

AML in 2026: Therapeutic Strategies

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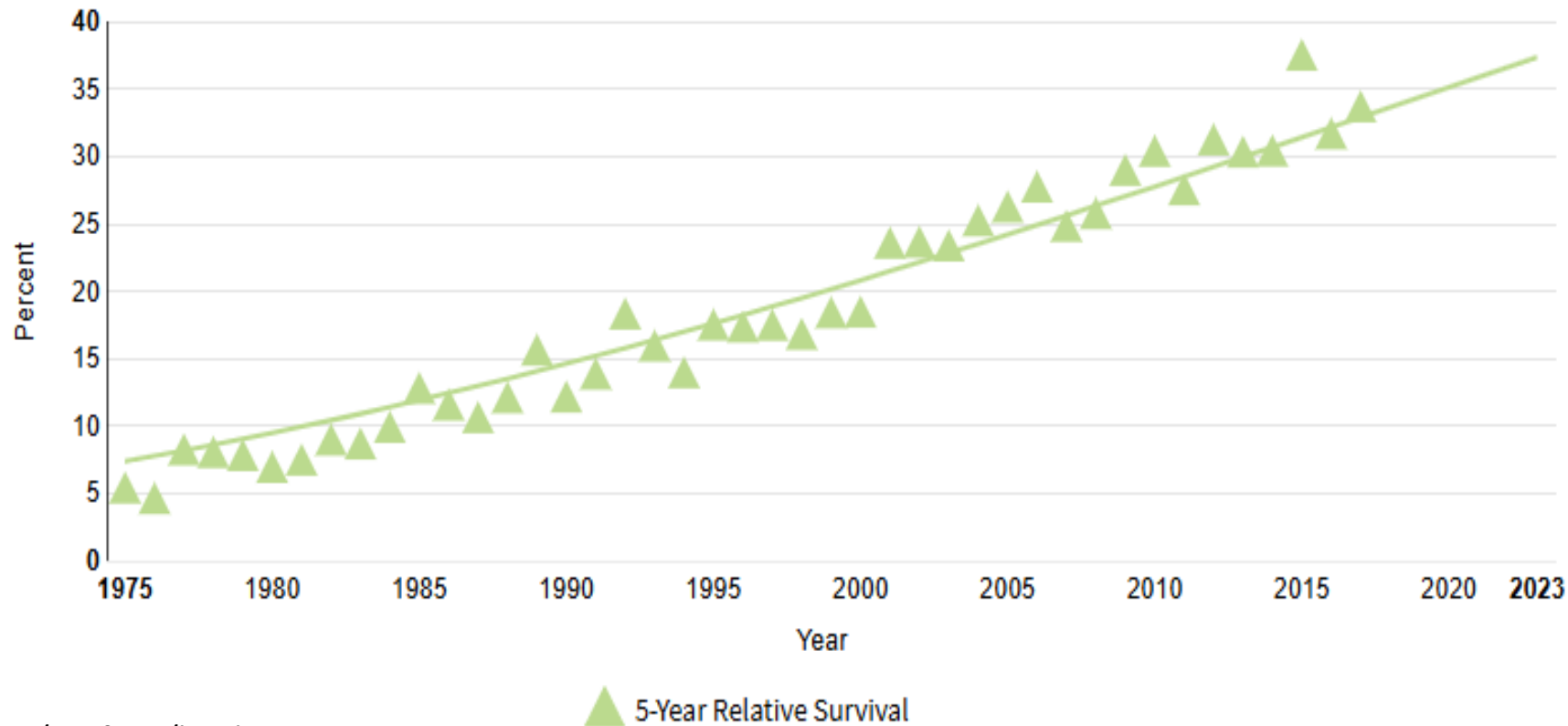
Department of Leukemia
UT MD Anderson Cancer Center



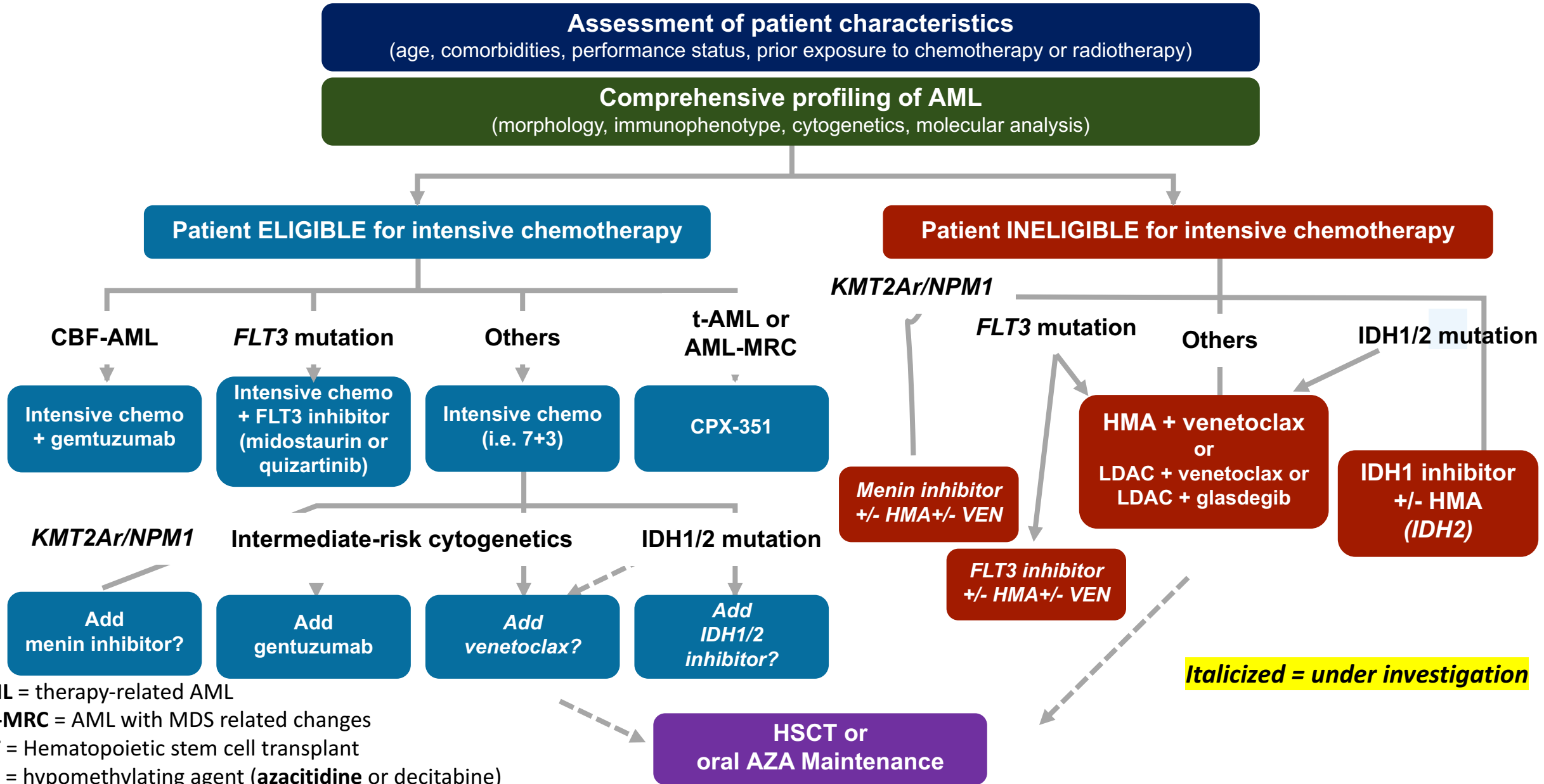
5-yr AML survival is 32.9%

5-yr Relative Survival (1975-2017*)

*We have a dozen new FDA approved drugs since 2017 which this graph doesn't incorporate – hopefully will be even better with time!

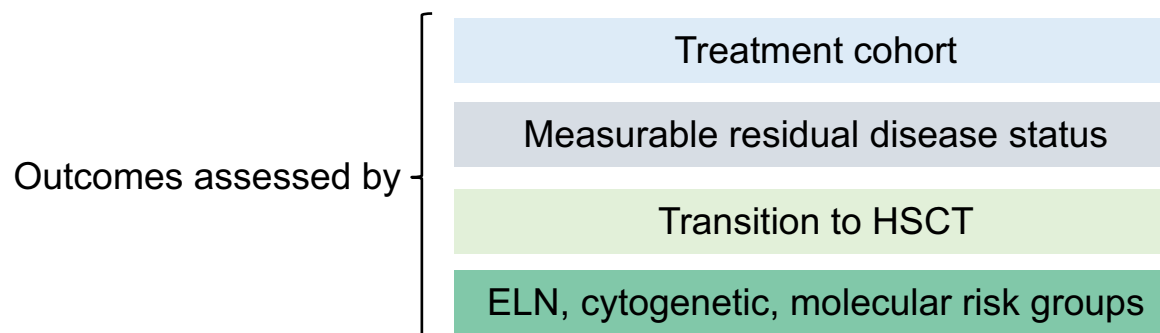
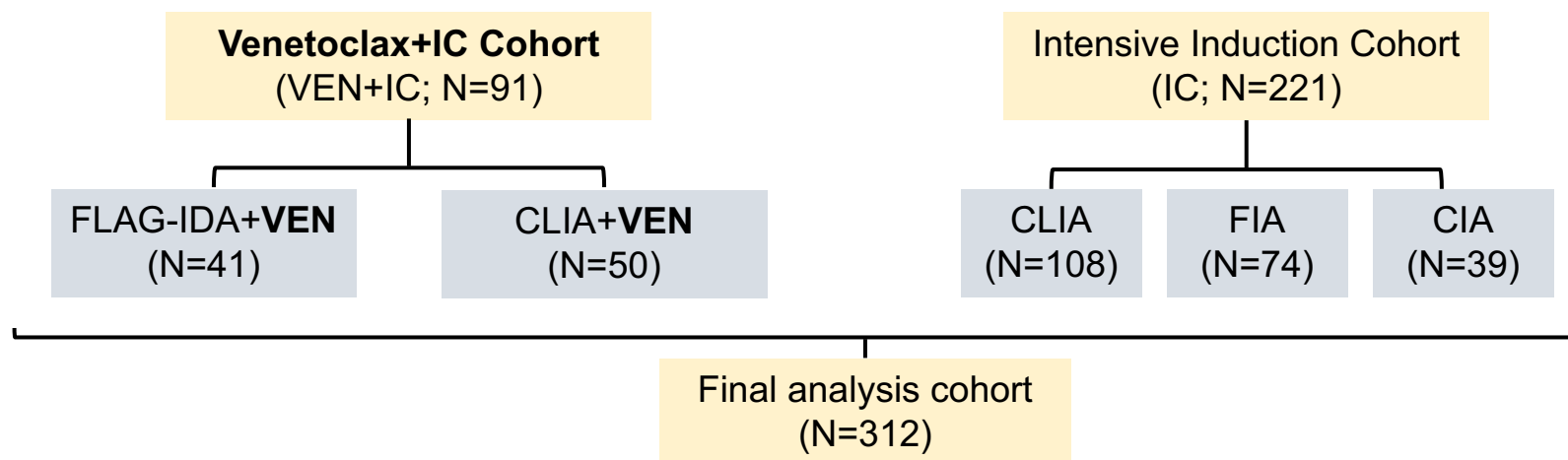


