Hochrisiko MDS/sAML

Katharina Götze
Medizinische Klinik III
TU München
Hamburg, 26.02.2020

TECHNISCHE UNIVERSITÄT MÜNCHEN

D·MDS
Deutsche MDS-Studiengruppe

CCC MÜNCHEN
COMPREHENSIVE
CANCER CENTER

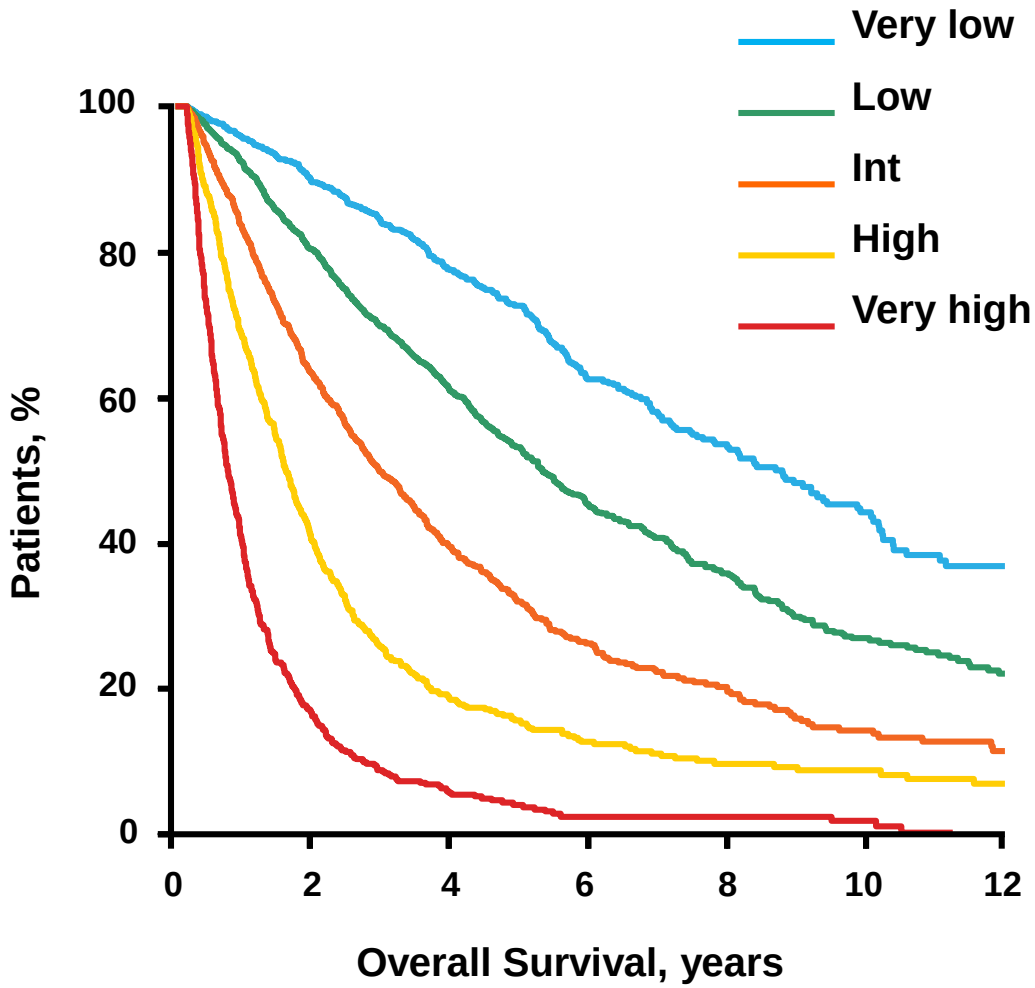
Hiermit erkläre ich, dass zu den Inhalten der Veranstaltung

- ☐ kein Interessenkonflikt vorliegt
- ☒ ein materieller Interessenkonflikt vorliegt: Honorare Celgene, Novartis, JAZZ
- ☐ ein immaterieller Interessenkonflikt vorliegt

Hinweis:
Gekreuzte Kästchen bzw. nicht gekreuzte Kästchen sind entsprechend der Angabe eines Interessenkonflikt zu verschieben. Liegt ein Interessenkonflikt vor, ist der/die Referent*in angehalten, dem Auditorium die Art des Interessenkonflikts zu erörtern.

Prognose des HR MDS

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤ 1.5	19 %	8.8	Not reached
Low	> 1.5 – 3	38 %	5.3	10.8
Intermediate	> 3 – 4.5	20 %	3.0	3.2
High	> 4.5 – 6	13 %	1.6	1.4
Very High	> 6	10 %	0.8	0.73



Schanz, J Clin Oncol 2012; Greenberg Blood 2012

Warum ist eine möglichst exakte Risikostratifizierung wichtig?

Unterschiedliche Therapieziele für Niedrigrisiko und Hochrisiko MDS:

Niedrigrisiko: **Reduktion der Morbidität**
- Verbesserung von Zytopenien
- Transfusionsfreiheit
- Verminderung von Infekten und Blutungen

Hochrisiko: **Veränderung des Krankheitsverlaufs**
- Verbesserung des Gesamtüberlebens
- Verzögerung der Zeit bis zur AML Transformation
- Heilung

- Therapeutische Konsequenzen, vor allem für jüngere Patienten
  -> allogene Stammzelltransplantation

- Planung der klinischen und diagnostischen Kontrolle bzgl. klonaler Evolution und Progression

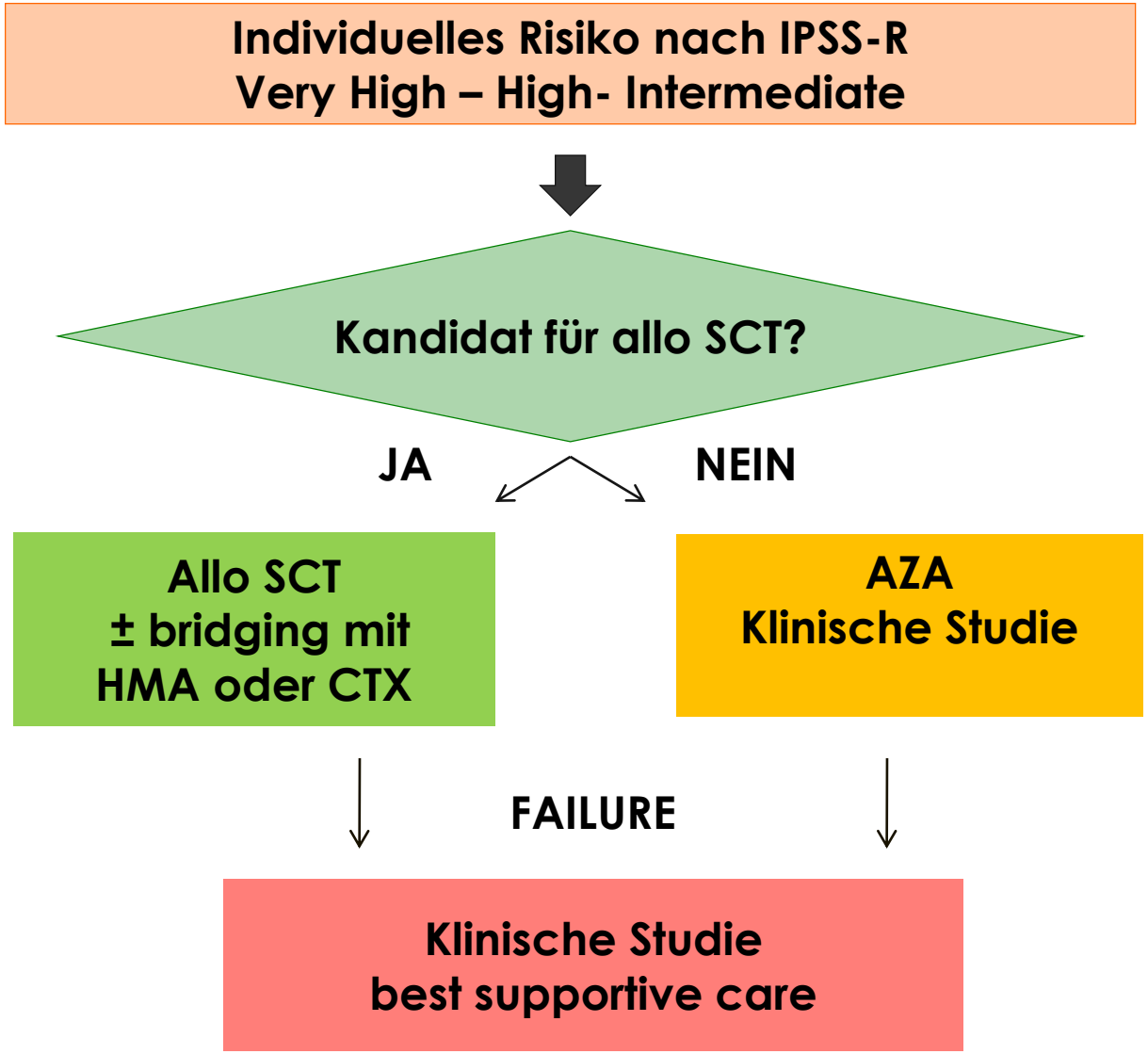
- Erwartungen des Patienten an seinen Krankheitsverlauf und Schweregrad der Erkrankung

Prognostische Bedeutung molekularer Mutationen nach Blastenzahl

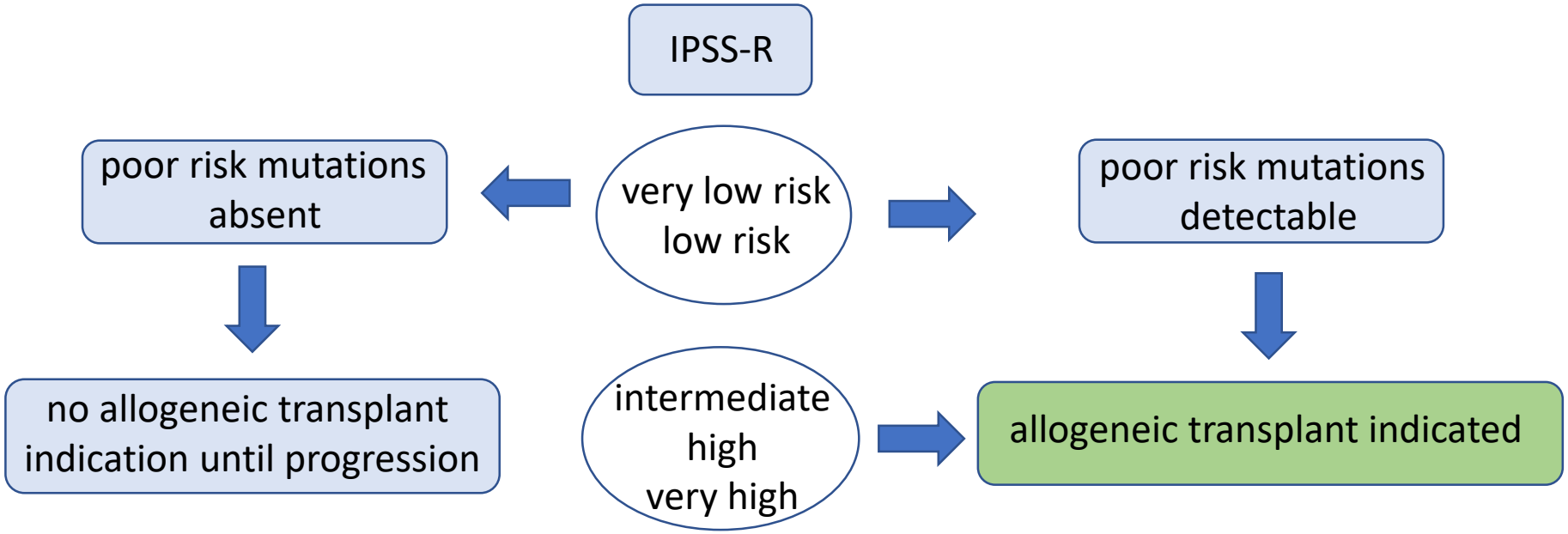
Mutation	Prognose	
	Blasten <5%	Blasten >5%
TP53, RUNX1, EZH2	ungünstig	ungünstig
SRSF2, ASXL1, U2AF1, DNMT3A NRAS	ungünstig	neutral
SF3B1	günstig	neutral
TET2,IDH1/2, JAK2	neutral	neutral
CBL	neutral	ungünstig

