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UNIVERSITÄTSMEDIZIN BERLIN

AML Therapie 2024:
Therapiekonzepte bei jüngeren AML Patienten

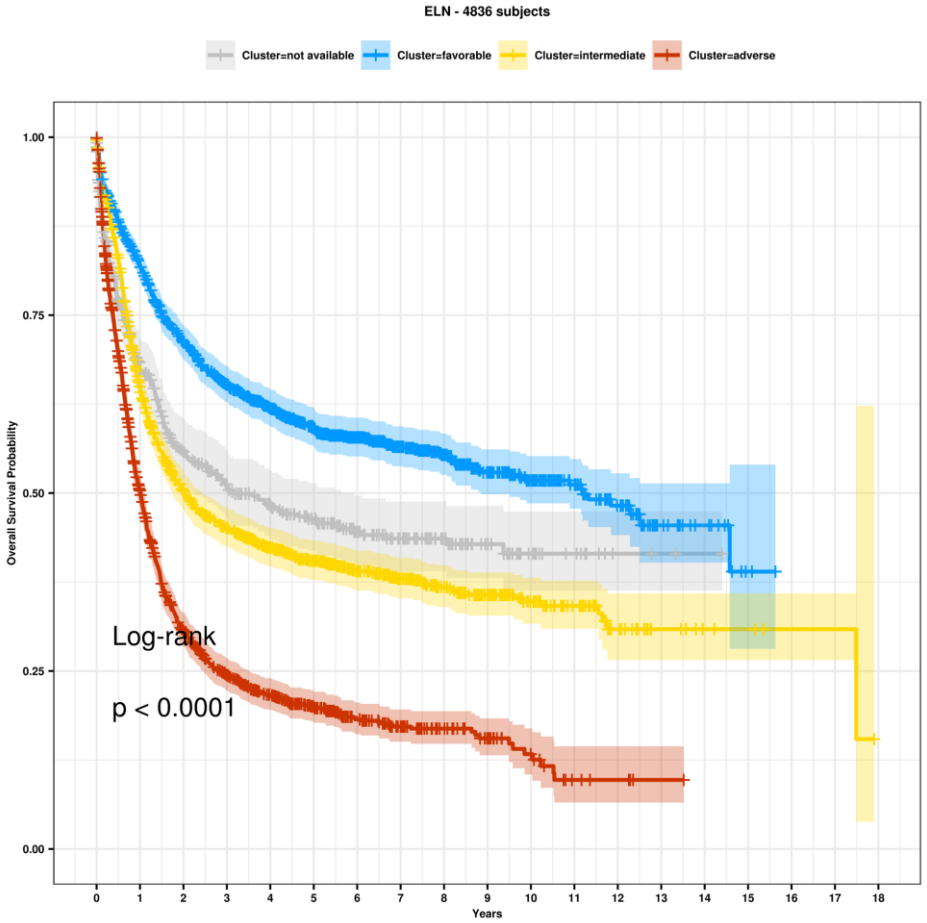
Lars Bullinger | 12. Oktober 2024 | Basel

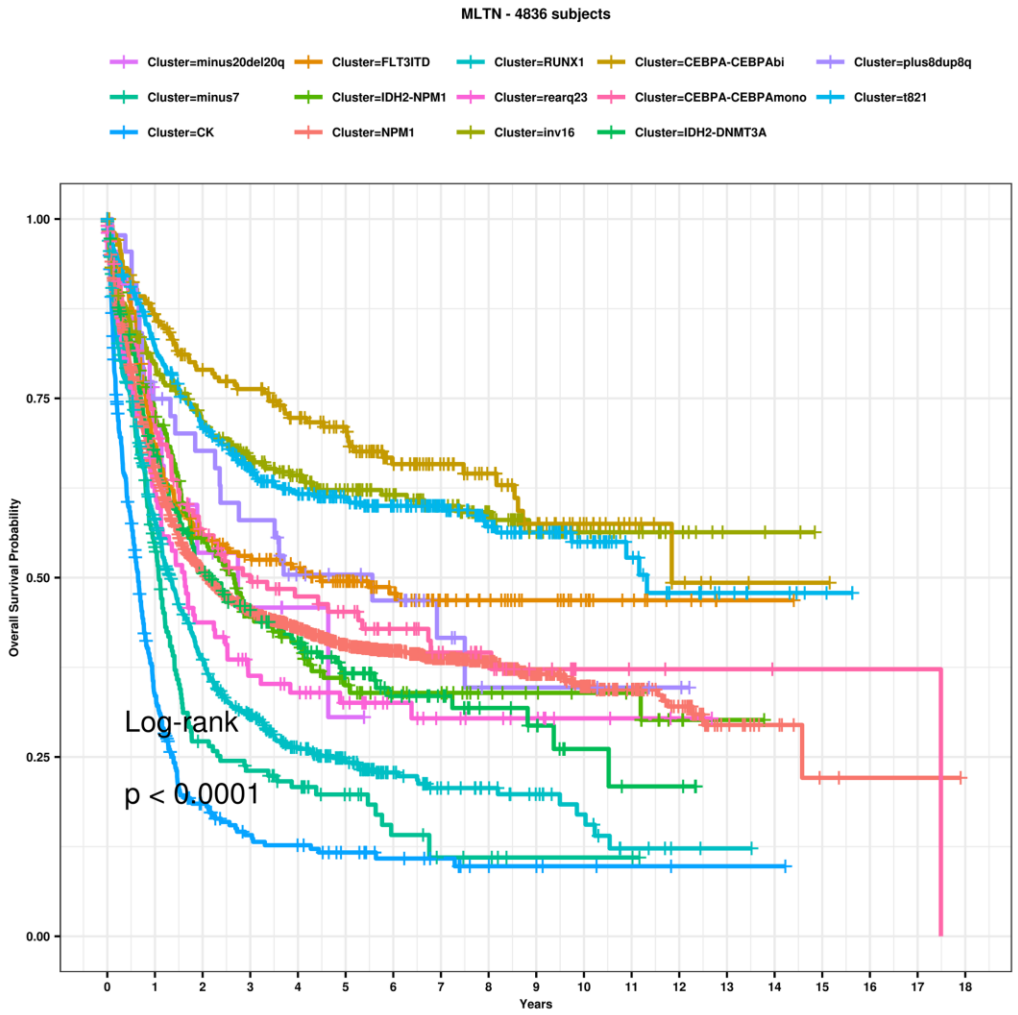
Department of
Hematology, Oncology and
Cancer Immunology (CVK)

Disclosures

- **Research Support/P.I.:** Bayer, Jazz Pharmaceuticals
- **Honoraria:** AbbVie, Amgen, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Janssen, Jazz Pharmaceuticals, Novartis, Otsuka, Pfizer, Sanofi, Seattle Genetics
- **Scientific advisory board:** AbbVie, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Hexal, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Pfizer

Outcomes of intensively-treated AML (n=4836) based on genetic risk groups





HARMONY
Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

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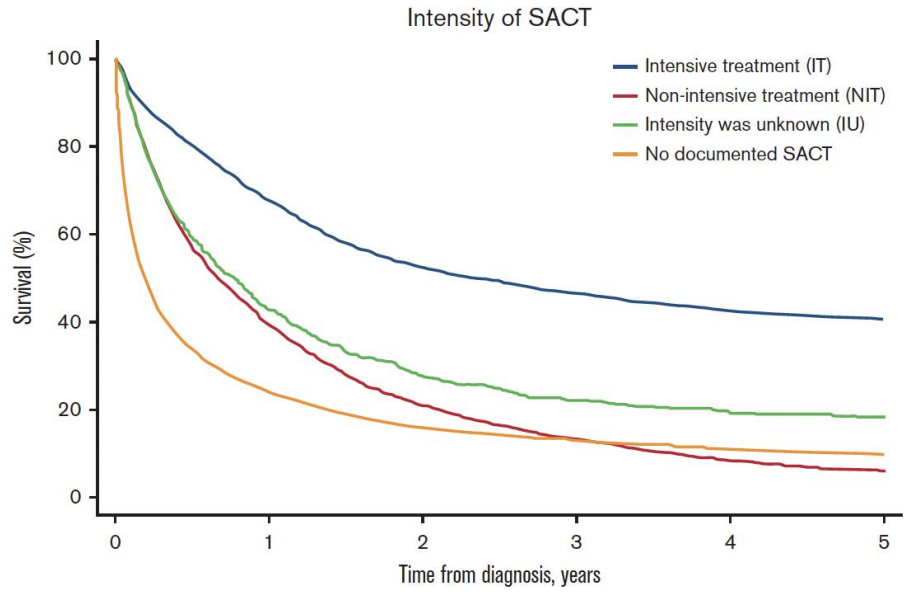
Turki et al. ELN 2024, unpublished data, do not post

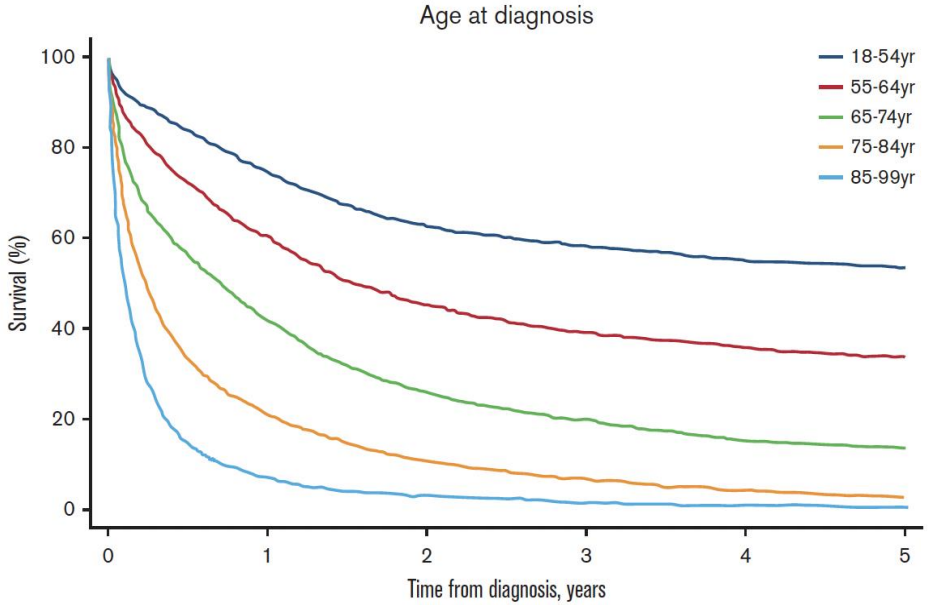
AML Outcome UK (NHS)

Population-based Registry 2013-2020, n= 17107



No. at risk (deaths)

IT	4971	(1609)	3361	(755)	2605	(281)	1997	(159)	1527	(62)	1179
NIT	2386	(1449)	937	(437)	499	(159)	236	(81)	116	(26)	57
IU	546	(312)	234	(84)	150	(27)	99	(12)	72	(3)	62
No documented SACT	8870	(6729)	2141	(738)	1403	(251)	1069	(165)	824	(77)	664



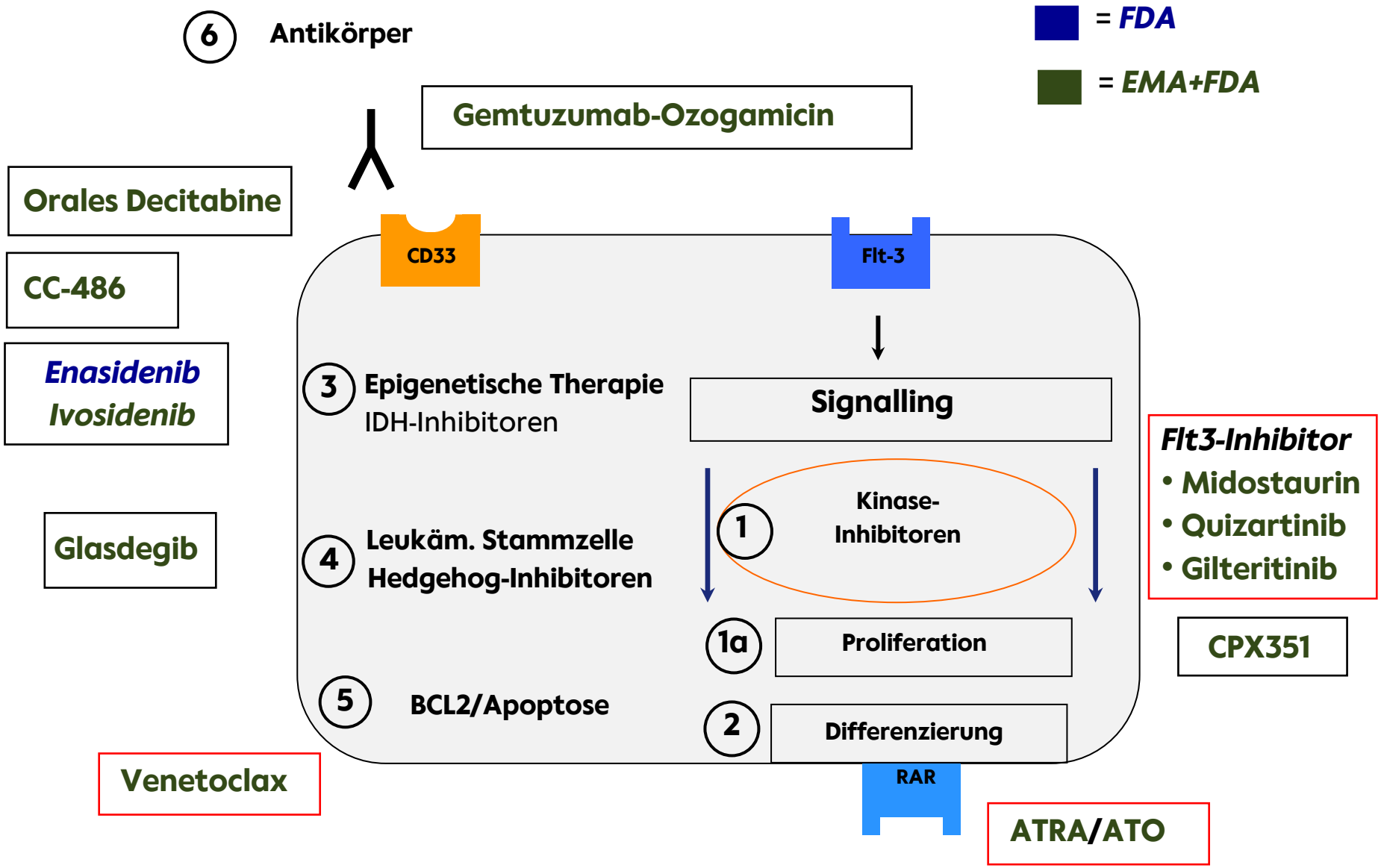
No. at risk (deaths)

