

# Erstlinientherapie-Algorithmus: Was ist Standard für welche Patienten?

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# Offenlegung Interessenskonflikte

## 1. Anstellungsverhältnis oder Führungsposition

keine

## 2. Beratungs- bzw. Gutachtertätigkeit

Novartis, Abbvie, Celgene-BMS, Jazz

## 3. Besitz von Geschäftsanteilen, Aktien oder Fonds

keine

## 4. Patent, Urheberrecht, Verkaufslizenz

keine

## 5. Honorare

Novartis, Celgene-BMS

## 6. Finanzierung wissenschaftlicher Untersuchungen

Apollo Therapeutics, UK

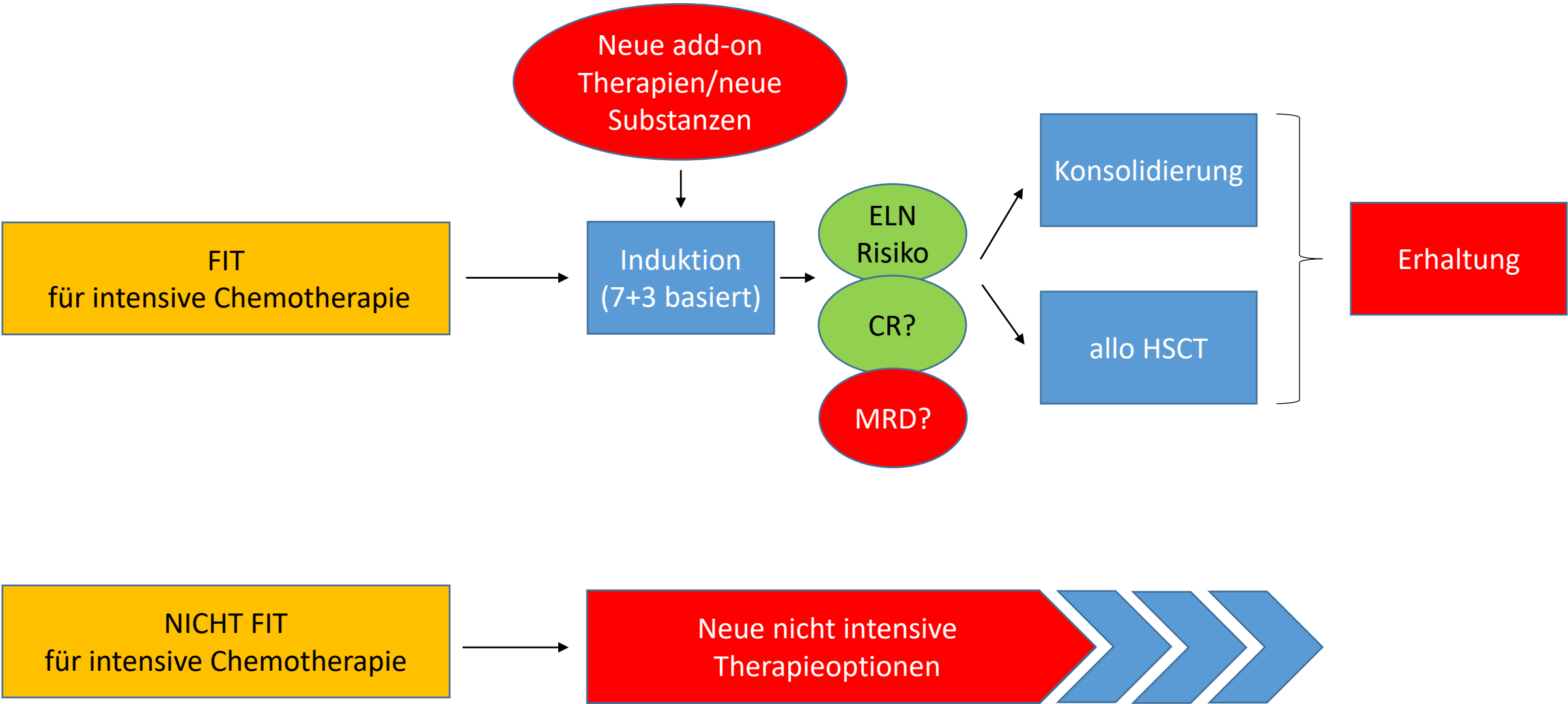
## 7. Andere finanzielle Beziehungen

keine

## 8. Immaterielle Interessenkonflikte

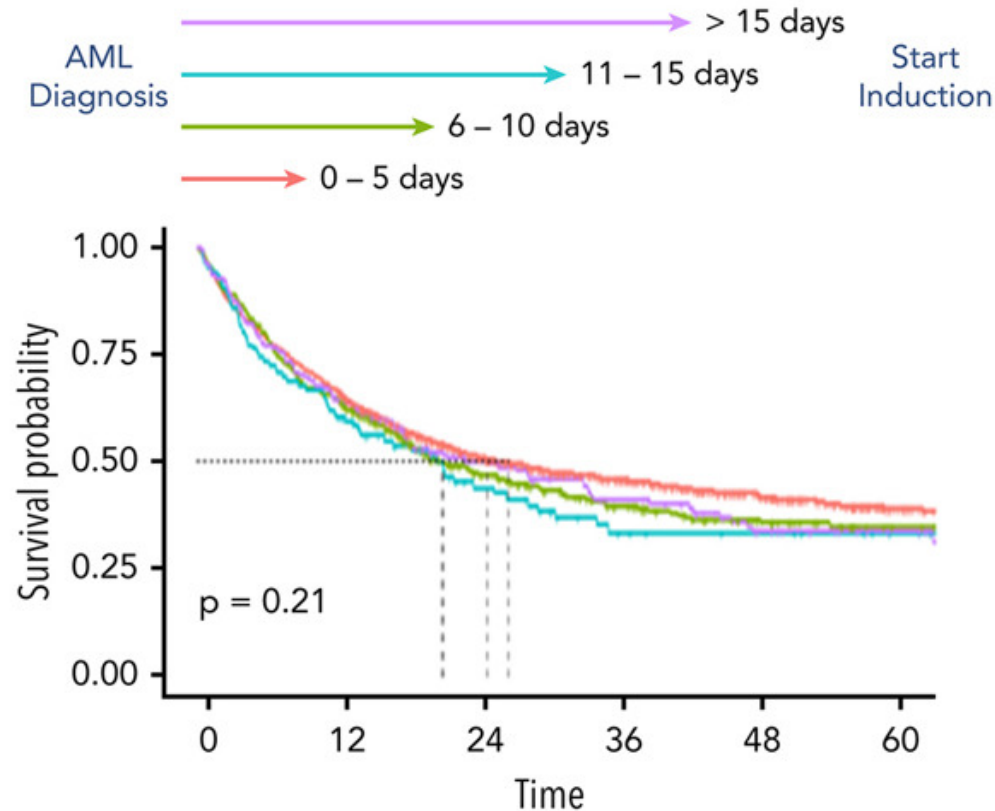
Keine

Die Folien wurden tlw. mittels Biorender.com gestaltet.

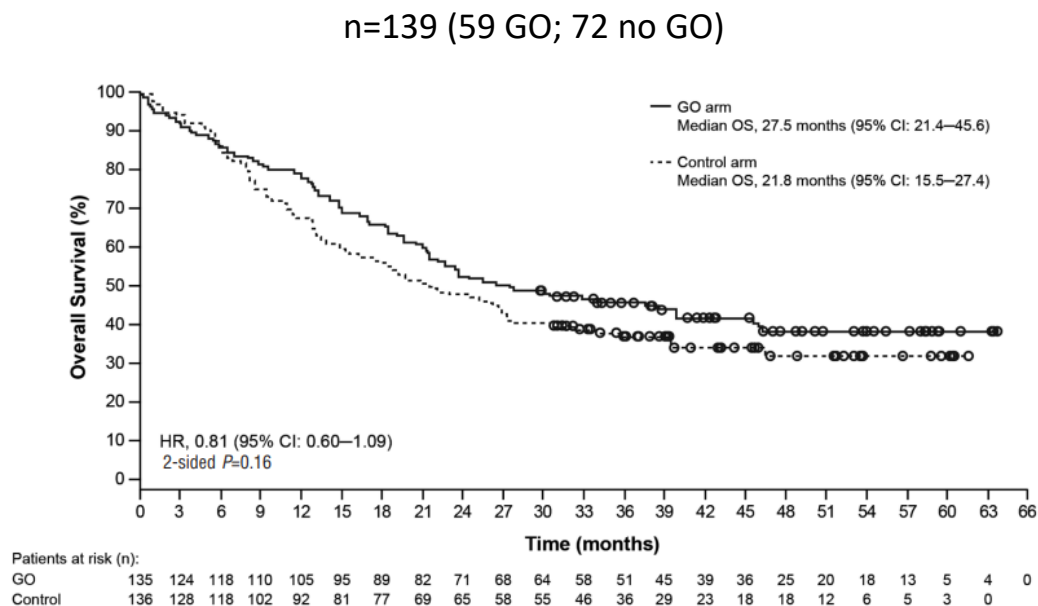


## Sofortiger Therapiestart?

Prognostic Impact of Time from Diagnosis to Treatment in Intensively Treated AML Patients  
Real-world data of 2263 patients treated in the AML registry of the SAL Cooperative Group Germany

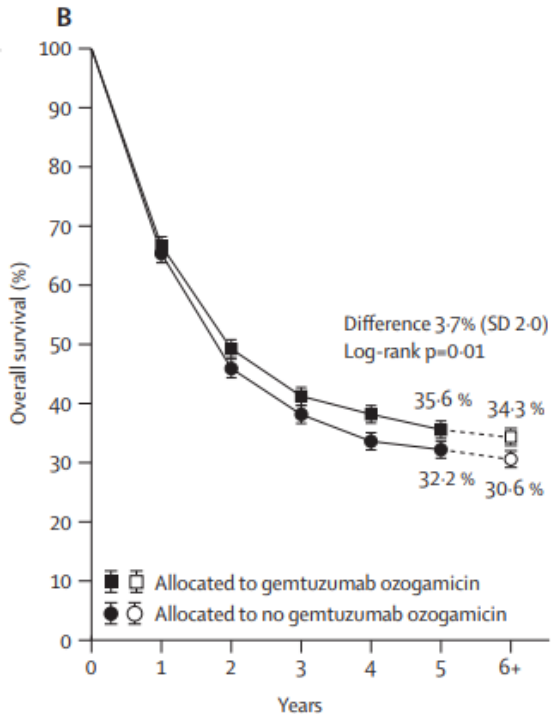


**ALFA-0701 trial: 7+3 mit Kons. +/- Gemtuzumab Ozogamizin (CD33-Antikörper und Zytotoxin Calicheamicin)**



Lambert J et al., Haematologica 2019

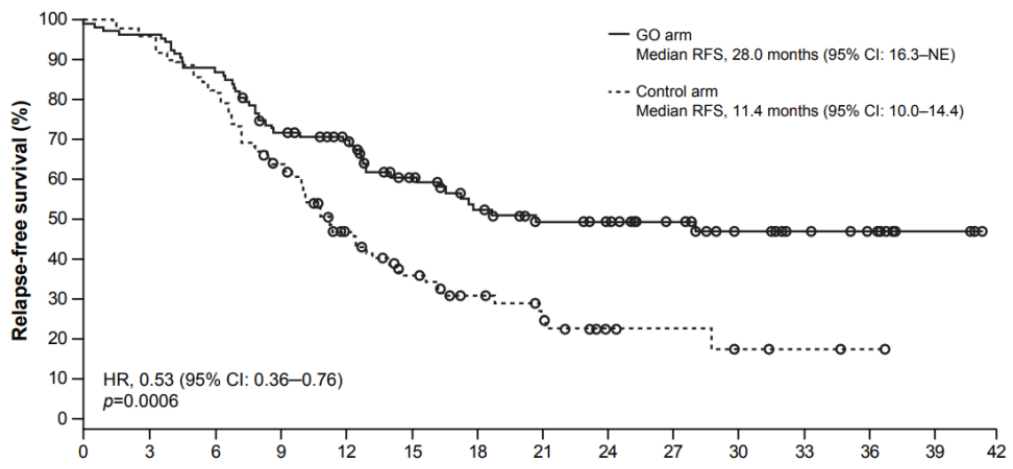
Meta-analysis from 5 randomized trials



Hills RK et al., Lancet Oncol 2014

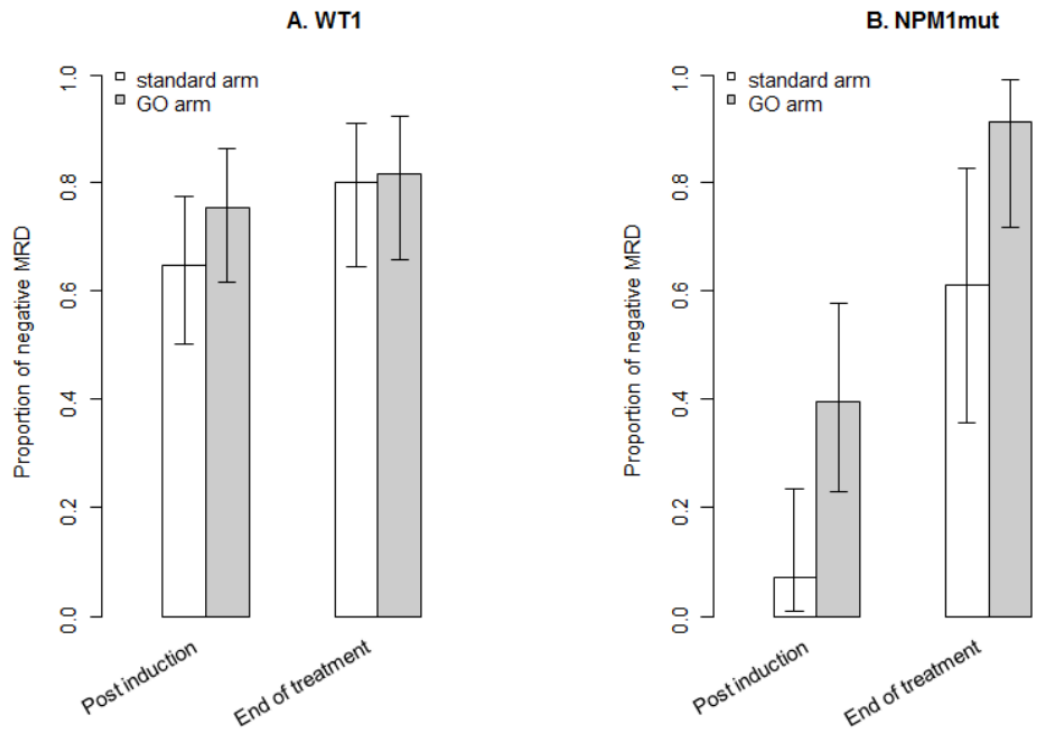
**Table S2. Response Rate by Investigator Assessment (mITT Population)**

	<b>GO (n=135)</b>	<b>Control (n=136)</b>	<b>P Value*</b>
Overall response, n (%)	110 (81.5)	100 (73.5)	0.15
95% CI	73.9–87.6	65.3–80.7	
CR, n (%)	95 (70.4)	95 (69.9)	
CRp, n (%)	15 (11.1)	5 (3.7)	

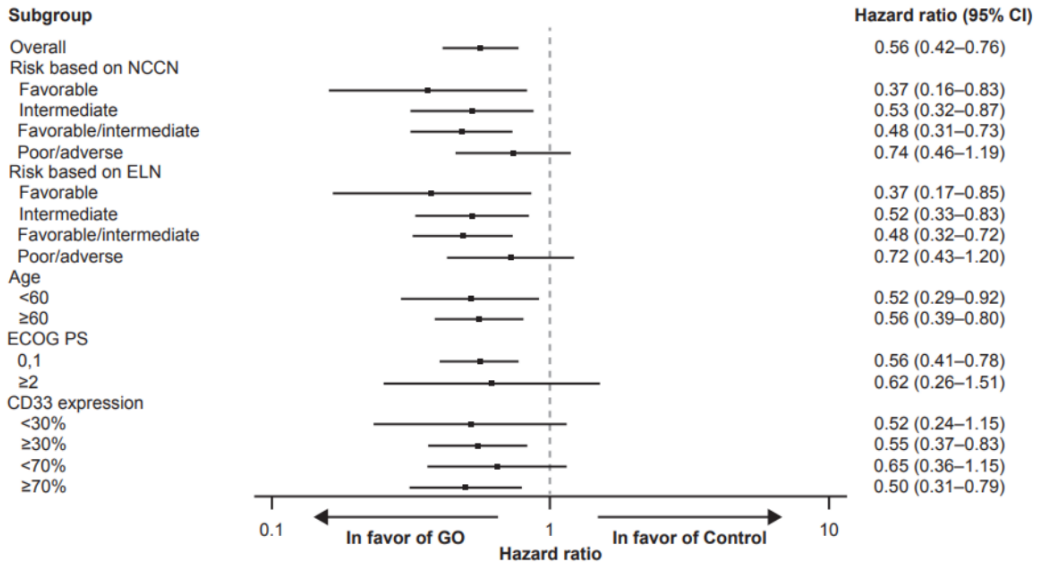


Patients at risk (n):

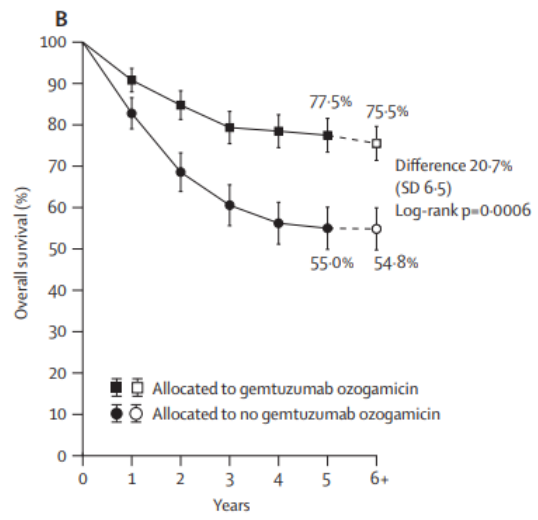
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
GO	110	108	97	77	67	50	40	32	29	23	16	11	8	3	0
Control	100	96	83	62	38	25	18	13	6	5	3	2	1	0	0



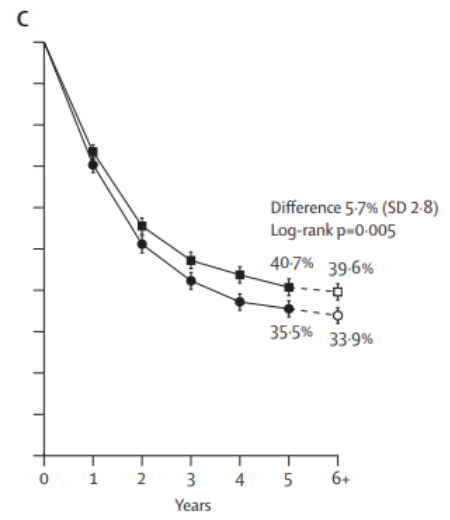
Lambert J et al., Oncotarget 2014



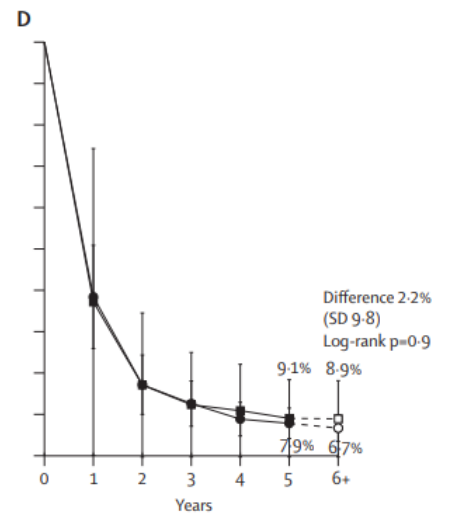
Lambert J et al., Haematologica 2019



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



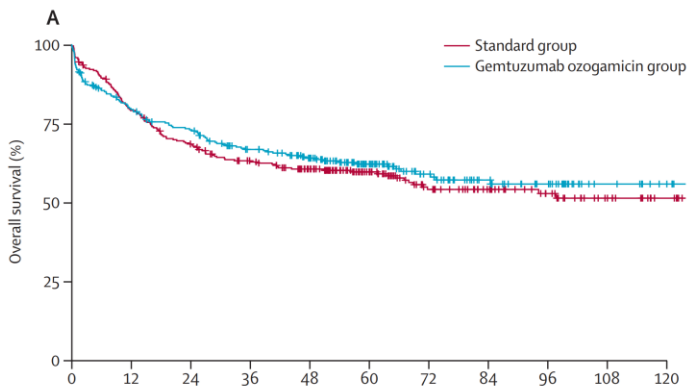
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No gemtuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3



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

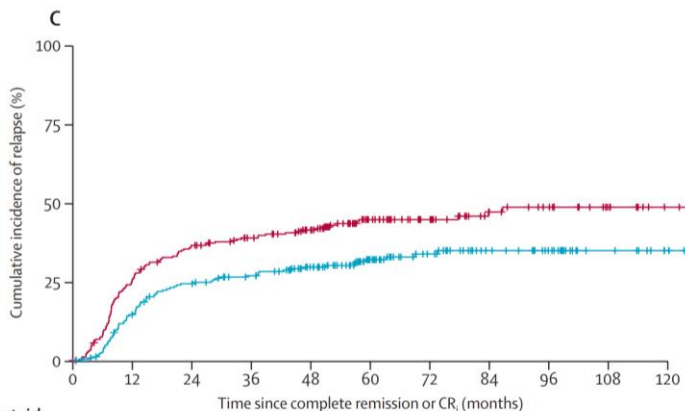
Hills RK et al., Lancet Oncol 2014

## AMLSG-0909 trial: ICT +/- GO in NPM1<sup>mut</sup> AML



Number at risk (number censored)

	0	12	24	36	48	60	72	84	96	108	120
Standard group	296 (0)	199 (5)	149 (33)	118 (33)	91 (33)	71 (101)	58 (101)	48 (101)	38 (133)	33 (133)	9 (161)
Gemtuzumab ozogamicin group	292 (0)	204 (11)	153 (38)	118 (38)	91 (118)	65 (118)	52 (118)	43 (118)	33 (147)	28 (147)	8 (172)



Number at risk (number censored)

