Current and Emerging Therapies Acute Myeloid Leukemias and Myelodysplastic Syndromes

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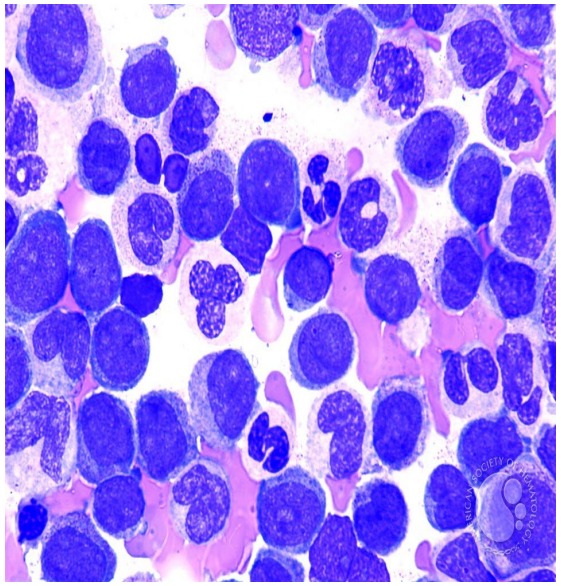
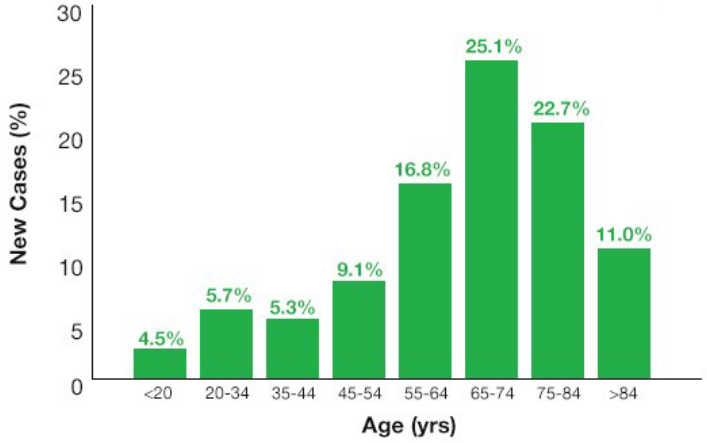
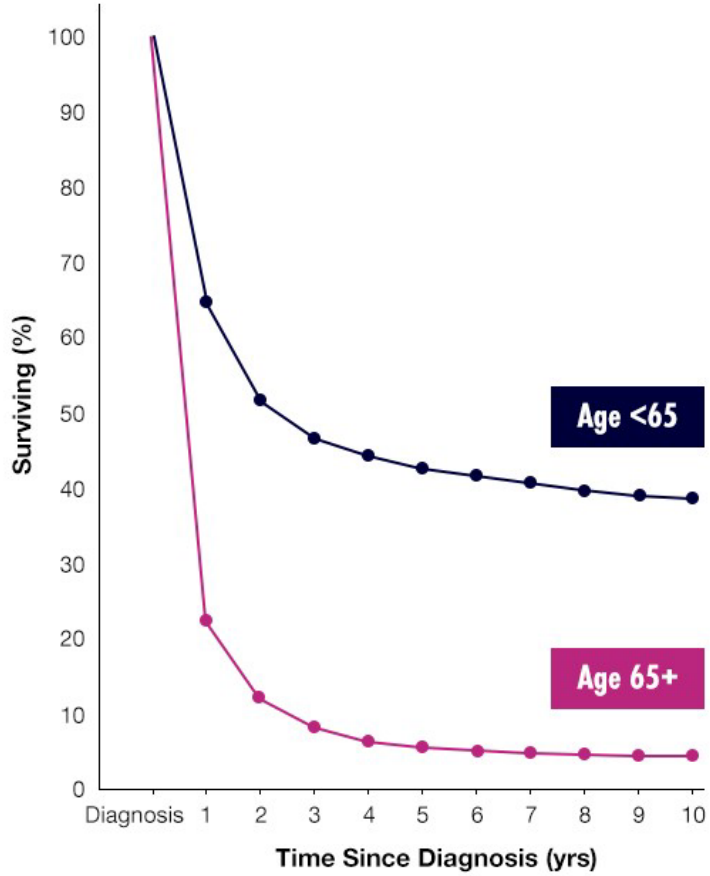
Acute Myeloid Leukemia







. American Society of Clinical Oncology. http://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/statistics. Accessed July 23, 2019

Diagnosis and work up for AML

Tests to establish the diagnosis	
Complete blood count and differential count[a]	
Bone marrow aspirate[b]	
Bone marrow trephine biopsy[c]	
Immunophenotyping by flow cytometry (see Table 5)	
Genetic analyses	Results preferably available within
Cytogenetics[d]	• 5-7 days
Screening for gene mutations required for establishing the diagnosis and to identify actionable therapeutic targets[e]	
• *FLT3*,[f] *IDH1*, *IDH2*	• 3-5 days
• *NPM1*	• 3-5 days
• *CEBPA*,[g] *DDX41*, *TP53*; *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*	• 1st cycle
Screening for gene rearrangements[h] • *PML*::*RARA*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1*, *KMT2A* rearrangements, *BCR*::*ABL1*, other fusion genes (if available)	• 3-5 days
Additional genes recommended to test at diagnosis[i] • *ANKRD26*, *BCORL1*, *BRAF*, *CBL*, *CSF3R*, *DNMT3A*, *ETV6*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *NRAS*, *NF1*, *PHF6*, *PPM1D*, *PTPN11*, *RAD21*, *SETBP1*, *TET2*, *WT1*	
Medical history	
Demographics and medical history[j]	
Detailed family history[k]	
Patient bleeding history[l]	
Analysis of comorbidities	
Additional tests and procedures	
Complete physical examination[m]	
Performance status (ECOG/WHO score)	
Geriatric assessment[n] (optional)	
Biochemistry, coagulation tests[o]	
Hepatitis A, B, C; HIV-1 testing; CMV, EBV, HSV, VZV	
Serum pregnancy test[p]	
Eligibility assessment for allogeneic HCT (incl. HLA-typing)[q]	
Chest x-ray, 12-lead electrocardiogram, echocardiography or MUGA (on indication)	
Computed tomography of the chest (on indication)[r]	
Lumbar puncture (on indication)[s]	
Information on oocyte and sperm cryopreservation[t]	
Biobanking[u]	

- Assure diagnosis.
- Obtain all information for risk stratification.
- Tailor treatment and baseline testing prior to treatment.
- **AML treatment is not Emergency in most of cases.**

Hartmut Döhner et al; Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. *Blood* 2022; blood.2022016867

AML Risk Stratification by Cytogenetics and Molecular Abnormalities (ELN 2022 Recommendations)

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]

Hartmut Döhner et al; Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. *Blood* 2022; blood.2022016867

Therapeutic Decision Making 2024

Induction Chemotherapy

Non induction treatment

Upfront Treatment of De Novo AML in patients eligible for Intensive chemotherapy

Who is eligible?

1. Non P53 MT AML
2. Absence of comorbidities
3. Not frail

Good risk AML

Induction: 3+7+GO

Consolidation: HiDAC/IDAC+/-GO

FLt-3 MT AML

Induction: 3+7 + Midostaurin

Consolidation : Allo-SCT

Maintenance post allo SCT: Sorafenib

Intermediate/poor risk

Induction: 3+7

Consolidation: allo SCT

Maintenance: oral azacitidine if no transplant

MT: mutation
GO: Gemtuzumab Ozogamicin
Allo-SCT: allogeneic stem cell transplant
HiDAC: high dose cytarabine
IDAC: intermediate dose cytarabine

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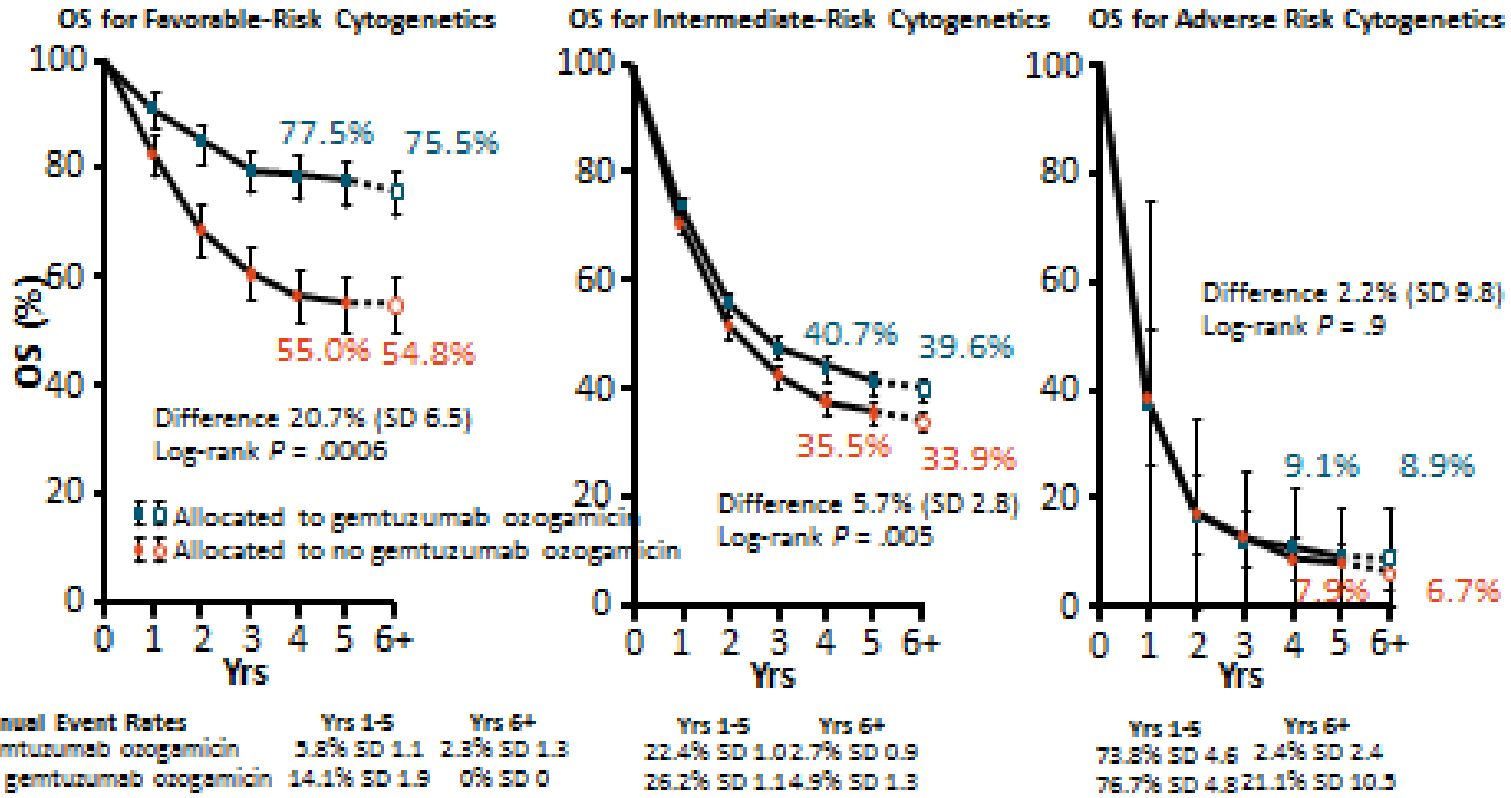
Addition of Gemtuzumab Ozogamicin to Induction Therapy: Meta-analysis of 5 Randomized Trials



Annual Event Rates	Yrs 1-5	Yrs 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No gemtuzumab ozogamicin	14.1% SD 1.9	0% SD 0

	Yrs 1-5	Yrs 6+
	22.4% SD 1.0	2.7% SD 0.9
	26.2% SD 1.1	4.9% SD 1.3

	Yrs 1-5	Yrs 6+
	73.8% SD 4.6	2.4% SD 2.4
	76.7% SD 4.8	21.1% SD 10.5

Hills RK, et al. Lancet Oncol. 2014;15:986-996.

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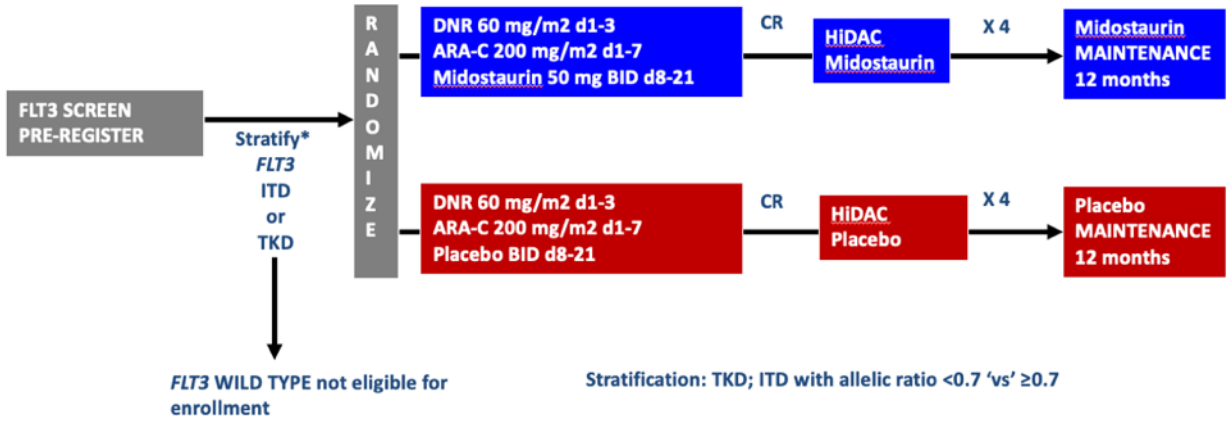
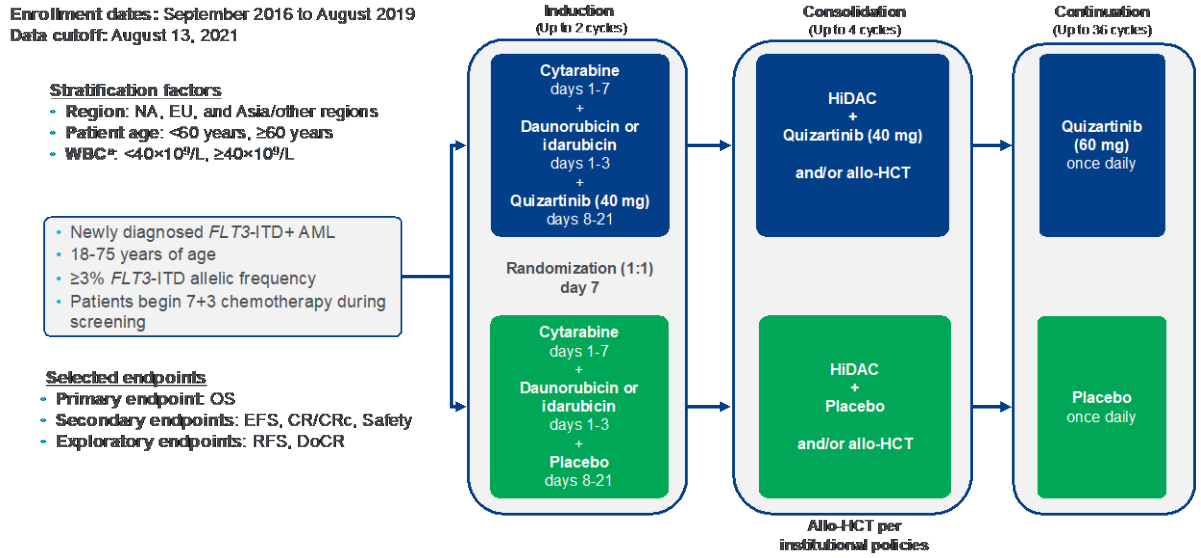
Comparing Ratify and Quantum-First: design/eligibility

RATIFY/C10603



QuANTUM-First



Primary endpoint: OS

- 3277 patients were screened, 717 were randomized (555 with FLT3-ITD)
- FLT3-ITD and TKD mutations
- Median age 48 years (range 18-60.9)
- Median follow-up 59 months
- HSCT was an off-protocol therapy
- maintenance given post-consolidation only
- MRD not collected

