AMGEN Adaptive biotechnologies®

Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

8–9 July 2020

Virtual Breakout: Adult ALL Patients

APTITUDE HEALTH®

Global Leukemia Academy

Virtual Breakout: Adult ALL Patients Session Opening

Elias Jabbour

APTITUDE HEALTH

Meet the Faculty

Elias JAbbour, MD
Professor of medicine, Department of Leukemia, University of Texas MD Anderson Cancer Center (MDACC), Houston, TX

Fatih Demirkan, MD
Professor of hematology and faculty member
Division of Hematology, Dokuz Eylul University Medical School, Izmir, Turkey

Josep-Maria Ribera, MD, PhD
Chair, Clinical Hematology Department, Catalan Institute of Oncology, University Hospital Germans Trias i Pujol

Andre Schuh, MD
Staff Physician,
Princess Margaret Cancer Centre

Objectives of the Program

- Understand current treatment patterns for ALL including incorporation of new technologies
- Uncover when genomic testing is being done for ALL, and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation in ALL as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring ALL
- Gain insights into antibodies and bispecifics in ALL: what are they? When and how should they be used? Where is the science going?
- Discuss the evolving role of ADC therapies in ALL
- Review promising novel and emerging therapies in ALL

Virtual Breakout: Adult ALL Patients (Day 2)

Chair: Elias Jabbour

TIME UTC+3	TITLE	SPEAKER
15.00 – 15.15	Session opening • Educational ARS questions for the audience	Elias Jabbour
15.15 – 15.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation • Q&A	Elias Jabbour
15.35 – 15.55	Current treatment options for relapsed ALL in adult and elderly patients • Presentation • Q&A	Fatih Demirkan
15.55 – 16.45	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in adult and elderly patients Panelists: Elias Jabbour, Fatih Demirkan, Andre Schuh, Josep-Maria Ribera	Fatih Demirkan Andre Schuh Discussion
16.45 – 17.00	Session close • Educational ARS questions for the audience	Elias Jabbour

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Educational ARS Questions

Elias Jabbour

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Question 1

What age group is considered elderly ALL patients?

a) **≥50 years**
b) **≥55 years**
c) **≥60 years**
d) **≥65 years**
e) **≥70 years**

Question 2

Which statement is NOT correct?

a) **There are more Ph+ and Ph-like adult ALL patients compared with pediatric ALL**
b) **ETV6-RUNX1 fusion (t12;21) is a common genetic subtype in pediatric ALL**
c) **Hyperdiploid phenotype is more prevalent in adult ALL compared with pediatric ALL**
d) **Patients with ETV6-RUNX1 fusion (t12;21) have favorable prognosis**

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Optimizing First-Line Therapy in Adult and Older ALL – Integration of Immunotherapy into Frontline Regimens

Elias Jabbour

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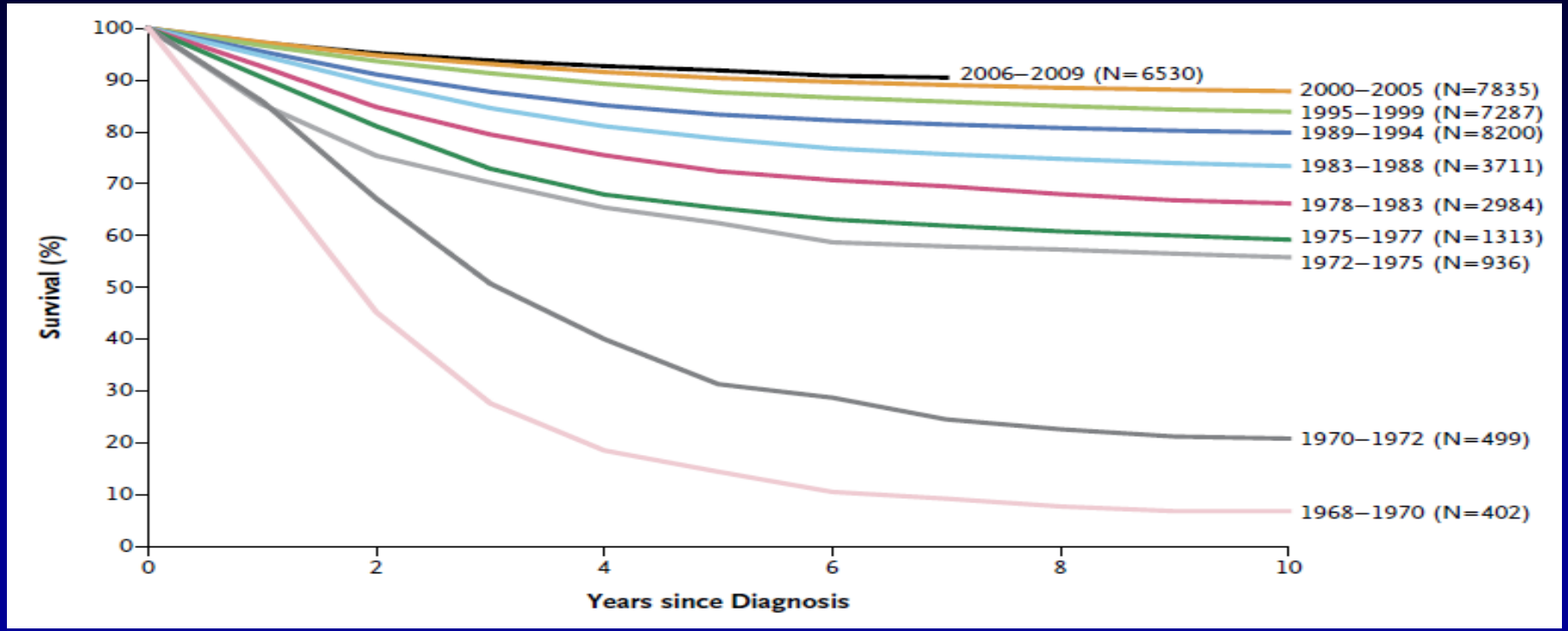
Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens

Elias Jabbour, MD
Professor of Medicine
Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, TX

Summer 2020

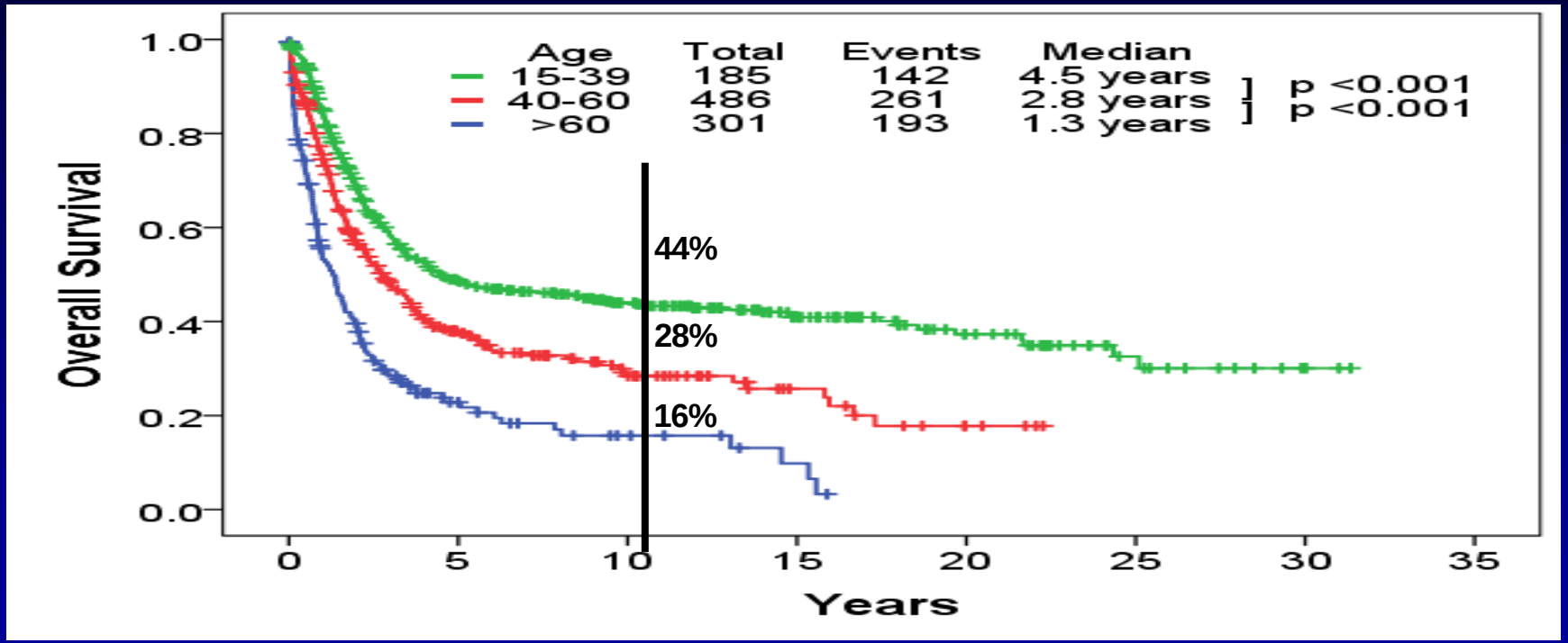
Survival of 39,697 Children With ALL Treated on Sequential CCG/COG Clinical Trials



Hunger, et al. *N Engl J Med.* 2015;373(16):1541-1552.

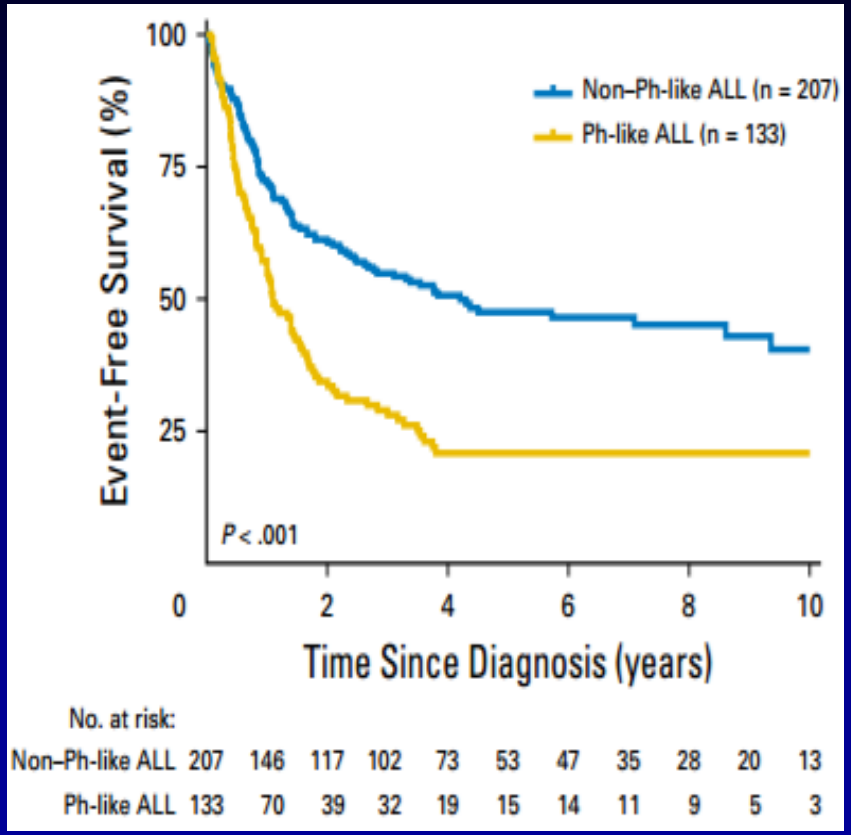
Survival of 972 Adults With Ph– ALL

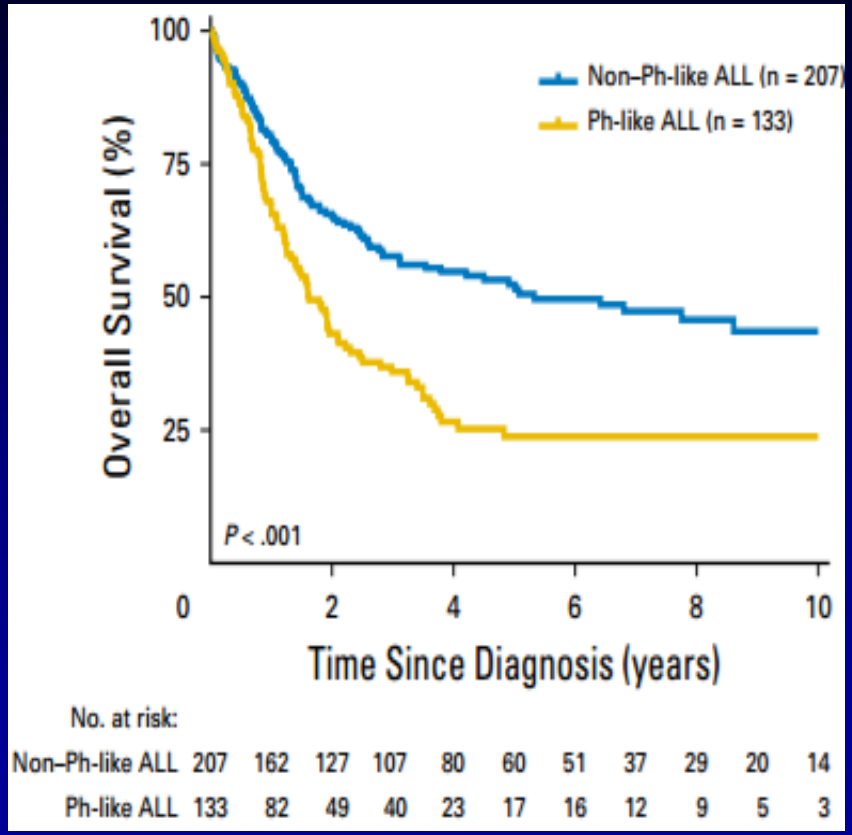
- 972 pts Rx 1980–2016; median F/U 10.4 years



Sasaki. *Blood*. 2016;128:3975.

Ph-Like ALL: Survival and EFS





Roberts, et al. *J Clin Oncol.* 2017;35:394.

Reasons for Recent Success in Adult ALL Rx

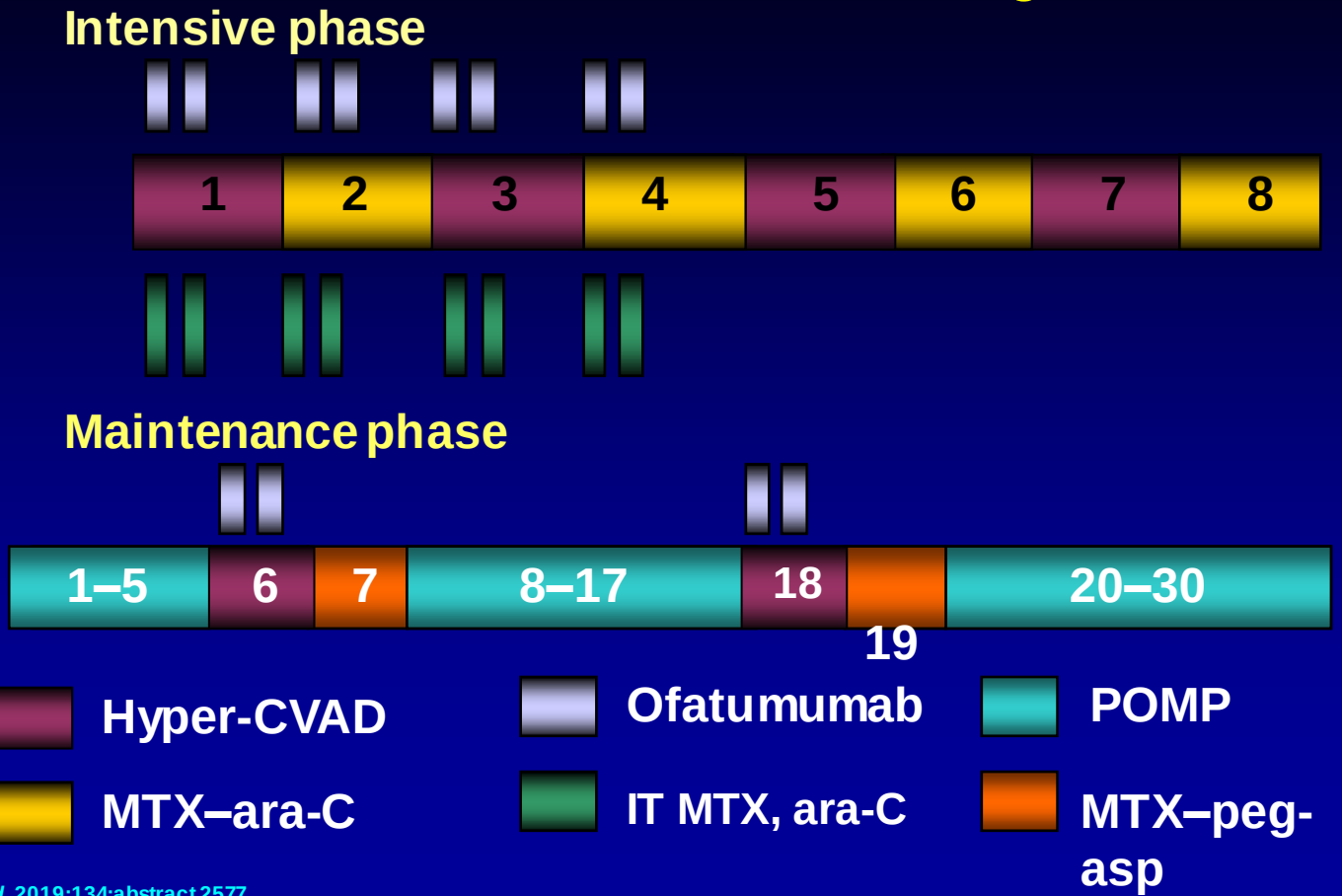
- Addition of TKIs to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Potential benefit of addition of CD19 bispecific antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- Eradication of MRD
- CAR T

The Present . . . ALL Therapy or "Personalized Therapy"

Entity	Management	Cure, %
Burkitt	HCVAD-R × 8; IT × 16; R/O-EPOCH	80–90
Ph+ ALL	HCVAD + TKI; TKI maintenance; allo-SCT in CR1	50+
T-ALL (except ETP-ALL)	Lots of HD CTX, HD ara-C, asp; nelarabine?	60
CD20+ ALL	ALL chemo Rx + rituximab-ofatumumab	50
Ph-like ALL	HCVAD + TKI/MoAbs	??
AYA	Augmented BFM; HCVAD-R/O	65+
MRD by FCM	Prognosis; need for allo-SCT in CR1	--

Personal communication from Dr Jabbour.

