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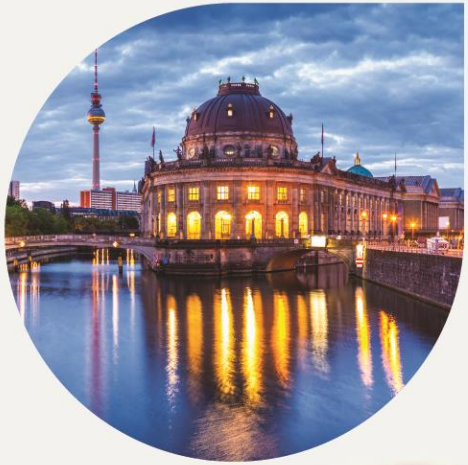

Global Leukemia Academy

Adult ALL Patients Breakout

Emerging and Practical Concepts and Controversies in Leukemias

23–24 October 2020

APTITUDE HEALTH

Global Leukemia Academy

Virtual breakout: Adult ALL patients – session open

Elias Jabbour

Global Leukemia Academy

APTITUDE HEALTH

Meet the Faculty

Elias Jabbour, MD
University of Texas MD Anderson Cancer Center
Houston, TX, USA

Josep Ribera, MD
Catalan Institute of Oncology
University Hospital Germans Trias i Pujol
Badalona, Spain

Philippe Rousselot, MD, PhD
University of Versailles
Saint-Quentin-en-Yvelines, France

Dieter Hoelzer, MD, PhD
University of Frankfurt, Germany

Virtual breakout – adult ALL patients (Day 2)

Time CET	Title	Speaker
18.00 – 18.15	**Session open** • Educational ARS questions for the audience	Elias Jabbour
18.15 – 18.35	**Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens** • Presentation (15 min) • Q&A (5 min)	Elias Jabbour
18.35 – 18.55	**Current treatment options for relapsed ALL in adult and elderly patients** • Presentation (15 min) • Q&A (5 min)	Dieter Hoelzer
18.55 – 19.45	**Case-based panel discussion** • **Management of long- and short-term toxicities and treatment selection in adult and elderly patients** – Case 1 (15 min) – Case 2 (15 min) – Discussion (20 min)	*Case 1*: Philippe Rousselot *Case 2*: Josep-Maria Ribera *Faculty panel*: E. Jabbour, D. Hoelzer, J.M. Ribera, P. Rousselot
19.45 – 20.00	**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

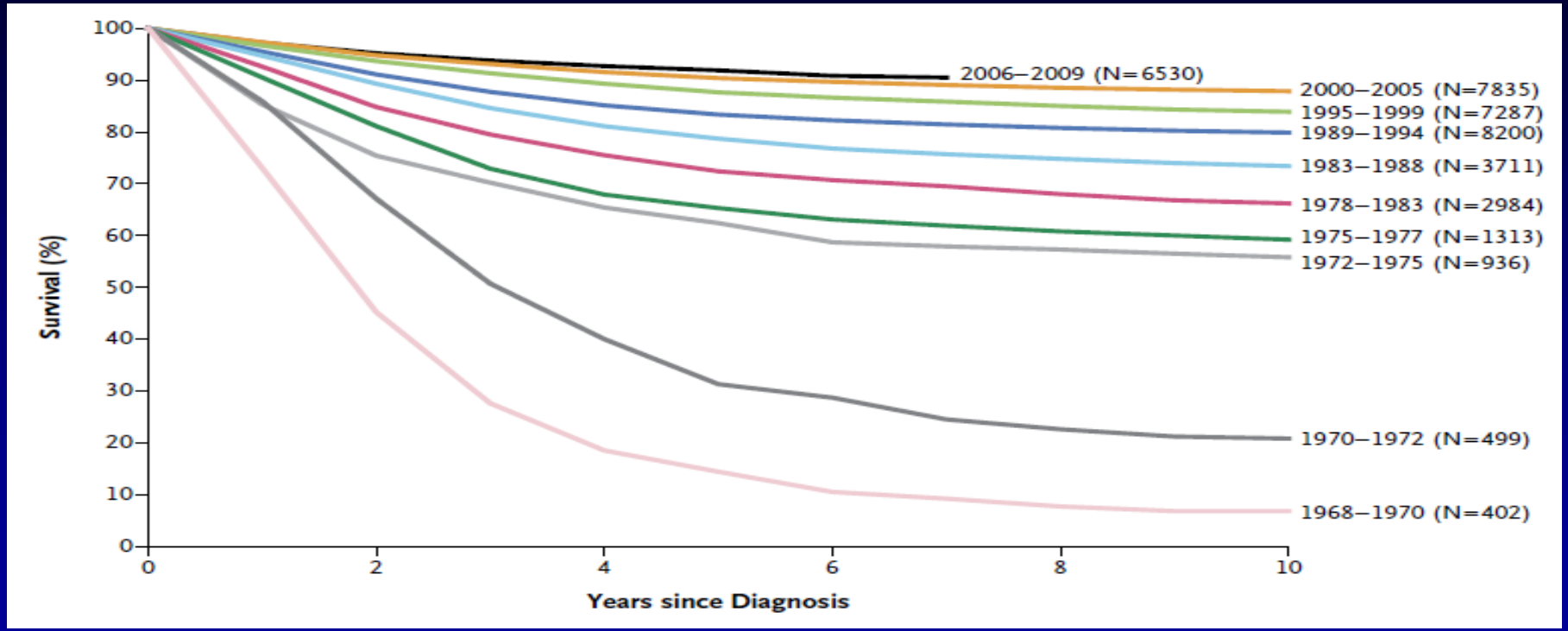
APTITUDE HEALTH

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

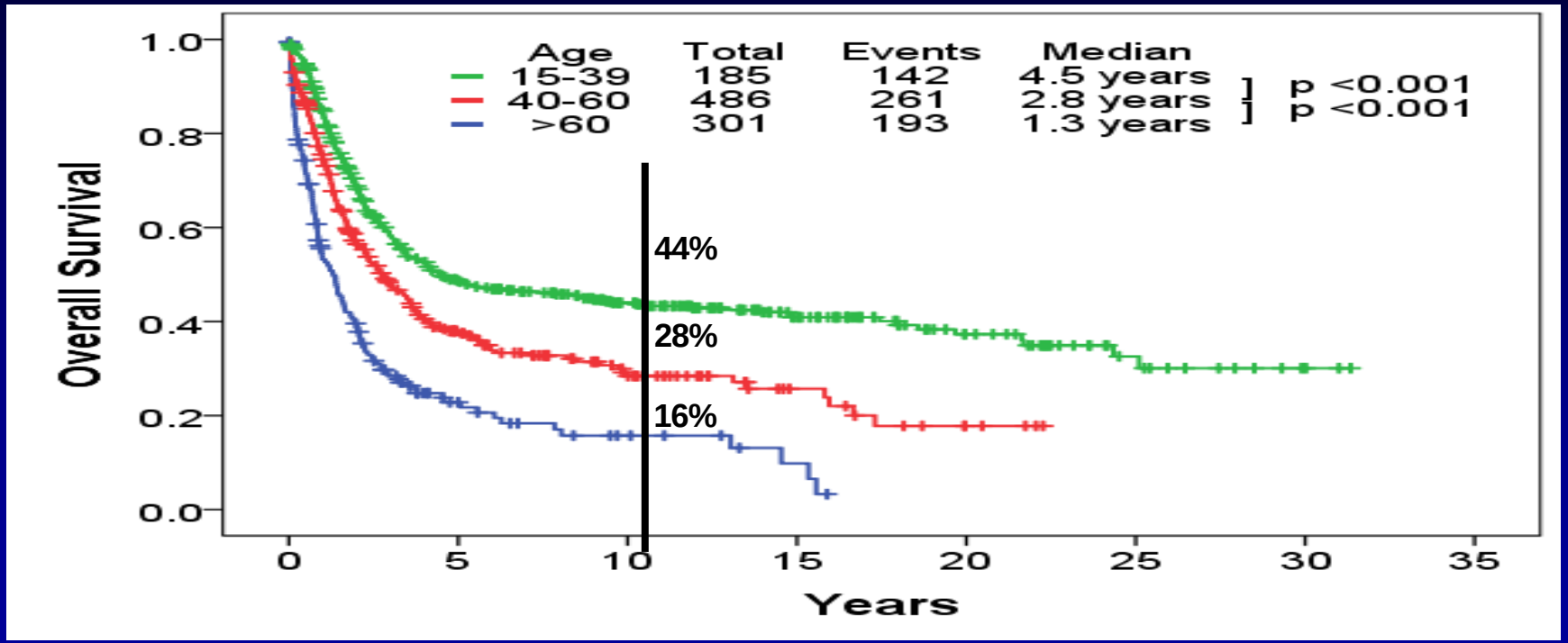
Survival of 39,697 Children With ALL Treated on Sequential CCG/COG Clinical Trials



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

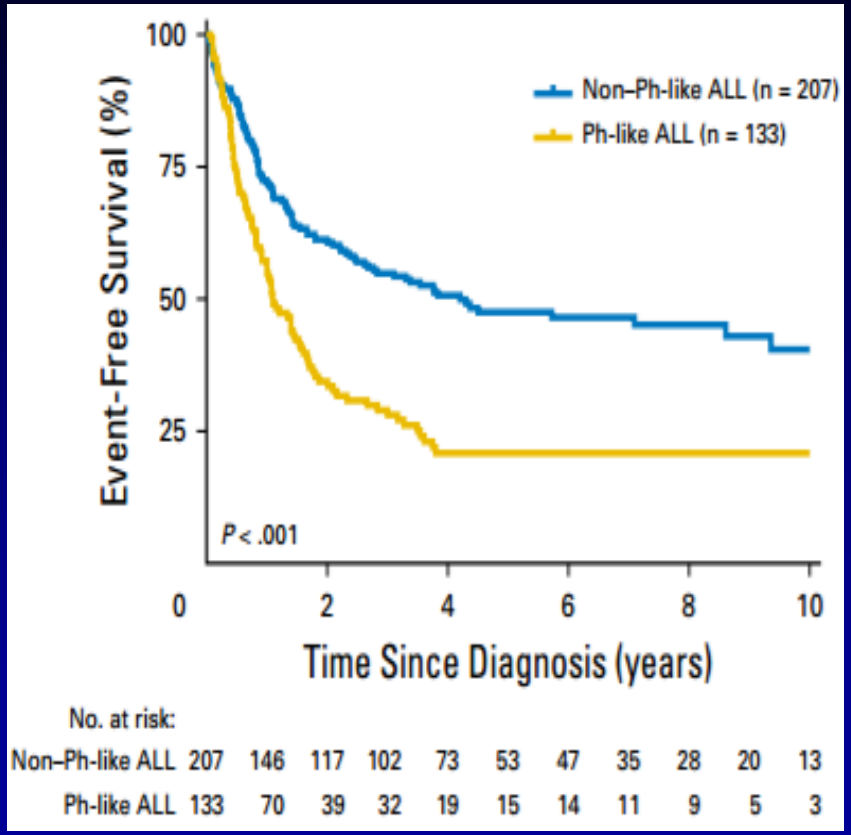
Survival of 972 Adults With Ph– ALL

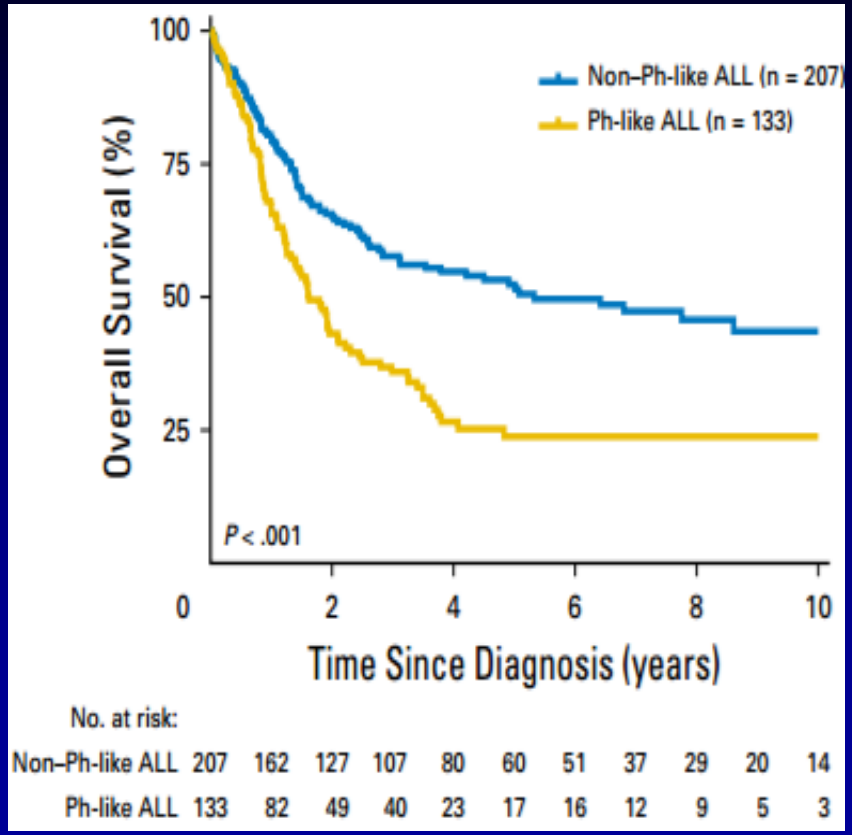
- 972 pts Rx 1980–2016; median F/U 10.4 years



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

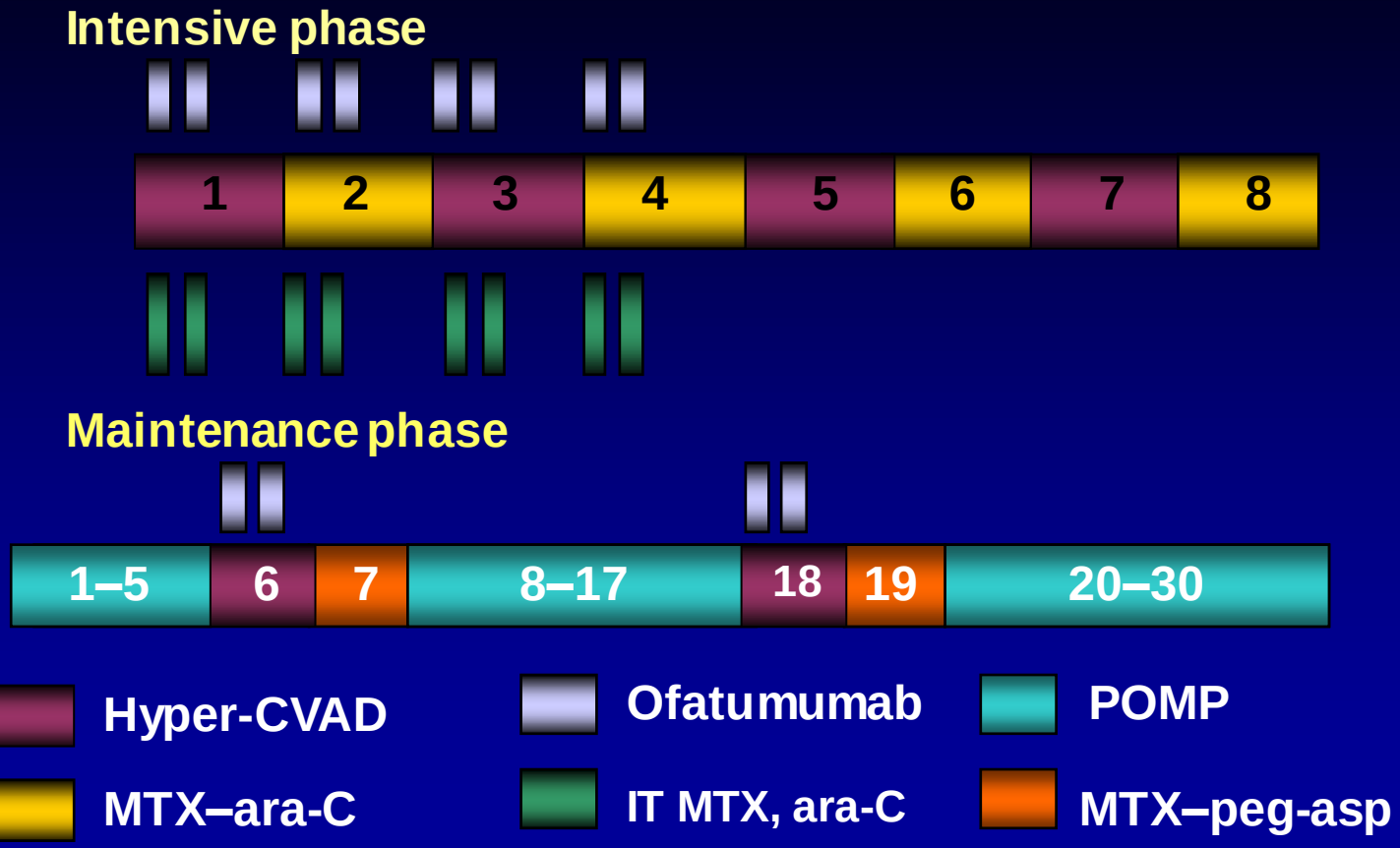
- Addition of TKIs to chemoRx in Ph+ ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Potential benefit of addition of CD19 bispecific antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- Eradication of MRD
- CAR T

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

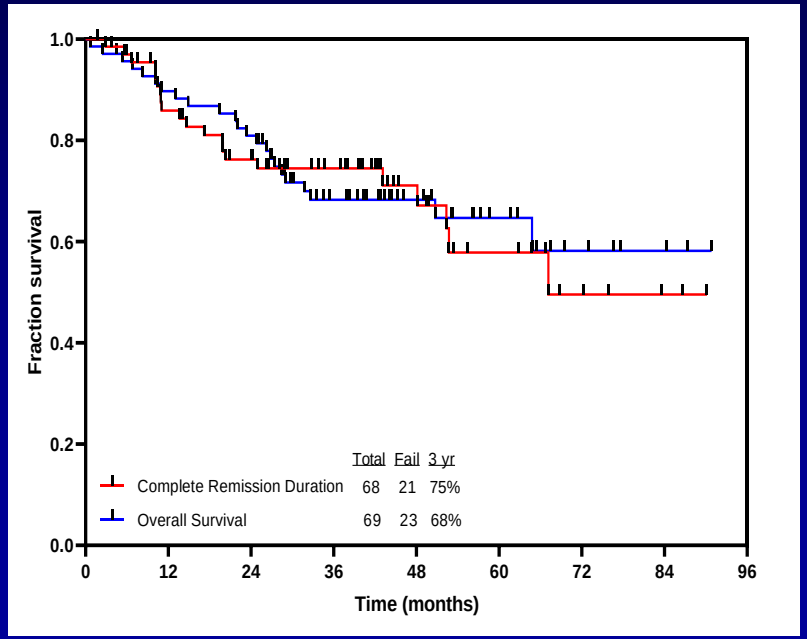


Richard-Carpentier. *Blood.* 2019;134:abstract 2577.

