Novità terapeutiche nella leucemia mieloide acuta (LMA)

F. Ferrara (Napoli)

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Research Paper

Goals, preferences, and concerns of patients with acute myeloid leukemia at time of treatment decision

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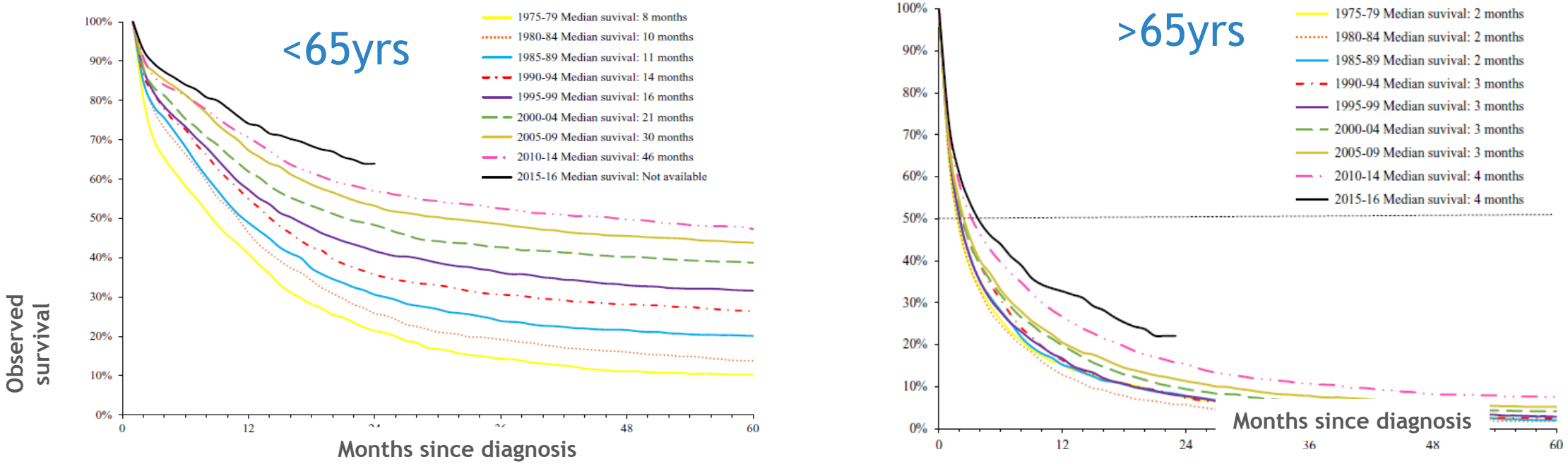
Jamy OA et al, J. Ger. Oncol, 2023

Table 2
Survey results.

	Yes		No	
Patient understanding of goals of care	N	%	N	%
My cancer is curable	57	74.0	20	26.0
The goal of my care is to live longer	76	98.7	1	1.3
The goal of my care is to feel better	77	100.0	0	0.0
The goal of my care is to get rid of all my cancer	75	97.4	2	2.6
Other				
Are you interested in clinical trial participation?	56	72.7	21	27.3
Do you have an advanced directive?	27	35.1	50	64.9
Decision Control Preferences (Patients select one)				
Make the final selection about which treatment I will receive	2	2.6		
Make the final selection after seriously considering my doctors opinion	14	18.4		
Have my doctor and I share responsibility for deciding what treatment is best	41	53.9		
Have my doctor make the final decision but consider my opinion	10	13.2		
Leave all decisions regarding treatment to my doctor	9	11.8		
Missing	1	1.3		

Jamy OA et al, J. Ger. Oncol, 2023

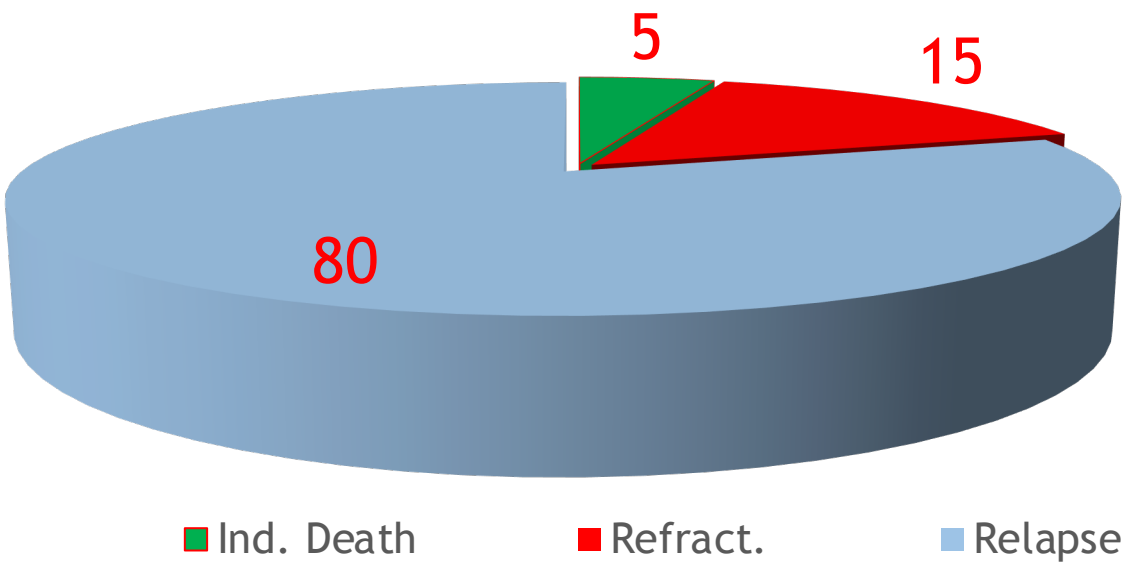
OS evolution over years in AML

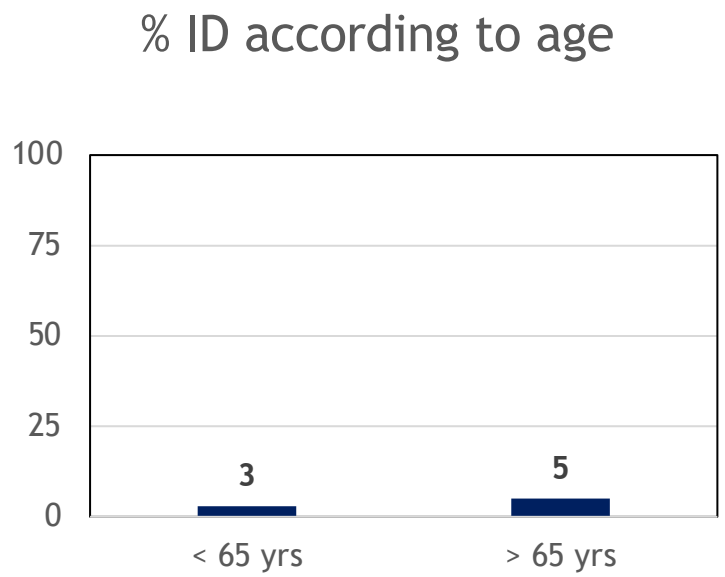


- Refinement of supportive care ➡ lower ID
- More older patients treated and better selection of them
- Lower TRM
- Increased allo-transplant rate up to 70-75 yrs.
- Risk adpated treatment (ELN risk, MRD)

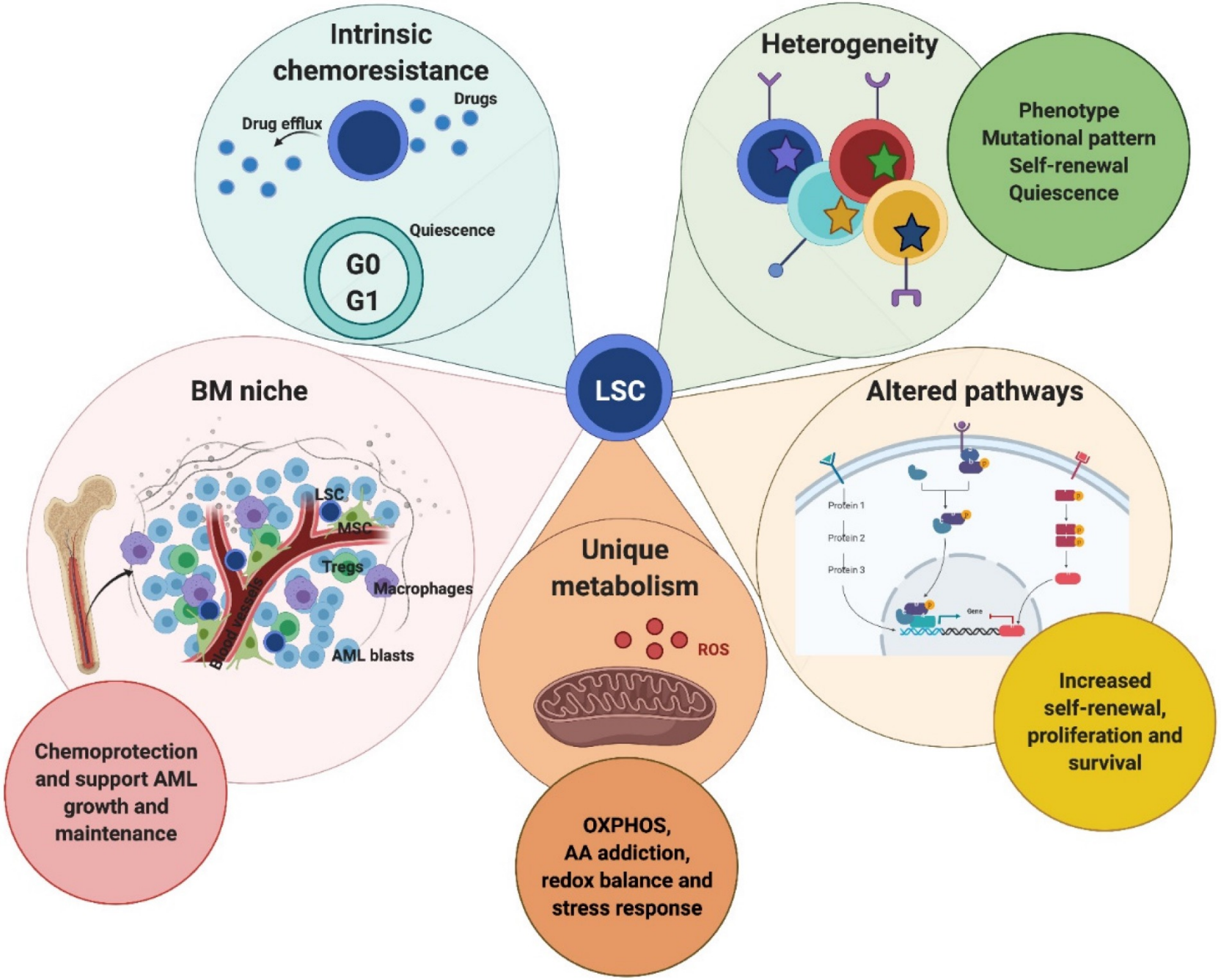
Shallis RM et al, Blood Rev, 2019

Failure in AML (%)