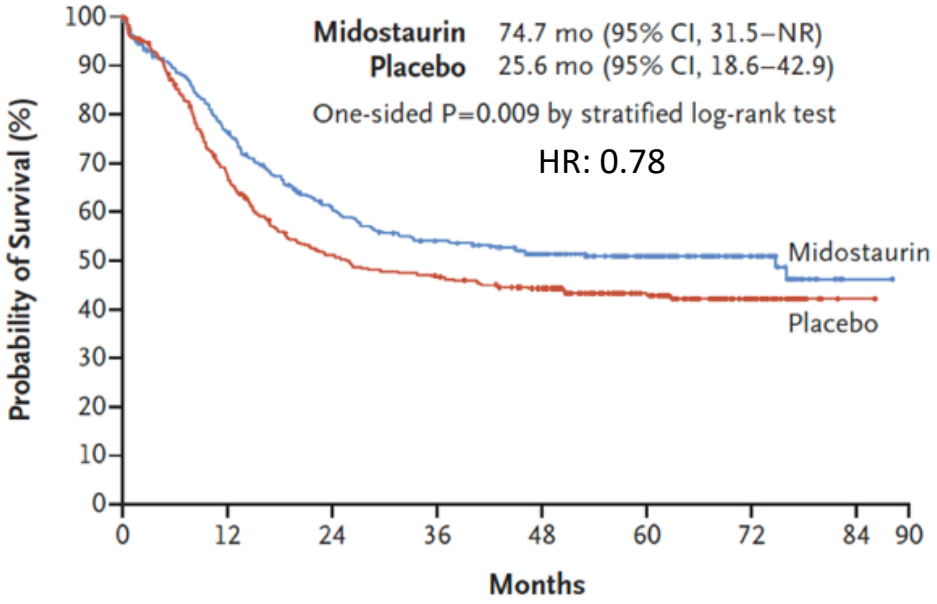
Primary endpoint: OS

- 3468 patients were screened, and 539 with FLT3-ITD were randomized
- FLT3 ITD only.
- Median follow-up 39 months
- Median age 56 (range 20-75)
- HSCT allowed on study
- maintenance given both post-HSCT and post-consolidation
- prospective monitoring of MRD

Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583

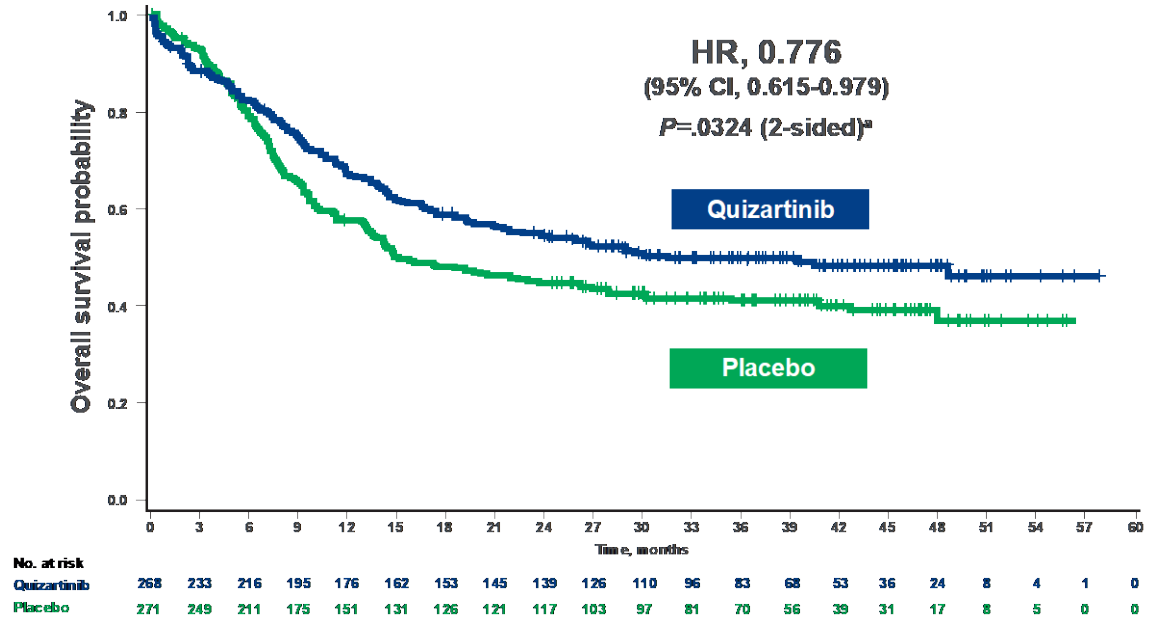
Response and survival

	CR
Midostaurin	68%
Placebo	61%



- 60-day mortality: not reported

	CR	CR/CRi
Quizartinib	54.9%	71.6
Placebo	55.4%	64.9

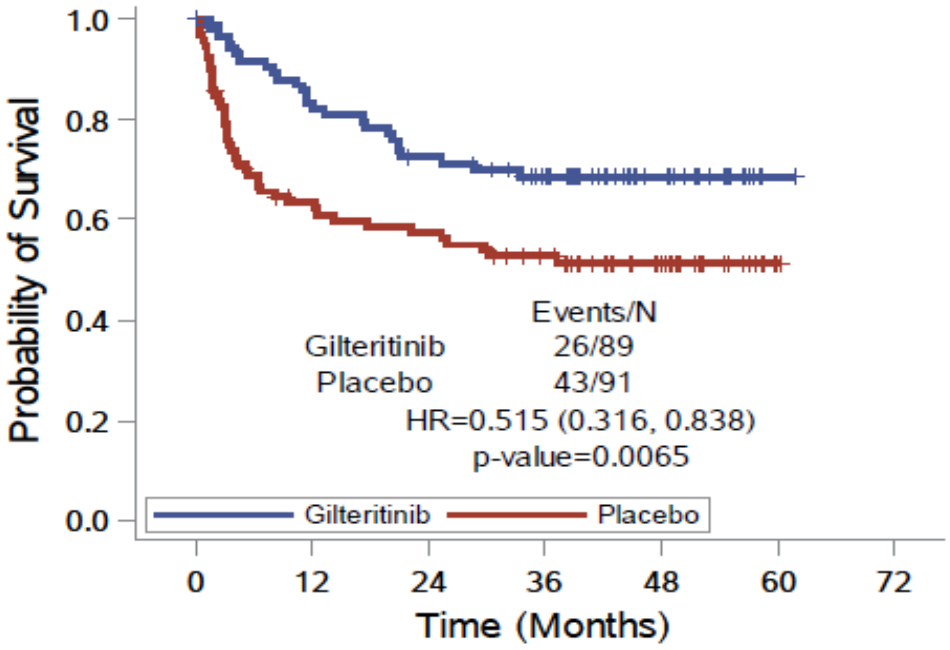


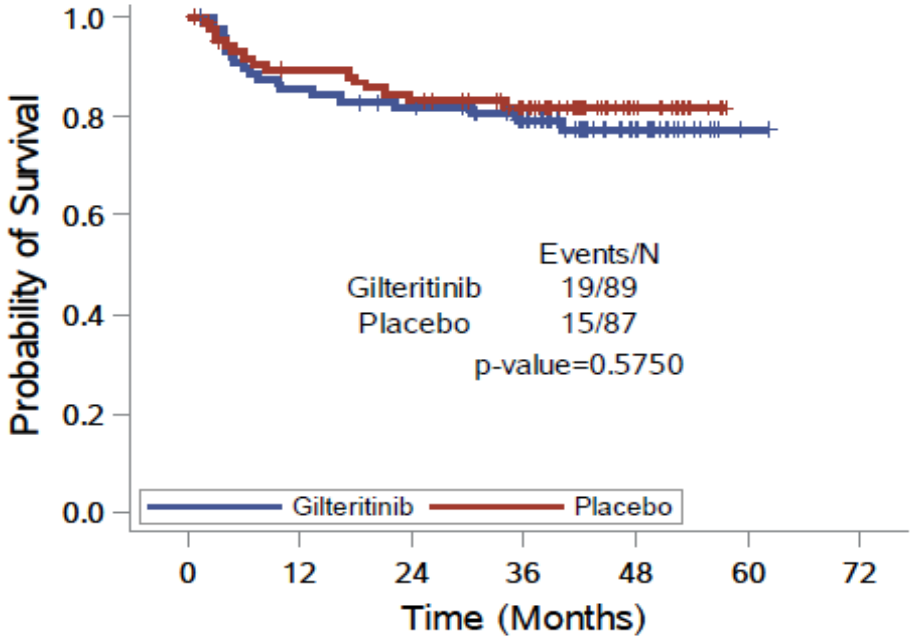
- 60-day mortality: quizartinib 7.5%, placebo 4.9% (mostly infections)
- ANC recovery was 7 days longer in quiz arm; platelets 2 days longer in quiz arm
- any grade QT prolongation: quizartinib 13.6%, placebo 4.1%
- 2 cases of cardiac arrest or VT in quiz arm (none in placebo)

Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583

BMT CTN
Blood & Marrow Transplant
Clinical Trials Network

Effect of detectable MRD6 on RFS by study arm





Levis MJ, et al. EHA 2023 LBA LB2711

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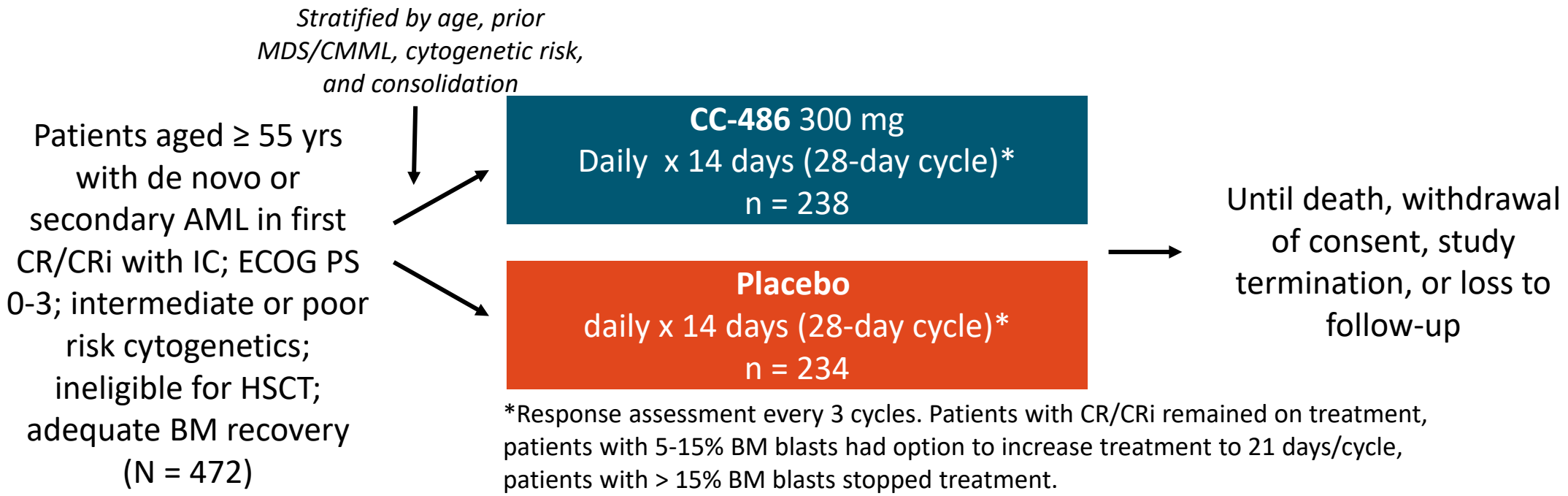
Phase III QUAZAR AML-001: CC-486 as Maintenance Therapy in First-Remission AML—Study Design

- Multicenter, randomized, placebo-controlled, double-blind, phase III study



- Primary endpoint: overall survival
- Key secondary endpoints: relapse-free survival, health-related QoL, and safety

Wei. ASH 2019. Abstr LBA_3.

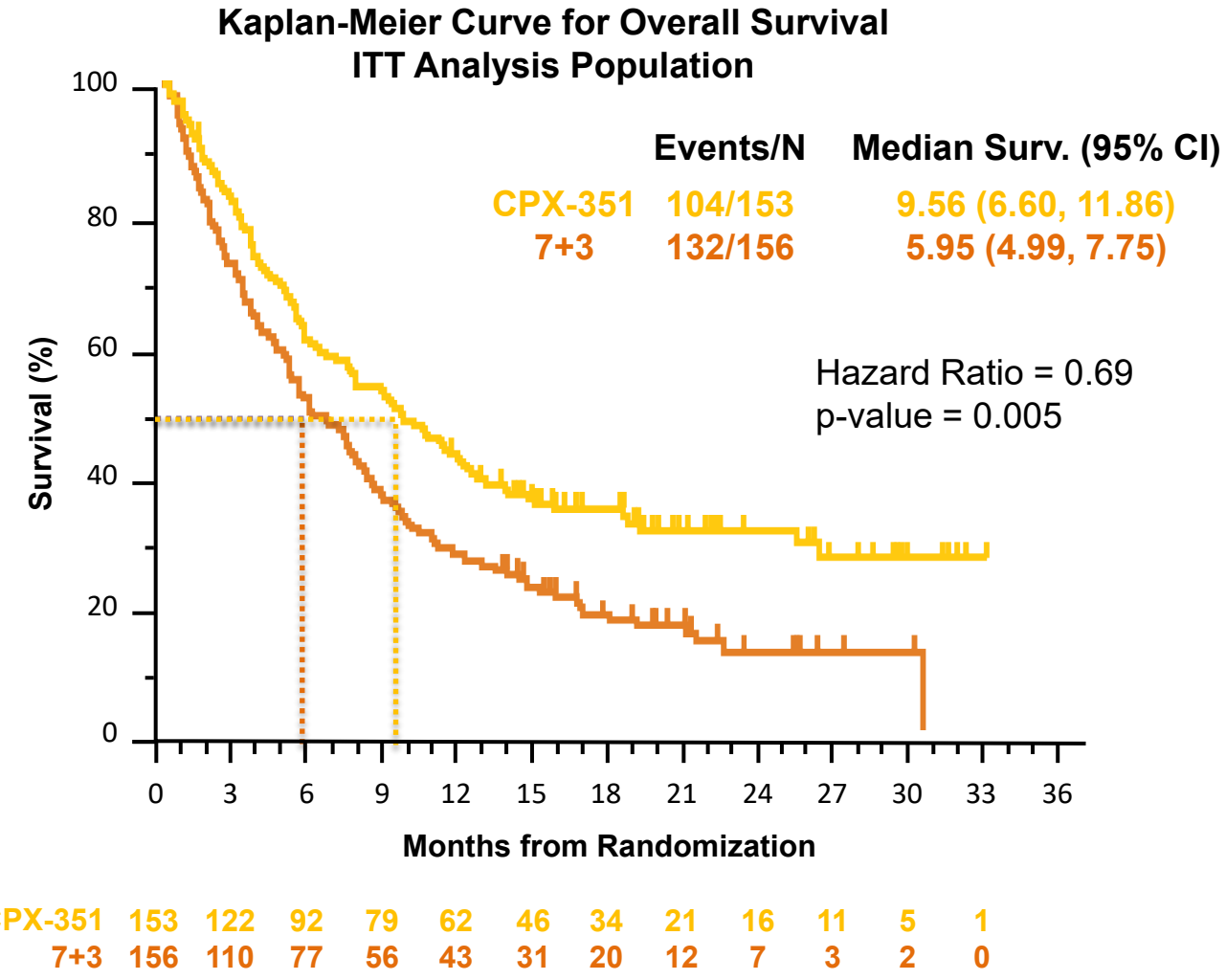
QUAZAR AML-001: Survival

Outcome	CC-486 n = 238	Placebo n = 234
Median OS, mos (95% CI)	24.7 (18.7-30.5)	14.8 (11.7-17.6)
▪ Stratified *P* value	.0009	
▪ Stratified HR (95% CI)	0.69 (0.55-0.86)	
1-yr survival rate, % (95% CI)	73 (67-78)	56 (49-62)
2-yr survival rate, % (95% CI)	51 (44-57)	37 (31-43)
Relapse-free survival, mos (95% CI)	10.2 (7.9-12.9)	4.8 (4.6-6.4)
▪ Stratified *P* value	.0001	
▪ Stratified HR (95% CI)	0.65 (0.52-0.81)	

- Median follow up: 41.2 months
- 1-yr relapse rate was 53% (95% CI: 46-59) in CC-486 arm vs 71% (95% CI: 65-77) in placebo arm

Wei. ASH 2019. Abstr LBA_3.

