What is the best induction treatment? FLAI/FLAG

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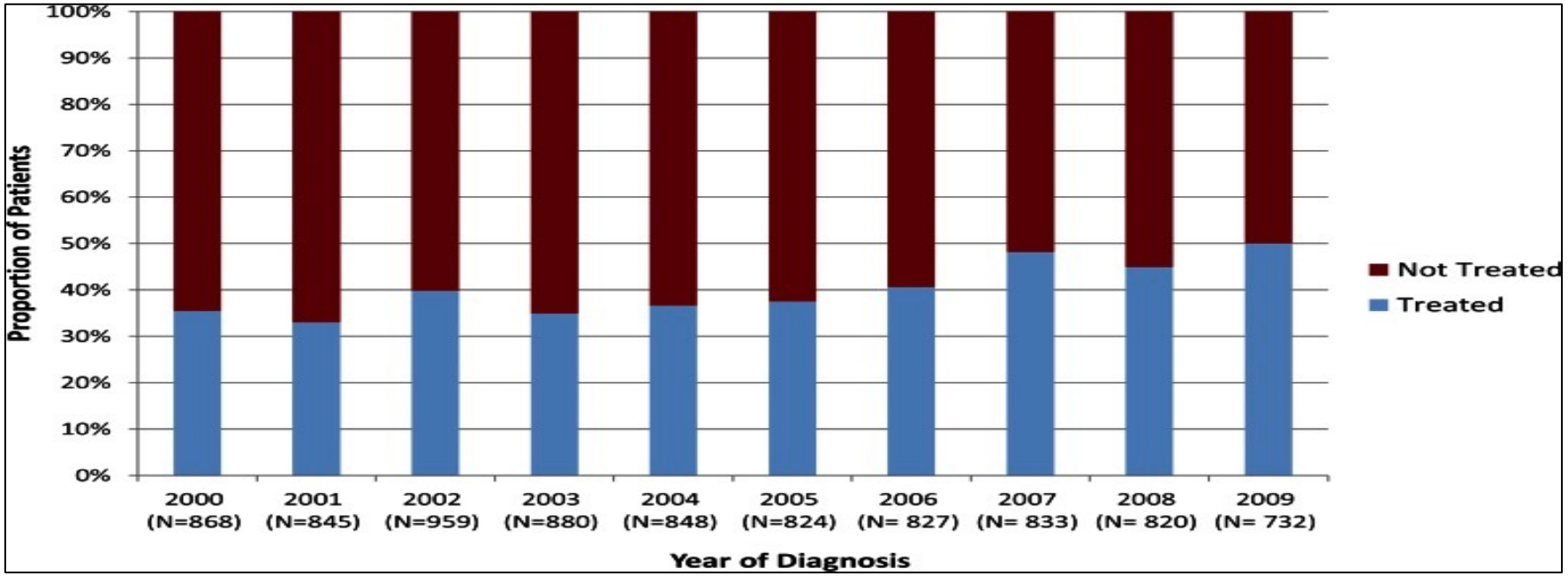
Disclosures of Cristina Papayannidis

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen						x	
Pfizer					x	x	
Blueprint						x	
Amgen					x		
Astellas					x	x	
Incyte						x	
Novartis					x	x	
Abbvie						x	
Menarini/Stemline					x	x	
GSK					x		
BMS					x		
Jazz Pharmaceuticals						x	
Servier						x	

AML in the elderly population: few patients are treated



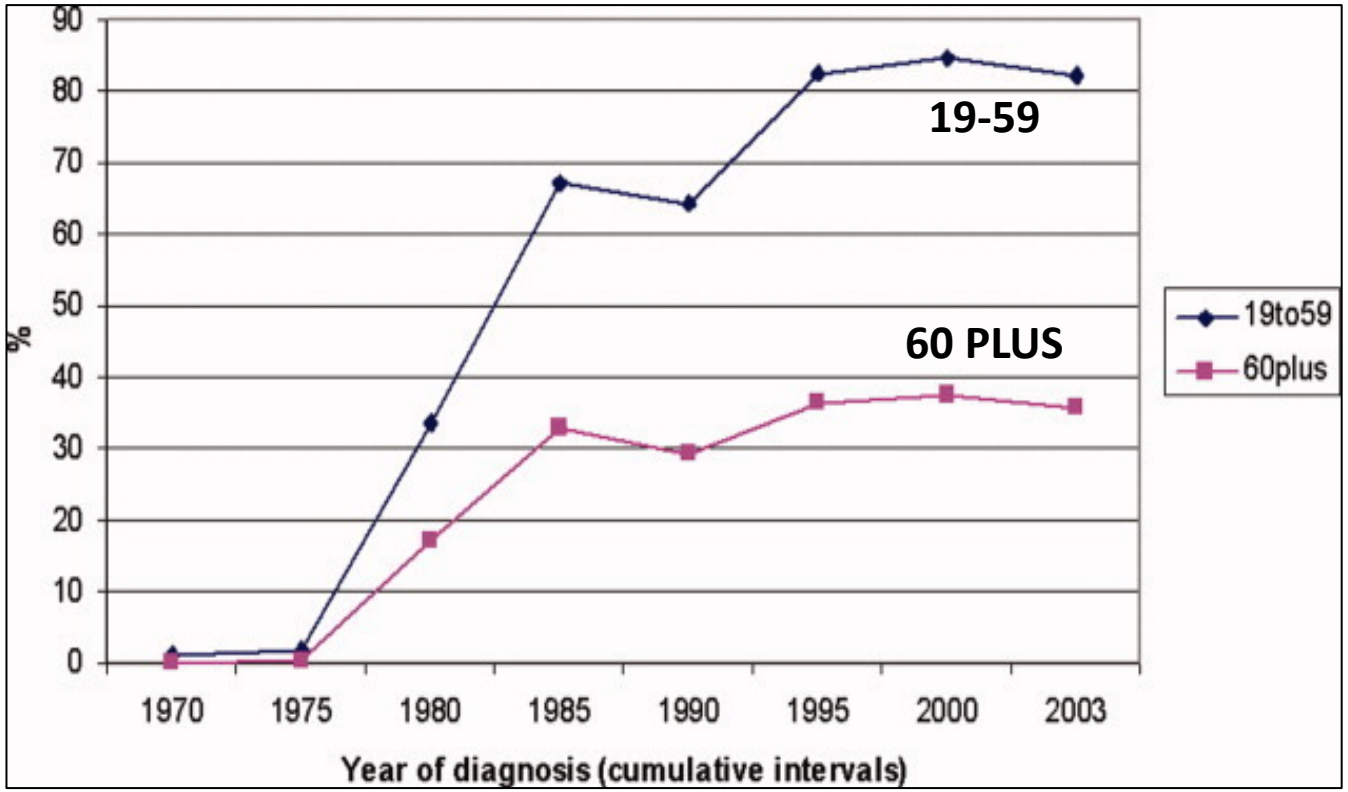
- 8336 patients were diagnosed between January 1, 2000 and December 31, 2009, >66 years.
- 3327 (**40 %**) patients **received chemotherapy** within 3 months of diagnosis.
- treated patients exhibited a significant 33 % lower risk of death compared to untreated patients.

Medeiros BC et al. Ann Hematol 2015

Why?

- High prevalence of comorbidities
- Bad biology, often secondary or therapy-related
- Views that AML is largely incurable in older pts, death is certain, and therapy is useless
- Patient preferences
- Fear of toxicity (low benefit : risk ratio)
- “Do no harm” approach by physicians
- Costs in face of very low expected benefits
- Lack of social support
- Few active, tolerated therapies (starting to change)

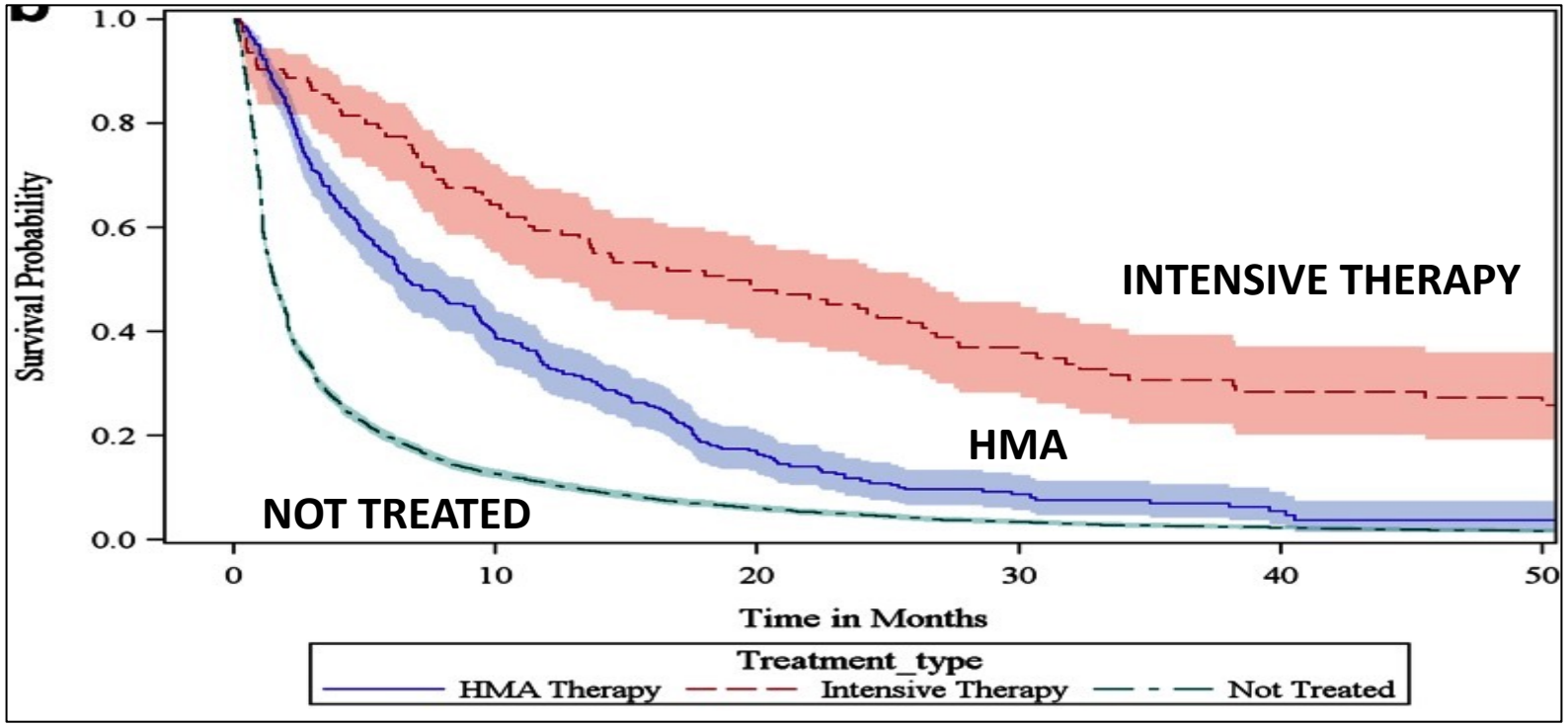
Disparity in the treatment of elderly AML patients



- a total of 9613 patients were diagnosed with AML.
- the proportion of patients receiving **chemotherapy declined with age** (59.0% vs 29.3% among patients ages 19-59 vs > or =60 years).

