3:15–4 PM

ALL

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THE 2nd ANNUAL HemOnc Pulse LIVE | AUSTIN 2025

Unanswered Questions in Frontline Treatment of B-Cell ALL: 2025 Edition

Presenter

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Disclosures for Nicholas Short MD

- Consulting fees from Pfizer Inc., GSK, NKARTA, Autolus, Adaptive Biotechnologies, and Sanofi
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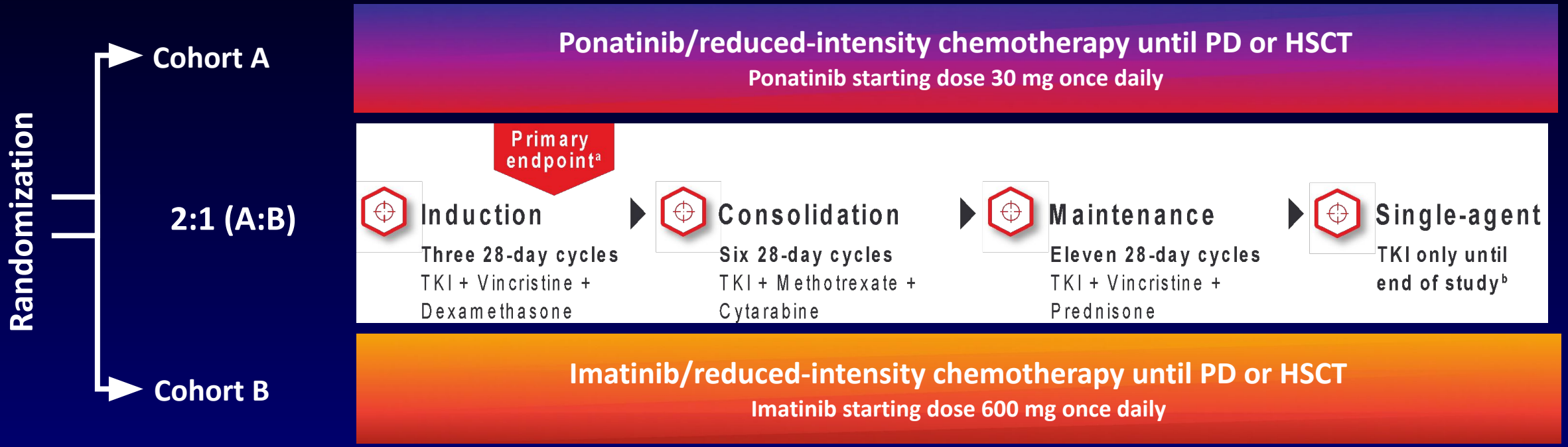
Reasons for Recent Success in Adult ALL

- Identification of high-risk subtypes where HSCT in CR1 should be considered (when standard therapies are given)
  - Poor-risk cytogenetics (eg, low hypodiploidy, *KMT2A*r, complex)
  - Ph-like ALL (especially *CRLF2*r + JAK mutation)
  - Early T-cell precursor ALL
  - Poor MRD clearance
- Introduction of novel agents
  - Addition of anti-CD20 antibody to chemotherapy in Burkitt and pre-B ALL
  - Addition of TKIs to chemotherapy in Ph+ ALL, chemotherapy-free regimens
  - Use of blinatumomab in the frontline setting (regardless of MRD)
  - Blinatumomab, inotuzumab ozogamicin and CAR T cells for R/R disease
  - Combinations of these novel agents in the frontline and salvage settings

Ponatinib Versus Imatinib With Reduced-Intensity Chemotherapy in Patients With Newly Diagnosed Ph+ Acute Lymphoblastic Leukemia: PhALLCON Study



<u>Primary end point:</u> MRD-negative (BCR-ABL1/ABL1 ≤0.01%) CR at the end of induction

- **Ponatinib associated with higher MRD-negative CR (34.4% vs 16.7%; *P*=0.0021)**
- **Similar TEAE rates**

Jabbour E et al. *JAMA*. 2024;331(12):1814-1823.

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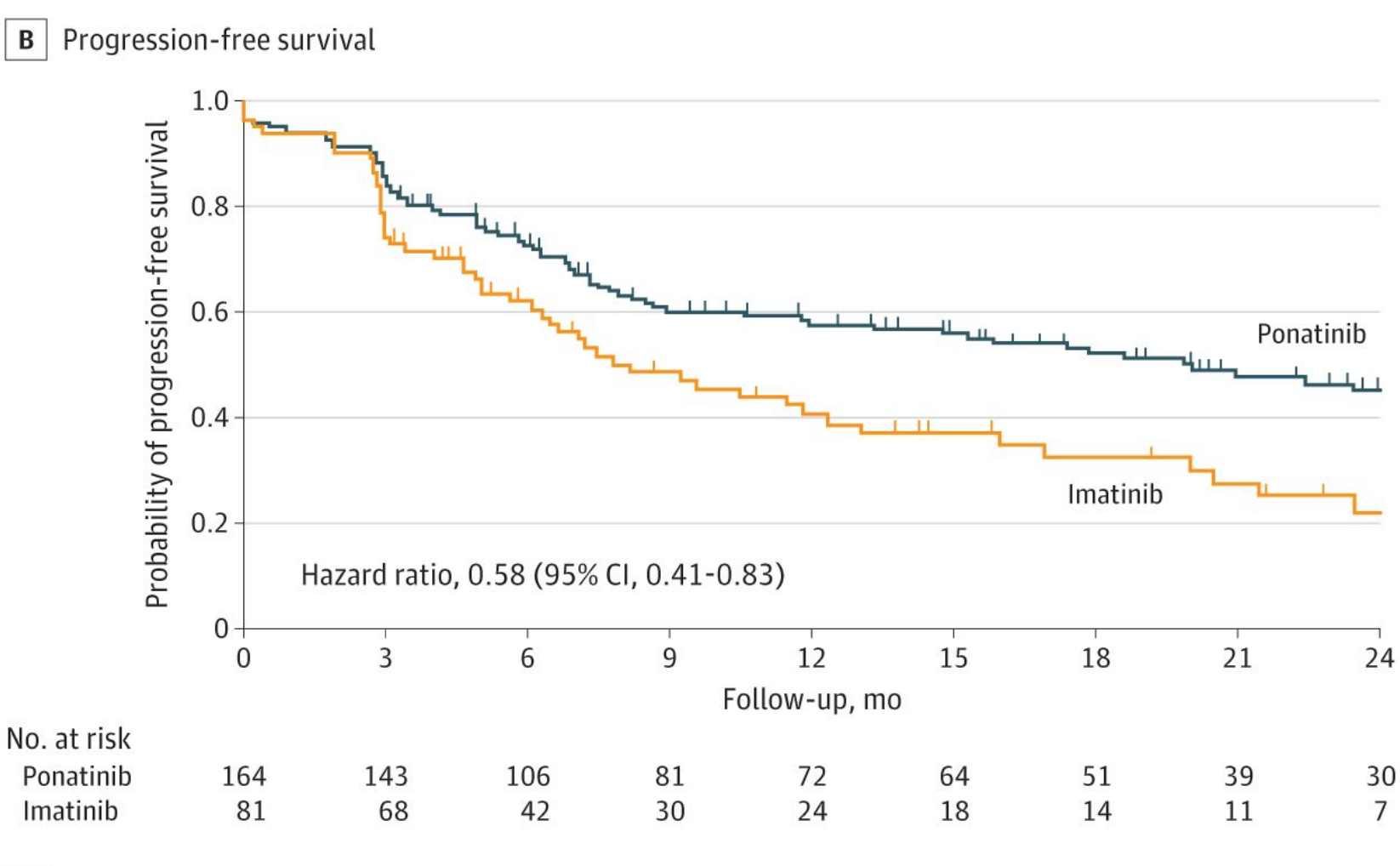
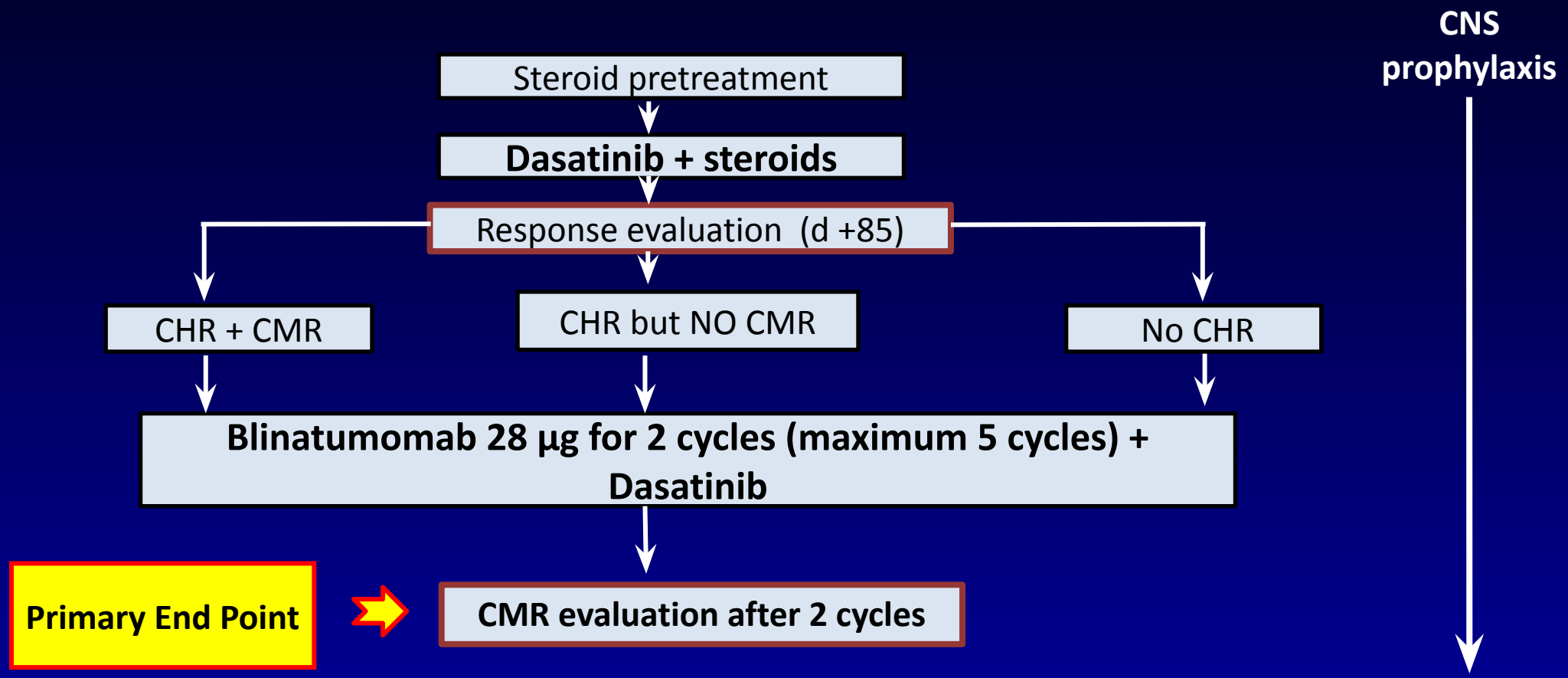