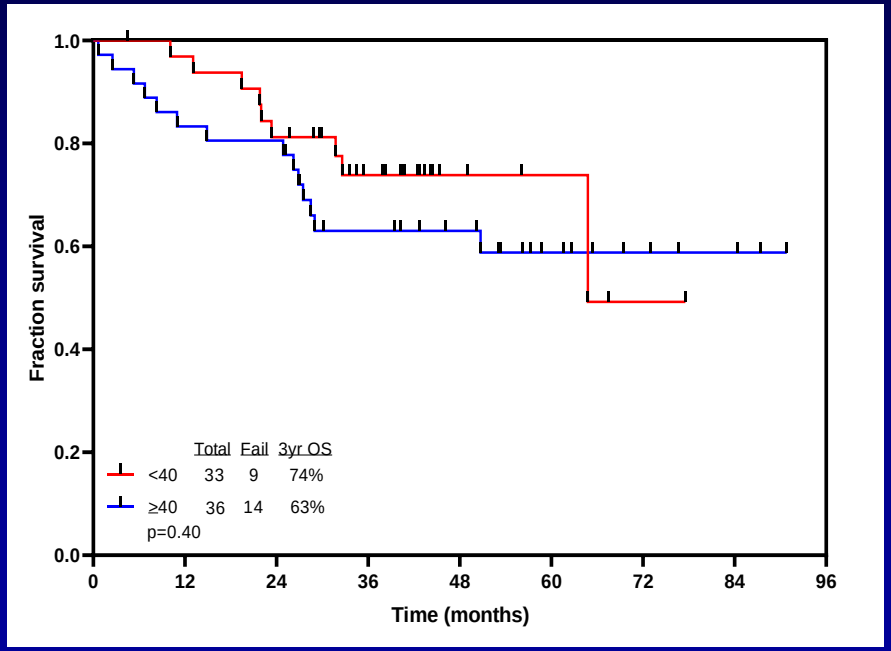
HCVAD + Ofatumumab: Outcome (N = 69)

- 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.

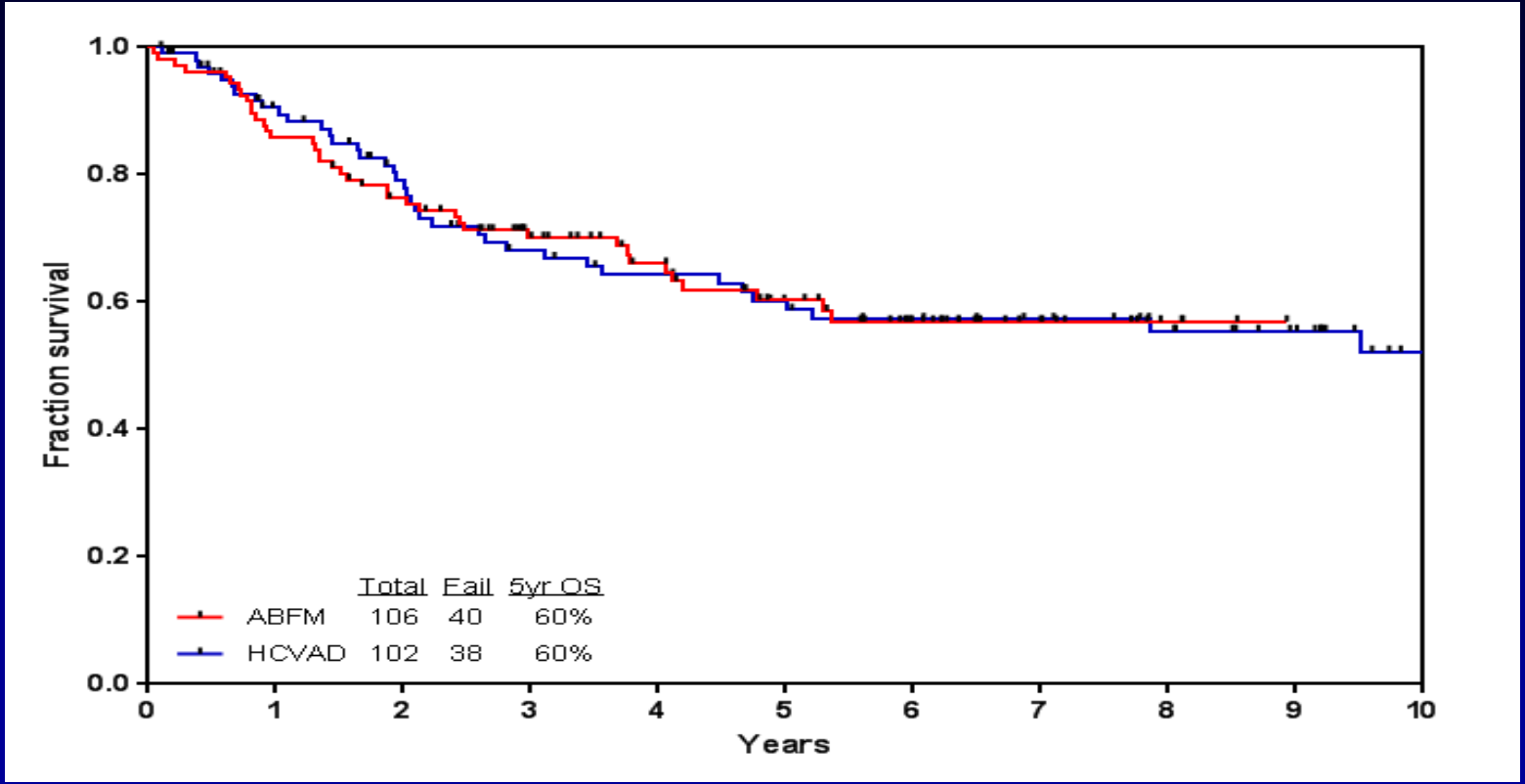
Comparison of HCVAD + Ofatumumab With CALGB 10403

- 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

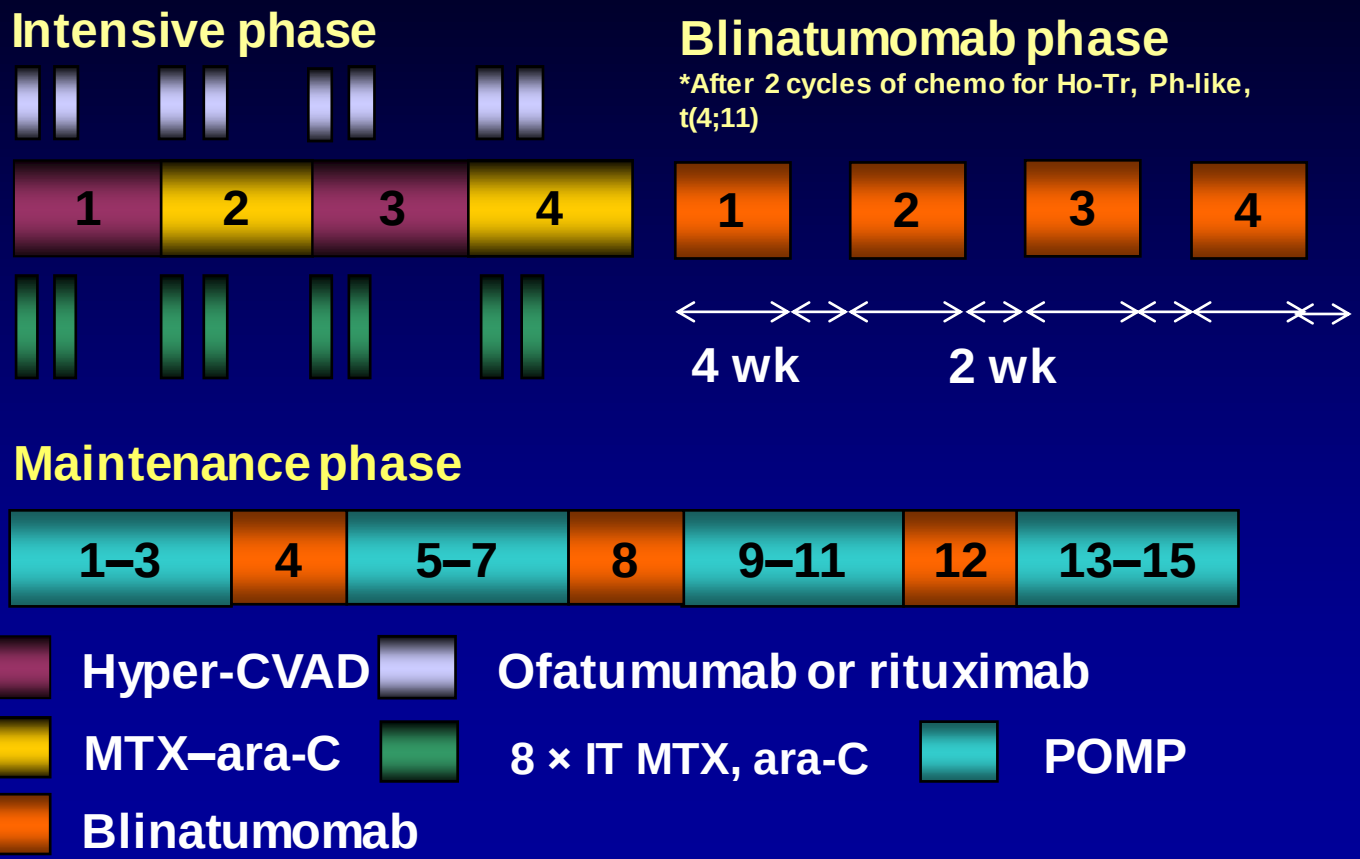
Stock. *Blood.* 2019.

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)

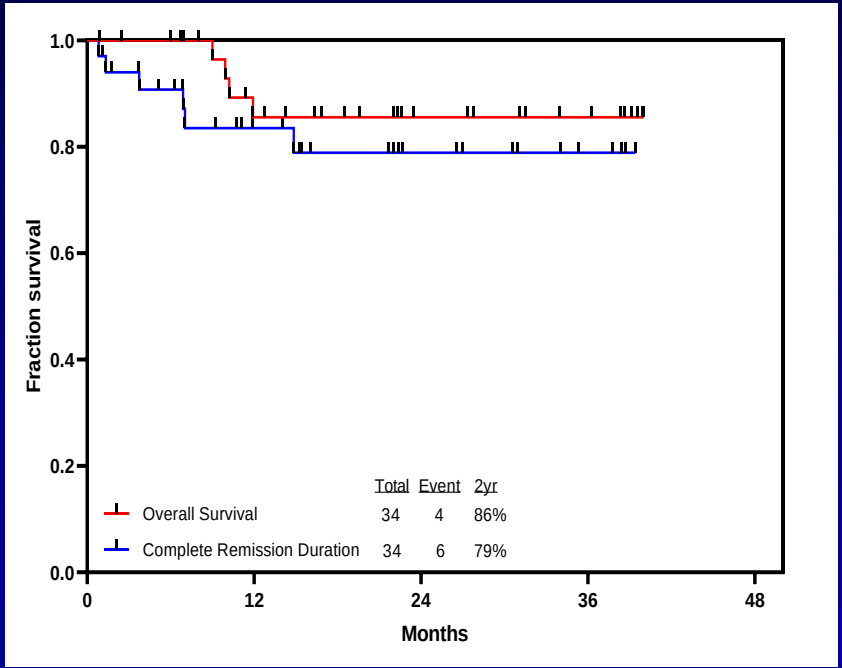
Characteristic (N = 34)		N (%) / Median [range]
Age (years)		36 [17–59]
Sex	Male	24 (71)
PS (ECOG)	0–1	28 (82)
WBC ($\times 10^9$/L)		3.12 [0.5–360.9]
CNS disease		4 (12)
CD19 ≥50 %		27/28 (96)
CD20 ≥20 %		13/29 (45)
***TP53* mutation**		**9/33 (27)**
Ph-like CRLF2+		**6/30 (20)**
Cytogenetics	Diploid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

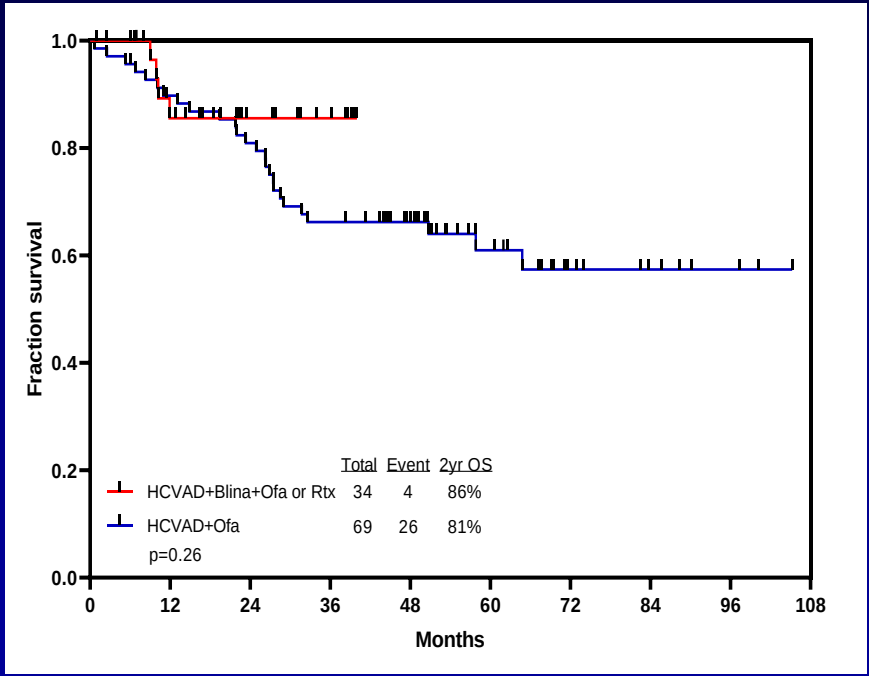
Hyper-CVAD + Blinatumomab in FL B-ALL (N = 34)

