LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

May 5-6, 2022

AIL President: G. Toro
Coordinators: A.M. Carella, S. Amadori

UNDER THE AUSPICES OF:

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

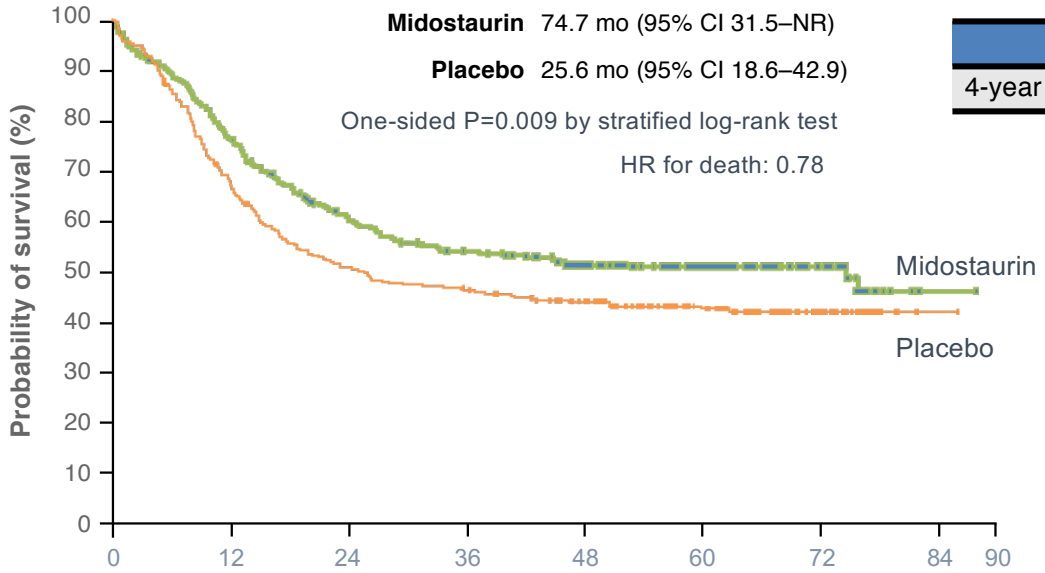
GITMO

SIE - Società Italiana di Ematologia

Agenda

1. FIt mut
2. IDH1 mut
3. Immune-therapy: Immune check-point based approaches

RATIFY: Overall survival (primary endpoint)

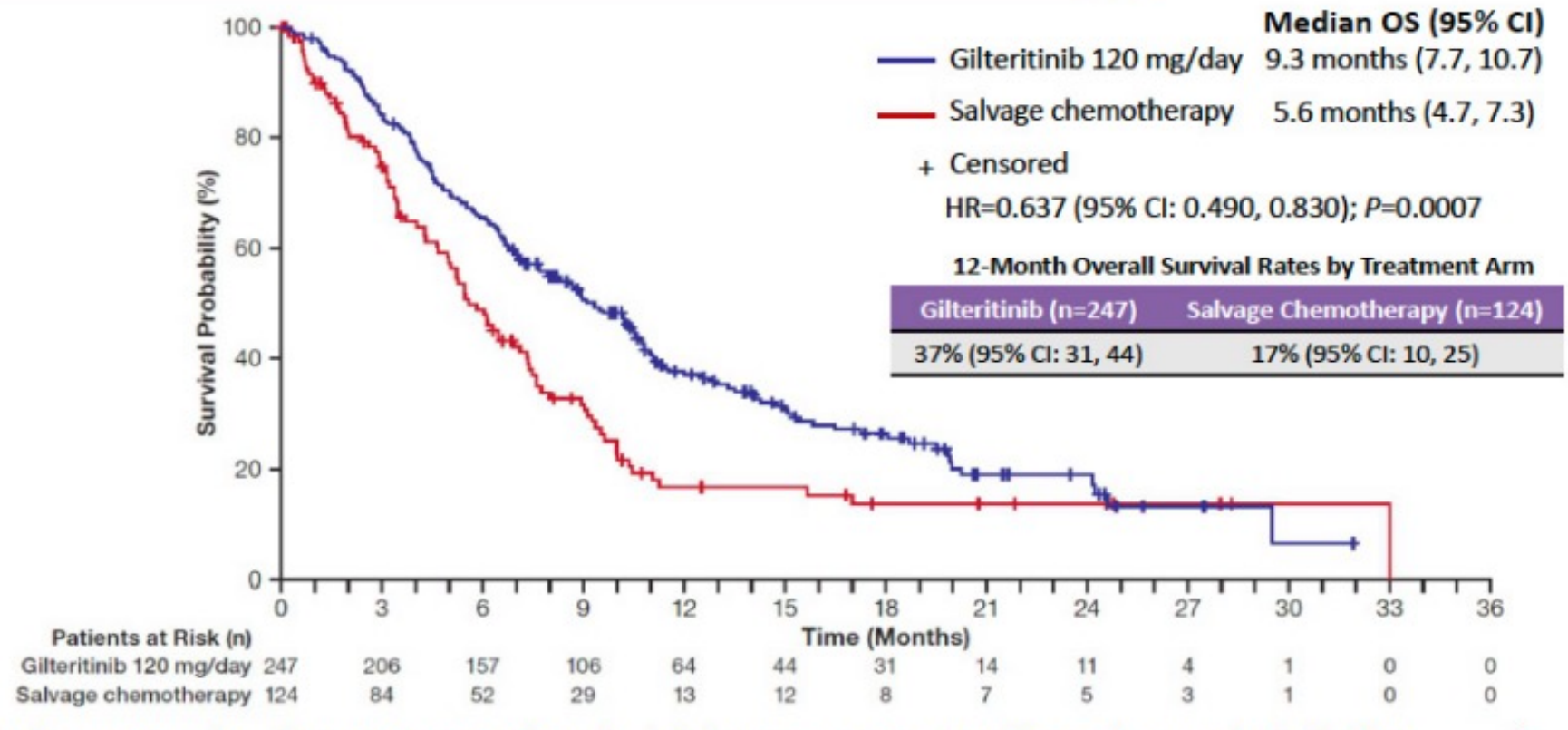


	Midostaurin	Placebo
4-year OS rate, %	51.4	44.3

Number at risk								
Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

Adapted from Stone *et al*. 2017
CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival
Stone RM *et al. N Engl J Med* 2017;377:454–464

ADMIRAL: Overall survival (primary endpoint)



Two-sided *P*-values were determined according to the log-rank test; the Kaplan-Meier method in combination with the Greenwood formula were used to determine overall survival and corresponding 95% confidence intervals.
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.

