AMGEN

Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

24 July 2020

Virtual Breakout: Adult ALL Patients

APTITUDE HEALTH®

Global Leukemia Academy

Welcome and Meeting Overview

Elias Jabbour and Eduardo Rego

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Meet the Faculty

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

Eduardo Rego, MD, PhD
Professor in the Faculty of Medicine
Medical School of Ribeirão Preto
São Paulo, Brazil

Roberta Demichelis, MD
Assistant Professor in the Department
of Hematology/Oncology
INCMNSZ*
Mexico City, Mexico

Aaron Logan, MD, PhD
Associate Professor of Clinical
Medicine, Director Hematologic
Malignancies Tissue Bank
University of California, San Francisco
San Francisco, CA, USA

*INCMNSZ, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

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
17.00 – 17.15	Session opening • Educational ARS questions for the audience	Elias Jabbour, Eduardo Rego
17.15 – 17.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation • Q&A	Elias Jabbour
17.35 – 17.55	Current treatment options for relapsed ALL in adult and elderly patients • Presentation • Q&A	Aaron Logan
17.55 – 18.45	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in adult and elderly patients Panelists: Elias Jabbour, Eduardo Rego, Aaron Logan, Roberta Demichelis	Roberta Demichelis Eduardo Rego Discussion
18.45 – 19.00	Session close • Educational ARS questions for the audience	Elias Jabbour

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Educational ARS Questions

Elias Jabbour

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Q

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

Q

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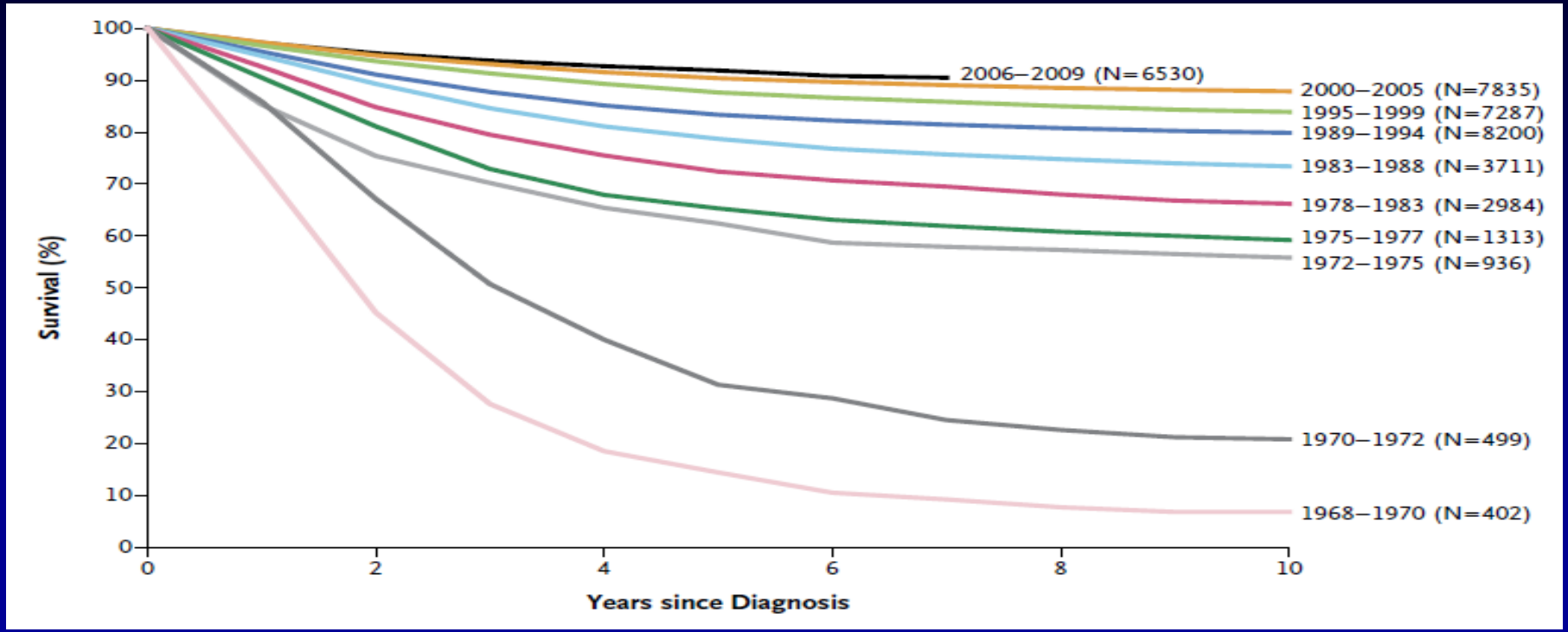
Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens

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

Summer 2020

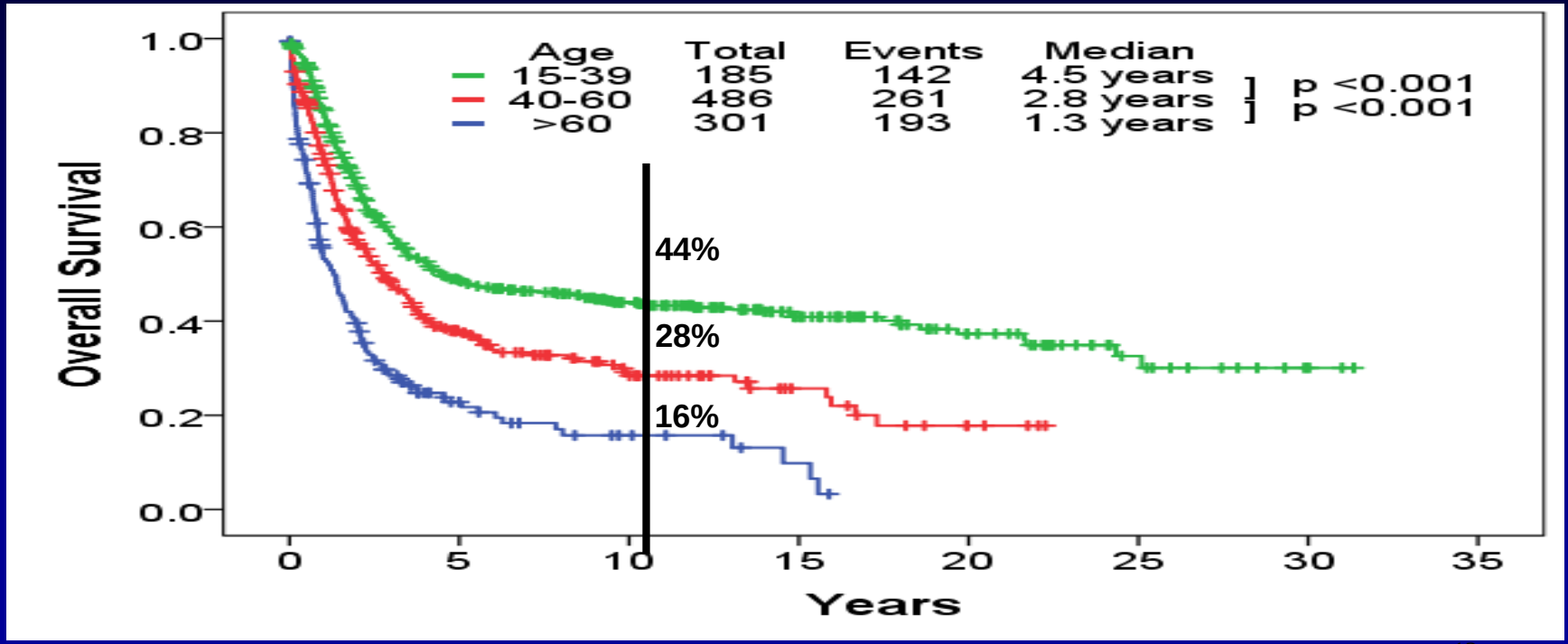
Survival of 39,697 Children With ALL Treated on Sequential CCG/COG Clinical Trials



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

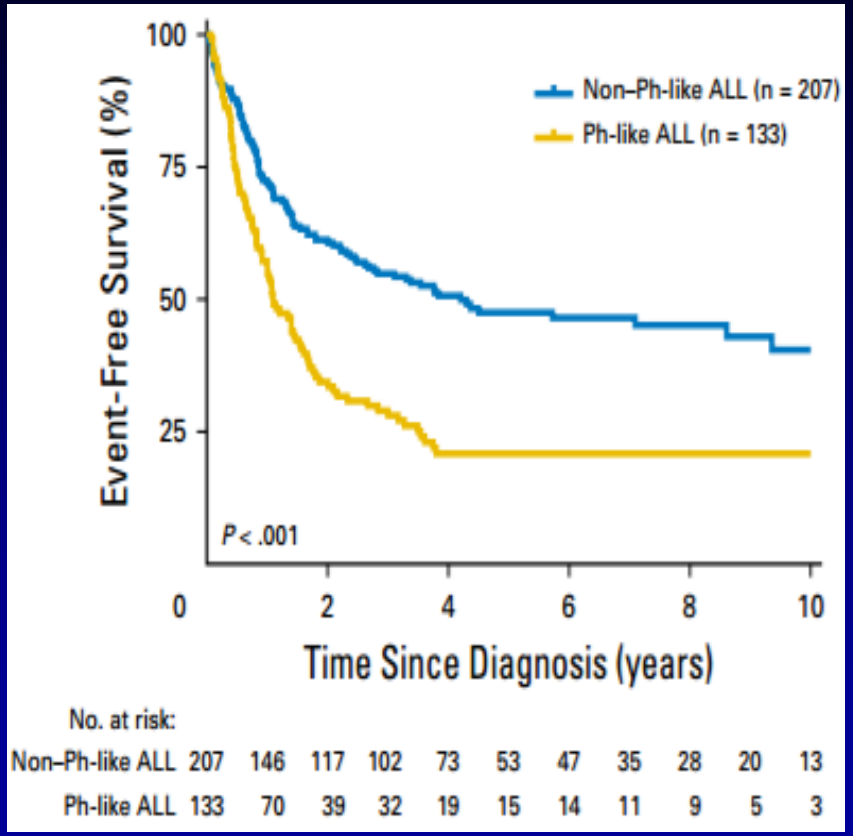
Survival of 972 Adults With Ph– ALL

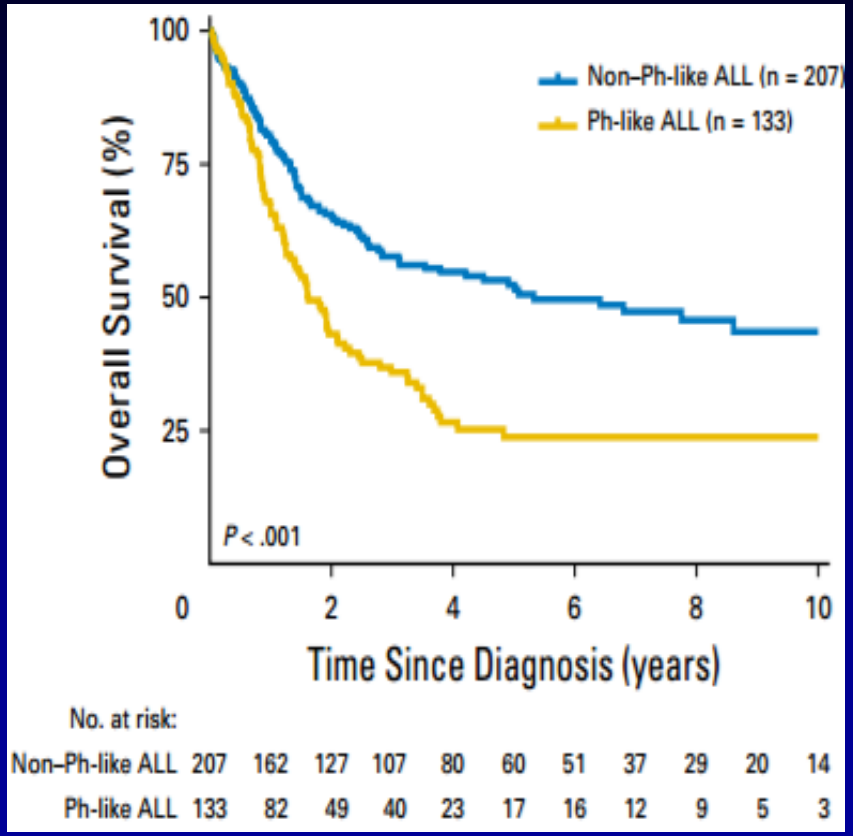
- 972 pts Rx 1980–2016; median F/U 10.4 years



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

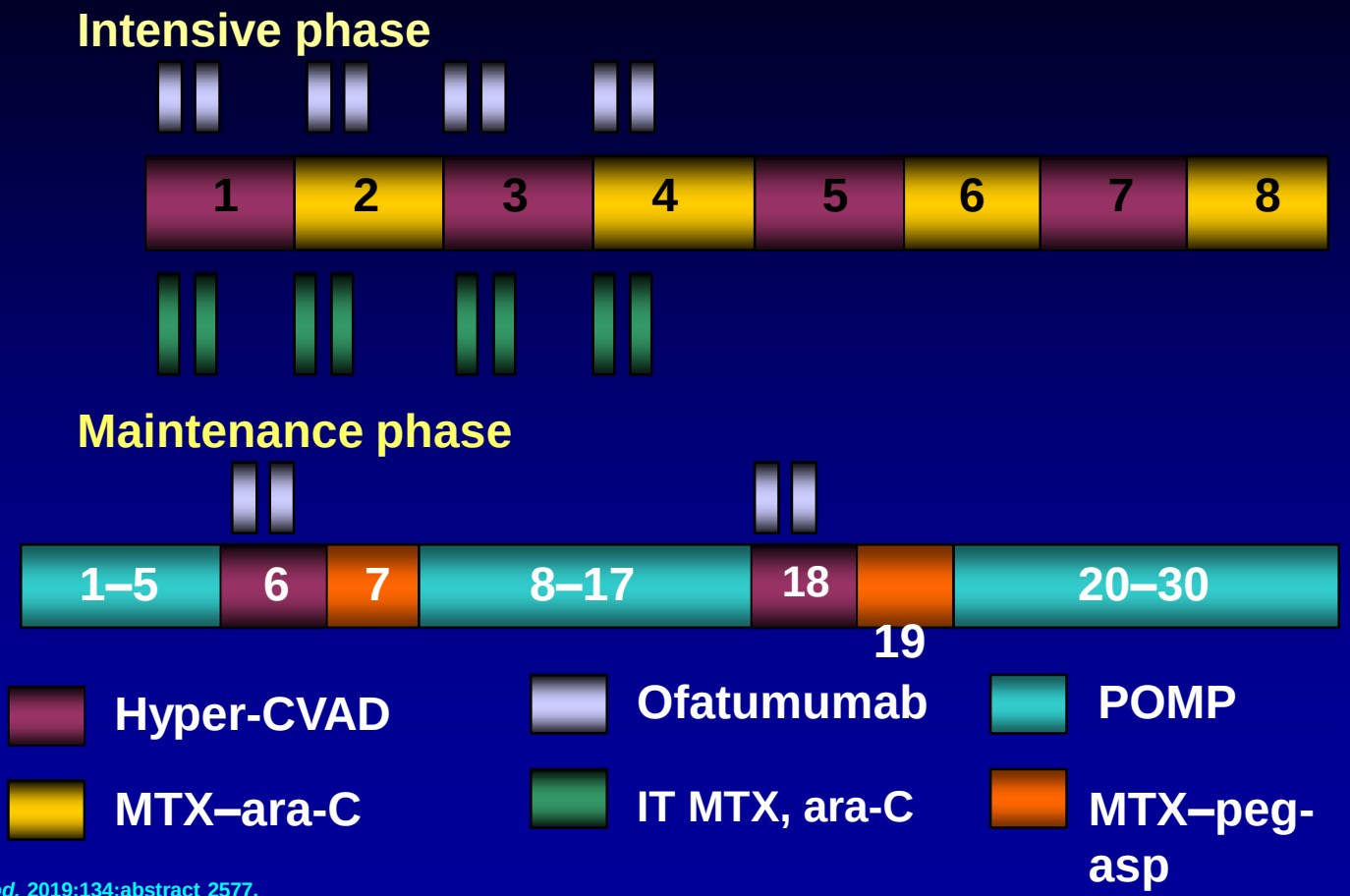
- Addition of TKIs to chemoRx in Ph+ ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Potential benefit of addition of CD19 bispecific antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- Eradication of MRD
- CAR T

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

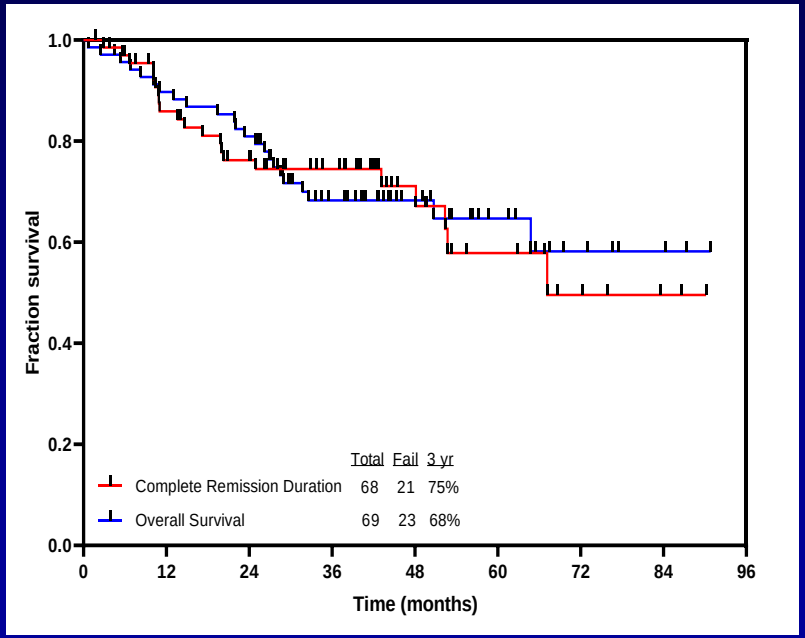


Richard-Carpentier. *Blood.* 2019;134:abstract 2577.

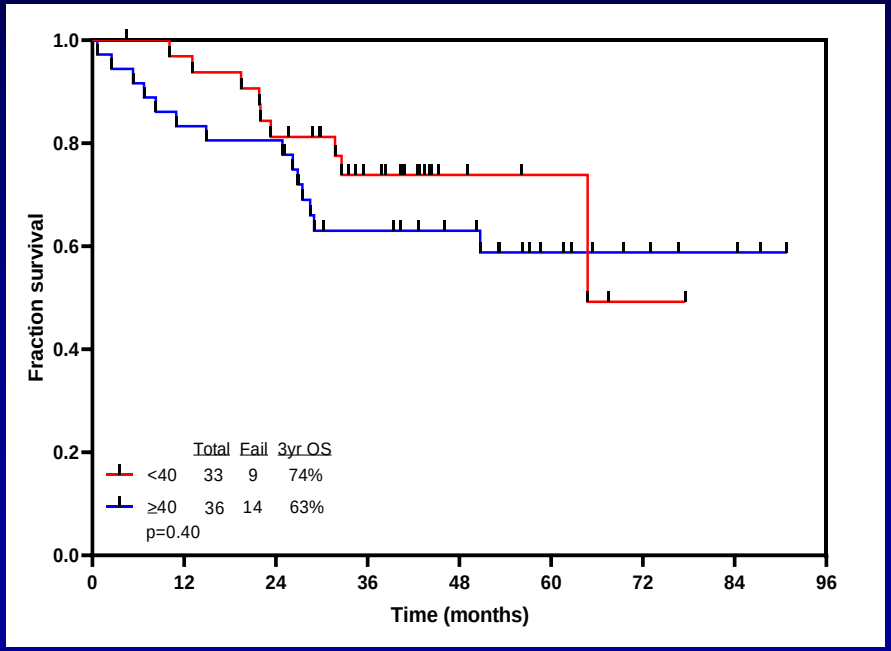
HCVAD + Ofatumumab: Outcome (N = 69)

- 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.

