Treatment of Fit and Unfit Acute Myeloid Leukemia Patients : An introduction

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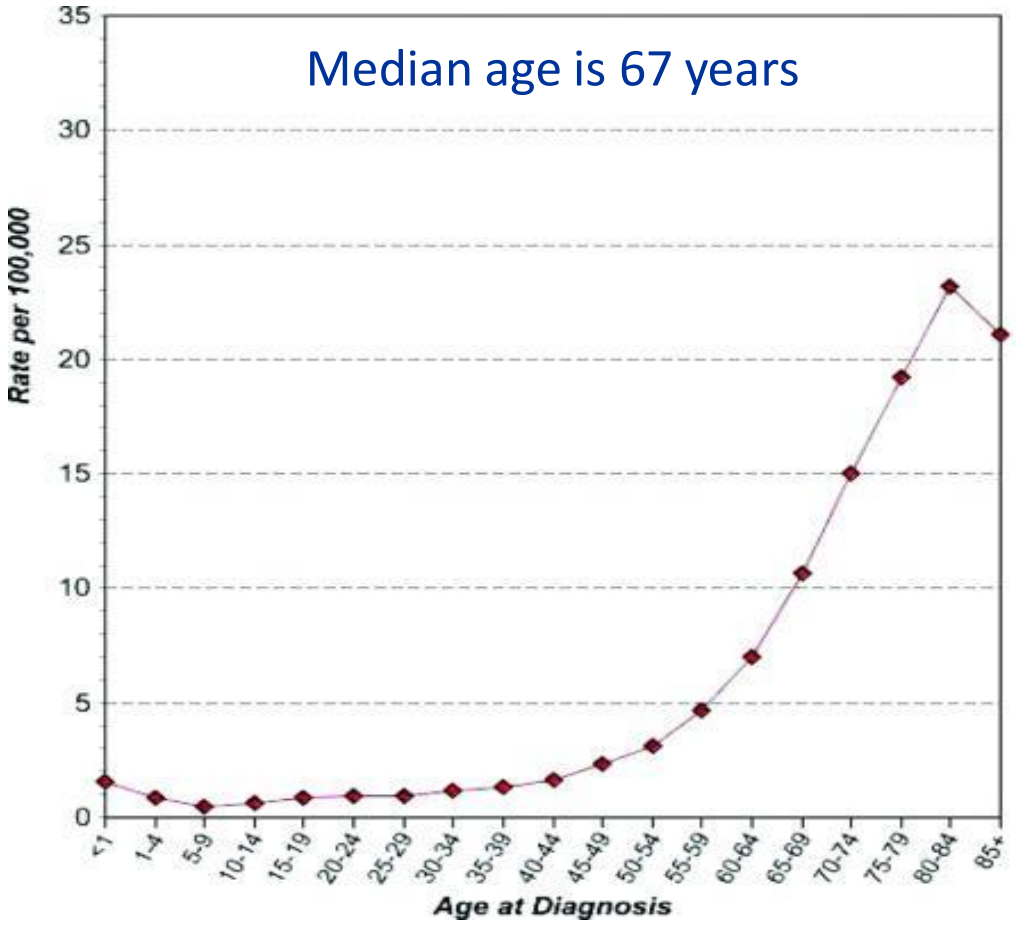
Incidence of AML as a function of age
2000-2005 Surveillance Epidemiology and End Results (SEER) Data



Klepin HD, Balducci L. The Oncologist 2009; 14: 222-232

Initial approach to a patient with a newly diagnosed acute myeloid leukemia

Initial approach to a patient with a newly diagnosed acute myeloid leukemia

- choosing the right patient for intensive treatment :

PATIENT CHARACTERISATION

- pulmonary function
- cardiac ultrasound
- extended laboratory work up (liver, kindney, serology,….)

- choosing targeted treatment in function of molecular targets

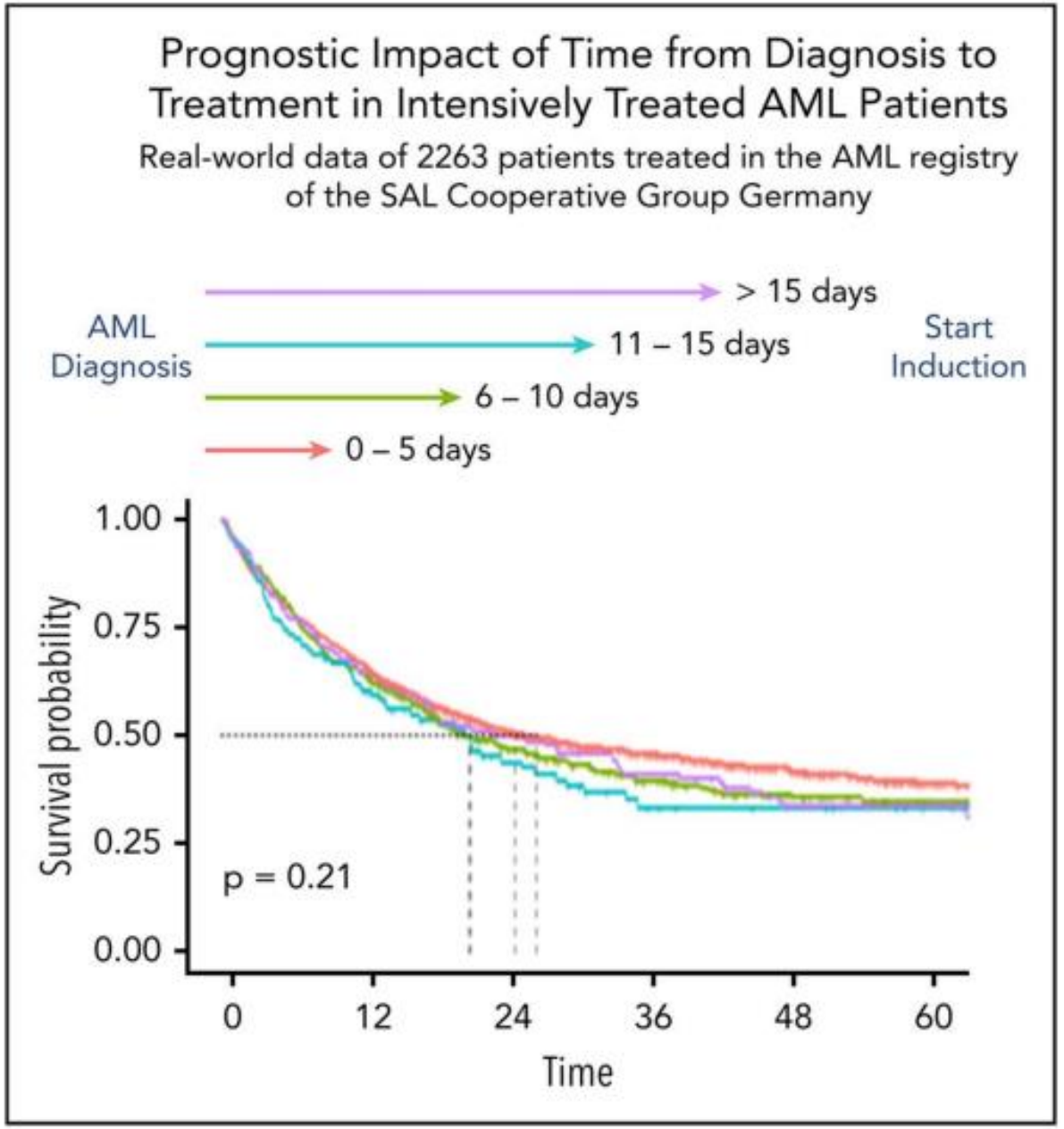
DISEASE CHARACTERIZATION

- Karyotype
- Flt3 and NPM1 PCR
- NGS

Table 5. 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Initial approach to a patient with a newly diagnosed acute myeloid leukemia



Rollig et al. Blood 2020; 136: 823-30

TAKE YOUR TIME : EXCEPTIONS!

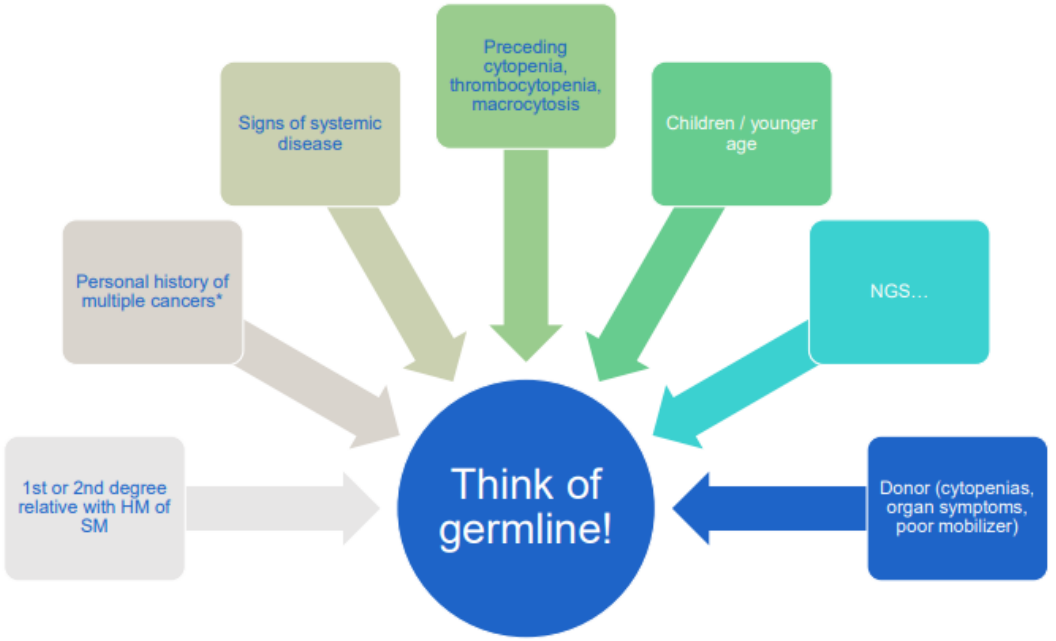
Life-threatening complications of AML: DIC, end-organ failure, infections (?), …

Hyperleukocytic acute leukemia (>100 K) uncontrolled by hydroxycarbamide

(suspicion of) Acute promyelocytic leukemia

Hereditary Myeloid Malignancy Syndromes (HMMS)

- 5-10% of AML/MDS diagnosis
- 3 subtypes :
  - Inherited bone marrow failure syndromes (IBMF)
  - Cancer Predisposition Syndromes
  - Familial MDS/AL syndrome



Hereditary myeloid malignancy syndrome: importance

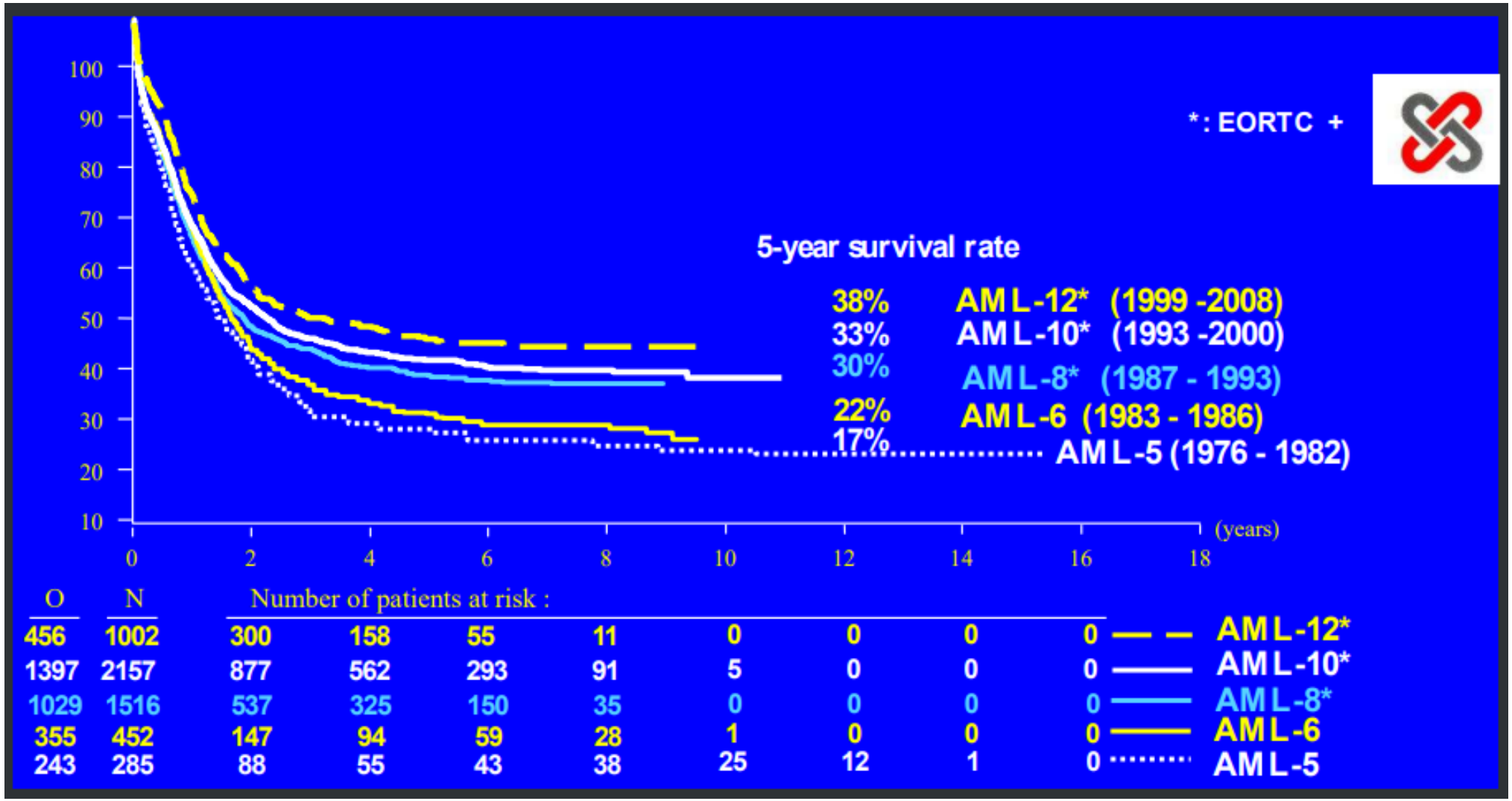
Avoid allogeneic transplantation with an asymptomatic HMMS mutation carrying related donor

Genetic counceling of (affected) family members

Even with high suspicion of HMMS, but no detectable mutation in the family, a matched unrelated donor is prefered over a family member

INTENSIVE TREATMENT OF ACUTE MYELOID LEUKEMIA

5 year Survival in young AML patients over time



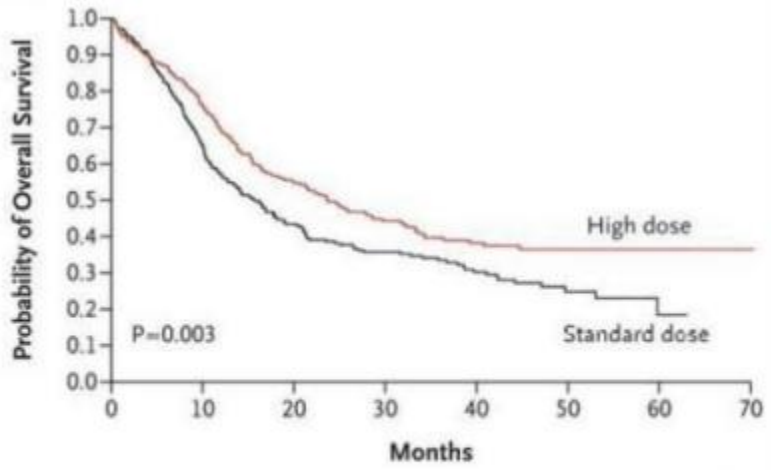
Induction therapy : 7 + 3

- Dosing cytarabine : 100-200 mg/m² in continuous infusion
- Choosing and Dosing anthracyclines
- Introduction of Flt3 inhibitors
- Introduction of Gemtuzumab Ozogamycin
- CPX 351 (Vyxeos)
- Venetoclax – Azacytidine
- Ivosidenib

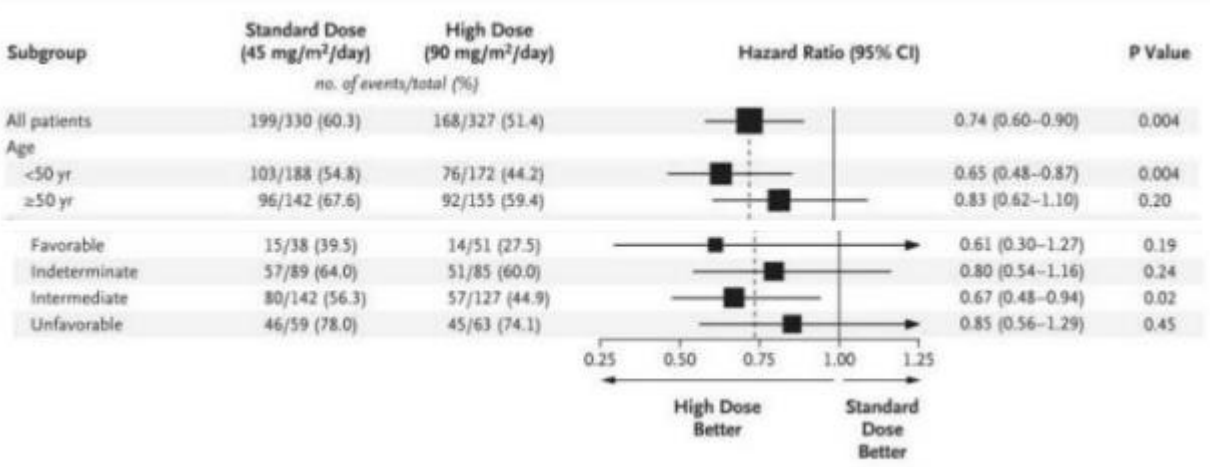
Dosing Daunorubicine?

- Fernadez et al, NEJM2009, 361 : 1249-1259
  - Randomized 330 patients (<60)

90 >45



Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	330	199	131	15.7 mo
High dose (90 mg/m²/day)	327	168	159	23.7 mo



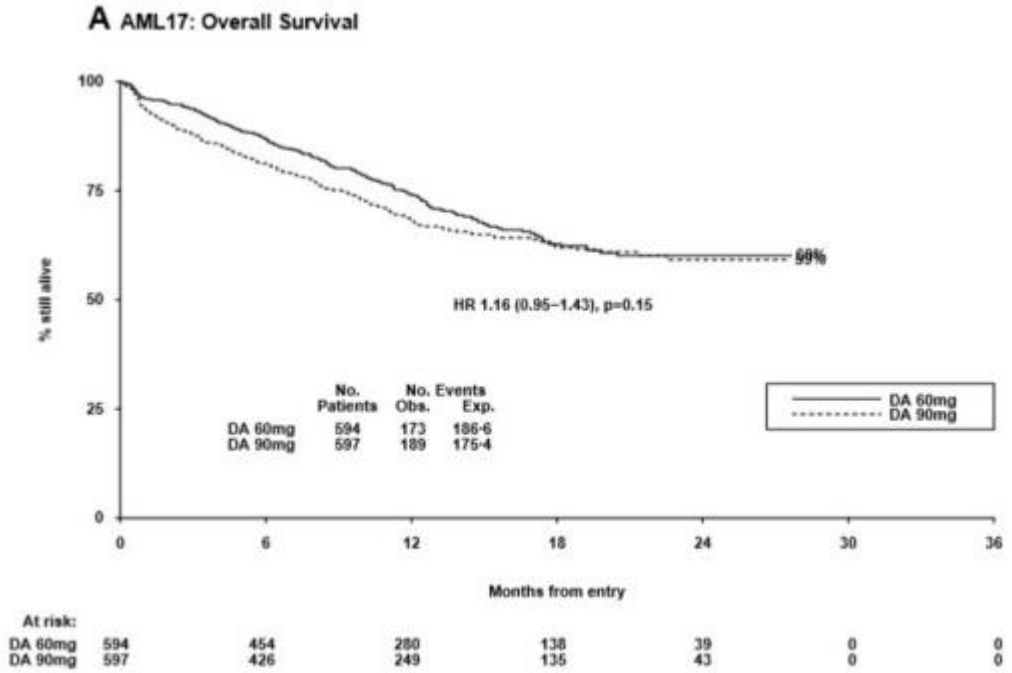
	45 mg/m²	90 mg/m²
CR	57%	71% (P < 0,01)
Median OS	16m	24m (P=0,003)

Mainly :
- Favorable and intermediate risk
- patients < 50 yo

Dosing Daunorubicine?

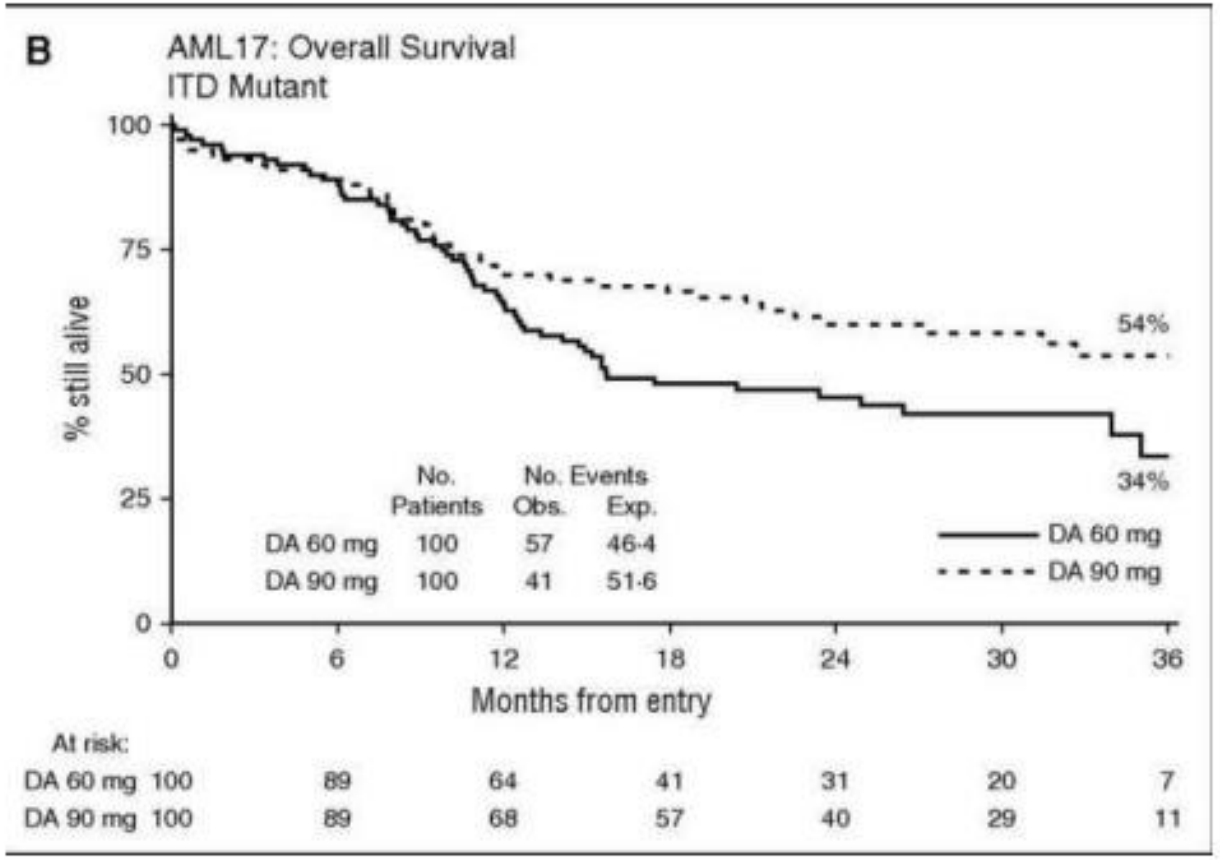
60=90

- MRC AML 17 trial (Burnett et al, Blood April 2015) : 60 vs 90 mg/m²
  - <60
  - Induction 90 or 60; consolidation 50 mg/m²



Equal CR rates
60 day mortality higher in 90 mg group (HR1.98)
Equal 2 y OS

Dosing Daunorubicine?



90>60

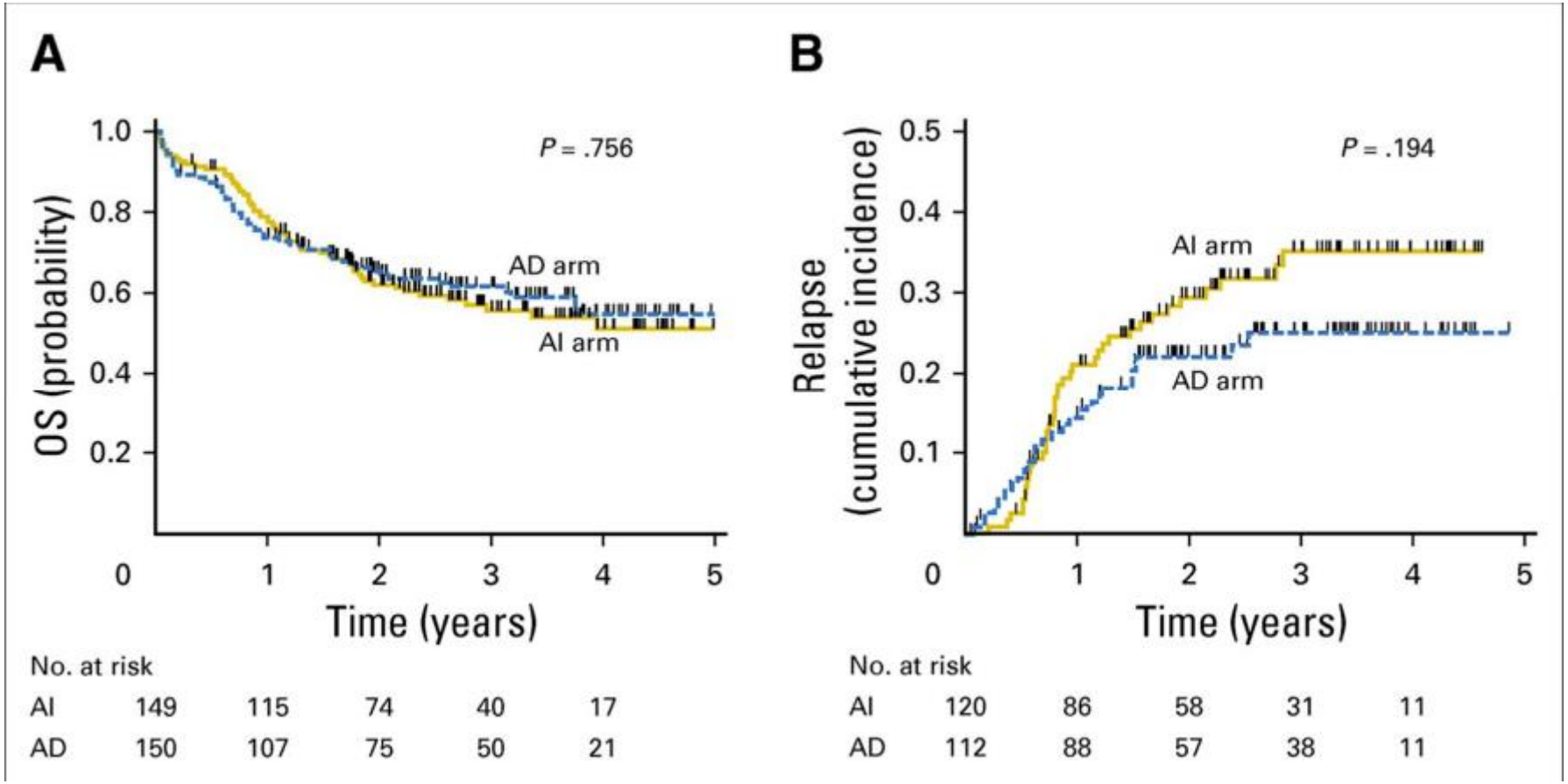
In Flt 3-ITD

Burnett et al , Blood 2016

Which Anthracycline?