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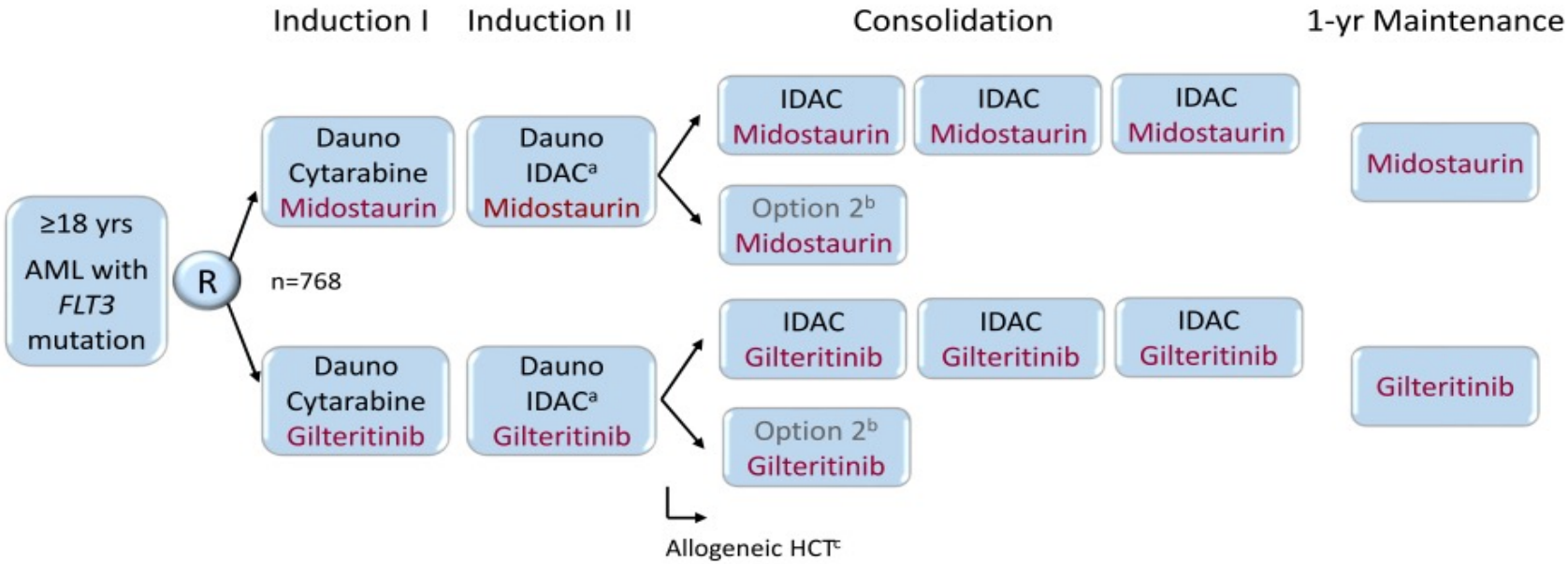
Perl AE, et al. New Engl J Med. 2019;381:1728-1740

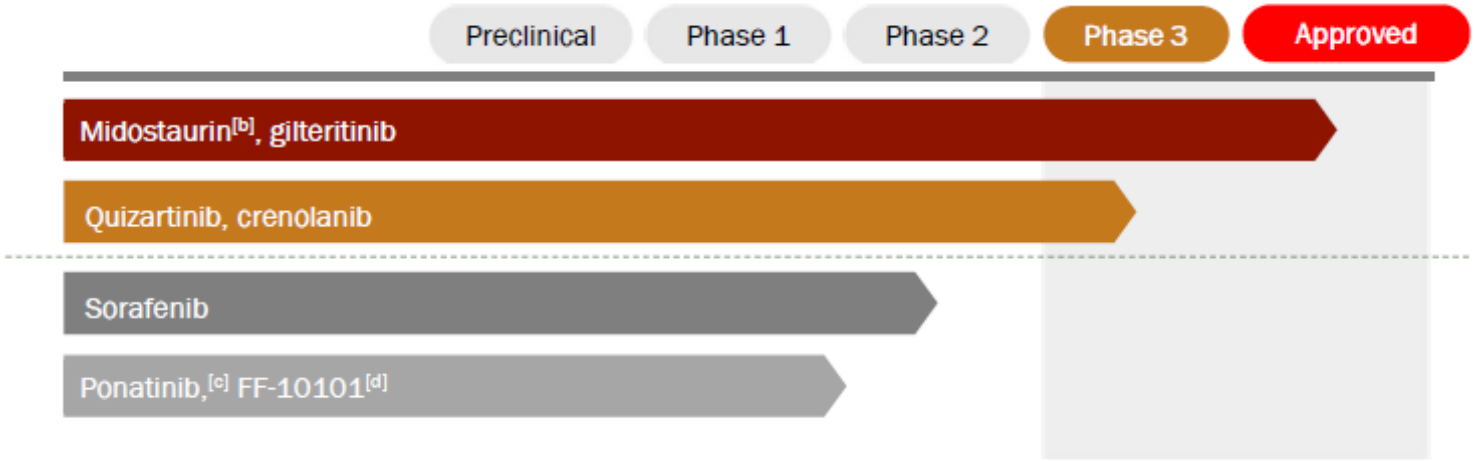
Midostaurin vs Gilteritinib plus chemotherapy for AML with *FLT3* mutation – HOVON 156 / AMLSG 28-18



Patients in CR/CRi after two cycles of induction proceed to AMLSG/HOVON-specific consolidation therapy; assignment to allogeneic hematopoietic cell transplantation (HCT) according to the local institutional or cooperative group prognostic algorithm; HCT can be performed at any time point following one induction cycle

[a] IDAC, intermediate-dose cytarabine; age-adapted dosing; no anthracycline ≥60 yrs
[b] HOVON consolidation: autologous HCT; or mitoxantrone / etoposide
[c] Maintenance with tyrosine kinase inhibitors (TKI) also after allogeneic HCT

FLT3 Inhibitors in Development



- Midostaurin is a first-generation, multikinase inhibitor[b]
- Quizartinib[e], gilteritinib[f], and crenolanib[g] are potent and selective FLT3 inhibitors

Other FLT3 inhibitors have entered clinical trials for the treatment of AML, eg, IMC-EB10, KW-2449, FLX925; however, they have been prematurely terminated.

a. Kantarjian H. *Am J Hematol*. 2016;91:131-145; b. Stone RM, et al. *N Engl J Med*. 2017;377:454-464; c. Musumeci F, et al. *Cancers (Basel)*. 2018;10:430; d. Yamaura T, et al. *Blood*. 2018;131:426-438; e. Zarrinkar PP, et al. *Blood*. 2009;114:2984-2992; f. Perl AE, et al. *Lancet Oncol*. 2017;18:1061-1075; g. ClinicalTrials.gov NCT03258931.

