Prise en charge en 1ere ligne du patient ‘unfit’ atteint de LAM

SYMPOSIUM LAM

La Baule

18/10/23

Dr Pierre Peterlin

Service hématologie clinique

CHU de Nantes

Déclaration de liens d’intéret

- Board Abbvie
- Board Servier
- Board BMS

To be **fit** or not to be..

Subject must be considered ineligible for induction therapy defined by the following:

- ≥ 75 years of age;

  OR

- ≥ 60 to 74 years of age with **at least one** of the following co-morbidities:
  - ECOG Performance Status of 2 or 3;
  - Cardiac history of CHF requiring treatment or Ejection Fraction ≤ 50% or chronic stable angina;
  - DLCO ≤ 65% or FEV1 ≤ 65%;
  - Creatinine clearance ≥ 30 mL/min to < 45 ml/min
  - Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN
  - Any other comorbidity that the physician judges to be incompatible with intensive chemotherapy must be reviewed and approved by the AbbVie TA MD before study enrollment

→ ok protocole unfit

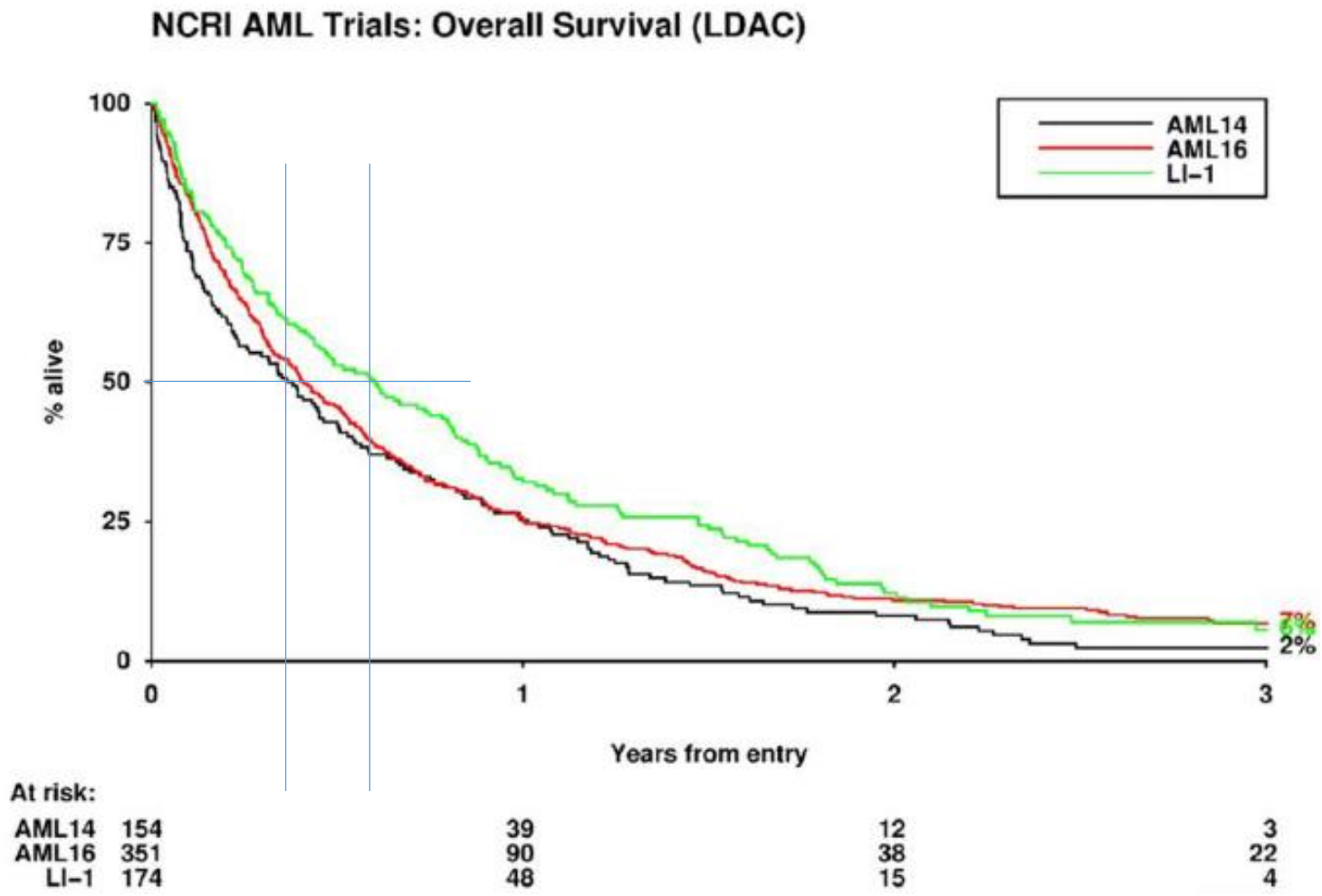
Supplemental, DiNardo et al.NEJM, 2020

SORROR ≥ 3 → Exclusion protocole fit

Sorror. Blood. 2013

1990-2020

Low Dose Cytarabine As Therapy for AML Patients Not Fit for Intensive Treatment

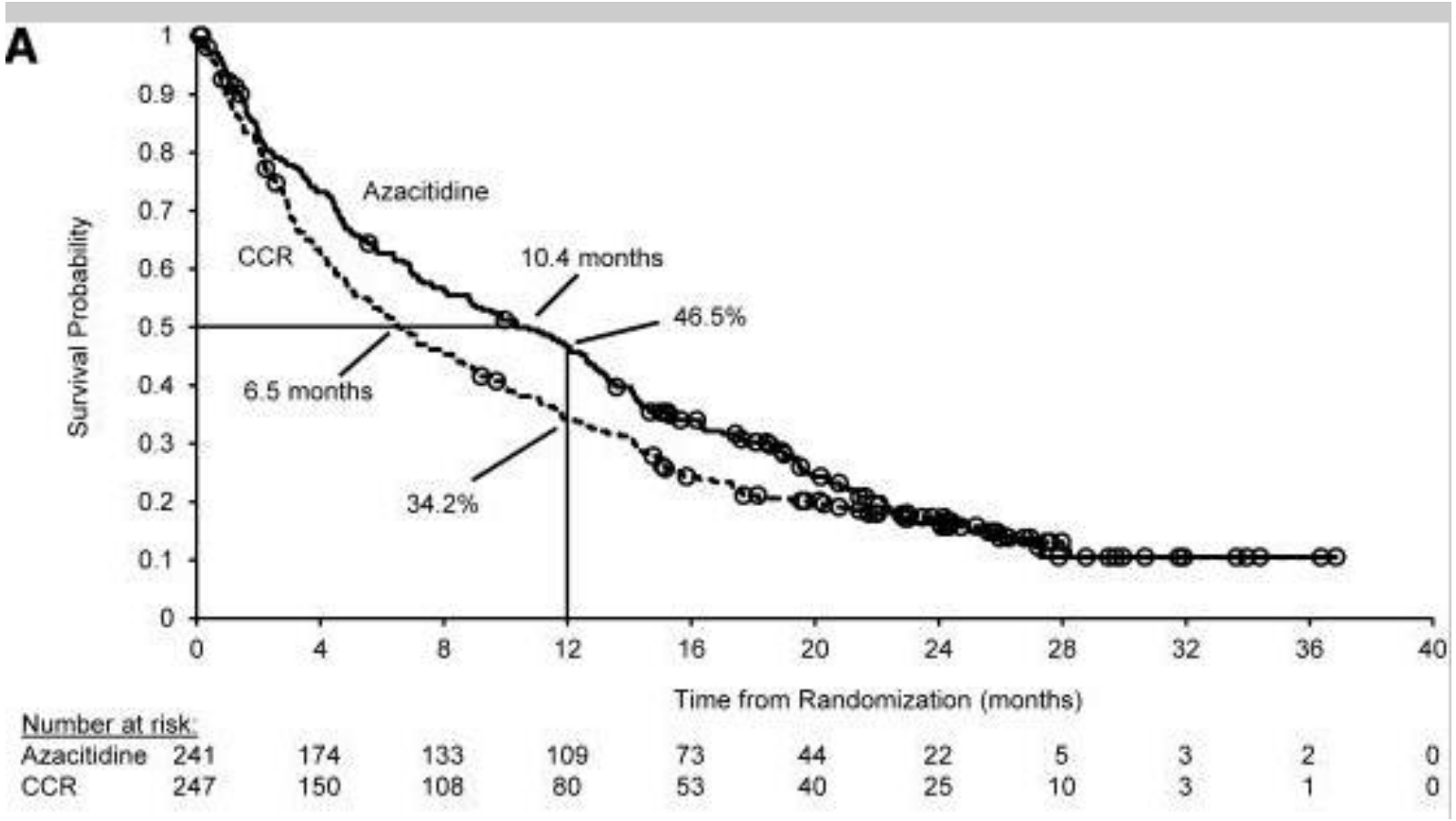


Dennis M et al. *Blood*. 2017;130(1). Abstract 3874

Azacitidine monothérapie

CLINICAL TRIALS AND OBSERVATIONS

International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts



Dombret et al. Blood. 2015

2020..