Evolving diagnostic and treatment paradigm for Newly Dx AML



VEN+IC in AML: Study Design

Patients with ND-AML (de novo, sAML, tAML, st-AML) treated with intensive chemotherapy (IC) at MDACC on prospective clinical trial protocols



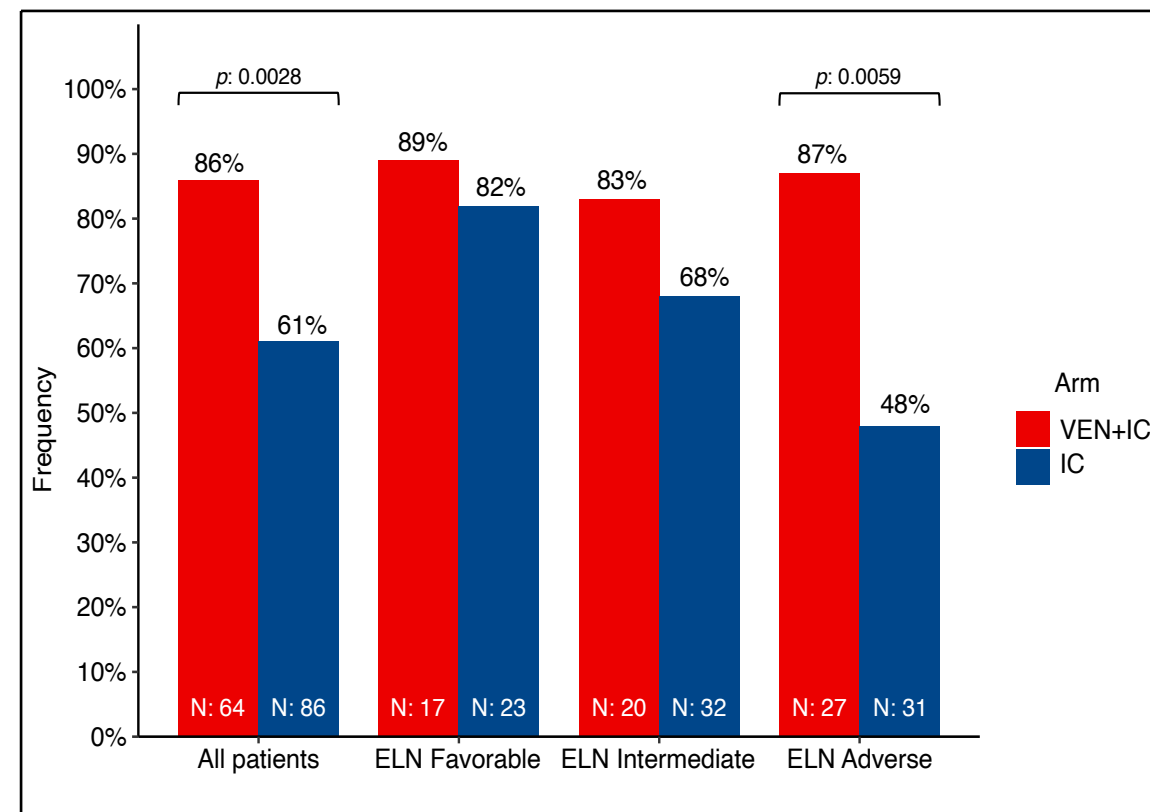
VEN+IC in AML: Response by cohort and MRD-negative response rates

Characteristic*	IC, N = 194	IC + VEN, N = 85	p-value
ORR	166 / 193 (86%)	81 / 85 (95%)	0.019
Composite CR	166 / 194 (86%)	77 / 85 (91%)	0.2
CR	153 / 194 (79%)	69 / 85 (81%)	
CRi	13 / 194 (6.7%)	4 / 85 (5%)	
MRD-negative CRc			
Negative	86 / 140 (61%)	64 / 74 (86%)	0.0028
Positive	54 / 140 (39%)	10 / 74 (14%)	
MLFS	0 / 194 (0%)	4 / 85 (5%)	
No Response	23 / 194 (12%)	3 / 85 (4%)	
Early Mortality (30-day)	4 / 194 (2%)	1 / 85 (1%)	
ELN Favorable Risk			
Composite CR	32 / 32 (100%)	19 / 21 (90%)	0.15
MRD-Negative CRc	23 / 28 (82%)	17 / 19 (89%)	0.43
ELN Intermediate Risk			
Composite CR	58 / 67 (87%)	26 / 29 (90%)	1.0
MRD-Negative CRc	32 / 47 (68%)	20 / 24 (83%)	0.14
ELN Adverse Risk			
Composite CR	76 / 95 (80%)	32 / 35 (91%)	0.12
MRD-Negative CRc	31 / 65 (48%)	27 / 31 (87%)	0.0059

VEN+IC compared to IC resulted in:

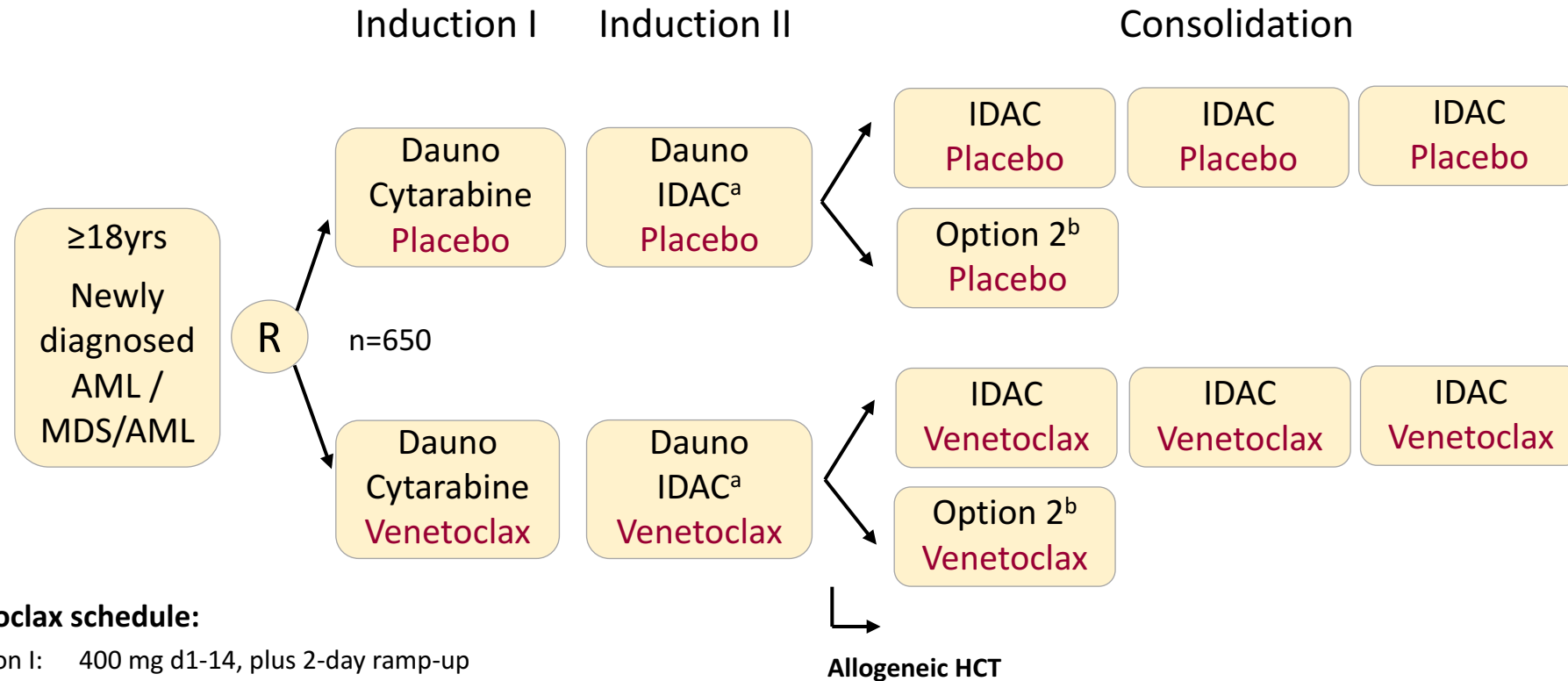
- Earlier responses
- Increased overall response rate
- **Increase in MRD-negative CR rates**
- **Increased alloSCT incidence (79% vs 57%)**

MRD-negative response rates between cohorts



A Phase 3 study of intensive induction and consolidation chemotherapy with or without venetoclax in adult patients with newly diagnosed AML or MDS/AML

AMLSG 31-19 / HOVON 501 / Abbvie B18-982



Venetoclax schedule:

Induction I: 400 mg d1-14, plus 2-day ramp-up
 Thereafter: 400 mg d1-7

Patients in CR/CRi after two cycles of induction proceed to AMLSG/HOVON-specific consolidation therapy; assignment to allogeneic hematopoietic cell transplantation (HCT) according to the local institutional or cooperative group prognostic algorithm; HCT can be performed at any time point following one induction cycle

^a IDAC, intermediate-dose cytarabine; age-adapted dosing; no anthracycline ≥60 yrs

^b HOVON consolidation: autologous HCT; or mitoxantrone / etoposide

Updated AML classifications reflect the impact on genomics associated with DIFFERENT AML therapies

ELN 2022¹

(Standard Intensively-treated patients)

- Favorable**
- t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*
 - inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*
 - Mut *NPM1* w/o *FLT3-ITD*
 - bZIP in-frame mut *CEBPA*

- Intermediate**
- Mut *NPM1* with *FLT3-ITD*
 - Wt *NPM1* with *FLT3-ITD*
 - t(9;11)(p21.3;q23.3)/*MLL3::KMT2A*
 - Cytogenetic and/or molecular

- Adverse**
- t(6;9)(p23.3;q34.1)/*DEK::NUP214*
 - t(v;11q23.3)/*KMT2A*-rearr
 - t(9;22)(q34.1;q11.2)/*BCR::ABL1*
 - t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
 - inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*
 - t(3q26.2;v)/*MECOM(EVI1)*-rearr
 - -5 or del(5q); -7; -17/abn(17p)
 - Complex/monosomal karyotype
 - Mut *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*
 - Mut *TP53*

ELN 2024²

(Less-intensive therapies)

- Favorable**
- Mutated *NPM1* (wild-type *FLT3-ITD, NRAS, KRAS, TP53*)
 - Mutated *IDH2* (wild-type *FLT3-ITD, NRAS, KRAS, TP53*)
 - Mutated *IDH1** (*TP53* wild type)

