Fred Hutch
Cancer Center

Acute Lymphoblastic Leukemia in Adults

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Comprehensive Hematology & Oncology Review
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UW Medicine

ALL in Adults

Discuss common presenting features and complications of ALL in adults

Review treatment options for newly-diagnosed and relapsed/refractory ALL

Summarize the role of hematopoietic cell transplantation

Case #1

Urgent Outpatient Referral

- Nurse practitioner covering local urgent care pages you about “urgent referral”
- 25-year-old woman presents with 2 weeks of progressive body aches, night sweats, and rash on legs
- Exam: pallor, no adenopathy/organomegaly, petechiae on both lower legs
- Labs: 8.2>6.9<13; WBC Diff: 10% N, 78% L (mostly “atypical”), 12% M; CMP unremarkable
- Bone marrow exam:
  - Extensive involvement by CD19+/CD20+/CD22+ B lymphoblasts
  - Cytogenetics: no growth
  - ALL FISH panel: no abnormalities

Work-Up of Suspected Acute Lymphoblastic Leukemia

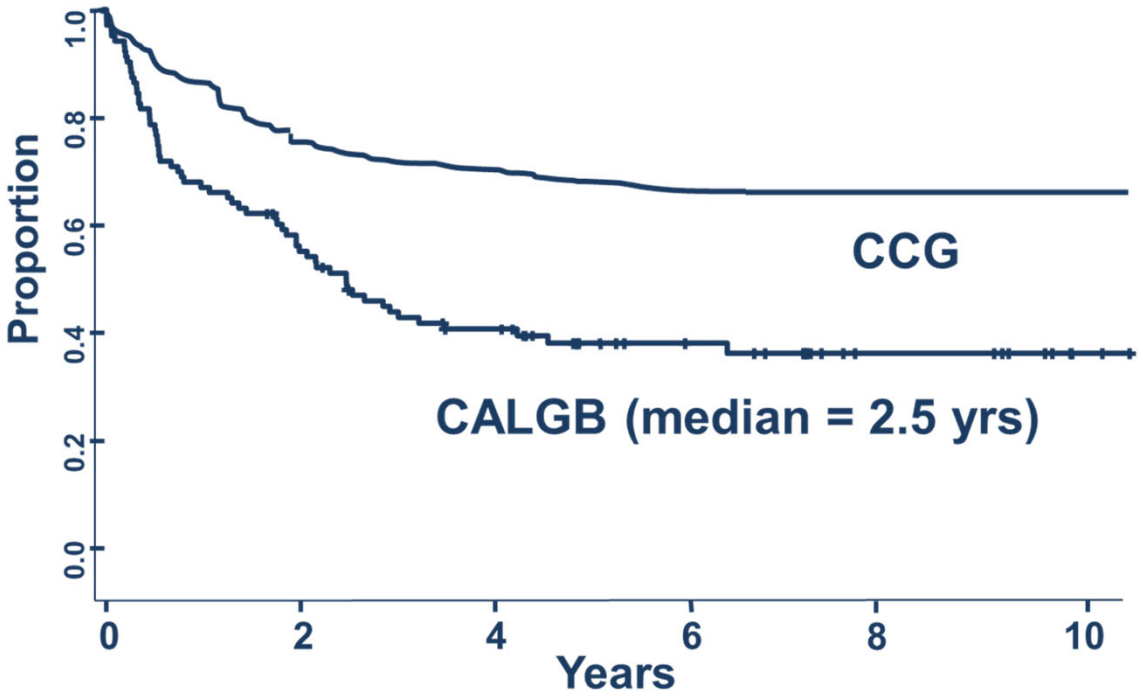
Essential Components

- Diagnostic evaluation:
  - Immunophenotype (flow cytometry)
  - Karyotype (metaphase cytogenetics and FISH)
  - Testing for subsequent MRD assessment
- Assessment of key sites of disease:
  - Testicular exam (scrotal US if abnormal and/or symptoms)
  - Lumbar puncture for cell count and evaluation for blasts (cytocentrifuge vs flow cytometry)
- Discuss options for fertility preservation

NCCN Guidelines: Acute Lymphoblastic Leukemia (v 2.2024); accessed 7/19/2024.

Pediatric-Inspired Therapy for Young Adults with Ph- ALL

EFS of Young Adults (16-21 yo) on CCG and CALGB Trials for ALL (1988-1995)



Stock, et al. *Blood*. 2008;112:1646-54.

CALGB 10403: Phase II Trial of Patients Aged 17-39 with Ph- ALL

Based on a High-Risk COG Regimen

- Investigators were oncologists trained to treat adults
- Protocol follows typical strategies used by COG
  - Strict treatment schedule
  - Less likely to make dose-modifications for toxicity/organ dysfunction

Remission Induction (Course I)
- **Allopurinol** –300 mg/day (unless allergic), to continue until peripheral blasts and extramedullary disease are reduced
- **IT-Ara-C** – Ara-C 70 mg IT on D 1.
- **Pred** –60 mg/m^2/day PO or IV in two divided doses on 01-28
- **VCR** –1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 8, 15, and 22
- **DNR** –25 mg/m^2 IV on D 1, 8, 15, and 22
- **PEG** –2500 IU/m^2 IM or IV D 4
- **IT-MTX** - 15 mg IT on D 8 & D 29 (also administered on D 15 and 22 for CNS3 patient)

Extended Remission Induction (if required)(Course IA)
- **Pred** –60 mg/m^2/day PO or IV (methylprednisolone) in two divided doses on D 1-14
- **DNR** –25 mg/m^2 IV on D 1
- **VCR** – Vincristine 1.5 mg/m2 (maximum 2 mg) IV on D 1 and 8
- **PEG** –2500 IU/m^2 IM or IV D 4

Remission Consolidation (Course II)
- **CTX** –1000 mg/m^2 IV on D 1 & 29
- **Ara-C** –75 mg/m^2 IV or SC on D 1-4, 8-11, 29-32, and 36-39
- **6-MP** –60 mg/m^2 PO on D 1-14 and 29-42
- **VCR** –1.5 mg/m^2 (maximum 2 mg) IV on D 15, 22, 43 and 50
- **PEG** –2500 IU/m^2 IM or IV on D 15 and 43
- **IT-MTX** -- 15 mg IT on D 1, 8, 15 and 22 (omit doses on D 15 & 22 for CNS3 patients)

Interim Maintenance (Course III)
- **IV-MTX** –starting dose 100 mg/m^2 IV (escalate by 50 mg/m^2 /dose on D 1, 11, 21, 31 and 41
- **PEG** –2500 IU/m^2 IM or IV on D 2 and 22
- **IT-MTX** - 15 mg IT on D 1 and 31

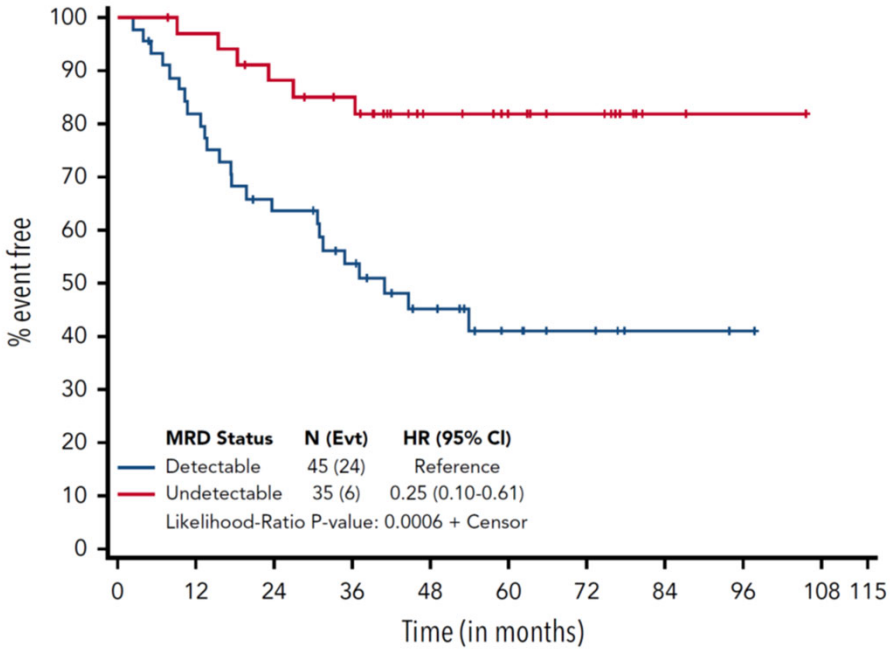
Delayed Intensification (Course IV)
- **VCR** – 1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 8, 43, and 50
- **DEX** – 10 mg/m^2 PO (or IV) divided BID on D 1-7 and 15-21
- **PEG** – 2500 IU/m^2 IM or IV D 4 (OR D 5 OR D 6) and D 43
- **CTX** – 1000 mg/m^2 IV on D 29
- **Ara-C** – 75 mg/m^2 IV or SC on D 29-32 and 36-39
- **6-TG** – 60 mg/m^2/day PO on D 29-42
- **IT-MTX** --15 mg IT on D 1, 29, & 36

Maintenance (Course V)*
- **VCR**–1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 29, and 57
- **DEX**– 6 mg/m^2/day PO (or IV) in 2 divided doses every 4 weeks on D 1-5, 29-33, and 57-61
- **6-MP**– 75mg/m^2/day PO on D 1-84
- **IT-MTX** -- 15 mg IT on D 1 (also is given on D 29 of the first 4 courses of maintenance)
- **PO-MTX** – 20 mg/m^2 PO weekly on D 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (held on D 29 of the first 4 courses of maintenance when IT-MTX is given)

Stock, et al. *Blood.* 2019;133:1548-59.

EFS by MRD Status on C10403

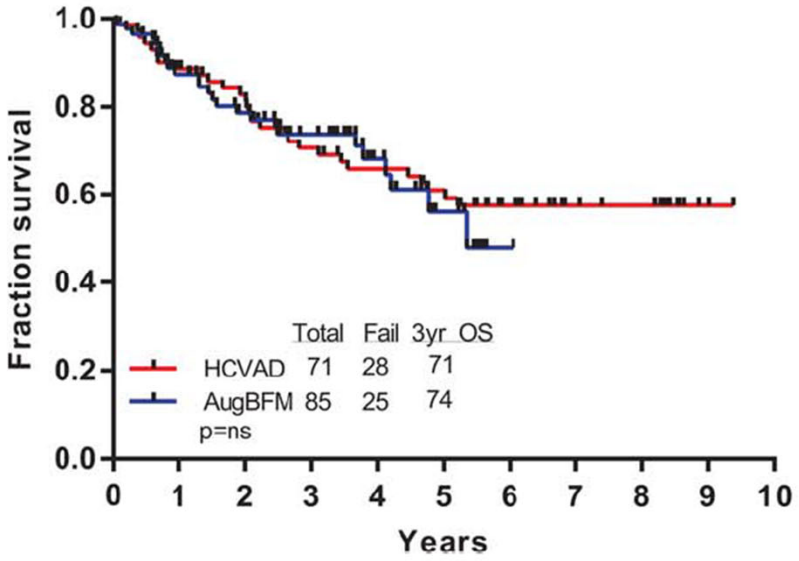
Multiparameter Flow Cytometry on End-of-Induction Bone Marrow Exam

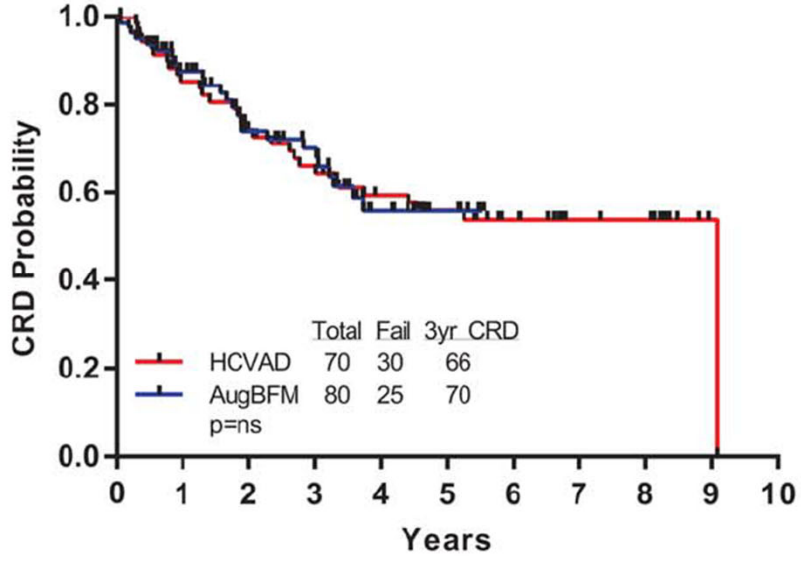


- Among those who achieved remission
  - Only 20 (8%) underwent HCT in CR1
  - Reserve HCT for MRD+?
- Factors associated with worse outcome:
  - Increased BMI
  - Ph-like

Stock, et al. *Blood.* 2019;133:1548-59.

