Bahnbrechendes vom ASH 2019

2. AML Symposium

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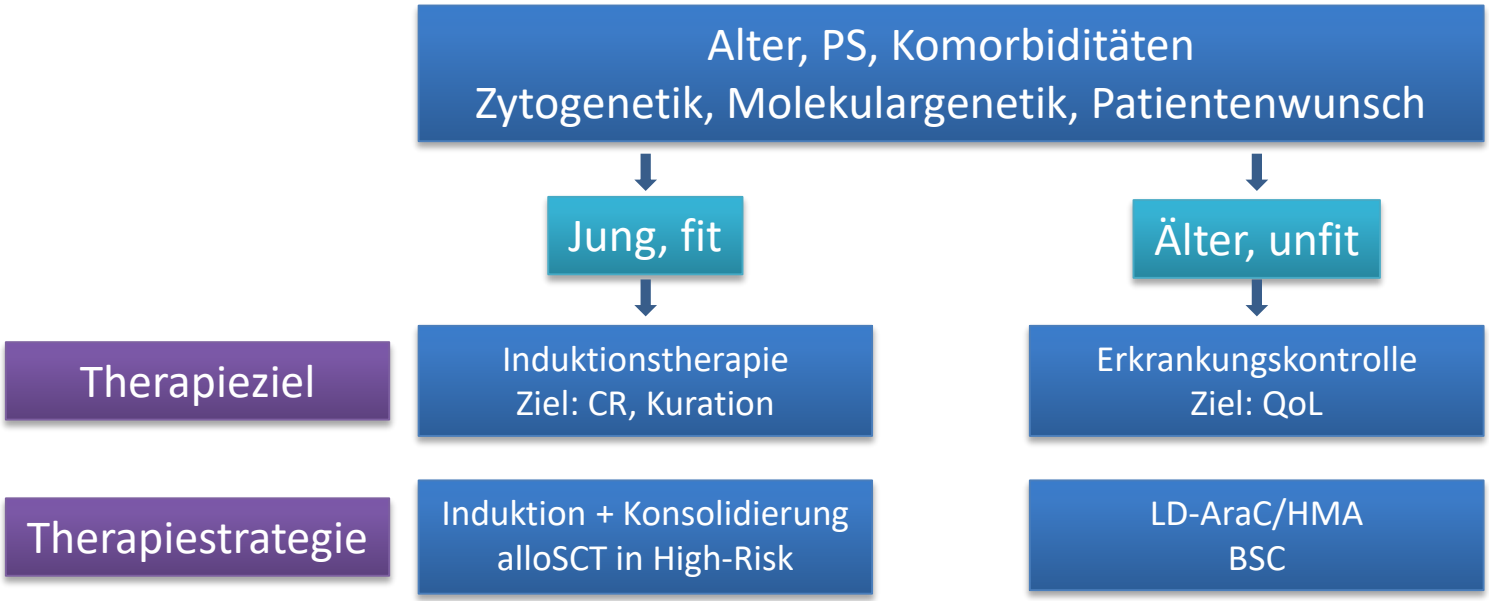
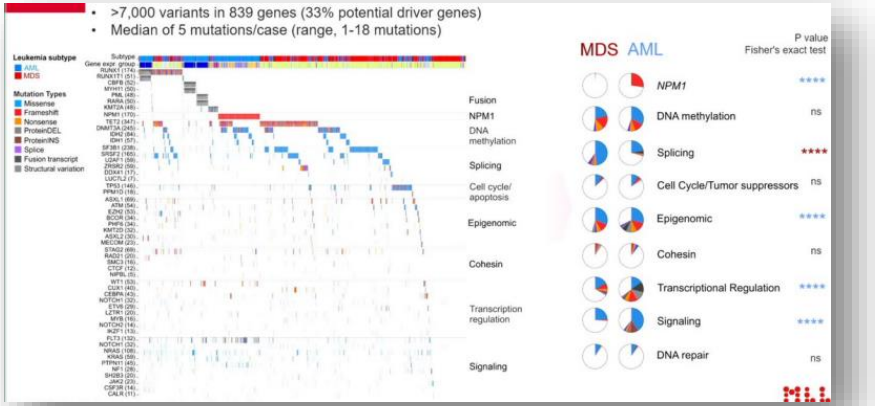
C A U Christian-Albrechts-Universität zu Kiel

AML Therapie - wo standen wir (noch vor 2 Jahren)

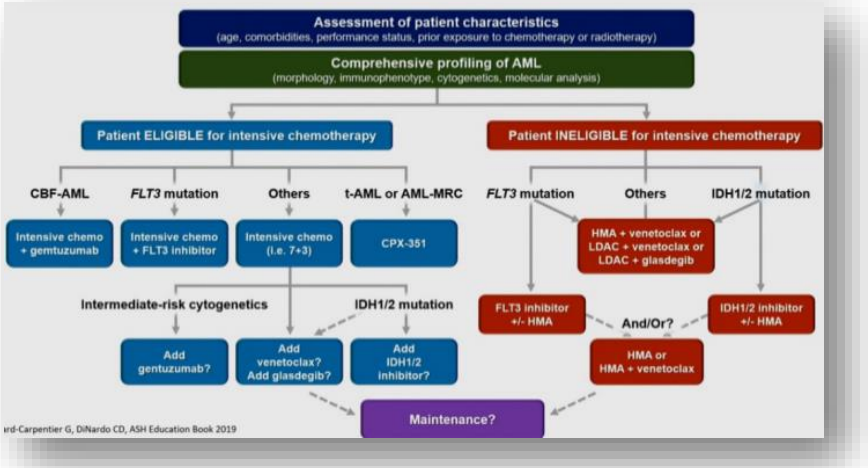


AML Therapie heute in 2020

1. Molekulare Diversität
Bedeutung der Molekularen Diagnostik



2. Einsatz von neuen Substanzen



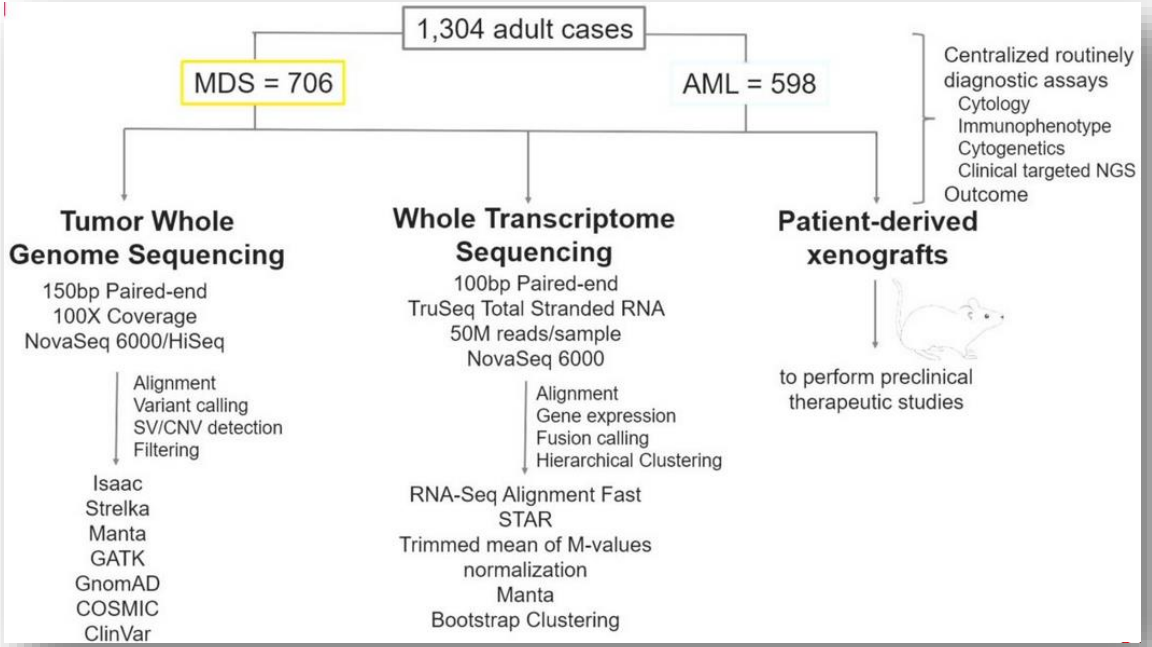
AML: MOLEKULARE DIVERSITÄT

LBA-4: Integrated Transcriptomic and Genomic Sequencing Identifies Prognostic Constellations of Driver Mutations in Acute Myeloid Leukemia and Myelodysplastic Syndromes.
Ilaria Iacobucci *et al.*

MDS/AML:
heterogene Erkrankungen mit Expansion klonaler transformierter Vorläuferzellen