• Mutated *DDX41*†

• Other cytogenetic and/or molecular abnormalities (wild-type *FLT3-ITD, NRAS, KRAS, TP53*)‡

- Intermediate**
- Mutated *FLT3-ITD* and/or Mutated *NRAS* and/or *KRAS* (*TP53* wild-type)

- Adverse**
- Mutated *TP53*

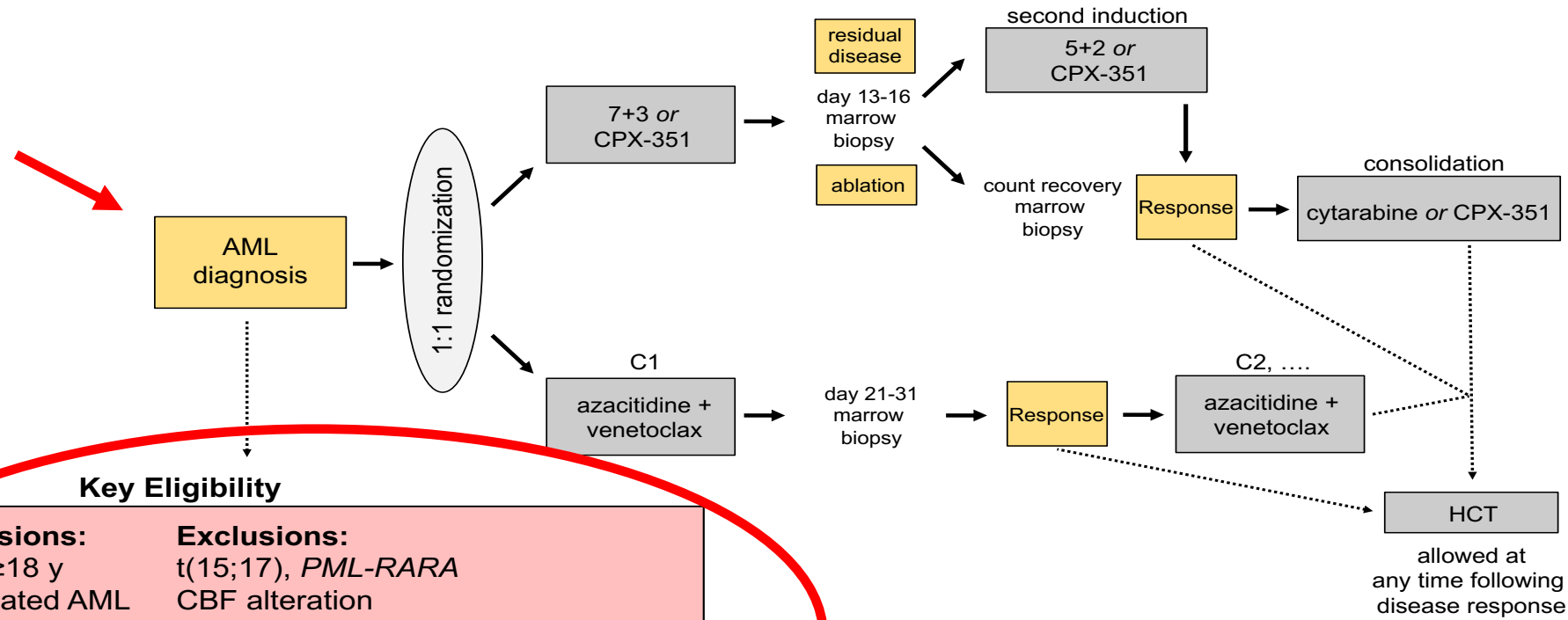
❖ This classification does not apply to pts that have received a prior HMA

* Favorable mutated *IDH1* risk applies specifically to patients treated with AZA + IVO and appears irrespective of signaling gene mutations

† Identification of a *DDX41* mutation (especially VAF ~ 50%) should prompt consideration of a germline mutation

‡ For many genomic abnormalities, not enough data is currently available

PARADIGM Study Design



Key Eligibility

Inclusions:

Age ≥ 18 y
Untreated AML
IC-eligible

Exclusions:

t(15;17), *PML-RARA*
CBF alteration
FLT3 ITD/TKD ($\geq 5\%$ VAF) mutations
NPM1 mutations (if aged < 60 years)
BCR::ABL1 fusion
Mixed phenotype

Primary endpoint:

Event free survival (EFS), with events defined as progressive disease, *persistent disease prompting therapy change*, relapse, hospice, or death.

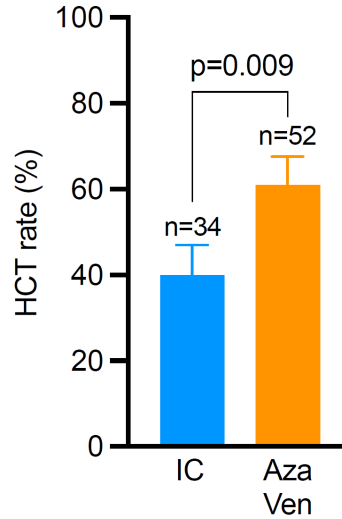
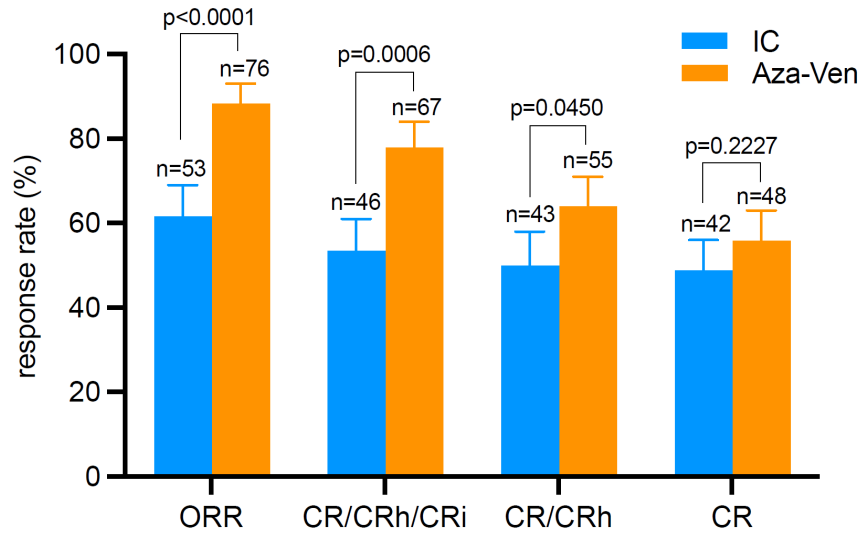
Significance was declared at the one-sided 0.1 type I error.

- Patients enrolled at 9 US academic centers from May 2021 through Jan 2025
- 472 screened, n=172 randomized (mostly excluded ineligible genotypes)
- Stratification: Age ($\leq 65 / > 65$) & pre-randomization IC selection (7+3 vs. CPX) median follow up: 21.9 months
- No patients remain on study treatment as of Oct 2025 data cut-off

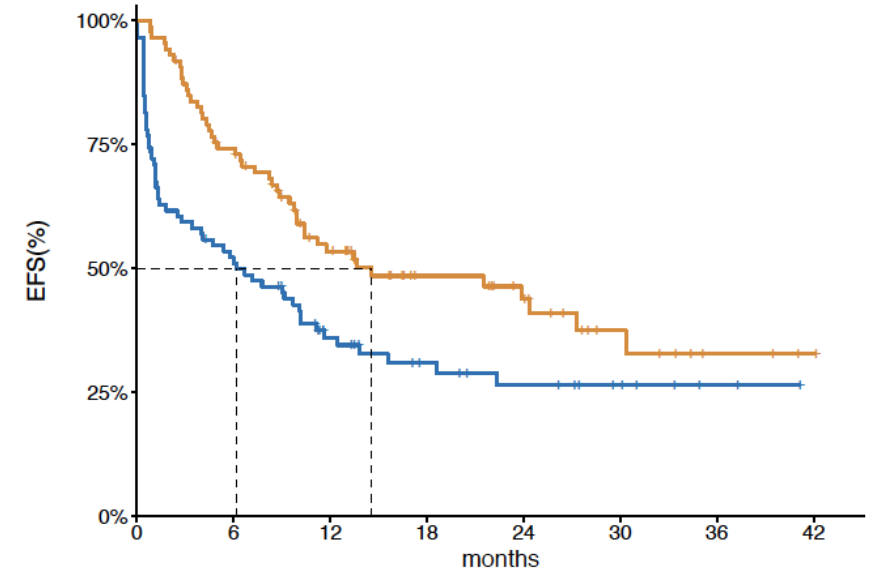
PARADIGM: Baseline Characteristics:

		Total	Aza-Ven	IC
		(N = 172)	(N = 86)	(N = 86)
Age	Median years, (range)	64 (23 - 79)	65 (23 - 79)	64 (28 - 79)
	Less than 65, n (%)	87 (50.6)	43 (50.0)	44 (51.2)
Sex, n (%)	Male	115 (66.9)	55 (64.0)	60 (69.8)
Race, n (%)	Caucasian	134 (77.9)	65 (75.6)	69 (80.2)
	African American	10 (5.8)	5 (5.8)	5 (5.8)
	Hispanic	13 (7.6)	6 (7.0)	7 (8.1)
	Asian	15 (8.7)	10 (11.6)	5 (5.8)
ECOG, n (%)	0/1	161 (93.6)	79 (91.9)	82 (95.4)
	2	10 (5.8)	7 (8.1)	3 (3.5)
ELN 2022 risk, n (%)	Favorable	22 (12.8)	13 (15.1)	9 (10.5)
	Intermediate	26 (15.1)	15 (17.4)	11 (12.8)
	Adverse	124 (72.1)	58 (67.4)	66 (76.7)
Mutations, n (%)	<i>NPM1</i>	16 (9.3)	11 (12.8)	5 (5.8)
	<i>IDH1</i>	15 (8.7)	8 (9.3)	7 (8.1)
	<i>IDH2</i>	28 (16.3)	19 (22.1)	9 (10.5)
	<i>TP53</i>	25 (14.5)	9 (10.5)	16 (18.6)
	<i>RUNX1</i>	32 (18.6)	14 (16.3)	18 (20.9)

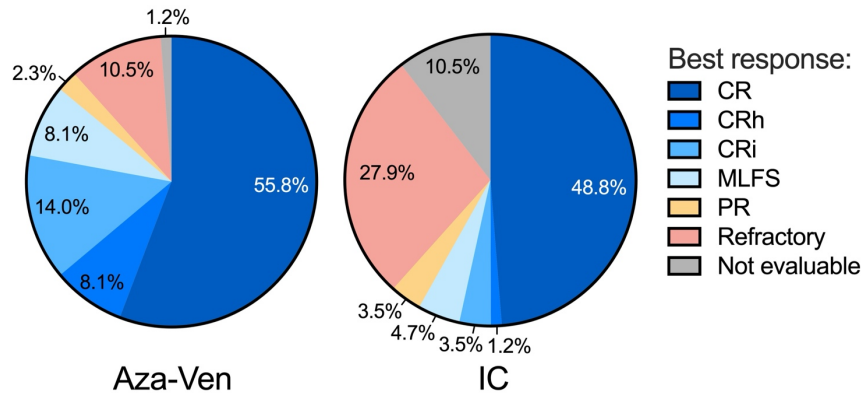
PARADIGM: Remission Rates and EFS



EFS (Primary Endpoint)