HyperCVAD vs Pediatric-Inspired Regimen at MDACC



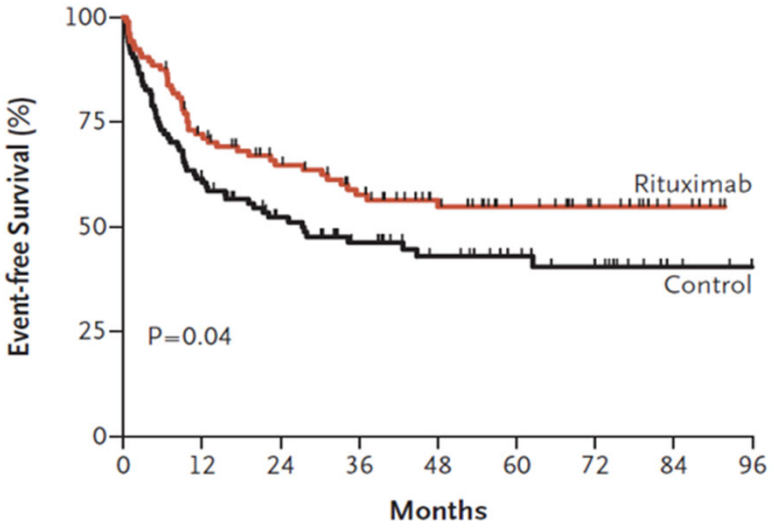


- "AugBFM": nearly identical to C10403
- Notable difference: rituximab only added to hyperCVAD

Rytting, et al. *Cancer.* 2014;120:3660-8.

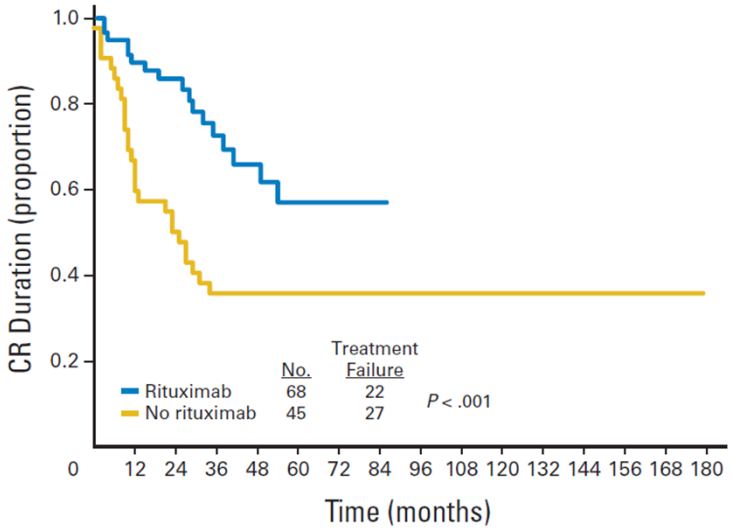
Rituximab for CD20+ Ph- B-Cell ALL

RCT with Pediatric-Inspired Regimen



Maury, et al. *N Engl J Med.* 2016;375:1044-53.

HyperCVAD (*NOT* randomized)



Thomas, et al. *J Clin Oncol.* 2010;28:3880-9.

For both studies, CD20+ defined as present on ≥ 20% of blasts

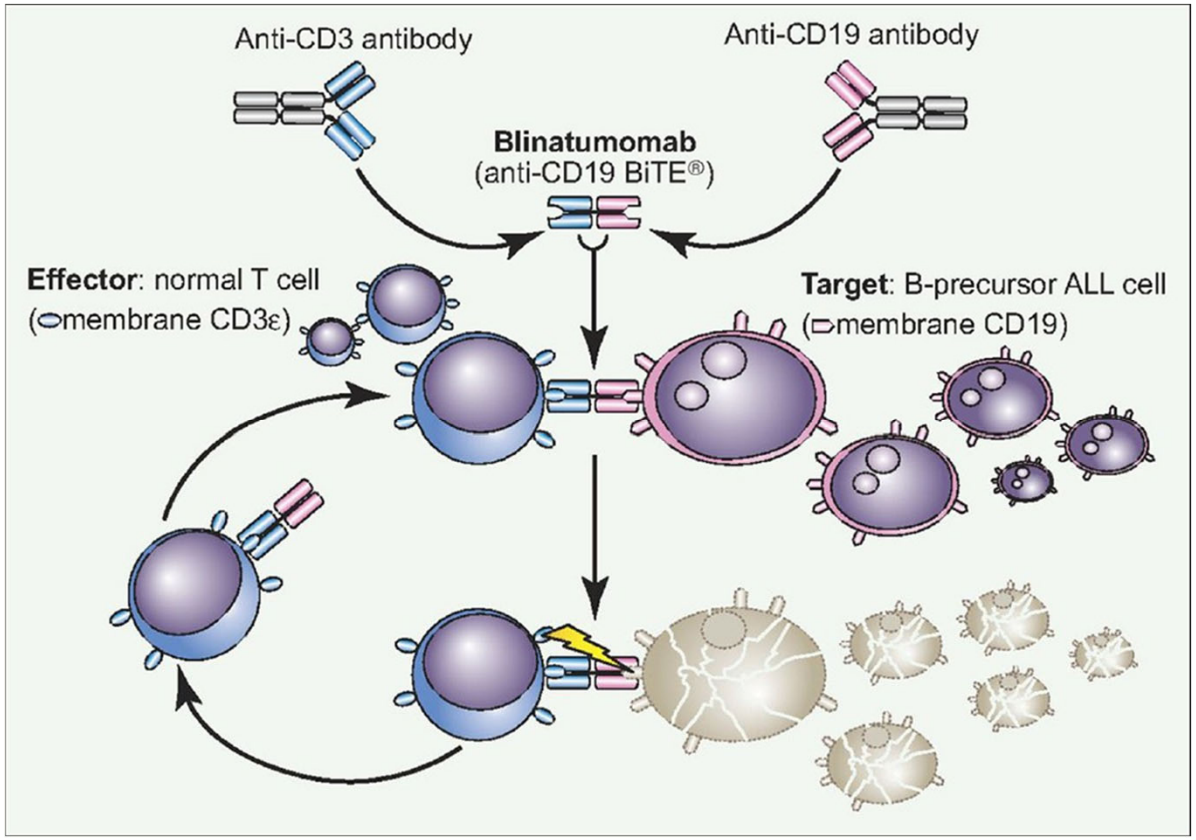
When To Use a Pediatric-Inspired Regimen

My Thoughts Based on Available Evidence and Clinical Experience

1. Ph- disease
2. Age 30+ and under (risk:benefit more challenging closer to age 40)
3. Able to receive all care in one system comfortable with this approach
4. BMI < 30

- WHY?
  – Better evidence supporting measurable residual disease (MRD)-based risk stratification

Blinatumomab (Blin) = Bispecific T-Cell Engager

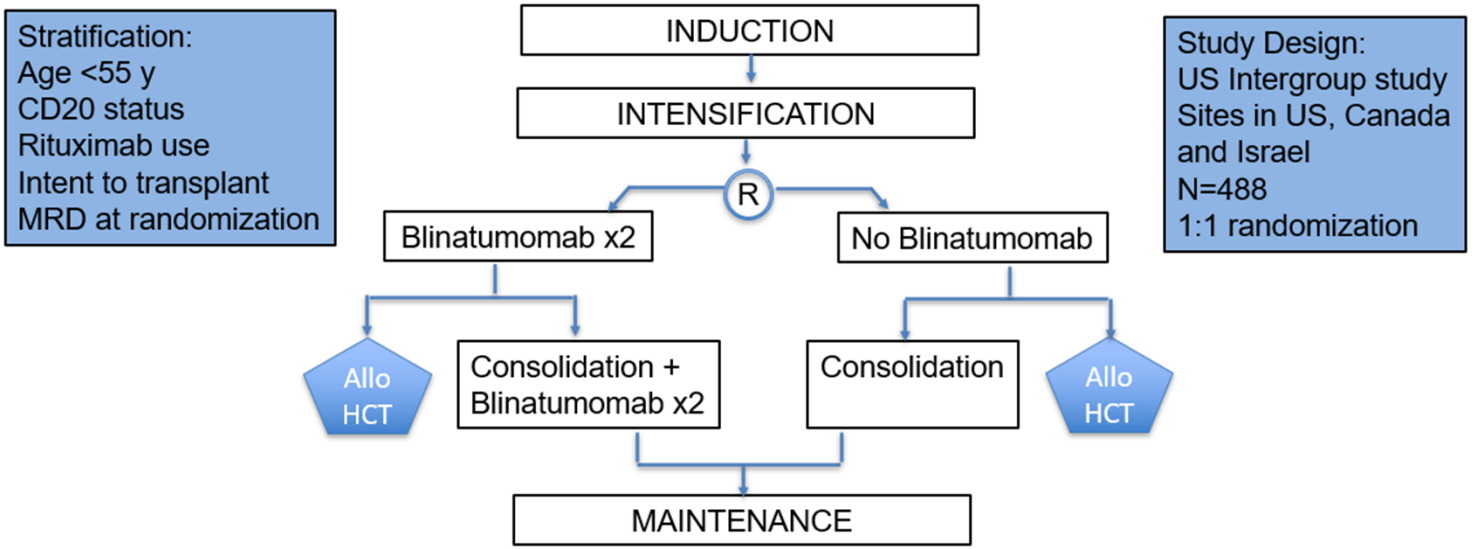


- 24-hour continuous IV infusion
- One cycle = 4 weeks on, 2 weeks off
- Distinct side-effect profile:
  - CRS
  - Neurotoxicity
- Response and toxicity rates are proportional to disease burden
  - More disease = more toxicity
  - Less disease = more response

Kapoor, et al. *Clin Cancer Invest J*. 2014;3:577-8.

Blinatumomab During Initial Treatment

Consolidation with Blin vs Chemo for Adults with Ph- B-ALL: E1910

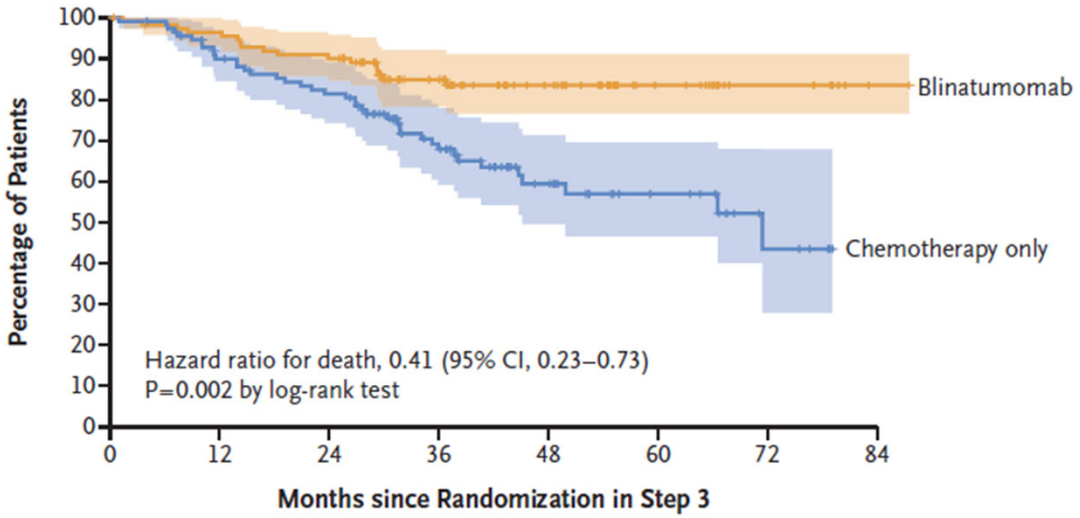


- Adds approximately 4-5 months to the duration of intense phase of treatment
- Total duration of treatment (with maintenance) is THE SAME

Litzow, et al. *N Engl J Med*. 2024;391:320-33.
Image from Liedtke, et al. *Blood*. 2024;144(Suppl 1):779.

Blinatumomab During Initial Treatment

Consolidation with Blin vs Chemo for Adults with Ph- B-ALL: E1910



No. at Risk								
Blin	112	106	99	65	41	19	8	1
Chemo Only	112	96	85	53	28	15	5	0

- REMEMBER: these are the ~30% who achieved MRD- and were randomized
- Outcomes in the “chemo” arm are relatively poor
  - Particularly for highly-selected subgroup
  - Reasons for this are not clear

Litzow, et al. *N Engl J Med*. 2024;391:320-33.