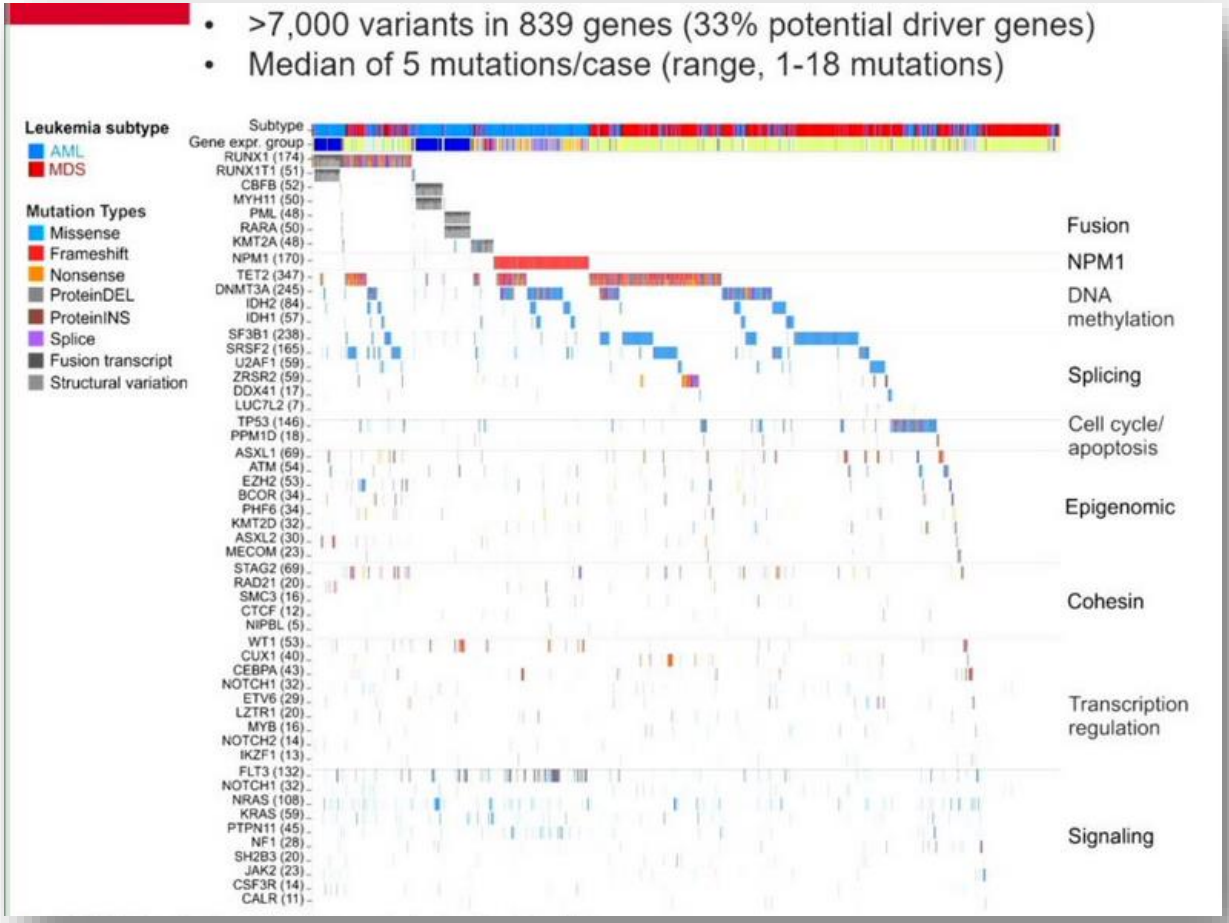
Blasten cut-off von 20%:
arbiträr

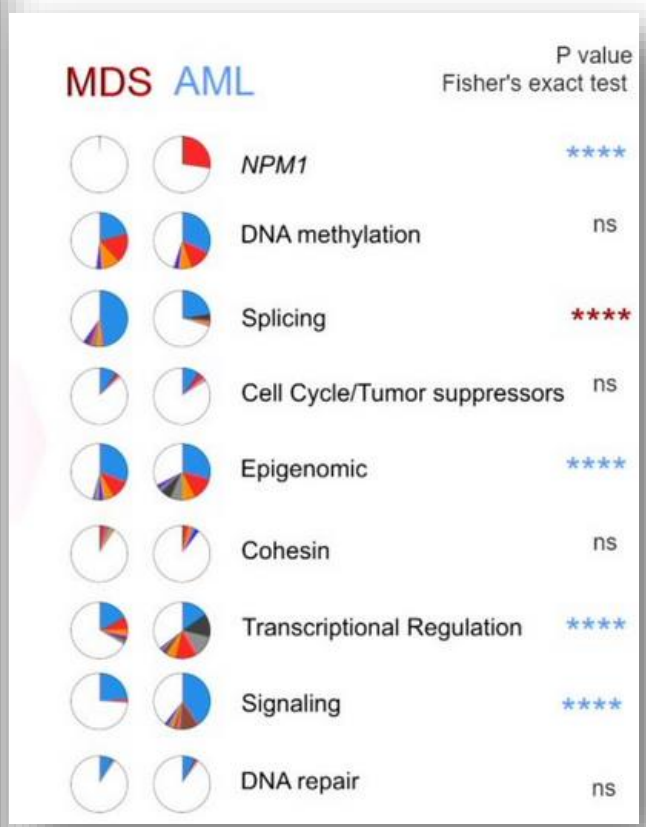
Ziel:
genomweite Analyse AML/MDS
Definition von Subgruppen mit klinischen/prognostischer Relevanz



AML/MDS Molekulare Charakterisierung

- >7,000 variants in 839 genes (33% potential driver genes)
- Median of 5 mutations/case (range, 1-18 mutations)

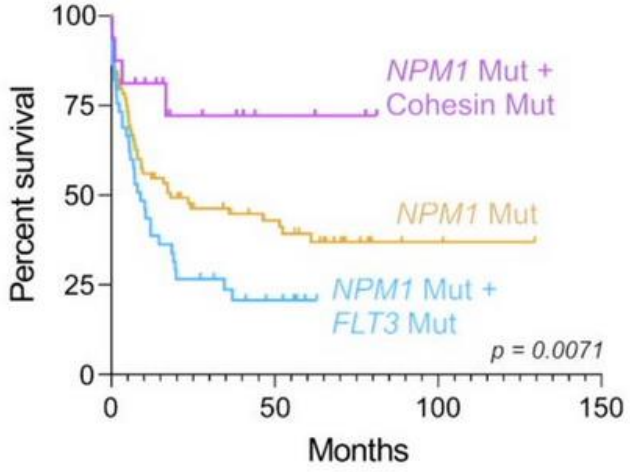




Prognostische Bedeutung: NPM1

- *NPM1* mutations accounted for 13% of all cases (27% of AML; 0.8% MDS)
- Frequent cooperating mutations in *DNMT3A, RAD21, SMC3, FLT3, PTPN11*

Combinatorial mutations of *NPM1* and cohesin, ± *FLT3*, conferred better outcome



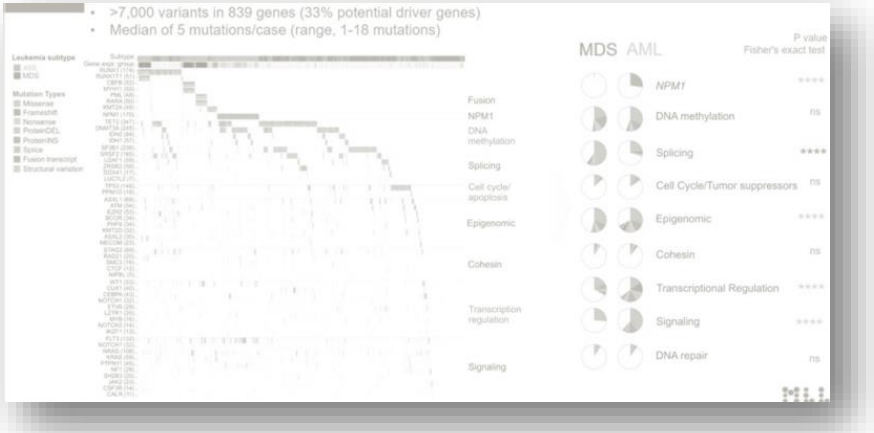
Take home

Molekulare Alterationen von prognostische Bedeutung

Beachtung der Ko-Mutationen!

