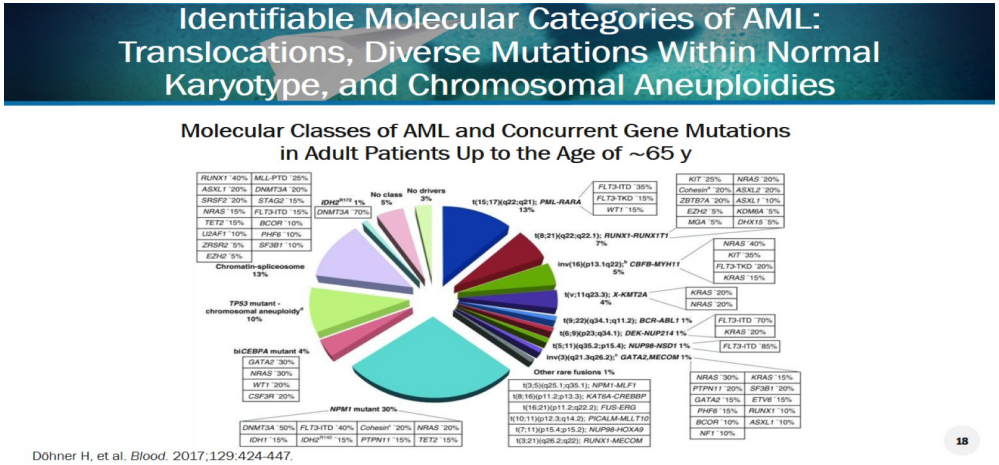
What is boring and disappointing in AML

- We still consider 3 + 7 chemotherapy
- We still transplant
- We still cure very few refractory/relapsed patients
- We still cure very few old patients

- Even though
- We know a lot about molecular pathogenesis



2013 marked the 40th anniversary of "3+7"

- DNR 45 mg/m^2, D 1-3
- Ara-C 100 mg/m^2, D 1-7

- **More than many italian marriages**
- **More than most italian politicians**

	No.	RC (%)
Untreated AML	8	5 (62)
Previously treated AML	8	2 (25)
Overall	16	7 (44)

Yates JW et al, Cancer Chemother Rep 1973

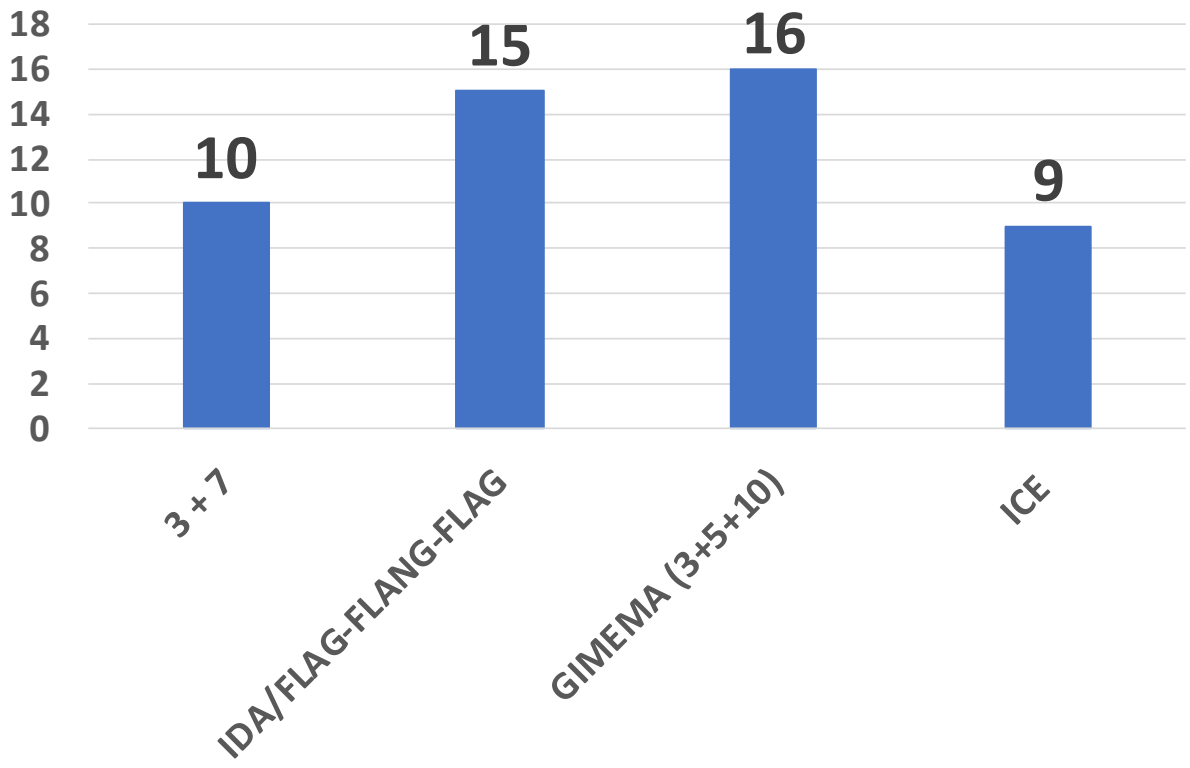
The “3+7” Longevity

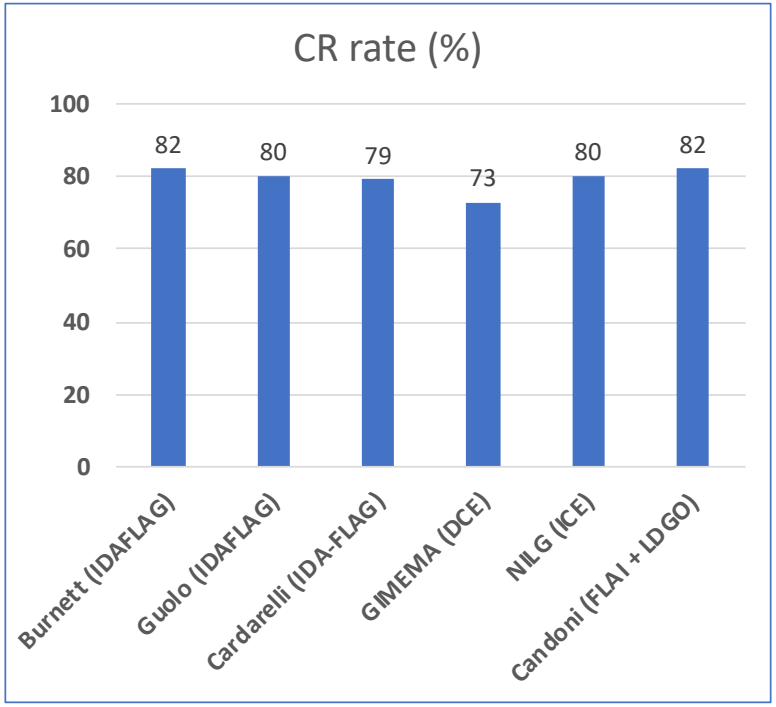
- Few therapeutic approaches for malignant diseases have remained essentially the same for 40 years
- Longevity due to a constellation of genetic patterns in AML explaining lack of significant advances with new approaches
- AML is considered a medical emergency, therefore it is no possible to stratify in induction (no true apart from APL)
  - Refinements rather than changes

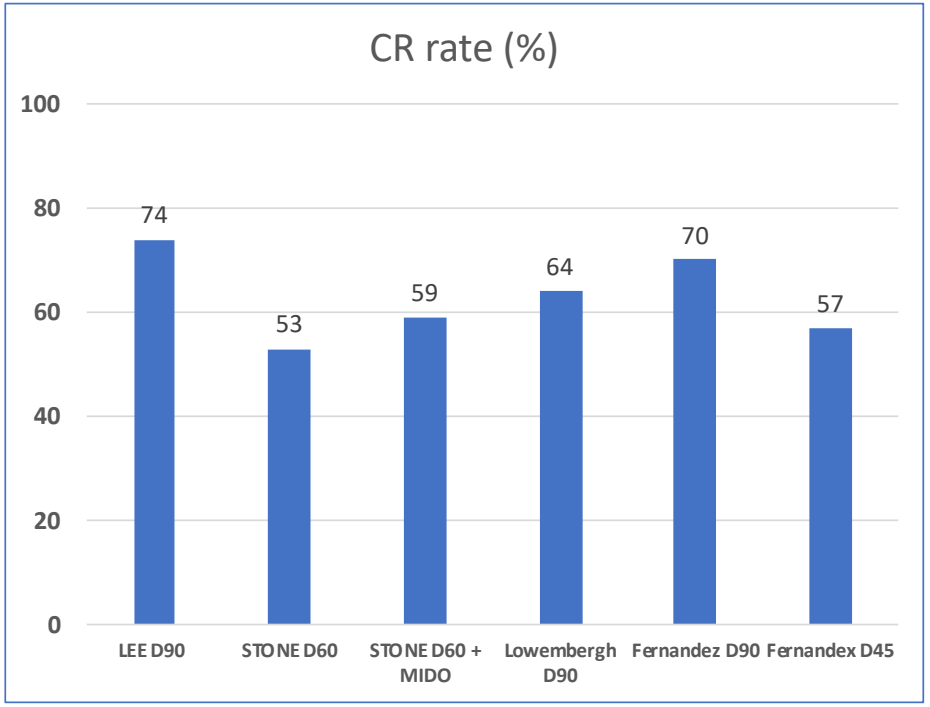
Quale regime usi in induzione:

- **3+7**
- **IDA-FLAG/FLANG/FLAG**
- **3+5+10 (GIMEMA)**
- **ICE**

Tot 3 + 7: 20%

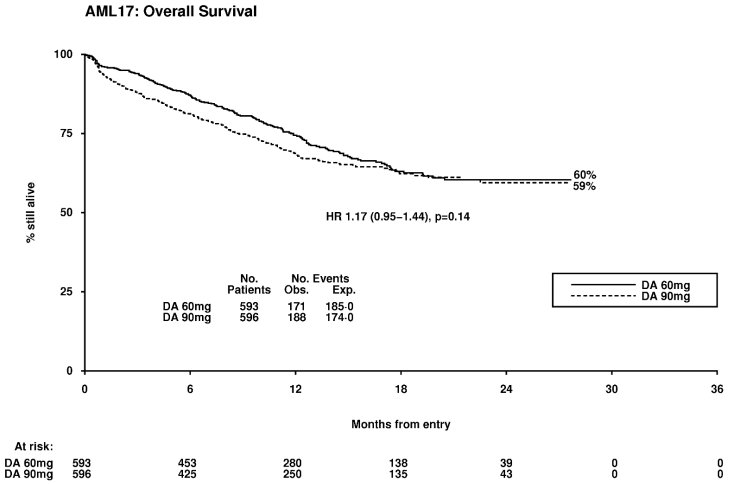



CR rate (%)
100
80
60
40
20
0
82
80
79
73
80
82
Burnett (IDAFLAG)
Guolo (IDAFLAG)
Cardarelli (IDA-FLAG)
GIMEMA (DCE)
NILG (ICE)
Candoni (FLAI + LDGO)