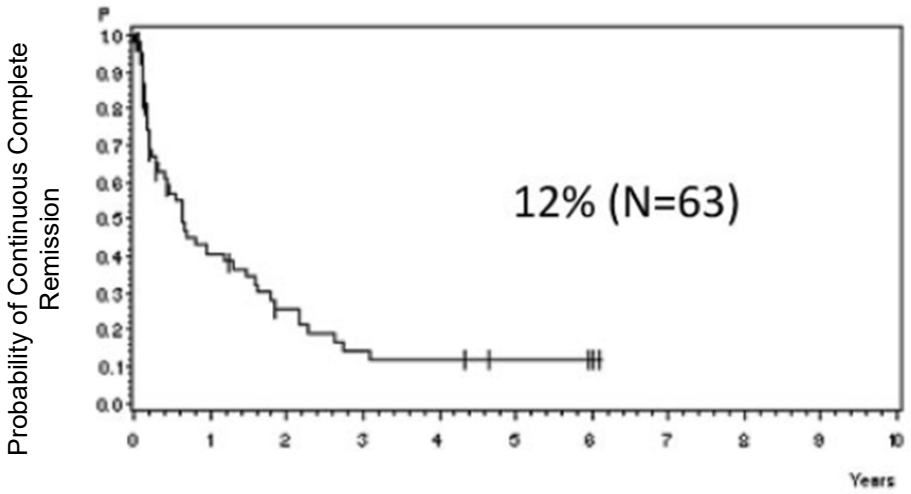
Back to Case #1

Initial Treatment & Response Assessments

- She started treatment with R-hyperCVAD
- BMA after cycle 1A:
  - Morphologic CR
  - 0.82% abnormal blasts by flow
- Continued through cycle 2B: tolerated well
- BMA: 0.16% abnormal blasts by flow (CD19+, CD22+)

Management of Chemorefractory MRD: Blinatumomab

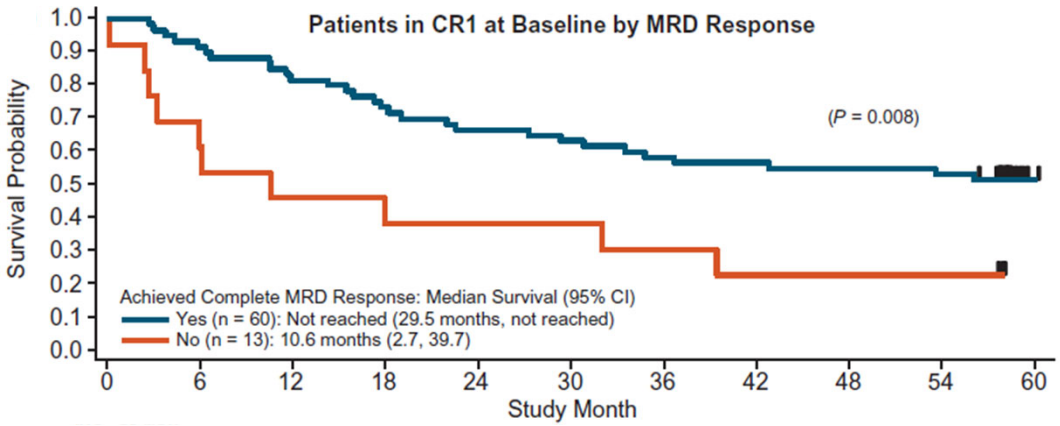
How It Started



Gökbuget, et al. *Blood.* 2012;120:1868-76.

How It's Going

FDA APPROVED



Gökbuget, *et al*. *Blood*. 2018;131:1522-31.
Gökbuget, et al. *Leuk Lymphoma.* 2020;61:2665-73.

- 78% achieve complete MRD response
- CRS and severe neurotoxicity are uncommon (~10%)
- If no HCT after complete MRD response to blin, 30% alive and in remission (median f/u 5 years)

Case #1

Conclusions

- Starts blinatumomab
  - Mild headache and fatigue
  - Feels “way better than during chemo”
- BMA after first cycle: no residual disease
- Receives a second cycle, also goes smoothly
- Undergoes allogeneic HCT from her HLA-identical sister
- Remains in remission with no GVHD ~2 years later

Case #1: Young Adult with Ph- B-ALL

My Opinions

- No “optimal” front-line regimen
  - Offer pediatric-inspired regimen if feasible
  - If not, hyperCVAD is reasonable alternative
- Add rituximab if CD20+
- Important to test for MRD after induction and (if +) consolidation
- Blinatumomab now approved for MRD- and MRD+ B-ALL
  - Quality of evidence is stronger for MRD-
  - Likely will never be a randomized trial for MRD+
- If MRD-, particularly early, generally defer HCT…but that means ~6 months of intense chemo and ~2 years of maintenance
  - One exception: *KMT2A*-rearrangement [e.g., t(4;11)]

Case #2

Middle-Aged Adult with Significant Social Issues

- 45 yom with PMH of alcohol use disorder
  - Previous admissions for withdrawal seizures
  - Currently binge drinks: 1 pint of vodka and several beers every few days
- Presented to local ED with worsening fatigue and bone pain
- CBC: 35.3>7.2<89; WBC diff: 93% blasts
- Additional work-up on peripheral blood:
  - PB flow cytometry: B lymphoblastic leukemia/lymphoma
  - Cytogenetics/FISH: t(9;22) and del 9p
  - *BCR::ABL1* RT-PCR: p190 positive at 87%
- Left AMA due to intense anxiety only to return few days later → transferred to our center

Ph+ ALL in Adults in 2024

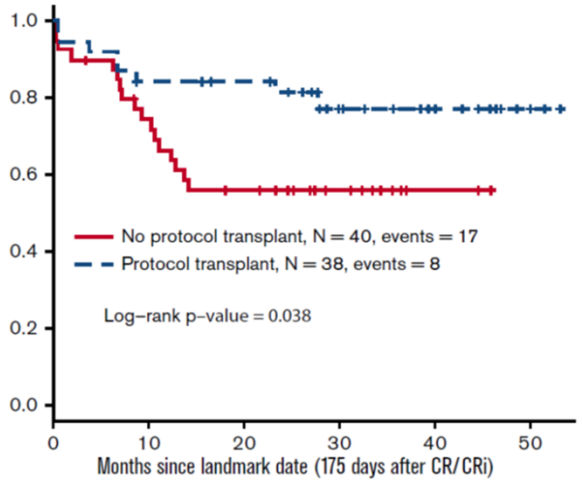
Arguably the Most Challenging Area in this Disease

- Several different strategies being explored
- One common theme: TKI + [something]
- After this, it gets **A LOT** more complicated

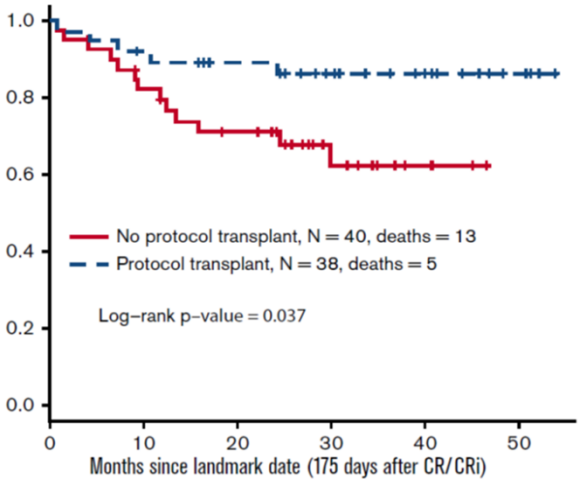
SWOG 0805: Phase II Study of HyperCVAD + Dasatinib

Traditional and Intense Approach that Only Applies to Selected Individuals

Relapse-Free Survival



Overall Survival

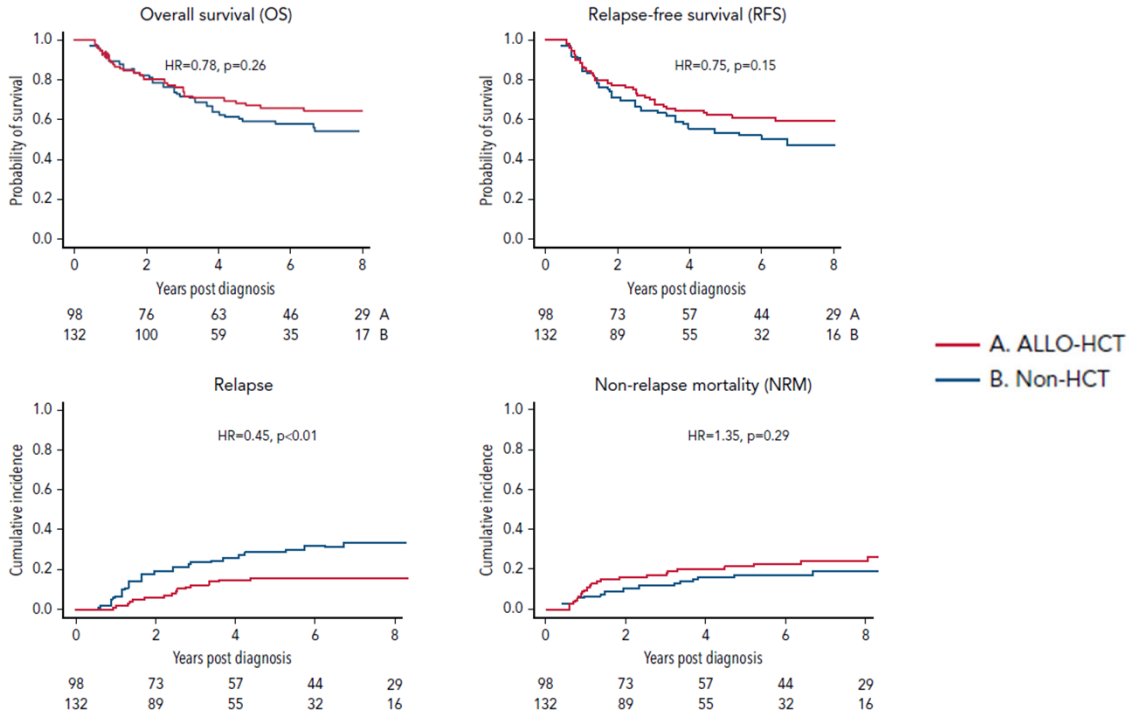


- All patients with matched donor were “encouraged” to undergo allogeneic HCT followed by dasatinib maintenance
- If no HCT, dasatinib-based maintenance therapy

Ravandi, *et al*. *Blood Advances*. 2016;1:250-9.

Complete Molecular Response with HyperCVAD + TKI

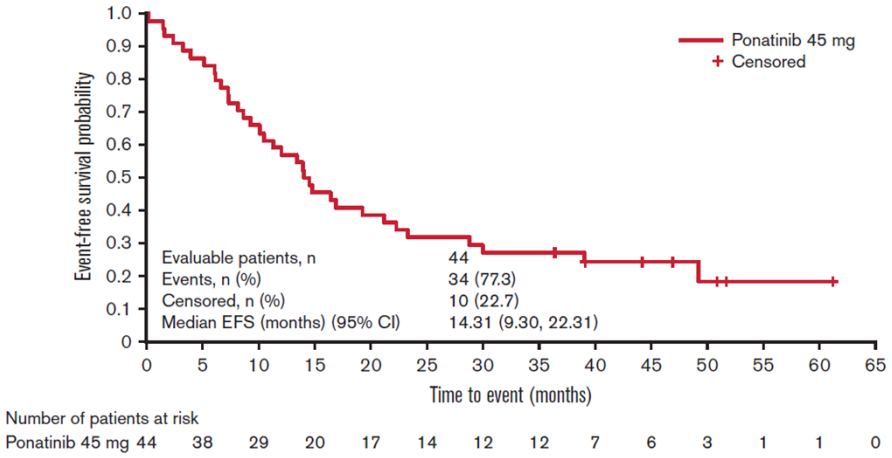
If Reached by Day 90, Benefit of HCT is Unclear



Ghobadi, *et al*. *Blood*. 2022;140:2101-12.

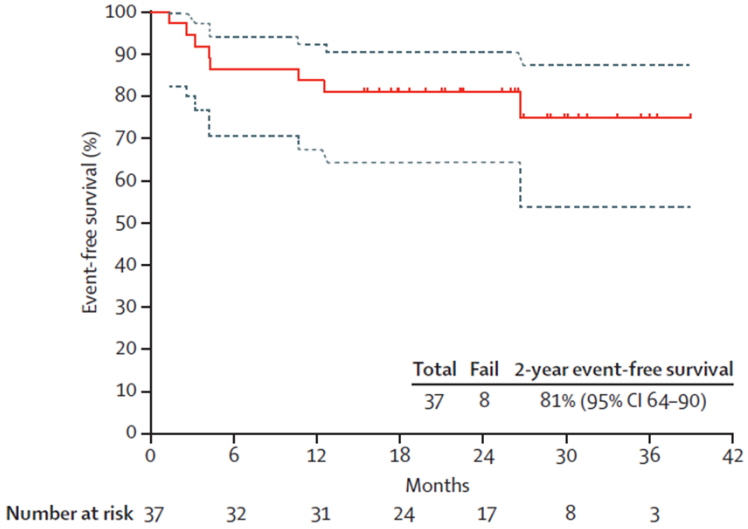
Ponatinib as Part of Front-Line Combinations

GIMEMA LAL 1811: Ponatinib + Prednisone



Martinelli, et al. *Blood Adv*. 2022;6:1742-53.