CPX-351 Improves Overall Survival in secondary AML



Lancet J. J Clin Oncol. 2018 Sep 10;36(26):2684-2692.

Upfront Treatment of De Novo AML in patients not eligible for Intensive chemotherapy

Who is ineligible?

1. P53 MT AML
2. Age > 75
3. Major comorbidities
4. frail

Intermediate/poor risk

Azacitidine + Venetoclax

FLt-3 MT AML

Azacitidine + Venetoclax

Or

Azactidine+Flt-3 inhibitor

P53 MT AML
Clinical trials
APR-246
Magrolimab

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Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

VIALE-A Study Design (NCT02993523)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment

Randomization 2:1
N=433*

Venetoclax + Azacitidine (N=286)
Venetoclax 400 mg PO, daily, days 1–28 +
Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine (N=145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors: Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up: Cycle 1 ramp-up Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
Cycle 2 → Day 1-28: 400 mg

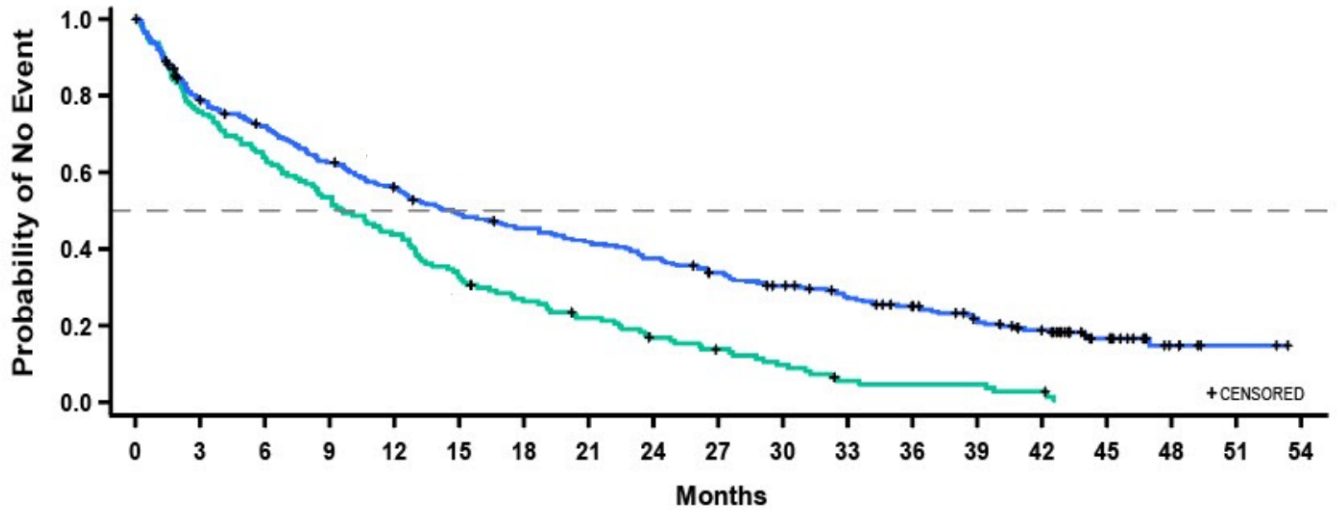
* 2 patients were not stratified by cytogenetic risk. They were excluded from efficacy analysis but included in the safety analysis. 6 patients who did not receive treatment were excluded from the safety analysis set.

AML: Acute myeloid leukemia; CHF: Congestive heart failure; CNS: Central nervous system; CR: Complete remission; CRi: CR+ incomplete marrow remission; CRh: CR+ incomplete hematologic recovery; DCLO: diffusion lung capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; FEV1 : Forced expiratory volume; HMA: Hypomethylating agent; NCCN: National Comprehensive Cancer Network

4

CD DiNardo et al. N Engl J Med 2020;383:617-629.

Longer term follow up of VIALE-A



Patients at Risk

Ven+Aza	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0
Pbo+Aza	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0	0	0	0

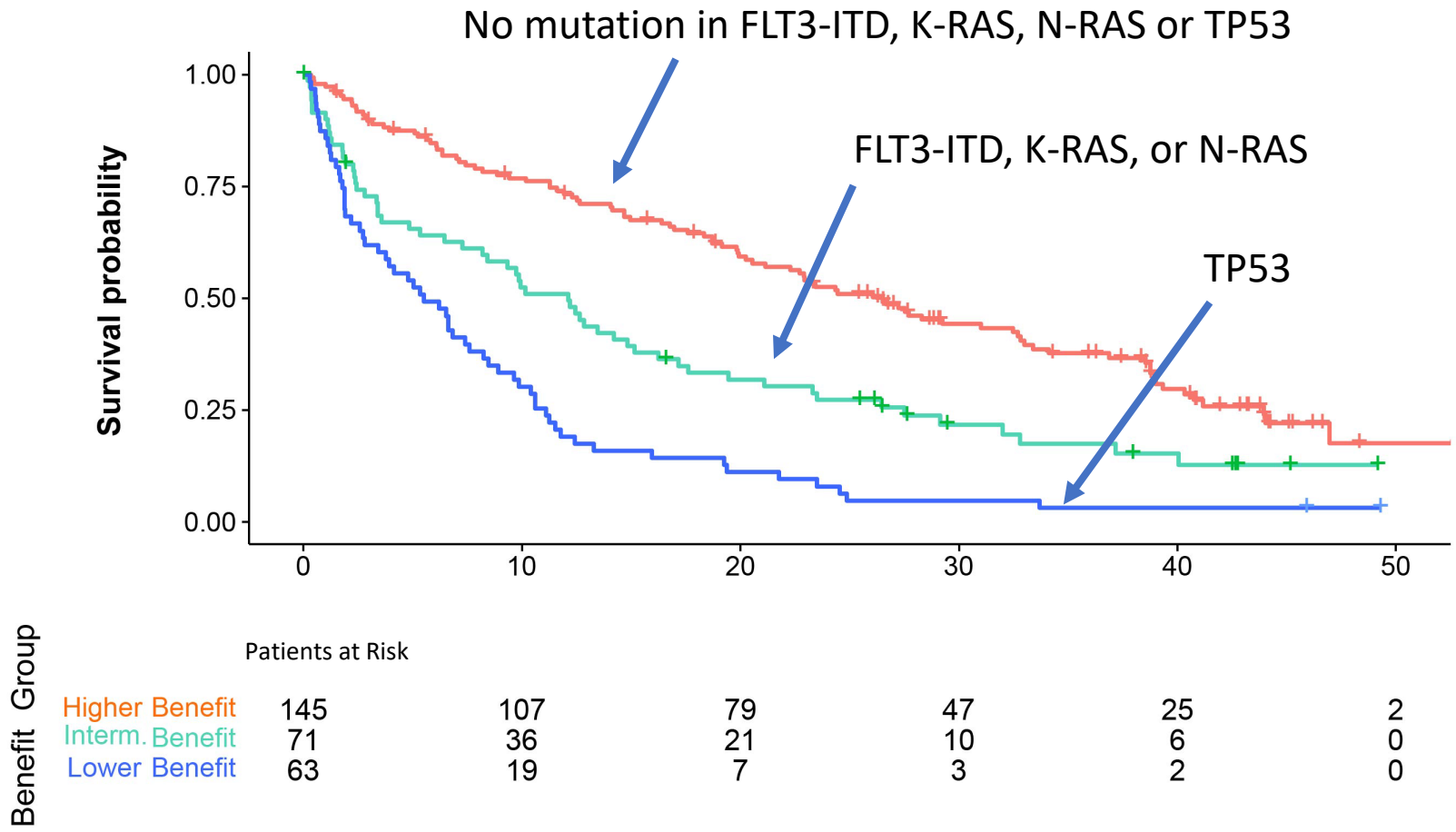
	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza	222/286 (77.6)	14.7 (12.1 - 18.7)
Pbo+Aza	138/145 (95.2)	9.6 (7.4 - 12.7)

Hazard ratio: 0.58 (95% CI, 0.465 - 0.723), P < 0.001

HR reduction from 0.66 (95% CI, 0.52 - 0.85) at 75% OS analysis

Pratz KW, et al. ASH 2022 #219

Lower intensity induction—predictors of benefit to VEN-AZA



Pratz KW, et al. ASH 2022 #219

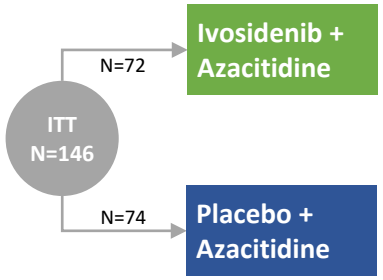
AGILE study: Azacitidine + Ivosidenib/Placebo

Key Eligibility

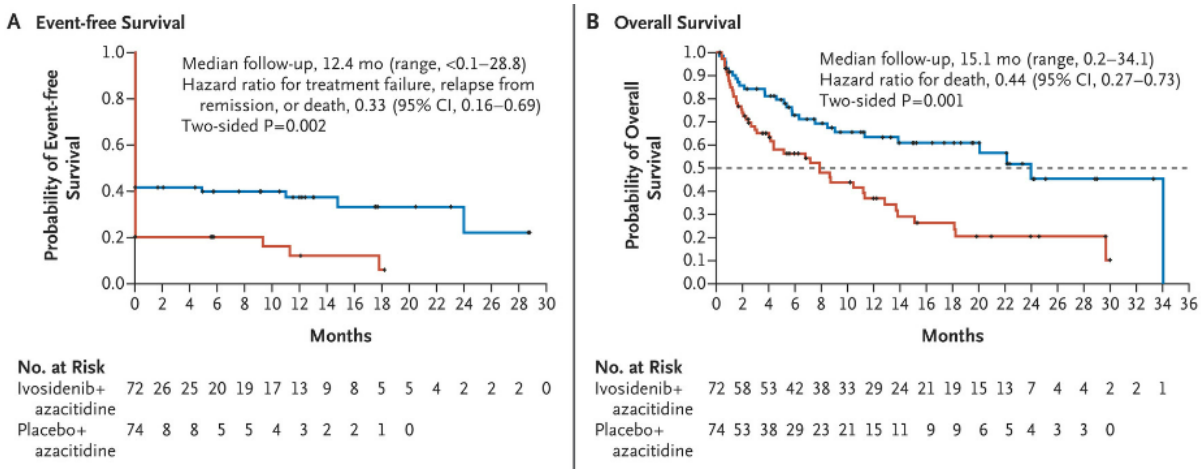
- Newly diagnosed AML with an *IDH1* mutation ineligible for intensive IC
- Aged ≥75 years
- ECOG PS 0-2

Stratification

- Stratified according to geographic region and disease status (primary vs secondary AML)



	Ivosidenib + azacitidine	Azacitidine + placebo (control)	HR for death
Median OS (months)	**24 months**	**7.9 months**	**0.44** (95% CI, 0.27-0.73); *P*=0.001
Median EFS (at median follow-up of 12.4 months)	**37%**	**12%**	**0.33** (95% CI, 0.16-0.69); *P*=0.002
CR	**47%**	**15%**	-



Montesinos P, et al. *N Engl J Med.* 2022;386(16):1519-1531

Doublet Therapy in *IDH* Mutated AML

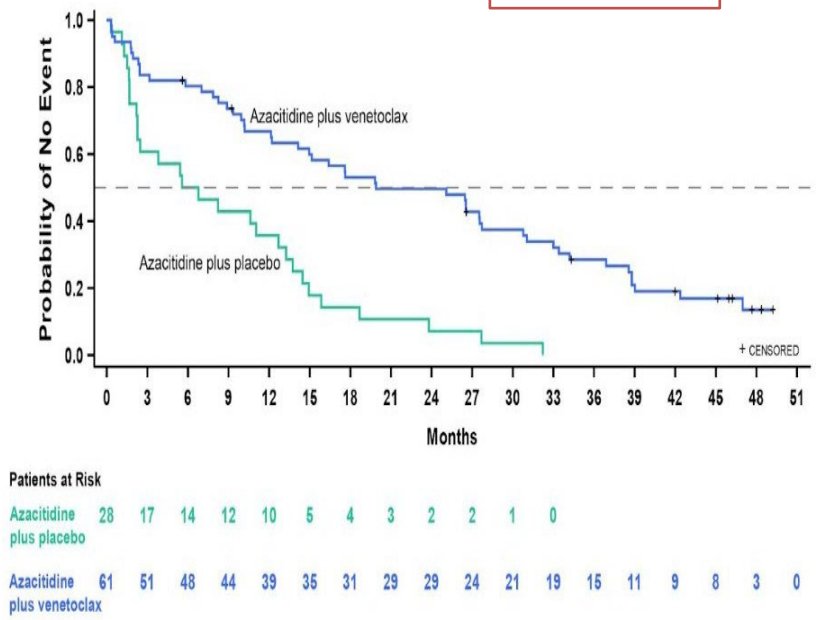
IDH is mutated in ~20% of AML

VEN and IDHi combinations with HMA have been shown to be effective therapies

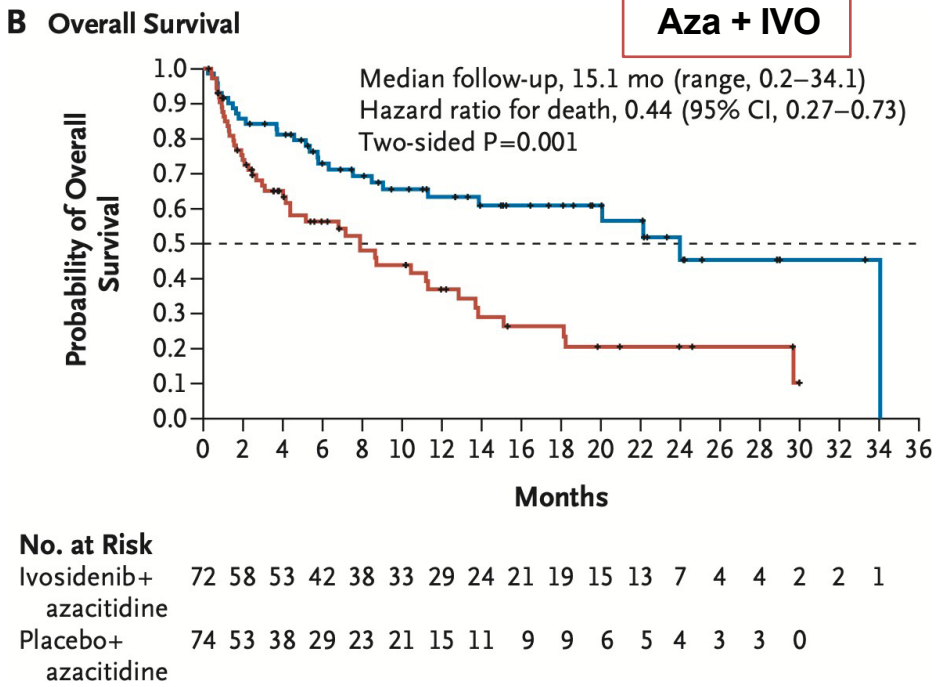
Most often seen in older patients and with diploid cytogenetics and frequently with *NPM1* mutations

IDH2 (12-15%) mutations more commonly seen than *IDH1* (6-8%) mutations

VIALE-A: Aza + VEN



AGILE: Aza + IVO

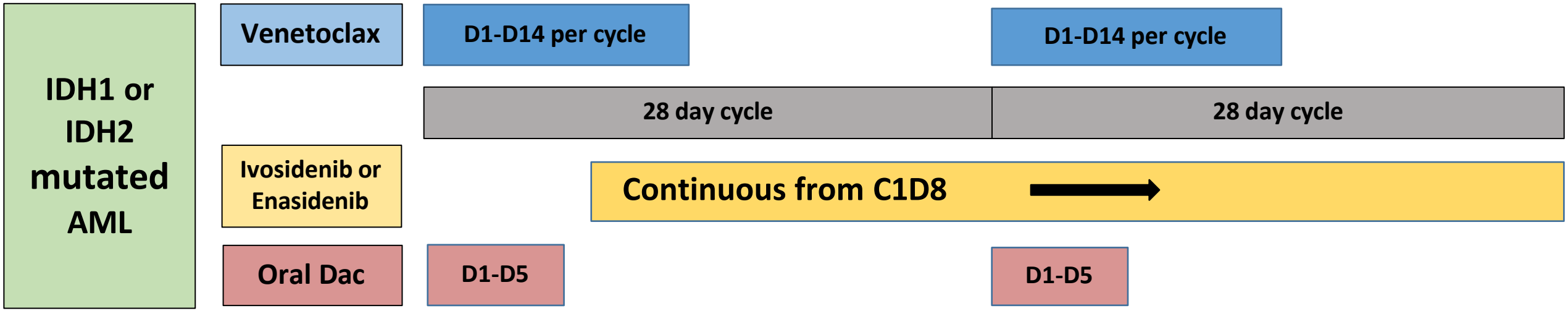


VIALE-A: Aza +VEN
OS 19.9 mos; CRc 56.6% (*IDH1*); 85% (*IDH2*)

