Acute Myeloid Leukemia and Myelodysplastic Syndromes:

Where are we in 2025?

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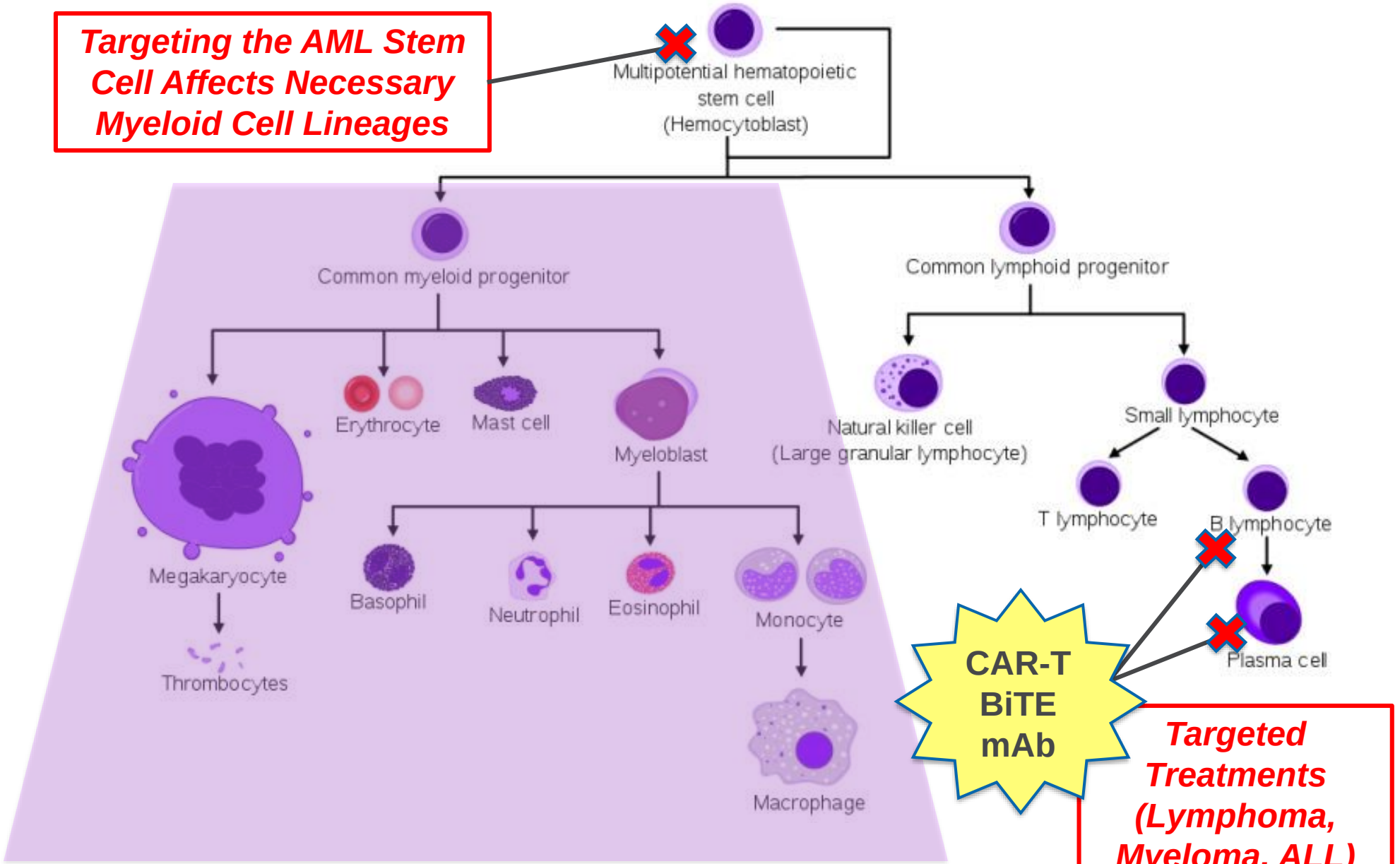
Disclosures

- Consulting: Bristol Myers Squibb, Gilead Sciences, Rigel Pharmaceuticals, Servier Laboratories

- Research Funding: Function Oncology

Normal Hematopoiesis

Targeting the AML Stem Cell Affects Necessary Myeloid Cell Lineages



A. Rad and M. Haggstrom (StatPearls Publishing LLC)

Overview

- AML
  - Blast Threshold (WHO 5th Edition vs ICC)
  - AML-defining cytogenetic/genetic lesions
  - Risk Stratification (ELN 2022)
  - Treatment challenges

- MDS
  - Risk Stratification (IPSS-R vs IPSS-M)
  - Sequencing therapies for lower risk MDS
  - Challenges in higher risk MDS

AML DIAGNOSIS

AML Diagnosis

- **Previously: ≥20% myeloid blasts in bone marrow or blood**
  - t(15;17), t(8;21), inv(16)/t(16;16) regardless of blast percentage
  - Myeloid sarcoma/chloroma (a tumor composed of myeloblasts)

- **WHO and ICC 2022 Updates**
  - Both retain recurrent genetic abnormalities as a primary consideration
  - For specific genetic abnormalities, ICC mandates ≥10% blasts in the bone marrow or blood but WHO does not specify a blast cut-off (next slide)
  - *BCR::ABL1* requires ≥20% blasts for both ICC and WHO
  - AML with MDS-related changes defined by cytogenetic or gene mutation criteria, not morphologic dysplasia
    - *ICC created a new category of "MDS/AML" for blasts 10-19% with designated genetic mutations*
  - *TP53* mutated AML, exclusive to ICC, requires ≥20% blasts and VAF ≥10%

Khoury *Leukemia* 2022, Arber *Blood* 2022

Two New Classification Systems in 2022

AML-Defining Genetic Lesion	AML Blast Threshold	
	WHO	ICC
t(15;17)(q24.1;q21.2)/*PML::RARA* and other *RARA* rearrangements	Any	≥10%
t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	Any	≥10%
inv(16)(p13.1;q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*	Any	≥10%
t(9;11)(p21.3;q23.3)/*MLLT3::KTM2A* and other *KMT2A* rearrangements	Any	≥10%
t(6;9)(p22.3;q34.1)/*DEK::NUP214*	Any	≥10%
inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2);*GATA2::MECOM(EVI1)*	Any	≥10%
MECOM rearrangements	Any	≥10%
Other recurring translocations including *NUP98* and *RBM15:MRTF1*	Any	≥10%
NPM1 mutated	Any	≥10%
In-frame bZIP *CEBPA* mutations	≥20%	≥10%
TP53 mutation	-	≥20%
t(9;22)(q34.1;q11.2)/*BCR::ABL1*	≥20%	≥20%
MDS-related cytogenetic/genetic abnormalities	≥20%	≥10%

Khoury *Leukemia* 2022, Arber *Blood* 2022

Rapid NGS Myeloid Panel

- Available at UCSD since May 2024 (Dr. Wei Song)
- Interrogates 45 DNA target genes and 35 RNA fusion driver genes
- Needed for diagnosis (AML-defining lesions), risk stratification, treatment selection