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

CRD and OS Overall



OS – HCVAD-Blina vs O-HCVAD



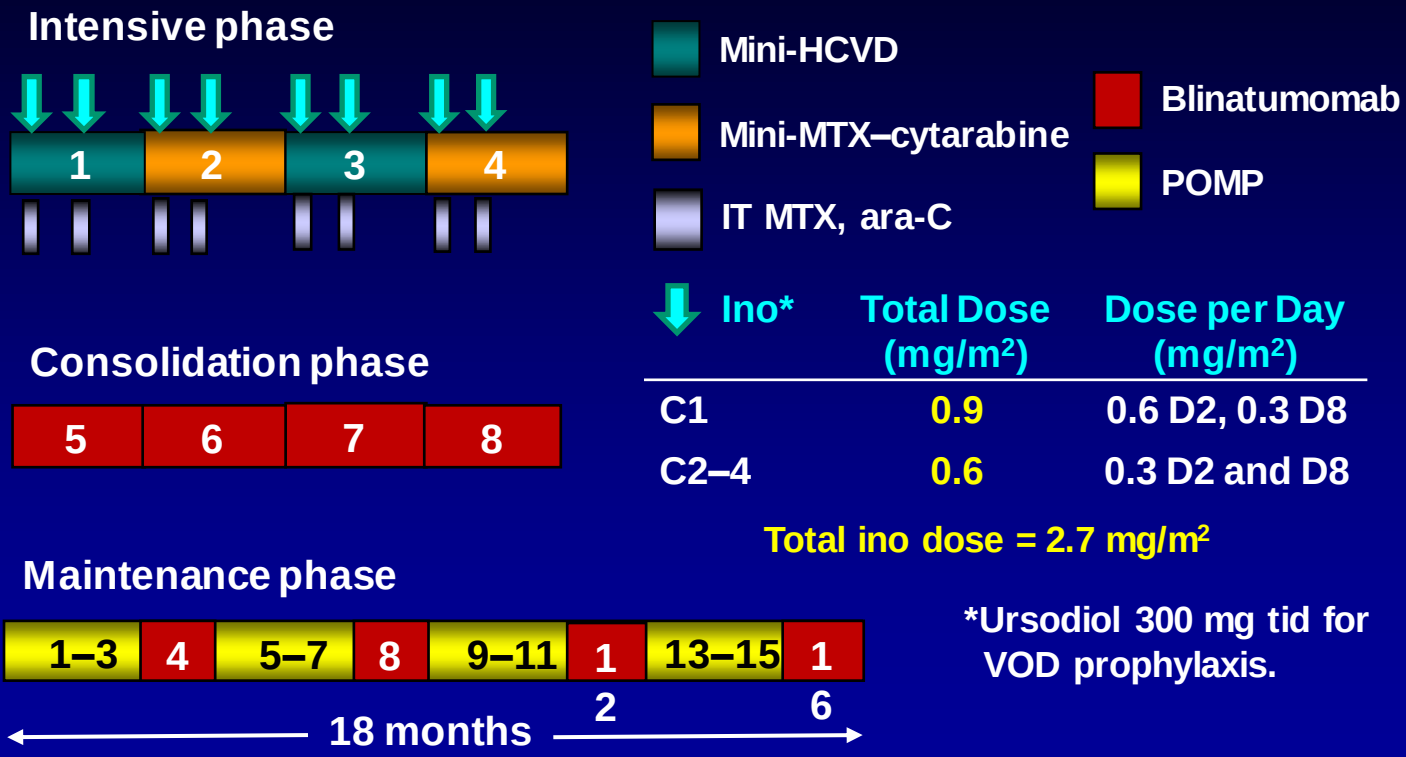
Richard-Carpentier. *Blood.* 2019;134:abstract 3807.

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)**

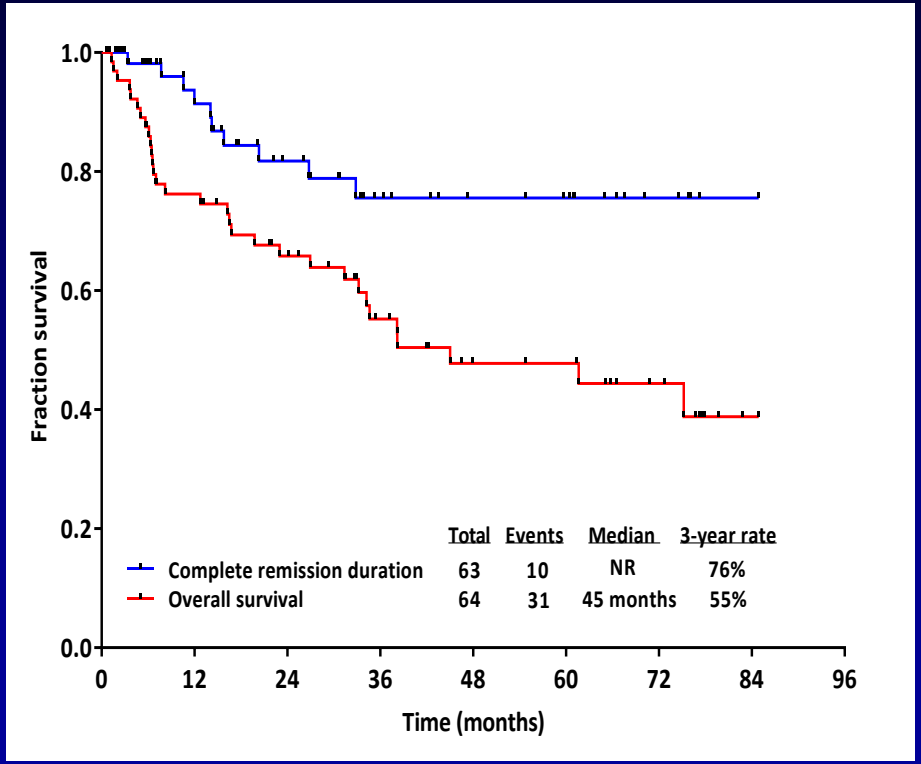
Response (N = 59)	N (%)
ORR	**58 (98)**
CR	51 (86)
CRp	6 (10)
CRi	1 (2)
No response	1 (2)
Early death	**0**

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

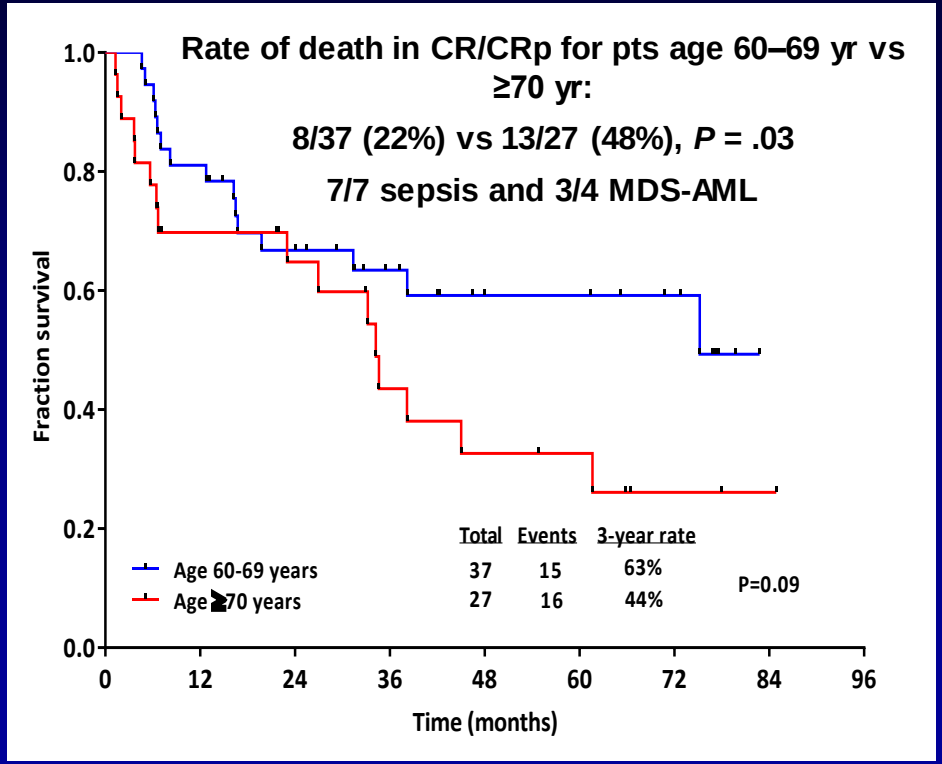
Short. *Blood.* 2019;134:abstract 823.

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

CRD and OS overall



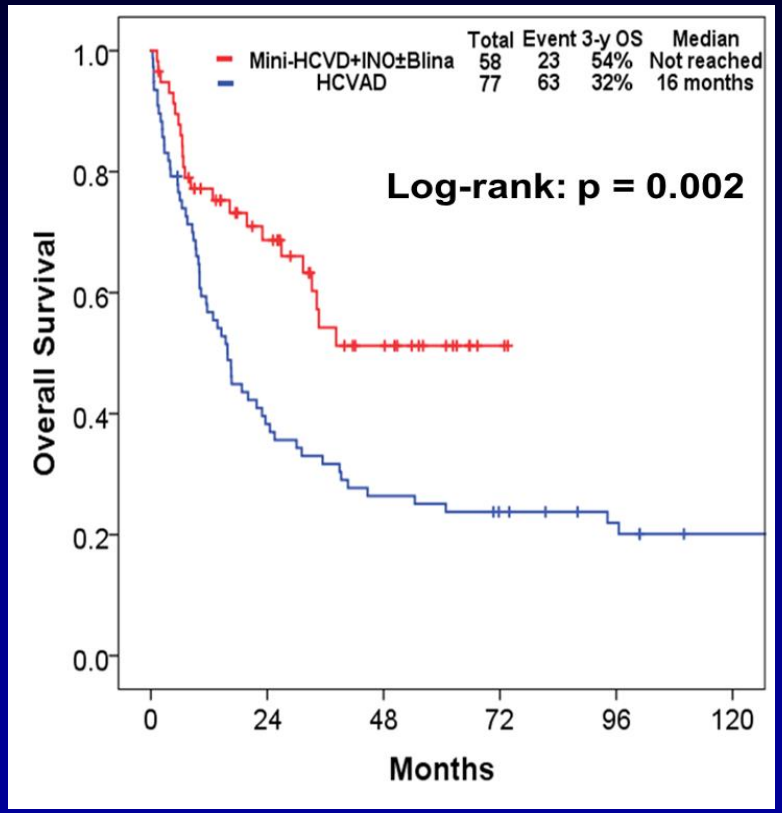
OS by age



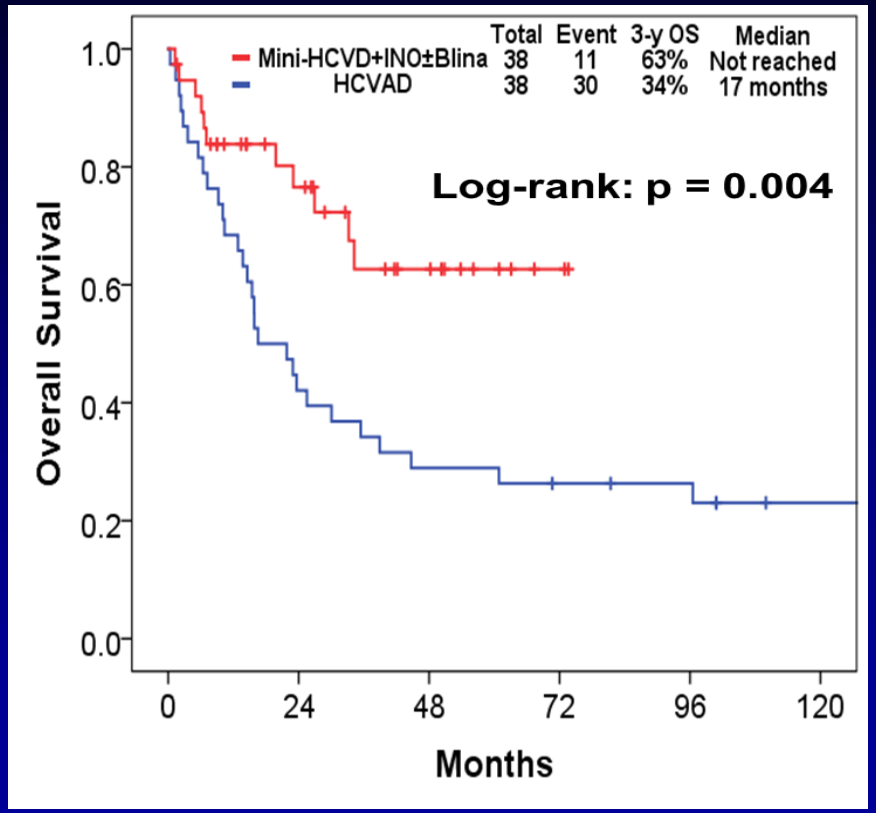
Short. *Blood.* 2019;134:abstract 823.

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

Prematched

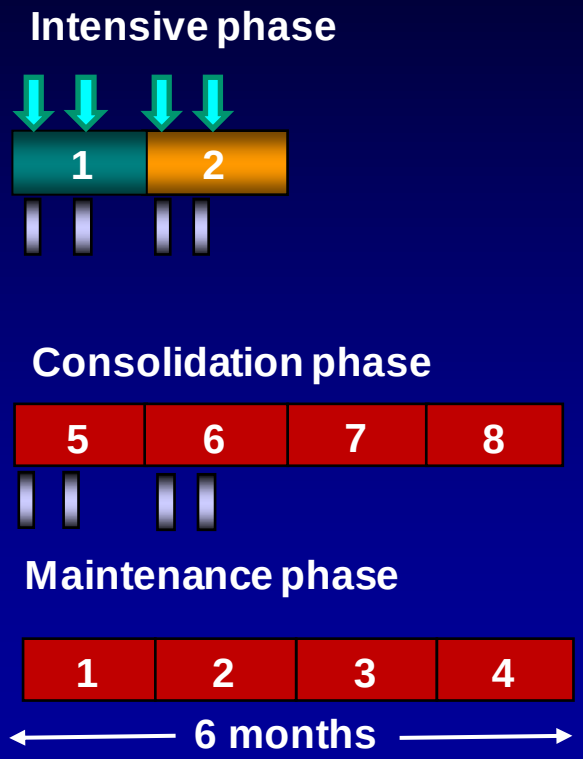


Matched



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

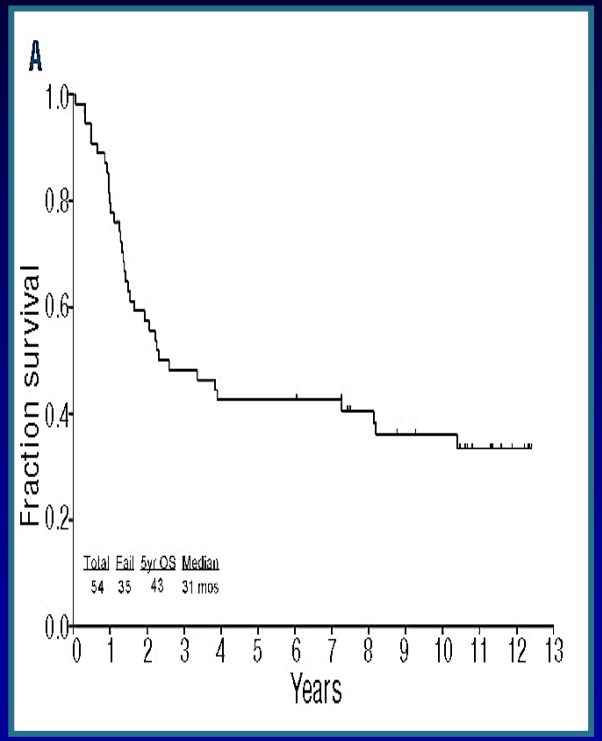
Total ino dose = 1.5 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis.

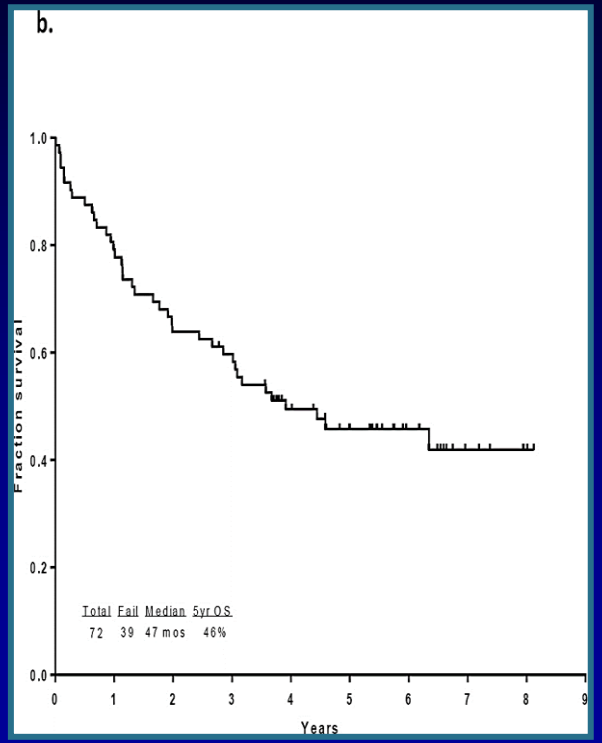
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Kantarjian H, et al. *Lancet Oncol.* 2018;19:240.