Adapted from Bejar, Curr Hematol Malig Rep, 2017

Therapieoptionen HR MDS



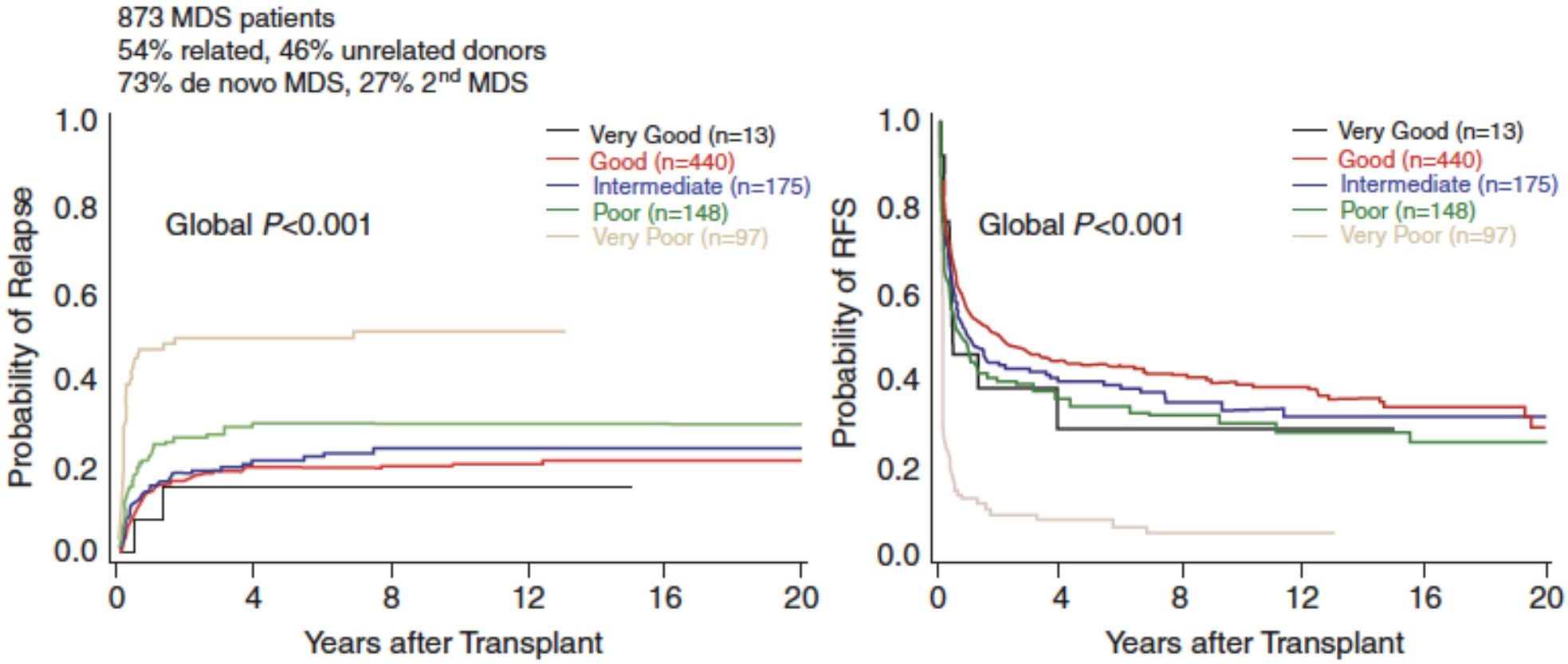
IPSS-R und Mutationen



Upstaging bei Nachweis von ungünstigen Mutationen,
i.e. TP53, RUNX1, ASXL1, DNMT3A, SRSF2, EZH2, U2AF1

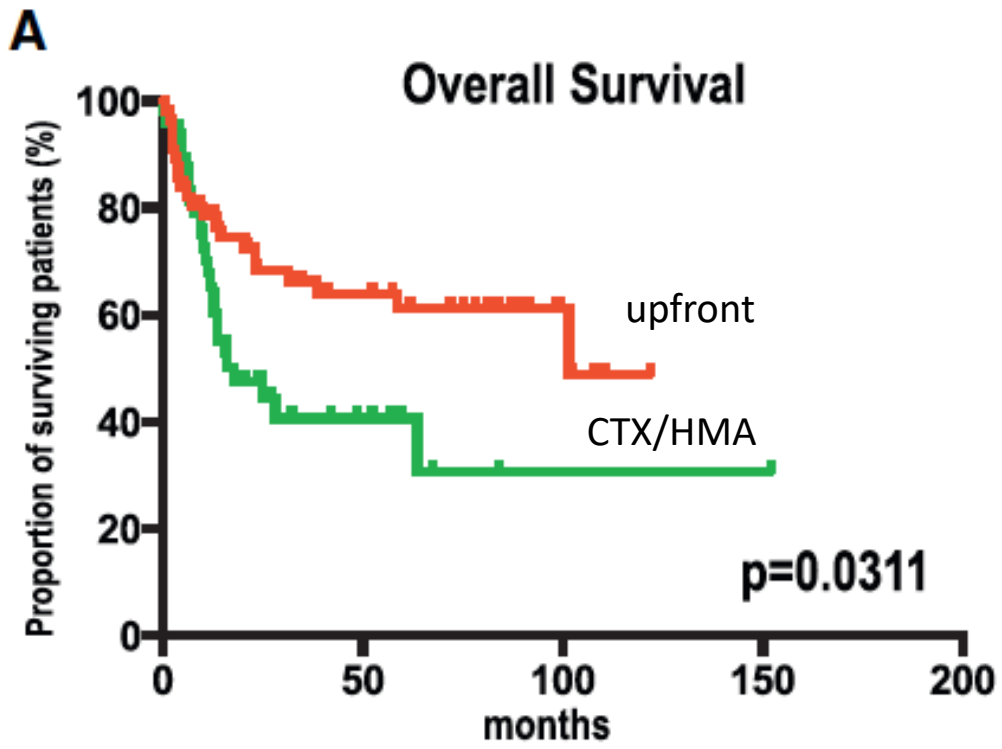
adaptiert nach Kobbe G, Expert Rev Hematol 2019

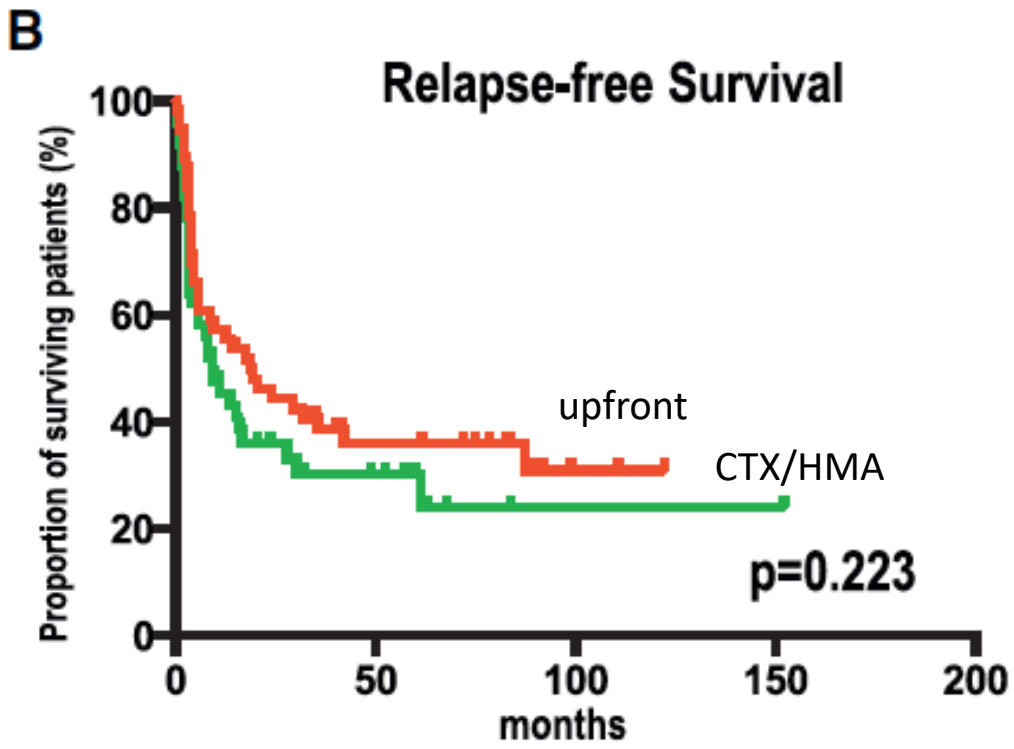
Allogene SCT und Zytogenetik (IPSS-R)



