Höhepunkte des Amerikanischen Krebskongresses

Akute Leukämien, MDS

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15. Januar 2020

Universitätsklinikum Tübingen

Akute lymphatische Leukämie

- **Blinatumumab in früheren Therapielinien einschließlich Erstlinientherapie**

➢ Erstlinientherapie bei Erwachsenen mit Ph+ ALL, chemotherapiefrei Dasatinib + Blinatumumab (Brown et al.)

➢ Kindliche ALL im 1. Rezidiv, Blinatumumab der Chemotherapie überlegen (Chiaretti et al.)

- **Neue Substanzen: Venetoclax und Navitoclax**

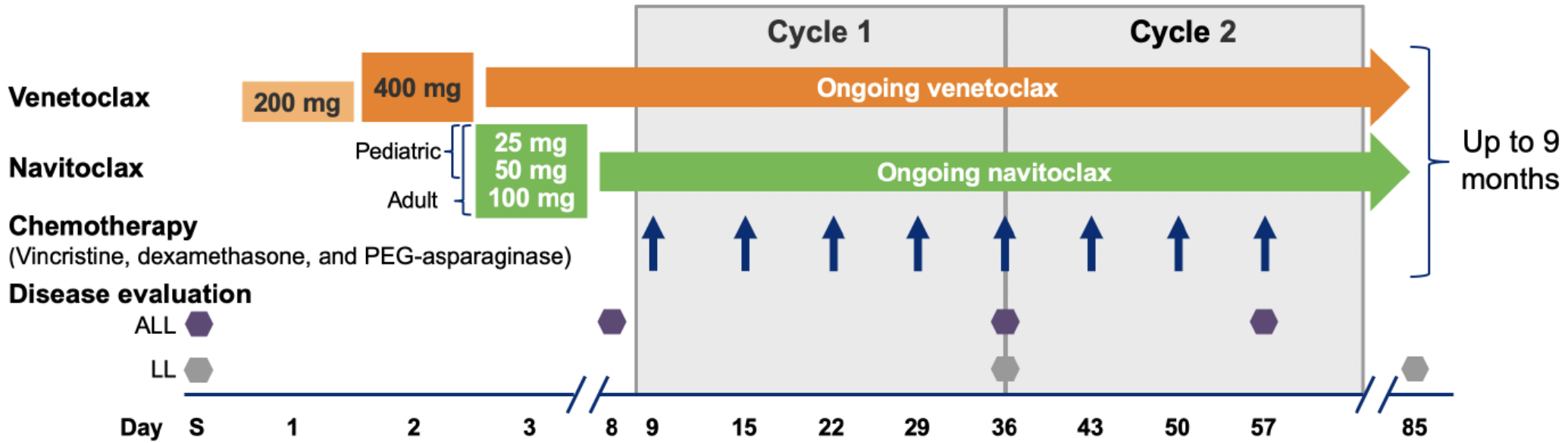
➢ Venetoclax (Ven): hoch-selektiver BCL-2 Inhibitor

➢ Navitoclax (Nav): BCL-2/BCL-XL/BCL-W-Inhibitor

➢ Ven+Nav zeigte bei 32 ALL-Patienten gute Toleranz, keine unerwartete Toxizität und vielversprechende, vorläufige Wirksamkeit (EHA 2019. Abstr #PS940)

➢ Vorstellung der Ergebnisse von Ven+Nav plus Chemotherapie bei 36 Patienten mit ALL oder LLy

M16-106 Studiendesign



Endpoints
Primary: Incidence of dose-limiting toxicities (DLTs), safety, and pharmacokinetics of venetoclax + navitoclax with chemotherapy
Secondary: Antitumor activity, patients proceeding to stem cell transplantation or CAR-T cell therapy

M16-106 Patientencharakteristika und Ergebnisse

Characteristic	Total (N=45)
Median age, y (range)	29 (6-72)
Diagnosis, n (%)	
B-ALL	24 (53)
T-ALL	18 (40)
LL	3 (7)[a]
ECOG performance status 0-2, n (%)	27[b] (100)
Median baseline BM blasts, % (range)	31 (0-99)
Median prior therapies, n (range)	4 (1-10)
Median time since last therapy, mo (range)	2 (0.1-21)
Median time on study, mo (95% CI)	8 (6-12)

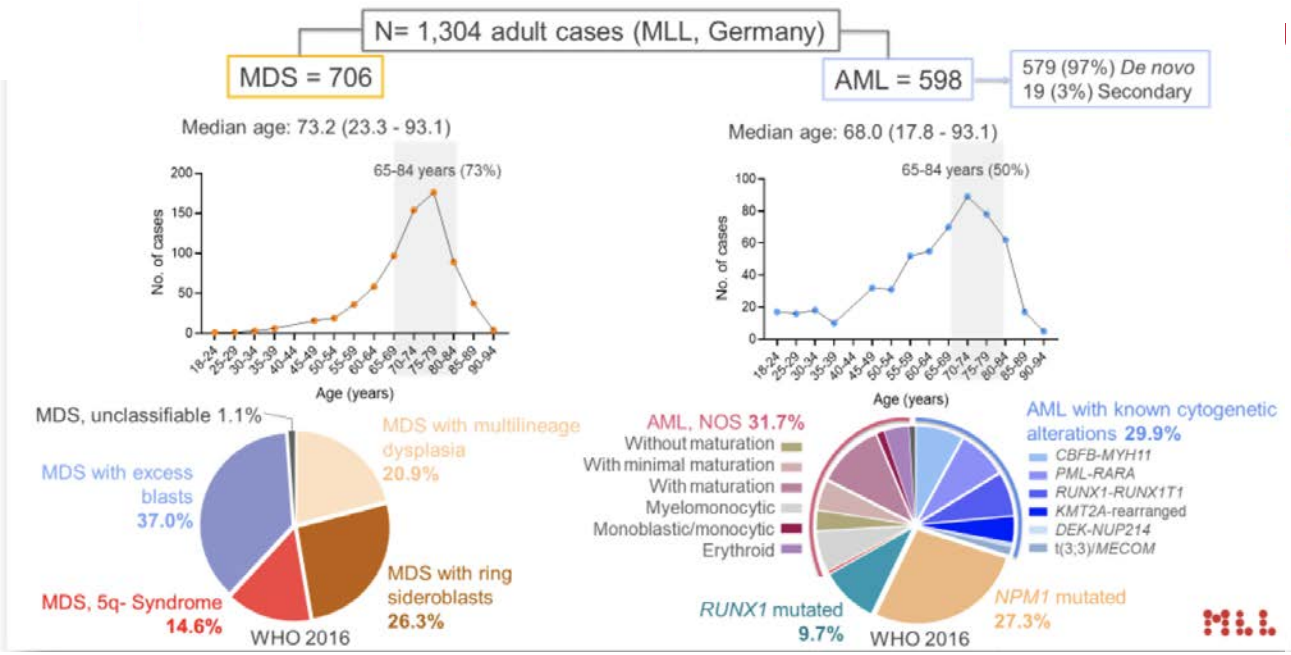
- Many patients had failed prior cellular therapies or immunotherapies
  - Of patients with B-ALL:
    - 50% had prior blinatumomab
    - 29% had prior inotuzumab
    - 29% had prior CAR-T
  - 1 patient with T-ALL had received prior daratumumab
  - 30% of all patients had received prior stem cell transplant

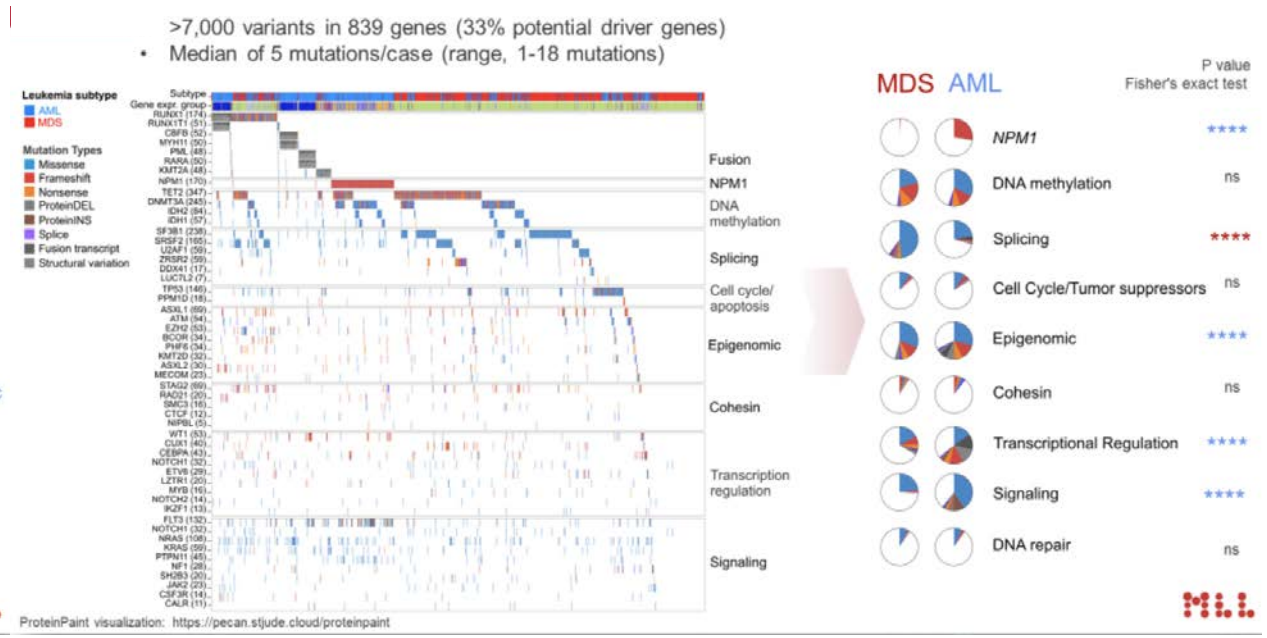
- Ven+Nav in Kombination mit Chemotherapie gut toleriert
- Vorläufige Wirksamkeit von Ven+Nav in dieser stark vorbehandelten Patientengruppe vielversprechend

Response	B-ALL (n=24)	T-ALL (n=18)	LL (n=3)	Total (N=45)
CR/CRi/CRp, n (%)[a]	**13 (54)**	**7 (39)**	**2 (67)**	**22 (49)**
CR	6 (25)	2 (11)	2 (67)	10 (22)
CRi	3 (13)	3 (17)	0 (0)	6 (13)
CRp	4 (17)	2 (11)	0 (0)	6 (13)
PR, n (%)[a]	3 (13)	0 (0)	1 (33)	4 (9)
MRD-negative CR/CRi/CRp in ALL, n (%)[b]	8 (33)	4 (22)	N/A[b]	12 (29)[b]
Median time to first response, mo (range)	1.1 (0.3-3.4)	1.1 (0.2-3.5)	1.2 (0.7-1.2)	1.2 (0.2-3.5)
Median DOR, mo (95% CI)[c]	9.1 (1.5-14.6)	4.2 (1.9-12.3)	NR (1.1-NE)	9.1 (1.9-11.5)
Median OS, mo (95% CI)	9.7 (4.0-15.7)	6.6 (3.3-12.5)	NR (2.1-NE)	9.7 (4.3-10.3)
Proceeded to SCT or CAR-T, n (%)	6 (25)	3 (17)	2 (67)	11 (24)