HCVAD + Ofatumumab: Design

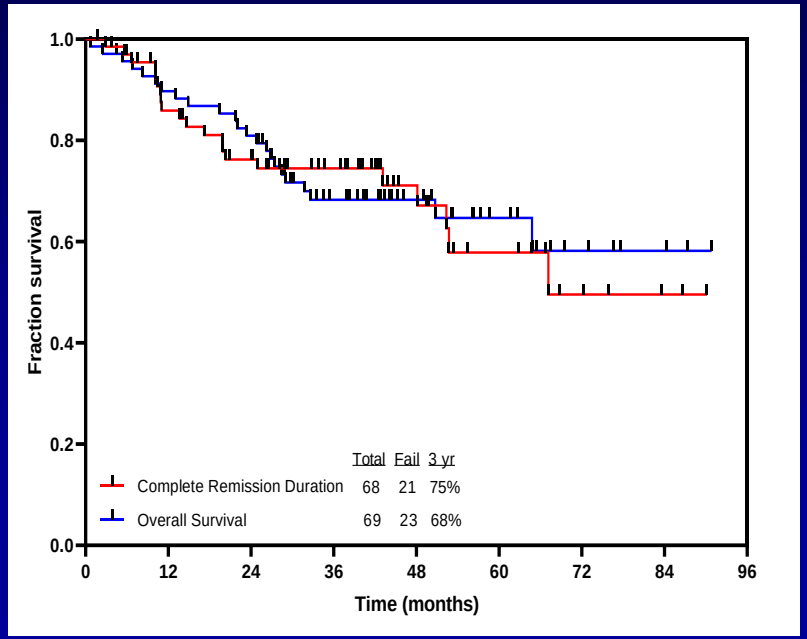


Richard-Carpentier. *Blood.* 2019;134:abstract 2577.

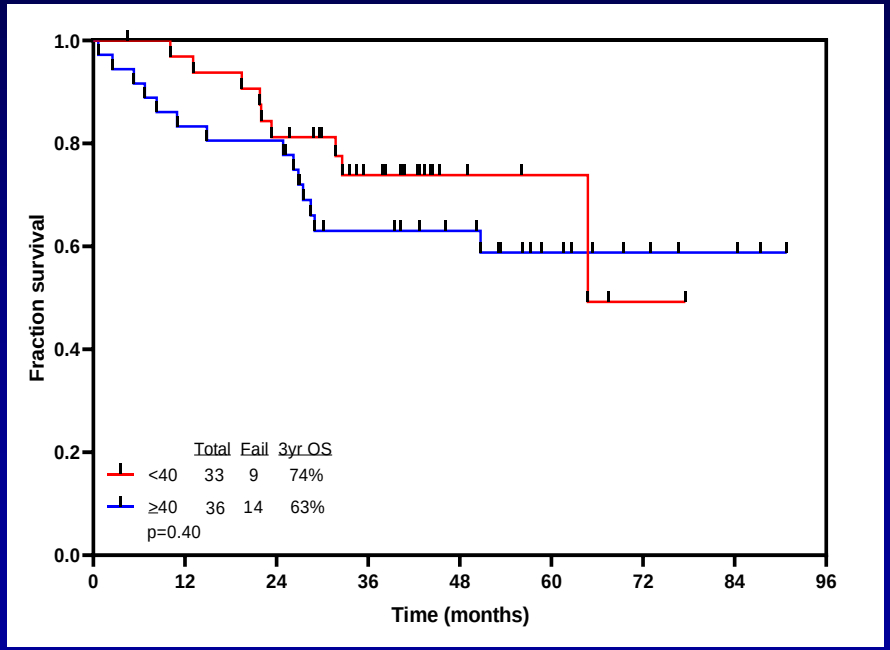
HCVAD + Ofatumumab: Outcome (N = 69)

- Median follow up of 44 months (4–91)
- CR 98%, MRD negativity 93% (at CR 63%), early death 2%

CRD and OS overall



OS by age



Richard-Carpentier. *Blood.* 2019;134:abstract 2577.

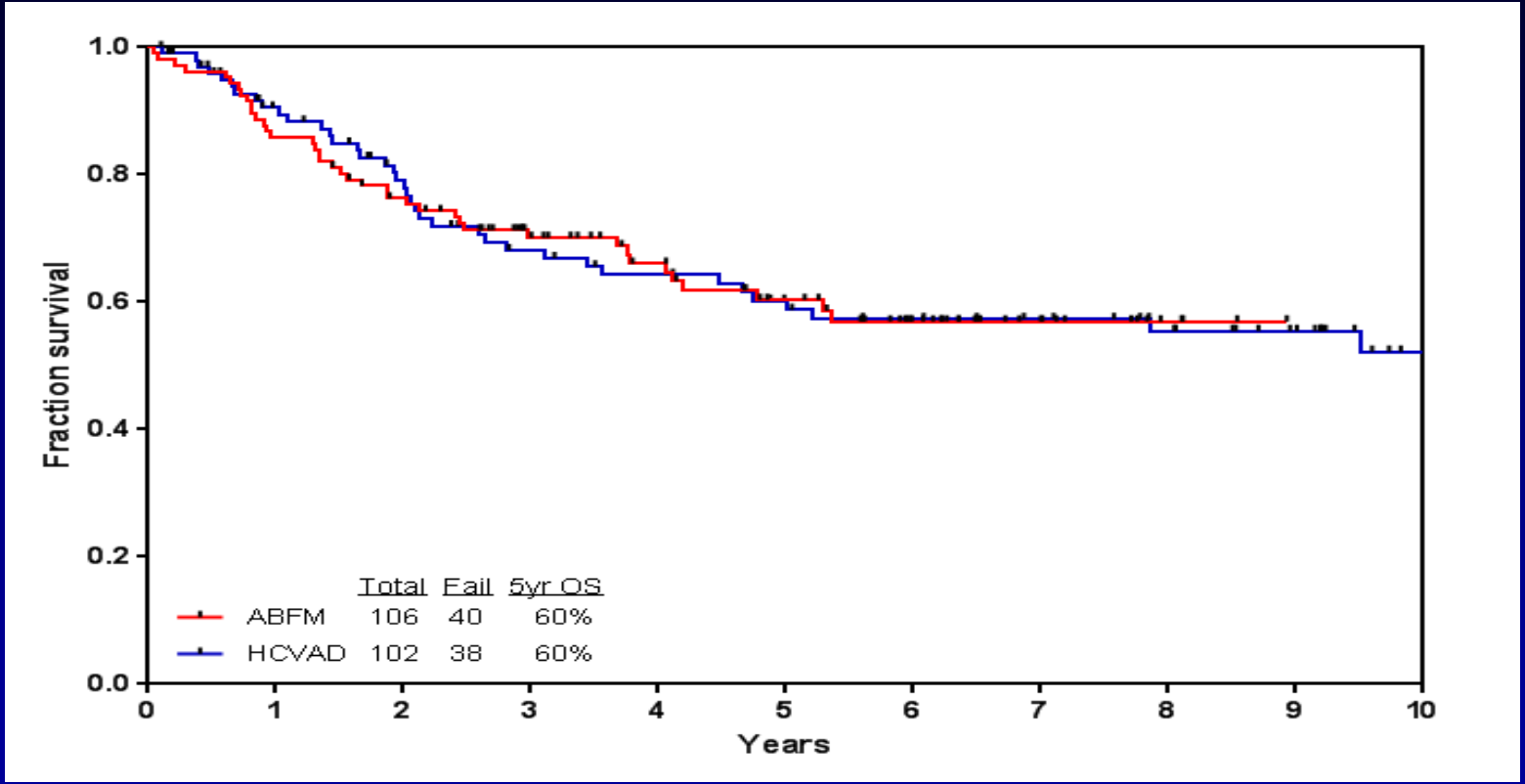
Comparison of HCVAD + Ofatumumab With CALGB 10403

- Hyper-CVAD + ofa for age ≤60 yr; CALGB 10403 for age <40 yr

		HCVAD + Ofa		
Parameter	**CALGB**	**Overall**	**Age <40**	**Age 40–60**
No. evaluable	295/318	69/69	33	36
Median age, yr	**24**	**48**	--	--
CR, %	89	98	--	--
Induction mortality, %	3	0	0	0
3-yr OS, %	**73**	**68**	**74**	63
5-yr OS, %	**60**	**64**	**74**	59

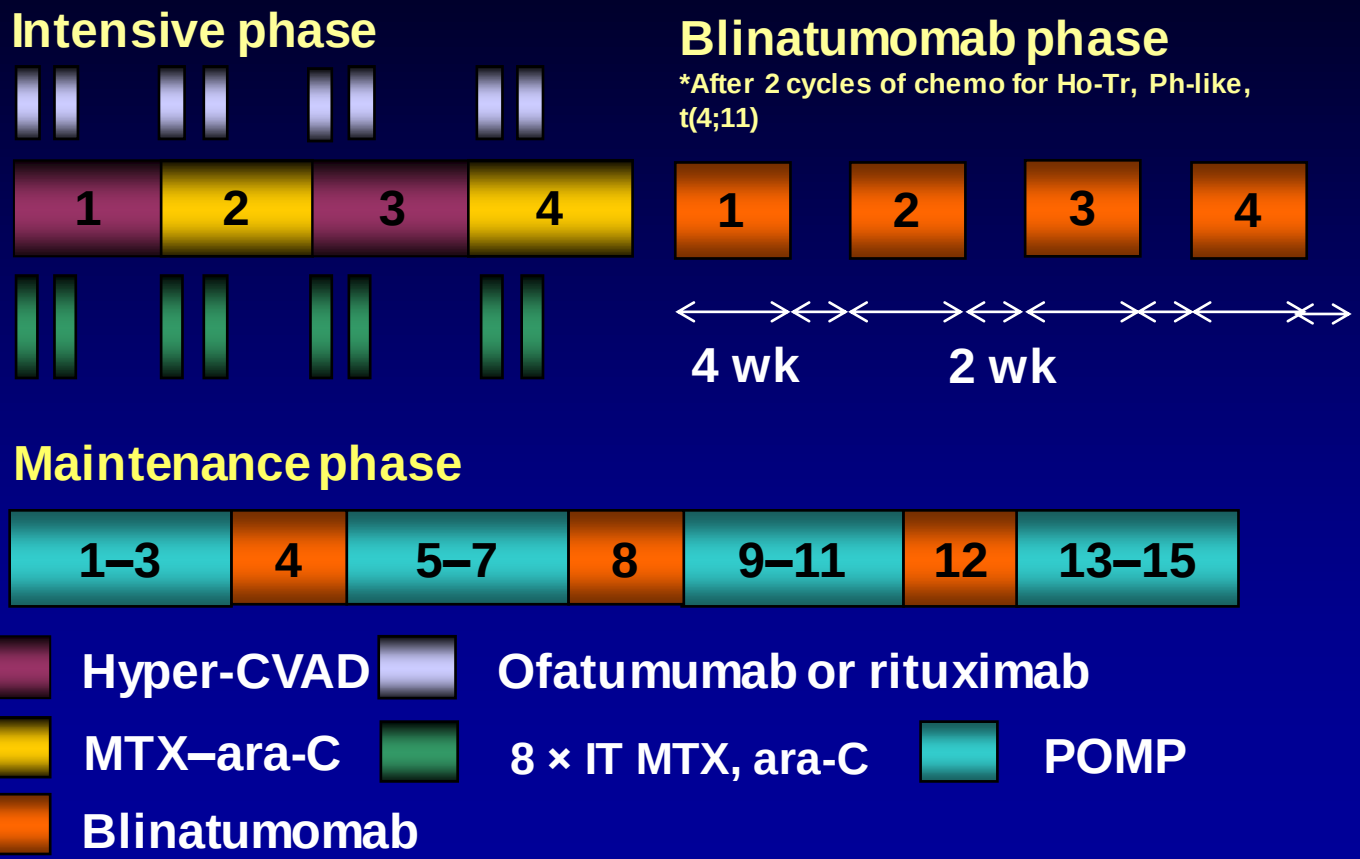
Stock. *Blood.* 2019.

Hyper-CVAD vs ABFM: Overall Survival



Rytting. *Cancer.* 2014;120:3660-3668; Rytting. *Am J Hematol.* 2016;91:819.

Hyper-CVAD + Blinatumomab in B-ALL (Ph– B-ALL <60 years): Treatment Schedule



Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

Hyper-CVAD + Blinatumomab in FL B-ALL
Patient Characteristics (N = 34)

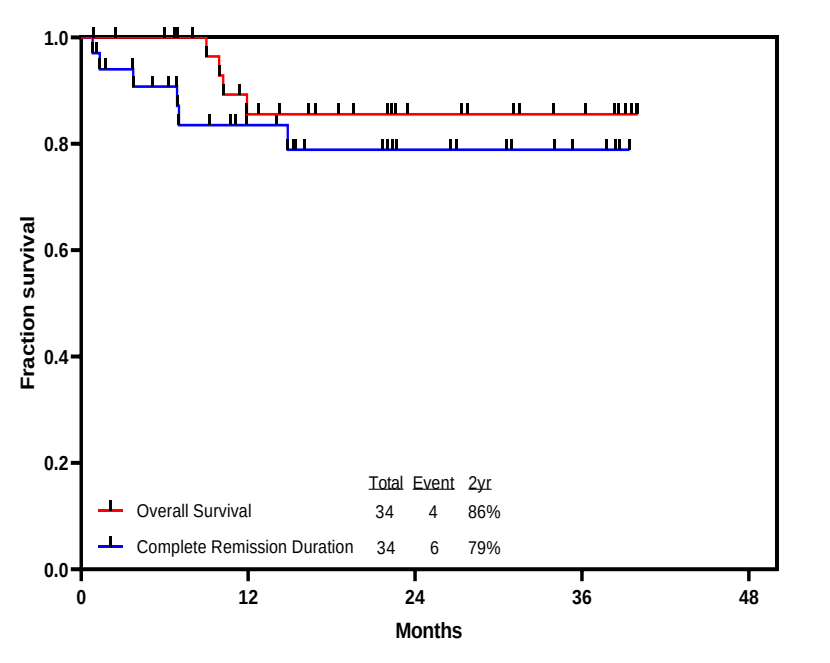
Characteristic (N = 34)		N (%) / Median [range]
Age (years)		36 [17–59]
Sex	Male	24 (71)
PS (ECOG)	0–1	28 (82)
WBC ($\times 10^9$/L)		3.12 [0.5–360.9]
CNS disease		4 (12)
CD19 ≥50 %		27/28 (96)
CD20 ≥20 %		13/29 (45)
***TP53* mutation**		**9/33 (27)**
Ph-like CRLF2+		**6/30 (20)**
Cytogenetics	Diploid	11 (32)
	Low hypodiploidy/Near triploidy	**5 (15)**
	Complex (≥5 anomalies)	**2 (6)**
	High hyperdiploidy	3 (9)
	MLL	**2 (6)**
	Other	11 (32)

Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

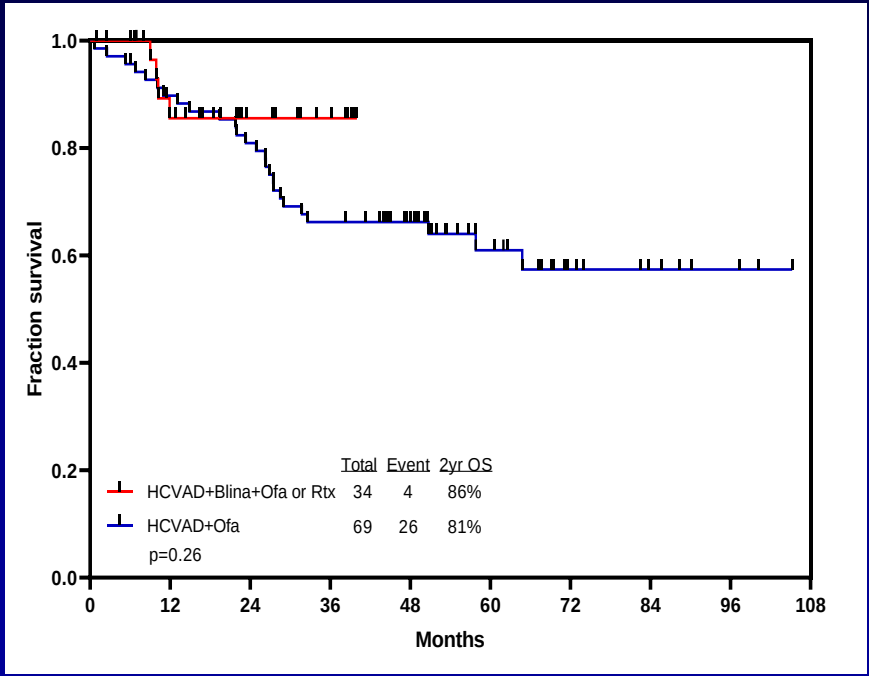
Hyper-CVAD + Blinatumomab in FL B-ALL (N = 34)