MDACC: HyperCVAD + Ponatinib



Jabbour, et al. *Lancet Oncol.* 2015;16:1547-55.

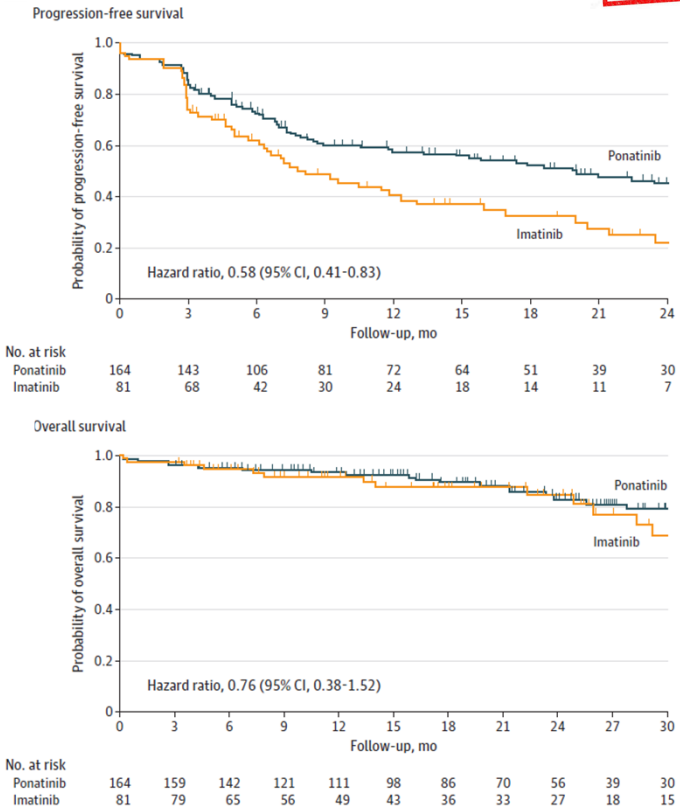
Median 80-month follow-up: 6-year OS = 75%

Kantarjian, et al. *Am J Hematol.* 2023;98:493-501.

PhALLCON: Ponatinib Superior to Imatinib in RCT

TKI + Reduced-Intensity Chemo Modeled after EWALL

- Randomized 2:1 so more received ponatinib
- Primary endpoint: MRD-negative CR after induction
  - *BCR::ABL1* RT-PCR ≤ 0.01% (MR4)
  - Morphologic CR for ≥ 4 weeks
- Used "response-adapted dosing" of ponatinib:
  - Start at 30 mg daily
  - If MRD- CR achieved, drop to 15 mg daily
- Response rates significantly favored ponatinib
  - MRD- CR after induction: 34.4% vs 16.7% (p = 0.002)
  - MRD- after induction: 43% vs 22.1% (p = 0.002)
- Survival analyses limited (median f/u = 20.1 mo)
- AE rates were comparable, including vascular events
- ISSUE: Would ***dasatinib*** have been a better control?

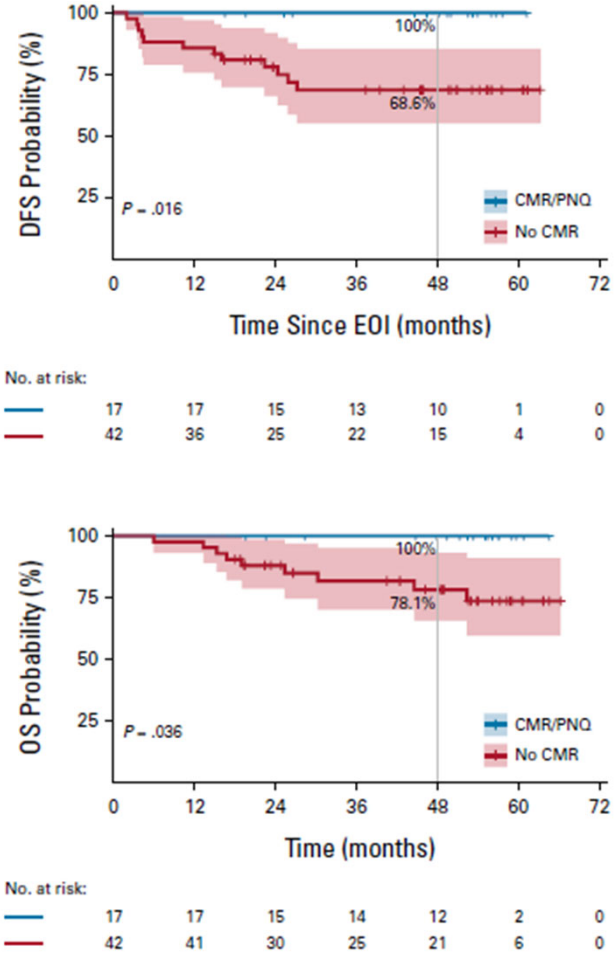


Jabbour, et al. *JAMA*. 2024;331:1814-23.

Blinatumomab During Initial Treatment

Following Dasatinib and Prednisone for Ph+ ALL: D-ALBA

- Enrolled 63 pts (median age = 54 yrs)
- Treatment:
  - Steroids Day -7 to Day 24, then tapered
  - Dasatinib 140 mg daily to Day 84
  - Blinatumomab x 2-4 cycles thereafter
  - IT chemotherapy x 12 doses
- Complete molecular response (CMR) rates are not very high:
  - At Day 85: 6/59 (10%)
  - After 1st blin cycle: 19/55 (35%)
- DFS only 46% for those with *IKZF1*^{plus} (n = 11)
- Median f/u: 53 months

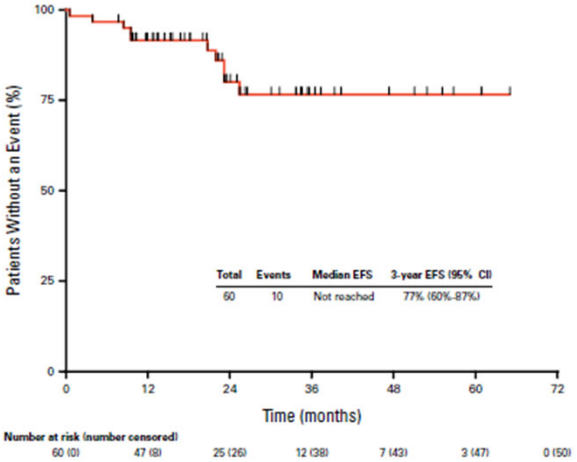


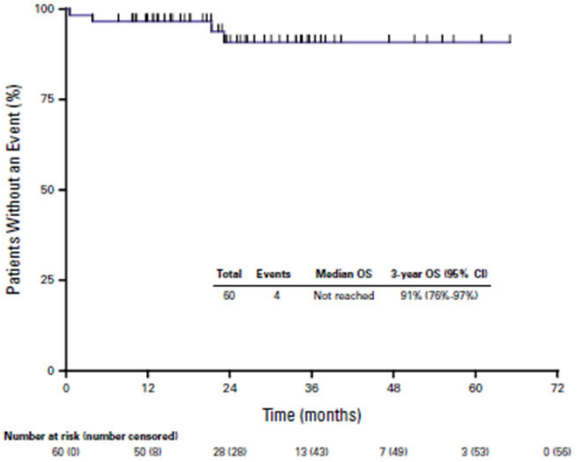
Foà, et al. *N Engl J Med*. 2020;383:1613-23.
Foà, et al. *J Clin Oncol*. 2024;42:881-5.

Blinatumomab During Initial Treatment

Combined with Ponatinib for Ph+ ALL: MDACC

- Treated 60 newly-diagnosed pts (median age = 55 yrs)
  - 21 (35%) were in CR at enrollment
  - 6 already in CMR
- Treatment:
  - Blinatumomab x 5 cycles
  - Ponatinib 30 mg starting with cycle 1, then 15 mg at CMR
- CMR rates:
  - After 1 cycle: 36/54 (67%)
  - At any time: 45/54 (83%)
- Only 2 pts underwent allo HCT in first remission
- 7 relapses, 4 of which were isolated CNS
- Median f/u: **<u>24 months</u>**





Jabbour & Short, et al. *Lancet Haematol*. 2023;10:e24-34.
Kantarjian, et al. *J Clin Oncol*. 2024;42:4246-51.

Back to Case #2

Multiple Appealing Options Colored by Social Context

- Went with HyperCVAD + Ponatinib
  - Unable to obtain ponatinib for cycle 1A
  - Received dasatinib instead
- Response assessments:
  - BMA after cycle 1A: 0.15% abnormal blasts by flow; *BCR::ABL1* p190 RT-PCR 0.05%
  - BMA after cycle 2B (approximately 90 days): no detectable disease by flow or *BCR::ABL1* p190 RT-PCR
- HCT deferred while in CR1
- Transitioned to maintenance after finishing cycle 3B (complications related to alcohol use):
  - Ponatinib 15 mg daily
  - Vincristine 2 mg IV Q 4 weeks
  - Prednisone 60 mg/m^2 PO Days 1-5 Q 4 weeks

Case #2: Middle-Aged Adult with Ph+ ALL

My Opinions

- NOT typically using rituximab
- HyperCVAD + ponatinib is preferred as long as:
  - Fit for intense therapy
  - Adequate financial and social support
- Switch to blin for persistent MRD after ~3 months
- Recommend HCT if not MRD- within 3 months OR not treated with ponatinib
- Reserve dasatinib + prednisone induction for unfit or limited support → blin consolidation per D-ALBA
- Impressed by ponatinib + blin, but follow-up is too short

Case #3

Middle-Aged Adult with No Significant Comorbidities

- 44 yom with no significant PMH
- Several months of progressive fatigue → fevers and night sweats → blurry vision
- Ophthalmologist noted bilateral retinal hemorrhages
- Sent to Urgent Care for evaluation
- CBC: 96>6<36; WBC diff: 98% blasts → → admitted for expedited work-up

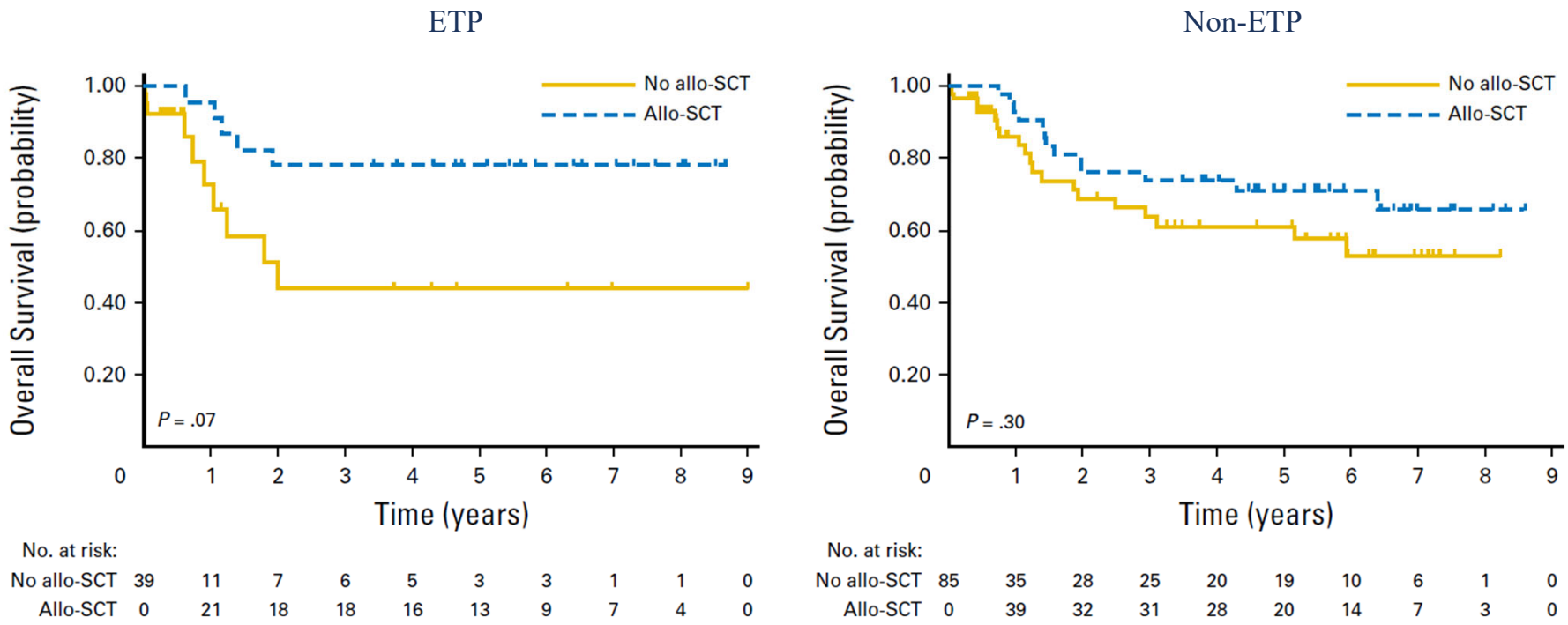
Case #3 (Continued)

Middle-Aged Adult with No Significant Comorbidities

- Started PO hydroxyurea
- CT C/A/P: scattered mild adenopathy (largest < 2 cm)
- PB flow cytometry: T- ALL, early thymic precursor (ETP)-subtype
- Cytogenetics/FISH: gain of material on 1q, otherwise normal
- Started treatment with hyperCVAD:
  - After cycle 1A: 9% blasts by morphology, 20% by flow
  - After cycle 1B: morphologic CR, 0.41% blasts by flow
  - After cycle 2B: no residual disease by morph or flow

ETP: Subgroup of T-ALL with Worse Prognosis

Possible Benefit with Allo HCT in CR1



Bond, *et al*. *J Clin Oncol*. 2017;35:2683-91.