Akute myeloische Leukämie und Myelodysplastisches Syndrom

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





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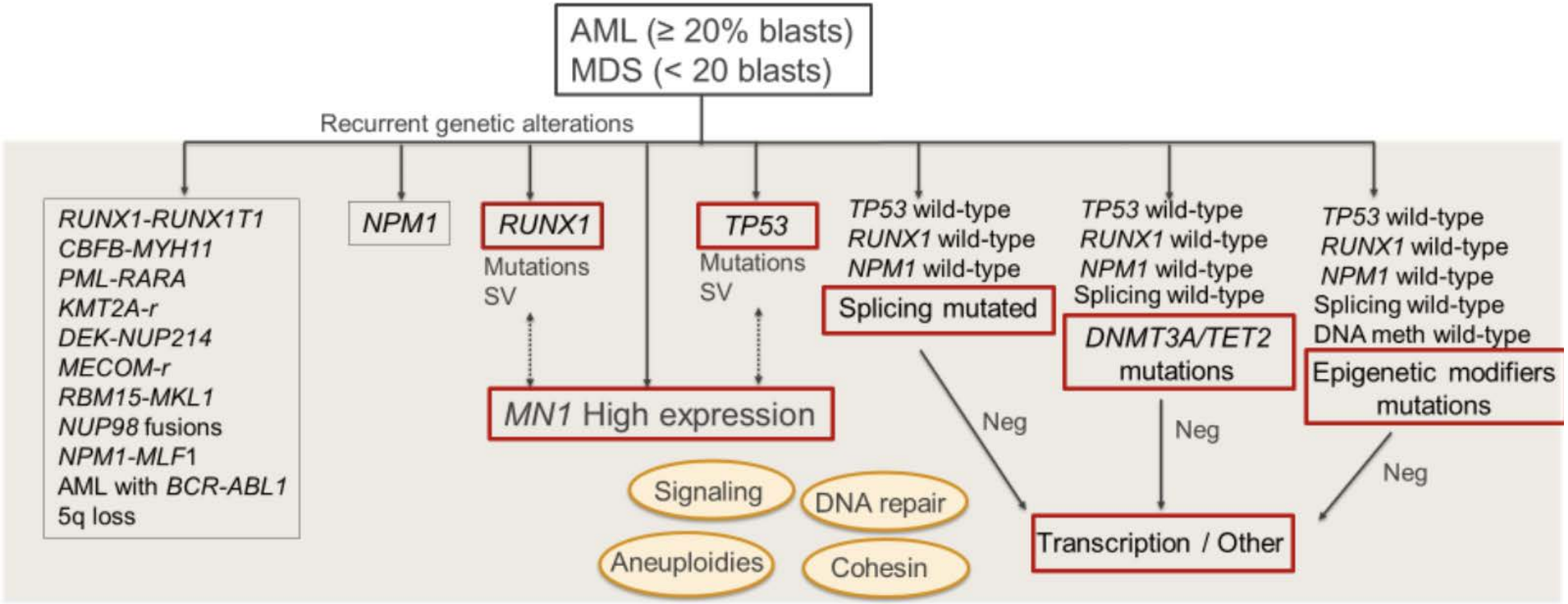
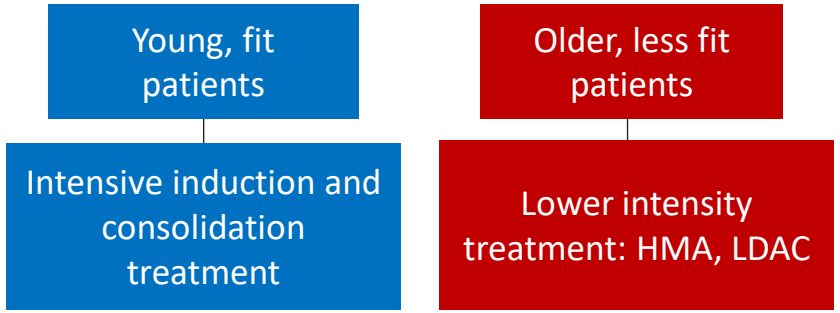
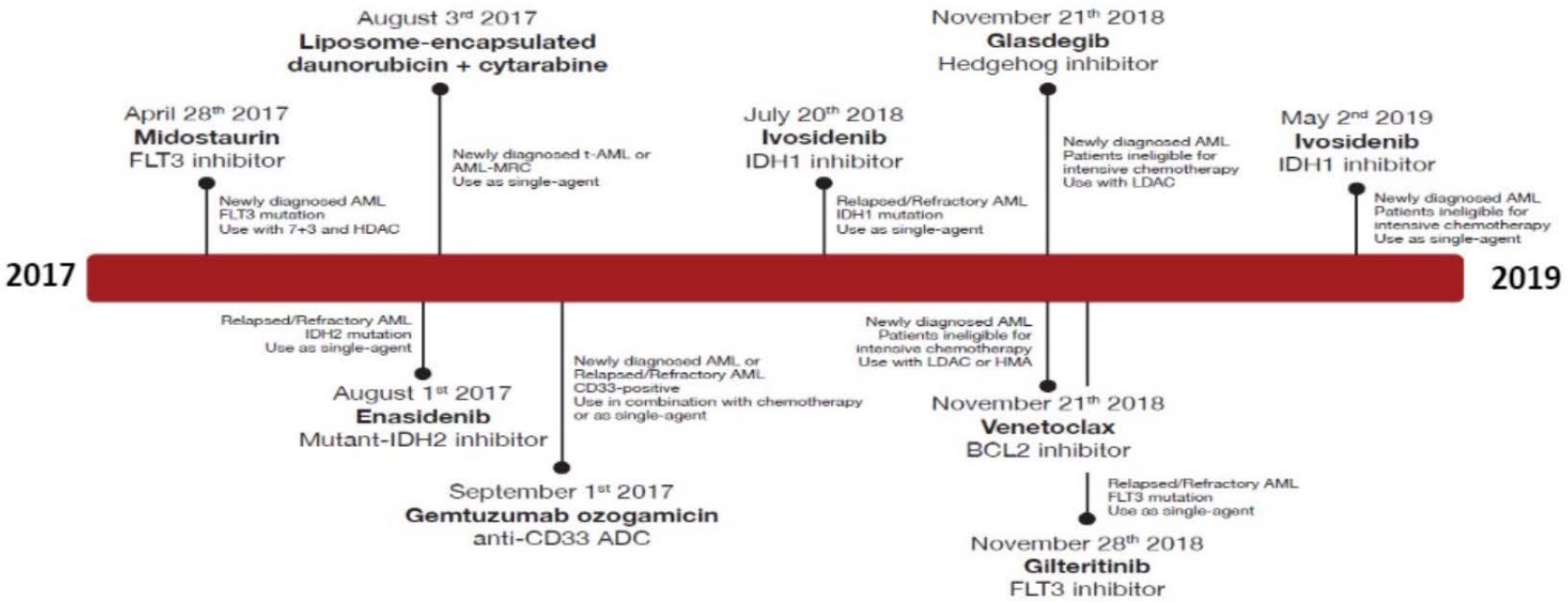


Fortschritte in der AML-Therapie

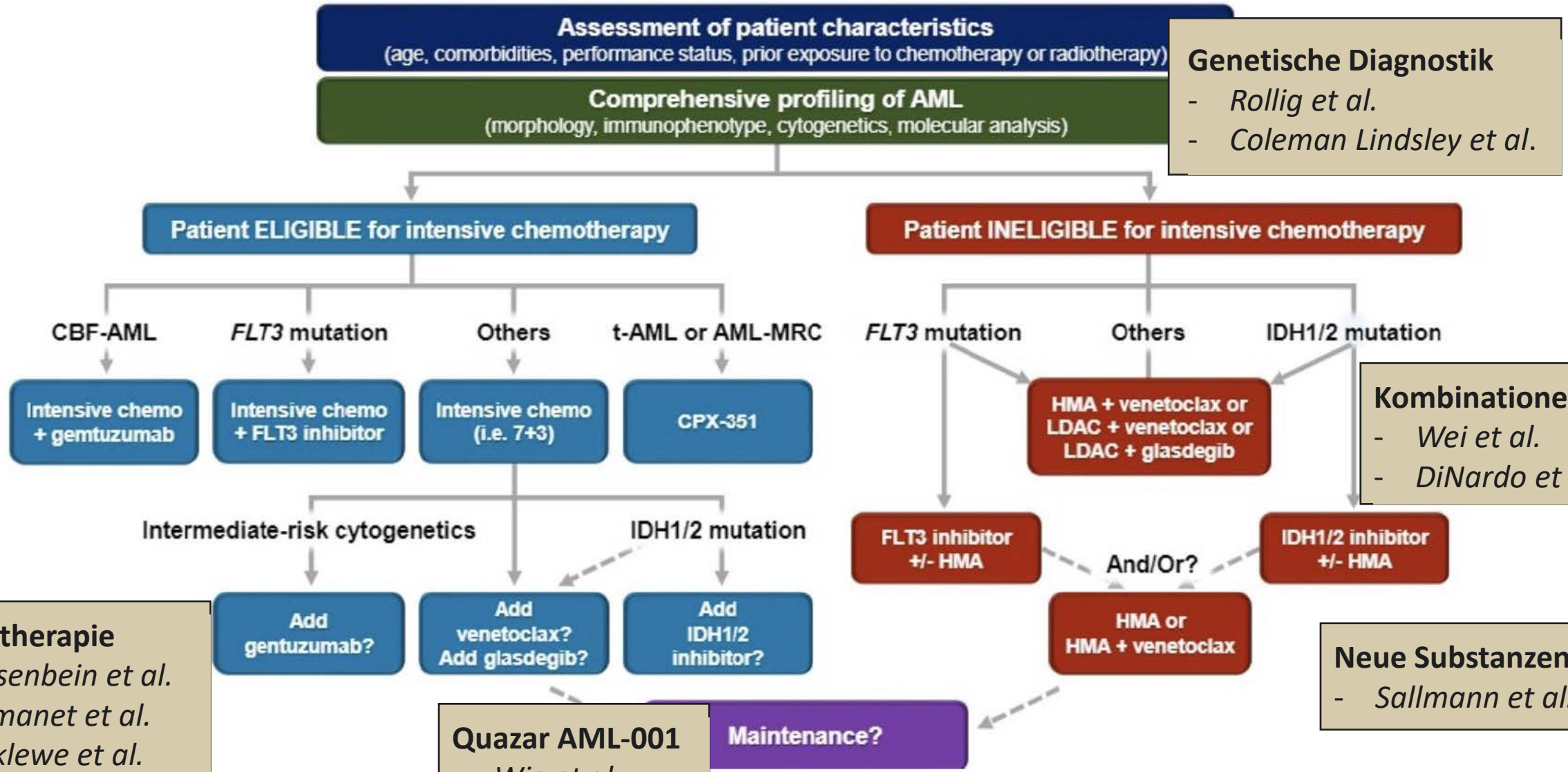
Therapiealgorithmus AML (vor 2017)





Richard-Carpentier et al. ASH Educational Book 2019

Therapiealgorithmus AML 2020



Genetische Diagnostik
- *Rollig et al.*
- *Coleman Lindsley et al.*

Kombinationen
- *Wei et al.*
- *DiNardo et al.*

Immuntherapie
- *Ochsenbein et al.*
- *Sallmanet et al.*
- *Subklewe et al.*
- *Kayser et al.*

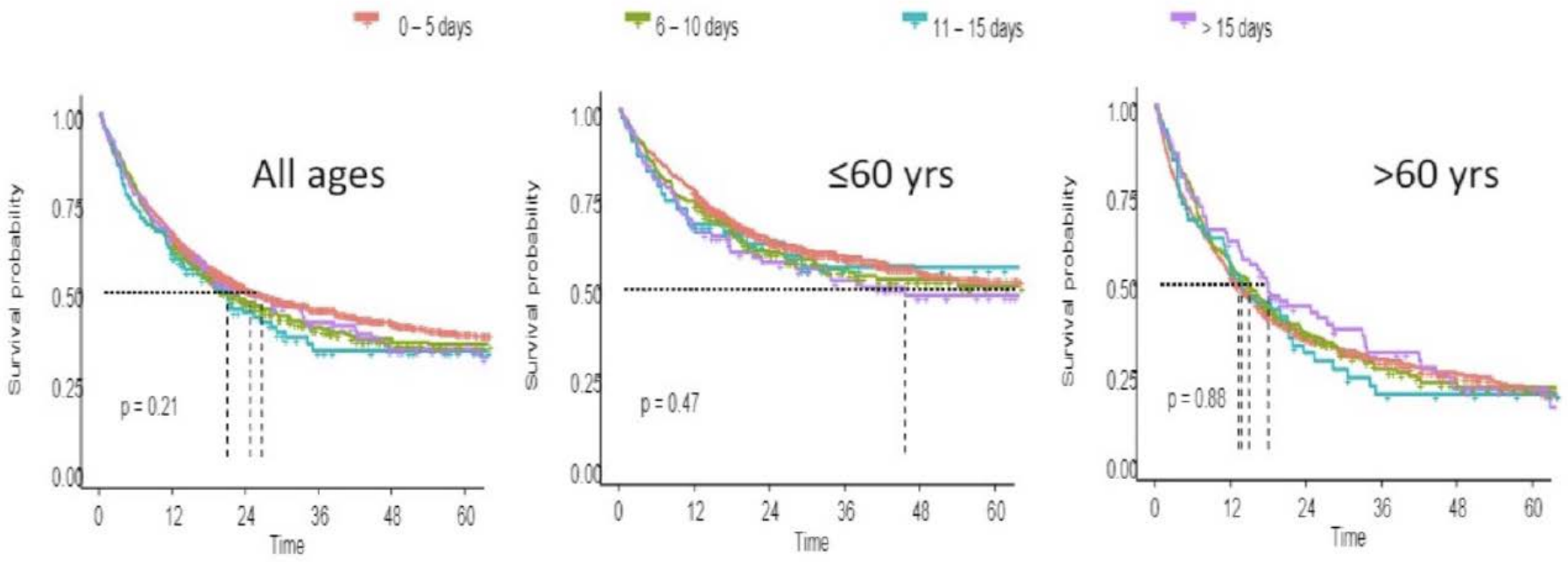
Quazar AML-001
- *Wie et al.*

Neue Substanzen
- *Sallmann et al.*

Richard-Carpentier et al. ASH Educational Book 2019

Ist das Warten auf genetische Befunde bei Erstdiagnose sicher?