ORR: CR+CRh+CRi+PR+MLFS



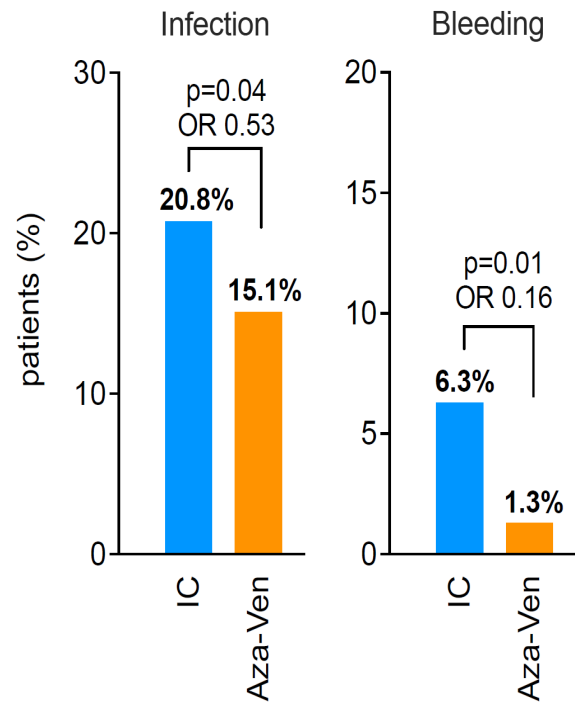
IC	86	43	24	15	11	7	2	0
Aza-Ven	86	62	38	23	17	8	3	1

- **Median EFS of 14.6 for Aza-Ven vs 6.15 months for IC (P=0.0021)**
- One-year EFS was 53.4% for Aza-Ven vs 36.0% for IC
- The HR for a univariate Cox model was 0.57 (P=0.0022)
- After adjustment for variables in a multivariable model, the effect of aza-ven remained protective for EFS (HR:0.66; P=0.0231)

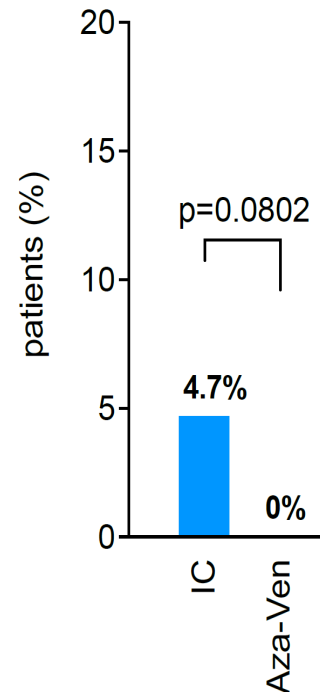
PARADIGM: Safety, Tolerability, Resource Utilization

Healthcare Utilization

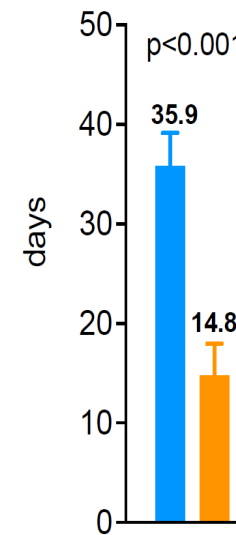
Treatment emergent adverse events (\geq grade 3)



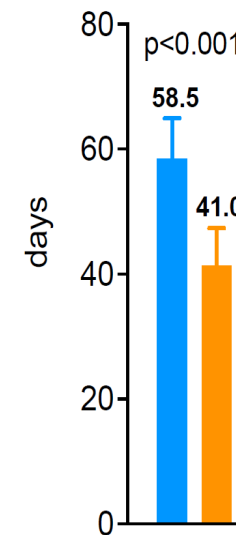
60-day mortality



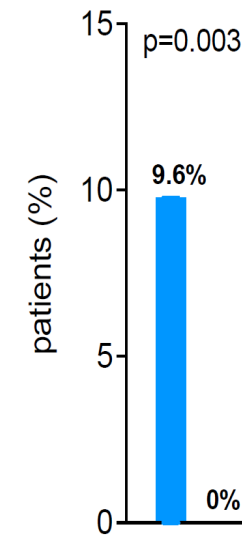
Index hospitalization length of stay



Hospital days in first 6 months

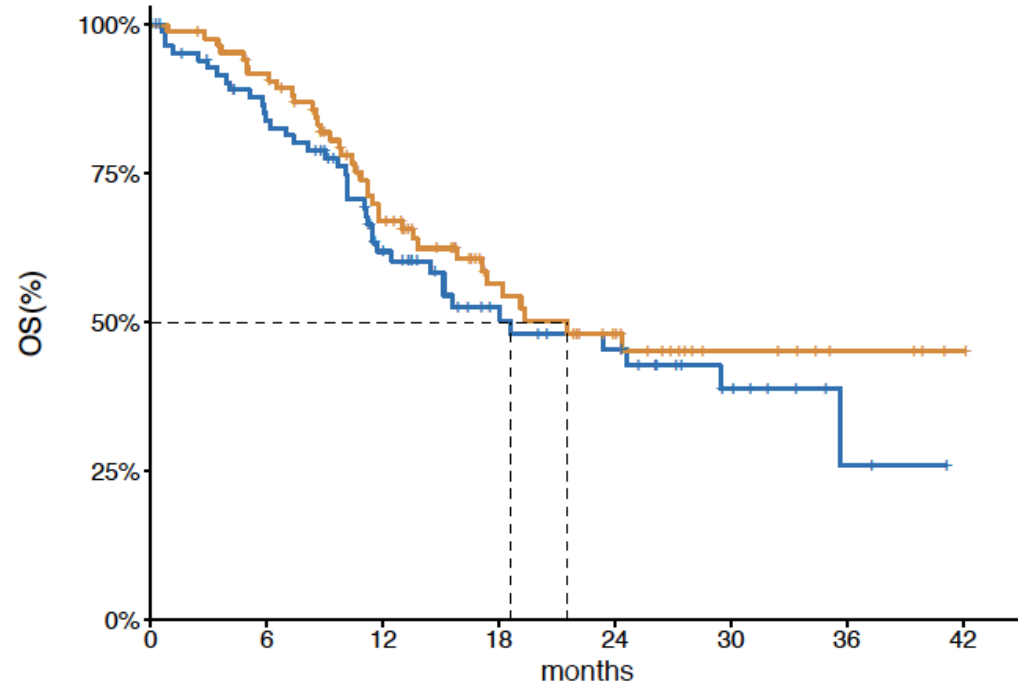


ICU admission in first 30 days



■ IC
■ Aza-Ven

PARADIGM: OS (Secondary Endpoint)



