LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

May 5-6, 2022

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

AIL
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

UNDER THE AUSPICES OF:

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

GITMO

SIES Società Italiana Ematologia Sperimentale

SIE - Società Italiana di Ematologia

Disclosures of Francesco Buccisano

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Jazz					x		
Abbvie						x	
Janssen					x		
Becton Dickinson	x						

Novel strategies to treat older patients with AML

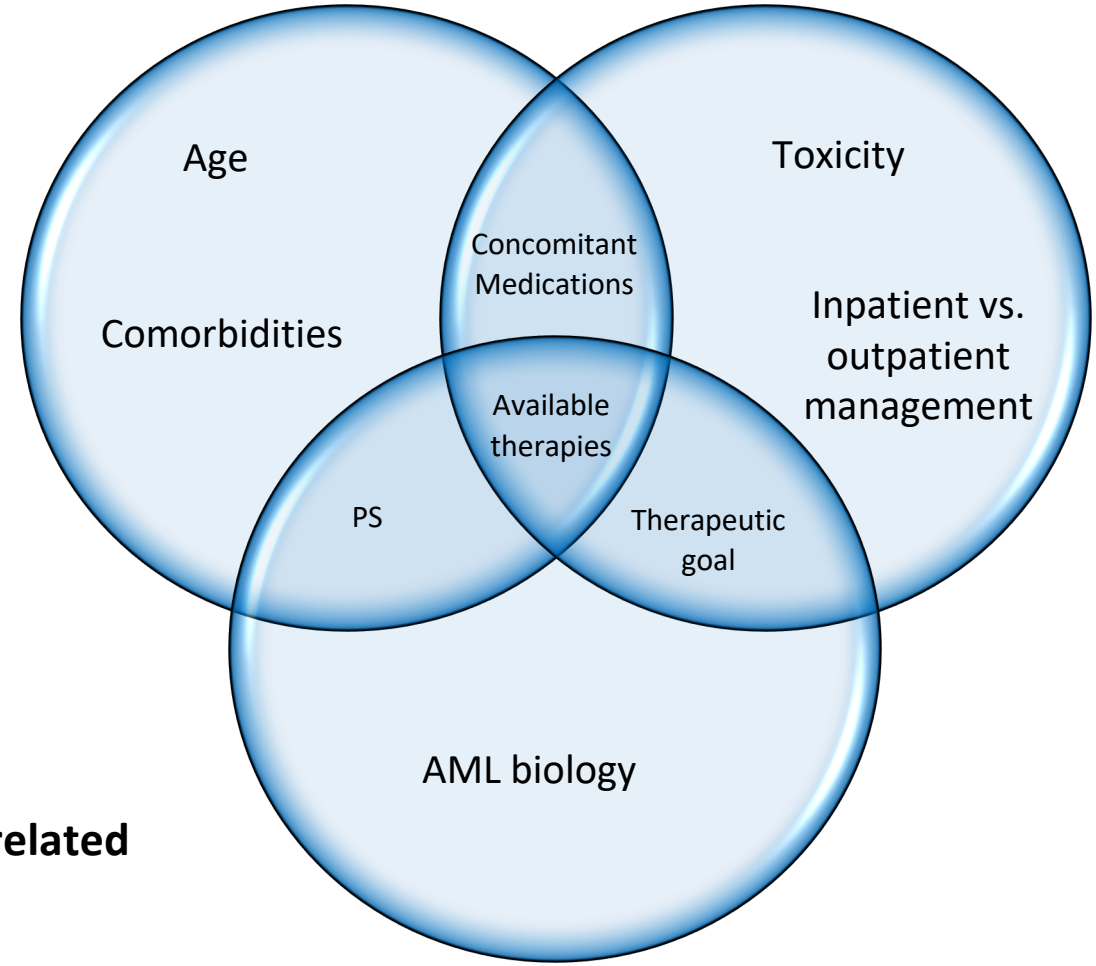
Prof. Francesco Buccisano

Department of Biomedicine and Prevention

Tor Vergata University of Rome

Patient-related

Treatment-related

