Blinatumomab Oral and Poster Presentations

Home

Table of Contents

Oral/Poster Presentations

Select Table of Contents to Begin

AMGEN

SC-AT-AMG103-00459 01.24

SC-AT-NP-00098 10.23

Blinatumomab Oral Presentations

Non-Amgen Sponsored Studies

Pediatric Patients with High-Risk B-Cell ALL in First Complete Remission May Benefit from Less Toxic Immunotherapy with Blinatumomab – Results from Randomized Controlled Phase 3 Trial AIEOP-BFM ALL 2017- Martin Schrappe
Oral Presentation ID: 825

Blinatumomab in Combination with Immune Checkpoint Inhibitors in Relapsed/Refractory CD19+ Leukemias: A Phase I Study – Jonathan A. Webster
Oral Presentation ID: 966

Oral

Poster

ALL, acute lymphoblastic leukemia; CD, cluster of differentiation.

Blinatumomab Poster Presentations

Non-Amgen Sponsored Studies

Assessment of Outcomes of Consolidation Therapy by Number of Cycles of Blinatumomab Received in Newly Diagnosed Measurable Residual Disease Negative Patients with B-lineage Acute Lymphoblastic Leukemia: in the ECOG-ACRIN E1910 Randomized Phase III National Clinical Trials Network Trial – Selina M. Luger
Poster ID: Poster 2877

Updated Results From a Phase II Study of Hyper-CVAD, with or without Inotuzumab Ozogamicin, and Sequential Blinatumomab in Patients With Newly Diagnosed B-Cell Acute Lymphoblastic Leukemia – Daniel Nguyen
Poster ID: Poster 4245

Chemotherapy Sparing Induction Followed By Consolidation and Maintenance with Blinatumomab and Concurrent Oral Tyrosine Kinase Inhibitor Therapy for Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia: Primary Endpoint Results from the BLISSPHALL Study – Mark Blaine Geyer
Poster ID: Poster 1510

A Phase IB/II Study of Blinatumomab in Patients with B-Cell Acute Lymphoblastic Leukemia (ALL) and B-Cell Non-Hodgkin Lymphoma (NHL) As Post-Allogeneic Blood or Marrow Transplant (alloBMT) Remission Maintenance – Jonathan A. Webster
Poster ID: Poster 3582

Oral | Poster

CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone.

Blinatumomab Poster Presentations

Non-Amgen Sponsored Studies

Phase 2 Trial of Mini-Hyper-CVD Plus Inotuzumab Ozogamicin, With or Without Blinatumomab, in Older Patients With Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia – Wei Ying Jen
Poster ID: Poster 2878

A Phase II Study of Low-Intensity Chemotherapy (Mini-Hyper-CVD) and Ponatinib Followed by Blinatumomab and Ponatinib in Patients With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia – Wei Ying Jen
Poster ID: Poster 2868

Chemotherapy-Free Combination of Blinatumomab and Ponatinib in Adults With Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: Updates From a Phase II Trial – Fadi G. Haddad
Poster ID: Poster 2827

Improved MRD Negativity Rates in Adverse Genomic Risk B-ALL Patients with Chemotherapy/ Blinatumomab Induction: Experience from the Australasian Leukaemia Lymphoma Group (ALLG) ALL06/09 Studies – Deborah L. White
Poster ID: Poster 1609

Oral | Poster

B-ALL, B-cell precursor acute lymphoblastic leukemia; CVD, cyclophosphamide, dexamethasone, methotrexate, cytarabine; MRD, minimal residual disease.

Blinatumomab Poster Presentations

Non-Amgen Sponsored Studies

Dose Dense Mini Hyper CVD, Inotuzumab Ozogamicin , and Blinatumomab Achieves Rapid MRD Negativity in Philadelphia Chromosome Negative Acute Lymphoblastic Leukemia – Trevor Jamison
Poster ID: Poster 1508

Oral

Poster

CVD, cyclophosphamide, dexamethasone, methotrexate, cytarabine; MRD, minimal residual disease.

Pediatric Patients with High-Risk B-C ALL in First Complete Remission May Benefit from Less Toxic Immunotherapy with Blinatumomab – Results from Randomized Controlled Phase 3 Trial AIEOP-BFM ALL 2017

Martin Schrappe, Franco Locatelli, Maria Grazia Valsecchi, Gunnar Cario, Michaela Vossen-Gajcy, Jan Stary, Andishe Attarbaschi, Nicole Bodmer, Draga Barbaric, Sarah Elitzur, Daniela Silvestri, Alexandra Kolenova, Anja Möricke, Jean-Pierre Bourquin, Luciano Dalla-Pozza, Martin Stanulla, Shai Izraeli, Carmelo Rizzari, Fiona Poyer, Arend von Stackelberg, Valentino Conter, Martin Zimmermann, and Andrea Biondi

on behalf of the AIEOP-BFM ALL Study Group

AIEOP-BFM ALL 2017

International investigator-initiated inter-group multi-center open-label randomized clinical trial (Phase III)

Trial Steering Committee (composed by National Coordinators):
A. Biondi (AIEOP), J. Starý (CPH), S. Elitzur (INS), A. Kolenova (SPHOS), A. Attarbaschi/ G. Mann (BFM-A), D. Barbaric (ANZCHOG), N. Bodmer/ F. Niggli (BFM-CH), M. Schrappe (BFM-G)

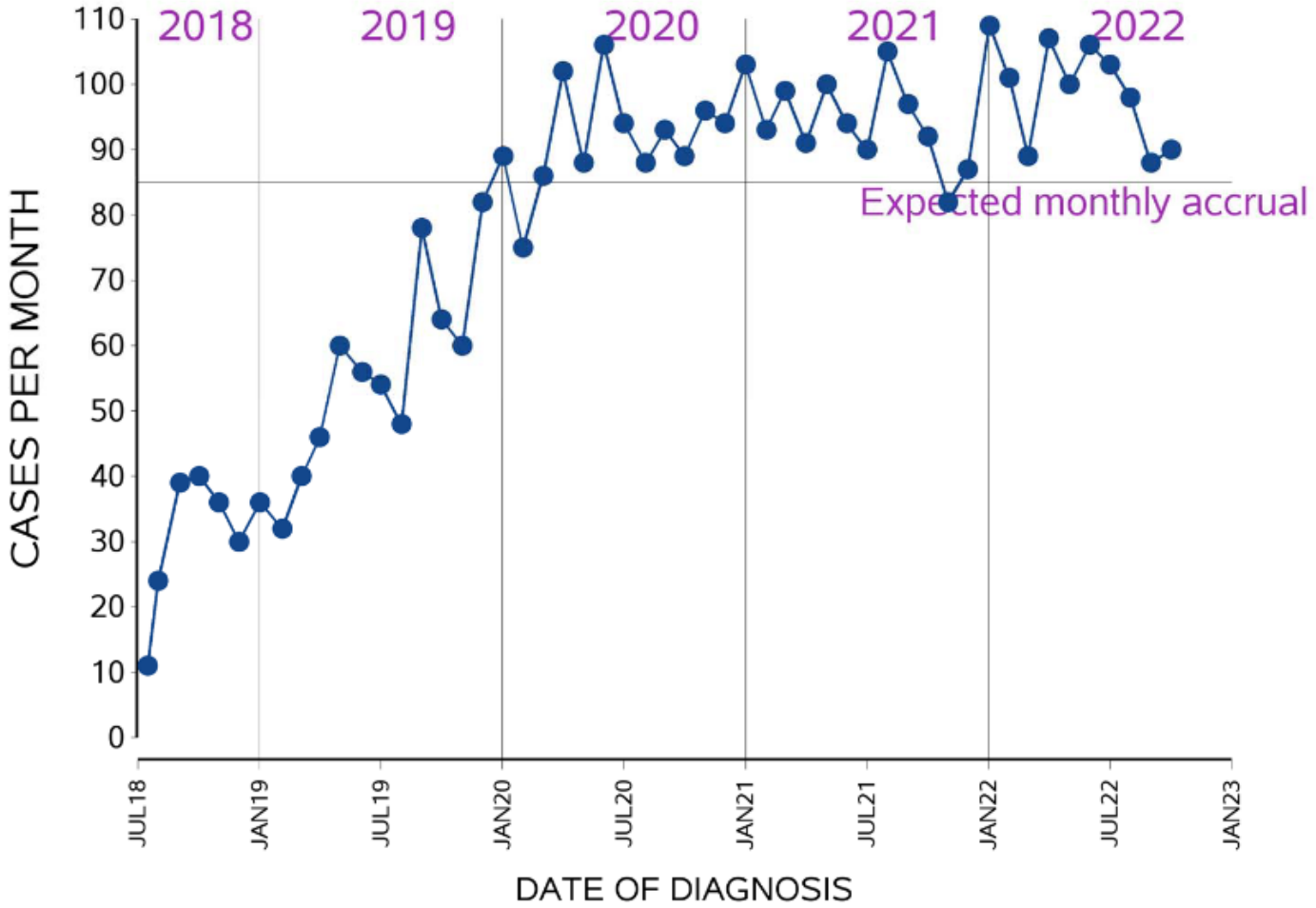
Sponsor:
University Medical Center Schleswig-Holstein (Kiel, Germany)

EudraCT Number: 2016-001935-12

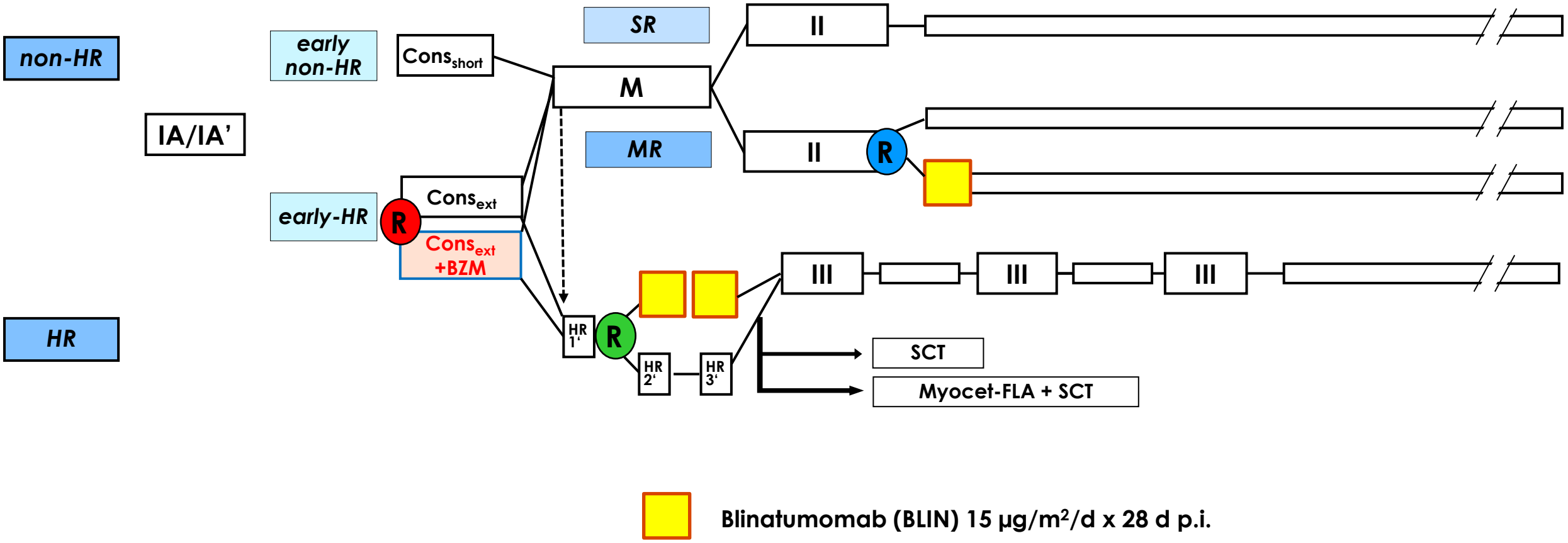
AIEOP-BFM ALL 2017

Participating countries (study groups)	• Australia (part of ANZCHOG) • Austria (BFM-A) • Czech Republic (CPH) • Germany (BFM-G) • Israel (INS) • Italy (AIEOP) • Slovakia (SPHOS) • Switzerland (BFM-CH)
Planned recruitment **Start of enrollment** **Patients enrolled for this report** Closure of enrollment in B-ALL	5 years, approx. 1000 new pts (per year) all subtypes of ALL, 0-<18 yrs of age 7-15-2018 up to October 31, 2022 August 31, 2023

Enrollment in trial AIEOP-BFM ALL 2017
(up to Oct. 31, 2022)



AIEOP-BFM ALL 2017: Treatment overview and randomizations for B-ALL



Blinatumomab (BLIN) 15 µg/m²/d x 28 d p.i.

Risk stratification for B-ALL in trial AIEOP-BFM ALL 2017

AIEOP-BFM ALL Study group

High risk (HR)

- no complete remission on day 33 or
- positivity for *KMT2A::AFF1*, or
- positivity for *TCF3::HLF1*, or
- hypodiploidy <45 chromosomes, or
- FCM-MRD in BM on day 15 ≥ 10% and not *ETV6::RUNX1* positive, or
- *IKZF1*^{plus} and PCR-MRD at TP1 positive or inconclusive, and not positive for *ETV6::RUNX1*, *TCF3::PBX1* or *KMT2A* rearr. other than *KMT2A::AFF1*, or
- PCR-MRD at TP1 ≥ $5x10^{-4}$ and positive < $5x10^{-4}$ at TP2 (PCR-MRD SER), or
- PCR-MRD at TP2 ≥ $5x10^{-4}$, or
- age < 1 year and any *KMT2A* rearrangement

Medium risk (MR)

- no HR criteria and no SR criteria

Standard risk (SR)

- no HR criteria *and*
- PCR-MRD at TP1 negative for all investigated markers with at least one marker with a quantitative range of ≤ 10^{-4} or
- inconclusive PCR-MRD result at TP1 and PCR-MRD not positive at TP2 and FCM-MRD in BM d15 < 0.1%

Combined use of FCM-based and ASO-PCR-based MRD-detection
(FCM: Flow cytometry; ASO RQ-PCR: allele-specific oligonucleotide real-time quantitative PCR)

AMGEN

Randomization in HR:
Experimental arm (EA): 2 courses of Blinatumomab (28-d continuous infusion) vs. Control arm (CA): 2 courses of chemotherapy (blocks HR-2 and HR-3)

AIEOP-BFM ALL Study group

Primary study question

- Can the pEFS from time of randomization be improved by replacing two conventional highly intensive chemotherapy courses by two cycles of post-consolidation immunotherapy with Blinatumomab (15 µg/m²/d for 28 days per cycle) plus 4 doses intrathecal Methotrexate?

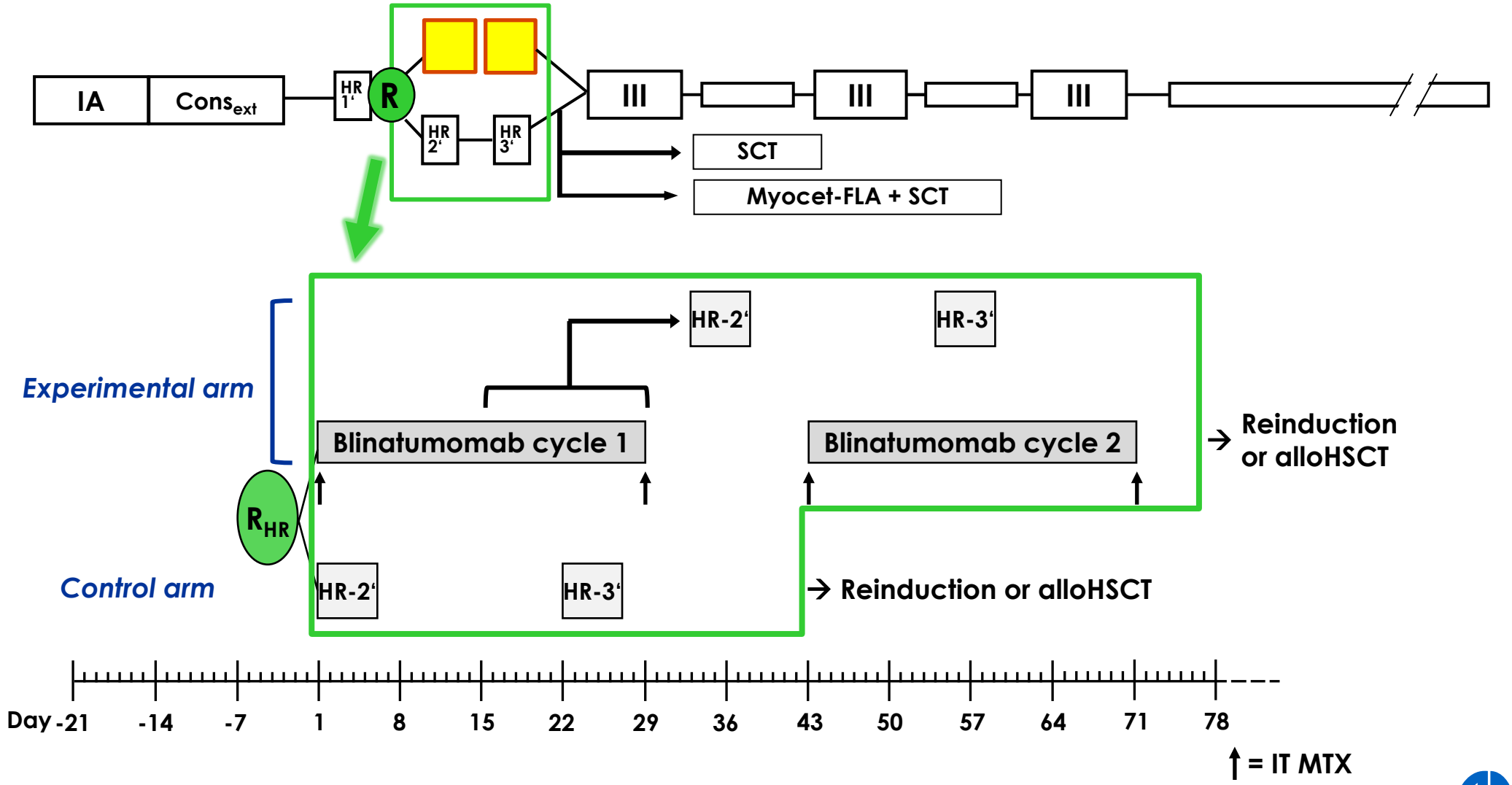
Secondary study questions

- Can treatment-related life-threatening complications and mortality during the intensified consolidation phase of high-risk treatment be reduced when replacing two intensive chemotherapy courses by two cycles of immunotherapy with Blinatumomab?
- What is the proportion of patients with insufficient MRD response to Blinatumomab as defined in the protocol as compared to the MRD response after the HR-2' block in the control arm?