DNA panel: hotspot genes (28)		DNA panel: full genes (17)		RNA panel: fusion driver genes (35)			RNA panel: expression genes (5)
ANKRD26	*KRAS*	*ASXL1*	*PRPF8*	*ABL1*	*HMGA2*	*NUP98*	*BAALC*
ABL1	*MPL*	*BCOR*	*RB1*	*ABL2*	*JAK2*	*NUP214*	*MECOM*
BRAF	*MYD88*	*CALR*	*RUNX1*	*BCL2*	*KAT6A (MOZ)*	*PAX5*	*MYC*
CBL	*NPM1*	*CEBPA*	*SH2B3*	*BRAF*	*KAT6B*	*PDGFRA*	*SMC1A*
CSF3R	*NRAS*	*ETV6*	*STAG2*	*CCND1*	*KMT2A*	*PDGFRB*	*WT1*
DDX41	*PPM1D*	*EZH2*	*TET2*	*CREBBP*	*KMT2A PTDs*	*RARA*	
DNMT3A	*PTPN11*	*IKZF1*	*TP53*	*EGFR*	*MECOM*	*RUNX1*	
FLT3 (ITD,	*SMC1A*	*NF1*	*ZRSR2*	*ETV6*	*MET*	*TCF3*	
TKD)	*SMC3*	*PHF6*		*FGFR1*	*MLLT10*	*TFE3*	
GATA2	*SETBP1*			*FGFR2*	*MRTFA (MKL1)*	*ZNF384*	
HRAS	*SF3B1*			*FUS*	*MYBL1*		
IDH1	*SRSF2*				*MYH11*		
IDH2	*U2AF1*				*NTRK2*		
JAK2	*WT1*				*NTRK3*		
KIT							

AML Defining Lesions

AML RISK STRATIFICATION

AML Risk (Staging) Is Determined by Genetic Abnormalities

Risk Category	Genetic Abnormality
Favorable (15%)	**t(8;21)(q22;22.1)/*RUNX1::RUNX1T1*** **inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*** **Mutated *NPM1* without *FLT3-ITD*** **bZIP in-frame mutated *CEBPA***
Intermediate (50%)	**Mutated *NPM1* with *FLT3-ITD*** **Wild-type *NPM1* with *FLT3-ITD* (without adverse-risk genetic lesions)** t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Poor/Adverse (35%)	t(6;9)(p23.3;q34.1)/*DEK::NUP214* t(v;11q23.3)/*KMT2A*-rearranged t(9;22)(q34.1;q11.2)/*BCR::ABL1* t(8;16)(p11.2;p13.3)/*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, monosomal karyotype** **Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1 and/or ZRSR2*** **Mutated *TP53***

Add gemtuzumab

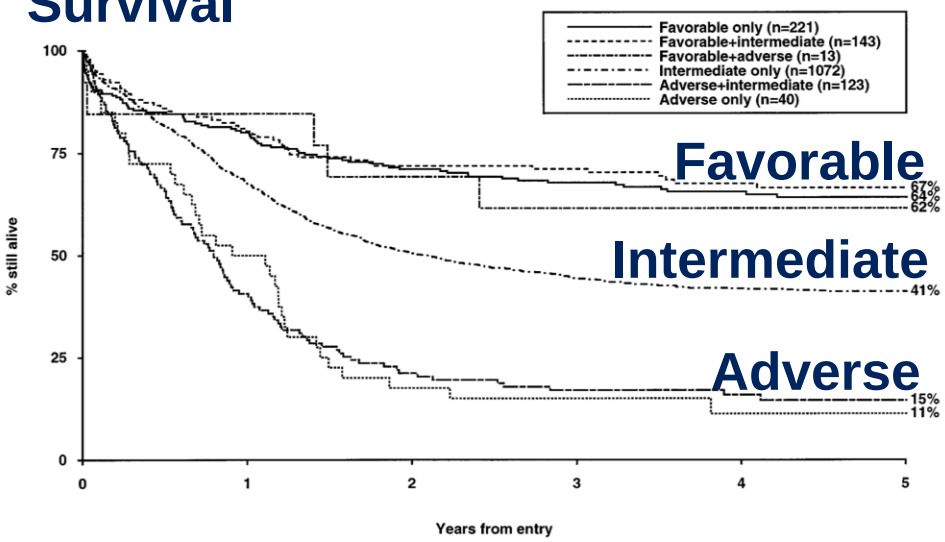
Add midostaurin, quizartinib

7+3 vs. CPX-351 vs. HMA/Ven

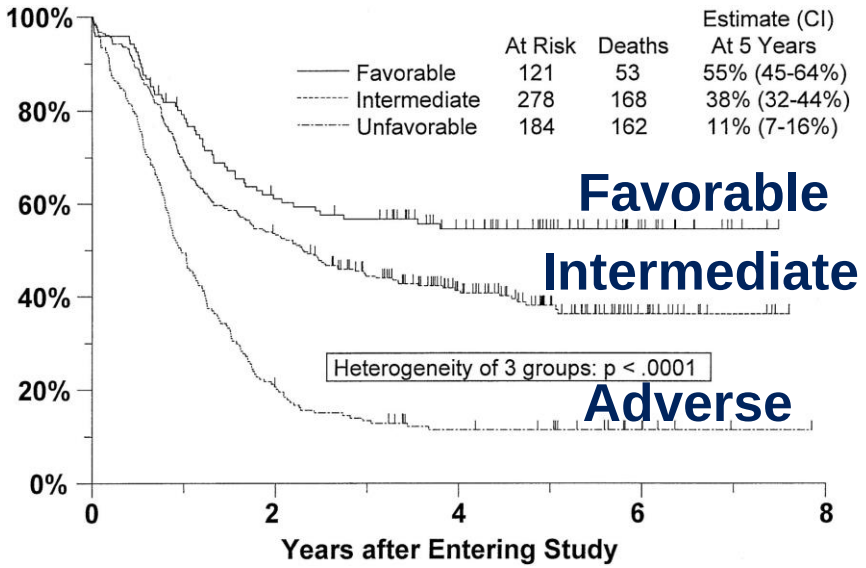
Döhner *Blood* 2022

AML 5-Year Survival by Risk Group

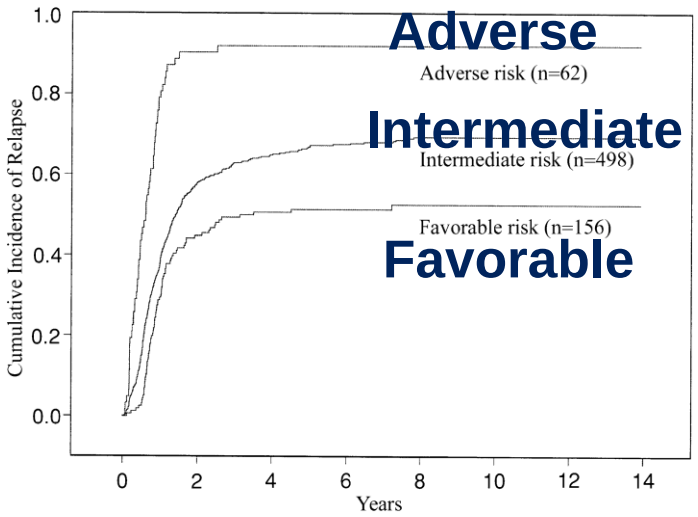
Survival



Survival



Relapse



UK MRC AML 10
n=1612

SWOG/ECOG
n=609

CALGB
n=1213

Grimwade *Blood* 1998; Slovak *Blood* 2000; Byrd *Blood* 2002

AML 5-Year Survival by Risk Group

	Favorable	Intermediate	Poor
UK MRC AML 10 n=1612	65%	41%	14%
SWOG/ECOG n=609	55%	38%	11%
CALGB n=1213	55%	24%	5%

