Treatment of Adults with ALL: Treatment (R)Evolution!

Wendy Stock, MD, MA
Professor of Medicine
University of Chicago Medicine

Is there an optimal frontline approach in 2024?

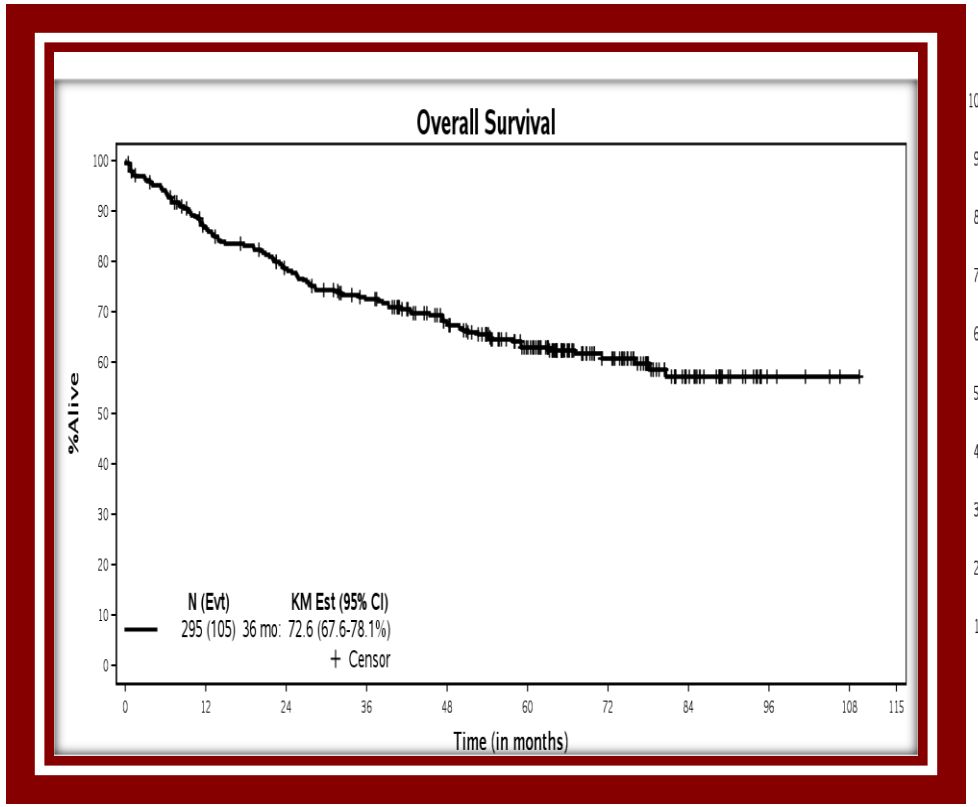
THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Outline: The ALL World has Changed

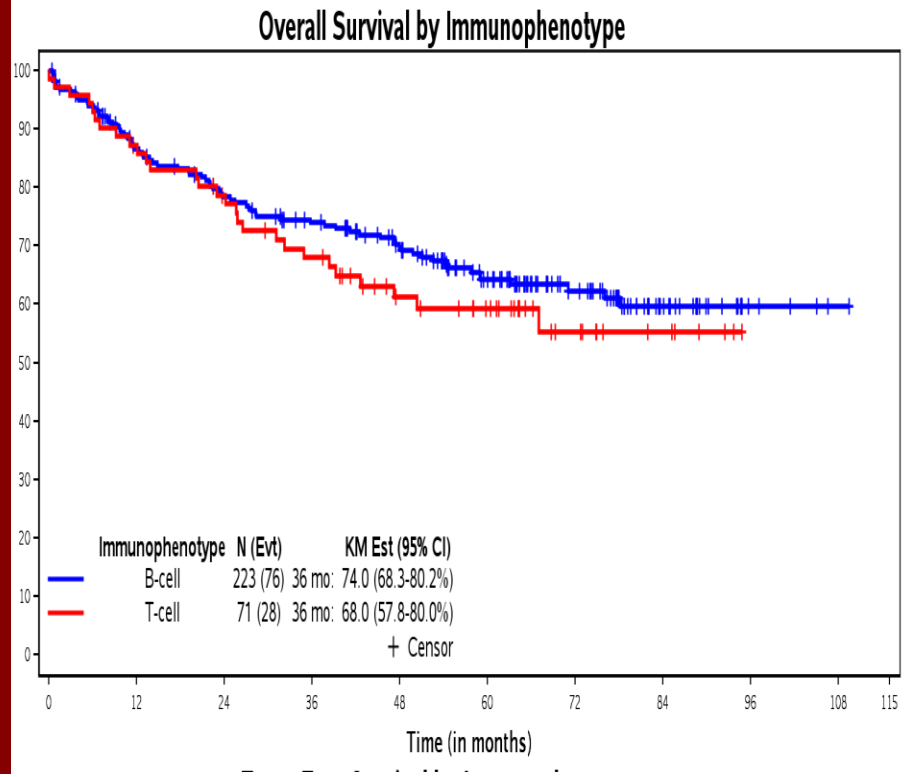
- Themes: MRD eradication, Blending of New and Old, Less is more!
- Frontline: Younger Adults
  - Pediatric regimens are now standard of care
  - Frontline trials incorporate chemo + targeted agents
- Frontline: Older Adults
  - Less intensive strategies lead the way: the “wisdom” of age!
- Ph+ ALL: Moving away from alloSCT in CR1
  - ”Chemo” free may be best

Improved Survival for AYAs: CALGB 10403

- 72% Survival at 3 years



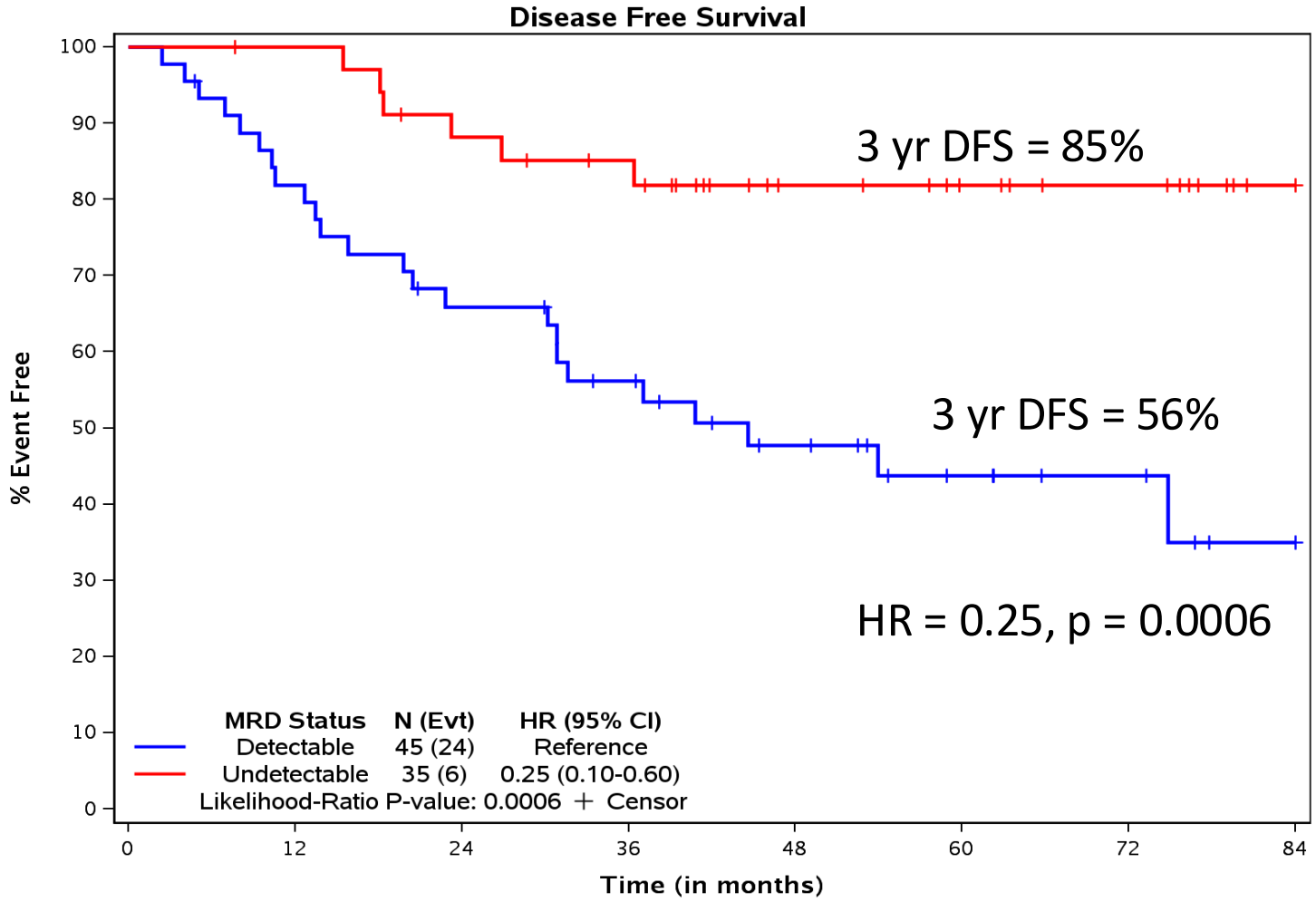
- Immunophenotype: B vs T



Stock et al, Blood 2019

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Excellent Outcomes: Achievement of early MRD neg CALGB 10403



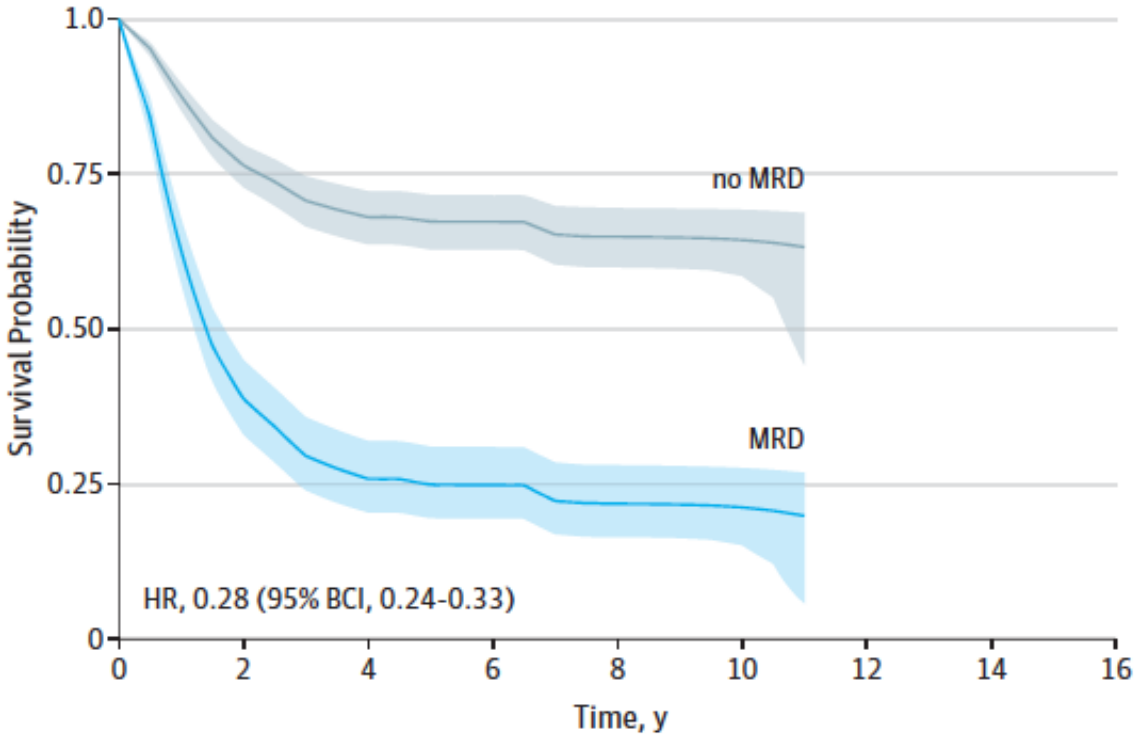
Q-PCR following Induction

Blood, 2019; 133, 1548-1559

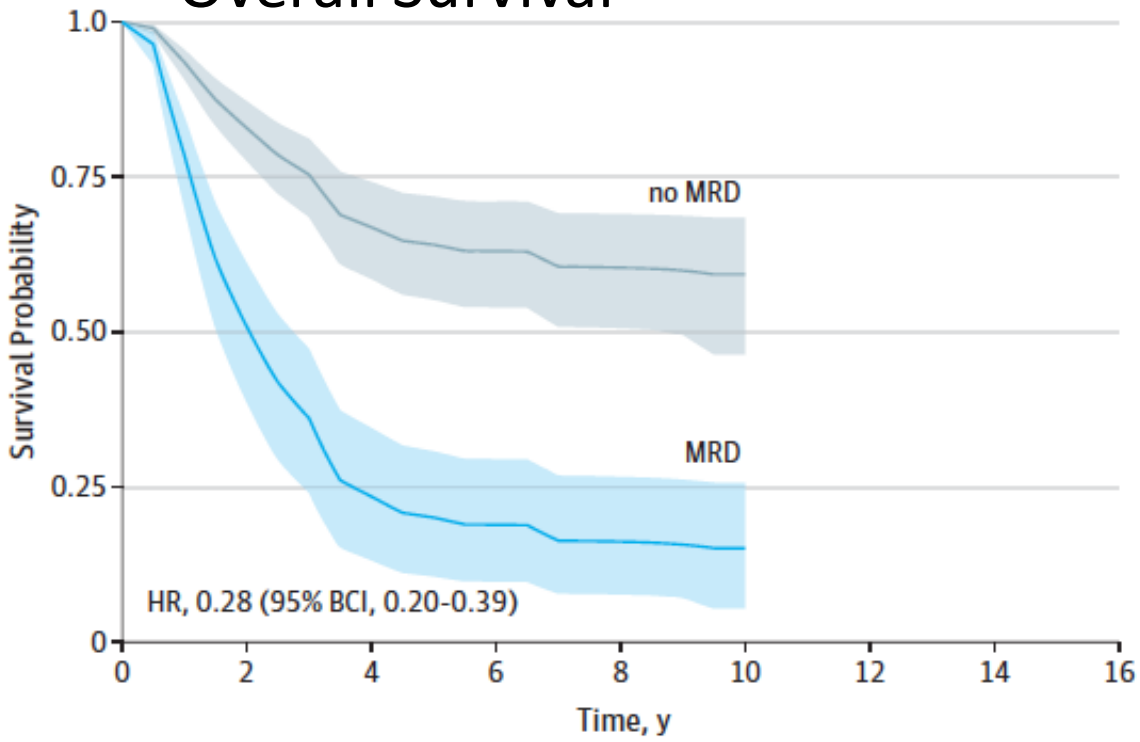
Only 40% of patients are MRD negative early in treatment

MRD associated with inferior EFS and OS in adult ALL

Event-Free Survival

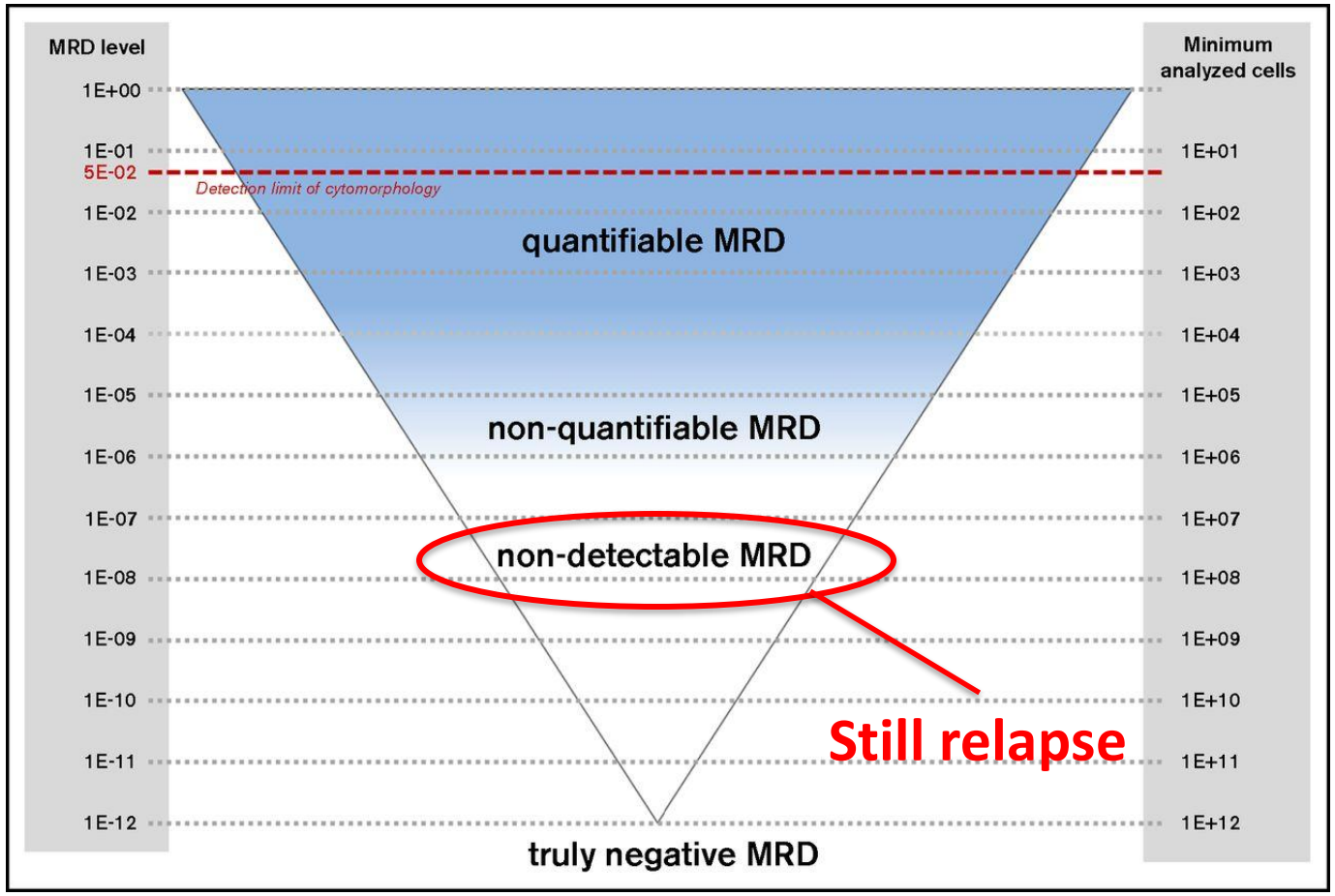


Overall Survival



Berry, et al. JAMA Oncol 2017

MRD: “Minimal” or “Measurable” Residual Disease



- **Multiparameter Flow Cytometry (MFC)**
  - Sensitivity: 10^{-4}
- **Allele-Specific Oligonucleotide PCR (ASO-PCR)**
  - Sensitivity 10^{-5} to 10^{-6}
- **Next Generation Sequencing (NGS)**
  - Sensitivity: 10^{-6}

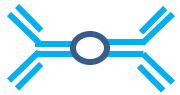
Bruggemann & Kotrova Blood Adv 2017

How can we best ”eradicate” MRD?