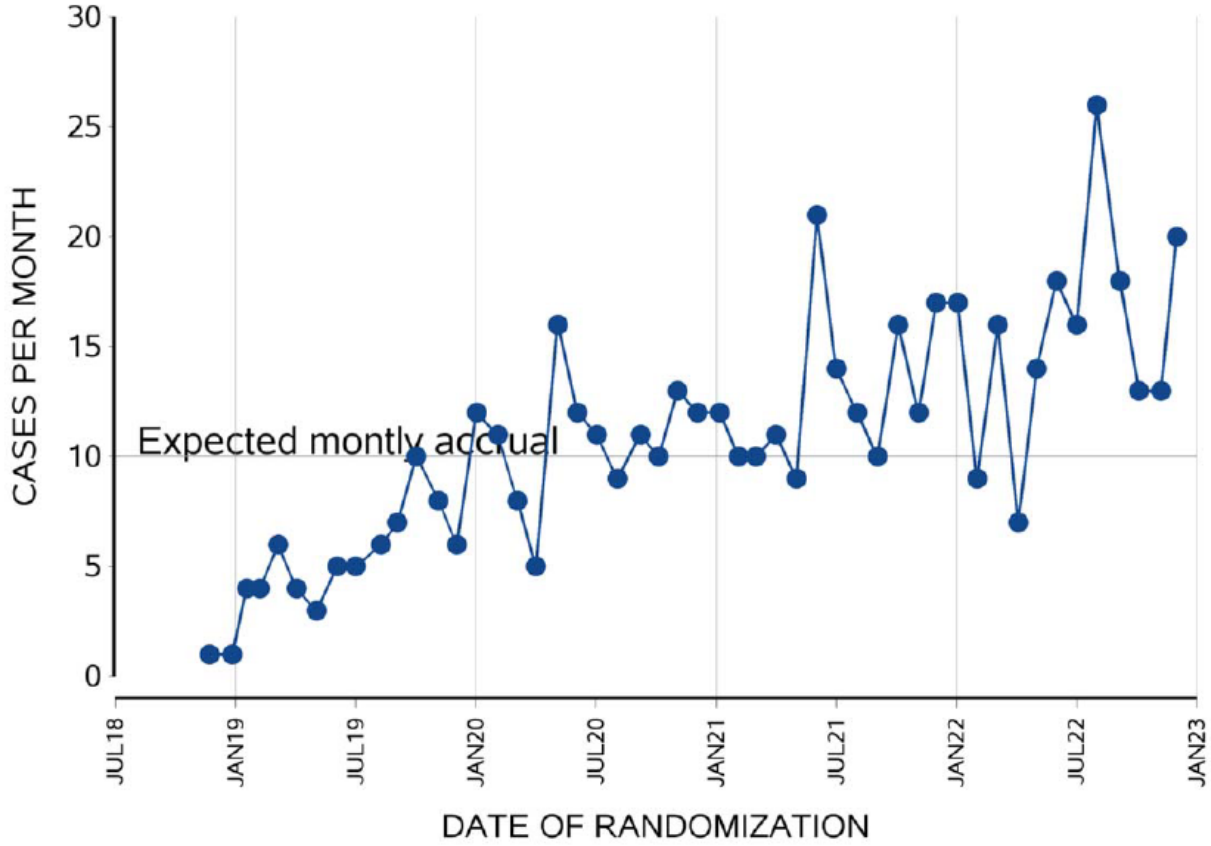
AMGEN

AIEOP-BFM ALL 2017: Randomization R-HR (B-ALL)

2 cycles Blinatumomab or courses HR-2' + HR-3'



AIEOP-BFM ALL 2017: Randomization in **HR-B-ALL (R-HR)** Enrollment



Patients and methods (1)

- 728 pts with HR B-ALL enrolled from July 15, 2018 to October 31, 2022 *
- 619 pts were eligible for randomization
- **572 pts were randomized** (92.4% of those eligible)
- Reasons for non-eligibility were:
  - Event (death or relapse) before randomization was due (26),
  - Down syndrome (25; scheduled for a non-randomized intervention with BLIN),
  - presence of *TCF3::HLF* (3; could receive any alternative therapy including BLIN),
  - discontinuation/substantial change of preceding therapy (23) or
  - other protocol exclusion criteria (32).
- One pt assigned to the experimental arm (EA) and 4 pts assigned to the control arm (CA) received the other arms, respectively.

* Data frozen in May 2023

Patients and methods (2)

- For this report on randomization of Blinatumomab (BLIN) vs intensive chemotherapy (HR-2, HR-3), **medically relevant adverse reactions of special interest (ARSI)** were analyzed (intent-to-treat analysis)
- +/- life-threatening ARSI
- Only events during the randomized treatment phase were analyzed (before the next treatment element was started)

Results in R-HR: overview

	All ARSI					Life-threatening ARSI				
	Control (HR-2, HR-3)		Experimental (BLIN cycles 1+2)		P (Fisher exact test)	Control (HR-2, HR-3)		Experimental (BLIN cycles 1+2)		P (Fisher exact test)
	N	%*	N	%*		N	%*	N	%*	
N of pts with ARSI	61	22.8	29	10.3	<0.001	14	5.2	0	0	<0.001
N of ARSI	71	26.5	33#	11.7		15	5.6	0	0	

* related to 268 pts in control arm, and 281 pts in experimental arm

NOTE: 16 pts switched in/after the first BLIN cycle to the HR blocks due to toxicity or poor response to BLIN

3 of the 33 ARSI in the EA were related to HR blocks (observed in 3 of the 16 pts that switched to HR blocks).

Results in R-HR (1)

	All ARSI				Life-threatening ARSI			
	Control (HR-2, HR-3)		Experimental (BLIN cycles 1+2)		Control (HR-2, HR-3)		Experimental (BLIN cycles 1+2)	
	N	% *	N	% *	N	% *	N	% *
Infections	20 §	7.5	1	0.4	9	3.4	0	0
Immune system disorders	27	10.1	7 #	2.5	3	1.1	0	0

*related to 268 pts in control arm, and 281 pts in experimental arm

§ bacterial infections most frequent but also some fungal infections (n=3), and some without clear data on origin

Cytokine release syndrom (CRS) ≥ grade 2 in 5 pts;
allergic reactions to asparaginase in 2 pts after having been switched to CA

Results in R-HR (2)

AIEOP-BFM ALL Study group

	All ARSI				Life-threatening ARSI			
	Control (HR-2, HR-3)		Experimental (BLIN cycles 1+2)		Control (HR-2, HR-3)		Experimental (BLIN cycles 1+2)	
	N	%*	N	%*	N	%*	N	%*
Nervous system disorders	6 #	2.2	21 #	7.5	1	0.4	0	0
Gastrointestinal disorders	6 §	2.2	0	0	1	0.4	0	0
Hepato-biliary disorders	2	0.7	0	0	1	0.4	0	0

2 in CA, and 17 in EA were seizures grade 2 or 3
§ 5 out of 6 were diagnosed with acute pancreatitis
*related to 268 pts in control arm, and 281 pts in experimental arm

AMGEN

Conclusions

- This first randomized trial in newly diagnosed pts with HR B ALL confirms the favorable toxicity profile previously reported with Blinatumomab in pediatric patients with 1st relapse (Locatelli F et al, JAMA 2021; Brown P et al, JAMA 2021; Hogan LE et al, J Clin Oncol 2022).
- If upcoming analyses of outcome data in trial AIEOP-BFM ALL 2017 will not show any inferiority of the EA in terms of anti-leukemia efficacy, blinatumomab replacement of some of the intensive chemotherapy blocks will become the new standard of care for treatment in newly diagnosed patients with HR B-ALL.

Acknowledgments
Trial AIEOP-BFM ALL 2017

Dept. of Pediatrics, University Medical Center Schleswig-Holstein, Campus Kiel
Anja Möricke, Julia Alten, Lile Bauer, Lennart Lenk, Jana Brazdova, Saskia Sonnenberg, Simon Vieth, Gunnar Cario

Dept. of Pediatric Hematology/ Oncology, Medical School Hannover
Martin Stanulla
Christian Kratz

Reference Laboratories
Giuseppe Basso †, Giovanni Cazzaniga, Giuseppe Gaipa, Michael Dworzak, Jan Trka, Monika Brüggemann, Matthias Ritgen, Brigitte Schlegelberger, Oskar Haas, Anke Bergmann, Doris Steinemann, Wolf-Dieter Ludwig, Beat Schäfer, Joelle Tchinda, Shai Izraeli, Renate Panzer-Grümayer, Rolf Köhler,
Stefan Koehrer, Claus R. Bartram

AIEOP-BFM Trial Steering Committee
Andrea Biondi, Georg Mann/Andishe Attarbaschi, Jan Stary, Felix Niggli/Nicole Bodmer, Sara Elitzur, Draga Barbaric, Alexandra Kolenova, Martin Schrappe

Task Force
Franco Locatelli, Andishe Attarbaschi, Arend Stackelberg, Birgit Burkhardt, Rita Beier, Anja Möricke, Gunnar Cario, Valentino Conter, Luciano dalla Pozza, Carmelo Rizzari, Claudia Rössig, Jean-Pierre Bourquin

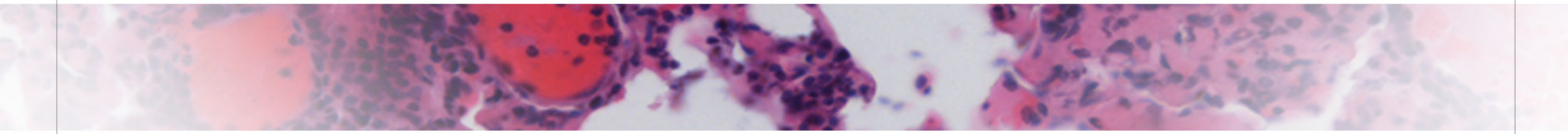
AMGEN:
Gerhard Zugmaier

Statistical analysis
Maria Grazia Valsecchi, Michaela Vossen-Gajcy, Daniela Silvestri, Martin Zimmermann

ALL-SCT-BFM and PedFORUM team:
Christina Peters
National ALL 2009 & 2017 Study Committees

Participating centers

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

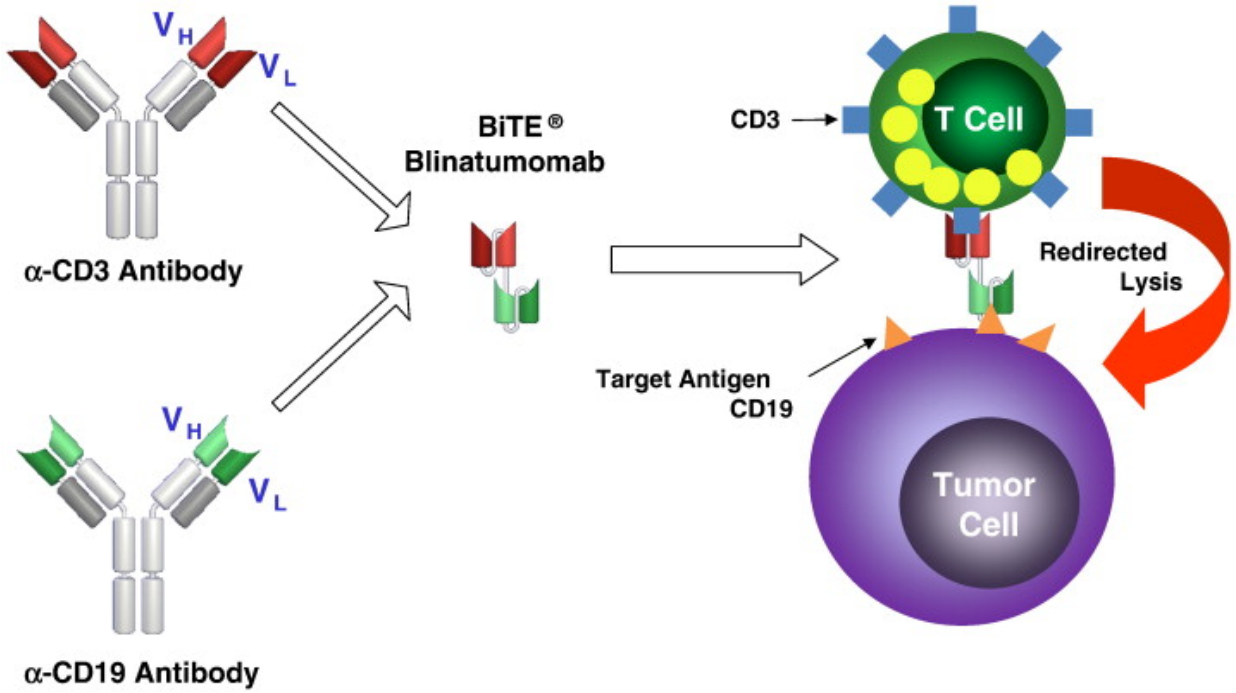


Blinatumomab in Combination with Immune Checkpoint Inhibitors in Relapsed/Refractory CD19+ Leukemias: A Phase I Study

Jonathan A. Webster, Marlise R. Luskin, Joseph Rimando, Amanda Blackford, Amer Zeidan, Elad Sharon, Howard Streicher, Daniel J. DeAngelo, Leo Luznik, and Ivana Gojo

Blinatumomab: a CD19/CD3 bichimeric T cell engager antibody construct (BiTE)

- MRD+ ALL pts:
  - 78% of pts converting to MRD- associated with a median survival of 40.4 months
- Overt relapse:
  - 44% CR rate associated with a median DOR of 7.3 months
  - 76% of responders MRD-
- PD-L1 and soluble CTLA-4 are more highly expressed in blinatumomab non-responders



Sources: Gokbuget et al. Blood. 2018. 131 (14)
Kantarjian et al. N Engl J Med. 2017. 376(9)
Kohnke et al. J Hematol Oncol. 2015. 8 (1).
Mansour et al. Leuk Lymphoma. 2014. 55 (9).

Phase I Dose Escalation Trial of Blinatumomab, Nivolumab, and Ipilimumab in CD19+ Pre-B ALL and MPAL

1⁰ Objectives:

- Evaluate the safety and tolerability of these combinations
- Determine the maximum tolerated dose (MTD)

2⁰ Objectives:

- Determine the anti-leukemia effect as measured by CR and MRD status

Exploratory:

- Examine changes in T cell subsets, T cell co-signaling receptor expression, co-signaling molecules on blasts, and levels of cytokines

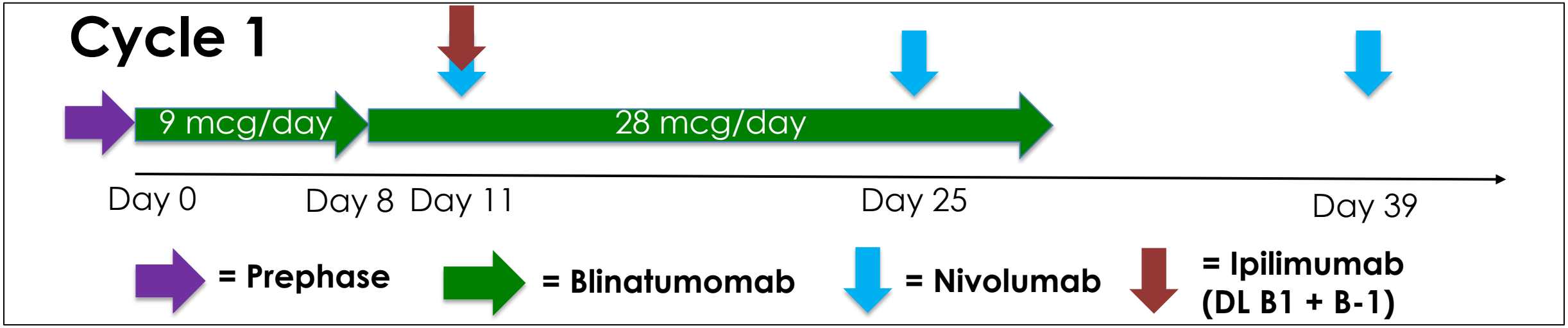
Eligibility:

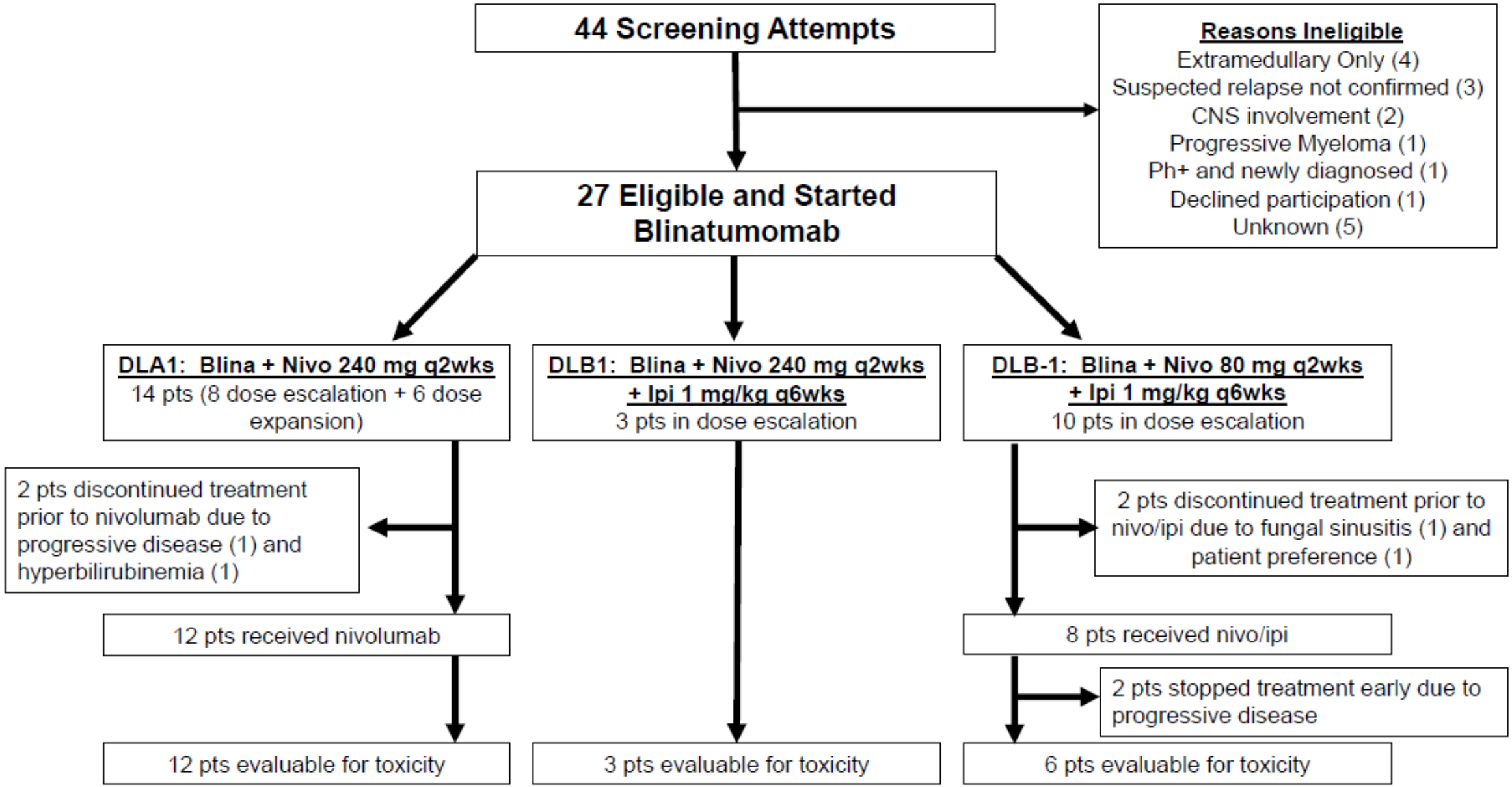
- Age ≥16 years-old with $CD19^+$ Pre-B ALL or $CD19^+$ MPAL
- Relapsed or refractory disease or newly diagnosed, ineligible for intensive chemotherapy
- Ph+ Pre-B ALL if failed at least one 2^{nd} generation TKI
- ECOG performance status 0-2 and adequate end organ function
- No Active CNS, testicular, or isolated extramedullary leukemia

Study Design

Dose Level	Dose		
	Blinatumomab[1]	Nivolumab[2]	Ipilimumab[2]
A1 (-)	9 µg/day IV on D1-7 28 µg/day IV on D8-28	80 mg IV q 2wks	(none)
A1	(same)	240 mg IV q 2wks	(none)
B1 (-)	(same)	80 mg IV q 2wks	1 mg/kg IV q6wks
B1	(same)	240 mg IV q 2wks	1 mg/kg IV q6wks

[1] After cycle 1, blinatumomab is given at 28 µg/day IV on D1-28 of a 42-day cycle
[2] Drug to start day #11 following blinatumomab




44 Screening Attempts
Reasons Ineligible
Extramedullary Only (4)
Suspected relapse not confirmed (3)
CNS involvement (2)
Progressive Myeloma (1)
Ph+ and newly diagnosed (1)
Declined participation (1)
Unknown (5)
27 Eligible and Started Blinatumomab
DLA1: Blina + Nivo 240 mg q2wks
14 pts (8 dose escalation + 6 dose expansion)
DLB1: Blina + Nivo 240 mg q2wks + Ipi 1 mg/kg q6wks
3 pts in dose escalation
DLB-1: Blina + Nivo 80 mg q2wks + Ipi 1 mg/kg q6wks
10 pts in dose escalation
2 pts discontinued treatment prior to nivolumab due to progressive disease (1) and hyperbilirubinemia (1)
2 pts discontinued treatment prior to nivo/ipi due to fungal sinusitis (1) and patient preference (1)
12 pts received nivolumab
8 pts received nivo/ipi
2 pts stopped treatment early due to progressive disease
12 pts evaluable for toxicity
3 pts evaluable for toxicity
6 pts evaluable for toxicity

Demographics

	All (N=27)	DL A1 (N=14)	DL B1 (N=3)	DL B-1 (N=10)
Median Age (Range)	55 (24-84)	56 (24-84)	57 (28-70)	53 (33-78)
Female Gender (%)	13 (48%)	6 (43%)	1 (33%)	6 (60%)
Median % BM Blasts (Range)	60 (0.2-98)	72 (10-98)	54 (43-95)	12 (0.2-95)
Median ECOG PS (Range)	1 (0-2)	1 (0-2)	1 (1-2)	1 (0-2)
Disease				
Ph- B ALL	20 (74%)	9 (64%)	3 (100%)	8 (80%)
Ph+ B ALL/LBC CML	4 (15%)	3 (21%)	0 (0%)	1 (10%)
MPAL	3 (11%)	2 (14%)	0 (0%)	1 (10%)
Disease Status				
Relapsed/Primary Refractory	25 (93%)	13 (93%)	3 (100%)	9 (90%)
MRD+	1 (4%)	0 (0%)	0 (0%)	1 (10%)
Newly Diagnosed	1 (4%)	1 (7%)	0 (0%)	0 (0%)
Prior Blinatumomab	7 (26%)	3 (21%)	0 (0%)	1 (10%)
Prior Inotuzumab	3 (11%)	0 (0%)	0 (0%)	3 (30%)
Prior AlloBMT	9 (33%)	4 (29%)	1 (33%)	4 (40%)
Prior EM Disease	4 (15%)	0 (0%)	0 (0%)	4 (40%)

Adverse Events

DLTs

DL A1 (1/12): G4 Infusion-related reaction with G3 hypotension 2/2 nivolumab

DL B1 (2/3): G5 Pneumonitis AND G2 GVHD both deemed likely 2/2 nivolumab + ipilimumab

DL B-1 (1/8): G3 Delirium 2/2 nivolumab + blinatumomab

iRAEs

Rash: Grade 2 (2) and Grade 3 (1)

Pneumonitis: Grade 2 (1) and Grade 5 (1)

Diarrhea: Grade 3 (1)

Hepatotoxicity (AST, ALT, GGT, and bili): Grade 2 (1) and Grade 3 (1)

Hypothyroidism: Grade 2 (1)

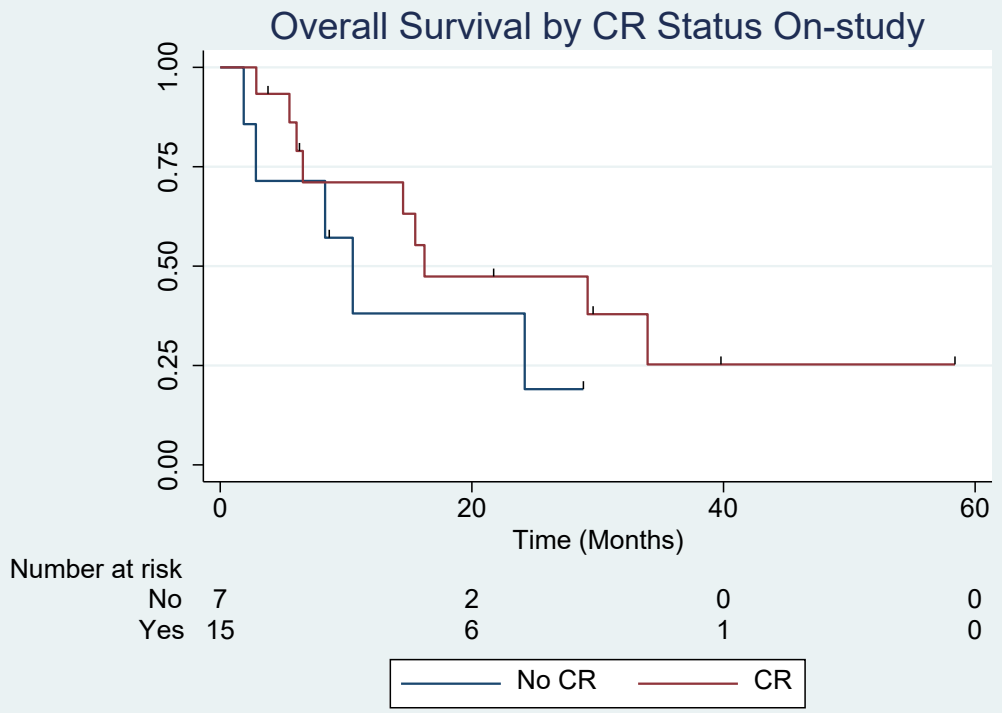
Responses (CR)

	All (N=22)*	DL A1 (N=12)	DL B1 (N=3)	DL B-1 (N=7)*
Unselected	15 (68%)	9 (75%)	3 (100%)	3 (43%)
Blasts >50% (N=13)	8 (62%)	5/8 (62.5%)	2/2 (100%)	1/3 (33%)
Blasts ≤50% (N=9)	7 (78%)	4/4 (100%)	1/1 (100%)	2/4 (50%)
Disease				
Ph- B ALL (N=16)	11 (69%)	6/8 (75%)	3/3 (100%)	2/5 (40%)
Ph+ B ALL/LBC CML (N=3)	3 (100%)	2/2 (100%)		1/1 (100%)
MPAL (N=3)	1 (33%)	1/2 (50%)		0/1 (0%)
Disease Status				
Relapsed (N=15)	10 (67%)	5/6 (83%)	3/3 (100%)	2/6 (33%)
Primary Refractory (N=6)	4 (67%)	3/5 (60%)		1/1 (100%)
Newly Diagnosed (N=1)	1 (100%)	1/1 (100%)		
Prior Blinatumomab (N=4)	1 (25%)	1/1 (100%)		0/3 (0%)
Prior Inotuzumab (N=2)	0 (0%)			0/2 (0%)
Prior AlloBMT (N=7)	6 (86%)	3/3 (100%)	1/1 (100%)	2/3 (67%)
Prior EM Disease (N=4)	1 (25%)			1/4 (25%)
*One patient was in CR at baseline with MRD and was not included in this response analysis				

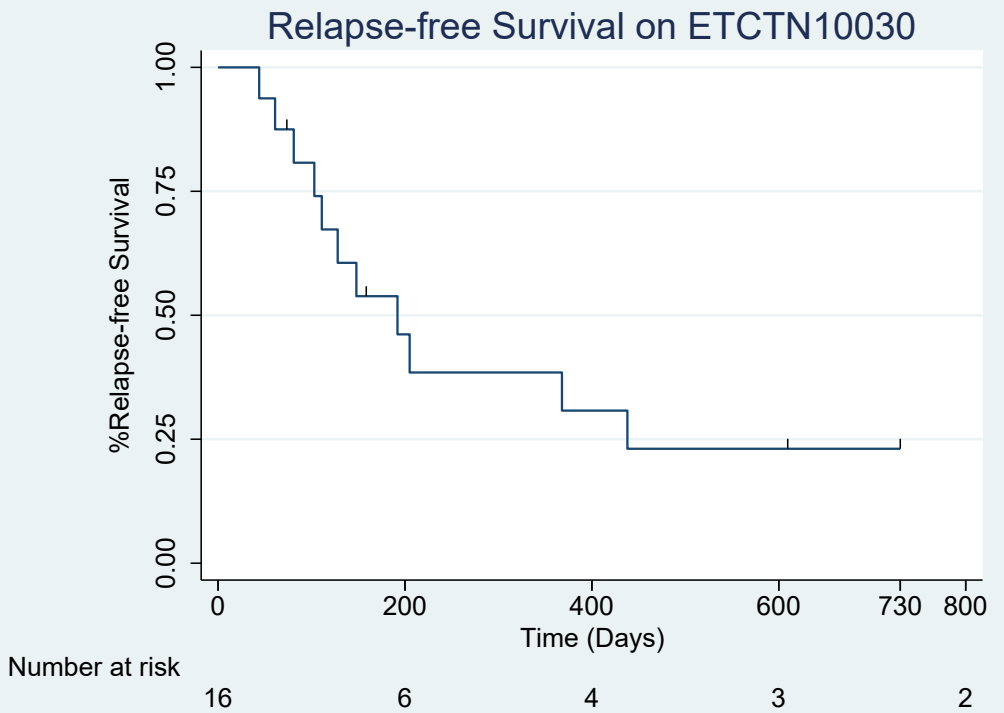
Response and Relapse Details

	All (n=23)	CR on-study (n=15)	No CR (N=7)	MRD+ at enrollment (n=1)
MRD- CR by MFC (sensitivity $<10^{-4}$)	**15 (65%)**	**15 (100%)**	**0 (0%)**	**0 (0%)**
Relapse/Primary Refractory		**9 (60%)**	**7 (100%)**	**0 (0%)**
Extramedullary Disease Present		3 (33%)	3 (43%)	
CD19-negative		2 (22%)	2 (29%)	
Subsequent Allogeneic Transplant	**12 (52%)**	**9 (60%)**	**2 (29%)**	**1 (100%)**
Transplant w/o Intervening Rx	8 (67%)	7 (78%)	0 (0%)	0 (0%)
Post-Transplant Relapse	2 (17%)	2 (20%)	0 (0%)	0 (0%)
Post-Transplant Death in Remission	3 (25%)	2 (22%)	1 (50%)	0 (0%)

Overall Survival

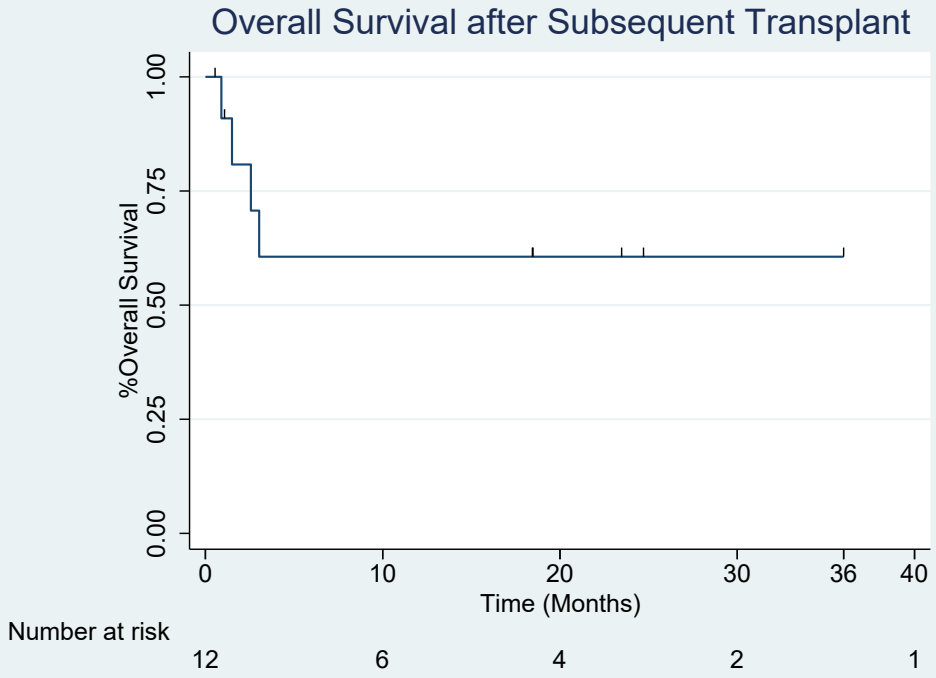


Relapse-free Survival

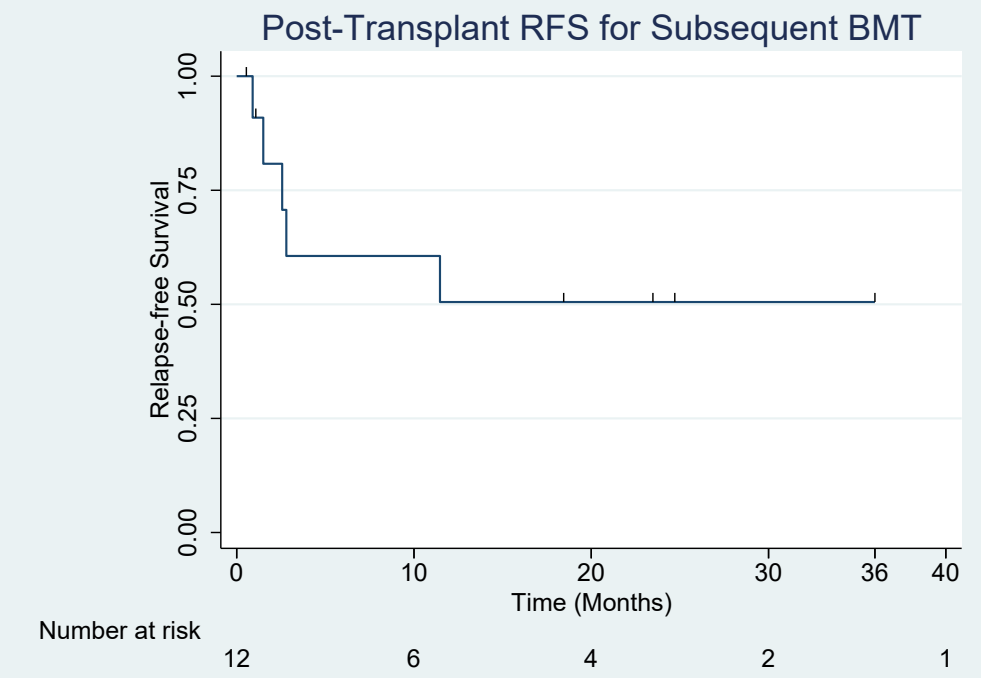


	1 year	2 years
RFS	27% (95% CI 10-46)	16% (95% CI 4-35)
OS	63% (95% CI 38-79)	47% (95% CI 25-67)

