Acute Lymphoblastic Leukemia *In Adults* Overview and Updates

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Clinical Focus: ALL, AML, CML, BPDCN, MDS, and MPNs
Research Focus: ALL, AYAs, novel therapeutics for acute leukemia.

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Disclosures

- Pfizer, Advisory Board
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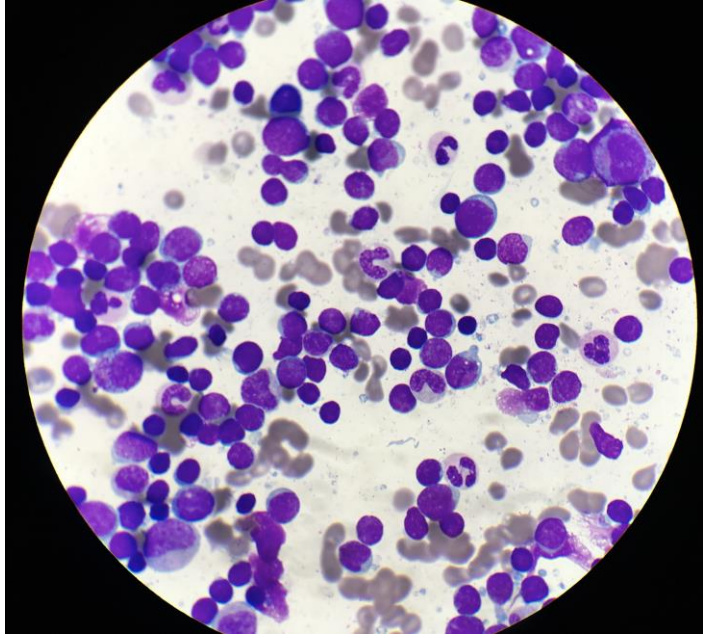
- Novartis, Research Funding

Acute Lymphoblastic Leukemia (ALL)



- **Aggressive hematologic neoplasm of B- or T-lymphoblasts**
  - Acute lymphoblastic leukemia (ALL)
  - Lymphoblastic lymphoma (LBL)
- **Clinical Presentation**
  - Cytopenias (bone marrow failure), adenopathy (enlarged lymph nodes), mediastinal mass (T-cell), hepatosplenomegaly, central nervous system.
  - Constitutional symptoms (fatigue, fevers, sweats, weight loss, bone pain).
- **Diagnosis: Morphology (blasts) and immunophenotype (flow cytometry/IHC) to determine lymphoid (B or T) and maturity stage.**
  - B-lymphoblasts: CD10, CD19, CD20 (some), and CD22; Ig negative
  - T-lymphoblasts: cCD3 and other T cell antigens.

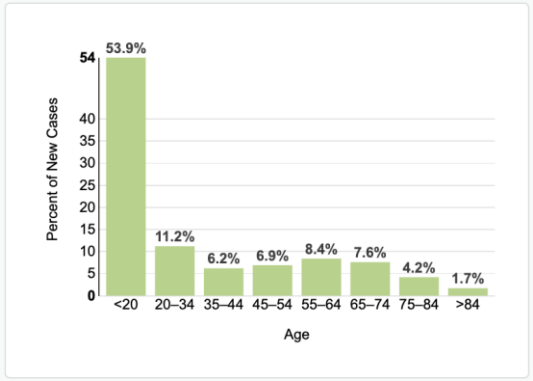
ALL – Epidemiology and Demographics

At a Glance

Estimated New Cases in 2022	6,660
% of All New Cancer Cases	0.3%

Acute lymphocytic leukemia represents 0.3% of all new cancer cases in the U.S.

Percent of New Cases by Age Group: Acute Lymphocytic Leukemia



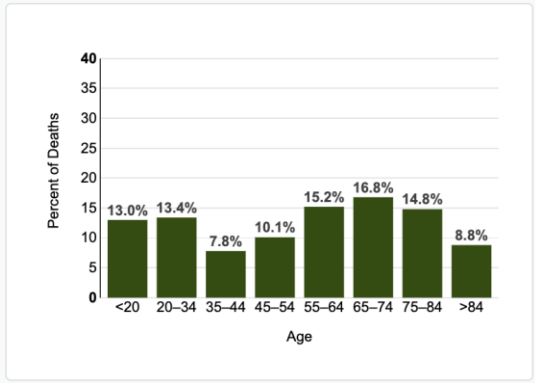
Acute lymphocytic leukemia is most frequently diagnosed among people aged <20.

Median Age At Diagnosis

17

SEER 22 2015–2019, All Races, Both Sexes

Percent of Deaths by Age Group: Acute Lymphocytic Leukemia



The percent of acute lymphocytic leukemia deaths is highest among people aged 65–74.

Median Age At Death

58

U.S. 2015–2019, All Races, Both Sexes

- Most common leukemia in children.
- Adults: ~50% of diagnoses, but majority of relapses and death.
- Risk factors: Down syndrome, prior chemo/radiation (myeloma).
- In adults, ~1/3 are Philadelphia-chromosome positive

https://seer.cancer.gov/statfacts/html/alyl.html

ALL: A Pediatric Oncology Success Story

- **1948:** Sidney Farber described 5 children who responded (temporarily) to the folic acid antagonist **aminopterin.**

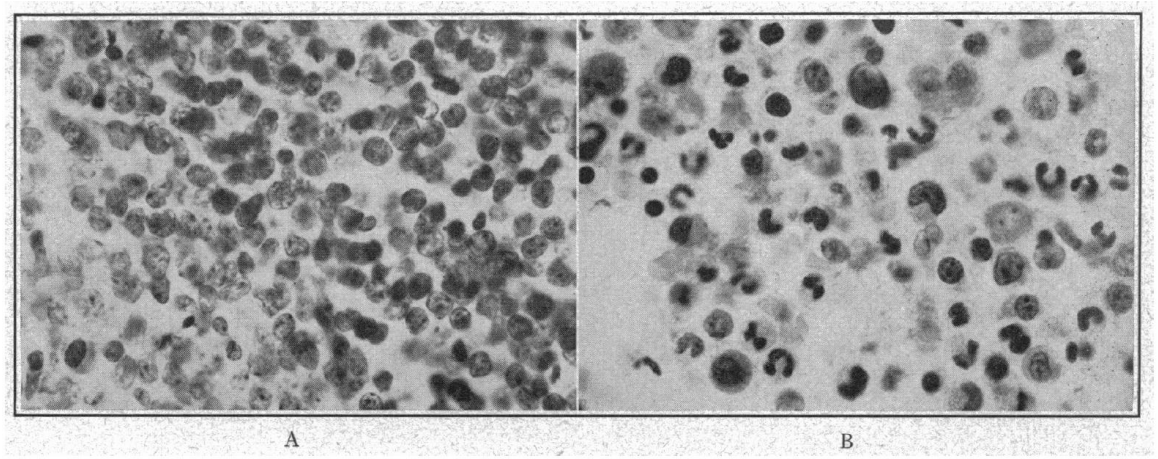
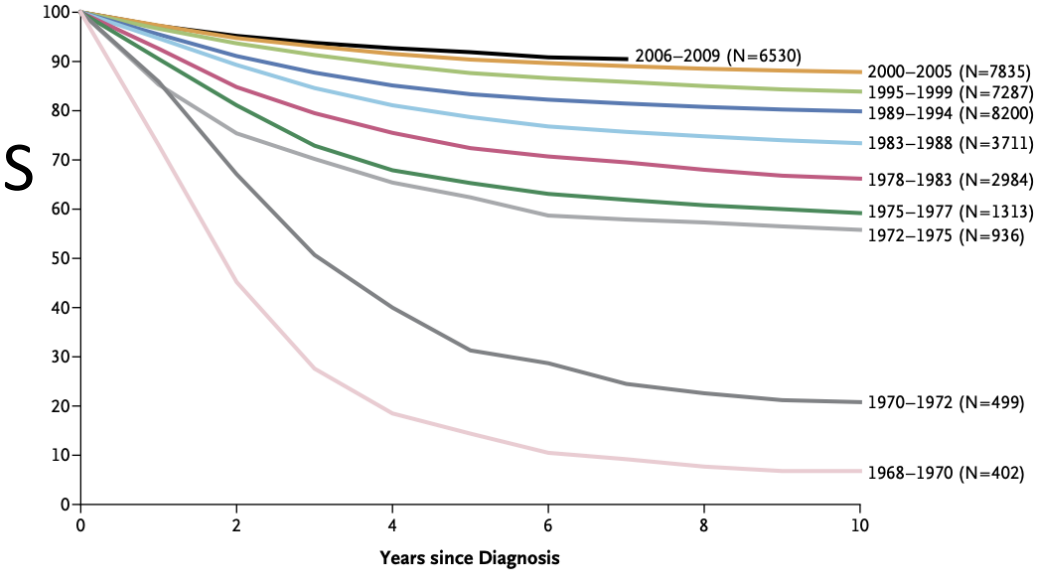


FIGURE 4. *Photomicrographs of the Sternal Bone Marrow in Case 3, Showing Giemsa-Stained Section on January 29, (A) and April 3 (B), 1948 (x1000).*

Note that the microscopical field is composed mainly of blast forms characteristic of leukemia (cell type undetermined) in the early section (A) and that a marked shift to mature cell forms, particularly of the polymorphonuclear series, with no leukemic cells, had occurred on the later examination (B).

OS

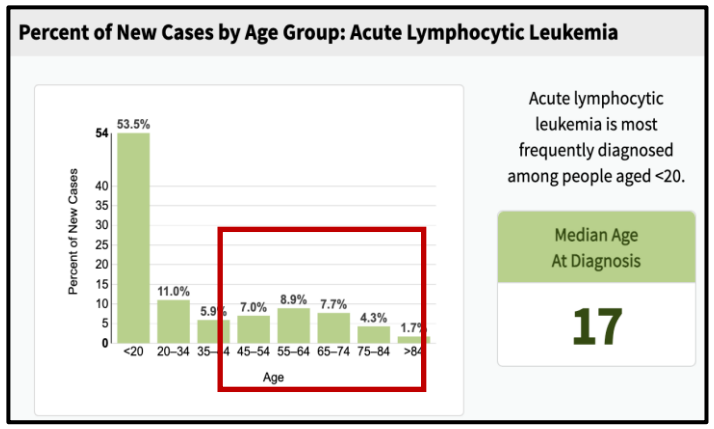


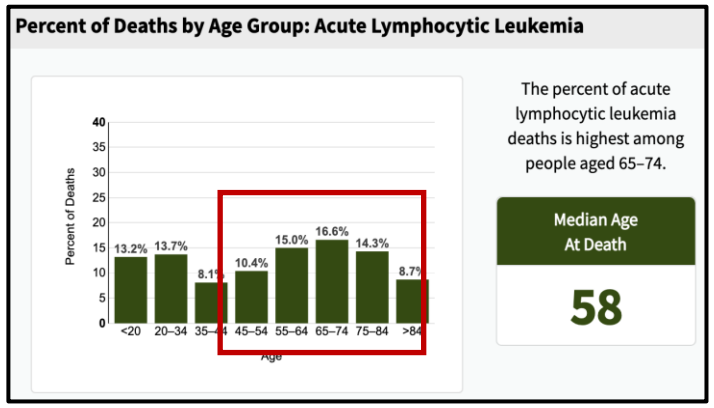
- **2022:** 73 years later, most children cured.

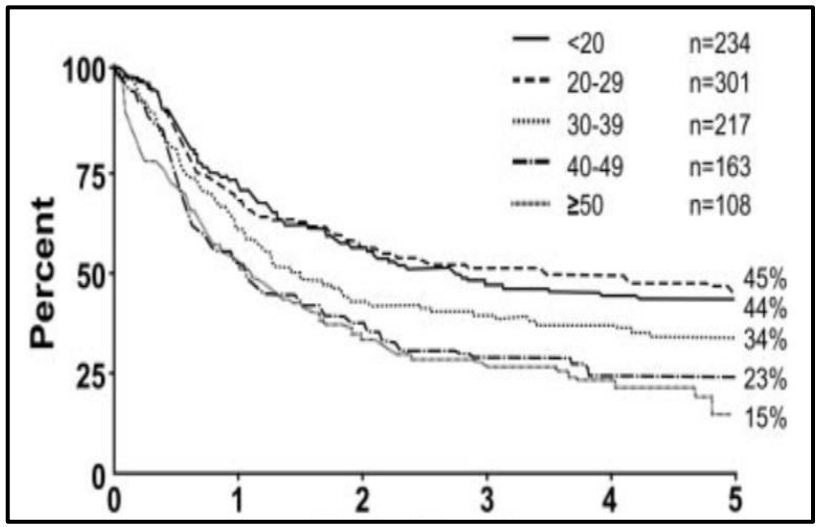
CCG and COG trials, 1968-2009

Farber et al. *N Eng J Med* 1948;238:787-93; Pui et al. *J Clin Oncol* 2015;33:2938-48; Hunger and Mulligan *N Eng J Med* 2015;373:1541-52

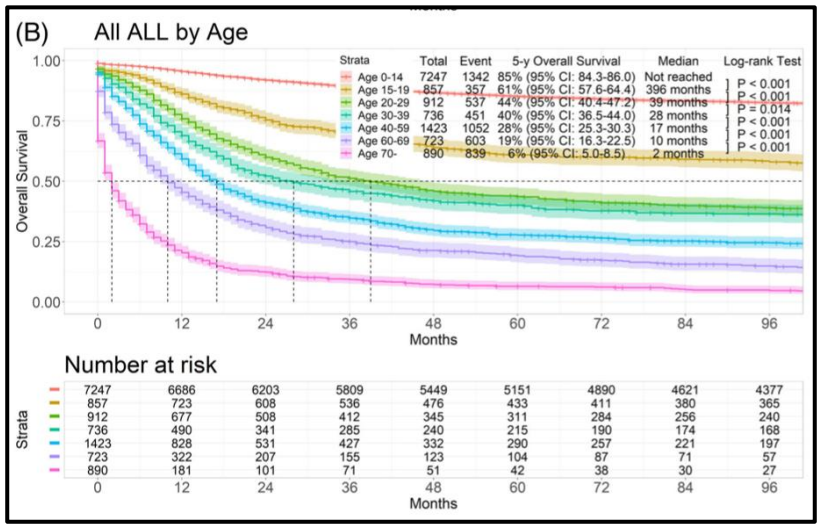
ALL in Adults: More Work to be Done







ECOG 2993

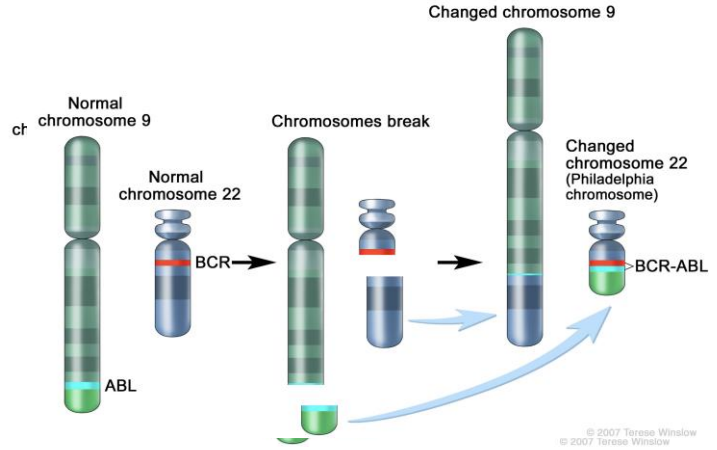


SEER Analysis 1980-2017

- Outcomes worsen with increasing age.
- Particularly impacting older adults.

https://seer.cancer.gov/statfacts/html/alyl.html; 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; Sasaki et al. *Am J Hematol* 2021;96:650-58

ALL – Framework for Initial Approach to Adult ALL

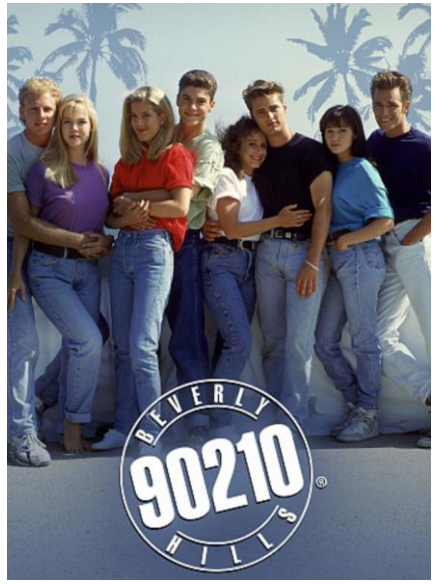


Initial therapeutic decisions guided by:

1) Philadelphia-chromosome status

2) Age/fitness for chemotherapy

- AYA: Pediatric-inspired
- Adult: Standard intensity
- Older/With Medical Problems: Less intense



ALL – Approach to Initial Treatment

- **Induction Goal → Achieve Remission**
  - Reduce morphologically apparent leukemia to undetectable levels → complete remission (CR).

- **Consolidation/Maintenance Goal → Prolong Remission/Cure**
  - Reduce minimal residual disease present at CR (*measured or presumed*) to a level low enough to achieve prolonged disease-free survival, sometimes cure.

Philadelphia Chromosome **Negative** Acute Lymphoblastic Leukemia

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ALL – Approach to Ph-Negative ALL Therapy (B and T)

	Age < ~40 (AYA)	**Age 40–70 (Fit) (Adult)**	**Age >70/Unfit**
Goal	Cure	Cure	Cure? Control!
Induction	**AYA induction**	**Adult induction**	**Less intense induction**
Consolidation	Low-risk: Chemotherapy High-risk: Transplant	Low-risk: Chemotherapy High-risk: Transplant	Less intense consolidation/ maintenance

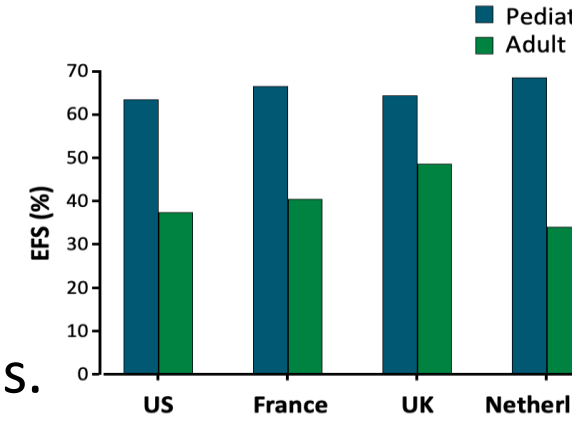
CLINICAL TRIALS

Philadelphia-chromosome-**negative** ALL

- **Multiple cycles of combination chemotherapy.**
  - *Complex: numerous drugs in different doses, combinations, and schedules*.
  - Prolonged chemotherapy (2-3 years from CR), unless transplant in first CR.
  - Phases: **1)** induction, **2)** consolidation with CNS phase, **3)** maintenance.
- "**Core" drugs: vincristine, steroids, anthracycline**
  - **YOUNG**: "Pediatric-inspired" or "AYA" (adolescent young adult) regimens are more intensive including asparaginase, steroids, vincristine, and escalated CNS prophylaxis, lead to improved outcomes.
  - **OLDER**: Dose-reduced chemo, *investigational: novel agents*
- **CNS prophylaxis is mandatory**
  - IT chemotherapy, high dose cytarabine/methotrexate, CNS radiation

Approach to Ph-Neg ALL in **Younger Adults**

- Patients aged ≤ 40 years (adolescent and young adults, "AYAs") have improved outcomes when treated on a pediatric-inspired regimen.
- Identified retrospectively → safety and efficacy demonstrated prospectively with favorable outcomes compared to historical controls.