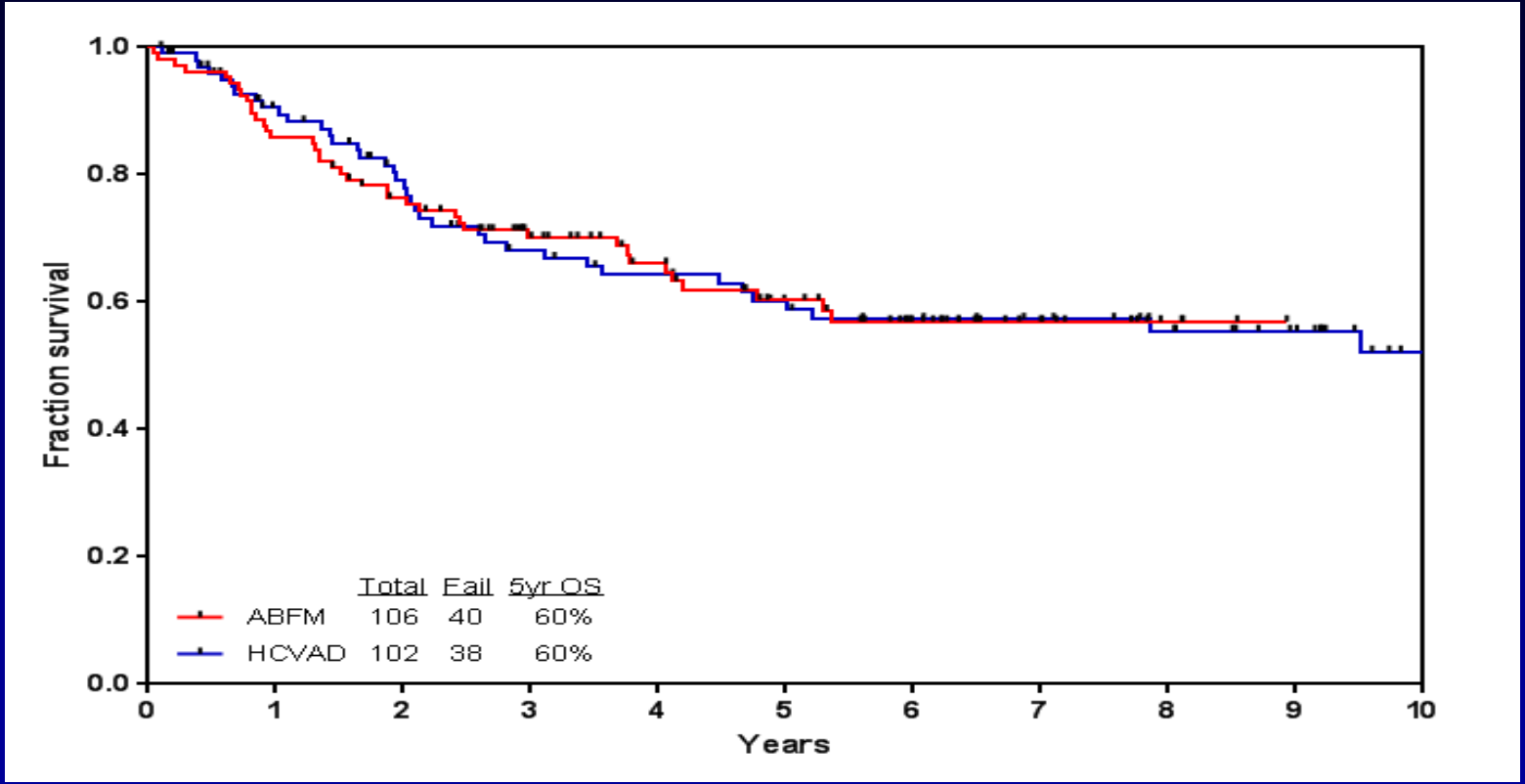
Comparison of HCVAD + Ofatumumab With CALGB 10403

- 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

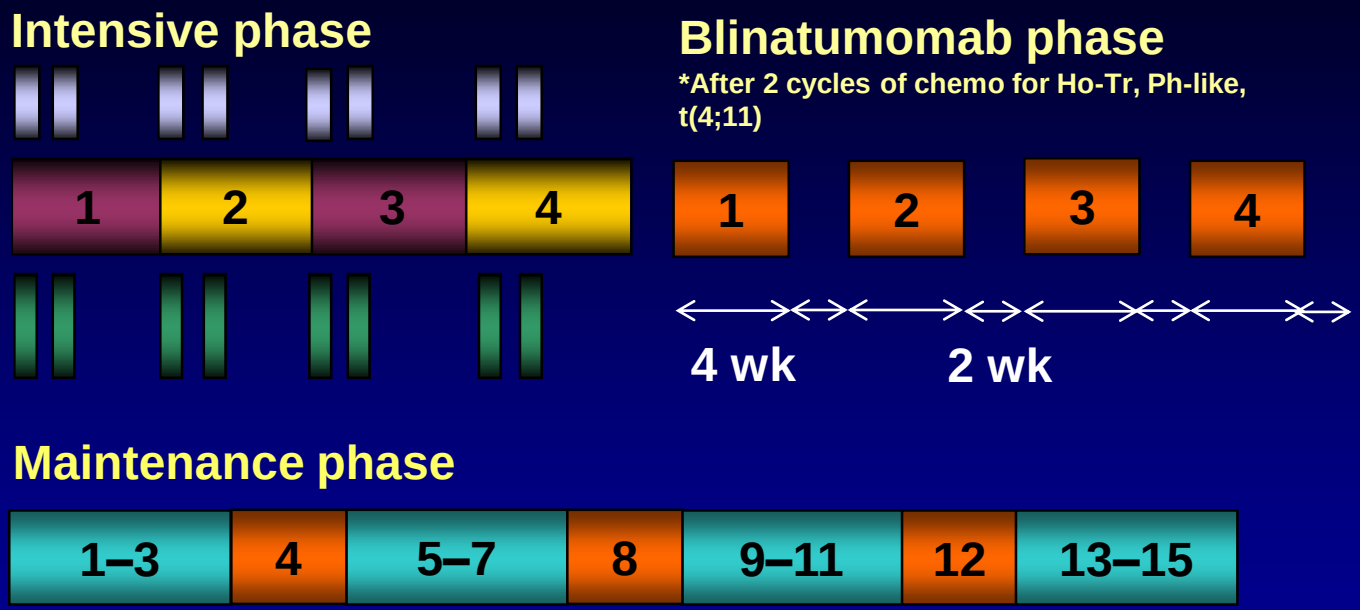
Stock. *Blood.* 2019.

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)

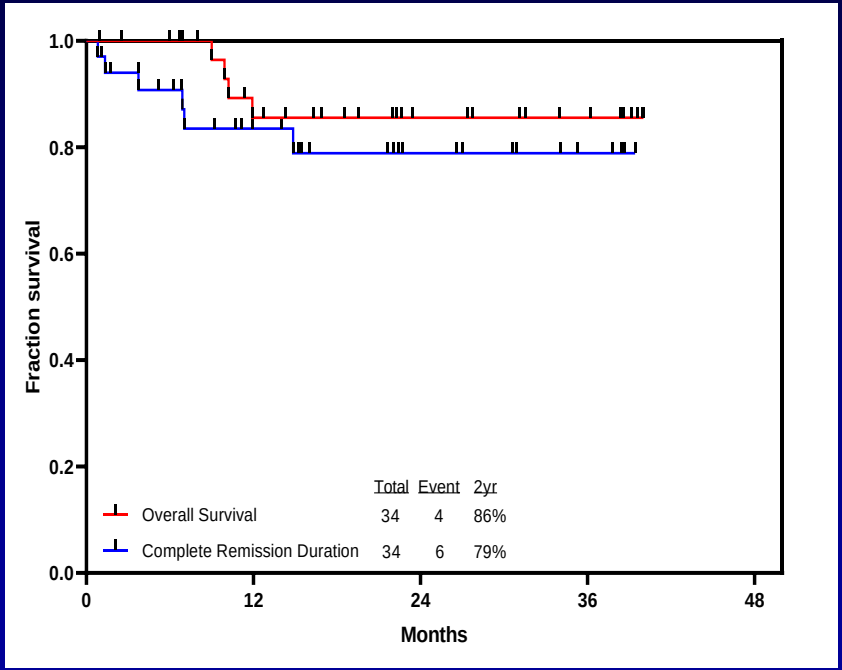
Characteristic (N = 34)		N (%) / Median [range]
Age (years)		36 [17–59]
Sex	Male	24 (71)
PS (ECOG)	0–1	28 (82)
WBC (× 10^9/L)		3.12 [0.5–360.9]
CNS disease		4 (12)
CD19 ≥50 %		27/28 (96)
CD20 ≥20 %		13/29 (45)
***TP53* mutation**		**9/33 (27)**
Ph-like CRLF2+		**6/30 (20)**
Cytogenetics	Diploid	11 (32)
	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.

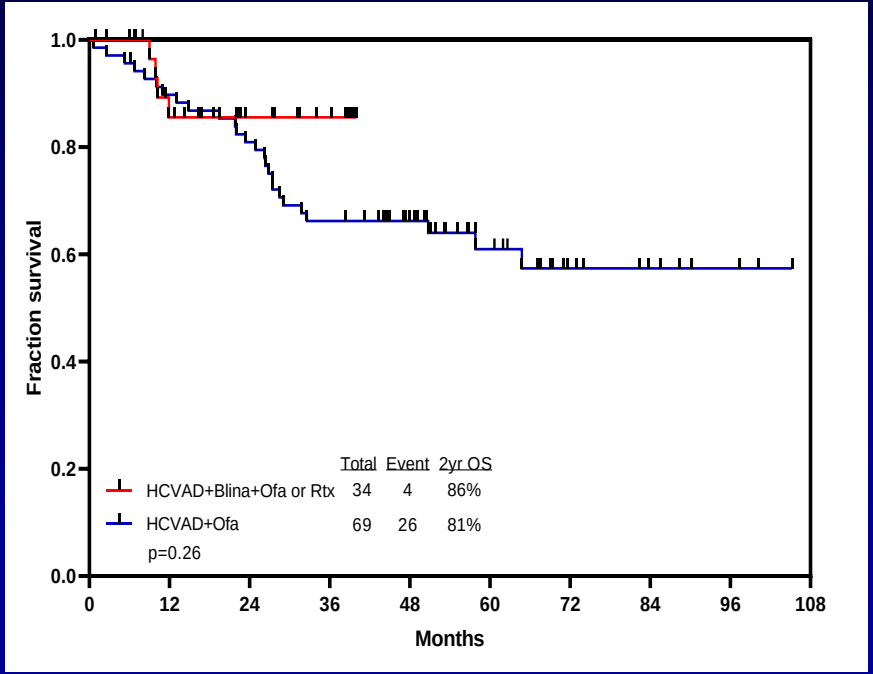
Hyper-CVAD + Blinatumomab in FL B-ALL (N = 34)

- 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.

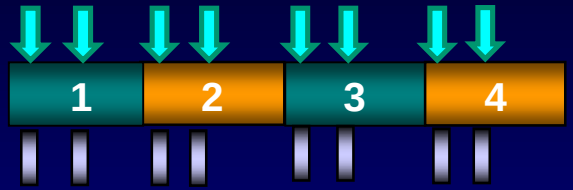
Older ALL: Historical Results

	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

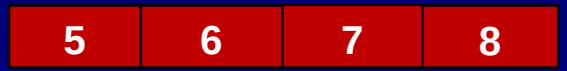
O'Brien. *Cancer.* 2008;113:2097; Gökbuget. *Blood.* 2013;122:1336; Li S. *Blood.* 2016;128:3981; Geyer. *Blood.* 2017;129:1878.

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

Intensive phase



Consolidation phase



Maintenance phase

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
C2–4	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)**

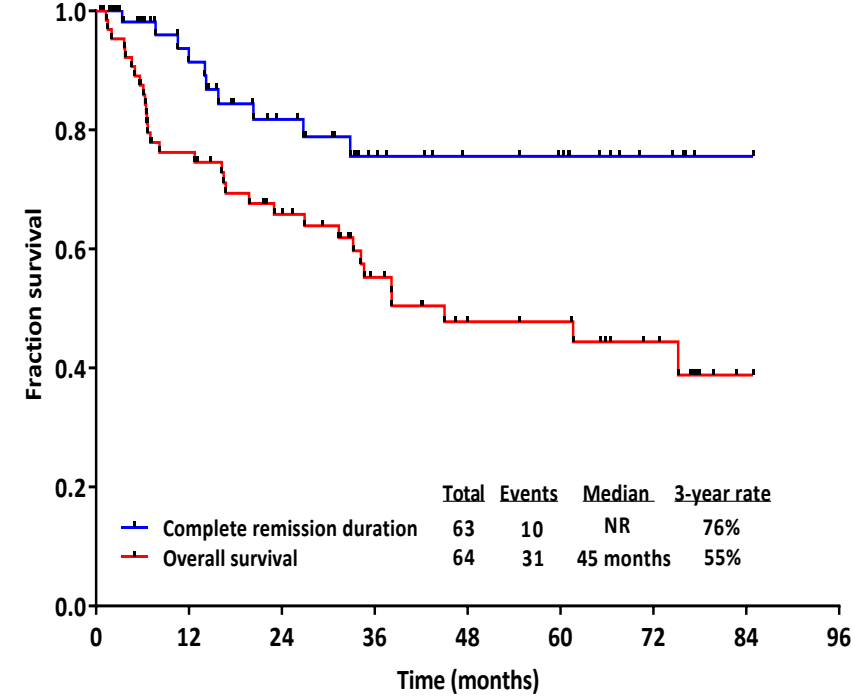
Response (N = 59)	N (%)
ORR	**58 (98)**
CR	51 (86)
CRp	6 (10)
CRi	1 (2)
No response	1 (2)
Early death	**0**

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

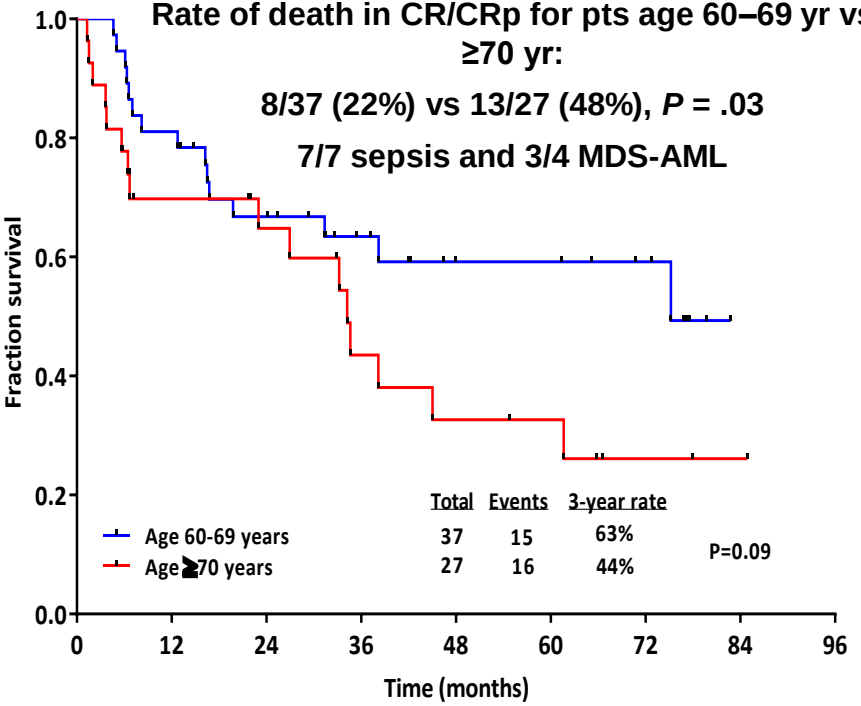
Short. *Blood.* 2019;134:abstract 823.

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

CRD and OS overall



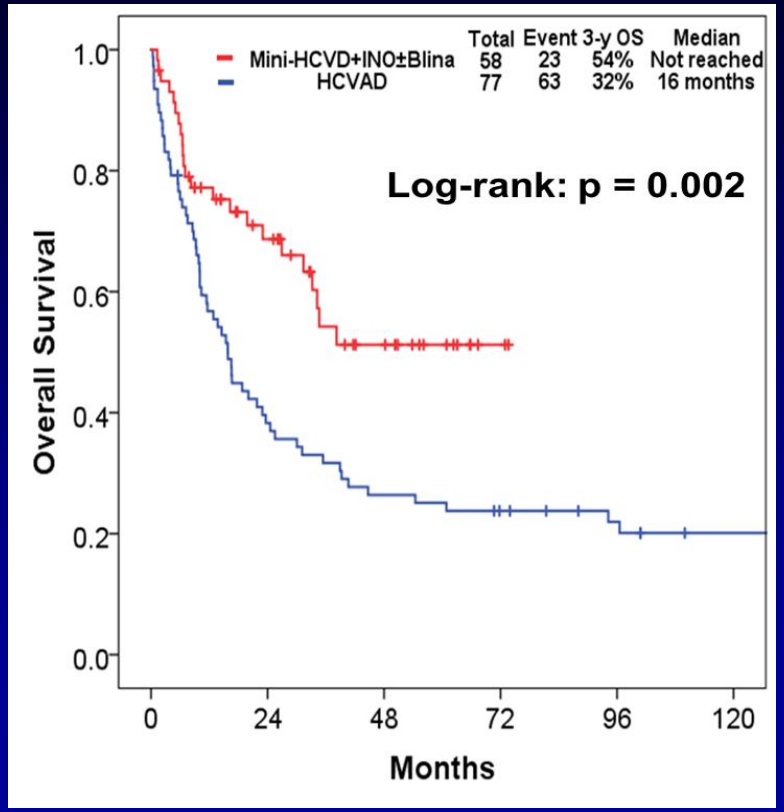
OS by age



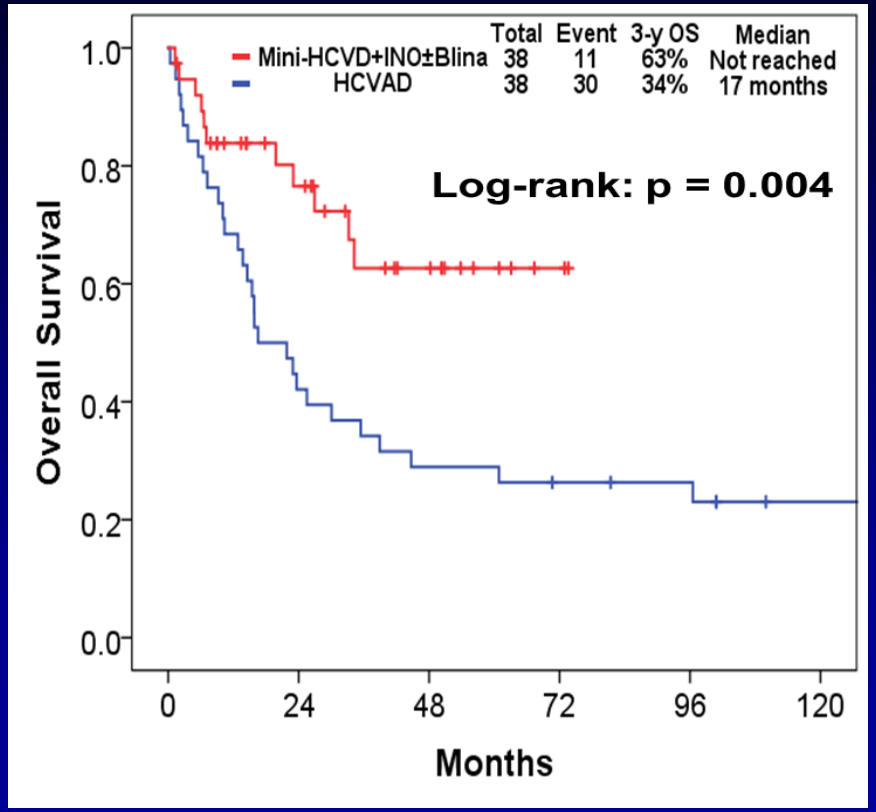
Short. *Blood.* 2019;134:abstract 823.

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

Prematched

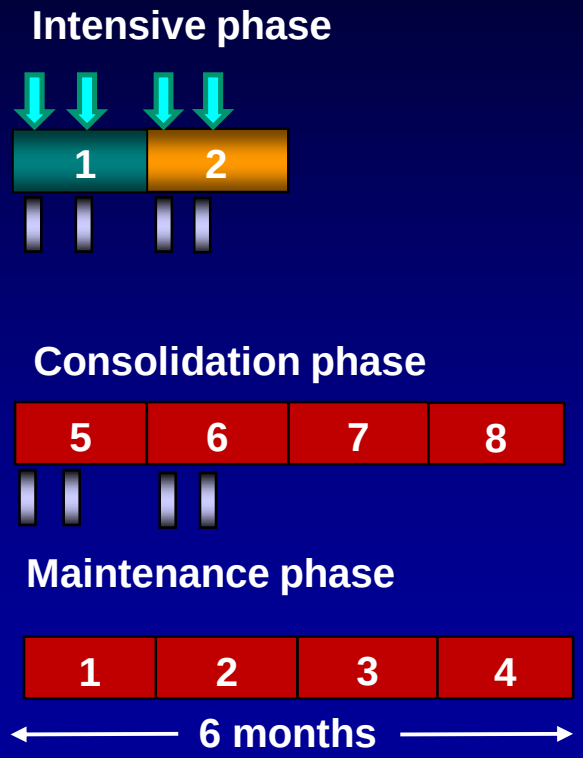


Matched



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

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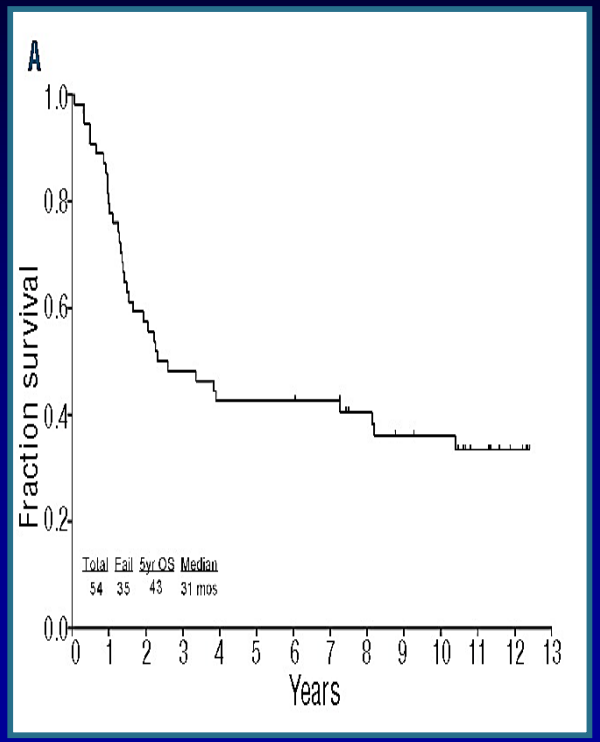
Total ino dose = 1.5 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis.

