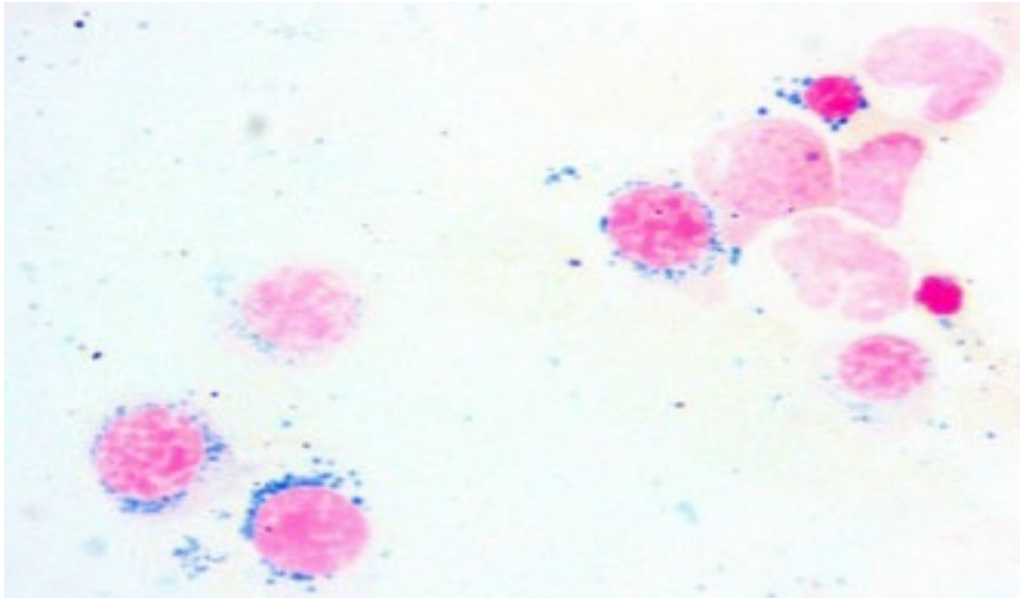
# Removing Bad Humor and Targeting Aberrant Signaling: Treatment Strategies in Myelodysplastic Syndromes and Acute Lymphoblastic Leukemia

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# Disclosures ( Past 3 years) - Richard M. Stone, MD

- **Consulting ( ad hoc, unless otherwise specified)**
  - **AbbVie* ( and steering committee) ; Actinium; Agios*; Amgen; Aptevo (DSMB); Arog*; Astellas; Avencell; BerGen Bio' Boston Pharmaceuticals; BMS/Celgene ; CTI Biopharma, Cellularity; Curis, Daiichi-Sankyo; Elevate Bio; Epizyme; GSK; Hemavant; Janssen; Jazz; Kura; Lava; Ligand; Novartis*; Redona; Rigel; Syndax*; Syntrix (DSMB only); Syros; Takeda ( also DSMB)**
    - *** denotes support to my institution for clinical trials on which I was local PI**
- **Securities, employment, promotional activities, intellectual property, gifts, grants**
  - **None**

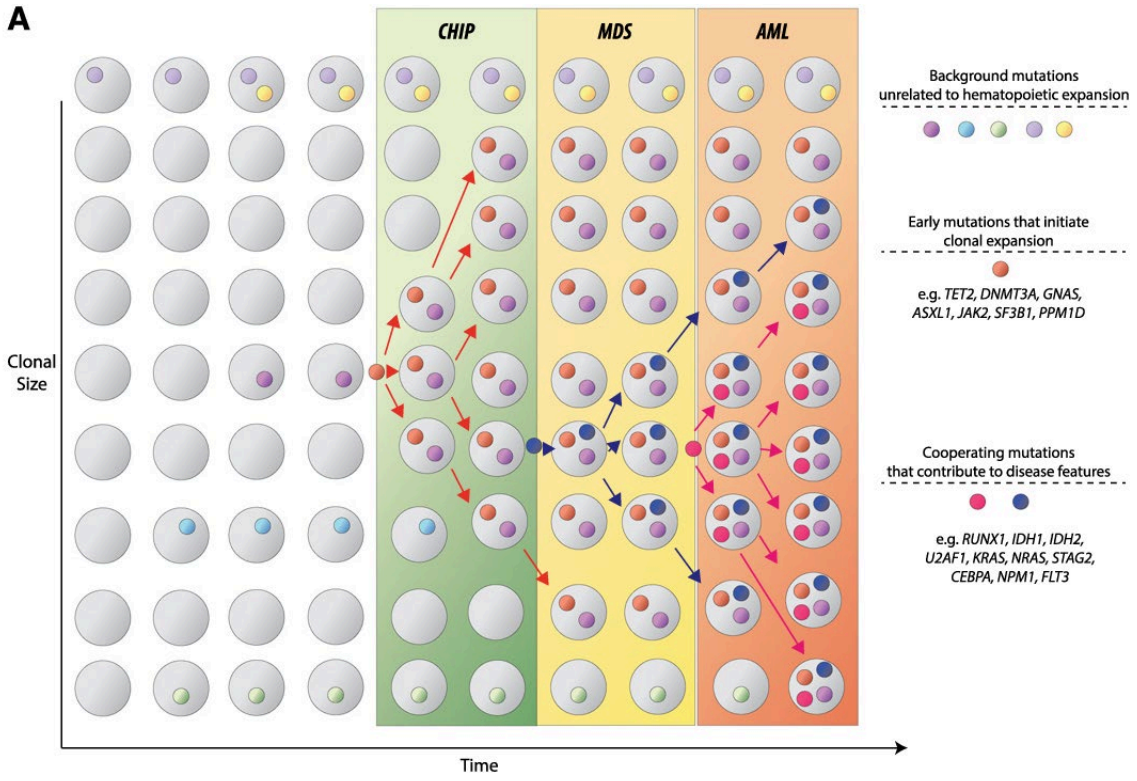
# MDS and ALL: SMART Learning Objectives

– Apply modern prognostic algorithms in MDS

– Analyze the developmental therapeutic landscape in higher risk and lower risk MDS

-Understand the genotype/phenotype/age-based approach to initial rx in ALL.

# Assessing risk of developing MDS: Myeloid precursor conditions (CHIP and CCUS)




Prevalence in the population → Risk for transformation into MDS/AML

| | CH | ICUS | CCUS (low risk) | CCUS (high risk) | MDS |
|---|---|---|---|---|---|
| Clonality | YES | NO | YES | YES | YES |
| Cytopenia | NO | YES | YES | YES | YES |
| Dysplasia | NO | NO | NO | NO | YES |
| High risk features* | NO | NO | NO | YES | YES/NO |
| ↑ Blasts | NO | NO | NO | NO | YES/NO |
| Risk of progression | **~ 0.5-1%/year** | **~ 1%/year** | **~ 10%/year** | **~ 20%/year** | |

* High risk features:
1. DTA mutation (*DNMT3A*, *TET2*, *ASXL-1*) + 1 other myeloid mutation
2. Spliceosome mutation (*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*)



Steensma Blood 2015

# Risk of developing myeloid malignancy for CH patients

**High Risk Mutations**
Absent

**single DNMT3A**
Absent

**Maximum VAF**
< 0.2 (20%)

**Number of Variants**
1

**CHIP or CCUS**
CHIP

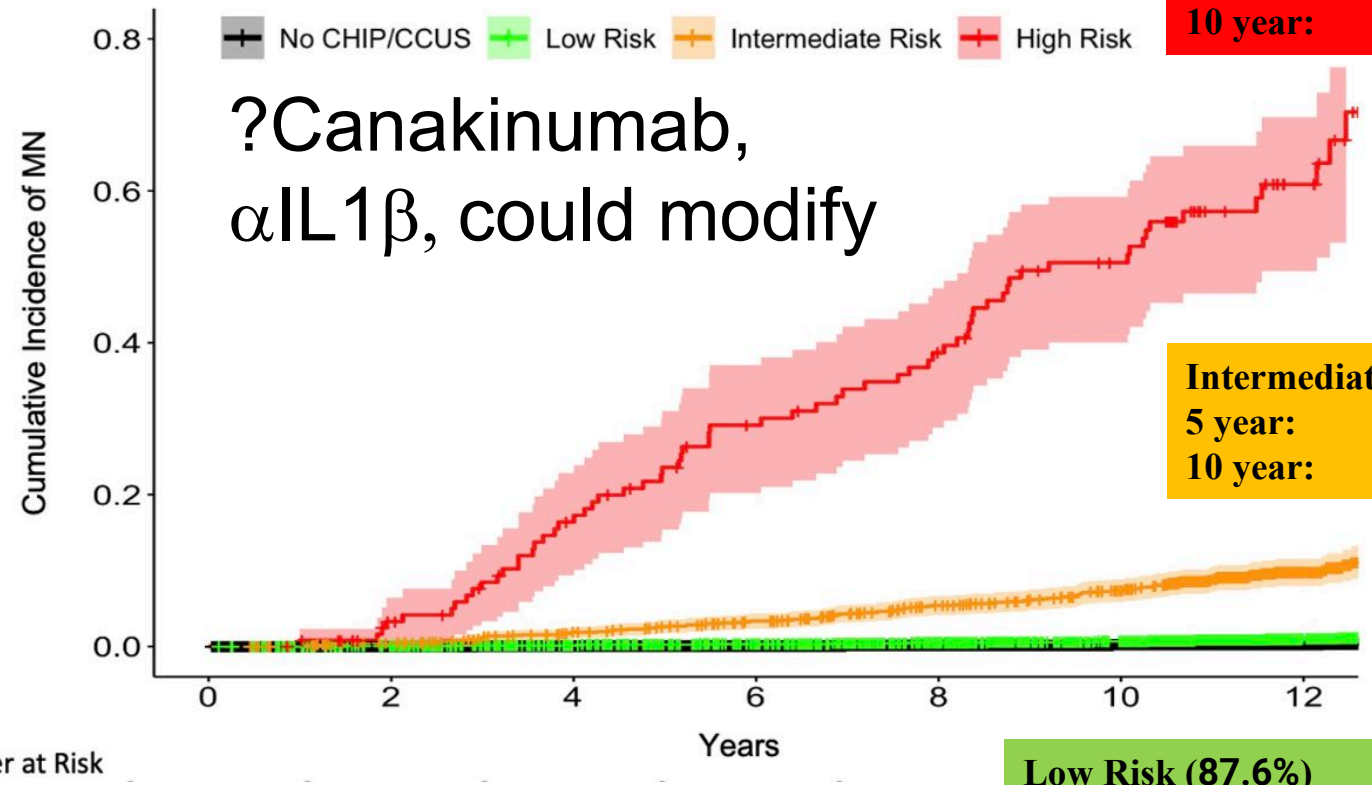
**Mean corpuscular volume**
< 100 fl

**Red cell distribution width**
< 15%

**Age**
< 65 years

***High risk mutations:***
*SF3B1, SRSF2, ZRSR2,*
*JAK2,*
*TP53,*
*RUNX1, FLT3, IDH1, and IDH2*

- UK Biobank: 193,743 healthy volunteers
- 11,337 (5.85%) had pathogenic variants




**High Risk (1.13%)**
**5 year: 24.4 ± 4.12%**
**10 year: 52.2 ± 4.96%**

**Intermediate Risk (11.3%)**
**5 year: 2.76 ± 0.482%**
**10 year: 7.83 ± 0.807%**

**Low Risk (87.6%)**
**5 year: 0.232 ± 0.0484%**
**10 year: 0.669 ± 0.0827%**

Weeks, L e tal, NEJM Evidence 2023

# 2022 ICC

| | Dysplastic lineages | Cytopenias | Cytoses* | BM and PB Blasts | Cytogenetics† | Mutations |
|---|---|---|---|---|---|---|
| MDS with mutated *SF3B1* (MDS-*SF3B1*) | Typically ≥1‡ | ≥1 | 0 | <5% BM <2% PB | Any, except isolated del(5q), −7/del(7q), abn3q26.2, or complex | *SF3B1* (≥ 10% VAF), without multi-hit *TP53*, or *RUNX1* |
| MDS with del(5q) [MDS-del(5q)] | Typically ≥1‡ | ≥1 | Thrombocytosis allowed | <5% BM <2% PB§ | del(5q), with up to 1 additional, except −7/del(7q) | Any, except multi-hit *TP53* |
| MDS, NOS without dysplasia | 0 | ≥1 | 0 | <5% BM <2% PB§ | −7/del(7q) or complex | Any, except multi-hit *TP53* or *SF3B1* (≥ 10% VAF) |
| MDS, NOS with single lineage dysplasia | 1 | ≥ | | | | |
| MDS, NOS with multilineage dysplasia | ≥2 | ≥ | | | | |
| MDS with excess blasts (MDS-EB) | Typically ≥1‡ | ≥ | | | | |
| MDS/AML | Typically ≥1‡ | ≥ | | | | |

**Table 21. Myeloid neoplasms with mutated *TP53***

| Type | Cytopenia | Blasts | Genetics |
|---|---|---|---|
| MDS with mutated *TP53* | Any | 0-9% bone marrow and blood blasts | Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p† |
| MDS/AML with mutated *TP53* | Any | 10-19% bone marrow or blood blasts | Any somatic *TP53* mutation (VAF > 10%) |
| AML with mutated *TP53* | Not required | ≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia | Any somatic *TP53* mutation (VAF > 10%) |

*Defined as 2 distinct *TP53* mutations (each VAF > 10%) OR a single *TP53* mutation with (1) 17p deletion on cytogenetics; (2) VAF of >50%; or (3) Copy-neutral LOH at the 17p *TP53* locus.

†If *TP53* locus LOH information is not available.

# Risk based on new 2022 WHO and ICC classification

## 2022 WHO

**Table 3.** Classification and defining features of myelodysplastic neoplasms (MDS).

| | Blasts | Cytogenetics | Mutations |
|---|---|---|---|
| **MDS with defining genetic abnormalities** | | | |
| MDS with low blasts and isolated 5q deletion (MDS-5q) | <5% BM and <2% PB | 5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion | |
| MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*) | | Absence of 5q deletion, monosomy 7, or complex karyotype | *SF3B1* |
| MDS with biallelic *TP53* inactivation (MDS-bi*TP53*) | <20% BM and PB | Usually complex | Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH |
| **MDS, morphologically defined** | | | |
| MDS with low blasts (MDS-LB) | <5% BM and <2% PB | | |
| MDS, hypoplastic[b] (MDS-h) | | | |
| MDS with increased blasts (MDS-IB) | | | |
| MDS-IB1 | 5–9% BM or 2–4% PB | | |
| MDS-IB2 | 10-19% BM or 5–19% PB or Auer rods | | |
| MDS with fibrosis (MDS-f) | 5–19% BM; 2–19% PB | | |

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
*BM* bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

To acknowledge the biologic continuum between MDS and AML, the name of the previous category of MDS-EB2 in adults with 10% or more blasts is changed to MDS/AML, defined as a cytopenic myeloid neoplasm and 10-19% blasts in the blood or BM. Patients with MDS/AML should be eligible for both MDS and AML trials.