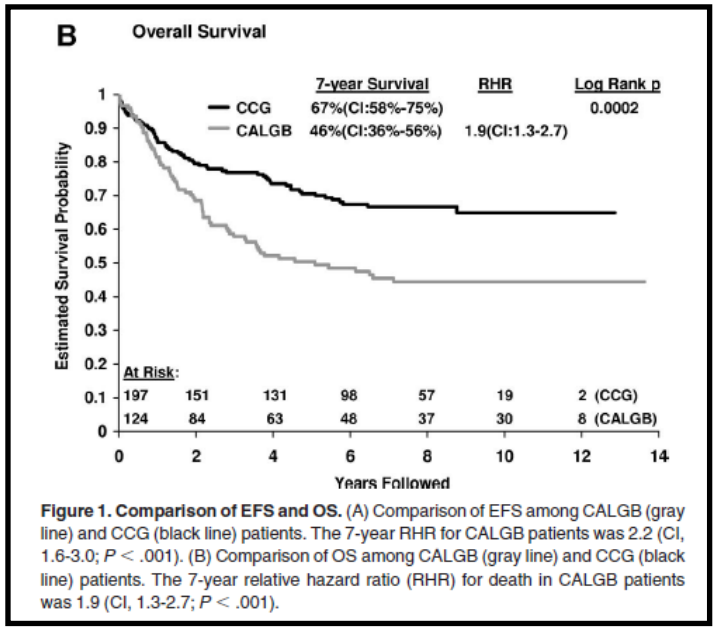


Figure 1. Comparison of EFS and OS. (A) Comparison of EFS among CALGB (gray line) and CCG (black line) patients. The 7-year RHR for CALGB patients was 2.2 (CI, 1.6-3.0; $P < .001$). (B) Comparison of OS among CALGB (gray line) and CCG (black line) patients. The 7-year relative hazard ratio (RHR) for death in CALGB patients was 1.9 (CI, 1.3-2.7; $P < .001$).

AYAs aged **16–20 years** treated on **pediatric (CCG)** or **adult (CALGB)** trials 1988–2001

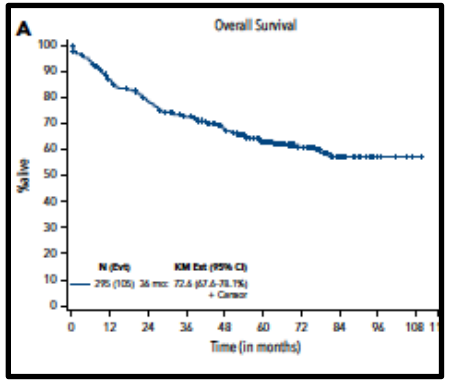
Identical CR rates (90%)

7-year survival:
CCG: 67%
CALGB: 46%

CLINICAL TRIALS AND OBSERVATIONS

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

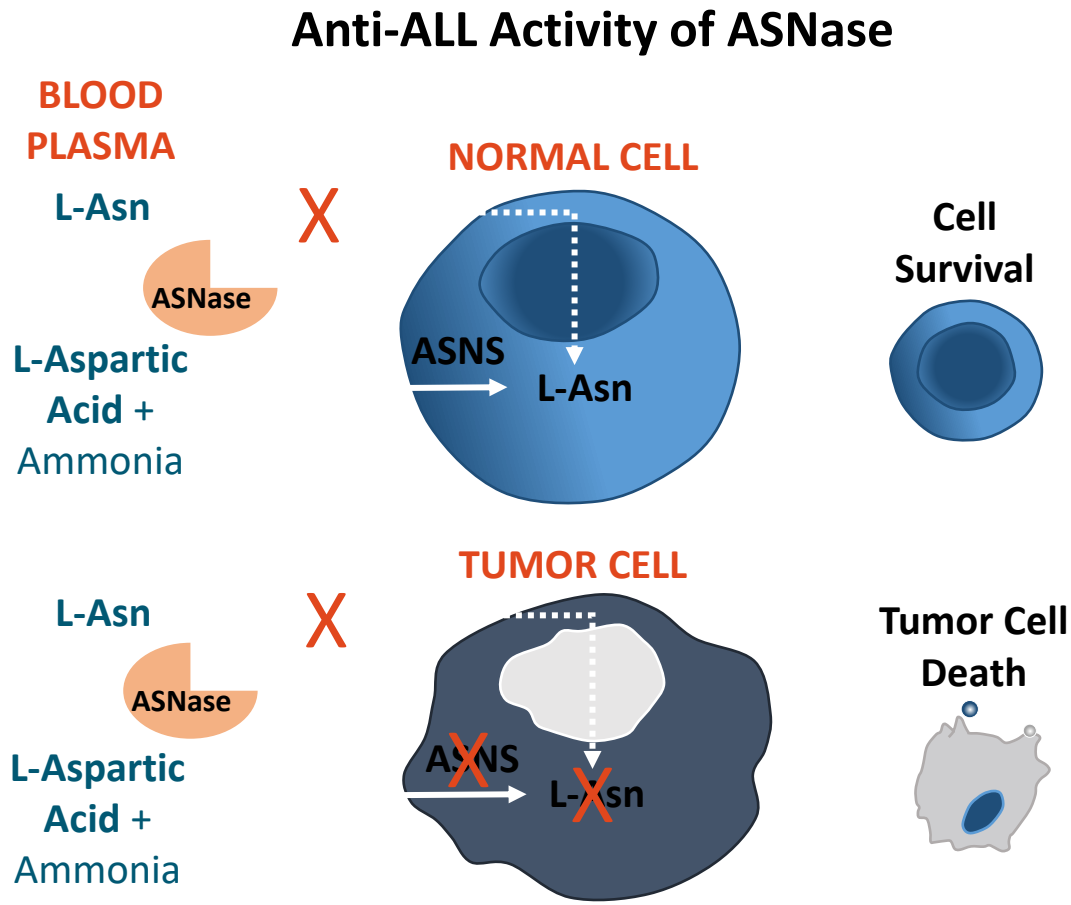
Wendy Stock,[1] Selina M. Luger,[2] Anjali S. Advani,[3] Jun Yin,[4] Richard C. Harvey,[5] Charles G. Mullighan,[6] Cheryl L. Willman,[5] Noreen Fulton,[1] Kristina M. Laumann,[4] Greg Malnassy,[1] Elisabeth Paietta,[7] Edy Parker,[8] Susan Geyer,[9] Krzysztof Mrózek,[10] Clara D. Bloomfield,[10] Ben Sanford,[8] Guido Marcucci,[11] Michaela Liedtke,[12] David F. Claxton,[13] Matthew C. Foster,[14] Jeffrey A. Bogart,[15] John C. Grecula,[16] Frederick R. Appelbaum,[16] Harry Erba,[17] Mark R. Litzow,[18] Martin S. Tallman,[19] Richard M. Stone,[20] and Richard A. Larson[1]



Stock et al. *Blood.* 2008;112:1646-54; Stock et al. *Blood* 2019;133:1548-59

Asparaginase (ASNase): Mechanism of Action

- Asparagine (Asn) is an amino acid that can be synthesized from aspartic acid by most cells using asparagine synthetase (ASNS).
- ALL cells lack ASNS, thus depend on import of Asn from plasma, making them sensitive to depletion of plasma Asn.
- ASNase breaks down Asn to aspartic acid and ammonia.
- ASNase depletes plasma Asn, thereby killing ALL cells but not normal cells that can make their own Asn.



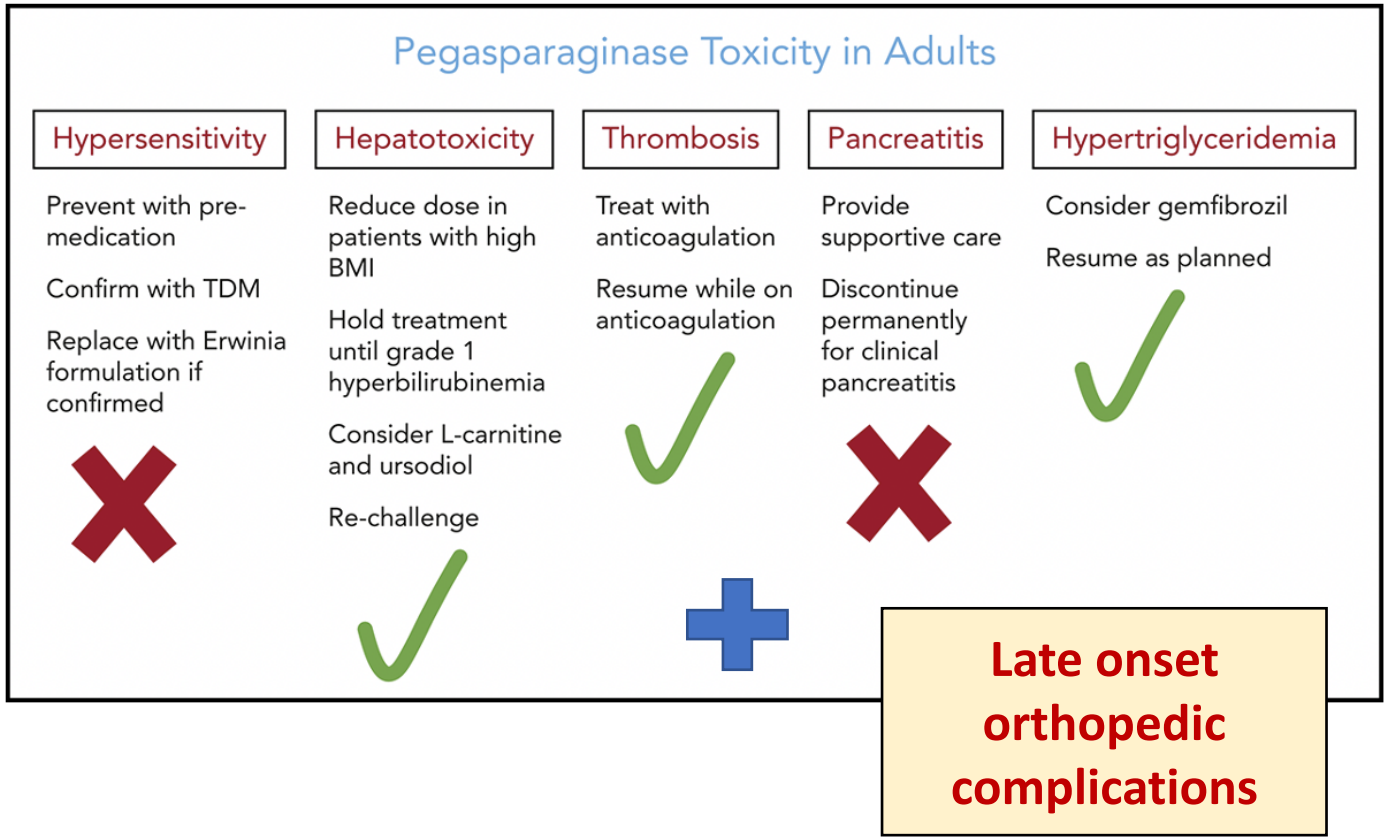
ASNase is a key component of effective contemporary pediatric ALL regimens

Avramis et al. Int J Nanomedicine. 2006;1:241.

Slide credit: clinicaloptions.com

AYA Regimens – Asparaginase a Particular Challenge

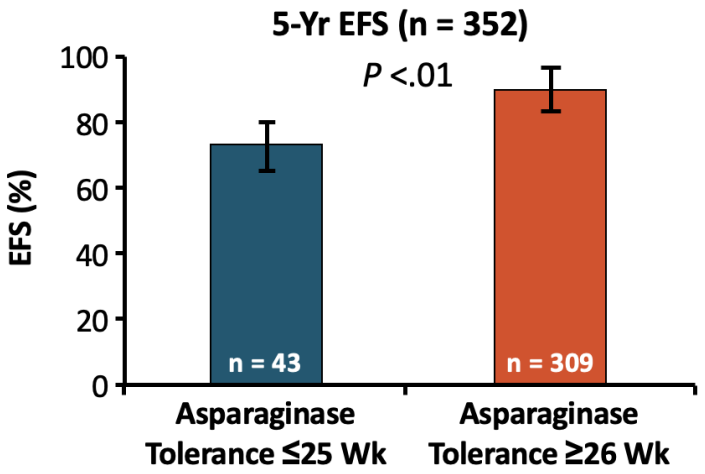
- **Asparaginase-related**
  - Thrombosis/hemorrhage
  - Liver toxicity
  - Pancreatitis
  - Hypertriglyceridemia
  - Hyperglycemia
  - Hypersensitivity
- **Steroid + asparaginase** related osteonecrosis



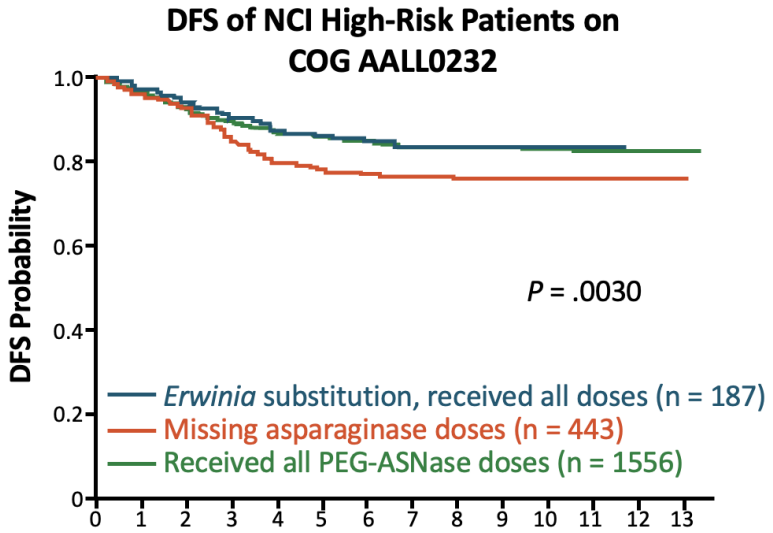
Stock et al. *Leuk Lymphoma* 2011;52:2237-53; Grace et al. *J Thrombosis Thrombolysis* 2018;45:306-14; Aldoss and Douer. *Blood.* 2020;135:987-95; Valtis…Luskin et al. *Blood Adv* 2022;6:72-81

Why Bother? More Asparaginase → Better Outcomes

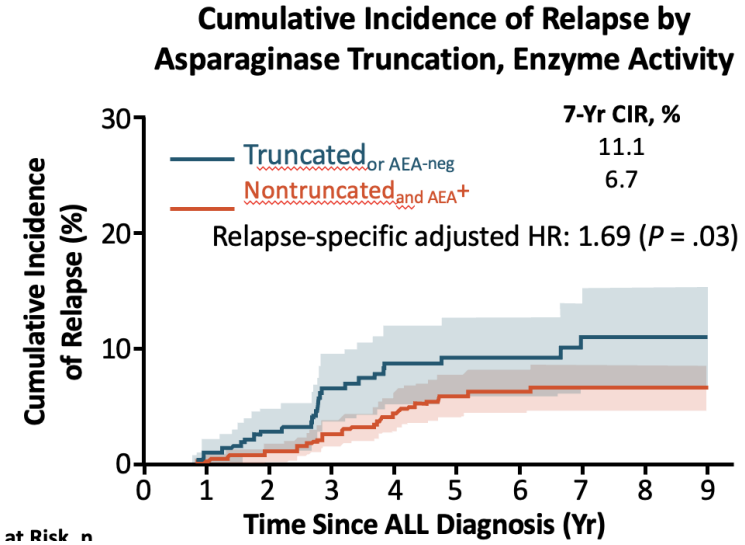
In DFCI 91-01, patients who tolerated <26 wk of planned 30 wk of ASNase therapy had inferior outcome[1]



DFCI



COG



NOPHO

Silverman et al. *Blood* 2001;97:1211-18; Gupta et al. *J Clin Oncol* 2020;38:1897-1905; Gottaschalk et al. *Blood* 2021;137:2373-82

as required per Section 6.2.

Course I is to begin ≤ 5 days of registration (Step 1).

COURSE I: REMISSION INDUCTION THERAPY (see Section 7.2)

	Allopurinol until peripheral blasts and extramedullary disease are reduced →			
	IT Ara-C			
	Dex Days 1 -			
	VCR			
	DNR			
Day	1	2	3	
Allopurinol				
IT-Ara-C				

COURSE II: REMISSION CONSOLIDATION (see Section 7.4)

Begin Course II within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. If counts not recovered within 4 weeks, then contact the study chairs. Therapy should be interrupted for patients who are febrile, neutropenic and proven infected, and resumed at the same point when the signs of infection have abated. Otherwise, therapy should not be interrupted for myelosuppression alone except on Day 29. **Hold Day 29 chemotherapy until ANC**

and submit specimens as re

	CTX			
	Ara-C Days 1 - 4			
	6-MP on Days 1-14			
	IT MTX			
	R			
Day	1	2	3	

	IT MTX*	
	VCR	
	PEG	
Day	15	16

*Day 15 and Day 2

	CTX
	Ar
	6-MP
	R
Day	29

* HOLD

Day

CTX Cyclophospham

Ara-C Cytarabine 75 m

COURSE III: INTERIM MAINTENANCE (Capizzi Methotrexate) (see Section 7.5)

Begin Course III within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. If counts not recovered within 4 weeks, then contact the study chairs.

Therapy should be interrupted for patients with severe infections and resumed when the signs of the infection have abated. VCR and IV methotrexate

treatment day (See Section 8.4.3)

If patient has consented to A0415

	VCR					
	IV MTX					
	R					
		PEG				
	IT MTX					
Day	1	2	3	4	5	

	PEG					
Day	22	23	24	25	26	

VCR Vincristine 1.5 mg/m

COURSE IV: DELAYED INTENSITIFICATION (see Section 7.6)

A bone marrow aspirate and biopsy must be obtained prior to initiation of Course IV.