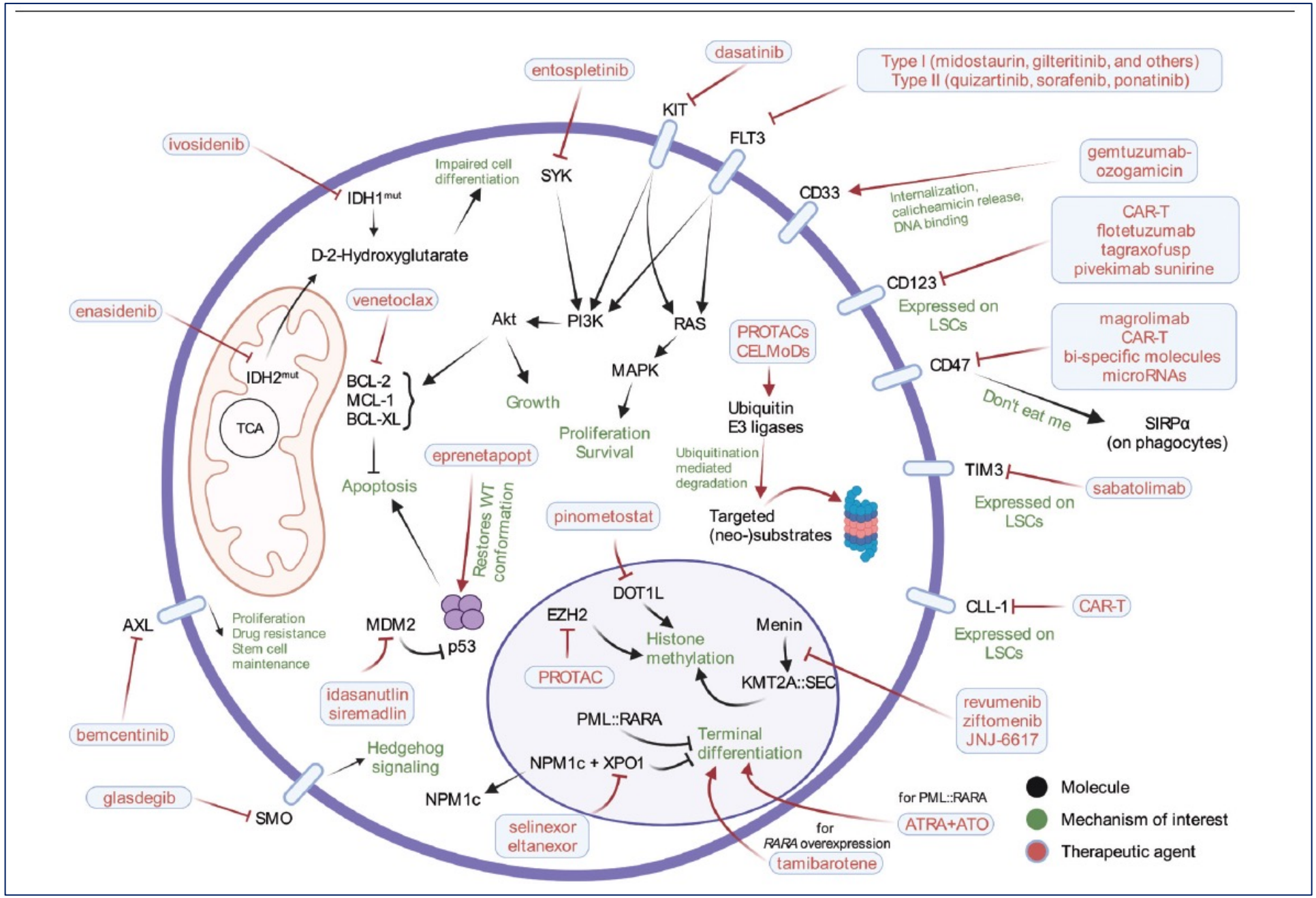




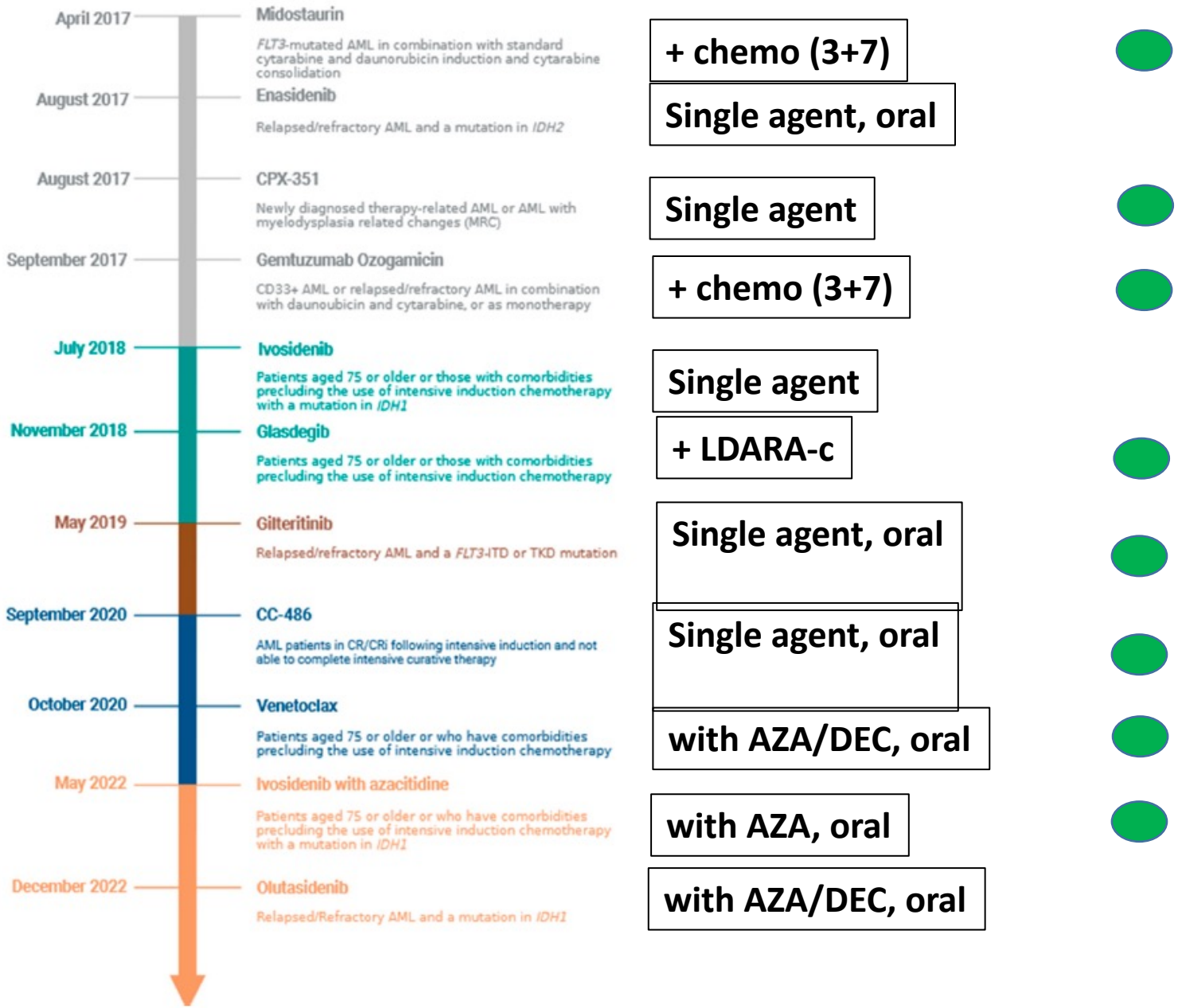
Speaker’s experience



Michelozzi IM et al. Cancers 2021, 13(11), 2816

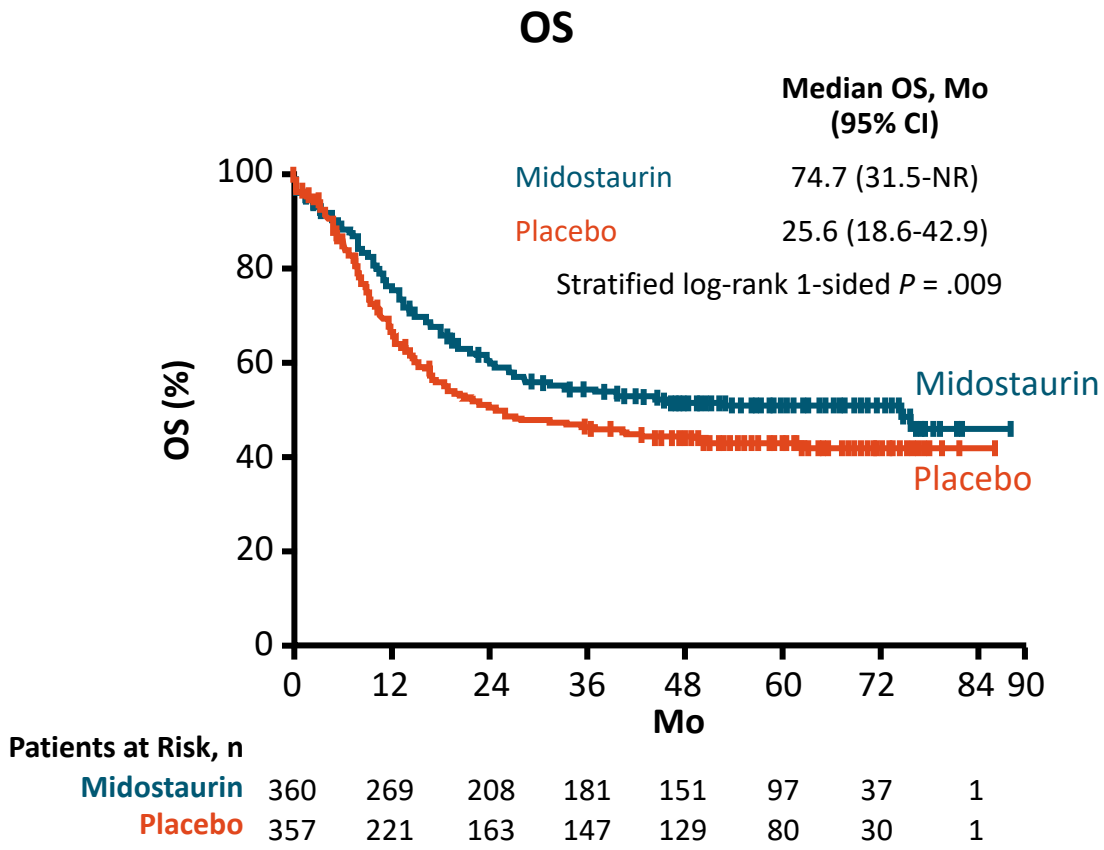


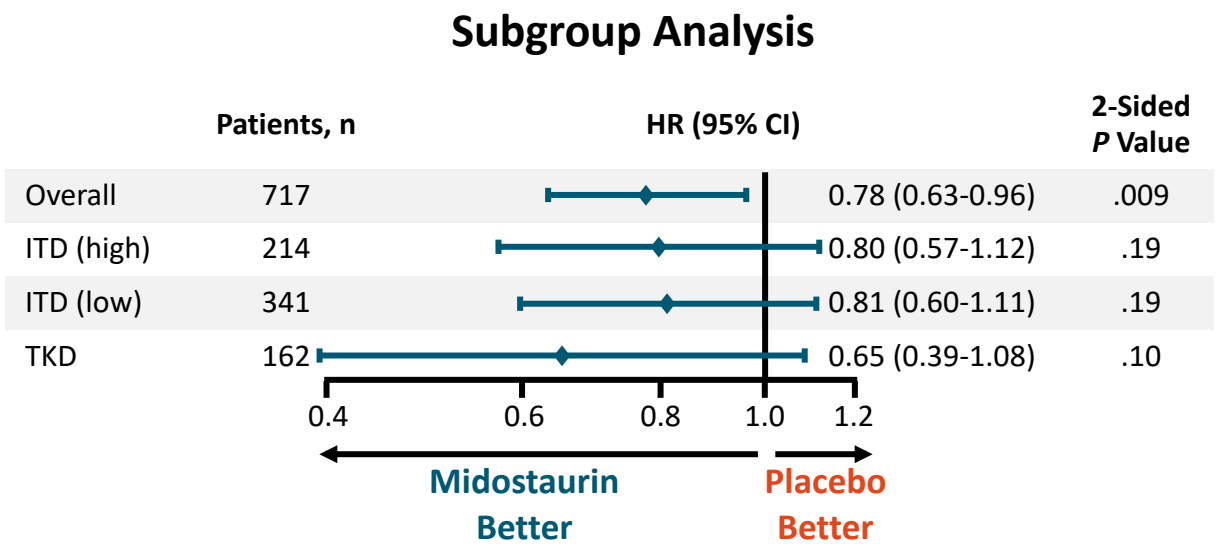
Michelozzi IM et al. Cancers 2021, 13(11), 2816



Lachowiez CC et al, Cancers, 2023, modified

RATIFY: Overall Survival

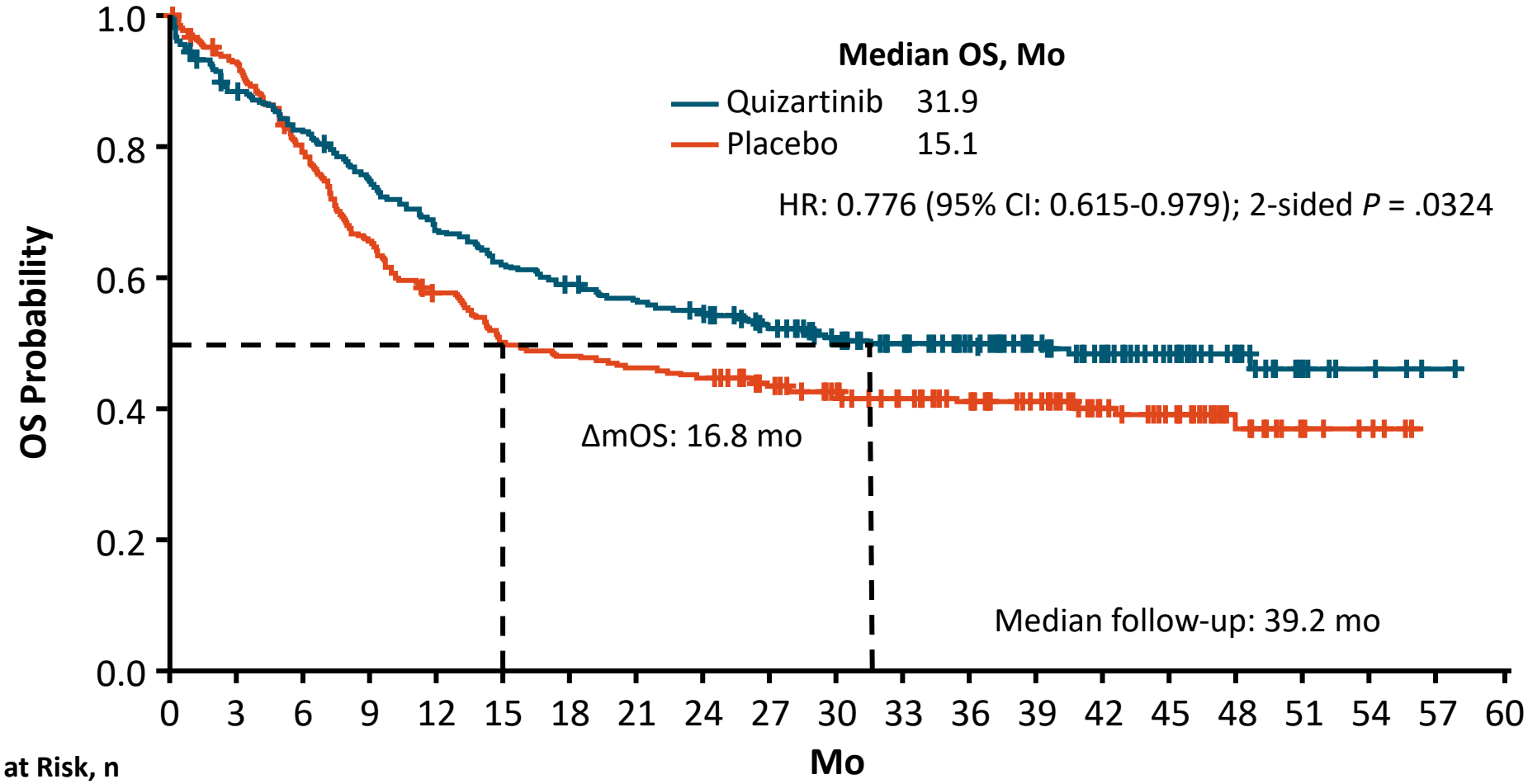




- **OS was significantly longer with midostaurin vs placebo group (HR: 0.78; *P* = .009)**
- 24.3% reduced risk of death in midostaurin arm
- At 4 yr, 63.7% were alive in midostaurin arm vs 55.7% in placebo arm

Stone. NEJM. 2017;377:454.

QuANTUM-First: OS (Primary Endpoint)

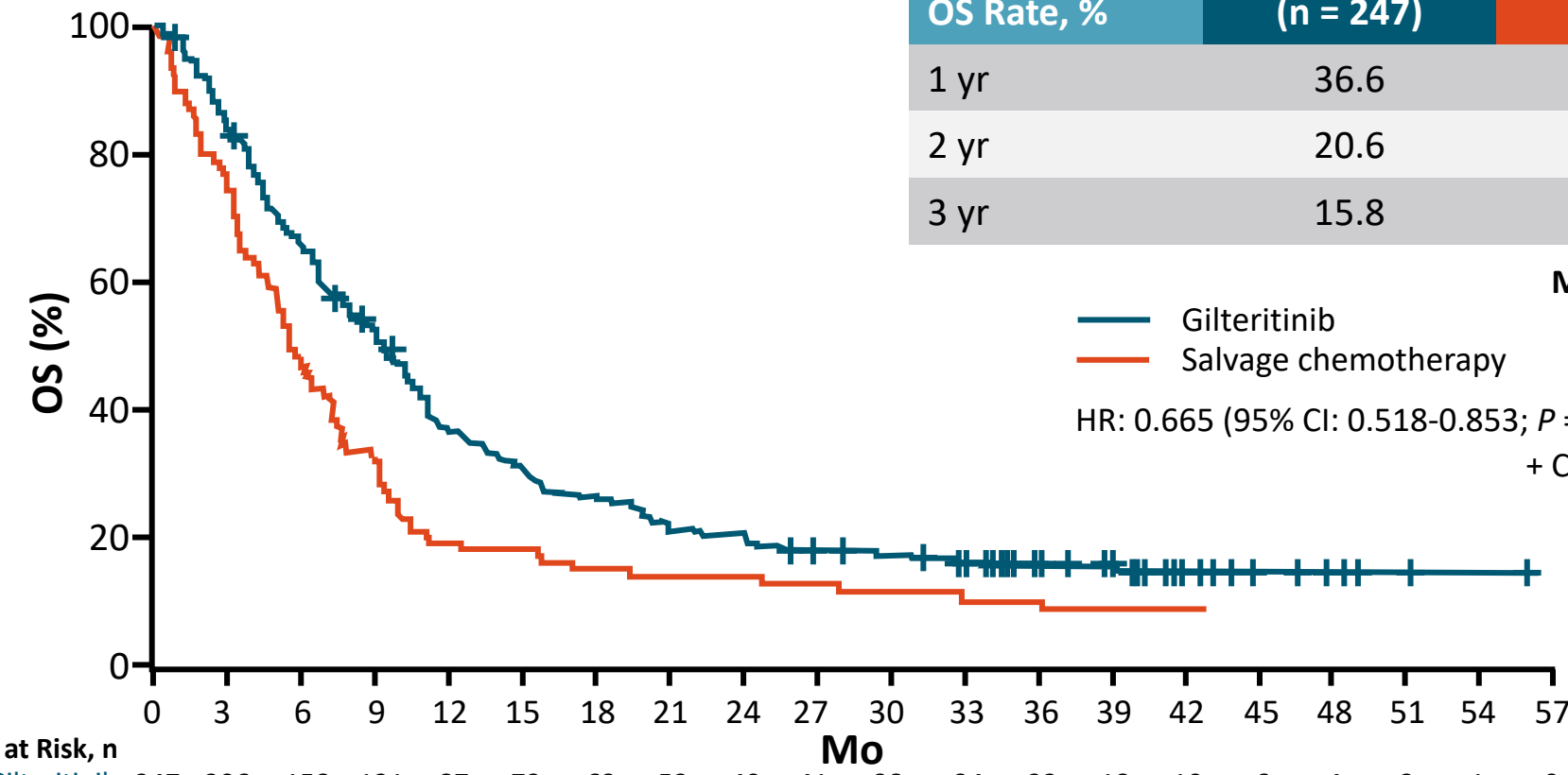


Patients at Risk, n																				
Quizartinib	268	233	216	195	176	162	153	145	139	126	110	96	83	68	53	36	24	8	4	1	0
Placebo	271	249	211	175	151	131	126	121	117	103	97	81	70	56	39	31	17	8	5	0	0

Erba. EHA 2022. Abstr S100.

