Therapie des älteren AML Patienten

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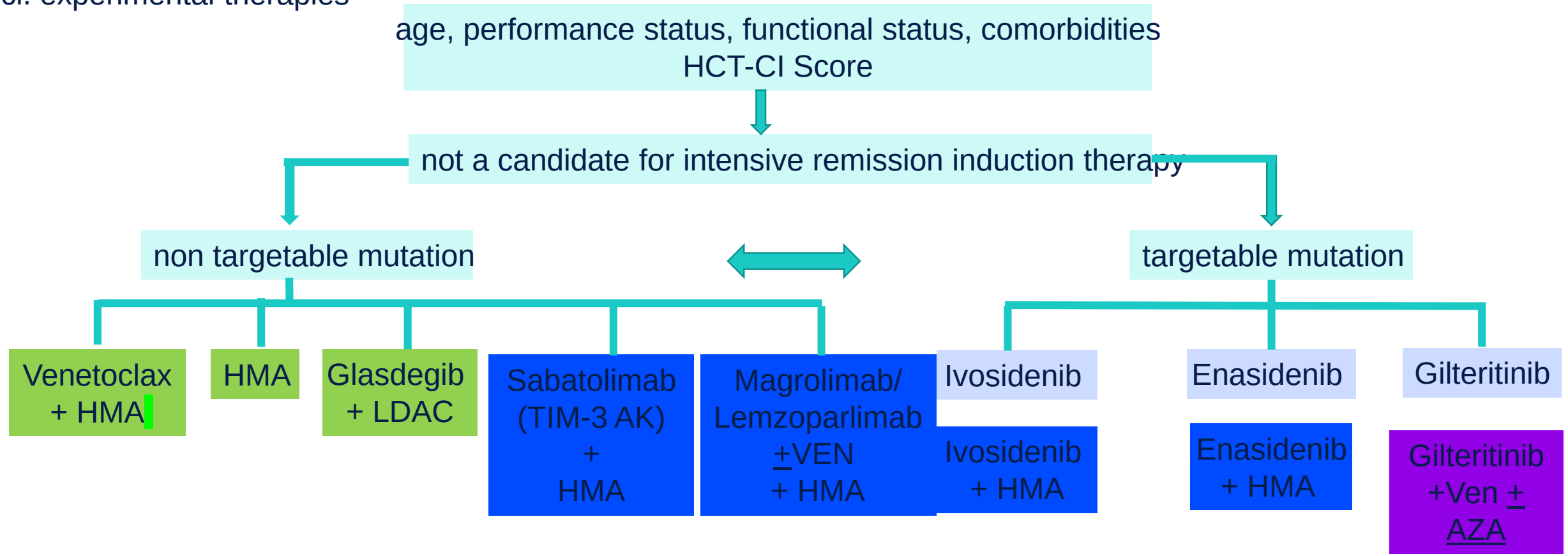
Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen	X					X	X
Pfizer						X	X
Jazz Pharmaceuticals						X	X
Daiichi Sankyo Oncology							X
Servier						X	X
Ariad/Incyte						X	
Novartis						X	
Abbvie						X	X
Celgene						X	
Morphosys						X	
Stemline						X	
Clinigen						X	

AML > 65 y not eligible for intensive CTx

Incl. experimental therapies



approved FDA/EMA

approved FDA

approved FDA R/R AML

in clinical trials

Courtesy: Prof. Dr. K. Götze

Study Design

VIALE-A

(NCT02993523)

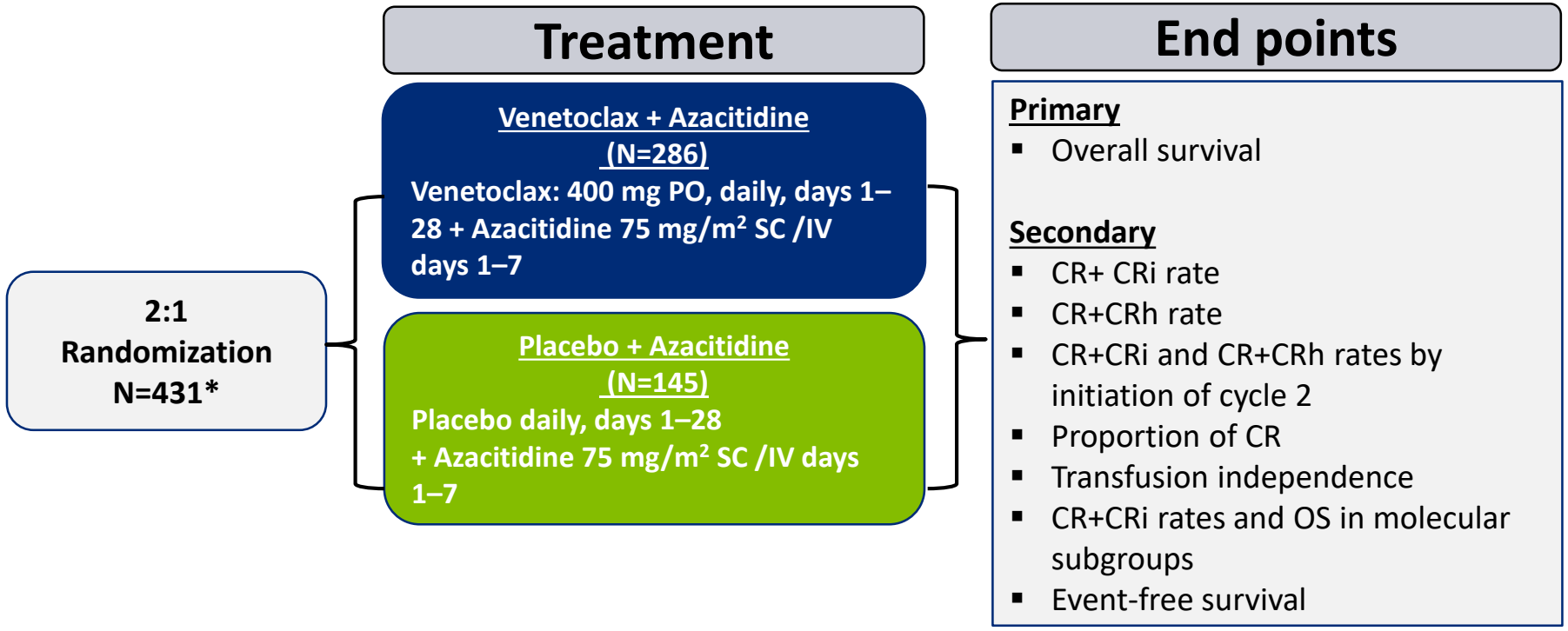
Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy, either ≥75 years of age OR 18 to 74 years of age with at least one of the following co-morbidities:
  - History of 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



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

DiNardo et al., NEJM 2020

* 6 patients did not receive treatment after randomization but included in the efficacy analysis

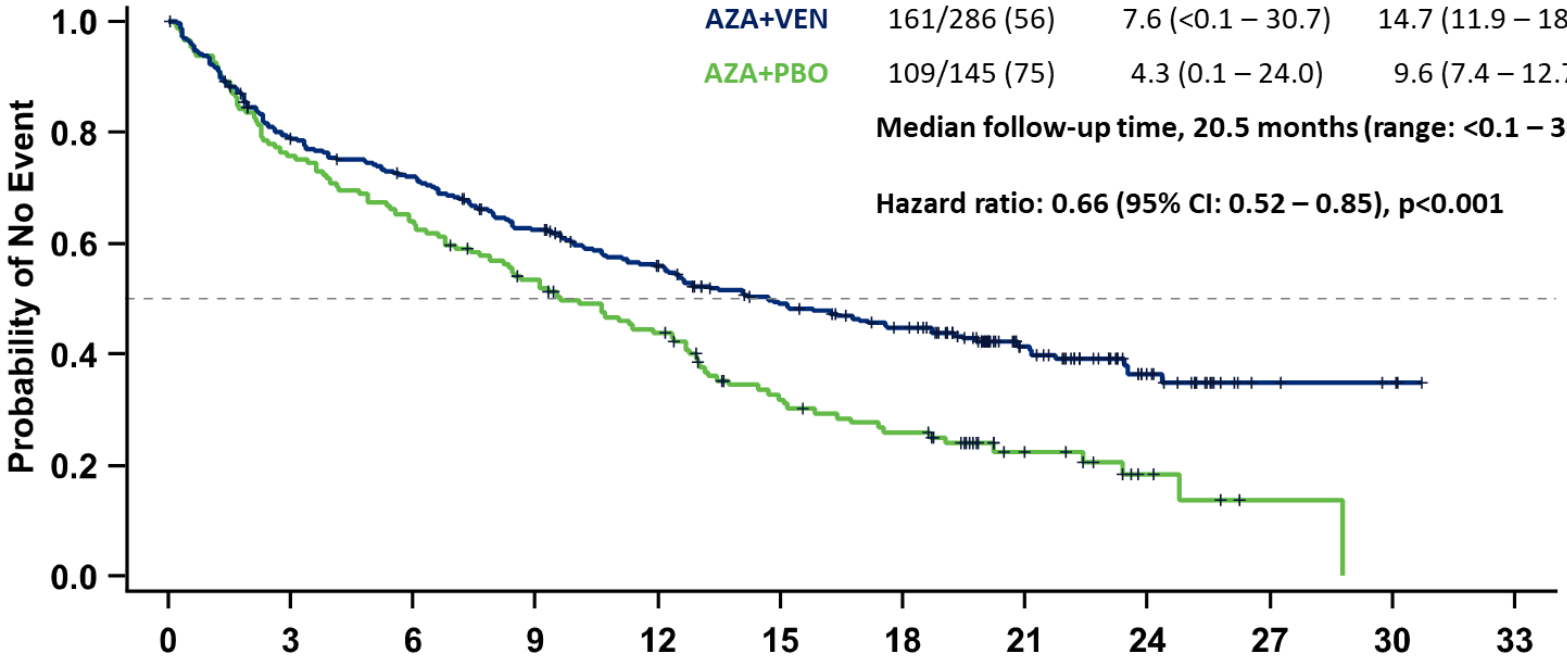
AML: Acute myeloid leukemia; CHF: Congestive heart failure; CNS: Central nervous system; CR: Complete remission; CRi: CR+ incomplete marrow remission; CRh: CR+ incomplete hematologic recovery; DCLO: diffusion lung capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; FEV1 : Forced expiratory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

