Blinatumomab for Minimal Residual Disease (MRD) in Adults with B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL): Median Overall Survival (OS) Is Not Reached in Complete MRD Responders at a Median Follow-up of 53.1 Months

Authors: Nicola Goekbuget, Hervé Dombret, Gerhard Zugmaier, Massimiliano Bonifacio, Carlos Graux, Christoph Faul, Max S. Topp, Monika Brüggemann, Kate Taylor and Ralf Bargou

Background: When adults with BCP-ALL achieve hematologic complete remission with intense chemotherapy, approximately 30% have persistent or recurrent MRD by real-time quantitative polymerase chain reaction or flow cytometry (Brüggemann et al, *Blood* 2006;107:1116-23). MRD is the strongest predictor of relapse in BCP-ALL. Blinatumomab is a bispecific antibody construct that redirects T cells to kill CD19+target cells. In a multinational, single-arm study (BLAST; NCT01207388) in adults with BCP-ALL and presence of MRD, we previously reported that 78% (88/113) of evaluable patients achieved a complete MRD response after cycle 1 of blinatumomab treatment (Gökbuget et al, *Blood* 2018;131:1522-31). Patient incidences of grade 3 or 4 adverse events, including neurologic events (13%) or cytokine release syndrome (2%), were consistent with previous blinatumomab studies. After a minimum patient follow-up of 18 months, median OS was 36.5 months (95% confidence interval [CI]: 19.8 to not estimable).

Objective: This report describes long-term OS for adults with BCP-ALL and MRD, with a minimum patient follow-up of 3 years after blinatumomab treatment.

Methods: The BLAST study enrolled adults with BCP-ALL in first (CR1) or subsequent (CR2+) hematologic complete remission after at least 3 intensive chemotherapy blocks, with MRD (at least 10^{-3}) at least 2 weeks after the last chemotherapy. All patients received blinatumomab 15 µg/m^2 per day for up to 4 cycles. Each cycle was 4 weeks of continuous infusion and 2 weeks off. Complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}. After MRD response assessment at the end of cycle 1, patients could undergo allogeneic hematopoietic stem cell transplantation (HSCT) at any time. Kaplan-Meier estimates of OS were determined, overall and by complete MRD response in cycle 1, after long-term follow-up (a minimum patient follow-up of 3 years). A conditional landmark of 45 days (the end of cycle 1) was used for the subgroup analyses by complete MRD response.

Results: Of the 116 patients with MRD who received blinatumomab, OS was evaluated for the 110 patients with Philadelphia chromosome-negative (Ph$^-$) BCP-ALL and less than 5% blasts at enrollment, including 74 who received HSCT while in continuous complete remission (CCR) after blinatumomab. With a median follow-up of 53.1 months, median OS was 36.5 months (95% CI: 22.0 to not estimable), and a plateau was reached (Figure 1A). In this analysis, 30 of 74 (40.5%) patients with HSCT in CCR and 12 of 36 (33.3%) patients without HSCT were alive in CCR. Analyses of OS by complete MRD response after cycle 1 in 107 patients excluded those with no central MRD assay (n=1) or inadequate MRD test sensitivity (n=2). In this population, median OS was not estimable (95% CI: 27.3 months

to not estimable) among complete MRD responders (n=85) and 12.5 months (95% CI: 3.2 to 39.7) among MRD nonresponders (n=22; p=.002 by log-rank test; Figure 1B). In the subset of patients who received HSCT in CCR, median OS from HSCT was not estimable (95% CI: 25.7 months to not estimable) among complete MRD responders (n=61) and 16.1 months (95% CI: 1.1 to not estimable) among MRD nonresponders (n=10). In the subset of patients with MRD in CR1, median OS was not estimable (95% CI: 29.5 months to not estimable) among complete MRD responders (n=60) and 10.6 months (95% CI: 2.7 to 39.7) among MRD nonresponders (n=13).

Conclusions: In this multinational study of adults with BCP-ALL in hematologic complete remission with persistent MRD or MRD relapse at baseline, median OS was 36.5 months after blinatumomab treatment, with median long-term follow-up of 53.1 months, and OS reached a plateau. Median OS was not estimable (ie, not reached) among the patients who had achieved a complete MRD response after cycle 1 of blinatumomab treatment, or among the subsets of patients who had achieved a complete MRD response with blinatumomab either in CR1 or with subsequent HSCT in CCR. These results provide further support for the long-term benefits in OS associated with blinatumomab treatment in adults with BCP-ALL and MRD.