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

Etude VIALE-A

VEN-AZA vs AZA

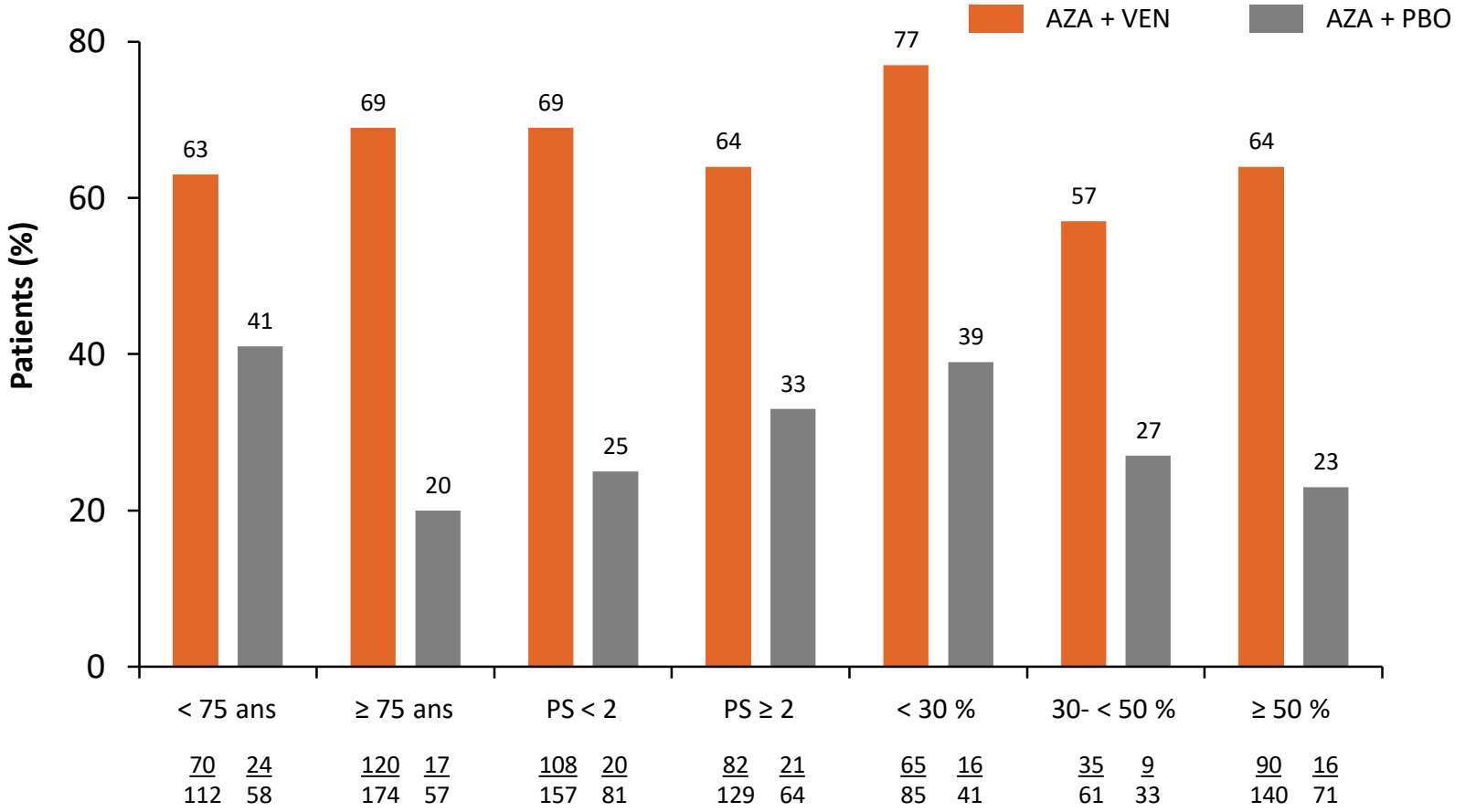
DiNardo et al.
NEJM, 2020

Table 1. **Baseline Demographic and Clinical Characteristics of the Patients.***

Characteristic	Azacitidine–Venetoclax Group (N=286)	Azacitidine–Placebo Group (N=145)
Age		
Median (range) — yr	76 (49–91)	76 (60–90)
≥75 yr — no. (%)	174 (61)	87 (60)
Male sex — no. (%)	172 (60)	87 (60)
AML type — no (%)		
De novo	214 (75)	110 (76)
Secondary	72 (25)	35 (24)
Secondary AML — no./total no. (%)		
History of myelodysplastic syndrome or CMML	46/72 (64)	26/35 (74)
Therapy-related AML	26/72 (36)	9/35 (26)
ECOG performance-status score — no. (%)†		
0–1	157 (55)	81 (56)
2–3	129 (45)	64 (44)
Bone marrow blast count — no. (%)		
<30%‡	85 (30)	41 (28)
≥30 to <50%	61 (21)	33 (23)
≥50%	140 (49)	71 (49)
AML with myelodysplasia-related changes — no. (%)	92 (32)	49 (34)
Cytogenetic risk category — no. (%)§		
Intermediate	182 (64)	89 (61)
Poor	104 (36)	56 (39)

Étude VIALE-A

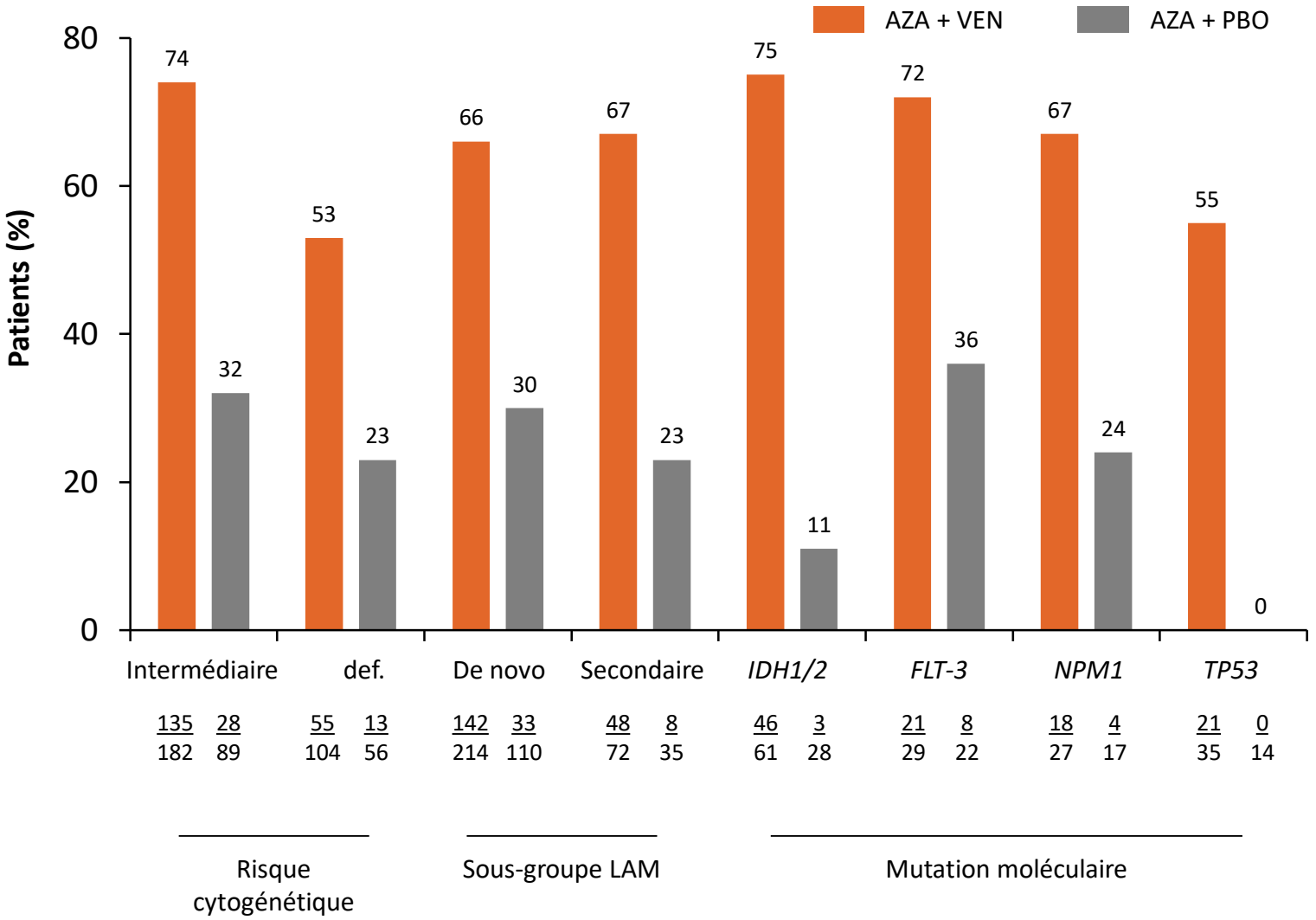
- Taux de réponse (RC + RCi) par sous-groupes



D'après DiNardo et al.NEJM, 2020

Étude VIALE-A

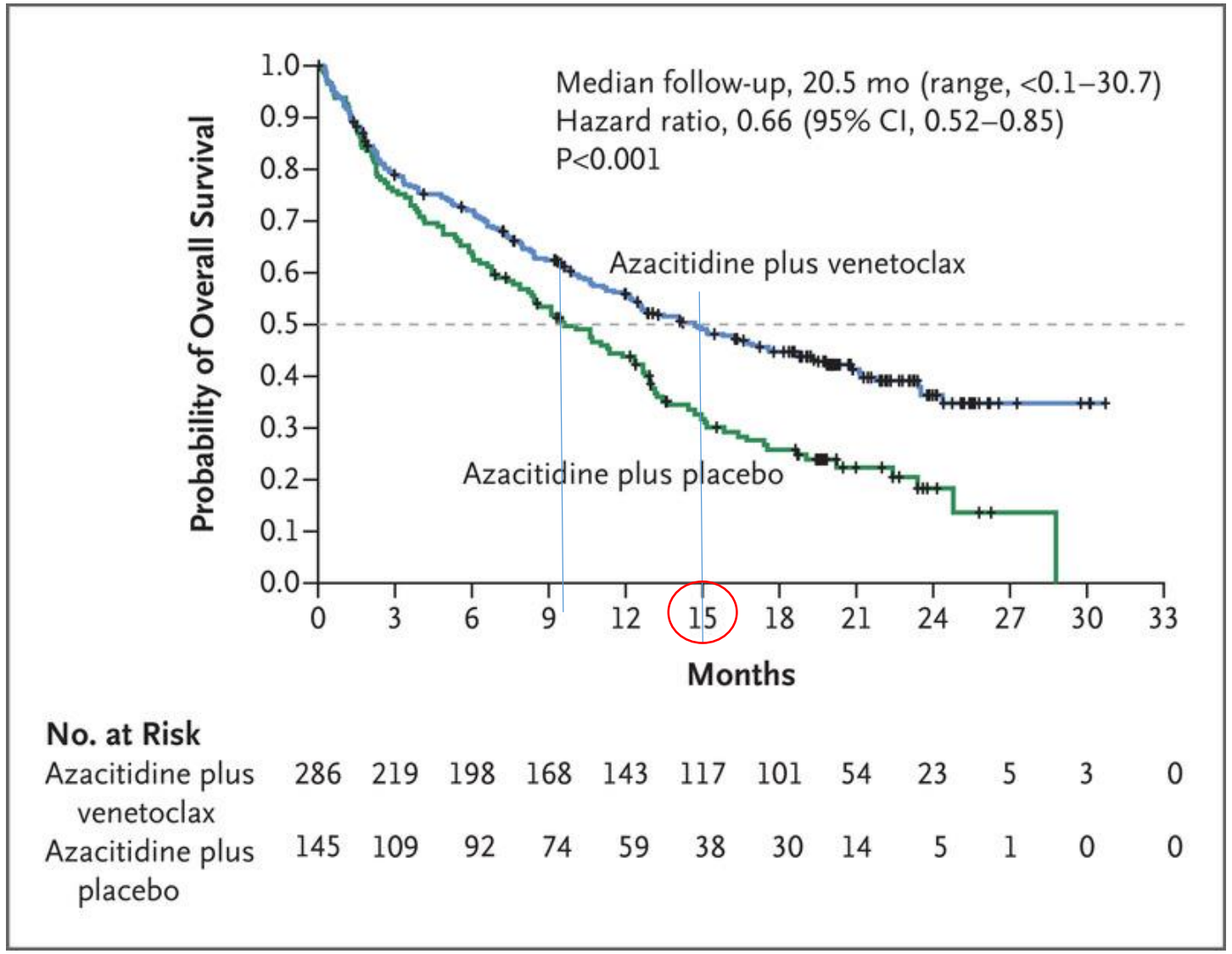
- Taux de réponse (RC + RCi) par sous-groupes