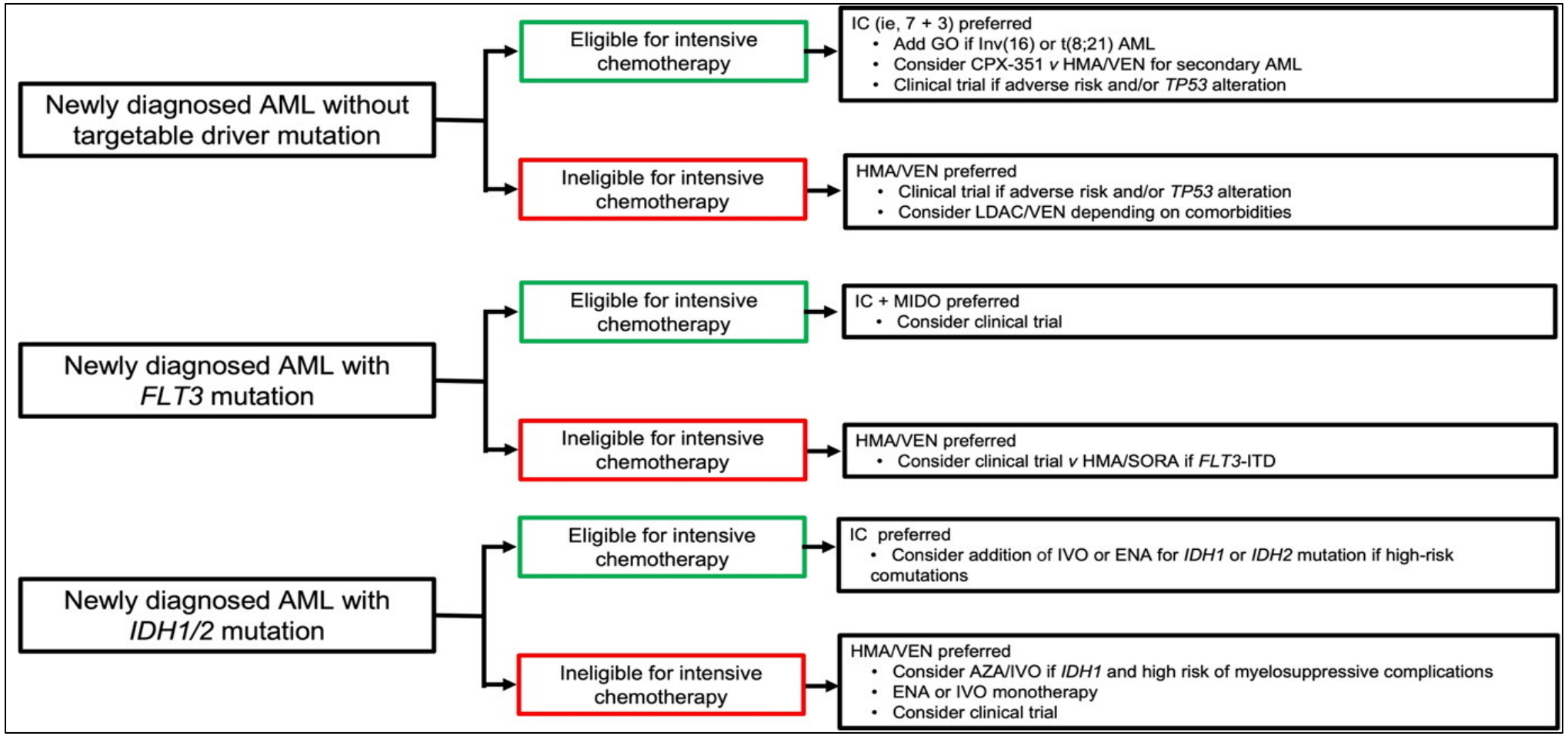
Alibhai SMH et al. Cancer 2009

Intensive treatment offers the best outcome



Medeiros BC et al. Ann Hematol 2015

Older patients with AML deserve individualized treatment



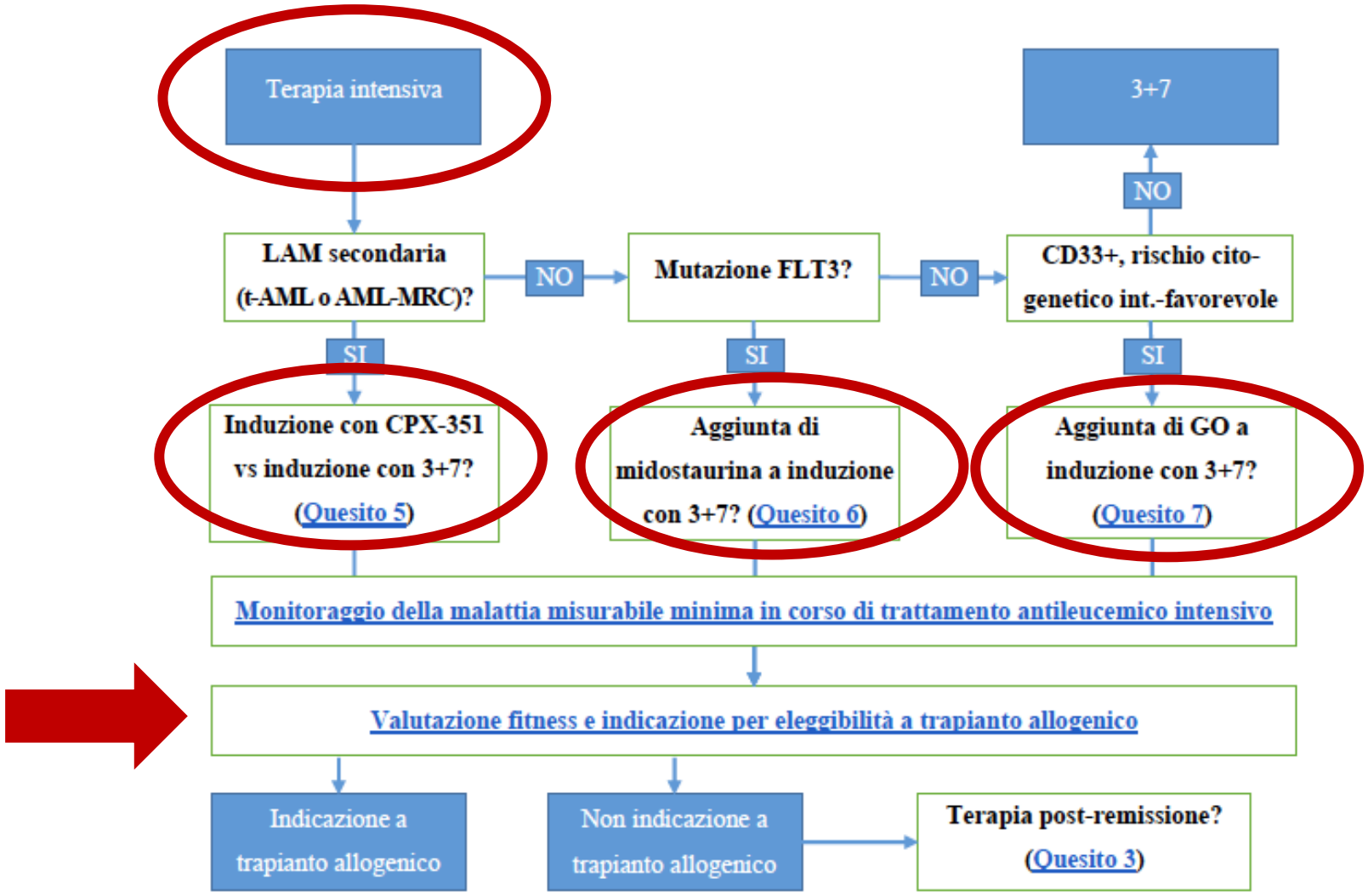
Lai et al. ASCO 2023

Older adults with newly diagnosed AML: hot topics for the practicing clinician

SIE guidelines for AML pts>60 years

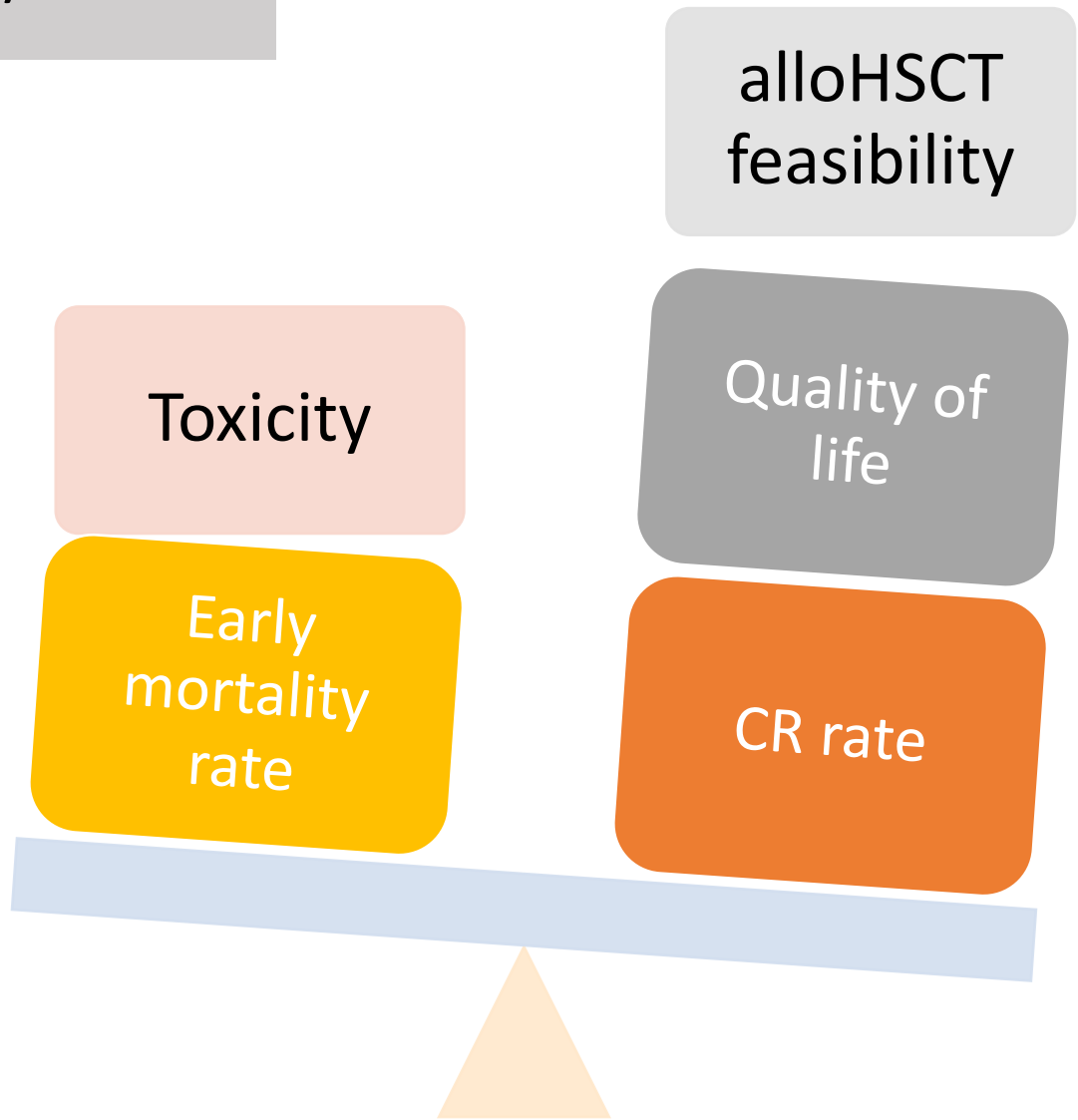
AML SIE guidelines, 2023

SIE guidelines for AML pts>60 years



AML SIE guidelines, 2023

FLAI/FLAG-IDA…why?



