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### Permalink

<https://escholarship.org/uc/item/37q486fh>

### Journal

Cancer, 125(15)

### ISSN

0008-543X

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### Publication Date

2019-08-01

### DOI

10.1002/cncr.32139

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Peer reviewed



Published in final edited form as:

*Cancer*. 2019 August 01; 125(15): 2579–2586. doi:10.1002/cncr.32139.

## Inotuzumab Ozogamicin in Combination with Low-Intensity Chemotherapy (mini-hyper-CVD) with or without Blinatumomab vs. Standard Intensive Chemotherapy (hyper-CVAD) as Frontline Therapy for Older Patients with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: a Propensity Score Analysis

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### Abstract

**Background:** The outcome of older patients with newly diagnosed Philadelphia chromosome (Ph)-negative acute lymphoblastic leukemia (ALL) is poor. The combination of targeted therapy with low-intensity chemotherapy was safe and effective. The aim of the analysis is to compare outcome of patients treated with the combination of inotuzumab ozogamicin with low-intensity chemotherapy (mini-HCVD) with or without blinatumomab to that of patients who received the standard intensive hyper-CVAD (HCVAD) regimen.

**Methods:** We analyzed 135 older patients with newly diagnosed Ph-negative ALL treated prospectively with standard HCVAD (n=77) or with the combination of inotuzumab ozogamicin with mini-HCVD with or without blinatumomab (n=58). A propensity score analysis was conducted using 1:1 matching with the nearest neighbor matching method.

**Results:** Propensity score matching identified 38 patients in each cohort. The antibody-low intensity chemotherapy combination induced higher response rates (98% vs 88%) with lower rates of early death (0% vs 8%) and lower rates of death in complete remission (5% vs 17%). With propensity score matching, the 3-year event-free survival (EFS) rates for HCVAD and the

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Authorship Contributions

E.J. treated patients, designed the study, analyzed the data, wrote, and edited the manuscript. K.S. treated patients, collected data, analyzed the data, and wrote the manuscript. J.J. M.K., and R.G. managed the data. N.J.S. treated patients and collected the data. H.K. treated patients, designed the study, wrote, and edited the manuscript. F.R., N.D., T.K., M.K., N.J., P.T., G.C.I., G.G.M., J.C., N.P., M.Y., and S.O. treated patients. All authors provided significant intellectual input, and reviewed and approved the final version of the manuscript.

Disclosure of Conflict of Interest

combination of inotuzumab ozogamicin with mini-HCVD with or without blinatumomab were 34% and 64%, respectively ( $p=0.003$ ). The 3-year OS rates were 34% and 63%, respectively ( $p=0.004$ ). By multivariate analysis, age ( $p=0.019$ ; HR=1.045) and the combination of inotuzumab with mini-HCVD with or without blinatumomab ( $p=0.020$ ; HR=0.550) were identified as independent prognostic factors for survival.

**Conclusion:** The combination of inotuzumab ozogamicin with mini-HCVD with or without blinatumomab is safe and effective in older patients with newly diagnosed Ph-negative ALL, and confers better outcome when compared with standard HCVAD chemotherapy.

### Precis:

The combination of inotuzumab ozogamicin with mini-HCVD with or without blinatumomab is safe and effective in older patients with newly diagnosed Ph-negative ALL, and confers better outcome when compared with standard HCVAD chemotherapy.

### Keywords

Older ALL; inotuzumab; blinatumomab; mini-HCVD; outcome

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### Introduction

Novel recent therapies are producing revolutionary results in adult acute lymphoblastic leukemia (ALL).<sup>1–12</sup> Similar intensive chemotherapy strategies have not yielded comparable results in older patients with ALL, who have estimated cure rates of only 10–20%.<sup>1–2, 13–17</sup>

In older patients with ALL, intensive chemotherapy results in lower response rates than those observed in younger patients with ALL, and high rates of toxicities.<sup>13–15</sup> One-third of patients achieving complete response (CR) may die of myelosuppression-associated complications.<sup>14</sup> Among 727 older patients (>65 years; 2007–2012) treated under Medicare, median survival was 10 months.<sup>16</sup> In the National Cancer Institute Surveillance, Epidemiology, and End Results database, among 1675 adults (age ≥60 years) with ALL (1980–2011), the median survival was 4 months, and the 3-year survival rate 12.8%.<sup>17</sup>

Inotuzumab ozogamicin, a CD22 monoclonal antibody bound to calicheamicin, resulted in an overall response rate of 80% and a median survival of 7.7 months among patients with relapsed-refractory ALL (R-R ALL).<sup>18</sup> The addition of targeted immunotherapy inotuzumab ozogamicin to effective low-intensity chemotherapy in patients with R-R ALL has shown promising results with an overall response rate of 80% and a median survival of 11 months, compared with 6 months with single-agent inotuzumab. Similarly, the combination of inotuzumab ozogamicin with effective low-intensity chemotherapy in patients 60 years and older was found to be safe and highly effective, with 2-year survival rate of 66%.<sup>19</sup>

There is no standard of care for older patients with ALL, and there is no randomized clinical trials comparing novel strategies including the combination of targeted immunotherapy inotuzumab ozogamicin and blinatumomab, a bispecific T-cell engager (BiTE) with dual affinity for CD19 and CD3,<sup>20</sup> with low-intensity chemotherapy with historical treatment strategies. Therefore the optimal frontline therapy for older patients with ALL is not well-

defined. The aim of this study is to compare clinical outcomes of older patients with newly diagnosed Philadelphia chromosome (Ph)-negative ALL treated with the combination of inotuzumab ozogamicin and low-intensity chemotherapy (mini-hyper-CVD), with or without blinatumomab, to those who received standard adjusted-dose intensive hyper-CVAD (HCVAD). A propensity score analysis was used in order to balance patient characteristics and reduce bias when performing a retrospective comparison of patients treated with each of these regimens.

