III Medizinische Klinik und Poliklinik
Hämatologie und Medizinische Onkologie

Therapiekonzepte bei älteren AML-Patienten: Jenseits von HMA + VEN

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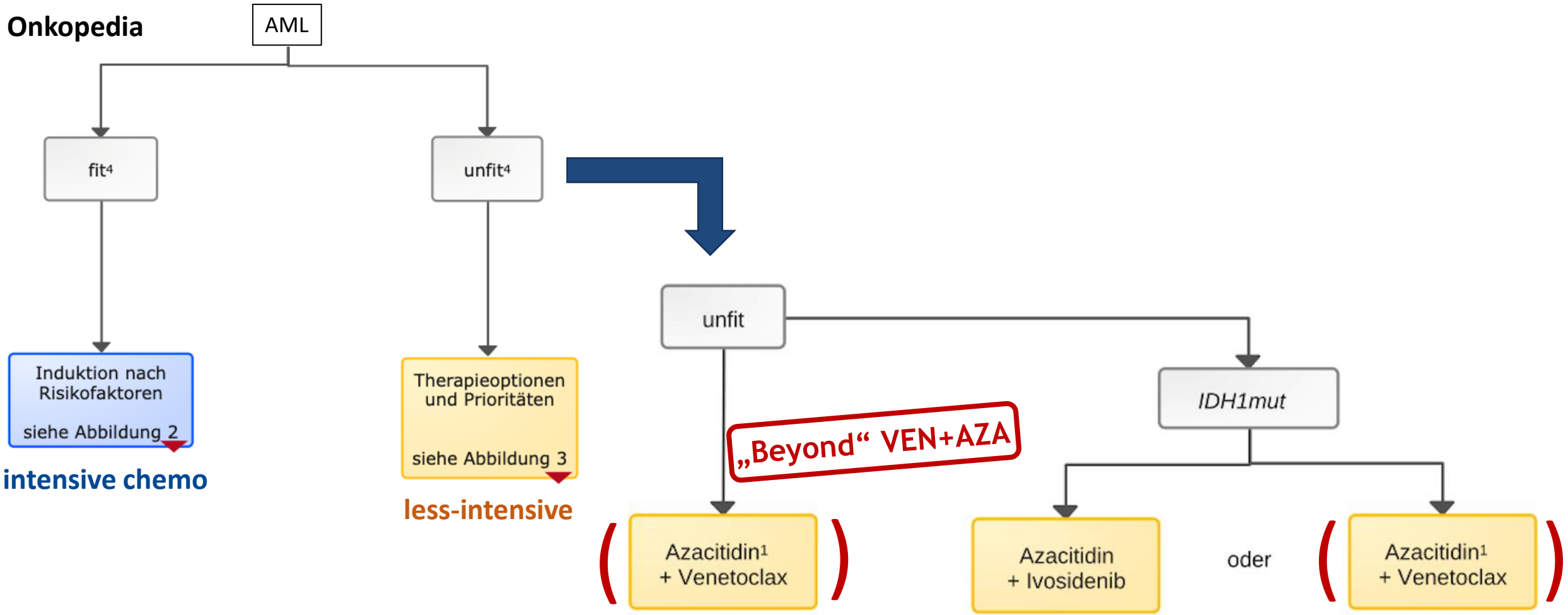
12. Oktober 2024

Disclosures

Abbvie:	**Consulting / Speaker Activity /Travel Support**
BMS / Celgene:	**Consulting / Travel Support**
Gilead:	**Speaker Activity**
Janssen	**Consulting**
Jazz:	**Consulting / Speaker Activity**
Kura-Oncology:	**Research Support**
Pfizer:	**Consulting**
Servier:	**Consulting / Speaker Activity / Travel Support**
Syndax:	**Research Support**

Treatment Recommendations for the Elderly AML Patient

...what do our current oncopedia „guidelines“ say ?



Adjusted from: *Röllig et al.* ONKOPEDIA *2023*

Agenda

(Targeted) AML therapy in non-fit patients

a) **Risk stratification for less-intensive AML treatment - ELN 2024** neu

b) **Ivosidenib (*IDH1*^{mut}) + Azacitidine**

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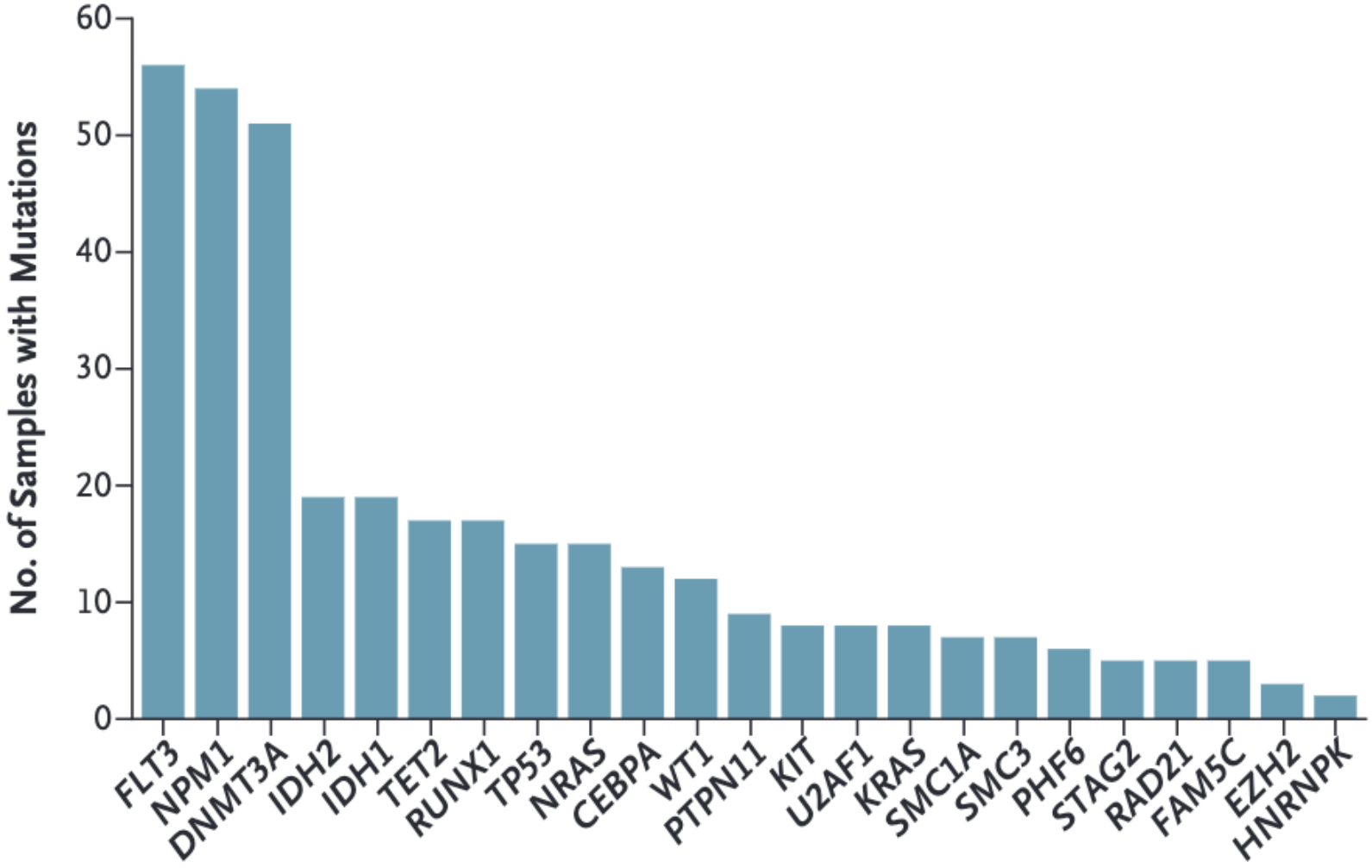
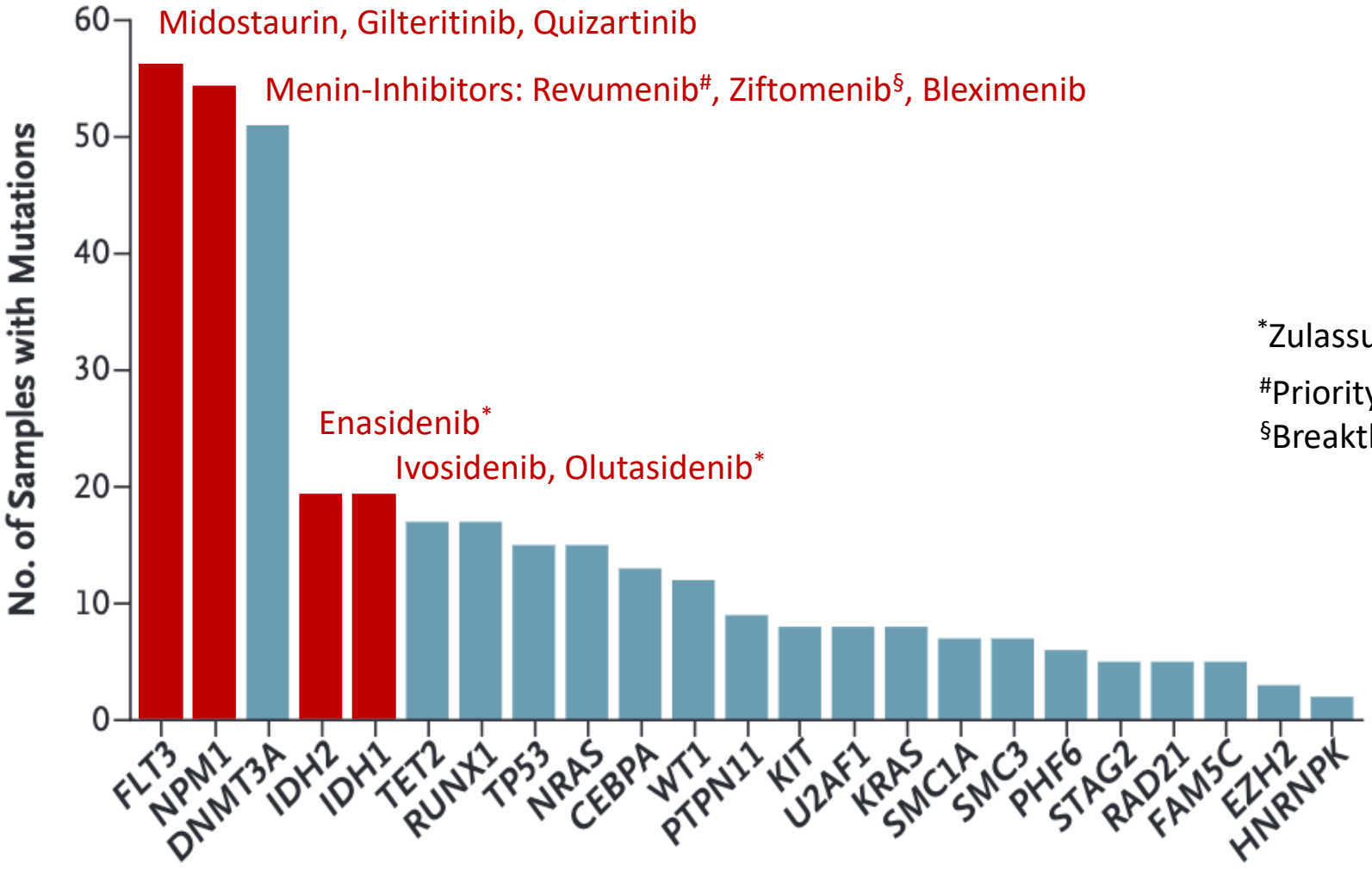
c) **Promising new options and triplets** } not yet approved