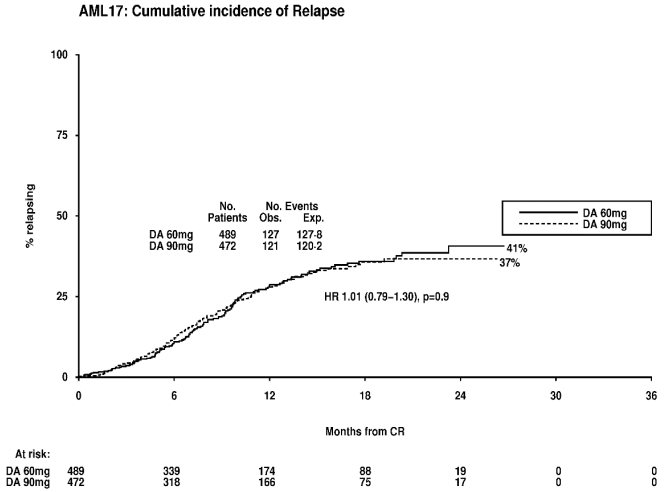

CR rate (%)
100
80
60
40
20
0
74
53
59
64
70
57
LEE D90
STONE D60
STONE D60 + MIDO
Lowembergh D90
Fernandez D90
Fernandex D45

DNR 90 vs 60 mg (NCRI AML17)

OS

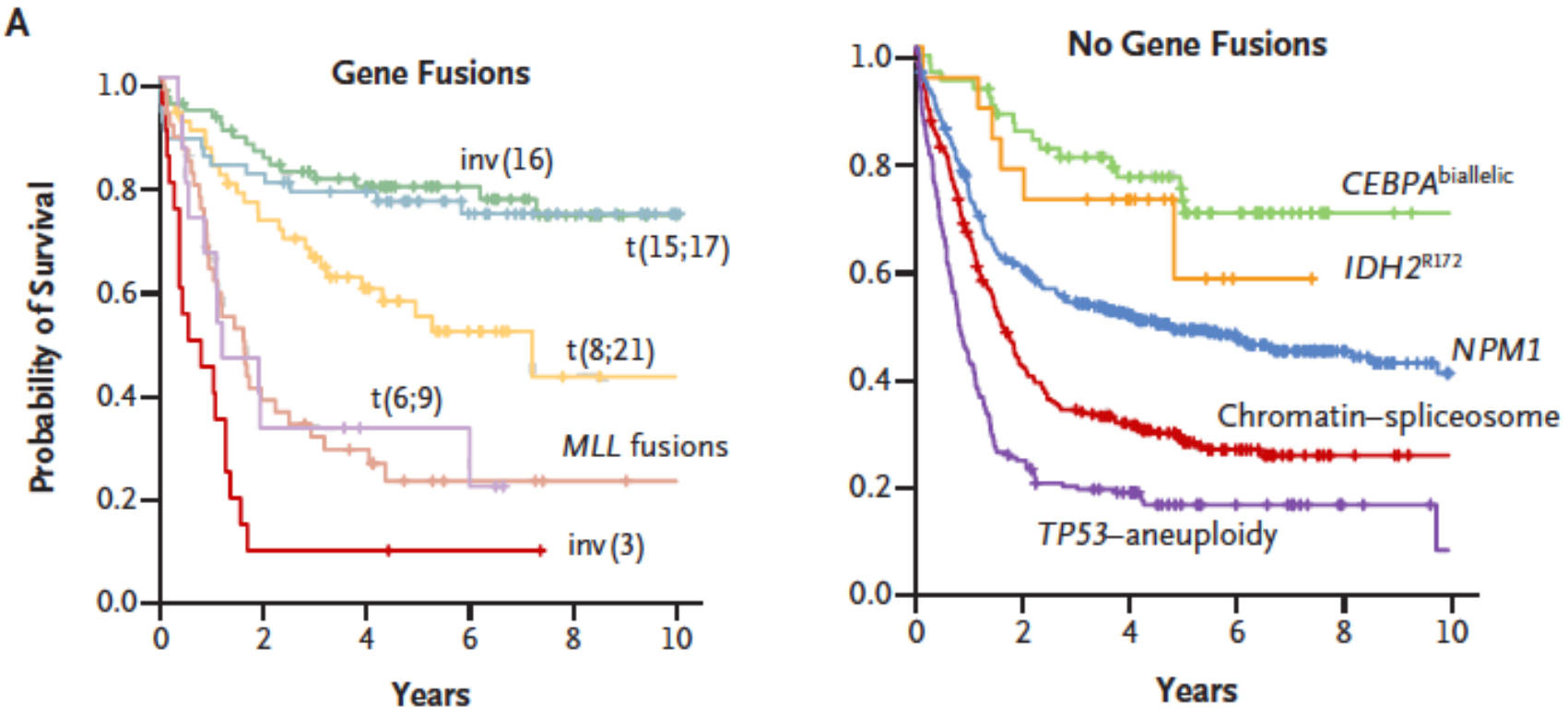


CIR



Burnett et al, Blood 2015

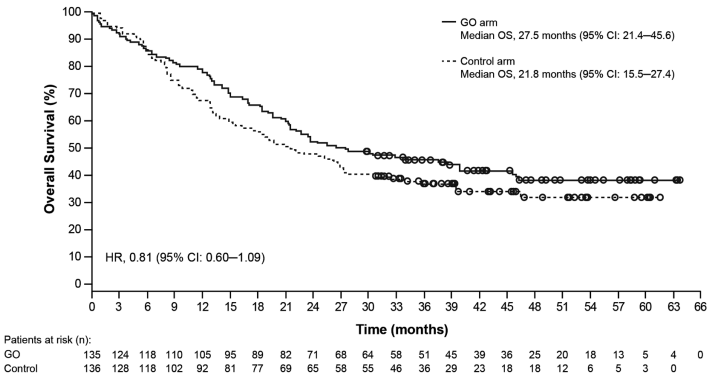
Outcomes of 7+3 by AML Disease Biology



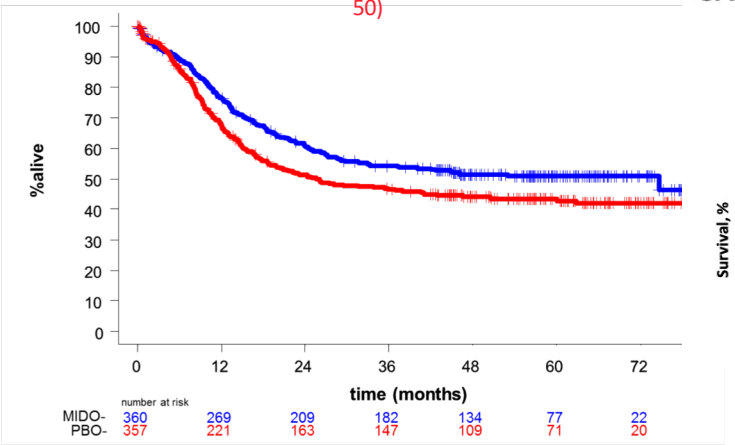
Papaemmanuil E, et al. *N Engl J Med*. 2016;74(23):2209-2221.

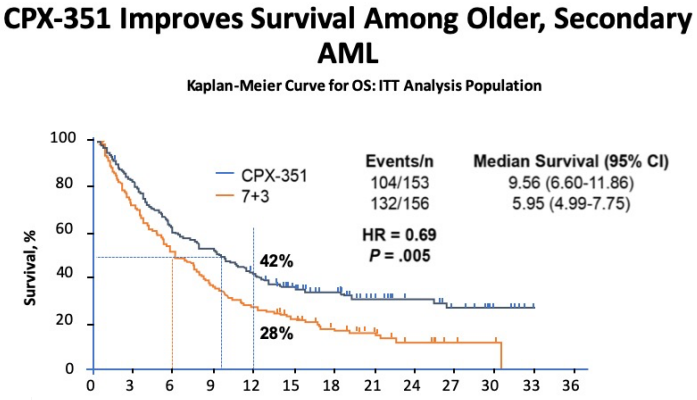
How and when 3 + 7 lost

GO



Arm	4-year Survival
MIDO	51.4% (95%CI: 46, 57)
PLACEBO	44.2% (95%CI: 39, 50)

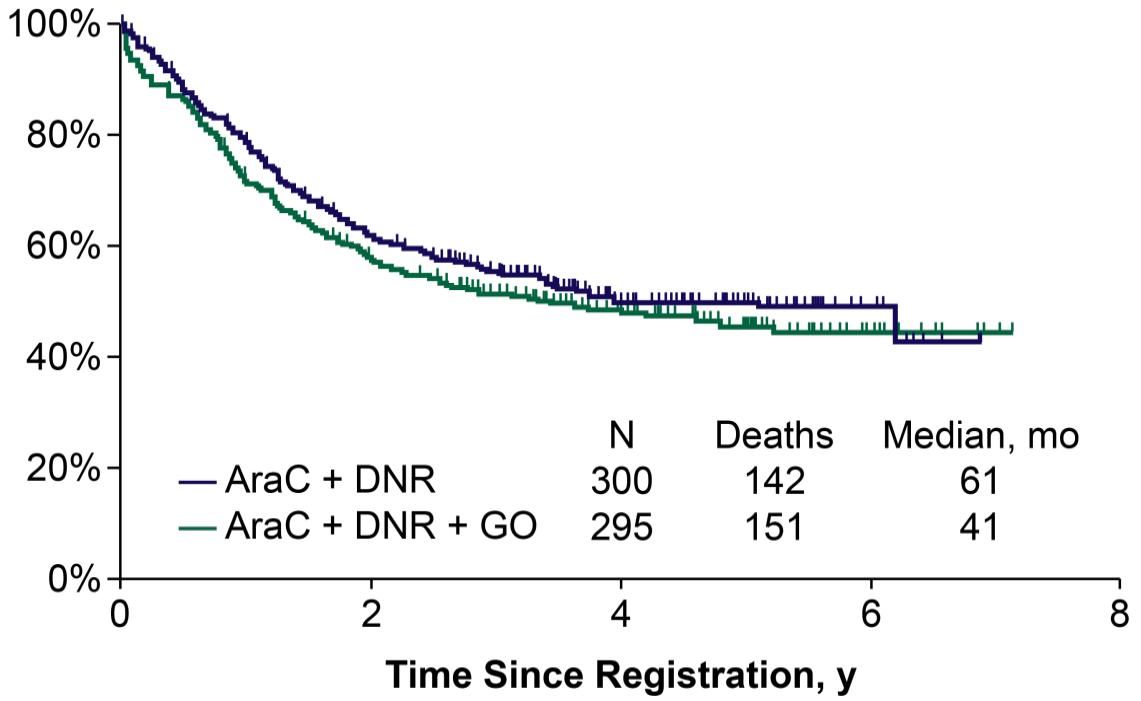




Gemtuzumab Ozogomycin: Confirmatory Trial

SWOG-0106

- 595 newly diagnosed patients with AML
- AraC + DNR vs
  AraC + DNR + GO
- No difference in OS
- ID 1% vs 6%
- Drug withdrawn from market…



Problem with DNR dose? GO at 6 mg/m^2 too high?