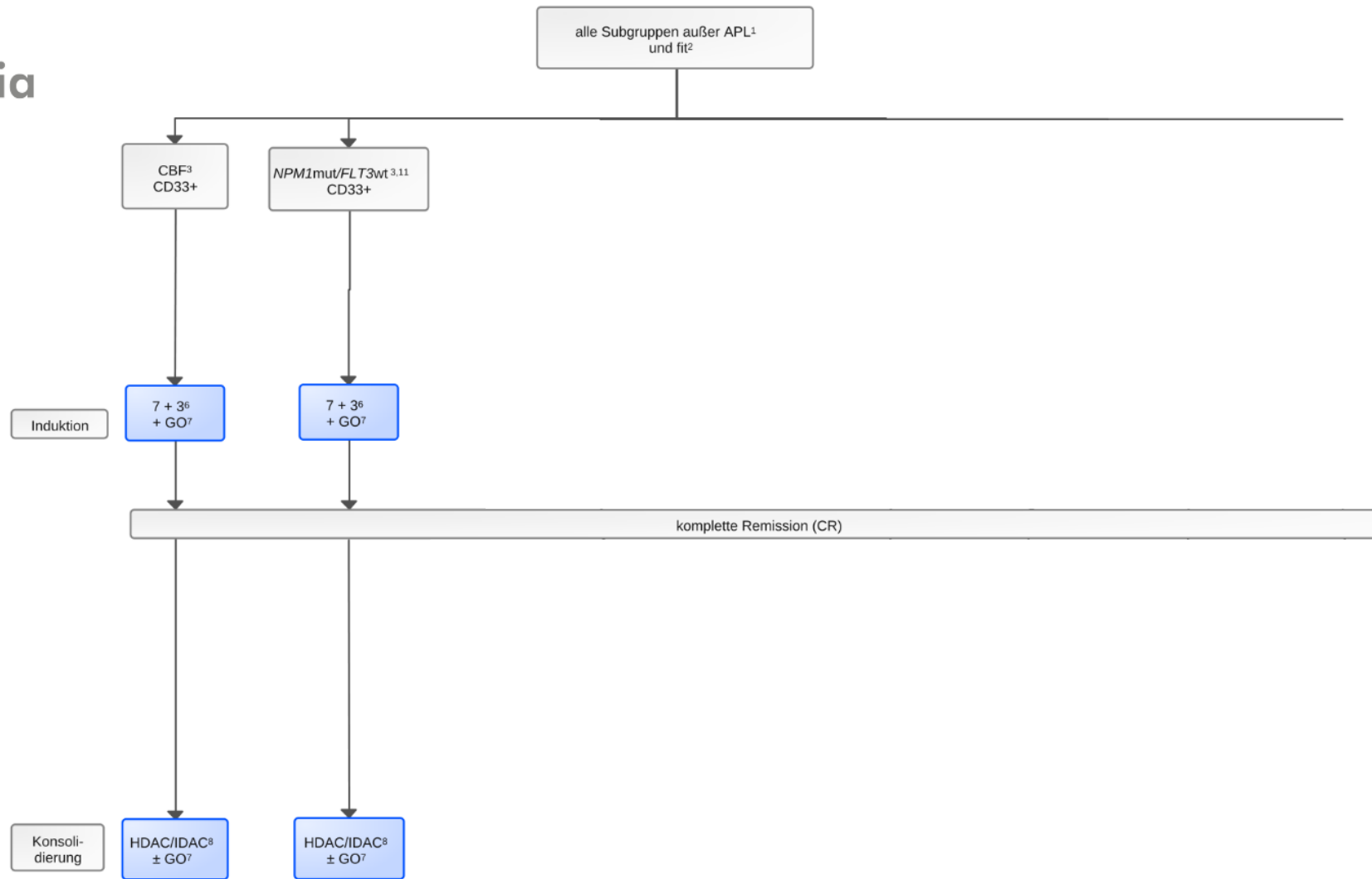
	0	12	24	36	48	60	72	84	96	108	120
Standard group	267 (0)	148 (5)	111 (28)	82 (28)	62 (28)	46 (82)	33 (82)	22 (103)	13 (103)	8 (103)	3 (122)
Gemtuzumab ozogamicin group	251 (0)	164 (9)	122 (35)	96 (35)	71 (35)	52 (96)	41 (96)	26 (121)	18 (121)	12 (121)	6 (141)

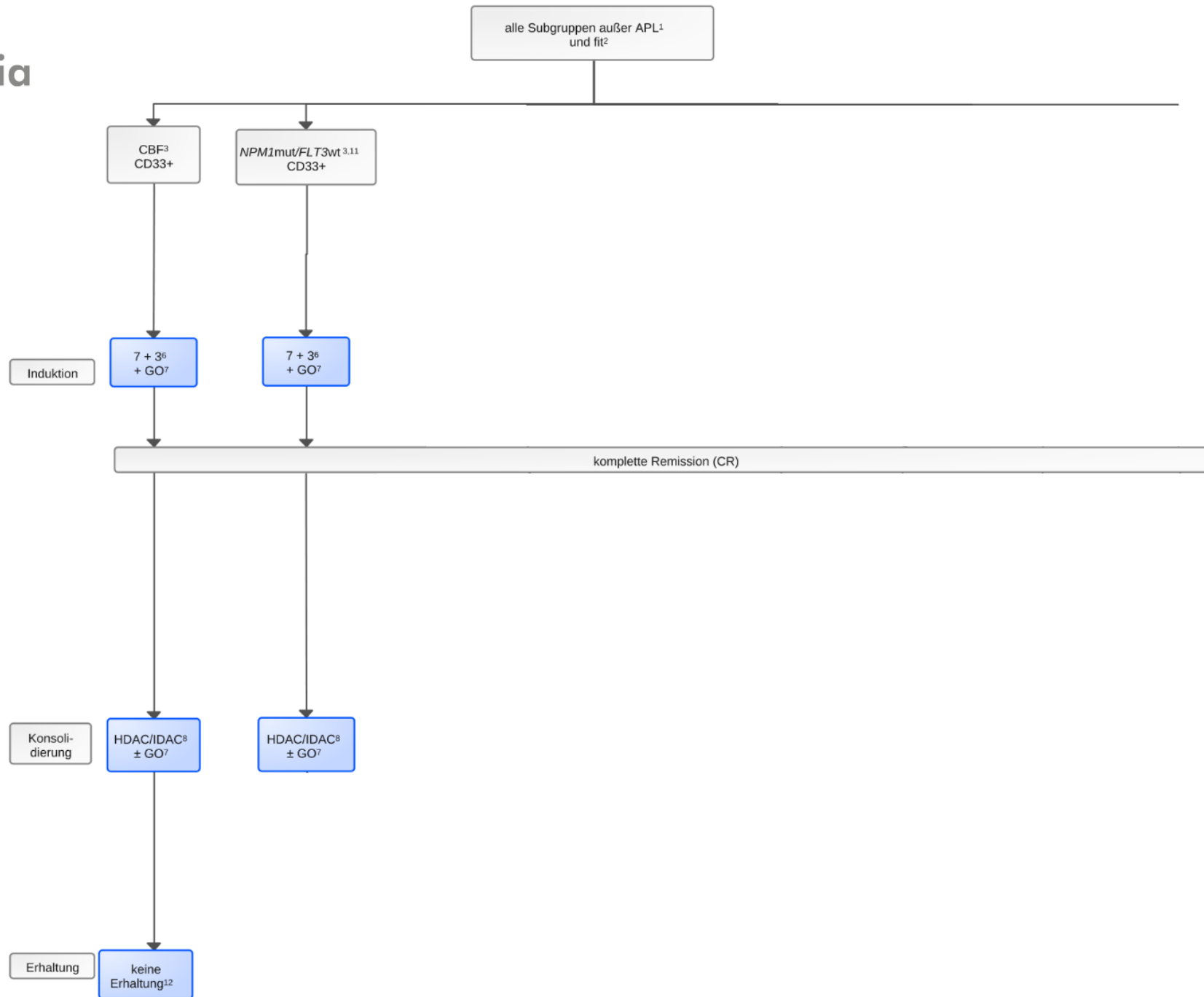
### Event-free survival

Subgroup effects of GO vs. Standard for EFS

Variable	HR (95% CI)	Standard Arm	GO Arm
Female	0.67 (0.5 to 0.9)	99/152	81/163
Male	1.04 (0.76 to 1.43)	82/144	71/129
De novo	0.83 (0.66 to 1.04)	170/276	140/271
sAML/tAML	0.85 (0.38 to 1.94)	11/20	12/21
Normal karyotype	0.84 (0.66 to 1.07)	139/231	120/235
Abnormal karyotype	0.81 (0.42 to 1.54)	18/32	19/38
FLT3-ITD negative	0.72 (0.56 to 0.92)	148/247	113/242
FLT3-ITD positive	1.54 (0.97 to 2.45)	33/49	39/50
FLT3-TKD negative	0.81 (0.65 to 1.03)	159/262	127/250
FLT3-TKD positive	0.91 (0.51 to 1.62)	22/34	25/42
DNMT3A wildtype	1.06 (0.76 to 1.48)	74/153	65/131
DNMT3A mutated	0.64 (0.48 to 0.85)	106/141	86/158
Age ≤60	0.71 (0.52 to 0.98)	92/165	67/160
Age 60-70	0.75 (0.51 to 1.12)	53/80	46/83
Age > 70	1.42 (0.9 to 2.24)	36/51	39/49
Wbc LQ	0.87 (0.69 to 1.09)	180/294	152/291
Wbc UQ	1.14 (0.45 to 2.91)		
<b>Global</b>	<b>0.83 (0.67 to 1.03)</b>	<b>181/296</b>	<b>152/292</b>



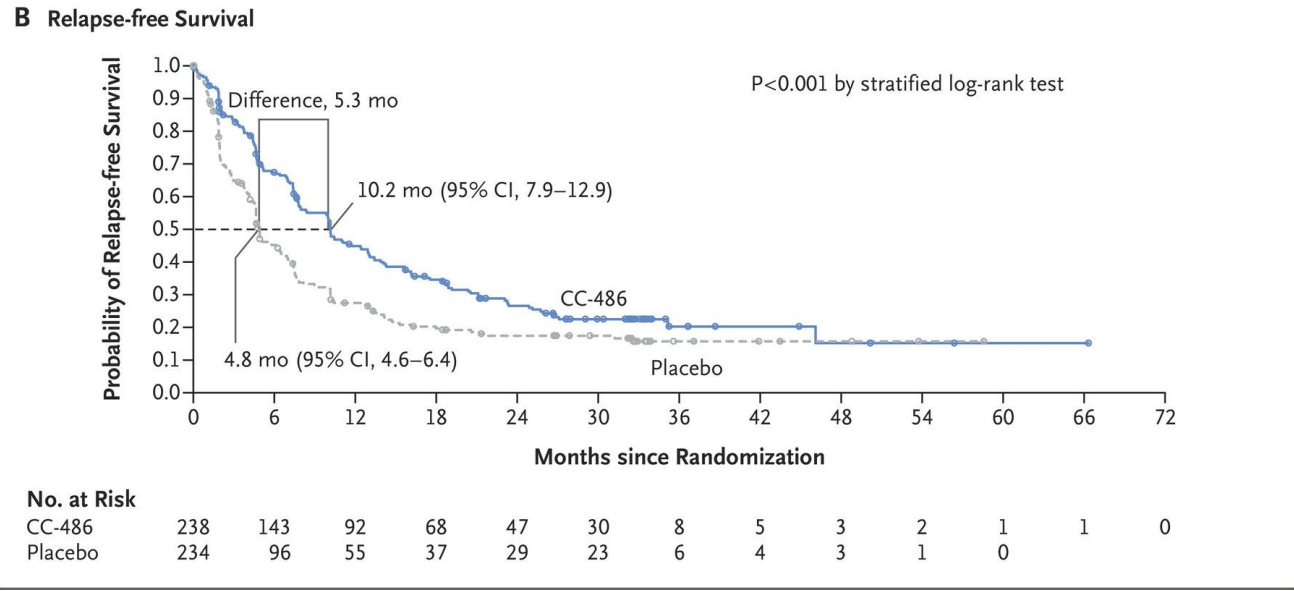
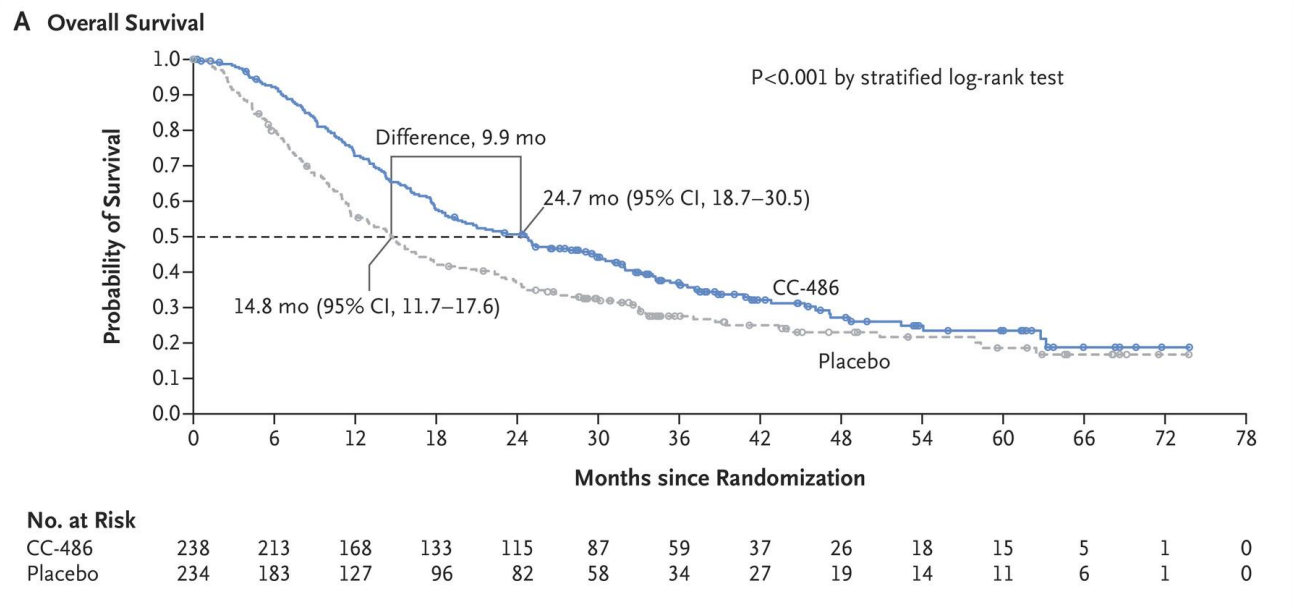


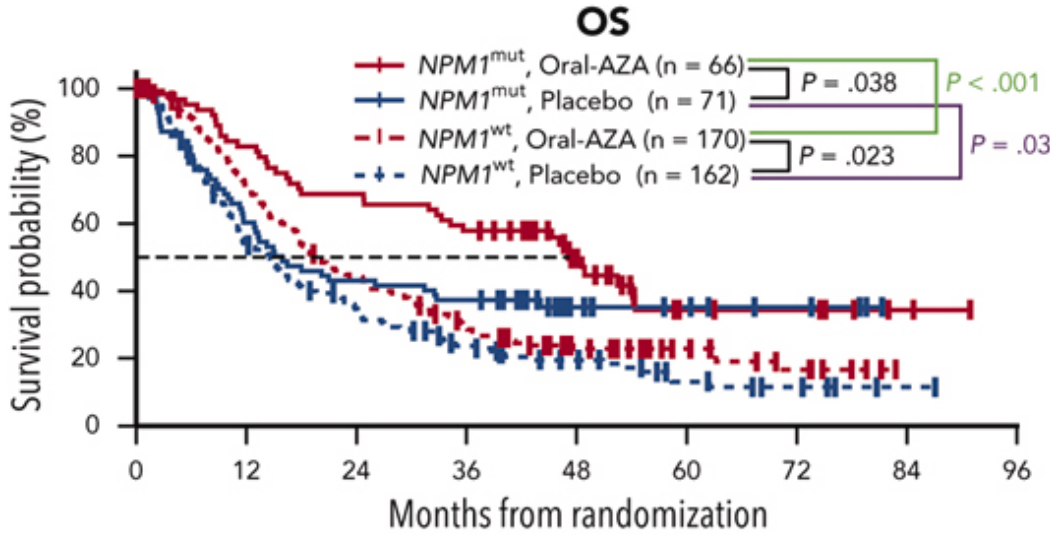


## QUAZAR AML-001: orale Azacitidin Erhaltung bei AML

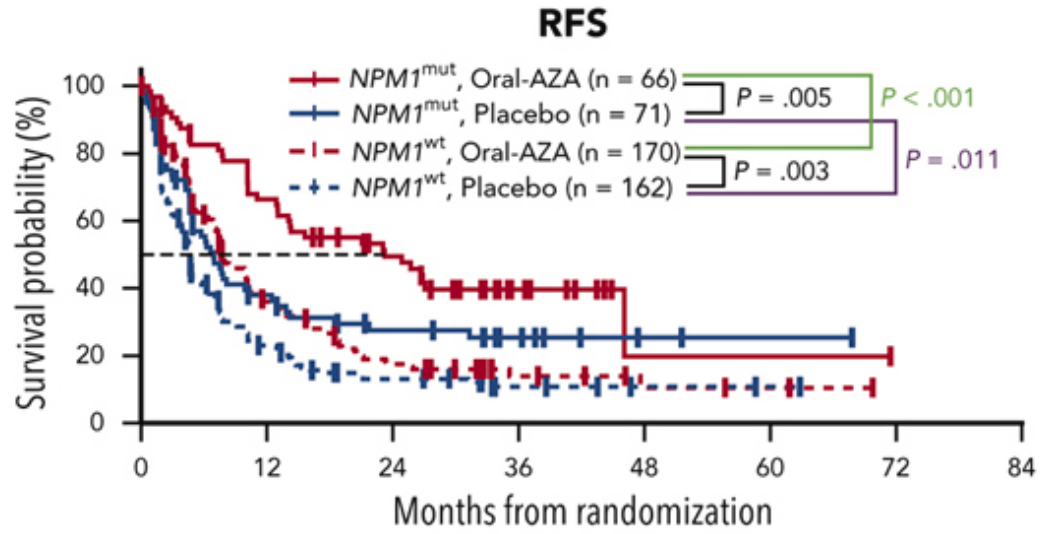
- Phase 3, randomisiert, doppelblind, Placebo-kontrollierte Studie
- Erhaltung mittels oralem Azacitidin (CC-486) vs Placebo
- n=472, ≥55 Jahre
- de-novo AML mit intermediate oder poor-risk Zytogenetik in CR1 (CR erreicht in 4 Monaten vor Randomisierung), die keine allo HSZT Kandidat\*innen waren
- CC-486 (300 mg OD) oder Placebo, Tag 1-14 von 28 Tage Zyklen.
- Bis zum Auftreten von >15% Blasten oder Unverträglichkeit
- Primary end point: OS
- Secondary end points: RFS, health-related quality of life.

## QUAZAR AML-001



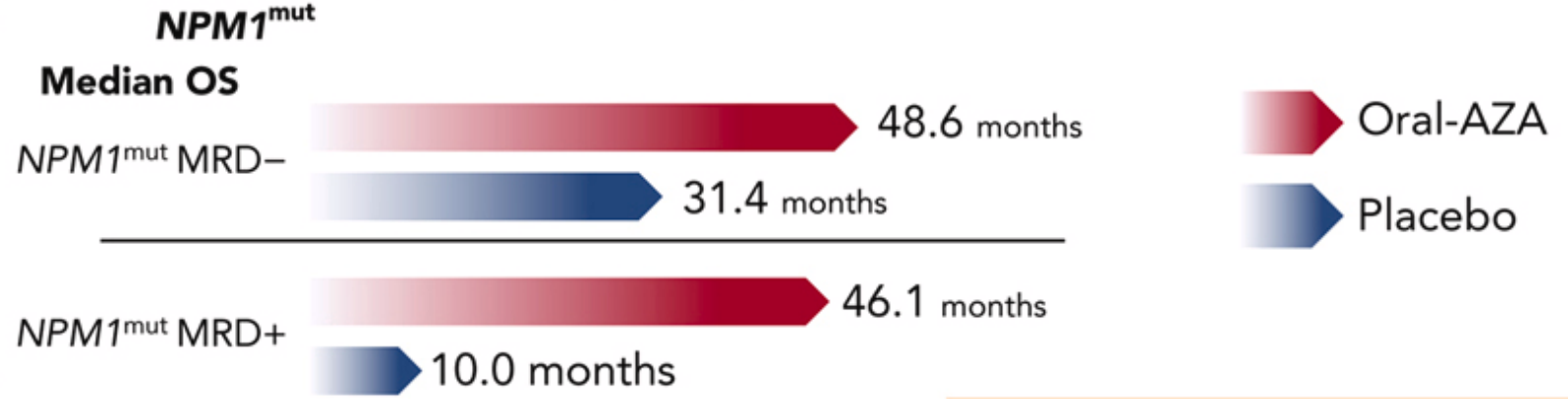
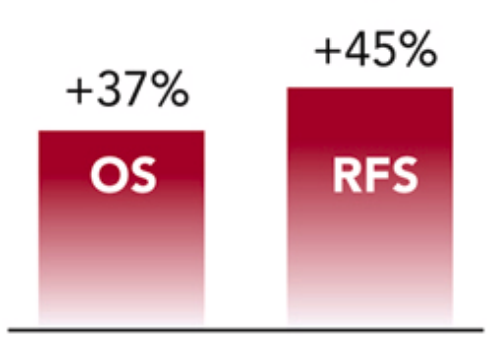


Median OS, months	<i>NPM1<sup>mut</sup></i> , Oral-AZA	<i>NPM1<sup>wt</sup></i> , Oral-AZA
	47.2	19.6
	<i>NPM1<sup>mut</sup></i> , Placebo	<i>NPM1<sup>wt</sup></i> , Placebo
	15.9	14.6