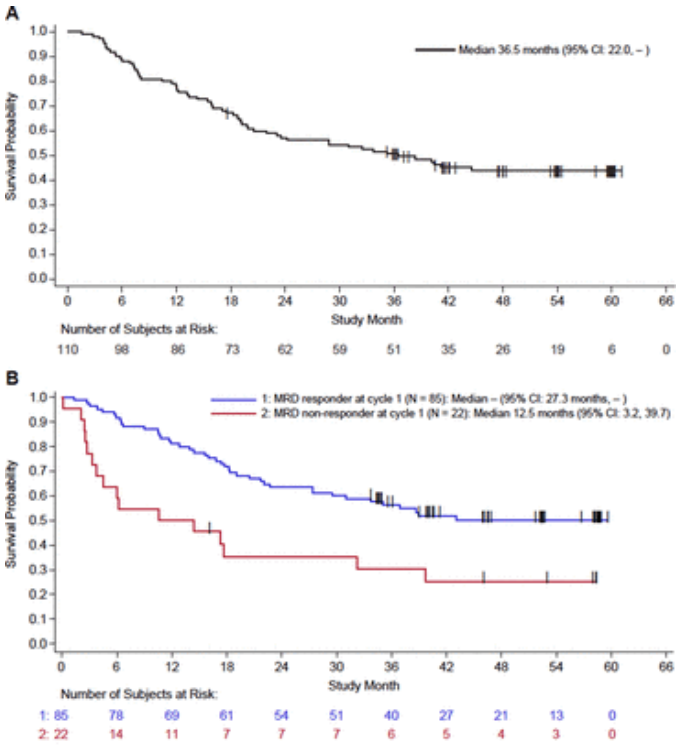


Figure 1. Overall survival. (A) Evaluable patients (Ph- BCP-ALL and <5% blasts at baseline; n = 110). (B) Evaluable patients with adequate MRD response assessment at cycle 1 (n = 107). Vertical bars indicate censoring; –, not estimable.

Poster Perspectives: Acute Lymphoblastic Leukemia Posters and Abstracts from San Diego

Chemoimmunotherapy with Inotuzumab Ozogamicin Combined with Mini-Hyper-CVD, with or without Blinatumomab, for Newly Diagnosed Older Patients with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: Results from a Phase II Study

Authors: Nicholas J Short, Elias J. Jabbour, Farhad Ravandi, Xuelin Huang, Nitin Jain, Koji Sasaki, Naveen Pemmaraju, Naval G. Daver, Joseph David Khoury, Jeffrey L. Jorgensen, Yesid Alvarado, Marina Y. Konopleva, Guillermo Garcia-Manero, Tapan M. Kadia, Musa Yilmaz, Gautam Borthakur, Jan A. Burger, Steven M. Kornblau, William G. Wierda, Courtney D. DiNardo, Alessandra Ferrajoli, Patrice Nasnas, Jovitta Jacob, Rebecca E. Garris, Susan M. O'Brien and Hagop M. Kantarjian

Background: Both the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin (INO) and the CD3-CD19 bispecific T-cell engager blinatumomab have single-agent activity in relapsed or refractory acute lymphoblastic leukemia (ALL). We previously reported the promising efficacy and survival of INO in combination with low-intensity mini-hyper-CVD chemotherapy in older adults with newly diagnosed ALL (Kantarjian H et al, *Lancet Oncol* 2018;19(2):240-8). We sought to improve these outcomes by adding blinatumomab to this regimen.

Methods: Patients (pts) ≥60 years of age with newly diagnosed Philadelphia chromosome-negative pre-B ALL were eligible. Pts were required to have a performance status of ≤3, total bilirubin ≤1.5 mg/dl, AST/ALT ≤3x ULN and creatinine ≤2 mg/dl. Pts received mini-hyper-CVD (cyclophosphamide and dexamethasone at 50% dose reduction, no anthracycline, methotrexate at 75% dose reduction, cytarabine at 0.5 g/m2 x 4 doses) for up to 8 cycles. INO was given at a dose of 1.3-1.8mg/m2 on day 3 of cycle 1 and 0.8-1.3mg/m2 on day 3 of cycles 2-4. Pts 1-6 received 1.3 mg/m2 for cycle 1 followed by 0.8 mg/m2 for subsequent cycles; pts 7+ received the phase II dose of 1.8 mg/m2 for cycle 1 followed by 1.3 mg/m2 for subsequent cycles. Rituximab (if CD20+) and prophylactic IT chemotherapy were given for the first 4 cycles. Responding pts received POMP maintenance for up to 3 years. After the observation of veno-occlusive disease (VOD), the protocol was amended in 9/2015 to use lower doses of INO. After this amendment (pts 35+), INO was given at 1.3 mg/m2 for cycle 1 and 1 mg/m2 for subsequent cycles. Another amendment was made in 3/2017 (pts 50+) to give INO in split doses each cycle (0.6 mg/m2 on day 2 and 0.3 mg/m2 on day 8 of cycle 1; 0.3 mg/m2 on day 2 and 8 of cycles 2-4) and 4 cycles of blinatumomab at standard dosing after the INO-based cycles, for a total of 4 cycles, and before the initiation of the maintenance therapy (i.e. cycles 5-8).