Jabbour E et al. *JAMA.* 2024;331(12):1814-1823.

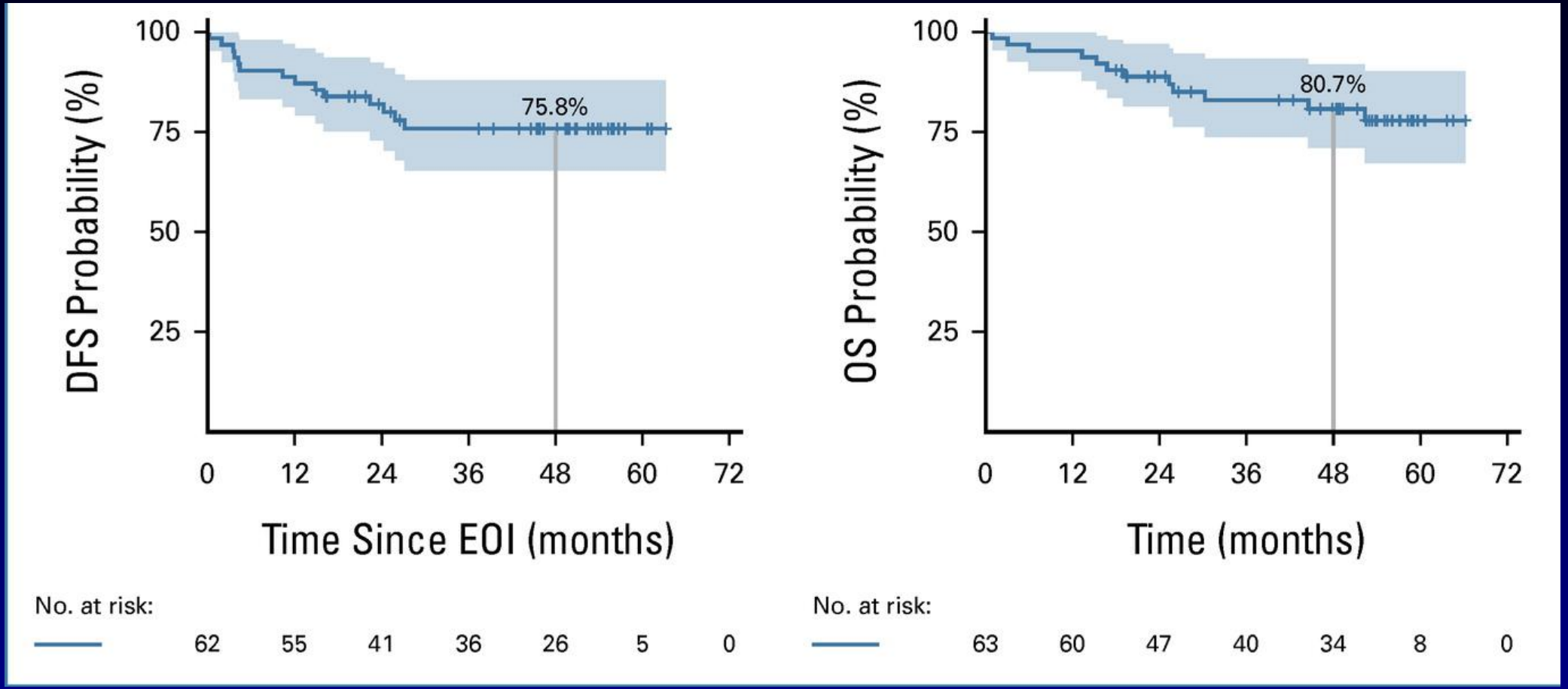
GIMEMA LAL2116 D-ALBA Trial: Dasatinib + Blinatumomab for Ph+ ALL

63 pts with newly diagnosed Ph+ ALL (median: 54 years)



Foa R et al. *N Engl J Med.* 2020;383(17):1613-1623.

GIMEMA LAL2116 D-ALBA Trial: Dasatinib + Blinatumomab



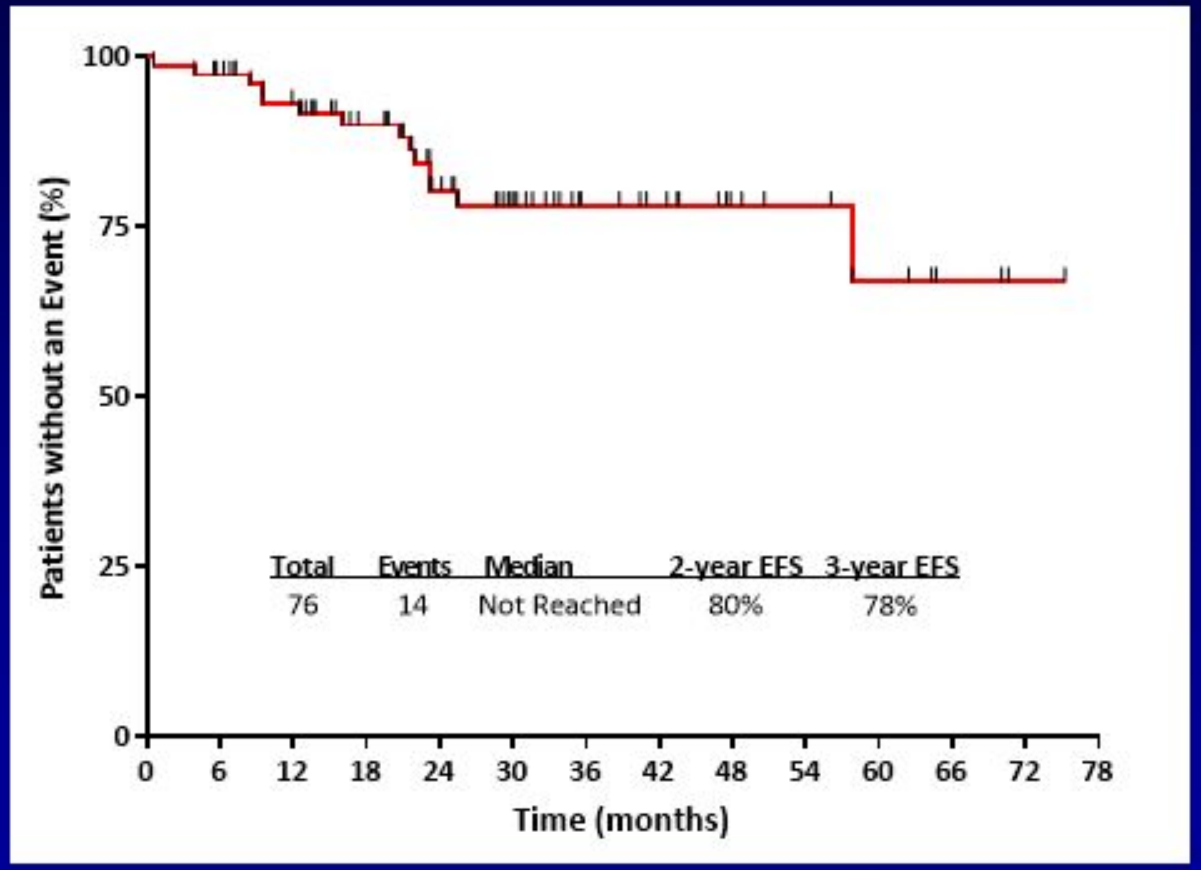
Worse outcomes for *IKZF1*^{plus} genotype (DFS 46% vs 82% without *IKZF1*del)

Foa R et al. *J Clin Oncol.* 2024;42(8):881-885.