Ida 12 = Dauno 90

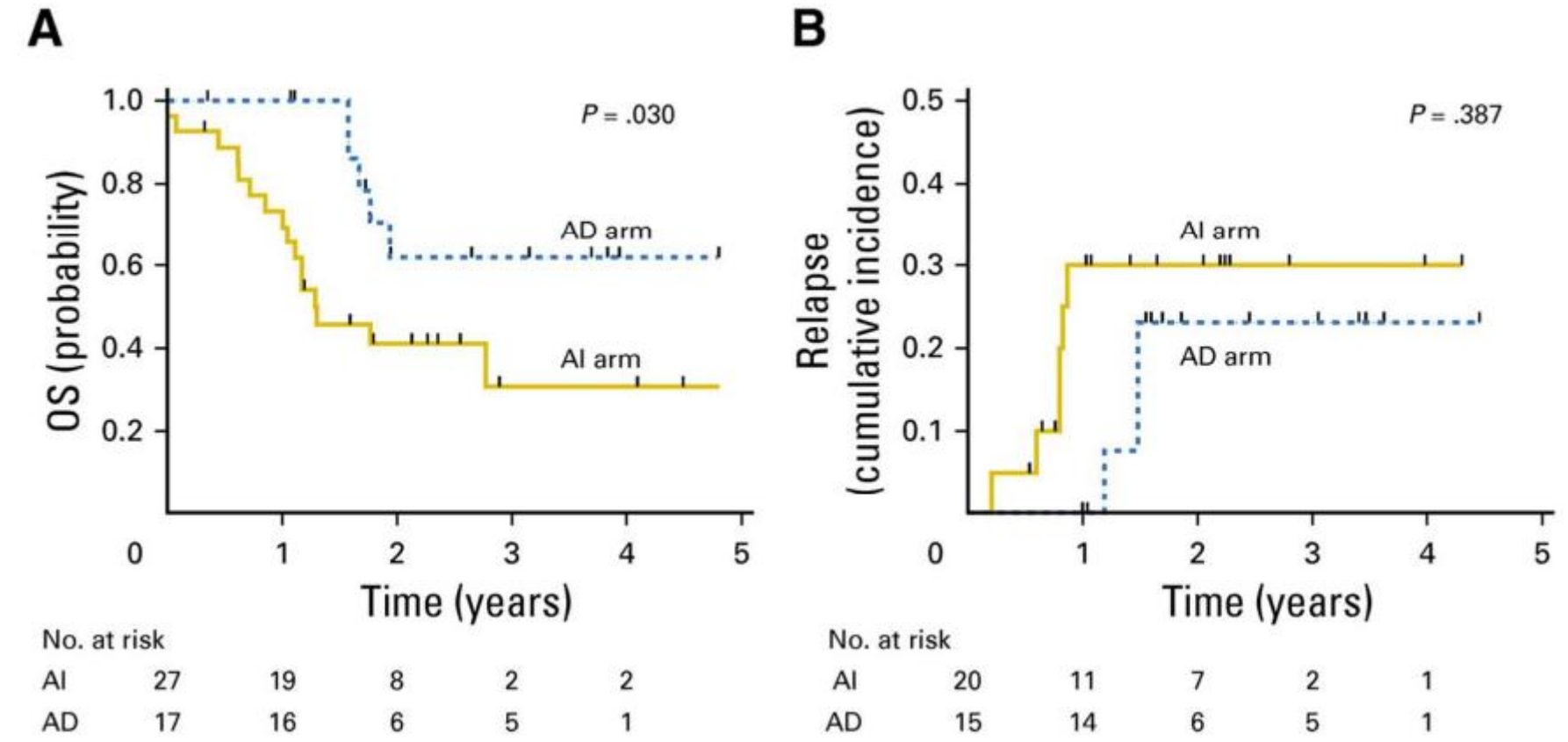
- Lee et al, JCO 2017



Which anthracycline?

Ida 12 < Dauno 90 In Flt3 - ITD

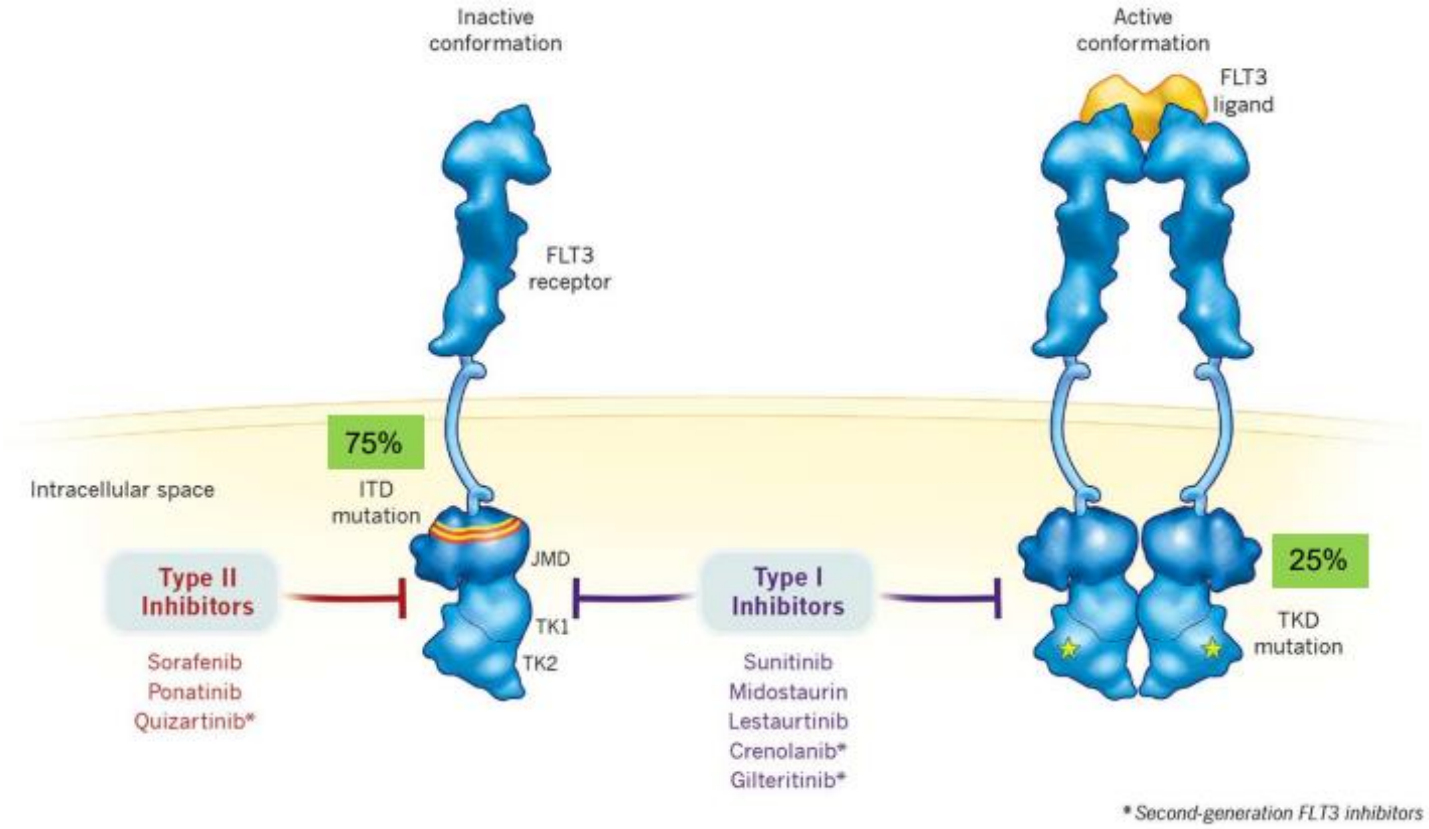
- Lee et al JCO 2017



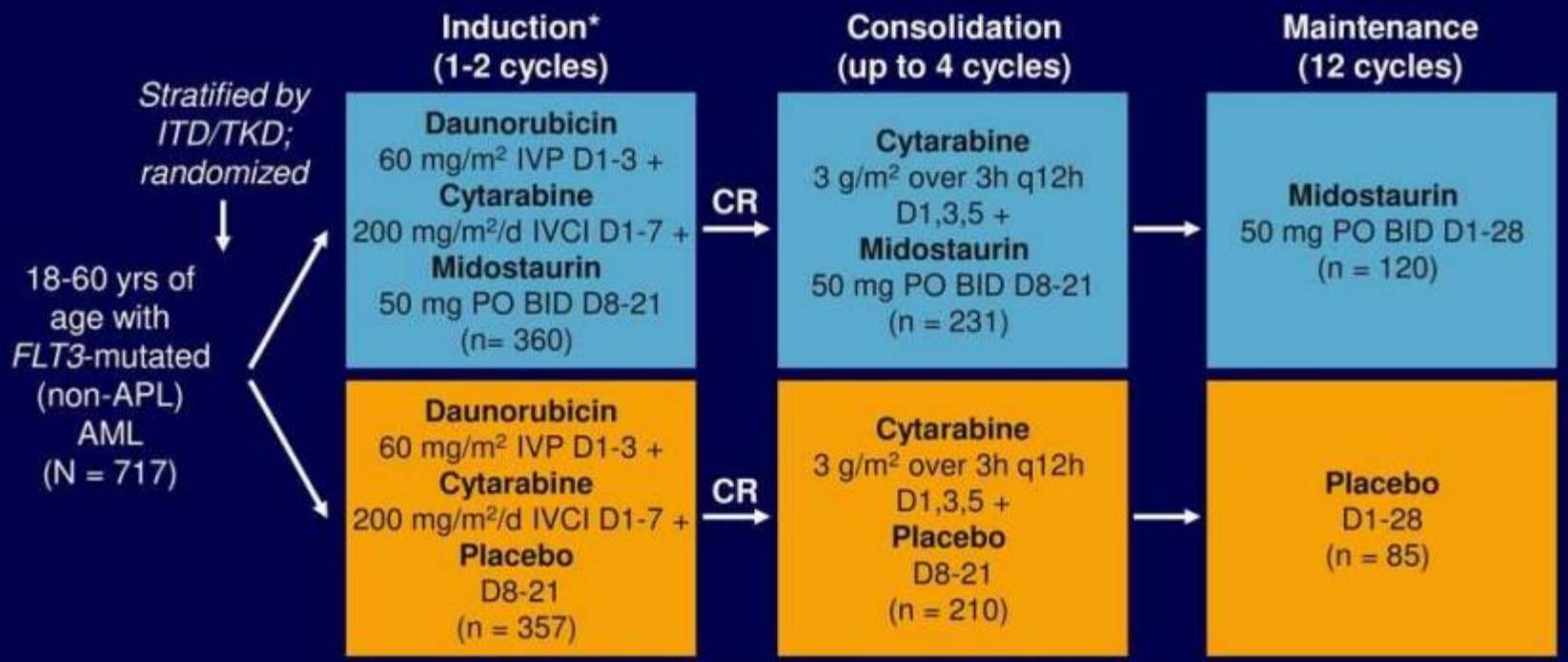
WHICH ANTHRACYCLINE?

- Idarubicine might be preferred in induction in younger patients
- When using daunorubicine : use 60mg/m²
- In Flt3-ITD positive patients : prefer dauno 90>dauno 60>ida12

Introducing FLT3 inhibitors



RATIFY: Study Design

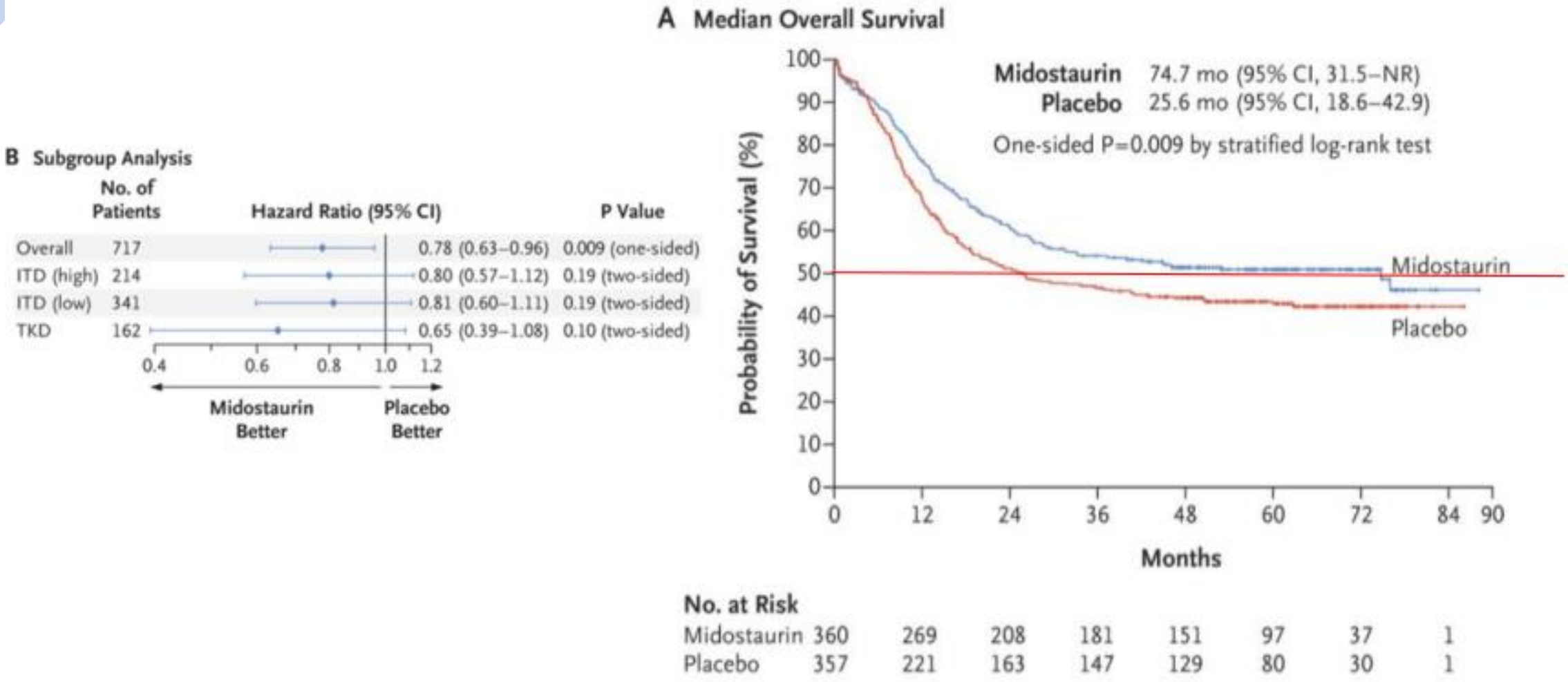


*Hydroxyurea allowed for ≤ 5 days prior to induction therapy.

- Double-blind, placebo-controlled, randomized phase III study
  - Primary endpoint: OS (not censored for SCT)
  - Secondary endpoint: EFS

Stone RM, et al. ASH 2015. Abstract 6.

Slide credit: clinicaloptions.com

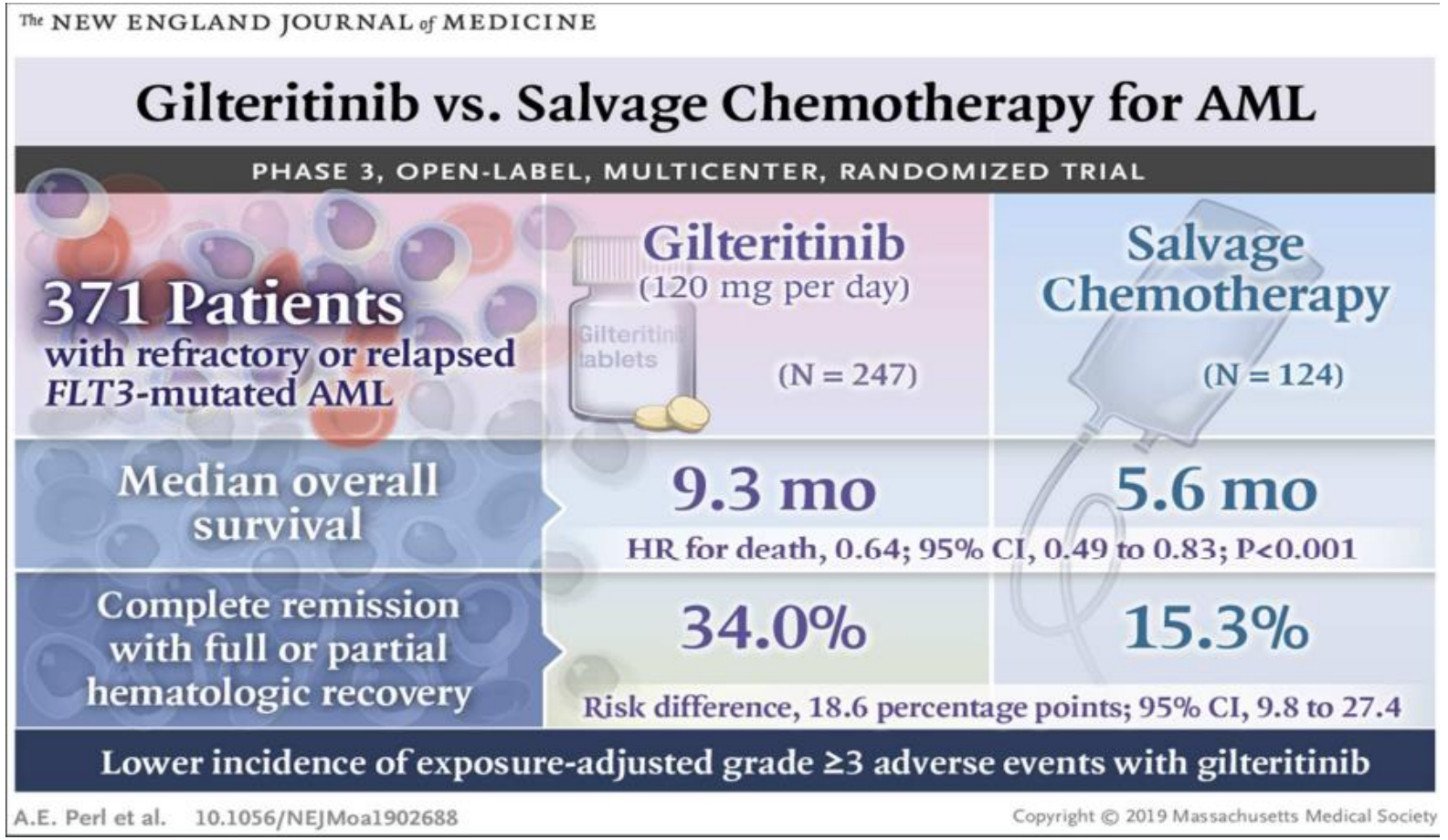


Stone et al, NEJM 2017; 377(5) 454-464

RATIFY : limitations

- Median duration of trial treatment was 3 months : effect was mainly in reduction of initial disease burden – trial not designed to evaluate effect of maintenance
- Maintenance was only foreseen in non alloSCT patients
  - 57% patients was allografted (intially not standard treatment – more allografting in the midostaurin arm)
- More adverse events in Midostaurin treated patients (anemia, rash, QTc prolongation,…)

Gilteritinib



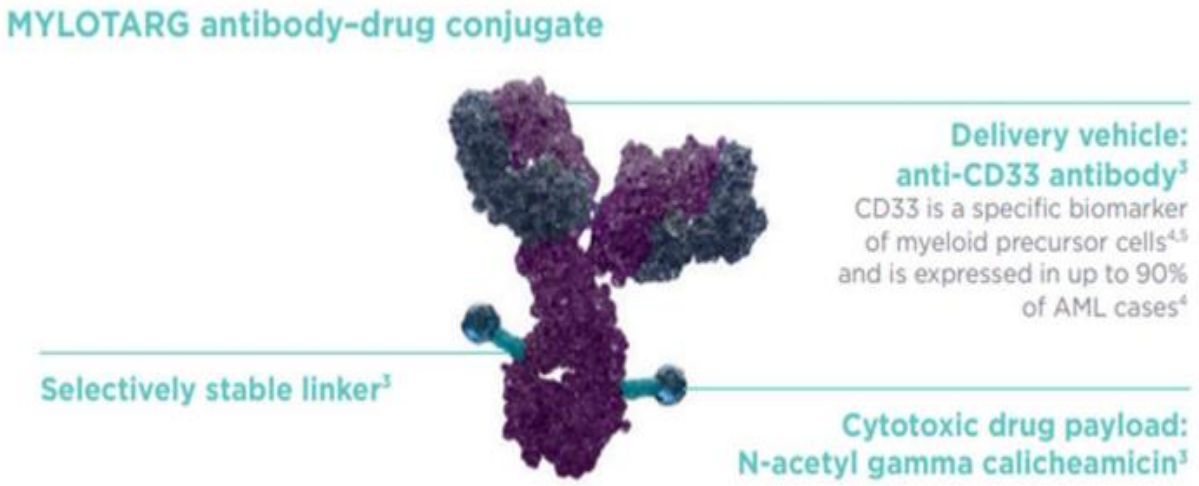
Quizartinib

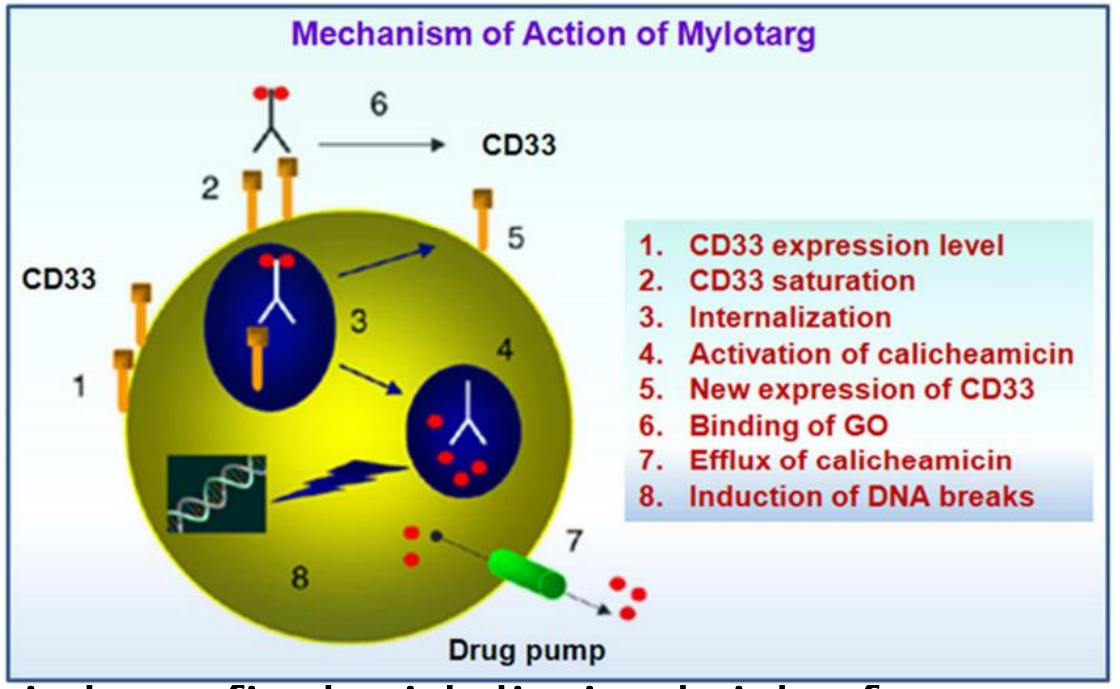
- Quantum first trial (Erba et al; Lancet, 401, 1571-1583):
  - adults aged 18-75, newly diagnosed Flt3 ITD pos AML, 7+3 + Quizartinib/placebo, allografting permitted, maintenance randomized for all
  - Median OS 31.9 vs 15.9 mths (HR 0,78 – p==0,032)
  - Similar safety
  - Based on these data EMA approval oct 2023