- Further intensification of traditional chemo not feasible for adults
- Intro of effective agents for relapse into frontline combinations
  - Intro of FDA Approved for Relapsed ALL:
    - CD19 target: Blinatumomab* (also approved for treatment of MRD+): E1910
    - CD22: Inotuzumab ozogamycin (A041501 for AYA ALL)
    - T- ALL: Nelarabine? (COG AALL0434)
  - Newer approaches: Early phase data
    - BH3 mimetics
    - Where will CAR-T “fit”?

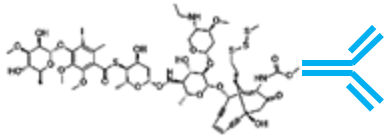
Relapsed/refractory B-ALL in Adults: Options!

Blinatumomab



- **CD19 - CD3 BiTE[1]**
- **CR:** 34%
- **ORR:** 44%
- **MRD-neg:** 76% of ORR
- **SCT:** 24%
- **Median OS:** 7.7 mos

Inotuzumab ozogamicin



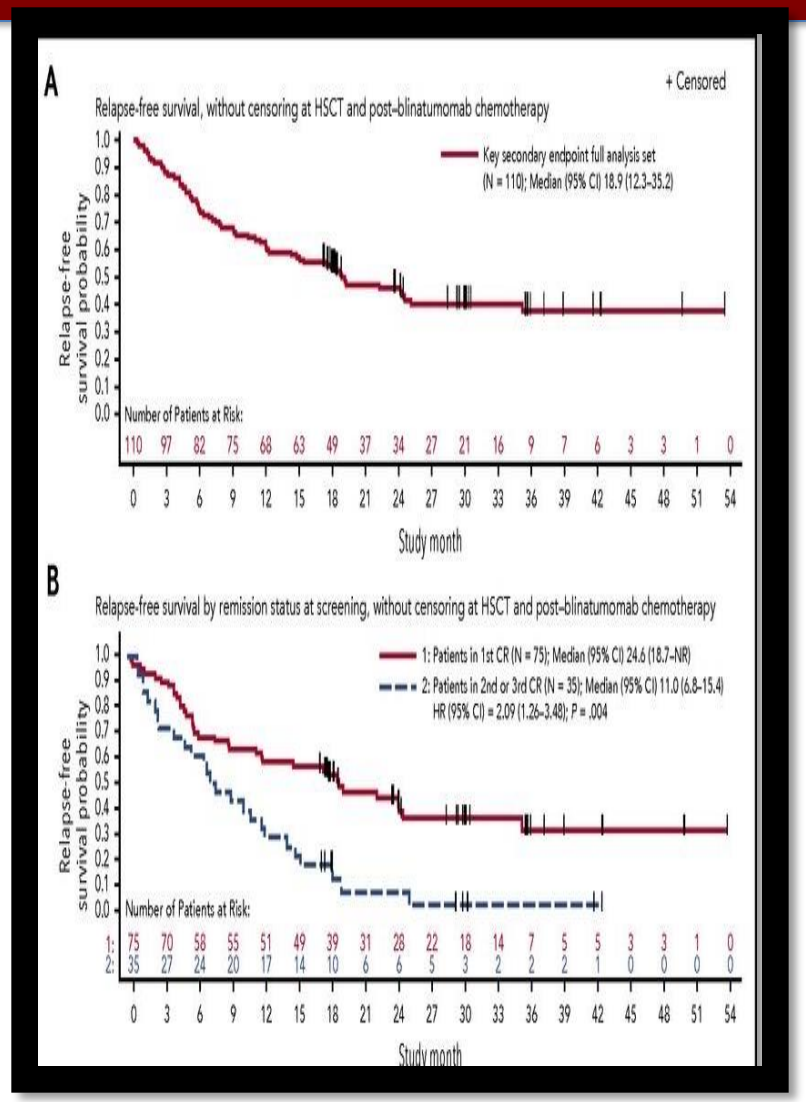
- **CD22 Ab drug conjugate[2]**
- **CR:** 36%
- **ORR:** 81%
- **MRD-neg:** 78% of ORR
- **SCT:** 41%
- **Median OS:** 7.7 mos

CAR T-cell Therapy

- **Anti-CD19 Zuma-3[3]**
- **CR:** 56%
- **MRD-neg:** 97% of CR
- **SCT:** 18%
- **Median PFS:** 12.8 months (95% CI 8·7-not estimable
- **Median OS:** 18.2 months (15·9-not estimable)

1: Kantarjian et al, N Engl J Med 2017; 376:836-847
2: Kantarjian et al, N Engl J Med 2016; 375:740-53
3: Shah et al, Lancet. 2021 Jun 3:S0140-6736

BLAST TRIAL: 88/113 (78%) of MRD+ ALL Achieve CMR with Blina: Improves RFS and OS



Nicola Gökbuget et al. Blood 2018;131:1522-1531

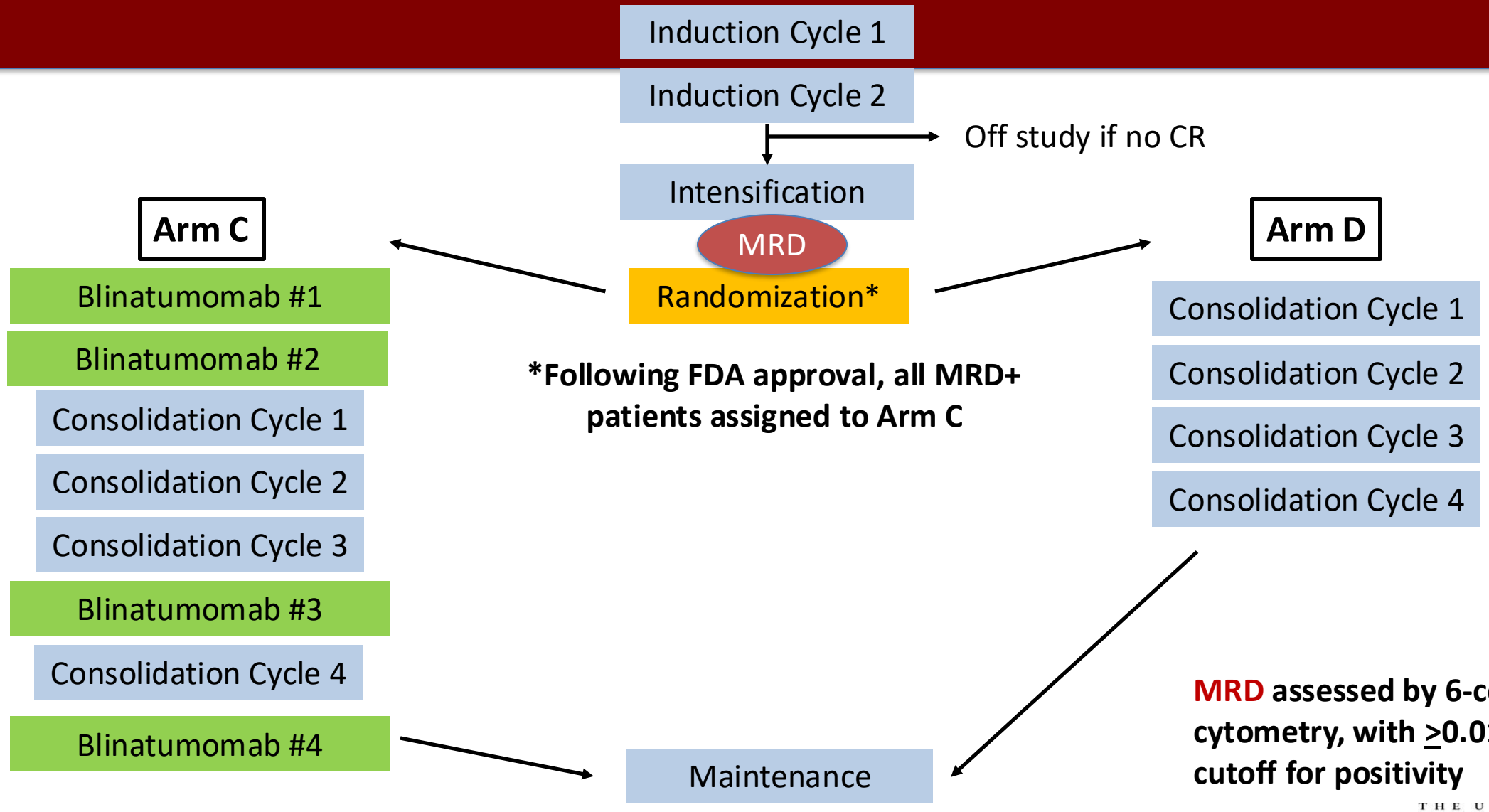
→ Overall RFS at 18 months = 54% (33-70)

→ Median RFS for CR1 patients = 18.9 mos (12.3-35)

4**/18: : FDA grants accelerated approval for use of Blina for MRD+ ALL; frontline and relapsed states**

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

E1910: Randomized CD19+ B- ALL



***Following FDA approval, all MRD+ patients assigned to Arm C**

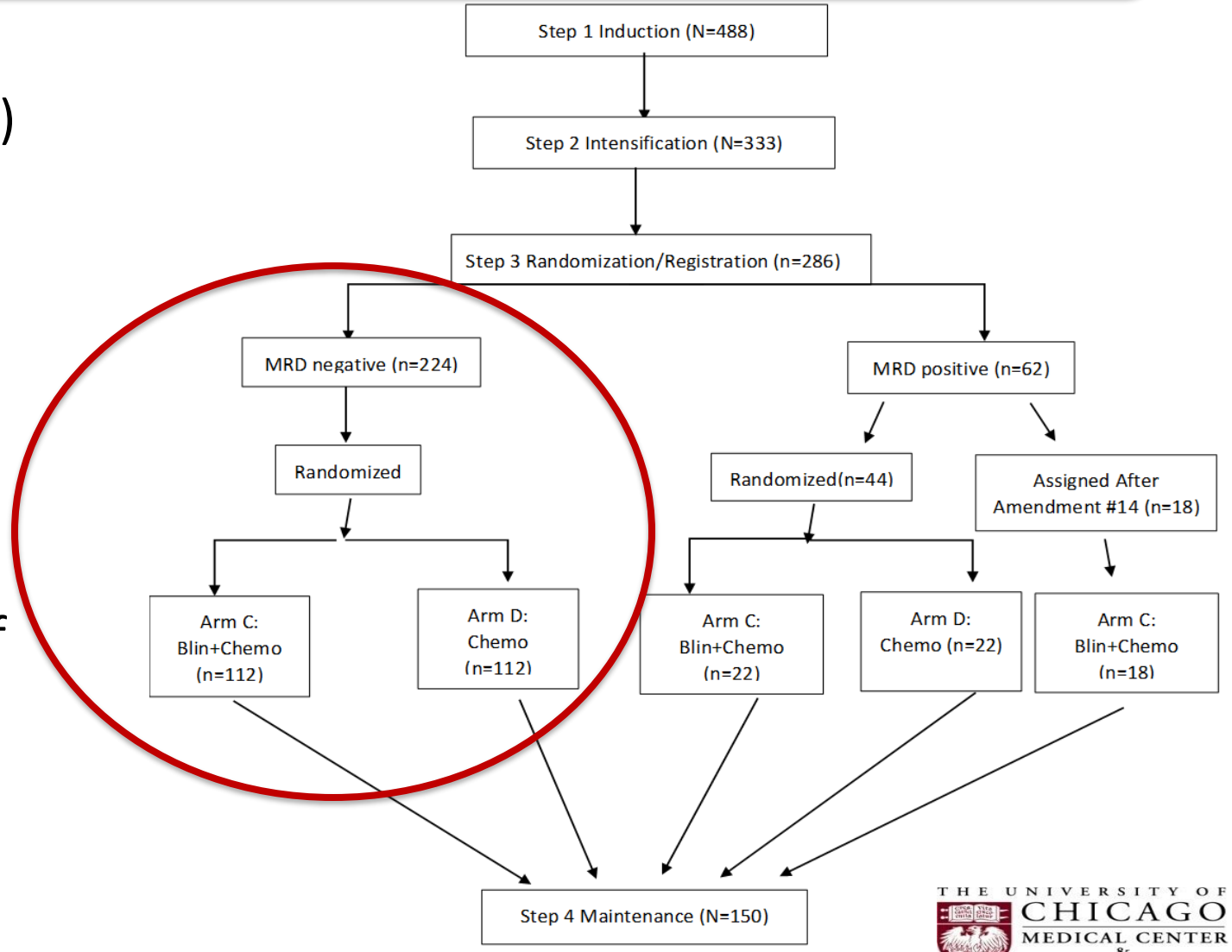
MRD assessed by 6-color flow cytometry, with ≥0.01% as the cutoff for positivity

Litzow et al, NEJM 2024

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

E1910 Results

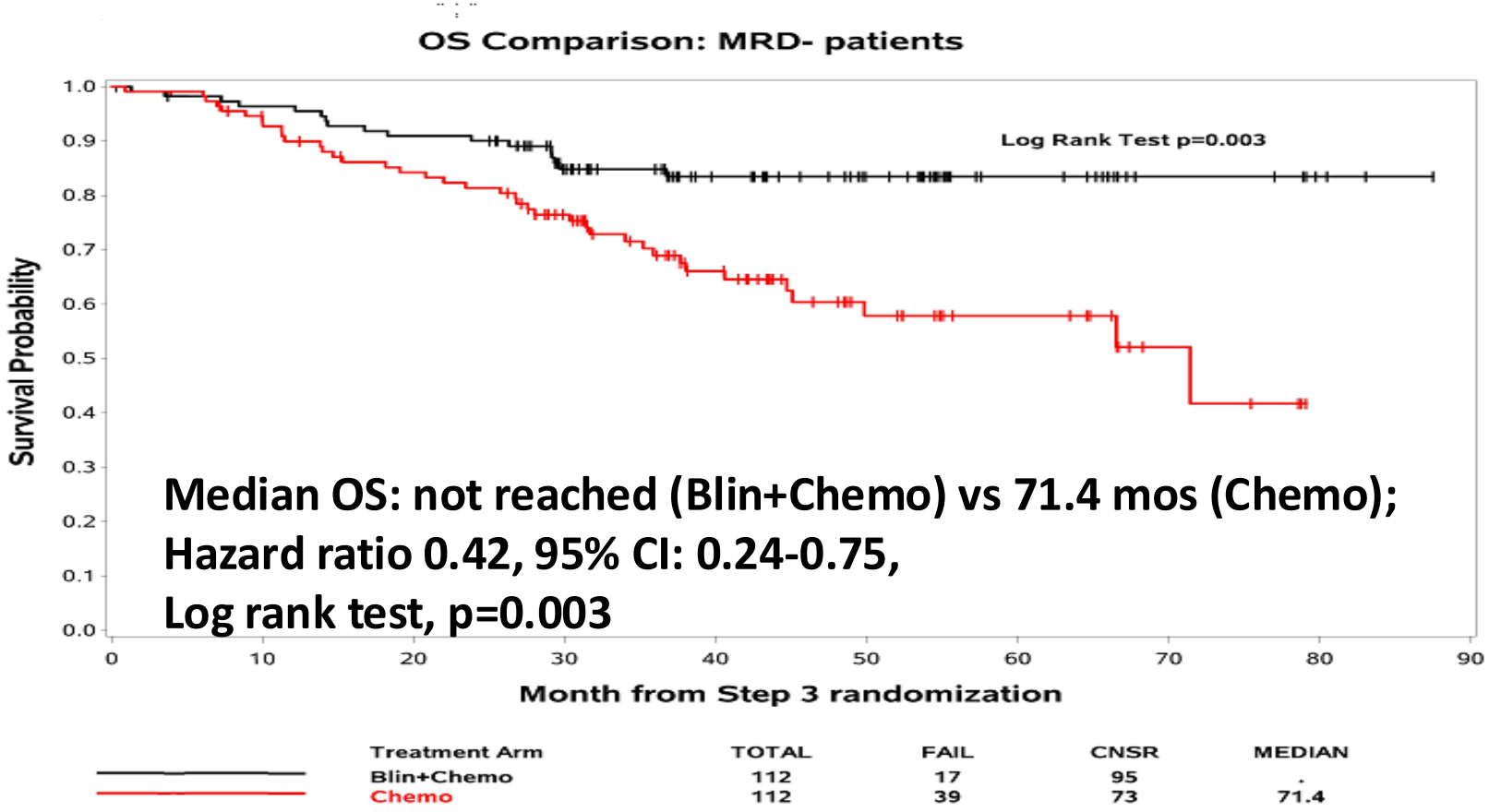
- 488 pts enrolled
- Median age: 51yrs (range 30-70yrs)
- Median follow-up 3.6 yrs
- CR/CRi rate 81% (395/488 pts)
  - CR 75% (364 pts)
  - CRi 6% (31 pts)
- 224 MRD – patients
  - Among MRD-neg, 22 patients in each arm underwent alloHSCT
  - 80% of pts received ≥2 cycles of blinatumomab



Litzow et al, NEJM 2024

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Overall Survival : MRD negative patients



Deaths on Blin+Chemo Arm=17 (2° to ALL=8, NRM=9), Chemo Arm=39 (2° to ALL=20, NRM=17, Unknown=2)

Litzow et al, ASH 2022

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

A041501, Randomized Phase 3 Trial for AYAs: Impact of Inotuzumab Ozogamycin on EFS, MRD

I		C**	IM	DI	M
DEX	*Inotuzumab*	Cyclo	MTX	DOX	DEX
DNR	*× 2 cycles*	VCR	VCR	Cyclo	VCR
VCR		DEX	PEG-ASP	DEX	6-MP
PEG-Asp		PEG-Asp	IT MTX	PEG-Asp	MTX
IT MTX		Ara-C	Rituximab	Ara-C	IT MTX
IT Ara-C		6-MP		6-TG	
		IT MTX		IT MTX	
		Rituximab		Rituximab	

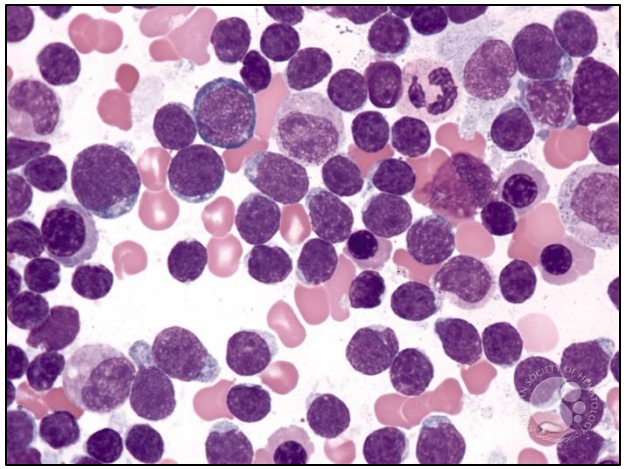
ClinicalTrials.gov; NCT03150693.