- CR 100%, MRD negativity 97% (at CR 87%), early death 0%

CRD and OS Overall



OS – HCVAD-Blina vs O-HCVAD



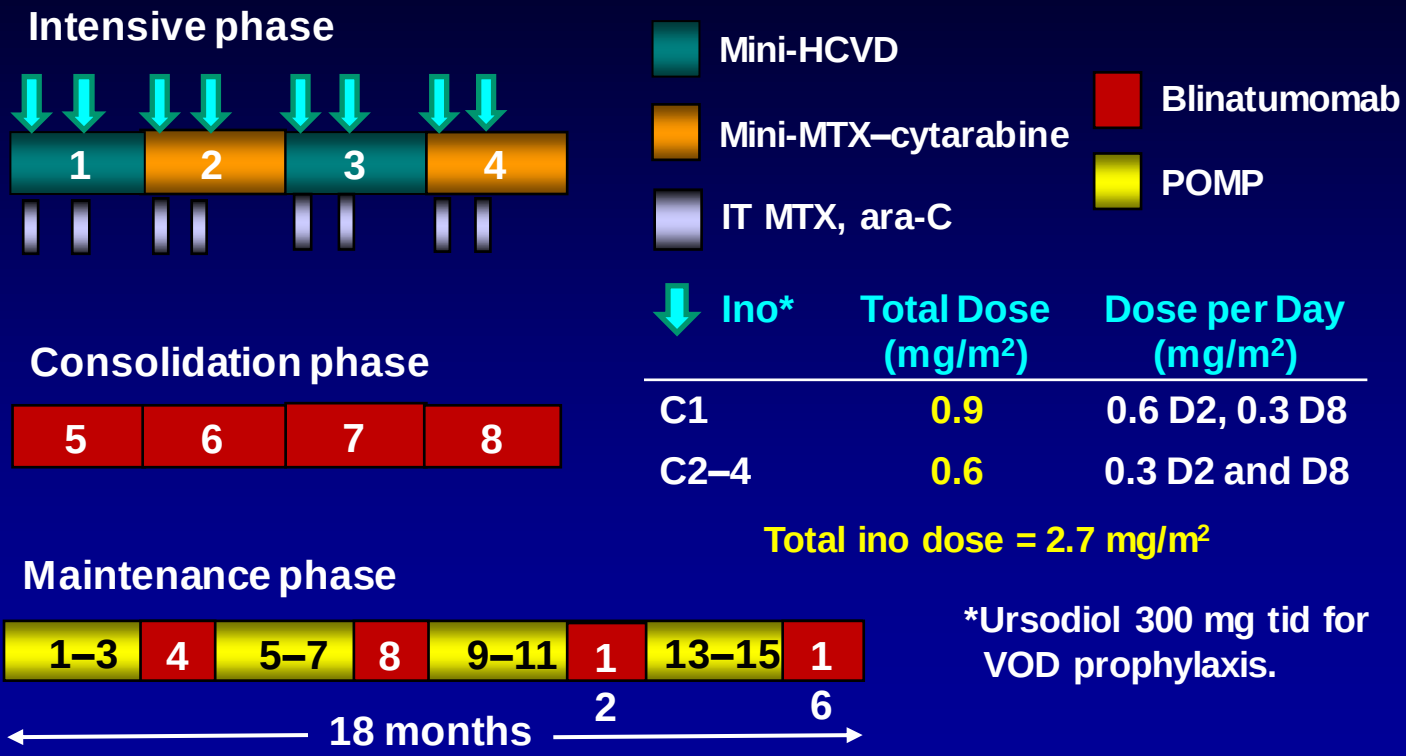
Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

Older ALL: Historical Results

	MDACC	GMALL	SEER	Medicare
N	122	268	1675	727
Median survival, mo	15	NA	4	10
OS, %	20 (3-yr)	23 (5-yr)	13 (3-yr)	NA

O'Brien. *Cancer.* 2008;113:2097; Gökbuget. *Blood.* 2013;122:1336; Li S. *Blood.* 2016;128:3981; Geyer. *Blood.* 2017;129:1878.

Mini-HCVD + Ino ± Blina in Older ALL: Modified Design (pts 50+)



Ino*	Total Dose (mg/m^2)	Dose per Day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total ino dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis.

Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Kantarjian. *Lancet Oncol*. 2018;19:240.

Mini-HCVD + Ino ± Blina in Older ALL (N = 64)

Characteristic	Category	N (%)/Median [range]
Age (years)	**≥70**	**68 [60-81]** **27 (42)**
Performance status	≥2	9 (14)
WBC (× 10^9/L)		3.0 [0.6-111.0]
Karyotype	Diploid HeH **Ho-Tr** **Tetraploidy** **Complex** **t(4;11)** Misc IM/ND	21 (33) 5 (8) **12 (19)** **3 (5)** **1 (2)** **1 (2)** 9 (14) 12(19)
CNS disease at diagnosis		4 (6)
CD19 expression, %		99.6 [30-100]
CD22 expression, %		96.6 [27-100]
CD20 expression	≥20%	32/58 (57)
CRLF2+ by flow		**6/31 (19)**
TP53 mutation		**17/45 (38)**

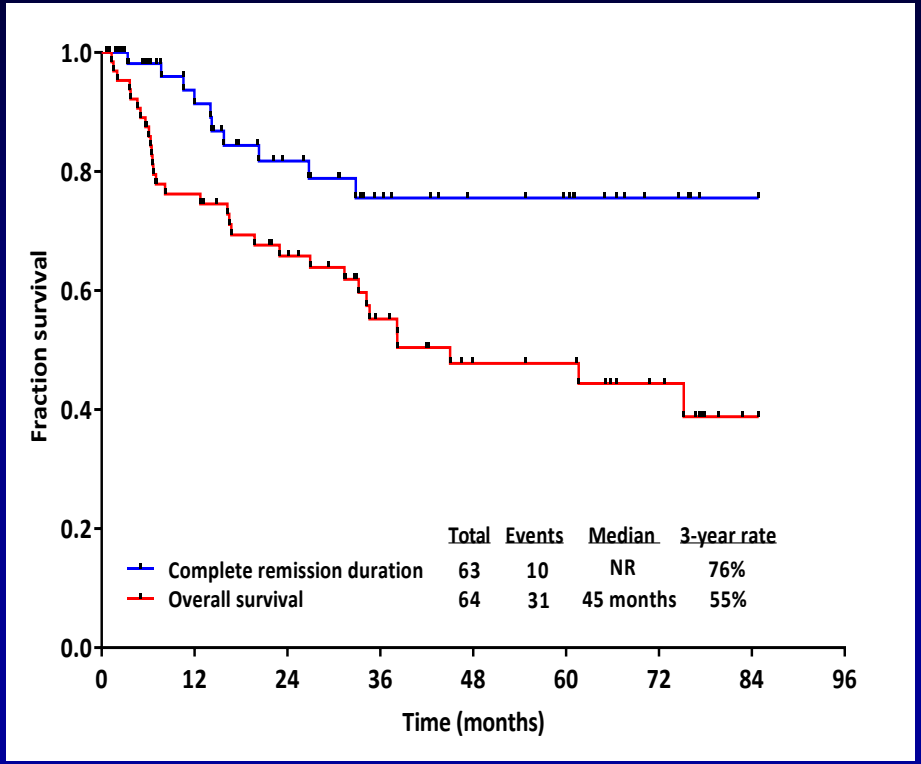
Response (N = 59)	N (%)
ORR	**58 (98)**
CR	51 (86)
CRp	6 (10)
CRi	1 (2)
No response	1 (2)
Early death	**0**

Flow MRD response	N (%)
D21	50/62 (81)
Overall	**60/63 (95)**

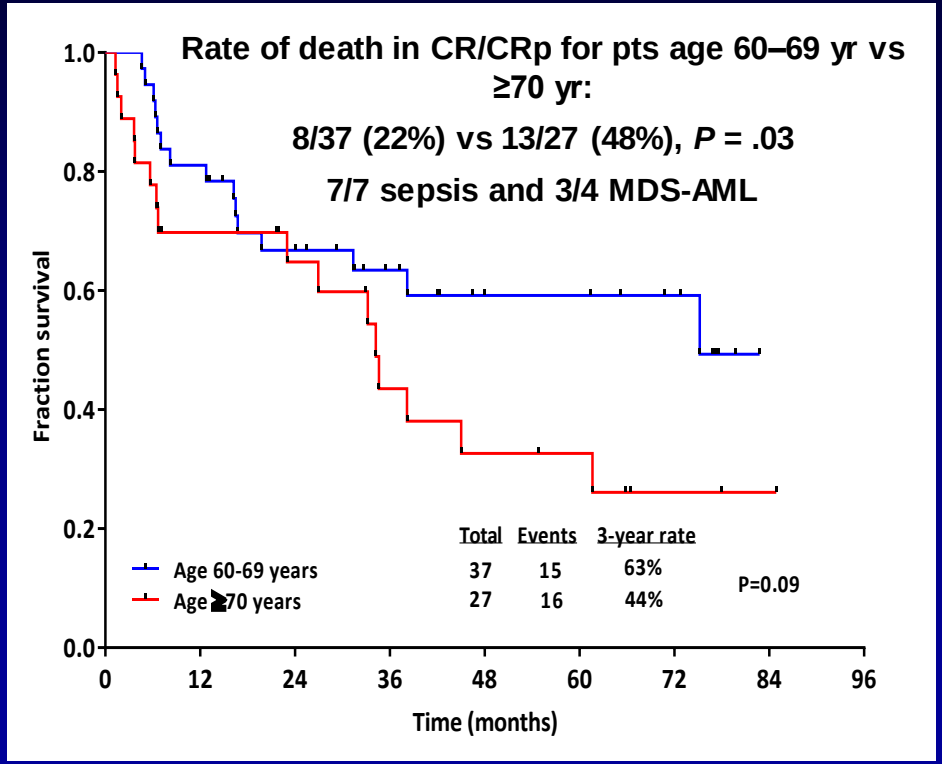
Short. *Blood.* 2019;134:abstract 823.

Mini-HCVD + Ino ± Blina in Older ALL: Outcome

CRD and OS overall



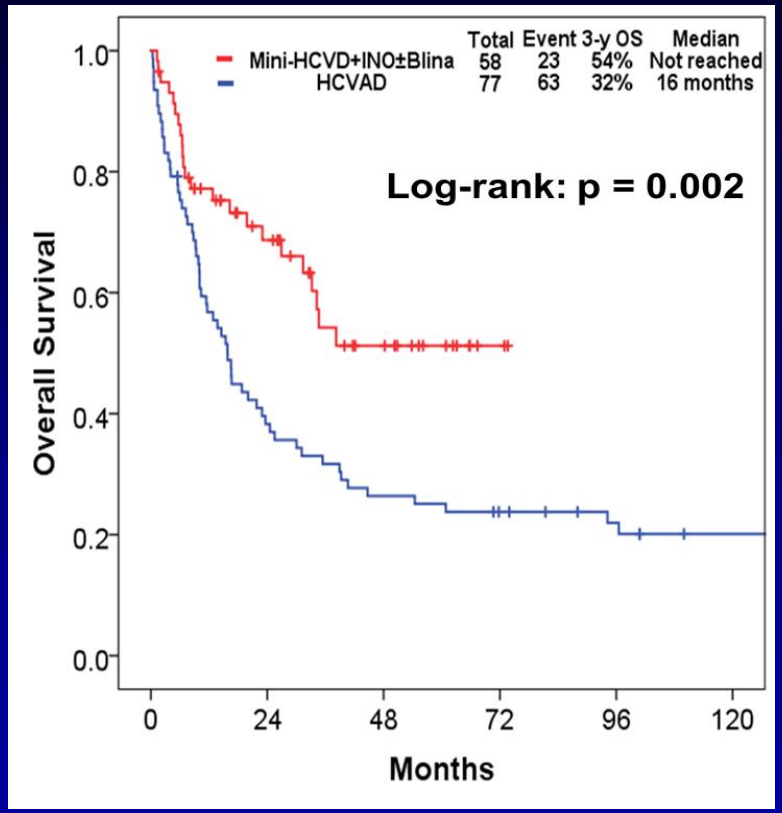
OS by age



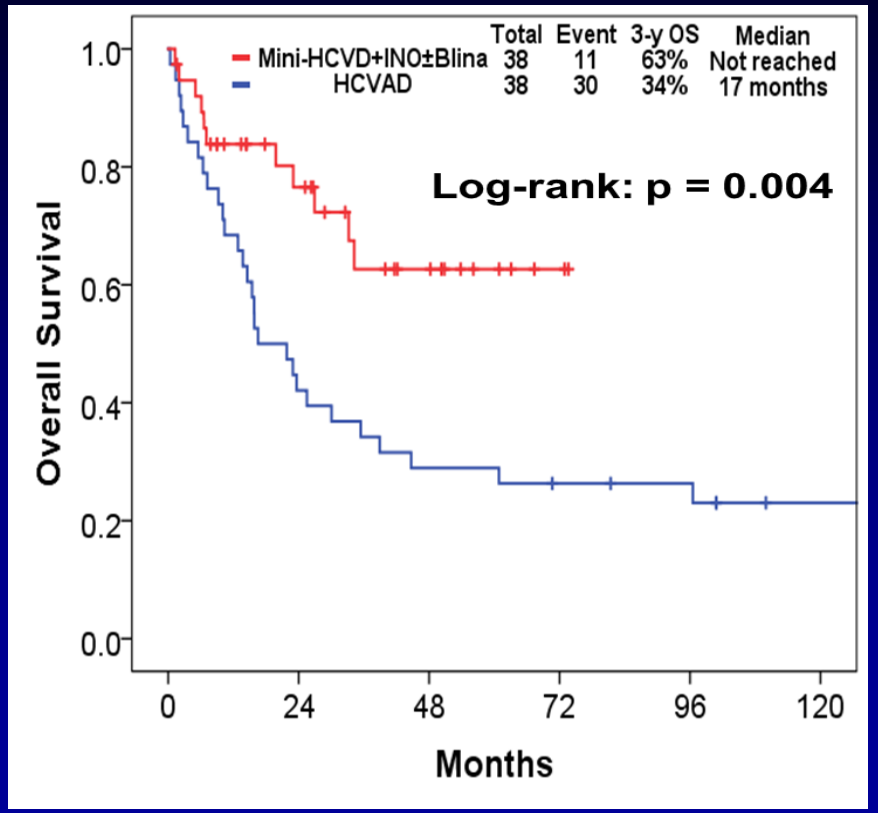
Short. *Blood.* 2019;134:abstract 823.

Mini-HCVD + Ino ± Blina vs HCVAD in Elderly ALL: Overall Survival

Prematched

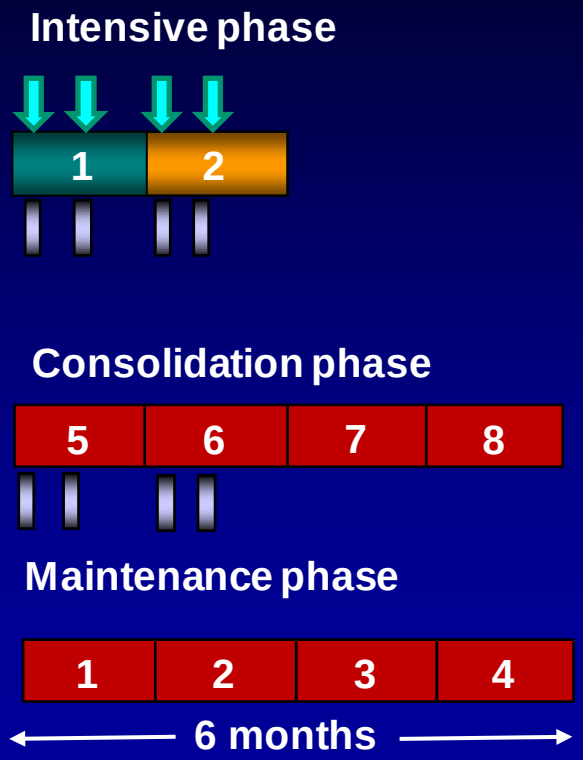


Matched



Sasaki. *Blood.* 2018;132:abstract 34.