Press Release – Daiichi-Sankyo 18 NOV 2021

Quizartinib Added to Chemotherapy Demonstrates Superior Overall Survival Compared to Chemotherapy Alone in Adult Patients with Newly Diagnosed FLT3-ITD Positive AML

- **Global pivotal QUANTUM First Phase III Trial meets primary end-point for OS**

AGILE - Phase III study in IDH1m AML

- Multicenter, double-blind, randomized phase III trial

Stratified by region (US/Canada vs Western Europe, Israel, and Australia vs Japan vs rest of world) and disease history (de novo vs secondary AML)

Patients with untreated AML (WHO criteria); centrally confirmed *IDH1* mutation status; ineligible for IC; ECOG PS 0-2 (planned N = 200)

→ **Ivosidenib** 500 mg PO QD + **Azacitidine** 75 mg/m^2 SC or IV (n = 72)*

→ **Placebo** PO QD + **Azacitidine** 75 mg/m^2 SC or IV (n = 74)*

Enrollment at time of data cutoff (March 18, 2021)

- Enrollment halted based on efficacy as of May 12, 2021 (N = 148)
- **Primary endpoint:** EFS with ~173 events (52 mo)
- **Secondary endpoints:** CRR, OS, CR + CRh rate, ORR

Montesinos P et al., NEJM 2022:386(16);1519-1531

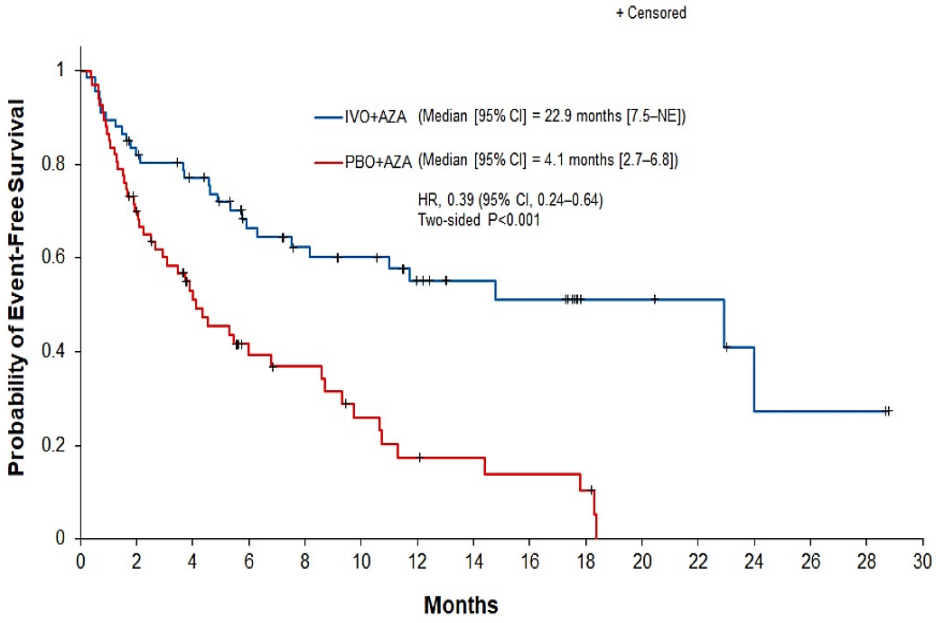
AGILE – baseline Characteristics

Characteristic	IVO + AZA (n = 72)	PBO + AZA (n = 74)
Median age, yr (range)	76.0 (58-84)	75.5 (45-94)
Sex, n (%)		
▪ Male	42 (58.3)	38 (51.4)
▪ Female	30 (41.7)	36 (48.6)
ECOG PS, n (%)		
▪ 0	14 (19.4)	10 (13.5)
▪ 1	32 (44.4)	40 (54.1)
▪ 2	26 (36.1)	24 (32.4)
Disease history, n (%)		
▪ De novo AML	54 (75.0)	53 (71.6)
▪ Secondary AML	18 (25.0)	21 (28.4)

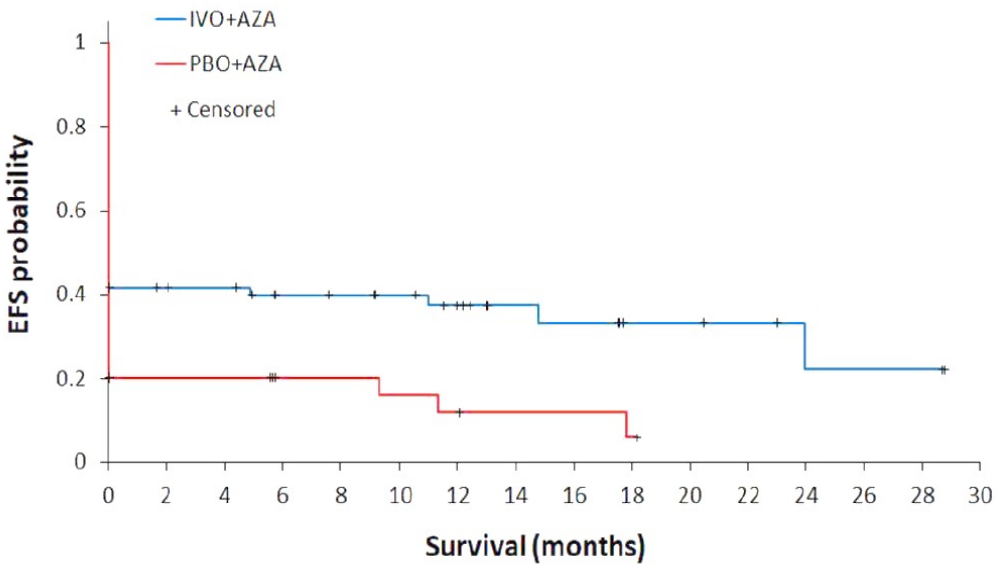
Characteristic	IVO + AZA (n = 72)	PBO + AZA (n = 74)
Median m*IDH1* VAF in BMA, % (range)	36.7 (3.1-50.5)	35.5 (3.0-48.6)
Cytogenetic risk, n (%)		
▪ Favorable	3 (4.2)	7 (9.5)
▪ Intermediate	48 (66.7)	44 (59.5)
▪ Poor	16 (22.2)	20 (27.0)
Median bone marrow blasts, % (range)	54.0 (20-95)	48.0 (17-100)