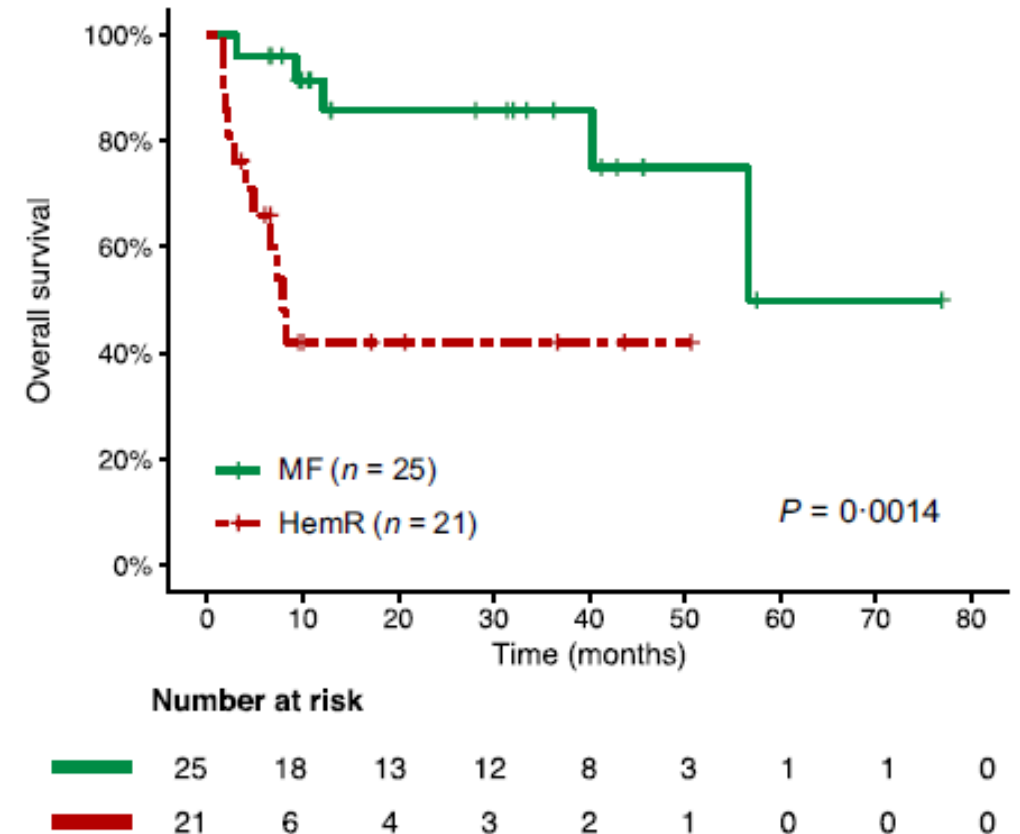
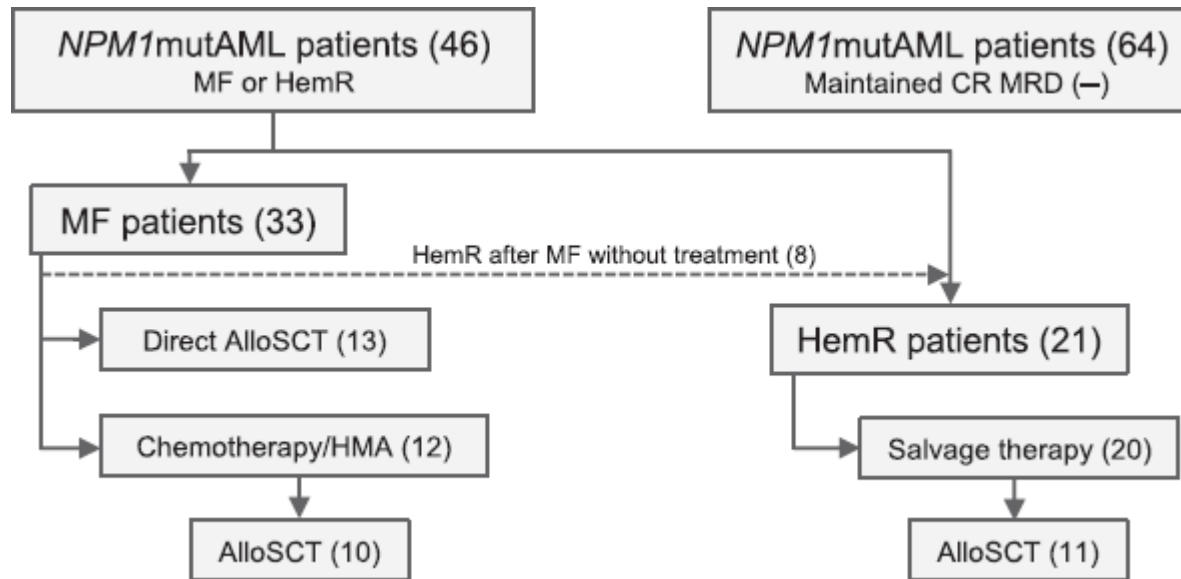
Median RFS, months	<i>NPM1<sup>mut</sup></i> , Oral-AZA	<i>NPM1<sup>wt</sup></i> , Oral-AZA
	23.2	7.7
	<i>NPM1<sup>mut</sup></i> , Placebo	<i>NPM1<sup>wt</sup></i> , Placebo
	6.9	4.6

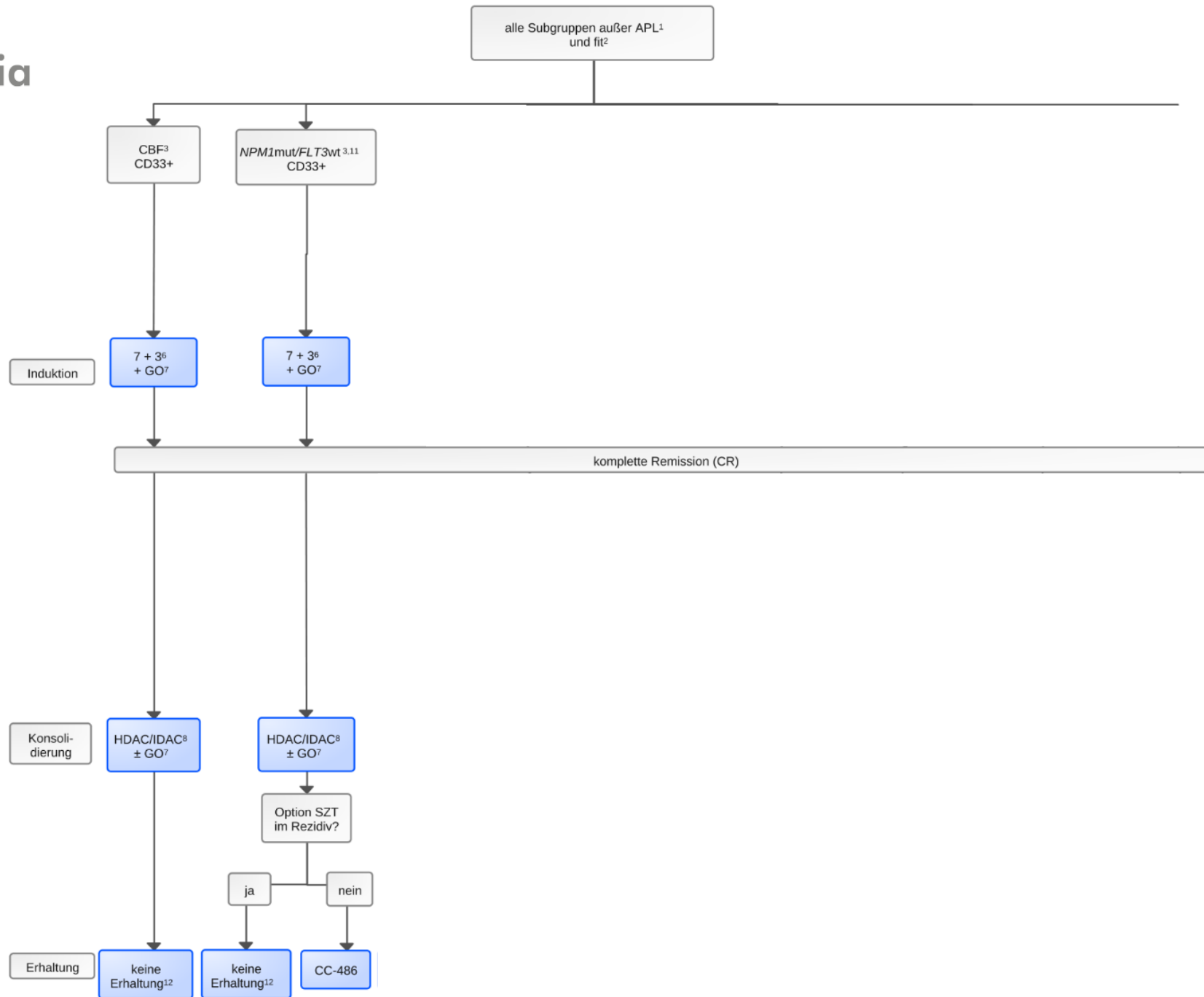
### *NPM1<sup>mut</sup>*: Oral-AZA vs placebo<sup>d</sup>



## CETLAM-12 Subanalyse

- CETLAM-12 inkludierte eine prä-emptive Intervention in Patient\*innen mit molecular failure (MF)
- 110 ELNfav NPM1 AML Patient\*innen in CR nach Induktionschemotherapie





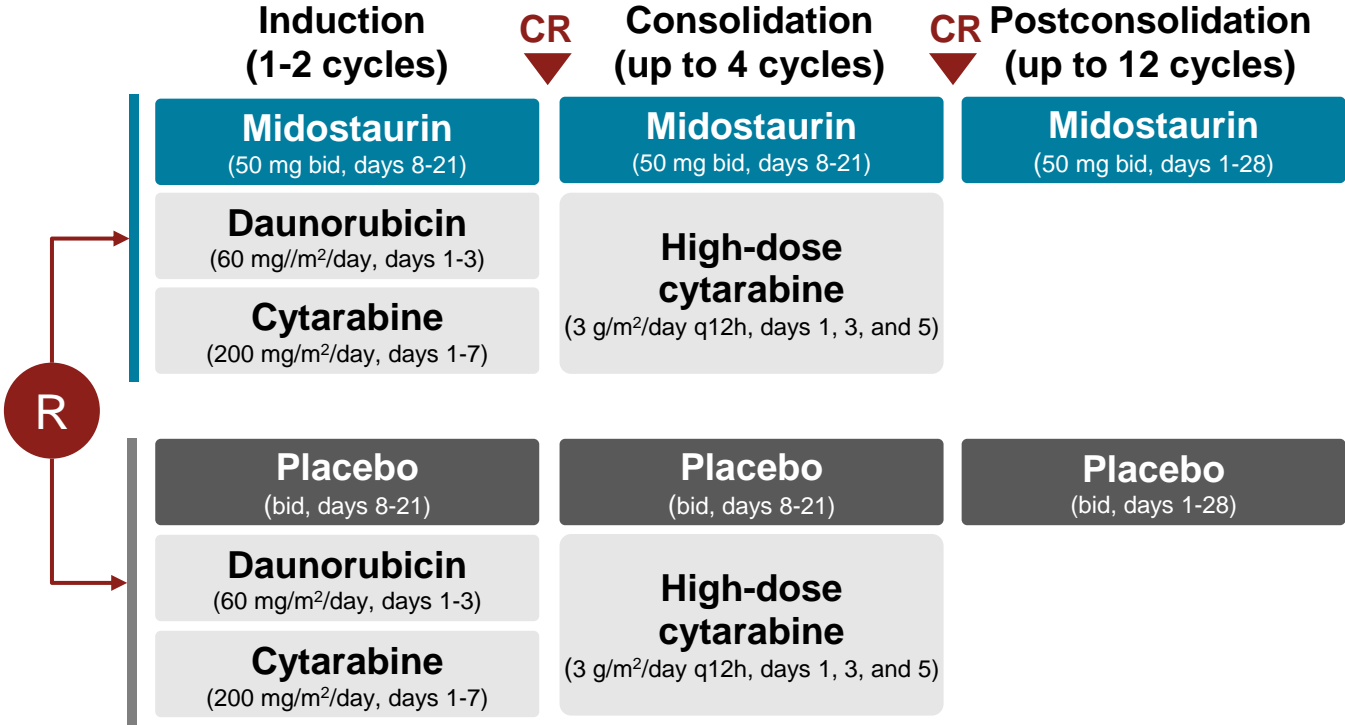
**RATIFY trial: 7+3 mit Kons. +/- Midostaurin inkl. Erhaltung**

- Phase 3, randomisiert, Placebo-kontrolliert, doppelblind
- CAVE: allo HSZT erlaubt, danach kein weiteres Midostaurin

**Patients with newly diagnosed AML aged  $\geq 18$  to  $< 60$  years with activating *FLT3* mutations<sup>a,b</sup>**

**Stratification by TKD and ITD<sup>c</sup> (ratio  $< 0.7$  vs  $\geq 0.7$ )**

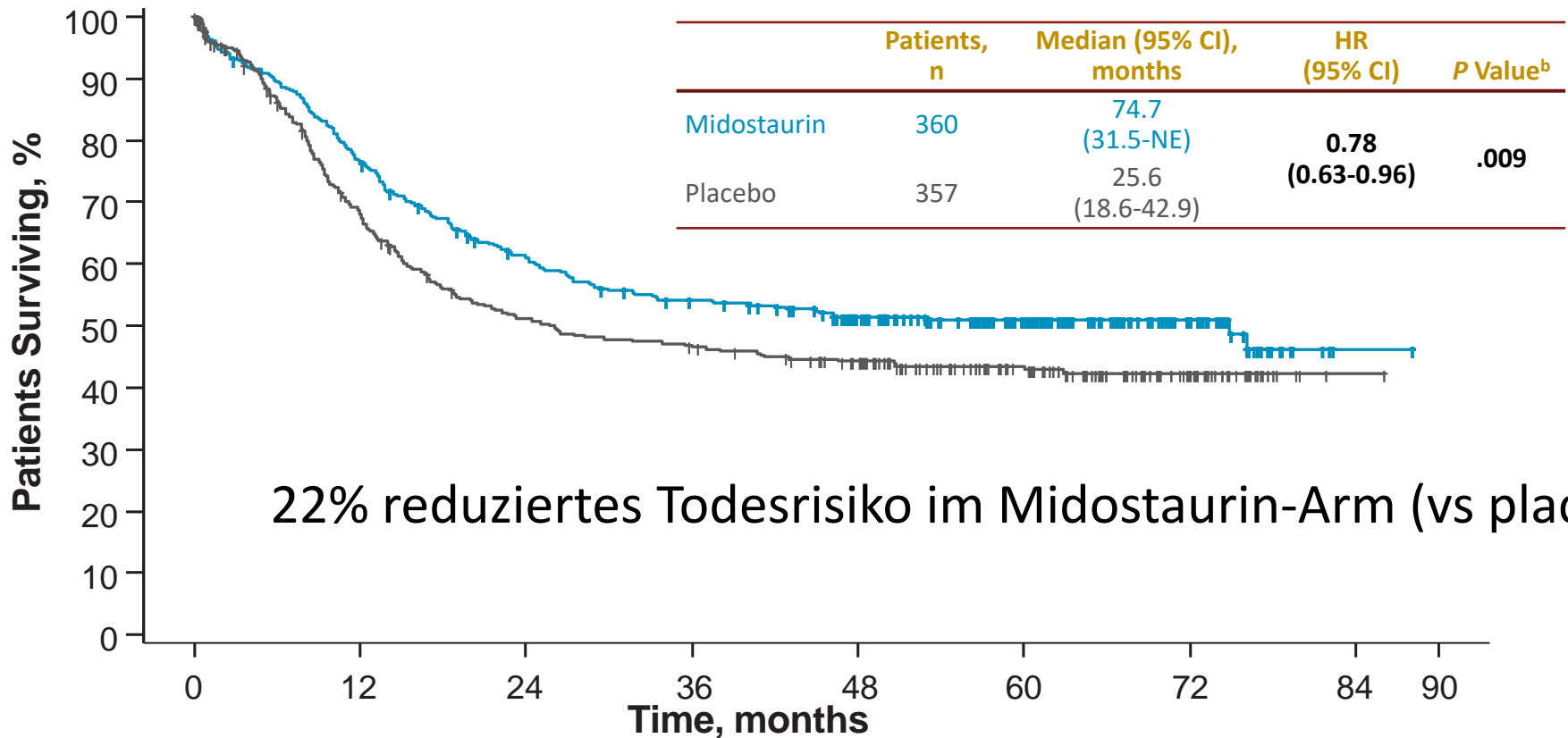
**(N = 717)**



**Primary endpoint: OS**  
**Key secondary endpoint: EFS**



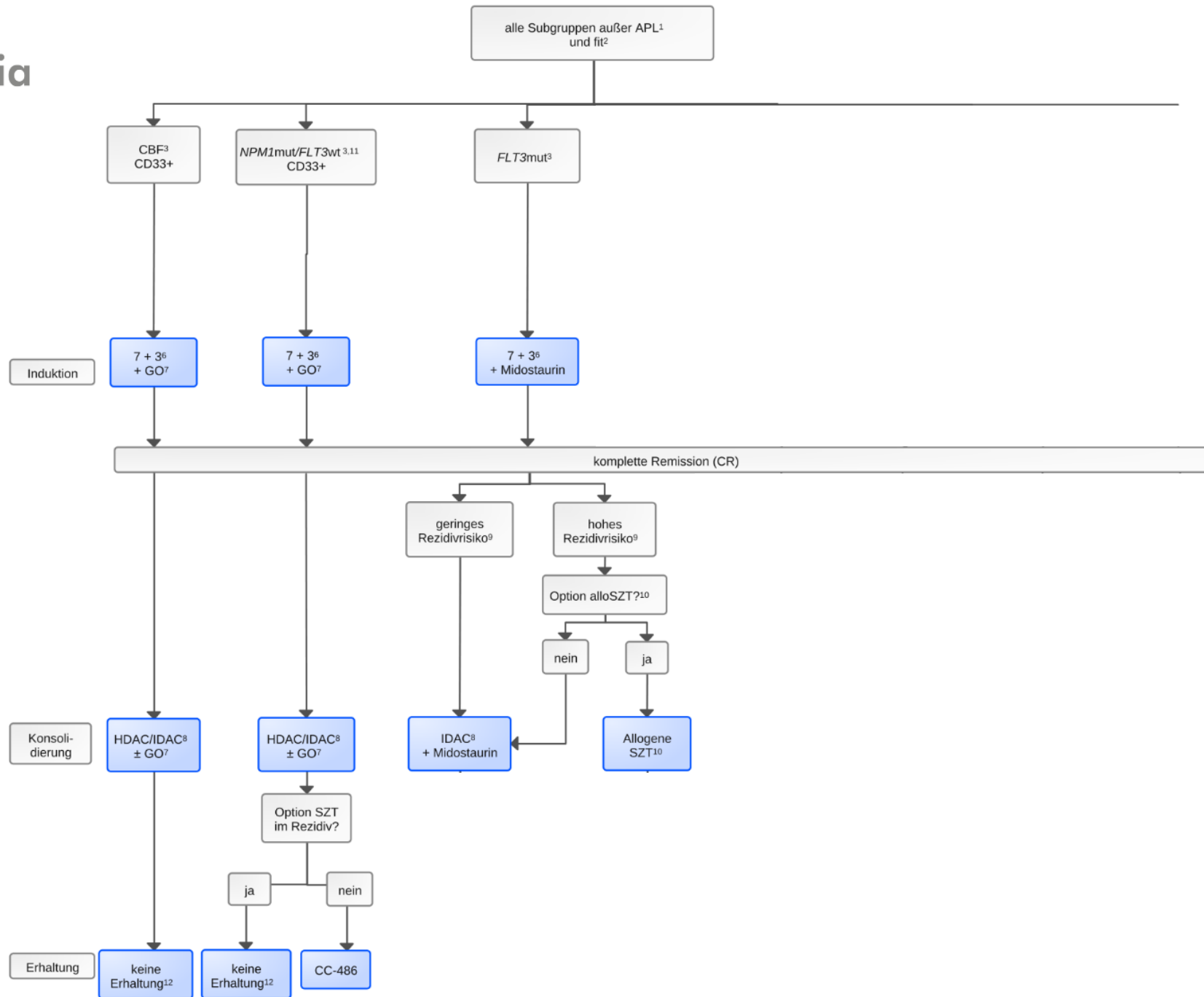
**RATIFY trial: OS noncensored für alle HSZT**

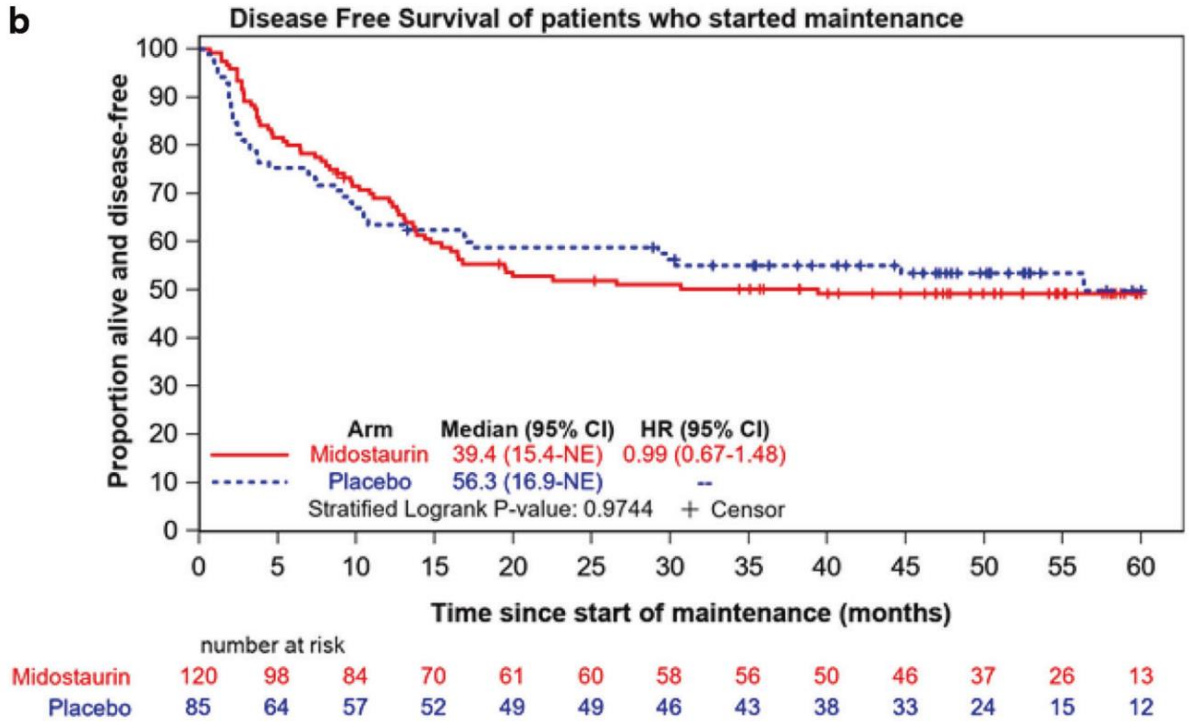
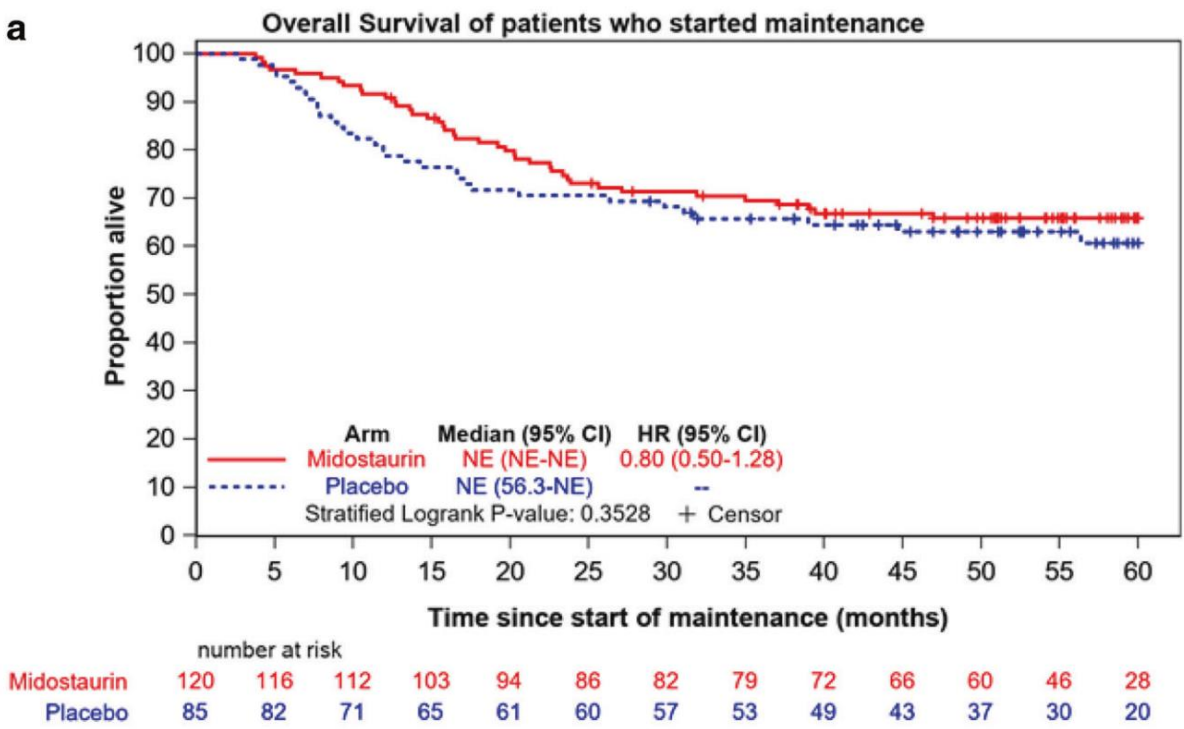