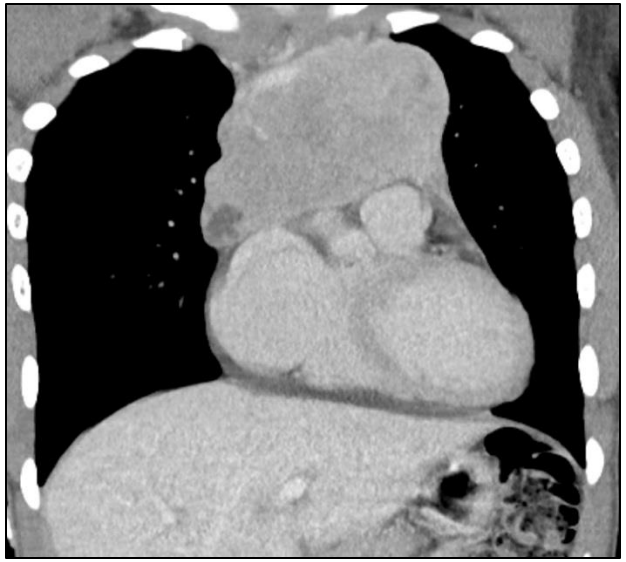
**Patients who remain MRD+ after "C" should receive Blinatumomab
$CD20^+$ patients receive rituximab (8 doses) with C, IM, DI.
Maintenance therapy continues for 2 (F) to 3 (M) years.

Commentary

- First evidence that Blina significantly improves survival for MRD negative patients in CR1: IMPRESSIVE!
- May be new standard for post remission Rx for CD19+ in CR1
- Comments:
  - Will be important to look at high risk subsets: Ph-Like, *KMT2A* rearranged
  - MRD method in E1910 was less sensitive flow cytometry
    - Wonder about impact of blina if MRD neg using more sensitive methods of detection: Can we have even better selection of pts?
  - Many patients were lost prior to blina – relapse, transplant, alternative therapies, toxicity
    - Likely more useful to introduce blina earlier in treatment

T-lineage acute lymphoblastic leukemia/lymphoma (T-ALL/LBL)



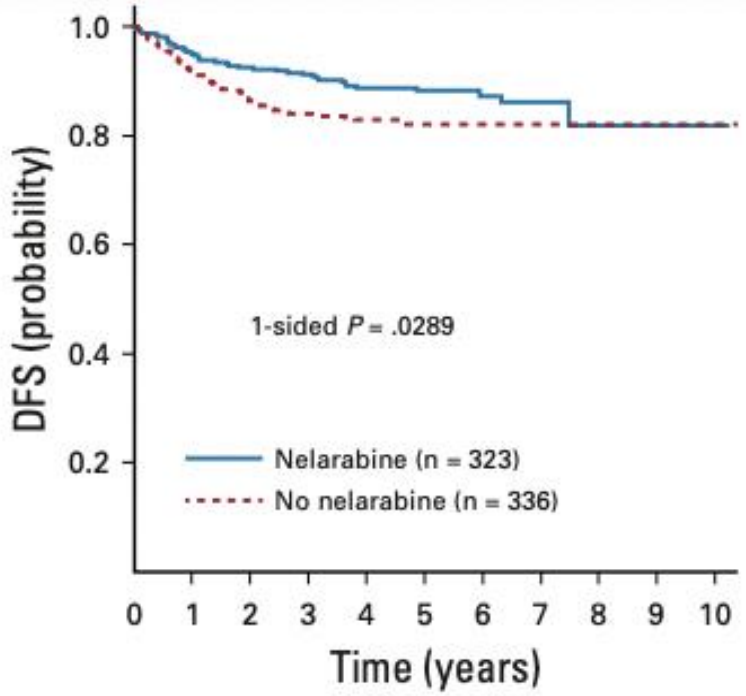


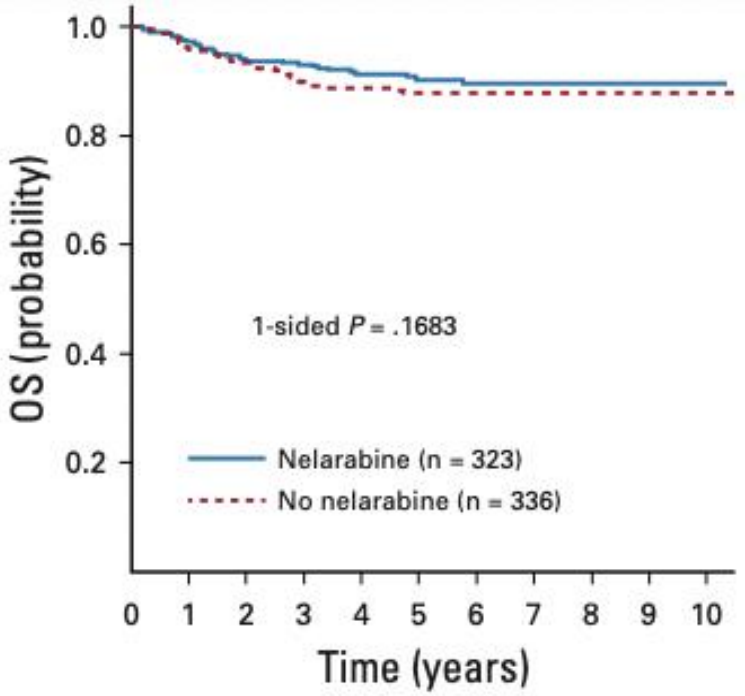
- 10-15% of pediatric and 25-30% of adult ALL cases
- Blood/bone marrow involvement (T-ALL) lymph node involvement common and/or sole extramedullary disease - mediastinal mass (T-LBL)
- **Nelarabine-containing pediatric-inspired regimens improves DFS in children and young adults**

Arber DA, *et al.* Blood 2016 Marks DI, *et al.* Blood 2017 Dunsmore KP, *et al.* J Clin Oncol 2020

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Nelarabine improves DFS





No. at risk:											
Nelarabine	323	303	293	285	222	156	91	32	15	6	1
No nelarabine	336	304	284	273	224	167	97	43	17	8	2

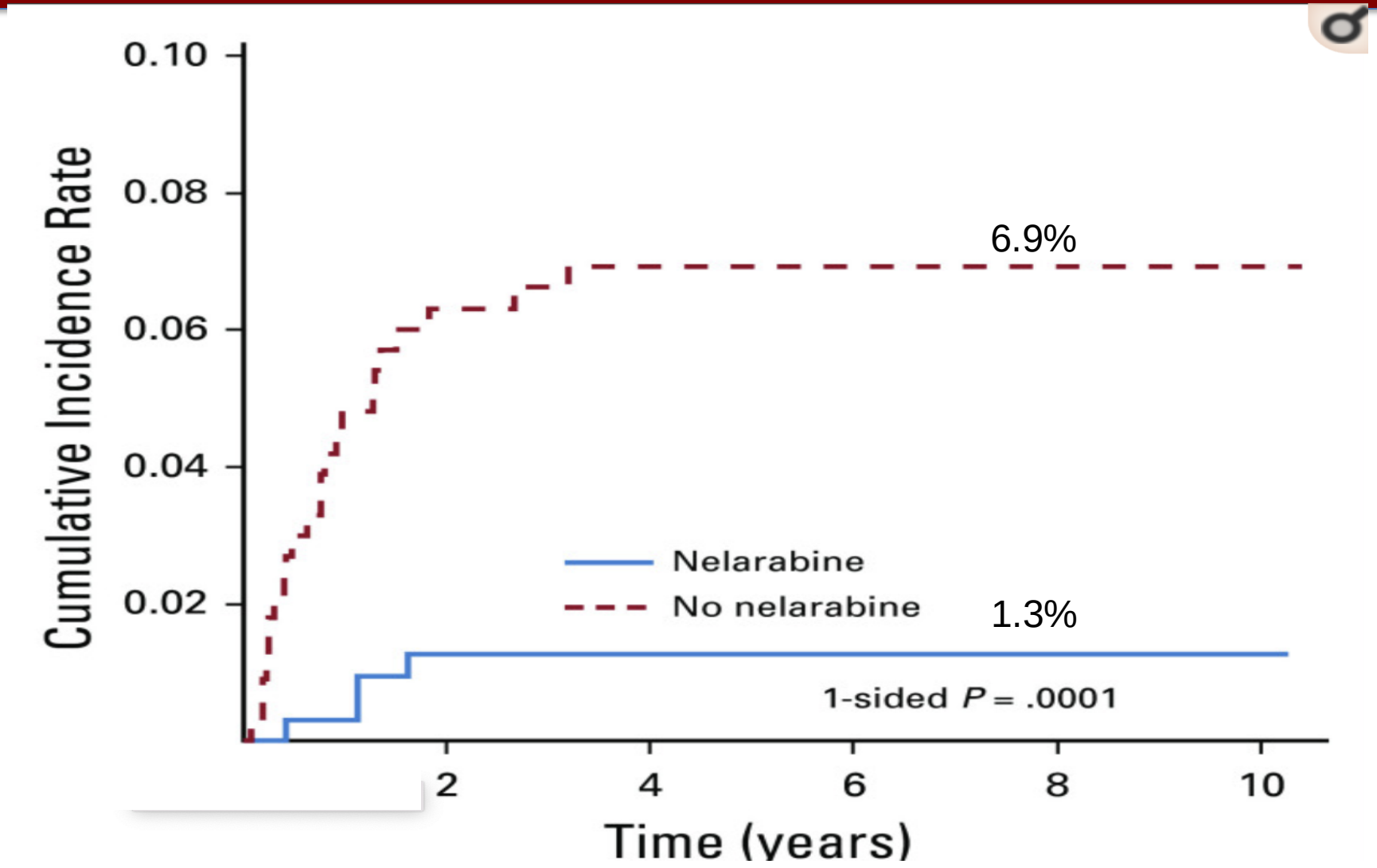
No. at risk:											
Nelarabine	323	310	296	291	234	164	100	37	15	6	2
No nelarabine	336	319	306	290	240	177	108	45	20	9	2

- **Nelarabine incorporated into ABFM; six 5-day courses**
- **3% of the 1895 patients were AYAs between 20-30 years old**
- **5 yr DFS was 88.2% with nelarabine vs 82% DFS without (p=.02)**

Dunsmore et al, J Clin Oncol 2020:28, 3282-3293

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

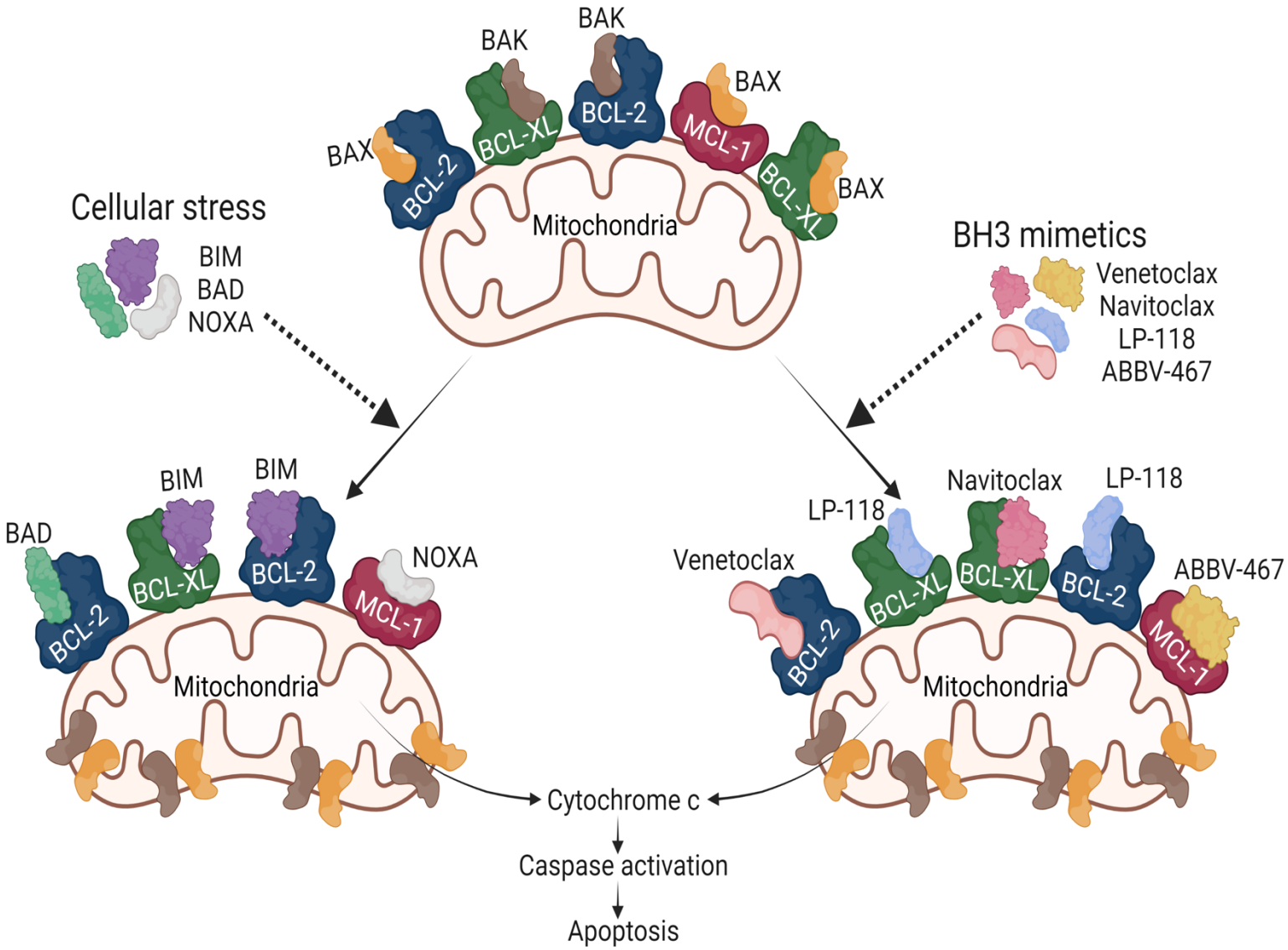
Nelarabine reduces CNS relapse



Dunsmore et al, J Clin Oncol 2020:28, 3282-3293

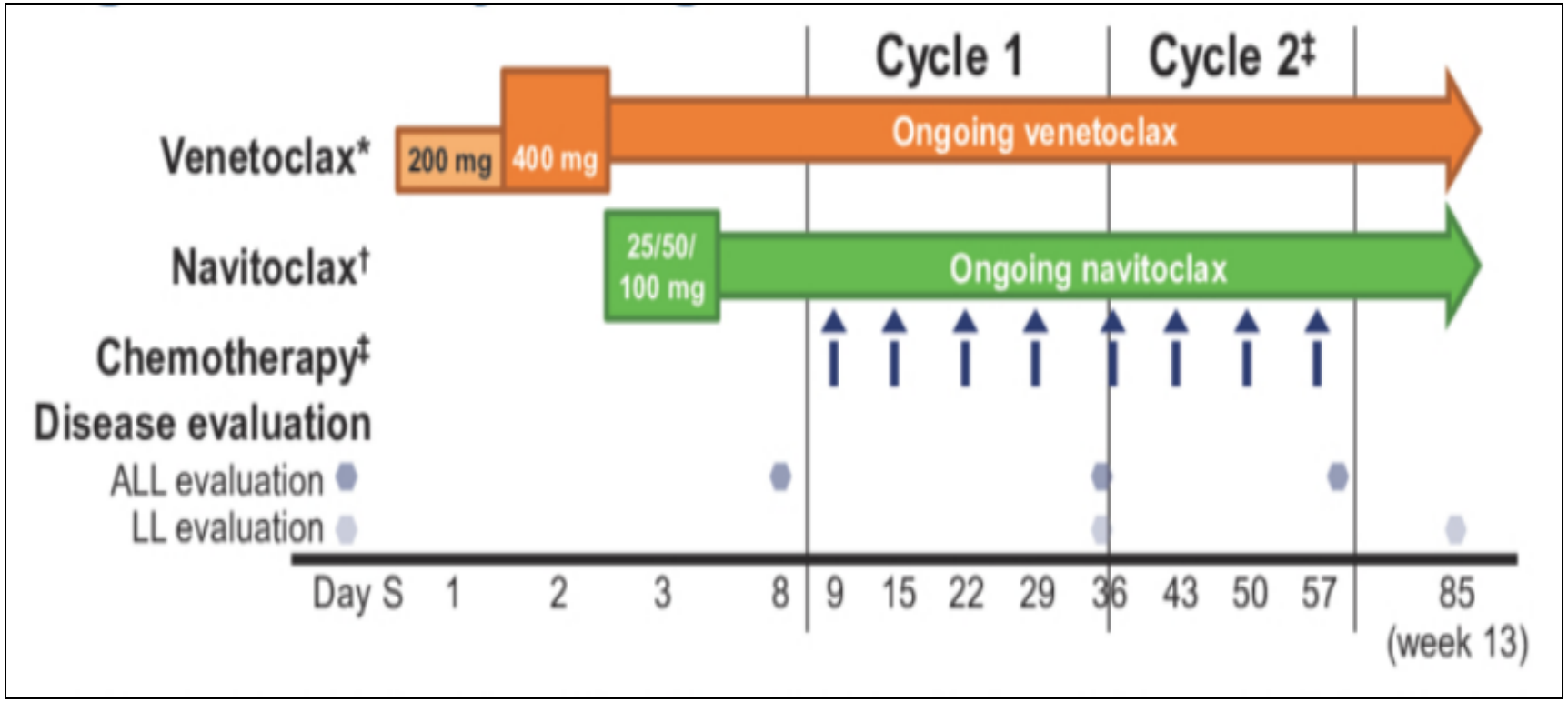
THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Apoptotic pathways and BH3 mimetics



THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Venetoclax and Navitoclax in Combination with Chemotherapy in Patients with Relapsed/Refractory ALL and Lymphoblastic Lymphoma



- **Pegylated-asparaginase 1250 IU/m2 IV, Days 9 and 22**
- **Vincristine 1.5 mg/m2 IV, Days 9, 15, 22 and 29**
- **Dexamethasone 20 mg/m2/day oral, Days 9-13 and 22-26**

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Cancer Discovery 2021 **DOI:** 10.1158/2159-8290.CD-20-1465

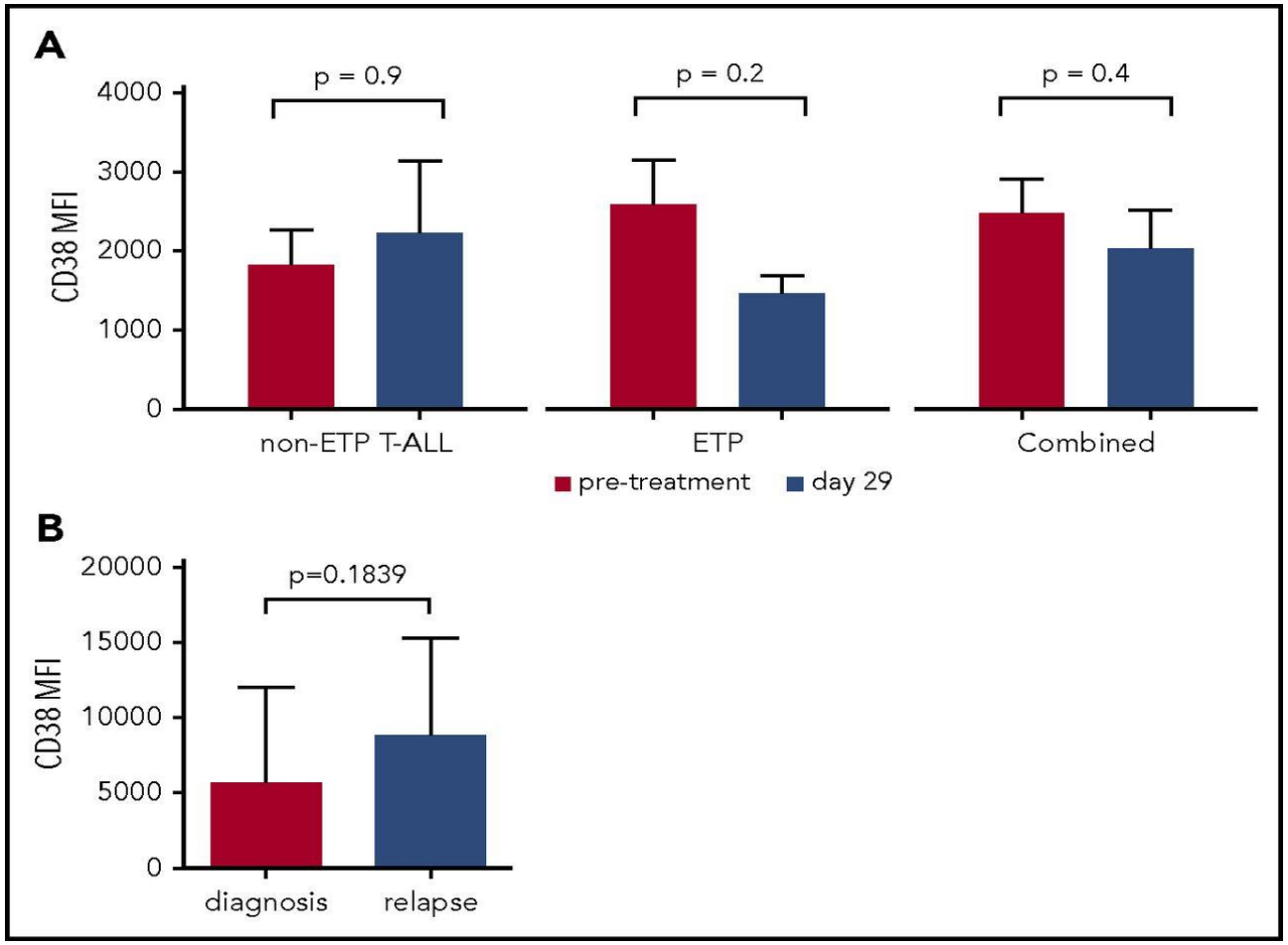
Venetoclax/Navitoclax in combination with chemotherapy has activity in relapsed/refractory T-ALL

Response	B-ALL (n=25)	T-ALL (n=19)	LL (n=3)	All Patients (N=47)
CR/CRi/CRp, n (%)	**16 (64)**	**10 (53)**	**2 (67)**	**28 (60)**
ALL patients with ≥5% BM blasts at baseline, n/N	15/23 (65)	7/14 (50)	NA	22/37 (59)
ALL patients with morphologic CR at baseline, n/N	0/1 (NE)	3/4 (75)	NA	3/4 (75)
PR, n (%)	3 (12)	0 (0)	0 (0)	3 (6)
MRD-negative CR/CRi/CRp in ALL, n/N (%)	9/16 (56)	6/10 (60)	NA	15/26 (58)
Median DOR (95% CI), mo	9.1 (1.4–14.6)	4.2 (0.8–12.3)	NE (NE–NE)	4.2 (2.3–11.5)
Median OS (95% CI), mo	9.7 (4.0–15.7)	6.6 (3.2–12.5)	NR (2.0–NE)	7.8 (4.0–12.5)
Proceeded to SCT or CAR-T, n (%)	8 (32)	3 (16)	2 (67)	13 (28)

- Of 12 pediatric patients, 9 (75%) achieved CR/CRi/CRp, and of those, 6 achieved MRD-negative CR/CRi/CRp
- 4/32 (13%) patients achieved CR/CRi/CRp on Day 8 with Ven + Nav prior to starting chemotherapy on Day 9
- **CR rates were ≥50% across patient subgroups, including in those who had relapsed or were refractory to:**
  - **Blinatumomab: 8/13 (62%)**
  - **Inotuzumab ozogamicin: 8/14 (57%)**
  - **SCT: 5/8 (63%)**
  - **CAR T-cell therapy: 3/6 (50%)**

Pullarkat et al, Cancer Discovery 2021

CD38: Good Target for T-ALL

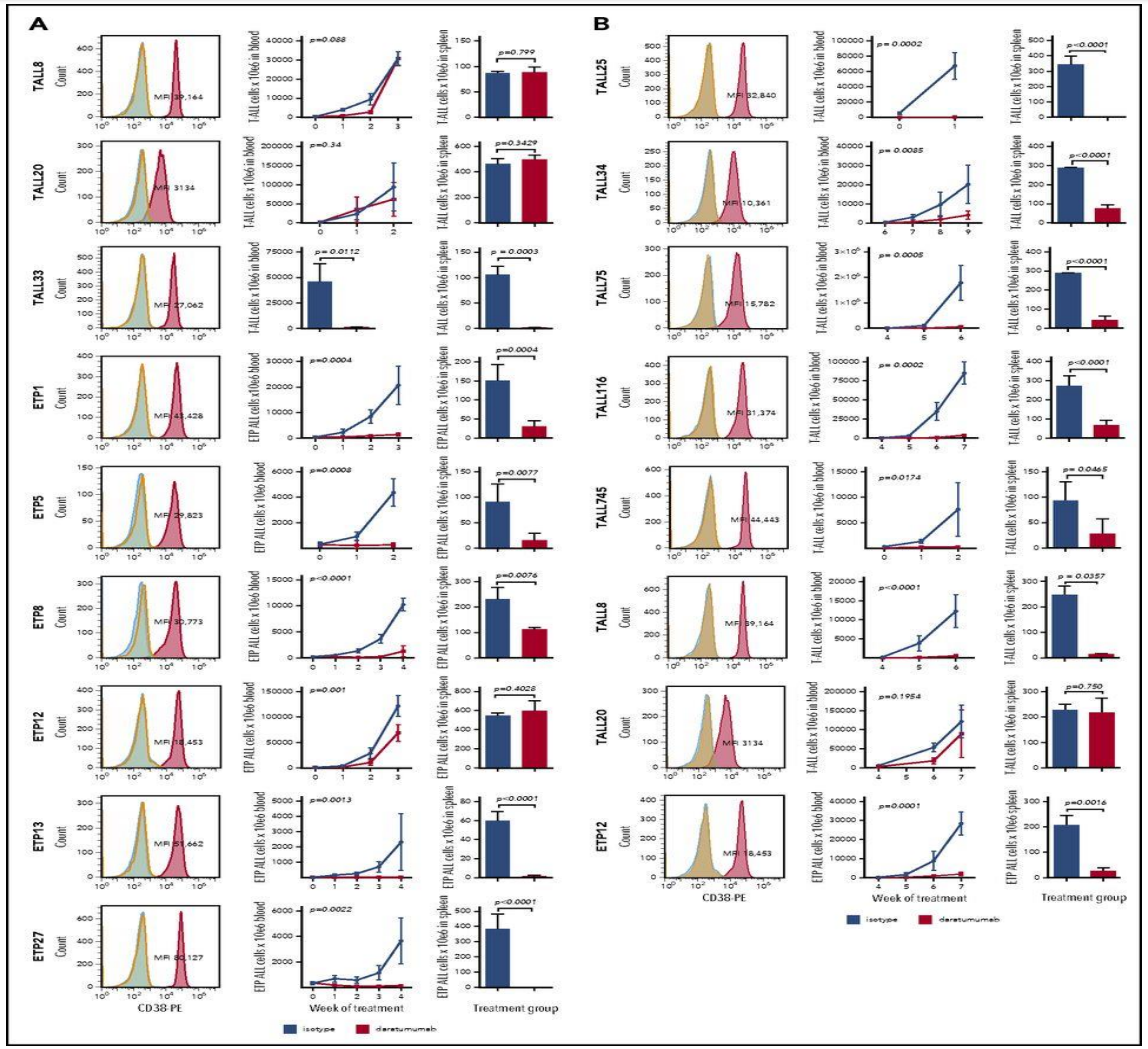


Karen L. Bride et al. Blood 2018;131:995-999

CD38 is expressed on T-ALL and ETP T-ALL blasts with stable expression following induction chemotherapy and at relapse.

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

PDX models of ETP T-ALL and non-ETP T-ALL: Excellent responses to Daratumomab

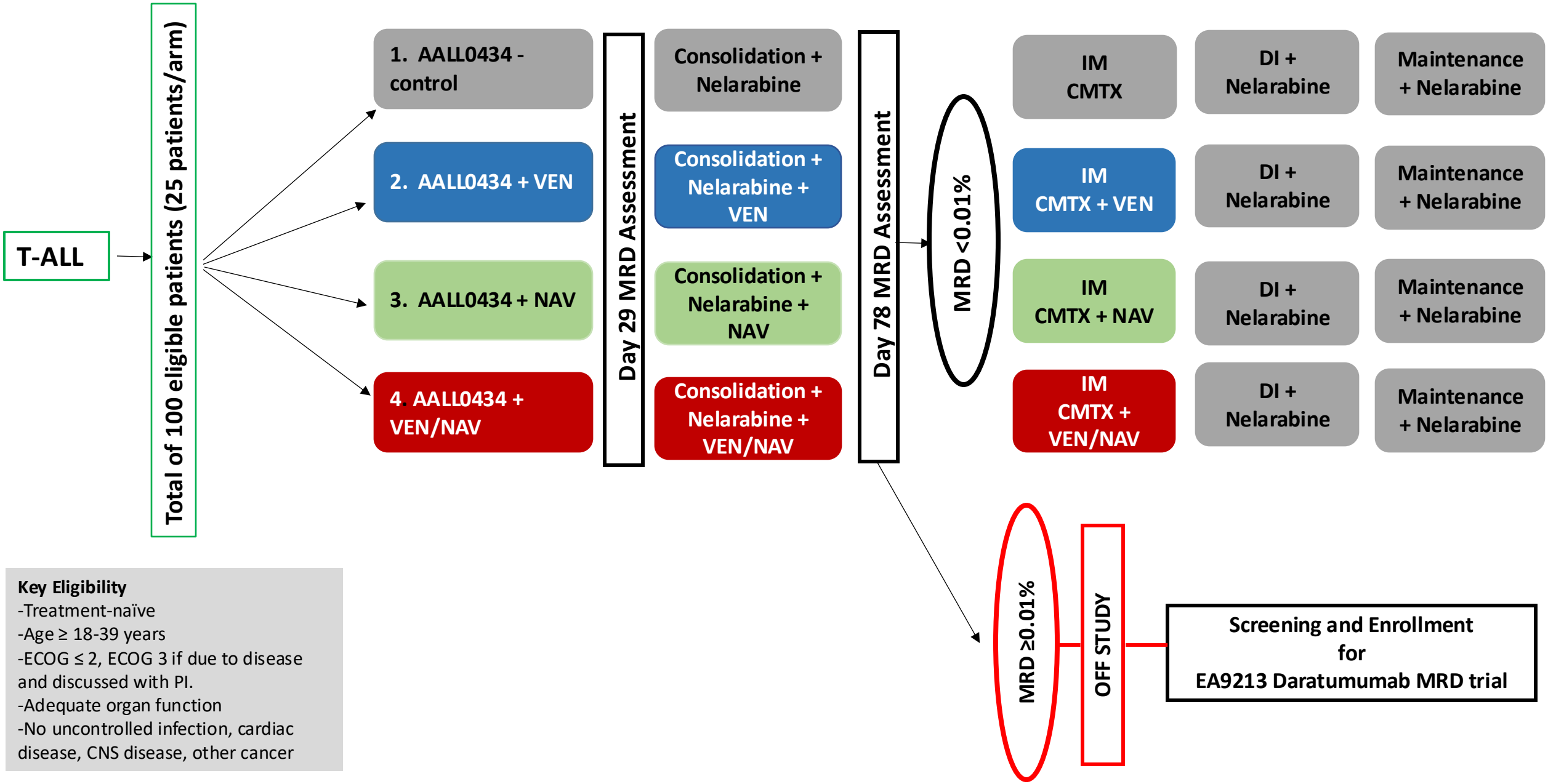


14/15 PDX responded to daratumomab

Best responses seen when mice treated early (MRD state)

Karen L. Bride et al. Blood 2018;131:995-999

S2306: Coming soon! Frontline Trial for T-ALL/T-LBL



Key Eligibility
-Treatment-naïve
-Age ≥ 18-39 years
-ECOG ≤ 2, ECOG 3 if due to disease and discussed with PI.
-Adequate organ function
-No uncontrolled infection, cardiac disease, CNS disease, other cancer

Transplant in CR1? No Survival Benefit

Hypothesis: AYA regimen is superior to alloHCT for post-remission "consolidation" in CR1