Median OS of 24.0 months in patients with *IDH1*; CRc 54%

Pratz et al. Blood. Dec 2022
Montesinos et al. NEJM. 2022
DiNardo et al. NEJM 2020

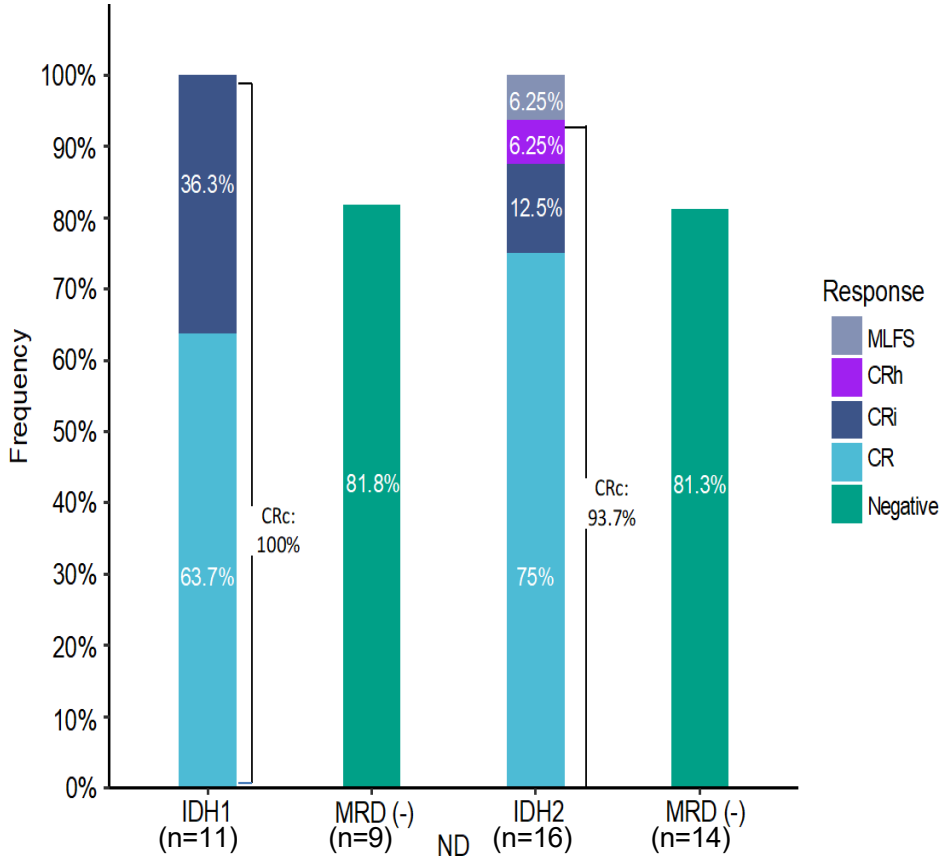
ASTX727 + Venetoclax + IDHi in Newly Diagnosed and Relapsed Refractory IDH mutated AML: ASH 2023 Abstract 968

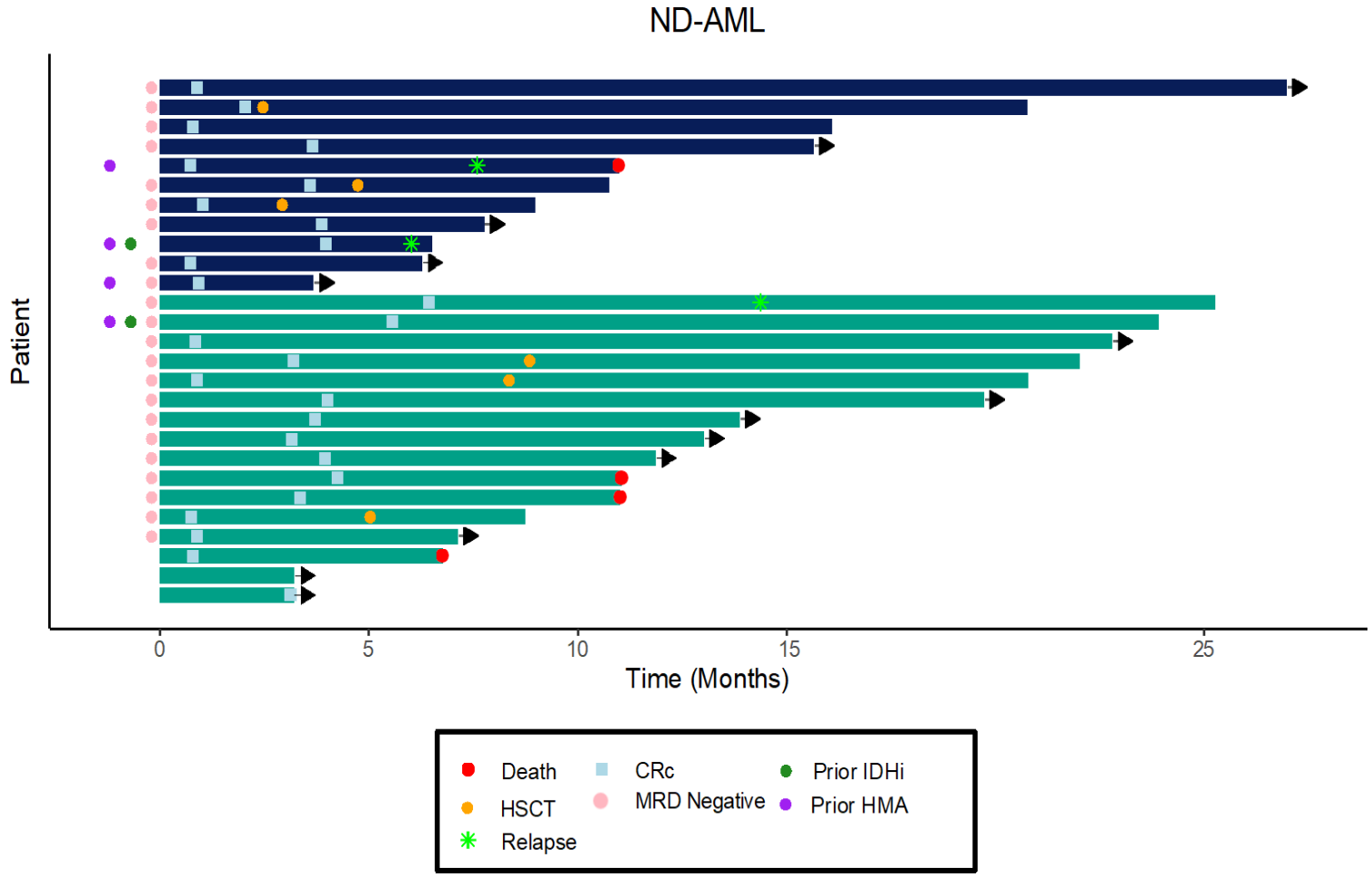


Selected RP2D Combination Doses
Arm A: ASTX727 (D1-5) + VEN 600 mg (D1-14) + Ivosidenib 500 mg daily (D8 onwards)
Arm B: ASTX727 (D1-5) + VEN 400 mg (D1-14) + Enasidenib 100 mg daily (D8 onwards)

Friese et al. J Clin Pharmacology. 2017
Lachowiez et al. Blood Advances. 2022

CRc Rates in ND-AML





Overall CRc 96.2% with 85% MRD negative by multiparameter flow cytometry

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4. frail

Intermediate/poor risk

Azacitidine + Venetoclax

FLt-3 MT AML

HMA+ Venetoclax+ Flt3-

P53 MT AML
Clinical trials
APR-246
Magrolimab

Decitabine, Venetoclax, Quizartinib in FLT3-ITD AML

- 50 pts-10 newly Dx; 40 R-R (prior FLT3i 85%, prior allo SCT 40%)
- DAC 20mg/m^2/Dx10→5; QUIZ 30-40mg/D; VENx14→7. Day 14 BM and stop if marrow CR

Parameter	Newly Dx	R-R
% CR-CRi	100	33
% CR	70	13
Median OS (mos)	NR	7.1
% 1-yr OS	-	22

Yilmaz. Blood 142: abst 158; 2023

Upfront Treatment of De Novo AML in patients not eligible for Intensive chemotherapy

Who is ineligible?

1. P53 MT AML
2. Age > 75
3. Major comorbidities
4. frail

Intermediate/poor risk

Azacitidine + Venetoclax

FLt-3 MT AML

Azacitidine + Venetoclax

Or

Azactidine+Flt-3 inhibitor

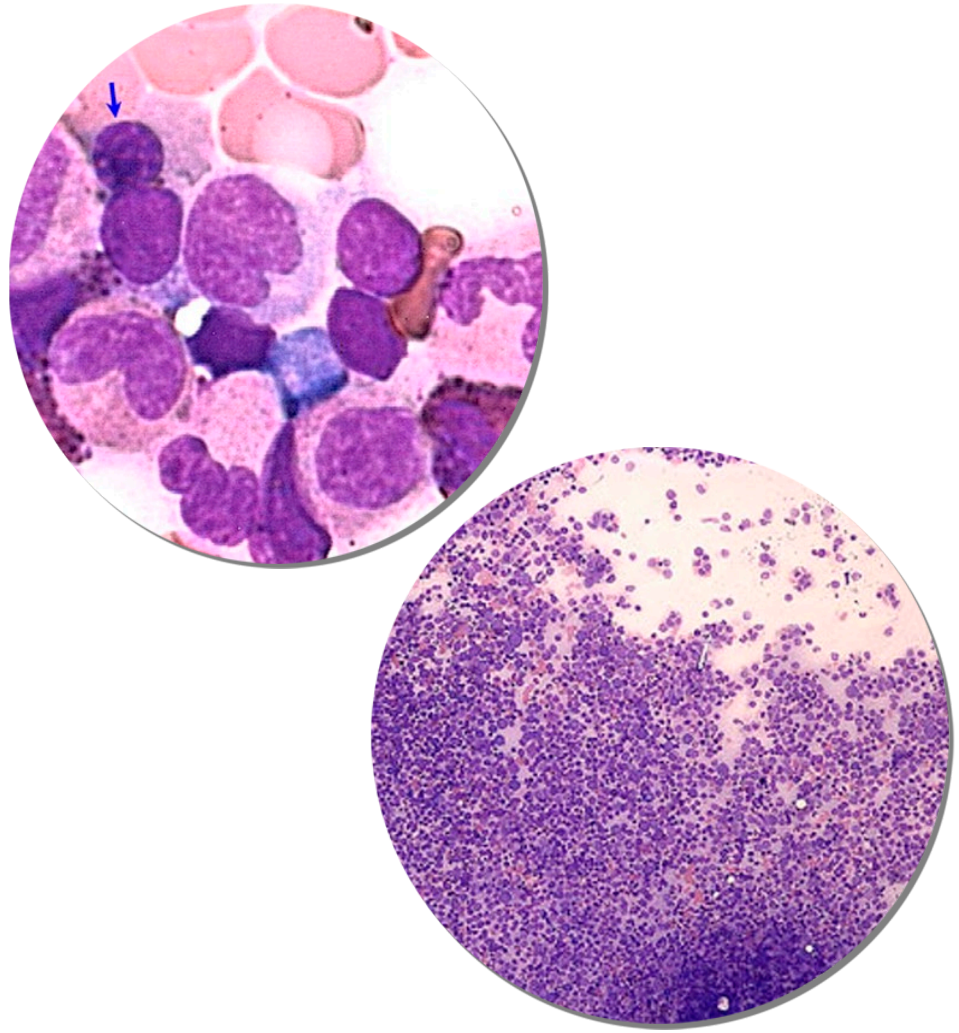
P53 MT AML
Clinical trials

Conclusions AML

- Landscape of AML management is changing and improved
- Molecular diagnostic and risk stratification should be standard approach.
- GO addition to intensive chemotherapy (IC) improves overall survival in Good risk AML.
- Flt-3 inhibitors combinations with IC is standard of care for FLT-3 MT AML.
- Maintenance therapy in AML is standard care now in FLT-3 AML after allo-SCT especially if MRD+ and for intermediate and poor risk AML after IC if no allo-SCT.
- Azacitidine and venetoclax combination is the new standard of upfront treatment in AML patients not eligible for IC.
  - Exceptions?: TP53, M5, FLT-3?
- Azacitidine and IDH inhibitors are option for patients with IDH mutations
- Patients with TP53 MT AML should be enrolled on clinical trials.
- CPX-351 is approved by FDA for induction therapy for secondary AML
- MRD assessment and disease status will guide our future tailoring of treatment.

Myelodysplastic Syndromes (MDS)

- A group of malignant hematopoietic neoplasms characterized by[1]:
  - Bone marrow failure with resultant cytopenia and related complications
  - Evidence of clonality by cytogenetic abnormalities or somatic gene mutations
  - Dysplastic cytologic morphology is the hallmark of the disease
  - Tendency to progress to AML
- Overall incidence 3.7-4.8/100,000[2]
  - In US (true estimates ≈37,000-48,000)
- Median age: 70 yrs; incidence: 34-47/100,000 >75 yrs[3]



1. Bennett J et al. *Clinical Oncology*. New York, NY: Churchill Livingstone; 2004:2849-2881; 2. SEER data. 2000-2009. 3. SEER 18 data. 2000-2009.

Similarities and Differences: WHO and ICC 2022 for MDS

Genetically Defined Subgroups	*SF3B1*	No specific category	**MDS-*SF3B1*:** MDS with low blasts (BM <5%, PB <2%) and *SF3B1* mutation - No del 5q, -7, complex karyotype - No biallelic *TP53*	**MDS-*SF3B1*:** MDS with low blasts (BM <5%, PB <2%) and *SF3B1* mutation - *SF3B1* VAF ≥10% - No del 5q, -7, inv3/t(3;3), complex karyotype - No multi-hit *TP53* or *RUNX1* mutations
	Del 5q	MDS with isolated del(5q)	**MDS-5q:** MDS with low blasts and isolated del 5q or with 1 other cytogenetic abnormality except -7/del(7)	**MDS del(5q):** MDS with isolated Del 5q or with 1 other cytogenetic abnormality except -7/del(7)
	TP53 mutation (supersedes all other MDS categories)	Not included	**MDS-bi *TP53:*** MDS with biallelic *TP53* inactivation - ≥2 *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH	**MDS with mutated *TP53*** **MDS/AML with mutated *TP53*** - MDS (blast <10%): Criteria same as WHO or, 1 *TP53* mutation plus complex karyotype - MDS/AML (blast 10-19%): Any *TP53* mutation (VAF ≥10%)
Other genetic Subgroups	MDS-related gene mutations and cytogenetic abnormalities	Not included		**MDS/AML with myelodysplasia related gene mutations** **MDS/AML with myelodysplasia related cytogenetic abnormalities**

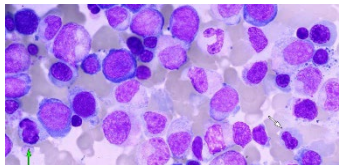
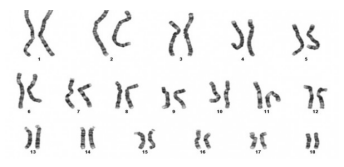
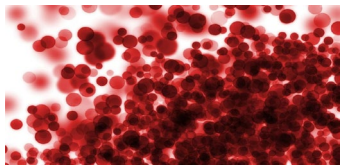
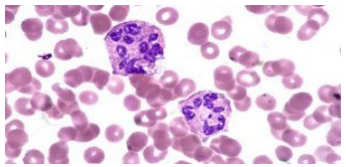
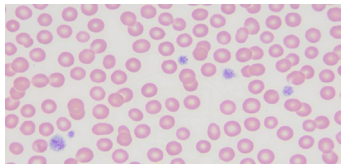
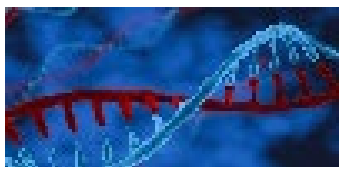
Arber et al. Blood. 2016; Khoury et al. Leukemia. 2022; Arber et al. Blood. 2022.