AML Therapie heute in 2020

1. Molekularen Diversität
Bedeutung der Molekularen Diagnostik √



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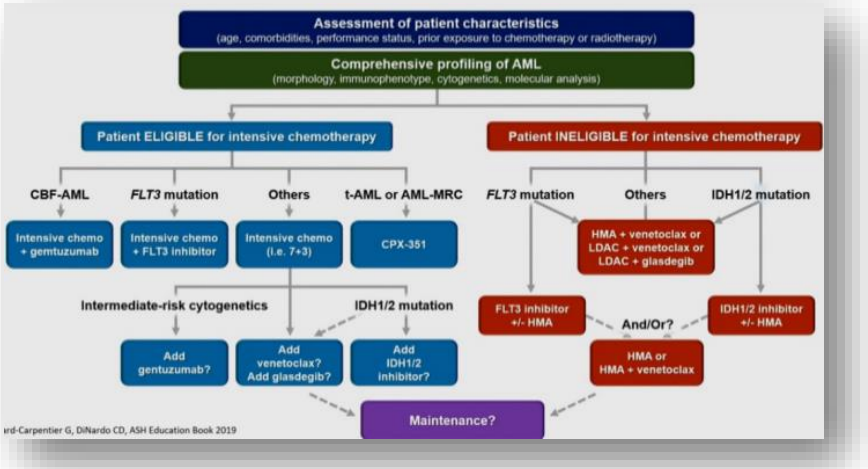
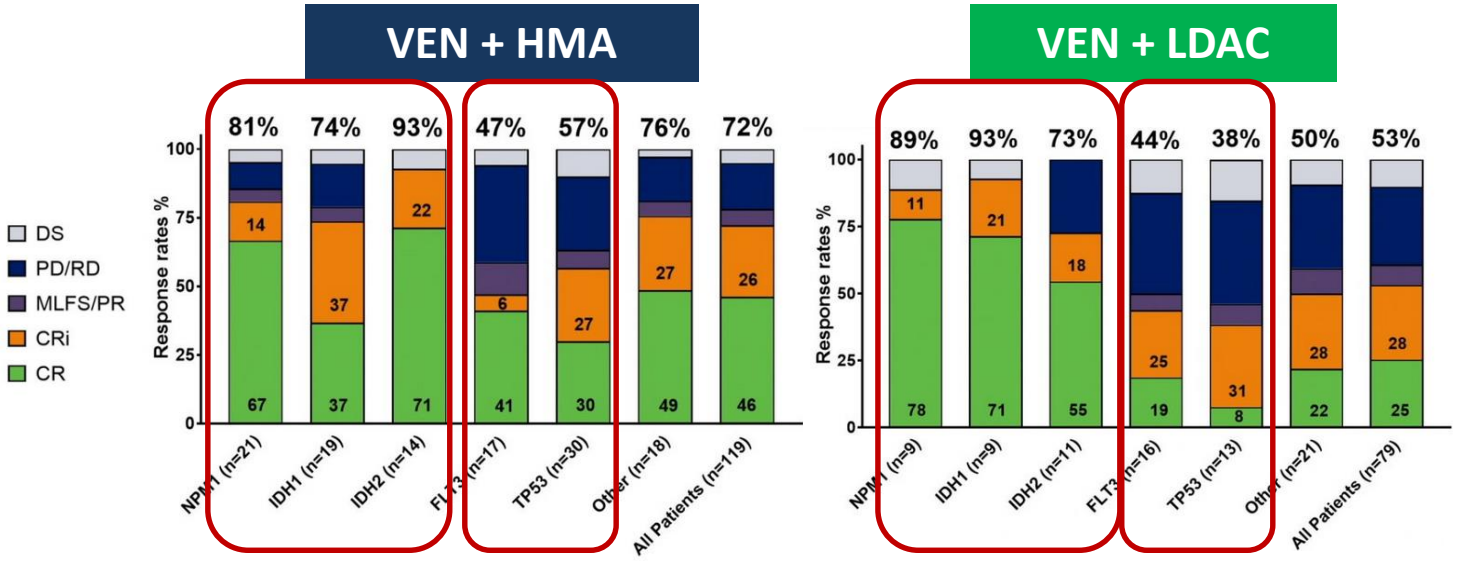


Frontline Venetoclax + LDAC/HMA

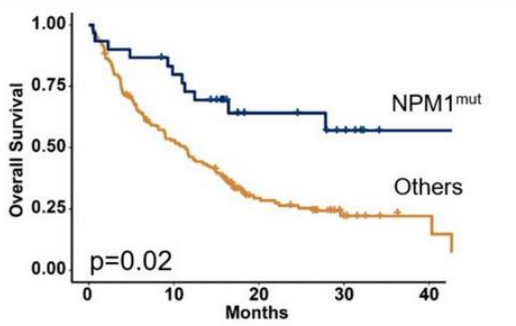
Blockbuster für alle molekularen Subgruppen?

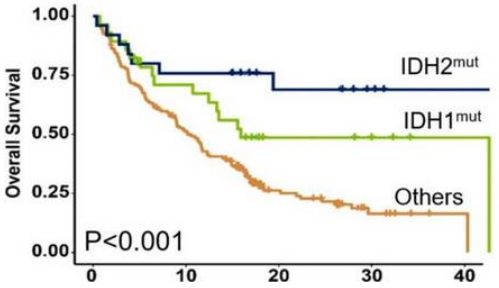
#546 Response to Venetoclax in Combination with Low Intensity Therapy (LDAC or HMA) in Untreated Patients with Acute Myeloid Leukemia Patients with IDH, FLT3 and Other Mutations and Correlations with BCL2 Family Expression

	Ven 400 mg+HMA (119/127 pts)	Ven 600 mg+LDAC (79/82 pts)
Recurrent AML aberrations NPM1, IDH1, IDH2, TP53 and/or FLT3	79 pts Ven+Aza 40 pts Ven+Dec*	79 pts Ven+LDAC
RNA expression of *BCL2* family genes in bone marrow aspirates with ≥ 50% blasts	28 pts Ven+Aza 14 pts Ven+Dec*	34 pts Ven+LDAC



VEN + HMA/LDAC in NPM1, IDH, FLT3, TP53





	Median OS, months (95% CI)	12 mo. est. of OS, % (95% CI)
NPM1 N = 30	NR (12.5, NR)	73 (53, 85)
IDH1 N = 28	15.9 (10.7, NR)	67 (46, 81)
IDH2 N = 25	NR (19.4, NR)	76 (54, 88)

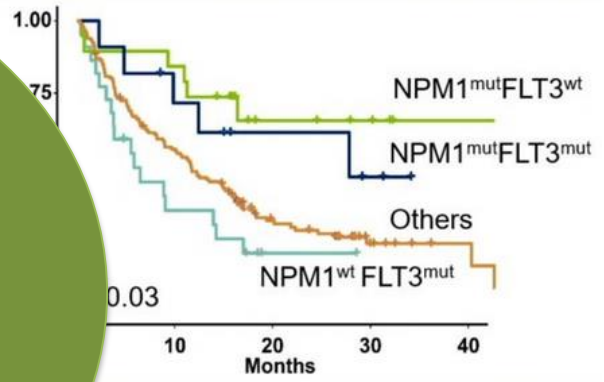
		(95% CI)
FLT3mut N = 33	9.9 (4.8, 17)	47 (29, 63)
TP53mut N = 43	6.4 (3.8, 8.9)	23 (11, 37)

Take home

Divergentes Ansprechen und Überleben in AML molekularen Subgruppen

Wichtig für weitere Therapieplanung!

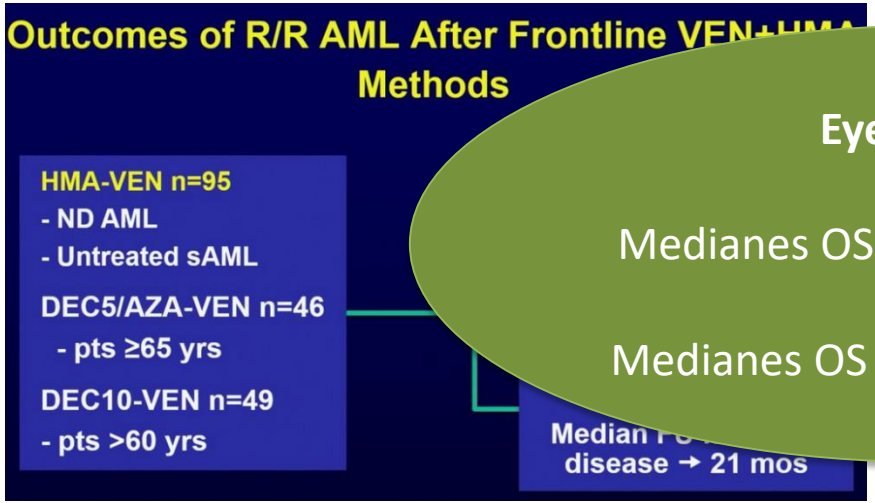
VEN + HMA/LDAC



	Median OS, months (95% CI)	12 mo. est. of OS, % (95% CI)
FLT3mut NPM1mut N = 11	27.8 (4.8, NR)	72 (35, 90)
FLT3mut NPM1wt N = 22	5.9 (3, 14)	35 (16, 54)
FLT3wt NPM1mut	NR (11, NR)	74 (48, 88)

Outcome von Venetoclax/HMA Versagern?