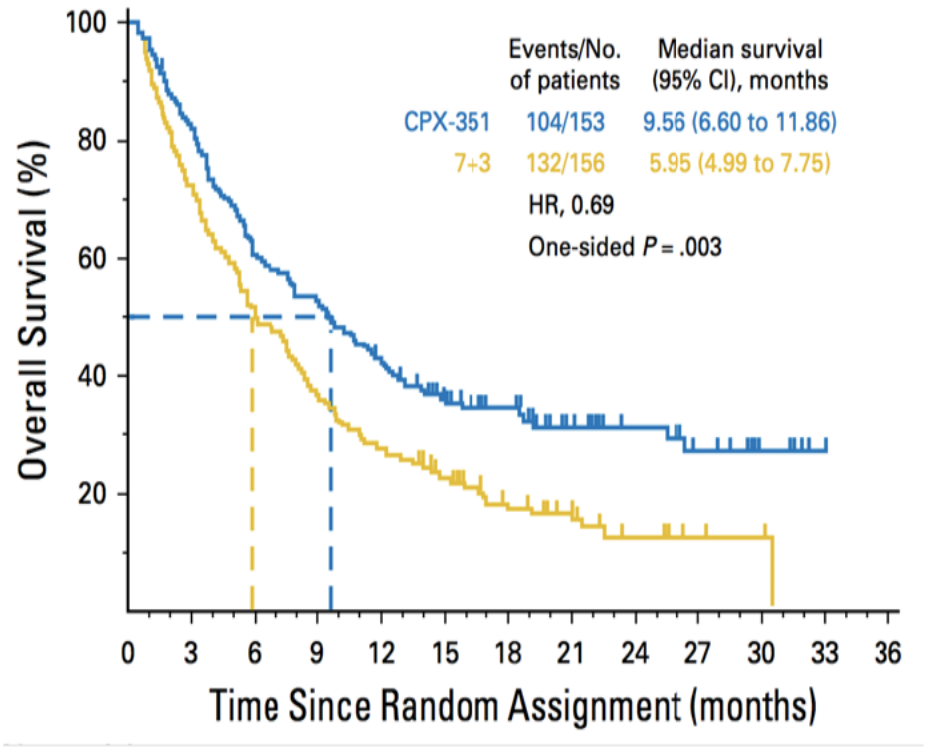
Over 2,200 patients treated with 7+3 based therapy through German SAL Registry



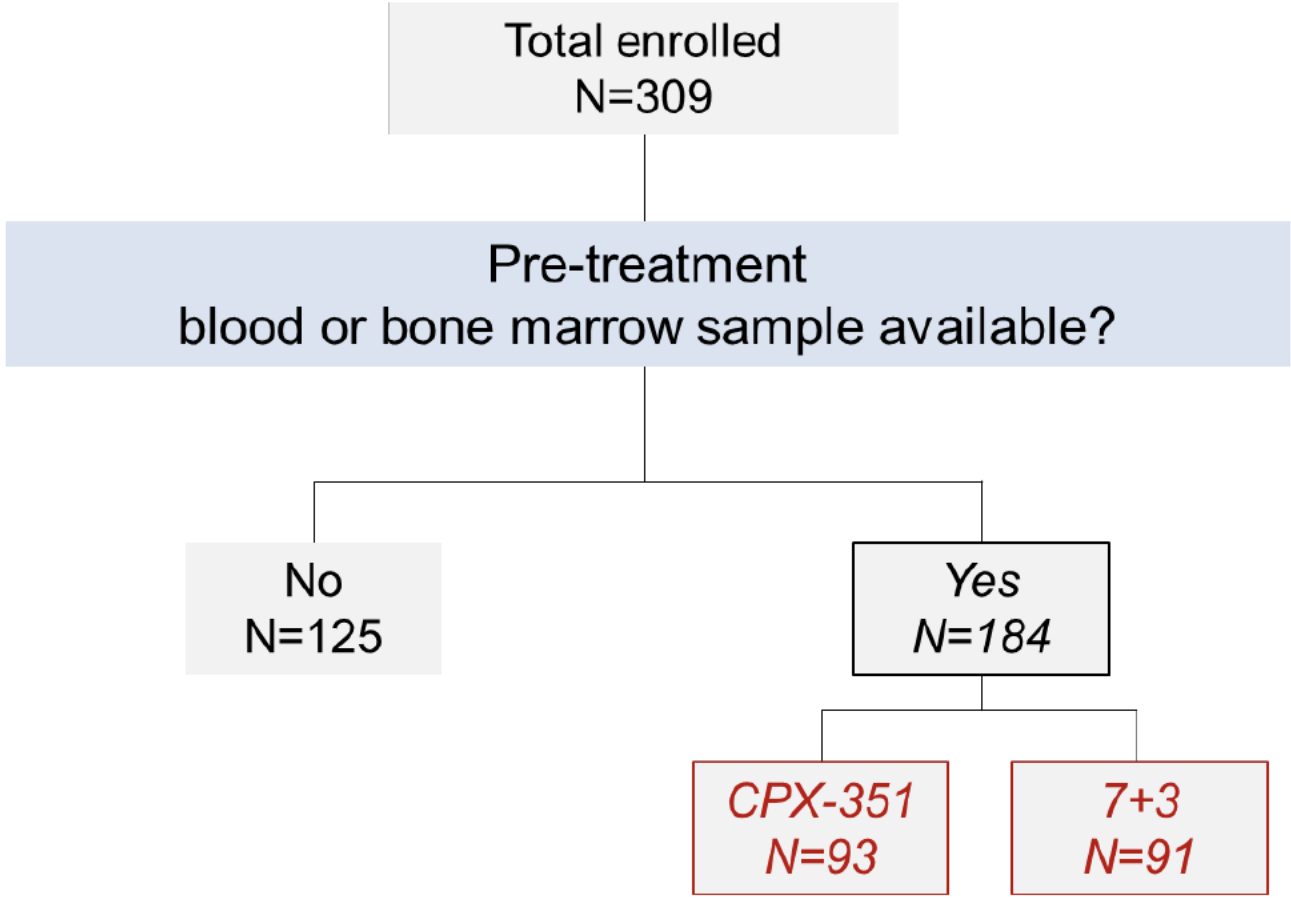
- Zeit von Diagnose bis Behandlungsbeginn beeinflusst weder CR, Frühmortalität noch OS in Patienten mit neu diagnostizierter AML und intensiver Therapie

Rollig et al.

Genetische Charakteristika und Ansprechen auf CPX-351?



Lancet, et al. *J Clin Oncol*, 2018



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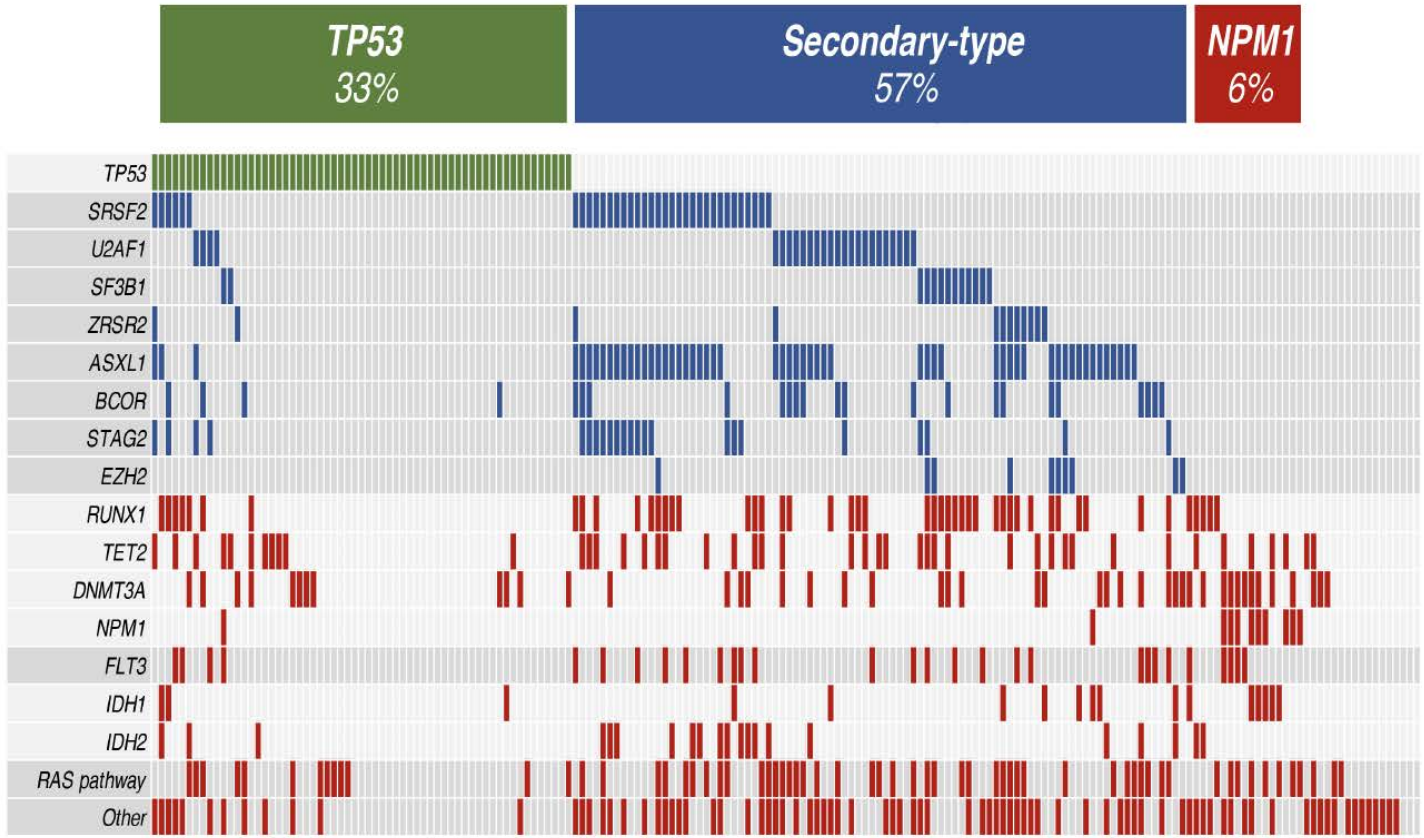
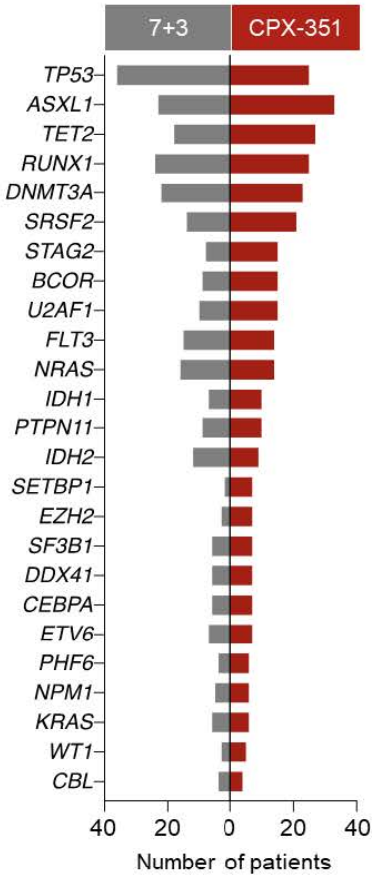
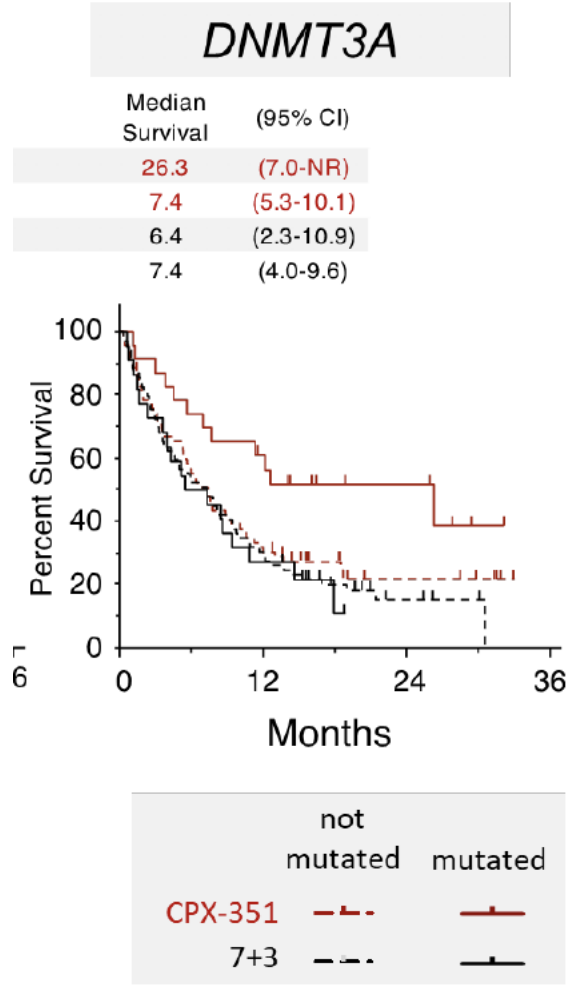
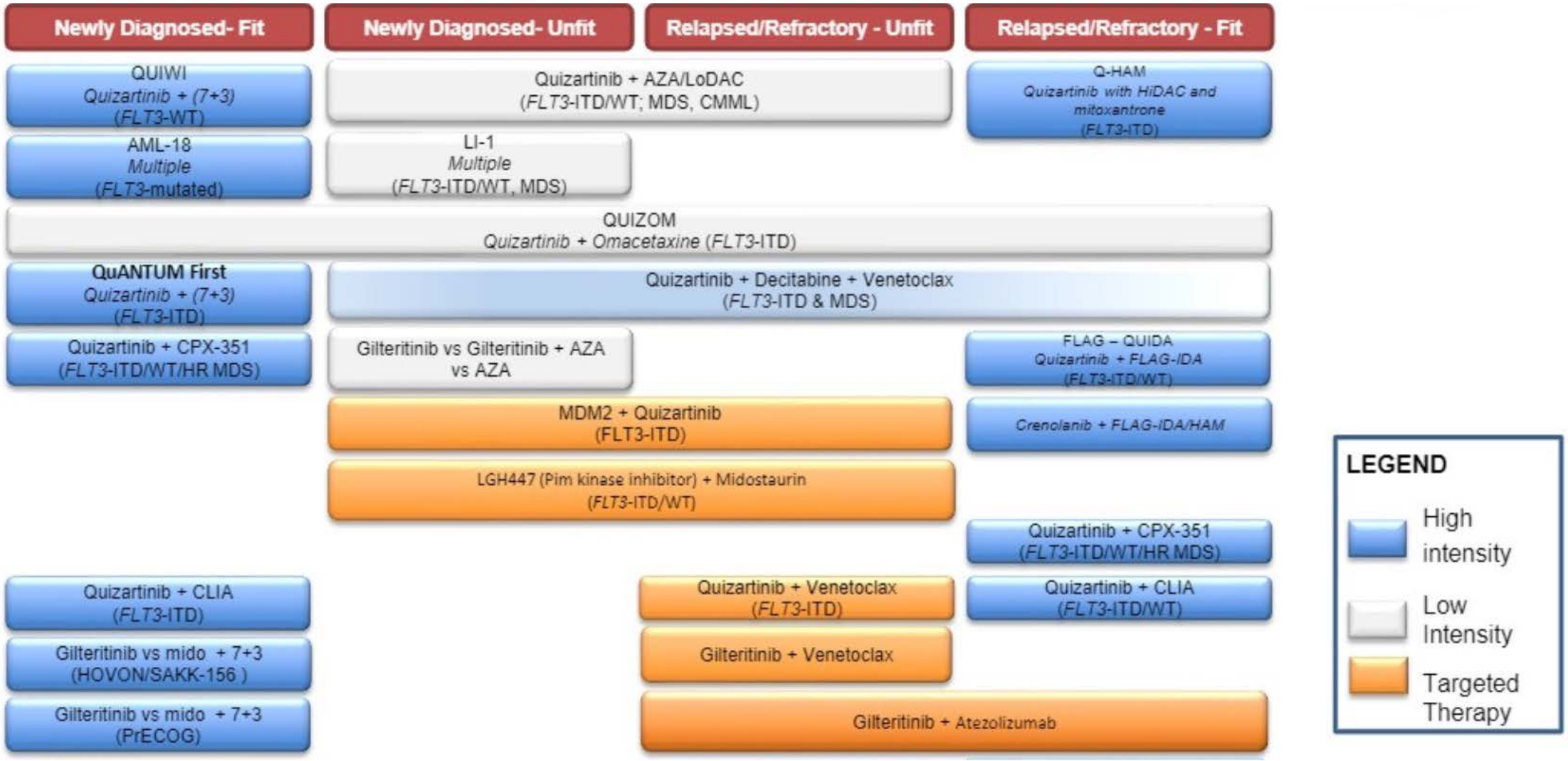






