2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2021
Starhotels Majestic

Scientific board:
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How I treat elderly Acute Myeloid Leukemia Patients

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Disclosures of Adriano Venditti

	Research Support	Advisory Board	Consultant	Invited Speaker	Speaker Bureau
Abbvie		X	X	X	
Amgen		X			
Astellas		X	X	X	
Celgene				X	
Daiichi-Sankyo		X		X	
Gilead		X			
Helsinn		X			
Janssen		X		X	
Jazz Pharmaceuticals	X	X	X	X	
Merus		X			
Novartis		X	X	X	
Pfizer		X	X	X	X
Sandoz	X				

Recent approval of recent new options

	Target	Approval		
Midostaurin (+IC)	FLT3	ND	✓	✓
CPX-351	t-AML, AML-MRC	ND	✓	✓
Enasidenib	IDH2	R/R		✓
Gemtuzumab ozogamicin (±IC)*	CD33	ND and R/R*	✓	✓
Ivosidenib	IDH1	ND and R/R		✓
Glasdegib (+LDAC)	Sonic hedgehog pathway	ND	✓	✓
Gilteritinib	FLT3	R/R	✓	✓
Venetoclax (+Aza/Dec/LDAC)†	BCL-2	ND	✓	✓
CC-486 (oral azacitidine)	Hypermethylation	Maintenance		✓

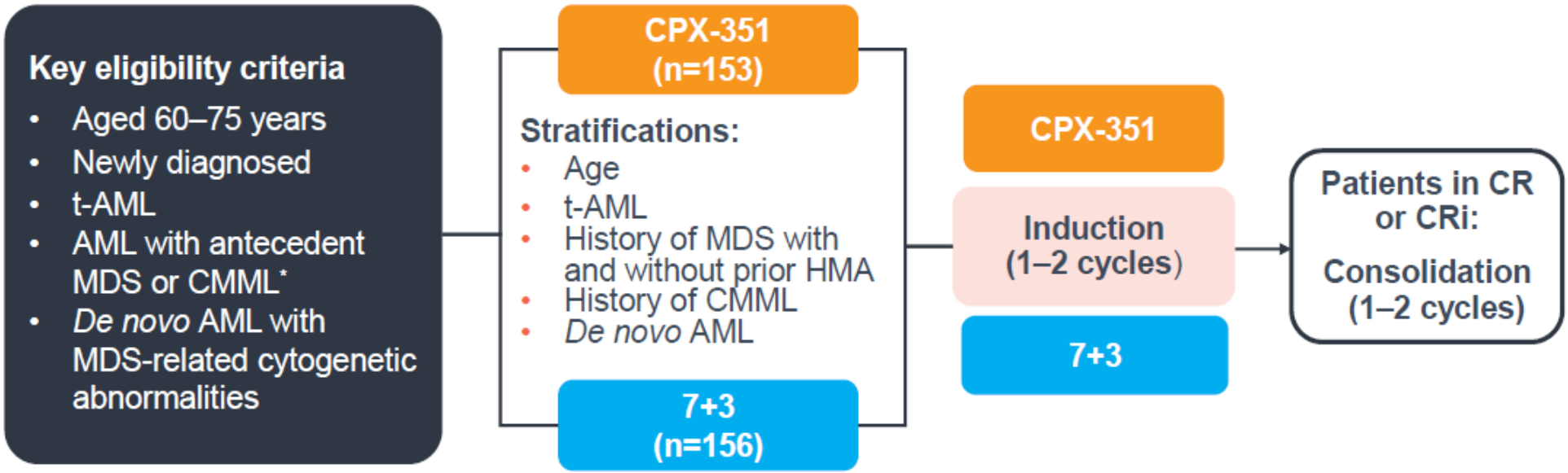
1. EMA website. Available at: https://www.ema.europa.eu/en/medicines/human (accessed May 2021);
2. FDA website. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed May 2021);
3. Venclyxto® (venetoclax). EMA Summary of Product Characteristics, May 2021.

New agents

- CPX-351
- CC-486
- Venetoclax
- Glasdegib

CPX-351 phase III study

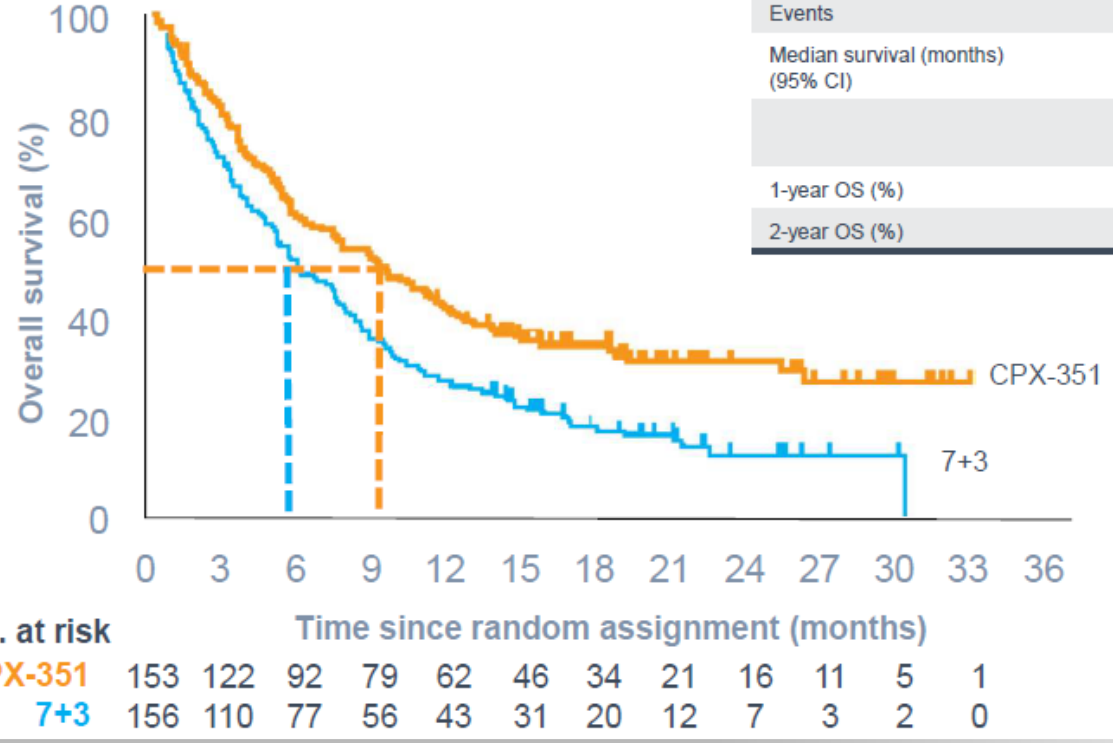
- Randomised, open-label, parallel-arm, standard therapy-controlled study
  - 1:1 randomisation, enrolled from December 2012 to November 2014
- Primary endpoint: OS
- Secondary endpoints: Remission rate, remission duration, EFS