Allogeneic HSCT for most fit/younger (<75 years) patients who have a donor

Grimwade *Blood* 1998; Slovak *Blood* 2000; Byrd *Blood* 2002

AML TREATMENT

AML Therapies

- **7+3 induction chemotherapy (1973), and other intensive chemo**
  **7+3 = 7 days of cytarabine, 3 days of anthracycline (daunorubicin, idarubicin)*

- **Hypomethylating Agents (HMAs): Azacitidine (2004)*, Decitabine (2006)***
  **Approved for MDS, used off-label for AML*

- Gemtuzumab (2010 → FDA hold, then approved 2017)
- CPX-351/liposomal cytarabine + daunorubicin (2017)
- Midostaurin (2017)
- Enasidenib (2017)
- ***Venetoclax (2018), with HMA***
- Glasdegib (2018)
- Ivosidenib (2018), +/- HMA
- Gilteritinib (2018)
- Azacitidine, oral tablets (2020)
- Olutasidenib (2022)
- Quizartinib (2023)
- Revumenib (2024)

AML drugs approved in the last decade!

AML Therapies 1970-2010

	FIT PATIENT	UNFIT PATIENT
Newly Diagnosed	7+3 Other intensive chemo	HMA LDAC Best supportive care
Relapsed/Refractory	Intensive chemo HMA	HMA LDAC Best supportive care

AML Therapies 2010 and beyond

	FIT PATIENT	UNFIT PATIENT
Newly Diagnosed	**7+3** **7+3** + Gemtuzumab (favorable risk) **7+3** + Mido/Quiz (FLT3-mutated) CPX-351 (t-AML, AML-MRC) **?HMA** + Venetoclax	**HMA** + Venetoclax **HMA** **LDAC** + Venetoclax **Best supportive care** **HMA** + Ivosidenib (IDH1-mutated) Enasidenib (IDH2-mutated) **LDAC** + Glasdegib
Relapsed/Refractory	**Intensive chemo** **HMA** + Venetoclax Ivosidenib (IDH1-mutated) Olutasidenib (IDH1-mutated) Enasidenib (IDH2-mutated) Gilteritinib (FLT3-mutated) Quizartinib (FLT3-mutated) Gemtuzumab (CD33-positive) Revumenib (KMT2A-r)	**HMA** + Venetoclax **HMA** Ivosidenib (IDH1-mutated) Olutasidenib (IDH1-mutated) Enasidenib (IDH2-mutated) Gilteritinib (FLT3-mutated) Quizartinib (FLT3-mutated) Gemtuzumab (CD33-positive) Revumenib (KMT2A-r)

AML Treatment Question 1:
Which FLT3 inhibitor for a chemo-eligible patient with newly diagnosed AML?

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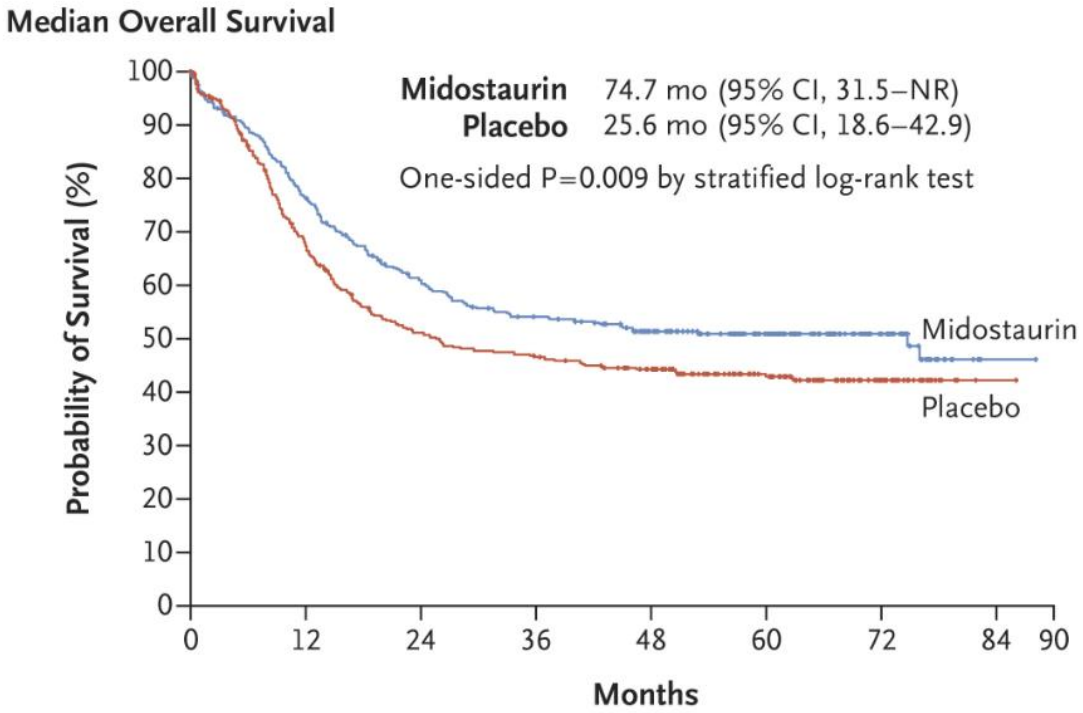
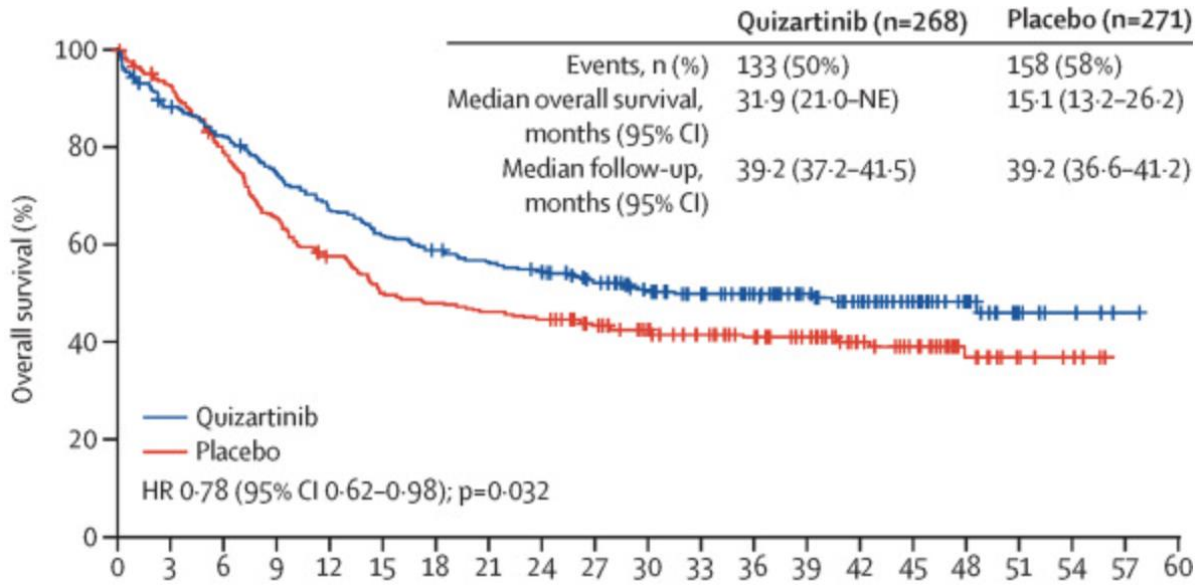
C10603/RATIFY
7+3/Midostaurin vs. 7+3/Placebo