## Methods

### Patients and Treatment

Patients 60 years and older with newly diagnosed Ph-negative ALL treated on consecutive prospective phase 2 clinical trials with either HCVAD or mini-hyper-CVD + inotuzumab, with or without blinatumomab, were analyzed. Patients who received HCVAD derived from our historical experience before November 1, 2011. The treatment schedules have been previously reported.<sup>6, 20–21</sup> Briefly, the mini-hyper-CVD backbone is a dose-reduced, modified hyper-CVAD with 50% reductions of cyclophosphamide and dexamethasone, omission of the anthracycline, 75% reduction of methotrexate and 83% reduction of cytarabine. Rituximab was given to all CD20-positive patients, and 8 doses of prophylactic intrathecal chemotherapy were given to all patients. After 8 cycles of mini-hyper-CVD, POMP (Prednisone, Vincristine, Methotrexate, 6-Mercaptopurine) maintenance was given for 3 years.<sup>19</sup>

The first 6 patients received inotuzumab 1.3 mg/m<sup>2</sup> during induction, and 0.8 mg/m<sup>2</sup> during consolidation. Subsequently, the dose was increased to 1.8 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup>, during induction and consolidation, respectively. However, due to the concern of veno-occlusive disease (VOD), the dose was reduced back to 1.3 mg/m<sup>2</sup> and 1 mg/m<sup>2</sup>, respectively.<sup>19</sup>

To minimize the risk of VOD, and beginning with Patient 50, the treatment schema was further amended.<sup>21</sup> Patients received 4 cycles of hyper-CVD plus inotuzumab, which is given in fractionated dosing on Days 2 and 8. During induction, patients receive inotuzumab 0.6 mg/m<sup>2</sup> on Day 2 and 0.3 mg/m<sup>2</sup> on Day 8; in Consolidations 2–4, they received 0.3 mg/m<sup>2</sup> on Days 2 and 8, respectively. The total cumulative dose of inotuzumab was 2.7 mg/m<sup>2</sup> with this modified design, compared to 4.3 mg/m<sup>2</sup> prior to this most recent amendment. The goal of this change was to reduce the incidence of VOD that has been observed with higher inotuzumab dosing.

In addition, after 4 cycles of hyper-CVD, patients received 4 cycles of blinatumomab consolidation at standard doses. Maintenance was with alternating blocks of 3 months of POMP and one cycle of blinatumomab for 16 total cycles. Notably, the maintenance period has been decreased to 18 months, which is half of the previous 3 years of POMP maintenance (Figure 1).<sup>21</sup> The schedule for prophylactic intrathecal therapy was not changed after the amendment. The decision to proceed to stem cell transplant was based on treating physician's discretion mainly in the presence of unfavorable biological factors, patient's comorbidity, and donors availability. The treatment protocols were approved by the

MD Anderson Cancer Center Institutional Review Board. Informed consent was obtained according to the Declaration of Helsinki and our institutional guidelines.

### Response Assessment and Definitions

CR was defined as the presence of  $\leq 5\%$  blasts in the bone marrow, with more than  $1 \times 10^9/L$  neutrophils, more than  $100 \times 10^9/L$  platelets in the peripheral blood, and no extramedullary disease. CR without platelet recovery (CRp) was defined as CR except for platelets less than  $100 \times 10^9/L$ . CR without complete hematologic recovery (CRi) was defined as CR but with an absolute neutrophil count of less than  $1 \times 10^9/L$  neutrophils and platelets less than  $100 \times 10^9/L$ .

Minimal residual disease (MRD) assessment by 6-color flow cytometry was performed on whole bone marrow specimens as previously described.<sup>22-24</sup> A distinct cluster of at least 20 cells that showed altered antigen expression was regarded as an aberrant population, which yielded a sensitivity of 1 in 10,000 cells (for adequate specimens in which  $2 \times 10^5$  cells could be collected).

### Statistical Methods

Multiple imputations were performed because exclusion of patients with at least one missing variable may cause bias.<sup>25</sup> Logistic regression was used for propensity score calculation from baseline patient characteristics including age, performance status, white blood cell count, percentage of blasts in peripheral blood and bone marrow, cytogenetics, percentage of CD20 and CD22 positive blasts, and the presence of central nervous system (CNS) disease. Propensity score analysis with 1:1 matching was performed with the nearest neighbor matching method using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score to balance baseline differences between cohorts.<sup>26</sup> Using prematched cohorts, univariate and multivariate analyses Cox regression analysis was performed to identify prognostic factors for overall survival (OS).<sup>27</sup>

Time from therapy to stem cell transplant (SCT) was handled as a time dependent variable. Event-free survival (EFS) was calculated from the time of treatment initiation until the date of no response (after 2 cycles), relapse, or death. OS was calculated from the time of treatment initiation until death. Survival curves were plotted by the Kaplan-Meier method and compared with the log-rank test. Differences in subgroups by different covariates were evaluated with the  $\chi^2$  test and Fisher exact test for nominal values and the Mann-Whitney U and Fisher exact tests for continuous variables. All the statistical data analyses were performed with SPSS version 24.0 software (SPSS, Chicago, IL) and R version 3.2.4. The cutoff date for follow-up was 7/2/2018.

## Results

### Patient Characteristics

Overall, we identified 135 patients age  $\leq 60$  years with newly diagnosed Philadelphia-negative ALL treated with frontline HCVAD (n=77), or the combination of inotuzumab with mini-HCVD with or without blinatumomab (n=58). The propensity score matching

identified 38 patients in each cohort (Table 1). Baseline patient characteristics before and after the propensity score matching are described in Table 1. Before the matching, patients who received the combination of inotuzumab with mini-HCVD with or without blinatumomab had a better performance status, a higher percentage of CD22 expression, and more received additional rituximab therapy. After the propensity score matching, no differences were observed between cohorts, and non-significant differences before matching were further minimized. Eight (14%) patients and 6 (16%) patients received blinatumomab in the prematched and matched cohort, respectively. In the pre-matched cohort, 3 patients, in the mini-HCVD and inotuzumab +/- blinatumomab cohort, received SCT due to the presence of low-hypodiploidy (n=1), TP53 mutations (n=1), and positive MRD after induction therapy (n=1). Two patients in the HCVAD cohort received SCT due to the presence of MLL rearrangement (n=1) and complex karyotype (n=1).

