Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

Bridging Science and Practice: From Newest Clinical Approaches to Real-World Clinical Cases

10 –11 September 2023 – Japan and Asia-Pacific Region

Meeting sponsors AMGEN astellas

APTITUDE HEALTH

Global Leukemia Academy

Welcome and meeting overview

Naval Daver

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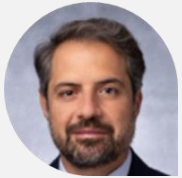
Meet the Faculty

CHAIR



Elias Jabbour, MD
MD Anderson Cancer Center,
Houston, TX, USA

CO-CHAIR

Naval Daver, MD
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FACULTY

Jae Park, MD
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Shaun Fleming, MBBS(Hons), FRACP, FRCPA
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Daniel J. DeAngelo, MD, PhD
Harvard Medical School,
Boston MA, USA

Junichiro Yuda MD, PhD
Department of Hematology and
Experimental Therapeutics,
National Cancer Center Hospital East,
Kashiwanoha, Kashiwa, Japan

Objectives of the program

- Understand current treatment patterns for acute leukemias including incorporation of new technologies
- Uncover when genomic testing is being done for acute leukemias, and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation in acute leukemias as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring acute leukemias
- Gain insights into antibodies and bispecifics in ALL: what are they? When and how should they be used? Where is the science going?
- Discuss the evolving role of ADC therapies in acute leukemias
- Review promising novel and emerging therapies in acute leukemias
- Explore regional challenges in the treatment of acute leukemias across JAPAC

Day 2: Virtual Plenary Sessions

Time (UTC+8)	Title	Speaker
8.00 AM – 8.10 AM	Welcome to Day 2	Elias Jabbour
8.10 AM – 8.30 AM	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
8.30 AM – 8.50 AM	Current treatment options for relapsed AML in adult and elderly patients	Junichiro Yuda
8.50 AM – 9.20 AM	Case-based panel discussion • Case AML – Rithin Nedumannil • Case ALL, elderly – Huai-Hsuan Huang • Discussion	Naval Daver and all faculty
9.20 AM – 9.30 AM	Break	
9.30 AM – 9.50 AM	AYA ALL patients: What is the current treatment approach for this diverse patient population? Special considerations for adolescents and young adults and how we can use this experience in adult patients	Daniel DeAngelo
9.50 AM – 10.20 AM	Current and future role of transplantation in acute leukemias • Jae Park (in general) • Shaun Fleming (in the JAPAC region) • Discussion	Jae Park/Shaun Fleming
10.20 AM – 10.50 AM	Panel discussion: How treatment in first line influences further approaches in ALL and AML • Will CAR T and bispecifics change the landscape? • Role of HSCT – is it still confirmed? • What does the future look like?	Elias Jabbour and all faculty
10.50 AM – 11.00 AM	Session close	Elias Jabbour and Naval Daver

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Introduction to the voting system

Naval Daver

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Question 1

What age group is considered elderly for AML patients?

A. ≥50 years

B. ≥55 years

C. ≥60 years

D. ≥65 years

E. ≥70 years

Question 2

How do you assess for minimal residual disease (MRD) for ALL?

A. Multicolor flow

B. Molecular PCR

C. Next-generation sequencing platform

D. We do not check for MRD

Question 3

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. ALK inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. CAR T approaches are active beyond second line in Ph– ALL

Question 4

The prognosis of R/R AML patients depends on:

A. Age
B. Prior therapy (eg, HSCT)
C. Timing of relapse
D. The mutational and cytogenetic profile of the disease
E. All of the above
F. A and D

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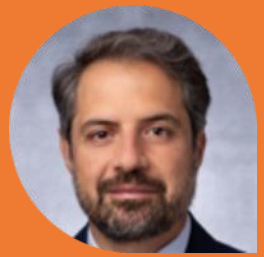
Current treatment options for relapsed ALL in adult and elderly patients

Elias Jabbour

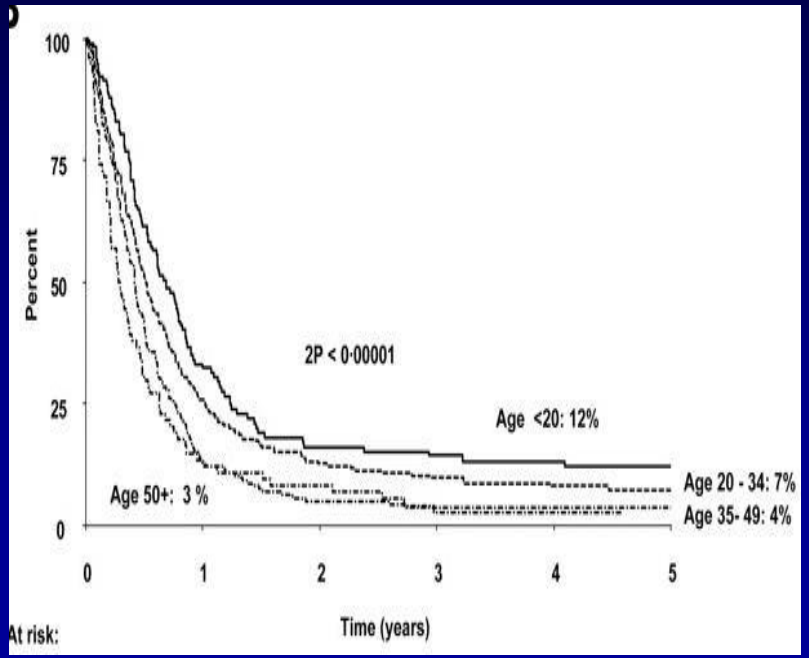


APTITUDE HEALTH

ALL – Historical Survival Rates After First Relapse

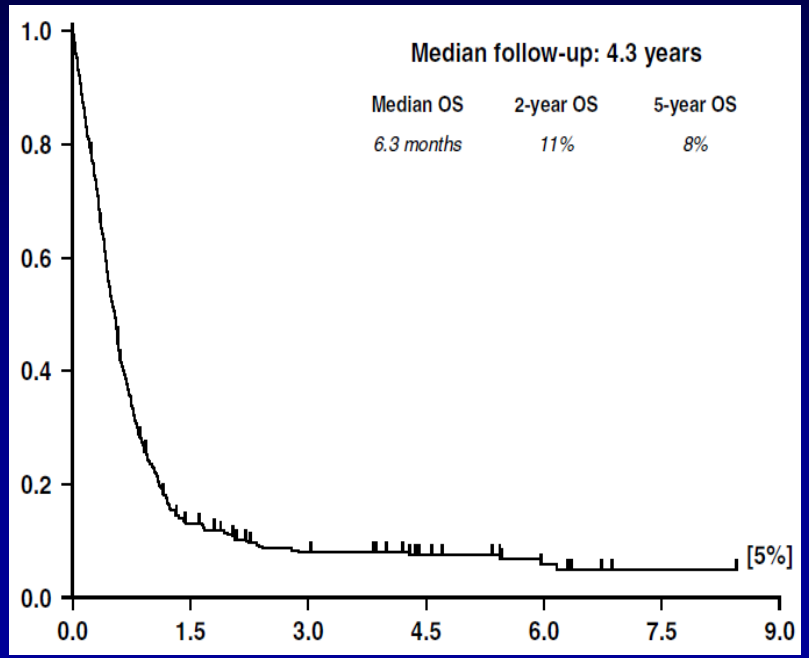
MRC UKALL2/ ECOG2993 Study (n = 609)

Outcome of patients after 1st relapse
5-yr OS: 7%



LALA-94 Study (n = 421)

Outcome of patients after 1st relapse
2-yr OS: 11% and 5-yr OS: 8%

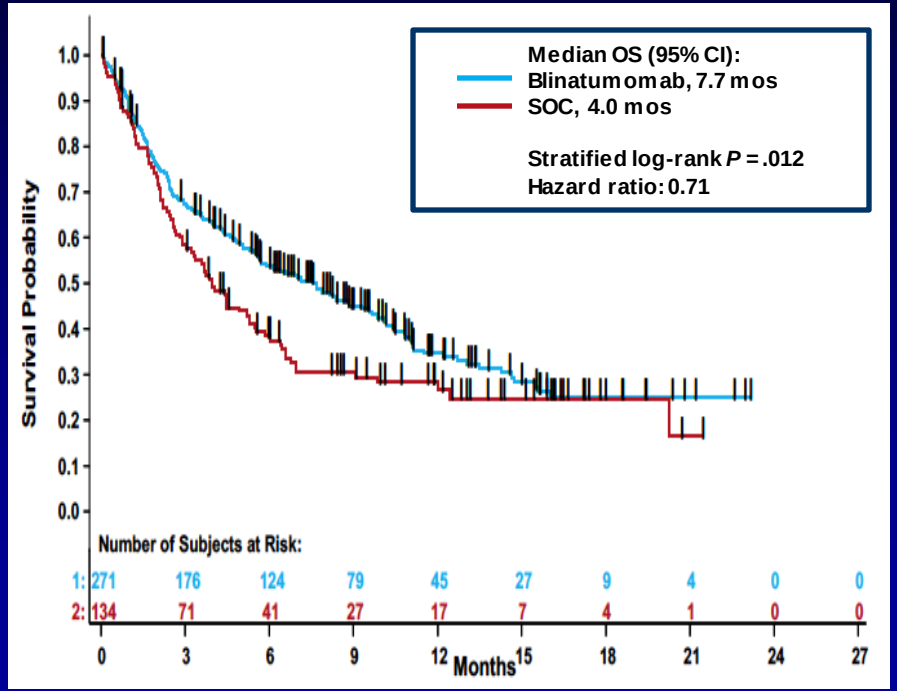


Fielding et al. *Blood*. 2007;109:944-950; Tavernier E, et al. *Leukemia*. 2007;21:1907-1914.

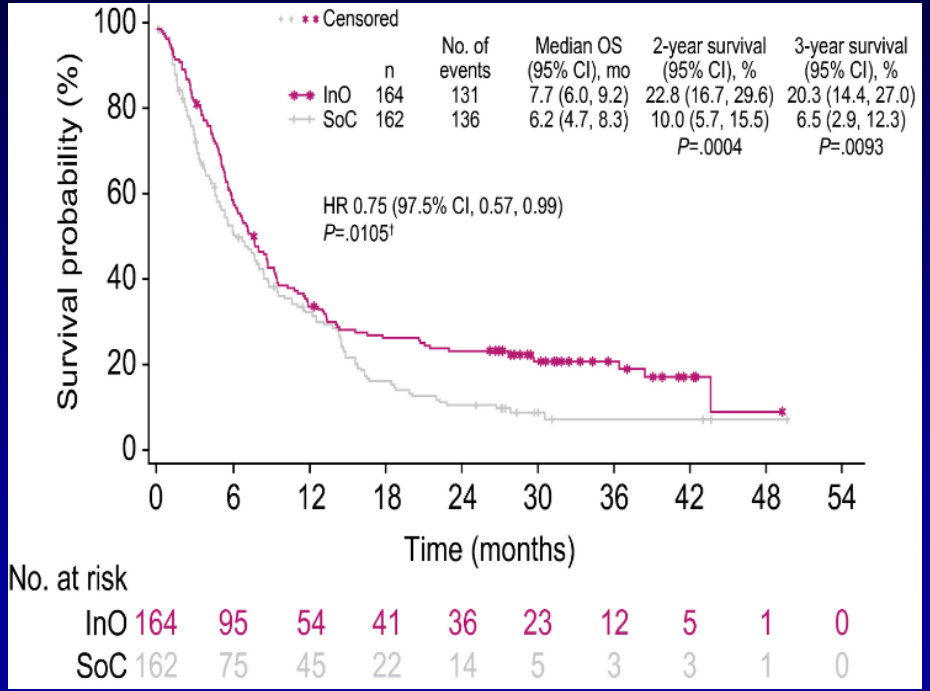
Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

- **Marrow CR**

Blina vs SOC: 44% vs 25%



Ino vs SOC: 74% vs 31%



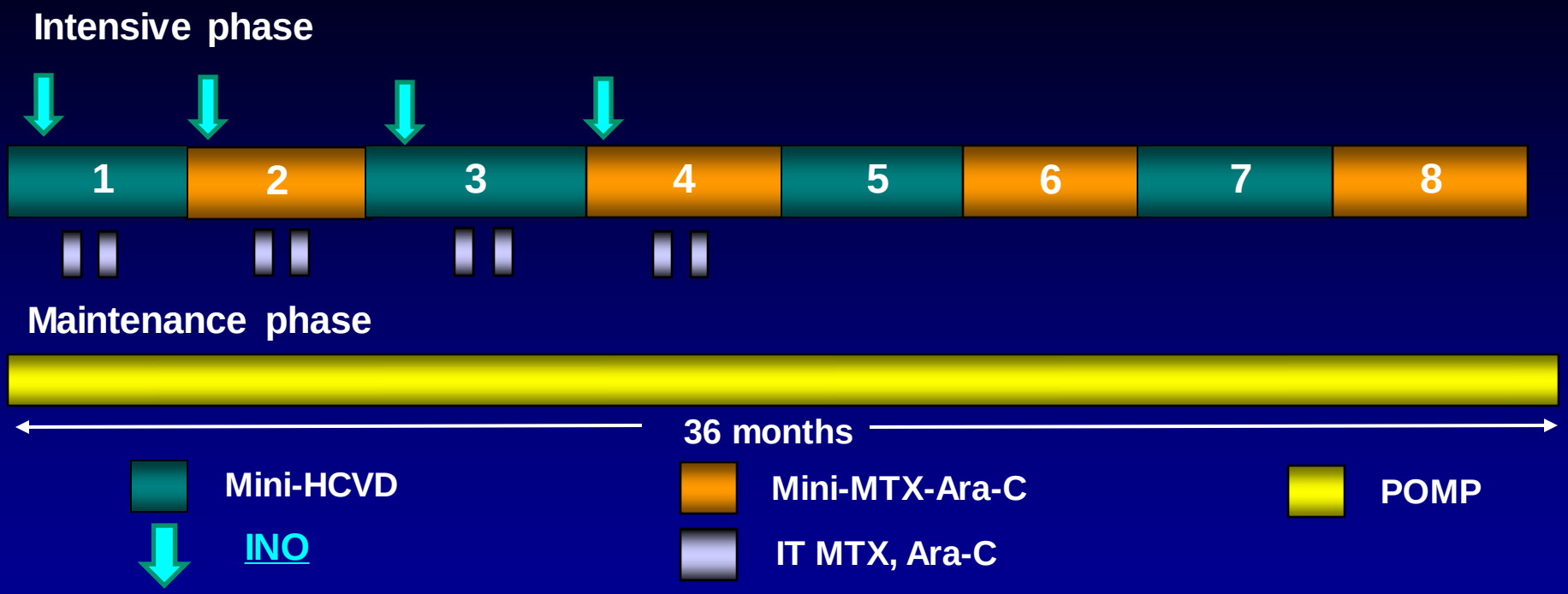
Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

Mini-HCVD + INO ± Blina in R/R B-ALL: Original Design

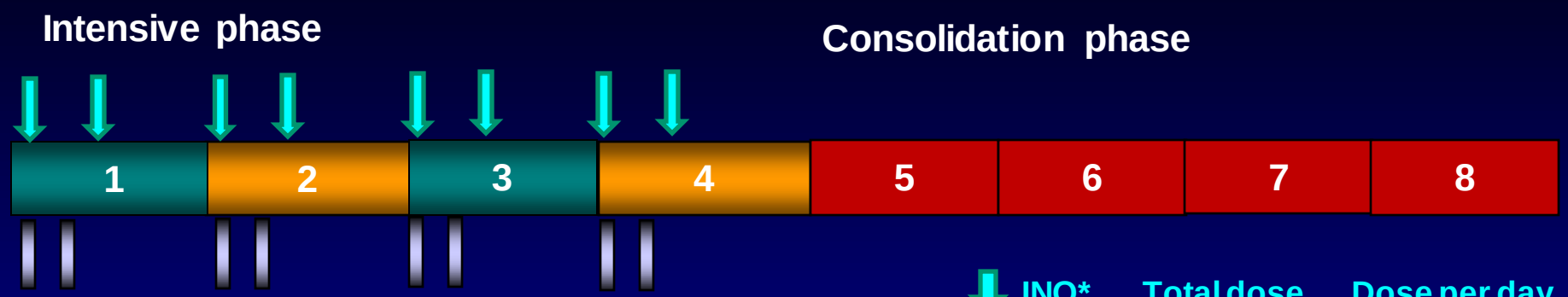
- Dose-reduced, modified hyper-CVAD ×8 courses
  - Cyclophosphamide (150 mg/m^2 ×6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 ×4) 83% dose reduction
- INO on day 3 (first 4 courses)
- Rituximab days 2 and 8 (first 4 courses) if CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- POMP maintenance ×3 years

Mini-HCVD + INO ± Blina in R/R B-ALL: Original Design (Pts #1–67)



INO	First 6 pts	7 to 34	35+
C1 (mg/m^2)	1.3	1.8	1.3
C2–4 (mg/m^2)	0.8	1.3	1.0

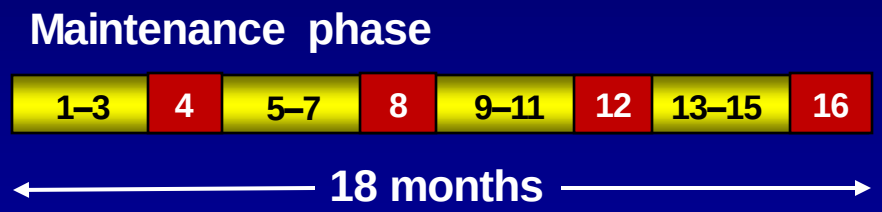
Mini-HCVD + INO ± Blina in R/R B-ALL: Modified Design (Pts #68–110)



INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis



Mini-HCVD

Mini-MTX-Ara-C

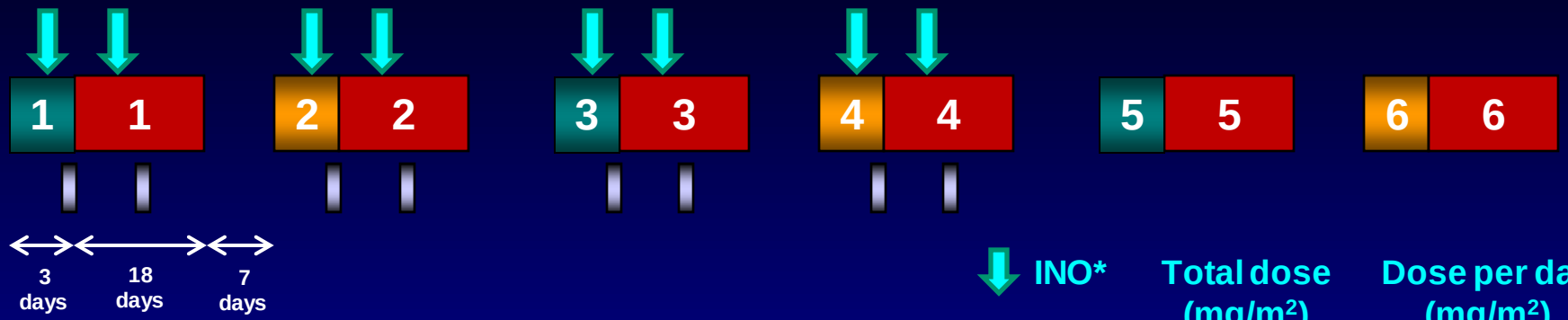
Blinatumomab

IT MTX, Ara-C

POMP

Short N, et al. HemaSphere. 2023;7:abstract S119.

Mini-HCVD + INO ± Blina in R/R B-ALL: "Dose-Dense" Design (Pts #111–125+)



INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Maintenance phase

Mini-HCVD

Mini-MTX-Ara-C

Blinatumomab

IT MTX, Ara-C

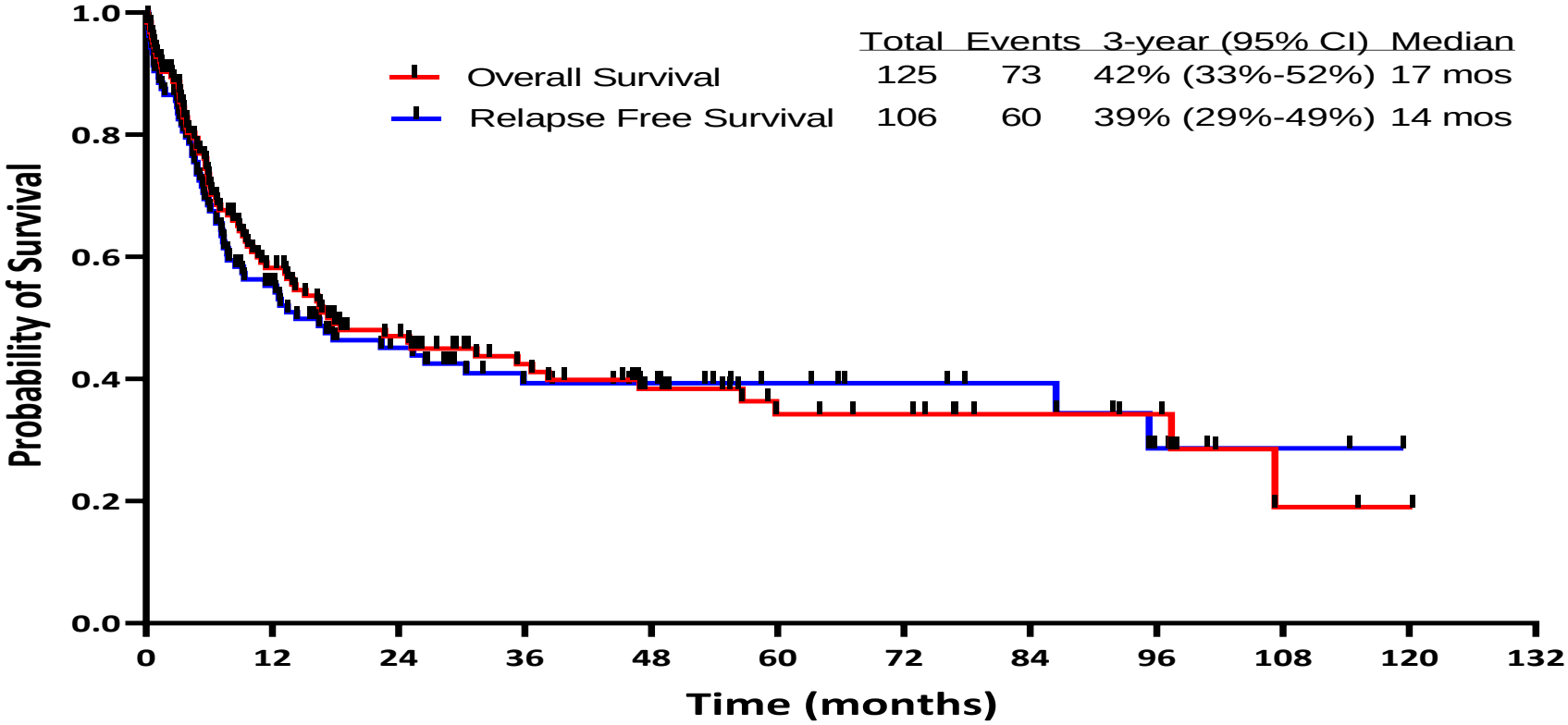
POMP

Short N, et al. HemaSphere. 2023;7:abstract S119.

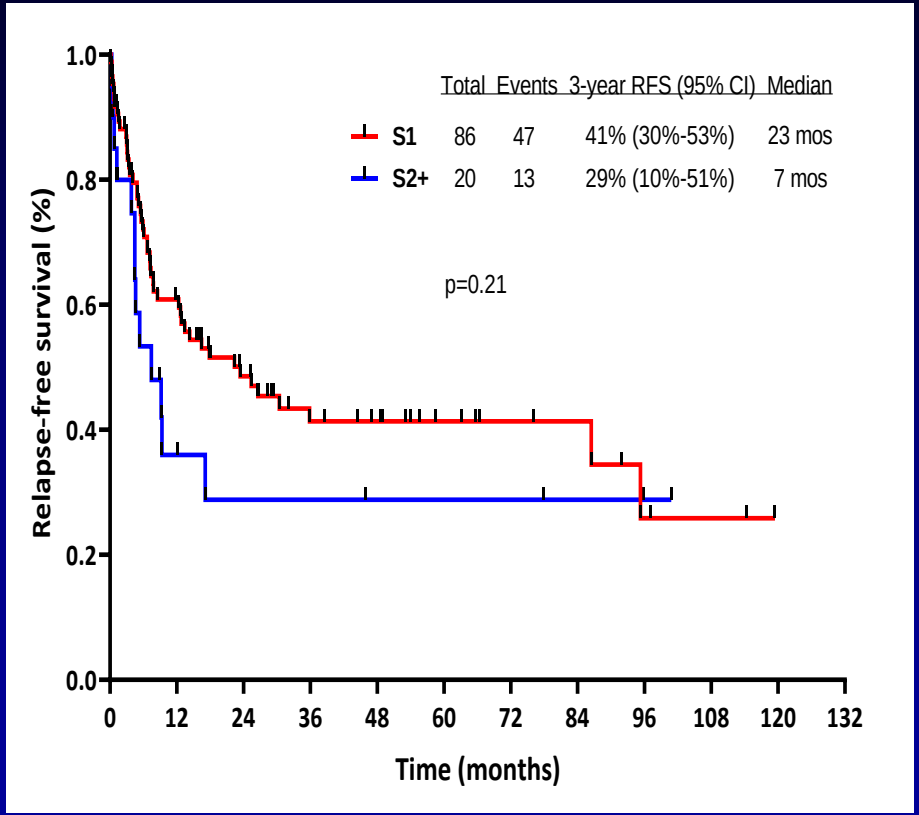
Mini-HCVD + INO ± Blina in R/R B-ALL: MRD Negativity Rates

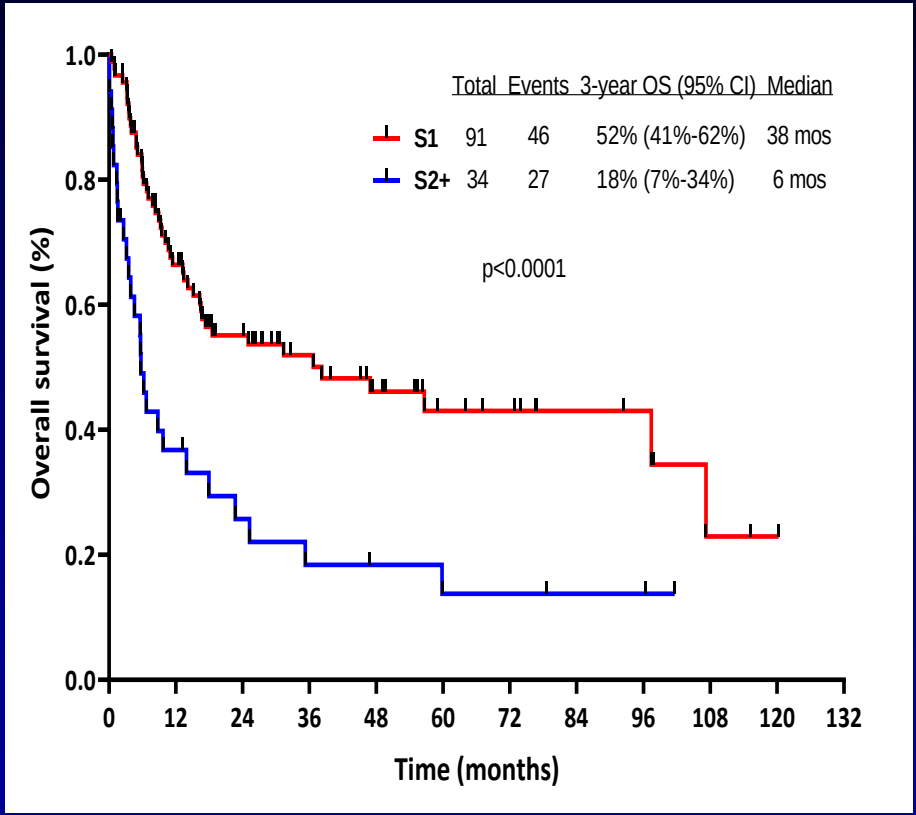
MRD Negativity by Flow Cytometry	N (%)			
	Overall (N = 125)	Before Blinatumomab (n = 67)	After Blinatumomab (n = 43)	Dose Dense (n = 15)
All patients				
End of cycle 1	53/100 (53)	25/49 (51)	18/38 (47)	10/13 (77)
Overall	87/102 (85)	41/50 (82)	34/39 (87)	12/13 (92)
Salvage 1				
End of cycle 1	45/82 (55)	22/34 (65)	17/37 (46)	8/11 (73)
Overall	73/83 (88)	31/35 (89)	32/37 (86)	10/11 (91)
Salvage 2+				
End of cycle 1	6/18 (33)	3/15 (20)	1/1 (100)	2/2 (100)
Overall	14/19 (74)	10/15 (67)	2/2 (100)	2/2 (100)

Mini-HCVD + INO ± Blina in R/R B-ALL: RFS and OS (Entire Cohort)

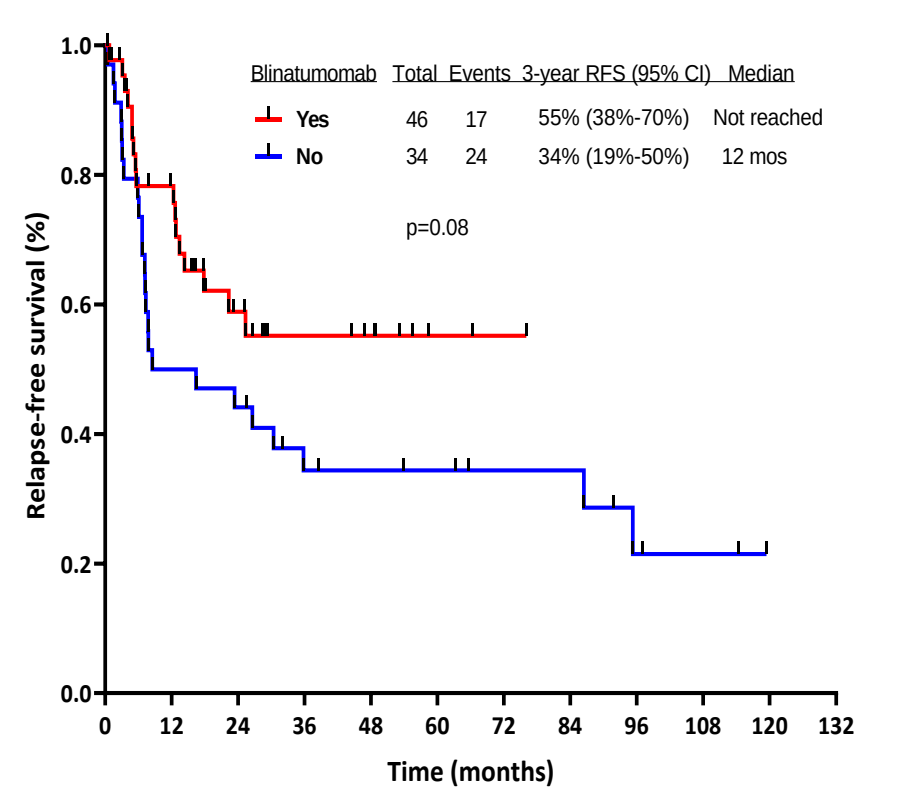


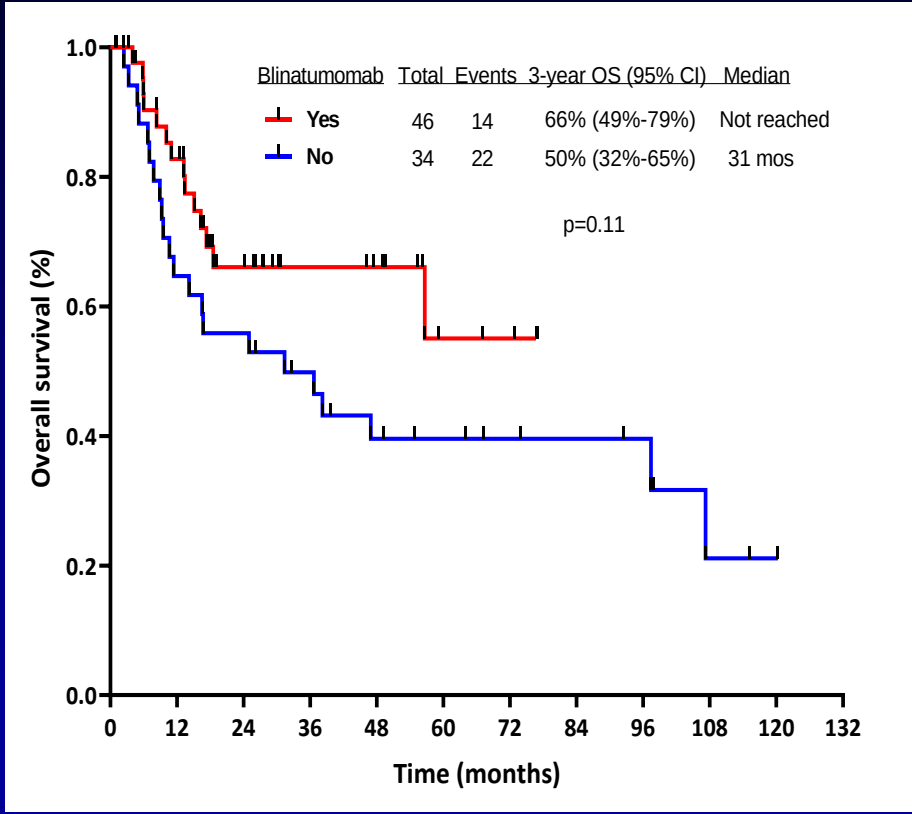
Mini-HCVD + INO ± Blina in R/R B-ALL: RFS and OS by Line of Salvage



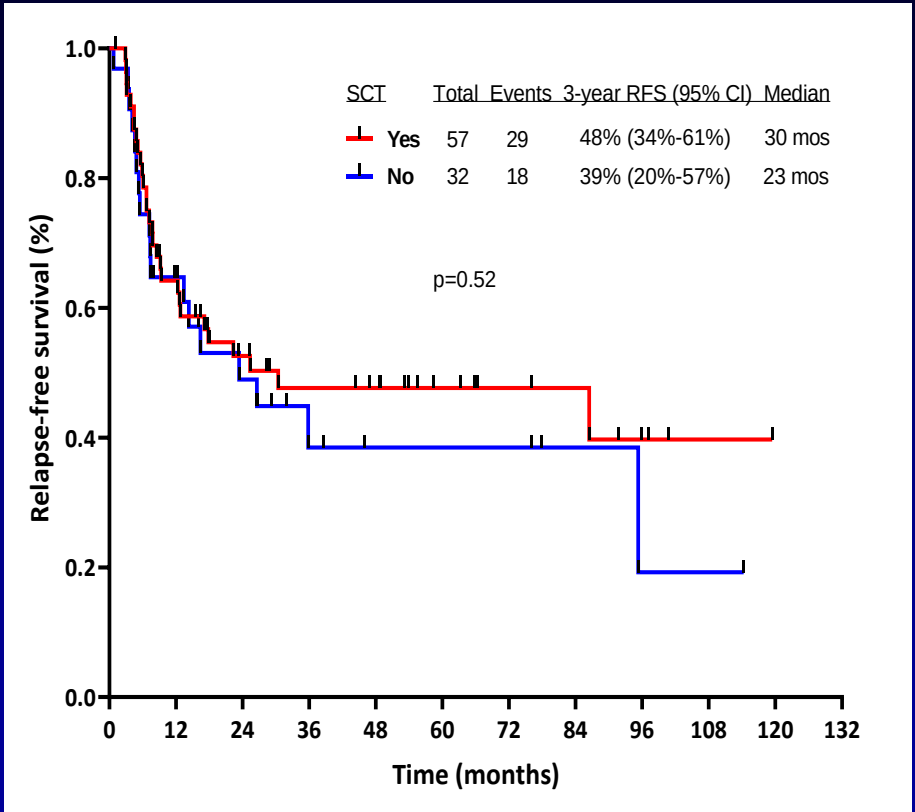


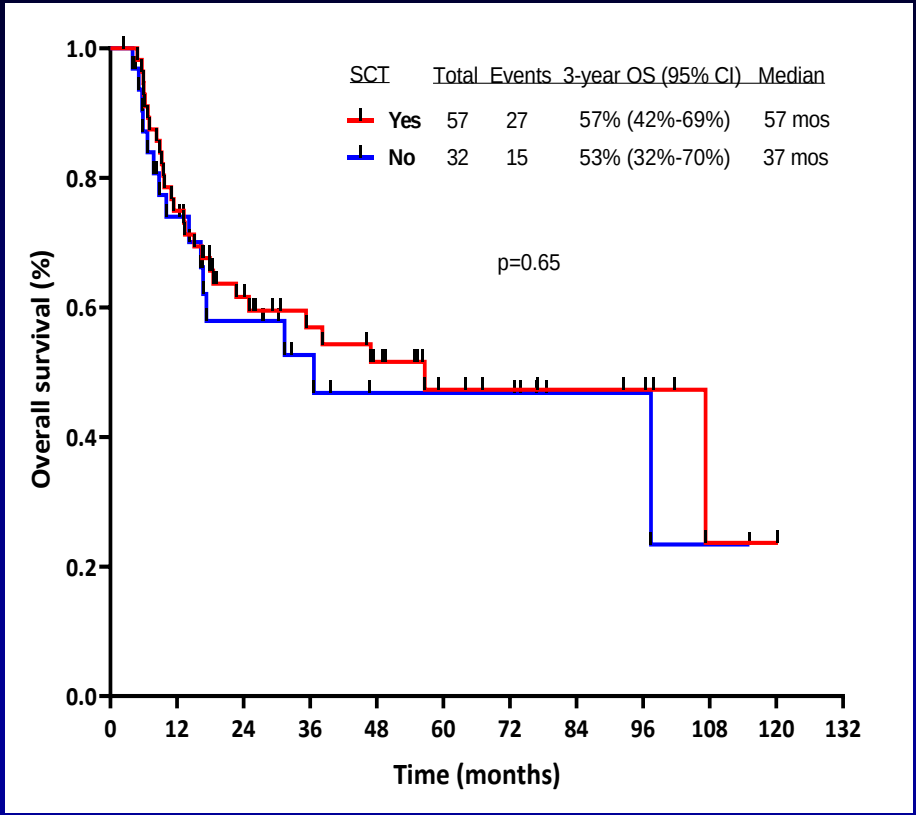
Mini-HCVD + INO ± Blina in R/R B-ALL: OS and RFS by Receipt of Blinatumomab (Salvage 1 Only)





Mini-HCVD + INO ± Blina in R/R B-ALL: OS and RFS by HSCT (Landmark Analysis)



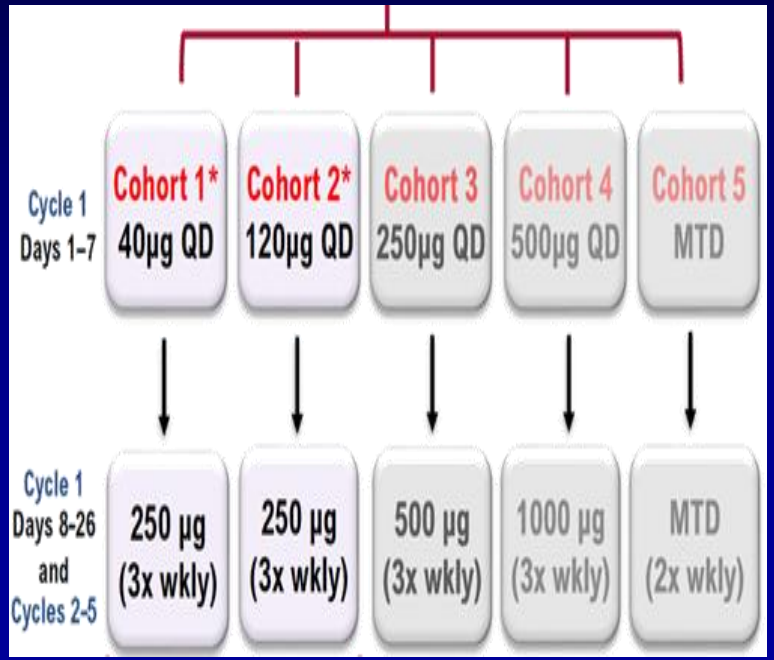


Subcutaneous Blinatumomab in R/R ALL

- 20 R/R pts, median age 58 yr (19–83)
- Median prior Rx = 2 (2–4)
- BLINA 40, 120, 250, 500 µg SQ daily × 7, then 250 µg TIW in cohorts 1 and 2, 500 µg in cohort 3, and 1000 mg in cohort 4
- 9/14 MRD-negative remission

Cohort	Marrow CR
1	3/6
2	2/3
3	4/5
4	5/7

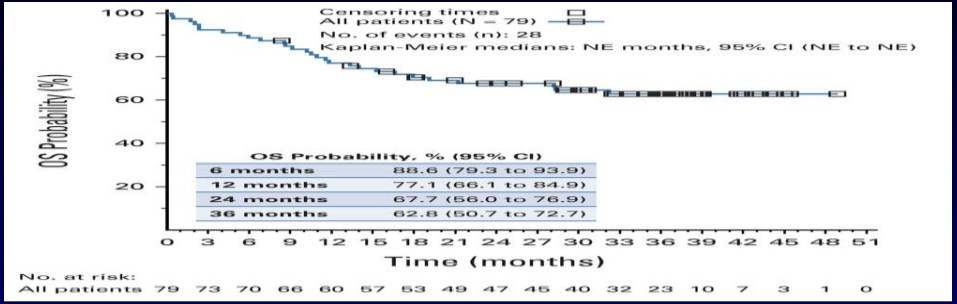
- No DLT; CNS toxicity G3: 4 (20%); CRS G3: 2 (10%)
- PK exposures similar to IV
- Possible phase II dose 250–500 µg

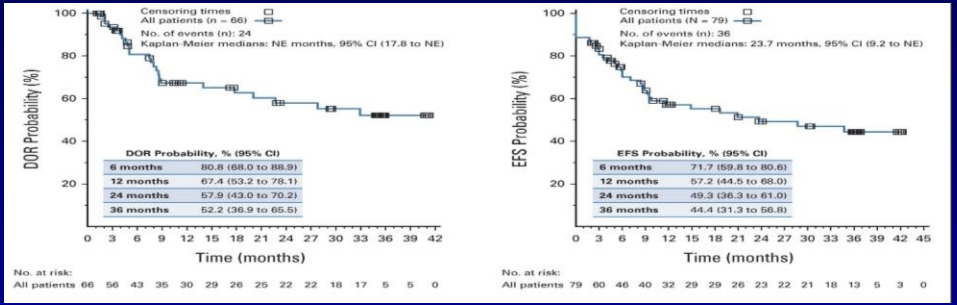


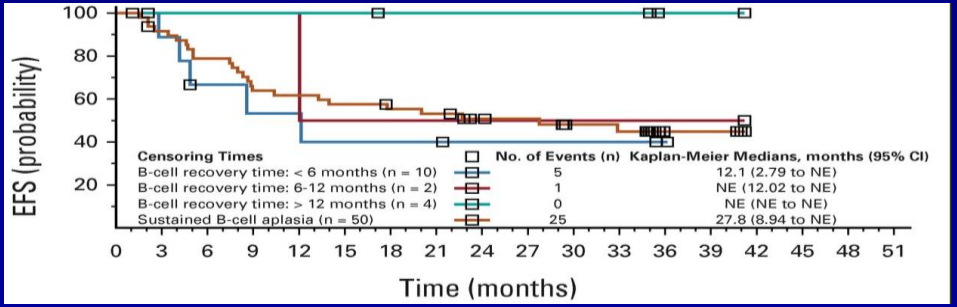
Martinez-Sanchez J, et al. *Blood*. 2022;140(suppl 1)6122-6124. Abstract 2727.

3-Year Update of Tisagenlecleucel in R/R ALL

- 97 pts ≤26 yrs enrolled;
  - 79 (81%) received tisa
- Median age 11 yrs (3–24)
- Median prior Rx 3 (1–8)
- Marrow CR 66 = 82%
  - 66% of denominator
- Median F/U 38.8 mos
- 5-yr RFS 49% in pts in CR/CRi
- 3-yr EFS 44%; 3-yr OS 63%
- G3/4 AE 29%



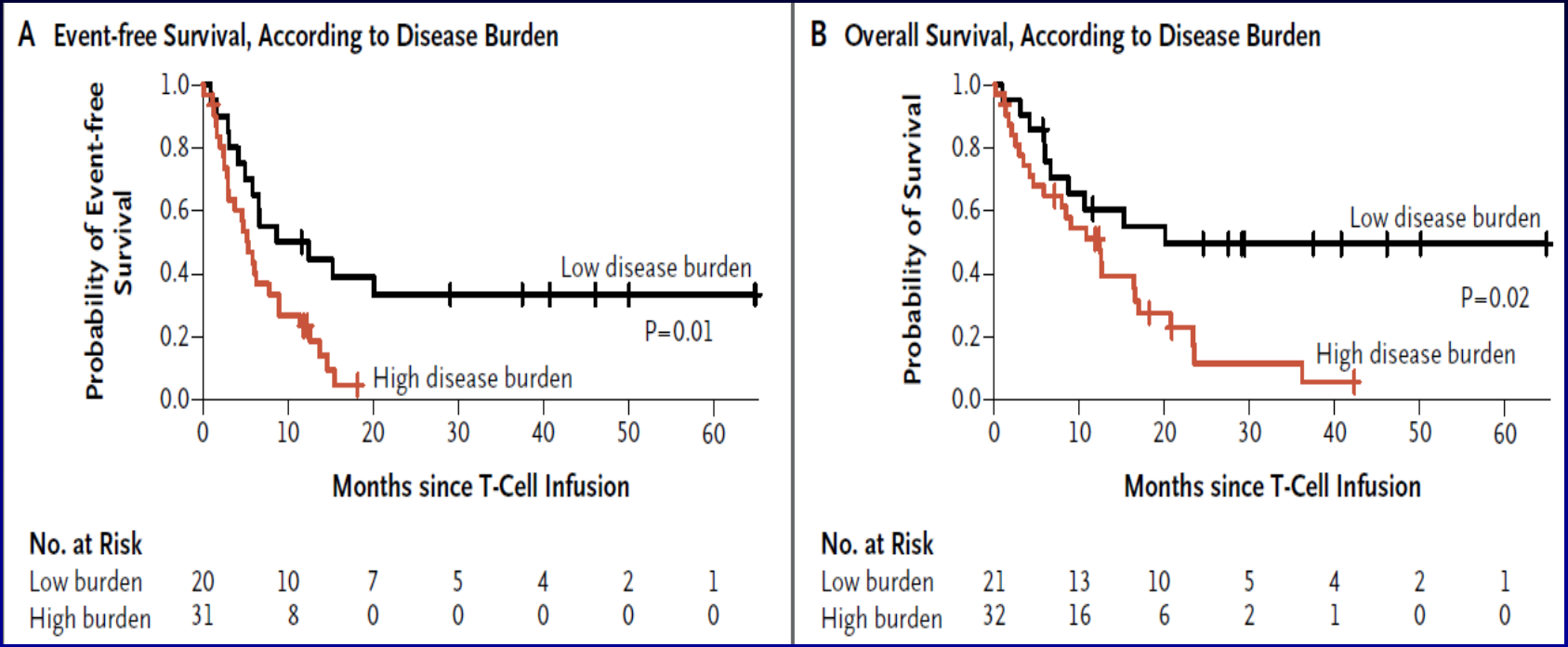




Laetsch et al. *J Clin Oncol.* 2023;41(9):1664-1669.

CD19-CD28z CAR (MSKCC): Responses by Tumor Burden

- High tumor burden: BM blasts ≥5% (n = 27); BM blasts <5% + EM disease (n = 5)
- Low tumor burden (MRD+ disease) (n = 21)



Median EFS
Low tumor burden: 10.6 mos
High tumor burden: 5.3 mos

Median OS
Low tumor burden: 20.1 mos
High tumor burden: 12.4 mos

Park et al. *N Engl J Med*. 2018;378:449.

CAR T (Kite) in ALL

- 55 pts Rx in phase II
- CR 56%; CRi 15%; CR + CRi 71%
- Median RFS 11.6 mo; 18-mo RFS 35%
- Median OS 25.4 mo
- Phase I–II = 78 pts

Parameter	24-mo OS, %
Age 18–39	48
40–59	54
≥60	57
BM blasts, % 25–50	58
51–75	55
>75	37

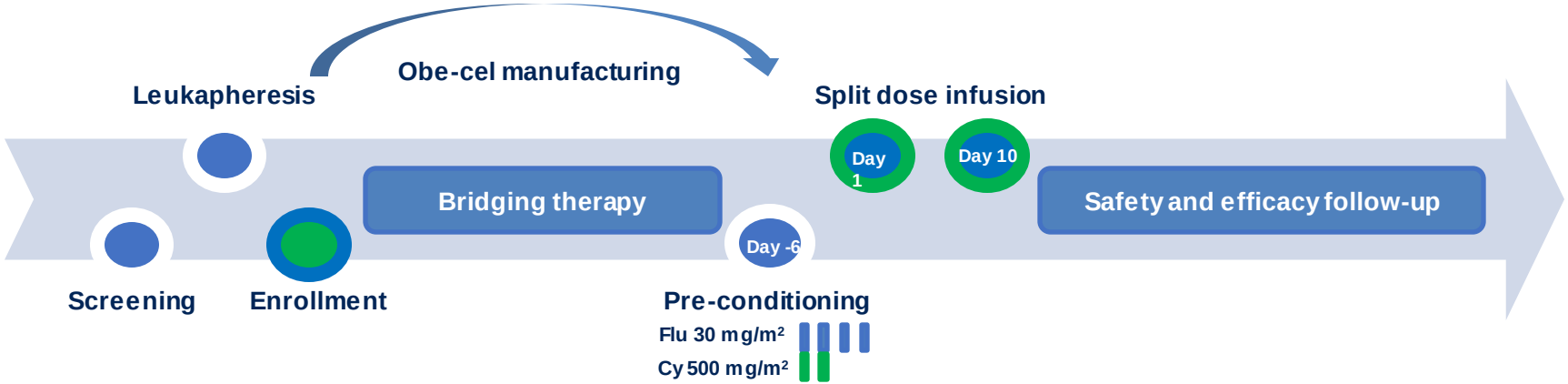
Shah BD, et al. *J Clin Oncol*. 2022;40(suppl 16): abstract 7010.

Obe-Cel – Fast-Off CD19 CAR T in R/R ALL: FELIX

- 112 pts enrolled, 94 infused
  - BM ≤20%: 100 × 10^6 CAR T cells on D1 and 310 × 10^6 CAR T cells on D10
  - BM >20%: 10 × 10^6 CAR T cells on D1 and 400 × 10^6 CAR T cells on D10
    31% S3+
- ORR = 76% (CR = 54%); ITT = 63% (CR = 46%)
- MRD negativity 97%; DOR 14.1 mos
- G3 CRS 3.2% and ICAN 7.4%

Roddie C, et al. *HemaSphere*. 2023;7:abstract S262.