Lancet JE et al. J Clin Oncol 2018;36:2684–2692

CPX-351 phase III study: Overall Survival

ITT population



	CPX-351 (n=153)	7+3 (n=156)
Events	104	132
Median survival (months) (95% CI)	9.56 (6.60–11.86)	5.95 (4.99–7.75)
	HR (95% CI) 0.69 (0.52–0.90) one-sided P=0.003	
1-year OS (%)	41.5	27.6
2-year OS (%)	31.1	12.3

Lancet JE et al. J Clin Oncol 2018;36:2684–2692

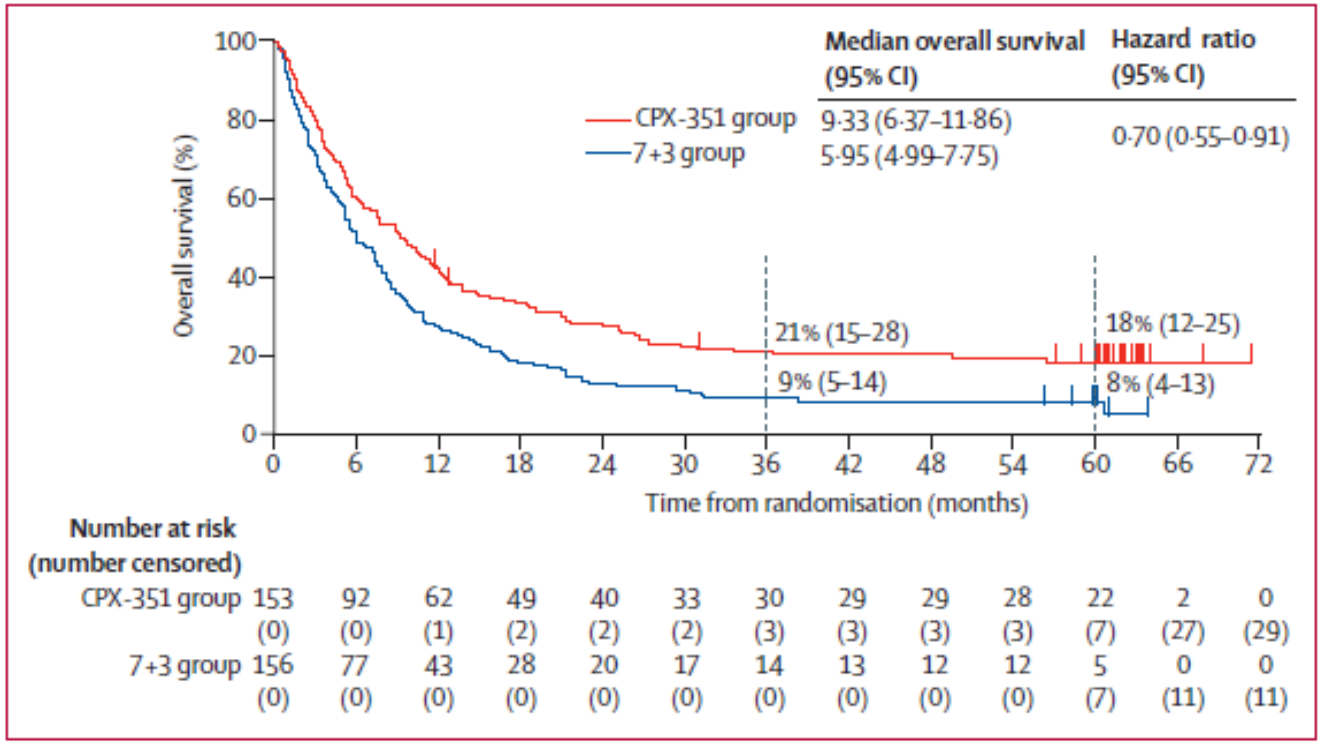


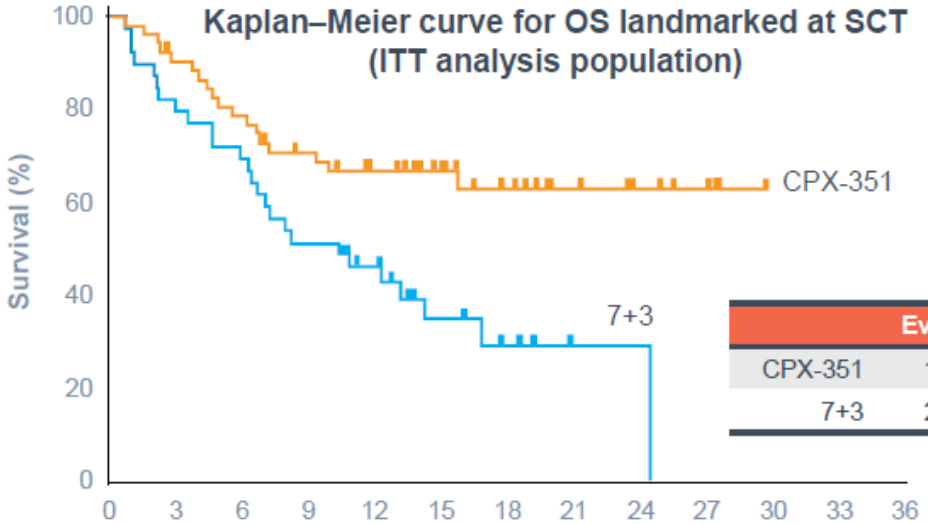
Figure 2: **Overall survival**

3-year and 5-year Kaplan-Meier-estimated survival rates are shown with 95% CI. 7+3=cytarabine and daunorubicin.

Lancet JE et al, Lanc Hematol, 2021

CPX-351 phase III study: OS landmarked from time of HSCT

- **Median OS not reached for CPX-351 versus 10.25 months for 7+3**
  - HR 0.46 favouring CPX-351 (P=0.009)



	Events/N	Median survival (95% CI)
CPX-351	18/52	Not reached
7+3	26/39	10.25 (6.21–16.69)