18-54yr	2937	(736)	2201	(352)	1848	(124)	1505	(75)	1222	(30)	995
55-64yr	2409	(948)	1460	(367)	1093	(138)	830	(68)	667	(38)	532
65-74yr	4441	(2577)	1864	(710)	1154	(256)	765	(165)	495	(52)	366
75-84yr	4717	(3726)	991	(492)	498	(172)	268	(95)	137	(39)	61
85-99yr	2269	(2112)	157	(93)	64	(28)	33	(14)	18	(9)	8

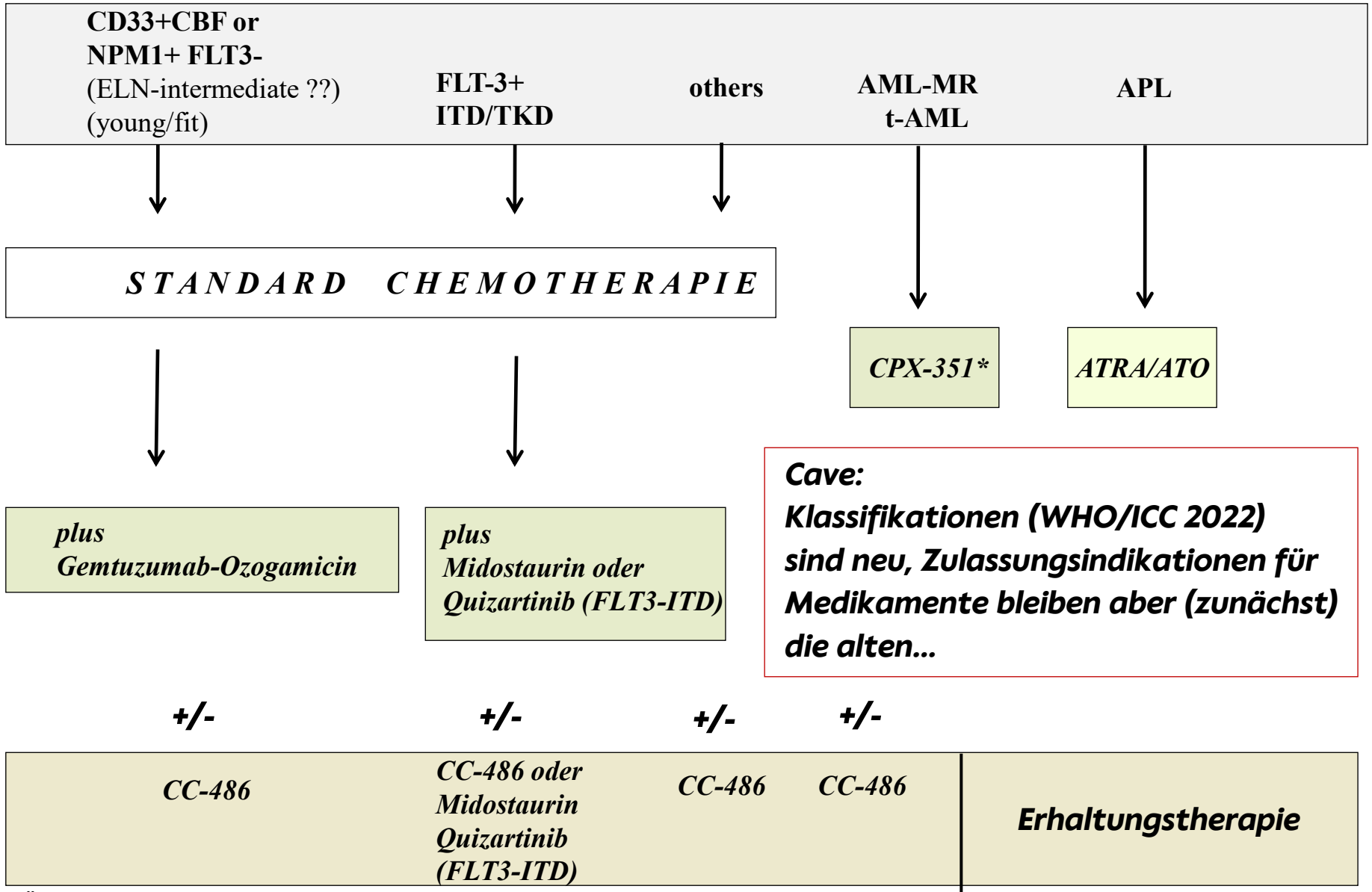
Patienten- und AML-assoziierte Basischarakteristika sowie Therapiemodalität sind/bleiben wichtigste prognostische Faktoren

Liu-H et al. Blood Adv 2024

AML: Zulassung neuer Medikamente (seit 2017)



AML: Therapie bei jüngeren/fitten Patienten 2024



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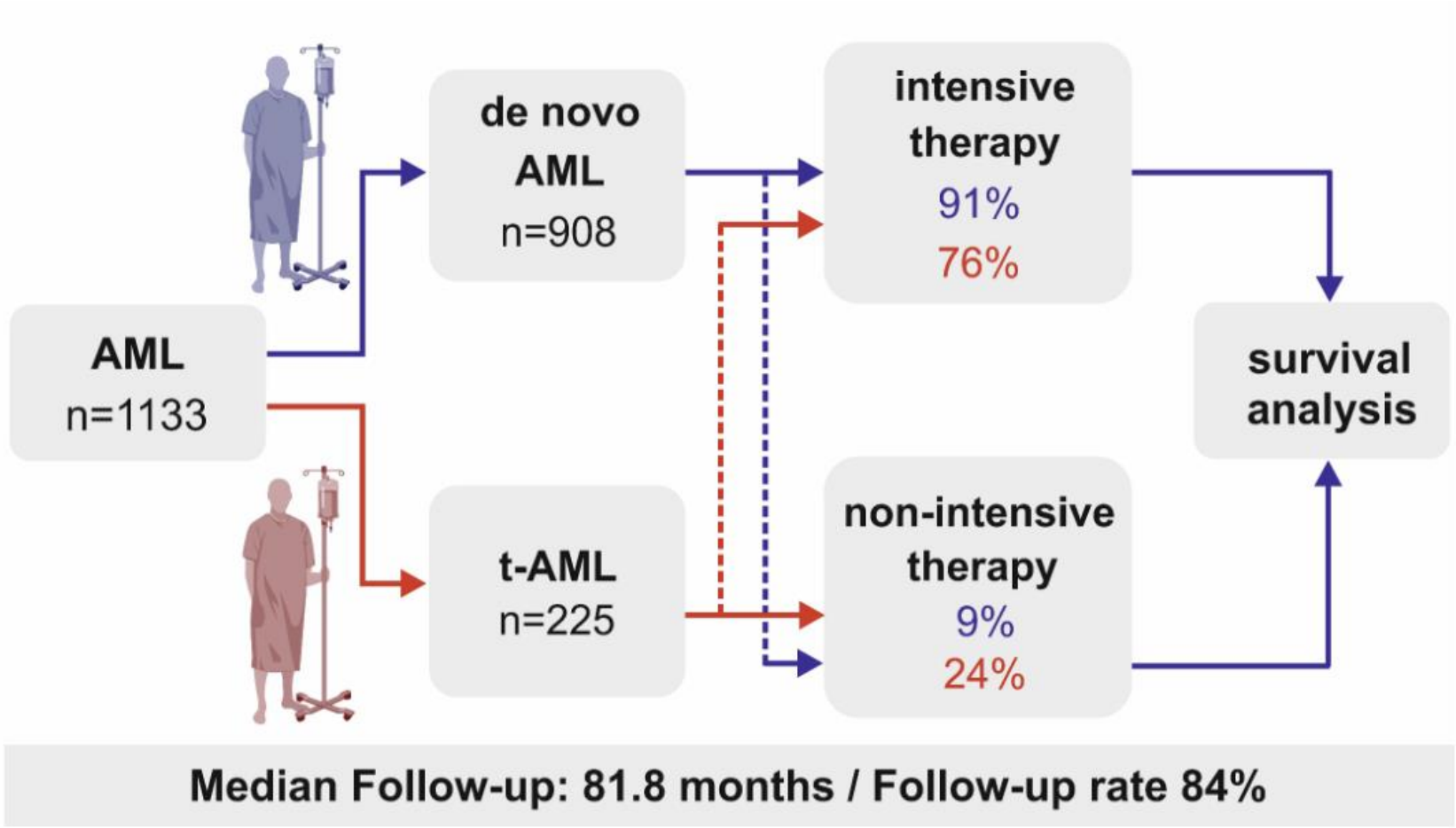
* = Überlegenheit formal für Pat ≥ 60 J. gezeigt

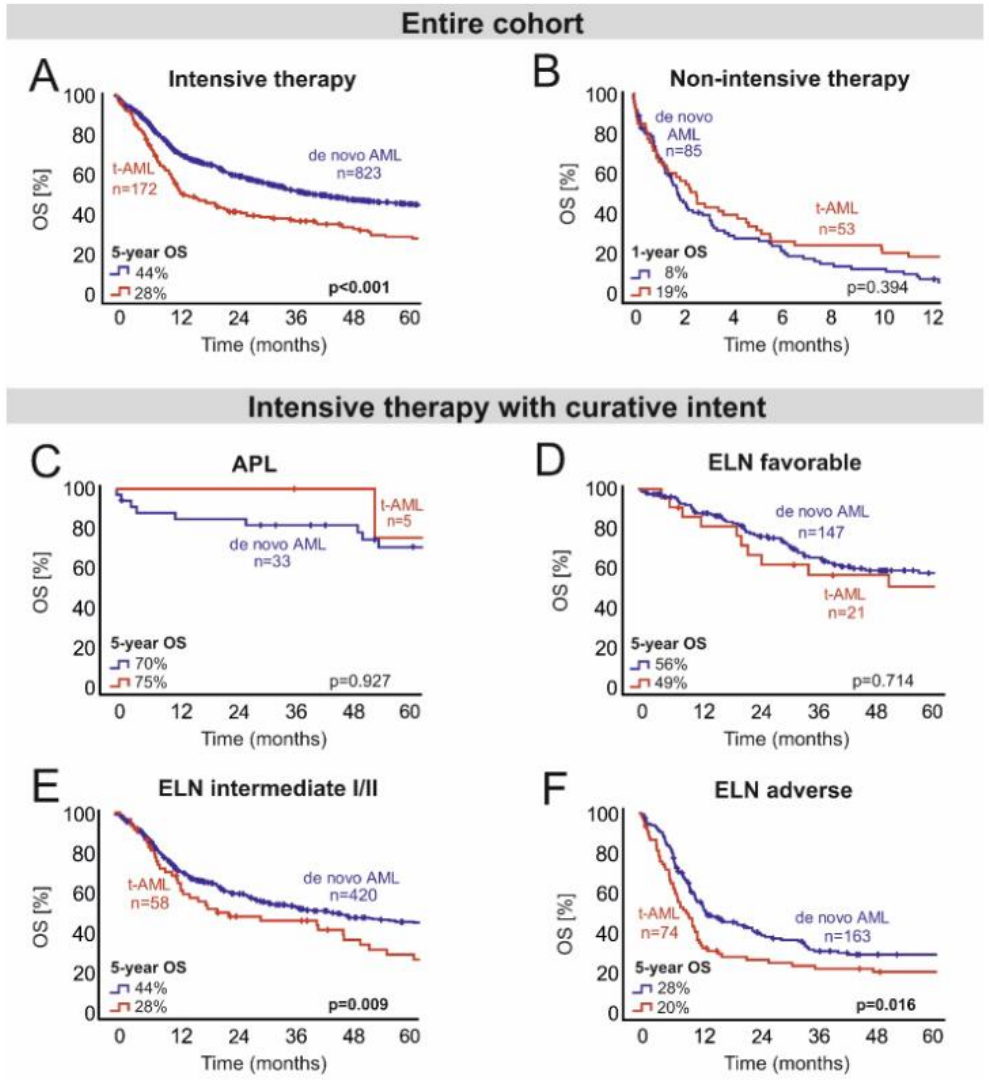
modif. nach Westermann-J & Bullinger-L; Sem Cancer Biol 2021

t-AML ist kein Risikofaktor per se Therapiekonzept (Allo-SZT) sollte in Analogie zu de novo AML erfolgen



Gross-S, Ihlow-J et al. Blood Cancer J 2024

t-AML ist kein Risikofaktor per se



Fazit:

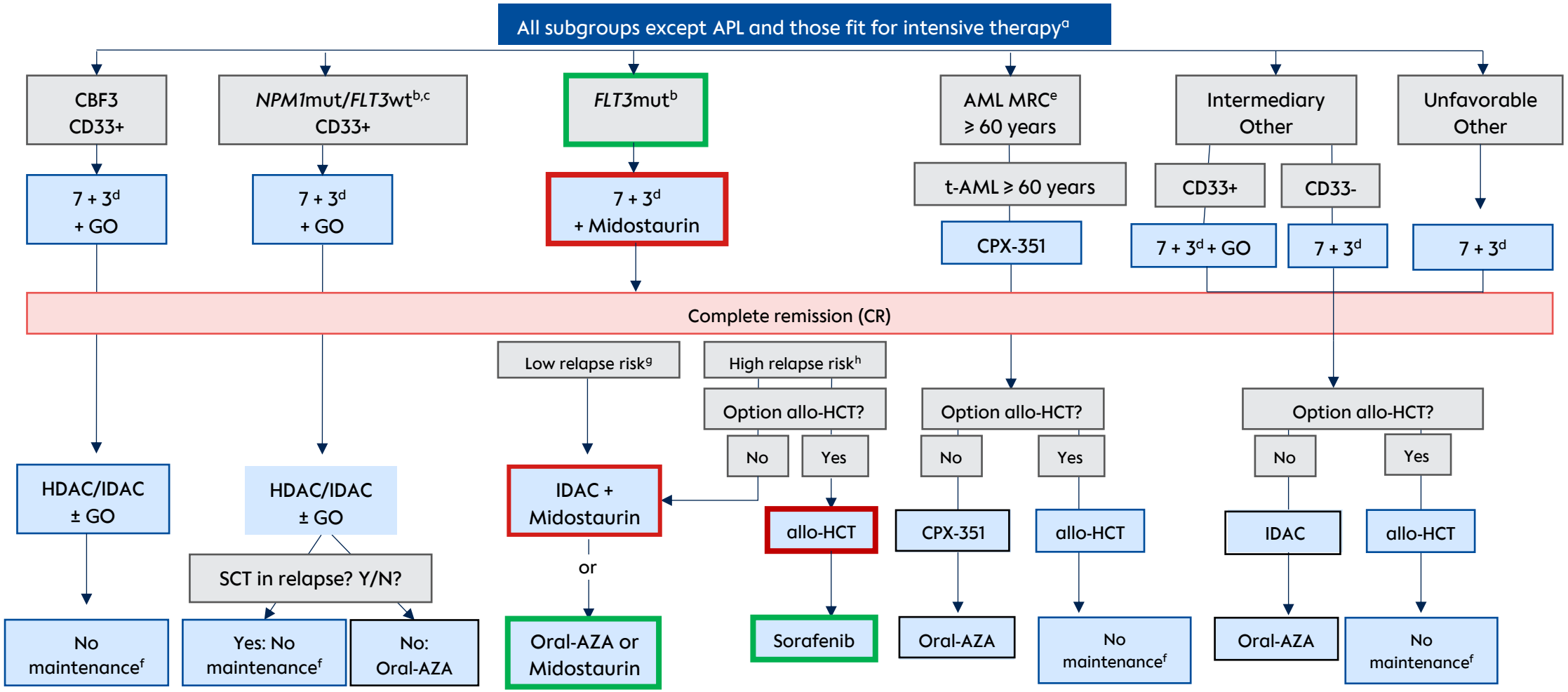
t-AML ist in multivariater Analyse kein Risikofaktor per se

Langzeitprognose wird von Patienten-assoziierten und genetischen Charakteristika der AML bestimmt

Hat Konsequenz insbesondere für Erstlinientherapie in ELN favorable Patienten

Gross-S, Ihlow-J et al. Blood Cancer J 2024

Onkopedia Guidelines 2024: Intensive Erstlinientherapie



Note: This slide may include information about investigational products and/or uses that are not approved for use in any country or in the country of your residence. [a] Based on ECOG status and comorbidity; [b] According to the European LeukemiaNet ELN classification; [c] Includes biallelic CEBPA mutated patients; [d] Therapy regimen with cytarabine on 7 days, daunorubicin on 3 days; [e] AML with myelodysplastic changes; [f] MRD monitoring if possible; [g] LT3-ITDlow + NPM1mut without relevant MRD or FLT3-TKD + NPM1mut without relevant MRD; [h] FLT3-ITDlow+NPM1mut with relevant MRD or FLT3-TKD+NPM1mut with relevant MRD or FLT3-ITDhigh+NPM1mut or FLT3-ITD+NPM1wt or FLT3-TKD+NPM1wt. allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CBF3, core-binding factor 3; CD, cluster of differentiation; CPX-351, cytarabine and daunorubicin; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; FLT3, FMS-like tyrosine kinase 3; GO, gemtuzumab ozogamicin; HDAC, high-dose cytarabine; IDAC, intermediate-dose cytarabine; MRD, minimal residual disease; NPM1, nucleophosmin 1; t-AML, therapy-associated AML; SCT, stem cell transplant. Adapted from Onkopedia. Accessed May 3, 2024. https://www.onkopedia.com/de/onkopedia/guidelines/akute-myeloische-leukaemie-aml/@@guideline/html/index.html. Onkopedia Guidelines for AML.

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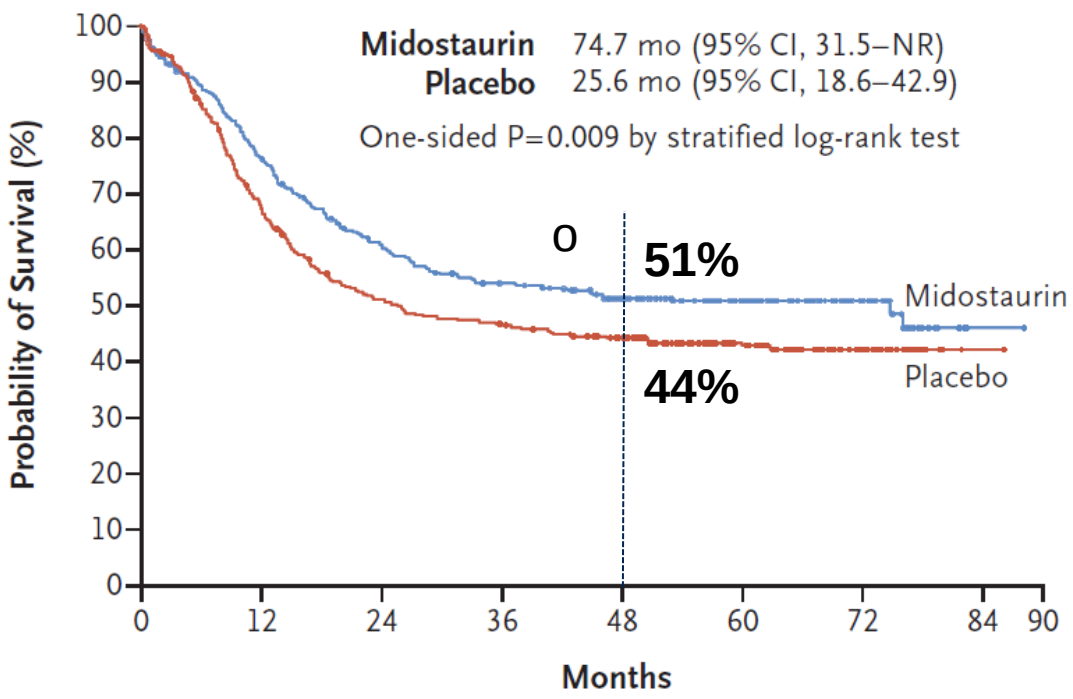
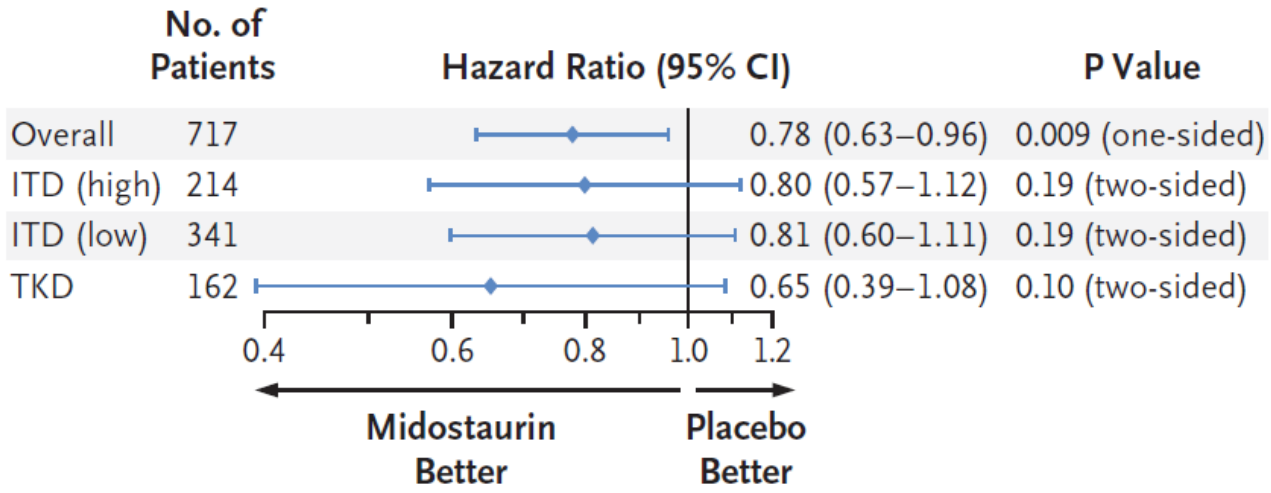
FLT3-mutierte AML: zielgerichtete Therapie (RATIFY Studie)

Median OS



OS Subgroup Analysis



Toxicity

No difference in early mortality

Higher rate of rash and GI toxicity with midostaurin

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CI, confidence interval; GI, gastrointestinal; ITD, internal tandem duplication; mo, month; NR, not reached; OS, overall survival; TKD, tyrosine kinase domain.

Stone RM et al. N Engl J Med 2017;377(5):454-464.

SORMAIN study: Sorafenib as post-transplant maintenance therapy

Study design

Randomized, placebo-controlled, double-blind, multicenter, Phase 2 trial

Eligibility:

- *FLT3*-ITD-positive
- CHR after HSCT

Upfront consolidation or conditioning HCT with or without prior CHR

N = 83

Randomized 1:1

Sorafenib (n = 43)

(escalation up to 800 mg daily)

Placebo (n = 40)

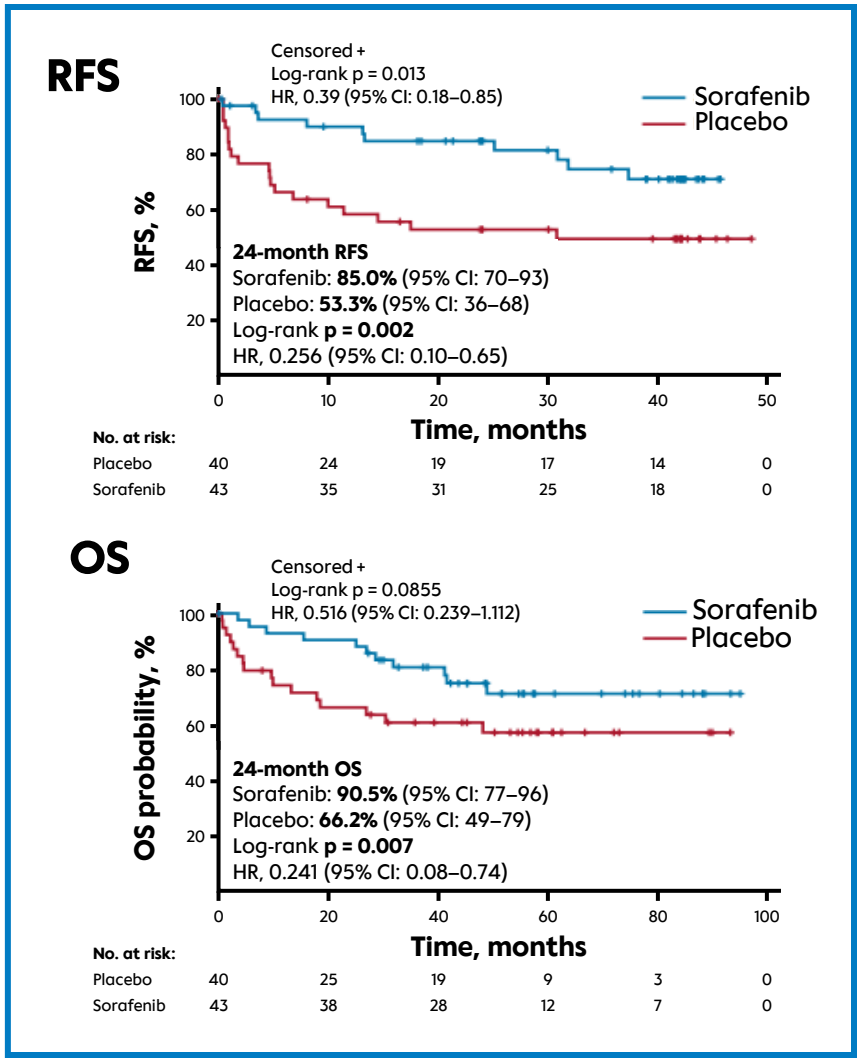
Continued for ≥ 24 months, or until disease relapse or unacceptable toxicity

Treatment after relapse performed according to center-specific standards

Primary Endpoint: RFS

Secondary Endpoints:

OS, *FLT3*-ITD ratio, *NPM1* mutational status, GvHD incidence, safety



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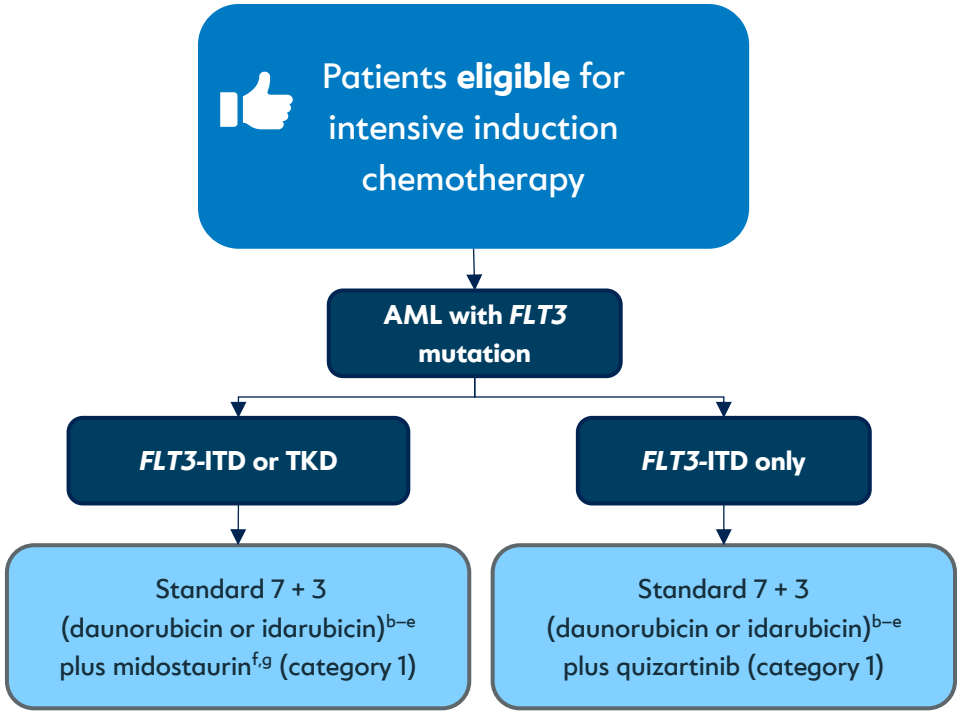
Note: Data not evaluated/approved by health authorities for sorafenib.