1. Petersdorf SH et al. *Blood*. 2013;121:4854-4860.

GO+IC: meta-analysis of RCT

Trial	GO dose/sched	Induction Chemo	No. of patients	Median age (years)	CG Risk (MRC)
MRC AML15	**3 mg/m^2 d1**	ADE,DA, FLAG-Ida	1099	50 (15-71)	All
NCRI AML16		DA, DClo	1115	67 (51-84)	All
SWOG-0106	**6 mg/m^2 d4**	DA (3+7)	595	47 (18-60)	All
GOELAMS AML2006/IR		DA (3+7)	238	50.5 (18-60)	Inter
ALFA-0701	**3 mg/m^2 d1,4,7**	DA (3+7)	278	62 (50-70)	Inter/Adv

Hills et al, Lancet Oncol 2014

Gemtuzumab Ozogamicin Meta-Analysis of Five AML Randomized Trials

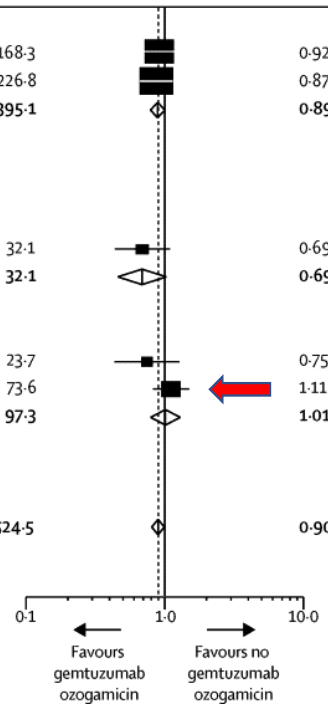
Five randomized trials of 3,325 patients:
SWOG, ALFA, UK-MRC AML15 and 16, GOELAMS

Addition of GO
❑ No ↑ CR rate: OR, 0.91; *P* = .3
❑ Did not increase mortality: OR, 1.13; *P* = .4
❑ Improved survival: OR, 0.89; *P* = .01
❑ Reduced relapse: OR, 0.81; *P* = .001
❑ Highly significant survival benefit for favorable risk (OR, 0.47; *P* = .006) and intermediate risk (OR, 0.84; *P* = .005)

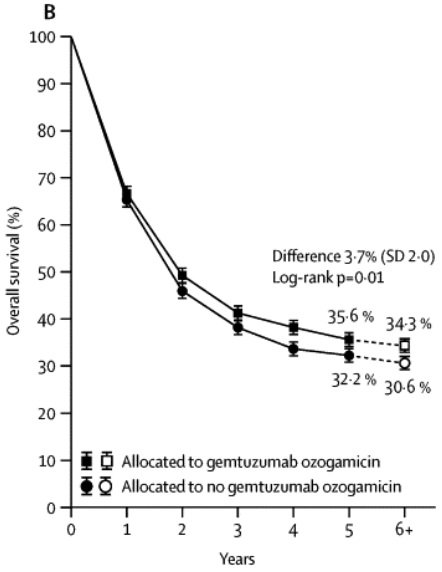
Overall Survival

A

	Events/patients		o–e	Variance	OR (CI*)	p value
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group				
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						



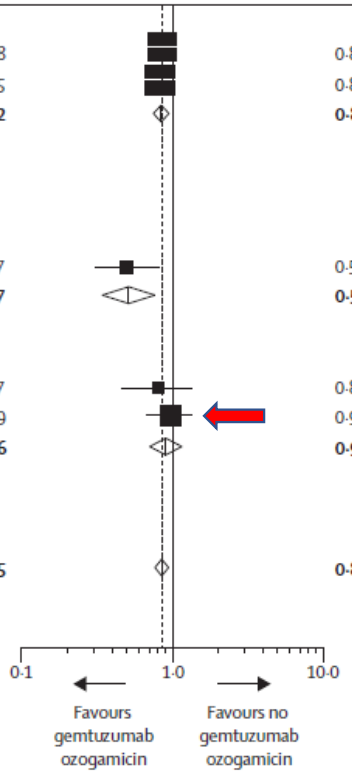
B



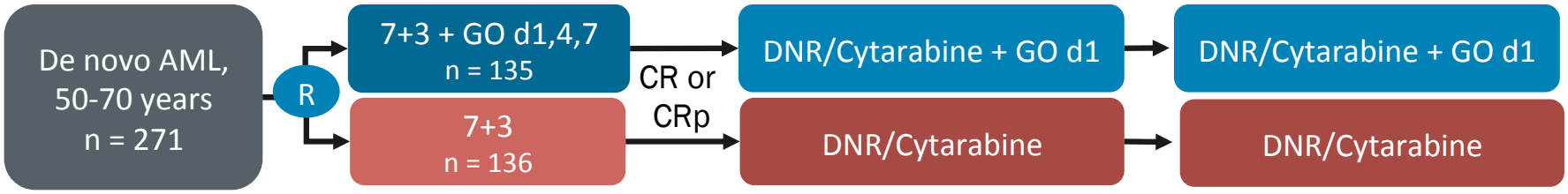
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	26·7 % SD 0·8	3·5 % SD 0·8
No gemtuzumab ozogamicin	29·5 % SD 0·9	5·2 % SD 1·0

Relapse

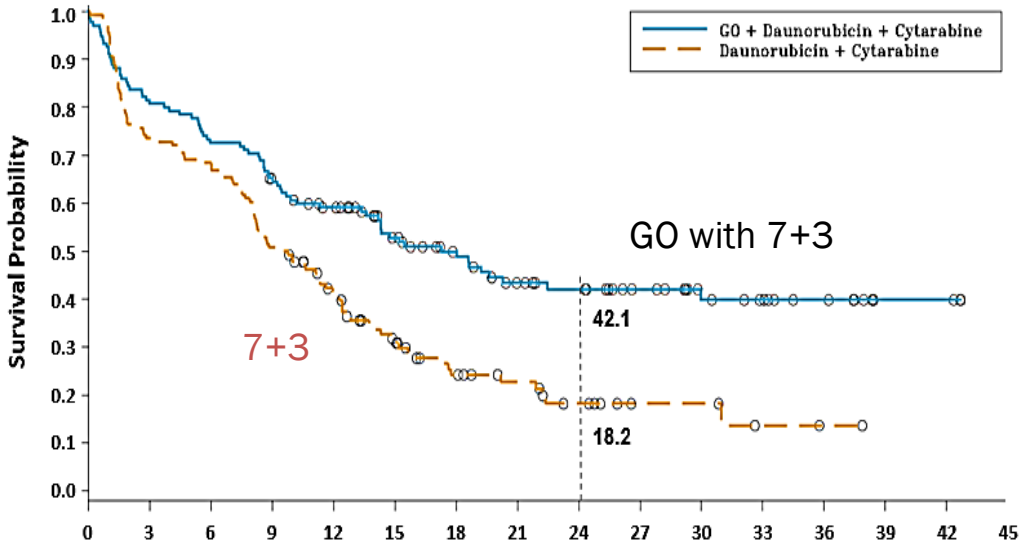
	Events/patients		o–e	Variance	OR (CI*)	p value
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group				
3 mg/m² single dose						
MRC AML15	282/466	314/478	–20·8	148·8	0·87 (0·70–1·07)	
NCRI AML16	325/396	321/376	–27·2	159·5	0·84 (0·69–1·03)	
Subtotal	**607/862**	**635/854**	**–48·0**	**308·2**	**0·86 (0·77–0·96)**	**0·006**
Test for heterogeneity between trials χ^2=0·1; p=0·8						
3 mg/m² fractionated						
ALFA-0701	51/113	69/104	–19·1	28·7	0·51 (0·32–0·83)	
Subtotal	**51/113**	**69/104**	**–19·1**	**28·7**	**0·51 (0·36–0·74)**	**0·0004**
6 mg/m² dose						
GOELAMS AML2006 IR	43/109	48/102	–4·9	22·7	0·81 (0·47–1·39)	
SWOG 0106	118/222	122/222	–2·5	59·9	0·96 (0·69–1·34)	
Subtotal	**161/331**	**170/324**	**–7·4**	**82·6**	**0·91 (0·74–1·14)**	**0·4**
Test for heterogeneity between trials χ^2=0·5; p=0·5						
Total	**819/1306**	**874/1282**	**–74·4**	**419·5**	**0·84 (0·76–0·92)**	**0·0003**
Test for heterogeneity (five trials) χ^2=8·2; p=0·08						
Test for heterogeneity between subtotals χ^2=7·7; p=0·02						



ALFA-0701: Phase 3 Trial of GO Plus 7+3 vs 7+3



Event-free survival

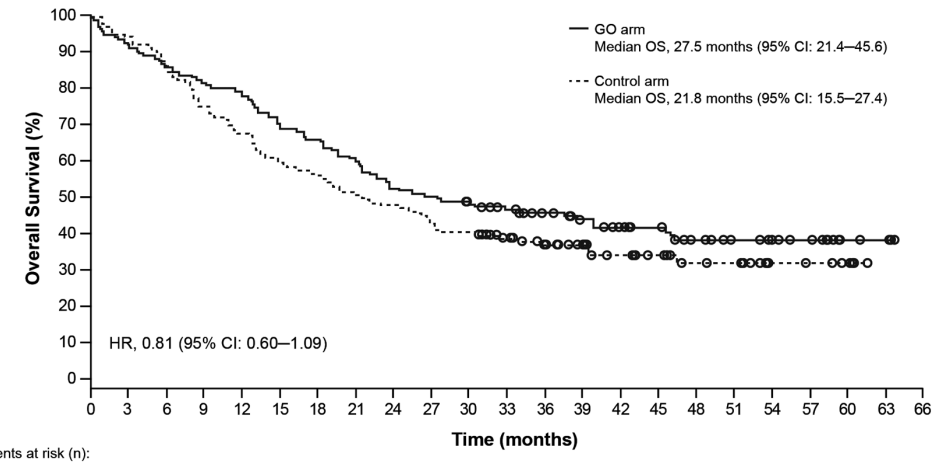


- GO better for favorable/intermediate risk

- Increased Gr3 hemorrhage
- Prolonged thrombocytopenia
- No increase in early mortality (3.8% vs 2.2%) with GO
- VOD 4.6% (GO/7+3) vs 1.5% (7+3)

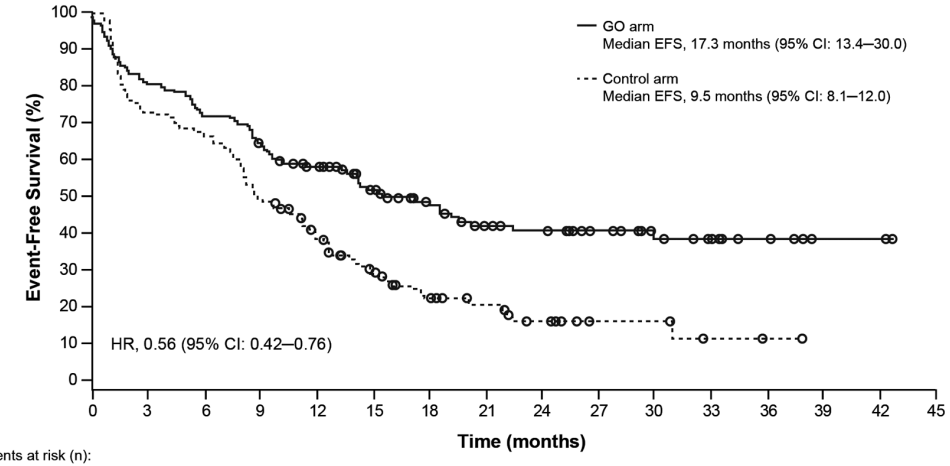
Lambert J, et al. *Haematologica*. 2018. [Epub ahead of print]

AGE: 50-70



Patients at risk (n):

GO	135	124	118	110	105	95	89	82	71	68	64	58	51	45	39	36	25	20	18	13	5	4	0
Control	136	128	118	102	92	81	77	69	65	58	55	46	36	29	23	18	18	12	6	5	3	0	



Patients at risk (n):

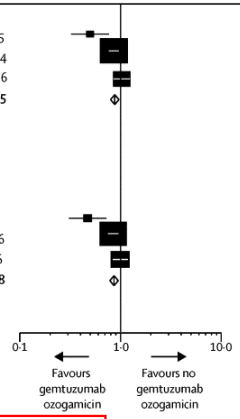
GO	135	109	98	86	74	57	47	36	32	25	18	15	10	3	3	0						
Control	136	100	93	69	51	32	21	16	10	5	5	2	1	0								