Overall Survival: Transplanted Patients



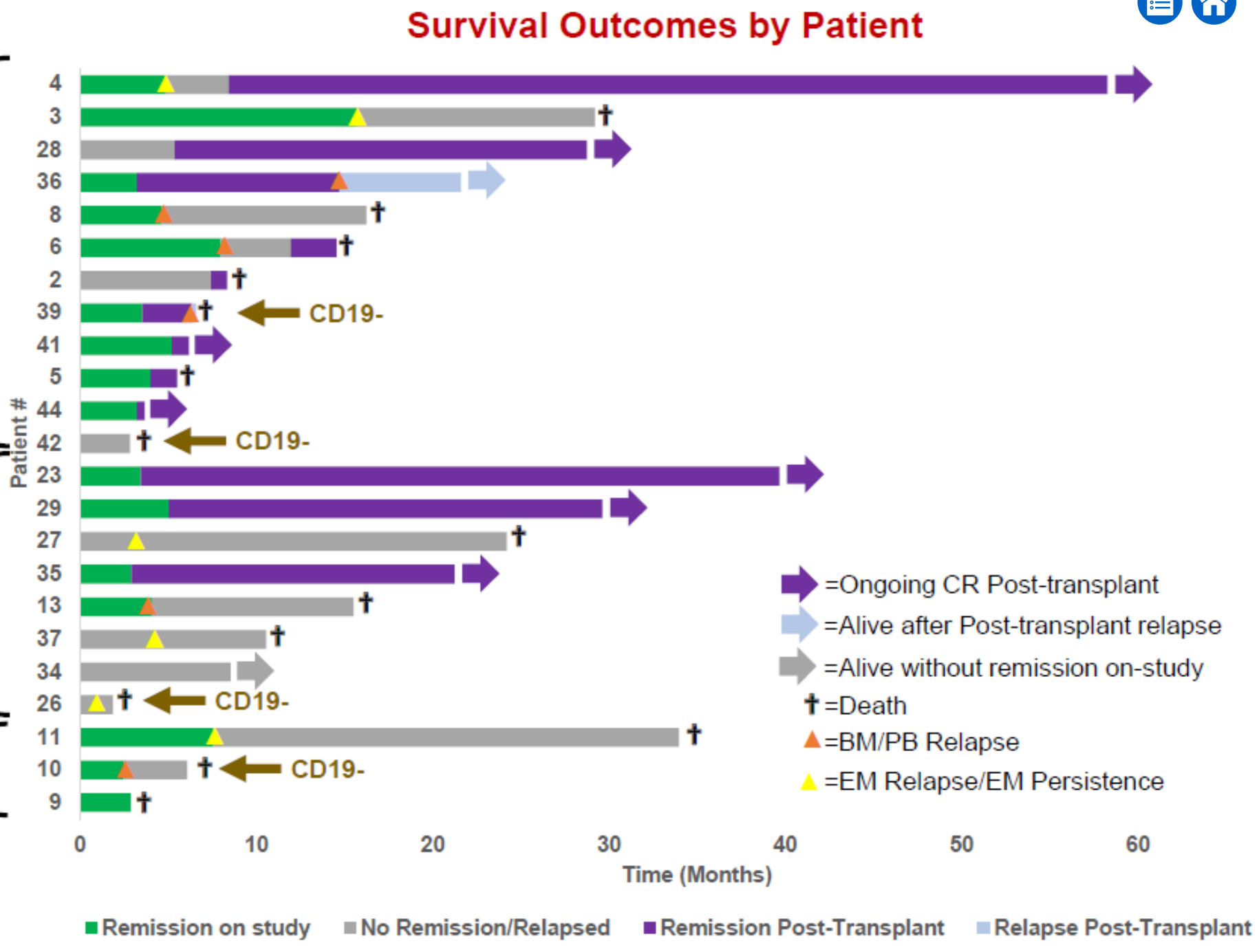
Relapse-free Survival: Transplanted Patients



	1 year	2 years
RFS	51% (95% CI 19-76)	51% (95% CI 19-76)
OS	61% (95% CI 26-83)	61% (95% CI 26-83)
NRM	29% (95% CI 7-57)	29% (95% CI 7-57)
CIR	20% (95% CI 3-48)	20% (95% CI 3-48)

Diagnosis	Prior Blina	Prior BMT	EM Disease	DL
B ALL	No	No	No	
B ALL	No	No	No	
B ALL	No	No	No	
B ALL	No	No	No	
CML-BP	No	Yes	No	
Ph+ B ALL	No	Yes	No	
B ALL	No	No	No	A1
B ALL	No	No	No	
B ALL	No	No	No	
B ALL	No	No	No	
B ALL	Yes	Yes	No	
B/T MPAL	No	No	No	
B/M MPAL	No	No	No	
B ALL	No	Yes	Yes	
B ALL	No	No	No	
B ALL	Yes	Yes	Yes	
B ALL*	Yes	No	No	B-1
Ph+ B ALL	No	Yes	No	
B ALL	Yes	No	Yes	
B ALL	Yes	No	No	
B/M MPAL	No	No	Yes	
B ALL	No	Yes	No	
B ALL	No	No	No	B1
B ALL	No	No	No	

* MRD only at study entry



Conclusions and Next Steps

- Blinatumomab in combination with immune checkpoint inhibitors is feasible and safe
  - Good outcomes with subsequent alloBMT (n=12) and those with a high baseline disease burden (>50% blasts in BM)
  - Poorer outcomes in small subsets with EM, MPAL, and prior blina exposure
- Correlative studies are ongoing in the Luznik Lab to include T-cell and blast co-signaling receptor expression and RNA seq studies with pre-treatment, post-treatment, and relapse samples
- Consideration of a randomized trial in R/R B ALL

Acknowledgements

- Patients and their caregivers
- The dedicated research staff at Johns Hopkins, Dana Farber, Yale, and the ETCTN
- Our collaborators at CTEP
- Ivana Gojo

ETCTN

Experimental Therapeutics Clinical Trials Network

Assessment of Outcomes of Consolidation Therapy by Number of Cycles of Blinatumomab Received in Newly Diagnosed Measurable Residual Disease Negative Patients with B-lineage Acute Lymphoblastic Leukemia: in the ECOG-ACRIN E1910 Randomized Phase III National Clinical Trials Network Trial

Selina M. Luger, Zhuoxin Sun, Ryan J. Mattison, Elisabeth M. Paietta, Kathryn G. Roberts, Yanming Zhang, Janis Racevskis, Hillard M. Lazarus, Jacob M. Rowe, Dan Arber, Matthew J. Wieduwilt, Michaela Liedtke, Julie Bergeron, Brent Wood, Yaqi Zhao, Gang Wu, Ti-Cheng Chang, Wenchao Zhang, Keith W. Pratz, Shira N. Dinner, Noelle Frey, Steven D. Gore, Bhavana Bhatnagar, Ehab L. Atallah, Geoffrey L. Uy, Deepa Jeyakumar, Tara L. Lin, Cheryl L. Willman, Daniel J. DeAngelo, Elad Sharon, Richard F. Little, Harry P. Erba, Richard M. Stone, Charles G. Mullighan, Mark R. Litzow, Martin S. Tallman

INTRODUCTION

ECOG ACRIN E1910 is a randomized phase III trial that showed adult patients (pts) with newly diagnosed BCR::ABL1 negative acute lymphoblastic leukemia (ALL) who become MRD negative (<0.01%) after induction chemo who receive blinatumomab with conventional chemotherapy have improved survival compared with those who received conventional chemo only.

However, not all pts were able to receive all four planned cycles of blinatumomab in consolidation. In this report we assessed outcomes of pts in the blinatumomab arm of the trial who received all 4 cycles of blinatumomab compared to those who received 1-2 cycles or 2 cycles only.

METHODS

Patients 30–70 years of age with newly diagnosed *BCR::ABL1* negative B-lineage ALL were enrolled and initially received 2.5 months of combination induction chemo utilizing a BFM-like regimen adapted from the E2993/UKALLXII clinical trial with extended remission induction, addition of pegaspargase for pts <55 years of age and addition of rituximab for CD20 positive patients.

After remission induction (step 1) pts in morphologic complete remission (CR/CRi) received high dose methotrexate intensification with pegaspargase for CNS prophylaxis (step 2).

METHODS

At the conclusion of step 2, remission and MRD status were determined centrally by 6-color flow cytometry with MRD negativity defined as <0.01%.

In the primary analysis subset, MRD negative pts were randomized to receive an additional 4 cycles of consolidation chemo or 2 cycles of blinatumomab at 28 mcg/day for 28 days each cycle followed by 3 cycles of consolidation chemo, a 3rd 4-week cycle of blinatumomab followed by an additional cycle of chemo and then a 4th cycle of blinatumomab (step 3).

Following completion of step 3, pts were given 2.5 years of POMP maintenance therapy timed from the start of the intensification cycle (step 4).

OS was calculated using the Kaplan-Meier method.

Landmark analysis was used to compare OS of pts in the blinatumomab arm who received all 4 cycles of blinatumomab to those who received 1-2 cycles or 2 cycles only.

Time 0 was chosen as 9 months post step 3 randomization (the time that pts were supposed to complete 4 cycles of blinatumomab). Four pts who received blinatumomab but died within 9 months post step 3 randomization were therefore excluded from this analysis.

RESULTS

Study Activation: Dec 2013 / Study Termination: Oct 2019

772 pts were screened, 488 were enrolled; Median age 51 years

CR/CRi rate after induction was 81%

224 MRD-negative pts were randomized, 112 in each arm

In the blinatumomab arm, 12 pts received 1 cycle (11%), 32 pts received 2 cycles (29%), 4 pts received 3 cycles (4%) and 63 pts received 4 cycles (57%) of blinatumomab.

The OS of pts who received 1-2 cycles of blinatumomab compared to control (Figure 1) was not significantly different (hazard ratio 0.62, 95% CI 0.28 to 1.34, p=0.22).

Fig 2 compares the survival of those who received 1-2 cycles to those who received 4 cycles (HR: 0.39, 95% CI 0.12 to 1.16, p=0.076).

Figure 1

1 - 2 Cycles Vs. Control

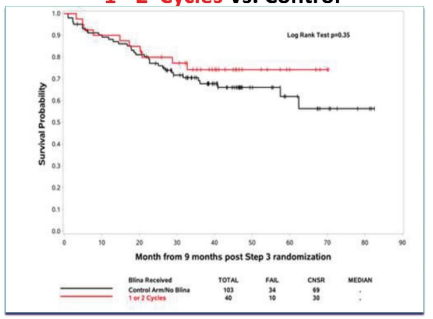
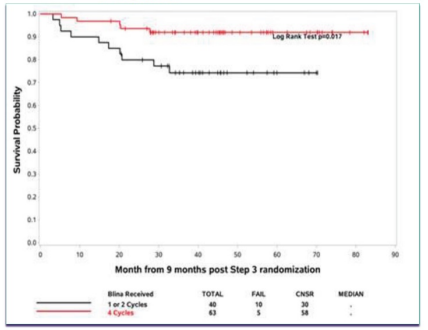


Figure 2

4 Cycles Vs. 1 – 2 Cycles



Landmark analysis was used, where time 0 is 9 months post step 3 randomization (the time that patients were supposed to complete 4 cycles of blinatumomab).

REFERENCES

1.Litzow et al, Blood (2022) 140: Supplement 2, LBA-1.

CONCLUSIONS

The addition of blinatumomab to consolidation chemo resulted in a significantly better overall survival in pts with diagnosed B-lineage ALL who were MRD negative after intensification chemo.

The optimal dose and number of cycles is however unknown.

In this unplanned subgroup analysis, we demonstrate that a survival benefit can only be confirmed in patients who receive the intended 4 cycles of blinatumomab during consolidation.

ACKNOWLEDGEMENTS

Coordinated by the ECOG-ACRIN Cancer Research Group: Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs

Supported by the National Cancer Institute of the National Institutes of Health under awards: U10CA180820, U10CA180794, U10CA180821, U10CA180863, Canadian Cancer Society #704970, U10CA180888, U10CA180868, UG1CA189856, UG1CA189859, UG1CA232760, UG1CA233180, UG1CA233198, UG1CA233234, UG1CA233253, UG1CA233277, UG1CA233290, UG1CA233320, UG1CA233196, UG1CA233331, UG1CA233337, and UG1CA233339.

This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Updated results from a phase II study of hyper-CVAD, with or without inotuzumab ozogamicin, and sequential blinatumomab in patients with newly diagnosed B-cell acute lymphoblastic leukemia

Daniel Nguyen, Hagop Kantarjian, Nicholas J Short, Nitin Jain, Fadi Haddad, Musa Yilmaz, Alessandra Ferrajoli, Tapan Kadia, Yesid Alvarado, Abhishek Maiti, Marianne Zoghbi, Cedric Nasnas, Lewis Nasr, Rebecca Garis, Min Zhao, Marina Konopleva, Farhad Ravandi, and Elias Jabbour
Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Background: Blinatumomab and inotuzumab ozogamicin (INO) both improve overall survival (OS) compared with chemotherapy in patients (pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL). Blinatumomab also improves OS when added to standard chemotherapy in newly diagnosed Philadelphia chromosome (Ph)-negative ALL. We hypothesized that the addition of INO to hyper-CVAD plus blinatumomab would lead to deeper and more durable responses, reduce relapses, and improve survival.

Methods: In this phase II study, pts age 14-59 with newly diagnosed Ph-negative B-cell ALL received hyper-CVAD alternating with high dose methotrexate (MTX) and cytarabine (Ara-C) for up to 4 cycles, followed by 4 cycles of blinatumomab at standard doses. Pts with CD20+ disease received 8 doses of ofatumumab or rituximab. Eight doses of prophylactic IT chemotherapy were given. Maintenance was with alternating blocks of POMP and blinatumomab. Beginning with pt #39, INO at a dose of 0.3mg/m^2 on day 1 and 8 was added to the 2 cycles of MTX/Ara-C (which was also dose reduced to 500mg/m^2 and 1g/m^2) and to 2 cycles of blinatumomab consolidation.

Results: As on June 2023, 75 pts have been treated (38 without INO and 37 with INO). Sixteen pts were in complete remission (CR) at enrollment after 1 cycle of off-protocol therapy, 10 of whom were MRD-negative by 6-color flow cytometry.
All 59 (100%) with active disease upon study entry achieved CR, with 50 pts (84%) achieving CR after the first cycle. MRD negativity by flow (sensitivity 10^{-4}) was achieved in 62 of 65 evaluable pts (95%), with 43 pts (66%) achieving MRD negativity after the first cycle.
Two of the 5 pts who did not achieve MRD negativity had HUP214::ABL1 fusion, 1 had KMT2A rearrangement, and 2 are still early in treatment and have not yet received blinatumomab. Overall, 27 of 37 tested pts (73%) achieved next-generation sequencing-based MRD negativity at a sensitivity of 10^{-6}.
The median duration of follow-up is 30 months (range, 4-81 months). Overall, 8 pts (11%) relapsed in the absence of SCT, 24 pts (32%) underwent stem cell transplantation (SCT) in first remission (2 of whom relapsed post-SCT), 3 pts (4%) died in CR, and 40 pts (53%) remain in continuous remission without SCT.
Across both cohorts, the estimated 4-year OS was 88% and the 4-year relapse-free survival (RFS) was 80%. In a landmark analysis, there was no difference in outcomes between pts who underwent SCT in first remission vs those who did not (4-year OS: 90% vs 87%). With a median follow-up of 22 months in the INO cohort, 3 pts (8%) have relapsed, 2 with CNS-only relapses, and none have died. The 2-year RFS in the cohorts with and without INO were 88% vs 74% (p=0.1), and the OS was 100% vs 82% (p=0.02).

Enrollment criteria

Inclusion Criteria

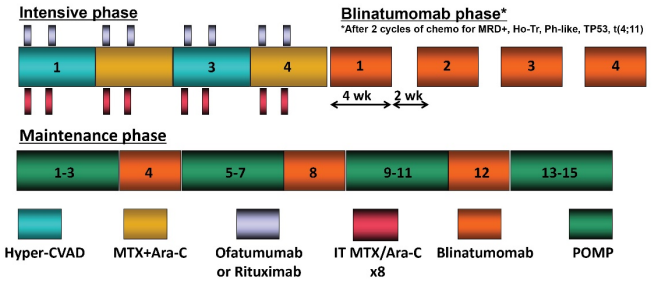
- Newly diagnosed Ph- B-cell ALL:
  - Previous therapy with 1 course of chemotherapy was allowed
  - Age ≥ 14 years
- ECOG performance status ≤ 3
- Adequate hepatic and kidney function:
  - Bilirubin ≤ 2 mg/dL
  - Creatinine ≤ 2 mg/dL

Exclusion Criteria

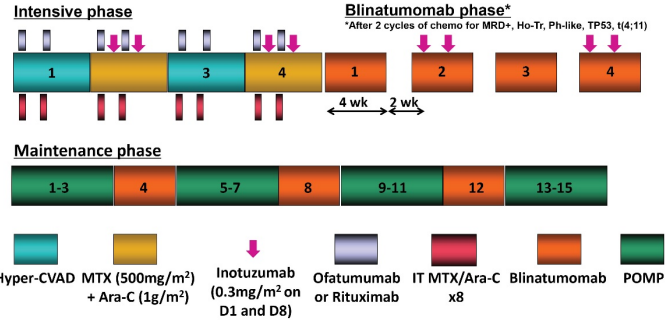
- Ph+ B-cell ALL
- Significant CNS pathology (excluding CNS leukemia)
- No active or co-existing malignancy with life expectancy ≤ 12 months

Study design

Hyper-CVAD + Blinatumomab (1st Cohort)



Hyper-CVAD + Blinatumomab + Inotuzumab (2nd Cohort)



Patients

Characteristic N (%) / median [range]	Overall N = 75	Cohort 1 (no INO) N = 38	Cohort 2 (with INO) N = 37
Age	33 [18-59]	37 [18-59]	25 [18-57]
Male	50 (67)	26 (68)	24 (65)
ECOG 0-1	64 (85)	30 (79)	34 (92)
WBC (x10^9/L) at start	4.7 [0.5-553]	3.1 [0.5-360.9]	7.6 [1.0-553]
CD19 expression ≥50%	65/66 (98)	31/32 (97)	34/34 (100)
CD20 expression ≥20%	34/67 (51)	17/33 (52)	17/34 (50)
***TP53* mutation**	14/74 (19)	10/37 (27)	4/37 (11)
CRLF2+ by flow	9/70 (13)	6/33 (18)	3/37 (8)
***JAK2* mutation**	4/74 (5)	2/37 (5)	2/37 (5)
Karyotype			
Diploid	24 (32)	11 (29)	13 (35)
High hyperdiploidy	5 (7)	3 (8)	2 (5)
Low hypodiploidy/Near triploidy	8 (11)	6 (16)	2 (5)
***KMT2A* rearranged**	6 (8)	3 (8)	3 (8)
Complex (≥5 anomalies)	6 (8)	3 (8)	3 (8)
Other	26 (35)	12 (32)	14 (38)

Results

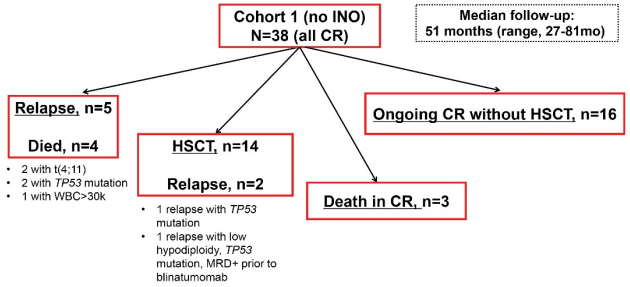
Response rates

Response N (%)	Overall N = 75	Cohort 1 (no INO) N = 38	Cohort 2 (with INO) N = 37
CR after induction*	50/59 (84)	26/32 (81)	24/27 (89)
CR at any time	59/59 (100)	32/32 (100)	27/27 (100)
Flow MRD negativity after induction**	43/65 (66)	25/33 (76)	18/32 (56)
Flow MRD negativity at any time	62/65 (95)	32/33 (97)	30/32 (94)
NGS MRD negativity at any time	27/37 (73)	2/4 (50)	25/33 (76)
Early death (30-day)	0	0	0

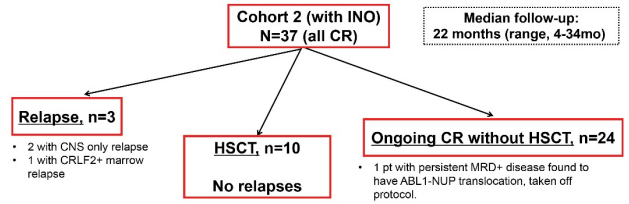
*Six pts in Cohort 1 (no INO) and 10 patients in Cohort 2 (with INO) were in CR at start.