TKI for Ph+ ALL

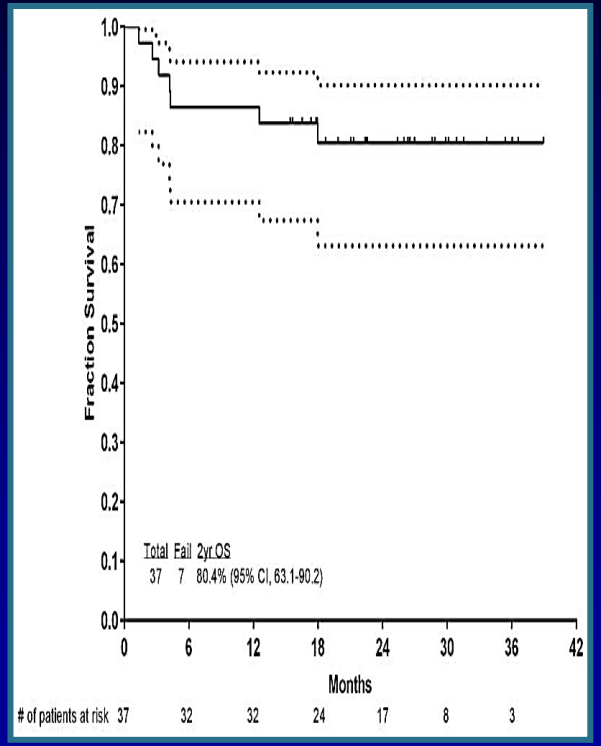
Imatinib: 5-yr OS = 43%



Dasatinib: 5-yr OS = 46%

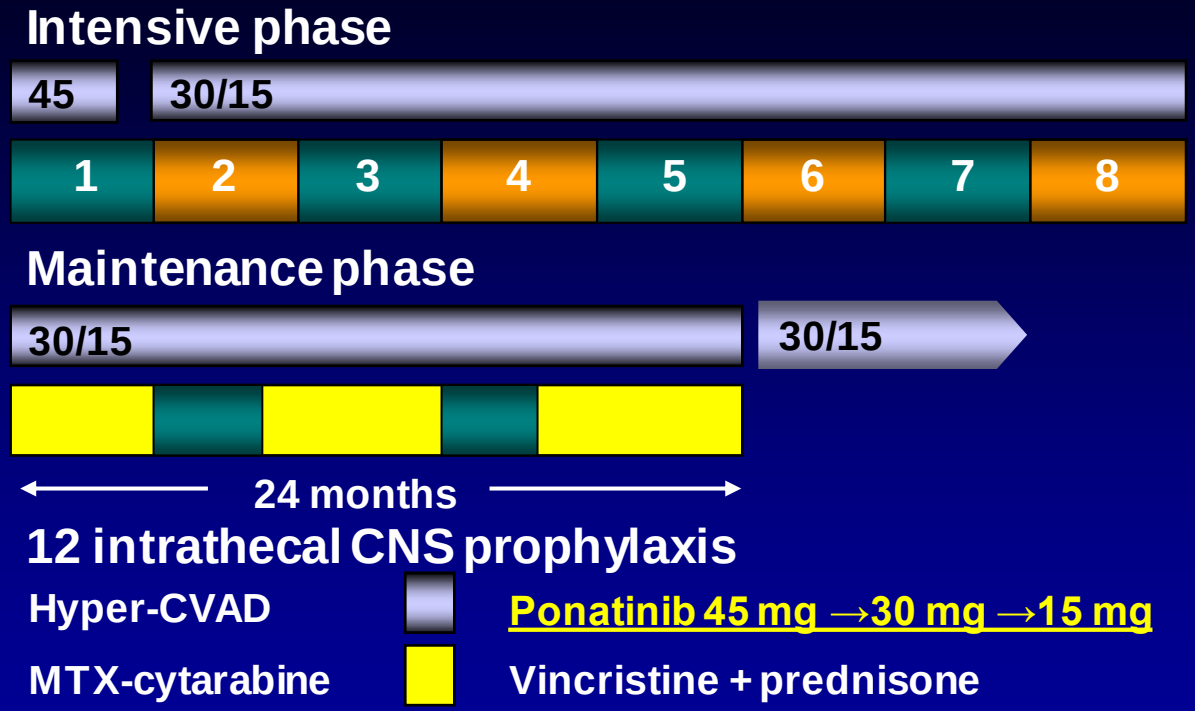


Ponatinib: 5-yr OS = 71%



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

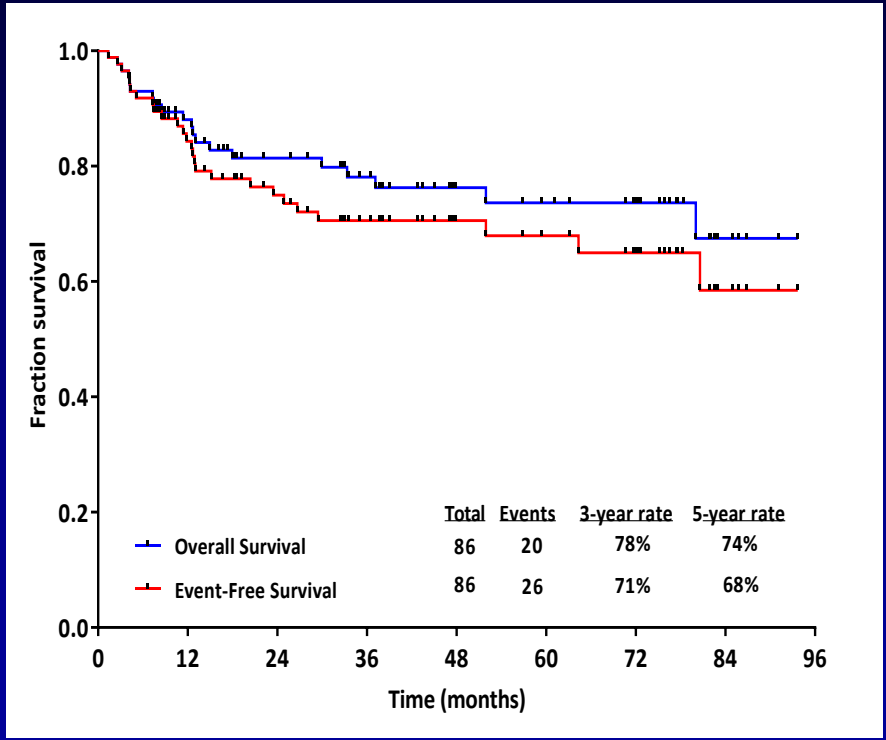
Median follow-up: 44 months (4–94 months)

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

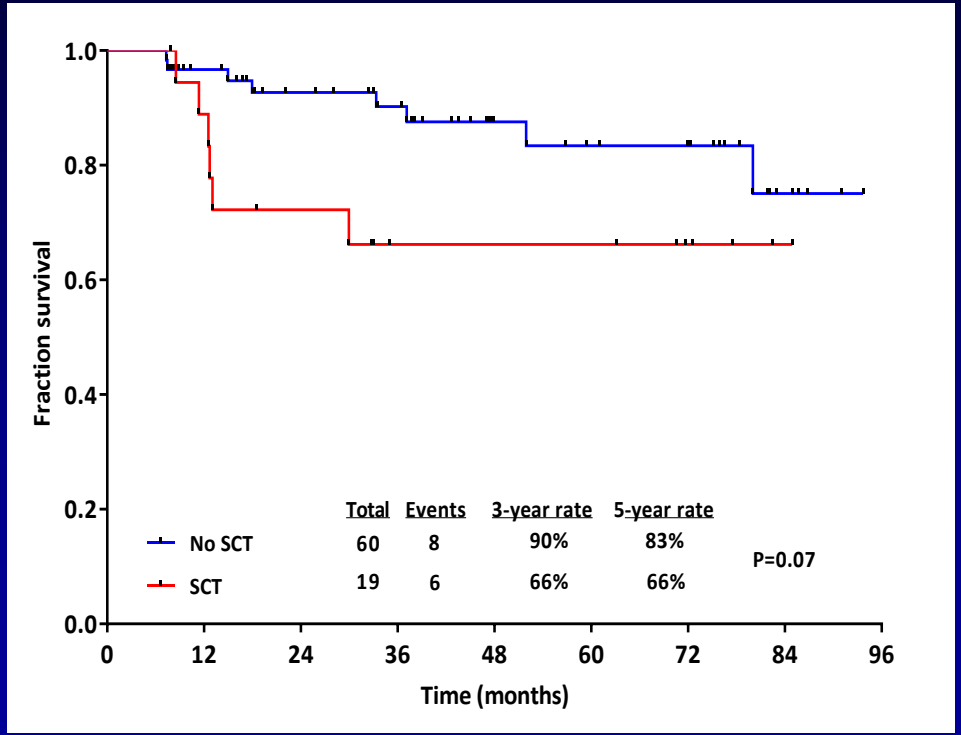
Short. *Blood*. 2019;134:abstract 283.

Hyper-CVAD + Ponatinib in Ph+ ALL: Outcome

EFS and OS



Impact of allo-SCT: 6-mo landmark

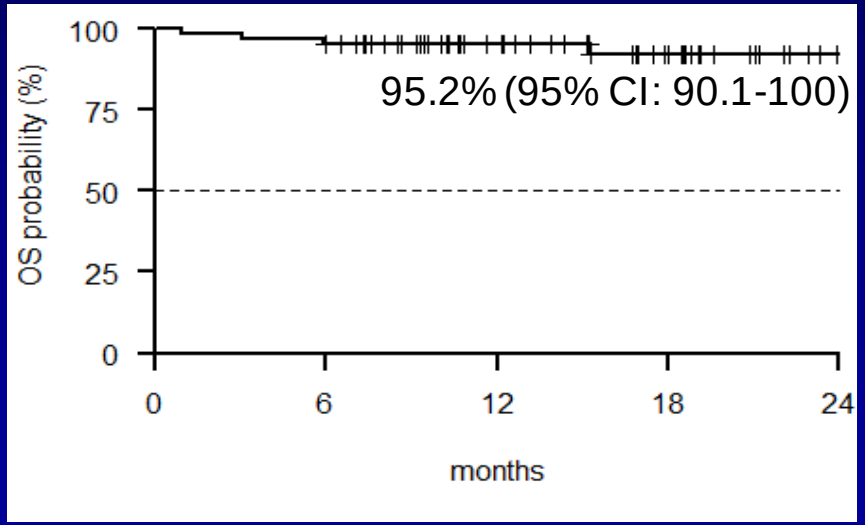


Short. *Blood*. 2019;134:abstract 283.

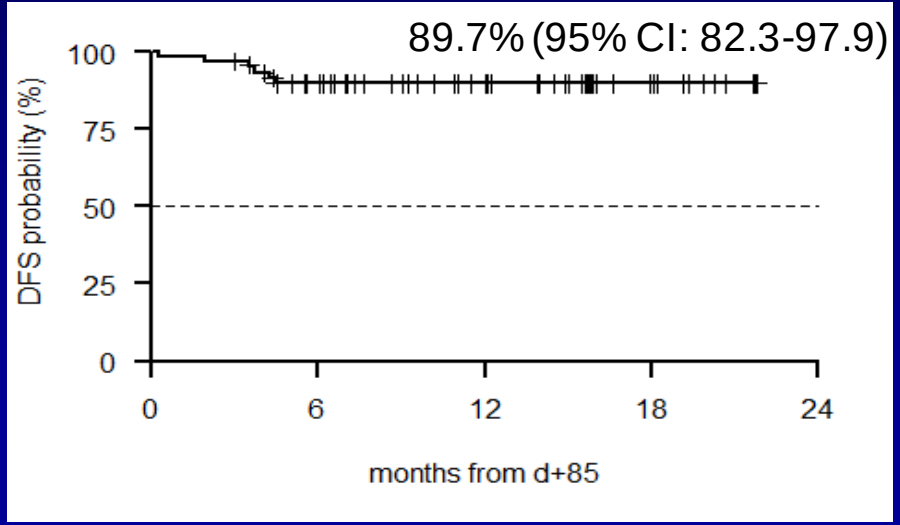
Dasatinib-Blinatumomab in Ph+ ALL

- 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

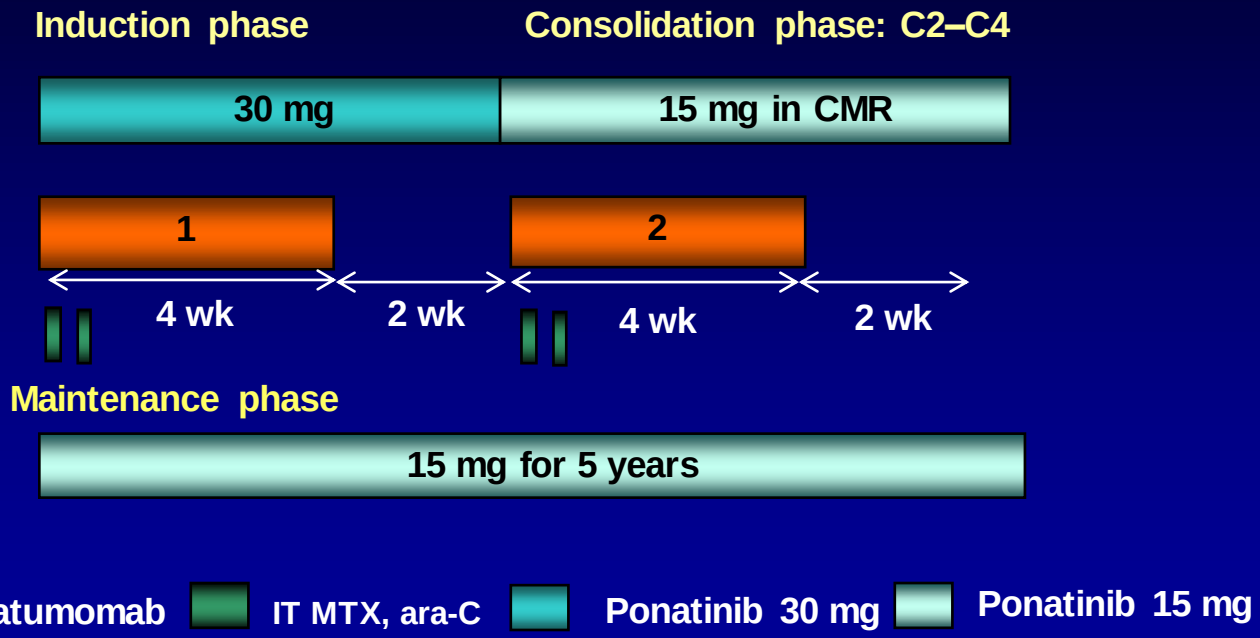


DFS



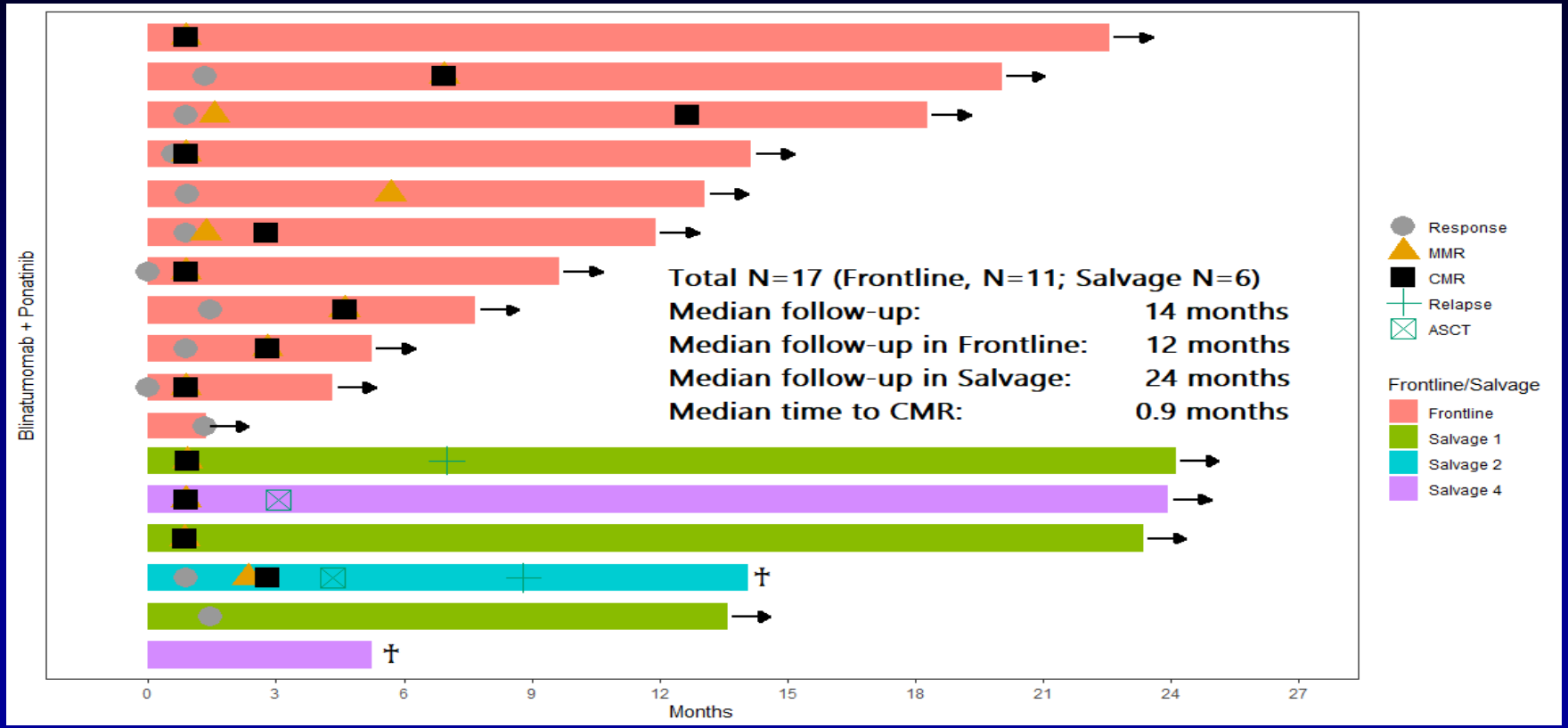
Chiaretti. *Blood.* 2019;134:abstract 615.