# MDS, New thoughts: Prognosis

– Increasingly sophisticated

1998: IPSS: BM blasts, # of cytopenias, KT ( 4 groups)

-ease, even # of groups, non-dynamic

2005: WPSS: WHO subgroups KT, RBC tx

-4 subgroups

2012: IPSS-R: BM basts, KT, depth of indiv cytopenias

-5 subgroups

2022: MIPSS: marrow blasts, plt, hgb, IPSS-R KT, # of mutations, yes/no on 17 mutations ( special emphasis: SF3B1 single, TP53 multihit)

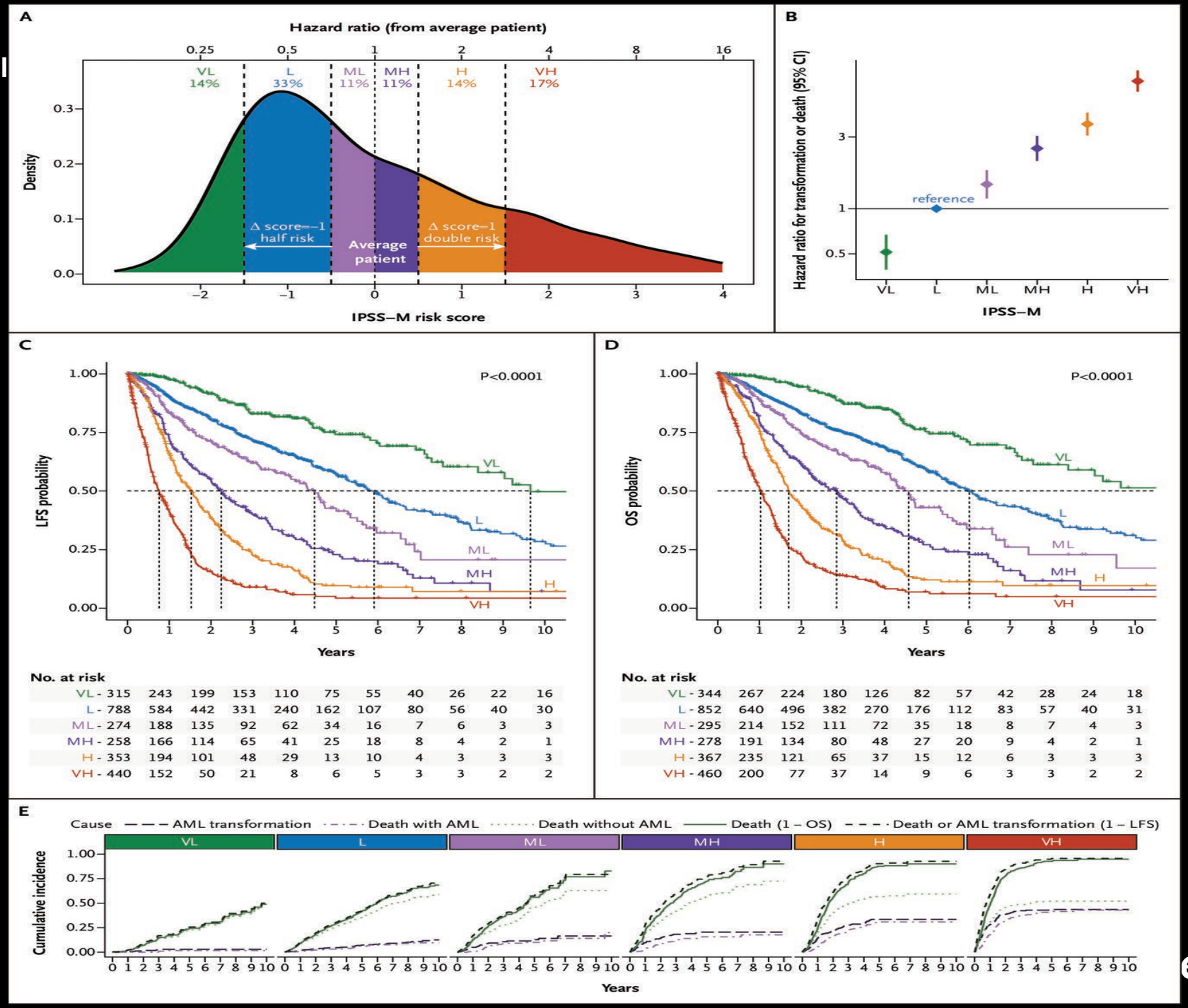
-6 subgroups

-works in s-MDS and t-MDS

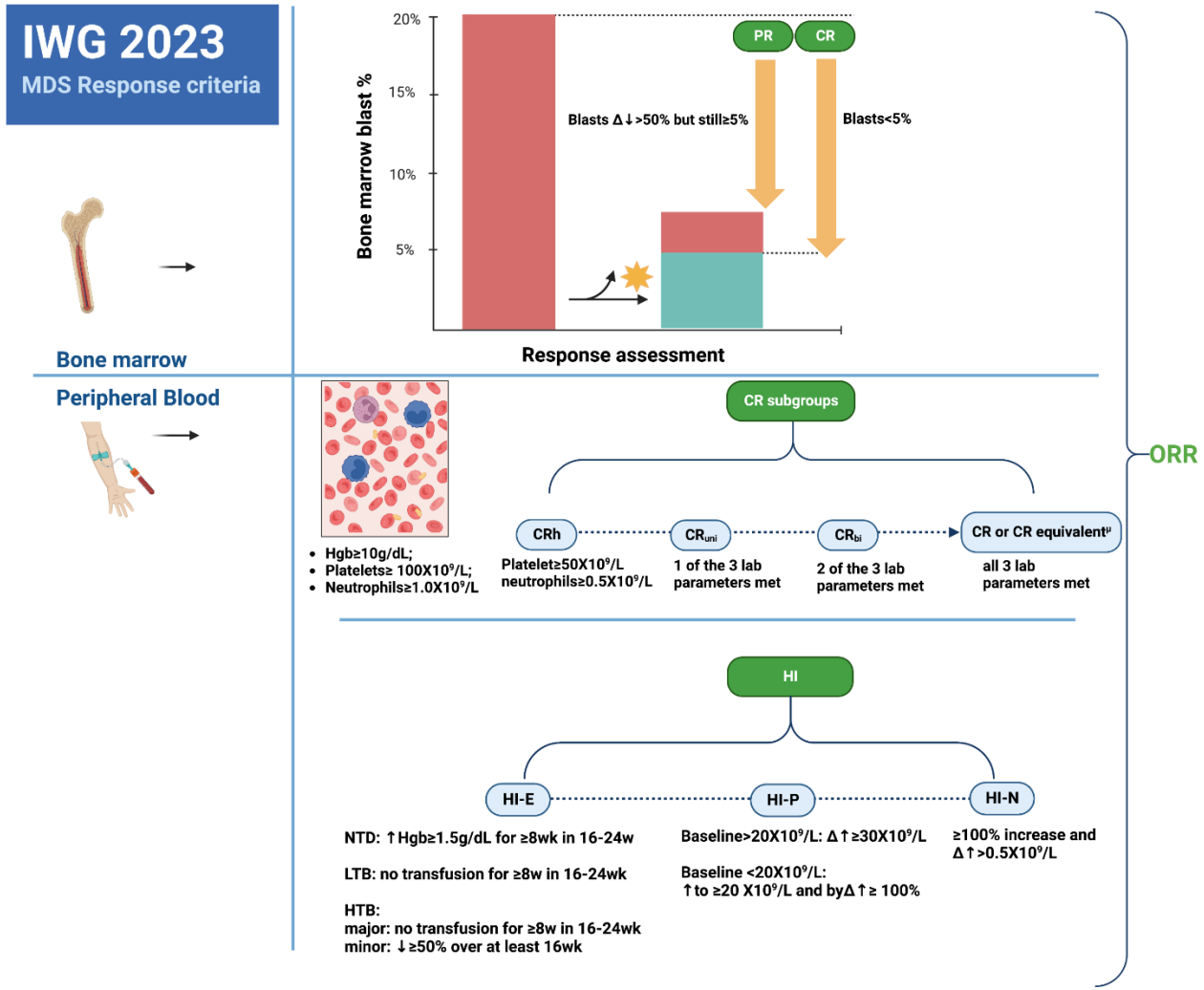
-outperforms IPSS-R

-https://mds-risk-model.com/

Bernard, E et al, *NEJM Evidence* 2022



# New Response Definitions: Key changes in IWG 2023 criteria




- **Formal SRMA followed by a modified Delphi consensus process of a large group of international experts**
- **Updated definition of CR (lower Hb threshold to 10g/dL; required BM blasts < 5%)**
- **Introduction of "near-CR" provisional endpoints (CRL and CRh)**
- **mCR and SD eliminated as formal response categories**
- **Molecular responses recommended as provisional endpoints**
- **Harmonization of time-to-event endpoints**
- **Operational recommendations to enhance inter- and intra observer reproducibility**



Zeidan A. et al. Blood 2023; Stempel J. et al. Cancer Journal 2023; Bewersdorf et al, ASH 2023

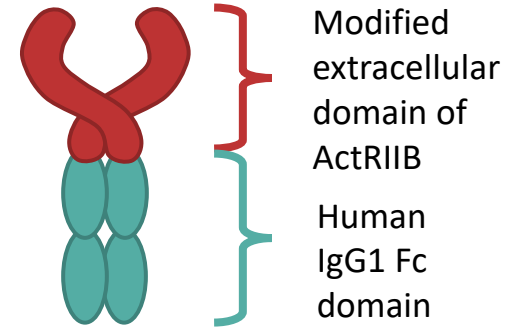
# MDS: New Approaches for Lower Risk

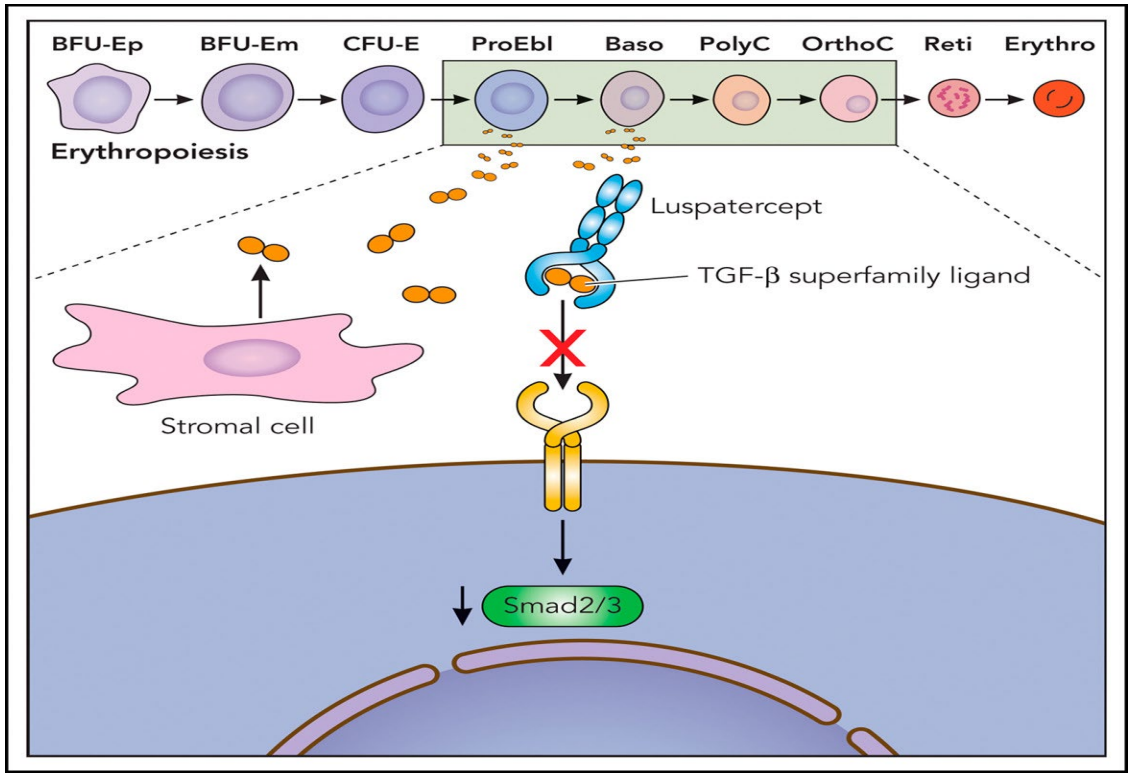
- **Reset Oxygen sensing: roxadustat**
  - Prevents HIF1a degradation, inhibits hepcidine
  - Based on work done by Wm Kaelin DFCI, Semenza, JHU and Ratcliffe, Crick
  - Some responses in MDS: Henry et al, ASH 2019 but oral rox v placebo phase III did not meet primary EP of Trans indep ( 48 v 33%) ( Mittelman, M et al, ASH 2023)

- **Short course hypomethylating agents for lower risk pts**
  - 3d decitabine higher ORR (70)% than 3d azacytidine ( 33%) (Sasaki et al., NEJM Evidence 2022)
  - DEC-C may have a role here ( subgroup analysis of ASCERTAIN equivalency trial ( Garcia-Manero, et al, Blood 2020, Garcia-Manero, et al ASH 2022)
- **Upfront luspatercept** (see COMMANDS trial)
- **Upfront imetelstat** (see IMERGE trial)

# **MEDALIST** Luspatercept Trial

- Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase II study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion-reduction or RBC-TI in patients with MDS-RS (52%) vs. other subtypes (30%)[2]

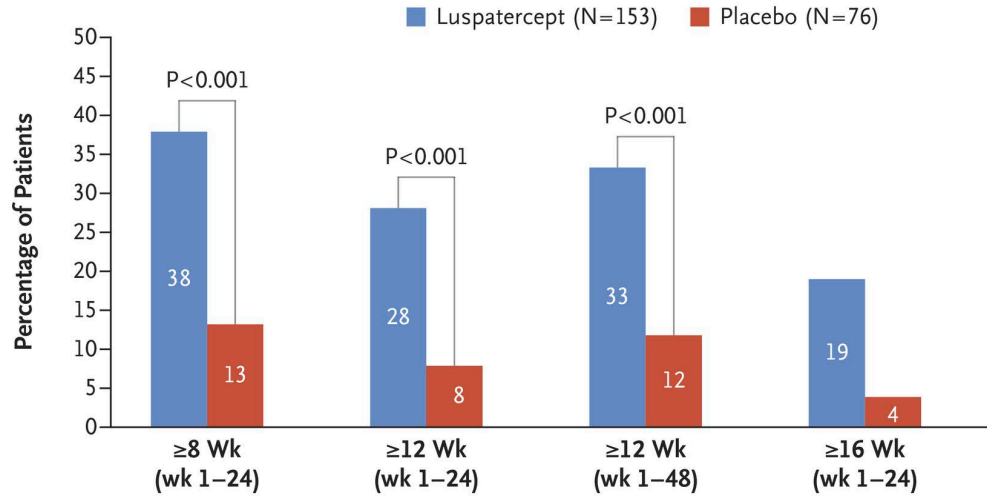



1. Suragani RN, et al. *Nat Med*. 2014;20:408.;
2. Platzbecker U, et. A. Lancet Oncol 2017; 18:1338.

ActB, activin B; ActRIIB, human activin receptor type IIB; BMP, bone morphogenetic protein; GDF, growth differentiation factor; IgG1 Fc, immunoglobulin G1 fragment crystallizable; LR, lower-risk; MDS, myelodysplastic syndromes; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-β, transforming growth factor-beta.