Quizartinib

Gemtuzumab Ozogamycin

- Historically : excess toxicity due to mainly veno occlusive disease



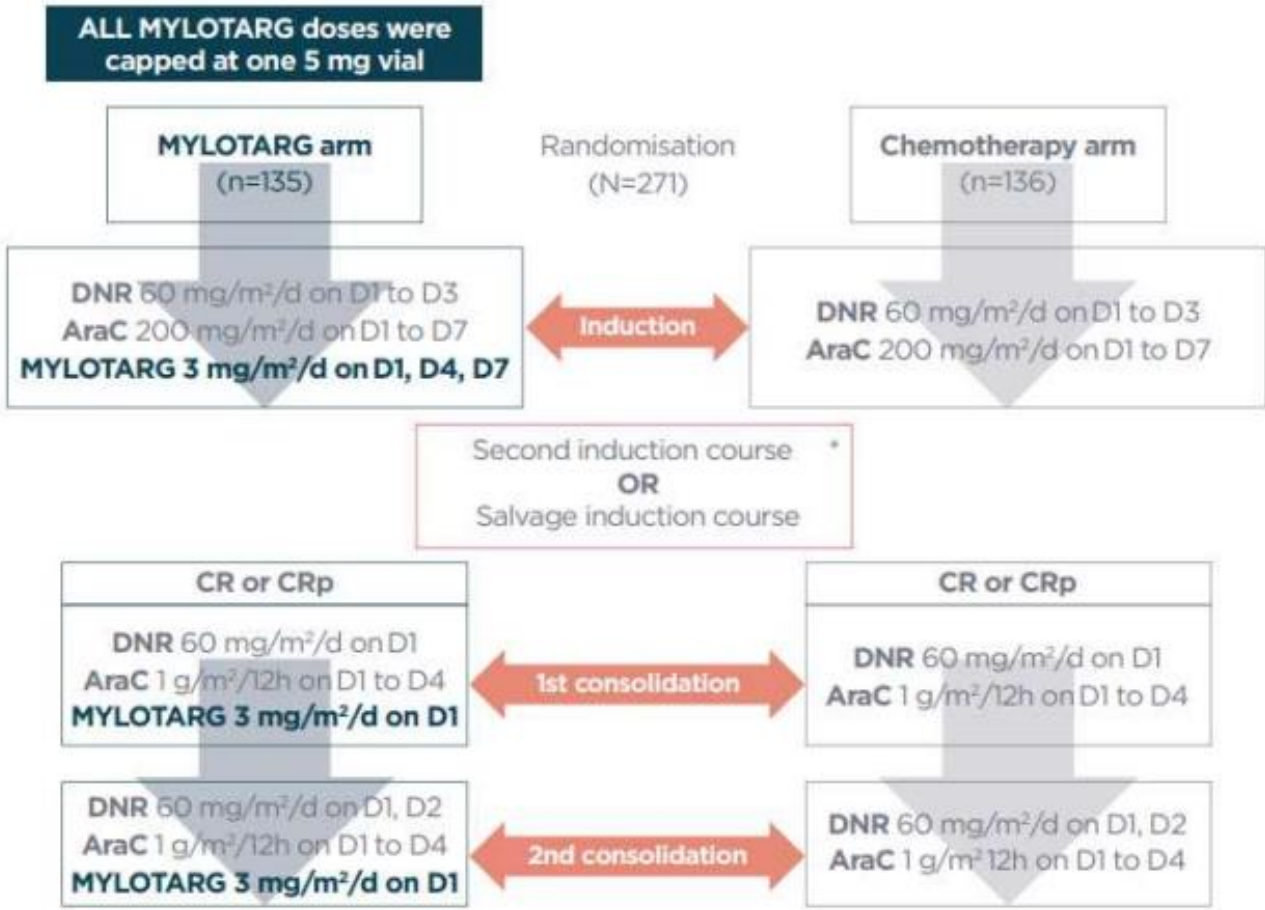


- New data :reduced and fractionated dose is benefical with limited risk of VOD

ALFA 0701 trial

Study design

n = 271
Age 50-70y



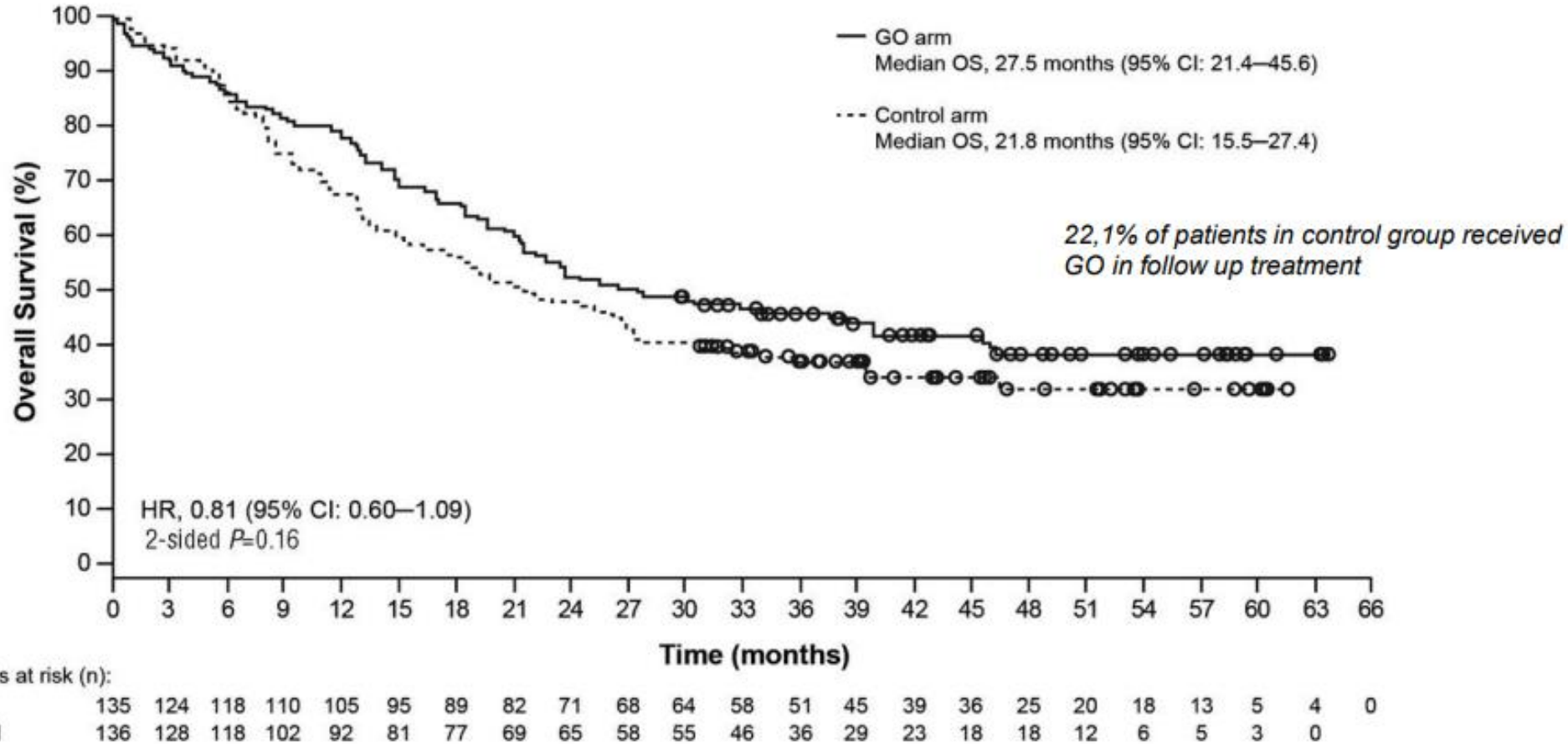
* Second induction course if leukemic blasts persisted at the D15 BMA : DNR 35mg/m²/d on D1-D2, AraC 1g/m²/12h on D1 to D3. Salvage induction course if no CR after induction : idarubicin 12mg/m² on D1-D2, AraC 1g/m² twice daily on D1 to D4.

Lambert J. et al. Haematologica 2019; 104 (1): 113-119

Median follow up 47,6m in Go group
41 months in control group

OS: trend for better OS in GO arm, not significant

ALFA 0701 - Overall survival



Juliette Lambert et al. Haematologica 2019;104:113-119

haematologica
journal of the European Hematology Association
Published by the Ferrata Storti Foundation

ALFA 0701 : adverse events

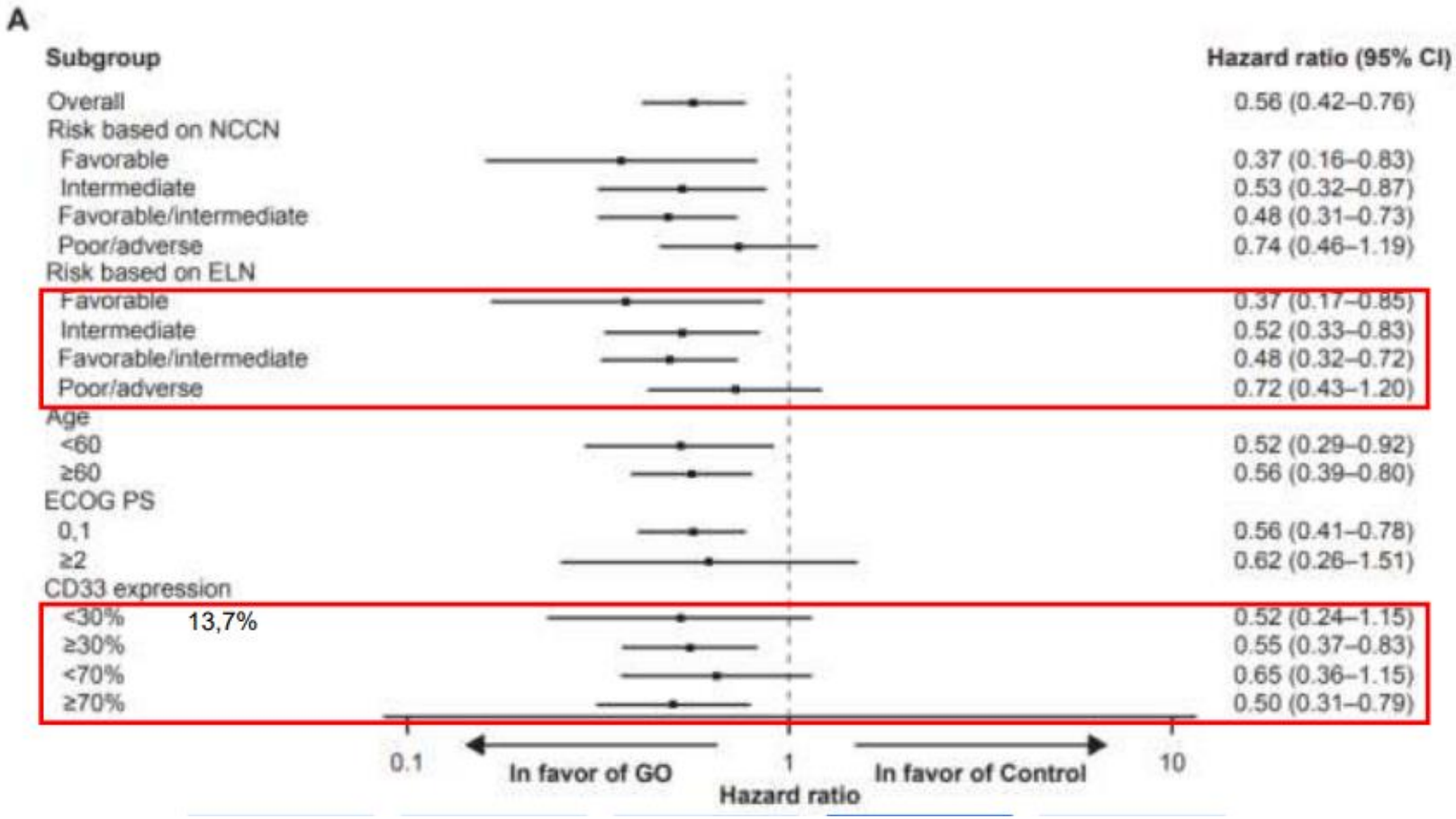
- Both arms : serious infections
- But prolonged thrombocytopenia , with more bleeding events, including more severe bleeding
- VOD : 6 in GO arm, vs 2 in control group (also after GO as FU treatment)

All-causality AEs of special interest in the as-treated population[1]

	MYLOTARG arm (n=131), n (%)	Chemotherapy arm (n=137), n (%)
Infections: Severe (Grade ≥3)	102 (77.9)	106 (77.4)
Haemorrhage: All Grade (Grade ≥1)	118 (90.1)	107 (78.1)
Grade 3	23 (17.6)	12 (8.8)
Grade 4	4 (3.1)	0
Grade 5	3 (2.3)	1 (0.7)
VOD: All Grade (Grade ≥1)	6 (4.6)	2 (1.5)
Grade 3	2 (1.5)	1 (0.7)
Grade 4	1 (0.8)	1 (0.7)
Grade 5	2 (1.5)	0

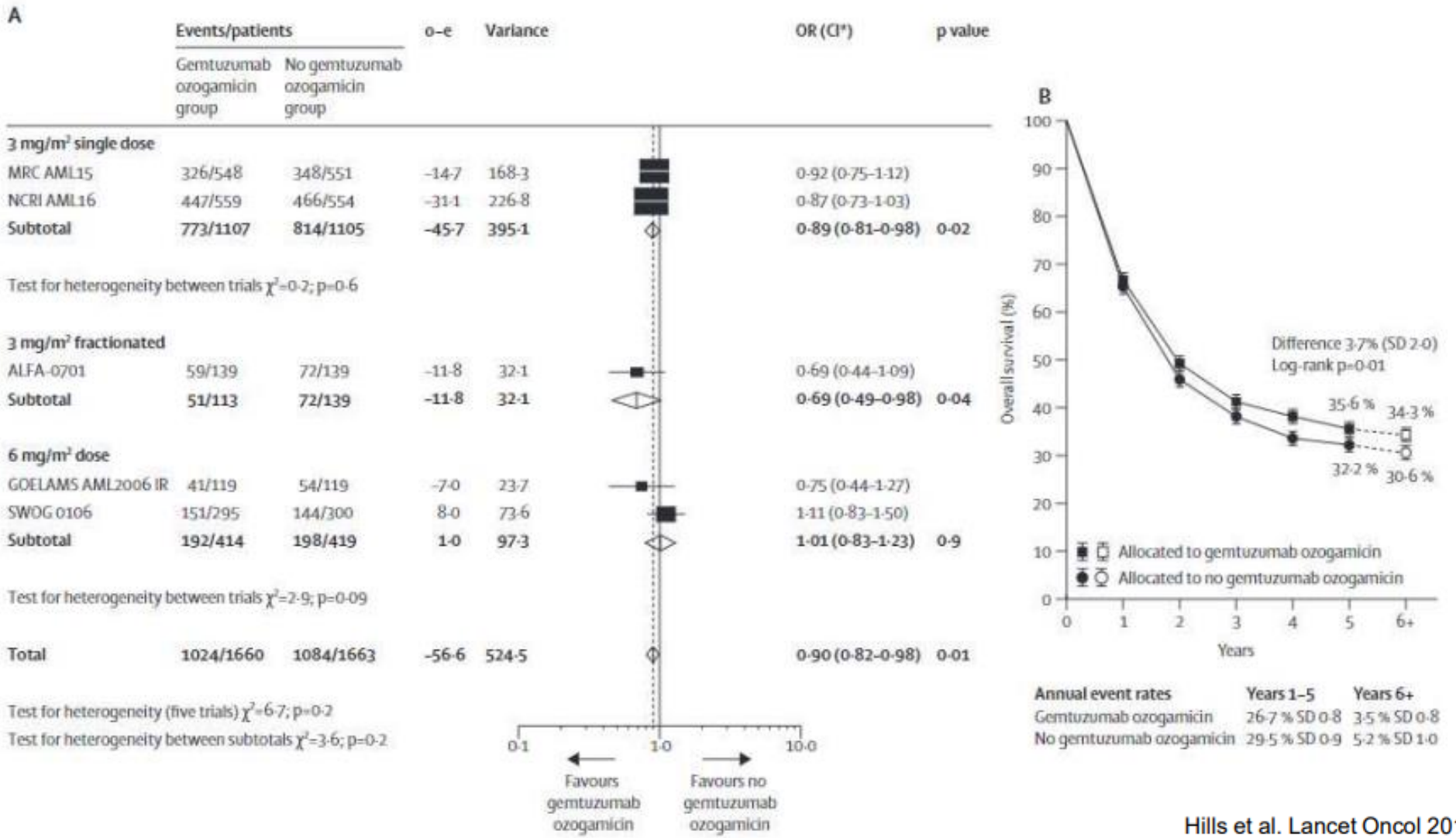
Lambert J. et al. Haematologica 2019; 104 (1): 113-119

ALFA0701 :
Advantage mainly in good/int risk patients



Lambert J. et al. Haematologica 2019; 104 (1): 113-119

GO : Meta analysis



A

	Events/patients: Gemtuzumab ozogamicin group	Events/patients: No gemtuzumab ozogamicin group	o–e	Variance	OR (CI*)	p value
3 mg/m² single dose						
MRC AML15	326/548	348/551	-14·7	168·3	0·92 (0·75–1·12)	
NCRI AML16	447/559	466/554	-31·1	226·8	0·87 (0·73–1·03)	
Subtotal	**773/1107**	**814/1105**	**-45·7**	**395·1**	**0·89 (0·81–0·98)**	**0·02**
Test for heterogeneity between trials χ^2=0·2; p=0·6						
3 mg/m² fractionated						
ALFA-0701	59/139	72/139	-11·8	32·1	0·69 (0·44–1·09)	
Subtotal	**51/113**	**72/139**	**-11·8**	**32·1**	**0·69 (0·49–0·98)**	**0·04**
6 mg/m² dose						
GOELAMS AML2006 IR	41/119	54/119	-7·0	23·7	0·75 (0·44–1·27)	
SWOG 0106	151/295	144/300	8·0	73·6	1·11 (0·83–1·50)	
Subtotal	**192/414**	**198/419**	**1·0**	**97·3**	**1·01 (0·83–1·23)**	**0·9**
Test for heterogeneity between trials χ^2=2·9; p=0·09						
Total	**1024/1660**	**1084/1663**	**-56·6**	**524·5**	**0·90 (0·82–0·98)**	**0·01**
Test for heterogeneity (five trials) χ^2=6·7; p=0·2						
Test for heterogeneity between subtotals χ^2=3·6; p=0·2						

0·1 1·0 10·0

Favours gemtuzumab ozogamicin

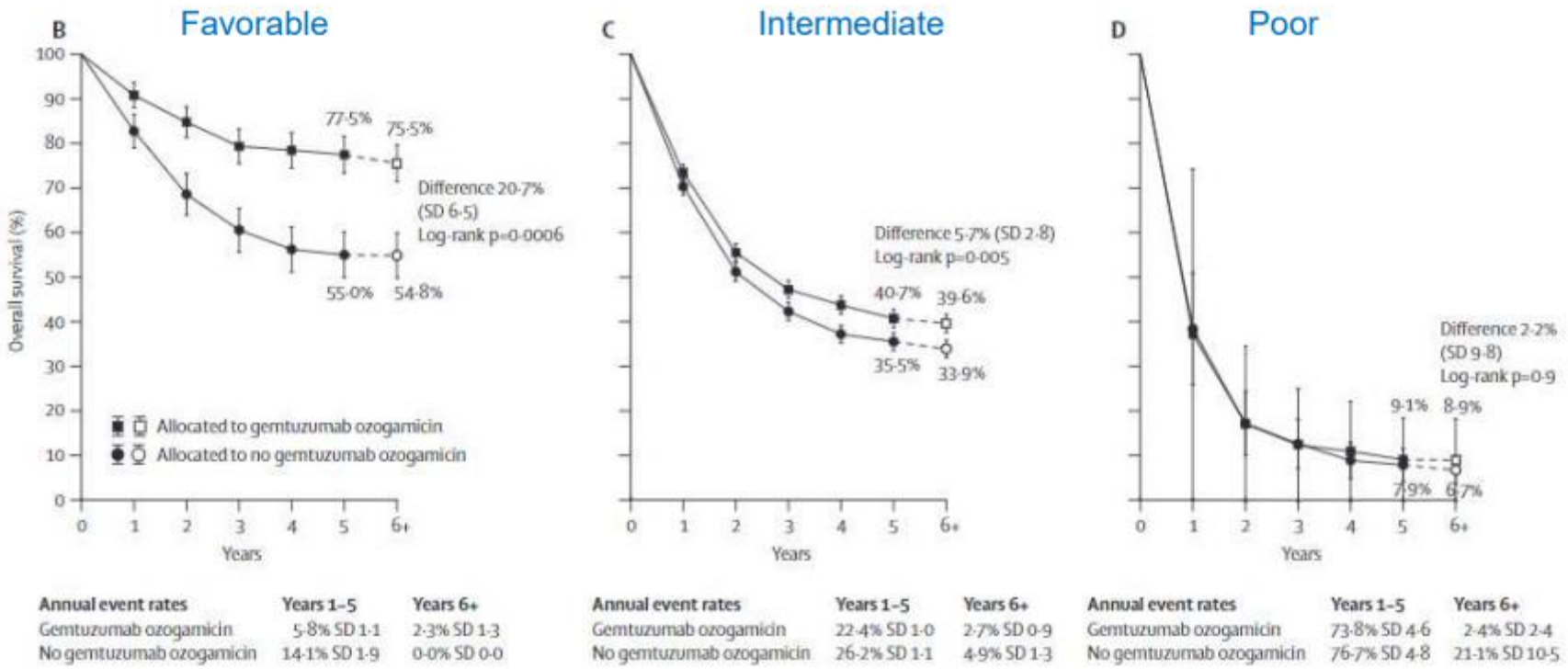
Favours no gemtuzumab ozogamicin

B

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	26·7 % SD 0·8	3·5 % SD 0·8
No gemtuzumab ozogamicin	29·5 % SD 0·9	5·2 % SD 1·0

Hills et al. Lancet Oncol 2014; 15: 986-996

GO META analysis : Subgroup analysis



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

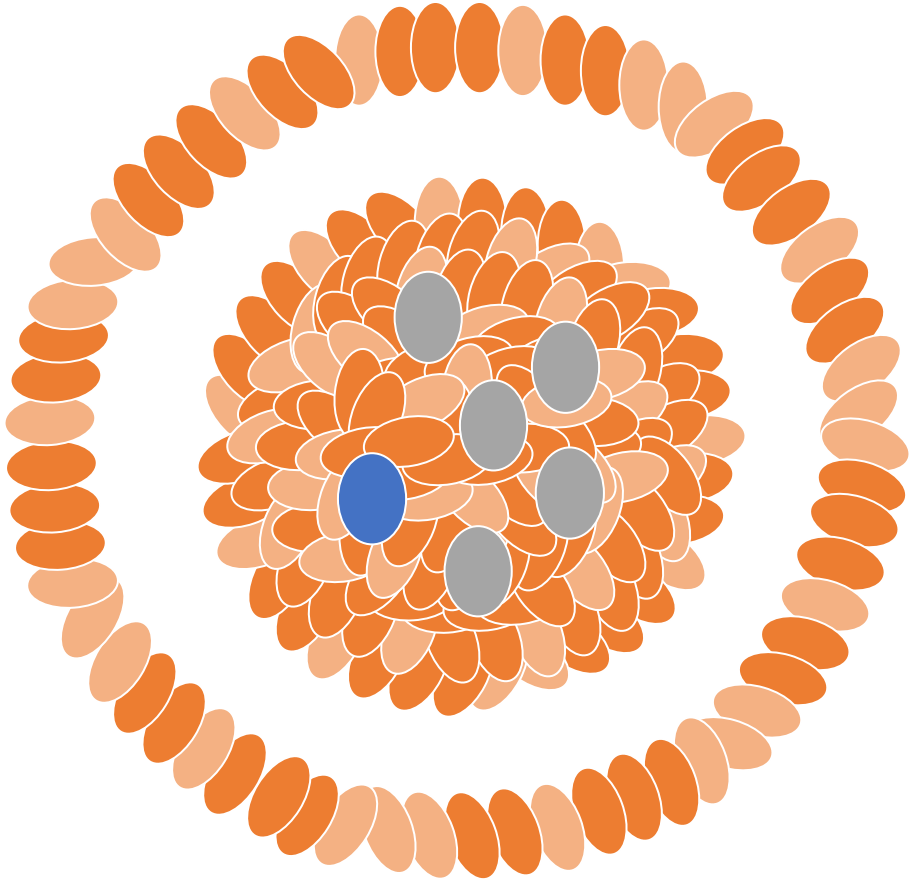
Hills et al. Lancet Oncol 2014; 15: 986-996

GO and CD33 expression

- No effect of CD 33 expression shown in ALFA0701, nor in mRC AML15
- IN ALFA 0701 : low inclusion rate of patients with low (<30%) CD33 expressing blasts

- NEEDED for reimbursement

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]

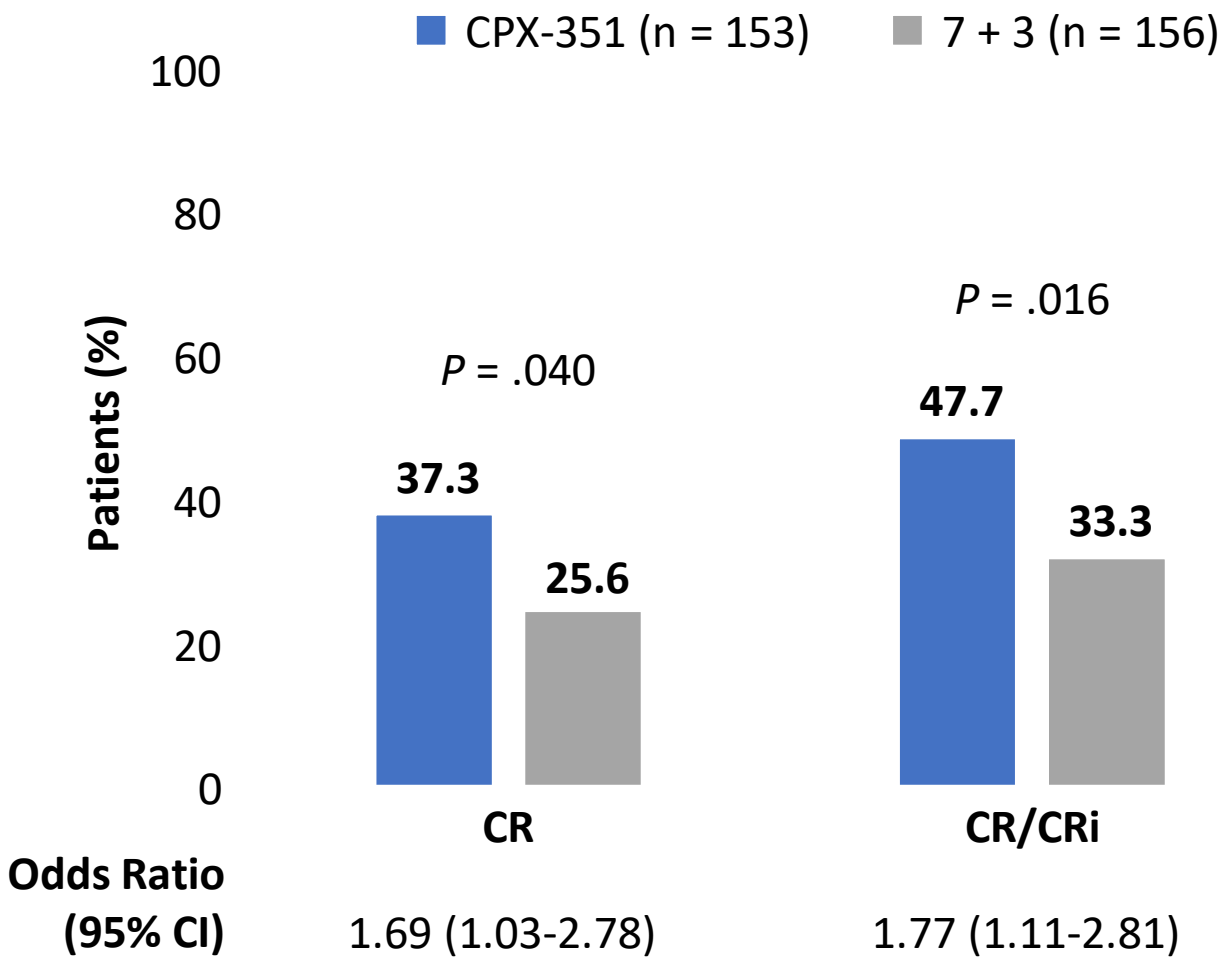
1. Tardi. Leuk Res. 2009;33:129. 2. Feldman. JCO. 2011;29:979. 3. Lim. Leuk Res. 2010;34:1214.