Et MRD neg dans ~ 25% des cas vs ~7%

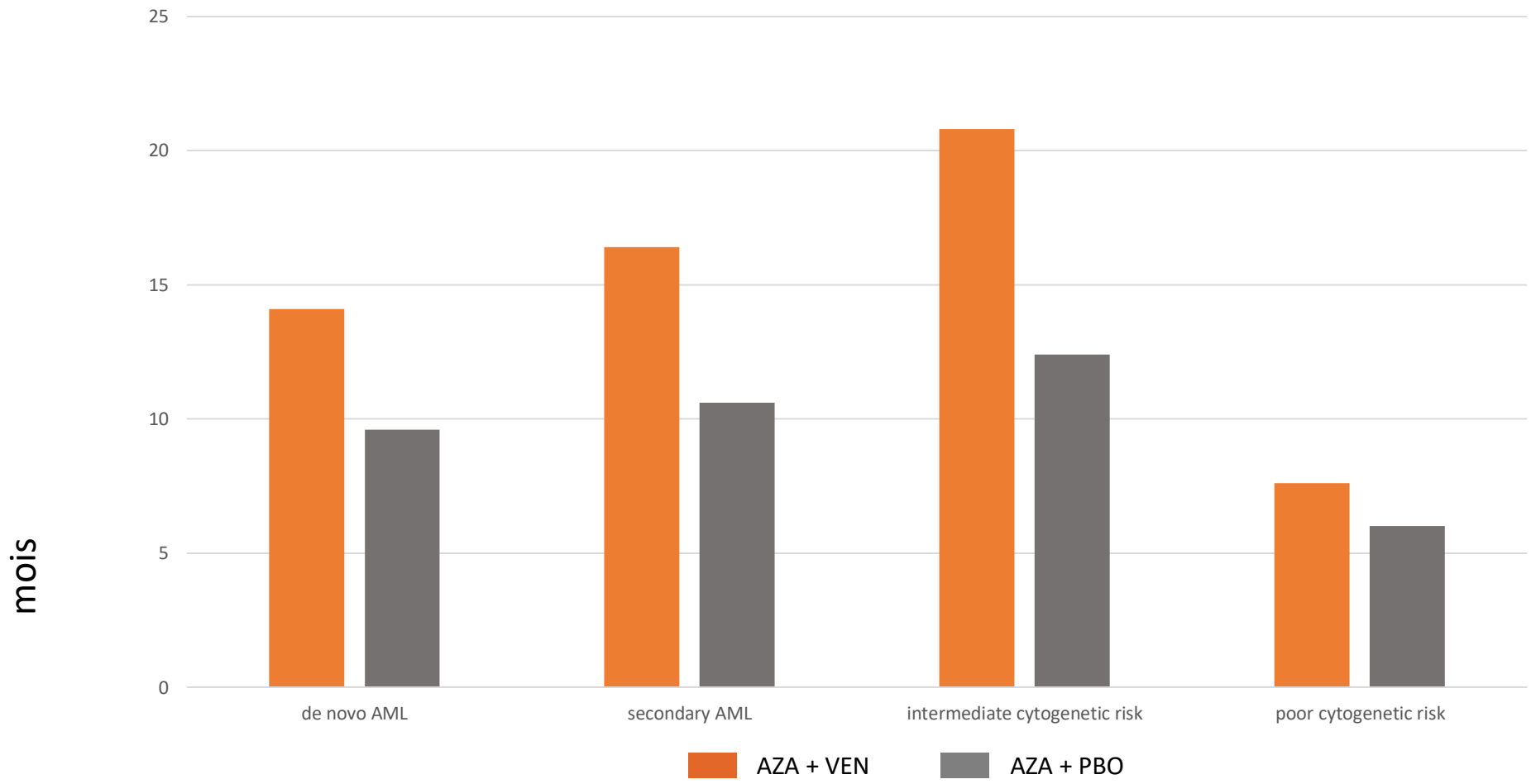
D'après DiNardo et al.NEJM, 2020

Overall Survival.



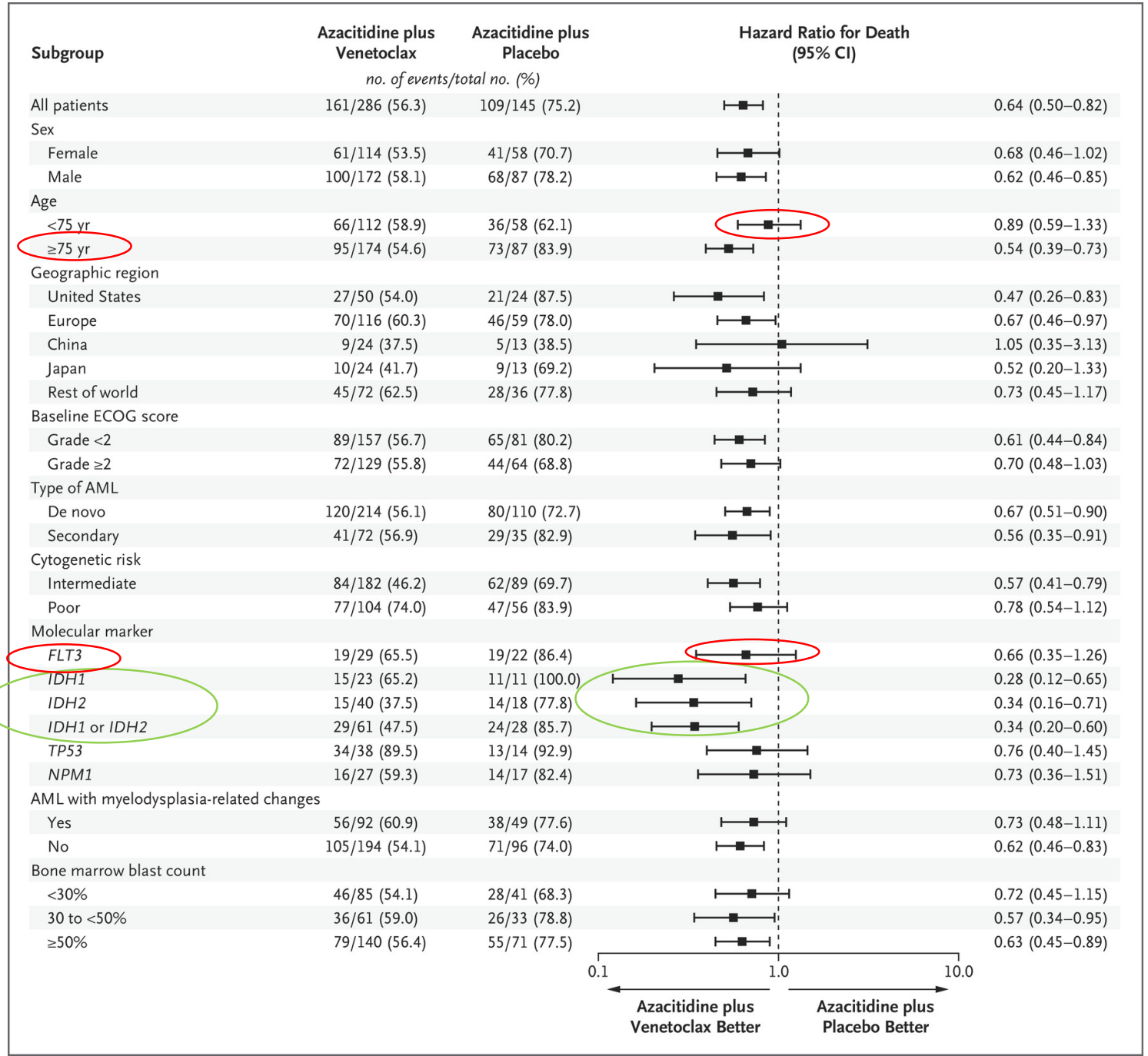
DiNardo et al.
NEJM, 2020

VIALE-A: OS selon caractère de novo/secondaire / cytogénétique



D'après DiNardo et al.NEJM, 2020

VIALE-A :Subgroup Analysis of Overall Survival.



Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
Female	61/114 (53.5)	41/58 (70.7)	0.68 (0.46–1.02)
Male	100/172 (58.1)	68/87 (78.2)	0.62 (0.46–0.85)
Age			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)

DiNardo et al.
NEJM, 2020

Table 2. Adverse Events.*

Event	Azacitidine–Venetoclax Group (N=283)		Azacitidine–Placebo Group (N=144)	
	All Grades†	≥Grade 3‡	All Grades†	≥Grade 3‡
	number of patients (percent)			
All adverse events	283 (100)	279 (99)	144 (100)	139 (97)
Hematologic adverse events	236 (83)	233 (82)	100 (69)	98 (68)
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (28)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anemia	78 (28)	74 (26)	30 (21)	29 (20)
Leukopenia	58 (21)	58 (21)	20 (14)	17 (12)
Nonhematologic adverse events				
Nausea	124 (44)	5 (2)	50 (35)	1 (1)
Constipation	121 (43)	2 (1)	56 (39)	2 (1)
Diarrhea	117 (41)	13 (5)	48 (33)	4 (3)
Vomiting	84 (30)	6 (2)	33 (23)	1 (1)
Hypokalemia	81 (29)	30 (11)	41 (28)	15 (10)
Peripheral edema	69 (24)	1 (<1)	26 (18)	0
Pyrexia	66 (23)	5 (2)	32 (22)	2 (1)
Fatigue	59 (21)	8 (3)	24 (17)	2 (1)
Decreased appetite	72 (25)	12 (4)	25 (17)	1 (1)
Infections	239 (84)	180 (64)	97 (67)	74 (51)

CORRESPONDENCE

Postremission cytopenia management in patients with acute myeloid leukemia treated with venetoclax and azacitidine in VIALE-A

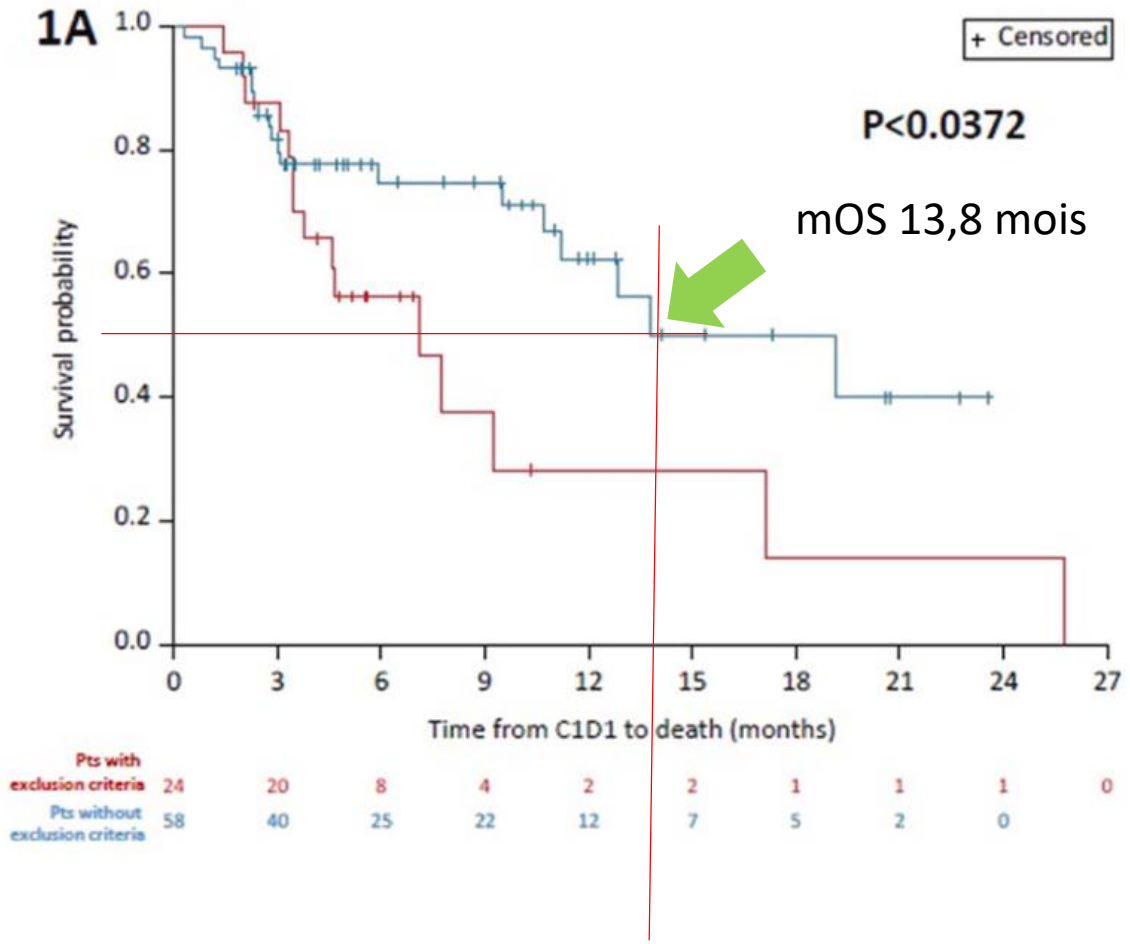
- évaluation précoce durant le cycle 1
- Environ 60% des répondeurs à VENAZA ont eu une diminution du schema 28 jours vers un schéma 21 jours
- Les patients qui ont eu une reduction de dose avec un schema à 21 jours précocément sont significativement moins thrombopéniques

- "*These data suggest that cytopenia events with Ven + Aza are manageable with Ven dosing modifications and GCSF, without adversely affecting outcomes*"

Pratz et al. Am J Hematol 2022

Diminuer la posologie du ven ?
Schéma 7+7

Figure 1: OS (1A) and EFS (1B) according to VIALE-A protocol exclusion crite



Willekens C. et al, abstract 222. ASH 2022.