Mini-HCVD + Ino ± Blina in Older ALL: Amended Design (pts ≥70 years)



Mini-HCVD

Mini-MTX–cytarabine

IT MTX, ara-C

Blinatumomab

POMP

Ino*	Total Dose (mg/m^2)	Dose per Day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2	0.6	0.3 D2 and D8

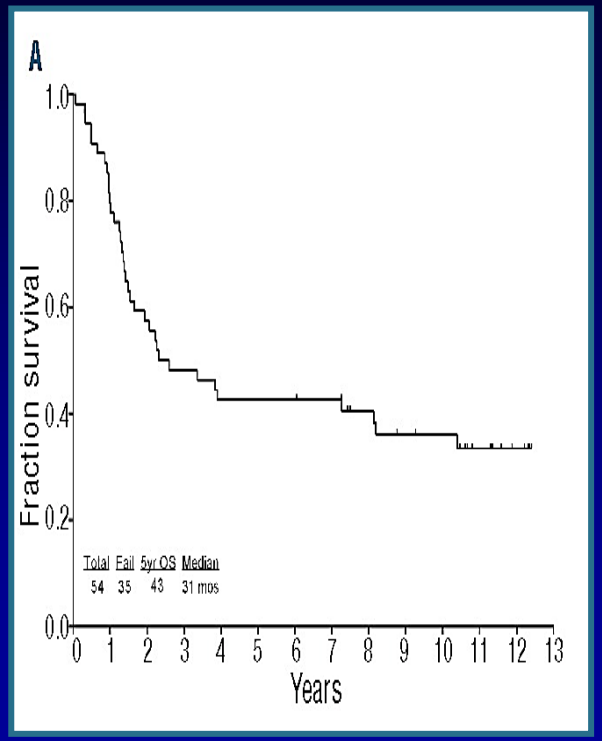
Total ino dose = 1.5 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis.

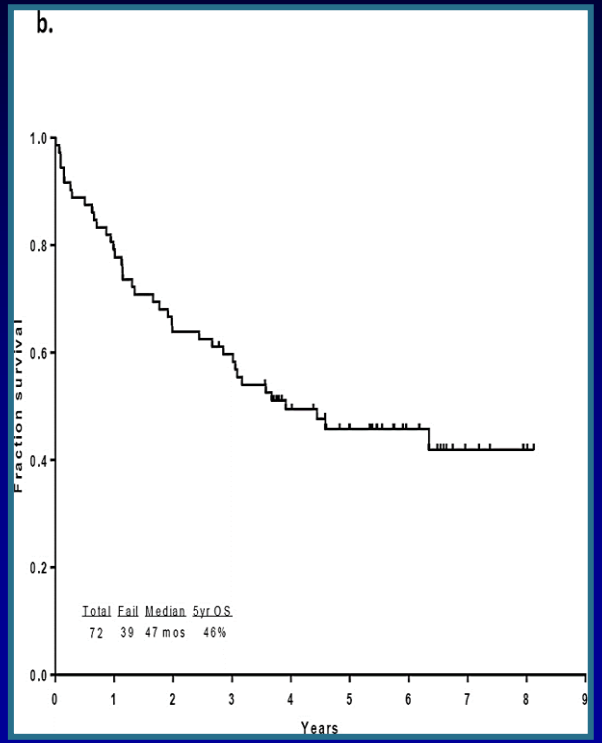
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Kantarjian H, et al. *Lancet Oncol.* 2018;19:240.

TKI for Ph+ ALL

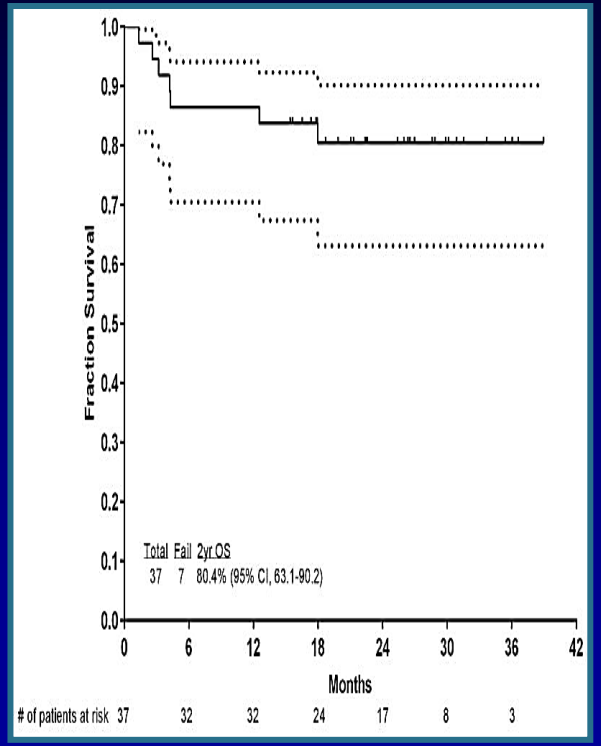
Imatinib: 5-yr OS = 43%



Dasatinib: 5-yr OS = 46%

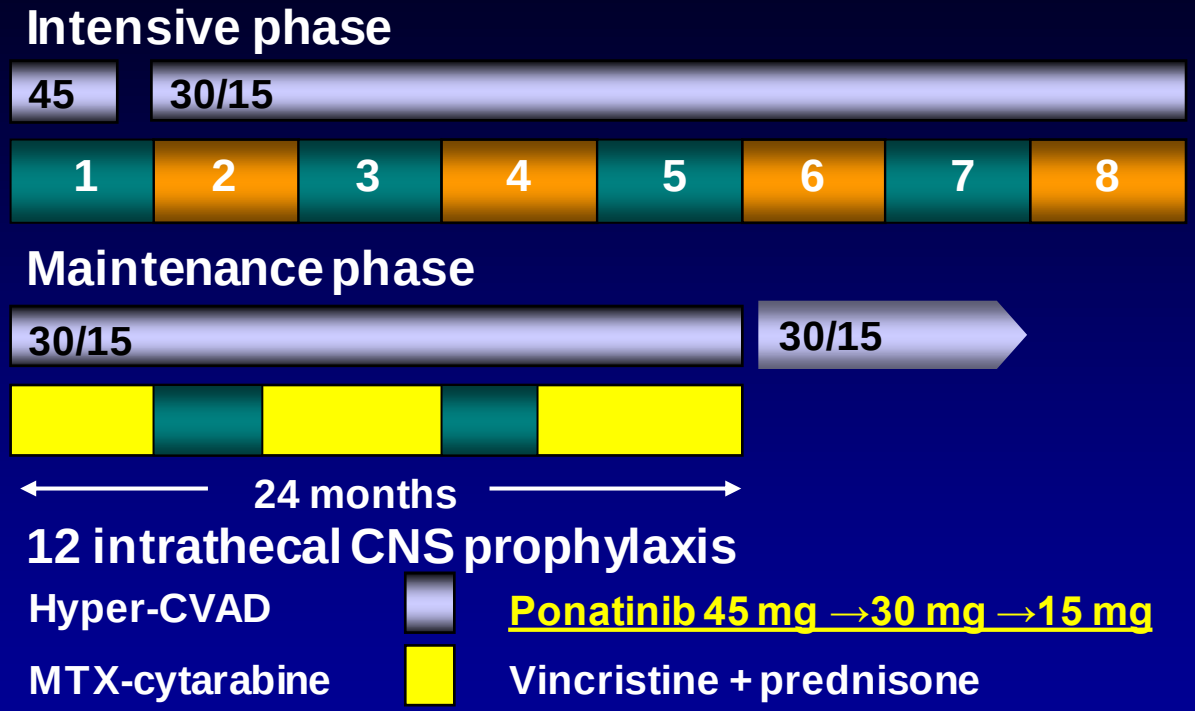


Ponatinib: 5-yr OS = 71%



Daver. *Haematologica*. 2015; Ravandi. *Cancer*. 2015; Jabbour. *Lancet Oncol*. 2015; Jabbour. *Lancet Hematol*. 2018.

Hyper-CVAD + Ponatinib: Design



- After the emergence of vascular toxicity, protocol was amended: beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

Jabbour. *Lancet Oncol.* 2015;16:1547; Jabbour. *Lancet Hematol.* 2018

Hyper-CVAD + Ponatinib in Ph+ ALL: Response Rates

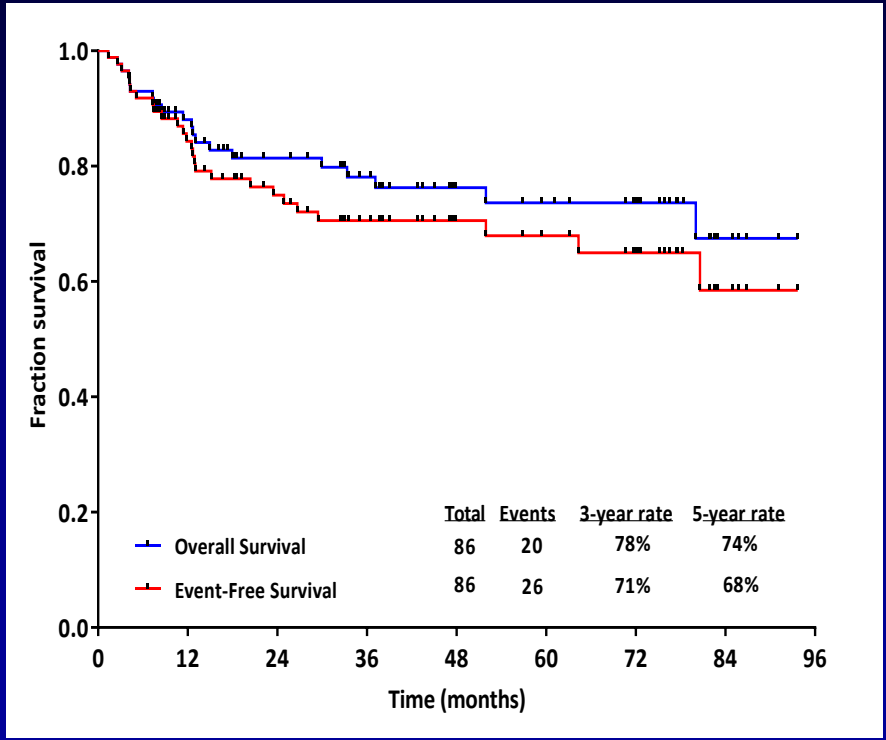
Median follow-up: 44 months (4–94 months)

Response	n/N (%)
CR	68/68 (100)
CCyR	58/58 (100)
MMR	80/85 (94)
CMR	**73/85 (86)**
3-month CMR	63/85 (74)
Flow negativity	83/85 (95)
Early death	0

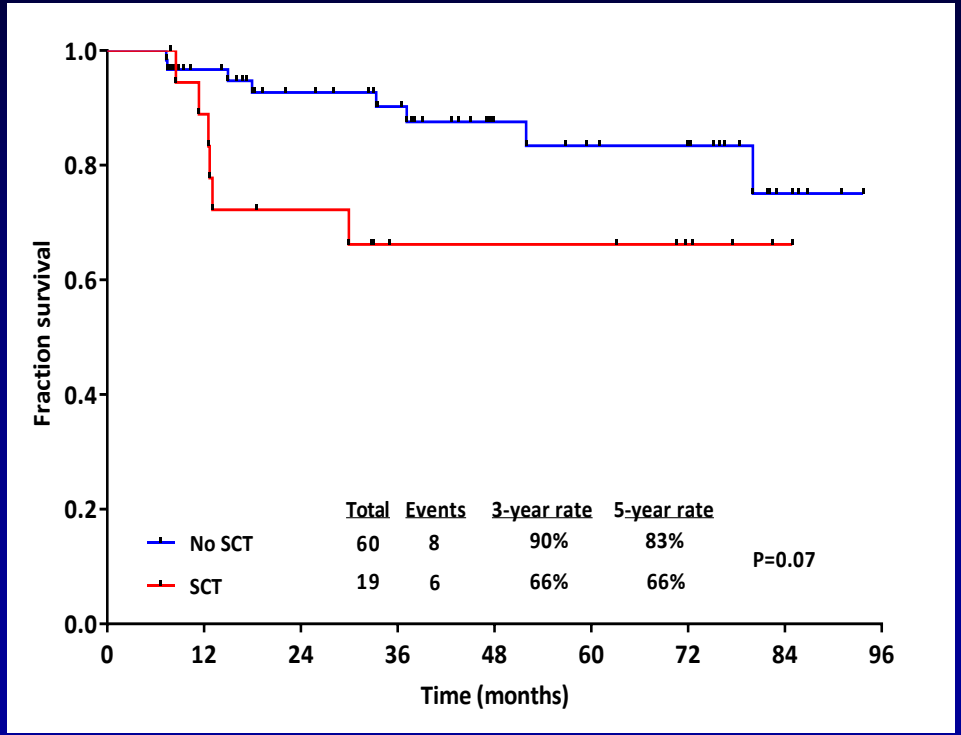
Short. *Blood*. 2019;134:abstract 283.

Hyper-CVAD + Ponatinib in Ph+ ALL: Outcome

EFS and OS



Impact of allo-SCT: 6-mo landmark

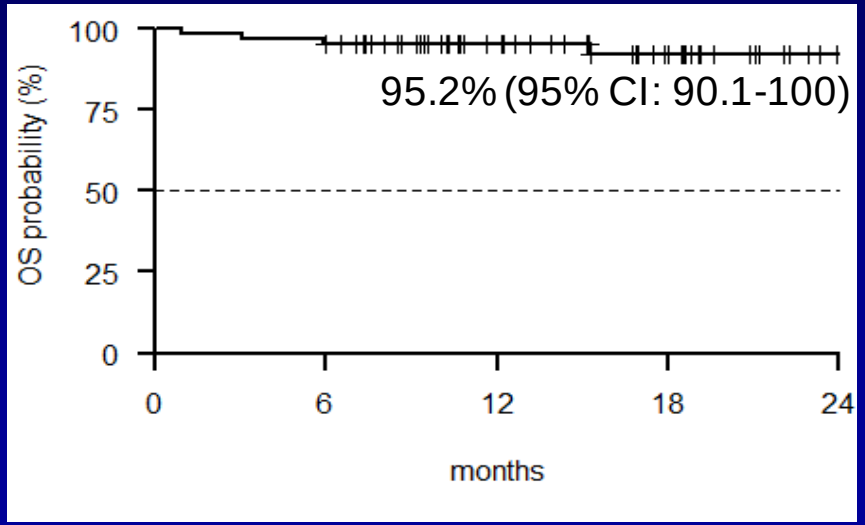


Short. *Blood*. 2019;134:abstract 283.

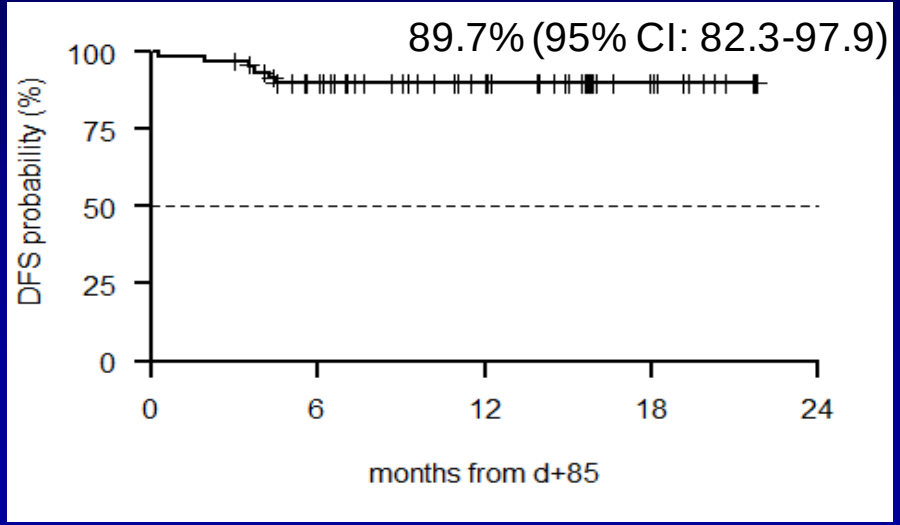
Dasatinib-Blinatumomab in Ph+ ALL

- 63 pts, median age 54 yr (24–82)
- Dasatinib 140 mg/D × 3 mo; add blinatumomab × 2–5
- 53 post–dasa-blina × 2 – molecular response 32/53 (60%), 22 CMR (41%); MRD ↑ in 15, 6 *T315I*; 12-mo OS 96%; DFS 92%