**Five pts in Cohort 1 (no INO) and 5 pts in Cohort 2 (with INO) were MRD negative by flow at start.
Abbreviations: CR, complete remission; MRD, measurable residual disease; NGS, next generation sequencing

Disposition of Hyper-CVAD + Blinatumomab (1st Cohort)



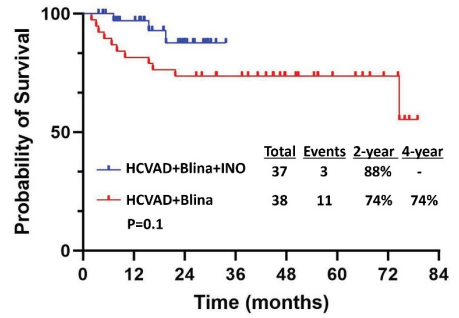
Disposition of Hyper-CVAD + Blinatumomab + INO (2nd Cohort)



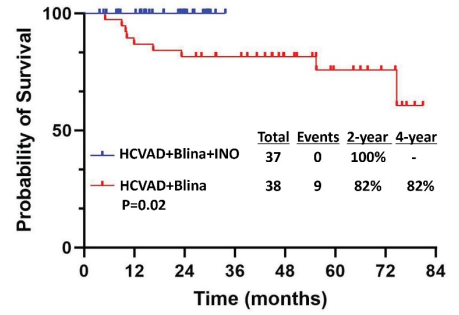
Results

Outcomes

Relapse Free Survival



Overall Survival



Safety (Related Adverse Events)

Blinatumomab
- 1 patient discontinued due to related adverse event (grade 2 encephalopathy and dysphasia)

Inotuzumab
- No patients discontinued due to toxicity
- No cases of veno-occlusive disease

Conclusions

- Hyper-CVAD with sequential blinatumomab +/- INO is highly effective and safe as frontline therapy for Ph-negative B-ALL
- Early data suggest possible benefit of the addition of INO to the chemotherapy + blinatumomab backbone
- Due to CNS relapses, the protocol has been amended to now administer 15 doses of IT chemotherapy

Correspondence
Elias Jabbour , The University of Texas MD Anderson Cancer Center, Department of Leukemia, 1515 Holcombe Boulevard, Houston, TX 77030, E-mail. E-mail: ejabbour@mdanderson.org

Chemotherapy-Sparing Induction Followed By Consolidation and Maintenance with Blinatumomab and Concurrent Oral Tyrosine Kinase Inhibitor Therapy for Newly-Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Primary Endpoint Results from the BLISSPHALL Study

Mark Blaine Geyer, MD[1,2], John Mascarenhas, MD[3], Marissa Smith[4], Shakira Pascual[1], Anmol Shah[1], Michael R. Silvestrone[1], Tina Czaplinska[3], Kathryn Johnson, DNP, MSc, FNP-BC[5], Meghan C. Thompson, MD[1] and Jae H. Park, MD[1,2]; [1]Cell Therapy Service, [2]Cell Therapy Service, [4]Nursing, Memorial Sloan Kettering Cancer Center, New York, NY; [3]Department of Medicine, Division of Hematology and Medical Oncology, [5]Department of Nursing, Icahn School of Medicine at Mount Sinai, New York, NY

Background

- Oral ABL-targeted kinase inhibitors (TKIs) have transformed treatment of BCR::ABL+ (Philadelphia chromosome-positive, Ph+) acute lymphoblastic leukemia (ALL).
- Induction with corticosteroids and dasatinib (DAS) alone results in morphologic complete response (mCR) rates approaching 100% but low rates of measurable residual disease (MRD) negativity.[1]
- The addition of intensive chemotherapy to TKIs improves rates of MRD negativity by flow cytometry and *BCR::ABL1* PCR but adds risks of myelosuppression.[2]
- DAS + the CD3/CD19 bispecific T-cell engager blinatumomab (BLIN) is effective consolidation for Ph+ ALL, though ABL kinase mutations conferring resistance arose in a subgroup of patients within the first 12 weeks of therapy, prior to initiation of BLIN.[3]
- We designed a phase II study of BLIN as part of a chemotherapy sparing strategy in patients with Ph+ ALL (BLISSPHALL), introducing BLIN as early as 6 weeks into treatment for pts in mCR, with the aim of expediting MRD clearance and suppressing resistant clones early in disease course, and including a maintenance phase of BLIN + TKI for patients in molecular response.

Methods

- We conducted a multicenter trial of TKI + corticosteroid induction and TKI + BLIN consolidation and maintenance in adults (≥18 yrs) w/ newly-diagnosed Ph+ ALL (NCT04329325). Study schema is depicted in **Figure 1**.
- **Induction**: Patients received a corticosteroid pre-phase followed by modified GIMEMA LAL1205 induction (dexamethasone + DAS 140 mg PO daily), with guidelines for DAS dose adjustments or TKI change per protocol if needed for toxicity/intolerance.
- **Consolidation**: Patients in mCR on day 43 of induction could proceed to consolidation with 3 cycles of BLIN (28 mcg IVCI daily) and TKI, with 14 days off between cycles.
- **Maintenance**: Patients in protocol-defined complete molecular response (CMR; MRD negative by FACS and no detectable *BCR::ABL1* transcripts) after consolidation could proceed to maintenance with an additional 4 cycles of BLIN (28 mcg IVCI daily) and TKI, with 28 days off between cycles.
- **Post-protocol maintenance**: At discretion of treating investigator.
- **Allogeneic hematopoietic cell transplantation (alloHCT)**: Patients could come off protocol at any point to pursue alloHCT at the discretion of the treating investigator; it was recommended that patients receive ≥2 cycles of BLIN if able to remain on study.
- **Intrathecal (IT) chemotherapy**: Administered days 22 and 43 of induction and between cycles of BLIN; methotrexate 12 mg IT recommended but agent(s) and dosing left to discretion of treating investigator.
- Bone marrow (BM) examination was performed at baseline, on days 22 and 43 of induction, following each of the first 3 cycles of BLIN consolidation, and following cycles 5 and 7 of BLIN in those proceeding to maintenance.
- BM bone marrow (BM) MRD assessments included FACS and *BCR::ABL1* PCR (mandatory), with many patients undergoing optional assessment for malignant clonal IgH/TCR rearrangements by next generation sequencing (NGS; Lymphotrack, Invivoscribe, San Diego, CA, or clonoSEQ, Adaptive Biotechnologies, Seattle, WA).
- **Primary objective**: Proportion of evaluable patients achieving CMR by the end of consolidation.
- **Secondary objectives**: Safety/toxicity of BLIN + DAS, duration of CMR, incidence of relapse, event-free/overall survival.
- **Exploratory objectives**: Safety/toxicity of BLIN + TKIs other than DAS, patterns of resistance by ABL kinase mutation studies, outcomes in patients not undergoing alloHCT in CR1.
- **Design**: Simon's Minimax two-stage design. After 3 or more of the first 10 enrolled patients achieved CMR (stage 1), we entered stage 2 of the study, at which time we continued enrollment to a maximum of 17 patients (stages 1 and 2 combined). A benchmark of ≥6 patients achieving CMR (stages 1 and 2 combined) was considered promising for further development and investigation.

Figure 1

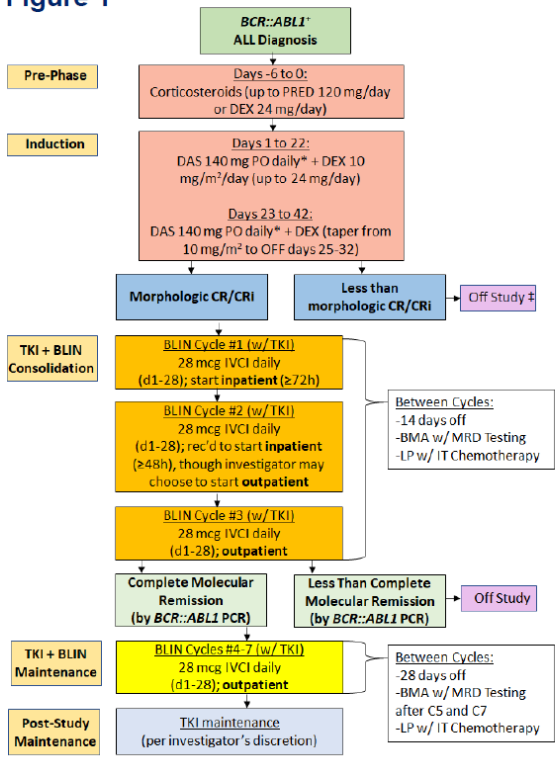
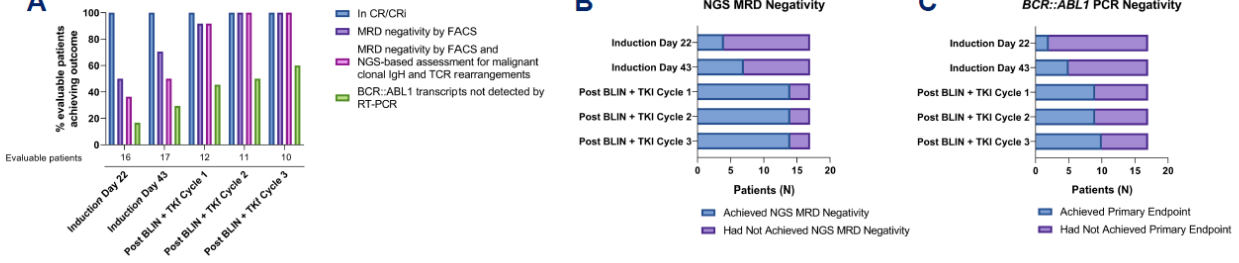


Figure 2



Results

- Of the 17 enrolled patients, 12 were women and 5 were men. Median age at Ph+ ALL diagnosis was 50 years (range, 21-87). Fifteen exhibited p190 *BCR::ABL1* transcript type and 2 had p210 *BCR::ABL1* transcript type.
- Median follow-up from enrollment is 14.5 months (range, 6.4-26.5 months)
- All 17 patients began DAS 140 mg/d as their initial TKI
- Four changed TKI for DAS intolerance per protocol (bosutinib, n=2; ponatinib [PON], n=2) and remained on study; TKI was changed to PON in one other patient to optimize *BCR::ABL1* transcript suppression pre-alloHCT and that patient was withdrawn from study.
- Two patients had interruption or delay of BLIN due to toxicity (grade [G] 3 transaminase elevation, n=1; G2 cytokine release syndrome, n=1); BLIN was resumed in both. BLIN cycle 1 was stopped in one patient due to discovery of extramedullary disease progression and that patient was withdrawn from study. BLIN cycle 7 was interrupted due to central venous catheter dysfunction in one patient and resumed following placement of new central access.
- **Table 1** lists nonhematologic adverse effects (AEs) seen in ≥2 pts at least possibly related to TKI or BLIN while on study. Additional AEs of note include Grade 3 pancreatitis arising in one patient after DAS was changed to PON; TKI was ultimately changed back to DAS. One patient developed a grade 2 pleural effusion possibly related to DAS. There were no grade 4-5 AEs.
- **Figure 2** summarizes responses. All 17 patients (100%) achieved morphologic CR during induction (median day 22). While 3 patients had CR with incomplete hematologic recovery (CRi) at day 22, hematologic parameters improved to CR in all.
- By FACS, 16/17 achieved BM MRD negativity.
- By NGS for malignant clonal IgH/TCR rearrangements, 14 of 17 (82%) enrolled patients achieved MRD negativity. Testing was persistently positive in the patient not achieving MRD negativity by FACS and was not performed in 2 other patients.
- By BCR::ABL1 PCR, 10 of 17 (59%) achieved CMR (5 during induction, 5 during consolidation) and 7 did not achieve CMR.
- Notably, 4 pts w/ persistent low-level *BCR::ABL1* transcripts had no evidence of MRD by NGS but were withdrawn post-consolidation as protocol required *BCR::ABL1* PCR negativity to proceed to maintenance. None of these patients have relapsed.
- Two patients relapsed, both after achieving CMR. One declined consolidation and self-discontinued TKI; one had extramedullary relapse w/ ABL T315I mutation during C1 of blinatumomab. These two patients died at 14.5 and 19.3 months from enrollment, respectively. All other patients remain alive in CR1 as of last follow-up.
- Four patients underwent alloHCT in CR1 (rising MRD levels on study leading to change in therapy, n=1; persistent *BCR::ABL1* PCR positivity, n=2; IKZF1^{plus} phenotype, n=1); one underwent alloHCT in CR2 following extramedullary relapse.

Table 1

Toxicity	Grade 1-2 (N)	Grade 1-2 (%)	Grade 3 (N)	Grade 3 (%)	Total (N)	Total (%)
Alanine aminotransferase increased	4	24%	2	12%	6	35%
Aspartate aminotransferase increased	5	29%	1	6%	6	35%
Nausea	5	29%	1	6%	6	35%
Rash (any one or more rashes)	6	35%	0	0%	6	35%
Rash, maculopapular	4	24%	0	0%	3	18%
Rash, acneiform	3	18%	0	0%	3	18%
Rash, papulopustular	1	6%	0	0%	1	6%
Arthralgia	5	29%	0	0%	5	29%
Anorexia	4	24%	0	0%	4	24%
Diarrhea	4	24%	0	0%	4	24%
Edema (one or more types)	3	18%	1	6%	4	24%
Edema, localized	2	12%	0	0%	2	12%
Edema, limb	0	0%	1	6%	1	6%
Edema, periorbital	1	6%	0	0%	1	6%
Fever	4	24%	0	0%	4	24%
Alopecia	3	18%	0	0%	3	18%
Bloating	3	18%	0	0%	3	18%
Constipation	3	18%	0	0%	3	18%
Cytokine release syndrome	3	18%	0	0%	3	18%
Headache	3	18%	0	0%	3	18%
Abdominal pain	1	6%	1	6%	2	12%
Alkaline phosphatase increased	2	12%	0	0%	2	12%
Fatigue	2	12%	0	0%	2	12%
Fibrinogen decreased	2	12%	0	0%	2	12%
Gastroesophageal reflux disease	2	12%	0	0%	2	12%
Vomiting	2	12%	0	0%	2	12%

Conclusions

- An initial treatment strategy of DAS + corticosteroid induction followed by addition of BLIN to TKI as early as 6 weeks into induction therapy leads to high rates of deep molecular response by NGS MRD and *BCR::ABL1* PCR studies with low risk of early relapse and low rates of severe regimen-related toxicity in patients with newly-diagnosed Ph+ ALL
- Use of PON as initial TKI may further suppress resistant clones, as arose in the one patient progressing on DAS + BLIN with T315I mutation and extramedullary disease.
- Further follow-up is needed to confirm durability of responses to BLIN consolidation and maintenance in absence of alloHCT.
- Subsequent studies may clarify whether the group of patients with MRD negativity by NGS-based assays but persistent *BCR::ABL1* PCR positivity has a favorable natural history, as observed in some other series as well[4], without alloHCT.

References

1. Foa R, Vitale A, Vignetti M, Meloni G, Guarini A, De Propris MS, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2011;118(25):6521-8.
2. Kantarjian H, Short NJ, Jain N, Sasaki K, Huang X, Haddad FG, et al. Frontline combination of ponatinib and hyper-CVAD in Philadelphia chromosome-positive acute lymphoblastic leukemia: 80-months follow-up results. Am J Hematol. 2023;98(3):493-501.
3. Foa R, Bassan R, Vitale A, Elia L, Piciocchi A, Puzzolo MC, et al. Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. N Engl J Med. 2020;383(17):1613-23.
4. Short NJ, Jabbour E, Macaron W, Ravandi F, Jain N, Kanagal-Shamanna R, et al. Ultrasensitive NGS MRD assessment in Ph+ ALL: Prognostic impact and correlation with RT-PCR for BCR::ABL1. Am J Hematol. 2023;98(8):1196-203.