Scott & Robin, in Myelodysplastic Syndromes 2019

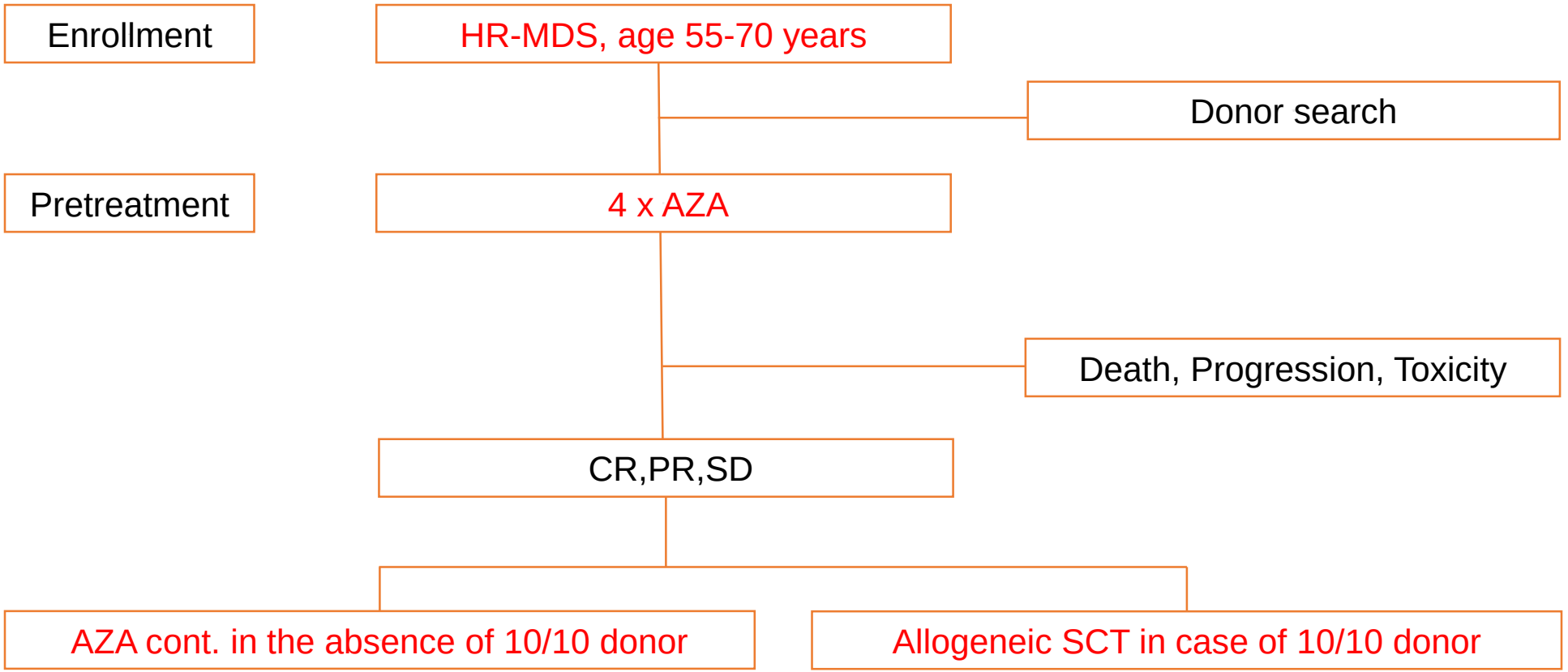
Vortherapie und Outcome nach allo SCT





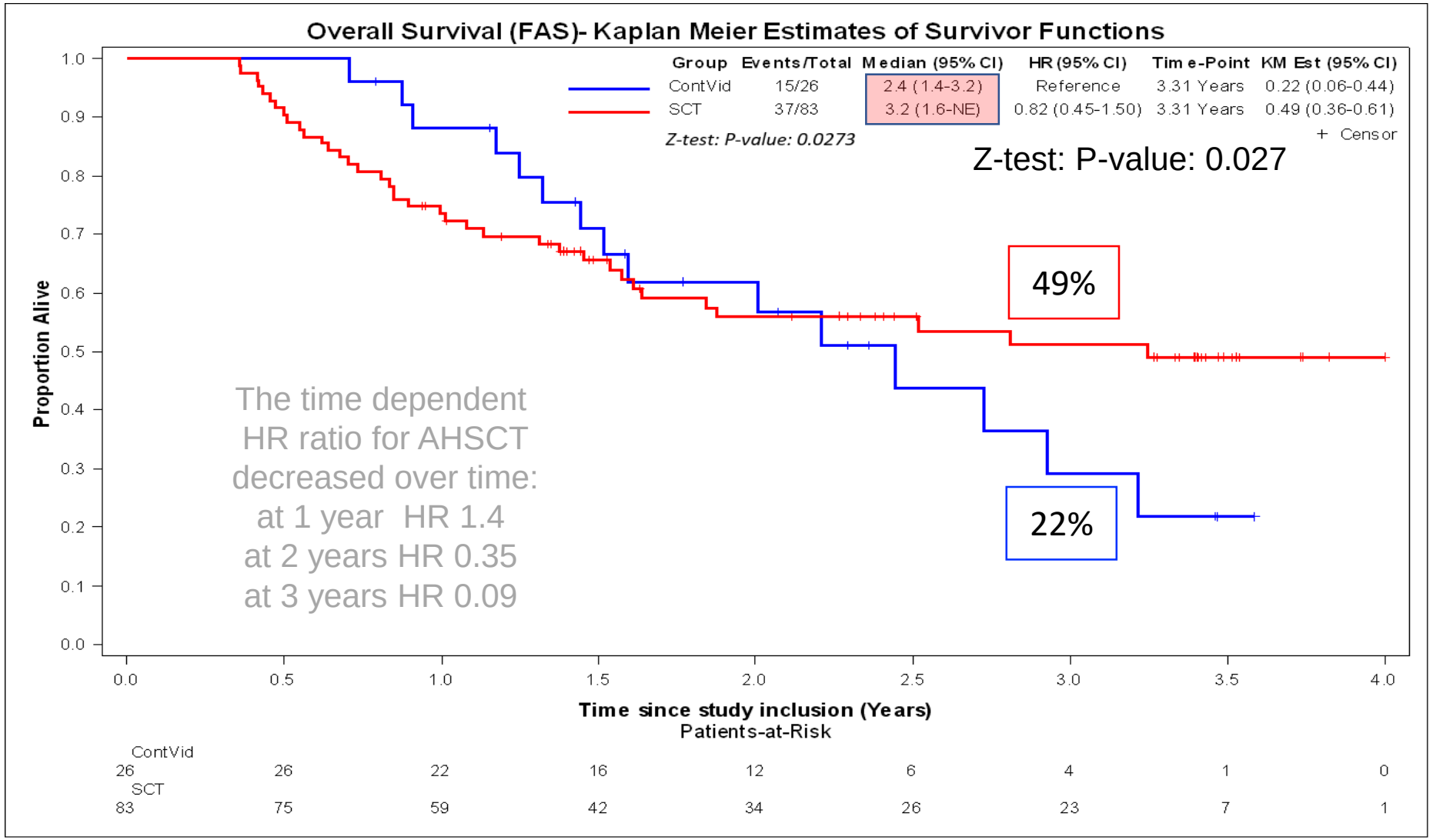
Schroeder et al, BBMT 2019

VidazaALLO Studie



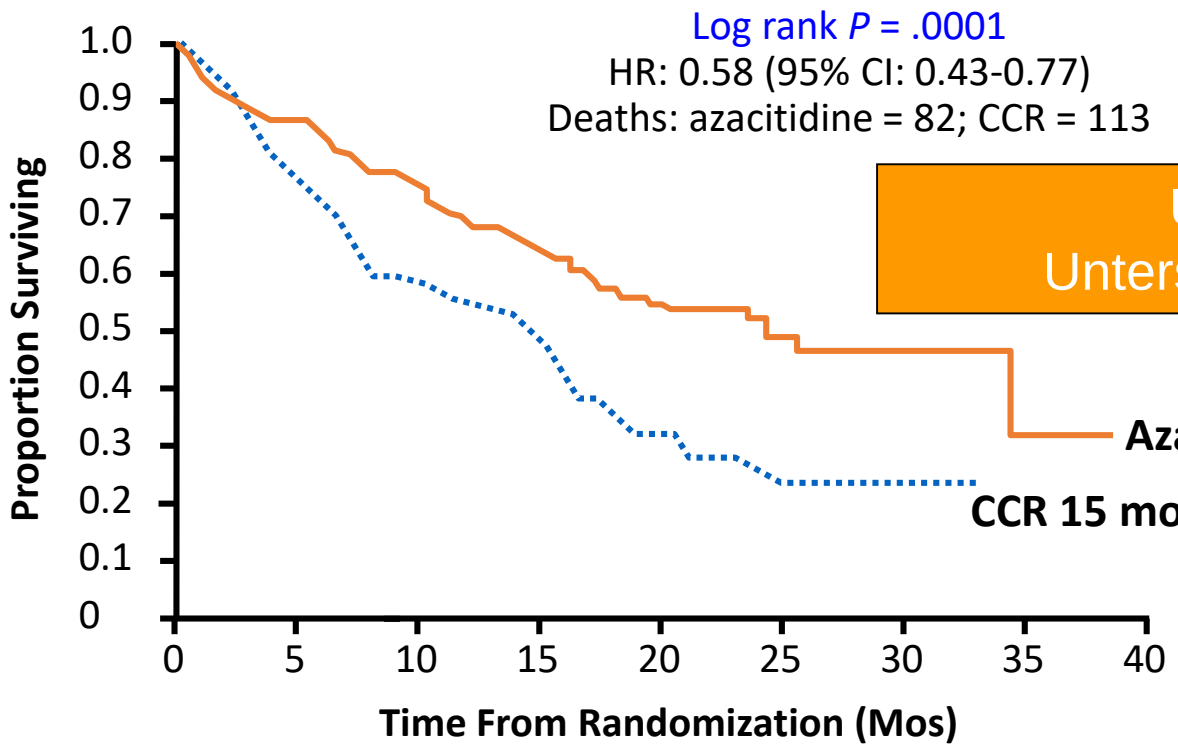
Platzbecker & Kröger et al. EBMT 2019

VidazaALLO Studie: Gesamtüberleben



Platzbecker & Kröger et al. EBMT 2019

AZA-001 MDS Studie



Unterschied im OS (Median): 9,4 Monate
Unterschied im 2-Jahresüberleben (Median): 24,6%

Median age 69 y
Median cycle number AZA 9
Median cycle number LDAC 4
Median follow up 21 mo

Number at risk

Azacitidine	179	152	130	85	52	30	10	1
CCR	179	132	95	69	32	14	5	0

Fenaux P, et al. Lancet Oncology 2009

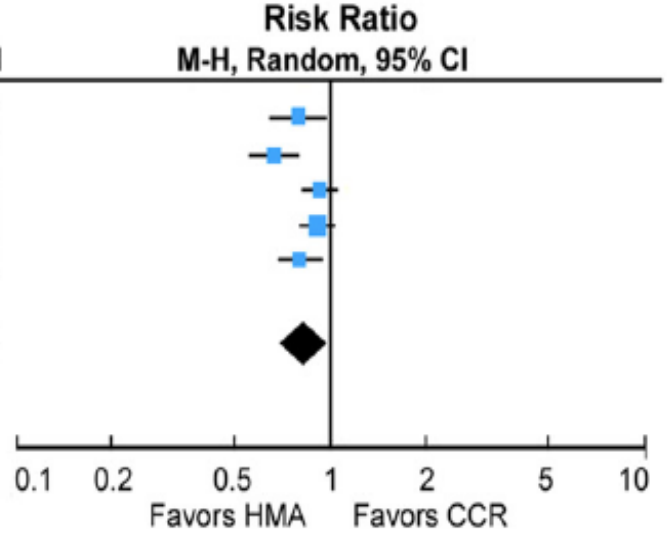
Meta Analyse HMA vs CCR

a OS

Study or Subgroup	HMA Events	HMA Total	CCR Events	CCR Total	Weight	Risk Ratio M-H, Random, 95% CI
2002 Silverman	57	99	67	92	17.0%	0.79 [0.64, 0.98]
2009 Fenaux	88	179	132	179	18.7%	0.67 [0.56, 0.79]
2011 Lubbert	96	119	99	114	21.3%	0.93 [0.83, 1.04]
2012 Kantarjian	219	242	227	243	23.2%	0.97 [0.92, 1.02]
2014 Dombret	128	241	163	247	19.8%	0.80 [0.69, 0.93]
Total (95% CI)		**880**		**875**	**100.0%**	**0.83 [0.71, 0.98]**
Total events	588		688			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 34.95$, df = 4 ($P < 0.00001$); $I^2 = 89\%$

Test for overall effect: $Z = 2.20$ ($P = 0.03$)



Yun et al, Clin. Epigenetics 2016

CAVEATS

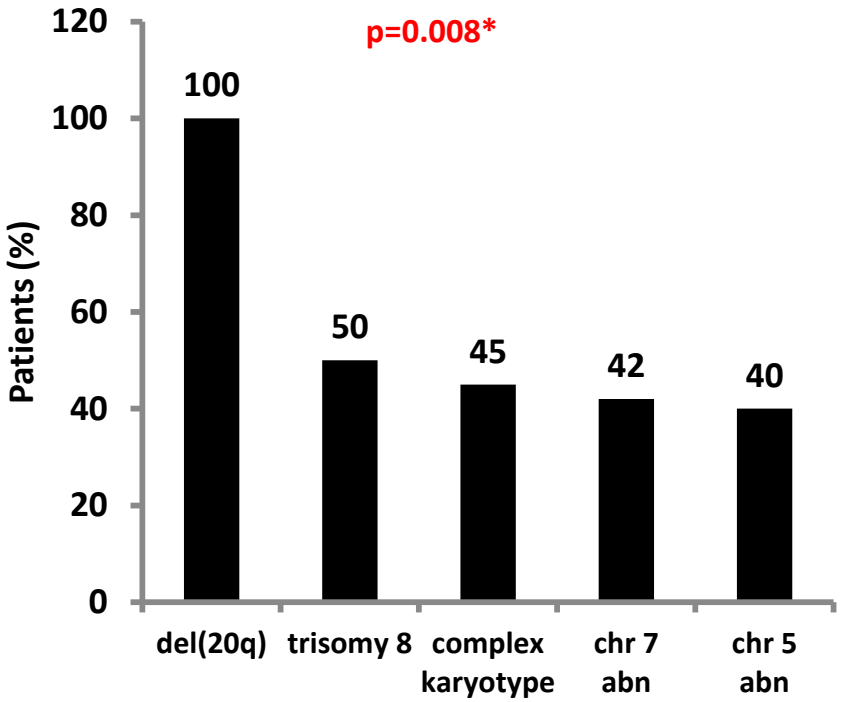
- Nur ca. 50% der Patienten sprechen auf HMA an (primäre Resistenz)
- Ansprechen kann bis zu 6 Monate dauern
- Mediane Ansprechdauer 14 Monate, medianes Gesamtüberleben 24 Monate
- Alle Patienten verlieren ihr Ansprechen (sekundäre Resistenz)

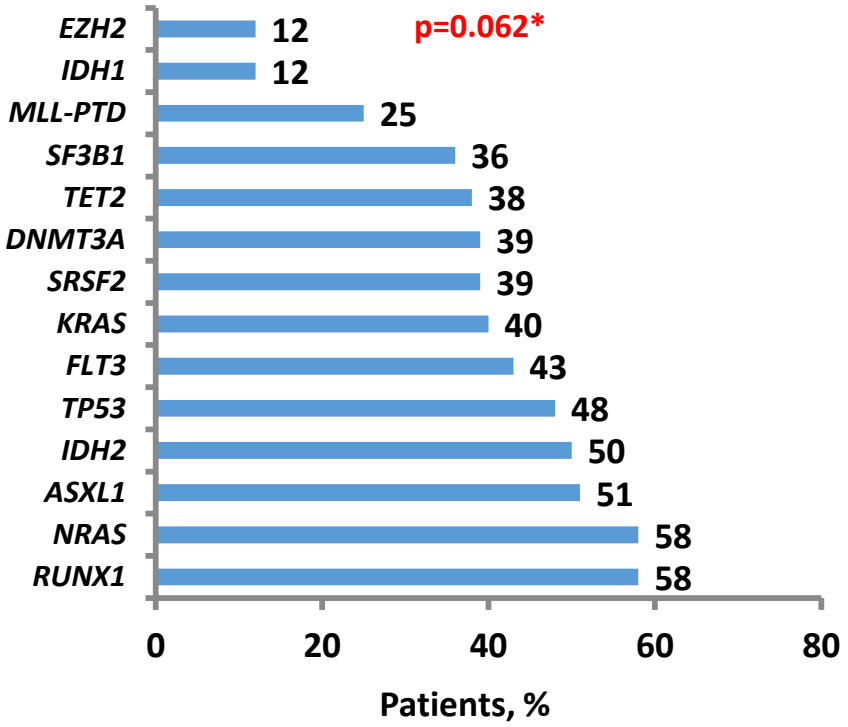
Wege zur Verbesserung

- Biomarker/Prädiktion des Ansprechens auf HMA
- Verbesserung der Ansprechrate durch Add-ons: Kombinationen weiterer Substanzen mit HMA
- Neue Therapien nach HMA Versagen

Prädiktive Faktoren für HMA Ansprechen

Zytogenetik

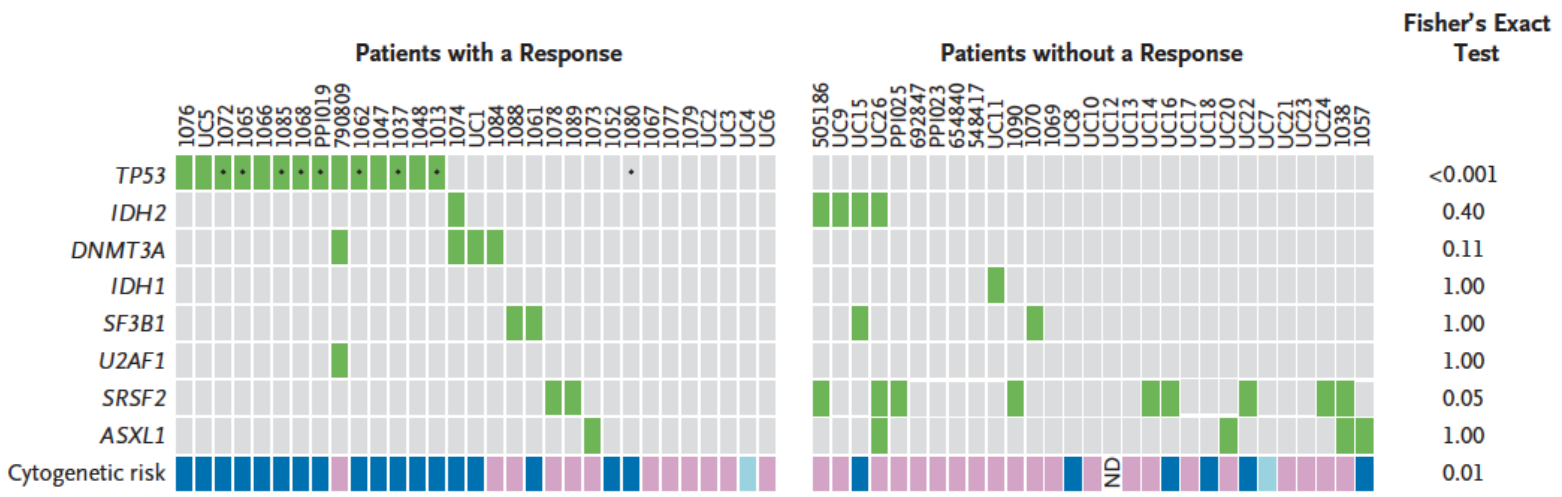


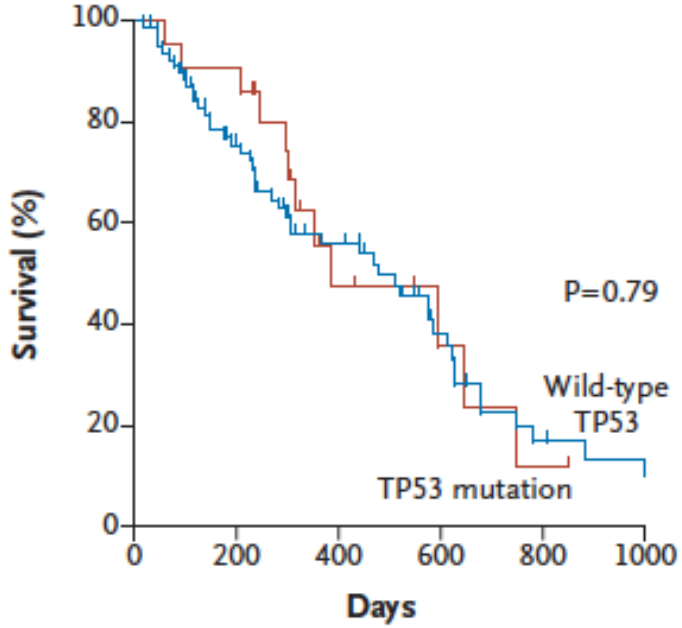


AZA conferred similar response rates in most patient subgroups. The only significant observation was that patients with del(20q) had a higher response rate than those without