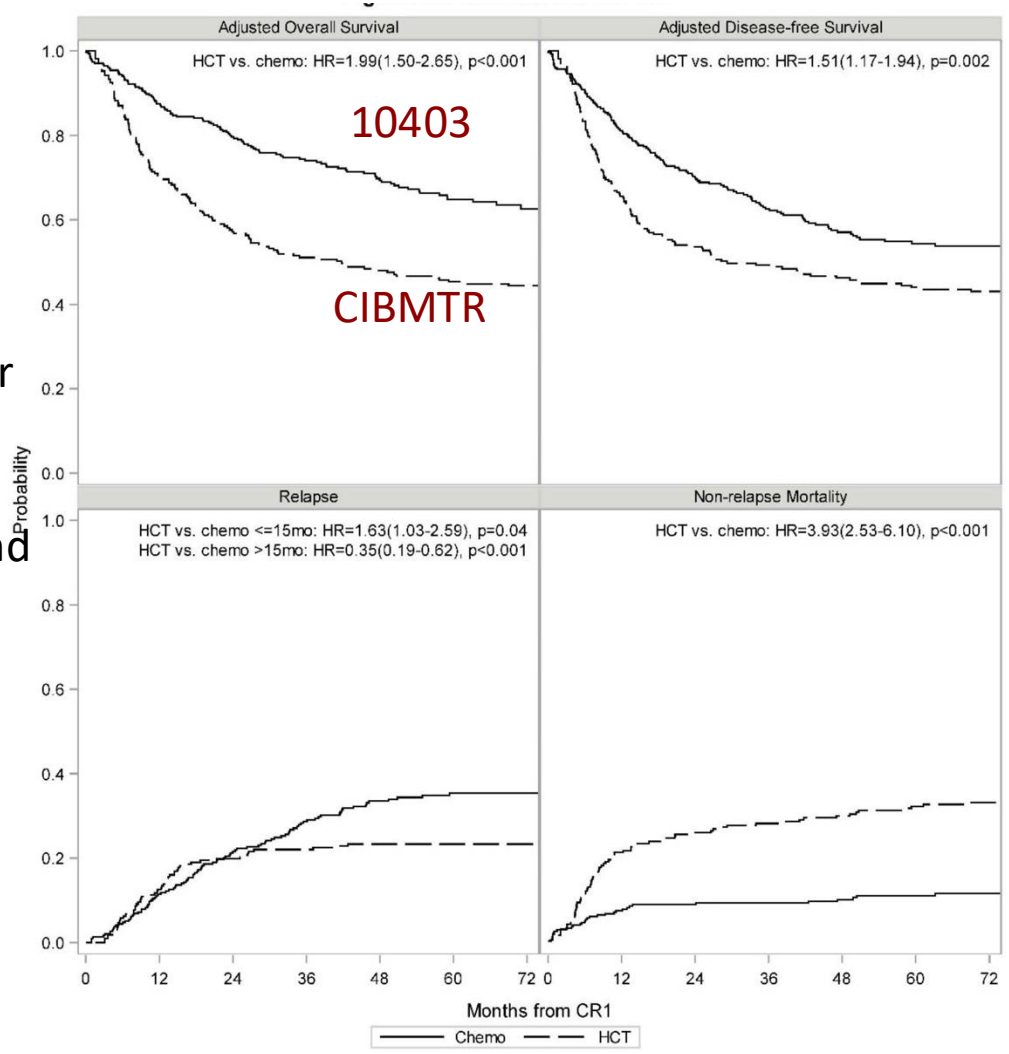
Compared 10403 (n= 295) to contemporary cohort undergoing myeloablative alloHCT in CR1 (n=217)

In multivariate analysis, alloHCT INFERIOR to AYA 10403 for both OS (HR= 1.99) , DFS (HR = 1.51) and non relapse mortality

- alloSCT associated with higher NRM; but beyond 15 mos, 10403 associated with higher relapse rate

Conclusions: CALGB 10403 SUPERIOR to alloHCT in newly diagnosed Ph-neg B cell and T cell ALL

Cautionary note: Further refinements by MRD in CR1, disease genetics needed to evaluate potential benefit of HCT in CR1 in selected subsets

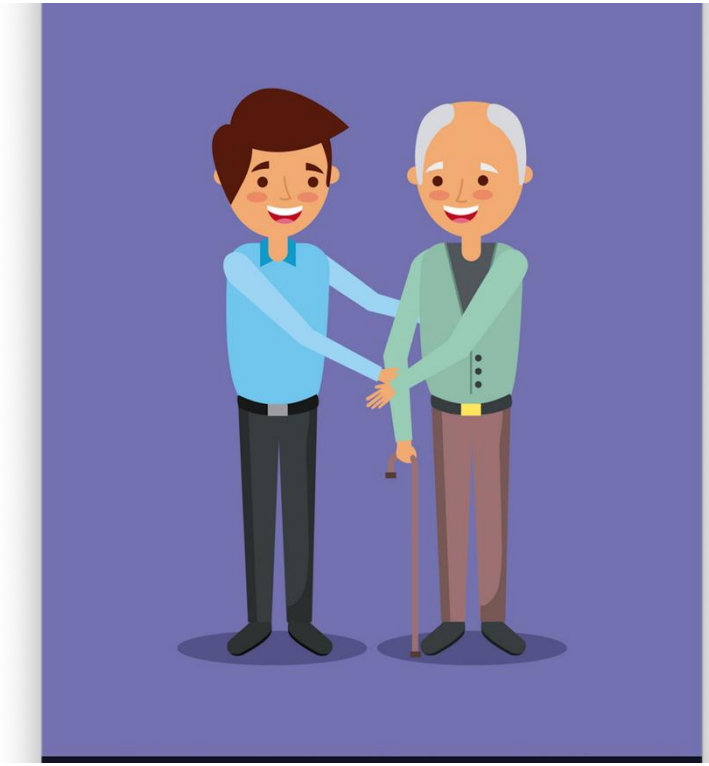


Wieduwilt et al, Leukemia 2021

Summary : Younger Adults

- Pediatric intensive regimens have improved survival
  - B-ALL: ongoing work to enhance EFS/ OS by addition of Antibody based therapies (INO/BLINA) in frontline
  - Paradigm shift E1910 data: Blina improves survival in MRD+ and MRD-
  - T-ALL: Nelarabine improves survival by decreasing CNS relapses
    - Targeting apoptotic pathways shows great promise: Next NCTN trial to test
    - Will daratumomab be useful (like blina) for MRD "erasing"?
- Allogeneic transplant in CR1: Not the "go to" for most pts
- Can we further minimize toxicity and improve responses?
- Can we improve access to care? Trial enrollment disparity

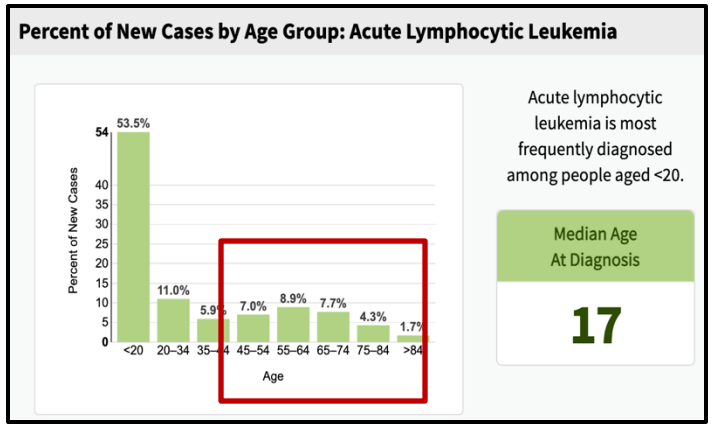
The Wisdom of Age: Older Adult Trials Inform!

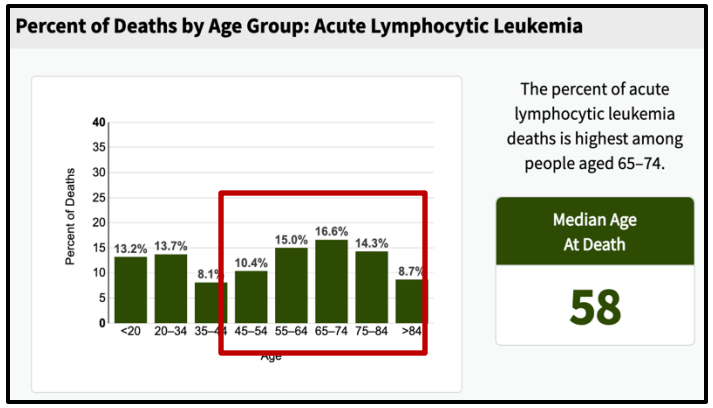


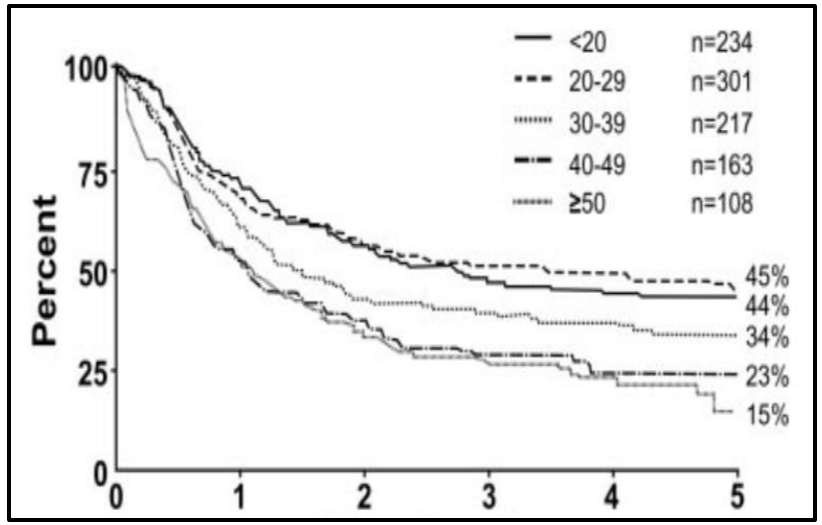
LESS (Chemo) IS MORE!!!!

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Older Adults: Poor Outcomes with Traditional Regimens

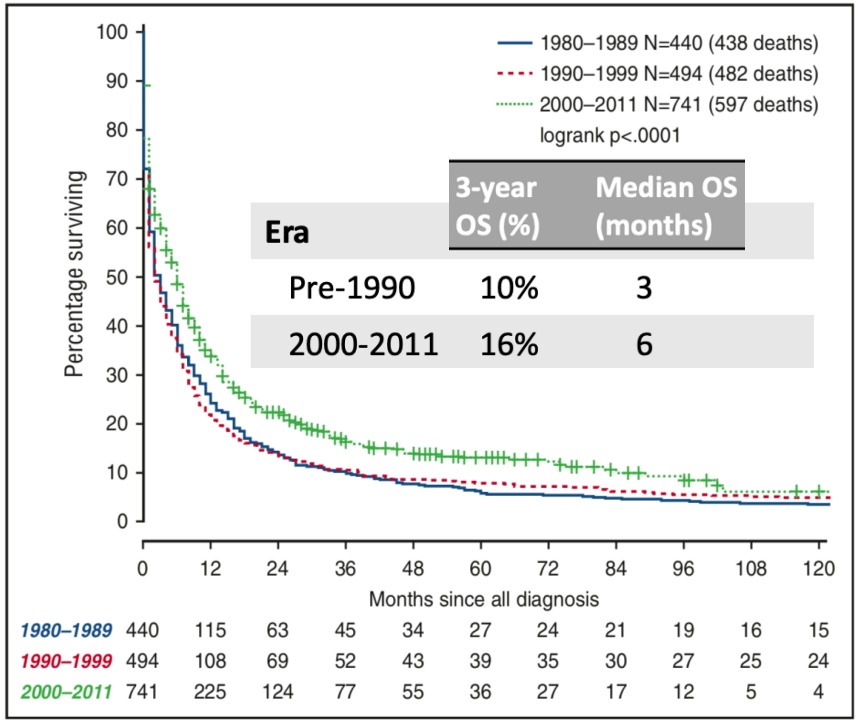






ECOG 2993[1]

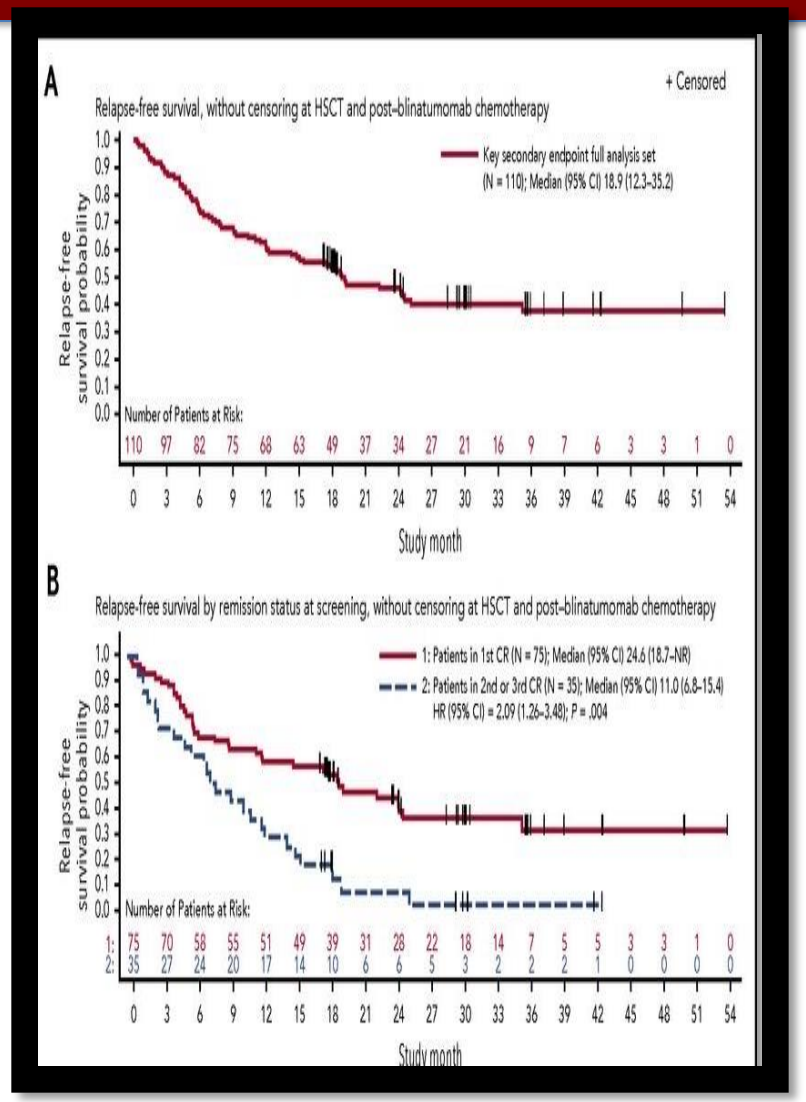
Fit for intensive trial



- Outcomes worsen with increasing age.
- Most ALL-related deaths occur in older adults.
- Little improvement in 3 decades (1980-2011).[3]

https://seer.cancer.gov/statfacts/html/alyl.html; [1]Rowe et al. *Blood* 2005;106:3760-67; Gokbuget N *Hematology Am Soc Hematol Educ Program* 2016;573-79; Luskin MR *Hematology Am Soc Hematol Educ Program* 2021; 1:7-14; [2]Sasaki et al. *Am J Hematol* 2021;96:650-58; [3]Kim et al. *Leuk Lymphoma* 2019;60:1462-68

BLAST TRIAL: 88/113 (78%) of MRD+ ALL Achieve CMR with Blina: Improves RFS and OS



Nicola Gökbuget et al. Blood 2018;131:1522-1531

→ Overall RFS at 18 months = 54% (33-70)

→ Median RFS for CR1 patients = 18.9 mos (12.3-35)

4**/18: : FDA grants accelerated approval for use of Blina for MRD+ ALL; frontline and relapsed states**

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Moving Away from Chemotherapy: Inotuzumab plus mini-Hyper-CVD

- Enrolled 52 patients
  - Median age: 68 years (IQR 64-72)
- Efficacy
  - 98% CR/CRp/CRi
  - 96% MRD-neg (flow) CR within 3 cycles
    - (78% at morphologic remission)
  - PFS 59% (95% CI, 32-54%) at 2 years.
  - Median PFS 35 months (95 CI, 15.3-NR).
- Toxicity
  - Thrombocytopenia (81%) beyond 6 weeks.
  - Hepatic adverse events
    - 17 (33%) grade 3 + (induction or later cycles)
    - 4 (8%) with VOD

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 Borthakhur, Jan Burger, Steven Kornblau, William Wierda, Courtney DiNardo, Alessandra Ferrajoli, Jovitta Jacob, Rebecca Garris, Susan O'Brien, Elias Jabbour

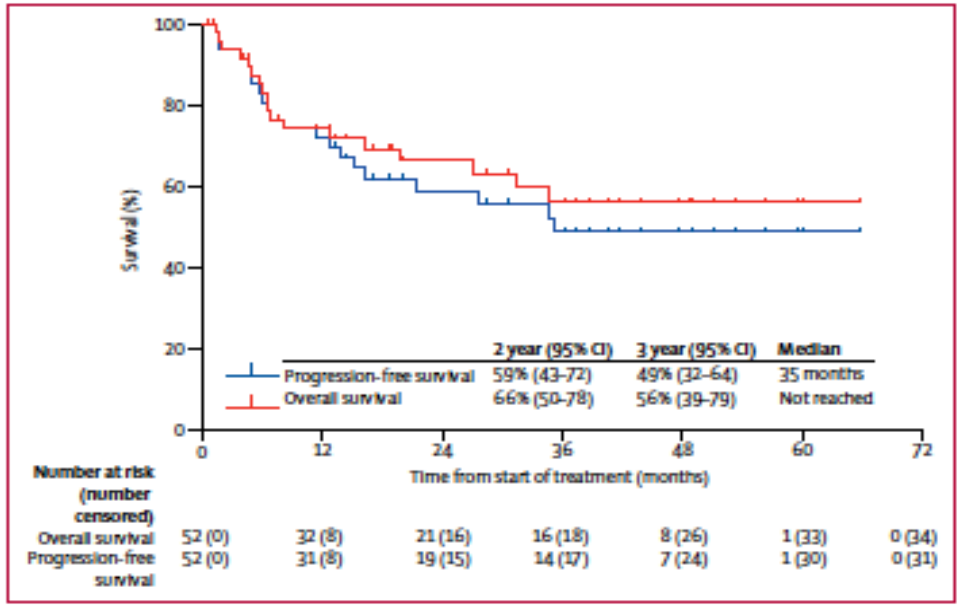
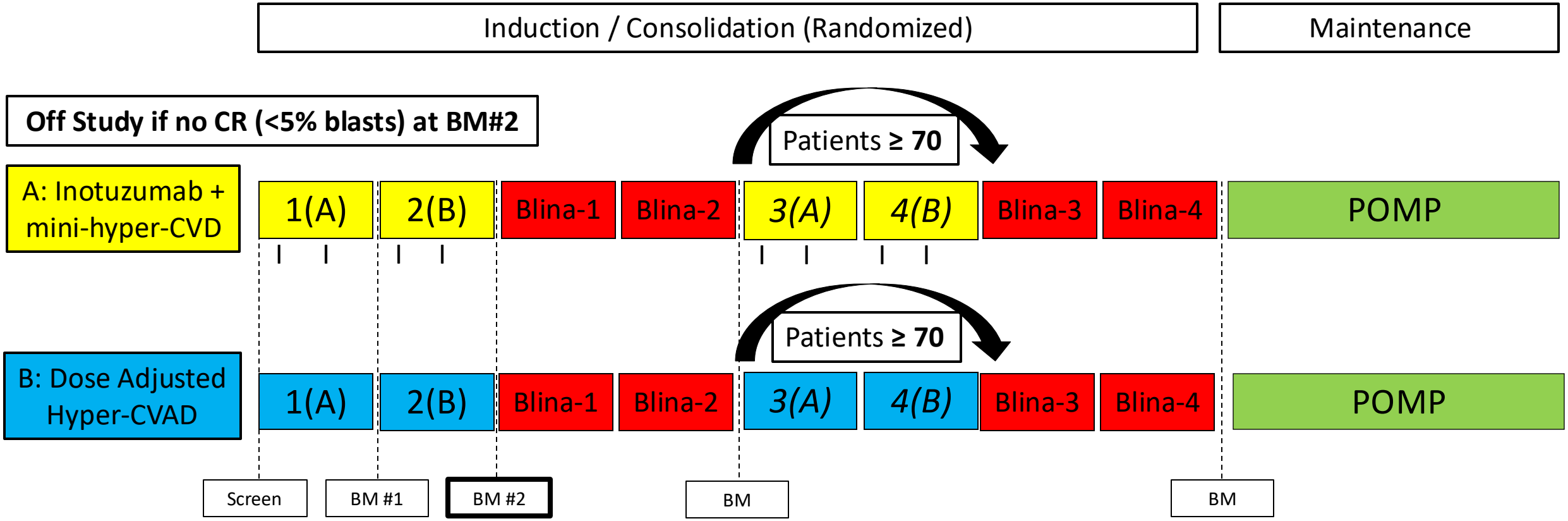


Figure 2: Progression-free and overall survival

Ino + mini-CVD (no anthracycline) : Ino given day 3 of first four cycles

Kantarjian et al. *Lancet Oncol.* 2018; 24-48.