A Phase IB/II Study of Blinatumomab in Patients with B-Cell Acute Lymphoblastic Leukemia (ALL) and B-Cell Non-Hodgkin Lymphoma (NHL) As Post-Allogeneic Blood or Marrow Transplant (alloBMT) Remission Maintenance

Jonathan A. Webster MD, Richard J Jones MD, Amanda Blackford, Audra Shedeck, Richard F Ambinder MD PhD, Lode J. Swinnen MD, Nina D. Wagner-Johnson MD, Ephraim J Fuchs MD, Javier Bolaños-Meade MD, Philip H. Imus MD, Challice L. Bonifant MD PhD, Heather J Symons MD, Tania Jain MD, Gabrielle T. Prince MD, Mark J. Levis MD PhD, Leo Luznik MD, and Ivana Gojo MD

Division of Hematologic Malignancies, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background

- Improvements in GVHD prophylaxis and supportive care have led disease relapse to replace non-relapse mortality as the leading cause of treatment failure following allogeneic blood or marrow transplantation (alloBMT) (Horowitz. *Bone Marrow Transplant.* 2018).
- Post-transplantation cyclophosphamide (PTCy) significantly reduces the incidence of both grade III/IV acute and chronic graft-versus-host disease (GVHD) following alloBMT with reduced-intensity conditioning compared to a conventional regimen of methotrexate and tacrolimus, leading to improved GVHD-free, relapse free survival (GRFS) (Bolanos-Meade. *N Engl J Med.* 2023).
- Blinatumomab eradicates MRD at levels $\geq 10^{-3}$ in 78% of B ALL (Gokbuget. *Blood.* 2018) and has shown a survival benefit in MRD-negative B ALL patients without alloBMT (Litzow. *Blood.* 2022).
- Blinatumomab has also proven effective in non-Hodgkin lymphoma (NHL), although its use is limited by toxicity due to the escalated doses necessary for efficacy (Goebeler. *J Clin Oncol.* 2016).
- *In vitro* studies suggest that blinatumomab leads to improved tumor specific lysis in the presence of allogeneic T cells compared to host T cells (Kohnke. *J Hematol Oncol.* 2015).
- Down-regulation of HLA Class II on leukemic blasts represents a well characterized mechanism of post-transplant relapse in AML (Christopher. *N Engl J Med.* 2018) and has also been found in relapsed lymphoid malignancies (de Charette. *Haematologica.* 2018).
- Blinatumomab increases HLA Class II expression on ALL blasts.
- A prior study exclusively in B ALL demonstrated that administration of blinatumomab as post-alloBMT remission maintenance is feasible but did not improve survival compared to historical controls in a cohort that universally continued tacrolimus during their first cycle of post-transplant treatment (Gaballa. *Blood.* 2022).
- We initiated a prospective phase Ib/II study of blinatumomab in B ALL and NHL to determine its feasibility and efficacy among patients undergoing alloBMT with PTCy who were universally off immunosuppression prior to the initiation of blinatumomab.

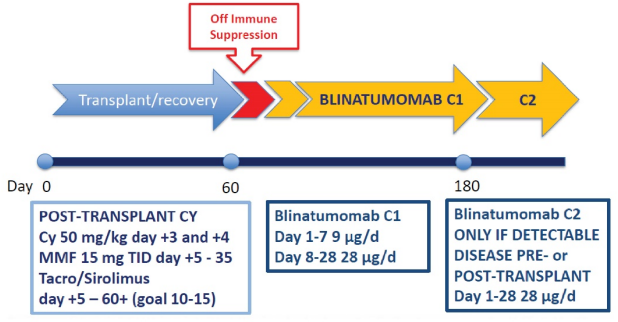
Methods

Inclusion Criteria

- Age: ≥ 1 month for B ALL OR ≥ 18 years for NHL
- Disease Characteristics: Pre-B ALL with high-risk disease in CR1 (per NCCN) or any patient in CR2+ OR low and high grade NHL
- Transplant Characteristics: Myeloablative or reduced-intensity conditioning with PTCy for B ALL OR non-myeloablative conditioning with PTCy for NHL
- Must be ≥ 60 days and ≤ 180 days post-transplant with ANC >1,000 and platelets >30K.
- No evidence of disease progression prior to treatment initiation.
- Patients with prior blinatumomab exposure are eligible as long as there is no evidence of CD19 loss

Exclusion Criteria

- Lack of engraftment (<85% donor DNA in bone marrow or peripheral blood after alloBMT).
- Active or untreated CNS or testicular disease.
- Receipt of chemotherapy or radiotherapy within 2 weeks of initiating blinatumomab (IT chemo allowed).
- History of Grade III/IV acute GVHD or severe chronic GVHD.
- Patients must be off all systemic treatment (steroids, tacrolimus, sirolimus, etc.) for the treatment or prevention of GVHD without evidence of GVHD for a minimum of 30 days prior to enrollment.
- Patients with Ph+ ALL who are eligible for post-transplant TKIs based on a demonstrated sensitivity to TKIs pre-transplant.



Demographics and Results

Table 1: Patient Demographics

Demographic	All (N=42)	NHL (N=23)	Pre-B ALL (N=19)
Median Age (Range)	54 (30-73)	59 (33-73)	47 (30-72)
Female Gender	15 (36%)	6 (26%)	9 (47%)
Diagnosis			
Ph-negative B ALL	19 (45%)		
B Cell Lymphoma	23 (55%)		
DLBCL		8 (35%)	
Transformed DLBCL		7 (30%)	
Mantle Cell Lymphoma		6 (26%)	
PCNSL		1 (4%)	
Follicular Lymphoma		1 (4%)	
CR Status			
CR1	21 (50%)	9 (39%)	12 (63%)
CR2	13 (31%)	8 (35%)	5 (26%)
CR3	4 (10%)	2 (9%)	2 (11%)
PR	4 (10%)	4 (17%)	
Prior Lines of Therapy			
1	13 (31%)	4 (17%)	9 (47%)
2	17 (40%)	9 (39%)	8 (42%)
3	7 (17%)	7 (30%)	1 (5%)
4	2 (5%)	2 (9%)	
5-6	3 (7%)	2 (9%)	1 (5%)
Reduced-intensity Conditioning	42 (100%)	23 (100%)	23 (100%)
Donor Type			
Haploidentical	30 (71%)	18 (78%)	12 (63%)
Matched Unrelated Donor	8 (19%)	4 (17%)	4 (21%)
Matched Related Donor	2 (5%)	1 (4%)	1 (5%)
Mismatched Unrelated Donor	2 (5%)		2 (10%)
Graft Source			
Bone Marrow	24 (57%)	18 (78%)	6 (32%)
PBSCT	18 (42%)	5 (22%)	13 (68%)
Median Time from Transplant to Blina Start	137 Days (90-182)	140 Days (90-182)	130 Days (91-178)
Prior AlloBMT	3 (7%)	1 (4%)	2 (9%)
Prior Autologous BMT	2 (5%)	2 (9%)	
Prior CD19 CAR T Cells	3 (7%)	3 (13%)	
Prior Blinatumomab	13 (30%)		13 (68%)
MRD negative by flow (LOD 1/10,000)			19 (100%)
ALL Cytogenetics			
MLL			2 (11%)
Ph-like			2 (11%)
Hypodiploidy			4 (21%)
PBX1/TCF3			1 (5%)
Unknown			3 (16%)
Other			5 (26%)
CDKN2A Deletion			2 (11%)

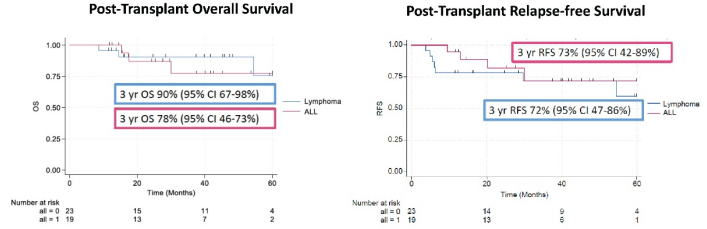
Table 2: Grade III/IV Adverse Events and GVHD (Possibly, Probably or Definitely r/t Blinatumomab)

Adverse Event	Grade II	Grade III	Grade IV
ALT Elevation		2 (5%)	1 (2%)
AST Elevation		2 (5%)	
Anemia		2 (5%)	
CNS Toxicity		3 (7%)	
Neutropenia		7 (17%)	8 (19%)
Chronic GVHD	2 (5%)		

Table 3: Early Discontinuation

Cause	Frequency	Time on Treatment
Transaminitis	1 (2%)	2 Days
G4 Neutropenia	2 (5%)	11 and 26 Days
Relapse	1 (2%)	21 Days
Tremor (Patient preference)	1 (2%)	4 Days

Figure 1: Survival Outcomes by Disease



Patients	3-yr OS (95% CI)	3-yr RFS (95% CI)	3-yr CIR (95% CI)	3-yr NRM (95% CI)
B ALL + NHL	85% (67-94%)	73% (54-85%)	24% (12-39%)	4% (0-17%)
B ALL	78% (46-93%)	73% (42-89%)	18% (4-39%)	10% (0-36%)
NHL	90% (67-98%)	72% (47-86%)	28% (11-48%)	-

Table 3: Characteristics of Relapsed Patients

Patient	Disease	Disease Status at Transplant	Time to Relapse (Months)	Genetics	Site of Relapse	CD19 Loss	Early Discontinuation
19	Mantle Cell Lymphoma	CR2	5.5	N/A	Brain	No	Yes (11 Days)
23	Mantle Cell Lymphoma	CR3	29.7	N/A	Mediastinum	No	Yes (2 Days)
49	Mantle Cell Lymphoma	PR	4.9	N/A	Skin	Unknown	
14	DLBCL (Transformed)	CR2	6.3	N/A	LN	No	
37	DLBCL	CR1	6.1	N/A	LS	Unknown	
43	DLBCL	PR	3.8	N/A	Skin	No	Yes (21 Days)
31	Pre-B ALL	CR2	12.9	Unknown	CNS + BM MRD	No	
33	Pre-B ALL	CR1	9.6	Other	CNS + BM MRD	No	
04	Pre-B ALL	CR3	20.3	Unknown	CNS	No	

Conclusions

- Post-transplant blinatumomab maintenance was feasible in Pre-B ALL and NHL with 5 (12%) discontinuing treatment early due to adverse events.
- Two patients (5%) developed chronic GVHD following post-transplant blinatumomab that required the resumption of immunosuppression. Other toxicities (neurologic, hepatic, and hematologic) were expected with blinatumomab.
- Outcomes among high-risk patients with B ALL and NHL were promising.
- Nine patients relapsed with 5 (55.5%) of the relapsed patients including all relapsed B ALL patients presenting with CNS involvement.
- There was no evidence of antigen escape (CD19 loss) among the relapsed patients for whom CD19 expression was characterized at relapse.
- Additional studies are ongoing to characterize MRD using NGS for both B ALL and NHL patients.
- Correlative studies examining T cell subsets are planned.

Phase 2 Trial of Mini-Hyper-CVD Plus Inotuzumab Ozogamicin, With or Without Blinatumomab, in Older Patients With Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia

Wei Ying Jen, MD, Elias Jabbour, MD, Fadi G. Haddad, MD, Nicholas J. Short, MD, Nitin Jain, MD, Tapan M. Kadia, MD, Naval Daver, MD, Gautam Borthakur, MD, Courtney DiNardo, MD, Lewis Nasr, Marianne Zoghbi, Jovitta Jacob, Edith Roy, Christopher Loiselle, Anna Milton, Juan Rivera, Rebecca Garris, Farhad Ravandi, MD and Hagop M. Kantarjian, MD

The University of Texas MD Anderson Cancer Center, Houston, TX

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Background

- Older patients with B-cell acute lymphoblastic leukemia (B-ALL) have worse outcomes compared with younger patients
- They are less able to tolerate intensive chemotherapy
- The introduction of blinatumomab (blina) and inotuzumab ozogamicin (InO) have improved overall survival in patients with relapsed / refractory B-ALL
- We aim to study the incorporation of InO and blina with low intensity chemotherapy in older patients with newly-diagnosed Philadelphia chromosome (Ph)-negative B-ALL.

Inclusion/Exclusion Criteria

Inclusion Criteria

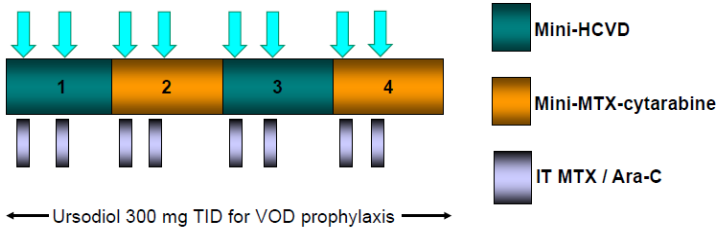
- Age 60 or older
- Newly diagnosed Ph-negative B-ALL
- Previous therapy with 1-2 courses of chemotherapy was allowed
- ECOG performance status ≤ 3
- Adequate renal function (estimated GFR ≥ 50mL/min)
- Adequate cardiac function (ejection fraction > 50%)
- Adequate hepatic function (bilirubin ≤ 1.95 mg/dL)

Exclusion Criteria

- Infection not controlled by antibiotics
- NYHA grade 3-4 heart failure
- Second malignancy

Study Treatment

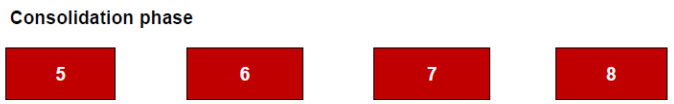
Intensive phase



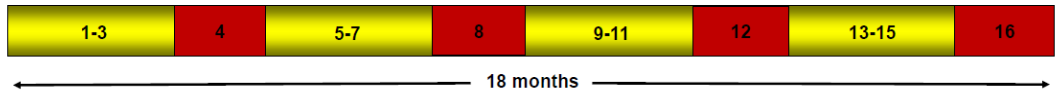
InO	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2-4	0.6	0.3 D2 and D8

Total INO dose = **2.7 mg/m²**

Consolidation phase



Maintenance phase



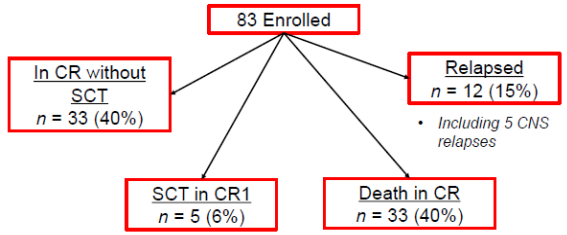
Results

Baseline Characteristics

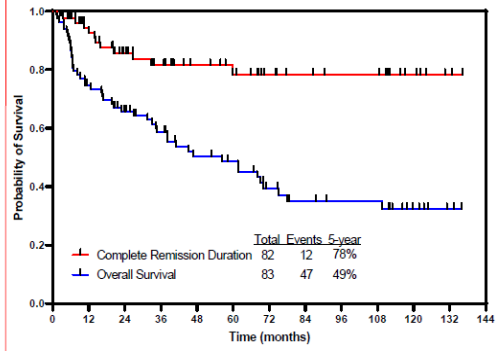
Characteristic	Category	N (%) / Median [range]
Age (years)	≥70	68 [60 - 87] 28 (34)
Cytogenetics	Diploid HeH Ho-Tr Tetraploidy Complex t(4;11) Misc IM/ND	27 (33) 5 (6) 12 (14) 3 (4) 3 (4) 1 (1) 16 (19) 16 (19)
CD19 (%)		99.6 [26-100]
CD22 (%)		96.9 [27-100]
CD20	≥20%	46/76 (61)
Ph-like ALL		9/50 (18)
TP53 mutation		25/64 (39)

HeH, high hyerdiploidy, Ho-Tr, low hypodiploidy / near triploidy, IM/ND, insufficient metaphases / not done.

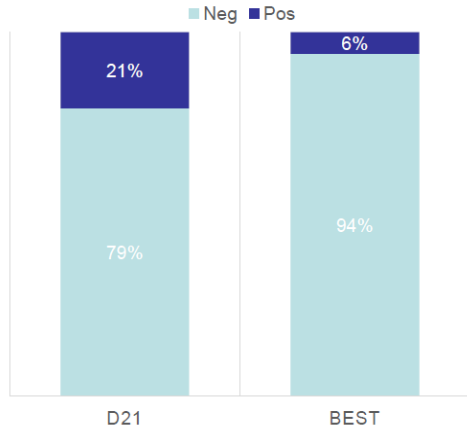
Patient Disposition



Overall Survival and Continuous Remission Duration



MRD Responses



Conclusions

- Older patients with Ph negative B-ALL have excellent responses and deep remissions when treated with mHCVD and intouzumab, with or without blinatumomab.
- Chemotherapy-free combinations with blina and InO are currently under investigation in patients aged over 70.

Correspondence

Elias Jabbour MD, The University of Texas MD Anderson Cancer Center, Department of Leukemia, 1515 Holcombe Boulevard, Houston, TX 77030, E-mail: ejabbour@mdanderson.org

A Phase II Study of Low-Intensity Chemotherapy (Mini-Hyper-CVD) and Ponatinib Followed by Blinatumomab and Ponatinib in Patients With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

Wei Ying Jen, MD, Elias Jabbour, MD, Fadi G. Haddad, MD, Lewis Nasr, MD, Nicholas J. Short, MD, Marianne Zoghbi, MD, Cedric Nasnas, MD, Ghayas C. Issa, MD, Musa Yilmaz, MD, Naval Daver, MD, Naveen Pemmaraju, MD, Lucia Masarova, MD, Farhad Ravandi, MD, Nitin Jain, MD, Wuliamatu Deen, BSN, RN, Christopher Loiselle, BS, Lourdes Waller, Glenda Banks, Rebecca Garris, Hagop Kantarjian, MD

The University of Texas MD Anderson Cancer Center, Houston, TX

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Abstract

Background: Patients with Philadelphia chromosome (Ph)-positive B-cell acute lymphoblastic leukemia (ALL) treated with Hyper-CVAD and ponatinib achieve deep responses and long-term overall survival (OS). We aim to investigate if a reduced intensity regimen of mini-Hyper-CVD (mini-HCVD) with sequential blinatumomab (blina) in combination with ponatinib may further improve outcomes while mitigating the toxicity of intensive chemotherapy and the need for hematopoietic stem cell transplantation (HSCT).

Methods: Patients age ≥18 years with newly diagnosed (ND) or relapsed/refractory (R/R) Ph-positive ALL, or chronic myeloid leukemia in lymphoid blast phase (CML-LBP) were eligible. Other inclusion criteria included adequate liver, renal and cardiac function, and ECOG performance status ≤2. Patients with baseline central nervous system (CNS) involvement were not excluded. All patients had BCR::ABL1 transcripts and fluorescence in situ hybridization (FISH) for t(9;22) done at baseline. Morphological analysis of FISH patterns was performed in ND patients to detect BCR::ABL1 signal in myeloid cells (e.g., segmented neutrophils). Four cycles (C) of mini-HCVD alternating with methotrexate (MTX) + cytarabine were followed by blina 28μg/d given for four weeks every six weeks during C5-8. Patients received ponatinib 30mg daily initially, with a dose reduction to 15mg daily once in complete molecular remission (CMR). CMR was defined as undetectable BCR::ABL1 with an assay sensitivity of 0.01%. Rituximab was given for CD20-positive disease. Maintenance ponatinib, vincristine and prednisone for 15 cycles with blina + ponatinib every three cycles was given, followed by ponatinib for at least five years. All patients without CNS disease received 12 intrathecal injections of MTX or cytarabine.