22% reduziertes Todesrisiko im Midostaurin-Arm (vs placebo)

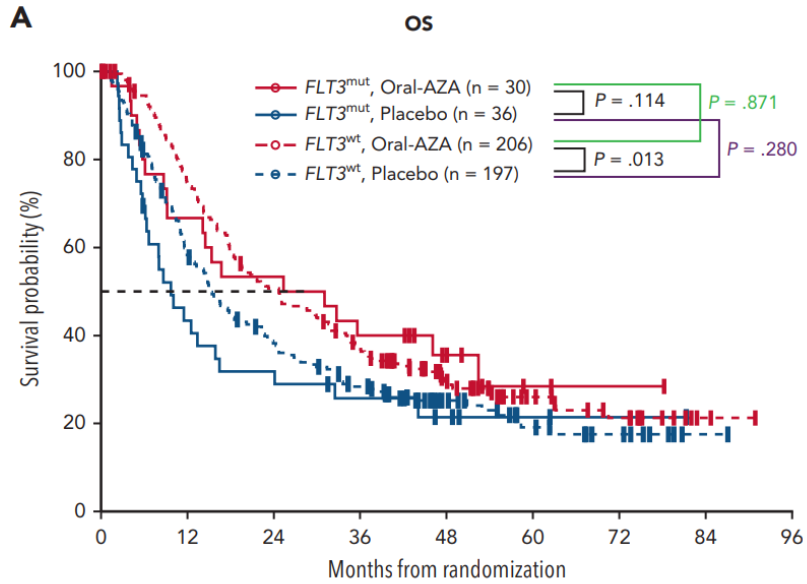
**Patients at risk**

Midostaurin	360	269	209	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1



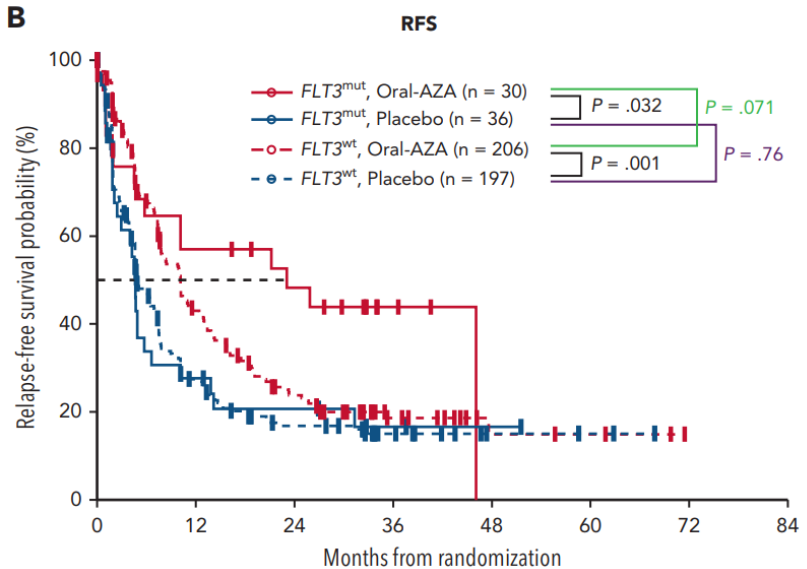


CAVE: no extra randomization before maintenance  
 Only patients <60 years



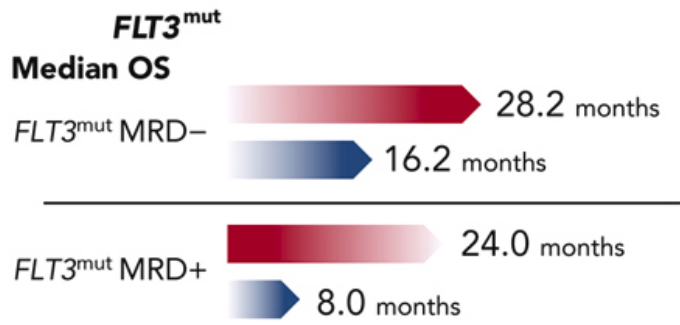
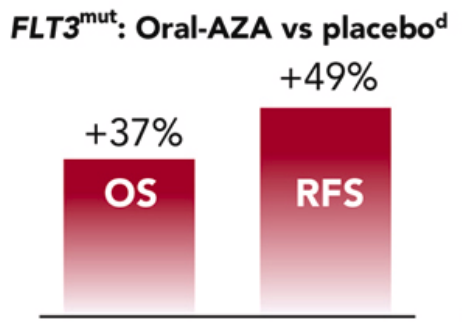
Median OS, months

FLT3 <sup>mut</sup> , Oral-AZA	28.2	FLT3 <sup>wt</sup> , Oral-AZA	24.7
FLT3 <sup>mut</sup> , Placebo	9.7	FLT3 <sup>wt</sup> , Placebo	15.2

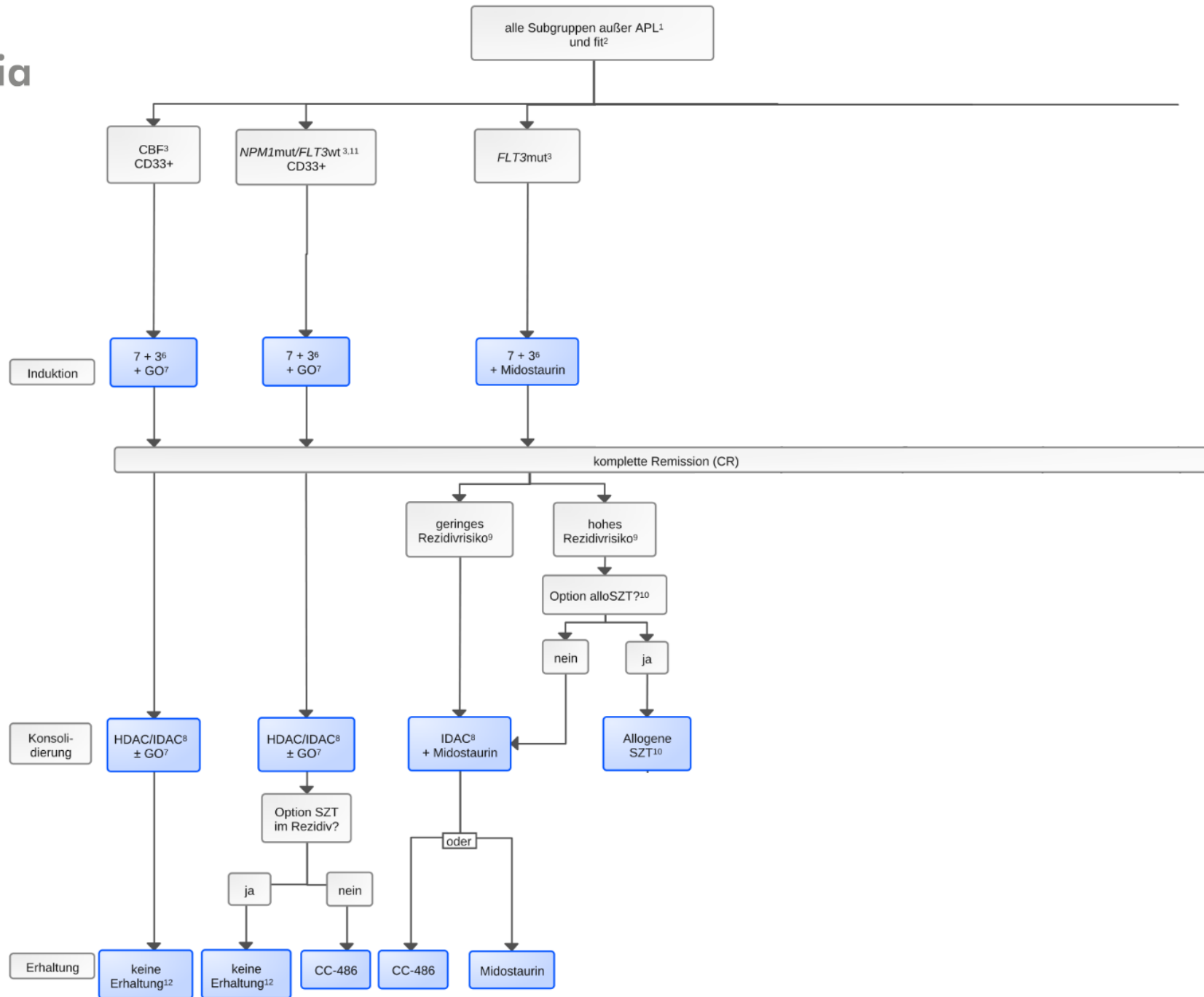


Median RFS, months

FLT3 <sup>mut</sup> , Oral-AZA	23.1	FLT3 <sup>wt</sup> , Oral-AZA	10.2
FLT3 <sup>mut</sup> , Placebo	4.6	FLT3 <sup>wt</sup> , Placebo	4.9



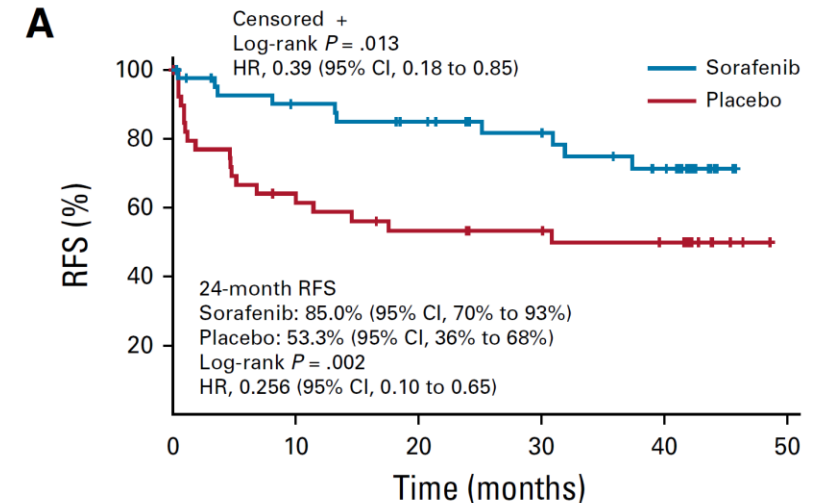
CAVE: Alter ≥55 Jahr  
FLT3mut nur 66 Patienten



## SORMAIN: Sorafenib Erhaltung nach allo HSZT

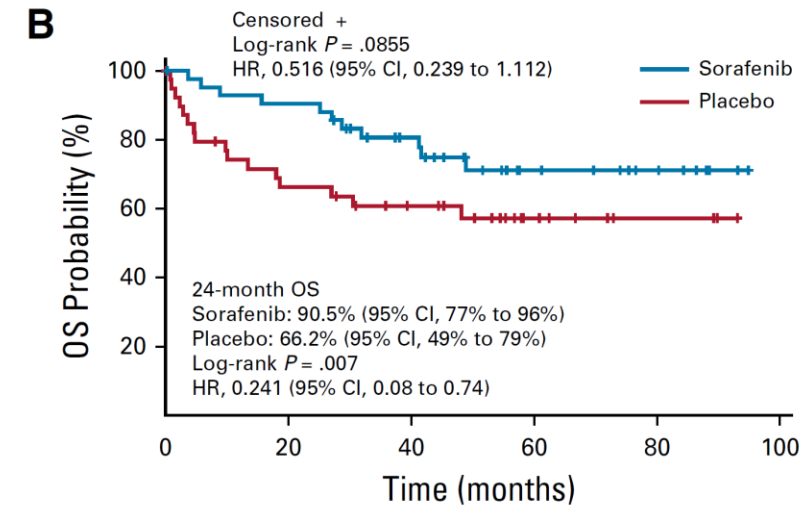
- Phase 2, randomisiert, Placebo-kontrolliert, doppelblinde Studie double-blind study, n=83
- FLT3-ITD AML in CHR nach allo HSZT (9/10 oder 10/10 MUD oder Geschwisterspender)
- HSZT als Konsolidierung oder upfront bei r/r AML
- Start Tag +60 bis +100; 800mg/d
- Sorafenib vs Placebo für 24 Monate
- Primary Endpoint: RFS
- Benefit v.a. in MRD- vor Transplant bzw. MRD+ nach Transplant

Burchert A et al., JCO 2020



No. at risk:

Placebo	40	24	19	17	14	0
Sorafenib	43	35	31	25	18	0

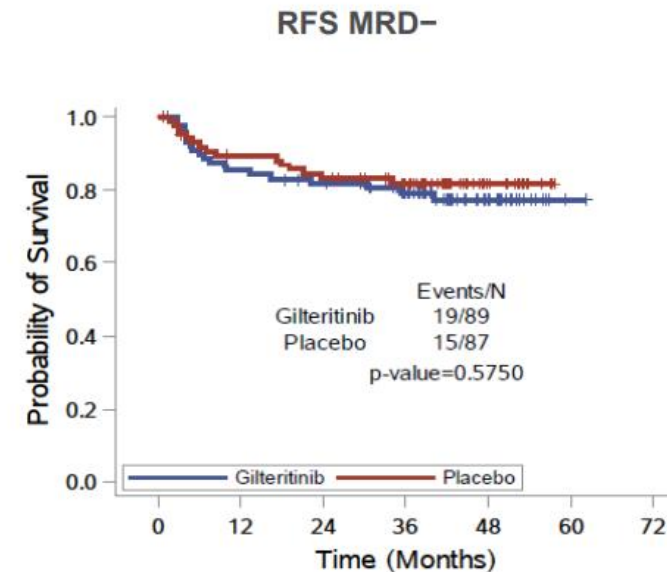
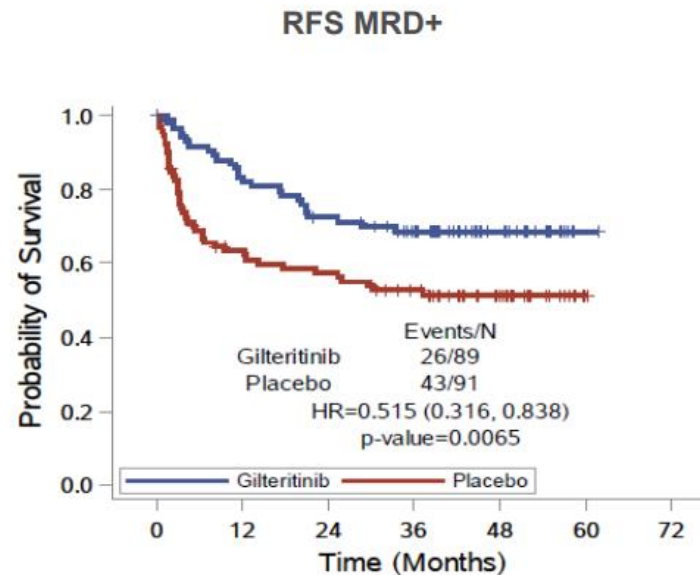


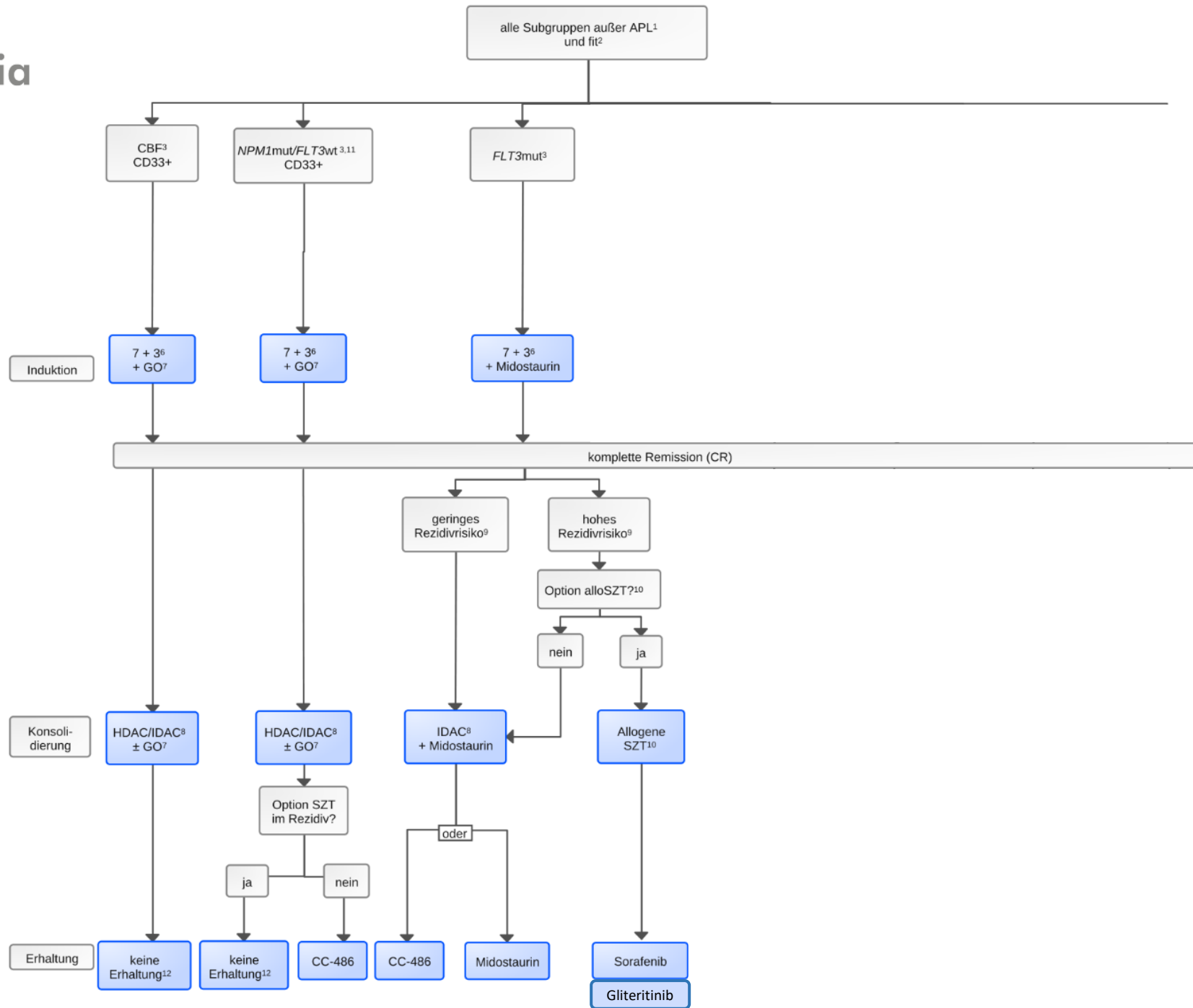
No. at risk:

Placebo	40	25	19	9	3	0
Sorafenib	43	38	28	12	7	0

## MORPHO: Gilteritinib Erhaltung nach allo HSZT

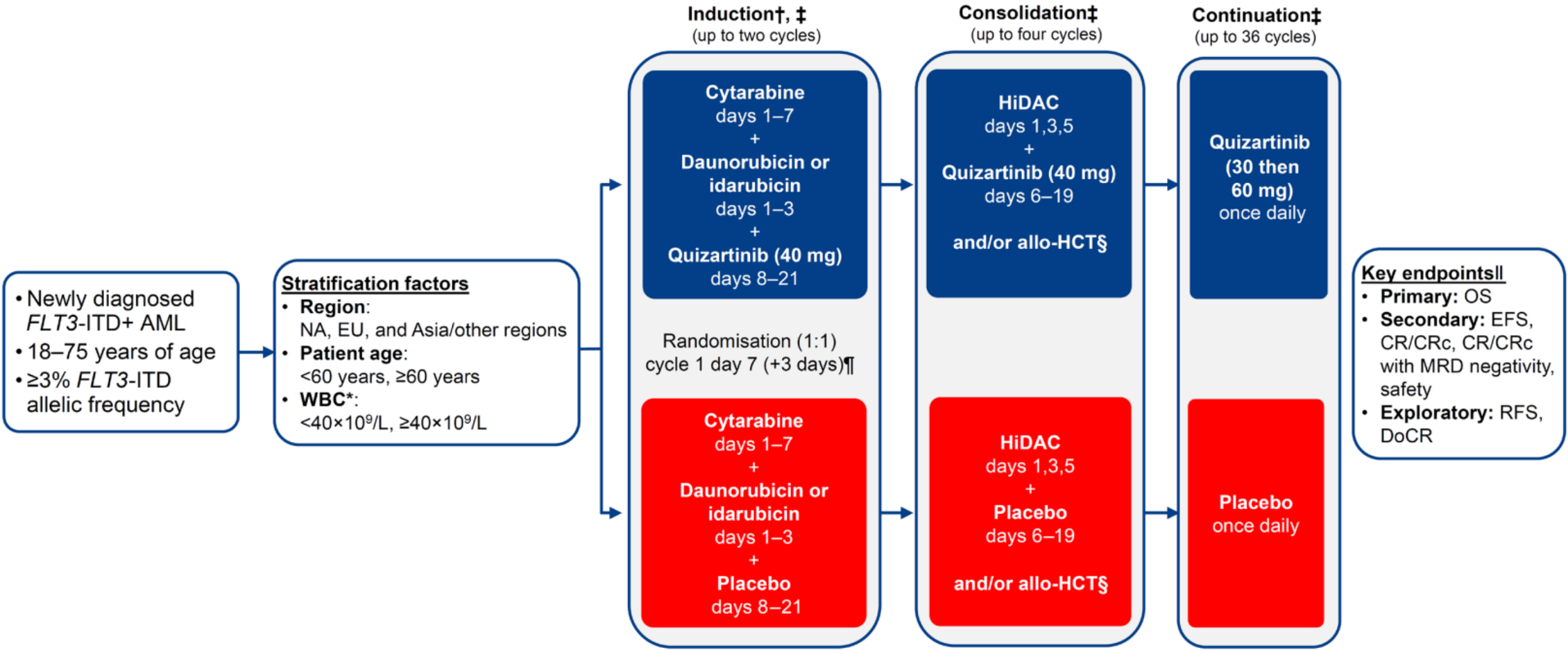
- Randomisiert, Placebo-kontrolliert, n=356
- FLT3-ITD+ AML nach allo HSZT in CR1
- Start Tag +30 bis +90, 120mg/d, 2 Jahre
- Primary endpoint: RFS HSZT