Similarities and Differences: WHO and ICC 2022 for MDS

MORPHOLOGY		WHO 2016	WHO 2022	ICC 2022
Ring Sideroblasts	RS ≥15%	MDS with ring sideroblasts and single lineage dysplasia (MDS-RS-SLD) and multi-lineage dysplasia (MDS-RS-MLD)	MDS with ring sideroblasts **(MDS-RS):** Low blast, *SF3B1* wild-type	No RS specific category
Number of Dysplastic Lineages	1 vs. >1	MDS with single lineage dysplasia (MDS-SLD) and multi-lineage dysplasia (MDS-MLD)	Dysplastic lineages are removed MDS with low blasts (**MDS-LB**): <5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (**MDS, NOS-SLD**) and multi-lineage dysplasia (**MDS, NOS-MLD**)
Blasts	5-9%	MDS with excess blasts-1 (MDS-EB1): 5-9% BM blasts	MDS with increased blasts-1 (**MDS-IB1**): 5-9% BM and/or 2-4% PB blasts	MDS with excess blasts (**MDS-EB**; 5-9% BM and/or 2-9% PB blasts or Auer rods)
	10-19%	MDS excess blasts-2 (MDS-EB2): 10-19% BM or PB blasts or Auer rods	MDS with increased blasts-2 (**MDS-IB2**): 10-19% BM or 5-19% PB blasts or Auer rods	**MDS/AML** (10-19% BM or PB blasts)
Added Subgroup	WHO	Not included	MDS, hypoplastic (**MDS-h**): Hypocellular marrow (age-adjusted)	Not included
		Not included	MDS with fibrosis (**MDS-f**): BM blasts 5-19%, PB blasts 2-19%; BM Fibrosis- grade ≥ 2	Not included
Removed		MDS unclassifiable	Not included	Not included

Arber et al. Blood. 2016; Khoury et al. Leukemia. 2022; Arber et al. Blood. 2022.

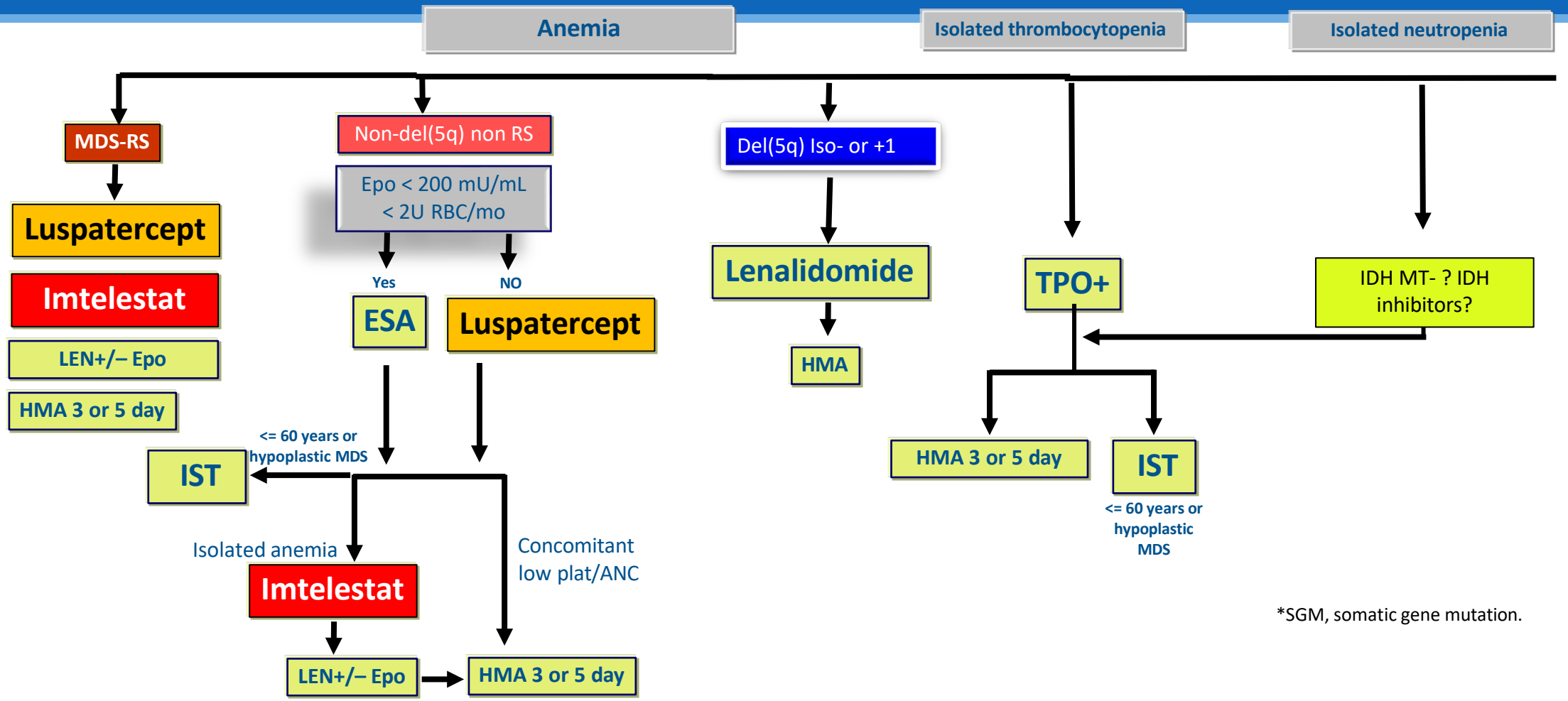
Risk stratification and clinical decisions in MDS – IPSS-M

Diagnosis[1]	Classification[1]	Incidence (%)[1]	Median OS (yrs)[1]	Progression risk (yrs)*,[1]	Treatment goal[2]	Current SoC[2]
	Very low *(Very low/low)*	14	10.6	2.8	Hematologic improvement (lower risk of infection & bleeding)	Transfusion ESAs Watch & wait
	Low *(Very low/low/int)*	33	6.0	5.1		
	Moderate low *(Low/int)*	11	4.6	11.4	?	
	Moderate high *(Low/int/high)*	11	2.8	18.9	Alter disease natural history (higher risk of infection & bleeding)	HMAs/ICT +/- ASCT
	High *(Int/high/very high)*	14	1.7	29.2		
	Very high *(High/very high)*	17	1.0	42.8		

* 4 years

1. Bernard E, *et al. NEJM Evid* 2022; **1**:7; 2. Fenaux P, *et al. Ann Oncol* 2021;**32:1**42–156.

How Would I Manage LR-MDS in 2024



*SGM, somatic gene mutation.

- **Allogeneic stem cell transplant maybe considered after standard therapy failure or in younger patients with higher-risk disease features by IPSS-M.**
- **Iron chelation should be considered in patients with evidence of iron overload.**

Adapted from Volpe VO, Komrokji RS. Ther Adv Hematol 2021;12:1-10.

Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive patients with transfusion-dependent lower-risk myelodysplastic syndromes: full analysis of the COMMANDS trial

Guillermo Garcia-Manero,[1] Uwe Platzbecker,[2] Valeria Santini,[3] Amer M. Zeidan,[4] Pierre Fenaux,[5] Rami S. Komrokji,[6] Jake Shortt,[7] David Valcarcel,[8] Anna Jonasova,[9] Sophie Dimicoli-Salazar,[10] Ing Soo Tiong,[11] Chien-Chin Lin,[12] Jiahui Li,[13] Jennie Zhang,[13] Ana Carolina Giuseppi,[13] Sandra Kreitz,[14] Veronika Pozharskaya,[13] Karen L. Keeperman,[13] Shelonitda Rose,[13] Thomas Prebet,[13] Andrius Degulys,[15,16] Stefania Paolini,[17] Thomas Cluzeau,[18] Matteo Giovanni Della Porta[19,20]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany; [3]MDS Unit, Hematology, University of Florence, AOUC, Florence, Italy; [4]Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; [5]Service d'Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France; [6]Moffitt Cancer Center, Tampa, FL, USA; [7]Monash University and Monash Health, Melbourne, VIC, Australia; [8]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [9]Medical Department Hematology, Charles University General University Hospital, Prague, Czech Republic; [10]Hôpital Haut-Lévêque, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; [11]Malignant Haematology & Stem Cell Transplantation, The Alfred, Melbourne, VIC, Australia; [12]Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan; [13]Bristol Myers Squibb, Princeton, NJ, USA; [14]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [15]Hematology, Oncology and Transfusion Medicine Center, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; [16]Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [17]IRCCS Azienda Ospedaliero-Universitaria di Bologna - Istituto di Ematologia “Seràgnoli”, Bologna, Italy; [18]Département d'Hématologie Clinique, Université Cote d'Azur, CHU Nice, Nice, France; [19]Cancer Center IRCCS Humanitas Research Hospital, Milan, Italy; [20]Department of Biomedical Sciences, Humanitas University, Milan, Italy

ASH 2023, Presentation 193

COMMANDS: study design

- COMMANDS is a global, phase 3, open-label, randomized controlled trial (NCT03682536)

Key patient eligibility criteria

- ≥ 18 years of age
- IPSS-R Very low-, Low-, or Intermediate-risk MDS (with or without RS) by WHO 2016, with < 5% blasts in bone marrow[a]
- Required RBC transfusions (2–6 pRBC units/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO < 500 U/L
- ESA-naive

Patients stratified by:

- Baseline RBC transfusion burden
- Baseline sEPO level
- RS status

R 1:1

Luspatercept (N = 182)
1.0 mg/kg s.c. Q3W
titration up to 1.75 mg/kg

Epoetin alfa (N = 181)[b]
450 IU/kg s.c. QW
titration up to 1050 IU/kg

Response assessment at day 169 and every 24 weeks thereafter

End treatment
Due to lack of clinical benefit[c] or disease progression per IWG 2006 criteria

Post-treatment safety follow-up

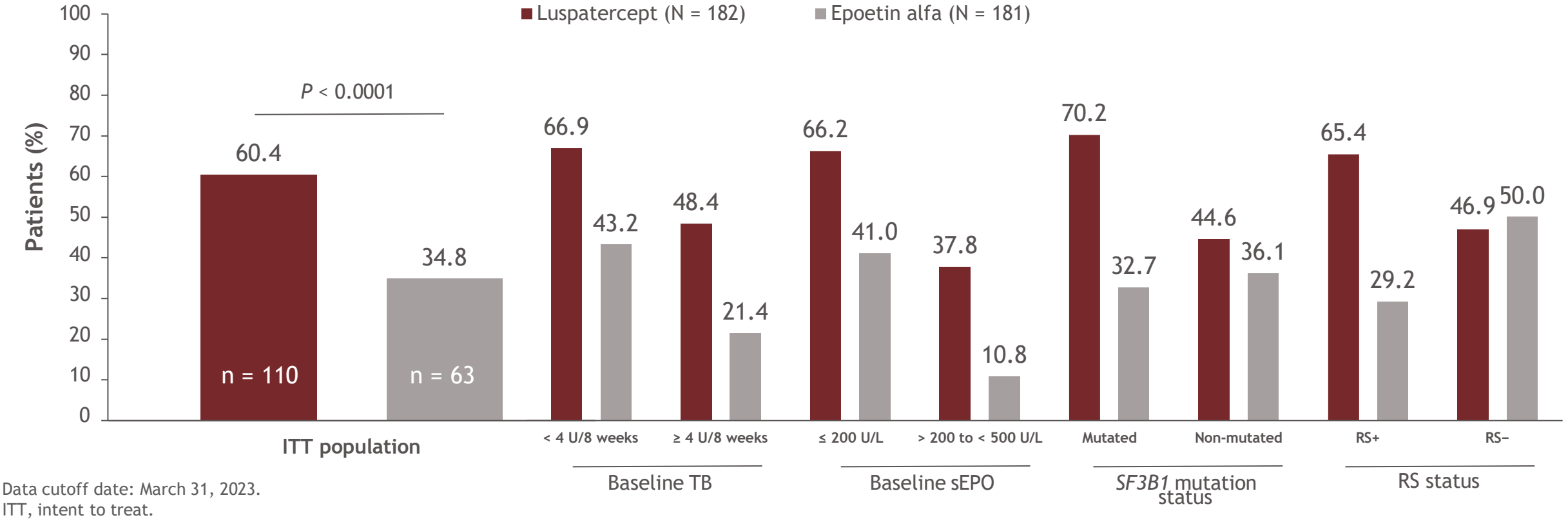
- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

[a]MDS patients with del(5q) were excluded; [b]2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose; [c]Clinical benefit defined as transfusion reduction of ≥ 2 pRBC units/8 weeks versus baseline.
AML, acute myeloid leukemia; HR-MDS, higher-risk MDS; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; pRBC, packed RBC; QW, once weekly; Q3W, every 3 weeks; R, randomized; RS, ring sideroblasts; s.c., subcutaneously; sEPO, serum erythropoietin; WHO, World Health Organization.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

COMMANDS: achievement of primary endpoint in ITT population and subgroups

- The primary endpoint was achieved by 110 (60.4%) patients in the luspatercept arm versus 63 (34.8%) patients in the epoetin alfa arm ($P < 0.0001$)
  - Subgroup analysis of the primary endpoint showed greater response rates with luspatercept regardless of baseline TB, sEPO category, or *SF3B1* mutation status



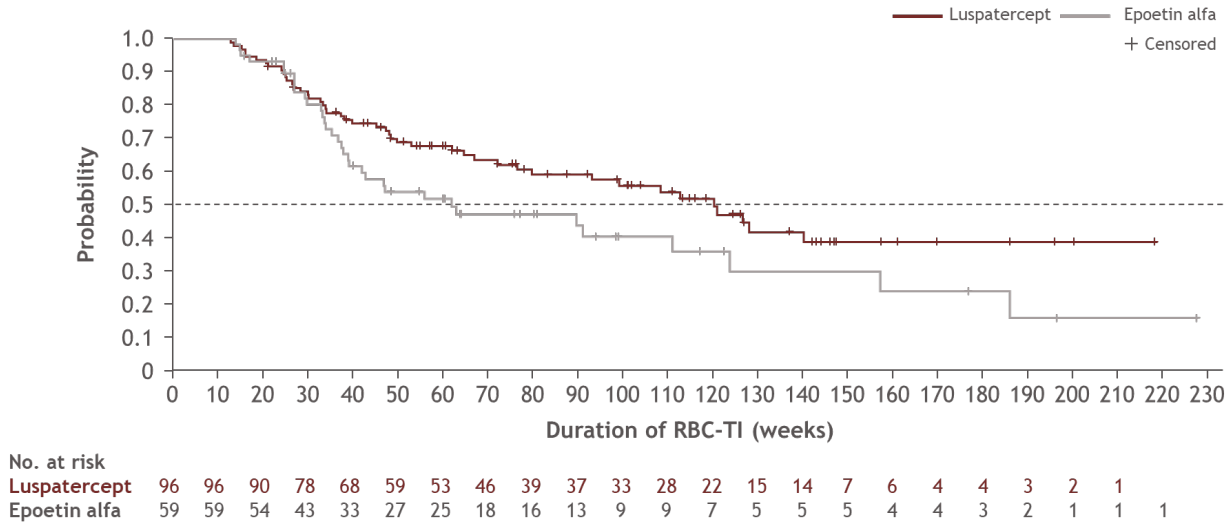
Data cutoff date: March 31, 2023.
ITT, intent to treat.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

COMMANDS: duration of RBC-TI ≥ 12 weeks by RS subgroups (week 1–EOT)