# MEDALIST trial: In Epo failures or high EPO level ( luspat v placebo) in MDS- RS ( lower risk)

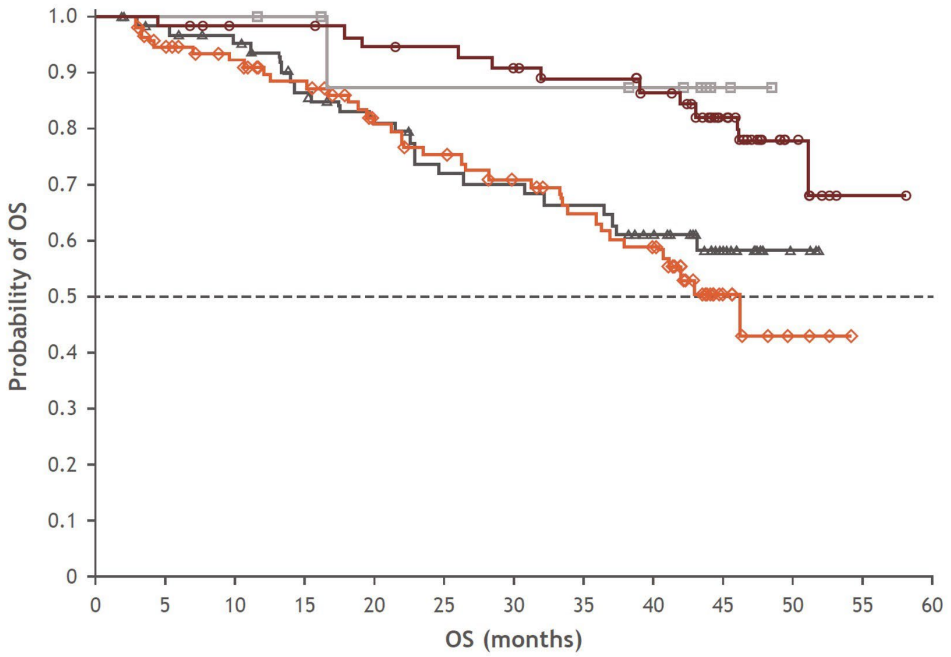



**Prim EP met, 8 wk trans indep**

| No. of Patients with Response (% [95% CI]) | ≥8 Wk (wk 1–24) | ≥12 Wk (wk 1–24) | ≥12 Wk (wk 1–48) | ≥16 Wk (wk 1–24) |
|---|---|---|---|---|
| Luspatercept | 58 (38 [30–46]) | 43 (28 [21–36]) | 51 (33 [26–41]) | 29 (19 [13–26]) |
| Placebo | 10 (13 [6–23]) | 6 (8 [3–16]) | 9 (12 [6–21]) | 3 (4 [1–11]) |

- **Shows that OS in the 2 groups are the same**
  - **But some subgroups: IPSS-R very low; high BL PLT count**
- **Luspat responders lived longer than luspat non-responders**
- **OVERALL; Reassuring that luspatercept had no negative Lt effects**

**Figure 1A. Kaplan–Meier estimates of OS by response and treatment arms**




| No. of patients at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Luspatercept responders | 58 | 57 | 54 | 54 | 51 | 50 | 47 | 44 | 39 | 23 | 9 | 1 | 0 |
| Luspatercept non-responders | 95 | 87 | 78 | 71 | 59 | 54 | 48 | 42 | 36 | 9 | 3 | 0 | 0 |
| Placebo responders | 10 | 10 | 10 | 9 | 7 | 7 | 7 | 7 | 6 | 2 | 0 | 0 | 0 |
| Placebo non-responders | 66 | 62 | 58 | 50 | 45 | 39 | 38 | 36 | 29 | 15 | 3 | 0 | 0 |

Luspatercept responders (events 11/58), median NA months (95% CI 51.1–NA)
Luspatercept non-responders (events 36/95), median 46.1 months (95% CI 36.3–NA)
Placebo responders (events 1/10), median NA months (95% CI 16.6–NA)
Placebo non-responders (events 23/66), median NA months (95% CI 37.0–NA)
Luspatercept responders vs placebo responders: HR 1.58 (95% CI 0.20–12.27), $P = 0.7595$
Luspatercept non-responders vs placebo non-responders: HR 1.25 (95% CI 0.74–2.11), $P = 0.4288$
Luspatercept responders vs luspatercept non-responders: HR 0.319 (95% CI 0.16–0.63), $P = 0.0003$

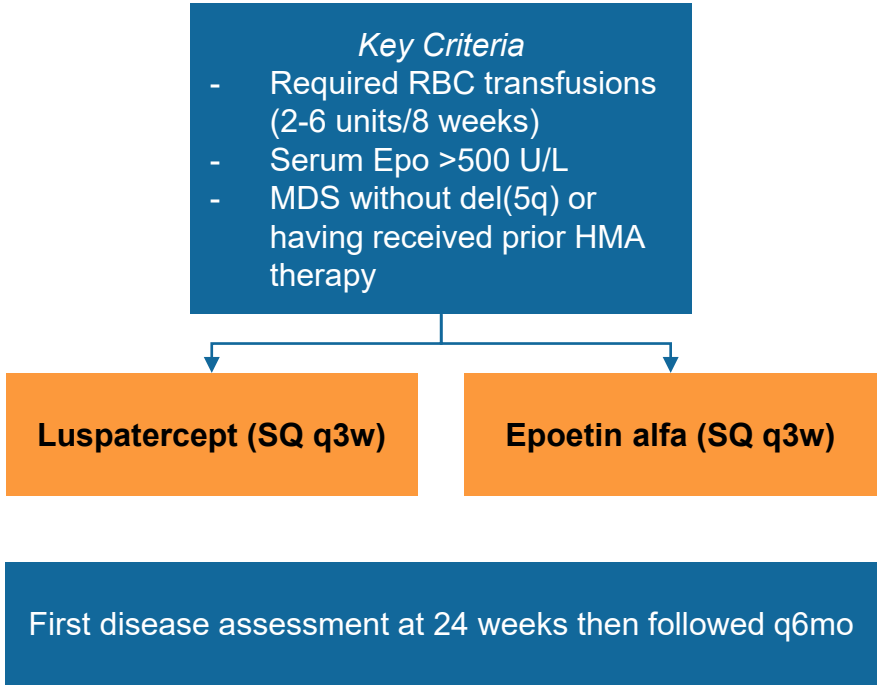


* Demographics not reported

THE LANCET

# Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial

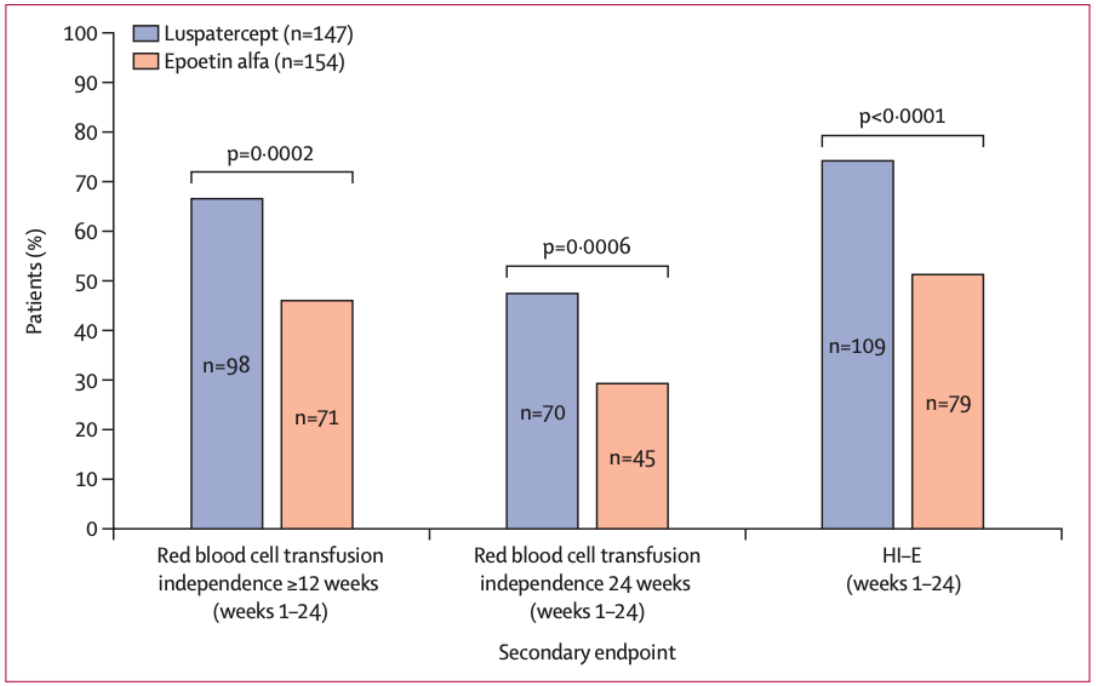
- Open-label, randomized phase III trial of patients with very-low, low, intermediate risk MDS (per IPSS-R) who were ESA-naive
- Patients assigned to receive luspatercept or epoetin alfa (stratified by transfusion burden, Epo level, and sideroblast status)
- Primary endpoint was RBC transfusion independence for ≥ 12 weeks with mean Hgb increase of ≥1.5g/dL during first 24 weeks

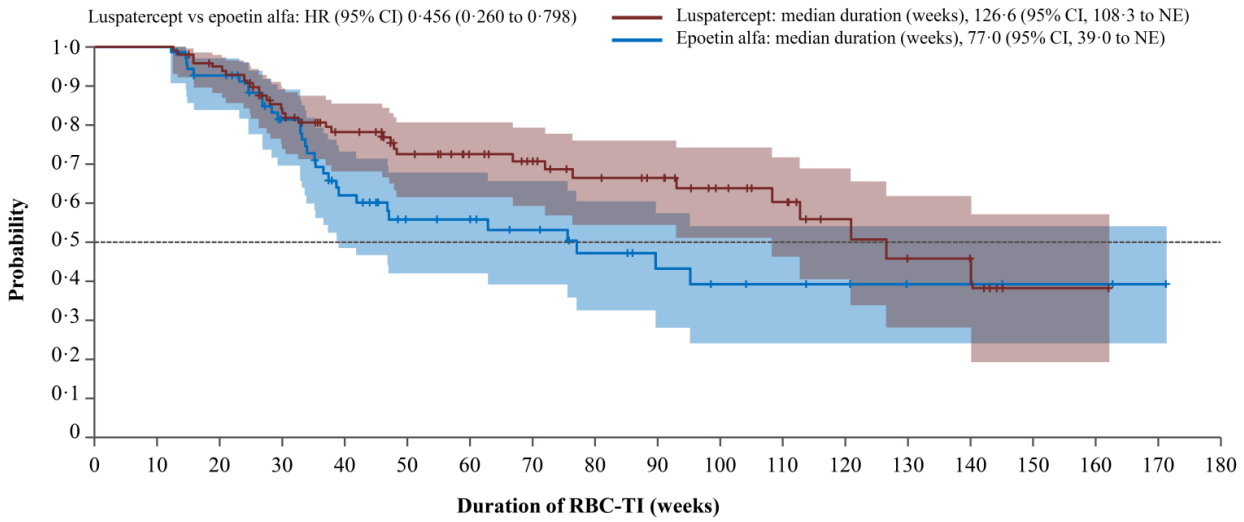





*Platzbecker et al, Lancet (2023)*

# Luspatercept demonstrated superior RBC transfusion independence and hematological improvement




benefit greater in those with serum EPO>200, SF3B1 mutations
- no diff in gr 3/4 tox in the arms

*Platzbecker et al, Lancet (2023)*

# IMerge Phase 3 Trial Design

**Phase 3**
Double-blind, randomized
**118 clinical sites in 17 countries**

**Patient population (ITT; N = 178)**

- IPSS low-risk or intermediate-1–risk MDS
- R/R[a] to ESA or EPO >500 mU/mL (ESA ineligible)
- Transfusion-dependent: ≥4 U RBCs/8 wk over 16 wk before study
- Non-del(5q)
- No prior treatment with lenalidomide or HMAs

**R 2:1**

**Imetelstat**
7.5 mg/kg IV every 4 wk
(n = 118)

**Stratification**
- Transfusion burden (4-6 U vs >6 U)
- IPSS risk category (low vs intermediate-1)

Supportive care, including RBC and platelet transfusions, myeloid growth factors (eg, G-CSF), and iron chelation therapy administered as needed on study per investigator discretion

**Placebo**
(n = 60)

**Safety population (treated; N = 177)**
**Imetelstat** (n = 118)
**Placebo** (n = 59)

**Primary end point**
- 8-wk RBC-TI[b]

**Key secondary end points**
- 24-wk RBC-TI[b]
- Duration of TI
- HI-E
- Safety

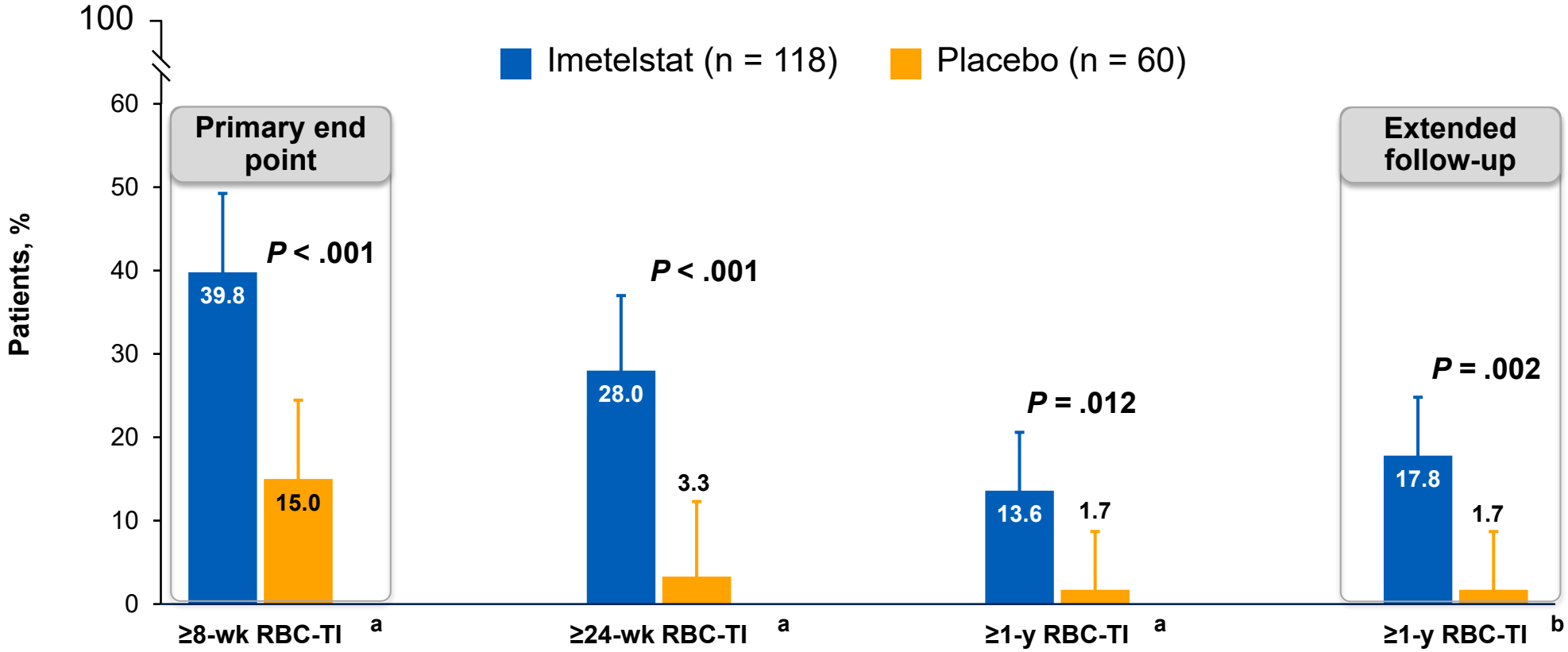
**Key exploratory end points**
- VAF changes
- Cytogenetic response
- PRO: fatigue measured by FACIT-Fatigue

[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U, darbepoetin alfa 150 µg, or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U/8 wk or transfusion dependence or reduction in Hb by ≥1.5 g/dL after HI-E from ≥8 weeks of ESA treatment. [b]Percentage of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); percentage of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI).
EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HI-E, hematologic improvement–erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; PRO, patient-reported outcome; R, randomization; RBC, red blood cell; R/R, relapsed/refractory; TI, transfusion independence, VAF, variant allele frequency.



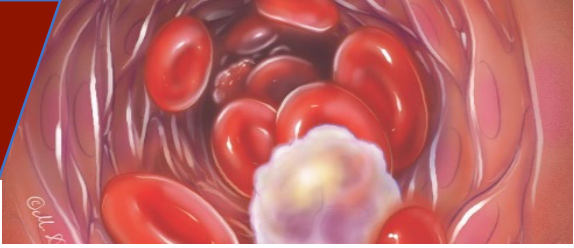
Platzbecker U, et al. *Lancet.* 2023.