Results: 58 pts have been treated, 4 of whom were in complete remission (CR) at enrollment. Median age was 68 years (range, 60-81 years) and median CD22 expression was 97% (range, 27-100%). 31 pts (53%) were CD20+ and received rituximab.

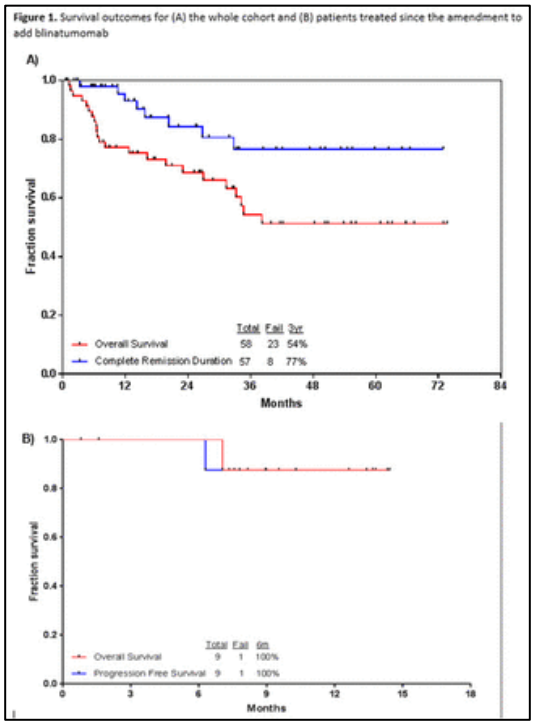
Among 54 pts evaluable for morphologic response, 53 (98%) responded (CR, n=47; CRp, n=5; CRi, n=1). Only 1 pt did not respond. MRD negativity by 6-color flow cytometry was

achieved in 39/52 pts (75%) after 1 cycle and 54/57 pts (95%) overall. There were no early deaths, and the 30-day and 60-day mortality rates were 0% and 3%, respectively.

Among 57 who achieved remission, 8 (14%) relapsed, 3 (5%) underwent allogeneic SCT in CR1, 31 (54%) remain on treatment or have completed maintenance, and 17 (30%) died in CR/CRp. Causes of death for pts in CR/CRp included: sepsis (n=8), VOD (n=3), gunshot wound (n=1), dementia and deconditioning (n=1), end stage renal disease (n=1) and unknown causes (n=3). 5 pts (8%) developed VOD, 1 after subsequent allogeneic SCT. The rate of VOD was 4/49 (8%) prior to amendment #2 and 1/9 (11%) after the amendment.

With a median follow-up of 28 months (range, 2-68 months), 35 pts (60%) were alive, 32 of whom (55%) were in CR and MRD negative status. The 3-year continued remission and OS rates were 77% and 54%, respectively (**Figure 1A**). The outcomes of the 9 pts treated since amendment #2 are shown in **Figure 1B.** One pt developed VOD and died after 4 cycles of mini-hyper-CVD. Compared to a similar historical cohort of older pts treated with hyper-CVAD ± rituximab (n=77), mini-hyper-CVD + INO ± blinatumomab resulted in significantly higher 3-year OS (54% vs 32%; P=0.002).

Conclusions: Mini-hyper-CVD + INO ± blinatumomab, is safe and effective in elderly pts with newly diagnosed Ph-negative ALL, with an overall response rate of 98% and 3-year OS rate of 54%.



Poster Perspectives: Acute Lymphoblastic Leukemia Posters and Abstracts from San Diego

Sequential Combination of Low-Intensity Chemotherapy (Mini-hyper-CVD) Plus Inotuzumab Ozogamicin with or without Blinatumomab in Patients with Relapsed/Refractory Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia (ALL): A Phase 2 Trial

Authors: Koji Sasaki, Hagop M. Kantarjian, Farhad Ravandi Nicholas J Short, Partow Kebriaei, Xuelin Huang, Michael E. Rytting, Nitin Jain, Marina Y. Konopleva, Guillermo Garcia-Manero, Richard E Champlin, Tapan M. Kadia, Jorge E. Cortes, Zeev E. Estrov, Koichi Takahashi, Morgan Mace, Maria Khouri, Patrice Nasnas, Jovitta Jacob, Rebecca E. Garris and Elias J. Jabbour

Background: The combination of low intensity therapy with inotuzumab ozogamicin improved survival compared to intensive chemotherapy and to single agent inotuzumab ozogamicin in first salvage (Jabbour et al. Cancer. 2018 (in press)). The incidence of veno-occlusive disease (VOD) is minimized with weekly divided dosage and reduced dose of inotuzumab ozogamicin per cycle.