- TP53 Mutation unabhänig vom behandlungsarm mit schlechter Prognose
- OS für Patienten mit DNMT3A oder TET2 Mut. Etwas besser im CPX-351 Arm

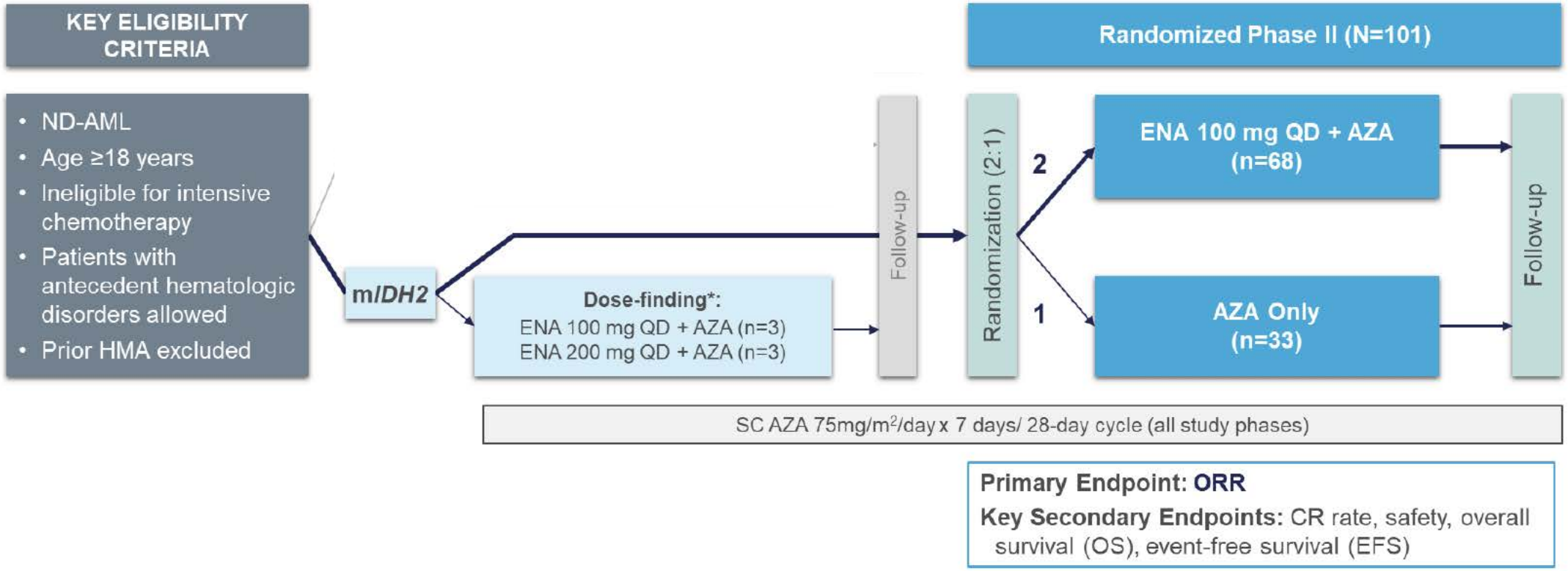
Kombinationstherapien mit FLT3-Inhibitoren



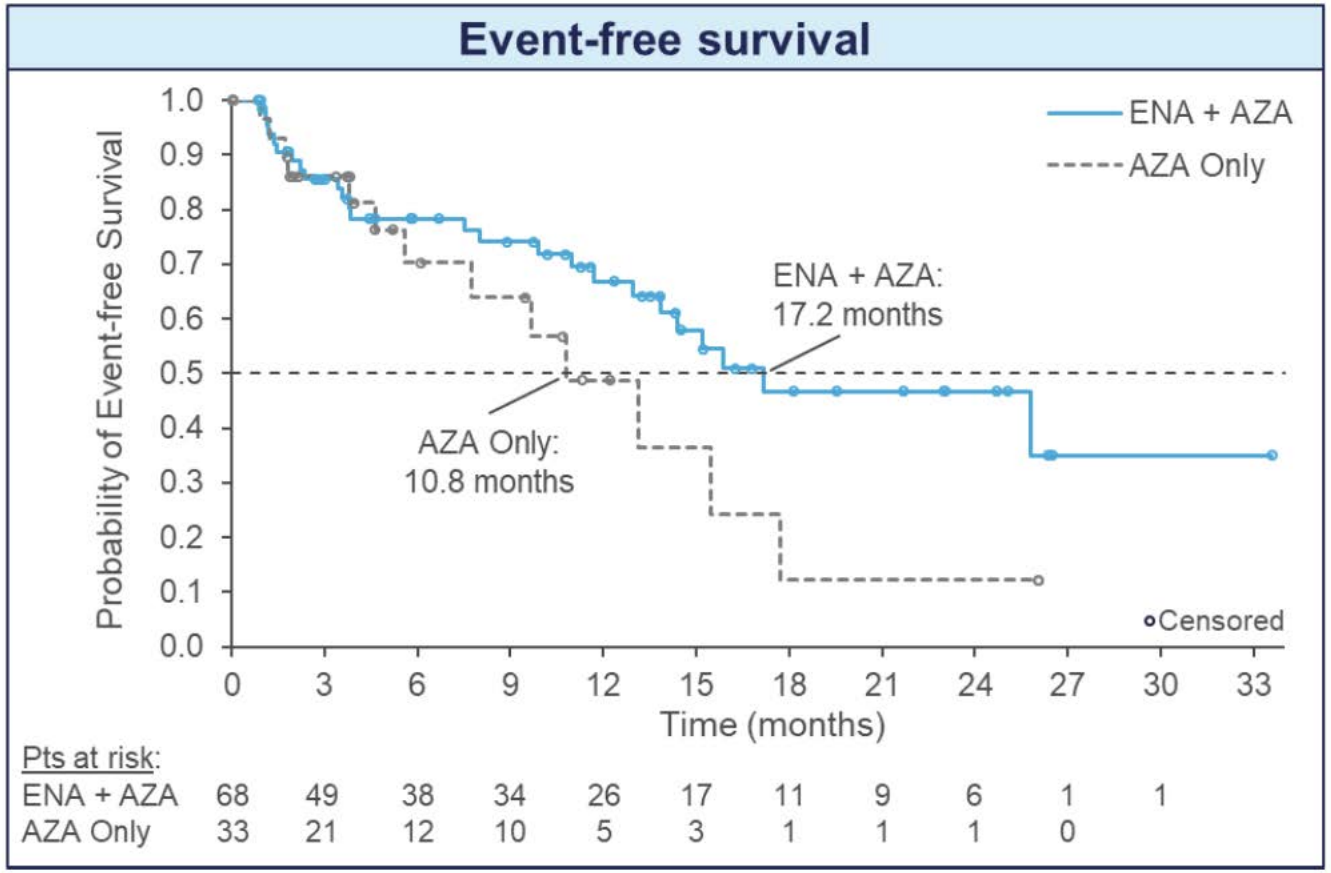
Kombination IDH2-Inhibition und Hypomethylierende Substanzen (HMA)

643: Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) with Isocitrate Dehydrogenase 2 (IDH2) Mutations: Interim Phase II Results from an Ongoing, Randomized Study

Courtney D. DiNardo *et al.*, Houston, USA.



Kombination IDH2-Inhibition und Hypomethylierende Substanzen (HMA)

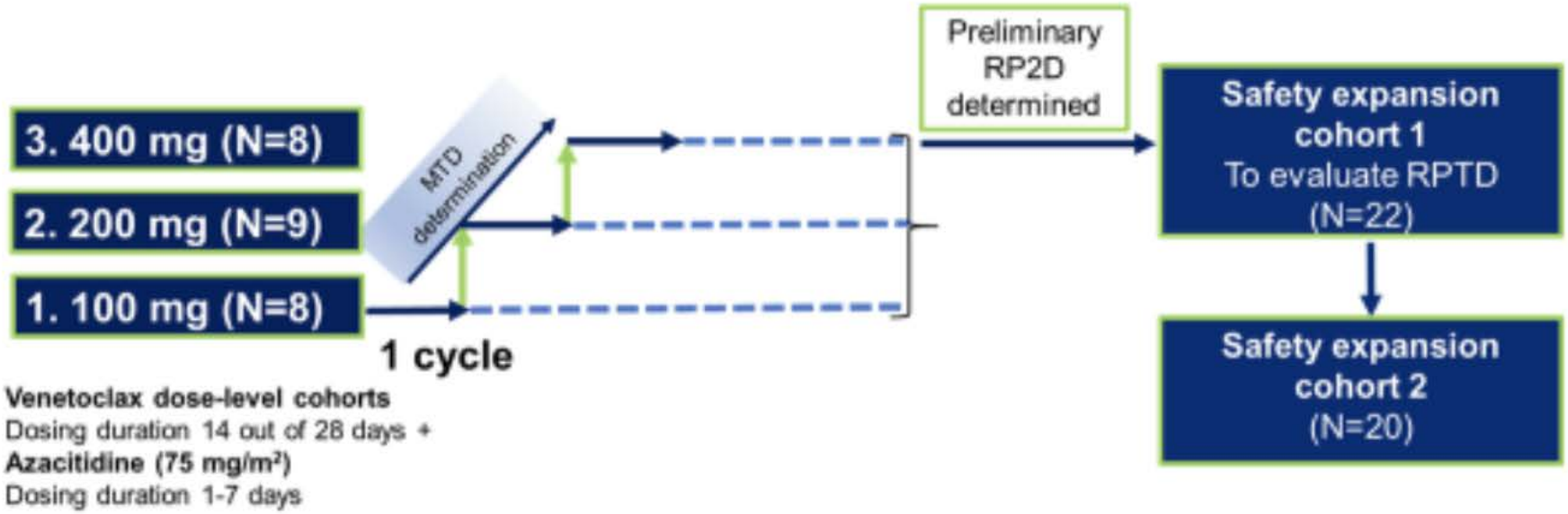


- ORR 71% ENA+AZA vs. AZA only
- CR 53% vs. 12%
- Ca. 20% MRD neg. in Kombinationsarm
- Gute Verträglichkeit