# Overall Population: Higher Rates of Longer-Term Duration of RBC-TI With Imetelstat vs Placebo[1,2]

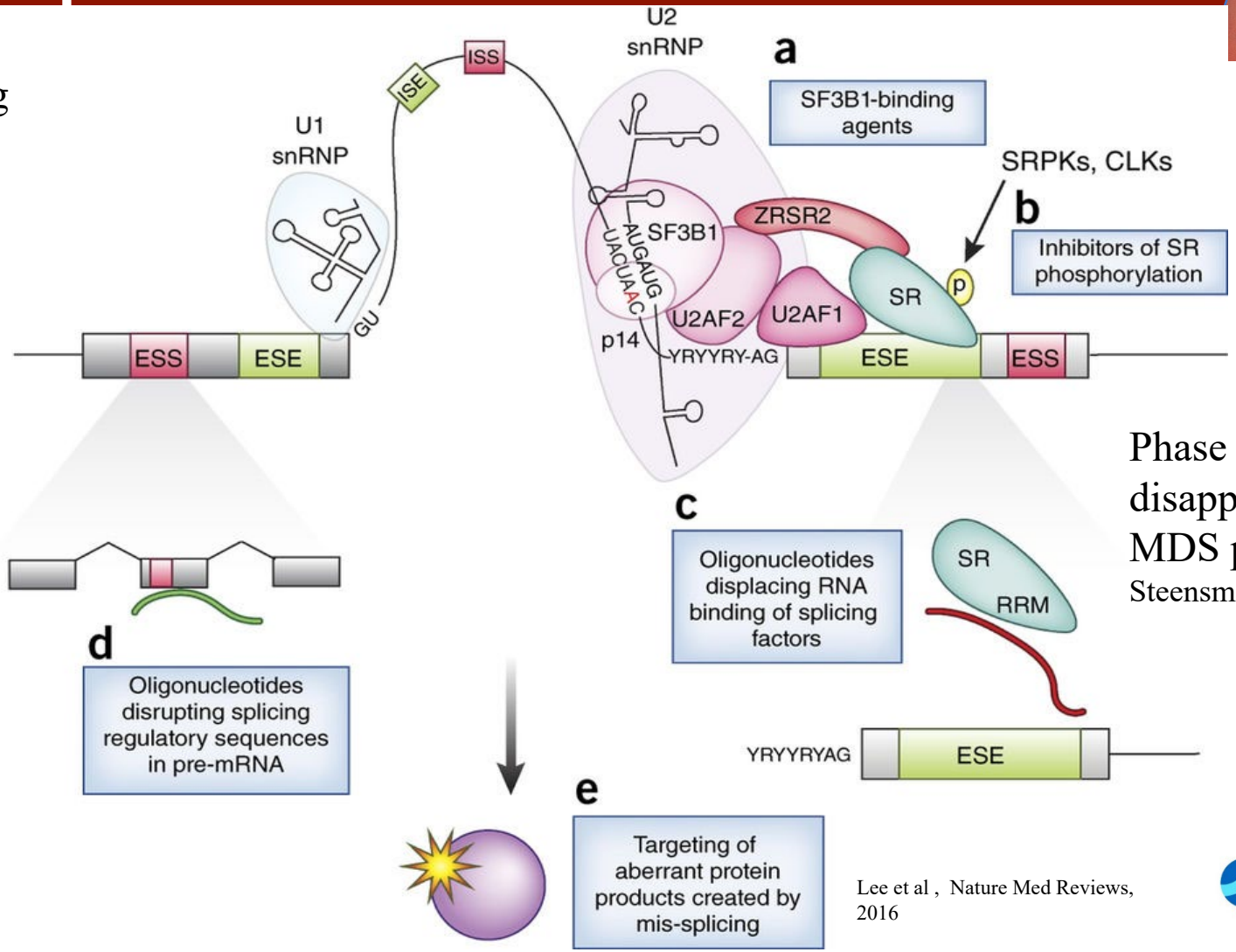



[a]Data cutoff date: October 13, 2022. [b]Data cutoff date: January 13, 2023.
The *P* value was determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC U/8 wk during a 16-week period before randomization) and baseline IPSS (low-risk vs intermediate-1–risk) applied to randomization.
IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.
1. Zeidan A, et al. ASCO 2023. Abstr 7004. 2. Platzbecker U, et al. *Lancet.* Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.

# Targeting MDS with splicing Complex mutations*



The splicing complex can be disrupted leading to synthetic lethality




Lee et al , Nature Med Reviews, 2016

Phase I trial of H3B-8800 was disappointing (though 5/15 MDS pt w SF2B1 muts exp TI)
Steensma, D et al. Leukemia 2021

Protein methyl arginase inhib

ATR inhib

*SF3B1, U2AF1, SRSF2, ZRSR2

Dana-Farber Cancer Institute

# Enasidenib in Higher-Risk *IDH2*-Mutated MDS: Response Rates

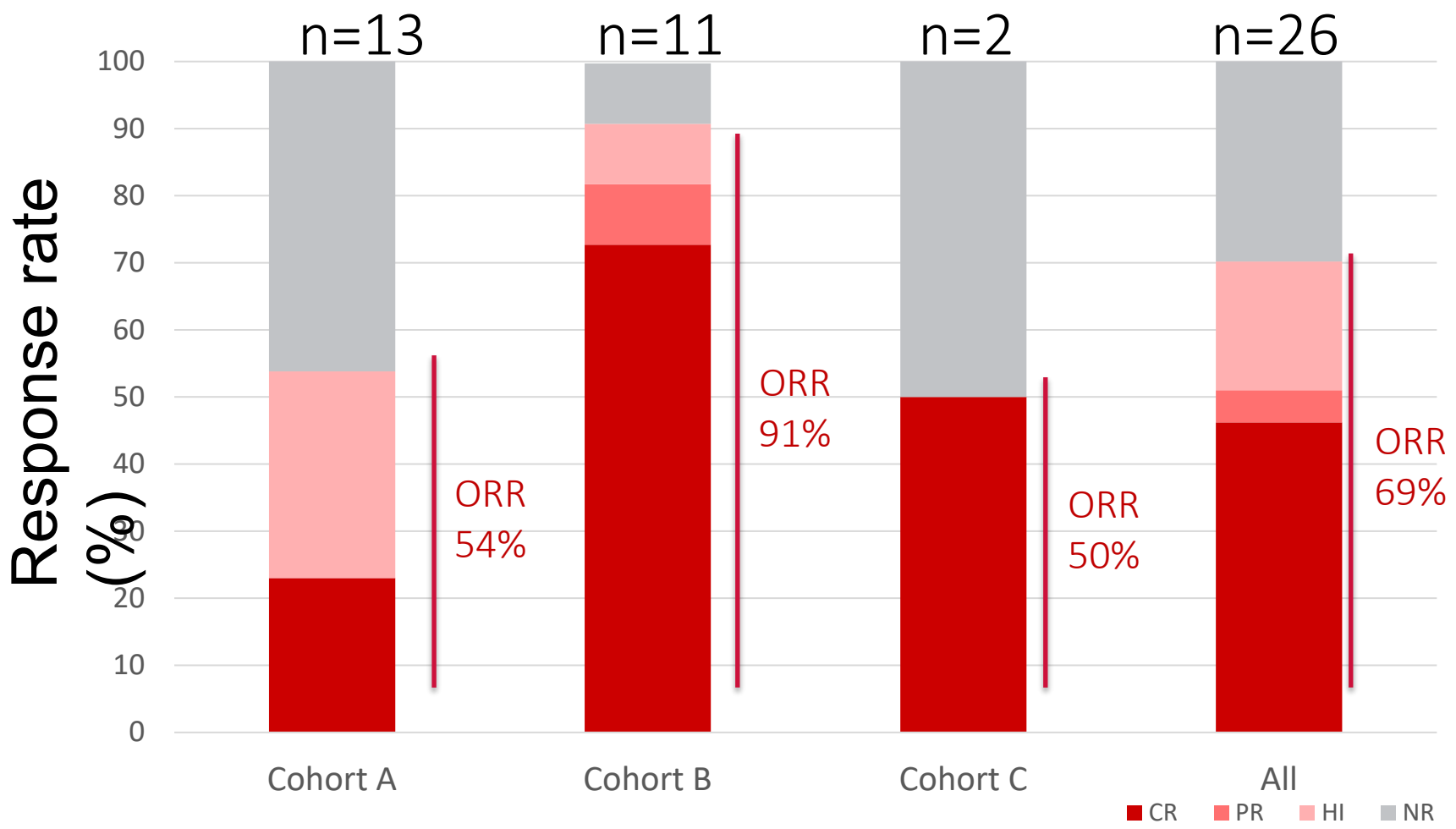
| | Total (N = 31) | Arm A (Untreated) Aza + ENA (N = 13) | Arm B (HMA-Failure) ENA (N = 18) |
|---|---|---|---|
| **ORR**, n (%) | **21 (68)** | **11 (85)** | **10 (56)** |
| Complete remission | 8 (26) | 3 (23) | 5 (28) |
| Partial remission | 1 (3) | 0 (0) | 1 (6) |
| Marrow complete remission | 9 (29) | 7 (54) | 2 (11) |
| HI only | 3 (10) | 1 (8) | 2 (11) |
| **No response**, n (%) | **10 (32)** | **2 (15)** | **8 (44)** |
| SD | 9 (29) | 2 (15) | 7 (39) |
| PD | 1 (3) | 0 (0) | 1 (6) |

Richard-Carpentier G, et al. ASH 2019. Abstract 678.

12 pts w R/R MDS rx w ivosidenib 500 mg/d: 5 (42%) CR

DiNardo C, *NEJM* 2019

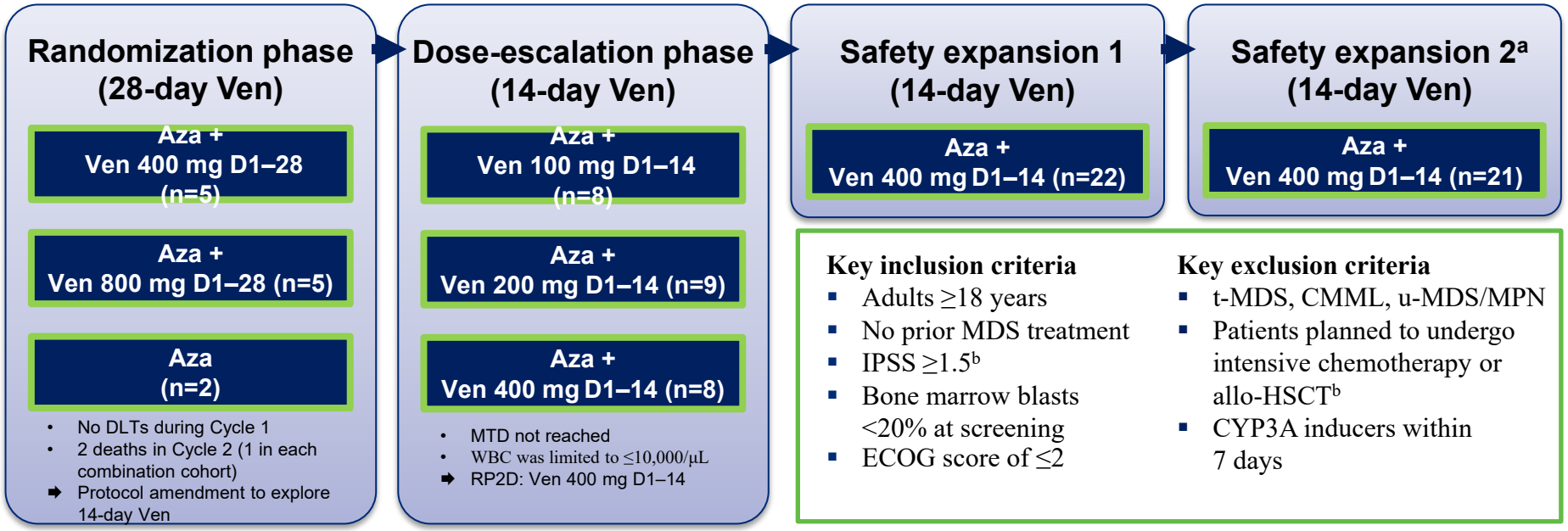
# Overall response rate, *IDH1* mut MDS ( Sebert ASH, 2021)




- 46% of CR (including 73% in cohort B)
- 94.4% of the responders achieved response at 3 cycles
- Only one patient received azacitidine in association with Ivo after three cycles of Ivo in cohort B, without additional response
- A. HMA failure, B. HR, naïve, C, EPO failure lower risk

# Phase Ib Study: Venetoclax + Azacitidine in Higher-Risk MDS

Treatment cohorts (28-day cycles); Aza 75 mg/m$^2$ D1–7




[a]Safety expansion 3 cohort is currently recruiting patients; [b]Study protocol has been amended to allow patients with higher-risk IPSS-Revised (intermediate, high, and very high) results and patients planning to undergo allo-HSCT

allo-HSCT, allogeneic hematopoietic stem cell transplantation; Aza, azacitidine; CMML, chronic myelomonocytic leukemia; D, Day; DLT, dose-limiting toxicity; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended phase 2 dose; Ven, venetoclax, WBC, white blood cell

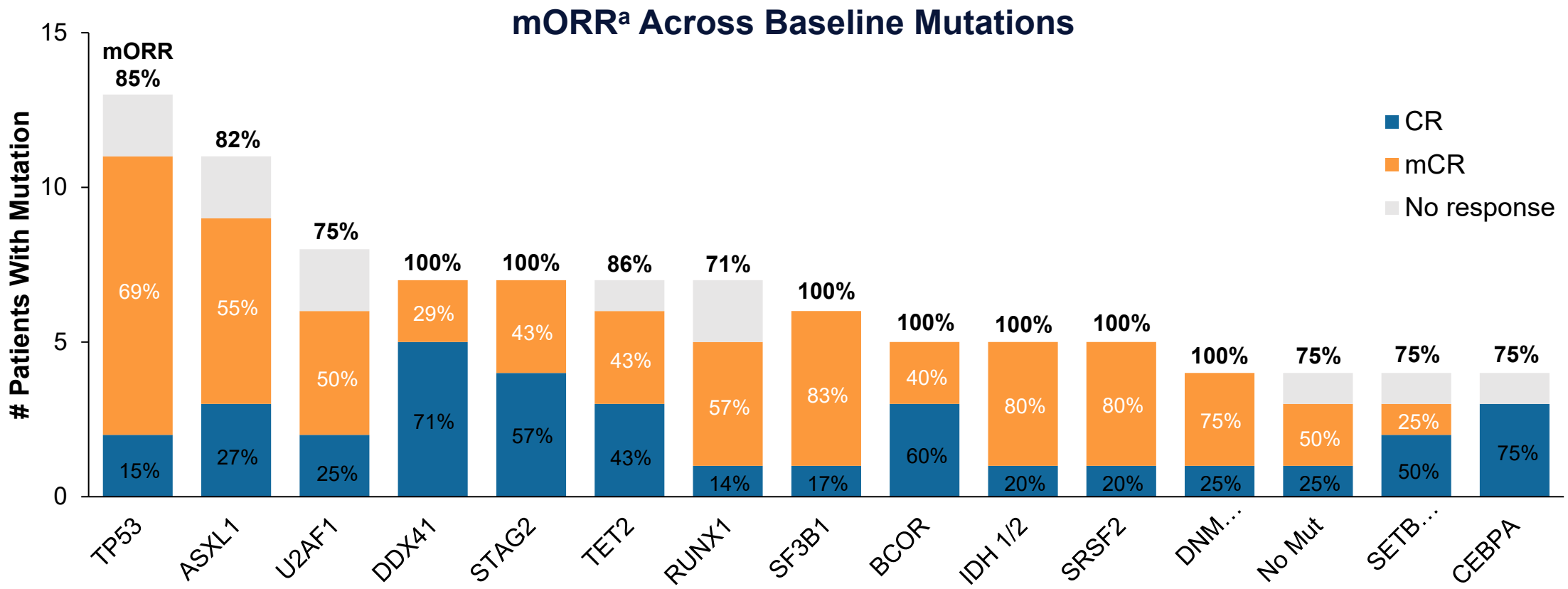
NCT02942290



Garcia et al ASH, 2020 , ASH 2021, ASH 2023

# Aza/Ven Phase 1b: Broad activity across mutational spectrum that is durable among responders

Garcia
ASH 2021.