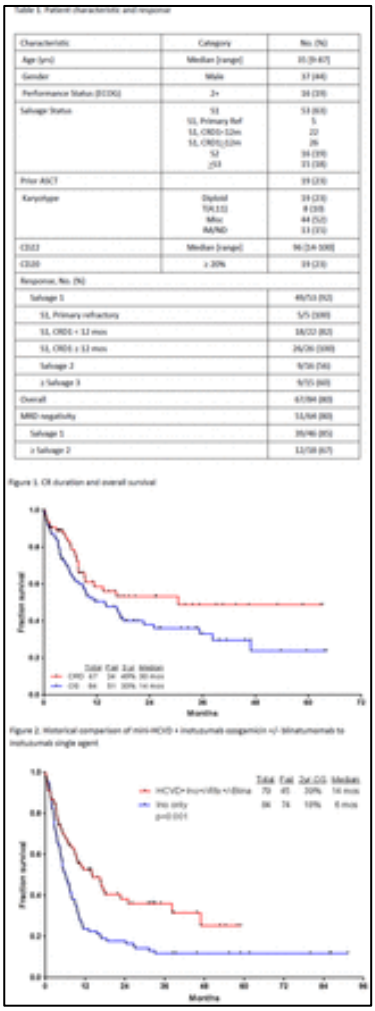
Blinatumomab single agent improves survival in relapsed / refractory ALL compared to that of standard chemotherapy. The sequential addition of blinatumomab to mini-hyper-CVD + inotuzumab ozogamicin might further improve survival and minimize the risk of veno-occlusive disease (VOD) by allowing a reduction of inotuzumab dose and spacing allogeneic stem cell transplant (ASCT) from the last dose of inotuzumab.

Methods: Patients with relapsed / refractory Philadelphia chromosome negative ALL were eligible. The mini-hyper-CVD (cycles 1, 3, 5, 7) comprised cyclophosphamide (150 mg/m^2 every 12 h on days 1-3), vincristine (2 mg flat dose on days 1 and 8), and dexamethasone (20 mg on days 1-4 and days 11-14) without anthracycline. Even cycles (cycles 2, 4, 6, 8) comprised methotrexate (250 mg/m^2 on day 1) and cytarabine (0.5 g/m^2 given every 12 h on days 2 and 3). Rituximab and intrathecal chemotherapy were given for first 4 courses. Inotuzumab ozogamicin was originally given on day 3 of the first four cycles at the dose of 1.3-1.8 mg/m^2 at cycle 1, followed by 1.0-1.3 mg/m2 in subsequent cycles. After 67 pts were treated, an amendment was made to incorporate 4 cycles of blinatumomab after 4 cycles of mini-hyper-CVD + inotuzumab ozogamicin. Inotuzumab ozogamicin was given on days 2 and 8 at the dose of 0.6 and 0.3 mg/m^2 at cycle 1, respectively, followed by days 2 and 8 at the dose of 0.3 and 0.3 mg/m^2 at subsequent cycles; blinatumomab was continuously infused over 28 days every 42-day cycle for 4 cycles. The decision to proceed with ASCT was based on the discretion of the treating physician after discussion with the patient.

Results: From 2/2013 to 5/2018, 84 patients were enrolled and treated including 17 patients with mini-hyper-CVD + inotuzumab + blinatumomab. The median follow-up is 31 months (range, 0.1-64.1). Patient characteristics and outcome are summarized in Table 1. The median age was 35 years (range, 9-87), and 23% of patients had received prior ASCT. The overall response rate was 80% (CR, 58%, CRp/CRi, 21%). These rates were 92% in S1 (primary refractory, 100%; CR1 duration <12 months, 82%; CR1 duration >12 months, 100%) and 56% in S2, and 60% in S3 or higher. Among 64 evaluable patients for minimal residual disease (MRD) assessment, 51 patients (80%) achieved negative MRD by 6-color

flow cytometry with higher rates of negative MRD at 85% in salvage 1. Thirty four patients (40%) received ASCT. Three-year CR duration and overall survival (OS) rates were 49% and 33%, respectively (Figure 1). The median OS was 25 months, 6 months, and 7 months in salvage 1, salvage 2, and salvage 3 or more, respectively (p=0.001). Historical comparison showed median OS of 14 months and 6 months in hyper-CVD + inotuzumab ozogamicin +/- blinatumomab and inotuzumab ozogamicin single agent, respectively (p=0.001) (Figure 2). Among the 79 evaluable patients, VOD was observed in 9 (11%). The incidence of VOD was reduced from 9/61 (15%) with single dose of inotuzumab ozogamicin to 0/18 (0%) with weekly divided dose schedule. Of the 17 patients treated with mini-hyper-CVD + inotuzumab ozogamicin + blinatumomab, 3 patients underwent ASCT (2, haploidentical transplant; 1, cord blood transplant).

Conclusions: The combination of inotuzumab ozogamicin plus/minus blinatumomab with low-intensity mini-hyper-CVD chemotherapy is effective and shows encouraging results in patients with relapsed/refractory ALL. The risk of VOD can be minimized with fractionated inotuzumab ozogamicin dosing.