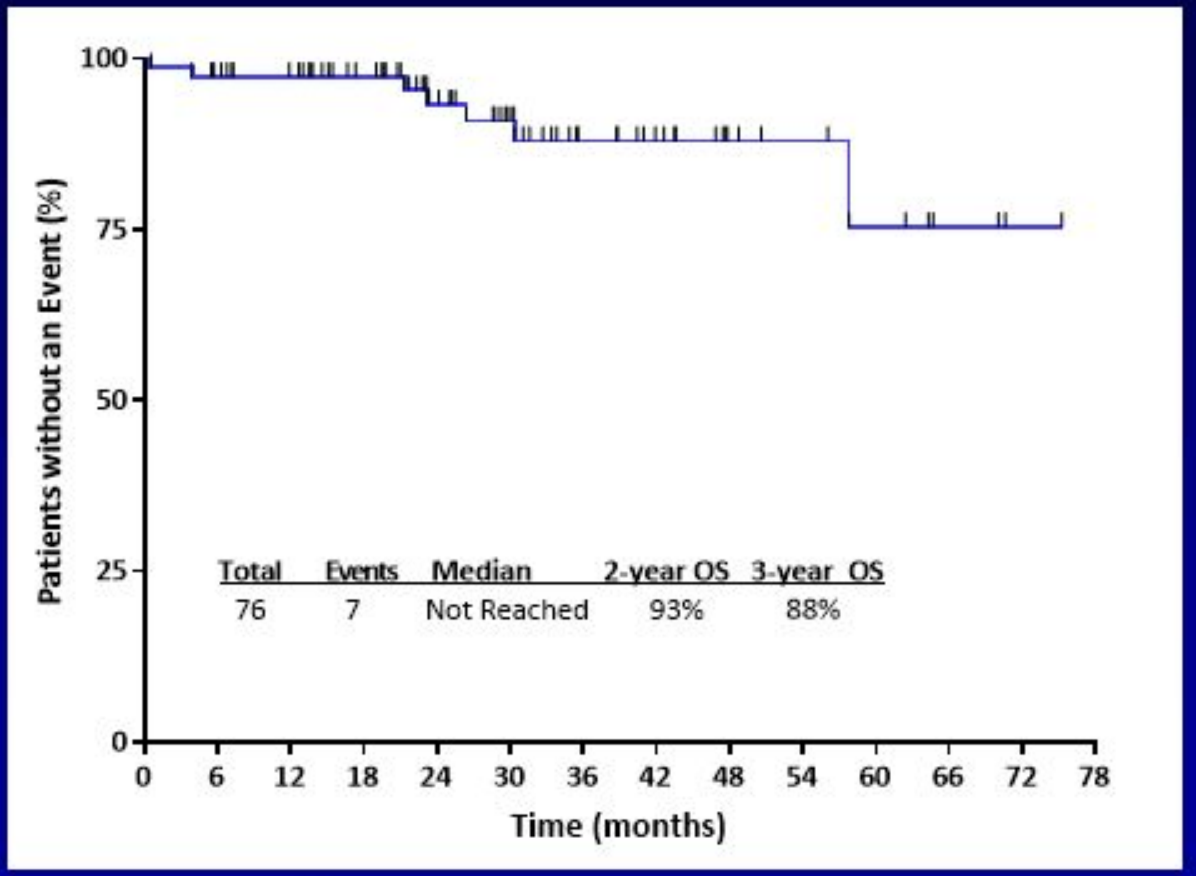
Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes

Median follow-up: 29 months (range, 5-75 months)

