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Contemporary Management of AML: Progress and Challenges

Miami Cancer Meeting 2025

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Learning objectives

How to utilize genomic data in sequencing therapy and treatment decisions for AML.

Significance of MRD in treatment decisions.

How to utilize venetoclax based therapy for AML

What are the unmet needs or unsolved issues in the management of AML.

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Background

- Understanding of pathobiology of leukemia, has led to identification of therapeutic targets and development of novel therapies.

- Highly sensitive monitoring techniques has led to more precise treatment decisions and sequencing of therapies.

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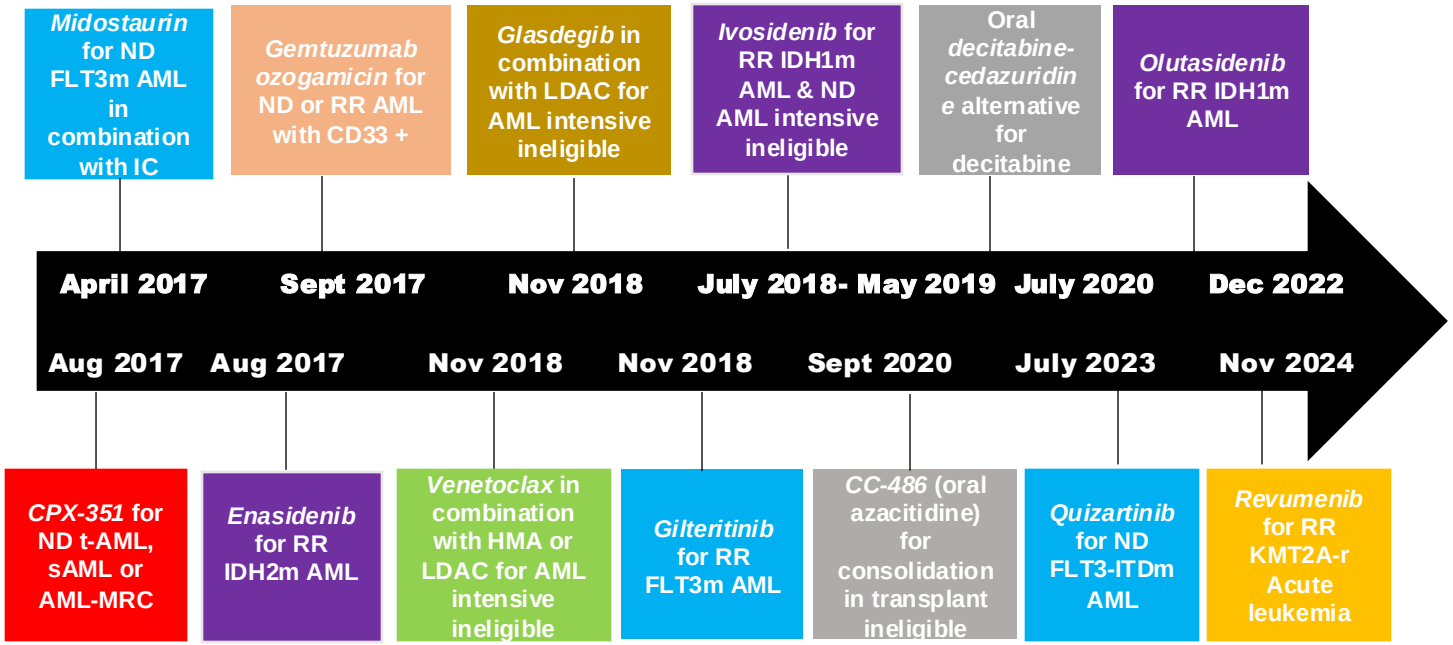
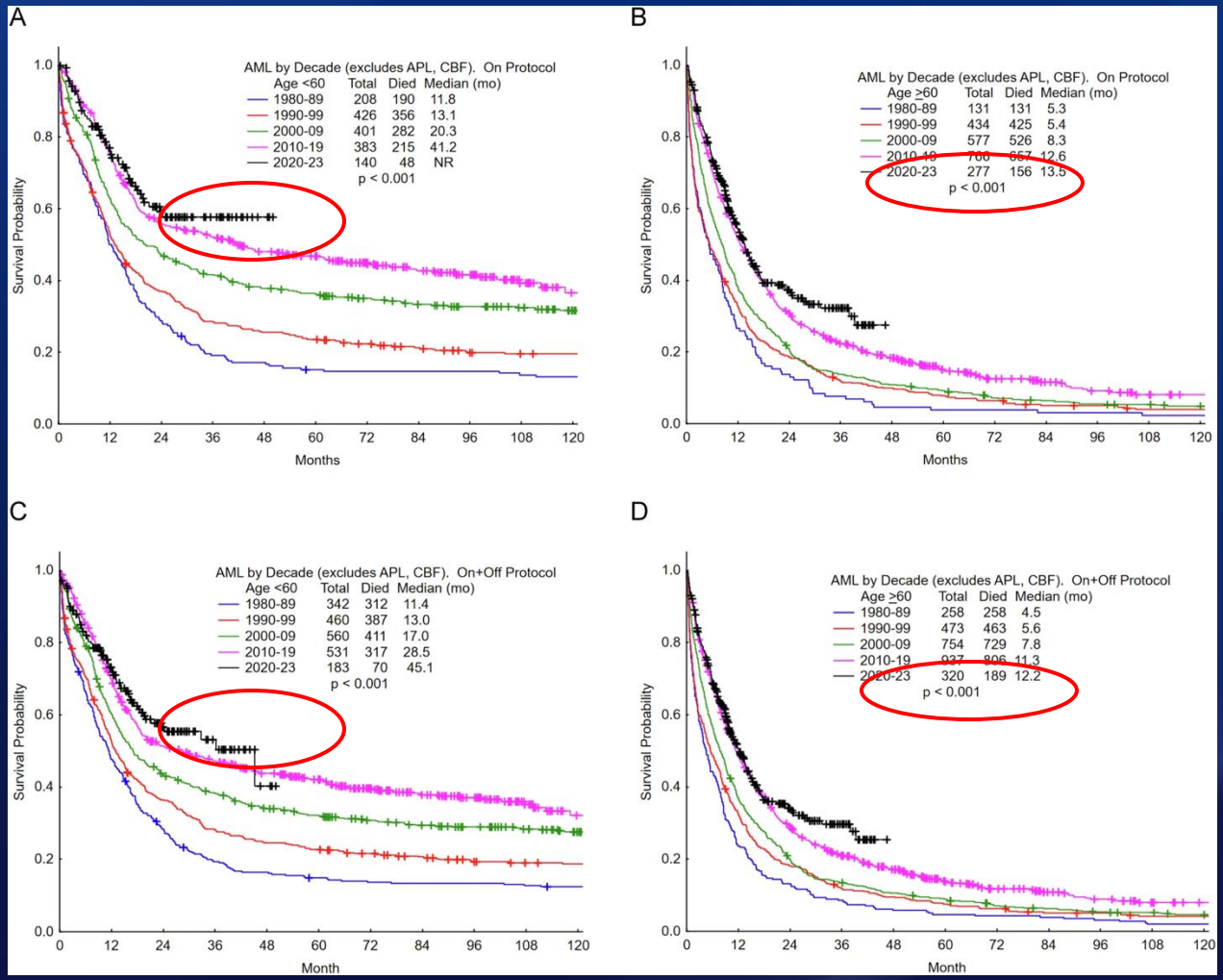
Drug approvals since 2017 for AML



