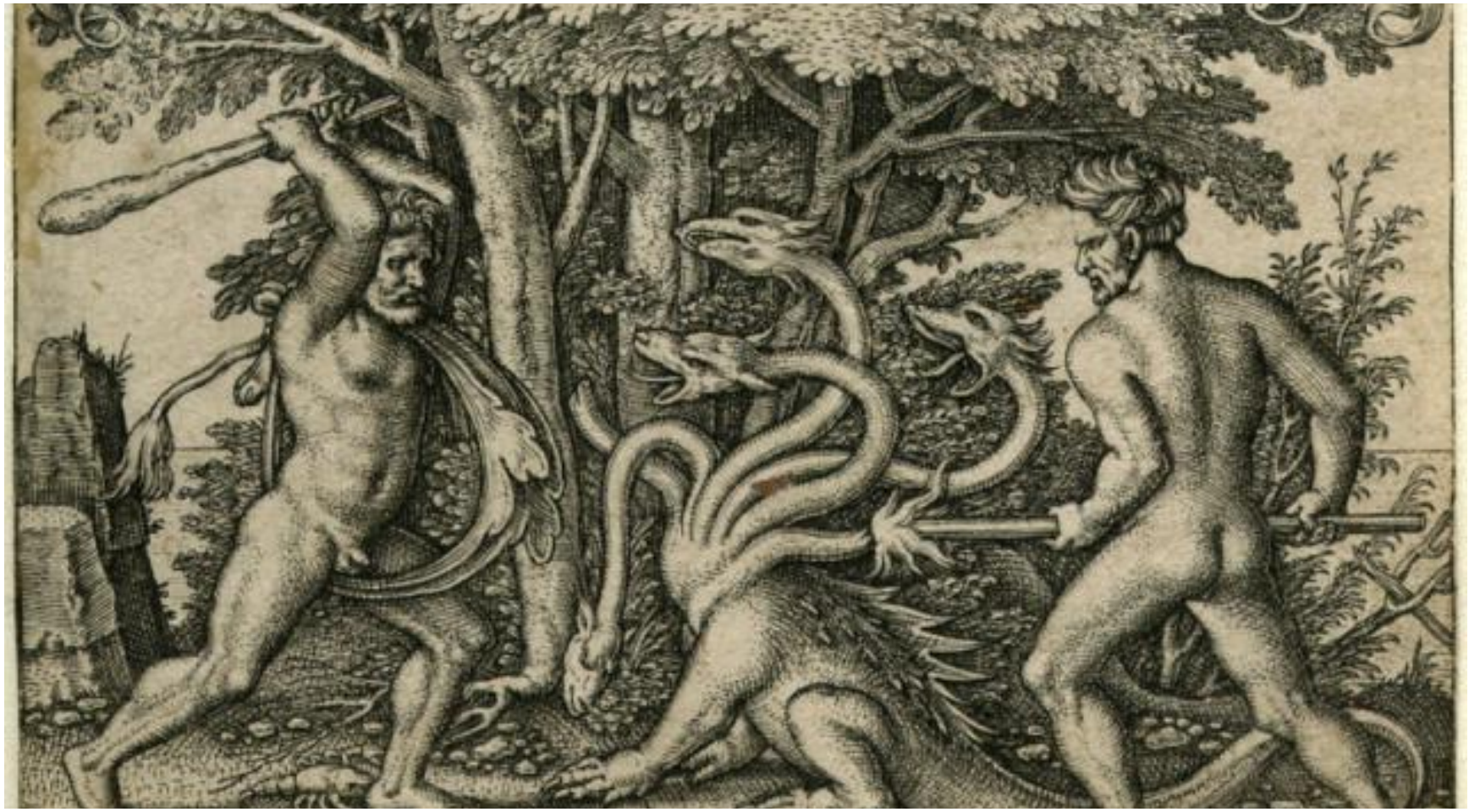
SVENSKA GRUPPEN AML

Behandling av äldre patienter med AML



It is not the most intellectual of the species that survives; it is not the strongest that survives; but the species that survives is the one that is able best to adapt and adjust to the changing environment in which it finds itself
Origin of Species; Charles Darwin, 1865

SVENSKA GRUPPEN AML

Intensiv kemo vs hypometylerare (AZA) hos äldre med AML - sammanfattning

- Den svenska traditionen att ge intensiv, toxisk kemoterapi till *i stort sett alla* i övrigt väsentligen friska äldre AML-patienter (<75 år)
- Äldre patienter (>75 år) med sekundär AML finns skäl att välja HMA behandling oavsett medsjuklighet
- Även hos äldre patienter med högriskgenetik bör HMA övervägas

SVENSKA GRUPPEN AML

ASH 2020 guidelines for treatment of newly diagnosed AML in older adults

Recommendation 1.
For patients who are candidates for such therapy, the ASH guideline panel recommends offering antileukemic therapy over best supportive care.©©©

Recommendation 2.
For patients considered candidates for intensive antileukemic therapy (see rec. 1), the ASH guideline panel suggests intensive antileukemic therapy over less-intensive antileukemic therapy. ©©

Recommendation 3.
For patients who achieve remission after at least a single cycle of intensive antileukemic therapy and who are not candidates for allogeneic hematopoietic stem cell transplantation (HSCT), the ASH guideline panel suggests post-remission therapy over no additional therapy. ©©

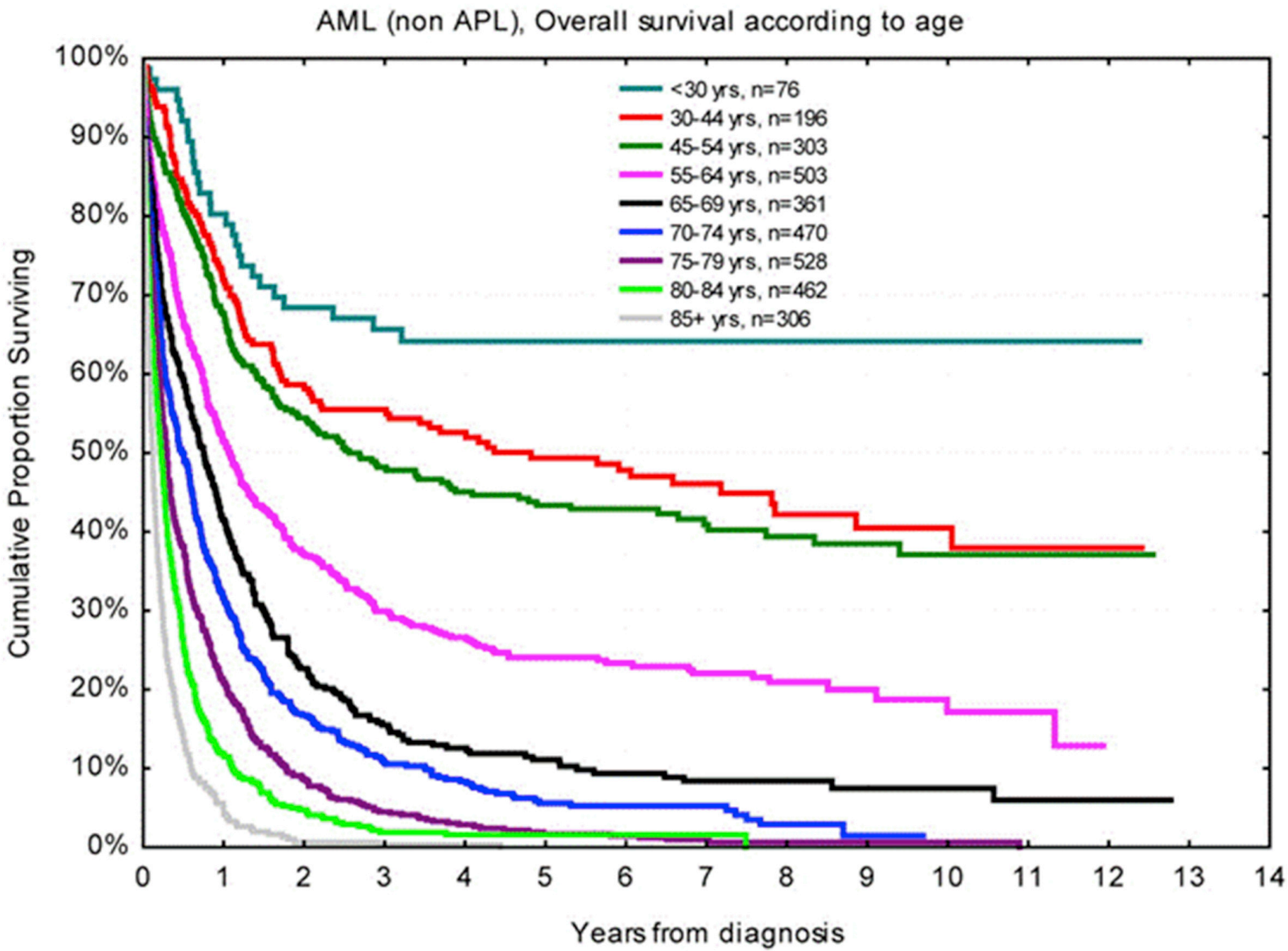
Recommendation 4a.
For patients considered appropriate for antileukemic therapy but not for intensive antileukemic therapy, the ASH guideline panel suggests using either of the options when choosing between hypomethylating-agent monotherapy and low-dose-cytarabine monotherapy. ©©©

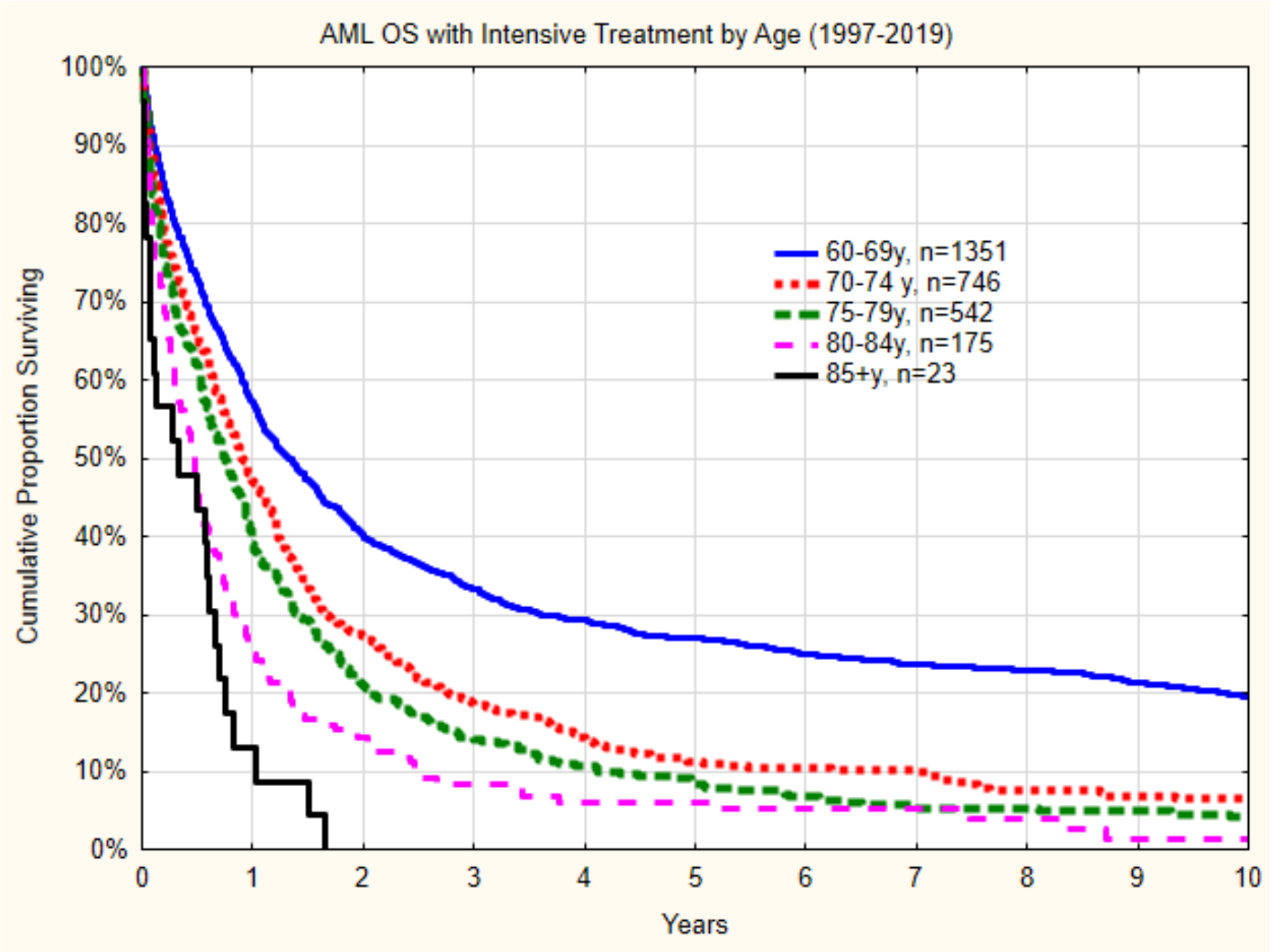
Recommendation 4b.
For patients considered appropriate for antileukemic therapy, such as hypomethylating agents (azacytidine and decitabine), but not for intensive antileukemic therapy, the ASH guideline panel suggests using monotherapy with 1 of these drugs over a combination of 1 of these drugs with other agents. ©©