OS 74.7 vs 25.6 mo, *p*=0.009
OS benefit in ITD only
OS in CR1 allo: 28.1 vs 22.7 mo, *p*=0.07
GI toxicity, rash

QUANTUM-FIRST
7+3/Quizartinib vs. 7+3/Placebo

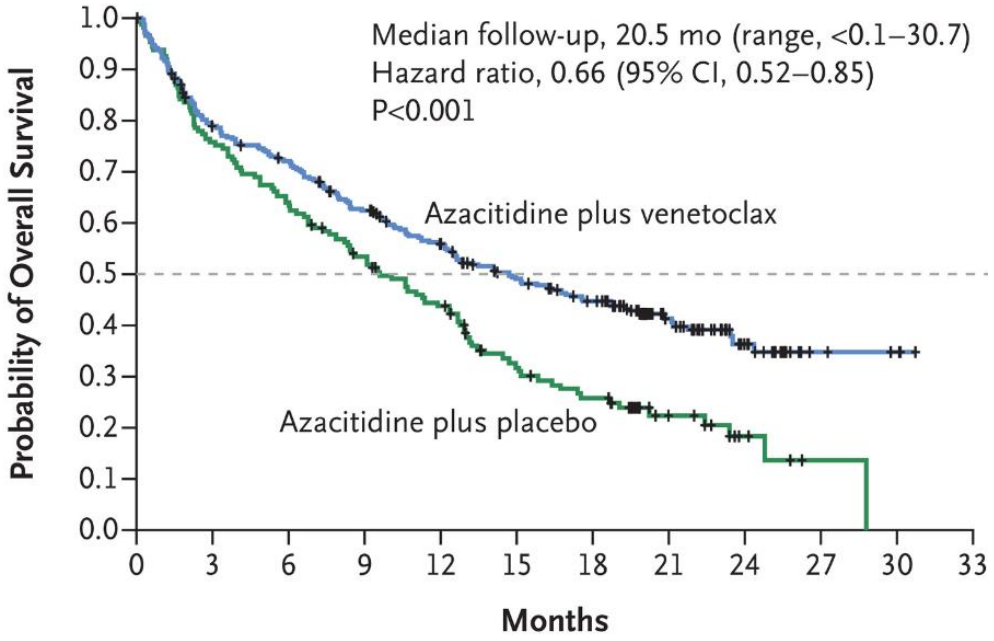


OS 31.9 vs. 15.1 mo, *p*=0.032
Activity against ITD only
Enrolled up to age 75 years
QTc prolongation

Stone *N Engl J Med* 2017; Erba *Lancet* 2023

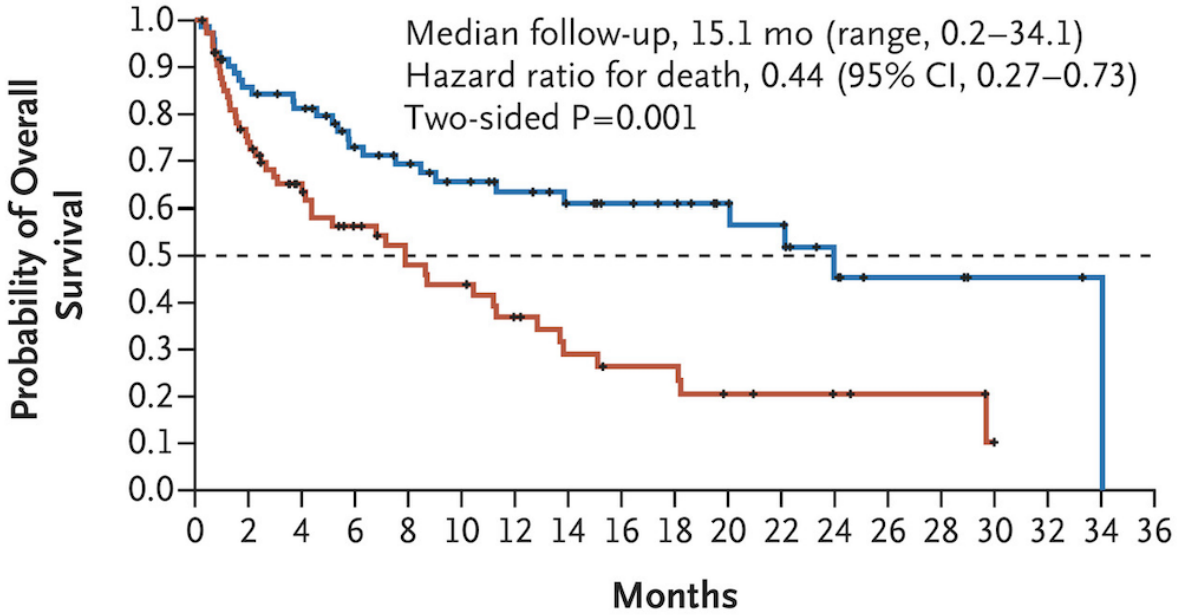
AML Treatment Question 2:
Which treatment for the non chemo-eligible patient with IDH1-mutated AML?