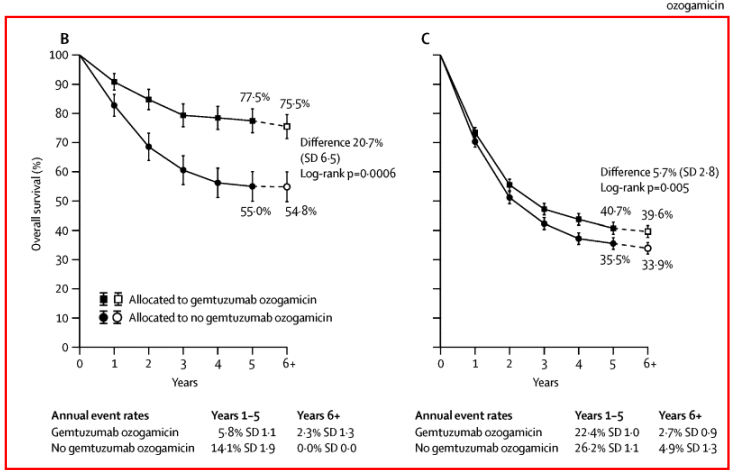
Lambert et al. Haematologica, 2019

Survival by Cytogenetics

A

	Events/patients		o–e	Variance	OR (95% CI)	p value
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group				
Original coding						
Favourable	32/125	54/126	−14·3	20·5	0·50 (0·32–0·77)	
Intermediate	549/962	596/964	−44·2	284·4	0·86 (0·76–0·96)	
Adverse	223/261	227/256	3·1	110·6	1·03 (0·85–1·24)	
Subtotal	**804/1348**	**877/1346**	**−55·4**	**415·5**	**0·88 (0·79–0·96)**	**0·007**
Test for heterogeneity between subgroups: χ^2=9·6; p=0·008						
Test for trend between subgroups: χ^2=7·8; p=0·005						
Revised MRC coding[12]						
Favourable	30/122	54/124	−15·5	20·6	0·47 (0·31–0·73)	
Intermediate	506/911	559/916	−45·3	264·6	0·84 (0·75–0·95)	
Adverse	260/299	258/284	−1·2	127·6	0·99 (0·83–1·18)	
Subtotal	**796/1332**	**871/1324**	**−61·9**	**412·8**	**0·86 (0·78–0·95)**	**0·002**
Test for heterogeneity between subgroups: χ^2=10·1; p=0·006						
Test for trend between subgroups: χ^2=7·7; p=0·006						





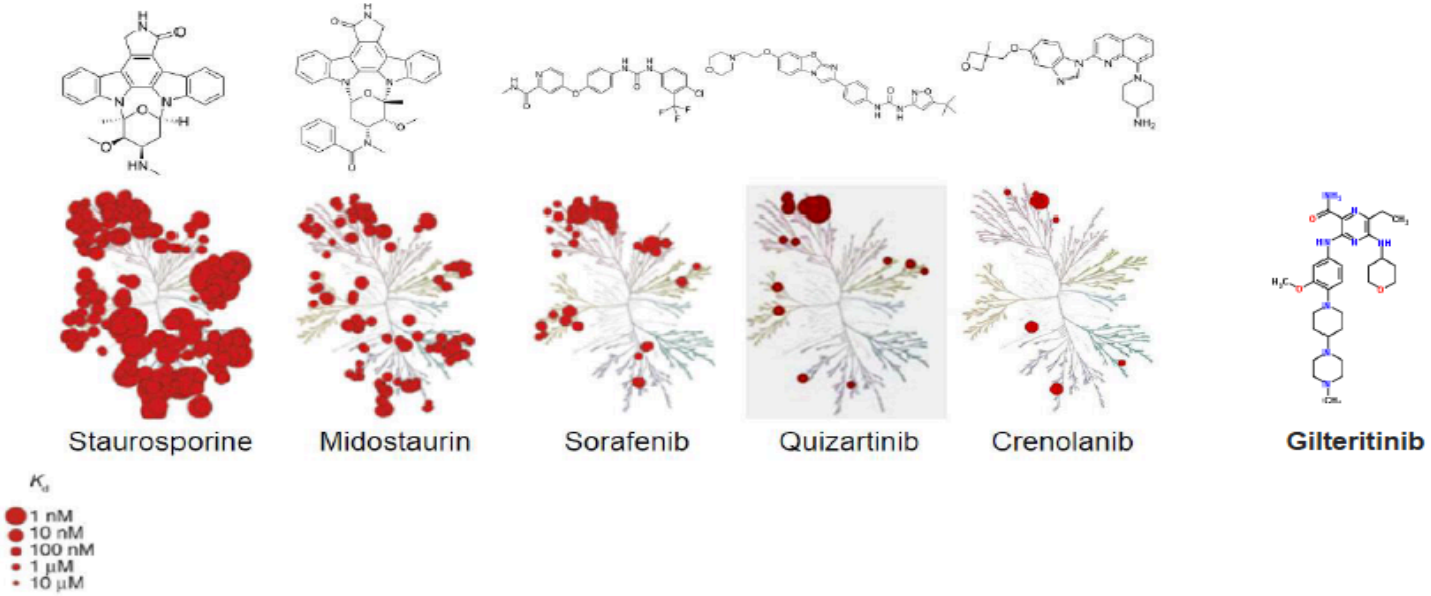
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

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

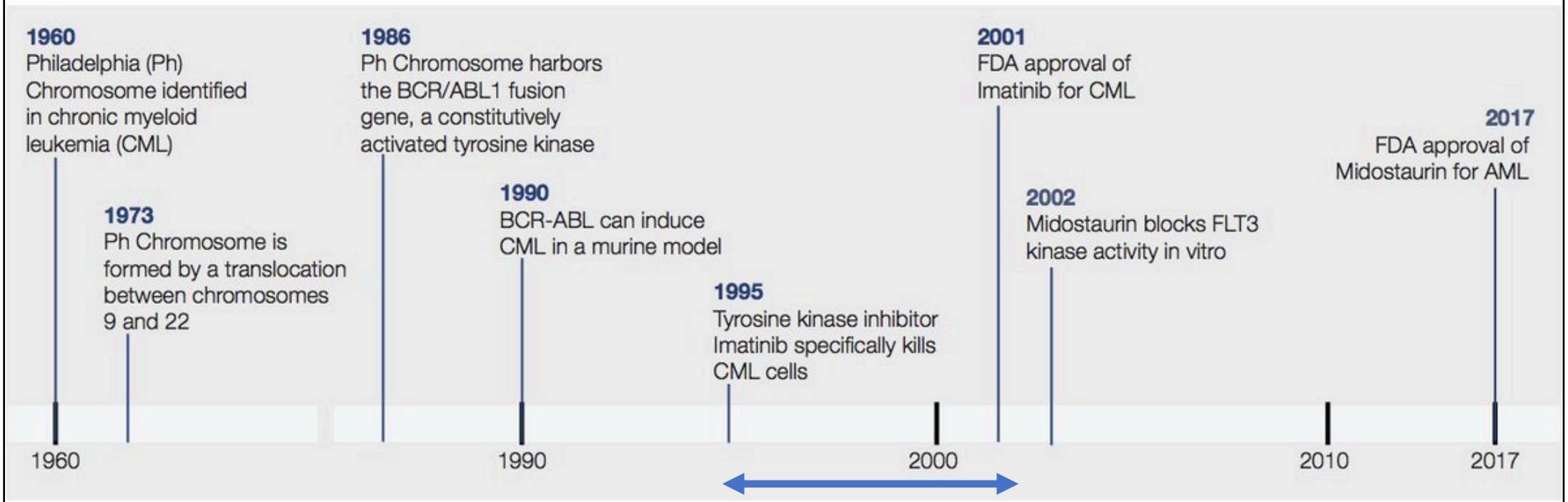
Addition of FLT3 inhibitors

Specificity and Potency of TKI Inhibitors

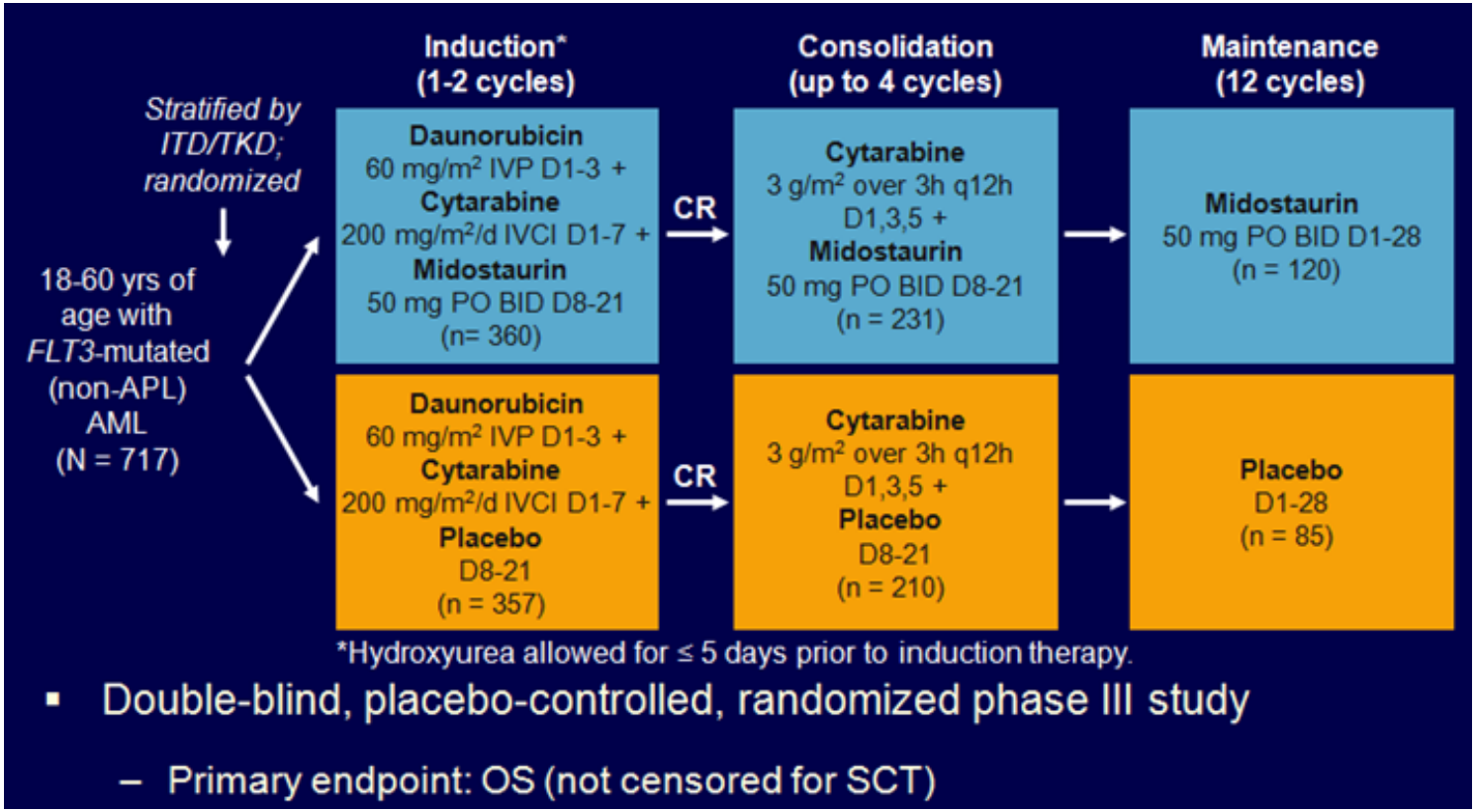


TKI, tyrosine kinase inhibitor

Karaman MW, et al. *Nat Biotechnol.* 2008;26(1):127-132. Karrinkar PP, et al. *Blood.* 2009;114(14):2984-2992.