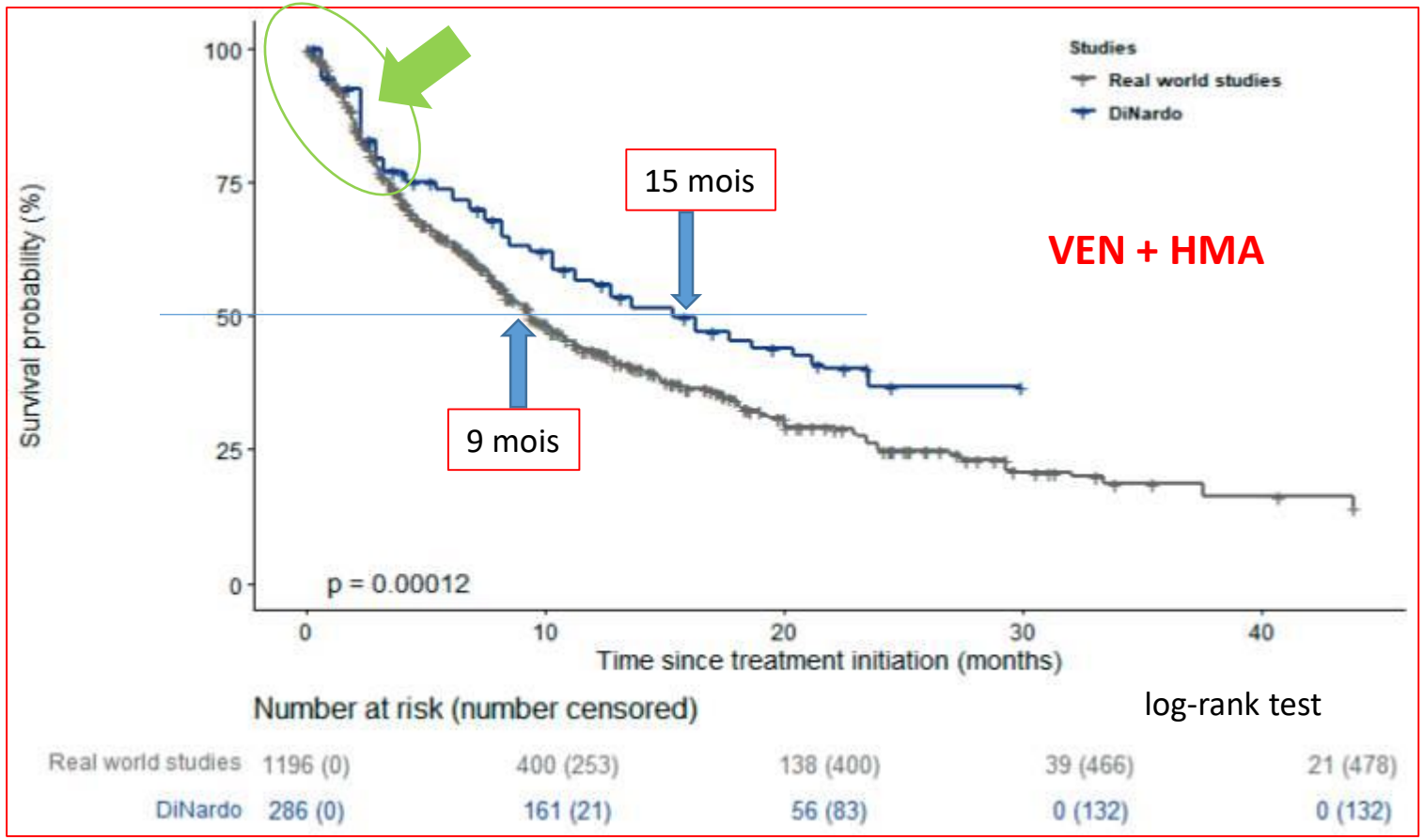
cancers

MDPI

Systematic Review

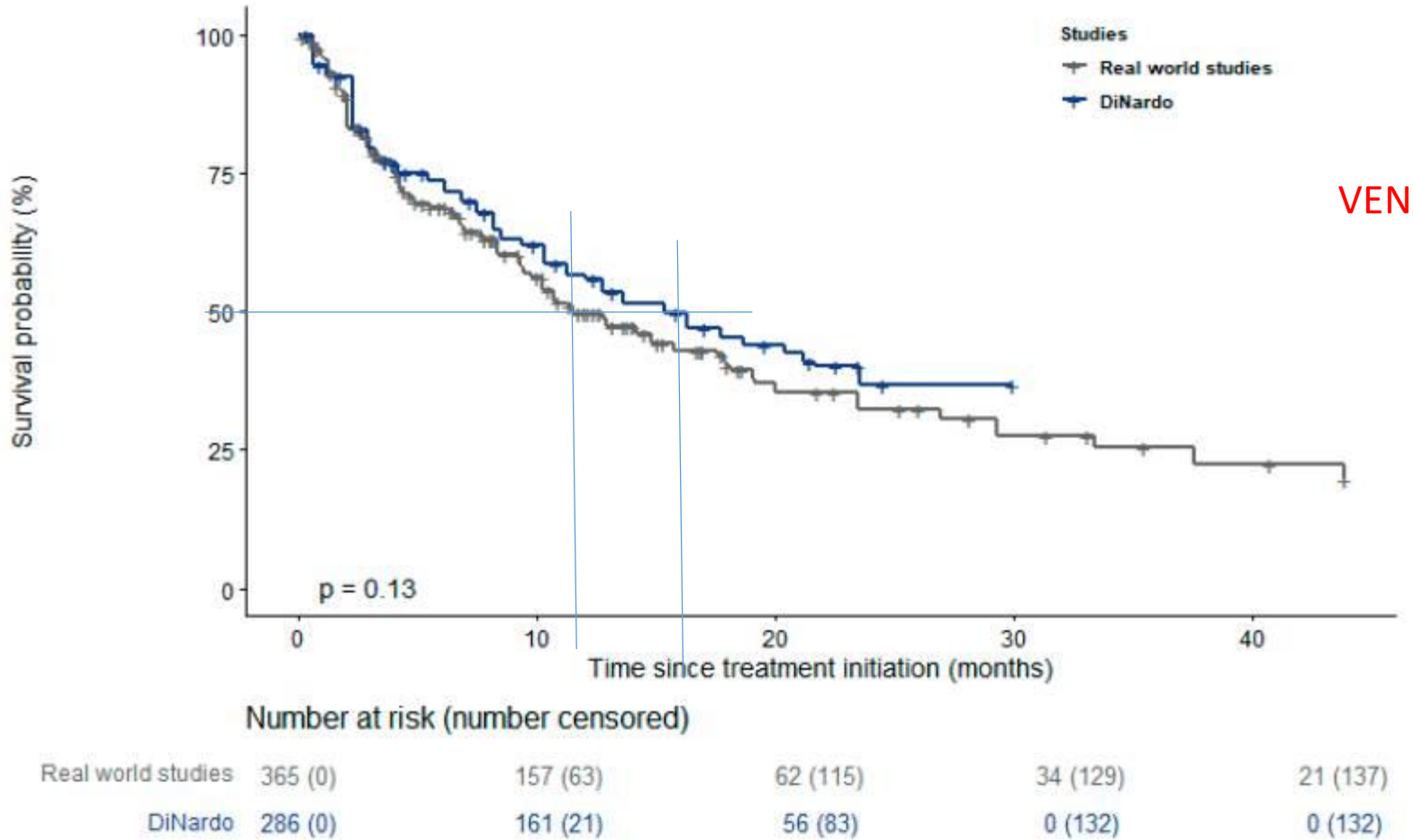
Venetoclax with Hypomethylating Agents in Newly Diagnosed Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis of Survival Data from Real-World Studies

- 1134 patients
- Age médian entre 60 et 79 ans; (DiNardo 76 ans)
- Dans la plupart des études, caryo normal (32% à 42% des pts), 44% dans DiNardo et al



Ucciero L et al. Cancers (Basel). 2023

OS, meta analyse, *real world study*



VEN + AZA only

Ucciero L et al. Cancers (Basel). 2023

LAM avec Mutations IDH1,2 ou FLT3

Mutation IDH

Molecular marker				
FLT3	19/29 (65.5)	19/22 (86.4)		0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)		0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)		0.34 (0.16–0.71)
IDH1 or IDH2	29/61 (47.5)	24/28 (85.7)		0.34 (0.20–0.60)
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DiNardo et al.
NEJM, 2020

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

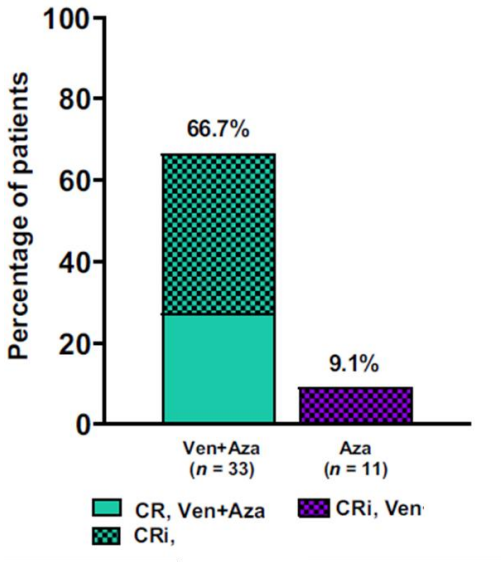
Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and *IDH1/2* Mutations

Daniel A. Pollyea[1], Courtney D. DiNardo[2], Martha L. Arellano[3], Arnaud Pigneux[4], Walter Fiedler[5], Marina Konopleva[2], David A. Rizzieri[6], B. Douglas Smith[7], Atsushi Shinagawa[8], Roberto M. Lemoli[9,10], Monique Dail[11], Yinghui Duan[12], Brenda Chyla[12], Jalaja Potluri[12], Catherine L. Miller[12], and Hagop M. Kantarjian[2]

- 44 malades : données ***"poolées"*** de 2 études :
  - phase III + phase Ib (venetoclax + azacitidine)
  - ≥75 ans ou avec comorbidités.
  - Patients recevant venetoclax 400 mg (J1–28) et azacitidine (75 mg/m2; j 1–7/cycle).

