decreased to 36.9%, but

Table 2 Comparison of median OS (months)

	Before matching		After matching	
	Estimate	**95% CI**	**Estimate**	**95% CI**
Median OS				
Blinatumomab	8.4	(6.4, 10.8)	9.3	(7.5, 14.3)
InO	7.7	(6.3, 9.2)	7.7	(6.3, 9.2)
SOC (TOWER)	4.0	(3.3, 6.4)	3.7	(2.6, 6.6)
SOC (INO-VATE-ALL)	6.2	(4.9, 8.4)	6.7	(5.0, 8.4)

CI confidence interval, *InO* inotuzumab ozogamicin, *OS* overall survival, *SOC* standard of care chemotherapy

remained numerically higher than the CR rate for InO (33.5%) [difference (95% CI) 3.3% (− 6.8%, 13.5%); $p = 0.520$]. When the CR rate of active treatment arms was anchored to the SOC arms, blinatumomab was associated with a similar relative CR rate before matching and a slightly lower relative CR rate after matching compared to InO [before matching: difference (95% CI) 0.3% (− 13.3%, 14.0%), $p = 0.963$; after matching: difference (95% CI) − 2.8% (− 17.5%, 11.9%); $p = 0.705$]. These differences were not statistically significant.

DISCUSSION

The absence of head-to-head clinical trials comparing blinatumomab versus InO for R/R ALL results in a knowledge gap regarding their comparative treatment efficacy. In addition, key differences in inclusion and exclusion criteria, outcome definitions, and baseline characteristics of the pivotal trials for blinatumomab (TOWER) and InO (INO-VATE-ALL) limit the interpretability of naïve comparisons. To address this gap, the present analysis used MAIC methods to match the trials' inclusion and exclusion criteria as well as adjust for available patient baseline characteristics between the blinatumomab and InO populations, and provides a fairer and more interpretable comparison of these therapies. The results indicated that, after matching, patients with R/R ALL receiving blinatumomab had similar rates of CR and longer median OS compared to those receiving InO, and statistically significantly longer RMST at 12 months on therapy. In other words, the average survival time during the first year was longer for patients who received blinatumomab than those who received InO, suggesting a potential OS benefit with blinatumomab.

The current analysis provided valuable evidence on the efficacy for the choice of therapies in treating patients with R/R ALL who received no more than one prior salvage therapy, and the findings have potential implications for real-world practice. Future studies are recommended to confirm the present findings. For example, studies that compare blinatumomab and InO in other ALL patient populations, such as patients treated with more than one prior salvage therapy, may provide further evidence on treatment selections. Additionally, there may be other factors besides efficacy that could impact the clinical decision of treatment (e.g., adverse events following the blinatumomab and InO treatments) which merit future investigation. Finally, future studies may assess whether these compounds could be used in combination given their structures, mechanisms of action, and potential for acting in a cooperative way.

The reliability of a MAIC depends on the proper implementation because different implementations could potentially lead to opposite conclusions. A previous analysis by Stelljes et al. also indirectly compared blinatumomab and InO and concluded that InO has a statistically significant advantage over blinatumomab with respect to remission and HSCT rate, and a favorable trend for EFS and long-term OS [15]. However, there are some major