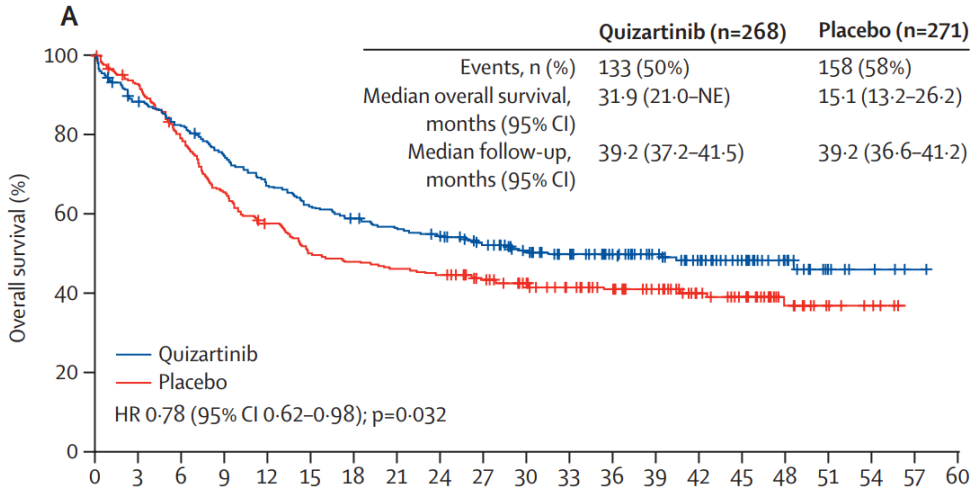






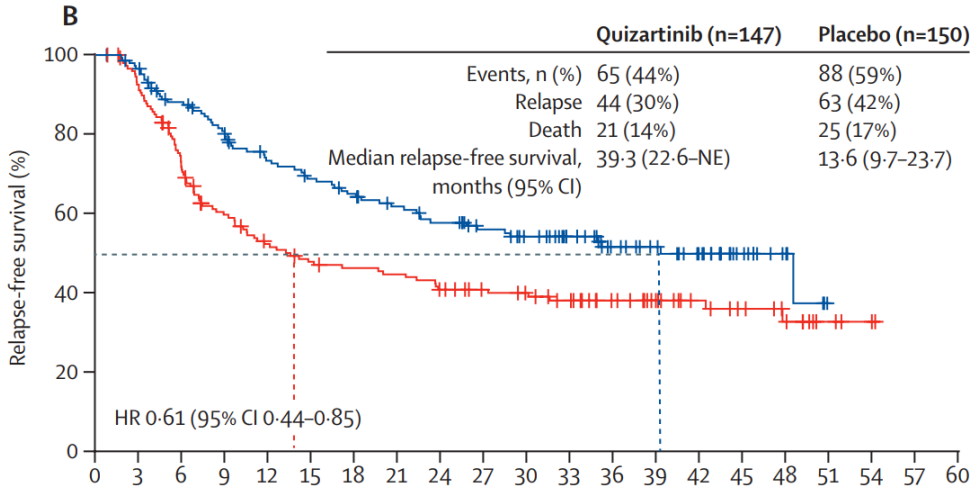
## QuANTUM-First trial: 7+3 mit Kons./alloSCT +/- Quizartinib inkl. Erhaltung





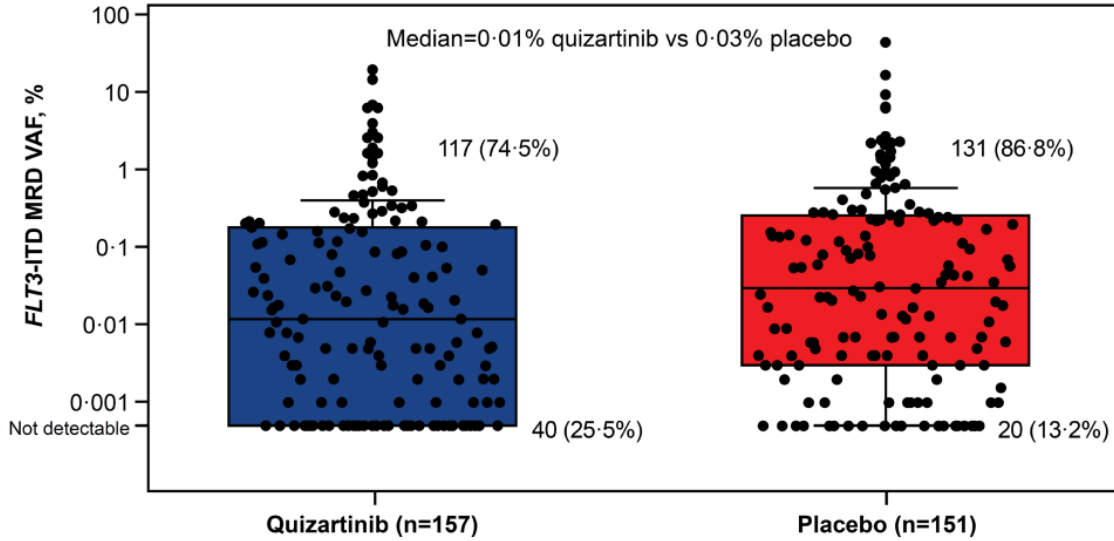
Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Quizartinib	268	233	216	195	176	162	153	145	139	126	110	96	83	68	53	36	24	8	4	1	0
Placebo	271	249	211	175	151	131	126	121	117	103	91	81	70	56	39	31	17	8	5	0	0



Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Quizartinib	147	140	123	111	97	90	84	77	71	63	57	48	36	31	24	13	6	0	0	0	0
Placebo	150	136	103	82	70	63	60	58	52	47	44	39	31	24	18	14	10	4	2	0	0

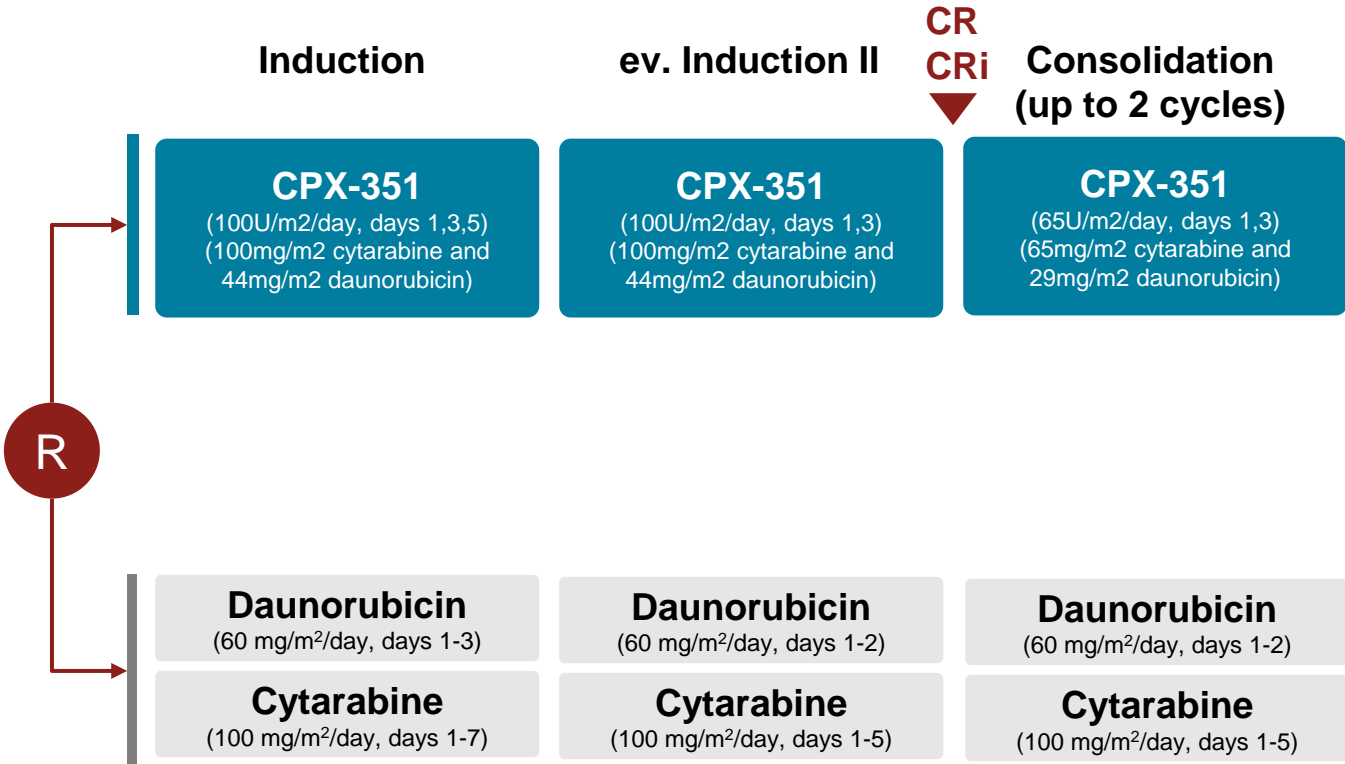


## CPX-351: Kombinationspräparat aus liposomalem Daunorubicin und Cytarabin (1:5)

- Phase 3, randomisiert, open-label
- allo HSZT erlaubt
- HMA Vortherapie erlaubt

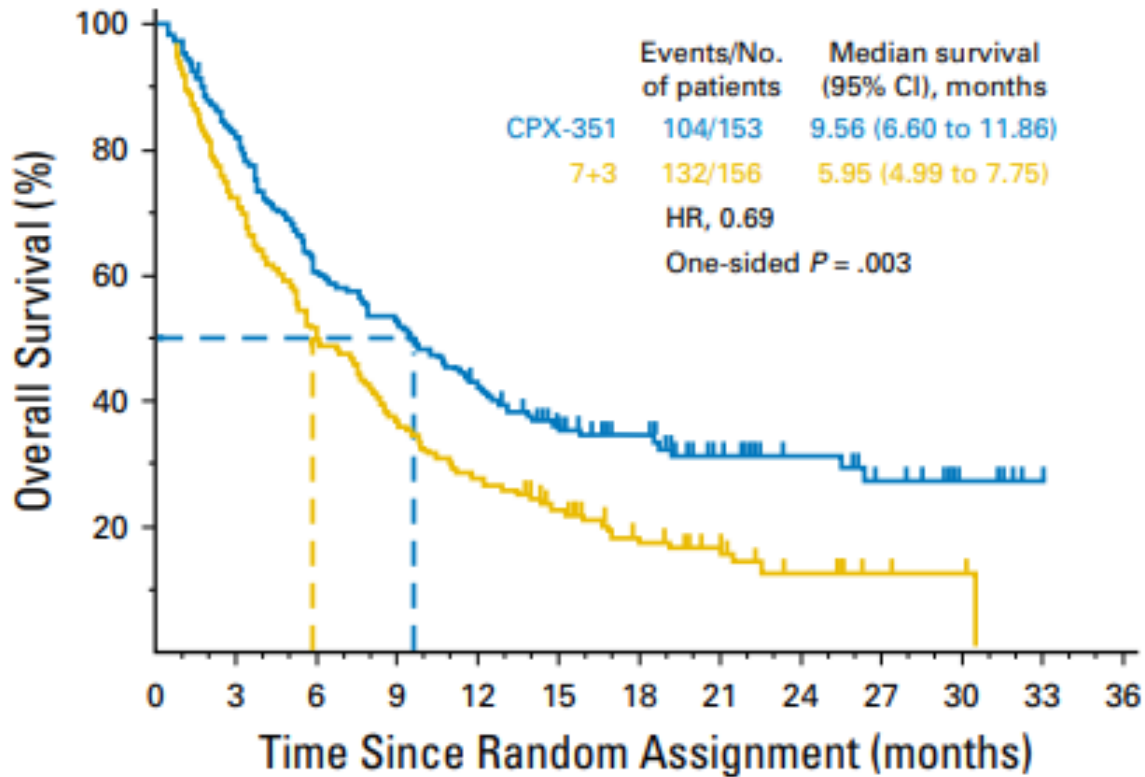
- $\geq 60$  to  $<75$  years
  - t-AML
- De novo AML with MDS-related CG
- sAML from MDS/CMML

(N = 309)



Primary endpoint: OS

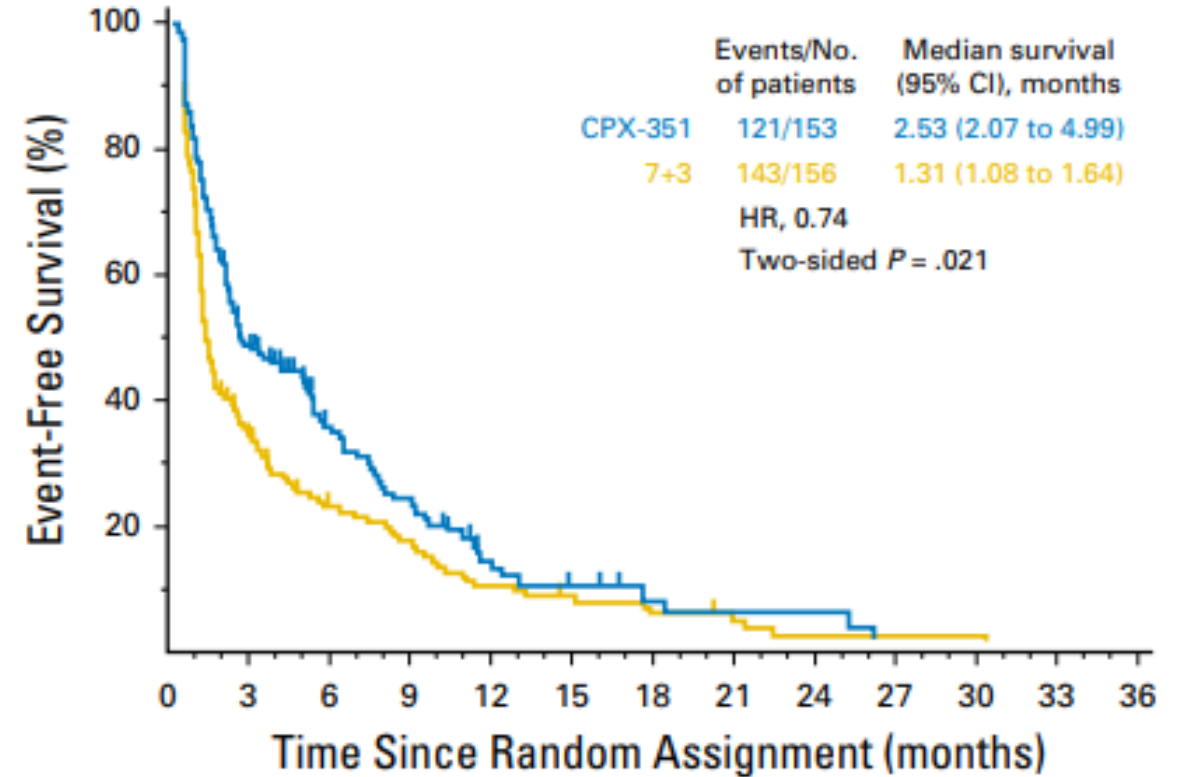
**A**



No. at risk

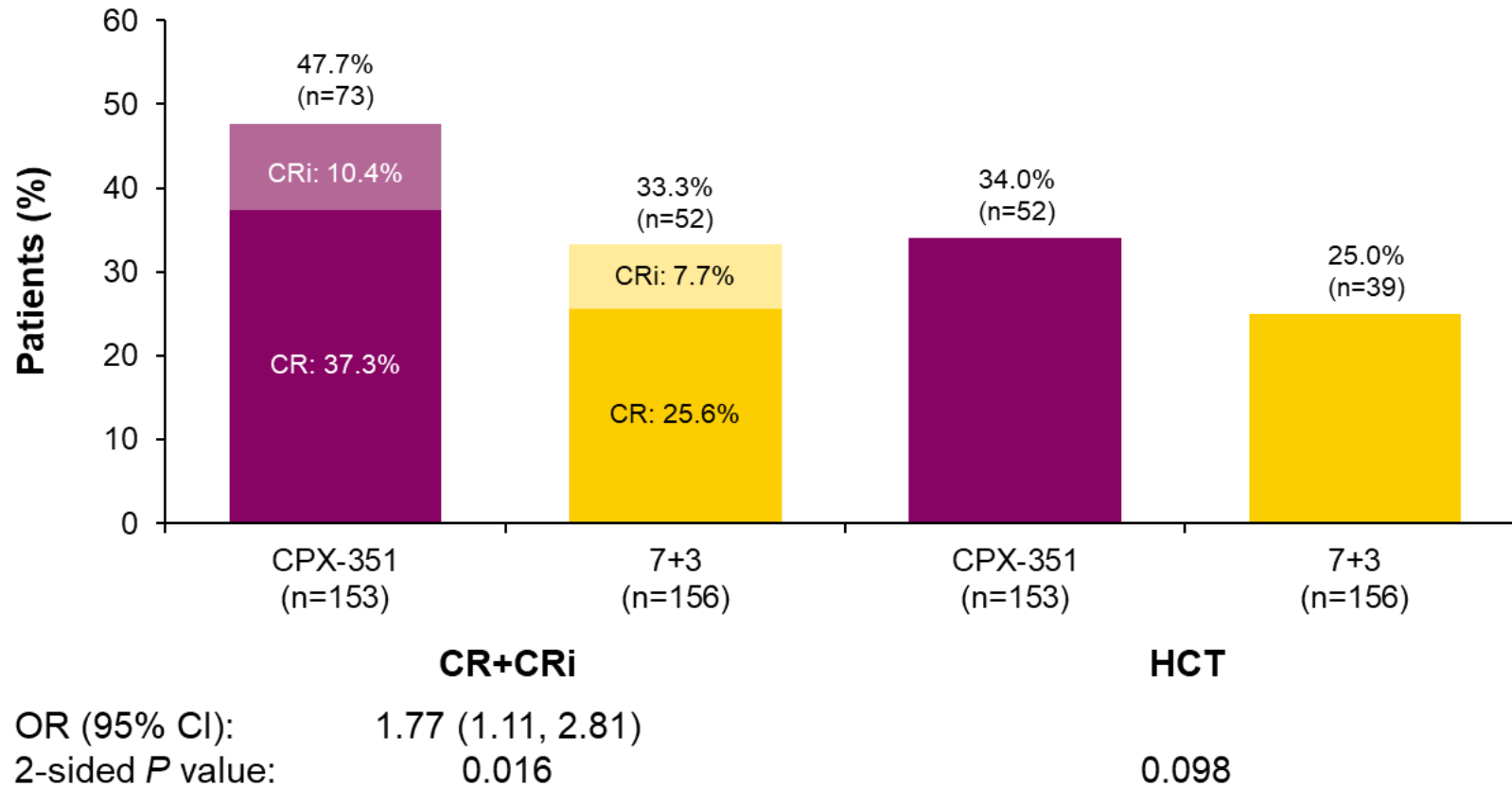
	0	3	6	9	12	15	18	21	24	27	30	33
CPX-351	153	122	92	79	62	46	34	21	16	11	5	1
7+3	156	110	77	56	43	31	20	12	7	3	2	0

**B**

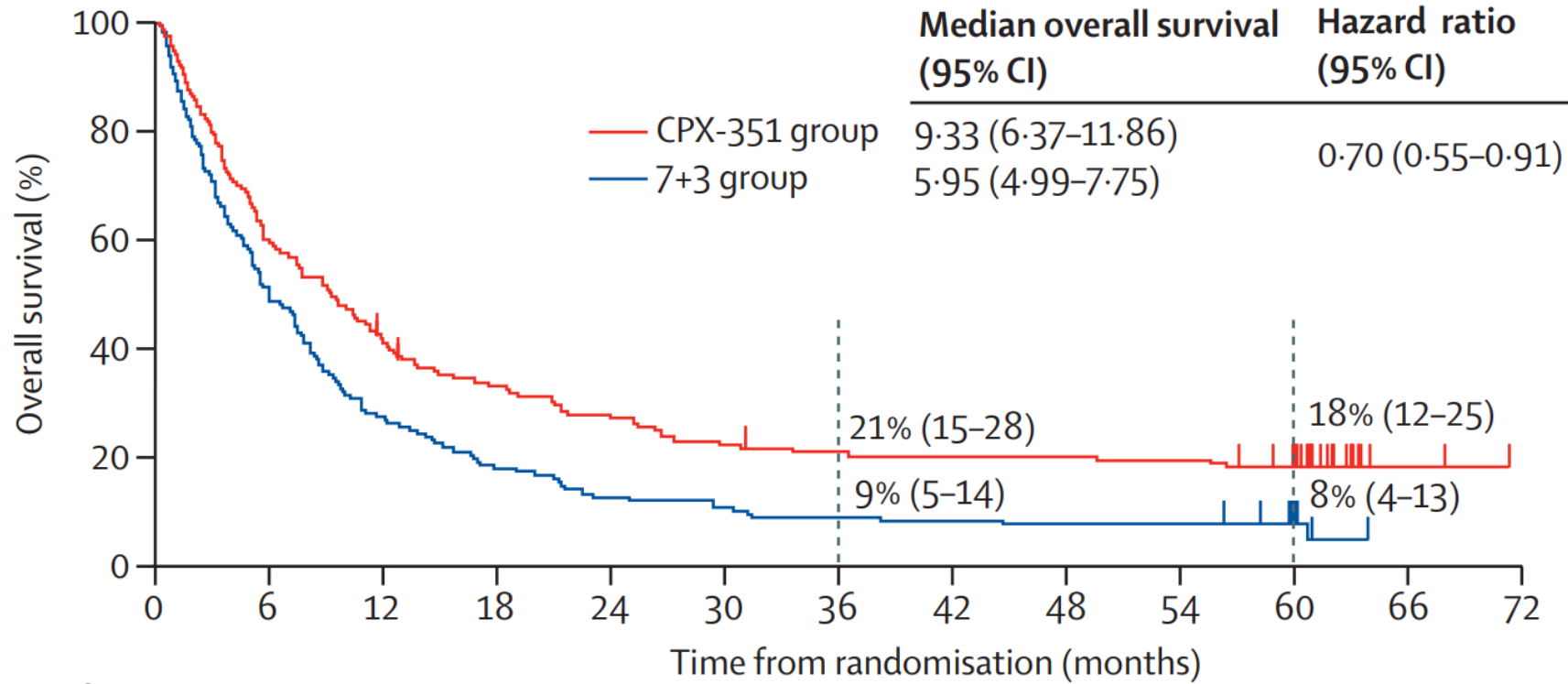


No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33
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