Event-Free Survival



Overall Survival

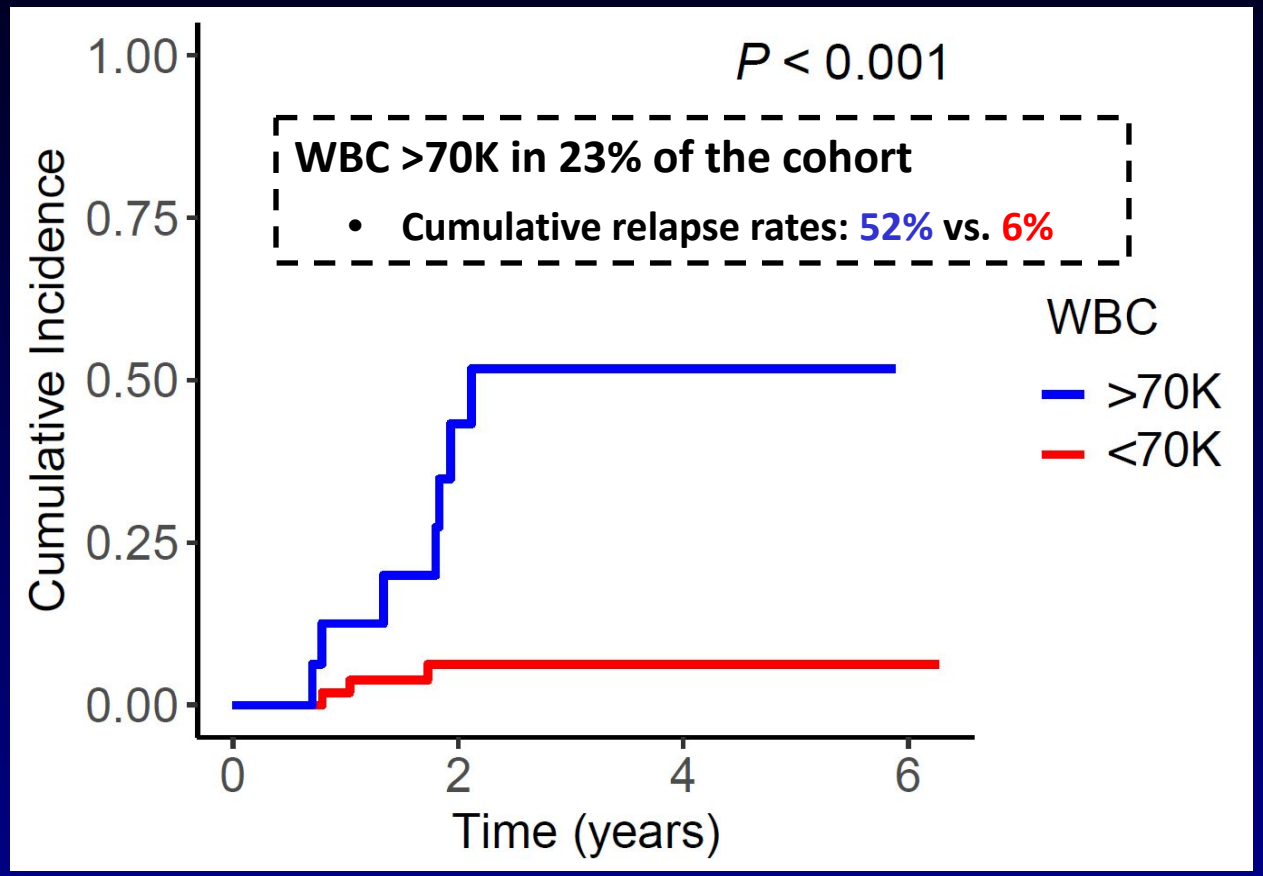


Only 2 patients transplanted

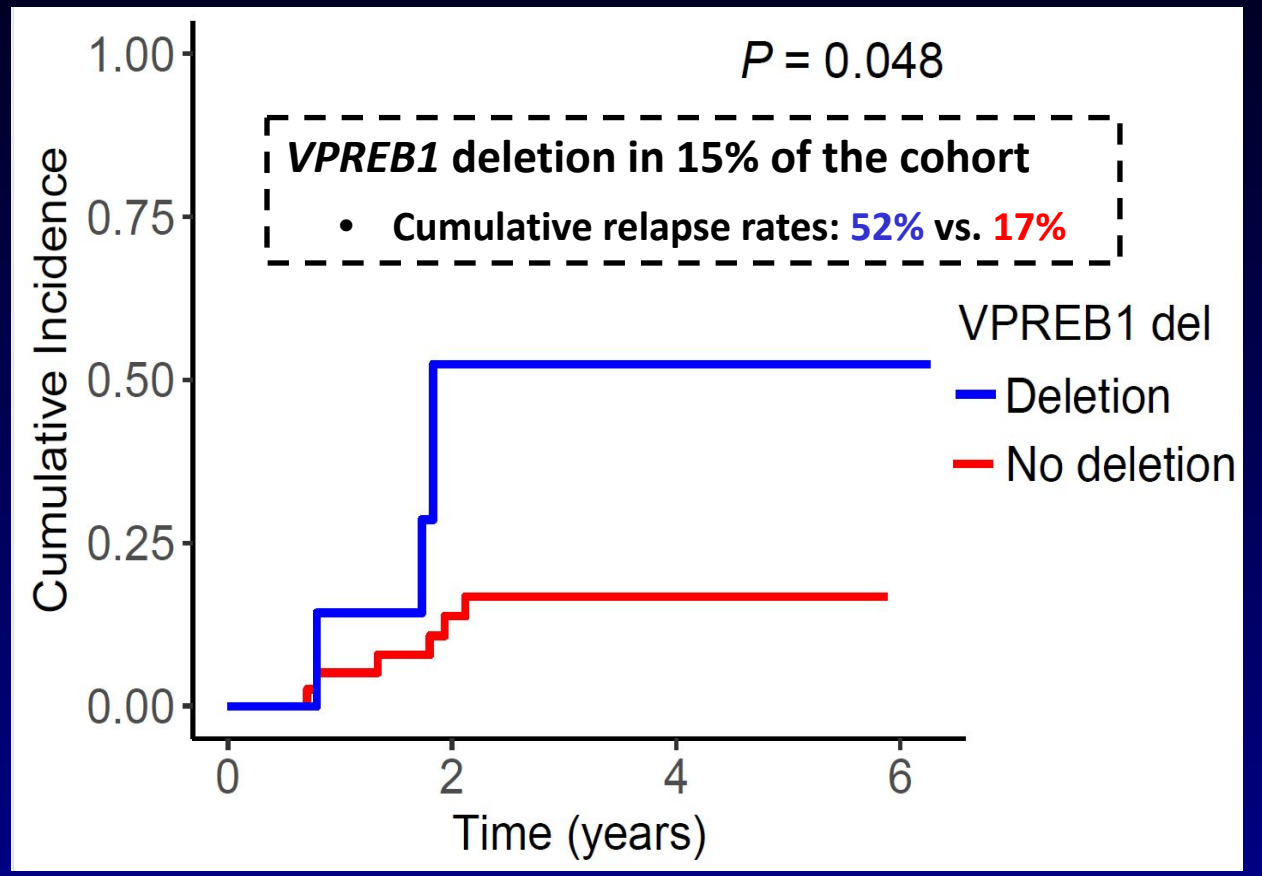
Short NJ et al. ASH 2024 (abstract #837)

Ponatinib + Blinatumomab in Ph+ ALL: Relapse Risk by WBC and *VPREB1* deletion

WBC at diagnosis



VPREB1 deletion



No significant impact of MRD dynamics or *IKZF1*^{plus} genotype

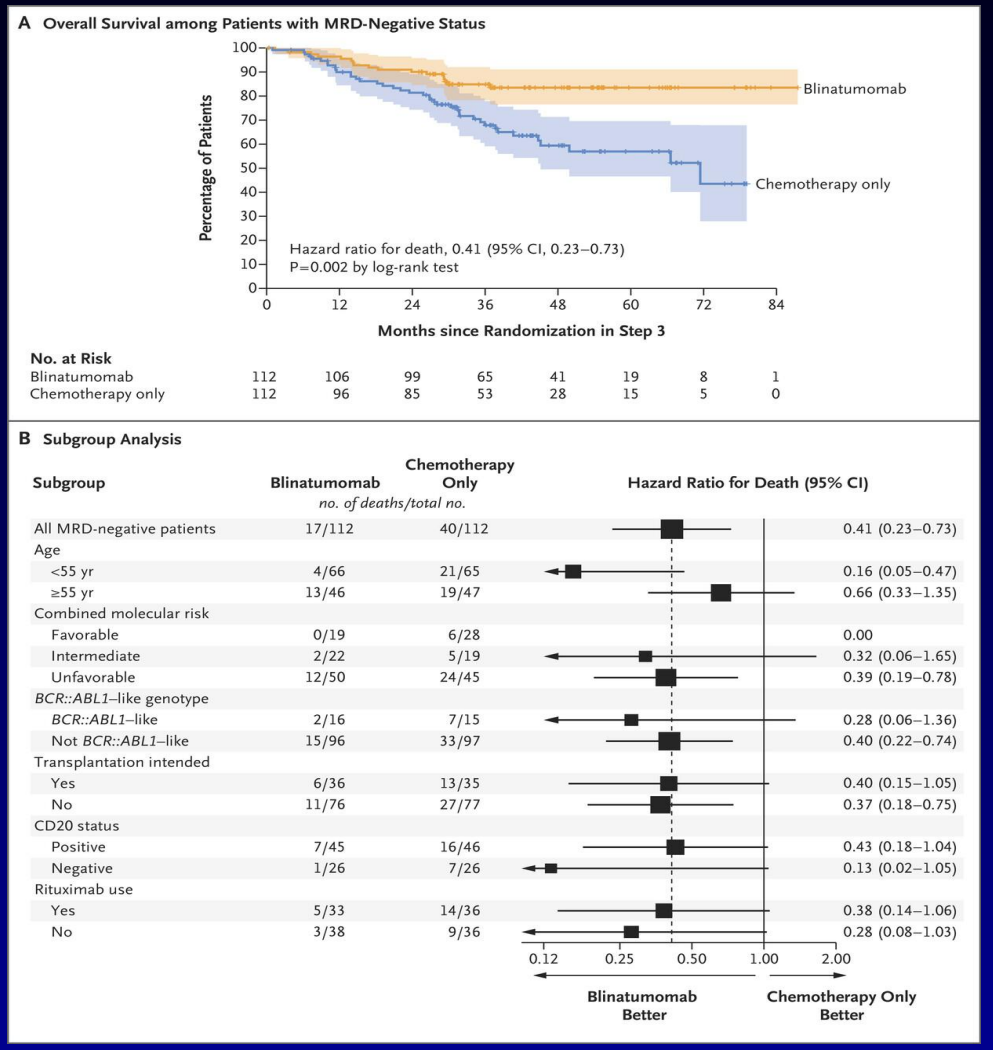
Short NJ et al. ASH 2024 (abstract #837).

Questions in Ph+ ALL

- Is ponatinib superior to second-generation TKIs in newly diagnosed Ph+ ALL?
- Should chemotherapy-free regimens be considered standard of care?
  - What constitutes “high-risk” Ph+ ALL with chemotherapy-free regimens?
    - High WBC? IKZF1plus? MRD dynamics?
  - Should we modify therapy (and how) for high-risk Ph+ ALL?
    - Intensive chemotherapy? Allogeneic SCT? CAR T cells?
- How long should TKI maintenance be continued in patients who did not undergo transplant?

E1910: Randomized Phase 3 Trial: Blina vs SOC as Consolidation in MRD-Negative CR

- 224 patients in MRD-negative CR after pediatric-inspired regimen randomized 1:1 to chemotherapy ± blinatumomab
- 20% in each arm underwent allogeneic SCT
- OS improved with blinatumomab vs chemotherapy alone (3-year OS 85% vs 68%; *P*=0.0002)
- **Frontline blinatumomab consolidation (regardless of MRD status) is new standard of care in Ph-negative B-cell ALL**