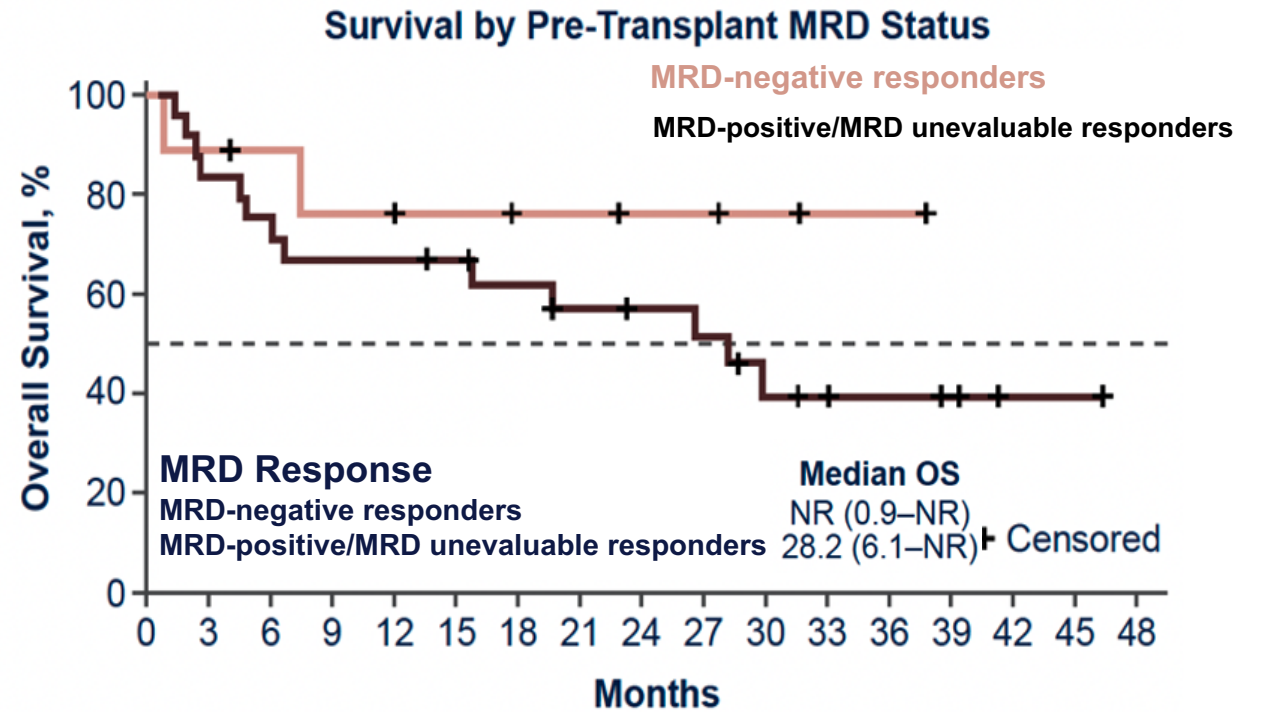
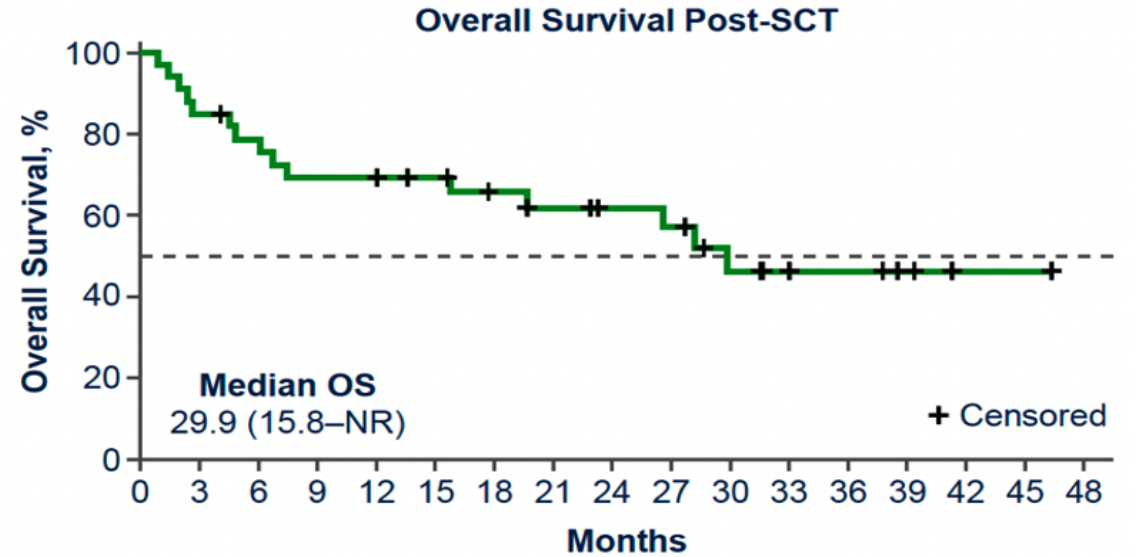
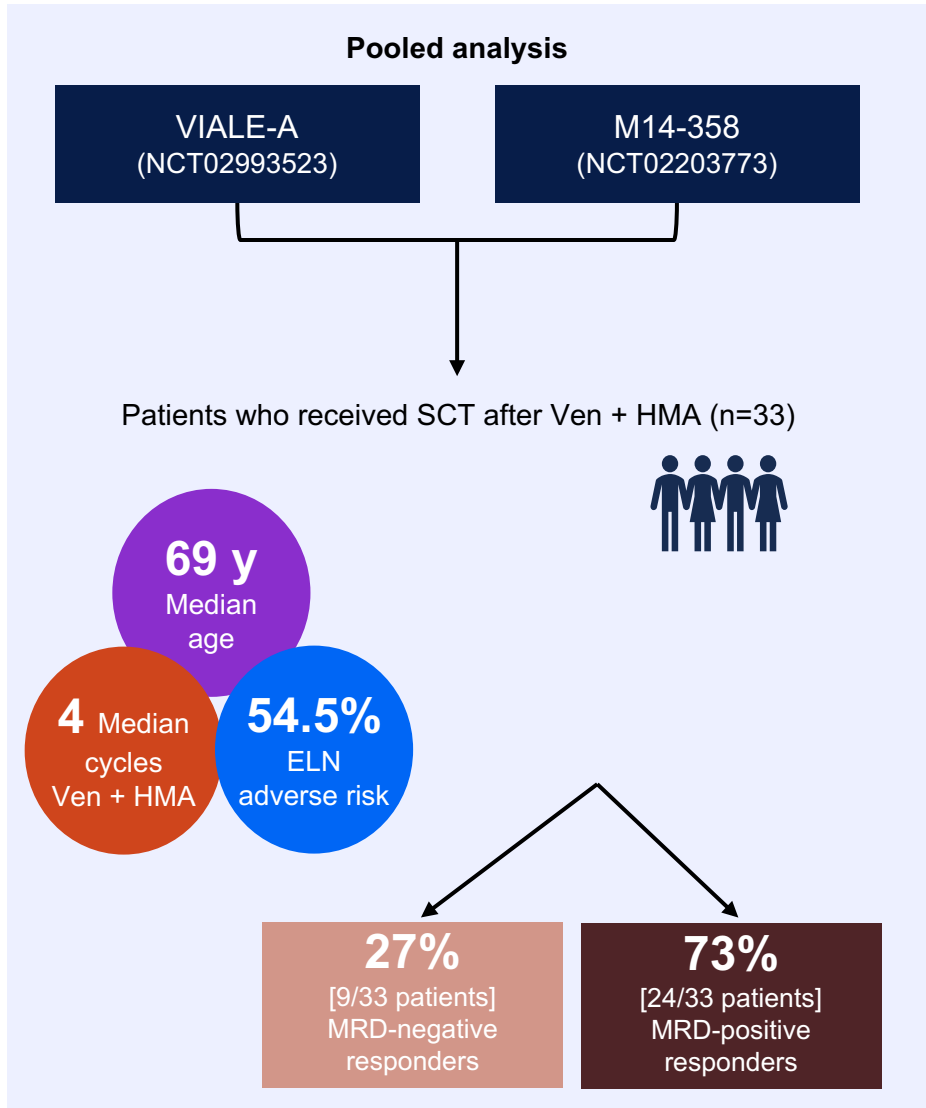
IC	86	66	39	23	18	9	2	0
Aza-Ven	86	77	49	27	18	8	4	1

Patients R/R to Study Treatment		N (%)
Patients on IC arm (N=37)	Received Subsequent HMA-Ven	25 (67.6)
Patients on Aza-Ven (N=36)	Received subsequent IC	17 (47.2)

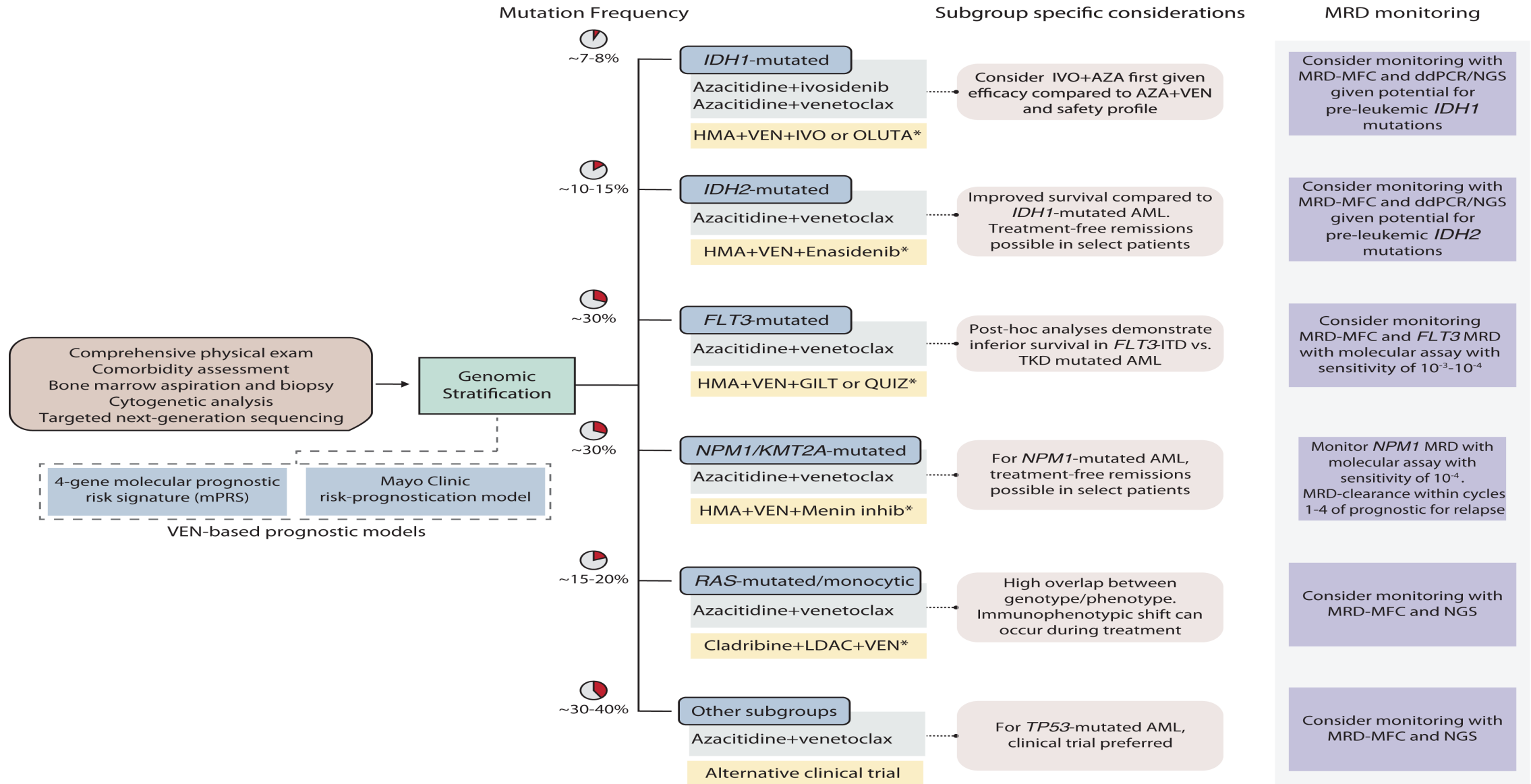
- High rates of crossover after study therapy were frequent - open label design

- Median OS=21.5 mo for aza-ven vs 18.6 mo. for IC (log rank, $P = 0.1873$)

HMA + Ven followed by transplant in VIALE-A



Genetically Informed “Beyond HMA+VEN” Treatment Decisions



EVOLVE-1: Ivosidenib + azacitidine plus placebo or venetoclax in newly dx older, unfit patients with *IDH1*-mutated AML



Venetoclax: 400 mg for 7 days

PI: H. Döhner (AMLSG); Co-PIs: G. Huls (HOVON), P. Vyas (UK)

CETLAM
Grupo cooperativo de estudio y tratamiento de las leucemias agudas y mielodisplasias

fil
FRENCH INNOVATIVE
LEUKEMIA ORGANIZATION

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. **FRANCO MANDELLI**

STUDY AML GROUP

HO173 / AMLSG 34-23 / ACT-HOV-AML-001
In collaboration with Servier

UK AML
Research Network

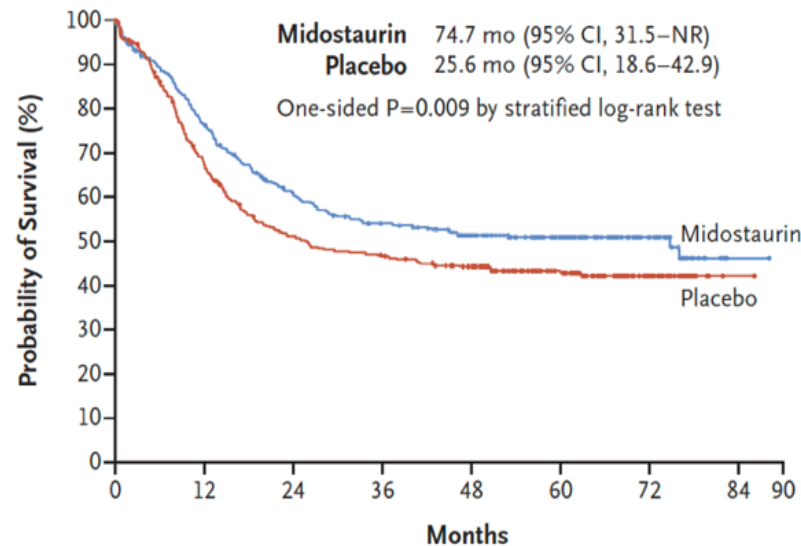
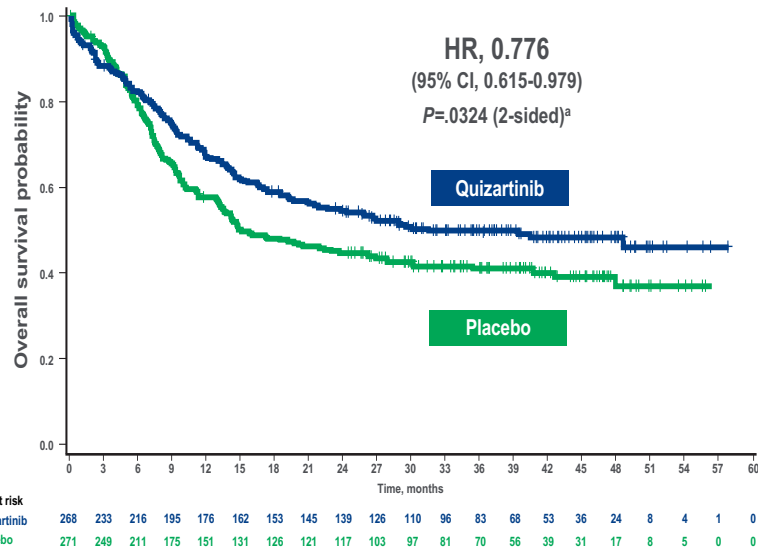
ALFA
Alla Leukemia French Association