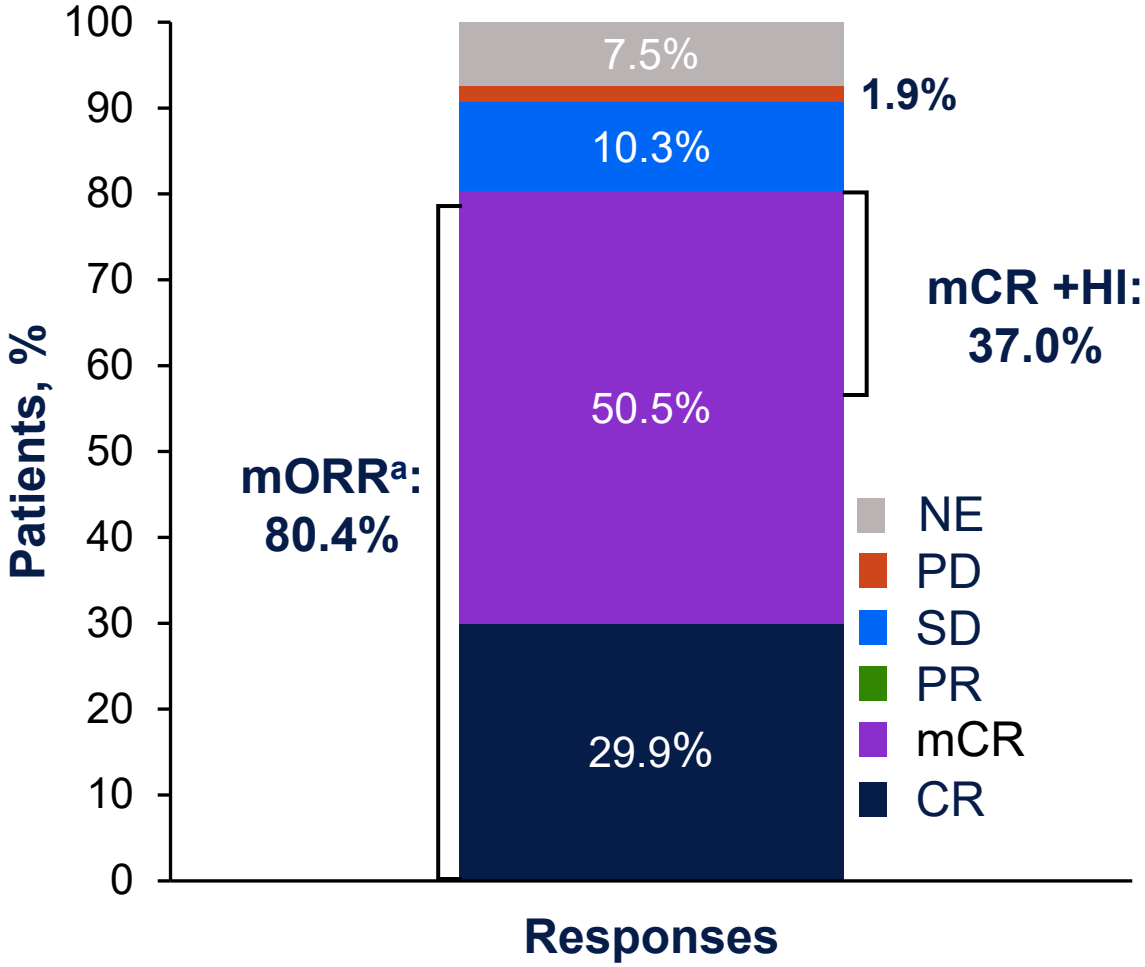



**Broad activity that is durable among responders at RP2D**

# Best Responses for Ven 400 mg + Aza

Garcia J et al
ASH 2023.

## >80% of Patients Who Received Ven + Aza Responded



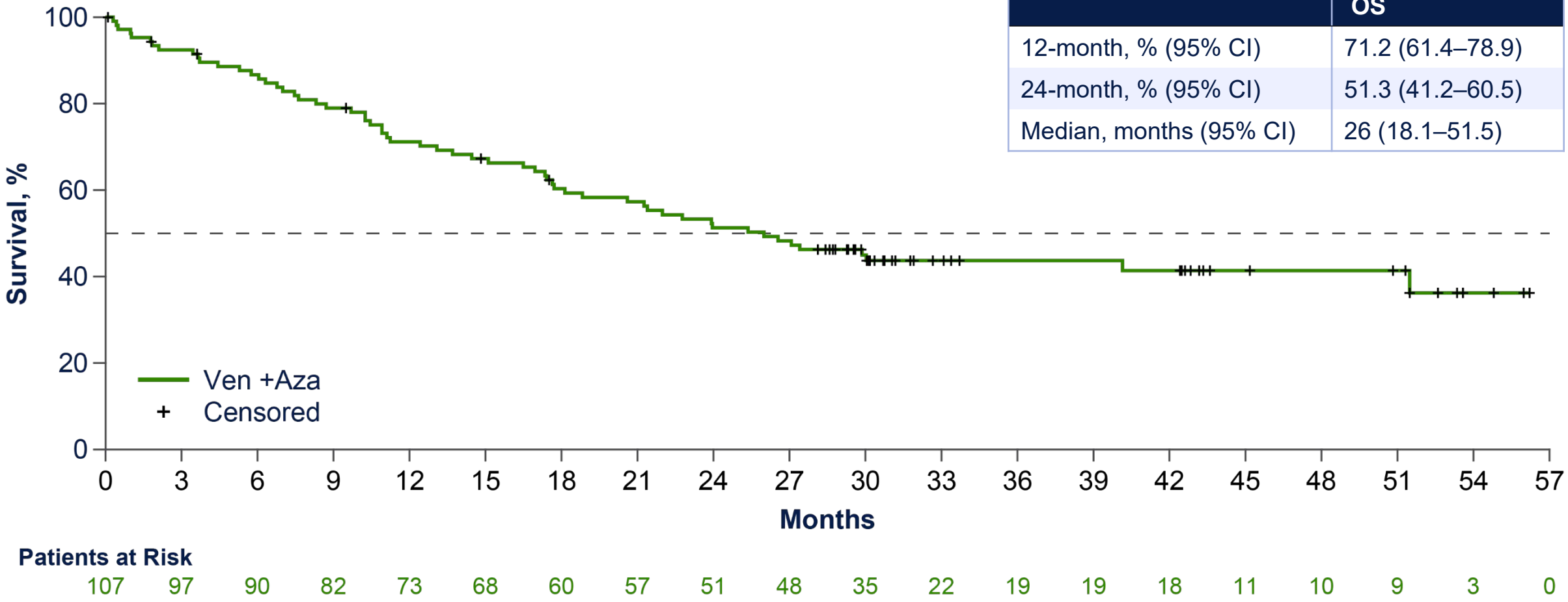

- Median number of treatment cycles with Ven 400 + Aza: 4.0 (range, 1–57)
- Median time to CR: 2.8 months (range, 1.0–16.1)
- Median duration of CR: 16.6 months (95% CI, 10.0–NR)
- MDS to AML transformation: in 13 (12.3%) patients (95% CI, 6.7–20.1)
  - Median time to AML transformation was 5.95 months (range, 0.72–29.31)

[a]mORR=CR+mCR+PR; PR, n=0; response rates based on International Working Group 2006 response criteria.
AML, acute myeloid leukemia; Aza, azacitidine; CR, complete remission; HI, hematologic improvement; mCR, marrow complete remission; MDS, myelodysplastic syndromes; mORR, modified overall response rate; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial remission; RP2D, recommended phase 2 dose; SD, stable disease; Ven, venetoclax.

# Overall Survival[a] for Patients Who Received Ven 400 mg + Aza

Garcia J et al ASH 2023.

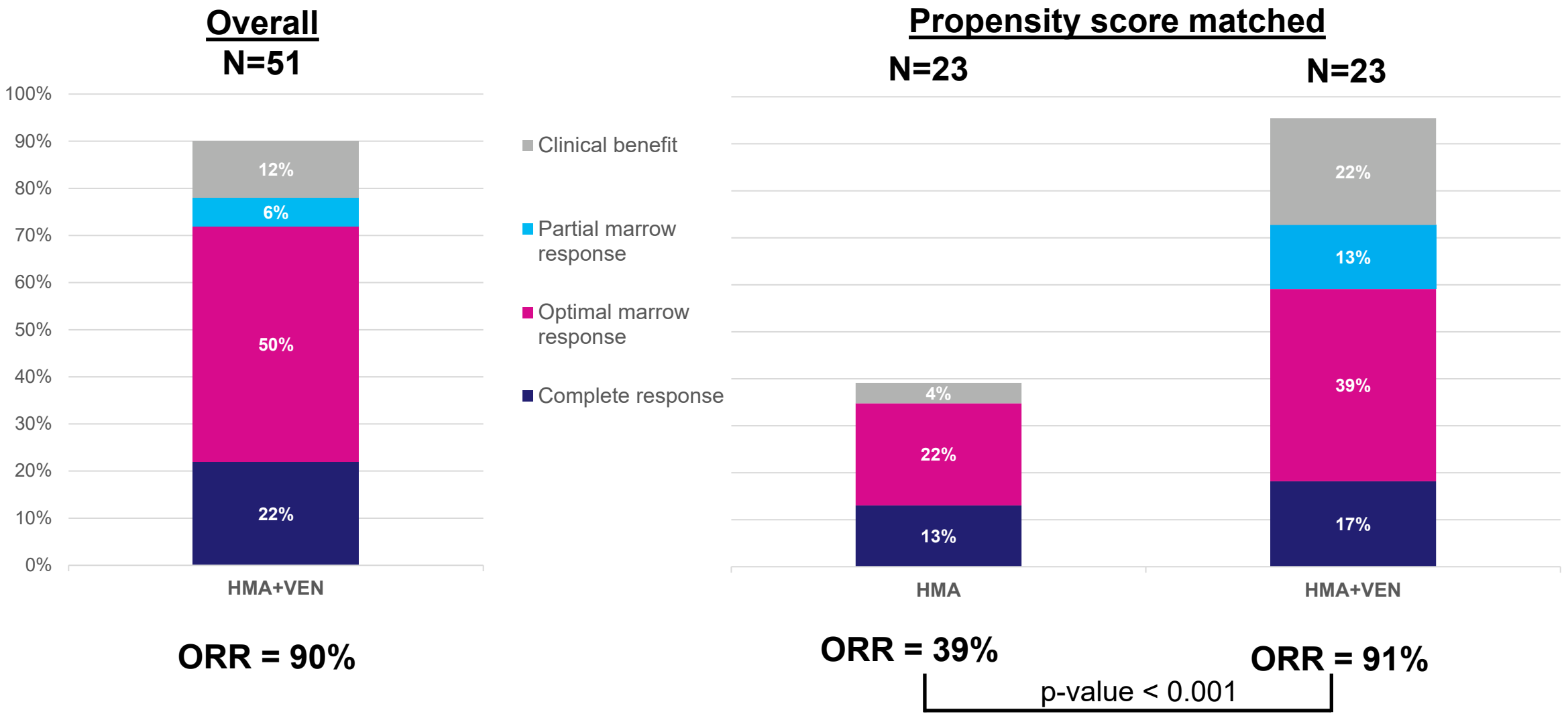
| | OS |
|---|---|
| 12-month, % (95% CI) | 71.2 (61.4–78.9) |
| 24-month, % (95% CI) | 51.3 (41.2–60.5) |
| Median, months (95% CI) | 26 (18.1–51.5) |




[a]Overall survival was defined as the number of months from the date of the first dose of study drug to the date of death. The data were censored at the date the patient was last known to be alive on or before the cutoff date. Aza, azacitidine; OS, overall survival; Ven, venetoclax.

# HMA + VEN: Response rates - CMML

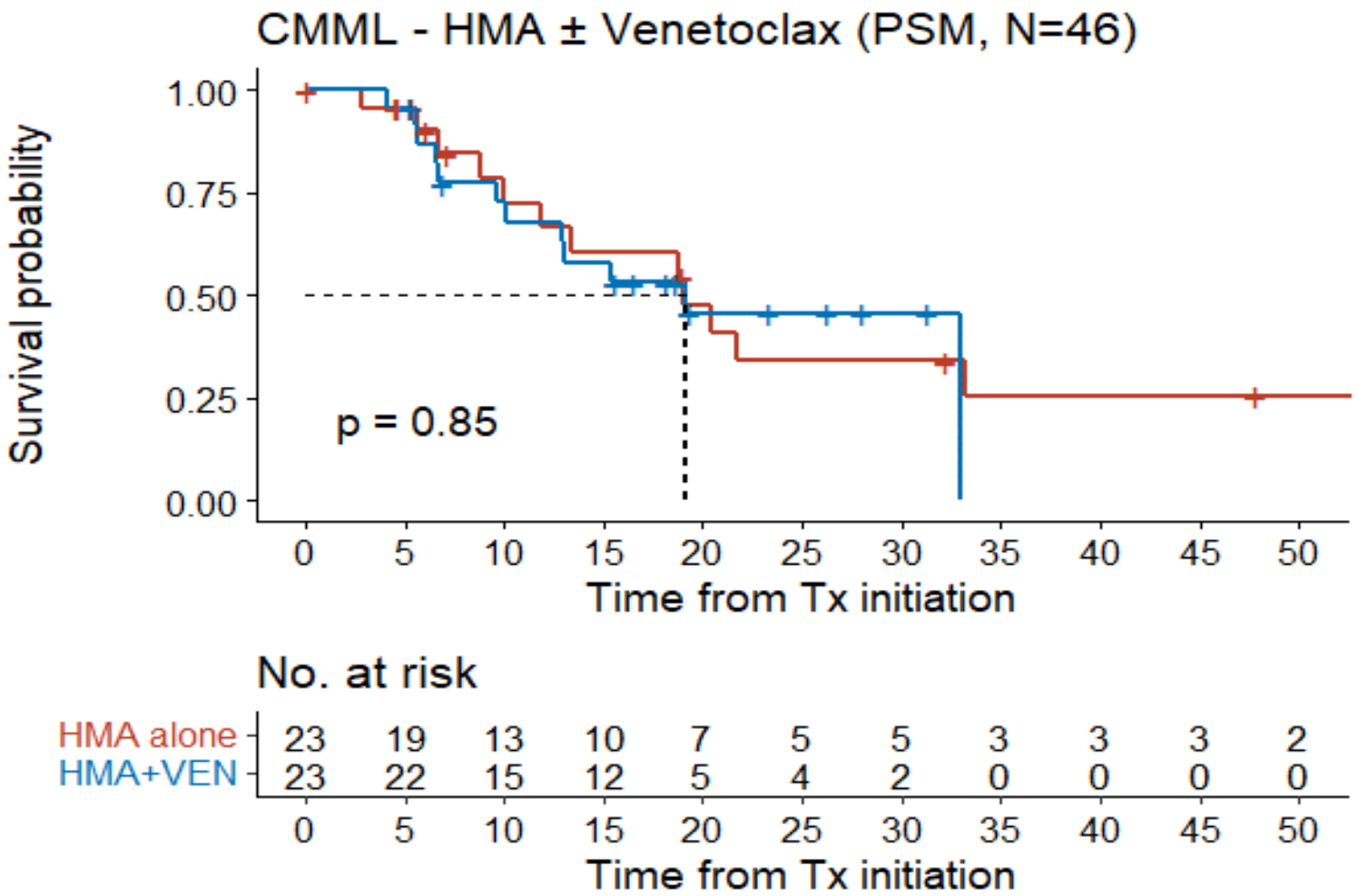
Tremblay D et al
ASH 2023.