Begin Course IV within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL.

If counts not recovered within 4 weeks, ther

≥ 75,000/µL prior to starting Delayed Inte

interrupted for patients with severe infecti

Otherwise, therapy should not be interrupt

	VCR						
	Dex Days 1-7 →						
	DOX						
	R						
				PEG			
	IT MTX						
Day	1	2	3	4	5	6	7

Day	22	23	24	25	26	27	2

* Hold Day 29 chemotherapy until ANC > 750/µ

	VCR				
	PEG				
Day	43	44	45	46	47

Repeat Maintenance Therapy courses (12 week courses; 84 day cycles) until total duration of therapy is 2 years from start of Interim Maintenance Therapy for female patients, or 3 years for male patients (see Section 7.7). Only mercaptopurine and methotrexate will be interrupted for myelosuppression.

	VCR																			
	Dex Days 1 - 5 →																			
	6-MP on Days 1-84 →																			
	IT MTX							PO MTX							PO MTX					
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

							VCR														
							Dex Days 29 – 33 →														
	6-MP on Days 1-84 →																				
							IT MTX*														
	PO MTX						PO MTX†								PO MTX						
Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42

* IT MTX is given on Day 29 of the first 4 courses of maintenance therapy.

† PO MTX is held on Day 29 of the first 4 courses of maintenance therapy.

															VCR						
															Dex Days 57-61 →						
	6-MP on Days 1-84 →																				
	PO MTX							PO MTX							PO MTX						
Day	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63

	6-MP on Days 1-84 →																				
	PO MTX							PO MTX							PO MTX						
Day	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84

VCR Vincristine 1.5 mg/m² (maximum dose 2 mg) IV on Days 1, 29, and 57. Voriconazole and posaconazole are contraindicated with vincristine.

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	

Philadelphia Chromosome **Negative** Acute Lymphoblastic Leukemia

New:
Pediatric Regimens for Adolescent and Young Adults (AYAs)

Dana-Farber Cancer Institute

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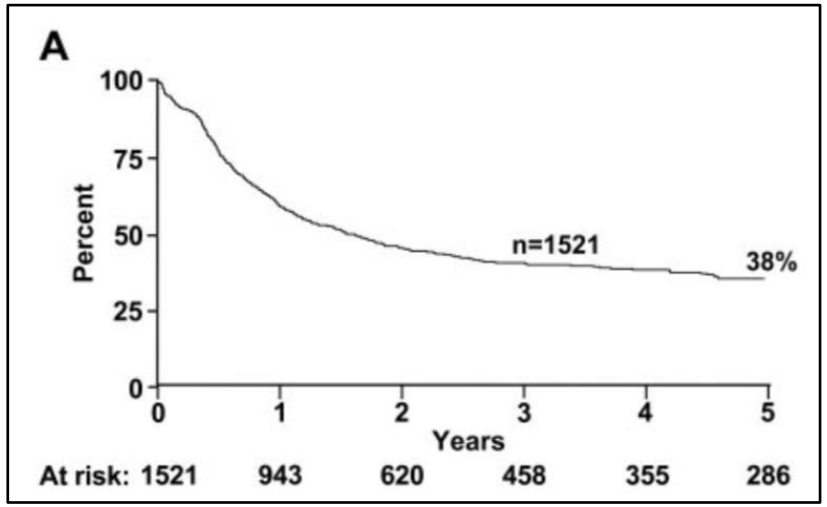
Approach to Ph-Neg ALL in Adults: Chemotherapy

- Regimens based on multiple cycles of intensive multi-agent chemotherapy.
  - Many ”standard” regimens.
- Common in the US: ECOG 2993[1], Hyper-CVAD[2] , CALGB 9111(“Larson”).[3]
- Similar Response Rates Across Trials:
  - CR: ~90%; OS/Cure: 40%
- The recent **ECOG 1910 trial** randomized to blinatumomab consolidation; results awaited.



ECOG 2993

[1]Rowe et al. *Blood* 2005;106:3760-67; [2]Kantarjian et al. *J Clin Oncol* 2000;18:547-61; [2]Kantarjian et al. *Cancer* 2004;101:2788-801;
[3]Larson et al. *Blood* 1998;92:1556-64; Wetzler et al. *Blood* 2007;109:4164-67

Older Adults: Poor Outcomes With Conventional Chemotherapy

	Age	CR (%)	Early Death (%)	OS (%)
Adult trials, older adult cohorts (dose modifications employed)				
CALGB 9111	≥60	77	17	17 (3 yr)
ECOG 2993 / UKALL XII	55-65	73	18	21 (5 yr)
Hyper CVAD	≥60	84	10	20 (5 yr)
Older adult trials				
Dana-Farber/Harvard	>50	67	13	52 (2 yr)
GMALL	≥55	76	14	23 (5 yr)
PETHEMA ALLOLD07	>55	74	13	12.4 mo med

Numbers reflect treated patients, *eligible for and interested in clinical trial.*

Resistant Disease

- Lower CR rate/refractory
- Relapse

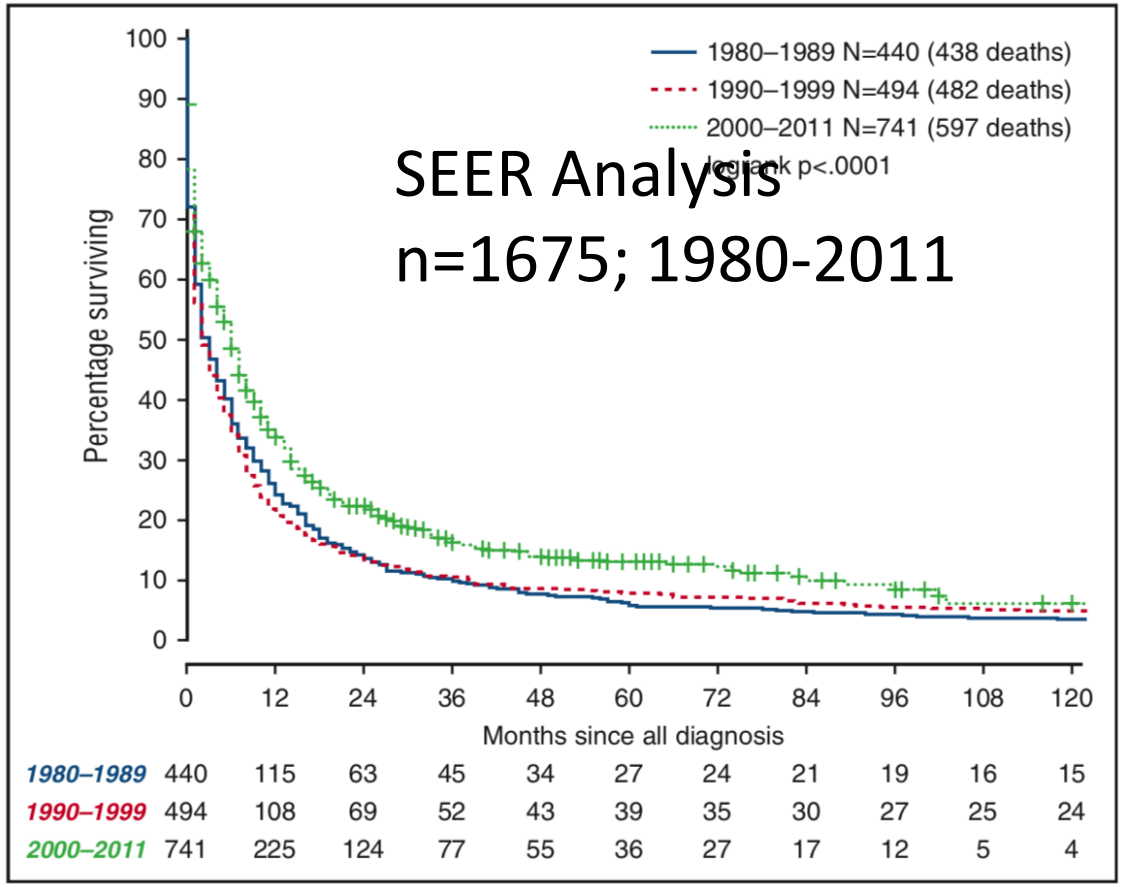
Toxicity

- High early death (10-20%)
- Death in CR

Many not even treated: US Medicare analysis (2019) – only 51.1% ≥ 66 years treated within 90 days. Most (78.3%) untreated were 75+ years.

Larson et al. *Blood* 1998;92:1556-64; Sive et al. *Br J Haematol* 2012;157:463-71; O'Brien et al. *Cancer* 2008;113:2097-101; Fathi et al. *Cancer* 2016;122:2379-88; Gokbuget et al. *Blood* 2012;120:Abstract 1493; Ribera et al. *Leuk Res* 2016;41:12-20; Kim et al. *Leuk Lymphoma* 2019;60:1462-68

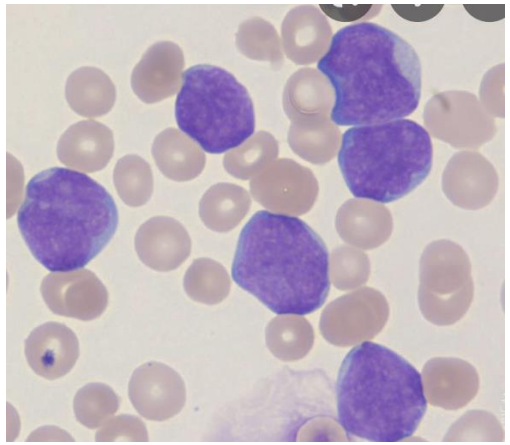
Extremely Poor Outcomes in Older Adults with ALL. Little Improvement for 3 decades.



Population	3-year OS (%)	Median OS (months)
Overall	13%	4
Age (years)		
60-64	24%	9
≥ 75	10%	<3
Era		
Pre-1990	10%	3
2000-2011	16%	6

Geyer et al. *Blood* 2017;129:1878-81; Dinmohamed et al. *Leukemia* 2016;30:310-17; Toft et al. *Br J Haematol* 2012;157:97-104

ALL in Older Adults: Improving Outcomes Conventional Chemotherapy → Novel Agents



Disease (Chemotherapy Resistance)

↓CR rate ↑Relapse

Need: More effective therapies

Patient (Chemotherapy Tolerability)

↑Early mortality, ↑Death in CR

Need: Less toxic therapies.

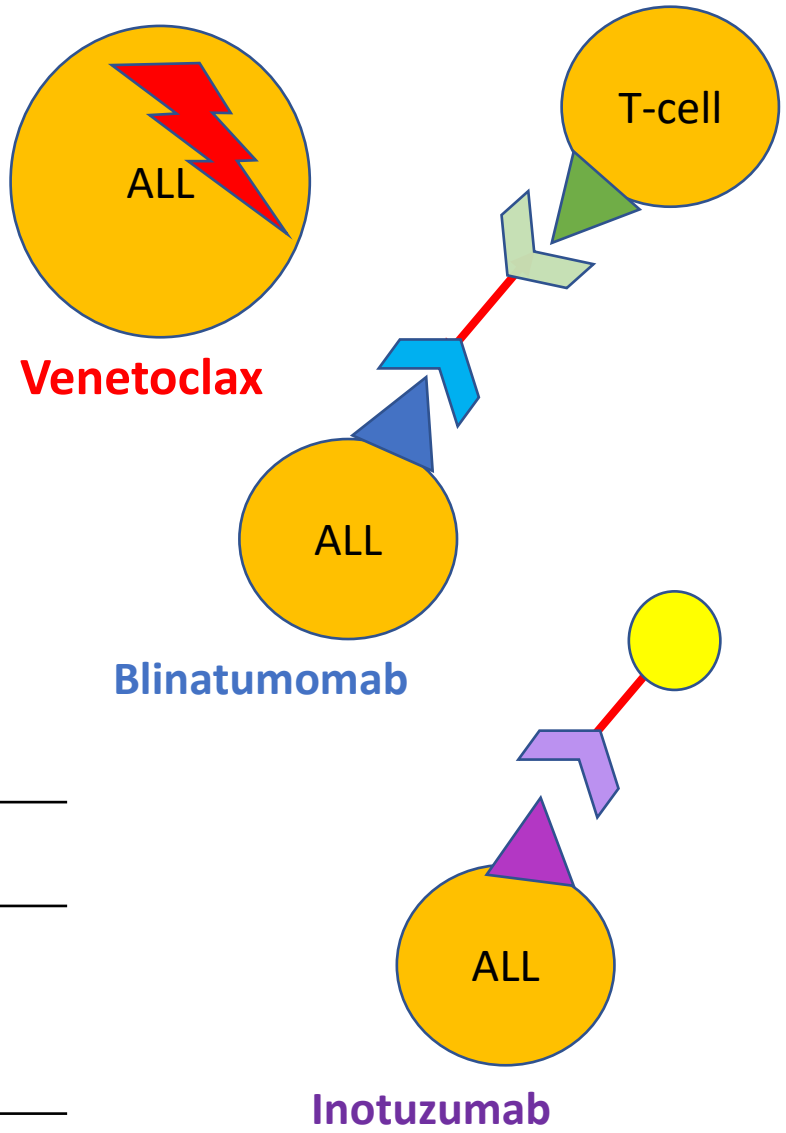
Social, Logistical (Access)

↑No or minimal treatment

Need: Therapies that are not too complicated.

Philadelphia-chromosome-negative (Ph-) ALL Incorporating Novel Agents

- Until recently, only option available for Ph- ALL was conventional chemotherapy.
- Blinatumomab (2014) and inotuzumab ozogamicin (2017) approved for relapsed and refractory B-ALL.
- Other novel agents being investigated for ALL, including venetoclax.



Goals	**Approach**
Better efficacy	Add novel agents
Less toxicity	Reduce/omit conventional chemotherapy

Inotuzumab + mini-hyper-CVD

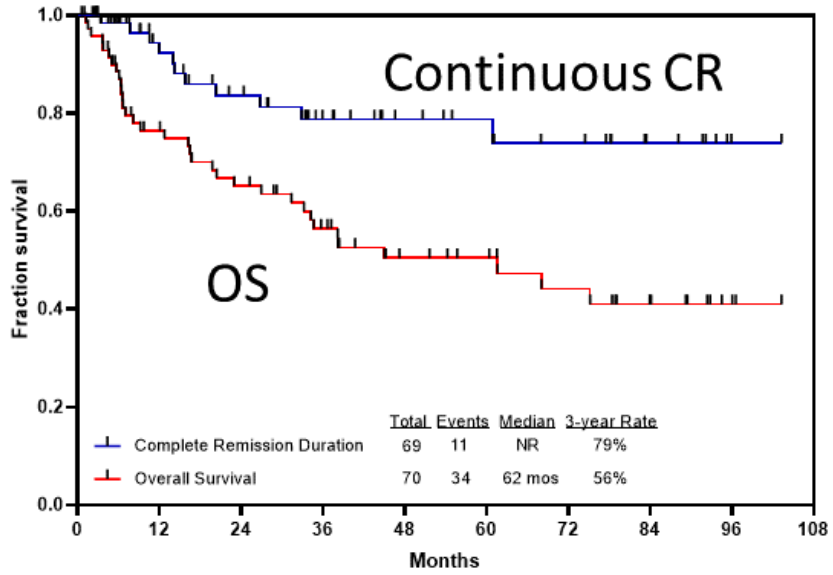
Phase 2, single center, untreated patients ≥ 60 years

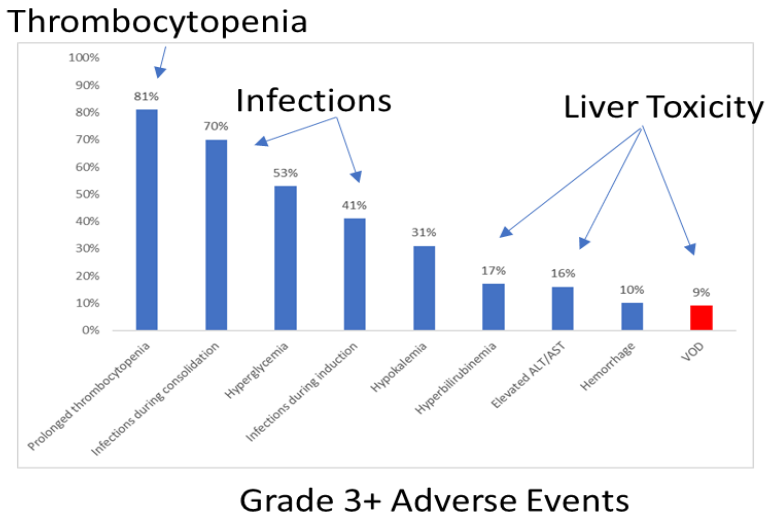
Outcomes updated ASH 2021 (n=79, 38% ≥ 70 years)

- Early mortality: 0%
- MRD-negative CR: 94%; 3-yr OS: 55%
- Death in CR: 34% (29/79); most ≥ 70 yrs (sepsis, VOD, MDS/AML).