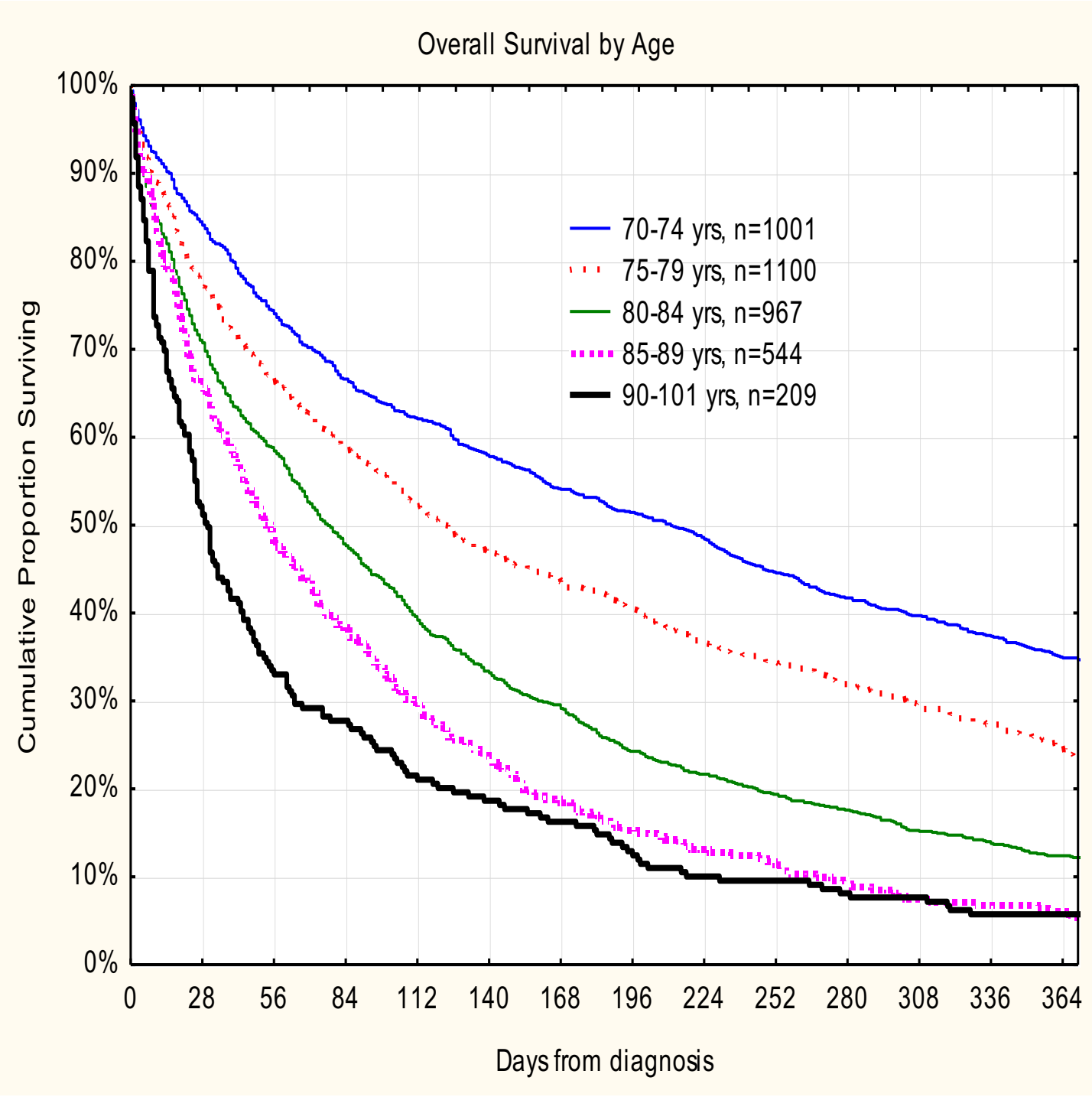
Recommendation 5.
For patients who achieve a response after receiving less-intensive therapy, the ASH guideline panel suggests continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy. ©

Recommendation 6.
For patients who are no longer receiving antileukemic therapy (inc. those receiving end-of-life care), the ASH guideline panel suggests having red blood cell transfusions available over not having transfusions available.©

Sekeres M, Guyatt G, Abel G, *et al.* American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. *Blood Advances.* 2020; 4(suppl 15):3528-3549.


AML (non APL), Overall survival according to age
Cumulative Proportion Surviving
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Years from diagnosis
<30 yrs, n=76
30-44 yrs, n=196
45-54 yrs, n=303
55-64 yrs, n=503
65-69 yrs, n=361
70-74 yrs, n=470
75-79 yrs, n=528
80-84 yrs, n=462
85+ yrs, n=306


AML OS with Intensive Treatment by Age (1997-2019)
Cumulative Proportion Surviving
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
9
10
Years
60-69y, n=1351
70-74 y, n=746
75-79y, n=542
80-84y, n=175
85+y, n=23


Overall Survival by Age
Cumulative Proportion Surviving
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
28
56
84
112
140
168
196
224
252
280
308
336
364
Days from diagnosis
70-74 yrs, n=1001
75-79 yrs, n=1100
80-84 yrs, n=967
85-89 yrs, n=544
90-101 yrs, n=209

SVENSKA GRUPPEN AML

Vad är det för typ av AML

(man kan oftast vänta på svar från genetik/genomik)

SVENSKA GRUPPEN AML

Huvudtyper av AML (modifierad från Lindsley et al. Blood 2017)

***De novo** AML ("Pan" AML)*

NPM1, FLT3, CBF, 11q23

***Sekundär** AML*

(transformation från MDS, MPN, MDS/MPN)

SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, or STAG2

***Terapi-relaterad** AML*

(med latens efter kemoterapi och/eller strålbehandling)

TP53, PPM1D

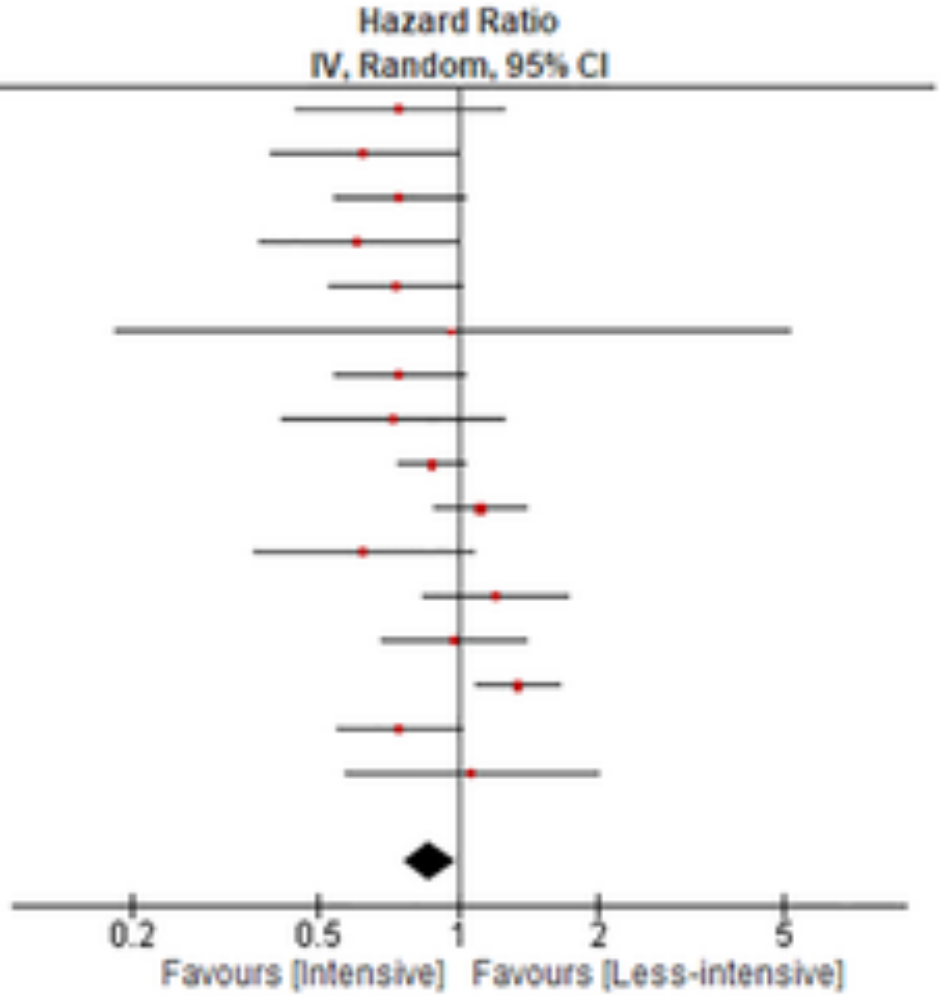
SVENSKA GRUPPEN AML

Intensiv *eller* icke-intensiv behandling

Meta-analys av HR för dödlighet (nyare observationsstudier); intensive *vs* icke-intensiv behandling

Study or Subgroup	log[Hazard Ratio]	SE	High Total	Low Total	Weight	Hazard Ratio IV, Random, 95% CI
Almeida 2017	-0.2877	0.2606	122	41	4.5%	0.75 [0.45, 1.25]
Bories 2014	-0.47	0.2347	115	95	5.1%	0.63 [0.39, 0.99]
Cannas 2015	-0.2877	0.1668	68	70	7.3%	0.75 [0.54, 1.04]
Dumas 2017	-0.4943	0.2471	92	107	4.8%	0.61 [0.38, 0.99]
El-Jawahri 2015	-0.3075	0.1672	197	133	7.3%	0.74 [0.53, 1.02]
Fenaux(a) 2010	-0.0305	0.8468	11	5	0.6%	0.97 [0.18, 5.10]
Heiblig 2017	-0.2852	0.1663	95	100	7.3%	0.75 [0.54, 1.04]
Michalski(b) 2019	-0.3216	0.2822	132	32	4.0%	0.72 [0.42, 1.26]
Osterroos 2020	-0.1278	0.0816	1529	302	10.9%	0.88 [0.75, 1.03]
Quintas-Cardama 2012	0.1098	0.1126	557	114	9.6%	1.12 [0.90, 1.39]
Scappaticci 2018	-0.4668	0.276	32	32	4.1%	0.63 [0.37, 1.08]
Solomon 2020	0.1823	0.182	205	57	6.7%	1.20 [0.84, 1.71]
Takahashi 2016	-0.0202	0.1783	95	95	6.9%	0.98 [0.69, 1.39]
Talati(a) 2020	0.3001	0.1045	360	255	9.9%	1.35 [1.10, 1.66]
Vachhani 2018	-0.2877	0.1569	98	103	7.7%	0.75 [0.55, 1.02]
van der Helm 2013	0.0677	0.3191	90	26	3.4%	1.07 [0.57, 2.00]
Total (95% CI)			**3798**	**1567**	**100.0%**	**0.87 [0.76, 0.99]**

Heterogeneity: Tau² = 0.04; Chi² = 34.39, df = 15 (P = 0.003); I² = 56%
Test for overall effect: Z = 2.05 (P = 0.04)