Results: 20 patients (12 ND, 4 R/R, 4 CML-LBP) were treated between November 2019 and May 2023. Baseline characteristics are shown in Table 1. One patient with CML-LBP had received prior dasatinib while in chronic phase. The predominant BCR::ABL1 transcript was p190 in 7 (58%) ND patients. All patients achieved a complete remission (CR). Among patients in the ND, R/R, and CML-LBP cohorts, CMR was achieved in 10/12 (83%), 3/4 (75%), and 4/4 (100%) patients, respectively. In the ND cohort, six (50%) patients achieved CMR after C1 and eight (67%) after C3. Five (42%) ND patients had documented *BCR::ABL1* signal in myeloid cells by FISH. Four of them achieved CMR, after C1, C3, C4 and C3 maintenance.
With a median follow-up of 25 months (range, 2-42), the 2-year continuous remission duration (CRD) and OS rates were 93% and 83% in the entire cohort (Figure 1), and 90% and 82% in the ND cohort, respectively. In the ND cohort, one (8%) patient had isolated CNS relapse (during C4 of maintenance with blina and ponatinib), three (25%) patients died (two in CR due to COVID-19 and one of HSCT complications), and eight (67%) patients are in remission without HSCT. No patients relapsed in the R/R cohort; one patient underwent HSCT, one patient died in CR from MTX-associated disseminated necrotizing leukoencephalopathy, and two patients are in remission without HSCT. None of the CML-LBP relapsed; one patient underwent HSCT in CR.
Ponatinib dose was reduced in two patients prior to obtaining CMR (one had pancreatitis, one had cardiomyopathy). One patient switched from ponatinib to dasatinib due to pulmonary embolism in C2. No patients required dose modification of blina. The 60-day mortality rate was 0%.

Conclusion: In patients with Ph-positive ALL, the combination of mini-HCVD and ponatinib followed by sequential blina and ponatinib yielded excellent outcomes with durable remissions. The toxicity profile was favorable and HSCT was avoided in most patients with ND disease. Longer follow-up is needed to confirm the durability of responses.

Background

- Standard of care in newly diagnosed Ph+ ALL: chemotherapy plus TKI
  - T315I mutations are dominant mechanism of relapse (up to 75% at relapse)
- Ponatinib: pan-BCR::ABL1 TKI with activity in T315I mutations
  - Combination of hyper-CVAD + ponatinib: high rates of complete molecular response (CMR) and 6-year OS of 74%, without need for HSCT in most pts
- Blinatumomab
  - Effective monotherapy in R/R Ph+ ALL: CR/CRh rate of 36%
  - Combination of blinatumomab + ponatinib is safe and effective in newly diagnosed Ph+ ALL: CMR rate of 84% and 2-year OS of 90%

Inclusion/Exclusion Criteria

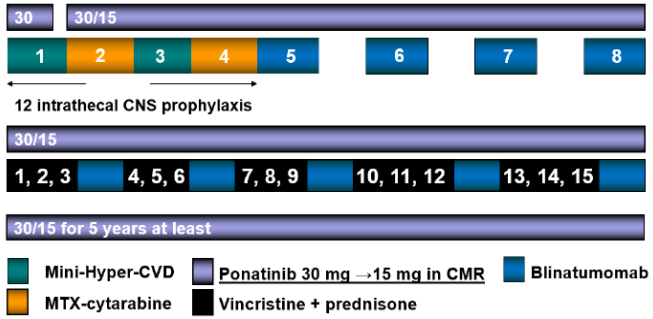
Inclusion Criteria

- Newly diagnosed Ph+ ALL, relapsed/refractory Ph+ ALL, or lymphoid blast phase CML:
  - Previous therapy with 1-2 courses of chemotherapy ± TKI was allowed in newly diagnosed cohort
- Age ≥ 18 years
- ECOG performance status ≤ 2
- Adequate renal function
- Adequate cardiac function
- Adequate hepatic function:
  - Bilirubin ≤ 2 mg/dL
  - AST and ALT ≤ 3 x ULN

Exclusion Criteria

- Uncontrolled, active CV disease
  - History of MI, CVA, or revascularization within 3 months
  - Congestive heart failure with reduced LVEF
  - Atrial of ventricular arrhythmia
  - History of arterial or venous thromboembolism
  - Uncontrolled hypertension (>140/90)
- Significant CNS pathology (excluding CNS leukemia)

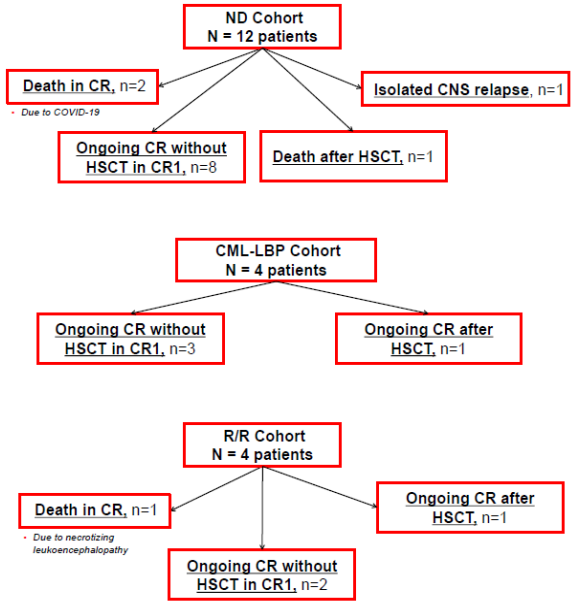
Study Design



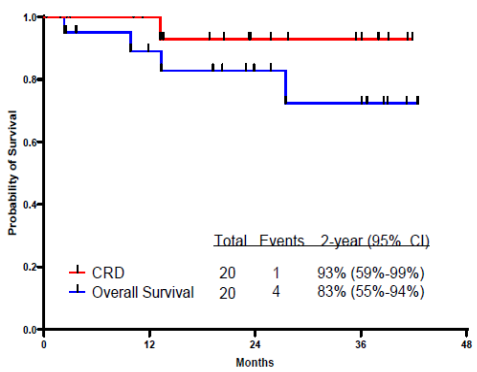
Results

Patient Characteristics and Responses

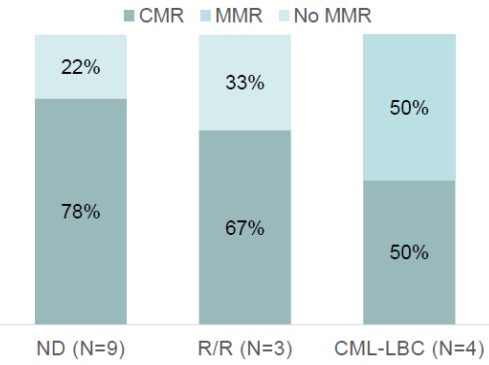
Characteristic N (%) / Median [range]	Total N = 20	ND N = 12	R/R N = 4	CML-LBP N = 4
Age	41 [25-61]	41 [25-59]	43 [31-49]	41 [33-61]
Female Gender	12 (60)	9 (75)	1 (25)	2 (50)
Performance Status <2	20 (100)	12 (100)	4 (100)	4 (100)
WBC (x10^9/L)	22 [2-267]	21 [2-267]	5 [4-7]	52 [14-146]
CNS involvement	1 (5)	0	0	1 (25)
CD20 expression ≥20%	5 (25)	5 (42)	0	0
BCR::ABL1 transcript p190 p210	7/19 (37) 12/19 (63)	7 (58) 5 (42)	0 3/3 (100)	0 4 (100)
CR/CRi	16 (100)	9 (100)	3 (100)	4 (100)
CMR	11 (69)	7 (78)	2 (67)	2 (50)
Frontline Salvage 1 Salvage 2+	16 (80) 3 (15) 1 (5)	12 (100) 0 0	0 3 (75) 1 (25)	4 (100) 0 0



Overall Survival and Continuous Remission Duration



MRD Response Rates



Conclusions

- mHCVD + Ponatinib + blinatumomab is safe and effective in Ph+ ALL
- In frontline Ph+ ALL: CR/CRi 100%; CMR 78%
- In R/R Ph+ ALL: CR/CRi 100%, CMR 67%
- The combination has excellent outcomes and durable remissions, with a favorable toxicity profile.
- Longer follow-up is needed to confirm durability of responses

Correspondence

Elias Jabbour MD, The University of Texas MD Anderson Cancer Center, Department of Leukemia, 1515 Holcombe Boulevard, Houston, TX 77030, E-mail: ejabbour@mdanderson.org

Chemotherapy-Free Combination of Blinatumomab and Ponatinib in Adults With Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: Updates From a Phase II Trial

Fadi G. Haddad, Elias Jabbour, Nicholas J. Short, Nitin Jain, Xuelin Huang, Guillermo Montalban-Bravo, Tapan M. Kadia, Naval G. Daver, Cedric Nasnas, Ejiroghene Mayor, Patrice E. Nasnas, Wuliamatu Deen, Marianne Zoghbi, Jennifer Thankachan, Christopher Loiselle, Rebecca Garris, Farhad Ravandi, Hagop M. Kantarjian

The University of Texas MD Anderson Cancer Center, Houston, TX

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Background

- Standard of care in newly diagnosed Ph+ ALL: chemotherapy plus TKI
  - T315I mutations are dominant mechanism of relapse (up to 75% at relapse)
- Ponatinib: pan-BCR::ABL1 TKI with activity in T315I mutations
  - Combination of hyper-CVAD + ponatinib: high rates of complete molecular response and 6-year OS of 75%, without need for HSCT in most patients
- Blinatumomab
  - Effective monotherapy in R/R Ph+ ALL: CR/CRh rate of 36%
  - Combination of blinatumomab + dasatinib safe and effective in newly diagnosed Ph+ ALL: high rates of molecular response, 4-year OS of 78%

Methods

Inclusion Criteria

- Age ≥ 18 years with newly diagnosed Ph+ ALL
- Previous therapy with 1-2 courses of chemotherapy ± TKI allowed
- ECOG performance status ≤ 2
- Adequate organ function

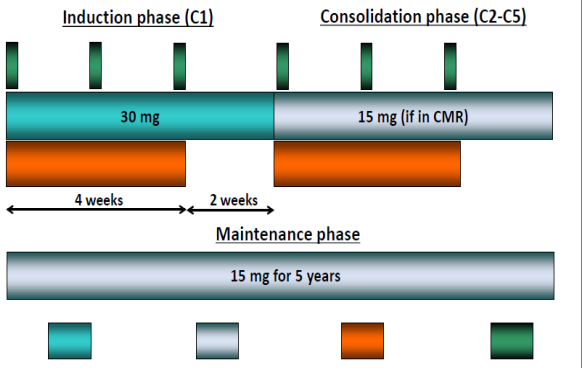
Exclusion Criteria

- Uncontrolled, active cardiovascular disease:
  - History of MI, CVA, or revascularization within 3 months
  - Congestive heart failure with reduced LVEF
  - Atrial of ventricular arrhythmia
  - History of arterial or venous thromboembolism
  - Uncontrolled hypertension (>140/90)
- Significant CNS pathology (excluding CNS leukemia)

Endpoints

- Primary: rate of complete molecular response
- Secondary: response rates, safety measures, event-free survival survival (EFS) and overall survival (OS)

Study Design



* Amended to increase IT chemotherapy from 12 to 15

Patient Characteristics

Characteristics N (%) / Median [range]	N = 62
Age (years)	56 [20 - 83]
≥ 60	25 (40)
WBC (x10^9/L) at start	4.65 [0.4 - 23.7]
Male gender	27 (44)
Performance Status	
0-1	52 (84)
2	10 (16)
Central nervous system involvement	3 (5)
CD19 expression	99.8 [74.9 - 100]
>1 cardiovascular risk factor(s)	36 (58)
BCR::ABL1 Transcript	
p190	47/61 (77)
p210	14/61 (23)

Correspondence

Elias Jabbour MD, The University of Texas MD Anderson Cancer Center, Department of Leukemia, 1515 Holcombe Boulevard, Houston, TX 77030, E-mail: ejabbour@mdanderson.org

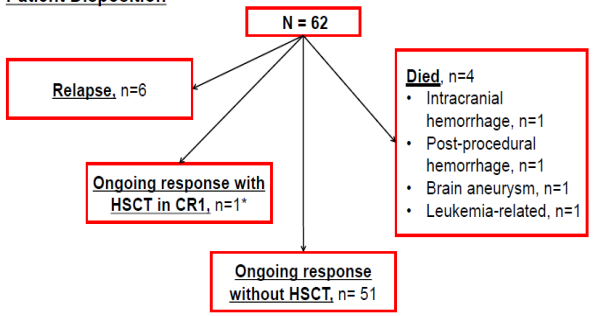
Results

Response Rates

Responses n/N (%)	N = 62
CR	38/40 (95)
CRi	1/40 (3)
*CR/Cri **	39/40 (98)
PR	0
No response	0
Complete molecular response (CMR) **	
After Cycle 1	37/55 (67)
Overall	46/55 (84)
Negative MRD by NGS	44/47 (94)
Early death	1/62 (2)

* 22 patients were in CR at the start of therapy
** 7 patients were in CMR at the start of therapy

Patient Disposition



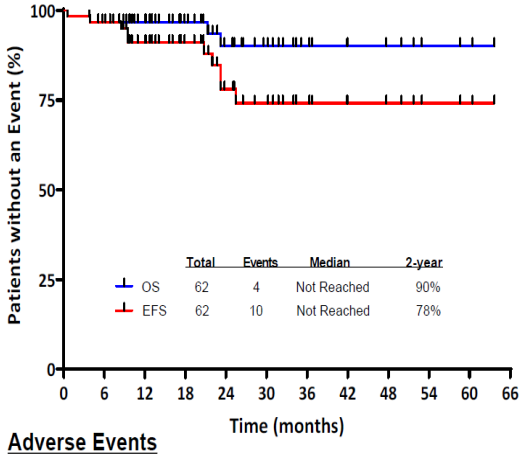
* Patient had persistently detectable *BCR::ABL1* transcript levels of 0.01%-0.05%

Conclusions

- Ponatinib + blinatumomab is safe and effective in Ph+ ALL
- In frontline Ph+ ALL: CR/CRi 98%; CMR 84%; 2-year OS 90%
- One patient underwent HSCT in CR1
- Combination of blinatumomab + ponatinib is a promising chemotherapy-free, HSCT-sparing regimen for Ph+ ALL

Results

Event-Free Survival and Overall Survival



Adverse Events

Adverse event	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
ALT increased	3 (5)	6 (10)	6 (10)	0
Elevated lipase	1 (2)	1 (2)	3 (5)	1 (2)
Pancreatitis	0	0	2 (3)	0
Fever / febrile neutropenia	8 (13)	6 (10)	1 (2)	0
Rash	7 (12)	0	1 (2)	0
Atrial fibrillation	1 (2)	1 (2)	1 (2)	0
Hypertension	0	0	1 (2)	0
GGT increased	0	0	1 (2)	0
Coronary artery stenosis	0	0	1 (2)	0
Headache	8 (13)	6 (10)	0	0
Constipation	5 (8)	4 (7)	0	0
Nausea/Vomiting	7 (11)	4 (6)	0	0
Cytokine release syndrome	2 (3)	4 (7)	0	0
Myalgia/arthralgia	4 (6)	1 (2)	0	0
Abdominal pain	0	3 (5)	0	0
Fatigue	2 (3)	1 (2)	0	0
Blurred vision, dry eye	0	3 (5)	0	0
Deep vein thrombosis	1 (2)	1 (2)	0	0
Cerebrovascular ischemia	0	1 (2)	0	0
Tremor	4 (7)	1 (2)	0	0
Peripheral neuropathy	7 (11)	0	0	0
Chills	2 (3)	0	0	0
Alkaline Phosphatase	1 (2)	0	1 (2)	0

Improved MRD Negativity Rates in Adverse Genomic Risk B-ALL Patients with Chemotherapy/ Blinatumomab Induction: Experience from the Australasian Leukaemia Lymphoma Group (ALLG) ALL06/09 Studies

Deborah L White[1,2,3], Rehn JA[1,3], Schutz CE[3], Heatley SL[1,3], Eadie LN[1,3], Thomson A[1,3], Page EC[1,3], Osborn M[2,4,5], Gangatharan S[2,6], Ng AP[2,7], Fleming S[2,8,9], Fedele P[2,8], Trahair T[2,10,11], Casey J[2,12], Mapp S[2,13], Cheung CCY[2,14], Armytage T[2,15], Henderson M[2,11,16], Sutton R[2,11,16], Larsen SR[2,17], Rowley L[2], Presgrave P[2,18], Kwan J[2,19], Bennett S[2,20], Fong CY[2,21], Dalla-Pozza L[2,22], Yeung DT[2,23-26] and Greenwood M[2,26,27]

[1]Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia; [2]Australasian Leukaemia and Lymphoma Group (ALLG), Melbourne; Australia; [3]Precision Cancer Medicine Theme, South Australian Health and Medical Research Institute, Adelaide, Australia; [4]The Women's and Children's Hospital, Adelaide, Australia; [5]Haematology Department, Royal Adelaide Hospital, Adelaide, Australia; [6]St John of God Murdoch Hospital, Murdoch, Australia; [7]Clinical Haematology, Peter MacCallum Cancer Centre & the Royal Melbourne Hospital, Melbourne, VIC, Australia; [8]Monash Health, Clayton, Australia; [9]The Alfred Hospital, Melbourne, VIC, Australia; [10]Sydney Children's Hospital, Randwick, Australia; [11]Children's Cancer Institute, Randwick, Australia; [12]The Townsville Hospital, Townsville, Australia; [13]Princess Alexandra Hospital, Woolloongabba, Australia; [14]Prince of Wales Hospital, Randwick, Australia; [15]Gosford Hospital, Gosford, Australia Prince Alfred Hospital, Camperdown, Australia; [16]School of Women's and Children's Health, University of New South Wales, Sydney, Australia; [17]Royal Prince Alfred Hospital, Camperdown, Australia; [18]Wollongong Hospital, Wollongong, Australia; [19]Westmead Hospital, Westmead, Australia; [20]Canberra Hospital, Garren, Australia; [21]Austin Hospital, Heidelberg, Australia; [22]The Children's Hospital at Westmead, Westmead, Australia; [23]Blood Cancer, Precision Medicine Theme, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, SA, Australia; [24]Haematology, Central Adelaide Local Health Network (CALHN), Adelaide, SA, Australia; [25]Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, SA, Australia; [26]Equal contributions, Australia, Australia; [27]Royal North Shore Hospital, St Leonards, Australia

BACKGROUND

- Adolescent and Young Adult (AYA) Acute Lymphoblastic Leukemia (ALL) patients experience inferior survival and greater toxicity than young children.
- Improved outcomes in AYA-ALL patients have been observed with the adoption of pediatric regimens with minimal residual disease (MRD) response to guide risk stratification.
- Recent advances in genomic analyses of ALL, have also significantly improved the sub-typing and risk stratification of ALL.