#738 Outcomes of Relapsed or Refractory Acute Myeloid Leukemia after Frontline Hypomethylating Agent with Venetoclax Regimens
MD Anderson

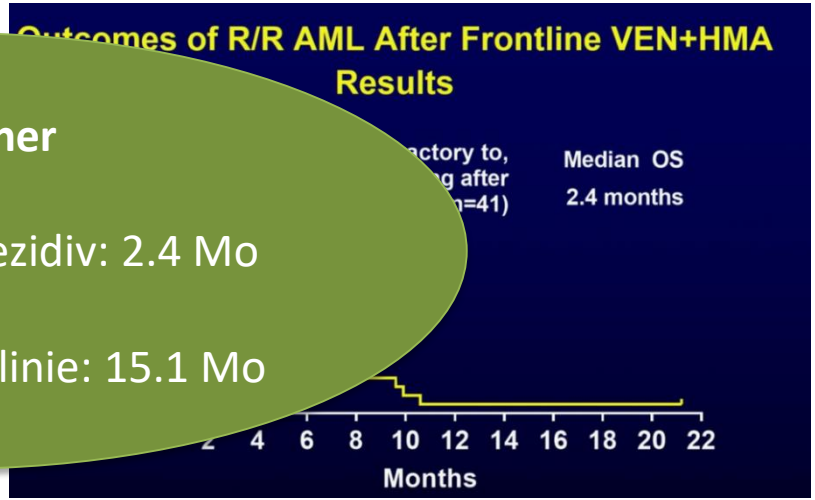


Eye opener

Medianes OS im Rezidiv: 2.4 Mo

vs

Medianes OS Frontlinie: 15.1 Mo



Sequenz Venetoclax -> SCT

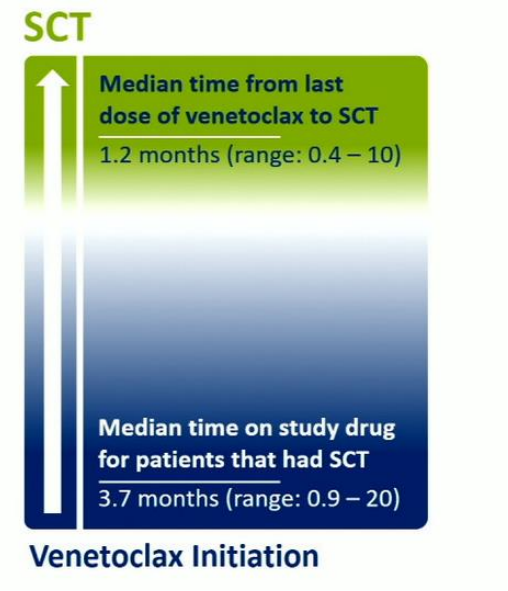
#264 Outcomes after Stem Cell Transplant in Older Patients with Acute Myeloid Leukemia Treated with Venetoclax-Based Therapies
Balitmore

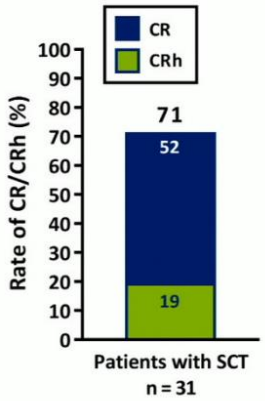
VEN-basierte Therapie als Chance zur kurativen SCT?

31/304 (10%) alloSCT
26/31 in CR/CRi

Characteristic	All Patients n = 304	SCT Patients n = 31
Treatment regimen, n (%)		
Venetoclax + azacitidine	127 (42)	19 (61)
Venetoclax + decitabine	85 (28)	11 (35)
Venetoclax + LDAC	92 (30)	1 (3)
Age, median (range)	74 (61–90)	69 (63–76)
Bone marrow blasts ≥50%, n (%)	123 (41)	13 (42)
Secondary AML, n (%)	100 (33)	9 (29)
ECOG performance score, n (%)		
0	50 (16)	10 (32)
1	176 (58)	11 (35)
2	74 (24)	10 (32)
Cytogenetic risk*, n (%)		
Intermediate	172 (57)	18 (58)
Adverse	123 (40)	12 (39)
Baseline mutations, n/N (%)		
TP53	49/218 (23)	3/18 (17)
FLT3	38/218 (17)	4/18 (22)
NPM1	34/218 (16)	6/18 (33)
IDH1/2	54/218 (25)	6/18 (33)

* 9 patients (3%) had no mitosis





Median time to best response	
CR/CRh	2.3 months (range: 0.9 – 7.1)
CR	2.8 months (range: 1.0 – 7.1)

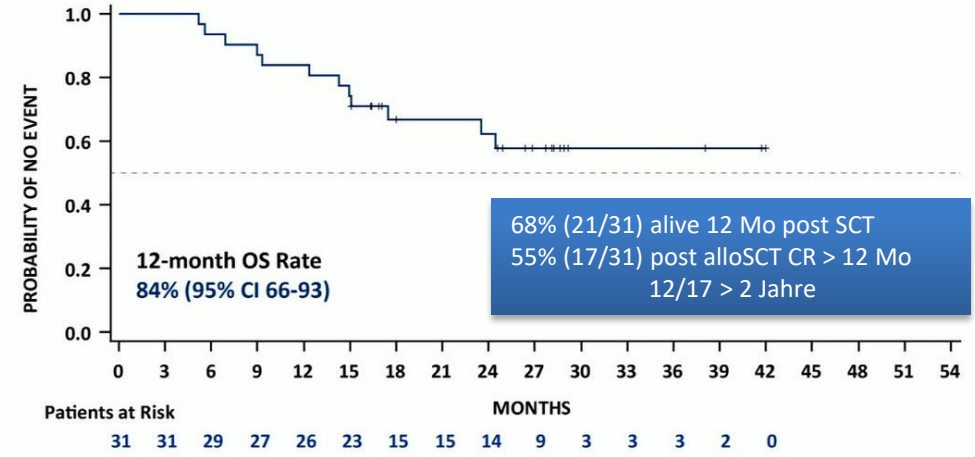
Best response prior to SCT, n (%)	SCT Patients n = 31
CR/CRi	**26 (84)**
CR	16 (52)
CRi	10 (32)
CRh	6 (19)
MLFS	2 (6)
RD	3 (10)

CR, complete response; CRi, CR with incomplete blood count; CRh, CR with partial hematologic recovery; MLFS, morphologic leukemia free state; RD, resistant disease

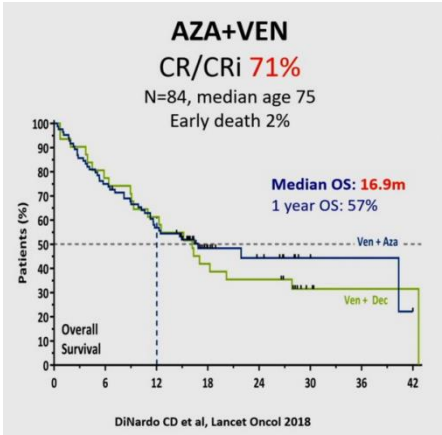
Take home

SCT nach VEN/HMA gut machbar

Kurative Option mit Langzeitüberleben



68% (21/31) alive 12 Mo post SCT
55% (17/31) post alloSCT CR > 12 Mo
12/17 > 2 Jahre



Immuntherapie AML

Zielstrukturen für Immuntherapie bei AML

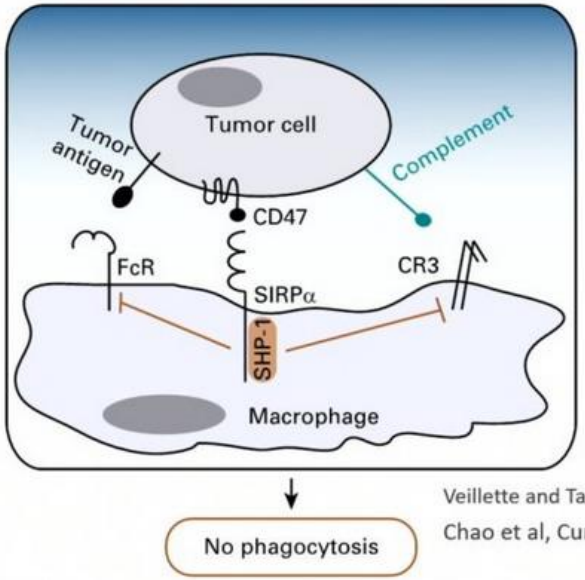
CD33 and CD123 agents:

- **IMGN632 (CD123) :** ADC with novel single strand alkylating payload
  - CR/CRi rate 17%, ORR 20% in n=66 evaluable AML pts *(Daver et al, ASH #734)*
- **Flotetuzumab (MGD006):** CD123xCD3 dual-affinity re-targeting (DART) molecule
  - CR/CRi 32% in n=30 primary refractory AML cohort *(Uy et al, ASH #733)*
- **AMG330 and AMG673** CD3xCD33
  - CR/CRi 15% in n=27 evaluable pts (AMG330)
  - *Subklewe et al, ASH #833 (AMG673)*
- **AMV564** CD3xCD33 bispecific
  - *Westervelt et al, ASH #834*
- **XmAb 14045** CD3xCD123 bispecific
  - CR/CRi rate 23% in Part A (Ravandi ASH 2018)

Other promising targets:

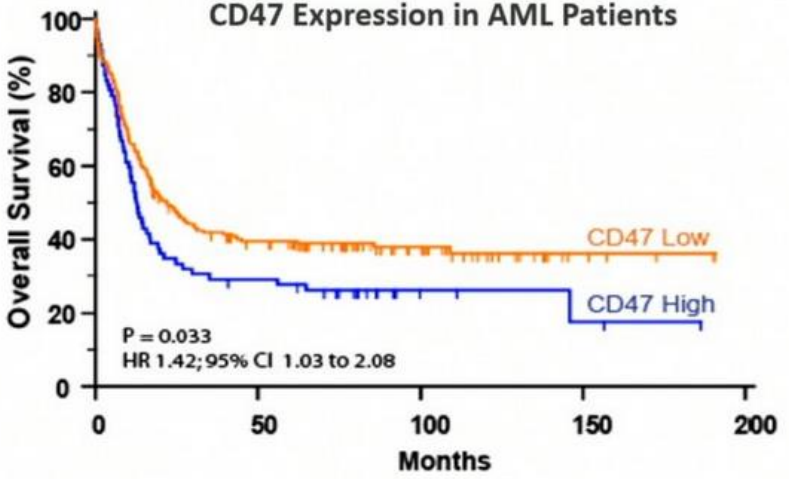
- **Cusatuzumab (ARGX-110): CD70 + AZA for Newly Dx Older AML**
  - CR/CRi 83% and ORR 92% in n=12 (Ochsenbein ASH 2018)
- **Magrolimab (5F9): CD47 + AZA**
  - CR/CRi 50% and ORR 69% in n=16 evaluable AML *(Sallman et al, ASH #569)*
- **MCLA-117: CD3 x CLL1**

Immuntarget: CD47 „Do not eat me“ Signal



Veillette and Tang, JCO 2019

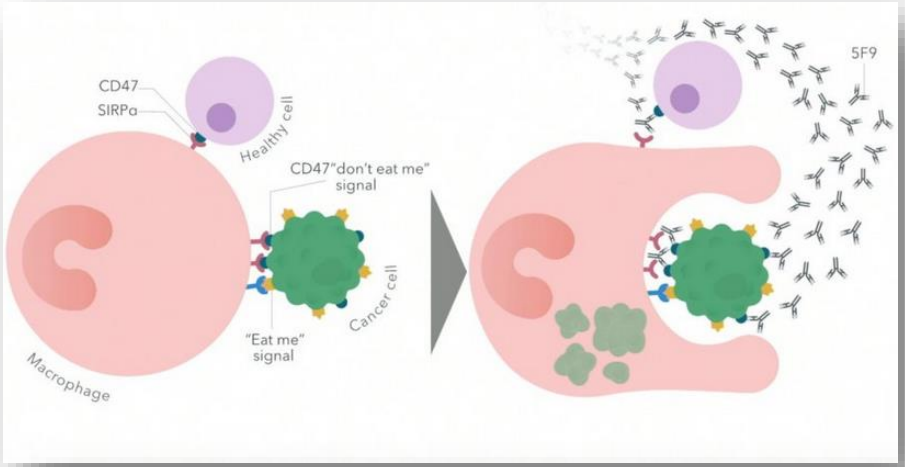
Chao et al, Current Opin Immunol 2012

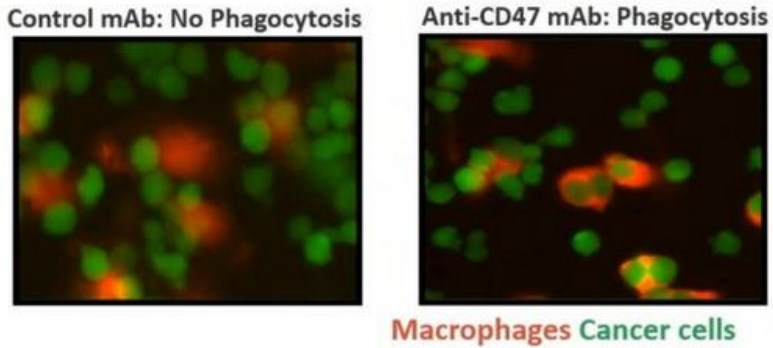


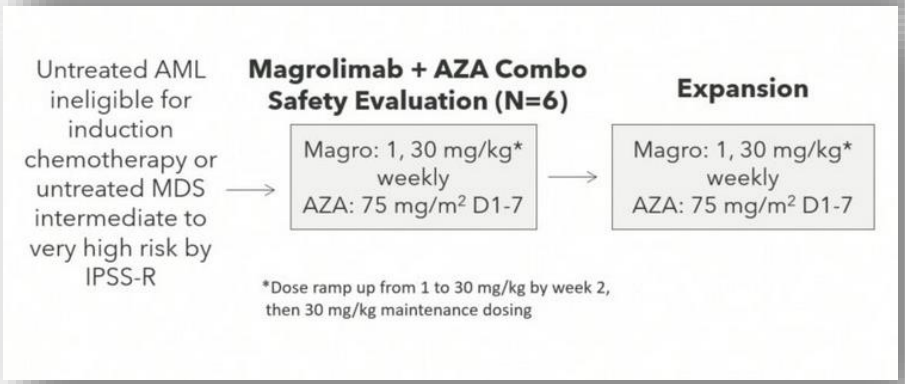
Majeti, Chao et al., Cell 2009

Immuntherapie: Anti-CD47 + HMA

 # 569: The First-in-Class Anti-CD47 Antibody Magrolimab (5F9) in Combination with Azacitidine Is Effective in MDS and AML Patients: Ongoing Phase 1b Results
Tampa, USA



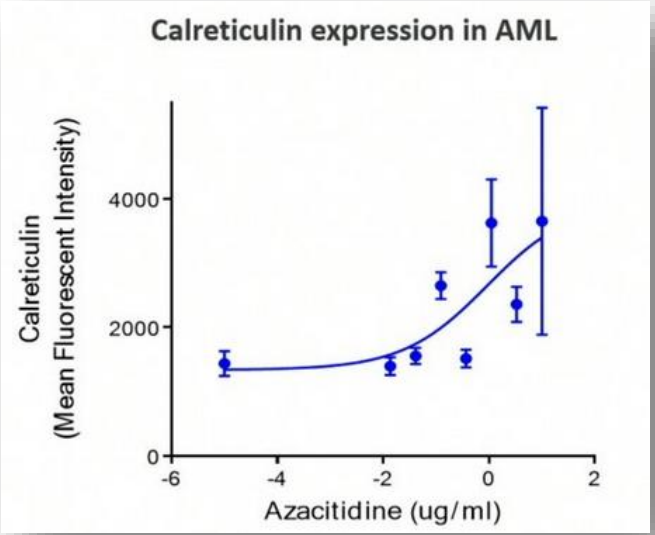


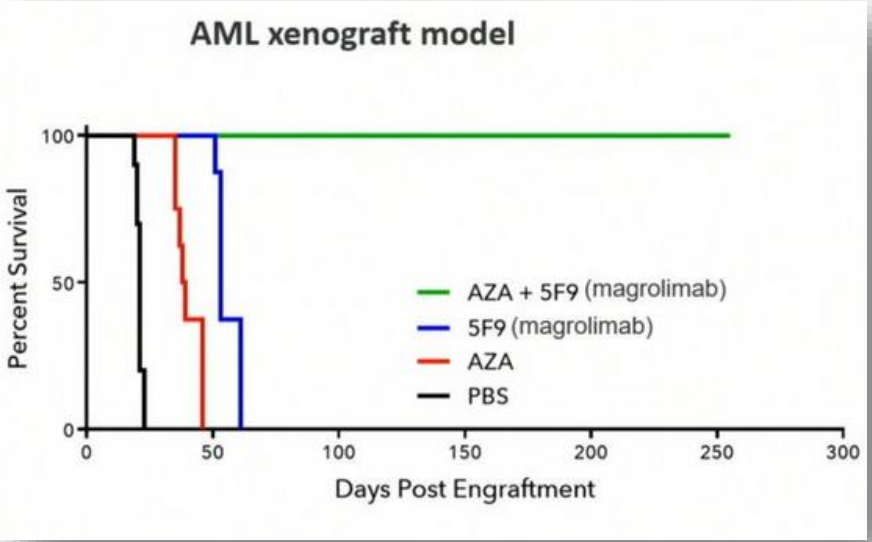


Magrolimab ist ein First-In-Class Antikörper gegen CD47
Pro-eat me nötig – exprimiert auf Tumorzellen
Phase 1 in r/r AML EHA 2018
Phase-1b: Magrolimab+AZA: MDS/AML-Patienten (n=62)