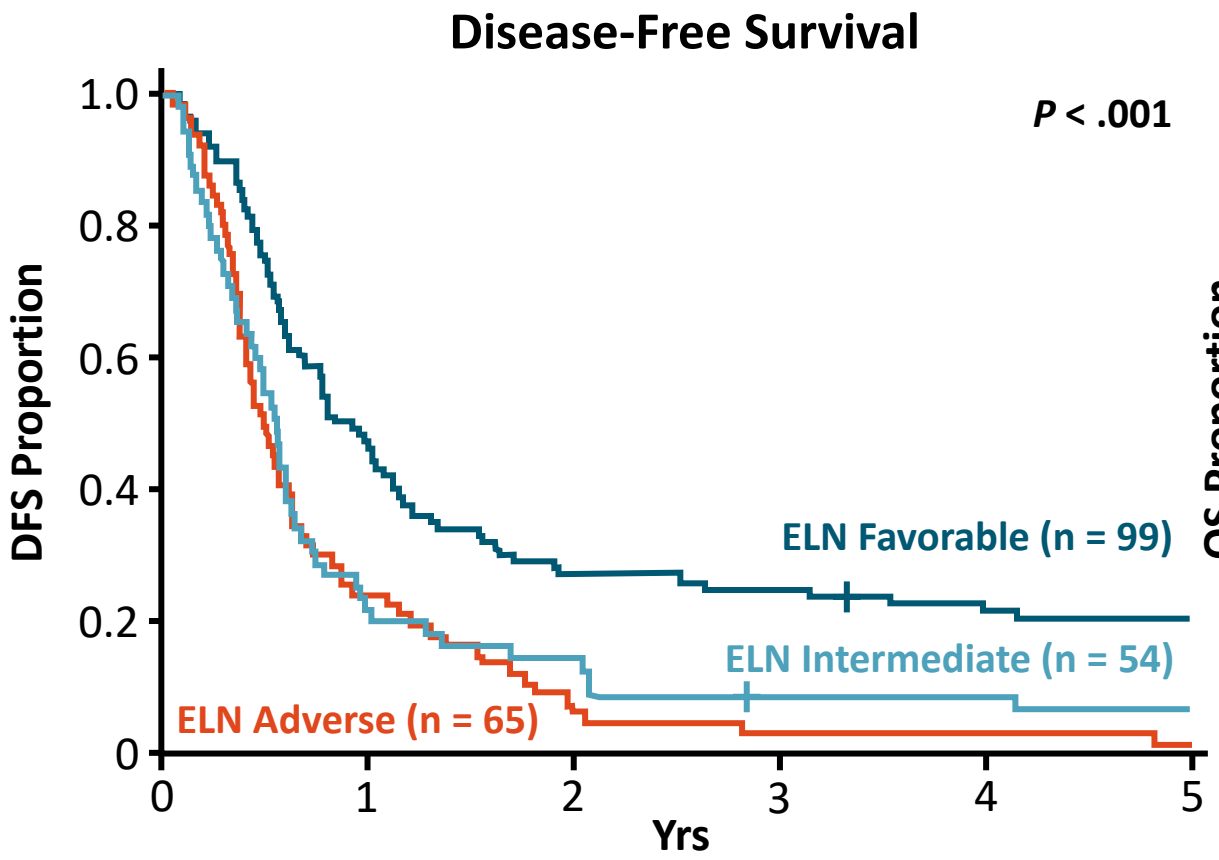


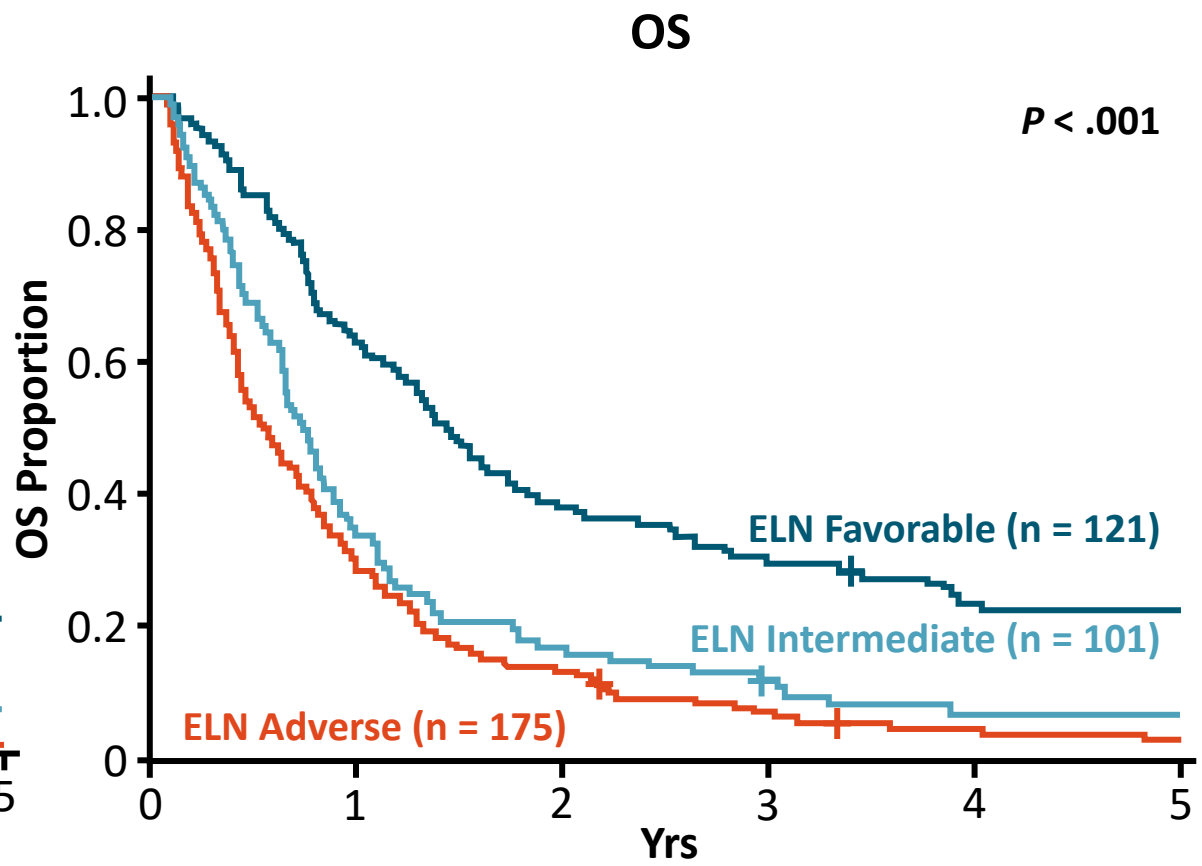
Chang Y, Guyatt GH, Teich T, Dawdy JL, Shahid S, et al. (2021) Intensive versus less-intensive antileukemic therapy in older adults with acute myeloid leukemia: A systematic review. PLOS ONE 16(3): e0249087. https://doi.org/10.1371/journal.pone.0249087
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0249087

SVENSKA GRUPPEN AML

- **Fit eller unfit**
- Ålder (”biologiskt ålder”) och performance status (beroende av sjukdomen eller ej)
- Ko-morbiditeter (t ex EF) och tidigare sjukdomar
- HCT-CI (”Sorror score”) skor
- Geriatrisk bedömning; (MMSE, SPPB), ADL, kognition, gånghastighet, grepstyrka
- Nutrition
- Antal av mediciner
- Vilja och social stöd

2017 ELN AML klassifikation
Överlevnad av Patienter ≥ 60 år beroende av risk grupp





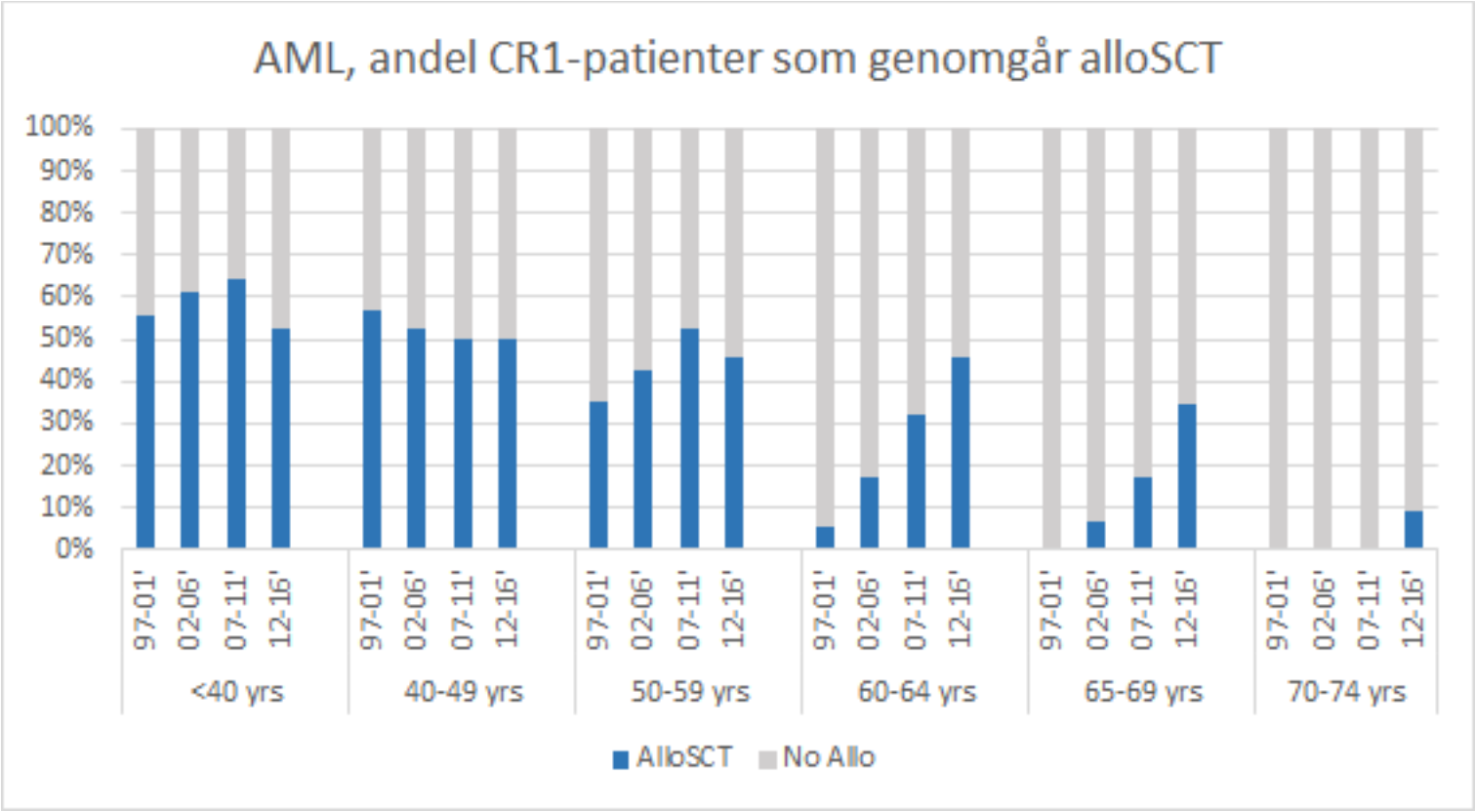
Eisfeld et al. JCO, 2019

SVENSKA GRUPPEN AML

Vilka äldre (oavsett ålder) patienter man har bra resultat med intensiv kemoterapi (om man bedömer att pat kan tolerera cytostatika)

- CBF AML /t(8;21); inv(16)/
- *NPM1mut* AML (*FLT3-ITD* negativ eller *FLT3-TKD* positiv)
- Om målet är allogen stamcellstransplantation

SVENSKA GRUPPEN AML



Hypomethylating agents (HMA)

- 5-Azacitidin (AZA, Vidaza®)

- Decitabin (Dacogen®) tillgänglig, registrerad för AML, använts inte mkt i Sverige
- Decitabine+cedazuridin (INQOVI®), oral decitabine, godkänt FDA 2020 för MDS/KMML, EMA ej godkänt
- CC-886 (Onureg®), ”oral AZA”, godkänt FDA underhållsbehandling AML, EMA ej godkänt än, ej tillgänglig april 2021

SVENSKA GRUPPEN AML

AZA vid AML (I)

SVENSKA GRUPPEN AML

- Huvudeffekter:
  - hypometylering av DNA
  - hämning DNA-/RNA-syntesen
- Ges sc 75 mg/m^2 x1x 7 dagar eller 100 mg/m^2 x1 x 5 dagar var 4-(6) vecka till progress eller intolerabel toxicitet
- Utvärdering – när? (efter 4-6 kurer)
- Liten slemhinne- och organtoxicitet och generellt bättre tolererbart jmf intensiv kemoterapi
- Cytopenier är att räkna med
- Mindre effektivt vid proliferativ sjukdom (ge HU mellan kurer men ej samtidigt!)