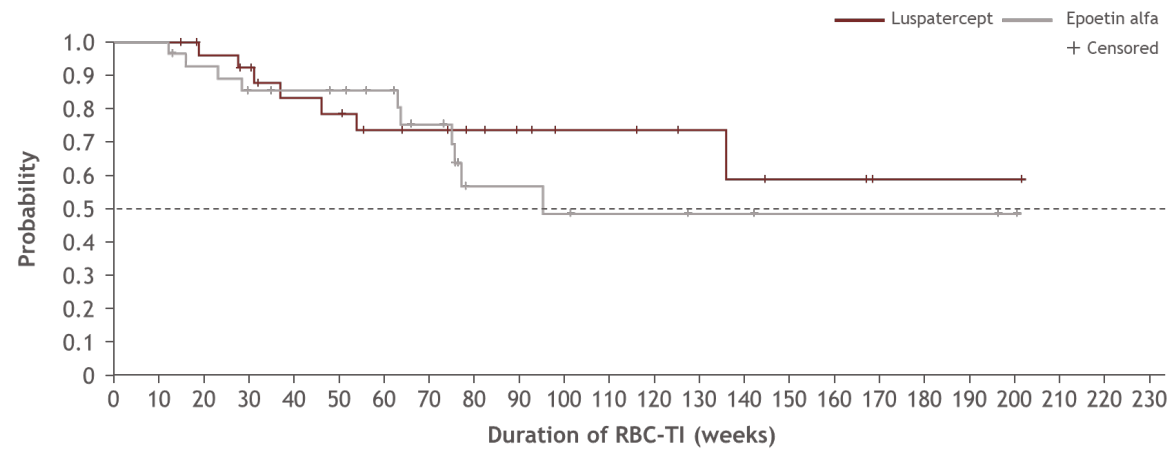
Duration, median (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)
RS+	120.1 (76.4-NE)	61.9 (38.9-123.9)	0.650 (0.415-1.018)
RS−	NE (135.9-NE)	95.1 (74.9-NE)	0.709 (0.269-1.866)

RS+



No. at risk																						
Luspatercept	96	96	90	78	68	59	53	46	39	37	33	28	22	15	14	7	6	4	4	3	2	1
Epoetin alfa	59	59	54	43	33	27	25	18	16	13	9	9	7	5	5	5	4	4	3	2	1	1	1

RS−

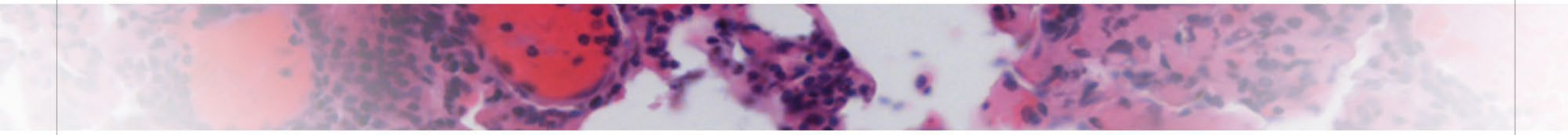


No. at risk																						
Luspatercept	28	28	25	22	18	17	14	13	11	9	7	7	6	5	4	3	3	1	1	1	1	
Epoetin alfa	29	29	25	22	21	20	18	14	7	7	6	5	5	4	4	2	2	2	2	2	1	

Data cutoff date: September 28, 2023.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Efficacy of Imetelstat in Achieving Red Blood Cell Transfusion Independence Across Different Risk Subgroups in Patients With Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis-Stimulating Agents in IMerge Phase 3 Study

Rami Komrokji,[1] Valeria Santini,[2] Pierre Fenaux,[3] Michael R. Savona,[4] Yazan F. Madanat,[5] Tymara Berry,[6] Laurie Sherman,[7] Shyamala Navada,[6] Faye Feller,[6] Libo Sun,[6] Qi Xia,[6] Ying Wan,[6] Fei Huang,[6] Amer M. Zeidan,[8] and Uwe Platzbecker[9]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]MDS Unit, Hematology, AOUC, University of Florence, Florence, Italy; [3]Hôpital Saint-Louis, Université de Paris 7, Paris, France; [4]Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; [5]Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [6]Geron Corporation, Parsippany, NJ, USA; [7]Vividion Therapeutics, San Diego, CA, USA; [8]Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; [9]Cellular Therapy and Hemostaseology, Leipzig University Hospital, Leipzig, Germany

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

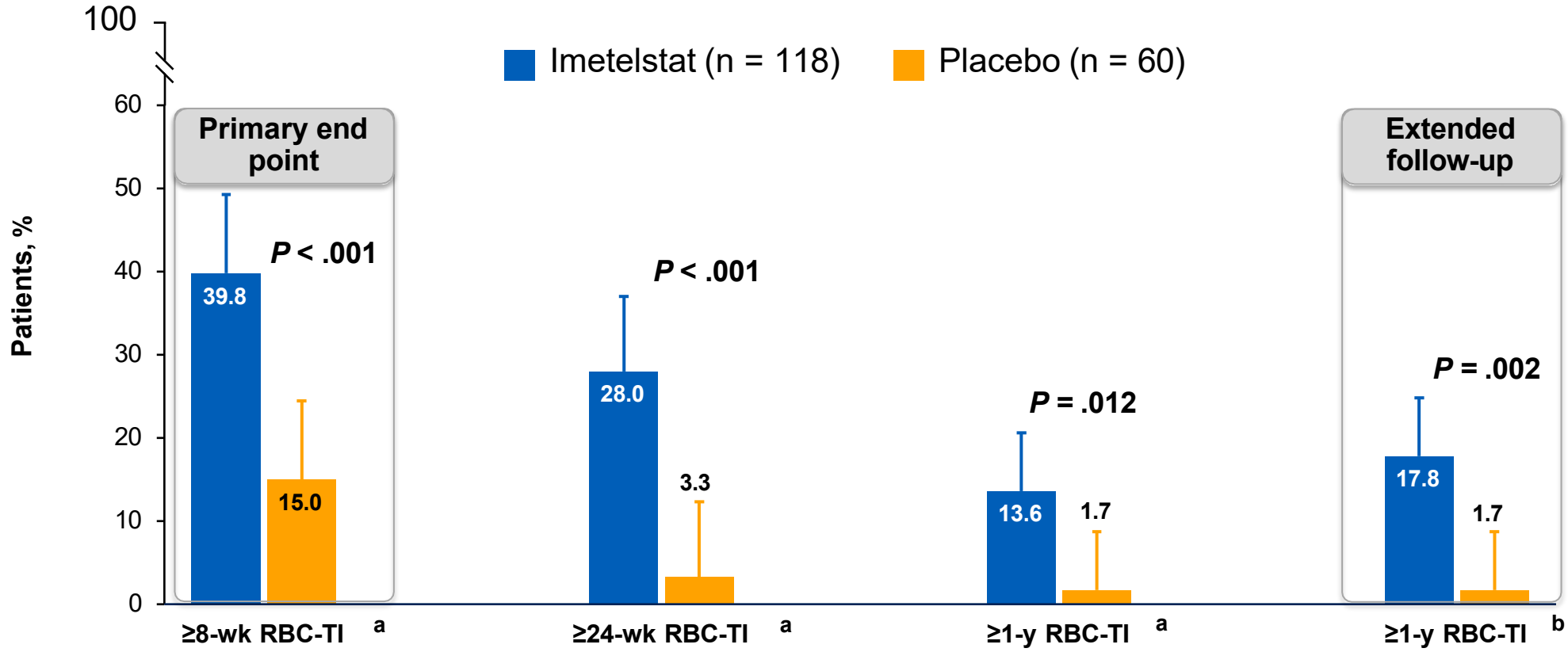
Key exploratory end points
- VAF changes
- Cytogenetic response
- PRO: fatigue measured by FACIT-Fatigue

[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.

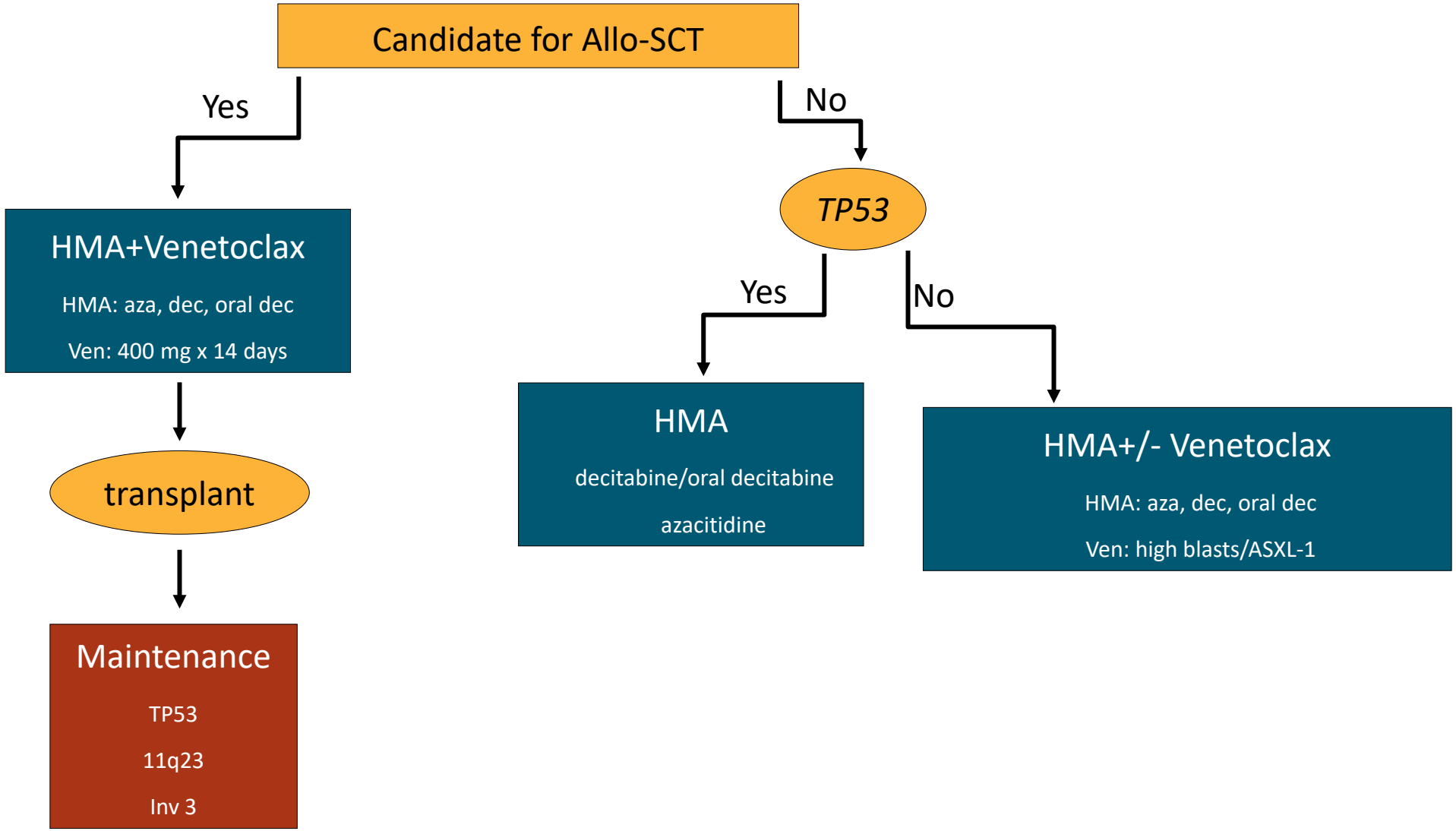
Platzbecker U, et al. *Lancet.* Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.

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.

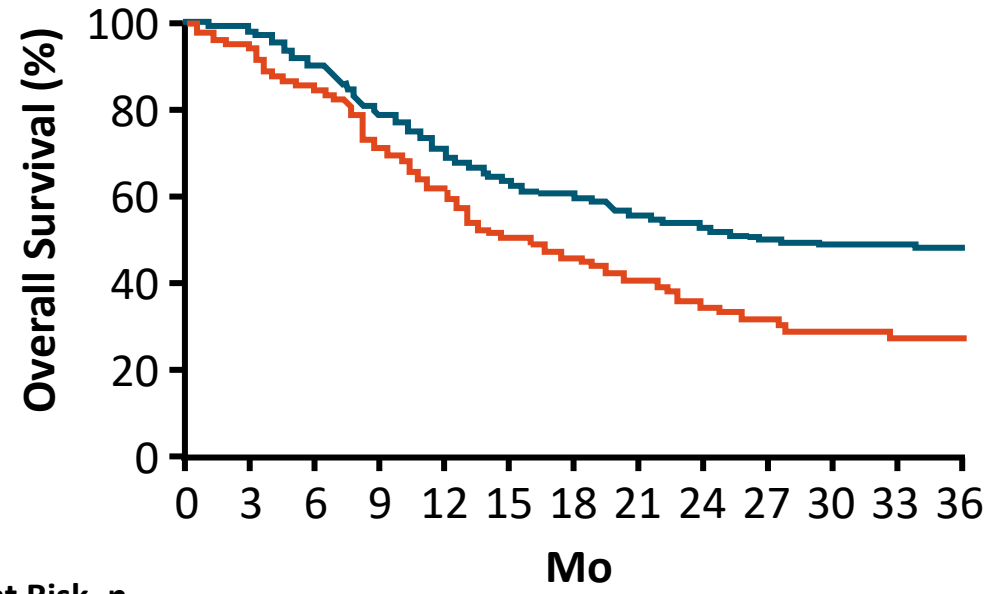
How do I manage Higher risk MDS 2024?



BMT CTN 1102: RIC Plus Allo-HSCT vs BSC in Older Patients With Higher-Risk MDS

Overall Survival

	Donor	No Donor
3-yr estimate, %	47.9	26.6
95% CI	41.3-54.1	18.4-35.6

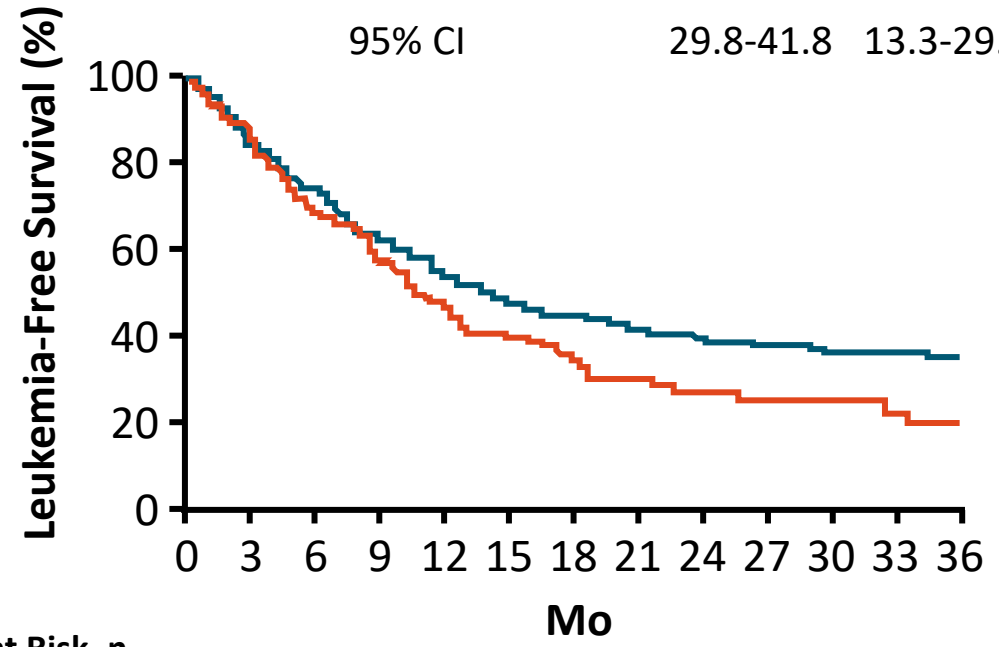


Patients at Risk, n

Donor	260	253	233	201	176	155	129	117	102	86	76	72	27
No donor	124	116	103	84	71	56	49	40	30	22	15	14	7