Non-Intensive Concepts for AML: Targeted Treatment Options



The Cancer Genome Atlas Research Network, N Engl J Med 2013

Targeted Treatment Options in AML



*Zulassung nur in den USA

#Priority Review (FDA)

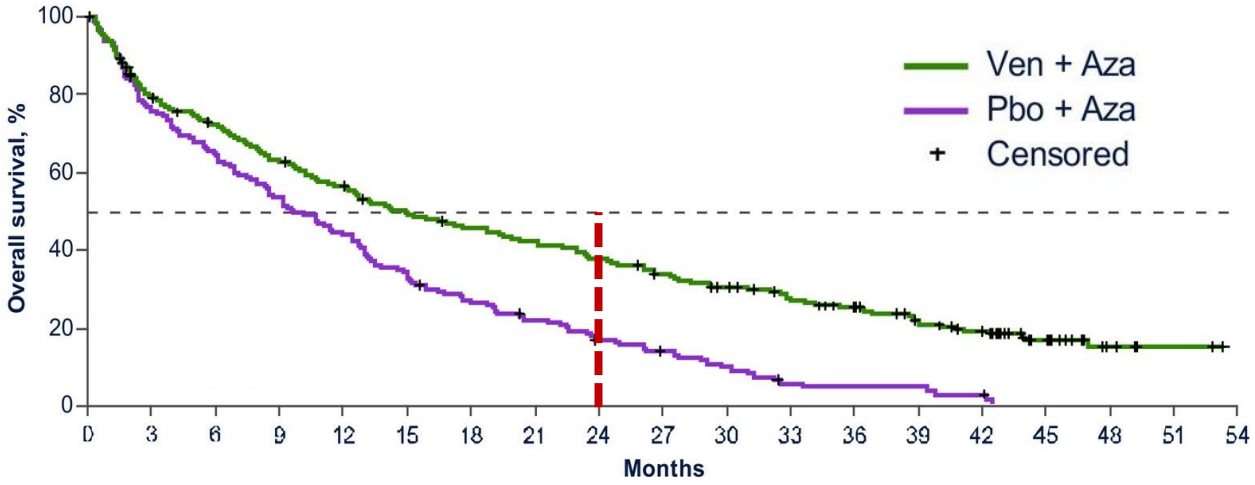
§Breakthrough Designation (FDA)

The Cancer Genome Atlas Research Network, N Engl J Med 2013

VIALE-A-Long-Term Follow-Up and VEN+AZA-Based Risk Stratification

Follow-up: VEN+AZA vs. Pbo+AZA

Survival estimate (%) at 24 mo. (95% CI)	Median OS, mo. (95% CI)	HR (95% CI)
37.5 (31.8–43.3)	14.7 (12.1–18.7)	0.58 (0.465–0.723),
16.9 (11.2–23.5)	9.6 (7.4–12.7)	$p < .001$*

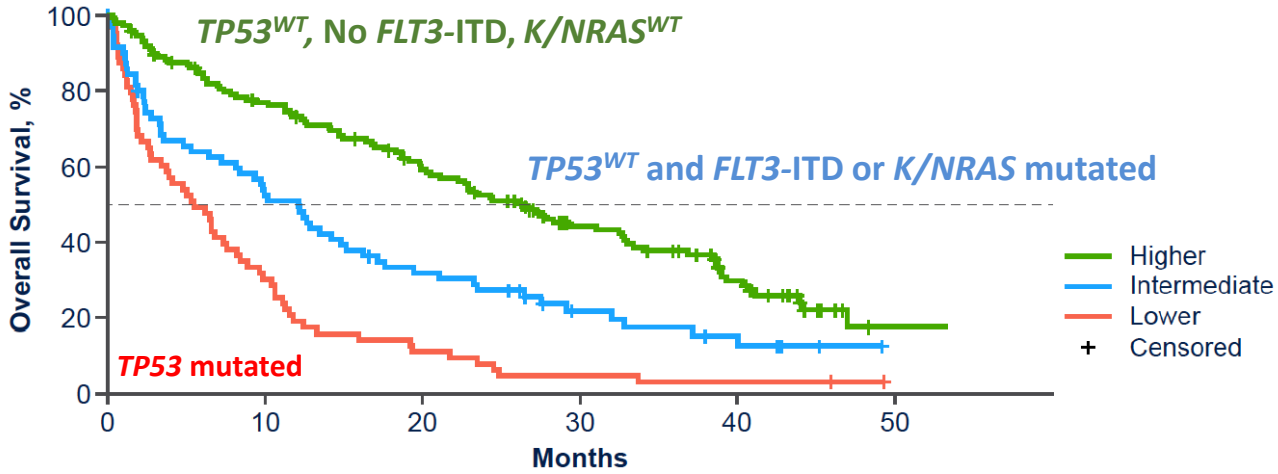


ELN 2022 (intensive): 72% adverse risk

Pratz et al. Am J. Hematol 2024,
update of: DiNardo et al. N Engl J Med 2020

VEN+AZA-based genetic „benefit“ groups

Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher benefit	145	96	26.5 (20.2, 32.7)
Intermediate benefit	71	57	12.1 (7.3, 15.2)
Lower benefit	63	61	5.5 (2.8, 7.6)

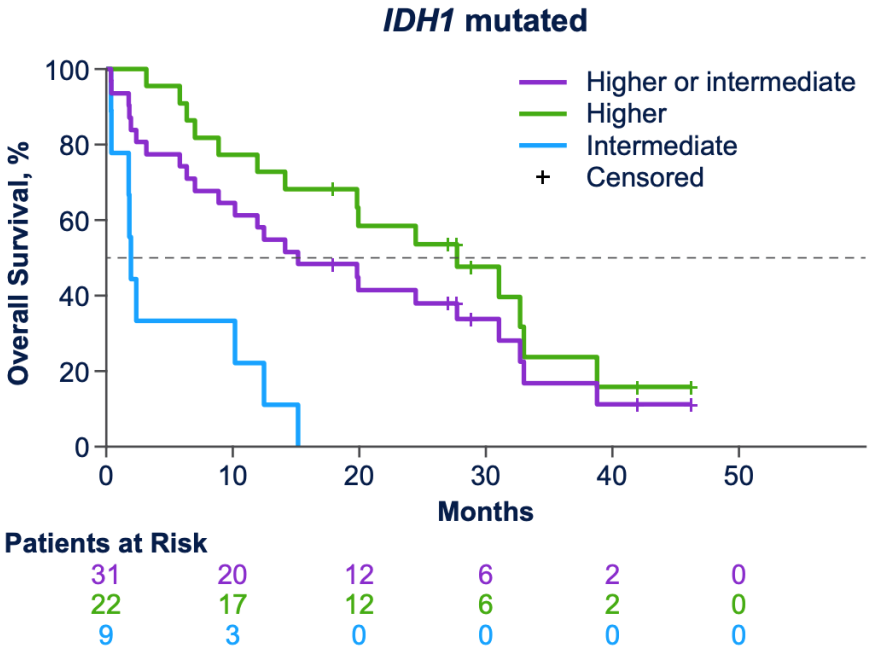


Döhner et al. Blood 2024 („VIALE-A“ prepublished online)