Kündgen, Germing & Götze, Oncotarget 2018

TP53 Mutation und HMA





No. at Risk

TP53 mutation	21	20	7	4	2
Wild-type *TP53*	78	51	31	16	7

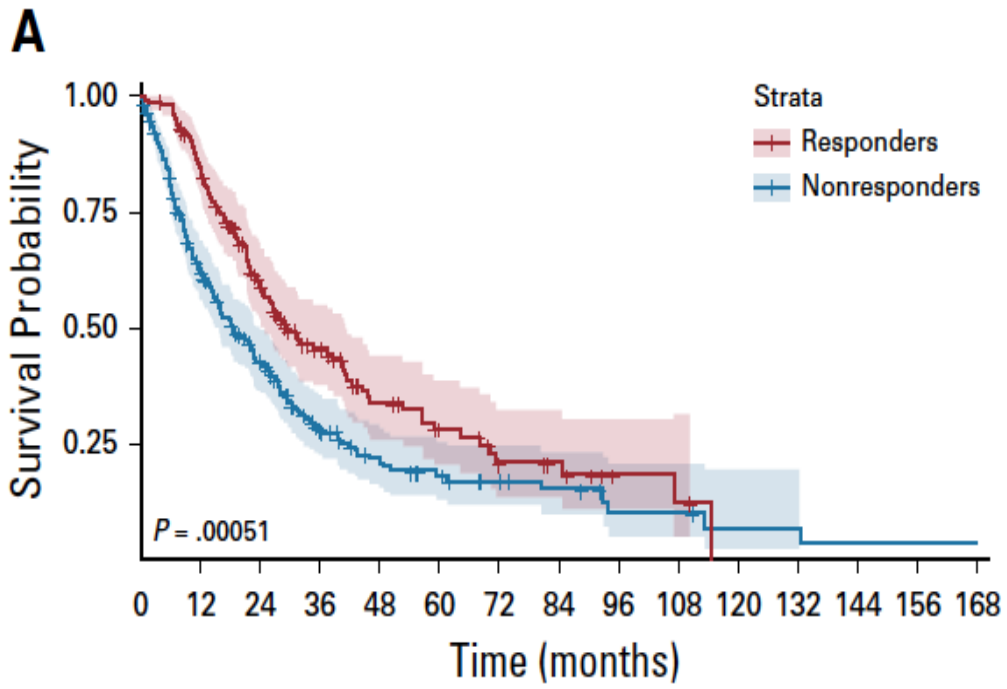
Welch et al, NEJM 2016

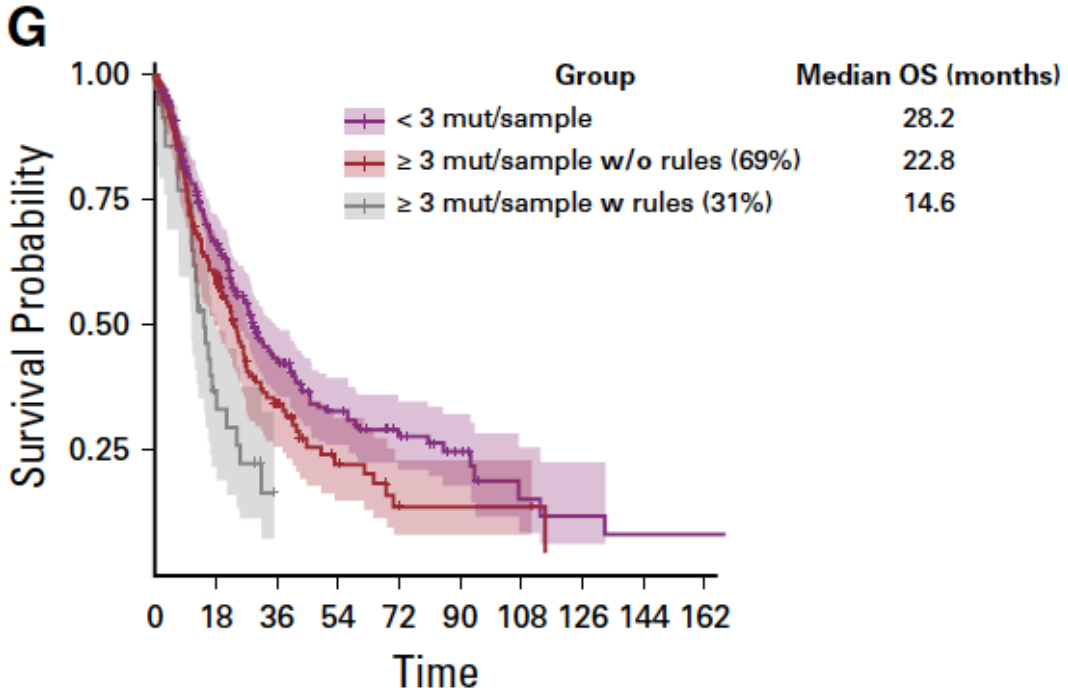
TP53 and HMA

Table 1. Outcomes of Patients with Acute Myeloid Leukemia and Myelodysplastic Syndromes (MDS) Treated with Hypomethylating Agents in Four Studies, According to *TP53* Mutation Status.*

Study	No. of Patients	Patients with Mutated *TP53*	Overall Response			Complete Response			Overall Survival		
			Mutated *TP53*	Wild-Type *TP53*	P Value	Mutated *TP53*	Wild-Type *TP53*	P Value	Mutated *TP53*	Wild-Type *TP53*	P Value
			no. of patients (%)			*no. (%)*					
Bally et al.†	62 (44 MDS)	23 (37)	10 (43)	20 (51)	0.60	5 (22)	15 (38)	0.26	Median of 12.4 mo	Median of 23.7 mo	<0.001
Bejar et al.‡	213 MDS	39 (18)	20 (51)	80 (46)	NS	NA	NA	NA	Hazard ratio for death, 2.01 (95% CI, 1.29–3.14)		0.002
Takahashi et al. §	168 MDS	38 (23)	15 (39)	41 (32)	0.13	13 (34)	35 (27)	0.38	Median of 9.4 mo	Median of 20.7 mo	<0.001
Jung et al.¶	107 MDS	13 (12)	10 (77)	47 (50)	0.08	NA	NA	NA	31% at 2 yr	67% at 2 yr	0.003

Machine Learning Algorithmus





Nazha et al, JCO Precision Oncol 2019

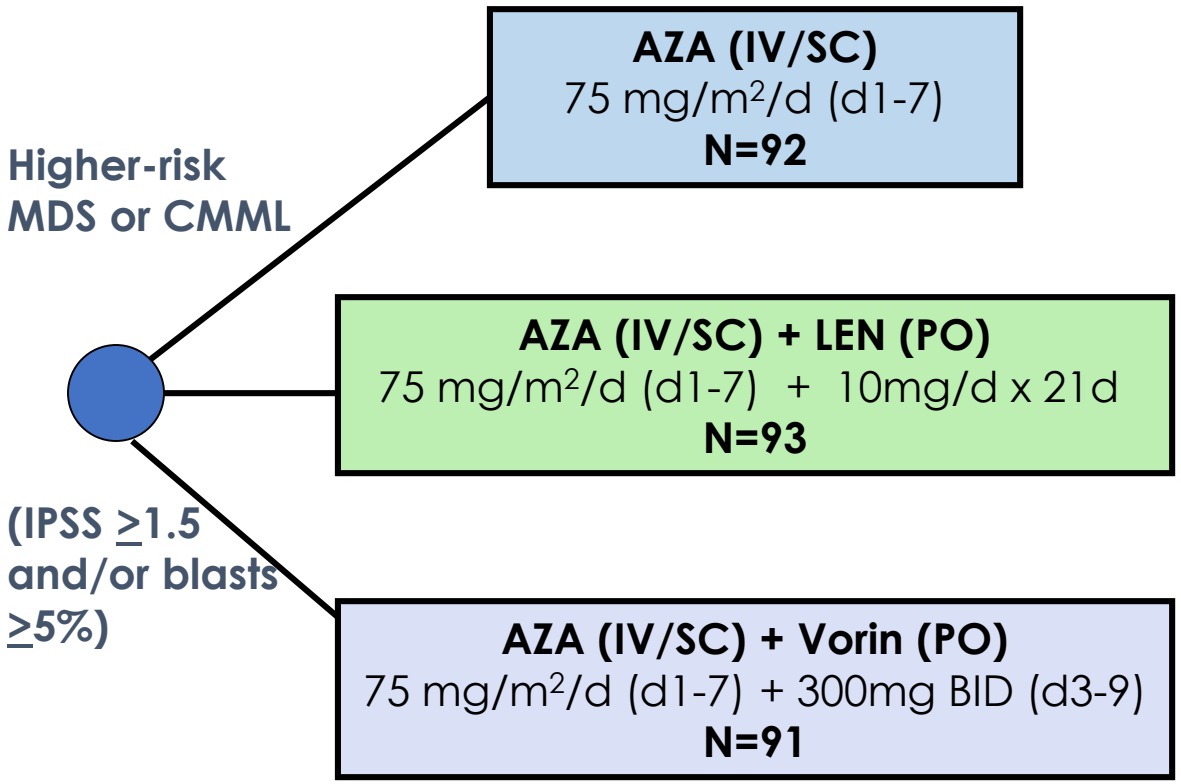
Genmutationen

- **TP53 Mutationen:**
  - kein schlechteres Ansprechen auf AZA
  - Aber kürzeres Gesamtüberleben (prognostisch ungünstig)
- **TET2 Mutationen:**
  - Besseres Ansprechen auf AZA
  - Kein Unterschied im Gesamtüberleben!
- **Weitere poor risk Mutationen (ASXL1, DNMT3A, RUNX1, EZH2, ETV6):**
  - Keine Assoziation mit Ansprechen auf AZA als Einzelmutationen
  - Kombinationen von Mutationen (>3) ungünstig für Ansprechen auf AZA

Itzykson, Leukemia 2011; Müller-Thomas, Haematologica 2014; Bally, Leuk Res 2014; Bejar, Blood 2014; Kündgen, Oncotarget 2018; Nazha; JCO Precision Oncol 2019

HMA + Add Ons

AZA + Lenalidomid/Vorinostat



Groups: SWOG, ECOG, Alliance, NCIC

Total Sample Size: 276

Primary Objective: 20% improvement of ORR (CR/PR/HI) based on 2006 IWG Criteria

Secondary Objectives: OS, RFS, LFS

Power 81%, alpha 0.05 for each combo arm vs. AZA

03/2012 – 06/2014

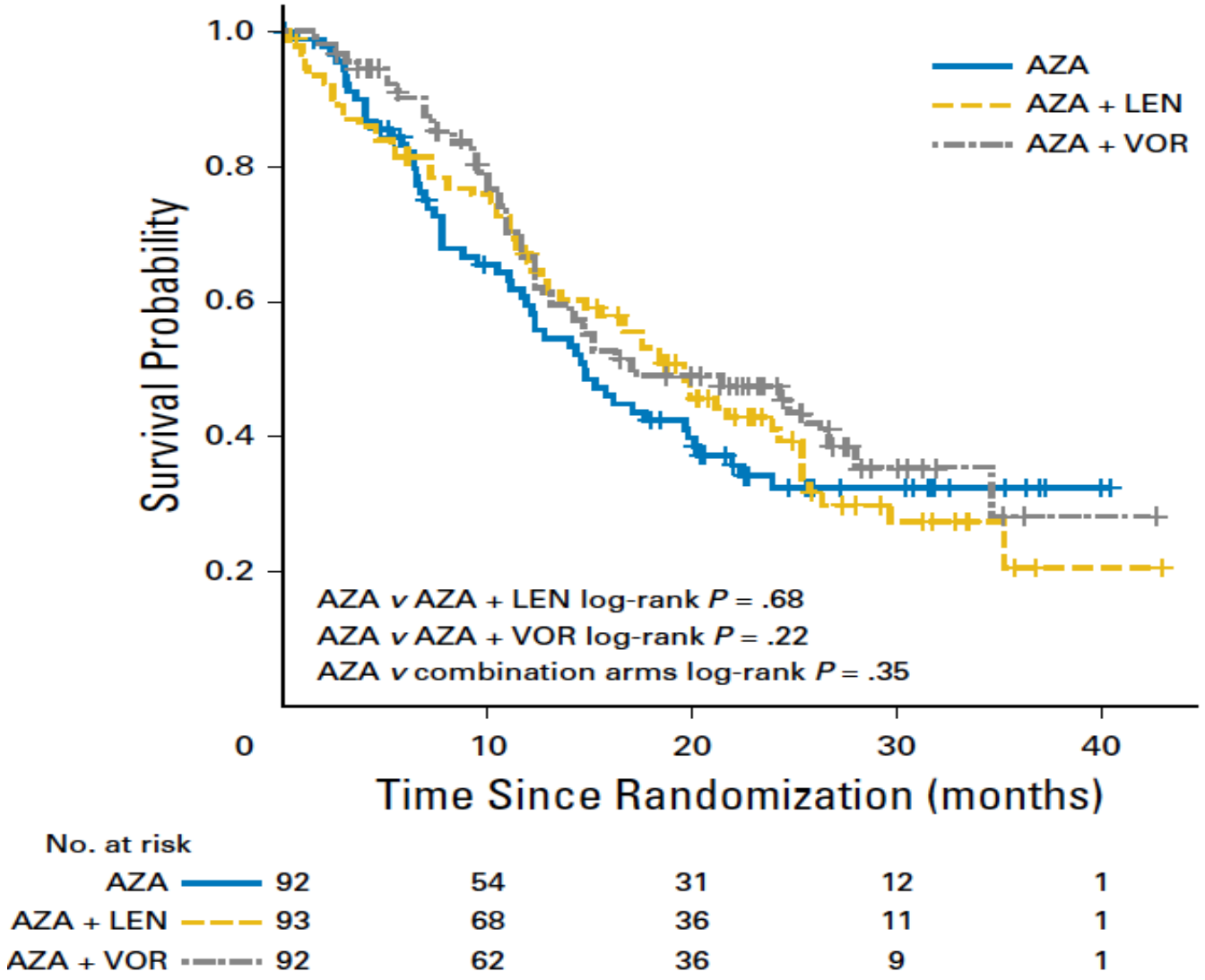
Sekeres et al. J Clin Oncol 2017

Toxizität

Toxicity Variable	AZA	AZA+LEN (P-value vs. AZA)	AZA+VOR (P-value vs. AZA)	Total n=260
Febrile neutropenia (n)	10	13 (0.66)	13 (0.51)	**36**
GI (n)	4	11 (0.10)	**23 (<0.001)**	**38**
Rash (n)	2	**12 (0.01)**	1 (1)	**15**
Off Tx due to Toxicity/Side Effect/Complication	9%	**23% (.04)**	**24% (.03)**	**19%**
Non-protocol defined dose modifications	23%	**41% (.01)**	**36% (.05)**	**33%**