Theorectical advantages

- Sustained exposure to cytarabine and daunorubicine in the bone marrow
  - Increased anti leukemic effect, but also prolonged cytopenia (neutropenia, thrombocytopenia, …)
  - Escape to drug efflux pumps by entering the leukemic cells as intact liposomes
  - Escape to early cytarabine deaminase-dependent cytarabine deactivation

  - => potentially more beneficial in elderly AML, sAML and tAML : more chemoresistant leukemia

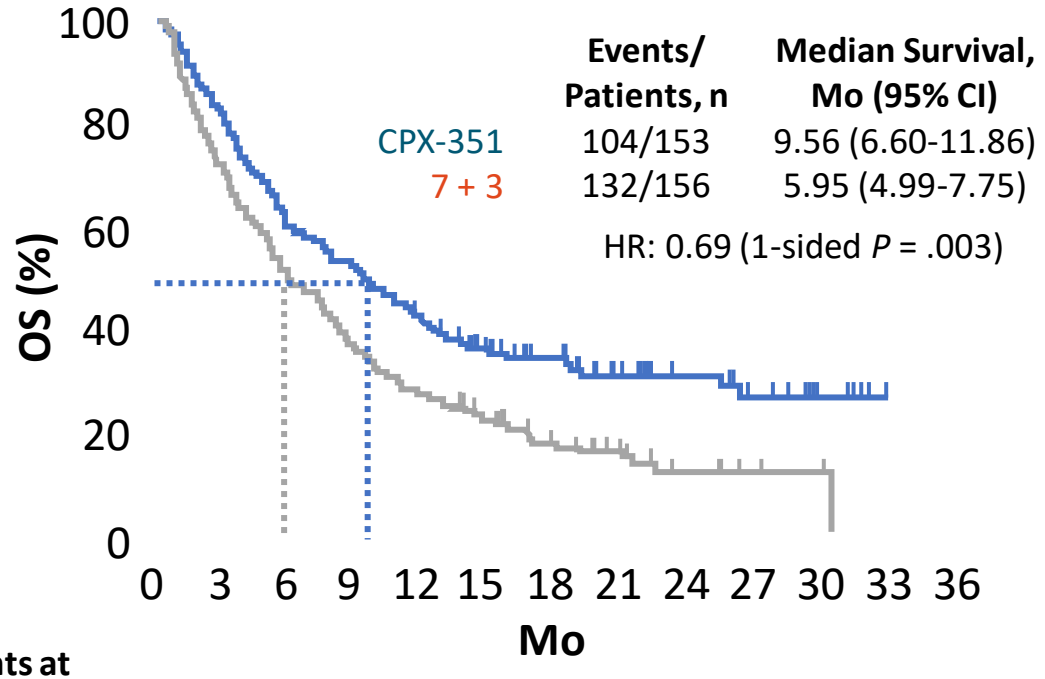
CPX-351 in Older Patients With Newly Diagnosed AML: Response



Lancet. JCO. 2018;36:2684.

CPX-351 in Older Patients With Newly Diagnosed AML: Median OS and EFS

OS in Overall ITT Population

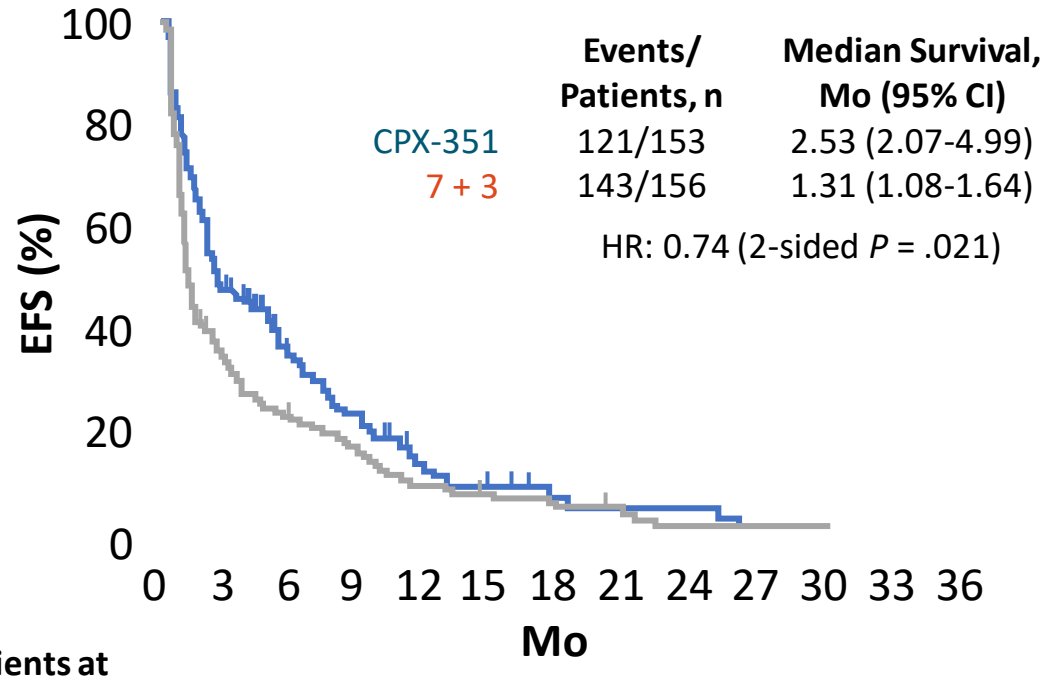


	Events/ Patients, n	Median Survival, Mo (95% CI)
CPX-351	104/153	9.56 (6.60-11.86)
7 + 3	132/156	5.95 (4.99-7.75)

HR: 0.69 (1-sided *P* = .003)

Patients at Risk, n												
CPX-351	153	122	92	79	62	46	34	21	16	11	5	1
7 + 3	156	110	77	56	43	31	20	12	7	3	2	0

EFS in Overall ITT Population



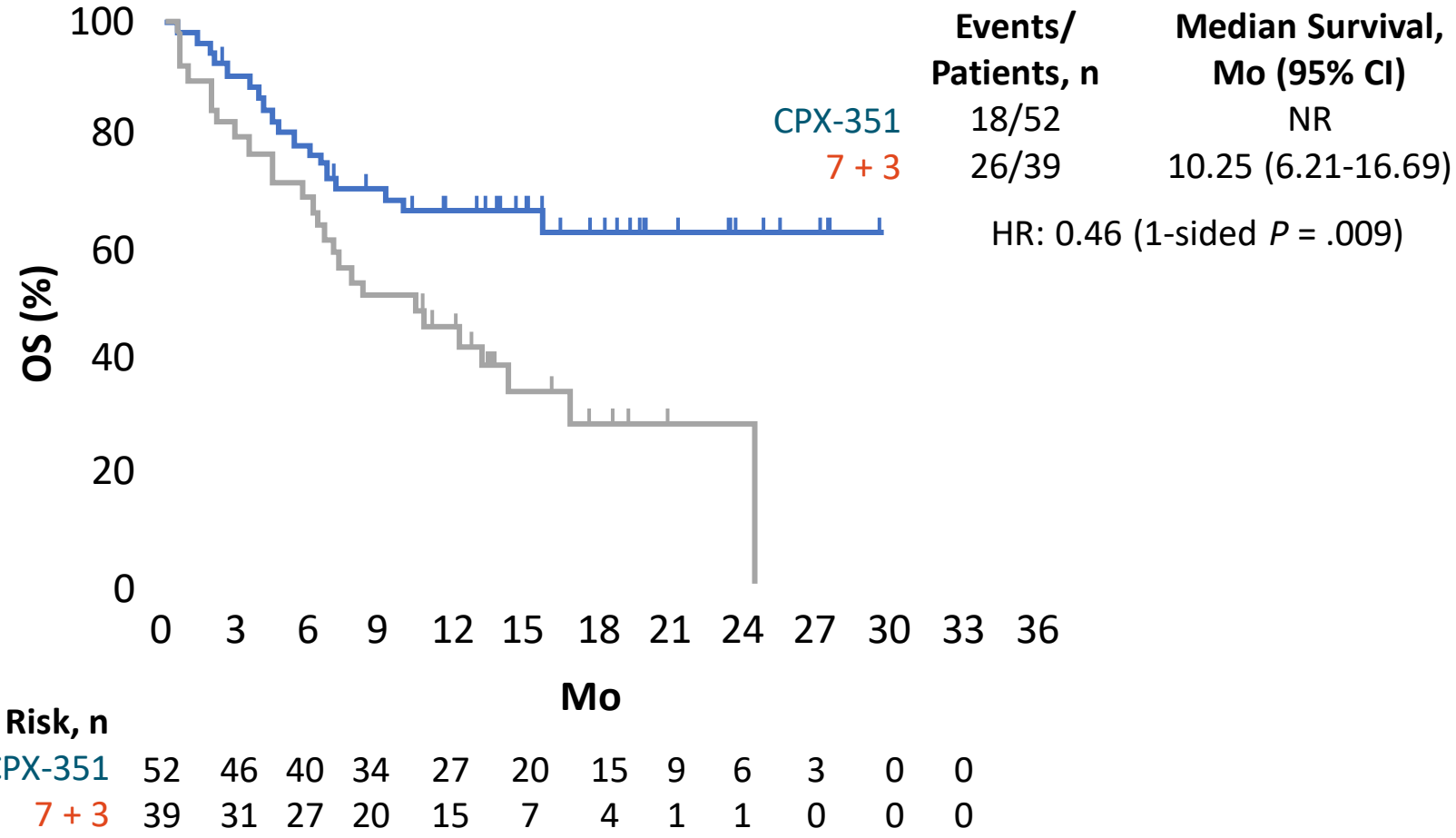
	Events/ Patients, n	Median Survival, Mo (95% CI)
CPX-351	121/153	2.53 (2.07-4.99)
7 + 3	143/156	1.31 (1.08-1.64)

HR: 0.74 (2-sided *P* = .021)

Patients at Risk, n												
CPX-351	153	65	34	23	9	6	3	2	2	0	0	0
7 + 3	156	88	27	20	11	8	5	3	1	1	1	0

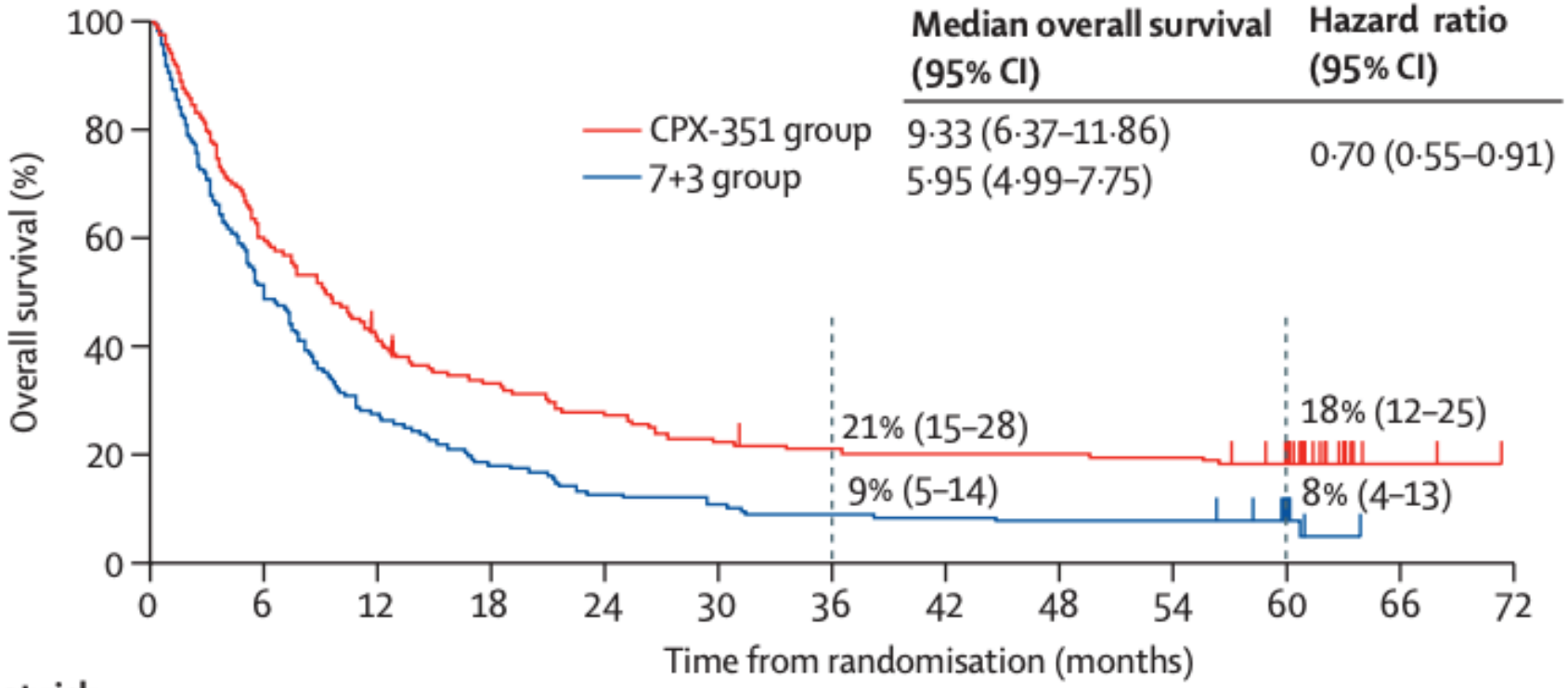
Lancet. JCO. 2018;36:2684.

CPX-351 in Older Patients With Newly Diagnosed AML: OS by Time Since HST



Lancet. JCO. 2018;36:2684.

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

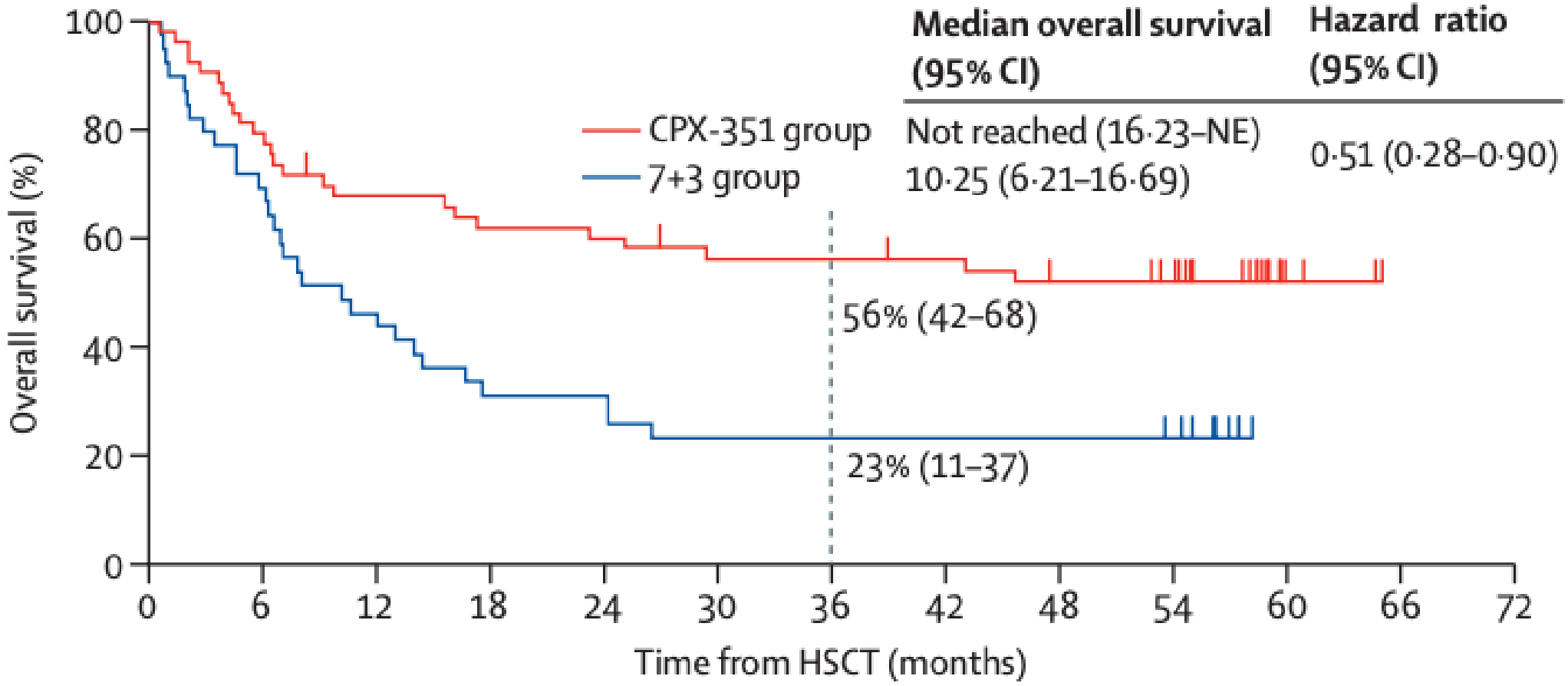


Number at risk (number censored)

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)

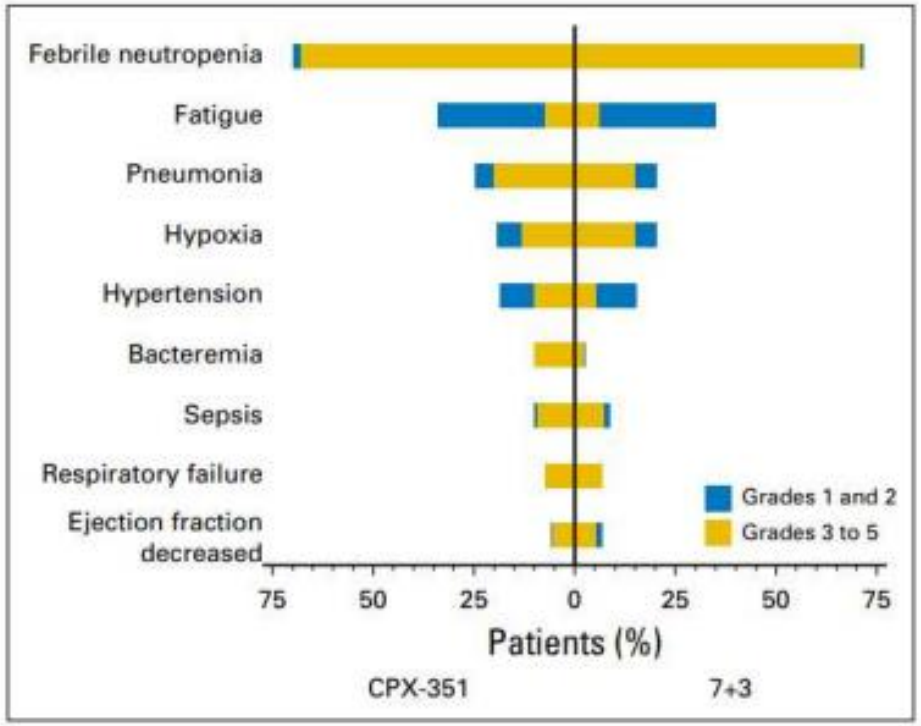
Lancet. Lancet Haematol. 2021;8:e481.

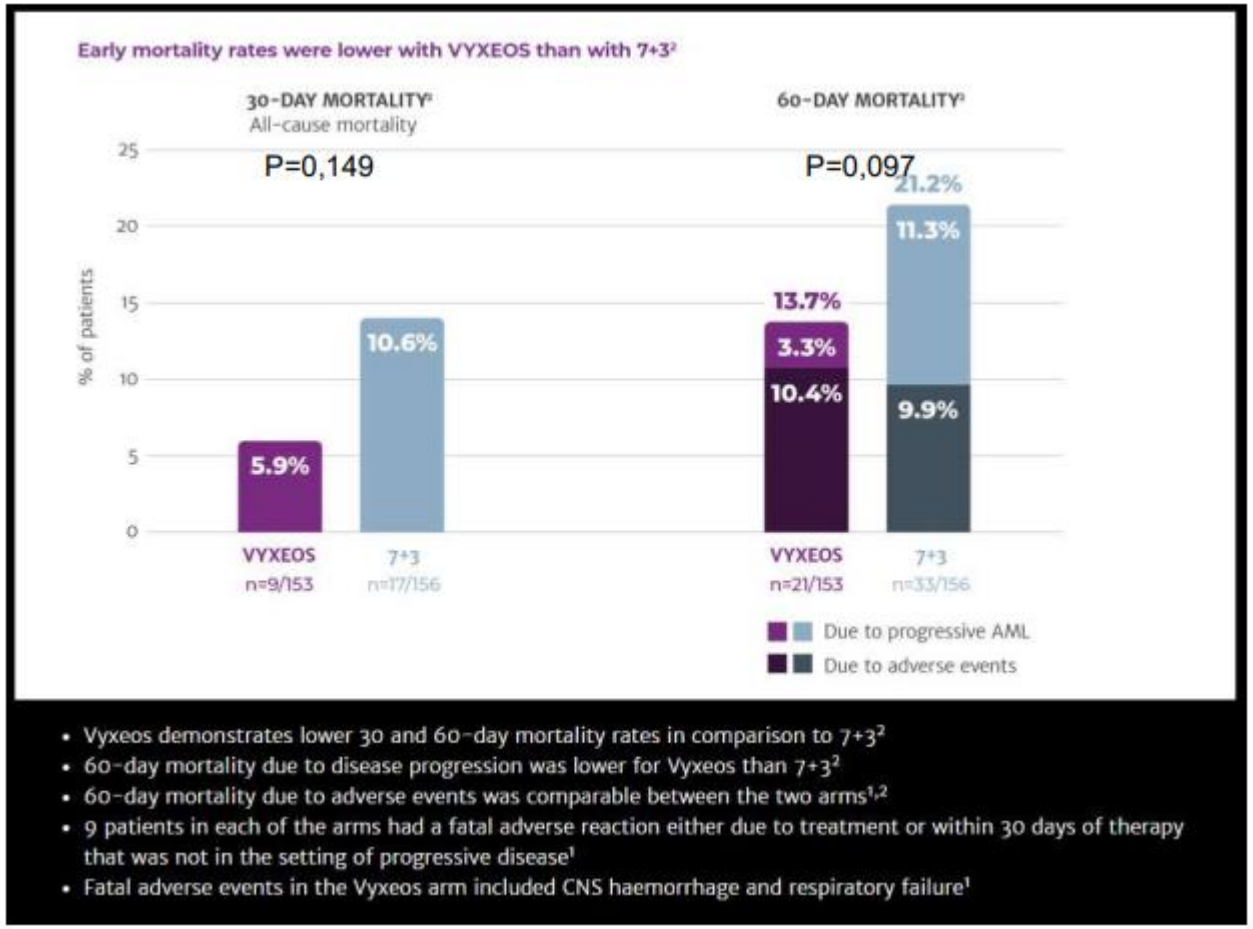
CPX-351 in Older Patients With Newly Diagnosed AML: Updated OS by Time Since HST (5-Yr Follow Up)



Lancet. Lancet Haematol. 2021;8:e481.