Blinatumomab-Ponatinib in Ph+ ALL



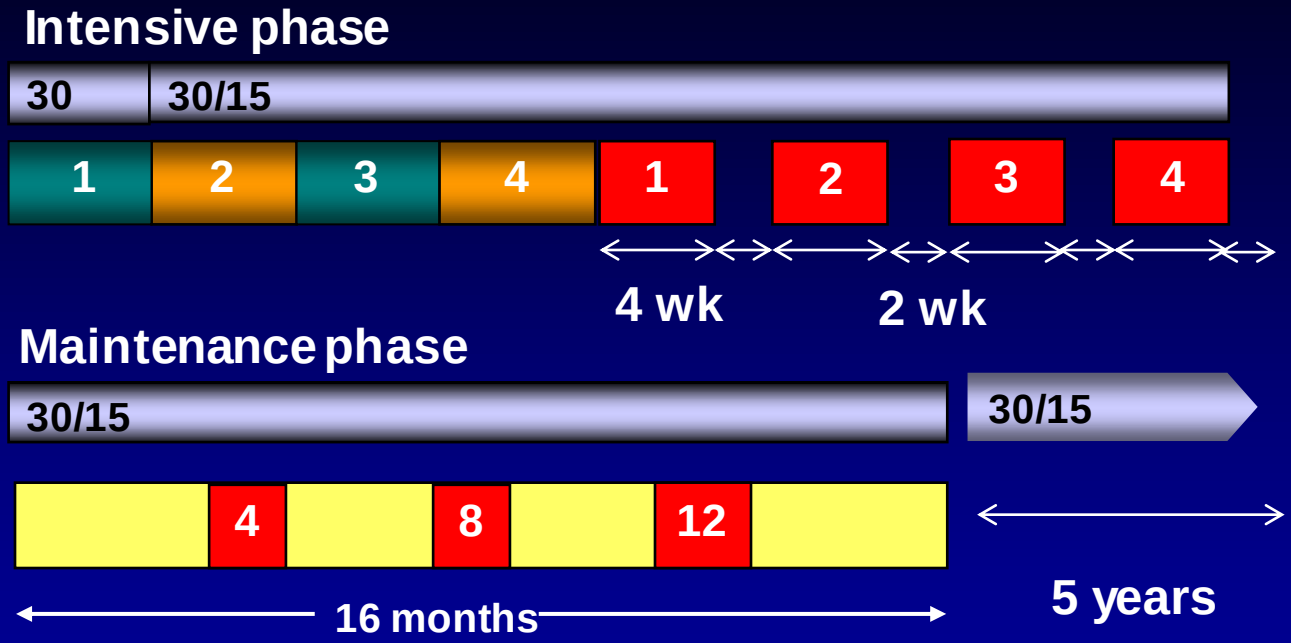
Assi. *Clin Lymphoma Myeloma Leuk.* 2017;17(12):897-901.

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

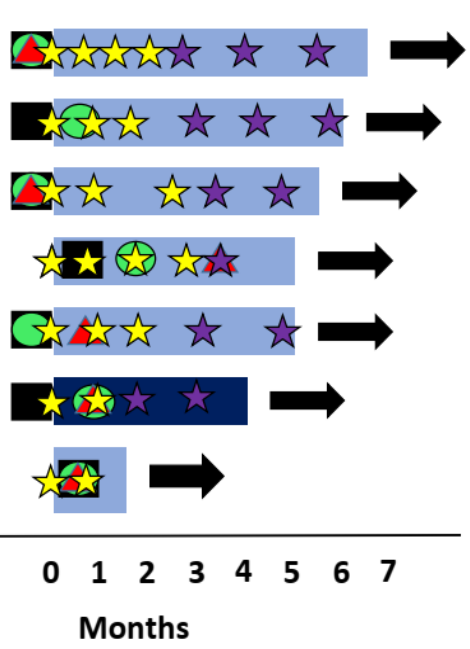
Vincristine + prednisone

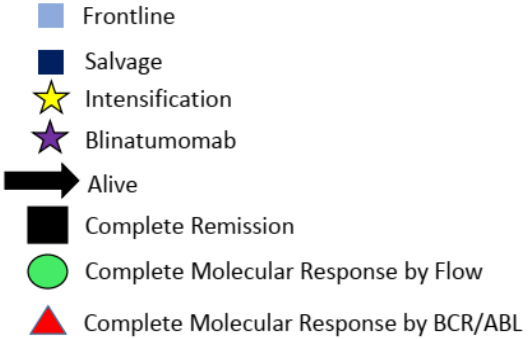
Blinatumomab

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?

a) Clinical trial
b) Hyper-CVAD
c) Rituximab–hyper-CVAD
d) Multidrug induction chemotherapy following previously published regimens (CALGB; Larson)
e) 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

Dieter Hoelzer

APTITUDE HEALTH

Current Treatment Options for Relapsed ALL in Adults and Elderly Patients

D. Hoelzer
J.W. Goethe University, Frankfurt

Emerging and Practical Concepts and Controversies in Leukemias
23–24 October 2020
VIRTUAL MEETING
Global Leukemia Academy

DISCLOSURES

- **Consultancy**:

  Amgen, Servier, Shire, Jazz Pharma, DKMS, GBG-IDMC, DSMB-Juno, Menarini

- **Honoraria (Invited Speaker):**

  Servier, Medac

- **Membership on an entity‘s Board**:

  DKMS, DJCLS, GBG-IDMC, DSMB-Juno

- **Discussion of off-label drug use**:

  not applicable

Question 1

For which targeted therapy is a loss of the targeted antigen/structure observed in the relapse situation? Several answers are possible

a) Rituximab
b) Inotuzumab
c) Ph+ ALL
d) BCR-ABL-like ALL
e) Blinatumomab
f) CAR T-cells

Question 2

What is the best option for a patient remaining MRD+ positive after induction/consolidation therapy?

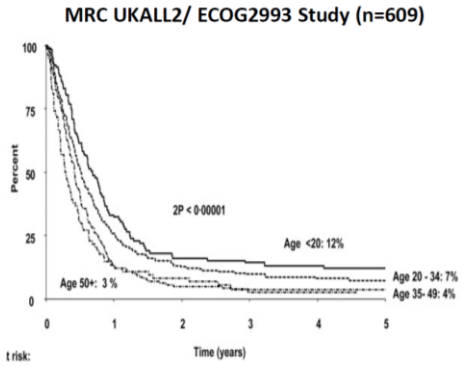
a) Other new drug/chemotherapy regimen
b) Autologous SCT
c) Allogeneic SCT
d) Immunotherapy

Results of Adult Pts With Rel./Refr. ALL

with Chemotherapy

Outcome of 609 adults after relapse of ALL

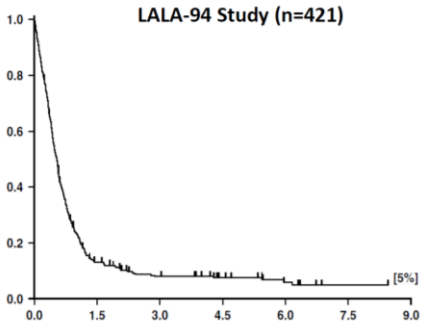
Fielding AK, et al. *Blood*. 2007;109:944-950



OS 7% at 5 yr

Outcome of treatment after 1st relapse in adult ALL

Tavernier E, et al. *Leukemia*. 2007; 21:1907-1914



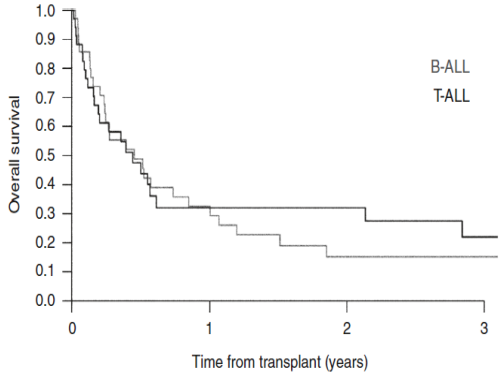
OS 8% at 5 yr

with allo-SCT

Outcome of allo-SCT in 115 adults with Rel/Ref ALL

Bazarbachi AH, et al. *BMT*. 2020;55:595-602

- **74% relapsed, 26% prim refractory**
- **49% T-ALL, 23% Ph+ ALL**



OS 17%, 14% LFS at 2 yr

- **Poor results with Chemotherapy**
- **Only moderate improvement with SCT**

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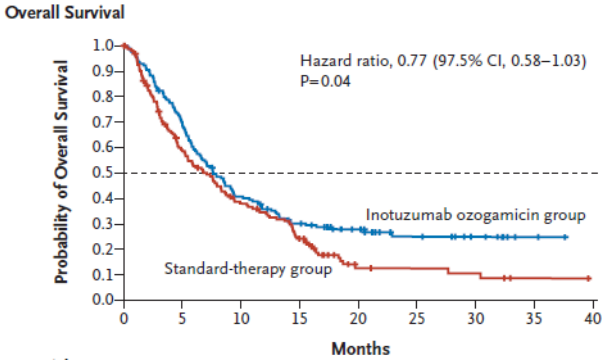
Randomized Trials with Immunotherapy in Relapsed/Refractory ALL

Inotuzumab

Kantarjian et al., New Engl J Med 2016

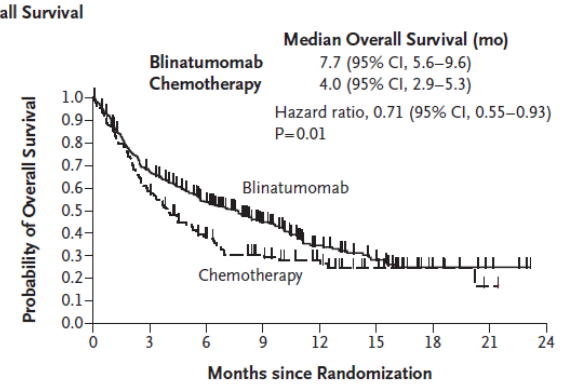
	Ino	SOC*
CR/CRi	81%	29%
MRD CR	78%	28%
Later SCT	41%	11%



Blinatumomab

Kantarjian et al. , New Engl J Med 2017

	Blina	SOC*
CR/CRh/CRp	44%	25%
Mol CR	76%	48%
SCT	24%	24%



- In current randomized trials, still very low CR rates and poor Overall Survival with Standard of Care (SOC) Chemotherapy

→ Need for improvement in Rel-/Refr. pts by inclusion of Targeted Therapy

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To Improve Outcome in Adult Rel./Refr. ALL, What are the next steps to do?

1. De-escalate chemotherapy and thereby, reduce toxicity, since death in CR after chemo ≥ 5%, by

   Low Intensive Chemotherapy, or even

   Chemo-free Therapy; only Corticosteroids + TKI

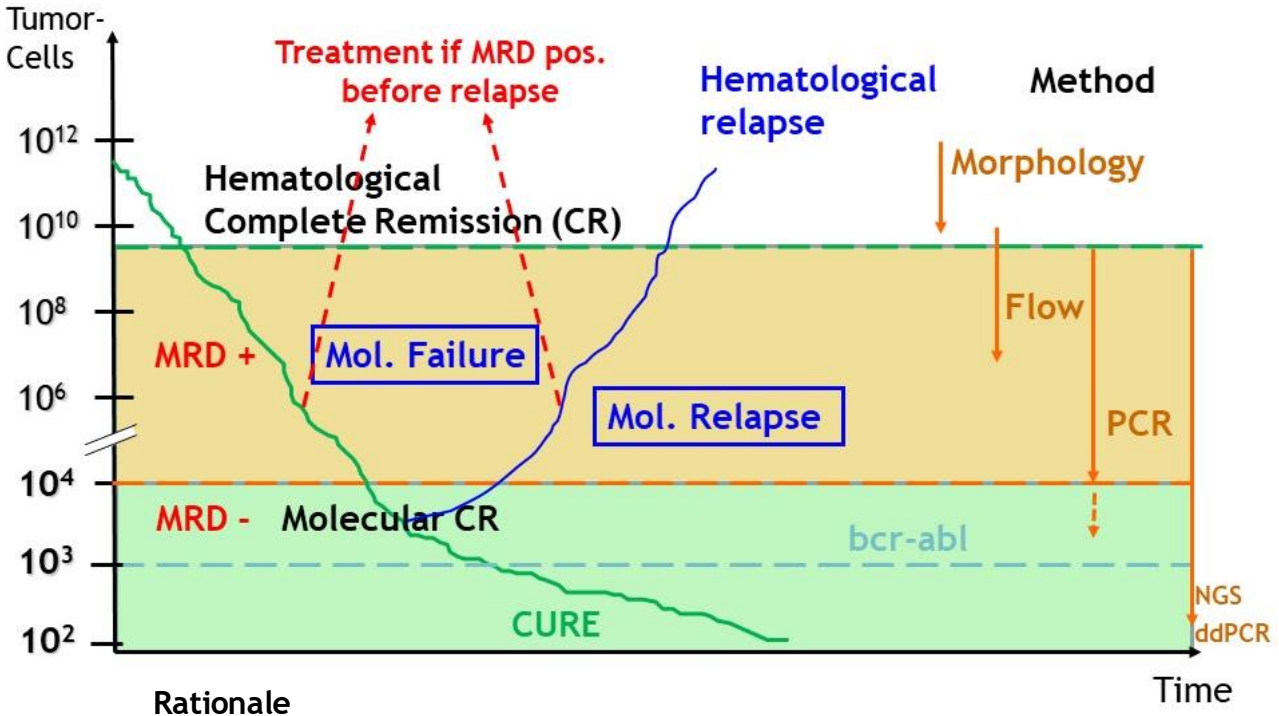
2. Make the SCT better tolerable, particularly reduce TRM

3. Include Targeted Therapies;

   - Tyrosine Kinase Inhibitors (TKIs)
   - Immunotherapies
   - Checkpoint Inhibitors

→ Increase the rate of Molecular Remission (MolCR)

Minimal Residual Disease Detection and Clinical Course



Rationale

- MRD positivity is a relapse ! at lower sensitivity level
- Adult MRD positive pts will <u>all</u> relapse