Sekeres et al. J Clin Oncol 2017

Gesamtüberleben



Sekeres et al. J Clin Oncol 2017

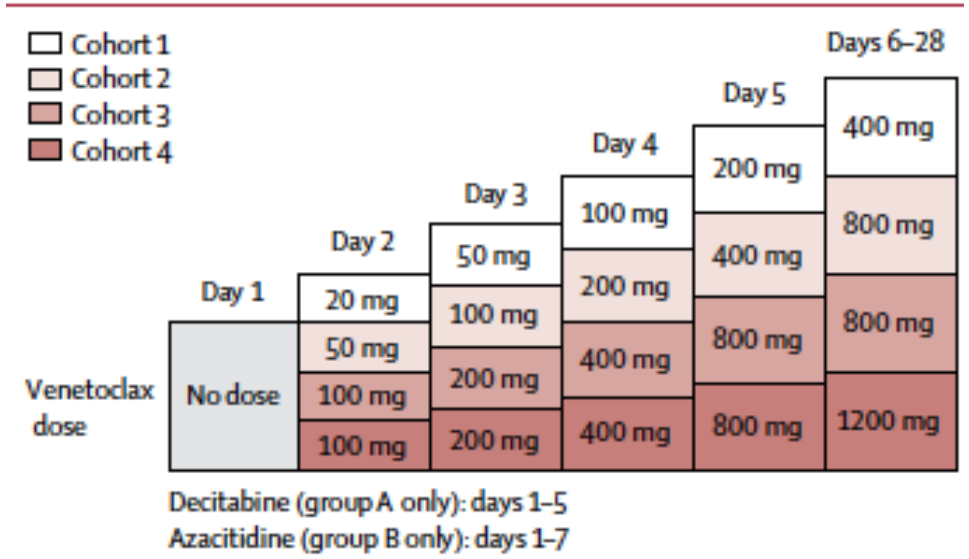
Venetoclax

Phase II single arm trial Venetoclax 800 mg/d

	All $N = 32$ (%)	*IDH* mutation $N = 12$ (%)
Objective response rate (CR + CRi) by IWG criteria	6 (19)	4 (33)
CR	2 (6)	2 (17)
CRi[a]	4 (13)	2 (17)
Antileukemic activity that did not meet IWG criteria	6 (19)	2 (17)
≥50% bone marrow blast reduction with two cell line recovery and transfusion independence[b]	2 (6)	0
≥50% bone marrow blast reduction with one cell line recovery[c]	2 (6)	2 (17)
≥50% bone marrow blast reduction with no hematologic recovery	2 (6)	0
Treatment failure[d]	20 (63)	6 (50)
Overall activity[e]	12 (38)	6 (50)

Konopleva et al, Cancer Discovery 2016

Venetoclax + HMA in AML



	DAC	AZA	
	Group A (n=23)	Group B (n=22)	Group C (n=12)
Complete remission	8 (35%)	6 (27%)	0
CRi	6 (26%)	7 (32%)	8 (67%)
Partial remission	1 (4%)	0	0
MLFS*	2 (9%)	5 (23%)	0
Resistant disease	3 (13%)	2 (9%)	3 (25%)
Non-evaluable†	3 (13%)	2 (9%)	1 (8%)
Complete remission and CRi	14 (61%)	13 (59%)	8 (67%)
Overall response‡	15 (65%)	13 (59%)	8 (67%)
Overall outcome§	17 (74%)	18 (82%)	8 (67%)

Data are n (%). CRi=complete remission with incomplete marrow recovery. MLFS=morphologically leukaemia-free state. *Less than 5% blasts in an aspirate sample with marrow spicules and a count of 200 or more nucleated cells. †Includes five patients who discontinued before end of cycle 1 because of adverse events of infections; one patient was found to have CNS leukaemia on day 7. ‡Including complete remission, CRi, and partial remission. §Including overall response and MLFS.

***Table 4*: Responses to treatment**

DiNardo et al, Lancet Oncology 2018

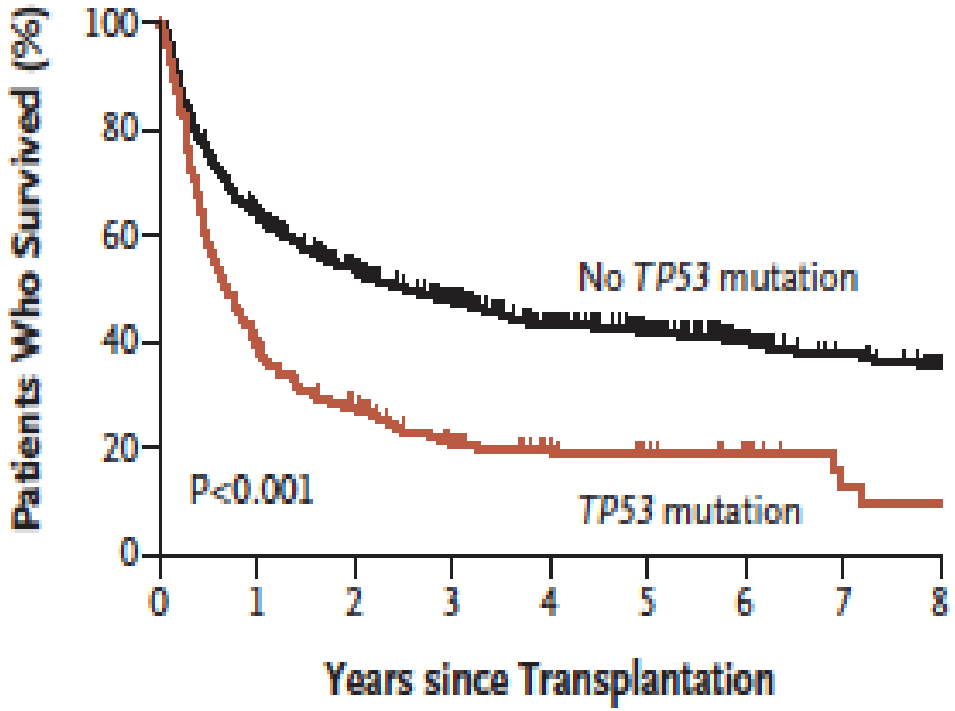
Venetoclax + HMA

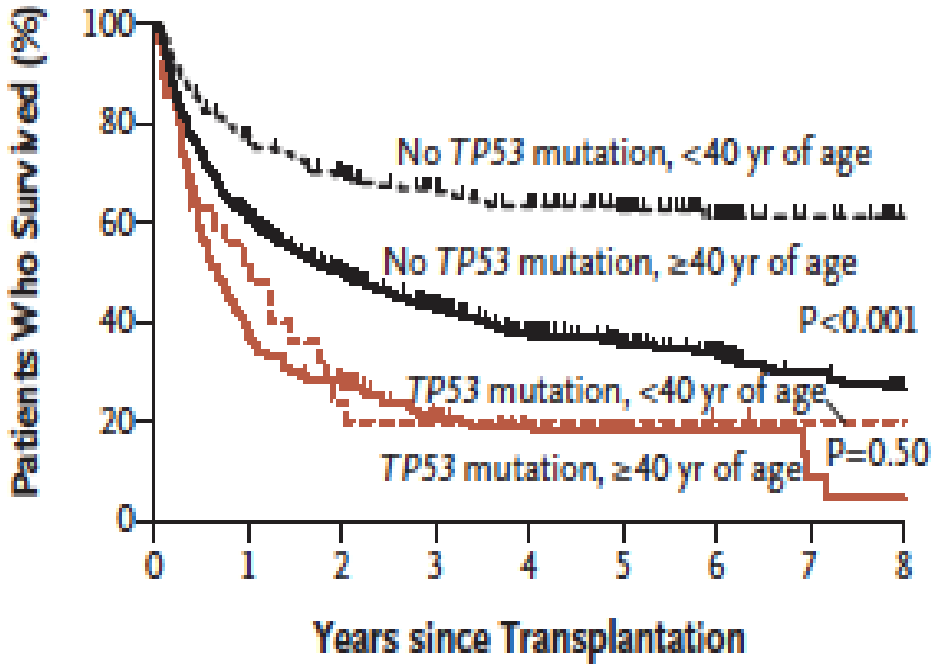
Treatment-emergent adverse events	Venetoclax 400 mg + azacitidine ($N = 84$) [14]	Azacitidine ($N = 236$) [6]
Leukopenia	33%	7%
Febrile neutropenia	39%	28%
Pneumonia	27%	20%
Thromboctyopenia	26%	24%
Anemia	31%	16%