AIM

To assess the impact of consolidation blinatumomab in defined genomic cohorts from the ALLG ALL09 (SUBLIME)(ACTRN 12618001734257) study and compare this to similar B cell genomic cohorts in the ALLG ALL06 (ACTRN12611000814976) study, which used standard cytotoxic consolidation.

METHODS

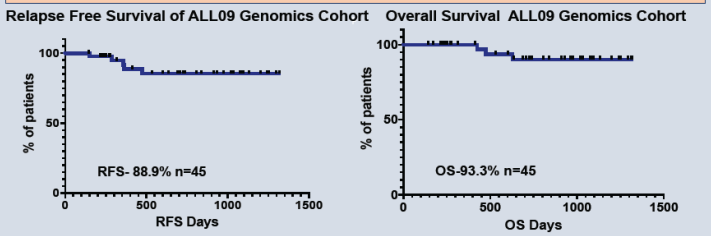
- Blood and/or Marrow (PB/BM) samples were collected from B cell ALL patients enrolled to ALL06 and ALL09. mRNA Sequencing was performed on the blast cells.
- MLPA was used to detect genomic copy number alterations, karyotype and FISH analyses were also performed.
- Genomic alterations were curated using our optimised ALL pipelines[1-3].Genomic drivers were subtyped and classified into adverse risk (AR) and standard risk (SR) using contemporary classifiers. BM MRD was assessed for IGH and TCR rearrangements post induction at day 33 (TP1) and post consolidation at day 79 (TP2) and in ALL09 for patients MRD pos at TP2, through intensive HR therapy (HR1-HR3)

RESULTS

Between Sep 2020 and April 2022 55 patients were enrolled to the ALLG-ALL09 study

- 45 of these patients had appropriate samples for genomic analyses and 39/45 had a MRD marker identified.
- These patients formed the genomic cohort.

Figure 1: The results from the genomic cohort were similar to the overall ALL09 3 year Relapse Free Survival (RFS) (84.5%) and Overall Survival (OS) (87.1%). These results compared favorably to the 3 yr RFS and OS of ALL06 (both 67.5%)



RESULTS

Figure 2: Genomic subtypes varied between ALL06 and 09. However, while the proportion of AR subtypes and Ph-like cases were similar (Table 1 and 2), the most frequent alteration varied between the 2 studies

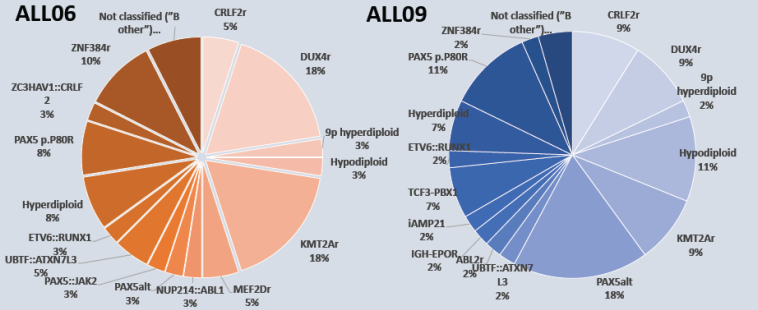


Table 1	Percentage of AR subtypes
ALL06 n=37	62.1% (n=23)
ALL09 n=40	72.5% (n=29)

Table 2	Most frequent alterations	
	ALL06	**ALL09**
	KMT2Ar (17.5%)	*PAX5*alt (18%)
	DUX4r (17.5%)	*PAX5* p.P80R (11%)
Ph-like[4]	12.5%	13%

Table 3: In ALL09 a greater proportion of AR patients achieved TP2 (Day 79 post consolidation) negativity than in ALL06 (61% vs 32%), suggesting blinatumomab consolidation is superior to standard chemo consolidation in AR genomic B cell AYA-ALL patients

Table 3: MRD positivity at TP1 and TP2 in ALL06 and ALL09

	ALL06				ALL09			
	TP1 (Day 33)		TP2 (Day 79)		TP1 (Day 33)		TP2 (Day 79)	
	MRD neg	MRD pos	MRD neg	MRD pos	MRD neg	MRD pos	MRD neg	MRD pos
AR Genomics	1 (4%)	22 (96%)	7 (32%)	15 (68%)	8 (28%)	21(72%)	17 (61%)	11 (39%)
SR Genomics	1 (7%)	14 (93%)	8 (53%)	7 (47%)	3 (33%)	6 (67%)	8 (73%)	3 (27%)

Table 4: Despite overall improvement in TP2 negativity in ALL09 blinatumomab responsiveness appears to be genomic subtype dependent with a greater proportion of *TCF3*r and *PAX5* p.P80R patients remaining MRD positive at TP2 in ALL09.

Table 4: TP2 MRD positivity in selected genomic subsets

	ALL06 (n=)	ALL09 (n=)
Ph-like (AR)	40% (5)	17% (6)
KMT2Ar (AR)	80% (5)	100% (3)
DUX4r (AR)	71% (7)	66%(3)
PAX5alt (AR)	100%(1)	14%(7)
PAX5 p.P80R (SR)	30% (3)	75% (4)
TCF3-PBX1 (AR)		100% (3)

Figure 3: Patients who remained TP2 MRD positive proceeded to High Risk 1-3 (HR) block therapy. The genomic subsets are shown below, with the number of patients who proceeded to HR blocks, those that remained positive after HR blocks, those that proceeded to transplant and those that relapsed.

Figure 3: Outcome of patients remaining TP2 MRD +

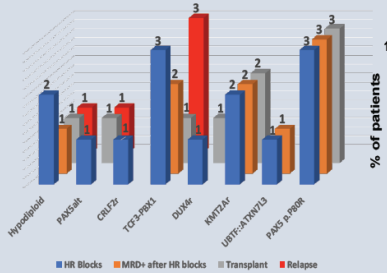


Figure 4: RFS based on Genomic Subtype and TP2 MRD

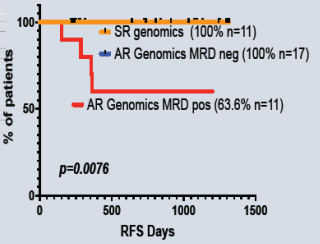


Figure 4: Patients with AR genomics and positive MRD at TP2 have significantly lower RFS than all other patient groups.

CONCLUSIONS

This is the first report of the impact of blinatumomab consolidation on genomic subsets in *de novo* AYA ALL.

- Our study suggests blinatumomab sensitivity, may be genomic subtype dependent
  - *TCF3r* (AR) ALL is associated with sustained MRD+, leading to eventual relapse (3/3 patients)
  - *PAX5* p.P80R (SR) subset was associated with sustained high levels of TP2 MRD+ (3/4 with an MRD marker) and allogeneic SCT (3/4 patients)
- Patients with Adverse Risk (AR) genomics who remain TP2 MRD+ have the greatest risk of relapse
- These results suggest that genomic analyses at diagnosis may identify AYA-ALL patients who will benefit from blinatumomab consolidation, and also those where alternate therapeutic approaches should be considered.

ACKNOWLEDGEMENTS

The authors acknowledge the funding bodies that supported this Correlative Sub-study; Cancer Council SA and the Leukaemia Foundation. We also acknowledge the ALLG, as trial Sponsor, their investigators and trial patients for provision of samples.

Neither the Trial Sponsor (ALLG) or the funders had any input into the analyses of the data presented or the conclusions drawn.

REFERENCES

1 Rehn J et al PLoS Genetics, **2022** doi.org/10.1371/journal.pgen.1010300
2 Mäkinen, V-P et al, **2022** Apr 20;23(9):4574. doi: 10.3390/ijms23094574.
3 Thomson A. et al Cancers. **9/2023** 15 (19) 4731-
4 Roberts KG et al N Engl J Med **2014** Sep 11;371(11):1005-15. doi: 10.1056/NEJMoa1403088

CONTACT:
Deborah.white@sahmri.com
Prof Deb White@ALL_genomics

Dose-Dense Mini-Hyper-CVD, Inotuzumab Ozogamicin, and Blinatumomab Achieves Rapid MRD-Negativity in Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia

Trevor Jamison, Hagop Kantarjian, Shilpa Paul, Branko Cuglievan, David McCall, Nitin Jain, Fadi G. Haddad, Kayleigh R. Marx, Caitlin Rausch, Michael Savoy, Lewis Nasr, Cedric Nasnas, Marianne Zoghbi, Rebecca Garris, Farhad Ravandi, Marina Konopleva, Elias Jabbour, Nicholas J. Short

The University of Texas MD Anderson Cancer Center, Houston, TX

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Background

- Inotuzumab ozogamicin (InO) and blinatumomab (Blina) improves overall survival in relapsed/refractory B-cell ALL
- Both InO and Blina are highly effective in eradicating measurable residual disease (MRD)
- The combination of low-dose chemotherapy with mini-hyper-CVD and InO with sequential Blina is safe and effective in both newly diagnosed and relapsed/refractory ALL
- **Hypothesis: Dose-dense administration of mini-hyper-CVD, InO and Blina (all given within the same cycle) will be safe and lead to rapid, deep responses in B-cell ALL**

Inclusion Criteria

- Children or adults with Philadelphia chromosome (Ph)-negative B-cell ALL receiving:
  - Frontline induction
  - Consolidation of MRD-positive complete remission (CR)
  - Treatment for relapsed/refractory disease
- Received at least 1 cycle of "dose-dense" mini-hyper-CVD (alternating with mini-MTX/Ara-C), InO and Blina
  - Defined as regimen consisting of mini-hyper-CVD (and/or mini-MTX/Ara-C), InO and Blina all given in the same cycle
  - Blina must be started by cycle 1, day 21
- Only patients treated outside of a clinical trial are included

Patients

- 21 patients were included
  - 9 received frontline treatment
  - 4 received therapy for consolidation of MRD-positive CR
  - 8 for relapsed/refractory disease

Baseline Patient Characteristics

Characteristic N (%),median [range]	Frontline (N=9)	MRD-positive consolidation (N=4)	Relapsed/refractory (N=8)
Age (years)	45 [20-74]	30 [19-42]	62 [4-97]
Bone Marrow Blast (%)	83 [33-95]	-----	8.3 [1.2-553]
Extramedullary disease	0	0	3 (38)
Karyotype			
Diploid	4 (44)	2 (50)	3 (38)
Low hypodiploidy / near triploidy	2 (22)	0	0
Complex	0	0	2 (25)
High hyperdiploidy	1 (11)	0	0
KMT2Ar	0	1 (25)	0
Others	2 (22)	1 (25)	3 (38)
Ph-like ALL	3 (33)	1 (25)	3 (38)
TP53 mutation	2 (22)	0	3 (38)
Number of prior therapies	-----	1 [1-1]	3 [1-7]
Prior InO	-----	1 (25)	2 (25)
Prior Blina	-----	0	3 (38)
Prior HSCT	-----	1 (25)	3 (38)
Prior CAR T-cells	-----	0	3 (38)

Treatment Received

- Patients received a median of 2 cycles (range 1-5) of the dose-dense regimen
- The median cumulative dose of InO was 1.2 mg/m^2 (range, 0.6-2.7 mg/m^2)
- The median day of Blina start was day 4 (range 4-17)
  - Blinatumomab was started by day 7 in 16 patients (76%)
- 18 patients (86%) received rituximab

Results

Response Rates

Response	Frontline (N=9)	MRD-positive consolidation (N=4)	Relapsed/refractory (N=8)
CR/CRi Rate	9 (100)	N/A	5 (63)
Flow MRD negative after cycle 1*	9 (100)	3/3 (100)	5/5 (100)
NGS MRD negative after cycle 1*	4/6 (67)	2 (50)	**
NGS MRD negative at any time*	7/7 (100)	3 (75)	**

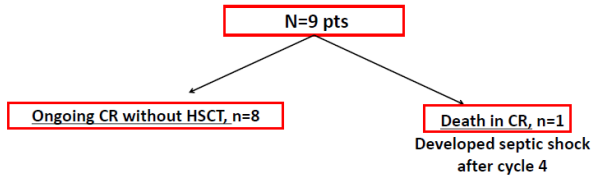
* MRD negativity rates are shown among patients who achieved CR/CRi

** NGS MRD was not evaluated in patients in the relapsed/refractory cohort

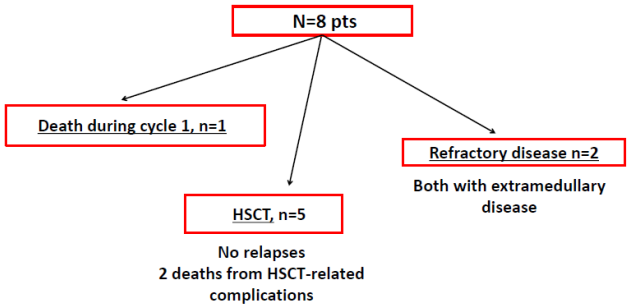
Patient Disposition

Median follow-up:
13.4 months (range, 0.5-20.6)

Frontline cohort

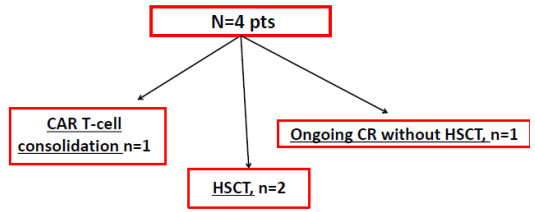


Relapsed/refractory cohort



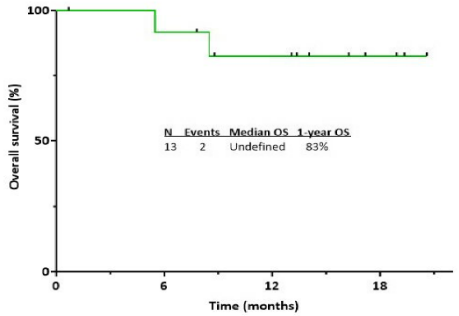
Results

MRD-positive consolidation cohort



1 relapse (patient with KMT2A translocation)
1 death from HSCT-related complications

Overall Survival for the Frontline + MRD Cohorts



Non-hematologic AEs

- One patient developed grade 1 cytokine release syndrome and two developed grade 1 tremor due to Blina
- No pts discontinued InO due to toxicity; 2 patients developed VOD/SOS after HSCT (1 of whom had also undergone a previous HSCT)

Conclusions

- A dose-dense regimen of mini-hyper-CVD, InO and Blina achieves high rates of rapid flow cytometry and NGS MRD negativity
  - All responding patients achieved flow MRD negativity after 1 cycle
- Early survival in the frontline and MRD+ cohorts are encouraging
- Prospective trials evaluating this regimen in older adults and in relapsed/refractory B-cell ALL are ongoing

Blinatumomab Non-Amgen Sponsored Studies

Titles	Oral Presentation/ Poster ID	Author
Oral Presentations		
Pediatric Patients with High-Risk B-Cell ALL in First Complete Remission May Benefit from Less Toxic Immunotherapy with Blinatumomab – Results from Randomized Controlled Phase 3 Trial AIEOP-BFM ALL 2017	825	Martin Schrappe
Blinatumomab in Combination with Immune Checkpoint Inhibitors in Relapsed/Refractory CD19+ Leukemias: A Phase I Study	966	Jonathan A. Webster

Blinatumomab Non-Amgen Sponsored Studies

Titles	Poster/Oral Presentation ID	Author
Posters		
Assessment of Outcomes of Consolidation Therapy by Number of Cycles of Blinatumomab Received in Newly Diagnosed Measurable Residual Disease Negative Patients with B-lineage Acute Lymphoblastic Leukemia: in the ECOG-ACRIN E1910 Randomized Phase III National Clinical Trials Network Trial	2877	Selina M. Luger
Updated Results From a Phase II Study of Hyper-CVAD, with or without Inotuzumab Ozogamicin, and Sequential Blinatumomab in Patients With Newly Diagnosed B-Cell Acute Lymphoblastic Leukemia	4245	Daniel Nguyen
Chemotherapy Sparing Induction Followed By Consolidation and Maintenance with Blinatumomab and Concurrent Oral Tyrosine Kinase Inhibitor Therapy for Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia: Primary Endpoint Results from the BLISSPHALL Study	1510	Mark Blaine Geyer
A Phase IB/II Study of Blinatumomab in Patients with B-Cell Acute Lymphoblastic Leukemia (ALL) and B-Cell Non-Hodgkin Lymphoma (NHL) As Post-Allogeneic Blood or Marrow Transplant (alloBMT) Remission Maintenance	3582	Jonathan A. Webster
Phase 2 Trial of Mini-Hyper-CVD Plus Inotuzumab Ozogamicin, With or Without Blinatumomab, in Older Patients With Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia	2878	Wei Ying Jen
A Phase II Study of Low-Intensity Chemotherapy (Mini-Hyper-CVD) and Ponatinib Followed by Blinatumomab and Ponatinib in Patients With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia	2868	Wei Ying Jen

Blinatumomab Non-Amgen Sponsored Studies

Titles	Poster/Oral Presentation ID	Author
Posters		
Chemotherapy-Free Combination of Blinatumomab and Ponatinib in Adults With Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: Updates From a Phase II Trial	2827	Fadi G. Haddad
Improved MRD Negativity Rates in Adverse Genomic Risk B-ALL Patients with Chemotherapy/ Blinatumomab Induction: Experience from the Australasian Leukaemia Lymphoma Group (ALLG) ALL06/09 Studies	1609	Deborah L. White
Dose Dense Mini Hyper CVD, Inotuzumab Ozogamicin , and Blinatumomab Achieves Rapid MRD Negativity in Philadelphia Chromosome Negative Acute Lymphoblastic Leukemia	1508	Trevor Jamison