AZA vid AML (II)

SVENSKA GRUPPEN AML

- Registrerat vid AML på indikationerna
  - AML, ej lämplig för allo-SCT, med 20-30% blaster och multilinjär dysplasi*
  - AML ≥ 65 år, ej lämplig för allo-SCT och > 30% blaster**

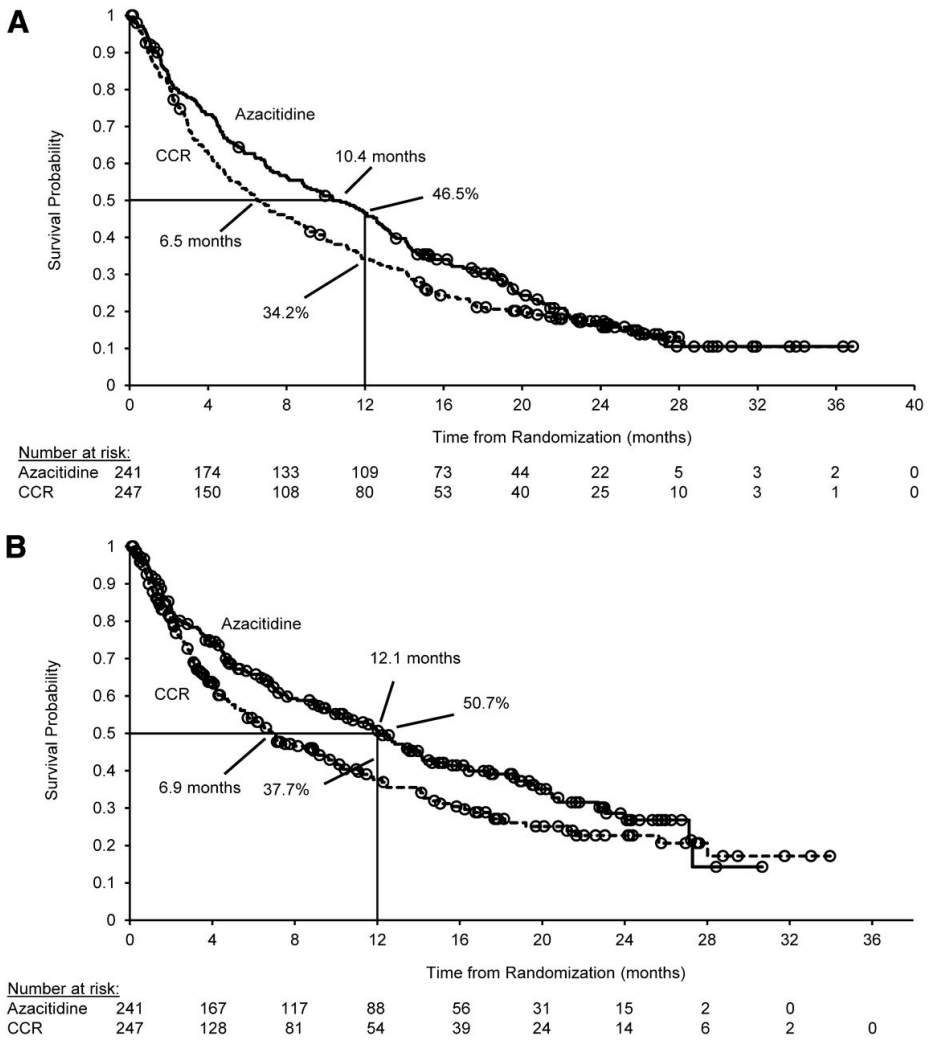
Två pivotala Fas-3-studier där azacitidin *jmf* med ”best supportive care” (intensiv kemo, lågdos cytarabin, bara supportive care)

** Fenaux P et al, JCO 2010; 28(4), 562-9*

*** Dombret H el al, Blood 2015;126(3), 291-9*

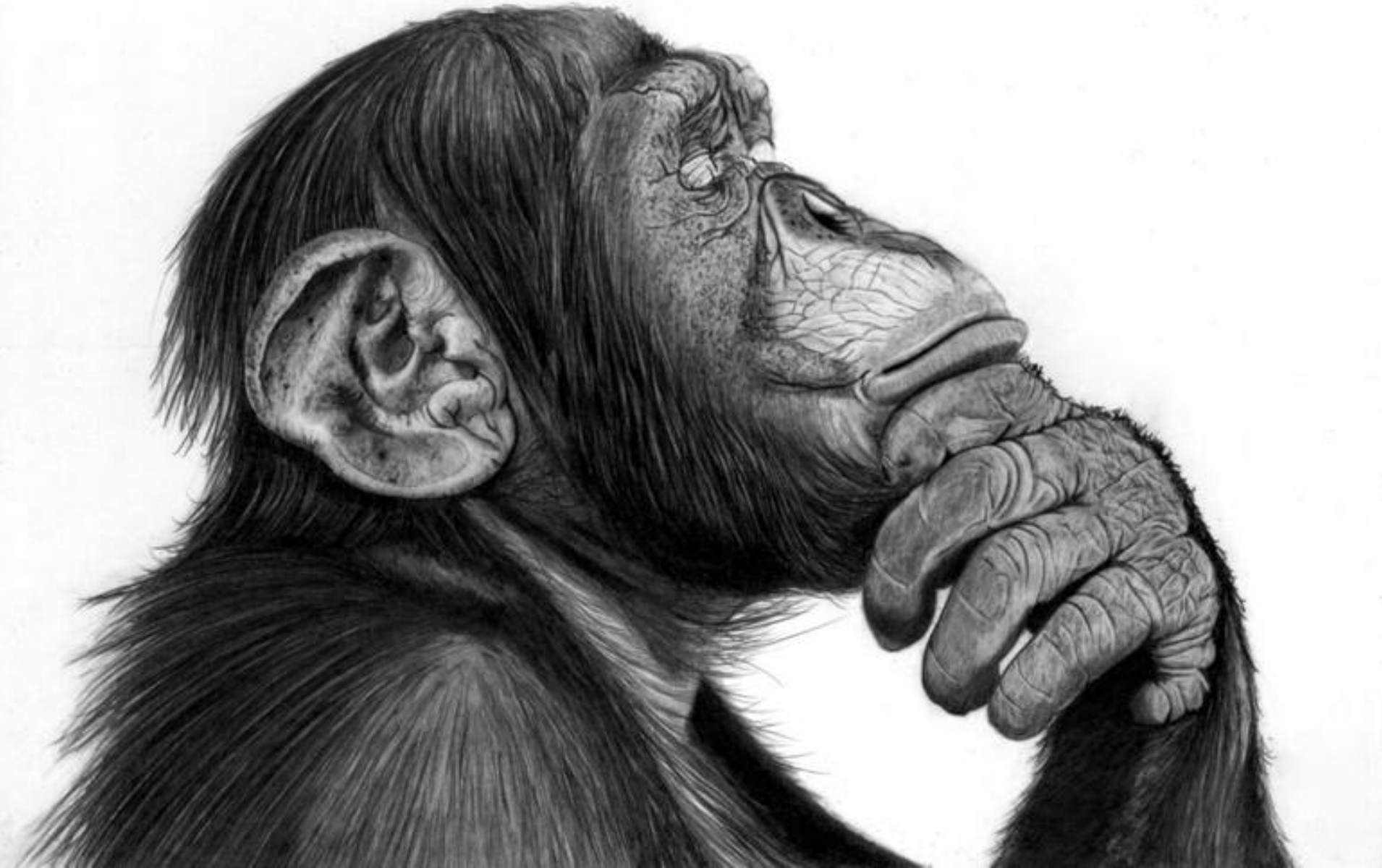
CR rate upp till 20%, även vid sekundär AML, median OS 13.3 mån

Primary and preplaned sensitivity analyses for OS of AML therapy.