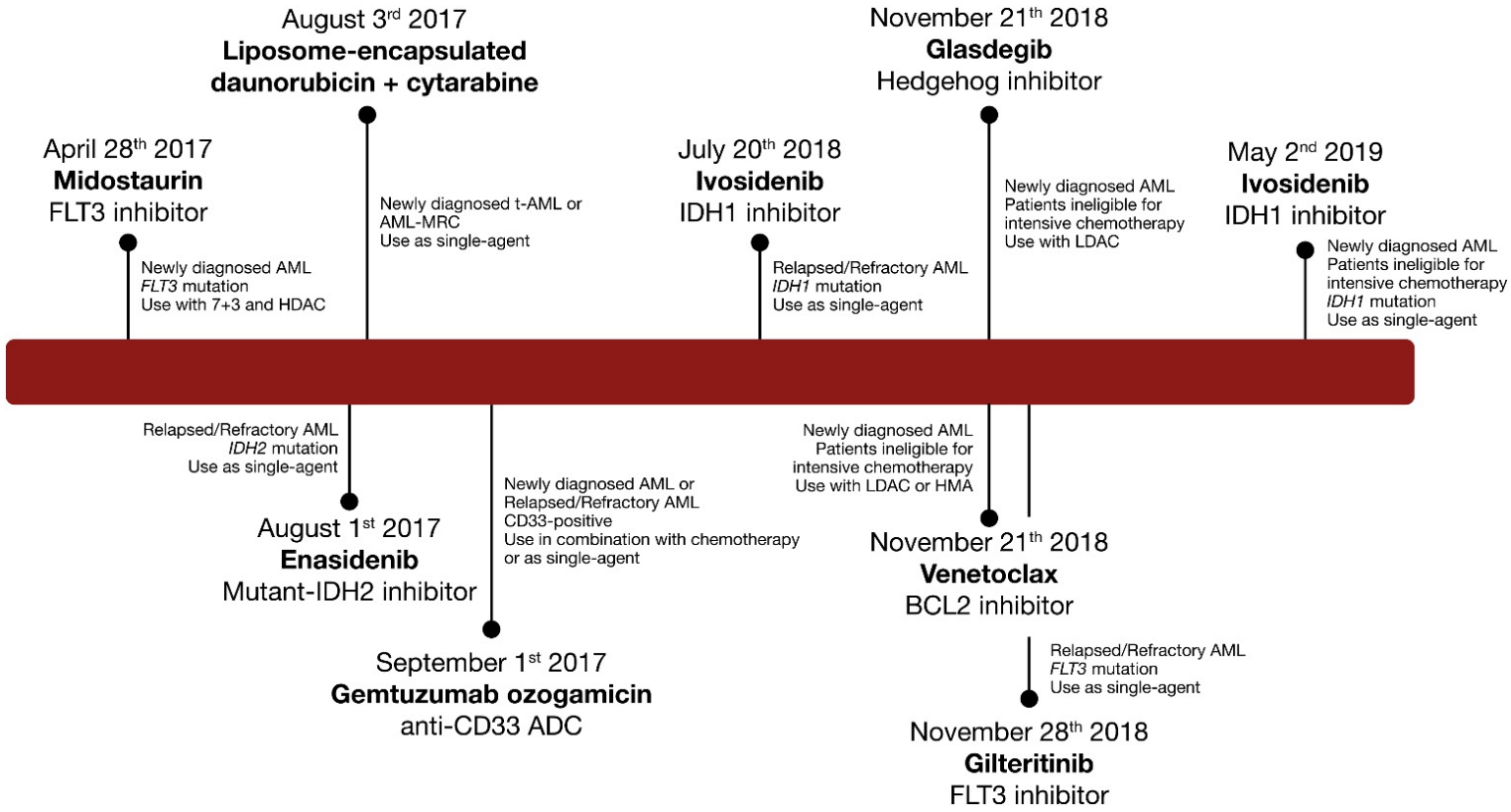


Disease-related

Additional factors

- QoL
- Care-giver
- Expectations

Single-agent and combination biologics in acute myeloid leukemia



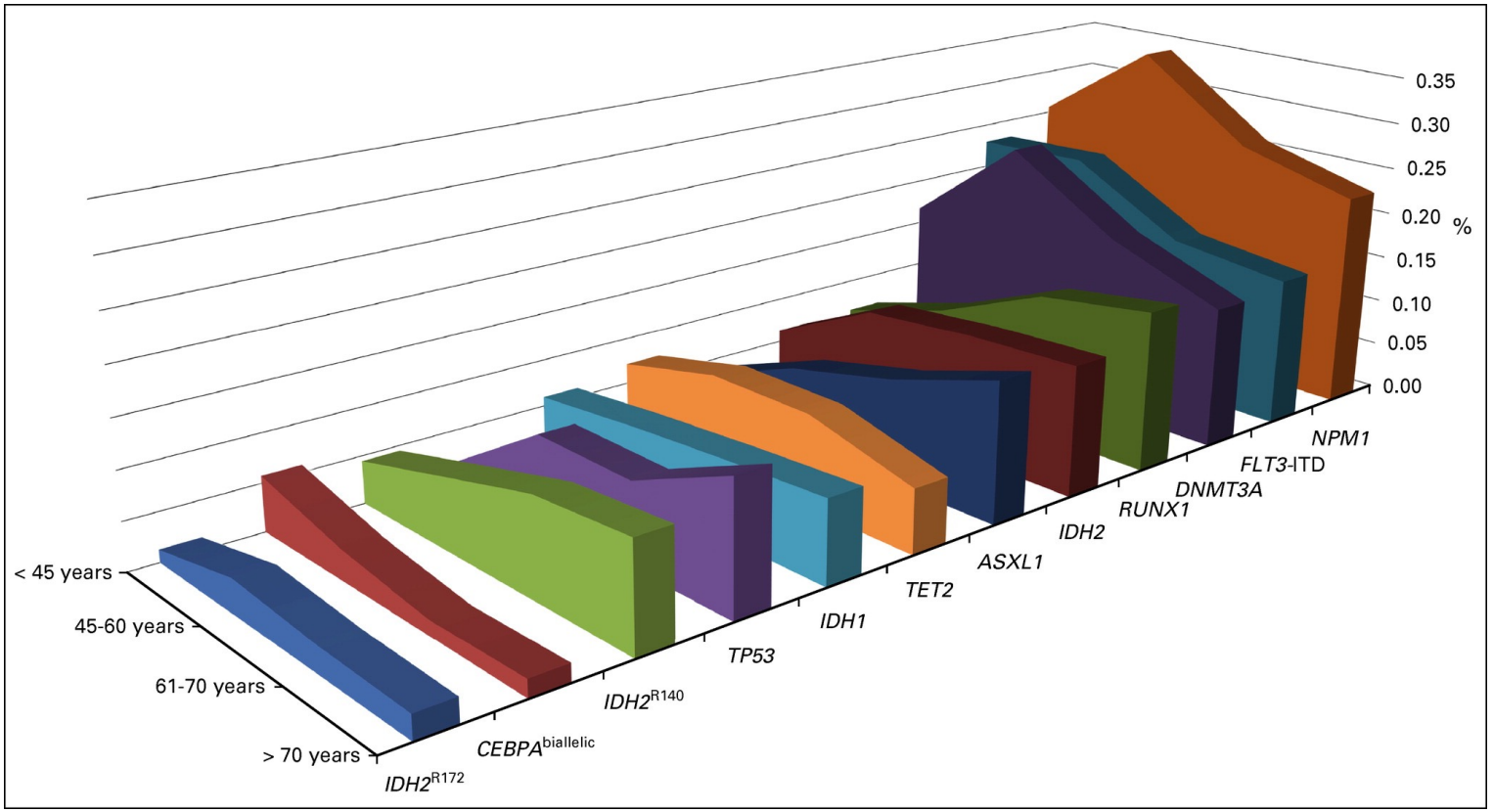
Richard-Carpentier & DiNardo, Hematology Am Soc Hematol Educ Program, 2019

Age and WHO PS in AML, the Swedish registry

	16-24y	25-29y	30-34y	35-39y	40-44y	45-49y	50-54y	55-59y	60-64y	65-69y	70-74y	75-79y	80-84y	85-89y	90+y		All ages
Missing	1	0	1	1	0	1	3	1	6	5	10	14	11	6	6		66
WHO IV	3	1	2	1	2	1	2	10	12	17	31	29	46	23	14		194
WHO III	1	1	1	2	3	6	9	16	22	31	66	87	89	65	17		416
WHO II	6	6	8	8	6	17	27	21	53	61	92	130	106	39	17		597
WHO I	16	13	24	30	32	56	76	91	93	138	147	133	112	43	14		1018
WHO 0	7	9	13	14	20	21	41	38	49	50	54	46	41	8	0		411