Is Chemo-ImmunoRx the new standard? A042001



If **< 70 years** – up to 4 cycles of chemo (two A cycles, two B cycles)
If **≥ 70 years** – max. 2 cycles of chemo (one A cycle, one B cycle)

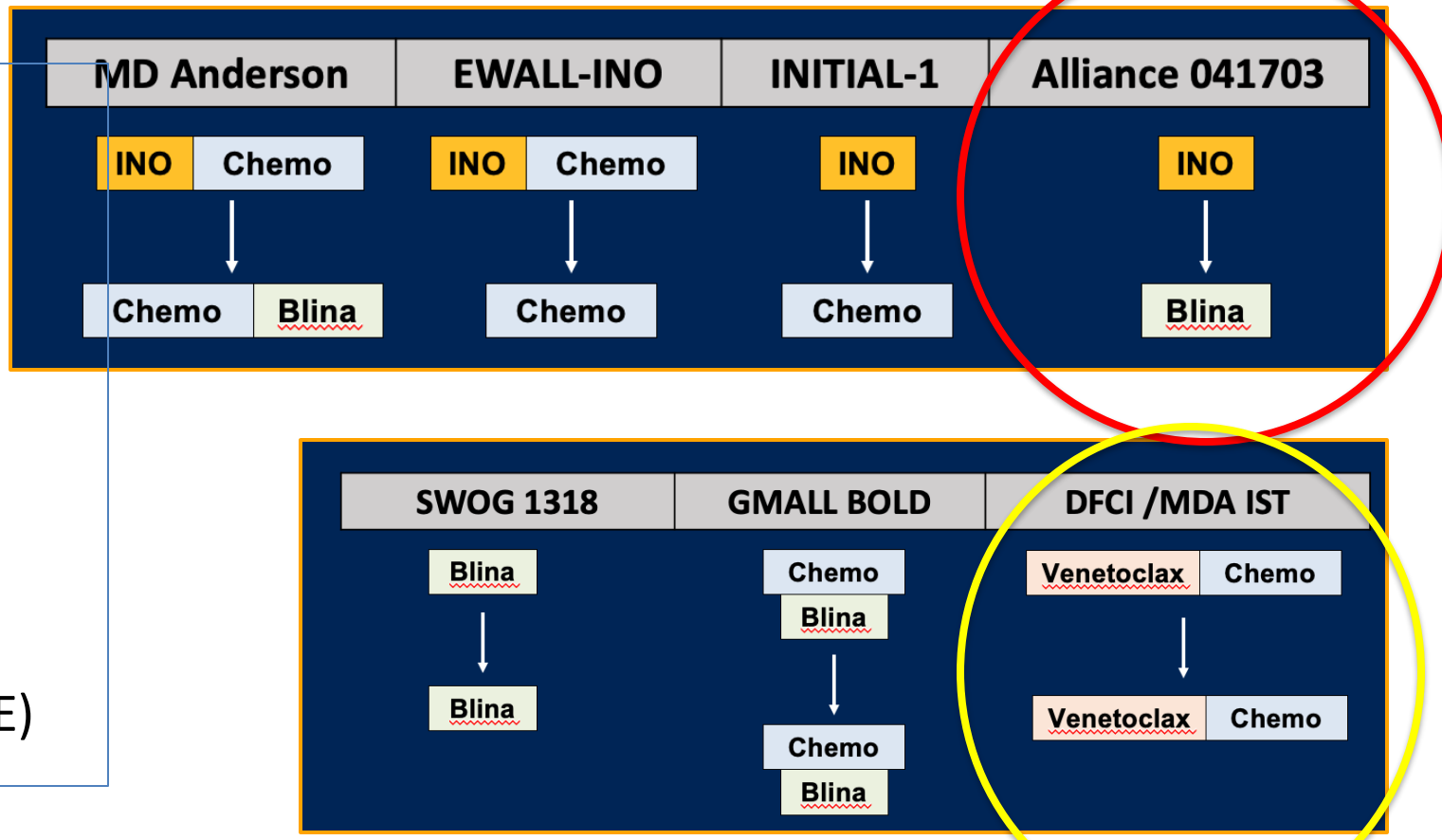
IT Chemo: 8 total
Two Per Cycle: Chemo 1A, 2B; Blina-1,-2

Rituximab added if CD20+

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Older Adults: Less is Very Likely MORE!

- High CR rates (80-90%).
- Most MRD negative (80-90%).
- Low induction mortality <5%.
- Late toxicity may still be a problem.
- *Long-term outcomes awaited!*
  - Mini-CVD venetoclax
  - Results of A041703 (CHEMO-FREE)



Kantarjian et al. *Lancet Oncol* 2018;19:240-9; Chevallier et al. *Blood* 2021;138:Abstract 511; Stelljes et al. *Blood* 2021;138:Abstract 2300; Advani et al. *J Clin Oncol* 2022;40:1574-82; Goekbuget et al. *Blood* 2021;139: Abstract 3399; Jain et al. *Blood* 2019;134:Abstract 3867

	A041703	INITIAL-1	EWALL-INO	MDA
Early mortality	**3% (1)**	**0%**	**0%**	**0%**
EFS	1 yr: 75% 2 yr: 55% *3 yr: 46%*	1 yr: 88% 2 yr: 69% *3 yr: 55%*	1 yr: 64% 2 yr: 46% *3 yr: 40%*	1 yr: A 62%, B 61% (PFS) 2 yr: A 62%, B 61% (PFS) 3 yr: A 50%, *B 60% (PFS)*
OS	1 yr: 84% 3 yr: 60%	1 yr: 91% 3 yr: 73%	1 yr: 73% 3 yr: 50%	1 yr: A 73%, B 80% 3 yr: A 60%, B 60% 5 yr: A 51%
CIR	1 yr: 16% 3 yr: 38%	1 yr: 5% 3 yr: 27%	1 yr: 25% 3 yr:45%	1 yr: A 7%, B 7% 3 yr: A 17%, B 12%
CI Death in remission	**6 mo: 3%** **1 yr: 6%** **3 yr: 9%**	**6 mo:0%** **1 yr: 7%** **3 yr: 17%**	**6 mo:3%** **1 yr: 8%** **3 yr: 12%**	**6 mo: A 18%, B 12%** **1 yr: A 23%, B 26%** **3 yr: A 33%, B 32%**
Risk factors	Lower CD22 Early MRD+	None	Lower CD22 HR CTG Early MRD+ KMT2Ar WBC >= 10k/mcl	HR CTG Early MRD+ (CD22 NR)

A041703: "Chemo-Free": InO ➡ Blina!

Hypothesis: Induction with Inotuzumab ozogamicin (InO) induction followed by consolidation with Blinatumomab would improve 1-year event-free survival (EFS) compared to historical outcomes with conventional chemotherapy (1-year EFS = 10%)

Treatment Plan:
Induction: 2 cycles Ino + IT chemo
Consolidation: 4 cycles Blinatumomab + IT chemo
NO maintenance therapy

	Total N=33
Age	
Median, years (Range)	71 (60-84)
³ 70 years	17 (52%)
Race	
White	28 (85%)
Asian	1 (3%)
Not Reported/Unknown	4 (12%)
Ethnicity	
Not Hispanic or Latino	27 (82%)
Hispanic or Latino	3 (9%)
Unspecified	3 (9%)
Gender	
Male	19 (58%)
ECOG Performance Status	
0	8 (24%)
1	19 (58%)
2	6 (18%)
Prior malignancy/chemo/XRT	
Any	8 (24%)
Multiple myeloma	6 (18%)
Presenting WBC (x1000/mcl)	
Median (range)	3.2 (0.6-38)
CD22 expression (%)	
Median (range)	92 (21-100)

UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

A041703 Hematologic Response

Best cumulative response (N=33)	N (%)
Composite CR (CR + CRh + CRi)	**32 (96%)**
CR	20 (60)
CRh	11 (33)
CRi	1 (3)
Refractory/progressive	**1 (3)**
Best response Course IA/B/C	**N (%)**
CR/CRh/CRi	30 (85)
Refractory	3 (9)
Undetermined*	2 (6)
Best response end Course II	**N (%)**
CR	19 (58)
CRh/CRi	13 (39)

*Hypocellular marrows without ALL present

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

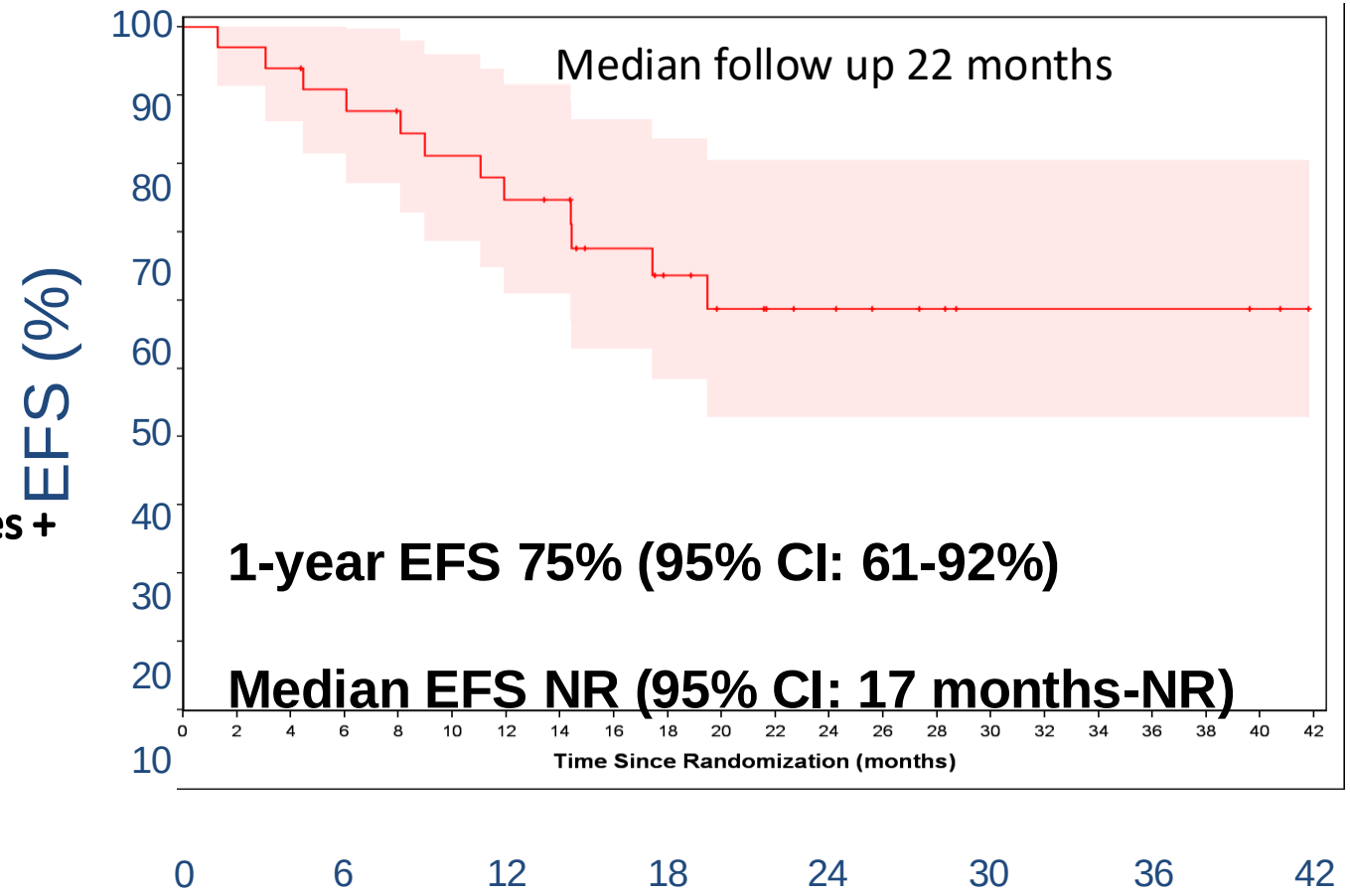
Alliance A041703: “Chemo-Free”, InO ➪ Blina