Leukemia-Free Survival

	Donor	No Donor
3-yr estimate, %	35.8	20.6
95% CI	29.8-41.8	13.3-29.1

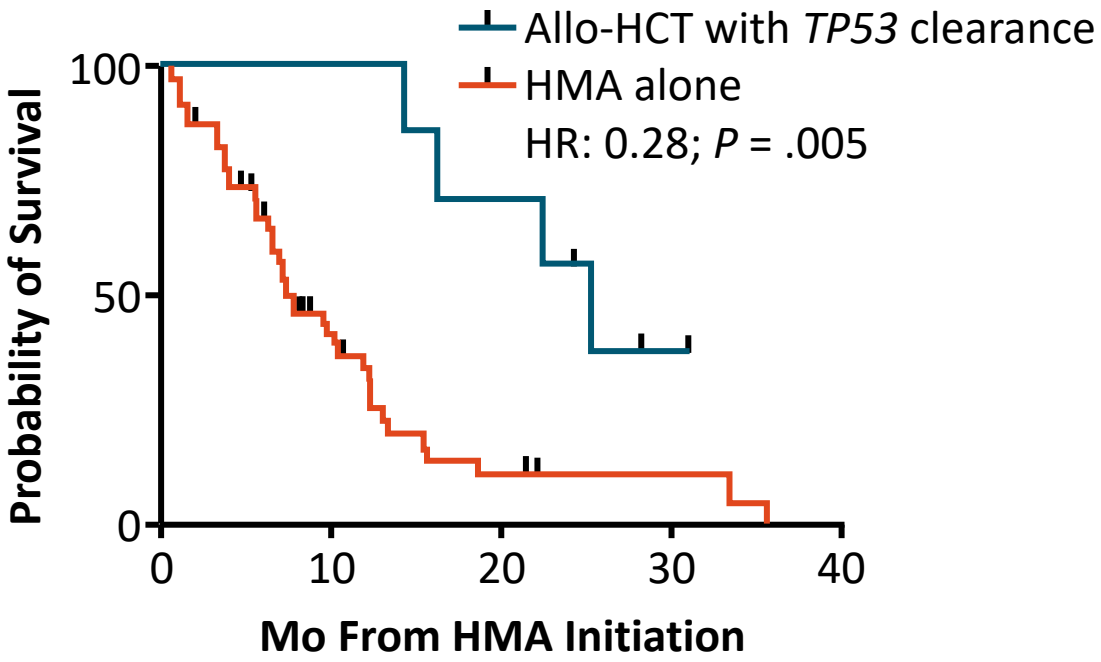


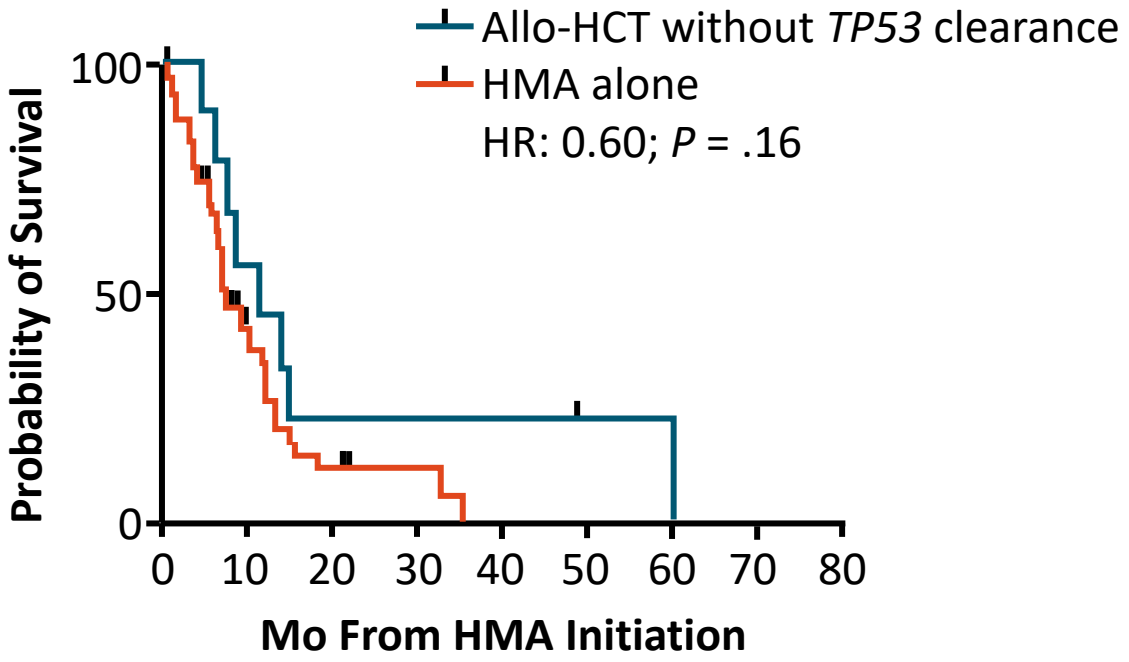
Patients at Risk, n

Donor	260	219	192	160	135	119	97	88	76	66	58	56	22
No donor	124	106	83	68	56	44	37	29	24	18	14	12	5

Nakamura. JCO. 2021;39: 3328.

Baseline and Serial Molecular Profiling Predicts Outcomes With HMAs in MDS





Proposed treatment algorithm for *TP53* mutated MDS:

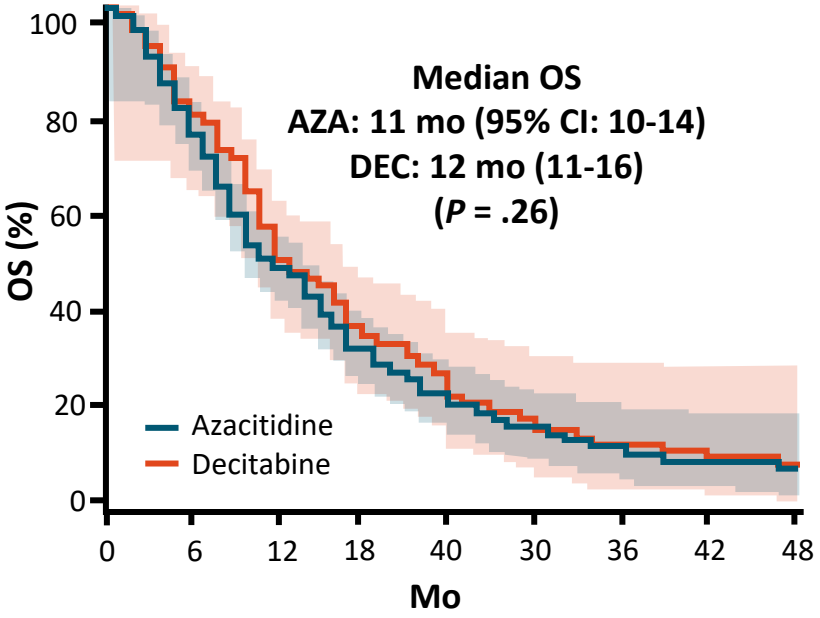
TP53 mutated, higher-risk MDS → Frontline therapy with a hypomethylating agent → Serial next generation sequencing to assess molecular response

- Clearance of *TP53* mutation → Proceed to allogeneic transplant (if candidate)
- Persistent *TP53* mutation detected → Clinical trial evaluating novel therapy

Hunter. Blood Adv. 2021;5:1017.

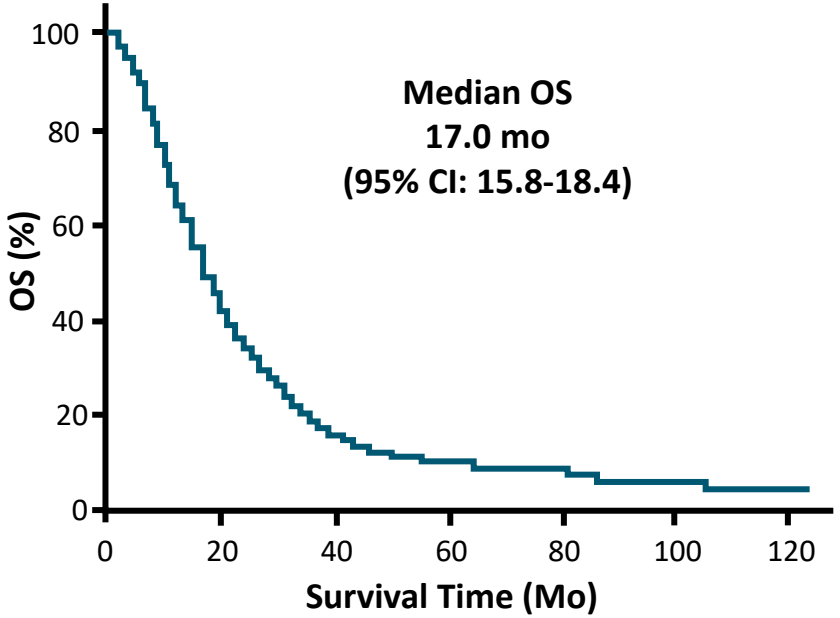
Survival of Patients With HR-MDS Remains Poor Despite Use of HMAs

OS: AZA vs DEC



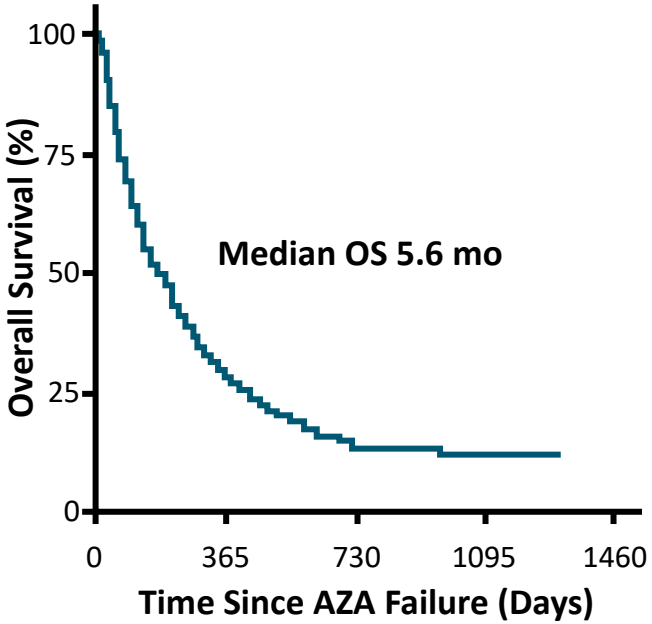
532 patients ≥66 yr at diagnosis who received ≥10 days of HMA therapy

OS: Median 5 Cycles HMA



636 HR-MDS of all ages in the MDS Clinical Research Consortium who received HMA (median 5 cycles), 72% received ≥4 cycles. 68% received AZA.

OS: Post-AZA Failure



Survival post-AZA failure for patients with HR-MDS

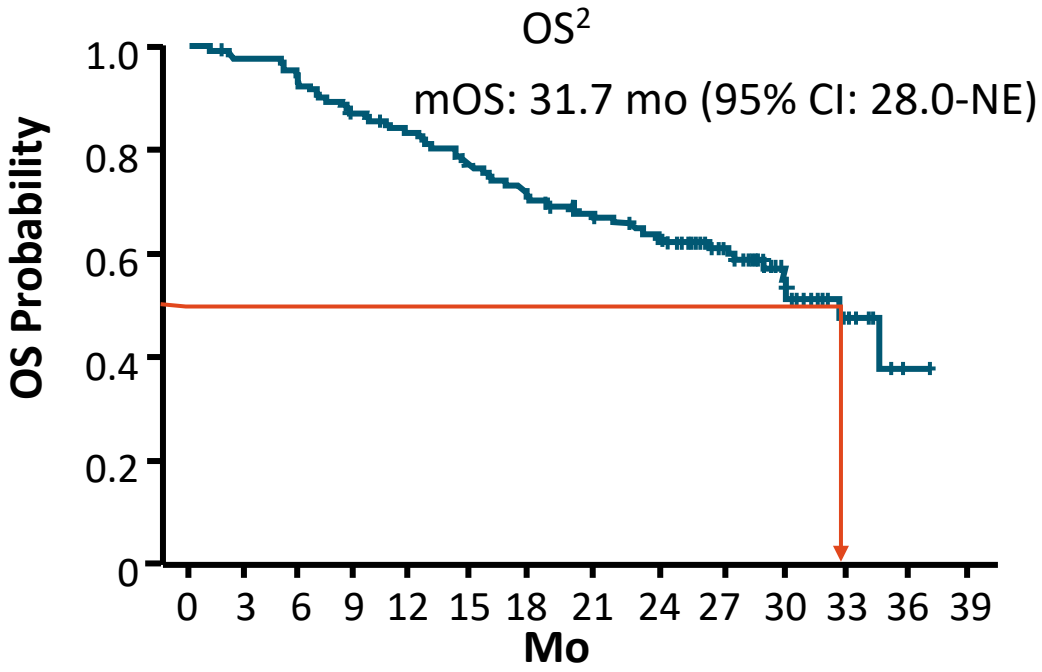
Zeidan. Br J Haematol. 2016;175:829. Zeidan. Leukemia. 2016;30:649. Prebet. JCO. 2011;29:3322.

ASCERTAIN: Update on Efficacy and Safety of Oral Decitabine/Cedazuridine in Patients With MDS and CMML

Response Category[1,2]	Treated Patients (N = 133)
CR, n (%)	29 (22)
PR, n (%)	0
mCR, n (%)	43 (32.3)
▪ mCR with HI	22 (16.5)
HI, n (%)	10 (7.5)
▪ HI-erythroid	2 (1.5)
▪ HI-neutrophils	1 (0.8)
▪ HI-platelet	7 (5.3)
Overall response (CR + PR + mCR + HI), n (%)	82 (61.7)
RBC transfusion independence, n/N (%)*	27/53 (51)
Platelet transfusion independence, n/N (%)*	6/12 (50)

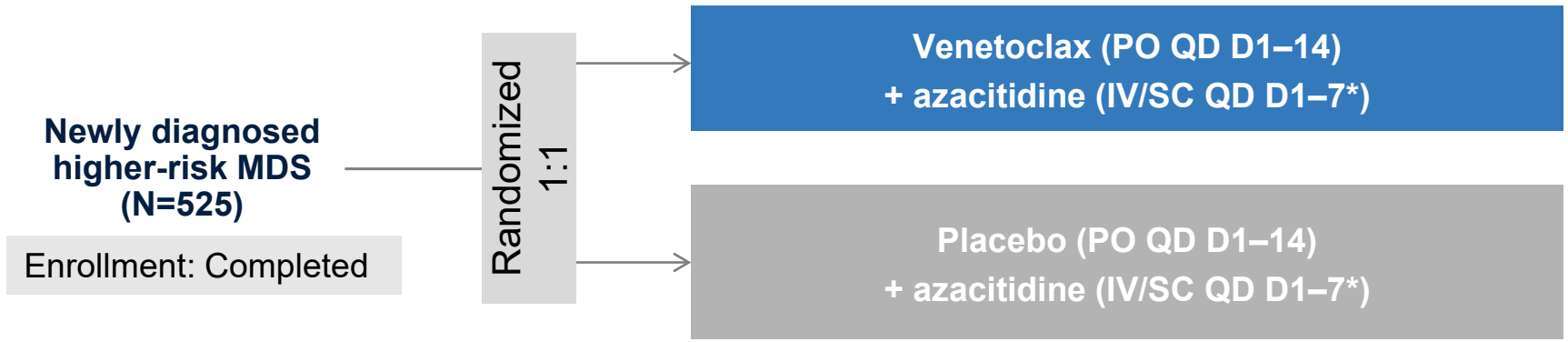
*# patients TI/# patients TD at baseline.