Response criteria = 2015 MDS/MPN IWG

# Propensity score matched overall survival - CMML

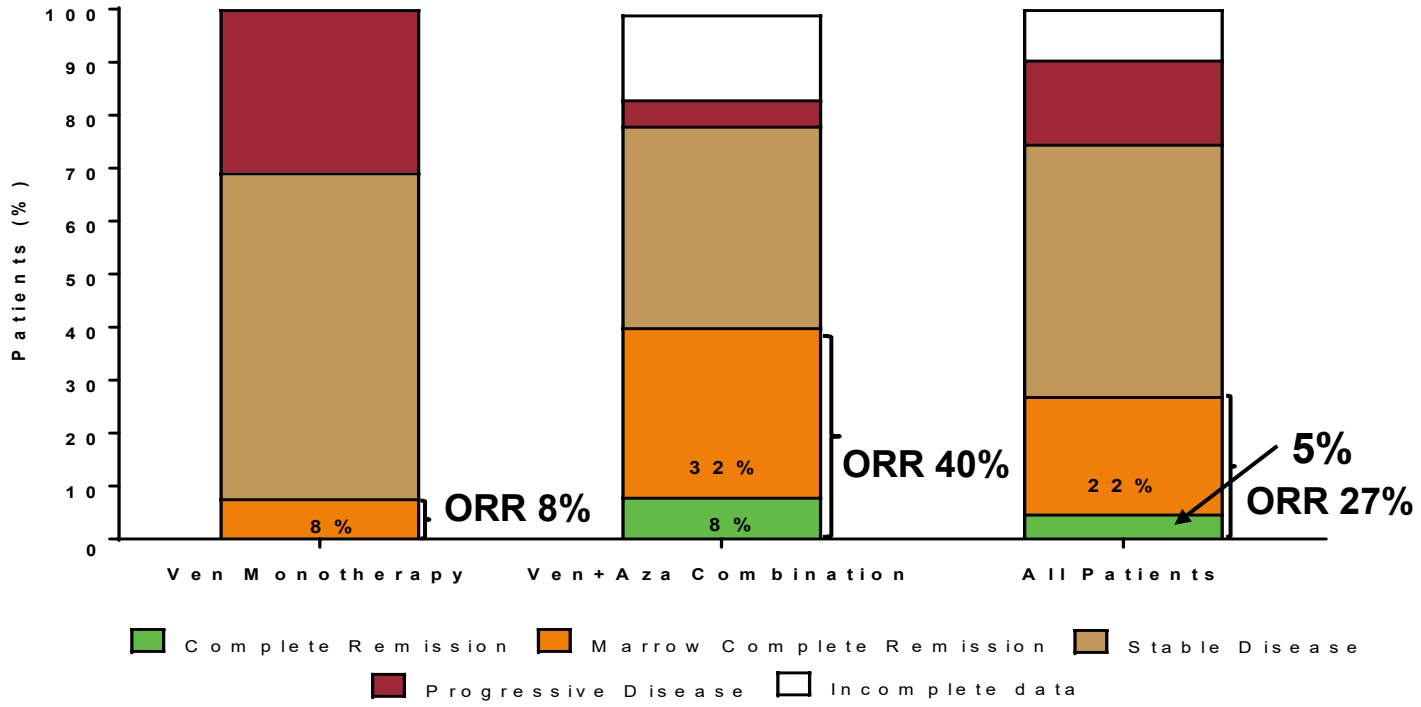
Tremblay D et al
ASH 2023.




| | Median OS (95% CI) |
|---|---|
| HMA+VEN (N=23) | 19.1 months (11.9-NR) |
| HMA alone (N=23) | 19.1 months (12.9-NR) |

- Similar findings when censored for HSCT

# Ven+/- AZA not so active in R/R HR MDS

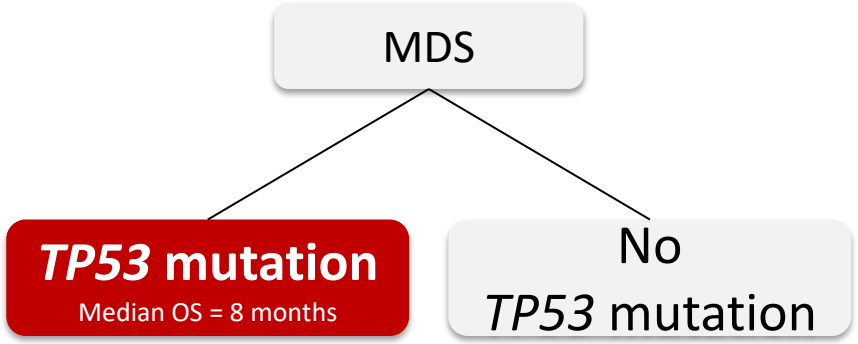


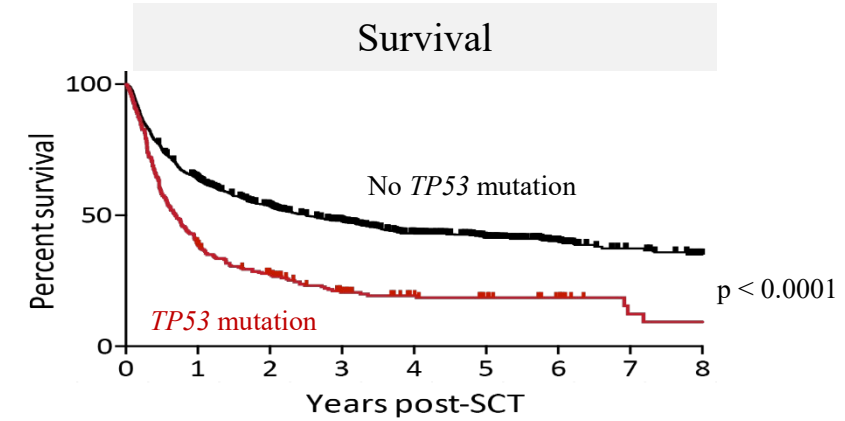

Data cutoff: Aug 30, 2019.

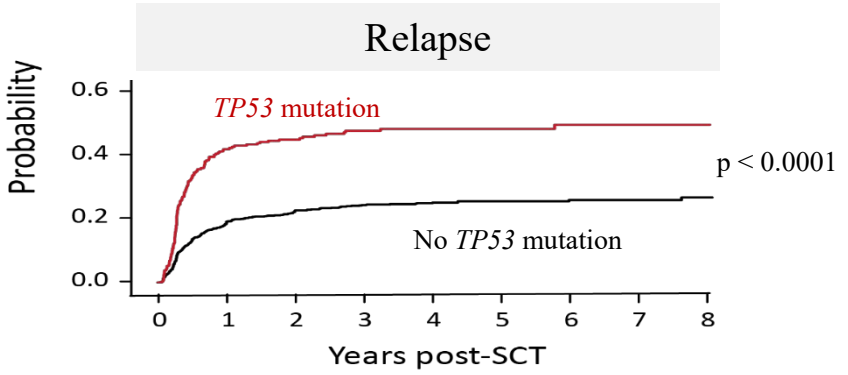
ClinicalTrials.gov. NCT02966782.
Zeidan A, et al. ASH 2019. Abstract 565.

# *TP53* mutated MDS

*Poor prognosis Post-SCT due to early relapse*



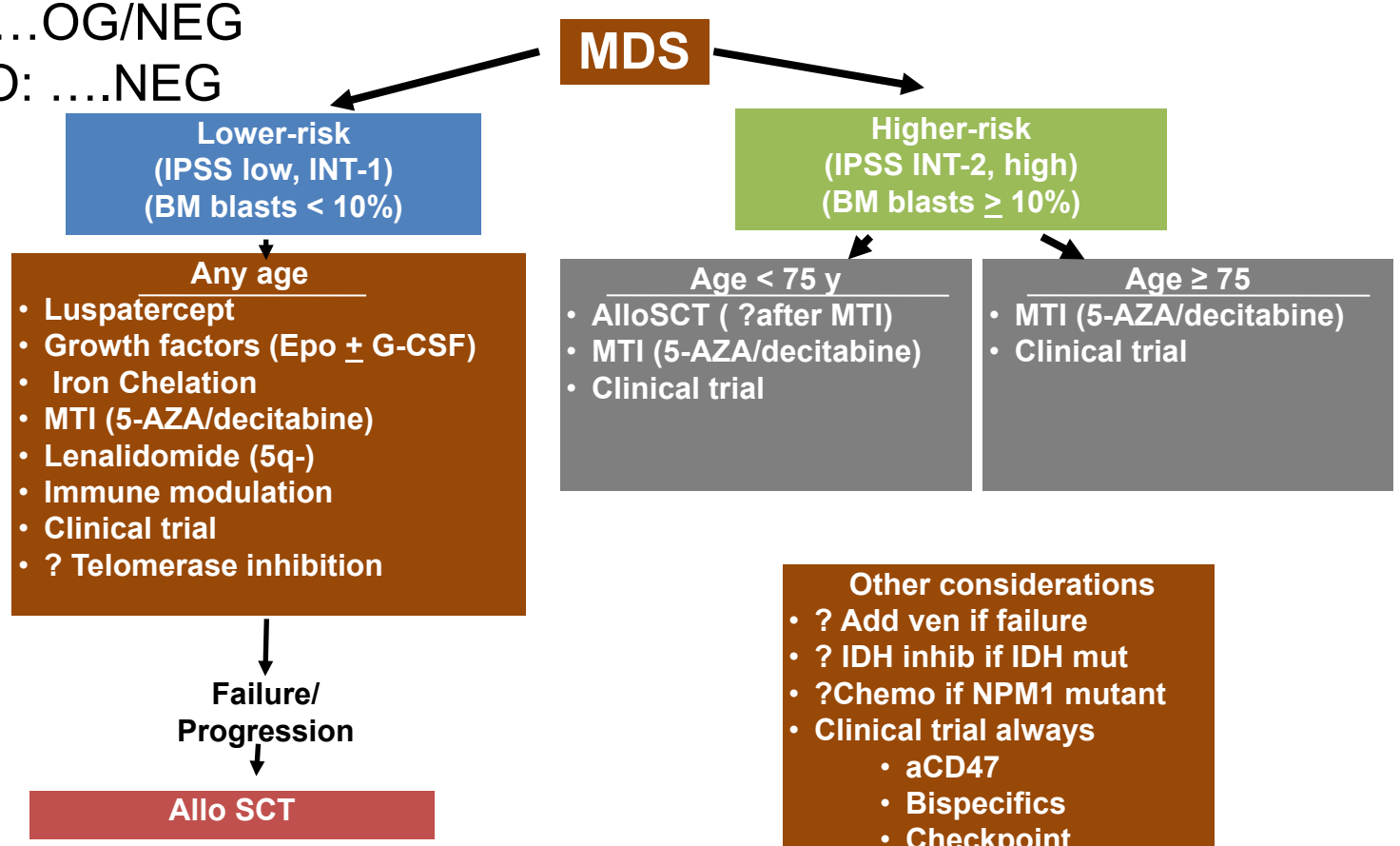




Cutler C, ASH 2020: donor v no donor higher risk MDS: n=384  48 v 27% 3 y OS in age 50-75

Lindsley C, et al. *N Engl J Med.* 2017;376(6):536-547.

Key clin trials
-aza+/-PEV…… NEG
-aza+/- APR ( TP53)…..NEG
-aza+/-VEN…accrued
-aza+/-MAG ( TP53) ….NEG
-aza+/-SAB…. ……OG/NEG
-Roduxastat v EPO: ….NEG

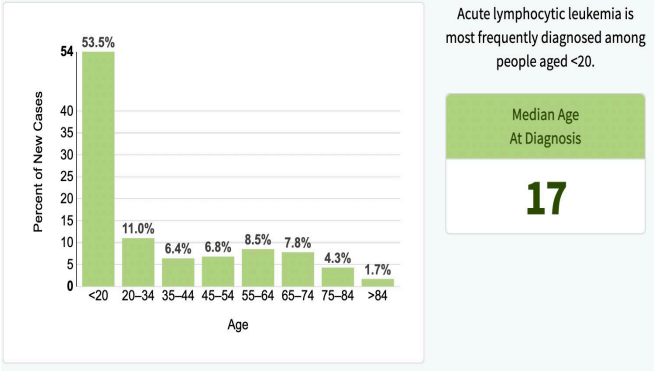
# Proposed Treatment Algorithm for Patients With MDS: 2024




- Modified from Atallah. *Cancer Inv*. 2008;26:208-216.

# Acute Lymphoblastic Leukemia in Adults

| | |
|---|---|
| Estimated New Cases in 2023 | 6,540 |
| % of All New Cancer Cases | 0.3% |




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

| Median Age At Diagnosis |
|---|
| 17 |

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

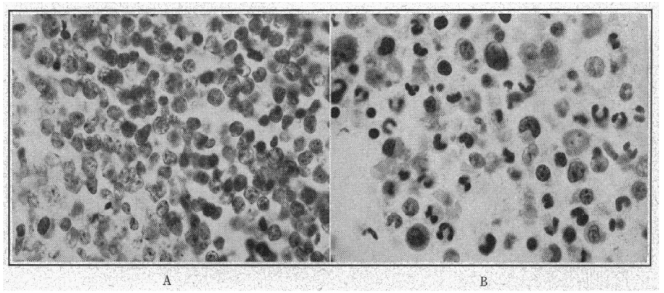
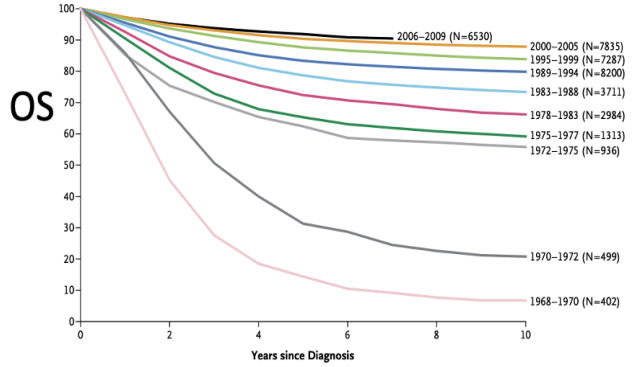


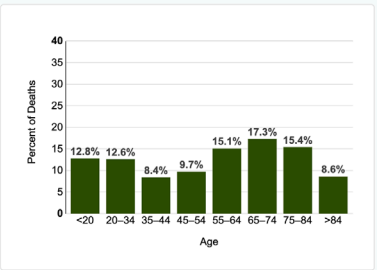

FIGURE 4. *Photomicrographs of the Sternal Bone Marrow in Case 3, Showing Giemsa-Stained Section on January 29, (A) and April 3 (B), 1948 (x1000).*
*Note that the microscopical field is composed mainly of blast forms characteristic of leukemia (cell type undetermined) in the early section (A) and that a marked shift to mature cell forms, particularly of the polymorphonuclear series, with no leukemic cells, had occurred on the later examination (B).*




- **2023:** 75 years later, most children cured.