FLAG-IDA schedule

Drug	Dose	Route	Day
Filgrastim	5 micrograms/kg	Subcut	0 to 5 and continue daily until neutrophil recovery
iDArubicin	10 mg/m^2	IV	1 to 3
Fludarabine	30 mg/m^2	IV infusion	1 to 5
Cytarabine (Ara-C)	2,000 mg/m^2	IV infusion	1 to 5

Burnett A et al, JCO 2013

Rationale

FDR triphosphate,

the **active metabolite of FDR**, inhibits ribonucleotide reductase with subsequent **accumulation of intracellular**

ara-CTP

A **positive correlation** has been found between

intracellular ara-CTP levels and remission rates

G-CSF prior to FDR **increases the fraction**

of cells in cycle when they are **most vulnerable to ara-C** and enhances the incorporation of ara-C into DNA

Idarubicin was found to be **less susceptible to multidrug resistance** compared with other anthracyclines in human leukaemia cell lines

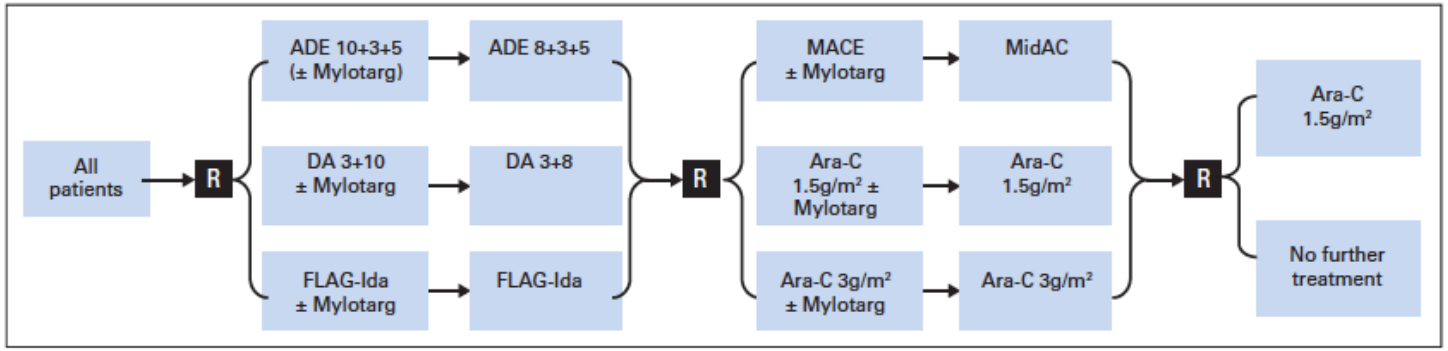
Virchis A et al, BJH 2004; Gandhi and Plunkett, 1988; Gandhi et al, 1993; Estey et al, 1990; Tafuri and Andreeff, 1990

Optimization of Chemotherapy for Younger Patients With Acute Myeloid Leukemia: Results of the Medical Research Council AML15 Trial

Alan K. Burnett, Nigel H. Russell, Robert K. Hills, Ann E. Hunter, Lars Kjeldsen, John Yin, Brenda E.S. Gibson, Keith Wheatley, and Donald Milligan

13% pts age>60 years

Characteristic	ADE (n = 989)		DA (n = 994)		ADE (n = 633)		FLAG-Ida (n = 635)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
0-14	0		0		52	8	52	8
15-29	120	12	119	12	73	12	73	12
30-39	136	14	141	14	83	13	85	13
40-49	231	23	229	23	132	21	132	21
50-59	370	37	372	37	214	34	213	34
60+	132	13	133	13	79	12	80	13
Median	50		50		48		48	
Range	16-68		16-73		0-67		0-71	



JCO 2013

ORR 86%
30 day mortality 10%

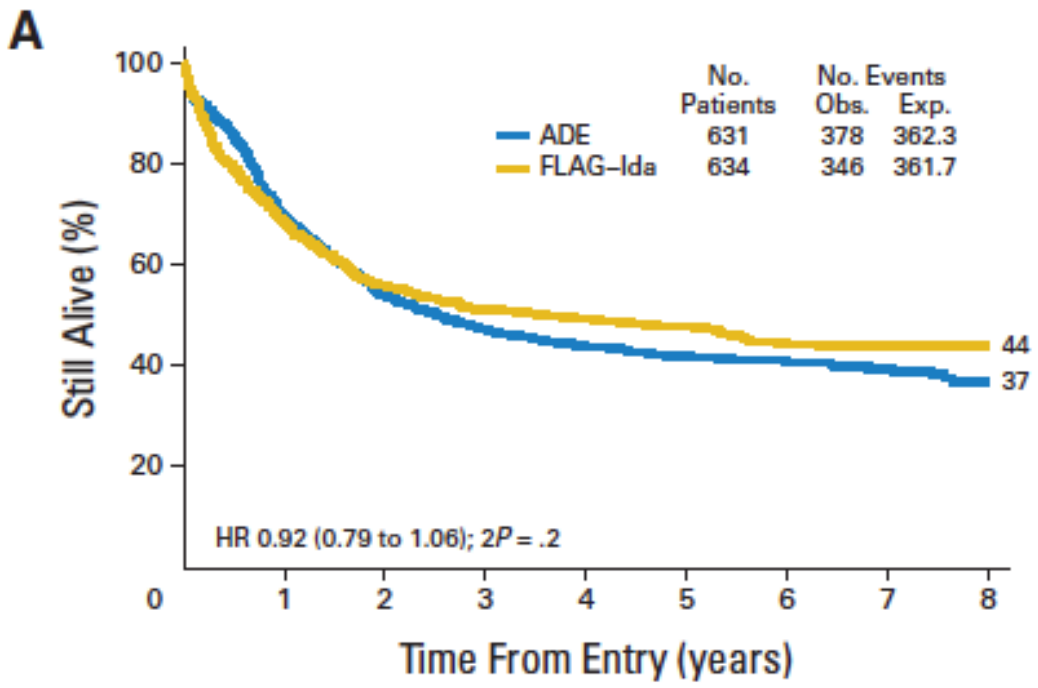
Table 3. Patient Outcomes: Induction (%)

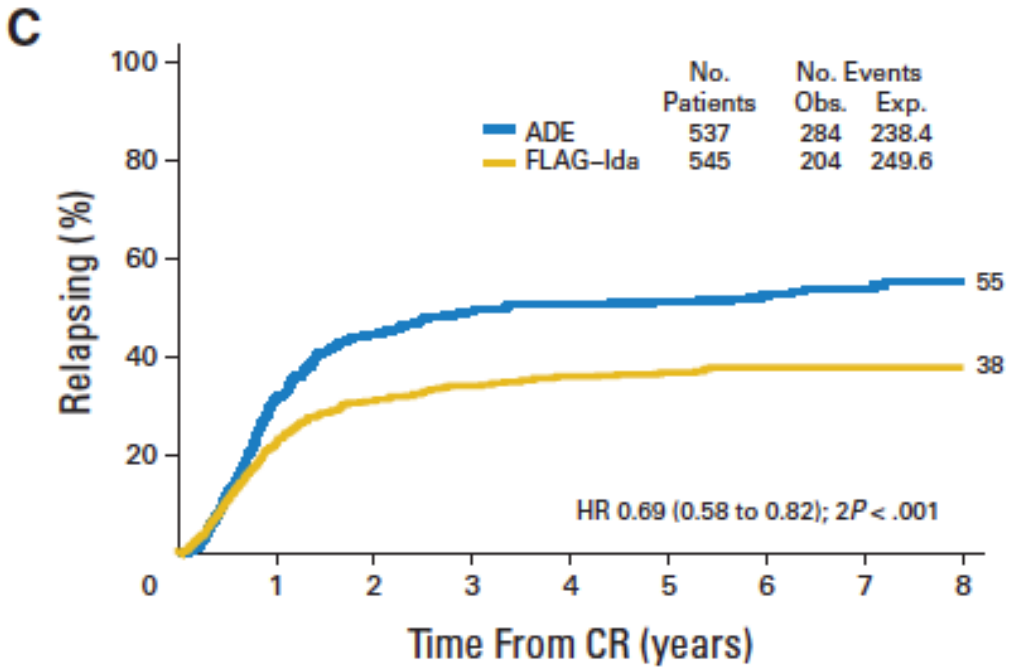
	CR	CRi	ORR (CR + CRi)	ORR post C1	Res Dis	Ind Death	30-Day Mortality	60-Day Mortality
DA	78	6	84	63	10	6	6	8
ADE	82	4	86	70	8	5	5	7
OR/HR	1.24		1.20	1.35	1.25	1.09		
95% CI	0.99 to 1.54		0.94 to 1.54	1.12 to 1.63	0.93 to 1.70	0.93 to 1.70		
P	.06		.14	.002	.14	.7		
FLAG-Ida	84	2	86	77	7	7	6	9
ADE	81	4	85	67	8	7	6	7
OR	0.84		0.94	0.60	0.82	1.09		
95% CI	0.63 to 1.13		0.69 to 1.29	0.47 to 0.76	0.54 to 1.26	0.71 to 1.68		
P	.2		.7	< .001	.4	.7		

Abbreviations: ADE, cytarabine, daunorubicin, and etoposide; CR, complete remission; CRi, complete remission with incomplete count recovery; DA, daunorubicin and cytarabine; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; HR, hazard ratio; Ind, induction; OR, odds ratio; ORR, overall response rate; Res Dis, residual disease.