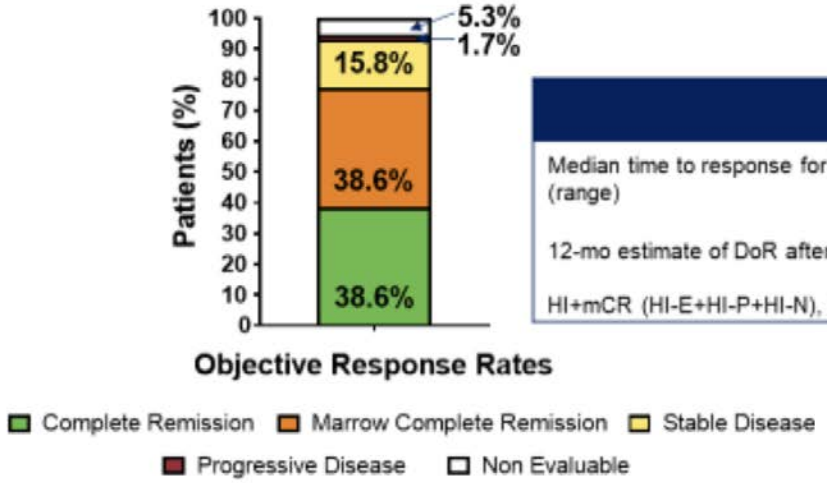
DiNardo et al.

Kombination BCL2-Inhibition und Hypomethylierende Substanzen (HMA)

568: A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax in Combination with Azacitidine in Treatment-Naïve Patients with Higher-Risk Myelodysplastic Syndrome.
Andrew H. Wei *et al.*, Melbourne, Australien.



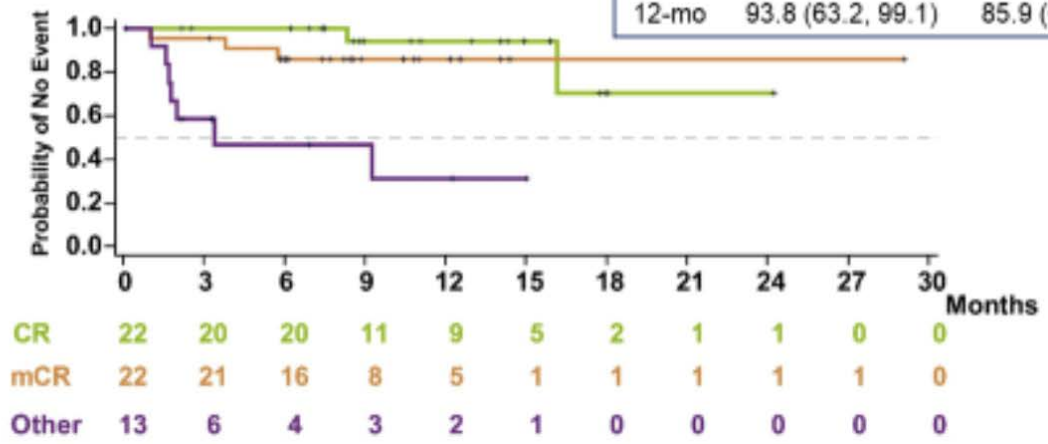
Kombination BCL2-Inhibition und Hypomethylierende Substanzen (HMA)



	All VEN+AZA Patients (N=57)
Median time to response for CR, months (range)	2.2 (1.2-11.1)
12-mo estimate of DoR after ORR, % (95% CI)	69.8 (47.4, 84.0)
HI+mCR (HI-E+HI-P+HI-N), n/N%	10/22 (45.5)

- VEN (400mg)+AZA gut verträglich
- Vielversprechende erste Wirksamkeitsdaten
- **V²**

Survival estimates* % (95% CI)	CR	mCR	Other
6-mo	100 (100, 100)	85.9 (62.4, 95.2)	46.7 (16.8, 72.2)
12-mo	93.8 (63.2, 99.1)	85.9 (62.4, 95.2)	31.1 (6.0, 61.7)



Wei et al.

Neue Substanzen: APR-264, Apoptoseinduktor bei p53 Mutation

676: Phase 2 Results of APR-246 and Azacitidine (AZA) in Patients with TP53 mutant Myelodysplastic Syndromes (MDS) and Oligoblastic Acute Myeloid Leukemia (AML)

David A Sallman *et al.*, Tampa, USA.

Phase 1b
Dose escalation (n=12)
Enrollment complete

55 patients

Phase 2
Dose expansion (n=43)
Enrollment complete

***TP53* mutant myeloid neoplasms**

APR-246 i.v. infusion days 1-4
+
AZA (s.c. or i.v.) days 4-10 or 4-5 and 8-12

28-day cycles

Doses: 50, 75, 100 mg/kg/d lean body mass

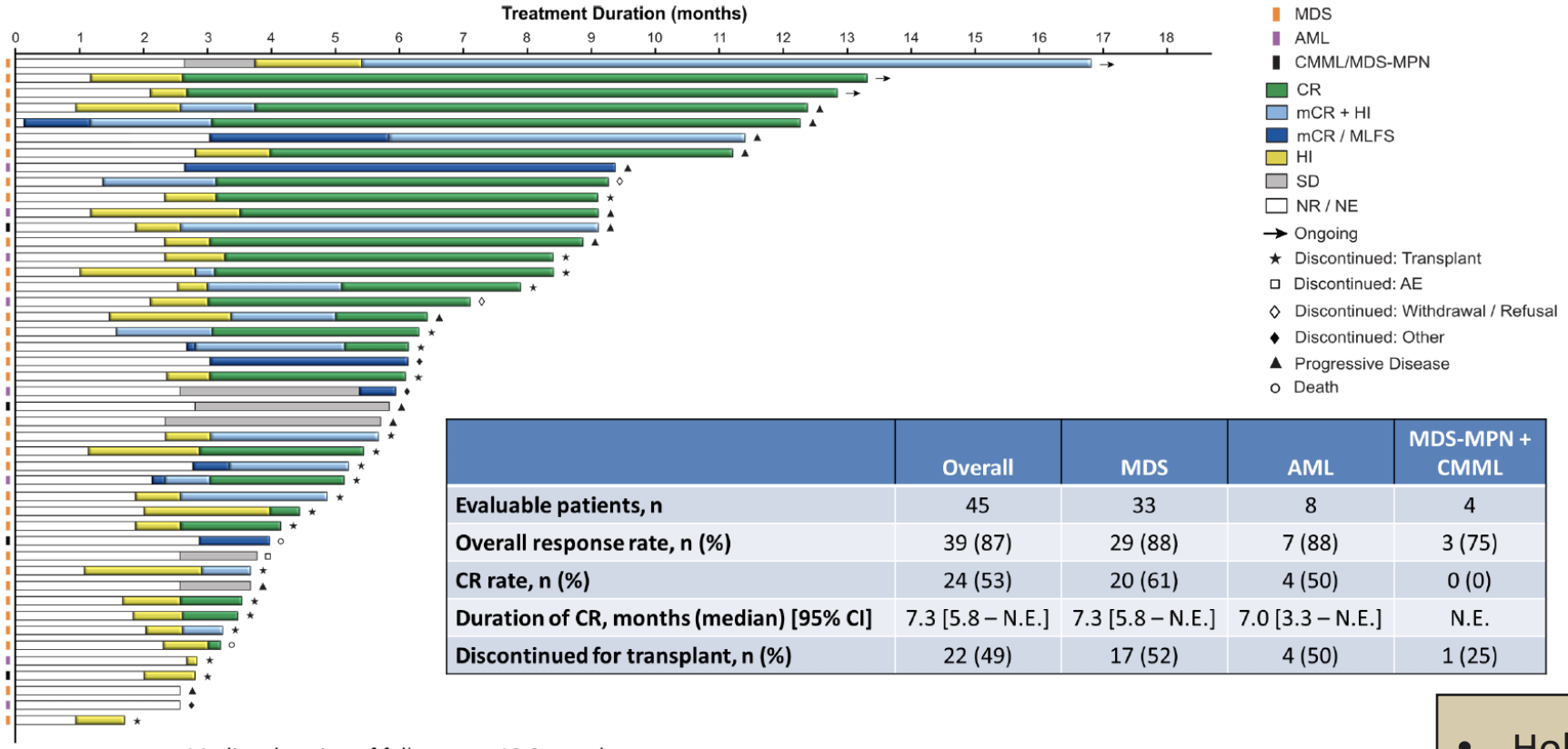
***TP53* mutant myeloid neoplasms**

APR-246 i.v. infusion days 1-4
+
AZA (s.c. or i.v.) days 4-10 or 4-5 and 8-12

28-day cycles

Dose: 4500 mg/d fixed dose (≈100 mg/kg)

Neue Substanzen: APR-264, Apoptoseinduktor bei p53 Mutation



	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)

Median duration of follow-up = 10.8 months

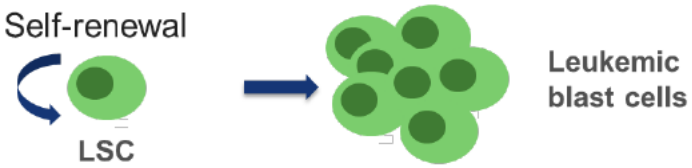
- Hohe Ansprechraten
- Vielversprechende Remissionsdauer mit molekularen Remissionen
- Phase III Studie läuft (NCT03745716)

Sallmann et al.

Immuntherapeutische Ansätze

234: Targeting CD70 with Cusatuzumab Eliminates Acute Myeloid Leukemia Stem Cells in Humans

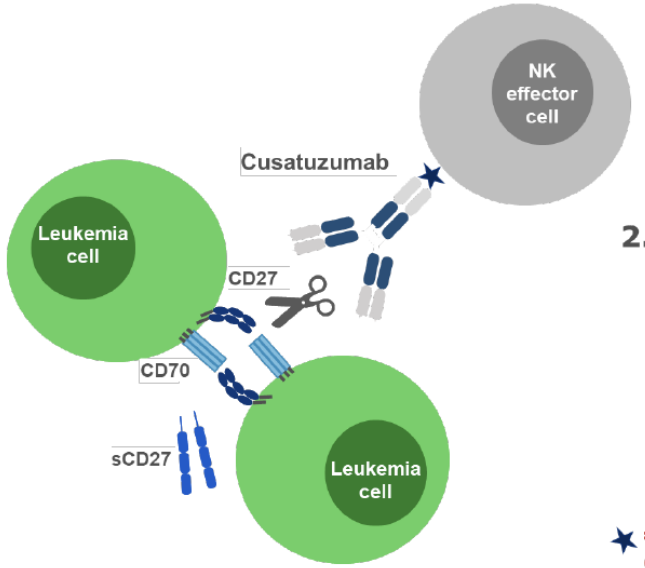
Adrian F Ochsenbein *et al.*, Bern, Schweiz



Rationale for targeting CD70:

- **CD34⁺ AML cells** (progenitors and LSCs) consistently express **CD70**, and its **receptor CD27**[7]
- **CD70 is not expressed on HSCs**, and is therefore a good target in AML[8]
- **Increased levels of CD70 expression** correlates with **resistance to chemotherapy** and **poor survival**[9,10]