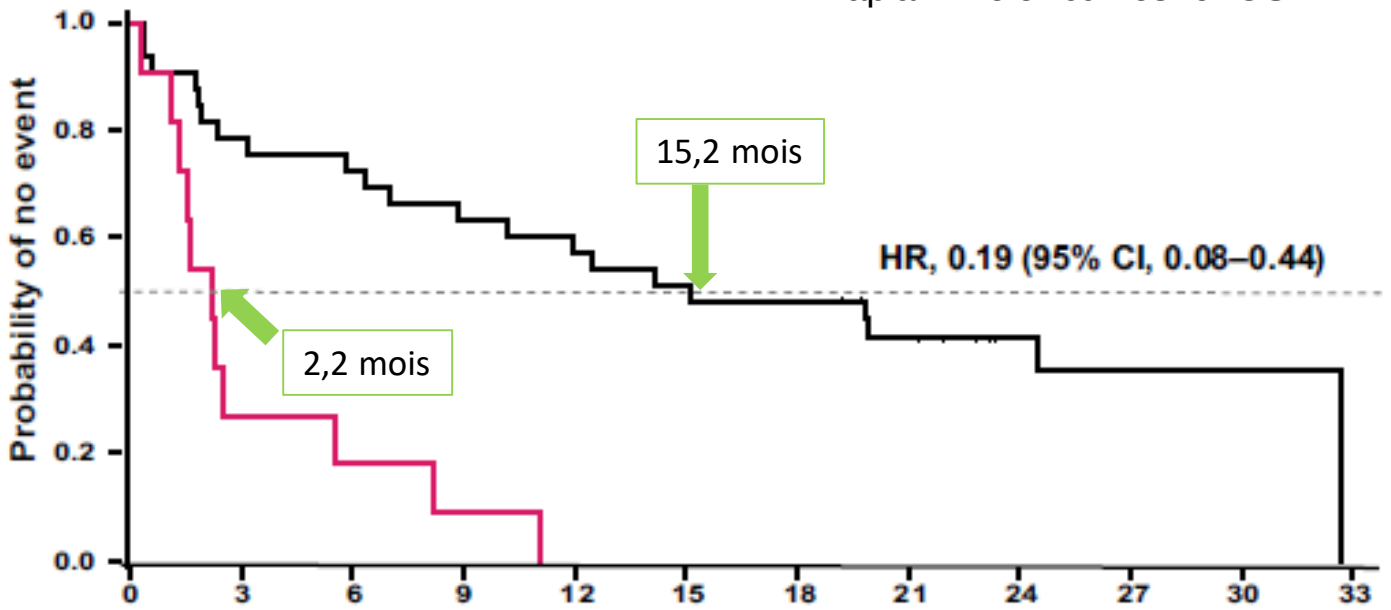
Pollyea et al. Clin Cancer Res 2022

Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and IDH1 Mutations



Taux de réponse
CR+ CRi

Kaplan–Meier curves for OS



Patients at risk												
Ven+Aza	33	26	24	21	19	17	16	12	7	5	1	0
Aza	11	3	2	1	0							

		Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven+Aza	(*N* = 33)	21	72.7 (54.1–84.8)	57.6 (39.1–72.3)	41.6 (24.6–57.7)	15.2 (7.0, -)
Aza	(*N* = 11)	11	18.2 (2.9–44.2)	NA	NA	2.2 (1.1–5.6)

Pollyea et al. Clin Cancer Res 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

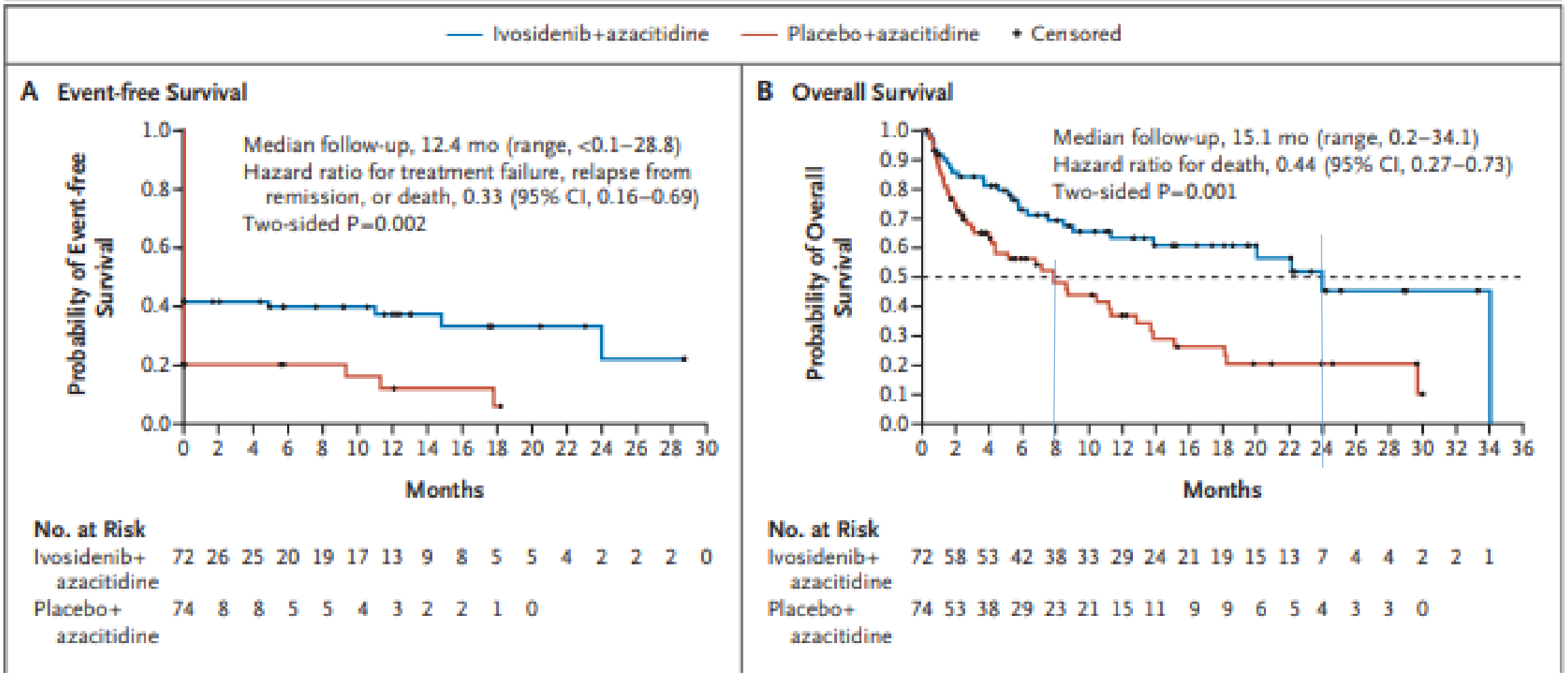
Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia

Montesinos et al. NEJM 2022

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Median age (range) — yr	76.0 (58.0–84.0)	75.5 (45.0–94.0)
Sex — no. (%)		
Male	42 (58)	38 (51)
Female	30 (42)	36 (49)
Race or ethnic group — no. (%)†		
Asian	15 (21)	19 (26)
White	12 (17)	12 (16)
Black	0	2 (3)
Other or not reported	45 (62)	41 (55)
ECOG performance-status score — no. (%)‡		
0	14 (19)	10 (14)
1	32 (44)	40 (54)
2	26 (36)	24 (32)
Disease history according to investigator — no. (%)		
Primary AML	54 (75)	53 (72)
Secondary AML§	18 (25)	21 (28)
History of myeloproliferative neoplasms	4 (6)	8 (11)
World Health Organization classification — no. (%)		
AML with recurrent genetic abnormalities	16 (22)	24 (32)
AML with myelodysplasia-related changes	28 (39)	26 (35)
Therapy-related myeloid neoplasms	1 (1)	1 (1)
IDH1 mutation type — no. (%)¶		
R132C	45 (62)	51 (69)
R132H	14 (19)	12 (16)
R132G	6 (8)	4 (5)
R132L	3 (4)	0
R132S	2 (3)	6 (8)
Median variant allele frequency of *IDH1* mutations in bone marrow aspirate (range) — %‖	36.8 (3.1–50.5)	35.5 (3.0–48.5)
Cytogenetic risk status — no. (%)**		
Favorable	3 (4)	7 (9)
Intermediate	48 (67)	44 (59)
Poor	16 (22)	20 (27)
Median bone marrow blast level (range) — %	54.0 (20.0–95.0)	48.0 (17.0–100)

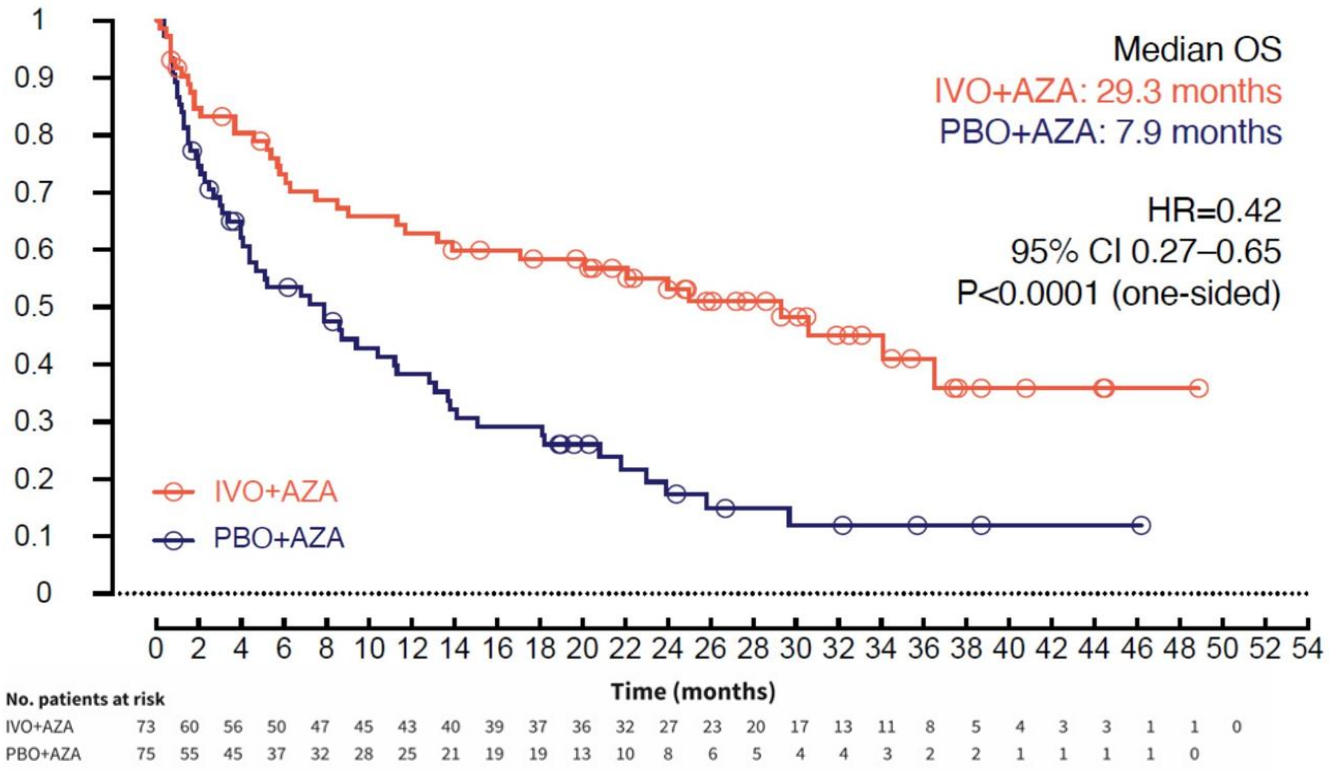
Montesinos et al. NEJM 2022



Montesinos et al. NEJM 2022

Long term follow-up of AGILE
Durable OS benefits with IVO+AZA

Data cut off : June 2022[2]



Median OS : **29.3 months** vs. 7.9 months
HR 0.42, 95% CI 0.27-0.65; one-sided p<0.001
Median follow-up time : 28.6 months