Overall Survival

	No. of events/ No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
AZA+VEN	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
AZA+PBO	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Median follow-up time, 20.5 months (range: <0.1 – 30.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001



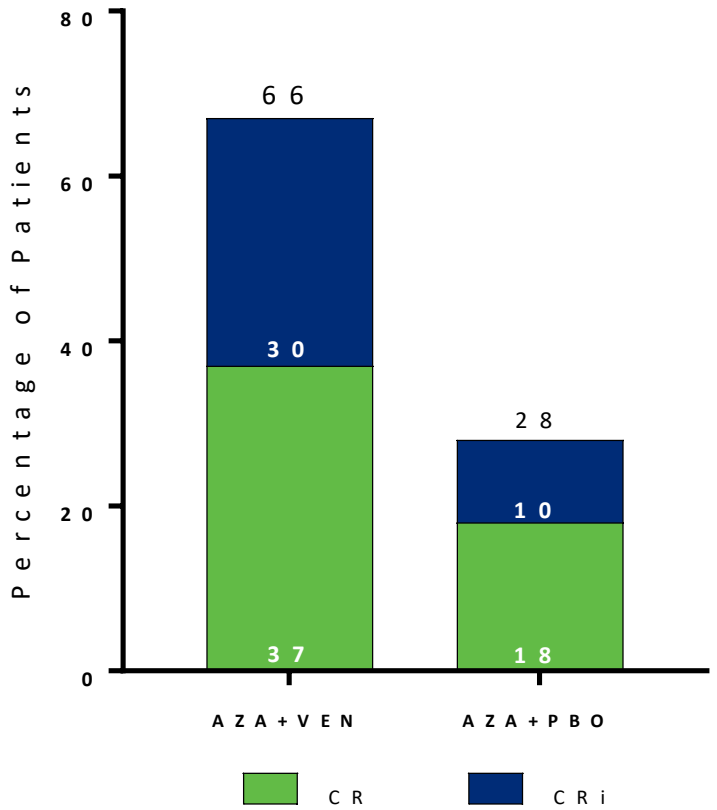
Patients at Risk

AZA+VEN	286	219	198	168	143	117	101	54	23	5	3	0
AZA+PBO	145	109	92	74	59	38	30	14	5	1	0	0

DiNardo et al., NEJM 2020

AZA: Azacitidine; PBO: Placebo; VEN: Venetoclax; The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk). The hazard ratio between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test.

Composite Response Rate (CR+CRi)



	No. of treatment cycles, median (range)	Median time to CR/CRi, Months*(range)	CR/CRi by initiation of Cycle-2*, n (%)
AZA+VEN (n=286)	**7.0 (1.0 – 30.0)**	**1.3 (0.6 - 9.9)**	**124 (43.4)**
	*p<0.001		
AZA+PBO (n=145)	**4.5 (1.0, 26.0)**	**2.8 (0.8 – 13.2)**	**11 (7.6)**

DiNardo et al., NEJM 2020

AZA: Azacitidine; CR: Complete remission; CRi: CR with incomplete marrow remission; PBO: Placebo; VEN: Venetoclax

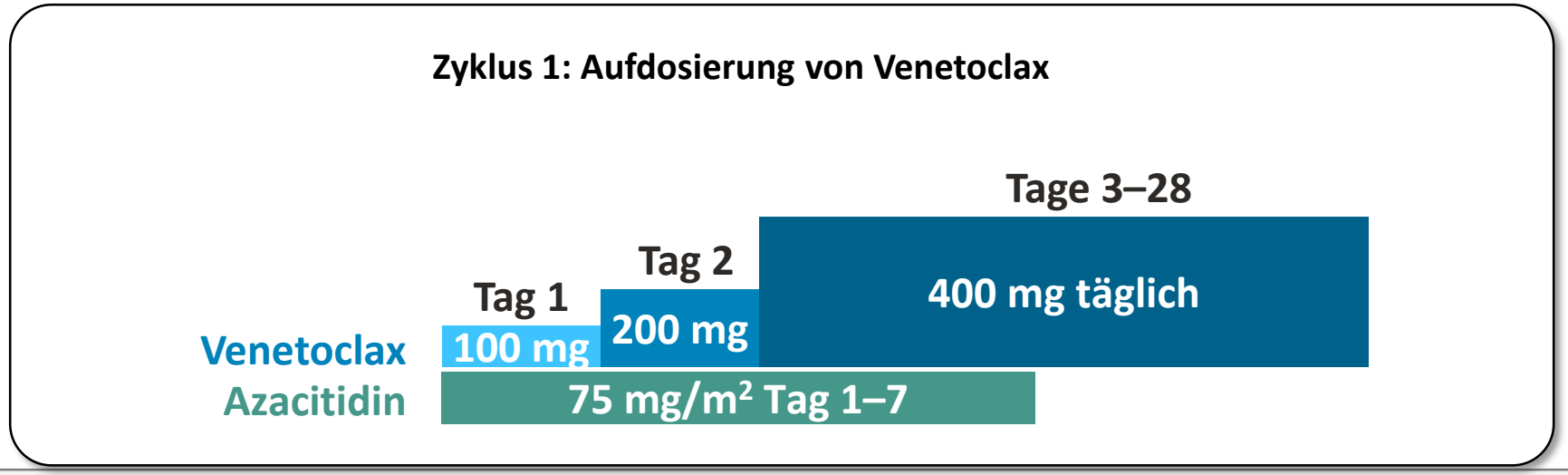
Standard-Dosierung von Venetoclax in VIALE-A[2]

Venetoclax

- Zyklus 1: Tag 1: 100mg, Tag 2: 200mg, Tag 3-28: 400mg oral täglich
- Ab Zyklus 2: Tag 1-28: 400mg oral täglich

Azacitidin

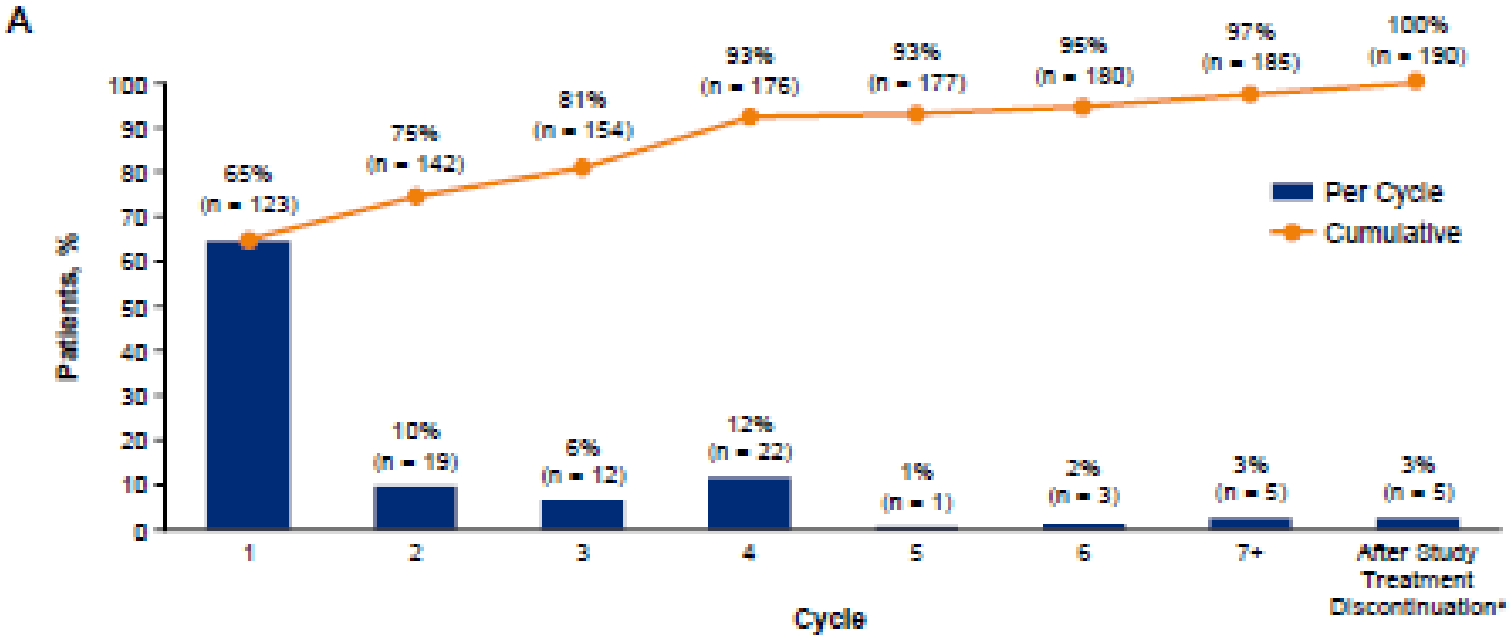
- Ab Zyklus 1: Tag 1-7: 75 mg/m² s.c./i.v. täglich, Tag 1–7 jedes 28-tägigen Zyklus



Um die mögliche Entwicklung schwerer Zytopenien während der Initiierung der Venetoclax-Therapie intensiv zu überwachen, sollte eine Hospitalisierung für den 1. Zyklus auf der Basis einer Risikobeurteilung in Betracht gezogen werden.