→ Conversion MRD positivity to MRD negativity thereby improve outcome

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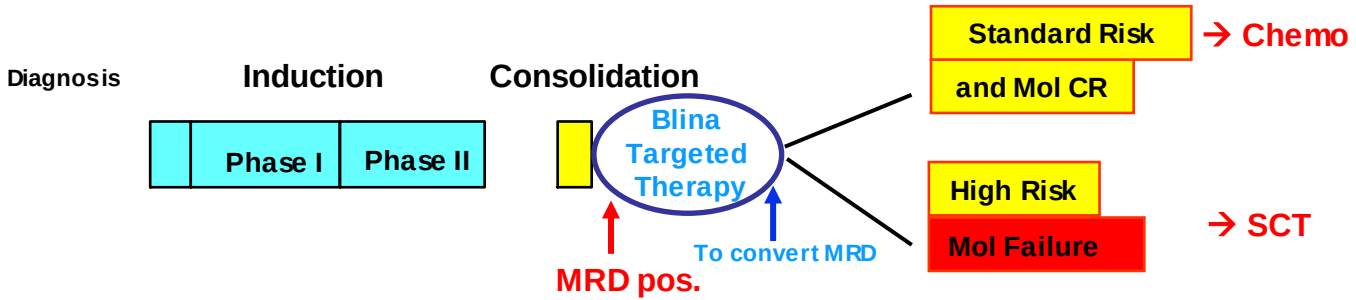
Conversion of MRD pos. to MRD neg in B-lineage ALL by Blinatumomab (GMALL Study 07/2003)

Gökbuget, N. + Hoelzer, D. et al_Blood ASH abstract 139_2017



Molecular Failure	N	Mol CR	Mol. F
Chemo	56	23%	64%
Blinatumomab	11	91%	9%
Molecular Relapse			
Chemo	26	42%	46%
Blinatumomab	15	100%	0%

→ B-lineage pts. MRD pos. after Ind/Cons can be converted to MRD neg. in on-going studies 70-80%

Hoe 6/2020

Anti-CD3/CD19 Bispecific Antibody Blinatumomab in Adult Relapsed or Refractory ALL

Reference	N	CR Rate	MRD Rate	HSCT Rate	Median OS
Topp et al *Lancet Oncol* 2015 NCT01466179	189	43%	82%	40%	6.1 mo
Martinelli et al *JCO* 2016 NCT02000427	45	36%	88%	44%	7.1 mo
Kantarjian et al *NEJM* 2017 NCT02013167	271	44%	76%	24%	7.7 mo
Topp et al *JCO* 2017 NCT02309286	36	69%	88%	52%	9.8 mo

- **High CR rate for Rel/Refr pts**
- **Substantially higher rate of MRD negativity, leading to more SCT**
- **But only marginal improvement in overall outcome**
- **Loss of CD19 in 10-20% of relapse pts**

Adapted from Richard-Carpentier G, et al. Curr Hematol Malig Rep. 2019;14:106-118.

Blinatumomab: Ongoing Studies in Rel./Refr. ALL pts.

Trial Identifier	Setting	Regimen	Ph	Phase
NCT01371630	R/R, frontline	Mini hyper-CVD + INO ± BLN	–	II
NCT03518112	R/R	Mini hyper-CVD + BLN	–	II
NCT02997761	R/R	BLN + ibrutinib	–/+	II
NCT03160079	R/R	BLN + pembrolizumab	–/+	I/II
NCT03263572	R/R, frontline	BLN + ponatinib	+	II
NCT03147612	R/R, frontline	BLN + hyper-CVD + ponatinib	+	II
NCT02003222	R/R, frontline	Chemotherapy + asparaginase ± BLN	–	III
NCT02877303	Frontline	Hyper-CVAD + BLN	–	II
NCT02143414	R/R, frontline	BLN + POMP	–	II
NCT02143414	R/R, frontline	BLN + dasatinib	+	II
NCT03628053	R/R	BLN or INO vs tisagenlecleucel	–/+	III
NCT03160079	R/R	BLN + pembrolizumab	–/+	I/II
NCT03512405	R/R	BLN + pembrolizumab	–/+	I/II
NCT02879695	R/R, frontline	BLN + nivolumab, BLN + nivolumab + ipilimumab	–/+	I

Abbreviations: Ph, Philadelphia chromosome; NCT, national clinical trial identifier; R/R, relapsed or refractory B-cell acute lymphoblastic leukemia; BLN, blinatumomab; INO, inotuzumab-ozogamicin; POMP, prednisone, vincristine, methotrexate, 6-mercaptopurine; CVD, cyclophosphamide, vincristine, dexamethasone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone.

→ **Blina combination with chemotherapy, TKIs, checkpoint inhibitors**

Franquiz MJ, Short NJ. Biologics. 2020;14:23-34.

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Anti-CD22 Inotuzumab for Rel./Refr. Adult ALL

References	N	ORR Rate	MRD Rate	HSCT Rate	Median OS
Inotuzumab (Besponsa®)					
Kantarjian et al *Lancet Oncol* 2012	49	57%	63%	40%	5.1 mo
Kantarjian et al *Cancer* 2013	90	58%	72%	40%	6.2 mo
Kantarjian et al *NEJM* 2016	109	81%	78%	41%	7.7 mo
De Angelo et al *Blood Adv* 2017	72	68%	84%	33%	7.4 mo
Inotuzumab (Besponsa) + mini-hyper-CVD					
Jabbour et al *JAMA Oncol* 2018	59	78%	82%	44%	11 mo

- In Rel/Ref pts high CR and high MolCR rate of ~70-80%
- Hepatotoxicity: VOD 8-16%
  Increased risk with number of prior chemo and/or SCT, current: lower dose and max 2-3 cycles, before SCT

→ Ino achieves fast tumor debulking!

Adapted from Richard-Carpentier G, et al. *Curr Hematol Malig Rep*. 2019;14:106-118.

Anti-CD19 CAR-T Cells and SCT in Rel./Ref. ALL

	Studies	No. of pts	Median age (range)	No. of allo SCT preCAR	CAR Design (vector)	No. of CR/CRi (%)	No. allo SCT postCAR
Adults (A)	**Frey** JCliOnco 2016	27	44 (21-72)	33 %	4-1BB/CD3ξ	56%	NA
	Turtle JCliInvest 2016	30	40 (20-73)	37 %	4-1BB/CD3ξ	97%	43 %
	DeAngelo Annu SITC 2017	38	39 (19-69)	37 %	CD28/CD3ξ	37%	NA
	Park NEJM 2018	53	44 (23-74)	36 %	CD28/CD3ξ	83%	32 %
	Shah JCliOnco 2018	18	42 (18-69)	NA	CD28/CD3ξ	72%	NA

- High CR and MRD rates of ~80% in advanced B-lin ALL
- CAR-T acts on extramedullary sites, particularly CNS
- Toxicity; particularly CRS and Neurotoxicity severe, but manageable, death < 1%
- High rate of CD19 neg relapse
- Need of SCT after CAR-T unclear
  Frequency of SCT from 10% to „all“ pts („bridge to SCT“)
- Frontline CAR-T cells trials ongoing !

Indications, Efficacy, and Toxicity in Immunotherapies for Rel./Refr. B-Lineage ALL

	Blinatumomab	InO	CAR T
Application	Mono ± Combi	Combi with chemo	Mono
FDA approval	R/R or MRD+ B-ALL	R/R B-ALL	R/R B-ALL
Age	Age: any ~80 yr	Age: 18+ yr ~80 yrs	Age: ≤26 yr ?
Efficacy	CR: 36-44% MRD-: 76% Median OS: 6.1-9.8 mo	CR: 58-80% MRD-: 78% Median OS: 5.1-7.7 mo	CR: 81-93% MRD-: 81% Median OS: 12.9 mo
Toxicity	Neuro, CRS reversible	VOD	Neuro, CRS reversible
Role of HSCT	Improves OS?	Effect?	Need, unclear
Potential indications	Low tumor burden MRD positivity Hepatic toxicity or comorbidity	High leukemia burden Neurologic toxicity or comorbidity	Low tumor burden Relapses after SCT Extramedullary relapse Failure of other immunotherapies

Adapted from Curran E. SOHO 2020.

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Q&A

APTITUDE HEALTH

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Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in adult and elderly patients

APTITUDE HEALTH

Global Leukemia Academy

Patient case presentation: Elderly patient with BCP-ALL

Philippe Rousselot

APTITUDE HEALTH

Case presentation (1)

- 72-year-old male
- Comorbidities
  - Arterial hypertension
  - Type 2 diabetes
- Medications: amiodarone, amlodipine, perindopril, verapamil, pravastatin, and insulin
- Autonomous at home with his wife
- Back and leg pain, fever
- WBC: Hb: 105 g/L, WBC count: 0.9×10^9/L, Platelets: 83×10^9/L
- Spontaneous tumor lysis syndrome

Case presentation (2)

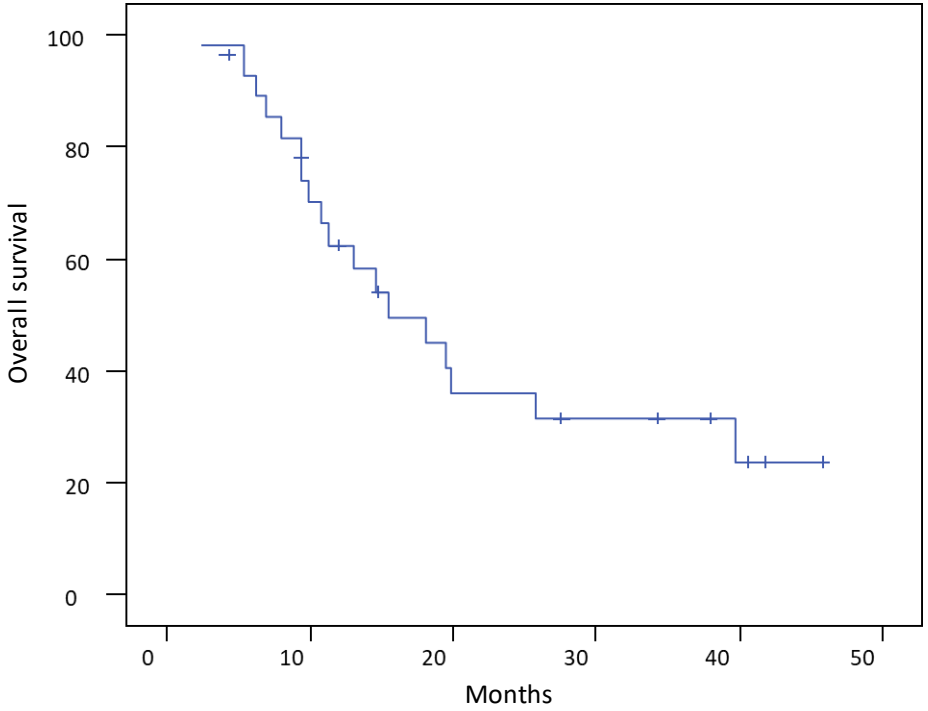
- BM aspiration
  - 95% blasts, CD34+, CD38+, CD123+, TdT+, CD10+, CD19+, CD20+, CD22+, cμIg, cCD3-, MPO- and aberrant CD13+, CD33+
- Normal karyotype
- Molecular biology
  - IKZF1 non deleted
  - ERG non deleted
  - IgH and TCR clonal rearrangements detected
  - BCR-ABL negative
  - No Ph-like

Question 1

What is your preferred therapeutic option?

a) Palliative care
b) Chemotherapy-based induction
c) Monoclonal antibody-based induction
d) Chemoimmunotherapy (B and C)

EWALL backbone (dose-adapted chemotherapy)



Median OS is 15.5 mos

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Unpublished data from the EWALL group.

Inclusion in the EWALL-INO European trial

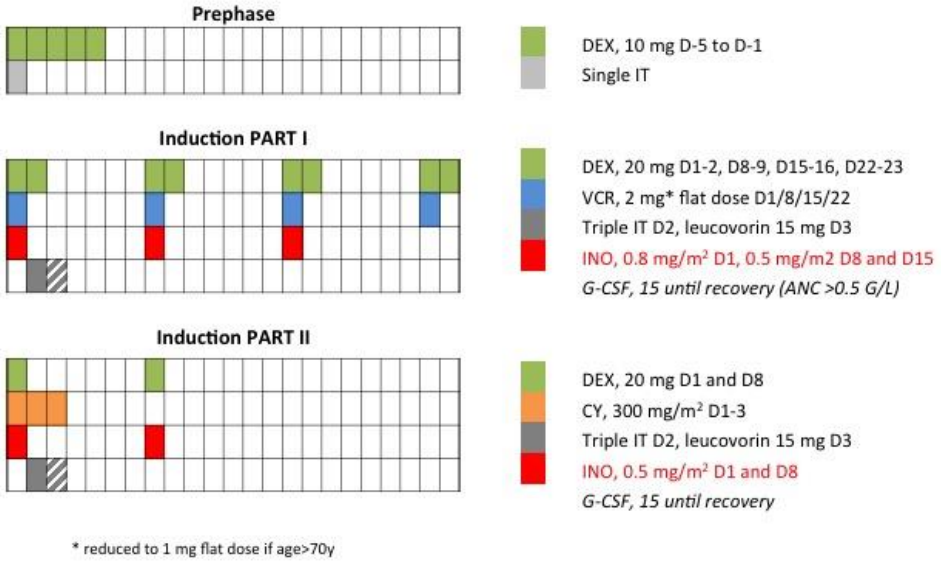
EudraCT: No. 2016-004942-27

A Phase II Study of **Inotuzumab Ozogamicin** (INO) Combined to Chemotherapy in Older Patients with Philadelphia Chromosome-negative CD22+ B-cell Precursor Acute Lymphoblastic Leukemia

130 patients planned

81 patient included
CR rate: 92%

Induction phase



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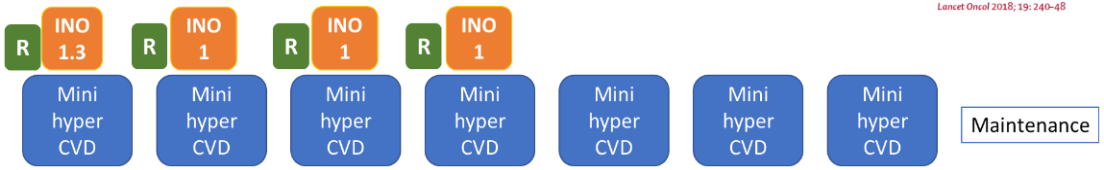
https://clinicaltrials.gov/ct2/show/NCT03249870

Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study

Hagop Kantarjian, Farhad Ravandi, Nicholas J Short, Xuelin Huang, Nitin Jain, Koji Sasaki, Naval Daver, Naveen Pemmaraju, Joseph D Khoury, Jeffrey Jorgensen, Yesid Alvarado, Marina Konopleva, Guillermo Garcia-Manero, Tapan Kadia, Musa Yilmaz, Gautam Bortakhur, Jan Burger, Steven Kornblau, William Wierda, Courtney DiNardo, Alessandra Ferrajoli, Jovitta Jacob, Rebecca Garris, Susan O'Brien, Elias Jabbour



Lancet Oncol 2018; 19: 240–48

- Pts ≥60 years (yrs) with newly-diagnosed B-cell ALL were eligible
- The first 6 pts received **1.3 mg/m² for cycle 1 followed by 0.8 mg/m²** for subsequent cycles
- Pts 7 onwards received **1.8 mg/m² for cycle 1 followed by 1.3 mg/m²** for subsequent cycles

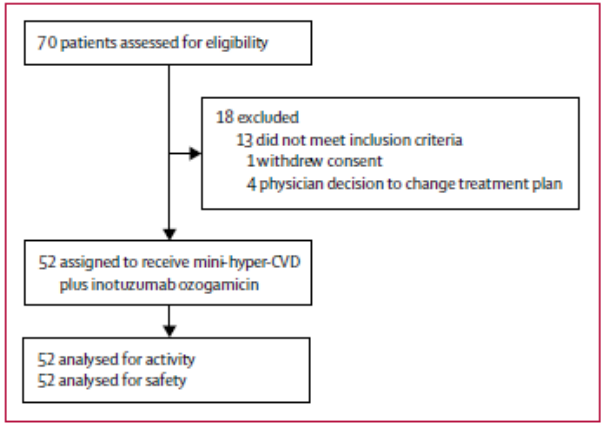


Figure 1: **Trial profile**
Mini-hyper-CVD=low-intensity cyclophosphamide, vincristine, and dexamethasone. No patients were lost to follow-up.