Modifications:

- Inotuzumab dose reduced/fractionated
- Chemotherapy cycles decreased, omitted ≥ 70 years
- Blinatumomab added

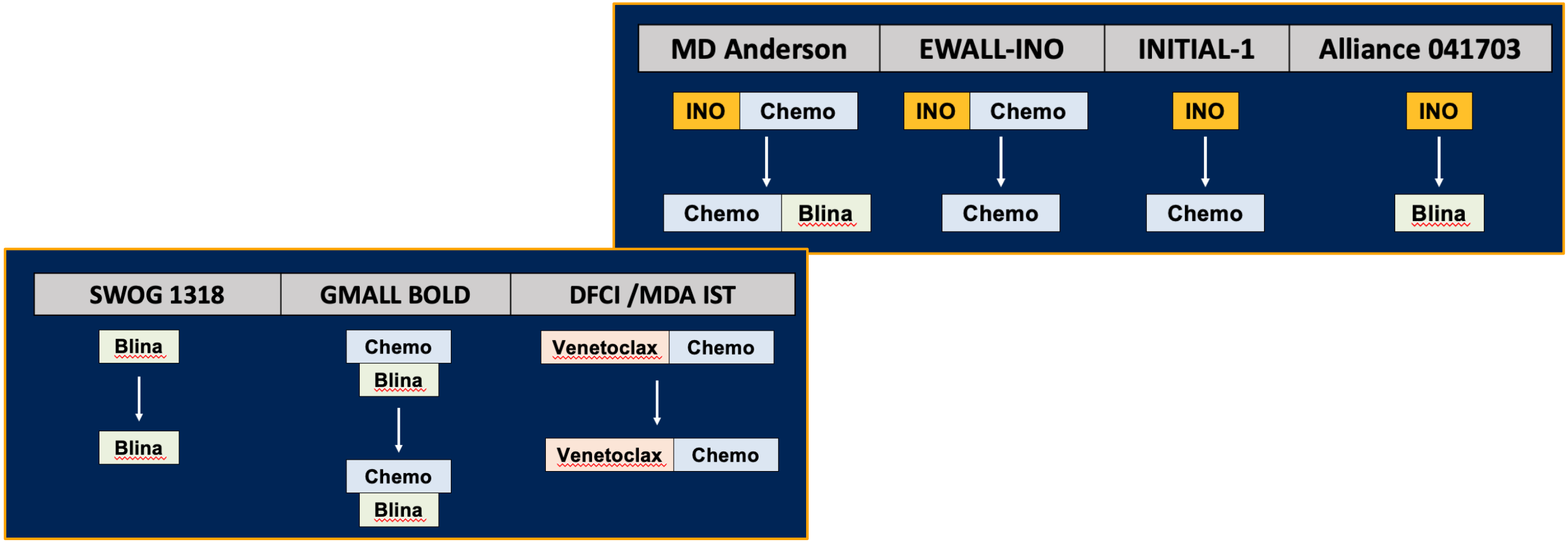




Grade 3+ Adverse Events

Kantarjian et al. *Lancet Oncol* 2018; 24-48; Short et al. *Blood* 2021; Abstract 3400 (ASH 2021)

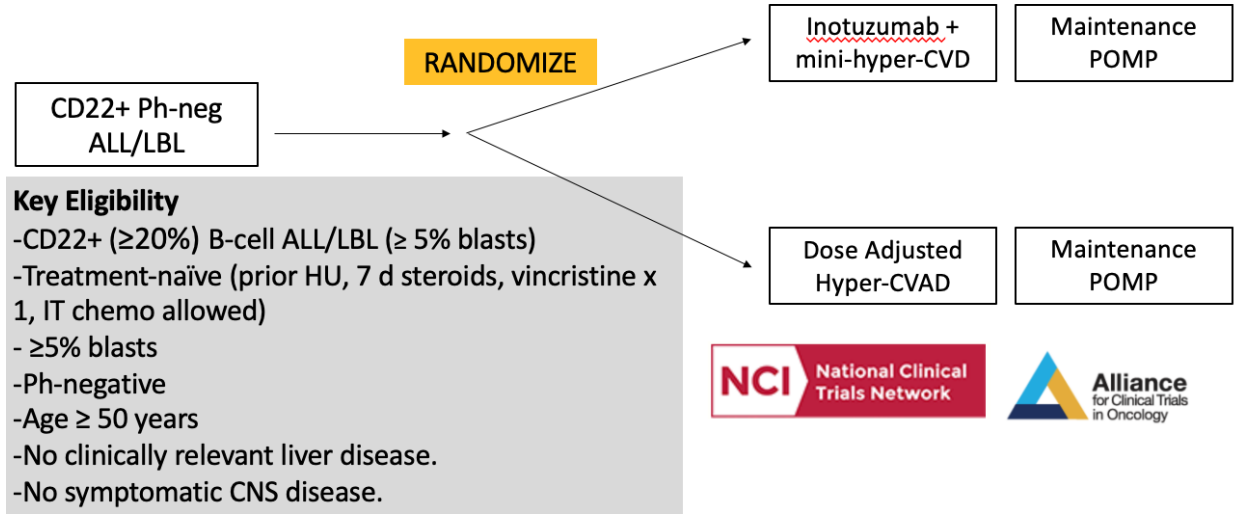
Philadelphia-chromosome-negative (Ph-) ALL Incorporating Novel Agents



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* 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

Philadelphia-chromosome-negative (Ph-) ALL Incorporating Novel Agents **SUMMARY**

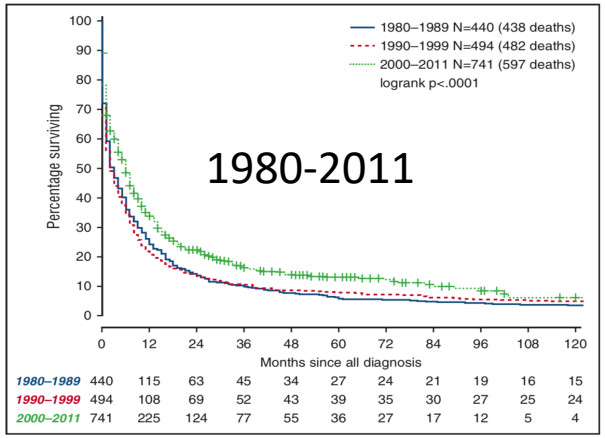
- High CR rates (80-90%).
- Most MRD negative (80-90%).
- Low induction mortality - <5%.
- Late toxicity still a problem.
- *Long-term outcomes awaited!*
- NCTN plans randomized comparison to establish new standard.

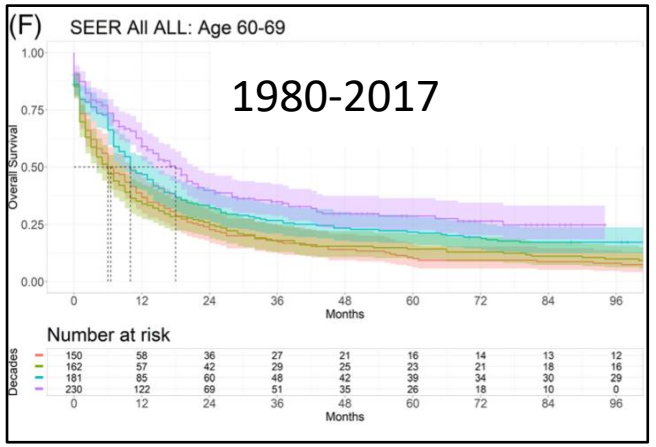


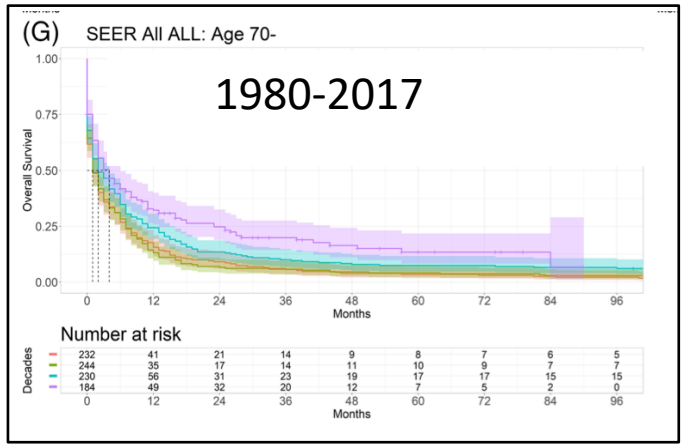
Alliance 042001 NCT05303792

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

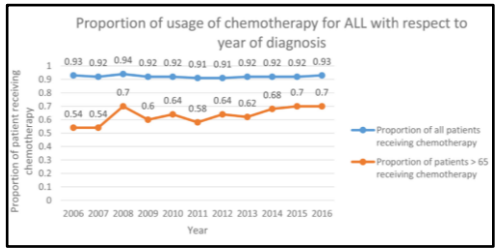
ALL in Older Adults: Starting to Improve?







- Little progress over time: US SEER (n=1675), >60 yrs, 3-yr OS 10% → 16% (1980-2011)
- **Now, glimmers of hope?**
- More patients being treated →



- Updated SEER analysis shows improvement in the 2010s
  - Age 60-69 (n=723): **1990s** Median OS 6 mos → **2010s** 18 mos (5-yr OS: 14→29%)
  - Age 70+ (n=890): **1990s** Median OS 1 mo → **2010s** 4 mos (5-yr OS: 4→13%)

Geyer et al. *Blood* 2017;129:1878-8 1; Sasaki et al. *Am J Hematol* 2021;96:650-58; Joshi et al. *Clin Lymphoma Myeloma Leuk* 2022; S2152-2650(22)00188-4.

Philadelphia Chromosome **Negative** Acute Lymphoblastic Leukemia

New:

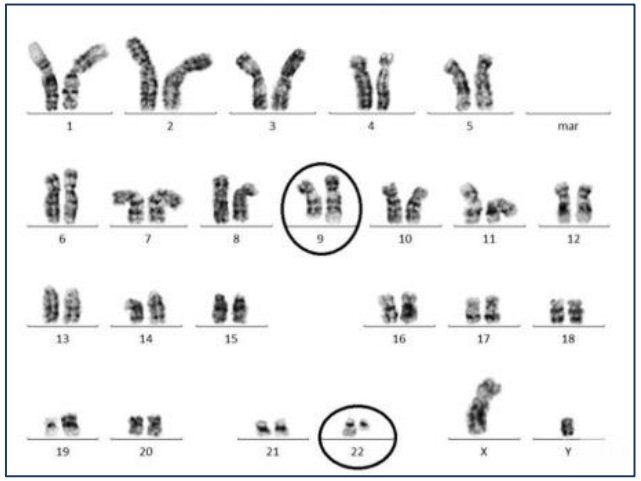
Novel Agent Being Studied In Initial Therapy To Improve Outcomes, Especially Important for Older Adults

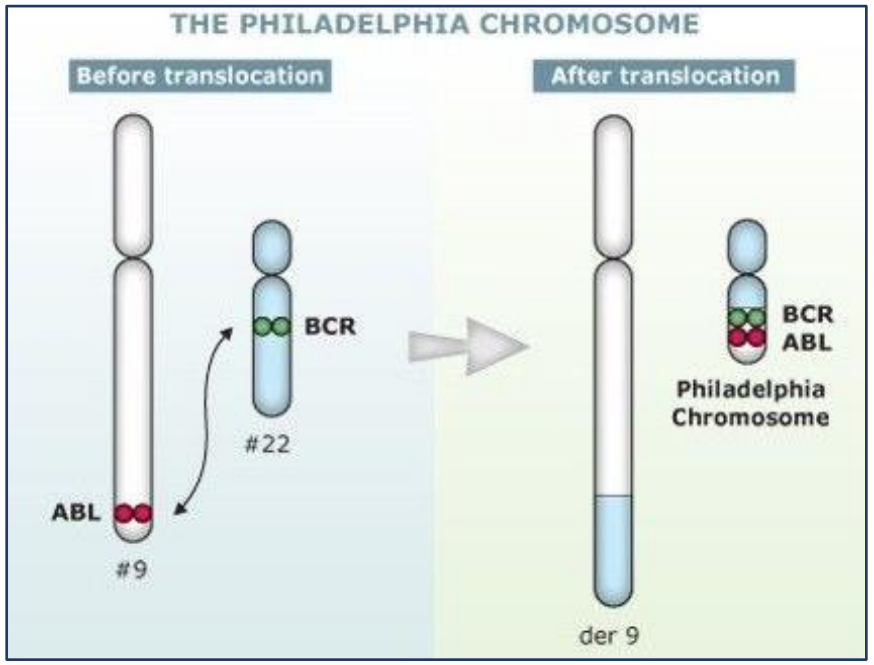
Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Philadelphia Chromosome **Positive** Acute Lymphoblastic Leukemia

Ph+ = t(9;22) = *BCR-ABL* fusion.
ABL kinase is a major driver of disease.





Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Philadelphia Chromosome Positive (Ph+) ALL

- Present in ~1/3% of ALL cases.
- Prevalence increases with age (>50% over age 50 years).
- Historically adverse prognosis.

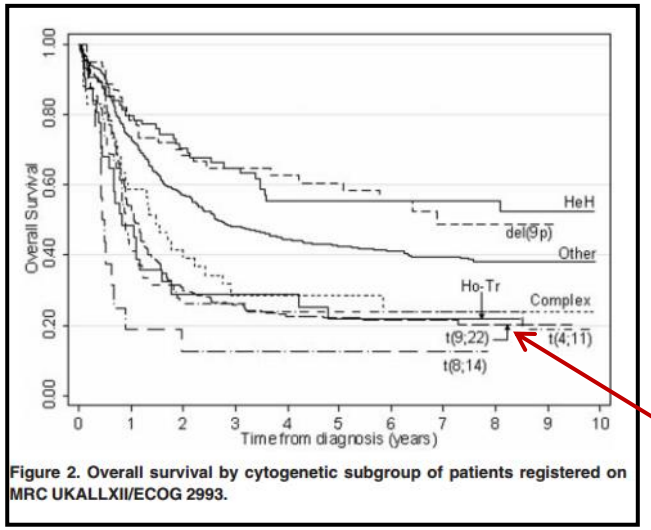
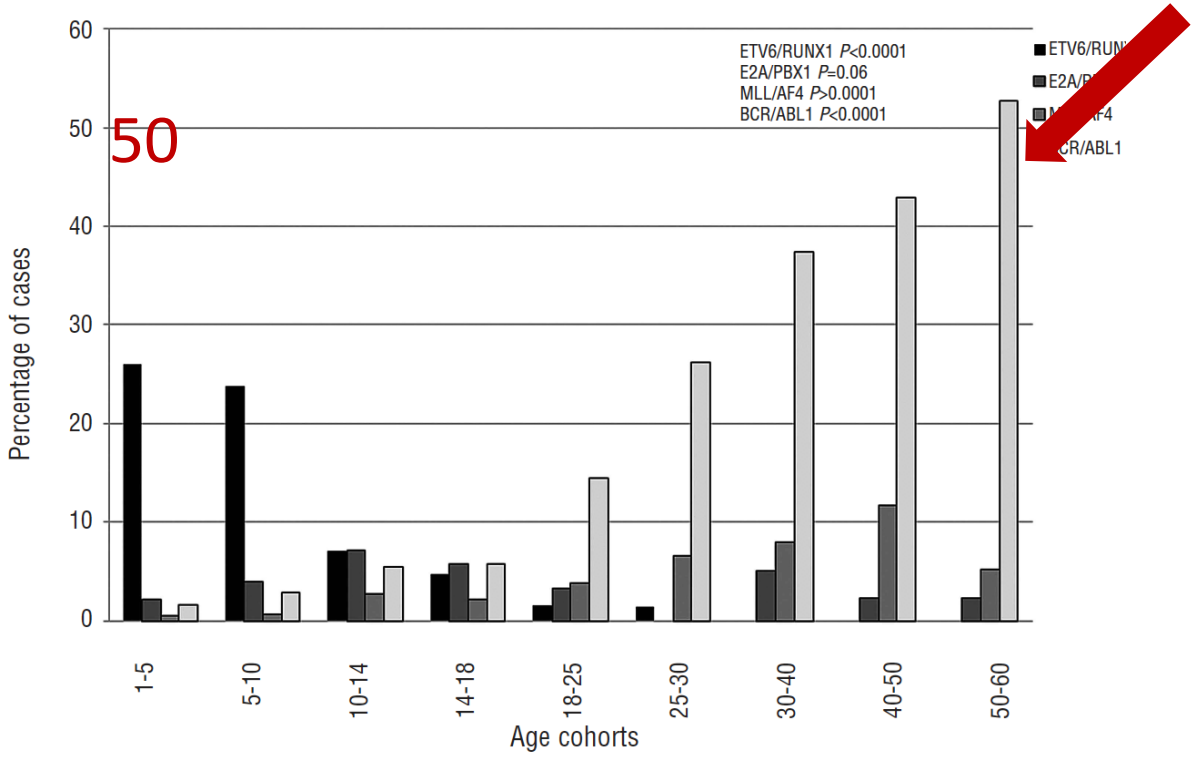


Figure 2. Overall survival by cytogenetic subgroup of patients registered on MRC UKALLXII/ECOG 2993.



50-60 years

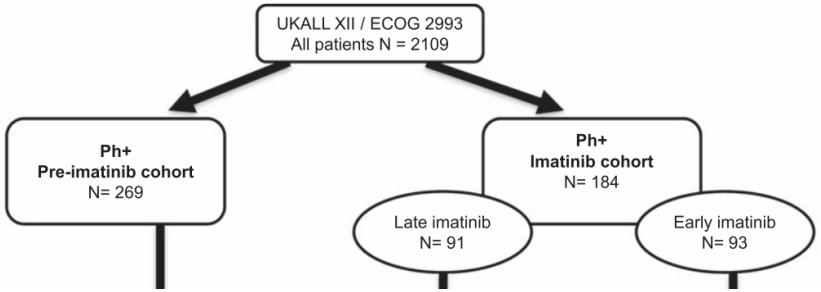
t(9;22)

Chiaretti et al. *Haematologica* 2013;98:1702-10; Burmeister et al. *Blood* 2008;112:918-9; Ribera et al. *Br J Haematol* 2012;159:485-88; Moorman et al. *Blood* 2007;109:3189-97

TKIs (Imatinib) Improve Outcome in Chemotherapy Treated Patients

- Imatinib improves outcome when combined with chemotherapy.
- Higher CR rates, higher OS, more patients → BMT.
- Better outcomes if introduced earlier in treatment.

ECOG 2993



Ph+ (20%): 25%

Ph– (80%): 41%

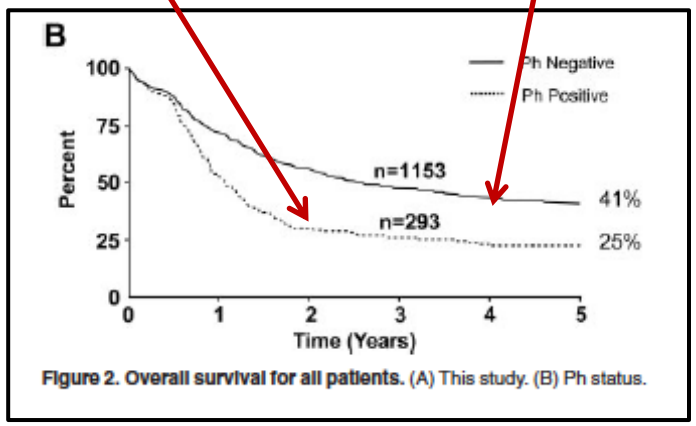
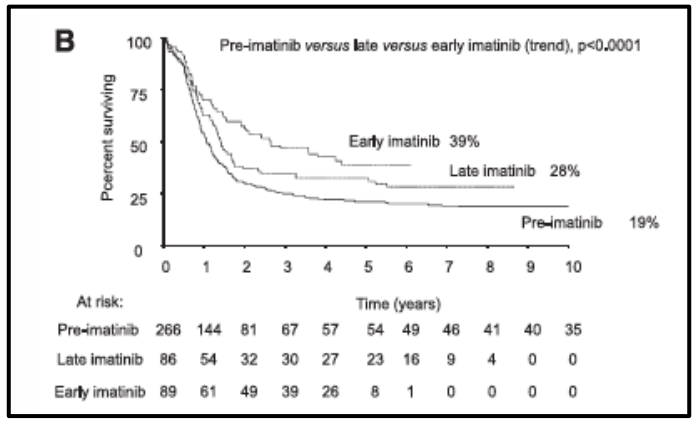


Figure 2. Overall survival for all patients. (A) This study. (B) Ph status.