Burnett A et al, JCO 2013

No differences in terms of OS

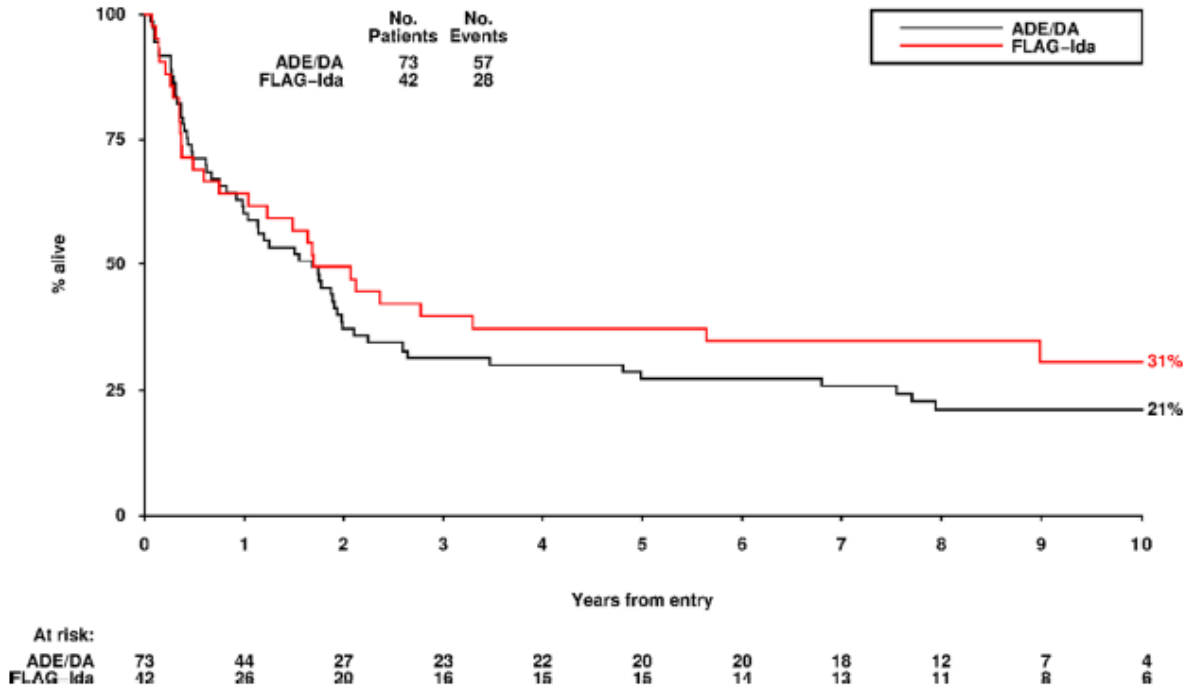




Burnett A et al, JCO 2013

bjh short report

Treatment intensification with FLAG-Ida may improve disease control in younger patients with secondary acute myeloid leukaemia: long-term follow up of the MRC AML15 trial



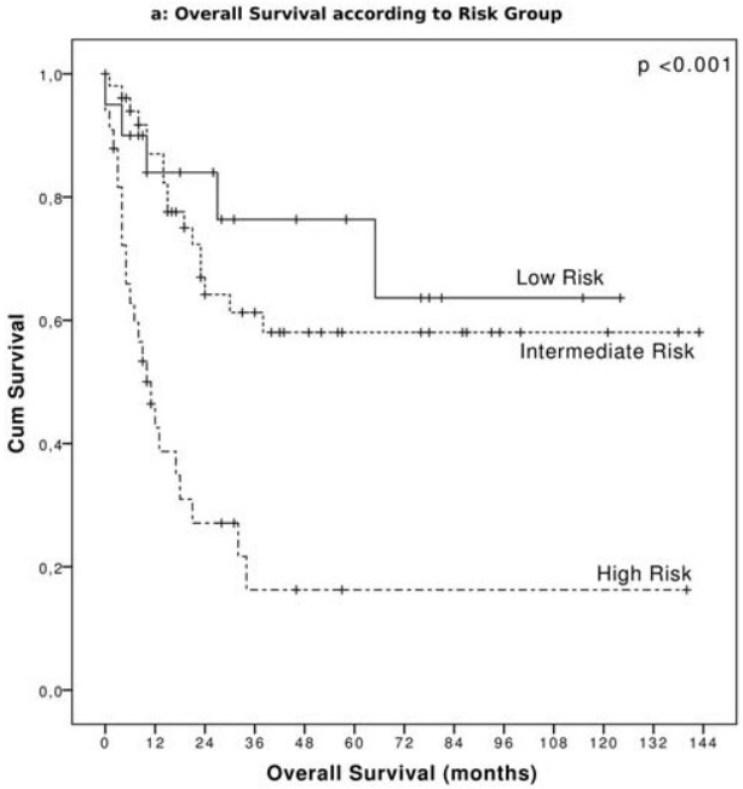
Russell N et al, BJH 2022

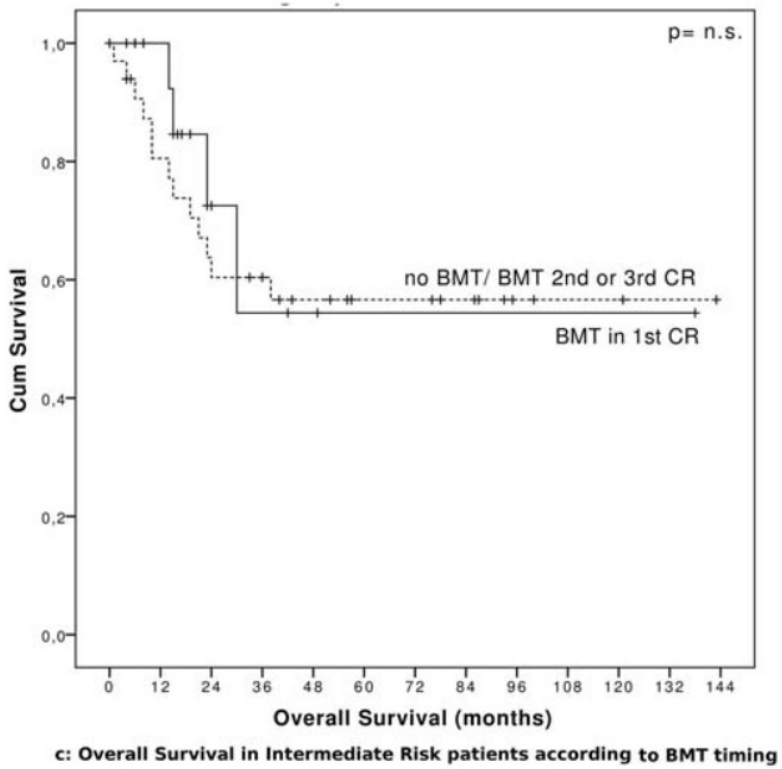
High feasibility and antileukemic efficacy of fludarabine, cytarabine, and idarubicin (FLAI) induction followed by risk-oriented consolidation: A critical review of a 10-year, single-center experience in younger, non M3 AML patients

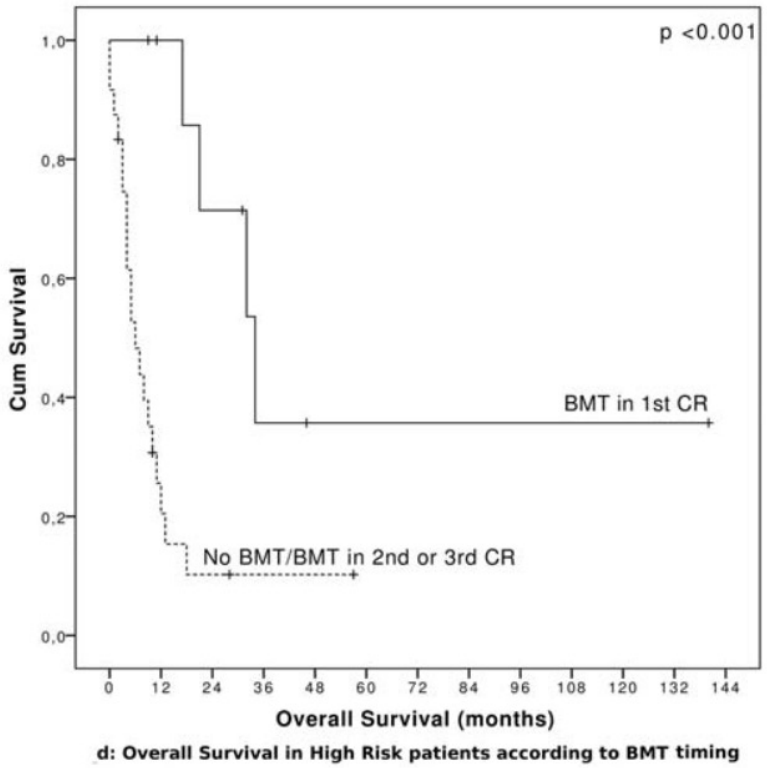
N=105
CR 1st course: 79.1%
CR 2nd course: 83.8%

30-day mortality: 4.8%

HIGH RISK







Guolo F et al, 2016

A comparison of FLAG-Ida and daunorubicin combined with clofarabine in high-risk acute myeloid leukaemia: data from the UK NCRI AML17 trial

A K Burnett[1] · R K Hills[2] · O J Nielsen[3] · S Freeman[4] · A Ali[5] · P Cahalin[6] · A Hunter[7] · I F Thomas[2] · N H Russell[8]

28% pts age>60 years

	DClo	FLAG-Ida
Number randomised	207	104
Age group (years)		
15–29 (16%)	6 (3%)	7 (7%)
30–39 (20%)	17 (8%)	8 (8%)
40–49 (19%)	29 (14%)	14 (13%)
50–59 (29%)	95 (46%)	46 (44%)
60+ (37%)	60 (29%)	29 (28%)
Gender		
Female	66 (32%)	35 (34%)
Male	141 (68%)	69 (66%)
Type of disease		
De novo	147 (71%)	74 (71%)
Secondary	38 (18%)	20 (19%)
High-risk MDS	22 (11%)	10 (10%)

Leukemia 2018

No differences in terms of ORR, 30 day mortality
Better long term OS for FLAG-IDA pts