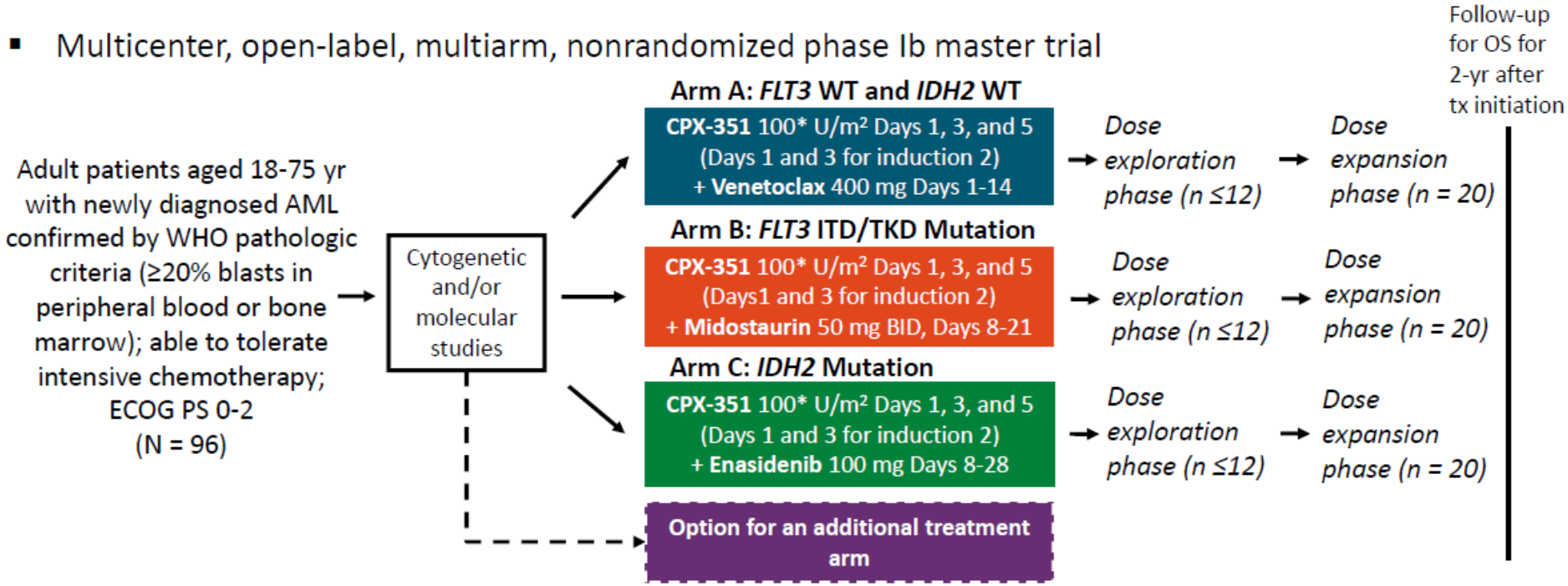
HR 0.46; P=0.009

Number at risk												
CPX-351	52	46	40	34	27	20	15	9	6	3	0	0
7+3	39	31	27	20	15	7	4	1	1	0	0	0

Lancet JE et al. J Clin Oncol 2018;36:2684–2692

V-FAST: CPX-351 + Targeted Agents in Newly Diagnosed AML

- Multicenter, open-label, multiarm, nonrandomized phase Ib master trial



- **Primary endpoints:** RP2D and safety
- **Secondary endpoints:** response, CR/CRi with MRD negative status, CR/CRh with MRD negative status

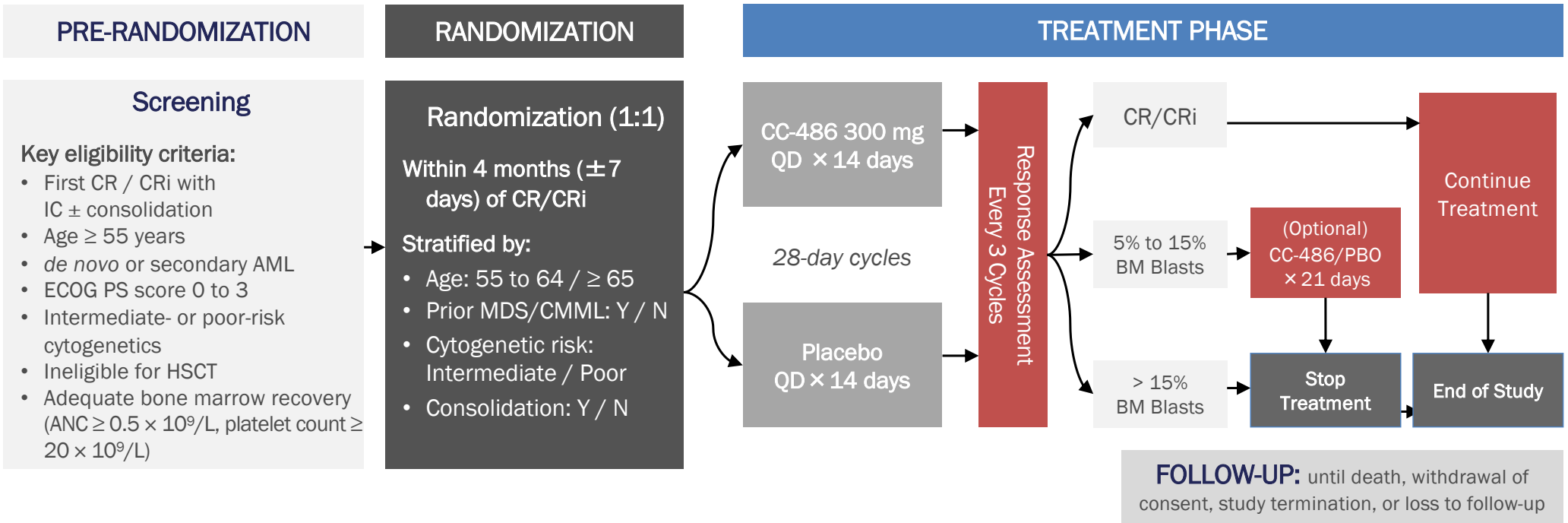
Pullarkat. EHA 2021. Abstr EP442. NCT04075747.

V-FAST: RP2D

- In arm A (CPX-351 + venetoclax), RP2D was determined to be:
  - Induction DL1: CPX-351 100 U/m^2 on days 1, 3, and 5 (days 1 and 3 for induction 2), venetoclax 400 mg on days 1 to 14
    - 1 of 6 patients in the dose exploration phase experienced DLTs of grade 4 neutropenia and thrombocytopenia
- In arm B (CPX-351 + midostaurin), RP2D was determined to be:
  - Induction DL1: CPX-351 100 U/m^2 on days 1, 3, and 5 (days 1 and 3 for induction 2), midostaurin 50 mg BID on days 8 to 21
  - No DLTs were observed
- In arm C (CPX-351 + enasidenib), RP2D has not yet been determined