ELN 2024: Genetic Risk Classification for Less-Intensive AML Treatment

Considering HMA, Venetoclax (VEN)+AZA, Ivosidenib (IVO)+AZA treatment

Genetic marker	Median overall survival (months)	Reference
Favorable-risk group		
• Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	39	4
• Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	37	4
• Mutated *IDH1*[a] (*TP53*^{wt})	29	6,17
• Mutated *DDX41*	>24	3,13
• AML with myelodysplasia-related gene mutations (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	23	4
Intermediate-risk group		
• AML with myelodysplasia-related gene mutations (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	13	4
• Other cytogenetic and molecular abnormalities (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	12	4
Adverse-risk group		
• Mutated *TP53*	5-8	3,4,7,10,14-16

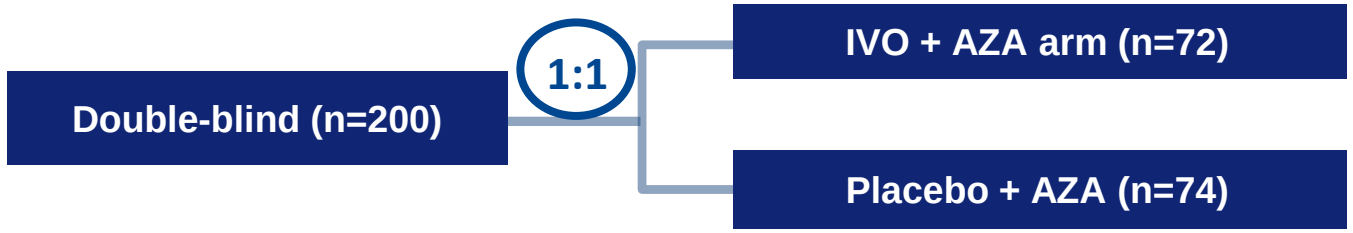


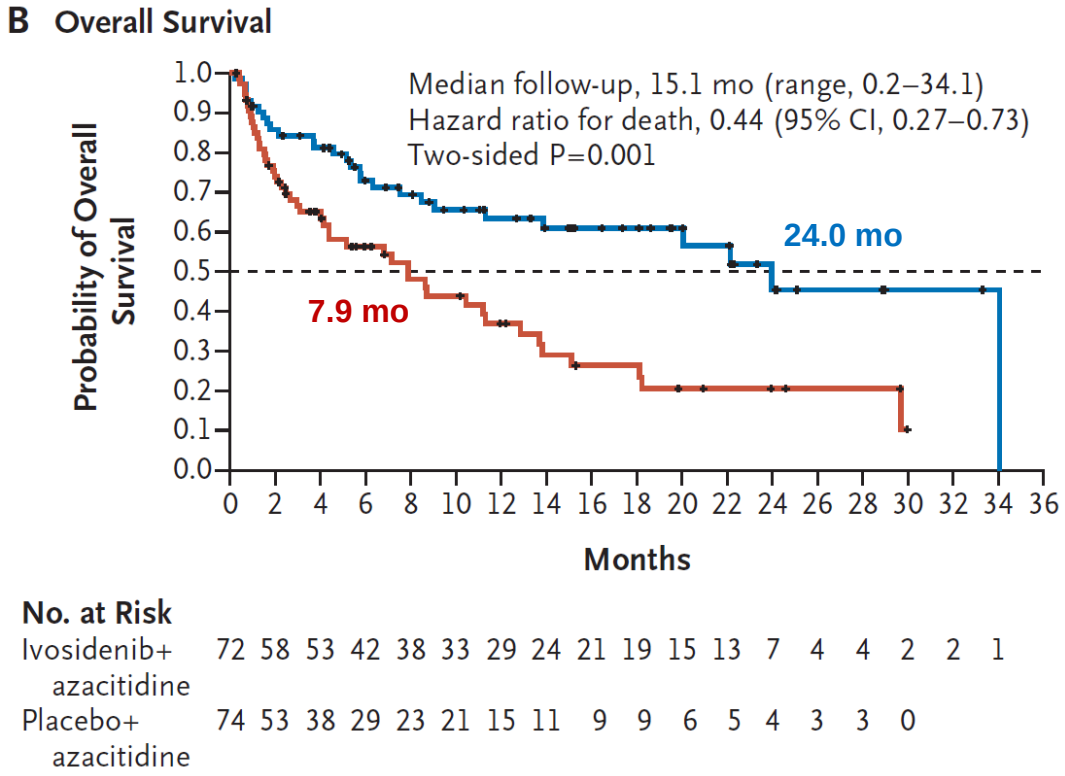
→ **VEN+AZA - median OS: 10.2 Mo**

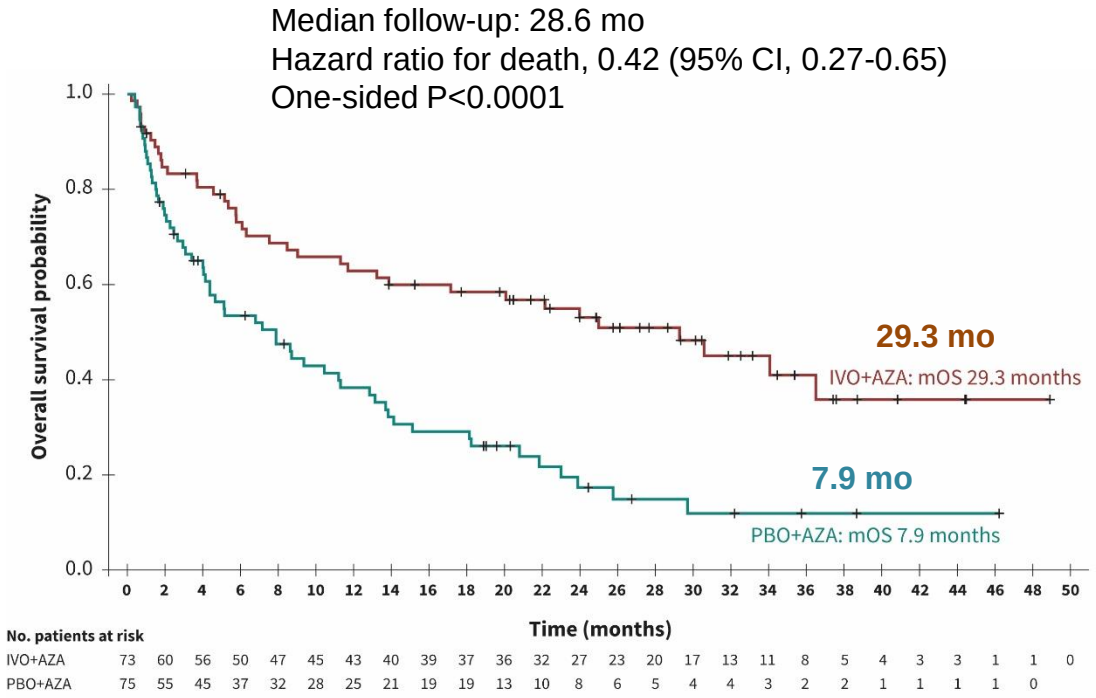
Döhner et al. Blood 2024 (ELN 2024, „less-intensive“)

Döhner et al. Blood 2024 („VIALE-A“ prepublished online)

AGILE: Ivosidenib (IVO) + AZA in *IDH1*-mutated AML







Montesinos P, et al. N Engl J Med. 2022;386(16):1519-31.

Döhner et al. EHA Meeting 2023, #P490.

IVO+AZA - Adverse Events

Event	Ivosidenib + Azacitidine (N = 71)		Placebo + Azacitidine (N = 73)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
	number (percent)			
Any adverse event	70 (99)	66 (93)	73 (100)	69 (95)
Hematologic adverse events	55 (77)	50 (70)	48 (66)	47 (64)
Anemia	22 (31)	18 (25)	21 (29)	19 (26)
Febrile neutropenia	20 (28)	20 (28)	25 (34)	25 (34)
Neutropenia	20 (28)	19 (27)	12 (16)	12 (16)
Thrombocytopenia	20 (28)	17 (24)	15 (21)	15 (21)
Leukocytosis	8 (11)	0	1 (1)	0
Nonhematologic adverse events				
Nausea	30 (42)	2 (3)	28 (38)	3 (4)
Vomiting	29 (41)	0	19 (26)	1 (1)
Diarrhea	25 (35)	1 (1)	26 (36)	5 (7)
Pyrexia	24 (34)	1 (1)	29 (40)	2 (3)
Constipation	19 (27)	0	38 (52)	1 (1)
Pneumonia	17 (24)	16 (23)	23 (32)	21 (29)
QT interval prolonged on ECG	14 (20)	7 (10)	5 (7)	2 (3)
Insomnia	13 (18)	1 (1)	9 (12)	0
Asthenia	11 (15)	0	24 (33)	5 (7)
Hypokalemia	11 (15)	2 (3)	21 (29)	6 (8)
Decreased appetite	11 (15)	1 (1)	19 (26)	6 (8)
Dyspnea	11 (15)	1 (1)	9 (12)	3 (4)
Differentiation syndrome	10 (14)	3 (4)	6 (8)	3 (4)
Pain in arm or leg	10 (14)	1 (1)	3 (4)	1 (1)
Fatigue	9 (13)	2 (3)	10 (14)	2 (3)
Hematoma	9 (13)	0	1 (1)	0
Edema, peripheral	8 (11)	0	16 (22)	1 (1)
Platelet count decreased	8 (11)	6 (8)	6 (8)	6 (8)
Arthralgia	8 (11)	0	3 (4)	0
Headache	8 (11)	0	2 (3)	0
Bleeding	29 (41)	4 (6)	21 (29)	5 (7)
Infections	20 (28)	15 (21)	36 (49)	22 (30)