Poster Perspectives: Acute Lymphoblastic Leukemia Posters and Abstracts from San Diego

A Phase II Study of the Hyper-CVAD Regimen in Sequential Combination with Blinatumomab As Frontline Therapy for Adults with B-Cell Acute Lymphoblastic Leukemia (B-ALL)

Authors: Guillaume Richard-Carpentier, Hagop M. Kantarjian, Nicholas J Short, Farhad Ravandi, Alessandra Ferrajoli, Heather M Schroeder, Maria Khouri, Guillermo Garcia-Manero, Guillermo Montalban Bravo, Jorge E. Cortes, Nitin Jain, Marina Y. Konopleva, Koichi Takahashi, Koji Sasaki, Rebecca E. Garris and Elias J. Jabbour

Background: Multi-agent combination chemotherapy regimens for the treatment of ALL are considered a cancer success story in the pediatric setting. For adults, the same magnitude of success has not been realized using similar strategies. These regimens produce high complete remission (CR) rates of 80-90% but the cure rates are 40-50%. The incorporation of targeted agents (tyrosine kinase inhibitors and monoclonal antibodies) has improved survival and cure rates in adult ALL subsets. Blinatumomab, a bispecific T-cell engaging (BiTE) CD19-CD3 antibody, is effective in patients with relapsed/refractory disease and in patients with measurable residual disease (MRD). Better outcomes were obtained when blinatumomab was administered earlier in the course of the disease. We hypothesized that incorporating blinatumomab in sequential combination with Hyper-CVAD in previously untreated patients with ALL would improve the eradication of MRD, decrease the need for intensive chemotherapy, and improve survival.

Methods: Patients were eligible to participate in this phase 2 single-arm study if they were at least 14 years old, had newly diagnosed untreated Philadelphia-negative B-ALL or B-cell lymphoblastic lymphoma, had ECOG performance status (PS) of 0-3, and normal liver, kidney and cardiac function. Patients in CR after one prior course of chemotherapy were also eligible. Therapeutic regimen consisted of 4 alternating cycles of Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone, cycles 1 & 3) and high-dose methotrexate/cytarabine (cycles 2 & 4) followed by 4 consecutive cycles of blinatumomab (4 weeks every 6 week-cycle). All patients received 8 prophylactic intrathecal injections with methotrexate and cytarabine during the first 4 cycles of treatment. Additionally, patients with CD20+ ALL (≥ 1% cells) received a total of 8 doses of rituximab (375 mg/m2) or ofatumumab (2000 mg) during the hyper-CVAD cycles. Maintenance phase consisted of POMP (6-mercaptopurine, vincristine, methotrexate, prednisone) on cycles 1-3, 5-7, 9-11 and 13-15 alternating with blinatumomab on cycles 4, 8 and 12. The primary outcome was relapse-free survival (RFS) and secondary outcomes were overall survival (OS), overall response rate and MRD negativity rate.

Results: To date, 17 patients were treated, three of them enrolled in CR after 1 cycle of Hyper-CVAD. Patient's characteristics are summarized in Table 1. Median age is 43 years (range, 20-59). All but one patient had CD20 expression. Six patients (35%) had *TP53* mutations. Four patients (24%) had low hypodiploidy-near triploidy. One patient (6%) had CRLF2 overexpression.

All 14 evaluable patients achieved CR for an overall response rate of 100%. Minimal residual disease (MRD) negativity, assessed by 6-color multicolor flow, was achieved in 93% of the patients after one cycle of therapy. No early death within 6 weeks was

reported. Patients have received a median of 4 cycles (1-4) of chemotherapy and 4 cycles (0-4) of blinatumomab. Two patients had early relapse during the Hyper-CVAD cycles after 2 and 4 cycles, respectively. Three patients underwent allogeneic stem cell transplantation (HSCT) (1 with histiocytic proliferation in the bone marrow, 1 with t(4;11) and 1 with CRLF2+ ALL). A total of 14 patients have initiated the blinatumomab phase. Nine patients received the total 8 courses of hyper-CVAD and blinatumomab and are currently receiving maintenance in CR.

The treatment was well tolerated. Grade 3-4 adverse events attributed to blinatumomab occurred in 2 patients (12%) and were manageable and reversible. One patient developed transient Grade 3 cytokine release syndrome and one had Grade 3 ataxia. Both recovered after holding blinatumomab therapy and dexamethasone administration. Treatment was resumed thereafter with no recurrence.

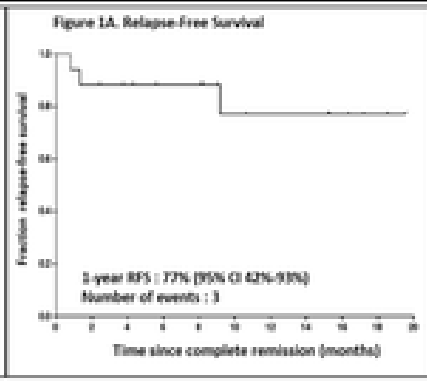
With a median follow up of 14 months (range, 3-20 months), 16 patients (94%) are alive (14 of them in first CR); one patient died after HSCT of a transplant-related complication. The 1-year RFS rate was 77% (95% CI 42-93%) (Figure 1A) and the 1-year OS rate was 90% (95% CI 47-99%) (Figure 1B).