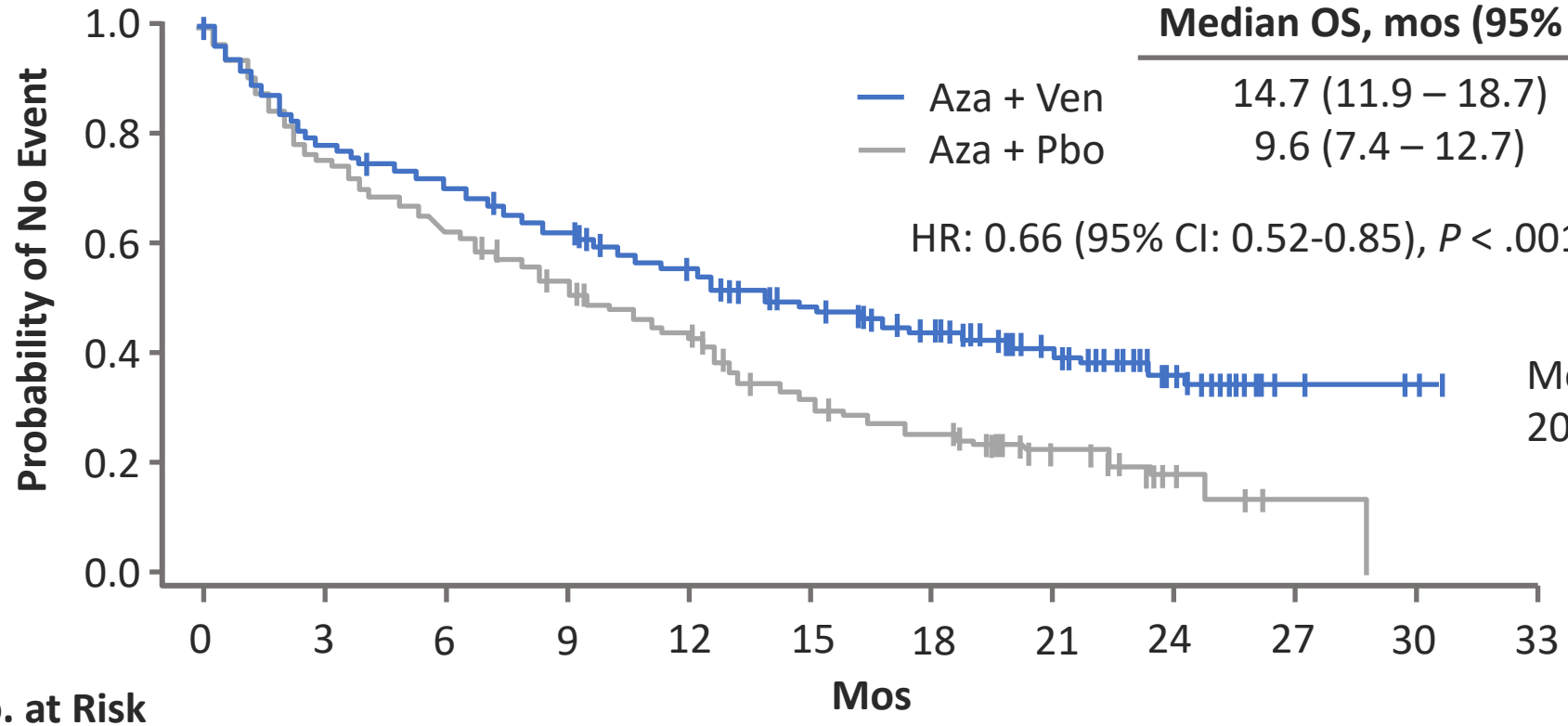


Hervé Dombret et al. Blood 2015;126:291-299

©2015 by American Society of Hematology



VIALE-A

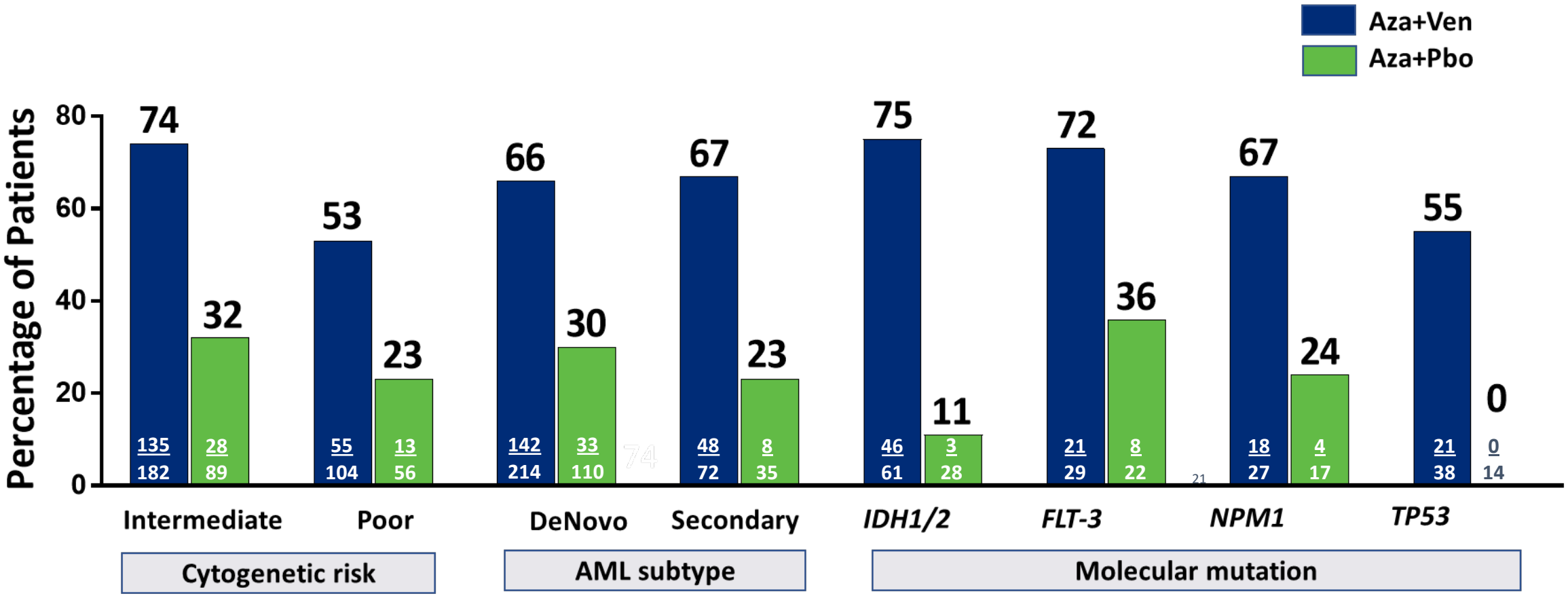


Median follow-up: 20.5 months

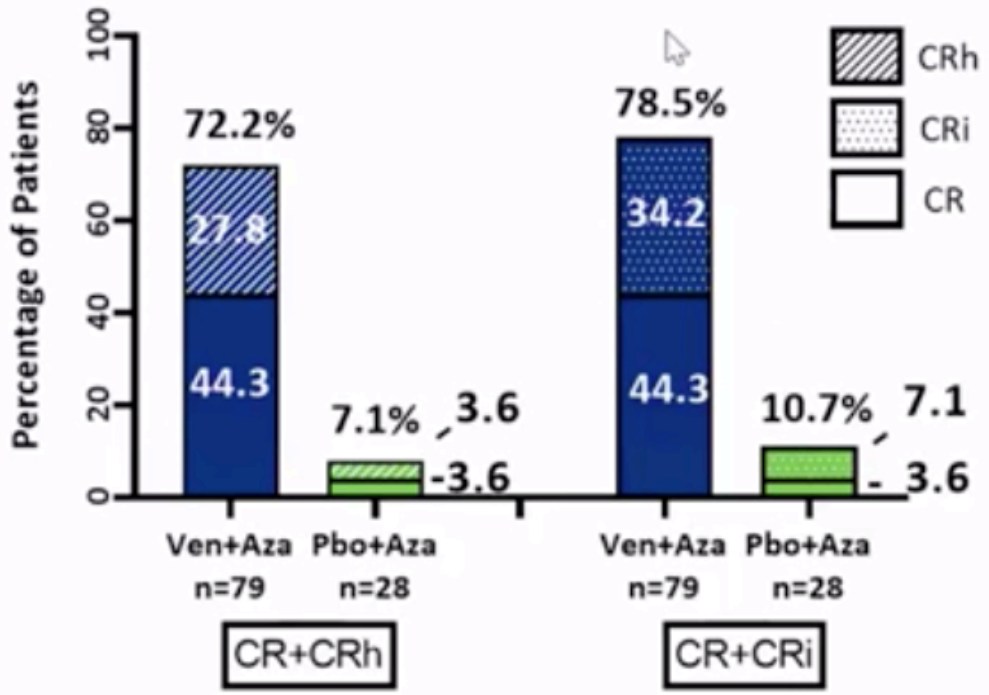
No. at Risk												
Aza + Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza + Pbo	145	109	92	74	59	38	30	14	5	1	0	0

Di Nardo et al. NEJM, 2020

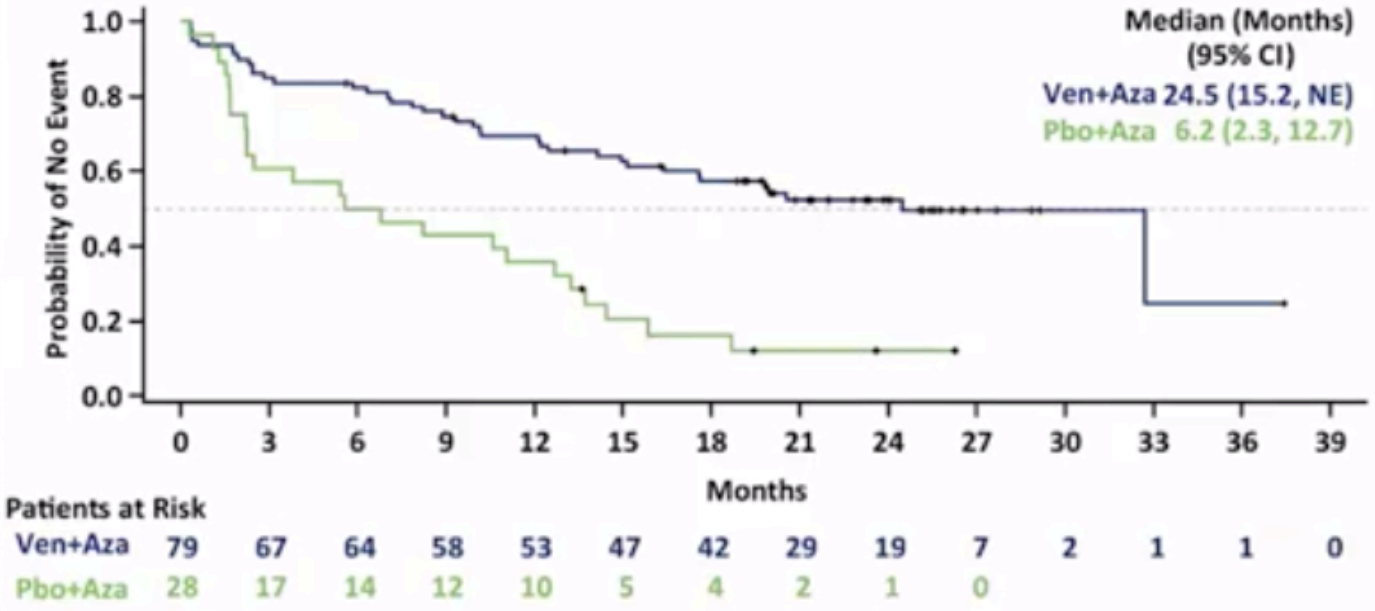
Response Rates (CR+CRi) by Subgroups



Response Rates and Overall Survival of Patients with *IDH 1/2* Mutations



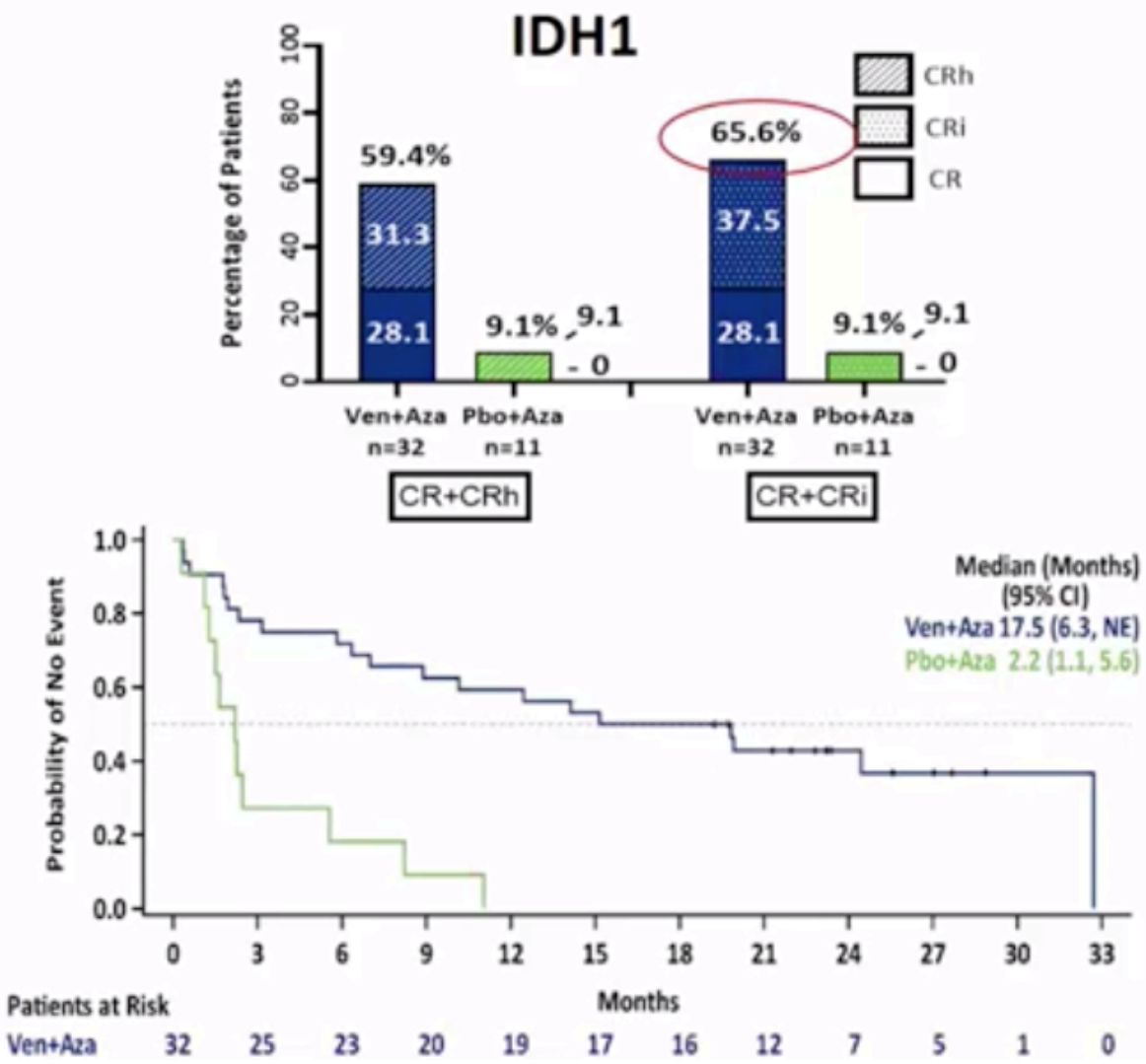
	Ven + Aza n = 79	Pbo + Aza n = 28
CR+CRh: Median time to first response, mo. (min, max) Median DoR, mo. (95% CI)*	1.0 (0.7, 9.6) 29.6 (16.7, NE)	2.6 (2.1, 3.1) 15.5 (NE)
CR + CRi: Median time to first response, mo. (min, max) Median DoR, mo. (95% CI)*	1.1 (0.7, 8.8) 29.5 (16.7, NE)	3.4 (2.1, 7.1) 9.5 (3.5, 15.5)
Median treatment cycles (min,max)	8.0 (1, 37)	2.5 (1, 18)