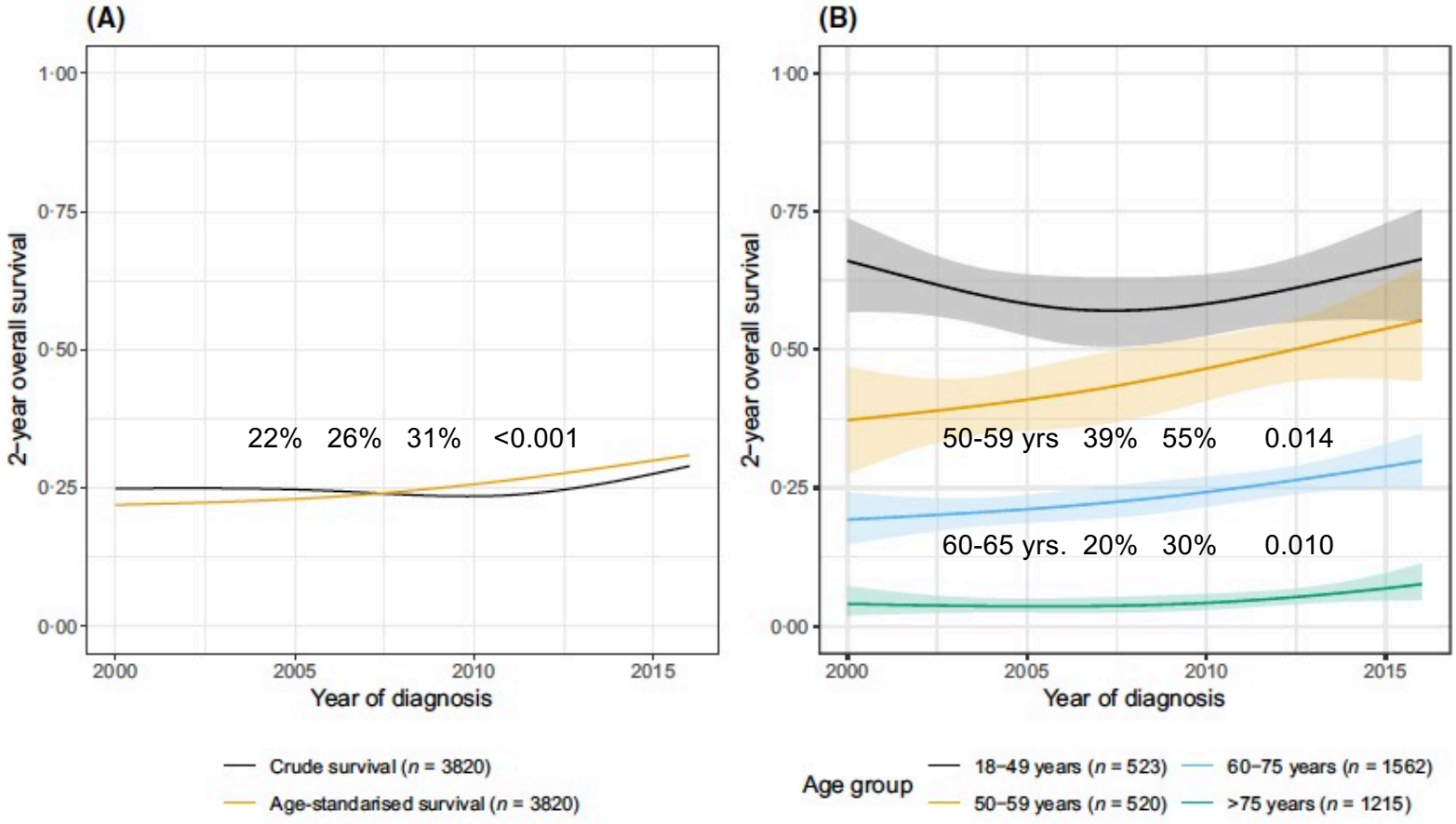
Juliusson G et al, Blood, 2009

Age-related frequency of selected recurring gene mutations



Lars Bullinger et al. Journal of Clinical Oncology 2017

AML OS improvement overtime (the Danish registry)



Jakobsen LH, BJH 2021

Operational criteria for fitness/unfitness to I-CHT/NI-CHT in elderly patients: SIE, SIES, GITMO score

Operational criteria to define unfitness to intensive chemotherapy in AML

1. An age older than 75 years
2. Congestive heart failure or documented cardiomyopathy with an EF ≤50%
3. Documented pulmonary disease with DLCO ≤65% or FEV1 ≤65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
4. On dialysis and age older than 60 years or uncontrolled renal carcinoma
5. Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (>3 times normal values) and an age older than 60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
6. Active infection resistant to anti-infective therapy
7. Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
8. ECOG performance status ≥3 not related to leukemia
9. Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

Abbreviations: AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1s.

Unfitness to Intensive Chemoterapy

Unfitness to Non-Intensive Chemoterapy

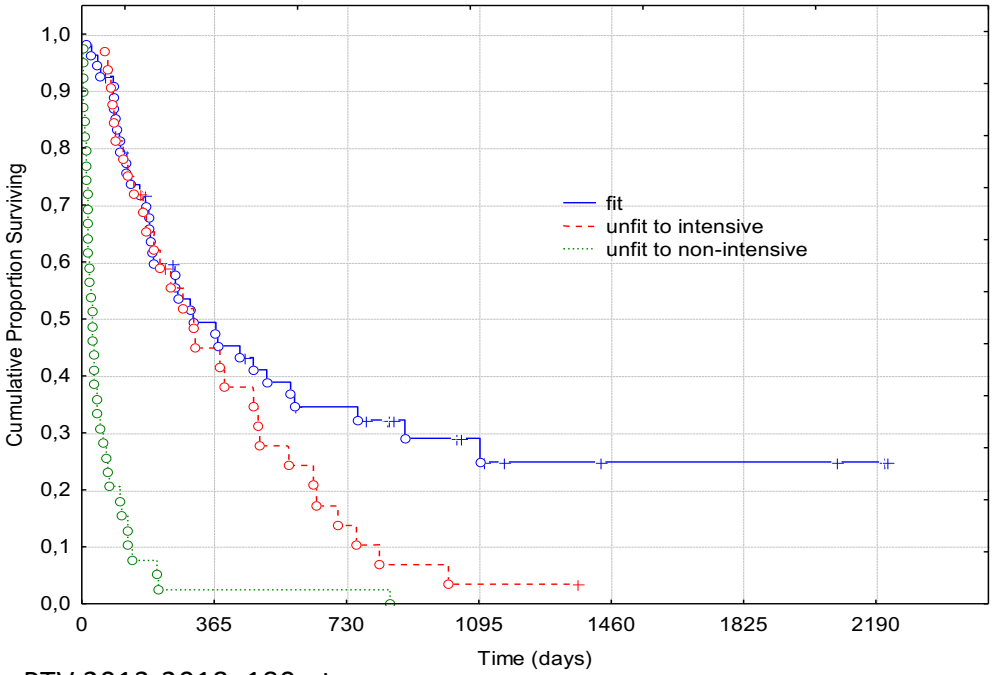
Operational criteria to define unfitness to non-intensive chemotherapy in AML

1. Refractory congestive heart failure
2. Documented pulmonary disease with DLCO ≤65% or FEV1 ≤65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
3. Liver cirrhosis Child B or C or acute viral hepatitis
4. Active infection resistant to anti-infective therapy
5. Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
6. Uncontrolled neoplasia

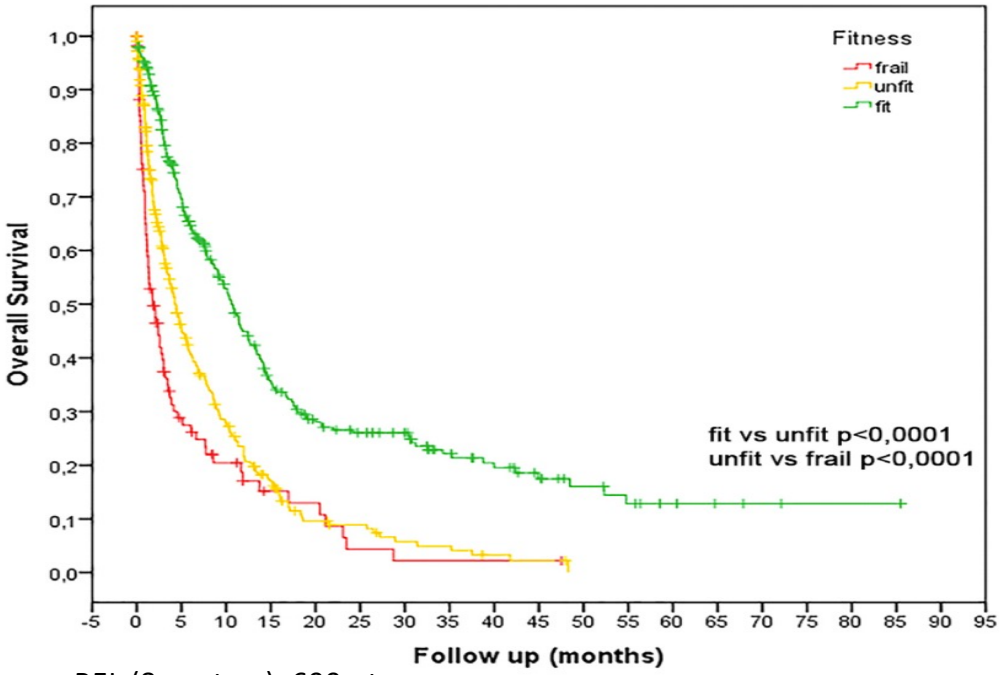
Abbreviations: AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1s.