VIALE-A
Azacitidine/Venetoclax vs. Azacitidine/Placebo



OS 14.7 vs 9.6 mo, *p*<0.001
ORR 66.4 vs 28.3%, *p*<0.001
**IDHm, ORR 75.4% vs 10.7%*
TTR 1 vs 2.6 mo, DOR 17.8 vs 13.9 mo
Gr 3/4 febrile neutropenia 30 vs 10%
Gr 3/4 thrombocytopenia 45 vs 38%

AGILE
Azacitidine/Ivosidenib vs. Azacitidine/Placebo

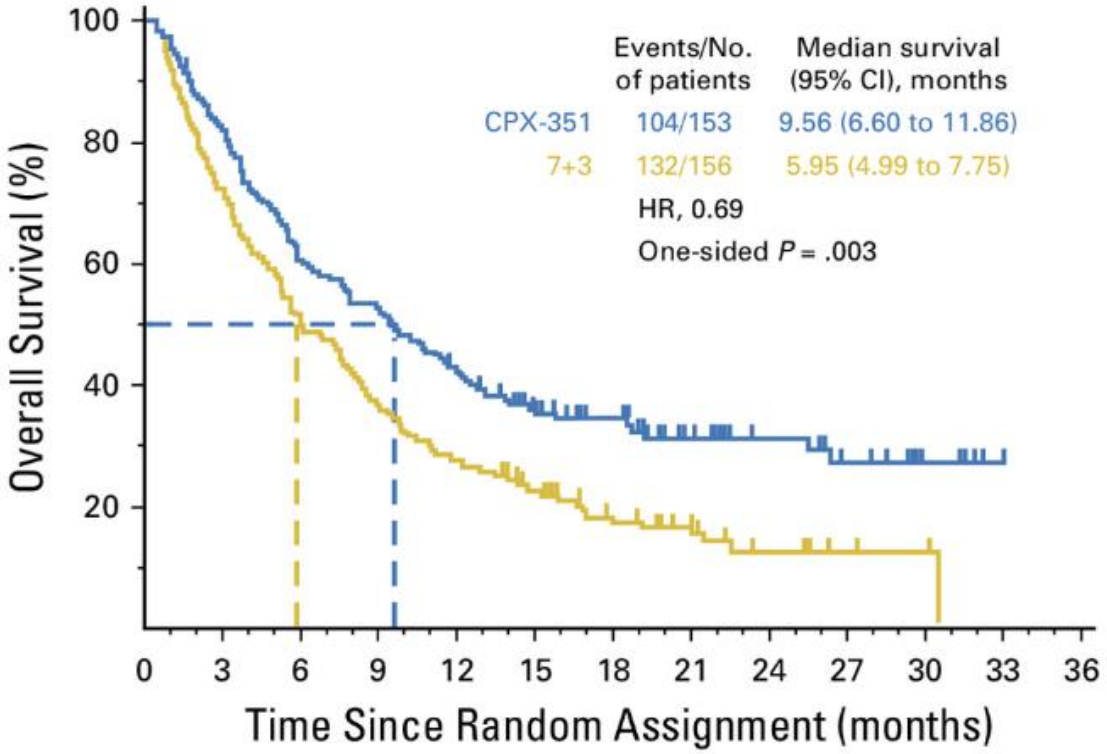


OS 24 vs 7.9 mo, *p*=0.001
ORR 63 vs 19%, *p*<0.001
TTR 2.1 vs 3.7 mo, DOR 22.1 vs 9.2 mo
DS 14 vs 8%
Gr 3/4 febrile neutropenia 28 vs 34%
Gr 3/4 thrombocytopenia 24 vs 21%

DiNardo *N Engl J Med* 2020; Montesinos *N Engl J Med* 2022

AML Treatment Question 3:
For adverse risk AML, intensive chemo vs HMA/Ven?

CPX-351 vs. 7+3



sAML (MDS, therapy-related), 60-75yr
OS 9.56 vs 5.95 mo, *p*=0.009
CR/CRi 47.7 vs 33.3%
60-day mortality 13.7 vs 21.2%
Gr 5 infection 7.2 vs 2.6%
Gr 5 bleeding 2.6 vs 2.6%

Subgroup	CPX-351	7+3
tAML, n=63	46.7%	36.4%
sAML, prior HMA, n=105	36%	32.7%
sAML, no prior HMA n=40	66.7%	36.8%
Poor Risk cytogenetics, n=155	43.1%	21.7%

Subgroup	Azacitidine + Venetoclax	Azacitidine + Placebo
AML-MRC, n=141	60.9%	22.4%
sAML, n=107	66.7%	22.9%
Poor Risk cytogenetics, n=160	52.9%	23.2%
***TP53*, n=52**	**55.3%**	**0%**

Lancet *J Clin Oncol* 2018; DiNardo *N Engl J Med* 2020

Targeted Therapies

Differentiation Syndrome Risk

IDH1 inhibitors

- **Ivosidenib**
  - Newly diagnosed AML (age ≥75) and R/R AML, R/R MDS
  - Ph 1 study, untreated AML age ≥75, n=34, CR/CRh 42%, median OS 12.6mo → R/R AML, n=179, CR/CRh 30%, median OS 8.8mo
  - Ph 1 study, R/R MDS, n=18, CR 38.9%, med CR duration NR (1.9-80.8+ mo)

- **Olutasidenib**
  - Ph 1/2 study, R/R AML, n=147, CR/CRh 35%, median OS 11.6mo

IDH2 inhibitor

- **Enasidenib**
  - Ph 1/2 study, R/R AML, n=239, ORR 40%, CR 19%, median OS 9.3mo

IDH2 inhibitor

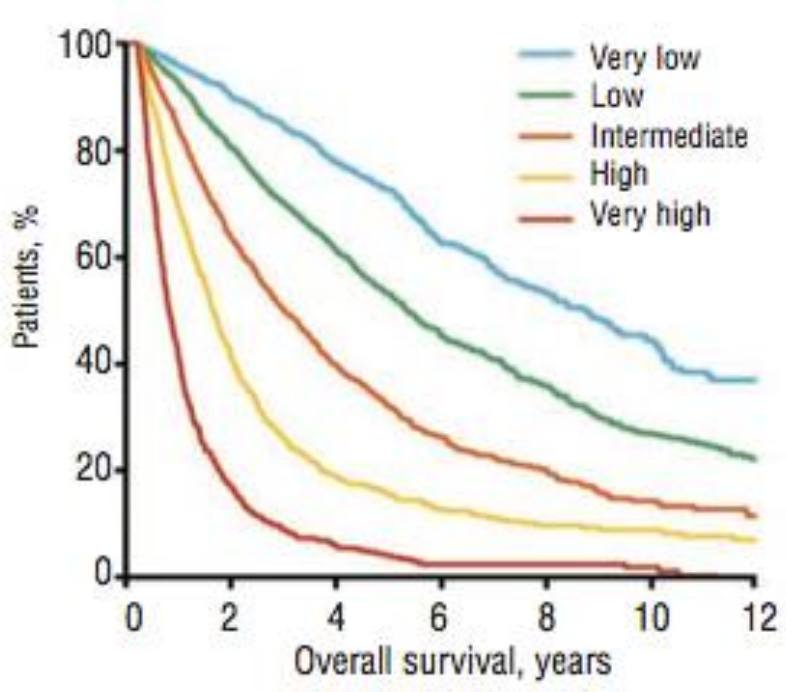
- **Revumenib**
  - Ph 1/2 study, R/R acute leukemia (adult+pediatric) with *KMT2A*-r, n=104, CR+CRh 21.2%, ORR 63.2%, median duration 6.4mo