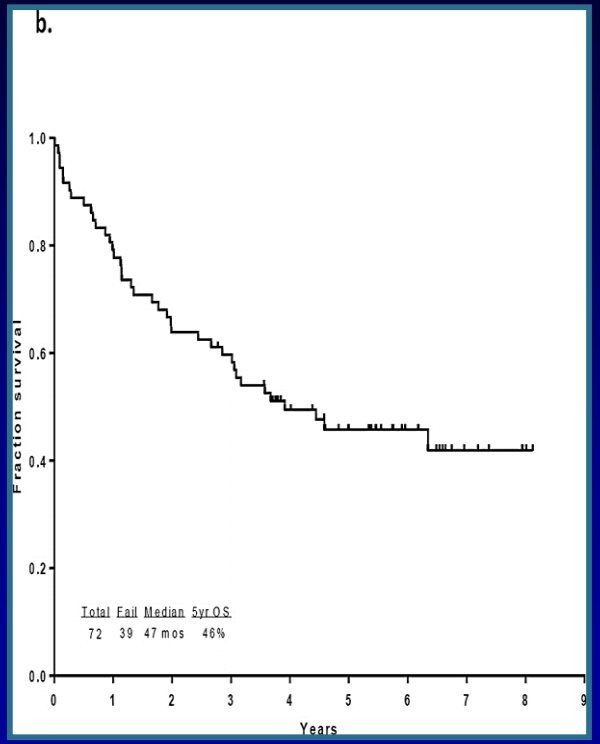
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Kantarjian H, et al. *Lancet Oncol.* 2018;19:240.

TKI for Ph+ ALL

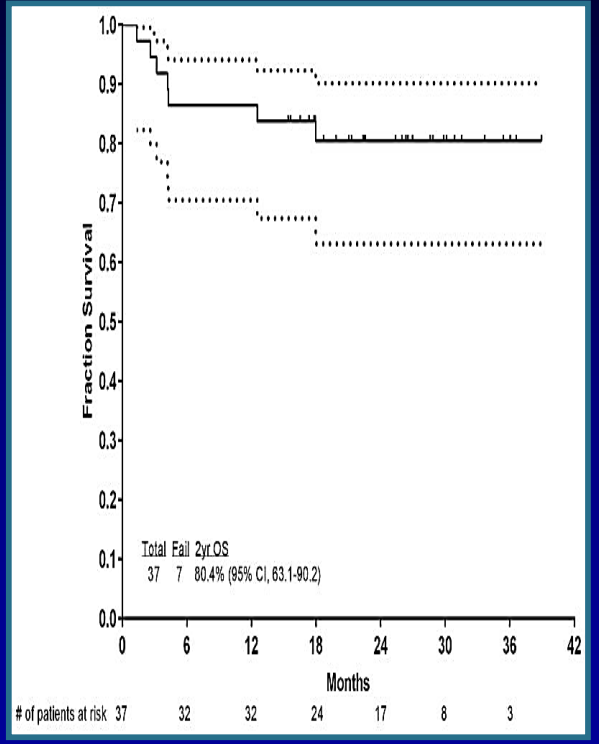
Imatinib: 5-yr OS = 43%



Dasatinib: 5-yr OS = 46%

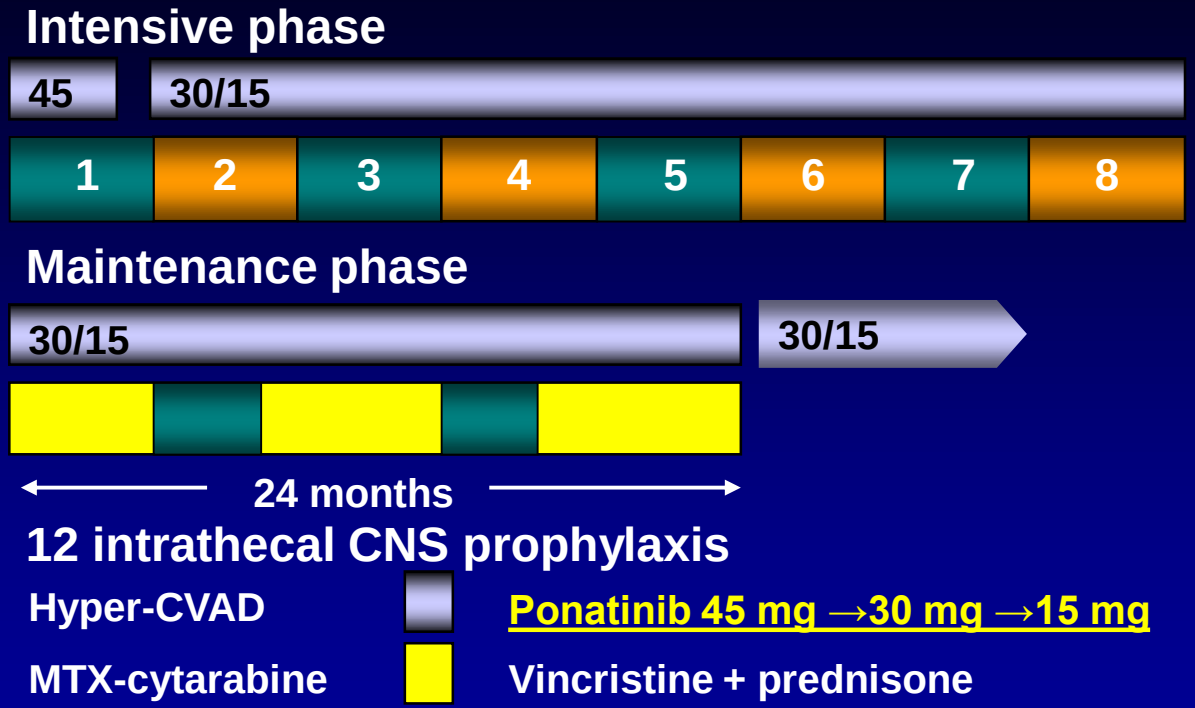


Ponatinib: 5-yr OS = 71%



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

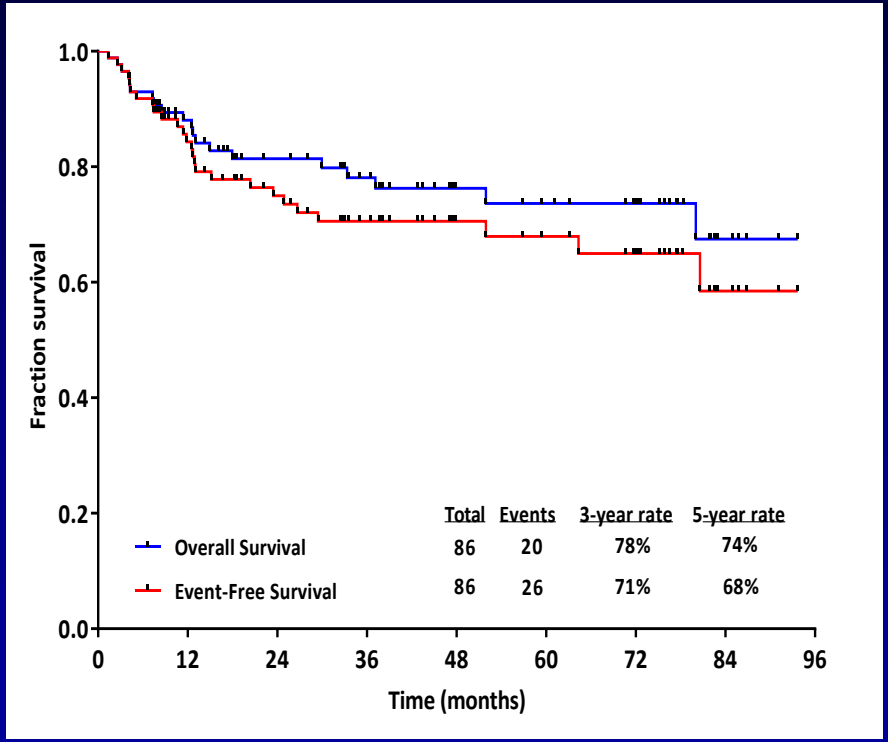
Median follow-up: 44 months (4–94 months)

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

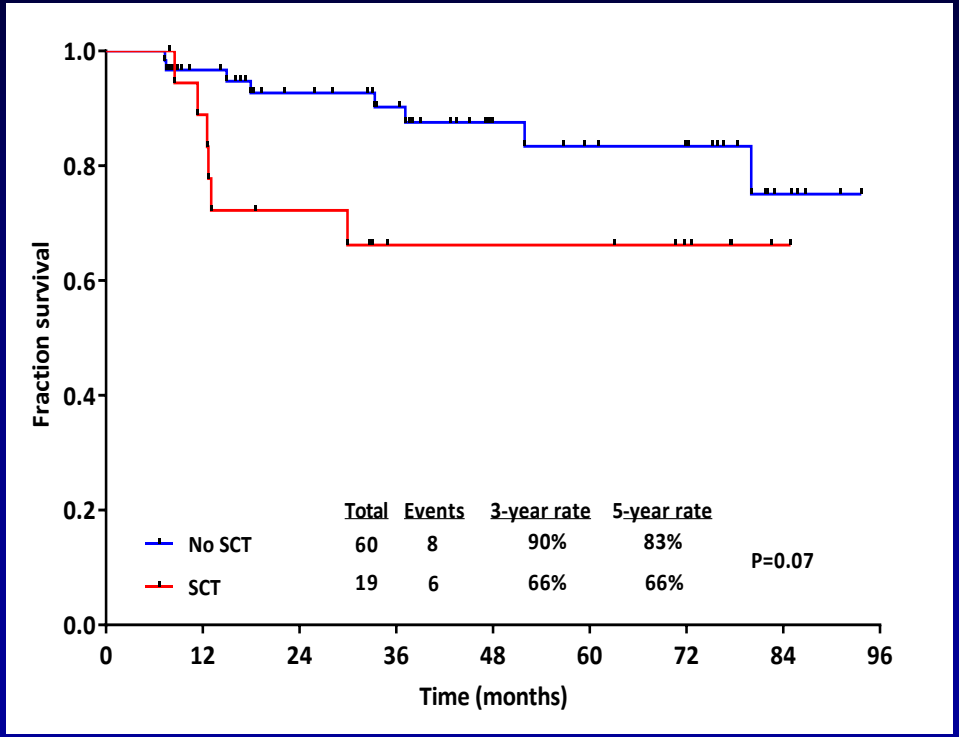
Short. *Blood*. 2019;134:abstract 283.

Hyper-CVAD + Ponatinib in Ph+ ALL: Outcome

EFS and OS



Impact of allo-SCT: 6-mo landmark

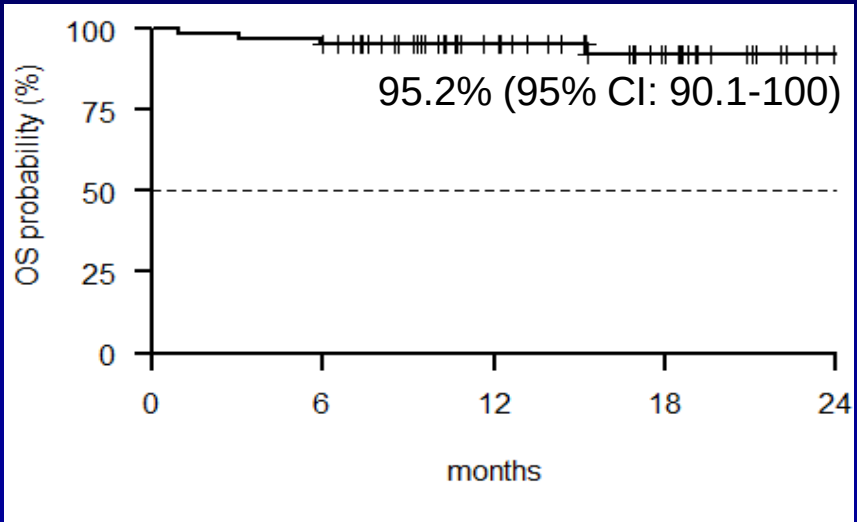


Short. *Blood*. 2019;134:abstract 283.

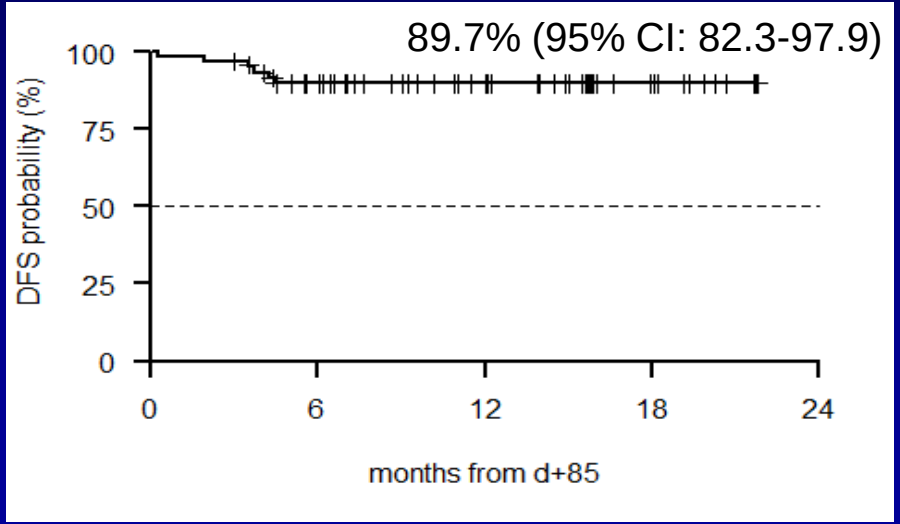
Dasatinib-Blinatumomab in Ph+ ALL

- 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

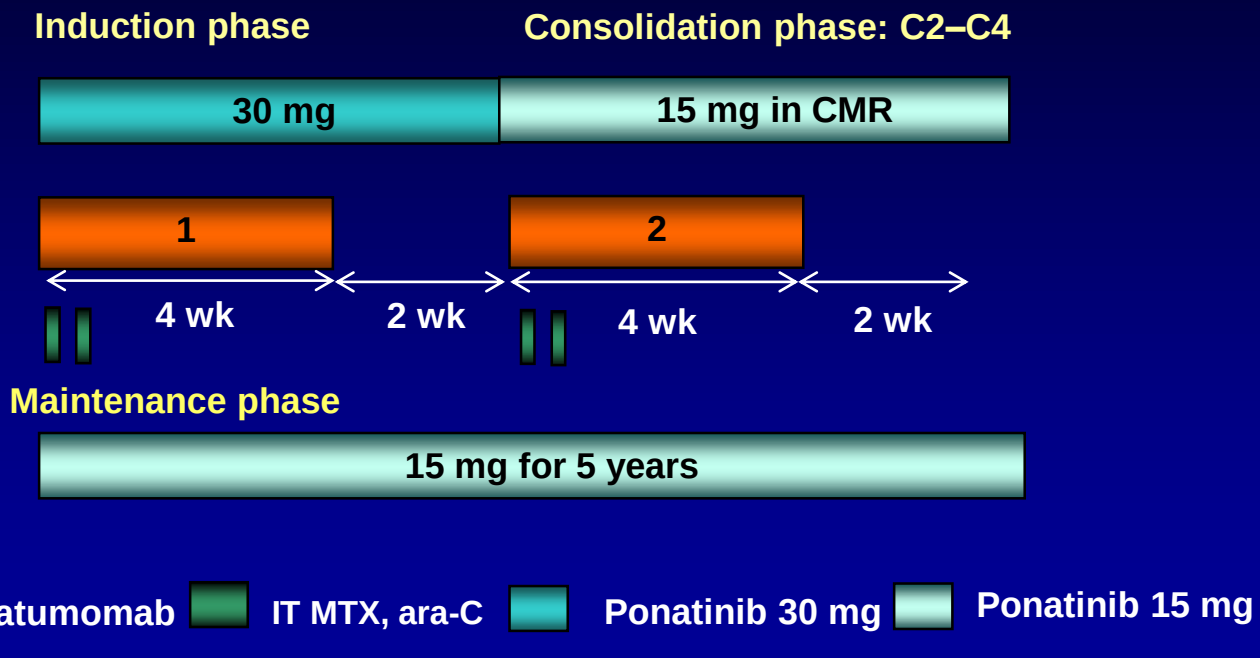


DFS



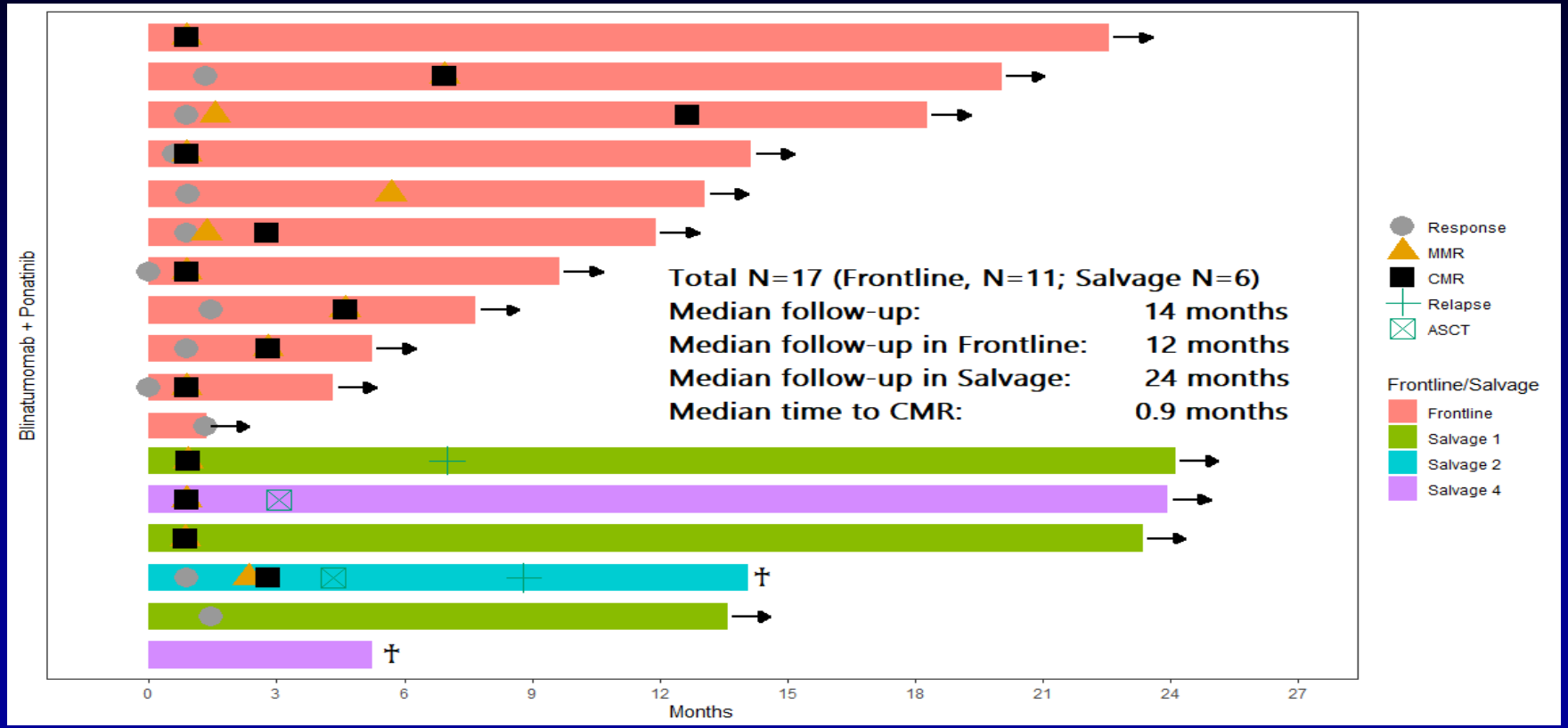
Chiaretti. *Blood.* 2019;134:abstract 615.

Blinatumomab-Ponatinib in Ph+ ALL



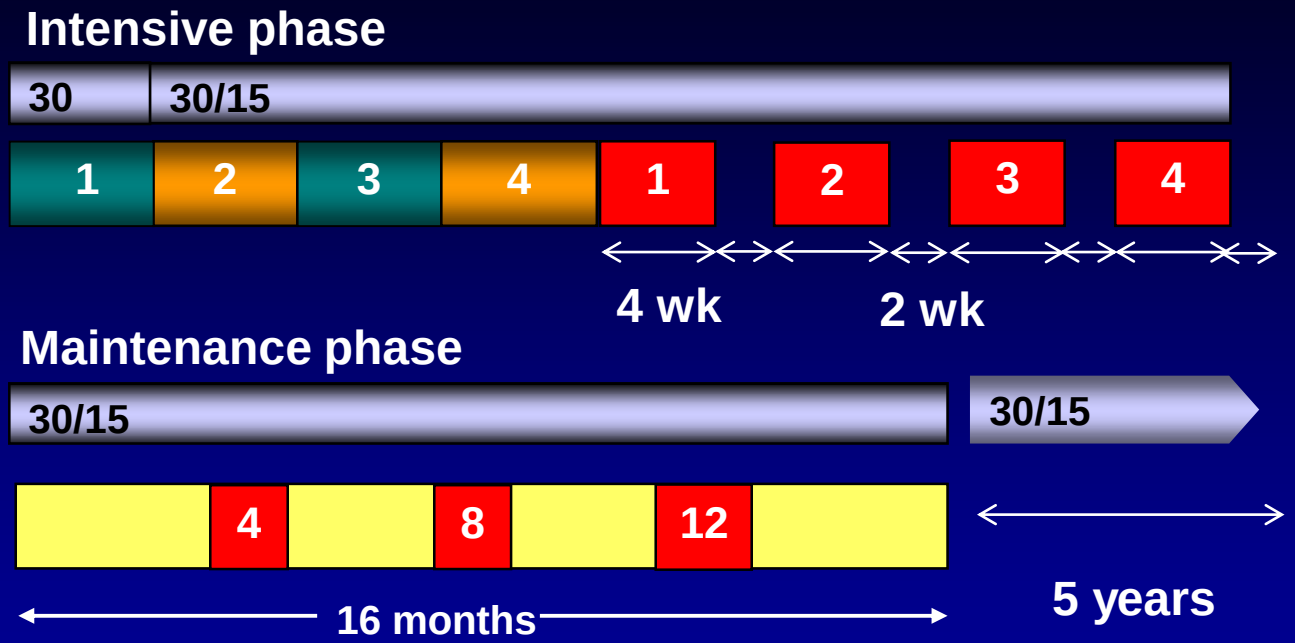
Assi. *Clin Lymphoma Myeloma Leuk.* 2017;17(12):897-901.