Synergie von Anti-CD47 + HMA im Mausmodel

Aza induziert pro-phagozytose Signale „eat-me“ wie Calreticulin
Aza + anti-CD47: verstärkte Phagozytose





Patient Characteristics (N=62): Magrolimab + AZA in Untreated (1L) MDS/AML

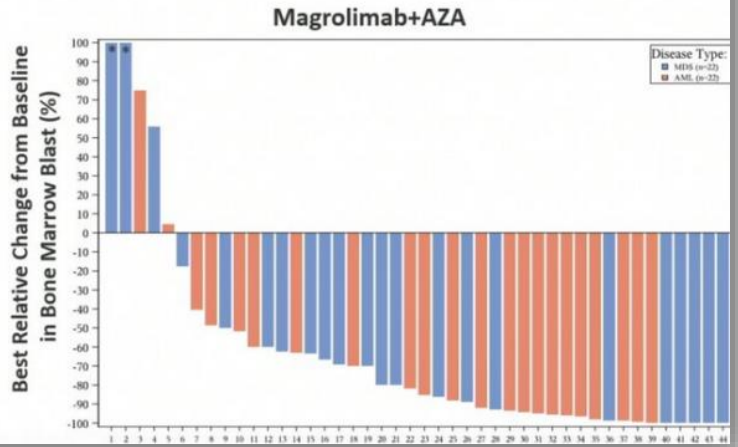
Characteristic	1L MDS 5F9+AZA (N=35)	1L AML 5F9+AZA (N=27)
Median age (range)	70 (47 – 80)	74 (60 – 89)
ECOG Performance Status: 0 1 2	13 (37%) 21 (60%) 1 (3%)	9 (33%) 16 (59%) 2 (7%)
Cytogenetic Risk: Favorable Intermediate Poor Unknown/missing	0 10 (29%) 23 (66%) 2 (6%)	0 2 (7%) 18 (67%) 7 (26%)
WHO AML classification: MRC Recurrent abnormalities Therapy-related NOS	-	19 (70%) 2 (7%) 1 (4%) 5 (19%)
WHO MDS classification: RS and single/multi-lineage dysplasia Multilineage dysplasia Excess blasts Unclassifiable/unknown/missing	 3 (9%) 6 (17%) 19 (54%) 7 (20%)	-
IPSS-R (MDS): Intermediate High Very High Unknown/missing	11 (31%) 18 (51%) 5 (14%) 1 (3%)	-
Therapy-related MDS Unknown/missing	11 (31%) 1 (3%)	-
Harboring a *TP53* mutation	4 (11%)	11 (41%)

- 66-67% of MDS and AML patients are poor cytogenetic risk
- 70% of AML patients have underlying myelodysplasia (MRC)
- 41% of AML patients are *TP53* mutant
- 31% of MDS patients are therapy-related
- The majority of MDS patients were high or very high risk by IPSS-R

IPSS-R: revised international prognostic scoring system
MRC: myelodysplasia-related changes
NOS: not otherwise specified
WHO: world health organization
"-" not applicable; All patients enrolled on study are shown

Anti-Leukemic Activity is Observed with Magrolimab + AZA in MDS and AML

Best Overall Response	1L MDS N=24	1L AML N=22
ORR	22 (92%)	14 (64%)
CR	12 (50%)	9 (41%)
CRi	-	3 (14%)
PR	0	1 (5%)
MLFS/ marrow CR	8 (33%) 4 with marrow CR + HI	1 (5%)
Hematologic improvement (HI)	2 (8%)	-
SD	2 (8%)	7 (32%)
PD	0	1 (5%)



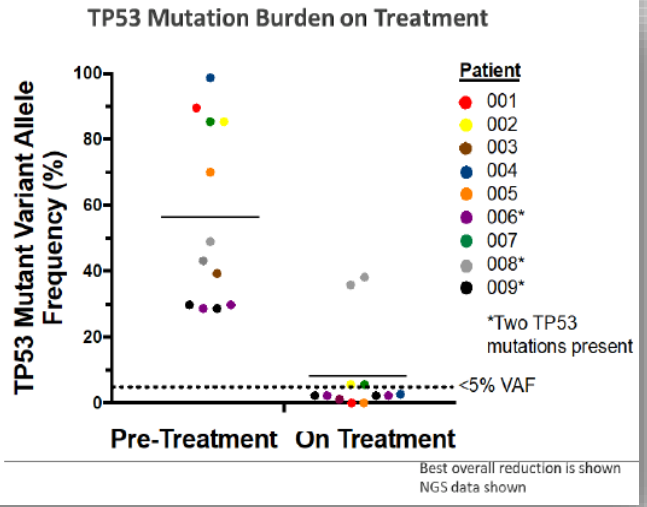
ORR: 92% in MDS
ORR: 64% in AML

Ansprechen: median 1.9 Mo

Efficacy in *TP53* Mutant AML Patients

Best Overall Response	AML *TP53* Mutant (N=9)
ORR	7 (78%)
CR	4 (44%)
CRi	3 (33%)
Complete cytogenetic response in responders*	4/6 (67%)
MRD negative of responders	4/7 (57%)
Median duration of response (months)	Not reached (0.03+ – 15.1+)
Median overall survival (months)	Not reached (3.8+ – 16.9+)
Median follow-up [range] (months)	6.9 [1.9 – 16.9]

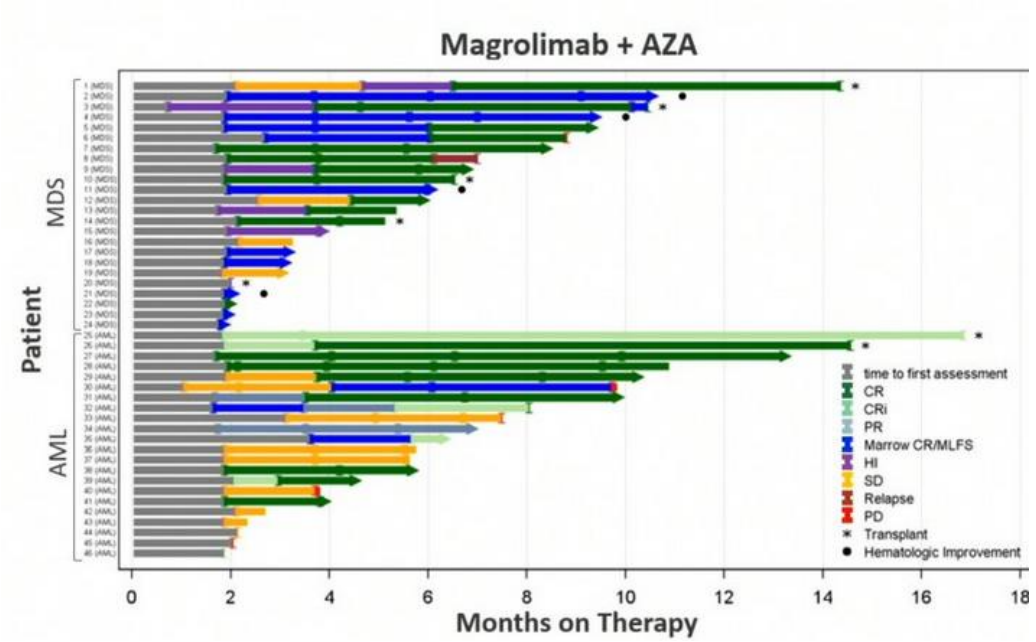
*For patients with abnormal cytogenetics at baseline