	DClo	FLAG-Ida	OR/HR, 95% CI	*p* Value
MRD status post C2				
CR/CRi, MRD −ve	20 (11%)	12 (13%)		MRD −ve vs. MRD +ve vs. no CR, $p = 0.08$
CR/CRi, MRD +ve	29 (15%)	18 (20%)		
CR/CRi, MRD unk	93 (49%)	49 (53%)		
Not in CR	47 (25%)	13 (14%)		
Not known	18	12		
ORR (CR + Cri)	83%	86%	1.24 (0.66–2.34)	0.5
CR	68%	72%	1.23 (0.74–2.05)	0.4
CRi	15%	13%		
30-day mortality	2%	4%	0.61 (0.15–2.45)	0.5
60-day mortality	9%	10%	0.95 (0.44–2.06)	0.9
5-year OS	26%	44%	1.40 (1.05–1.86)	0.02
4-year OS censored at SCT	15%	28%	1.27 (0.87–1.85)	0.2
5-year CIR	51%	39%	1.38 (0.95–2.01)	0.09
5-year CIDCR	24%	17%	1.45 (0.83–2.51)	0.19
5-year RFS	25%	44%	1.40 (1.03–1.91)	0.03

Burnett A et al, Leukemia 2018

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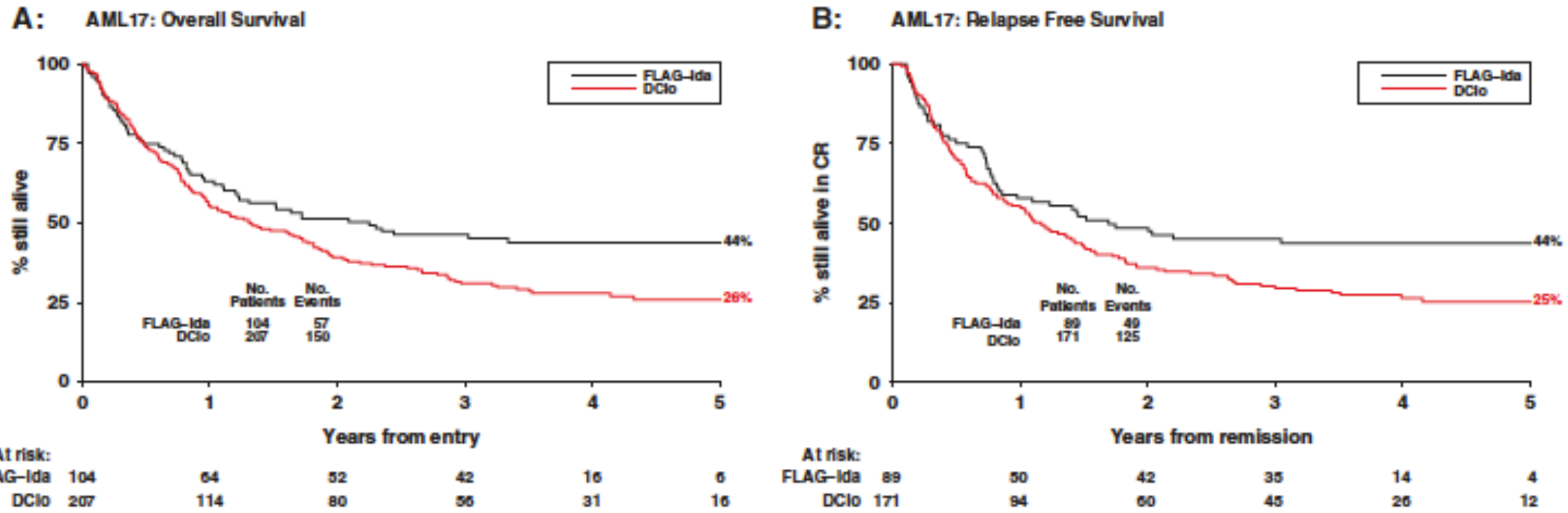

Burnett A et al, Leukemia 2018

FLAGIDA-lite is an effective regimen for patients between 70 and 80 years with acute myeloid leukemia or refractory anemia with excess blasts-2 and is feasible as outpatient treatment

Arancha Bermúdez,[1] German Pérez-Vázquez,[1] Andres Insunza,[1] Julio Baro,[1] Mercedes Colorado,[1] Eulogio Conde,[1] Zuriñe Díez-Gallarreta,[1] Maria Luisa Gutiérrez,[3] Monica López-Duarte,[1] Ignacio Olalla,[3] Pedro Sanroma,[2] Lucrecia Yañez,[1] Arturo Iriondo,[1] and Carlos Richard[1]

ORR 55%; Ind death 16% (32%>80 yrs)

Characteristics	Value	
Number of patients (*n*)	38	
Sex, male/female	22	16
Age (years), median (range)	78	(71-91)
71-79 years, *n* (%)	25	(66)
>80 years, *n* (%)	13	(34)
ECOG performance status, *n* (%)		
0-1	27	(71)
2-3	11	(29)
Charlson comorbidity index, *n* (%)		
Medium	8	(21)
High	23	(61)
Very high	7	(18)
Prior nonhematological malignancy, *n* (%)	5	(13)
Diagnosis, *n* (%)		
AML	32	(84)
RAEB-2	6	(16)

TABLE II. Response and Tolerability

Variable	Value	
Response to induction therapy, *n* (%)		
Overall response (CR + PR)	21	(55)
CR	13	(34)
CRi	5	(13)
Partial response	3	(8)
Resistant disease	12	(32)
CR + CRi in patients 70-79 years	13	(52)
CR + CRi in patients >80 years	5	(38)
CR + CRi with one cycle	15	(83)
Tolerability		
Induction therapy cycles, *n*	47	
Hospitalization	11	(23)
Home care	10	(21)
Ambulatory	26	(56)
Need for hospital admission, *n* (%)	6	(12)
Mortality during induction (<4 weeks), *n* (%)	6	(16)
70-79 years	2	(8)
≥80 years	4	(32)
Global mortality (8 weeks), *n* (%)		
70-79 years	2	(8)
≥80 years	7	(54)
Consolidation therapy cycles, *n*	18	
Home care	7	(27)
Ambulatory	11	(73)
Need for hospital admission, *n* (%)	2	(13)
Total number of cycles administered	65	
Cycles administered without need for admission, *n* (%)	46	(70)

AJH 2011

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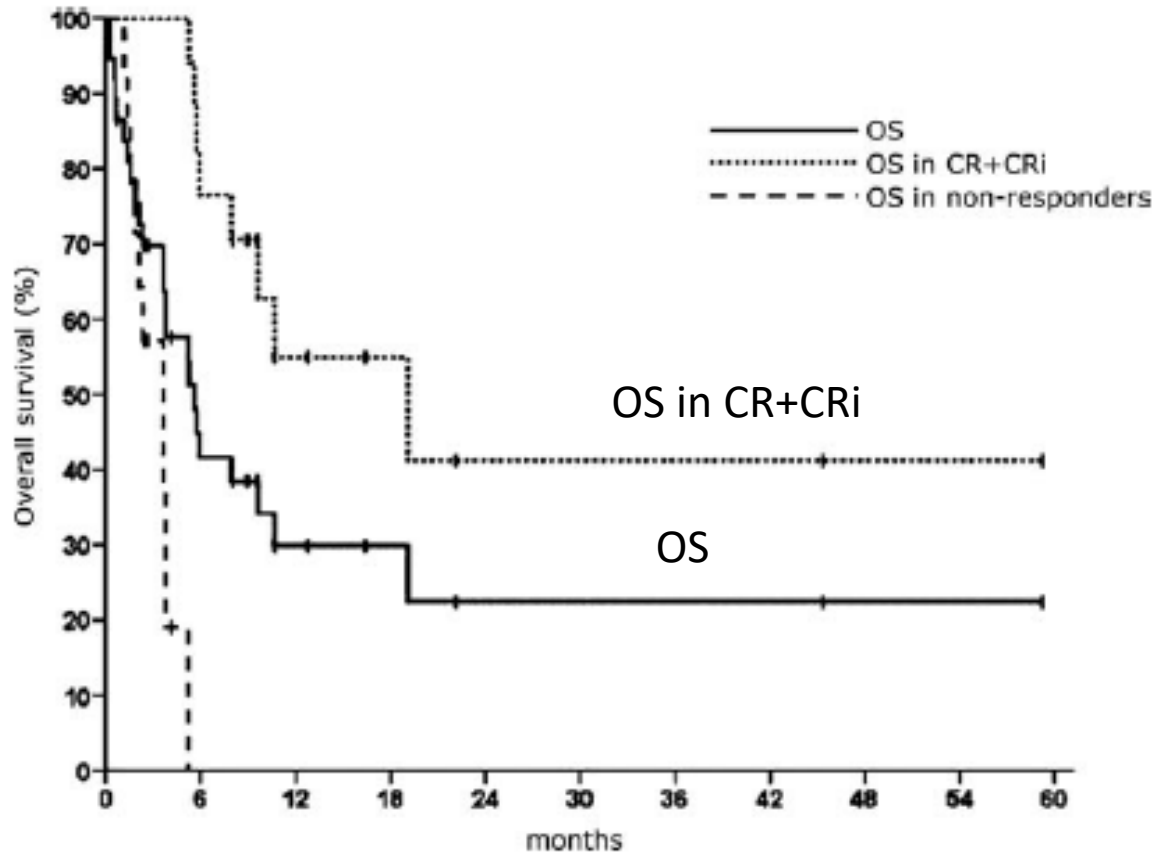
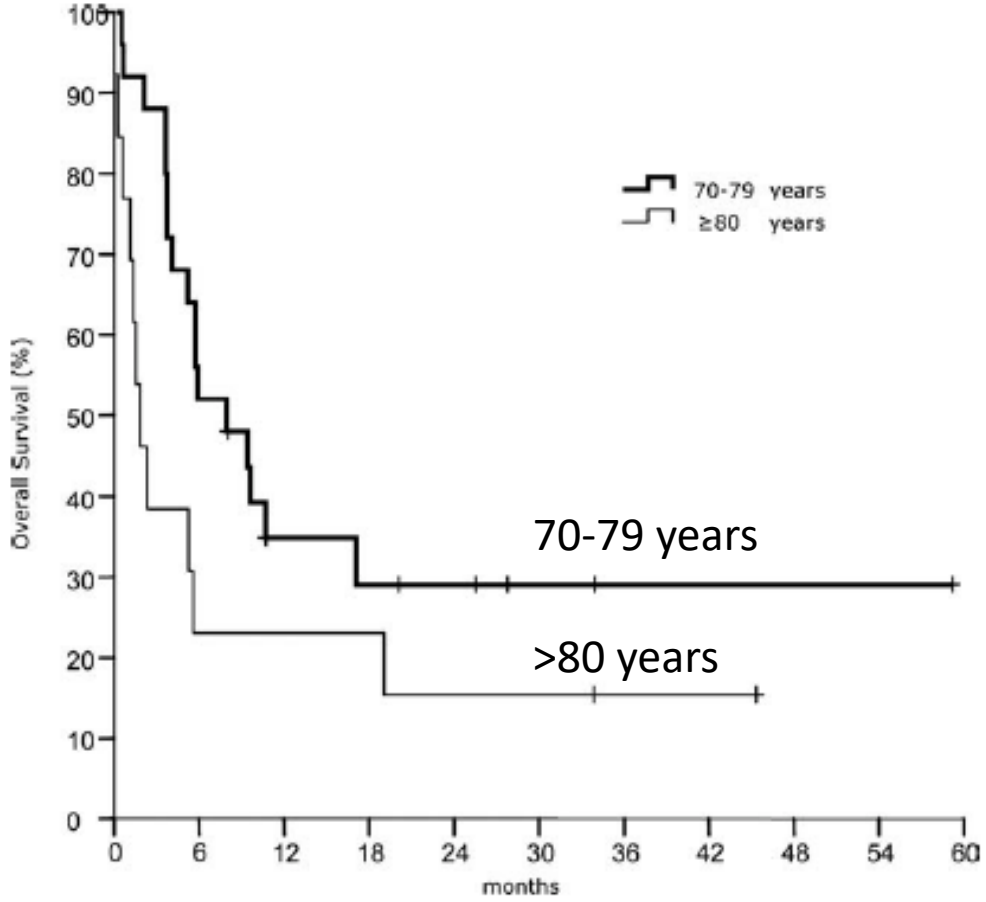