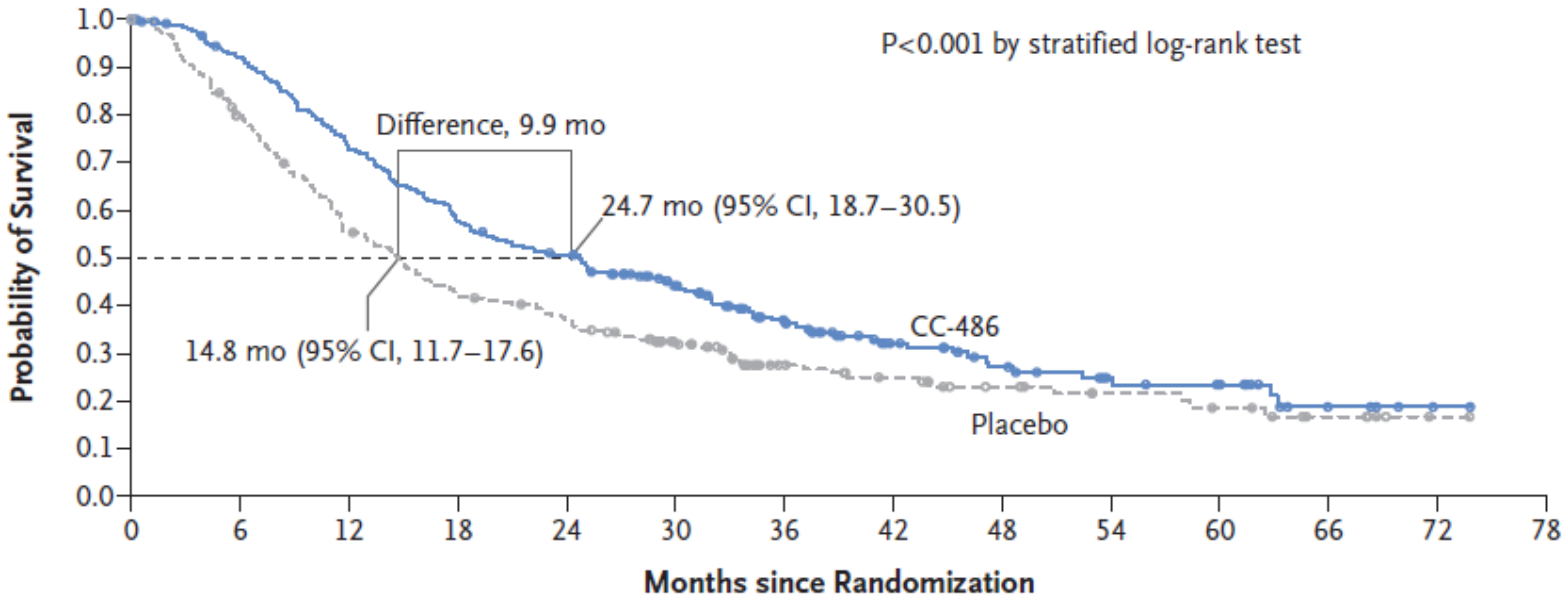
Pullarkat. EHA 2021. Abstr EP442. NCT04075747.

QUAZAR AML-001: Oral AZA for pts with AML in CR after iCHT



Wei AH, et al. N Engl J Med. 2020;383:2526-2537.

QUAZAR AML-001: Oral AZA for pts with AML in CR after iCHT



No. at Risk													
CC-486	238	213	168	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	127	96	82	58	34	27	19	14	11	6	1	0

Wei AH, et al. N Engl J Med. 2020;383:2526-2537.

QUAZAR AML-001: OS and RFS by NPM1 status

Outcome	Mutated *NPM1*		Wild-Type *NPM1*	
	Oral Azacitidine (n = 66)	Placebo (n = 71)	Oral Azacitidine (n = 170)	Placebo (n = 162)
OS				
Median, mo	47.2	15.9	19.6	14.6
P value	.038		.023	
RFS				
Median, mo	23.2	6.9	7.8	4.6
P value	.005		.003	

- In patients treated with oral azacitidine, the *P* value for OS or RFS difference among patients with mutated *NPM1* vs wild type *NPM1* was <.001
- In patients receiving placebo, the *P* value for OS and RFS difference among patients with mutated *NPM1* vs wild type *NPM1* was .032 and .011, respectively

Döhner. EHA 2021. Abstr S131.

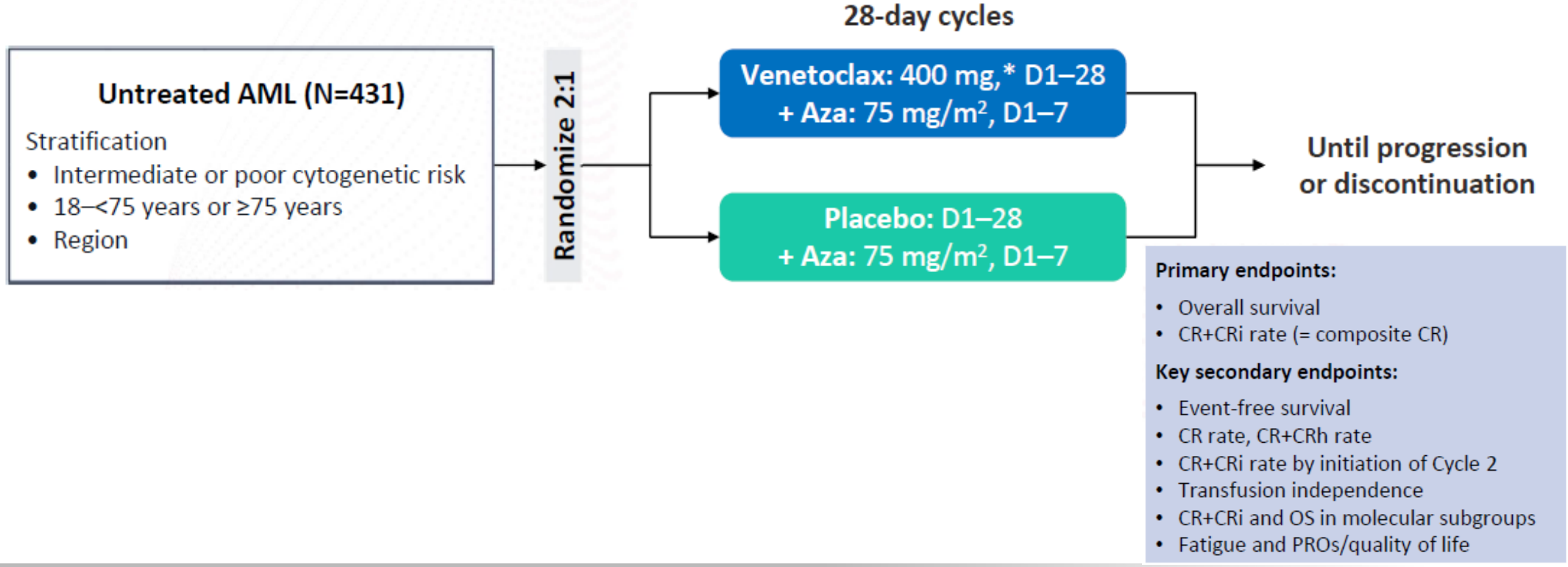
QUAZAR AML-001: OS and RFS by FLT3 status

Outcome	Mutated *FLT3*		Wild Type *FLT3*	
	Oral Azacitidine (n = 30)	Placebo (n = 36)	Oral Azacitidine (n = 206)	Placebo (n = 197)
OS				
Median, mo	28.2	9.7	24.7	15.2
P value	.114		.013	
RFS				
Median, mo	23.1	4.6	10.2	4.9
P value	.032		.001	