Back to Case #3

Hope for Long-Term Remission for High-Risk Disease

- Underwent myeloablative HCT from 10/10 MUD in MRD- CR
- Relatively uncomplicated course initially:
  - Mild skin & gut acute GVHD
  - Tapered off immunosuppression ~ 9 months post-HCT
- Developed new thrombocytopenia 15 months post-HCT
- Bone marrow exam: Relapsed ETP-ALL
- 1 cycle of nelarabine: no response
- 1 cycle of mini-hyperCVD + venetoclax: no response
- Transitioned to hospice

Case #3: Middle-Aged Adult with T-ALL

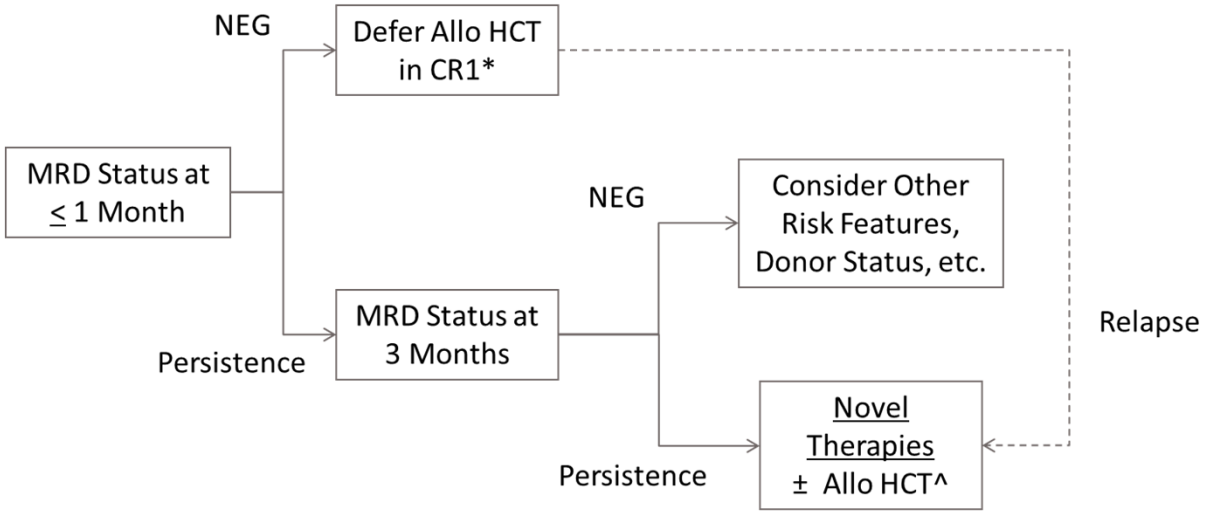
My Thoughts

- Similar to B-ALL, several reasonable options for front-line treatment
  - Prefer pediatric-inspired approach (e.g., C10403) when feasible
  - Not including nelarabine, except for those at high risk of CNS relapse (e.g., CSF+ by flow[1])
  - Defer HCT in MRD- CR1 (***except*** for ETP-ALL)
- Unlike B-ALL, salvage options are limited and poor
  - Among the greatest areas of unmet need in heme malignancies
  - Refer for clinical trials when possible

[1]Garcia, et al. *Cancer.* 2022;128:1411-7.

MRD and Transplant for non-ETP, *KMT2A*-wt ALL

The Cassaday Approach



* Assuming (1) reliable MRD testing and (2) patients can complete a *relatively* full course of treatment and (3) remain MRD negative

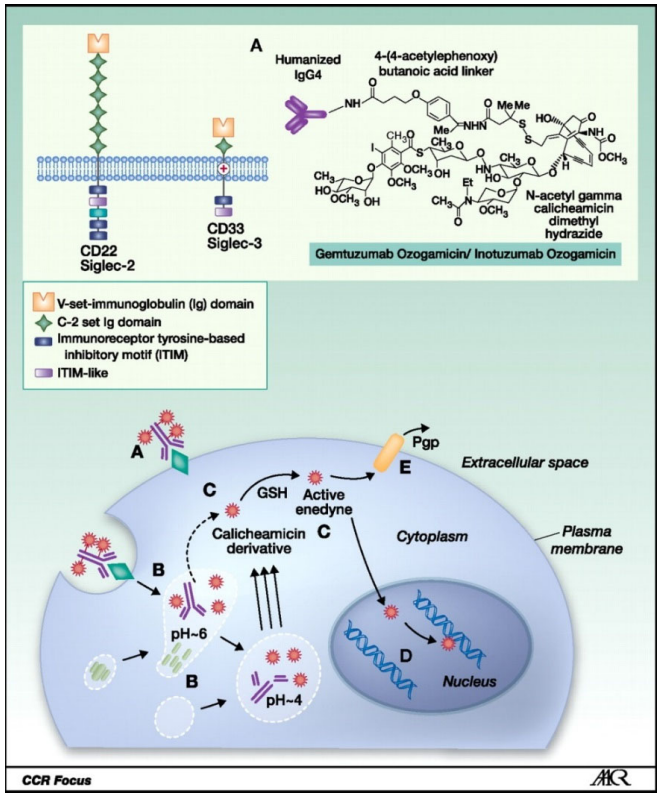
^ Assuming patients are eligible for and interested in HCT

Case #4

Older Adult Living in Remote Area

- 67 yof with a h/o DM2
- Presents to local ED with progressive dyspnea
- CBC: 1.8>6.3<98; WBC diff: 20% blasts
- Transferred to nearest tertiary center ~2 hours away
- BMA: CD20+ B lymphoblastic lymphoma/leukemia
- Cytogenetics/FISH: *IGH* rearrangement, no t(9;22)
- Limited resources for travel or relocation

Inotuzumab Ozogamicin (InO): Anti-CD22 Antibody-Drug Conjugate

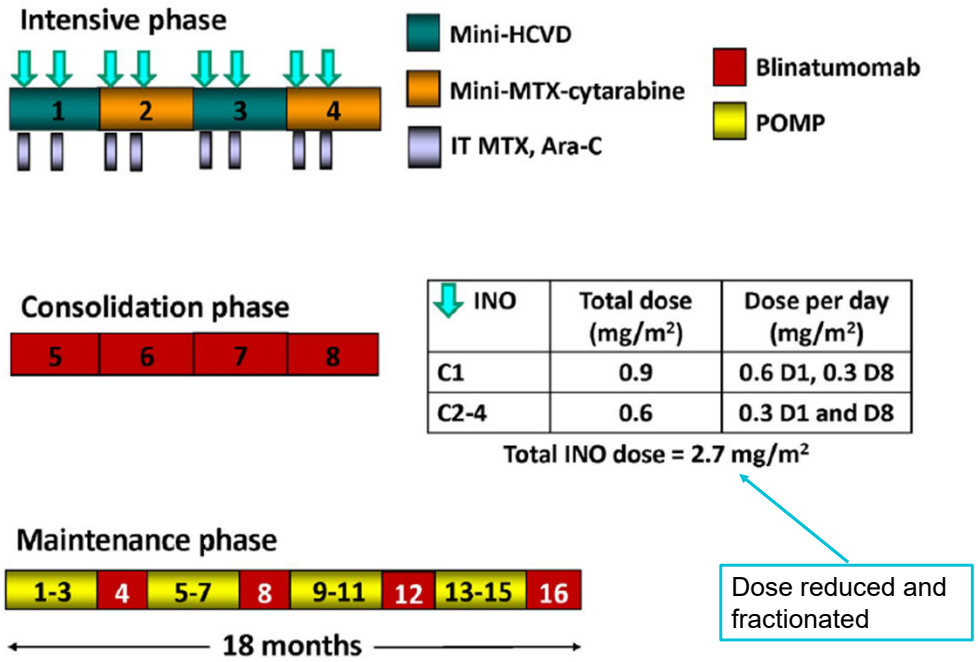


- Similar mechanism of action as gemtuzumab ozogamicin (anti-CD33)
- Antibody-antigen complex is rapidly internalized upon binding to CD22
- Cytotoxic agent calicheamicin is released inside the cell
- Calicheamicin binds to DNA, inducing double-stranded DNA breaks
- DNA breaks lead to apoptosis

Ricart, et al. *Clin Cancer Res.* 2011;17:6417-27.

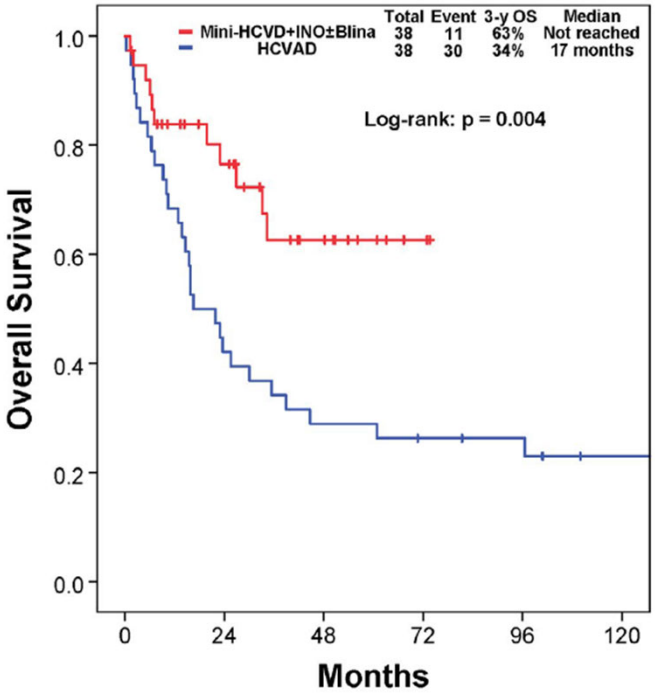
InO and Blinatumomab During Initial Treatment

Propensity Score Analysis: Standard HyperCVAD vs Mini-HyperCVD + InO **± Blin** for Older Adults with Ph- B-ALL at MDACC



INO	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2-4	0.6	0.3 D1 and D8

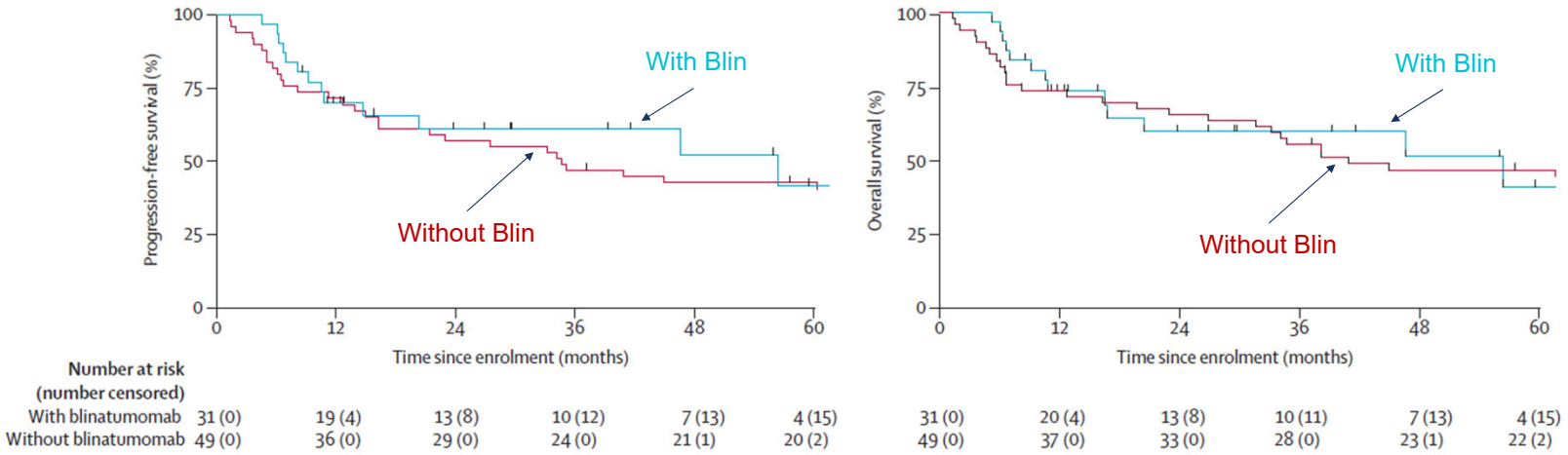
Total INO dose = 2.7 mg/m²



Jabbour, et al. *Cancer*. 2019;125:2579-86.