FELIX Study: Obe-Cel for Adults With R/R CD19+ B-ALL



Pre-conditioning

Tumor burden-adjusted split dosing to maximize the therapeutic index

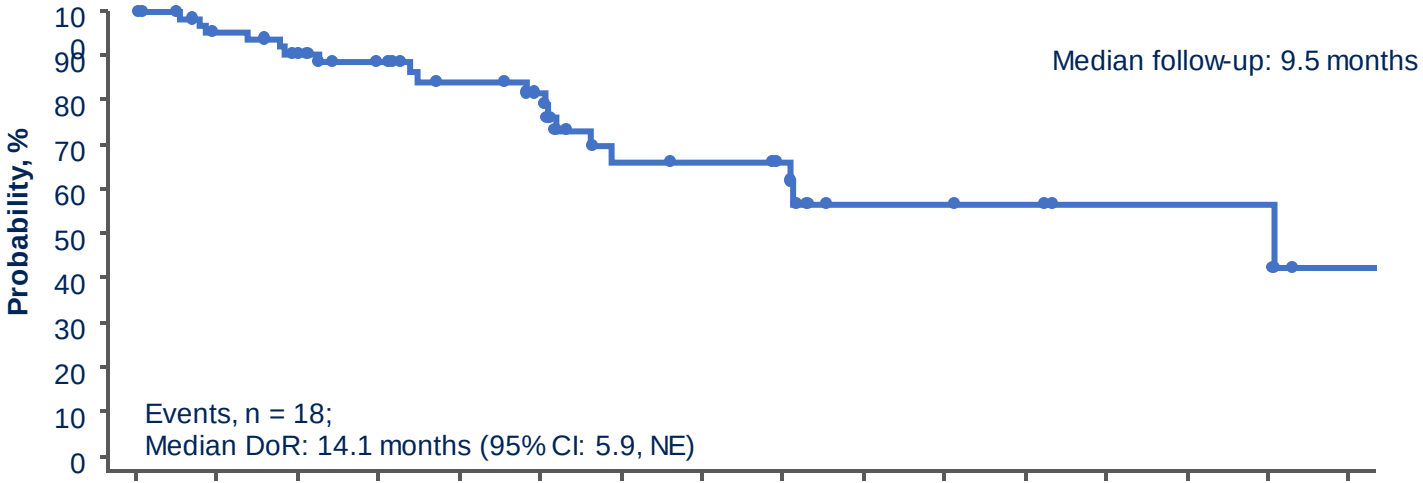
BM blasts ≤20%	100 × 10^6 CAR T cells	CRS Grade <2 No ICANS		310 × 10^6 CAR T cells
BM blasts >20%	10 × 10^6 CAR T cells			400 × 10^6 CAR T cells

94% of infused patients received both obe-cel infusions

CRS, cytokine release syndrome; cy, cyclophosphamide; flu, fludarabine; ICANS, immune effector cell-associated neurotoxicity syndrome.

FELIX: Duration of Remission

61% responders in ongoing remission without new anticancer therapies



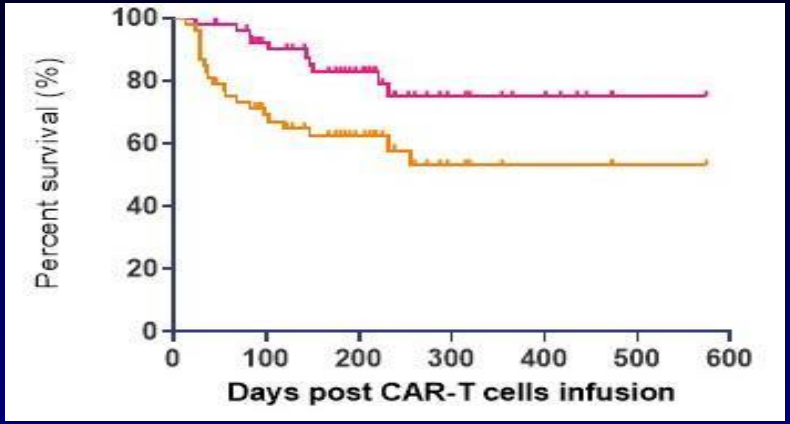
Patients at risk, n	71	60	55	46	36	30	19	18	15	8	8	7	4	4	4	1

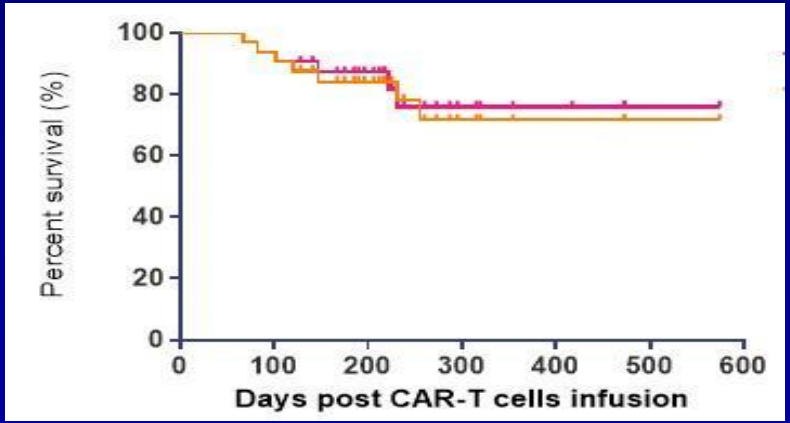
13% responders who proceeded to SCT while in remission were censored at the time of SCT

NE, not estimable.

R/R T-ALL and T-LBL Rx With CD7-Targeted CAR T Cell

- Novel fratricide-resistant approach to derive naturally selected 7 CAR T cells (NS7CAR) from bulk T cells without additional genetic
- 52 pts with R/R T-ALL (n = 34) and T-LBL (n = 18); median age 22 yr (2–47)
- Median prior lines of Rx 5 (2–15)
- Median FU 206 days
- MRD-negative CR 96%
- 5 pts G3 CRS, and 1 had G4 CRS
- 18-mo OS 75%; EFS 53%
- 32 pts (61%) had allo SCT; 18-mo OS 76% and EFS 71.5%

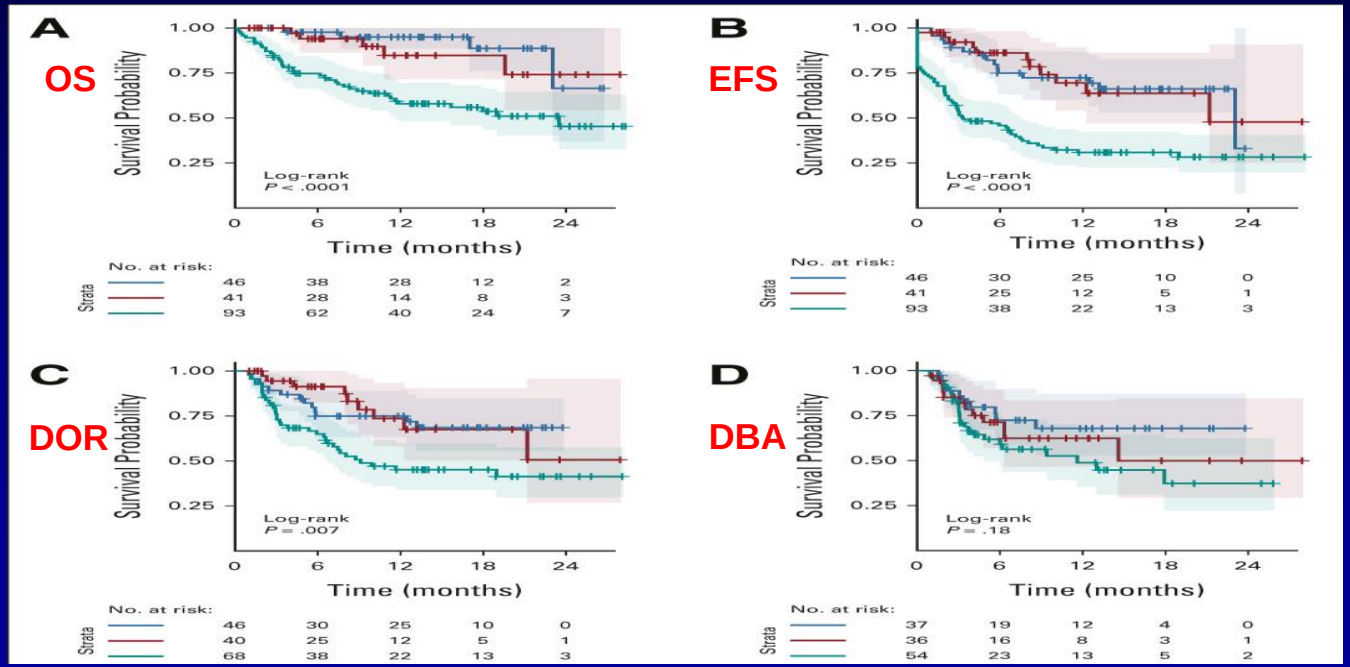




Zhang X, et al. *Blood*. 2022;140(suppl 1):2369-2370. Abstract 980.

Real-World CAR Consortium and Disease Burden

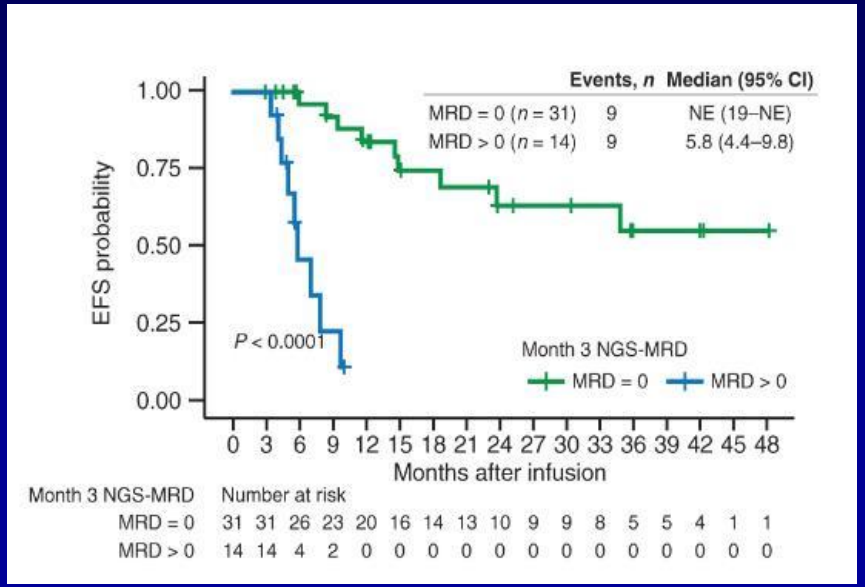
- 200 pts (185 pts infused); median age 12 yr (0–26 yr); CR = 85%
- HBD n = 94 (47%); LBD n = 60 (30%); ND n = 46 (23%)
- 12-mo EFS = 50%, 12-mo OS = 72%
- G3 CRS = 21% (35% in HBD); G3 NE = 7% (9% in HBD)

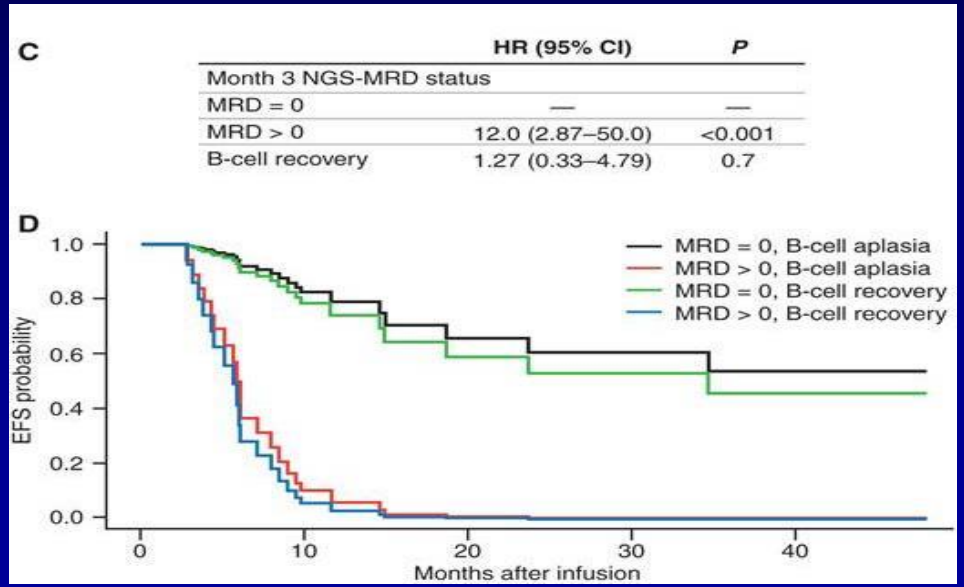


Schultz LM, et al. *J Clin Oncol*. 2022;40(9):945-955.

NGS MRD Negativity After CAR T-Cell Therapy for ALL

- Detectable MRD after tisagenlecleucel by NGS independently predicted for EFS and OS on multivariate analysis
- NGS MRD status at 3 months was superior to B-cell aplasia/recovery at predicting relapse/survival

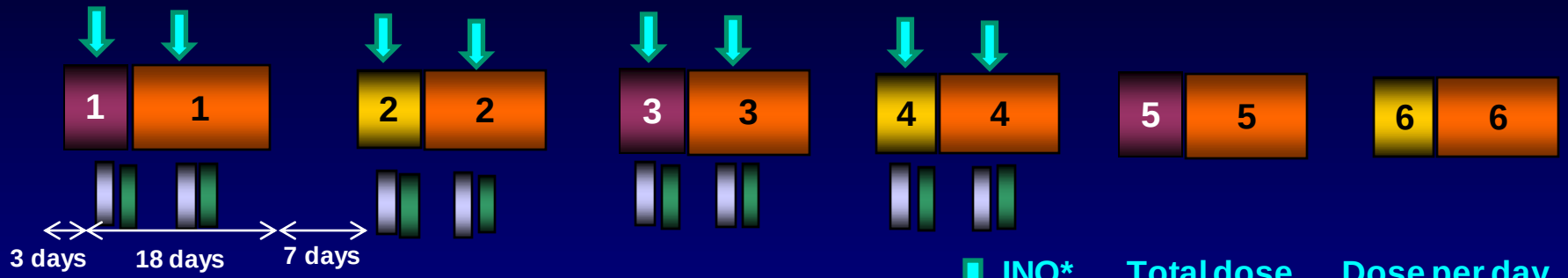




Pulsipher MA, et al. *Blood Cancer Discov.* 2022;3(1):66-81.

Dose-Dense Mini-HCVD + INO + Blina + CAR T Cells in ALL: The CURE

Induction phase: C1–C6



INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Consolidation phase

CAR T Consolidation

Mini-HCVD

Mini-MTX, Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

ALL 2023: Conclusions

- Significant improvements across all Jayakumar categories
- Incorporation of Blina-InO in FL therapy highly effective and improves survival
- Early eradication of MRD predicts best overall survival
- Antibody-based Rxs and CAR Ts both outstanding; not mutually exclusive/competitive (vs); rather, complementary (together)
- Future of ALL Rx
  1) Less chemotherapy and shorter durations
  2) Combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22
  3) SQ blinatumomab
  4) CAR Ts CD19 and CD19 allo and auto in sequence in CR1 for MRD and replacing ASCT

Thank You

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Global Leukemia Academy

Q&A

APTITUDE HEALTH

Global Leukemia Academy

Current treatment options for relapsed AML in adult and elderly patients

Junichiro Yuda

APTITUDE HEALTH

Current treatment options for relapsed AML in adult and elderly patients

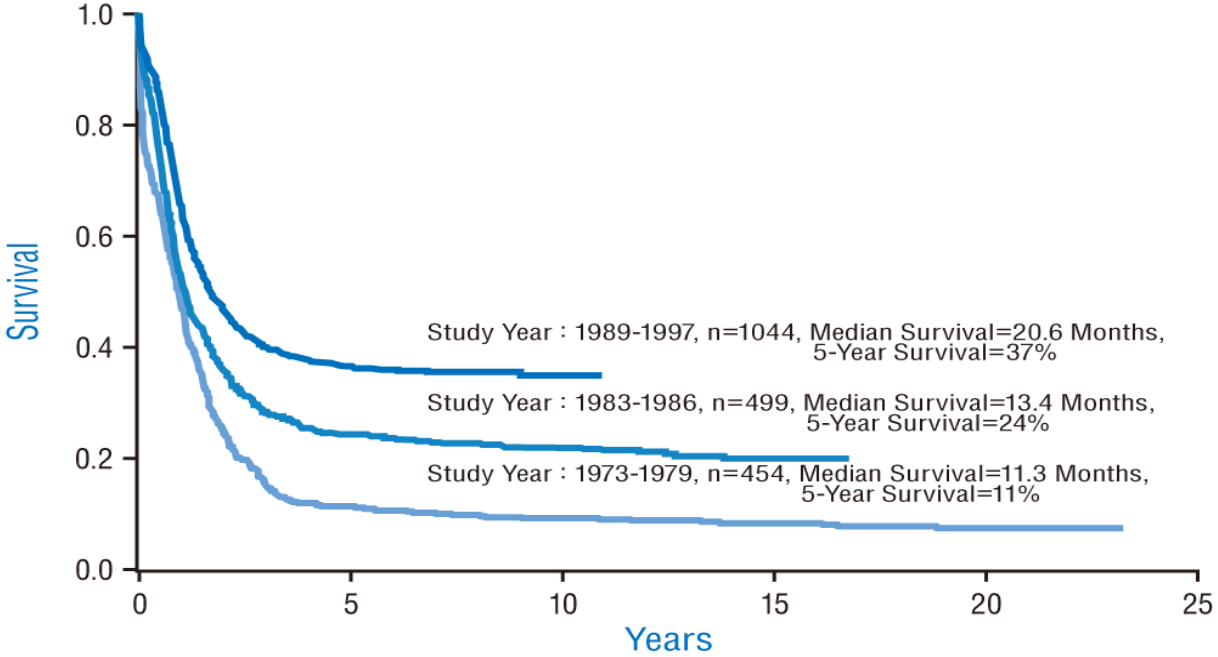
Junichiro Yuda M.D., Ph.D.

National Cancer Center Hospital East
Department of Hematology and Experimental Therapeutics
Hematological Treatment Development Promotion Office,
Department for the Promotion of Drug and Diagnostic Development

2020's

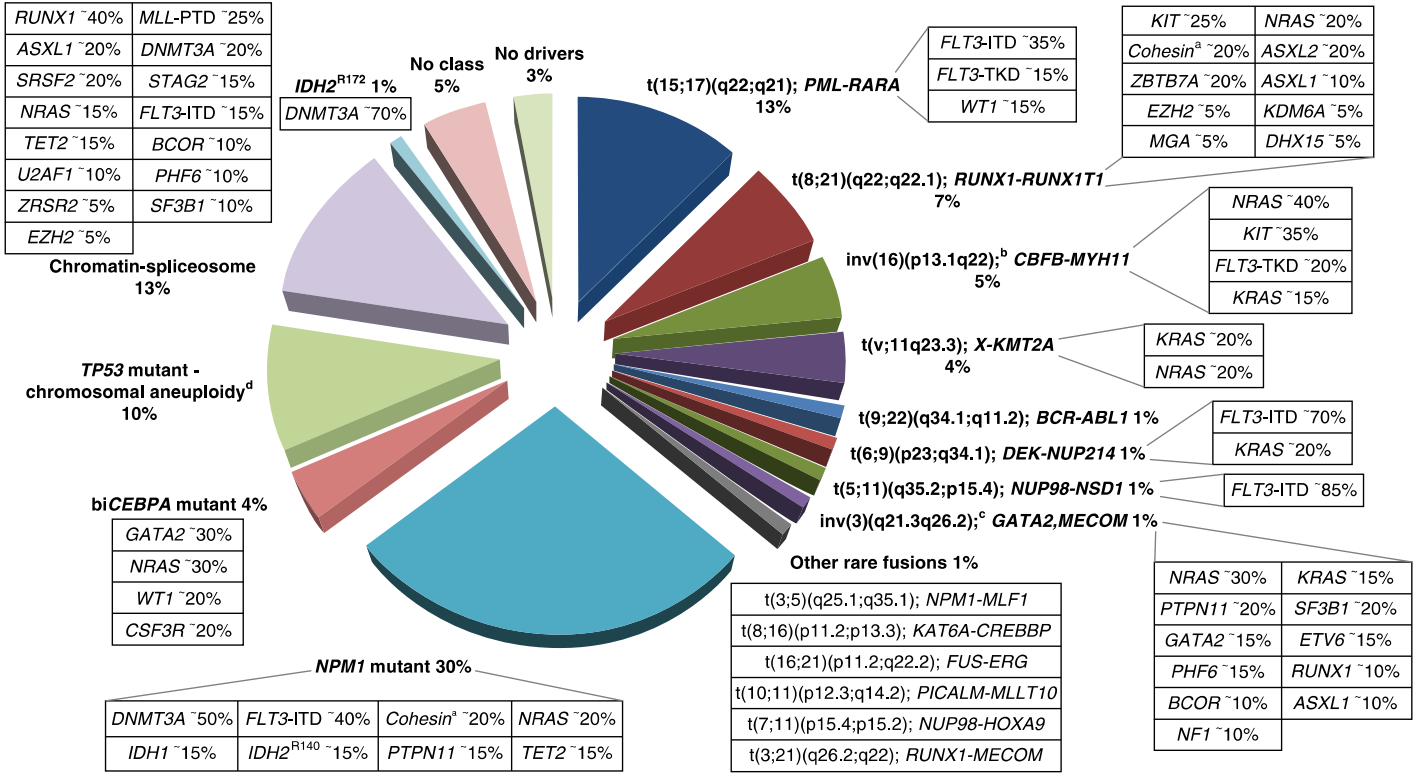
2030's

Changes in treatment outcomes for AML



Frederick, R., et al. : Hematology (Am Soc Hematol Edue Program)., : 62-86, 2001

Genetic mutations in adult AML patients



Dohner H. Blood. 2017.

ELN stratification system (2022)

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[b,c] • Mutated *NPM1*[b,d] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*[e]
Intermediate	• Mutated *NPM1*[b,d] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype,[h] monosomal karyotype[i] • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*[j] • Mutated *TP53*[k]

Döhner H. Blood. 2022.

INTENSIVE INDUCTION ELIGIBLE

Induction eligible[a,b]

RISK GROUP	TREATMENT INDUCTION[e,f,g,h,t] Principles of Venetoclax, see AML-K
Favorable-risk AML (CBF-AML,[c] *NPM1*-mutated/*FLT3* wild-type AML, in-frame basic leucine zipper [bZIP] mutation in *CEBPA*)[y]	**Preferred:** • Standard 7+3 (daunorubicin)[k,l,u,v] + gemtuzumab ozogamicin[d,i] (CD33 positive)[j] **Other Recommended:** • Standard 7+3 (daunorubicin or idarubicin)[k,l,u,v] • 7+3 (mitoxantrone)[k,l,u,v] (for age ≥60 y) • FLAG-IDA (fludarabine + HiDAC[z] + granulocyte colony-stimulating factor [G-CSF][m] - idarubicin) + gemtuzumab ozogamicin[d,i] (category 2B; use with caution in patients >60 y)
AML with *FLT3*-ITD/TKD mutation	Standard 7+3 (daunorubicin)[k,l,u,v] + midostaurin[n,w]
Intermediate-risk AML	**Preferred:** • Standard 7+3 (daunorubicin or idarubicin)[k,l,u,v] (category 1) • 7+3 (mitoxantrone)[k,l,u,v] (for age ≥60 y) **Other Recommended:** • Standard 7+3 (daunorubicin)[k,l,u,v] + gemtuzumab ozogamicin[i] (CD33 positive)[j] • FLAG-IDA[m,z] ± gemtuzumab ozogamicin[i] (category 2B; use with caution in patients >60 y) • FLAG-IDA[m,s] + venetoclax (category 3)
Poor risk groups	See AML-2

→ See Follow-Up and Re-Induction After Standard-Dose Cytarabine Induction (AML-3)

See AML-5 (Intensive Induction Ineligible)

INTENSIVE INDUCTION ELIGIBLE

RISK GROUP	TREATMENT INDUCTION[f,g,h,e,t] Principles of Venetoclax, see AML-K
Induction eligible[a,b] → Favorable and intermediate risk groups	See AML-1
Induction eligible[a,b] → Poor-risk AML with and without *TP53* mutation or del17p abnormality[o,x]	• Standard 7+3 (idarubicin or daunorubicin)[k,l,u,v] (category 1) • 7+3 (mitoxantrone)[k,l,u,v] (for age ≥60 y) • HiDAC[l,z,aa] + idarubicin or daunorubicin[u,v] + etoposide (category 1 for patients ≤45 y, category 2B for other age groups) • FLAG-IDA[m,z] (category 2B) • FLAG-IDA[m,s] + venetoclax (category 3) • Decitabine (days 1–5) + venetoclax[q] • Decitabine (days 1–10) + venetoclax[q] (category 3) • Azacitidine + venetoclax[q] • Low-dose cytarabine (LDAC) + venetoclax[q] • Low-intensity therapy (azacitidine [category 2B] or decitabine)
Induction eligible[a,b] → • Therapy-related AML other than CBF-AML • Antecedent MDS/chronic myelomonocytic leukemia (CMML) • Cytogenetic changes consistent with MDS (AML with myelodysplasia-related changes [AML-MRC])[x]	• Standard 7+3 (daunorubicin or idarubicin)[k,l,u,v] (category 1) • CPX-351/dual-drug liposomal cytarabine and daunorubicin[p] (category 1 for ≥60 y, category 2B for <60 y) • Decitabine (days 1–5) + venetoclax[q,r] • Azacitidine + venetoclax[q,r] • LDAC + venetoclax[q] • Low-intensity therapy (azacitidine or decitabine)[r]

→ See Follow-Up and Re-Induction After Standard-Dose Cytarabine Induction (AML-3) or Follow-Up After High-Dose Cytarabine Induction for Poor-Risk AML (AML-4)

Outcomes for patients with poor-risk AML with TP53 mutation remain poor with conventional induction chemotherapy (Rücker FG, et al. Blood 2012;119:2114-2121) and the panel prioritizes clinical trial enrollment in this setting. While conventional induction chemotherapy regimens can be given in the setting of a TP53 mutation, less intensive chemotherapy is preferred for patients not enrolled in clinical trials. (DiNardo CD, et al. N Engl J Med 2020;383:617-629;Welch JS, et al. N Engl J Med 2016;375:2023-2036).

LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE)

Not a candidate for intensive induction therapy[a,b]

RISK GROUPS

AML without actionable mutations

TREATMENT INDUCTION[e,g,h,t]
Principles of Venetoclax, see AML-K

Preferred
- Azacitidine + venetoclax (category 1)[q,r,oo]
- Decitabine (days 1–5) + venetoclax[q,r,oo]

Other Recommended
- LDAC + venetoclax[oo]
- Azacitidine or decitabine[r,jj]
- Glasdegib + LDAC[kk]
- Gemtuzumab ozogamicin[ll] (CD33 positive)[j] (category 2B)
- LDAC (category 2B)
- Best supportive care (hydroxyurea, transfusion support)

***IDH1* or *IDH2* mutation**

Preferred
- Azacitidine + venetoclax (category 1)[q,r,oo]
- Ivosidenib[mm,pp] + azacitidine[nn] (category 1) (*IDH1* only)
- Decitabine (days 1–5) + venetoclax[q,r,oo]
- Ivosidenib[mm,pp] (*IDH1* only)
- Enasidenib[mm,pp] (*IDH2* only)

Other Recommended
- LDAC + venetoclax[oo]
- Azacitidine, decitabine[r,jj]

Useful in Certain Circumstances
- Enasidenib[mm,pp] + azacitidine (*IDH2* only) (category 2B)

***FLT3* mutation**

Preferred
- Azacitidine + venetoclax (category 1)[q,r,oo]
- Decitabine (days 1–5) + venetoclax[q,r,oo]

Other Recommended
- LDAC + venetoclax[oo]
- Azacitidine or decitabine[r,jj] or sorafenib
- (Azacitidine or decitabine)[r] + sorafenib

Useful in Certain Circumstances
- Gilteritinib + azacitidine (category 2B)

Follow-Up After Induction Therapy With Lower Intensity Therapy (Intensive Induction Ineligible) (AML-6)

See footnotes on AML-5A

MAINTENANCE THERAPY | **TREATMENT[t]**

No allo-HCT

- Patient with intermediate or adverse risk disease:
  - Who received prior intensive chemotherapy and whose disease is now in remission
  - Completed no consolidation, some consolidation or a recommended course of consolidation and
  - No allogeneic HCT is planned

→

- Maintenance therapy with oral azacitidine until progression or unacceptable toxicity (category 1, preferred for age ≥55 y)[zz]
- Maintenance therapy with HMA until progression or unacceptable toxicity
  - Azacitidine
  - Decitabine (category 2B)

allo-HCT

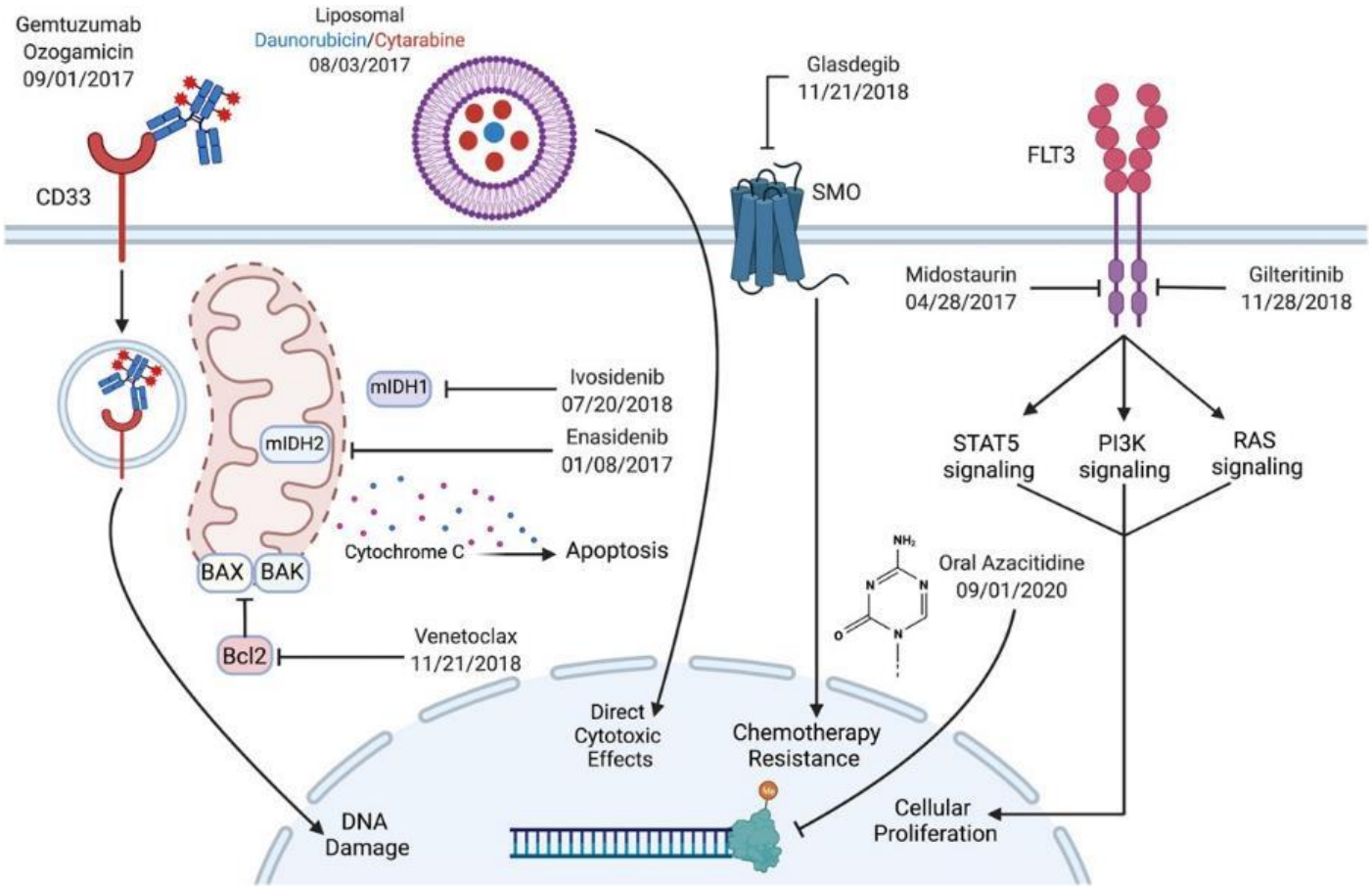
Post allogeneic HCT, in remission, and history of *FLT3*-ITD →

FLT3 inhibitor maintenance
- Sorafenib
- Midostaurin (category 2B)
- Gilteritinib (category 2B)

Neither of the above scenarios is applicable → Maintenance therapy not recommended

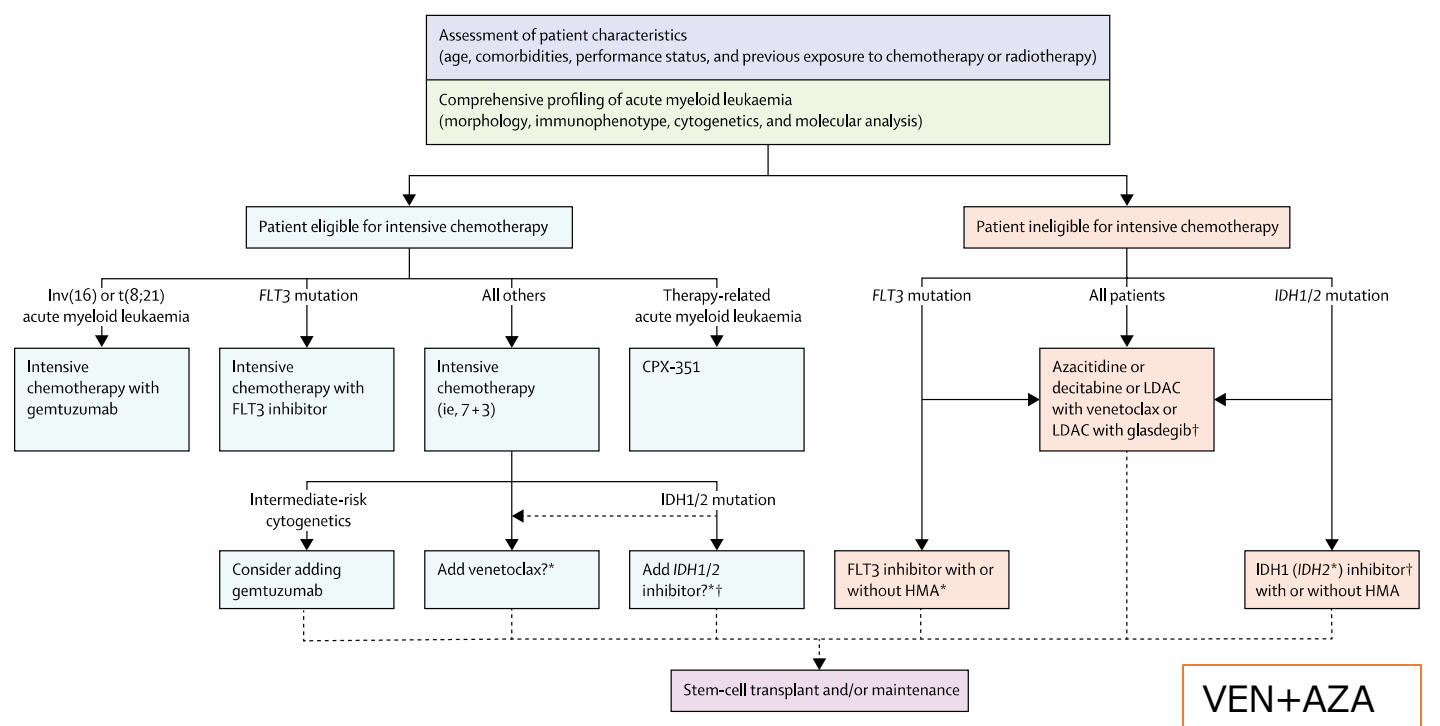
→ See Surveillance (AML-10)

Overview of Recently Approved Agents for AML



Roloff GW. 2022 ASCO EDUCATIONAL BOOK

Evolving treatment paradigm for newly diagnosed AML: US



VEN+AZA
VEN+LDAC
Gilteritinib
Quizartinib
GO

The latest AML treatment strategies

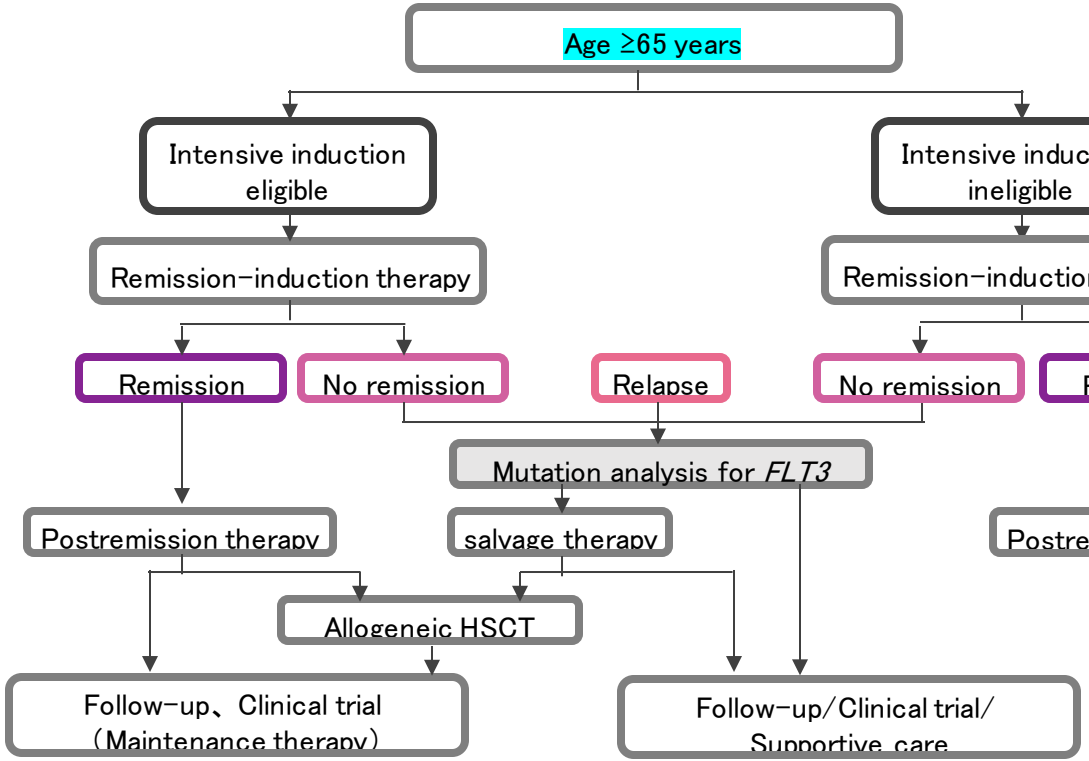
- Acute myeloid leukemia treatment is evolving rapidly with several new drugs approved in the past 5 years
- Treatment decisions are based on a comprehensive assessment of patient and disease-specific factors, including frailty, the molecular profile of acute myeloid leukemia, and patient preference
- Combination therapy integrating methylation inhibitors, BCL-2 inhibitors, and specific targeted inhibitors may be considered in AML cases not indicated for intensive chemotherapy
- Maintenance therapy with oral azacitidine may be an option for patients who achieve CR or CRi after intensive chemotherapy
- Several new drugs are under development, including immunotherapeutics and targeted drugs

Other important points

- ✓ **Cellularity of bone marrow**
- ✓ **Degree of residual normal hematopoietic capacity**
- ✓ **Timing of allogeneic transplantation**

Roloff GW. 2022 ASCO EDUCATIONAL BOOK

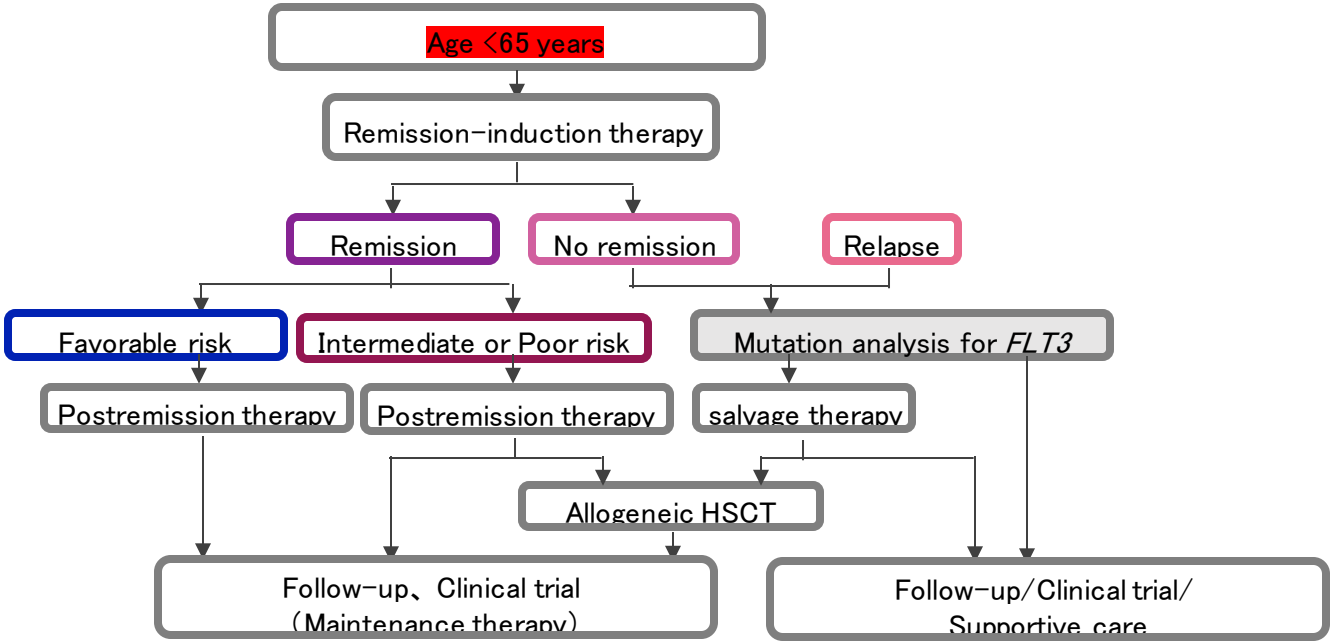
Evolving treatment paradigm for newly diagnosed AML: JAPAN



VEN+AZA
VEN+LDAC
Gilteritinib
Quizartinib
GO

JSH guideline 2023

Evolving treatment paradigm for newly diagnosed AML: JAPAN



VEN+AZA
VEN+LDAC
Gilteritinib
Quizartinib
GO

JSH guideline 2023

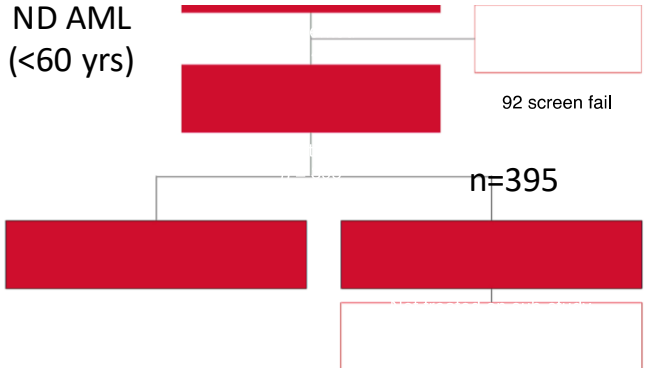
AML Master Trial

Genomic testing
(within 7days)

a

- Core binding factor
- *NPM1*⁺ *FLT3*-ITD WT
- MLL-rearranged
- *IDH2*⁺
- *IDH1*⁺
- *TP53*⁺
- *TP53* complex karyotype (>3 abn)
- *FLT3*-ITD⁺ or *FLT3*-TKD⁺
- Hypermethylation*
- Marker-negative

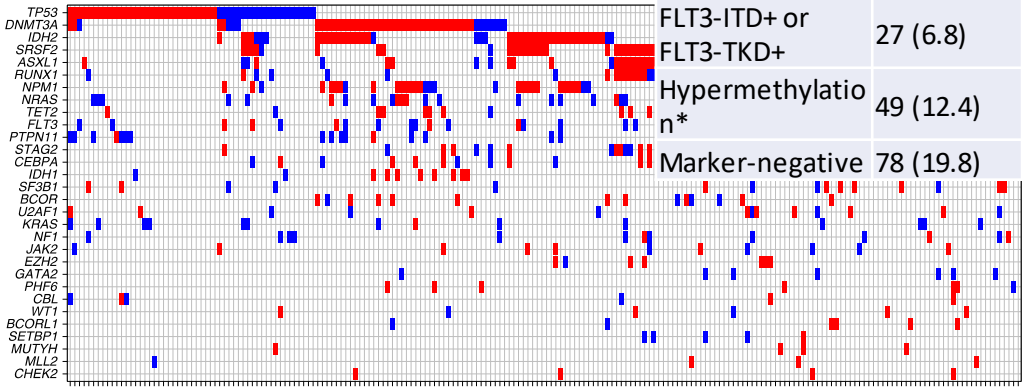
ND AML
(<60 yrs)



Target therapy
(n=224)

56.7%

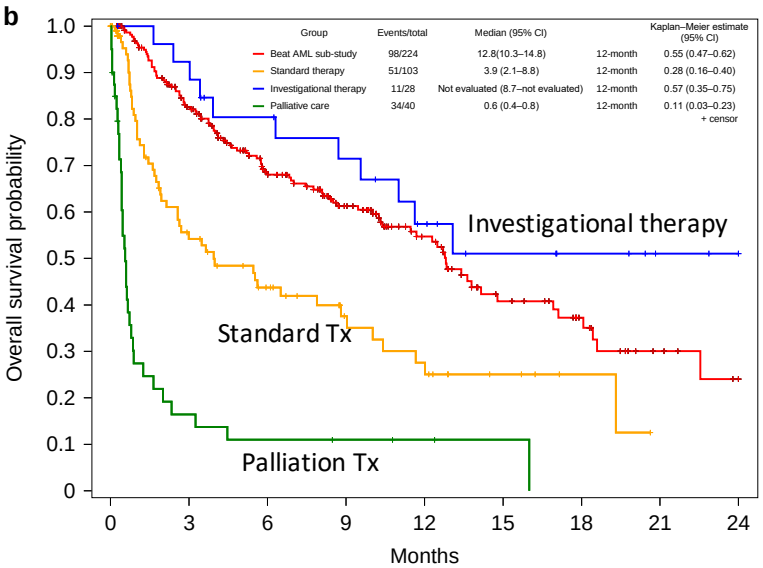
SOC
(n=171)



GROUP, n (%)	PRIORITIZED SCHEMA (n = 395)
Core binding factor	9 (2.3)
NPM1+ FLT3-ITD WT	46 (11.7)
MLL-rearranged	11 (2 .8)
IDH2 +	45 (11.4)
IDH1 +	23 (5 .8)
TP53 +	76 (19.2)
TP53 complex karyotype (>3 abn)	31 (7.9)
FLT3-ITD+ or FLT3-TKD+	27 (6.8)
Hypermethylation*	49 (12.4)
Marker-negative	78 (19.8)

Burd A. Nature Medicine. 2020.

AML Master Trial

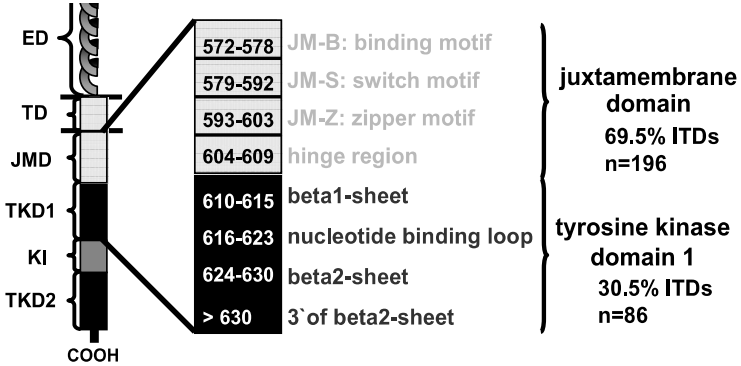


Core binding factor	Samalizumab(CD200Ab)+Induction
NPM1+ FLT3-ITD WT	Entospletinib(SYKi)+/-Induction
MLL-rearranged	Entospletinib(SYKi)+/-AZA
IDH2 +	Enasideniib+/-AZA
IDH1 +	Ivosidenib+AZA
TP53 +	Entospletinib(SYKi)+Decitabine, Pevonedistat(Nedd8i)+AZA
TP53 complex karyotype (>3 abn)	Entospletinib(SYKi)+Decitabine
FLT3-ITD+ or FLT3-TKD+	Giliteritinib+/-Decitabine
TET2/WT1	CD33 Ab+AZA
Marker-negative	CD33 Ab+AZA

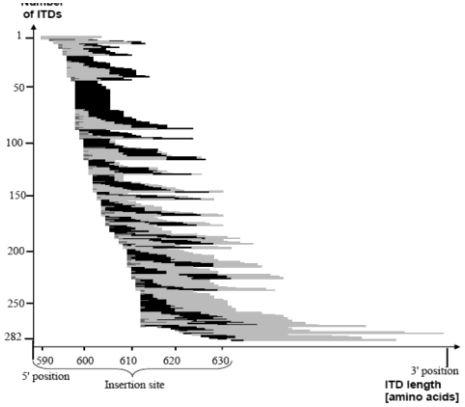
- ✓ Standard treatment 103, investigational treatment 28, palliative care 40 patients
- ✓ Thirty-day mortality: Sub-study 3.7%, standard treatment selected 20.4%
- ✓ Median overall survival: Study treatment 12.8 months, standard treatment 3.9 months, palliative care 0.6 months

Burd A. Nature Medicine. 2020.

Schematic structure of the FLT3 receptor

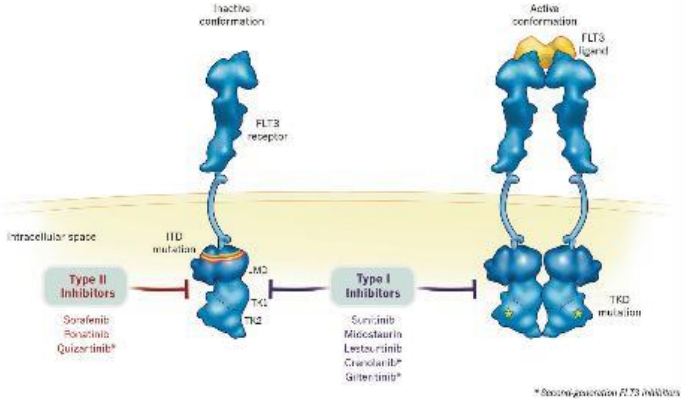


Correlation between ITD insertion site & length

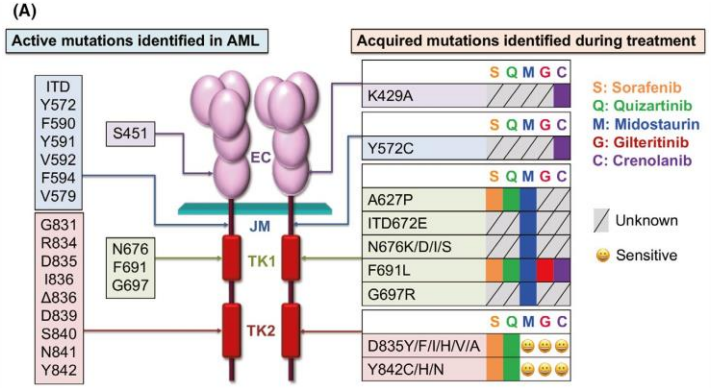


Kayser S. Blood. 2009.

Schematic structure of the FLT3 receptor



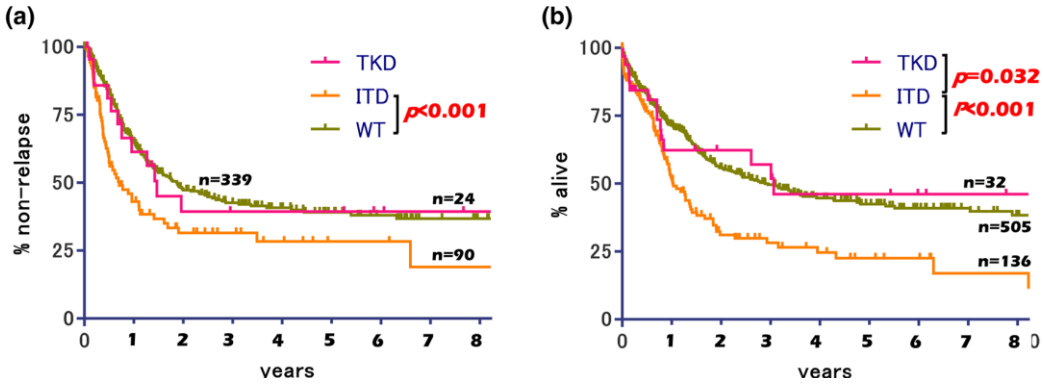
Daver N. Leukemia. 2019.