Viale A/C

- Punktion nach dem ersten Zyklus
  - Wenn Blasten unter 5%, in Ruhe die Regeneration abwarten
  - Wenn Blasten über 5%, Start 2. Zyklus



Phase-III-Studie VIALE-A

Sicherheitsprofil

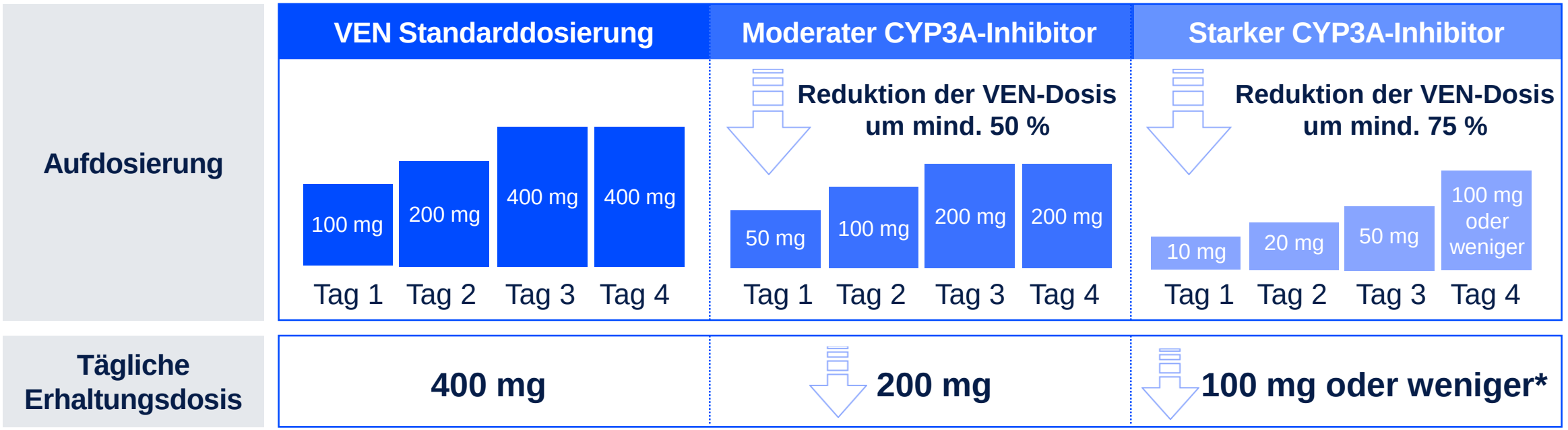
Unerwünschte Ereignisse (UE) Grad ≥ 3 (Häufigkeit ≥ 10 %)	VEN+AZA (n=283)	PBO+AZA (n=144)
Alle UE (%)	99	97
Hämatologische UE (%)	82	68
Thrombozytopenie	45	38
Neutropenie	42	28
febrile Neutropenie	42	19
Anämie	26	20
Leukopenie	21	12
Nicht-hämatologische UE (%)		
Hypokalämie	11	10
Infektionen (%)	64	51
Pneumonie	20	25

Mediane Anzahl erhaltener Therapiezyklen

- Allgemein gut charakterisierte und kontrollierbare Nebenwirkungen
- Stärker ausgeprägte **Myelosuppression** erfordert die folgenden Maßnahmen:
  - **ein engmaschiges Monitoring**
  - **zeitnahe Dosisanpassungen je nach Remissionsstatus und Blutbild**
  - **einen risikoadaptierten Einsatz der antiinfektiven Prophylaxe**
- Behandlungsabbruch aufgrund Zytopenien nur in seltenen Fällen

DiNardo CD et al. N Engl J Med 2020;383(7):617-629

Venetoclax + HMA: Dosisanpassungen Venetoclax bei gleichzeitiger Anwendung bestimmter Prophylaxen (CYP3A-Inhibitoren)



CAVE: 2 bis 3 Tage nach Absetzen des Inhibitors Wiederaufnahme der Therapie mit derselben Dosis von Venetoclax wie vor Beginn der Behandlung mit dem CYP3A-Inhibitor!

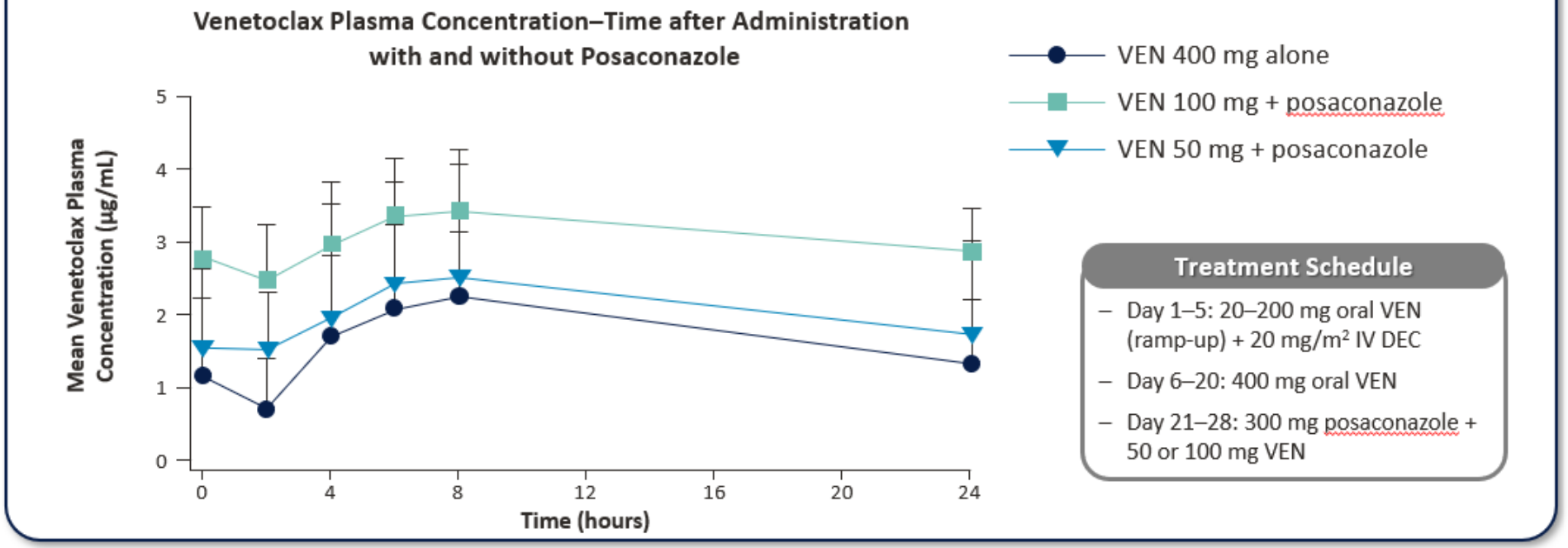
* Im Studienprotokoll VIALE-A wurde 50 mg als tägliche Erhaltungsdosis bei gleichzeitiger Anwendung eines starken CYP3A-Inhibitors festgelegt.

DiNardo CD et al. N Engl J Med 2020;383(7):617-629,
Fachinformation VENCLYXTO®; Stand Juni 2021.

Erhöhung der Venetoclax Exposition bei gleichzeitiger Anwendung von CYP3A Inhibitoren

Da Venetoclax vorwiegend durch CYP3A metabolisiert wird, erhöht die gleichzeitige Anwendung mit Antimykotika, die starke oder moderate CYP3A-Inhibitoren sind, die Exposition gegenüber Venetoclax.

Based on a posaconazole DDI substudy from M14-358, posaconazole increases venetoclax dose-normalized C_{max} 7.1-fold and $AUC_{0–24}$ 8.8-fold

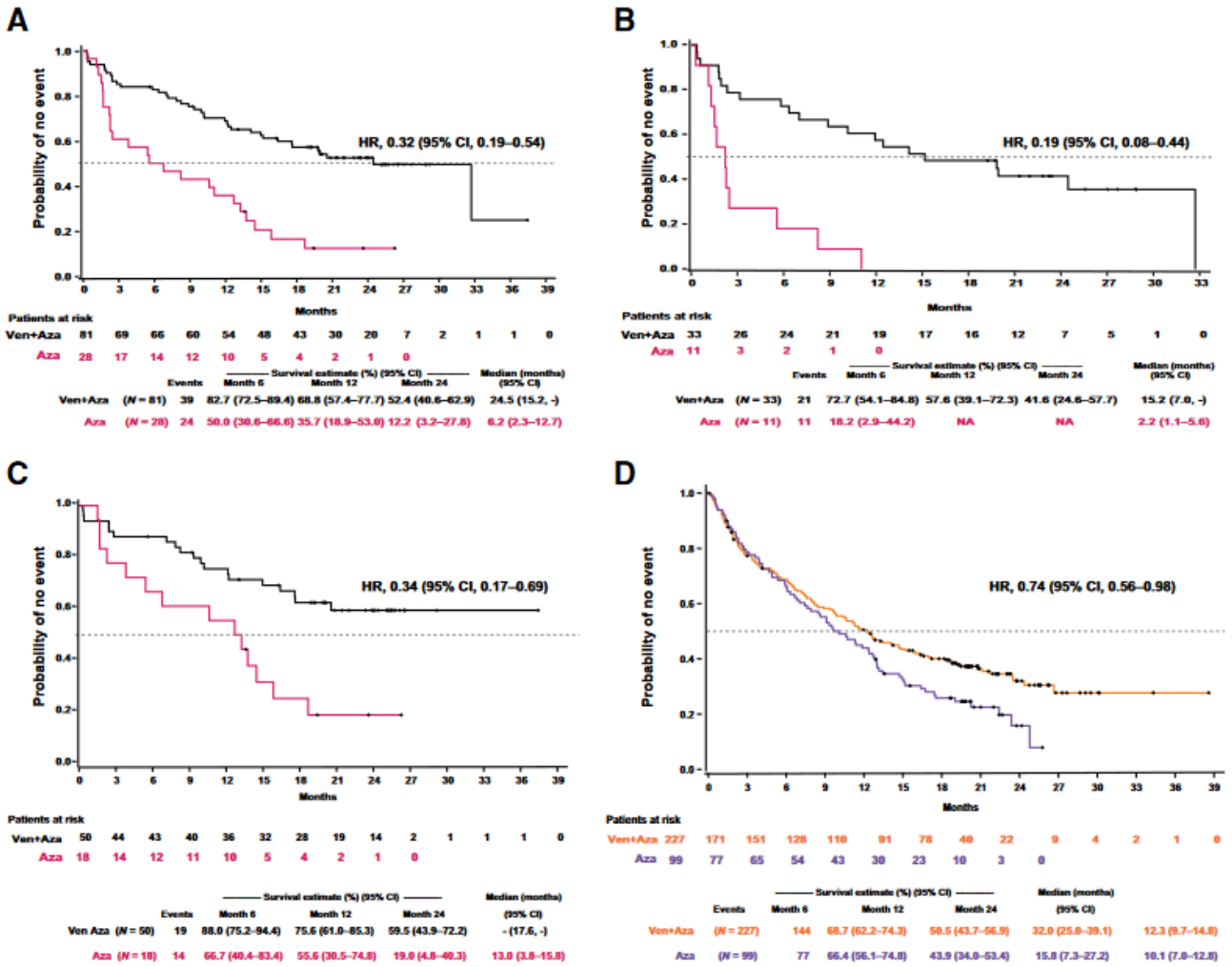


$AUC_{0–24}$=Area Under Curve Over 24 Hours. C_{max}=Maximum Serum Concentration. CYP3A=Cytochrome P450 3A. DEC=Decitabine. DDI=Drug-Drug Interaction. VEN=Venetoclax.

Agarwal SK, et al. Clin Ther 2017; 39:359-367.