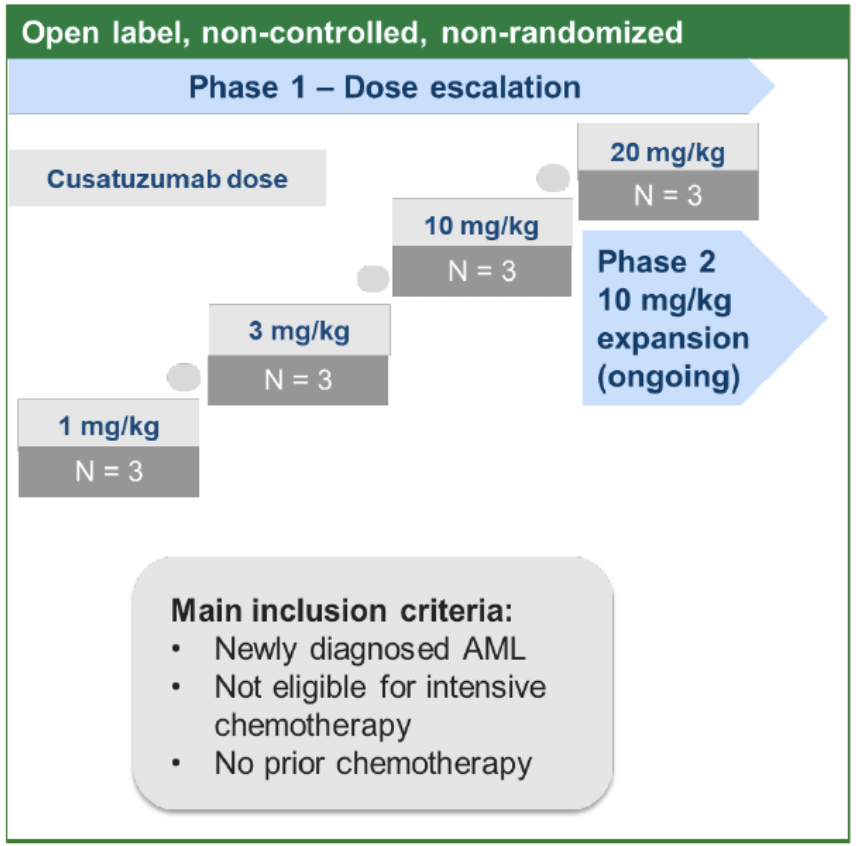
1. **Blocking CD70-CD27 signaling,** which leads to myeloid differentiation and stops proliferation of LSCs
   - **Blocking release of soluble CD27,** which is generated by CD70-CD27 ligation

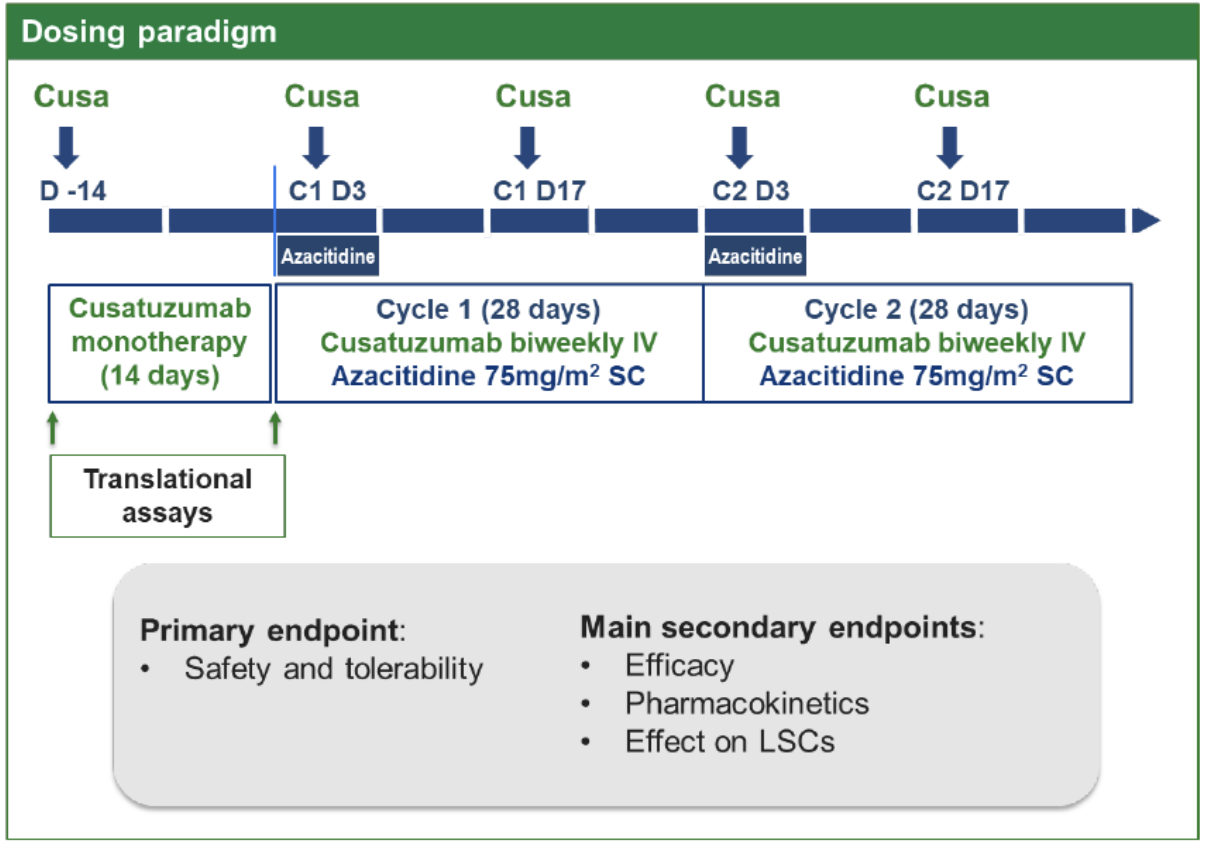


2. **Killing cells** via Fc-dependent, complement dependent cytotoxicity and enhanced antibody-dependent cellular cytotoxicity (ADCC)

★ = ADCC enhanced antibody (using POTELLIGENT® for defucosylation)

Casatuzumab (Monoklonaler CD70 Antikörper)





Ochsenbein et al.

Casatuzumab (Monoklonaler CD70 Antikörper)

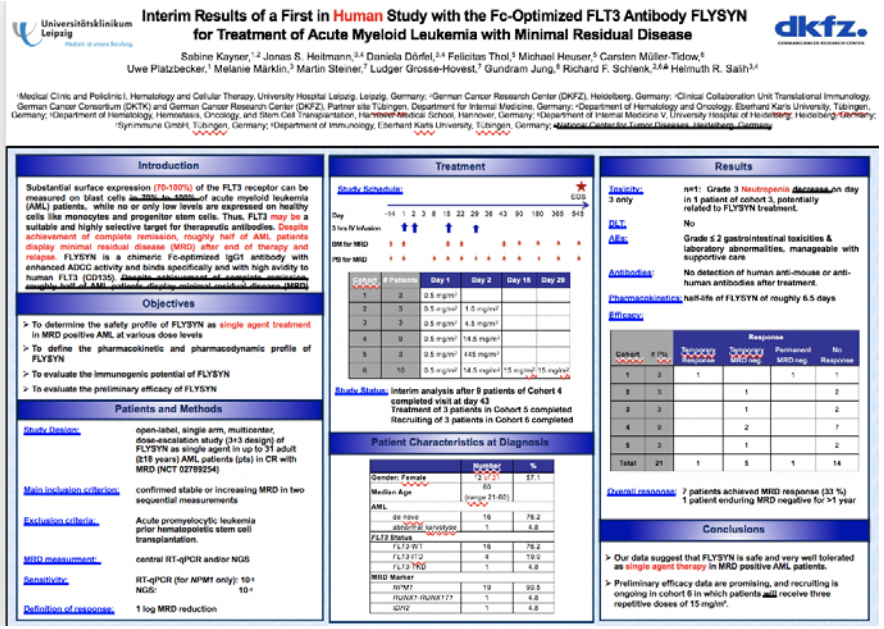
- 100% Ansprechen mit 83% CR/CRi
- 44% MRD Negativität
- Ansprechen auch bereits auf Monosubstanz

Ochsenbein et al.

Flysyn (Monoklonaler, Fc-Optimierter FLT3 Antikörper)

3928: Interim Results of a First in Man Study with the Fc-Optimized FLT3 Antibody Flysyn for Treatment of Acute Myeloid Leukemia with Minimal Residual Disease

Kayser et al.



Interim Results of a First in Human Study with the Fc-Optimized FLT3 Antibody FLYSYN for Treatment of Acute Myeloid Leukemia with Minimal Residual Disease

Sabine Kayser,[1,2] Jonas S. Heitmann,[3,4] Daniela Dörfel,[3,4] Felicitas Thol,[5] Michael Heuser,[5] Carsten Müller-Tidow,[6] Uwe Platzbecker,[1] Melanie Märklin,[3] Martin Steiner,[7] Ludger Grosse-Hovest,[7] Gundram Jung,[8] Richard F. Schlenk,[2,6,9] Helmuth R. Salih[3,4]

Introduction

Substantial surface expression (70-100%) of the FLT3 receptor can be measured on blast cells in 70% to 100% of acute myeloid leukemia (AML) patients, while no or only low levels are expressed on healthy cells like monocytes and progenitor stem cells. Thus, FLT3 may be a suitable and highly selective target for therapeutic antibodies. Despite achievement of complete remission, roughly half of AML patients display minimal residual disease (MRD) after end of therapy and relapse. FLYSYN is a chimeric Fc-optimized IgG1 antibody with enhanced ADCC activity and binds specifically and with high avidity to human FLT3 (CD135). Despite achievement of complete remission, roughly half of AML patients display minimal residual disease (MRD)

Objectives

- To determine the safety profile of FLYSYN as single agent treatment in MRD positive AML at various dose levels
- To define the pharmacokinetic and pharmacodynamic profile of FLYSYN
- To evaluate the immunogenic potential of FLYSYN
- To evaluate the preliminary efficacy of FLYSYN

Patients and Methods

Study Design: open-label, single arm, multicenter, dose-escalation study (3+3 design) of FLYSYN as single agent in up to 31 adult (≥18 years) AML patients (pts) in CR with MRD (NCT 02789254)

Main inclusion criterion: confirmed stable or increasing MRD in two sequential measurements

Exclusion criteria: Acute promyelocytic leukemia prior hematopoietic stem cell transplantation

MRD measurment: central RT-qPCR and/or NGS

Sensitivity: RT-qPCR (for *NPM1* only): 10^{-4} NGS: 10^{-4}

Definition of response: 1 log MRD reduction

Treatment

Study Schedule:

Study Status: Interim analysis after 9 patients of Cohort 4 completed visit at day 43
Treatment of 3 patients in Cohort 5 completed
Recruiting of 3 patients in Cohort 6 completed

Patient Characteristics at Diagnosis

Results

Toxicity: 3 only — n=1: Grade 3 Neutropenia decrease on day in 1 patient of cohort 3, potentially related to FLYSYN treatment.

PLT: No

AEs: Grade ≤ 2 gastrointestinal toxicities & laboratory abnormalities, manageable with supportive care

Antibodies: No detection of human anti-mouse or anti-human antibodies after treatment.

Pharmacokinetics: half-life of FLYSYN of roughly 6.5 days

Efficacy:

Overall response: 7 patients achieved MRD response (33 %)
1 patient enduring MRD negative for >1 year

Conclusions

- Our data suggest that FLYSYN is safe and very well tolerated as single agent therapy in MRD positive AML patients.
- Preliminary efficacy data are promising, and recruiting is ongoing in cohort 6 in which patients will receive three repetitive doses of 15 mg/m².

		Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
Patienten		1-3	4-6	7-9	10-18	19-21	22-31
FLYSYN	Tag1	0,5mg/m²	0,5mg/m²	0,5mg/m²	0,5mg/m²	0,5mg/m²	0,5mg/m²
	Tag2 Tag15 Tag29	--	1,0mg/m²	4,5mg/m²	14,5mg/m²	14,5mg/m²	14,5mg/m² 15mg/m² 15mg/m²

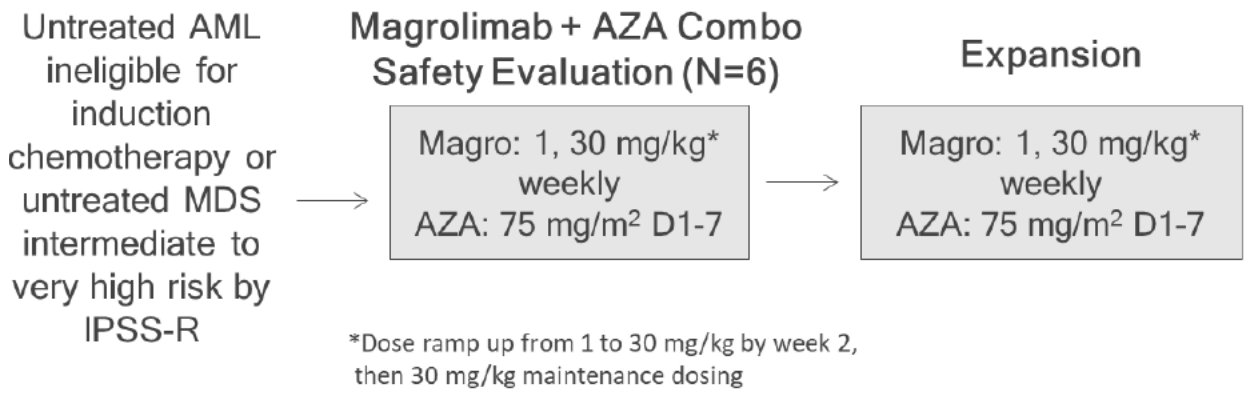
- 21 Patienten behandelt
- Keine relevante Toxizität
- 33% (7 Pat.) zeigten MRD-Ansprechen, 5 Patienten wurden MRD negativ

Studienanfragen:
KKE Translationale Immunologie
KKETI@med.uni-tuebingen.de

Magrolimumab (Monoklonaler, Anti-CD47 Antibody)

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

David A Sallmanet *et al.*, Tampa, USA.