FLT3 inhibitors ADC CPX-351 Hedgehog inhibitor BCL2 inhibitors IDH inhibitors HMA

Menin inhibitors

Outcome of AML over the last decades; on and off clinical trials



Kantarjian et al. BCJ 2024

Risk stratification in AML

ELN classification 2022	
Risk category	**Genetic lesion**
Favorable	**t(8;21)(q22;q22); *RUNX1::RUNX1T1*** **inv(16)(p13.1q22); *CBFB::MYH11*** **Mutated *NPM1* without *FLT3*-ITD** **bZIP in-frame mutated *CEBPA***
Intermediate	**Mutated *NPM1* with *FLT3*-ITD** **Wild type *NPM1* with *FLT3*-ITD** **t(9;11)(p21.3;q23.3); *MLLT3::KMT2A*** **Cytogenetic abnormalities not classified as favorable or adverse**
Adverse	**t(6;9)(p23;q34.1); *DEK::NUP214*** **t(v;11q23.3); *KMT2A*-rearranged** **t(9;22)(q34.1;q11.2); *BCR*::*ABL1*** **inversion(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *MECOM(EVI1)*** **-5 or del(5q); −7; −17/abnormality (17p)** **Complex karyotype (≥ 3), monosomal karyotype** **Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSF2*** **Mutated *TP53***