OS

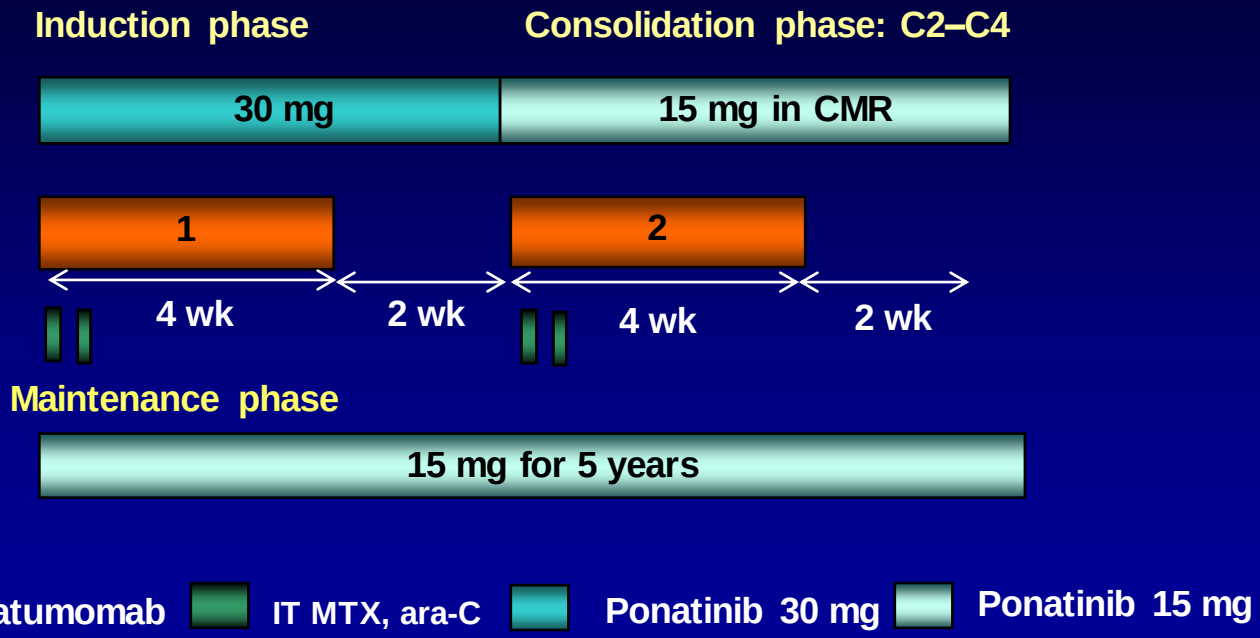


DFS



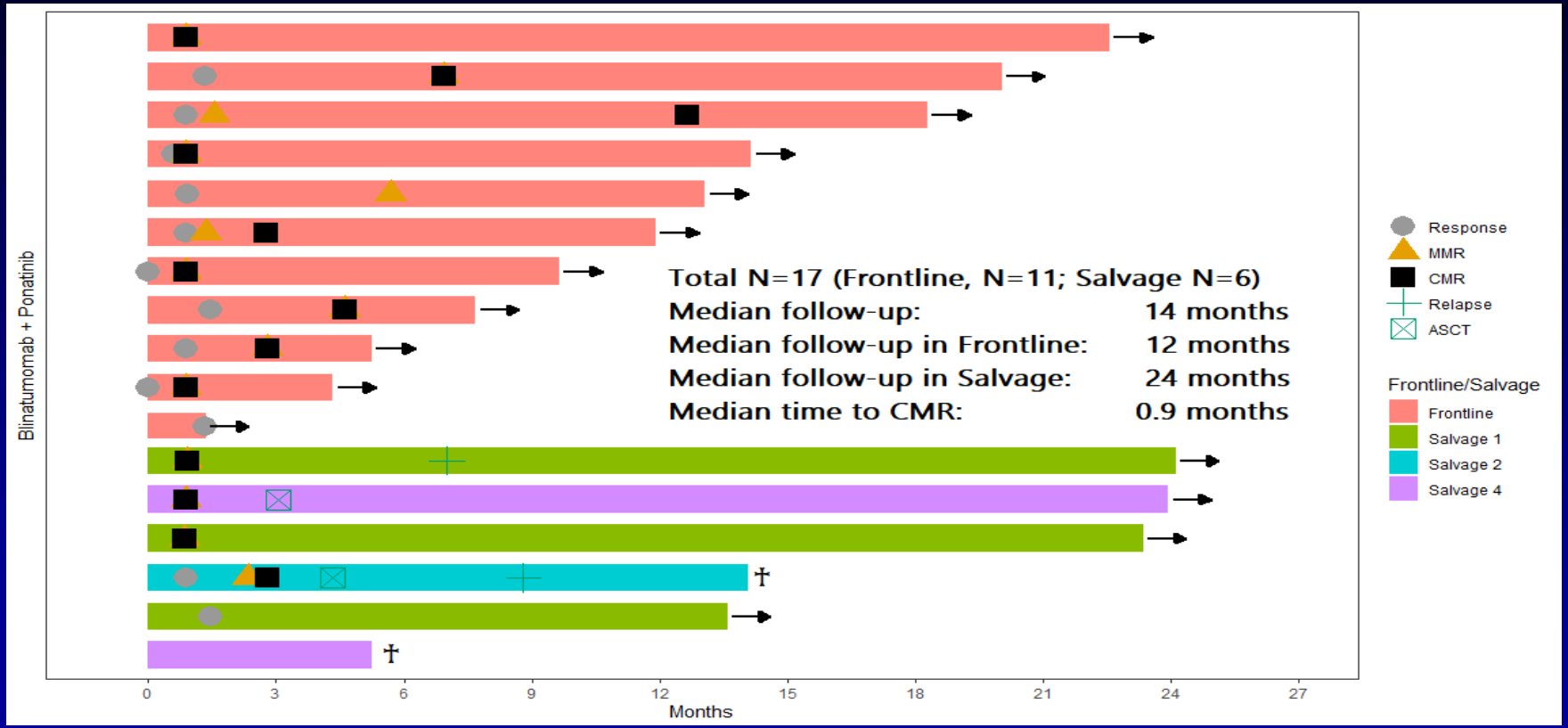
Chiaretti. *Blood.* 2019;134:abstract 615.

Blinatumomab-Ponatinib in Ph+ ALL



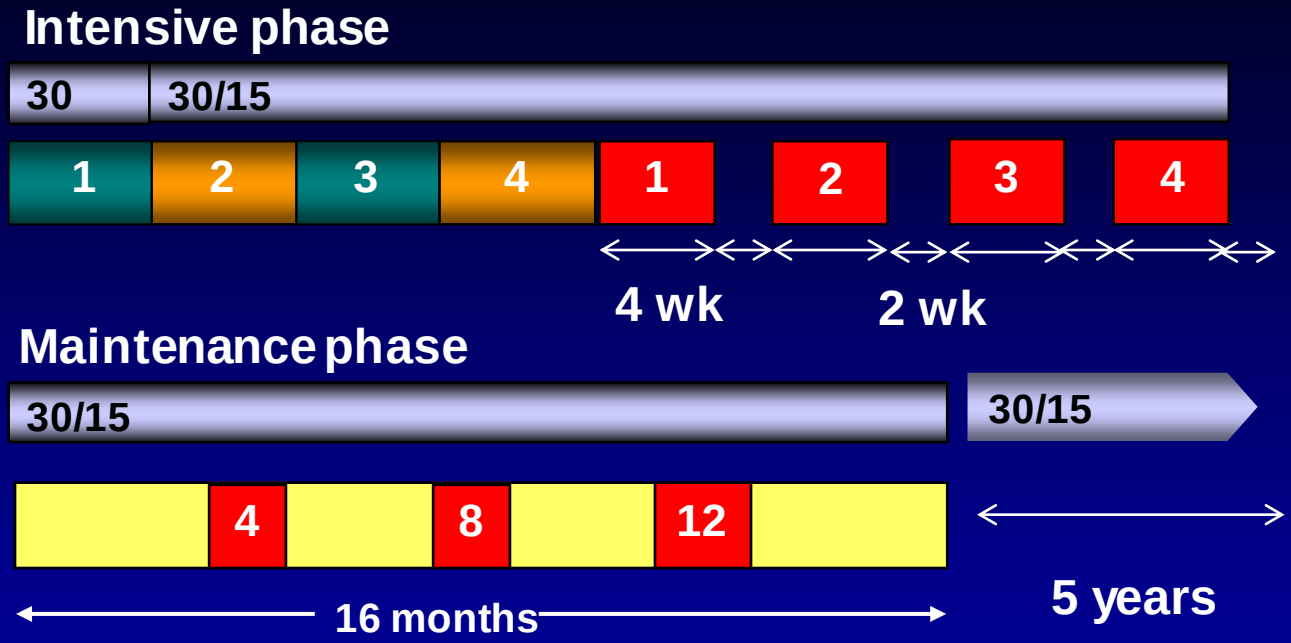
Assi. *Clin Lymphoma Myeloma Leuk.* 2017;17(12):897-901.

Blinatumomab + Ponatinib Swimmer Plot (N = 17)



Personal communication from Dr Jabbour.

Hyper-CVD + Ponatinib + Blinatumomab in Ph+ ALL



Risk-adapted intrathecal CNS prophylaxis (N = 12)

Mini-Hyper-CVD

Mini-MTX-cytarabine

Ponatinib 30 mg →15 mg

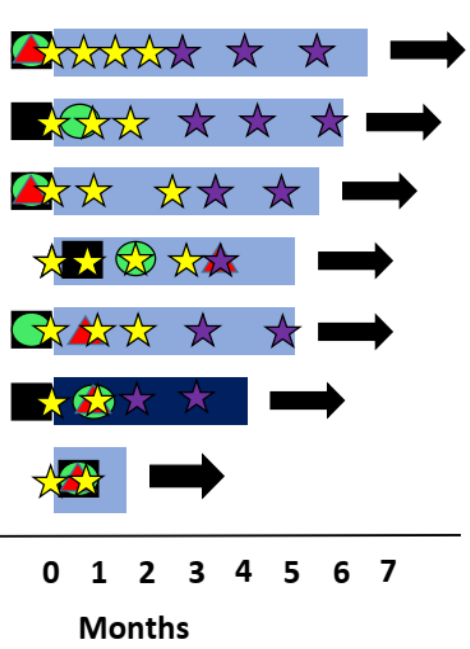
Vincristine + prednisone

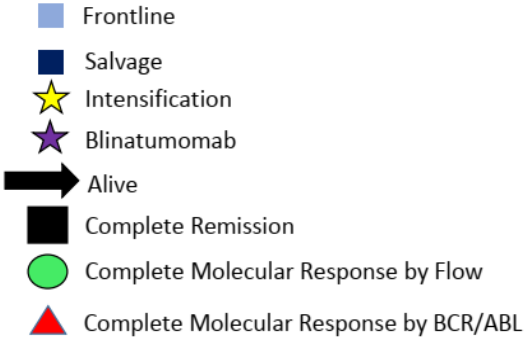
Blinatumomab

https://clinicaltrials.gov/ct2/show/NCT03147612

MiniHyper-CVD + Ponatinib + Blina in Ph+ ALL

Age	Sex	BCR/ABL	WBC>50	Rtx
25	M	p190		no
52	F	p190		yes
59	F	p190	yes	yes
28	F	p210		yes
30	F	p190		yes
31	M	p210		no
35	M	p210		no





Personal communication from Dr Jabbour.

Question 1

Case: Twenty-four-year-old female patient with no PMH presents with fatigue, and easy bruising for 2 weeks. Her peripheral blood counts are: WBC = 18,500 with 55% blasts and 5% polys; Hct = 23% with MCV = 91; platelet count = 33,000. BM biopsy is performed: 55% blasts; MPO negative, PAS positive. Flow: immature cells positive for CD45 (dim), CD34, CD10, CD19, CD20, CD22, TdT; negative for CD13, CD33, and CD17, and mono and T-cell markers; negative for immunoglobulin. Cytogenetics reveals normal 46 XX karyotype. She has 1 sibling.

How would you treat her?

- Clinical trial
- Hyper-CVAD
- Rituximab–hyper-CVAD
- Multidrug induction chemotherapy following previously published regimens (CALGB; Larson)
- Pediatric-inspired induction regimen

ALL 2020 – Conclusions

- Ino and blina + chemoRx in salvage and frontline
  - S1 – mini-CVD-ino-blina CR 90%; 2-yr OS 46%
  - Older frontline – CR 90%; 3-yr OS 50%
  - Moving younger adults (HCVAD-Blina-ino)
- Great outcome in Ph+ ALL
  - 5-yr OS 74%
  - Ponatinib-blinatumomab and mini-CVD +ponatinib + blinatumomab
- Bcl2-Bclxl inhibitors
  - Venetoclax-navitoclax combo in R/R ALL RR 50%
  - Mini-CVD + ven in older frontline – CR 90+%
  - Mini-CVD + ven + navitoclax
- CAR T cells; strategies redefining their role in early salvage and frontline
  - Dual CD19-22-20; Fast-off CD19; allo CAR T cells (CD19, CD22, CD20?)
- Incorporate new strategies – SQ blina, blina + checkpoint inhibitors, "better inos", venetoclax, navitoclax

The Future of ALL Therapy . . .

It is plausible that incorporating active monoclonal antibodies/CAR T cells Rx into frontline adult ALL therapy, in a concomitant or sequential fashion, may induce higher rates of MRD negativity and increase the cure rates to levels achieved in pediatric ALL, and may reduce the need for allo-SCT and intensive and prolonged chemotherapy schedules.

Jabbour E. *Blood.* 2015;125:4010.

Thank You

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Global Leukemia Academy

Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Current Treatment Options for Relapsed ALL in Adult and Elderly Patients

Fatih Demirkan

APTITUDE HEALTH®

Survival in relapsed ALL

- Follow-up study of 609 patients who relapsed on the MRC UKALL12/ECOG 2993 study: the OS at 5 years after first relapse was only 7%
- German ALL group data: 3-year OS is 24% in a group of patients who relapsed, among whom, remarkably, 75% actually proceeded to allogeneic transplantation
- Among 547 patients who relapsed, none of the patients who were not transplanted survived more than 1 year
- Salvage treatments are at best bridge therapies for patients who are candidates for transplant

• Fielding, et al. *Blood.* 2007;109(3):944-950, Gokbuget N, et al. *Blood.* 2012;120(10):2032-2041

Salvage regimens in ALL

Table 1. Response to first salvage therapy in patients with relapse during/after chemotherapy

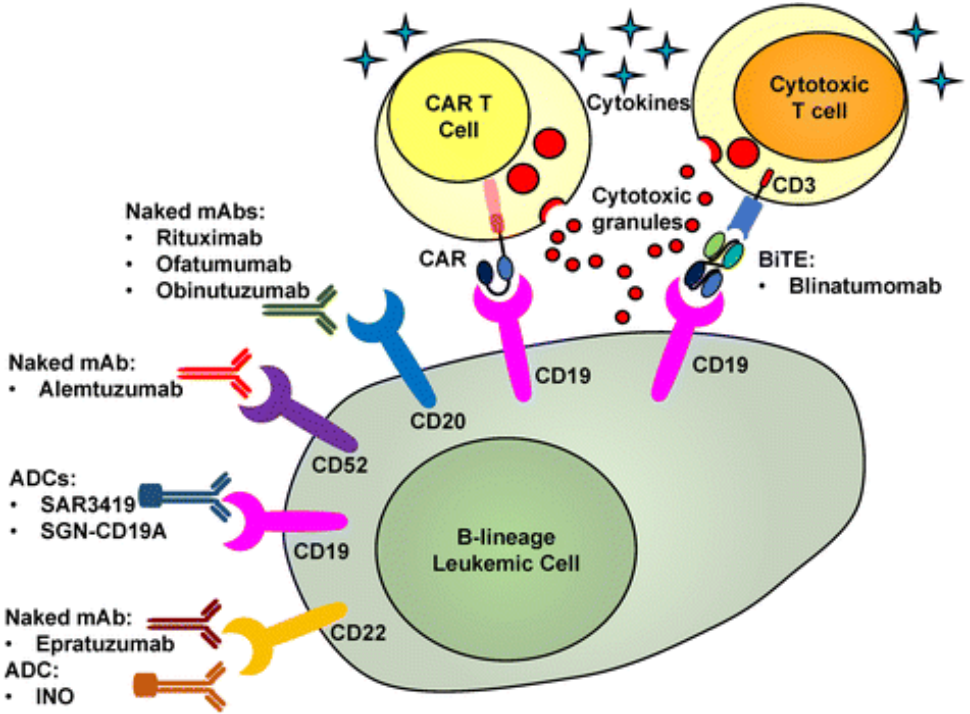
	Total			B-lineage			T-lineage		
	n = 224	CR = 95 (42%)*	*P*	n = 159	CR = 73 (46%)*	*P*	n = 65	CR = 22 (34%)*	*P*
Early relapse	160	58 (36%)	> .05	114	44 (39%)	> .05	46	14 (30%)	> .05
Consolidation I	47	13 (28%)		38	11 (29%)		9	2	
FLAG-IDA	39	16 (41%)		38	16 (42%)		1	0	
CLAEG	16	3 (19%)		0	0		16	3 (19%)	
Standard induction	9	3		8	2		1	1	
HDAC ± Mitox	9	4		5	2		4	2	
HDMTX	7	3		3	1		4	2	
Other chemotherapy	15	6 (40%)		8	4		7	2	
SCT in relapse†	18	10 (56%)		14	8 (57%)		4	2	
Late relapse	64	37 (58%)	< .0001	45	29 (64%)	.0003	19	8 (42%)	> .05
CLAEG	9	2					9	2	
Standard induction	30	27 (90%)		27	24 (88%)		3	3	
SCT in relapse†	1	1		1	1		0	0	
FLAG-IDA	15	4 (27%)		14	4 (29%)		1	0	
HDAC ± Mitox	1	0		1	0		0	0	
Other	8	3		2	0		6	3	