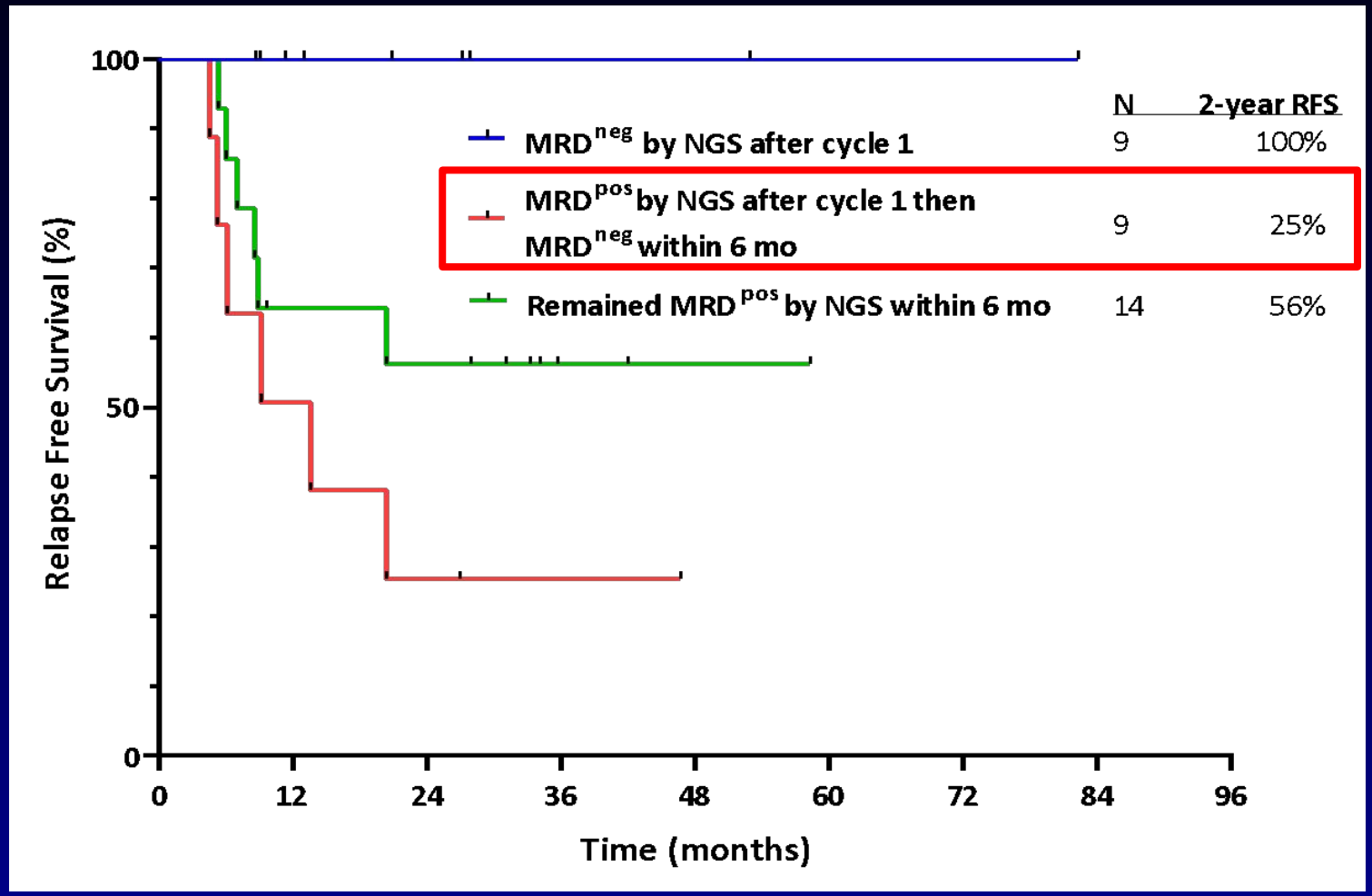
Litzow MR et al. *N Engl J Med.* 2024;391:320-333.

E1910: Lack of Impact of Allogeneic SCT

- 44 pts underwent allogeneic SCT (22 in each arm)
- No difference in post-SCT outcomes by treatment arm
- In pts with unfavorable-risk Ph-negative B-cell ALL, 3-year OS was 71% for transplanted pts vs 90% for nontransplanted pts
- **Allogeneic SCT did not impact OS on multivariate analysis (HR, 1.00; 95% CI, 0.49-2.01)**

Liedtke M et al. ASH 2024 (abstract #779).

NGS MRD in B-cell ALL: RFS by MRD Dynamics (HR Ph-Negative B-cell ALL)

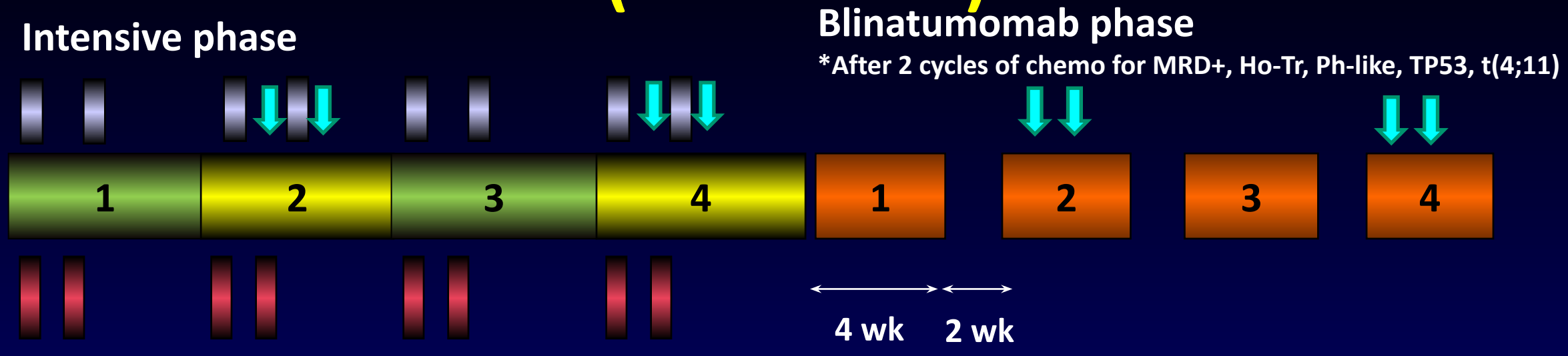


SCT rates higher in the NGS MRD nonresponder group (50%) than in the late responder group (33%)

"High risk" = Low hypodiploidy/near triploidy, complex, *KMT2A* rearranged, Ph-like, and/or *TP53*-mutated

Macaron W et al. ASH 2024 (abstract #727).

Hyper-CVAD + Blina + INO in B-ALL: Regimen (2nd Cohort)