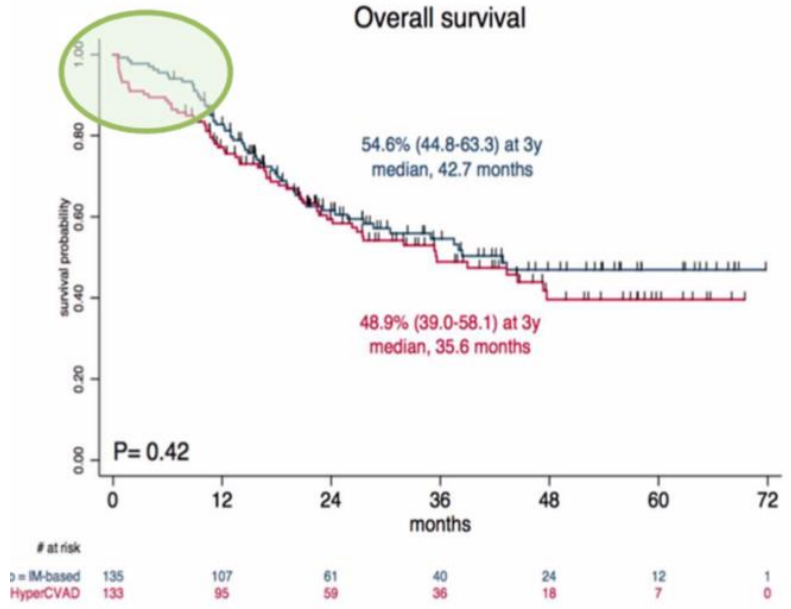
Key Points

- Imatinib improves outcomes for adults with Ph+ ALL at least in part by facilitating allogeneic stem cell transplant.

Fielding et al. *Blood* 2014;123:843-50

Tyrosine Kinase Inhibitors → CR with Minimal Tox

- **GRAAPH-2005** → IM + VCR/Dex: ↑CR rate and ↓mortality compared to IM + hyperCVAD.
- **GIMEMA** → Successful "chemotherapy-free" induction (imatinib LAL 0201-B; dasatinib LAL 1205, ponatinib LAL 1811).
  - High CR rates (>90%).
  - 2G/3G TKIs - Deeper and more durable.
  - Minimal toxicity.



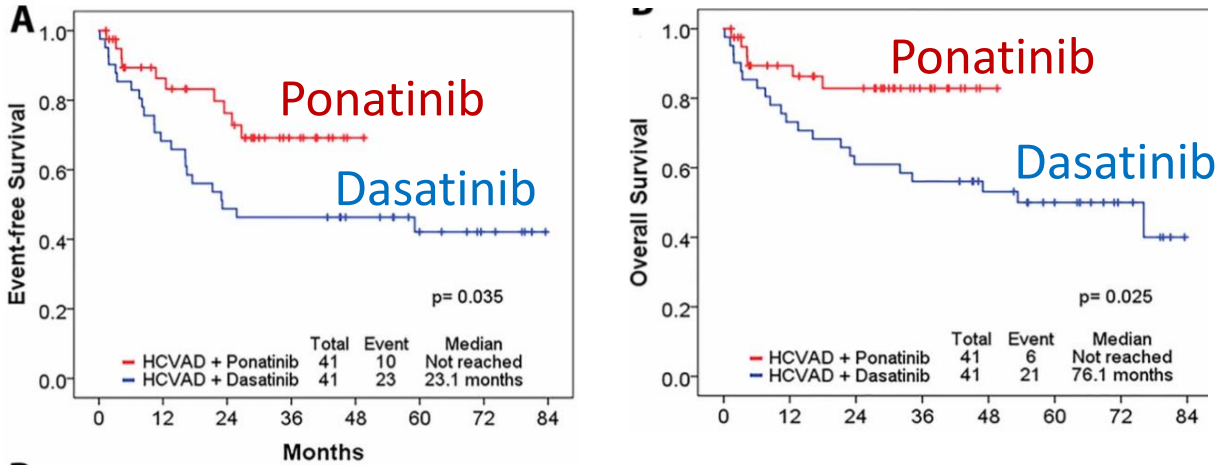
TKIs allow reduction or omission of conventional chemotherapy during induction in Ph+ ALL.

Chalandon et al. *Blood* 2015;125:3711-9; Vignetti et al. *Blood* 2007;109:3676-8; Foa et al. *Blood* 2011;118:6521-8; Martinelli et al. *Blood Adv* 2022;6:17-42-53; Wieduwilt et al. *Blood Adv* 2021;23:4691-700; Sugiura et al. *Blood Adv* 2022;6:624-36; Rousselot et al. *Blood* 2016;128:774-82

Ph+ ALL: Which TKI is Best?

- In combination with chemotherapy, retrospective comparison (hyper-CVAD context) suggest better outcomes with 2G and 3G TKIs (deeper remissions, improved survival).
- Ponatinib is potent and active again T315I, a common mechanism of resistance to earlier generation TKIs, but associated with cardiovascular toxicity.

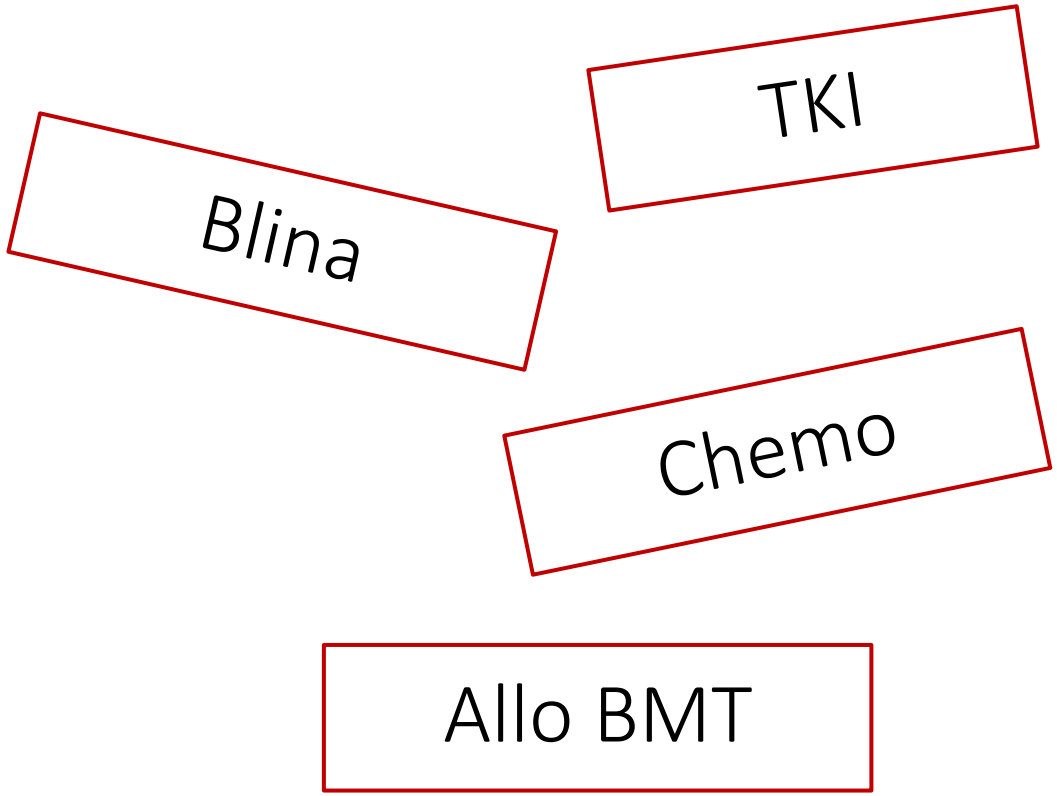
MD Anderson Propensity Score Retrospective Analysis



Sasaki et al. *Cancer* 2016;122:3650-6; Jabbour et al. *Clin Lymphoma Myeloma Leukemia* 2018;18:257-65

Ph+ ALL: Best Post-Remission Approach Not Defined, Approach Individualized

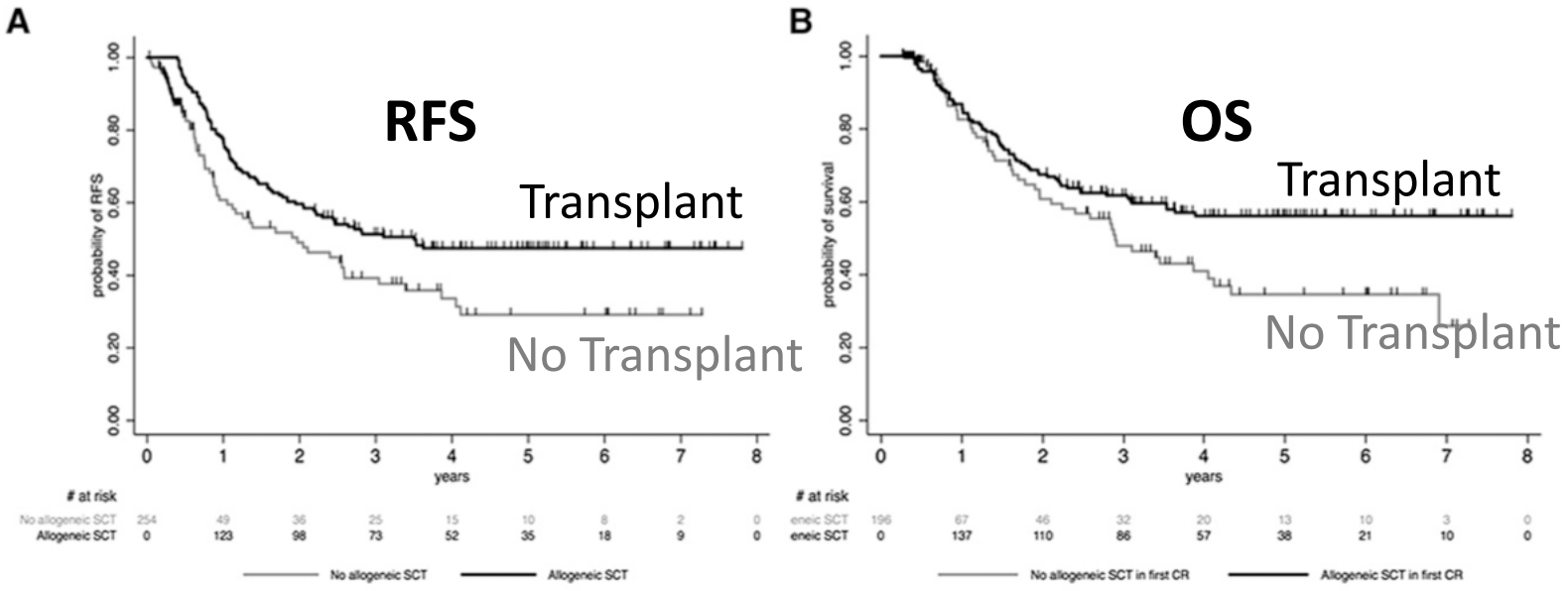
- **<u>TKI is not curative</u>**.
- **Options (and/or):**
  - **Allogeneic hematopoietic stem cell transplant (HSCT)**
  - **Chemotherapy:** Age-adjusted
  - **?Novel agents**: Blinatumomab
- One size fits all vs age/co-morbidity tailored and risk adapted approach.
  - Here is where roads diverge!



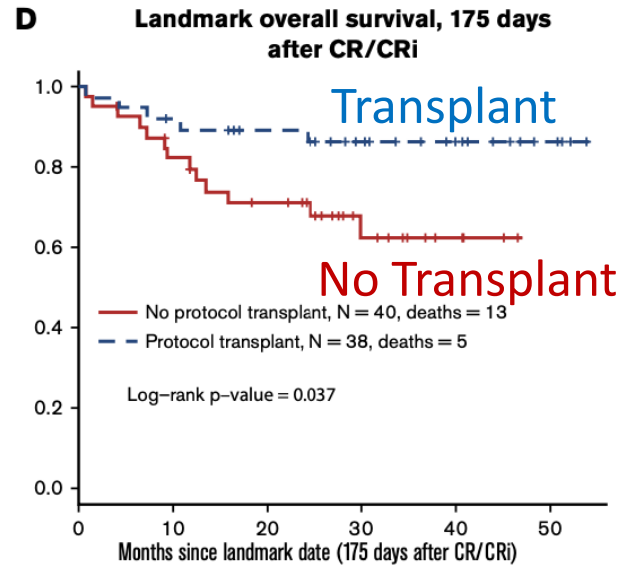
Martinelli et al. *Blood Adv* 2022;6:17-42-5; Luskin et al. *Blood* 2021; Rousselot et al. *Blood* 2016;128:774-82;
Foa et al. *N Eng J Med* 2020;383:1613-23; Wieduwilt et al. *Blood Adv* 2021;23:4691-700; Bachanova et al. *Leukemia* 2014;28:658-65

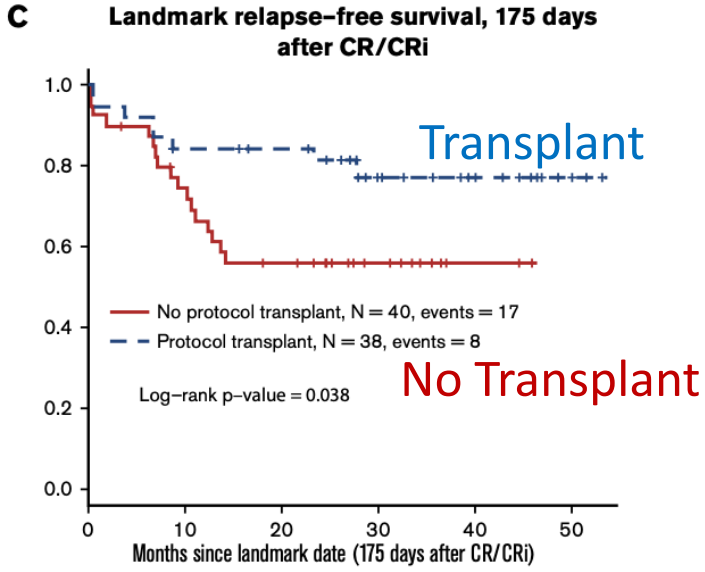
Benefit of HSCT for Ph+ ALL in CR1

GRAAPH-2005
imatinib + chemotherapy



US Intergroup
dasatinib + hyperCVAD

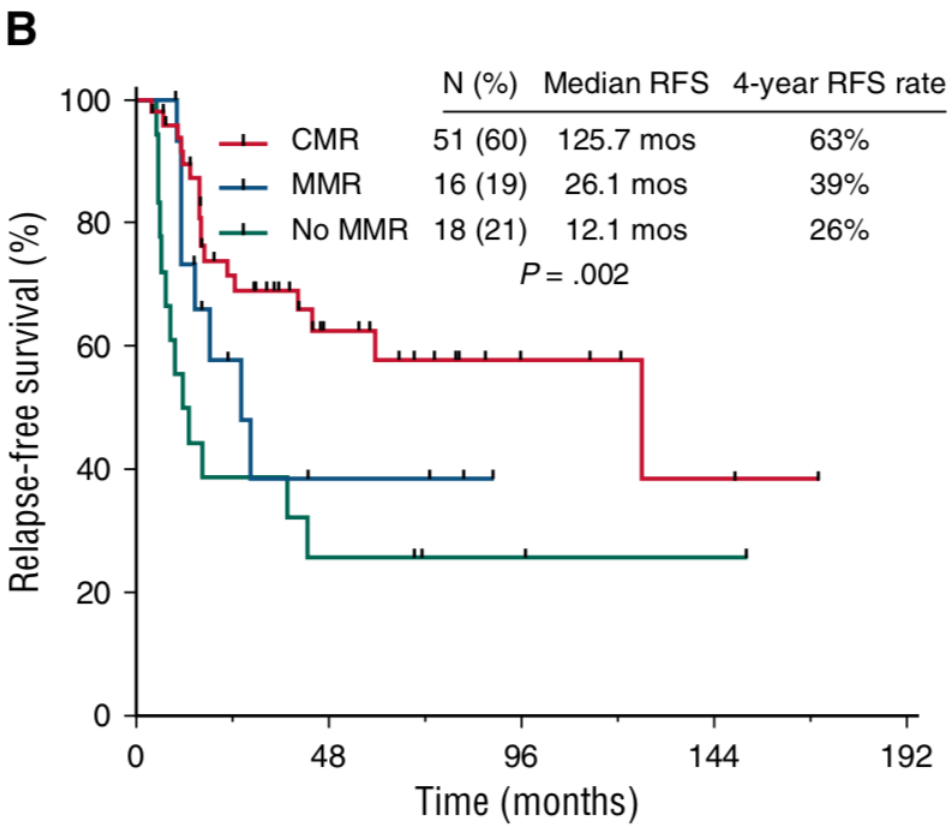




Chalandon et al. *Blood* 2015;125:3711-19; Ravandi et al. *Blood Advances* 2016;1:250-59

Ph+ ALL: Do All Patients Need HSCT for Cure?

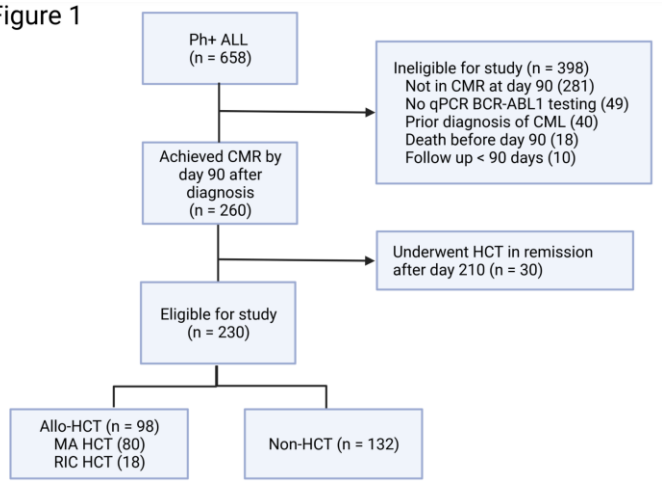
- Some patients may not benefit. But which ones?
- **Good outcomes without HSCT.**
  - Some patients treated with TKI + chemo rapidly achieve deep responses → favorable long-term outcomes without HSCT.
- **Risk of HSCT.**
  - Increased patient age, comorbidities increase toxicity.
  - Transplant advances may reduce toxicity.