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

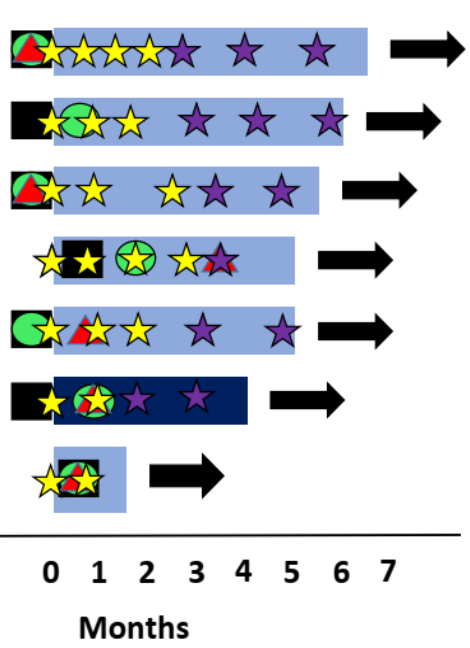
Vincristine + prednisone

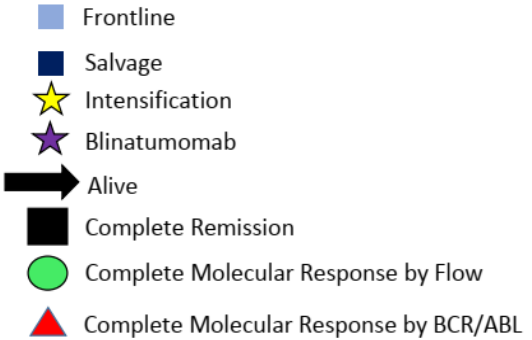
Blinatumomab

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.

Q

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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Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Current Treatment Options for Relapsed ALL in Adult and Elderly Patients

Aaron Logan

APTITUDE HEALTH®

UCSF Helen Diller Family Comprehensive Cancer Center

Current Treatment Options for Relapsed Ph negative ALL in Adults and Elderly Patients

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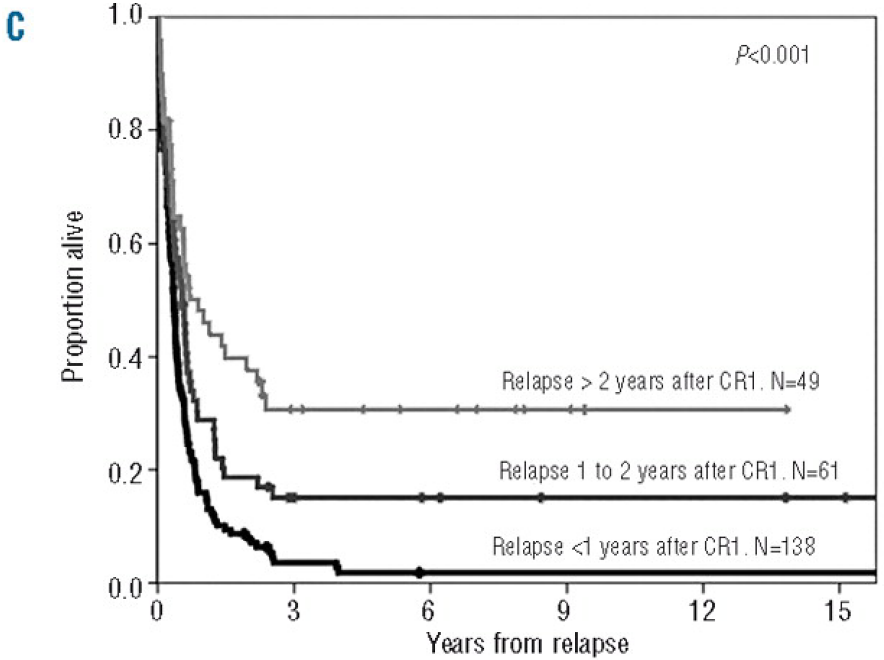
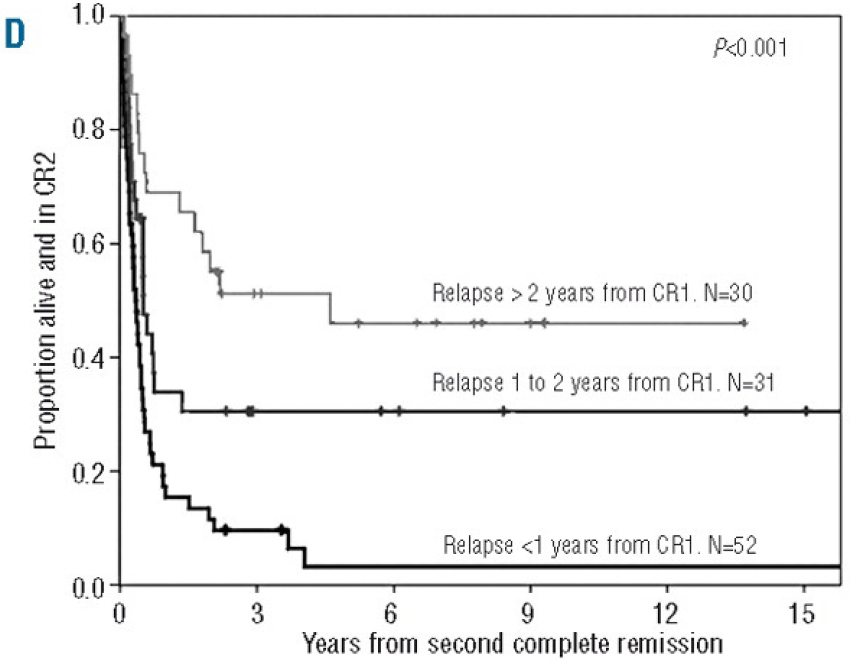
Management of Relapsed/Refractory Adult ALL Patients





Oriol, et al. Haematologica. 2010;95:589-596.

Treatment for 29 y/o Female With Relapsed ALL?

Q.

a. Reinduce with hCVAD and continue until alloHCT

b. Blinatumomab until alloHCT

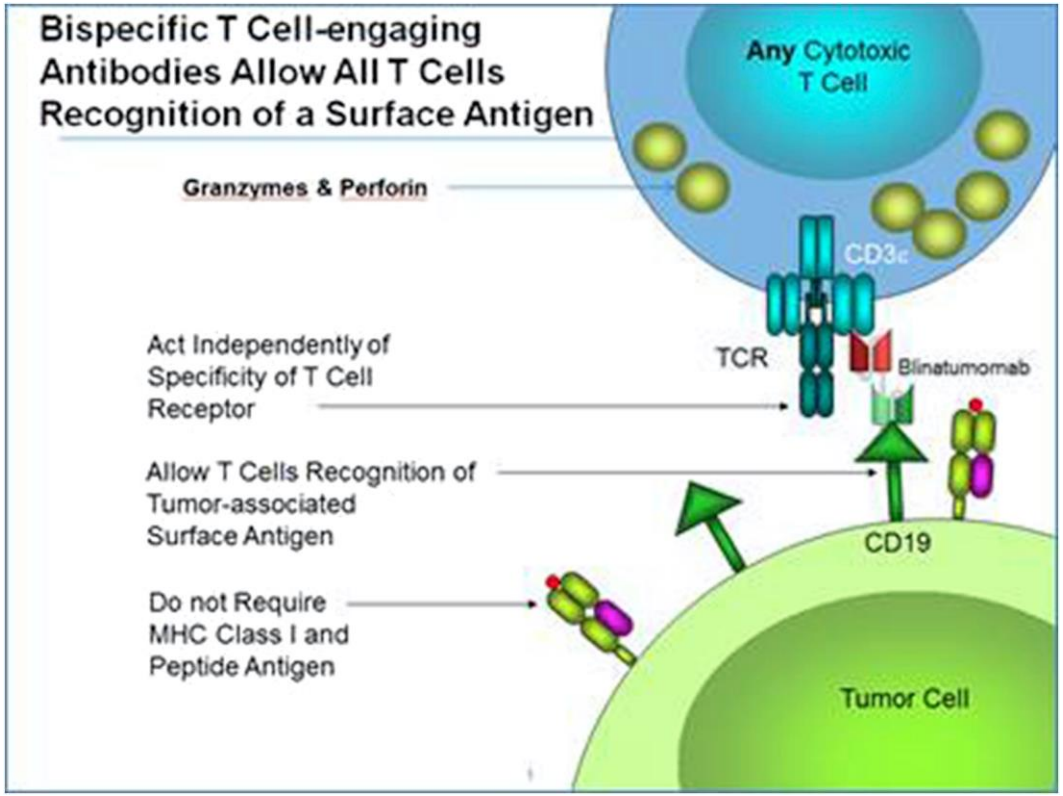
c. Debulk with one cycle of hCVAD followed by blinatumomab until alloHCT

d. Inotuzumab until alloHCT

e. CAR T cells then alloHCT

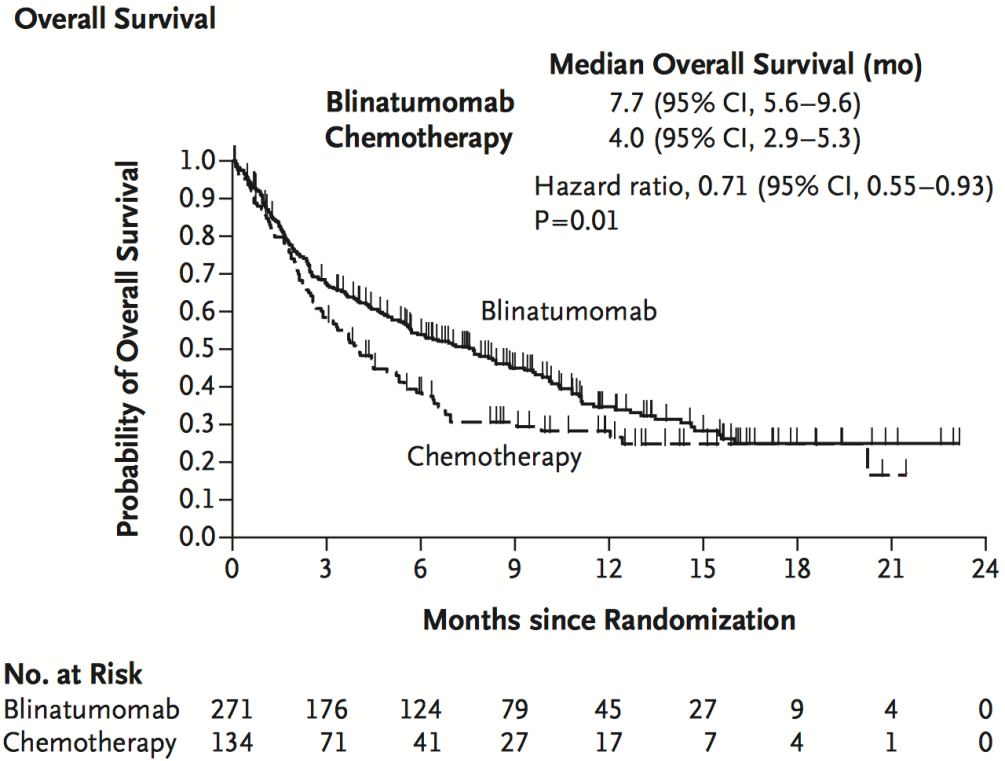
f. CAR T cells without alloHCT

Blinatumomab: Bispecific T-Cell Engager (BiTE) Therapy



Advani A. *Best Pract Res Clin Haematol.* 2015;28:116-123.

Treatment of Relapsed/Refractory ALL – Blinatumomab

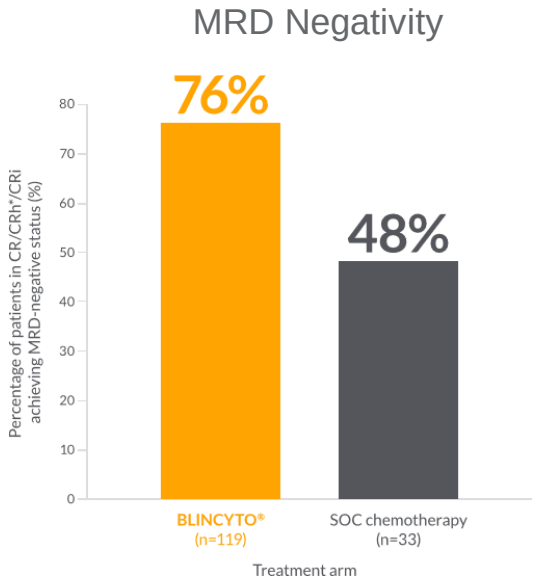


Advani A. *Best Pract Res Clin Haematol.* 2015;28:116-123; Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Treatment of Relapsed/Refractory ALL – Blinatumomab

Table 2. Best Hematologic Response Within 12 Weeks after Treatment Initiation.*

Response Category	Blinatumomab Group (N=271)		Chemotherapy Group (N=134)		Treatment Difference (95% CI)	P Value†
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	*percentage points*	
Complete remission with full hematologic recovery	91	33.6 (28.0–39.5)	21	15.7 (10.0–23.0)	17.9 (9.6–26.2)	<0.001
Complete remission with full, partial, or incomplete hematologic recovery	119	43.9 (37.9–50.0)	33	24.6 (17.6–32.8)	19.3 (9.9–28.7)	<0.001
Complete remission with partial hematologic recovery	24	8.9 (5.8–12.9)	6	4.5 (1.7–9.5)		
Complete remission with incomplete hematologic recovery	4	1.5 (0.4–3.7)	6	4.5 (1.7–9.5)		

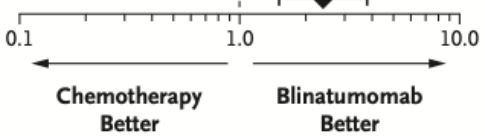


Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Treatment of Relapsed/Refractory ALL – Blinatumomab

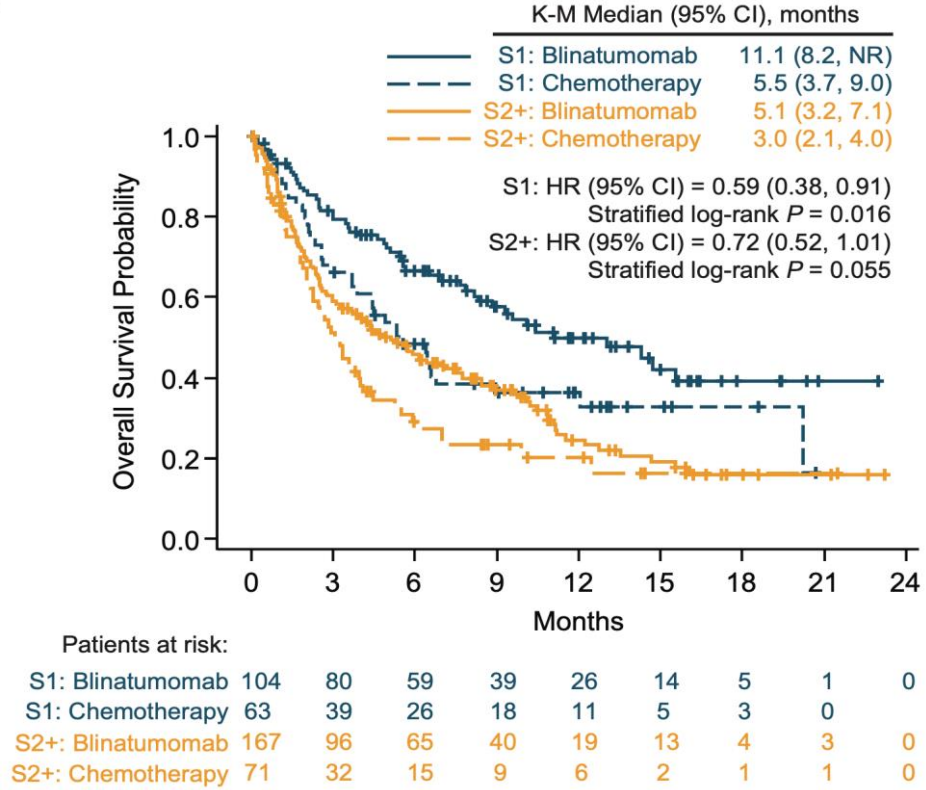
B **Prespecified Subgroup Analysis of Remission Rate**

Subgroup	Blinatumomab	Chemotherapy	Odds Ratio (95% CI)
	no. of events/no. of patients (%)		
Age			
<35 yr	53/123 (43.1)	15/60 (25.0)	2.27 (1.15–4.50)
≥35 yr	66/148 (44.6)	18/74 (24.3)	2.50 (1.34–4.66)
Salvage-treatment phase			
First	60/114 (52.6)	23/65 (35.4)	2.03 (1.08–3.80)
Second	36/91 (39.6)	7/43 (16.3)	3.37 (1.35–8.38)
Third or later	23/66 (34.8)	3/26 (11.5)	4.10 (1.11–15.12)
Previous allogeneic stem-cell transplantation			
Yes	38/94 (40.4)	5/46 (10.9)	5.56 (2.02–15.36)
No	81/177 (45.8)	28/88 (31.8)	1.81 (1.06–3.09)
Bone marrow blasts			
<50%	55/84 (65.5)	13/38 (34.2)	3.65 (1.63–8.17)
≥50%	64/186 (34.4)	20/96 (20.8)	1.99 (1.12–3.55)
Overall	119/271 (43.9)	33/134 (24.6)	2.40 (1.51–3.80)



Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Blinatumomab TOWER Study — Results Best in 1st Salvage



Dombret, et al. *Leuk Lymphoma.* 2019;60:2214-2222.

Treatment of Relapsed/Refractory ALL – Blinatumomab

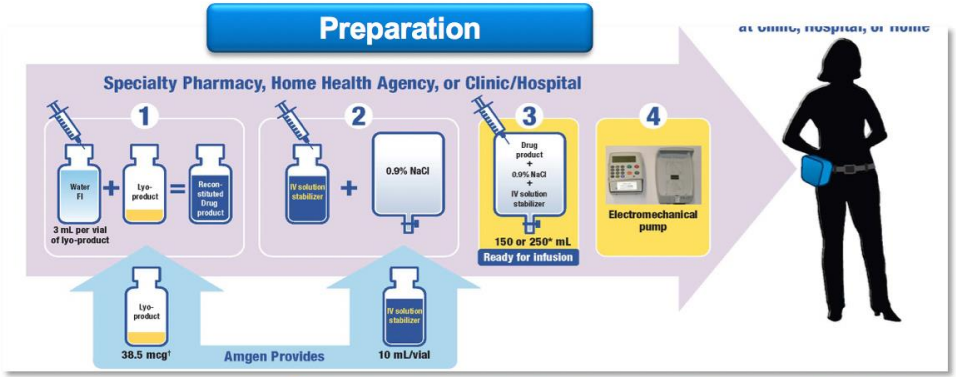
Table 3. Adverse Events.*

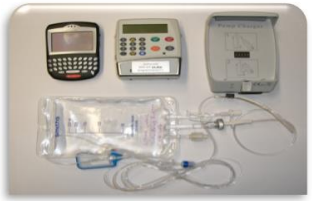
Event	Blinatumomab Group (N=267)	Chemotherapy Group (N=109)
	no. of patients (%)	
Any adverse event	263 (98.5)	108 (99.1)
Event leading to premature discontinuation of trial treatment	33 (12.4)	9 (8.3)
Serious adverse event	165 (61.8)	49 (45.0)
Fatal serious adverse event	51 (19.1)	19 (17.4)
Any adverse event of grade ≥3	231 (86.5)	100 (91.7)
Grade ≥3 adverse event of interest reported in at least 3% of patients in either group		
Neutropenia	101 (37.8)	63 (57.8)
Infection	91 (34.1)	57 (52.3)
Elevated liver enzyme	34 (12.7)	16 (14.7)
Neurologic event	25 (9.4)	9 (8.3)
Cytokine release syndrome	13 (4.9)	0
Infusion reaction	9 (3.4)	1 (0.9)
Lymphopenia	4 (1.5)	4 (3.7)
Any decrease in platelet count	17 (6.4)	13 (11.9)
Any decrease in white-cell count	14 (5.2)	6 (5.5)

* Data are summarized for all patients who received at least one dose of trial treatment.

Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Treatment of Relapsed/Refractory ALL – Blinatumomab





CIV Administration via Pump

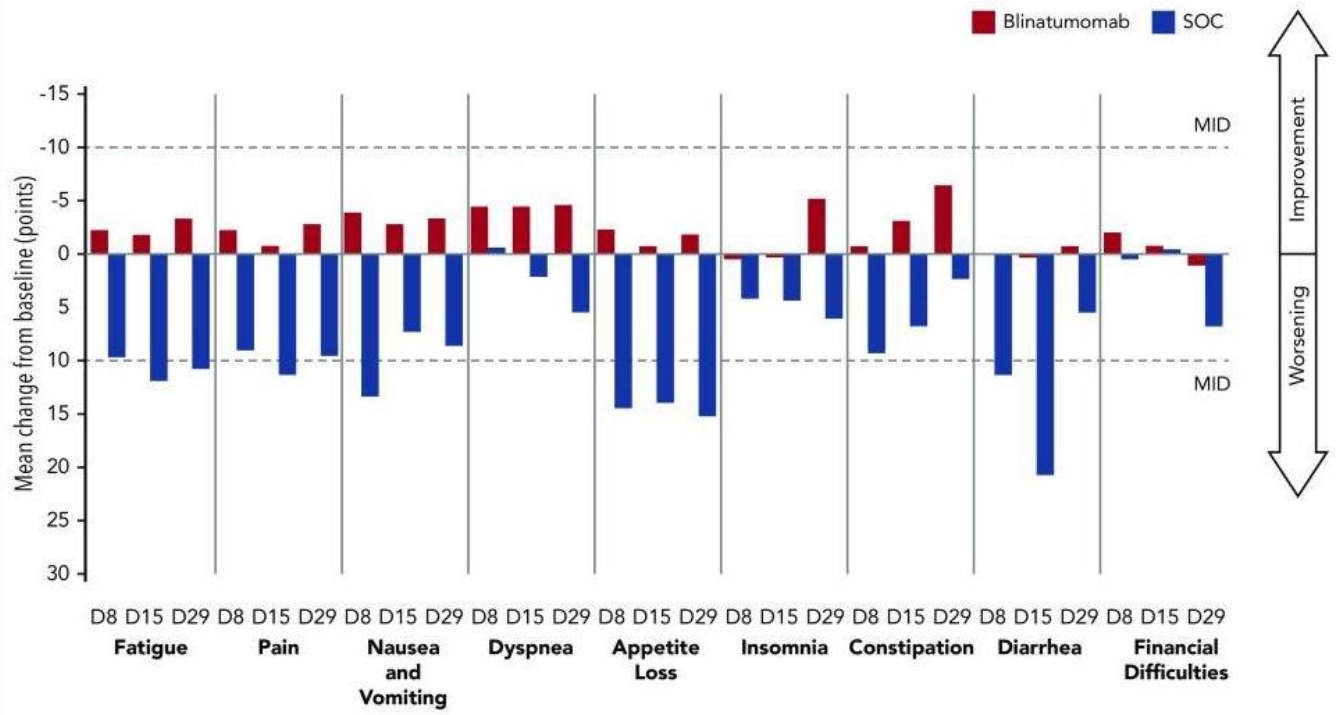
Overview of key steps and HCP involvement		CYCLE 1	CYCLE 2 +
4 WEEKS ON THERAPY: BLINATUMOMAB	Hospital-based treatment • Hospital/specialty pharmacist • Infusion nurse • Floor nurses • Attending hem/onc	DAYS 1-9	DAYS 1-2
q24H q48H q96H (EU)	Potential for outpatient treatment Physician will determine: 1) If outpatient administration via ambulatory pump is viable 2) Frequency of observation required	DAYS 10-28	DAYS 3-28
2 WEEKS OFF THERAPY	Rest period 2 weeks	DAYS 29-42	DAYS 29-42

*In study 205, the bag change frequency was 24–48 hours in the US and 96 hours in EU.

BLINCYTO (blinatumomab) [prescribing information]. Thousand Oaks, CA: Amgen Inc. 2016 DRAFT.

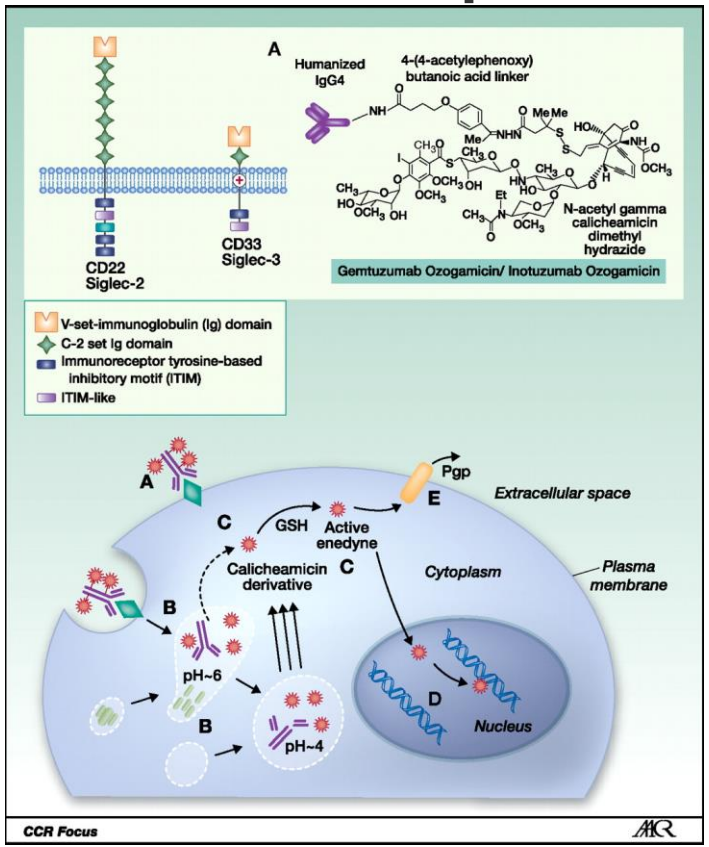
AMGEN Oncology

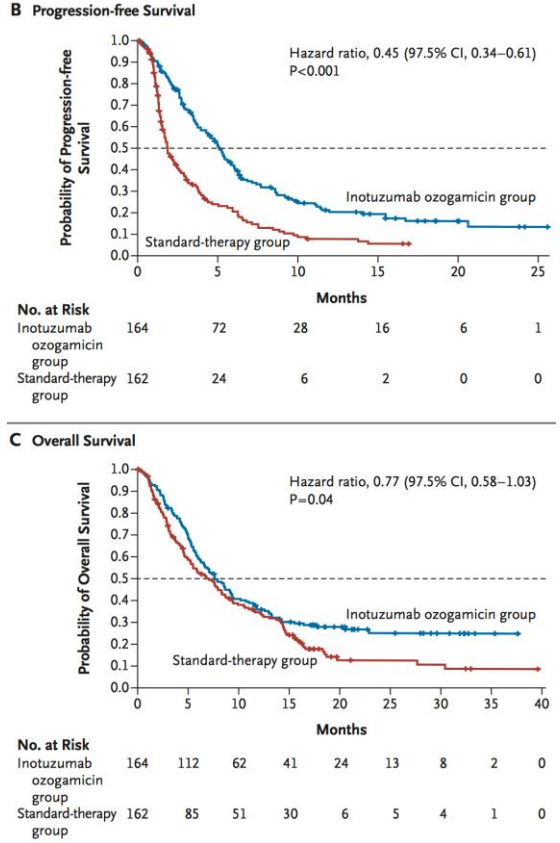
Blinatumomab TOWER Study – Health-Related QOL



Topp M, et al. *Blood.* 2018;131:2906-2914.

Treatment of Relapsed/Refractory ALL – Inotuzumab





Ricart. *Clin Cancer Res.* 2011;17:6417-6427; Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753.

Treatment of Relapsed/Refractory ALL – Inotuzumab

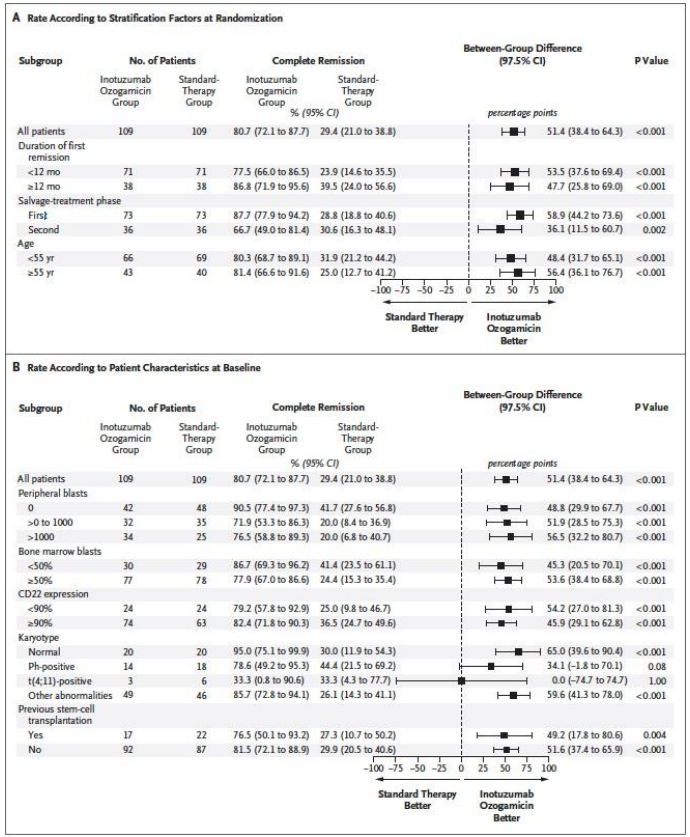


Table 2. Trial End Points in the Remission-Analysis Population.*

End Point	Inotuzumab Ozogamicin Group		Standard-Therapy Group		Between-Group Difference (97.5% CI)	P Value†
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*percentage points*	
Complete remission or complete remission with incomplete hematologic recovery						
Total	88/109	80.7 (72.1–87.7)	32/109	29.4 (21.0–38.8)	51.4 (38.4–64.3)	<0.001
Bone marrow blast results below threshold for minimal residual disease	69/88	78.4 (68.4–86.5)	9/32	28.1 (13.7–46.7)	50.3 (29.9–70.6)	<0.001
Complete remission						
Total	39/109	35.8 (26.8–45.5)	19/109	17.4 (10.8–25.9)	18.3 (5.2–31.5)	0.002
Bone marrow blast results below threshold for minimal residual disease	35/39	89.7 (75.8–97.1)	6/19	31.6 (12.6–56.6)	58.2 (31.9–84.4)	<0.001
Complete remission with incomplete hematologic recovery						
Total	49/109	45.0 (35.4–54.8)	13/109	11.9 (6.5–19.5)	33.0 (20.3–45.8)	<0.001
Bone marrow blast results below threshold for minimal residual disease	34/49	69.4 (54.6–81.7)	3/13	23.1 (5.0–53.8)	46.3 (16.2–76.4)	0.004

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

Treatment of Relapsed/Refractory ALL – Inotuzumab

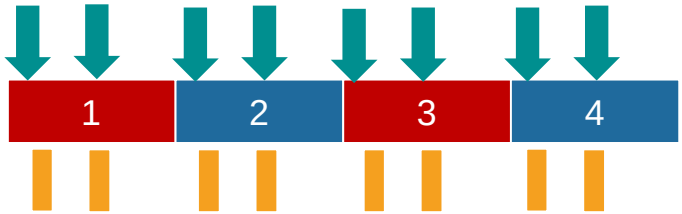
Table 3. Serious Adverse Events That Occurred during Treatment.*

Serious Adverse Event	Inotuzumab Ozogamicin Group (N=139)		Standard-Therapy Group (N=120)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Any event	67 (48)	64 (46)	55 (46)	52 (43)
Febrile neutropenia	16 (12)	15 (11)	22 (18)	21 (18)
Veno-occlusive disease	15 (11)	13 (9)	1 (1)	1 (1)
Sepsis	3 (2)	3 (2)	6 (5)	6 (5)
Pyrexia	4 (3)	2 (1)	3 (2)	1 (1)
Disease progression	5 (4)	5 (4)	2 (2)	2 (2)
Pneumonia	5 (4)	5 (4)	1 (1)	0
Neutropenic sepsis	3 (2)	3 (2)	3 (2)	3 (2)
Respiratory failure	1 (1)	1 (1)	4 (3)	4 (3)
Abdominal pain	3 (2)	2 (1)	1 (1)	1 (1)
Septic shock	2 (1)	2 (1)	1 (1)	1 (1)
Escherichia sepsis	1 (1)	1 (1)	2 (2)	2 (2)
Multiorgan failure	1 (1)	1 (1)	2 (2)	2 (2)
Hyperbilirubinemia	0	0	3 (2)	2 (2)
Hypotension	0	0	3 (2)	2 (2)
Stomatitis	2 (1)	2 (1)	1 (1)	1 (1)
Bacteremia	2 (1)	2 (1)	1 (1)	1 (1)
Clostridium difficile colitis	2 (1)	2 (1)	1 (1)	1 (1)
Nausea	2 (1)	2 (1)	0	0
Influenza	2 (1)	2 (1)	0	0
Asthenia	2 (1)	2 (1)	0	0
Pancytopenia	0	0	2 (2)	2 (2)
Tumor lysis syndrome	2 (1)	1 (1)	0	0
Acute renal failure	2 (1)	1 (1)	0	0
Klebsiella infection	0	0	2 (2)	2 (2)
Fungal pneumonia	0	0	2 (2)	2 (2)

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

Mini-HyperCVD + Inotuzumab – R/R ALL

Intensive phase



Mini-hCVD

Mini-MTX-cytarabine

Blinatumomab

POMP

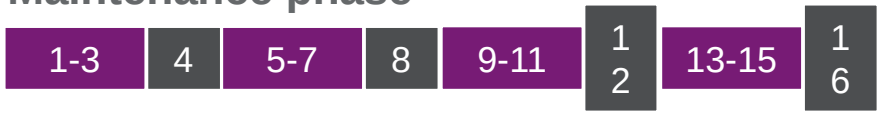
IT MTX/AraC

Consolidation phase

Inotuzumab	Dose per day (mg/m²)
C 1	0.6 D1, 0.3 D8
C2-4	0.3 D1 and D8

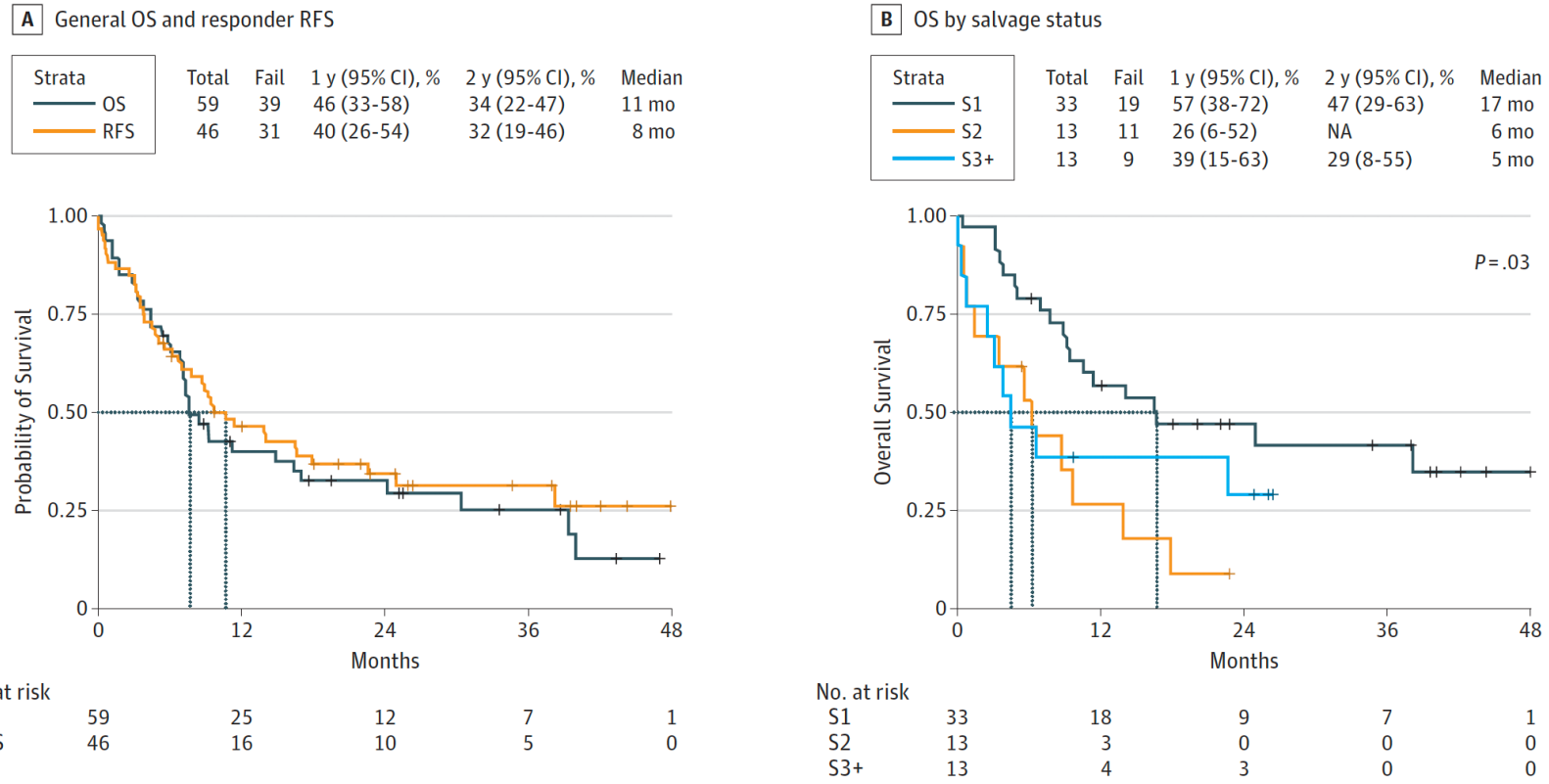
Total Ino dose = 2.7 mg/m²

Maintenance phase



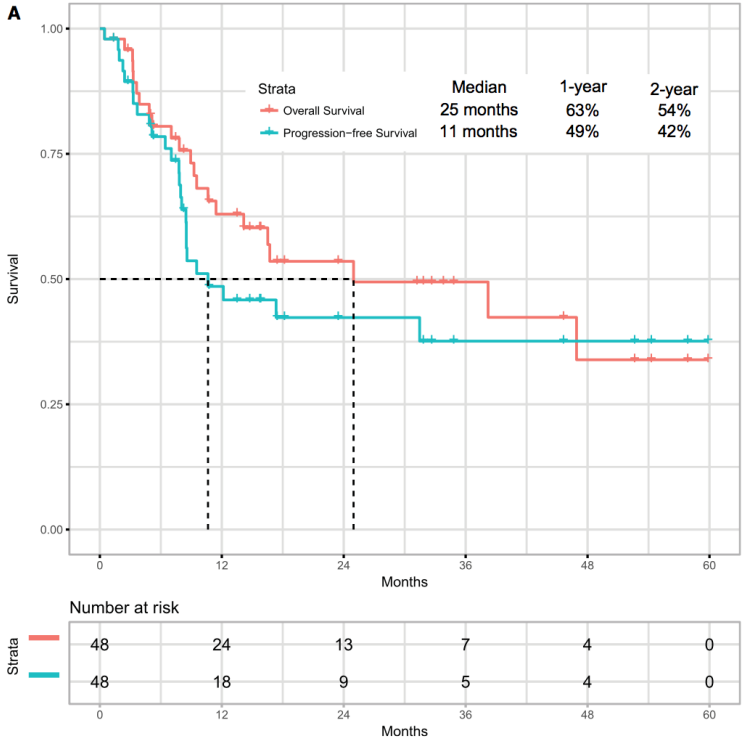
Jabbour E, et al. *JAMA Oncol.* 2018;4(2):230-234; Jabbour E, et al. *Cancer.* 2018;124:4044-4055.

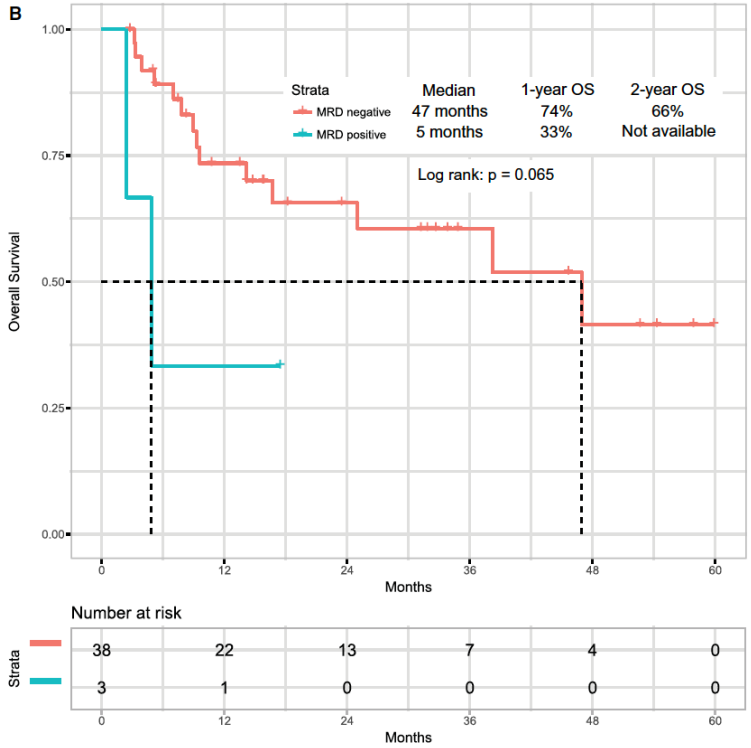
Mini-hyperCVD + Inotuzumab – R/R ALL



Jabbour E, et al. *JAMA Oncol.* 2018;4(2):230-234.