AJH 2011

Outcomes of previously untreated elderly patients with AML: a propensity score-matched comparison of clofarabine vs. FLAG

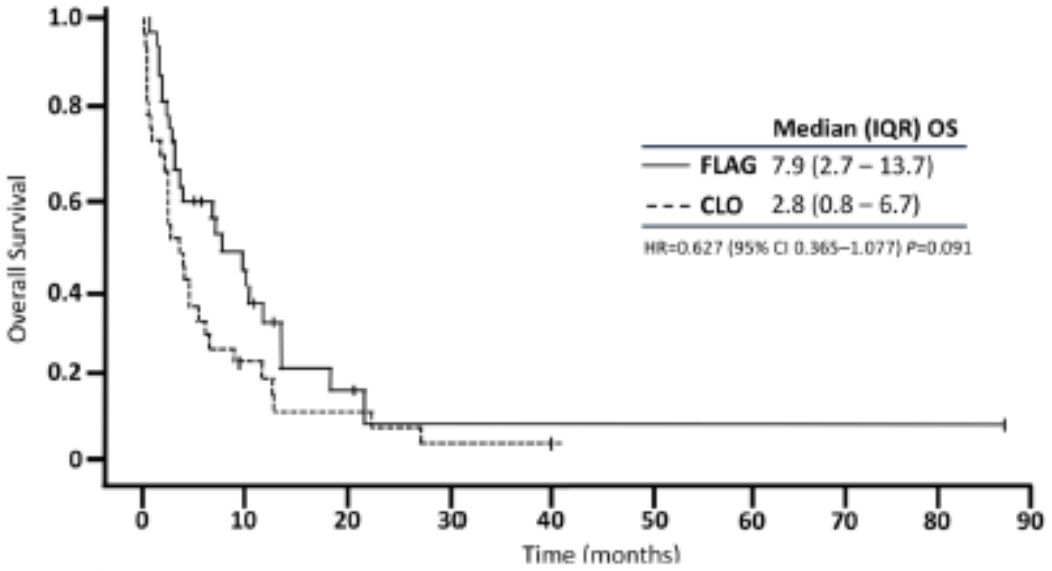
ORR: **65.6% (FLAG)** vs **37.5% (CLOFA)**
alloHSCT: **19% vs 8.3%**
30 day mortality: 3.1% vs 21.9%

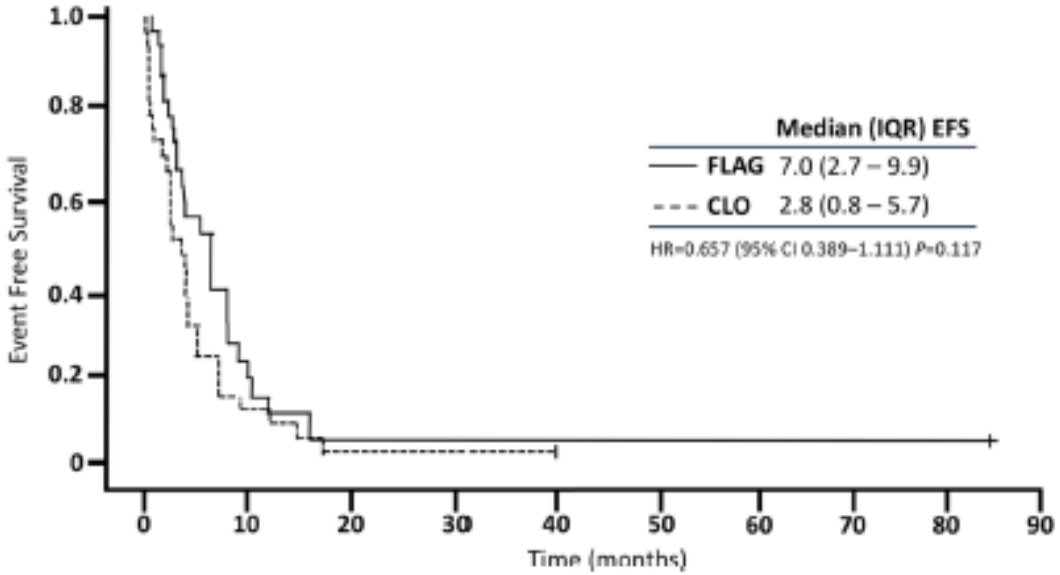
Induction response	FLAG [N = 32]	Clofarabine [N = 32]	P value
CR/CRi	21 (65.6%)	12 (37.5%)	0.045[b]
CR	18 (56.3%)	10 (31.3%)	0.077
CRi	3 (9.4%)	2 (6.3%)	1.000
Resistant disease	11 (34.4%)	20 (62.5%)	0.045[b]
Days to CR[a]	34 (32–38)	33 (26–41)	0.646
De novo AML CR/CRi	8 (88.9%)	5 (41.7%)	0.067
sAML CR/CRi	13 (56.5%)	7 (35%)	0.223
2 induction cycles	1 (3.1%)	3 (9.4%)	0.613
CR duration[a] (months)	5.5 (2.9–8)	5.3 (2.9–12)	0.897
Induction modifications[c]	0 (0%)	6 (18.8%)	0.024[b]
Consolidation after CR	[N = 21]	[N = 12]	P value
Chemotherapy only	10 (47.6%)	7 (58.3%)	0.721
alloHCT after chemotherapy	1 (4.8%)	0 (0%)	1.000
Number induction cycles[a]	1.5 (1–2)	1 (1–2)	0.389
1 cycle	2 (9.5%)	2 (16.7%)	0.610
2 cycles	9 (42.9%)	4 (33.3%)	0.719
3 cycles	0 (0%)	1 (8.3%)	0.364
alloHCT only	4 (19%)	1 (8.3%)	0.630
Total alloHCT	5 (23.8%)	1 (8.3%)	0.379
No consolidation	5 (23.8%)	4 (33.3%)	0.691
Dose reduction	0 (0%)	1 (8.3%)	0.364
Relapse	14 (66.7%)	7 (58.3%)	0.716

Grade 3/4 toxicities	FLAG [N = 32]	Clofarabine [N = 32]	P value
SCr increase	0 (0%)	1 (3.1%)	1.000
Hepatotoxicity	9 (28.1%)	18 (56.3%)	0.042[b]
T. bilirubin increase	2 (6.3%)	4 (12.5%)	0.672
AST increase	5 (15.6%)	15 (46.9%)	0.014[b]
ALT increase	7 (21.9%)	16 (50%)	0.036[b]
Neurotoxicity	0 (0%)	0 (0%)	1.000
Total hospital LOS, days[a]	27 (23–33.5)	29.5 (22.5–38)	0.397
ICU admission	7 (21.9%)	9 (28.1%)	0.774
Duration ICU, days[a]	9 (3–15.5)	3 (1–3)	0.142
Febrile neutropenia	31 (96.9%)	30 (93.8%)	1.000
Duration of neutropenia, days[a]	18.5 (14.5–24)	30 (21.5–38.5)	0.002[c]
Bacteremia	14 (43.8%)	14 (43.8%)	1.000
30-day mortality	1 (3.1%)	7 (21.9%)	0.053
Overall mortality	24 (75%)	30 (93.8%)	0.082

Scappaticci G et al, Ann of Hematol 2018

Outcomes of previously untreated elderly patients with AML: a propensity score-matched comparison of clofarabine vs. FLAG





Scappaticci G et al, Ann of Hematol 2018

blood advances

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A Randomised Comparison of CPX-351 and FLAG-Ida in Adverse Karyotype AML and High-Risk MDS: The UK NCRI AML19 Trial

1. In high-risk AML and MDS CPX-351 did not improve response or survival compared to FLAG-Ida but produced better relapse-free survival

2. In the exploratory sub-group of patients defined by the presence of mutations in MDS-related genes CPX-351 improved overall survival

Othman J et al, Blood Adv 2023

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	FLAG-IDA (n=82)	CPX-351 (n=105)
Median age, years (range)	55 (18-67)	57 (23-70)
Age group		
<39	14 (17%)	9 (8.6%)
40-49	12 (15%)	16 (15%)
50-59	34 (41%)	51 (48%)
60+	22 (27%)	29 (28%)
Female sex	34 (41%)	45 (43%)
Diagnosis		
De Novo AML	42 (51%)	50 (48%)
Secondary AML	17 (21%)	21 (20%)
High Risk MDS	23 (28%)	34 (32%)
Prior history		
History of prior cytotoxic / radiotherapy	9 (11%)	7 (6.8%)
History of MDS/MPN	17 (21%)	16 (16%)