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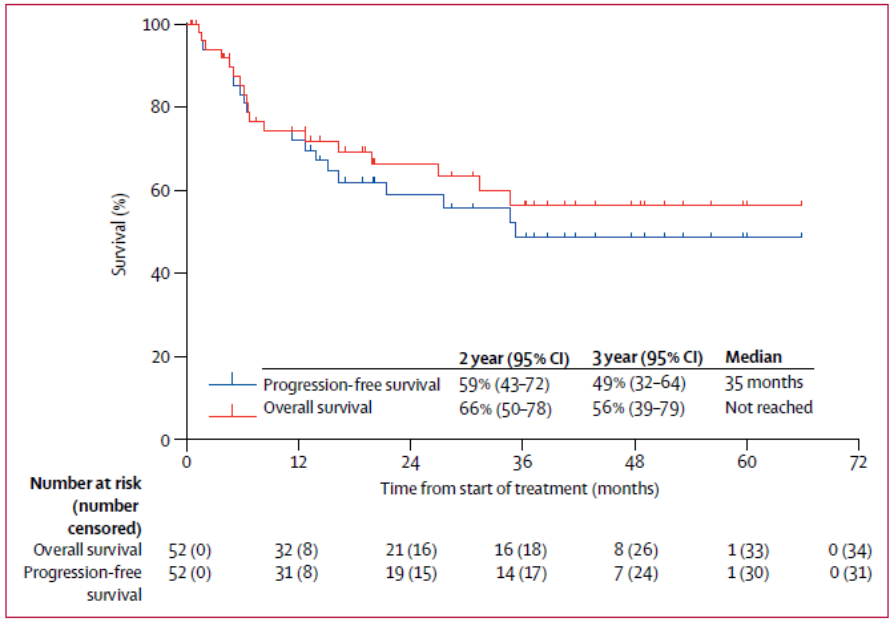
Jabbour E, et al. ASH 2014 & 2015; Kantarjian HG, et al. *Lancet Oncol.* 2018;19(2):240-248.

MiniHCVD-INO in elderly de novo ALL – results



N = 52
CR: 84%
Age: 68 y (64–72)
Median 4 cycles (1–8)
No death in induction!
Grade 3/4 hepatic: 33%
VOD: n = 4, 8% (1 post allo)
3 allo
3y OS: 56%

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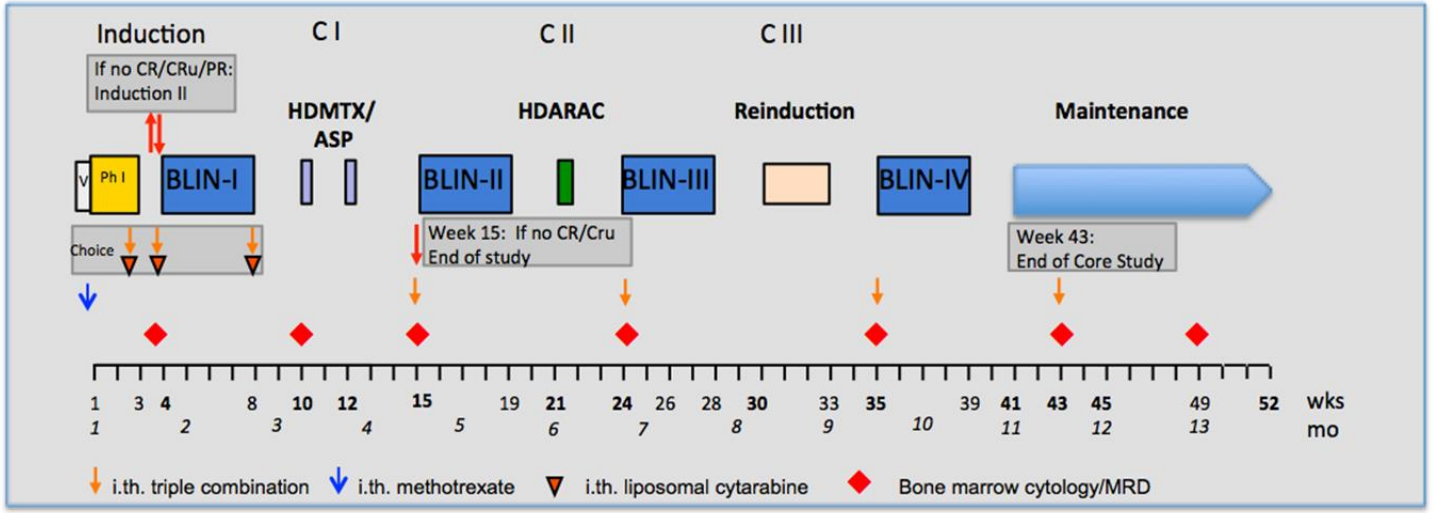
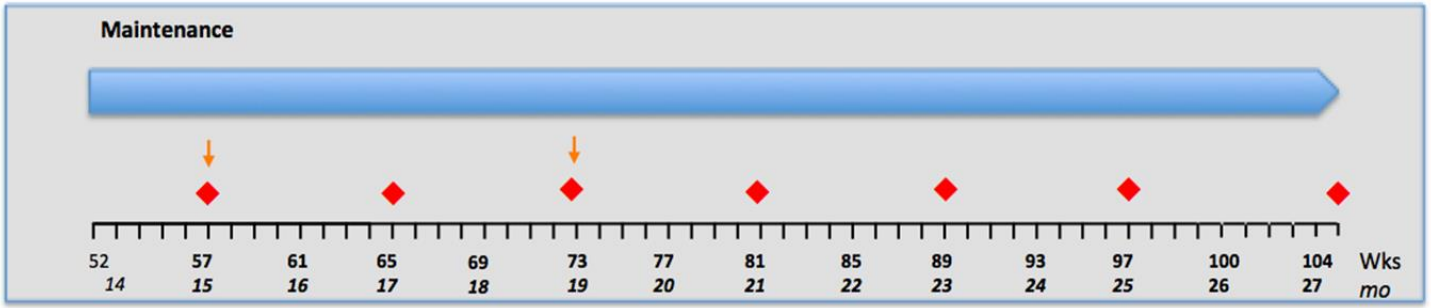
Kantarjian HG, et al. *Lancet Oncol.* 2018;19(2):240-248.

EWALL - BOLD: Overview





https://clinicaltrials.gov/ct2/show/NCT03480438.

Case presentation (3)

- Myocardial infarction during aplasia (recovered)
- Klebsiella pneumonia infection during aplasia (recovered)

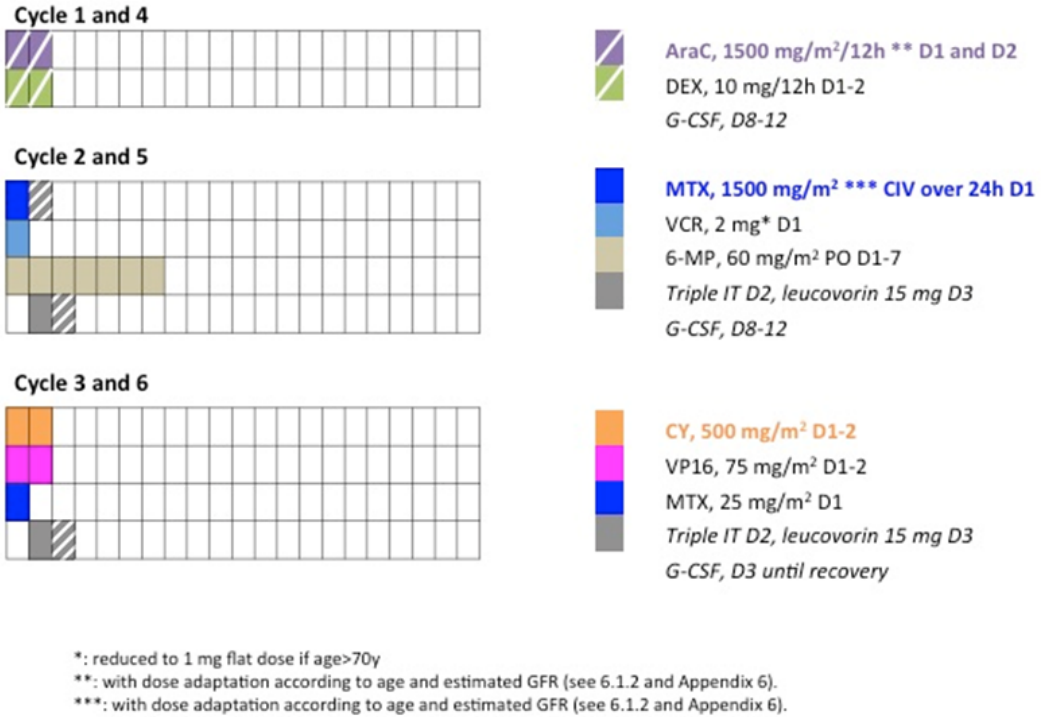
- Complete remission
- MRD IgH/TCR: 5×10^{-3}

Question 2

What is your preferred therapeutic option?

a) Chemotherapy-based consolidation
b) Blinatumomab
c) Continue inotuzumab
d) Rituximab
e) Allogenic HSC transplantation
f) CAR T cells
g) No consolidation

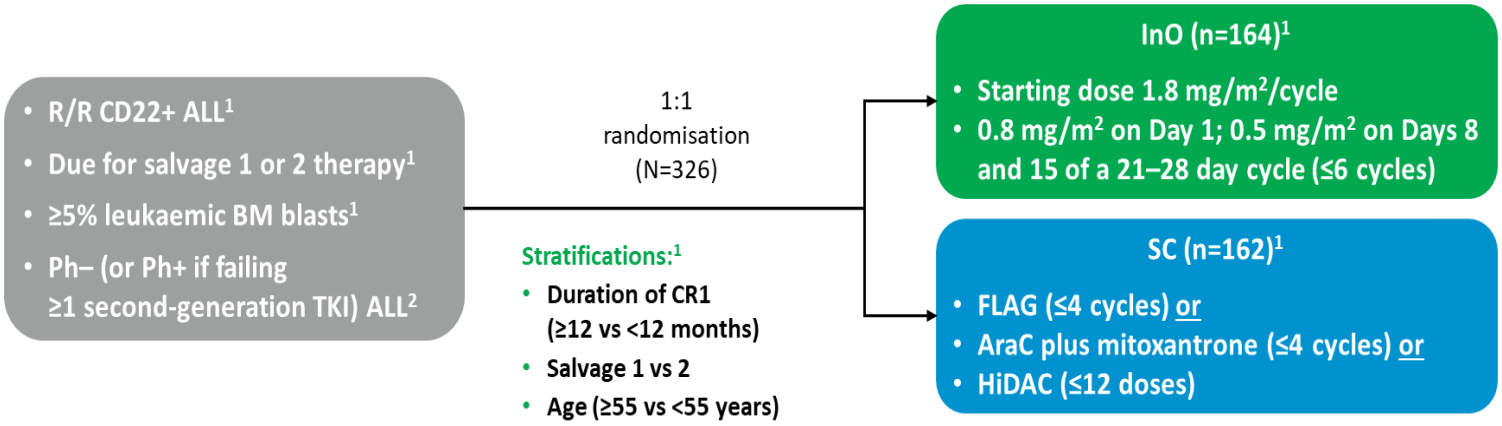
Consolidation in the EWALL-INO study



*: reduced to 1 mg flat dose if age>70y
**: with dose adaptation according to age and estimated GFR (see 6.1.2 and Appendix 6).
***: with dose adaptation according to age and estimated GFR (see 6.1.2 and Appendix 6).

https://clinicaltrials.gov/ct2/show/NCT03249870.

VOD risk and INO cycles – Lessons from INO-VATE



Cycle 1: 8.3% (1/12)	Cycle 2: 18.5% (5/27)	Cycle 3: 23.1% (6/26)	Cycles 4–6: 41.7% (5/12)

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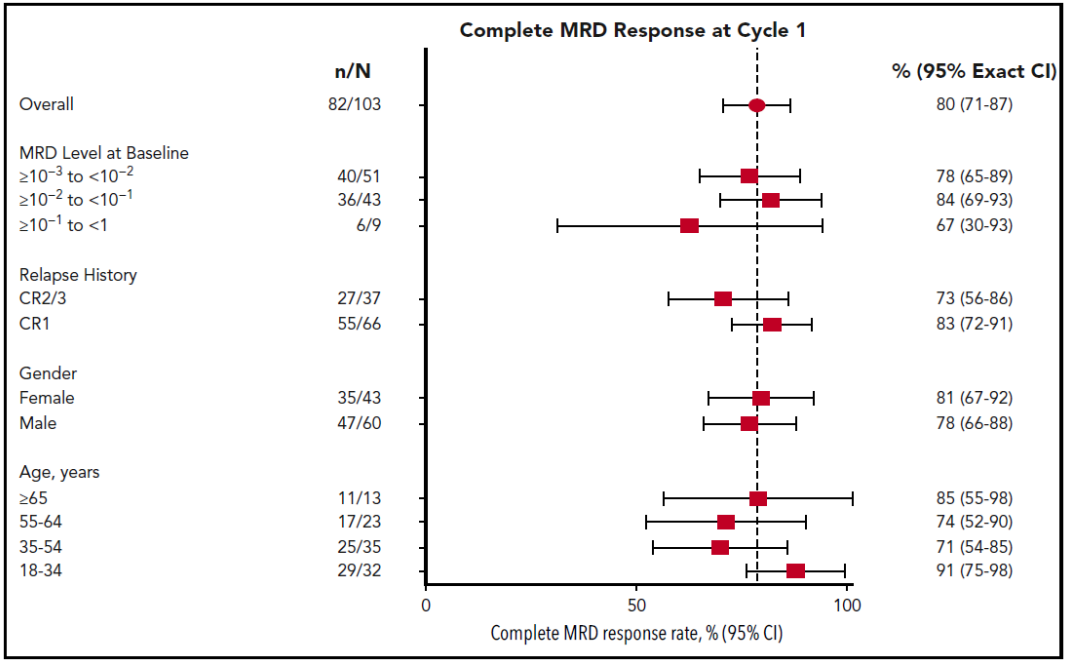
Kantarjian HM, et al. *Lancet Haematol*. 2017;4:e387-e398.

Blinatumomab in MRD+ BCP-ALL – the BLAST trial

- Phase II
- MRD-positive BCP-ALL
- Blina 15 μg/m²/day 4w on, 2w off
- 1 + 3 cycles
- Primary enpoint : MRD negativity rate
  - **Overall: 80%**



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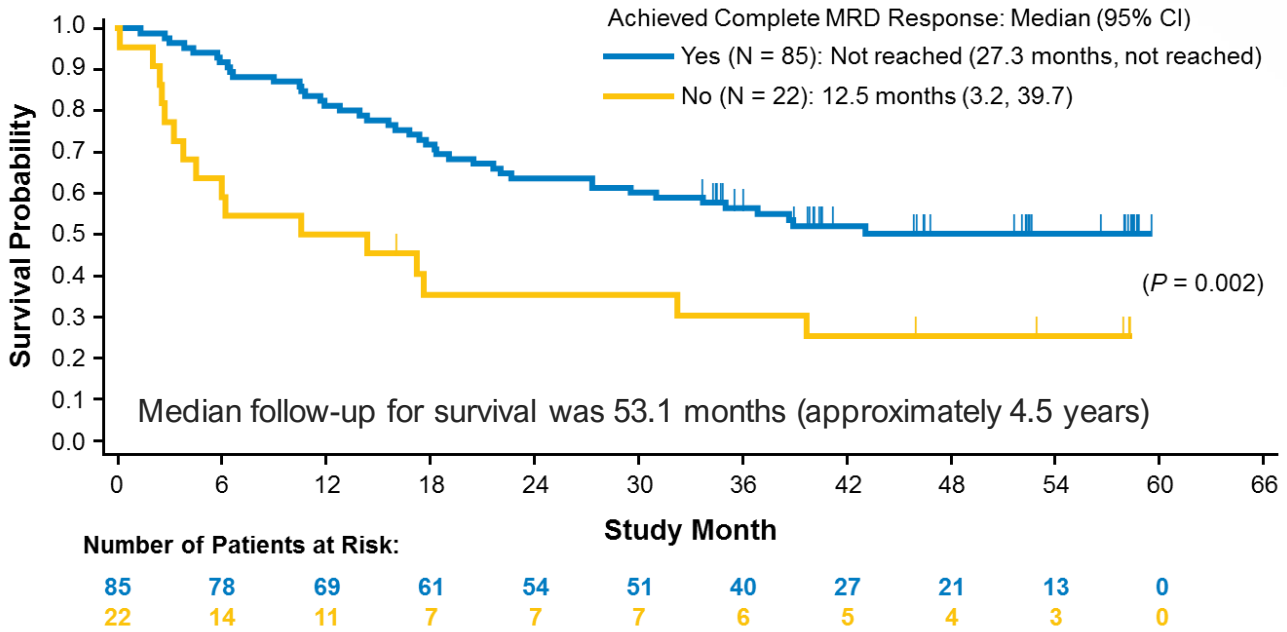
Gökbuget N, et al. *Blood.* 2018;131(14):1522-1531.