- **Less infections with IVO+AZA (28.2%) vs. PBO+AZA (49.3%).**

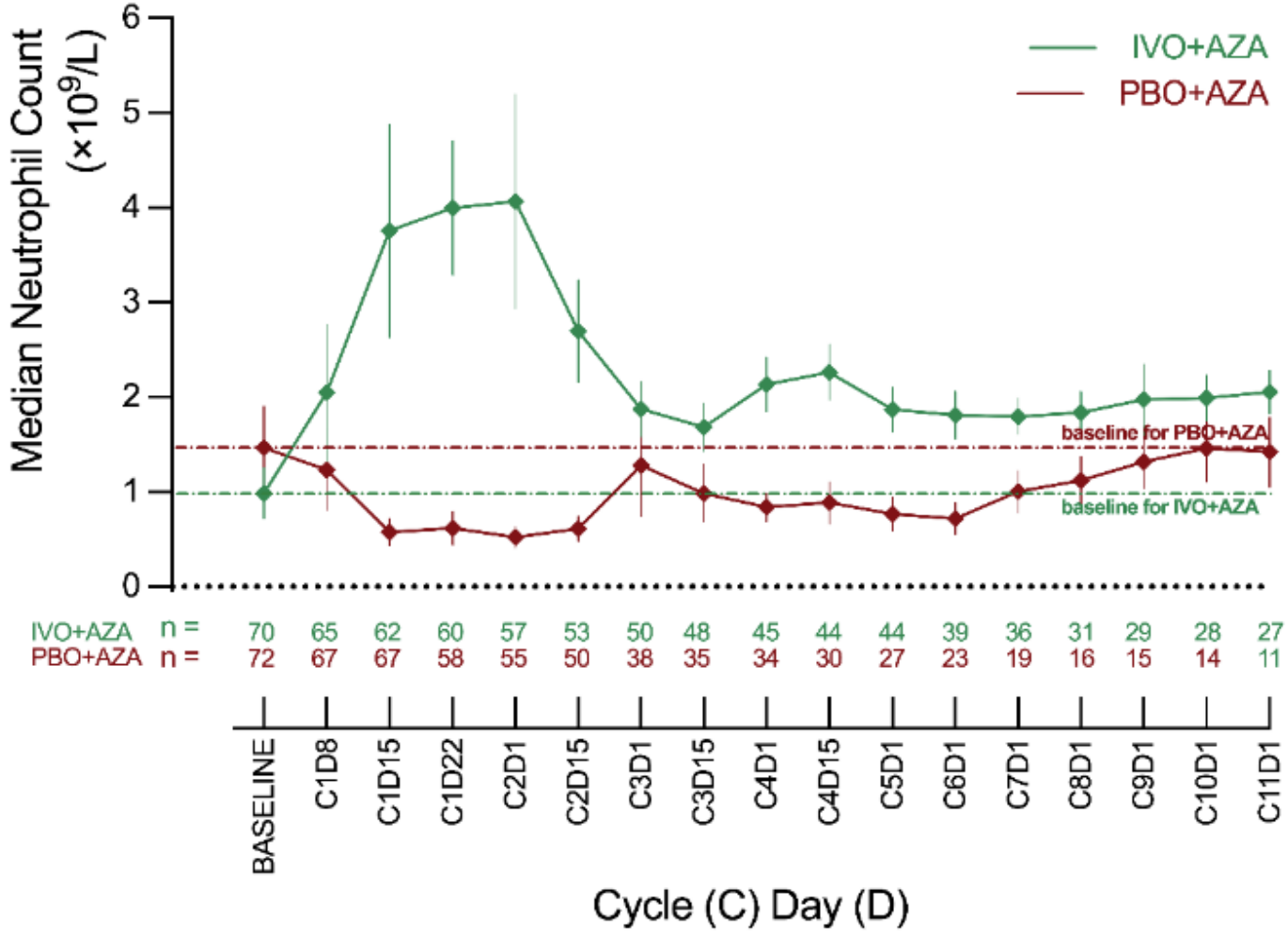
- TEAEs of special interest with IVO+AZA vs PBO+AZA included grade ≥2 **differentiation syndrome** (14.1% vs 8.2%)

Montesinos P, et al. N Engl J Med. 2022;386(16):1519-31.

Neutrophil Counts Upon IVO+AZA vs PBO+AZA Treatment

- **IVO+AZA increases absolute neutrophil count**
- **Less infections with IVO+AZA**