- In patients treated with oral azacitidine, the *P* value for OS and RFS difference among patients with mutated *FLT3* vs wild-type *FLT3* was .715 and .285, respectively
- In patients receiving placebo, the *P* value for OS and RFS difference among patients with mutated *FLT3* vs wild-type *FLT3* was .351 and .594, respectively

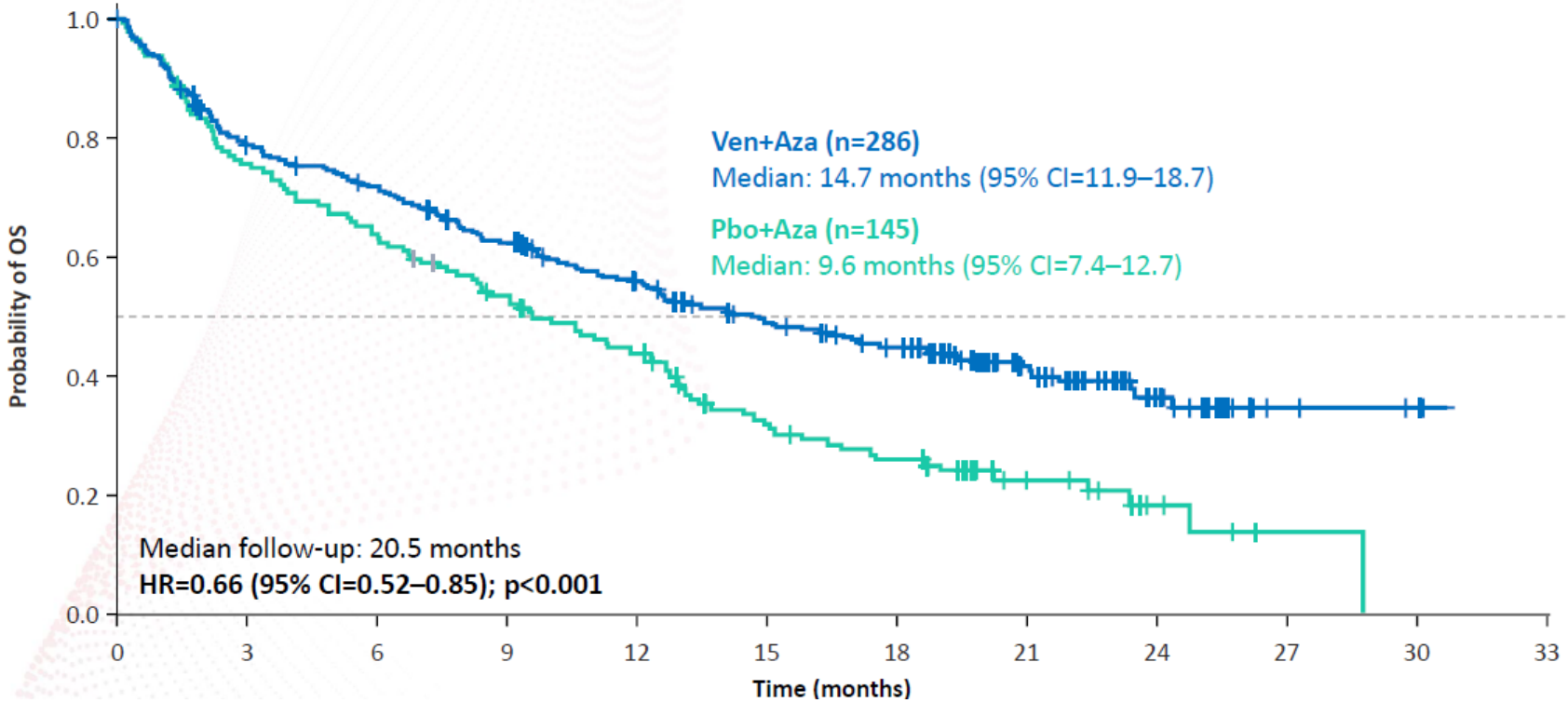
Döhner. EHA 2021. Abstr S131.

VIALE-A: Phase 3, double-blind, randomized trial of Ven+Aza vs Pbo+Aza in patients with newly diagnosed AML ineligible for iCHT



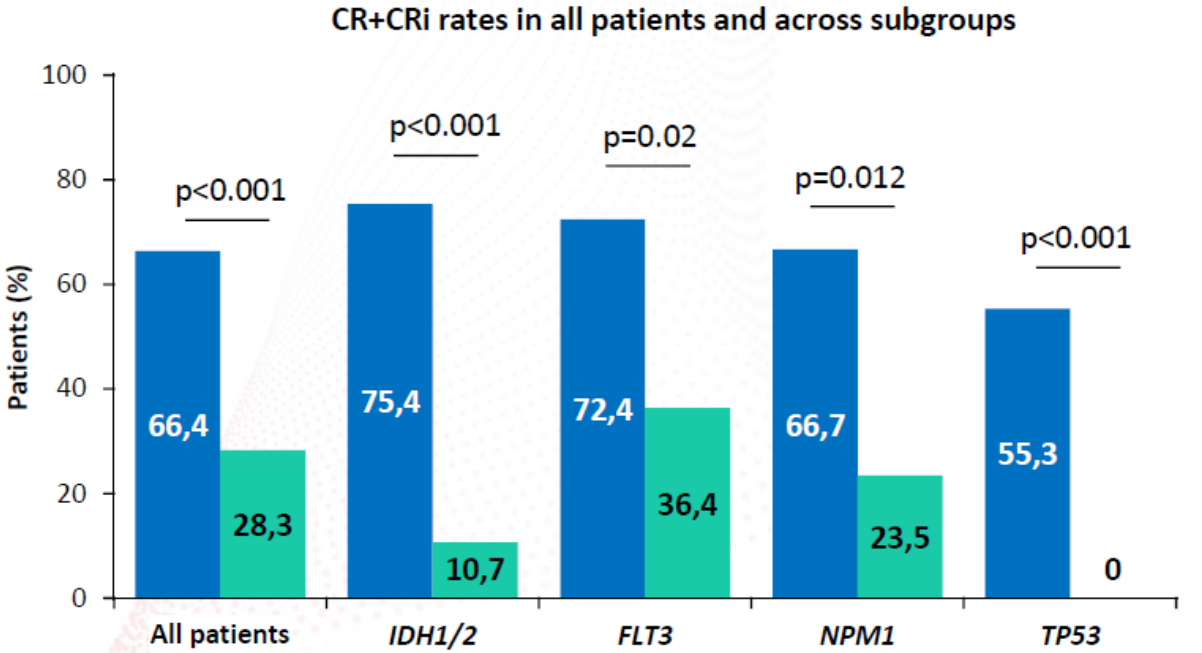
1. ClinicalTrials.gov. NCT02993523 (accessed April 2021);
2. DiNardo CD, et al. N Engl J Med 2020; **383:**617–629 (incl. suppl.).