Ferrara et al., Leukemia, 2013

Concordance between Fitness, treatment received and outcome



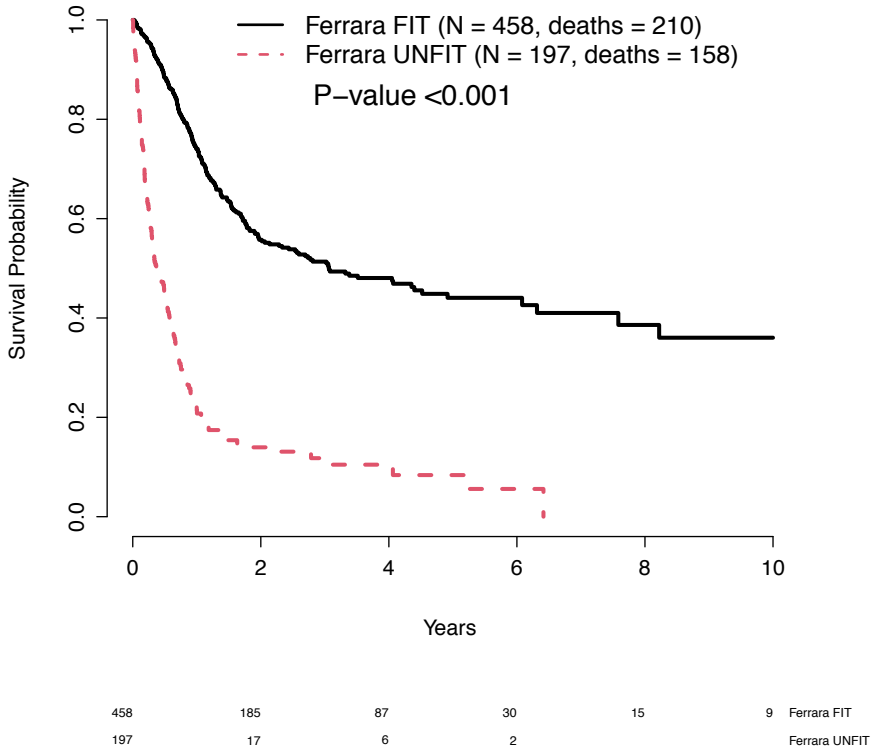
PTV 2013-2018, 180 pts.
Overall concordance was 92% (90% for IC-Fit, 91% for NIC-Unfit to IC, 98% for BSC-Unfit to NIC)



REL (8 centers), 699 pts.
Overall concordance was 79.4% (76% for IC-Fit, 82.7% for NIC-Unfit to IC, 80% for BSC-Unfit to NIC)

Palmieri et al., ASH 2019, Borlenghi t al., Journal of Geriatric Oncol, 2020

OS according to the Ferrara score in patients with a low (<13) TRM mortality score

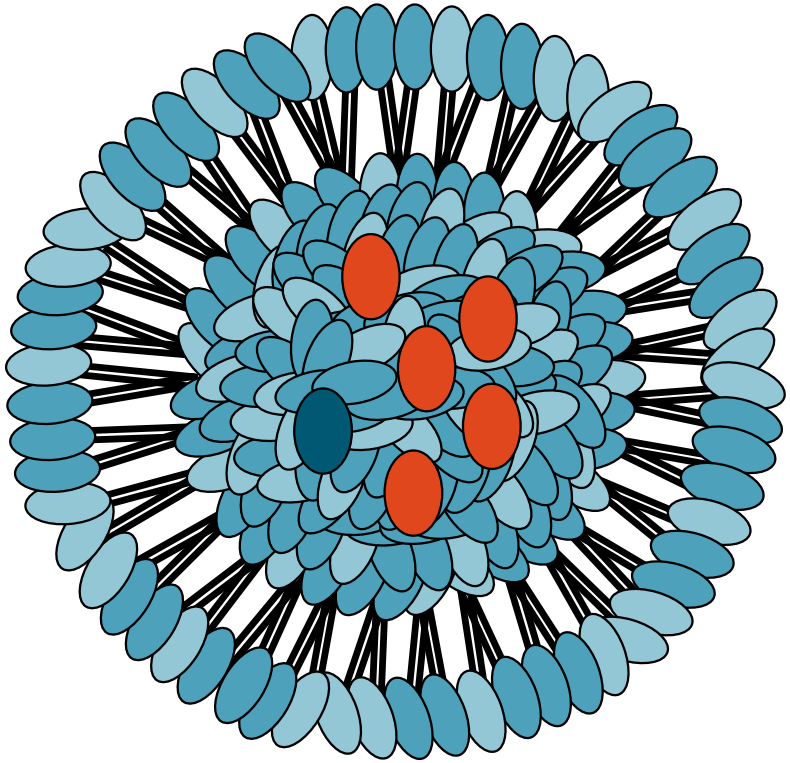


F-Fit pts had a median OS of 36.8 months vs 4.8 months of the F-Unfit ones

	28 days mortality	100 days mortality
F-Fit	7/457 (2%)	22/444 (5%)
F-Unfit	28/196 (14%)	78/185 (42%)