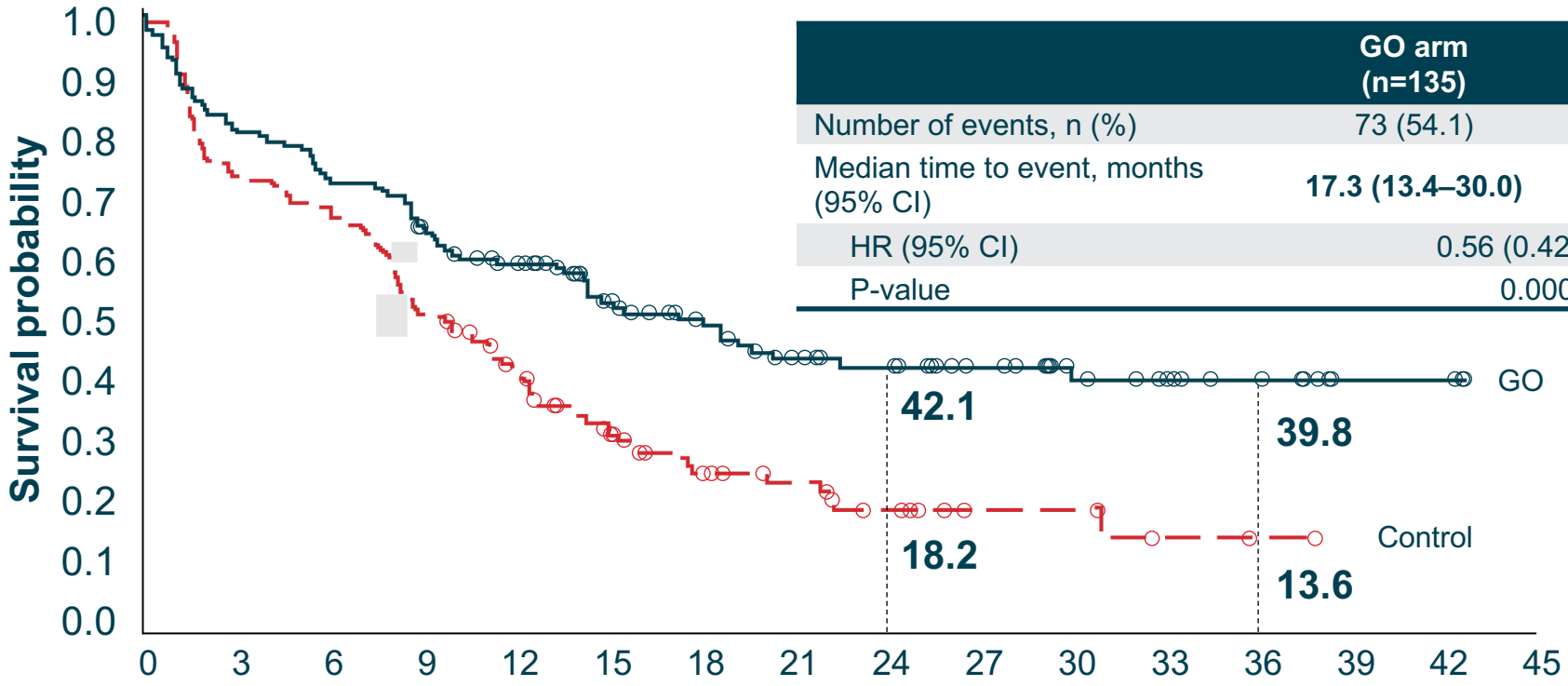
ADMIRAL: Gilteritinib Prolongs OS in m*FLT3* R/R AML

OS Rate, %	Gilteritinib (n = 247)	Salvage CT (n = 124)
1 yr	36.6	19.2
2 yr	20.6	14.2
3 yr	15.8	10.4



Perl. Blood 2022;139:3366.

ALFA-0701: Event-free survival (primary endpoint)



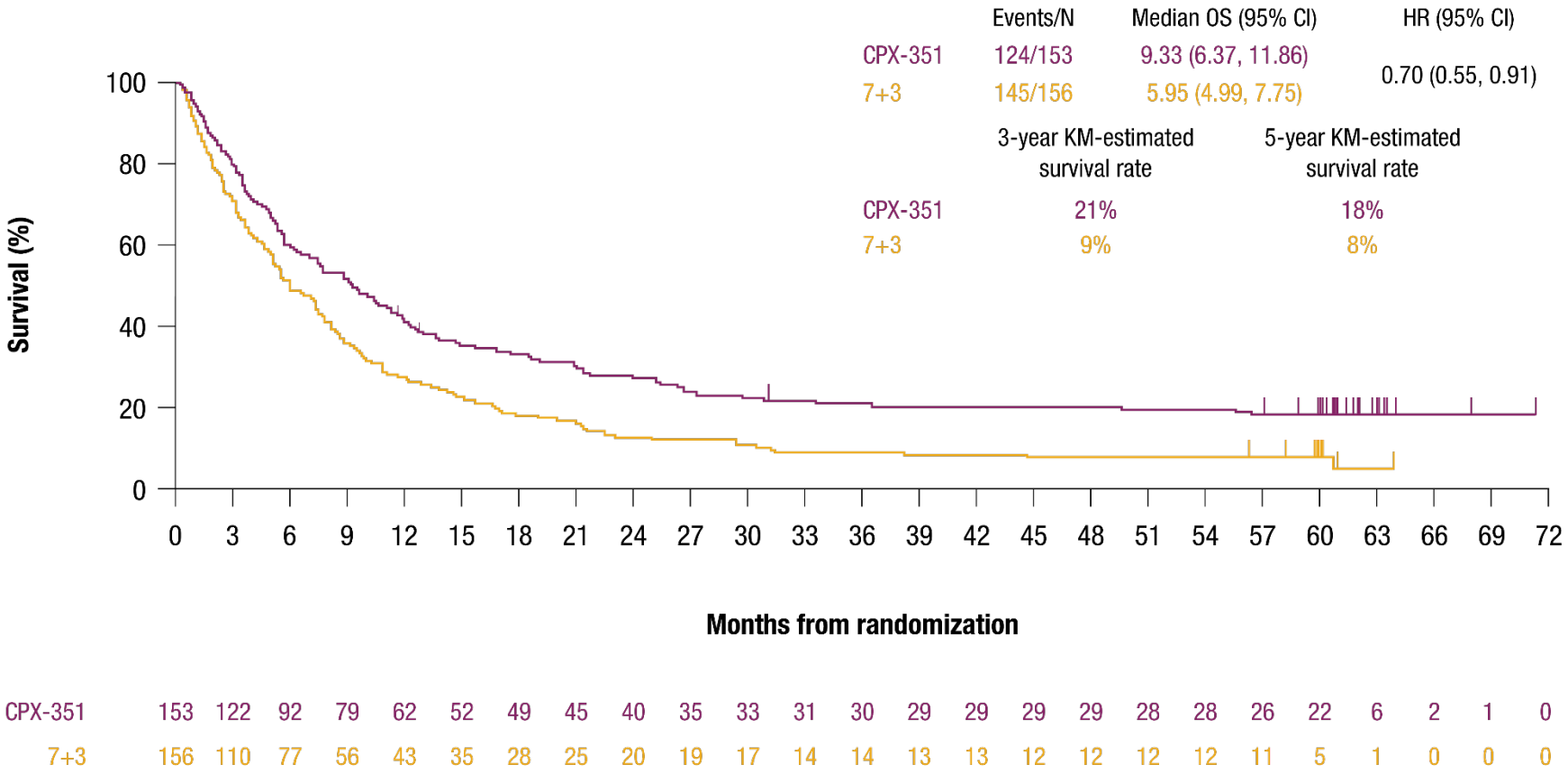
	GO arm (n=135)	Control arm (n=136)
Number of events, n (%)	73 (54.1)	102 (75.0)
Median time to event, months (95% CI)	**17.3 (13.4–30.0)**	**9.5 (8.1–12.0)**
HR (95% CI)	0.56 (0.42–0.76)	
P-value	0.0002	

Number at risk

GO	135	109	98	86	74	57	47	36	32	25	18	15	10	3	3	0
Control	136	100	93	69	51	32	21	16	10	5	5	2	1	0		

Adapted from Lambert *et al*. 2019
Modified intention-to-treat population; Data cut-off date: 1 August 2011
CI, confidence interval; GO, gemtuzumab ozogamicin; HR, hazard ratio
Lambert J *et al. Haematologica* 2019;104:113–119

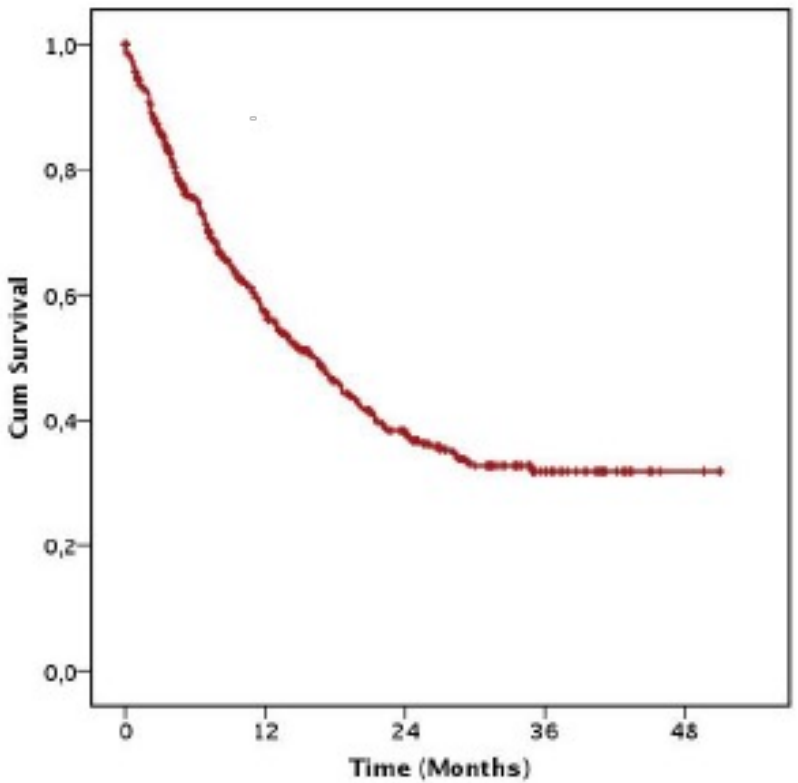
Study 301: OS (5-year final results)



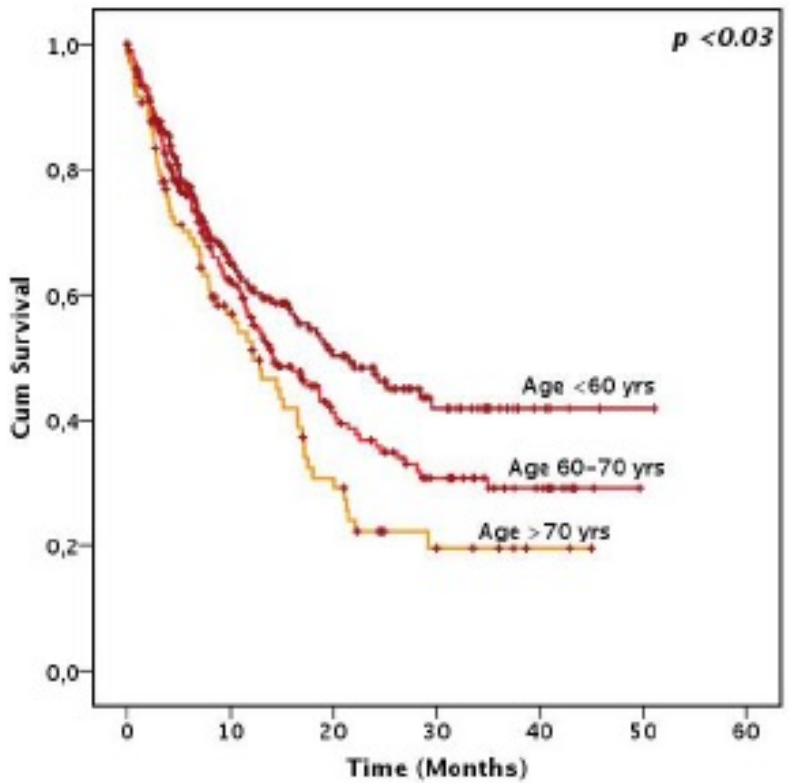
- After a median follow-up of 60.65 months, improved median OS with CPX-351 versus 7+3 was maintained, with a HR that was very stable and consistent with the primary endpoint analysis
- KM-estimated survival rates were higher for CPX-351 versus 7+3 at 3 and 5 years