HOVON

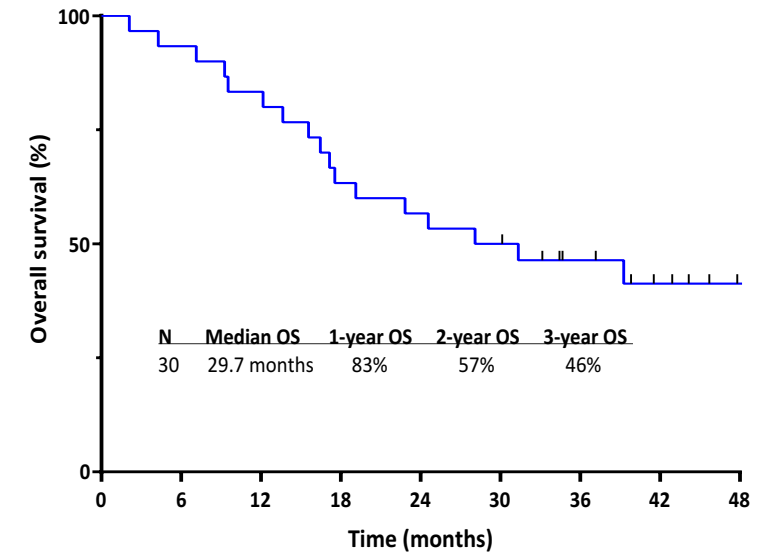
Could triplet therapies (i.e. HMA+VEN+FLT3i) be effective option even for younger/fitter pts?

QUIZZICAL: Randomized Ph II HMA+VEN+Quiz vs IC+QUIZ for FLT3-ITD AML(50-75 yr)

UK-MRC and US sites
PIs: Craddock and Daver



AZA + VEN + GILT



EVOLVE-2: Azacitidine + venetoclax +/- revumenib

In newly dx older, unfit patients with *NPM1m* or *KMT2Ar* AML



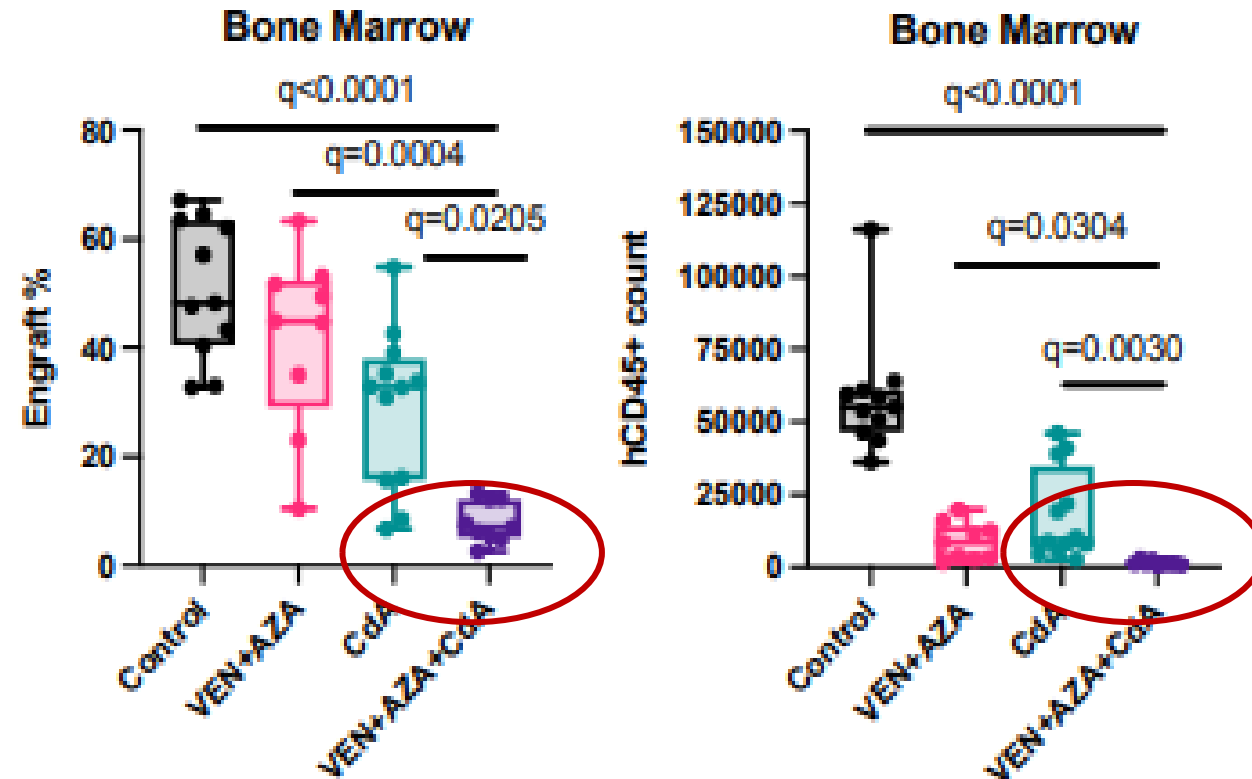
PI: M. Kuhn (AMLSG)

HO177 / AMLSG 35-24 / ACT-HOV-AML-002

Start: Q4 2024

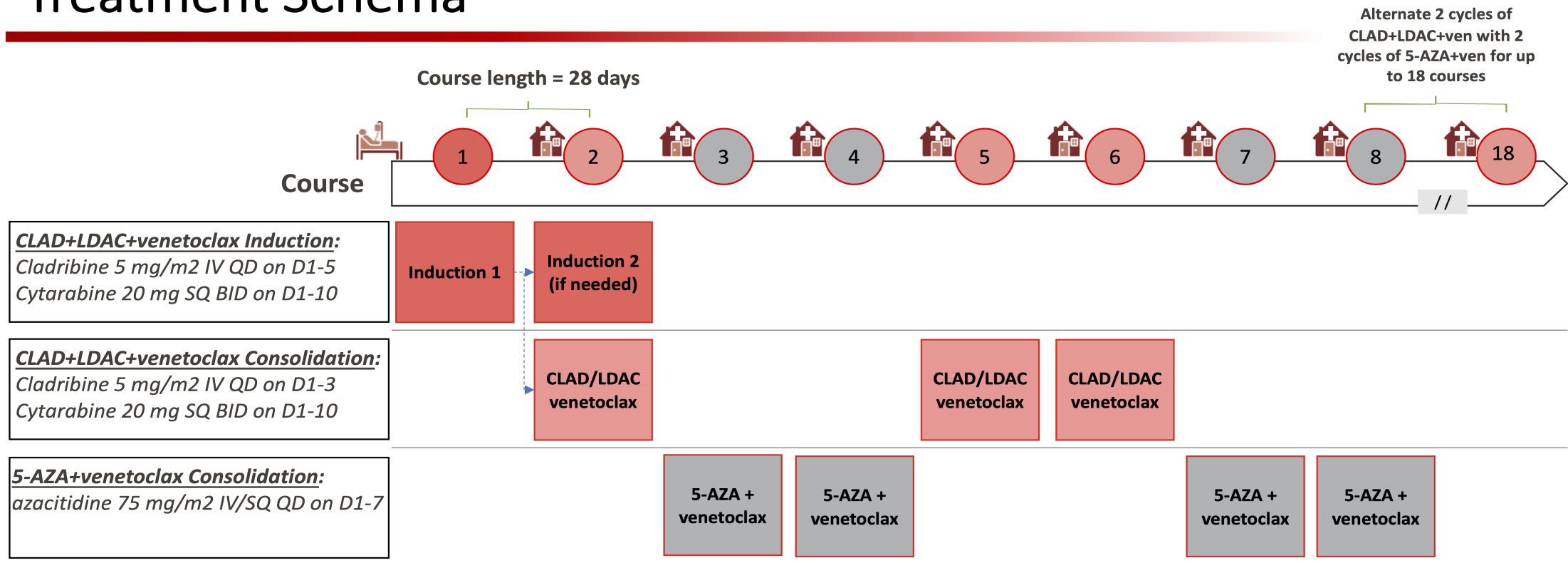
Resistance related to monocytic disease

- Post HMA + VEN relapses often manifest with a more differentiated monocytic phenotype
- **Stem cells driving monocytic relapse are distinct** from other AML LSCs with a unique immunophenotype: CD34-, CD4+, CD14-, CD11b-, CD36-
- “m-LSCs” have selective reliance on one-carbon metabolism and purine/pyrimidine metabolism
- **The purine analogue cladribine was particularly effective in eradicating m-LSC stem and progenitor potential both *in vitro* and *in vivo* preclinical models**
- may help explain results reporting superior CR/CRi and MRD negativity rates with VEN plus cladribine or its analogue fludarabine – containing regimens
 - namely FLAG-Ida, CLIA, CLAG or Clad/LDAC + VEN



Cladribine/LDAC + VEN: An “intermediate intensity” approach [especially for pts with monocytic and RAS-driven disease]