AML TP53 mut:
57% MRD neg in TP53mut
OS in TP53 not reached

(Ven-Aza: ORR 47%, OS 6.4 Mo)

Parameter	1L MDS N=24	1L AML N=22
RBC transfusion independence[1]	4/9 (44%)	8/11 (73%)
Complete cytogenetic response in responders[2]	5/19 (26%)	6/10 (60%)
MRD negativity in responders	5/22 (23%)	8/14 (57%)
Median duration of response (months)	Not reached (0.03+ – 9.76+)	Not reached (0.03+ – 15.1+)
Median follow-up [range] (months)	6.4 [2.0 – 14.4]	8.8 [1.9 – 16.9]



Immuntherapie: Anti-CD47 + HMA

Magrolimab: first in class AK gegen CD47

Kombinationstherapie gut verträglich

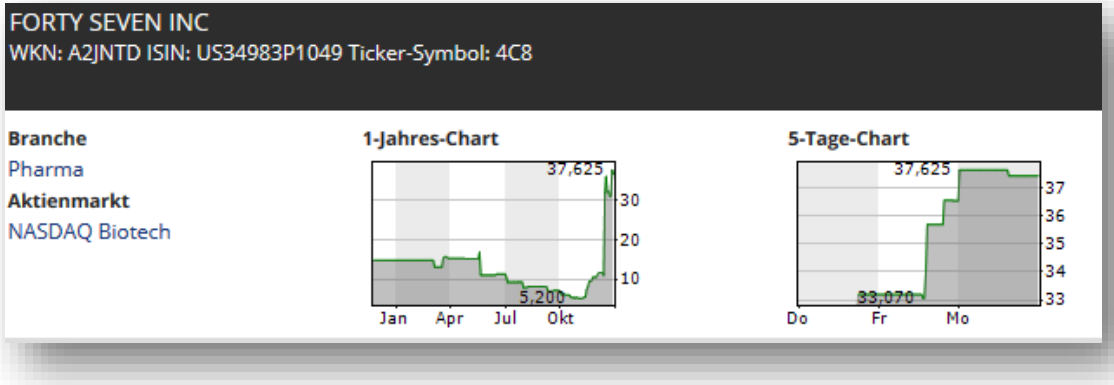
MDS ORR 92%, CR: 50%

AML ORR 64%, CR/CRi: 55%; v.a. in TP53 mut (78% CR/CRi)

Erweiterungskohorten (NCT03248479) laufen

Zulassungsstudien für MDS eingeleitet

Aktienverlauf am Tag der Präsentation



CAR-T über den Tellerrand geschaut
(noch ohne AML)

CAR-T in r/r ALL

 # 224: Analysis of Factors Predicting Treatment Response of 254 Patients Who Received CD19-Targeted CAR-T Cell Therapy for Relapsed/Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (B-ALL).
Xian Zhang *et al*., Bejing, China.

Monozentrisch Lu Daopei Hospital
Patienten: **n=254** R/R B-Vorläufer-ALL
Zeitraum: **4/2017 – 9/2019**
Follow-up 11 mo
Kinder und Erwachsene (1-61 Jahre)
CAR-T-Zellen von **5 Herstellern** (90% 4-1BB basiert, 10% CD28)
Mediane Dosis: $3x10^5$/kg

NGS Screening auf Mutationen
Uni- und multivariate Analyse

Frage: Identifizierung von Prädiktiven Markern für das Therapieansprechen

Ansprechen - CAR-T in r/r ALL

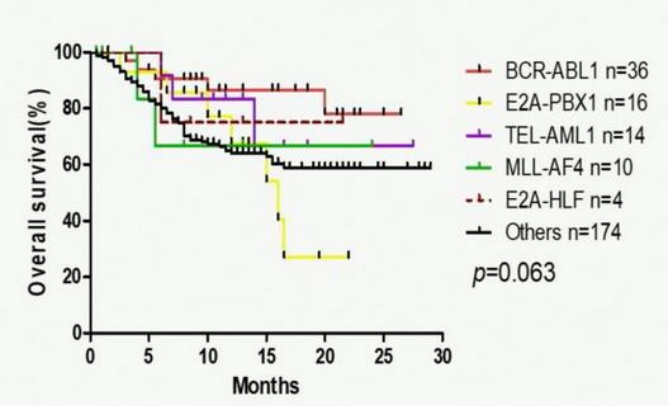
Tag 30 CR Rate 90.6 % (230/254)

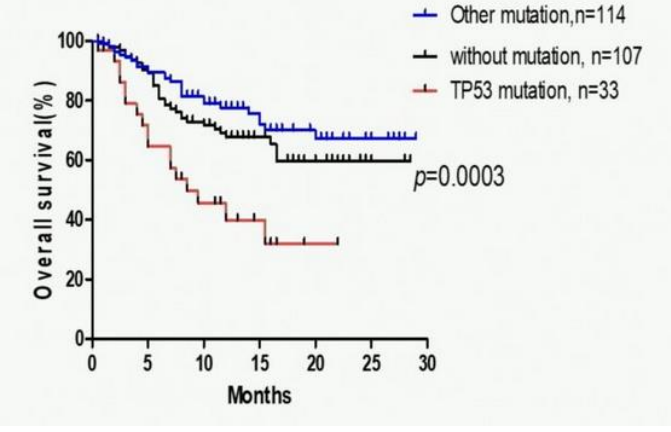
MRD neg (89.4%; 227/254)

Vortherapie keinen Einfluss (SCT, Chemo)

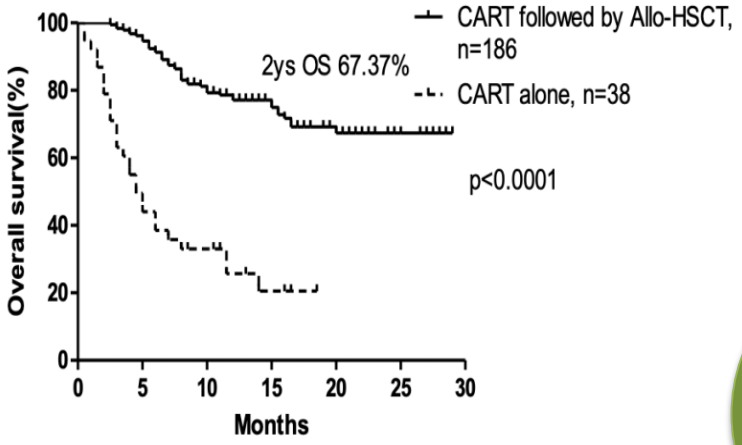
Bessere CR Rate in 4-1BB (92% vs 77%)

Multivariate analysis of CR rate post CAR-T			
Efficacy of CAR-T(NR/CR)	Wald	P value	Exp(B) (95%CI)
Male vs. female	5.815	0.006	0.232(0.082-0.652)
TP53 mutation vs. No mutations	4.408	0.025	4.511(1.295-16.895)
BM blasts≤20% vs. >20%	13.847	<0.001	0.095(0.022-0.260)
Neurotoxicity Grade 0-1 vs. grade 2-4	12.316	0.003	34.796(3.232-374.659)
CAR-T co-stimulatory domain CD28 vs. 4-1BB	5.957	0.007	7.141(1.722-29.612)





Outcome CAR-T +/- alloSCT



High risk factors predicting NR:
Female gender
BM blasts >20%
With a TP53 mutation
CAR-T with a CD28 co-stimulatory domain

High risk factors for lower OS and LFS:
Not bridging into Allo-HSCT,
With a TP53 mutation,
Severe CRS and CAR-T related neurotoxity

Take home

China: CAR-T global player
Erste Daten für Biomarker

alloSCT in r/r ALL:
bisher hier nicht als stand-alone

BITE (post CAR-T) - Mosunetuzumab in NHL

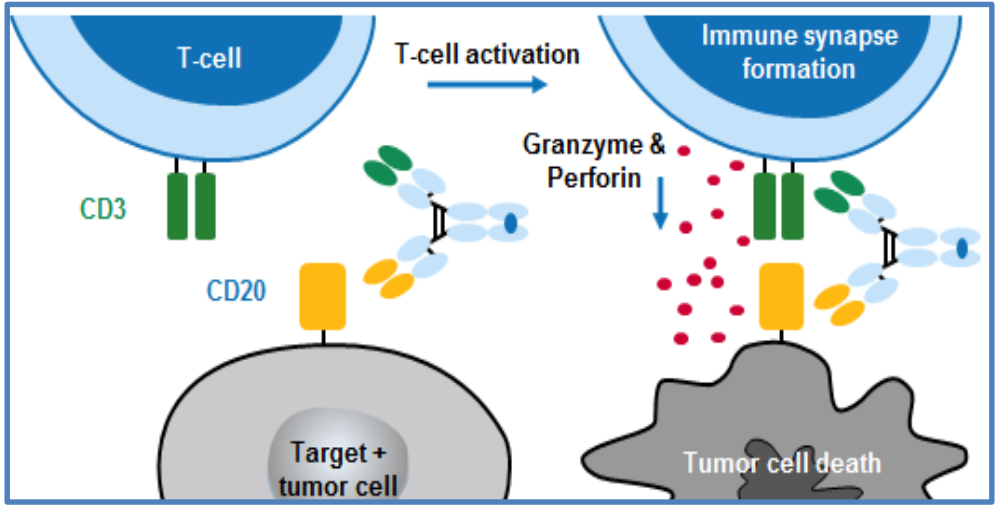
Mosunetuzumab (RG7828; BTCT4465A)