### Response Rates

The median follow-up was 110 months and 42 months in the matched HCVAD, and the combination of inotuzumab with mini-HCVD with or without blinatumomab cohorts, respectively. In the prematched cohorts, the composite CR rates were higher in the combination of inotuzumab with mini-HCVD with or without blinatumomab (98% vs 88%;  $p=0.037$ ). The rates of early death and death in CR within 3 months were higher in the standard HCVAD cohort (Table 2). The differences of all clinical variables were minimized after the propensity score matching. After matching, there was a trend for a higher CR rate and a lower rate of early death with inotuzumab and mini-HCVD. VOD was observed in one (3%) patient after matching [5 (9%) before matching]. In the prematched cohort, the median total dose of inotuzumab till the development of VOD was 3.1 mg/m<sup>2</sup> with the median of 3 cycles of mini-HCVD+INO+-blinatumomab. One patient developed VOD after the amendment in the prematched cohort.

### Survival Outcomes

Outcome has significantly improved with the combination of inotuzumab with mini-HCVD with or without blinatumomab compared with historical HCVAD therapy. The 3-year EFS rates were 49% (median 35 months) and 29% (median 11 months), respectively ( $p=0.001$ ; Figure 1A). The 3-year OS rates were 54% (median not reached) and 32% (median 16 months), respectively ( $p=0.002$ ; Figure 2A). The dose reduction of inotuzumab did not affect so far, EFS and OS in the prematched cohort, respectively ( $p=0.486$ ;  $p=0.559$ ; Supplemental Figures 1 and 2). Given the small size of the patients sample and the short follow-up, lower dose of weekly inotuzumab in addition of blinatumomab did not so far improve significantly EFS and OS ( $p=0.255$  and  $p=0.355$ , respectively; Supplemental Figures 3 and 4). With propensity score matching, the 3-year EFS rates of the combination of inotuzumab with mini-HCVD with or without blinatumomab and historical HCVAD were 64% (median not reached) and 34% (median 15 months), respectively ( $p=0.003$ ; Figure 1B). The 3-year OS rates were 63% (median not reached) and 34% (median 17 months), respectively ( $p=0.004$ ; Figure 2B). In each cohort, only 1 patient (3%) proceeded to allogeneic SCT ( $p=1.0$ ). After propensity score matching, 11 deaths and 30 deaths were observed in the mini-HCVD and inotuzumab +/- blinatumomab cohort, and HCVAD cohort, respectively. Eleven deaths in the mini-HCVD and inotuzumab +/- blinatumomab included 4 relapses and 7

deaths in CR (2 sepsis, 2 unknown causes, 1 acute myeloid leukemia, 1 myelodysplastic syndrome, and 1 VOD). Thirty deaths in the HCVAD cohort included 11 relapses and 19 deaths in CR (10 sepsis, 4 unknown causes, 2 myelodysplastic syndrome, 1 stem cell transplant-related complications, 1 progressive deconditioning, and 1 cardiopulmonary arrest).

### Multivariate Analysis for Survival

To confirm our findings, we performed univariate and multivariate Cox regression analyses for overall survival using pre-matched cohort. We identified two independent significant prognostic factors, age and the combination of inotuzumab with mini-HCVD with or without blinatumomab (Table 3). The combination of inotuzumab with mini-HCVD with or without blinatumomab confers a hazard ratio of 0.55 (risk of death decreased by 45%) with the combination compared to standard HCVAD.

### Discussion

This is the first report on clinical outcomes of the combination of inotuzumab with mini-HCVD with or without blinatumomab compared to that of historical HCVAD therapy in older patients with Philadelphia-negative ALL. Using a propensity score matching to balance baseline patient characteristics, we showed improved outcomes with the combination of targeted therapy with low dose chemotherapy. In both the pre-matched and matched cohorts, the combination of inotuzumab with mini-HCVD (with or without blinatumomab) was associated with prolonged EFS and OS compared to the HCVAD therapy. In the absence of a randomized prospective clinical trial, these results suggest that the combination of inotuzumab with mini-HCVD with or without blinatumomab is a superior frontline approach for older patients with Philadelphia-negative ALL.

Current treatment approaches for adult ALL result in long-term survival in approximately 50%–60% of patients.<sup>1–12</sup> This success rate is not paralleled in older patients where the 5-year survival remains dismal (~20%).<sup>13–17</sup> Li and colleagues recently reported a median survival of 10 months among 727 older patients (>65 years) diagnosed between 2007 and 2012 and treated under Medicare.<sup>16</sup> Using the National Cancer Institute's SEER database to assess survival among 1675 older US adults (age ≥ 60 years) with ALL between 1980 and 2011, Park and colleagues reported a median survival of 4 months and 3-year survival rate of 12.8%.<sup>17</sup> Consequently, the current standard of care is extremely poor. Often, these patients are offered hospice care.

Therapies targeting either specific molecular targets (e.g. BCR-ABL1 tyrosine kinase inhibitors) or specific leukemic cell surface antigens (e.g. CD20, CD22, and CD19 monoclonal antibodies) are major breakthroughs in the treatment of ALL.<sup>6, 11, 18, 20</sup> The addition of targeted therapy to low-intensity chemotherapy in older patients with ALL might improve their outcome.<sup>19</sup> The combination of inotuzumab with low dose chemotherapy in older ALL was shown to be safe and effective. The overall response rate was 98%. Minimal residual disease negativity rate was 96% (78% after cycle 1). The 2-year event-free and overall survival rates were 59% and 66%, respectively.<sup>19</sup> Furthermore, this combination was able to overcome the negative baseline prognostic features such as low hypodiploidy or near

triploidy (18%), and presence of TP53 mutation (38%), commonly present among older patients with ALL.<sup>28–29</sup> Advani and colleagues reported preliminary results on 31 older patients (median age 75 years, range 66–84) with newly diagnosed ALL who were treated with 3 cycles of blinatumomab followed by POMP maintenance for 18 months. The overall response rate was 66% and the 1-year survival rate was 65%. Among 13 patients evaluable for MRD assessment, 12 achieved negative MRD status.<sup>30</sup>

The efficacy of this combination may be further improved. Fractionated lower doses of weekly inotuzumab may reduce liver toxicities and the rate of VOD, and decrease the rate of prolonged thrombocytopenia.<sup>31–32</sup> The sequential addition of blinatumomab may allow the use of less chemotherapy, lower doses of inotuzumab, intensify the depth of responses, and provide a longer duration between inotuzumab and SCT, which could theoretically decrease VOD rates.<sup>32–33</sup> If the results are further improved (less relapses, better outcomes), thus would warrant the assessment of this regimen in young adults with ALL.