Mini-HyperCVD + InO ± Blinatumomab in Older Adults

Long-Term Follow-Up (Median = 92.8 months) of Study at MDACC



Number at risk (number censored)						
With blinatumomab	31 (0)	19 (4)	13 (8)	10 (12)	7 (13)	4 (15)
Without blinatumomab	49 (0)	36 (0)	29 (0)	24 (0)	21 (1)	20 (2)

	31 (0)	20 (4)	13 (8)	10 (11)	7 (13)	4 (15)
	49 (0)	37 (0)	33 (0)	28 (0)	23 (1)	22 (2)

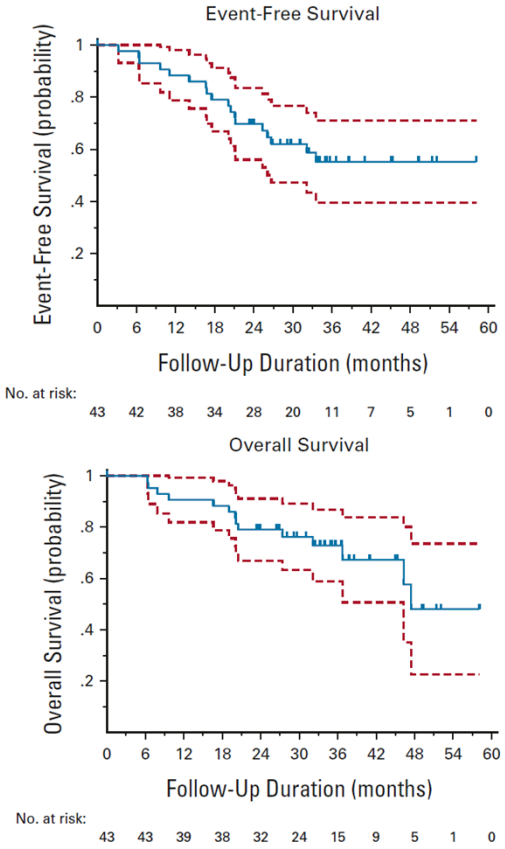
- 12 (15%) of 79 responders relapsed, 5 were extramedullary (all included CNS)
- 35 (44% of total population) died in remission: 9 due to 2^{o} MDS/AML, 8 infections, 4 SOS without HCT, etc.

Modified from Jabbour, et al. *Lancet Haematol*. 2023;10:e433-44.

Single-Agent InO followed by Chemotherapy for Older Adults

GMALL INITIAL-1 Trial: Results

- 45 patients enrolled, with 43 analyzed
- Median age 64 years (range: 56-80)
- Response assessments
  - All 43 (100%) achieved CR/CRi
  - 30/42 (71%) MRD- by RT-PCR by end of 3rd Induction cycle
- Key safety/toxicity data
  - No patients died in the first 6 months
  - Grade 3+ liver enzyme elevation in ~15%
  - One case of SOS after 2nd induction cycle



1-year EFS = 88%
3-year EFS = 55%

1-year OS = 91%
3-year OS = 73%

Stelljes, et al. *J Clin Oncol*. 2024;42:273-82.

Back to Case #4

Older Adult Living in Remote Area

- Enrolled in a phase II study[1]
- Received dose-adjusted EPOCH-R
- MRD- after 1 cycle
- Completed 6 cycles
  - Able to stay at home between hospital stays
  - Lab monitoring occurred at local clinic
- Received 2 years of POMP
- Still in remission 4 years later (over 6 years from diagnosis)

[1]Cassaday, et al. *Leuk Lymphoma*. 2023;927-37.

Case #4: Older Adult with Ph- B-ALL

My Opinions

- No accepted standard
- Treatment must be individualized
- Standard hyperCVAD can be challenging
- Mini-hyperCVD + InO ± Blin yields provocative results
  - Pretty complicated and toxic
  - Difficult in limited-resource settings
  - What will work when this fails?
- Offer clinical trials when available

Case #1 Revisited

Post-Transplant Relapse

- Now 28 yo and 2+ years out from matched sib myeloablative HCT
  - Ph- B-ALL with persistent MRD after hyperCVAD
  - MRD- after blinatumomab
- Recently noticed body aches like those at presentation
- CBC: 2.4>12<201; WBC diff: ANC 0.8, no blasts; LDH elevated
- Bone marrow exam: hypercellular marrow (90%), 78% blasts by morphology, 82% by flow (CD19+, CD22+)
- ECOG 0-1, wants to be aggressive

Optimal Use of Immunotherapy Agents for Relapsed/Refractory B-ALL

Opinions Based on Available Evidence and Practical Experience

Agent	Favorable Circumstance
Blinatumomab (CD3-CD19 Bispecific T-cell Engager)	Persistent MRD
	Low-burden relapse (< 50% blasts) or able to receive cytoreduction
	Uncertain candidacy for HCT
	Logistically feasible (IV access, home infusion & caregiver support)
Inotuzumab Ozogamicin (CD22 Antibody-Drug Conjugate)	High-burden relapse (≥ 50% blasts)
	Good candidate for HCT
	No major risk factors for VOD/SOS (Salvage 2+, prior HCT, ≥ 55 yo, liver disease)
Brexucabtagene Autoleucel & Tisagenlecleucel (CD19 CAR-T Cells)	Adequate disease control
	Due for Salvage 2+
	Uncertain candidacy for HCT
	Logistically feasible (travel & lodging, caregiver support)

Kimble & Cassaday. *Leuk Lymphoma.* 2021;62:3333-47.

Case #1: Updated

Management of High-Burden Relapsed Ph- B-ALL

- CAR-T cells will take too long, not comfortable waiting
- Low probability of success with blinatumomab for high disease burden
- Given InO x 1 cycle → morphologic CR, 0.3% blasts by flow
- Switched to blin → MRD- after 1 cycle
- Proceeded to cycle 2
- Being considered for 2nd HCT (now from cord-blood donor)

Current Approaches to Adults with ALL

Summary

- Front-line treatment:
  - HyperCVAD remains an option across the spectrum
  - Pediatric-inspired regimens (when feasible) for young adults with Ph- ALL
  - TKI + [something] for Ph+ ALL
  - Older adults pose a unique challenge
  - HCT typically reserved for high-risk patients, defined mostly by MRD
- Relapsed/refractory disease:
  - Several options for B-ALL, but optimal sequence unknown
  - Need new approaches for T-ALL

Fred Hutch
Cancer Center

Thank you

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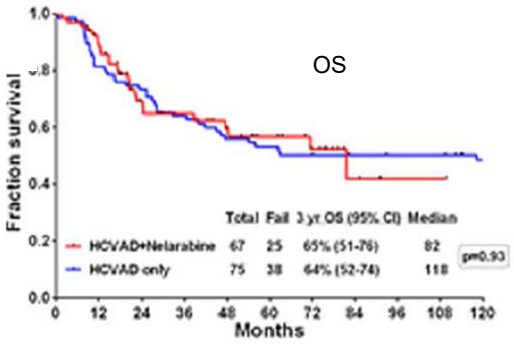
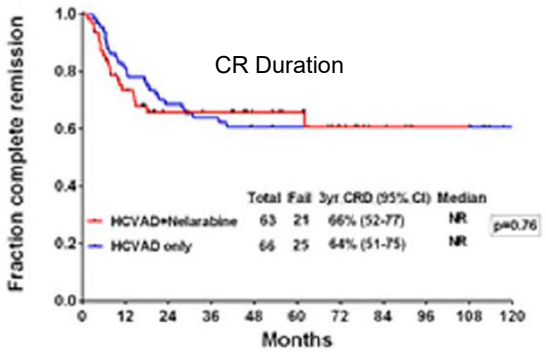
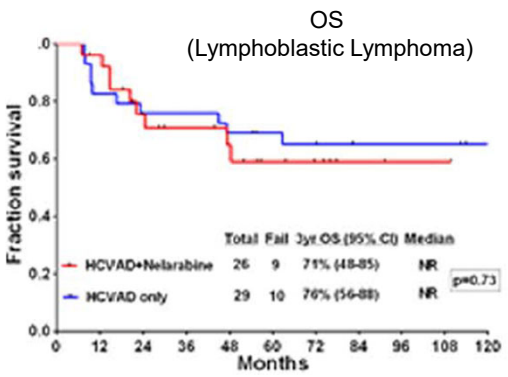
Extra Slides

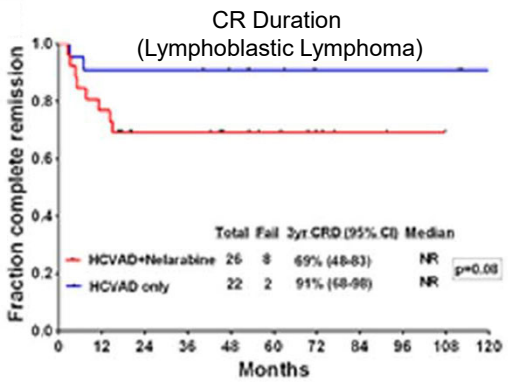
What About HyperCVAD + Nelarabine?

Phase II Study at MDACC







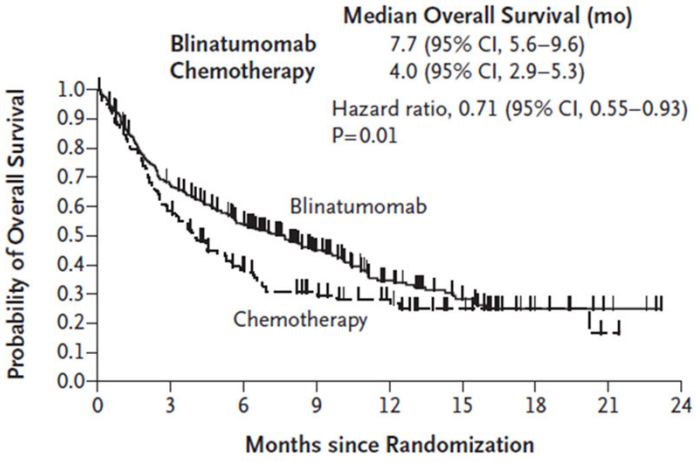


- No clear benefit from adding nelarabine[1,2]
- May reduce risk of CNS relapse from pediatric study (COG AALL0434)[3]

[1]Abaza, et al. *Am J Hematol*. 2018;93:91-9. [2]Morita, et al. *Am J Hematol*. 2021;96:589-98. [3]Dunnsmore, et al. *J Clin Oncol* 2020;38:3282-93.

Blinatumomab for Relapsed/Refractory Disease

Ph-: TOWER (RCT)

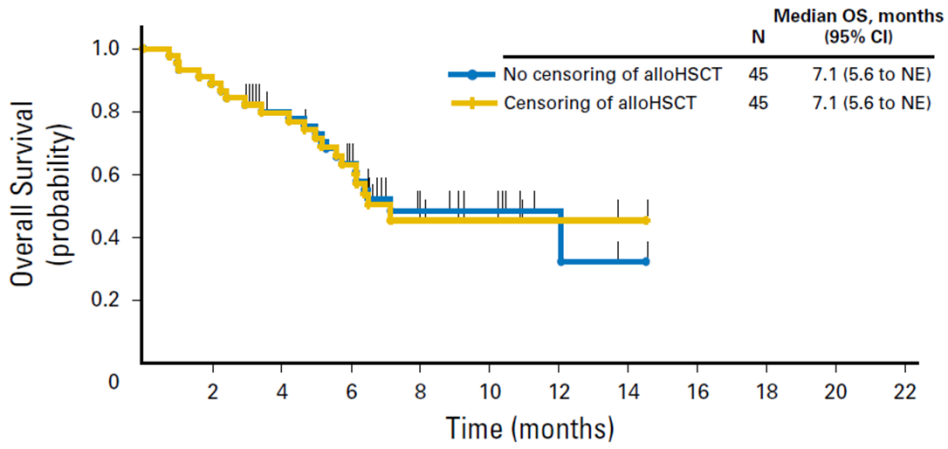


No. at Risk									
Blinatumomab	271	176	124	79	45	27	9	4	0
Chemotherapy	134	71	41	27	17	7	4	1	0

CR/CRi Rate: 44% (Blin) vs 25% (Chemo)

Kantarjian, et al. *N Engl J Med.* 2017;376:836-47.