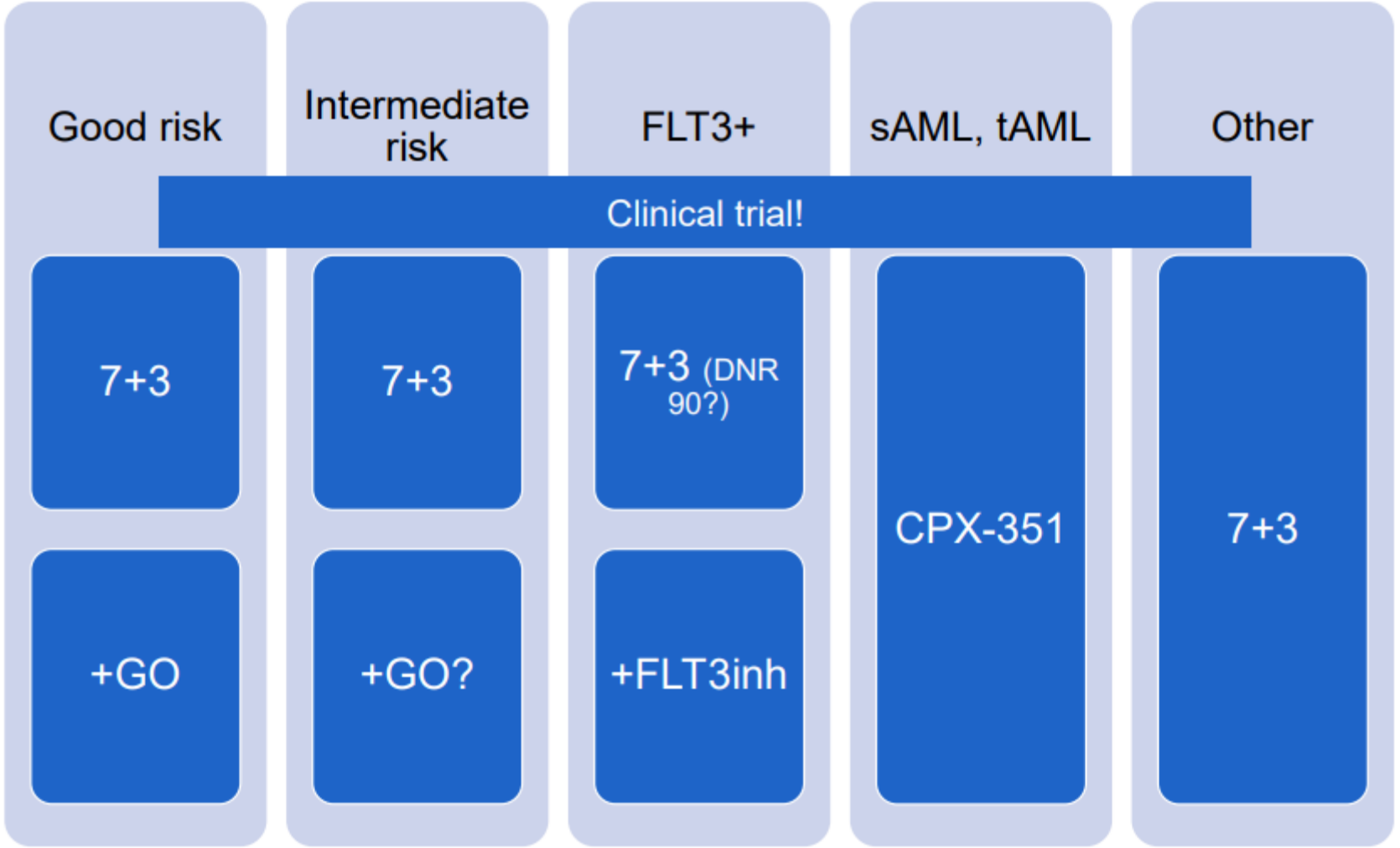
CPX-351 and safety



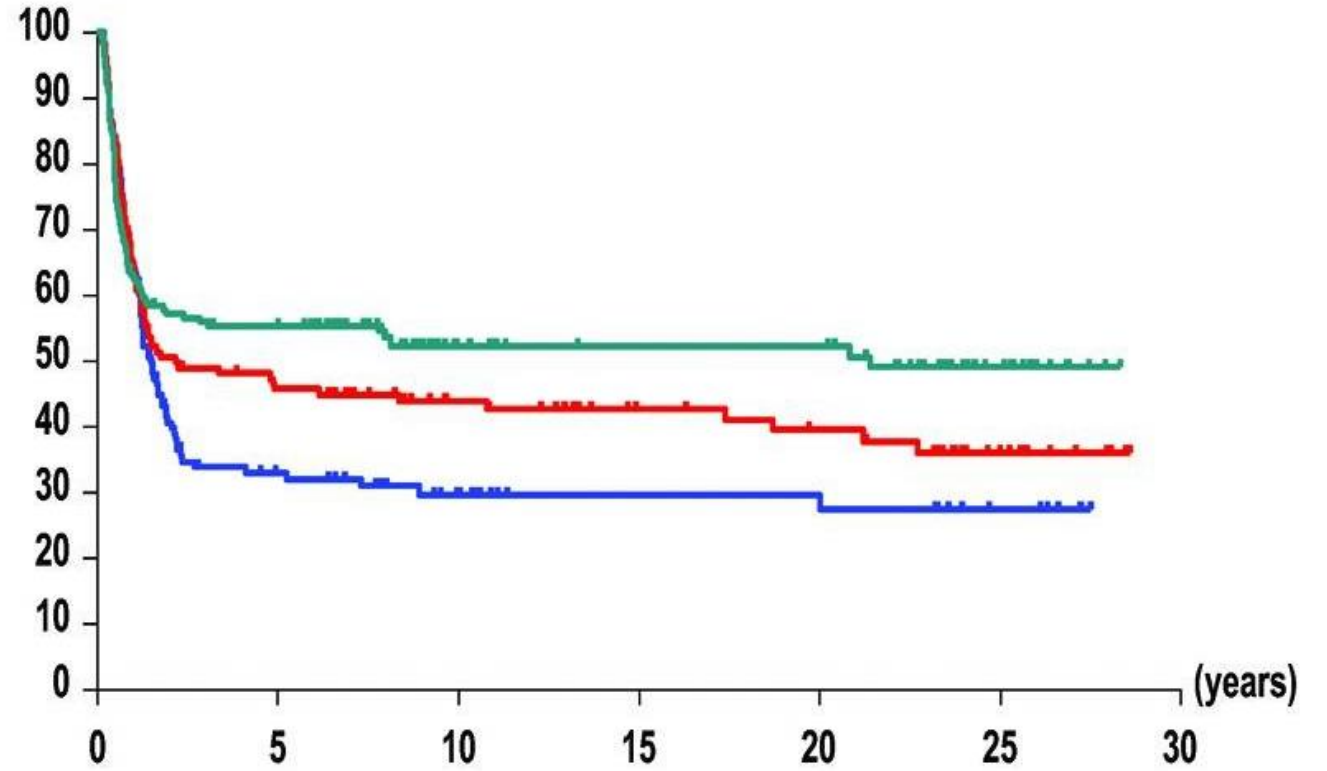


- Vyxeos demonstrates lower 30 and 60-day mortality rates in comparison to 7+3[2]
- 60-day mortality due to disease progression was lower for Vyxeos than 7+3[2]
- 60-day mortality due to adverse events was comparable between the two arms[1,2]
- 9 patients in each of the arms had a fatal adverse reaction either due to treatment or within 30 days of therapy that was not in the setting of progressive disease[1]
- Fatal adverse events in the Vyxeos arm included CNS haemorrhage and respiratory failure[1]

INTENSIVE INDUCTION : CONCLUSION

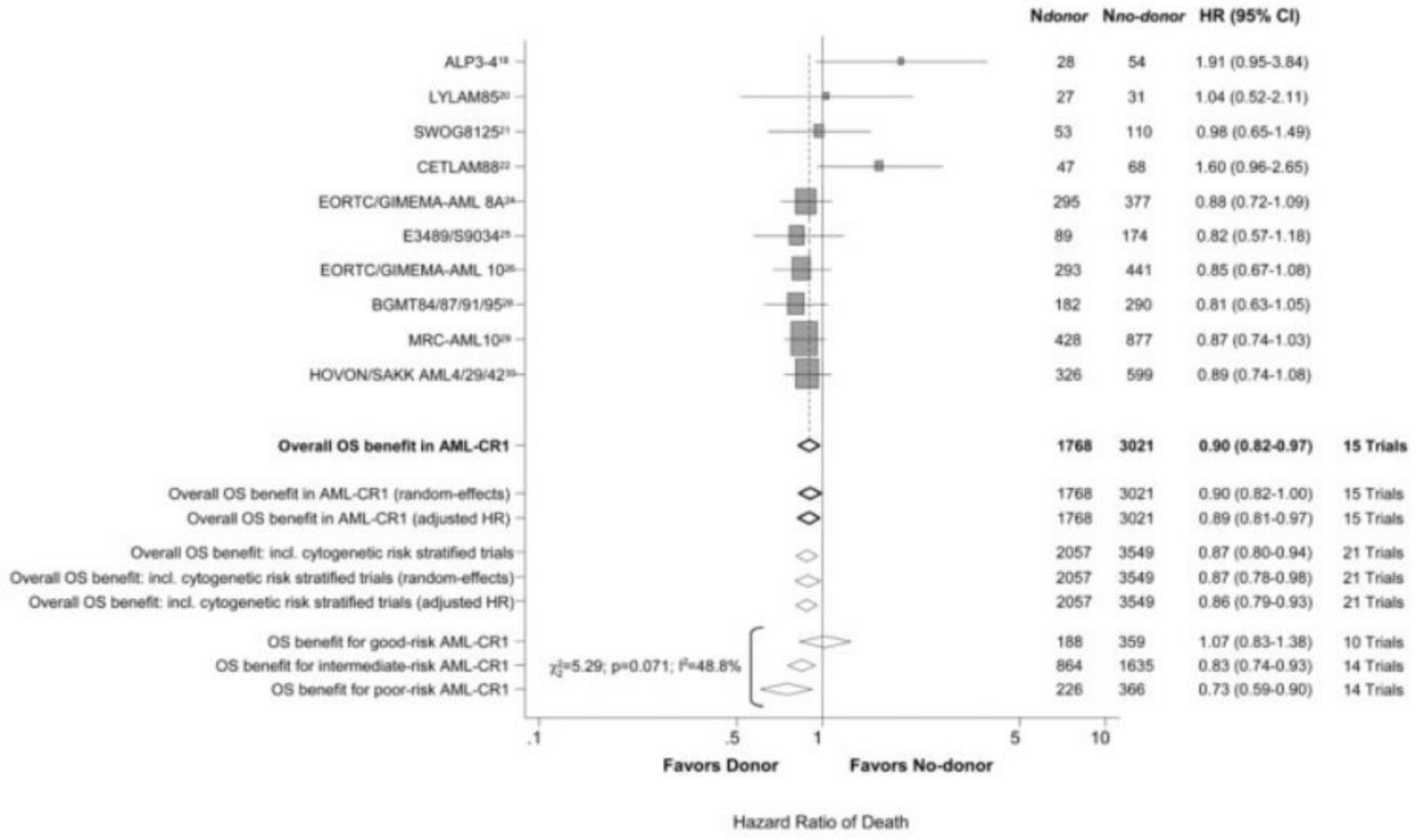


Postremission therapy



Baron et al Haematologica 2019

Allogeneic stem cell transplantation

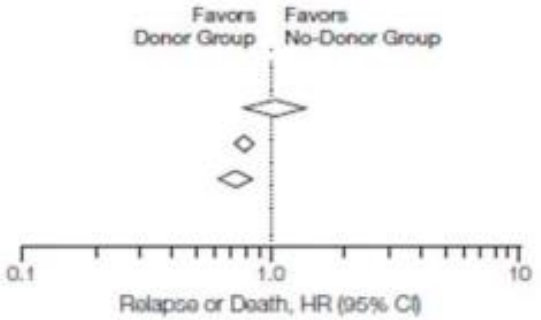


JAMA 2009; 301(22): 2349-2361

Allogeneic stem cell transplantation

Figure 2. Relapse-Free Survival (RFS) Benefit of Allogeneic SCT for AML in First Complete Remission

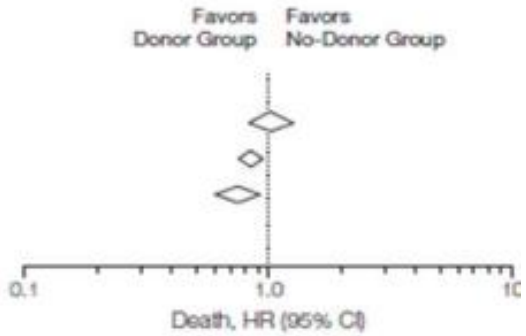
Source	No. of Patients: Donor Group	No. of Patients: No-Donor Group	No. of Trials	HR (95% CI)
RFS benefit by cytogenetic risk				
Good-risk AML	188	359	10	1.06 (0.80-1.42)
Intermediate-risk AML	864	1635	14	0.76 (0.68-0.85)
Poor-risk AML	226	366	14	0.69 (0.57-0.84)
Test for heterogeneity: $\chi^2_2=6.09$; $P=.049$; $I^2=67.2\%$				



Black rectangles indicate summary effects estimates (hazard ratios [HRs]) for individual study reports. Sizes of data markers are proportional to the study weights. Error bars indicate 95% confidence intervals (CIs). AML indicates acute myeloid leukemia; RFS, relapse-free survival.
[a]Studies only reporting RFS end points.

Figure 3. Overall Survival Benefit of Allogeneic SCT for AML in First Complete Remission

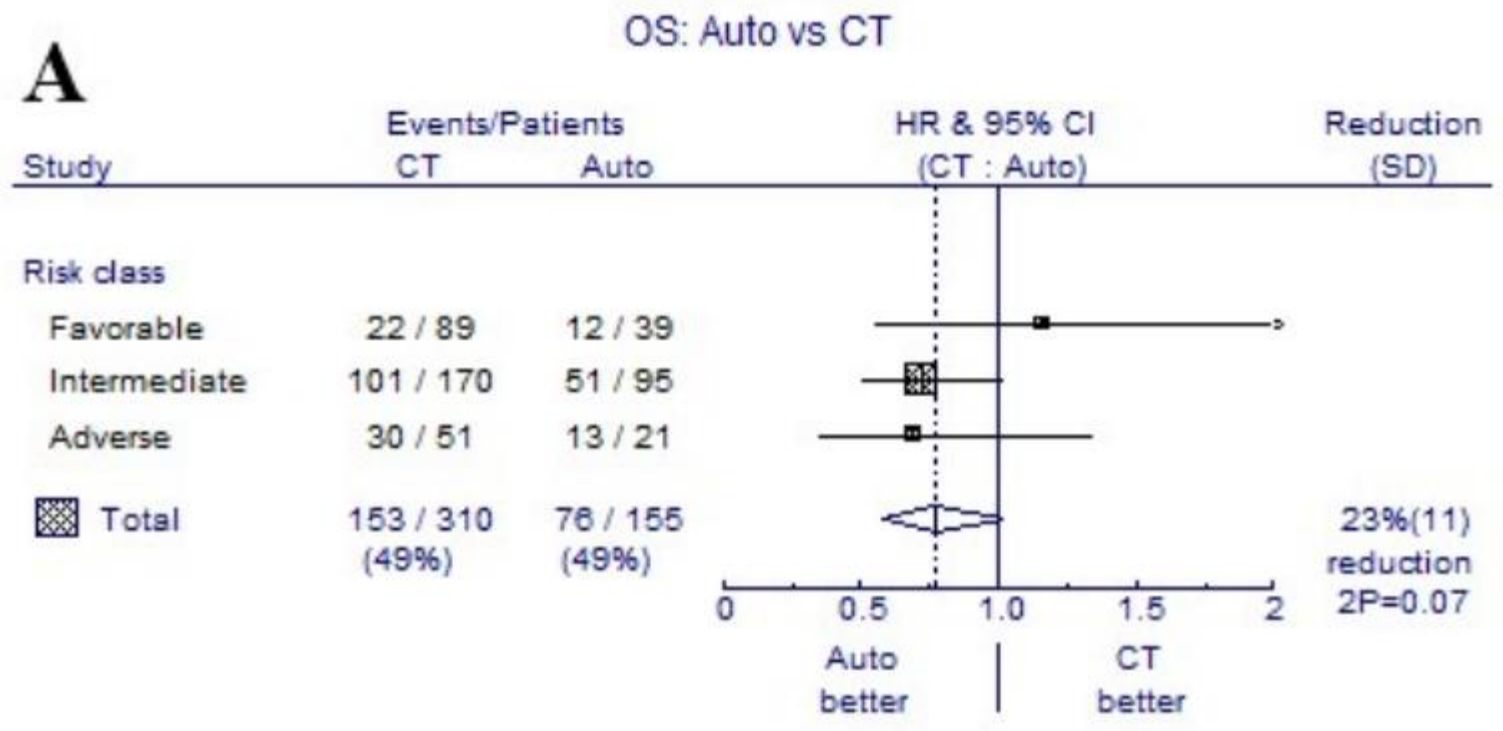
Source	No. of Patients: Donor Group	No. of Patients: No-Donor Group	No. of Trials	HR (95% CI)
Overall survival benefit by cytogenetic risk				
Good-risk AML	188	359	10	1.07 (0.83-1.38)
Intermediate-risk AML	864	1635	14	0.83 (0.74-0.93)
Poor-risk AML	226	366	14	0.73 (0.59-0.90)
Test for heterogeneity: $\chi^2_2=5.29$; $P=.07$; $I^2=62.2\%$				



Black rectangles indicate summary effects estimates (hazard ratios [HRs]) for individual study reports. Sizes of data markers are proportional to the study weights. Erro
bars indicate 95% confidence intervals (CIs). AML indicates acute myeloid leukemia.

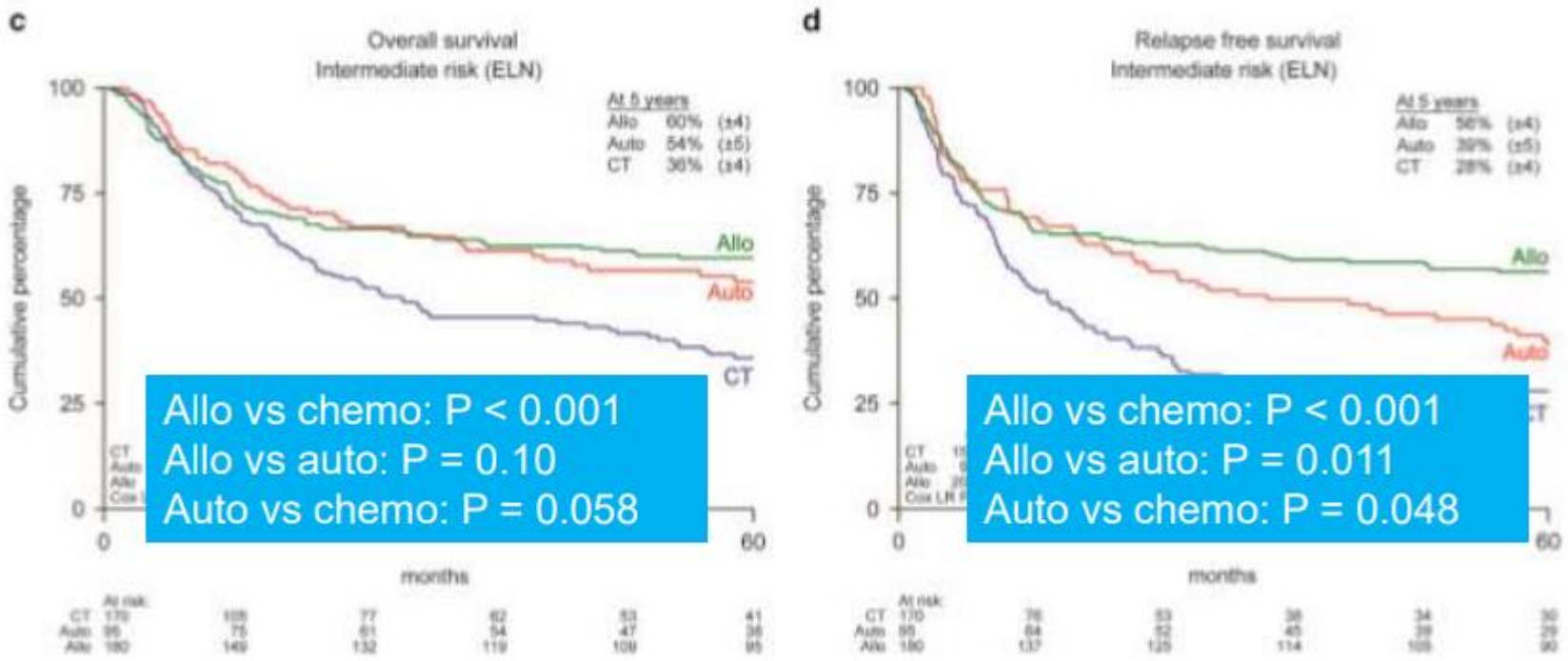
JAMA 2009; 301(22): 2349-2361

Autologous stem cell transplantation



Cornelissen et al. Leukemia 2014 , 1-10

Autologous stem cell transplantation

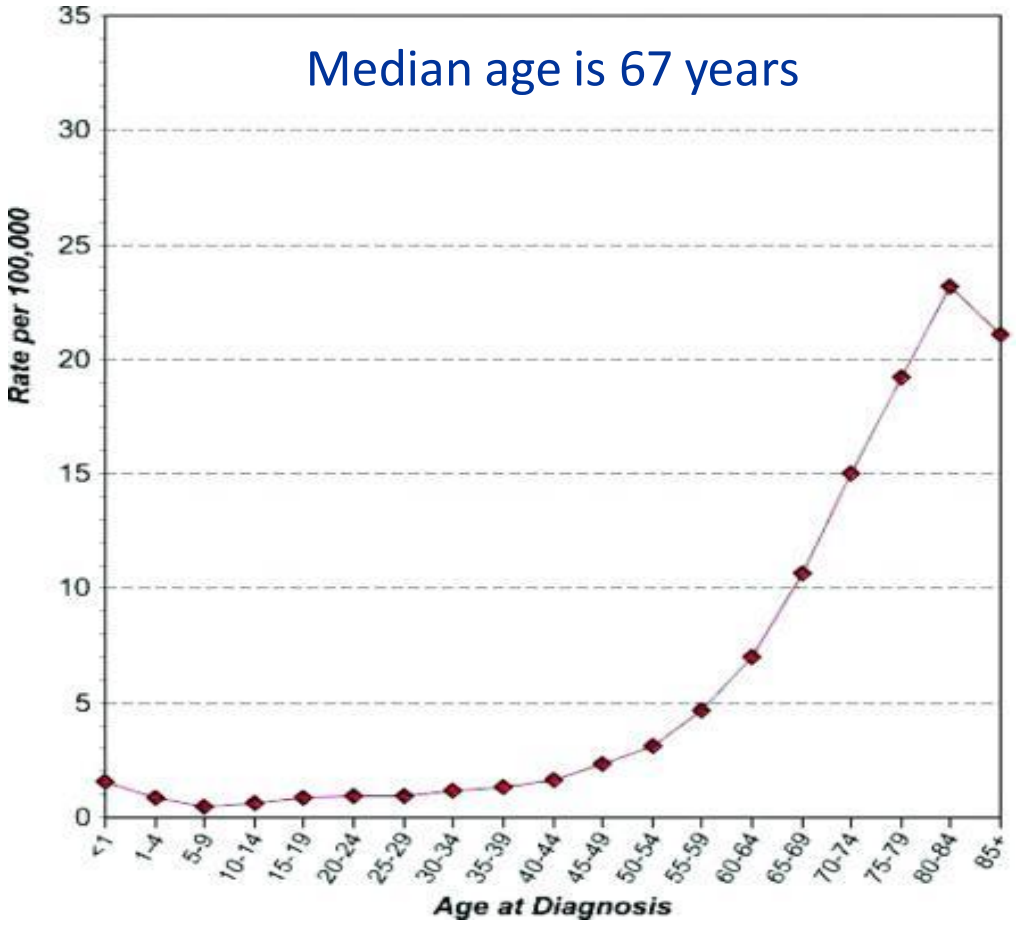


Cornelissen et al. Leukemia 2014 , 1-10

POSTREMISSION THERAPY : CONCLUSION

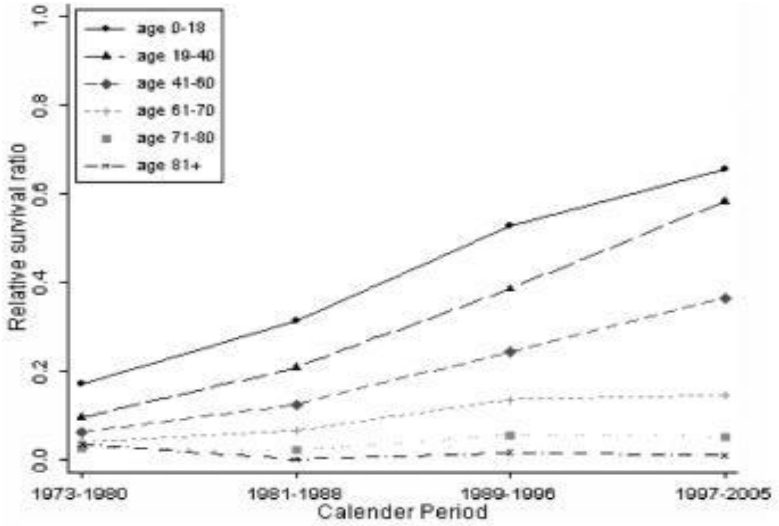
- Allogeneic transplantation in CR1 is superior for intermediate and poor risk patients, but not for favourable risk patients
- Consolidation for favourable risk patients:
  - At least 2 courses of intermediate dose Cytarabine monotherapy
- Consider combination chemotherapy (MRC AML 15) in poor risk patients not able to receive an allogeneic stem cell transplantation
- Autologous stem cell transplantation can be an alternative post remission treatment in intermediate risk patients

Incidence of AML as a function of age
2000-2005 Surveillance Epidemiology and End Results (SEER) Data



Klepin HD, Balducci L. The Oncologist 2009; 14: 222-232

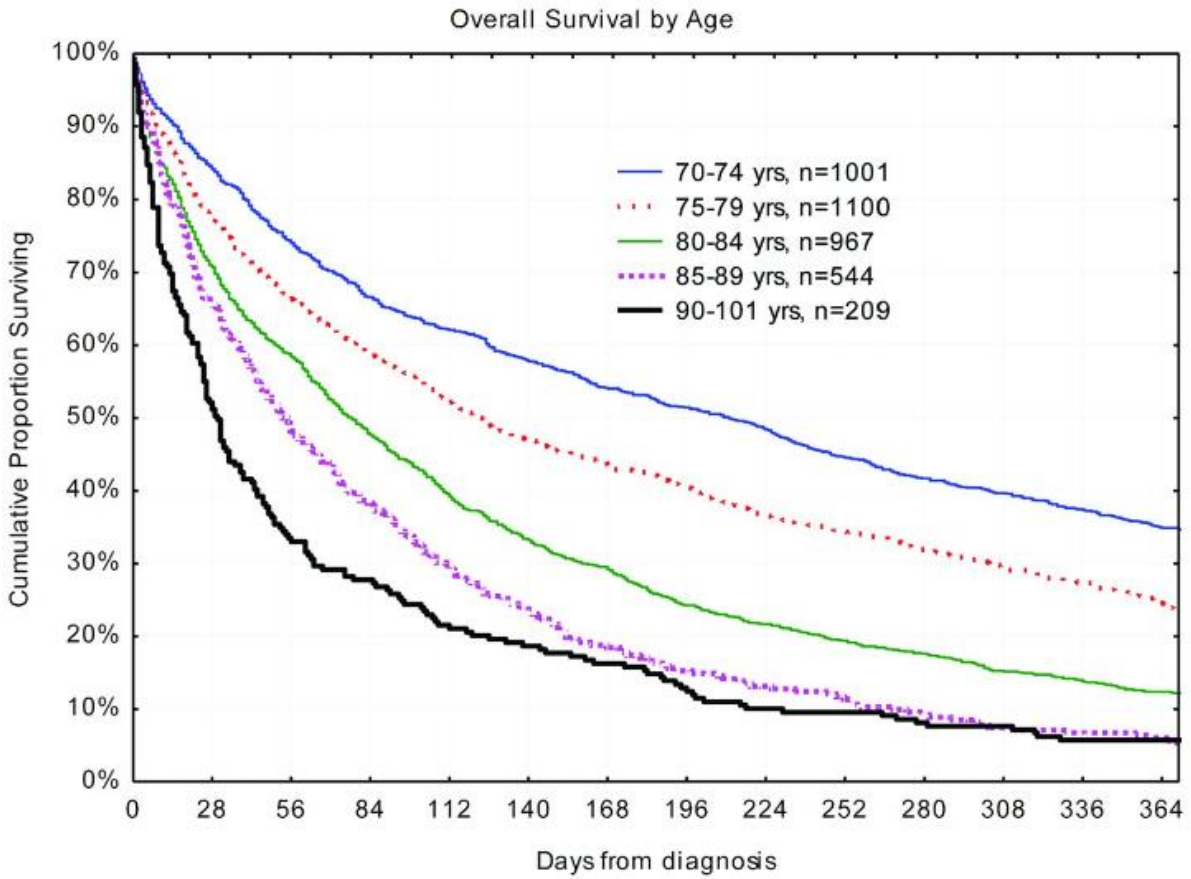
Five-year relative survival rate of AML stratified by age category and calendar period



Age category (years)	Calendar period 1973-1980 (95% CI)	1981-1988 (95% CI)	1989-1996 (95% CI)	1997-2005 (95% CI)
0-18	0.17 (0.10,0.25)	0.31 (0.22,0.41)	0.53 (0.42,0.62)	0.65 (0.56,0.73)
19-40	0.09 (0.06,0.14)	0.21 (0.15,0.27)	0.38 (0.32,0.45)	0.58 (0.51,0.65)
41-60	0.06 (0.04,0.09)	0.12 (0.09,0.16)	0.24 (0.21,0.29)	0.36 (0.32,0.41)
61-70	0.04 (0.02,0.06)	0.07 (0.05,0.09)	0.14 (0.11,0.17)	0.15 (0.12,0.18)
71-80	0.03 (0.01,0.05)	0.02 (0.01,0.04)	0.06 (0.04,0.08)	0.05 (0.04,0.07)
81+	0.03 (0.009,0.09)	0.00 (0.00,0.00)	0.01 (0.004,0.04)	0.01 (0.001,0.04)

Derolf AR et al. Blood 2009; 113: 3666-3672

AML Survival in elderly patients



Lazarevic et al, Haematologica Dec 2018

Why are treatment results poor(er) in the elderly?