IDH1/IDH2 AML Patienten haben eine gute Prognose unter Aza/Venetoclax

IDH2 Mutierte



IDH1 Mutierte

Viale-A Überleben der IDH1/2 mutierten Patienten

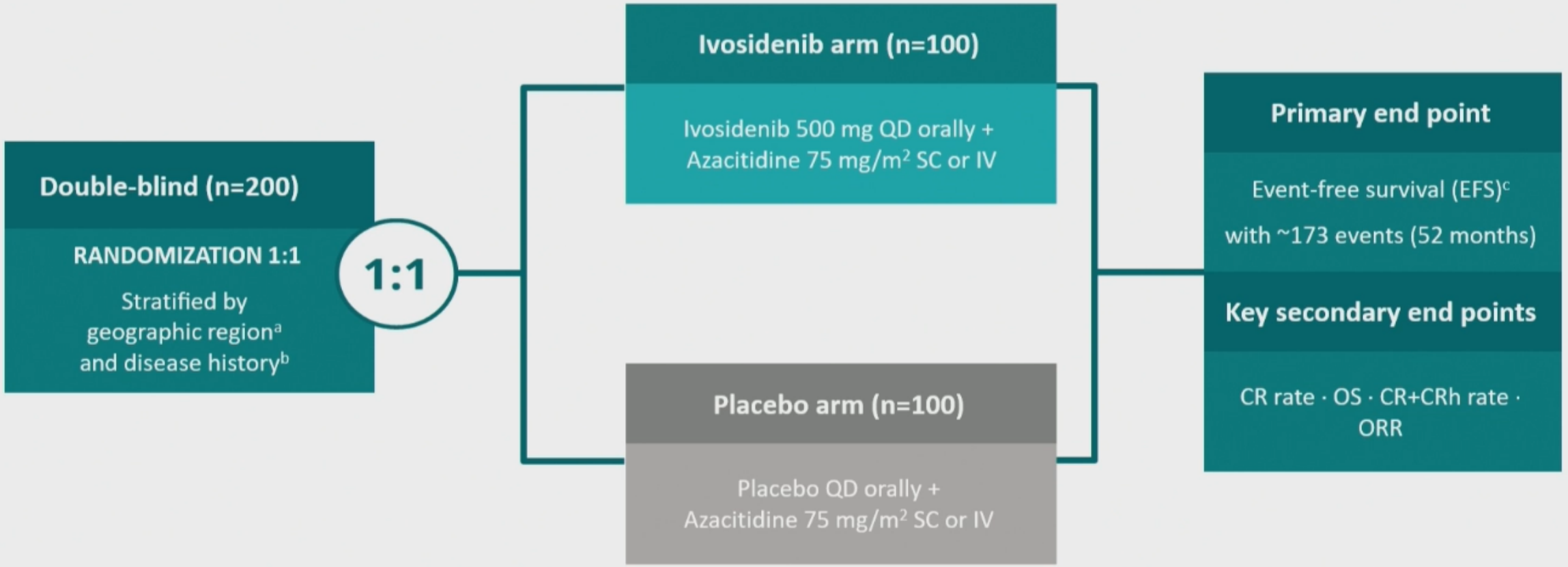
Pollyeda et al. CCR, 2022

AGILE: A Global, Randomized, Double-Blind, Phase 3 Study of Ivosidenib + Azacitidine Versus Placebo + Azacitidine in Patients with Newly Diagnosed Acute Myeloid Leukemia with an *IDH1* Mutation

Pau Montesinos, PhD, MD, Christian Recher, MD, Susana Vives, MD, Ewa Zarzycka, MD, Jianxiang Wang, MD, Giambattista Bertani, MD, Michael Heuser, MD, Rodrigo T. Calado, MD, PhD, Andre C. Schuh, MD, Su-Peng Yeh, MD, Scott R. Daigle, MS, Jianan Hui, PhD, Vickie Zhang, PhD, Shuchi S. Pandya, MD, Diego A. Gianolio, PhD, Stephane de Botton, MD, PhD and ***Hartmut Döhner, MD***

Presented at ASH 2021

AGILE: study design and end points



- As of the data cutoff date for this analysis (18March2021), 146 patients have been randomized (IVO+AZA, n=72; PBO+AZA, n=74).
  - As of 12May2021, the IDMC recommended to halt enrollment based on a noted difference in clinical importance between the treatment groups, not related to safety.
    - A total of 148 patients were enrolled at 155 active sites in 20 countries.

[a]Geographic regions: US/Canada; Western Europe, Israel and Australia; Japan; and Rest of the World. [b]Disease history: de novo vs secondary AML
[c]**EFS is defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve CR by week 24**
CR = complete remission; CRh = complete remission with partial hematologic recovery; IDMC = independent data monitoring committee; IV = intravenously; ORR = objective response rate; OS = overall survival; PBO = placebo; QD = once daily; SC = subcutaneously

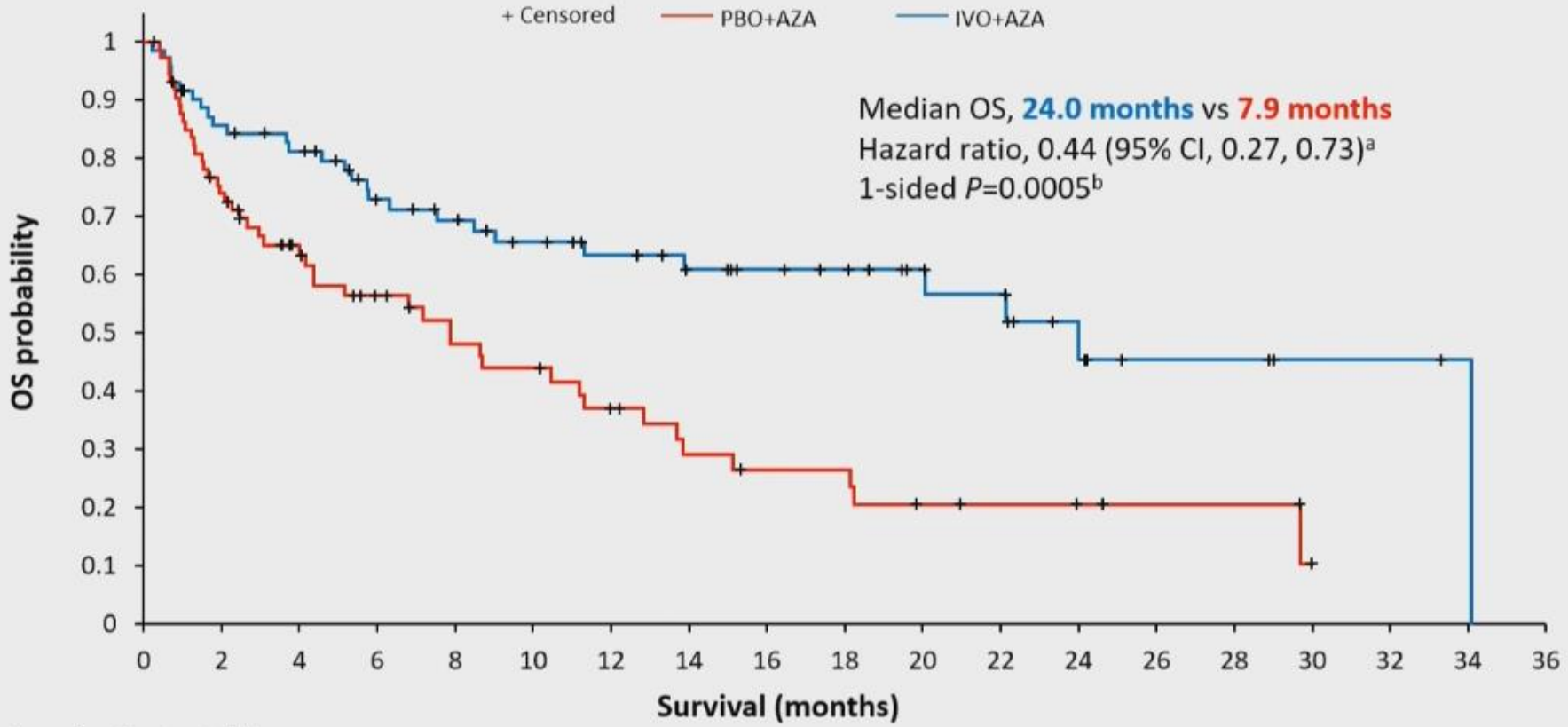
Baseline demographic and disease characteristics

Characteristic	IVO+AZA (n=72)	PBO+AZA (n=74)
Median (range) age, years	76 (58–84)	75.5 (45–94)
Sex, n (%)		
Male/Female	42 (58.3)/30 (41.7)	38 (51.4)/36 (48.6)
ECOG PS score, n (%)		
0/1/2	14 (19.4)/32 (44.4)/26 (36.1)	10 (13.5)/40 (54.1)/24 (32.4)
Disease history (per investigator), n (%)		
De novo AML	54 (75.0)	53 (71.6)
Secondary AML[a]	18 (25.0)	21 (28.4)
Median (range) m*IDH1* VAF in BMA, % (range)[b]	36.7 (3.1–50.5)	35.5 (3.0–48.6)
Cytogenetic risk, n (%)[c]		
Favorable/intermediate/poor	3 (4.2); 48 (66.7); 16 (22.2)	7 (9.5); 44 (59.5); 20 (27.0)
Median (range) bone marrow blasts, %	54 (20–95)	48.0 (17–100)

[a]Secondary AML included patients with treatment-related AML, with history of MDS, or with history of MPN. [b]IVO+AZA, n=49; PBO+AZA, n=58; VAF was quantified by next-generation sequencing. [c]Cytogenetic risk status was reported as other or missing for 5 patients (6.9%) in the IVO+AZA arm and 3 patients (4.1%) in the PBO+AZA arm

BMA = bone marrow aspirate; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasms; VAF = variant allele frequency

IVO+AZA significantly improves OS



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

- OS benefit was consistent across subgroups: de novo status, region, age, baseline ECOG PS score, sex, race, baseline cytogenetic risk status, WHO classification of AML, baseline white blood cell count, baseline percentage of bone marrow blasts.