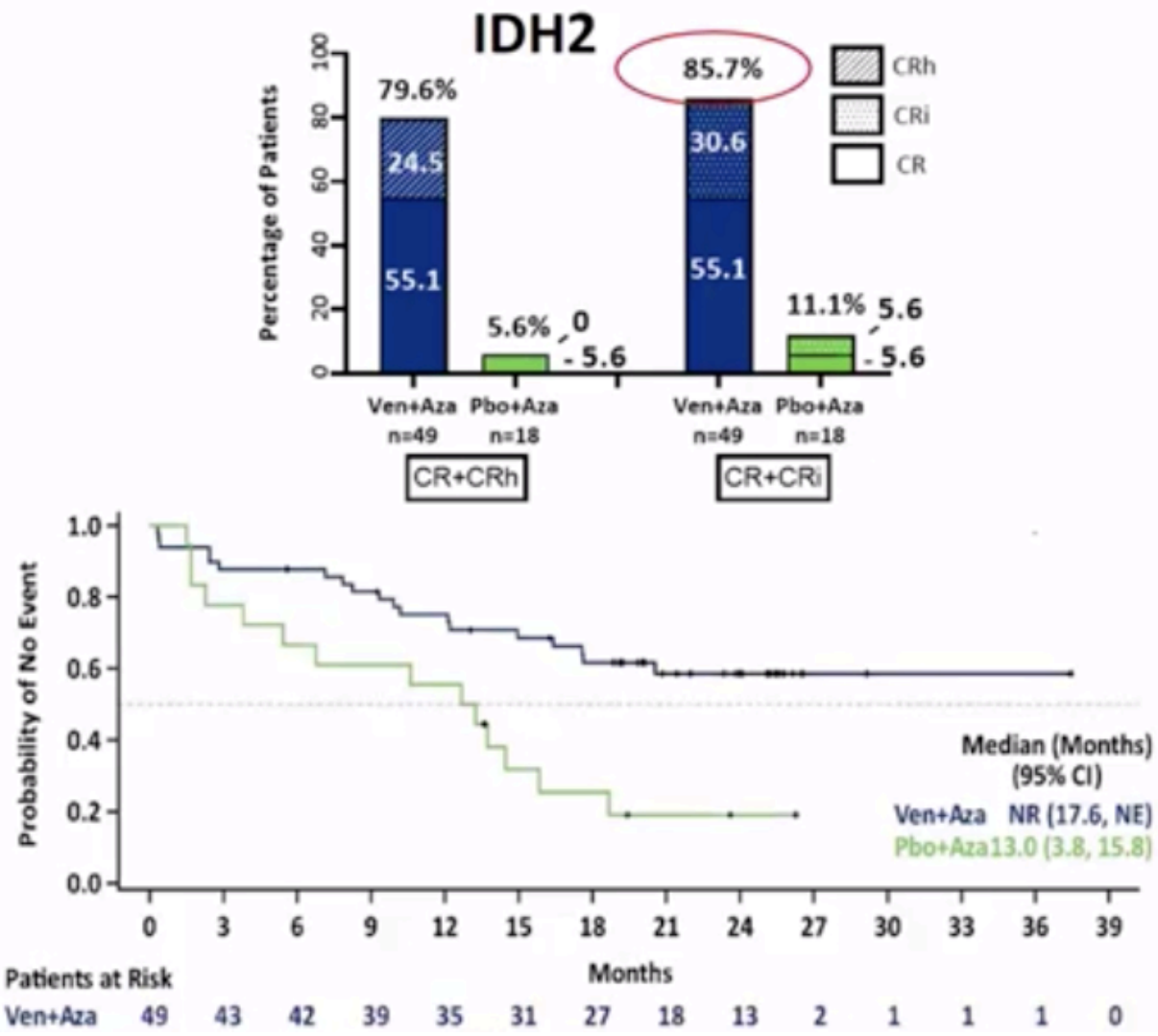


Survival Estimate (%) (95% CI)

	Month 6	Month 12	Month 24
Ven+Aza	82.3 (71.9, 89.1)	69.3 (57.8, 78.3)	52.4 (40.4, 63.1)
Pbo+Aza	50.0 (30.6, 66.6)	35.7 (18.9, 53.0)	12.2 (3.2, 27.8)

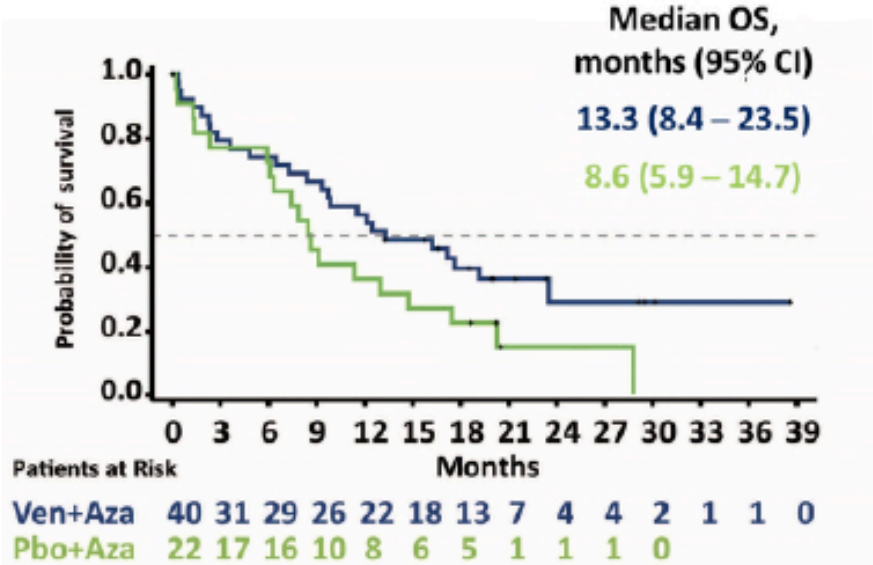
Response Rates and OS of Patients with *IDH1 or IDH2* Mutations