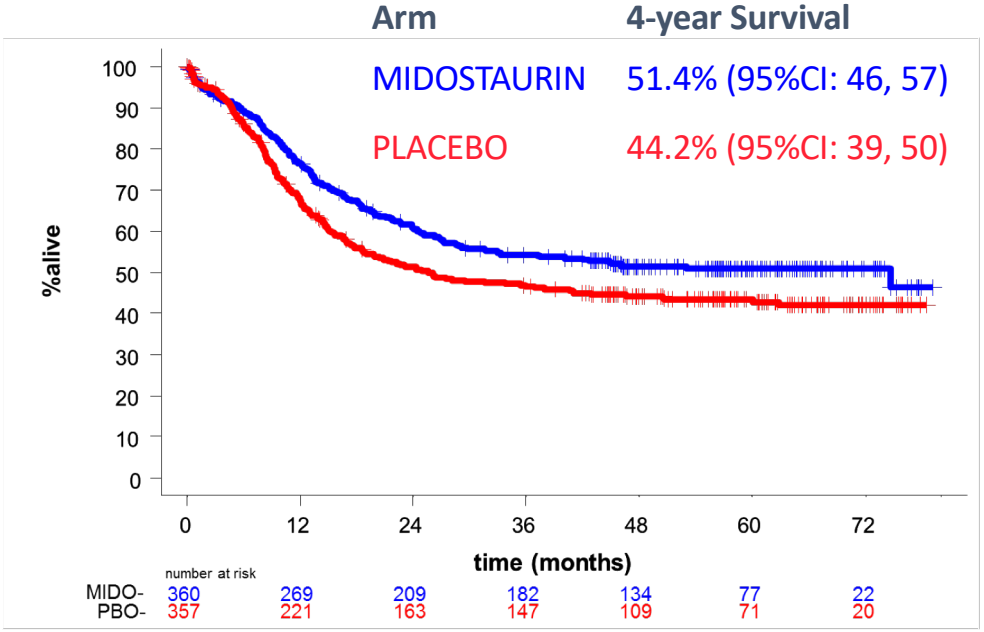

1960
Philadelphia (Ph) Chromosome identified in chronic myeloid leukemia (CML)
1973
Ph Chromosome is formed by a translocation between chromosomes 9 and 22
1986
Ph Chromosome harbors the BCR/ABL1 fusion gene, a constitutively activated tyrosine kinase
1990
BCR-ABL can induce CML in a murine model
1995
Tyrosine kinase inhibitor Imatinib specifically kills CML cells
2001
FDA approval of Imatinib for CML
2002
Midostaurin blocks FLT3 kinase activity in vitro
2017
FDA approval of Midostaurin for AML
1960
1990
2000
2010
2017

RATIFY: study design

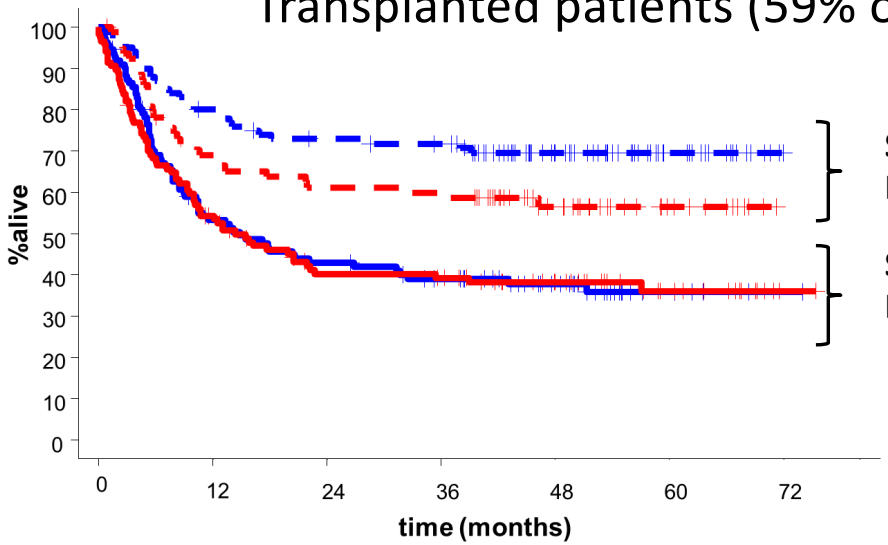


Stone RM et al, NEJM, 2017

Survival on Midostaurin



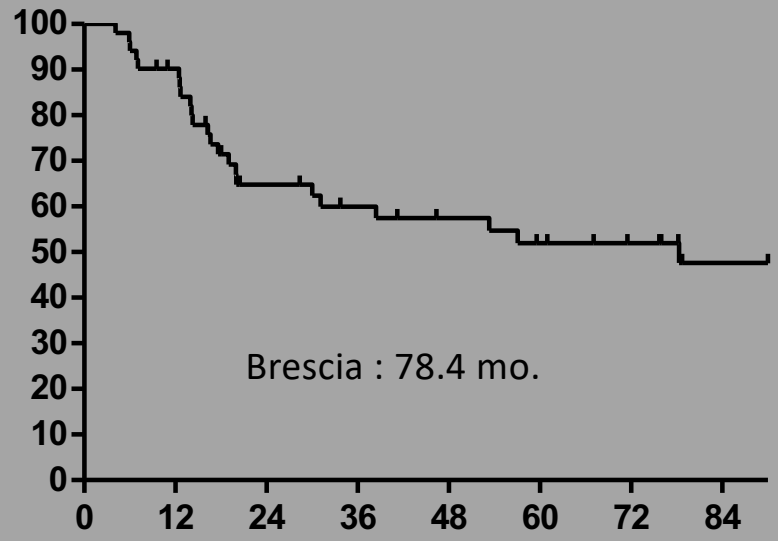
Transplanted patients (59% of enrolled)

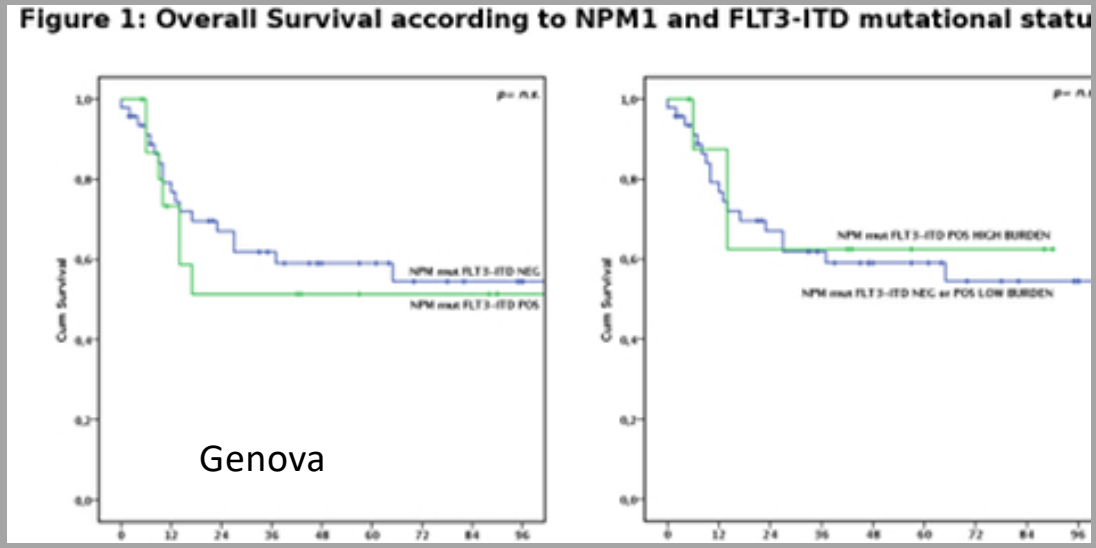


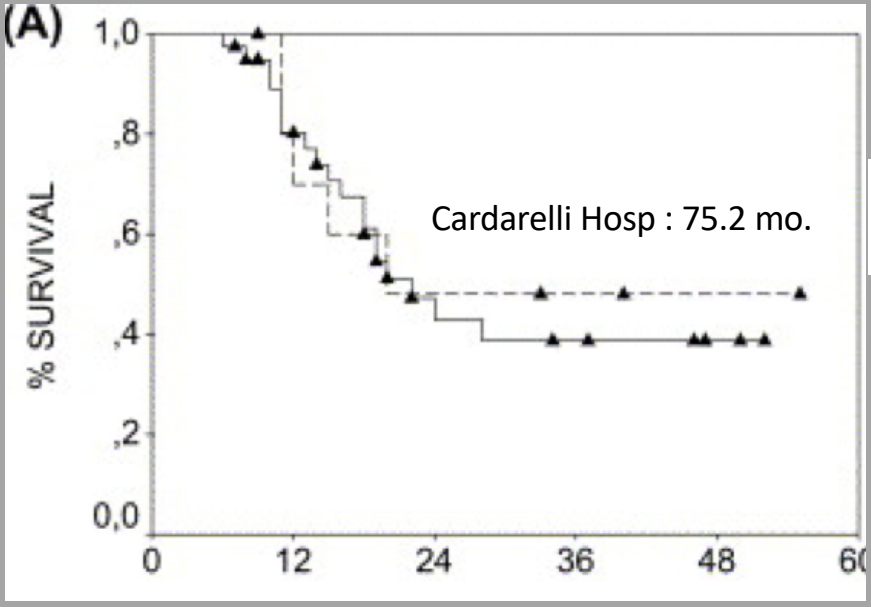
	MIDO (N=360)	PBO (N=357)	p *
CR by day 60	212 (59%)	191 (53%)	0.15
CR in induction/consolidation	239 (66%)	211 (59%)	0.045
Time to CR, median (range)	37 days (20-99)	36 days (20-112)	

RATIFY/C10603

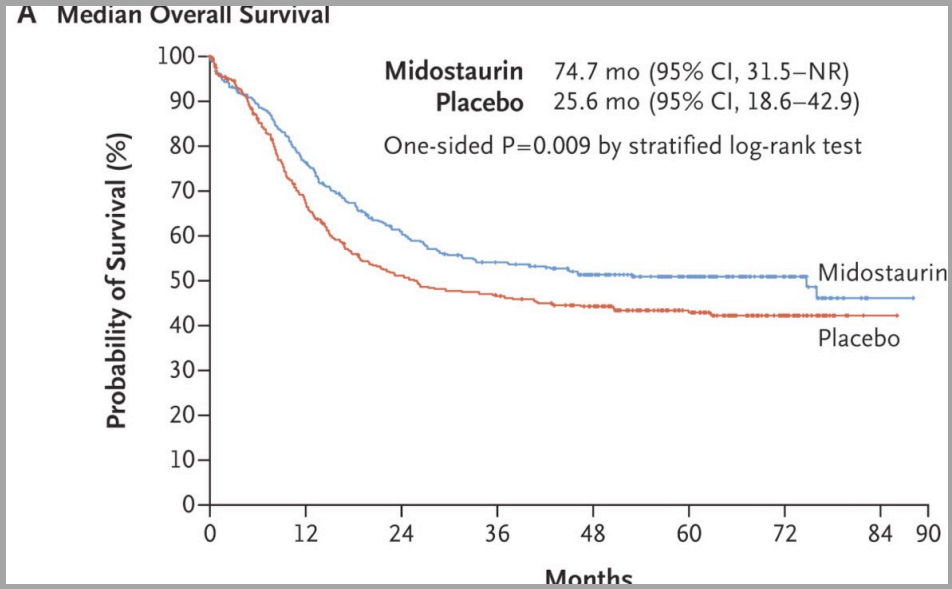
Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464