[a]Hazard ratio was estimated using a Cox's proportional hazards model stratified by the randomization stratification factors
[b]*P* value was calculated from the one-sided log-rank test stratified by the randomization stratification factors

IVO+AZA improved clinical and hematologic response

Response rates	IVO+AZA (n=72)	PBO+AZA (n=74)
CR rate, n (%) [95% CI]	34 (47.2) [35.3, 59.3]	11 (14.9) [7.7, 25.0]
Odds ratio (95% CI); 1-sided *P* value	4.8 (2.2, 10.5); *P*<0.0001	
Median duration of CR (95% CI), months	NE (13.0, NE)	11.2 (3.2, NE)
Median time to CR (range), months	4.3 (1.7–9.2)	3.8 (1.9–8.5)
CR+CRh rate, n (%) [95% CI]	38 (52.8) [40.7, 64.7]	13 (17.6) [9.7, 28.2]
Odds ratio (95% CI); 1-sided *P* value	5.0 (2.3, 10.8); *P*<0.0001	
Median duration of CR+CRh (95% CI), months	NE (13.0, NE)	9.2 (5.8, NE)
Median time to CR+CRh (range), months	4.0 (1.7–8.6)	3.9 (1.9–7.2)
ORR, n (%) [95% CI]	45 (62.5) [50.3, 73.6]	14 (18.9) [10.7, 29.7]
Odds ratio (95% CI); 1-sided *P* value	7.2 (3.3, 15.4); *P*<0.0001	
Median duration of response (95% CI), months	22.1 (13.0, NE)	9.2 (6.6, 14.1)
Median time to first response (range), months	2.1 (1.7–7.5)	3.7 (1.9–9.4)

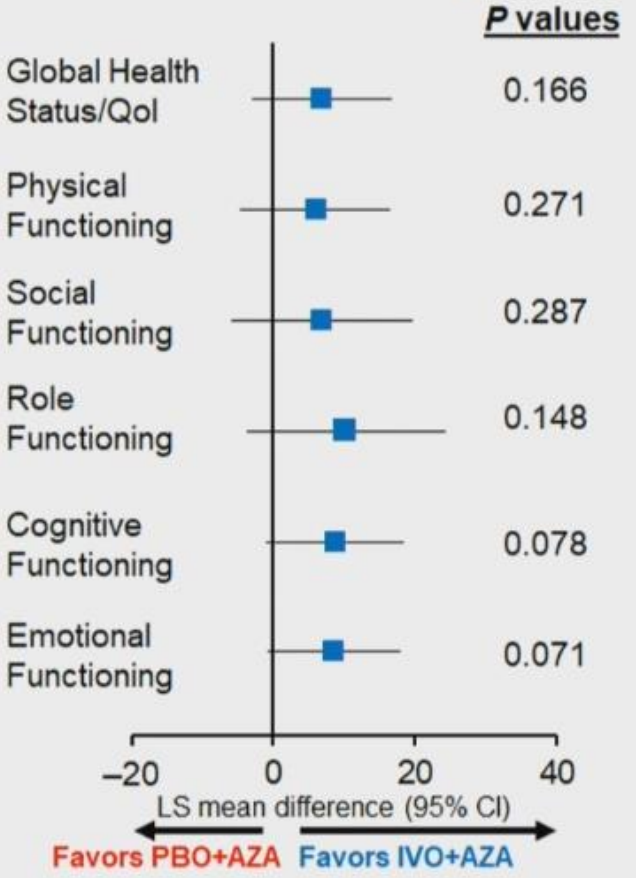
m*IDH1* clearance[a] in BMMCs by response, n/N[b] (%)	IVO+AZA (n=43[c])	PBO+AZA (n=34[c])
CR+CRh	17/33 (51.5)	3/11 (27.3)
CR	14/29 (48.3)	2/10 (20)
CRh	3/4 (75)	1/1 (100)
Non–CR+CRh responders	2/4 (50)	0/2 (0)
Nonresponders	1/6 (16.7)	0/21 (0)

[a]Assessed by BEAMing Digital PCR (limit of detection 0.02–0.04%) in patients with at least one on-treatment sample available. [b]N being the total number of patients with available biomarker samples in the corresponding category. [c]Total number of patients with available biomarker samples in the corresponding treatment group

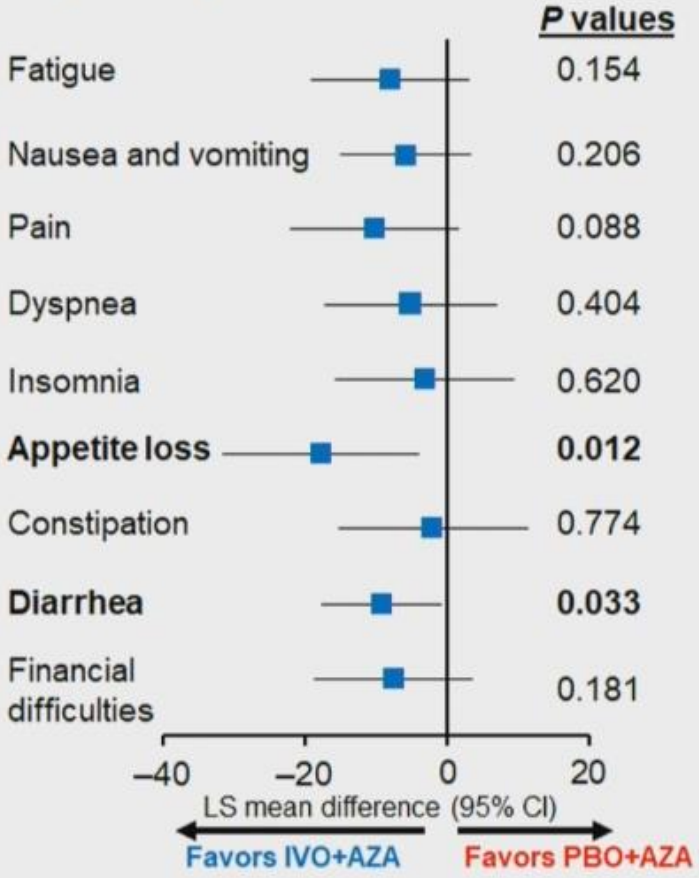
BMMC = bone marrow mononuclear cell; PCR = polymerase chain reaction

HRQoL: change from baseline (additional secondary end point)

A. EORTC QLQ-C30 Global Heath Status/QoL and functional subscales at cycle 5 day 1[a]



B. EORTC QLQ-C30 symptom subscales at cycle 5 day 1[b]



- HRQoL results favored IVO+AZA across all subscales.
- No subscales improved for PBO+AZA when applying a 10-point threshold[1] for clinically meaningful change across visits.
- Notably, there were clinically meaningful improvements in Global Health Status/QoL and Fatigue subscales over time in the IVO+AZA arm and compared with PBO+AZA.

At cycle 5 day 1: IVO+AZA, n=40; PBO+AZA, n=25. Bold text indicates $P<0.05$. [a]Higher scores denote better health status or function. [b]Higher scores denote worse symptoms
EORTC = European Organisation for Research and Treatment of Cancer; HRQoL = health-related quality of life; LS = least squares; QLQ-C30 = Quality of Life Questionnaire Core 30

1. Osoba D et al. *J Clin Oncol*. 1998;16:139–144.

Treatment-emergent adverse events (TEAEs)

	IVO+AZA (n=71)		PBO+AZA (n=73)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE, n (%)	70 (98.6)	66 (93.0)	73 (100)	69 (94.5)
Any hematologic TEAEs, n (%)	55 (77.5)	50 (70.4)	48 (65.8)	47 (64.4)
Most common hematologic TEAEs (>20%[a]), n (%)				
Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Most common TEAEs (>20%[a]), n (%)				
Nausea	30 (42.3)	2 (2.8)	28 (38.4)	3 (4.1)
Vomiting	29 (40.8)	0	19 (26.0)	1 (1.4)
Diarrhea	25 (35.2)	1 (1.4)	26 (35.6)	5 (6.8)
Pyrexia	24 (33.8)	1 (1.4)	29 (39.7)	2 (2.7)
Constipation	19 (26.8)	0	38 (52.1)	1 (1.4)
Pneumonia	17 (23.9)	16 (22.5)	23 (31.5)	21 (28.8)
Bleeding, n (%)	29 (40.8)	4 (5.6)	21 (28.8)	5 (6.8)
Infections, n (%)	20 (28.2)	15 (21.1)	36 (49.3)	22 (30.1)

- TEAEs of special interest with IVO+AZA vs PBO+AZA included grade ≥2 differentiation syndrome (14.1% vs 8.2%) and grade ≥3 QT prolongation (9.9% vs 4.1%[b]).
- Infections were less common with IVO+AZA (28.2%) compared with PBO+AZA (49.3%).
- There were no deaths deemed related to treatment.

[a]>20% cutoff used for any-grade TEAEs based on IVO+AZA
[b]QT prolongation with PBO+AZA includes electrocardiogram QT prolonged (2.7%) and syncope (1.4%)

Venetoclax in Combination With Gilteritinib Demonstrates Molecular Clearance of *FLT3* Mutation in Relapsed/Refractory *FLT3*-mutated Acute Myeloid Leukemia

Naval Daver,[1] Alexander E. Perl,[2] Joseph Maly,[3] Mark Levis,[4] Ellen Ritchie,[5] Mark Litzow,[6] James McCloskey,[7] Catherine C. Smith,[8] Gary Schiller,[9] Terrence Bradley,[10,11] Ramon V. Tiu,[12] Kiran Naqvi,[13] Monique Dail,[13] Satya Siddani,[14] Jing Wang,[14] Brenda Chyla,[14] Paul Lee,[14] Jessica K. Altman[15]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [3]Norton Cancer Institute, Louisville, KY, USA; [4]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [5]Division of Hematology and Oncology, Weill Cornell Medical College, New York, NY, USA; [6]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [7]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ, USA; [8]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [9]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [10]University of Miami, Department of Medicine, Miami, FL, USA; [11]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [12]Astellas Pharma US, Northbrook, IL, USA; [13]Genentech, South San Francisco, CA, USA; [14]AbbVie Inc., North Chicago, IL, USA; [15]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA

American Society of Hematology Annual Meeting, December 11–14, 2021, Atlanta, Georgia