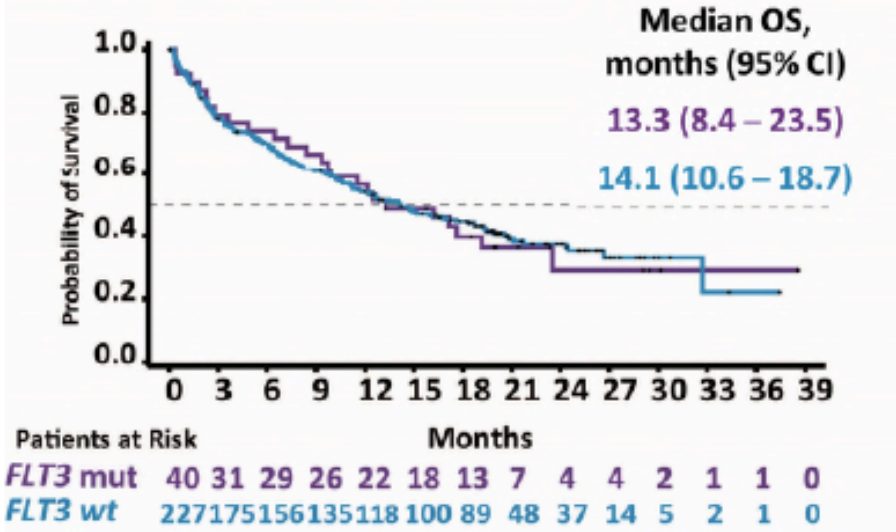


Overall survival in patients with *FLT3* mutation

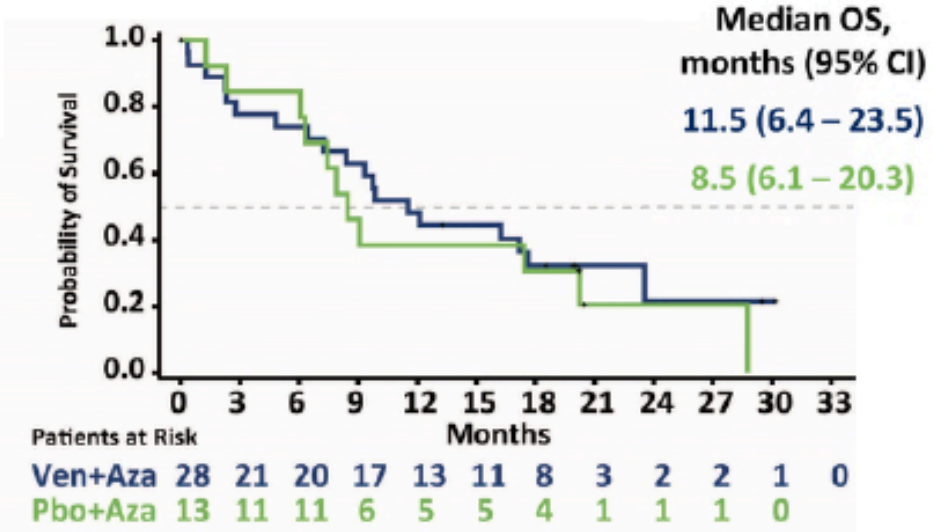
A. FLT3mut



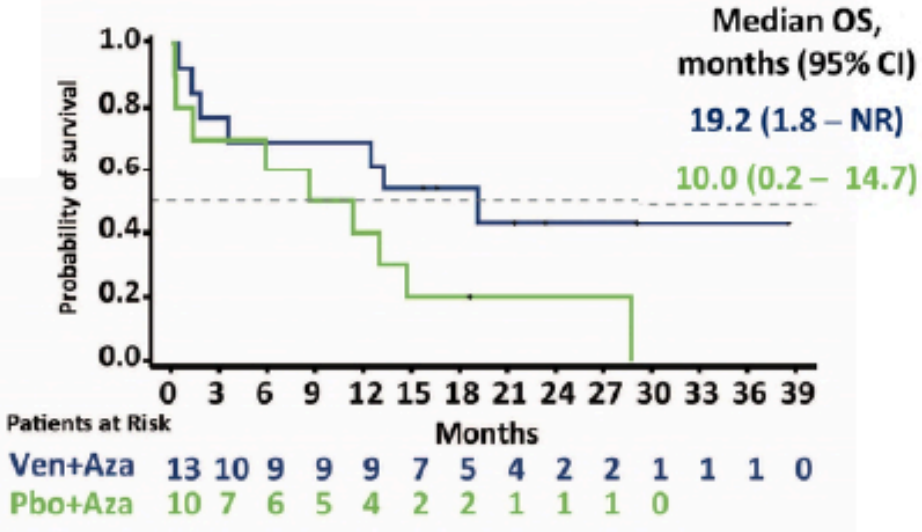
B. FLT3mut vs. wt in Ven+Aza



C. FLT3-ITD

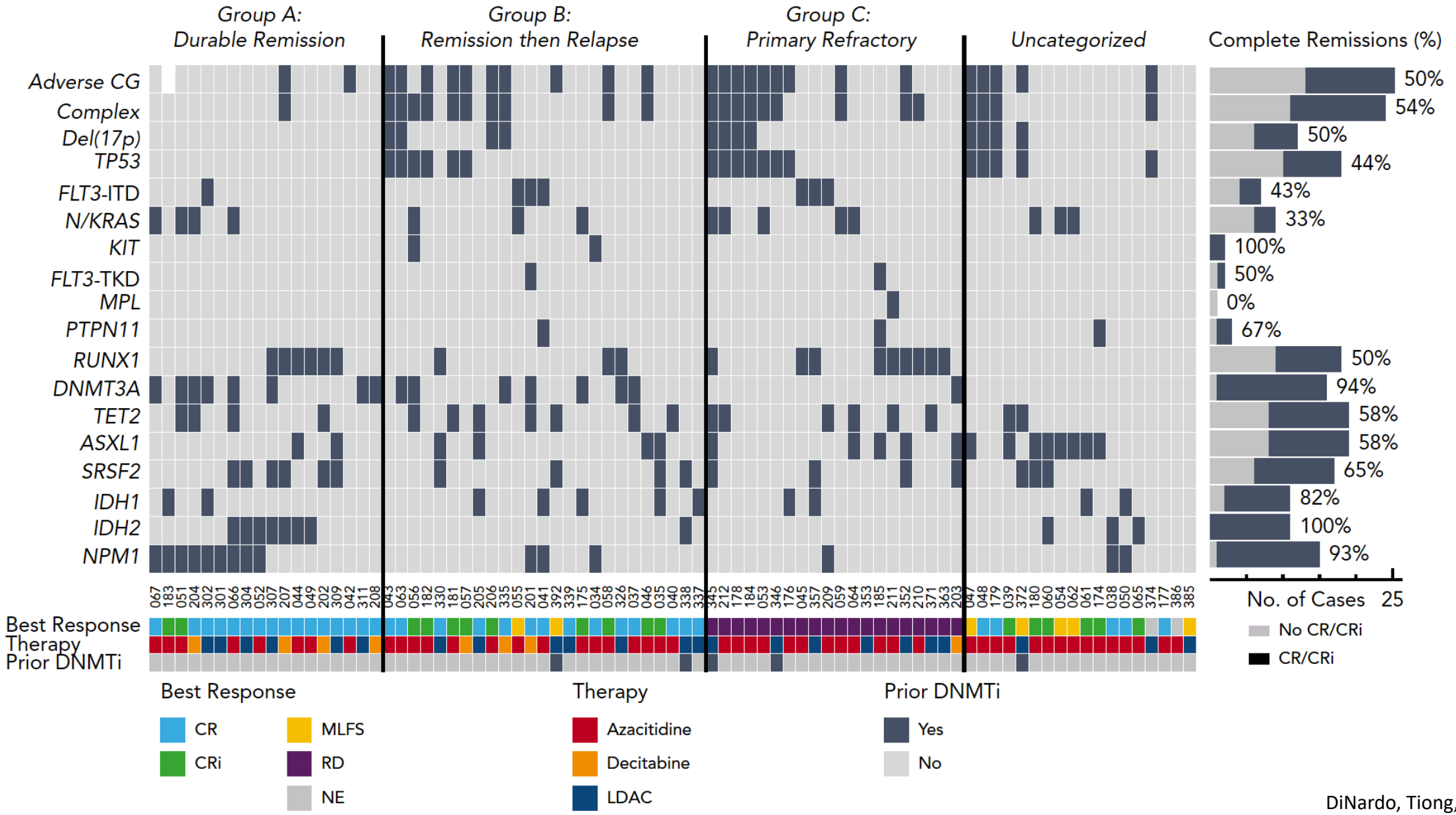


D. FLT3-TKD



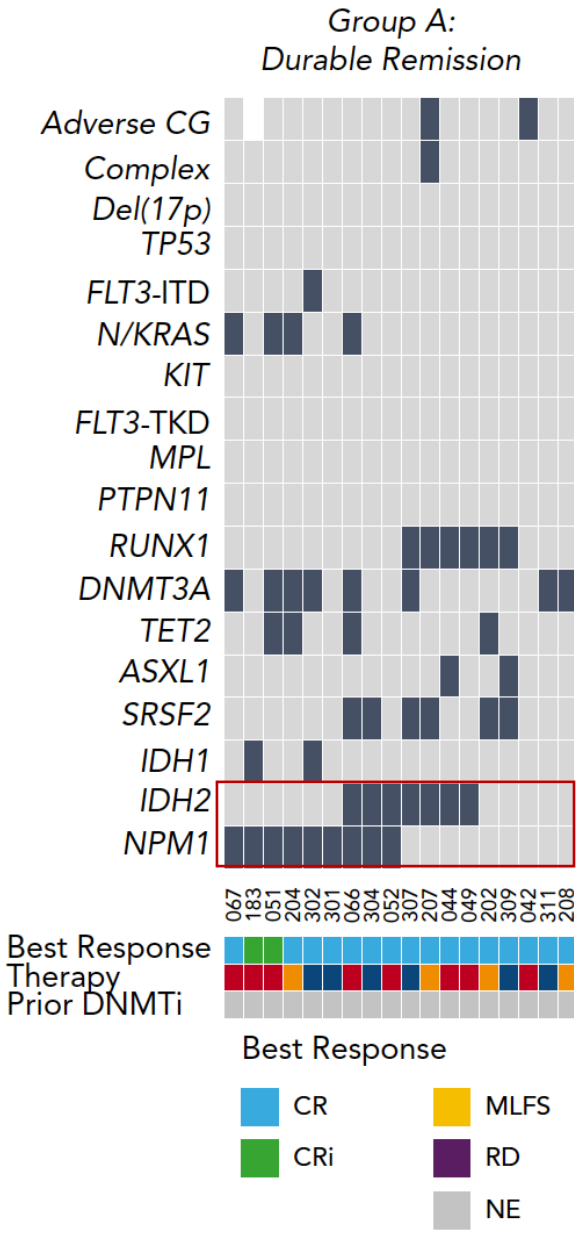
Overall survival (OS) was defined as the time from randomization to the date of death from any cause

Korrelation mellan molekylära karakteristika för patienter som fick venetoclax för AML och utfall

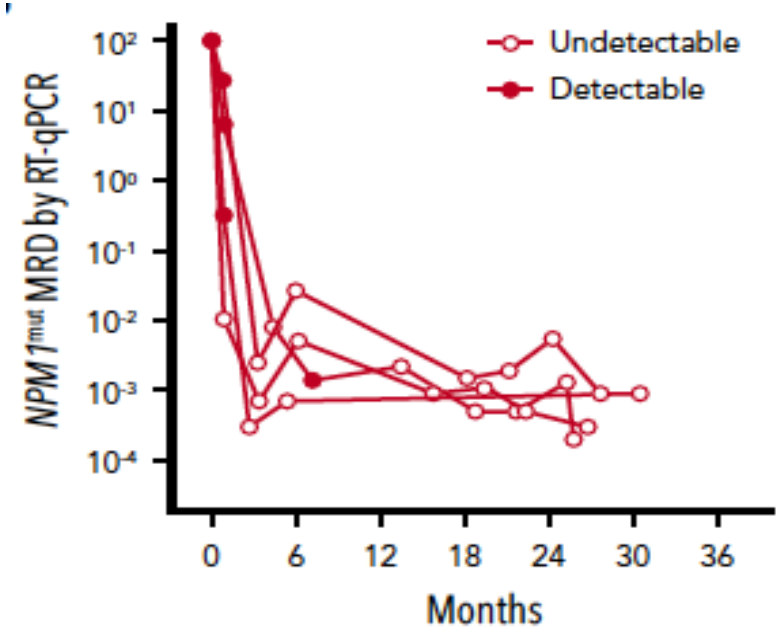


DiNardo, Tiong, Blood 2020

NPM1 and IDH2 muterad AML har väldigt bra utfall

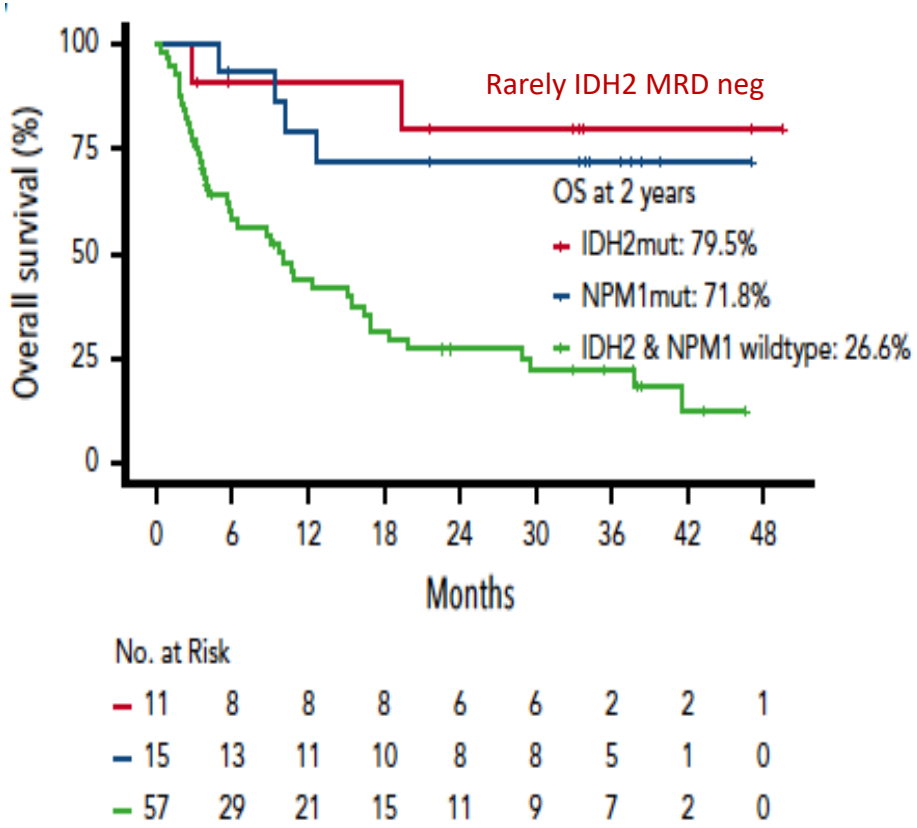


Frequent eradication of NPM1 MRD



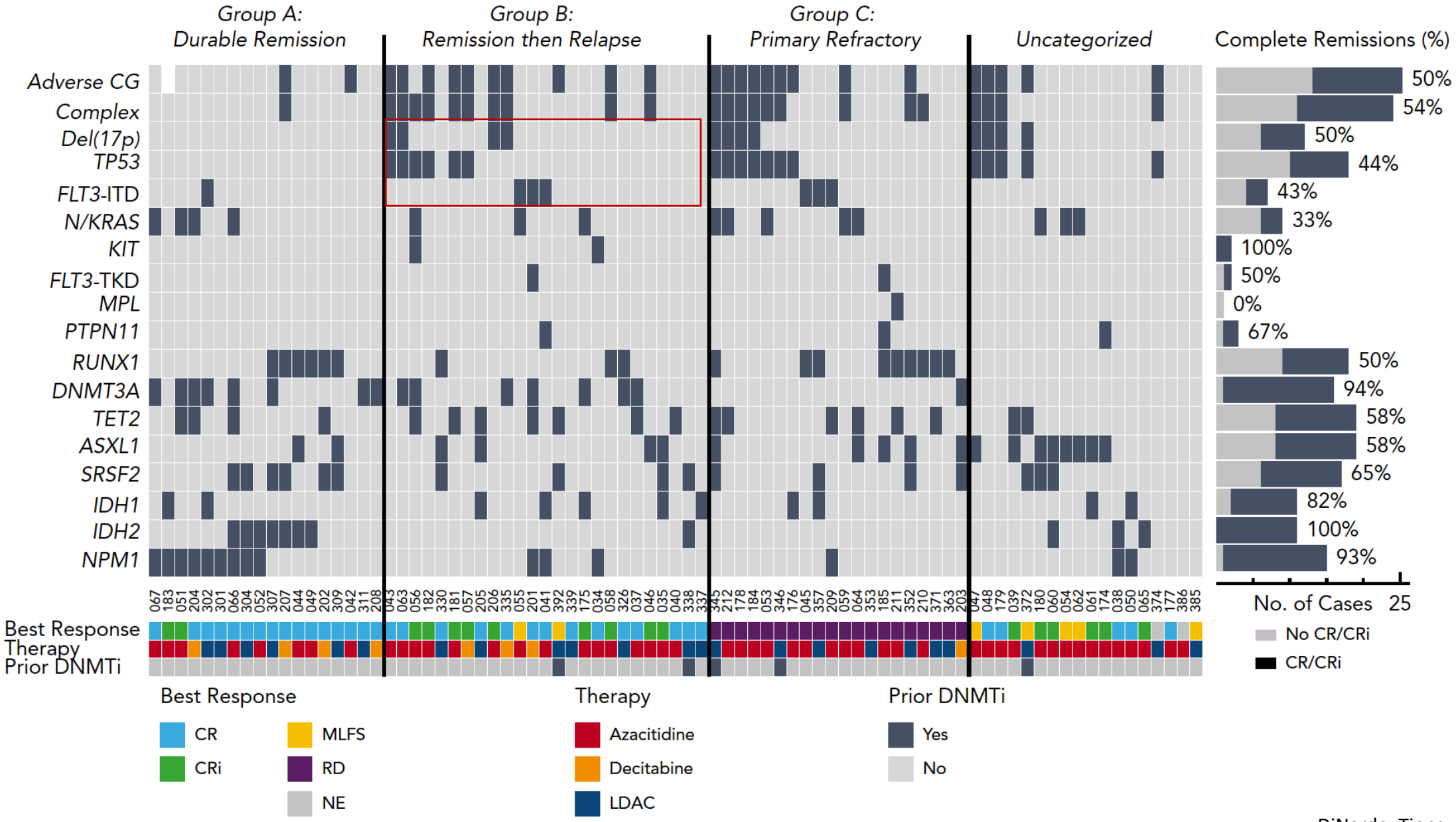
Typically several cycles before NPM1 MRD neg

High rate of OS in NPM1 and IDH2mut



DiNardo, Tiong, Blood 2020

Vad ligger bakom tidig relaps?