AML, acute myeloid leukemia; CHR, complete hematologic remission; CI, confidence interval; FLT3, FMS-like tyrosine kinase 3; GvHD, graft versus host disease; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; NPM1, nucleophosmin 1; OS, overall survival; RFS, relapse-free survival; R/R, relapsed or refractory.

Burchert A, et al. J Clin Oncol. 2020;38:2993–3002.

Treatment options for AML with *FLT3* mutation

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1,a]



EMA 2023[2]

On September 14, 2023, the CHMP recommended the granting of a marketing authorisation for **quizartinib**, intended for the treatment of *FLT3*-ITD positive AML

Quizartinib is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by **quizartinib** single-agent maintenance therapy for adult patients with newly diagnosed AML that is *FLT3*-ITD positive[2]

[a] National Comprehensive Cancer Network® (NCCN®) makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. [b] For patients who exceed anthracycline dose or have cardiac issues but are still able to receive aggressive therapy, alternative non-anthracycline-containing regimens may be considered (e.g. FLAG, clofarabine-based regimens [category 3]). [c] ECOG reported a significant increase in CR rates and overall OS using daunorubicin 90 mg/m^2 x 3 days versus 45 mg/m^2 x 3 days in patients < 60 years of age.[3] If there is residual disease on Days 12–14, the additional daunorubicin dose is 45 mg/m^2 x 3 days.[4] [d] For patients with impaired cardiac function, other cytarabine-based regimens alone or with other agents can be considered. [e] The CR rates and 2-year OS in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m^2 are also comparable to the outcome for idarubicin 12 mg/m^2; the higher-dose daunorubicin did not benefit patients > 65 years of age.[5] [f] While midostaurin is not FDA-approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months.[6] [g] The RATIFY trial studied patients aged 18–60 years with *FLT3*-mutated AML. An extrapolation of the data suggests that patients aged 61–70 years with *FLT3*-mutated AML who are fit to receive 7 + 3 should be offered midostaurin since it seems to provide a survival benefit without undue toxicity.[7] AML, acute myeloid leukemia; CHMP, Committee for Medicinal Products for Human Use; ChT, chemotherapy; EMA, European Medicines Agency; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; NCCN, National Comprehensive Cancer Network; TKD, tyrosine kinase domain.

1. Adapted with permission from the NCCN Clinica Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia v.2.2024. © 2024 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available; 2. European Medicine Agency. CHMP summary of positive opinion for Vanflyta. Available at: www.ema.europa.eu/en/medicines/human/summaries-opinion/vanflyta. Accessed October 2023; 3. Fernandez HF, et al. N Engl J Med. 2009;361:1249–1259; 4. Burnett AK, et al. Blood. 2015;125:3878–3885; 5.Löwenberg B, et al. N Engl J Med. 2009;361:1235–1248; 6. Stone RM, et al. N Engl J Med. 2017;377:454–464; 7. Schlenk RF, et al. Blood. 2019;133:840–851.

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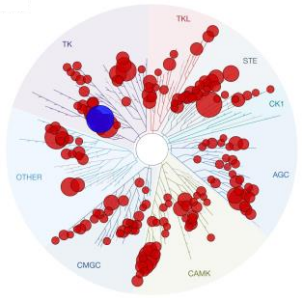
Quizartinib:
A Highly Potent and Selective Type II FLT3 Inhibitor

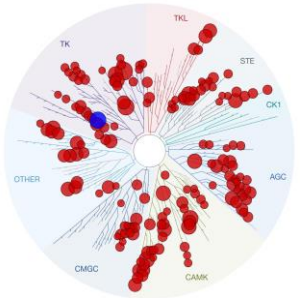
Quizartinib is a highly potent, selective type II FLT3 inhibitor and is more potent in vivo than any other FLT3 inhibitor to date.[1,2]

Type I FLT3 inhibitors[5]

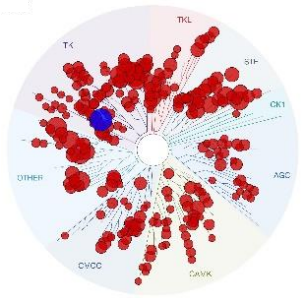
(targets ITD and TKD mutations)



Crenolanib[6]



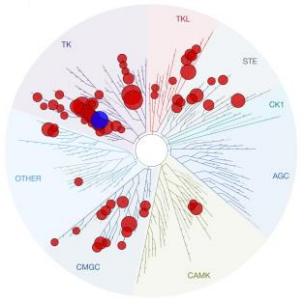
Midostaurin[6]



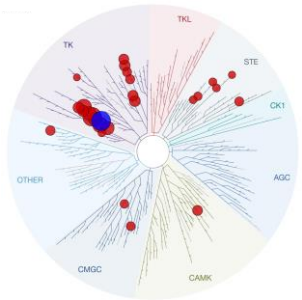
Gilteritinib[6]

Type II FLT3 inhibitors[5]

(targets ITD mutations only)



Sorafenib[6]



Quizartinib[6]

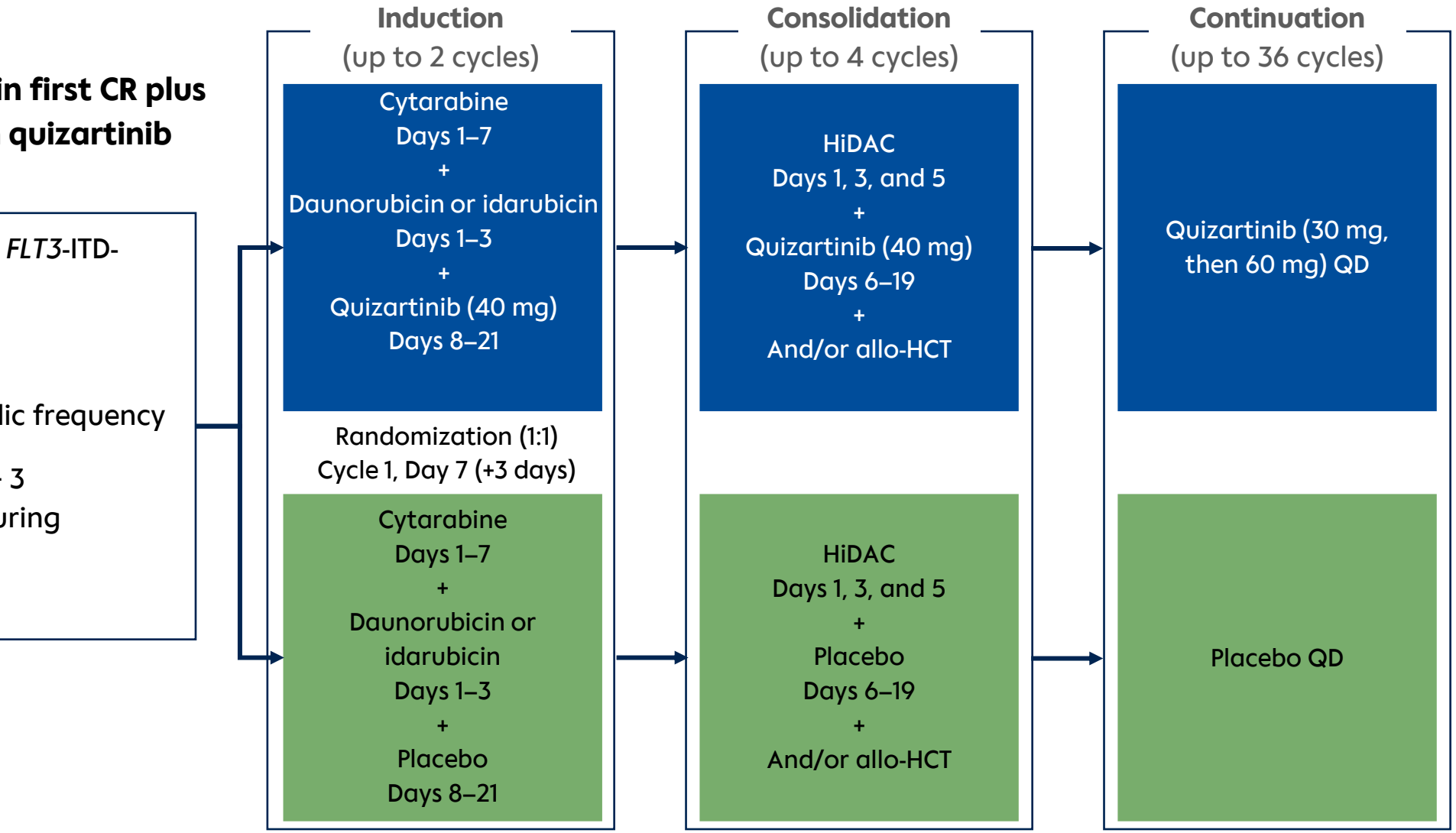
Disclaimer: Please note that a correlation between the PK and PD data of quizartinib and clinical effect has not been established

1. Pratz KW, et al. *Blood.* 2010;115:1425-1432. 2. Lee LY, et al. *Blood.* 2017;129:257-260. 3. Assi R, et al. *Am J Hematol.* 2018;93:553-563.
4. Aikawa T, et al. *Oncotarget*. 2020;11:943-955.

QuANTUM-First: Study design[1,2]

Impact of allo-HCT in first CR plus FLT3 inhibition with quizartinib

- Newly diagnosed *FLT3*-ITD-positive AML
- 18–75 years
- ≥ 3% *FLT3*-ITD allelic frequency
- Patients begin 7 + 3 chemotherapy during screening



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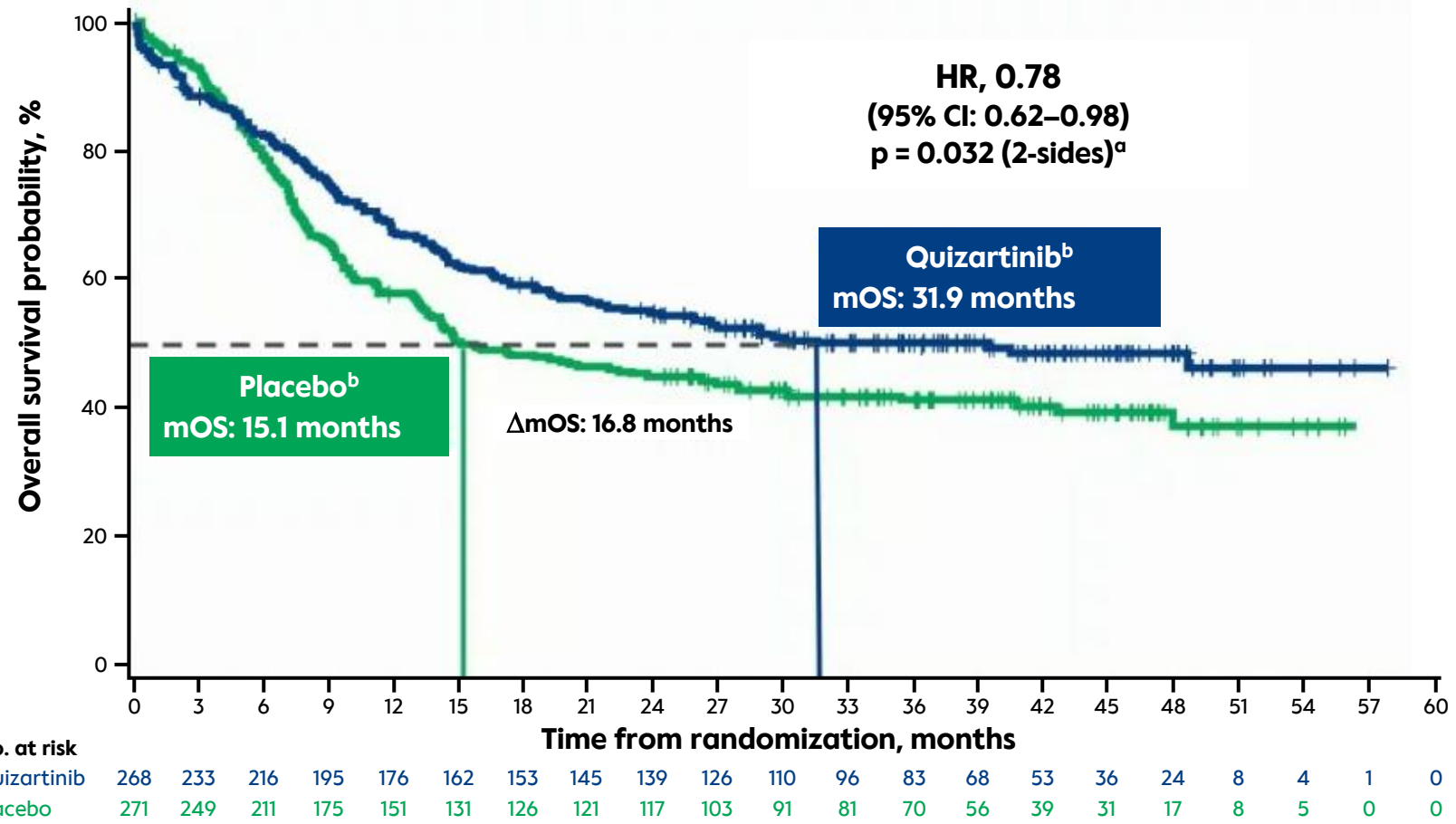
allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CR, complete remission; FLT3, FMS-like tyrosine kinase 3; HiDAC, high-dose cytarabine; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; QD, once daily.