Othman J et al, Blood Adv 2023

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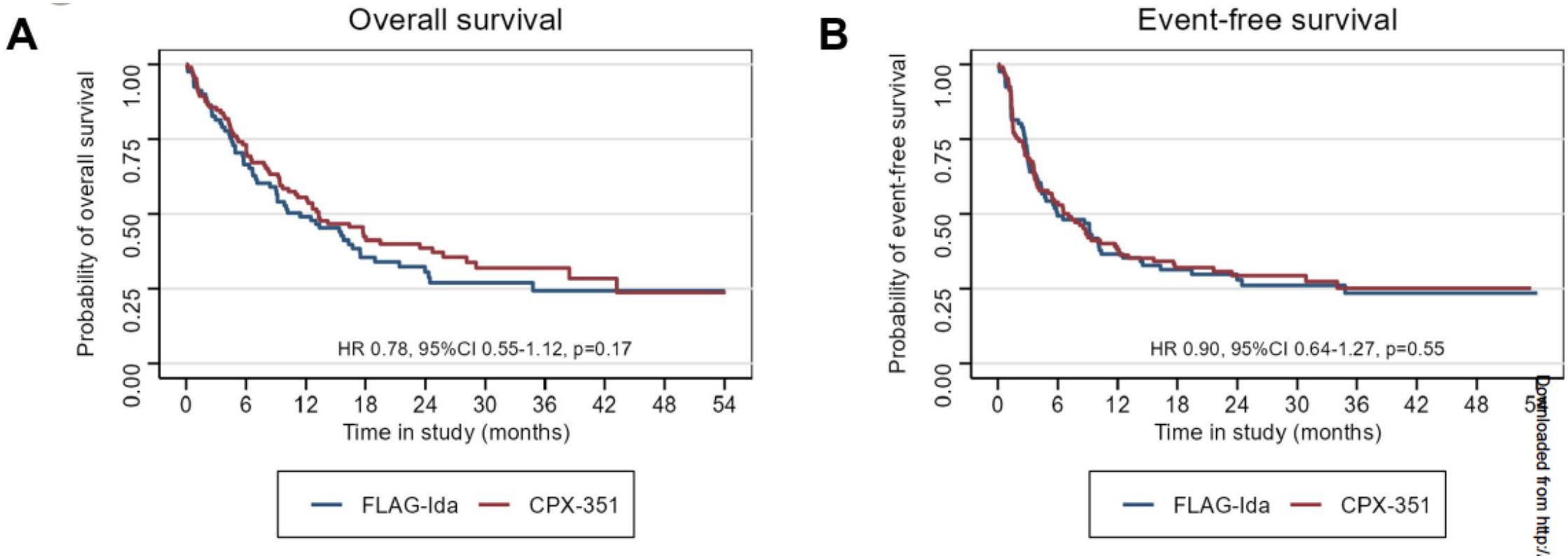

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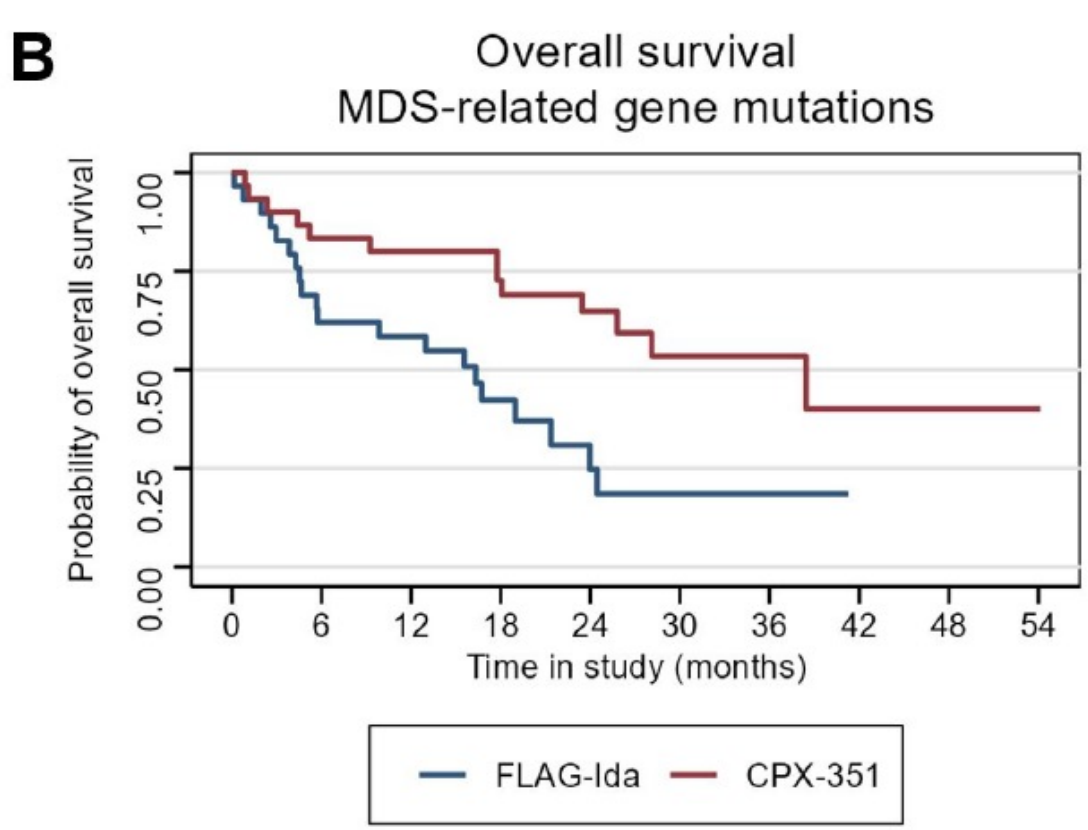
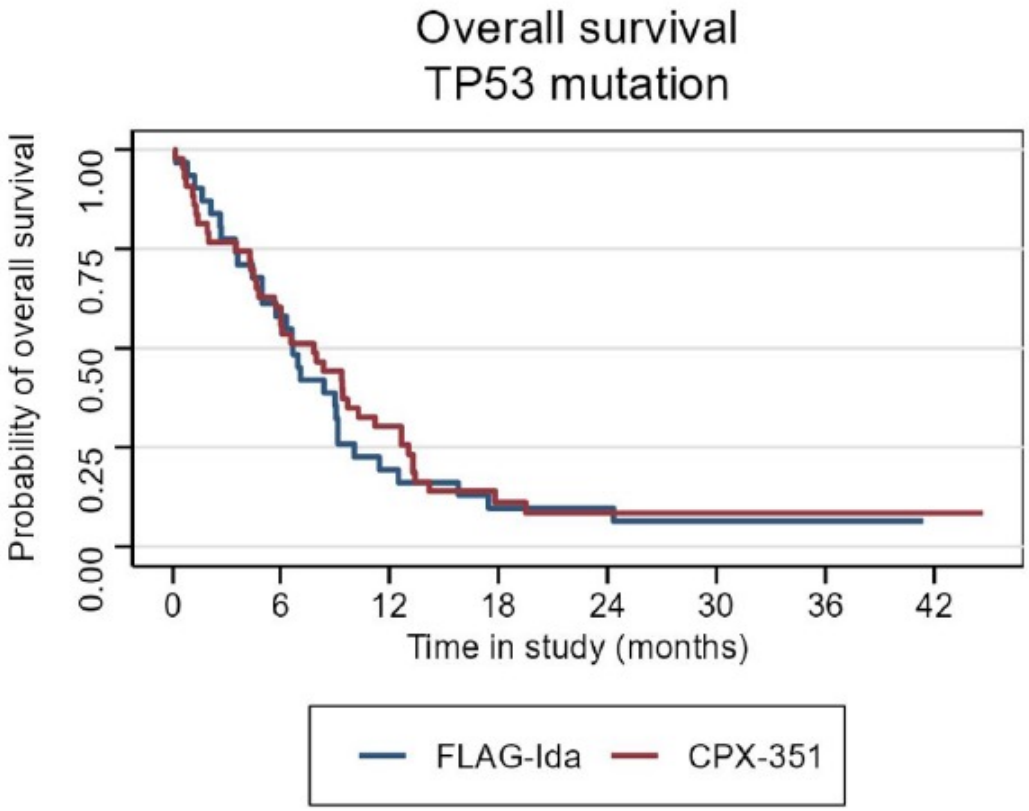
A Randomised Comparison of CPX-351 and FLAG-Ida in Adverse Karyotype AML and High-Risk MDS: The UK NCRI AML19 Trial

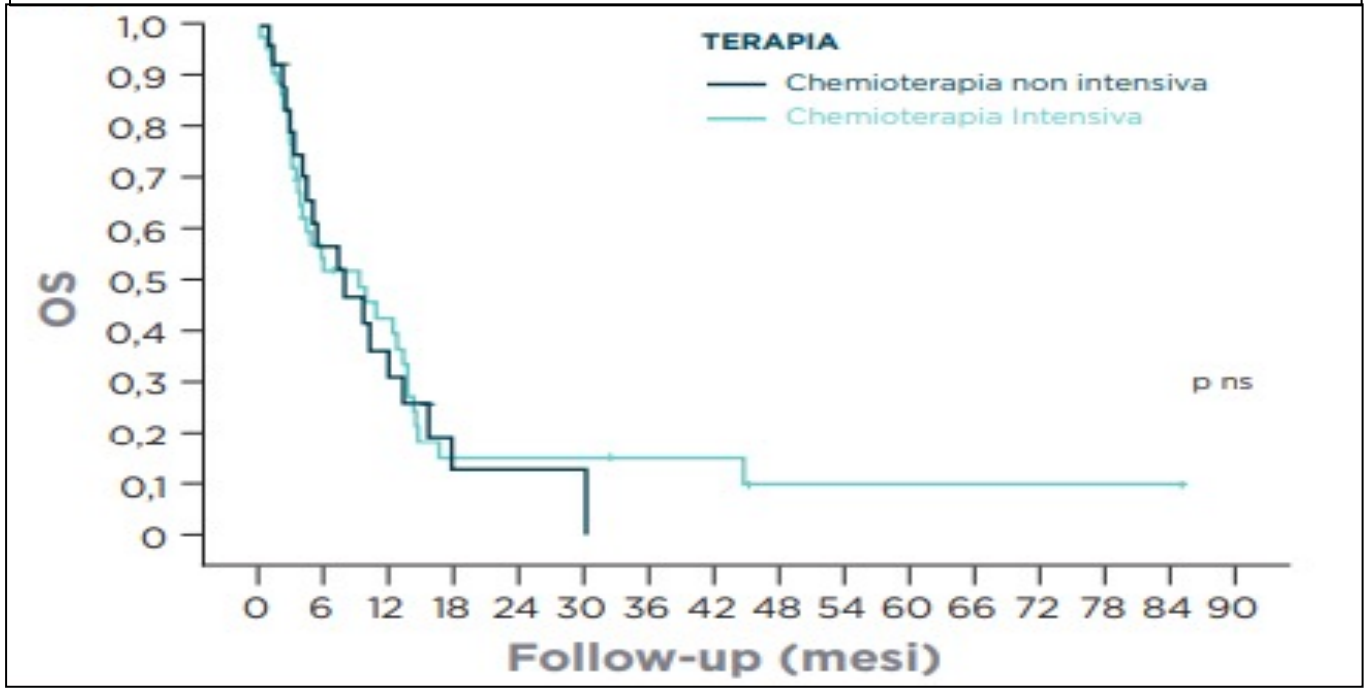




Othman J et al, Blood Adv 2023

Biological fitness plays a key role in elderly HR patients

OS in fit patients with adverse cytogenetic risk stratified by treatment



Median OS in FIT patients with adverse cytogenetic risk:

Intensive chemotherapy: **9.2 months** (CI 95%: 2,7–15,8)