Roboz *Blood* 2020, DiNardo *N Engl J Med* 2018, de Botton *Blood Adv* 2023, Stein *Blood 2017*; Issa *J Clin Oncol* 2025

MDS Updates

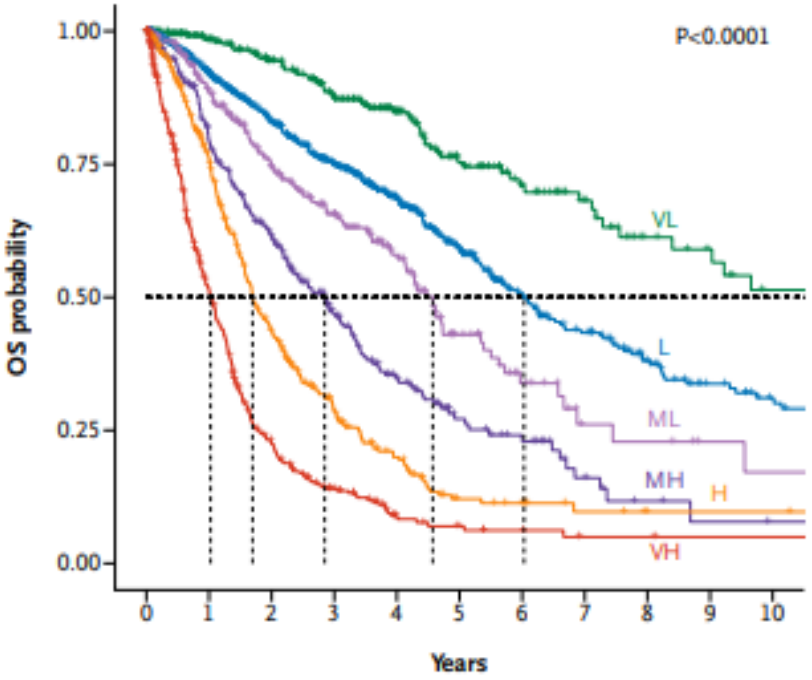
MDS Risk Stratification (Staging)

IPSS-R



Cytogenetic Risk
Bone marrow blast %
Hemoglobin
Platelet count
Absolute Neutrophil Count

IPSS-M



Cytogenetic Risk
Bone marrow blast %
Hemoglobin
Platelet count
(Absolute Neutrophil Count)

Mutation data

ASXL1*, *CBL*, *DNMT3A*, *ETV6*, *EZH2*, *FLT3*, *IDH2*, *KRAS*, *MLL*^{PTD}, *NPM1*, *NRAS*, *RUNX1*, *SF3B1*, *SRSF2*, *TP53*^{multihit}, *U2AF1

Greenberg *Blood* 2012, Bernard *NEJM Evidence* 2022

Approved MDS Therapies

Lower Risk MDS

- Erythropoiesis Stimulating Agents (ESA)
- Lenalidomide (2005)
- Luspatercept (2020)
- Ivosidenib (2023)
- Imetelstat (2024)
- Hypoplastic MDS: Immunosuppressive Therapy (IST)*

Higher Risk MDS

- Hypomethylating Agents aka HMAs
    - Azacitidine, IV or SQ (2004)
    - Decitabine, IV (2006)
    - Decitabine/Cedazuridine, PO (2020)
- Ivosidenib (2023)
- Hematopoietic Stem Cell Transplantation

MDS Treatment Question 1: Luspatercept vs ESA for lower-risk MDS?

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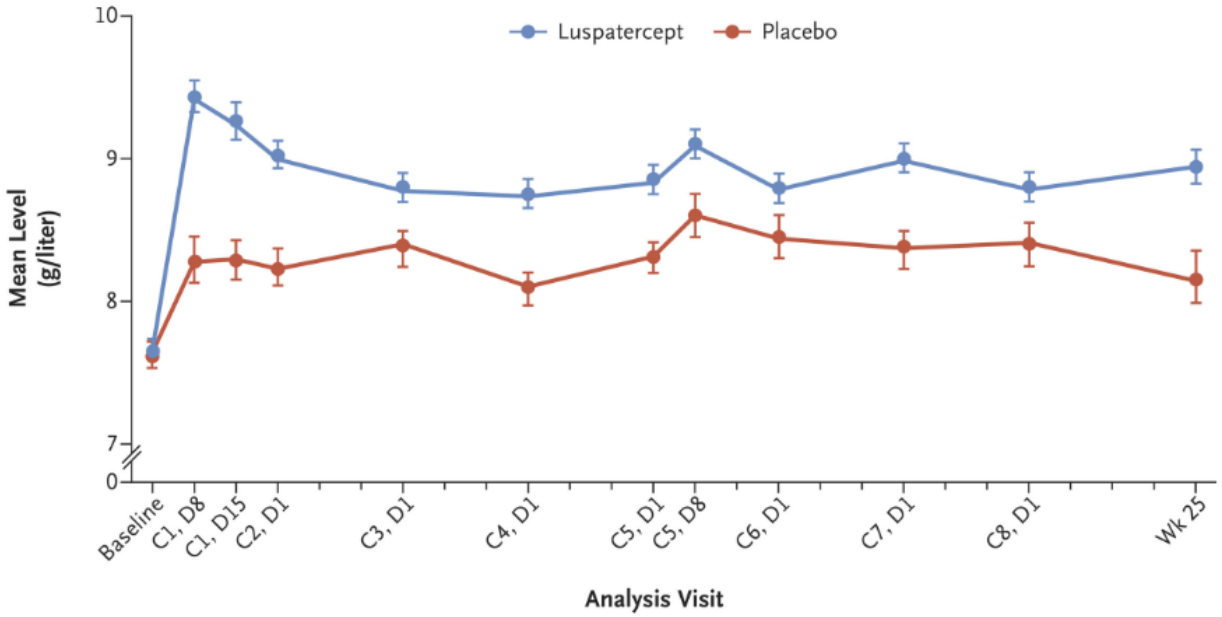
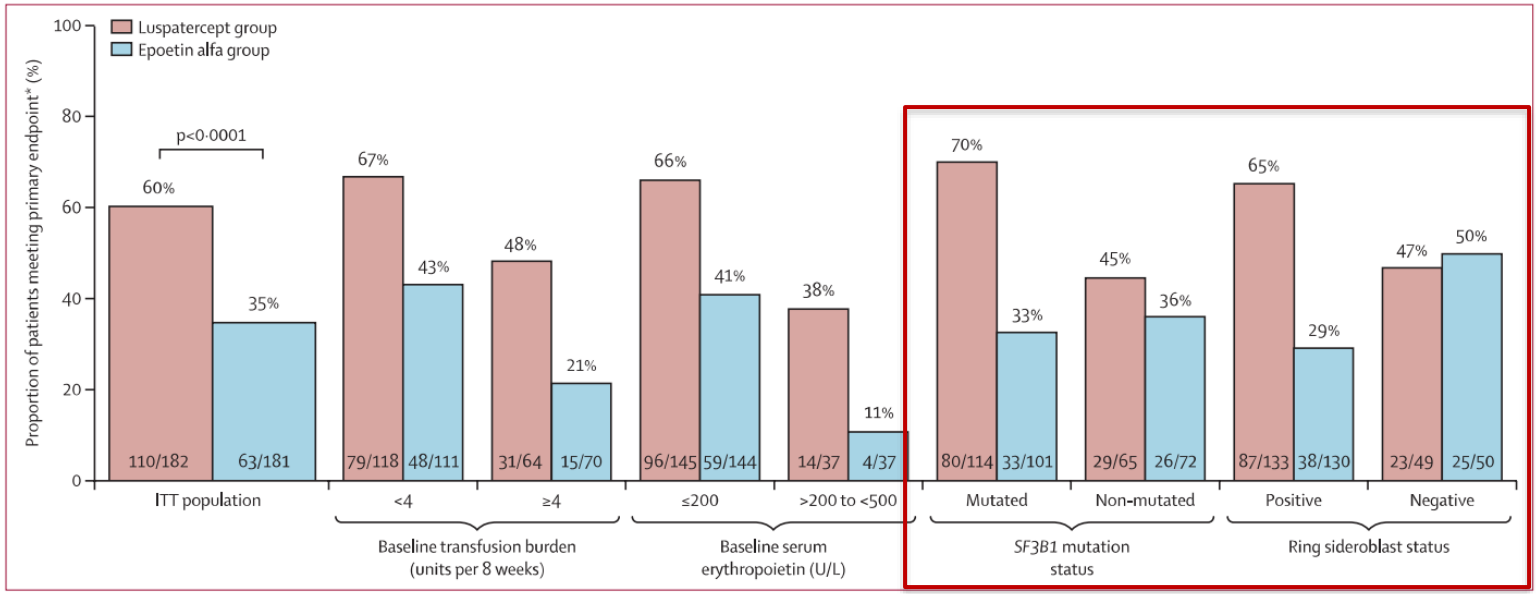
MEDALIST
Luspatercept vs. Placebo
Lower-risk MDS-RS, R/R ESA