Inotuzumab X 2 cycles
+ IT chemo

↓

Blinatumomab X 4 cycles + IT chemo

NO long term maintenance therapy



33 Adults ≥ 60 years old with CD22+ B-ALL

Median Age = 71 years

Included t-ALL

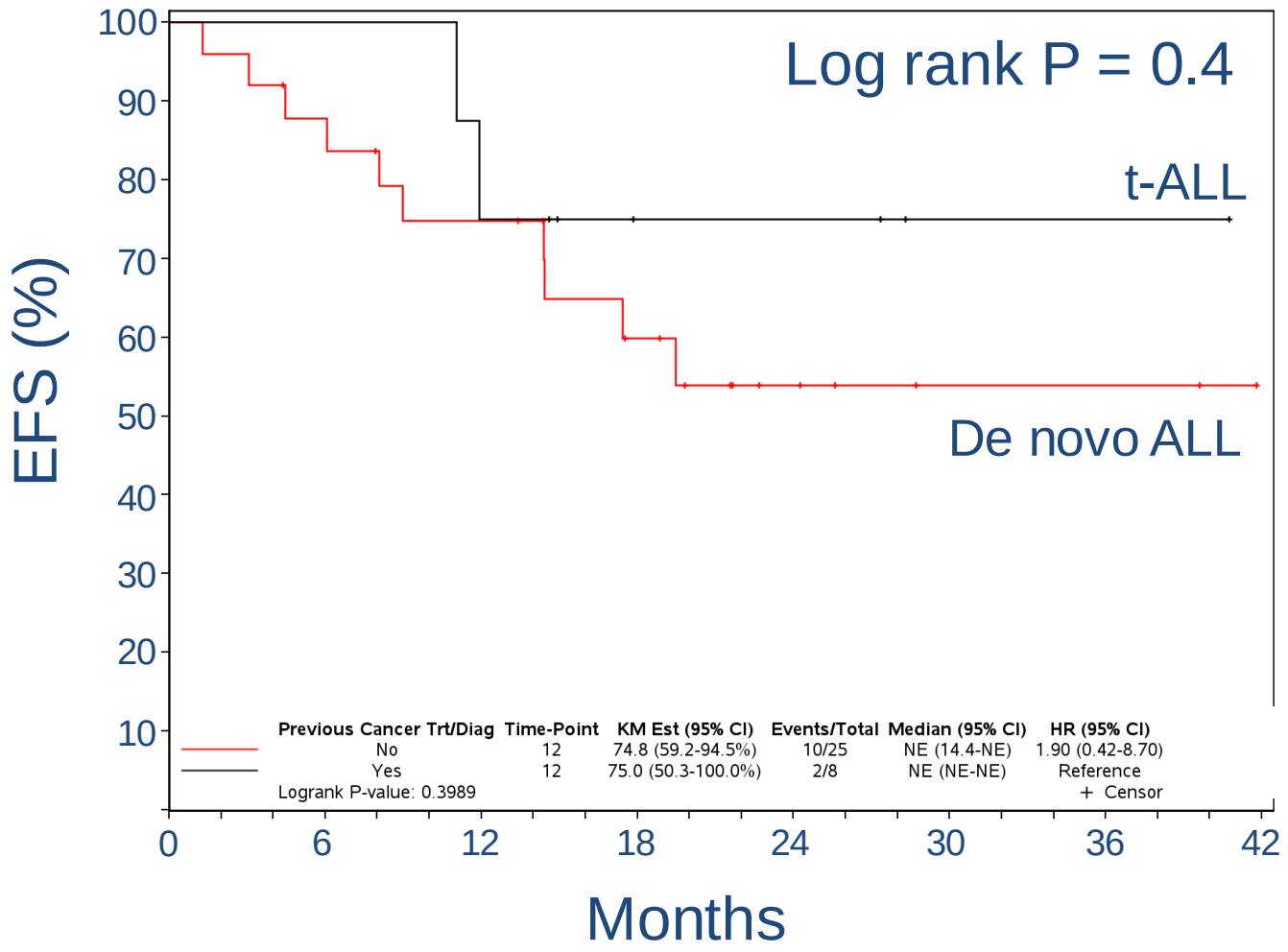
CR = 96%

2 Treatment-related deaths

Wieduwilt et al, EHA 2023

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

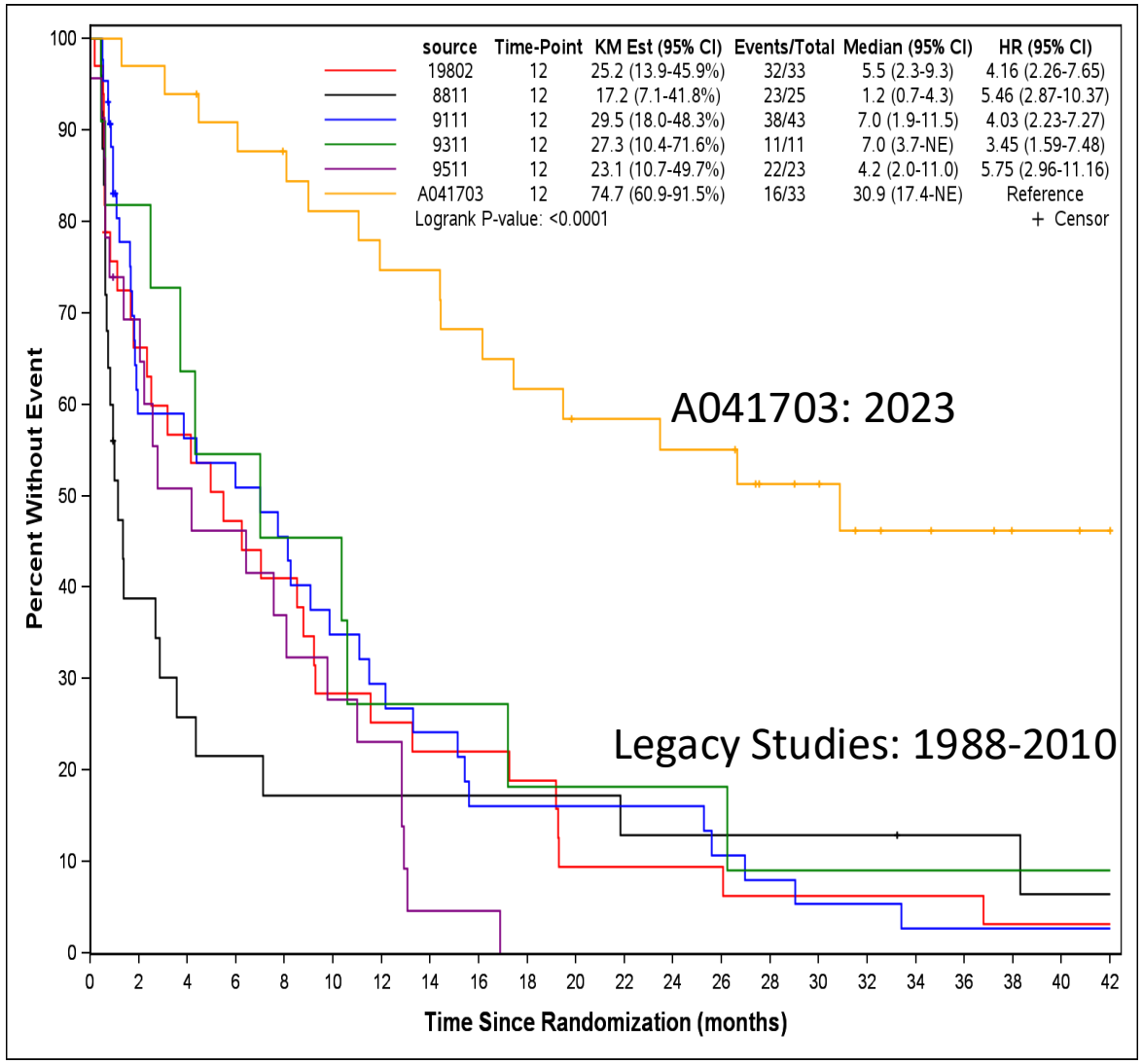
A041703: Equivalent outcomes for therapy related ALL



Wieduwilt, ASCO 2023

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Older Adults: The tide is turning!



ALL > 60 years over 4 decades in CALGB/ALLIANCE:

- **Legacy Studies From 1988-2010:**
  - **Median Survival = 4.1 months (2.5-7.0)**
- **A041703 (2023)**
  - **Median Survival = 30.9 months (17.4-NE) , HR=.23**

Courtesy, Vivien Yin, Alliance

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Ph- ALL in Older Adults– How I Treat in 2023

- *Assess comorbidities, fitness, goals.*
- **CNS prophylaxis:** IT chemo- Don't neglect!
- **Induction and Consolidation:**
  - Role of novel agents being established, be wary of adopting novel approaches outside of a clinical trial
- **Clinical trial whenever possible! Alliance 042001 NCT05303792 now open**
  - **Will establish new platform for treatment of adults with ALL > 50 years**

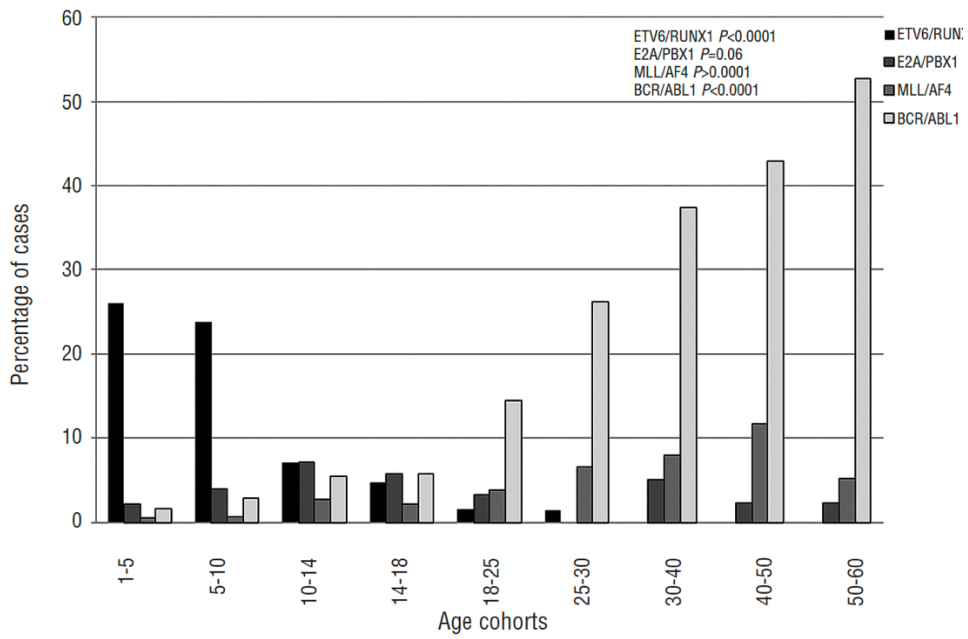
Huguet et al. *J Clin Oncol* 2018;36:2514-2523; Derman et al. *Leuk Lymphoma* 2020;614-622; Patel et al. *eJHaem* 2021;2:413-420

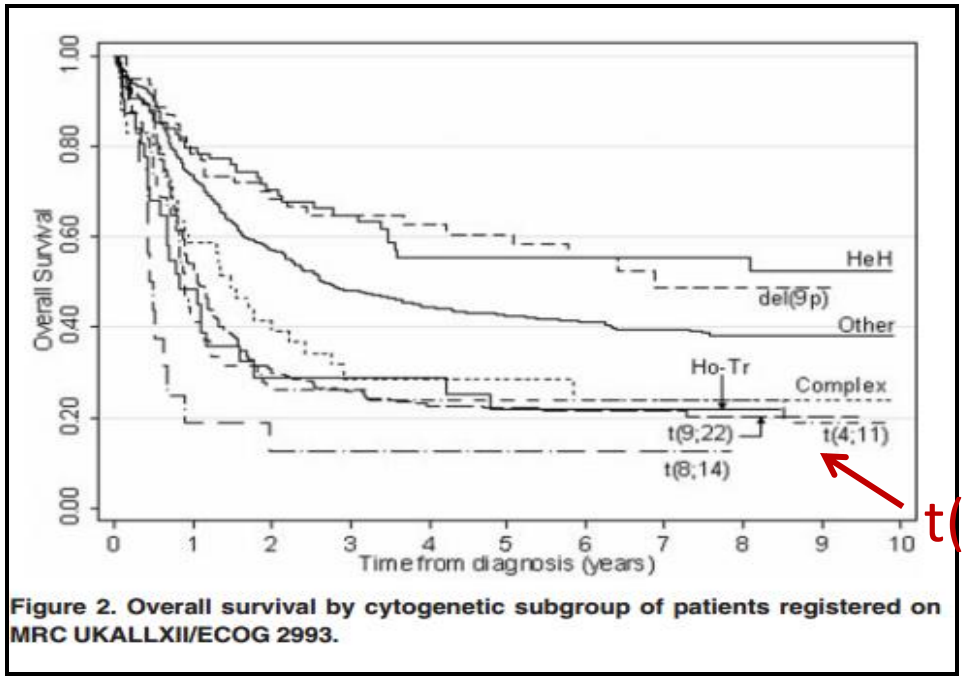
Targeted Agents Replace Chemotherapy

PH+ ALL: THE “NEW” APL?

Ph+ ALL Treatment (R)EVOLUTION!

- Philadelphia chromosome/BCR-ABL1 fusion present in ~1/3 of ALL cases.
- Prevalence increases with age (>50% in patients >50 years).
- Historically adverse prognosis prior to 2nd and 3rd generation TKIs.





t(9;22)

Figure 2. Overall survival by cytogenetic subgroup of patients registered on MRC UKALLXII/ECOG 2993.

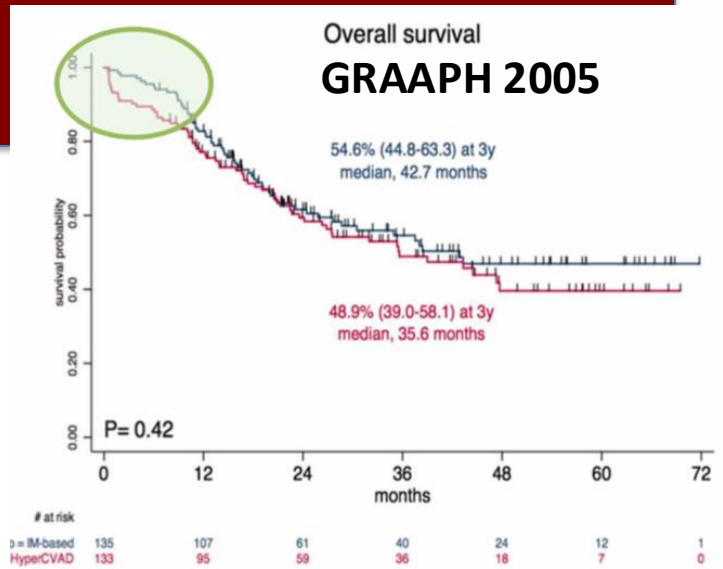
Chiaretti S, et al. *Haematologica* 2013;98:1702–10; Burmeister T, et al. *Blood* 2008;112:918–9; Ribera JM, et al. *Br J Haematol* 2012;159:485–8; Moorman AV, et al. *Blood* 2007;109:3189–97; Rowe JM, et al. *Blood* 2005;106:3760–7.

Ph+ ALL, recent context

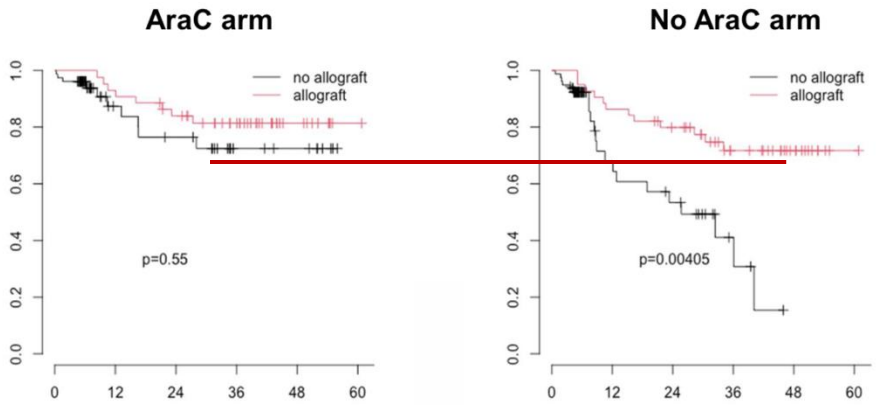
- **GRAAPH 2005 (IMATINIB)** → IM + VCR/Dex: ↑CR rate and ↓mortality compared to IM + hyperCVAD (**lesson**: reduce chemo in induction)

- **GIMEMA** → "chemotherapy-free" induction (imatinib LAL 0201-B; dasatinib LAL 1205, ponatinib LAL 1811).
  - High CR rates (>90%); (**lesson: 2G**/3G TKIs - Deeper and more durable); minimal toxicity

- **GRAAPH-2014 (NILOTINIB)** → Omission of HiDAC consolidation associated with more relapse in non-transplanted patients (**lesson:** still need intensive conventional chemo or BMT *in context of 2G TKI*)



GRAAPH 2014

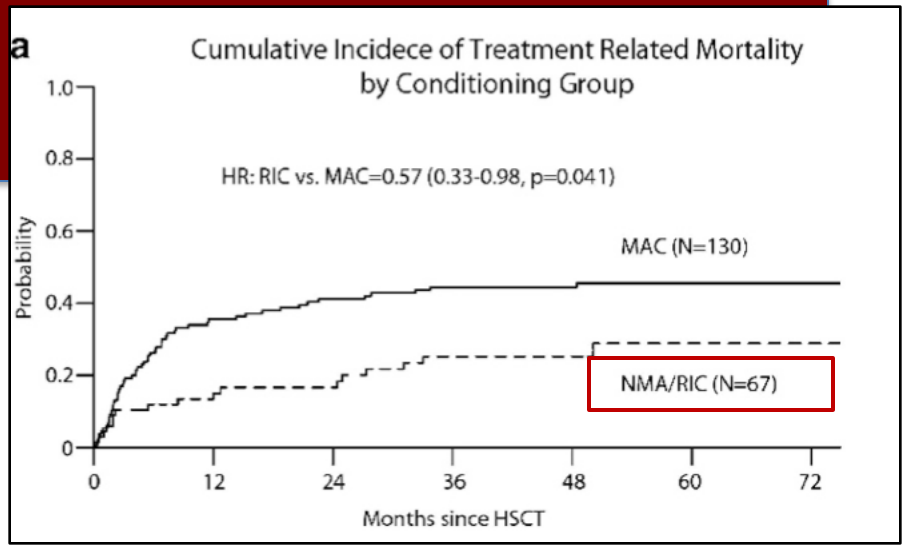


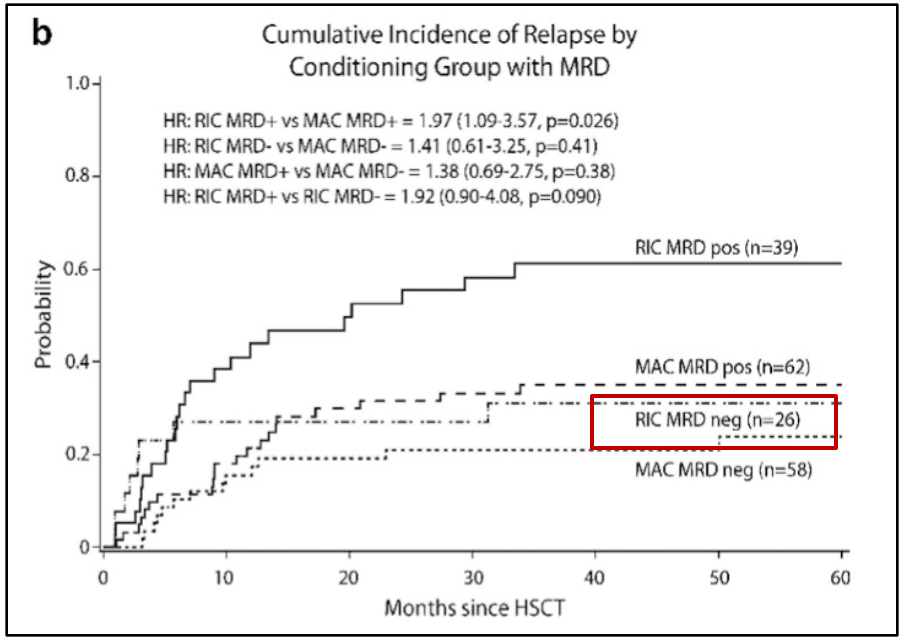
THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Chalandon et al. *Blood* 2015;125:3711-9; Rousselot ASH 2021 Abstract 614