1. Schlenk R, et al. EHA 2023. Abstract S137; 2. Erba H, et al. Lancet. 2023;401:1571–1583.

QuANTUM-First: Overall survival[1,2]

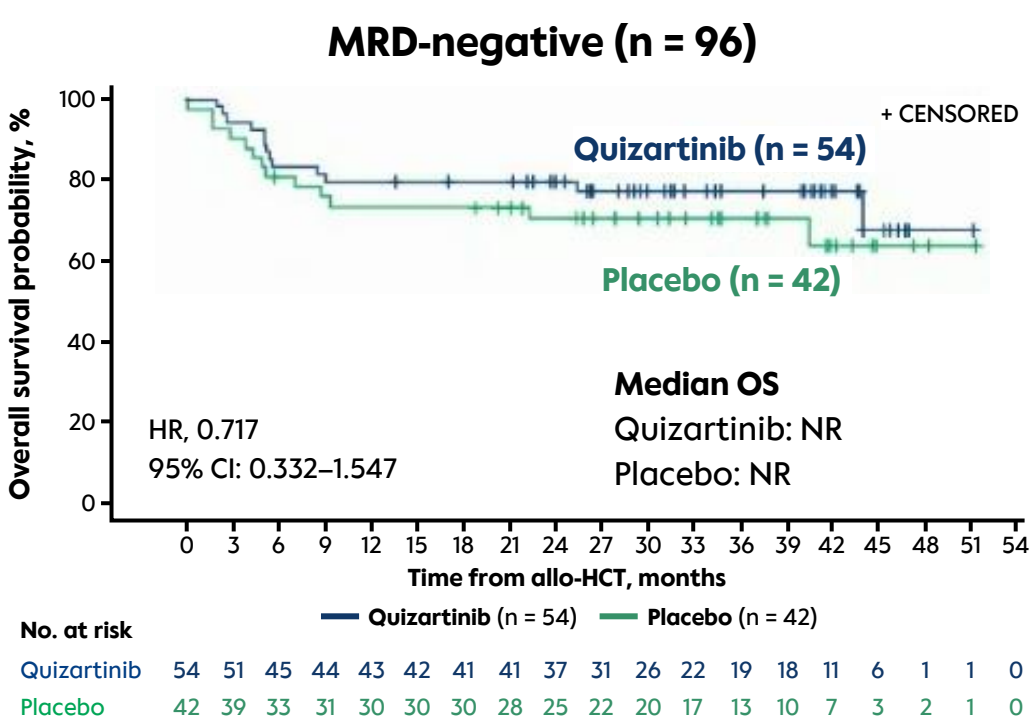


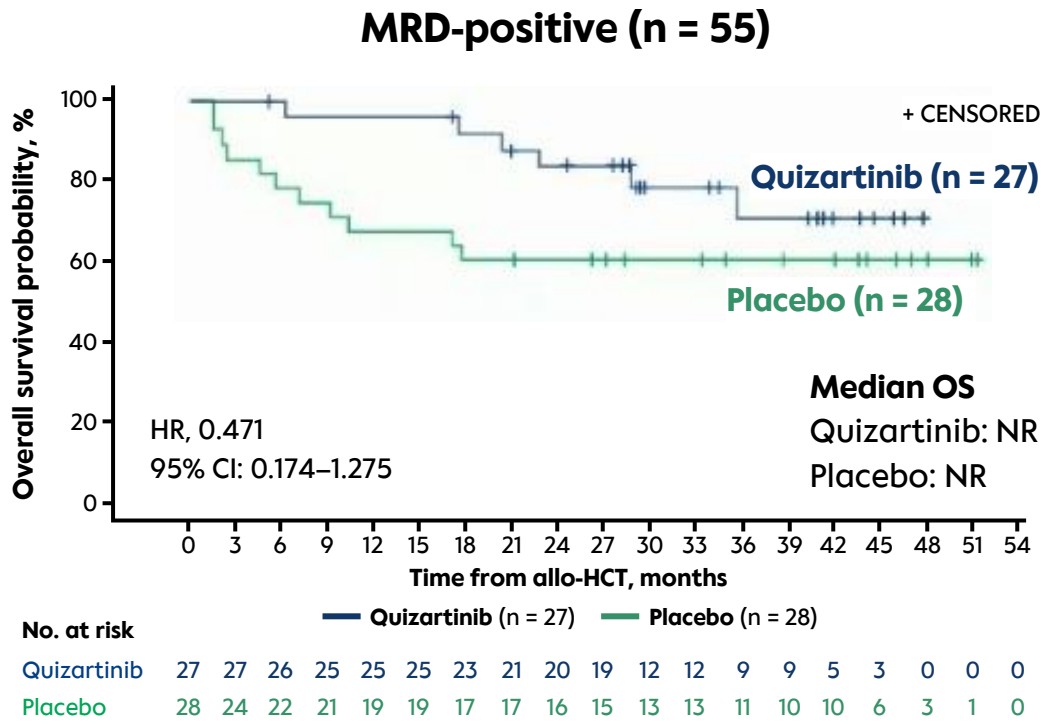
[a] P value was calculated using a stratified log-rank test. [b] Median follow-up time for both arms was 39.2 months.

allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CR, complete remission; FLT3, FMS-like tyrosine kinase 3; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; mOS, median overall survival.

1. Schlenk R, et al. EHA 2023. Abstract S137; 2. Erba H, et al. Lancet. 2023;401:1571–1583(Suppl).

QuANTUM-First: Post-hoc analysis of overall survival in patients undergoing allo-HCT in CR1 by latest pre–allo-HCT *FLT3*-ITD MRD status





[a] Note that of the 157 patients (84 in the quizartinib arm and 73 in the placebo arm) who underwent allo-HCT in CR1, 151 with MRD data were analyzed (81 in the quizartinib arm and 70 in the placebo arm).
Post hoc analysis using Kaplan-Meier plots.

allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CR, complete remission; CR1, first complete remission; FLT3, FMS-like tyrosine kinase 3; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; MRD, minimal residual disease; NR, not reached; OS, overall survival.

Schlenk R, et al. EHA 2023. Abstract S137.

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ELN 2022: treatment recommendations

Patients assessed for IC

Patients fit for IC

Patients not suitable for IC[b]

- Azacitidine or decitabine plus venetoclax
- Low-dose cytarabine plus venetoclax
- Azacitidine plus ivosidenib (AML with *IDH1* mutation)
- Ivosidenib (AML with *IDH1* mutation)
- Best supportive care

Note: management recommendations are given on how to limit the prolonged myelosuppression and risk of TLS associated with the regimens

	Induction	*Consolidation[a]*	*Maintenance*
AML with *FLT3* mutation	Daunorubicin or idarubicin and cytarabine plus midostaurin	IDAC plus midostaurin	Midostaurin
Non-*FLT3* mutant	Daunorubicin, idarubicin, or mitoxantrone and cytarabine	IDAC	Oral azacitidine
CD33-positive AML, favorable (or intermediate) cytogenetic risk	GO, daunorubicin and cytarabine	IDAC/GO may be added	N/S
AML-MRC or t-AML	CPX-351	CPX-351	N/S

Patients not responding to initial induction or with relapsed disease (salvage therapy)

- Gilteritinib (AML with *FLT3* mutation)
- Ivosidenib (AML with *IDH1* mutation)
- Enasidenib (AML with *IDH2* mutation)

Patients not responding to initial induction or with relapsed disease (salvage therapy)

Gilteritinib (AML with *FLT3* mutation)	MEC
Intermediate dose cytarabine (with or without anthracycline)	CLAG-M
FLAG-IDA	Allogeneic HCT

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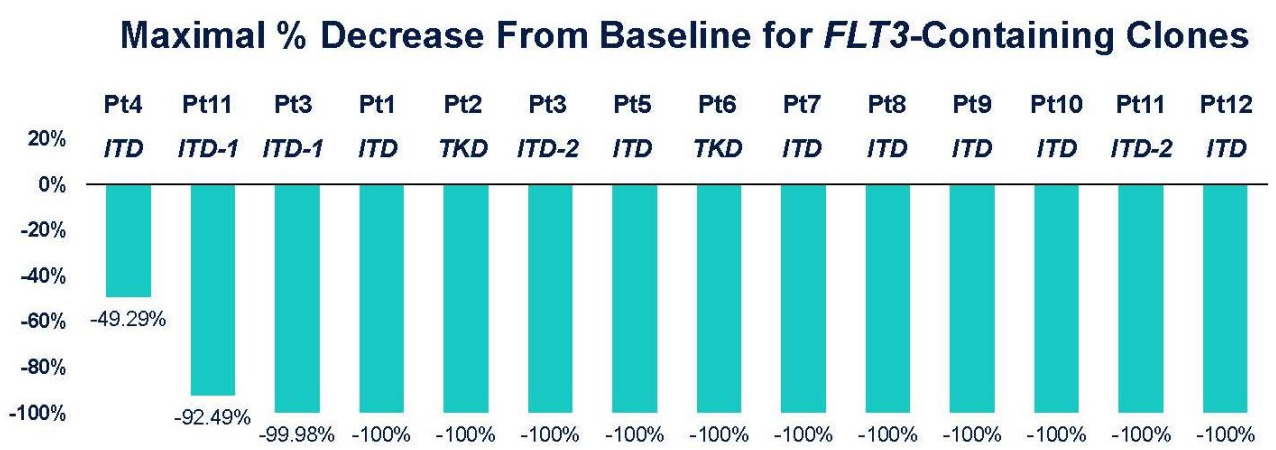
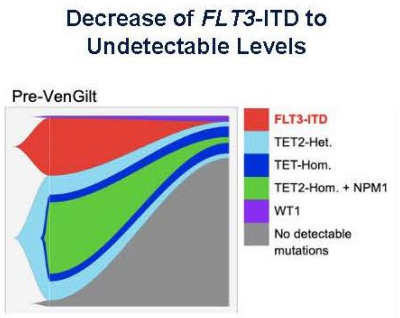
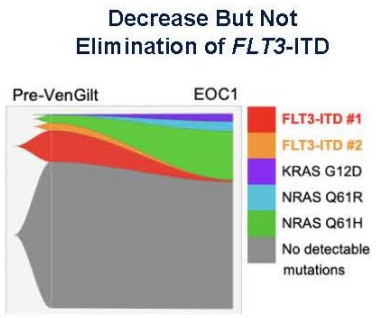
Döhner H, et al. *Blood*. 2022;140:1345–77.

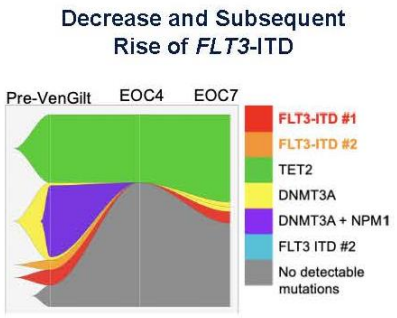
Emerging first-line AML therapies: novel combination therapies