Re-induction success：

- CR1 <6 mo: 14%
- CR1 7–18 mo: 36%
- CR1 >18 mo: 57%

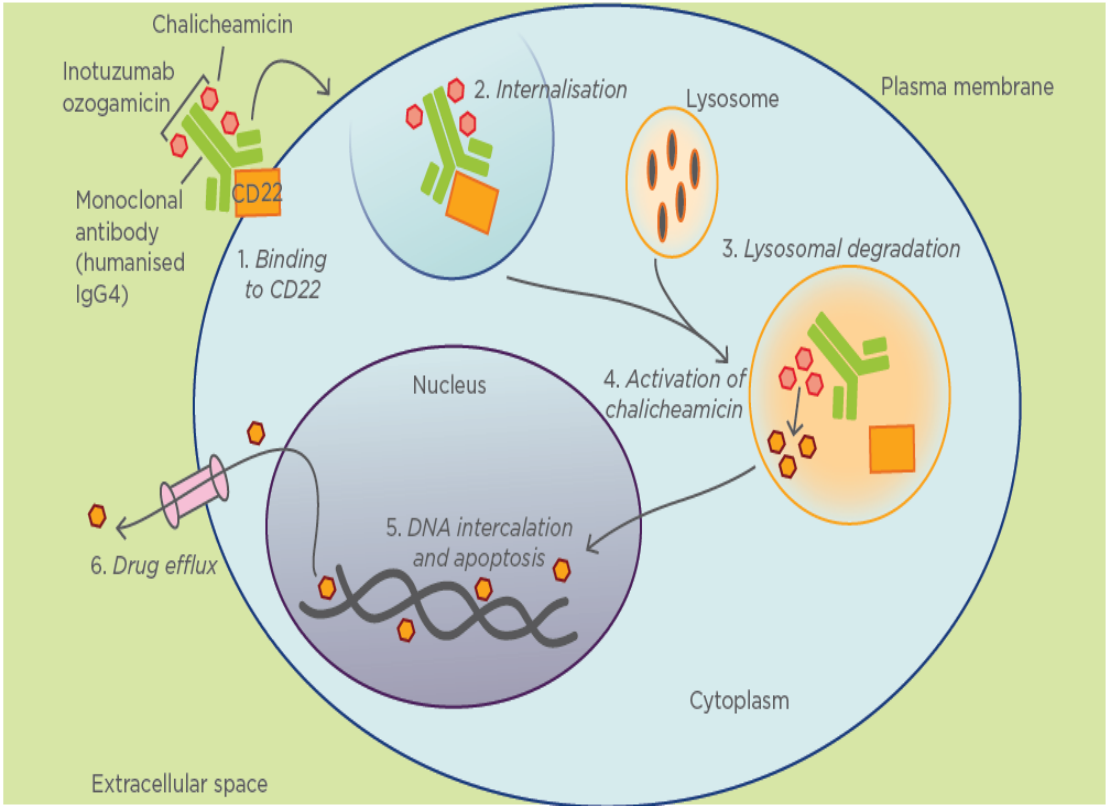
Forman SJ, Rowe JM. *Blood*. 2013;121(7):1077-1082. Tavernier E, et al. *Leukemia*. 2007;21(9):1907-1914

Immunotherapy as salvage therapy in relapsed ALL

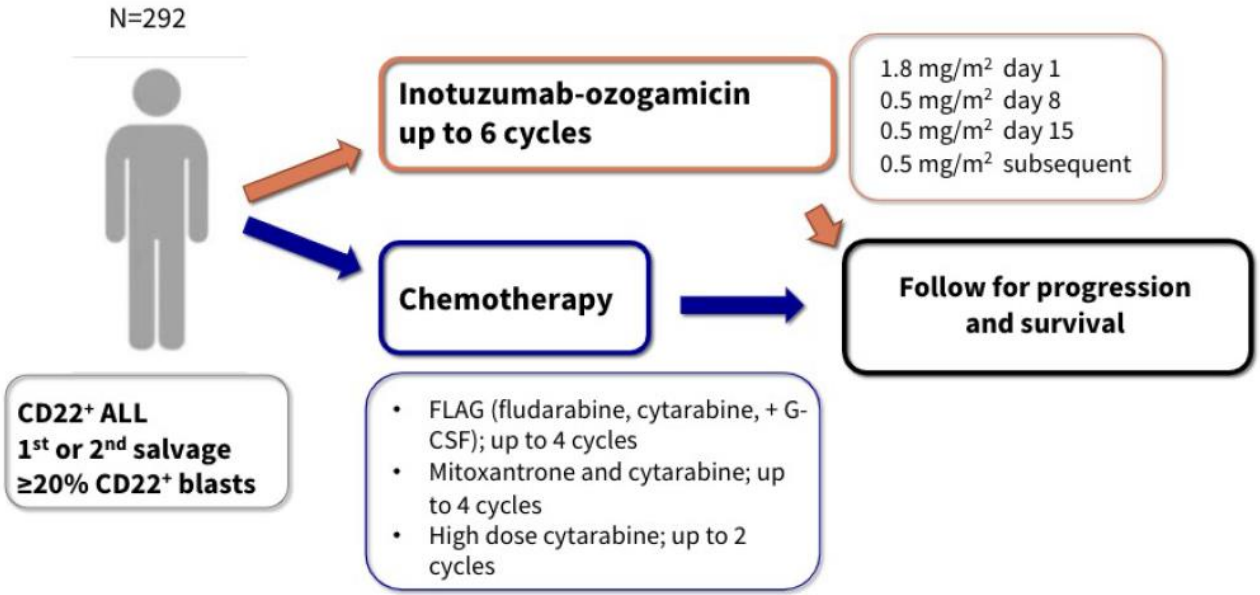


Inotuzumab

- Antibody-drug conjugate between a CD22 antibody and calicheamicin
- Antibody-drug conjugate is internalized after binding
- Calicheamicin induces DNA strand breaks



INO-VATE: Inotuzumab ozogamicin in relapsed/refractory ALL



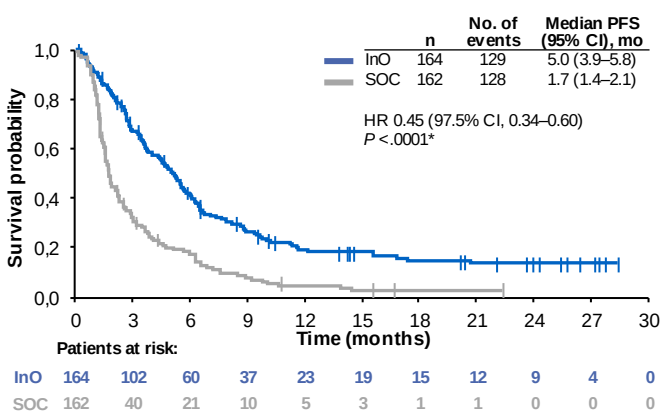
INO-VATE: Key overall outcomes

Outcome	Inotuzumab	Standard chemo
CR/CRh	81%	29%
MRD neg (of CR pts)	78%	28%
PFS median	5 mo	1.8 mo
OS median	7.7 mo	6.7 mo
HSCT	48%	32%

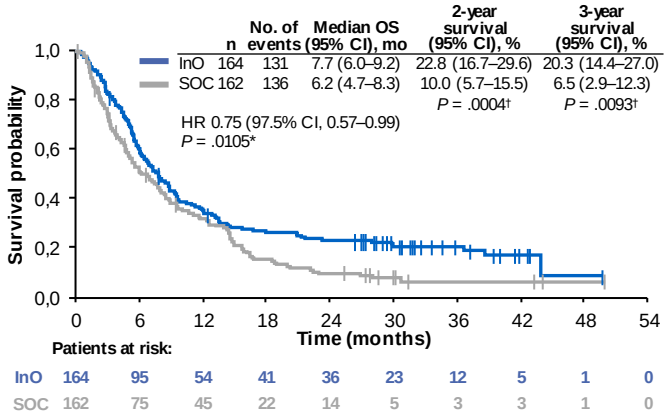
Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753.

Progression-free and overall survival in patients with R/R BCP-ALL who received inotuzumab ozogamicin: The INO-VATE ALL trial

Progression-free survival with inotuzumab ozogamicin



Overall survival with inotuzumab ozogamicin



Patients receiving inotuzumab ozogamicin had longer median progression-free survival (5.0 vs 1.7 months) and 3-year overall survival (20.3% vs 6.5%) than patients receiving SOC chemotherapy

The INO-VATE ALL trial was a phase 3 clinical study designed to assess the clinical activity and safety of inotuzumab ozogamicin compared with standard intensive chemotherapy in adult patients (N = 326) with Ph-positive or Ph-negative R/R BCP-ALL.

A censored patient is indicated by a vertical bar |.

*One-sided log-rank test. †For 2- and 3-year survival, the 1-sided *P* value was based on the chi-square test or the Fisher exact test (if any cell count was < 5).

INO-VATE: Multivariate analysis

Factors associated with longer survival[1]

- Longer duration of first remission
- Attaining CR
- Subsequent HSCT
- MRD negativity: 14.1 MRD neg vs 7.2 po

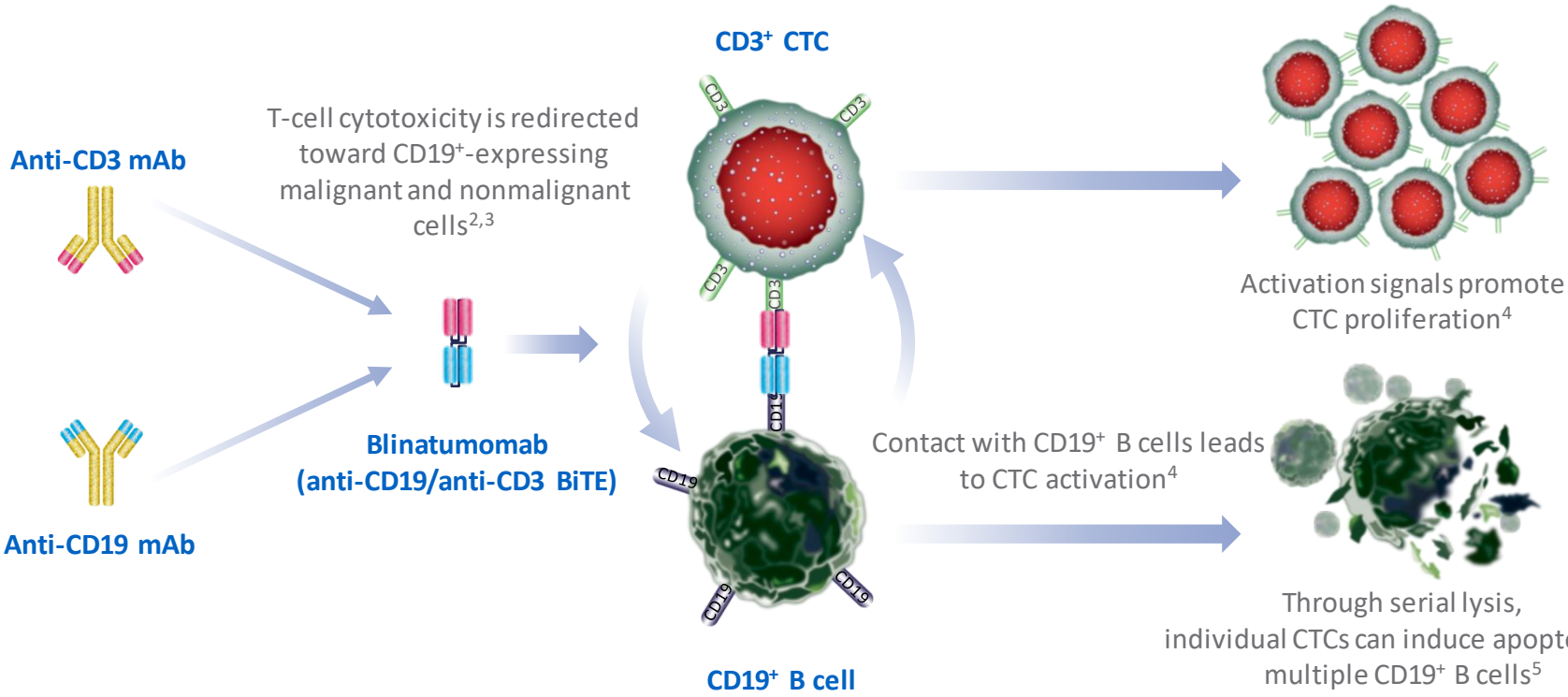
More patients proceeded to HSCT at any time after study treatment in the InO arm than the SOC arm (79 of 164 vs 36 of 162; 1-sided *P* <.0001[2]

Patients treated with InO who proceeded to HSCT had a median OS of 12.6 months vs 7.1 months for those who did not (overall HR 0.55; *P* = .0065)[2]

1. Jabbour E, et al. *J Clin Oncol*. 2018;36(suppl):abstract 7013; 2. Kantarjian H, et al. *Cancer*. 2019;125:2474-2487.

Blinatumomab

BiTE® antibody construct designed to bridge CTCs to CD19-expressing B cells, resulting in cell death[1]

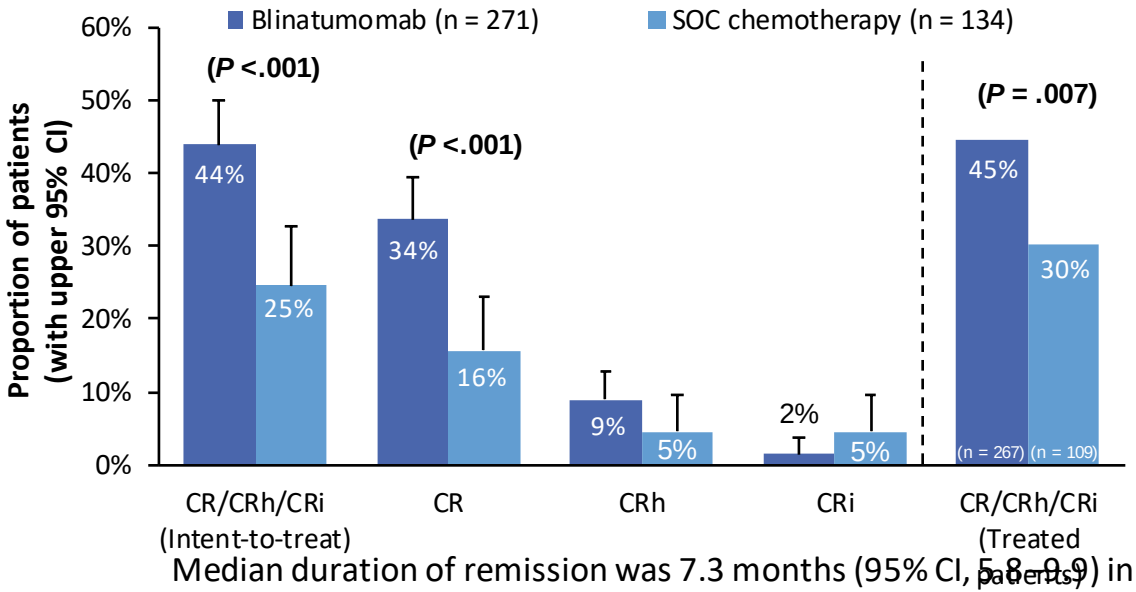


1. Baeuerle PA, et al. *Cancer Res.* 2009;69:4941-4944; 2. Bargou R, et al. *Science.* 2008;321:974-977; 3. Topp MS, et al. *Lancet Oncol*. 2015;16:57-66; 4. Klinger M, et al. *Blood.* 2012;119:6226-6233; 5. Hoffmann P, et al. *Int J Cancer.* 2005;115:98-104.

TOWER: Blinatumomab compared with SOC chemotherapy in adults with R/R Ph– B-cell precursor ALL:

Primary analysis results

Remission rates within 12 weeks[1,2]



Complete MRD response* among responders	Blinatumomab	SOC chemotherapy
CR/CRh/CRi [intent-to-treat], n (%)	74 (76)	16 (48)
CR, n (%)	57 (77)	11 (52)

Median duration of remission was 7.3 months (95% CI, 5.8–9.9) in the blinatumomab group and 4.6 months (95% CI, 1.8–19.0) in the SOC chemotherapy group

*Molecular remission was defined as $<10^{-4}$ blasts in the first 12 weeks.

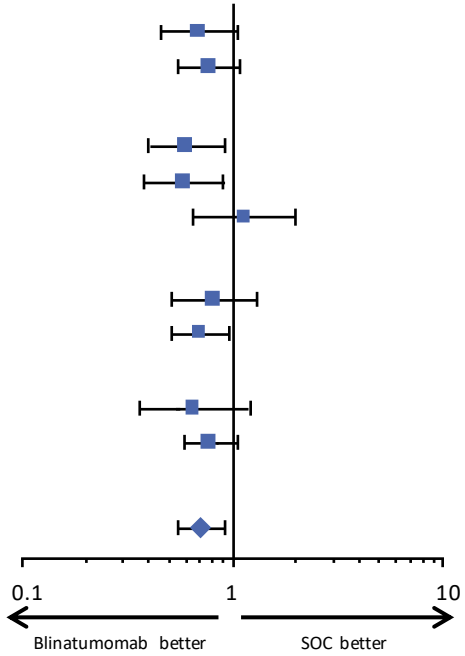
CR, complete remission, CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete he matologic recovery; MRD, minimal residual disease; SOC, standard of care.