Treatment Schema



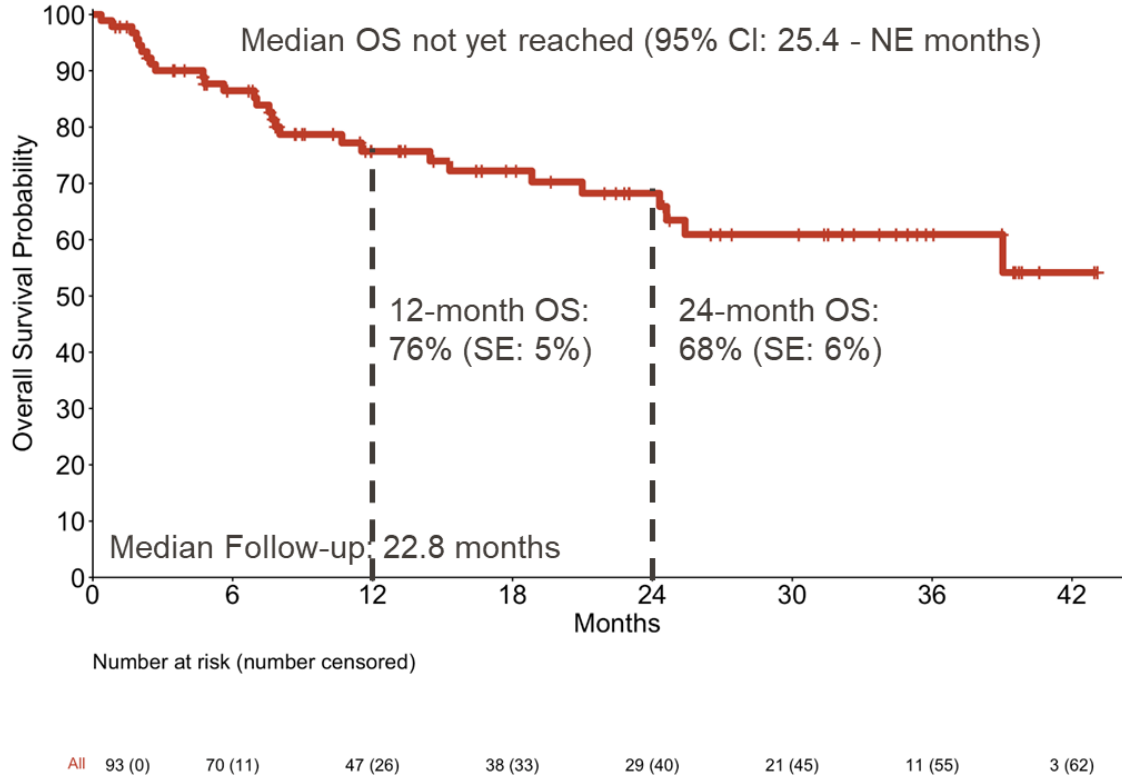
	Suggested Ramp Up for Venetoclax			
	Day 1	Day 2	Day 3	Target Dose
Strong CYP3A4 Inhibitor	50mg	50 mg	100 mg	100 mg
Moderate CYP3A4 Inhibitor	50mg	100 mg	200 mg	200 mg
No CYP3A4 Inhibitor	100mg	200 mg	400 mg	400 mg

Venetoclax dosing:

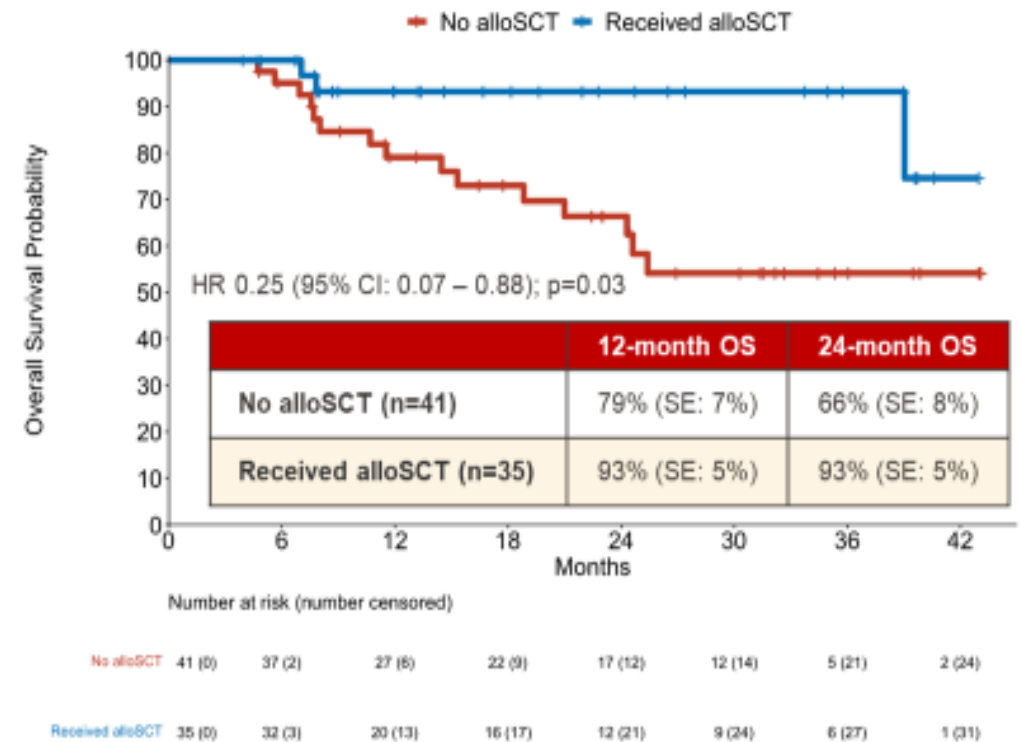
- Cycle 1: 21 days
- Cycle 2+: 7 – 14 days, based on MRD and tolerability

Cladribine/LDAC + VEN : Newly Dx AML

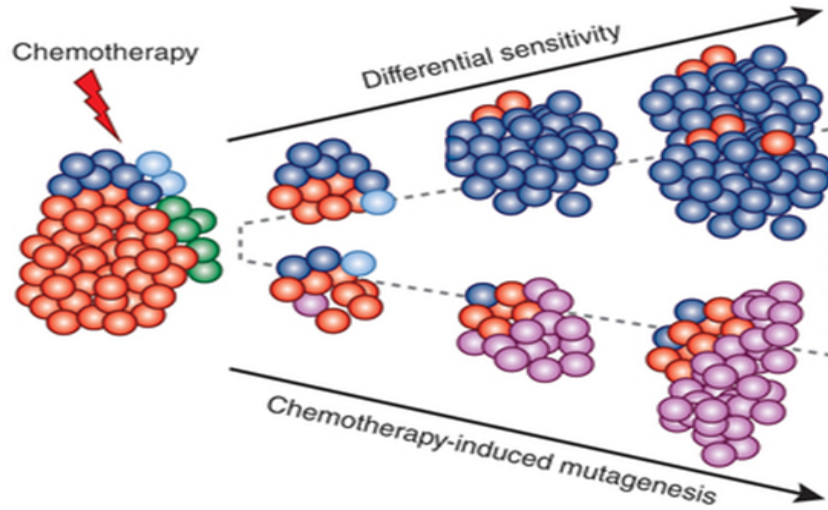
- Median age was 68 (range 57-84 yrs); 23% had secondary AML
- N=93 patients. The CRc rate was 92%; CR = 78% and MRD neg = 84%
- Estimated 12 mo and 24 mo OS are 76% and 68%. 41% pts underwent alloSCT



OS by Receipt of SCT

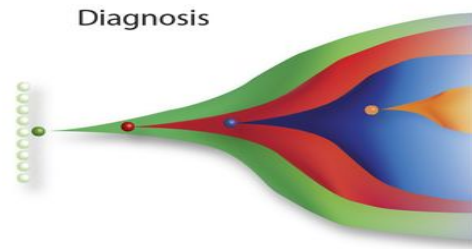


Individualizing Therapy at Relapse



Leukemia is not a static condition!

Repeat genomic analysis at relapse is necessary



Relapse
1.



Major clone

2.



Minor clone

3.



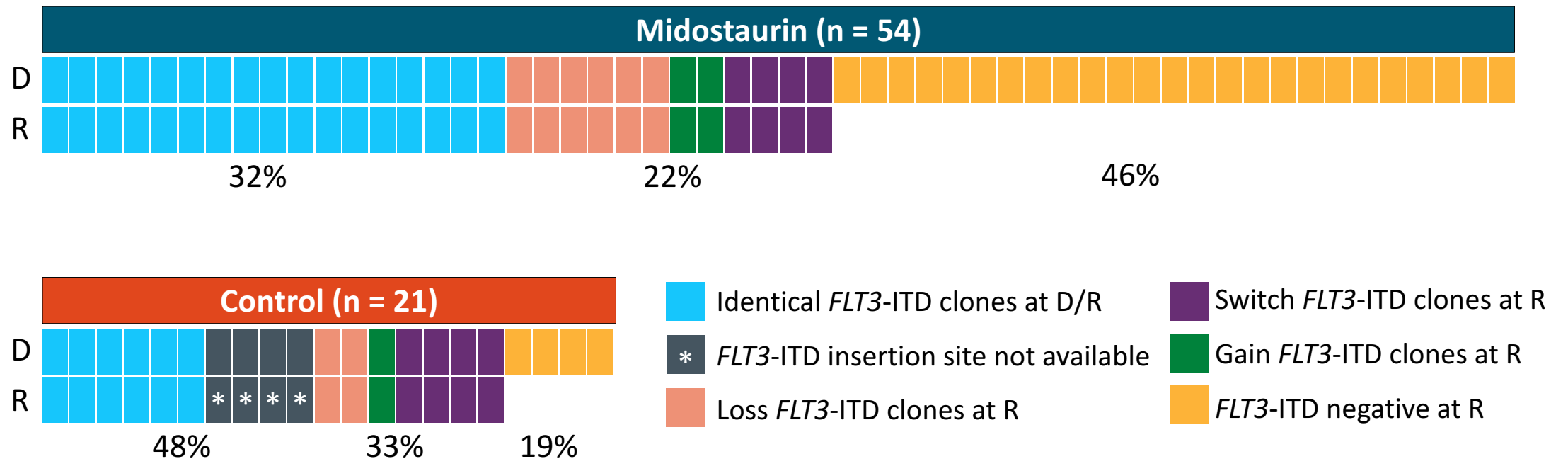
Evolution of an ancestral clone

4.