FLT3-mutant AML treated with gilteritinib and venetoclax







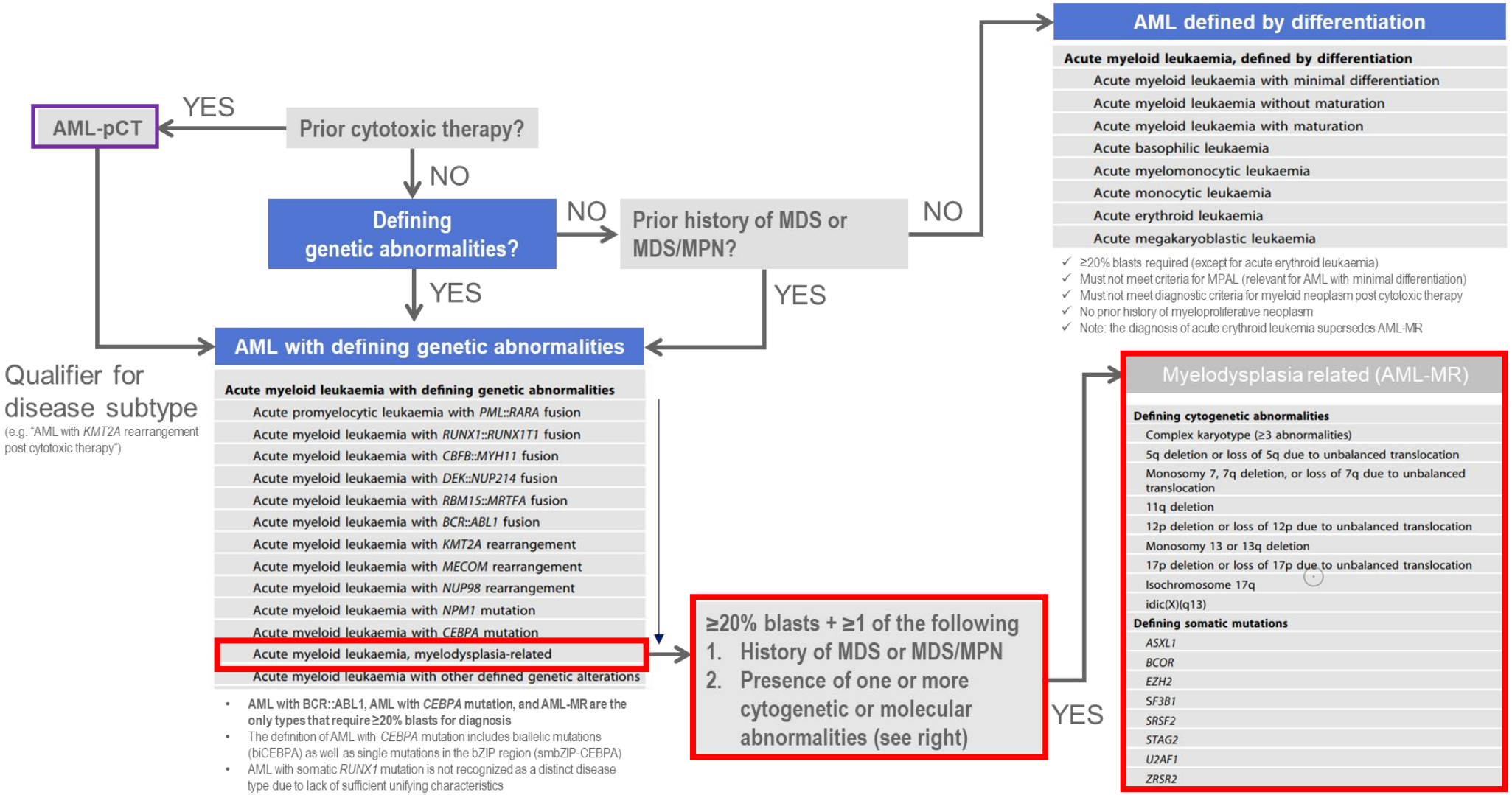


- **All 14** *FLT3*^{mut} clones **decreased** in size on therapy
- **11 clones** from 9 patients decreased to an **undetectable** level at maximum response
- **2 clones** returned at a later time point
- Response was frequently rapid, with maximal decrease of *FLT3* by cycle 1, day 28 of therapy in 5 of 8 evaluable patients
- 7 patients had matching time points where *FLT3*-ITD was evaluated by MyFLT3 specific MRD assay. Sensitivity of decrease ranged between 10^{-2} to 10^{-6}

EOC, end of cycle; ITD, internal tandem duplication; MRD, measurable residual disease; pt, patient; TKD, tyrosine kinase domain; VenGilt, venetoclax and gilteritinib.

Kennedy et al. ASH 2022
Daver et al. J Clin Oncol 2022

WHO Klassifikation 2022 – AML-MR



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1. Adapted from: Khoury JD, et al. Leukemia. 2022

Improved OS with CPX-351 vs conventional chemotherapy

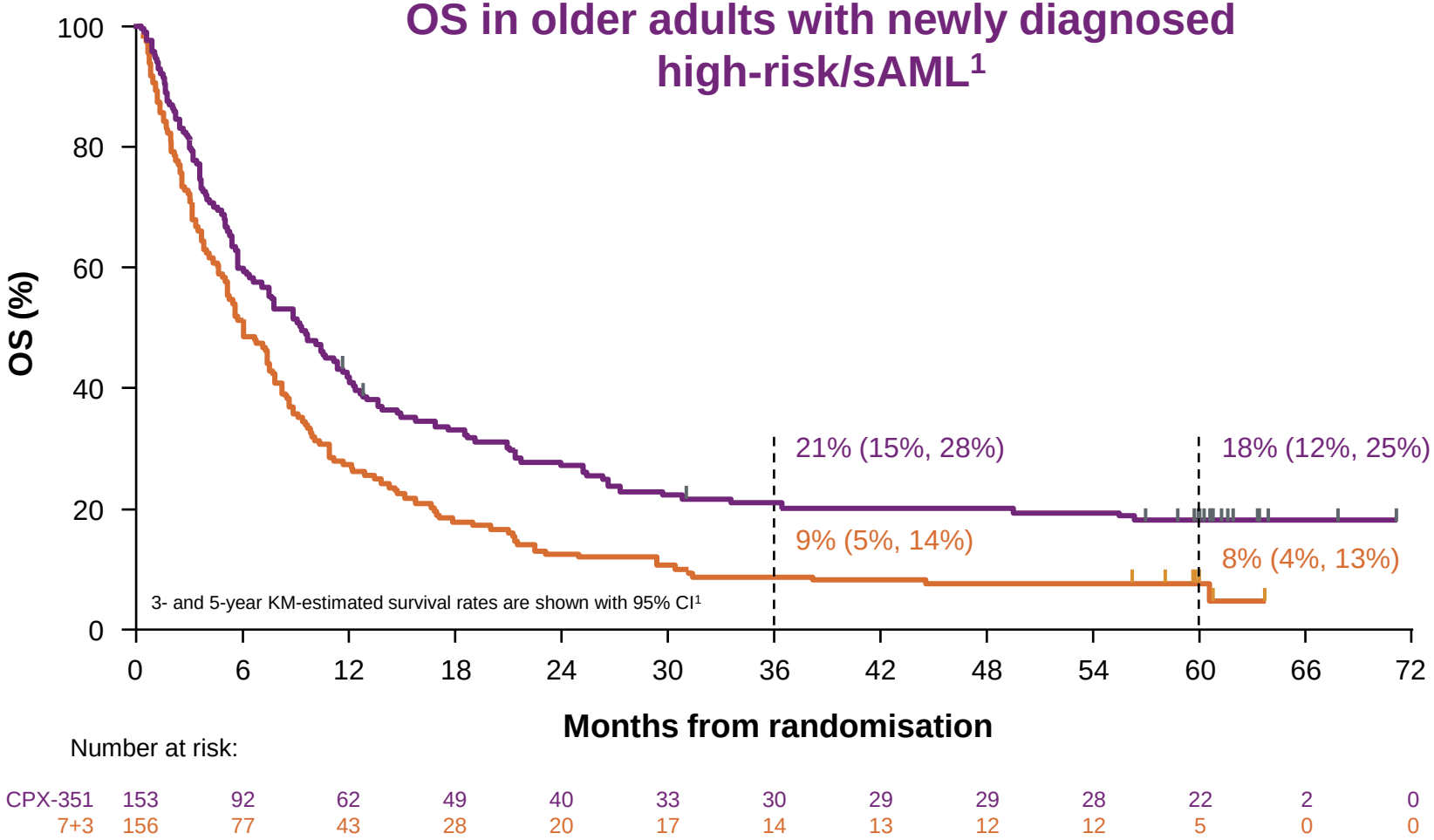
Primary endpoint analysis:[2]

Median OS was significantly improved with **CPX-351 (9.56 months)** compared with **7+3* (5.95 months)**

(HR, 0.69; 95% CI: 0.52, 0.90; 1-sided P=0.003)

Median follow-up of 20.7 months

OS in older adults with newly diagnosed high-risk/sAML[1]



Lancet JE, et al. *Lancet Haematol.* 2021;8:e481–91; 2. Lancet JE, et al. *J Clin Oncol.* 2018;36:2684–92.

Median OS landmarked from the date of HSCT

HCT was performed in **53/153 patients (35%)** in the CPX-351 arm and **39/156 patients (25%)** in the conventional chemotherapy* arm[1]

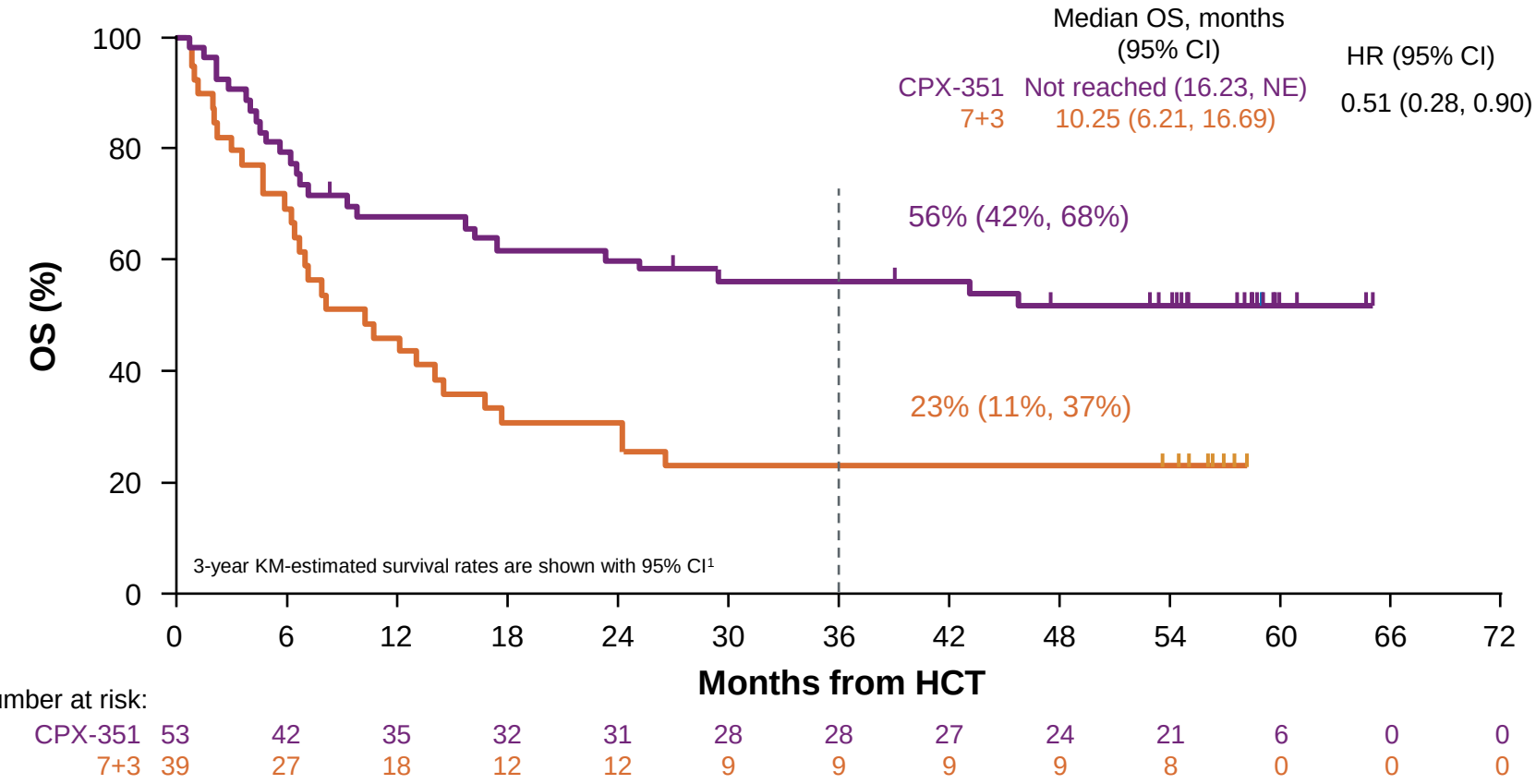
Post hoc analysis[1,3]

In patients who received CPX-351 and underwent HCT, OS was maintained at

>50% at 5 years

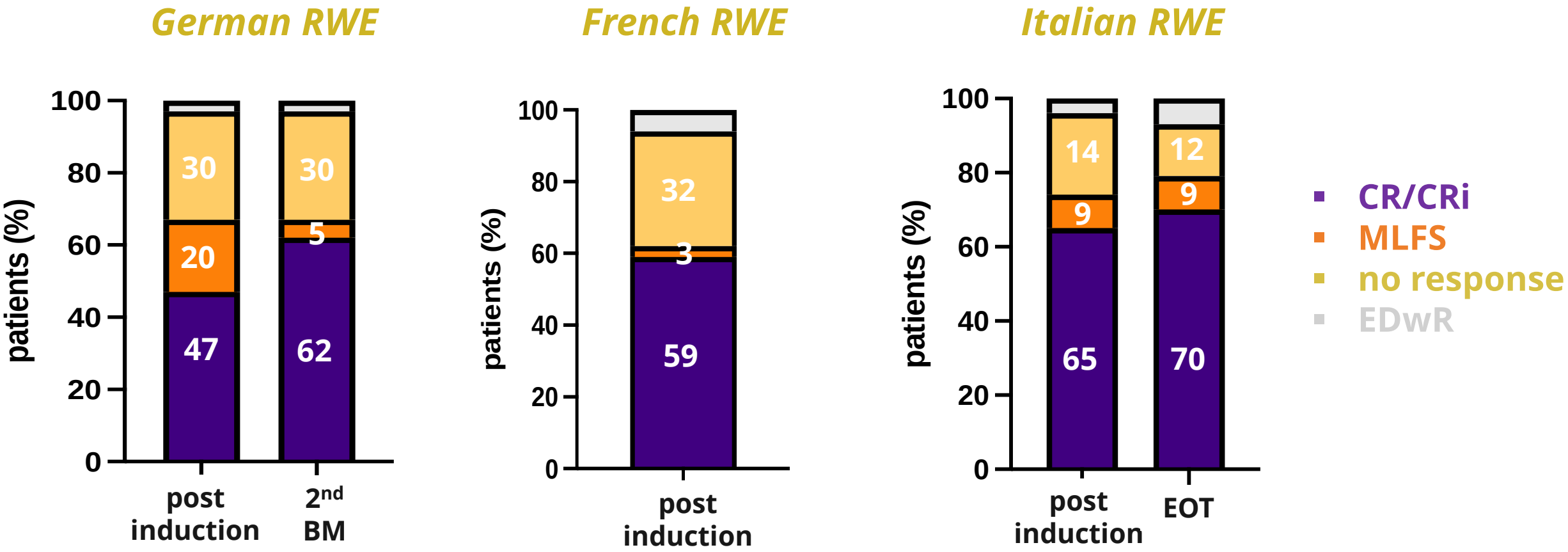
post randomisation

Post hoc analysis: OS from date of HCT in older adults with newly diagnosed high-risk/sAML[1]



Lancet JE, et al. *Lancet Haematol.* 2021;8:e481–91; 2. Lancet JE, et al. *J Clin Oncol.* 2018;36:2684–92.