Montesinos P et al., NEJM 2022:386(16);1519-1531

AGILE - EFS



No. at Risk																
IVO+AZA	72	53	46	34	29	26	19	14	13	6	6	5	2	2	2	0
PBO+AZA	74	44	28	17	14	9	6	5	4	3	0					

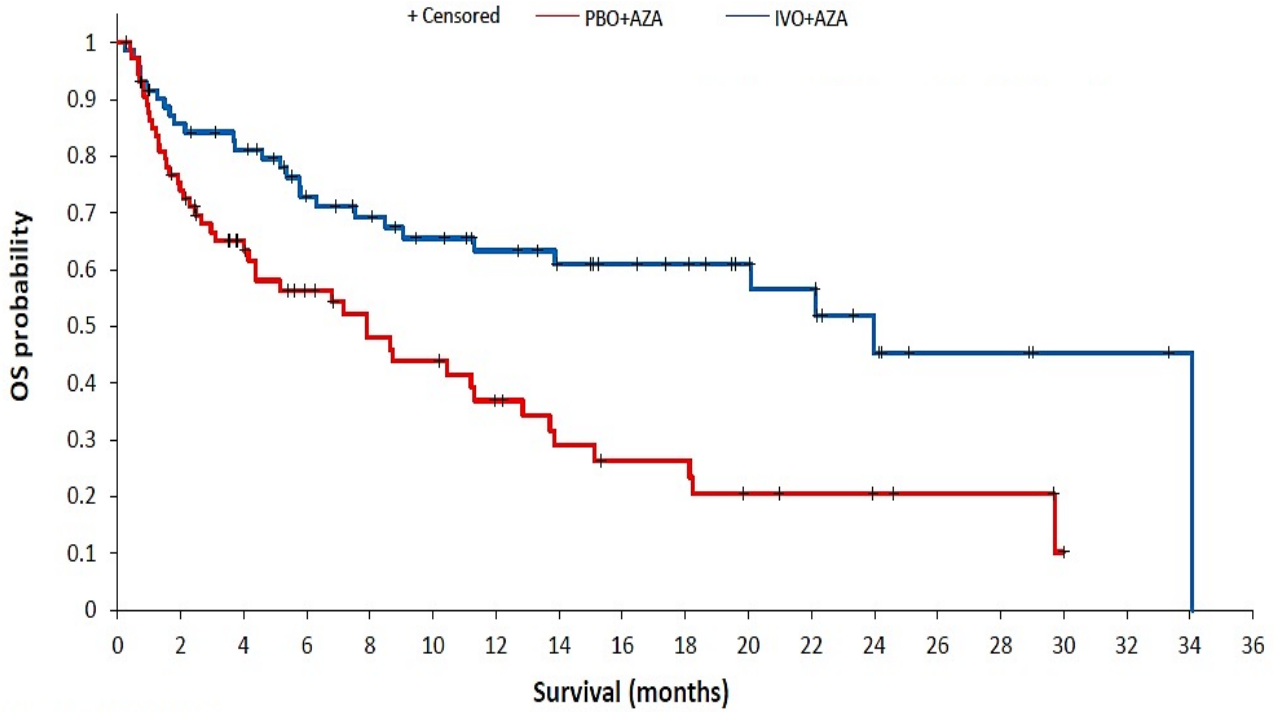


Number of patients at risk:																
IVO+AZA	72	26	25	20	19	17	13	9	8	5	5	4	2	2	2	0
PBO+AZA	74	8	8	5	5	4	3	2	2	1	0					

Montesinos P et al., NEJM 2022:386(16);1519-1531

AGILE - OS

The **mOS** with IVO+AZA was **24.0 months** vs **7.9 months** with PBO+AZA
(HR 0.44, 95% CI 0.27–0.73; two-sided P=0.001)