VIALE-A: OS estimate



*DiNardo CD, et al. N Engl J Med 2020; **383:**617–629 (incl. suppl.).*

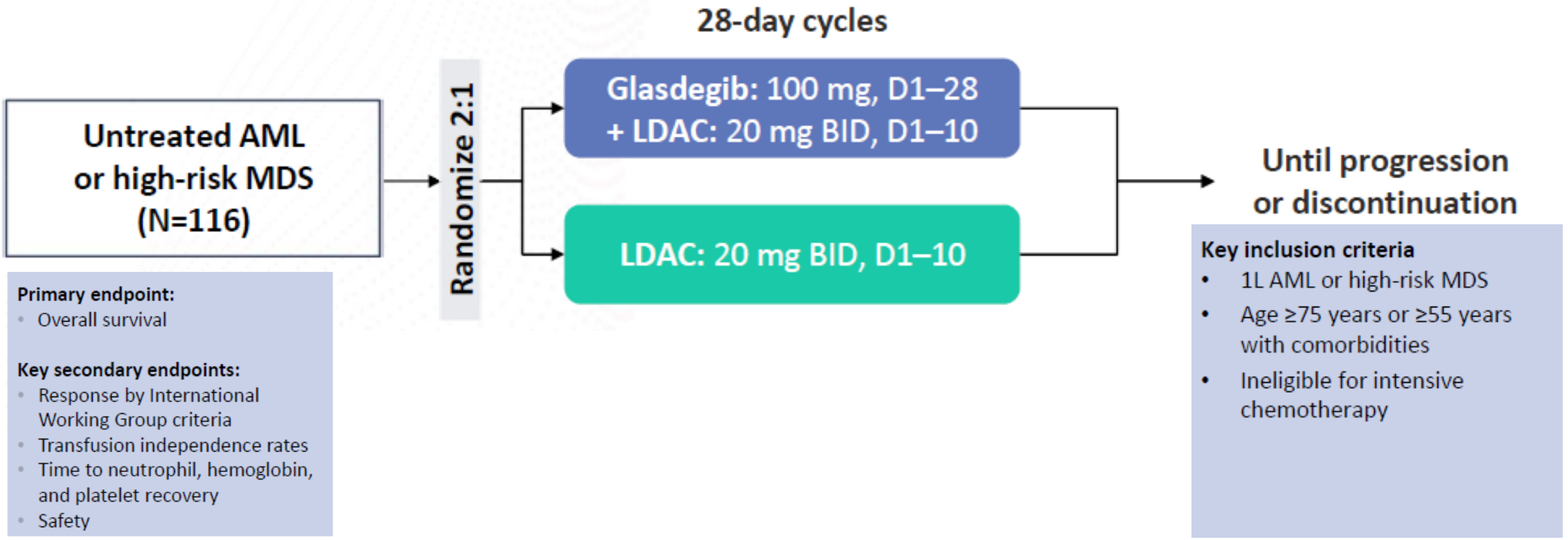
VIALE-A: CR/CRi rate across genetic subgroups



	Ven+Aza	Pbo+Aza
Median duration of CR, months (95% CI)	17.5 (15.3–NR)	13.3 (8.5–17.6)
Median duration of CR+CRi, months (95% CI)	17.5 (13.6–NR)	13.4 (5.8–15.5)

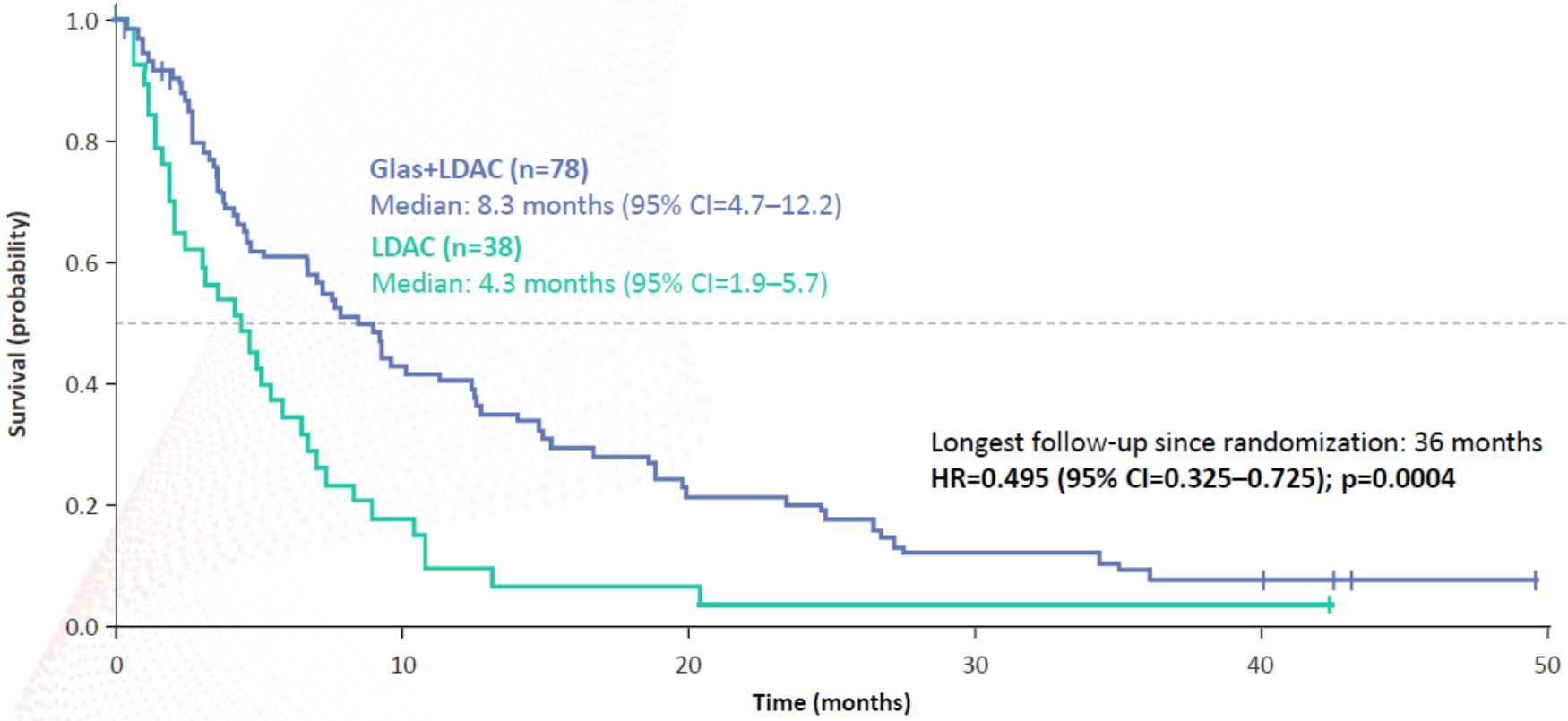
*DiNardo CD, et al. N Engl J Med 2020; **383:**617–629 (incl. suppl.).*