Lancet JE, et al. *Lancet Haematol* 2021;8:e481–91

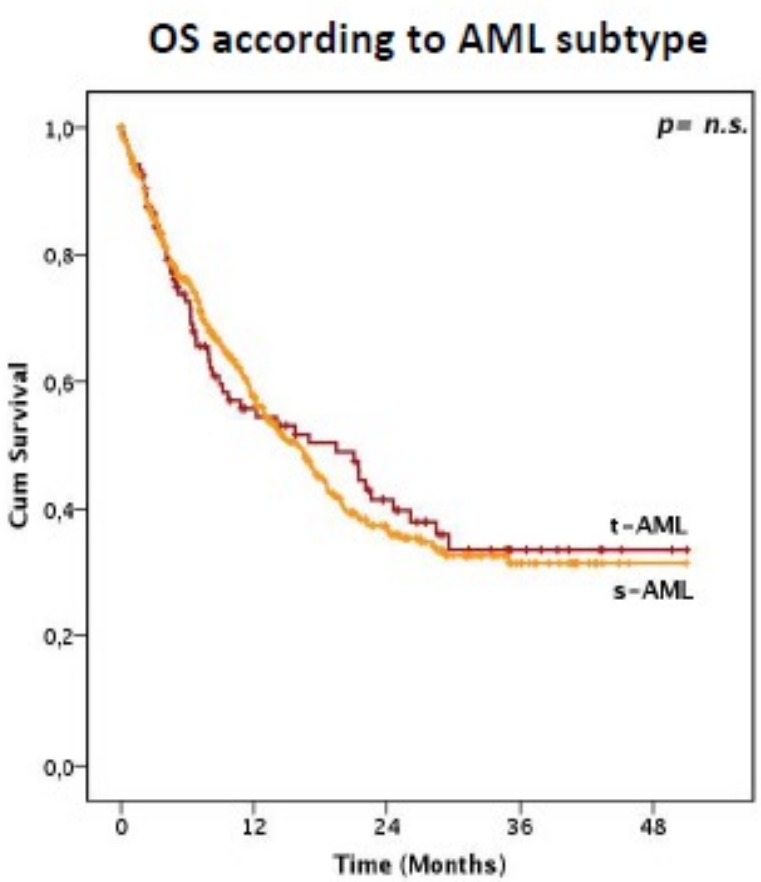
Overall Survival in all patients

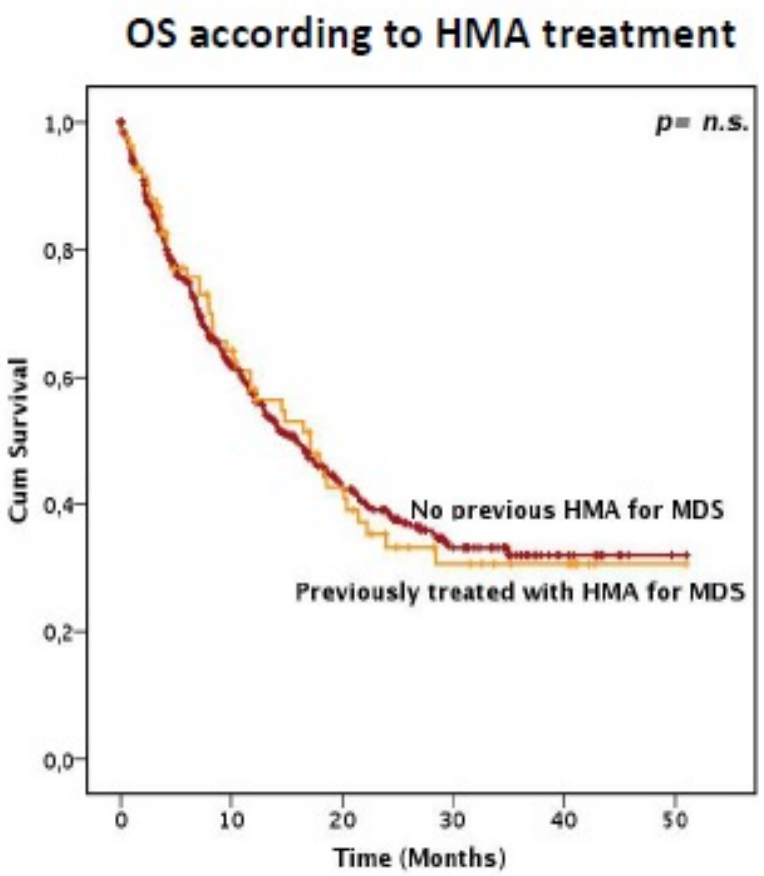


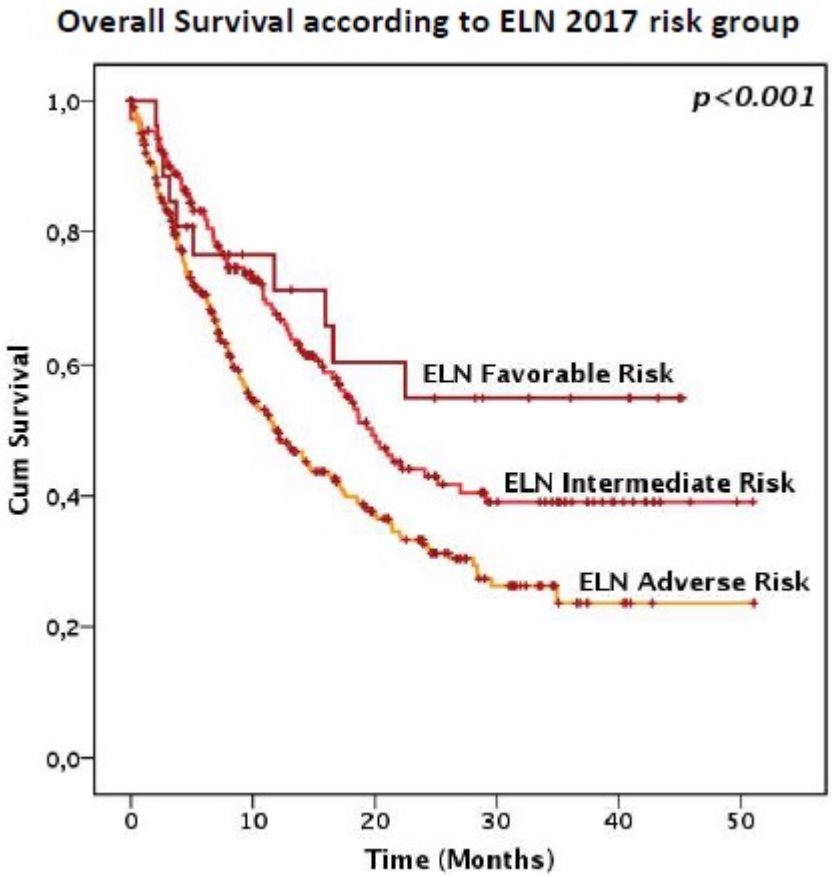
OS according to age



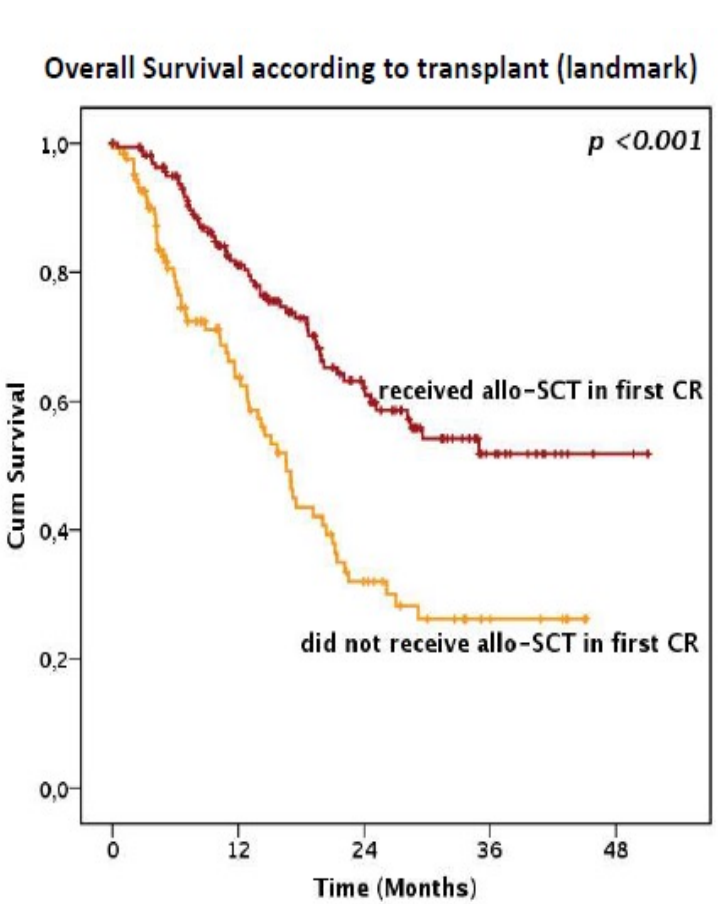
Guolo F et al, ASH 2023 abstr no. 731

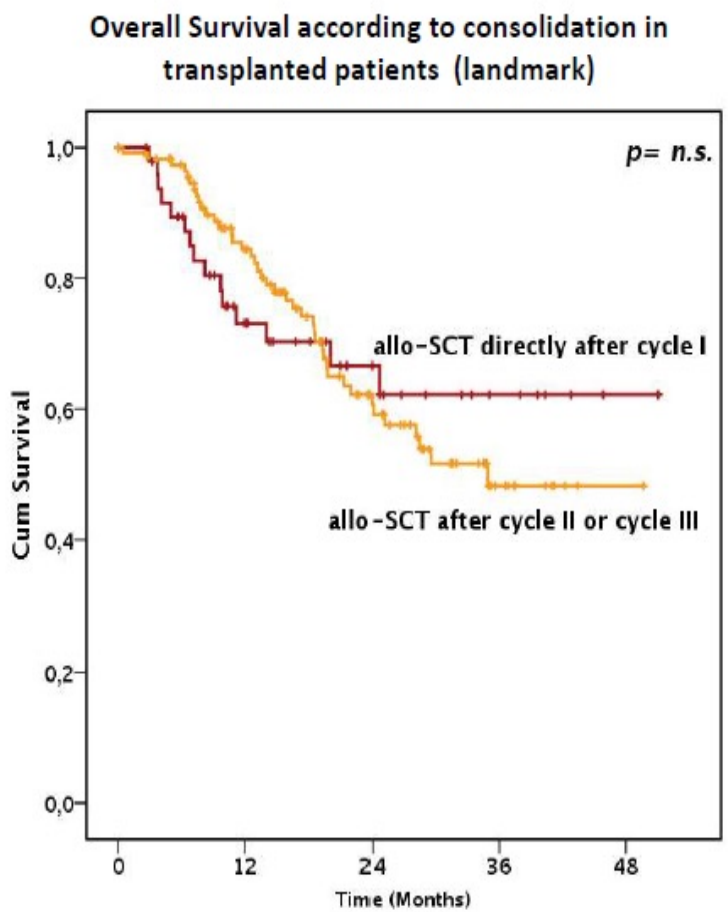


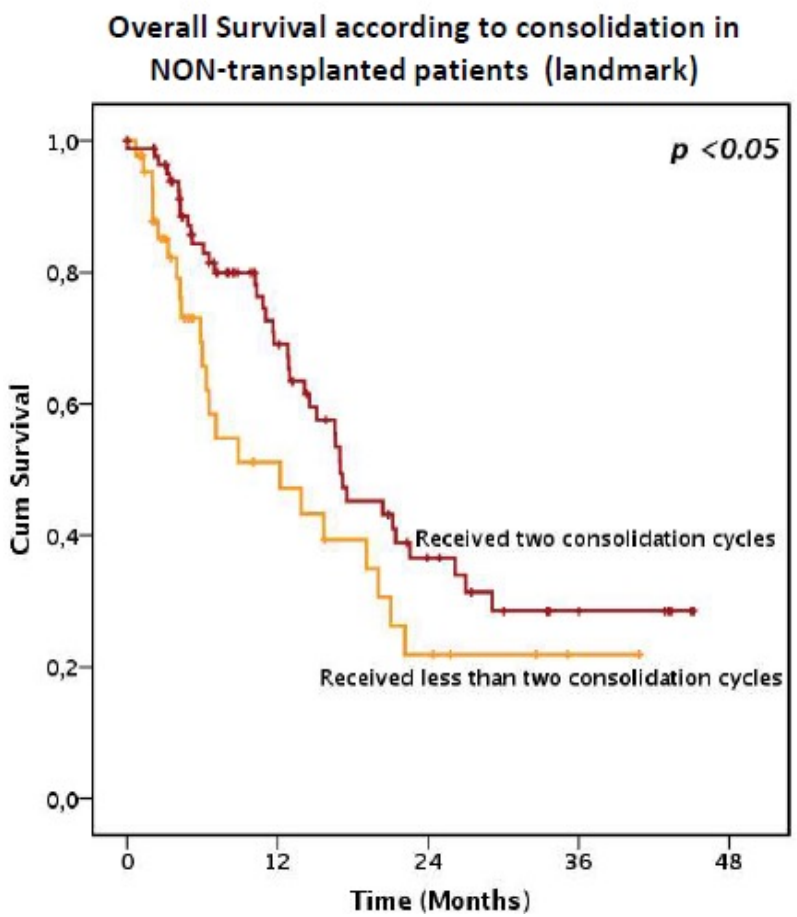




Guolo F et al, ASH 2023 abstr no. 731



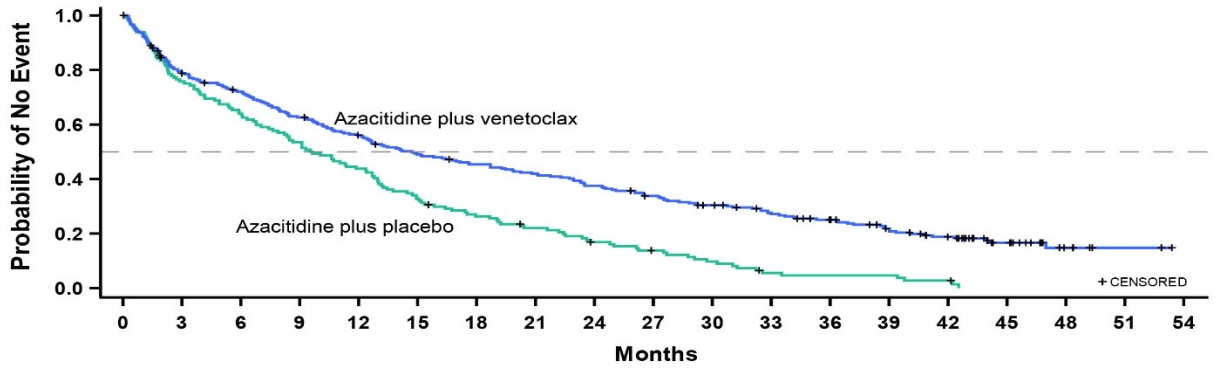




Guolo F et al, ASH 2023 abstr no. 731

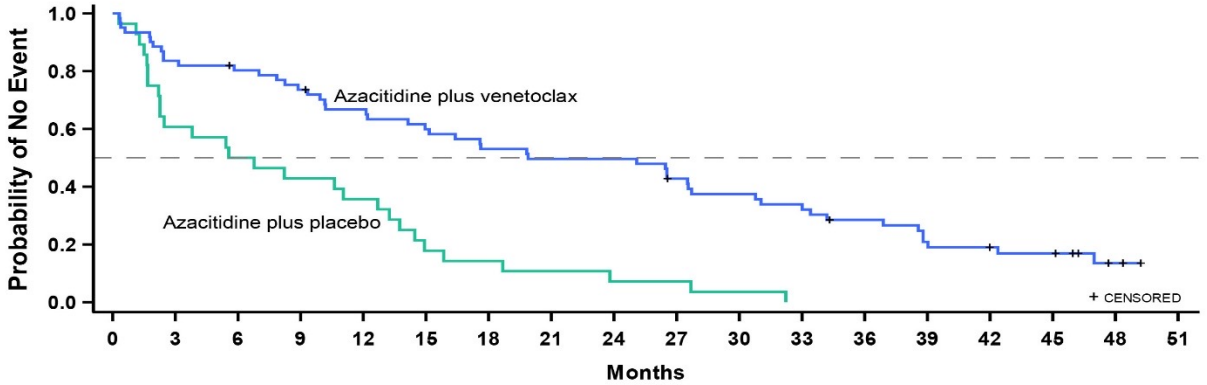
219 Long-Term Follow-up of the Phase 3 Viale-A Clinical Trial of Venetoclax Plus Azacitidine for Patients with Untreated Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

Figure 1. Overall Survival



Patients at Risk																			
Azacitidine plus placebo	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0			
Azacitidine plus venetoclax	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0

Figure 2. Median OS reached for patients with IDH1/2 mutations treated with azacitidine plus venetoclax



Patients at Risk																		
Azacitidine plus placebo	28	17	14	12	10	5	4	3	2	2	1	0						
Azacitidine plus venetoclax	61	51	48	44	39	35	31	29	29	24	21	19	15	11	9	8	3	0

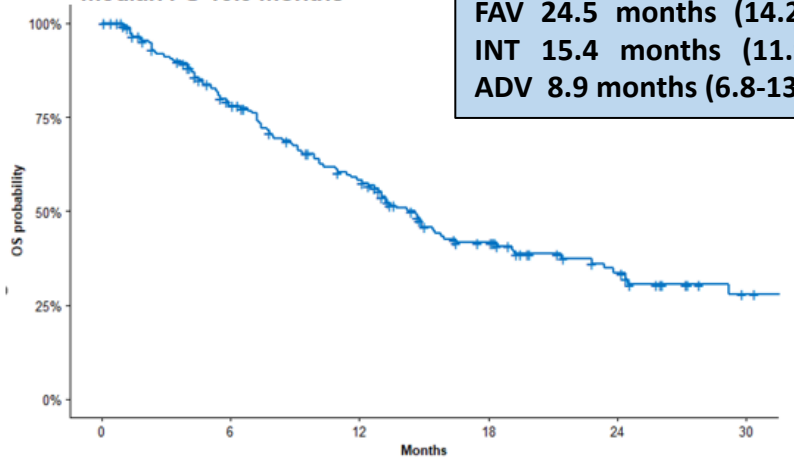
Pratz et al. ASH 2022, OP

Real World Outcome of Unfit Patients with Acute Myeloid Leukemia Treated with the Combination Venetoclax Plus Hypomethylating Agents in the GIMEMA AML2320 Observational Trial

Venditti A, et al.