Primary objectives

1) Safety of magrolimab alone or with AZA
2) Efficacy of magrolimab + AZA in untreated AML/MDS

Secondary objectives

1) PK, PD and immunogenicity of 5F9
2) Additional measures of efficacy (DOR, PFS, OS)

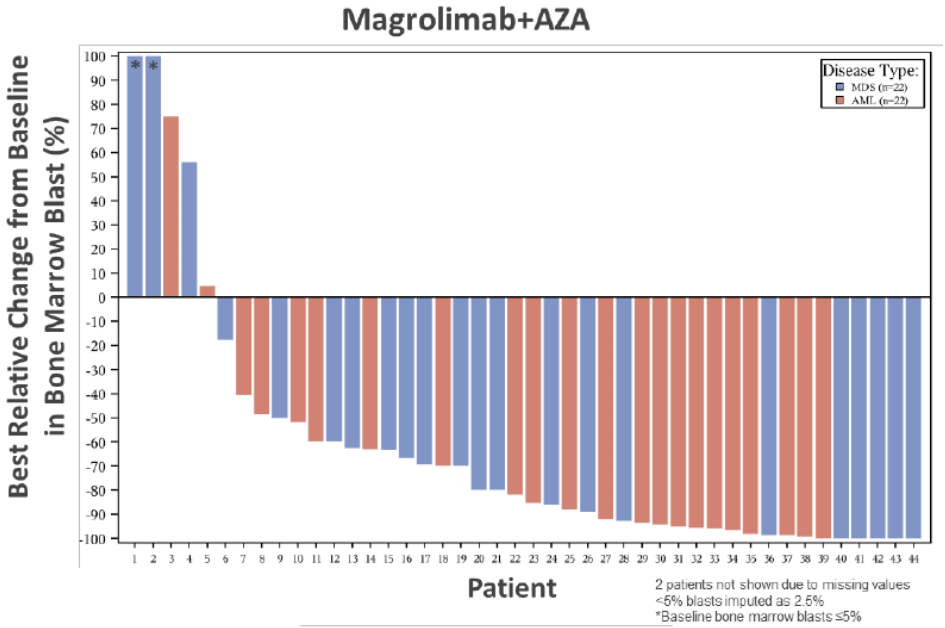
Exploratory objectives

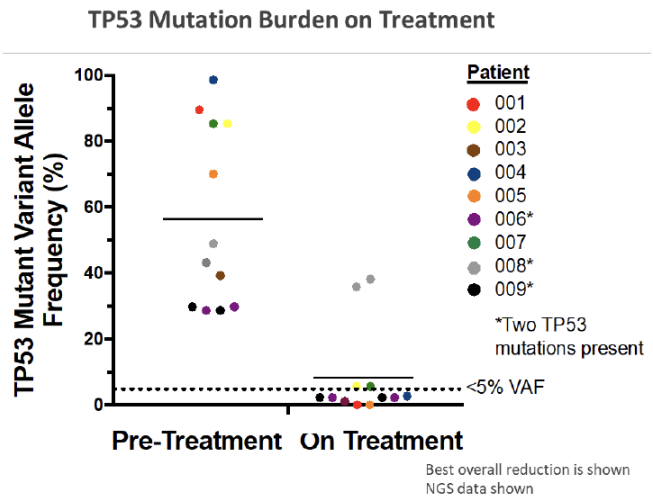
1) To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

Magrolimumab (Monoklonaler, Fc-Optimierter FLT3 Antikörper)

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%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria; Patients with at least one post-treatment response assessment are shown, all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML (1 AE, 2 early withdrawal)
"-" not applicable





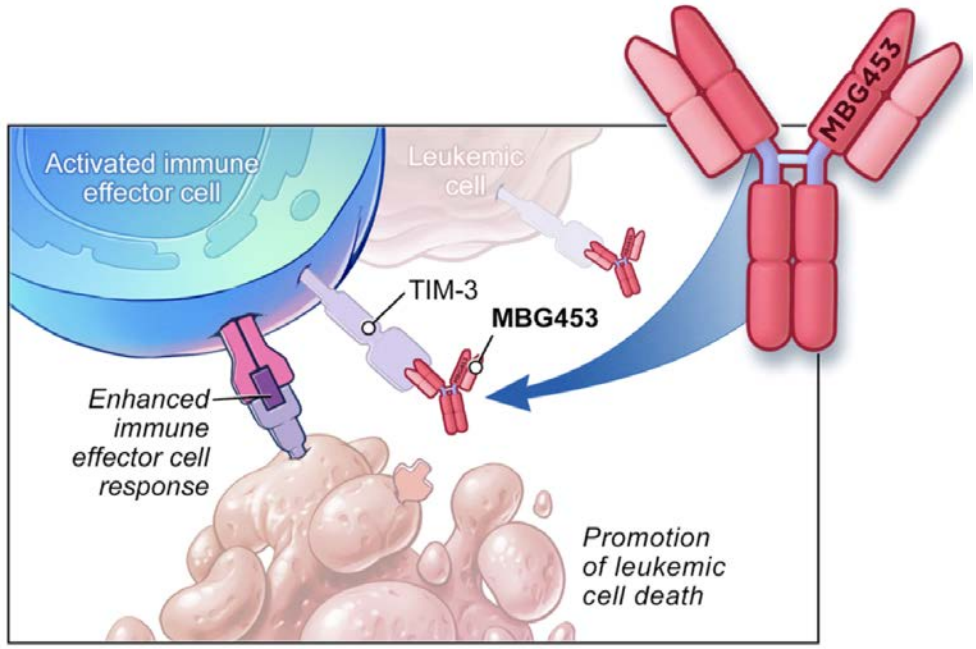
- 46 Patienten behandelt
- Gute Verträglichkeit
- Hohe ORR und CR Raten
- Hohe Ansprechrate und MRD Negativität auch in TP53 mut. Patienten

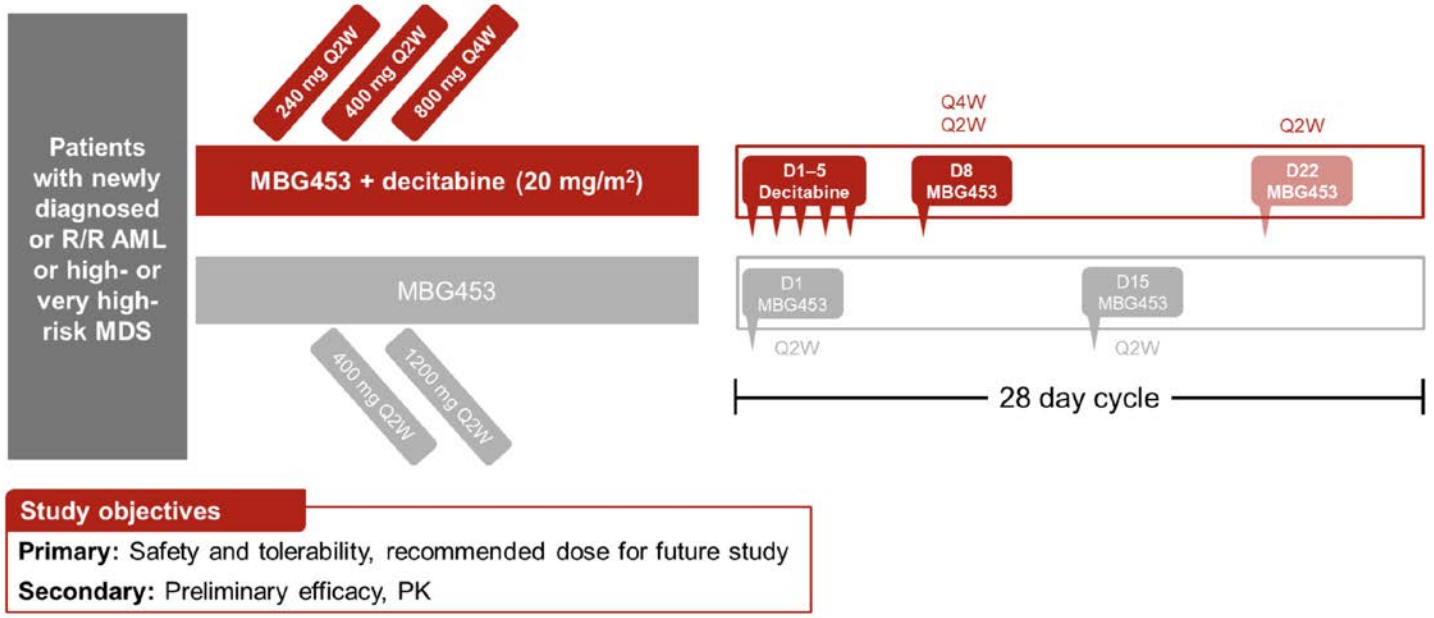
Sallmanet et al.

MBG453 (Anti-TIM3-Antibody)

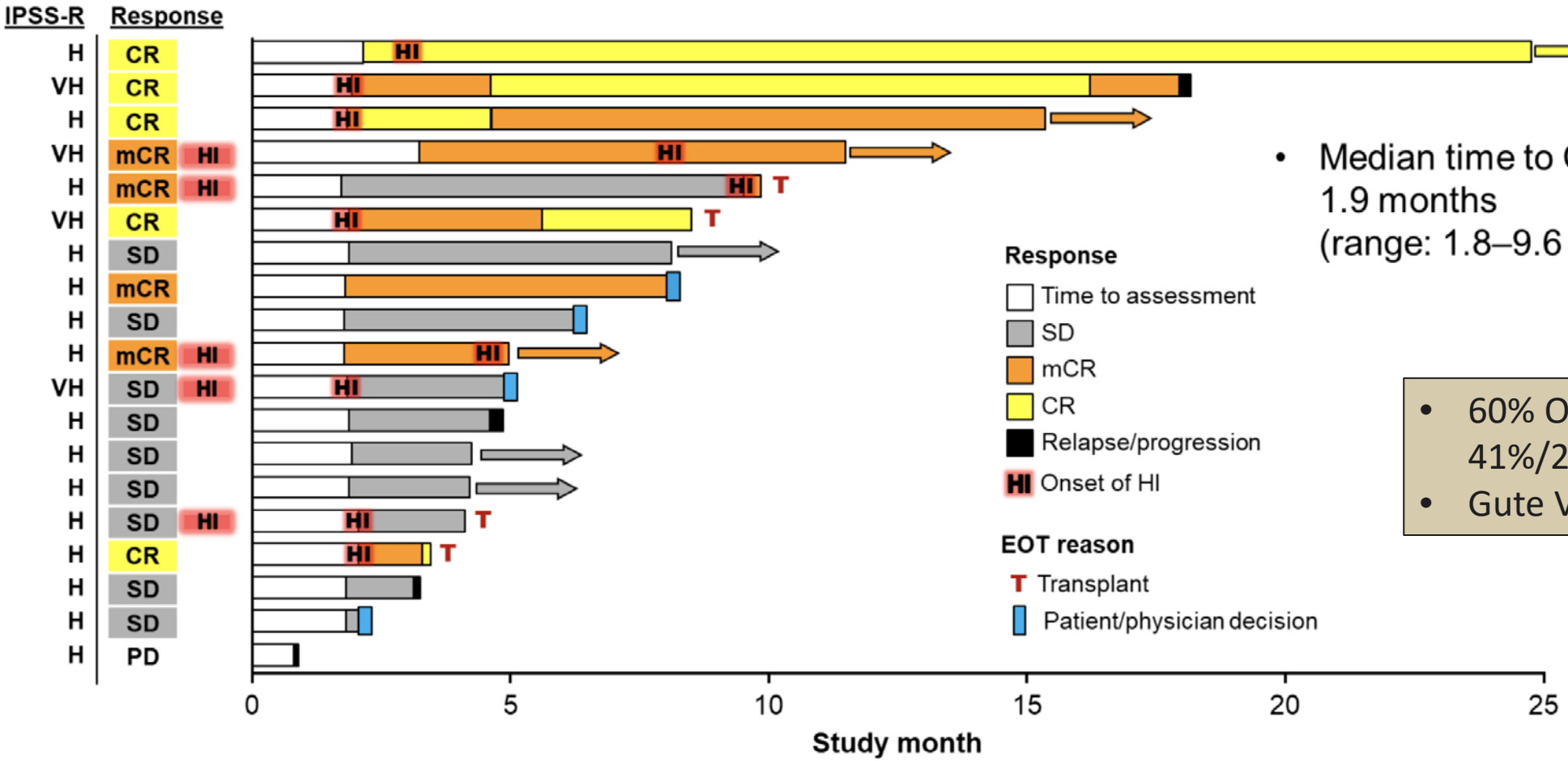
570: Phase Ib Study of the Anti-TIM-3 Antibody MBG453 in Combination with Decitabine in Patients with High-Risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)

Uma Borate *et al.*, Portland, USA.