Kiyoi H. Cancer Science. 2019.

Investigation of FLT3 mutation-positive Japanese AML patients

Before the era of FLT3 inhibitors



- ✓ TKD mutations have less prognostic impact
- ✓ FLT3-TKD-positive cases are less common in Asia than in Europe and US.

Sakaguchi M. IJH. 2019.

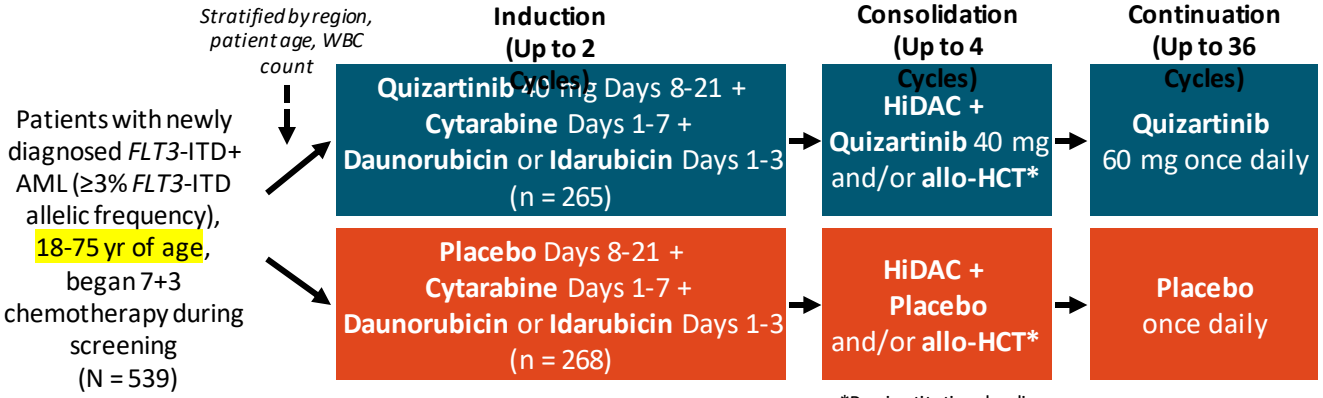
Table 1. FLT3 mutations features and association with prognosis in AML.

FEATURES	COMMENTS
TYPE of mutaion (ITD/TKD)	ITD mutations has traditionally been associated with adverse outcome, while the TKD mutations probably has less prognostic impact
ITD length	Patients with longer ITDs (>48 bps) seem to have more chemoresistance disease
Allelic ratio	High *FLT3*-ITD allelic ratio has been associated with an unfavorable prognosis, although methodical standardization has been an obstacle
Insertion site	Studies have demonstrated that ITDs outside the JMD have been associate with resistance to chemotherapy and inferior outcome
Presence of *NPM1* mutation	Coexistent of *NPM1* mutation in *FLT3* mutated cases have been of conflicting results, although MRD monitoring by PCR is currently preferable for reprognostication
Prescence of other mutations	Cooccurrence of *WT1*, *RUNX1*, and *ASXL1* mutations have been linked to inferior outcome
Presecnce of cytognetic alteations	Favorable and adverse cytogenetic prognostic alterations are mainly not affected by *FLT3* mutations which has strongest impact in normal karyotype AML

Haakon Reikvam. Expert Review of Hematology. 2023.

QuANTUM-First: Quizartinib + Chemotherapy in Newly Diagnosed *FLT3*-ITD+ AML

- Randomized, double-blind, placebo-controlled phase III trial



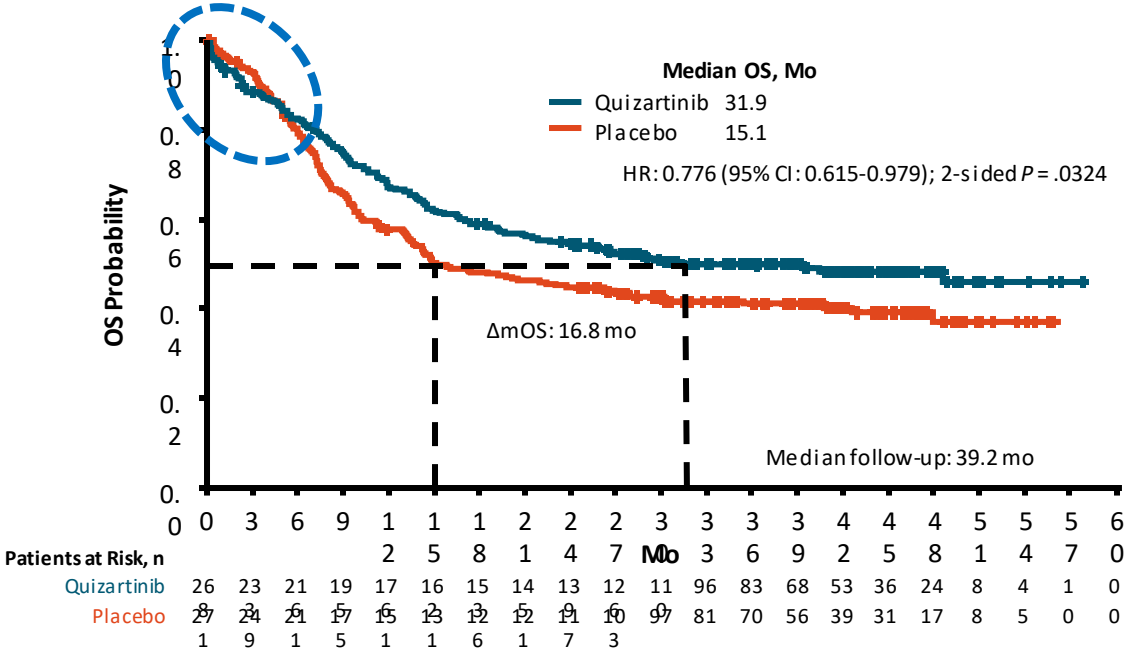
*Per institutional policy.

- **Primary endpoint:** OS
- **Secondary endpoints:** EFS and CR/CRc (hierarchical testing), safety
- **Exploratory endpoints:** RFS, DoCR

Erba. EHA 2022. Abstr S100.

QuANTUM-First: OS (Primary Endpoint)

FLT3-ITD陽性, 18-75歳, 移植移行率 35.8%



Erba. EHA 2022. Abstr S100.

Clinical Question

- ✓ Management of complications, including infection, associated with prolonged myelosuppression

- ✓ Policy for FLT3 mutated AML patients over 75 years of age

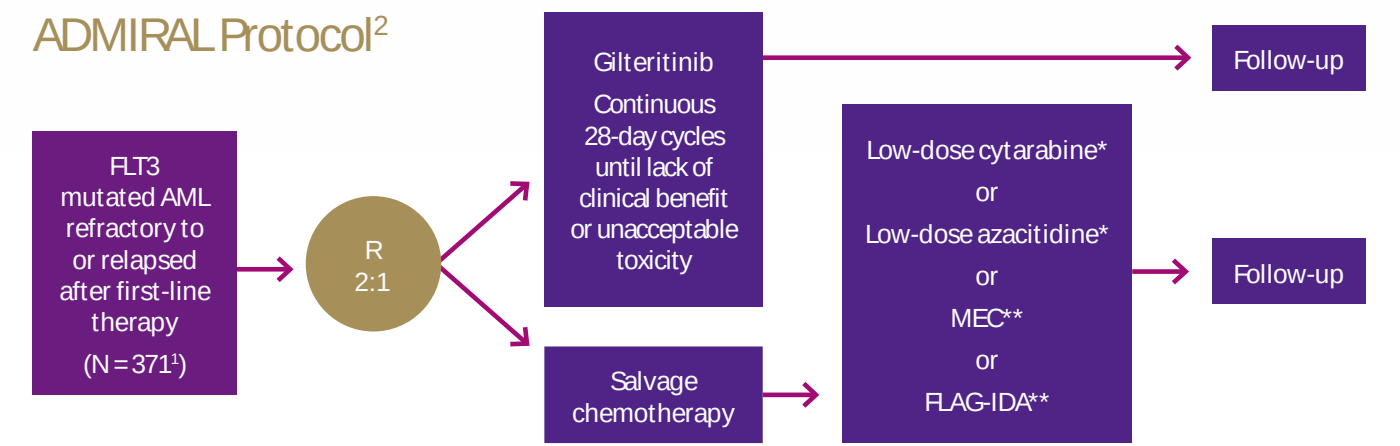
  - Reduced-dose chemotherapy + FLT3i
  - vs. AZA+VEN (+FLT3i)

- In Japan, only quizartinib + chemotherapy is currently indicated in ND FLT3 mutation-positive AML

- Giliteritinib monotherapy is indicated only in r/r FLT3 mutated AML

ADMIRAL
Phase3試験

Gilteritinib vs Chemotherapy for r/r FLT3-Mutated AML



AML = Acute Myeloid Leukemia
FLT3 = FMS-like tyrosine kinase 3
FLAG-IDA = fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin
MEC = mitoxantrone, etoposide and intermediate-dose cytarabine

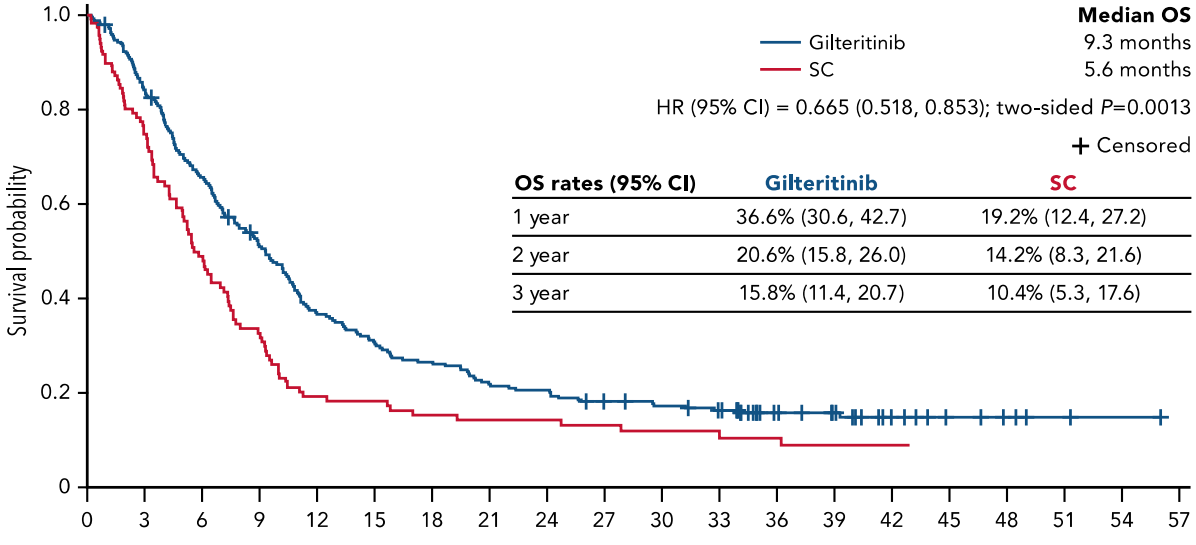
NR = no response
PD = progressive disease
R = randomized

*Continuous 28-day cycles until lack of clinical benefit or unacceptable toxicity.
**For a maximum of 2 cycles or until NR or PD.

Perl AE, et al.: N Engl J Med. 2019; 381（18）: 1728-40.

ADMIRAL
Phase3

Gilteritinib or Chemotherapy for r/r FLT3-Mutated AML



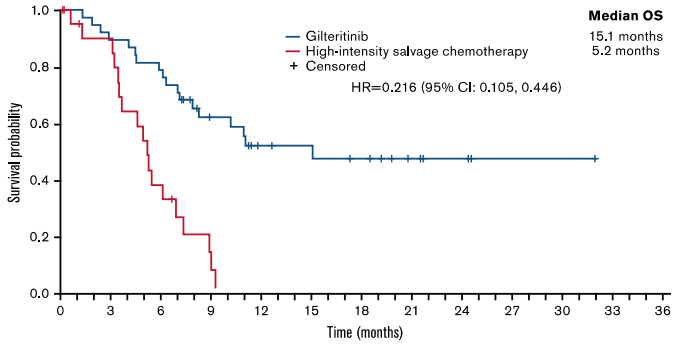
OS rates (95% CI)	Gilteritinib	SC
1 year	36.6% (30.6, 42.7)	19.2% (12.4, 27.2)
2 year	20.6% (15.8, 26.0)	14.2% (8.3, 21.6)
3 year	15.8% (11.4, 20.7)	10.4% (5.3, 17.6)

Patients at risk (n)																				
Gilteritinib	247	206	158	121	87	73	63	52	49	41	38	34	22	18	10	6	4	2	1	0
SC	124	84	52	34	20	18	15	14	14	11	10	7	7	1	1	0	0	0	0	0

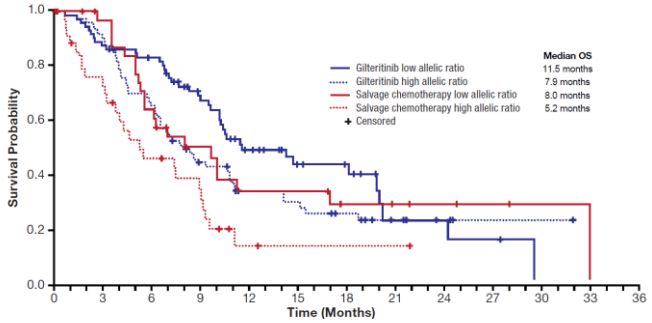
Perl AE, et al.: N Engl J Med. 2019; 381（18）: 1728-40

ADMIRAL
Phase3

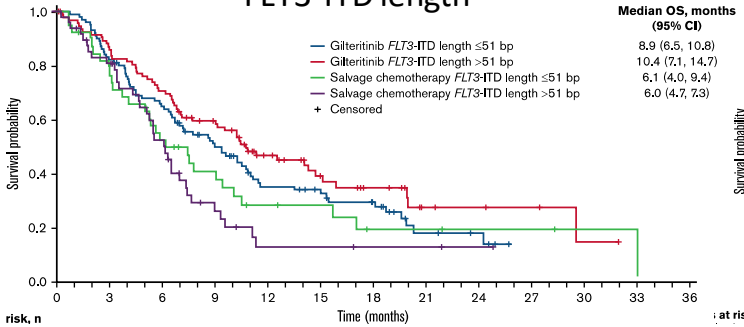
FLT3-ITD+DNMT3Am+NPM1m+



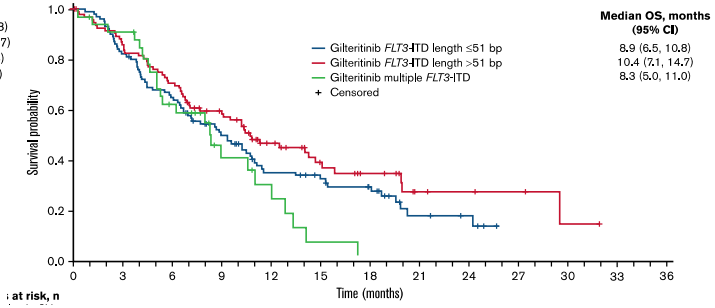
FLT3-ITD allelic ratio



FLT3-ITD length



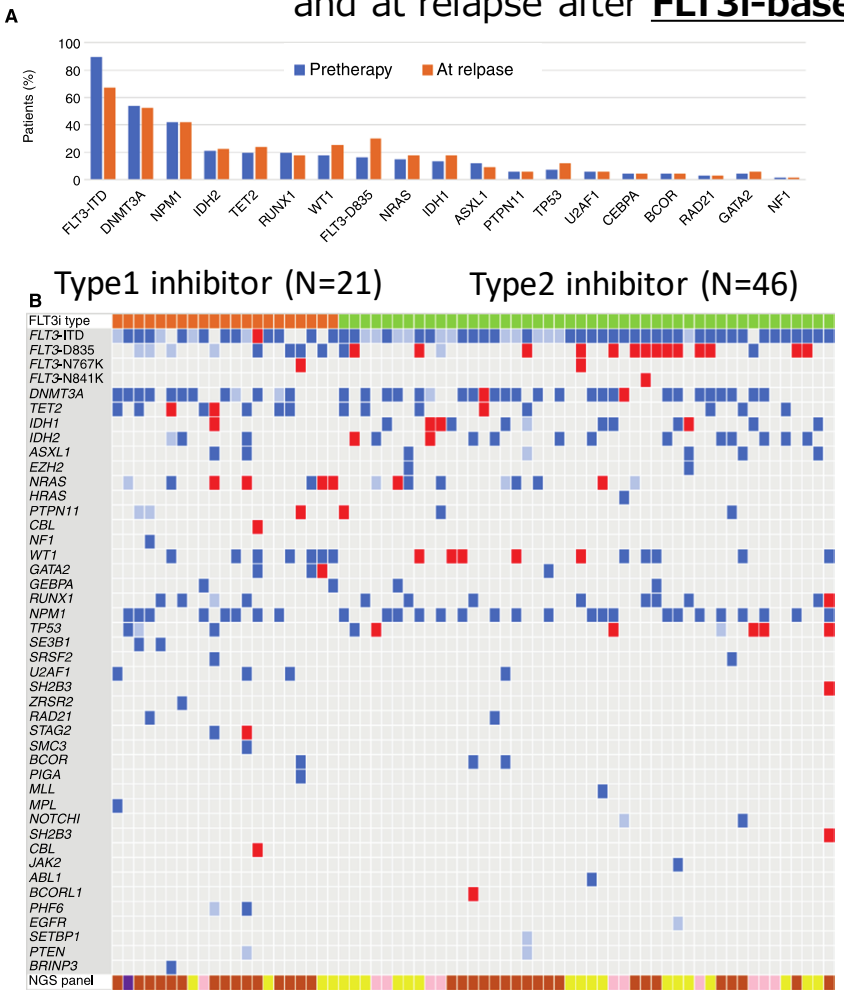
Multiple FLT3-ITD



Gilteritinib was useful regardless of mutation status, allelic ratio of FLT3-ITD, and length of FLT3-ITD.

Smith CC. Blood advances. 2022.

Frequency & landscape of somatic mutations pretherapy and at relapse after **FLT3i-based therapies**



- ✓ Targeted next-generation sequencing (NGS) at relapse identified emergent mutations involving on-target FLT3, epigenetic modifiers, RAS/MAPK pathway, and less frequently WT1 and TP53.
- ✓ RAS/MAPK and FLT3-D835 mutations emerged most commonly following type I and II FLT3i-based therapies, respectively.
- ✓ Among pre-treatment RAS-mutated patients, pretreatment cohort-level variant allelic frequencies for RAS were higher in nonresponders, particularly with type I FLT3i-based therapies, suggesting a potential role in primary resistance as well.

Alotaibi AS. Blood cancer discovery. 2021.

Second-generation FLT3 inhibitors for r/r FLT3 mutated AML

Trial	QuANTUM-R (PIII, n=367)	ADMIRAL (PIII, n=371)
Drug	Quizartinib	Gilteritinib
Effective mutation	ITD	ITD & TKD
CR rate	CR 4%, CRc 48%	CR 21%, CRc 54%
Time to CRc Time to Best Res	1.1 mon 1.9 mon (CRc)	1.8 mon 3.8 mon
Median OS	6.2 mon	9.3 mon
Median DoR	3.0 mon (CRc)	4.6 mon (CRc)
QTc prolongation(≧G3)	4.1%	0.4%
CPK increased (≧G3)	NA	2.4%
Resistance mechanism	TKD、F691L Ras/MAPK	F691 Ras/MAPK
The rate of Allo-HSCT	31.8% (78/245)	35.5% (63/247)

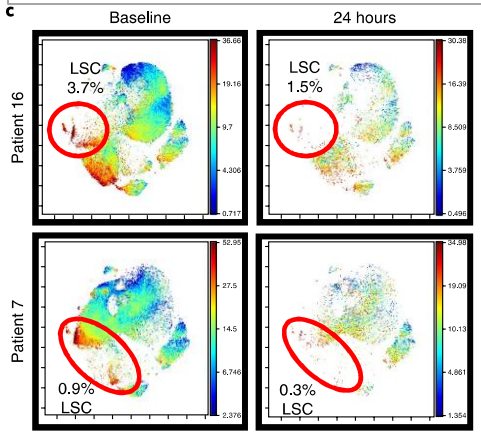
*Unfair comparison as different patient populations

Efficacy of Venetoclax against AML stem cells

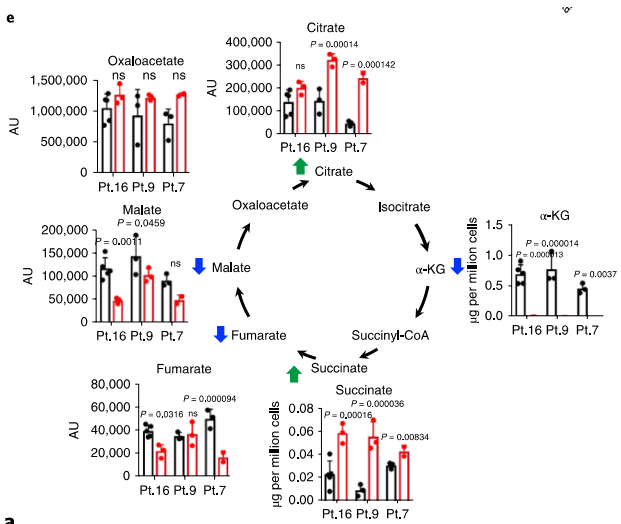
	VEN+DEC	VEN+AZA
Complete remission	8 (35%)	6 (27%)
CRi	6 (26%)	7 (32%)
Partial remission	1 (4%)	0
MLFS*	2 (9%)	5 (23%)
Resistant disease	3 (13%)	2 (9%)
Non-evaluable†	3 (13%)	2 (9%)
Complete remission and CRi	14 (61%)	13 (59%)
Overall response‡	15 (65%)	13 (59%)
Overall outcome§	17 (74%)	18 (82%)

Most common grade 3–4 TEAE:
Thrombocytopenia (9 in group A, 13 in group B), febrile neutropenia (11 in group A, ten in group B,), and neutropenia (12 in group A, eight in group B).

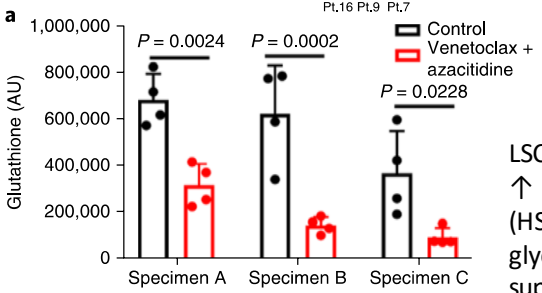
Reduction in LSCs after VEN Tx



Suppression of oxidative phosphorylation by VEN+AZA



Succinate↓
↓
electron transport system ↓
↓
glutathione ↓
↓
antioxidant effect
↓



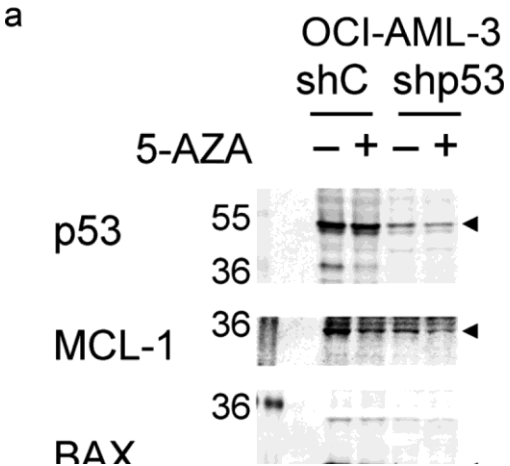
LSC is OXPHOS dependent
↑
(HSCs compensate for glycolysis when OXPHOS is suppressed)

DiNardo CD, et al. Lancet Oncol. 2018.
Pollyea DA, et al. Nat Med. 2018.

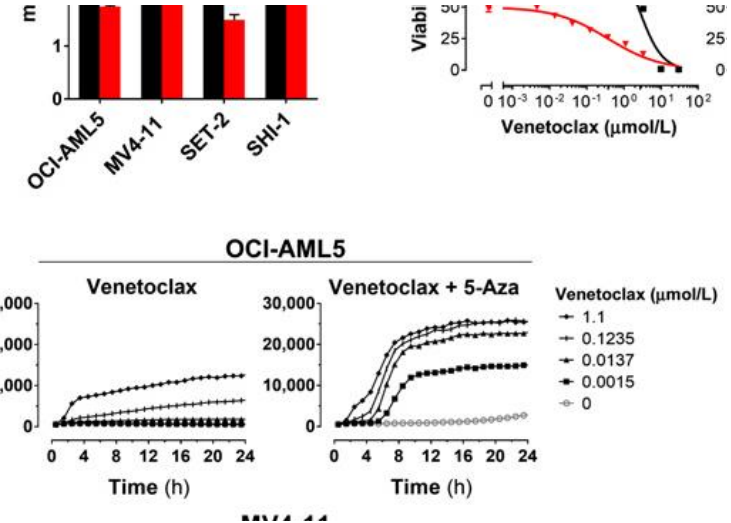
ベネトクラクスの用法・用量は添付文書をご参照ください

Synergistic apoptosis-inducing effect of VEN+AZA

Expression of MCL-1
in Primary AML Samples

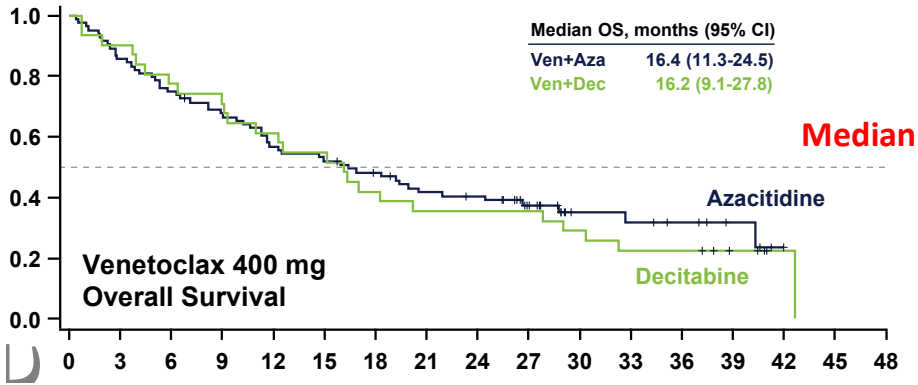


Synergistic effect of VEN+AZA

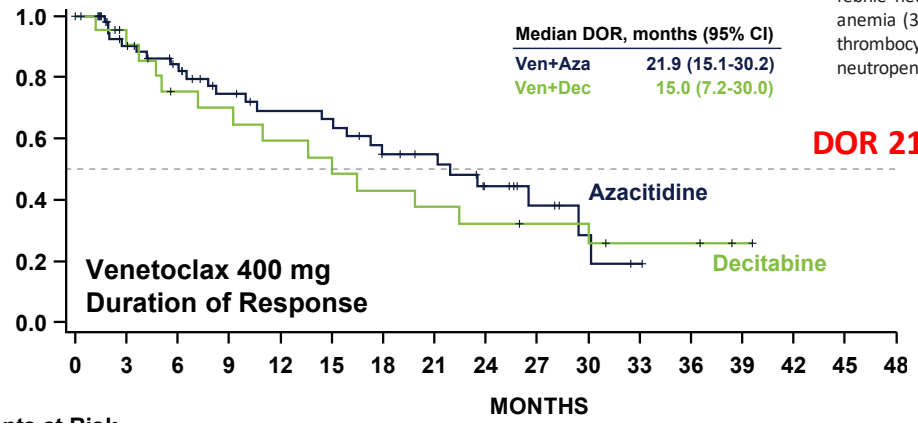


Tsao T. Ann Hematol. 2012. Jin S. Clin Cancer Res. 2020.

Long-term follow-up data of VEN-based regimen



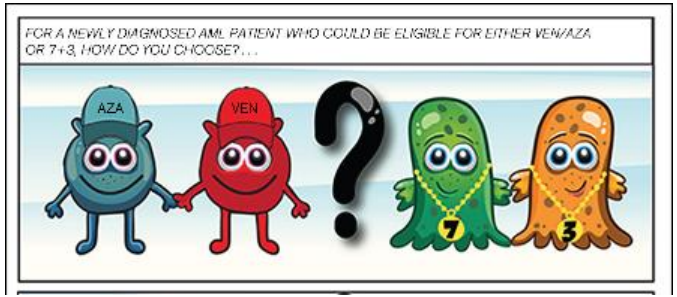
Key Grade ≥ 3 AEs (AZA and DEC)
febrile neutropenia (39% and 65%)
anemia (30% and 26%)
thrombocytopenia (25% and 23%)
neutropenia (20% and 10%)

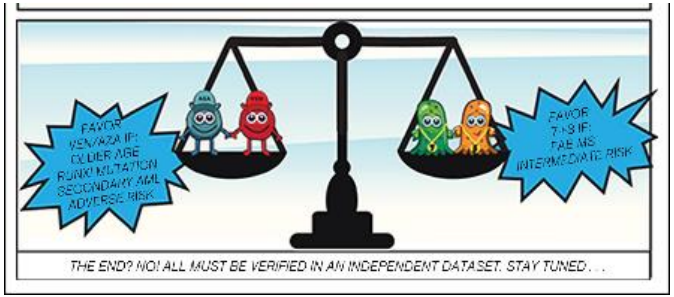


ベネトクラクスの用法・用量は添付文書をご参照ください

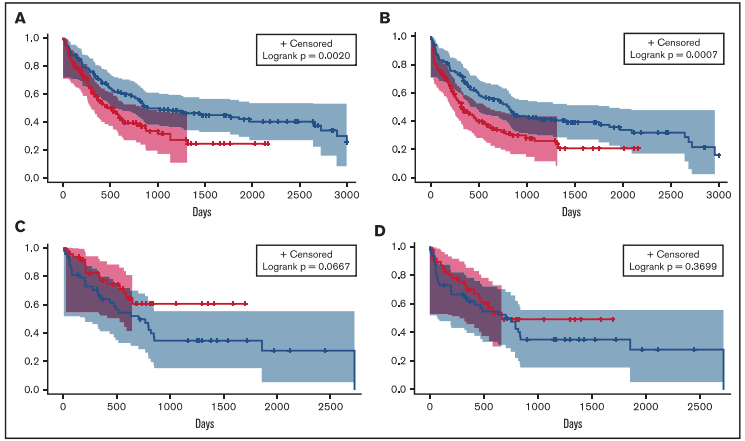
Pollyea DA. Am J Hematol. 2021.

Newly diagnosed AML: AZA+VEN vs. intensive chemotherapy





Retrospective analysis
AZAVEN: n=143, IC: n=149



Propensity-matched cohort

CR/CRi

- AZAVEN: Elderly, secondary AML, RUNX1mut
- IC: AML M5

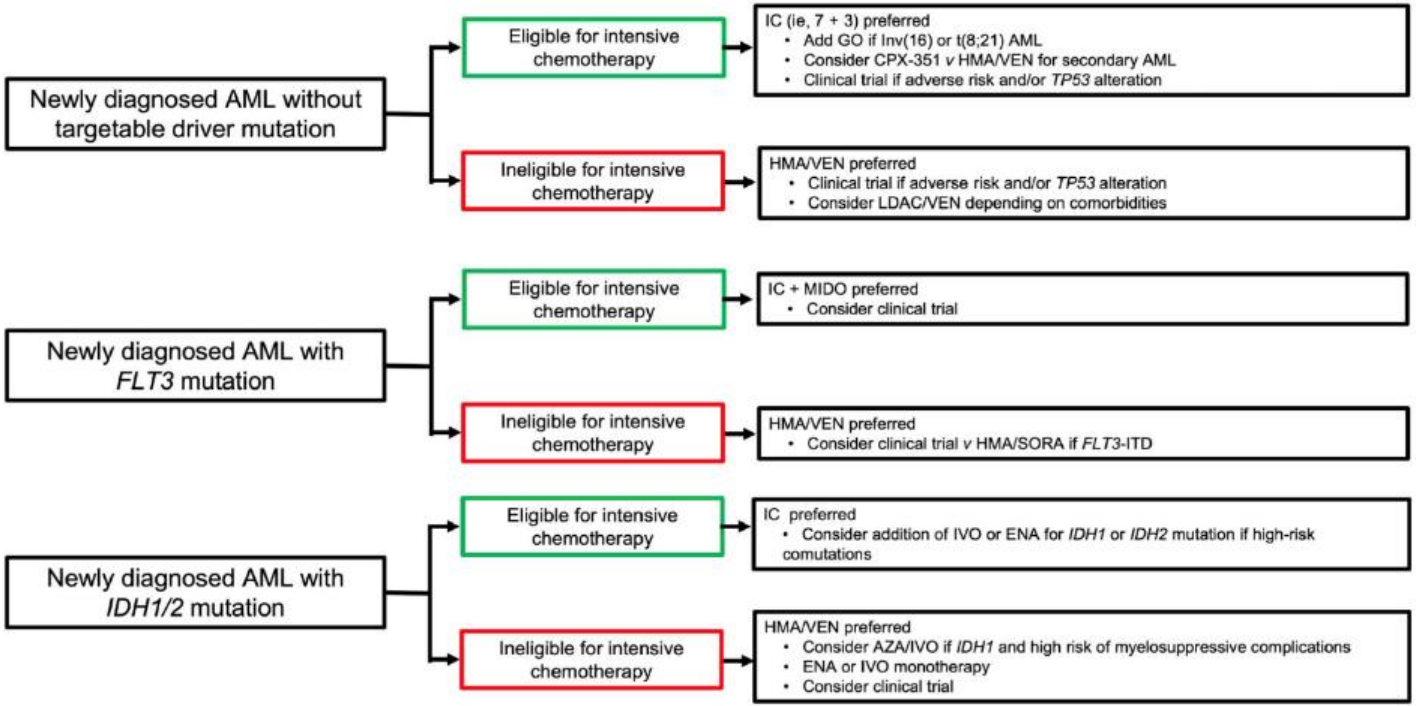
OS

- AZAVEN: Elderly, secondary AML, RUNX1mut
- IC: AML M5

After adjusting for baseline factors, the VENAZA group had better OS.

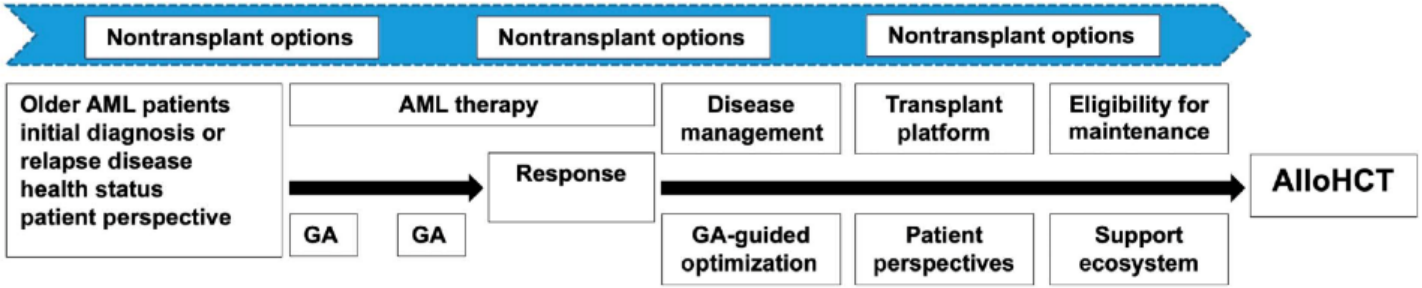
Evan MC. Blood advances. 2021.

Older Adult with Newly Diagnosed AML



Catherine Lai et al. Am Soc Clin Oncol Educ Book. 2023 May;43:e390018.

Older Adult with Newly Diagnosed AML



- ✓ Treatment of elderly patients with AML may reduce treatment-related mortality by incorporating early diagnosis, long-term geriatric assessment (GA), and GA-guided management.
- ✓ GA is combined with disease risk assessment for early transplant evaluation to maximize the likelihood of cure in elderly patients.

Catherine Lai et al. Am Soc Clin Oncol Educ Book. 2023 May;43:e390018.

2022 ELN AML Reccomendation

AE management

Agent	AE requiring special attention (incidence all grades)	Management
Midostaurin	QT prolongation (10%)	Dose interruption/reduction, substitution of QT prolonging co-medication if possible, otherwise additional ECG controls
Gilteritinib	Transaminase elevation (81%) QT prolongation (9%) PRES (1%)	Dose interruption/reduction (if grade ≥3) Dose interruption/reduction, substitution of QT prolonging co-medication if possible Discontinuation
Ivosidenib	Differentiation syndrome (25% single agent, 17% in combination with azacitidine) QT prolongation (21% single agent, 26% combination with azacitidine)	Dexamethasone, hydroxyurea for co-occurring leukocytosis, Dose interruption/reduction Dose interruption/reduction, substitution of QT prolonging co-medication if possible
Enasidenib	Differentiation syndrome (14% single agent, 10% in combination with azacitidine) Bilirubin elevation (81%)	Dexamethasone, hydroxyurea for co-occurring leukocytosis, Dose interruption/reduction Dose interruption/reduction
Gemtuzumab ozogamicin	Transaminase elevation (24.5%)[a] Bilirubin elevation (13%)[a] VOD/SOS (2.9-4.6%)	Dose interruption/reduction Dose interruption, supportive care, fluid management, possibly defibrotide
Venetoclax	Neutropenia Thrombocytopenia	Early response assessment, eg, on day 14-21 of cycle 1, if bone marrow blasts <5%, cease venetoclax for up to 14 days to allow count recovery to ≥ CRh. If neutropenia does not recover with 7 days of ceasing venetoclax, addition of G-CSF may augment recovery. Subsequent cycles: azacitidine 75 mg/m^2 SC/IV d1-7 (or d1-5 + d8-9) or decitabine 20 mg/m^2 IV d1-5 plus venetoclax 400 mg QD, or LDC 20 mg/m^2 SC d1-10 plus venetoclax 600 mg QD q4 weeks until progression. Delayed count recovery or recurrent treatment-emergent grade 4 neutropenia/thrombocytopenia lasting ≥7 days require reductions in the duration of administered venetoclax (from 28 to 21 or 14 days, or even less) and/or reductions in the dose of azacitidine, decitabine, or LDC if severe bone marrow hypoplasia.
	Tumor lysis syndrome	Dose ramp up in cycle 1; hydration, the prophylactic use of uric acid lowering drugs, close electrolyte monitoring and reduction of WBC to <25 x 10^9/L (<25,000/μL) is recommended.
	Interaction with CYP3A inhibitors	• Moderate CYP3A inhibitors (eg, ciprofloxacin): reduce the venetoclax dose by at least 50%; ramp-up phase: 50 mg on d1, 100 mg on d2, 200 mg PO QD from d3 • Strong CYP3A inhibitors (eg, posaconazole): ramp-up phase: 10 mg on d1, 20 mg on d2, 50 mg on d3, 100 mg (or less[c])[206] QD PO from d4.
Glasdegib	Muscle spams (15%) QT prolongation (8.3%)	Dose interruption/reduction Dose interruption/reduction, substitution of QT prolonging co-medication if possible
CPX-351	Prolonged myelosuppression[b]	Consequent anti-infectious prophylaxis
CC-486/oral azacitidine	Neutropenia (44%) Thrombocytopenia (35%) Nausea (65%), vomiting (60%),	Dose interruption/reduction, myeloid growth factors Prophylactic anti-emetics

Diarrhea(50%)

gilteritinib

venetoclax

Doner H. Blood. 2022.

Antifungal Prophylaxis for Adults with AML Receiving Novel Targeted Therapies

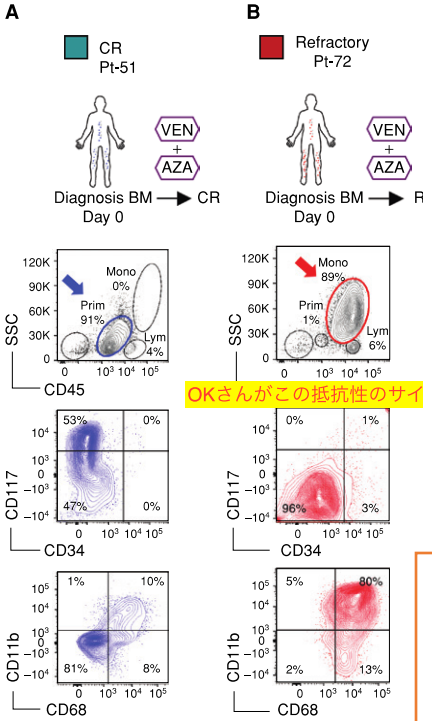
European Society of Hematology Initiative Systematic Review/Expert Consensus Recommendations

	Molecular target	Licensed indication or approval status (in the EU) in adults	Antifungal prophylaxis—recommendation	Antifungal prophylaxis—comment
Azacitidine	Inhibition of DNA methyltransferases that aberrantly hypermethylate tumour suppressor gene promoters	Acute myeloid leukaemia (>30% BM blasts); secondary acute myeloid leukaemia from myelodysplastic syndrome (20–30% BM blasts); myelodysplastic syndrome (intermediate to high risk on the IPSS-R); chronic myelomonocytic leukaemia (10–29% abnormal BM cells)	Conditional for antifungal prophylaxis; low certainty of evidence	Not generally recommended, but should be considered in patients pretreated with chemotherapy, in those with neutropenia at treatment initiation, or those with previous invasive fungal disease
Decitabine	Inhibition of DNA methyltransferases aberrantly hypermethylating tumour suppressor gene promoters	De-novo or secondary acute myeloid leukaemia	Conditional for antifungal prophylaxis; low certainty of evidence	Extrapolated from azacitidine
Venetoclax	Selective inhibitor of BCL2 (ie, antiapoptotic protein)	Chronic lymphocytic leukaemia; acute myeloid leukaemia (combination with HMA)	Conditional for antifungal prophylaxis; low certainty of evidence	Preferably with a triazole; adapt dose when using posaconazole or voriconazole concomitantly

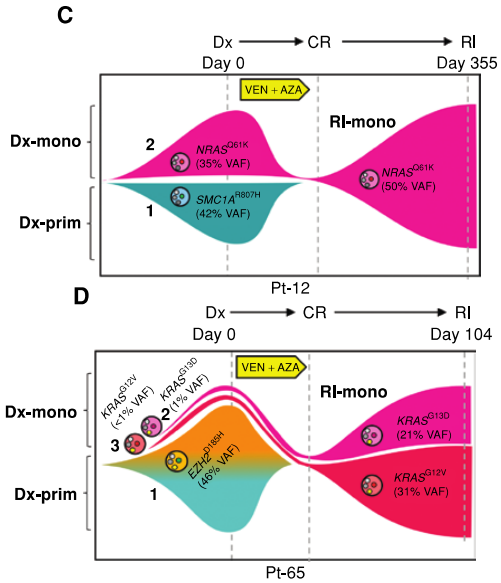
- ✓ Antifungal prophylaxis is recommended at moderate intensity in most treatment settings. It is strongly recommended when new acute myeloid leukemia drugs are combined with intensive induction chemotherapy.
- ✓ <u>For ivosidenib, restaurtinib, quizartinib, and venetoclax, moderate adjustment of the antileukemic drug dose during triazole administration is recommended</u>.

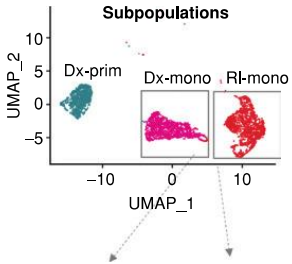
Stemler J. Lancet Hematol. 2022.

Monocytic Subclones Confer Resistance to Venetoclax-Based Therapy in Patients with AML



OKさんがこの抵抗性のサイ





D

gprofiler

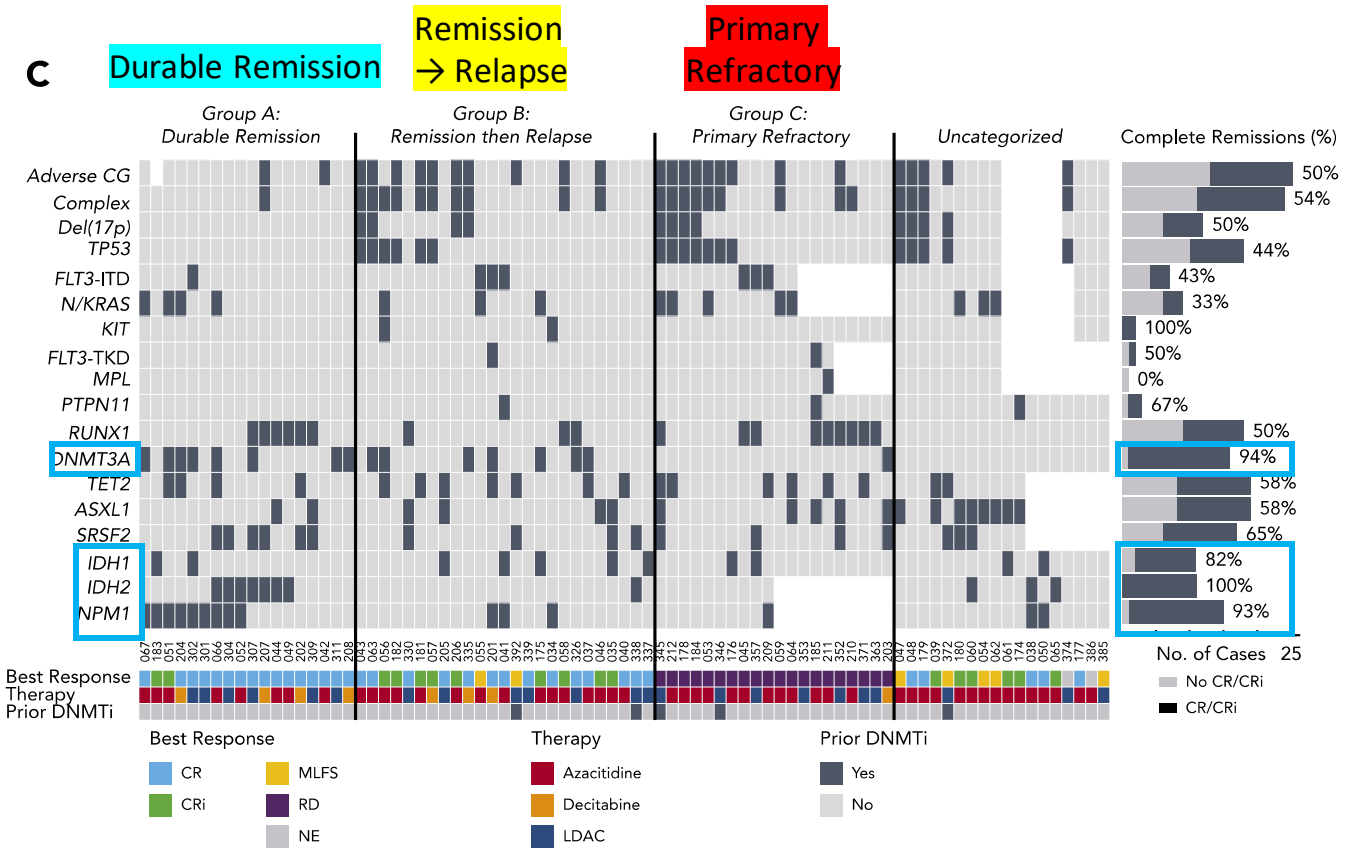
Upregulated in RI-mono relative to Dx-mono:

Gene set	FDR
CLEARY_MLL_LSC_UP	5.27E-04
YAGI_AML_WITH_T_9_11_TRANSLOCATION	4.58E-10
ROSS_LEUKEMIA_WITH_MLL_FUSIONS	1.34E-09
HESS_HOXA9_DEPENDENT_TOP_1000	2.46E-09
ROSS_AML_WITH_MLL_FUSIONS	3.57E-06
YAGI_AML_WITH_11Q23_REARRANGED	4.14E-06
WANG_MLLENT_TARGETS	1.79E-05
MOOTHA_MITOCHONDRIA	4.30E-07
PALMIERI_TFEB_CLEAR	1.30E-04
GO_OXIDATIVE_PHOSPHORYLATION	4.10E-09
HALLMARK_OXIDATIVE_PHOSPHORYLATION	5.93E-08
KEGG_OXIDATIVE_PHOSPHORYLATION	3.70E-06

Why monocyte AML becomes VEN-resistant
- high MCL1 expression
- Involvement of KRAS mutation
- Gene expression patterns in MLL+ leukemia

Pei S. Cancer Discovery. 2020.

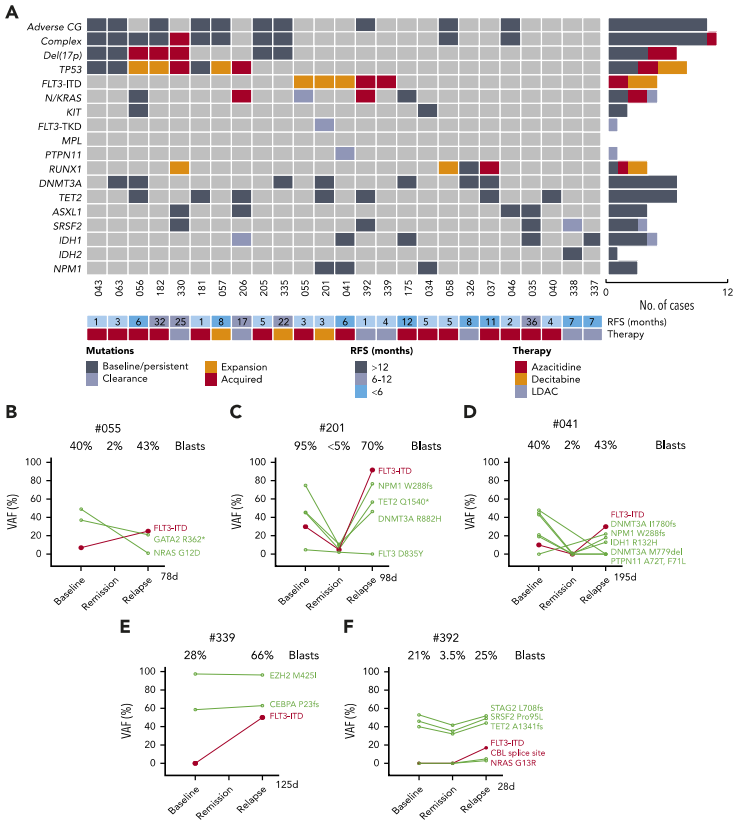
Treatment response of VEN by genetic mutation

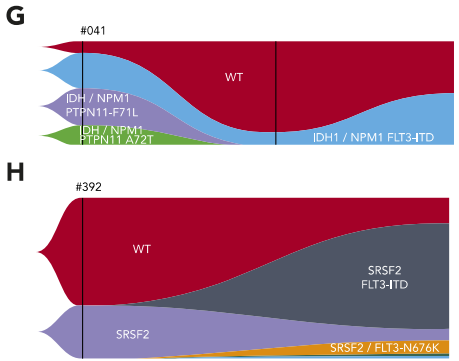


ベネトクラクスの用法・用量は添付文書をご参照ください

DiNardo CD, et al. Blood. 2020 Mar12;135(11):791-803.