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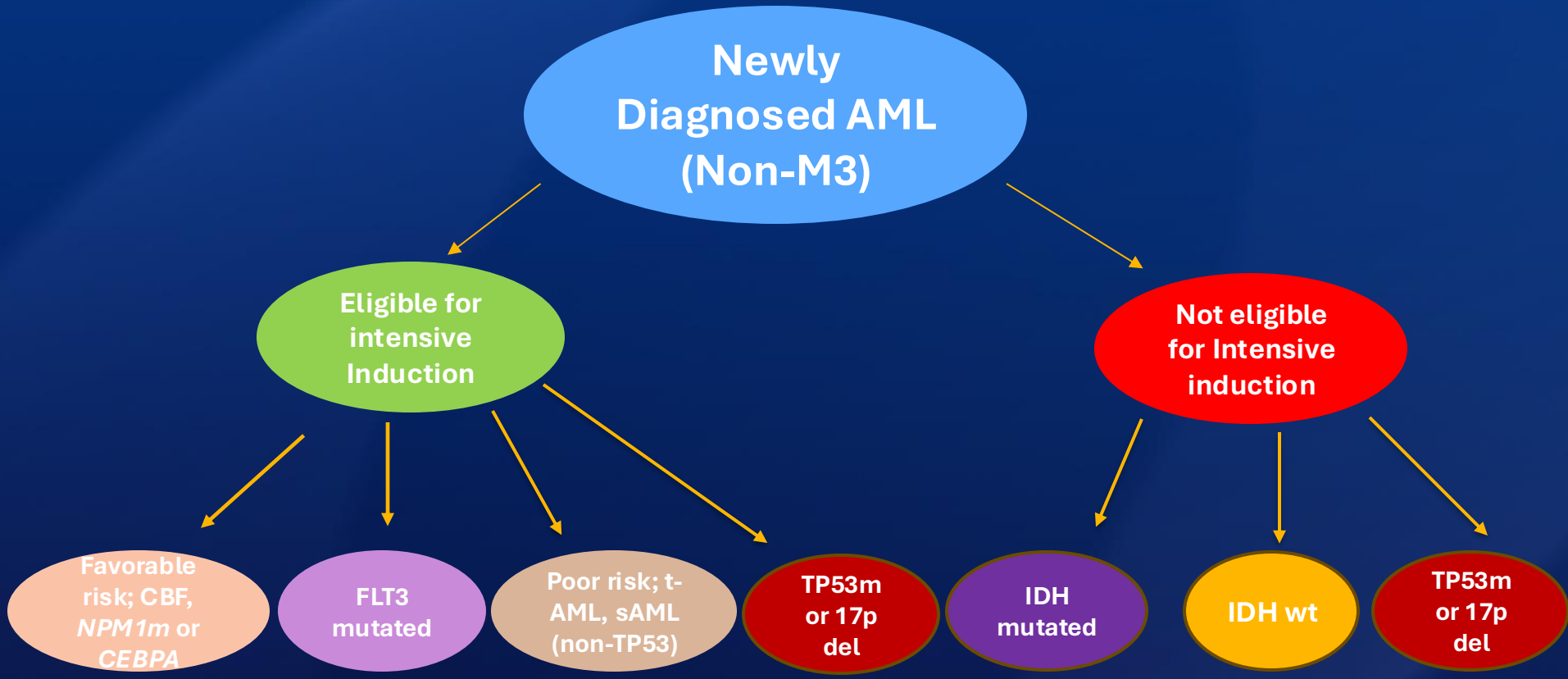
Big Picture



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Unmet needs or unsolved issues for induction in newly diagnosed AML

- Duration of Venetoclax during induction (7 vs 14 vs 28 days).
- Molecular signature predicting outcome with venetoclax plus azacitidine.
- FLT3m AML in elderly: venetoclax plus AZA or Venetoclax+AZA+FLT3i
- Rx of newly diagnosed AML with *TP53* mutation or 17p del.
- Ven plus HMA is equivalent or better to intensive induction in poor risk AML.