Jonas & Pollyea, Leukemia 2019

TP53 und allogene SCT

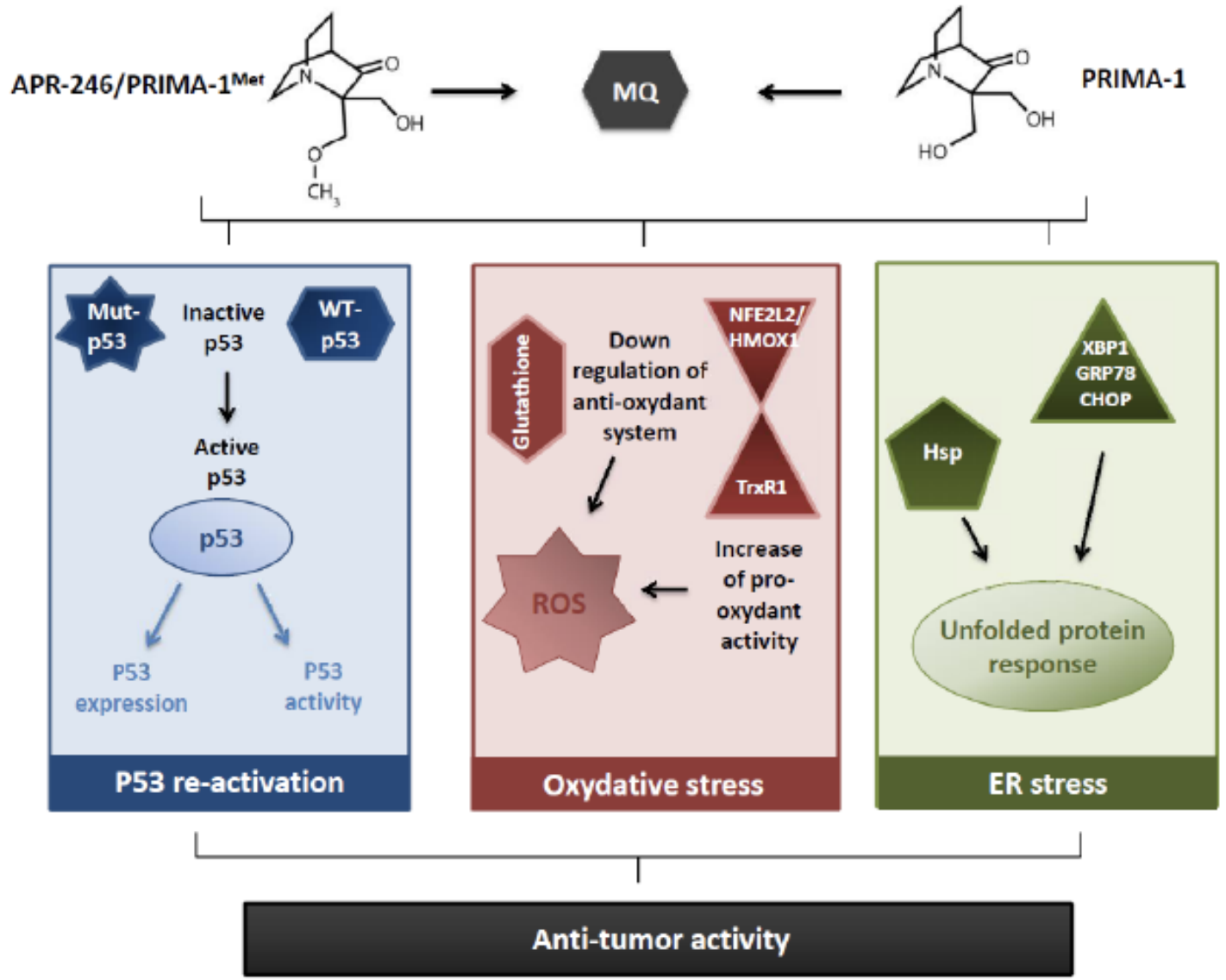
Gesamtüberleben nach allogener SCT



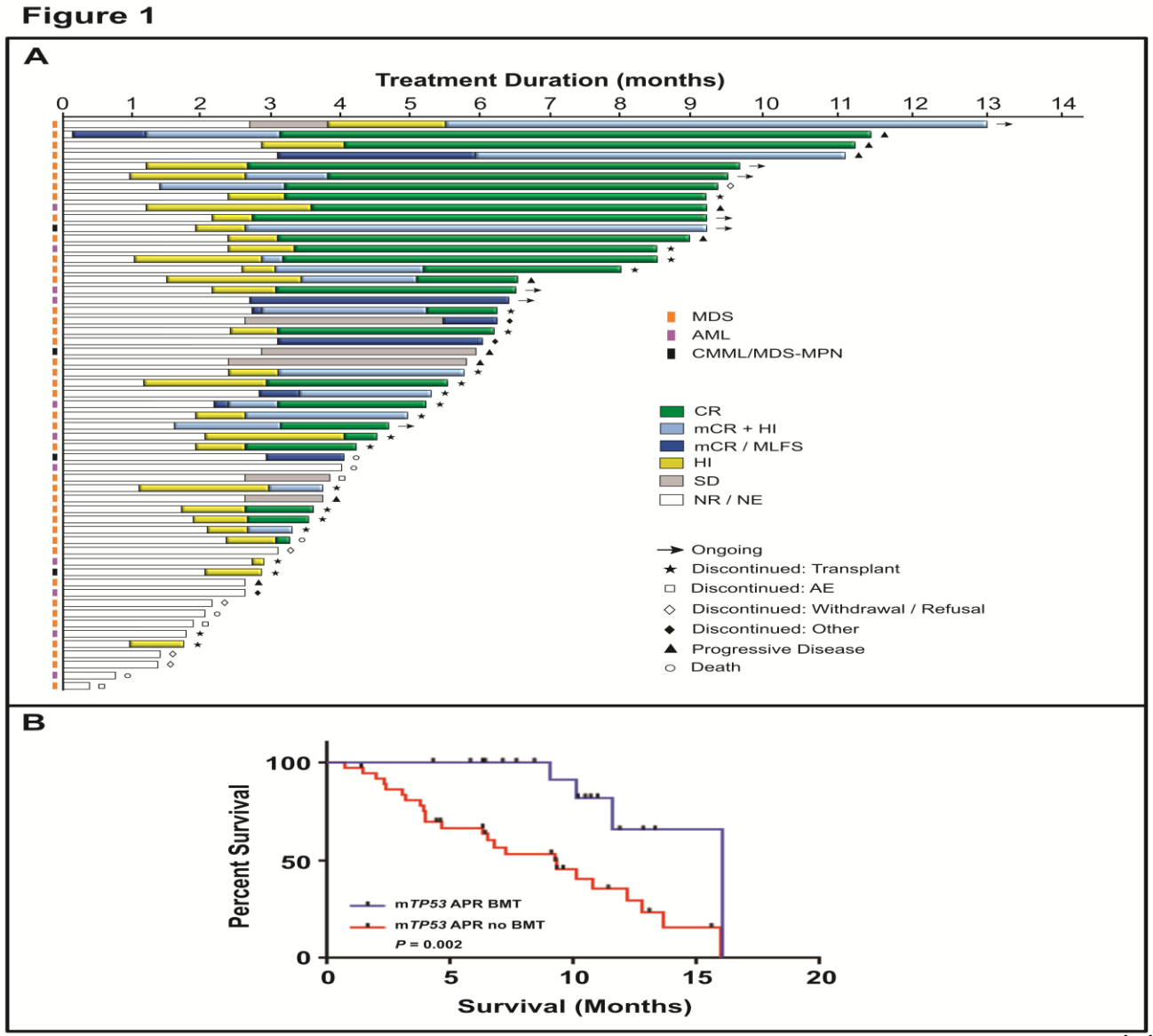


Lindsley et al, NEJM 2017

TP53 Reaktivierung: APR-246 (PRIMA-1)



APR-246 + AZA in HR-MDS/AML



PHASE II trials in HMA naive MDS/AML
APR 246 d1-4, AZA d41-0

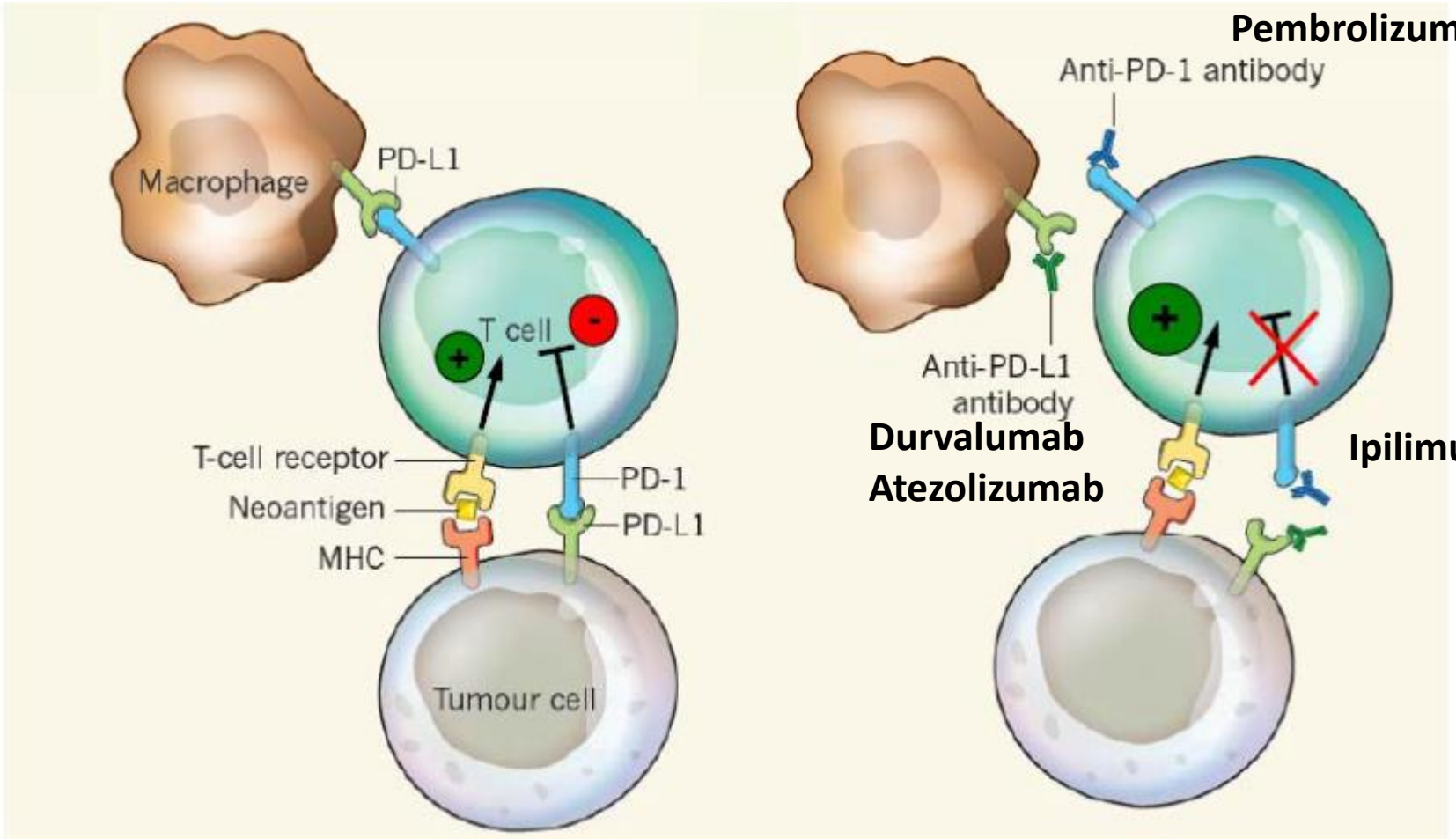
- ORR 87%
- CR 53 - 61%
- OS 12 mo
- deep molecular remissions
- median duration of response 8.4 mo
- 52% allo SCT

- neurological AEs

- Orphan drug designation FDA and EMA/Fast track status FDA

Maslah et al, Haematologica 2019; Cluzeau et al ASH 2019; Sallmann et al, ASH 2019

Checkpoint Modulators



Nivolumab
Pembrolizumab

Durvalumab
Atezolizumab

Ipilimumab

PD-1 and CTLA4 inhibition

Pts aged 18 yrs or older with WHO MDS; no prior tx, or HMA failure*; no history of inflammatory or autoimmune disease or HIV; no active HCV infection **(N = 54)**

Primary Endpoint: ORR, Safety

HMA Failure Cohorts†

Cohort #1
Nivolumab
3 mg/kg IV Q2W
(n = 15)

Cohort #2
Ipilimumab
3 mg/kg IV Q3W
(n = 18)

Cohort #3
Nivolumab
3 mg/kg IV Q2W
+ **Ipilimumab**
3 mg/kg IV Q4W

Tx-Naive Cohorts

Cohort #4
Azacitidine
75 mg/m^2 IV x 5d
Q4W + **Nivolumab**
3 mg/kg IV D6, D20
(n = 21)

Cohort #5
Azacitidine
75 mg/m^2 IV x 5d
Q4W +
Ipilimumab
3 mg/kg IV D6

Cohort #6
Azacitidine
75 mg/m^2 IV x 5d Q4W +
Nivolumab
3 mg/kg IV D6, D20 +
Ipilimumab
3 mg/kg IV D6

*Last HMA cycle within 4 mos; no other tx after HMA. †AZA added if no response or progression after 6 cycles

Garcia-Manero et al, ASH 2016. Abstract 344

PD-1 and CTLA4 inhibition

Outcome, n (%)	HMA Failure		Treatment-Naive
	Nivolumab (n = 15)	Ipilimumab (n = 18)	Azacitidine + Nivolumab (n = 20)
ORR	**0**	**5 (30)**	**13 (80)**
CR	0	1 (6)	6 (35)
mCR	0	2 (12)	6 (35)
No response	8 (53)	9 (56)	2 (11)
PD	6 (40)	2 (12)	2 (11)
SD	1 (6)	NR	NR
HI-N, n (%)	NR	2 (12)	NR
HI-P, n (%)	NR	NR	1 (5)
TE, n (%)	NR	2 (11)	3 (15)

Median
3 Zyklen
(1-11)

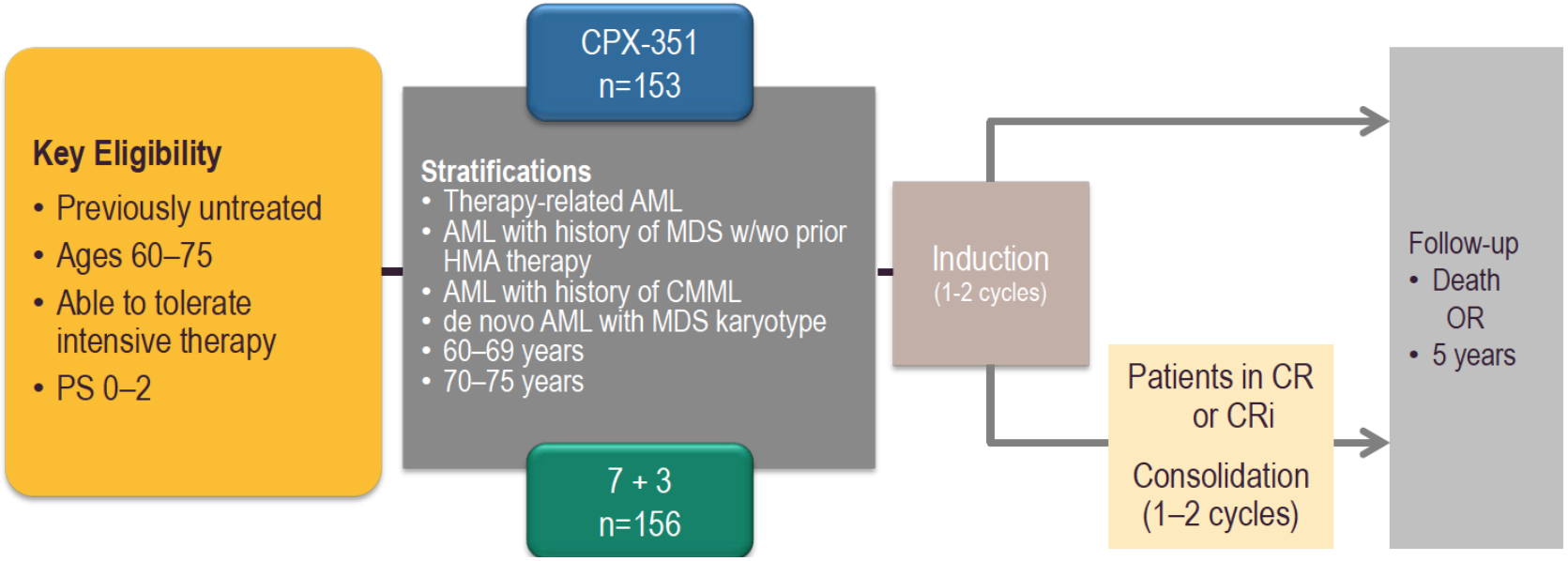
Garcia-Manero et al, ASH 2016. Abstract 344

Neue Substanzen

CPX-351

CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

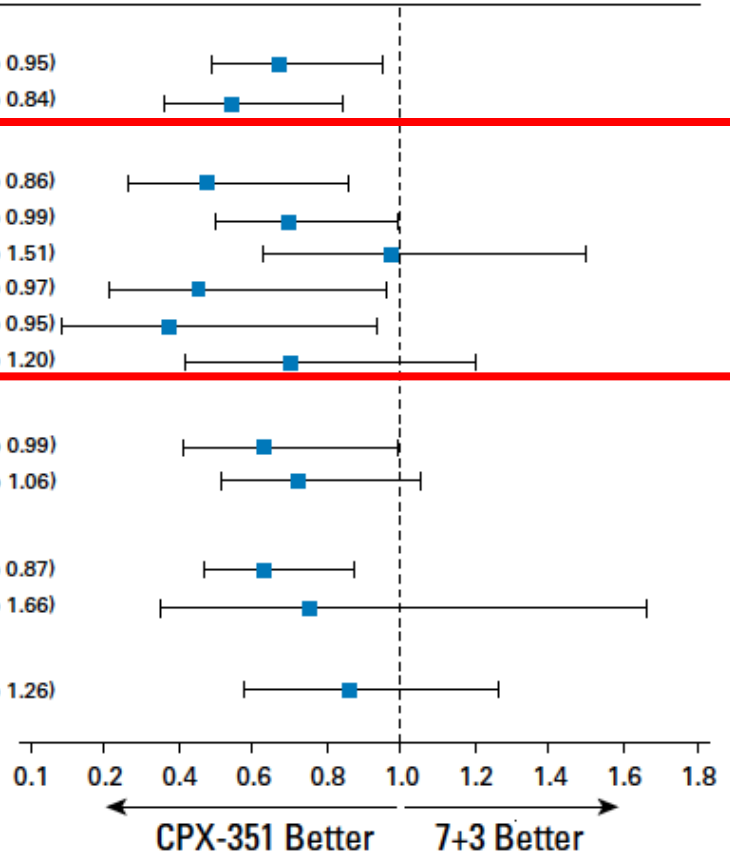
Jeffrey E. Lancet, Geoffrey L. Uy, Jorge E. Cortes, Laura F. Newell, Tara L. Lin, Ellen K. Ritchie, Robert K. Stuart, Stephen A. Strickland, Donna Hogge, Scott R. Solomon, Richard M. Stone, Dale L. Bixby, Jonathan E. Kolitz, Gary J. Schiller, Matthew J. Wieduwilt, Daniel H. Ryan, Antje Hoering, Kamalika Banerjee, Michael Chiarella, Arthur C. Louie, and Bruno C. Medeiros