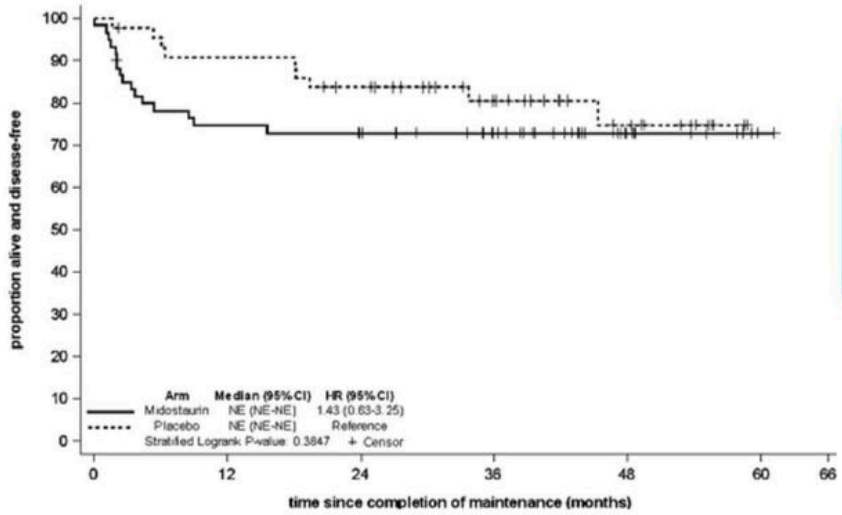


CR rate > 75 %
in all series



DFS After Maintenance
CALGB 10603 (RATIFY), Phase 3

- Landmark analysis of DFS for patients who completed planned maintenance (n = 104), starting at time of last dose of study drug



DFS at 1 year from end of maintenance
- Midostaurin, 75%
- Placebo, 91%

Larson RA, et al. *Blood.* 2017;130. Abstract 145.

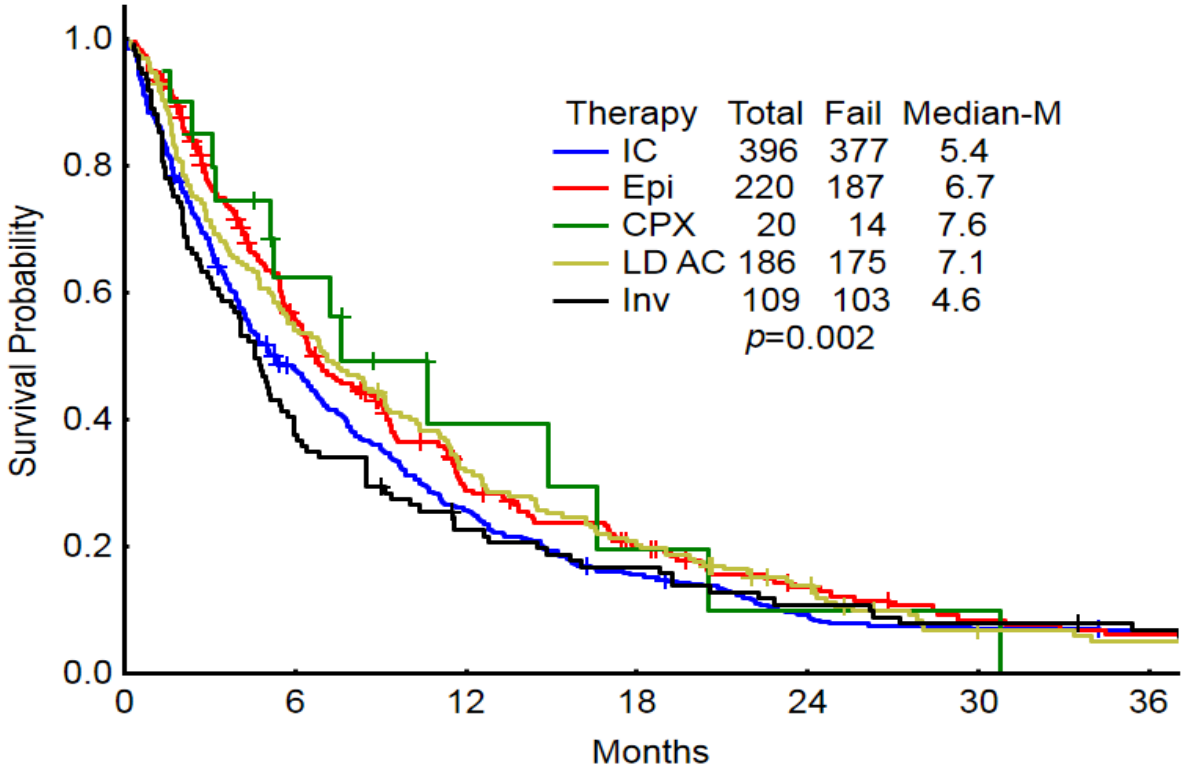
Midostaurin in AML

- First agent with (sustained) regulatory approval in 40 years

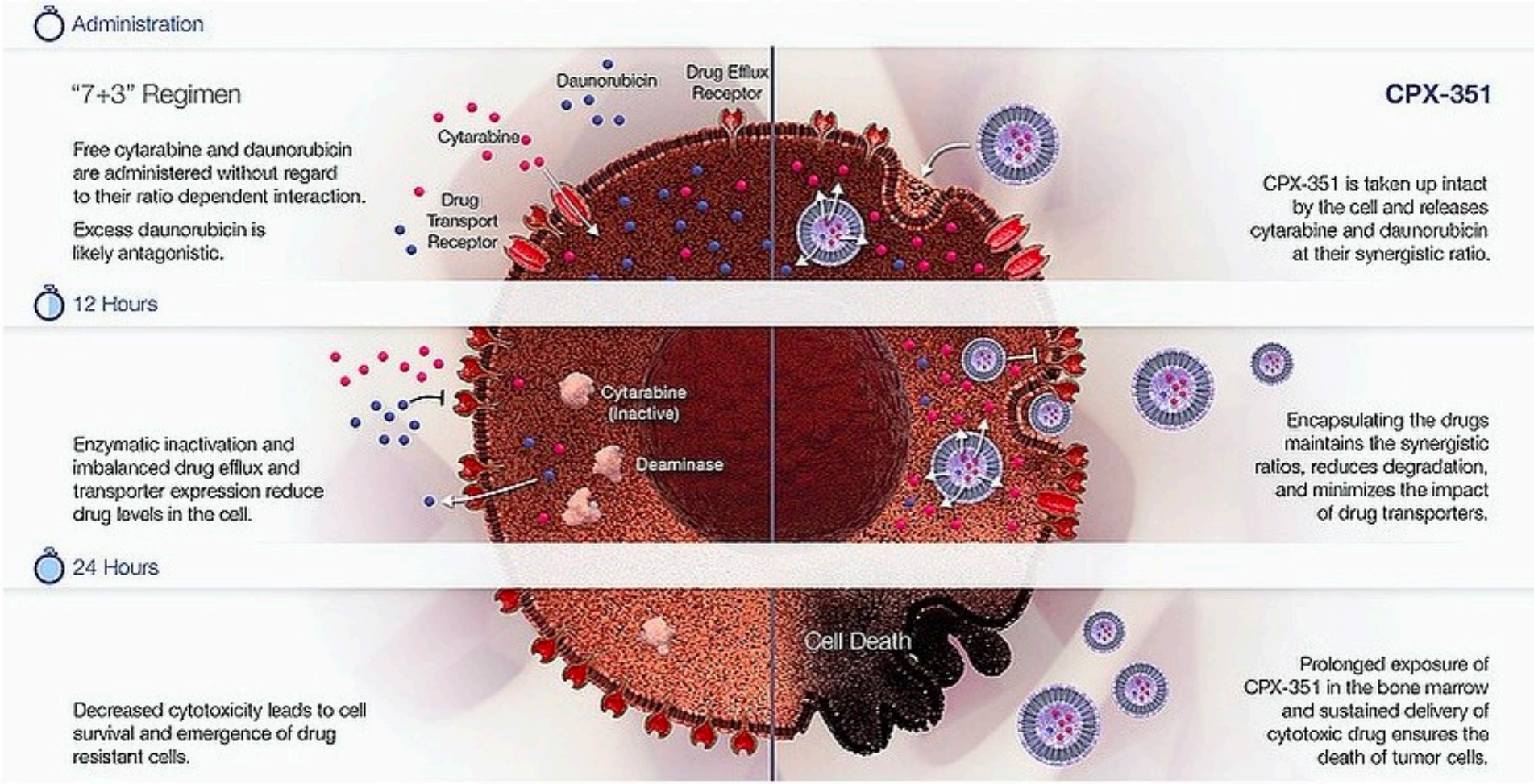
- But, will it be practice changing ? Will it have a true (clinically meaningful) impact ?

✓ OS increase only 7 %
✓ Benefit more in FLT3-TKD
✓ Which phase of treatment important ?
✓ Among the least potent FLT3 inhibitor
✓ Role in maintenance unclear (probably not)
✓ Beneficial effect most pronounced in $NPM1^{WT}/^{FLT3high}$ group

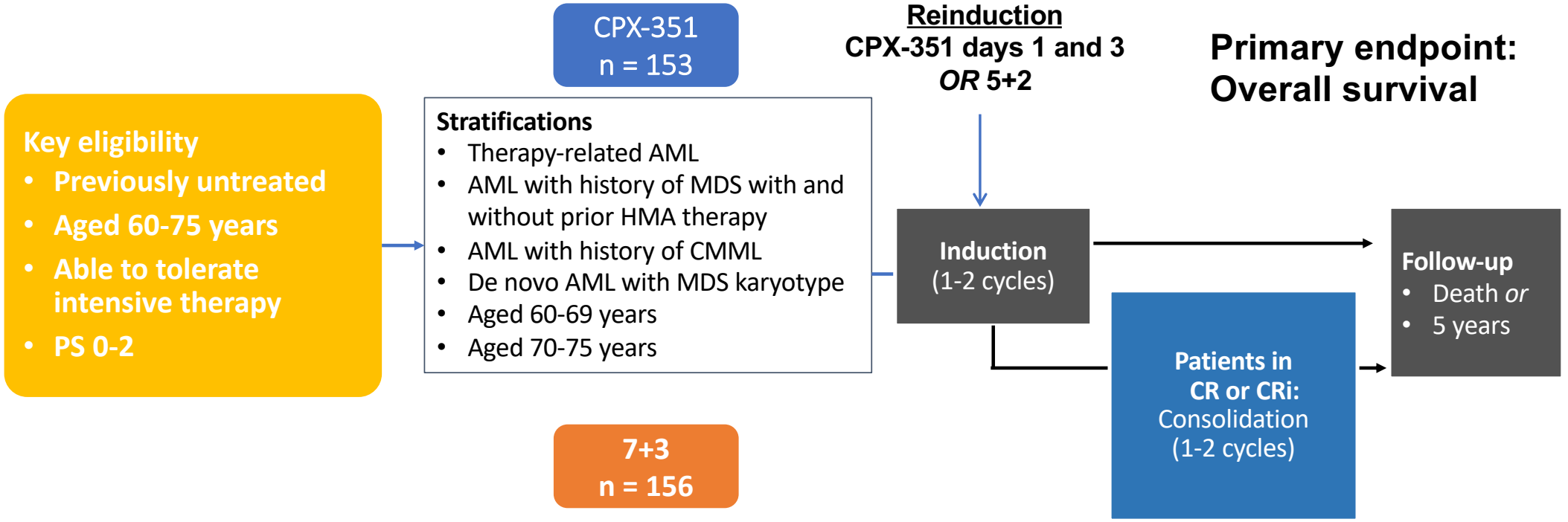
OS By Treatment Regimen in s-AML



Boddu P, et al. *Cancer* 2017;123:3050-60.