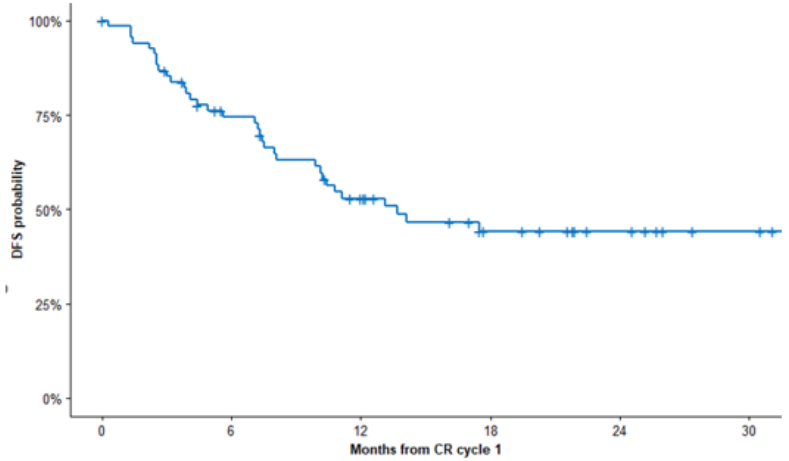
- **Prospective, observational** investigating the outcome of pts treated with the combination **Ven+HMA**, in a **real-world** setting
- **Primary endpoint OS**
- November 2020 - December 2021, **188 pts**, median age 74 years (49-85)
- 68% "*de novo*", 32% secondary AML
- **ELN 2017** (151 pts): FAV 23%, INT 46% , ADV 32%
- 75% pts received VEN+AZA , 25% VEN+DEC
- The **median** no. of delivered **courses** was **5** (1-27).
- Eleven (**6%**) underwent **HSCT** after having received 4 courses of VEN+HMA and being in CR/CRi
- After 1st course, response assessment was evaluated in 123/178 (69%) pts with 70 (57%) being in CR/CRi.
- 153 pts were given a 2nd course, 47/73 evaluable pts (64%) were in CR/CRi

Figure n. 1a: Overall Survival median FU 19.9 months



Median OS according to ELN:
FAV 24.5 months (14.2-NR),
INT 15.4 months (11.9-NR)
ADV 8.9 months (6.8-13.4)

Figure n. 1b: Disease Free Survival of responding pts

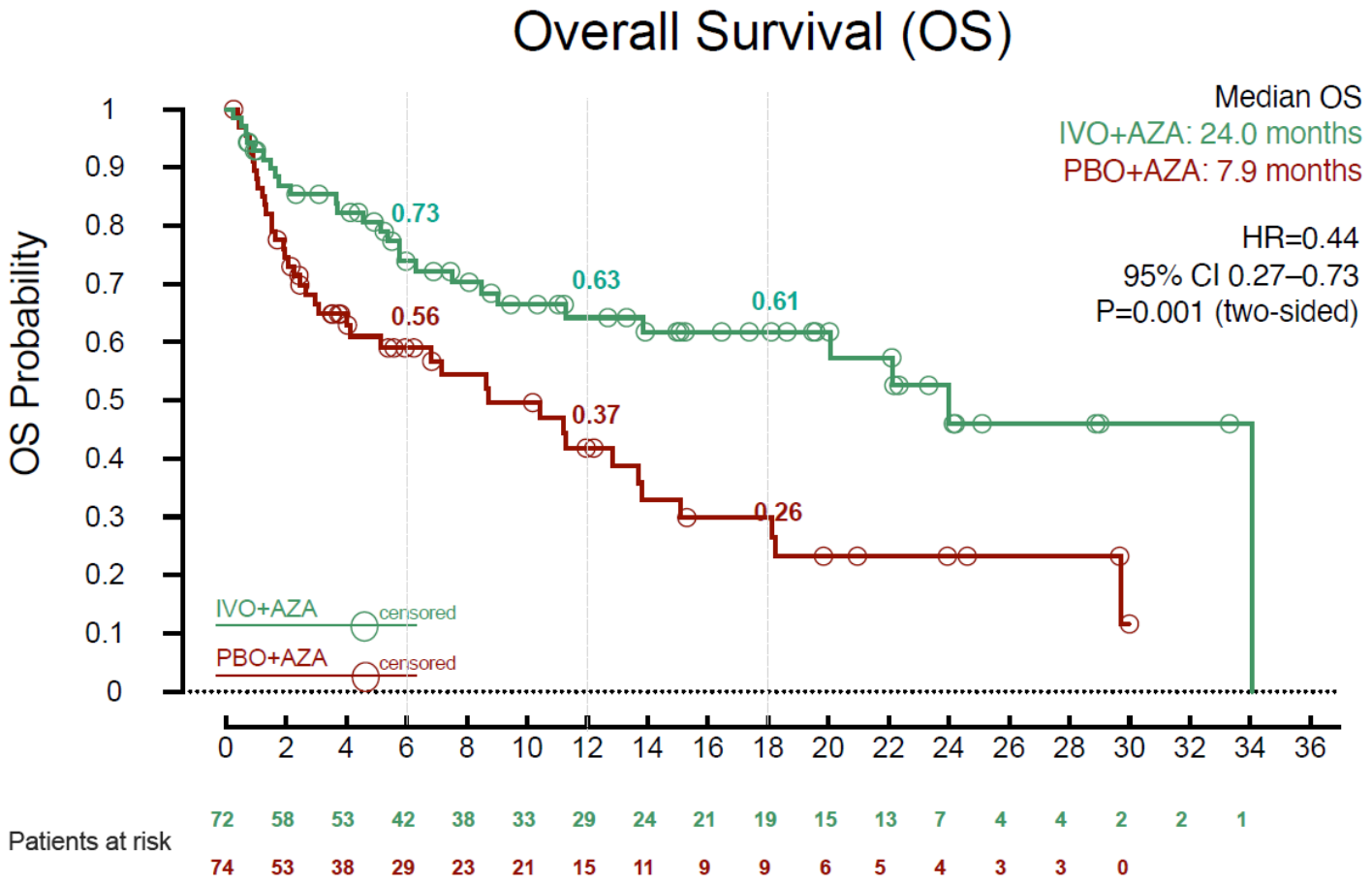


Blood (2023) 142 (Supplement 1): 1514.

Significant improvement in OS observed with IVO+AZA vs PBO+AZA (AML with IDH1 mut,)

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)

Benefit in OS with IVO+AZA vs PBO+AZA was consistent across subgroups

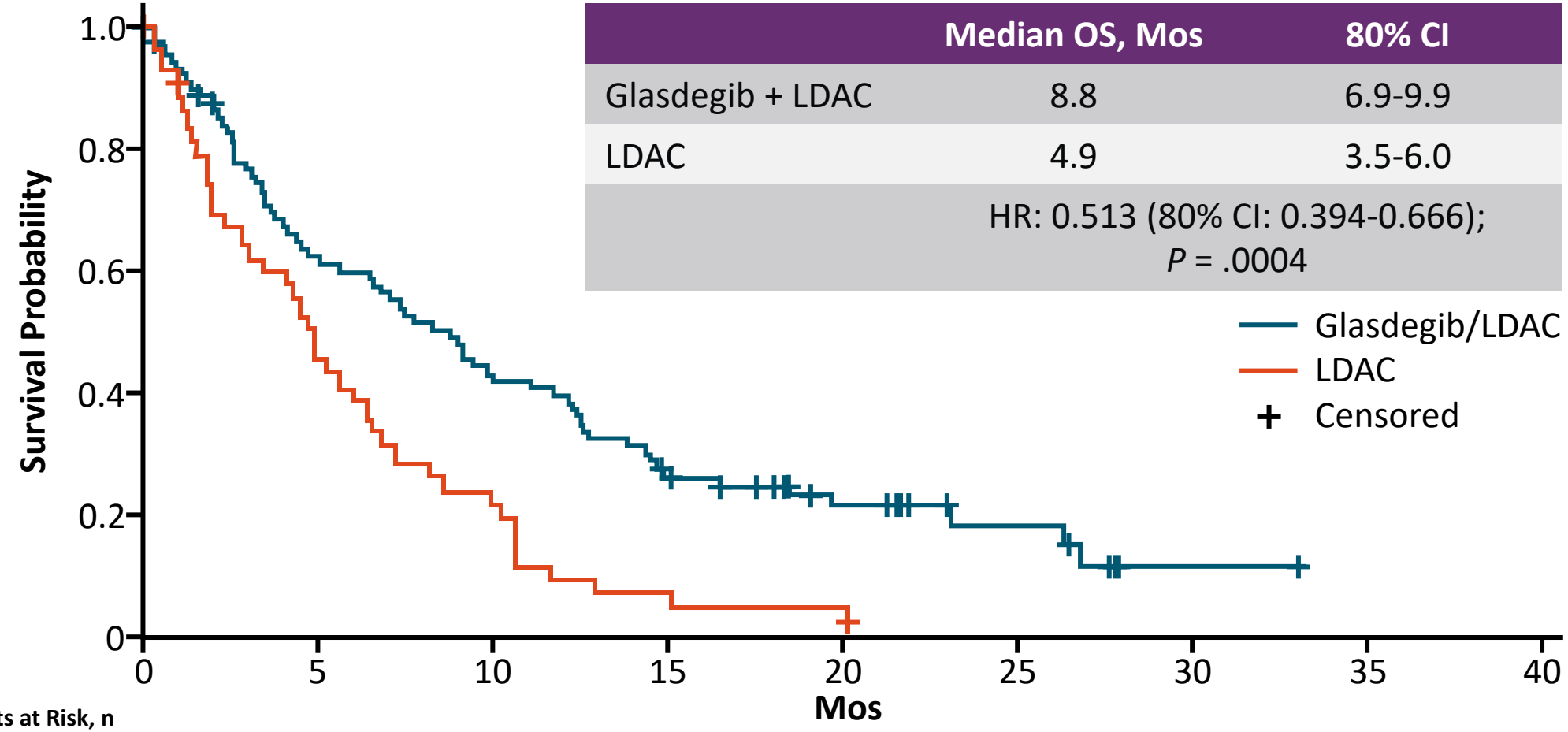


Abbreviations: AZA, azacitidine; CI, confidence interval; EFS, event-free survival; CR(i), complete response (with incomplete hematologic recovery); EFS, event-free survival; HR, hazard ratio; IVO, ivosidenib; PBO, placebo

Reference: Montesinos P, et al. N Engl J Med. 2022 .
OS was the original primary endpoint.
Abbreviations: AZA, azacitidine; CI, confidence interval; HR, hazard ratio; IVO, ivosidenib; (m)OS, (median) overall survival; PBO, placebo.

BRIGHT AML 1003: Overall Survival

	Median OS, Mos	80% CI
Glasdegib + LDAC	8.8	6.9-9.9
LDAC	4.9	3.5-6.0
	HR: 0.513 (80% CI: 0.394-0.666); *P* = .0004	

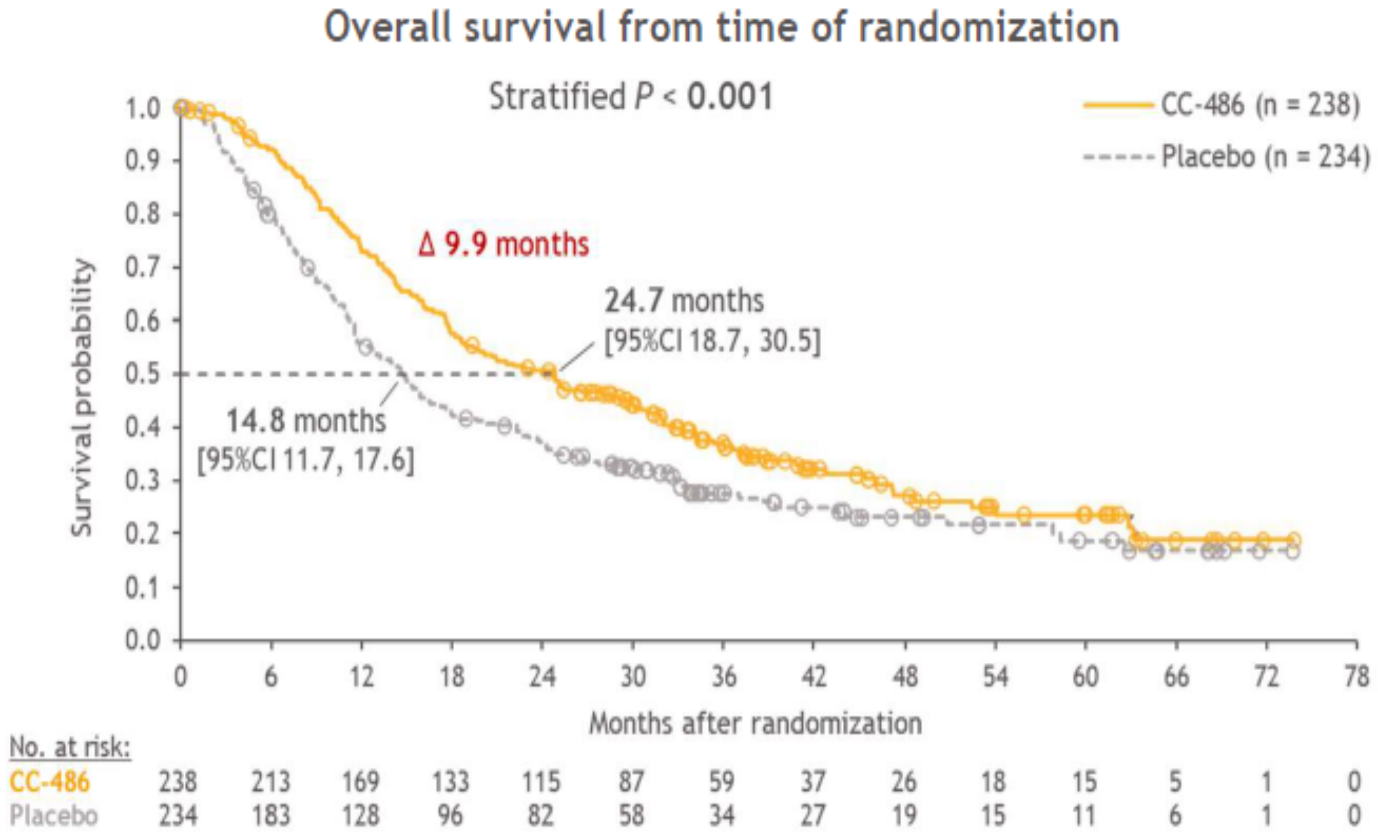


Patients at Risk, n

Glasdegib/LDAC	88	81	74	64	57	52	50	47	43	41	36	35	33	27	26	21	20	18	17	14	12	12	8	7	6	6	6	3	1	1	1	1	1	1	0
LDAC	44	38	29	27	25	19	16	13	12	10	9	5	4	3	3	3	2	2	2	2	2	0													

Cortes. Leukemia. 2019;33:379.