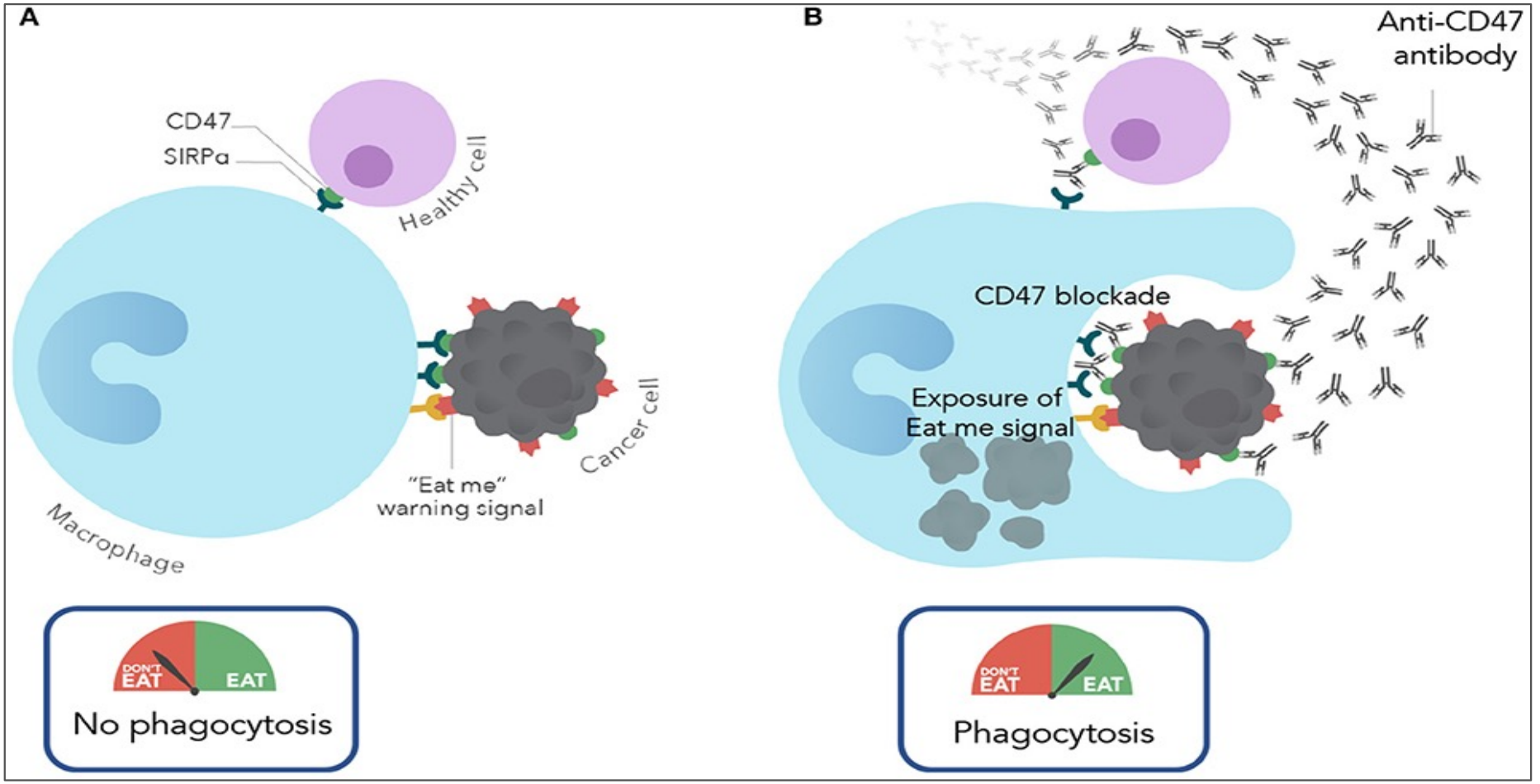


Number of patients at risk:

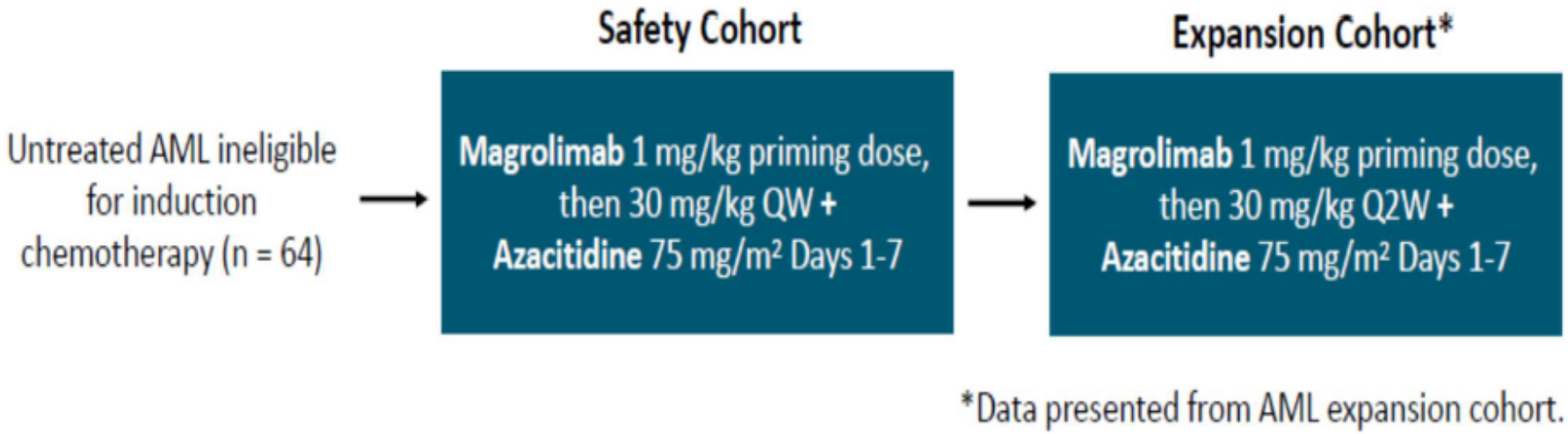
PBO+AZA	74	53	38	29	23	21	15	11	9	9	6	5	4	3	3	0		
IVO+AZA	72	58	53	42	38	33	29	24	21	19	15	13	7	4	4	2	2	1

Montesinos P et al., NEJM 2022:386(16);1519-1531

Magrolimab + Azacitidine in Untreated AML: Background



Magrolimab + Azacitidine in Untreated AML
phase Ib Study Design



*Data presented from AML expansion cohort.

- Primary endpoints: safety of magrolimab alone or with azacitidine; efficacy of combination in untreated AML/MDS
- Secondary endpoints: magrolimab PK, PD, immunogenicity
- Exploratory endpoints: CD47 receptor occupancy, immune activity biomarkers, molecular profiling in AML/MDS