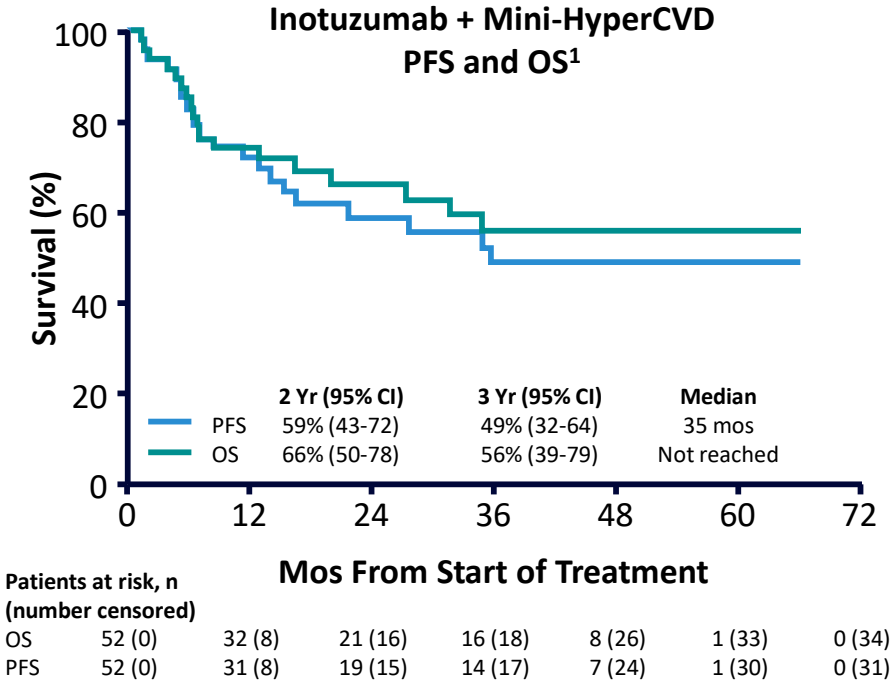
Mini-hCVD/Ino + Blinatumomab – R/R ALL

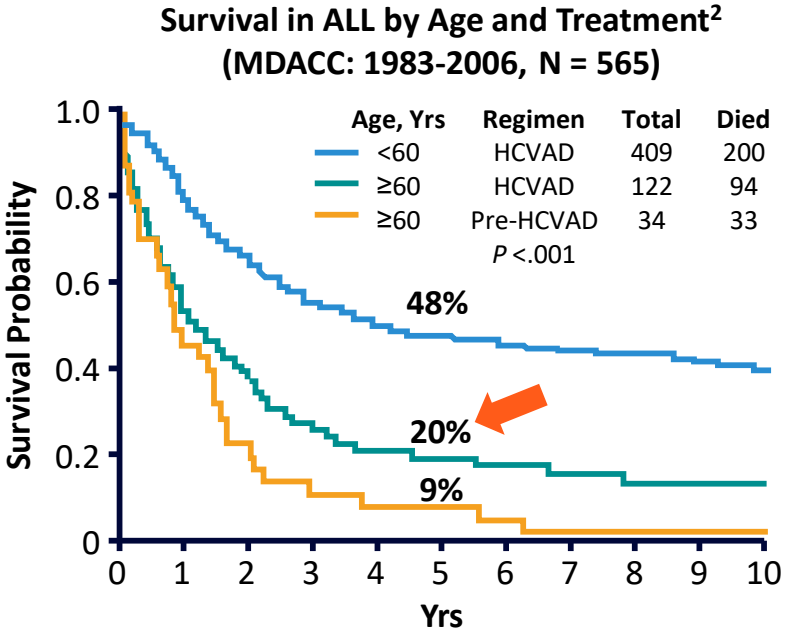




Jabbour E, et al. *Cancer.* 2018;124:4044-4055.

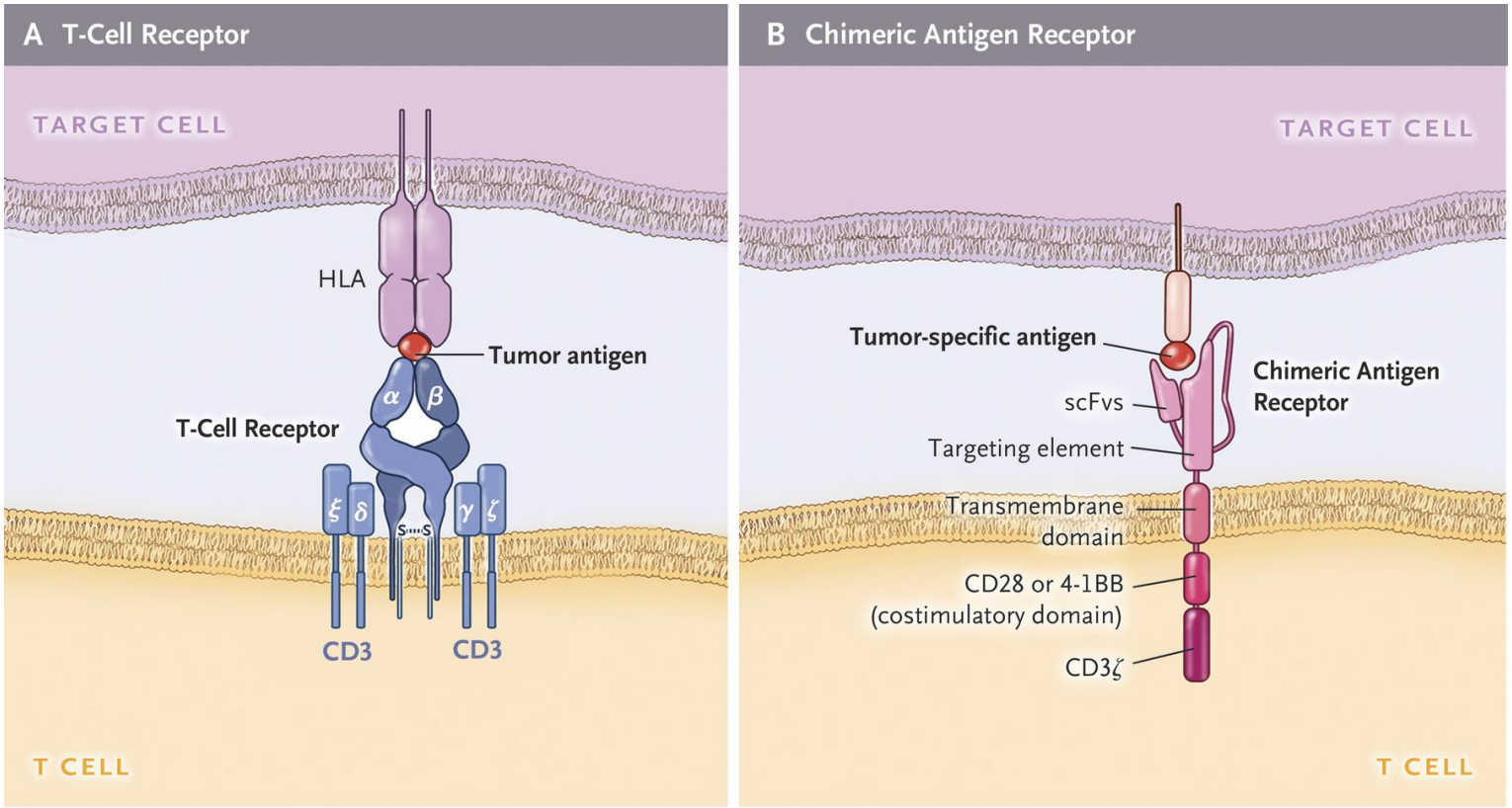
Mini-hCVD/Ino as Frontline Therapy in Patients >60 y/o





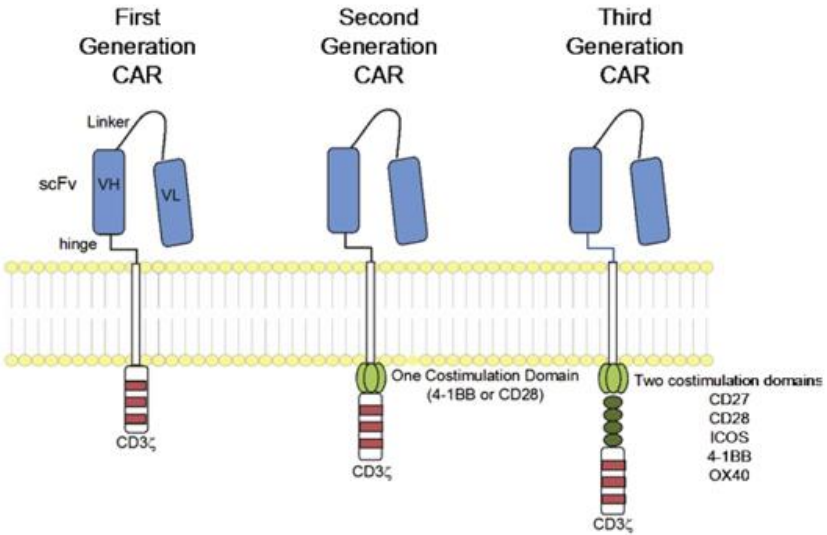
1. Kantarjian H, et al. *Lancet Oncol.* 2018;19:240-248; 2. O'Brien S, et al. *Cancer.* 2008;113:2097-2101.

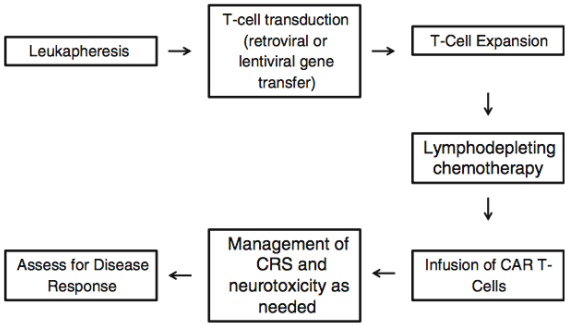
Chimeric Antigen Receptor (CAR) T Cells



June, Sadelain. *N Engl J Med.* 2018;379:64-73.

Treatment of Relapsed/Refractory ALL – CAR T Cells





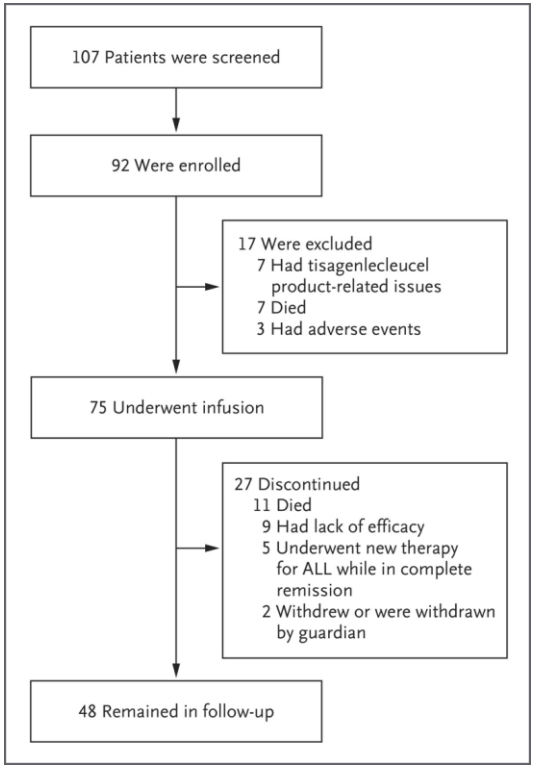
	MSKCC [33••, 37]	NCI [34••]	CHOP/UPENN [35••, 36]	FHCRC [51•]
Vector	Retroviral	Retroviral	Lentiviral	Lentiviral
Transmembrane	CD28	CD28	4-1BB	4-1BB
Signaling domain	CD3z	CD3z	CD3z	CD3z
Persistence	Short (~30 days)	Short (~30 days)	Long (~4 years)	Long
CR rate in ALL	~90%	~80%	>90%	~90%
Defined CD4/CD8 ratio	No	No	No	Yes

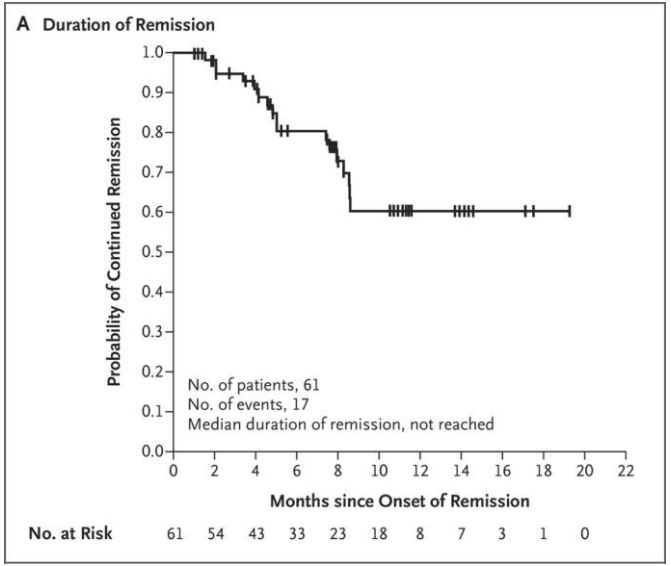
CAR chimeric antigen receptor, *ALL* acute lymphoblastic leukemia, *MSKCC* Memorial Sloan Kettering Cancer Center, *NCI* National Cancer Institute, *CHOP* Children's Hospital of Philadelphia, *UPENN* University of Pennsylvania, *FHCRC* Fred Hutchinson Cancer Research Center, *CR* complete remission

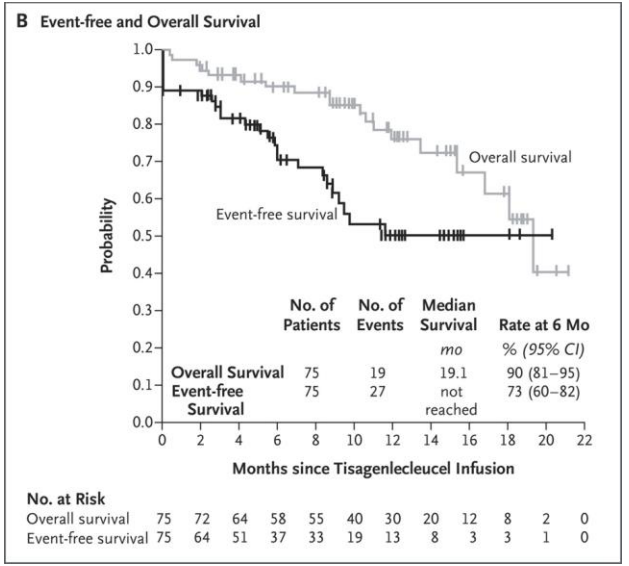
Maude, et al. *Blood.* 2015;125:4017-4023.

Luskin M, DeAngelo D. *Curr Hematol Malig Rep*. 2017;12(4):370-379.

Treatment of Relapsed/Refractory ALL – Tisagenlecleucel

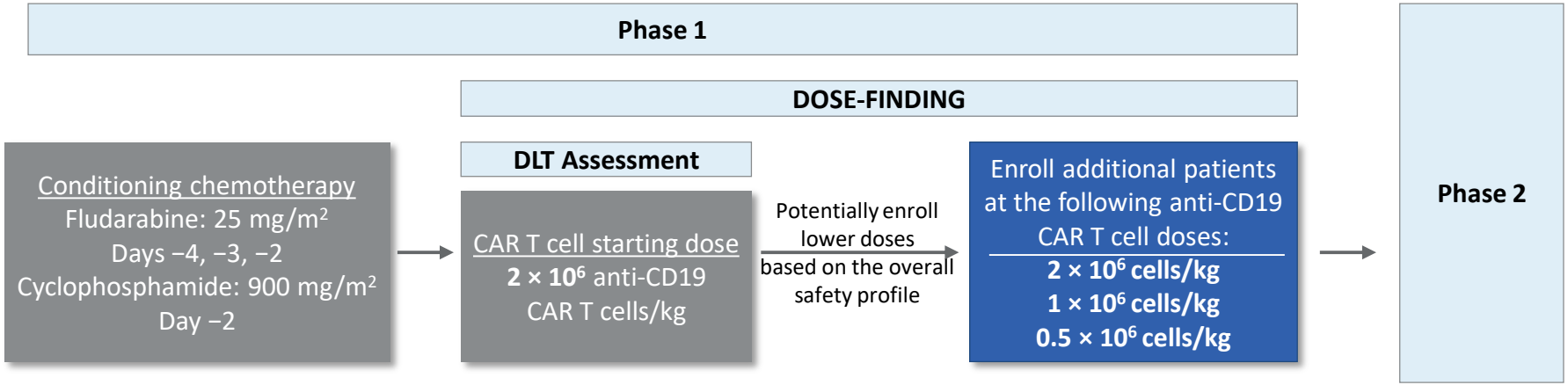






Maude, et al. *N Engl J Med.* 2018;378:439-448.

Treatment of Relapsed/Refractory ALL – KTE-X19 (Kite)



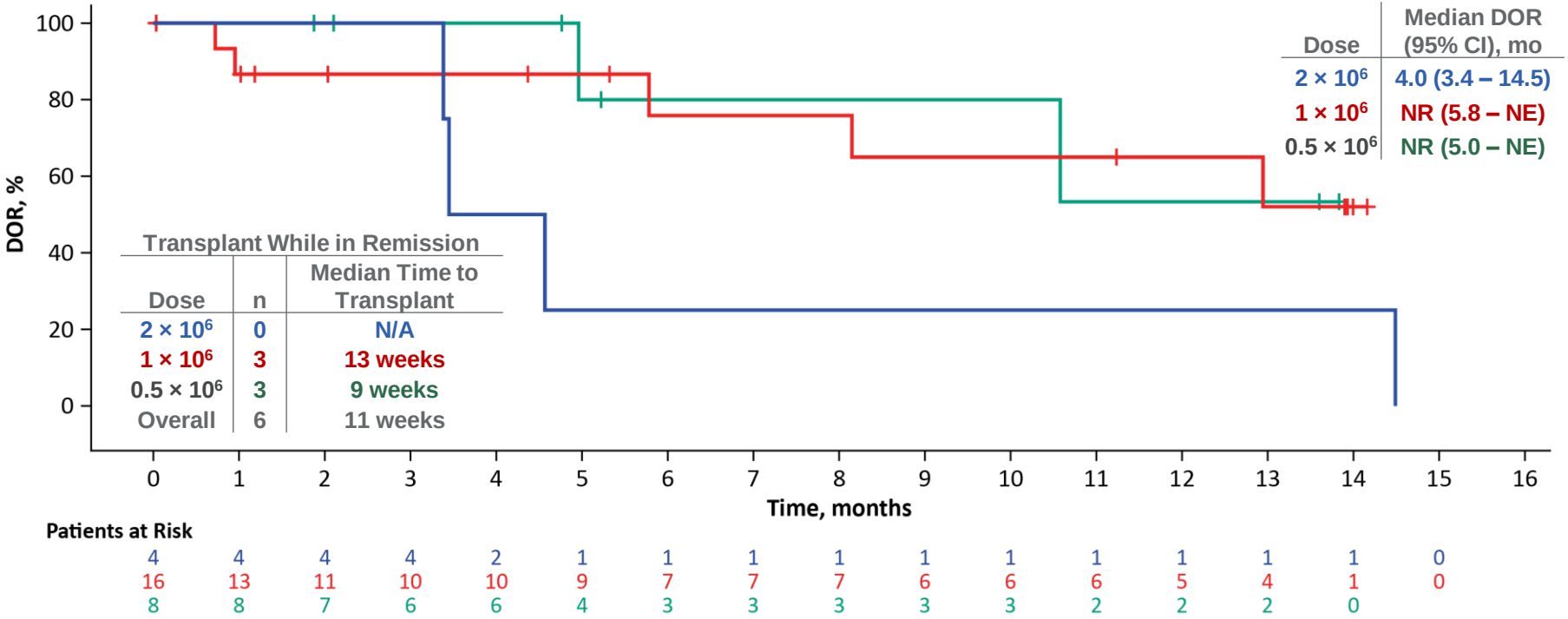
Phase 1 endpoints

Primary: Incidence of DLTs and safety

Secondary: ORR, DOR, RFS, MRD-negative rate, safety, CAR T-cell levels

Shah E, et al. ASCO 2019. Abstract 7006.

Treatment of Relapsed/Refractory ALL – KTE-X19 (Kite)

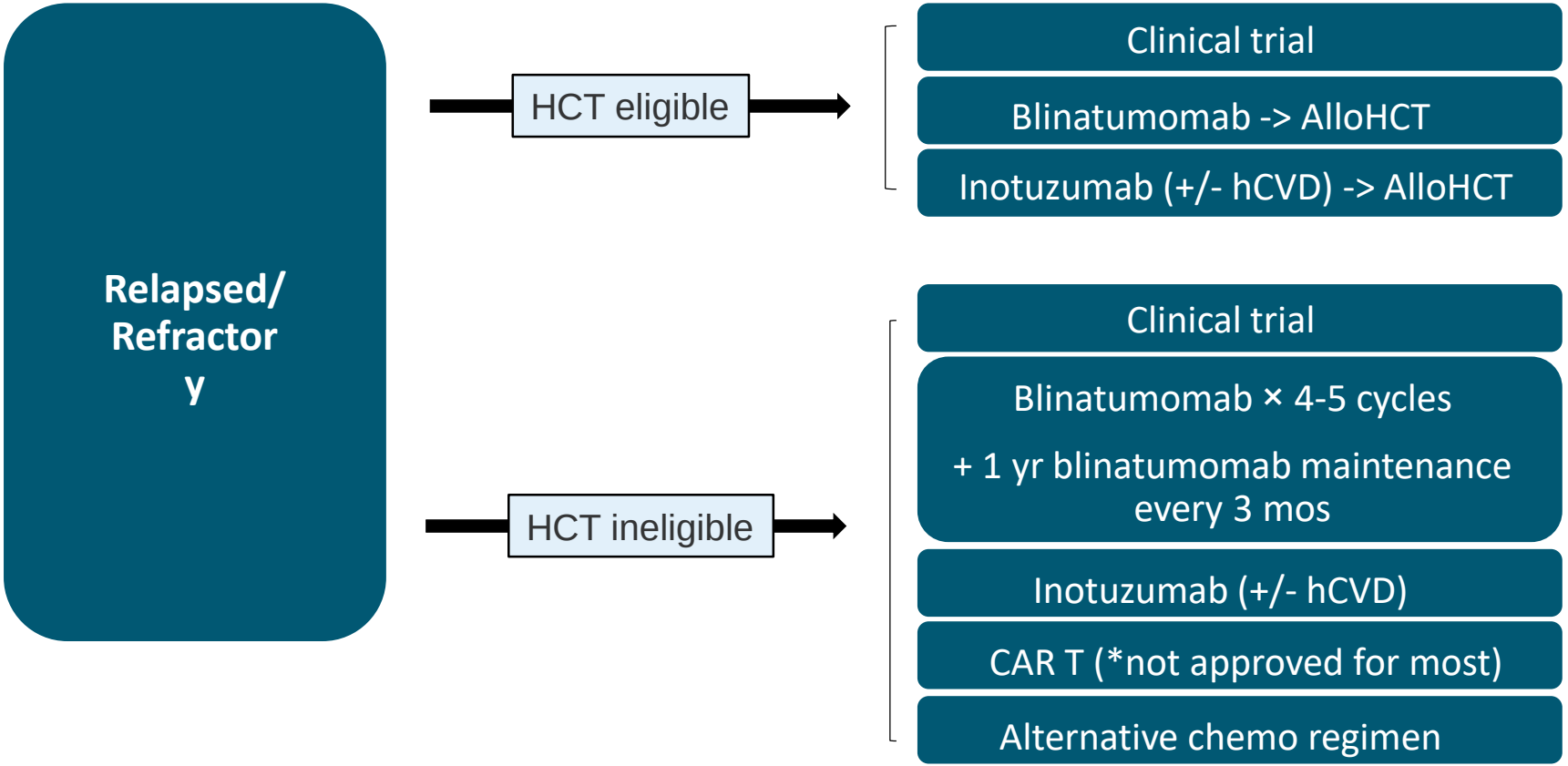


Shah E, et al. ASCO 2019. Abstract 7006.