One potential limitation to propensity score analysis is that this type of analysis only balances known and selected variables. It is therefore possible that unrecognized risk factors might affect these findings. Furthermore, patients with significant comorbidities that might affect survival outcome were excluded from our study. Given the short follow-up after amendment of the protocol, the safety of blinatumomab during POMP maintenance therapy and the degree of long-term immunosuppression are unknown. Finally, HCVAD may not be the most appropriate and used regimen in this patient population, limiting therefore our comparison. However as mentioned before, there is no satisfactory standard of care for older patients with ALL. Thus, in the absence of randomized, controlled phase III trial, the present study offers convincing evidence for the superiority of combination of inotuzumab with mini-HCVD (with or without) blinatumomab in older patients with newly diagnosed Philadelphia-negative ALL.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Funding source

Pfizer provided free drug from the Pfizer Investigator Sponsored Trial program. Amgen provided free drug from the Amgen Investigator Sponsored Trial program.

E.J. received research grants and consultancy fees from Amgen and Pfizer. K.S. reported consultancy fees from Pfizer. H.K. reported grants from Abb Vie, grants from Agios, grants from Amgen, grants from Ariad, grants from Astex, grants from BMS, grants from Cyclacel, grants from Daiichi-Sankyo, grants from Immunogen, grants from Jazz Pharma, grants from Novartis, grants from Pfizer, other from AbbVie, other from Actinium (Advisory Board), other from Agios, other from Amgen, other from Immunogen, other from Orsinex, other from Pfizer, other from Takeda, during the conduct of the study.

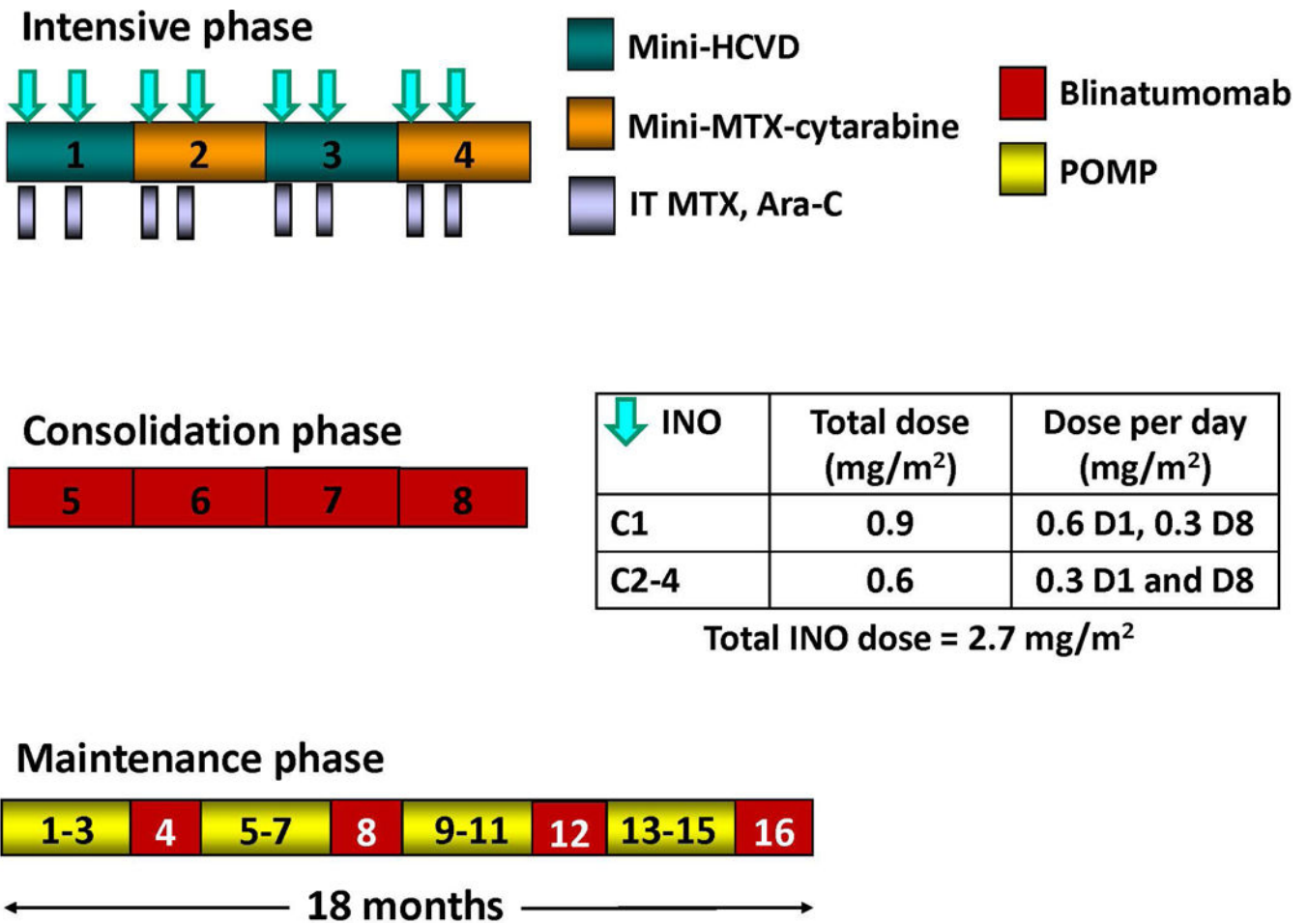
## References

1. Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia. *Cancer*. 2015;121(15):2517–28 [PubMed: 25891003]