MBG453 (Anti-TIM3-Antibody)



- Median time to CR/mCR: 1.9 months (range: 1.8–9.6 months)

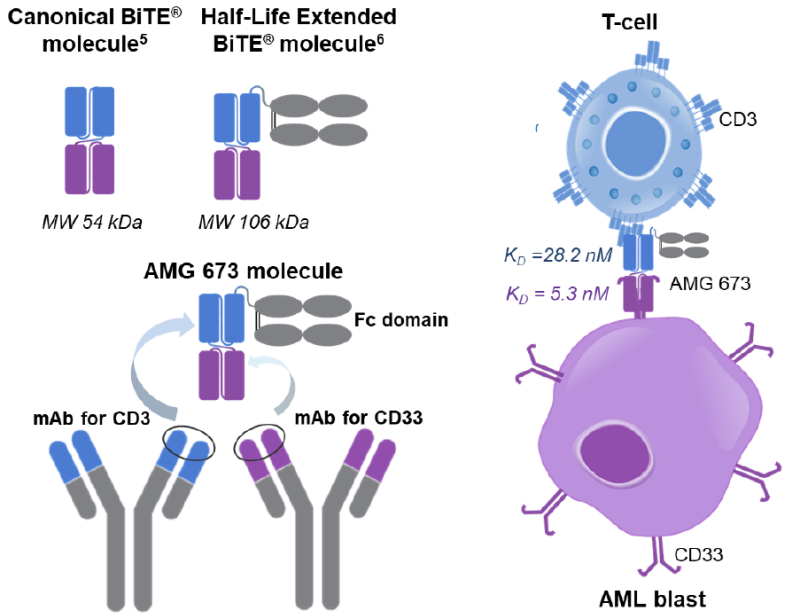
- 60% ORR in MDS, 41%/24% in AML
- Gute Verträglichkeit

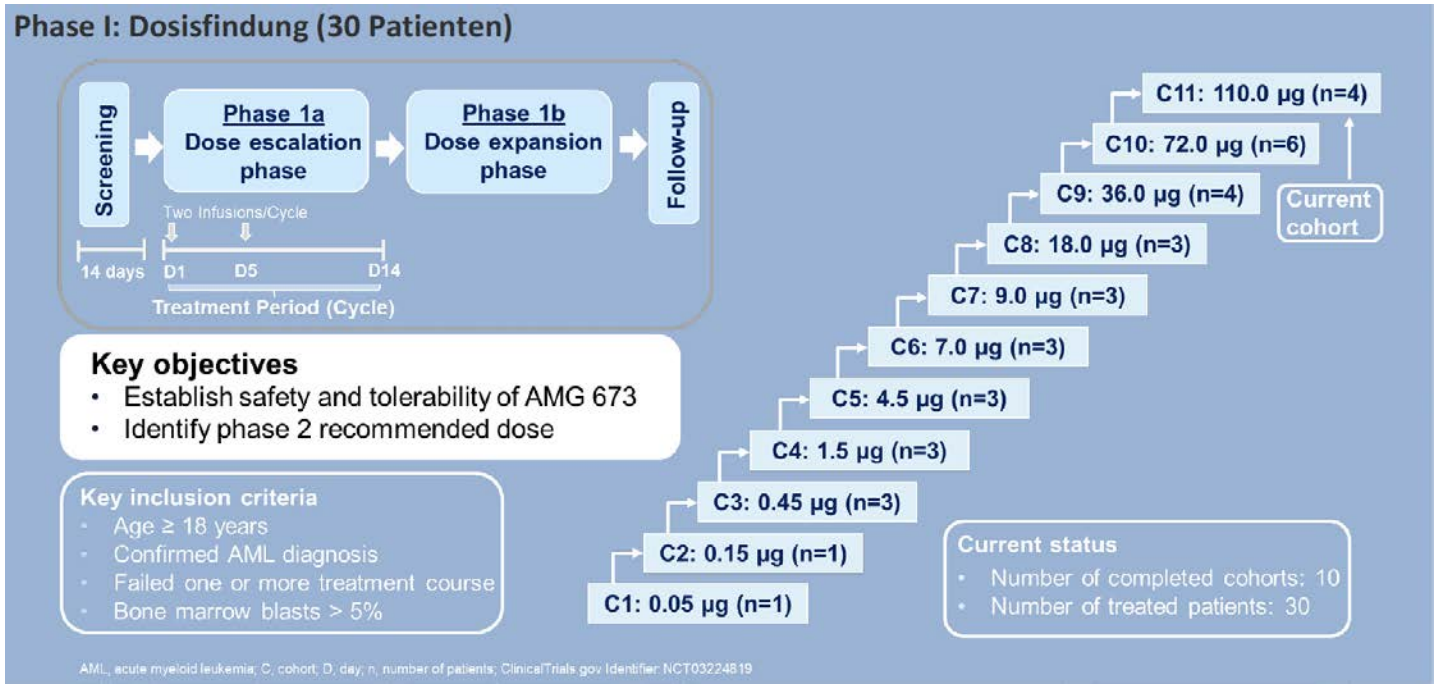
Borate et al.

AMG 673 (Bispezifischer Anti-CD33/CD3 BiTE®)

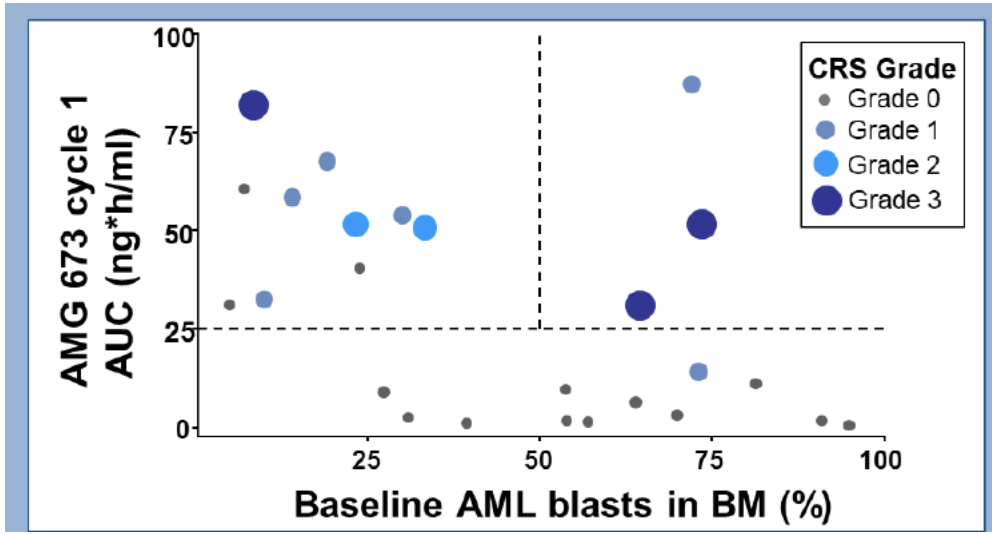
833: Preliminary Results from a Phase 1 First-in-Human Study of AMG 673, a Novel Half-Life Extended (HLE) Anti-CD33/CD3 BiTE® (Bispecific T-Cell Engager) in Patients with Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML)

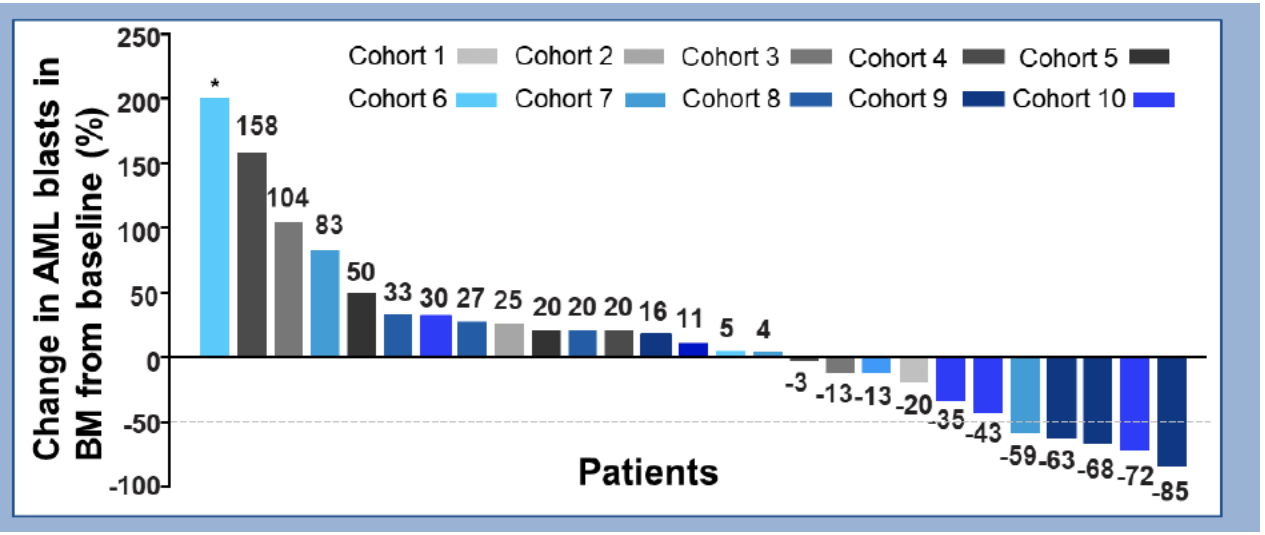
Marion Subklewe *et al.*, München, Deutschland.





AMG 673 (Bispezifischer Anti-CD33/CD3 BiTE®)





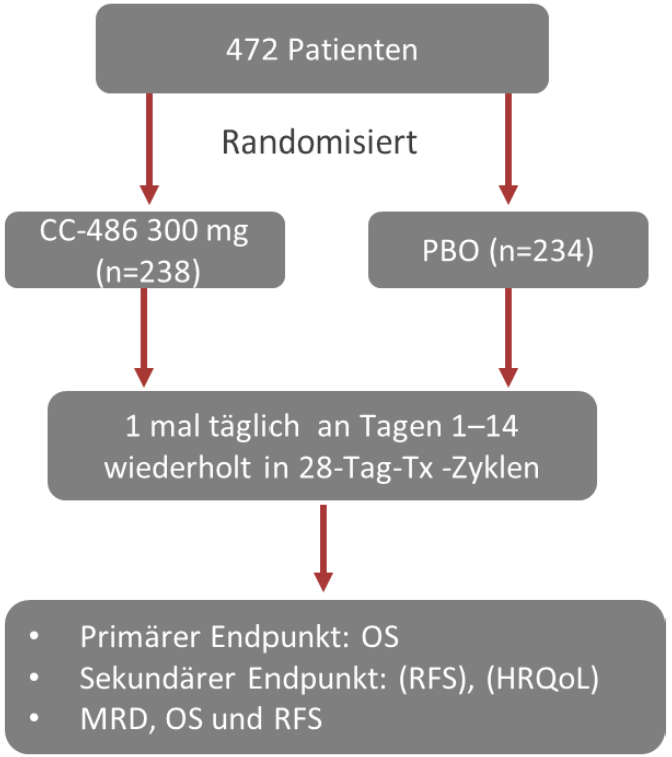
- Auftreten und Schwere eines CRS Korreliert mit AK Dosis und Blastenzahl
- Erst Wirksamkeitsdaten
- Dosisexpansionsphase läuft

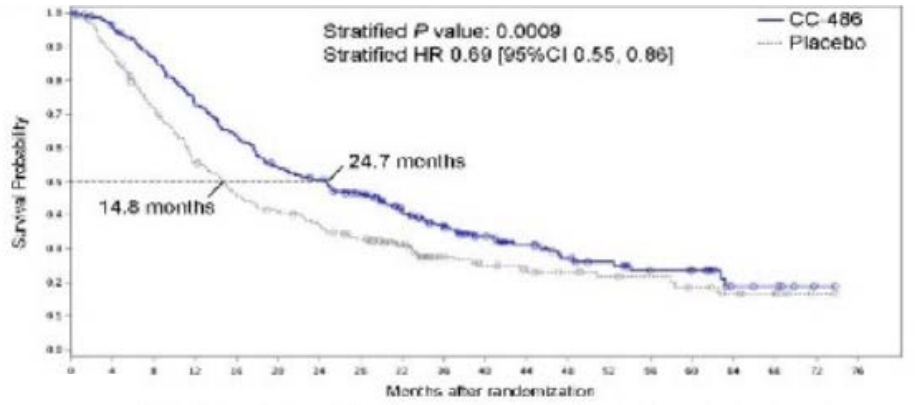
Subklewe et al.

Erhaltungstherapie mit oralem Azacitidin

LBA-3: The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 (Oral Formulation of Azacitidine) in Patients with Acute Myeloid Leukemia (AML) in First Remission.

Andrew H. Wie *et al.*





	CC-486
De Novo AML	91%
CR	81%
CRi	19%
(CC-486 vs. PBO) OS	24.7* Monate vs 14.8 Monate
(CC-486 vs. PBO) RFS	10,2** Monate vs 4,8 Monate

*P=0.0009

**P=0.0001

Vielen Dank für Ihre Aufmerksamkeit!

Manatees at Blue Spring State Park, Florida

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Universitätsklinikum Tübingen