BRIGHT AML 1003: Phase 2, open-label, randomized trial of Glas+LDAC vs LDAC in patients with newly diagnosed AML ineligible for iCHT



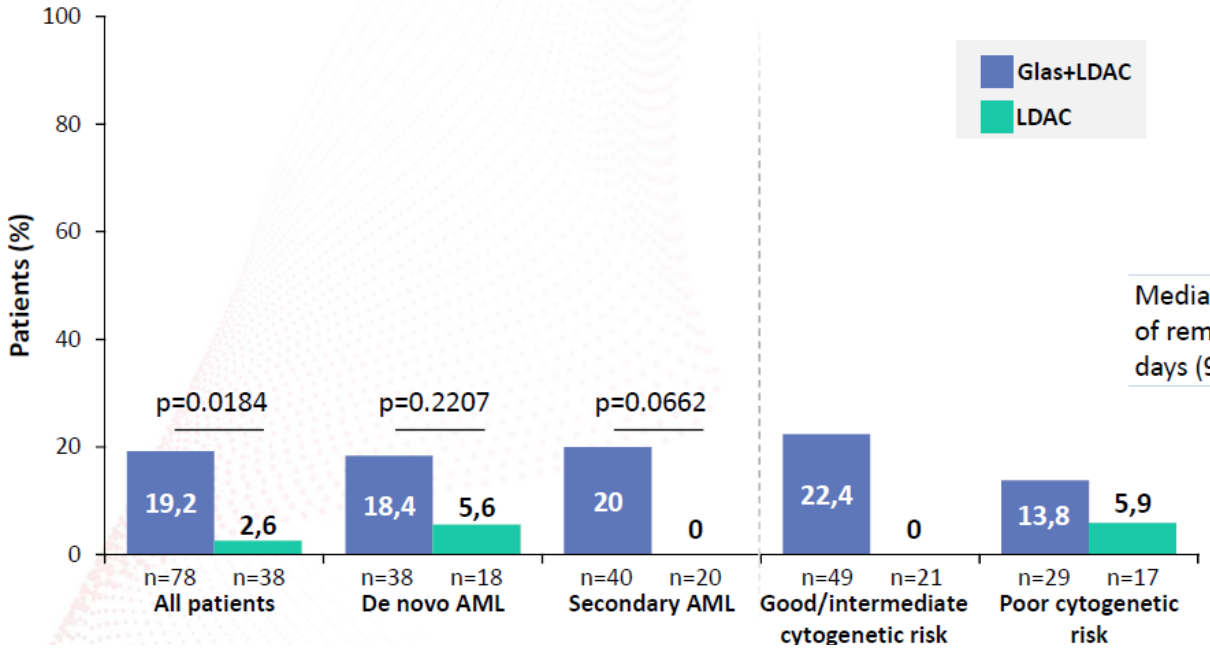
*Heuser M, et al. Ann Hematol 2021; **100:**1181–1194.*

BRIGHT AML 1003: OS estimate



Heuser M, et al. Ann Hematol 2021; ***100:****1181–1194.*

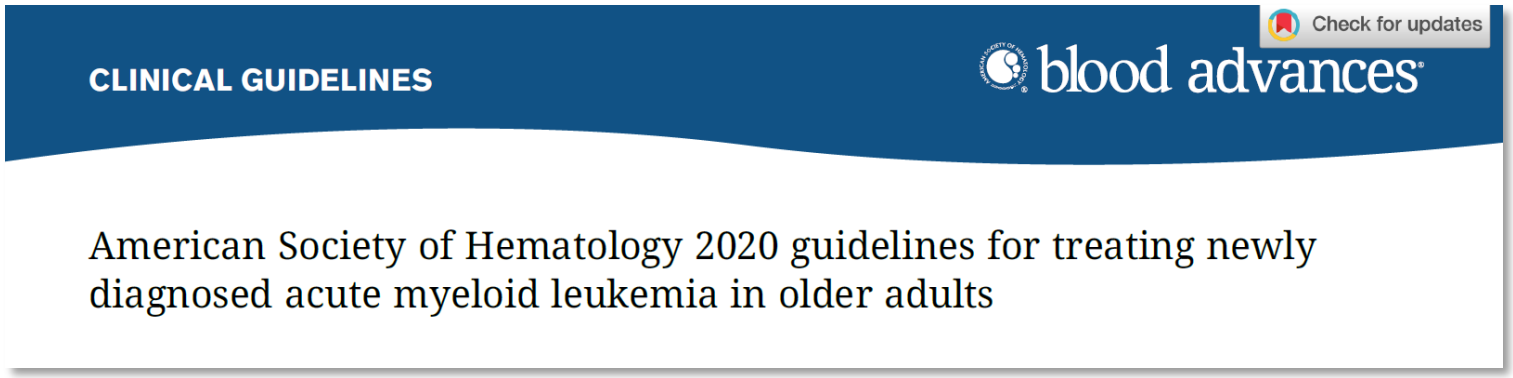
BRIGHT AML 1003: CR rates



	Glas+LDAC n=78	LDAC n=38
Median duration of remission, days (95% CI)	302 (1–1262)	91 (91–91)

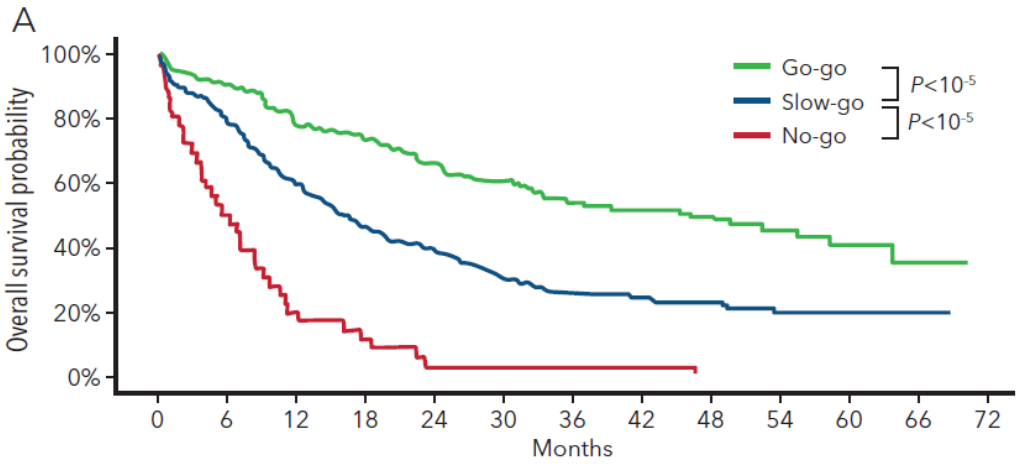
*Heuser M, et al. Ann Hematol 2021; **100:**1181–1194.*