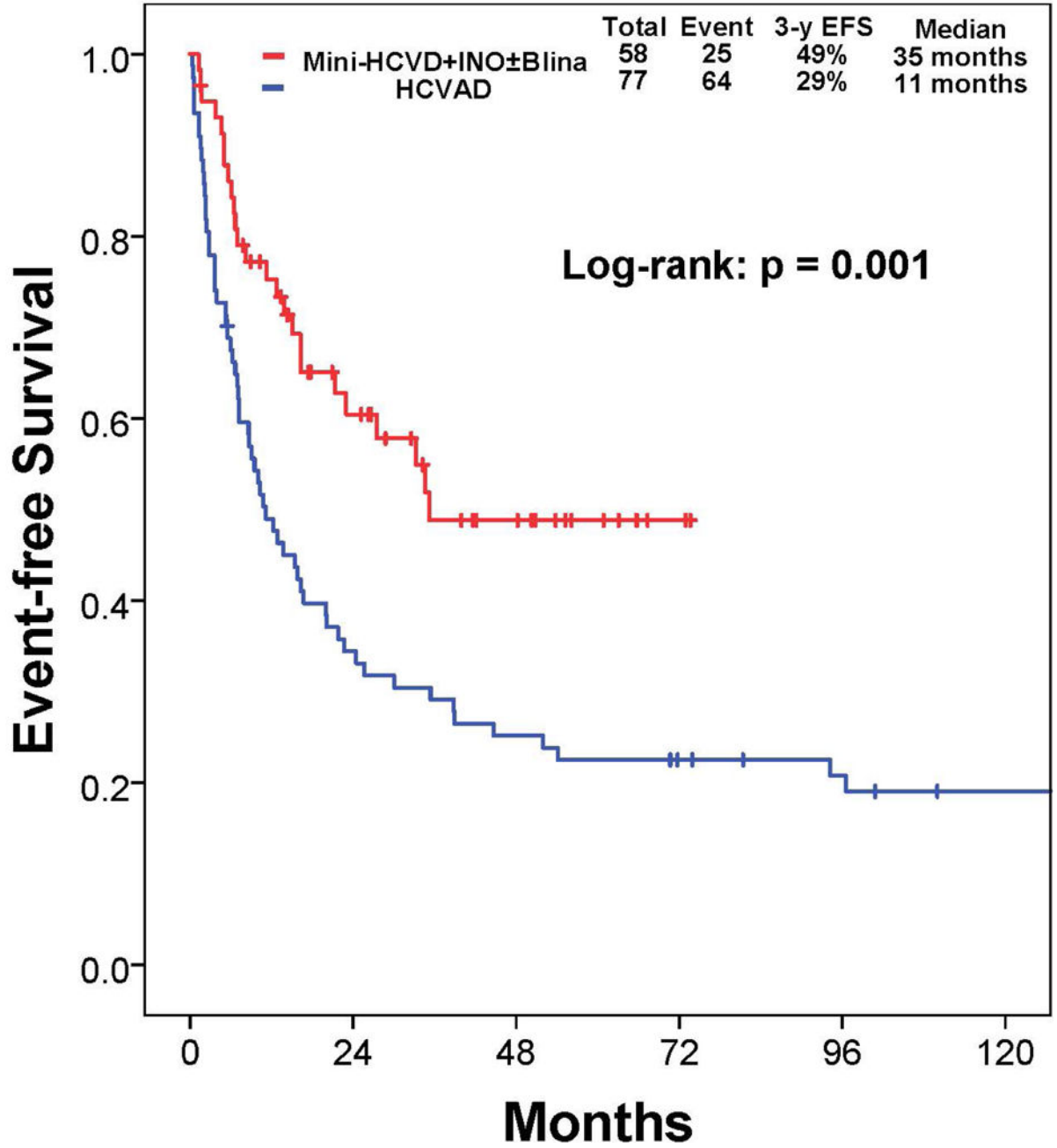
2. Jabbour E, Pui CH, Kantarjian H. Progress and Innovations in the Management of Adult Acute Lymphoblastic Leukemia. *JAMA Oncol.* 2018;4(10):1413–1420 [PubMed: 29931220]
3. Hoelzer D, Walewski J, Döhner H, et al. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. *Blood.* 2014;124(26):3870–3879 [PubMed: 25359988]
4. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer.* 2006; 106(7):1569–1580 [PubMed: 16502413]
5. Ribrag V, Koscielny S, Bosq J, et al. Dose-dense chemotherapy and rituximab versus dose-dense chemotherapy alone for HIV-negative adult patients with Burkitt Leukaemia/lymphoma: a multicentre phase 3 randomised controlled trial from the intergroup GRAALL-Lysa. *Lancet.* 2016;387(10036):2402–241 [PubMed: 27080498]
6. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol.* 2010; 28 (24):3880–3889 [PubMed: 20660823]
7. Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. *N Engl J Med.* 2016;375(11):1044–53 [PubMed: 27626518]
8. Fielding AK, Rowe JM, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. *Blood.* 2014;123(6):843–850 [PubMed: 24277073]
9. Ravandi F, O'Brien S, Thomas D, et al. First report of phase II study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood* 2010;116:2070–2077 [PubMed: 20466853]
10. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol.* 2015;16(15):1547–1555 [PubMed: 26432046]
11. Jabbour E, Short NJ, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. *Lancet Haematol.* 2018 12;5(12):e618–e627 [PubMed: 30501869]
12. Jain P, Kantarjian H, Ravandi F, et al. The combination of hyper-CVAD plus nelarabine as frontline therapy in adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma: MD Anderson Cancer Center experience. *Leukemia.* 2014;28(4):973–975 [PubMed: 24157581]
13. Gökbuget N How I treat older patients with ALL. *Blood.* 2013;122(8):1336–75. [PubMed: 23970355]
14. O'Brien S, Thomas DA, Ravandi F, et al. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. *Cancer.* 2008;113(8):2097–101 [PubMed: 18720356]
15. Gökbuget N, Joachim B, Bruggemann M, et al. Moderate intensive chemotherapy including CNS-prophylaxis with liposomal cytarabine is feasible and effective in older patients with Ph-negative acute lymphoblastic leukemia (ALL): results of a prospective trial from the German multicenter study group for adult ALL (GMALL). *Blood.* 2012;120 Abstract 1493
16. Li S, Molony JT, Chia V, Katz AJ. Patient characteristics and treatment patterns in elderly patients newly diagnosed with acute lymphoblastic leukemia (ALL) using 100% Medicare ALL data. *Blood.* 2016;128:3981
17. Geyer MB, Hsu M, Devlin SM, Tallman MS, Douer D, Park JH. Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis. *Blood.* 2017;129(13):1878–1881 [PubMed: 28122741]
18. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med.* 2016;375(8):740–53 [PubMed: 27292104]
19. Kantarjian H, Ravandi F, Short N, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. *Lancet Oncol.* 2018;19(2):240–8 [PubMed: 29352703]

20. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med.* 2017;376(9):836–47 [PubMed: 28249141]
21. Jabbour E, Sasaki K, Ravandi F, et al. Chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab, is highly effective in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first salvage. *Cancer.* 2018;124(20):4044–4055 [PubMed: 30307611]
22. Ravandi F, Jorgensen JL, O'Brien SM, et al. Minimal residual disease assessed by multi-parameter flow cytometry is highly prognostic in adult patients with acute lymphoblastic leukaemia. *Br J Haematol.* 2016;172(3):392–400 [PubMed: 26492205]
23. Jabbour E, Short NJ, Jorgensen JL, et al. Differential impact of minimal residual disease negativity according to the salvage status in patients with relapsed/refractory B-cell acute lymphoblastic leukemia. *Cancer.* 2017;123(2):294–302 [PubMed: 27602508]
24. Short NJ, Jabbour E, Albitar M, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts. *Am J Hematol.* 2018 11 5.
25. Rubin DB. *Multiple Imputation for Non-Response in Surveys.* New York, NY: John Wiley 1987
26. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70: 41–55
27. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011;46:399–424 [PubMed: 21818162]
28. Kanagal-Shamanna R, Jain P, Takahashi K, et al. TP53 mutation does not confer a poor outcome in adult patients with acute lymphoblastic leukemia who are treated with frontline hyper-CVAD-based regimens. *Cancer.* 2017;123(19):3717–3724 [PubMed: 28608976]
29. Short NJ, Jabbour E, Ravandi F, et al. 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. *Blood* 132: abst 36; 2018
30. Advani A, Moseley A, O'Dwyer KM, et al. 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. *Blood* 132: abst 33; 2018
31. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calicheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol.* 2012; 13(4):403–411 [PubMed: 22357140]
32. Kantarjian HM, DeAngelo DJ, Advani AS, et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. *Lancet Haematol.* 2017; S2352–3026(17)30103–5
33. Kantarjian HM, Stein AS, Bargou RC, et al. Blinatumomab treatment of older adults with relapsed/refractory B-precursor acute lymphoblastic leukemia: Results from 2 phase 2 studies. *Cancer.* 2016;122(14):2178–85 [PubMed: 27143254]

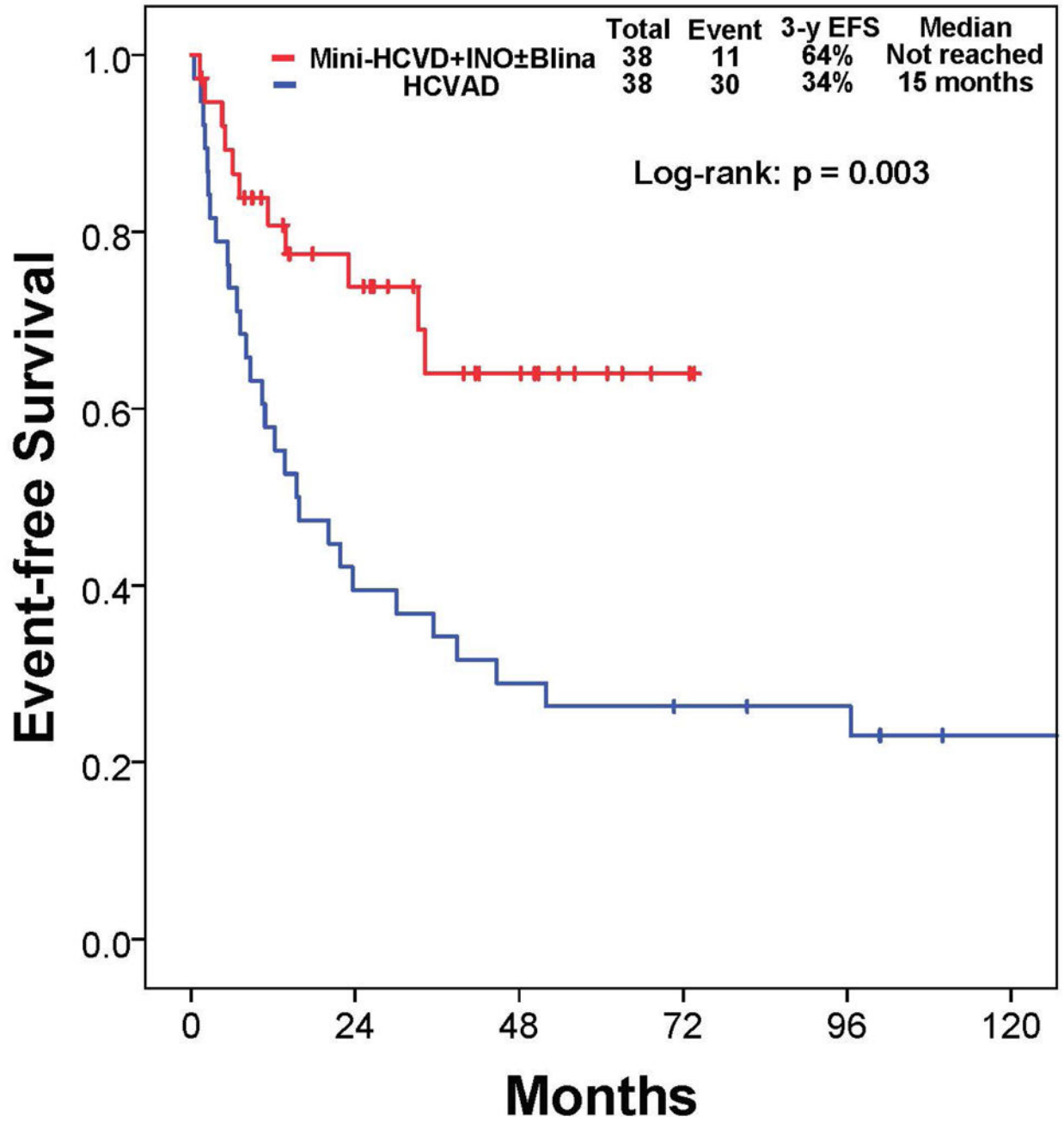


**Figure 1.**  
Treatment schedule of mini-HCVD + INO +/- Blina

a)