FLT3-positive recurrence after VEN-based regimen





Sample	Date	Blast %	WT	IDH1/NPM1 FLT3-ITD	IDH1/NPM1 PTPN11-F71L	IDH1/NPM1 PTPN11-A72T
Screen	03/06/15	66%	11.3%	33.0 %	35.8 %	20.0 %
Relapse	10/26/15	43%	87.2%	12.8 %	0 %	0 %
Relapse	11/10/15	PB 10%	49.4%	50.6 %	0 %	0 %

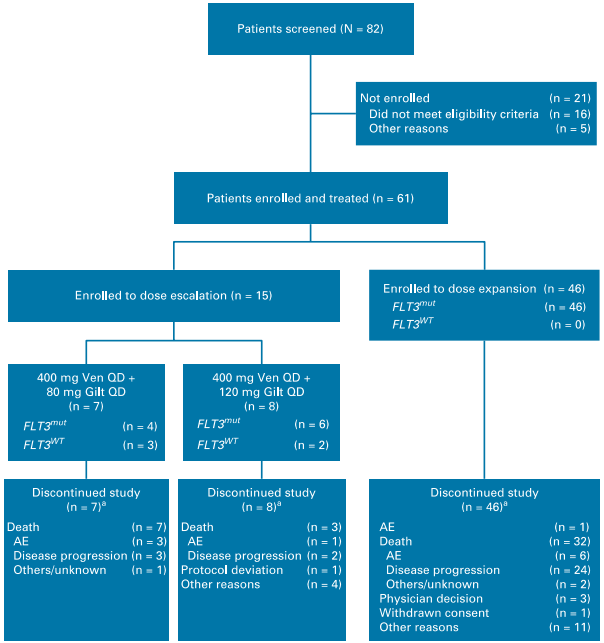
Sample	Date	Blast %	WT	SRSF2 FLT3-ITD	SRSF2	SRSF2 FLT3-N676K	FLT3 D835H	SRSF2 NRAS-G13R	NRAS G12A	NRAS Q61k
Screen	04/26/17	29 %	67.1%	0 %	32.8%	0.1 %	0 %	35.8 %	0 %	0 %
Relapse	07/06/17	25 %	15.5 %	65.8 %	7.0 %	8.2 %	1.6 %	0 %	0.3 %	0.3 %

ベネトクラクスの用法・用量は添付文書をご参照ください

DiNardo CD, et al. Blood. 2020 Mar12;135(11):791-803.

Venetoclax Plus Gilteritinib for FLT3-Mutated Relapsed/Refractory AML

Patient enrollment and disposition



- 61 patients enrolled, median age 63 years (range: 21~85 years)
- Prior treatment: 19 patients (31%) received allogeneic transplantation, 10 patients received VEN (no prior giliteritinib)
- 36 of 56 Flt3 mutation-positive patients had received FLT3 TKIs
- The median duration of exposure was 2.6 months (range: 0.07-16.8) for VEN and 2.6 months (range: 0.1-17.2) for GIL

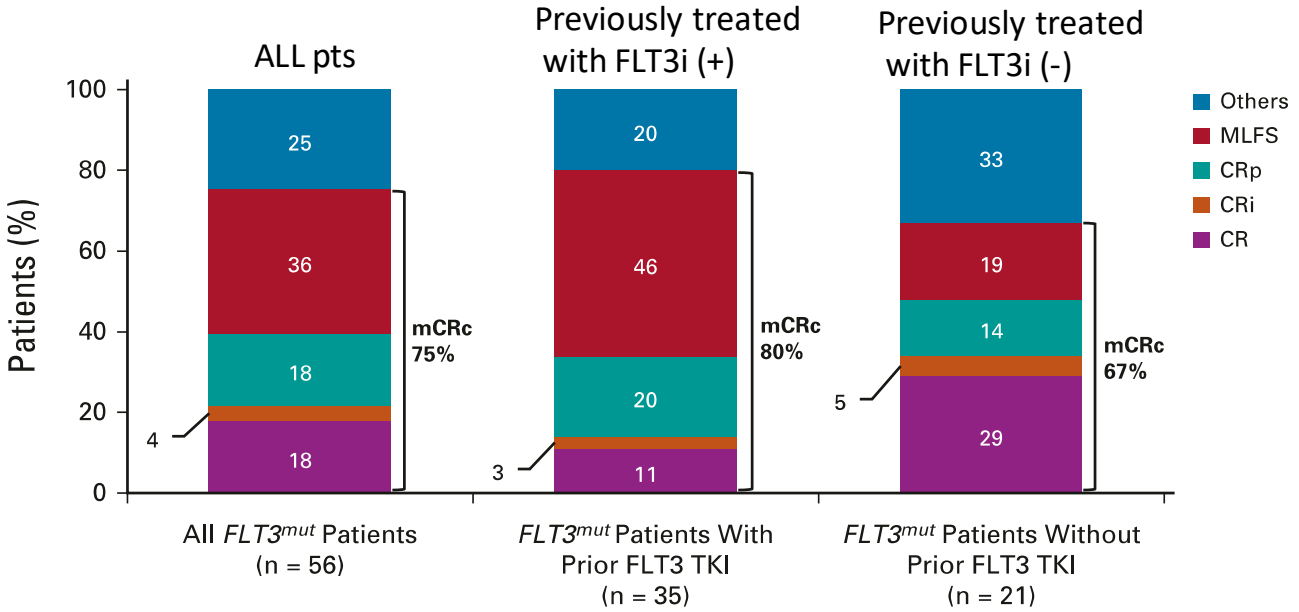
Characteristic	All Patients (N = 61)
Median age, years (range)	63 (21-85)
Sex, No. (%)	
Female	30 (49)
Race, No. (%)	
White	53 (88)
Black or African American	3 (5)
American or Alaska Native	4 (7)
Hawaiian Native or Pacific Islander	0
Missing	1 (2)
ECOG PS, No. (%)	
0	10 (16)
1	42 (69)
2	9 (15)
Cytogenetic risk, No. (%)	
Favorable	2 (3)
Intermediate	33 (56)
Poor	20 (34)
No mitoses or missing	6 (10)
Relapsed disease, No. (%)	42 (69)
Refractory disease, No. (%)	19 (31)
FLT3 mutation, No. (%)	56 (92)
ITD alone	44 (72)
TKD alone	9 (15)
Both	3 (5)
Median prior lines of t	
Prior lines of therapy,	
1	
2	
≥ 3	
Prior venetoclax, No. (%)	10 (16)
Prior alloSCT, No. (%)	19 (31)
Prior FLT3 TKI in *FLT3*^{mut} patients, n/n (%)	36/56 (64)
1 prior FLT3 TKI	22/56 (39)
> 1 prior FLT3 TKI	14/56 (25)

Midostaurin as induction therapy
Sorafenib after transplantation

Daver N. JCO. 2022.

Venetoclax Plus Gilteritinib for FLT3-Mutated Relapsed/Refractory AML

Response rates in all FLT3mut patients treated at any dose (n = 56)

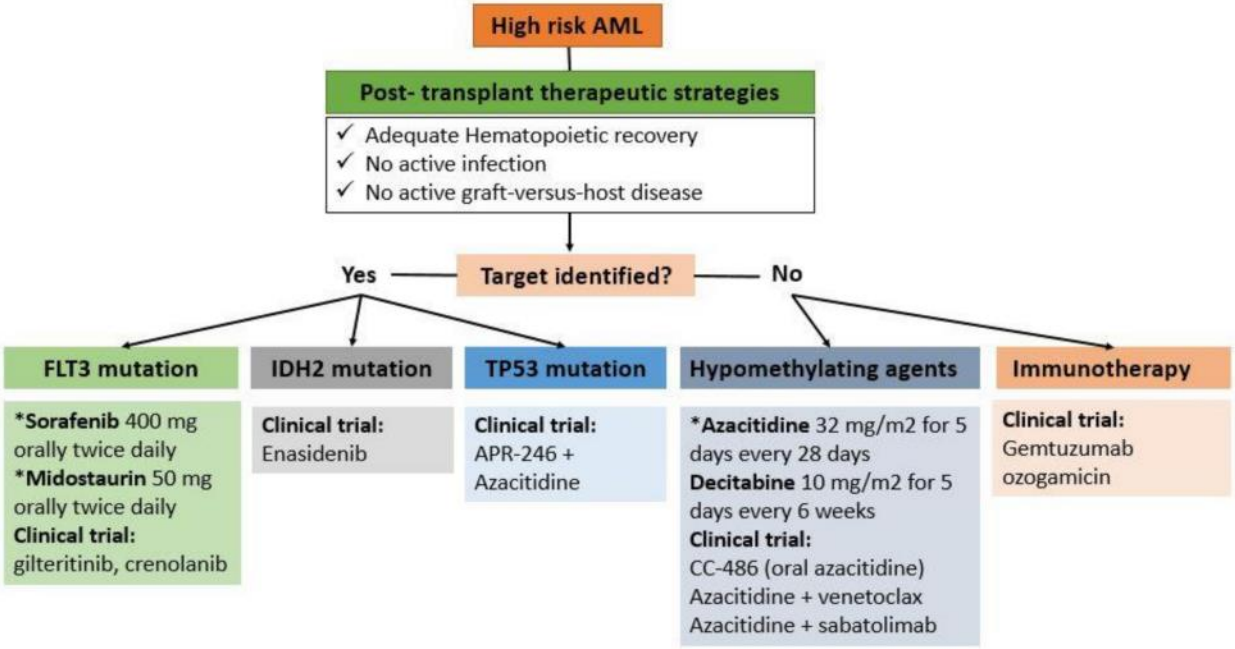


mCRc (modified composite complete response)
: CR + CRi + CRp (Defined in ADMIRAL trial)

- ✓ Modified composite complete response was achieved in 75% of patients
- ✓ Response rates were 67% and 80% in patients who had not previously received FLT3i

Daver N. JCO. 2022.

Maintenance therapy after allogeneic transplantation

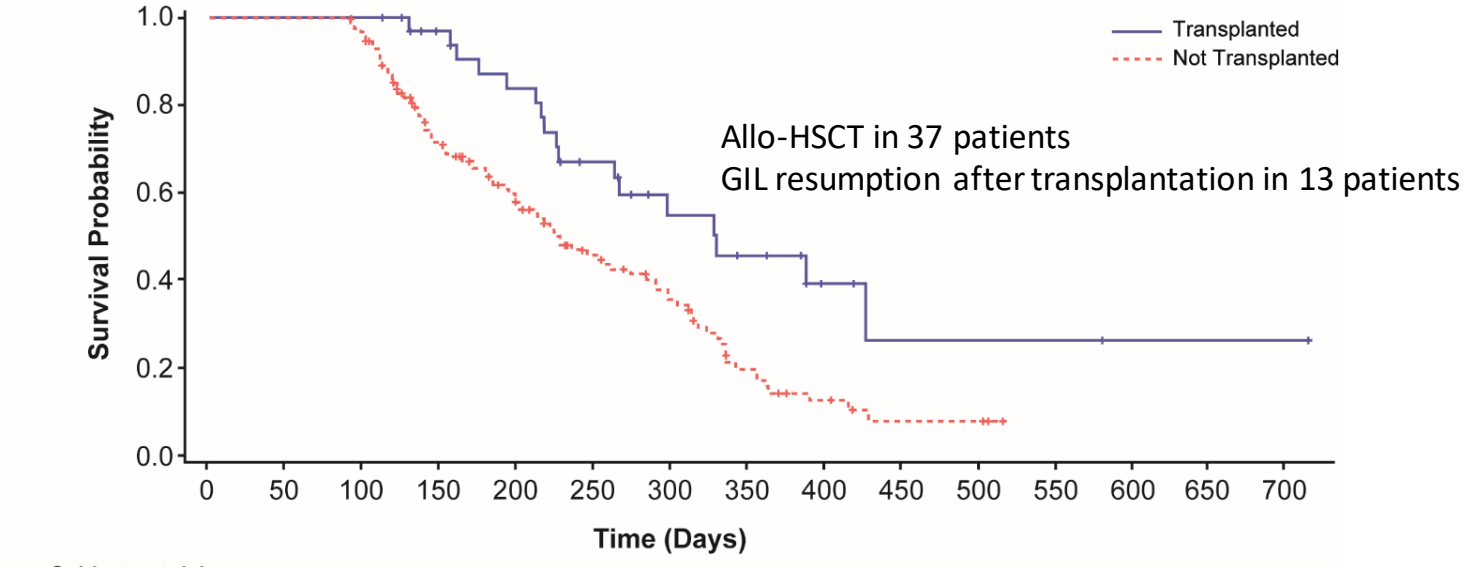


Dalle IA. Cancers. 2022.

Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1–2 study

Alexander E Perl*, Jessica K Altman*, Jorge Cortes, Catherine Smith, Mark Litzow, Maria R Baer, David Claxton, Harry P Erba, Stan Gill, Stuart Goldberg, Joseph G Jurcic, Richard A Larson, Chaofeng Liu, Ellen Ritchie, Gary Schiller, Alexander I Spira, Stephen A Strickland, Raoul Tibes, Celalettin Ustun, Eunice S Wang, Robert Stuart, Christoph Röllig, Andreas Neubauer, Giovanni Martinelli, Erkut Bahceci, Mark Levis

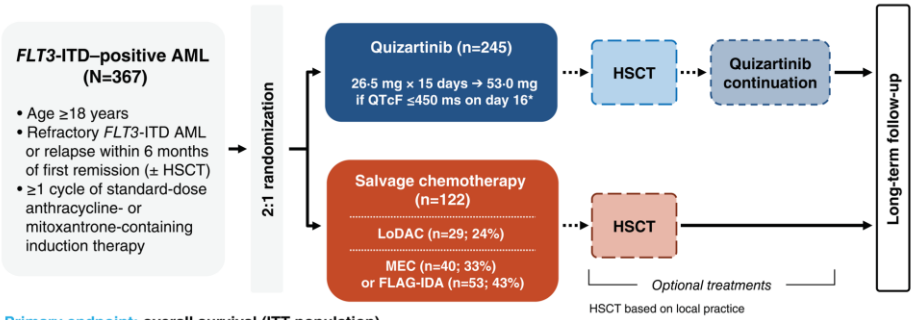
CHRYSALIS Study



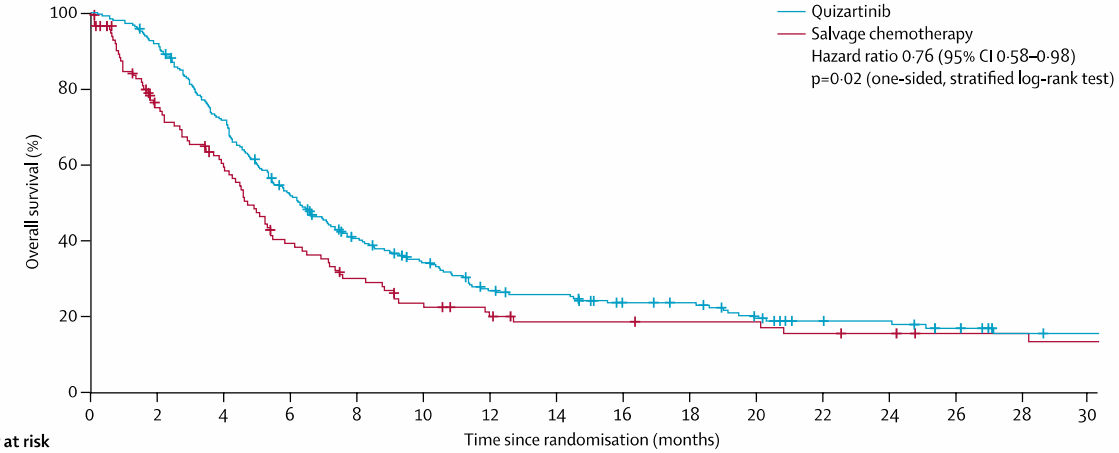
Bridging to allo-HSCT after successful treatment with GIL

Perl AE. Lancet Oncol. 2017.

QuANTUM-R study



Primary endpoint: **overall survival (ITT population)**
Secondary endpoint: **event-free survival (ITT population)**
Select exploratory endpoints: **CRc rate, duration of CRc, and transplant rate**
Enrollment dates: May 2014 (first patient) to September 2017 (last patient)
Data cutoff: February 2018



Number at risk (number censored)

Quizartinib	245 (0)	224 (1)	173 (3)	122 (6)	89 (13)	71 (17)	53 (20)	48 (23)	38 (29)	36 (31)	27 (34)	20 (40)	20 (40)	16 (42)	11 (46)	10 (47)
Salvage chemotherapy	122 (0)	77 (18)	59 (20)	38 (21)	28 (22)	21 (23)	15 (26)	13 (27)	13 (27)	12 (28)	12 (28)	10 (28)	9 (29)	7 (31)	7 (31)	6 (31)

Cortes JE. Lancet. Lancet Oncol. 2019.

BMT-CTN 1506 (MORPHO): A RANDOMIZED TRIAL OF THE FLT3 INHIBITOR GILTERITINIB AS POST-TRANSPLANT MAINTENANCE FOR FLT3-ITD AML

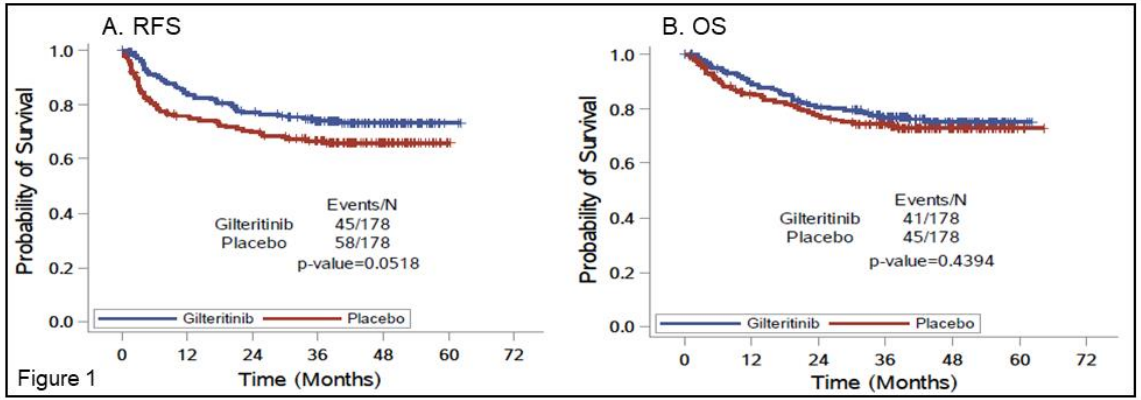


Figure 1

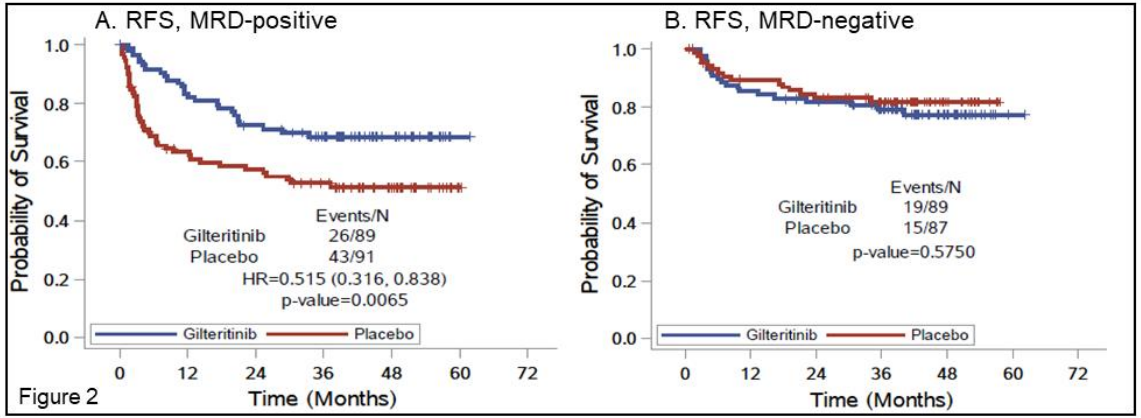
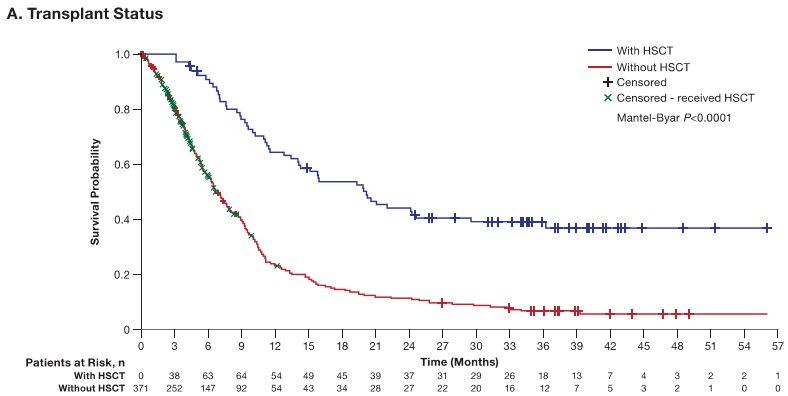
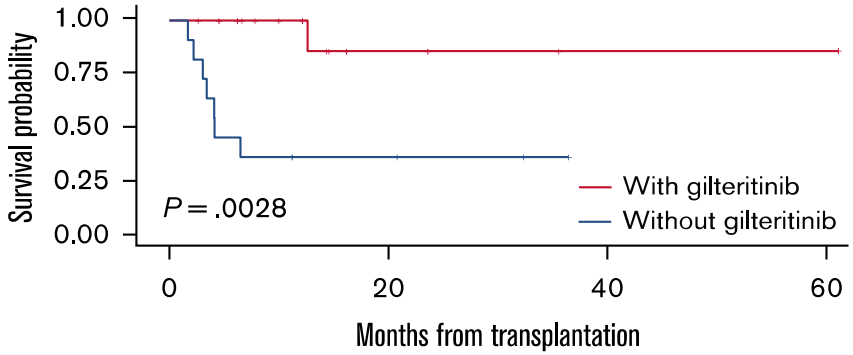


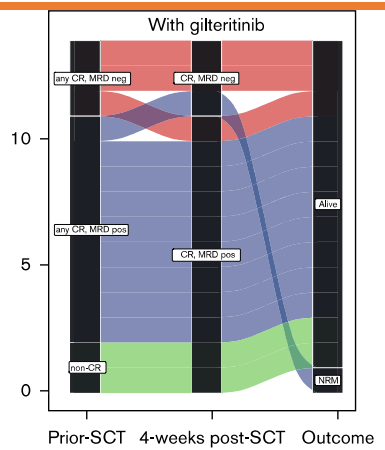
Figure 2

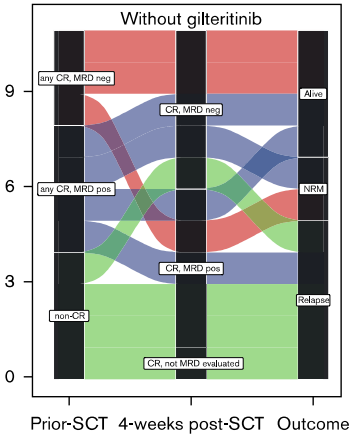
Levis M. EHA. 2023.

Early initiation of low-dose gilteritinib maintenance improves posttransplant outcomes in patients with R/R FLT3^{mut} AML









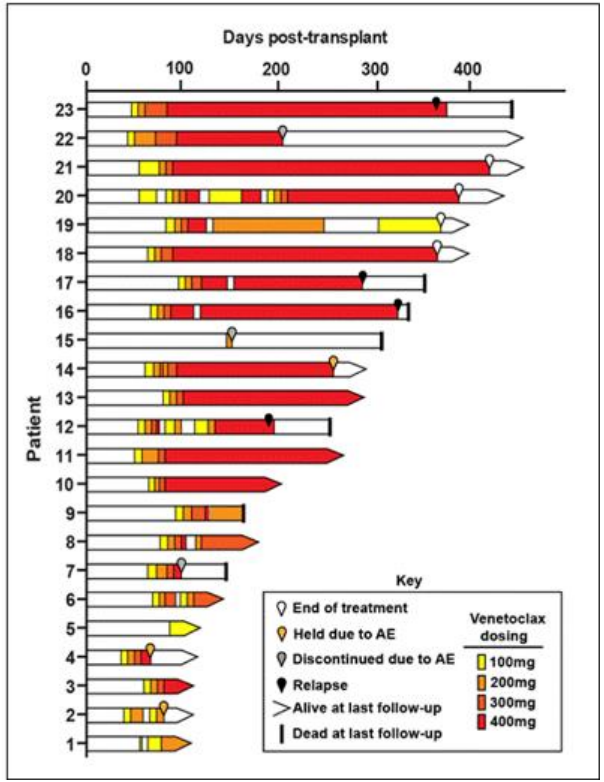
T Terao. Blood Advances. 2023.

VEN maintenance therapy in high-risk patients with post-transplant recurrence

Table 1: Patient Demographics and pre-ASCT data			
Total # of patients		23	
Median age at transplant (range)		65 (19 - 73)	%
Sex	Male	12	52.2
	Female	11	47.8
Disease type	AML	16	69.6
	MDS transformed to AML	6	26.1
	MDS	1	4.3
MRD detection method	Cytogenetics/FISH	15	65.2
	Flow cytometry	10	43.5
	Digital droplet PCR	6	26.1
# of pre-transplant lines of therapy	1	15	65.2
	2	4	17.4
	3	3	13.0
Conditioning regimen	Flu/Cy/Thio/TBI	17	73.9
	Flu/Cy/TBI	2	8.7
	Flu/TBI	1	4.3
	Flu/Melphalan	3	13.0
Disease status at transplant	Complete remission	15	65.2
	MLFS	6	26.1
	CRi	1	4.3
	Aplastic	1	4.3
	MDS w/ sideroblasts and dysplagia	1	4.3
Transplant Type	Cord	15	65.2
	Haplo-cord	5	21.7
	Matched-related donor	4	17.4
Median follow up time (range)		254 (92 - 445)	

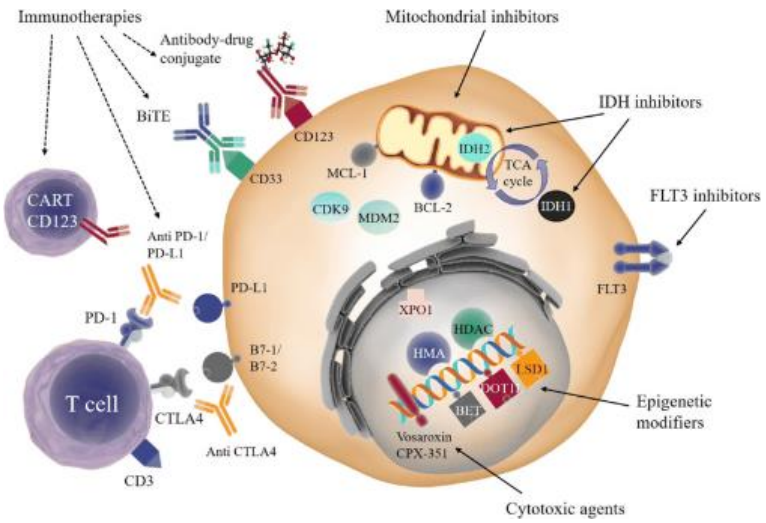
Flu = fludarabine, Cy = cyclophosphamide, Thio = thiotepa; MLFS = morphologic leukemia free state, CRi = complete remission with incomplete count recovery.

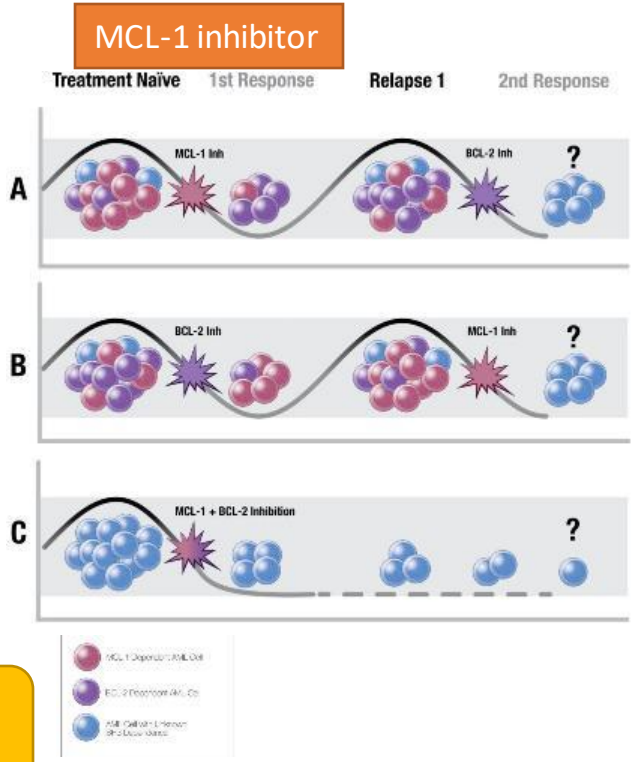
Figure 1: treatment timeline for each patient



ベネトクラクスの用法・用量は添付文書をご参照ください　Kent A. ASH. 2021.

Development of new drugs for AML





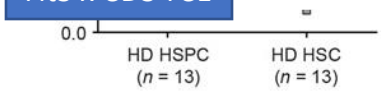
Combination therapy
Management of cardiotoxicity

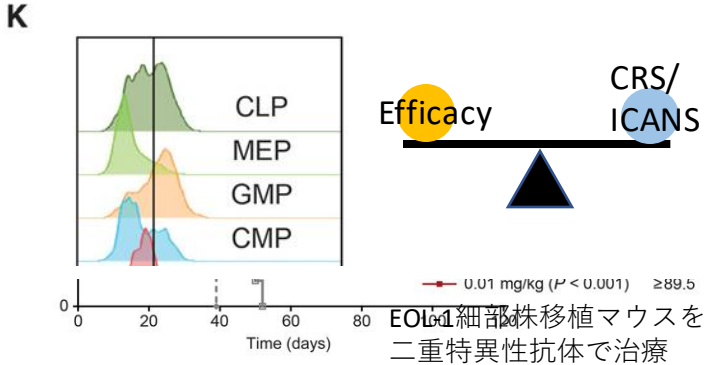
Ramsey HE. Cancer Discov. 2018.
Motesinos P. Ann Hematol 2019.

Characterization of a Novel FLT3 BiTE Molecule for the Treatment of Acute Myeloid Leukemia

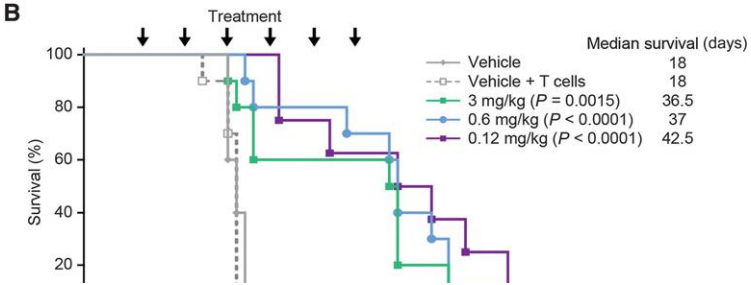
Bettina Brauchle[1,2], Rebecca L. Goldstein[3], Christine M. Karbowski[4], Anja Henn[5], Chi-Ming Li[3], Veit L. Bücklein[1,2], Christina Krupka[1,2], Michael C. Boyle[4], Priya Koppikar[4], Sascha Haubner[1,2], Joachim Wahl[5], Christoph Dahlhoff[5], Tobias Raum[5], Matthew J. Rardin[3], Christine Sastri[3], Dan A. Rock Michael von Bergwelt-Baildon[1,2,6], Brendon Frank[3], Klaus H. Metzeler[2,6], Ryan Case[3], Matthias Friedrich Mercedesz Balazs[3], Karsten Spiekermann[2,6,7], Angela Coxon[5], Marion Subklewe[1,2,6], and Tara Arvedsor

Flt3 x CD3 TCE



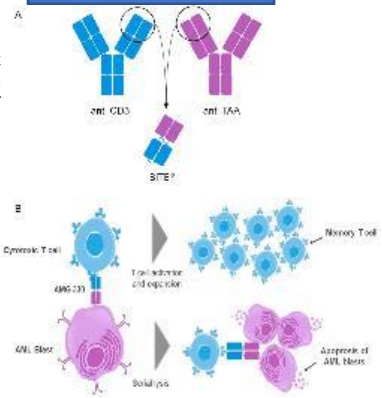


EOL-1細部株移植マウスを
二重特異性抗体で治療



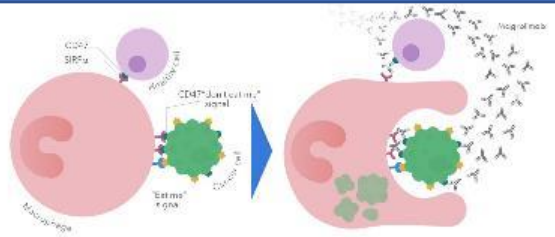
Molecular Cancer Therapeutics. 2020.

CD33 x CD3 TCE



Mary C. Clark.
Best Practice & Research Clinical Haematology. 2020.

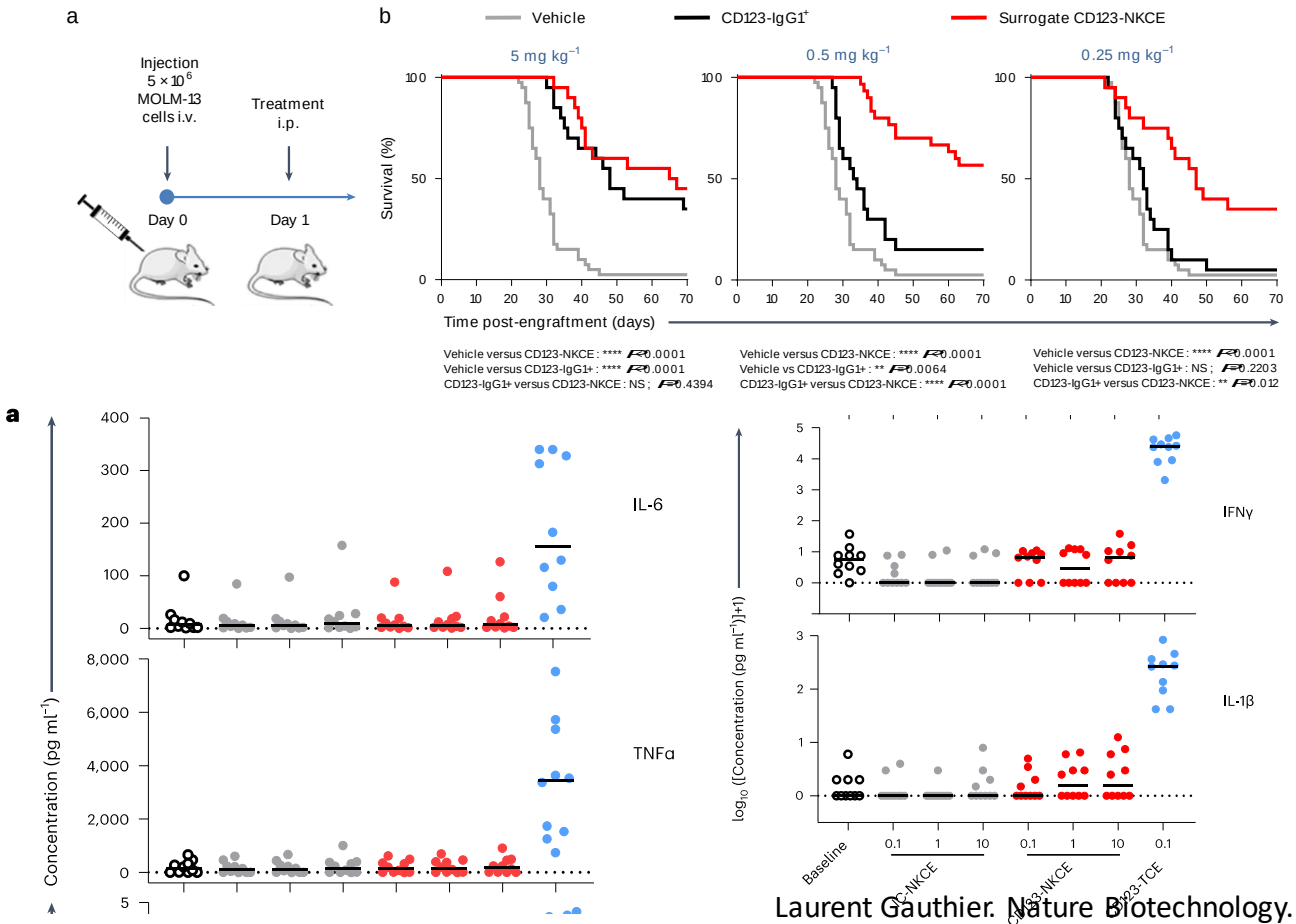
Inhibition of Don't eat me signal: ant-CD47 antibody



- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

David Sallman. ASCO 2020.

Trifunctional NKp46-CD16a-NK cell engager targeting CD123

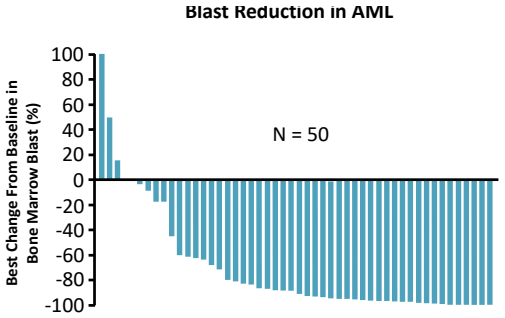


Laurent Gauthier. Nature Biotechnology. 2022.

Magrolimab + Azacitidine in Untreated AML (TP53 wt & mutated)

Phase1b試験

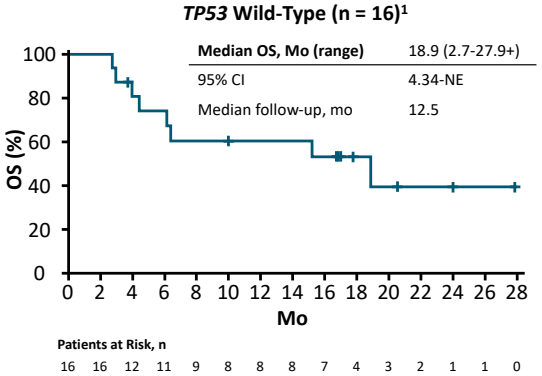
Outcome	*TP53* Mutant (n = 72)
ORR, n (%)	45 (48.6)
§ CR	24 (33.3)
§ CRi/CRh	6 (8.3)
§ PR	4 (5.6)
§ MLFS	1 (1.4)
Median DoR, mo	8.7
Median DCR, mo	7.7
Median TOR, mo	2.0
Median TCR, mo	3.0
CCyR, n/N (%)	10/31 (32.3)
MRD negativity in CR, n/N (%)	12/24 (50)
Median PFS, mo	7.3
Median OS, mo	10.8

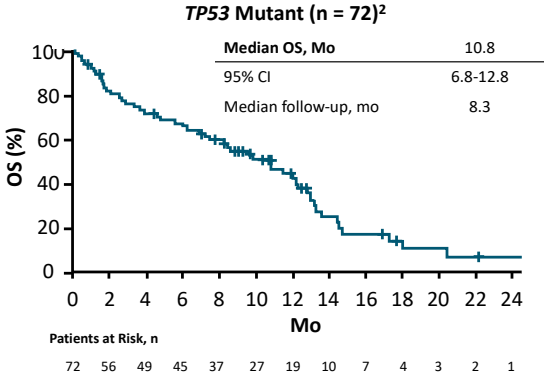


§ n = 9 proceeded to bone marrow stem cell transplant

§ Conversion to red blood cell transfusion independence: 29.7% in *TP53*-mutant AML

Daver. EHA. 2022. Abstr S132.

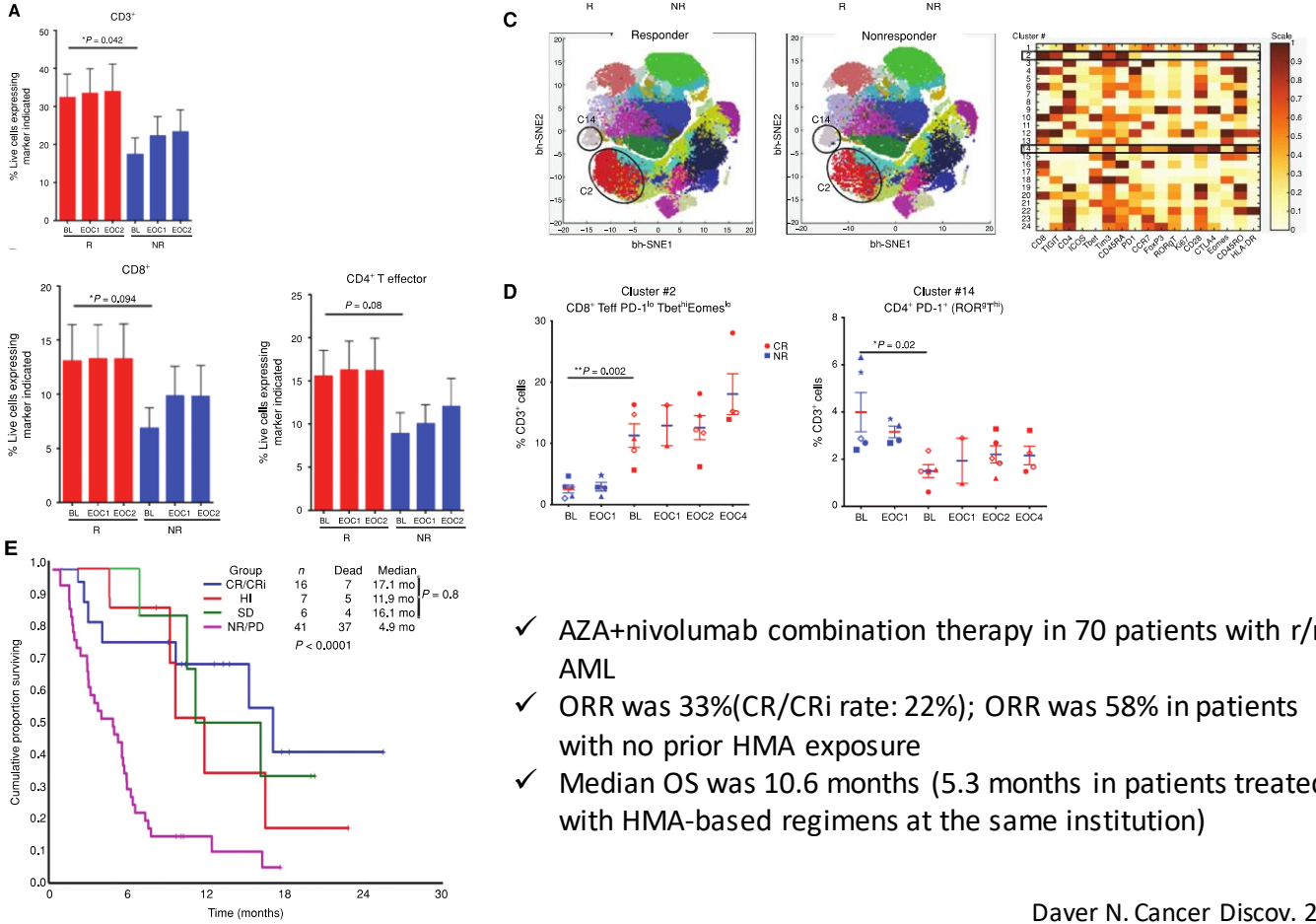




§ ENHANCE-2: ongoing phase III trial of magrolimab + azacitidine vs venetoclax/azacitidine or intensive CT in newly diagnosed *TP53*-mutant AML (NCT04778397)

1. Sallman. ASH 2020. Abstr 330. 2. Daver. ASCO 2022. Abstr 7020.

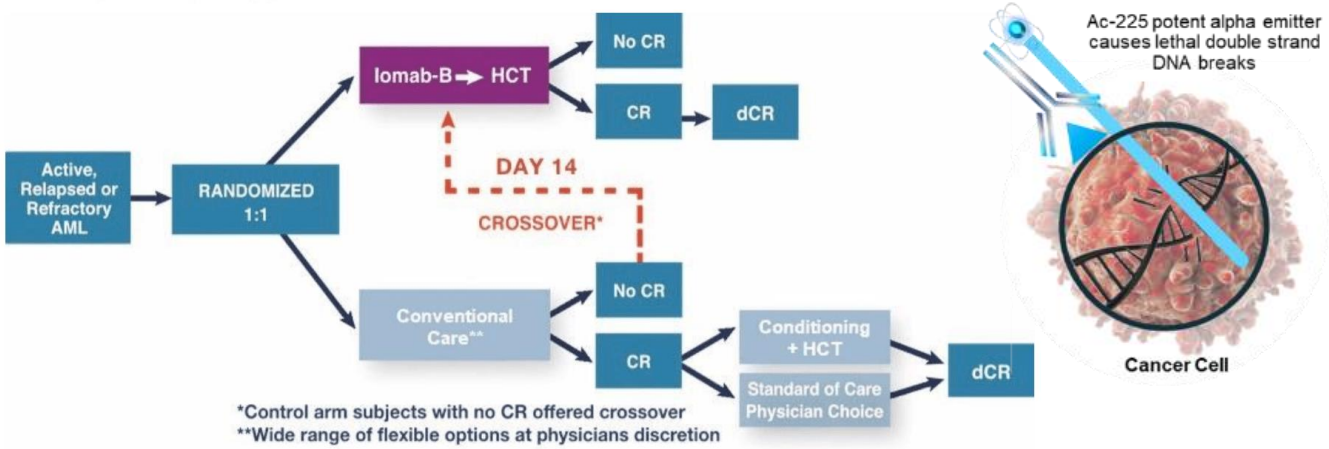
Azacitidine + nivolumab for AML (Phase 2)



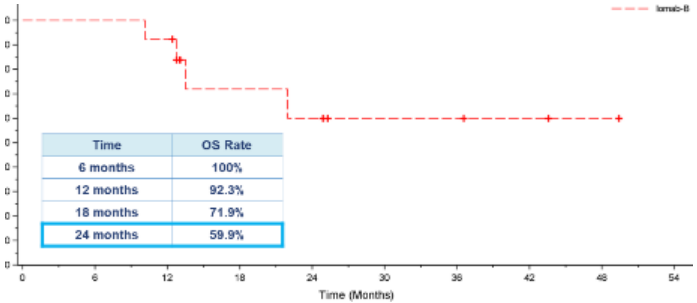
- ✓ AZA+nivolumab combination therapy in 70 patients with r/r AML
- ✓ ORR was 33%(CR/CRi rate: 22%); ORR was 58% in patients with no prior HMA exposure
- ✓ Median OS was 10.6 months (5.3 months in patients treated with HMA-based regimens at the same institution)

Daver N. Cancer Discov. 2019.

Sierra trial (Phase3): R/R AML patients
Iomab-B before Allo-HSCT vs conventional salvage chemotherapy

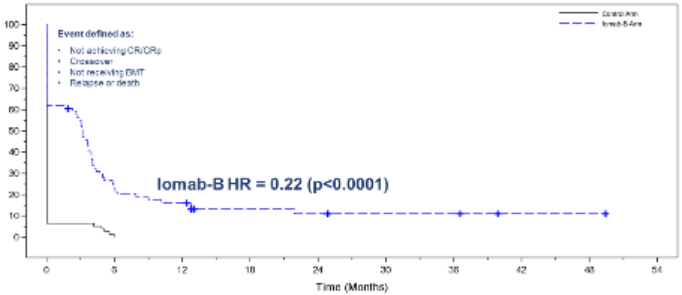


Overall Survival for Patients
who Achieved 6-month dCR with Iomab-B



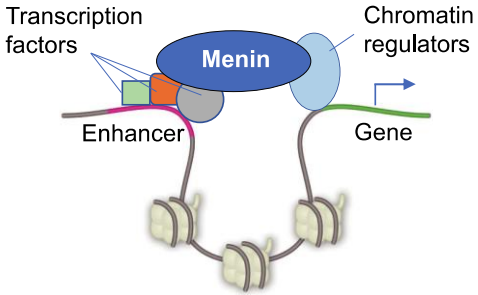
Time	OS Rate
6 months	100%
12 months	92.3%
18 months	71.9%
24 months	59.9%

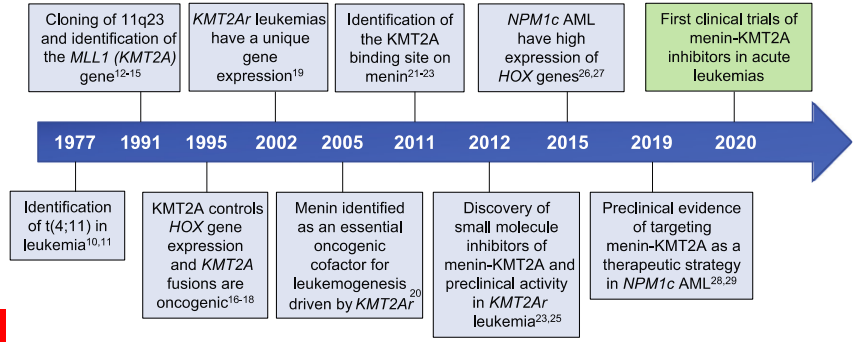
Event-Free Survival
Iomab-B Versus Control Arm

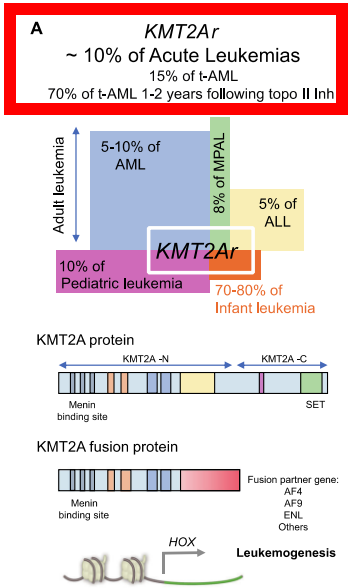


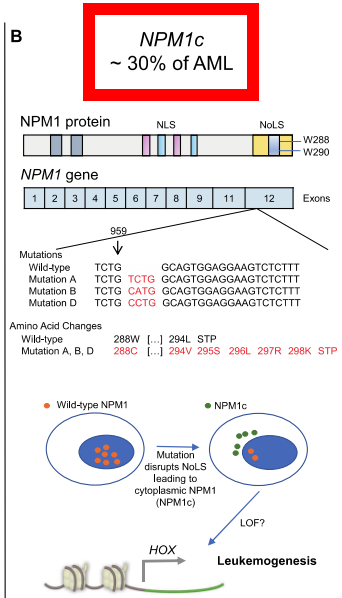
Boglarka Gyurkocza. ASH2021. Boglarka Gyurkocza. Tandem Meeting.