- Biological factors: age → more resistant disease
  - **Higher frequency of pre-existing hematological disease/secondary AML**
  - **More immature stem cell phenotype (CD34+, MDR+)**
  - **More unfavorable cytogenetic abnormalities**
- Host factors: age → poor treatment tolerance
  - **Decreased performance status**
  - **More co-morbidities**
  - **Differences in drug PK/PD (e.g. clearance)**
  - **More prone to infections and bleeding**

Patient and disease characteristics at presentation of AML, by age

	< 56 yr.	56-65 yr.	66-75 yr.	> 75 yr.
PS 0 (%)	**35**	**29**	**27**	**18**
PS < 2 (%)	**84**	**75**	**73**	**68**
PS > 2 (%)	**2**	**10**	**7**	**14**
Cytogenetics				
Favorable (%)	**16**	**5**	**5**	**4**
Intermediate (%)	**46**	**55**	**55**	**44**
Unfavorable (%)	**33**	**38**	**39**	**50**
MDR + (%)	**33**	**62**	**61**	**57**
Response				
CR (%)	**64**	**46**	**39**	**33**
Resistant (%)	**27**	**37**	**37**	**36**
Survival (months)	**18.8**	**9**	**6.9**	**3.5**

Appelbaum et al. (SWOG) Blood 2006; 107: 3481

Guidelines for treatment choice (focus on elderly)

Prediction of induction mortality (day 30): performance score > age

Age	< 56 yr.	56-65 yr.	66-75 yr.	> 75 yr.
PS 0	2 %	11 %	12 %	14 %
PS 1	3 %	5 %	16 %	18 %
PS 2	2 %	18 %	31 %	50 %
PS 3	0 %	29 %	47 %	82 %
% PS 2-3	15 %	24 %	26 %	32 %

Appelbaum et al. Blood 2006

How to select patients for intensive chemotherapy?

- **Patients with**
  - **UNFAVORABLE CYTOGENETICS and/or**
  - **2 RISK FACTORS (age >75, PS > 1, WBC > 50.000)**
- **Have a 1 yrs. OS of 19 % with IC**
- **And should not be treated with IC….**

Malfuson at al. Haematologica 2008; 93: 1806-1813.

How to select patients for intensive chemotherapy?

- **Age (≥ 75 yrs.)**
- **Unfavorable cytogenetic**
- **Poor performance score (> 2)**
- **≥ 12-month history of antecedent hematologic disorder (AHD)**
- **LDH > 600 IU/ml**
- **Elevated creatinine**
- **Treatment outside a laminar flow room**

- **No adverse factors: CR > 60%, induction mortality 10%, 1-yr survival > 50 %**
- **≥ 3 adverse factors: CR < 20%, induction mortality > 50%, and 1-yr survival >10%**

Kantarjian et al. Cancer 2006; 106:1090-1098.

How to select patients for intensive chemotherapy?

- **Poor prognosis (MRC AML 11 trial)**
  - **Cytogenetic group**
  - **Age**
  - **WBC count**
  - **PS**
  - **de novo vs. secondary AML**

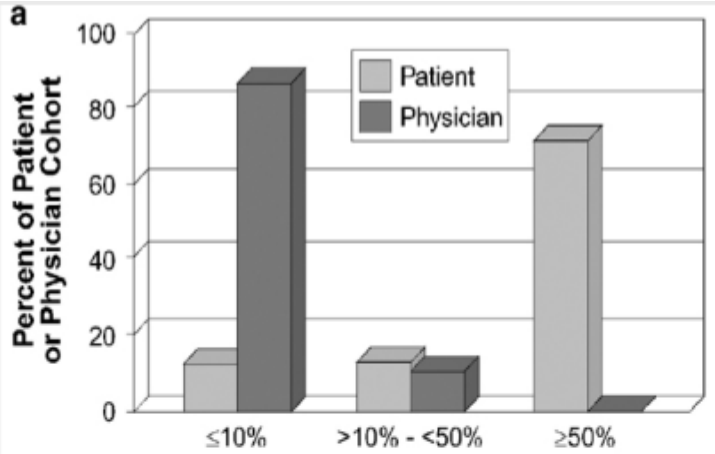
Wheatley et al. Br J Haematol 2009; 145: 598-605

Guidelines for treatment choice (focus on elderly)

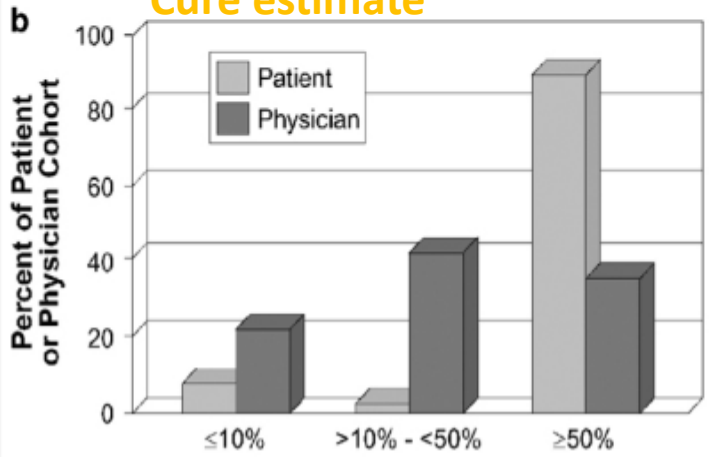
- **Interaction (discussion) with PATIENT and FAMILY (and GP)**
  - **Prospective study of 43 AML patients > 60 yrs. to gain insights in clinical decision making**
  - **Based on patient and physician questionnaires at specific time points**
  - **63% of patients denied being offered other treatment options than the one they have chosen**
  - **Patients significantly overestimated their outcomes (cure rates and survival rates)**

Sekeres et al. Leukemia 2004; 18: 809-816

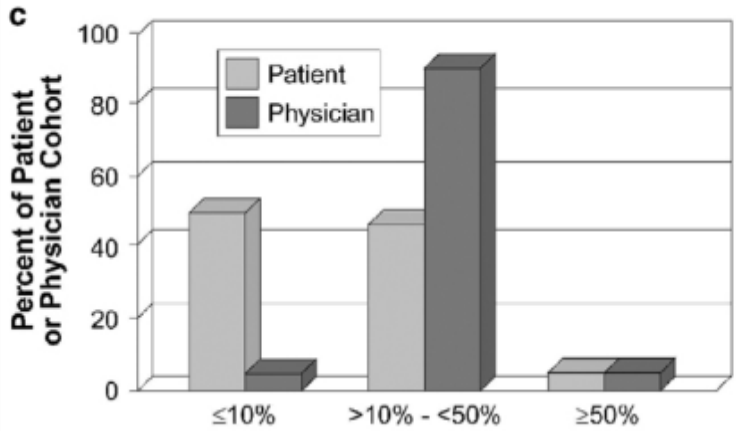
Patients and physicians have different estimates and expectations



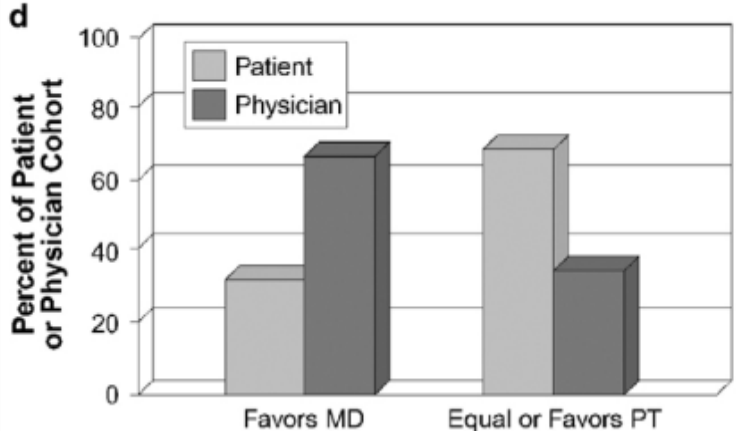
Cure estimate



1 yr. survival estimate



Treatment related mortality estimate



Patient participation in decision-making

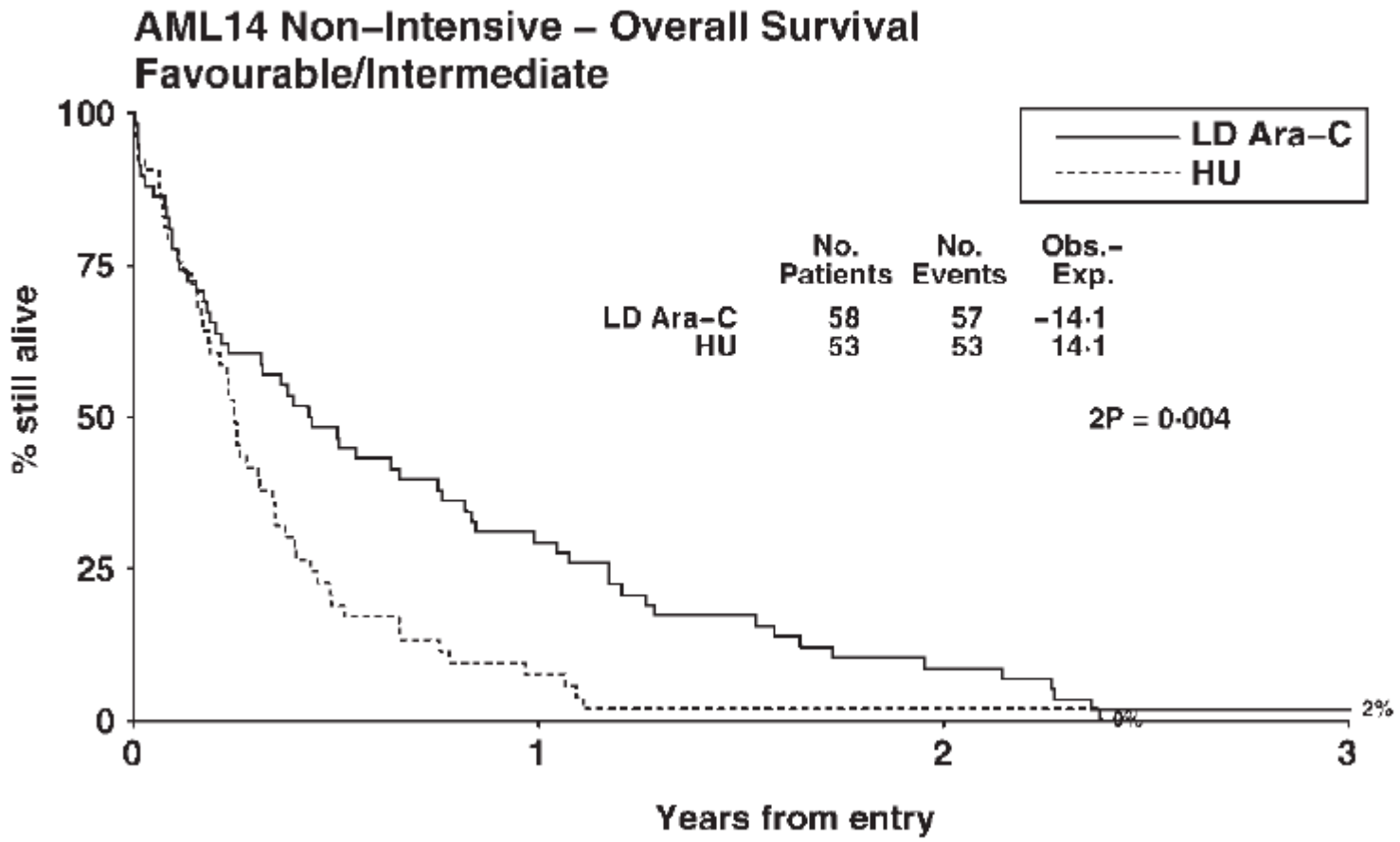
Sekeres et al. Leukemia 2004; 18: 809-816.

Non-intensive chemotherapy: a new standard?
AML 14 (MRC): hydroxyurea (HU) vs. LD Ara-C

- 212 patients were deemed unfit for IC by the local investigator
- They were randomized between HU and sc. LD Ara-C
- Outcome was better with LD Ara-C in favorable and intermediate karyotypes:
  - CR 18 % vs. 1 %
  - Median survival 575 days (CR) vs. 66 days (Non-R)
  - Early death rate 39 % @ 8 weeks
- LD Ara-C became the standard of care for unfit patients (but should not be given to those with poor risk cytogenetics).

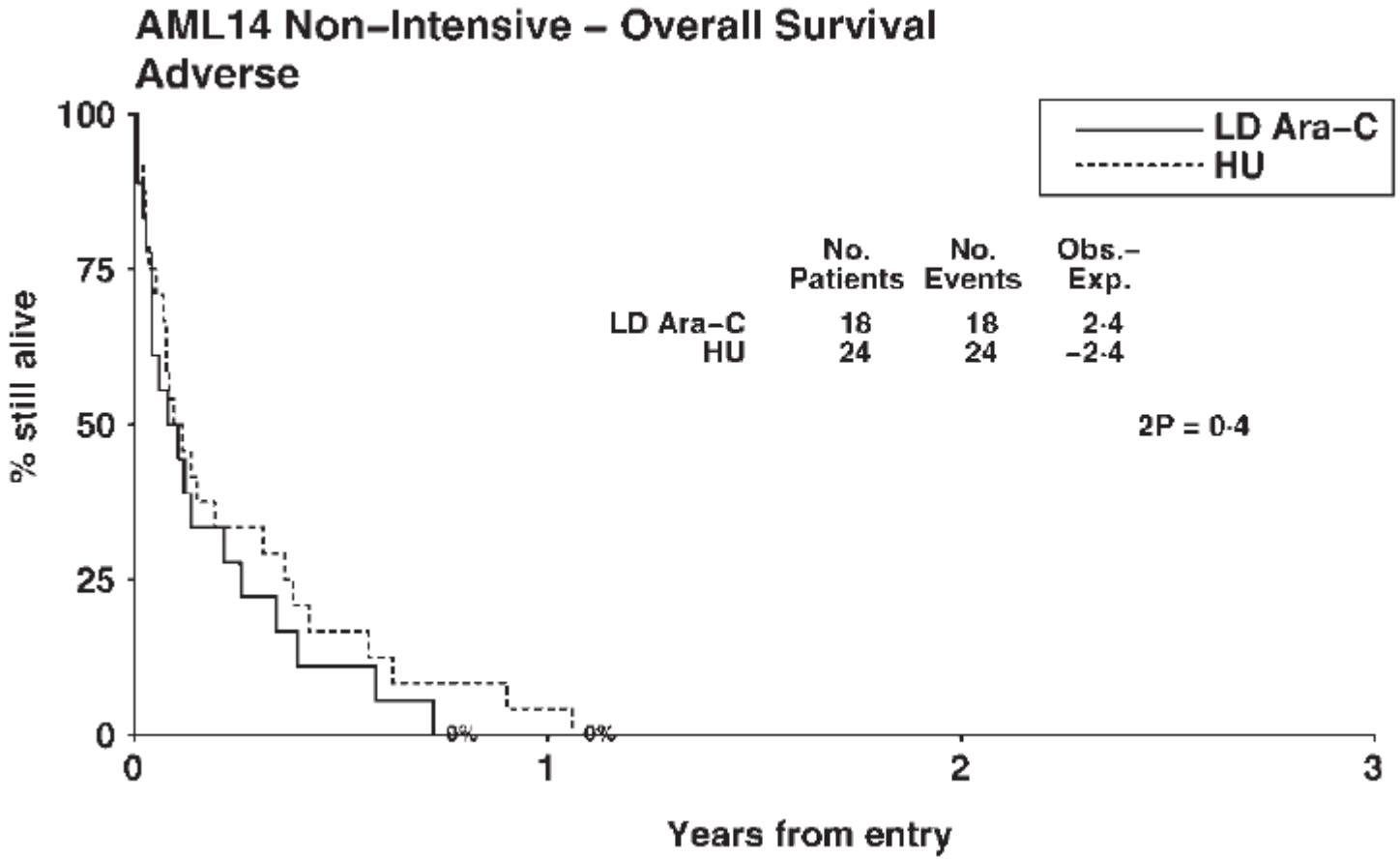
Burnett A et al. Cancer 2007

Non-intensive chemotherapy: AML 14 (MRC): hydroxyurea (HU) vs. LD Ara-C



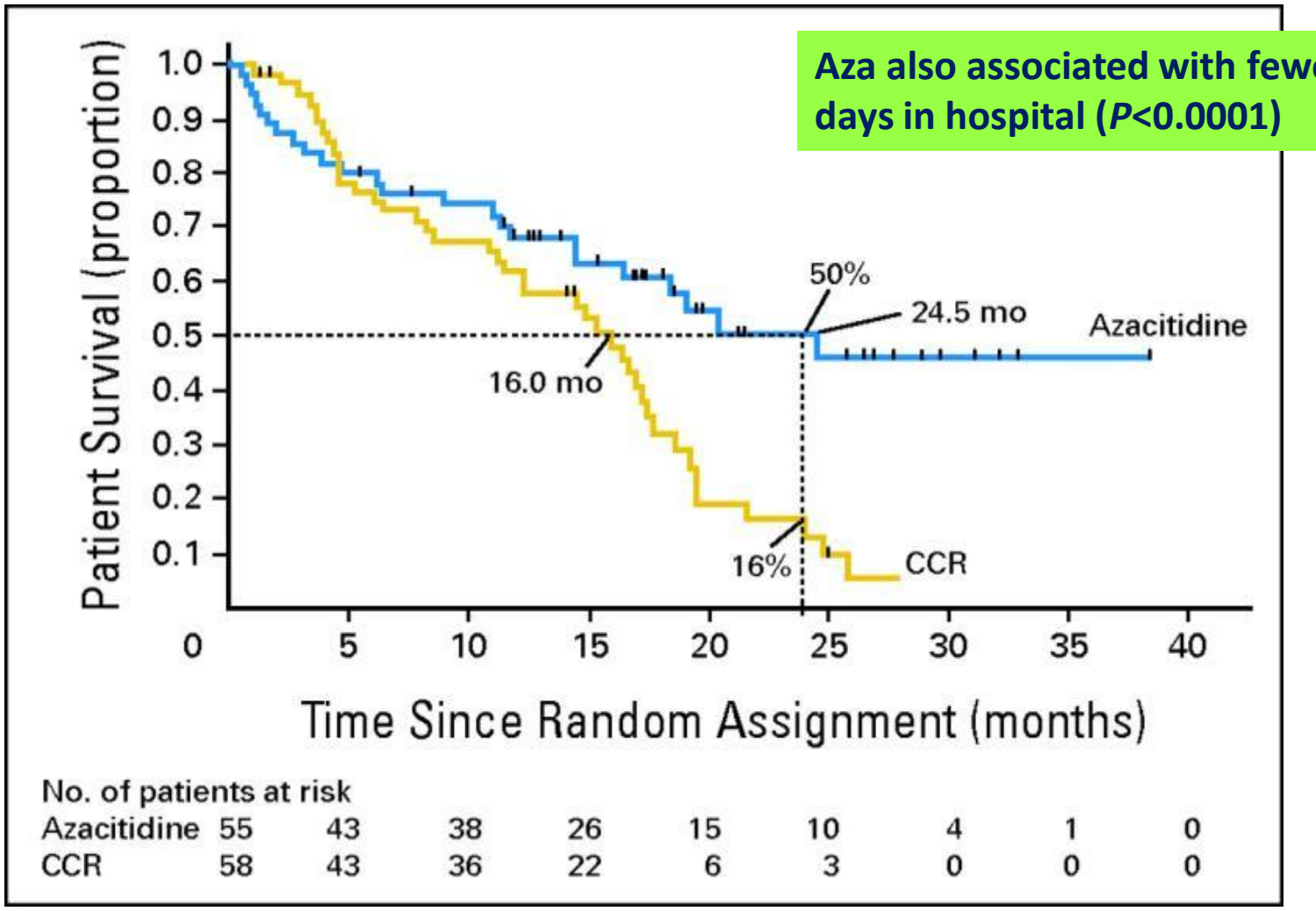
Burnett A et al. Cancer 2007

Non-intensive chemotherapy: AML 14 (MRC): hydroxyurea (HU) vs. LD Ara-C



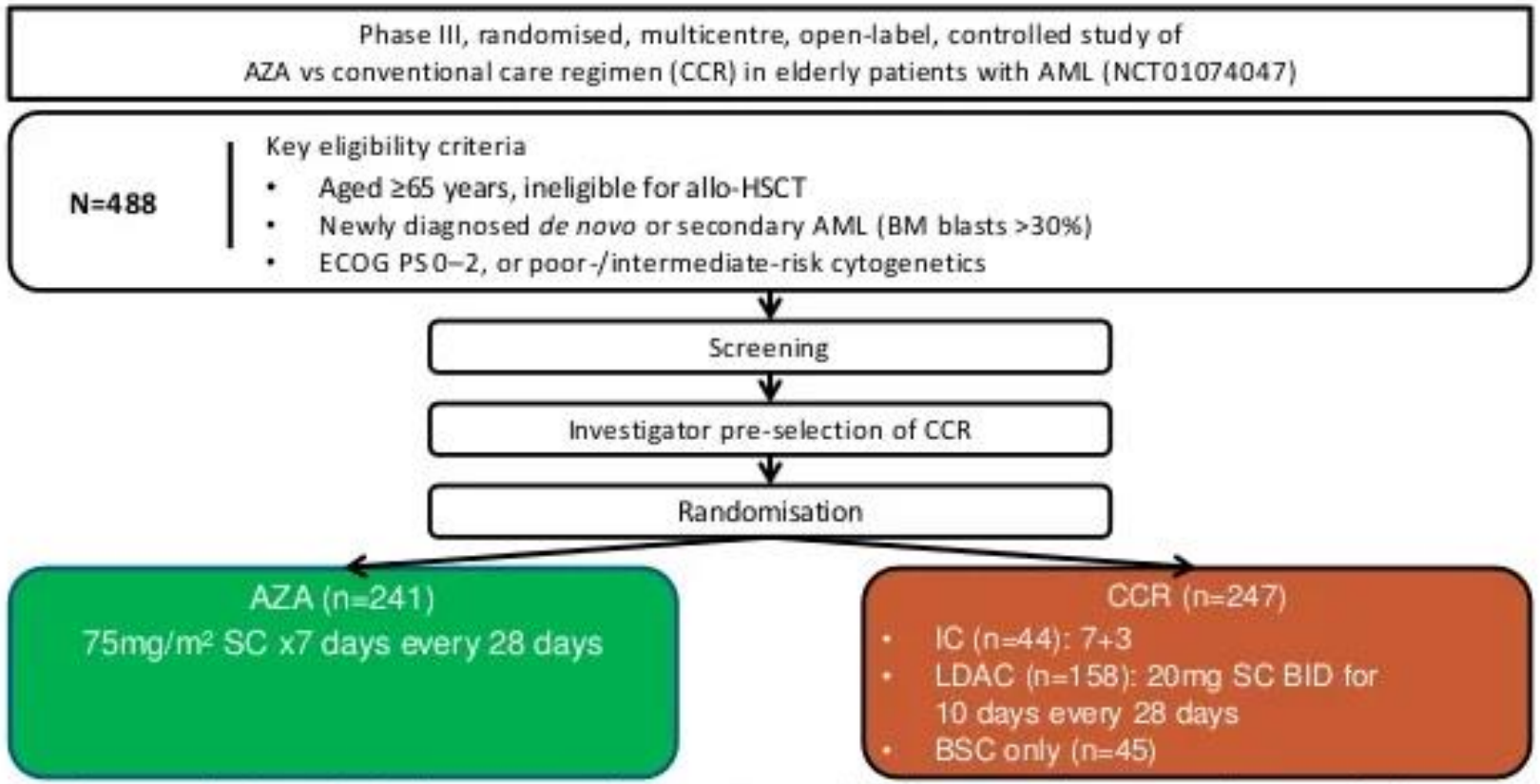
Burnett A et al. Cancer 2007

overall survival in patients with AML (20-30% blasts) receiving azacitidine or conventional care regimens (CCR)