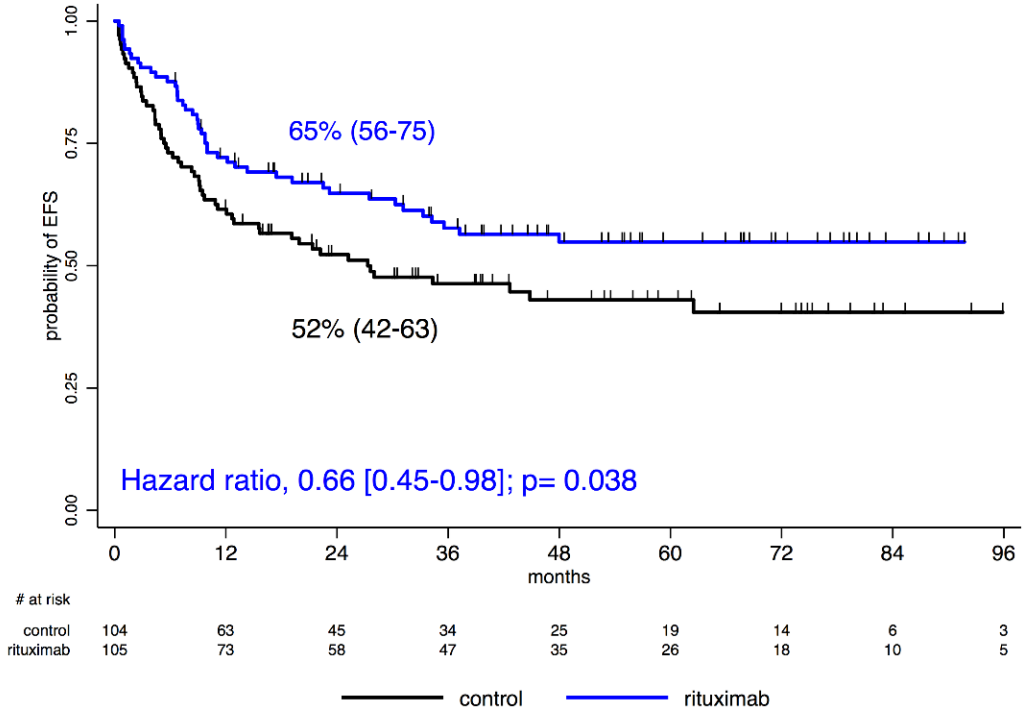
Blinatumomab, LAL-Ph1–, MRD+ BLAST study, OS by CMR



Landmark analysis from day 45;
Complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}.

Gökbuget N, et al. ASH 2018. Abstract 554; Gökbuget N, et al. *Blood.* 2018;131(14):1522-1531.

Rituximab in BCP-ALL
GRAALL-2005: Event-free survival



Maury S, et al. *N Engl J Med.* 2016;375:1044-1053.

Case presentation (4)

- End of consolidation
  - MRD: negative
- Start maintenance

- Persistent cytopenia during maintenance
- BM: 37% blasts, unmodified phenotype
- CR1 duration: 6 months

Question 3

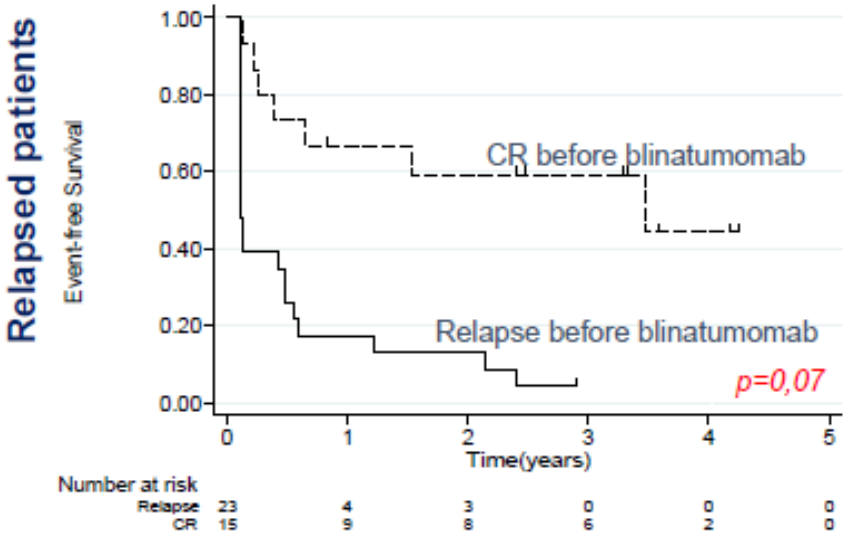
What is your preferred therapeutic option?

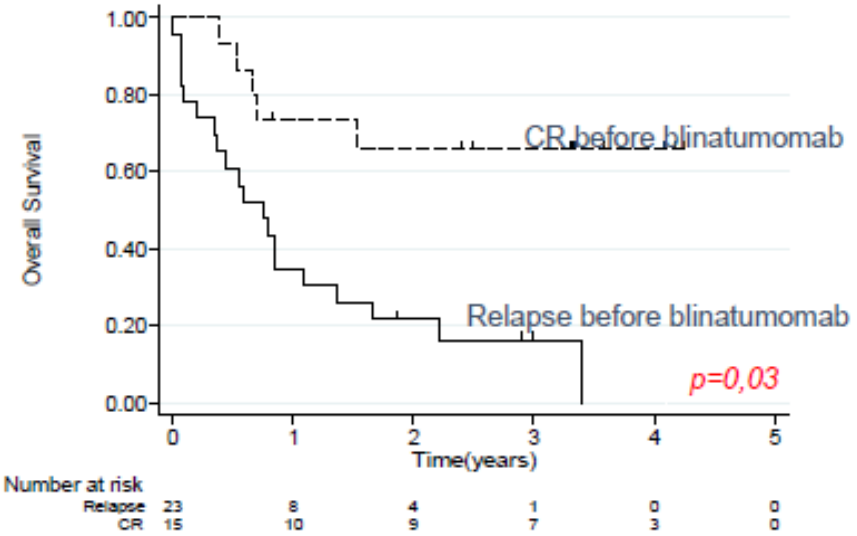
a) Palliative care
b) CAR T cells
c) Blinatumomab
d) Salvage chemotherapy

Salvage with blinatumomab . . . after cytoreduction!

> The retrospective FrenchCyto study: 38 patients with R/R BCP-ALL

> CR 68%, MRD neg 84%, allo-HSCT in CR 46%





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Cabannes-Hamy A, et al. SFH 2020.

Conclusions

- Chemotherapy alone is no longer an option in eligible elderly patients with BCP-ALL
- Trials combining monoclonal antibodies and reduced (adapted) intensity chemotherapy are ongoing with promising results
- Despite high rates of CR and MRD negativity, relapses are still occurring
- Allogenic HSCT and CAR T options are limited in this patient population

Global Leukemia Academy

Patient case presentation: Patient with HR-ALL with multiple relapses

Josep-Maria Ribera

APTITUDE HEALTH

BCP ALL, Ph– Patient

- August 2014: 27 yo, male. Fever and malaise. No significant findings on physical exam
- Hb: 86 g/L. WBC count: 1.1 × 10^9/L. Platelets: 8 × 10^9/L, BM: 96% blasts, CD10+, cμIg+, CD20 10%
- Cytogenetics: 46, XY [20], FISH: BCR-ABL neg, MLL neg
- **Diagnosis:** Pre-B ALL. CNS+
- Initially considered SR-ALL
- **Treatment: PETHEMA ALL-IR08** (pediatric-derived trial for AYAs)

  Pre-phase
  - PDN 60 mg/m^2 d–7 to –1
  - TIT: MTX 12 mg + AraC 30 mg + hydrocortisone 20 mg

  Induction
  - VCR 1.5 mg/m^2 IV, d 1, 8, 15, 22
  - DNR 30 mg/m^2 IV, d 1, 8, 15, 22
  - PDN 60 mg/m^2 IV or PO, d 1–27; 30 mg/m^2 d 28–35
  - Native *E. coli* ASP 10,000 IU/m^2 IV, d 16–20, d 23–27
  - Cyclophosphamide 1,000 mg/m^2 IV, d 36 – TIT d 1, 29

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- Cytogenetics: 46, XY [20], FISH: BCR-ABL neg, MLL neg
- Diagnosis: Pre-B ALL. CNS+
- Treatment: **PETHEMA ALL-IR08 (BFM-derived trial for AYAs)**
- BM study on d 14: 42% blasts. **Moved to HR protocol (PETHEMA HR11)**
  - Idarubicin 12 mg/m^2 IV, d 1, 3, 5
  - Fludarabine 30 mg/m^2 IV, d 1, 5
  - AraC 2 g/m^2 IV, d 1, 5
- **CR after induction. Flow MRD: <0.1%**

Early consolidation 1

- DXM
  - 20 mg/m^2 PO or IV, d 1–5
  - 10 mg/m^2 PO or IV, d 6
  - 5 mg/m^2 PO or IV, d 7
  - 2.5 mg/m^2 PO or IV, d 8
- VCR: 1.5 mg/m^2 IV (capped at 2 mg) d 1, 8
- MTX: 3 g/m^2 IV over 24 hr, day 1
- PEG-ASP 1500 IU/m^2 d 3

Early consolidation 2

- DXM
  - 20 mg/m^2 PO or IV, d 1–5
  - 10 mg/m^2 PO or IV, d 6
  - 5 mg/m^2 PO or IV, d 7
  - 2,5 mg/m^2 PO or IV, d 8
- VCR: 1,5 mg/m^2, IV, (capped at 2 mg) d 1, 8
- AraC: 2 g/m^2 every 12 h, d 1 and 2
- PEG-ASP 1500 IU/m^2 d 3

Early consolidation 3

- DXM
  - 20 mg/m^2 PO or IV, d 1–5
  - 10 mg/m^2 PO or IV, d 6
  - 5 mg/m^2 PO or IV, d 7
  - 2.5 mg/m^2 PO or IV, d 8
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- Diagnosis: Pre-B ALL. CNS+
- Treatment: PETHEMA ALL-IR08 (BFM-derived trial for AYAs)
- BM study on d14: 42% blasts. Moved to HR protocol (PETHEMA HR11)
- CR with MRD <0.1% after second induction
- **MRD <0.01% after early consolidation. Proceed to delayed consolidation**

Delayed consolidation 1

- DXM
  - 20 mg/m^2 PO or IV d 1–5
  - 10 mg/m^2 PO or IV, d 6
  - 5 mg/m^2 PO or IV, d 7
  - 2,5 mg/m^2 PO or IV, d 8
- VCR: 1.5 mg/m^2 IV (capped at 2 mg) d 1, 8
- MTX: 3 g/m^2 IV over 24 hr, d 1
- PEG-ASP 1500 IU/m^2 d 3

Delayed consolidation 2

- DXM
  - 20 mg/m^2 PO or IV d 1–5
  - 10 mg/m^2 PO or IV, d 6
  - 5 mg/m^2 PO or IV, d 7
  - 2.5 mg/m^2 PO or IV, d 8
- VCR: 1.5 mg/m^2 IV (capped at 2 mg) d 1, 8
- AraC: 2 g/m^2 every 12 h, d 1, 2
- PEG-ASP 1500 IU/m^2 d 3

Delayed consolidation 3

- DXM
  - 20 mg/m^2 PO or IV d 1–5
  - 10 mg/m^2 PO or IV, d 6
  - 5 mg/m^2 PO or IV, d 7
  - 2,5 mg/m^2 PO or IV, d 8
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- CR with MRD <0.1% after induction
- MRD <0.01% after early consolidation
- **MRD <0.01% after delayed consolidation**
- **Maintenance 1 (up to 1 yr after dx)**
  - 6-mercaptopurine 50 mg/m^2 PO, daily
  - MTX 20 mg/m^2 IM, weekly
- **Reinductions (every month)**
  - VCR 1.5 mg/m^2 IV, d 1
  - PDN 60 mg/m^2 IV or PO, d 1–7
  - Native ASP 20,000 IU/m^2 IM or IV, d 1
  - TIT d 1
- **MRD <0.01% after maintenance**
- **Stop therapy in August 2016**

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- CR with MRD <0.1% after induction. MRD <0.01% after consolidation. MRD <0.01% after maintenance
- Stop therapy in August 2016
- **April 2017: BM and CNS relapse**

BCP ALL, Ph– patient

- Blinatumomab (after CNS clearance) 2 cycles: CR with MRD <0.000%
- Myeloablative HSCT from MUD (10/10; August 2017). No GVHD. CCR with MRD negative
- December 2017: MRD 0.8%. Hematologic CR
  - DLI (2 doses). MRD <0.01%
- June 2018: MRD 0.44%. BM: 5% blasts, CD22+
  - Inotuzumab (2 doses, waiting for CAR T)
  - Academic CD19 CAR T (infusion on Sept 5, 2018). No complications
- November 2019: MRD (BM): 0.9%. CNS involvement (CD19+, CD22+)
  - TIT: (5 doses) – CNS clearance
  - Inotuzumab (2 cycles): MRD <0.001%
  - Second myeloablative HSCT from MUD 10/10 (different donor) (9/1/2020)
- October 2020: Alive and in CR

BCP ALL, Ph– patient: Summary

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- BM study on d14: 42% blasts. Moved to HR protocol (PETHEMA HR11)
- CR with MRD <0.1% after induction. MRD <0.01% after consolidation. MRD <0.01% after maintenance
- Stop therapy in August 2016
- **April 2017**: **BM and CNS relapse**
- Blinatumomab (after CNS clearance) 2 cycles: CR with MRD <0.000%
- Myeloablative HSCT from MUD (10/10; August 2017). No GVHD. CCR with MRD negative
- **December 2017**: MRD 0.8%. Hematologic CR
  - DLI (2 doses); MRD <0.01%
- **June 2018**: MRD 0.44%. BM: 5% blasts, CD22+
  - Inotuzumab (2 doses)
  - CD19 CAR T (infusion on Sept 5, 2018)
- **November 2019**: **BM and CNS relapse**
  - Inotuzumab (2 cycles)
  - 2nd 10/10 MUD myeloablative HSCT from different donor (**January 2020**)

Main message

- ✓**Sequential use of immunotherapeutic approaches is feasible for BCP ALL patients with multiple relapses**
- ✓**In this patient . . .**
  1. Blinatumomab
  2. Allogeneic HSCT
  3. DLI
  4. CD19 CAR T
  5. Inotuzumab
  6. Second allogeneic HSCT

Question 1

- In patients with R/R ALL, CAR T cells have shown activity in
  a. Bone marrow relapse
  b. Extramedullary relapses
  c. Only in MRD-positive status
  d. Only in patients with previous debulking of the disease
  e. a and b are correct

Question 2

- Regarding the use of blinatumomab and inotuzumab, indicate the false proposition
  a. Can be only used as single drugs
  b. Can be safely combined with chemotherapy
  c. Can be used sequentially in the same therapeutic schedule
  d. Can be used as bridging therapy before CAR T infusion
  e. Can be used in patients with CNS relapse, after clearing the CSF

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Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in adult and elderly patients

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Educational ARS questions

Elias Jabbour

Global Leukemia Academy

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

Question 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)

Question 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

Question 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**

Question 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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Session close

Elias Jabbour

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Thank you!

- Please complete the **evaluation survey** that will be sent to you by email
- The meeting recording and slides presented today will be shared on the www.globalleukemiaacademy.com website
- You will also receive a certificate of attendance by email by October 30

THANK YOU!

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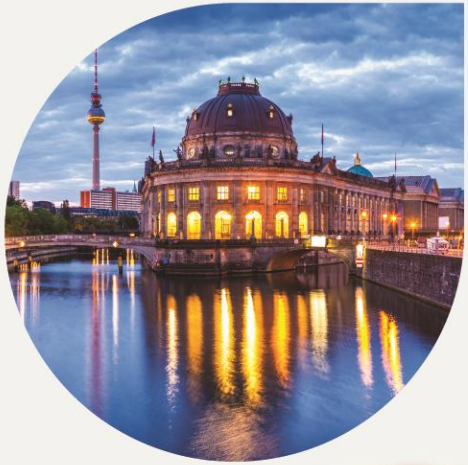

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Emerging and Practical Concepts and Controversies in Leukemias

THANK YOU FOR YOUR PARTICIPATION!

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