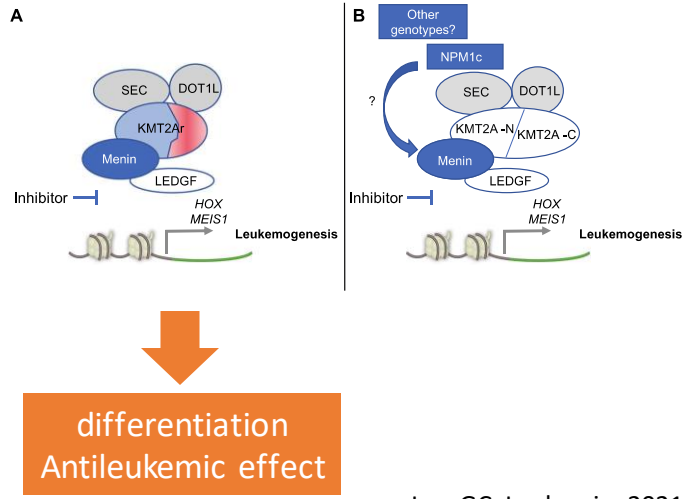
Menin inhibition: KMT2Ar/m or NPM1m-positive AML





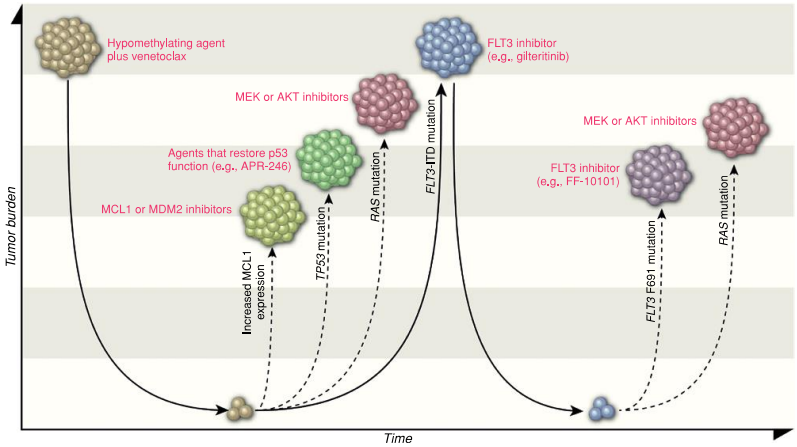




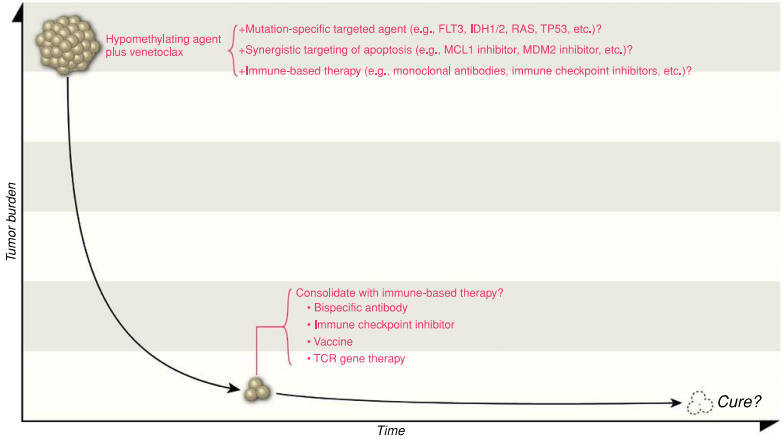


Issa GC. Leukemia. 2021.

Primary or secondary resistance to the VEN +AZA combination therapy



Potential future treatment paradigm in AML



Short N. Cancer Discovery. 2020.

Thank you for kind attention!

Global Leukemia Academy

Q&A

APTITUDE HEALTH

Global Leukemia Academy

Case-based panel discussion

Case 1: Rithin Nedumannil

Case 2: Huai-Hsuan Huang

Moderator: Naval Daver

APTITUDE HEALTH

Global Leukemia Academy

Case 1: Adult AML

Rithin Nedumannil

Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

APTITUDE HEALTH

Case Presentation

- 56-year-old woman, ECOG 0, with no major comorbidities
- Presented to an external institution with B symptoms in January 2022

Hb 91 g/L, WCC 54.5 × 10^9/L, platelets 34 × 10^9/L
Film: 83% blasts, occasional Auer rods seen
84% bone marrow blasts, consistent with AML
Flow cytometry: blasts positive for CD13/15 (dim)/33/34/117/HLA-DR/MPO with aberrant co-expression of CD19/79a (subset)
CG: 46,XX,t(3;9)(q27;q34),der(8)t(8;21)(q21.3;q22),add21(q22)[20]
FISH: *RUNX1*::*RUNX1T1*, no evidence of *MECOM* rearrangement
Molecular (incl. WES): *FLT3*-ITD (AR 0.46), *RUNX1*::*RUNX1T1* *(532.2%)*

AML With t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* and *FLT3*-ITD Mutation

How would you treat this patient?

A. 7+3 and FLT3 inhibitor (midostaurin)
B. 7+3 and GO (gemtuzumab ozogamicin)
C. 7+3 and FLT3 inhibitor and GO
D. Venetoclax and azacitidine
E. Enroll on to a clinical trial

Combination of GO and Midostaurin With Standard Intensive Induction Chemotherapy

- Use of multitarget combination therapy in CBF AML with *FLT3*-ITD described
  - Due to rarity, no large prospective studies
  - Retrospective subgroup analyses (ALFA-0701 trial) or case series exist

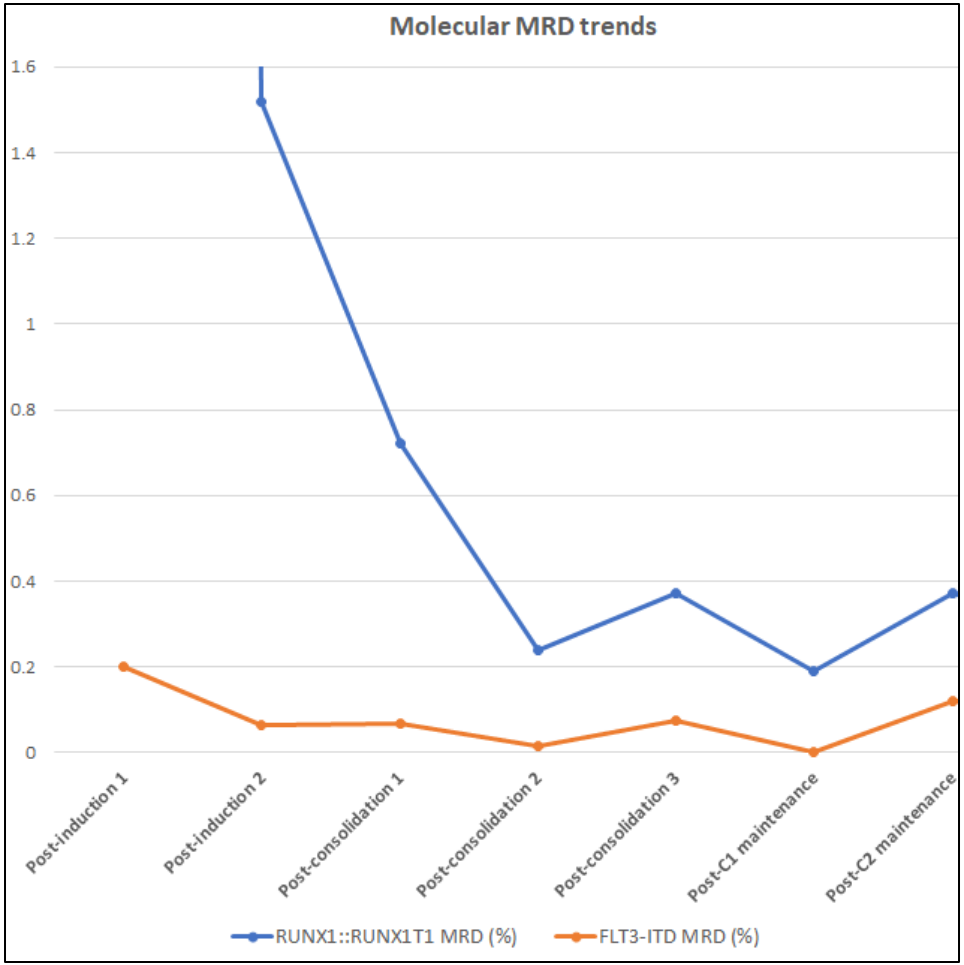
Study	Response	Adverse events	References
Phase I (n = 11) 3 DL GO 3 mg/m^2 on D1 and 4 + mido 25 mg BD (D8–21) (DL1) **GO 3 mg/m^2 on D1 and 4 + mido 50 mg BD (D8–21) (DL2)** GO 3 mg/m^2 on D1, 4, and 7 + mido 50 mg BD (D8–21) (DL3)	CR/CRi 91%	DLT = Gr 3 neutropenic colitis, SOS SAEs: infusion-related reaction, colitis, parvo-B19 infection, Gr 4 prolonged neutropenia, and SOS	Rollig C, et al. *Blood*. 2021;138 (suppl 1): abstract 2324.
Phase I (n = 8) 3 DL: IV GO 3 mg/m^2 on D1 (DL1), on D1 and 4 (DL2), on D1, 4, and 7 (DL3) Midostaurin 50 mg BD (D8–21)	CR/CRi 75%	No DLT Febrile neutropenia in 75%, sepsis (25%), mucositis (25%), SOS (12.5%)	Borate U, et al. *Blood*. 2021;138 (suppl 1): abstract 1269.

HOVON 156 AML Trial Enrolment

- Received 7+3 and midostaurin during induction 1 → achieved CR with negative flow MRD
  - Followed by induction 2, 3 cycles of high-dose cytarabine consolidation, and midostaurin maintenance
- Frequent molecular MRD monitoring
  - *RUNX1*::*RUNX1T1* rt-PCR MRD (RNA-based) – sensitivity 10^{-4}
    - Expressed as the number of fusion gene transcripts divided by *ABL* control gene expression × 100
  - *FLT3*-ITD NGS MRD (DNA-based) – sensitivity 10^{-5}
    - Expressed as a variant allele frequency percentage (VAF%) = number of ITD reads divided by sequencing coverage × 100
- Fully matched sibling donor available

MRD Trends

Months From Diagnosis	Time Point	*RUNX1::RUNX1T1* MRD, %	*FLT3*-ITD MRD, %
0	**Diagnosis**	**532.2**	**AR 0.46**
1.2	Post-induction 1	39.55	N/A
2.5	Post-induction 2	1.52	0.063
3.7	Post-consolidation 1	0.72	0.066
4.8	Post-consolidation 2	0.24	0.015
6.1	Post-consolidation 3	0.37	0.075
7.1	Post-C1 maintenance	0.19	0.002
8.5	Post-C2 maintenance	0.37	0.118


Molecular MRD trends
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Post-induction 1
Post-induction 2
Post-consolidation 1
Post-consolidation 2
Post-consolidation 3
Post-C1 maintenance
Post-C2 maintenance
RUNX1::RUNX1T1 MRD (%)
FLT3-ITD MRD (%)

MRD Trends

Months From Diagnosis	Time Point	*RUNX1::RUNX1T1* MRD, %	*FLT3*-ITD MRD, %	Other Information
0	**Diagnosis**	**532.2**	**AR 0.46**	
1.2	Post-induction 1	39.55	N/A	
2.5	Post-induction 2	1.52	0.063	
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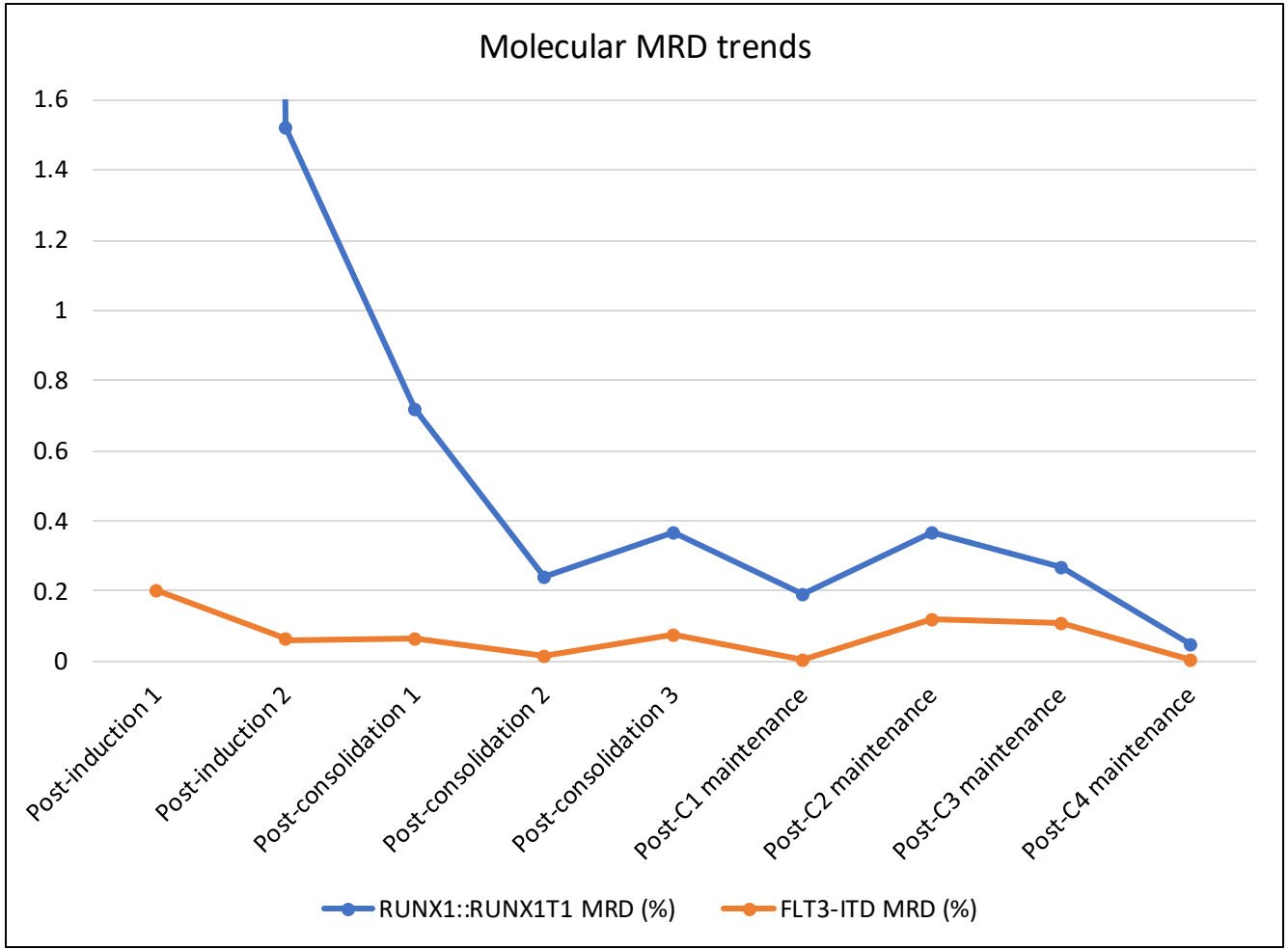
6.1	Post-consolidation 3	0.37	0.075	
7.1	Post-C1 maintenance	0.19	0.002	
8.5	Post-C2 maintenance	0.37	0.118	
9.3	Post-C3 maintenance	0.27	0.107	
10.7	**Post-C4 maintenance**	**0.05**	**0.004**	**New *TP53* mutation (VAF = 2%)**


Molecular MRD trends
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Post-induction 1
Post-induction 2
Post-consolidation 1
Post-consolidation 2
Post-consolidation 3
Post-C1 maintenance
Post-C2 maintenance
Post-C3 maintenance
Post-C4 maintenance
RUNX1::RUNX1T1 MRD (%)
FLT3-ITD MRD (%)

Persistence of MRD and New *TP53* Mutation

Next step: would this change your management?

1. Continue maintenance midostaurin
2. Change to gilteritinib
3. Enroll on to an MRD-based clinical trial (INTERCEPT)
4. Proceed to allogeneic stem cell transplant (allo-SCT)

Reassessment of Disease Status

- Patient subsequently moved state and was referred to our institution

<u>BMAT post-C7 maintenance</u>

- Hb 114 g/L, Neut 2.1 × 10^9/L, Plt 120 × 10^9/L
- MCV = 120 fL
- 0.5% blasts = CR; mild trilineage dysplasia
- Normal karyotype
- *RUNX1*::*RUNX1T1* MRD: **0%**
- *FLT3*-ITD MRD: **0%**
- NGS: ***TP53* (VAF 1%)**

MRD Trends

Months From Diagnosis	Time Point	*RUNX1::RUNX1T1* MRD, %	*FLT3*-ITD MRD, %	Other Information
10.7	Post-C4 maintenance	0.05	0.004	*TP53* (VAF = 2%)
12.9	Post-C7 maintenance	0	0	*TP53* (VAF = 1%)
15.6	Post-C10 maintenance	0.05	0.006	*TP53* (VAF = 1%)
16.5	Post-C11 maintenance	0.042	0.009	*TP53* (VAF = 1%)
17.6	Post-C12 maintenance	0.009	0.004	*TP53* (VAF <1%)

Where to From Here?

- Concerns about an evolving therapy-related myeloid neoplasm
  - Persistent macrocytosis ~120 fL
  - Newly acquired and persistent *TP53* mutation (low-level residual disease vs presence of a preleukemic clone)
- Molecular MRD persistence at low copy numbers despite midostaurin maintenance
- Proceeded to reduced intensity allo-SCT with fludarabine and melphalan conditioning
  - Tolerated well with no significant complications

Post–Allo-SCT Progress

D+30 post–allo-SCT BMAT

- Hb 110 g/L, Neut 1.5 × 10^9/L, Plt 155 × 10^9/L
- MCV = 109 fL
- 1% blasts = CR; mild dyserythropoiesis
- *RUNX1*::*RUNX1T1* MRD: 0%
- *FLT3*-ITD MRD: pending
- Chimerism: 97% CD3+/98% CD3–

MRD Trends

Months From Diagnosis	Time Point	*RUNX1::RUNX1T1* MRD, %	*FLT3*-ITD MRD, %
0	**Diagnosis**	**532.2**	**AR 0.46**
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9.3	Post-C3 maintenance	0.27	0.107
10.7	Post-C4 maintenance	0.05	0.004
12.9	Post-C7 maintenance	0	0
15.6	Post-C10 maintenance	0.05	0.006
16.5	Post-C11 maintenance	0.042	0.009
17.6	Post-C12 maintenance	0.009	0.004
19.6	**D+30 post–allo-SCT**	**0**	**Pending**

Global Leukemia Academy

Case 2: Elderly ALL

Huai-Hsuan Huang

National Taiwan University Hospital,
Taipei, Taiwan

APTITUDE HEALTH

83-Year-Old Man

- Past history
  - Hypertension
  - BPH
- He presented with fever for 3–4 days

83-Year-Old Man

Feb 2016

Fever,
cough

Mar 3

Our hospital

Hb: 9.6g/dL
WBC: 1.39 K/μl, blast: 7.0%
elevated LDH (601)

Mar 4

Our hospital

BM smear and flow report

Early pre-B ALL, CD20+

Positive: CD19, CD20, CD13, CD16, partial CD2, cyto CD79a
Negative: cytoplasmic mu chain
BCR-ABL1: ***NOT*** detected!
Cytogenetics
add(1)(p13),dup(3)(p21p25),+del(7)(p11p22),t(10;13)(q26;q12),del(12)(q2?2q24),del(13)(q12q22),add(14)(q32),der(17)add(17)(p11)add(17)(q23),add(18)(q21)

Available Treatments for Frontline Non-Ph B-ALL in Taiwan

- Chemotherapies
- Targeted therapies
  - Rituximab (self-paid)
  - ~~Blinatumomab (self-paid ... but too expensive)~~ Available from 2017
  - ~~Inotuzumab ozogamicin (self-paid ... also very expensive)~~ Available from 2019

Which treatment will you suggest for him?

A. Low-dose chemotherapy
B. Low-dose chemotherapy with rituximab
C. Pediatric-inspired regimens for adult ALL patients, such as GRAALL
D. Pediatric-inspired regimens combined with rituximab
E. Palliative care

Which treatment will you suggest for him?

A. Low-dose chemotherapy
B. Low-dose chemotherapy with rituximab
C. Pediatric-inspired regimens for adult ALL patients, such as GRAALL
D. Pediatric-inspired regimens combined with rituximab
E. Palliative care

Which treatment will you suggest for him?

A. Low-dose chemotherapy
B. Low-dose chemotherapy with rituximab
C. Pediatric-inspired regimens for adult ALL patients, such as GRAALL
D. Pediatric-inspired regimens combined with rituximab
E. Palliative care

83-Year-Old Man

Feb 2016

Fever,
cough

Mar 3

Our hospital

Hb: 9.6g/dL
WBC: 1.39 K/μl, blast: 7.0%
elevated LDH (601)

Mar 4

Our hospital

BM smear and flow report

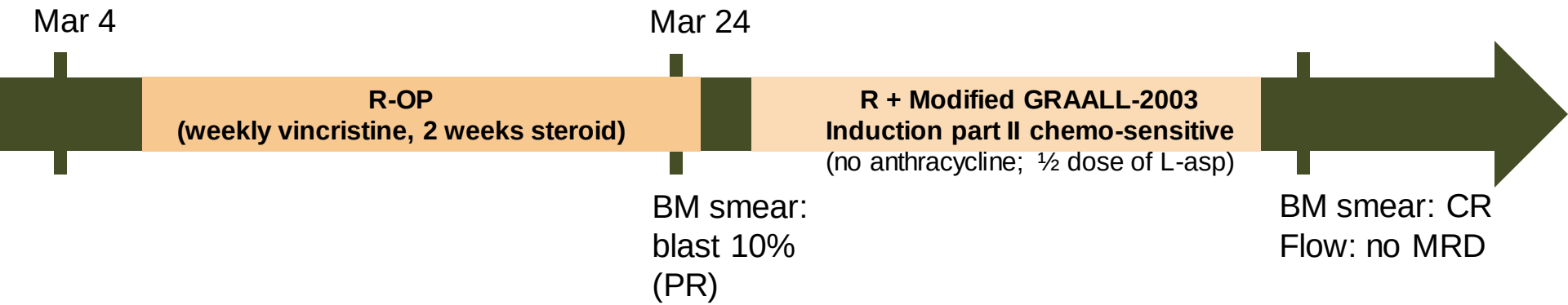
Early pre-B ALL, CD20+

Similar dose to GRAALL induction part I

R-OP
(weekly vincristine, 2 weeks steroid)

Positive: CD19, CD20, CD13, CD16, partial CD2, cyto CD79a
Negative: cytoplasmic mu chain
BCR-ABL1: ***NOT*** detected!
Cytogenetics
add(1)(p13),dup(3)(p21p25),+del(7)(p11p22),t(10;13)(q26;q12),del(12)(q2?2q24),del(13)(q12q22),add(14)(q32),der(17)add(17)(p11)add(17)(q23),add(18)(q21)

83-Year-Old Man



83-Year-Old Man

Acute hepatitis B!!

2020

Entecavir (for HBV Tx)

***bloc* MTX** | ***bloc* cyclophosphamide with R** | ***bloc* MTX** | ***bloc* cyclophosphamide with R** | **Maintenance: R, 6-MP**

BM smear: CR
Flow: no MRD

BM smear: CR
Flow: no MRD

Died of bladder cancer

HBsAg(-), anti-HBs(+), anti-HBc(+)

↓ **Rituximab**

HBsAg(+), anti-HBs(-), anti-HBc(+), **HBV DNA >170,000,000**

Summary

- 83-year-old man
  - Diagnosis: early pre-B ALL, Ph(-), CD20+
  - Induction: R-OP → GRAALL-2005-R induction part II
    - Rituximab for CD20+
  - Response: CR without MRD by flow cytometry
  - Current status
    - 4 years later, he died of bladder cancer

Conclusion

- For elderly patients with ALL
  - Low-dose chemotherapy might be effective for some elderly patients
  - Novel agents might provide another drug of choice for frontline treatments

Thank you

Global Leukemia Academy

Case-based panel discussion

Moderator: Naval Daver

APTITUDE HEALTH

Global Leukemia Academy

BREAK

APTITUDE HEALTH

Global Leukemia Academy

AYA ALL patients: What is the current treatment approach for this diverse patient population?

Daniel DeAngelo

APTITUDE HEALTH

Disclosure Information

The following relationships exist related to this presentation

- I serve as a consultant for Amgen, Autolus, Blueprint, Gilead, Incyte, Jazz, Kite, Novartis, Pfizer, Servier, and Takeda
- I receive research funding from AbbVie, GlycoMimetics, Novartis, and Blueprint Medicines
- I am on the DSMB for Daiichi-Sankyo, FibroGen, and Mt Sinai Myeloproliferative Neoplasms Consortium
- I am the co-chair of the NCI (CTEP) Leukemia Steering Committee

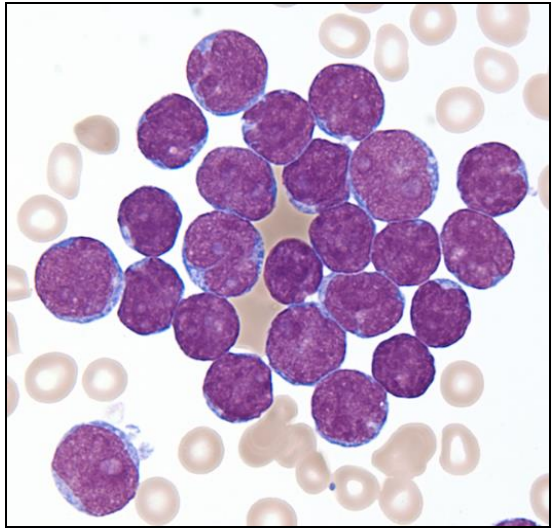
Off-Label/Investigational Discussion

In accordance with CME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations. None

Let’s Consider a Patient Case

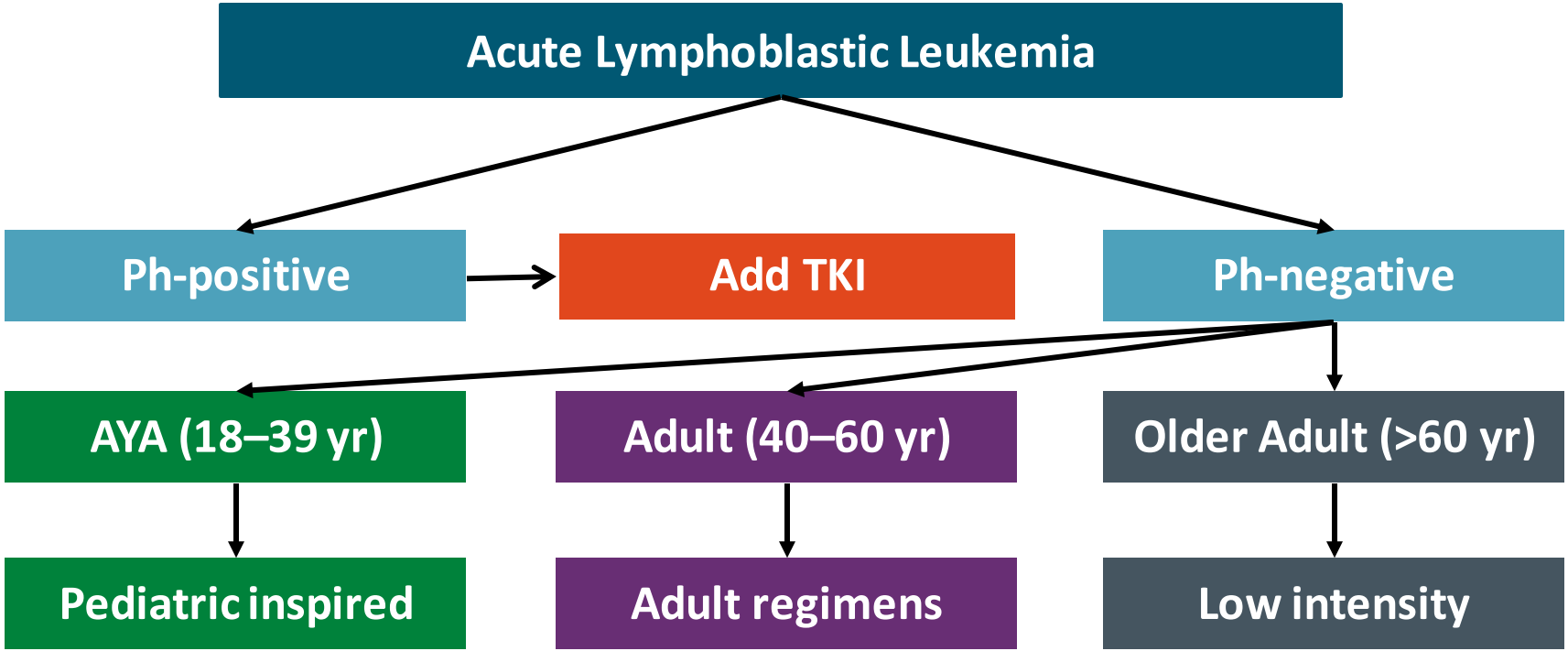
Patient Case 1: Presentation

- 21-yr-old woman with 2-wk history of fatigue, dizziness, and bleeding after dental procedure
- WBC: 85×10^9/L; Hgb: 10.3 g/dL; PLT: 17×10^9/L; differential showed 92% blasts
- Bone marrow aspirate: >90% blasts
- **How would you evaluate this patient?**
- **How would you treat this patient?**



Patient Case 1: Evaluation

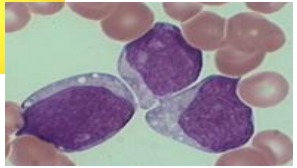
- Flow cytometry
  - Immunophenotyping showed positivity for CD10, CD19, HLA-DR, TdT (precursor B-cell, common ALL); negative for CD20, Ig, and myeloid antigens
- Cytogenetics
  - 46 XX, del19 t(1;19)(q23; p13) consistent with a *TCF3(E2A)-PBX1* fusion
- Molecular studies
  - PCR negative for *BCR-ABL1*, both p210 and p190
  - NGS sequencing negative
  - Sample sent for patient-specific probes to measure MRD (after induction)
- Gene fusion assay (Archer) to r/o Ph-like ALL
  - Positive for *TCF3-PBX1* fusion transcript (not a Ph-like gene)


Acute Lymphoblastic Leukemia
Ph-positive
Add TKI
Ph-negative
AYA (18–39 yr)
Adult (40–60 yr)
Older Adult (>60 yr)
Pediatric inspired
Adult regimens
Low intensity

When Does a Child Become an Adult?

- Independent decision-making
- Financial independence
- Mature support systems
- Physiologic and hormonal maturation

When Does Childhood ALL Become Adult ALL?



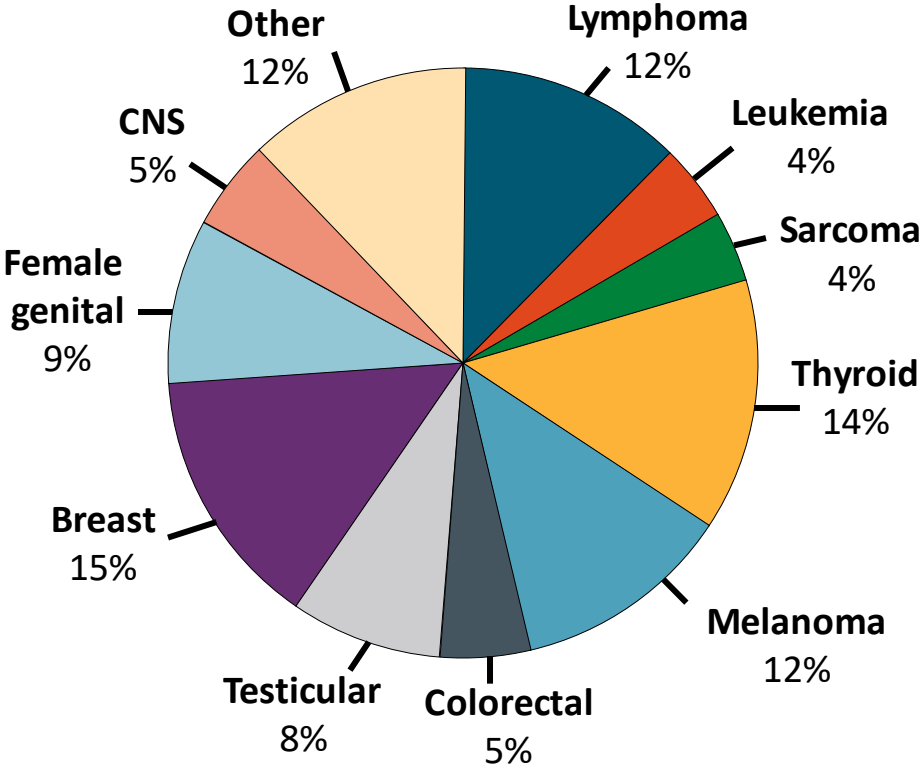
Definition of AYA Can Vary Depending on Trial

Group	Age Group (Yr)
DFCI	18–50
Spanish	15–30
French	15–60
CALGB 10403	17–39
SWOG 805	18–50

AYA definition is relatively loose

De Angelo DJ, et al. *Leukemia*. 2015;29:526-534; Huguet F, et al. *J Clin Oncol*. 2009;27:911-918; Ribera JM, et al. *J Clin Oncol*. 2008;26:1843-1849.

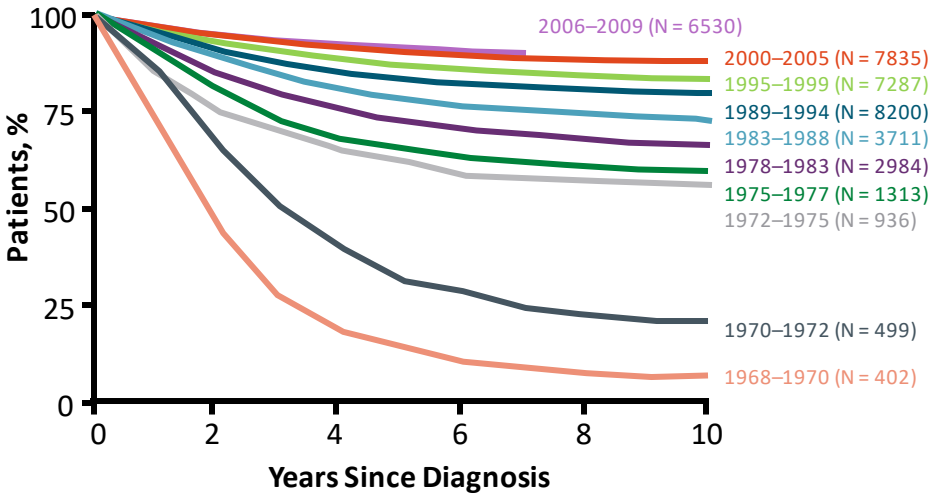
Cancer Incidence Rates per 100,000 in AYA Patients (aged 15–39 Yr)



Baker KS, Syrjala KL. *Hematology Am Soc Hematol Educ Program*. 2018;2018:146-153.

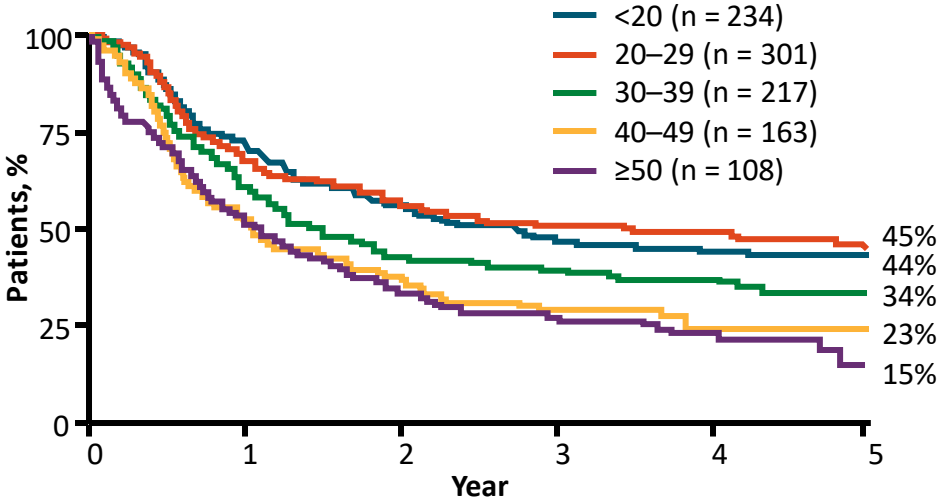
Problem: Poor Outcomes in ALL in Adults

OS among children with ALL in clinical trials: 1968–2009[1]



ALL in Children: A Success Story

OS by age among adults with Ph-negative ALL in ECOG E2993[2]



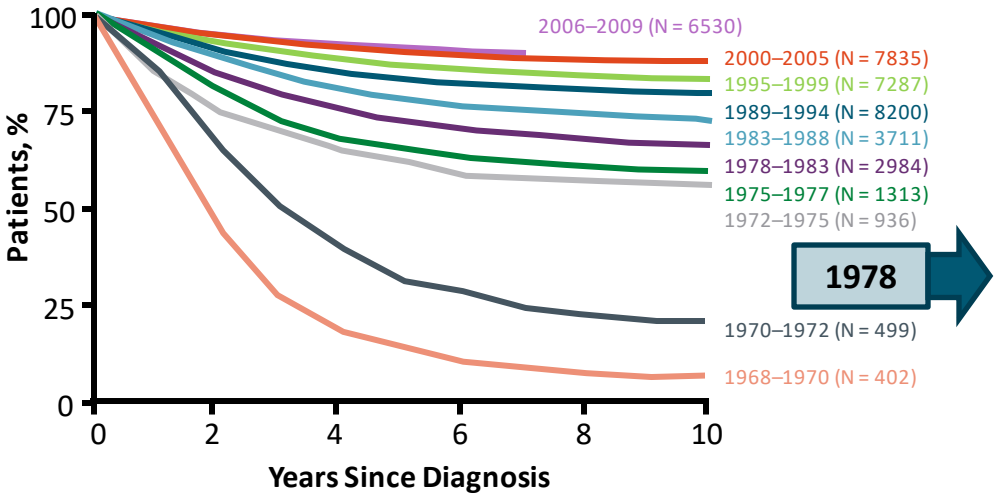
ALL in Adults: We Have a Problem!

One Size Does NOT Fit All!

1. Hunger SP, et al. *N Engl J Med*. 2015;373:1541-1552; 2. Rowe JM, et al. *Blood*. 2005;106:3760-3767.

ALL in Children: A Success Story

OS among children with ALL in clinical trials: 1968–2009



First anti-asparaginase (ASNase) approved by FDA

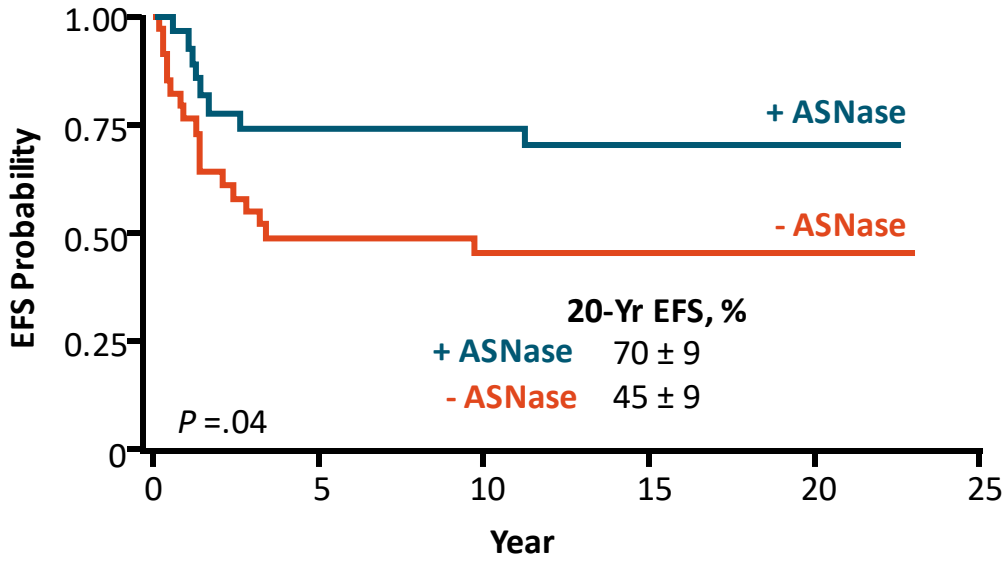
Native *E coli*-derived L-asparaginase in multiagent chemotherapy regimens for treatment of patients with ALL

ALL in Children: A Success Story

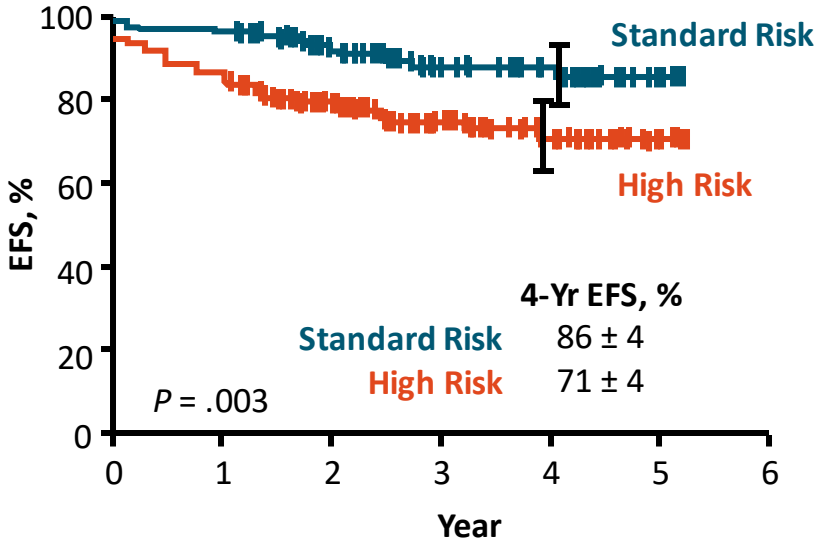
Hunger SP, et al. *N Engl J Med*. 2015;373:1541-1552.

Why Do We Use Asparaginase?

Protocol 77-01:
3-drug induction ± weekly high-dose ASNase[1]



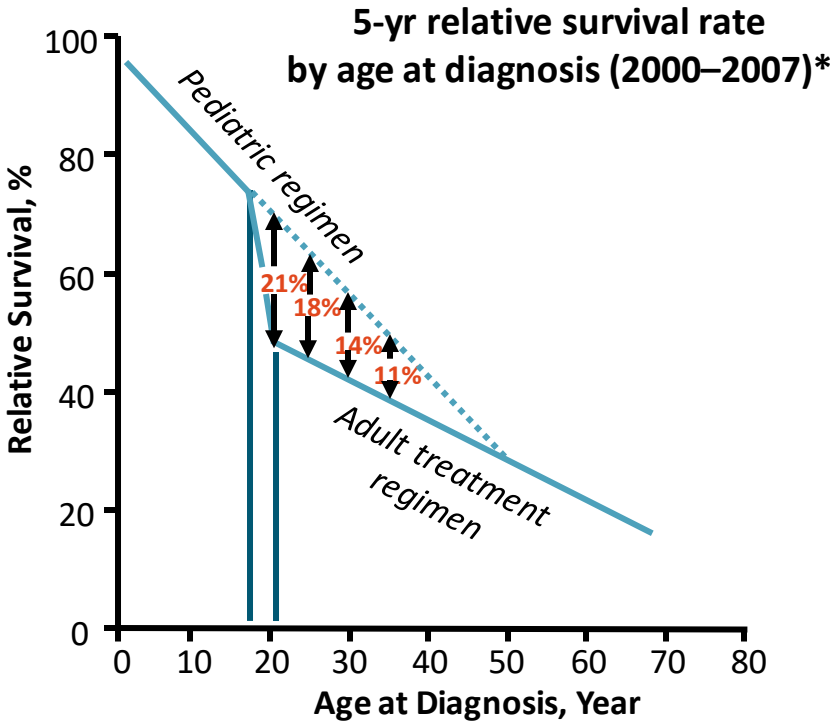
4-drug induction ± intensive ASNase[2]



1. Courtesy of Steve Sallan, MD; 2. Clavell LA, et al. *N Engl J Med.* 1986;315:657-663.

Adolescents and Young Adults With ALL Have Inferior Outcomes Compared With Children

- Acute leukemia is a leading cause of cancer mortality in US in AYA patients aged 15–39 yr
- AYA patients with ALL have worse survival than children
- A major clinical advance was recognition that pediatric regimens improve outcomes among AYA



Siegel SE, et al. *JAMA Oncol*. 2018;4:725-734; National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Cancer Among Adolescents and Young Adults (AYAs) (Ages 15–39). 2022.

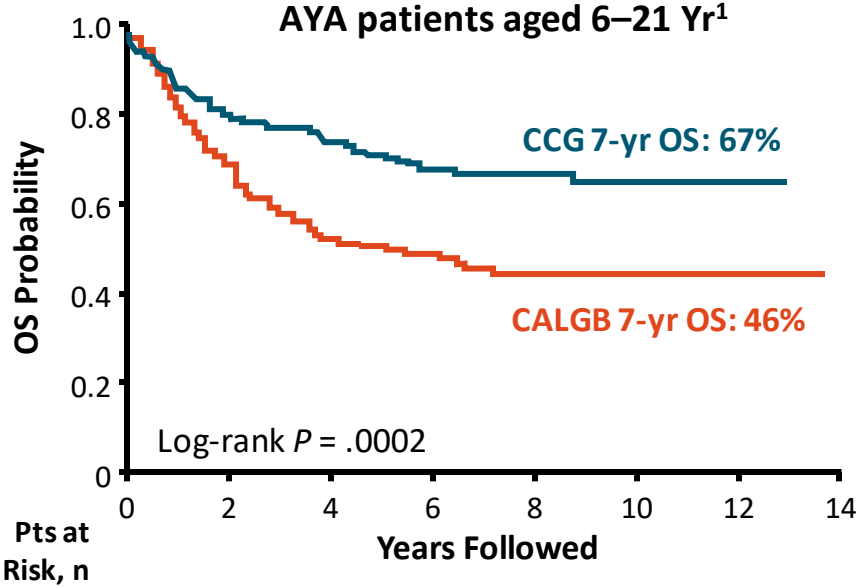
*Extrapolation by joinpoint analysis into adult age range.

Outcomes in AYA Patients Improved With Pediatric Regimens

- AYA patients with ALL have better outcomes when receiving pediatric-inspired regimens
  - Reported by Stock et al in 2008 retrospective study of AYA patients aged **16–20 yr** who received treatment on **pediatric (CCG)** or **adult (CALGB) trials** from 1988–2001

Regimen	No. AYA	7-Yr OS, %	Relative HR	Log-Rank *P* Value
CCG	197	67	--	.0002
CALGB	124	46	1.9	--

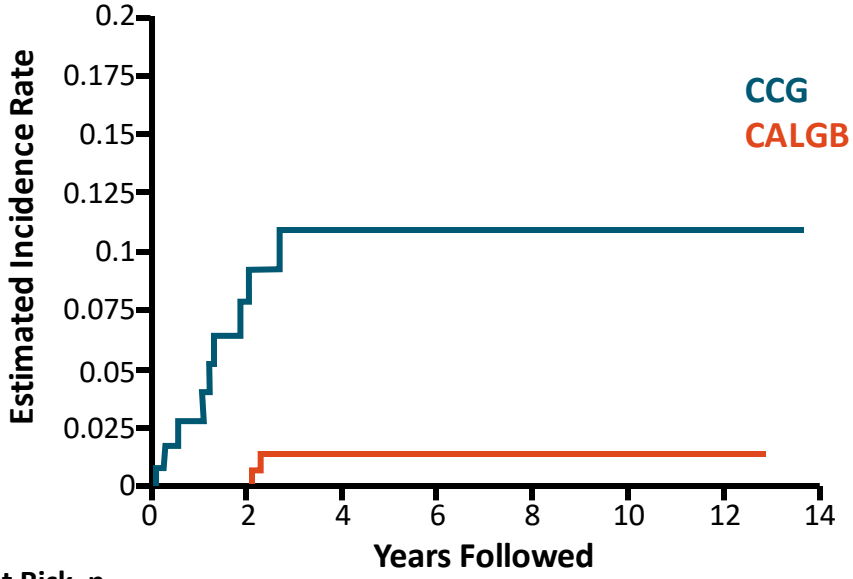
OS with historical CALGB vs CCG in AYA patients aged 6–21 Yr[1]



Pts at Risk, n							
CCG	197	151	131	98	57	19	2
CALGB	124	84	63	48	37	30	8

Stock W, et al. *Blood*. 2008;112:1646-1654.

Pediatric Regimens Decrease CNS Relapse Rates in AYA Patients



	7-Yr Rate, %	Relative Incidence Rate
CCG	1	9.2 (CI: 2.0–42.7;
CALGB	11	log-rank *P* = .0006)

Patients at Risk, n

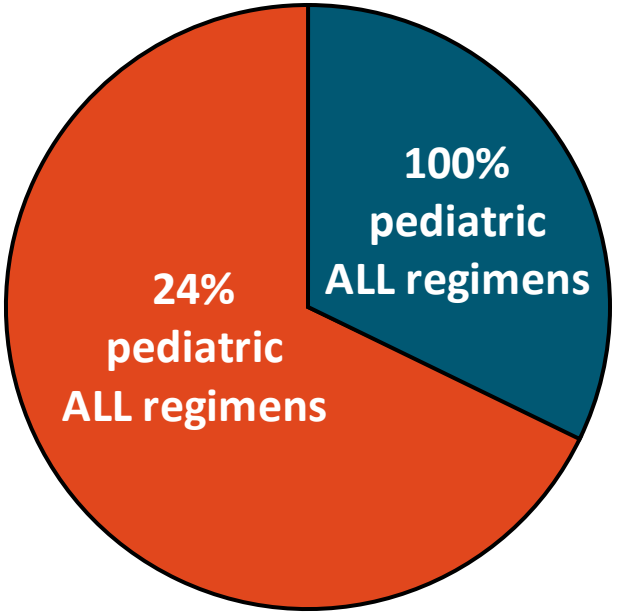
CCG ICNS	197	145	120	93	56	19	2
CALGB ICNS	124	66	47	34	27	21	6

Stock W, et al. *Blood*. 2008;112:1646-1654.

Regimens Used in AYA Patients With ALL

- California residents aged 15–39 yr at time of ALL diagnosis between January 1, 2004, and December 31, 2014, from the California Cancer Registry

AYA patients with ALL receiving pediatric regimens by treatment setting (N = 1473)



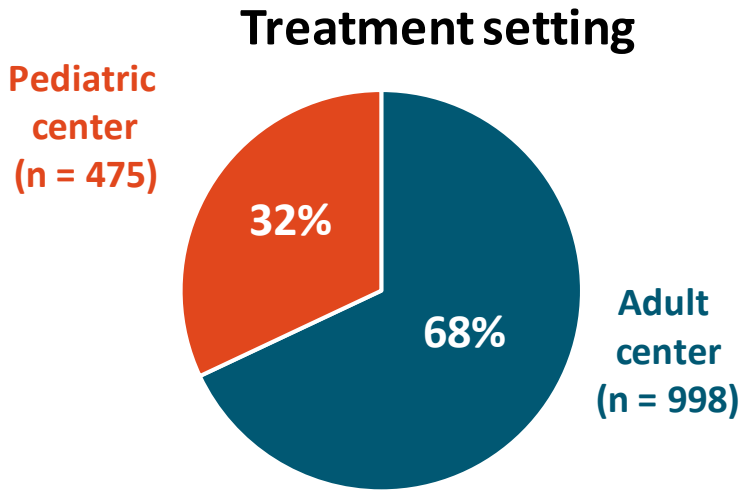
Pediatric cancer treatment setting (n = 475)

Adult cancer treatment setting (n = 998)

Muffly L, et al. *Blood Adv.* 2018;2:895-903.

AYA ALL: Patterns of Care and Outcomes

- Observational study of frontline ALL regimens in AYA patients in California from 2004–2014 (N = 1473)



- Adult regimens (75.6%)
  - Hyper-CVAD: 42.6%
  - Cooperative Group: 17.4%
  - Linker: 11.6%
  - Other: 3.8%
- Pediatric regimens (24.3%)
  - C10403: 9.3%
  - BFM: 6.2%
  - Cooperative Group: 5.2%
  - Other: 3.4%

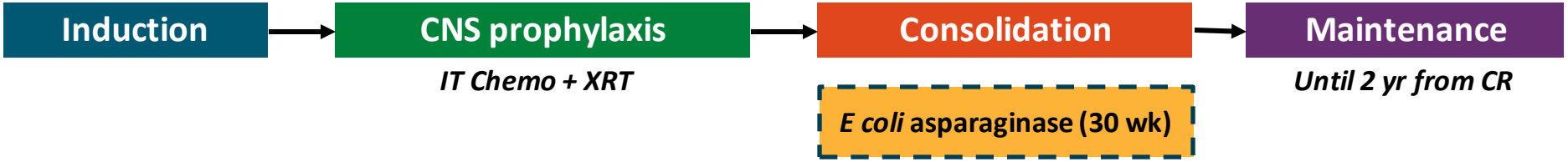
Muffly L, et al. *Blood Adv.* 2018;2:895-903.