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

MTX + Ara-C

IT MTX/Ara-C x 8

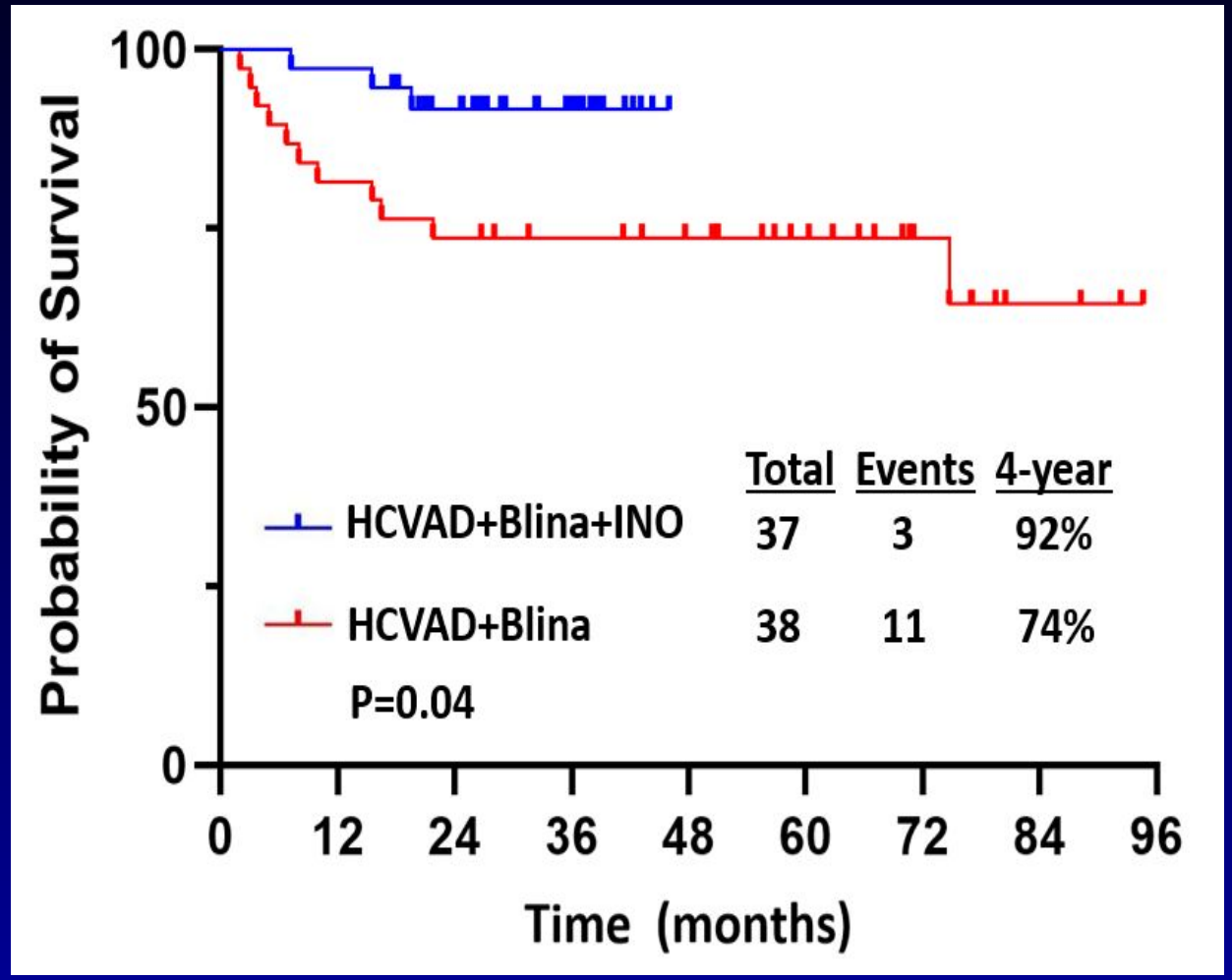
POMP

Inotuzumab 0.3 mg/m^2 on D1 and D8

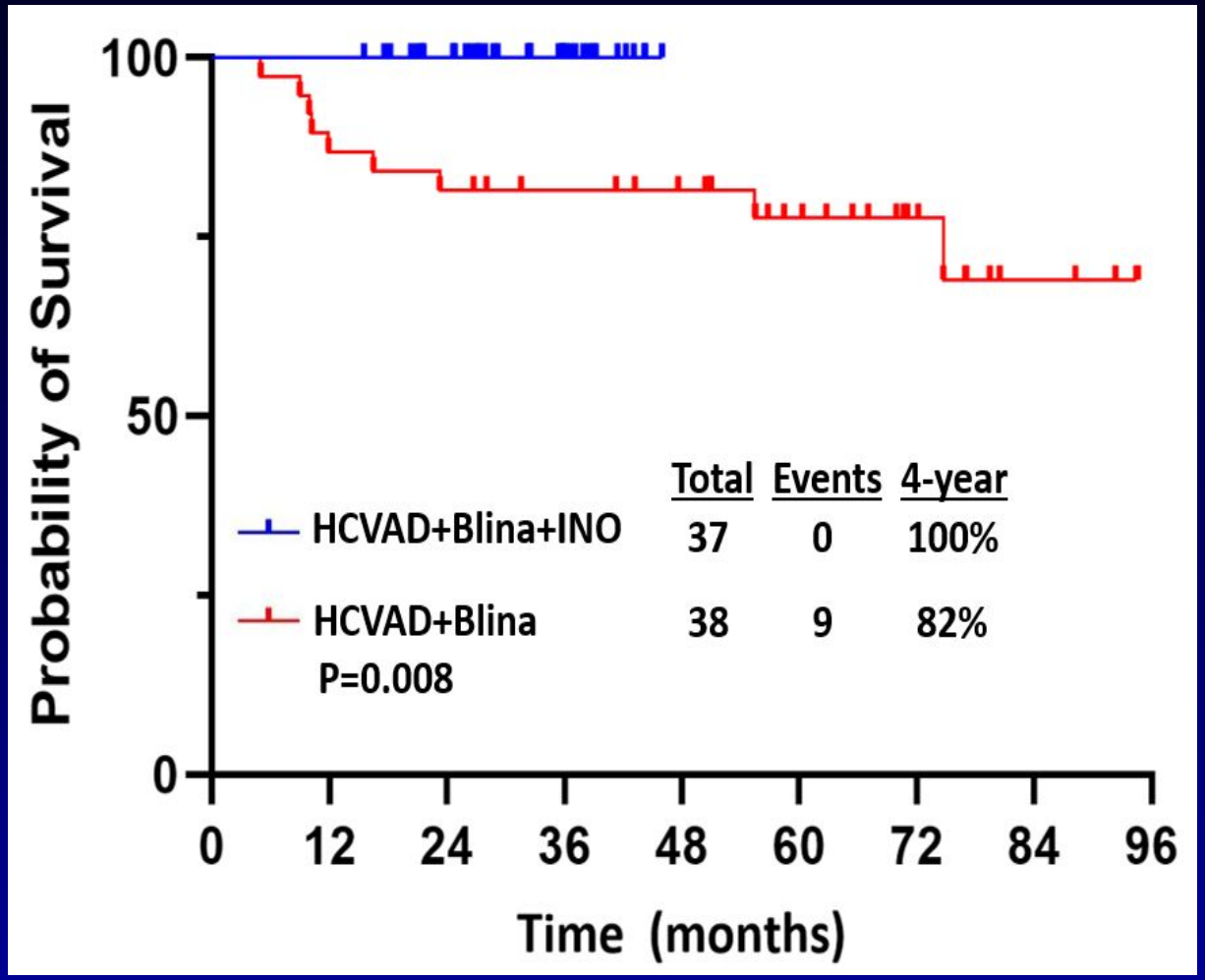
Nguyen D et al. ASH 2024 (abstract #1439).

Hyper-CVAD + Blina + INO in B-ALL: Outcome by Cohort

Relapse-free survival

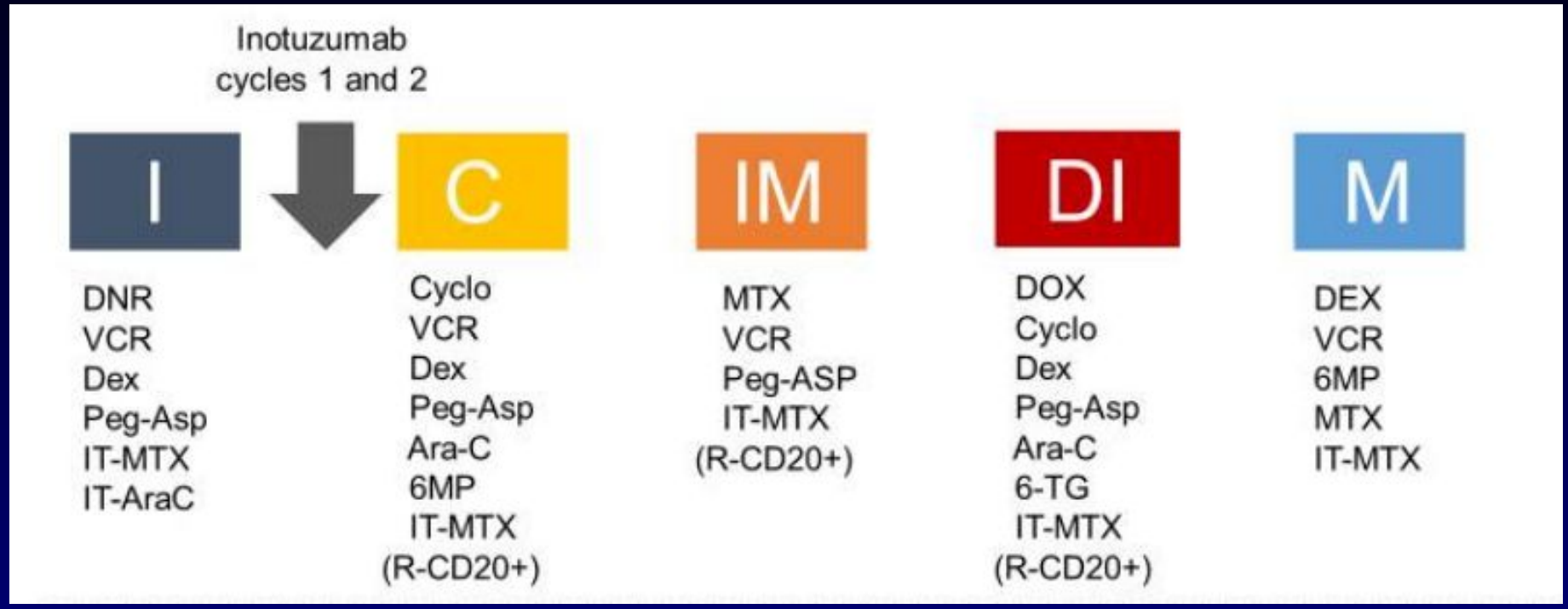


Overall survival



Nguyen D et al. ASH 2024 (abstract #1439).

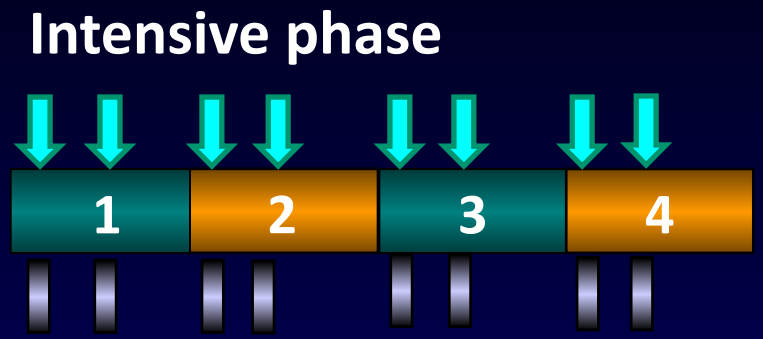
CALBG 10403 +/- INO in Ph-Negative B-cell ALL (Alliance A041501)



- Study ended early due to increase in grade 5 events in the INO arm (12 vs 3), all during intensive consolidation courses
- No difference in 3-year EFS or OS

Deangelo DJ et al. ASH 2024 (abstract #308).