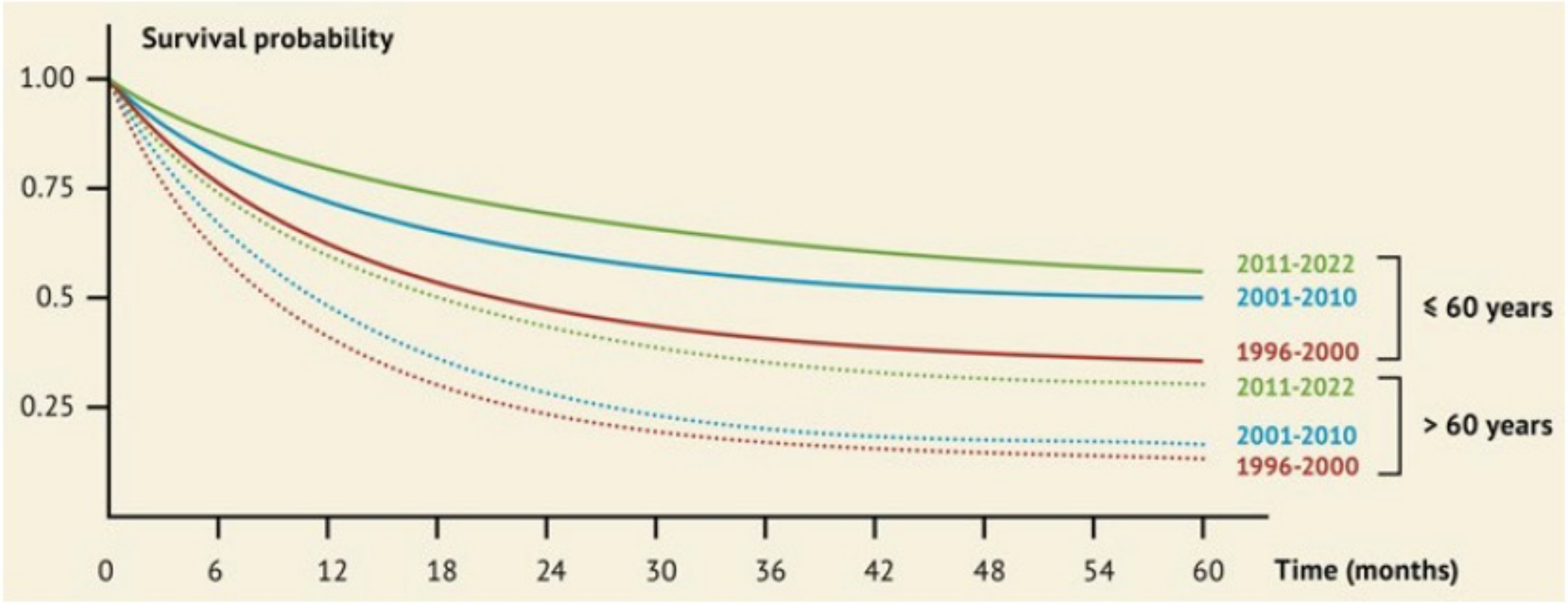
Overall Survival (QUASAR trial)



1-year and 2-year survival rates

Parameter	oral-AZA N=238	Placebo N=234
1-year OS rate	72.8%	55.8%
	95% CI (8.4, 25.6)	
2-year OS rate	50.6%	37.1%
	95% CI (4.5, 22.5)	

Wei et al. NEJM 2020;383:2526-2537



Rollig C, ASH Ed. Progr., 2023

Uptake of novel therapies into first-line treatment for acute myeloid leukemia patients: EU4 + UK perspective

Magdalena Ruiz*,[1], Kriti Jindal[2], Vicky Casey[3], Luana Margotto Soares[4], Fil Manuguid[5] & Thomas Moehler[1]

- **To explore the incorporation of novel agents in the first line setting for acute myeloid leukemia patients.**
- **Observational study based on data from a multi-country crosssectional retrospective web-based survey sent to 518 physicians in Europe between 2020 and 2021. Information from 2040 patients was analyzed.**
- **604 patients (29.6%) received novel agents in both intensive and non-intensive setting.**
- **Comorbidities were not a barrier for the use of novel agents.**

Ruiz M et al, Fut Oncol, 2023

Ruiz M et al, Fut Oncol, 2023

Table 1. Patient characteristics.

	All N = 2040	Novel agents N = 604
Median age, years (range)	60–64	65–69
Sex ratio, M/F %	58/41	57/43
ECOG at diagnosis, %		
0	14.9	11.4
1	45.6	47.2
2	19.7	21.7
3	4.6	5.3
4	0.8	1
Unknown	14.5	13.3
Co-morbidities, n (%)		
Cardiac disease (arrhythmias, heart failure, ischemia)	359 (17.7)	99 (16.4)
Cerebrovascular disease	78 (3.8)	23 (3.8)
Peripheral vascular disease	88 (4.3)	32 (5.3)
Chronic pulmonary disease	182 (8.9)	54 (8.9)
Diabetes	270 (13.2)	78 (12.9)
Hyperlipidaemia	283 (13.9)	90 (14.9)
Hypertension	722 (35.4)	213 (35.3)
Obesity	127 (6.2)	35 (5.8)
Liver cirrhosis (w/w portal hypertension, bleeding varices)	58 (2.8)	12 (2)
Chronic renal failure (creatinine ≥3 mg/dL)	187 (9.1)	54 (8.9)
Severe renal failure (on dialysis, renal transplant)	24 (1.2)	5 (0.8)
Peptic ulcer disease	58 (2.8)	16 (2.6)
AIDS (not just HIV positive)	5 (0.2)	2 (0.3)
None of the above	591 (29)	175 (29)
Unknown	28 (1.4)	7 (1.2)

Ruiz M et al, Fut Oncol, 2023

Table 1. Patient characteristics (cont.).

	All N = 2040	Novel agents N = 604	Ref.
Molecular and genetic risk stratification			[9]
Favorable Risk	557 (27.3)	105 (17.4)	
Intermediate Risk	782 (38.3)	252 (41.3)	
Adverse Risk	577 (28.3)	221 (36.6)	
Not tested	65 (3.2)	10 (1.7)	
Unknown	59 (2.9)	16 (2.7)	
Treatment Program			
Clinical trial	108 (5.3)	46 (7.6)	
Compassionate use program	82 (4.0)	38 (6.3)	
Neither of them	1850 (90.7)	520 (86.1)	

Ruiz M et al, Fut Oncol, 2023

Table 2. Use of novel agents in first line acute myeloid leukemia patients by type of regimen.

Treatment regimen	Use of novel agents (n = 2040 patients)		
	No	Yes/combo	Yes/monotherapy
Intensive	946	337	2
Non-intensive	490	261	4
Total (%)	1436 (70.3)	598 (29.3)	6 (0.3)

Table 3. Novel agents in combination administered in first line treatment acute myeloid leukemia patients.

Treatment regimen	Use of novel agents in combination (n = 604 patients)		
	Chemotherapy + novel agent	HMA + novel agent	LDAC + novel agent
Intensive (%)	316 (91.8)	20 (8.3)	1 (8.3)
Non-intensive (%)	28 (8.2)	222 (91.7)	11 (91.7)
Total (%)	344 (57.5)	242 (40.5)	12 (2.0)

HMA: Hypomethylating agents; LDAC: Low dose cytarabine.

Ruiz M et al, Fut Oncol, 2023

Table 4. Use of novel agents across time.

Novel agent	Novel agents across time, in 1st Line			
	Jan–Mar 2020		Dec 2020–Feb 2021	
	Patients (n)	Freq. (%)	Patients (n)	Freq. (%)
No	709	70.0	727	70.7
Yes/combo	298	29.4	300	29.2
Yes/monotherapy	5	0.5	1	0.09
Total	1012		1028	

Table 5. Different treatments combination with novel agents across time.

Treatment	Type of treatment with novel agents across time, in 1st Line			
	January–March 2020		December 2020–February 2021	
	Patients (n)	Freq. (%)	Patients (n)	Freq. (%)
Chemo regimen + Novel Agent	198	65.4	146	48.5
HMA + Novel Agent	100	33.0	142	47.2
LDAC + Novel Agent	0	0	12	4.0
Novel Agent monotherapy	5	1.65	1	0.3
Total	303		301	

HMA: Hypomethylating agents; LDAC: Low dose cytarabine.

Ruiz M et al, Fut Oncol, 2023

Summary points

- There are novel targeted drugs approved for acute myeloid leukemia in the first line setting although there is uncertainty with respect to their incorporation in routine clinical practice.
- Data from 2040 patients from a European multi-country cross-sectional retrospective online web-based survey have been analyzed and presented in this article.
- In our study population, 29.6% of patients were treated with novel agents in the first line setting mainly in combination and as part of non-intensive regimens.
- There were a higher number of patients harboring a specific mutation (*FLT3-ITD, FLT3-TKD, NPM1* or expression of CD33) who were treated with novel agents in the first line setting.
- We observed a trend toward selecting patients classified as having adverse risk prognosis to be treated with novel agents compared with the overall population.
- A higher proportion of patients treated with novel agents were included in clinical trials or received therapy as part of a compassionate use program compared with the overall population.
- The benefit of novel agents in terms of leukemia response improvement was more evident when combined with hypomethylating agents and in the non-intensive setting.

Ruiz M et al, Fut Oncol, 2023

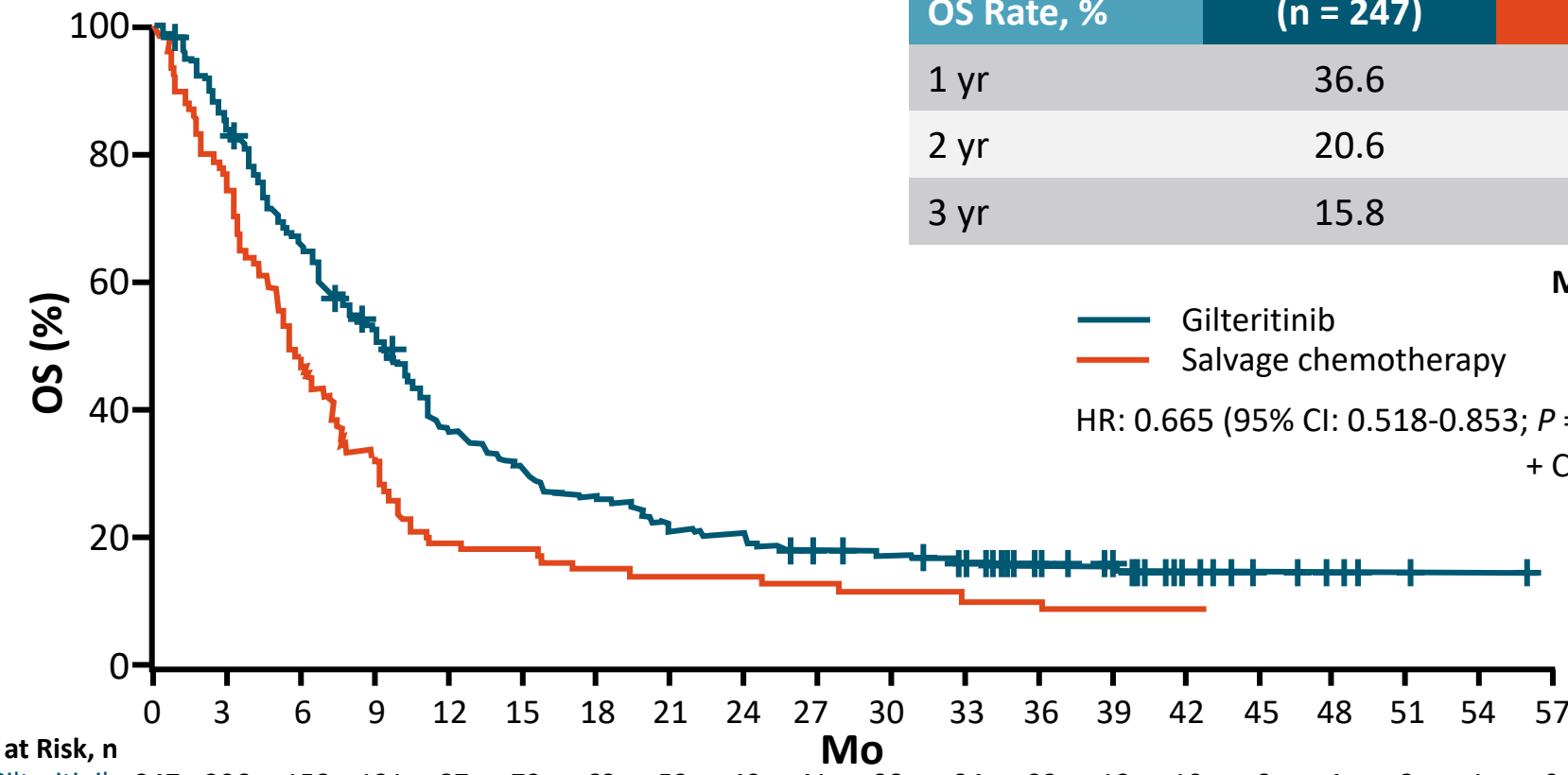
Novel agents in AML: why not more extensively used ?

- **In ELN intermediate AML FLT3 negative AML low appraisal of GO, perceived as more effective in CBF and NPM1mut AML**
- **Feeling with FLAG-IDA (no association with new agents)**
- **High risk, no t-AML, no MRC AML: no indication**
- **Costs and availability**

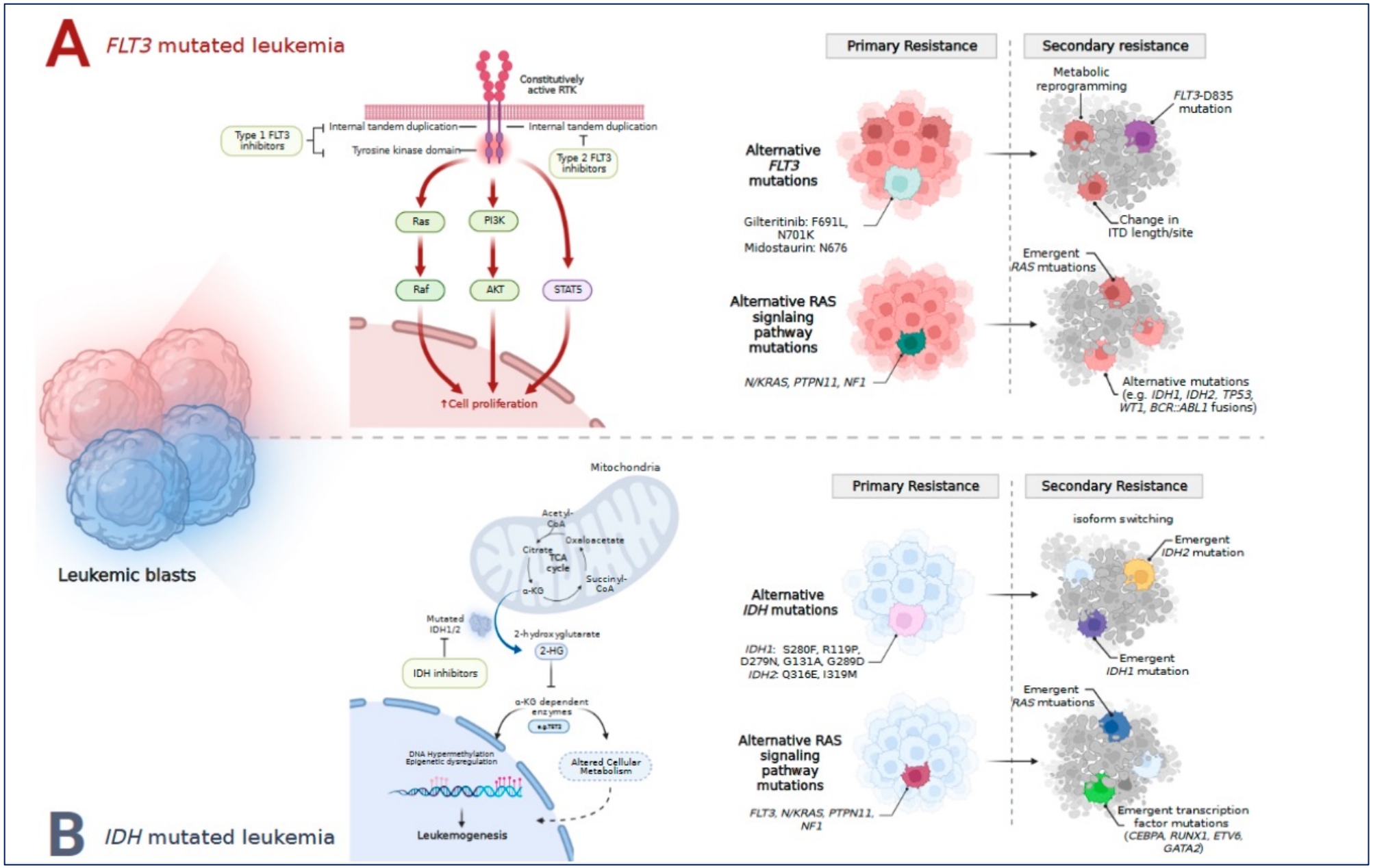
Speaker opinion

ADMIRAL: Gilteritinib Prolongs OS in m*FLT3* R/R AML

OS Rate, %	Gilteritinib (n = 247)	Salvage CT (n = 124)
1 yr	36.6	19.2
2 yr	20.6	14.2
3 yr	15.8	10.4



Perl. Blood 2022;139:3366.