Administration
"7+3" Regimen
Free cytarabine and daunorubicin are administered without regard to their ratio dependent interaction.
Excess daunorubicin is likely antagonistic.
Daunorubicin
Drug Efflux Receptor
Cytarabine
Drug Transport Receptor
CPX-351
CPX-351 is taken up intact by the cell and releases cytarabine and daunorubicin at their synergistic ratio.
12 Hours
Cytarabine (Inactive)
Deaminase
Enzymatic inactivation and imbalanced drug efflux and transporter expression reduce drug levels in the cell.
Encapsulating the drugs maintains the synergistic ratios, reduces degradation, and minimizes the impact of drug transporters.
24 Hours
Cell Death
Decreased cytotoxicity leads to cell survival and emergence of drug resistant cells.
Prolonged exposure of CPX-351 in the bone marrow and sustained delivery of cytotoxic drug ensures the death of tumor cells.

Phase 3 Study of CPX-351 vs 7+3 in Older Patients With Newly Diagnosed Secondary AML

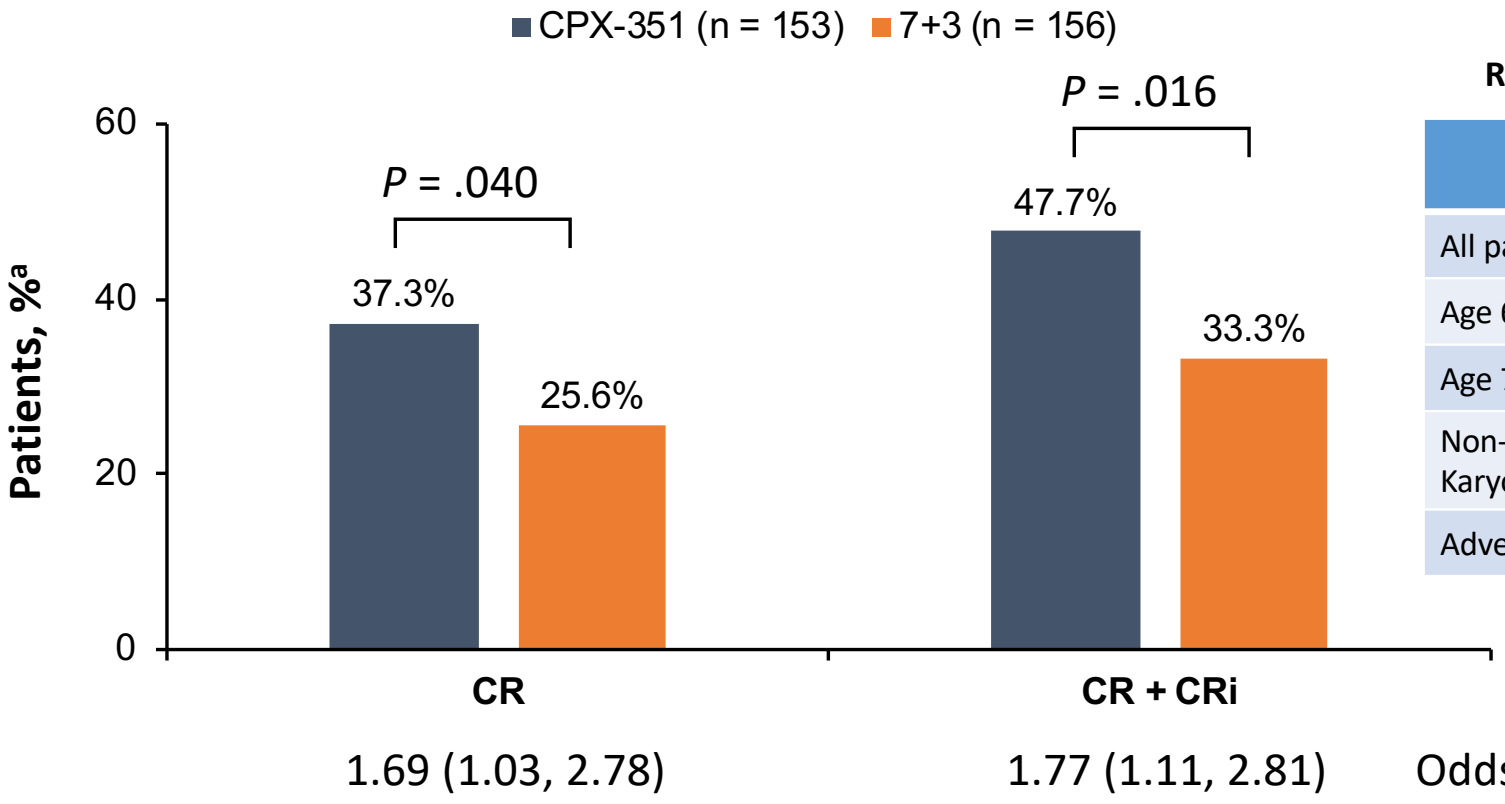


Induction
- CPX-351 44 mg/100 mg per m^2 IV days 1, 3, 5
- Cytarabine 100 mg/m^2/day x 7 plus daunorubicin 60 mg/m^2/day x 3

Consolidation
- CPX-351 29 mg/65 mg per m^2 IV days 1, 3
- Cytarabine 100 mg/m^2/day x 5 plus daunorubicin 60 mg/m^2/day x 2

Lancet JF et al. *J Clin Oncol.* 2018;36:2684-92

Phase 3 Study of CPX-351 vs 7+3 in High-Risk AML: Response Rate



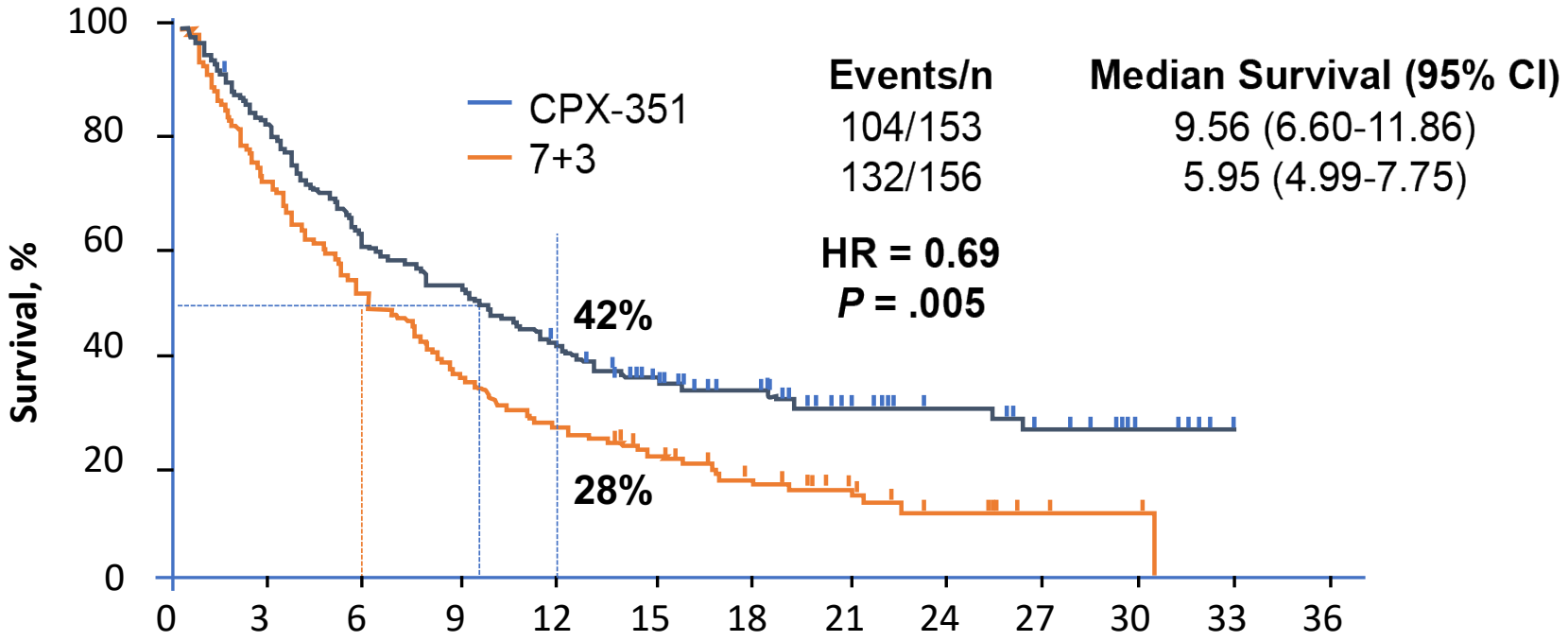
Rate of CR + CRi / CR in Patient Subsets

	CPX351	7+3
All patients	48/37%	33/40%
Age 60-69 years	50/40%	36/26%
Age 70-75 years	44/33%	29/24%
Non-adverse Risk Karyotype	55/42%	48/33%
Adverse Risk Karyotype	43/35%	22/18%

Lancet JF et al. *J Clin Oncol.* 2018; 36: 2684-92

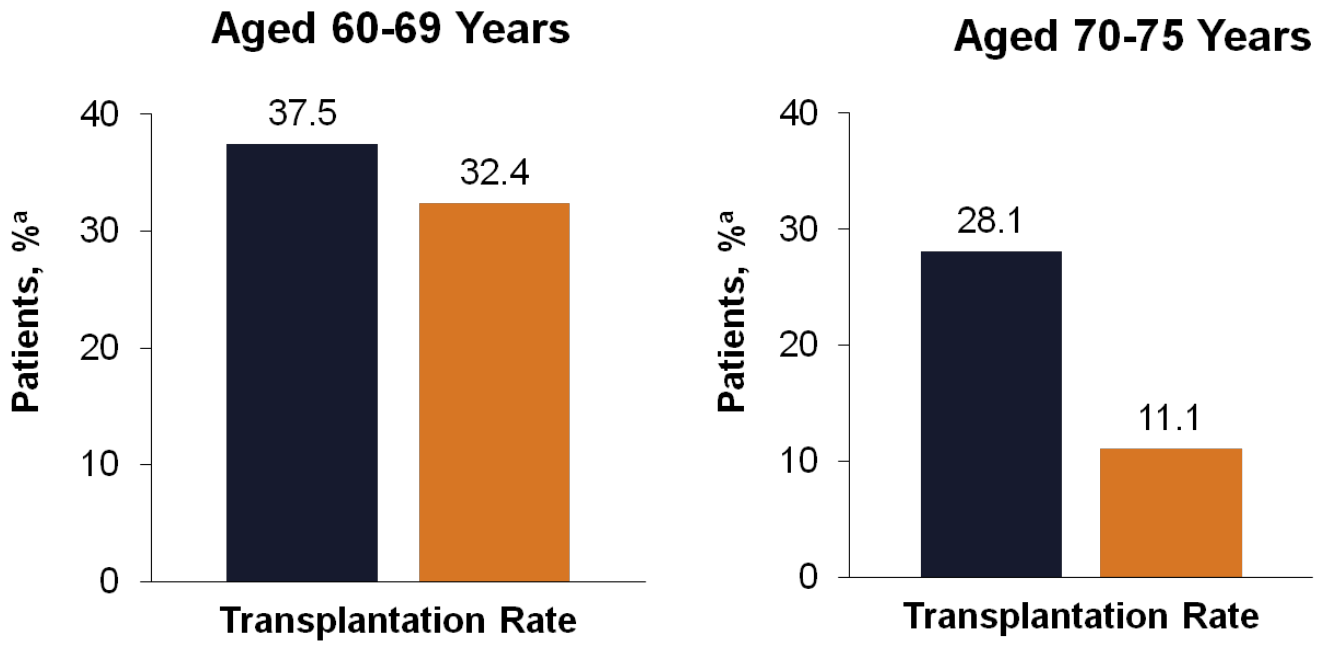
CPX-351 Improves Survival Among Older, Secondary AML