Full-length, fully humanized IgG1 bispecific antibody

Phase I/Ib dose-escalation and expansion study in heavily pre-treated R/R B-cell NHL

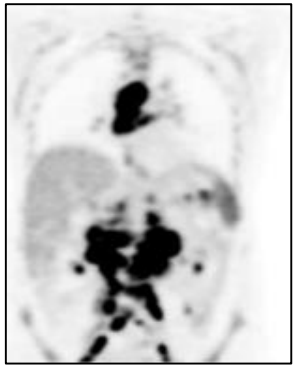
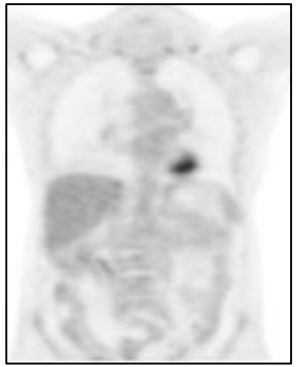
270 R/R B-cell NHL pts, incl. 30 pts with prior CAR-T

Aggressive NHL: ORR 37.1%; Indolente NHL: ORR 82.7%



6 Mosunetuzumab Induces Complete Remissions In Poor Prognosis Non-Hodgkin Lymphoma Patients, Including Those Who Are Resistant To Or Relapsing After Chimeric Antigen Receptor T-cell (CAR-T) Therapies, And Is Active In Treatment Through Multiple Lines (ASH 2019)

Mosunetuzumab post CAR-T in NHL

	Day -12 (baseline)	After Cycle 3 of mosunetuzumab
		
CAR-T PCR:	≤50 copies/µg DNA	380 copies/µg DNA

8 months in CR off treatment

BITEs + CARs:

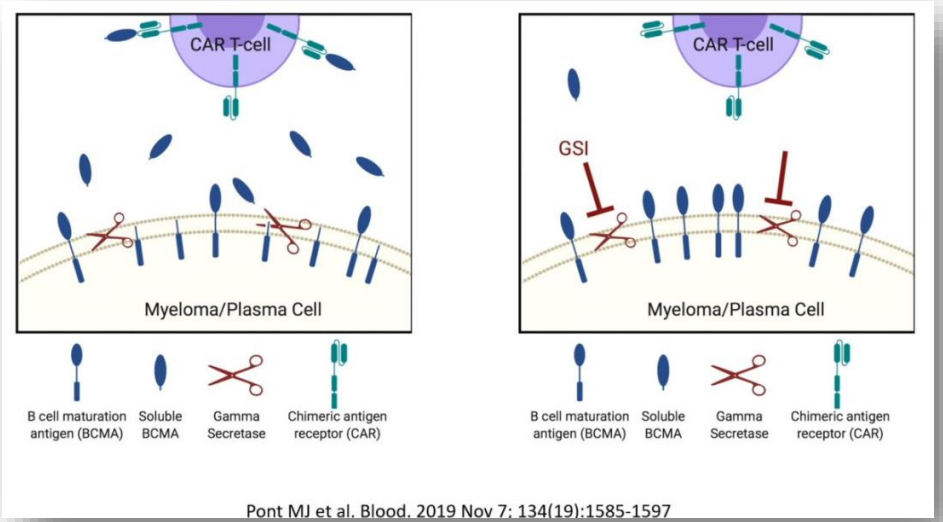
„Reaktivierung“ von CAR-T Zellen

CAR-T für Myelom

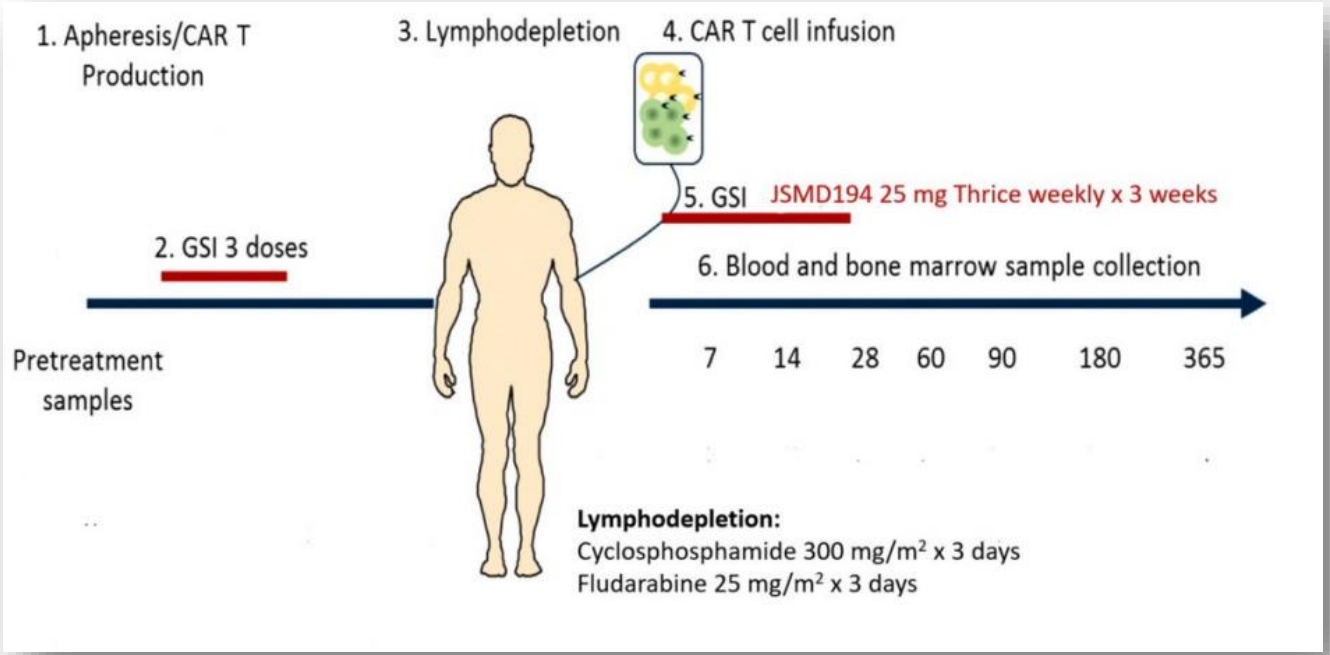
Problem für CAR-T im MM:
Ansprechen meist unvollständig und kurzfristig, die meisten Patienten bekommen innerhalb 1 Jahres ein Rezidiv

Gamma-Sekretase Inhibitoren (GSI)
erhöhen BCMA Oberflächenexpression, vermindern lösliche BCMAs
verstärken Wirksamkeit von BCMA CAR T-Zellen in experimentellen Modellen

Option?
Gabe von BCMA CAR T-Zellen gemeinsam mit einem oralen Gamma-Sekretase-Inhibitor



Pont MJ et al. Blood. 2019 Nov 7; 134(19):1585-1597



#204: Efficacy and Safety of Fully Human BCMA CAR T Cells in Combination with Gamma Secretase Inhibitor to Increase BCMA Surface Expression in Patients with Relapsed or Refractory Multiple
Seattle, USA

N=10 Patienten
Nach 3 Gaben von GSI: Erhöhung der BCMA Expression/Intensität

Kombination GSI + BCMA CAR-T: schnelles Therapieansprechen
bessere Wirksamkeit auf BCMA-CAR-T-Zellen (100% ORR)
Längeres Follow-up nötig für Dauer des Therapieansprechens

Best of ASH 2019

Umfangreiche molekulare Testung bei Akuten Leukämien notwendig, therapie-relevant und zeitunproblematisch

Kombinationstherapien (mit Ven, IDH,..) sind „best SOC“

Immuntherapie bei AML: spannende Option

CAR-T: Trend zu Kombinationen (BITE, Ibrutinib, GSI, PDL1,..)

Vielen Dank für die Aufmerksamkeit