Lachowiez CA et al, Cancers, 2023

FLT3 inhibition – future perspectives

	Frontline + 3+7	Frontline unfit	Post-transplant	R/R
FLT3i	Quizartinib Crenolanib Gilteritinib	Time for triplets? Gilteritinib + VEN + HMA Quizartinib + VEN + HMA	Gilteritinib – MORPHO study Quizartinib Crenolanib	Novel FLT3i (MKIA-088-001-Nerviano) Triplets vs doublets: TKI+AZA +/- VEN

Quizartining and crenolanib are NOT APPROVED by EMA for use in AML
Gilteritinib in association to AZA and Venetoclax is NOT APPROVED by EMA for use in AML

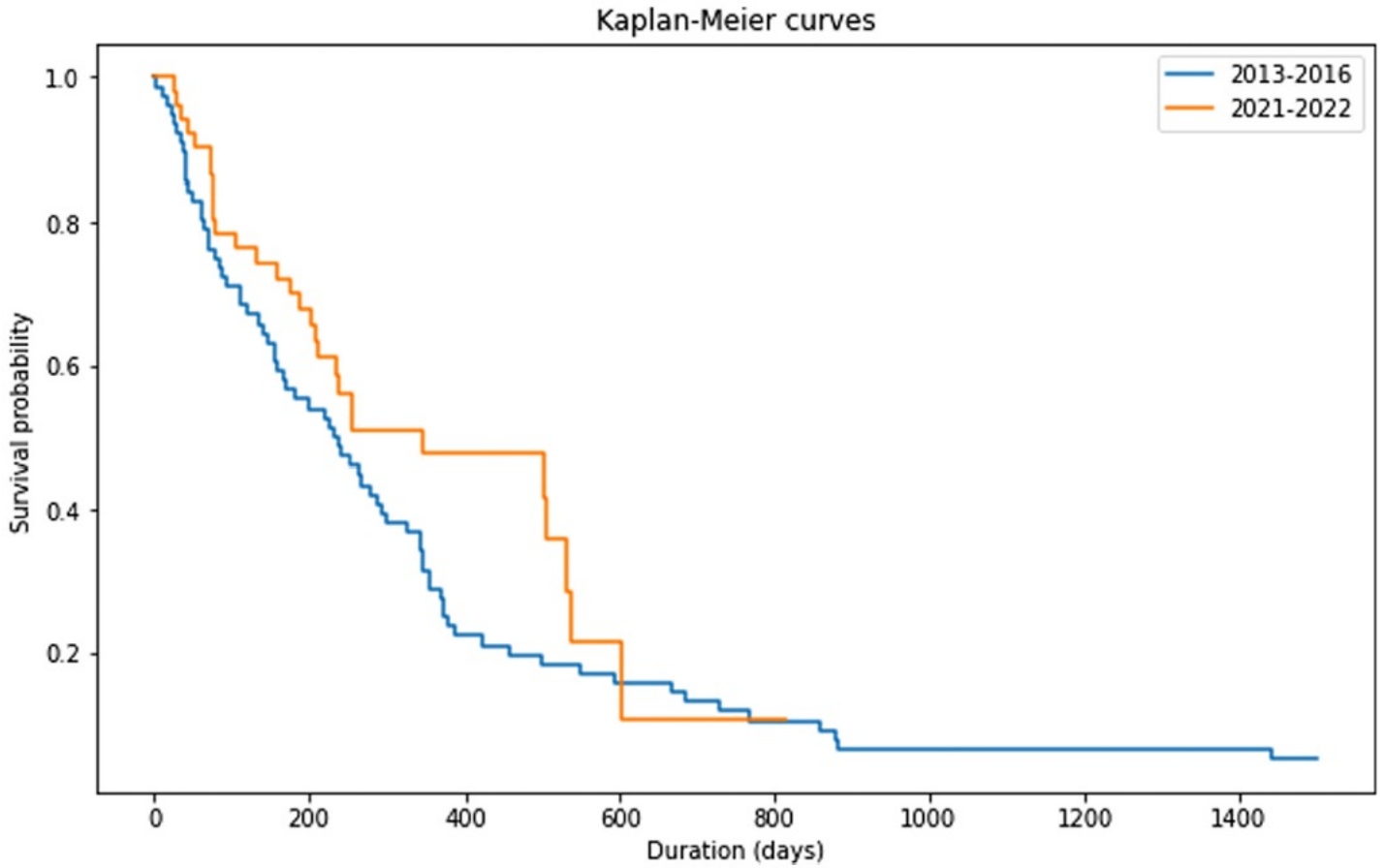
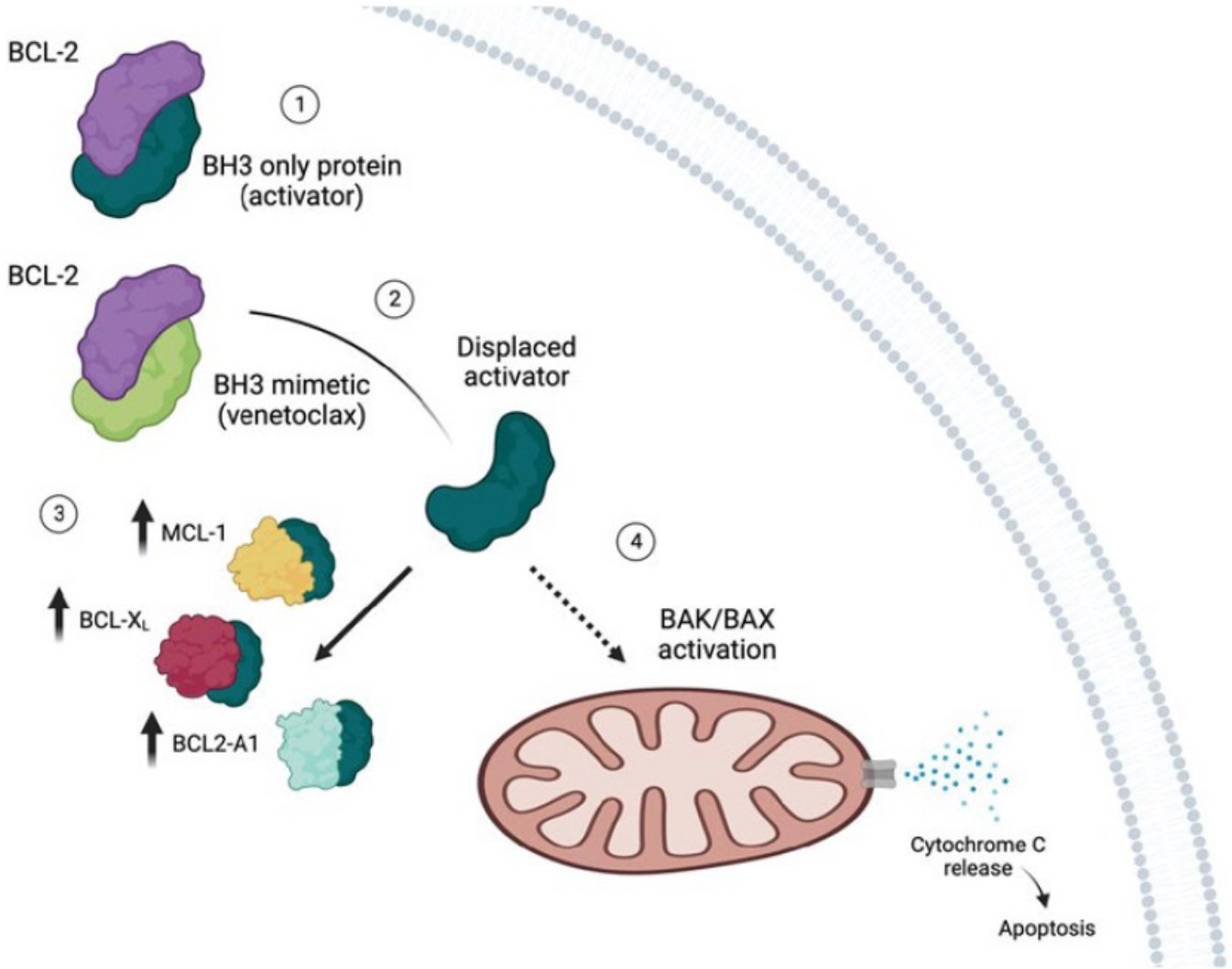


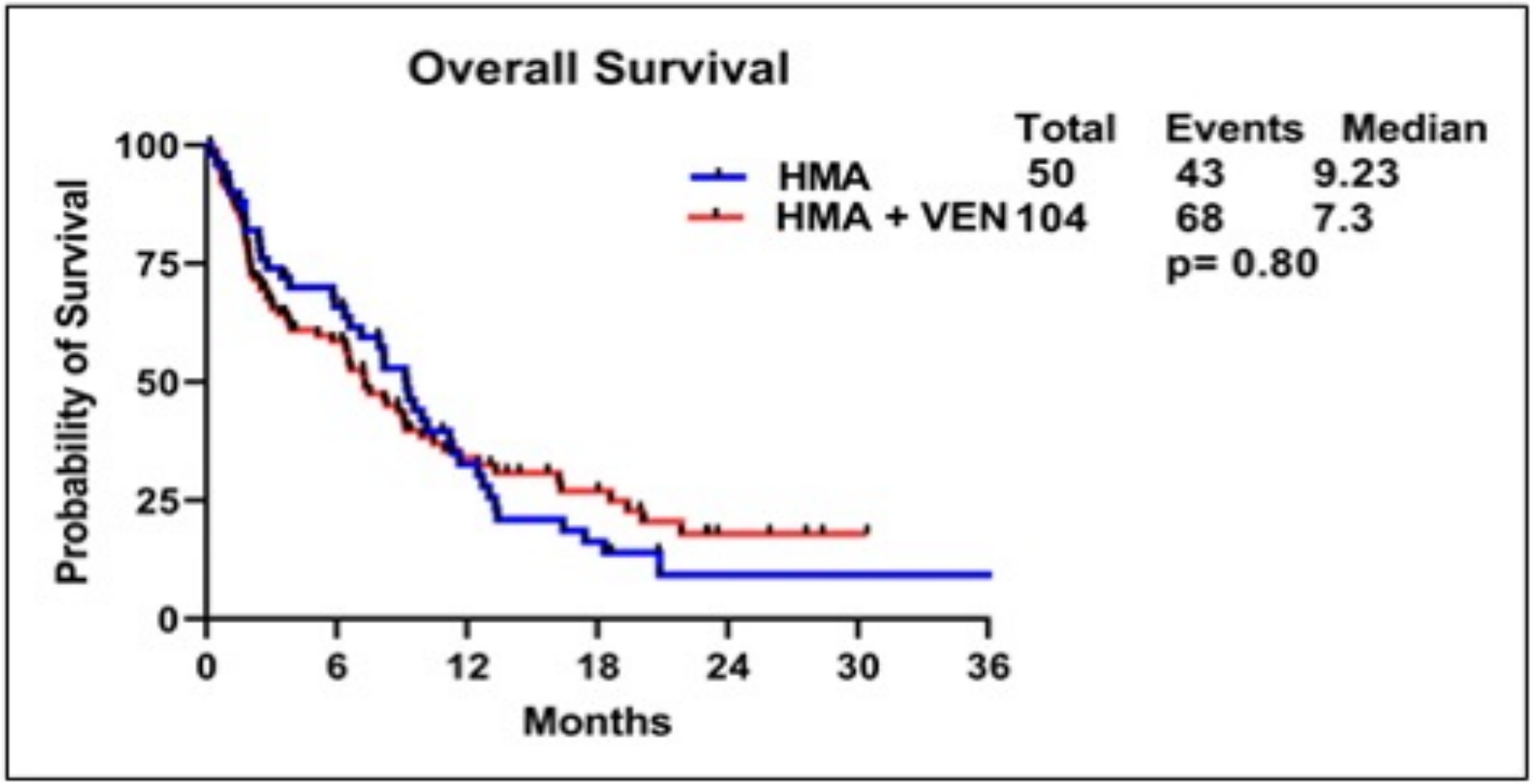
Fig. 1. Overall survival of patients in the 2013–16 and the 2021–22 cohorts who received non-intensive therapy (NIT).

Brandwein JM et al, Leuk Res, 2023

Mechanism of VEN resistance

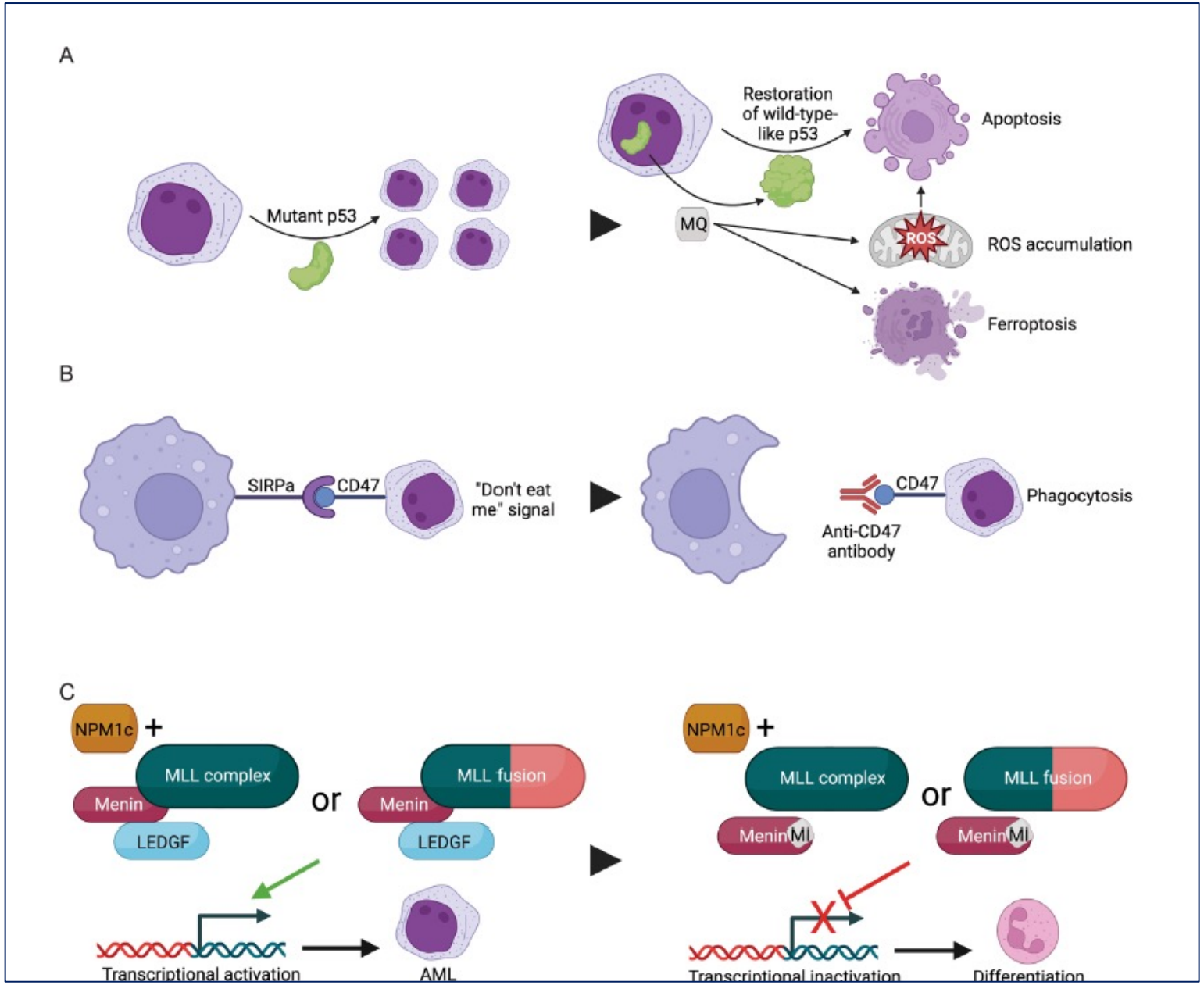


Chan & Walker, ASH Ed. Progr., 2023



In this multi-center real-world study, while HMA+VEN led to improvement in CR rates and a higher proportion of pts were bridged to allo-HCT, it did not associate with an improvement in OS when compared with HMA monotherapy.