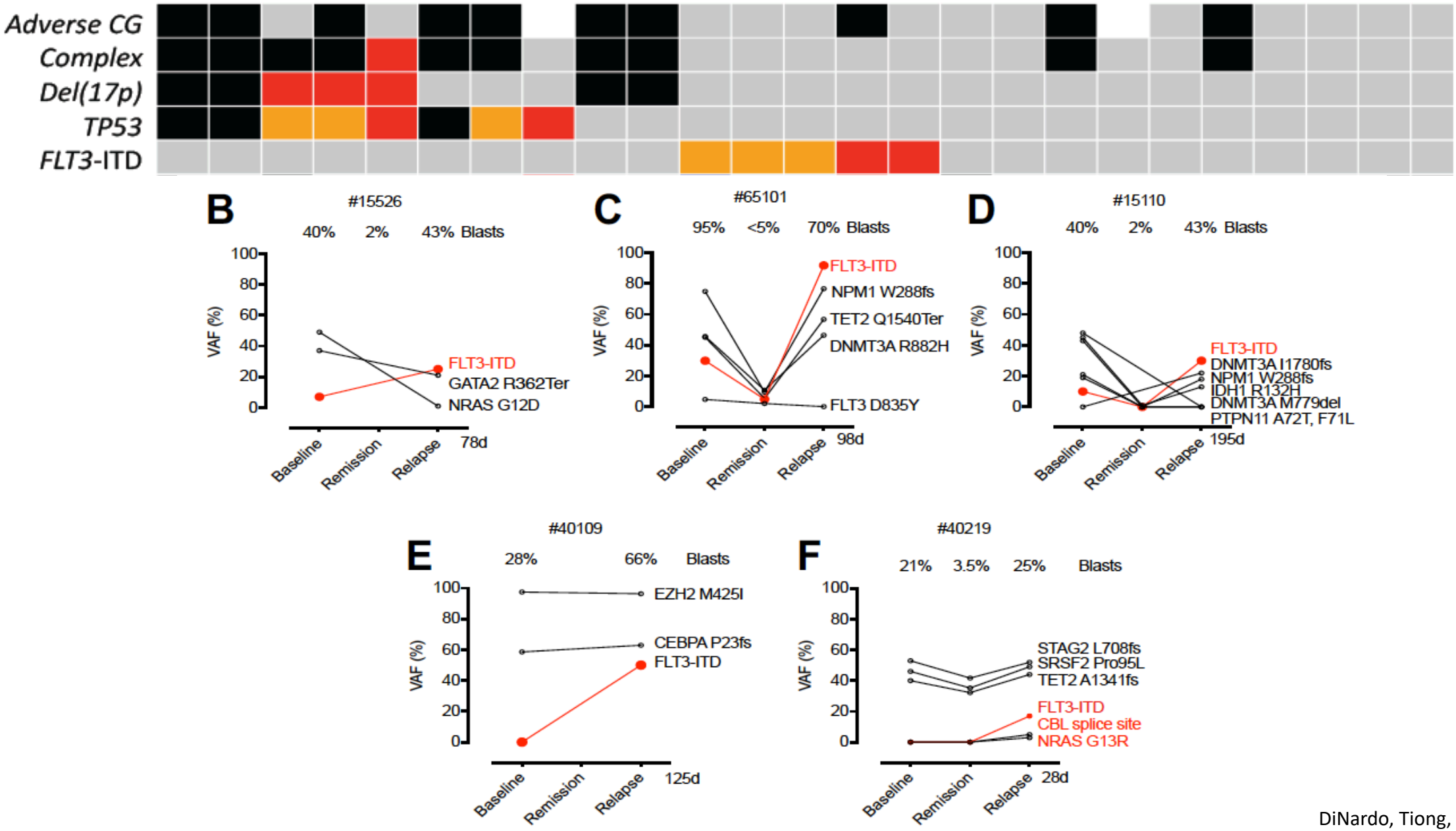
DiNardo, Tiong, Blood 2020

Bi-alleliska TP53 muterade kloner selekterade vid relaps

AML	TP53 defects at diagnosis	Relapse
15528	R342* 2% P278H 0%	R342* 48% P278H 2%, del (17p)
29411	E336fs 31%	E336fs 81% del (17p)
40205	-	Y126 splice 4% G154V 11% A161T 12% -17
65507	V272M 58%	V272M 95%
40106	-	R248W 80% M246K 5%

DiNardo, Tiong, Blood 2020

FLT3-ITD muterade kloner selekterade vid relaps



DiNardo, Tiong, Blood 2020

Polyklonal molekylär re-modeling under selektiv tryck

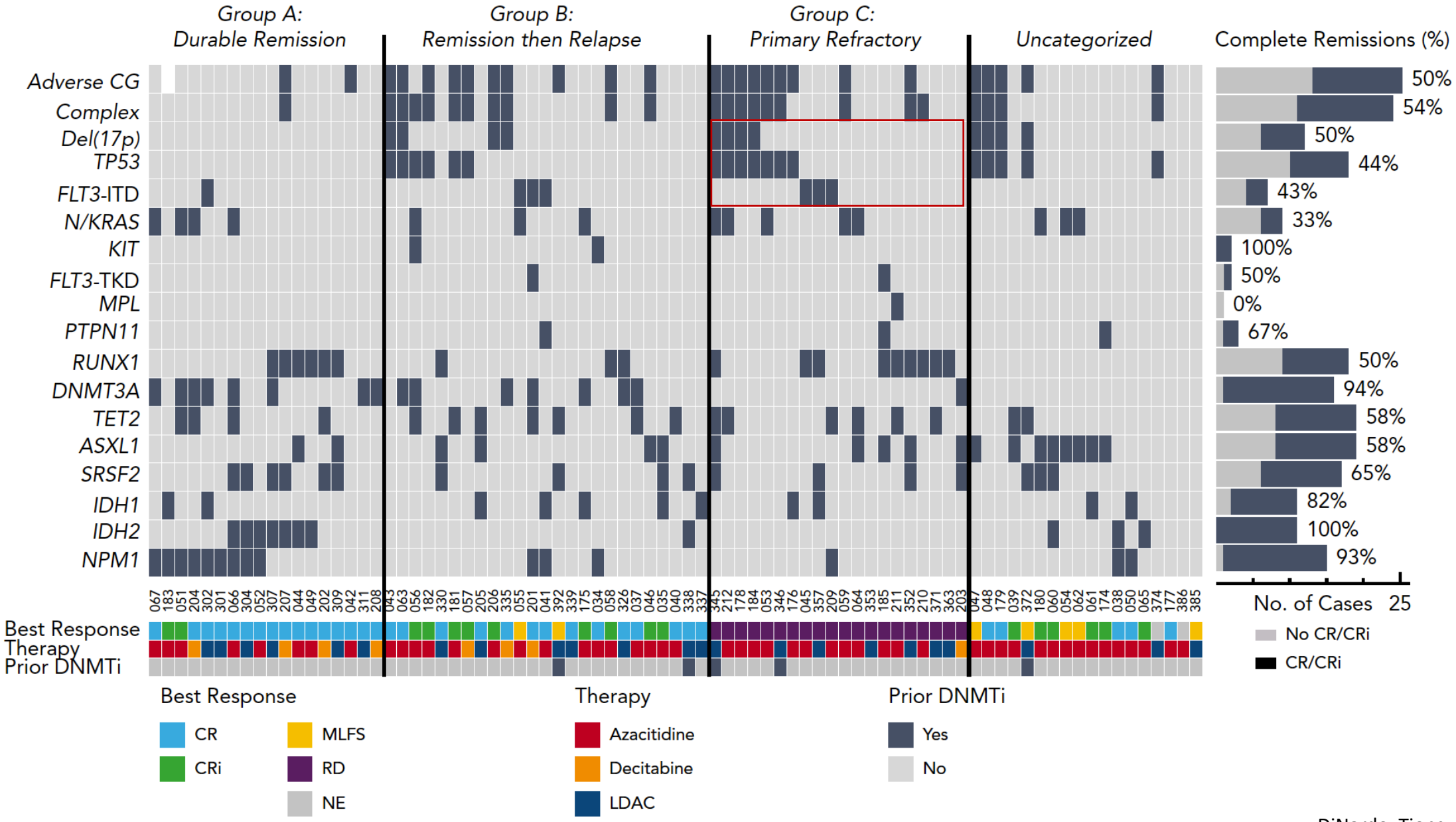
#40219

MUT	MIDO	GILT	QUIZ
FLT3-ITD	✓	✓	✓
FLT3 N676K	X	?	?
FLT3 D835	✓	✓	X
NRAS	?	X	?

Sample	Date	Blast %	WT	SRSF2 FLT3-ITD	SRSF2	SRSF2 FLT3-N676K	FLT3 D835H	SRSF2 NRAS-G13R	NRAS G12A	NRAS Q61K
Screen	04/26/17	29 %	67.1 %	0 %	32.8 %	0.1 %	0 %	0 %	0 %	0 %
Relapse	07/06/17	25 %	15.5 %	65.8 %	7.0 %	8.2 %	1.6 %	1.2 %	0.3 %	0.3 %

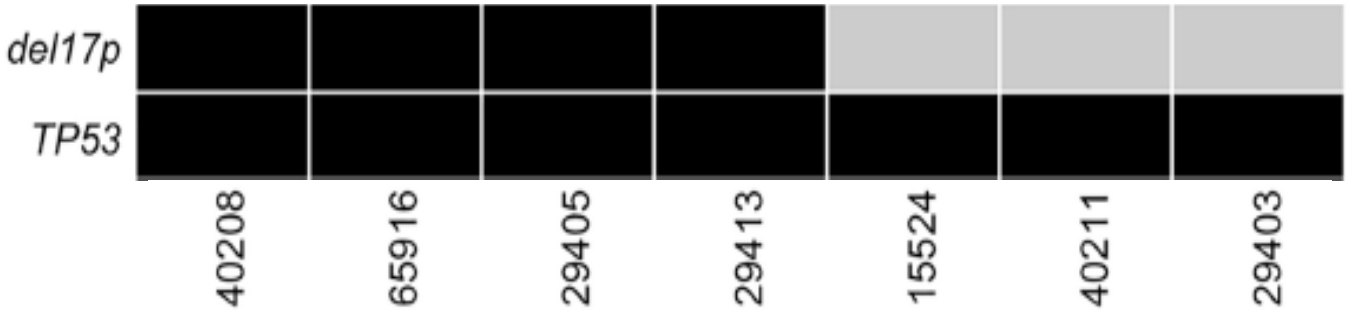
DiNardo, Tiong, Blood 2020

Primära refraktära fall



DiNardo, Tiong, Blood 2020

Bi-alleliska TP53 muterade kloner finns vid refraktära fall



AML	TP53 defects
15524	C242* 44% and V272M 51%
40211	R175H 81%
29403	K120R 22% and C238Y 12%

Behandling av TP53mut AML är fortfarande problematiskt

SVENSKA GRUPPEN AML

Therapy	N	CR/CRi	OS	Ref
AZA	21	NA	7.2m	Tang, et al. Blood 2016
5d DAC	7	29%	5.5m	Short, et al. Lancet Haematol 2019
10d DAC	17	47%	4.9m	Short, et al. Lancet Haematol 2019
LDAC + VEN	10	20%	3.7m	Wei, et al. JCO 2019
HMA + VEN	36	47%	7.2m	DiNardo, et al. Blood 2019
AZA + APR-246	11	64%	NA	Sallman, et al. JCO 2021