Principles of Pediatric vs Adult ALL Regimens

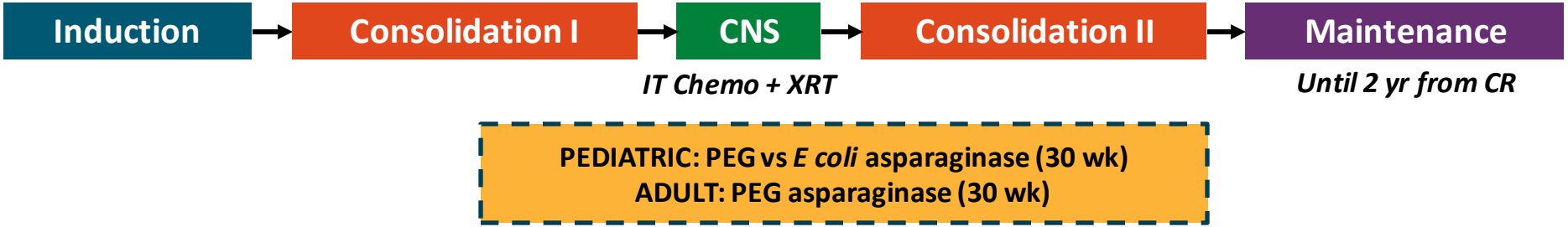
- Multiple chemotherapy drugs
- **More** asparaginase and corticosteroids
- **Less** myelotoxic drug
  - Anthracyclines
  - Alkylating agents
- Better time and dose adherence
- Allo-BMT only for very high risk

Overview of DFCI Consortium ALL AYA Protocols: Multicenter Studies

DFCI 00-001 (PEDS) and DFCI 01-175 (ADULT)

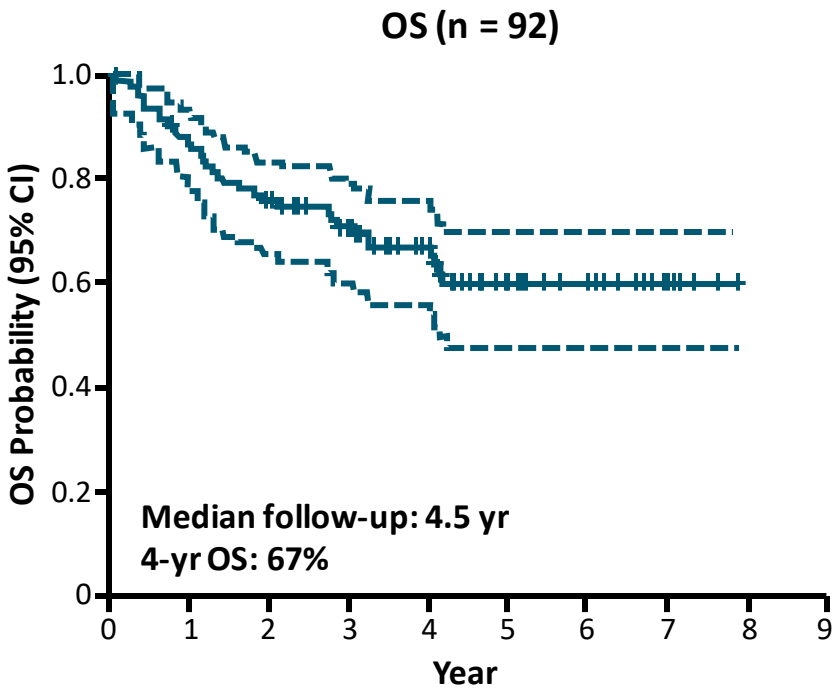


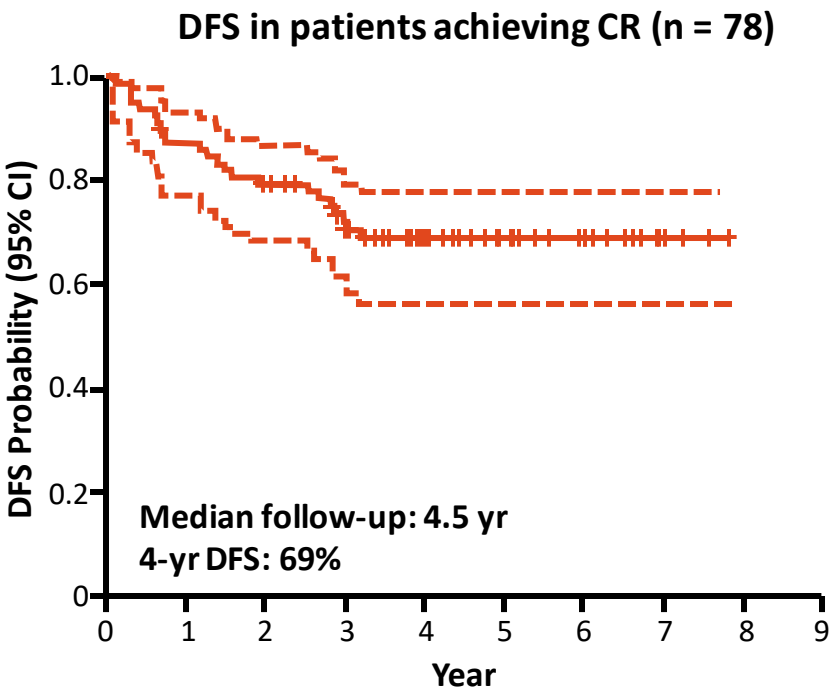
DFCI 05-001 (PEDS) and 06-254 (ADULT)



Vrooman LM, et al. *J Clin Oncol*. 2013;31:1202-1210; DeAngelo DJ, et al. *Leukemia*. 2015;29:526-534; DeAngelo DJ, et al. ASH 2015. Abstract 80.

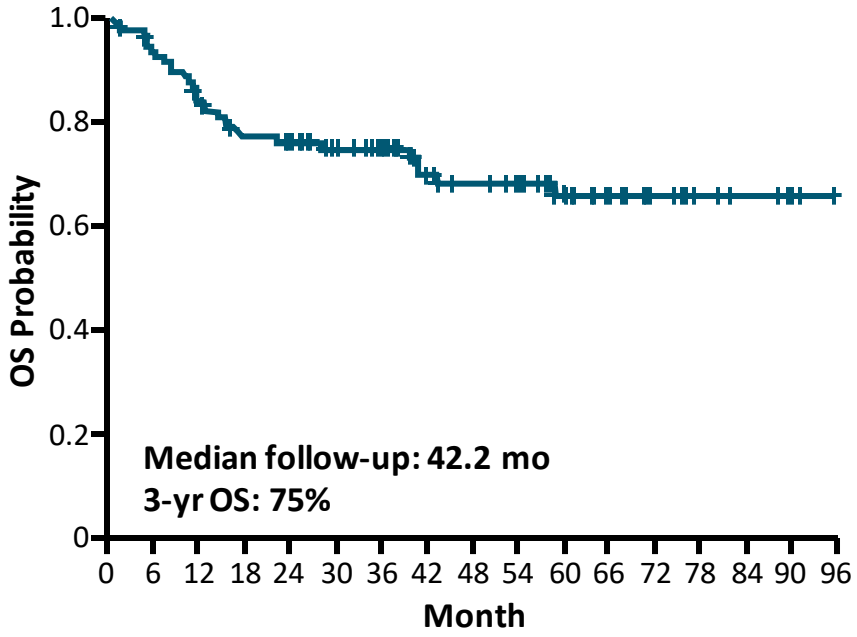
DFCI Adult Consortium Trial (01-175): OS, DFS in Adults Receiving Pediatric Regimen

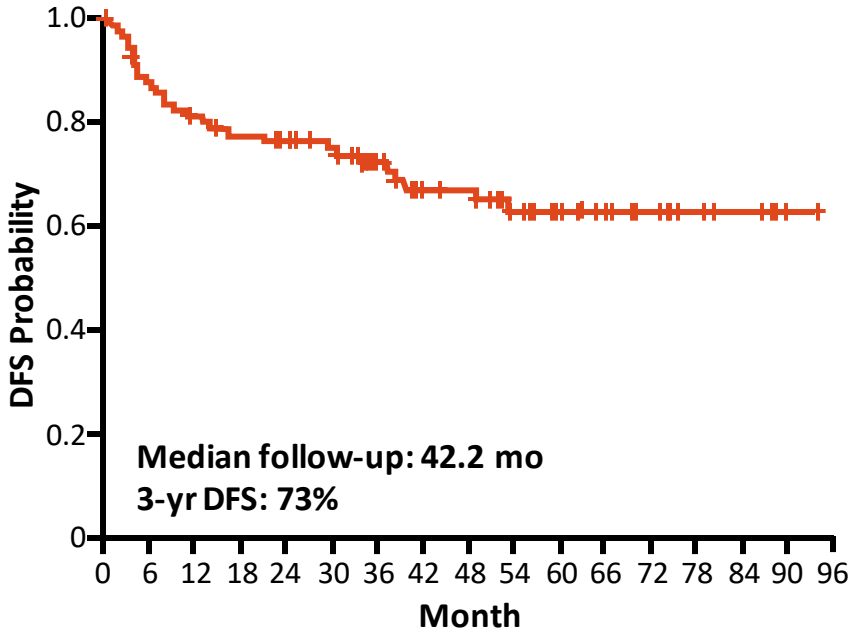




De Angelo DJ, et al. *Leukemia*. 2015;29:526-534.

DFCI Adult Consortium Trial (06-254): OS, DFS in Adults Receiving Pediatric Regimen + PEG-Asparaginase



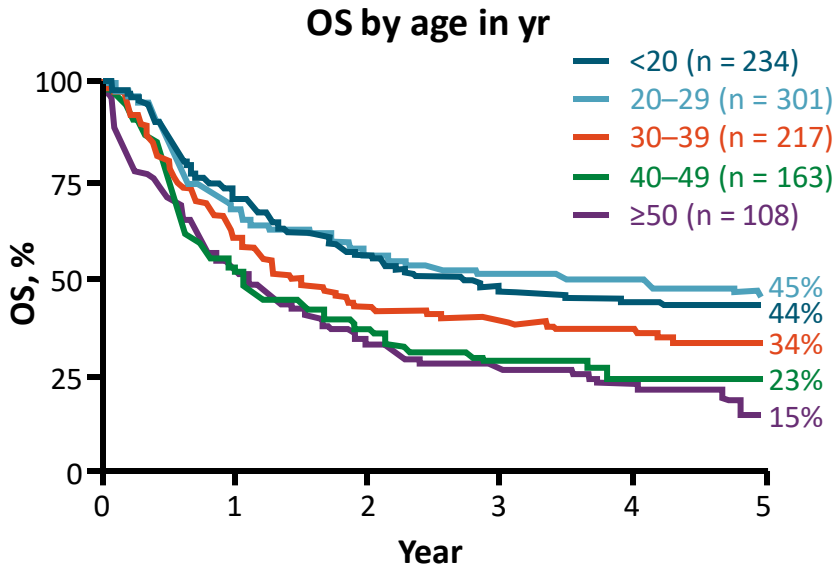


De Angelo DJ, et al. ASH 2015. Abstract 80.

Prognosis of AYA Patients Improved With Pediatric Regimens

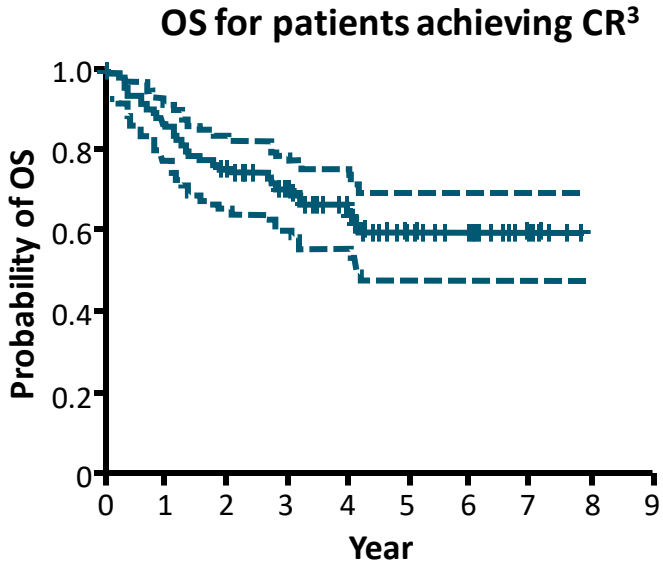
E2993 "Adult" Protocol[1]

5-yr OS for patients aged 20–50 yr: 20% to 45%



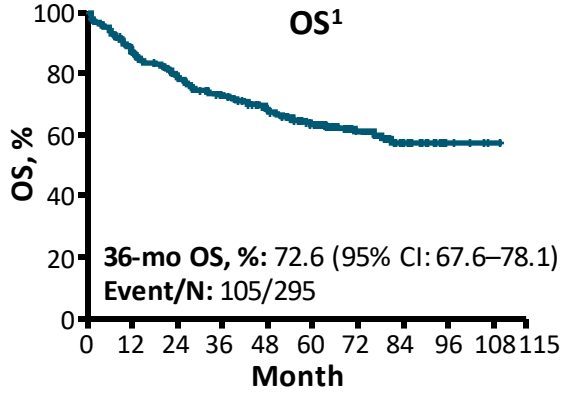
DFCI "Pediatric" Protocol[2,3]

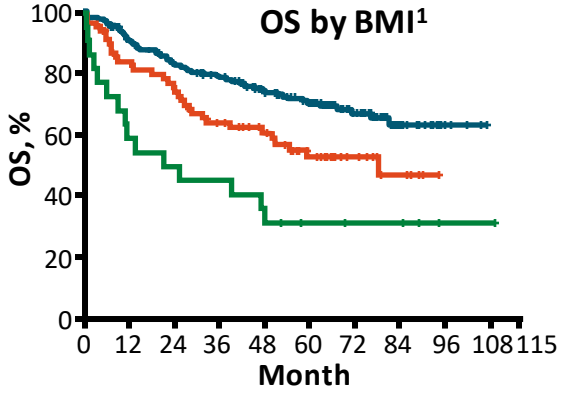
5-yr OS for patients aged 20–50 yr: 60% to 70%



1. Rowe JM, et al. *Blood*. 2005;106:3760-3767; 2. Vrooman LM, et al. *J Clin Oncol*. 2013;31:1202-1210; 3. DeAngelo DJ, et al. *Leukemia*. 2015;29:526-534.

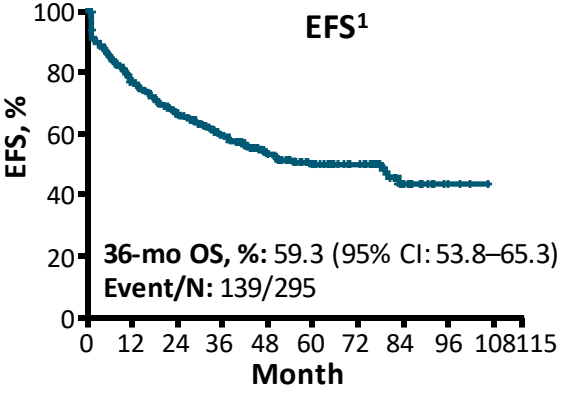
CALGB 10403: Outcomes With Pediatric Regimen in AYA Patients

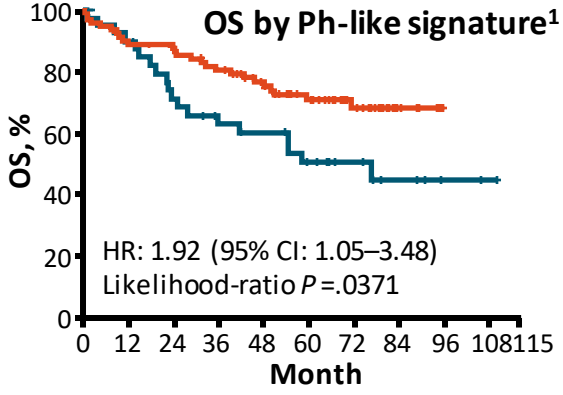




BMI, kg/m²	36-mo OS, % (95% CI)
<30	78.8 (73.2–84.9)
30–40	64.3 (54.0–76.6)
40+	45.5 (28.8–71.8)

3-yr OS[1]: 72%
3-yr EFS[1]: 59%
CALGB OS[2]: 46%



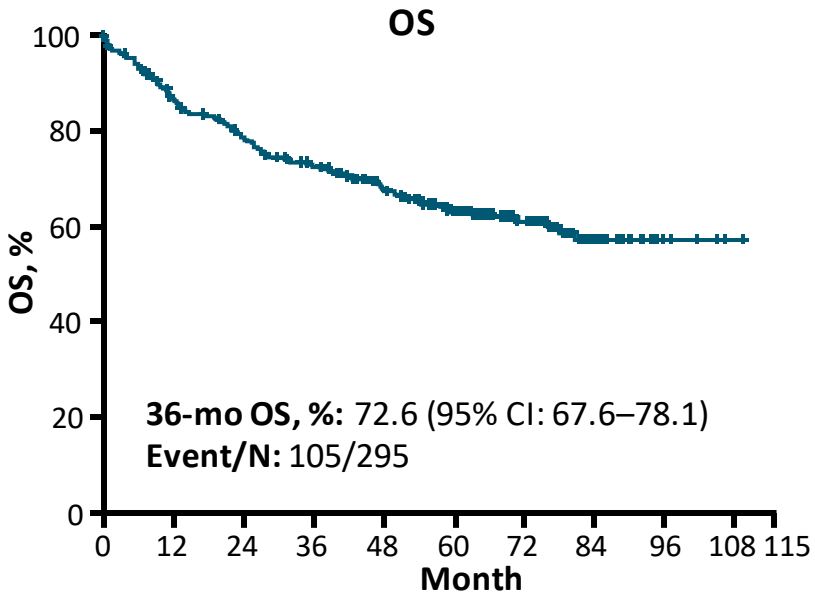


Ph-like	36-mo OS, % (95% CI)
Yes	63.3 (49.6–80.7)
No	80.5 (72.6–89.3)

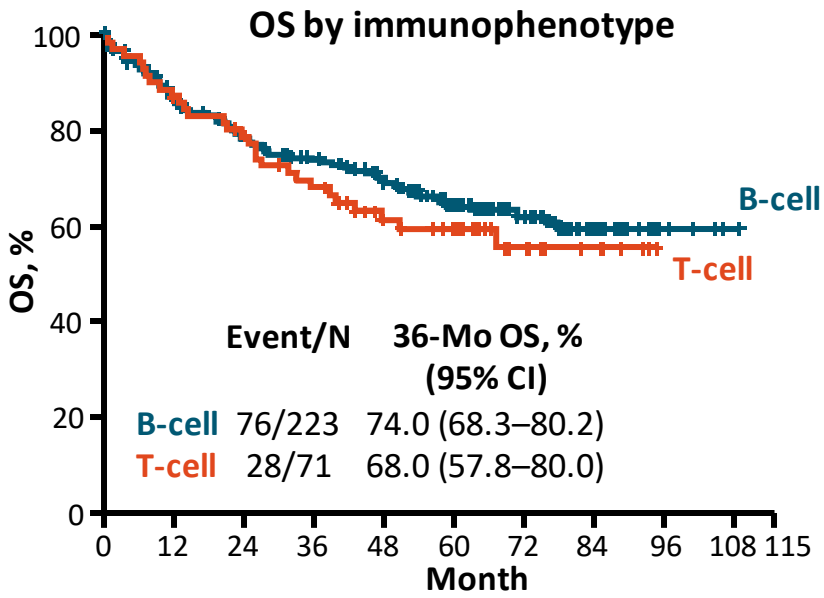
1. Stock W, et al. *Blood*. 2019;133:1548-1559; 2. Stock W, et al. *Blood*. 2008;112:1646-1654.

Improved Survival for AYA Patients: CALGB 10403

- 72% survival at 3 years

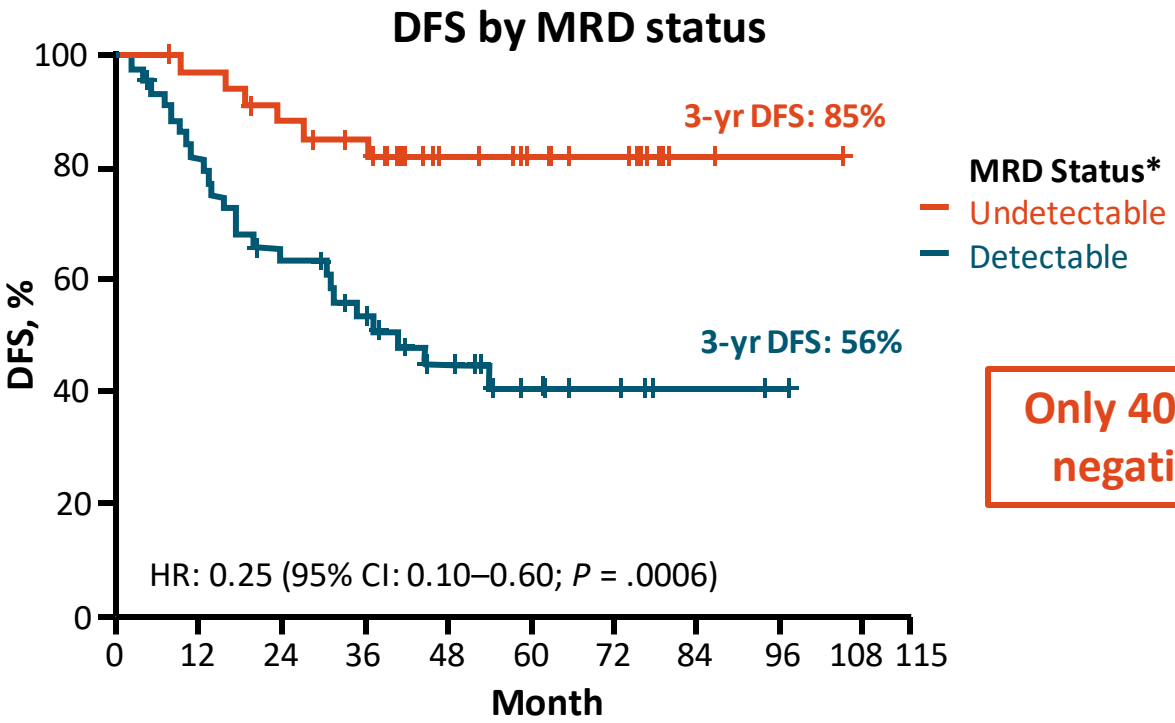


- Immunophenotype: B-cell vs T-cell



Stock W, et al. *Blood*. 2019;133:1548-1559.

Early MRD Eradication: CALGB 10403

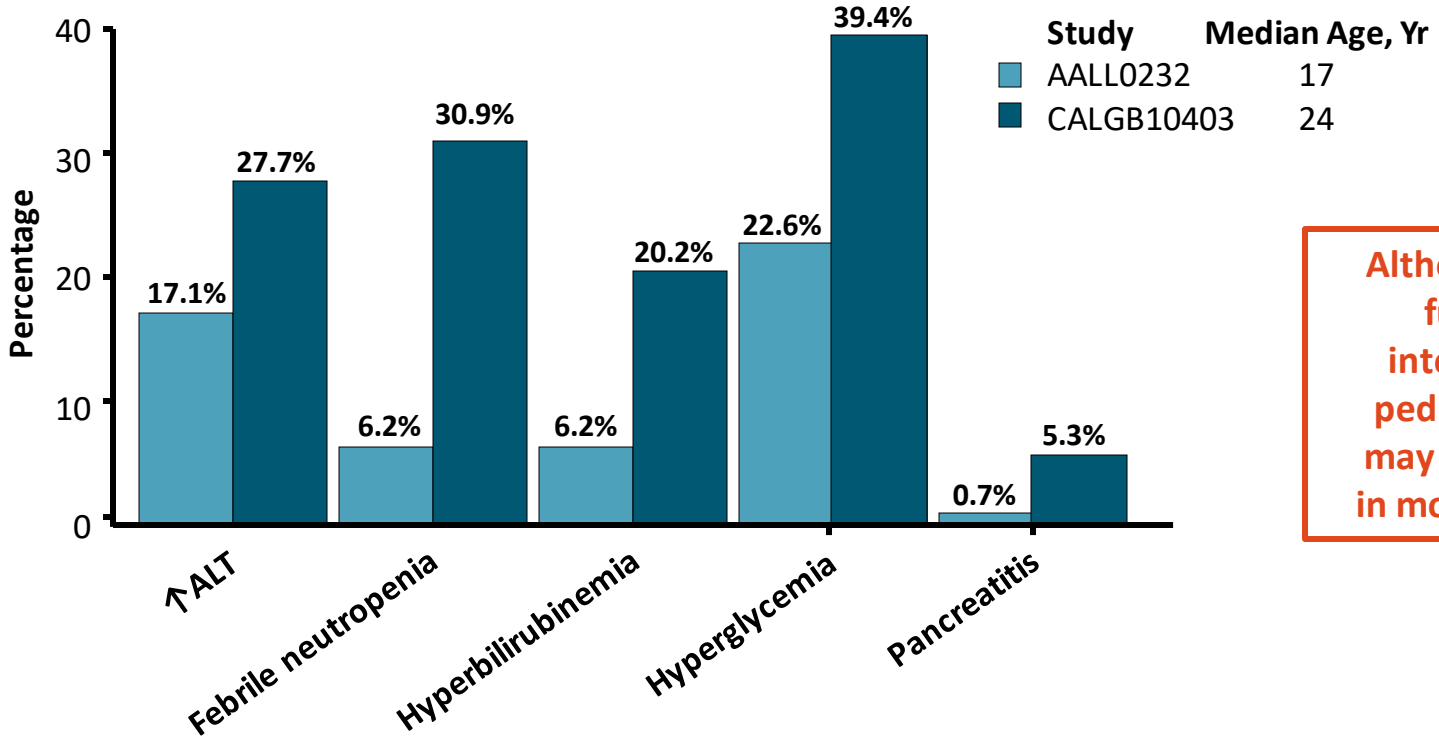


Only 40% of patients are MRD negative early in treatment

Stock W, et al. *Blood*. 2019;133:1548-1559.

*QT-PCR following induction.

Toxicity Profile in AYAs: Differences in “Young” vs “Old”

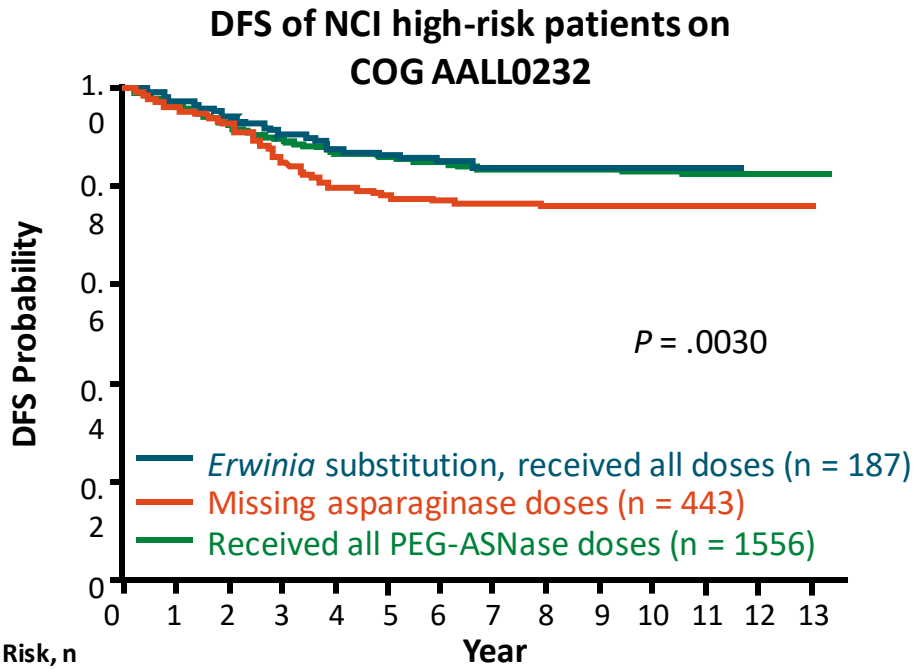


Although tolerable, further dose intensification of pediatric regimens may not be feasible in most AYA patients

Advani AS, et al. *Blood Adv.* 2021;5:504-512.

Impact of Omitting Asparaginase Doses in ALL

- *Erwinia* ASNase as substitution was approved in 2011 for allergic reactions
  - However, it has been intermittently unavailable because of drug supply issues
- Higher-risk patients who missed prescribed doses of ASNase altogether had 50% increased risk of relapse



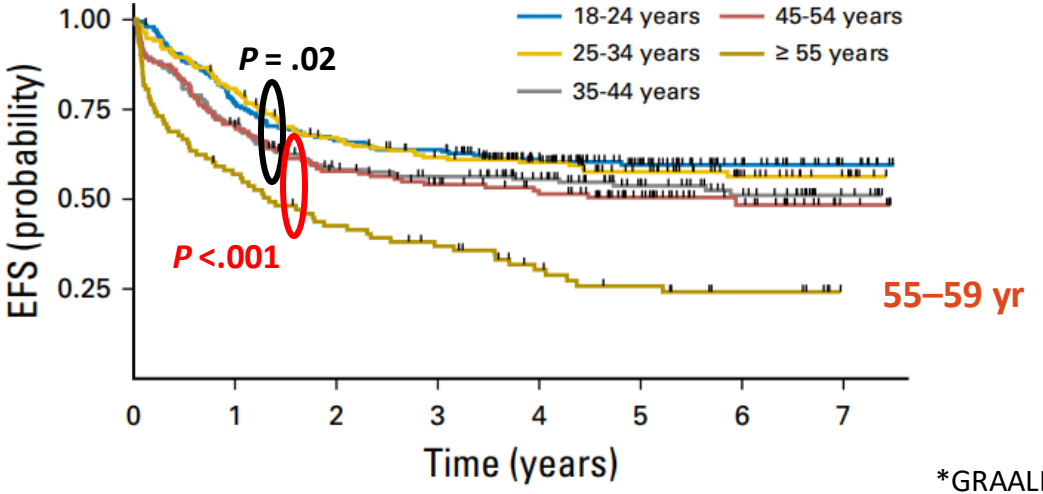
Patients at Risk, n

Erwinia	187	176	169	159	147	140	130	97	61	36	19	5	0	0
Not all doses	443	422	400	351	320	294	268	218	157	118	77	51	19	1
All doses	1556	1487	1410	1322	1225	1131	1002	771	584	430	259	143	48	13

Gupta S, et al. *J Clin Oncol*. 2020;38:1897-1905.

Aged Older Than 50 Yr Is *Too* Old for Pediatric Regimen: Toxicities

EFS by age subsets*

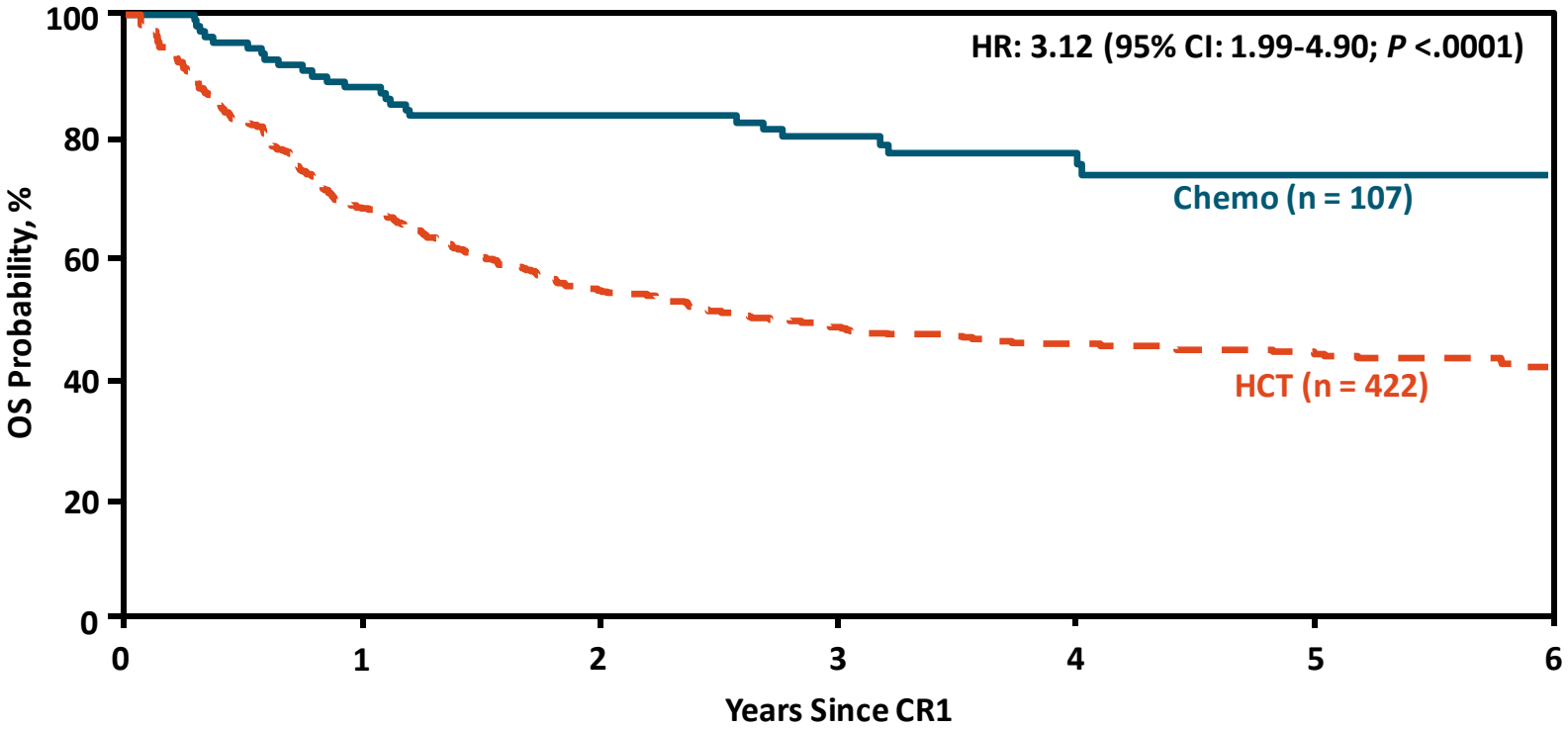


No. at risk:								
18-24 years	200	153	130	124	92	65	38	20
25-34 years	172	138	112	98	78	56	35	24
35-44 years	171	122	93	87	72	49	36	21
45-54 years	151	104	81	68	57	38	23	8
≥ 55 years	93	52	38	31	21	16	11	5

*GRAALL-2005: randomized trial evaluating a pediatric-inspired hyper-CVAD protocol in adults aged 18–59 yr with Ph-negative ALL.

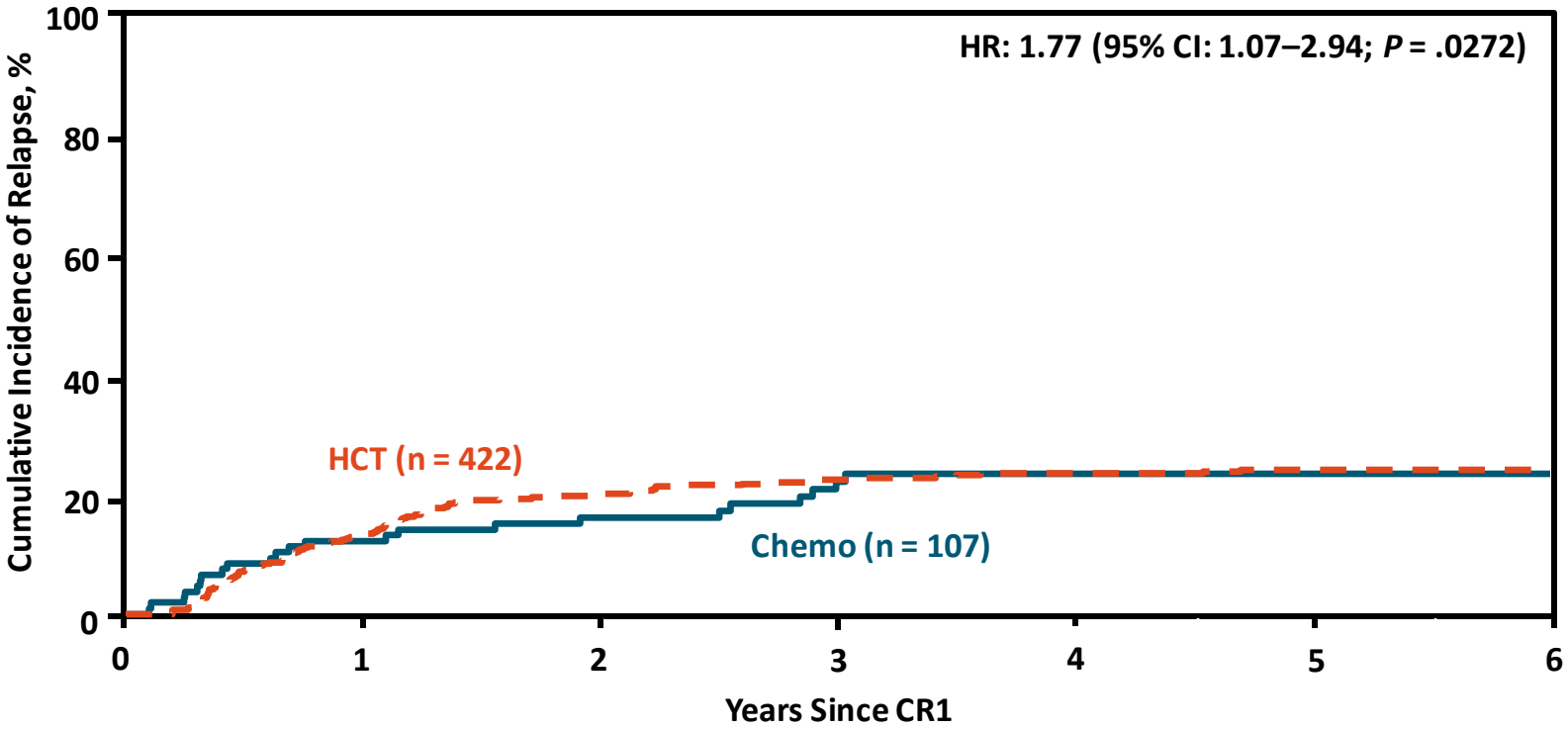
Huguet F, et al. *J Clin Oncol.* 2018;36:2514-2523.

Pediatric-Inspired Chemotherapy Regimen vs HCT: Overall Survival



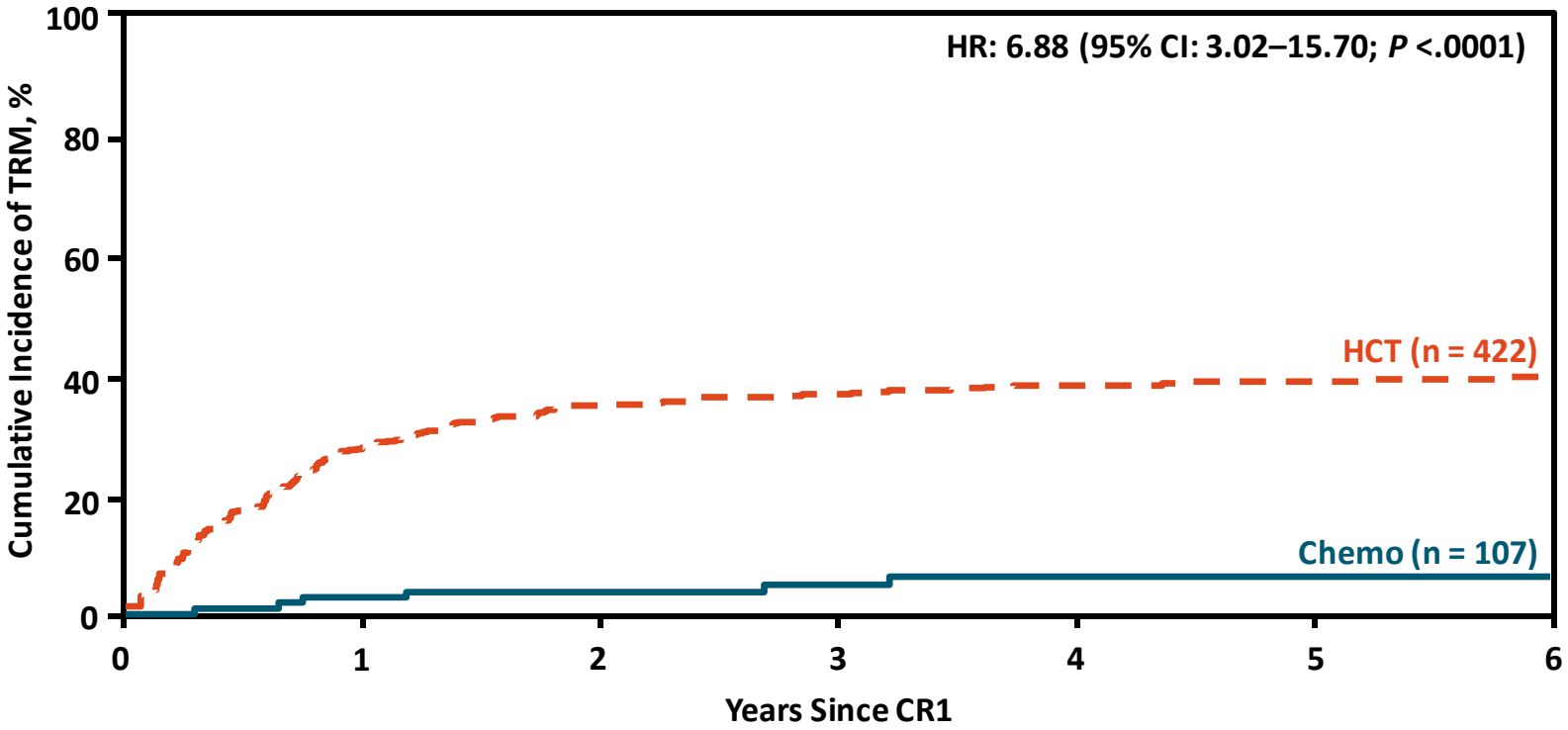
Seftel MD, et al. *Am J Hematol*. 2016;91:322-329.

Chemotherapy vs HCT: Cumulative Incidence of Relapse



Seftel MD, et al. *Am J Hematol*. 2016;91:322-329.

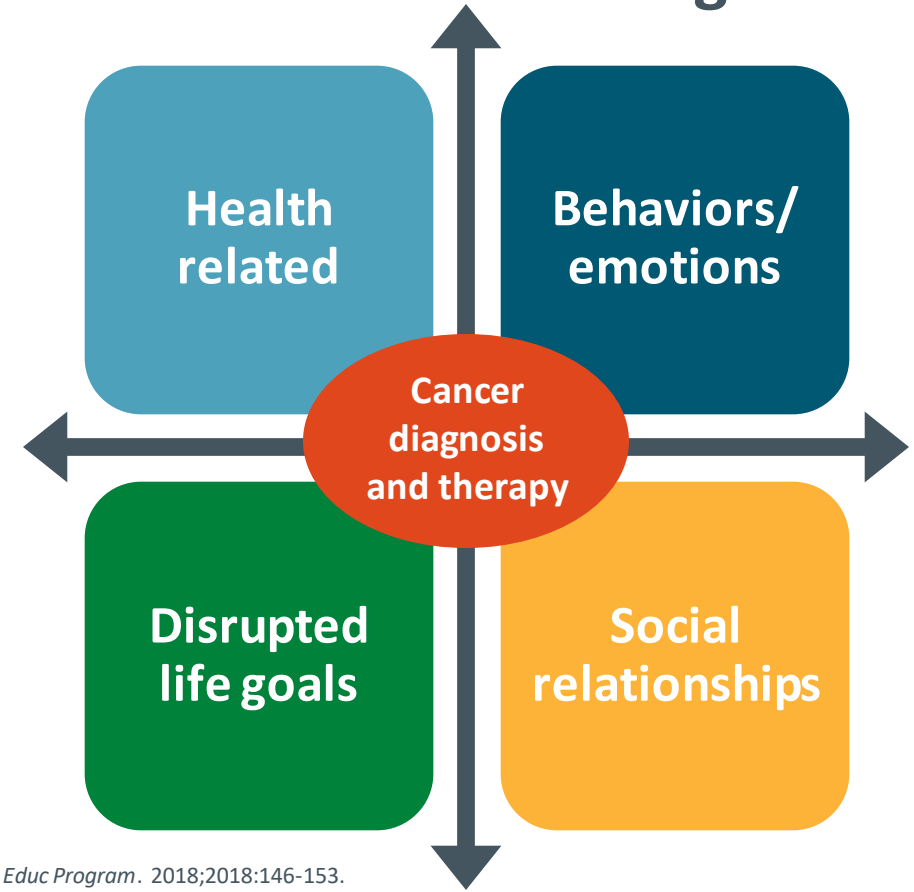
Chemotherapy vs HCT: Cumulative Incidence of Treatment-Related Mortality



Seftel MD, et al. *Am J Hematol*. 2016;91:322-329.

AYA Survivorship

Major Patient-Centered Concerns Facing AYA Cancer Survivors



Baker KS, Syrjala KL. *Hematology Am Soc Hematol Educ Program*. 2018;2018:146-153.

AYA Cancer Survivorship

Treatment Complications

- Health behaviors
  - Risky behaviors
  - Diet/exercise
- Healthcare needs
  - Chronic healthcare needs
  - Access
- Emotional adjustment
  - Fear of recurrence
  - Anxiety/PTSD
- Social relationships
- Employment/finances
  - Complete education
  - Career/debt/financial stress

Psychosocial Impact

- Cardiac
  - Cardiomyopathy
  - Obesity, HTN, dyslipidemia
  - Thrombosis
- Endocrine
  - Anterior pituitary dysfunction: GH, LH, FSH, ACTH, TSH
  - Ovarian dysfunction
  - Testicular dysfunction
- Reproductive
  - Fertility
  - Sexual dysfunction
- Musculoskeletal
  - Osteonecrosis
  - Osteopenia

Baker KS, Syrjala KL. *Hematology Am Soc Hematol Educ Program*. 2018;2018:146-153.

Pediatric Regimens Rely on Steroids and Asparaginase With Unique Toxicities

- Thrombosis and bleeding
- Pancreatitis
- Hepatic toxicity
- Metabolic syndrome (hyperglycemia, hypertriglyceridemia)
- Osteonecrosis – late toxicity, less understood

Toxicities disproportionately affect older children and adults

Mattano LA Jr, et al. *J Clin Oncol*. 2000;18:3262-3272; Patel B, et al. *Leukemia*. 2008;22:308-312; Vrooman LM, et al. *J Clin Oncol*. 2013;31:1202-1210; Albertsen BK, et al. *J Clin Oncol*. 2019;37:1638-1646; Burke PW, et al. *ESMO Open*. 2020;5:e000858.

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	

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 Cyclophosphamide

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 A041

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, then ≥ 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/m^2 (maximum dose 2 mg) IV on Days 1, 29, and 57. Voriconazole and posaconazole are contraindicated with vincristine.

DFCI AYA Program

- **Treatment of ALL at the DFCI**
  - Pediatric trials for young (<40 yr) adult patients
  - All patients <30 yr of age seen by social worker and psychologist for evaluation
  - AYA support group
  - Focused treatment team: MD/PA/RN/social worker/psychologist

IT TAKES A VILLAGE!

The AYA "Village"

- 7 MDs, 2 specifically for ALL
- MD-NP teams
- RN infusion teams (primary nurse model)
- AYA monthly interdisciplinary meetings
- Clinical trials that cross age boundaries
- Clinical and scientific pediatric/adult ALL conferences

Impact of COVID-19 pandemic

- Multidisciplinary support
  - Infectious disease, dermatology (same clinic)
  - Fertility/endocrine
  - Cardio-oncology, renal-oncology, neuro-oncology
- Social work, psychology, psychiatry
- AYA support group
- Non-English speakers paired with primary translator; consent forms translated into native language

Conclusions

- Administration of dose-intensified pediatric regimen in adults is feasible with acceptable toxicity
- This approach **translates** into better survival for adults with ALL
  - 3-yr OS: 75%; 3-yr DFS: 73% (42.2-mo f/u)[1]
  - PEG-ASNase has increased toxicity in older adult patients as well as patients with high BMI (>30)
- Many challenges remain
  - Psychosocial issues
  - Practice patterns
  - Biology (Ph-like signature)
  - MRD status
- We need more AYA trials!

1. DeAngelo DJ, et al. ASH 2015. Abstract 80.

Acknowledgements

DFCI Clinical Leukemia Team

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Martha Wadleigh
Eric Winer
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Rahul Vedula
Chris Reilly
Sagar Koduri
Evan Chen
Virginia Volpe

Ilene Galinsky, NP
Patrice O'Sullivan, NP
Theresa Nguyen, NP
Mary Gerard, PA
Kelly Ling, PA
Ryan Osborn, PA
Ellen Toomey-Mathews, RN

Special thanks:
Patients and their Families!!!

The End: questions?

Questions or need help?