Palmieri et al., JCO, 2020

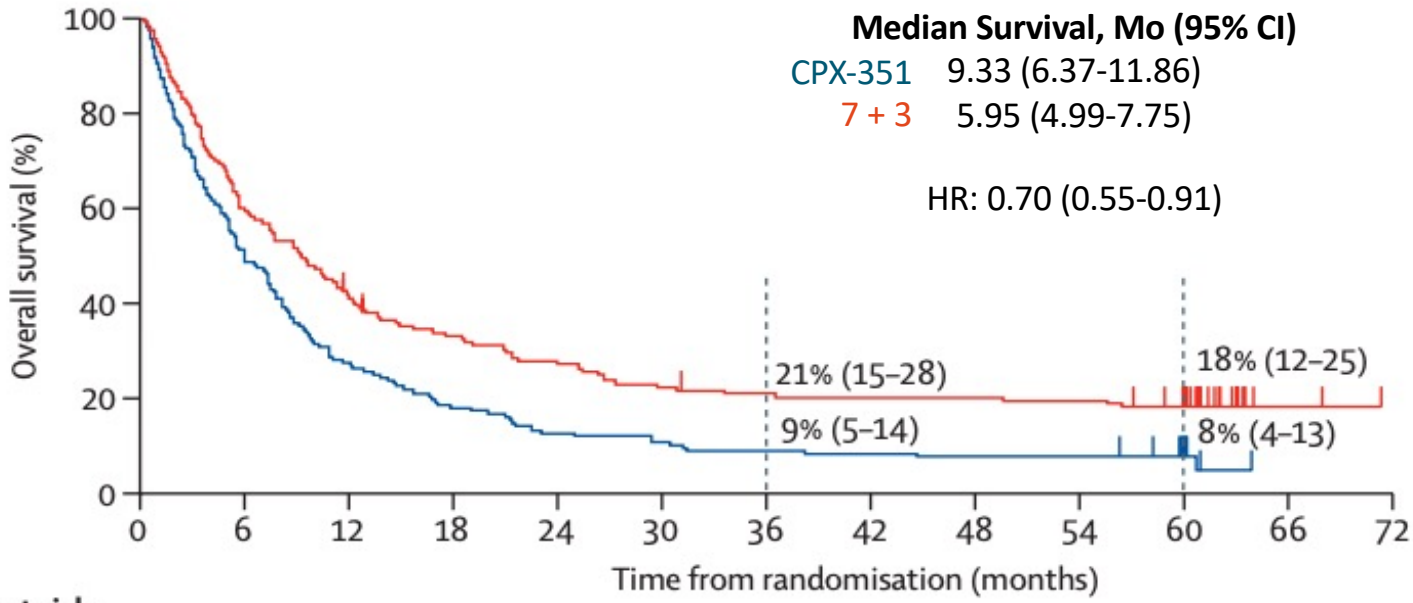
Liposomal Cytarabine and Daunorubicin (CPX-351)



- CPX-351 a 5:1 molar ratio of cytarabine:daunorubicin
- Formulation provides synergistic leukemia cell killing in vitro[1]
- In humans
  - CPX-351 preserved delivery of 5:1 drug ratio for >24 hr
  - Drug exposure maintained for 7 days[2]
- Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]
- Indicated for the treatment of adults with newly diagnosed, therapy-related AML or AML with myelodysplasia-related changes[4]

1. Tardi. Leuk Res. 2009;33:129. 2. Feldman. JCO. 2011;29:979. 3. Lim. Leuk Res. 2010;34:1214. 4. Liposomal cytarabine and daunorubicin PI.

CPX-351 in Older Patients With Newly Diagnosed AML: Updated OS (5-Yr Follow Up)



Median Survival, Mo (95% CI)

CPX-351 9.33 (6.37-11.86)

7 + 3 5.95 (4.99-7.75)

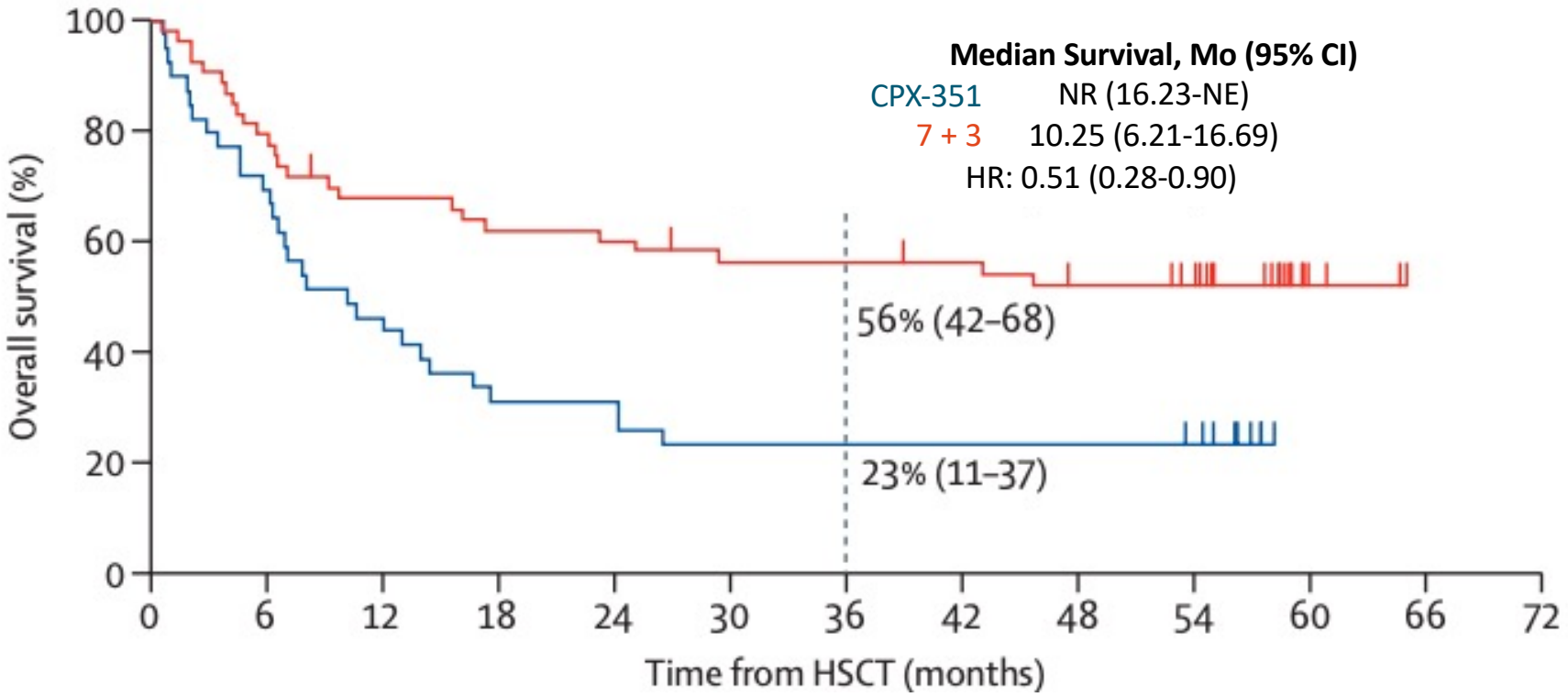
HR: 0.70 (0.55-0.91)

Number at risk (number censored)

CPX-351 group	153	92	62	49	40	33	30	29	29	28	22	2	0
	(0)	(0)	(1)	(2)	(2)	(2)	(3)	(3)	(3)	(3)	(7)	(27)	(29)
7+3 group	156	77	43	28	20	17	14	13	12	12	5	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(7)	(11)	(11)