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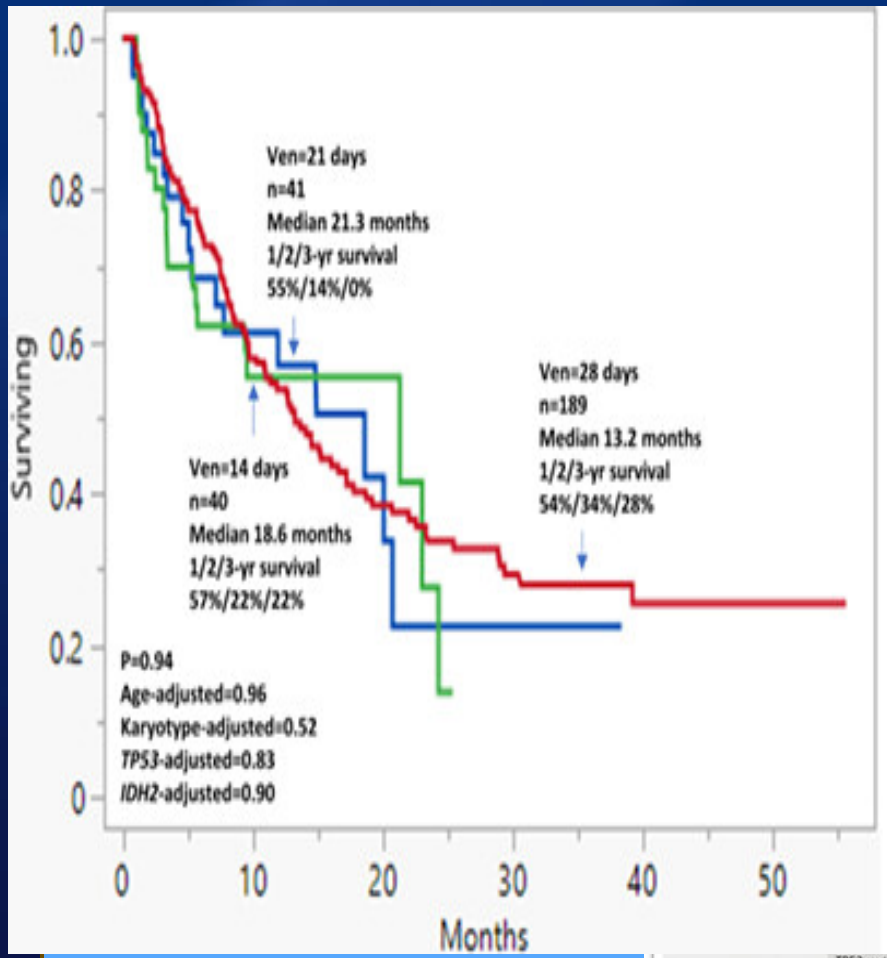
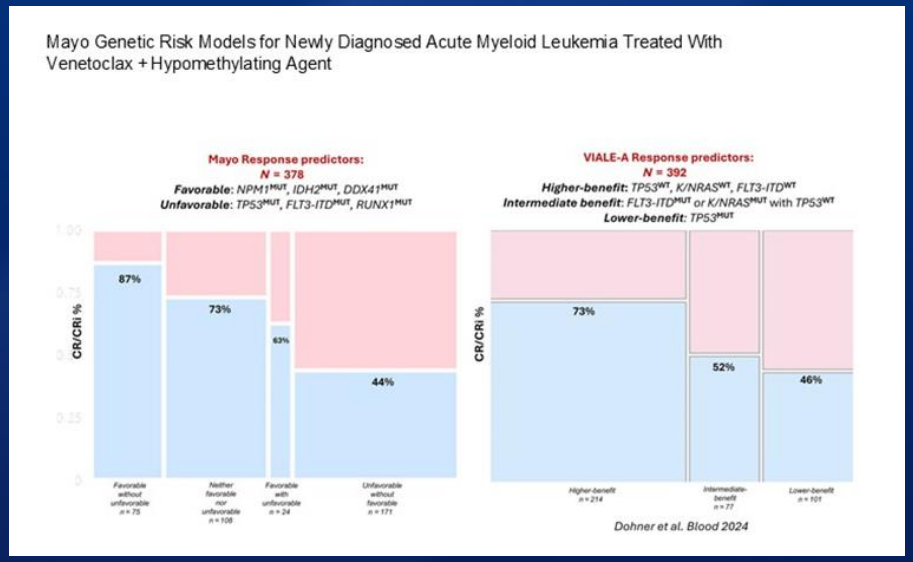
Duration of venetoclax during induction