- RBC-TI (8wk) 38 vs 13%, *p*<0.001
- RBC-TI (48wk) 33 vs 12%, *p*<0.001
- OS similar in both groups (46+ mo)



COMMANDS
Luspatercept vs. ESA
Lower-risk MDS, untreated

- RBC-TI (12wk, 24 wk) 59 vs 31%, 48 vs 29%
- RBC-TI (≥1yr, ≥1.5yr) 45 vs 28%, 30 vs 14%
- **Significant benefit to *most* subgroups (*SF3B1*, not RS-neg)**



Fenaux *N Engl J Med* 2020; Platzbecker *The Lancet* 2023

MDS Treatment Question 2: Luspatercept vs Imetelstat vs ESA for lower-risk MDS, *SF3B1*-WT, RS-neg?

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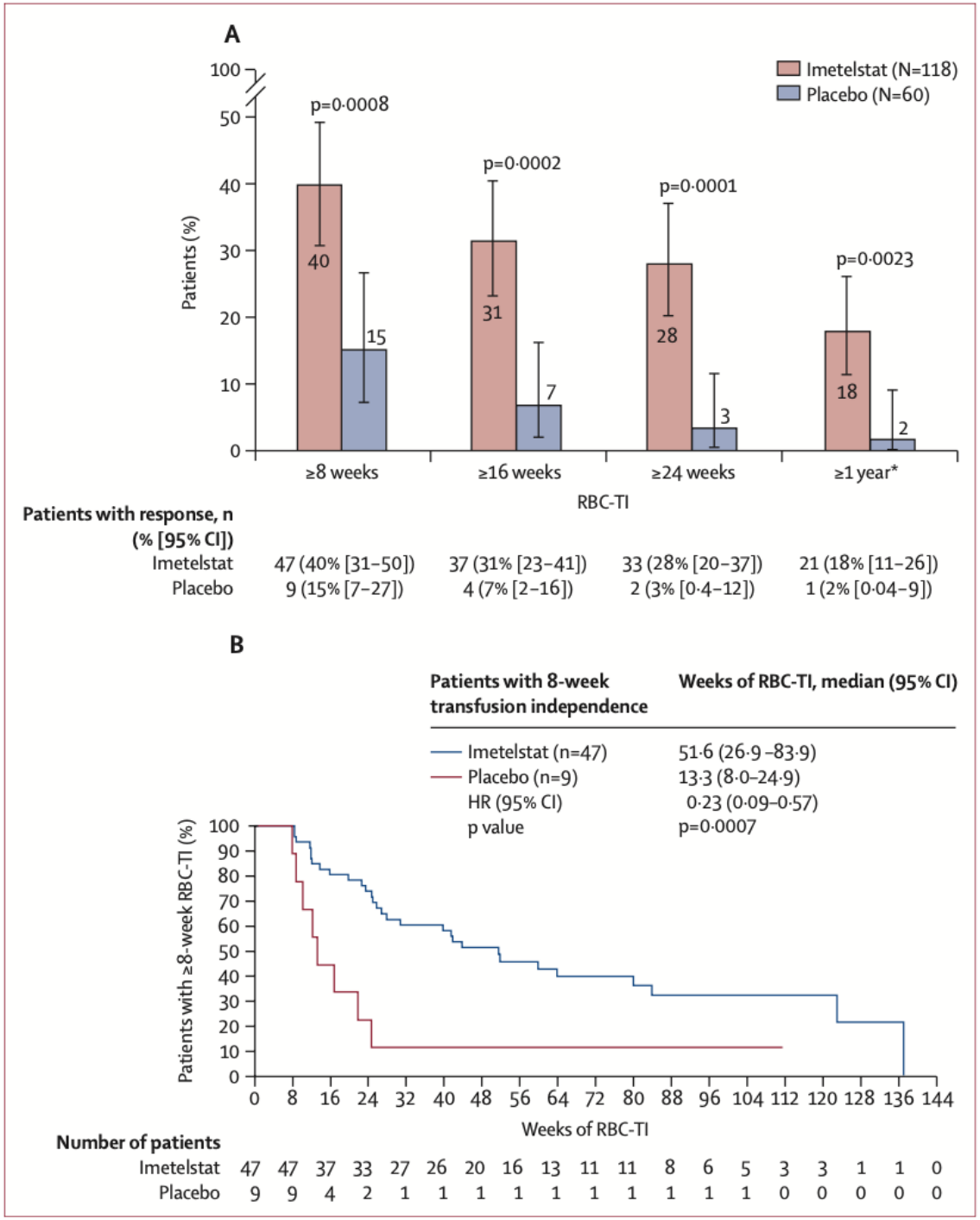
IMerge
Imetelstat vs. Placebo
Lower-risk MDS-RS, R/R ESA

- RBC-TI (8wk) 40 vs 9%, *p*=0.0008
- RBC-TI (24wk) 28 vs 3%, *p*=0.0001
- RBC-TI (8wk, 24wk) with prior therapy:
  - ESA: 40%, 28%
  - ESA ineligible: 36%, 14%
  - Luspatercept: 29%, 20%
  - Lenalidomide: 23%, 12%

- ***Toxicity (Gr 3/4)***
  - ***Neutropenia 68 vs 3%***
  - ***Thrombocytopenia 62 vs 8%***
  - ***Median duration 1.9wk, 1.4wk***



Platzbecker *The Lancet* 2024

MDS Treatment Question 3:
HMA monotherapy vs HMA/Venetoclax for higher-risk MDS?