Sallman DA, et al. ASH Meeting 2020, Abstr no. 330

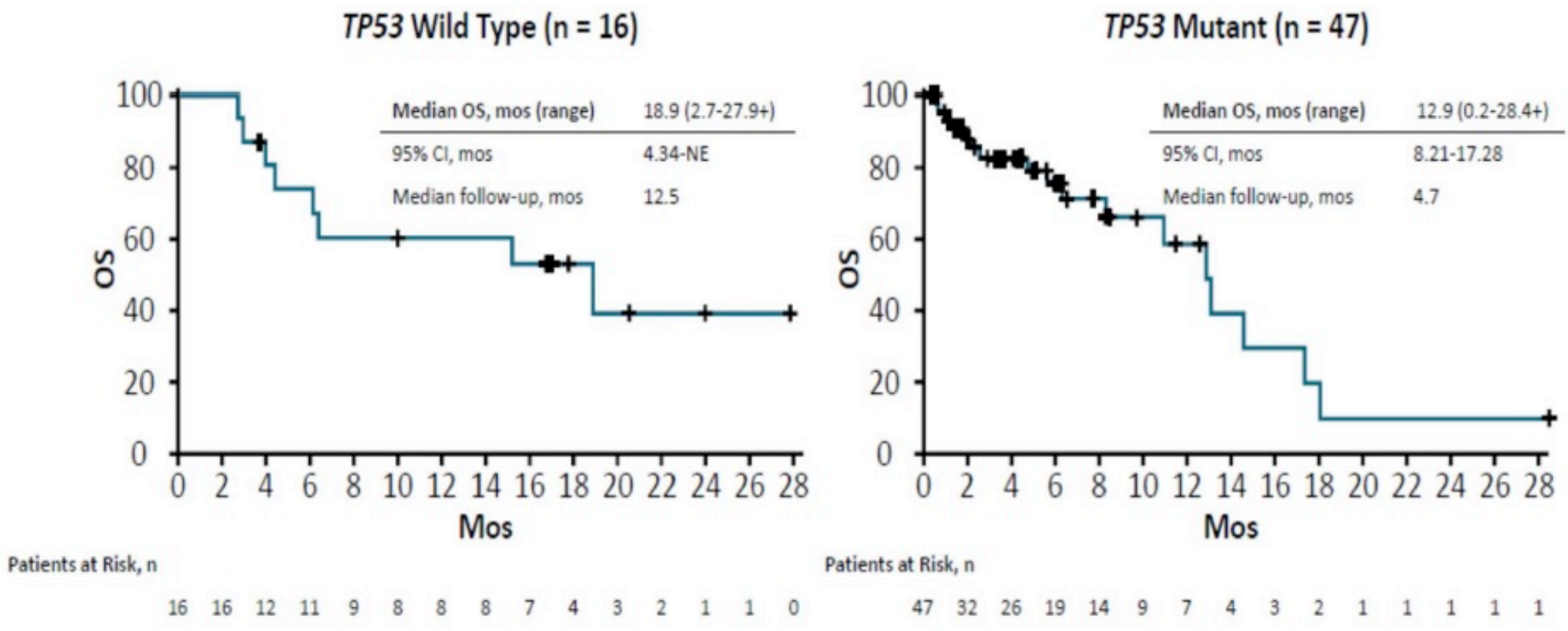
Magrolimab + Azacitidine: Efficay

Outcome	All AML pts (n = 43)	*TP53*-mutant (n = 29)
ORR, n (%)	27 (63)	20 (69)
▪ CR	18 (42)	13 (45)
▪ CRi	5 (12)	4 (14)
▪ PR	1 (2)	1 (3)
▪ MLFS	3 (7)	2 (7)
▪ SD	14 (33)	8 (28)
▪ PD	2 (5)	1 (3)
Median time to response, mos (range)	1.95 (0.95-5.6)	NR
Median duration of response, mos	9.6	7.6
Complete cytogenic response, n/N (%)	9/20 (45)	7/16 (44)
MRD negativity in CR/CRi, n/N (%)	8/23 (35)	5/17 (29)

- 9.6% proceeded to bone marrow stem cell transplant
- High rates of red blood cell transfusion independence (68% in all AML, 63% in *TP53*-mutant AML)
- Multiple patients deepened their response over time on several months of therapy

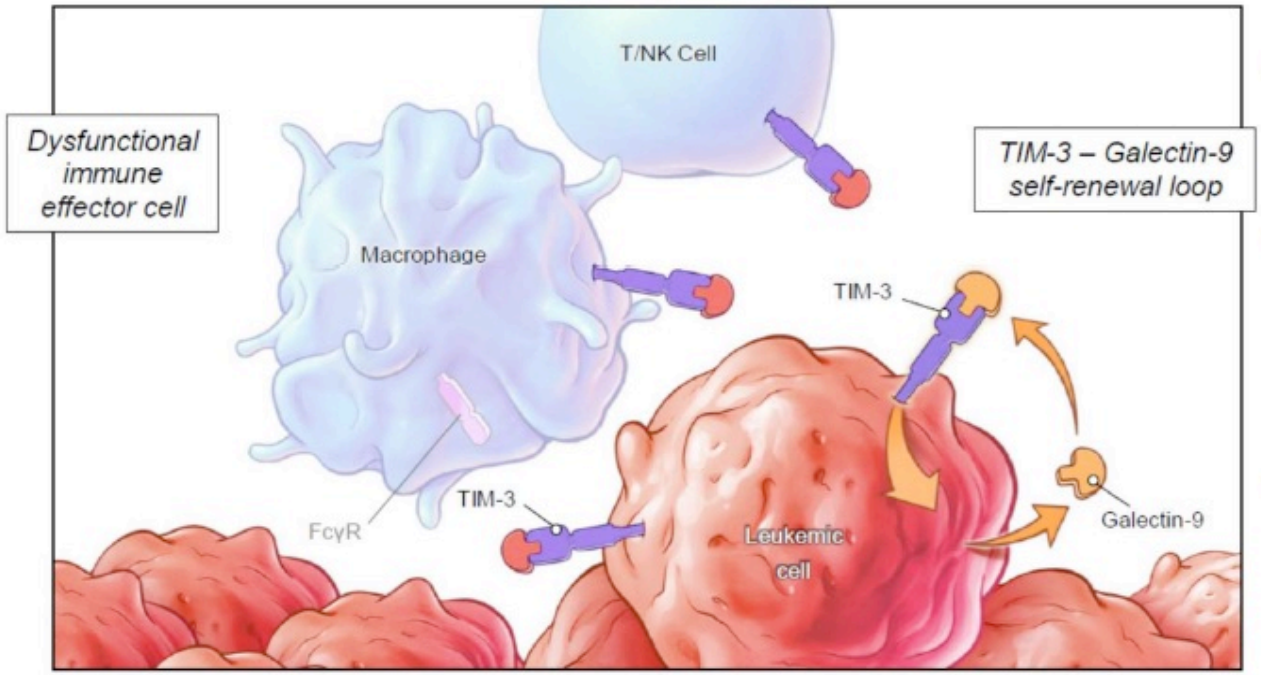
Sallman DA, et al. ASH Meeting 2020, Abstr no. 330