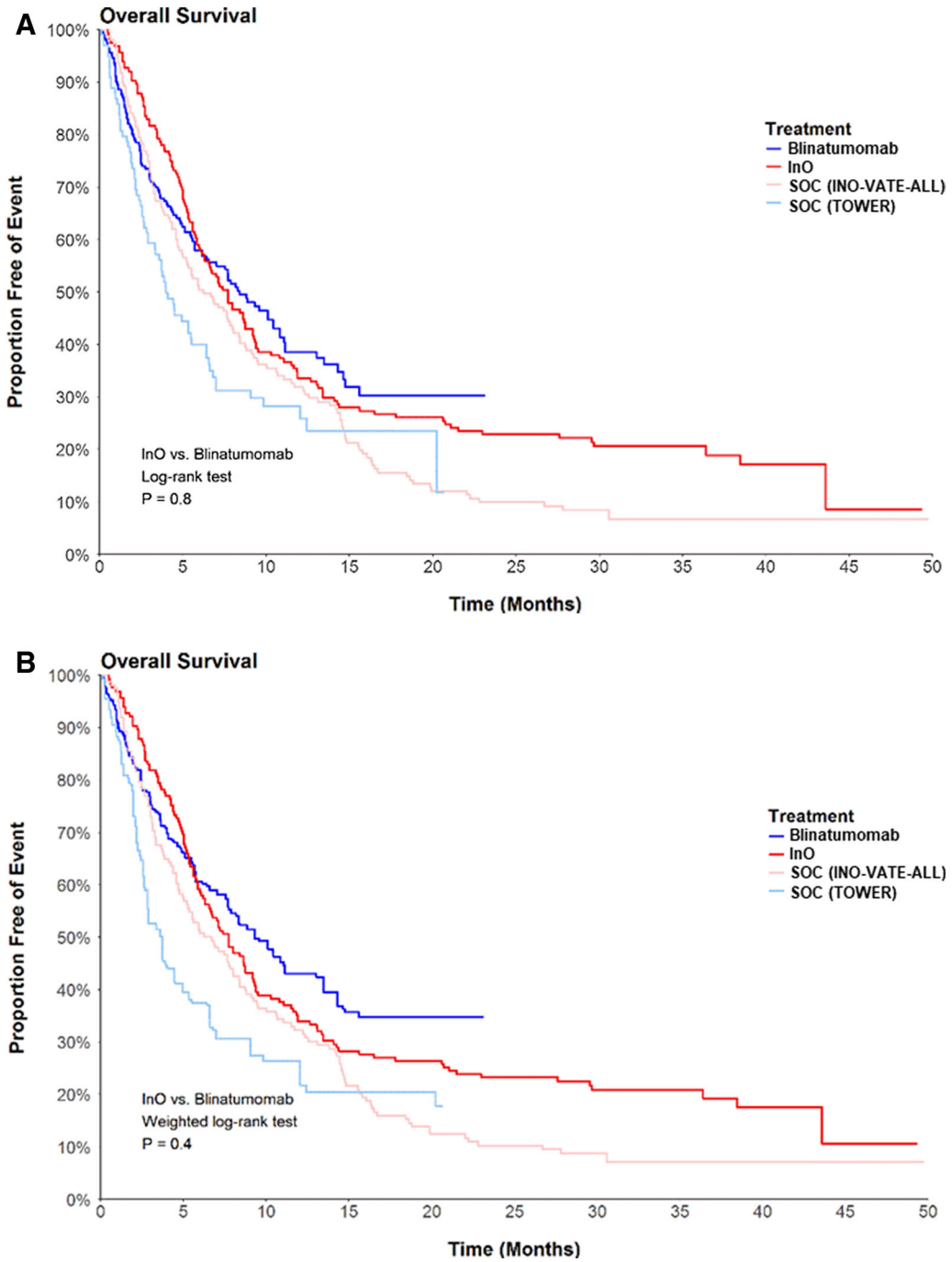

Fig. 1 Comparison of OS before (**a**) and after (**b**) matching. *InO* inotuzumab ozogamicin, *OS* overall survival, *SOC* standard of care chemotherapy

differences between that analysis and the current analysis. First, the two analyses used different data sources: the previous analysis used patient-level data for INO-VATE-ALL and aggregated data for TOWER, while the current analysis utilized patient-level data for TOWER and aggregated data for INO-VATE-ALL. Because the INO-VATE-ALL trial only enrolled patients with one or fewer prior salvage therapy, the analysis by Stelljes et al. [15]. was not able to

Table 3 Comparison of RMST at 12 months

	Before matching			After matching		
	Estimate	**95% CI**	***P* value**	**Estimate**	**95% CI**	***P* value**
RMST (months)						
Blinatumomab	7.42	(6.78, 8.06)	–	7.77	(7.02, 8.53)	–
InO	7.60	(7.00, 8.21)	–	7.63	(7.03, 8.22)	–
SOC (TOWER)	5.71	(4.82, 6.60)	–	5.46	(4.42, 6.50)	–
SOC (INO-VATE-ALL)	6.91	(6.23, 7.59)	–	6.93	(6.27, 7.60)	–
Difference in RMST (months)						
Blinatumomab vs. InO						
Non-anchor-based	− 0.18	(− 1.06, 0.70)	0.69	0.15	(− 0.81, 1.11)	0.76
Anchor-based	1.02	(− 0.41, 2.44)	0.16	1.62	(0.06, 3.19)	0.04*

CI confidence interval, *InO* inotuzumab ozogamicin, *RMST* restricted mean survival time
*Significant at $p < 0.05$