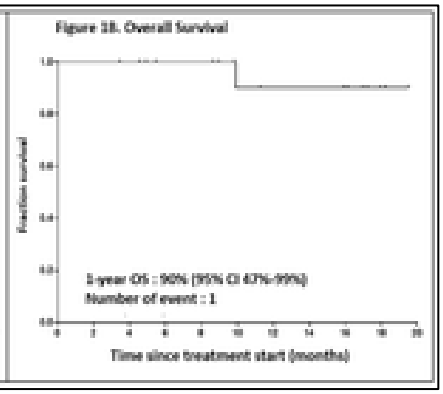
Conclusions: The sequential combination of Hyper-CVAD and blinatumomab in newly diagnosed adult patients with B-ALL is safe and highly effective. These early results are favorable. The study continues to accrue patients.

Table 1. Baseline Clinical Characteristics of the patients

Characteristic		N (%) / Median (range)
Age (years)		43 (20-59)
Sex	Male	12 (71)
PS (ECOG)	0-1	16 (76)
WBC (x 10^9/L)		2.9 (0.5-360.9)
CNS disease		1 (6)
CD20+ (%)	0 (Negative)	1 (6)
	1-19	6 (35)
	≥ 20	9 (53)
	Positive (% unavailable)	1 (6)
TP53 mutation		7 (41)
CRLF2+		1 (6)
Cytogenetics	Diploid	4 (24)
	Hyp-Tr	4 (24)
	Complex (≥ 5 anomalies)	1 (6)
	Hiahl	1 (6)
	t(4;11)(q21;q23)	1 (6)
	Other	6 (35)

Abbreviations: WBC, white blood cell count; Hyp-Tr, low hypodiploidy / near triploidy; Hiahl, high hyperdiploidy.





Results of SWOG 1318: A Phase 2 Trial of Blinatumomab Followed by POMP (Prednisone, Vincristine, Methotrexate, 6-Mercaptopurine) Maintenance in Elderly Patients with Newly Diagnosed Philadelphia Chromosome Negative B-Cell Acute Lymphoblastic Leukemia

Authors: Anjali S. Advani, Anna Moseley, Kristen Marie O'Dwyer, Brent Wood, Min Fang, Matthew J. Wieduwilt, Ibrahim Aldoss, Jae H. Park, Rebecca Klisovic, Maria R. Baer, Wendy Stock, Rupali Bhave, Megan Othus, Mark R. Litzow, Richard M. Stone and Harry P. Erba

Background: The prognosis of elderly patients (pts) with acute lymphoblastic leukemia (ALL) remains poor, and novel therapeutic approaches are clearly needed. CD19 is expressed on the majority of precursor-B ALLs and represents an attractive therapeutic target. The anti-CD19 bi-specific engager antibody blinatumomab has demonstrated significant activity in both relapsed/refractory ALL and minimal residual disease (MRD) positive ALL. Therefore, we evaluated blinatumomab as a single agent in the upfront treatment of newly diagnosed elderly pts with Philadelphia chromosome (Ph) negative B-lineage ALL to determine response rates and overall survival (OS).

Methods: Pts were treated at National Clinical Trial Network sites from June 2015 to September 2017. The primary objective of the study was to estimate 3-year OS. An IND was approved by the FDA and the protocol was approved by a central institutional review board. Eligibility: age > 65 years, newly diagnosed Ph negative B-lineage ALL with adequate organ function and no evidence of central nervous system (CNS) disease. Pts received blinatumomab for induction at standard dosing for 1-2 cycles until attainment of complete response (CR) or CR with incomplete count recovery (CRi) (defined below). Pts then received 3 cycles of blinatumomab post-remission therapy followed by 18 months of maintenance POMP (prednisone, vincristine, 6-mercaptopurine, methotrexate). A total of 8 doses of intrathecal methotrexate were administered as CNS prophylaxis. Cytogenetic risk was ascribed by NCCN 2018 criteria and bone marrow samples were analyzed for the presence of the Ph-like signature. MRD was assessed centrally by 8 color flow cytometry pre-treatment, on Day 35 of induction cycle 1, and on Day 35 of re-induction (if applicable). Response was assessed at the completion of 1-2 cycles of blinatumomab. CR was defined as < 5% marrow blasts with no evidence of extramedullary disease and recovery of counts [absolute neutrophil count (ANC) > 1000/uL, platelets >100,000/uL]. CRi was defined the same as CR but ANC < 1000/ uL and/ or platelets ≤ 100,000/ uL. OS was measured from day of registration on trial until the date of death. Disease-free survival (DFS) was measured from the date the pt achieved CR/ CRi until relapse or death. Toxicities were graded according to NCI CTCAE version 4.0.