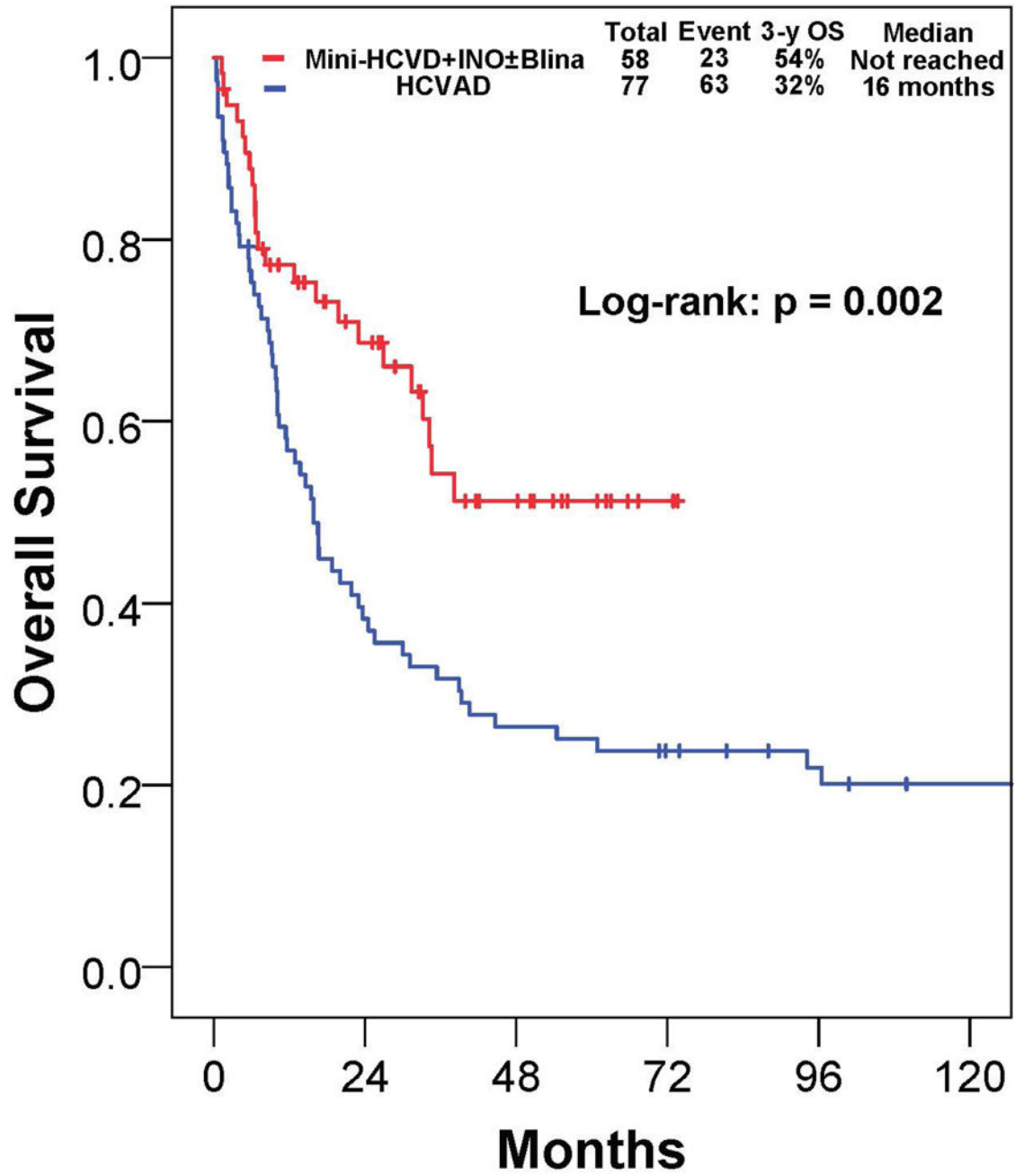


b)