Ph+ ALL: Transplant in Older Adults

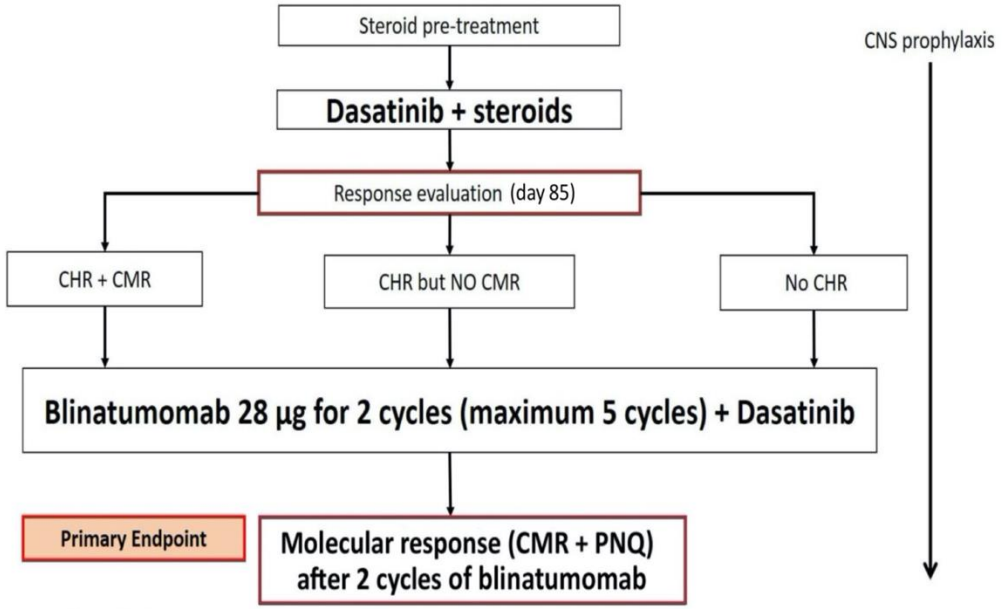
- Potentially curative.
- Compared to non-HCT chemotherapy approaches, ↓relapse but ↑non-relapse mortality, ↑graft-versus-host-disease (↓GRFS).
- **CIBMTR analysis (2014)[1]:** RIC vs MAC HSCT in Ph+ ALL (CR1). Among **RIC vs MAC**:
  - ↓ **1-yr TRM** (13 *vs* 36%, *P*=0.002).
  - ↑ **relapse** (49 *vs* 28% *P*=0.058).
  - = **OS similar** (39 *vs* 35%, *P*=0.62).
  - ***Patients receiving pre-HCT TKI (imatinib) and MRD-neg at time of HCT, 3-yr OS of RIC (55%)*** *superior to MAC (33%, P=0.0042).*





Mohty et al. *Blood* 2010;116:4439-43; Marks et al. *Blood* 2010;116:366-74; [1]Bachanova et al. *Leukemia* 2014;28:658-65; Rosko et al. *Am J Hematol* 2016;92:42-49; Roth-Guepin et al. *Oncotarget* 2017;8:112972-79; Leonard et al. *Curr Hematol Malig Rep* 2018;4:329-340

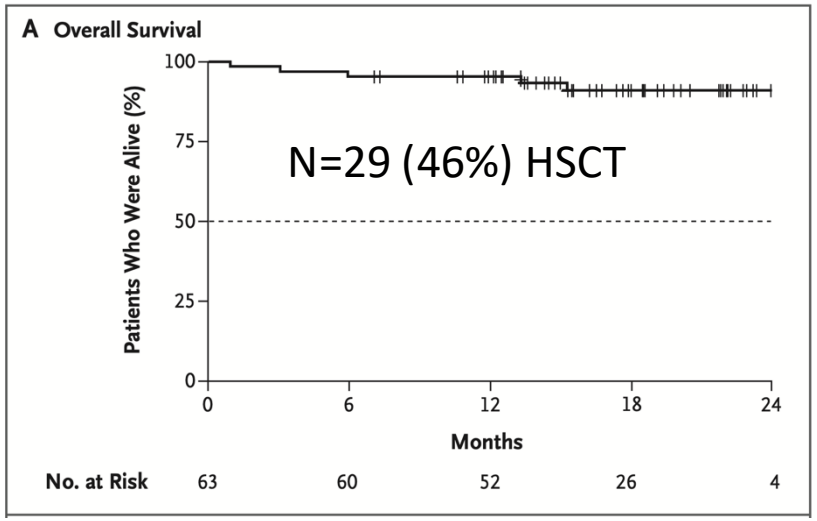
Ph+ ALL: Blinatumomab Consolidation (GIMEMA D-ALBA)



N=63, median age 54 (range 24-82) yrs

Note:
Follow-up still short.
Approximately half → HSCT.

- Day 85 – 29% Molecular Response
- Blina C2 (n=55) – 60% Molecular Response
- Blina C4 – 81% Molecular Response



- 36-mo DFS (71%) and OS (80%), respectively, median follow-up 28.8 mos.
- Worse outcomes in *IKZF1* deletion.

Foa et al. *N Eng J Med* 2020;383:1613-23

T315 drives most relapses after 2nd generation TKIs, role for novel agents and ponatinib?

- *BCR::ABL1* T315I KD mutation common at relapse after dasatinib (~70-75%).
- Ponatinib is a 3rd gen TKI active against T315I.
- Ponatinib associated with serious arterial thrombotic events, hepatotoxicity, and pancreatitis (unrandomized).
- IS THERE A BEST STRATEGY?

Foa et al. *Blood* 2011;118:6521-28; Rousselot et al. *Blood* 2016; 128:774-82; Wieduwilt et al. *Blood Advances* 2021;4691-700; Moslehi et al. *J Clin Oncol* 2015;33:4210-8; Martinelli et al. *Blood Advances 2022;6.1742-53*

Ponatinib/Blinatumomab for Newly-diagnosed Ph+ ALL

Eligibility

Adults: Median age = 57

Newly-diagnosed Ph+ ALL

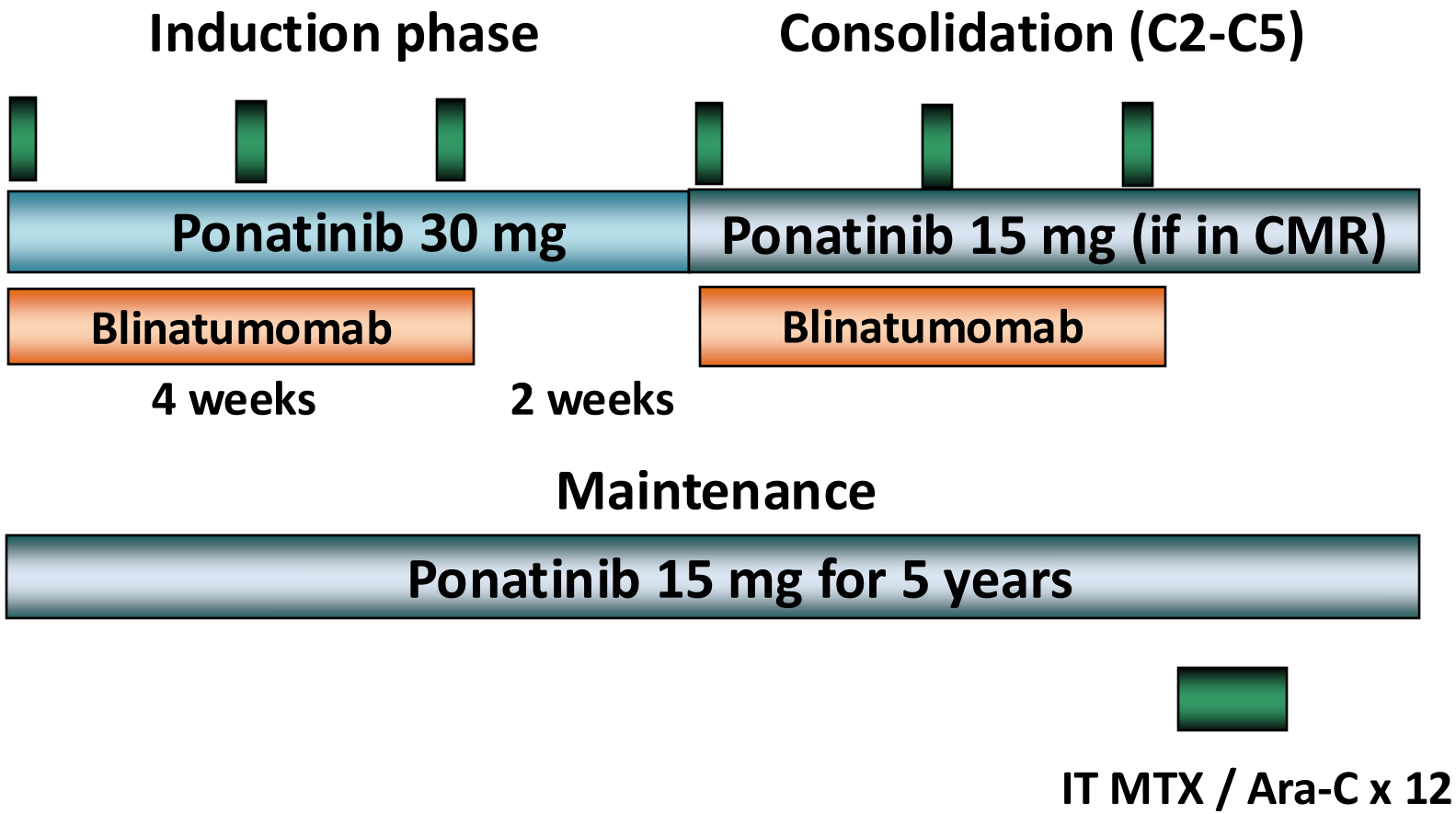
ECOG PS 0-2

No active CV disease

No CNS pathology

Primary endpoint

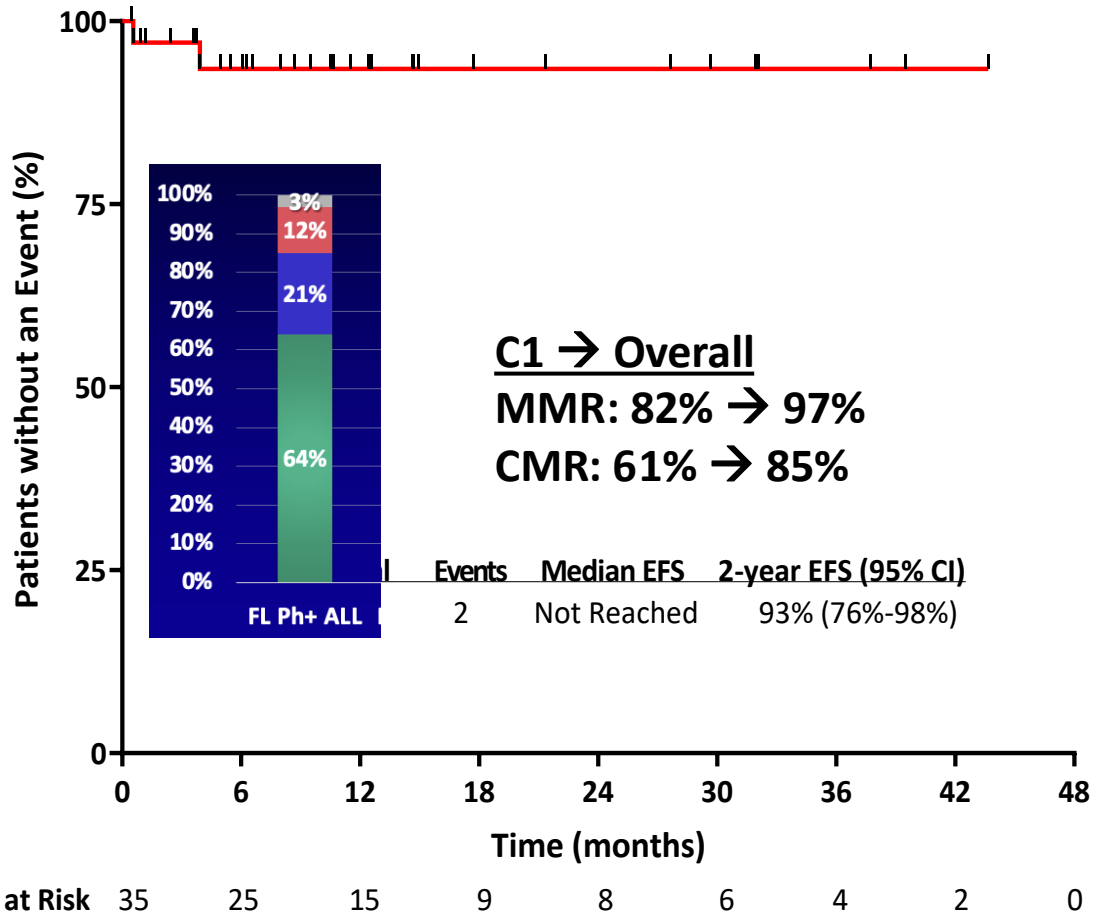
CMR rate

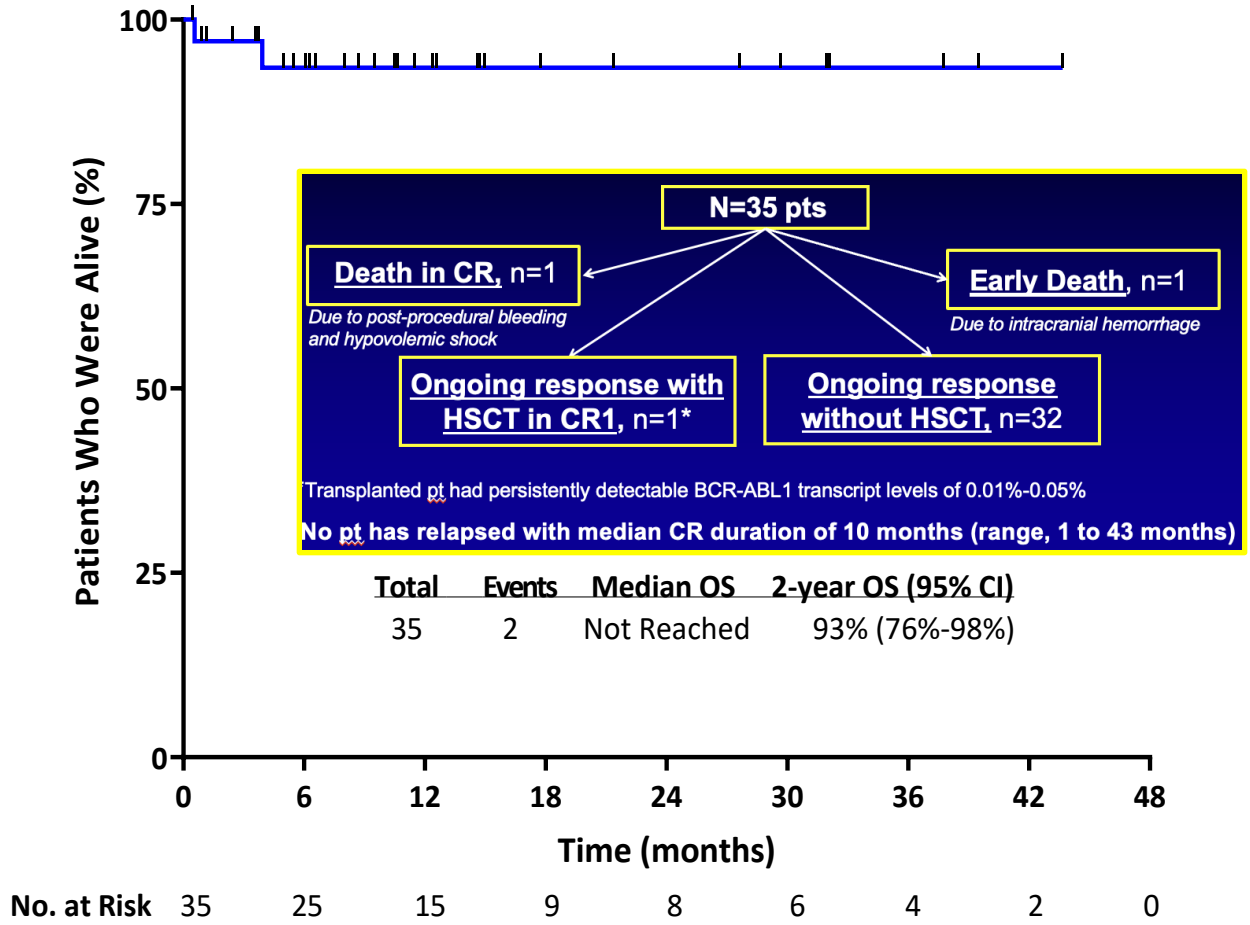


Short et al, ASH 2022: Jabbour et al, Lancet Haematology 2023

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes for Frontline Cohort





Short et al, ASH 2022: Jabbour et al, Lancet Haematology 2023

Summary: Ph+ ALL

- TKIs have dramatically changed remission rates, survival
  - Further refinements: Ponatinib may be most effective TKI given ability to overcome emergent T315I resistance mutations
- Aggressive CNS prophylaxis still essential
- Low intensity treatments with minimal or NO traditional chemotherapy becoming standard of care
  - TKI + BLINA
- Evolving role of Allogeneic transplant
  - If no transplant can TKI ever be discontinued?

Vision for the Future in ALL Therapy

- ”Less” is More!
  - More targeted therapy, less traditional chemotherapy
  - Older adult trials are paving the pathway for reduction of chemotherapy!
  - Novel BH3 mimetics, Menin inhibitors all coming our way
- Will CAR-T therapy be incorporated into frontline therapy?
  - Response Rates in relapsed setting are very high (80+%) but access, toxicities and durability of response may be limiting
    - New products are exciting: Obi-cel (more durable responses)?
    - CD7 CAR-T for T-ALL developing

Acknowledgements

NCTN ALL working group

Anjali Advani
Ibrahim Aldoss
Emily Curran
Dan Deangelo
Shira Dinner
Eli Jabbour
Mark Litzow
Selina Luger
Marlise Luskin
Kristen O'Dwyer
Matt Wieduwilt

Saygin/Stock Lab

Caner Saygin
Noreen Fulton
Arda Karaoglu
Olivia Arnold
Ella Postich
Kate Shimamoto

UCCCC Leukemia and AYA Programs

Michael Drazer
Adam DuVall
Emily Dworkin
Tara Henderson
Satyajit Kosuri
Richard Larson
Mariam Nawas
Rafael Madero Marroquin
Austin Wesevich
Toyosi Odenike
Anand Patel
Greg Roloff
Caner Saygin
Michael Thirman
Sam Yates

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

Lauren Agostinacchio
Terry DiJoseph
Juli Dziuban
Sayyeda Fatima
Tetyana Pytel
Melissa Tumpich.
Jamie Mathews
Afsheen Noorani
Karine Otten
Tyler Tschida.
Shreya Vasavada

Howie Weiner
Judith Murray
Hamed Youshanlouei
Kristy Johnson
Ellen Malone
Angie Smigilus
Allison Marthaler
Allison Mulchrone
Ginta Ginatye
Zariya Gonzalez

Alliance for Clinical Trials in Oncology

LEUKEMIA & LYMPHOMA SOCIETY®