Fenaux P et al. JCO 2010;28:562-569

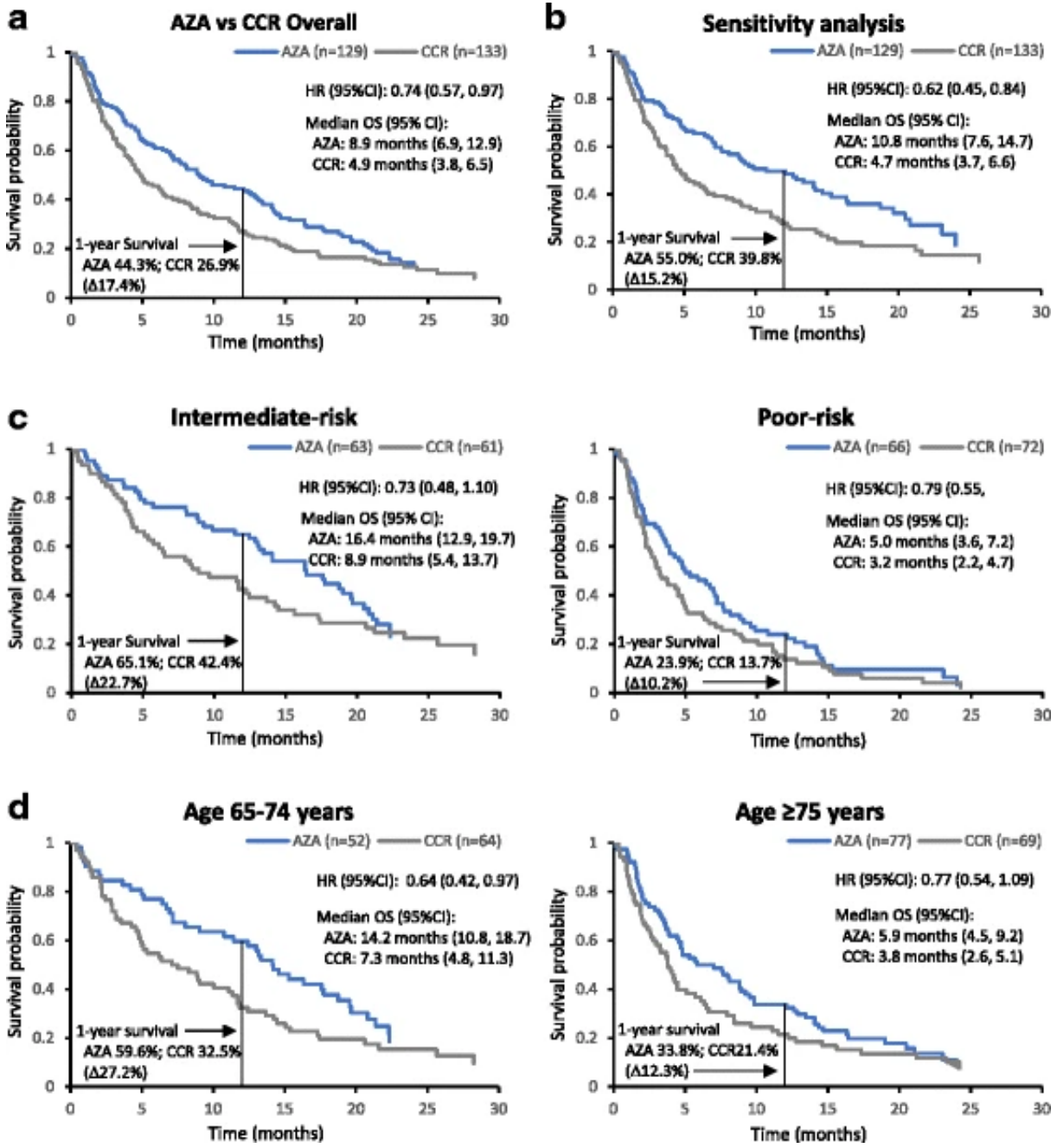
Study design of the phase III randomised AZA-AML-001 trial



- **Primary endpoint:** OS (including a pre-specified sensitivity analysis that censored patients at the start of subsequent AML therapy)
- **Secondary endpoints:** 1-year OS, response, safety

AZA = azacitidine; CCR = conventional care regimens; allo-HSCT = allogeneic haematopoietic stem cell transplantation; BM = bone marrow; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IC = intensive chemotherapy; LDAC = low-dose cytarabine; BSC = best supportive care; SC = subcutaneous; BID = twice daily; OS = overall survival

Dombret H, et al. Oral presentation at EHA 2014. Abstract LB2433



JF Seymour et al, BMC cancer 2017 Dec 14; 17(1): 852

VIALE-A: Study Design

VIALE-A (NCT02993523) – Phase 3 randomized, double-blind study of VEN + AZA vs PBO + AZA in treatment-naïve patients with AML who are ineligible for standard induction therapy

Phase 3
1L AML Ineligible for Standard Induction
(N=433*)

*433 were randomized, and 431 patients were included in the intention to treat population

Randomized 2:1

28-day cycles

Venetoclax: 400 mg PO, daily, days 1–28
+ AZA: 75 mg/m^2 SC/IV daily, days 1–7 (N=286)

PBO: PO, daily, days 1–28
+ AZA: 75 mg/m^2 SC/IV daily, days 1–7 (N=145)

Until disease progression, unacceptable toxicity, withdrawal of consent, or meet other protocol criteria for discontinuation

Key inclusion criteria
- Ineligible for standard induction therapy
- ≥75 years
- ≥18 years with comorbidities

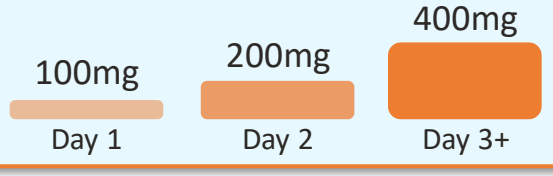
Key exclusion criteria
- Prior HMA treatment for MDS
- APL or favorable risk cytogenetics
- Active CNS involvement with AML
- Prior MPN

Primary endpoint: Overall Survival

Secondary endpoints:
- Composite CR (CR+CRi) rate
- CR rate, CR+CRh rate
- CR+CRi rate by initiation of Cycle 2
- Transfusion independence
- CR+CRi and OS in molecular subgroups
- Fatigue and GHS/QoL
- EFS

Study designed to detect a **30% reduction in mortality with 86.7% power** and a **significance level with two-sided alpha of 0.04. (HR=0.7)**

Venetoclax Ramp-Up (Cycle 1)



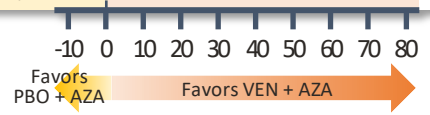
Randomization stratification
- AML cytogenetic risk (intermediate or poor)
- Age (18–<75 or ≥ 75)
- Region (US, EU, China, Japan, rest of world)

1L=First-Line. AML=Acute Myeloid Leukemia. APL=Acute Promyelocytic Leukemia. AZA=Azacitidine. CNS=Central Nervous System. CR=Complete Response. CRi=CR with Incomplete Blood Count Recovery. CRh=CR with Partial Hematologic Recovery. ECOG PS=Eastern Cooperative Oncology Group Performance Status. EFS=Event Free Survival. GHS=Global Health Status. HMA=Hypomethylating Agent. HR=Hazard Ratio. IV=Intravenous. MDS=Myelodysplastic Syndromes. MPN=Myeloproliferative Neoplasms. OS=Overall Survival. PBO=Placebo. PO=Oral. QoL=Quality of Life. SC=Subcutaneous. VEN=Venetoclax.

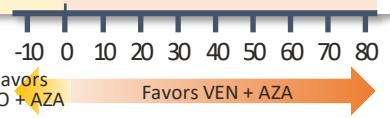
1.Data on File, Abbvie Inc. ABVRRTI70104.
2. ClinicalTrials.gov. NCT02993523 (accessed February 2022)).
3. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29.

VIALE-A: Secondary Endpoint: Response by Subgroups

CR + CRi	VEN + AZA n/N (%)	PBO + AZA n/N (%)	Risk Difference % (95% CI) VEN + AZA vs PBO + AZA
All Subjects	190/286 (66.4)	41/145 (28.3)	38.16 (29.0, 47.3)
Gender			
Female	78/114 (68.4)	17/58 (29.3)	39.11 (24.6, 53.6)
Male	112/172 (65.1)	24/87 (27.6)	37.53 (25.7, 49.3)
Age (years)			
<75	70/112 (62.5)	24/58 (41.4)	21.12 (5.6, 36.7)
≥75	120/174 (69.0)	17/87 (19.5)	49.43 (38.6, 60.2)
Region			
US	40/50 (80.0)	6/24 (25.0)	55.00 (34.4, 75.6)
EU	72/116 (62.1)	15/59 (25.4)	36.65 (22.5, 50.8)
China	17/24 (70.8)	5/13 (38.5)	32.37 (0.3, 64.5)
Japan	16/24 (66.7)	2/13 (15.4)	51.28 (24.1, 78.5)
Rest of World	45/72 (62.5)	13/36 (36.1)	26.39 (7.1, 45.7)
Baseline ECOG			
Grade <2	108/157 (68.8)	20/81 (24.7)	44.10 (32.2, 56.0)
Grade ≥2	82/129 (63.6)	21/64 (32.8)	30.75 (16.6, 44.9)
Type of AML			
De novo	142/214 (66.4)	33/110 (30.0)	36.36 (25.7, 47.0)
Secondary	48/72 (66.7)	8/35 (22.9)	43.81 (26.1, 61.5)



CR + CRi	VEN + AZA n/N (%)	PBO + AZA n/N (%)	Risk Difference % (95% CI) VEN + AZA vs PBO + AZA
Cytogenetic risk			
Intermediate	135/182 (74.2)	28/89 (31.5)	42.72 (31.2, 54.3)
Poor	55/104 (52.9)	13/56 (23.2)	29.67 (15.0, 44.3)
Molecular marker			
FLT3	21/29 (72.4)	8/22 (36.4)	36.05 (10.2, 61.9)
IDH1	13/23 (56.5)	1/11 (9.1)	47.43 (21.0, 73.9)
IDH2	34/40 (85.0)	2/18 (11.1)	73.89 (55.6, 92.1)
IDH1/2	46/61 (75.4)	3/28 (10.7)	64.70 (49.0, 80.4)
TP53	21/38 (55.3)	0/14	55.26 (39.5, 71.1)
NPM1	18/27 (66.7)	4/17 (23.5)	43.14 (16.3, 70.0)
AML-MRC			
Yes	56/92 (60.9)	11/49 (22.4)	38.42 (23.1, 53.8)
No	134/194 (69.1)	30/96 (31.3)	37.82 (26.5, 49.2)
BM blast count			
<30%*	65/85 (76.5)	16/41 (39.0)	37.45 (20.0, 54.9)
30 - <50%	35/61 (57.4)	9/33 (27.3)	30.10 (10.5, 49.7)
≥50%	90/140 (64.3)	16/71 (22.5)	41.75 (29.2, 54.3)



*Blast counts between 20 and <30%.

In the analysis of molecular subgroups, VEN + AZA provided significant improvement in CR + CRi compared to PBO + AZA.

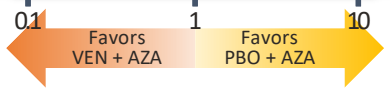
AML=Acute Myeloid Leukemia. AZA=Azacitidine. BM=Bone Marrow. CI=Confidence Interval. CR=Complete Remission. CRi=CR with Incomplete Blood Count Recovery. ECOG=Eastern Cooperative Oncology Group. MRC=Myelodysplasia-Related Changes. PBO=Placebo. VEN=Venetoclax.

Data cutoff date: January 4, 2020.

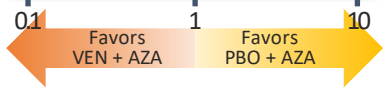
DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29 [suppl].

VIALE-A: Sec Endpoint: Overall Survival by Subgroup

Events	VEN + AZA n/N (%)	PBO + AZA n/N (%)	HR (95% CI)† VEN + AZA vs PBO + AZA
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 (years)			
<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)
Region			
US	27/50 (54.0)	21/24 (87.5)	0.47 (0.26, 0.83)
EU	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			
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)



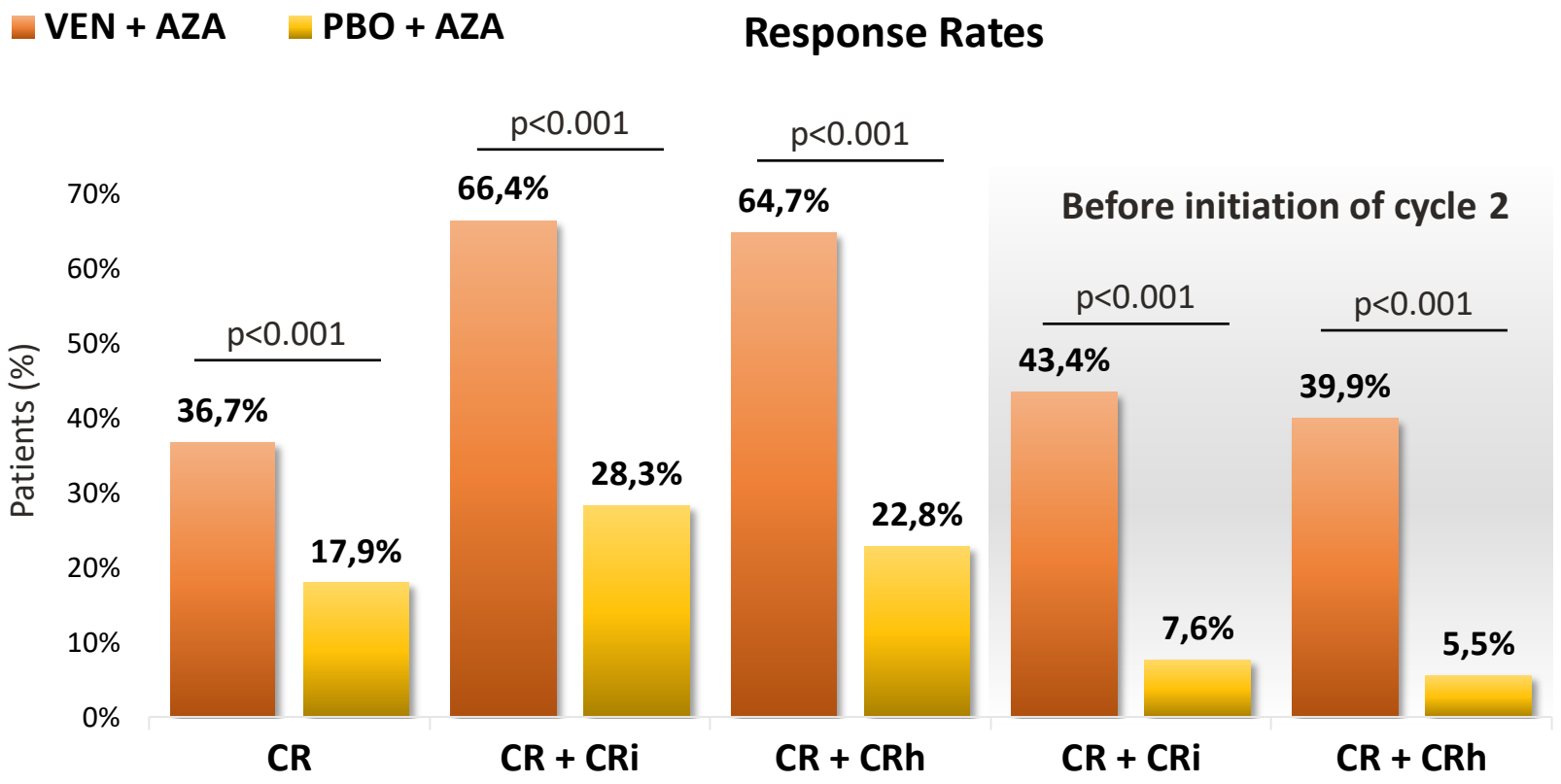
Events	VEN + AZA n/N (%)	PBO + AZA n/N (%)	HR (95% CI)† VEN + AZA vs PBO + AZA
All Subjects	161/286 (56.3)	109/145 (75.2)	0.64 (0.50, 0.82)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41, 0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54, 1.12)
Molecular marker			
FLT3	19/29 (65.5)	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)
IDH1/2	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)
AML-MRC			
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)
BM blast count			
<30%*	46/85 (54.1)	28/41 (68.3)	0.72 (0.45, 1.15)
30 - <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)



In patients with CR + CRi who achieved MRD <10^{-3}, OS at 24-months was **73.6%** in the VEN + AZA arm vs. **63.6%** in the PBO + AZA arm

*Blast counts between 20% and <30%. †The HR for death was estimated using the unstratified Cox proportional hazards model. AML=Acute Myeloid Leukemia.
AZA=Azacitidine. BM=Bone Marrow. CI=Confidence Interval. CR=Complete Remission. CRi=CR with Incomplete Count Recovery. ECOG=Eastern Cooperative Oncology Group. Data cutoff date: January 4, 2020.
HR=Hazard Ratio. MRC=Myelodysplasia-Related Changes. MRD=Measurable Residual Disease. OS=Overall Survival. PBO=Placebo. VEN=Venetoclax. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29.

VIALE-A: Secondary Endpoint: Responses



Median months (range)	VEN + AZA (N=286)	PBO + AZA (N=145)
Time to first response (CR or CRi)	**1.3** (0.6-9.9)	**2.8** (0.8-13.2)
Time to first response (CR or CRh)	**1.0** (0.6-14.3)	**2.6** (0.8-13.2)

In patients with CR + CRi, MRD negativity occurred in:

- **23.4%** receiving VEN + AZA vs
- **7.6%** receiving PBO + AZA

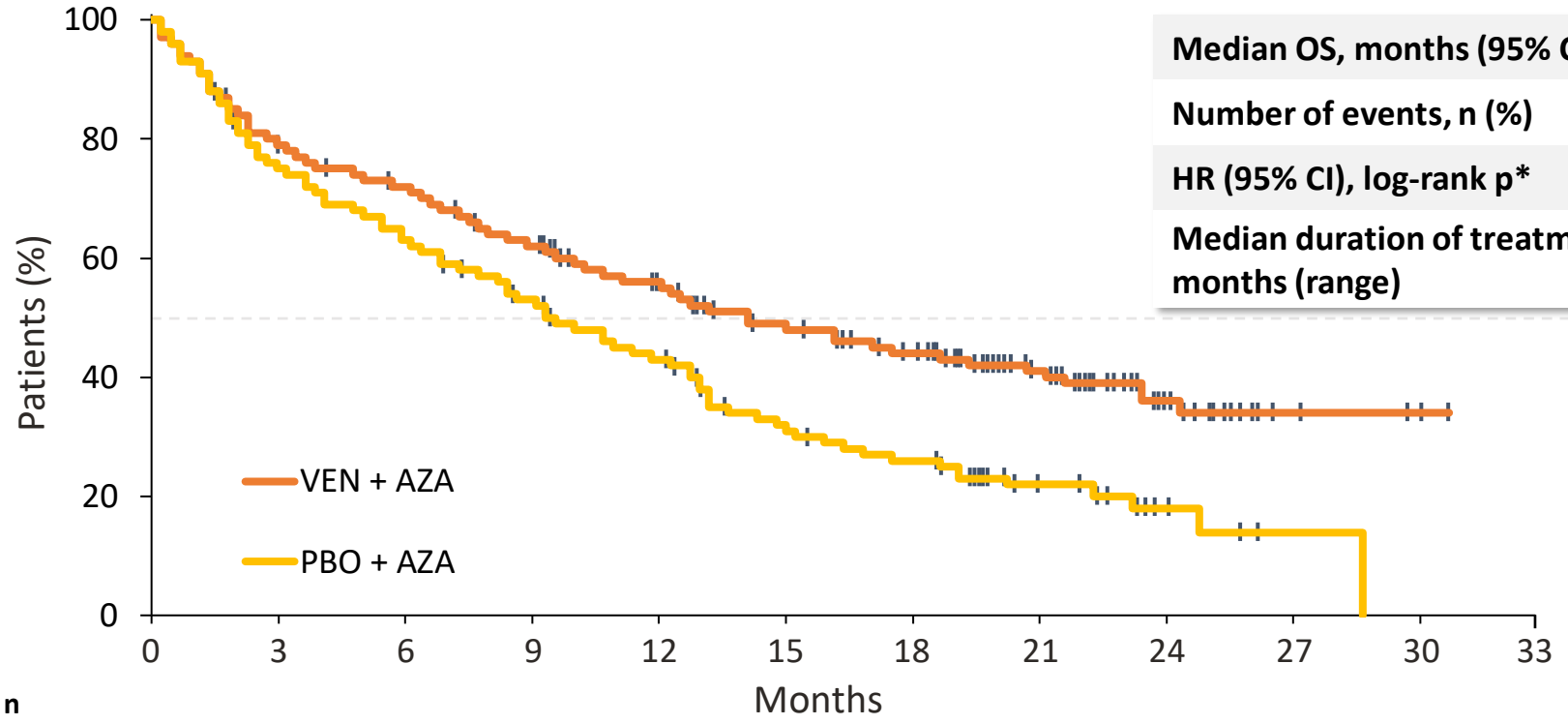
CR + CRi was achieved in 66.4% receiving VEN + AZA vs 28.3% receiving PBO + AZA (p<0.001), while CR + CRi before initiation of cycle 2 was achieved by 43.4% vs 7.6% (p<0.001), respectively

AZA=Azacitidine. CI=Confidence Interval. CR=Complete Remission. CRi=CR with Incomplete Blood Count Recovery. CRh=CR with Partial Hematologic Recovery. MRD=Measurable Residual Disease. NR=Not Reached. PBO=Placebo. VEN=Venetoclax.

Data cutoff date: January 4, 2020.

DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29.

VIALE-A: Overall Survival



At Risk, n												
VEN + AZA	286	219	198	168	143	117	101	54	23	5	3	0
PBO + AZA	145	109	92	74	59	38	30	14	5	1	0	0

	VEN + AZA (N=286)	PBO + AZA (N=145)
Median OS, months (95% CI)	**14.7** (11.9-18.7)	**9.6** (7.4-12.7)
Number of events, n (%)	161 (56)	109 (75)
HR (95% CI), log-rank p*	0.66 (0.52-0.85), p<0.001	
Median duration of treatment, months (range)	7.0 (1.0-30.0)	4.5 (1.0-26.0)

Median follow-up:

20.5 months
(range <0.1 - 30.7 months)

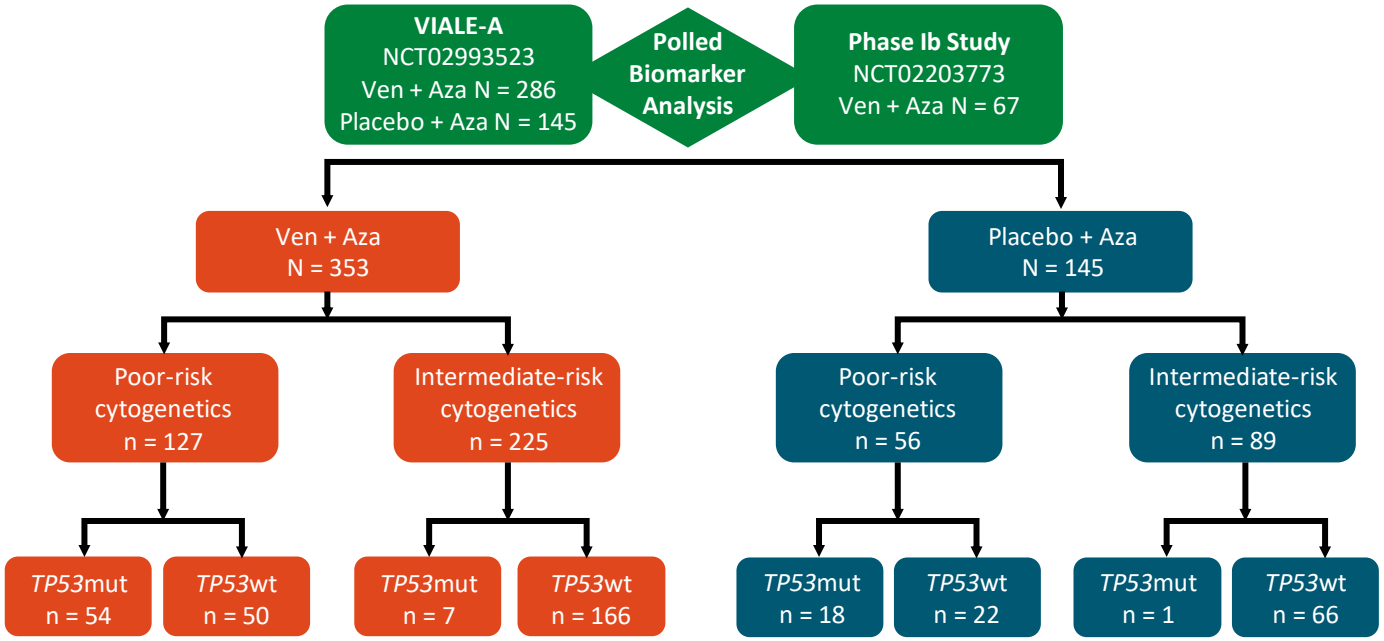
*The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk). The HR between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test. AZA=Azacitidine. CI=Confidence Interval. HR=Hazard Ratio. OS=Overall Survival. PBO=Placebo. VEN=Venetoclax.

Data cutoff date: January 4, 2020.

1. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29.