Table 4 Comparison of RMST at 20.7 months

	Before matching			After matching		
	Estimate	**95% CI**	***P* value**	**Estimate**	**95% CI**	***P* value**
RMST (months)						
Blinatumomab	10.25	(9.05, 11.45)	–	10.97	(9.47, 12.47)	–
InO	10.04	(8.94, 11.14)	–	10.09	(8.99, 11.20)	–
SOC (TOWER)	7.71	(6.11, 9.31)	–	7.23	(5.40, 9.06)	–
SOC (INO-VATE-ALL)	8.65	(7.57, 9.73)	–	8.71	(7.64, 9.77)	–
Difference in RMST (months)						
Blinatumomab vs. InO						
Non-anchor-based	0.21	(− 1.42, 1.83)	0.80	0.87	(− 0.99, 2.73)	0.36
Anchor-based	1.15	(− 1.38, 3.67)	0.37	2.35	(− 0.47, 5.17)	0.10

CI confidence interval, *InO* inotuzumab ozogamicin, *RMST* restricted mean survival time

match the number of prior salvage therapies across the two trials. This limitation led to a much higher proportion of patients with two or more prior salvage therapies in TOWER even after matching, which introduced bias in favor of InO. On the other hand, the previous analysis was able to exclude Philadelphia-chromosome-positive (Ph+) patients from the INO-VATE-ALL population to match the TOWER population, which was not feasible in the current analysis. Finally, the previous analysis compared CR/CRi rate, HSCT rate, EFS, and OS despite the inconsistencies in the definitions. Therefore, the conclusions from the analysis by Stelljes et al. need to be interpreted with these limitations in mind.

Table 5 Comparison of CR before and after matching

	INO-VATE-ALL	Before matching			After matching		
		TOWER	TOWER vs. INO-VATE-ALL		TOWER	TOWER vs. INO-VATE-ALL	
	CR	CR	Difference in CR (95% CI)	*p* value	CR	Difference in CR (95% CI)	*p* value
Active treatment	33.5%	37.4%	3.9% (− 5.9%, 13.7%)	0.437	36.9%	3.3% (− 6.8%, 13.5%)	0.520
SOC	16.0%	19.6%	3.6% (− 5.9%, 13.0%)	0.458	22.2%	6.2% (− 4.4%, 16.8%)	0.254
Active treatment—SOC	17.5%	17.8%	0.3% (− 13.3%, 14.0%)	0.963	14.7%	− 2.8% (− 17.5%, 11.9%)	0.705

CI confidence interval, *CR* complete remission with full hematological recovery, *SOC* standard of care chemotherapy

Limitations

This analysis is subject to the following limitations. First, as with any comparison of non-randomized treatment groups, the method assumed that there were no unmeasured confounding variables. While this method accounted for observed baseline characteristics, differences between the trials and unobserved baseline characteristics may impact outcomes and could not be eliminated in this indirect comparison. Only a properly randomized head-to-head trial can avoid the potential impact of differences in unobserved baseline characteristics.

Second, after matching, the SOC chemotherapy arm for TOWER had a shorter median OS and RMST than the SOC chemotherapy arm for INO-VATE-ALL. Because INO-VATE-ALL was conducted more recently than TOWER, this difference could be due to an improvement in the quality of SOC chemotherapy.

In addition, some differences between TOWER and INO-VATE-ALL could not be eliminated by matching baseline characteristics due to a lack of overlap in the patient population. For example, the percentage of Ph + patients was not matched in the anchor-based comparison because the TOWER trial only included Ph− patients. The efficacy and tolerability of blinatumomab among adult patients with Ph+ R/R precursor B cell ALL have been evaluated in a Phase II trial [27] which did not include a SOC arm nor a maintenance phase of blinatumomab. Therefore, it was not pooled with TOWER for the comparisons versus InO.

Finally, as with any indirect treatment comparison based on clinical studies, the results should be interpreted under the treatment schedules used in TOWER and INO-VATE-ALL trials.

CONCLUSIONS

This analysis indirectly compared efficacy outcomes between blinatumomab and InO as the treatment options for adult patients with R/R ALL who received no more than one line of salvage therapy using MAIC methodology and following implementation guidelines by HTA bodies. After adjusting for heterogeneity in patient characteristics between the trial populations, blinatumomab exhibited a similar CR rate as InO and a potential OS benefit, with statistically significantly longer RMST at 12 months. Further analyses are suggested to confirm these findings.

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