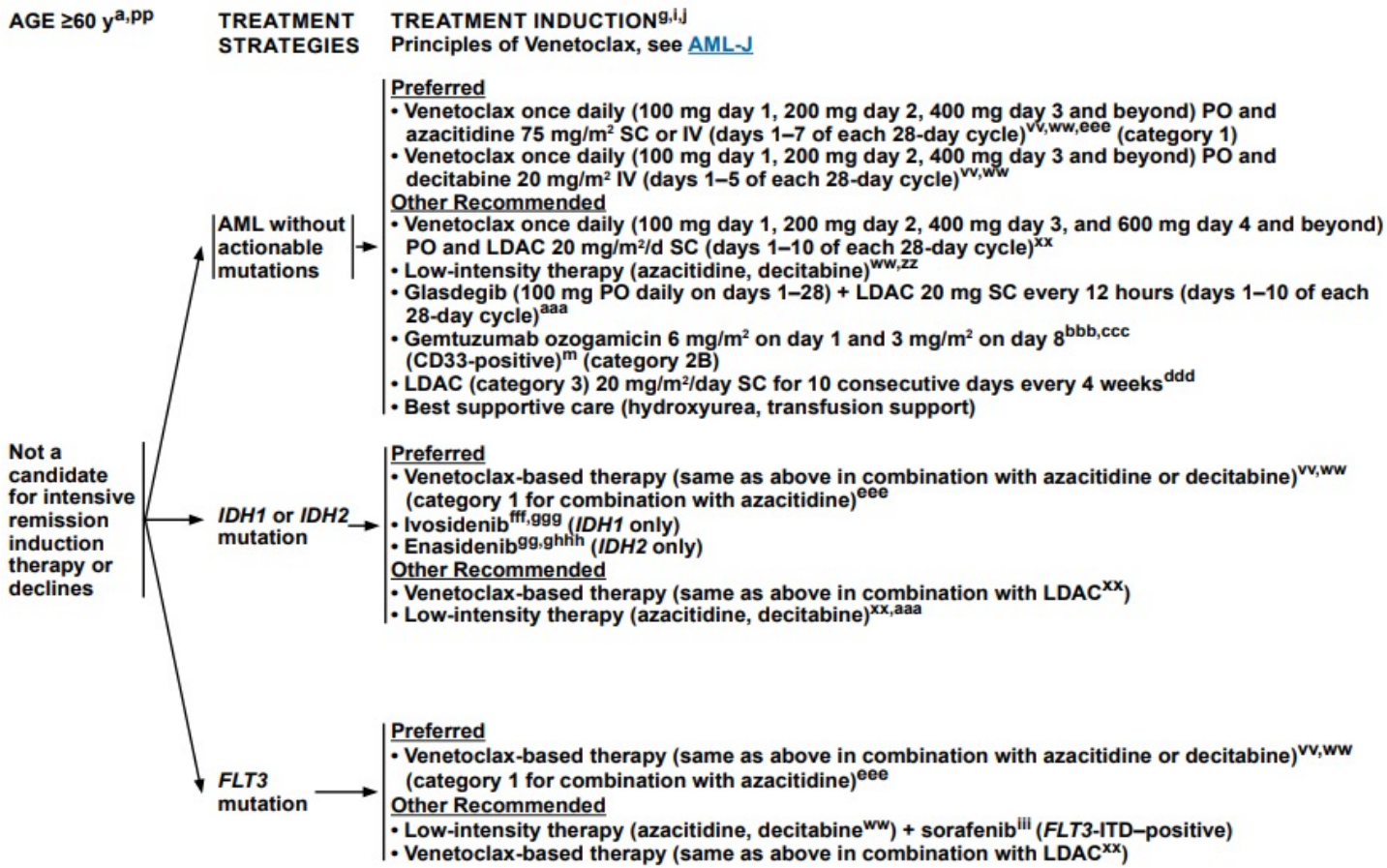
Lancet. Lancet Haematol. 2021;8:e481.

CPX-351 in Older Patients With Newly Diagnosed AML: Updated OS by Time Since HST (5-Yr Follow Up)



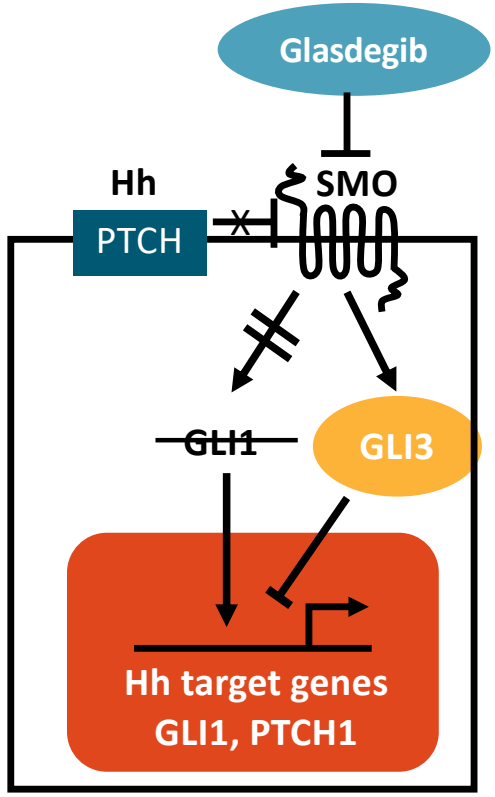
Lancet. Lancet Haematol. 2021

NCCN Guidelines® Recommendations: AML Aged ≥60 Yr



Targeting Hedgehog Pathway Signaling in AML

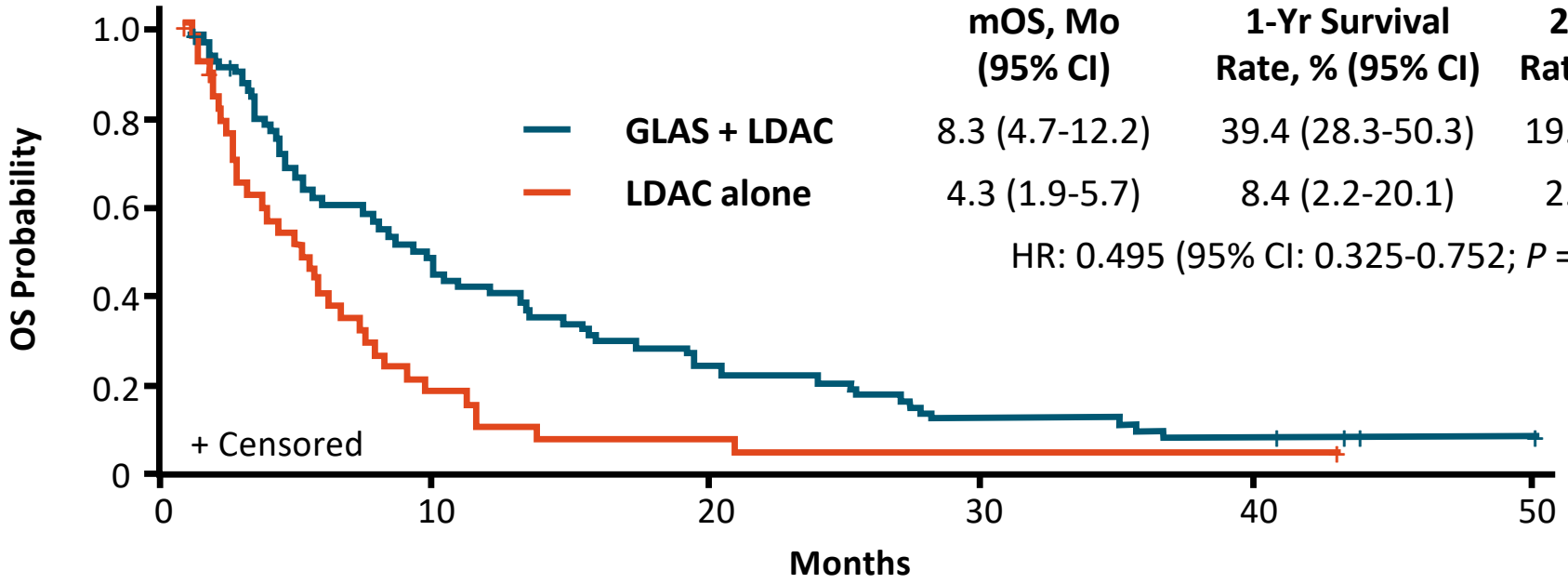
- Aberrant Hh pathway signaling critical for leukemia stem cell survival and expansion
- Overexpression of Hh pathway components observed in chemotherapy-resistant myeloid leukemia cells
- Inhibition of Hh pathway enhanced sensitivity to chemotherapy
- Glasdegib is a potent, selective oral inhibitor of HH signaling pathway through binding to Smoothened



Typical Hh Pathway

Fathi. Clin Cancer Res. 2019;25:6015.