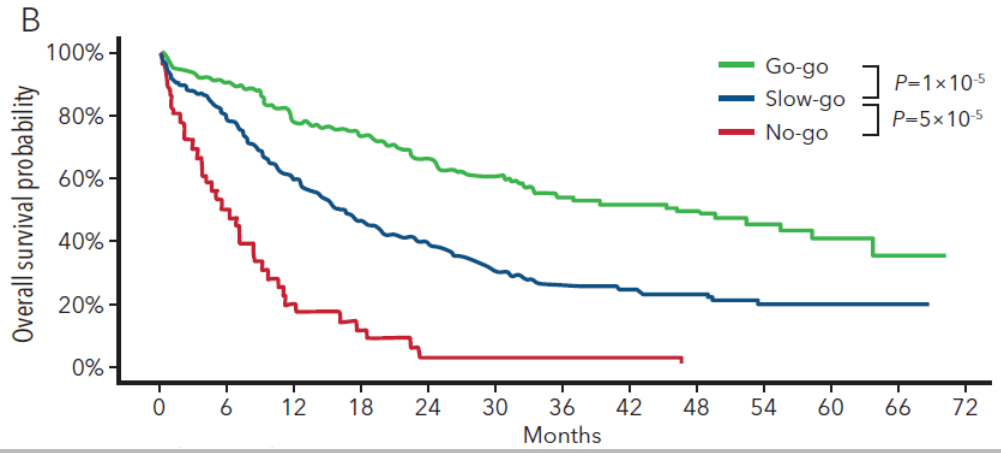
Who is ineligible for intensive chemotherapy?



"…the panel could not clearly define a patient population 'unfit' for intensive chemotherapy, despite models that have been developed to help in this determination."

*Sekeres MA, et al. Blood Adv 2020; **4**:3528–3549.*

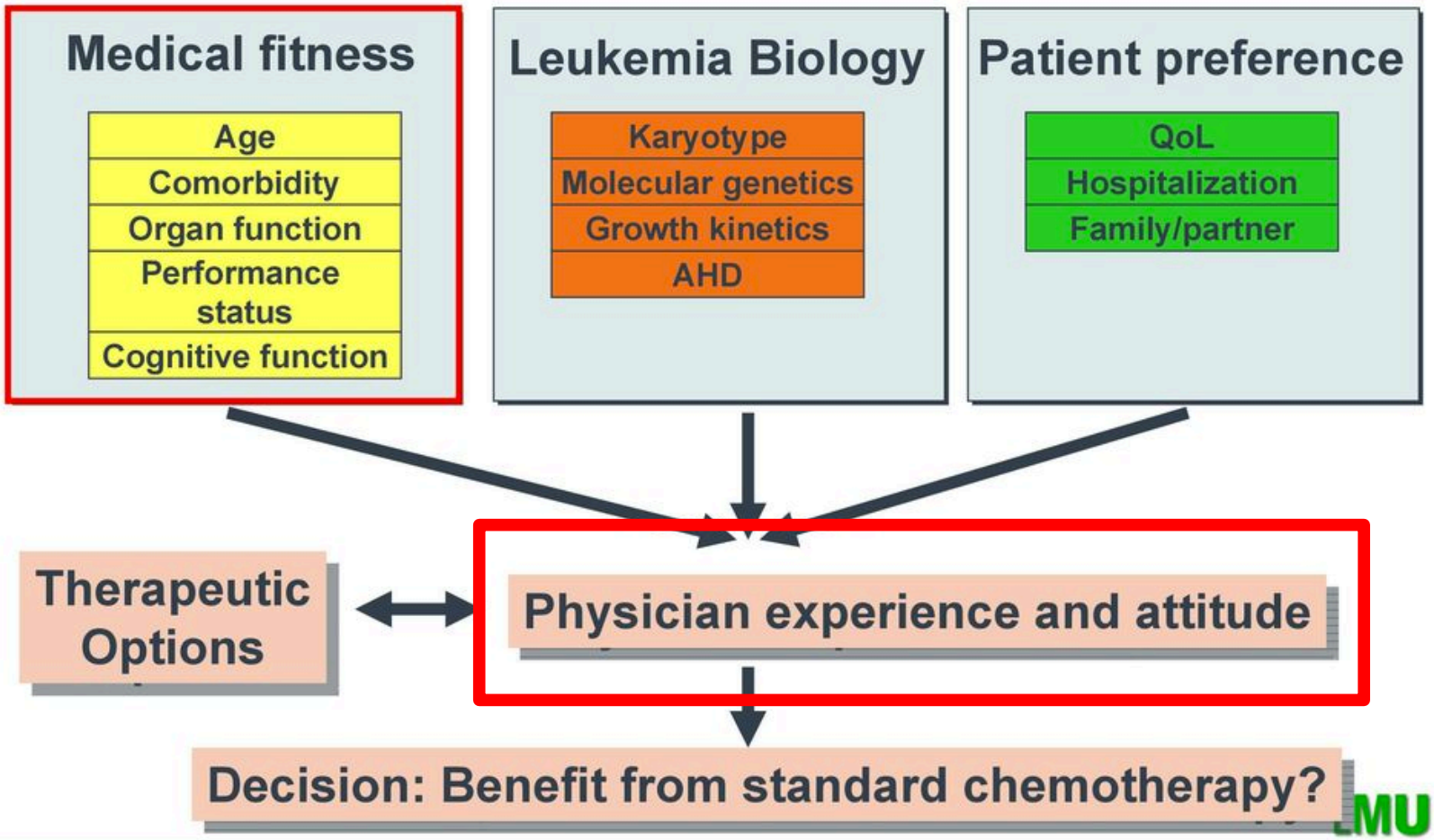




Variable	HR	95% CI	P
Non–poor risk cytogenetics (n = 387)			
NPM1 mutation	0.57	0.41-0.77	.0004
FLT3-ITD low ratio	1.85	1.31-2.62	.0005
FLT3-ITD high ratio	3.51	2.03-6.08	<.0001
NRAS mutation	1.54	1.07-2.20	.019
ASXL1 mutation	1.89	1.34-2.67	.0003
DNMT3A mutation	1.86	1.40-2.47	<.0001
Poor risk cytogenetics (n = 84)			
KRAS mutation	3.60	1.68-7.72	.001
TP53 mutation	2.49	1.53-4.04	.0003

Itzykson R et al. Blood 2021; 138(7):507-519.

Therapeutic decisions in elderly AML



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Conclusions

- More treatment options available for older pts
  - –Reducing the rate of those addressed to BSC
- Integrating physical and biologic/genetic fitness
- Role of immune-therapy (Magrolimab)
- Role of maintenance
- Development of an «all oral therapy»
- Role of MRD
  - –MRD-driven post remission therapy
  - –MRD-driven de-escalation strategies