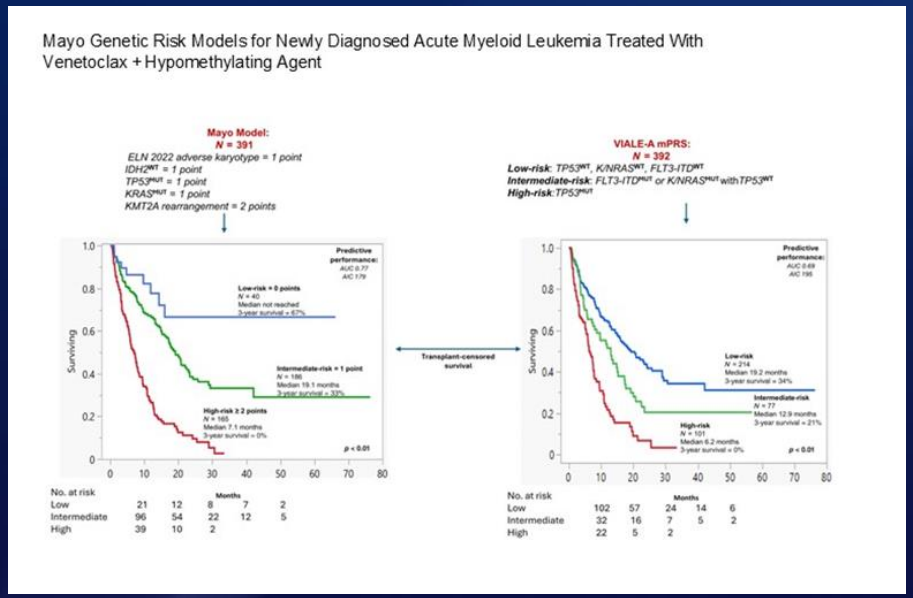


CR/CRi	All patients n=270	ELN adverse Karyotype n=101	ELN non-adverse Karyotype n=169
Ven 14 days	27/40 (68%)	2/9 (22%)	25/31 (81%)
Ven 21 days	27/41 (66%)	9/15 (60%)	18/26 (69%)
Ven 28 days	117/189 (62%)	34/77 (44%)	83/112 (74%)
P-values			
Ven 14 vs 21	0.88	0.07	0.32
Ven 14 vs 28	0.50	0.19	0.44
Ven 21 vs 28	0.63	0.26	0.62

C Willekens et al. ASH 22 Abstract # 222, O Karrar et al . AJH 2923

Molecular signature predicting outcome with Azacitidine plus venetoclax





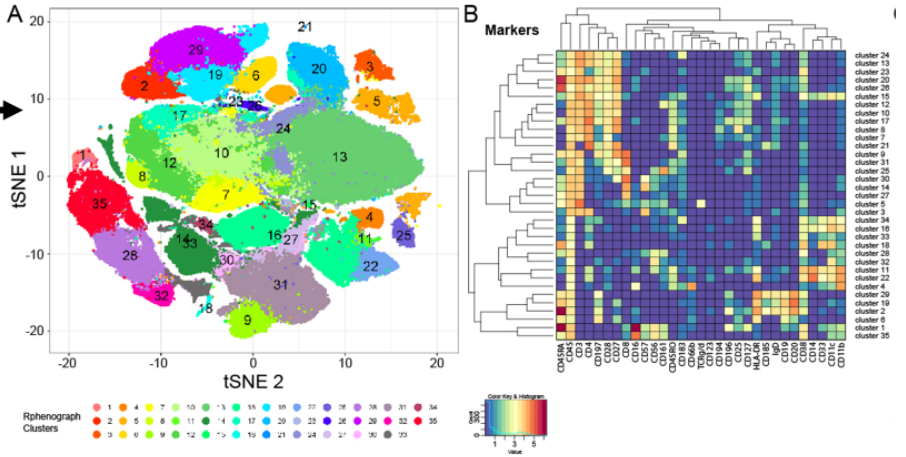
Gangat et al. AJH 2024, Dohner et al. Blood 2024