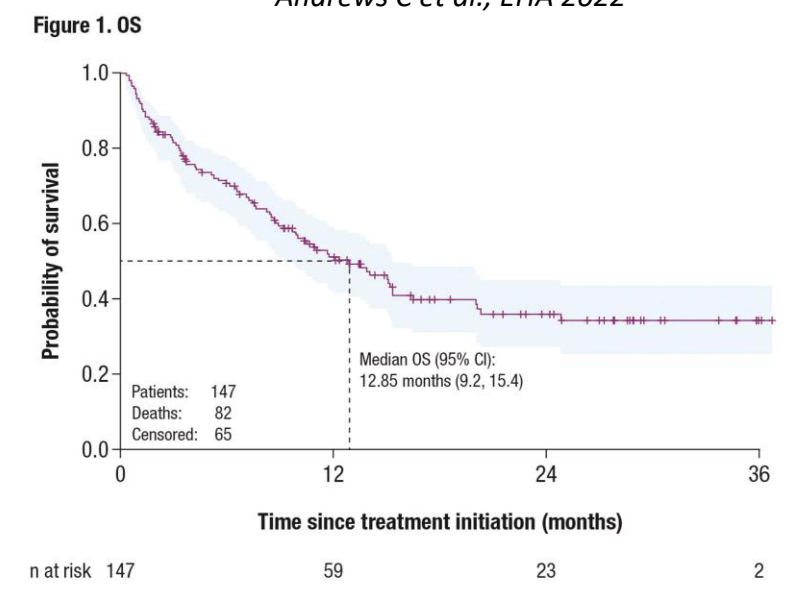
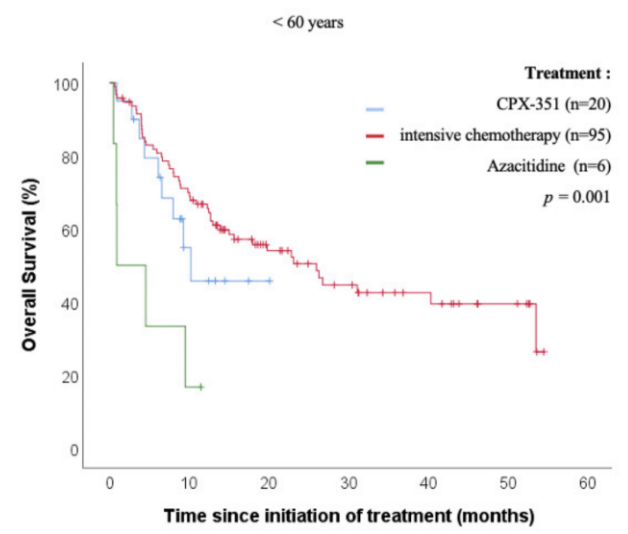
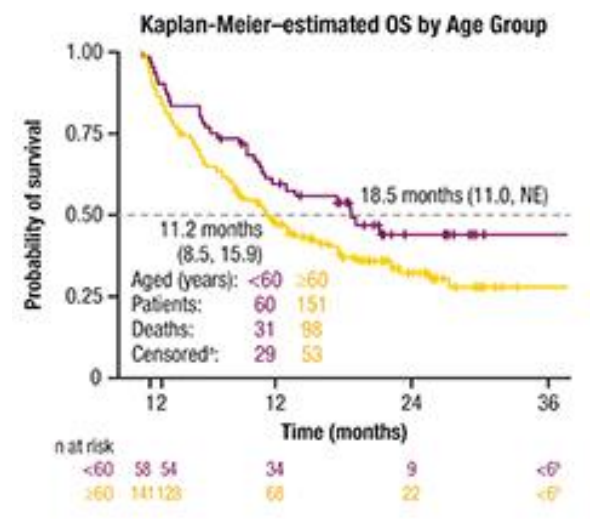
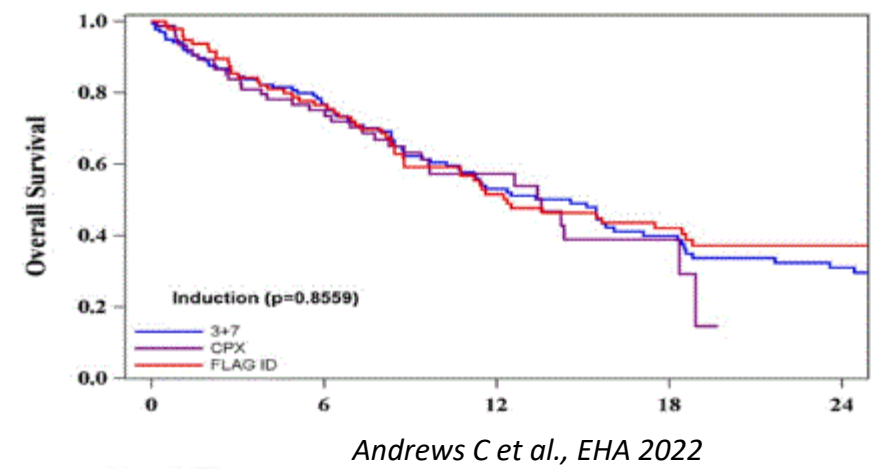
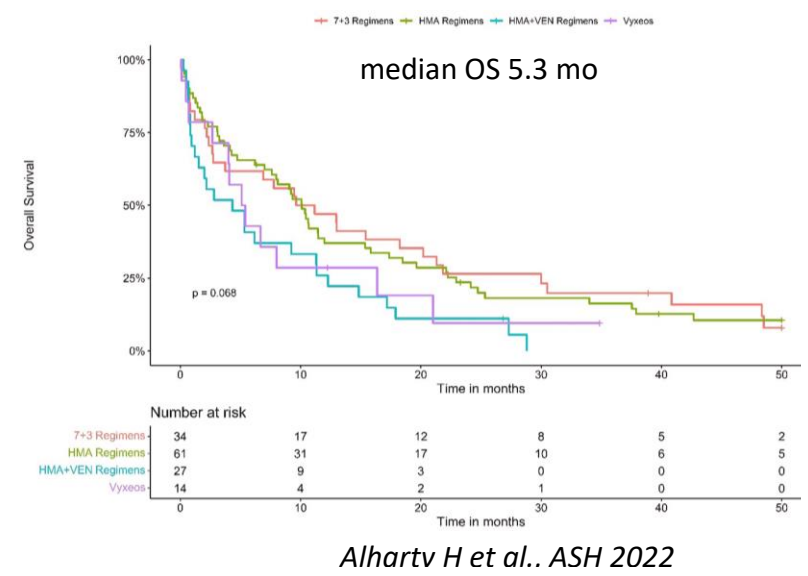
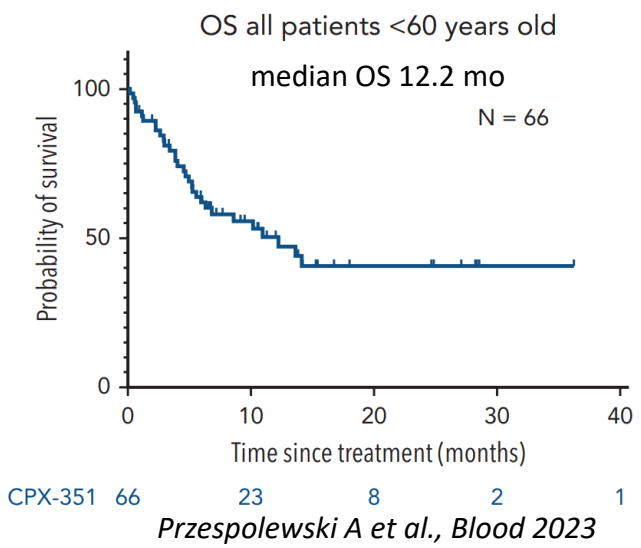
- CPX-351 was associated with a significantly higher overall remission rate (CR+CRi)



**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)

median OS Zulassungsstudie: 9.56 mo



**Zulassungsstudie**

- Pat. >60a
- t-AML
- AML mit MDS-related ZG
- sAML aus MDS/CMML

**Zulassung:**

- Erwachsene Patient\*innen
- t-AML
- AML-MRC

**2022:**

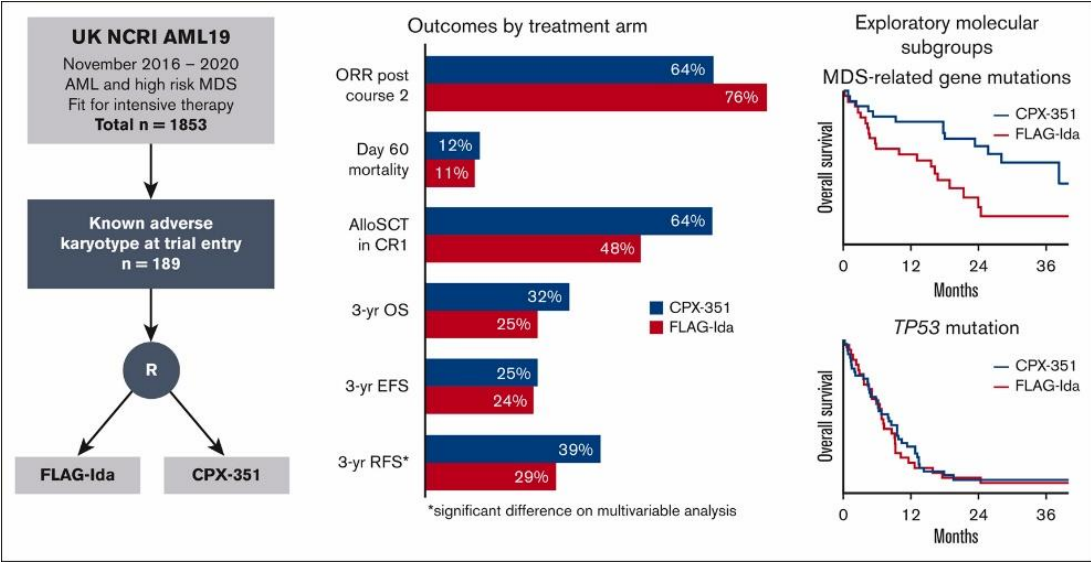
WHO und ICC Klassifikation inkludieren Mutations für die Diagnose der Myelodysplasie-assoziierten subgruppen

### Molecular analysis of licensing study

Outcome	ASXL1		DNMT3A		RUNX1		TET2		TP53	
	CPX-351 (n = 30)	7+3 (n = 20)	CPX-351 (n = 20)	7+3 (n = 21)	CPX-351 (n = 21)	7+3 (n = 22)	CPX-351 (n = 26)	7+3 (n = 17)	CPX-351 (n = 24)	7+3 (n = 35)
CR, n (%)	5 (17)	4 (20)	7 (35)	11 (52)	5 (24)	6 (27)	5 (19)	7 (41)	7 (29)	12 (34)
OR (95% CI)	0.80 (0.19-3.43)		0.49 (0.14-1.72)		0.83 (0.21-3.29)		0.34 (0.09-1.34)		0.79 (0.26-2.43)	
CR+CRi, n (%)	11 (37)	7 (35)	12 (60)	12 (57)	7 (33)	7 (32)	9 (35)	8 (47)	7 (29)	14 (40)
OR (95% CI)	1.08 (0.33-3.50)		1.13 (0.32-3.90)		1.07 (0.30-3.84)		0.60 (0.17-2.08)		0.62 (0.20-1.87)	
Median remission duration, <sup>b</sup> mo	6.37	4.11	9.89	4.32	8.05	3.45	6.37	3.45	8.05	3.45
HR (95% CI)	0.69 (0.18-2.58)		0.33 (0.10-1.06)		0.56 (0.17-1.87)		0.43 (0.13-1.38)		0.63 (0.24-1.65)	
Transplant, n (%)	8 (27)	6 (30)	11 (55)	8 (38)	6 (29)	4 (18)	6 (23)	3 (18)	3 (13)	11 (31)
OR (95% CI)	0.85 (0.24-2.97)		1.99 (0.57-6.90)		1.80 (0.43-7.59)		1.40 (0.30-6.56)		0.31 (0.08-1.27)	
Median OS, <sup>b</sup> mo	9.10	6.29	12.62	5.49	8.87	4.09	9.10	3.68	4.53	5.13
HR (95% CI)	0.67 (0.35-1.27)		0.41 (0.19-0.89)		0.58 (0.30-1.11)		0.47 (0.23-0.93)		1.19 (0.70-2.05)	
Median EFS, <sup>b</sup> mo	1.58	1.41	5.98	3.58	2.00	1.22	1.59	1.64	0.97	1.64
HR (95% CI)	0.79 (0.42-1.48)		0.45 (0.21-0.95)		0.57 (0.30-1.08)		0.93 (0.49-1.77)		1.13 (0.66-1.93)	

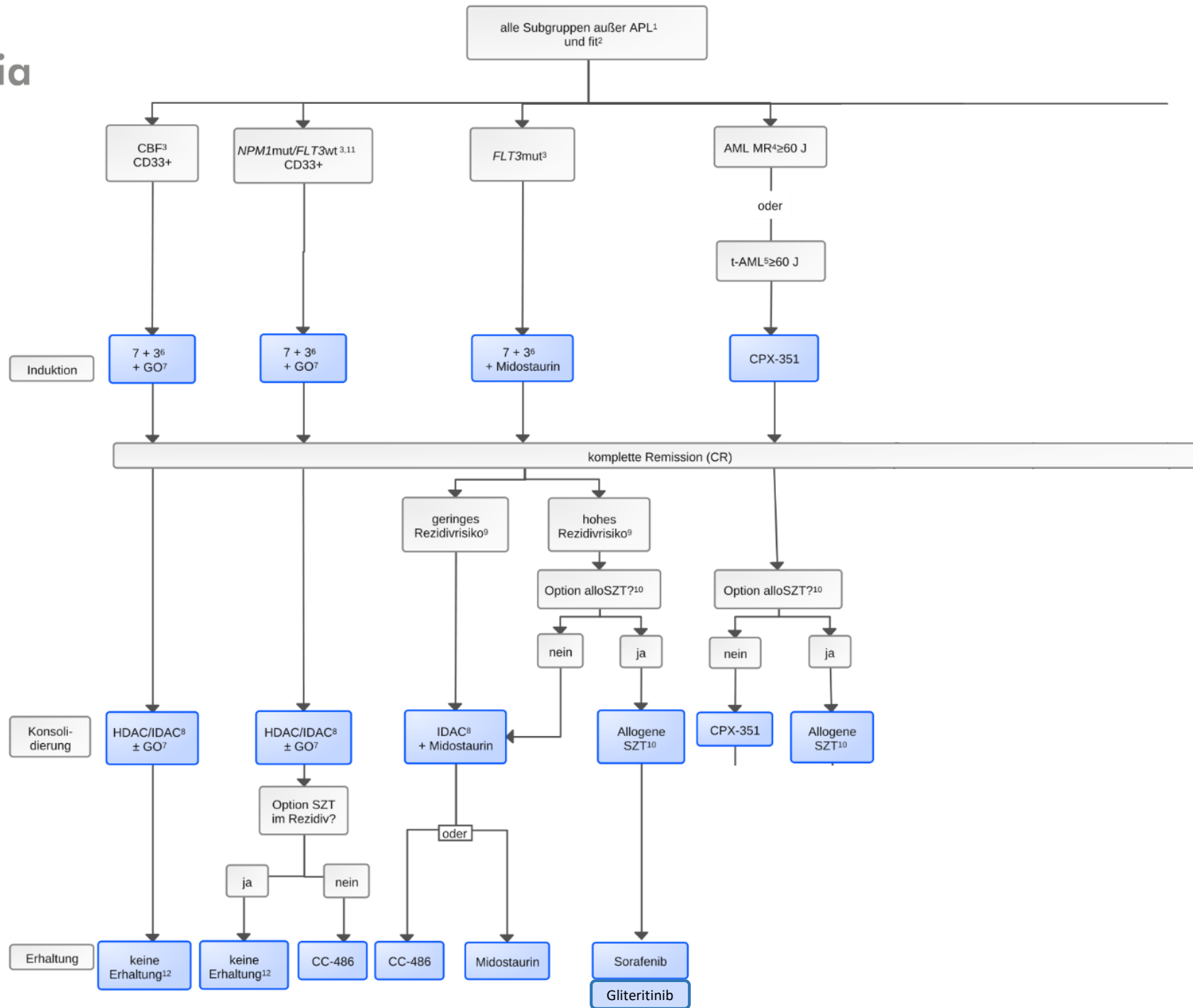
Lindsley RC et al., Blood (2019) 134 (Supplement\_1): 15.

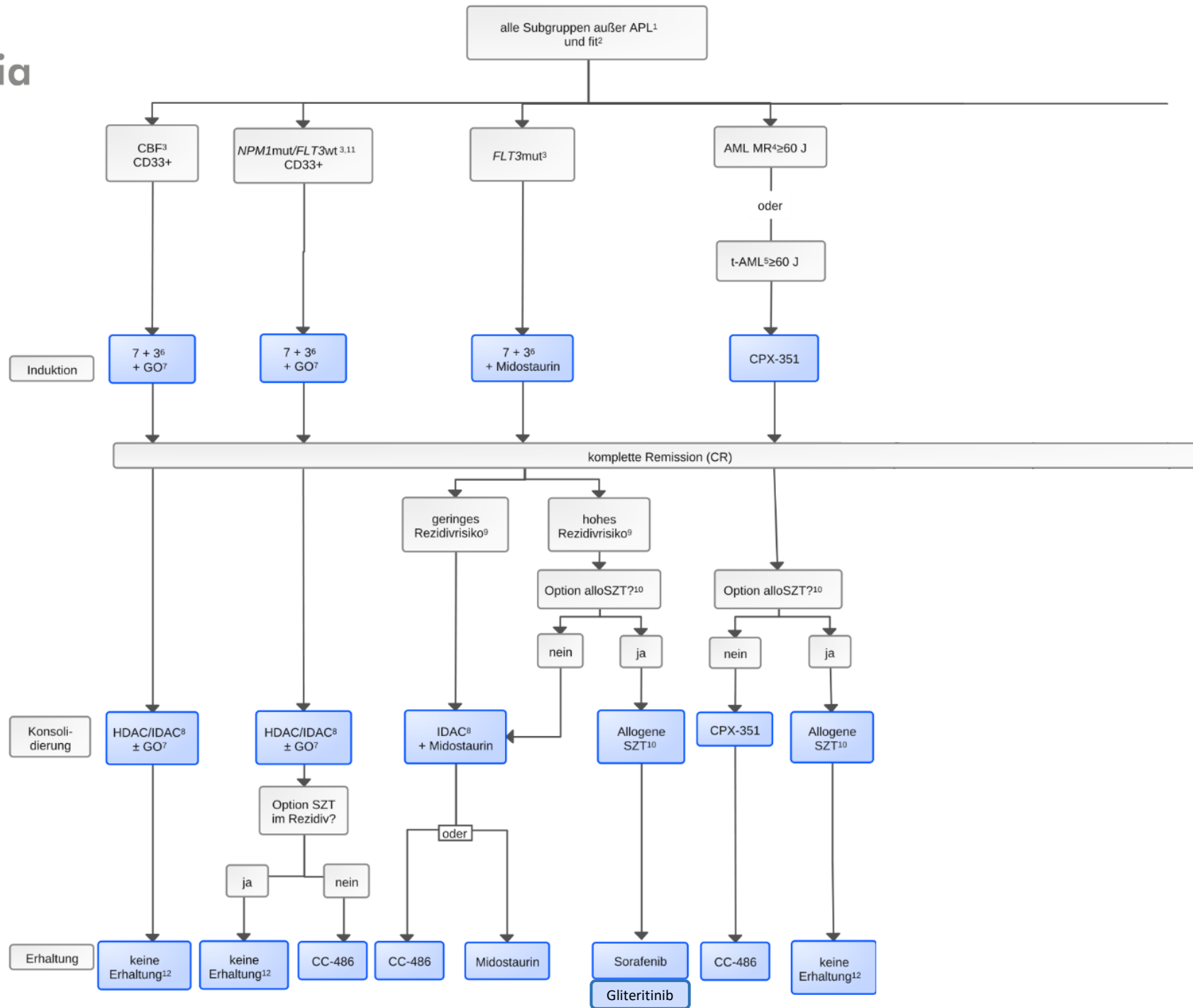
### UK NCRI AML19 FLAG-Ida vs CPX-351

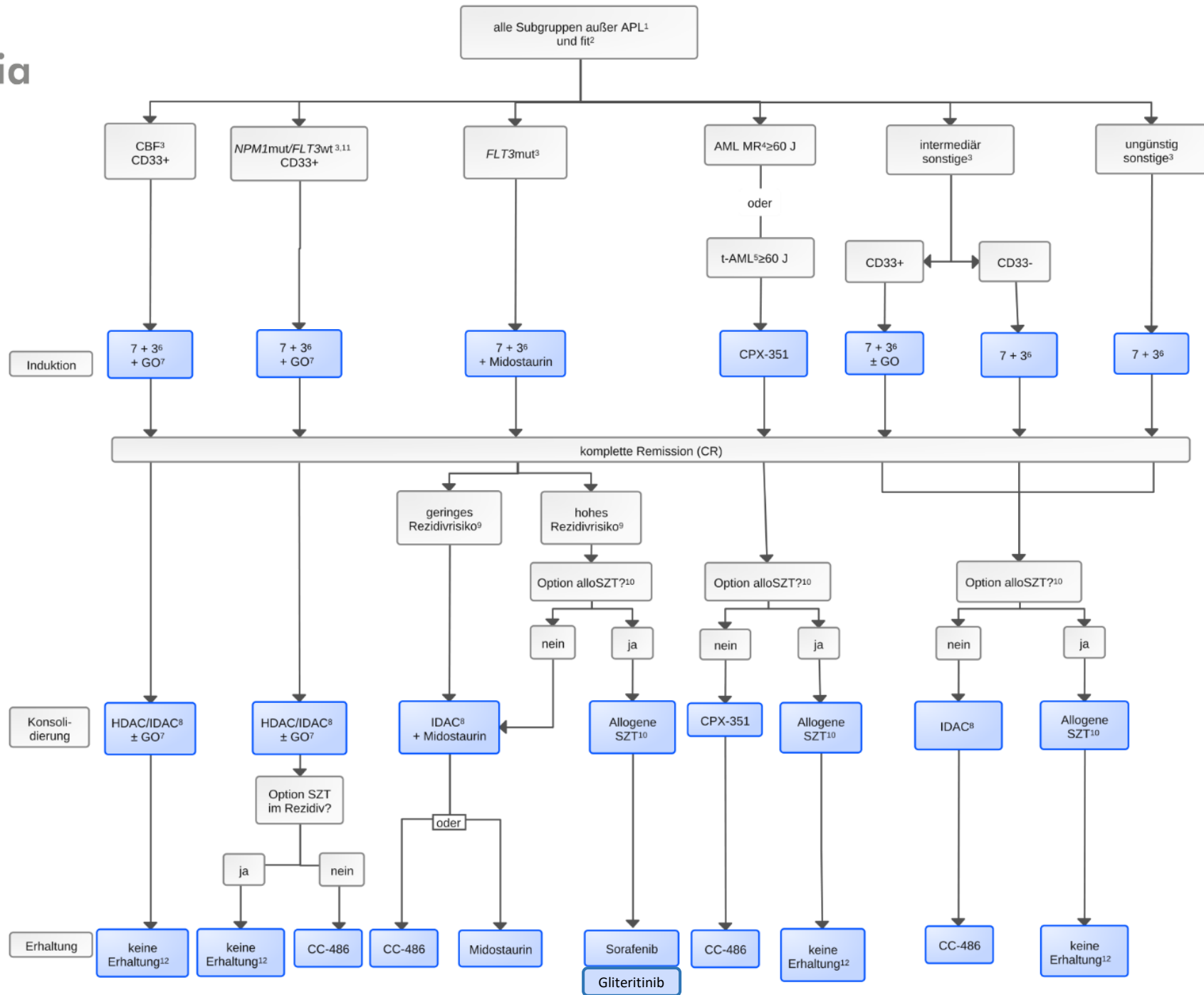


Othman J et al., Blood Adv (2023) 7 (16): 4539–4549.