- Median CR duration: 14.0 mo (range: 2-29)
- Median duration of best response: 12.7 mo (range: 1-33)
- Number of patients proceeding to HCT: 34 (26%)
- Leukemia-free survival: 29.1 mo (95% CI: 22.1-NE)



1. Savona. ASH 2020. Abstr 1230. 2. Savona. MDS 2021. Abstr P48.

VERONA: Phase 3 study of Ven+Aza in higher-risk MDS



Key inclusion criteria

- ≥18 years old with newly diagnosed MDS according to 2016 WHO classification
- <20% BM blasts
- ECOG PS 0–2
- IPSS-R score of >3 (Intermediate, high, very high)
- No planned HSCT at the time of C1D1

Primary endpoints

- CR
- OS

Secondary endpoints

- Modified overall response (mOR)
- Transfusion independence (TI)
- ORR
- QoL

Efficacy and Safety of Venetoclax in Combination With Azacitidine for the Treatment of Patients With Treatment-Naive, Higher-risk Myelodysplastic Syndromes

Jacqueline S. Garcia[1], Uwe Platzbecker [2], Olatoyosi Odenike[3], Shaun Fleming[4], Chun Yew Fong[5], Rachel Cook[6], Meagan Jacoby[7], Daniel Nowak[8], Brenda Chyla[9], Huipei Wang[9], Grace Ku[10], Jalaja Potluri[9], Guillermo Garcia-Manero[11]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Universitätsklinikum Leipzig, Saxony, Germany; [3]The University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL, USA; [4]Alfred Health, Melbourne, Australia; [5]Austin Health, Heidelberg, Australia; [6]Oregon Health and Science University, Portland, OR, USA; [7]Washington University-School of Medicine, St. Louis, MO, USA; [8]Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [9]AbbVie Inc, North Chicago, IL, USA; [10]Genentech Inc., South San Francisco, CA, USA; [11]University of Texas MD Anderson Cancer Center, Houston, TX, USA

American Society of Hematology Annual Meeting, December 9-12, 2023, San Diego, California

Study Design for M15-531

Phase 1b Study of Venetoclax Plus Azacitidine in Patients With Treatment-Naive Higher-Risk Myelodysplastic Syndromes[1]

Patients (N=107)

- Adult patients with de novo treatment-naive HR MDS defined by IPSS/IPSS-R risk categories (IPSS score ≥1.5 or IPSS-R score >3)
- BM blasts <20% at baseline
- ECOG PS ≤2
- No prior therapy for MDS or with a BH3 mimetic
- No prior SCT or solid organ transplantation
- No history of an active malignancy within the past 2 years prior to study entry[a]

Primary End Point

- CR per IWG 2006

Venetoclax 400 mg orally daily on Days 1–14 of each 28-day cycle[b]
+
Azacitidine 75 mg/m^2 IV or SC on Days 1–7 or Days 1-5, 8, 9

Treatment until progression

Key Secondary End Points

- mCR, ORR, DOR, DoCR: per IWG 2006
- TTNT, overall survival
- Safety
- Hematologic improvement
- Postbaseline RBC and platelet TI
- Rate, time to AML transformation

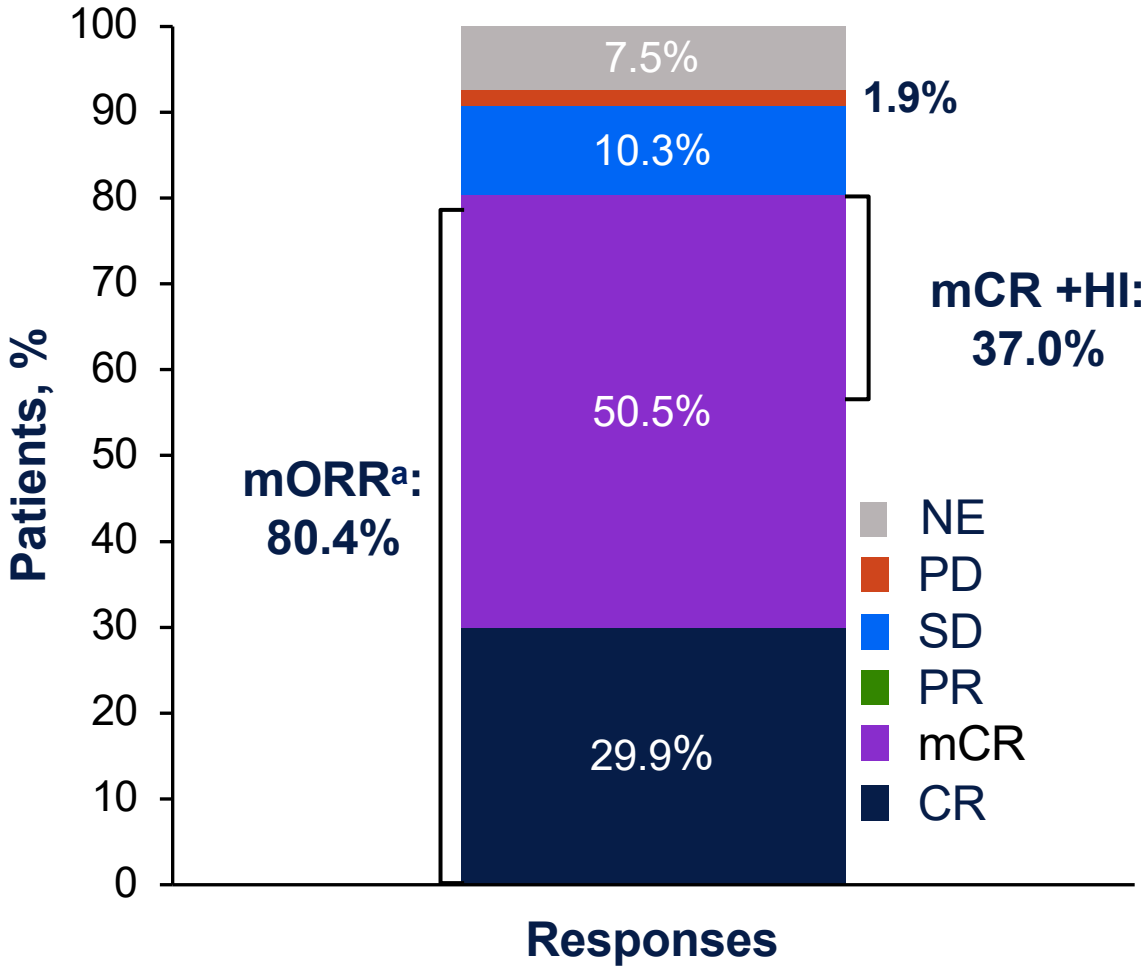
[a]With the exception of asymptomatic prostate cancer without known metastases and no requirement for therapy; adequately treated in situ carcinoma of the cervix uteri; adequately treated basal cell/localized squamous cell carcinoma of the skin. [b]Prophylactic antibiotics were mandated in Cycle 1 and for patients with grade ≥3 neutropenia thereafter.

1. ClinicalTrials.gov. Accessed August 15, 2023. https://www.clinicaltrials.gov/study/NCT02942290

AML, acute myeloid leukemia; BH3, BCL-2 Homology 3; BM bone marrow; CR, complete remission; DOR, duration of response; DoCR, duration of CR; ECOG PS, Eastern Cooperative Oncology Group performance status; IPSS-R, International Prognostic Scoring System-Revised; IV, intravenous; IWG, International Working Group; mCR, marrow complete remission; MDS, myelodysplastic syndromes; ORR, overall response rate; RBC, red blood cell; SC, subcutaneous; SCT, stem cell transplantation; TTNT, time to next treatment, TI, transfusion independence.

Best Responses for Ven 400 mg + Aza

>80% of Patients Who Received Ven + Aza Responded



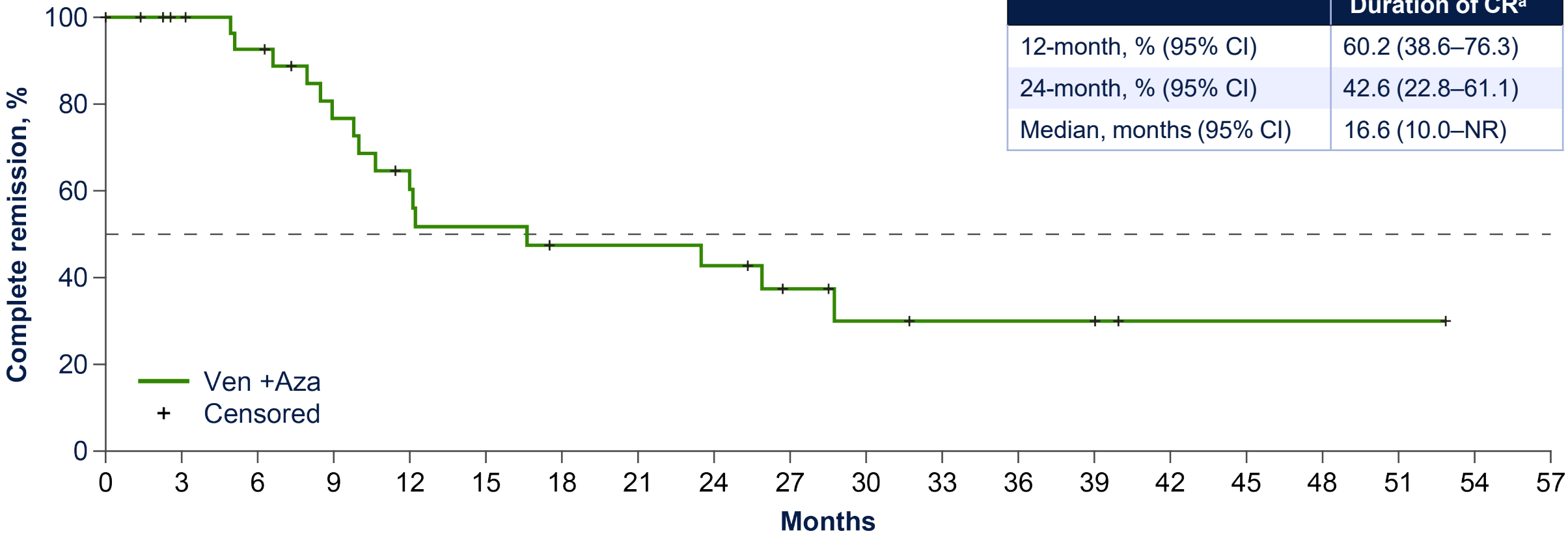
- Median number of treatment cycles with Ven 400 + Aza: 4.0 (range, 1–57)
- Median time to CR: 2.8 months (range, 1.0–16.1)
- Median duration of CR: 16.6 months (95% CI, 10.0–NR)
- MDS to AML transformation: in 13 (12.3%) patients (95% CI, 6.7–20.1)
  - Median time to AML transformation was 5.95 months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

Duration of CR in Patients Who Received Ven 400 mg + Aza

	Duration of CR[a]
12-month, % (95% CI)	60.2 (38.6–76.3)
24-month, % (95% CI)	42.6 (22.8–61.1)
Median, months (95% CI)	16.6 (10.0–NR)



Patients at Risk

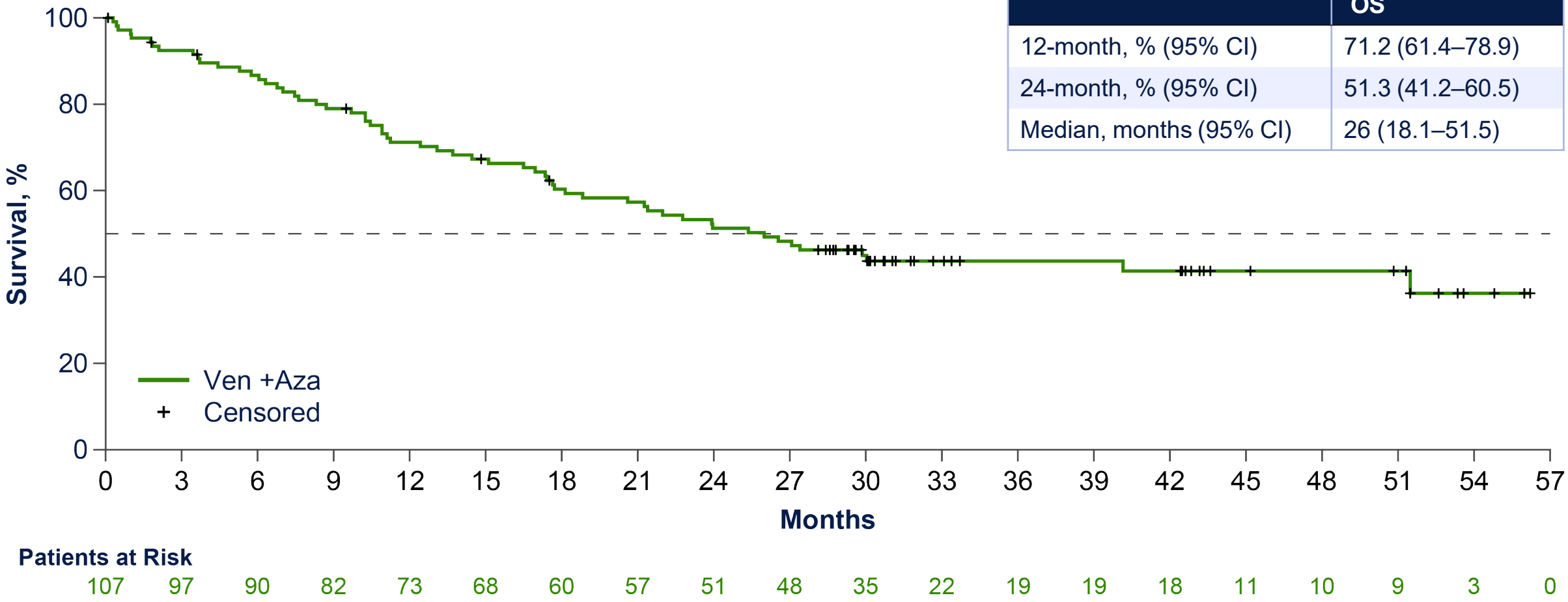
32	28	25	19	14	12	10	10	9	6	4	3	3	3	1	1	1	1	0

Median follow-up: 31.9 months (range, 0.1–56.2)

[a]Duration of CR is defined as the number of days from the date of first response CR to the earliest documentation of progressive disease or death of any cause, whichever occurs earlier. The data were censored at the date the patient was last known to be alive on or before the cutoff date. Aza, azacitidine; CR, complete remission; Ven, venetoclax.

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

	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.

Ivosidenib for R/R *IDH1*-Mutant MDS

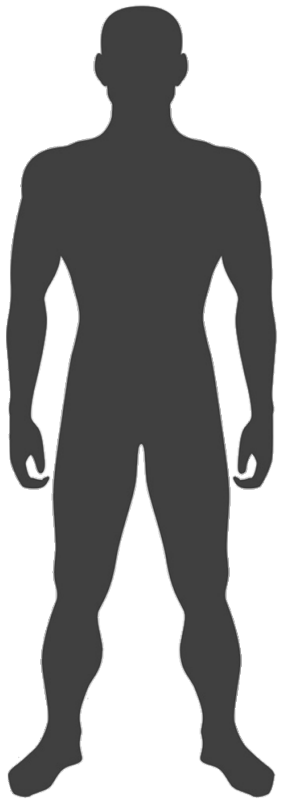
Ivosidenib: Phase I AG120-C-001 Trial (NCT02074839)

Patient Population

- ✓ *IDH1-mutated advanced hematologic malignancy*
  - *MDS cohort (N = 19): relapsed/refractory disease following prior standard therapy, including intensive chemotherapy and HMA*
- ✓ *ECOG PS 0-2*

Adverse Event Profile

- *1 patient with grade 1 corrected QT interval increase*
- *1 patient with grade 3 fatigue*
- *1 patient with grade 3 hyponatremia*
- *2 patients with grade 2 differentiation syndrome*
- *1 patient with grade 2 skin infection*



83%

Overall Response Rate

39%

Complete Response Rate

71%

Achieved RBC TI

75%

Achieved Platelet TI

FDA approved for patients with relapsed/refractory MDS with a IDH1-mutation 10/24/23

35.7 months

Median Overall Survival

HMA = Hypomethylating Agent; RBC = Red Blood Cell; TI = Transfusion Independent; ORR = Overall Response Rate; mOS = median Overall Survival

DiNardo CD, et al. EHA 2023. Abstract P724

Conclusions MDS

- New classification systems for MDS recognize molecularly defined entities.
- Molecular risk stratification (IPSS-M) is better prognostic tool.
- Luspatercept is new standard of care for treating anemia in lower risk MDS-RS+ and ? Selected MDS-RS- cases.
- Imetlestat shows promising activity and if approved by FDA will be second line treatment for lower risk MDS patients with anemia.
- Allogeneic hematopoietic stem cell transplant is only curative option for higher risk MDS pts.
- Hypomethylating agents including oral approved formulation remain standard of care.
- Venetoclax addition is borrowed from AML literature and we use in practice now particularly for MDS/AML, bridge to allo-SCT or ASXL-1 MT HR-MDS.
- Ivosidenib is approved by FDA for R/R MDS IDH-1 mutant.

Thank You

Rami.Komrokji@moffitt.org

Moffitt Myeloid team: Only perfect counts !!!

Acknowledgements:

- Our patients and their caregivers
- Moffitt Myeloid team