Immune signature and outcome with VEN+HMA

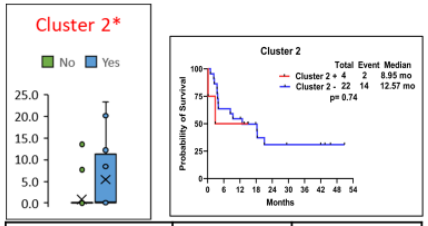
T-Cells Immune Clustering Identifies Distinct Immune Phenotype of *TP53* mutated AML and responders to Venetoclax plus hypomethylating agent

We performed a Rphenograph clustering on 25 paired BMMC and PBMC samples to create 35 unique clusters for each.

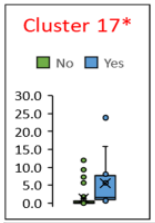
We discover immune depleted among responders (CR/CRh/CRi) and immune infiltrated phenotype in *TP53*-m AML.

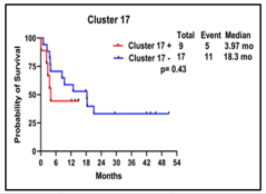


T cell clusters among patients with *TP53* mutation



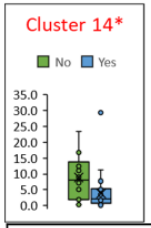
B-cell activated	High expression	P = 0.01

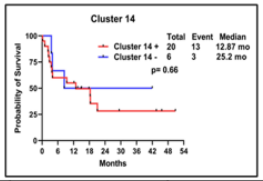




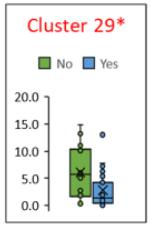
CD4 Memory T-cells	High expressio n	P = 0.005

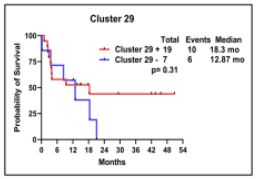
T cell clusters among patients with CR





CD8 T-cells	low expression	P = 0.01





B cell activated	low expression	P = 0.01

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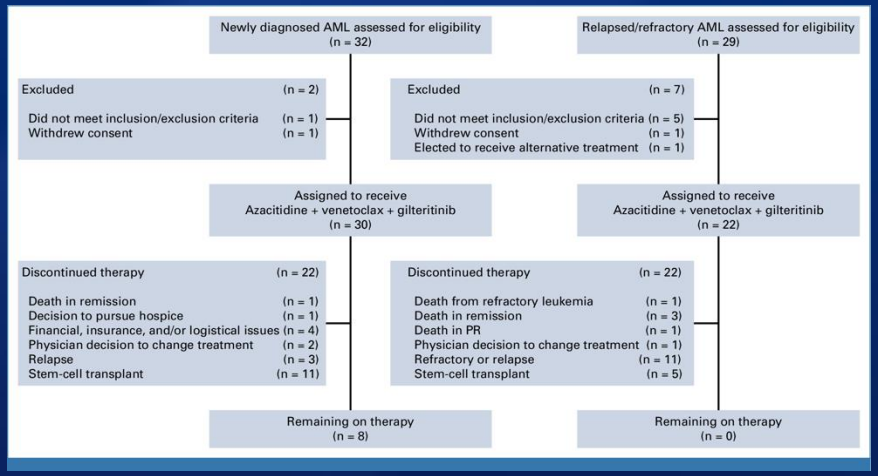
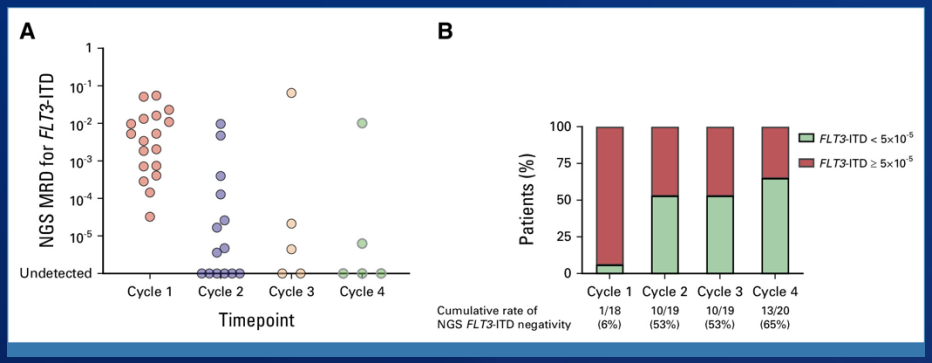
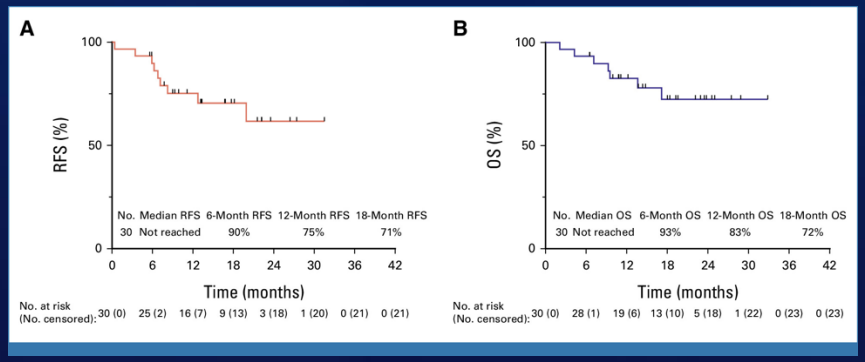
Badar et al. Blood Adv 2024