Ven + Aza in Poor-Risk AML: Study Design

- Data pooled from phase III VIALE-A trial and phase Ib trial of Ven + Aza
- Eligibility: treatment-naive patients with AML, ineligible for CT due to age ≥75 yr and/or comorbidities
- Assessment: local analysis of cytogenetics, central analysis of mutations
- Endpoints: CR + CRi, DoR, OS



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Ven + Aza in Poor-Risk AML: Baseline Characteristics

Characteristic, n (%)	Poor-Risk Cytogenetics				Immediate-Risk Cytogenetics	
	Ven + Aza		Aza		Ven + Aza	Aza
	*TP53*mut (n = 54)	*TP53*wt (n = 50)	*TP53*mut (n = 18)	*TP53*wt (n = 22)	*TP53*wt (n = 166)	*TP53*wt (n = 66)
Median age, yr	77	74.5	75	76.5	77	76.5
Age ≥75 yr	33 (61.1)	25 (50.0)	8 (44.4)	15 (68.2)	106 (63.9)	39 (59.1)
de novo AML	42 (77.8)	30 (60.0)	14 (77.8)	13 (59.1)	128 (77.1)	52 (78.8)
Blast count						
▪ <30%	24 (44.4)	14 (28.0)	8 (44.4)	6 (27.3)	38 (22.9)	16 (24.2)
▪ ≥30% to <50%	12 (22.2)	12 (24.0)	5 (27.8)	6 (27.3)	36 (21.7)	14 (21.2)
▪ ≥50%	18 (33.3)	24 (48.0)	5 (27.8)	10 (45.5)	92 (55.4)	36 (54.5)
ECOG PS 3/4	22 (40.7)	21 (42.0)	8 (44.4)	6 (27.3)	68 (41.0)	28 (42.4)
Mutations						
▪ *FLT3*	3 (5.6)	6 (12.0)	0	2 (9.1)	37 (22.3)	25 (37.9)
▪ *IDH1/2*	2 (3.7)	15 (30.0)	0	6 (27.3)	58 (34.9)	15 (22.7)
▪ *NPM1*	0	0	0	1 (4.5)	42 (25.3)	17 (25.8)
Cytogenetics						
▪ t1 1q23	7 (13.0)	4 (8.0)	1 (5.6)	1 (4.5)	0	0
▪ t3_3	1 (1.9)	5 (10.0)	0	0	0	0
▪ del 5 or 7	42 (77.8)	31 (62.0)	16 (88.9)	16 (72.7)	0	0
▪ Complex karyotype	46 (85.2)	25 (50.0)	17 (94.4)	7 (31.8)	1 (0.6)	0
▪ del 17	9 (16.7)	2 (4.0)	4 (22.2)	0	0	1 (1.5)

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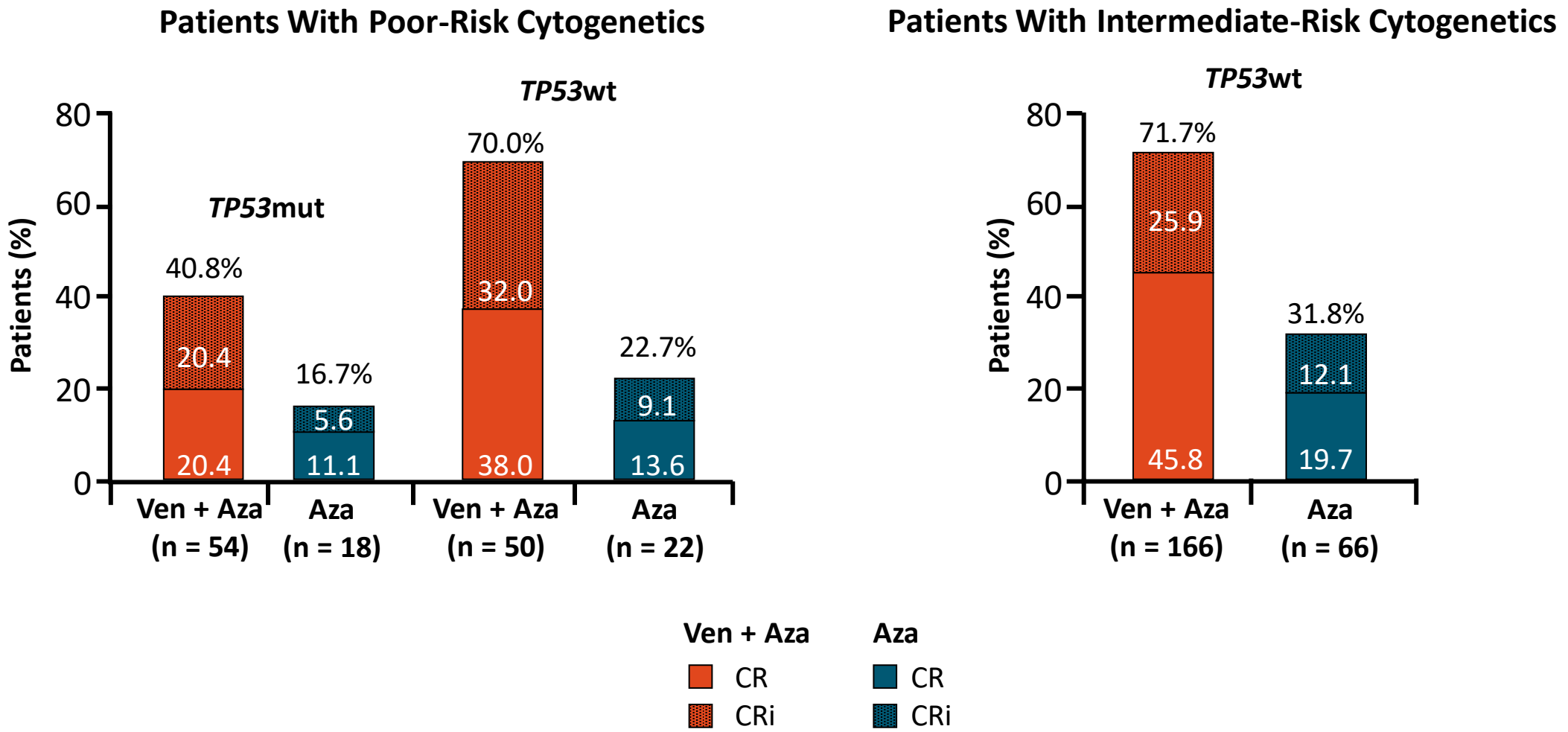
Ven + Aza in Poor-Risk AML: CR/CRi Rates by *TP53* Mutation Status



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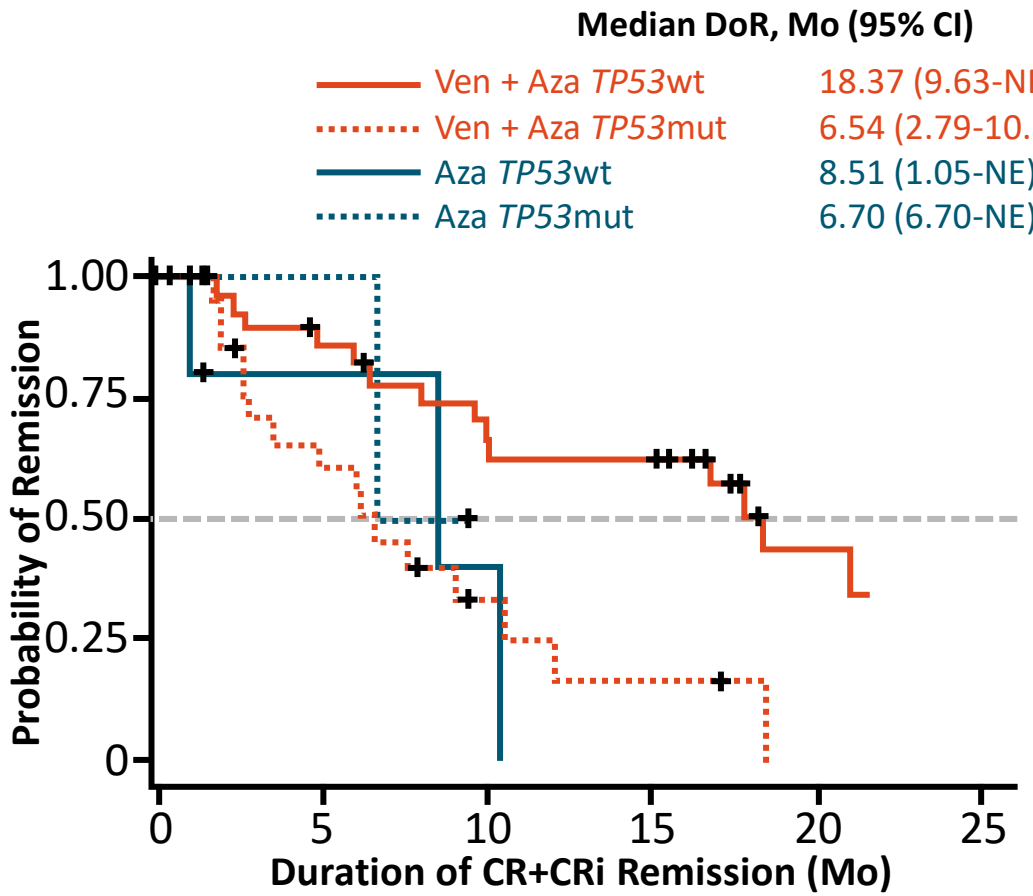
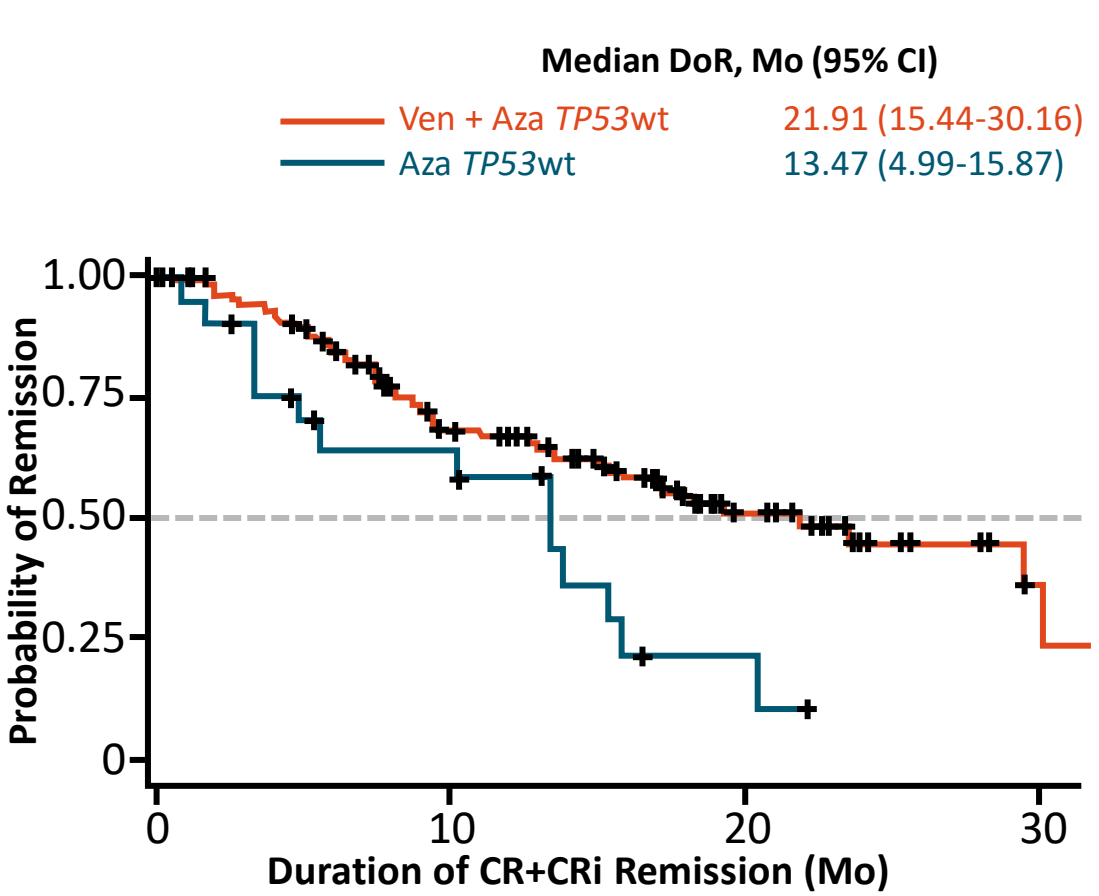
Ven + Aza in Poor-Risk AML: DoR by *TP53* Mutation Status

Poor-Risk Cytogenetics



Intermediate-Risk Cytogenetics



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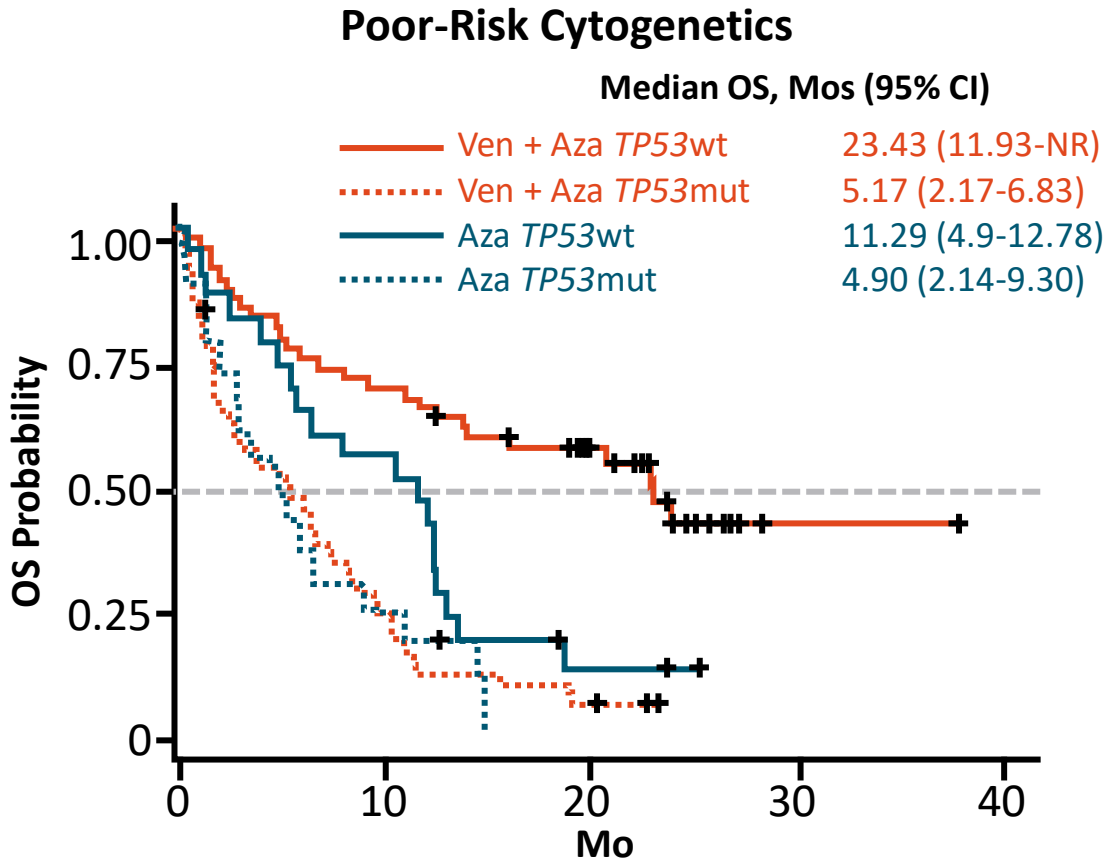
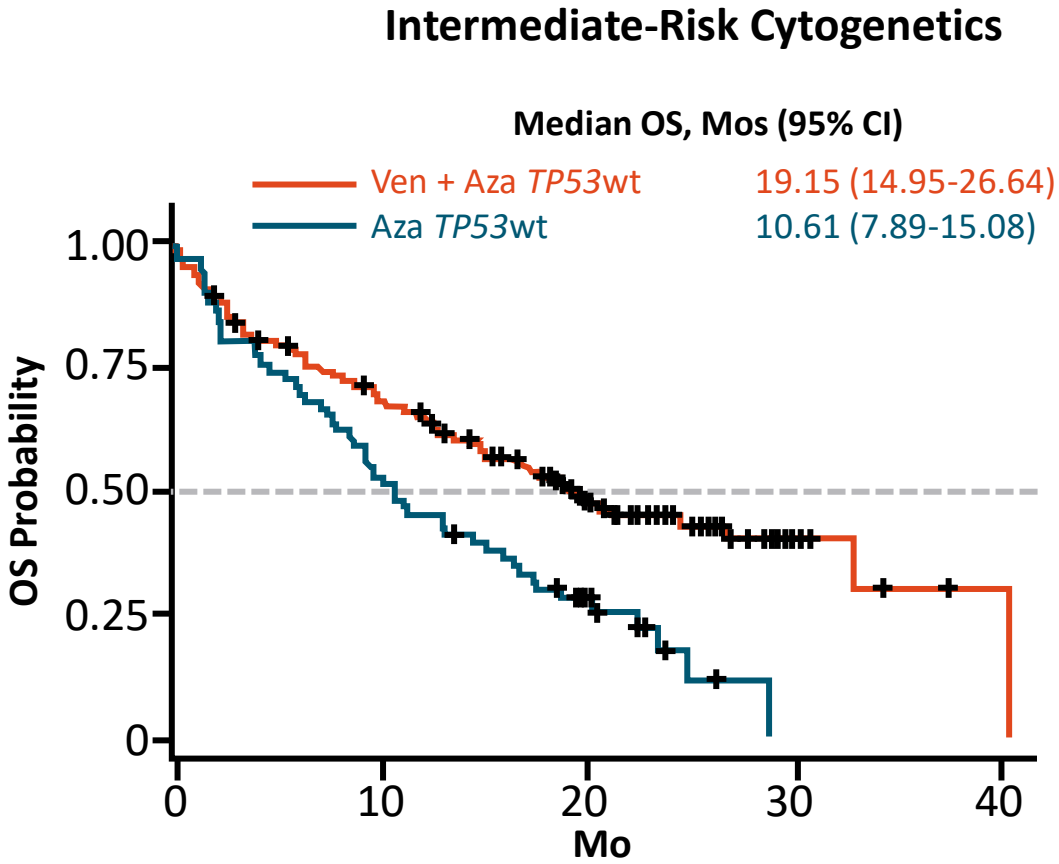
Ven + Aza in Poor-Risk AML: OS by *TP53* Mutation Status





- Variant allele frequency of *TP53* mutations not associated with remission or OS in patients treated with Ven + Aza

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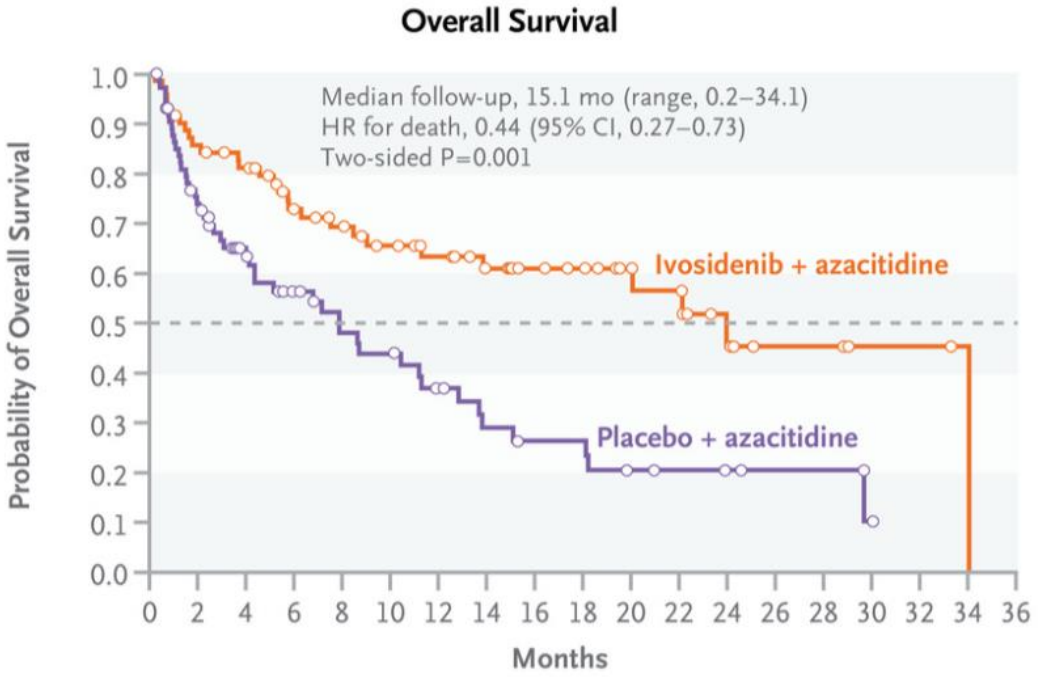
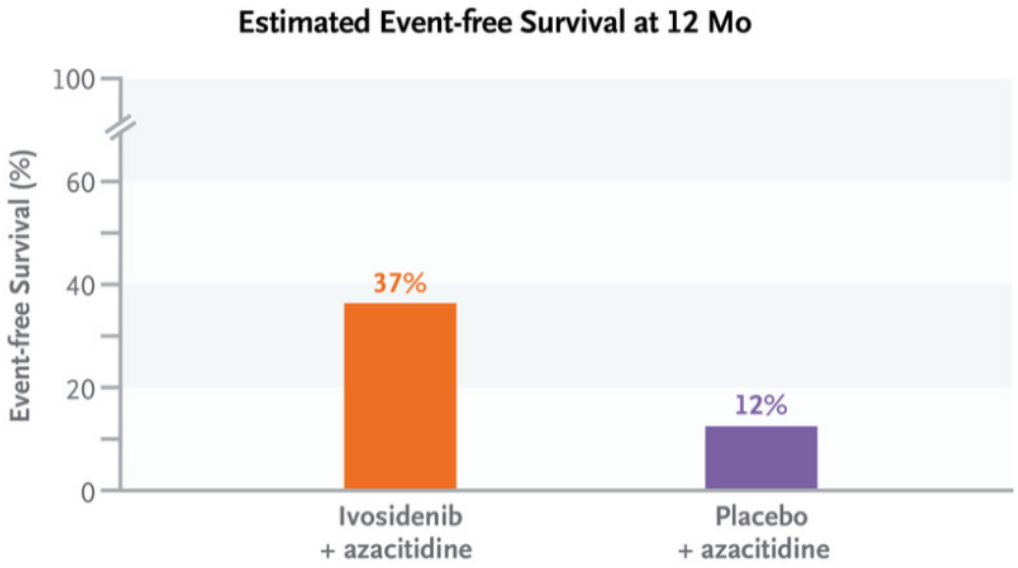
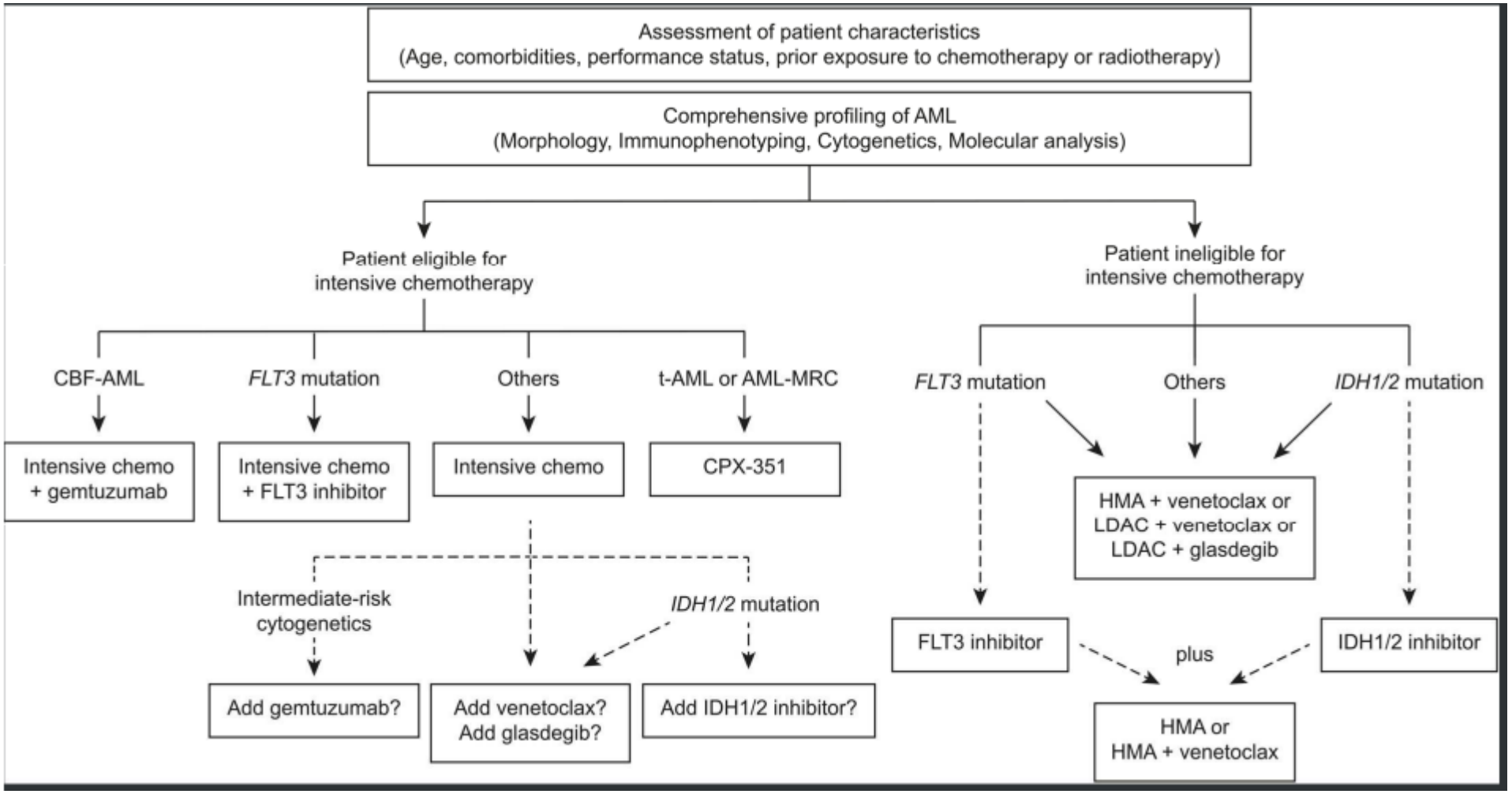
ALIDHE trial : Unfit IDH1 mutated AMl

Ivosidenib vs Placebo met Azacytidine





CONCLUSION



Guillaume Richard-Carpentier,Courtney D. DiNardo, Single-agent and combination biologics in acute myeloid leukemia, Hematology Am Soc Hematol Educ Program, 2019, Figure 2.