Treatment of Relapsed/Refractory ALL – Chemo Options

Regimen	CR rate	Duration of Remission	Overall Survival
Augmented hCVAD + Asparaginase	47%	5 months	6 months
FLAG-Ida	39%	6 months	9 months
MOAD	28%	4.3 months	10.4 months
Liposomal Vincristine	20%	5.3 months	Not reported
Clofarabine/Cytarabine (SWOG 0530)	17%	Not reported	3 months

Management of Relapsed/Refractory Adult ALL Patients



Treatment of Relapsed ALL in Adults – Summary

- Blinatumomab is effective therapy for R/R ALL and may serve bridge to alloHCT (but most effective application is in MRD+ remission)
- Inotuzumab is associated with high rate of remission, but failed to demonstrate an OS advantage vs SOC chemotherapy
  - Pertinent risk of VOD must be kept in mind
- CAR T cells have marked efficacy and marked toxicity in adult ALL patients (currently approved only for age <26, but likely available soon for all adults)
  - Modern toxicity management strategies appear to be mitigating the risks
- An exciting development pathway exists for both the bispecific mAb and CAR T platforms in ALL
- All relapsed ALL patients should be considered for alloHCT


Thank you!

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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

Roberta Demichelis

Eduardo Rego

APTITUDE HEALTH®

Global Leukemia Academy

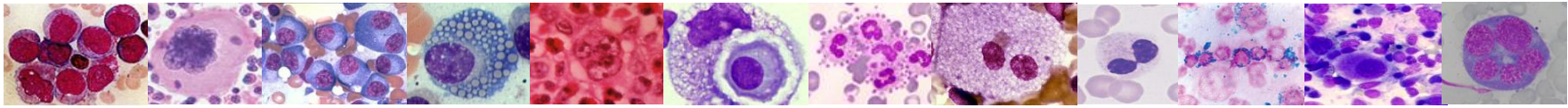
Case-Based Panel Discussion: Patient Case Presentation

Roberta Demichelis

APTITUDE HEALTH®

ALL in Hispanic Adults
Clinical Case

Dra Roberta Demichelis
INCMNSZ
Mexico City



Disclosures

- **Advisory/speaker: AbbVie, Amgen, Celgene, Novartis**

- **Research funding: Novartis**

Clinical Case

19-year-old man

Relevant history:
BMI 30.5
Family history: diabetes

June 2017

- ✓ WBC 2.2 $\times 10^9$/L, Hb 7.5 g/dL, plat 106 $\times 10^9$/L
- ✓ BMA: 52% blasts
- ✓ FC: CD34, CD10, CD19, CD20, CD22, CD79a and CRLF2
- ✓ Cytogenetics: 46 XY (20)
- ✓ FISH: t(9;22) and t(v;11q23) negative

Ph-negative B-cell ALL
AYA with obesity
CRLF2 overexpression

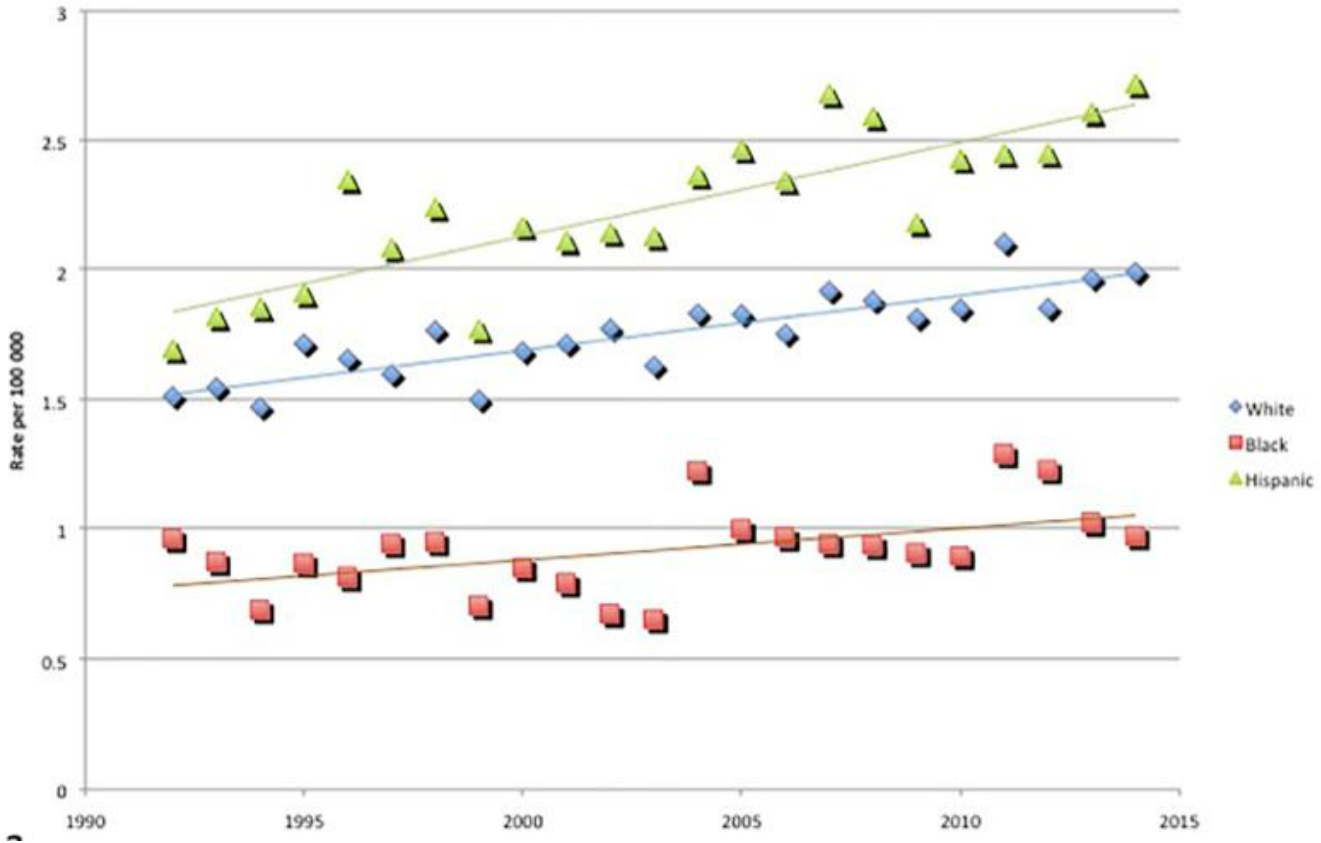
Q.

Question

In your practice, what would be the frontline treatment for this patient?

a. **Rituximab + HyperCVAD**
b. **Rituximab + pediatric-inspired regimen (BFM-like)**
c. **HyperCVAD**
d. **Pediatric-inspired regimen (BFM-like)**
e. **Other**

Hispanics: The Highest Incidence



Quiroz, et al. *Blood Rev*. 2019;33:98-105.

Hispanics Are Underrepresented in Clinical Trials

ORIGINAL ARTICLE

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Hagop Kantarjian, M.D., Anthony Stein, M.D., Nicola Gökbuget, M.D., Adele K. Fielding, M.B., B.S., Ph.D., Andre C. Schuh, M.D., Josep-Maria Ribera, M.D., Ph.D., Andrew Wei, M.B., B.S., Ph.D., Hervé Dombret, M.D., Robin Foà, M.D., Renato Bassan, M.D., Önder Arslan, M.D., Miguel A. Sanz, M.D., Ph.D., et al.

8.9%–9.6%

A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403

Wendy Stock, Selina M. Luger, Anjali S. Advani, Jun Yin, Richard C. Harvey, Charles G. Mullighan, Cheryl L. Willman, Noreen Fulton, Kristina M. Laumann, Greg Malnassy, Elisabeth Paietta, Edy Parker, Susan Geyer, Krzysztof Mrózek, Clara D. Bloomfield, Ben Sanford, Guido Marcucci, Michaela Liedtke, David F. Claxton, Matthew C. Foster, Jeffrey A. Bogart, John C. Grecula, Frederick R. Appelbaum, Harry Erba, Mark R. Litzow, Martin S. Tallman, Richard M. Stone, and Richard A. Larson

Blood 2019 133:1548–1559; doi: https://doi.org/10.1182/blood-2018-10-881961

15.3% (N = 45)

ORIGINAL ARTICLE

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

Hagop M. Kantarjian, M.D., Daniel J. DeAngelo, M.D., Ph.D., Matthias Stelljes, M.D., Giovanni Martinelli, M.D., Michaela Liedtke, M.D., Wendy Stock, M.D., Nicola Gökbuget, M.D., Susan O'Brien, M.D., Kongming Wang, Ph.D., Tao Wang, Ph.D., M. Luisa Paccagnella, Ph.D., Barbara Sleight, M.D., et al.

"Other" 9%–10%

¿Hyper-CVAD?

¿ALL particularities in Mexico (and Latin America)?

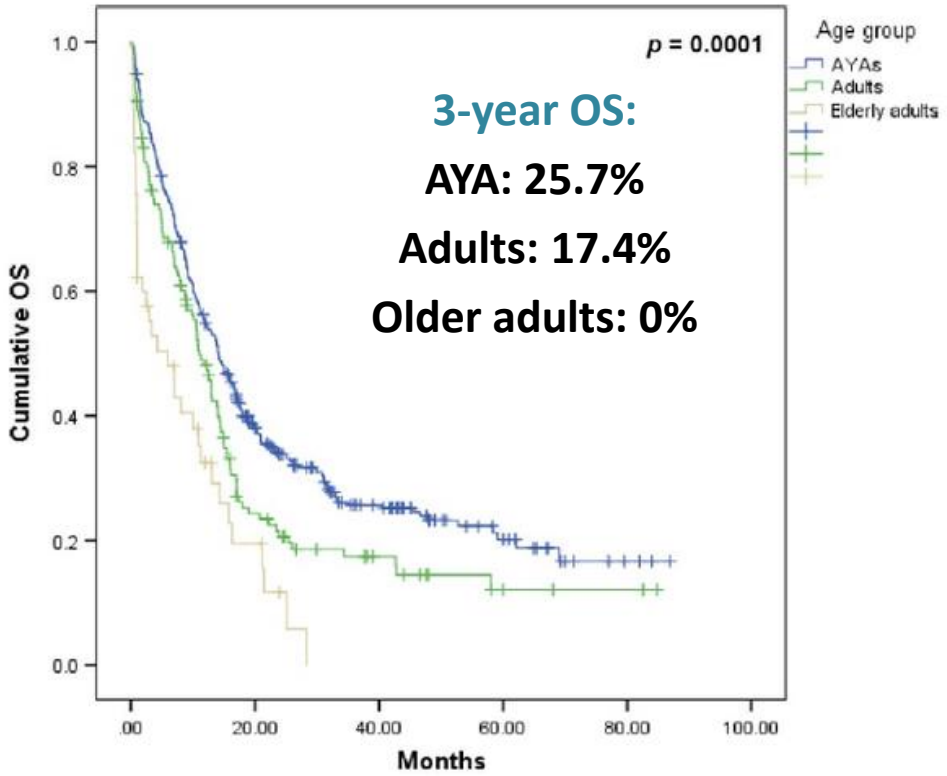
1. Very Frequent Prevalence and Poor Outcomes

Mexico: 51% of acute leukemia in adults

N = 559
47% treated with HyperCVAD

Induction-related mortality: 10.6%
In >39 years: 18%

Mortality during consolidation: 10.6%
AlloHSCT: 5.7%



Crespo. Cancer Med. 2018;7(6)2423-33. Gómez-Almaguer. Clin Lymphoma Myeloma Leuk. 2017;17(1):46-51

2. High Prevalence of Ph-Like?

Ph-like: 20%–30%

MDACC cohort
Ph-like: 33%

Hispanics 68% vs
White 23%
***P* <.001**

Mexico:
CRLF2 overexpression by FC: 41%

Table 2. Outcomes	n = 40 n (%)	CRLF2+ (n=16)	CRLF2- (n=24)	Chi-square *p*
CR	34 (85)	13 (32.5)	21 (52.5)	0.58
R/R	18 (45)	10 (25)	8 (20)	0.06
U-MRD 1 (n=38)	14 (36.8)	5 (5.3)	12 (31.6)	0.015
U-MRD 2 (n=31)	12 (38.7)	1 (3.2)	11 (35.5)	0.003
U-MRD 3 (n=22)	9 (40.9)	0 (0)	9 (40.9)	0.001
Dead	12 (30%)	6 (15)	6 (15)	.39

1-year DFS: 57% vs 30 % (NS)

Jain, et al. *Blood.* 2017;129(5):572-581; Almanza, et al. EHA 2020. EP429.

3. More Risk of Asparaginase Toxicity?

Hepatotoxicity

Type of toxicity Events per cycle	Grade 3-4 Elevation, Yes vs No Transaminases 148 in 512 cycles	 Triglycerides 123 in 324 cycles[1]	 Bilirubin 49 in 522 cycles
Cycle 1	–	0.51 (0.25–1.04)	22.56 (4.72–107.8)
Cycles 2–3	–	1	1
Cycles 4–7	–	1	1
Year of Age	–	0.84 (0.71–0.99)	–
$(Age)^2$	–	1.002 (1.0–1.004)	–
(log) Age	–	–	4.00 (1.57–10.19)
Hispanic Ethnicity	3.03 (1.67–5.50)	–	–
Male	–	–	–
Per unit maximum grade of same toxicity in a prior cycle	–	5.04 (2.47–10.3)	2.36 (1304–4.29)
Any grade of same toxicity in a prior cycle	–	–	–
Fibrinogen <100 mg/dL in a Prior Cycle	–	–	–
Per Unit BMI	1.07 (1.00–1.15)	1.04 (1.00–1.09)	–
Obesity defined as BMI >30	–	–	2.87 (1.33–6.20)
Obesity defined as BMI >35	–	–	–

In Mexico:

- ✓ **Obesity: 34% of >15 years**
- ✓ **Hypertriglyceridemia: up to 50%**
- ✓ **NAFLD: up to 62.9%**

Next case

Aldoss, et al. *Eur J Haematol.* 2016;96(4):375-380; Aguilar-Salinas, et al. *Metabolism.* 2014;63(7):887-89; Bernal-Reyes, et al. *Rev Gastroenterol Mex.* 2019;84(1):69-99.

Clinical Case

19-year-old man
B-cell ALL

Modified CALGB 10403 (*E. Coli* asparaginase) + rituximab

Induction

- ***Grade 3 hyperbilirubinemia***

+ 28 CR with MRD–

Consolidation 1

- ***Grade 3 transaminitis***
  - **Liver US: diffuse fatty infiltration**
  - **Biopsy: NASH**
- ***Hypertriglyceridemia*: TG 3317 mg/dL**

Delays
Dose reductions

Clinical Case

19-year-old man
B-cell ALL

April 2019, during maintenance

- **Dysarthria + ataxia**
- **MRI: normal**
- **LP: 35 blasts/mm^3, FC: CD34, CD10, CD19, negative CD20**
- **BMA: no blasts**
- **MRD + 0.02%**

CNS relapse

How to manage CNS relapses?

Q.

Question

What would be the ideal management at this moment?

a. IT chemotherapy ± RT, followed by blinatumomab
b. IT chemotherapy ± RT, followed by inotuzumab
c. IT chemotherapy ± RT, followed by intensive chemotherapy
d. IT chemotherapy ± RT and continuing maintenance
e. Systemic chemotherapy

Q.

Question

In which cases do you treat CNS relapses with radiation therapy?

a. Never
b. Always
c. Cranial nerve involvement/masses
d. When refractory to IT chemotherapy
e. C + D

Clinical Case

19-year-old man
B-cell ALL

CNS relapse

- IT-chemotherapy twice weekly until CNS1
- Methotrexate + cytarabine (HyperCVAD)
- Cranial irradiation

AlloHSCT (identical sibling donor)
Conditioning regimen: busulfan + cyclophosphamide

3 months after alloHSCT: systemic + extramedullary relapse (gastric, parotid, bone marrow)

Open Questions

1. Ideal management for CNS involvement in ALL?

2. Is there a role for immunotherapy (blinatumomab or inotuzumab) in patients with CNS disease?

3. Can TBI be omitted in the conditioning regimen of patients with ALL?

Conclusions

1. **Hispanic/Latino patients with ALL**
   A. **ALL is more frequent in Hispanic/Latino**
   B. **More Ph-like**
   C. **Asparaginase-related toxicity**

Biobank of adults with ALL
Diagnosis and relapse

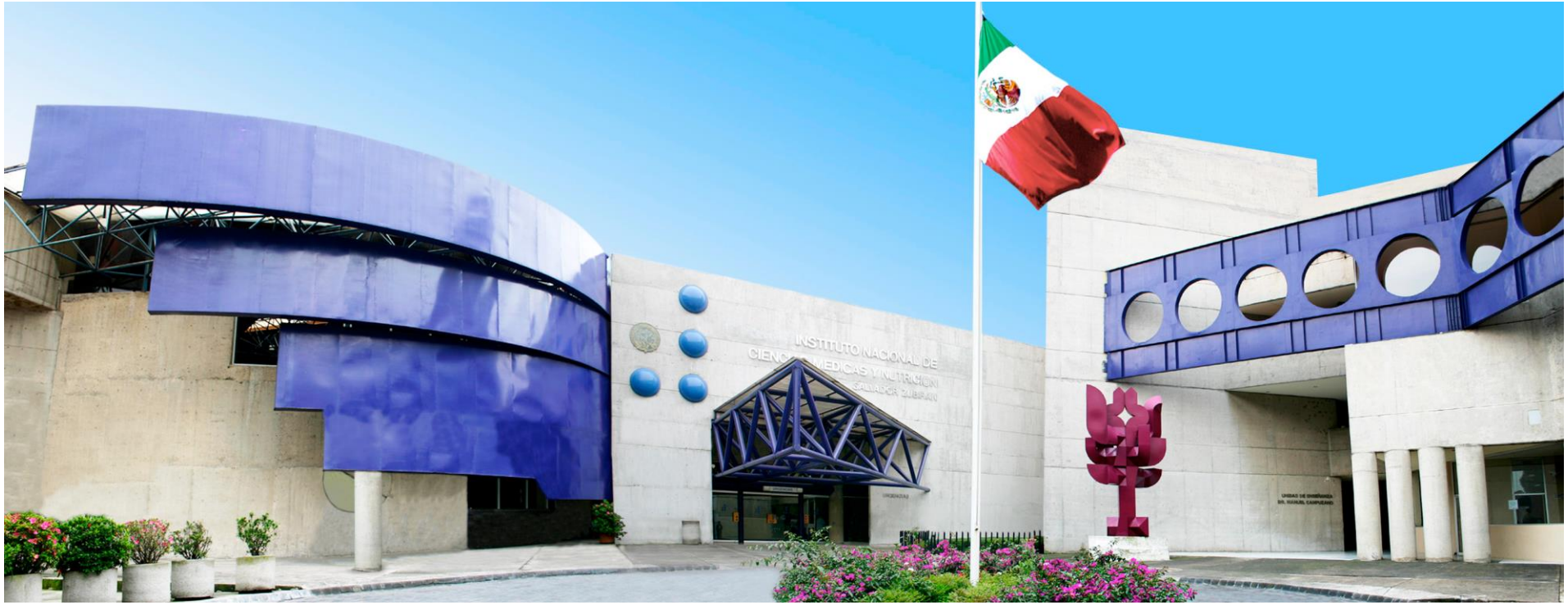
Pharmacogenomics and asparaginase toxicity

Conclusions

2. **CNS/extramedullary disease are still a problem in ALL**

Ideal prevention and management?