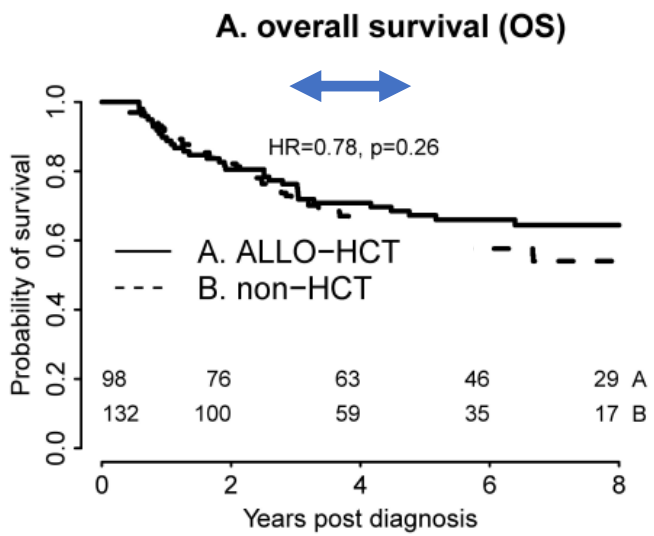


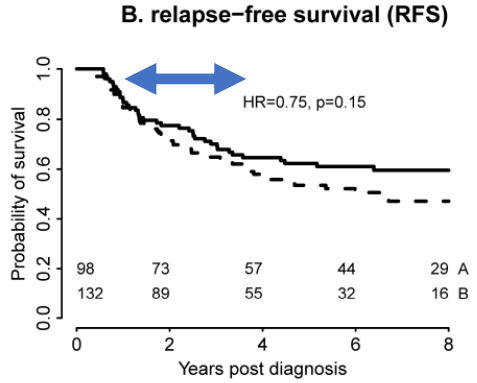
Chalandon et al. *Blood* 2015;125:3711-19; Kim et al. *Blood* 2015;126:746-756; Ravandi et al. *Blood Advances* 2016;1:250-9; Ravandi et al. *Blood* 2013;122:1214-21; Short et al. *Blood* 2016;128:504-7

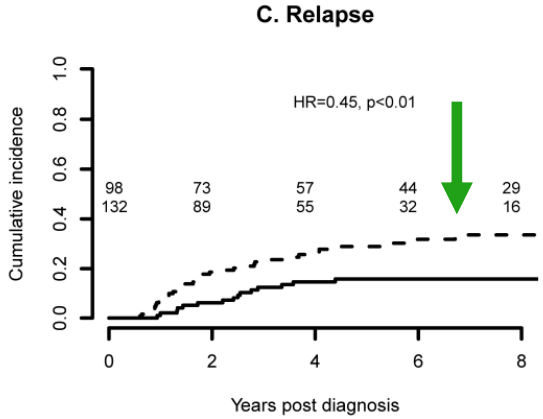
HSCT May Be Unnecessary after Optimal Response to Intensive Chemo (hyper-CVAD)

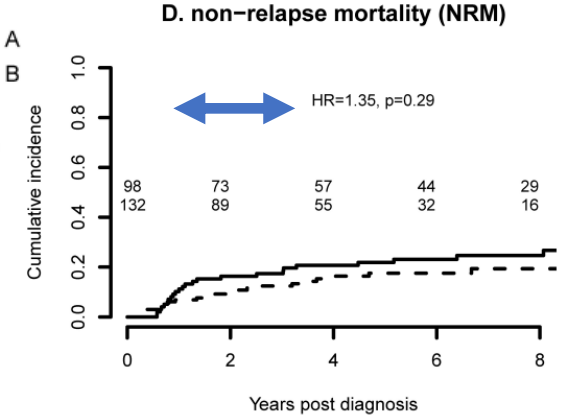
Figure 1

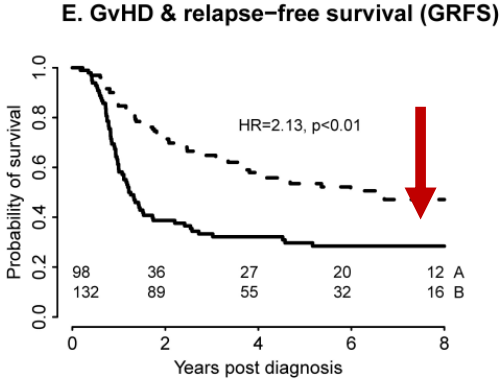








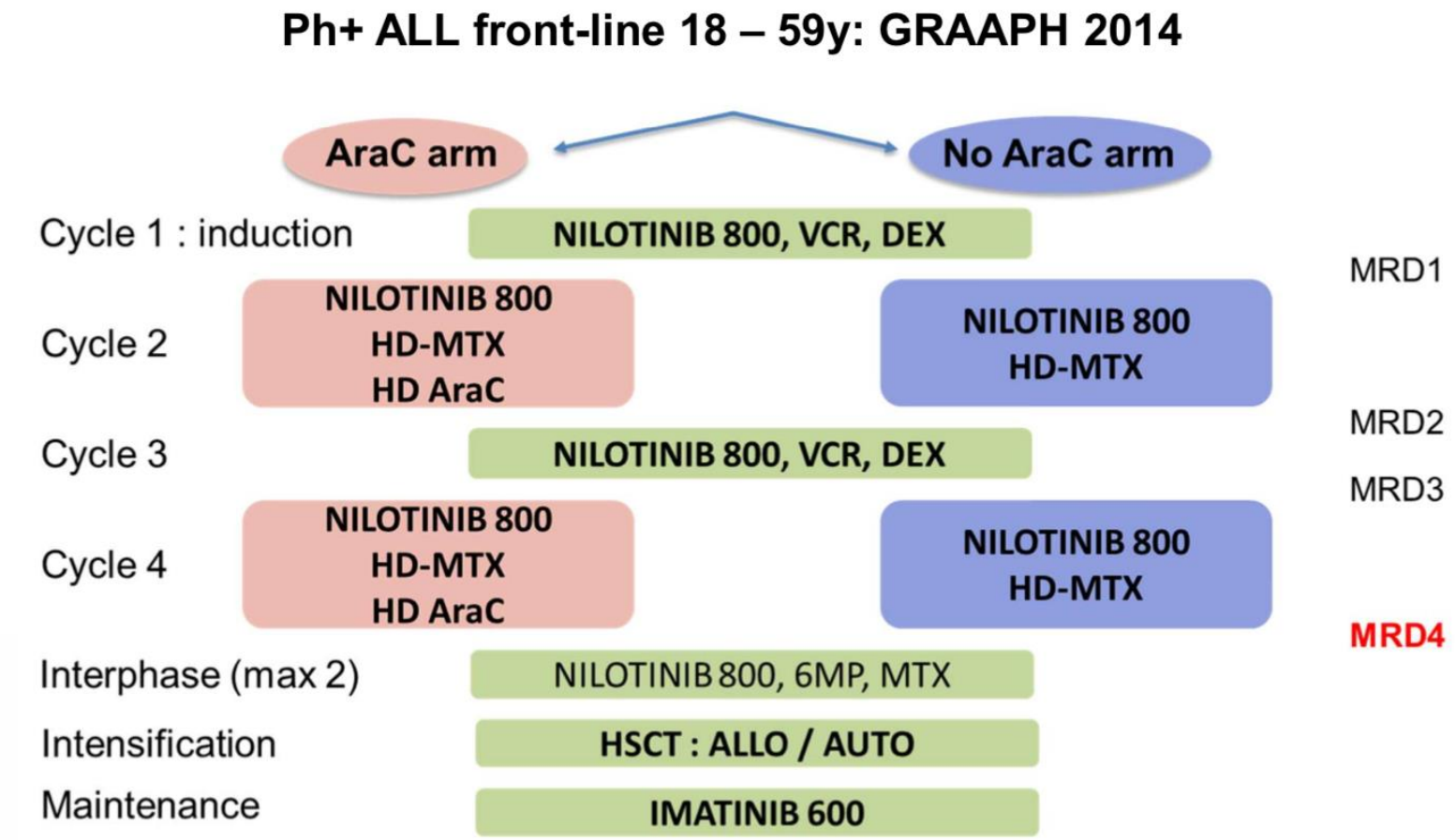




Ghobadi et al. *Blood* 2022 doi: 10.1182/blood.2022016194

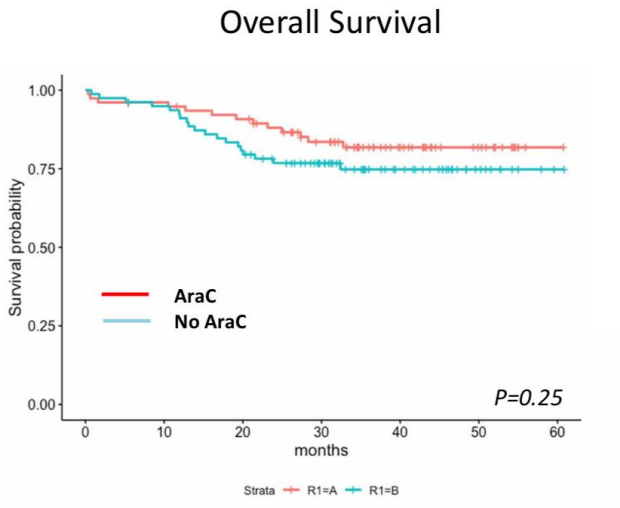
GRAAPH-2014: TKIs are Great, but Not Enough

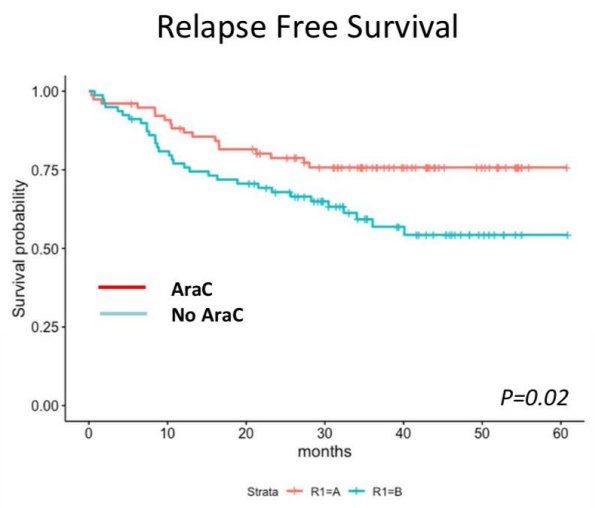
- New Ph+ ALL, ages 18-60
- **Design:** Random evaluation of no HiDAC consolidation.
- **Primary endpoint:** MMolR BCR-ABL1 ≤0.1% after 4th treatment cycle (MRD4).
- **TKI:** Imatinib → nilotinib.
- **Chemo:** 4 cycles prior to BMT.
- **BMT:** Allo HSCT in CR1 if matched donor (MSD or MUD).
- **Maintenance:** 2-yr IM post BMT.

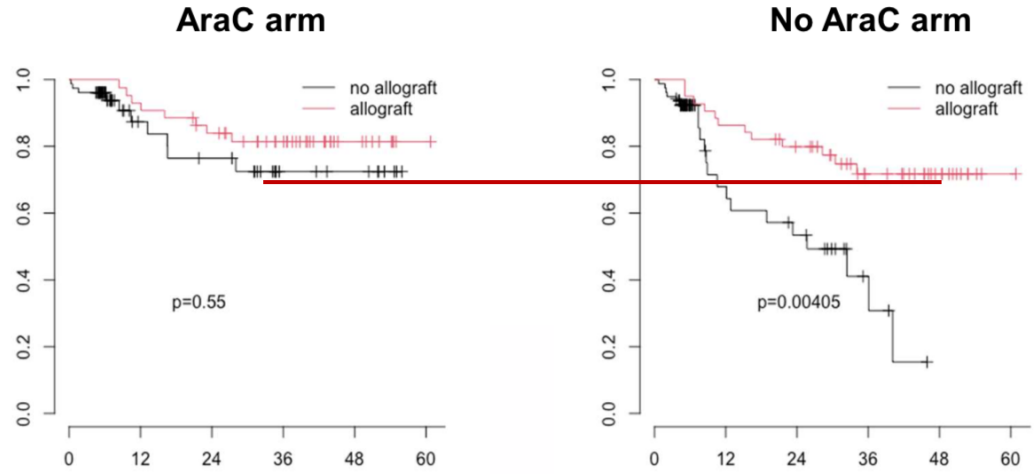


ASH 2021 Abstract 614: Rousselot et al.

GRAAPH-2014: TKIs are Great, but Not Enough





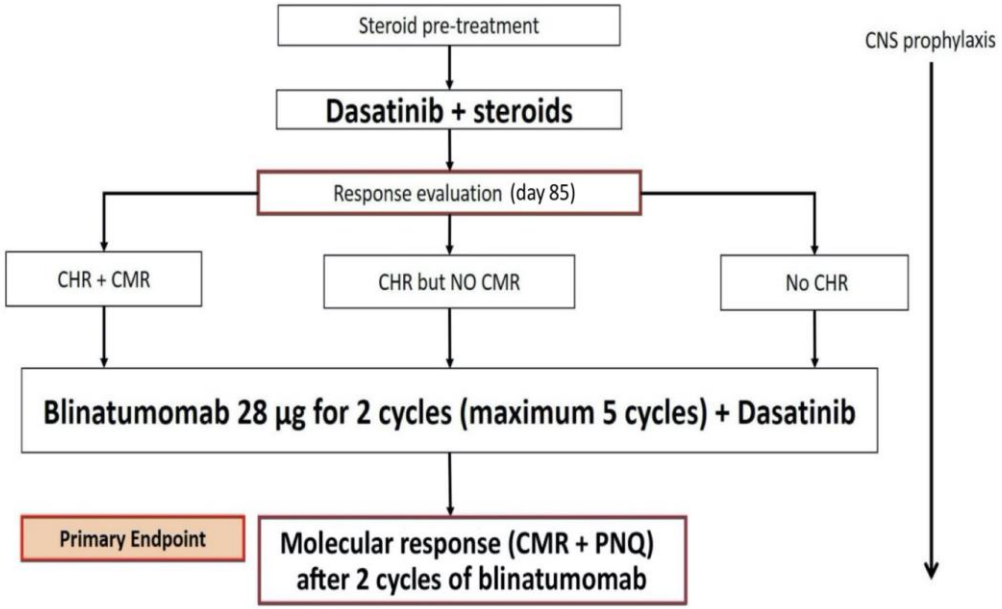


- Randomization stopped early due to excess relapse in Arm B (no HiDAC).
- Transplanted patients in Arm B (no HiDAC) had dramatically better outcomes.
- Outcomes of patients in Arm A (HiDAC) were similar regardless of alloSCT status.

GRAAPH-2014 study – Omission of HiDAC consolidation in younger patients (18-60 years) → frequent relapses in the absence of HSCT (Take Home: Need intensification with chemotherapy or HSCT, can't omit both!)

Abstract 614: Rousselot et al.

GIMEMA D-ALBA Study



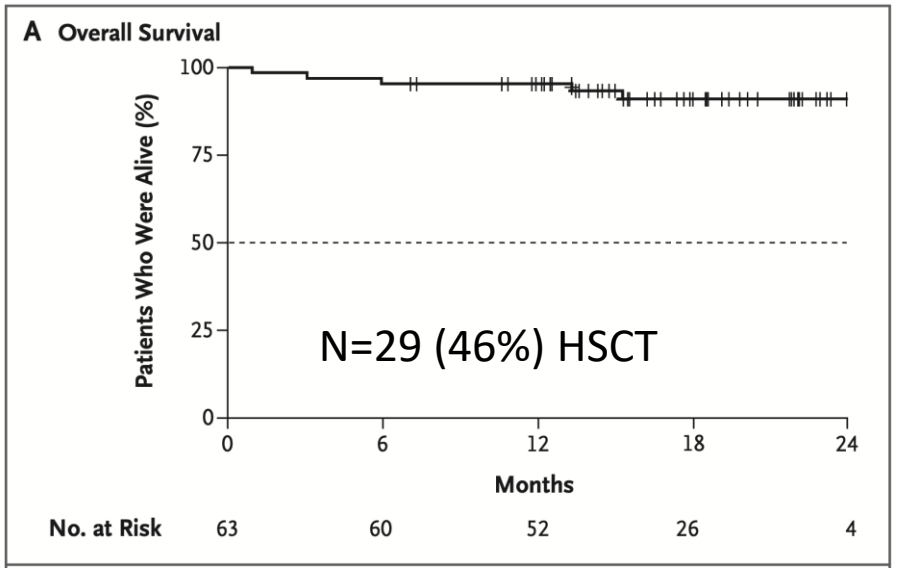
N=63, median age 54 (range 24-82) yrs

***Note*:**

Follow-up still short.

Approximately half → HSCT.