CPX-351 Response by AML Type

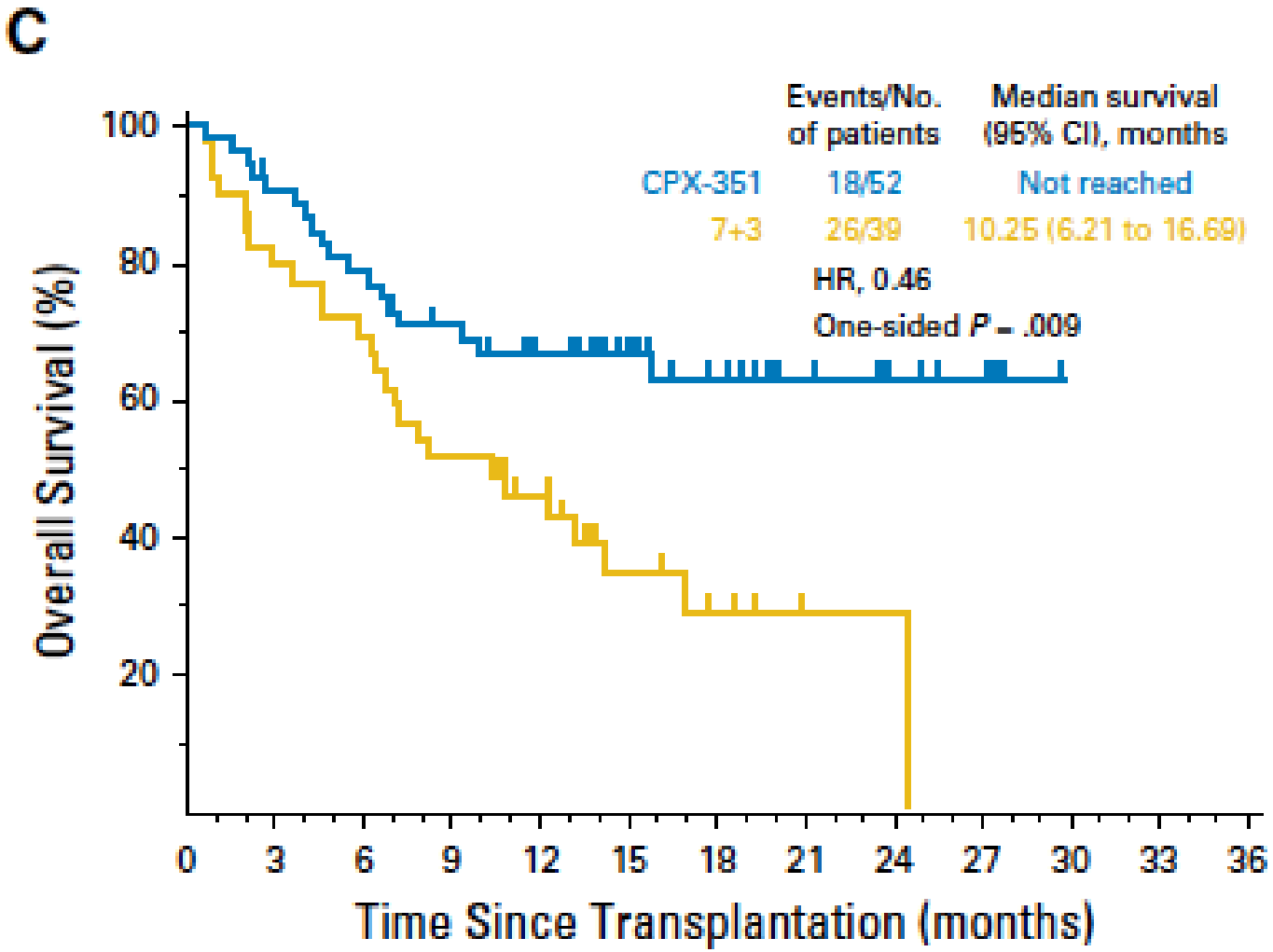
B

Subgroup	CPX-351 No.	CPX-351 Median OS, months	7+3 No.	7+3 Median OS, months	HR (95% CI) for Death
Age					
60-69 years	96	9.63	102	6.87	0.68 (0.49 to 0.95)
70-75 years	57	8.87	54	5.62	0.55 (0.36 to 0.84)
Type of AML					
Therapy-related AML	30	12.17	33	5.95	0.48 (0.26 to 0.86)
AML with antecedent MDS or CMML	82	7.38	86	5.95	0.70 (0.50 to 0.99)
MDS with prior HMA exposure	50	5.65	55	7.43	0.98 (0.64 to 1.51)
MDS without prior HMA exposure	21	15.74	19	5.13	0.46 (0.21 to 0.97)
CMML	11	9.33	12	2.28	0.37 (0.14 to 0.95)
De novo AML with MDS karyotype	41	10.09	37	7.36	0.71 (0.42 to 1.20)
Cytogenetic risk at screening					
Favorable/intermediate	71	14.72	63	8.41	0.64 (0.41 to 0.99)
Unfavorable	72	6.60	83	5.16	0.73 (0.51 to 1.06)
Baseline *FLT3* mutation status					
FLT3 wild type	116	9.33	120	5.98	0.64 (0.47 to 0.87)
FLT3 mutation	22	10.25	21	4.60	0.76 (0.34 to 1.66)
Overall HMA experience					
All patients with prior HMA exposure*	62	5.65	71	5.90	0.86 (0.59 to 1.26)



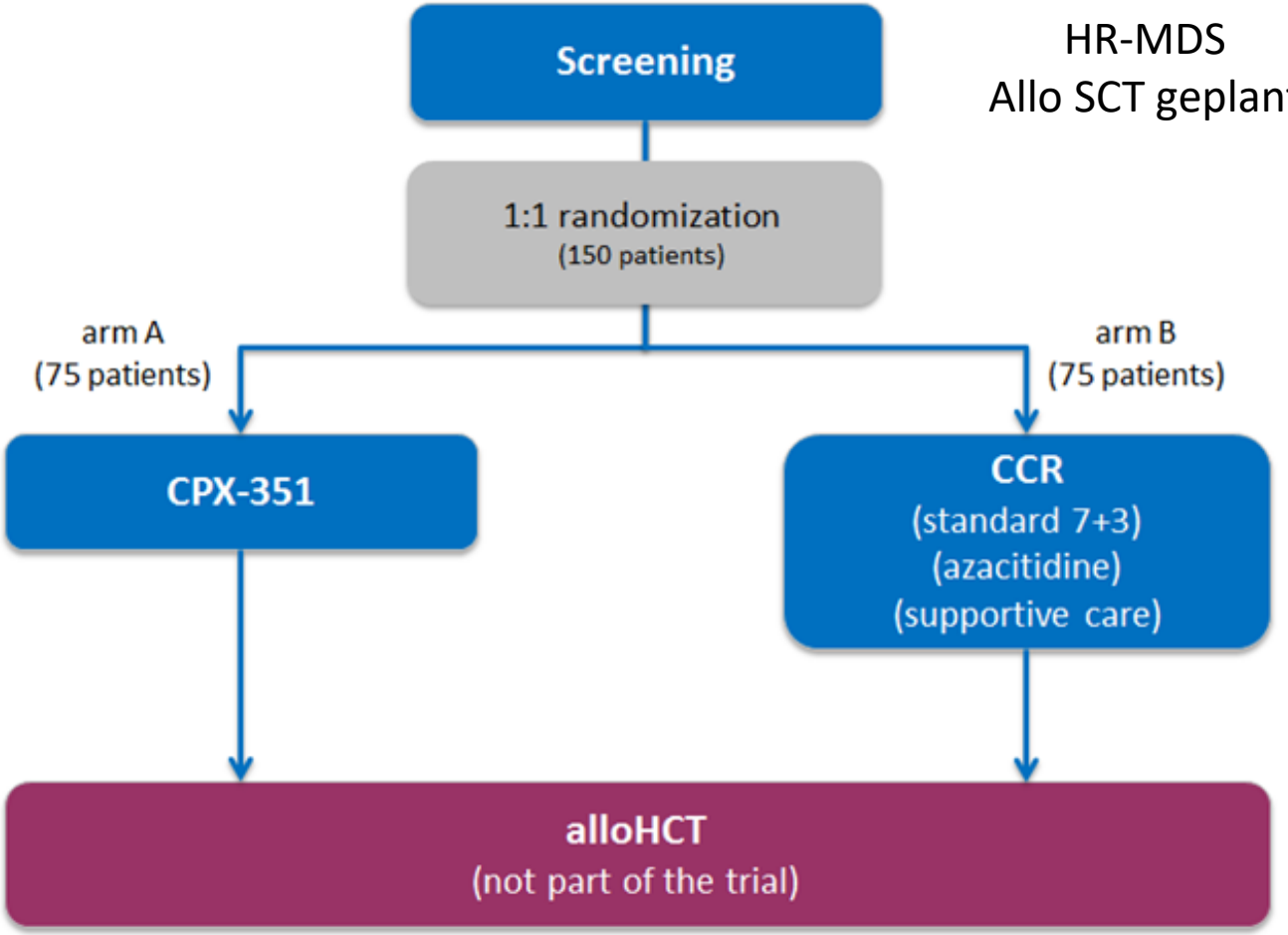
Lancet et al, J Clin Oncol 2018

Gesamtüberleben



Lancet et al, J Clin Oncol 2018

PALOMA Studie



HR-MDS
Allo SCT geplant

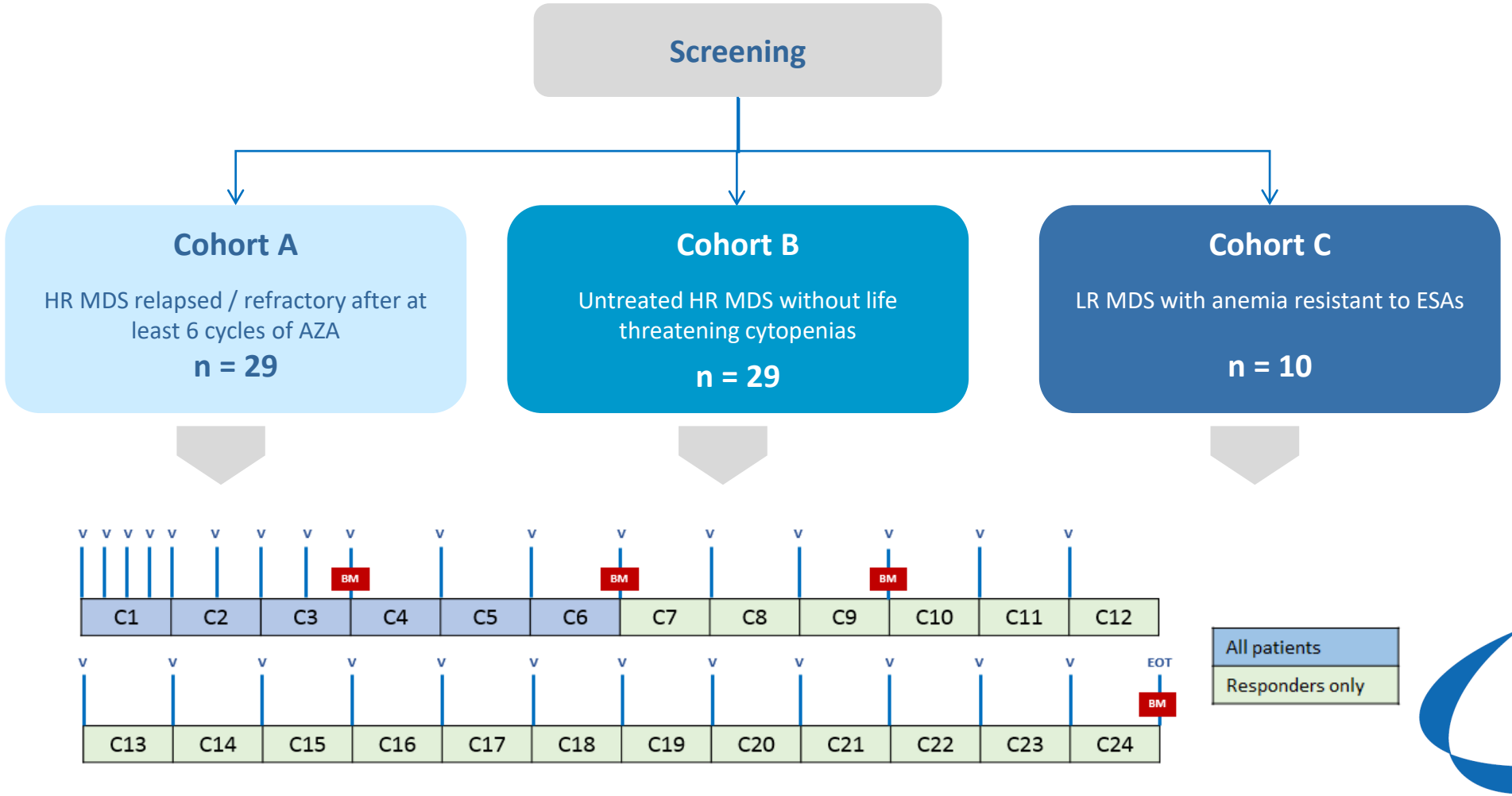
Primärer Endpunkt 2J EFS

EMSCO
MYELODYSPLASTIC
SYNDROMES

D·MDS
Deutsche MDS-Studiengruppe

IDEAL Studie

A single-arm Phase II Multicenter Study of IDH2 (AG 221) Inhibitor in Patients with IDH2 Mutated Myelodysplastic Syndrome