1Presented at ASCO & EHA 2023

C Event-free Survival in Key Subgroups

Subgroup	Ivosidenib+ Azacitidine (no. of events/no. of patients)	Placebo+ Azacitidine (no. of events/no. of patients)	Hazard Ratio for Treatment Failure, Relapse from Remission, or Death (95% CI)
Overall	46/72	62/74	0.35 (0.18–0.67)
Primary AML on basis of interactive response technologies			
Yes	35/56	46/55	0.33 (0.16–0.69)
No	11/16	16/19	0.32 (0.07–1.56)
Primary AML on basis of investigator from electronic CRF			
Yes	33/54	44/53	0.32 (0.15–0.69)
No	13/18	18/21	0.34 (0.07–1.61)
Region			
United States, Canada, western Europe, Israel, or Australia	30/48	44/50	0.22 (0.09–0.54)
Japan or rest of the world	16/24	18/24	0.73 (0.26–2.08)
Age			
<75 yr	21/33	25/31	0.43 (0.17–1.11)
≥75 yr	25/39	37/43	0.27 (0.10–0.71)
Baseline ECOG performance-status score			
0 or 1	30/46	43/50	0.31 (0.12–0.76)
≥2	16/26	19/24	0.39 (0.14–1.10)
Sex			
Female	19/30	29/36	0.35 (0.12–1.00)
Male	27/42	33/38	0.32 (0.13–0.79)
Race or ethnic group			
White	9/12	10/12	0.72 (0.16–3.20)
Asian	9/15	14/19	0.54 (0.14–2.01)
Other	28/45	38/43	0.21 (0.08–0.54)
Baseline cytogenetic risk status			
Favorable or intermediate risk	30/51	44/51	0.25 (0.11–0.55)
Poor risk	12/16	16/20	0.76 (0.16–3.57)
World Health Organization classification of AML			
AML with recurrent genetic abnormalities	11/16	21/24	0.41 (0.11–1.50)
AML with myelodysplasia-related change	18/28	20/26	0.47 (0.15–1.52)
Therapy-related myeloid neoplasms or AML not otherwise specified	17/28	21/24	0.33 (0.12–0.93)
Baseline white-cell count			
≤5×10^9/liter	33/51	41/49	0.36 (0.16–0.79)
>5×10^9/liter	13/21	21/25	0.35 (0.10–1.21)
Baseline bone marrow blast level			
≤50%	19/30	32/40	0.43 (0.17–1.09)
>50%	26/41	30/34	0.26 (0.09–0.69)

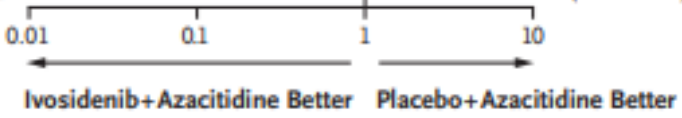


Table 2. Hematologic Response, Response Duration, and Time to Response (Intention-to-Treat Population).*

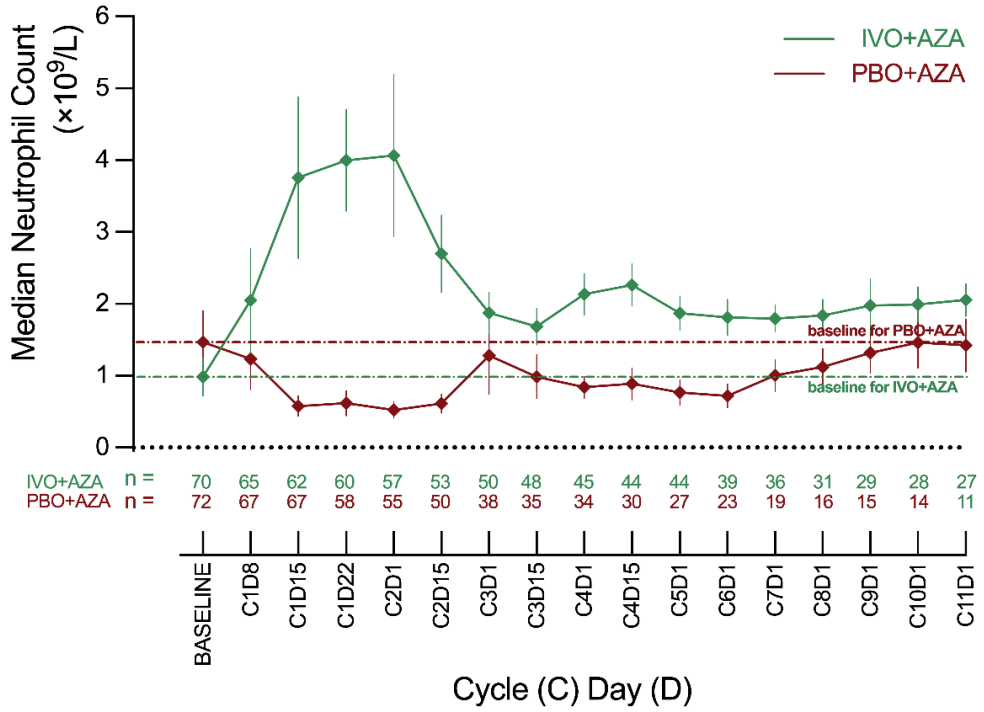
Response Category	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Best response — no. (%)		
Complete remission	34 (47)	11 (15)
Complete remission with incomplete hematologic or platelet recovery	5 (7)	1 (1)
Partial remission	4 (6)	2 (3)
Morphologic leukemia-free state	2 (3)	0
Stable disease	7 (10)	27 (36)
Progressive disease	2 (3)	4 (5)
Could not be evaluated	1 (1)	2 (3)
Not assessed	17 (24)	27 (36)
Complete remission		
Percentage of patients (95% CI)	47 (35–59)	15 (8–25)
Odds ratio vs. placebo (95% CI); P value	4.8 (2.2–10.5); two-sided P<0.001	
Median duration of complete remission (95% CI) — mo	NE (13.0–NE)	11.2 (3.2–NE)
Median time to complete remission (range) — mo	4.3 (1.7–9.2)	3.8 (1.9–8.5)
Complete remission or complete remission with partial hematologic recovery		
No. of patients	38	13
Percentage of patients (95% CI)	53 (41–65)	18 (10–28)
Odds ratio vs. placebo (95% CI); P value	5.0 (2.3–10.8); two-sided P<0.001	
Median duration of complete remission or complete remission with partial hematologic recovery (95% CI) — mo	NE (13.0–NE)	9.2 (5.8–NE)
Median time to complete remission or complete remission with partial hematologic recovery (range) — mo	4.0 (1.7–8.6)	3.9 (1.9–7.2)
Objective response		
No. of patients	45	14
Percentage of patients (95% CI)	63 (50–74)	19 (11–30)
Odds ratio vs. placebo (95% CI); P value	7.2 (3.3–15.4); two-sided P<0.001	
Median duration of response (95% CI) — mo	22.1 (13.0–NE)	9.2 (6.6–14.1)
Median time to first response (range) — mo	2.1 (1.7–7.5)	3.7 (1.9–9.4)

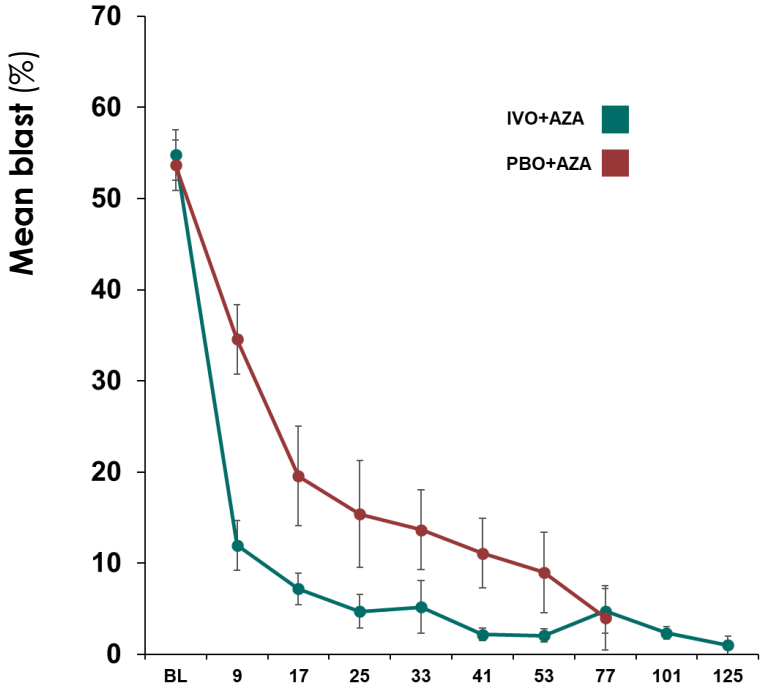
Table 3. Adverse Events (Safety Population).*

Event	Ivosidenib + Azacitidine (N = 71)		Placebo + Azacitidine (N = 73)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
	number (percent)			
Any adverse event	70 (99)	66 (93)	73 (100)	69 (95)
Hematologic adverse events	55 (77)	50 (70)	48 (66)	47 (64)
Anemia	22 (31)	18 (25)	21 (29)	19 (26)
Febrile neutropenia	20 (28)	20 (28)	25 (34)	25 (34)
Neutropenia	20 (28)	19 (27)	12 (16)	12 (16)
Thrombocytopenia	20 (28)	17 (24)	15 (21)	15 (21)
Leukocytosis	8 (11)	0	1 (1)	0
Nonhematologic adverse events				
Nausea	30 (42)	2 (3)	28 (38)	3 (4)
Vomiting	29 (41)	0	19 (26)	1 (1)
Diarrhea	25 (35)	1 (1)	26 (36)	5 (7)
Pyrexia	24 (34)	1 (1)	29 (40)	2 (3)
Constipation	19 (27)	0	38 (52)	1 (1)
Pneumonia	17 (24)	16 (23)	23 (32)	21 (29)
QT interval prolonged on ECG	14 (20)	7 (10)	5 (7)	2 (3)
Insomnia	13 (18)	1 (1)	9 (12)	0
Asthenia	11 (15)	0	24 (33)	5 (7)
Hypokalemia	11 (15)	2 (3)	21 (29)	6 (8)
Decreased appetite	11 (15)	1 (1)	19 (26)	6 (8)
Dyspnea	11 (15)	1 (1)	9 (12)	3 (4)
Differentiation syndrome	10 (14)	3 (4)	6 (8)	3 (4)
Pain in arm or leg	10 (14)	1 (1)	3 (4)	1 (1)
Fatigue	9 (13)	2 (3)	10 (14)	2 (3)
Hematoma	9 (13)	0	1 (1)	0
Edema, peripheral	8 (11)	0	16 (22)	1 (1)
Platelet count decreased	8 (11)	6 (8)	6 (8)	6 (8)
Arthralgia	8 (11)	0	3 (4)	0
Headache	8 (11)	0	2 (3)	0
Bleeding	29 (41)	4 (6)	21 (29)	5 (7)
Infections	20 (28)	15 (21)	36 (49)	22 (30)

Impact on neutrophils and blasts count

Median follow up time :15.1 months
(Data cut off : March 2021)





Only the IVO+AZA treatment group showed an increase in absolute neutrophil count from baseline

Increased blood counts with IVO+AZA came with a rapid decline in mean BM blasts (54.8% at baseline to 12.0% and 7.2% at week 9 and 17, respectively)

Montesinos et al. NEJM 2022 Supplementary Appendix.
Döhner H, et al. Presented at ASCO 2022; poster #P273.6

IDH1+: VENAZA ou VENIVO?

AML unfit IDH1 + = quel ttt en 1ere ligne ?