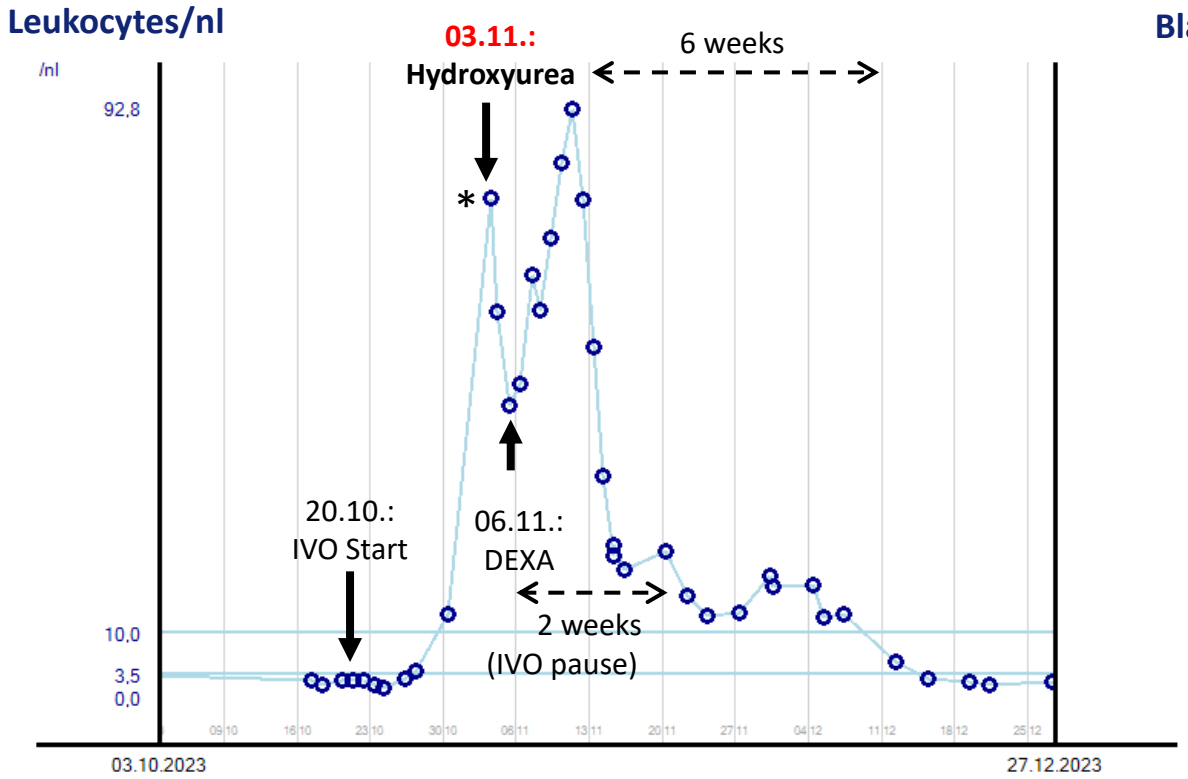
Change in absolute neutrophil count

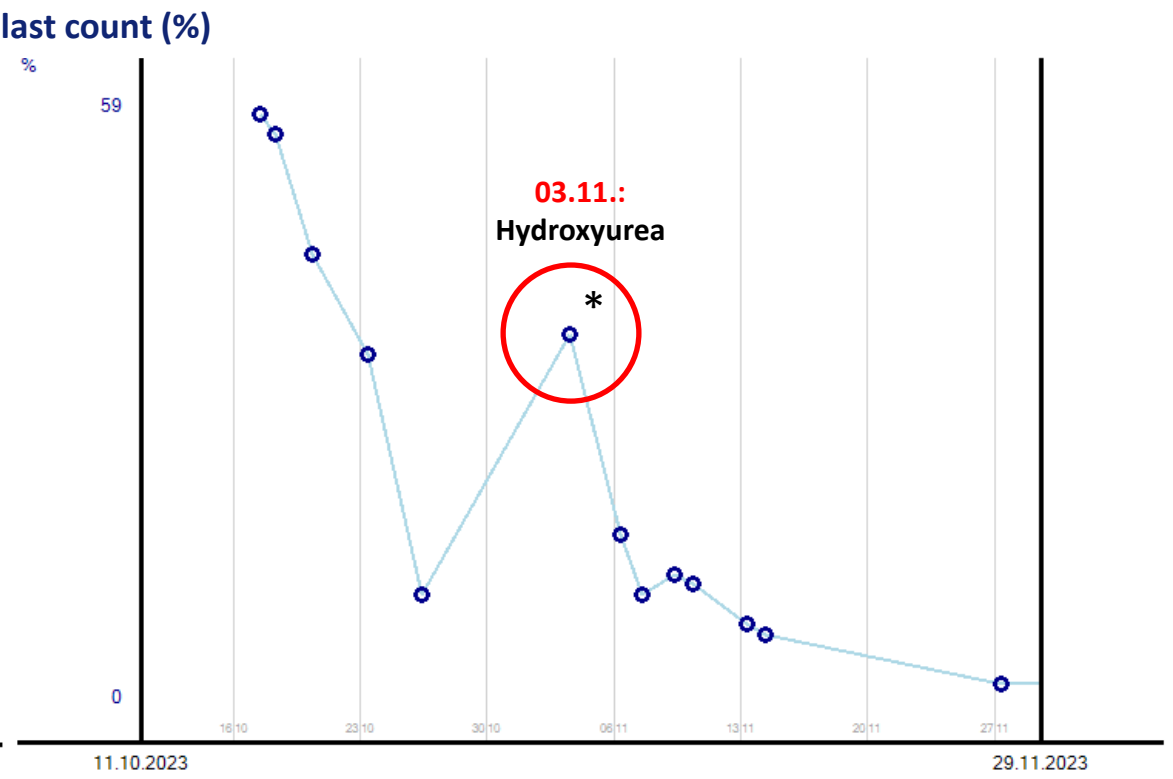


Montesinos P, et al. N Engl J Med. 2022;386(16):1519-31, Supplementary Fig.S8

Leukozytosis and Differentiation Syndrome Upon IVO+AZA

Single-center experience: initial leukocytosis and transient blast „flare“ – not uncommon





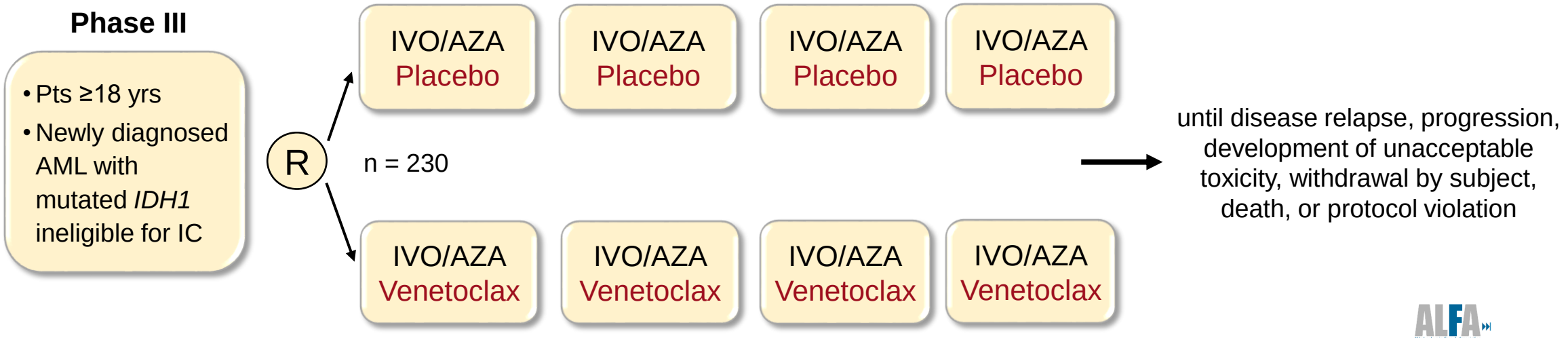
Results: - Complete remission (CR) after cycle 2

- Ongoing CR (cycle 7)

EVOLVE-1: IVO + AZA with or without VEN in *IDH1*-mutated AML

→ **Rationale from Phase Ib/2 Study: CRc 91% vs. 83% (*Lachowiez et al. Blood Cancer Discov. 2023*)**

180 sites in > 15 countries



Primary endpoint: Event-free survival
Start: Q4/2024

Courtesy: Hartmut Döhner

Background: Menin Inhibition in AML

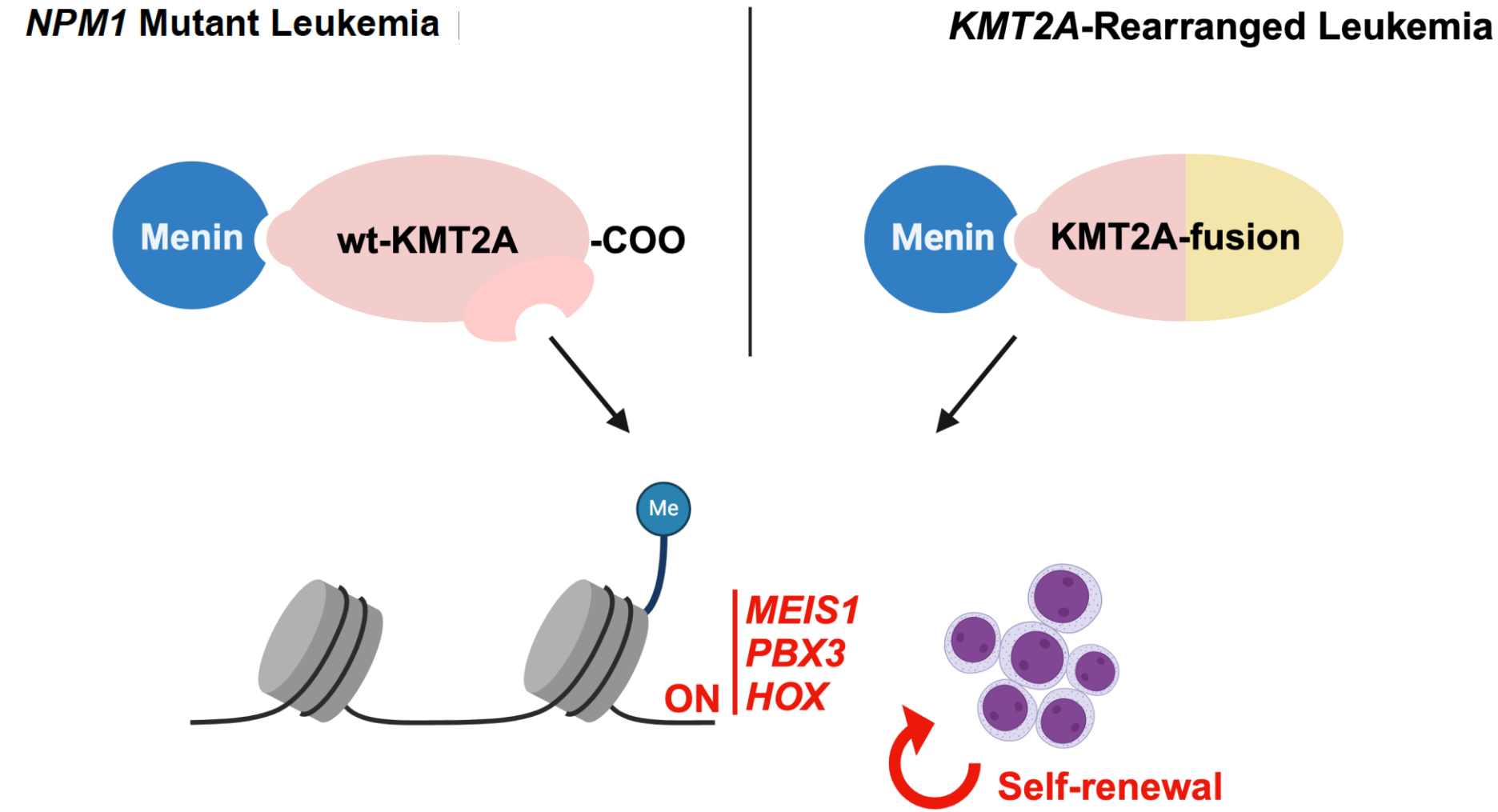
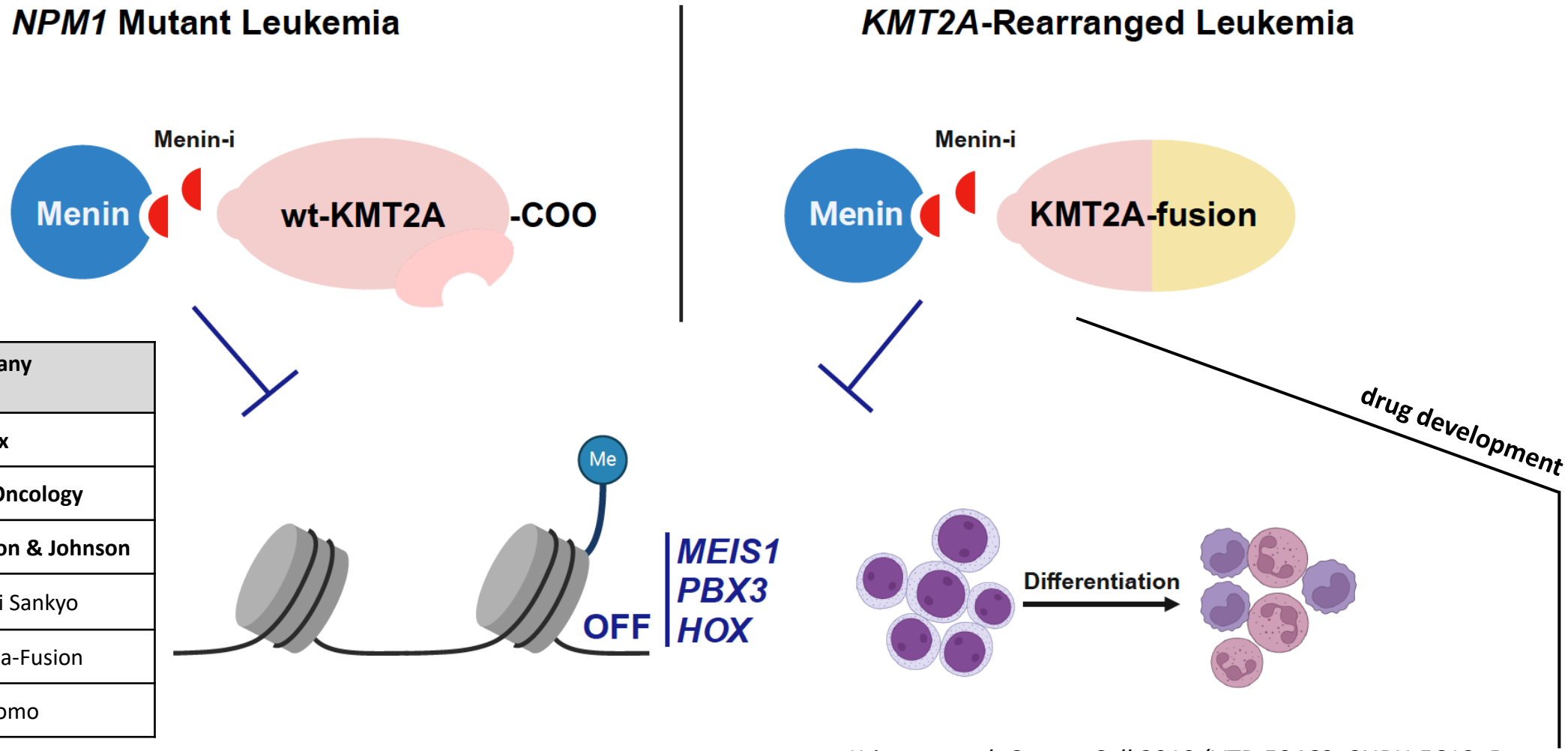