CCG and COG trials, 1968-2009

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



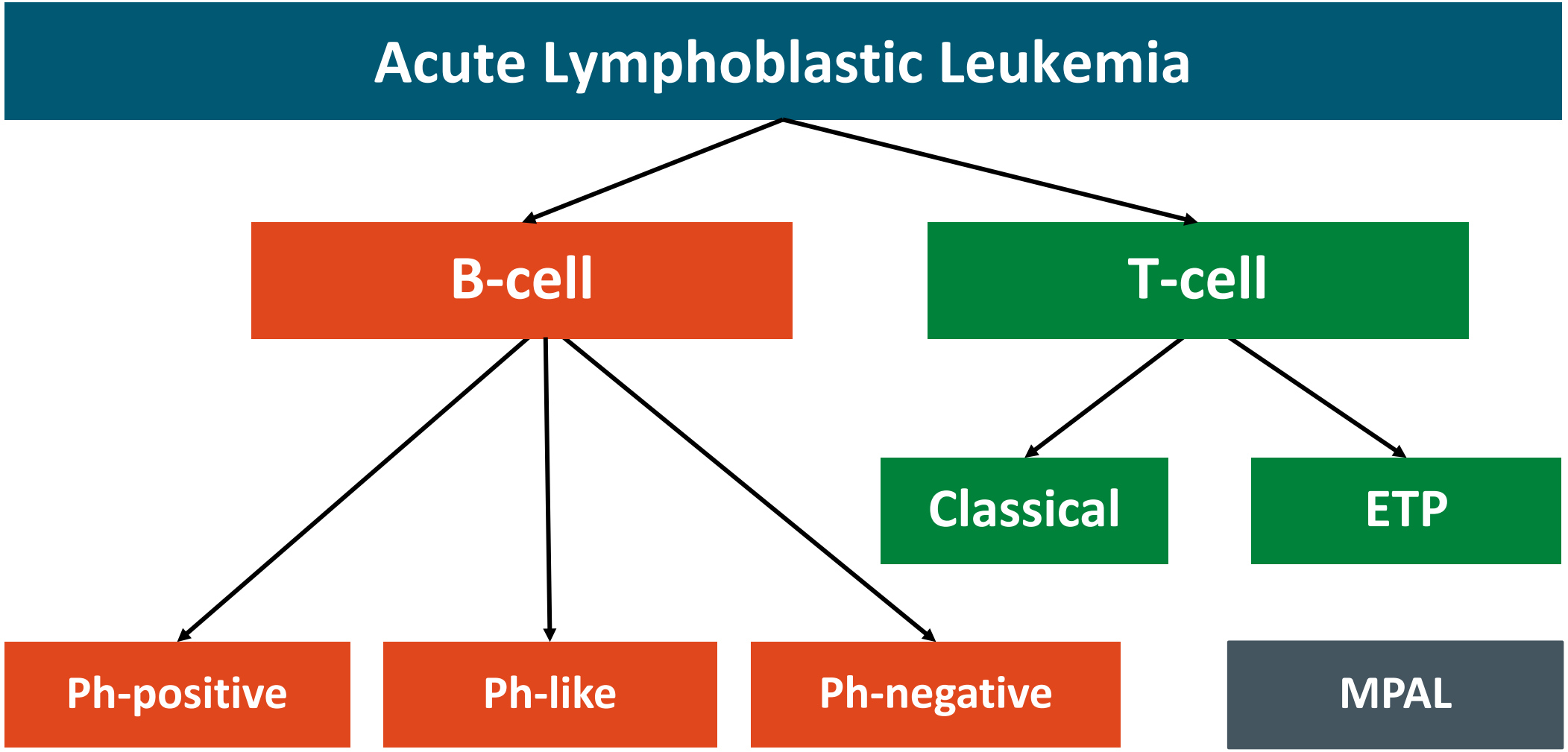

The percent of acute lymphocytic leukemia deaths is highest among people aged 65–74.

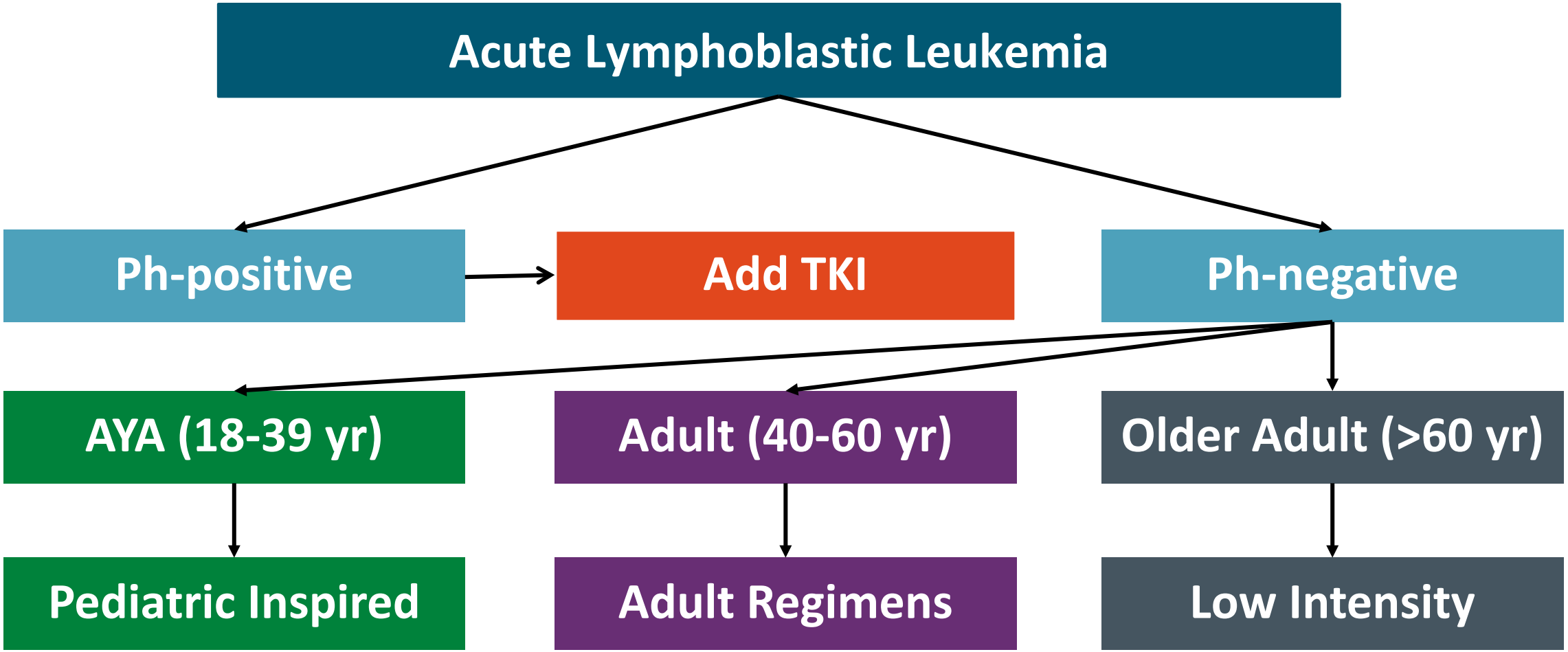
| Median Age At Death |
|---|
| 59 |


Farber S et al. *N Engl J Med.* 1948;238(23):787-793. Pui CH et al. *J Clin Oncol.* 2015;33(27):2938-2948. Hunger SP et al. *N Engl J Med.* 2015;373(16):1541-1552. NCI. Cancer Stat Facts: Leukemia – ALL. https://seer.cancer.gov/statfacts/html/alyl.html

# Take Home Messages from prognosis and classification

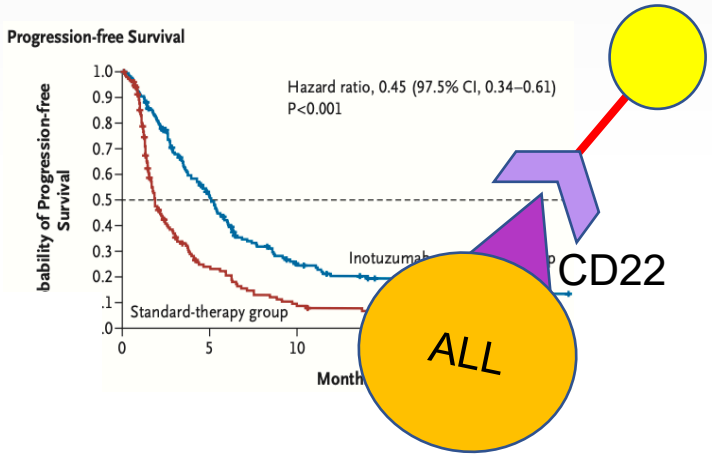
- Immunophenotyping
  - Must differentiate between ‘classical’ T-cell and ETP-ALL
  - Must differentiate MPAL from ALL with aberrancy
- Severe hypodiploid often associated with TP53 mutations
  - *Think* germline in young adults
- Ph-like ALL associated with poorer prognosis
  - FISH for *CRLF2*, all others need gene fusion assay
  - Look for *IKZF* deletions
- MRD ***must*** be assessed in all patients with ALL
  - MRD trumps all other prognostic factors
  - Blinatumomab now approved for MRD positive ALL


Acute Lymphoblastic Leukemia
B-cell
T-cell
Classical
ETP
Ph-positive
Ph-like
Ph-negative
MPAL


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

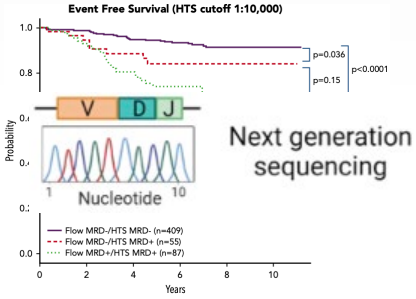
# ALL: Incredible Progress in 10 Years!

## Controversy! Questions! (Good Problems To Have)!

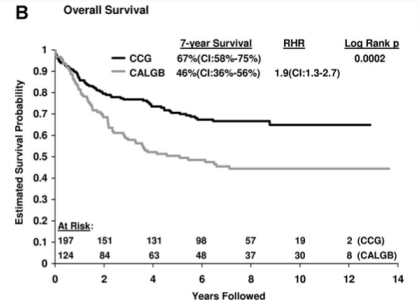



**Inotuzumab ozogamicin (INO-VATE)**

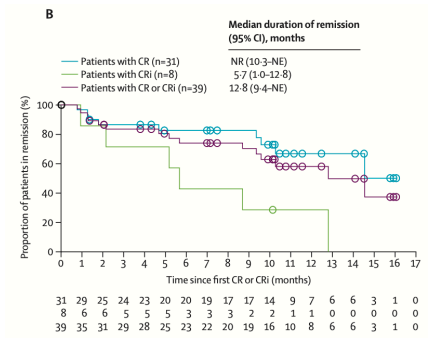
Improved MRD assays, genetic risk understanding → improved prognostication & risk adapted therapy

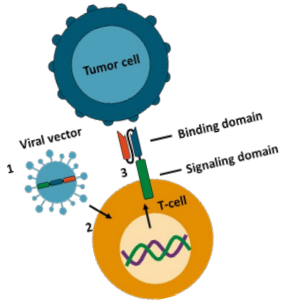



| I | C | IM | DI | M |
|---|---|---|---|---|
| DNR | Cyclo | MTX | DOX | DEX |
| VCR | VCR | VCR | Cyclo | VCR |
| Pred | Dex | Peg-ASP | Dex | 6MP |
| Peg-Asp | Peg-Asp | IT-MTX | Peg-Asp | MTX |
| IT-MTX | Ara-C | | Ara-C | IT-MTX |
| IT-AraC | 6MP | | 6-TG | |
| | IT-MTX | | IT-MTX | |

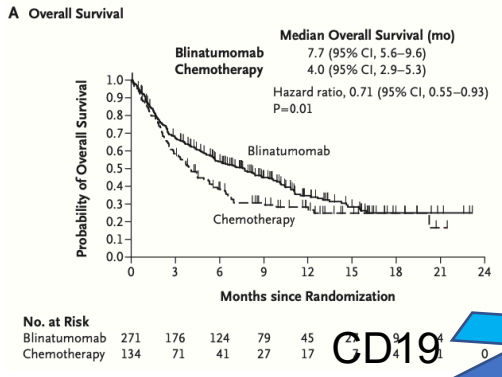


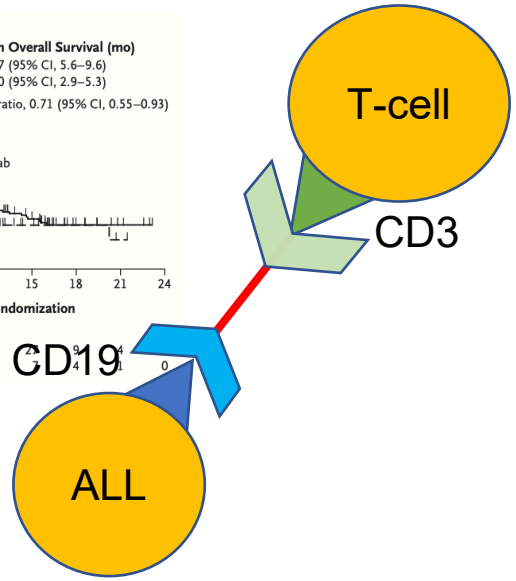

**"Pediatric-inspired" regimens**



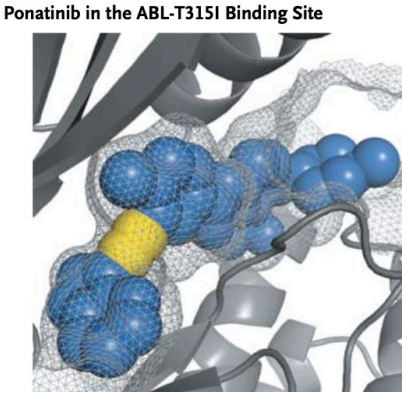




**Brexucabtagene autoleucel (ZUMA-3)**




**Blinatumomab (TOWER)**



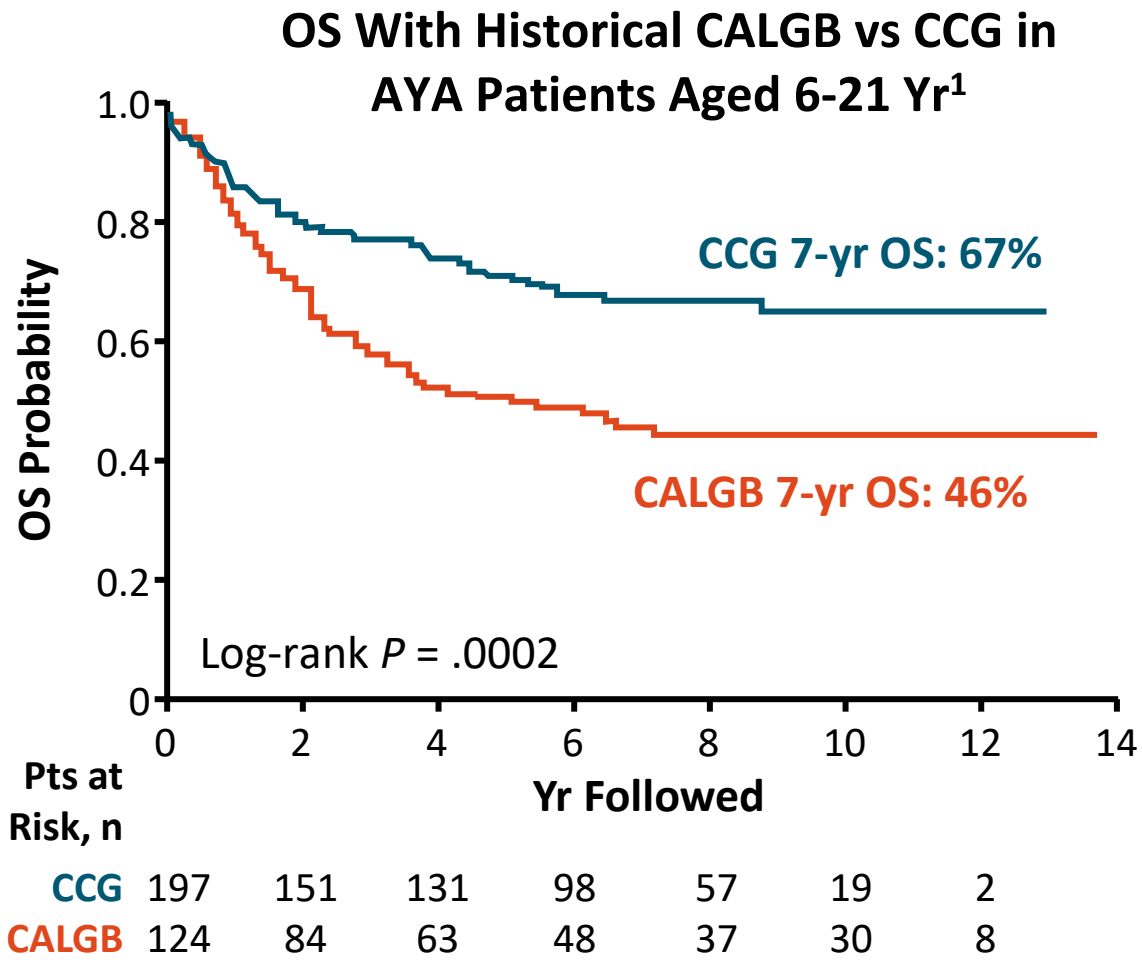

**TKIs that target T315I (Ponatinib)**

Kantarjian HM et al. *New Engl J Med.* 2016;375(8):740-753. Kantarjian H et al. *N Engl J Med.* 2017;376(9):836-847. Wood B et al. *Blood.* 2018;131(12):1350-1359. Cortes JE et al. *N Engl J Med.* 2012;367(22):2075-2088. Stock W et al. *Blood.* 2008;112(5):1646-1654. Shah BD et al. *Lancet.* 2021;398(10299):491-502.