Response Rates and Predictors for Response – Real World Evidence (RWE) CPX-351



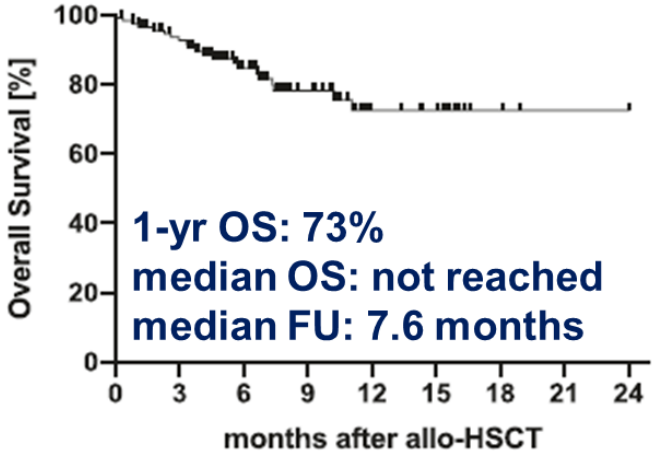
Rautenberg et al. Blood Cancer J 2021; Chiche et al., Blood Adv 2021; Guolo et. al., Blood Cancer J 2020

Outcome after allo-SCT – German RWE

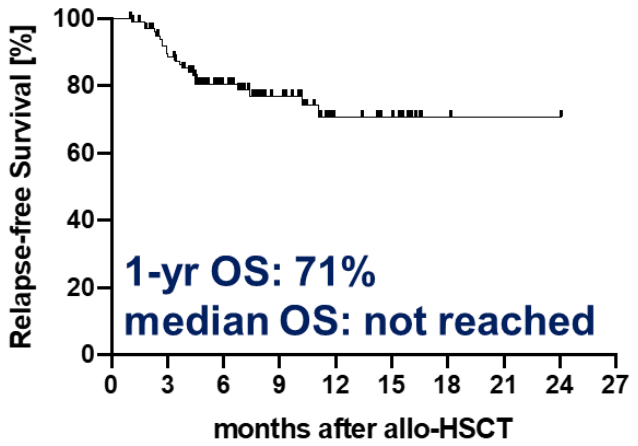
116 patients (62%) proceeded to allo-HSCT

- 82 pts without further therapy
- 34 pts had ≥1 cycle of intermittent therapy (consolidation, HMA or salvage therapy)
- Median time from induction to allo-HSCT was 70 days (range: 11–215 days)

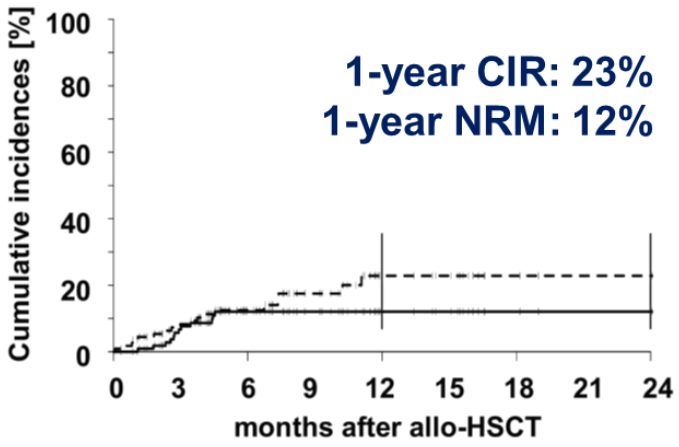
OS transplant cohort



RFS transplant cohort

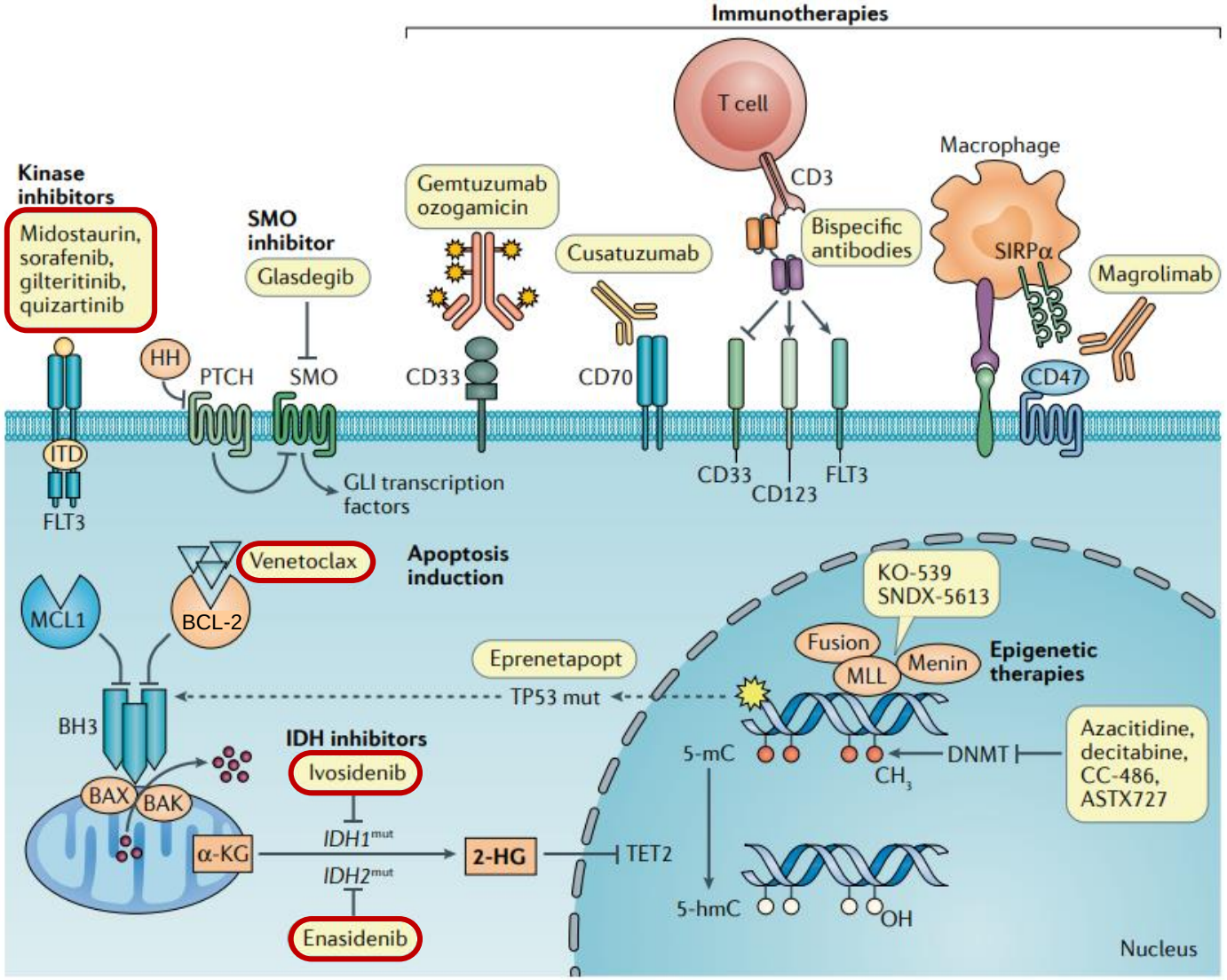


CIR/NRM transplant cohort



Rautenberg et al. Blood Cancer J 2021

Emerging novel compounds for (first-line) AML therapy



Novel small molecule inhibitors

- FLT3 inhibition
- menin inhibition

Immunological treatment approaches

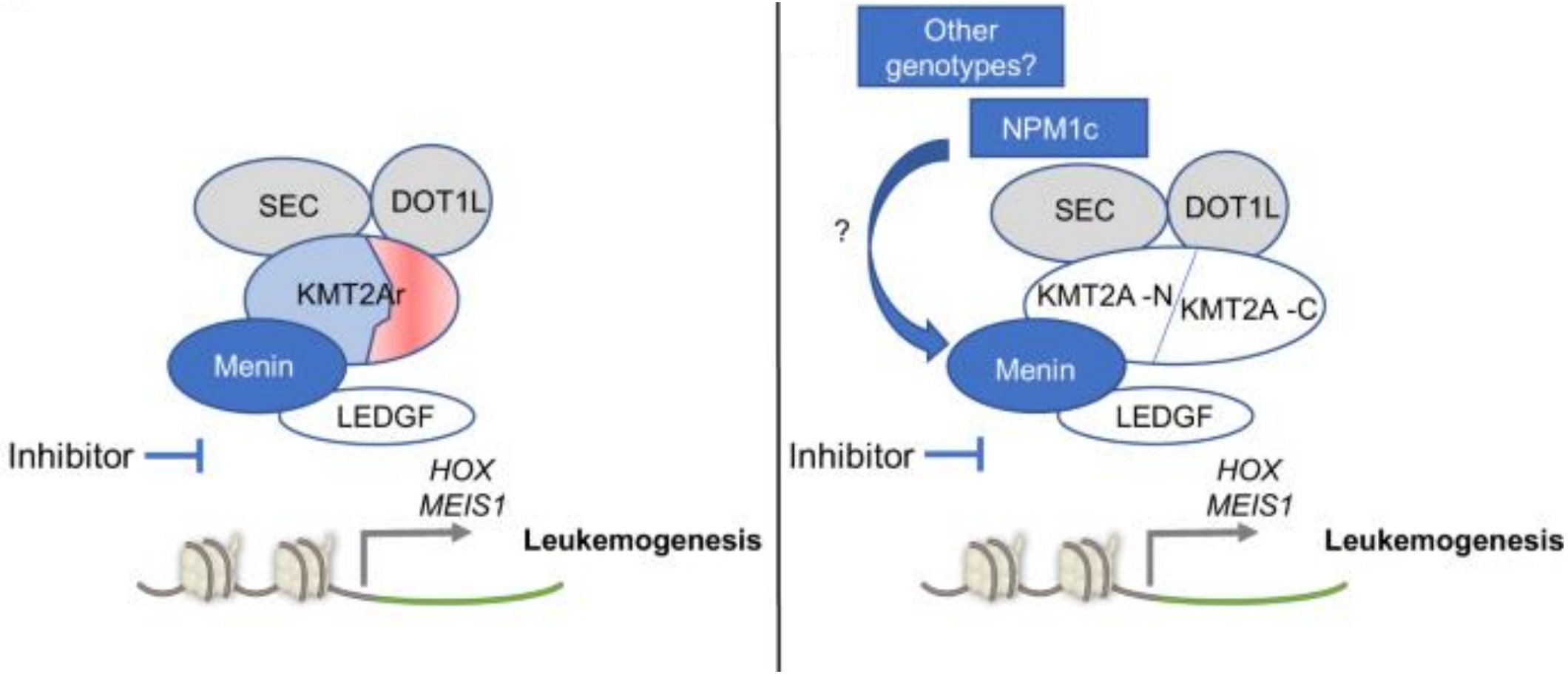
- checkpoint inhibition
- bispecific antibodies / CAR T cell constructs

Additional approaches

- MCL1 inhibition
- TP53 reactivation
- ...

Döhner H, Wei AH, Löwenberg B.
Towards precision medicine for AML.
Nat Rev Clin Oncol. 2021 May 18.

Menin Inhibition (I)

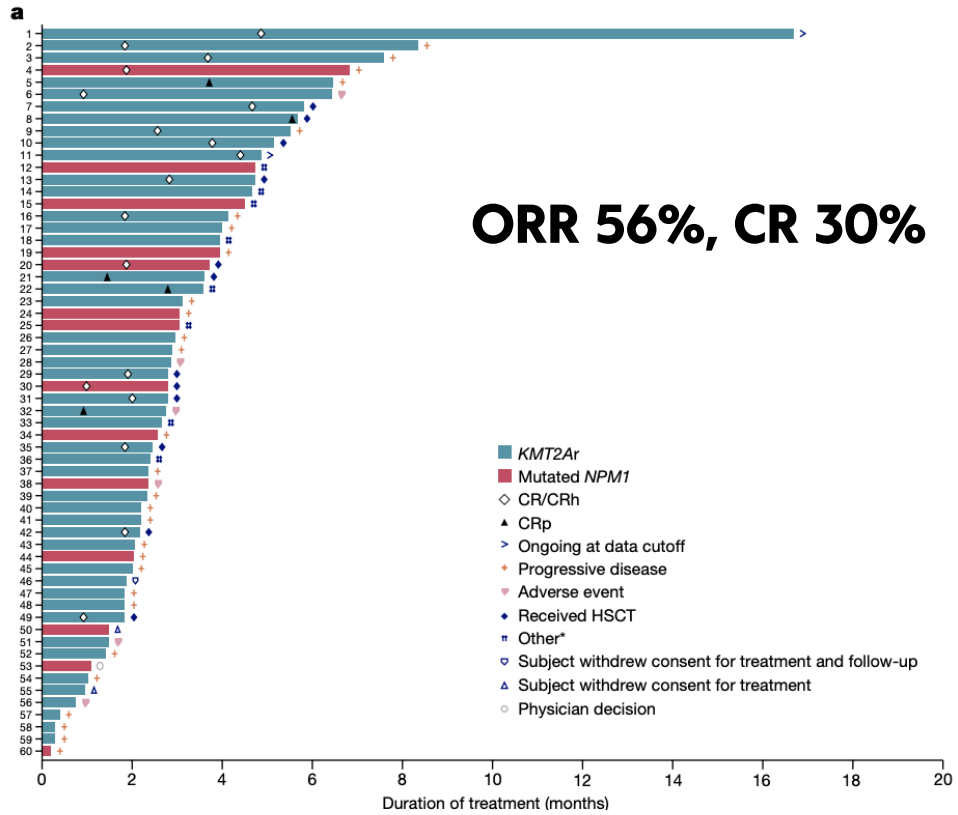


Issa et al. Leukemia 2021

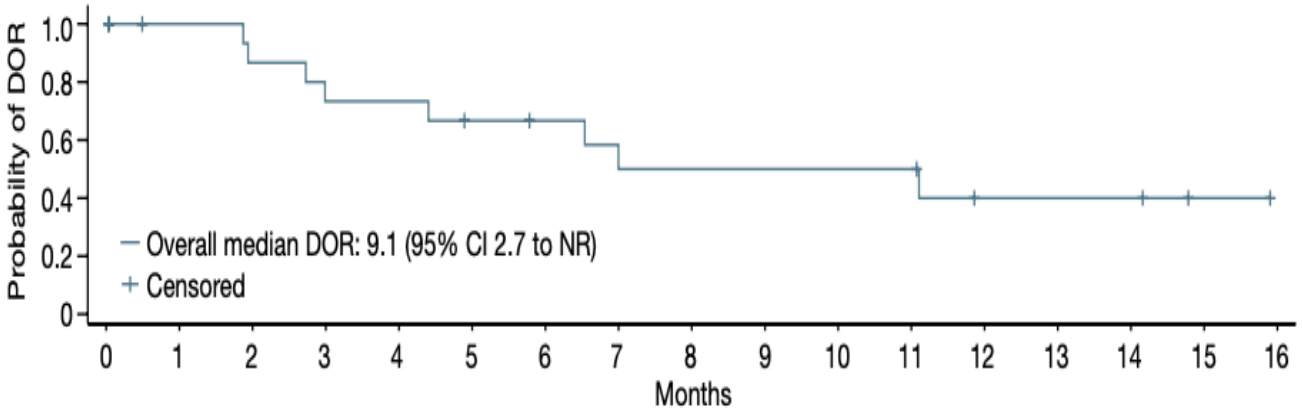
Menin Inhibition (II)