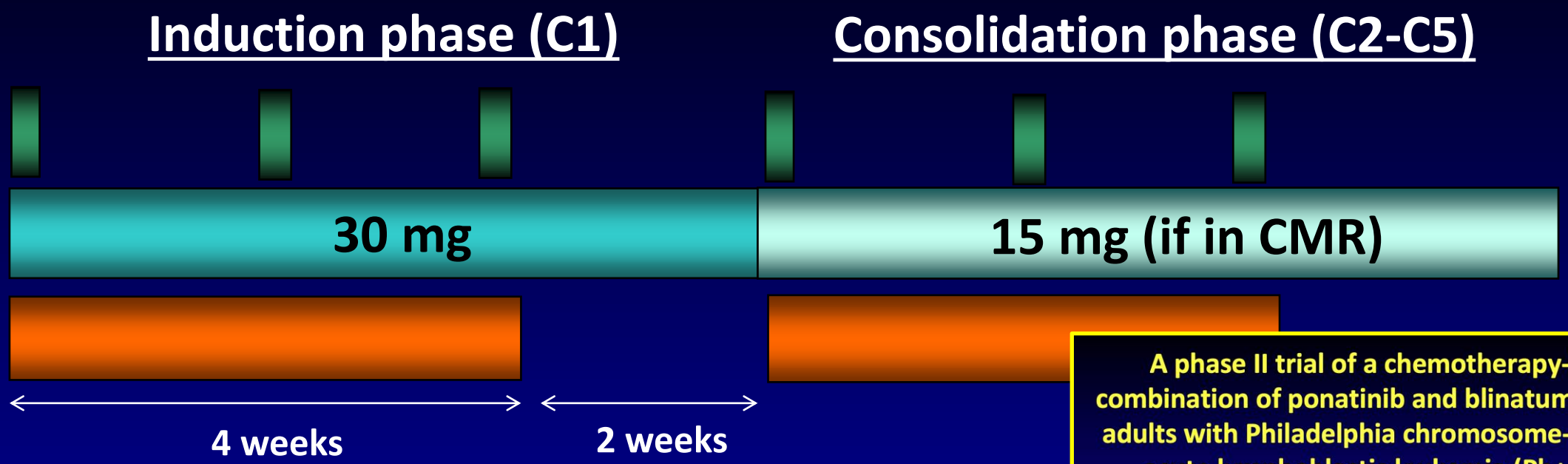
- Day 85 – 29% Molecular Response
- Blina C2 (n=55) – 60% Molecular Response
- Blina C4 – 81% Molecular Response



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

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

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



A phase II trial of a chemotherapy-free combination of ponatinib and blinatumomab in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)

Nicholas Short, Hagop Kantarjian, Marina Konopleva, Guillermo Montalban-Bravo, Farhad Ravandi, Nitin Jain, Tapan Kadia, Yesid Alvarado, Kelly Chien, Naval Daver, Walid Macaron, Koji Sasaki, Jennifer Thankachan, Ricardo Delumpa, Ejiroghene Mayor, Wuliamatu Deen, Christopher Loiselle, Monica Kwari, Rebecca Garris, Elias Jabbour

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

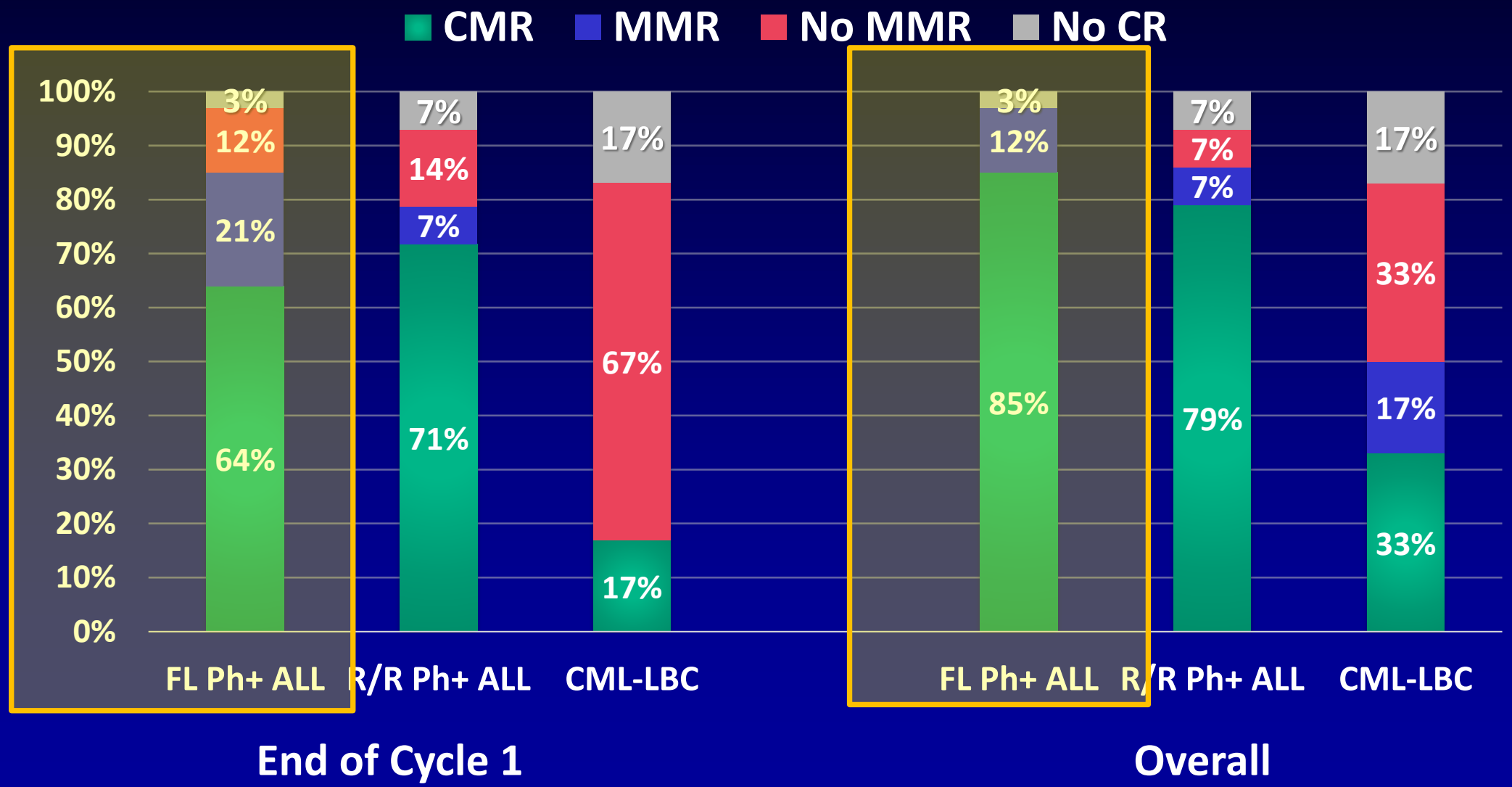
Ponatinib 30 mg

Ponatinib 15 mg

Blinatumomab

IT MTX / Ara-C x 12

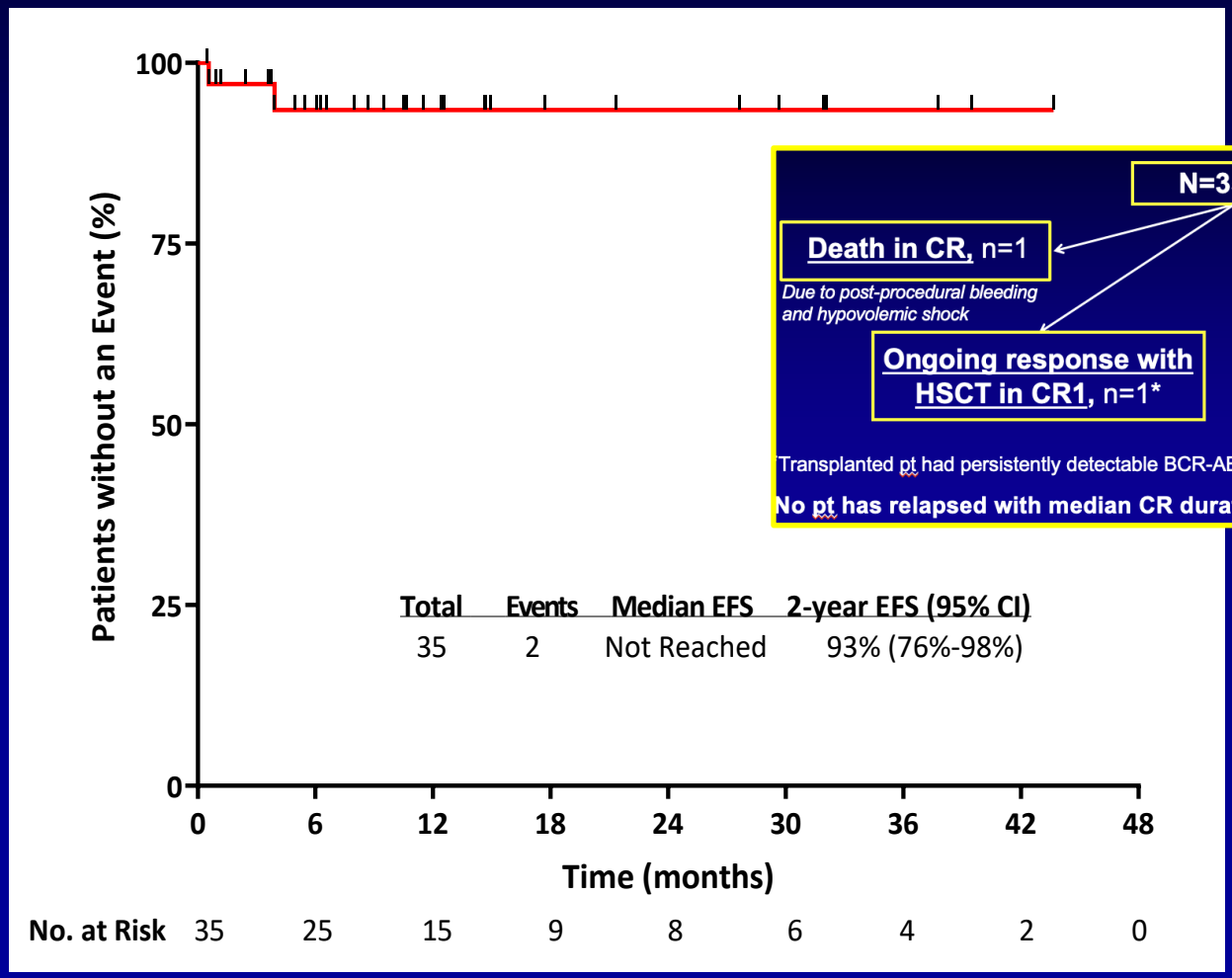
Ponatinib + Blinatumomab in Ph+ ALL: MRD Response Rates



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

Median follow-up: 11 months (range, 1-41)

Event-Free Survival



N=35 pts

Death in CR, n=1
Due to post-procedural bleeding and hypovolemic shock

Early Death, n=1
Due to intracranial hemorrhage

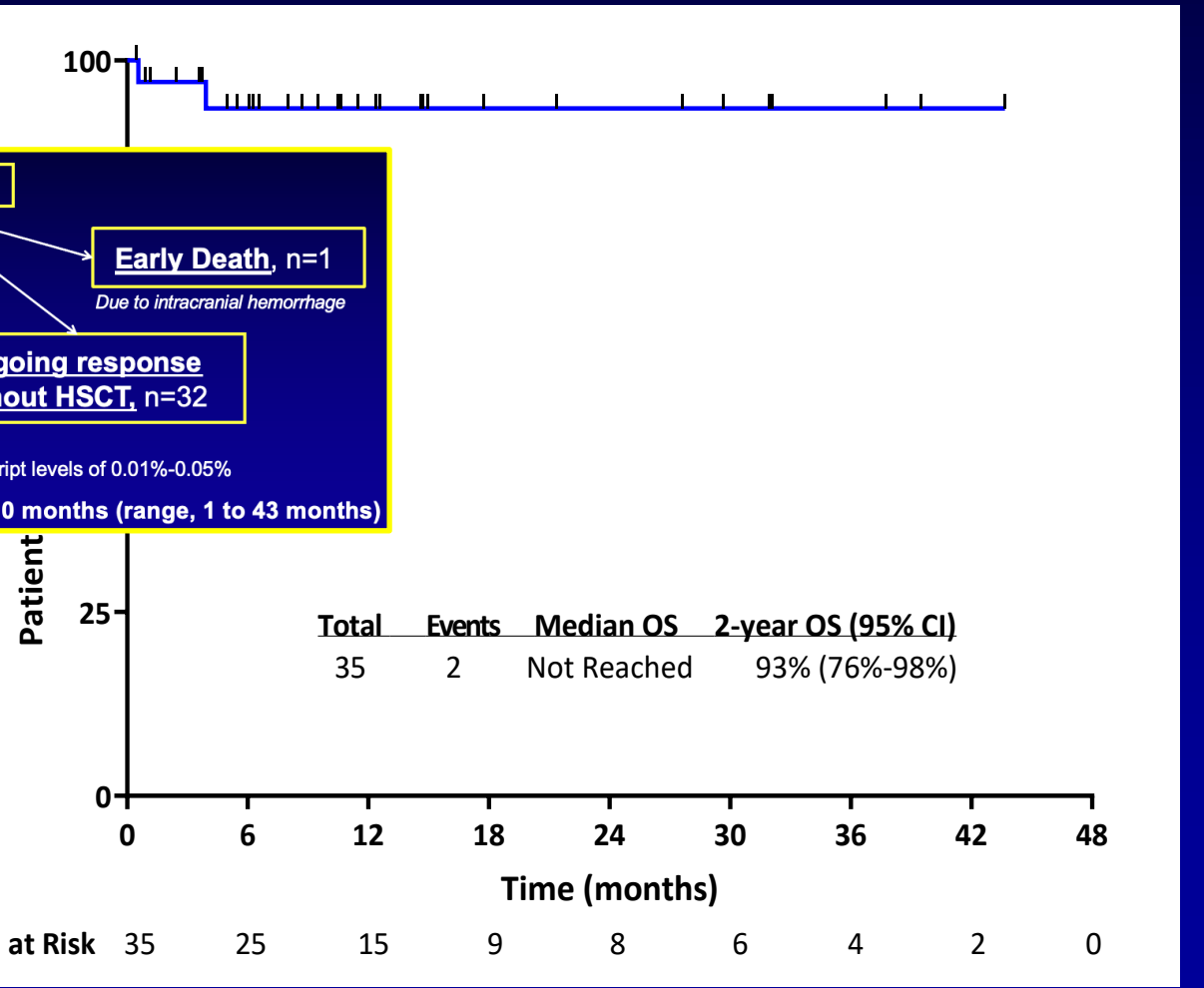
Ongoing response with HSCT in CR1, n=1*

Ongoing response without HSCT, n=32

Transplanted pt had persistently detectable BCR-ABL1 transcript levels of 0.01%-0.05%

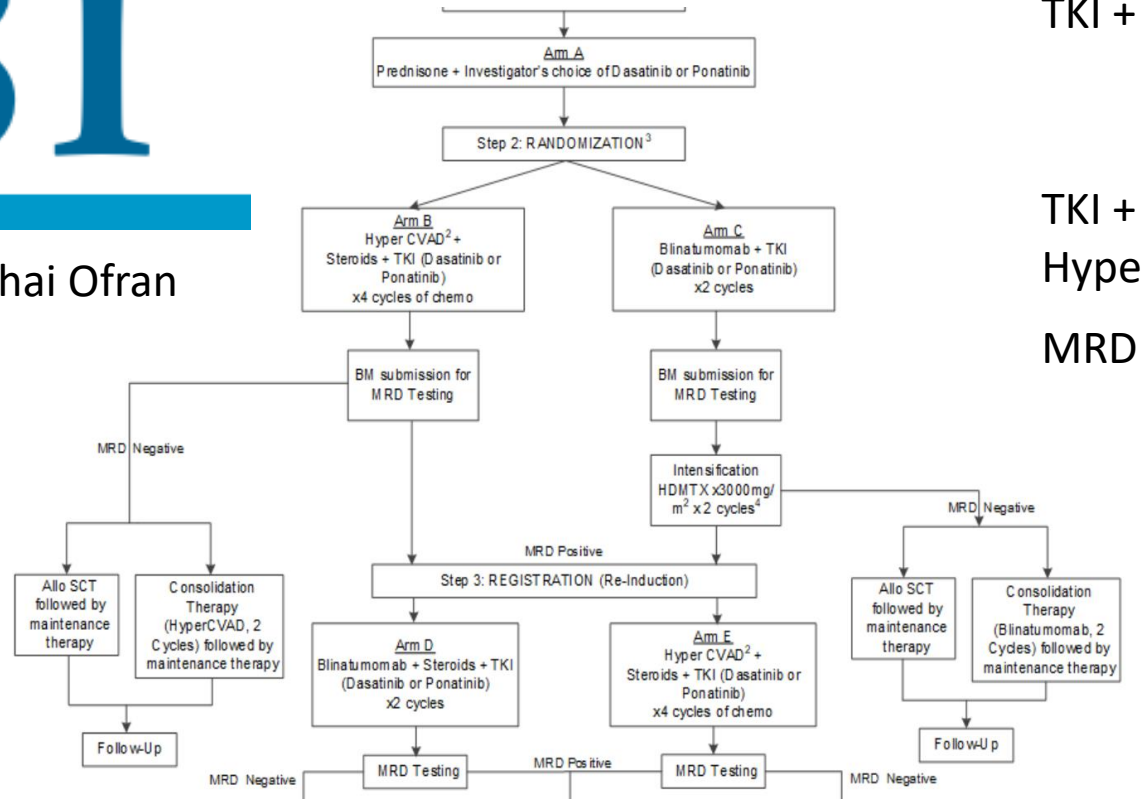
No pt has relapsed with median CR duration of 10 months (range, 1 to 43 months)

Overall Survival



EA9181

PI: Yishai Ofran



TKI + steroids

TKI + HyperCVAD vs Blina

MRD testing

Swap if MRD+ Transplant Option

- Currently accruing.
- **Induction:** TKI plus steroids.
  - *Choice*: DAS or PON
- **Consolidation:** Randomized to TKI+hyper-CVD orTKI+ blinatumomab.
- **Transplant:** Allowed, not proscribed.

- Will we get answers about best consolidation approach?
- Enrolling to randomized trials is important.

Ph+: ALL Conclusions and Questions

- **Known: TKIs improve outcomes and are an essential component of therapy for Ph+ B-ALL.**
- **Question: What is the best TKI?**
  - In US, most use 2G dasatinib, but there is interest in 3G TKI ponatinib.
  - Concerns about toxicity of 3G TKI.
    - Mitigated by optimized dosing (de-escalate after response)?
    - Can patients be appropriately selected based on disease risk and comorbidities?
  - Investigational: combination of catalytic domain and allosteric inhibitor?
    - Dasatinib plus ABL001 – DFCI protocol 18-170

Ph+: What We Know and (Mostly) What Don't Know

INDUCTION: Is intensive chemotherapy needed? In general no, associated with higher toxicity/early mortality.

- Do some patients benefit from early chemotherapeutic intensification?
- Should less toxic, novel agents (i.e. blina) be introduced early (before CR)?

CONSOLIDATION (FIT): TKI is not enough. Best addition? HSCT or intensive chemo, ?blina

- HSCT remains an accepted standard, but patients who respond optimally to intensive chemotherapy may not need.
- Long-term outcomes in patients treated with 2G/3G TKI plus novel agents (blina) unknown. Appear very effective, but curative?
- For transplant INeligible, how to best consolidate?

Philadelphia Chromosome **Negative** Acute Lymphoblastic Leukemia

<u>New</u>:

Many options – Potent TKIs, novel agents (blinatumomab), chemotherapy, BMT.

Adverse prognosis being reversed?