Figure adapted from: *Kühn & Ganser Br J Haematol. 2024*
*Borkin et al. Cancer Cell 2015 (Inhibition in **KMT2A-r AML**)*
*Kühn et al. Cancer Discovery 2016 (Target / Inhibition **NPM1mut AML**)*

“Hot Stuff”: Menin Inhibition in AML



Menin-Inhibitor	Company
Revumenib	**Syndax**
Ziftomenib	**Kura Oncology**
Bleximenib	**Johnson & Johnson**
DS-1594b	Daiichi Sankyo
BMF-219	Biomea-Fusion
DSP-5336	Sumitomo

Figure adapted from: *Kühn & Ganser Br J Haematol. 2024*
*Borkin et al. Cancer Cell 2015 (Inhibition in **KMT2A-r AML**)*
*Kühn et al. Cancer Discovery 2016 (Target / Inhibition **NPM1mut AML**)*

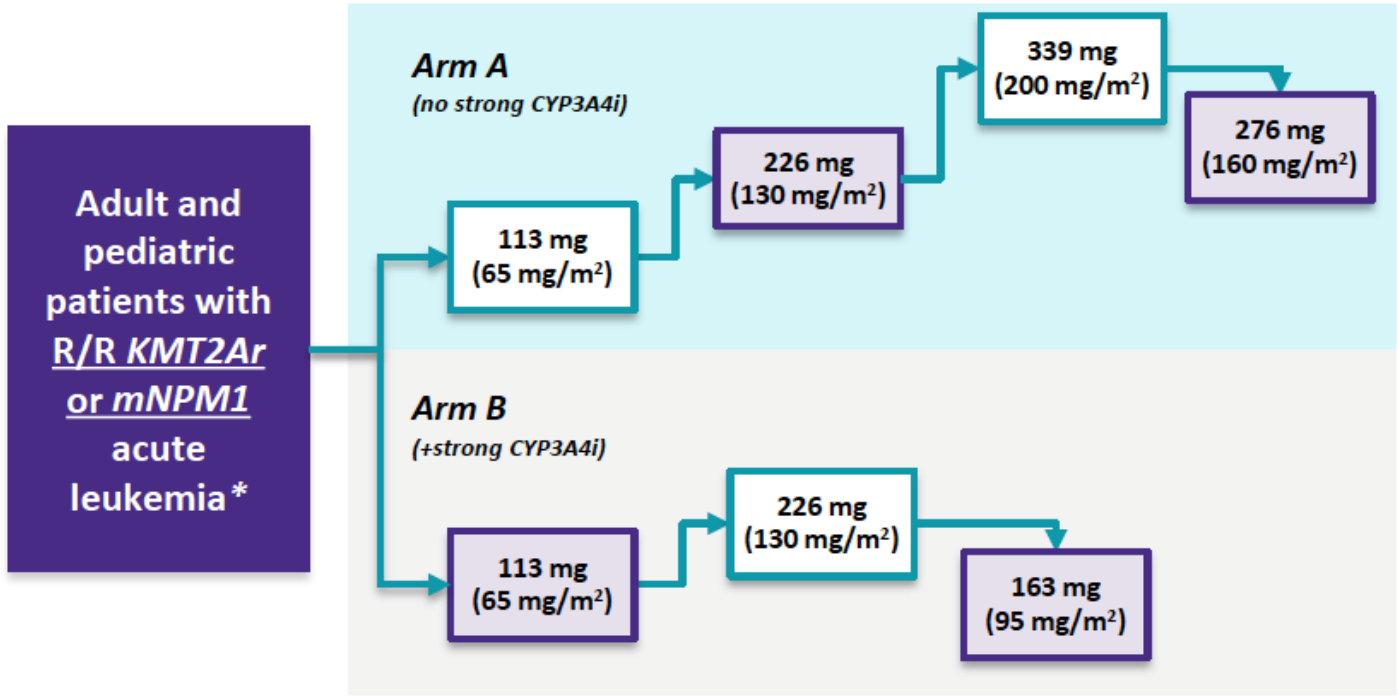
*Krivtsov et al. Cancer Cell 2019 (VTP-50469, SNDX-5613, **Revumenib**)*
*Uckelmann et al. Science 2020 (VTP-50469, SNDX-5613, **Revumenib**)*
*Klossowski et al. J Clin Invest. 2020 (MI-463, KO-539, **Ziftomenib**)*
*Kwon et al. Blood 2024 (JNJ75276617, **Bleximenib**)*

Article nature

The menin inhibitor revumenib in *KMT2A*-rearranged or *NPM1*-mutant leukaemia

AUGMENT-101-Trial

Revumenib p.o. q12h, 28-day cycle



Primary objectives: Safety, tolerability, PK, RP2D
Exploratory: Efficacy

Adapted from: *Issa et al. Nature 2023*
(Phase II: *Issa et al. 2024*)

Heavily pretreated R/R acute leuekmia patients

Baseline Characteristics	Safety Population N=68
***KMT2Ar*, n (%)**	46 (68)
***mNPM1*, n (%)**	14 (21)