BRIGHT AML 1003: Glasdegib + LDAC OS

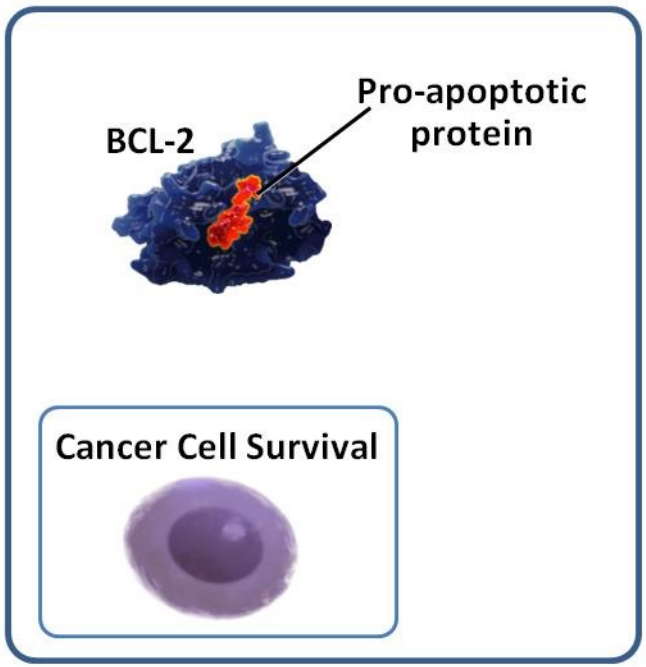


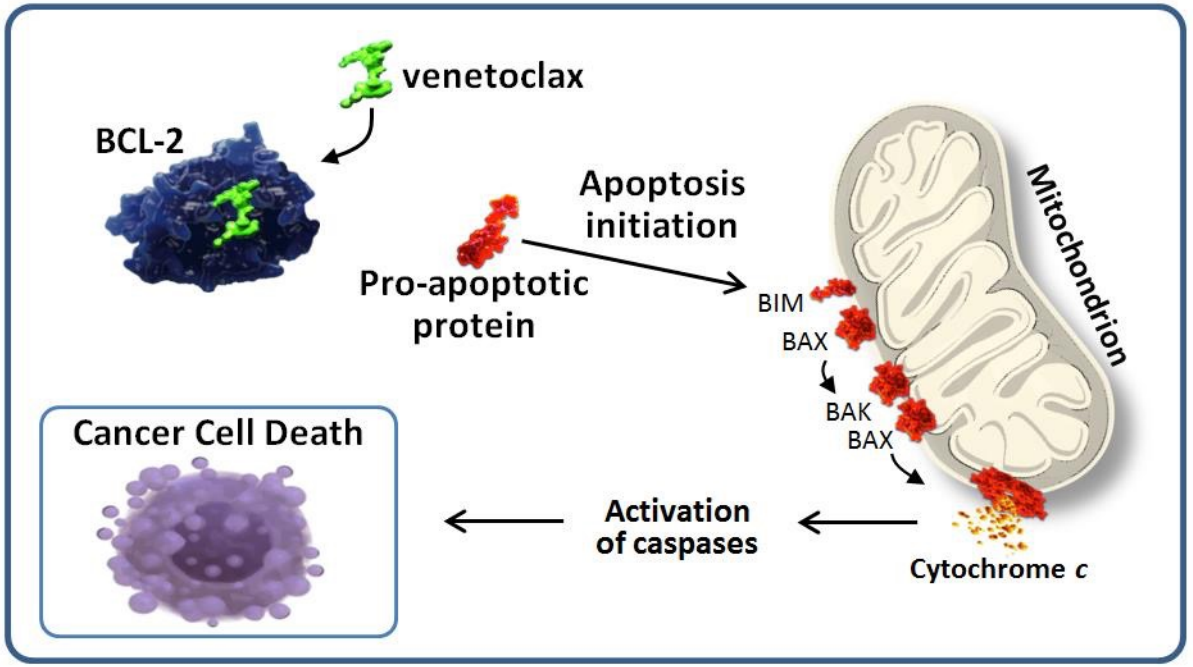
	mOS, Mo (95% CI)	1-Yr Survival Rate, % (95% CI)	2-Yr Survival Rate, % (95% CI)
GLAS + LDAC	8.3 (4.7-12.2)	39.4 (28.3-50.3)	19.0 (11.0-28.7)
LDAC alone	4.3 (1.9-5.7)	8.4 (2.2-20.1)	2.8 (0.2-12.4)

HR: 0.495 (95% CI: 0.325-0.752; *P* = .0004)

Heuser. Ann Hematol. 2021;100:1181.