Mini-HCVD + INO ± Blina in Older ALL: Modified Design (Pts #50+)



Mini-HCVD

Mini-MTX-cytarabine

IT MTX, Ara-C

Blinatumomab

POMP

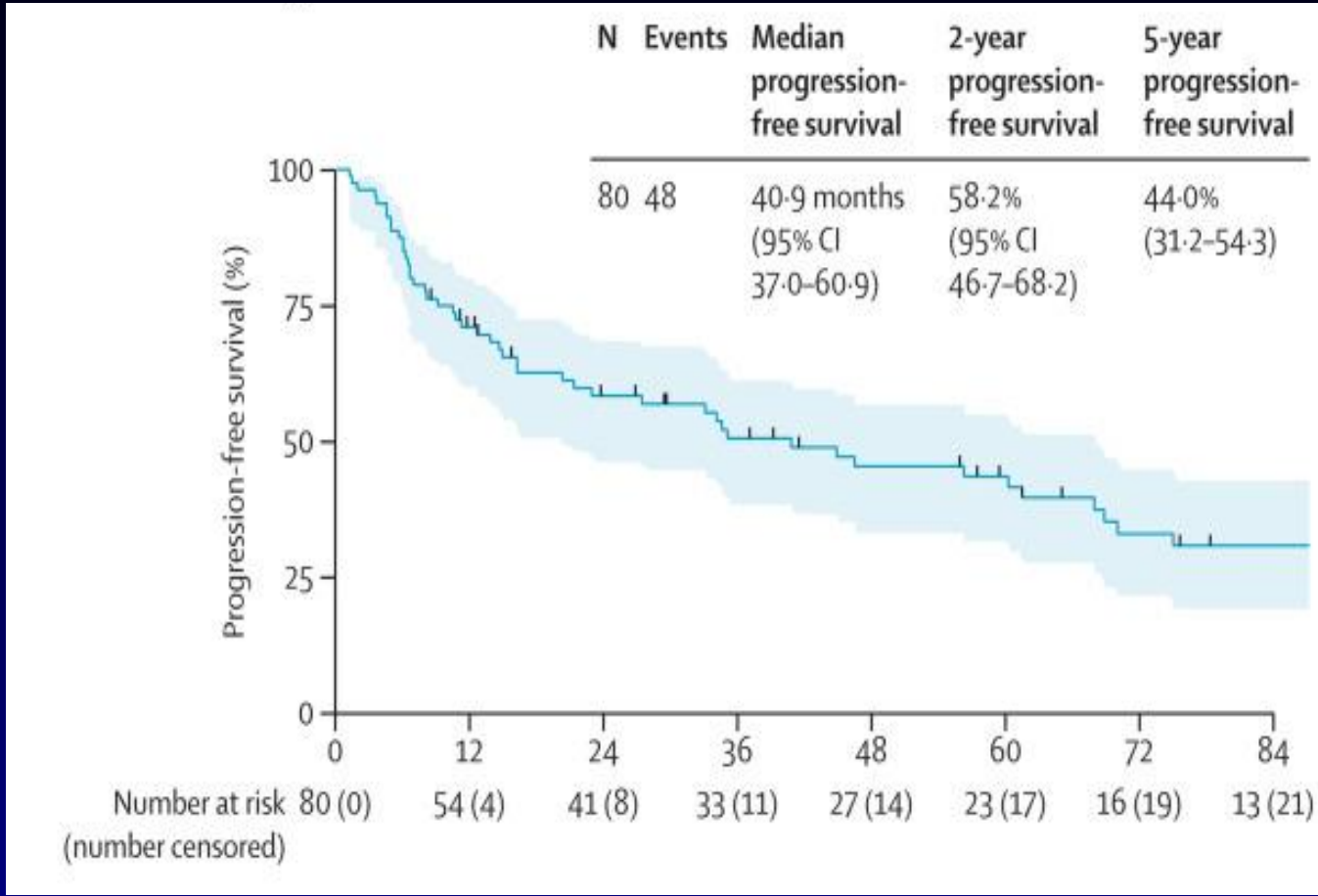
INO*	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2-4	0.6	0.3 D2 and D8

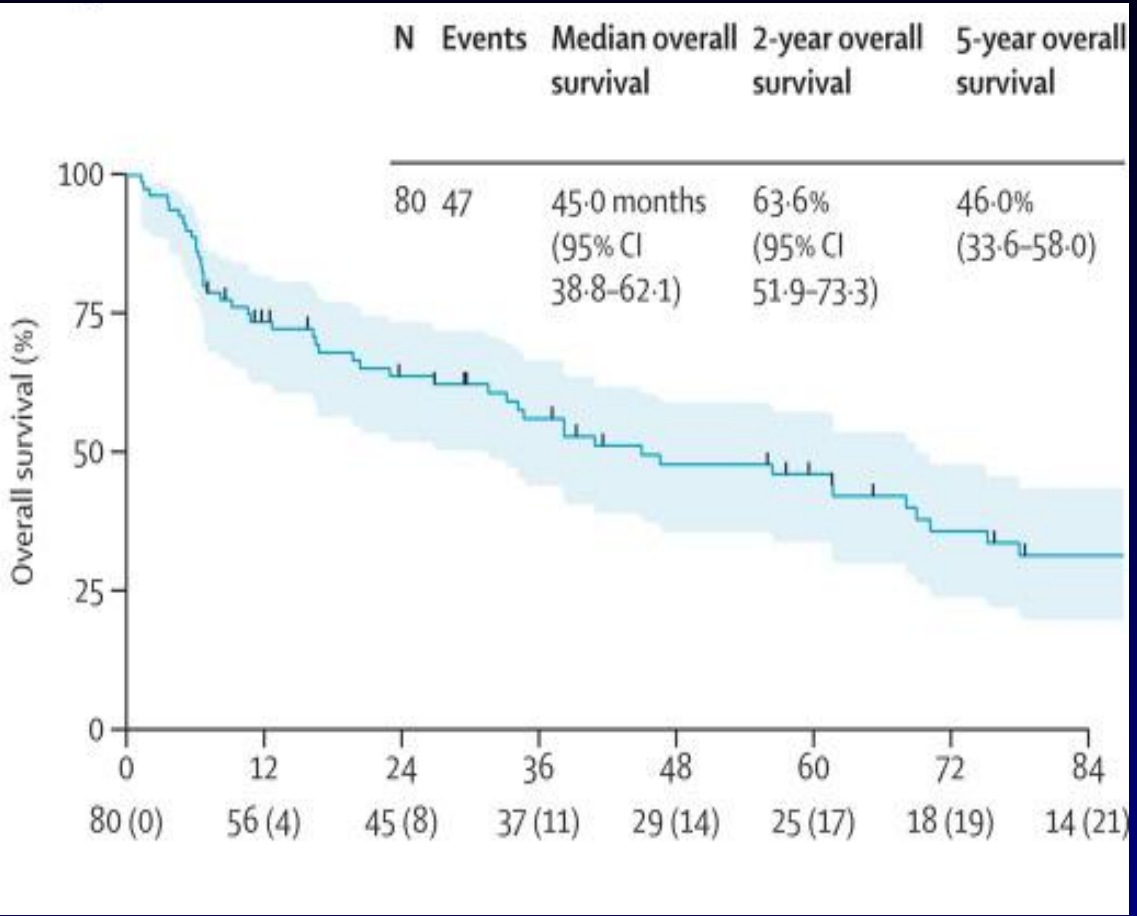
Total INO dose = 2.7 mg/m^2

*Ursodiol 300mg tid for VOD prophylaxis

Jabbour E et al. *Lancet Haematol.* 2023;10(6):e433-e444.

Mini-HCVD + INO ± Blina in Older ALL: PFS and OS (Entire Cohort)