Most Patients (59%) Had Received ≥1 Prior FLT3 TKI

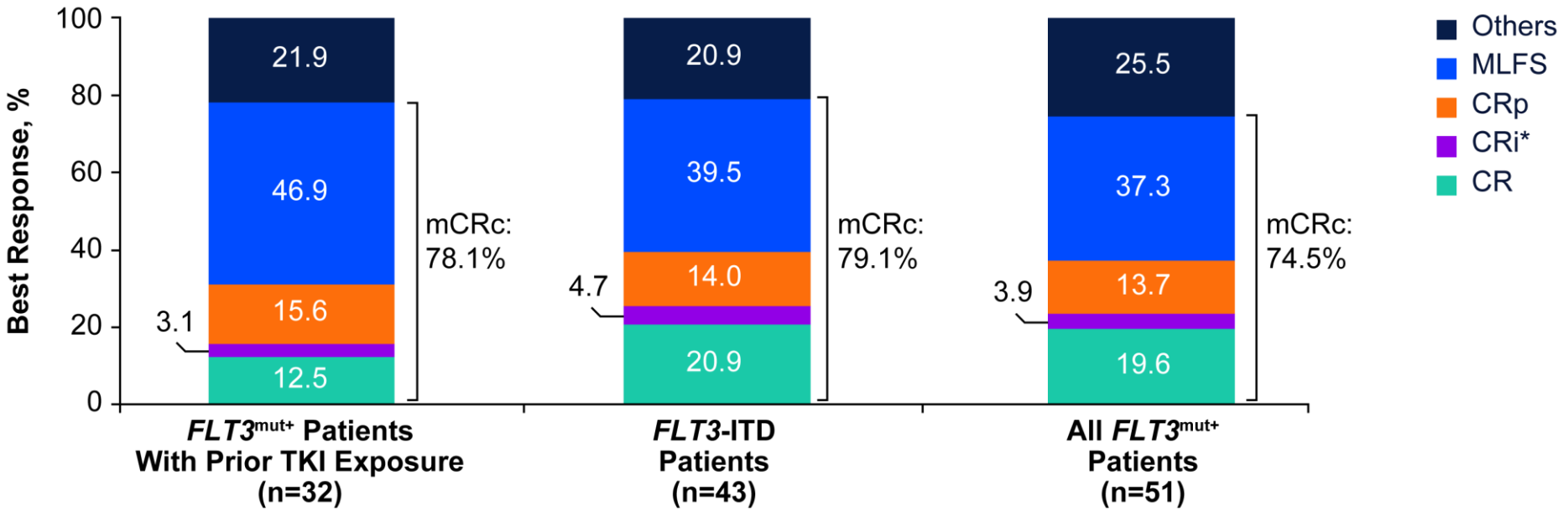
Baseline Characteristics

	Patients receiving Ven + Gilt at RP2D (N=54)
Median age, years (range)	64.0 (21.0–85.0)
***FLT3* mutation, n (%)**	
ITD only	41 (76)
TKD only	8 (15)
ITD and TKD	3 (6)
NCCN cytogenetic risk, n (%)[a]	
Favorable	2 (4)
Intermediate	28 (54)
Poor	18 (35)
No mitoses	4 (8)
AML type, n (%)	
De novo	42 (78)
Secondary	12 (22)

	Patients receiving Ven + Gilt at RP2D (N=54)
Median no. prior therapies (range)	2.0 (1–5)
Prior therapies, n (%)	
1	13 (24)
2	23 (43)
≥3	18 (33)
Prior therapy, n (%)	
≥1 prior FLT3 TKI	32 (59)
Prior Gilt	0
Prior Ven	10 (19)
Prior allo-transplant, n (%)	17 (31)

[a]Percentages are calculated on non-missing values (n=52).
Gilt, gilteritinib; LoT, line of therapy; NCCN, National Comprehensive Cancer Network; RP2D, recommended Phase 2 dose; TKI, tyrosine kinase inhibitor; Ven, venetoclax.

Summary of Best Responses



	FLT3^{mut+} Patients With Prior TKI Exposure (n=32)	*FLT3*-ITD Patients (n=43)	All *FLT3*$^{mut+}$ Patients (n=51)
mCRc[a], n (%)	25 (78.1)	34 (79.1)	38 (74.5)
CR+CRp+CRi[b]*	10 (31.3)	17 (39.5)	19 (37.3)
MLFS	15 (46.9)	17 (39.5)	19 (37.3)

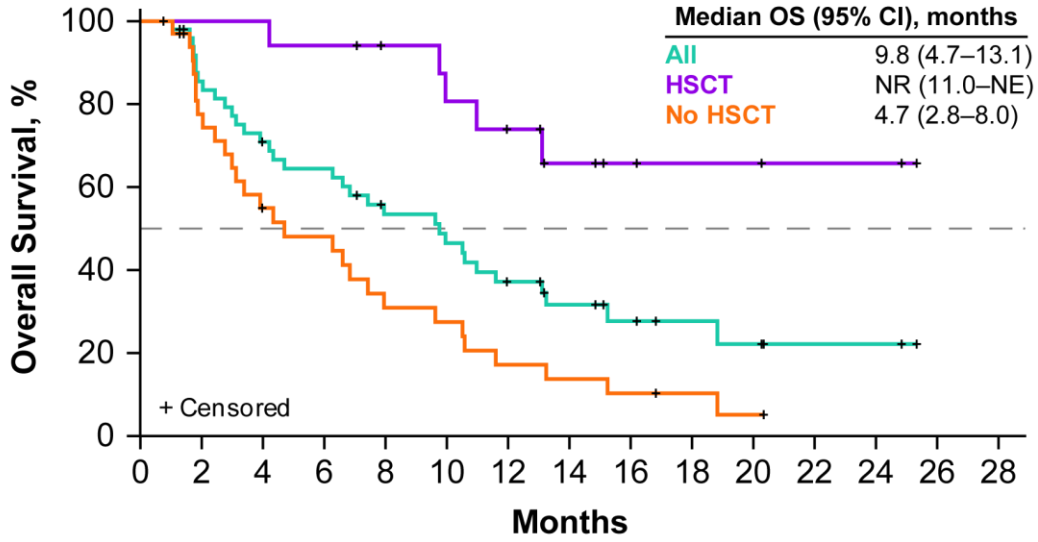
The mCRc rate in this study was **74.5**%. The CRc rate in the ADMIRAL Phase 3 study for single agent Gilt was 54.3% (using the same response parameters).[1]

[a]mCRc defined as CR+CRp+CRi*+MLFS, per modified IWG response criteria. [b]Hematology criteria for CRi* is ANC ≤1×10^9/L and platelet >100×10^9/L, which is mutually exclusive with IWG response CRp.
CR, complete remission; CRi*, complete remission with incomplete neutrophil count recovery; CRp, complete remission with incomplete platelet recovery; ITD, internal tandem duplication; IWG, International Working Group; mCRc, modified composite complete remission; MLFS, morphologic leukemia-free state; TKI, tyrosine kinase inhibitor.

1. Perl AE, et al. *N Engl J Med.* 2019;381(18):1728–1740.

OS by Transplant or Response Status

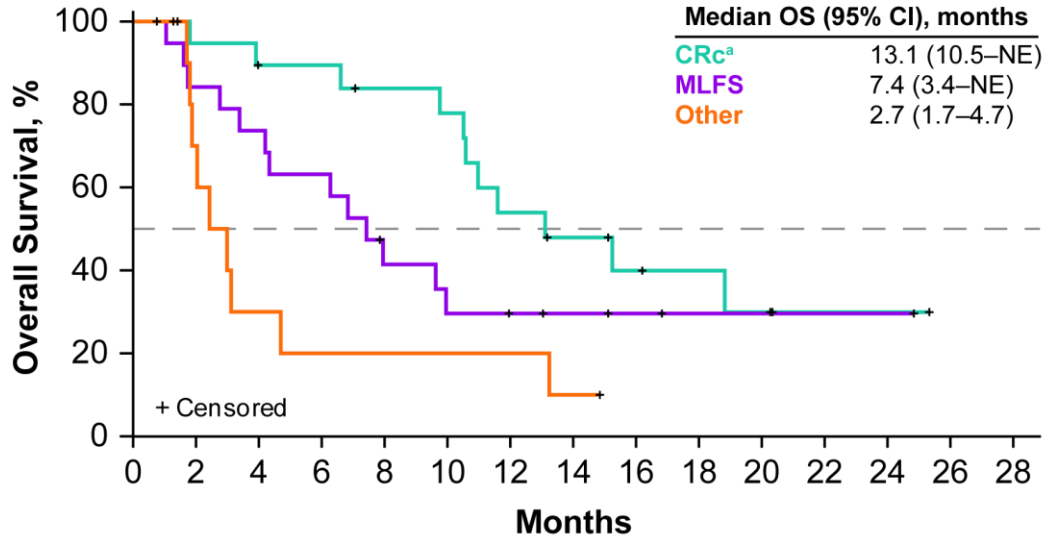
OS by Transplant Status (*FLT3*$^{mut+}$ Patients)



Patients at Risk

All	51	41	33	30	23	20	15	11	7	5	4	2	2	0
HSCT	17	17	17	16	14	12	10	7	4	3	3	2	2	0
No HSCT	34	24	16	14	9	8	5	4	3	2	1	0		

OS by Best Response Status (*FLT3*$^{mut+}$ Patients)



Patients at Risk

CRc	19	18	16	16	14	13	9	7	5	4	3	1	1	0
MLFS	19	16	14	12	7	5	4	3	2	1	1	1	1	0
Other	13	7	3	2	2	2	2	1	0					

- Median duration of follow-up was 15.1 months (range, 0.8–25.3)
- Median OS for *FLT3*-ITD patients was 10.0 months (95% CI, 6.6–13.2)

[a]CRc defined as CR+CRp+CRi*.

CR, complete remission; CRc, composite complete remission; CRi*, complete remission with incomplete neutrophil count recovery; CRp, complete remission with incomplete platelet recovery; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; MLFS, morphologic leukemia-free state; NE, not estimable; NR, not reached; OS, overall survival.