BCL-2 inhibition in AML



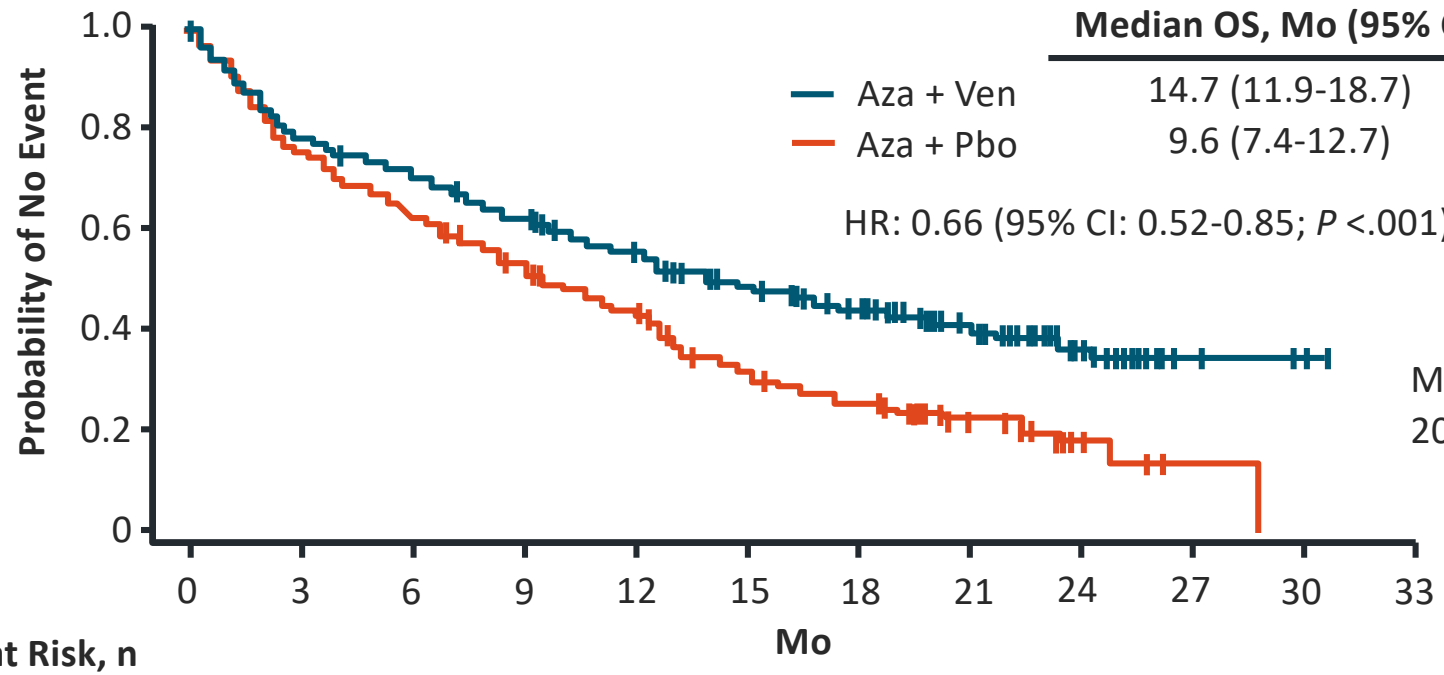


Cancer cells evade cell death through overexpression of BCL-2 which sequesters pro-apoptotic proteins

Venetoclax is a potent small molecule BCL-2 inhibitor which binds to BCL-2, "freeing" pro-apoptotic proteins which then initiate cell death

Wei AH et al, ASH 2016, Leverson JD et al Sci Transl Med 2015, Souers AJ et al Nat Med 2013, Certo M et al, Cancer Cell 2006

VIALE-A: Aza ± Venetoclax OS



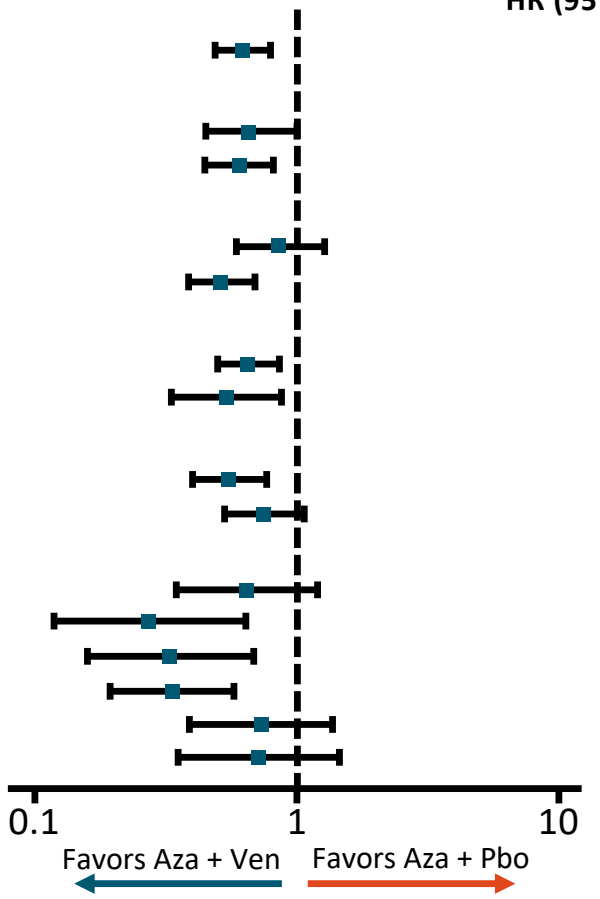
Patients at Risk, n

Aza + Ven	286	219	198	168	143	117	101	54
Aza + Pbo	145	109	92	74	59	38	30	14

DiNardo. NEJM. 2020;383:617.

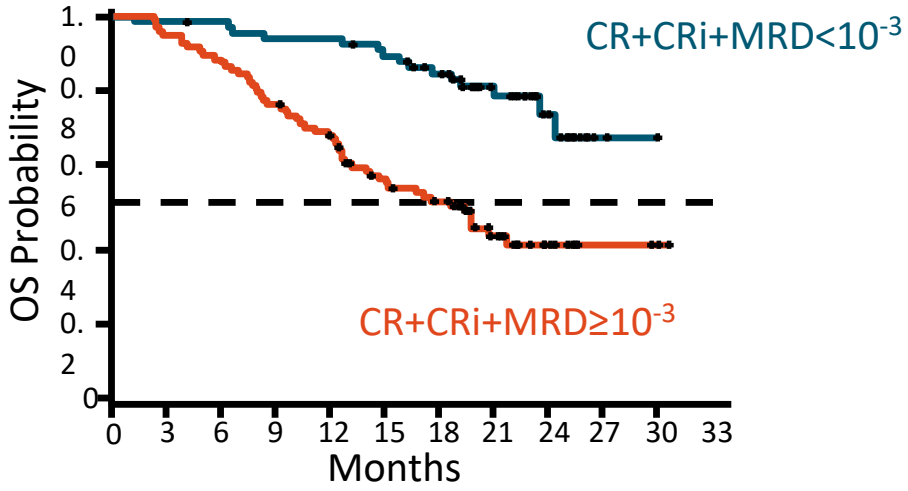
VIALE-A: Aza ± Venetoclax OS by Subgroup

	Aza + Ven, n/N (%)	Aza + Pbo, n/N (%)	HR (95% CI) Aza + Ven vs Aza + Pbo
All Subjects	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, Yr			
<75	66/112 (58.9)	36/58 (62.1)	0.89 (0.59-1.33)
≥75	95/174 (54.6)	73/87 (83.9)	0.54 (0.39-0.73)
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)	0.28 (0.12-0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16-0.71)
IDH1/2	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)



DiNardo. NEJM. 2020;383:617.

MRD Status and Prognosis With Ven + Aza in Treatment-Naive AML: OS



Multivariate Analysis for OS	Adjusted HR (95% CI)	*P* Value
MRD response ($<10^{-3}$ vs $\geq 10^{-3}$)	0.285 (0.159-0.510)	<.001
Cytogenetic risk (poor vs int)	2.062 (1.260-3.374)	.004

OS, % (95% CI)	Events, n	12 Mo	18 Mo	Median
CR/CRi + MRD $<10^{-3}$	15	94.0 (84.7-97.7)	84.6 (73.3-91.4)	NR (24.4-NR)
CR/CRi + MRD $\geq 10^{-3}$	52	67.9 (57.6-76.2)	50.1 (39.6-59.8)	18.7 (12.9-NR)

Pratz. JCO 2022

Conclusions

- ✓ AML in older patients is an unique clinic-biological entity and has an overall dismal prognosis
- ✓ In the last decade several promising drugs have been licensed for this category of patients
- ✓ Improvement of prognosis both in intensive and less-intensive treatment schedules has been observed
- ✓ Careful assessment of fitness is a prerequisite for a proper treatment selection