Email: daniel_deangelo@dfci.harvard.edu
Phone: 617-632-2645
Administrative Assistant: 617-582-8410
New Patients: 617-632-6028
Page: 617-632-3352 #41284

Global Leukemia Academy

Q&A

APTITUDE HEALTH

Global Leukemia Academy

Current and future role of transplantation in acute leukemias

Jae Park and Shaun Fleming

APTITUDE HEALTH

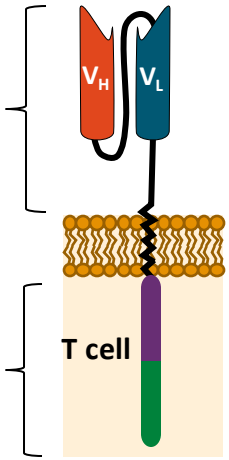
Global Leukemia Academy

Current and future role of transplantation in acute leukemias: Global

Jae Park

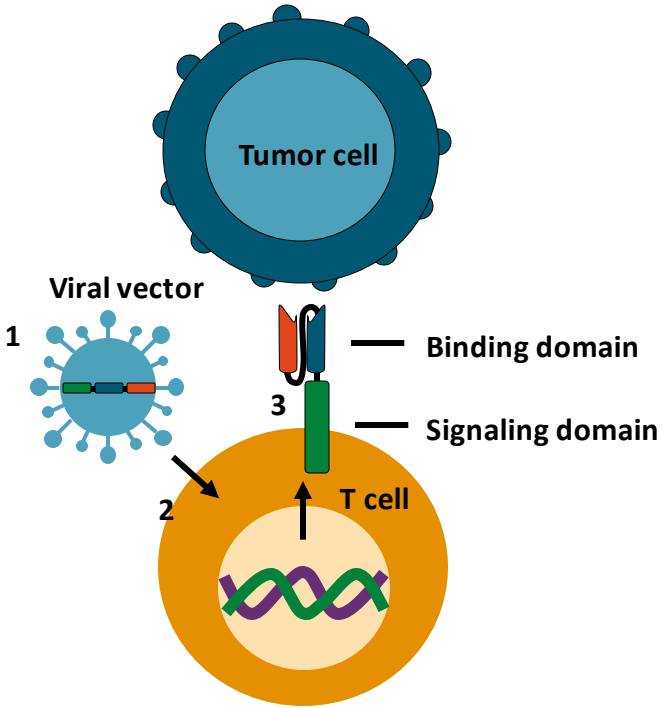
APTITUDE HEALTH

CD19-Directed CAR T Cells



Fusion protein

- T-cell costimulatory receptor-signaling domain
- TCRζ-activation domain



CD19-directed CAR T cell

- Comprising a CD19 antigen-binding domain, a costimulatory domain (generally CD28 or 4-1BB), and CD3ζ-signaling domain

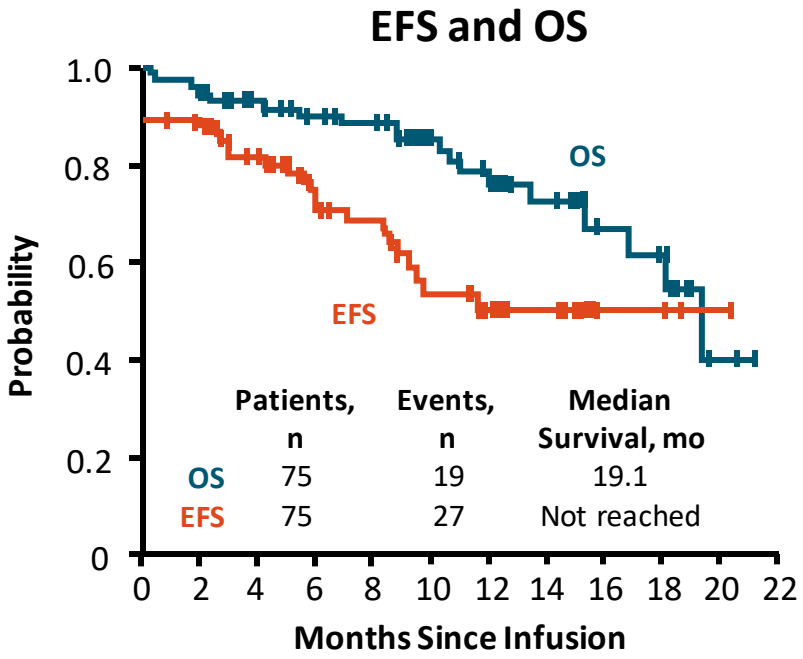
FDA-Approved CAR T-Cell Therapies in ALL in US

Therapy	Target	Approval Date	Indications
Tisagenlecleucel	CD19	August 30, 2017	**Patients up to age 25 yrs with B-cell precursor ALL that is refractory or in second/later relapse**
Brexucabtagene autoleucel	CD19	October 1, 2021	**Adults with relapsed or refractory B-cell ALL**

ELIANA: Tisagenlecleucel in Children and Young Adults With R/R B-ALL

- International, open-label, single-arm phase II study (N = 92)
  - Patients aged 3–21 yr with relapsed or refractory B-cell ALL
  - Patients underwent lymphodepletion with fludarabine + cyclophosphamide followed by single-dose tisagenlecleucel
  - At baseline: median number of prior therapies, 3; prior allogeneic SCT, 46%; median BM blast count at time of treatment, 74%
- **ORR at 3 mo: 81%**

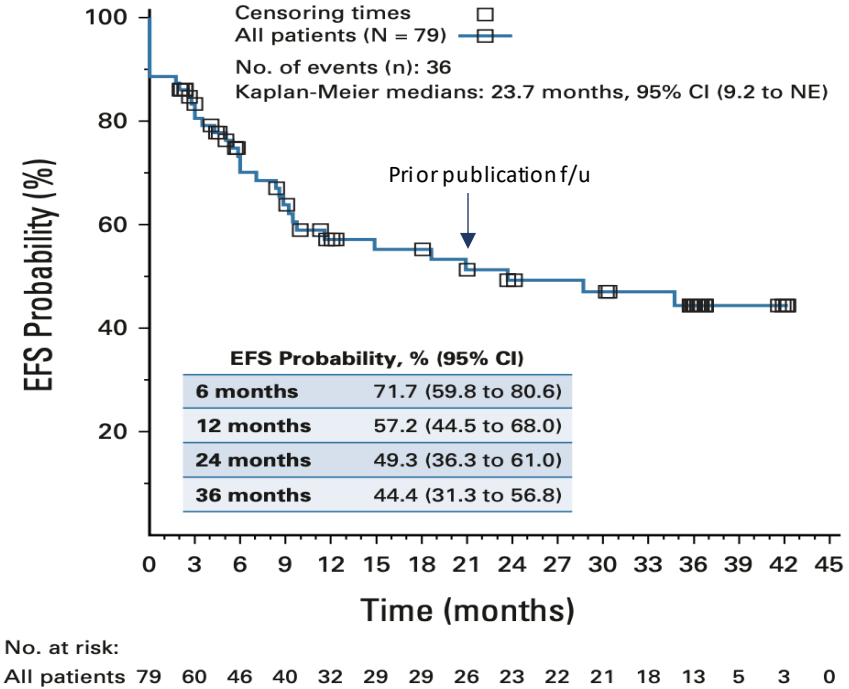
Outcome, %	Mo 6	Mo 12
OS	90	76
Event-free survival	73	50



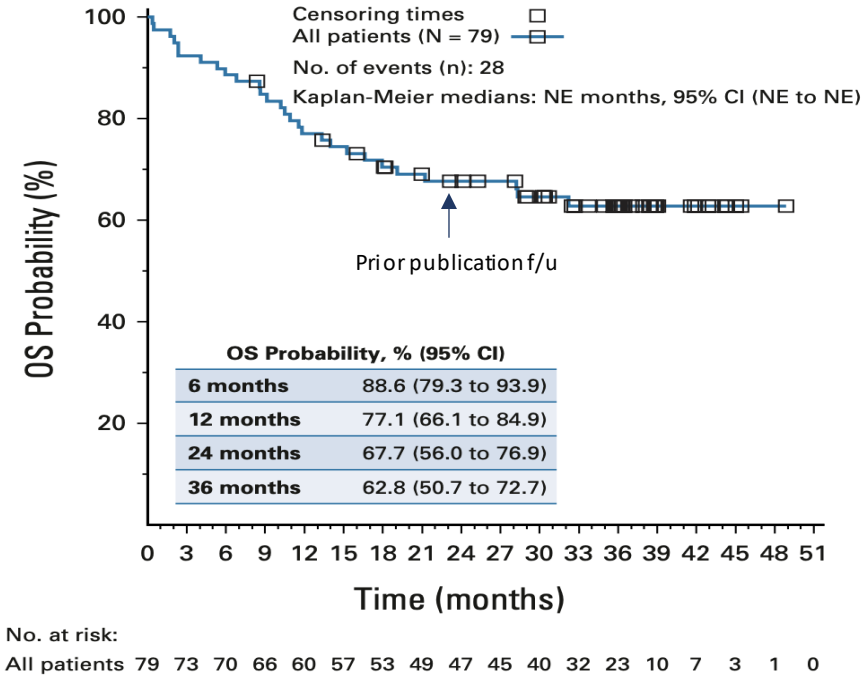
11% proceeded to HSCT

Maude SL, et al. *N Engl J Med*. 2018;378:439-448.

ELIANA: 3-Year Update of Tisagenlecleucel in Children and Young Adults With R/R B-ALL



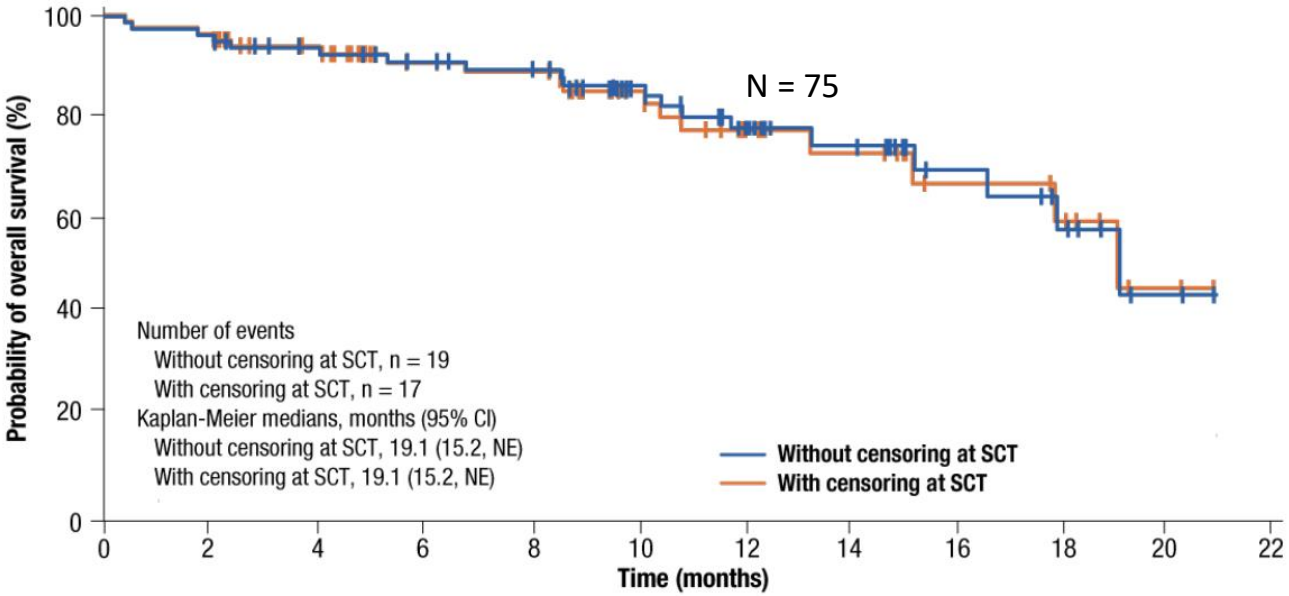
EFS Probability, % (95% CI)	
6 months	71.7 (59.8 to 80.6)
12 months	57.2 (44.5 to 68.0)
24 months	49.3 (36.3 to 61.0)
36 months	44.4 (31.3 to 56.8)



OS Probability, % (95% CI)	
6 months	88.6 (79.3 to 93.9)
12 months	77.1 (66.1 to 84.9)
24 months	67.7 (56.0 to 76.9)
36 months	62.8 (50.7 to 72.7)

Laetch T, et al. *J Clin Oncol.* 2022;41:1664-1669.

ELIANA: Overall Survival With or Without Censoring for HSCT



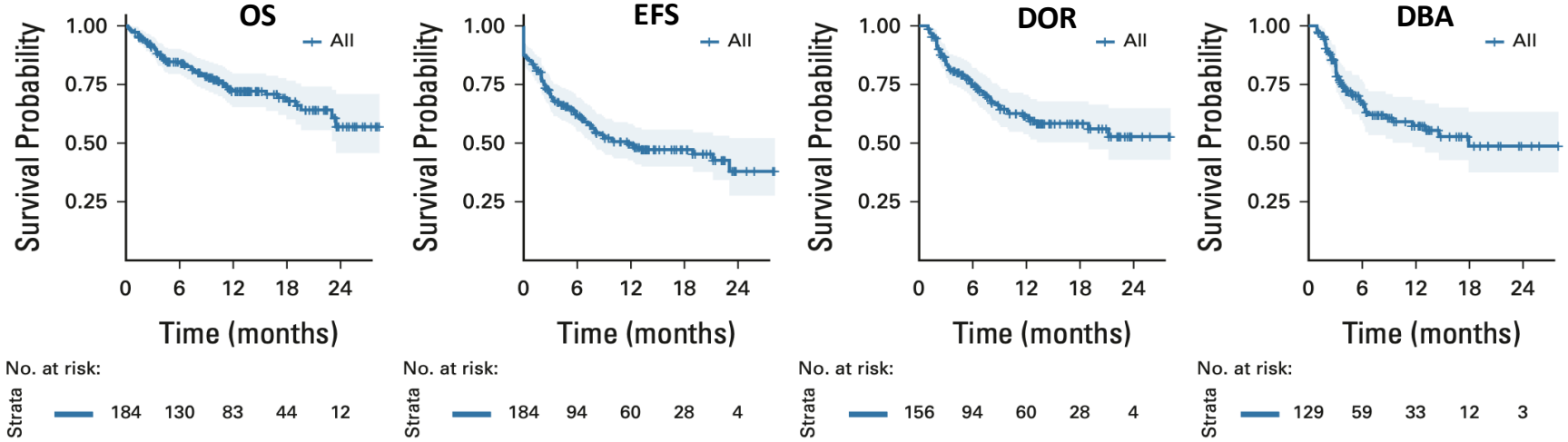
Patients at risk												
Without censoring at SCT	75	72	64	58	55	40	30	20	12	8	2	0
With censoring at SCT	75	72	60	48	45	31	21	15	9	7	2	0

13% of those with response (11% overall) proceeded to HSCT

Maude SL, et al. *N Engl J Med*. 2018;378:439-448.

Tisagenlecleucel Real-World Data: Baseline Patient Characteristics of Pediatric and AYA ALL Patients

N = 184



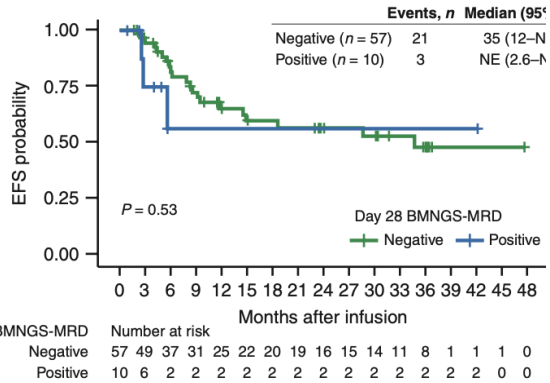
Outcome	6-Month OS	1-Year OS	6-Month EFS	1-Year EFS	6-Month DOR	1-Year DOR	6-Month DBA	1-Year DBA
All patients	0.85	0.72	0.62	0.5	0.75	0.62	0.68	0.57

26% underwent post-CAR T allo-HSCT: **13% in CR after CAR** + 12% for relapse after CAR T + 1% for post-CAR T MDS

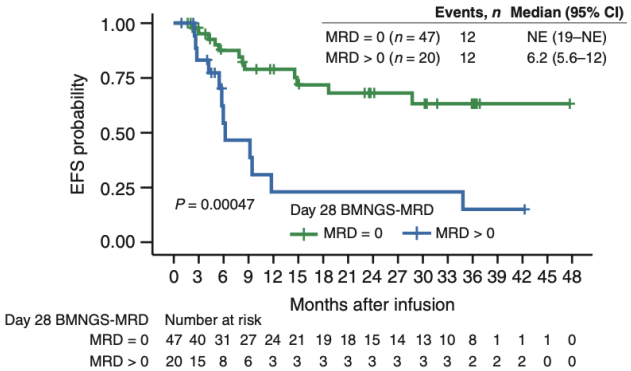
Schultz L, et al. *J Clin Oncol.* 2022;40:945-955.

ELIANA: Undetectable NGS MRD Associated With Improved EFS

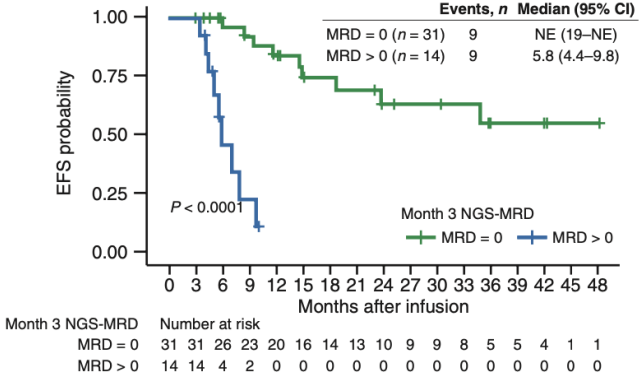
D28 BM NGS (negative vs positive)



D28 BM NGS (0 vs >0)

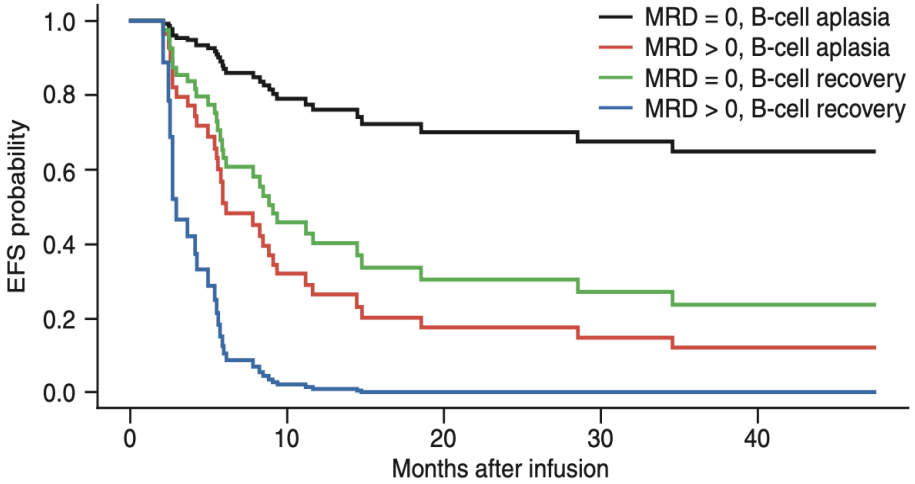


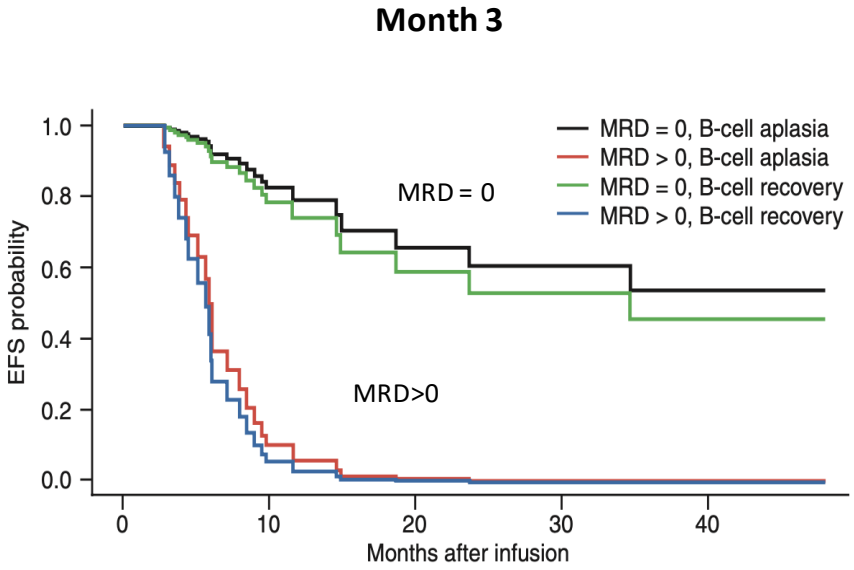
Month 3 BM NGS (0 vs >0)



Pulsipher M, et al. *Blood Cancer Discov.* 2022;3:66-81.

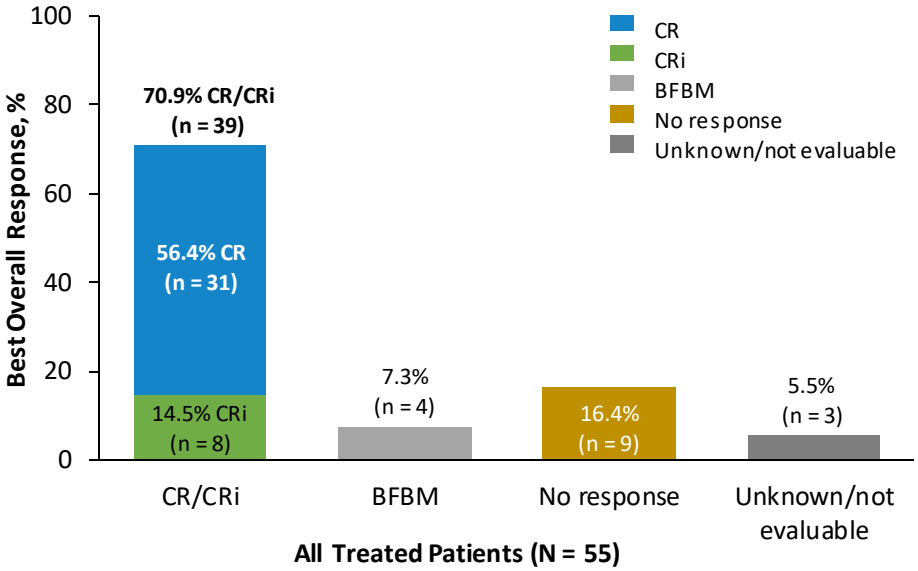
ELIANA: Relationship Between NGS MRD + B-Cell Aplasia and EFS

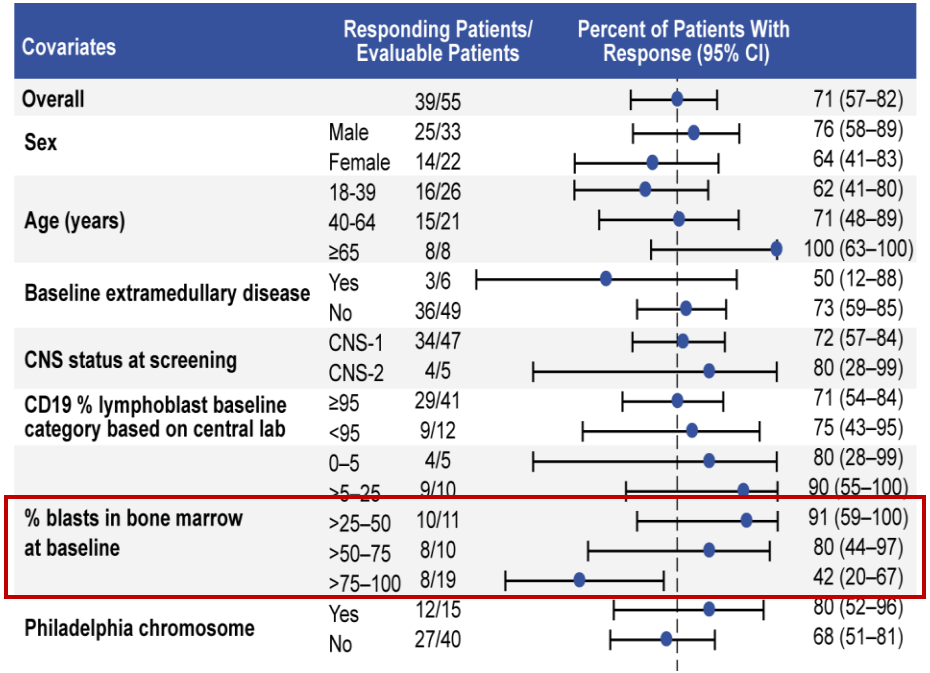




Pulsipher M, et al. *Blood Cancer Discov.* 2022;3:66-81.

ZUMA-3: Clinical Outcome





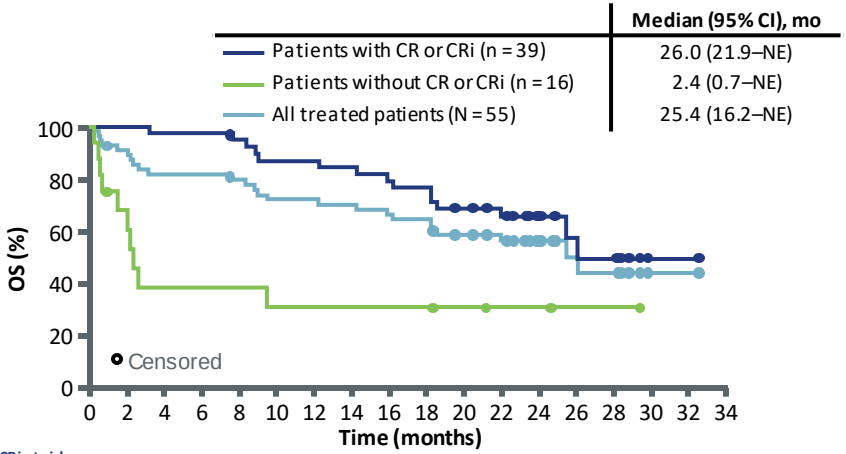
- CRS: all grade, 89%; grade ≥3, 24%
- ICANS: all grade, 60%; grade ≥3, 25%

Two grade 5 events (neurotoxicity, sepsis): 3.6% TRM

Shah BD, et al. *Lancet*. 2021;398:491-502.

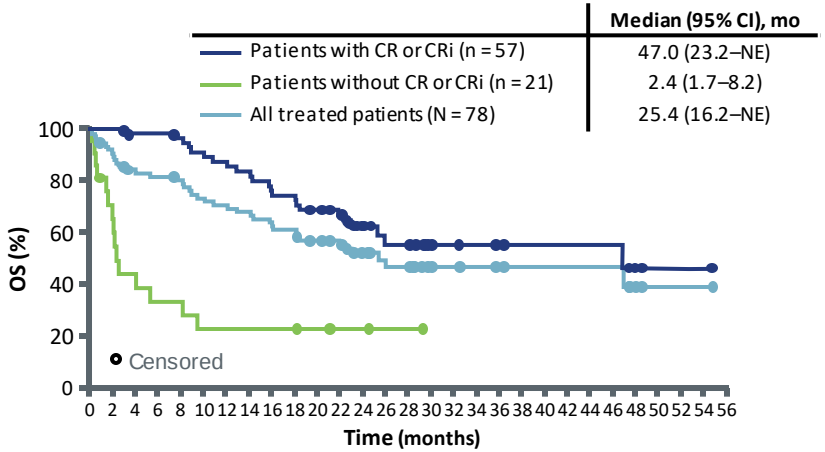
Kaplan-Meier OS Curves for Phase II-Treated Patients and Pooled Phase I- and II-Treated Patients

OS in phase II-treated patients (N = 55)



CR+CRi at risk	39	39	38	38	36	33	33	32	30	29	25	22	14	7	6	1	1	0
(CR+CRi censored)	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(4)	(12)	(18)	(18)	(23)	(23)	(24)
Others at risk	16	9	5	5	5	4	4	4	4	4	3	2	2	1	1	0	0	0
(Others censored)	(0)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(4)	(4)	(5)	(5)	(5)	(6)	(6)	(6)
All dosed at risk	55	48	43	43	41	37	37	36	34	33	28	24	16	8	7	1	1	0
(All dosed censored)	(0)	(2)	(2)	(2)	(3)	(3)	(3)	(3)	(3)	(3)	(5)	(8)	(16)	(23)	(23)	(29)	(29)	(30)

OS in pooled phase I- and II-treated patients (N = 78)



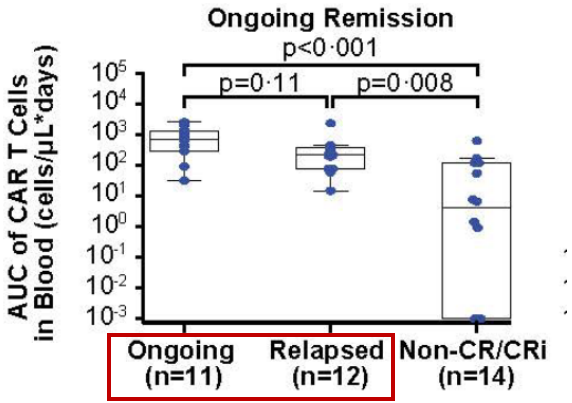
CR+CRi at risk	57	57	54	54	52	49	47	45	42	40	36	33	23	16	15	10	9	8	7	6	6	6	6	3	1	1	1	0
(CR+CRi censored)	(0)	(0)	(2)	(2)	(3)	(3)	(3)	(3)	(3)	(3)	(4)	(6)	(14)	(20)	(20)	(25)	(26)	(27)	(28)	(29)	(29)	(29)	(29)	(31)	(33)	(33)	(33)	(34)
Others at risk	21	13	8	6	6	4	4	4	4	4	3	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
(Others censored)	(0)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(4)	(4)	(5)	(5)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)
All dosed at risk	78	70	62	60	58	53	51	49	46	44	39	35	25	17	16	10	9	8	7	6	6	6	6	3	1	1	1	0
(All dosed censored)	(0)	(2)	(4)	(4)	(5)	(5)	(5)	(5)	(5)	(5)	(7)	(10)	(18)	(25)	(25)	(31)	(32)	(33)	(34)	(35)	(35)	(35)	(35)	(37)	(39)	(39)	(33)	(40)

26% of the patients received allo-SCT at a median 98 days (range, 60–207) post–KTE-X19 infusion

- Median DOR of HSCT vs no-HSCT patients: NR vs 14.6 mo (8.7–23.6)
- Median OS of HSCT vs no-HSCT patients: NR (7.6–NE) vs 26.0 mo (18.6–NE)

Shah BD, et al. ASCO 2022. Abstract 7010.

ZUMA-3: CAR T-Cell Persistence



No detectable CAR T cells beyond 6 months.
AUC of CAR T cells not correlated with DOR.

Parameter	N=55
Peak (cells/µL)	(n=50)
Median	20·62
IQR	4·58–62·97
AUC_{0-28} (cells/µL•days)	(n=50)
Median	220·60
IQR	56·25–676·94
Time-to-Peak (days)	(n=50)
Median	15
IQR	11–16
Week 4 (cells/µL)	(n=41)
Median	1·62
IQR	0·12–5·87
Week 8 (cells/µL)	(n=37)
Median	0·24
IQR	0–0·94
Month 3 (cells/µL)	(n=31)
Median	0·02
IQR	0–0·49
Month 6 (cells/µL)	(n=28)
Median	0
IQR	0–0
Month 9 (cells/µL)	(n=22)
Median	0
IQR	0–0

Shah BD, et al. *Lancet*. 2021;398:491-502.

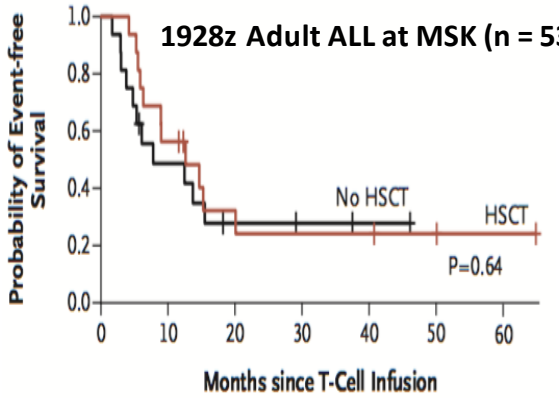
ZUMA-3: Relationship Between B-Cell Aplasia and Relapse

	Ongoing CR/CRi* n=12			Relapsed n=13			Non-CR/CRi n=16		
	n (%)	B cell ,% Median (IQR)	CAR T, cells/µL Median (IQR)	n (%)	B cell ,% Median (IQR)	CAR T, cells/µL Median (IQR)	n (%)	B cell ,% Median (IQR)	CAR T, cells/µL Median (IQR)
B cells tested at baseline	12 (100)	18·00 (4·93–33·95)	0·00 (0·00–0·00)	13 (100)	55·73 (39·29–77·46)	0·00 (0·00–0·00)	11 (68·8)	50·84 (14·67–63·36)	0·00 (0·00–0·00)
No B cells									
With B cells	12 (100)	18·00 (4·93–33·95)	0·00 (0·00–0·00)	13 (100)	55·73 (39·29–77·46)	0·00 (0·00–0·00)	11 (100)	50·84 (14·67–63·36)	0·00 (0·00–0·00)
B cells tested at month 6	10 (83·3)	14·08 (0·05–22·00)	0·08 (0·00–0·71)	7 (53·8)	30·93 (10·60–69·58)	0·00 (0·00–0·00)	1 (6·3)	1·18 (1·18–1·18)	0·00 (0·00–0·00)
No B cells	2 (20·0)		0·70 (0·30–1·10)						
With B cells	8 (80·0)	14·08 (0·05–22·00)	0·00 (0·00–0·44)	7 (100)	30·93 (10·60–69·58)	0·00 (0·00–0·00)	1 (100)	1·18 (1·18–1·18)	0·00 (0·00–0·00)
B cells tested at month 12	10 (83·3)	12·60 (0·57–29·66)	0·00 (0·00–0·00)	5 (38·5)	38·56 (35·00–69·18)	0·00 (0·00–0·00)	2 (12·5)	11·81 (2·19–21·43)	0·22 (0·00–0·44)
No B cells									
With B cells	10 (100)	12·60 (0·57–29·66)	0·00 (0·00–0·00)	5 (100)	38·56 (35·00–69·18)	0·00 (0·00–0·00)	2 (100)	11·81 (2·19–21·43)	0·22 (0·00–0·44)

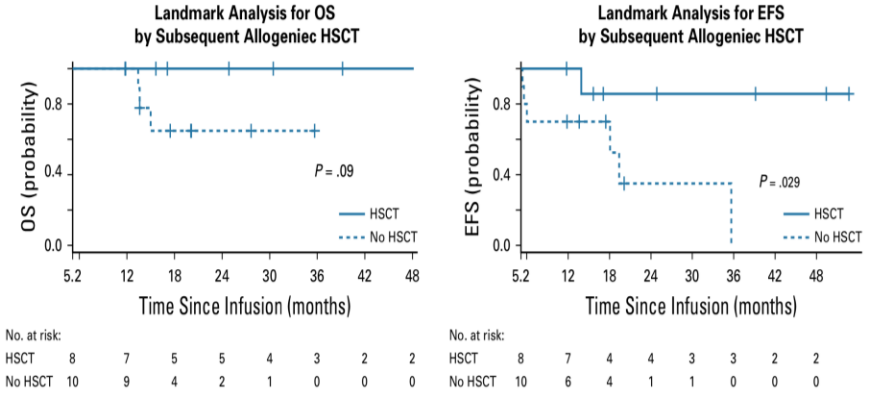
Most patients recover B cells by 6 months, but no correlation with DOR.

Post-CAR T HSCT in CD19 CAR T Clinical Trials in Adults and Peds/AYA

1928z Adult ALL at MSK (n = 53)

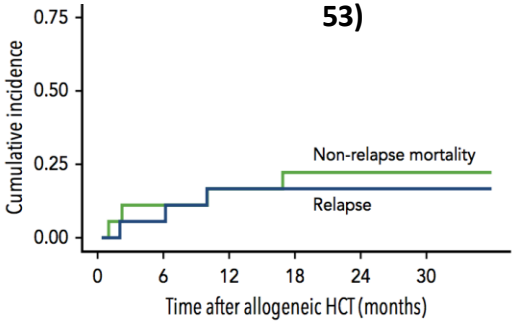


CTL019 (BBz) in Adult ALL at UPenn (n = 35)



38% of patients with response proceeded to allo-HSCT

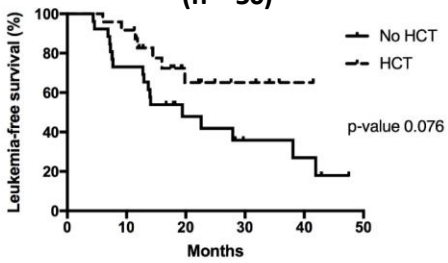
19BBz Adult ALL at FHRC (n = 53)



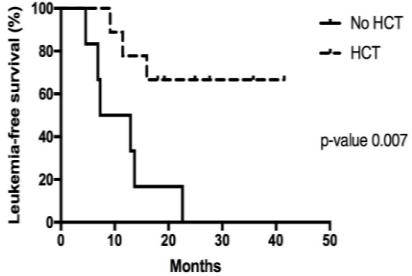
Variable	Multivariable analysis HR	95% CI	P
LDH prelymphodepletion (per 100 U/L increment)	1.39	1.11-1.73	.004
Platelets prelymphodepletion (per 50 000/μL increment)	0.74	0.53-1.03	.069
Fludarabine added to lymphodepletion	0.25	0.15-0.78	.003
HCT after CAR T-cell therapy	0.39	0.13-1.15	.088

~40% of patients with response proceeded to allo-HSCT

19BBz Pediatric ALL [PLAT-02] (n = 50)



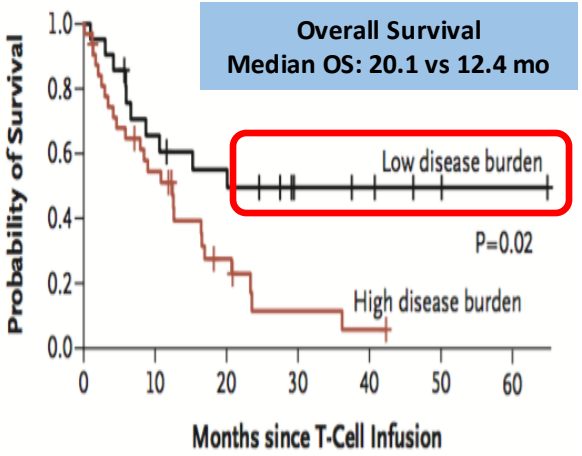
Short BCA (n = 15)



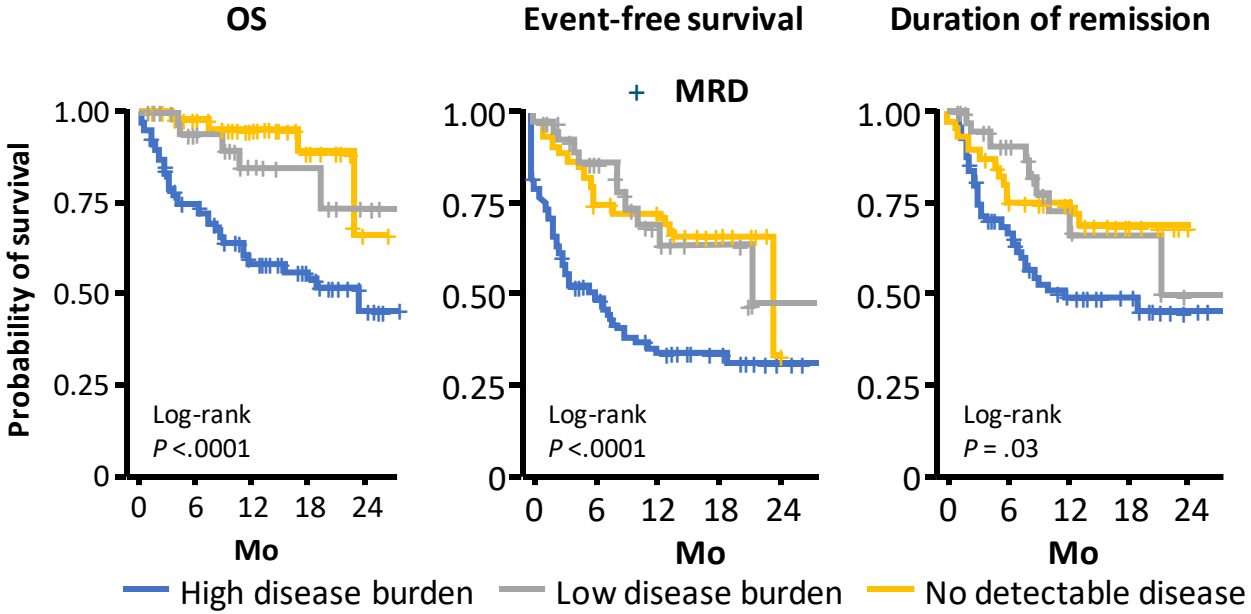
Park J, et al. *N Engl J Med.* 2018;378:449-459; Hay K, et al. *Blood.* 2019;133:1651-1663; Frey N, et al. *J Clin Oncol.* 2019;38:415-422; Gardner R, et al. *Blood.* 2017;129:3322-3331.

Low Disease Burden Associated With Improved Remission Duration and Long-Term Survival

1928z CAR T in Adult ALL



Tisagenlecleucel in children and AYA R/R ALL



Park J, et al. *N Engl J Med.* 2018;378:449-459.

Schultz LM, et al. ASH 2020. Abstract 468.

Summary

- CD19 CAR T-cell therapy is the most potent single-agent therapy in ALL
  - 80% CR/CRi in R/R B-ALL regardless of BM blasts and prior therapy including EMD vs blinatumomab with lower overall CR rates and less efficacy in EMD
  - 1-time treatment, a single infusion of cells with no GvHD risk
  - A subset of patients can achieve durable remissions w/o HSCT
  - Post-CAR HSCT for those who are at high risk of relapse: high disease burden, persistent NGS MRD at any level at D28/month 3, early B-cell recovery within 6 months (for tisagenlecleucel only)
- Toxicity profiles of CAR T and management strategies are improving
- Our current approach of allogeneic HSCT in CR1 for high-risk patients (MRD+ CR, hypodiploid, Ph-like, etc) might change in the future with movement of CD19 CAR T cells in this space

Global Leukemia Academy

Current and future role of transplantation in acute leukemias: Asia-Pacific

Shaun Fleming

APTITUDE HEALTH

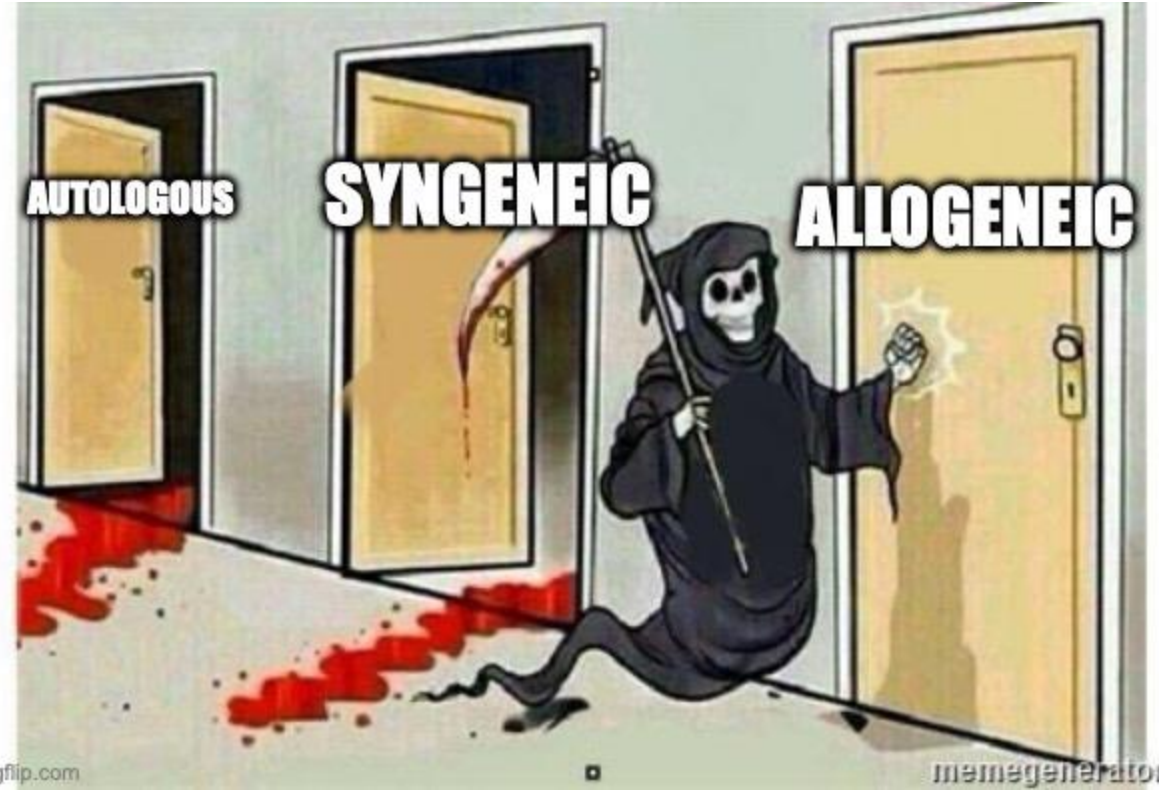
Disclosures

Consultancy/advisory board participation/honoraria

- Amgen
- Novartis
- Servier
- AbbVie
- Pfizer
- Gilead
- BMS

Research grants

- Amgen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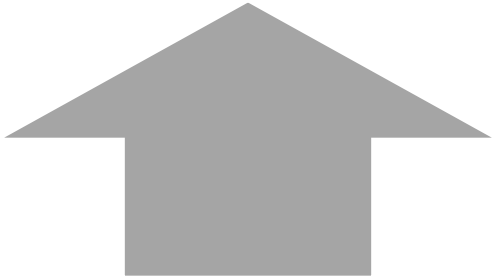
The Balance Is Shifting in Allo-HSCT, but Not Universally

- Ongoing impact of TRM
- Availability of new drugs in frontline and relapsed disease
- CAR T

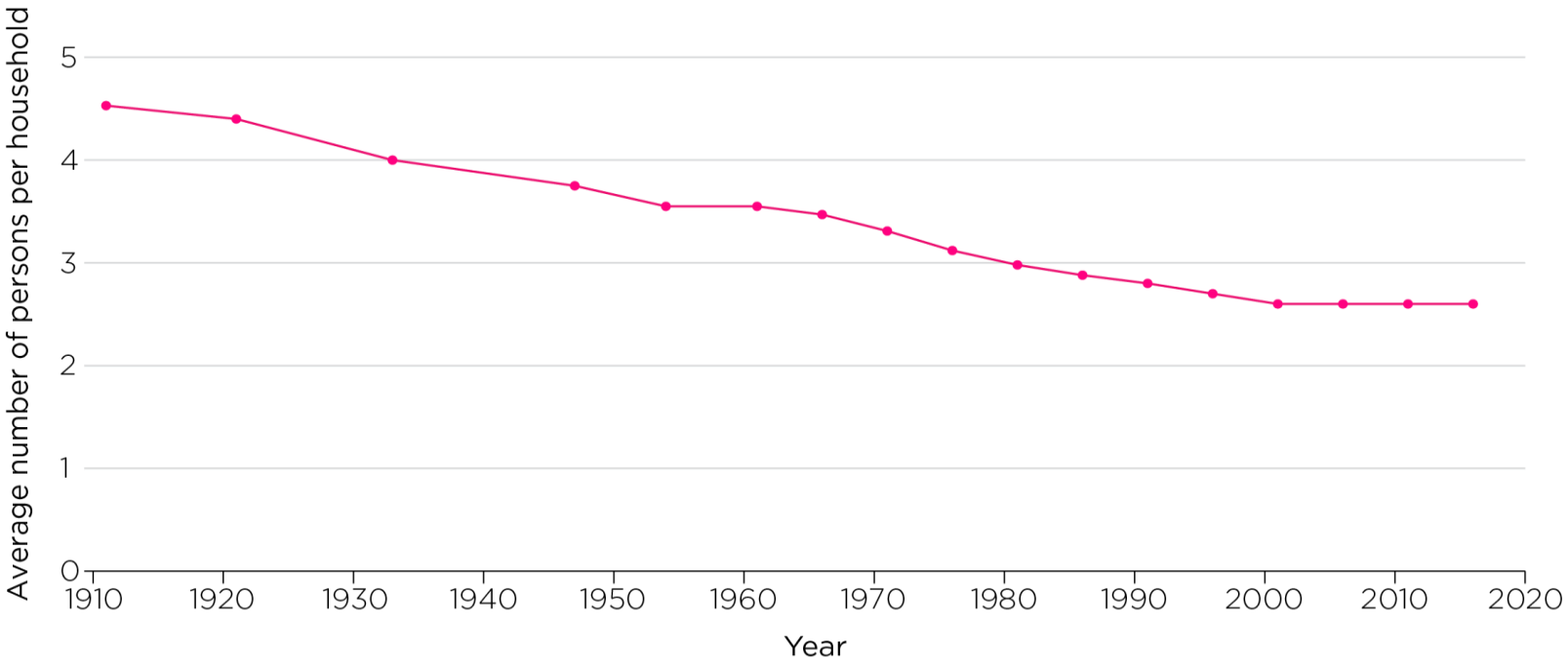
- Remains highly effective at controlling leukemia – can we make that even better?
- More access to donors through haploidentical transplantation
- New approaches to GVHD prophylaxis



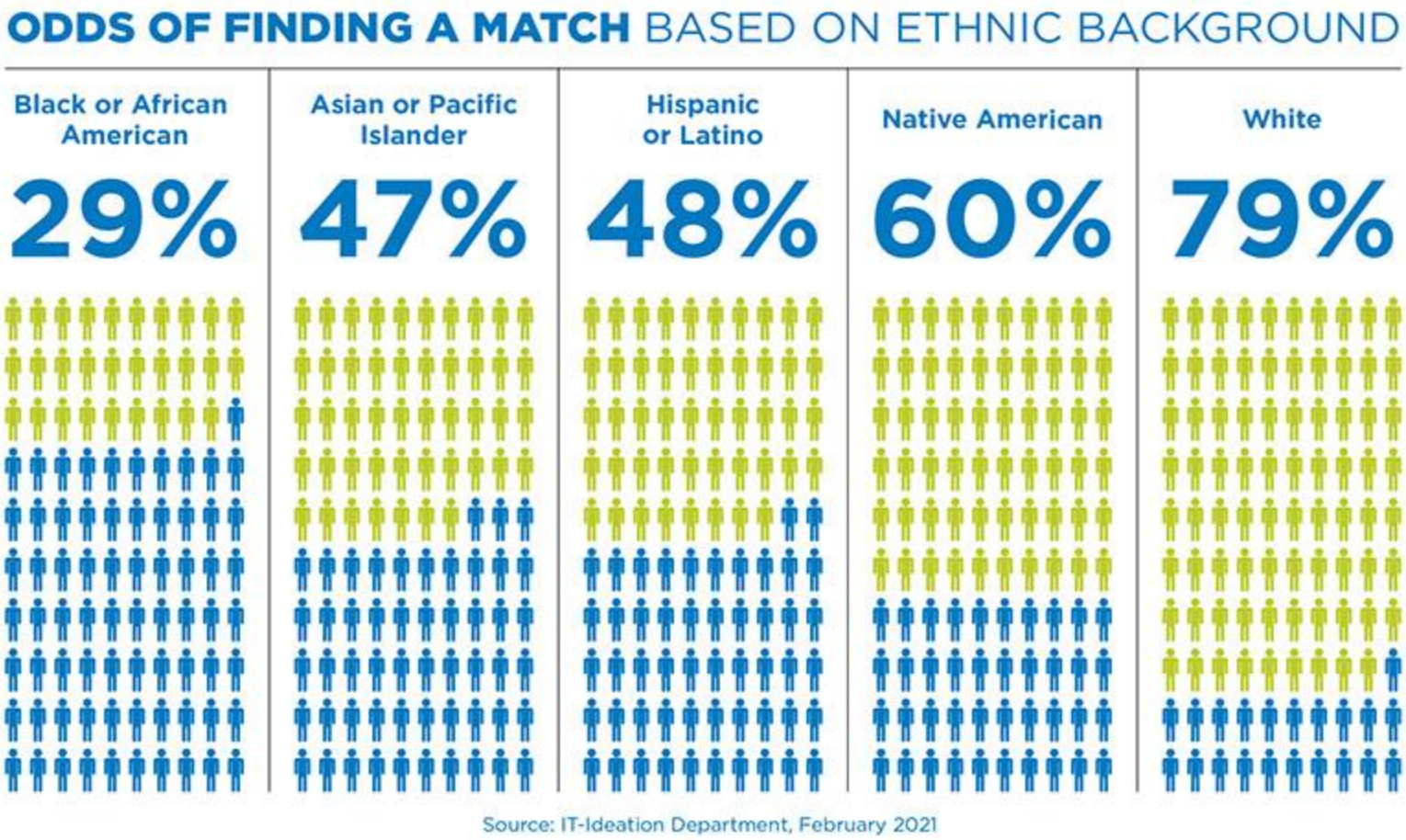
Expanding the Donor Pool: Haploidentical Transplantation