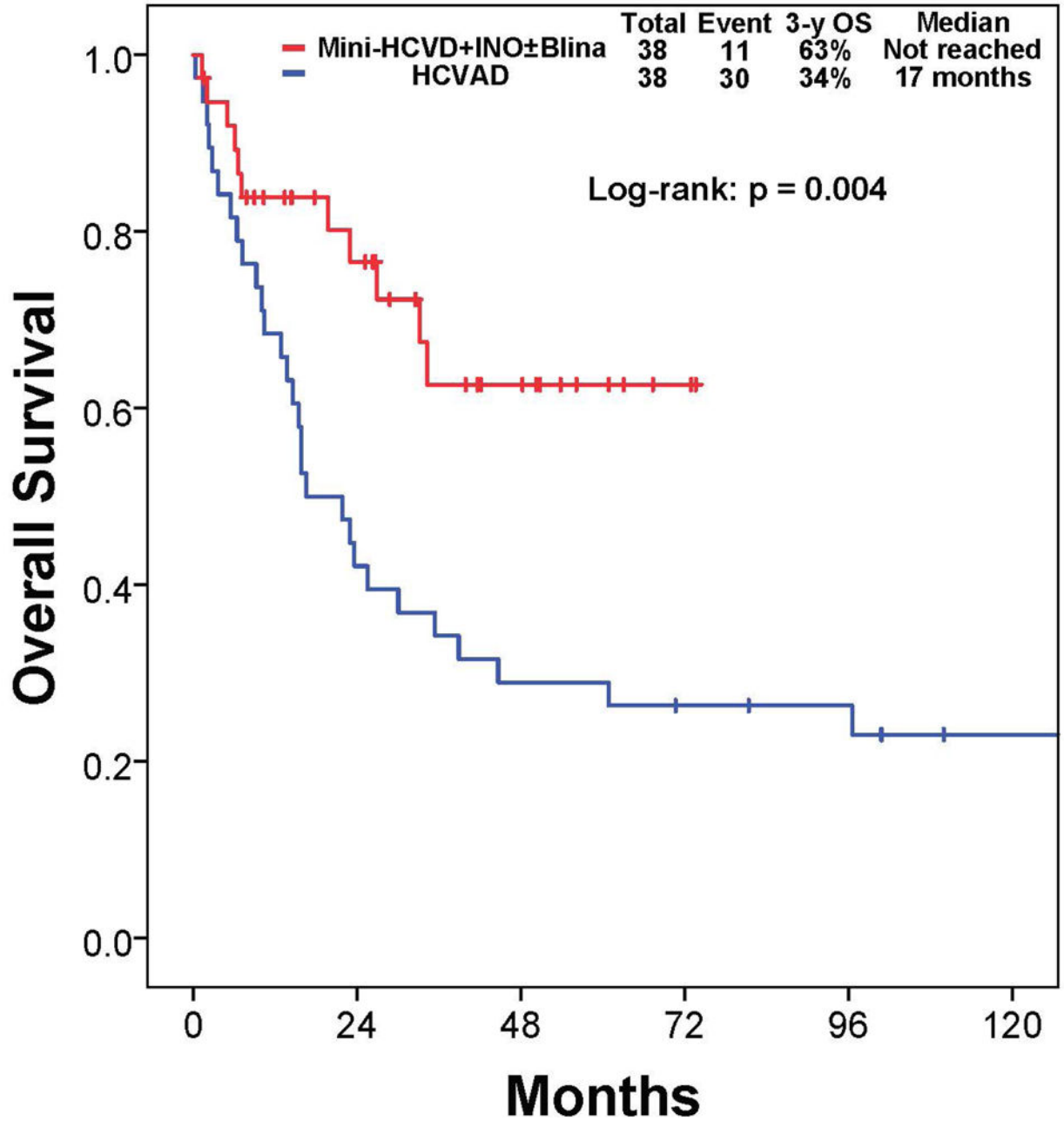


**Figure 2.** Event-free survival: HCVAD and mini-HCVD + INO +/- Blina: A) before matching, B) after matching

a)



b)



**Figure 3.** Overall survival: HCVAD and mini-HCVD + INO +/- Blina: A) before matching, B) after matching

**Table 1.**

Baseline patient characteristics before and after propensity score matching

No. (%) / Median	Pre-matched cohorts			Matched cohorts		
	Mini-HCVD-INO+/-Blina N=58	HCVAD N=77	P	Mini-HCVD-INO+/-Blina N=38	HCVAD N=38	P
Age, years	68 (60–81)	69 (60–83)	0.483	68 (60–81)	66 (60–83)	0.654
PS 2 (%)	8 (14)	23 (30)	0.028	3 (8)	5 (13)	0.711
WBC, / $\mu$ L	3.0	3.9	0.081	3.1	3.1	0.901
% PB blasts	11	27	0.100	12	7	0.871
% BM blasts	82	80	0.592	81	79	0.693
CD20, %	28	40	0.625	49	54	0.913
CD22, %	97	90	<0.001	96	95	0.557
CNS +, (%)	3 (6)	8 (10)	0.312	3 (8)	4 (11)	1.000
Karyotype, No (%)						
Diploid	19 (33)	24 (31)	0.445	13 (34)	13 (34)	0.983
HeH	6 (10)	5 (7)		4 (11)	2 (5)	
Ho-Tr	10 (17)	6 (8)		5 (13)	4 (11)	
Misc.	11 (19)	20 (26)		8 (21)	10 (26)	
T(4;11)	1 (2)	5 (7)		1 (3)	1 (3)	
Complex	1 (2)	2 (3)		1 (3)	1 (3)	
Not available	10 (17)	15 (20)		6 (16)	7 (18)	
Therapy, No (%)						
Rituximab	46 (79)	36 (47)	<0.001	27 (71)	28 (74)	0.798
ASCT	3 (5)	2 (3)	0.443	1 (3)	1 (3)	1.000

Abbreviations: mini-HCVD, mini-hyper-CVD; INO, inotuzumab ozogamicin; Blina, blinatumomab; HCVAD, hyper-CVAD; PS, performance status; WBC, white blood cell; PB, peripheral blood; BM, bone marrow; CNS, central nervous system; HeH, high hyperdiploidy; Ho-Tr, low hypodiploidy / near triploidy; Misc., miscellaneous; ASCT, allogeneic stem cell transplant.



**Table 2.**

Responses and outcomes before and after matching

	Pre-matched cohorts			Matched cohorts		
	<u>Mini-HCVD-INO+/-Blina</u> N=58	<u>HCVAD</u> N=77	<u>P</u>	<u>Mini-HCVD-INO+/-Blina</u> N=38	<u>HCVAD</u> N=38	<u>P</u>
Response (%)						
CR/CRi/CRp	53/57 (98)	68/77 (88)	0.037	33/34 (97)	34/38 (90)	0.361
Early death (%)	0	6 (8)	0.030	0	2 (5)	0.493
Death in CR within 3 months	3 (5)	13 (17)	0.032	2 (5)	5 (13)	0.215

Abbreviations: mini-HCVD, mini-hyper-CVD; INO, inotuzumab ozogamicin; Blina, blinatumomab; HCVAD, hyper-CVAD; CR, complete response; CRi, CR without complete hematologic recovery; CRp, CR without platelet recovery.

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**Table 3.**

Multivariate analysis for survival

Parameter	Multivariate analysis		
	P	HR	95% CI
Age	0.019	1.045	1.007–1.085
ECOG PS 2	0.170	1.402	0.865–2.273
WBC	0.106	1.002	1.000–1.004
HCVAD vs mini-HCVD + INO +/- Blina	0.020	0.550	0.332–0.911

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell; HCVAD, hyper-CVAD; mini-HCVD, mini-hyper-CVD; INO, inotuzumab ozogamicin; Blina, blinatumomab.

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