CORRESPONDENCE

Ivosidenib and Azacitidine in *IDH1*-Mutated AML

Gil-Sierra et al. and Goodman et al. N Engl J Med 2022

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

The AGILE trial of ivosidenib plus azacitidine versus azacitidine alone: How many limitations is too many?

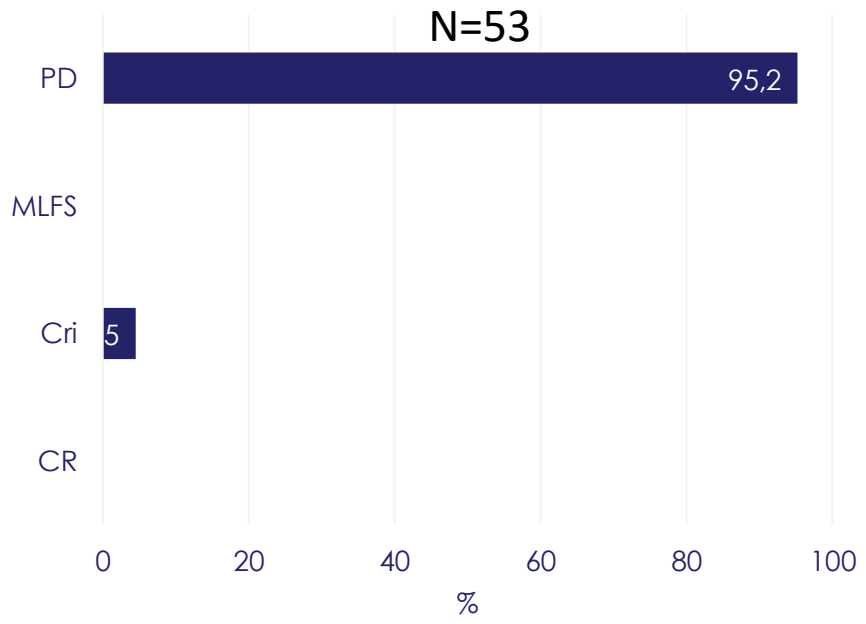
Bhatt et al. Transl Oncol. 2022

- Comparaison difficile car résultats de sous-groupes / analyse poolée versus une étude de phase 3 randomisée spécifiquement pour IDH1m

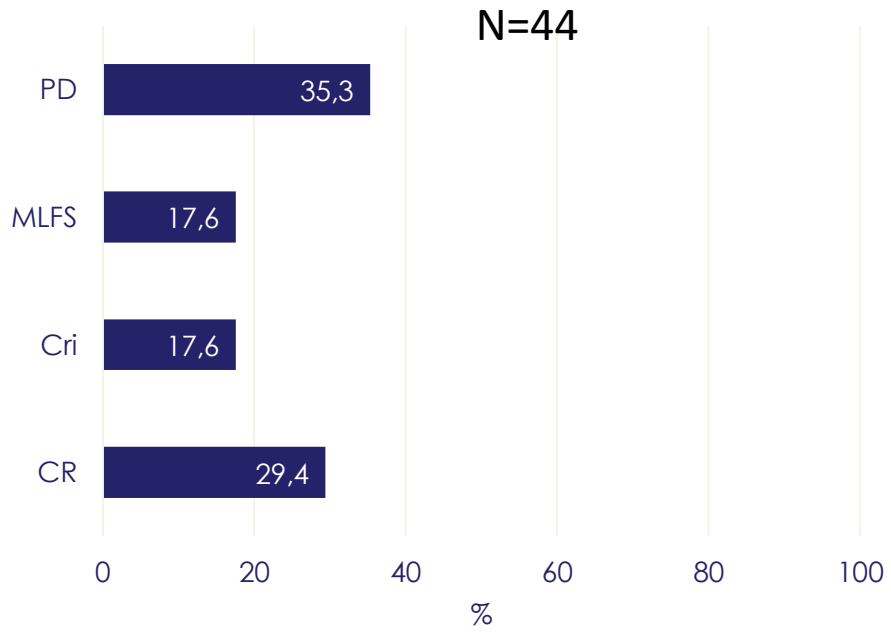
- VIALE-A (sous-groupe IDH1m ; N=34 patients): mOS de **10,2** mois versus 2,2 mois
- Pollya (N=44 patients): mOS de **15,2 mois** versus 2,2 mois
- AGILE (N=146 patients): mOS de **29,3 mois** versus 7,9 mois

Efficacy of IDH1/2 inhibitors in patients with AML previously treated with venetoclax[1] vs IDH1/2 inhibitor treatment prior to ven-based therapy[2]

Response rates (%) among patients receiving VEN-based regimen and then IDH1/2 inhibitors



Response rates (%) among patients receiving IDH1/2 inhibitors and then VEN-based regimen

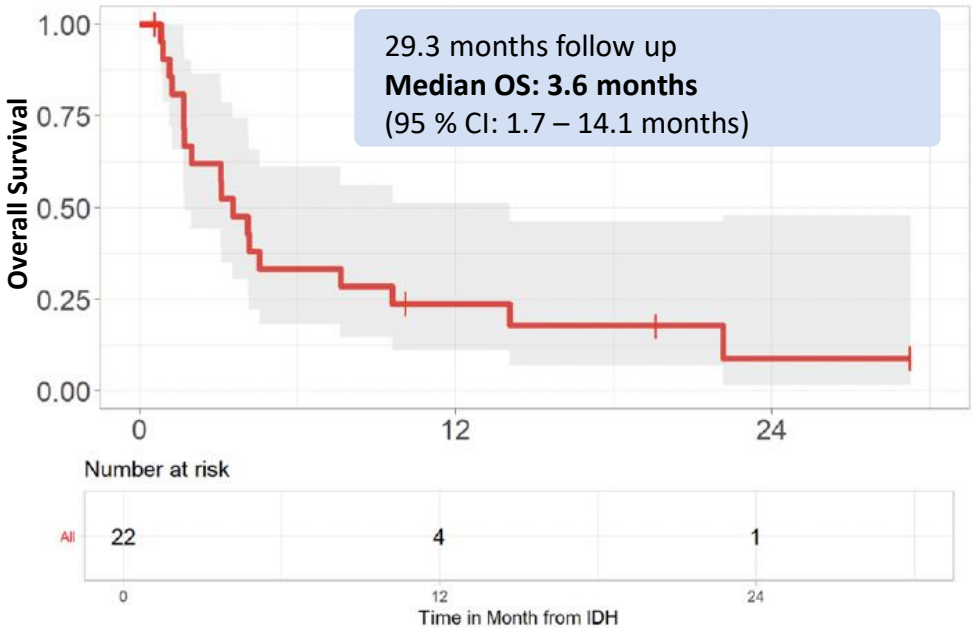


1. Bewersdorf JP et al. *Leukemia Research*. 2022 Nov 1;122:106942.
2. Bewersdorf JP et al. *Leukemia & Lymphoma*. 2022 Dec 9:1-9.

Efficacy of IDH1/2 inhibitors in patients with AML previously treated with venetoclax[1] vs IDH1/2 inhibitor treatment prior to ven-based therapy[2]

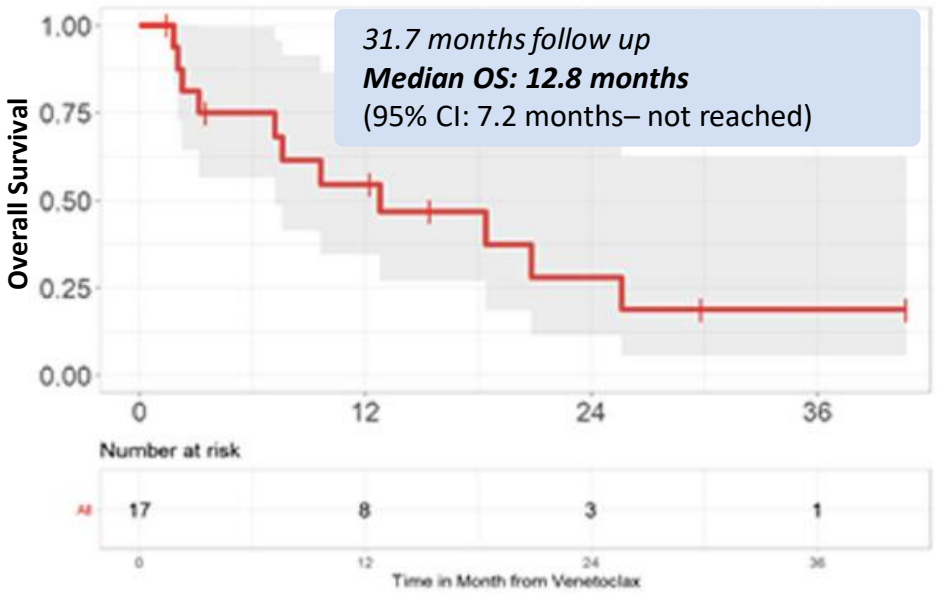
Response rates (%) among patients receiving VEN-based regimen and then IDH1/2 inhibitors

N=53



Response rates (%) among patients receiving IDH1/2 inhibitors and then VEN-based regimen

N=44



1. Bewersdorf JP et al. *Leukemia Research*. 2022 Nov 1;122:106942.
2. Bewersdorf JP et al. *Leukemia & Lymphoma*. 2022 Dec 9:1-9.

IDH2

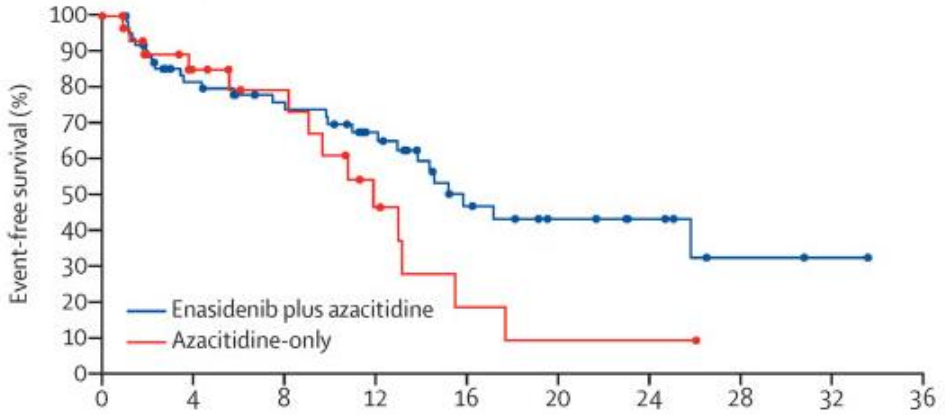
Mutation IDH2

Enasidenib plus azacitidine versus azacitidine alone in patients with newly diagnosed, mutant-*IDH2* acute myeloid leukaemia (AG221-AML-005): a single-arm, phase 1b and randomised, phase 2 trial

ORR = 74% bras AZA+ENA vs 36% AZA, mais..