Families Are Getting Smaller – Fewer Sibling Donors

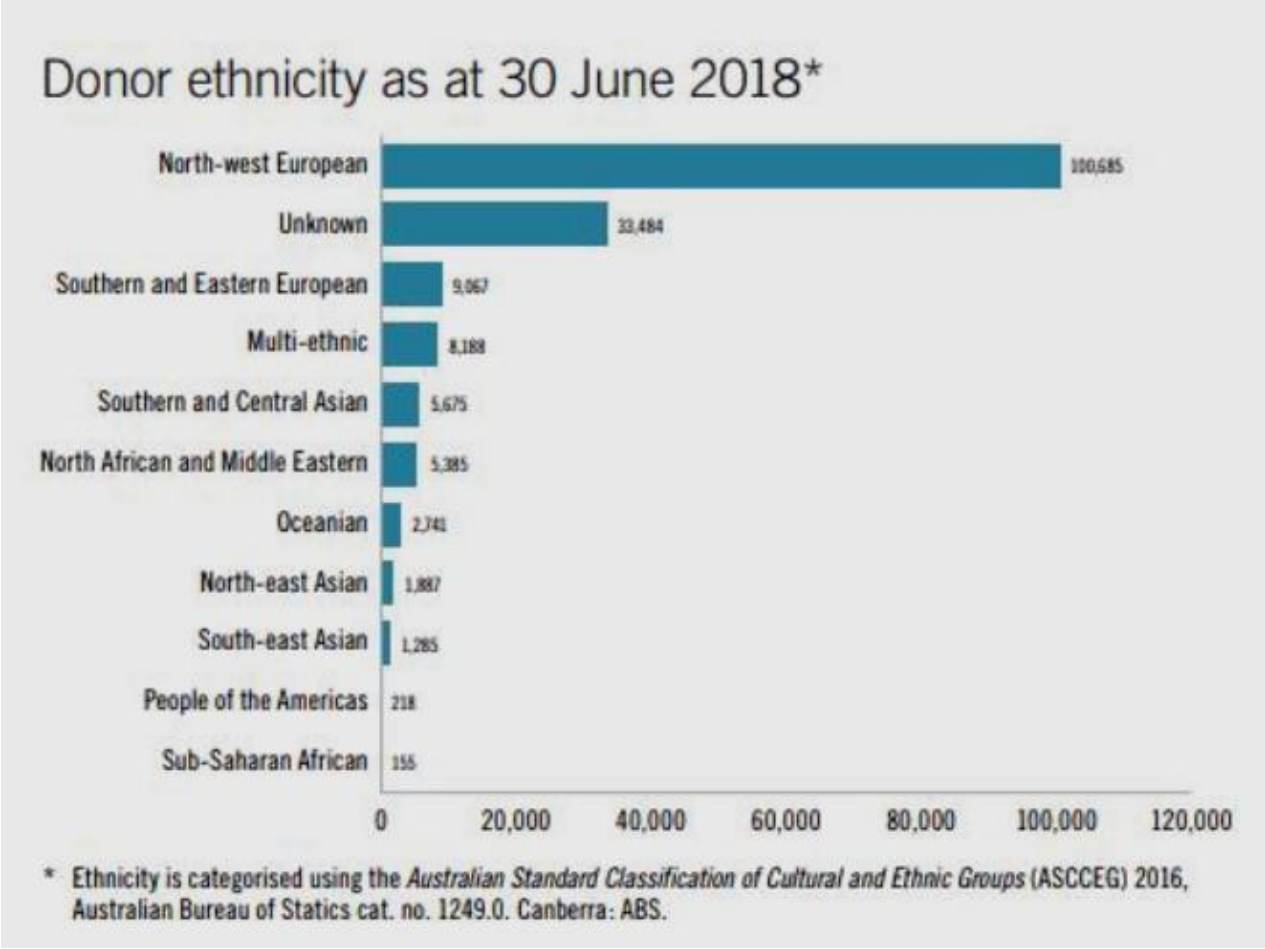
Average household size, 1911–2016



Australian Institute of Family Studies. Population and Households. Accessed Sep 7, 2023.
https://aifs.gov.au/research/facts-and-figures/population-and-households

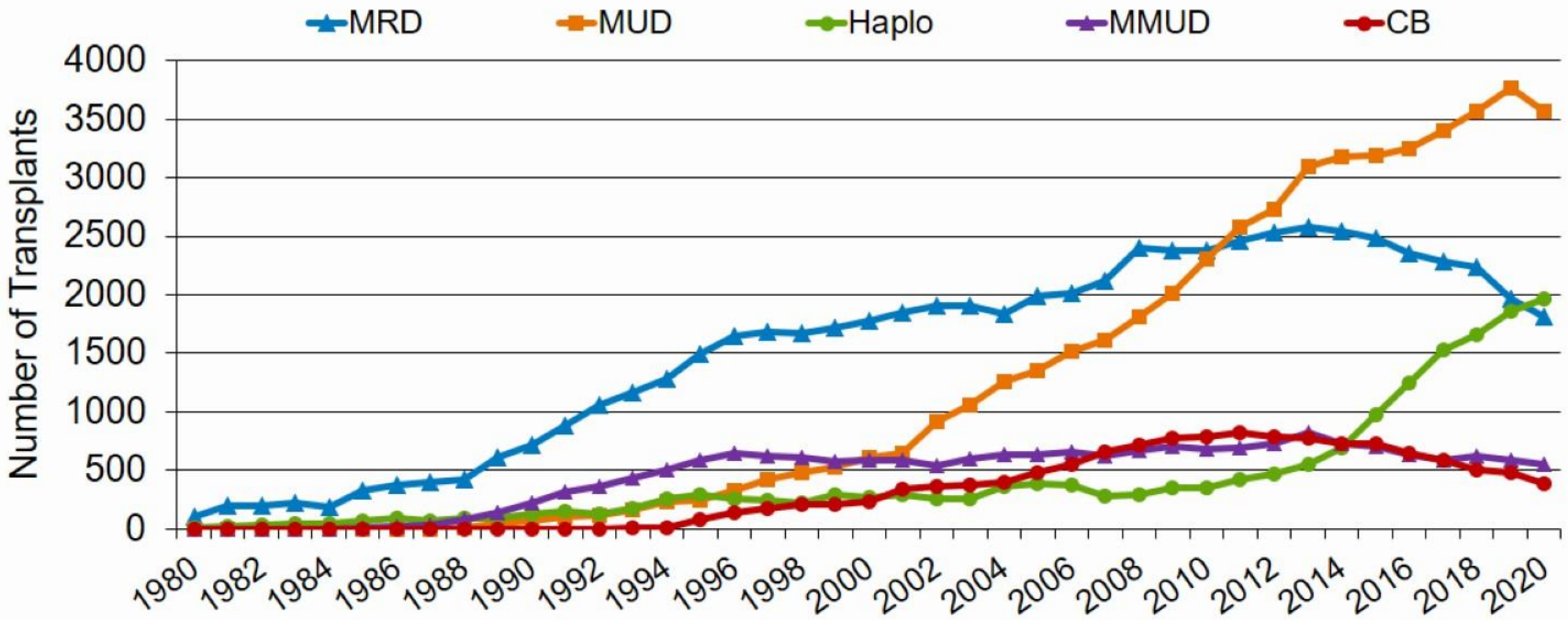


Be the Match. Accessed Sep 7, 2023. https://www.bethematchhosa.org/



Miles D. ABC News. Oct 1, 2019. Accessed Sep 7, 2023.
https://www.abc.net.au/news/2019-10-02/donor-registry-plea-for-ethnic-diversity-to-save-cancer-patients/11563250

Number of Allogeneic HCTs in the US by Donor Type



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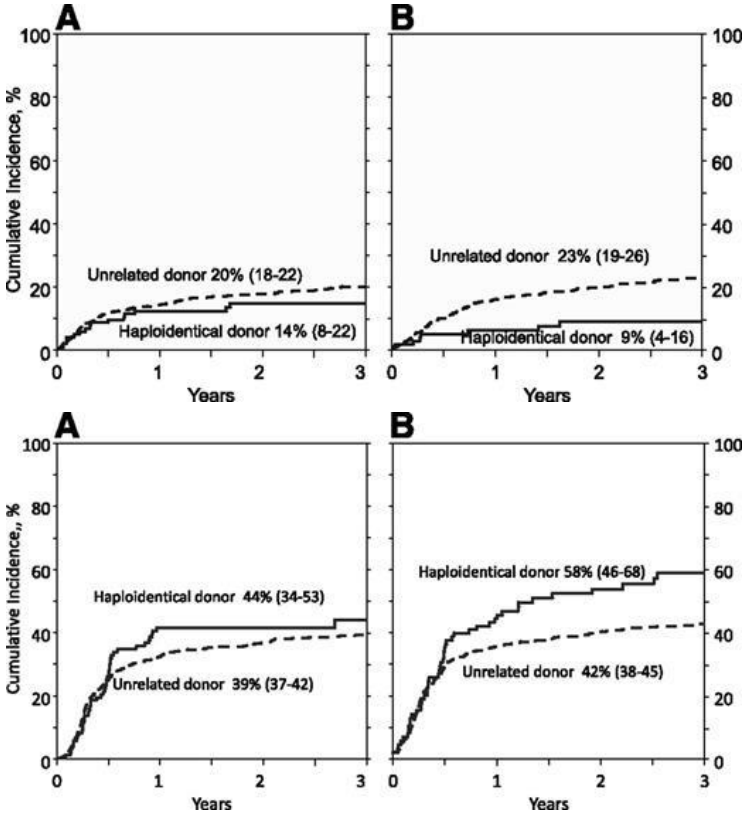
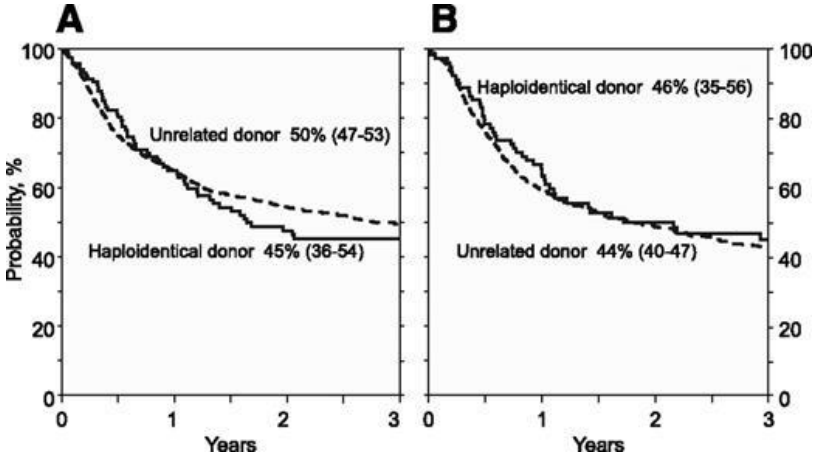
Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor;
Haplo: Haploidentical donor (includes all mismatched related donors); MMUD: Mismatched unrelated donor; CB: Cord blood

Haplo vs VUD Donors in Acute Leukemia

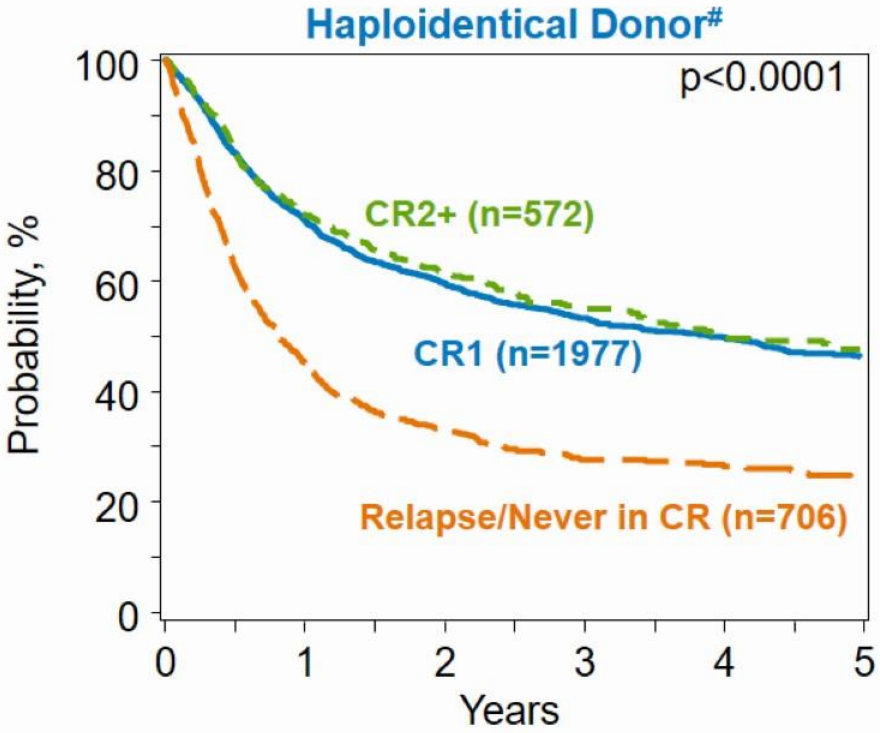


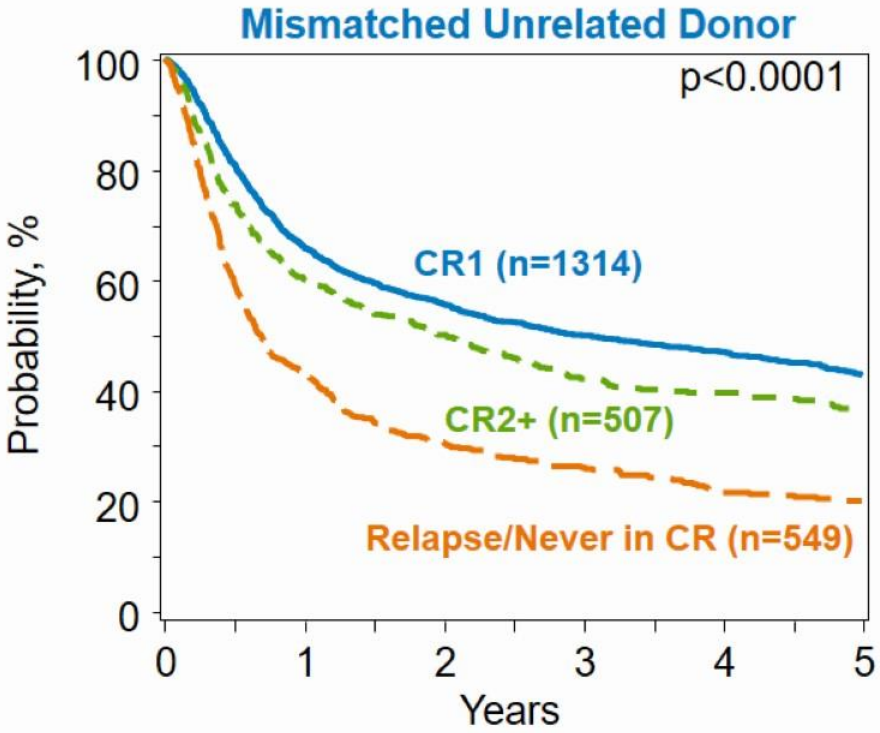
- Ciurea et al compared patients receiving haploidentical transplants with unrelated donor transplants
  - 192 haplos vs 1982 VUDs



Ciurea SO, et al. *Blood*. 2015;126:1033-1040.

Survival after Allogeneic HCTs for Acute Myelogenous Leukemia (AML), Using Mismatched Donors, Age ≥18 Years, in the US, 2009-2019





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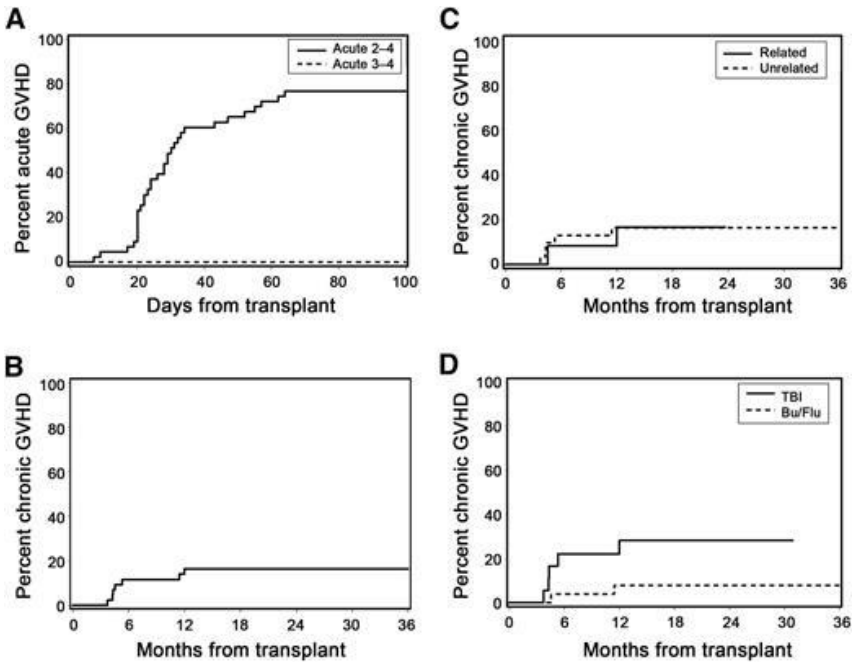
#includes all mismatched related donors; Abbreviation – CR: Complete remission

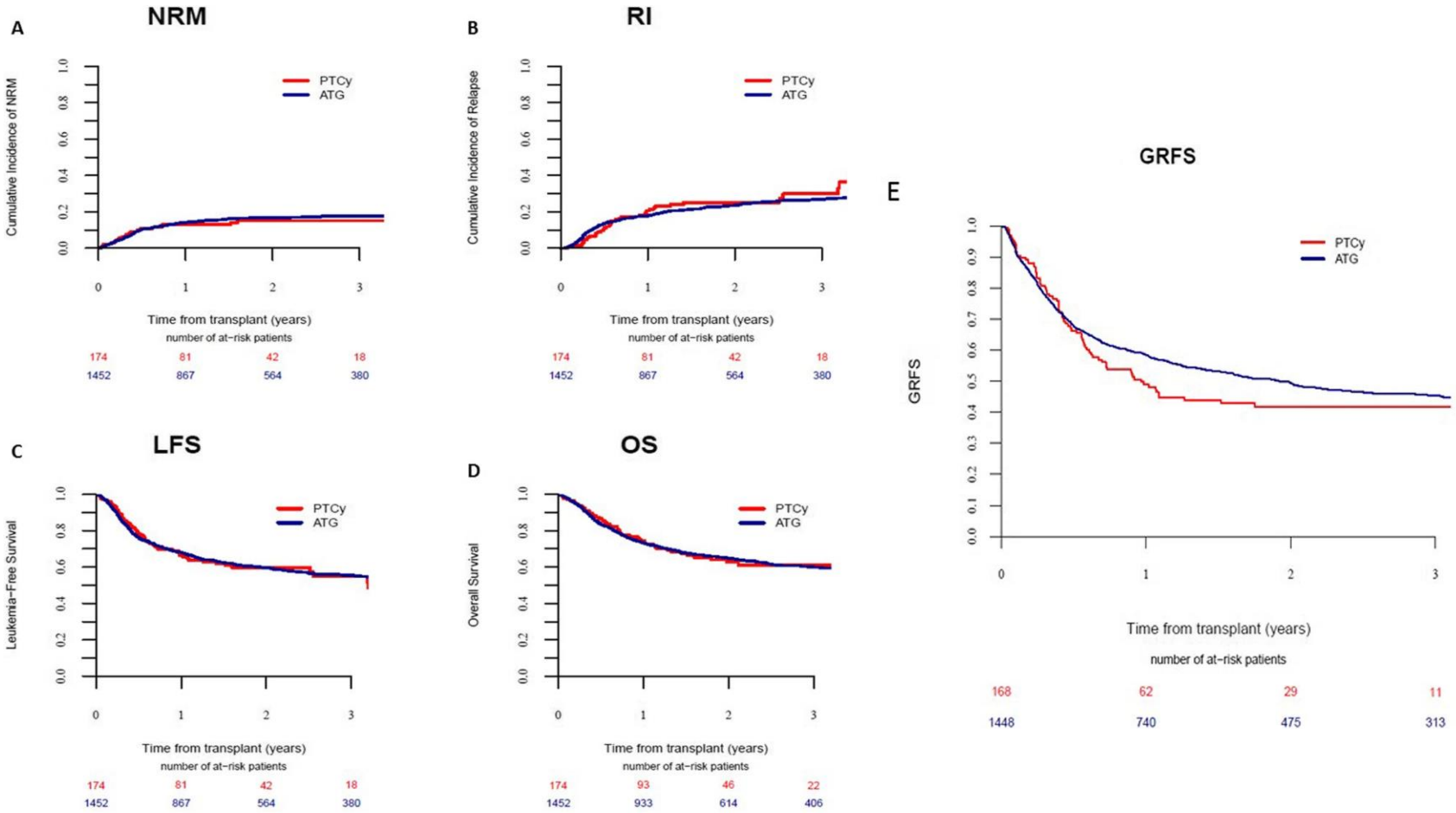
Post-Transplant Cyclophosphamide (PTCy) in Non-Haplo Transplants

Use of PTCy With Matched Grafts

- Mielcarek et al explored the use of PTCy with matched grafts (either sib or 10/10 VUD)
  - Demonstrated deliverability of PTCy with non-haplo transplants
  - Low rates of acute graft-versus-host disease (GVHD) and chronic GVHD
  - Survival outcomes were good, suggesting this is a valid strategy for further evaluation

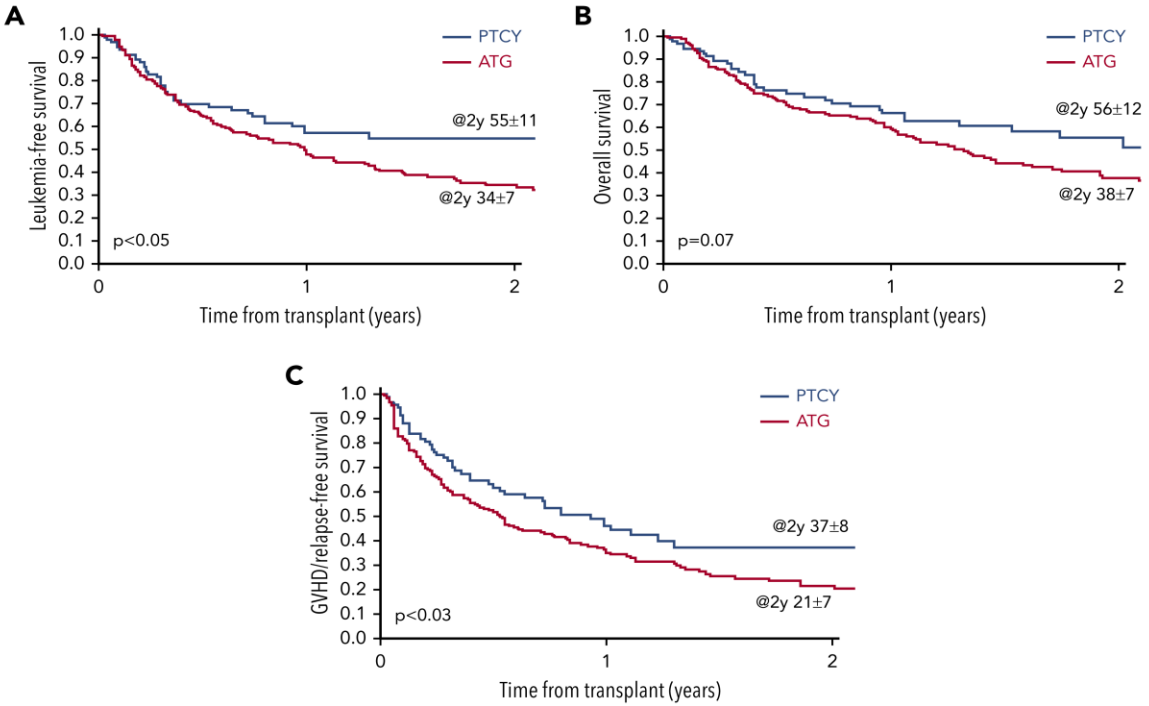


Mielcarek M, et. *Blood*. 2016;127:1502-1508.



Brissot E, et al. *J Hematol Oncol.* 2020;13:87.

If PTCy Allows Overcoming Haplotype Mismatched, What About 9/10 VUDs?

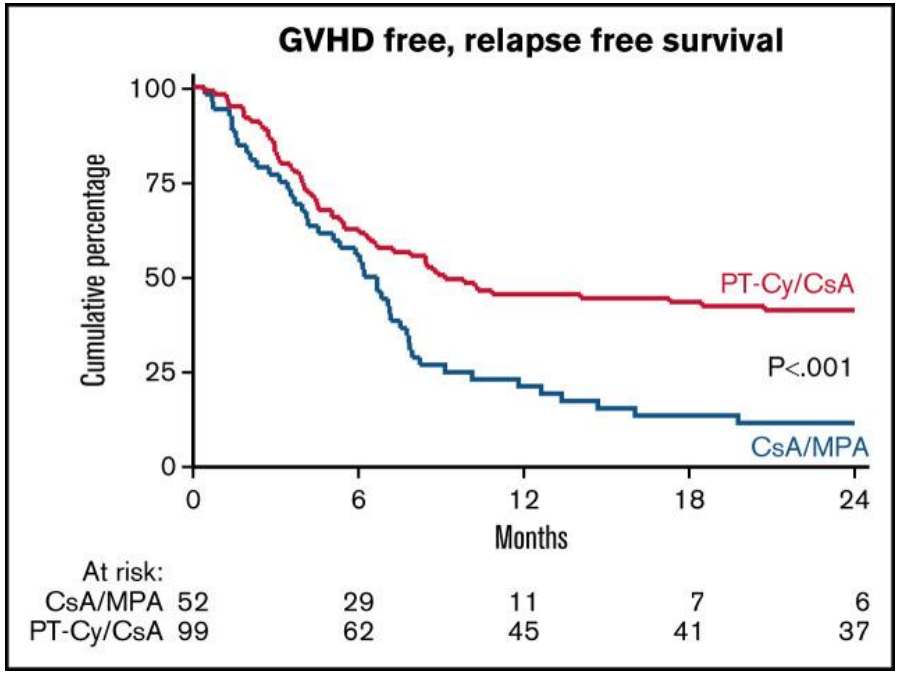


- Use of post-transplant cyclophosphamide is associated to lower rates of severe acute graft-versus host disease in patients undergoing transplant from a 9/10 mismatched unrelated donor for acute myeloid leukemia

- Superior survival outcomes are observed when using post-transplant cyclophosphamide as compared to the standard of care with antithymocyte globulin in patients undergoing transplant from a 9/10 mismatched unrelated donor for acute myeloid leukemia

Battipaglia B, et al. *Blood*. 2021;134:892-899.

HOVON-96 Study: PTCy vs SOC



- HOVON-96 study randomized 151 patients to receive PTCy + CsA vs SOC (MTX + CsA) immunosuppression
  - Lower rates of Gr II–IV aGVHD (30% vs 48%, *P* = .007)
  - Lower rates of extensive cGVHD (16% vs 48%, *P* <.001)
  - Similar EFS, OS across both modalities

Broers AEC, et al. *Blood Adv.* 2022;6:3378-3385.

BMT CTN 1703

Randomized, multicenter, Phase III trial

Eligible subjects receiving RIC allogeneic HCT (n = 428)

Tacrolimus / Methotrexate (n = 214)

Tacrolimus: Initiate Day -3, goal blood level 5-15, begin taper after Day +90 is no active GVHD

Methotrexate: 15 mg/m^2 on Day +1, 10 mg/m^2 on Days +3, +6, +11

Post-transplant cyclophosphamide / Tacrolimus / Mycophenolate mofetil (n=214)

Post-transplant cyclophosphamide: 50 mg/kg on Days +3 and +4

Tacrolimus: Initiate Day +5, goal blood level 5-15, begin taper after Day +90 is no active GVHD

Mycophenolate mofetil: Initiate Day +5 at 15 mg/kg/dose TID, stop Day +35 if no active GVHD

Primary Hypothesis

GRFS at 1 year will be ≥15% greater for PTCy/Tac/MMF compared to Tac/MTX

Eligibility

- ≥18 years of age
- Controlled malignant disease
- Undergoing allogeneic HCT
- MRD, MUD, or MMUD
- PBSC
- RIC or NMA regimen

Primary Endpoint

- GRFS at 1 year

Secondary Endpoints

- Acute GVHD
- Chronic GVHD
- Neutrophil and platelet engraftment
- Donor cell engraftment
- Immune reconstitution
- Infectious events
- Adverse events
- PTLD
- Patient-reported outcomes
- Non-relapse mortality
- Relapse or progression
- Overall survival

Bolaños-Meade J, et al. *N Engl J Med*. 2023;388:2338-2348.

CAST Study: ALLG BM12

- Randomized study
  - 134 adult patients with AML, ALL, or MDS
  - Available sibling donor
  - Receiving either MAC or RIC transplant with defined regimens
- Currently enrolling in 8 Australian and 2 NZ sites
- 73 patients randomized to January 2022
- Plan to complete accrual by 2023

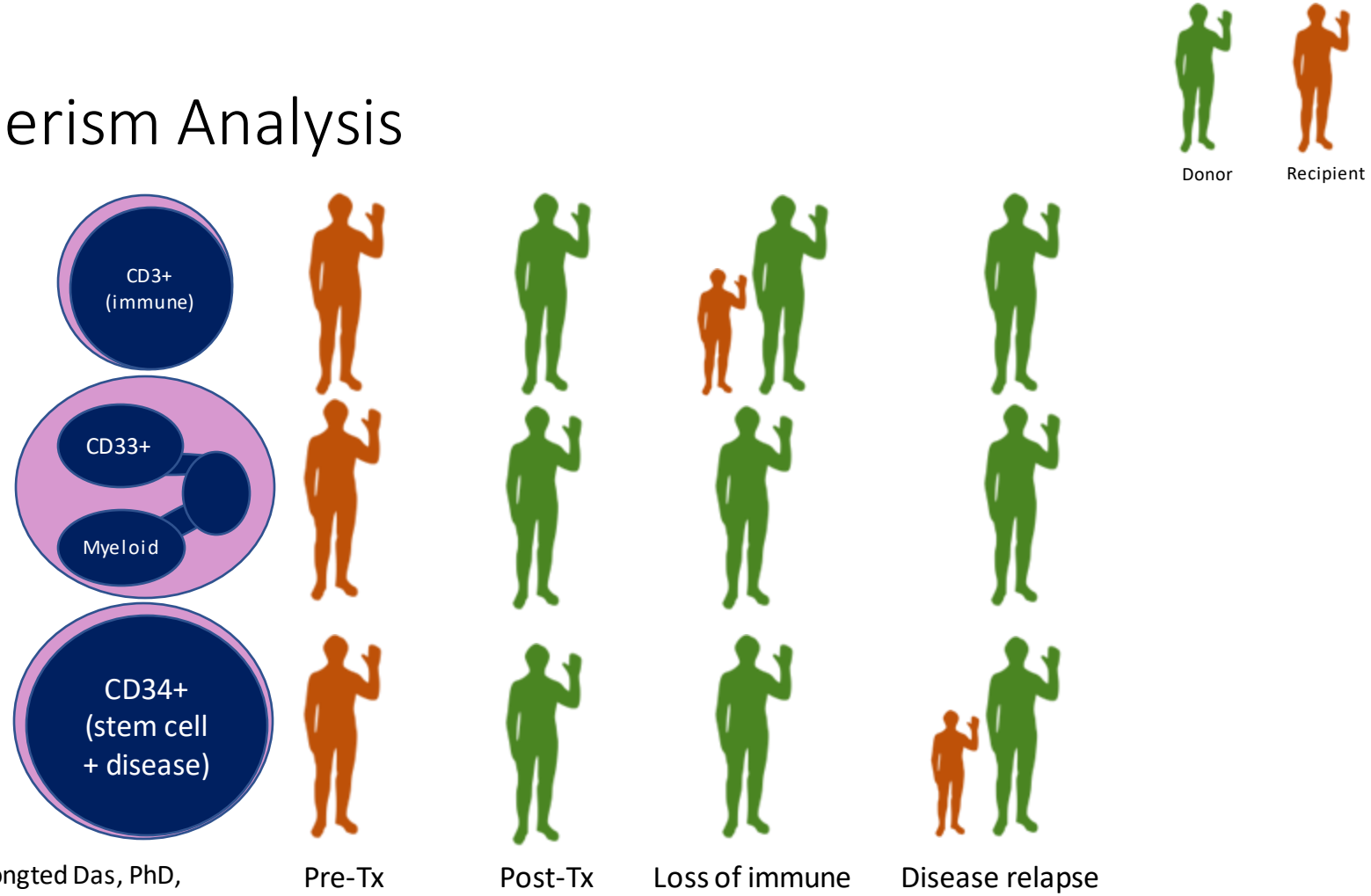
Source: allg.org.au

Conclusion: PTCy

- PTCy reduces rates of severe GVHD when compared with standard immunosuppression in non-haplo transplants
  - Caveat of the possible impact of in vivo T-cell depletion with ATG
  - Outcomes at least equivalent; however, most data here are based on BM as donor source, where GVHD rates are lower
- Current trials overseas and in Australia are exploring the use of PTCy as immunosuppression

CD34+ Chimerism

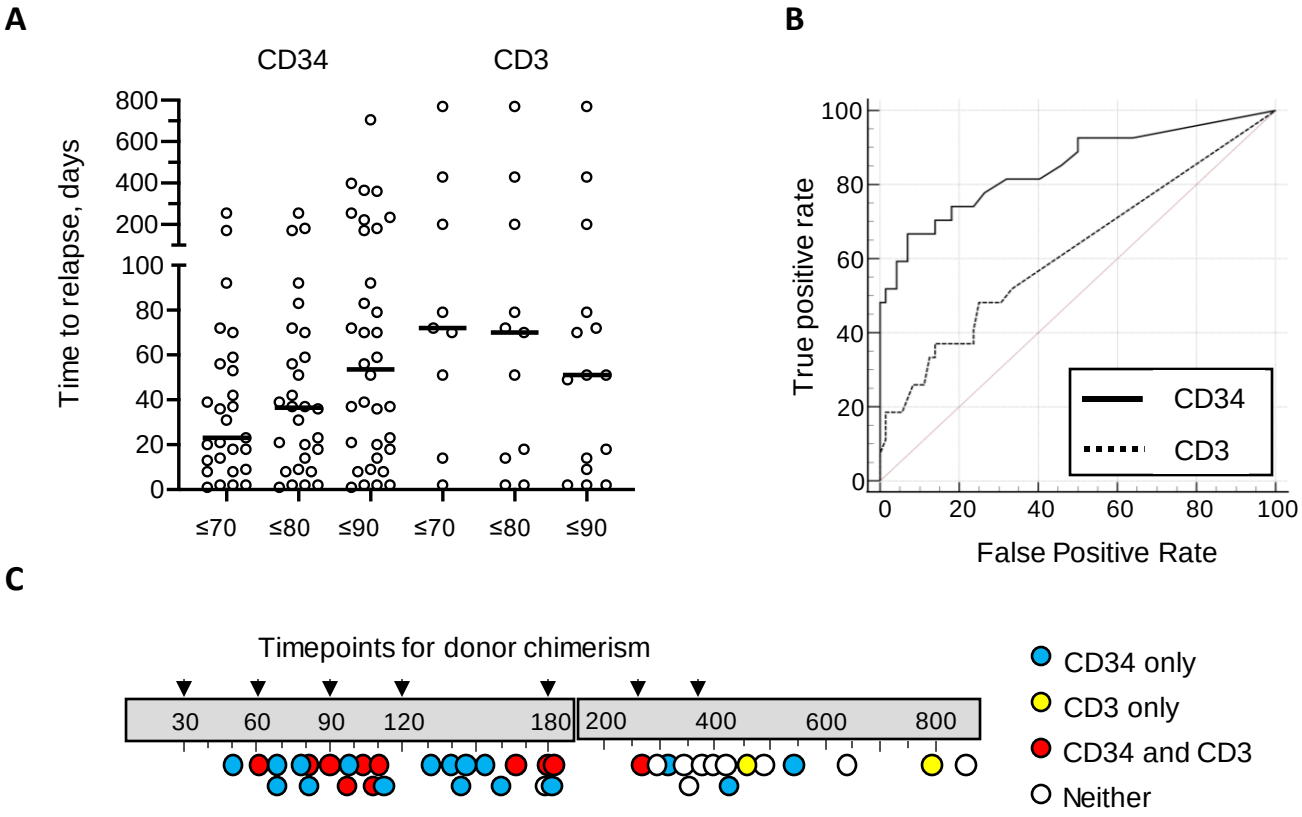
Chimerism Analysis



Chimerism analysis: Tongted Das, PhD, Clinical Haematology, Alfred Health

Total, n	134
Median age, yr (range)	52 (19–70)
Male, n (%)	75 (56)
Indication, n	
AML (Fav, Int, Adv, Unk)	115 (19, 56, 39, 1)
MDS	19
CD34 expression, n (%)	98 (85)
Stage of AML at BMT, n (%)	
CR	98 (85)
Conditioning, n (%)	
MAC	68 (51)
RIC	51 (38)
NMA	15 (11)
Donor, n (%)	
Matched related	56 (42)
Matched unrelated	72 (54)
Cord/mismatch	6 (4)
TCD (%)	76 (57)
ATG/Campath/PTCy, n	40/13/23
Median follow-up, d (range)	508 (41–2973)
Relapse, n	40
Death, n	66
Infection/GVHD, n	34
Disease, n	27
Other, n	5

Unpublished data



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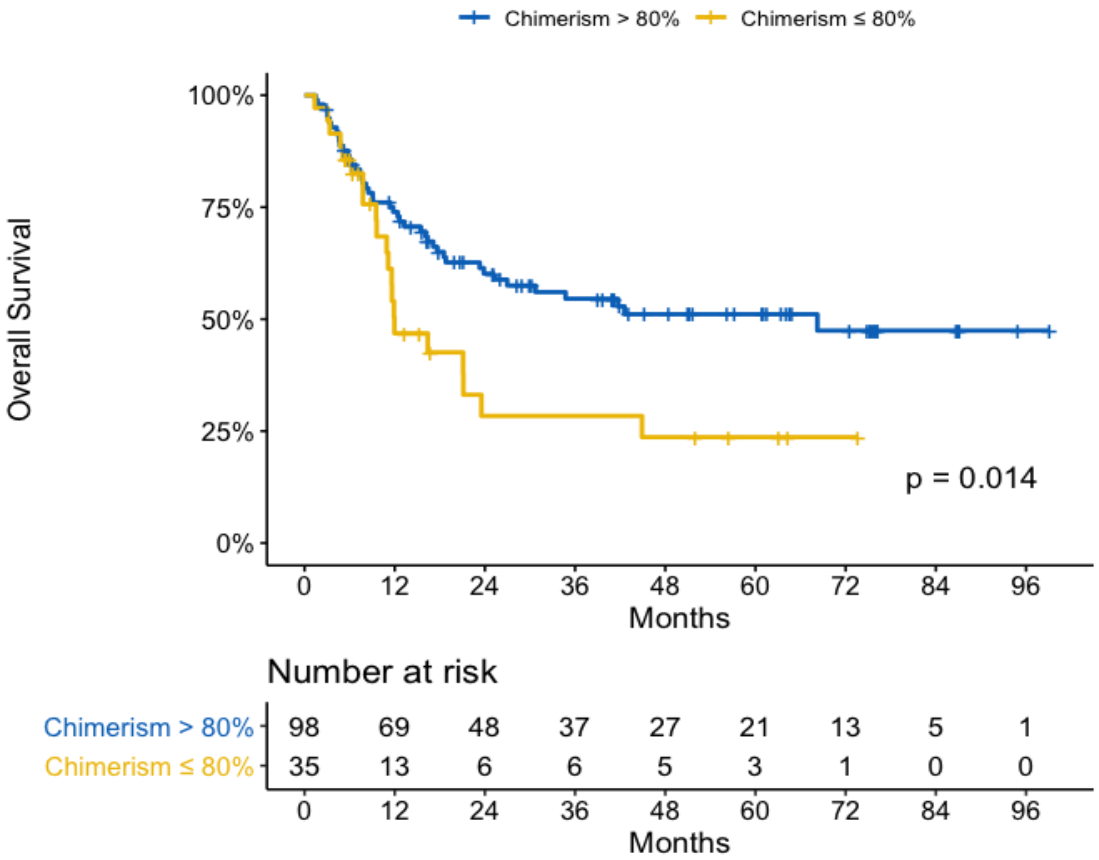

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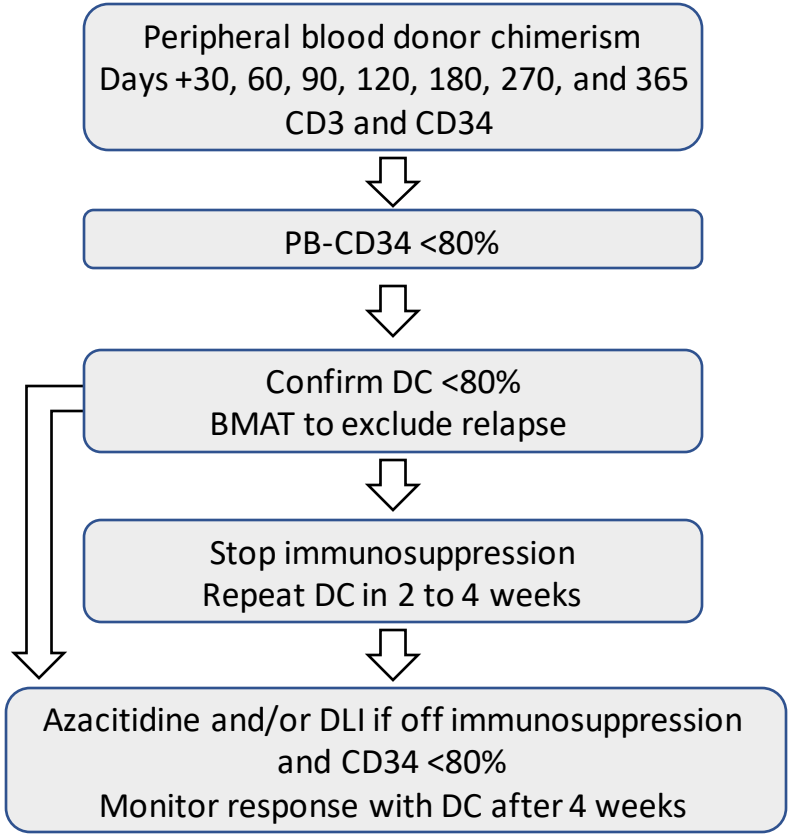
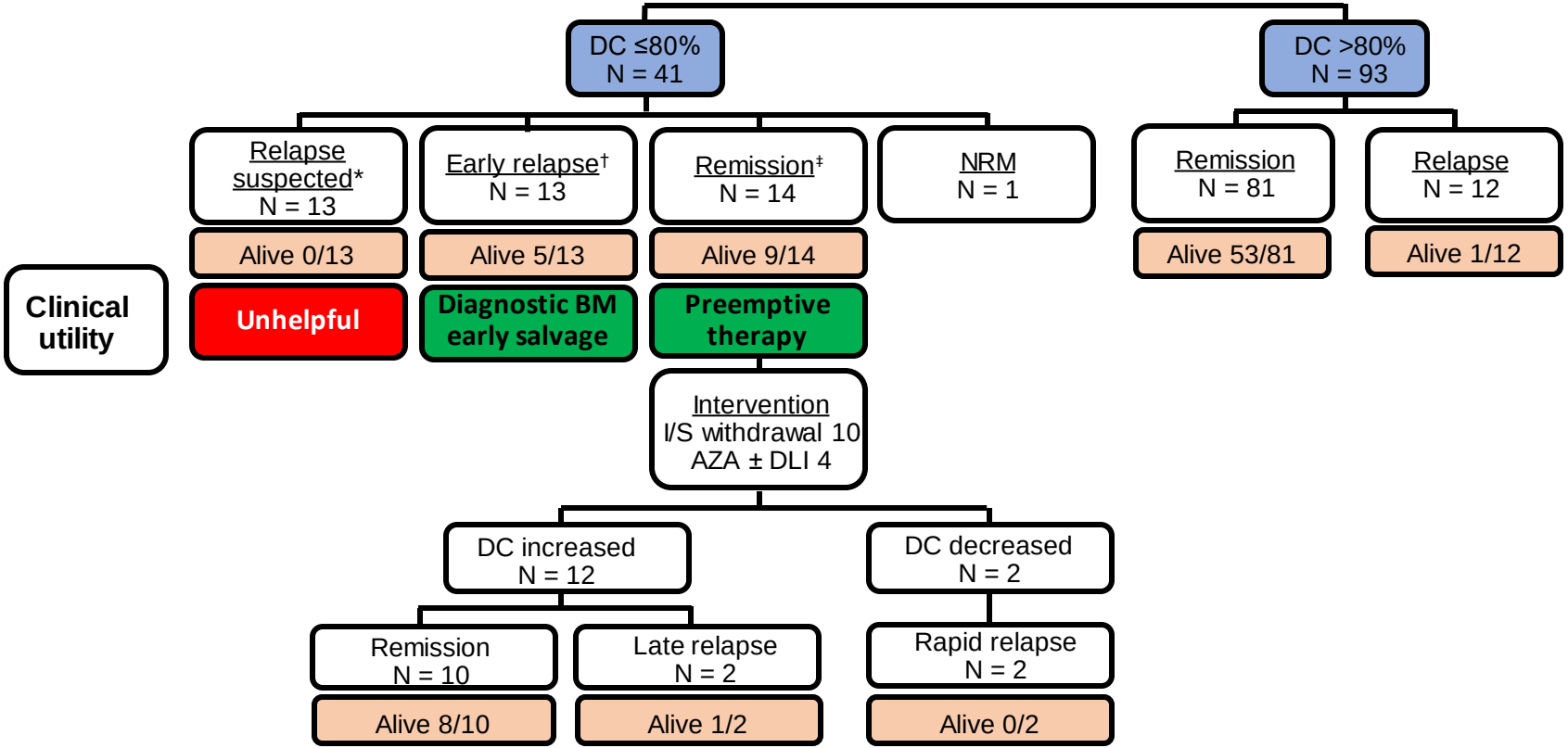

Peripheral blood donor chimerism
Days +30, 60, 90, 120, 180, 270, and 365
CD3 and CD34
PB-CD34 <80%
Confirm DC <80%
BMAT to exclude relapse
Stop immunosuppression
Repeat DC in 2 to 4 weeks
Azacitidine and/or DLI if off immunosuppression
and CD34 <80%
Monitor response with DC after 4 weeks



*Circulating blasts and/or new cytopenias attributable to morphologic relapse;
†Normal peripheral blood counts, but either morphologic relapse or MRD in the bone marrow;
‡Morphologic remission and no MRD where available.

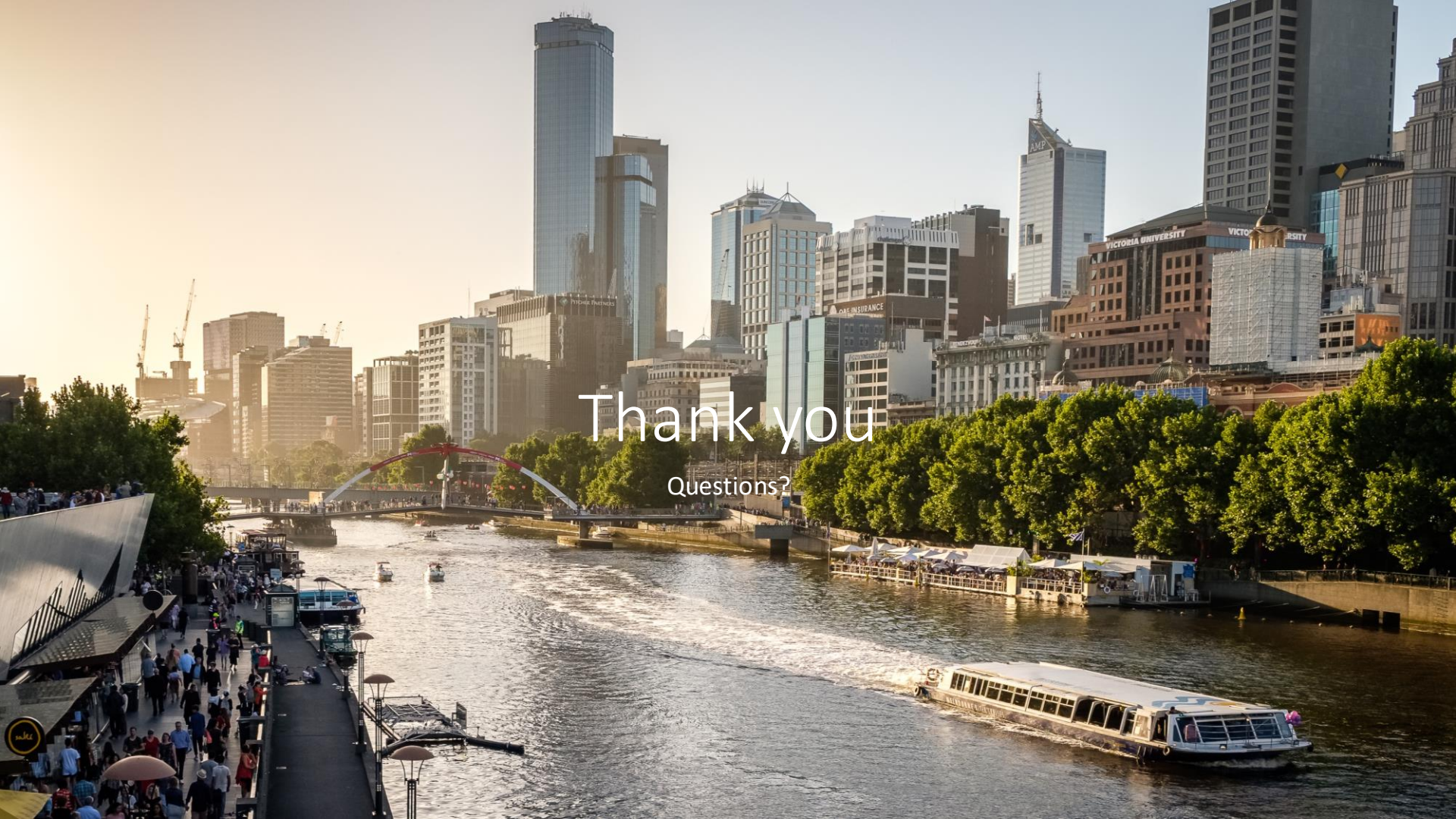
Das et al. *Transplant Cell Ther.* 2023.

Conclusion: CD34+ Chimerism

- CD34+ chimerism provides a reliable and broadly applicable method to detect imminent relapse following allogeneic stem cell transplant
- The 80% cutoff maximizes sensitivity and specificity for detection of disease relapse
- Most relapses are detected by earlier timepoints – calls into question the need for later chimerism monitoring
- Withdrawal of immunosuppression and intervention with azacitidine ± donor lymphocyte infusion may salvage a proportion of patients

Conclusion

- Transplantation numbers continue to increase globally as the access to donors, advancing age of eligibility for transplant, and increased indications for transplant all lead to increasing numbers
- Haploidentical transplantation has expanded the number of patients who are eligible for transplant and is particularly important in our culturally diverse community with smaller family sizes
- PTCy has allowed us to overcome the HLA-mismatch barrier and may be a superior method of immunoprophylaxis in matched transplants
- CD34+ chimerism monitoring allows early detection of imminent relapse, allowing time for interventions to avert relapse



Thank you

Questions?

Global Leukemia Academy

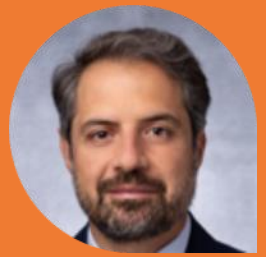
Q&A

APTITUDE HEALTH

Global Leukemia Academy

Panel discussion: How treatment in first line influences further approaches in ALL and AML

Moderator: Elias Jabbour



APTITUDE HEALTH

Interactive Discussion

How treatment in first line influences further approaches in ALL and AML

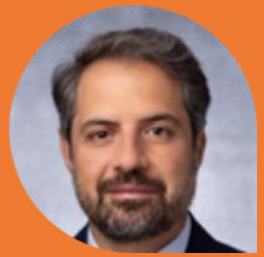
- Will CAR T and bispecifics change the landscape?
- Role of HSCT – is it still confirmed?
- What does the future look like?

We encourage our audience to ask questions using the Q&A box

Global Leukemia Academy

ARS questions

Elias Jabbour



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Question 3 [REPEATED]

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. ALK inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. CAR T approaches are active beyond second line in Ph– ALL

Question 4 [REPEATED]

The prognosis of R/R AML patients depends on:

A. Age
B. Prior therapy (eg, HSCT)
C. Timing of relapse
D. The mutational and cytogenetic profile of the disease
E. All of the above
F. A and D

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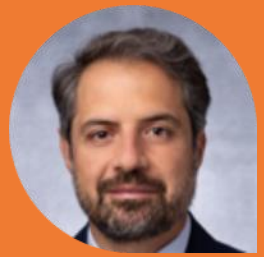
Session close

Elias Jabbour and Naval Daver



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- Thank you to our sponsors, expert presenters, and to you for your participation
- Please complete the **evaluation link** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the globalleukemiaacademy.com website within a few weeks
- If you have a question for any of our experts that was not answered today, you can submit it through the GLA website in our Ask the Experts section

THANK YOU!

Global Leukemia Academy

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