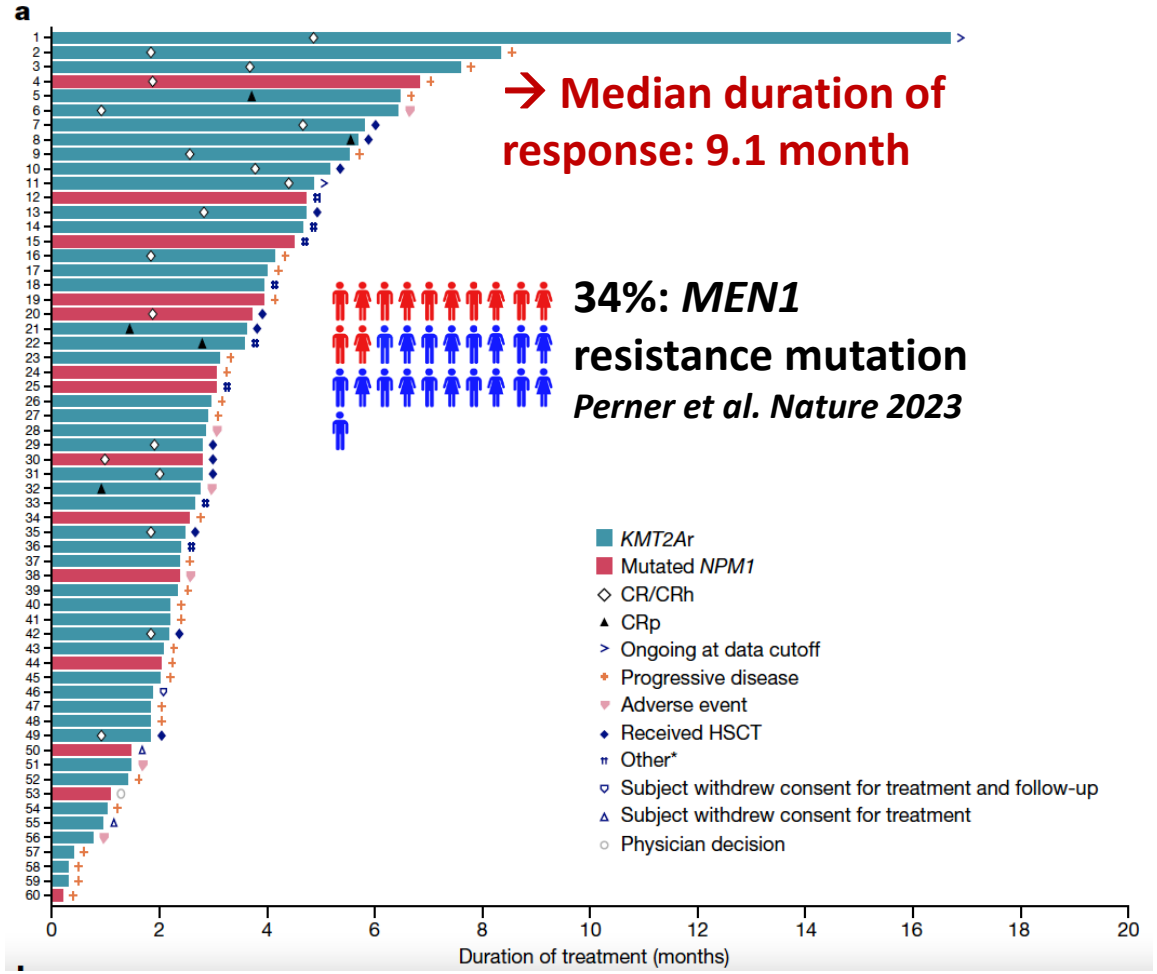
Baseline Characteristics	Safety Population N=68
Median age, years (range)	42.5 (0.8, 79)
Adult (n=60)	50.5
Pediatric (n=8)	2.5
Female, n (%)	42 (62)
Leukemia type, n (%)	
AML	56 (82)
ALL	11 (16)
MPAL	1 (2)
Median prior therapies (range)	4 (1,12)
Stem cell transplant, n (%)	31 (46)
Venetoclax, n (%)	41 (60)

Revumenib - Phase 1: Response

Phase I

Best Response, n (%)	Efficacy Population n=60	
ORR*	**32/60 (53%)**	
Best Response		
CR	12 (20%)	CR/CRh: 30%
CRh	6 (10%)	
CRp	5 (8%)	
MLFS	9 (15%)	
MRD^{neg} rate†	**18/32 (56%)**	
CR/CRh MRD^{neg}	14/18 (78%)	
CR/CRh/CRp MRD^{neg}	18/23 (78%)	
Genetic alteration	***KMT2Ar* n=46**	***mNPM1* n=14**
ORR	**27/46 (59%)**	**5/14 (36%)**
CR/CRh	15 (33%)	3 (21%)
CR/CRh MRD^{neg} rate	11/15 (73%)	3/3 (100%)

Duration of treatment

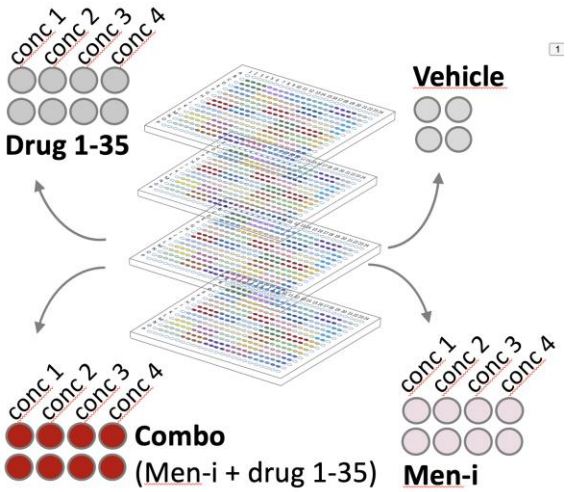


Adapted from: *Issa et al. Nature 2023*
(Phase II: *Issa et al. 2024*)

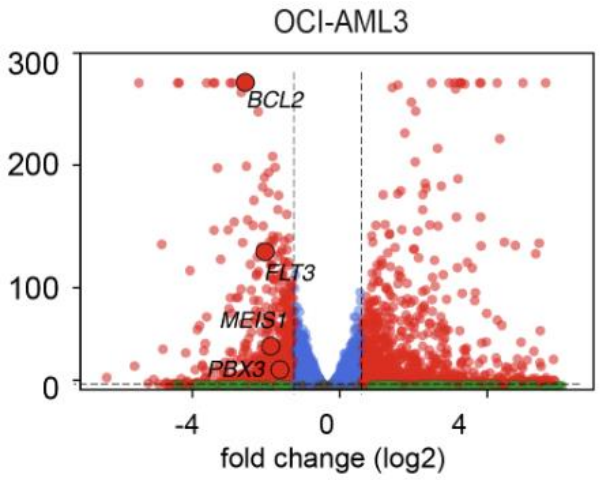
→ ***Drug application*" for Revumenib (*KMT2A*-r, PDUFA action date: december 26, 2024)**

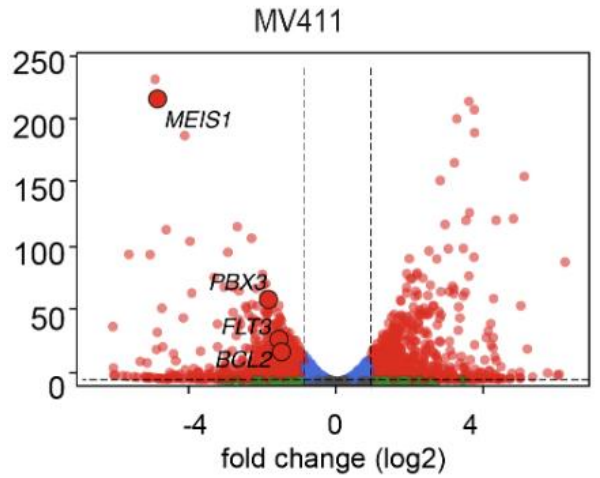
Screening Menin inhibitors for Synergistic Drug Combination Partners

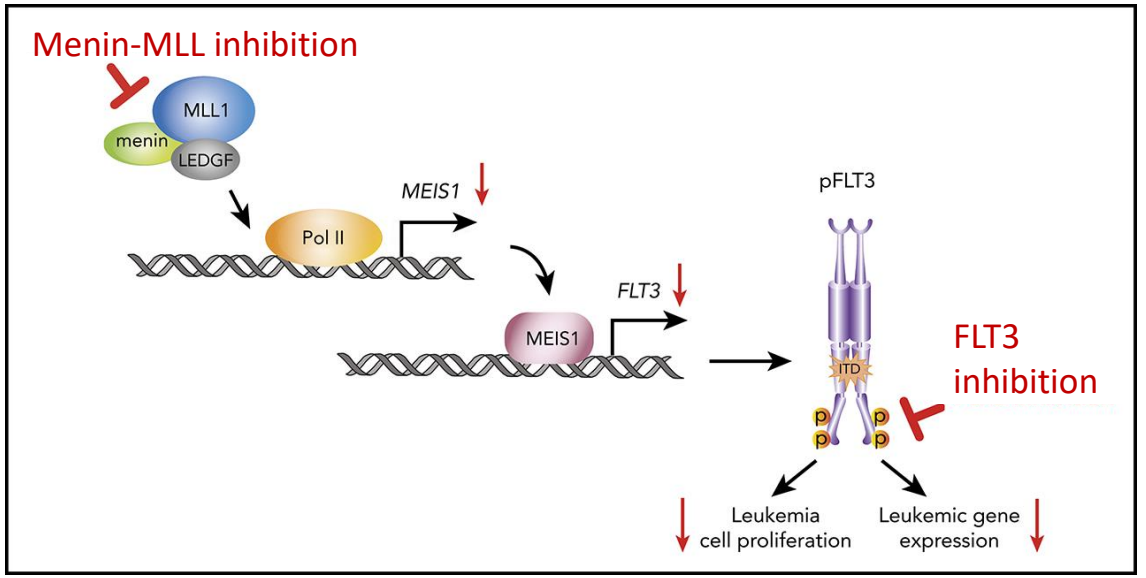
Synergy screen in *NPM1*^{mut} or *KMT2A*-r AML