Relapsed ALL

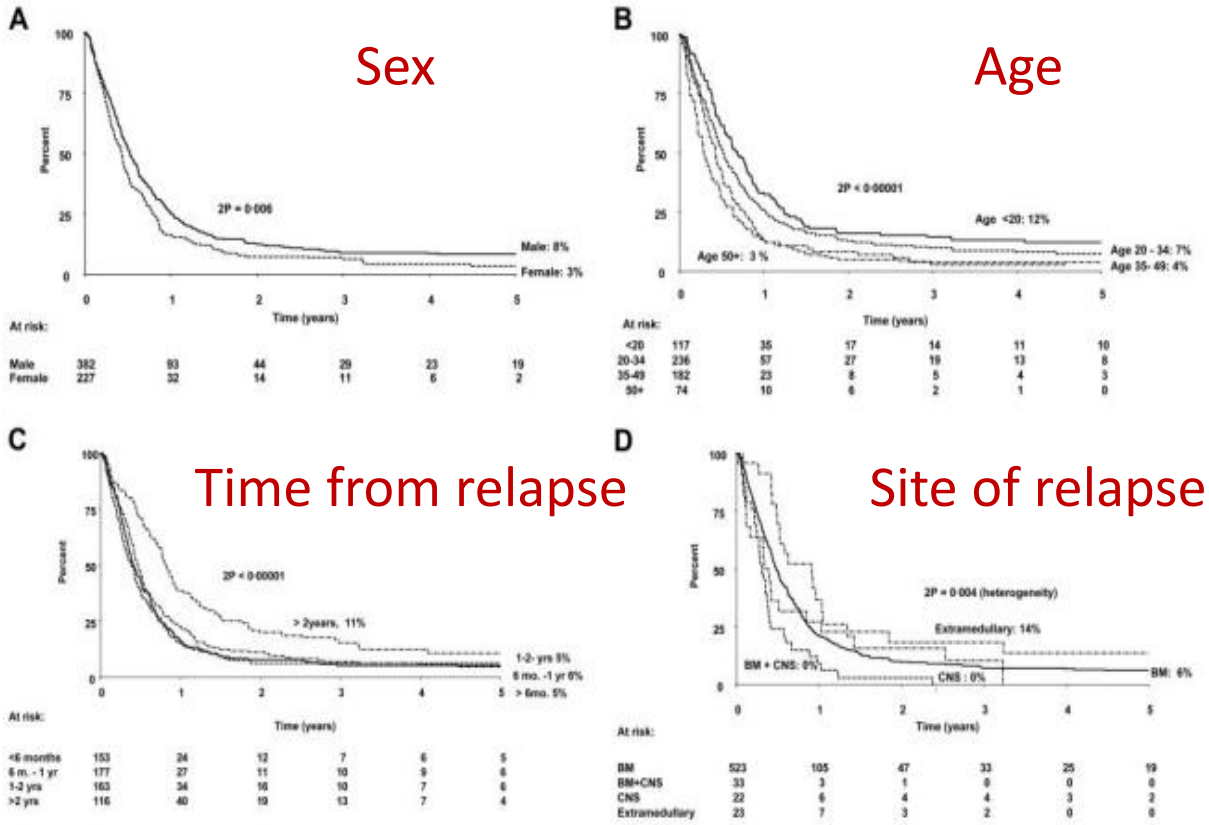
Relapsed ALL: Historically, Dismal Prognosis

OS at 5 years after relapse was 7% (95% CI: 4%–9%)

609 adults with
relapsed ALL
treated on ECOG 2993

"Favorable" findings
- Younger (<20 years)
- Long first remission

HSCT needed



Fielding et al. *Blood* 2007;109:944-50; Gokbuget et al. *Blood* 2012;120:2032-41; Tavernier et al. *Leukemia* 2007;21:1907-14.

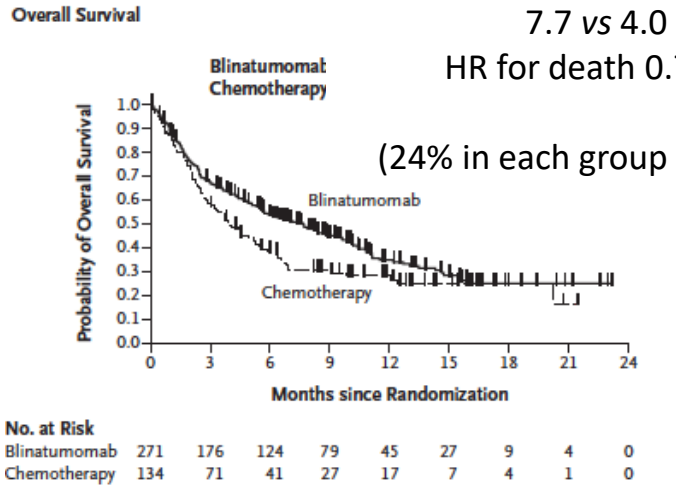
ALL – Antibodies for B-ALL in Relapse

CR: 34 vs 16% (P<0.001)
CR plus CRi: 44 vs 25% (P<0.001)

- **Blinatumomab (TOWER)** - Bispecific monoclonal antibody targeting CD19 and CD3. Enables CD3+ T-cells to recognize and destroy CD19+ cells (malignant and normal).
  - Toxicity: CRS, neurotoxicity
  - Strengths: Lower disease burden, MRD +
  - Logistics: Continuous infusion.

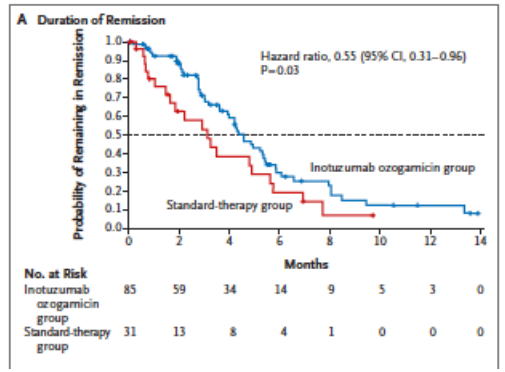
Median OS
7.7 *vs* 4.0 mos
HR for death 0.71 (*P*=0.01)

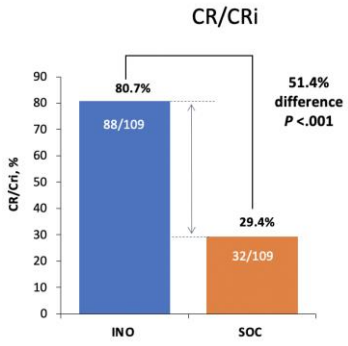
(24% in each group → transplant)



- **Inotuzumab ozogamicin (INO-VATE)** - Humanized IgG4 anti-CD22 antibody covalently linked to a cytotoxic agent (calicheamicin) → double-strand DNA breaks and apoptosis.
  - Toxicity: Cytopenias, liver toxicity (VOD)
  - Strengths: Effective at high and low disease burden, extramedullary disease
  - Logistics: Weekly Infusion

51.34% difference
***P* <.001**





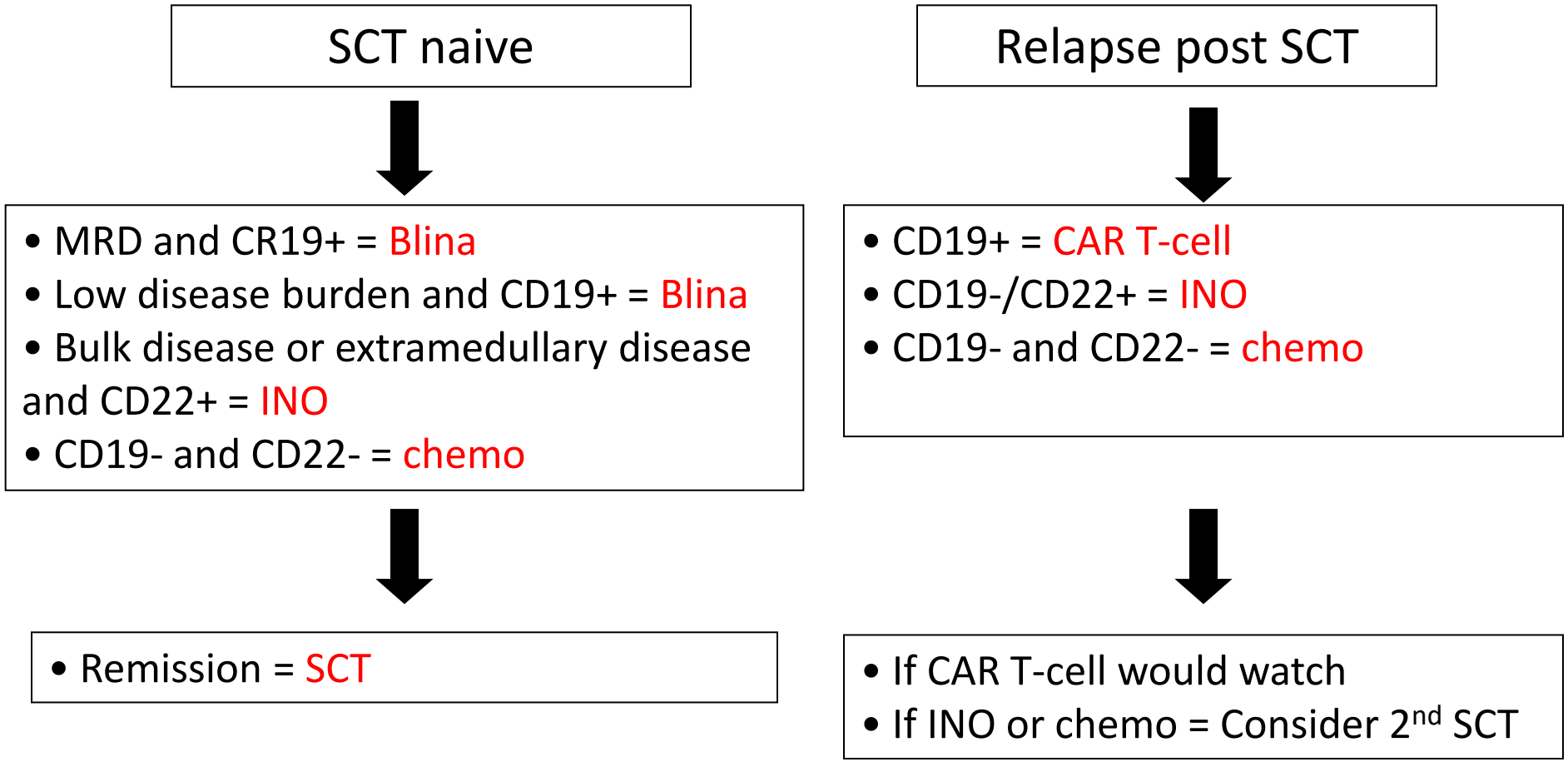
Kantarjian et al. *N Engl J Med* 2017;376:836-47; Kantarjian et al. *N Engl J Med* 2016;375:740-53; Maude et al. *N Eng J Med* 2018;378:439-48

Key Anti-CD19 CAR T-Cell Therapy Trials: B-ALL

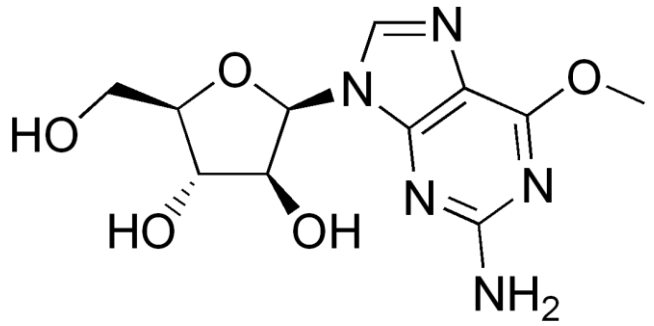
	ELIANA[1] (N = 75)	MSKCC[2] (N = 53)	ZUMA-3[3] (N = 45)
CAR T-cell agent	**Tisagenleucel**	**JCAR015**	**KTE-X19**
Study phase	II	I	I/II
Study population	Pediatric/young adults with R/R B-ALL	Adults with relapsed B-ALL	Adults with R/R B-ALL
CR, %	MRD negative: 81	Overall: 83	Overall: 68 RP2D: 84
Median OS, mos	19.1	12.9	--
Median EFS, mos	NR	6.1	--
Median DoR, mos	NR	--	RP2D: 12.9
Median follow-up, mos	13.1	29	16
	FDA approved	**Halted**	**FDA approved**

1. Maude. NEJM. 2018;378:439. 2. Park. NEJM. 2018;378:449. 3. Shah. ASCO 2019. Abstr 7006.

Current Treatment Algorithm for R/R B-ALL



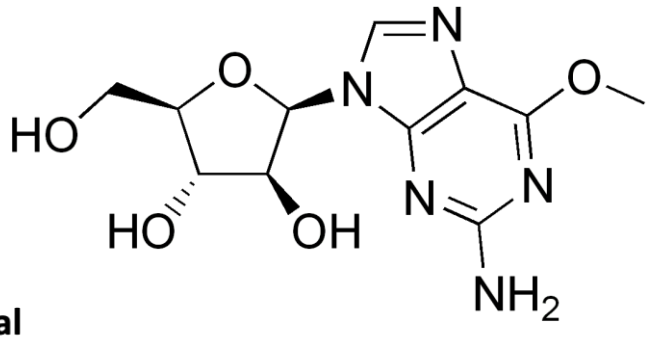
Relapsed T-ALL: Nelarabine

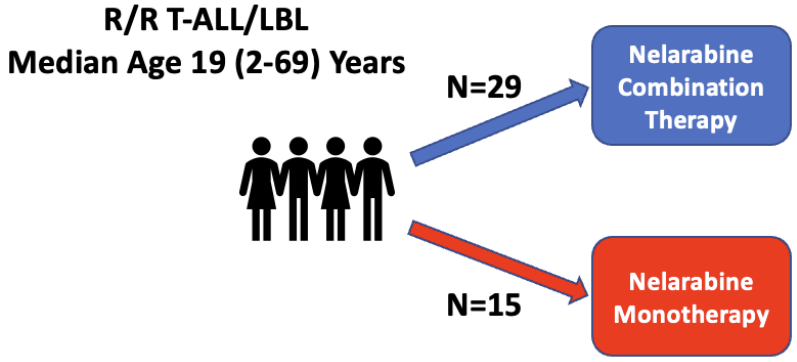


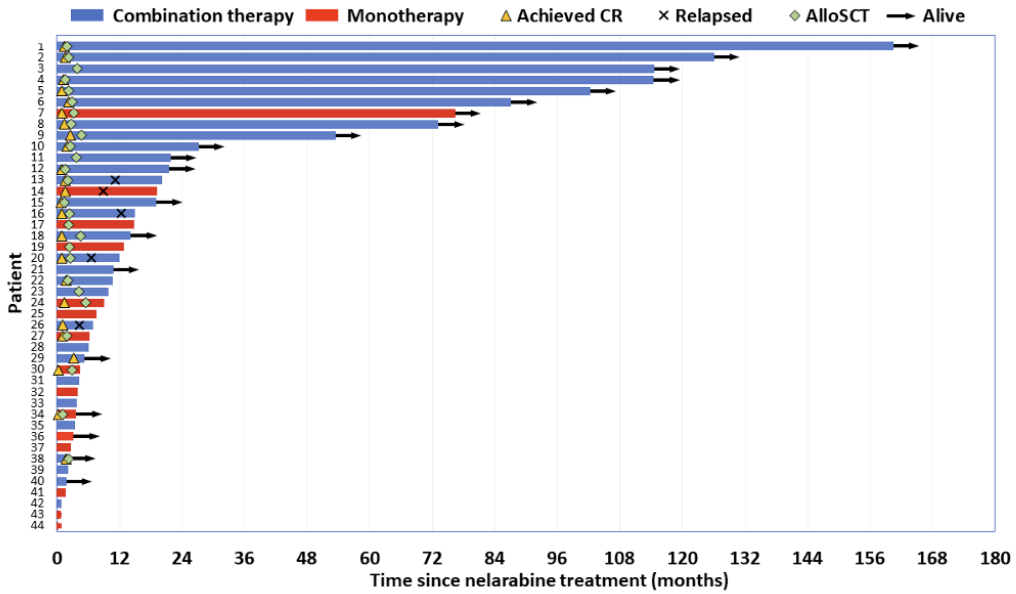
- Nelarabine is the prodrug of AraG; the active metabolite AraGTP accumulates in T lymphoblasts to a greater extent than in B cells or mature T cells due to decreased AraGTP degradation
- Associated with peripheral and CNS toxicities, myelosuppression dose dependent
- In adult R/R setting, 31% CR rate, 1-year OS 28% (DeAngelo Blood 2007); similar in children (Berg J Clin Oncol 2005)
- Approved for relapsed/refractory T-cell ALL

DeAngelo et al. *Blood* 2007;109:5136-42; Berg et al. *J Clin Oncol* 2005;23:3376-82

Relapsed T-ALL: Nelarabine Combinations

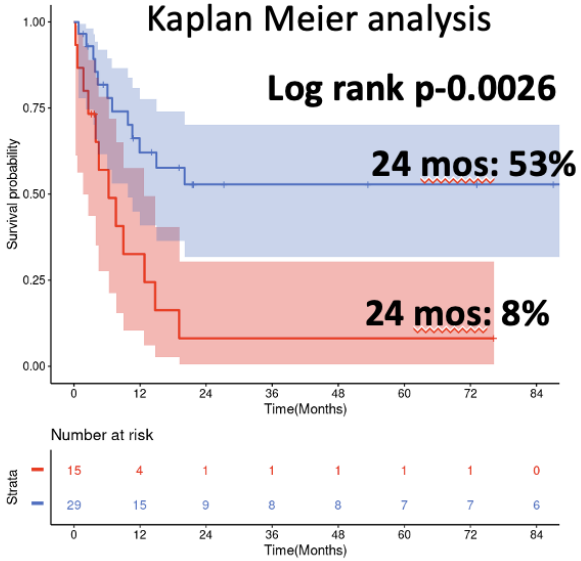






Overall survival

Kaplan Meier analysis



Overall Survival

Multivariable analysis

	HR	CI 95%	P value
AlloSCT (as time dependent variable)	0.17	0.06-0.48	< 0.001
Combination vs monotherapy	0.36	0.14-0.94	0.037

Shimony, Luskin, DeAngelo DFCI experience, unpublished data

Relapsed ALL

New: Effective salvage, particularly for B-ALL

ALL Conclusions

- ALL is a rare disease - approximately 50% of cases in adults.
- Outcomes in adults lag excellent pediatric outcomes, but improving.
- Treatment is dictated by age and Philadelphia chromosome status.
- Innovation is focused on improved risk stratification (MRD techniques) and incorporation of novel agents – TKIs, antibody therapies, cellular therapy, and optimization of transplant – in first line and relapsed disease.

Much Left To Be Done.

- T-cell ALL remains an area of unmet need.
- Further studies to define best way to incorporate novel agents, CAR-T, BMT into the treatment of adults with ALL, tailored to age, disease subtype (B vs T, genetic subtype), and response.
- Careful reporting of long-term as well as short term outcomes.
- Attention to representative enrollment to clinical trials based on age, race, ethnicity, socio-economic resources, geography – this is key.

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