Kaplan-Meier Curve for OS: ITT Analysis Population



Lancet JF et al. *J Clin Oncol.* 2018;36:2684-92

CPX-351 vs 7+3: Transplantation Rate

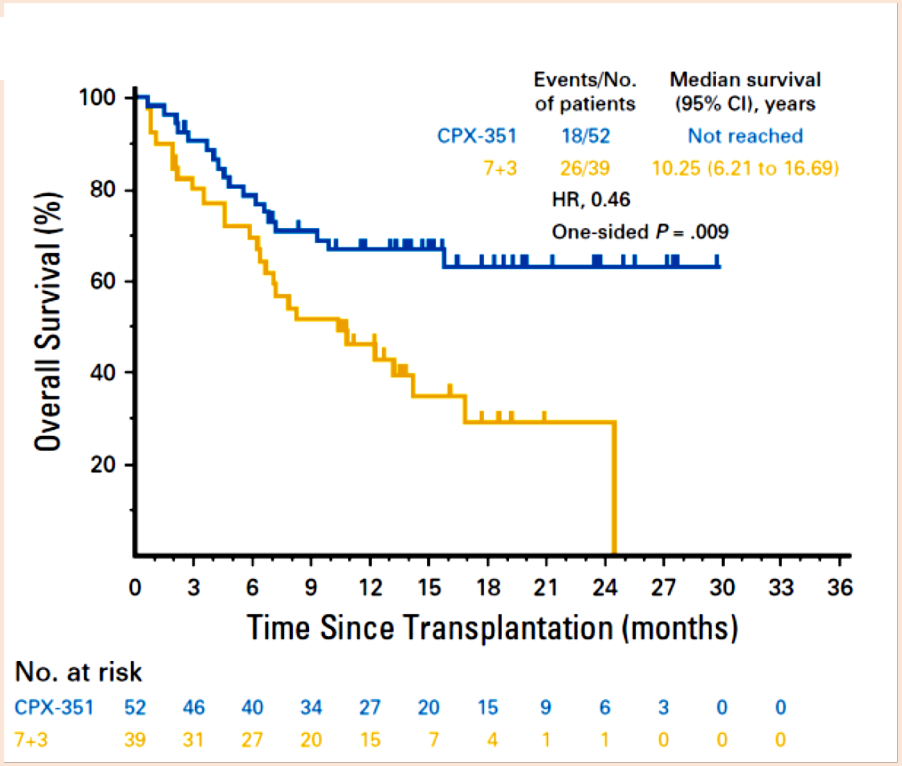


Odds ratio (95% CI)	1.25 (0.70-2.25)	3.12 (1.12-8.72)
	CPX-351 (n = 36) 7+3 (n = 33)	CPX-351 (n = 16) 7+3 (n = 6)

[a] Percentages reflect number with endpoint out of column total; odds ratios calculated with 7+3 arm as reference group.

Lancet JE et al. BMT Tandem 2017. Oral Presentation.

Landmark Analysis of Overall Survival Following Allo-HSCT

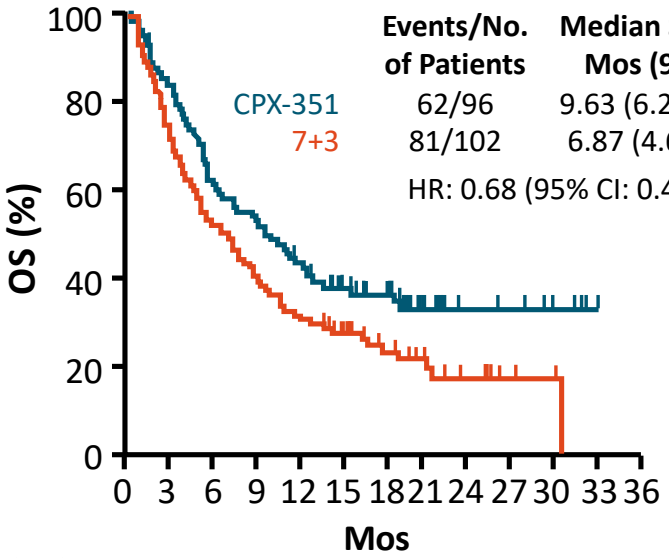


53% fewer deaths within 100 days of transplant in CPX-351 vs 7+3 arm

Lancet JF et al. *J Clin Oncol.* 2018;36:2684-92

CPX-351 in Older Patients With Newly Diagnosed AML: OS by Age Group

60-69 Yrs of Age

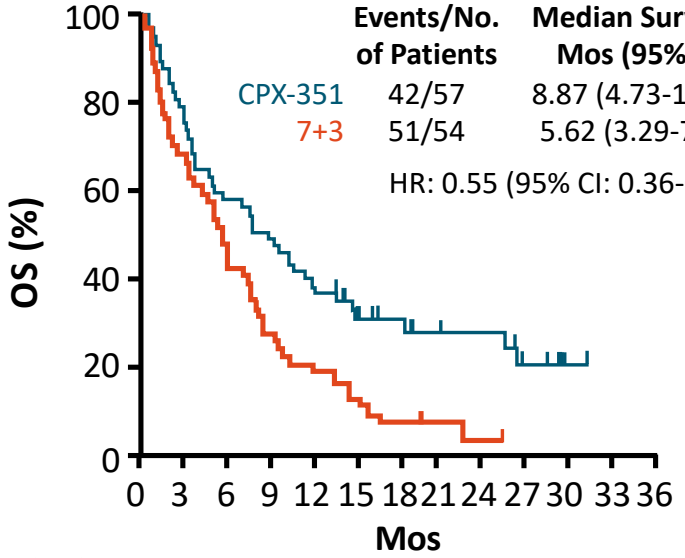


	Events/No. of Patients	Median Survival, Mos (95% CI)
CPX-351	62/96	9.63 (6.24-12.62)
7+3	81/102	6.87 (4.63-8.84)

HR: 0.68 (95% CI: 0.49-0.95)

Patients at Risk, n												
CPX-351	96	79	59	51	40	31	23	13	8	7	4	1
7+3	102	73	53	41	32	24	16	10	6	3	2	0

70-75 Yrs of Age



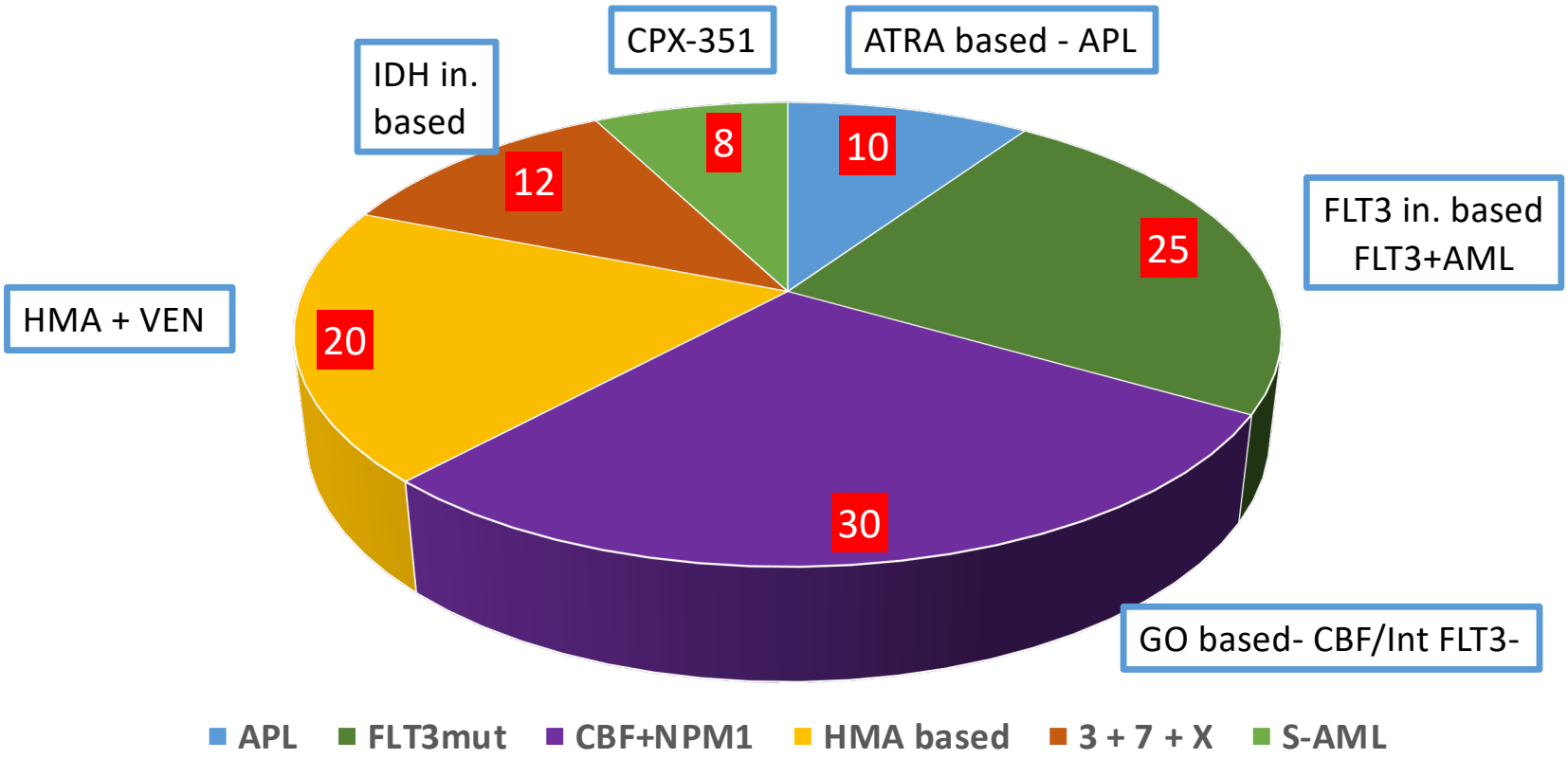
	Events/No. of Patients	Median Survival, Mos (95% CI)
CPX-351	42/57	8.87 (4.73-12.19)
7+3	51/54	5.62 (3.29-7.52)

HR: 0.55 (95% CI: 0.36-0.84)

Patients at Risk, n												
CPX-351	57	43	33	28	22	15	11	8	8	4	1	0
7+3	54	37	24	15	11	7	4	2	1	0	0	0

Lancet J et al 2017; *Biol Blood Marrow Transplant* 23:S38–S39.

AML > 18 years: 2019-2020



No place for standard 3 + 7