Magrolimab + Azacitidine: Preliminary Os



Sallman DA, et al. ASH Meeting 2020, Abstr no. 330

TIM-3 is an inhibitory receptor expressed on immune and leukemic cells



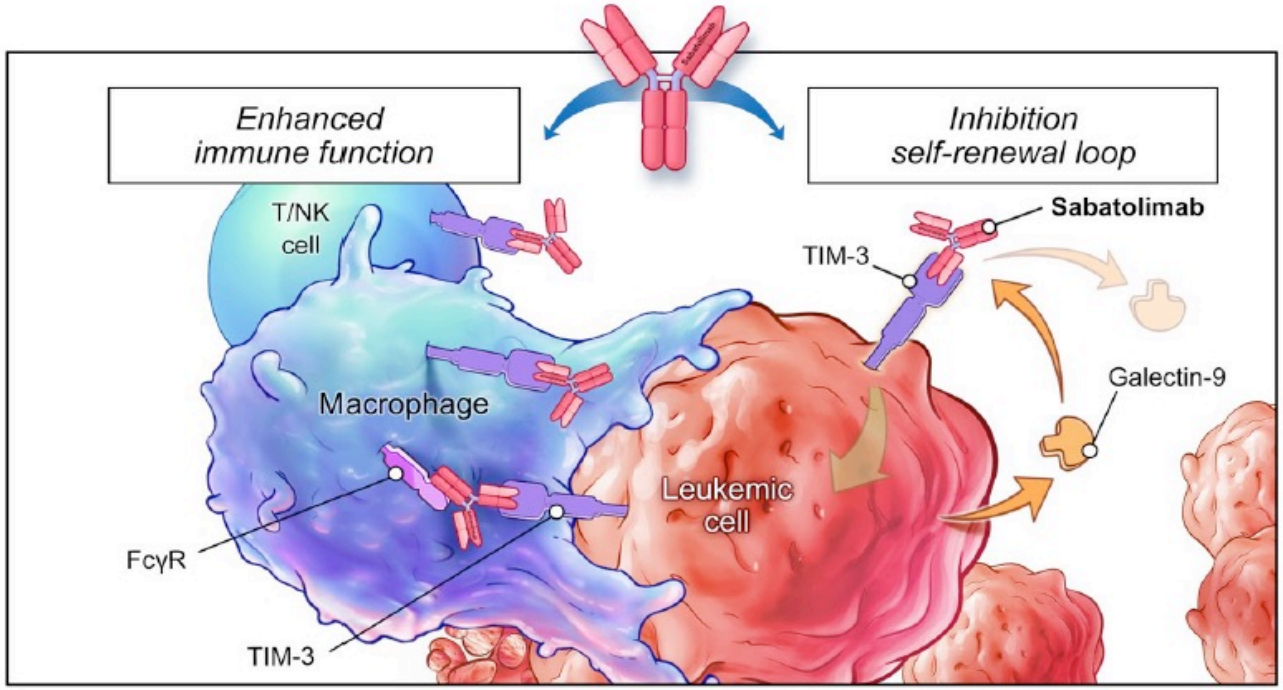
TIM-3

- Involved in regulating innate and adaptive immune responses[1,2]
- Aberrantly expressed on LSCs and blasts, but not on normal HSCs,[1-5] making it a promising target in MDS/AML[2,4,6]
- TIM-3/galectin-9 interaction forms an autocrine stimulatory loop promoting LSC self-renewal[2,7,8]

AML, acute myeloid leukemia; HSC, hematopoietic stem cell; LSC, leukemic stem cell; MDS, myelodysplastic syndrome; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264; 2. Das M, et al. *Immunol Rev*. 2017;276(1):97-111; 3. Kikushige Y, Miyamoto T. *Int J Hematol*. 2013;98(6):627-633; 4. Kikushige Y, et al. *Cell Stem Cell*. 2010;7(6):708-717; 5. Ngiow SF. *Cancer Res*. 2011;71(10):3540-3551; 6. Sakuishi K, et al. *Trends Immunol*. 2011;32(8):345-349; 7. Sabatos-Peyton C. AACR 2016. Oral presentation; 8. Borate U, et al. ASH 2019. Oral presentation.

Sabatolimab targets TIM-3 on immune and leukemic cells



- Sabatolimab binds TIM-3 on immune cells, which enhances antileukemic immune function and phagocytic killing of LSCs and blasts[1-4]
- Sabatolimab directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9–driven self-renewal[1,2]

1. Acharya N, et al. *J Immunother Cancer*. 2020;8(1):e000911; 2. Sabatos-Peyton C, et al. SITC 2020. Abstract 439; 3. Borate U, et al. *HemaSphere*. 2020;4(suppl 1):Abstract S185; 4. Borate U, et al. EHA 2020. Oral presentation.

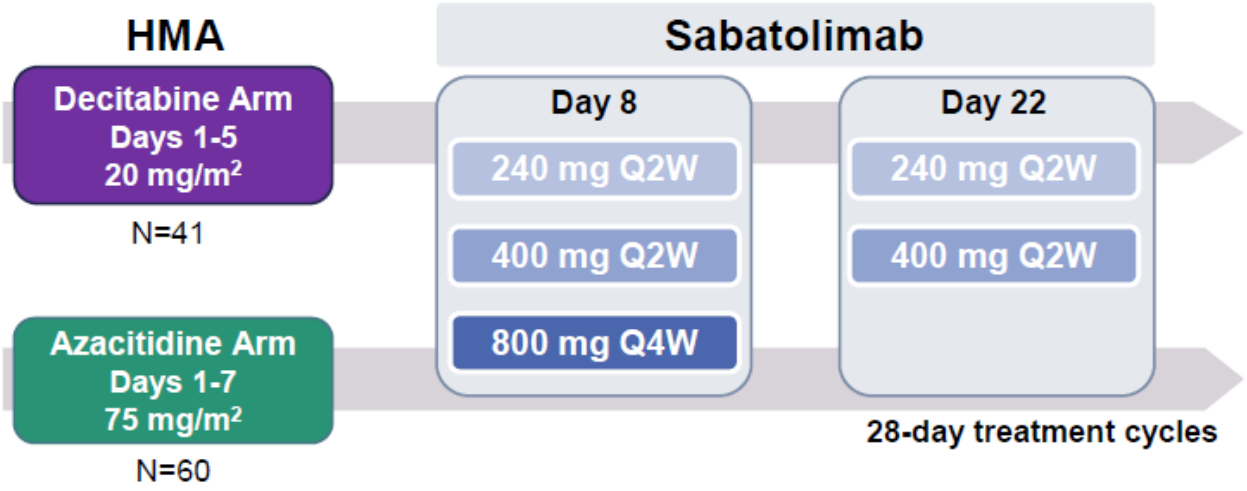
Phase Ib study of Sabatolimab in high/very high-risk MDS and AML

vHR/HR-MDS: IPSS-R high- or very high-risk MDS

ND-AML: Unfit, newly diagnosed AML, ineligible for standard chemotherapy

Patients with prior HMA treatment excluded

ClinicalTrials.gov Identifier: NCT03066648[a]