Ph+: ALCANTARA (single-arm)



No. at risk												
No censoring of alloHSCT	45	40	34	24	11	8	3	1	0	0	0	0
Censoring of alloHSCT	45	40	30	21	8	5	2	1	0	0	0	0

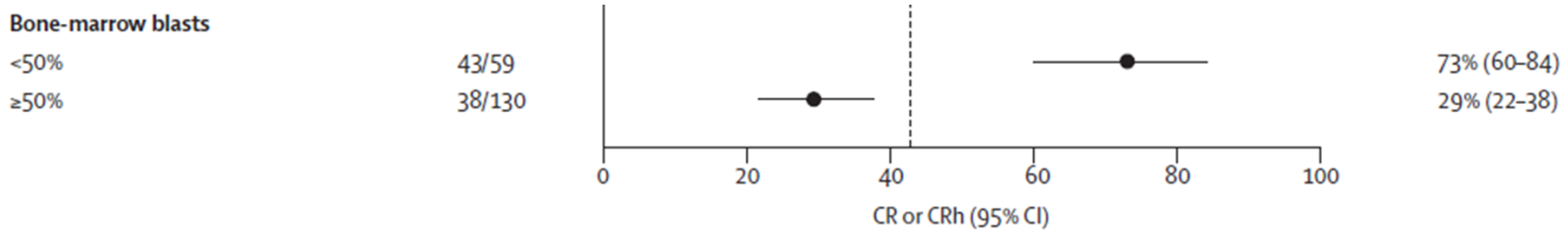
CR/CRh Rate: 36%

Martinelli, et al. *J Clin Oncol.* 2017;35:1795-802.

Important Limitation with Blinatumomab

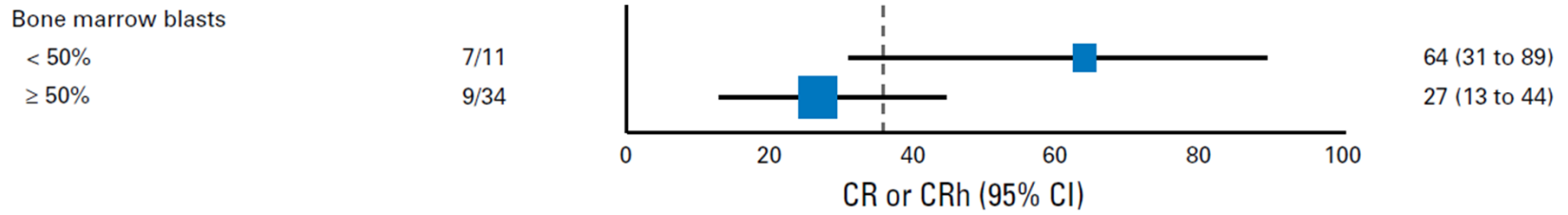
Disease Burden is Correlated with Response

Ph-, Phase II Study (Germany):



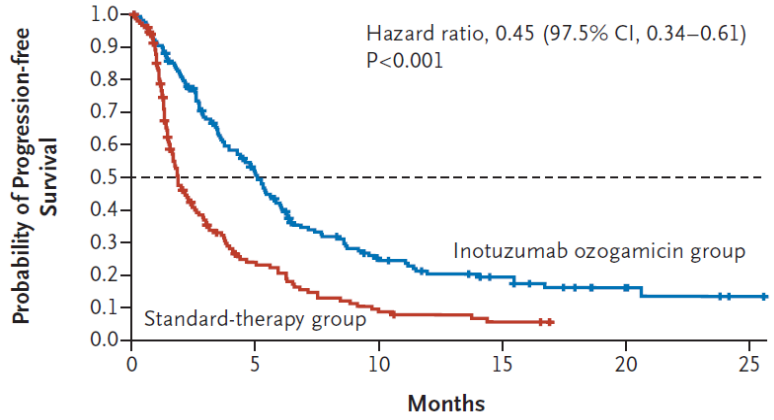
Topp, et al. *Lancet Oncol.* 2015;16:57-66.

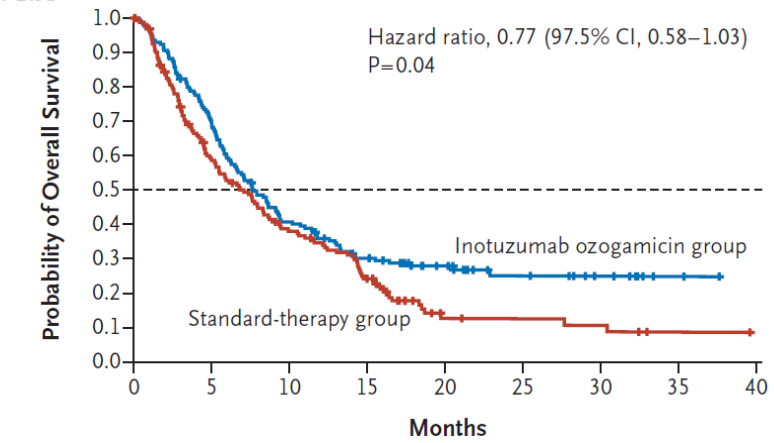
Ph+, Phase II Study (Italy):



Martinelli, et al. *J Clin Oncol.* 2017;35:1795-802.

Inotuzumab Ozogamicin for Relapsed/Refractory Disease





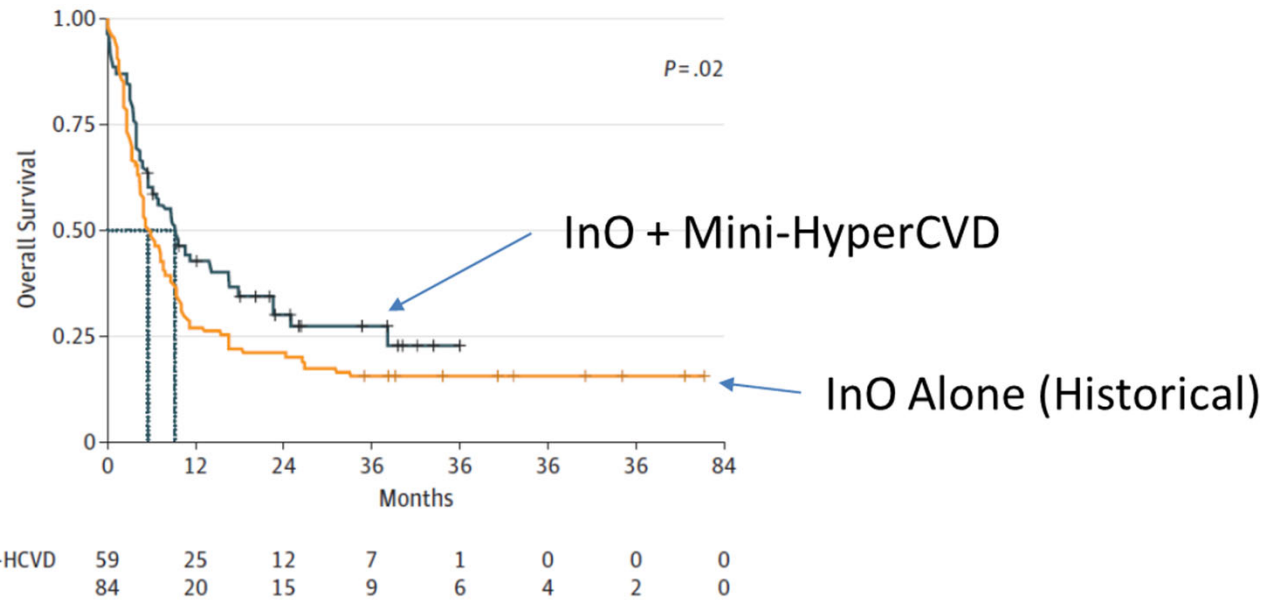
- Dosing:
  - 1-hr IV infusion
  - Days 1, 8, &15
  - Every 21 (C1) to 28 (C2+) days
- Side effects:
  - SOS/VOD
  - Elevated ALT/AST
  - Cytopenias

Kantarjian, et al. *N Engl J Med*. 2016;375:740-53.

Mini-HyperCVD + InO for Relapsed/Refractory Disease

Combined with Low-Intensity Chemotherapy and Compared to Historical Single-Agent Results

- InO dosing: Day 3 of each cycle
  - Cycle 1: 1.3 mg/m^2
  - Cycle 2+: 1 mg/m^2
- CR rate: 59% (83% of which were MRD-)
- Rate of SOS: 15% (n = 9)

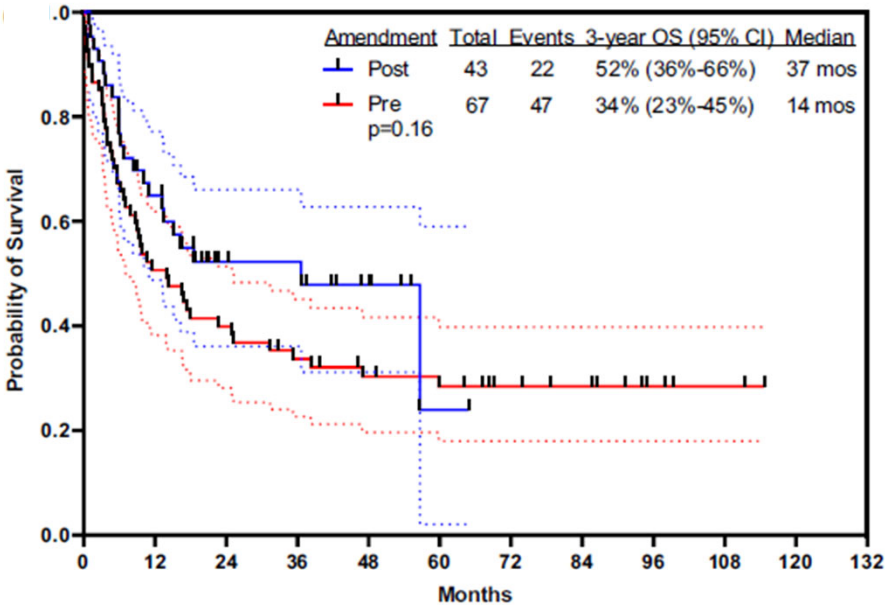


Modified from Jabbour, et al. *JAMA Oncol*. 2018;4:230-4.

Mini-HyperCVD + InO ± Blin for Relapsed/Refractory Disease

Study Amendment Modified Previous Treatment Plan

- Mini-hyperCVD limited to 4 coures
- Fractionated and reduced InO dosing:
  - 0.6 mg/m^2 on Day 2 + 0.3 mg/m^2 on Day 8 of Course 1
  - 0.3 mg/m^2 on Day 2 + 0.3 mg/m^2 on Day 8 of Courses 2-4
  - Total cumulative planned dose = 2.7 mg/m^2
- Followed by blin x 4 courses
- Maintenance: POMP for 12 weeks, then blin for 4 weeks; repeat x 3 (~1 year)
- 48% proceeded to HCT



Kantarjian, et al. *J Hematol Oncol*. 2023;16:44-55.

Phase I Study of DA-EPOCH-InO for Rel/Ref B-ALL

High Marrow and EMD Response Rates Despite Relapsed/Refractory Disease

Morphologic Responses and MRD Assessment

Method of Evaluation	Number Evaluable	Undetectable	Percentage
Morphology (CR/CRi)	19	16	**84%**
Flow cytometry	20	14	**70%**
BCR::ABL1 RT-PCR	7	3	42%
HTS	15	5	33%

EMD Responses

Method of Evaluation	Number Evaluable	Responses	Percentage
Imaging	6	5*	**83%**

Composite Overall Response Rate

Total Evaluable	Responses	Percentage^
24	20	**83%**

MRD = measurable residual disease; HTS = high-throughput sequencing (clonoSEQ)
*4 complete responses and 1 partial response
^***With 100% of screened patients enrolled and evaluable, this represents the per-protocol and intent-to-treat response rate***

Kopmar…& Cassaday. *JAMA Oncol*. 2024;10:961-5.