A

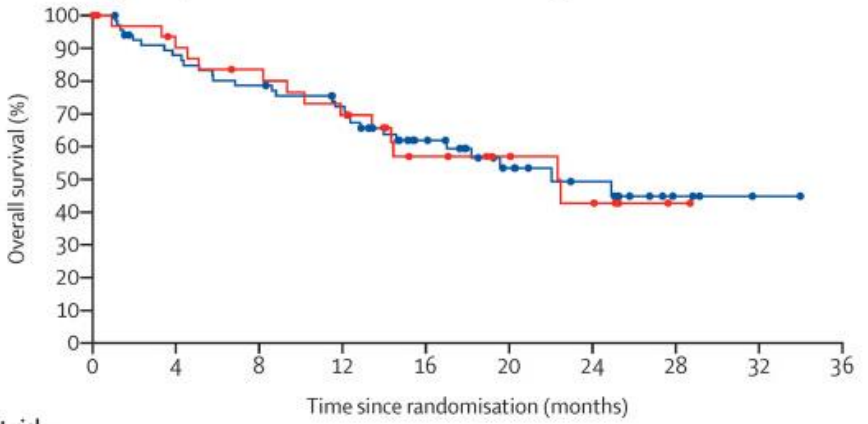
	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	27 (40%)	14 (42%)
Censored	41 (60%)	19 (58%)
Median event-free survival, months	15·9 (95% CI 13·0–NR)	11·9 (95% CI 8·2–15·5)
Hazard ratio	0·59 (95% CI 0·30–1·13)	
Log-rank p value	0·11	



Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	45 (12)	37 (17)	27 (23)	14 (29)	9 (33)	6 (36)	2 (39)	1 (40)	0 (41)
Azacitidine only	33 (0)	18 (11)	13 (15)	6 (17)	2 (18)	1 (18)	1 (18)	0 (19)	..	..

B

	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	29 (43%)	14 (42%)
Censored	39 (57%)	19 (58%)
Median overall survival, months	22·0 (95% CI 14·6–NR)	22·3 (95% CI 11·9–NR)
Hazard ratio	0·99 (95% CI 0·52–1·87)	
Log-rank p value	0·97	



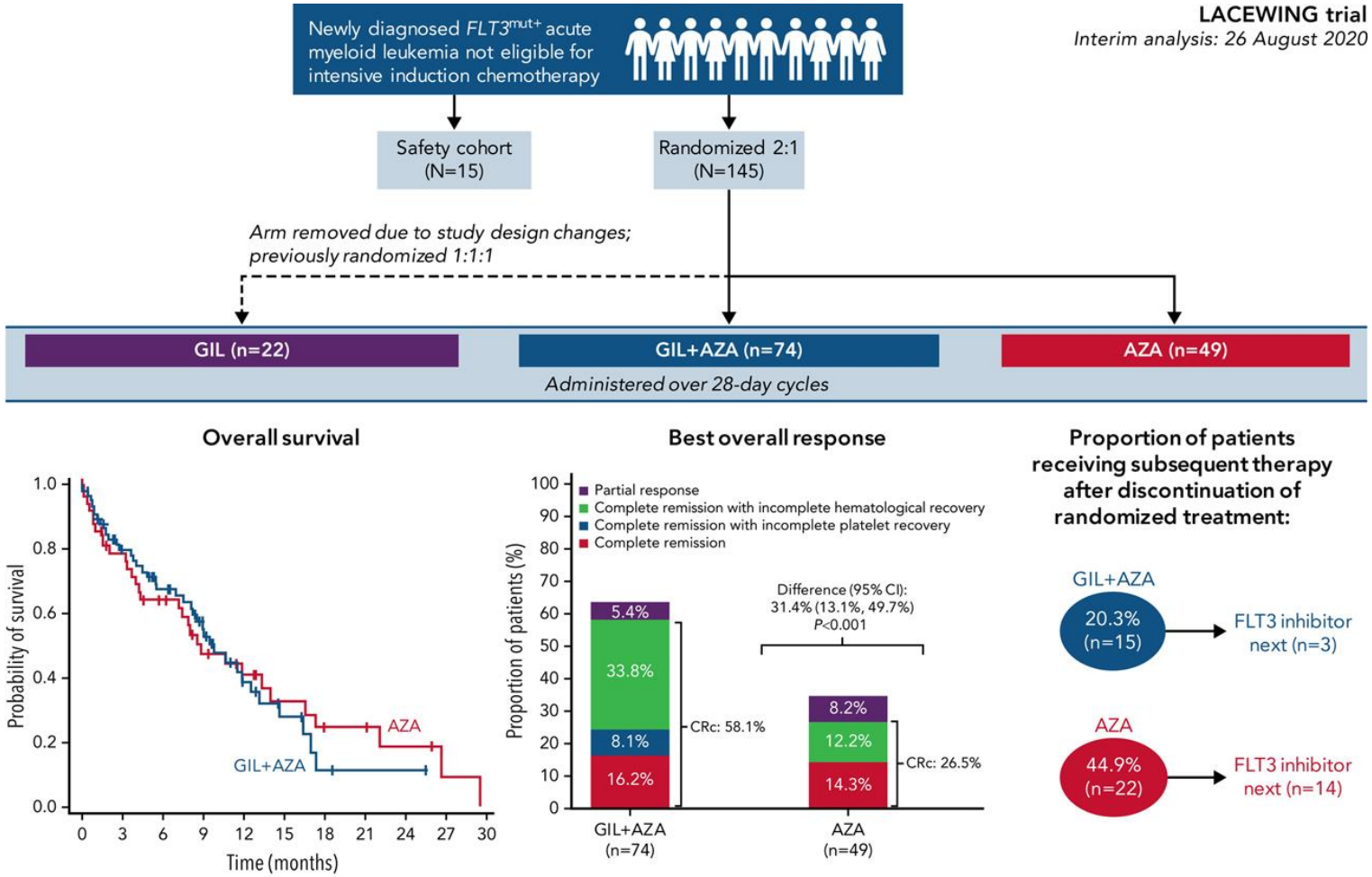
Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	57 (3)	51 (3)	44 (6)	28 (16)	16 (25)	11 (29)	4 (35)	1 (38)	0 (39)
Azacitidine only	33 (0)	27 (3)	24 (4)	20 (4)	12 (9)	9 (12)	6 (13)	1 (18)	0 (19)	..

Di Nardo et al. Lancet Oncol, 2021

FLT3

Mutation
FLT3

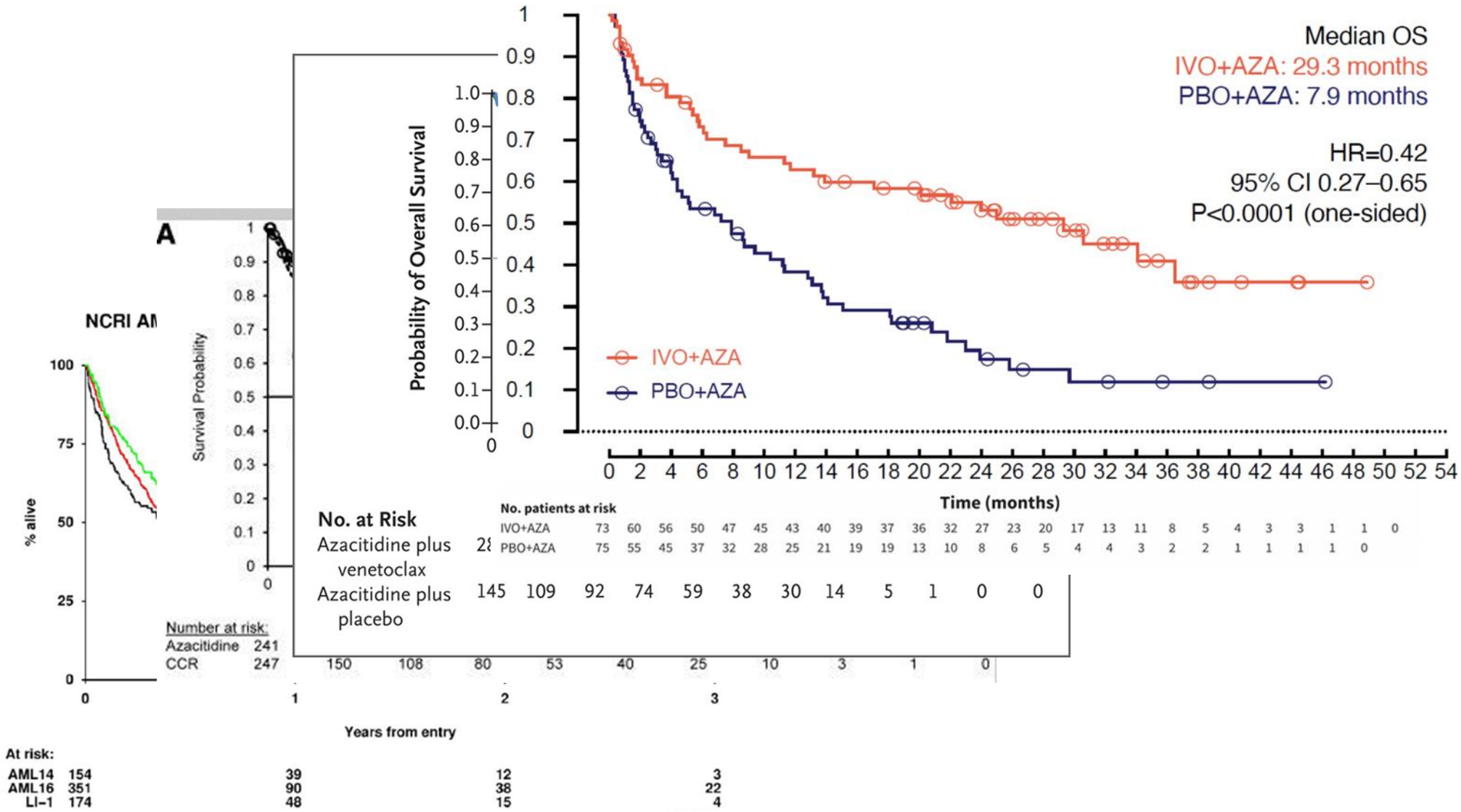
Phase 3 trial of gilteritinib plus azacitidine vs azacitidine for newly diagnosed FLT3mut+ AML ineligible for intensive chemotherapy



Abbreviations: AZA, azacitidine 75 mg/m^2 intravenously or subcutaneously daily on days 1–7; CI, confidence interval; CRc, composite complete remission; FLT3, FMS-like tyrosine kinase 3; GIL, gilteritinib 120 mg orally daily on days 1–28; HR, hazard ratio.

Eunice S. et al Blood, 2022

Conclusions


Median OS
IVO+AZA: 29.3 months
PBO+AZA: 7.9 months
HR=0.42
95% CI 0.27–0.65
P<0.0001 (one-sided)
IVO+AZA
PBO+AZA
Probability of Overall Survival
Time (months)
No. patients at risk
IVO+AZA 73 60 56 50 47 45 43 40 39 37 36 32 27 23 20 17 13 11 8 5 4 3 3 1 1 0
PBO+AZA 75 55 45 37 32 28 25 21 19 19 13 10 8 6 5 4 4 3 2 2 1 1 1 1 0
No. at Risk
Azacitidine plus venetoclax 28
Azacitidine plus placebo 145 109 92 74 59 38 30 14 5 1 0 0
A
Survival Probability
Number at risk:
Azacitidine 241
CCR 247
150 108 80 53 40 25 10 3 1 0
% alive
Years from entry
At risk:
AML14 154 39 12 3
AML16 351 90 38 22
LI–1 174 48 15 4

Protocoles !

- Aza + ven + anti sirpalpha (NCT05168202)
- Aza + ven + ICT01 (stimulation des LTγ9δ2) (NCT04243499)
- Aza + ven +/-tamibarotene (NCT04905407)
- Aza + ven +/- magro *hold* (NCT05079230)
- « Ivosidenib and Venetoclax With or Without Azacitidine in Treating Patients With IDH1 Mutated Hematologic Malignancies » NCT03471260
- *Et les inhibiteurs de Menin.. (pas encore en 1ere ligne)*

En dehors des protocoles..

- Aza seule
  - K très défavorable ?
  - Patient très comorbide?
- Patient IDH1 muté
  - Aza-ivo
- Les autres
  - Aza-ven
- Parfois rien ..