HMA Versagen

Prognose nach HMA Versagen

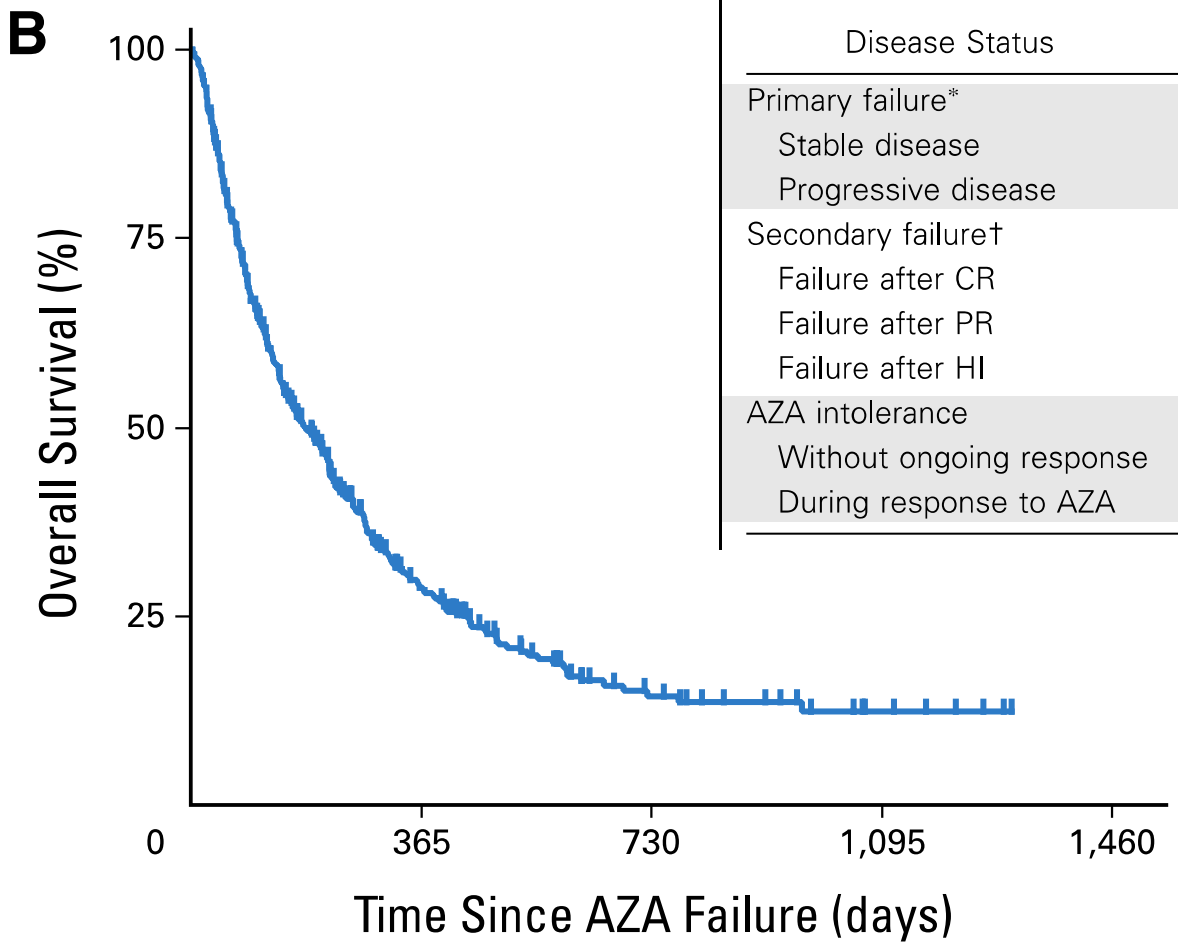


Table 2. Distribution of Patients According to the Type of Failure

Disease Status	Patients	
	No.	%
Primary failure*	229	55
Stable disease	91	24
Progressive disease	138	31
Secondary failure†	164	36
Failure after CR	32	7
Failure after PR	12	2
Failure after HI	120	27
AZA intolerance	42	9
Without ongoing response	29	6
During response to AZA	13	3

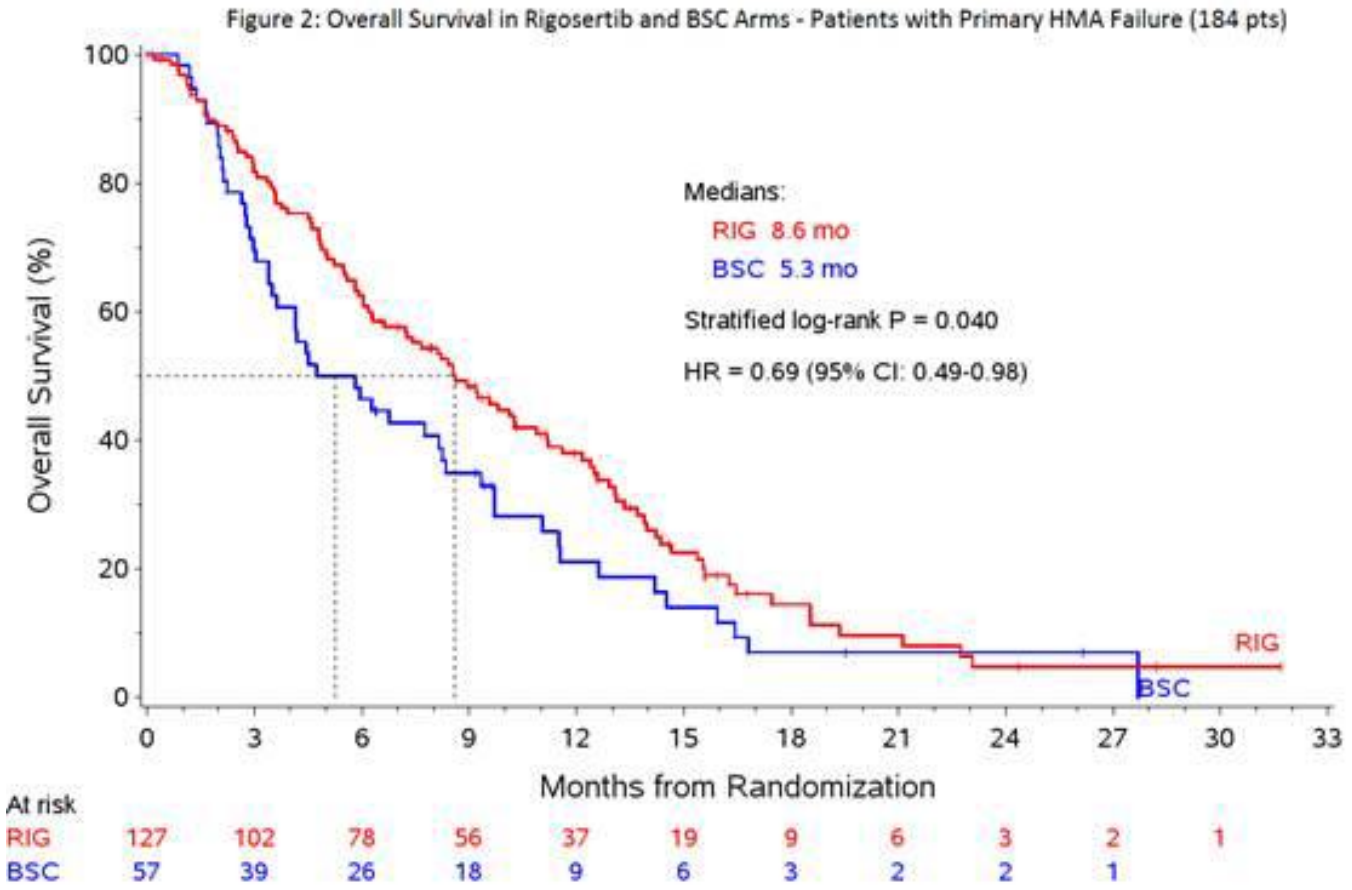
Medianes OS 5.6 Mo

2y OS 15%

Prebet et al., JCO 2011

Rigosertib

Subgruppenanalyse: 184 Patienten mit primärem AZA Versagen



Garcia-Manero et al, Lancet 2016

Bemcentinib (BERGAMO) Studie

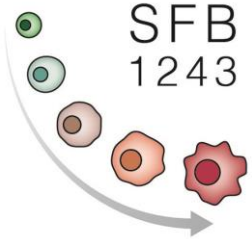
- AXL Inhibitor
- Tyrosinkinase AXL hochreguliert in CD34+ Zellen bei Therapieresistenz
- Überexpression des Liganden Gas6 in MSC von MDS Patienten

- Phase II Studie zur Evaluation der Wirksamkeit von 400 mg in MDS
- Primärer Endpunkt: Gesamtansprechrate nach 17 Wochen (5 Zyklen)
- Patienten nach Versagen von Azacitidine (auch bei Übergang in sAML)

Zusammenfassung

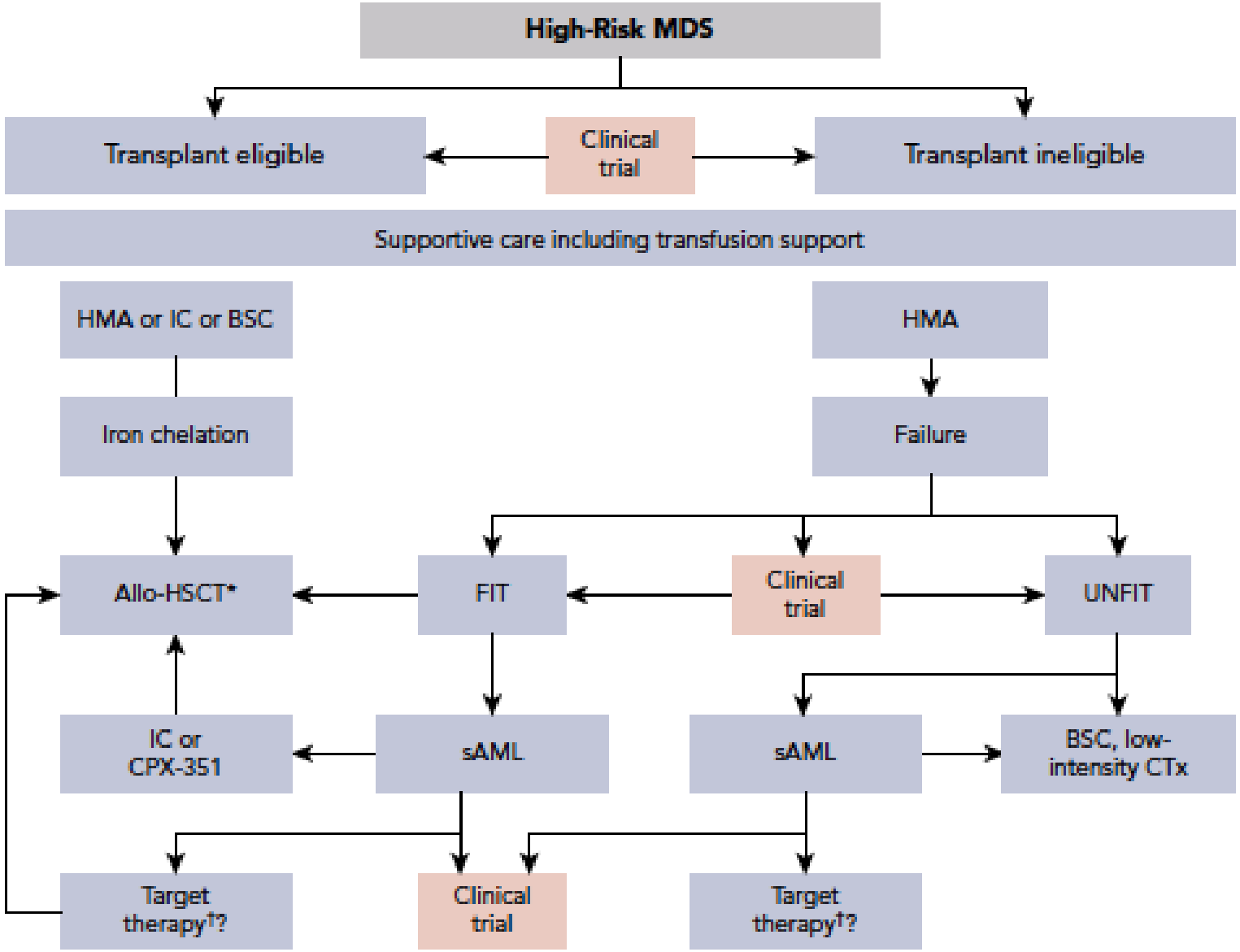
- MDS Patienten, die eine Indikation zur allo SCT haben sollten wenn möglich upfront ohne bridging Therapie transplantiert werden
- AZA bleibt Standardtherapie für HR MDS Patienten, die nicht für eine allo SCT geeignet sind
- Ansprechrate 50% mit Verlängerung des Überlebens und der Zeit bis zur AML Progression
- mediane Dauer bis zur Progression 14 Monate (AZA001 Studie)
- kein dauerhafter Therapieerfolg
- Gründe für Therapieversagen unklar
- Prognose nach AZA Versagen extrem ungünstig
- keine etablierte Standardtherapie nach AZA Versagen
- dringend innovative Studienkonzepte nötig
- Venetoclax sowie CPX351 zeigen ermutigende Ergebnisse in AML, Studien in MDS laufen

DANKE



- **TU Munich**
  - Mareike Verbeek
  - Sandra Eckert
  - Judith Hecker
  - Isabella Miller
- **AMLSG**
  - Hartmut Döhner
  - Konstanze Döhner
  - Arnold Ganser
  - Lars Bullinger
  - Peter Paschka
  - Michael Heuser
- **German MDS Study Group**
  - Ulrich Germing
  - Uwe Platzbecker
  - Wolf-Karsten Hofmann
  - Aristoteles Giagounidis
  - Detlef Haase
  - Felicitas Thol
- **MLL Lab Munich**
  - Torsten Haferlach

High Risk MDS



Platzbecker, Blood 2019