1. Kantarjian H, et al. *N Engl J Med*. 2017;376:836-847; 2. Topp MS, et al. EHA 2016. Oral Presentation S149.

TOWER: Primary analysis results

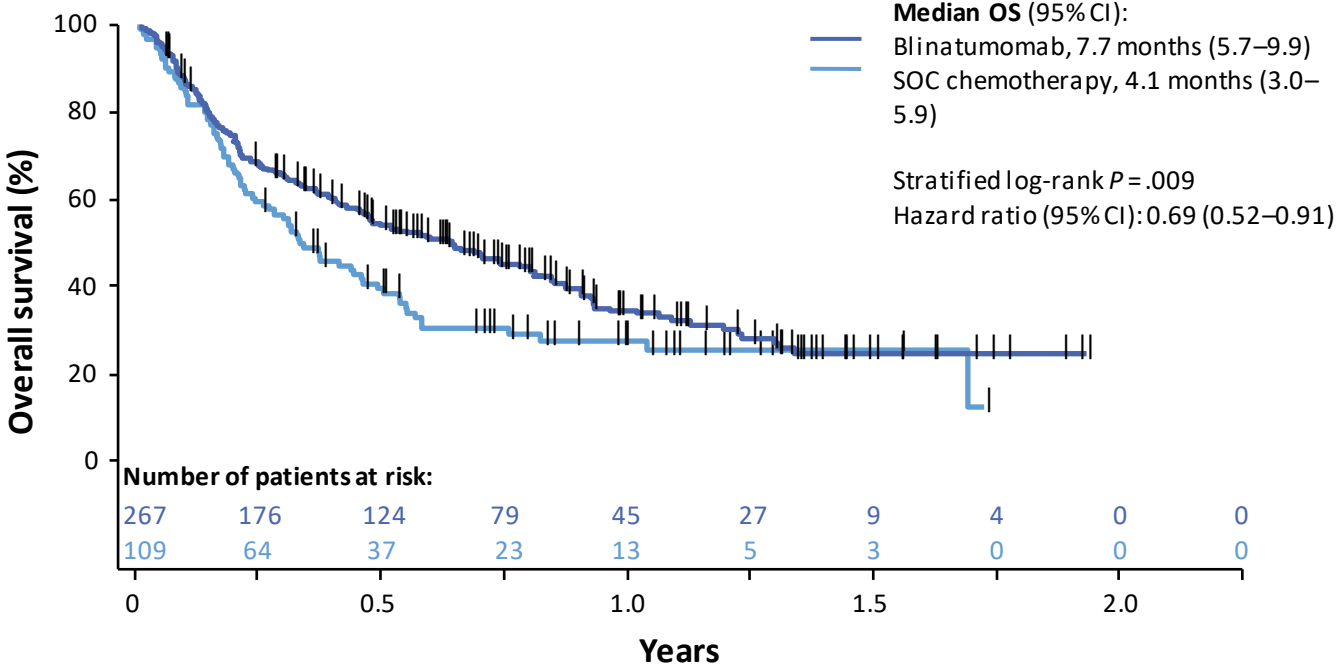
Overall survival: Subgroup analysis

Subgroup	Median survival, months (n)		Hazard ratio (95% CI)
	Blinatumomab	SOC chemotherapy	
Age			
<35 years	9.9 (123)	4.5 (60)	0.70 (0.46–1.06)
≥35 years	5.6 (148)	3.8 (74)	0.77 (0.55–1.08)
Salvage status			
First	11.1 (114)	5.3 (65)	0.60 (0.39–0.91)
Second	5.1 (91)	3.3 (43)	0.59 (0.38–0.91)
Third or later	3.7 (66)	3.0 (26)	1.13 (0.64–1.99)
Prior alloHSCT			
Yes	7.7 (94)	5.3 (46)	0.81 (0.51–1.29)
No	7.7 (177)	3.7 (88)	0.70 (0.51–0.96)
Baseline bone marrow blasts			
<50%	11.5 (84)	6.8 (38)	0.60 (0.35–1.03)
≥50%	5.0 (86)	3.7 (96)	0.82 (0.61–1.10)
Overall	7.7 (271)	4.0 (134)	0.71 (0.55–0.93)



TOWER: Primary analysis results

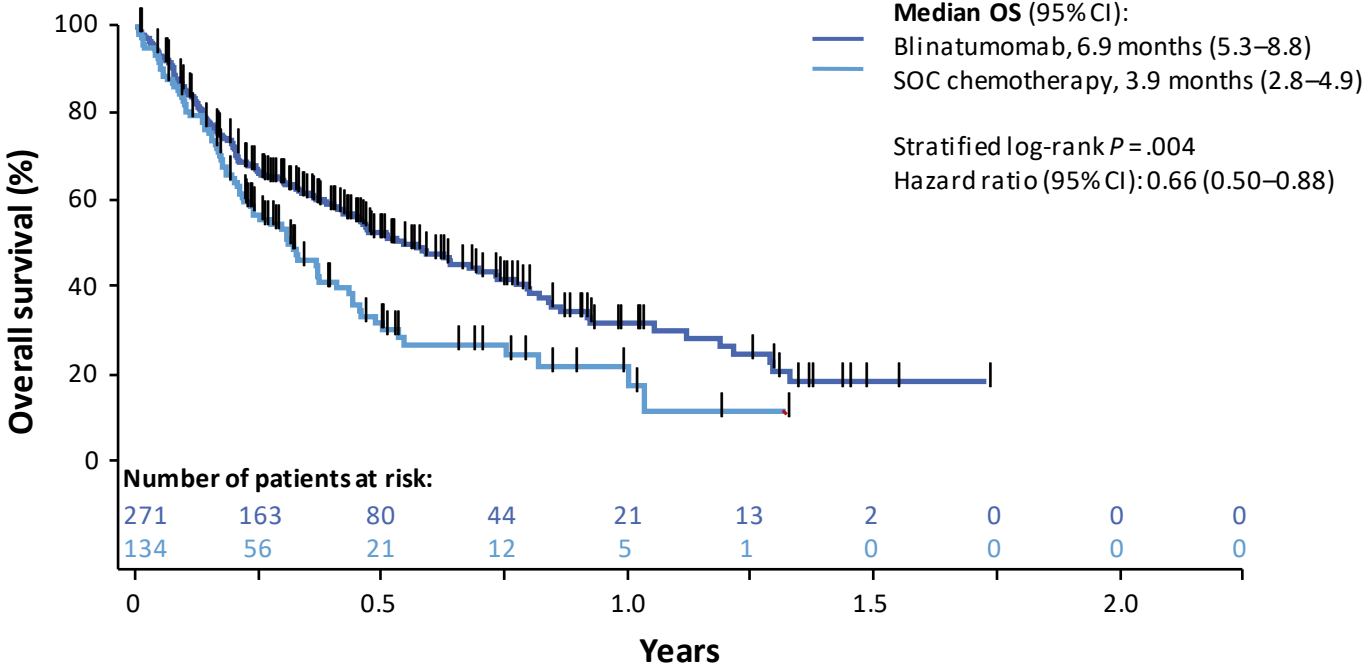
Overall survival: As-treated population[1,2]



Patients still alive were censored at the date they were last known to be alive. A censored patient is indicated by a vertical bar |.
OS, overall survival; SOC, standard of care.

TOWER: Primary analysis results

Overall survival: Censoring at the time of alloHSCT



Patients censored at the time of alloHSCT. A censored patient is indicated by a vertical bar |.
alloHSCT, allogeneic hematopoietic stem cell transplantation; OS, overall survival; SOC, standard of care.

INO vs BLINA summary

INOTUZUMAB	BLINATUMOMAB
T-cell independent, anti-CD22 conjugated	T-cell dependent, anti-CD19 bispesific
IV infusion over 1 hr	IV 24-hr pump infusion
Toxicity: hepatotoxicity, VOD (8%–16%), AST elevation	Toxicity: CRS (16%, 5% grade ≥3)
Resistance mechanism: Downregulation of antigen expression Poor uptake of conjugated antibody Resistance to calicheamicin	Resistance mechanism: Antigen escape: CD19 loss at relapse (10%–20%) Failure to activate T cells Primary T-cell failure T-cell exhaustion

- No direct comparisons between inotuzumab and blinatumomab are available
- Patient populations in phase 3 studies were different with regard to prior therapy

Outcomes are poor for adults with R/R Ph+ ALL

- Ph+ is the most common cytogenetic abnormality associated with ALL[1]
  - ~25% of adult ALL is Ph+ and frequency of Ph+ disease increases with age[2,3]
- TKIs have improved outcomes[2,4-6]
  - Addition to frontline therapy has increased response rates and likelihood of achieving alloHSCT[2]
  - Sequential use of chemotherapy ± TKIs of choice is the dominant approach to treating R/R Ph+ ALL[4,5]
  - Emergence of single and compound point mutations in *BCR-ABL* is responsible for a significant proportion of TKI resistance[6]

TKI monotherapy	Nilotinib[5] (N = 41)	Dasatinib[1] (N = 36)	Ponatinib[4] (N = 32)
Complete hematologic response	45%	33%	41%
Median OS OS at 1 year	5.2 months 27%	3.3 months NA	8.0 months 40%

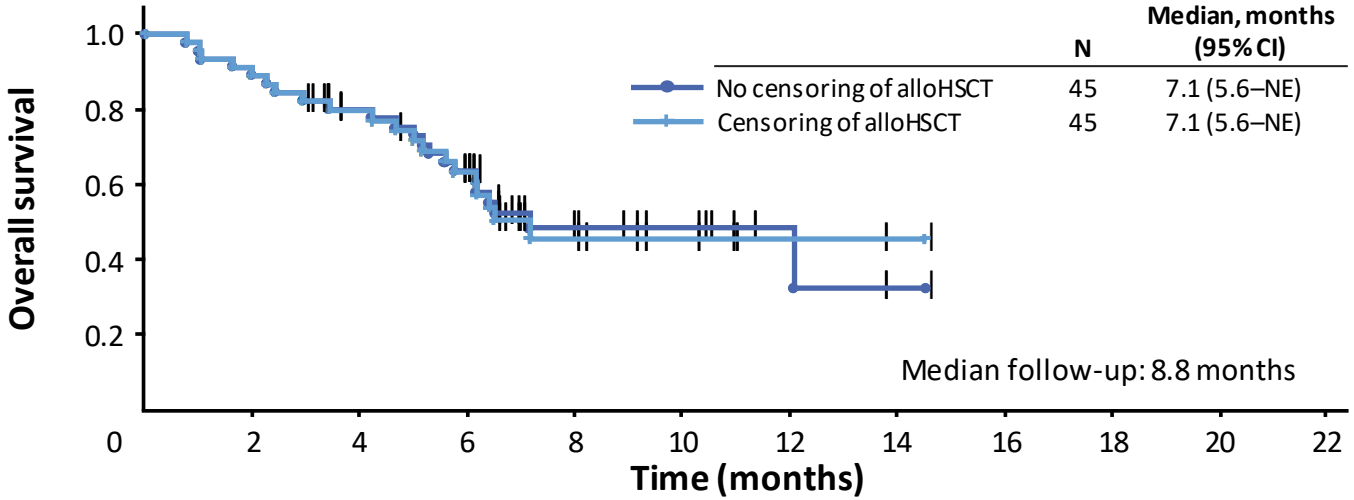
1. Ottmann O, et al. *Blood.* 2007;110:2309-2315; 2. Fielding AK, et al. *Blood.* 2014;123:843-850. 3. Ottmann OG, et al. *Hematology Am Soc Hematol Educ Program*. 2009;371-381;
4. Cortes JE, et al. *N Engl J Med.* 2013;369:1783-1796; 5. Ottmann OG, et al. *Leukemia.* 2013;27:1411-1413; 6. Zabriskie MS, et al. *Cancer Cell.* 2014;26:428-442.

Open-label, single-arm, multicenter, phase 2 study in R/R Ph+ B-precursor ALL: Blinatumomab Response during first 2 cycles and transplant realization

Secondary endpoints	n/N1	%	95% CI
Best response during the first 2 cycles			
CR	14/45	31	18–47
CRh	2/45	4	1–15
Complete MRD response*	14/16	88	62–98
AlloHSCT after blinatumomab-induced remission†	4/16	25	7–52
Age 18 to <55 years	2/8	25	3–65
Age ≥55 years	2/8	25	3–65
100-day posttransplant mortality rate†	1/4	25	4–87

*Among CR/CRh responders only; includes all 4 CR/CRh patients with the *T315I* mutation. †For patients who received alloHSCT during blinatumomab-induced remission without other antileukemia therapy. Complete MRD response was defined as no detectable PCR amplification of *BCR-ABL1* genes in a central laboratory with a sensitivity of 10^{-5}.
N1 = number of patients with evaluable data under each category.
alloHSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; CRh, CR with partial hematologic recovery of peripheral blood counts (platelets >50,000/µL and ANC >500/µL); MRD, minimal residual disease; PCR, polymerase chain reaction.

Overall survival



Number at risk

No censoring of alloHSCT	45	40	34	24	11	8	3	1	0	0	0	0
Censoring of alloHSCT	45	40	30	21	8	5	2	1	0	0	0	0

- Median OS was 7.1 months
- Median OS was not reached for the 18 complete MRD responders, with a median follow-up of 5.3 months
- Median OS was 3.9 months (95% CI, 3.0–not estimable [NE]) for the MRD nonresponders

alloHSCT, allogeneic stem cell transplantation; NE, not estimable.

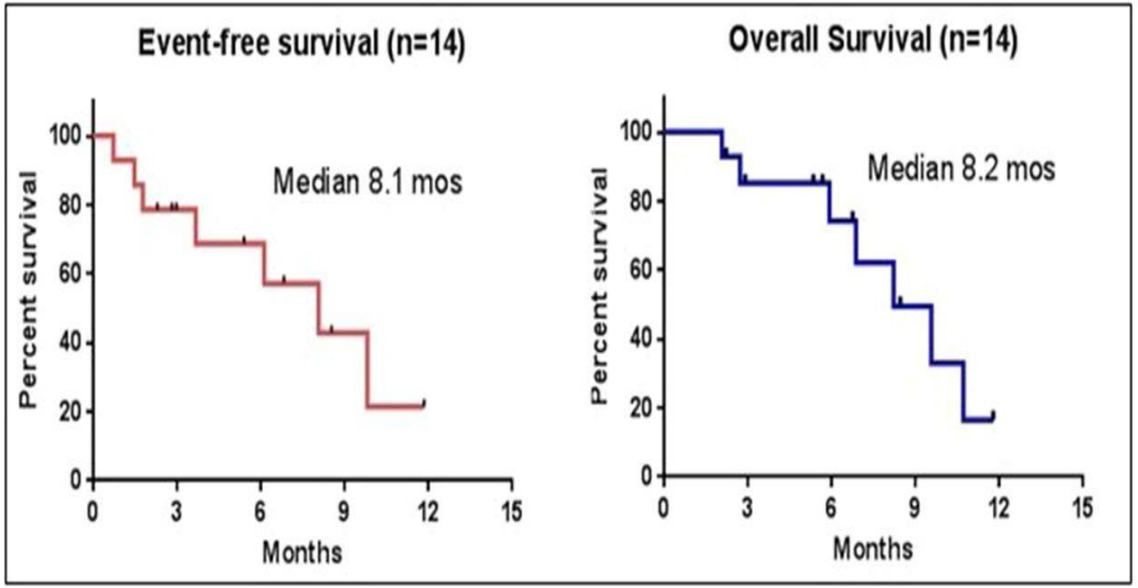
Inotuzumab ozogamicin in Ph+ pts with R/R ALL for whom prior TKIs +/– SCT failed

Efficacy Endpoints	InO-1010 (n = 16)	InO-1022 (n = 22)	SC (1022) (n = 27)
Complete remission (CR/CRi), n (%)	9 (56)	16 (73)	15 (56)
Minimal residual disease (MRD) negativity, n (%)	10 (63)	14 (64)	5 (19)
Overall survival (mos), median (95% CI)	7.4 (4.3–11.3)	8.7 (3.6–14.1)	8.4 (5.0–14.3)
Progression-free survival (mos), median (95% CI)	4.4 (1.8–5.9)	3.9 (2.1–9.2)	3.1 (1.1–6.2)

Pts with R/R ALL received InO in a phase 1 dose-finding/phase 2 study (1010; DeAngelo et al, Blood Adv 2017) and a phase 3 trial (1022; Kantarjian et al, N Engl J Med. 2016) comparing InO vs standard chemotherapy (SC).

InO-treated pts had higher rates of CR/CRi, MRD negativity, and subsequent SCT. Overall outcomes in 1022 InO vs SC were still inferior to those reported in Ph– pts.