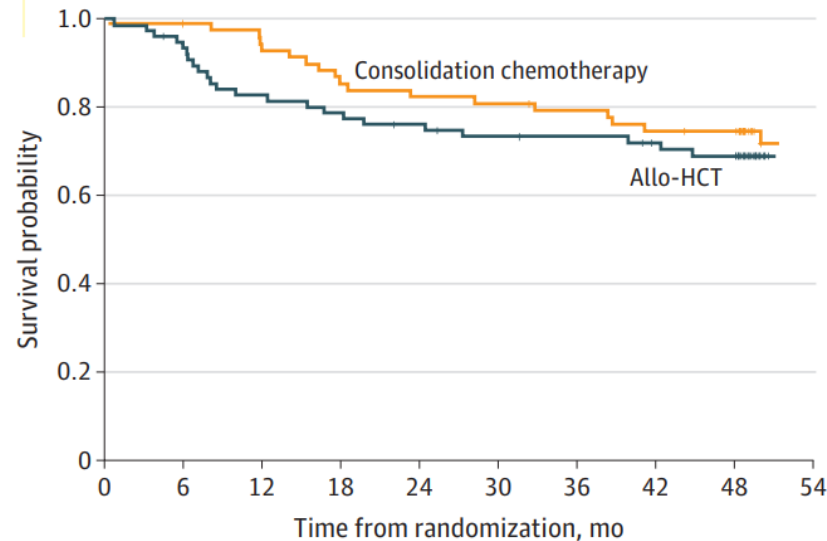




## ETAL-1: alloHSCT vs Consolidation Chemotherapy in Int-risk CG AML in CR1

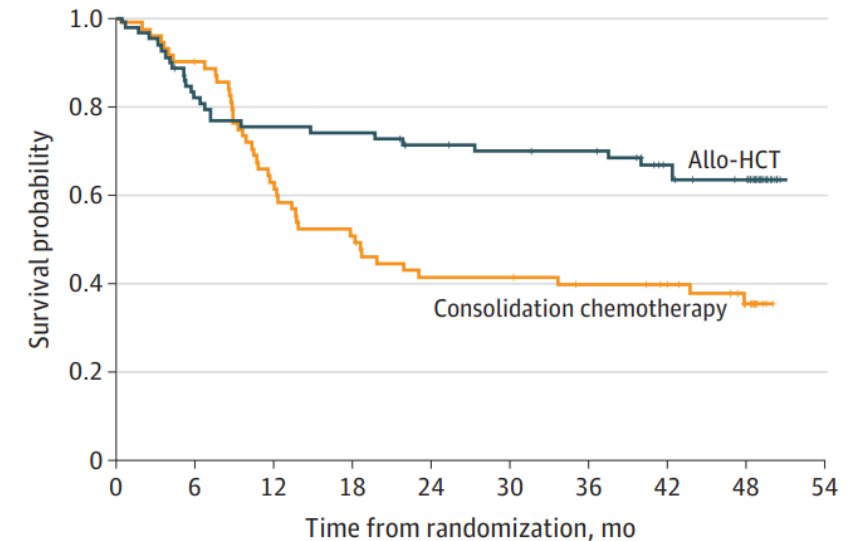
- N=143
- (n=76 alloHSCT, n=67 Chemo)
- MRC-CG int AML
- 18-60y
- alloHSCT nach Relaps in Chemo Gruppe möglich

**A** Overall survival



No. at risk	0	6	12	18	24	30	36	42	48	54
Consolidation chemotherapy	67	66	62	57	55	54	52	49	48	
Allo-HCT	76	70	62	59	56	53	52	49	47	

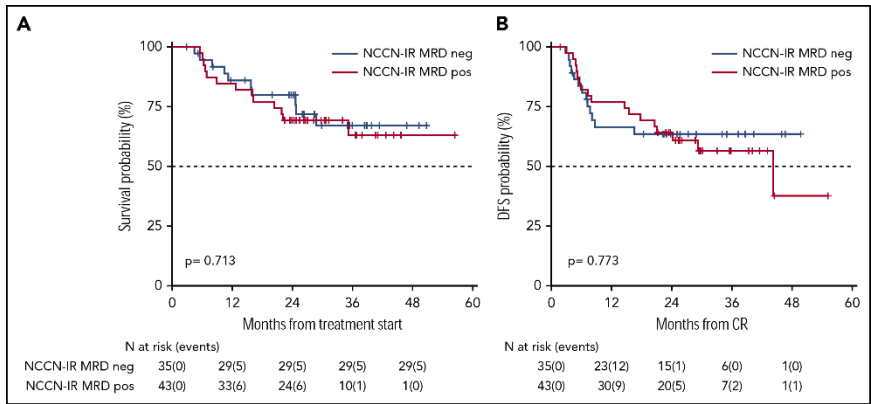
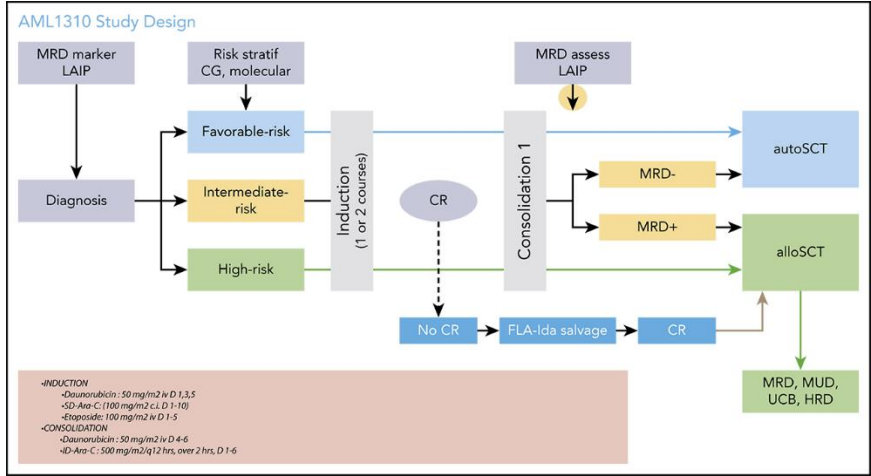
**B** Disease-free survival



No. at risk	0	6	12	18	24	30	36	42	48	54
Consolidation chemotherapy	67	59	41	33	26	26	23	20	12	
Allo-HCT	76	61	56	55	50	48	47	39	34	

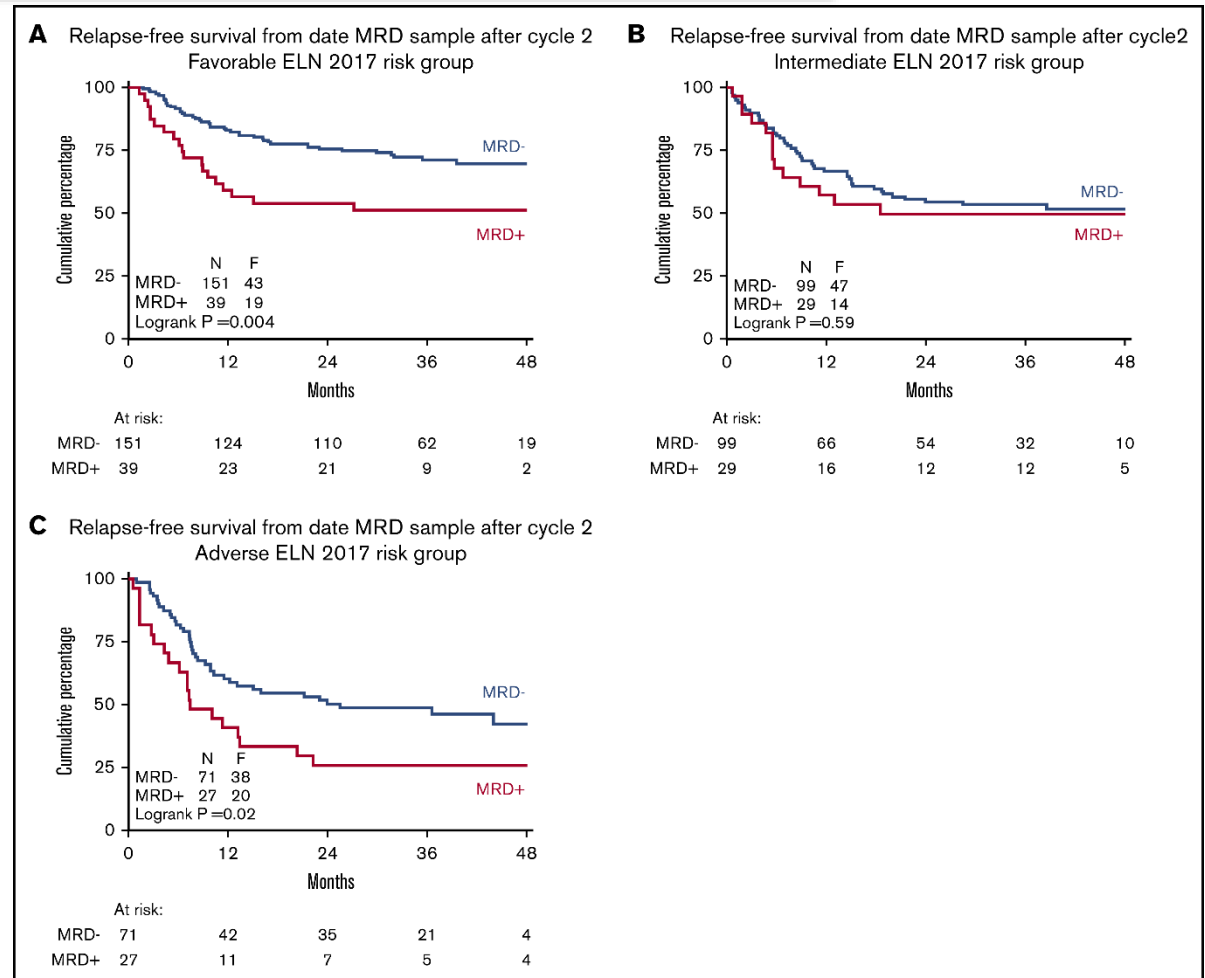
## GIMEMA AML1310: risk-adapted, MRD-directed therapy

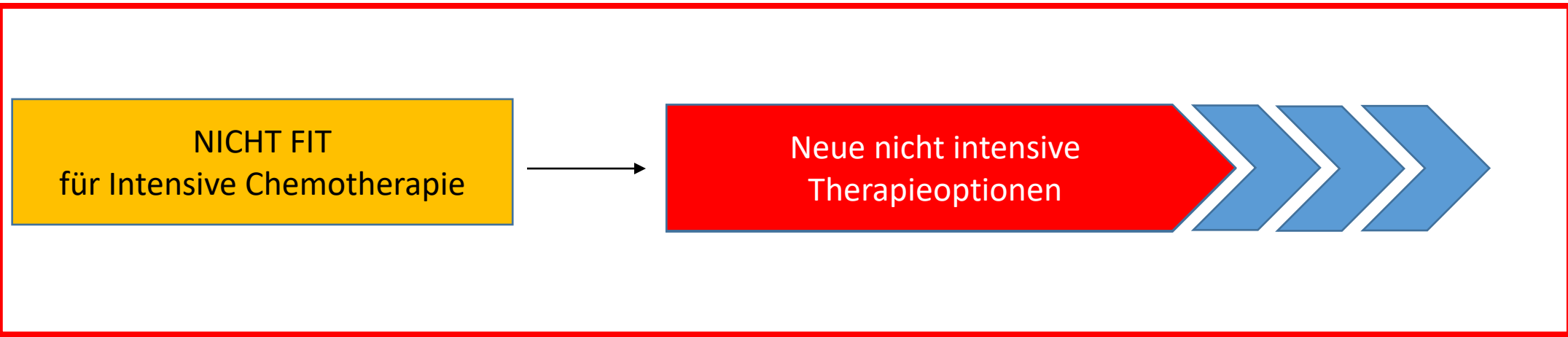
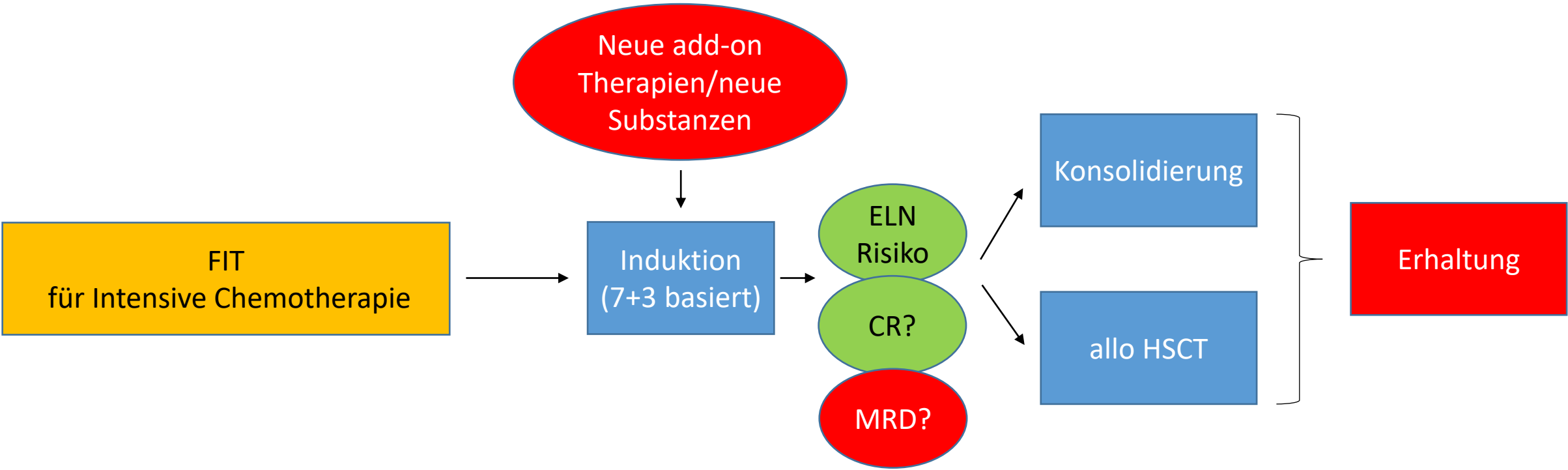
- N=515
- 127 (25%) waren NCCN-IR,
- 35 NCCN-IR-Neg
- 43 NCCN-IR-Pos

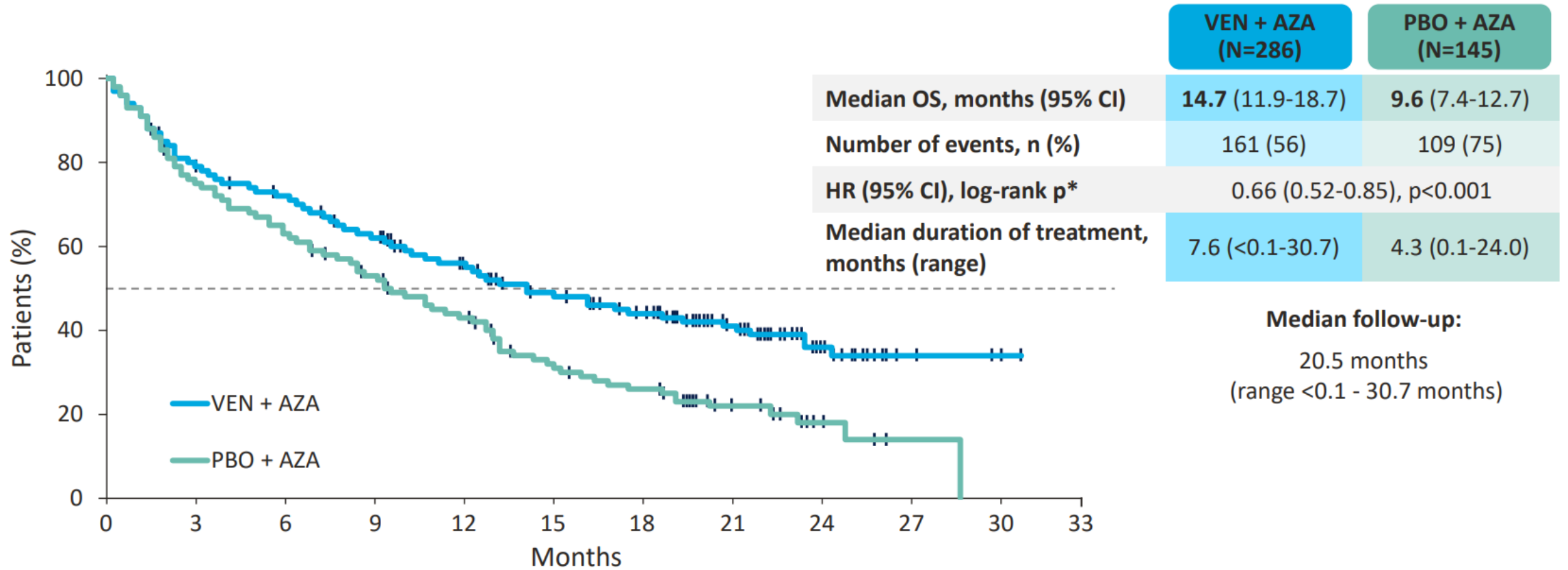


## HOVON-SAKK-132 trial: Addition of lenalidomide to intensive treatment

- N=780
- MRD Assessment nach 2 Zyklen mit flow und molekularen Methoden
- Intermediate-risk Gruppe mit negativer MRD: 31% auto-SCT; 55% allo-SCT
- Intermediate-risk Gruppe mit positiver MRD: 8% auto-SCT; 88% allo-SCT







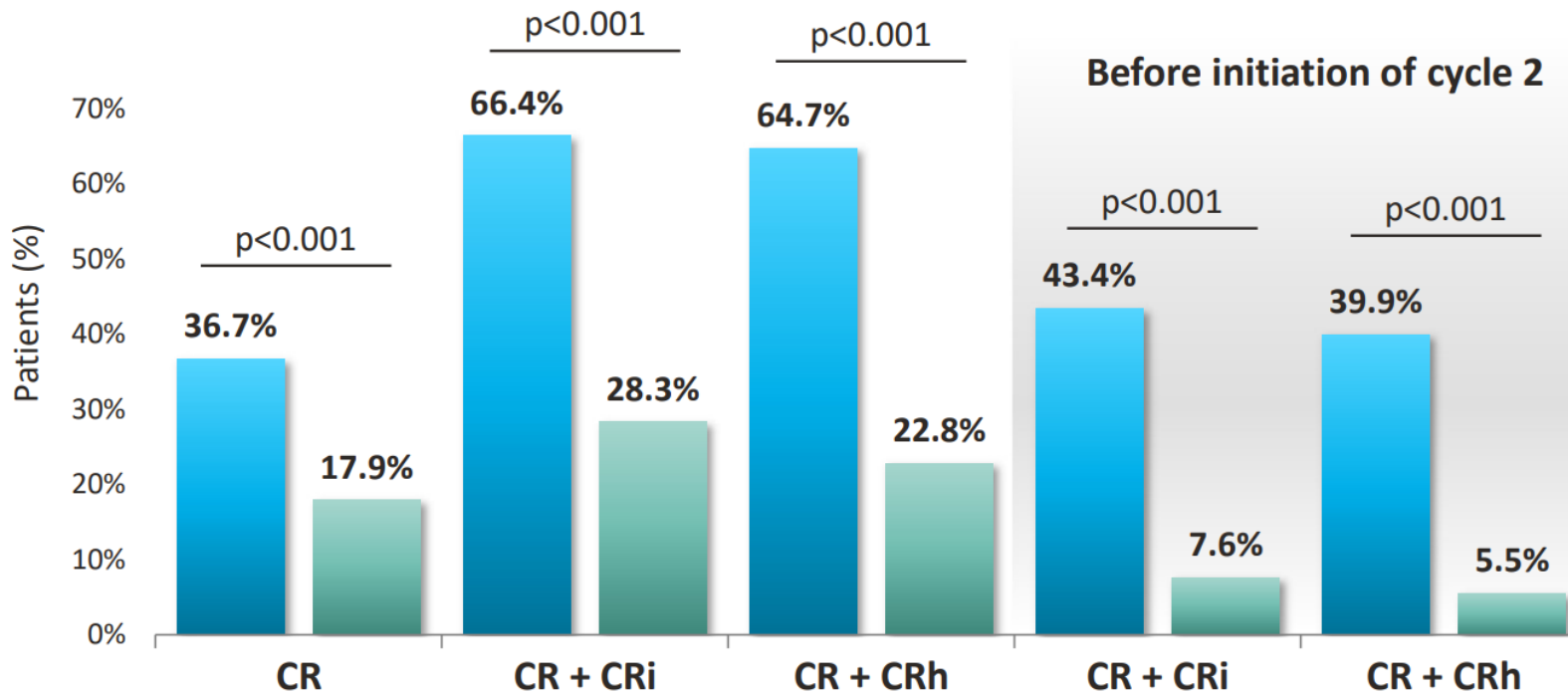
VEN + AZA	286	219	198	168	143	117	101	54	23	5	3	0
PBO + AZA	145	109	92	74	59	38	30	14	5	1	0	0