# 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
  - Replicated by several groups

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

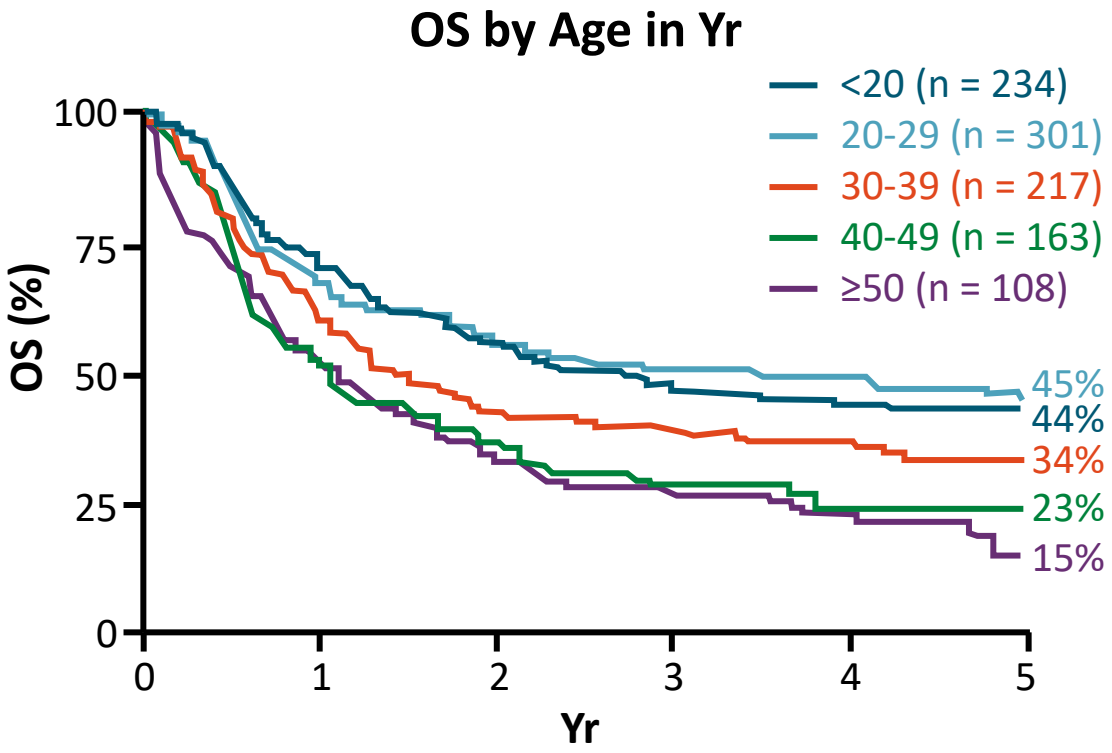



Stock. Blood. 2008;112:1646.

# Prognosis of AYA Patients Improved With Pediatric Regimens

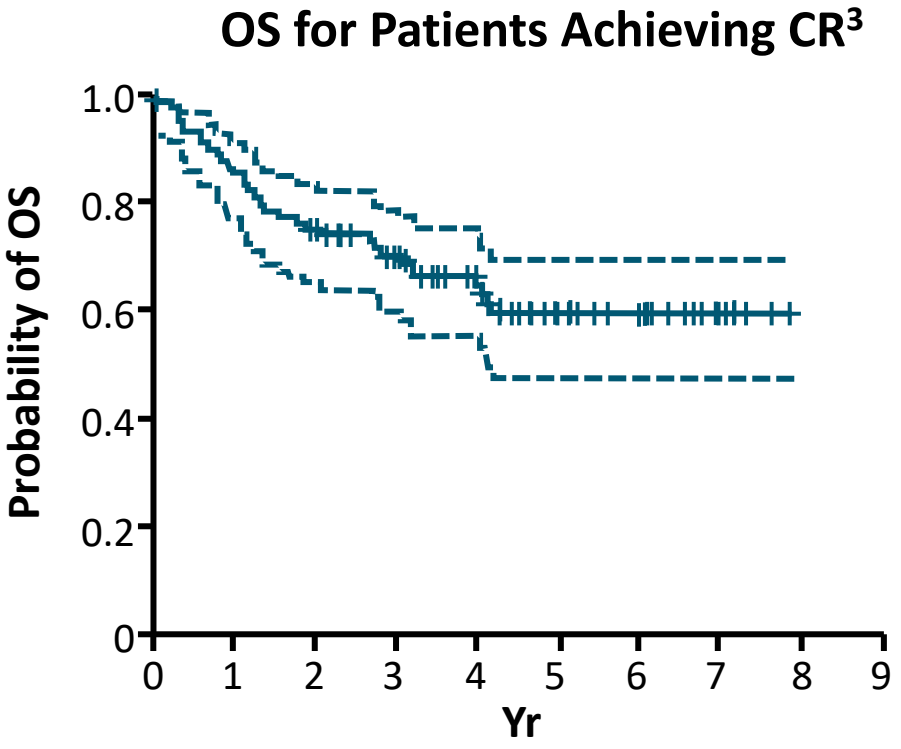
## E2993 "Adult" Protocol[1]

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




## DFCI "Pediatric" Protocol[2,3]

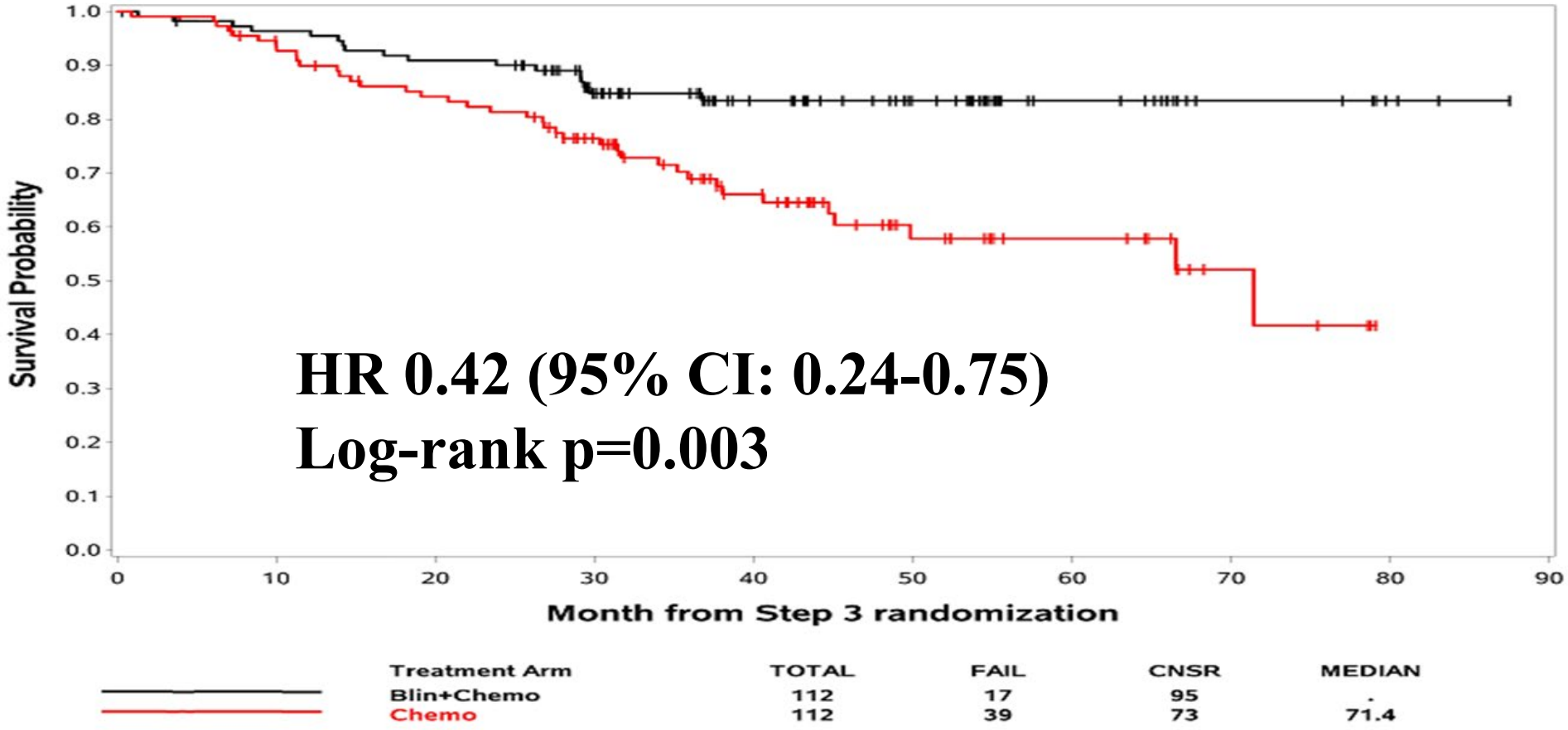
**5-yr OS for patients 20-50 yr: 60% to 70%**




1. Rowe. Blood. 2005;106:3760. 2. Vrooman. JCO. 2013;31:1202. 3. DeAngelo. Leukemia. 2015;29:526.

# Pre-B ALL, aged 30-70
# : E1910: Overall Survival (MRD-negative)

Median follow-up 3.6 yrs




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

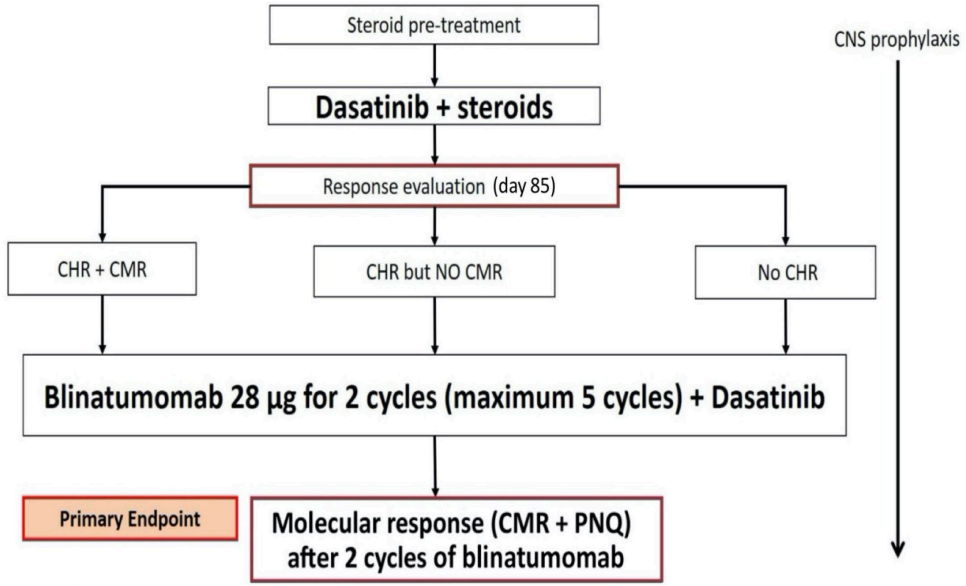
Litzow et al ASH 2022

# Other induction regimens for PH- NEG older adults

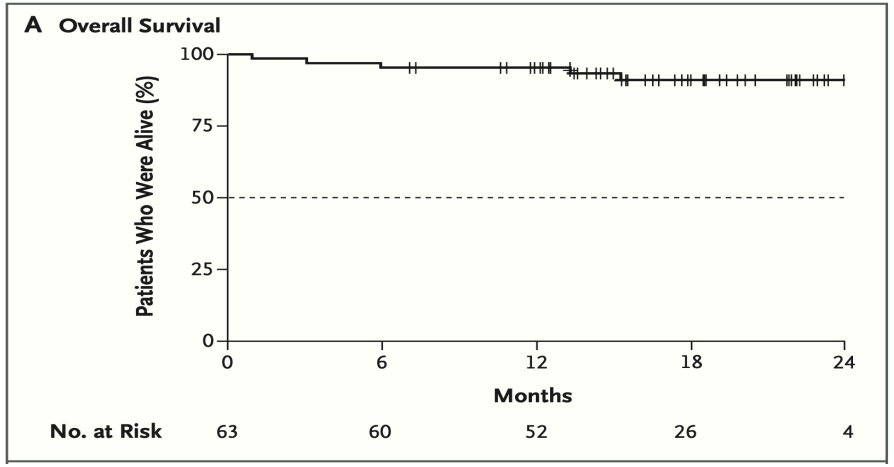
- Larson/CALGB 9111 ( Larson, R et al, Blood 1998)
- Dose adjusted hyerCVAD ( Thomas, D et al, J Clin Oncol 2010)
- MinihyperCVD ( Luskin M, Clin Lymphoma, Myeloma, Leuk, 2022)
- Inotuzumab+ mini-hyperCVD (Jabbour E, etal, Lancet Haematol, 2023)
- Inotuzumab ( Wieduwilt, M, etal, ASCO 2023)
- Venetoclax + mini-hyperCVD ( Luskin M, et al , ASH 20203)

- Would now add blinatumomab to all (Litzow ASH 2022)
- Consider nelarabine for T-ALL ( Dunsmore K, et al, J Clin Oncol 2020)
- Consider add rituximab if CD 20 pos (Maury S, NEJM, 2016)

# Dasatinib + Blinatumomab (D-ALBA)
# ? Ponatinib or add asciminib in future

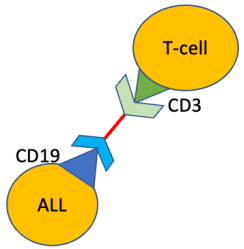



- Day 85 – 29% Molecular Response
- Blina C2 (n=55) – 60% Molecular Response
- Blina C4 – 81% Molecular Response




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

***Note***: Approximately half transplanted.




- 18-mo DFS was 88%.
- Worse outcomes in *IKZF1* plus (2-year OS 84% vs 54%, P=.026).
- T315I in 5/6 relapses tested.

Foa R et al. *N Engl J Med.* 2020;383(17):1613-1623. Chiaretti S et al. EHA 2022. Abstract P353. Advani AS et al. *Blood Adv.* 2023;7(7):1279-1285.

# Relapsed ALL: Controversies

- Should CAR-T be used in first relapse if other approaches available? (ie, InO salvage→allo HSCT).
- Should patients who optimally respond to CAR-T be transplanted?
- What is the optimal bridging therapy for CAR-T?
- What will be new challenges for managing relapsed ALL as more patients exposed to novel therapies as part of first-line therapy.
- Will CAR-T be successful for T-ALL?

# Acknowledgements


Clinical Team at DFCI:

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Alliance

- R Larson, G Marcucci, W Blum, G Uy, G Roboz, J Kolitz, S. Mandrekar ,W Stock, G Uy, C. Bloomfield*

Academic Collaborators

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- Worldwide: E. Estey*, C Schiffer, H Dohner, C Thiede, F. LoCoco* and many others.

* In memory

# The End

**Questions or need help?**

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**Administrative Assistant: 617-632-2168**
**New Patients: 617-632-6028**
**Page: 617-632-3352 #42194**