A Triplet Combination of Azacitidine, Venetoclax and Gilteritinib for Patients with FLT3-mutated AML: Results from a Phase I/II Study

NJ Short, CD Dinardo, N Daver, D Nguyen, M Yilmaz, T Kadia, G Garcia-Manero, GC Issa, X Huang, W Qiao, K Sasaki, G Montalban-Bravo, K Chien, G Borthakur, R Delumpa, A Milton, S Pierce, E Jabbour, M Konopleva, H Kantarjian, F Ravandi

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Aza+Ven+Gilteritinib in FLT3-mutated AML: Regimen

- Relapsed/refractory *FLT3*-mutated* AML or high-risk MDS or CMML

or

- Newly diagnosed *FLT3*-mutated* AML unfit for intensive chemotherapy

Induction

Azacitidine
75 mg/m² IV/SC on D1-7

Venetoclax#
D1-28 (bone marrow on D14)%

Gilteritinib
80-120 mg on D1-28

Consolidation (up to 24 cycles)

Azacitidine
75 mg/m² IV/SC on D1-5

Venetoclax
400mg on D1-7

Gilteritinib
80-120 mg on D1-28

* FLT3-ITD or FLT3 D835 mutations allowed

Venetoclax ramp-up during cycle 1: 100mg on D1, 200mg on D2, 400mg on D3+

% If <5% blasts or insufficient on C1D14, venetoclax held (both cohorts) and gilteritinib held (frontline only)

- Primary endpoints: MTD of gilteritinib in combination (phase I), CR/CRi rate (phase II)
- Secondary endpoints: CR rate, MRD negativity rate, duration of response, OS, safety

Aza+Ven+Gilteritinib in FLT3-mutated AML: Patients

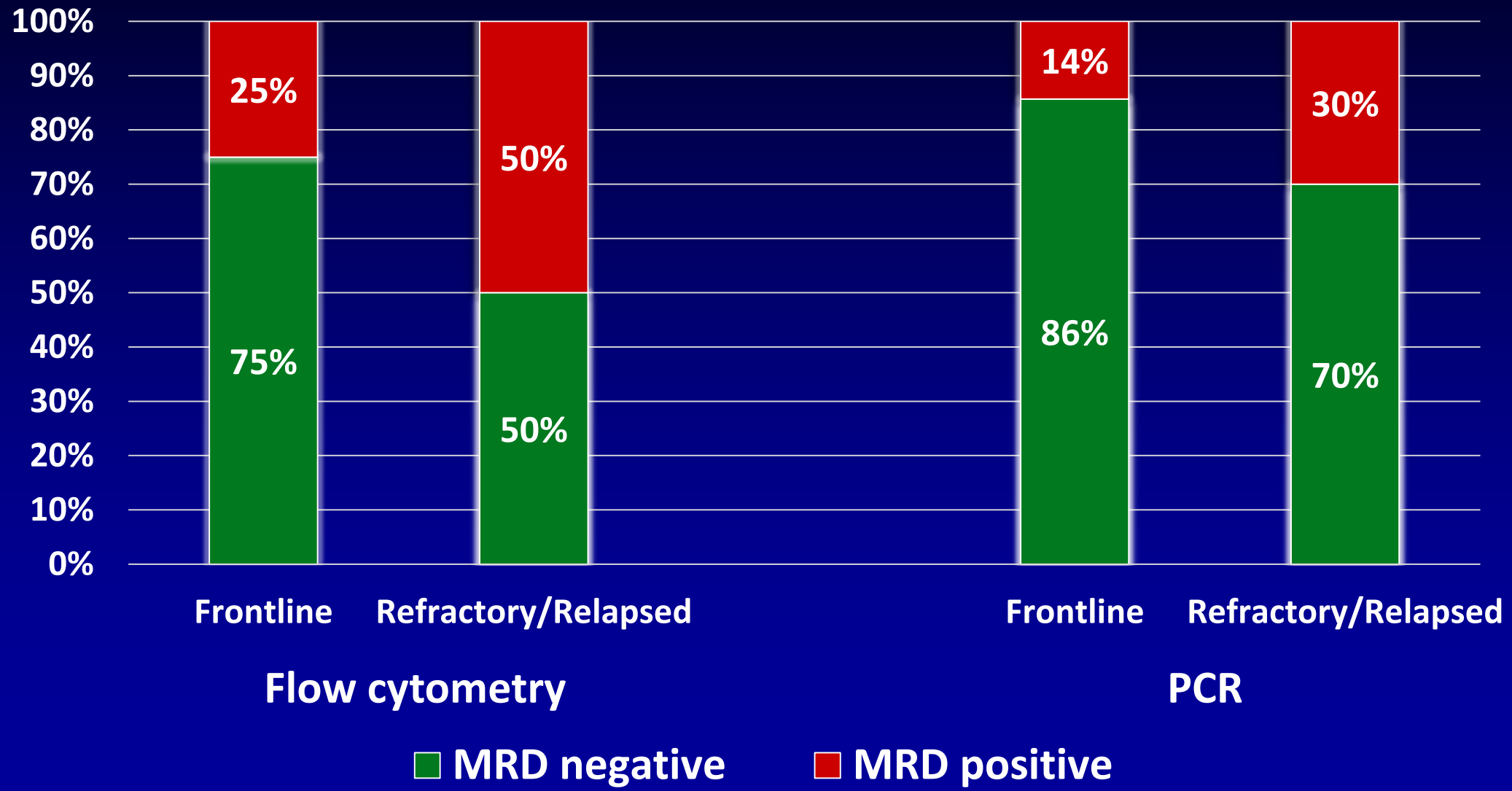
		Frontline (N=14)	Relapsed/Refractory (N=16)
Characteristic	Category	N (%) / median [range]	N (%) / median [range]
Age (years)		71 [61-82]	68 [19-90]
	≥60 years	14 (100)	12 (75)
	≥75 years	4 (29)	3 (19)
Diagnosis	AML	14 (100)	15 (94)
	MDS/CMML	0	1 (6)
Cytogenetics	Diploid	7 (50)	6 (37)
	Adverse-risk	3 (21)	6 (37)
	Others	4 (29)	4 (26)
FLT3 mutation type	ITD	11 (79)	7 (44)
	TKD	3 (21)	6 (37)
	ITD+TKD	0	3 (19)
FLT3 allelic ratio	ITD	0.29 [0.04-3.35]	0.61 [0.03-15.7]
	TKD	0.85 [0.03-1.11]	0.59 [0.01-1.35]
Number of prior therapies		---	2 [1-5]
Prior FLT3 inhibitor		---	5 (31)
Prior HMA + venetoclax		---	7 (44)
Prior HSCT		---	5 (31)

Aza+Ven+Gilteritinib in FLT3-mutated AML: Responses

Response, n/N (%)	Frontline N = 14	R/R N = 16
mCRc (CR/CRi/MLFS)	14 (100)	11 (69)
CR	13 (93)	3 (19)
CRi	0	2 (13)
MLFS	1 (7)	6 (37)
PR**	0	1 (6)
No response	0	4 (25)
Early death	0	0

** PR in 1 patient with extramedullary-only disease (assessed by PET scan)

Aza+Ven+Gilteritinib in FLT3-mutated AML: Best MRD Response



Prognostic impact of *NPM1* and *FLT3* mutations at diagnosis and presence of measurable residual disease (MRD) after intensive chemotherapy for patients with acute myeloid leukemia in remission: outcomes from the QUAZAR AML-001 trial of oral azacitidine maintenance

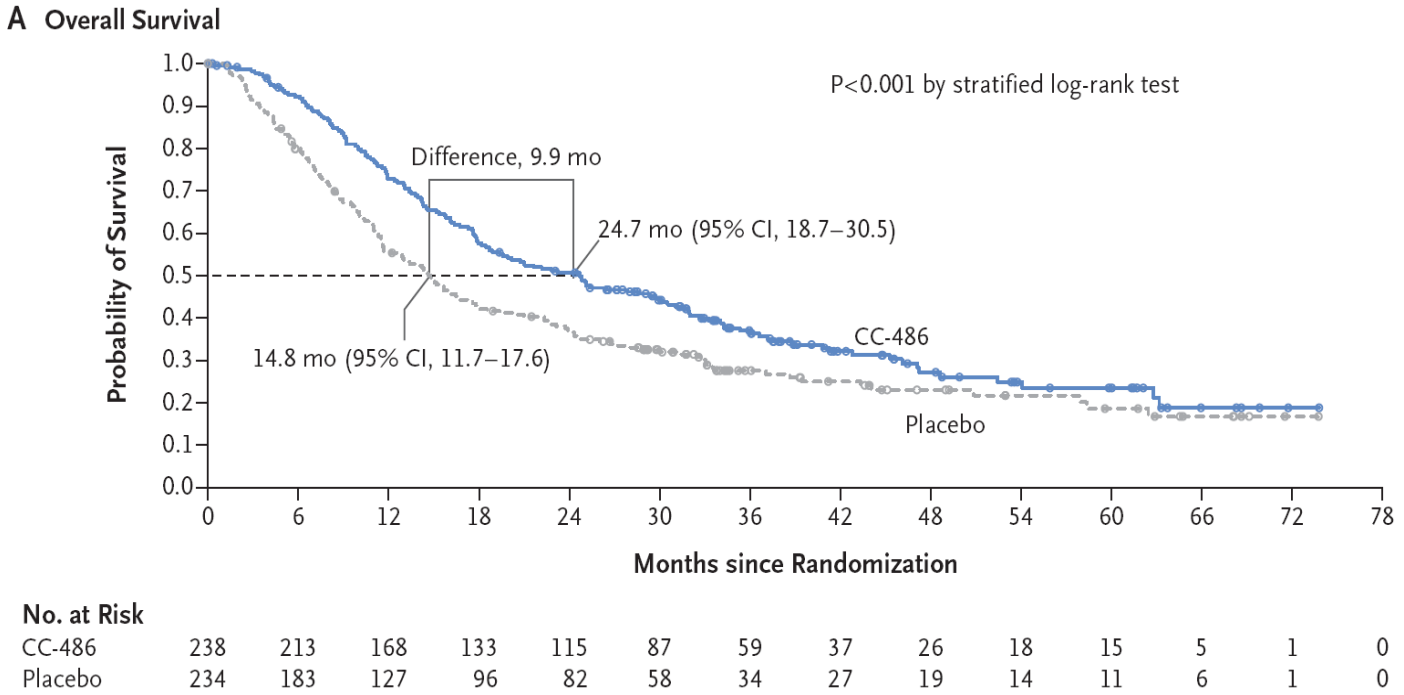
Hartmut Döhner,[1] Andrew H. Wei,[2,3] Gail J. Roboz,[4,5] Pau Montesinos,[6] Felicitas R Thol,[7] Farhad Ravandi,[8] Hervé Dombret,[9,10] Kimmo Porkka,[11] Irwindeep Sandhu,[12] Barry Skikne,[13,14] Wendy L. See,[14] Manuel Ugidos,[15] Alberto Risueño,[15] Esther Chan,[14] Anjan Thakurta,[16] C.L. Beach,[14] Daniel Lopes de Menezes[14]