Important Limitation of Inotuzumab Ozogamicin

Sinusoidal Obstructive Syndrome (SOS)/Veno-Occlusive Disease (VOD)

Factors Affecting Risk of SOS/VOD:

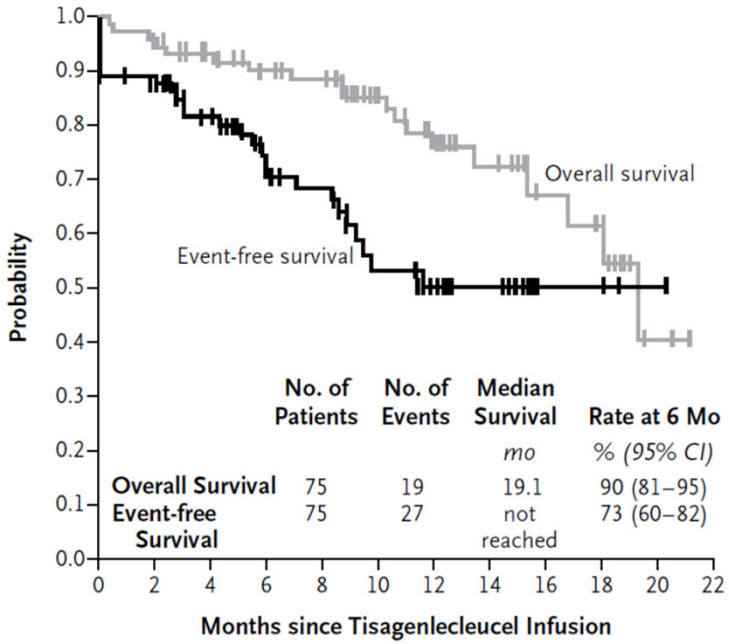
Multivariate analysis (n=62)	OR (95% CI)	P-value
Dual alkylator conditioning (dual vs single)	**8.606 (1.516–48.861)**	**0.015**
Pre-HCT bilirubin level (≥ULN vs <ULN)	**15.308 (1.950–120.206)**	**0.009**
Pre-HCT AST or ALT level (>1.5× ULN vs ≤1.5× ULN)	0.027 (<0.001–0.833)	0.039
Prior history of liver disease (yes vs no)	5.133 (0.907–29.060)	0.064

Kantarjian, et al. *Lancet Haematol.* 2017;4:e387-98.

Tisagenlecleucel in Children and Young Adults with Relapsed/Refractory Disease

Phase II ELIANA Trial

- 107 pts screened → 92 enrolled → 75 treated
  - Median age = 11 yr
  - Median prior therapies = 3 (range: 1-8)
- CR/CRi rate within 3 mo:
  - Treated: 81% (all MRD-)
  - ITT: 66% (all MRD-)
- Toxicity:
  - 77% developed CRS
  - 47% admitted to ICU
  - 13% had Grade 3 neuro events
  - 19 deaths, 4 not due to relapse

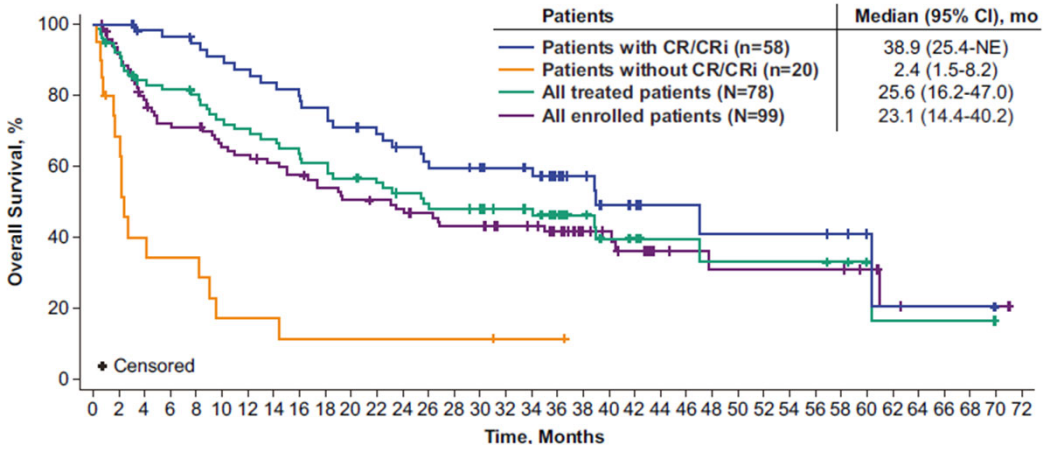


Maude, et al. *N Engl J Med*. 2018;378:439-48.

Brexucabtagene Autoleucel for Adults with Relapsed/Refractory Disease

Phase I/II ZUMA-3 Trial

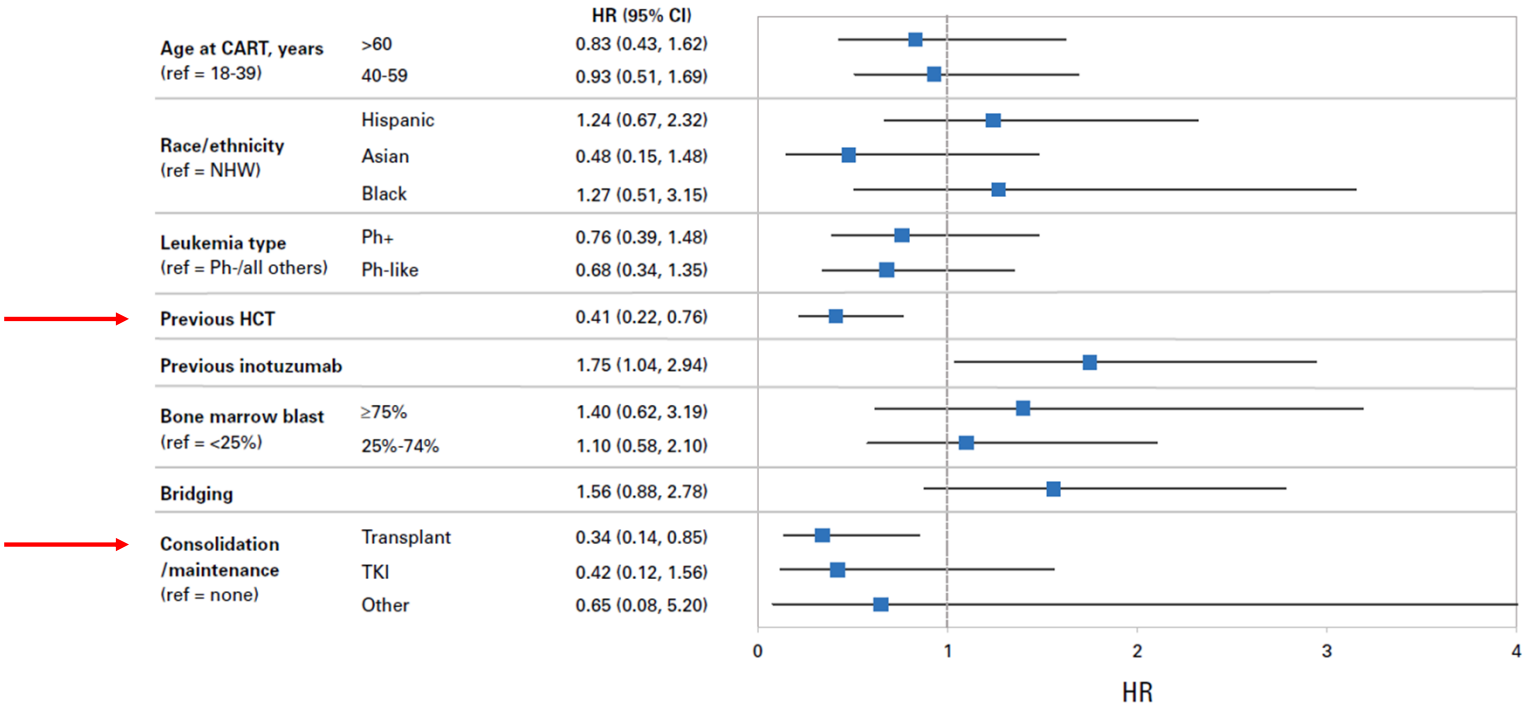
- 71 enrolled → 65 had manufactured product → 55 treated
  - Attrition rate = 23%
- Among treated patients:
  - 71% (95% CI = 57-82%) achieved remission
  - 97% of these were MRD-
- Median duration of remission (with >3 yrs f/u) = 14.6 mo
- Key toxicity events:
  - Grade 3+ CRS = 24%
  - Grade 3+ neurologic events = 25%
  - Treatment-related death = 4%



Shah, et al. *Lancet*. 2021;398:491-502.
Shah, et al. *Leukemia*. 2025;39:1058-68.

Real-World Evidence: Predictors of Outcome after Brexu-Cel

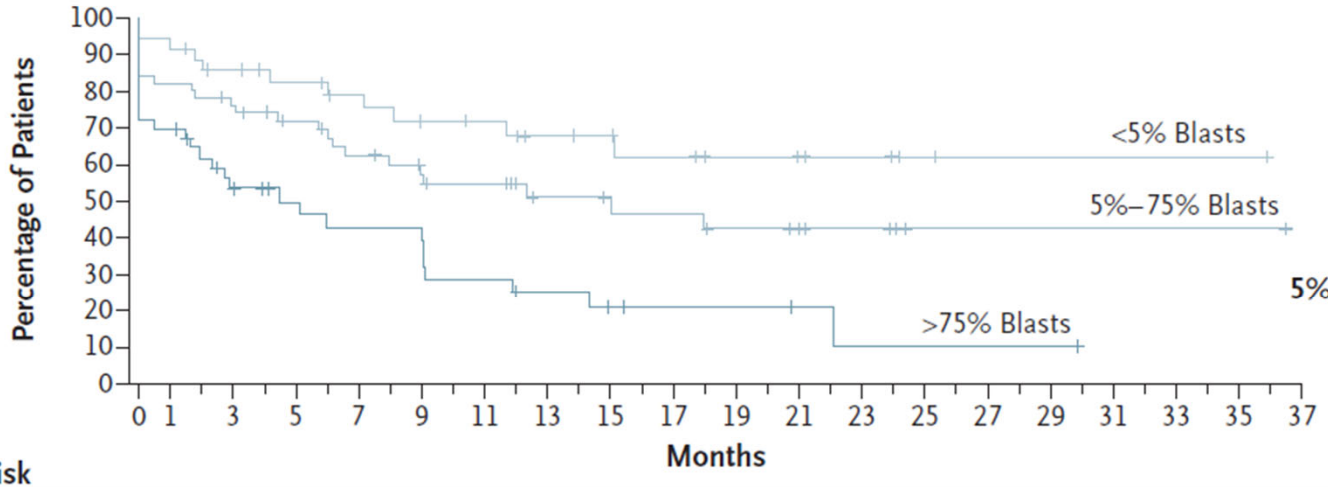
Previous HCT and Post-Remission Consolidative HCT Associated with Better PFS



Roloff, et al. *J Clin Oncol*. 2025;43:558-66.

Event-Free Survival after Obe-cel Correlated with Disease Burden

Similar Pattern Observed for Overall Survival



No. at Risk																				
<5% Blasts	36	34	28	25	22	19	18	14	13	11	9	7	6	3	1	1	1	1	1	0
5%–75% Blasts	51	42	38	31	26	22	20	13	11	11	9	6	5	1	1	1	1	1	1	0
>75% Blasts	40	28	19	14	12	12	8	6	4	3	3	2	1	1	1	1	0	0	0	0

	No. of Events	Median Event-free Survival (95% CI)
		mo
<5% Blasts	11	NE
5%–75% Blasts	24	15.0 (6.1–NE)
>75% Blasts	28	5.1 (1.6–9.0)

- Our current practice is typically to use CAR-T as consolidation following some induction/cytoreduction

Roddie, et al. *N Engl J Med*. 2024;391:2219-30.

Important Limitation of CAR-T Cells

Access

- Only available at certain centers (e.g., FACT-accredited)
- Limited bandwidth for cell collection and manufacturing
- Subspecialty expertise to handle complications
  - Critical care
  - Neurology
- Very expensive

LOTS of ongoing effort to address these complex challenges.

What About CNS Disease?

Limited Data Support the Use of These Agents, But Some Evidence is Emerging

Agent	Mechanism of Action	Evidence of CNS Activity
Blinatumomab	CD3-CD19 Bispecific T-cell Engager	**Limited**: 1 retrospective series
Inotuzumab Ozogamicin	CD22 Antibody-Drug Conjugate	**None**
Tisagenlecleucel	CD19 CAR-T Cells	**Moderate**: pooled *post hoc* analysis of prospective studies and multiple retrospective series
Brexucabtagene autoleucel	CD19 CAR-T Cells	**Limited**: extrapolated from experience with other CAR T-cell therapies*

*Evidence from ROCCA collaboration of CNS activity of brexu-cel: Muhsen, Roloff, et al. *Transplant Cell Therapy*. 2024;30(25):S7

Reviewed by: Kopmar & Cassaday. *Blood.* 2023;141:1379-88.