8 countries

11 trial centers

Primary Endpoints:
Maximum tolerated dose/recommended dose, safety, and tolerability
Secondary Endpoints:
Preliminary efficacy: Response rates and duration of response

Brunner AM ASH 2021. Abstr 244.

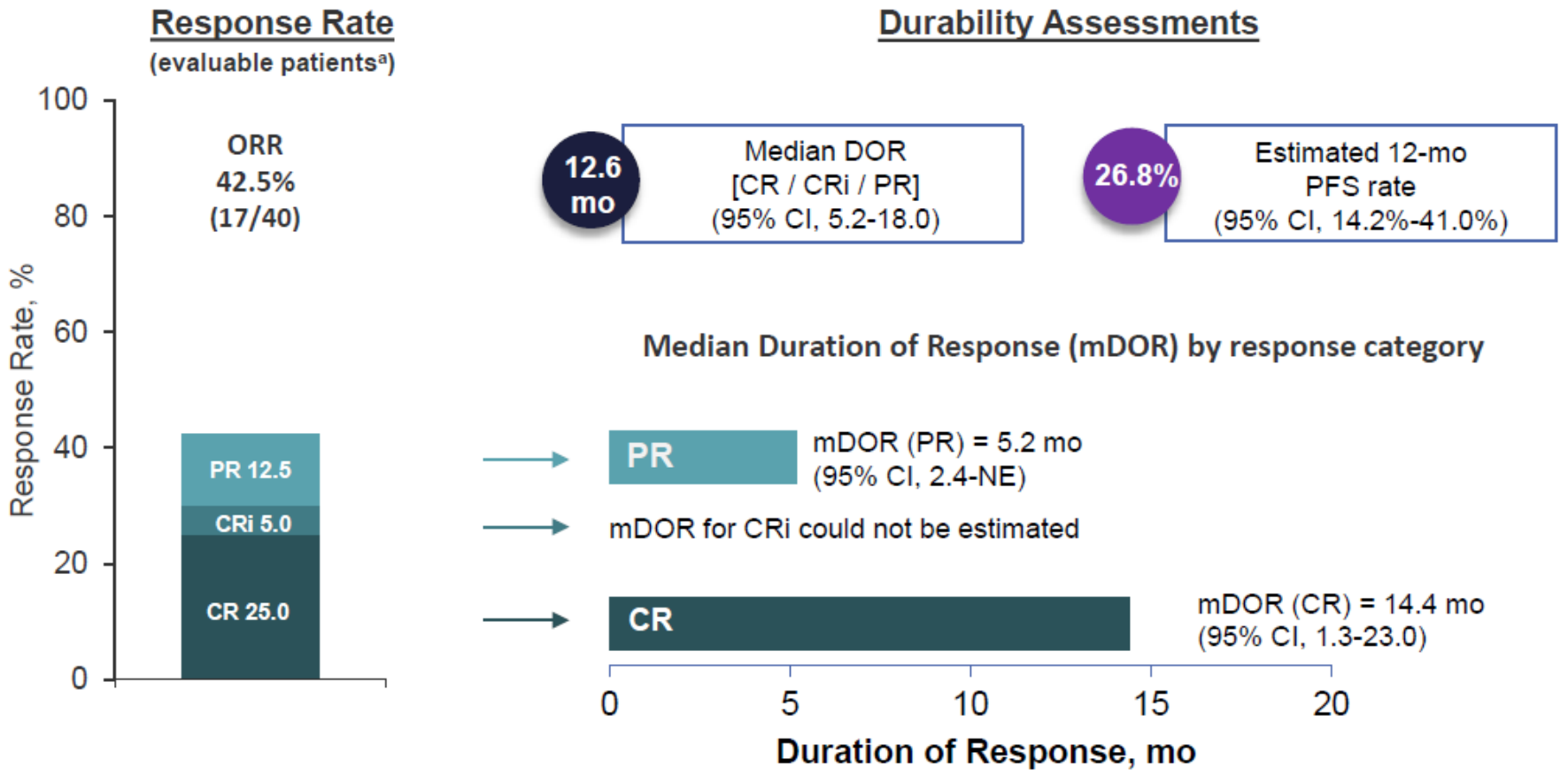
Patient Characteristics

Parameter	ND-AML n=48
Sabatolimab + decitabine, n	22
Sabatolimab + azacitidine, n	26
Median age (range), years	75 (59-89)
Male, n (%)	26 (54.2)
ECOG performance status, n (%)	
0	14 (29.2)
1	29 (60.4)
2	5 (10.4)
Risk Category n (%)	2017 ELN risk[2]
	Intermediate: 18 (37.5)
	Adverse: 30 (62.5)

Select available mutation data:	TP53 (n)	≥1 ELN adverse risk mutation (n)[a]
ND-AML (n=33[b])	6	14

Brunner AM ASH 2021. Abstr 244.

Efficacy Data



Brunner AM ASH 2021. Abstr 244.

Conclusions

- Adaptive or innate immune system harnessing therapies
  - ✓ BiTe (AMG330 - Anti-CLEC12A)
  - ✓ CAR-T; CAR-NK; (> 20 ongoing AML CAR-T CT registered with clinicaltrials.gov)
  - ✓ Vaccines
- Radioimmunetherapy in AML (α-particle emitting radionuclides)
  - ✓ actinium-225 (^{225}Ac) or astatine-211 (^{211}At)
- Chemoresistance and microenviroment in AML
  - ✓ Adrenomedullin
- Therapeutic potential of genetic reprogramming of LSC