- [1]Ulm University Hospital, Ulm, Germany; [2]Australian Centre for Blood Diseases, Monash University, Melbourne, Australia; [3]Department of Clinical Haematology, The Alfred Hospital, Melbourne, Australia; [4]Weill Cornell Medicine, New York, NY; [5]New York Presbyterian Hospital, New York, NY; [6]Hospital Universitario y Politécnico La Fe, Valencia, Spain; [7]Medizinische Hochschule Hannover, Hannover, Germany; Department of Leukemia, [8]The University of Texas MD Anderson Cancer Center, Houston, TX; [9]Hôpital Saint-Louis, Assistance Publique – Hôpitaux de Paris (AP-HP),Paris, France; [10]Institut de Recherche Saint Louis, Université de Paris, Paris, France; [11]Hospital District of Helsinki and Uusimaa (HUS) Comprehensive Cancer Center, Hematology Research Unit Helsinki and iCAN Digital Precision Cancer Center Medicine Flagship, University of Helsinki, Helsinki; [12]University of Alberta, Edmonton, Canada; [13]University of Kansas Medical Center, Kansas City, KS; [14]Bristol Myers Squibb, Princeton, NJ; [15]BMS Center for Innovation and Translational Research Europe (CITRE), a Bristol-Myers Squibb Company, Seville, Spain; [16]Translational Development and Diagnostics, Bristol Myers Squibb, Summit, NJ

QUAZAR AML-001: OS outcomes at the primary data cutoff (Jul-2019)

- The study was unblinded in Aug 2019 (data cutoff 15-Jul 2019)
- At a median follow-up of 41.2 months, Oral-AZA significantly prolonged OS *vs*. PBO (*P*<0.001)
  - The tails of the OS curves began to converge after ~48 mo
  - 125/472 pts (26.5%) were still alive in survival follow-up at the primary cutoff
- After unblinding, 39 pts receiving Oral-AZA entered an extension phase and continued Tx
- **Objective:** Assess longer-term OS using a data cutoff of Sep 2020, providing > 1 additional year of survival follow-up

Overall survival (primary data cutoff)



Median OS follow-up: 41.2 mo

OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for Oral-AZA *vs*. PBO by stratified log-rank test.

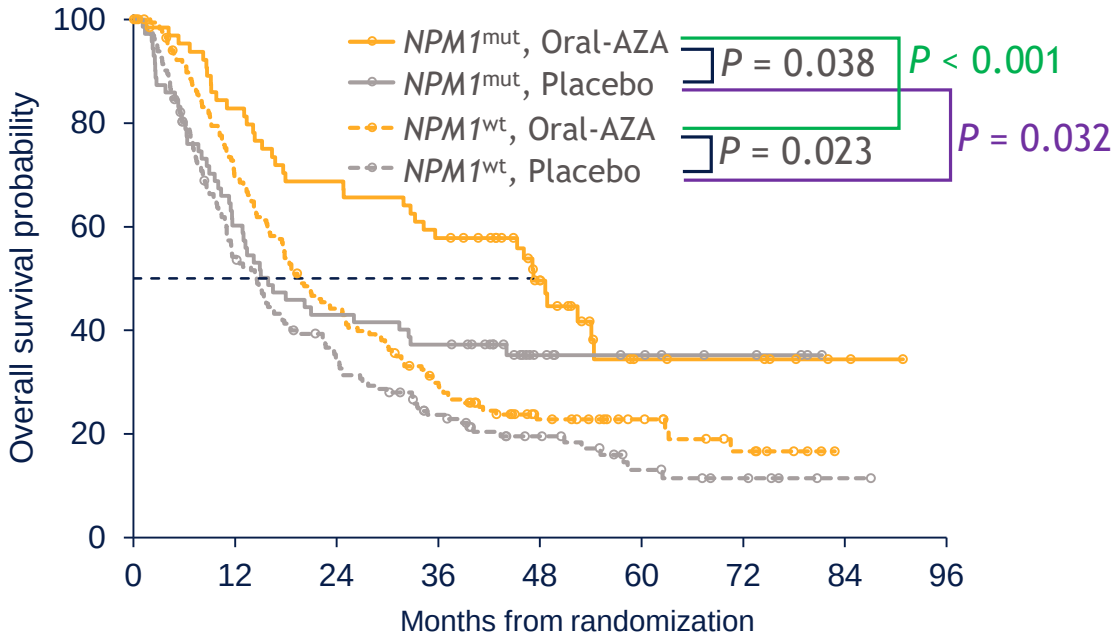
1. Wei AH et al. *N Engl J Med*. 2020;383:2526-2537. (Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission.)

mo, months; No., number.

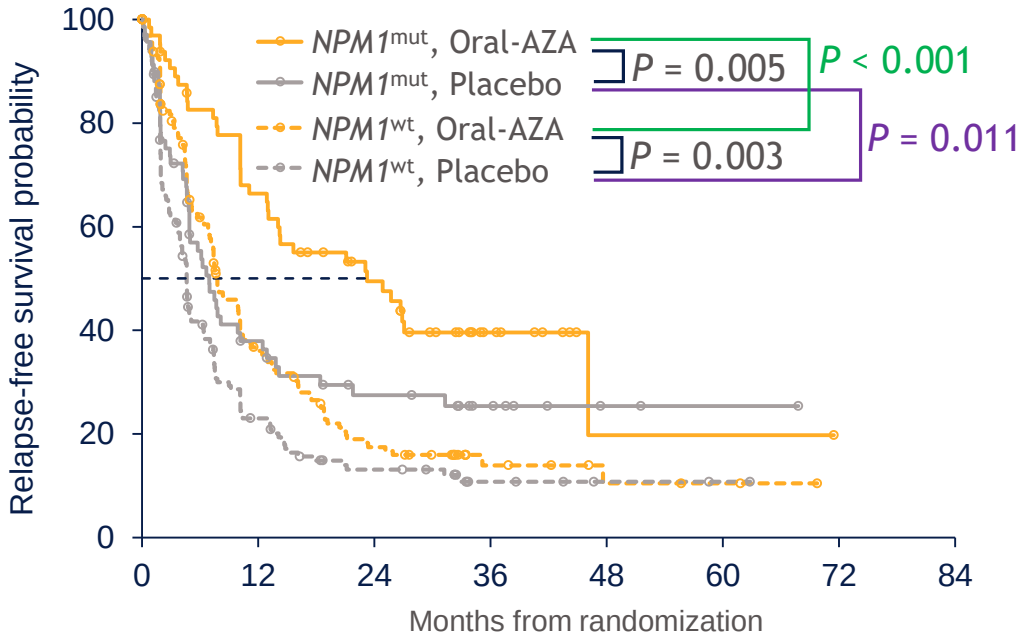
Oral-AZA significantly prolonged OS and RFS in patients with *NPM1*^{mut} at diagnosis

- *NPM1*^{mut} status at AML Dx was prognostic for OS and RFS
- Oral-AZA also significantly improved OS and RFS in pts with *NPM1*^{wt} at Dx

Overall survival



Relapse-free survival



Median OS, months

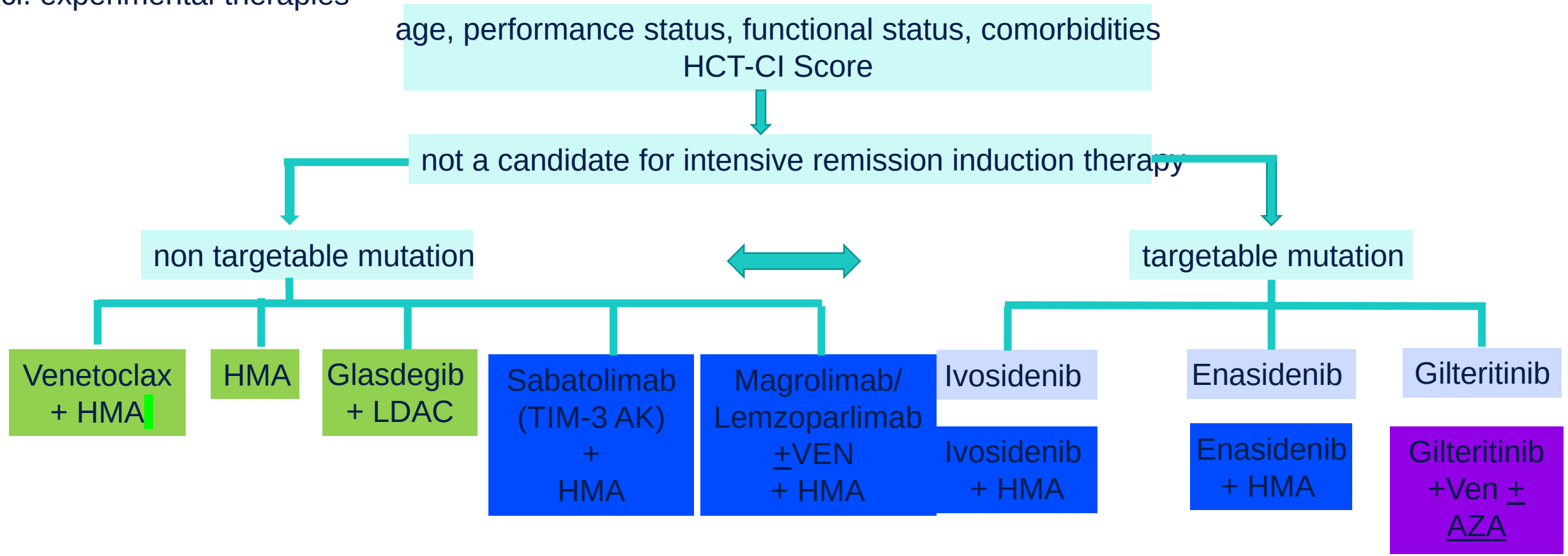
NPM1^{mut}, Oral-AZA (n=66)	**47.2**	*NPM1*^{wt}, Oral-AZA (n=170)	**19.6**
NPM1^{mut}, Placebo (n=71)	**15.9**	*NPM1*^{wt}, Placebo (n=162)	**14.6**

Median RFS, months

NPM1^{mut}, Oral-AZA (n=66)	**23.2**	*NPM1*^{wt}, Oral-AZA (n=170)	**7.8**
NPM1^{mut}, Placebo (n=71)	**6.9**	*NPM1*^{wt}, Placebo (n=162)	**4.6**

AML > 65 y not eligible for intensive CTx

Incl. experimental therapies



approved FDA/EMA

approved FDA

approved FDA R/R AML

in clinical trials

Courtesy: Prof. Dr. K. Götze

Fragen?

Ich freue mich auf eine lebhafte Diskussion