InO in combination with bosutinib for patients with relapsed or refractory Ph+ ALL or CML in lymphoid blast phase

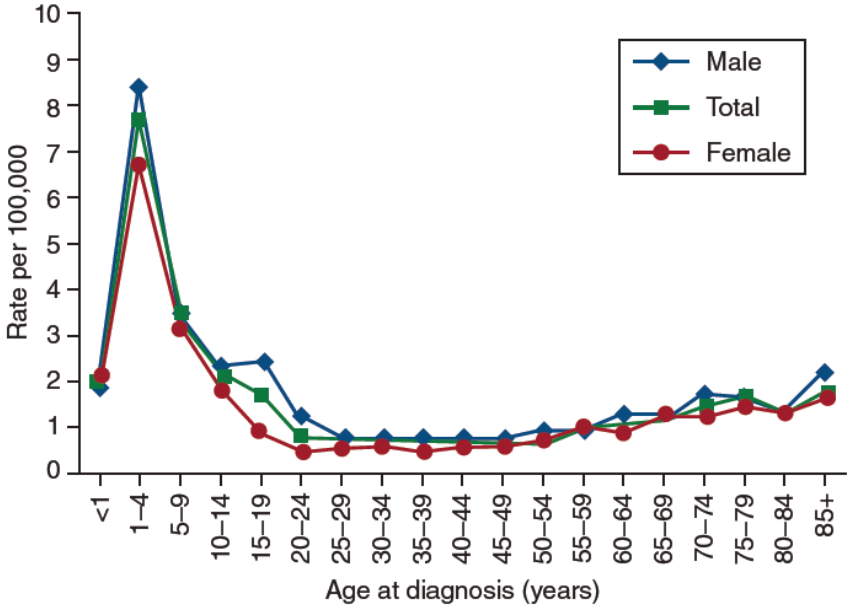


- Median age 62 yr (range, 19–74); diagnosis Ph+ ALL, n = 12 and CML LBP, n = 2
- Six pts had a prior alloSCT, and 8 pts had an ABL kinase domain mutation
- Five pts underwent a subsequent alloSCT (4 of these are alive and in remission post-SCT)

Comparison of CAR T cells and BiTEs

	CAR T	BITE
Structure	A synthetic gene construct encoding an scFv against tumor antigen linked to activation and costimulatory motifs	A recombinant protein composed of 2 linked scFvs; one binds to CD3 on T cells and the other to target a tumor antigen on tumor cells
Effector cell types	Engineered CD8+ and CD4+ T cells	Endogenous CD8+ and CD4+ T cells
Immune synapse	Atypical	Typical
Serial killing	Yes	Yes
Killing mechanisms	Perforin and granzyme B, Fas/Fas-L, or TNF/TNF-R	Perforin and granzyme B
Trafficking	Active. Trafficking of CAR T cells involves comprehensive interactions between various molecules and cell-cell interactions	Passive. Biodistribution depends on factors related to rates of diffusion through vascular endothelium, fluid flow rates, and interaction with target
Toxicity	CRS, neurotoxicity, B-cell aplasia	CRS, neurotoxicity
Clinical applications	Pretreatment lymphodepleting regimen using cyclophosphamide and fludarabine. Premedicate with acetaminophen and an H1-antihistamine. One infusion	No lymphodepletion regimen required. Premedicate with dexamethasone. Repeat administration as necessary, including continuous IV infusion regimens
Other characteristics	Individually produced for each patient	"Off the shelf" reagents

Definition of older ALL



- >40: No longer tolerates pediatric regimens
- >60: Typical cutoff for ALL trials?
- >70: Too old for alloHSCT?

Data from SEER Cancer Statistics Review, 1975–2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010.

If an older adult is refractory to initial therapy

- Enroll the patient in a clinical trial
- If ineligible for a clinical trial, Blina or InO is treatment choice
- Ph+ ALL: TKIs + blinatumomab/Ino
- Highly selected older patients may have acceptable outcomes with reduced-intensity conditioning (RIC) transplants
- Relapsed or refractory T-cell ALL carries a dismal prognosis with limited salvage treatment options (nelarabine..)

Question #1

Which is not true for the effect of blinatumumab in R/R ALL in phase 3 TOWER trial?

a) Overall survival at 1st salvage is better than 2nd salvage

b) Median duration of remission in blinatumumab group is longer than SOC group (7.3 vs 4.6 months)

c) In patients with marrow blasts >50% median survival in blinatumab group is not better than SOC group

d) MRD neg response in blina group is better than SOC group (76% vs 48% at 12 wks) among responders

e) all above is true

Question #2

Which is not true for the effect of immunotherapy agents?

a) Inotuzumab is an anti-CD22 antibody conjugated with **calicheamicin** which is toxic to DNA

b) Synapse between CD3 T cell and CD19 B cell via BITE antibody causes proliferation and re-distribution of circulating T cells in the body

c) CRS and neurotoxicity is the major concern for CAR T cell therapies

d) Hepatotoxicity; VOD (8-16%) is the majör concern for InO therapy

e) Relapse after blina therapy, always occurs with CD19 loss

Thank you

Global Leukemia Academy

Q&A

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Case-Based Panel Discussion Management of Long- and Short-Term Toxicities and Treatment Selection in Adult and Elderly Patients

Fatih Demirkan

Andre Schuh

APTITUDE HEALTH®

Global Leukemia Academy

Case-Based Panel Discussion: Patient Case Presentation

Fatih Demirkan

APTITUDE HEALTH®

Case

- 34-year-old male patient diagnosed as Philadelphia-positive ALL in Jan 2019
- 8 cycles hyperCVAD: CR
- Dasatinib 100 mg/day + voriconazole PO for pulmonary aspergillosis on discharge
- 10/10 HLA-compatible matched unrelated donor was found
- Patient disengaged from follow-up because of compliance problems

Case

- Jan 2020: patient admitted to Dokuz Eylul University hospital with diagnosis of relapsed ALL. Patient report obtained from the hospital where he was diagnosed
- Hemogram at admission: WBC 2000/mm^3, Neu 100/mm^3, Hgb 8.9 g/dL, Plt 86,0000/mm^3. Bone marrow aspiration 90% ALL blasts. RT-PCR bcr/abl p190 positive. Flow cytometry: CD19+ precursor B-ALL
- FLAG-Ida chemotherapy administered. Feb 5, 2020: CR achieved. Patient was put on dasatinib 100 mg/day (as he was receiving voriconazole secondary prophylaxis)

Case

- April 8, 2020: bone pain
- Hemogram: WBC 6300/mm^3, Neu 2600/mm^3, Hgb 13.1 g/dL, Plt 122,000/mm^3, peripheral smear 5% lymphoblast. Aspiration: 30% lymphoblast
- Blinatumomab license in Turkey is for Ph– patients who are at hematologic relapse. MoH approval was obtained for Blina prescription for this patient
- April 30, 2020: Blina infusion started with 9 µg/day for the first week; infusion bags are replaced every 72 hr. Hemogram 13.6 g/dL, WBC 4900/mm^3, Plt 130,000/mm^3. Peripheral blasts 10%. Steroid and antihistamine was administered at the beginning of infusion. No reaction observed during the first week

Case

- Second-week infusion with a dose of 28 µg/day started with dexamethasone prophylaxis
- On the second day of infusion (May 7, 2020), fever (>39C°) headache, back pain, and disseminated extremity pain appeared. Hemogram showed developing cytopenia and neutropenia: WBC 800/mm^3, Neu 700/mm^3, Hgb 11.8 g/dL, Plt 27,000/mm^3. With CRP (120 mg/L) and procalcitonin (6 ng/mL) elevation, sepsis was considered and patient was put on meropenem + liposomal amphotericin
- Over the following 2 days fever continues (38–39.5C°)
- May 10, 2020: dexamethasone 20 mg administered
- May 11, 2020: fever dropped for the first time; neutrophils elevated 1400/mm^3

Case

- May 12, 2020: fever (39°C), pain, cytopenia reappeared. HRCT normal, antibiotics revised. No hypotension, renal and hepatic biochemistry normal
- May 14, 2020: dexamethasone 12 mg
- May 15, 2020: no fever
- May 16, 2020: dexamethasone 8 mg
- May 17, 2020: the patient was put on routine daily 8-mg dexamethasone with the diagnosis of CRS. Fever, pain, cytopenia, and CRP elevation did not reoccur
- May 27, 2020: Dexa dropped with the end of 4 weeks of Blina infusion
- June 16, 2020: myeloablative alloHSCT from matched unrelated donor. Waiting for engraftment

Reported rates of toxicity with blinatumomab

	Phase II (*n* = 21)	Phase II (*n* = 36)	Phase II (*n* = 189)	Phase III TOWER study (*n* = 405)	Phase II, Ph positive (*n* = 45)	Phase II, MRD positive patients (*n* = 116)
CRS	NA	All grade: NA Grade ⩾ 3: 6%	All grade: NA Grade ⩾ 3: 2%	All grade: 14% Grade ⩾ 3: 5%	All grade: 7% Grade ⩾ 3: 0	All grade: 3% Grade ⩾ 3: 2%
Neurotoxicity	20% (grades no specified)	All grade: 36% Grade ⩾ 3: 14%	All grade: 52% Grade ⩾ 3: 13%	All grade: 45% Grade ⩾ 3: 9%	All grade: 47% Grade ⩾ 3: 7%	All grade: 53% Grade ⩾ 3: 13%

CRS, cytokine release syndrome; NA, not available.

Jain T, Litzow MR. *Ther Adv Hematol.* 2020;11:1-13.

Cytokine release syndrome (CRS)

- High disease burden and a higher initial dose of blinatumomab are risk factors
- High fevers, headache, and malaise
- Hypotension, hypoxia, hepatic or renal dysfunction in higher grades
- Pulmonary edema, capillary leak, and disseminated intravascular coagulopathy and hemophagocytic lymphohistiocytosis in severe and life-threatening cases

Topp MS, et al. *J Clin Oncol*. 2014;32:4134-4140; Teachey DT, et al. *Blood*. 2013;121:5154–5157.

CRS management

- Early recognition is important
- Dexamethasone prophylaxis is recommended at the time of initiation of infusion in all patients, at the time of dose increase, and when dose is interrupted for longer than 4 h
- Treatment strategies include corticosteroids or temporary discontinuation of infusion
- Tocilizumab, an IL-6 receptor blocker, has been used in higher grades of CRS, such as hemophagocytic lymphohistiocytosis

Jain T, Litzow MR. *Ther Adv Hematol*. 2020;11:1-13; Teachey DT, et al. *Blood*. 2013;121:5154–5157.

FDA-REQUIRED UPDATED REMS SAFETY INFORMATION

March 2019

BOXED WARNING: Cytokine Release Syndrome

New

- In patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
- In patients treated for relapsed or refractory B-cell precursor ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.

New

- Administer corticosteroids for severe or life-threatening CRS.

FDA Label Blincyto® https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125557s015s016lbl.pdf. Accessed July 2020.

Questions

1. What is the rate of grade 3 CRS with blinatumomab infusion?
    a. 20%–36%
    b. 14%–20%
    c. 7%–10%
    d. 2%–3.5%
    e. None of the above

Questions

2. Which is true for management of CRS occurring after blinatumomab infusion?
    a. Administer steroids for severe and life-threatening CRS
    b. Tocilizumab, an IL-6 receptor blocker, can be used in higher grades if no improvement occurs with steroids
    c. In patients treated for R/R ALL, hospitalization is recommended for the first 9 days of the first cycle
    d. Permanent discontinuation of the drug is discouraged, given the life-saving potential of treatment of ALL
    e. **All of above**

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Q&A

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Case-Based Panel Discussion: Patient Case Presentation

Andre Schuh

APTITUDE HEALTH®

Case

Ms BS, age 61, originally from Iran

- PMH breast Ca treated with surgery, radiation, tamoxifen >15 years earlier

May 2017

- Diagnosed with Ph+ ALL (p210)
- WBC 27 bil/L; CNS–; no other cytogenetic abnormalities; NGS not contributory
- Received induction chemotherapy at another center (1 hour away) with modified DFCI protocol (age ≥60; Ph+) with imatinib 600 mg
- Achieved CR
- Postinduction MRD 3.1-log reduction (done at different center)

Question 1:

At this point you would

1. Initiate HLA typing and donor search
2. Refer to alloSCT
3. Continue with DFCI regimen + TKI
4. 1 + 2
5. 1 + 2 + 3
6. 1 + 3

June 2017

- First seen at our center (she actually lived in Toronto)
- Initiated HLA typing and donor search, etc
- Daughter was haploidentical
- Patient strongly anti-alloSCT
- Continued with DFCI
- Repeated problems with delayed counts recovery, febrile neutropenia, and fungal pneumonia

September 2017

- After 2 intensification cycles, MRD 3.8-log reduction (~3½ months)
- Ongoing medical issues, largely infectious

Question 2:

At this point you would

1. Refer to alloSCT
2. Continue with DFCI regimen but change TKI
3. Switch to Blinatumomab + TKI
4. 1 + 2
5. 1 + 3

September 2017

- Empirically switched to dasatinib 100 mg

November 2017 – June 2018

- MRD repeatedly undetectable
- But during this period
  - Cytopenias poorly responsive to G-CSF and dose reductions
  - Therapy repeatedly delayed
  - Repeat admissions for febrile neutropenia and pneumonia (fungal, and then *Mycobacterium avium* complex)
  - Influenza A
  - Emotional issues
  - Signed out against medical advice
  - Etc

July 2018

- MRD 3.4-log reduction

August 2018

- 3% leukemic blasts and MRD “diagnostic levels”
- ABL1 KD analysis
  - c827A>G (pAsp276Gly)
  - c949T>C (pPhe317Leu)
- At this point still quite ill with pneumonia, etc

Question 3:

At this point you would

1. Refer to alloSCT
2. Continue with DFCI regimen but change TKI
3. Switch to blinatumomab + ponatinib
4. Switch to inotuzumab
5. 1 + 2
6. 1 + 3
7. 1 + 4

September 2018

- Started on ponatinib (30 mg) + blinatumomab
- Enterocolitis

November 2018

- After 1 cycle, marrow CR (CR2) and MRD undetectable
- Continued ponatinib (15 mg) + blinatumomab while trying to make her well enough for alloSCT

February 2019

- After 3 cycles blinatumomab . . . haploidentical alloSCT
- Very complicated course
  - Recovered Hb and WBC/neuts, but not platelets
  - Severe GVHD gut
  - *C. diff* diarrhea
  - Shingles
  - Pneumonia
  - Influenza A
  - CMV reactivation
  - In and out of ICU

May 2019

- Dropping counts and molecular relapse . . .
- 3.6- (day 83) and then 1.0-log (day 97) reductions
- Still very ill with GVHD + infections

Question 4:

At this point you would

1. Restart blinatumomab + ponatinib
2. DLI/second transplant
3. Inotuzumab
4. CAR T
5. Other clinical trial
6. Refer to palliative care

Ponatinib restarted day 90

- Thereafter re-treated with blinatumomab + ponatinib . . .
- Achieved MRD– status in one cycle, and completed a subsequent cycle
- Counts did not recover to level of CRi; marrow remained hypocellular

- Progressive deterioration
- Never left hospital
- Recurrent gut GVHD
- *C. diff* enterocolitis
- Parainfluenza pneumonia?
- Hepatic failure with ascites
- Profound weight loss
- Died after 3 months

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Q&A

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Case-Based Panel Discussion: Management of Long- and Short-Term Toxicities

Discussion

Elias Jabbour
Fatih Demirkan
Andre Schuh
Josep-Maria Ribera

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Educational ARS Questions

Elias Jabbour

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Case 1: How I treat an older adult with ALL

Case: 67-year-old man presents to VA hospital with fatigue; also notes increasing bruising

History of heavy alcohol use; non-smoker

No family history of malignancy

Lives alone with a cat; former journalist

Exam: extensive cervical adenopathy, lungs clear, normal cardiac exam, no hepatosplenomegaly, occasional bruising, cranial nerves intact, normal musculoskeletal exam

Labs: WBC 3.3 (7 Segs/13 Lymph/1 Mono/79 blasts); Hgb 7.6, Platelets 19K

LDH = 483, LFTs, Bili – normal, Creatinine 0.8

Uric acid = 7.8

BM exam: 95% cellular; 90% blasts – CD10+, CD19+, CD22+, CD34+, HLA-DR+

Molecular diagnostics: BCR/ABL negative; FISH panel for Ph-like ALL negative

Cytogenetics: 9p deletion

Case 1

How do you treat this gentleman?

a) **HCVAD**
b) **Pediatric-inspired regimen**
c) **Palliative care**
d) **Mini-HCVD–inotuzumab–blinatumomab**
e) **CVP**

Case 2: How I treat an adult with relapsed ALL

- Mr K is a 20-year-old gentleman who presents with a 2-week history of fatigue, bleeding, and low-grade fevers
- Labs: WBC 2K/µL, Hgb 6.0 g/dL, platelets 20K/µL
- Bone marrow aspirate and biopsy: 70% blasts – CD10+, CD19+, CD20-, TdT+, CD34+, consistent with pre-B ALL
- Cytogenetics: normal
- He receives treatment with a pediatric regimen (C10403) and achieves CR with complete molecular remission (based on flow MRD)

Case 2

- He relapses 2 years later . . .
- Bone marrow aspirate/biopsy: 30% blasts – CD19+, CD20–, CD22+

How would you treat him at this point?

a) **Blinatumomab**
b) **CAR T cells**
c) **Inotuzumab**
d) **Salvage high-dose cytarabine**
e) **Mini-HCVD–inotuzumab–blinatumomab**

Case 3: How I treat ALL with positive MRD

Identification

Age	27
Sex	Female
Diagnosis	Ph-like B-cell ALL

Presentation at Time of Diagnosis

CBC	WBC count: 28,000/µL Hgb: 7.9 g/dL Platelet count: 32,000/µL
Blast count	78% peripheral and marrow blasts
Immunophenotype	CD10+, CD19+, CD20+, CD34+, TdT+
Karyotype/Mutations	IGH-CRLF2+

Treatment History

Received frontline treatment with HCVAD-R regimen

Achieved **complete remission** with normalization of blood counts after first block of induction therapy

Case 3

At what time points are MRD quantification prognostic for survival?

a) **End of induction (at CR)**
b) **After consolidation**
c) **Prior to allogeneic hematopoietic cell transplant**
d) **After transplant**
e) **All of the above**

Case 3

MRD at 3 months shows 0.22% residual ALL cells.
What is the best course of action at this point?

a) **Reinduction with asparaginase-containing regimen**
b) **Blinatumomab × 1–2 cycles followed by alloHCT**
c) **Inotuzumab × 1–2 cycles followed by alloHCT**
d) **Immediate alloHCT without additional interval treatment**
e) **CAR T cells**

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Closing remarks

Elias Jabbour

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Thank You!

- Please complete the **evaluation page** that will appear on your screen momentarily
- Your notes on the slides will be emailed to you by July 17
- The meeting recording and slides presented today will be shared on the globalleukemiaacademy.com website by July 17
- You will also receive a certificate of attendance by email by July 17

THANK YOU!

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