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Phase 1b, Garcia (ASH 2021, 2023)

- Aza/Ven, treatment-naïve, HR MDS
- n=107, median OS 26 mo
- CR 29.9%, duration CR 16.6mo

Phase 1b, Zeidan (Am J Hematol 2023)

- Aza/Ven, R/R MDS
- n=37, median OS 12.6 mo, ORR 39%

VERONA Phase 3 Study

- Results pending
- Planned n=500, treatment-naïve, HR MDS
- 1:1 Aza/Ven vs Aza/Placebo

If MDS/AML category (>10% blasts) and patient is robust/fit, favor HMA/Ven, especially if goal is transplant

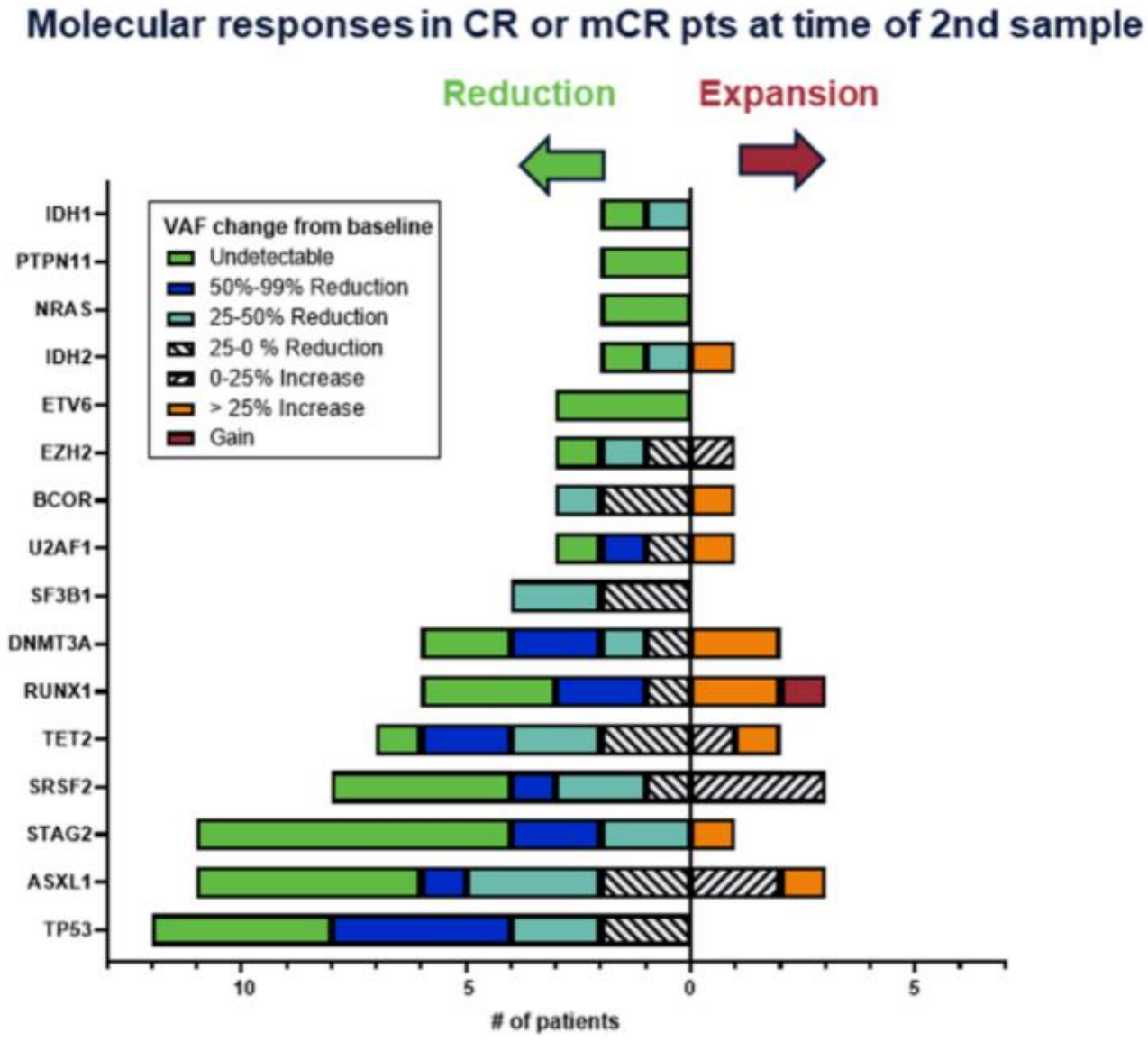

Figure. VAF dynamics in samples collected from patients in CR or mCR at the time of sample acquisition compared to baseline samples collected from bone marrow or the peripheral blood.

Garcia ASH 2021

“Failed” Drugs in Higher-Risk MDS

- Most experimental treatments are added to an HMA “backbone”
  - Need to balance increased efficacy with more toxicity

- Phase 3 trials that did not find improved outcomes:
  - Pevonedistat, NEDD8 inhibitor, for higher-risk MDS, CMML, AML
  - Magrolimab, CD47 antibody, higher-risk MDS and AML
  - APR-246, restores p53 function, for TP53 mutated higher-risk MDS
  - Sabatolimab, TIM3 inhibitor, higher-risk MDS
  - Tamibarotene, synthetic retinoid, higher-risk MDS

Summary

- **Genetic mutations matter**
  - Lower/irrelevant blast thresholds if an AML-defining lesion is present
  - Absolutely needed for AML and MDS staging

- **AML therapies**
  - Many drug approvals for AML since 2010, after 40+ years of minimal options
  - 7+3 remains the standard induction chemo for younger/fit patients, with drugs added to this backbone for added efficacy
  - Hypomethylating Agent (HMA) + Venetoclax is the most transformative regimen for AML since 7+3 – potentially beneficial for most patients with AML (elderly/unfit)

- **MDS therapies**
  - Luspatercept > ESA for *SF3B1*-mutated or RS+ (unclear for *SF3B1*-WT or RS-neg)
  - Higher-risk MDS remains challenging to treat

THANK YOU!

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