Treatment-related secondary clone

RATIFY Example: Front-line 7+3 +/- midostaurin *FLT3*-ITD Clones Can Be Differentially Present at Diagnosis and Relapse, i.e. **Repeat Testing is Necessary**



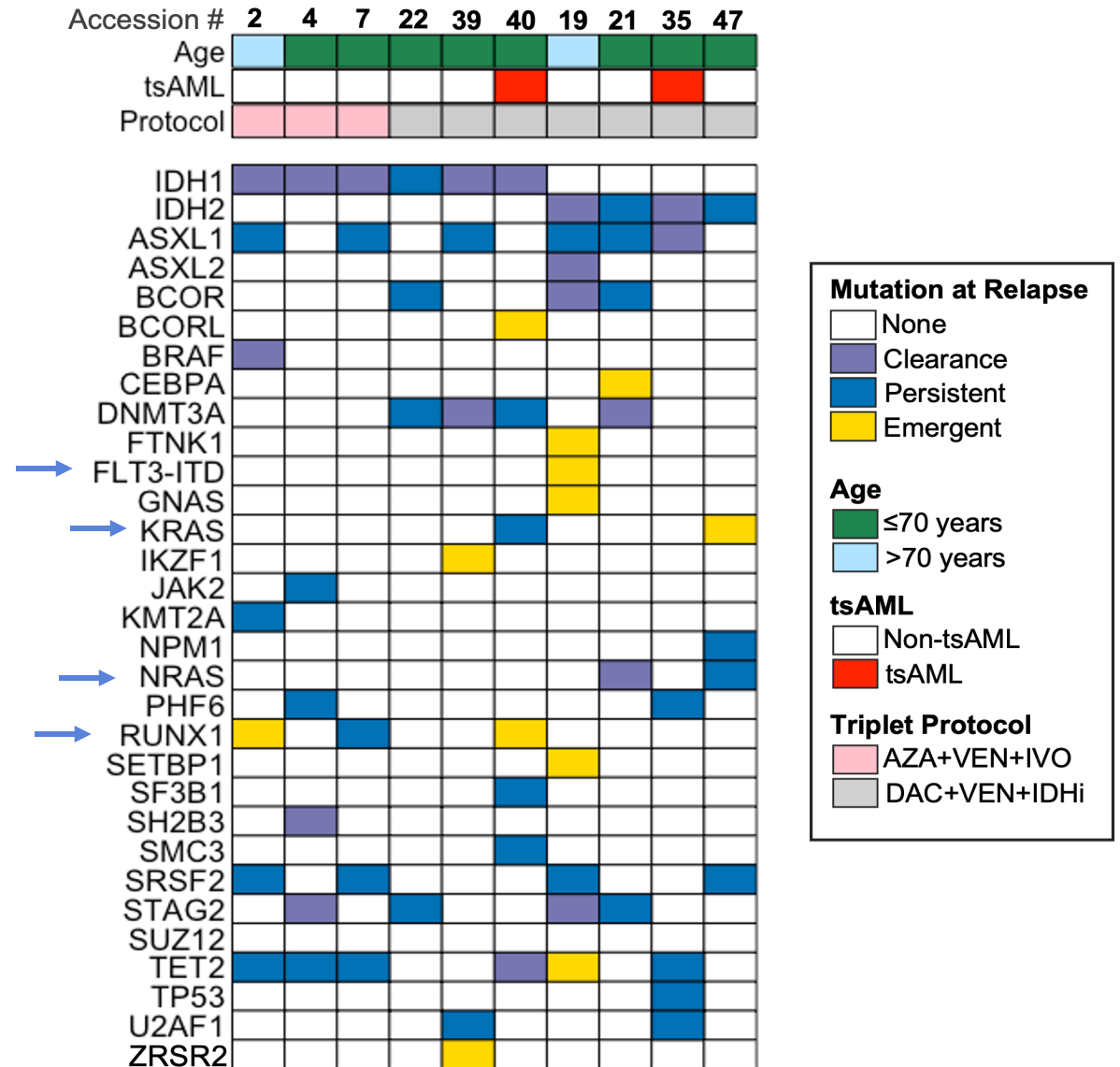
*Higher allelic ratio.

Schmalbrock. Blood. 2021;137:3093.

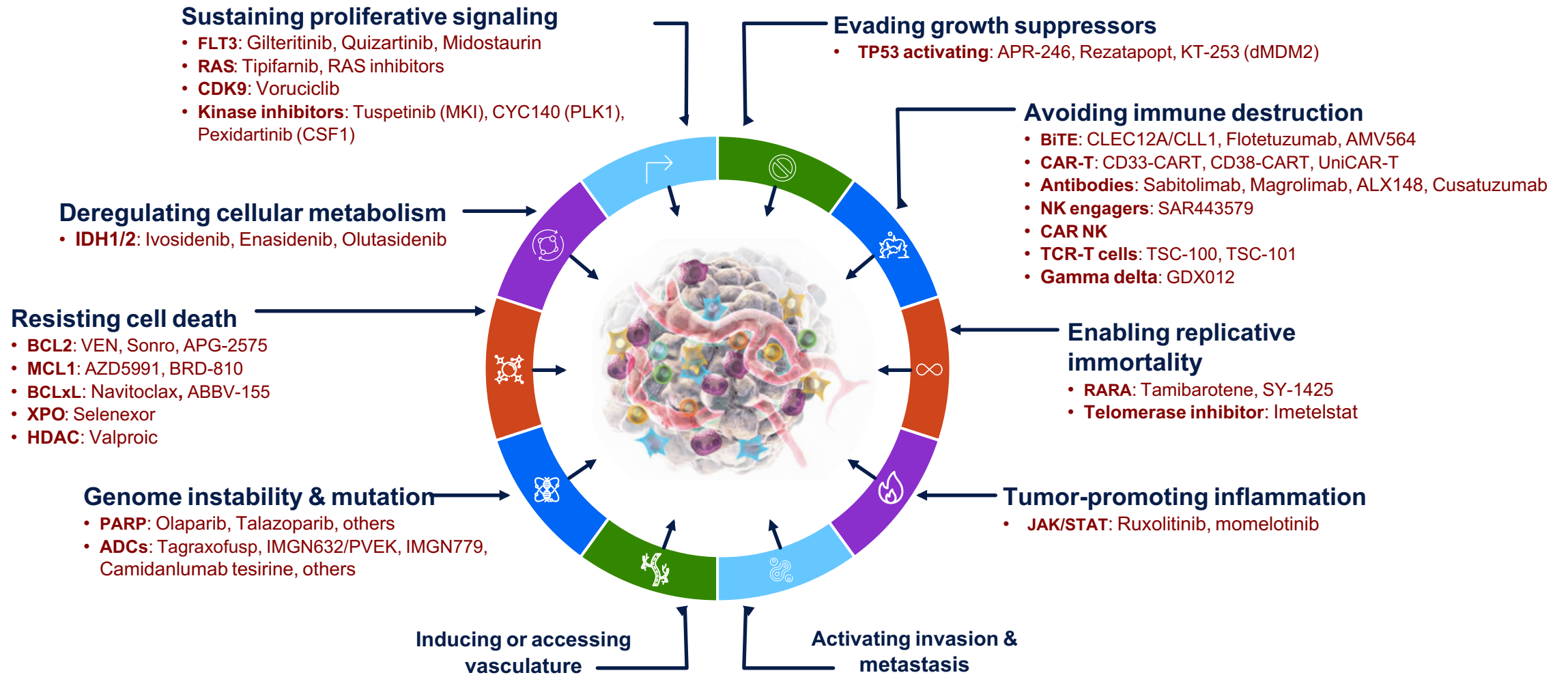
Slide credit: clinicaloptions.com

Mutations at Relapse : IDH triplets

- 10 patients relapsed
 - 6 with *IDH1* mutations → only 1 *IDH1* persisted at relapse
 - 4 with *IDH2* mutations → 2 persisted
- 3 patients with RAS mutations relapsed (33%)
- 2 emergent *RUNX1*, 1 *KRAS*, 1 *CEBPA*, no clear pattern
- **None of the 4 pts with dual *IDH1* and *IDH2* mutations relapsed**

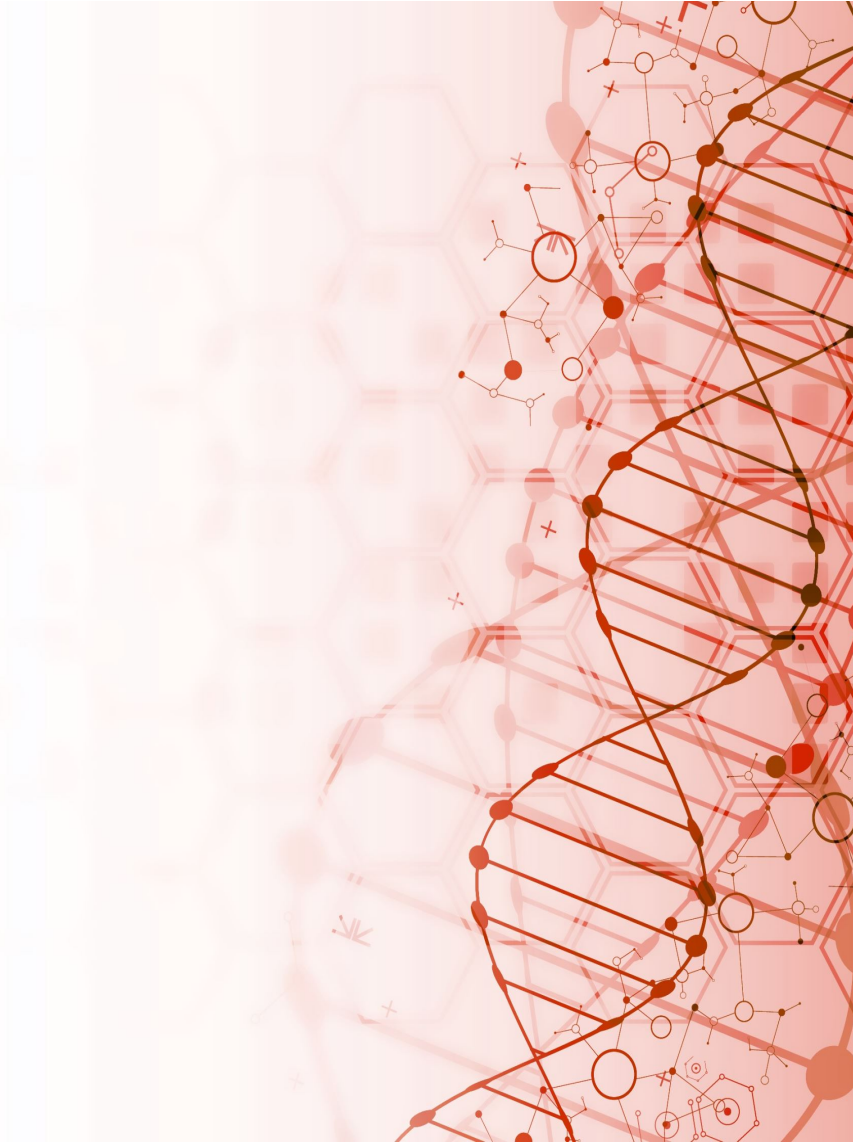


An array of future promising targets in AML



Conclusions

- AML therapeutic options continue to improve, with increasingly individualized and effective treatments
- Venetoclax has improved expectations for older / IC-ineligible patients with AML:
But it is NOT curative for the majority of pts
- Awareness of genomics (cytogenetics and mutational data) are essential to determine optimal treatment
- Future strategies to move “**beyond HMA+VEN**” include triplet regimens, intermediate-intensity regimens (i.e. cladribine/LDAC+VEN), immunotherapy approaches, and other novel targets



THANK YOU!



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