Results: Of 31 pts enrolled, 29 were eligible. The median age was 75 years (range 66 - 84), 22 (76%) were male, median baseline white blood count was 3.7 x 10^3/uL (range 0.3 - 7,100), and median bone marrow blast count percentage was 86.5% (range 30-100). Three pts received hydroxyurea or steroids prior to treatment initiation. Cytogenetic risk at diagnosis was: poor (34% of pts; n=10), standard (55% of pts; n=16), good (3% of pts; n=1) and unknown (7% of pts, n=2). Testing for the Ph-like signature is being completed. The most common Grade 3-5 non-hematologic toxicities related to treatment during

induction were hyperglycemia (14%), dyspnea (10%), febrile neutropenia (10%), hypertension (10%), and lung infection (7%). One pt developed Grade 3 cytokine release syndrome and 1 developed Grade 3 neurotoxicity. No pts died during the first 28 days of treatment. The overall response rate (CR + CRi) was 66% (all CRs). Thirteen of the 19 responders have available MRD data post-treatment. Of these, 12 pts (92%) achieved MRD negativity, all at Cycle 1 Day 35. One pt required 2 cycles of blinatumomab to achieve CR. One pt proceeded to allogeneic hematopoietic stem cell transplant. The median follow-up time is 1 year and median duration on trial is 170 days (6 pts are still on maintenance therapy). OS estimated by Kaplan Meier at 6 months is 79% (95% CI 58%-90%) and at 1 year is 65% (95% CI 43%-80%). DFS estimated at 6 months is 68% (95% CI 43%-84%) and at 1 year is 56% (95% CI 31%-75%). No baseline features including CD19 expression (by percentage or mean-fluorescent intensity) or presence of a CD19 negative subpopulation were associated with response.

Conclusions: Blinatumomab was well tolerated and effective in the treatment of newly diagnosed elderly patients with Ph negative B-lineage ALL. Further follow up will determine the durability of these responses.

Poster Perspectives: Acute Lymphoblastic Leukemia Posters and Abstracts from San Diego

Disease Burden Subgroup Analysis of Health-Related Quality of Life of Blinatumomab Versus Standard-of-Care Chemotherapy in Patients with Relapsed or Refractory Philadelphia Chromosome-Negative B-Cell Precursor Acute Lymphoblastic Leukemia in a Randomized, Open-Label Phase 3 Study (TOWER)

Authors: Anthony S. Stein, Zachary F. Zimmerman, Paul Cannell, Hervé Dombret, Johan Maertens, Max S. Topp, Janet L. Franklin, Ze Cong, Xinke Zhang, Yan Li and Andre Schuh

Background: In the phase 3 TOWER study, patients with relapsed or refractory (r/r) Philadelphia chromosome-negative (Ph-) B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) who received bispecific T-cell engager (BiTE®) antibody construct blinatumomab had improved overall survival (OS; median, 7.7 vs 4.0 months; *P*=0.01;) and health-related quality of life (HRQoL) compared with those who received standard of care (SOC) chemotherapy (Kantarjian H, et al. *N Engl J Med*. 2017;376:836-847; Topp MS, et al. *Blood*. 2018;131:2906-2914). In this subgroup analysis of TOWER, we assessed the HRQoL between patients with low versus high baseline disease burden (low versus high bone marrow blast levels) who received blinatumomab or SOC chemotherapy.

Methods: Patients (N=405) with r/r Ph- BCP ALL were randomized 2:1 to receive 2 cycles of induction blinatumomab by continuous intravenous infusion (n=271) or SOC (n=134). Those in remission could receive up to 3 consolidation cycles; 12 months of maintenance was allowed for those who received up to 3 consolidation cycles and had bone marrow response. HRQoL was assessed using the EORTC QLQ-C30 Questionnaire on days 1 (baseline), 8, and 15; on day 29 of cycle 1; days 1, 15, and 29 of consolidation; and at the safety follow-up. The questionnaire included 1 global health status scale, 5 functioning scales, 3 symptom scales, and 6 single-symptom items. For global health status and functioning scales, a higher score indicates better HRQoL; for symptom scales/items, a lower score indicates better HRQoL. A 10-point change was viewed as the minimum clinically important difference in EORTC QLQ-C30 (Zikos E, et al. EORTC. 2016). HRQoL was assessed in patient subgroups by screening the bone marrow aspirates for low blast levels (<50% blasts) versus high blast levels (≥50% blasts). Although blast count was not a randomization stratification factor in TOWER, baseline HRQoL values were assessed for blinatumomab versus SOC in both subgroups; in the high blasts group, for blinatumomab versus SOC, the only differences were cognitive functioning and constipation scores, which were significantly higher, and for the diarrhea score, which was significantly lower. Between the subgroups, only physical functioning was significantly different (higher in the high blasts group). Analyses included patients with baseline and ≥1 postbaseline result of any multi-item scale or single-item measure. Mean change from baseline in scores for each scale/item were summarized for cycle 1. Time to deterioration (TTD) analyses assessed the treatment effect based on timing from the initiation of treatment to a 10-point deterioration from baseline.