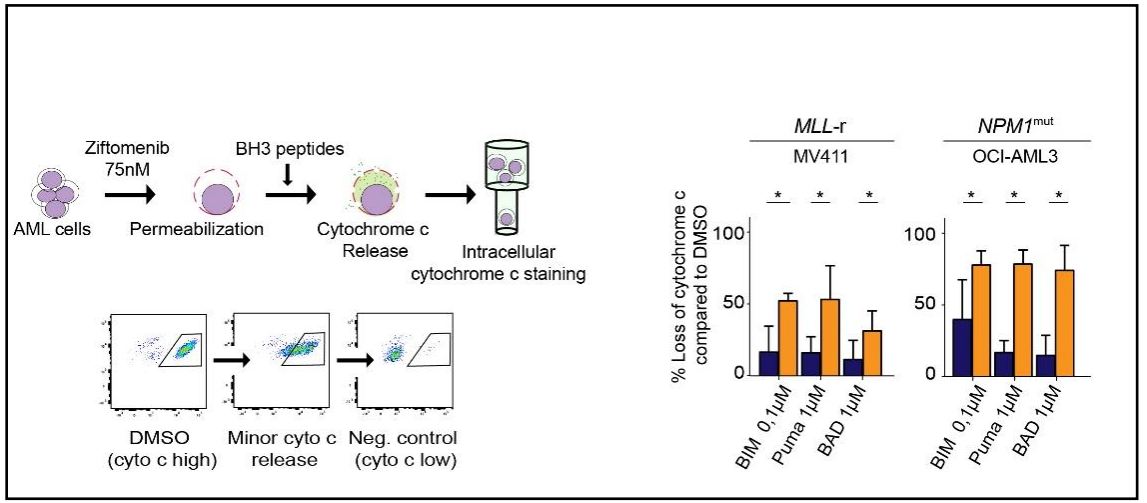


Apoptosis & cell cycle	Intracellular pathway inhibitors
Venetoclax	Entospletinib
MK2206	Cobimetinib
Palbociclib	Binimetinib
Ribociclib	
	Surface kinase inhibitors
Epigenetic & DNA damage	Nilotinib
JNJ64619178	Dasatinib
GSK3326595	Gilteritinib
ORY1001	**Various drugs**
Olaparib	Eltanexor
Talazoparib	









Dzama et al Blood 2020
Rausch et al. Haematologica 2023

EVOLVE-2: VEN+AZA + Revumenib vs. VEN+AZA + PBO

Rationale: BEAT-AML Phase I (n=26): Revumenib + VEN/AZA, CRc: 96%, „clean“ CR: 69% (*Zeidner et al. S411 EHA 2024*)

Phase III

180 sites in > 15 countries

- Pts ≥18 yrs
- Newly diagnosed AML with mutated *NPM1* or *KMT2A*-rearrangement
- **ineligible for IC**

R

n ≈ 400*

VEN/AZA Placebo	VEN/AZA Placebo	VEN/AZA Placebo	VEN/AZA Placebo
VEN/AZA Revumenib	VEN/AZA Revumenib	VEN/AZA Revumenib	VEN/AZA Revumenib

→ until disease relapse, progression, development of unacceptable toxicity, withdrawal by subject, death, or protocol violation

Primary endpoint: Overall survival

Key secondary endpoints: Event-free survival; CR / CRh rate

PIs: G. Huls (HOVON); M. Kühn (AMLSG), P. Vyas (UK)

Fazit

III Medizinische Klinik und Poliklinik
Hämatologie und Medizinische Onkologie

1. **Mehrzahl d. AML-Pt. profitieren von zugelassenen Dublets (VEN+AZA, IVO+AZA)**

2. **Pt. mit *IDH1*-Mutationen profitieren (früh) von IVO+AZA: → Mutations-Sreening (!)**
   - Rascher Neutrophilen-Anstieg, weniger Infektionen; langanhaltende Remissionen
   - CAVE: Differenzierungs-Syndrom

3. **Vielversprechende „*New kids on the block*“: Menin Inhibitoren (*NPM1*^{mut}, *KMT2A*-r AML)**

4. **„Extrem“ hoffnungsvolle Triplets in klinischen Studien**

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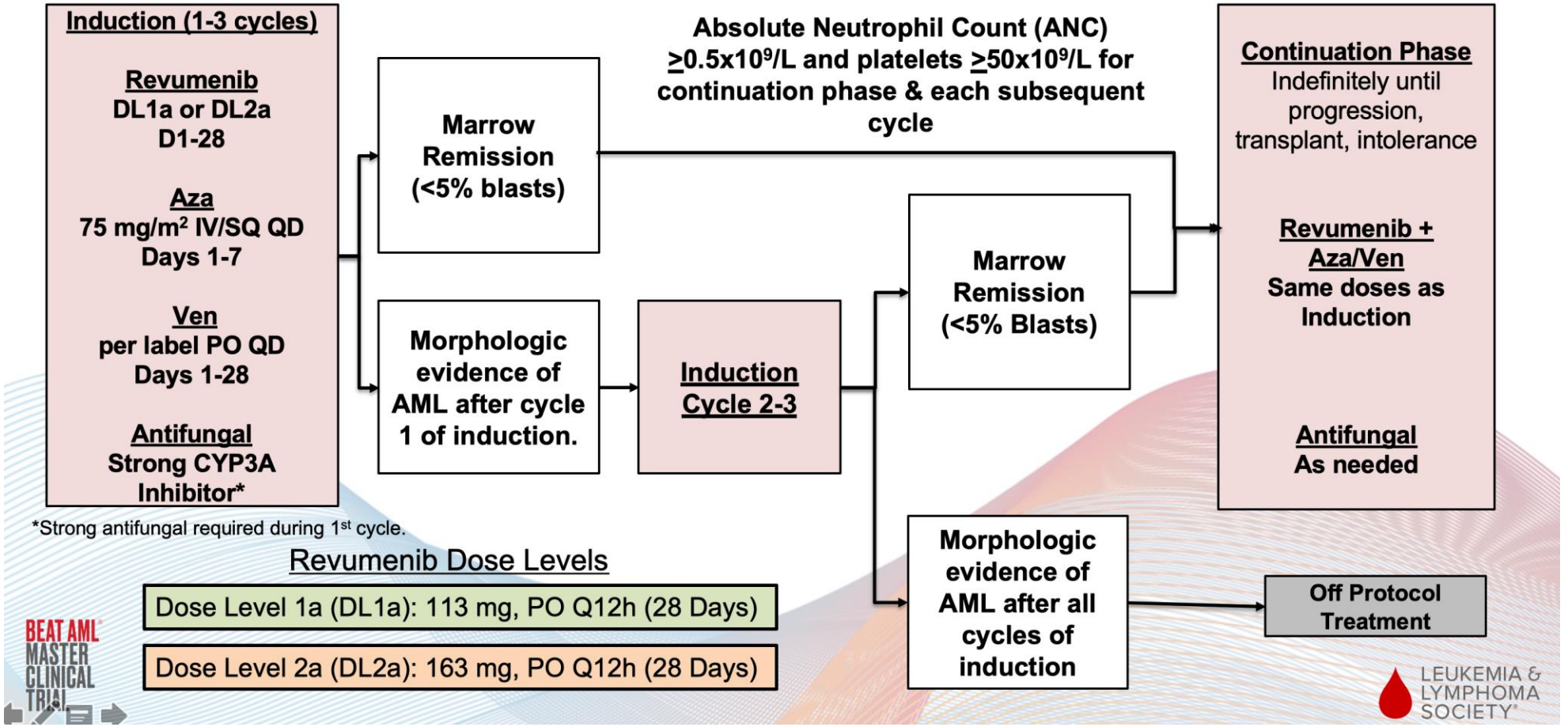
BEAT AML: Revumenib + VEN + AZA in Newly Diagnosed AML

Phase Ib

- Pts ≥ yrs 60
- unfit for IC
- With **frontline** *NPM1*mut or *KMT2A-r* AL



- **Primary endpoint: safety & RP2D**
- **Secondary: exploratory efficacy**

- N=26
- Median age: 70 (60-85)
- *NPM1*mut: 65.4%
- *KMT2A*-r: 34.6%

Courtesy of Joshua Zeidner, ***S411 EHA 2024***

BEAT AML: Revumenib + VEN + AZA in Newly Diagnosed AML

Treatment Outcomes	Escalation DL1a (n=7)	Escalation DL2a (n=6)	Expansion DL2a (n=13)	All (n=26)
Best Response, no. (%)				
CR	5 (71)	5 (83)	8 (62)	18 (69)
CRh	0 (0)	1 (17)	1 (8)	2 (8)
CRi	2 (29)	0 (0)	1 (8)	3 (12)
MLFS	0 (0)	0 (0)	1 (8)	1 (4)
NE[1]	0 (0)	0 (0)	2 (15)	2 (8)
Response Rates for Evaluable Patients[2]				
Composite CR (CR/CRh/CRi), no. (%)	**7/7 (100)**	**6/6 (100)**	**10/11 (91)**	**23/24 (96)**
Overall (CR/CRh/CRi/MLFS), no. (%)[3]	**7/7 (100)**	**6/6 (100)**	**11/11 (100)**	**24/24 (100)**
MRD[4] Neg., no. (%)	6 (86)	6 (100)	10 (91)	22 (92)
Required Only 1 Induction for marrow remission, no. (%)	7 (100)	5 (83)	9 (82)	21 (88)
On-treatment Status, no. (%)	2 (29)	1 (17)	8 (62)	11 (42)
Allo-Stem Cell Transplant, no. (%)	1 (14)	1 (17)	1 (9)	3 (13)
Relapse, no. (%)[5]	2 (29)	1 (17)	0 (0)	3 (13)
Survival				
Death, no. (%)	1 (14)	3 (50)	2 (15)	6 (23)
30/60 Day Mortality, no. (%)	0 (0)	0 (0)	1 (8)	1 (4)
12-Month Survival Estimate, % (95% CI)[6]	100 (100-100)	N/A	N/A	62.2 (27.8-83.9)

Courtesy of Joshua Zeidner, ***S411 EHA 2024***