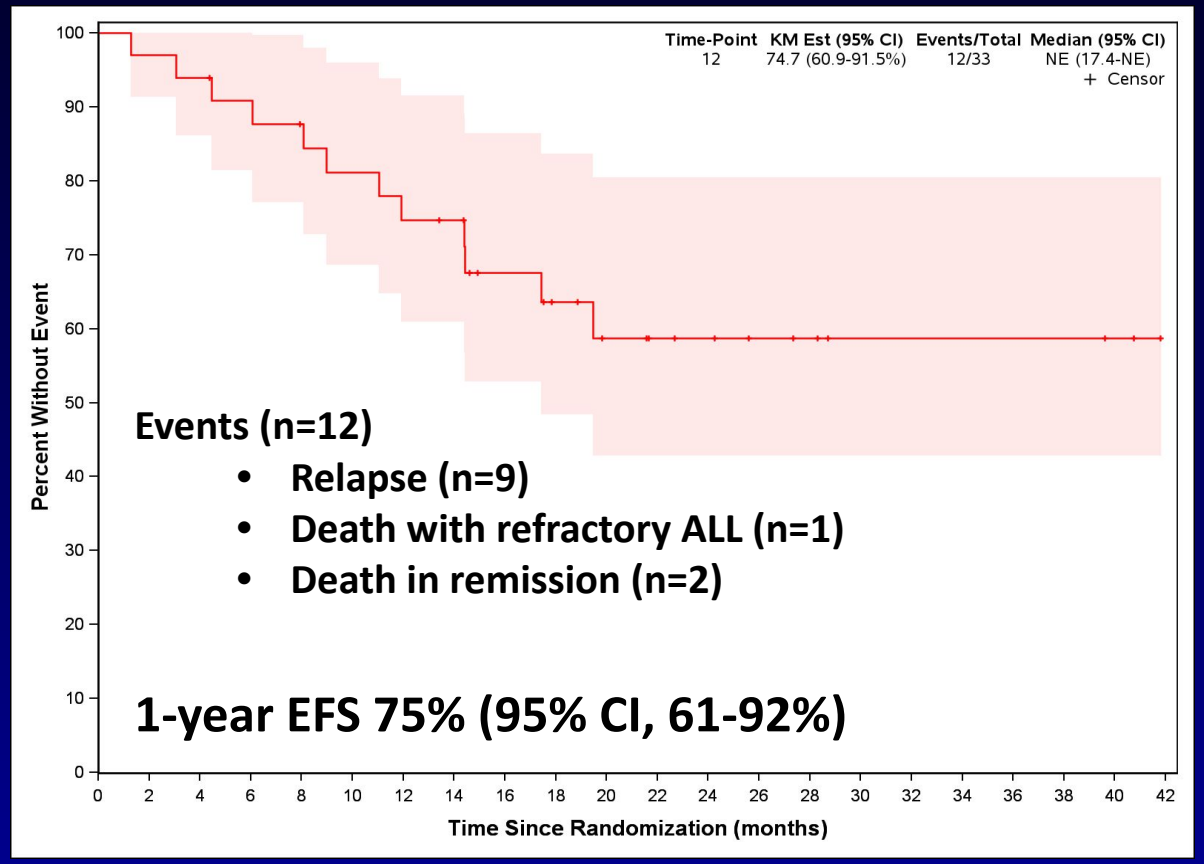


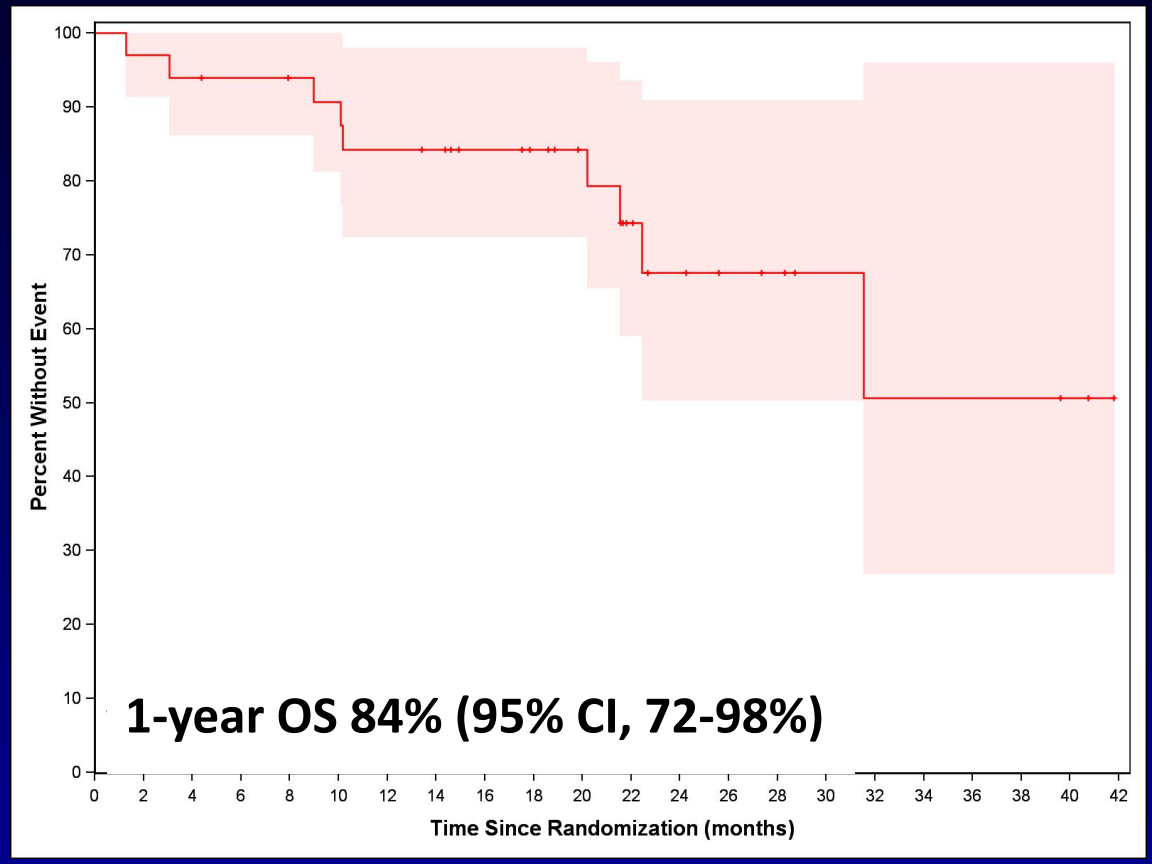
- 35 pts (44%) died in CR (including 9 due to t-MN, 8 due to infection, 4 due to VOD/SOS)
- Death in CR accounted for 74% of deaths

Jabbour E et al. *Lancet Haematol.* 2023;10(6):e433-e444.

INO + Blinatumomab in Older ALL (Alliance A041703)

Overall response rate: 32/33 (96%) – 85% after INO

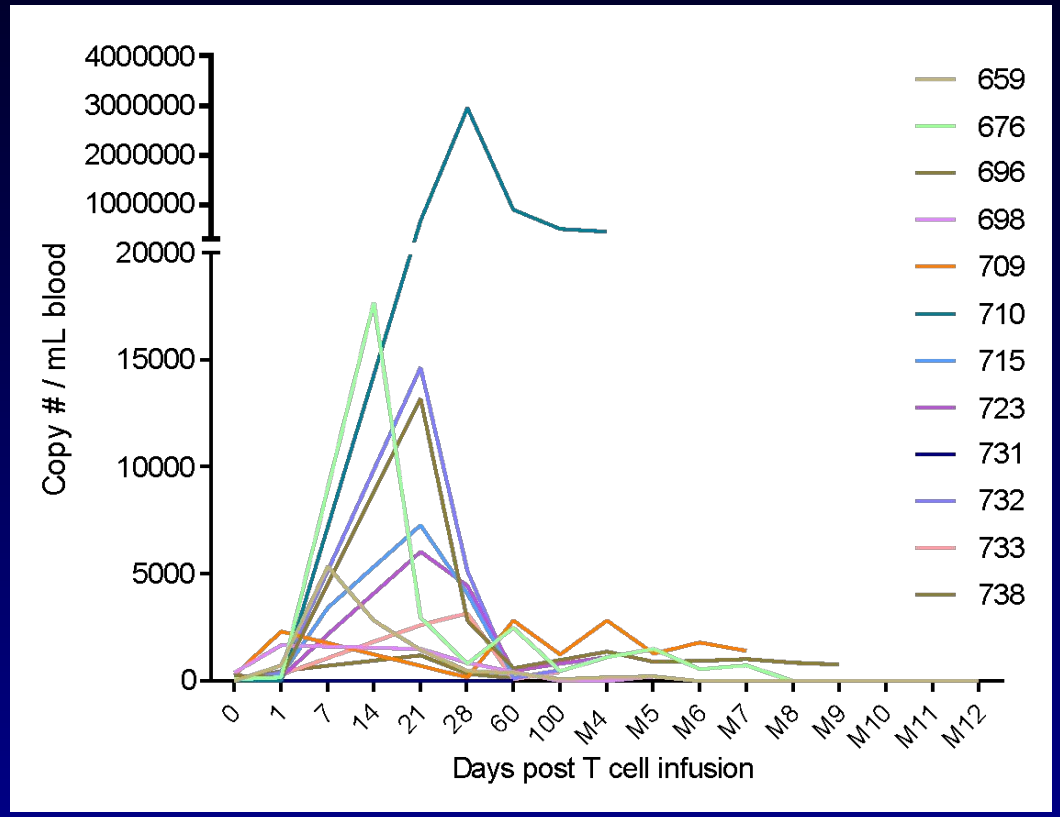




Wieduwilt MJ et al. EHA 2023 (abstract S117).

CD19 CAR T cells in Older Adults as Consolidation Therapy

- Pts ≥55 years of age who achieved CR1 with frontline therapy memory-enriched CD19 CAR T cells as consolidation therapy
- 14 pts treated, no DLTs, grade 1 CRS 64% (no grade 2+ CRS, no ICANS)
- Median follow-up 244 days – 1 pt with Ph+ ALL with clonoSEQ relapse
- CAR T-cell expansion in blood and CSF



Aldoss I et al. ASH 2024 (abstract #966).

Questions in Ph-negative B-cell ALL

- Which patients should undergo allogeneic SCT in CR1 after frontline chemotherapy + blinatumomab?
  - Cytomolecular features? MRD dynamics?
  - Or can we do CAR T-cell consolidation for high-risk patients?
- Should INO be added to frontline treatment for younger patients with Ph-negative B-cell ALL (and how)?
- What is the optimal therapy for older adults with Ph-negative B-cell ALL?
  - Can chemotherapy-free regimens mitigate toxicity?

Other Unanswered ALL Questions

- How can we improve outcomes in T-cell ALL?
  - Nelarabine? Venetoclax? CAR T cells?
- In the new era of universal frontline blinatumomab, what is the optimal salvage regimen for Ph-negative B-cell ALL?
- Which patients should undergo allogeneic SCT after CAR T-cell therapy?
  - MRD? CAR T-cell expansion/persistence?
- For transplanted patients, is there a role for post-SCT maintenance?

PANEL DISCUSSION

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Q & A

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