Results: In total, 342 patients (blinatumomab, n=247; SOC, n=95) had ≥1 HRQoL result: low blasts, n=87 (blinatumomab, n=64; SOC, n=23); high blasts, n=255 (blinatumomab, n=183; SOC, n=72). The EORTC QLQ-C30 analysis set included all randomized subjects with a nonmissing baseline result and at least 1 nonmissing post-baseline result of any

EORTC QLQ-C30 scale/item. There was no statistically significant difference in baseline HRQoL scores between the high and low blasts groups; however, the high blasts group had worse HRQoL overall. Baseline HRQoL scores were also similar between blinatumomab arm and SOC arm for each group. Global health status was improved by blinatumomab regardless of baseline blast level; however, this effect was somewhat greater in the low blasts group. When the function scores worsened, the extent of worsening was almost always smaller for blinatumomab versus SOC, particularly in the high blasts group. Functioning status scores tended to stay the same or worsen with both blinatumomab and SOC regardless of blast level, except emotional scores, which improved with blinatumomab regardless of blast level (Figure 1). Symptom scores generally improved with blinatumomab but not with SOC, particularly in patients with high blasts (Figure 2). TTD analyses showed that hazard ratios favored blinatumomab over SOC, particularly in patients with high blasts (Table).

Conclusions: Blinatumomab improved HRQoL in patients with r/r Ph- BCP ALL and delayed the time to clinically meaningful deterioration in HRQoL compared with SOC. The treatment effects of blinatumomab versus SOC on HRQoL were particularly larger among patients with high disease burden.

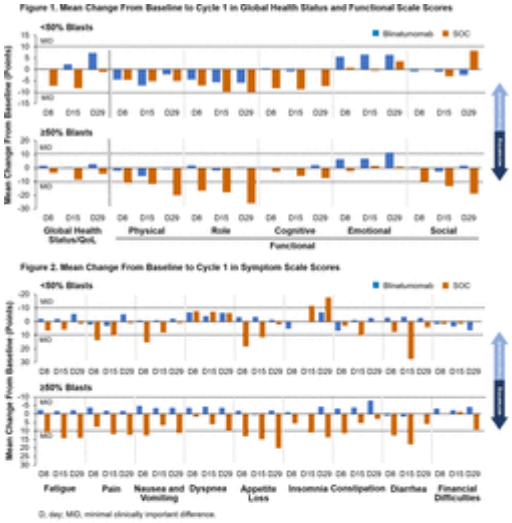


Table 1. HR and Log-Rank *P* Values of TTD Analyses

	<50% Blasts		≥50% Blasts	
	HR (95% CI)	*P*[a]	HR (95% CI)	*P*[a]
Global health status	0.46 (0.23–0.94)	0.023	0.69 (0.46–1.04)	0.063
Physical functioning	1.16 (0.58–2.30)	0.66	0.61 (0.43–0.87)	0.004
Role functioning	0.80 (0.43–1.51)	0.43	0.56 (0.40–0.80)	0.001
Cognitive functioning	0.79 (0.40–1.56)	0.41	0.63 (0.44–0.92)	0.008
Emotional functioning	0.79 (0.40–1.56)	0.41	0.58 (0.36–0.92)	0.017
Social functioning	2.48 (0.93–6.61)	0.056	0.62 (0.43–0.88)	0.005
Fatigue	0.71 (0.37–1.38)	0.28	0.52 (0.37–0.72)	<0.001
Pain	0.54 (0.29–1.03)	0.046	0.52 (0.37–0.74)	<0.001
Nausea and vomiting	0.48 (0.23–1.04)	0.058	0.52 (0.37–0.74)	<0.001
Dyspnea	0.91 (0.39–2.73)	0.86	0.55 (0.35–0.84)	0.004
Appetite Loss	0.60 (0.28–1.27)	0.17	0.37 (0.25–0.54)	<0.001
Insomnia	2.00 (0.84–4.77)	0.11	0.65 (0.44–0.96)	0.022
Constipation	0.60 (0.28–1.26)	0.15	0.43 (0.27–0.68)	<0.001
Diarrhea	0.16 (0.06–0.44)	<0.001	0.38 (0.25–0.58)	<0.001
Financial difficulties	0.71 (0.32–1.61)	0.39	0.86 (0.51–1.44)	0.52

CI, confidence interval; HR, hazard ratio.
[a]Log-rank test stratified by age, prior salvage therapy, and prior alloHSCT; HR <1.0 indicates a lower average event rate and longer survival for blinatumomab versus SOC.

http://www.bloodjournal.org/content/132/Suppl_1/3967