## Response Rates

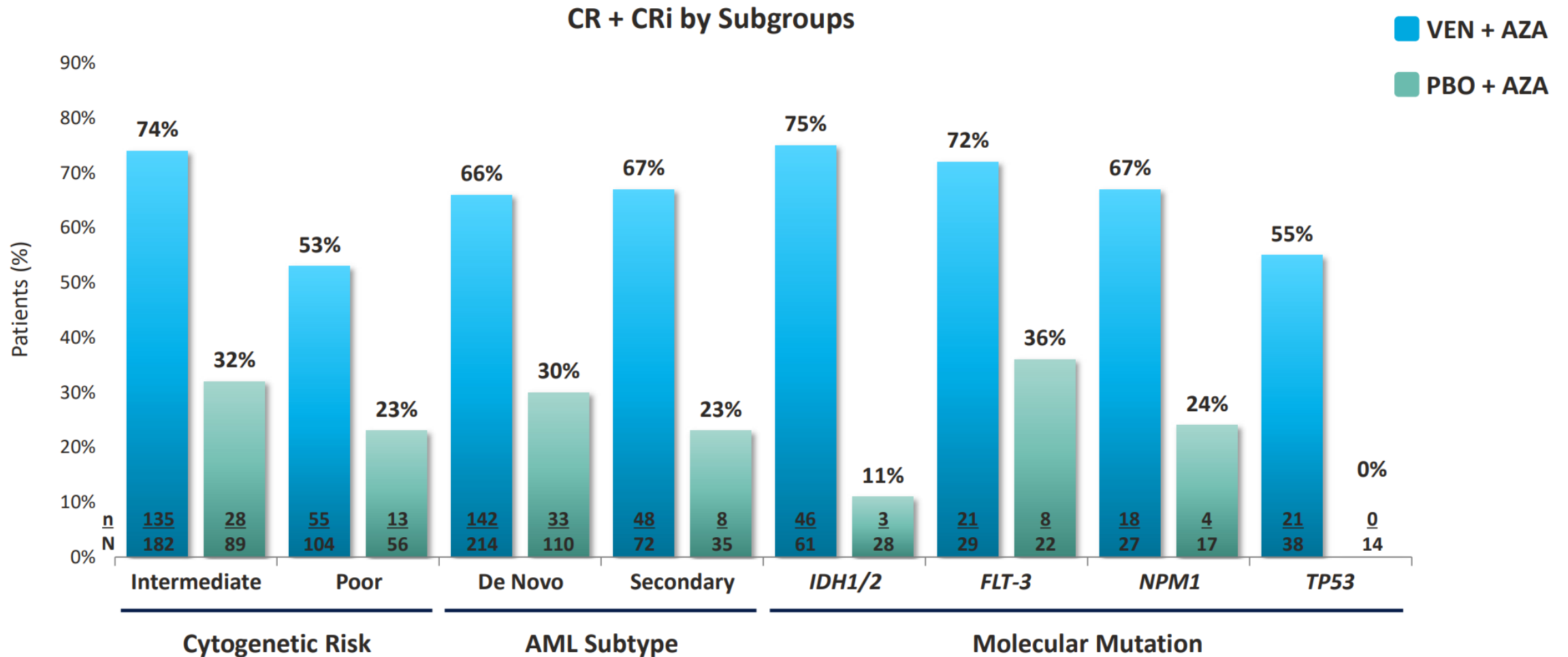
### Response Rates

■ VEN + AZA    ■ PBO + AZA



Median months (range)	VEN + AZA (N=286)	PBO + AZA (N=145)
Time to first response (CR or CRi)	<b>1.3</b> (0.6-9.9)	<b>2.8</b> (0.8-13.2)
Time to first response (CR or CRh)	<b>1.0</b> (0.6-14.3)	<b>2.6</b> (0.8-13.2)
Number of treatment cycles	<b>7.0</b> (1.0-30.0)	<b>4.5</b> (1.0-26.0)

## Response Rates (CR+CRi) by Subgroups



**Erste Priorität**

**unfit**

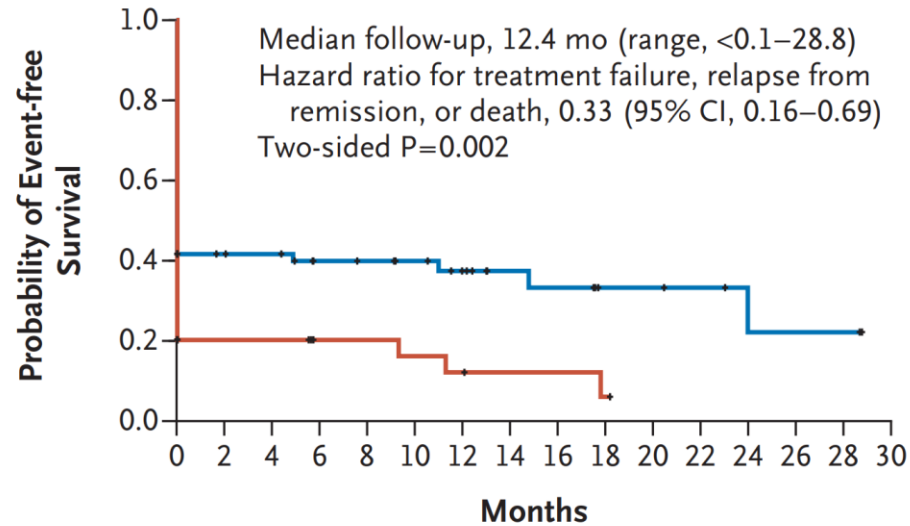


**Azacitidin<sup>1</sup>  
+ Venetoclax**



- Data for VEN/DEC less robust
- No licensing for VEN/LDAC in Europe

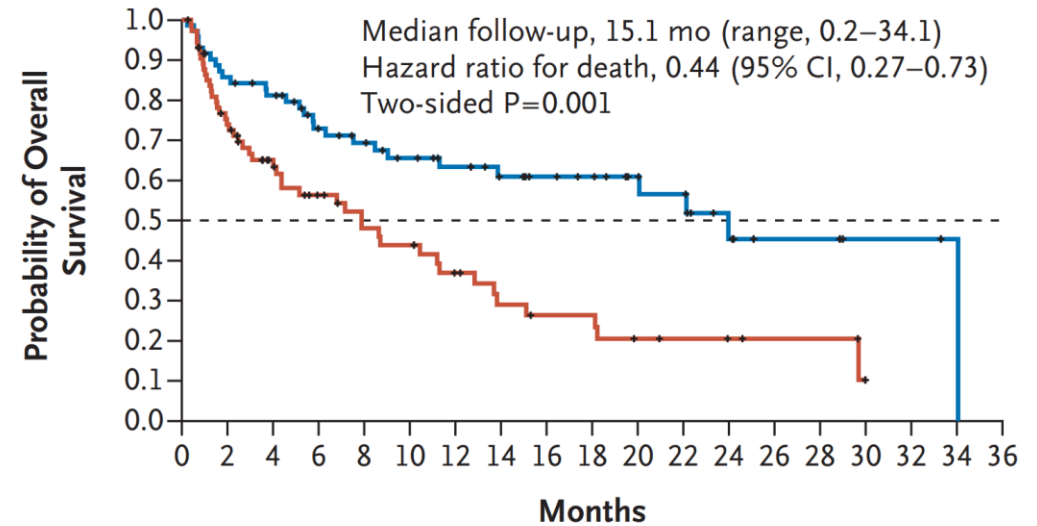
## A Event-free Survival



### No. at Risk

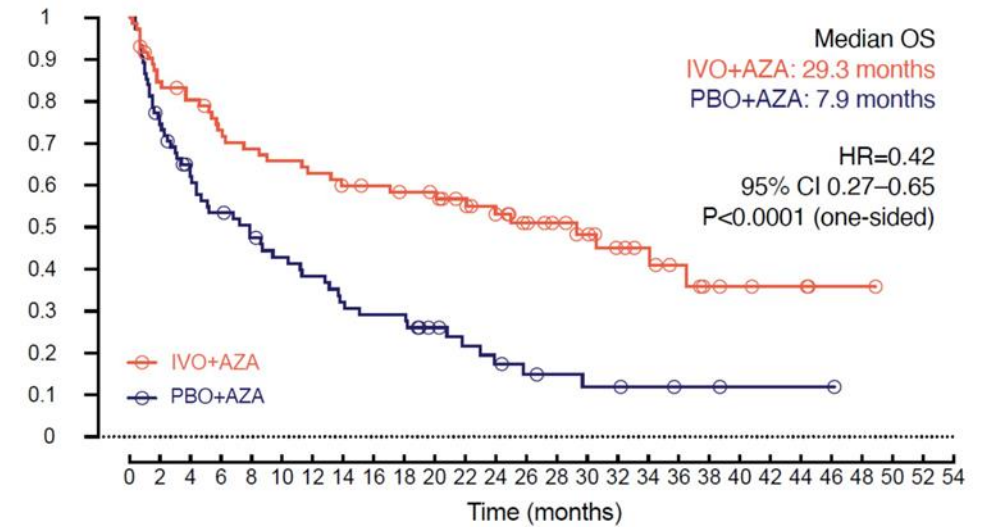
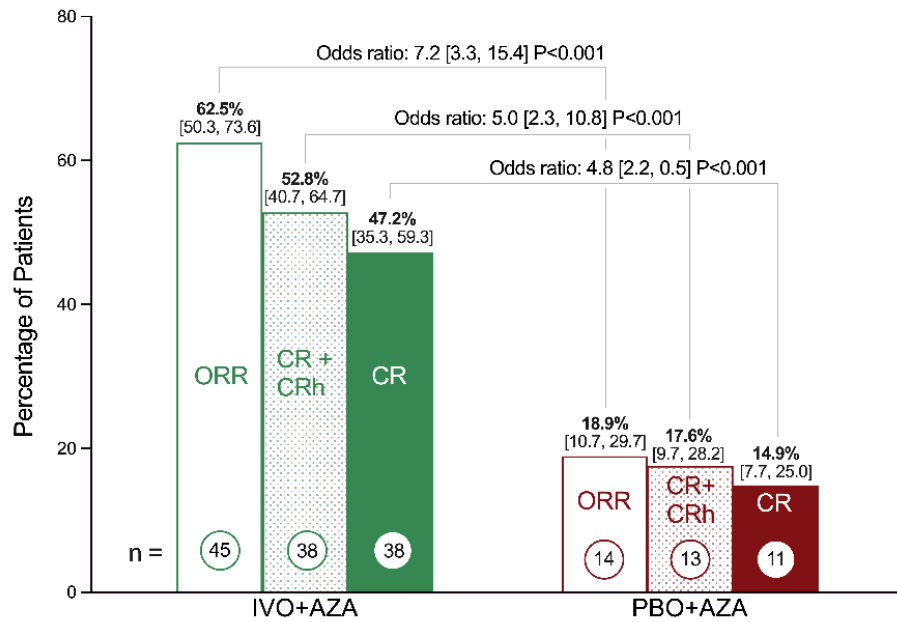
Ivosidenib+ azacitidine	72	26	25	20	19	17	13	9	8	5	5	4	2	2	2	0
Placebo+ azacitidine	74	8	8	5	5	4	3	2	2	1	0					

## B Overall Survival



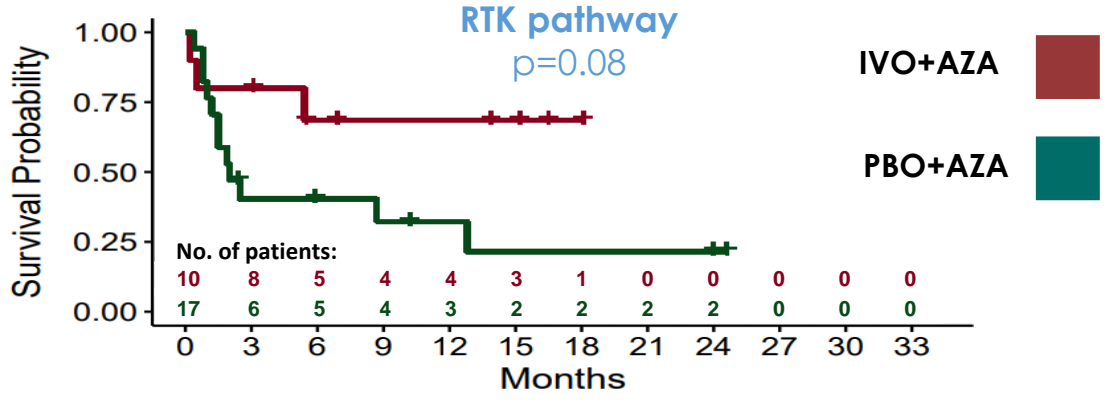
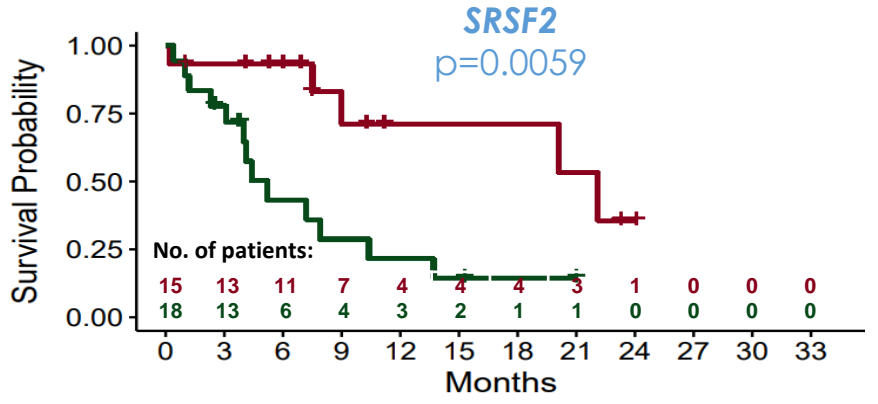
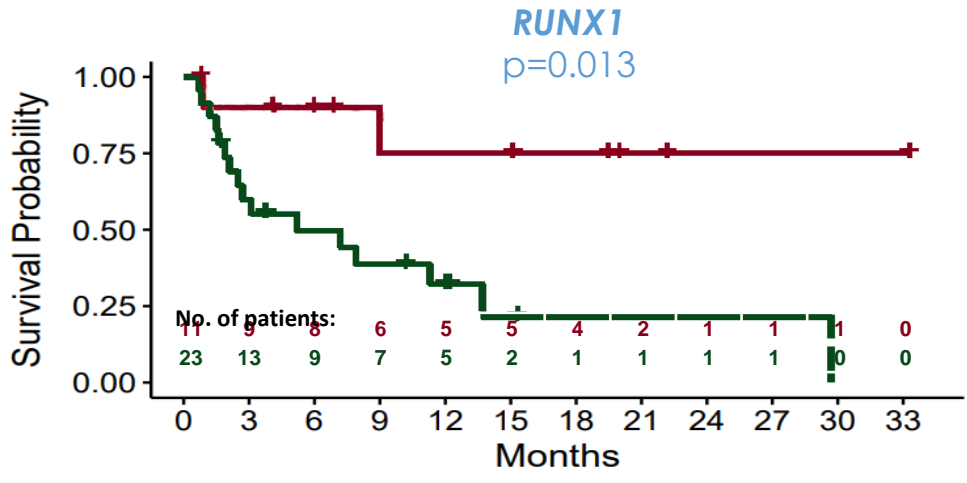
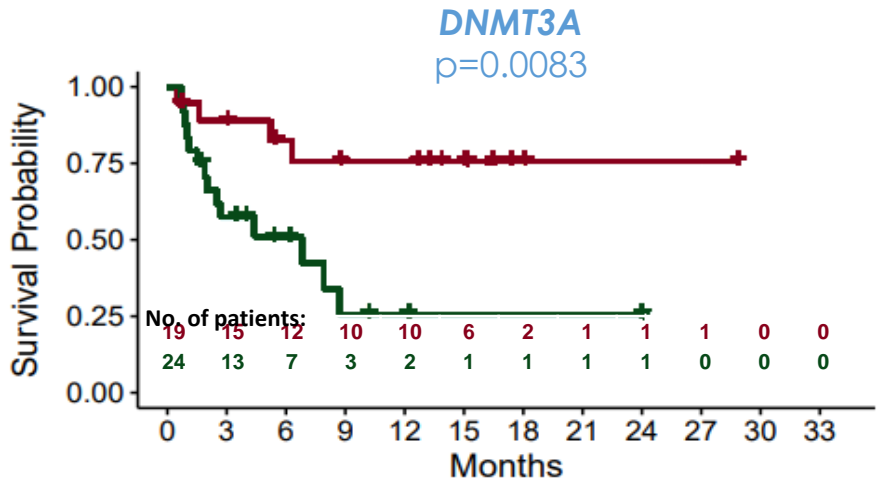
### No. at Risk

Ivosidenib+ azacitidine	72	58	53	42	38	33	29	24	21	19	15	13	7	4	4	2	2	1
Placebo+ azacitidine	74	53	38	29	23	21	15	11	9	9	6	5	4	3	3	0		



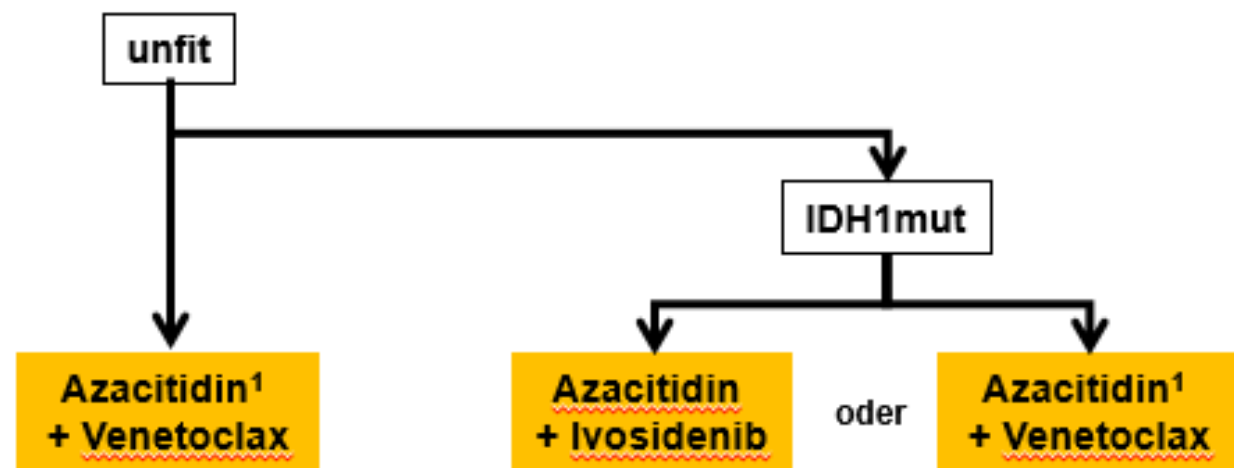
Montesinos P et al., N Engl J Med 2022

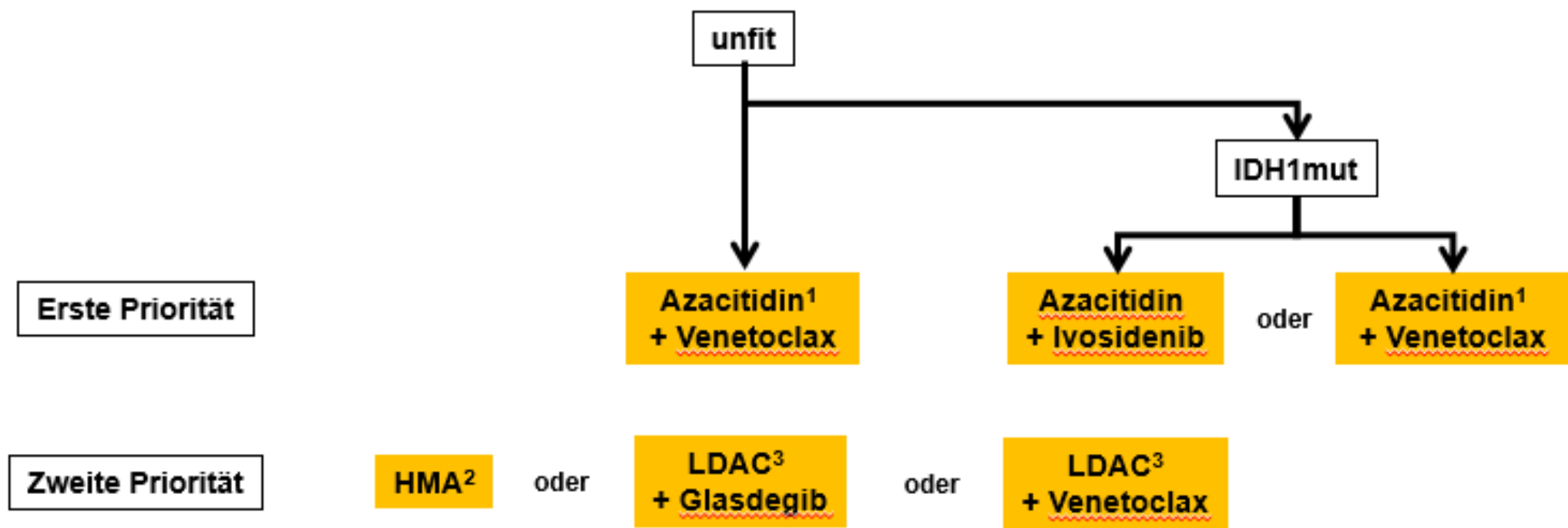
De Botton S et al., ASCO 2023, P142



IVO+AZA ■  
PBO+AZA ■

Erste Priorität







- Die Intensive Chemotherapie wurde durch neue Substanzen, v.a. als add-on zur konventionellen Therapie, signifikant weiterentwickelt. Auch MRD Monitoring nimmt mittlerweile einen großen Stellenwert bei der Therapieplanung der hochdosierten Therapie ein.
- Erhaltungstherapie wird zunehmend zu einem etablierten Konzept bei hochdosierter AML Therapie.
- Auch bei nicht-intensiver AML Therapie haben sich neue Substanzen in der klinischen Routine etabliert.



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## Akute Myeloische Leukämie (AML)

Autoren: *Christoph Röllig, Francis Ayuketang Ayuk, Jan Braess, Michael Heuser, Markus G. Manz, Jakob Passweg, Dirk Reinhardt, Richard F. Schlenk und Armin Zebisch*

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