Badar et al. ASH 2023, Abs 592



Bhansali RS et al. J Hemat Onc, 2023

Table 1. Emerging novel therapies in R/R AML

Phase	Regimen	Mechanism of action	Number of patients	Median age (range)	Response	Reference
1	SNDX-5613	Menin inhibitor	68 (56 R/R AML)	51 (19–79) among adults	ORR: 53% (32/60) CR/CRi: 38% (23/60) ORR in *KMT2A*: 59% (27/46) ORR in *NPM1*: 36% (5/14)	Wang et al[26]
1	HDM201	MDM2 inhibitor	208 (91 R/R AML)	~70 (23–85)	CR/CRi: 13.2% (12/91) CR/CRi in 45mg: 22.2% (6/28)	Klossowski et al[28]
1/2	HM43239	FLT3/SYK inhibitor	28	60 (35–83)	CR/CRi in 80mg: 26.3% (5/19) CR/CRi in *FLT3* 80mg: 37.5% (3/8)	Konopleva et al[31]
1b/2	IMGN632 + AZA + Ven	CD123 antibody-drug conjugate	35 (29 efficacy evaluable R/R AML)	69 (range not available)	ORR: 55% (16/29) CR/CRi: 31% (9/29)	Daver et al[35]
1/2	Magrolimab + AZA + Ven	CD47 inhibitor	74 (29 R/R, 45 newly diagnosed)	Not available	ORR in R/R Ven-naïve: 75% ORR in R/R Ven prior: 12%	Kuruvilla et al[38]
1b/2	APR-246	p53 reactivator	55 (11 R/R oligoblastic AML)	66 (34–85)	ORR: 64% (n=7) CR: 36% (n=4) Median OS 10.8 months	Daver et al[39]

Chan & Walker, ASH Ed. Progr., 2023

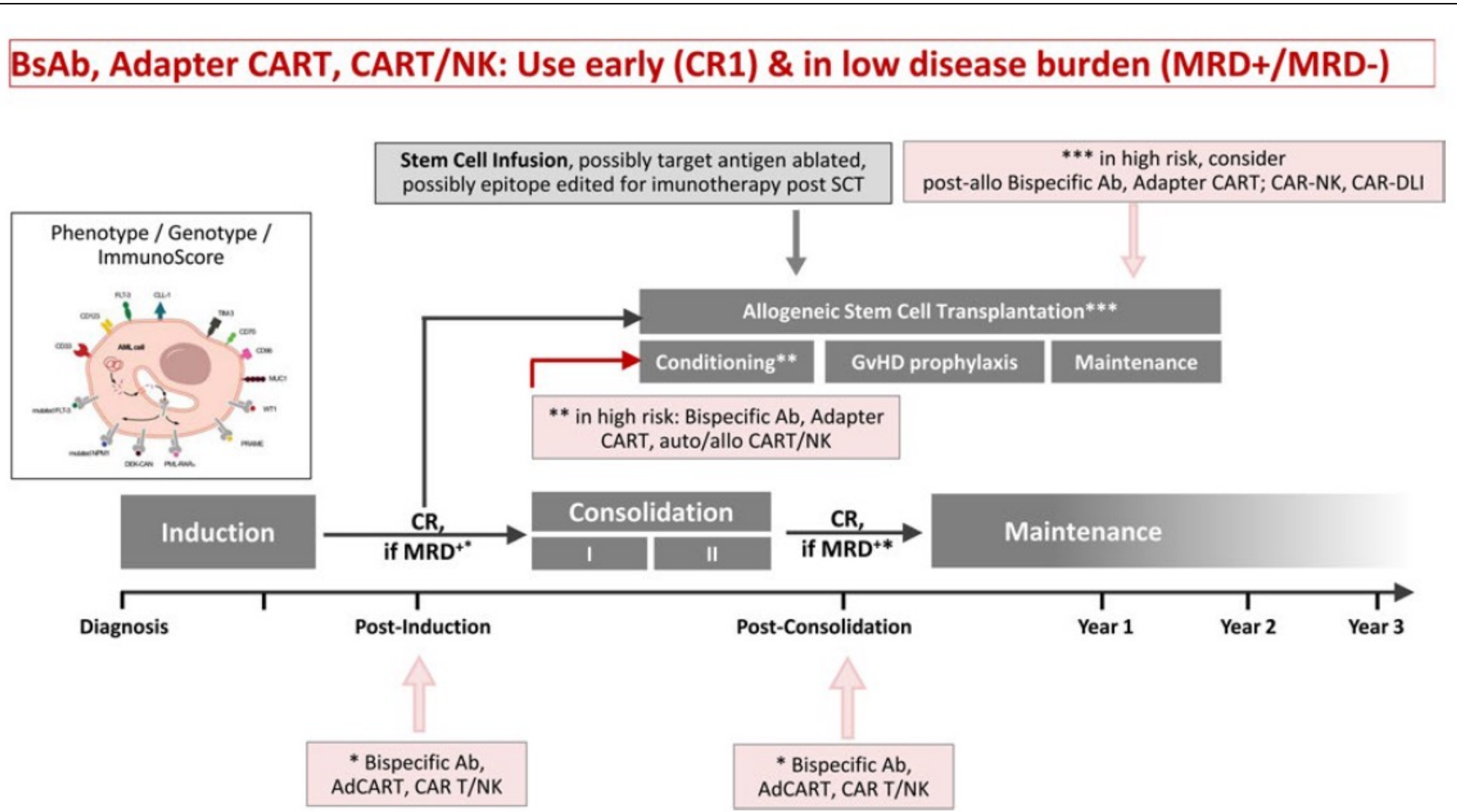


Figure 1. Mode of action of the different immunotherapy platforms in AML. BsAb, bispecific antibody.

Subkleve, ASH Ed. Progr., 2023

Table 1. Selected AML target antigens used in clinical trials

Target antigen	Target antigen category	Expression localization	Physiological function	Expression on bulk AML cells/LSCs	HSCs	Expression on nonhematopoietic cells	Immunotherapy platforms used/evaluated in AML
CD33	Lineage restricted	Surface	Cytoadhesion	+++/+	+	Kupffer cells, microglia	ADC, bispecifics, CAR T
CD123	Lineage restricted	Surface	Interleukin-3 receptor	++/++	(+)	Endothelial cells (upon inflammation), lung, GI	ADC, bispecifics, CAR T
CLL-1/CLEC12A	Lineage restricted	Surface	Inhibitory lectin-like receptor	++/+	–	Not reported	CAR T
CD135/FLT3	Lineage restricted	Surface	Cytokine receptor	+/++	(+)	CNS, GI, testis (intracellular)	Bispecifics, CAR T
IL1RAP	Lineage restricted	Surface	Interleukin-1 receptor accessory protein	++/+	–	GI	CAR T
CD44v6	Leukemia associated	Surface	Cell–cell/cell–matrix interactions	++/+	–	Keratinocytes	CAR T
CD70	Leukemia associated	Surface	T-cell coactivation	(+)–++*/(+)–++*	(+)-++*	Thymic epithelial cells	ADCC-optimized antibody, CAR T
TIM-3	Leukemia associated	Surface	Immunoregulatory protein	++/++	–	Not reported	High-affinity antibody
WT1	Leukemia associated	Intracellular	Transcription factor	++/++	+	Kidney, spleen, heart, lung, prostate	Vaccination, TCR-transgenic T cells
PRAME	Leukemia associated	Intracellular	Cancer testis antigen	+/+	(+)	Testis	Vaccination, TCR-transgenic T cells
NPM1 (mut)	Leukemia specific	Intracellular					Preclinical
FLT3-ITD	Leukemia specific	Intracellular					Preclinical
$IDH1^{R132H}$	Leukemia specific	Intracellular					Preclinical
$TP53^{R175H}$ (and other TP53 mutations)	Leukemia specific	Intracellular					Preclinical

Expression levels: +++ ubiquitous; ++ frequent; + present; (+) rare; – absent; *reported expression varies significantly between publications.

ADCC, antibody-dependent cellular cytotoxicity; GI, gastrointestinal; HSC, hematopoietic stem cells; LSC, leukemic stem cells.

Adapted from Daver et al.[12]

Subkleve, ASH Ed. Progr., 2023

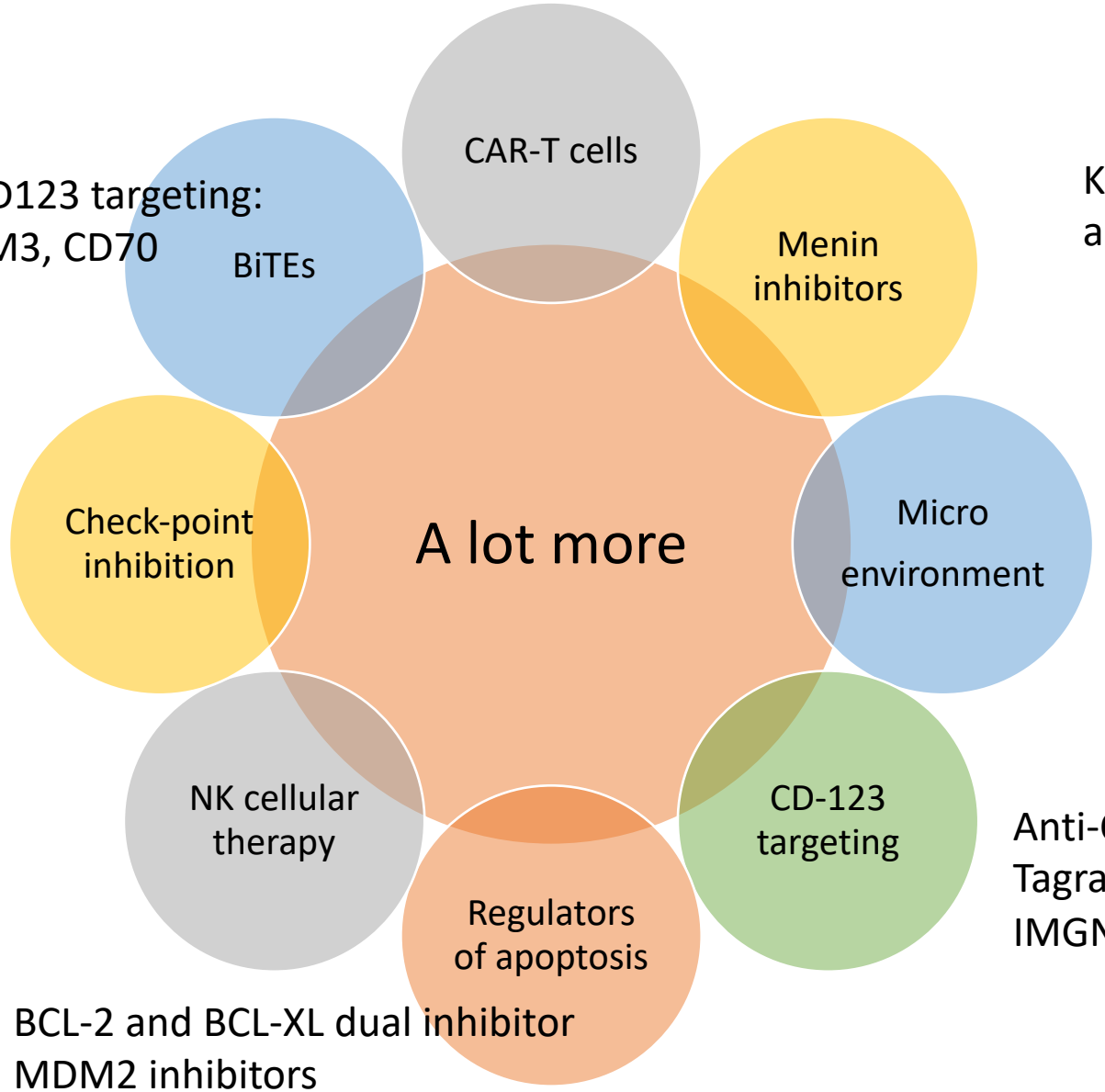
Table 2. Results of early clinical trials on bispecific antibodies for AML

Clinical trial no.	Target	Construct design	Dosing	Safety	Efficacy (CR/CRi)	No. patients treated to date	Enrollment stage
NCT02520427	CD33	BiTE	0.5–720 µg/day; 0–3 dose steps; 14–28 days CIV	CRS 67% (≥G3 13%)	7/42	96	Terminated
NCT03224819	CD33	HLE-BiTE	0.05–72 µg per dose, 2 IV infusions in 14 days	CRS 50% (≥G3 13%)	1/27	46	Terminated
NCT03144245	CD33	TandAb	0.5–300 µg/day; 14 days CIV; 28-day cycle	CRS NA (≥G3 0%)	2/35	53	Completed
NCT02152956	CD123	DART	RP2D: 500 ng/kg/day; 7 dose steps; 28 days CIV; then 4 days/week	CRS 50% (≥G3 7%)	8/30	246	Terminated
NCT02715011	CD123	DuoBody	0.6–6 µg/kg Q2W IV; 0.15-4.8 µg/kg twice weekly IV; 2.4–4.8 µg/kg twice weekly SC; 0–4 dose steps	CRS 44% (≥G3 15%)	0/62	62	Completed
NCT02730312/ NCT05285813	CD123	XmAb	1.7 µg/kg IV; 4 dose steps on days 1, 3, 5, and 8 followed by weekly administration	CRS 44% (≥G3 15%)	5/51	106	Dose finding completed/ phase 2 initiated
NCT05086315	CD123	Trifunctional NK cell engager	10–3000 µg/kg/dose in cycle 1; 100–3000 µg/kg QW for the rest of induction cycles	CRS 9% (≥G3 n.r.), IRR 43%	3/23	23	Recruiting
NCT03038230	CLL1	Biclonics IgG format	0.675–240 mg weekly after initial ramp-up dosing; 3–4 dose steps	CRS 36% (≥G3 9%)	0/58	62	Active, not recruiting

IV, intravenous; IRR, infusion-related reaction; NA, not applicable; QW, once weekly; Q2W, once every 2 weeks; SC, subcutaneous injection; TandAb, tandem diabody.

Subkleve, ASH Ed. Progr., 2023

The future in AML is bright



Beyond CD33/CD123 targeting:
CLL1, IL1RAP, TIM3, CD70

KO-530 phase I: *NPM1*^{mut} and *KMT2A* rearranged AML

E-selectin antagonist:
Uproleselan (GMI-1271)

Anti-CD123 Ab drug-conjugate:
Tagraxofusp
IMGN-636

BCL-2 and BCL-XL dual inhibitor
MDM2 inhibitors

Speaker's opinion
Tagraxofsup and Uproselan are NOT APPROVED by EMA for use in AML