***p*=ns**

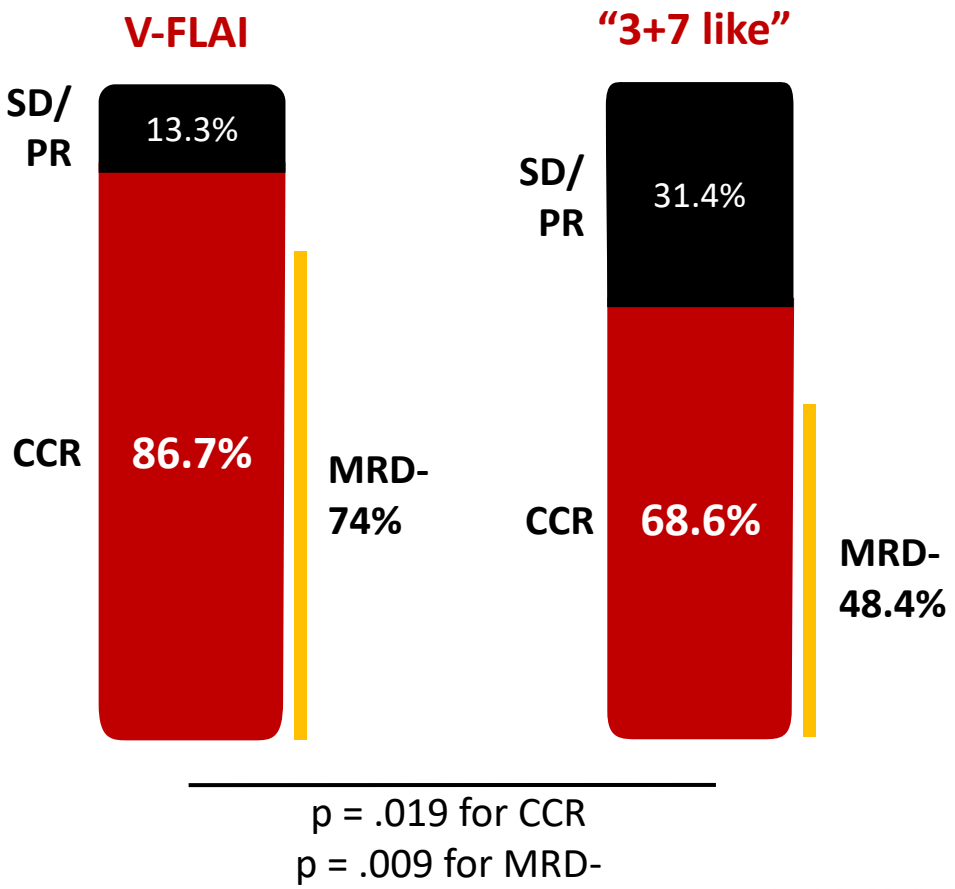
Non-intensive chemotherapy: **7.8 months** (CI 95%: 1,9–13,7)

NEW APPROACHES ARE REQUIRED!

Borlenghi E et al. J Geriatr Oncol 2021

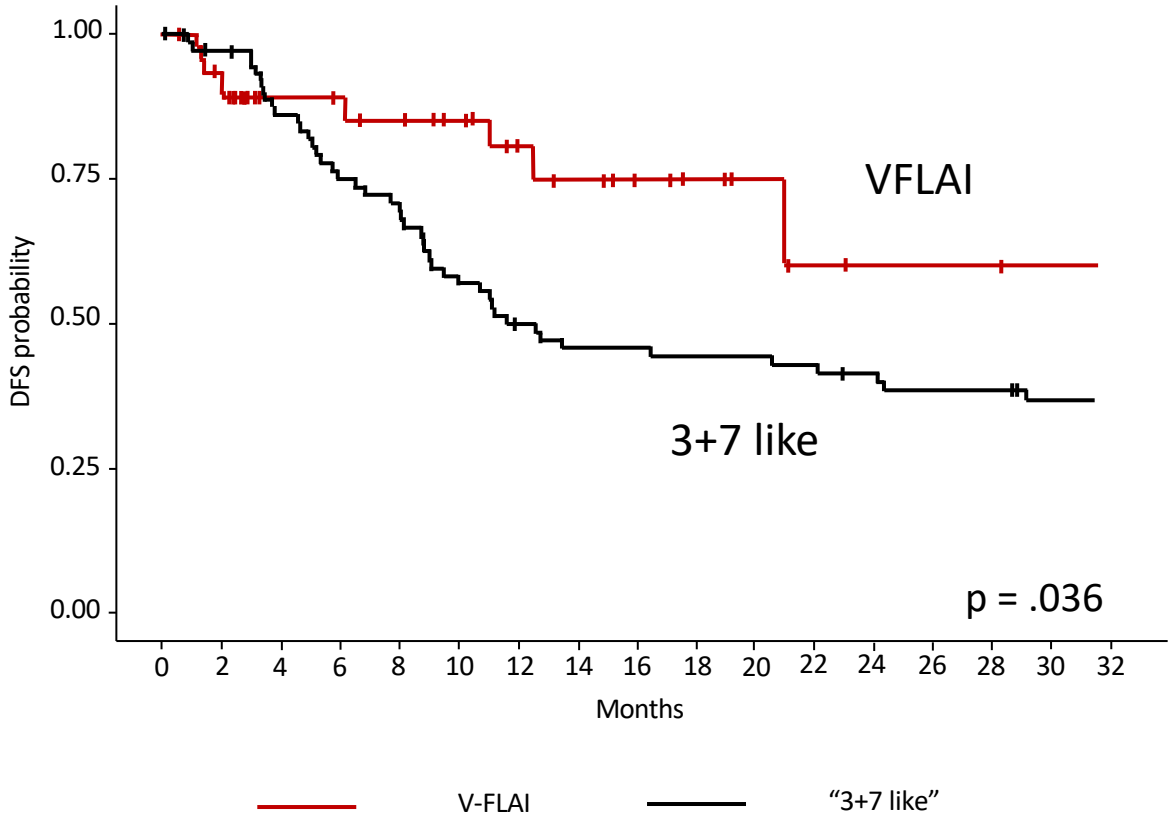
59 The Addition of Venetoclax to Induction Chemotherapy in No Low-Risk AML Patients: A Propensity Score-Matched Analysis of the Gimema AML1718 and AML1310 Trials

CCR



p = .019 for CCR
p = .009 for MRD-

DFS

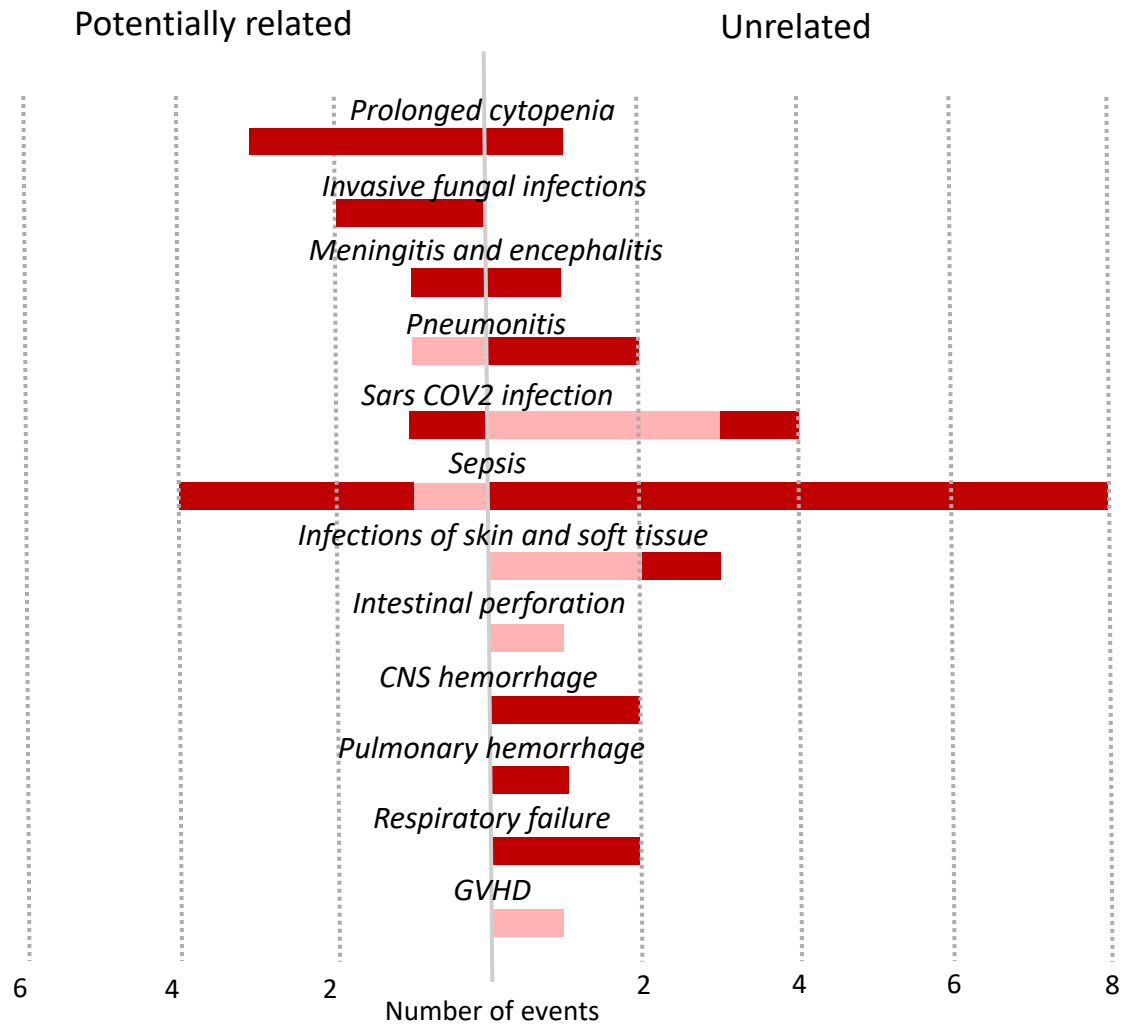


fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

64th ASH Annual Meeting and Exposition
December 10 – 13, 2022 • New Orleans, Louisiana

Piciocchi A et al, ASH 2022

Safety



1.8%

30-days mortality

5.3%

60-days mortality

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Marconi G et al, ASH 2022

Take-home message

- **Age** should **not be the only determining factor** in the choice of treatment for elderly **(importance of biology)**

- Need for applicable and reproducible **fitness algorithms** aimed to better identify older patients who potentially could benefit from intensive treatment

- **IC** remains the treatment strategy offering better chances for prolonged survival in **fit elderly patients and FLAI/FLAGIDA as induction is a valuable option (offering high CR rates), mostly for those pts who can proceed to an alloSCT (interaction with BMT unit is mandatory!)**

- However, in **elderly patients disease biology should drive our choices** (eg CPX for AML with MDS related genes)

- **New approaches, beyond chemotherapy, are required** for those patients (eg TP53 mut) who, despite an excellent fitness, are not likely to respond to IC

- **Maintenance therapy** should be contemplated in the therapeutic algorithm for **elderly AML patients after achieving CR/CRi with intensive treatment**

Thank you!

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