Thank You



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Q&A

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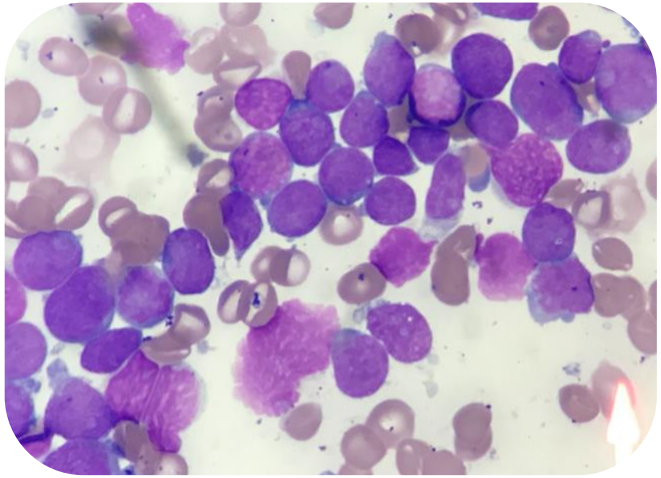
Case-Based Panel Discussion: Patient Case Presentation

Eduardo Rego

APTITUDE HEALTH®

Case presentation 1

- Female, 28 y/o
- Without prior conditions
- Diagnosed with B-lymphoblastic leukemia in July 2018
  - Initial WBC: 7.1x10^9/L
  - Immunophenotyping: Pre-B/CD20 neg
  - Genetics: t(1;19) – *TCF3-PBX1* rearrangement
  - Initial CNS evaluation: CNS 1 (no CNS disease)



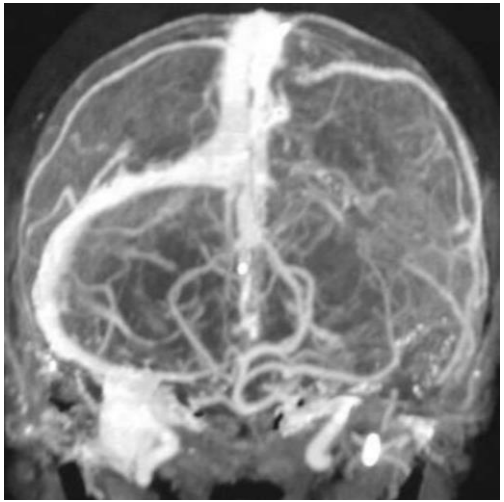
Treatment

- BFM-inspired regimen

INDUCTION

Induction phase I
- Corticosteroid
- Daunorubicin
- Vincristine
- Peg-asparaginase 2000 IU/m^2 – D12 and D26

Induction phase II
- Cytarabine
- Cyclophosphamide
- 6-mercaptopurine



20 days after the first dose of PEG-asp → generalized tonic-clonic seizure, rapidly stabilized

→ **cerebral vein thrombosis**

Common Toxicities Associated with Asparaginase Treatment

Toxicity	Any grade (%)	High grade (≥3) (%)	Risk factors
Hypersensitivity	7-22	4-10	Second dose and future doses, HLA-DRB1*07:01 polymorphism, no concurrent rituximab administration, younger age, no pre-medications
Hyperbilirubinemia	86	24-39	During the induction cycle, older age, obesity, higher dose of peg-asparaginase, low albumin, low platelet count, CC genotype of rs4880 polymorphism
Pancreatitis	24	5-13	Older age, high-risk ALL stratification, germline polymorphisms in ULK2 variant rs281366 and RGS6 variant rs17179470
Hypertriglyceridemia	77	11-51	Beyond first cycle, high BMI, younger age
Thrombosis		11-27	First cycle, older age, obesity, mediastinal mass, cryoprecipitate replacement
Hypofibrinogenemia (<100)		48-51	First cycle, severe obesity (BMI >35)
Hyperglycemia	91	31-33	Concomitant use of steroid

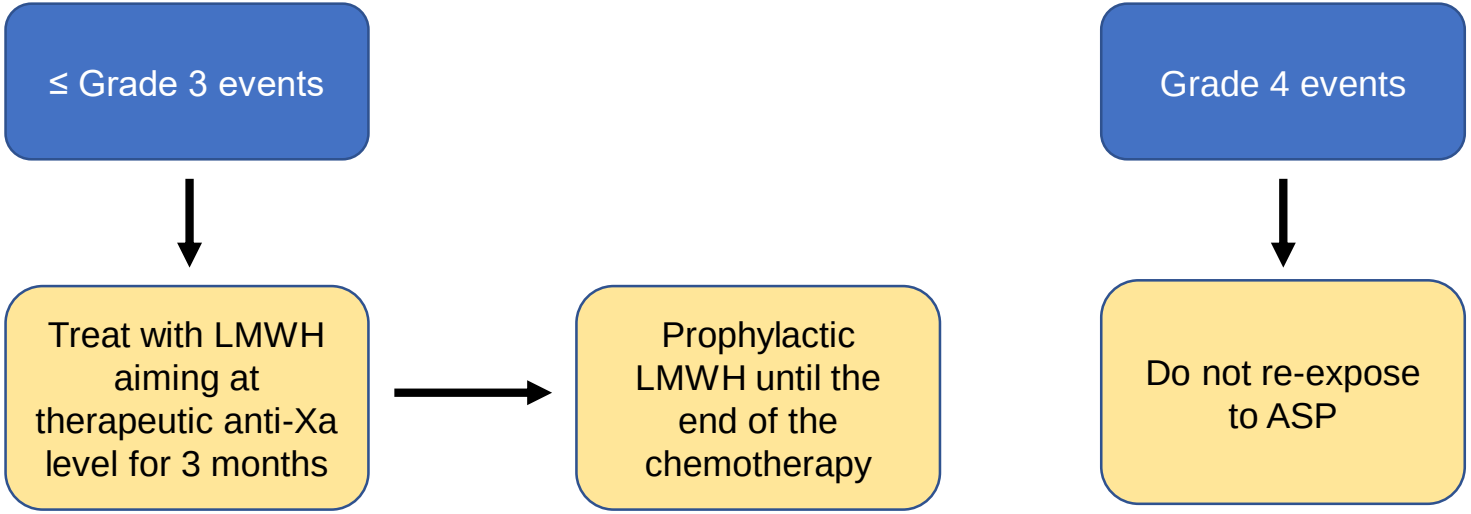
Aldoss, Douer. *Blood.* 2020;135(13):987-995.

Regarding central venous thrombosis associated with asparaginase

Q.

1. Which the following statements about antithrombotic treatment/prophylaxis is true?
    a. Events classified as grade ≤3 do not require antithrombotic treatment
    b. Any event precludes new exposure to ASP
    c. Requires treatment with LMWH aiming at therapeutic anti-Xa level for 3 months followed by prophylactic use until the end of treatment
    d. Requires treatment with LMWH aiming at therapeutic anti-Xa level for 3 months after which no antithrombotic prophylaxis/therapy is required

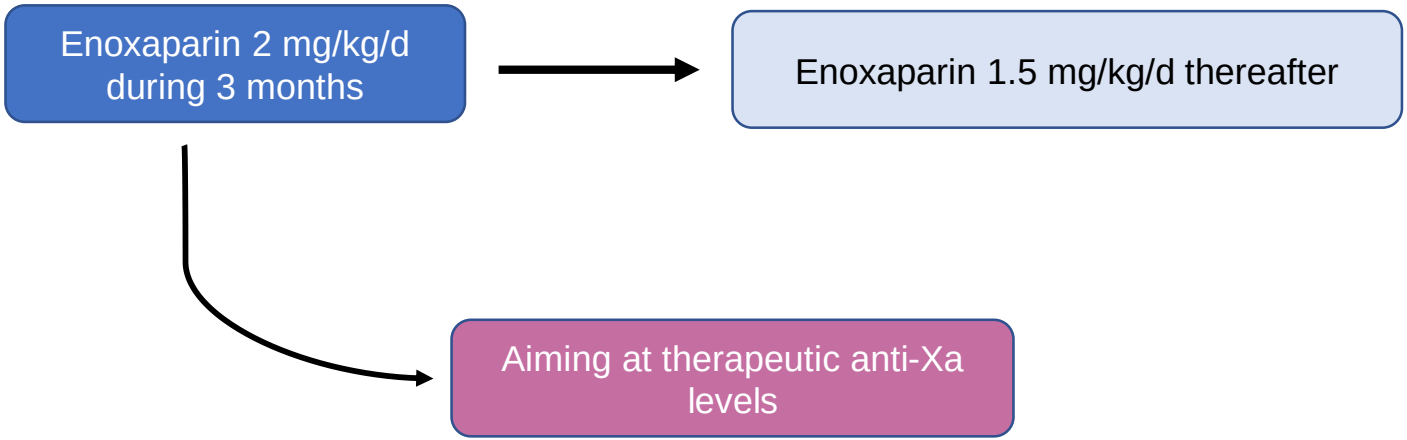
Our approach to thromboembolism due to ASP



Bade NA, et al. *J Oncol Pharm Pract.* 2019 (in press); GMALL – unpublished data; NCCN Guidelines 2019.1.

Cerebral venous thrombosis

- Mediated by asparaginase and other factors such as hormones and potential CNS invasion



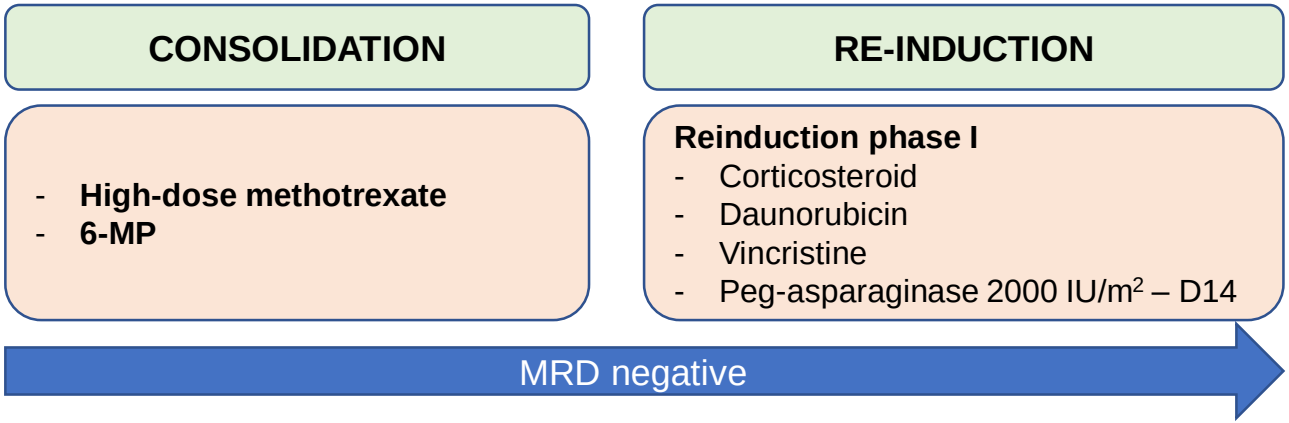
Thrombosis and Hypofibrinogenemia

TOXICITY	MANAGEMENT	PREVENTION
Thrombosis	Anticoagulation “not clear”	ATIII replacement for low activity level is not yet standard
	Maintain adequate platelet counts while patient is receiving anticoagulation	Prophylactic anticoagulation is controversial
		Not an indication to discontinue peg-asparaginase
		Avoid replacement with cryoprecipitate to correct laboratory abnormalities in the absence of clinical bleed
Hypofibrinogenemia	Cryoprecipitate replacement only during active bleeding or before procedures	Not an indication to discontinue peg-asparaginase

Aldoss, Douer. *Blood.* 2020;135(13):987-995.

Treatment

- BFM-inspired regimen



We decided to resume PEG-asp in the reinduction, but we failed at the prior checking of the anti-Xa level → New seizure

Dural venous sinus thrombosis

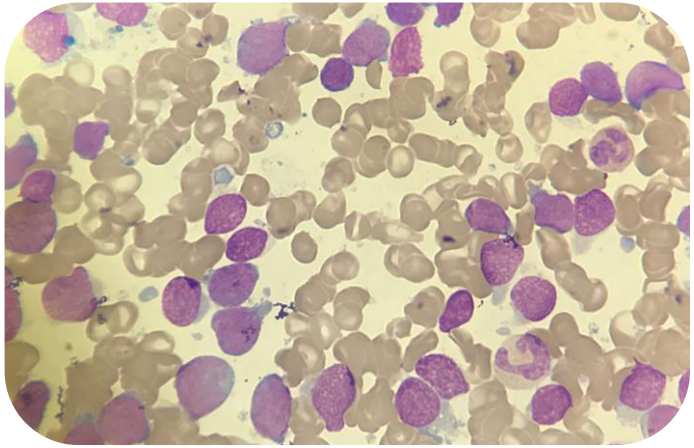
Follow up

- BFM-inspired regimen

- She is currently at the end of maintenance, with no recurrence of thrombosis and with negative MRD

Case presentation 2

- Male, 53 y/o
- Without prior conditions
- Serologic evaluation: immune hepatitis B (anti-HBs positive)
- Diagnosed with B-lymphoblastic leukemia in April 2019
  - Initial WBC: $1.5x10^9/L$
  - Immunophenotyping: Common B/CD20 neg
  - Genetics: 46,XY[20], negative BCR-ABL1 and other fusions
  - Initial CNS evaluation: CNS 1 (no CNS disease)



Treatment

- It was decided to include him in the BFM-inspired regimen despite his age

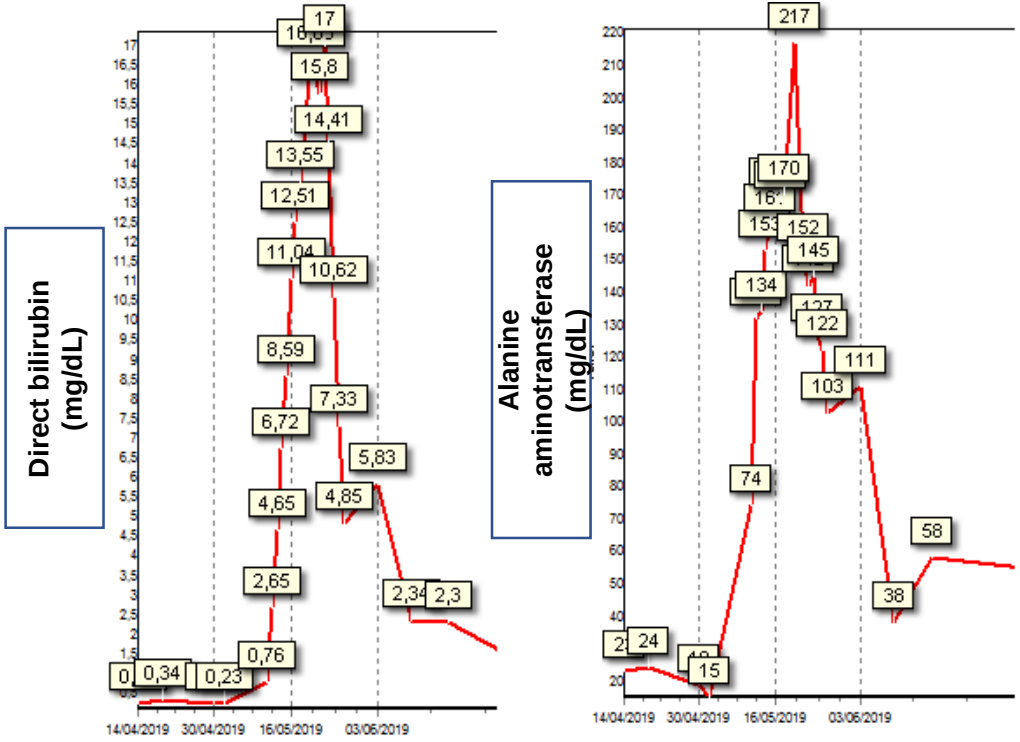
INDUCTION

Induction phase I
- Corticosteroid
- Daunorubicin
- Vincristine
- Peg-asparaginase 2000 IU/m^2 – D12 and D26

Induction phase II
- Cytarabine
- Cyclophosphamide
- 6-mercaptopurine

Elevation of liver enzymes and bilirubin → Ultrasound showing **hepatic steatosis**, with no other alterations; Negative PCR for HBV.

Treatment



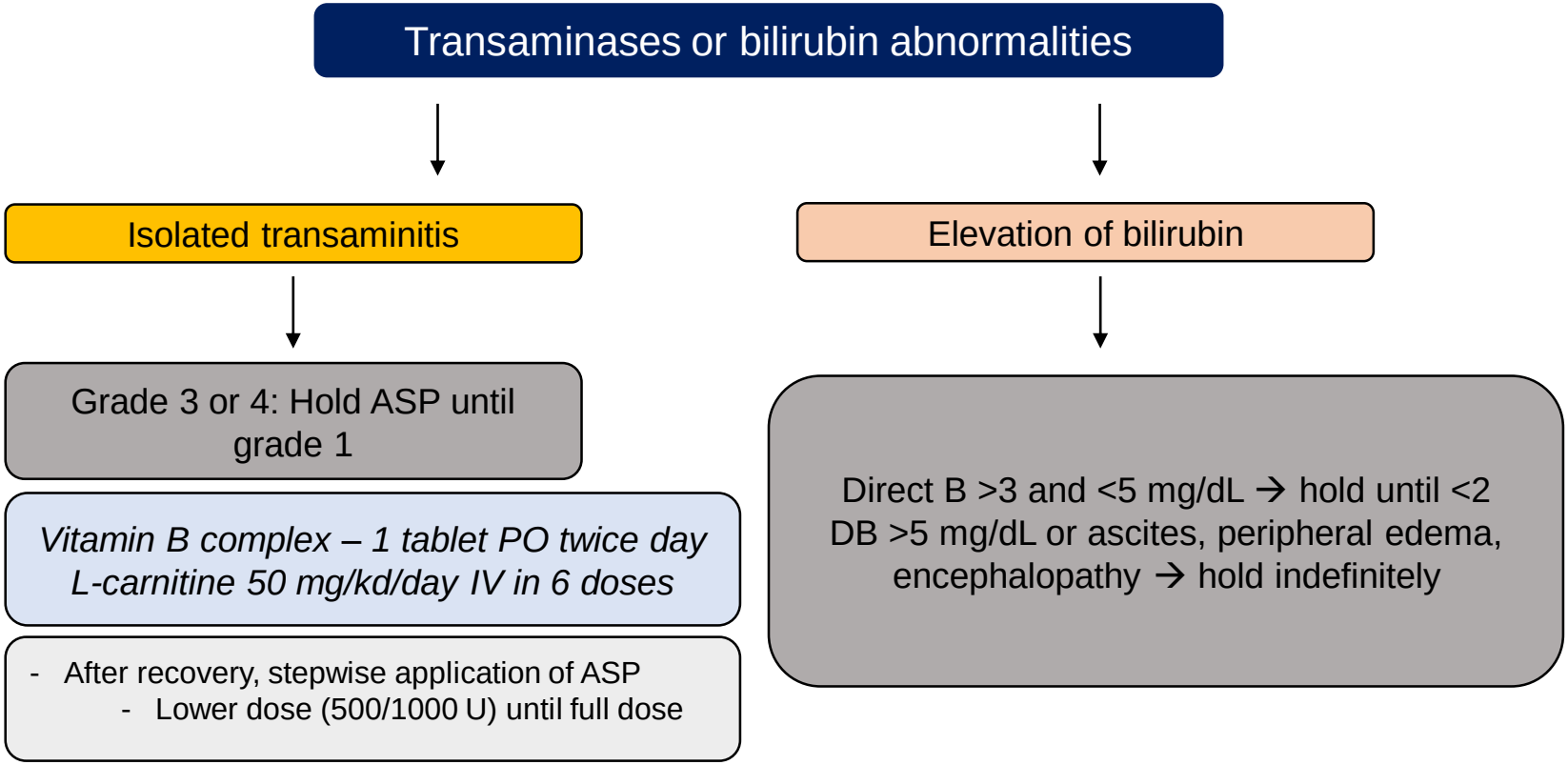
- Hyperbilirubinemia precluded the use of anthracycline and vincristine at this time
- Minor peripheral edema and ascites developed, but they were rapidly managed with diuretics
- Oral L-carnitine was empirically offered
- We kept the patient on prednisone plus low-dose 6-MP

Regarding hepatotoxicity associated with asparaginase

Q

1. Which the following statements about its management is true?
    a. Plasma levels of direct bilirubin up to 5 mg/dl do not require specific management
    b. Plasma levels of direct bilirubin >5 mg/dl preclude new exposure to ASP
    c. Isolated transaminitis does not require specific management
    d. Requires treatment with LMWH aiming at therapeutic anti-Xa level for 3 months

Asparaginase – Hepatotoxicity



Bade NA, et al. *J Oncol Pharm Pract.* 2019 (in press); GMALL – unpublished data; NCCN Guidelines 2019.1.

Hyperbilirubinemia and Transaminitis

TOXICITY	MANAGEMENT	PROPHYLAXIS
Hyperbilirubinemia	Adjust other medications and delay subsequent cycle until grade 1 is achieved	Avoid hepatotoxic medications or adjust doses
	Consider L-carnitine and ursodiol	Not an indication to discontinue peg-asparaginase or reduce the dose
Transaminitis	Consider delaying therapy for grades 3 and 4 until resolved to grade 2	Avoid hepatotoxic medications or adjust doses
	Consider L-carnitine	Not an indication to discontinue peg-asparaginase or reduce dose

Aldoss, Douer. *Blood.* 2020;135(13):987-995.

Follow up

- After this major toxicity (grade 4 liver toxicity after PEG), we moved this patient to GRAALL-Elderly

- Currently, he is under maintenance, with negative MRD

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Q&A

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Global Leukemia Academy

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

Discussion

Elias Jabbour

Roberta Demichelis

Aaron Logan

Eduardo Rego

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Global Leukemia Academy

Educational ARS Questions

Elias Jabbour

APTITUDE HEALTH®

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

Q

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)

Q

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

Q

Case 3

At what time points is 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**

Q

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 and Eduardo Rego

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Emerging and Practical Concepts and Controversies in Leukemias

THANK YOU FOR YOUR PARTICIPATION!

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