Phase 1 Revumenib (SNDX-5613)

n=60 relapsed AML with *NPM1*^{mut} or MLLr



ORR 56%, CR 30%



<u>Menin Inhibitors in Clinical Trials</u>

Revumenib (SNDX-5613)

KO-539 (ziftomenib)

JNJ-75276617

BMF-219

BN104

DS-1594

DSP-5336

<u>Toxicity</u>

Differentiation Syndrome

QT Prolongation

CHARITÉ

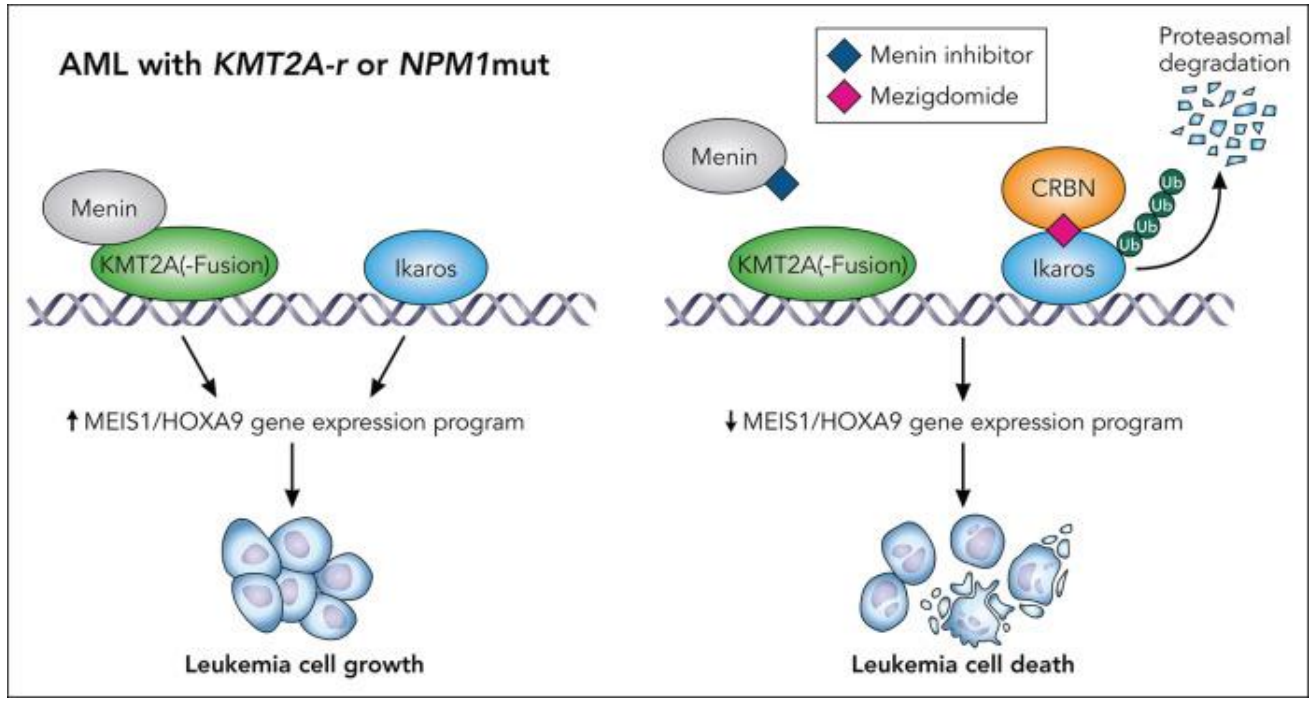
Issa et al. Leukemia 2021

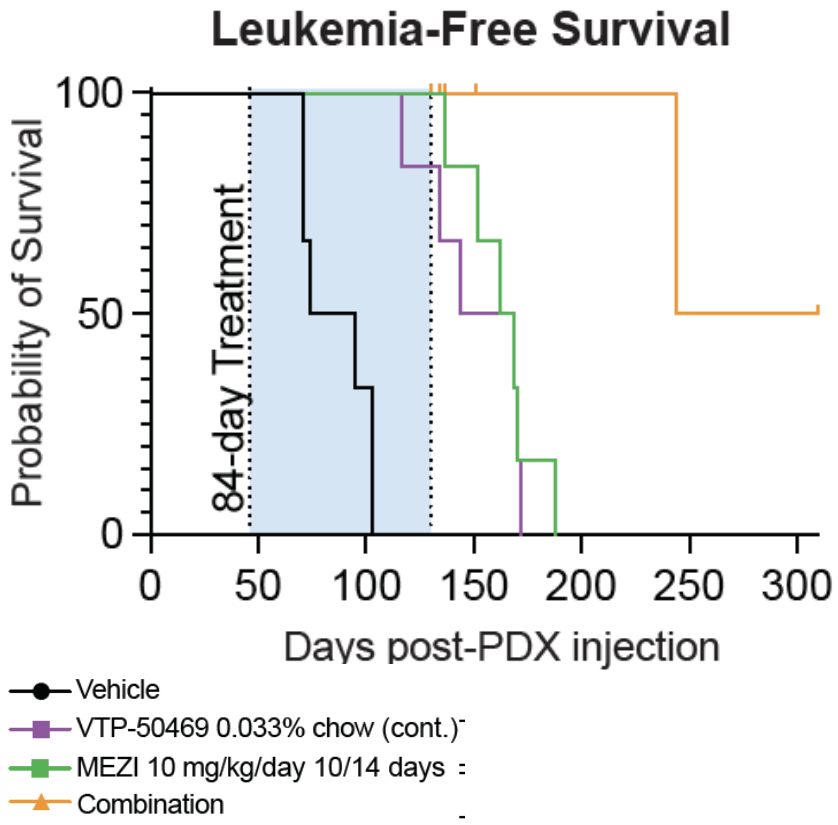
Menin Inhibition (III)

Combination therapies: MENi with Venetoclax + azacytidine

MENi with chemotherapy

MENi with mezigdomide

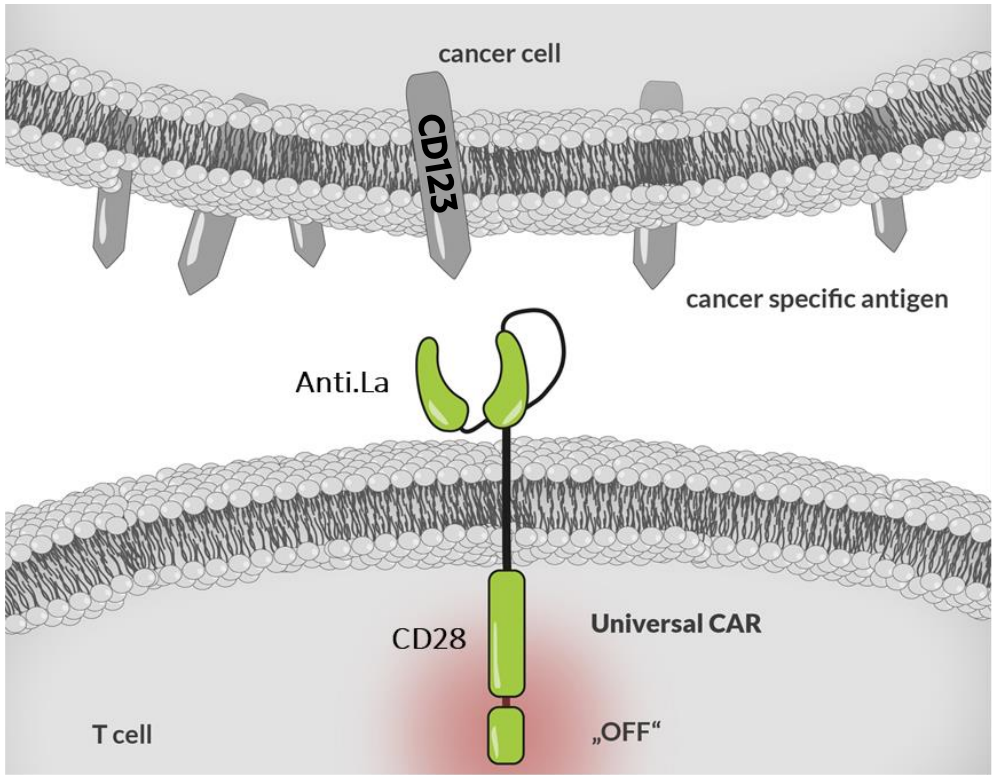




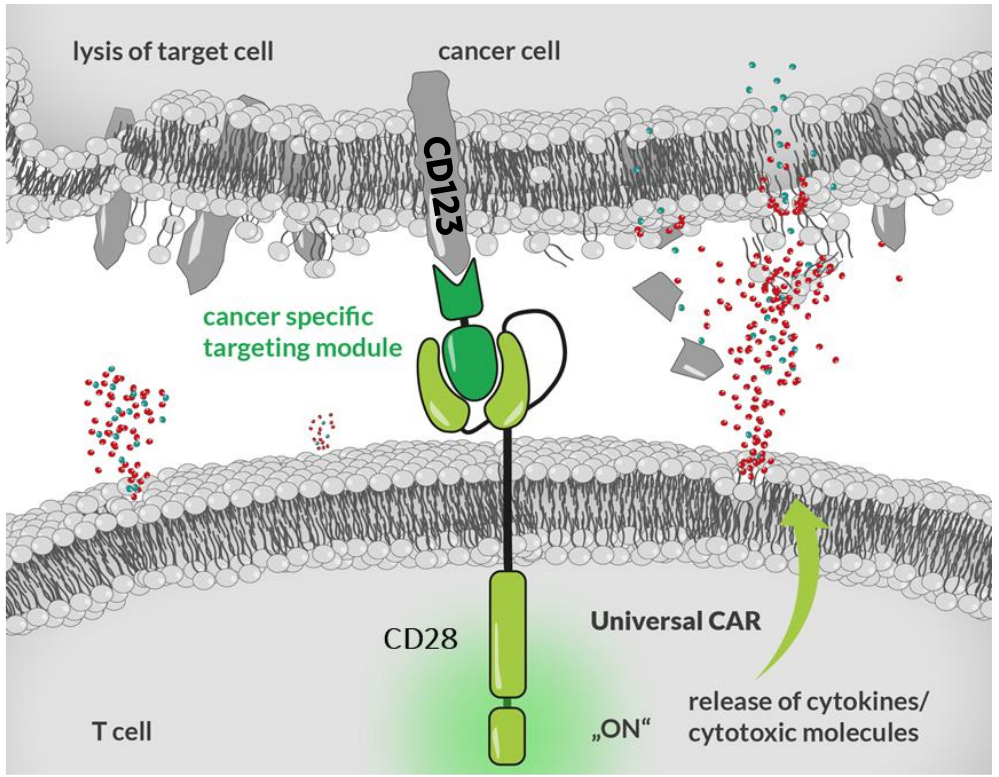
Bullinger&Krönke. Blood 2024; Bourgeois et al. Blood 2024

Allogenic UniCAR targeting CD123 in relapsed/refractory AML

Prinzip: Targeting Module mit Leukämie-Antigen-Spezifität und UniCAR-Epitop wird infundiert
allogene, partiell HLA-gematchte CART mit Spezifität für UniCAR-Epitop



No targeting module: CAR T cells in „off“ mode



CD123 targeting module: CAR T cells in „on“ mode

CHARITÉ

Ehninger et al. ASH 2022

Looking to the future

Precision medicine in AML

Genomic features at diagnosis	• Frontline targeted-therapies that improve outcomes • Patient risk stratification and potential allo-HSCT planning • Individualized estimation of treatment response rate for both intensive chemotherapy and non-intensive treatments
Treatment approaches	• Novel targeted approaches for an increasing number of clinical scenarios / development of novel targeted therapies • Intelligent combination therapies for both fit and unfit patients
Measurable residual disease	• Dynamic risk assessment that allows early intervention in certain situations

Thanks for your attention!