Management of *FLT3* mutated AML in intensive ineligible



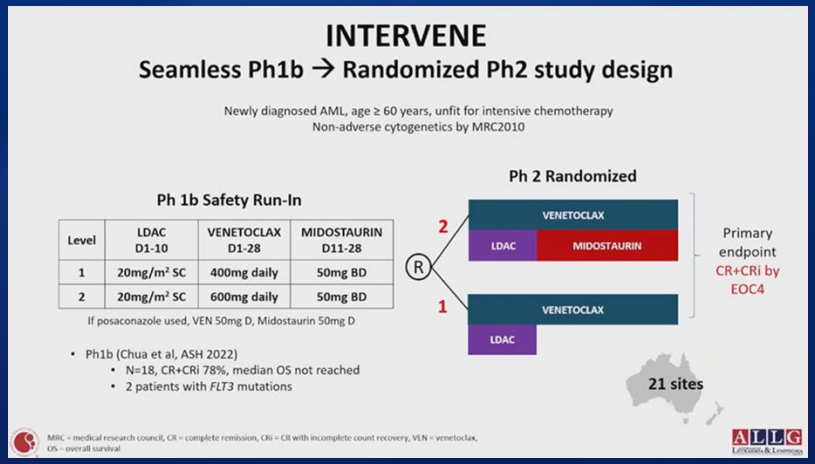


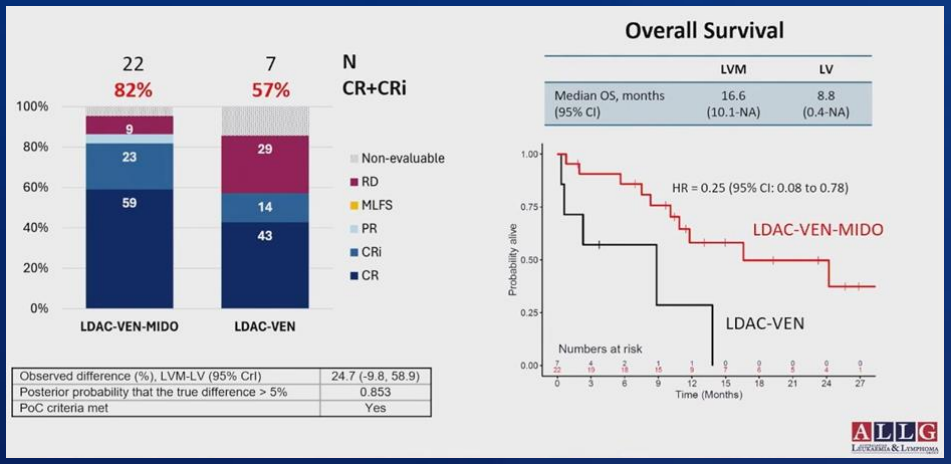


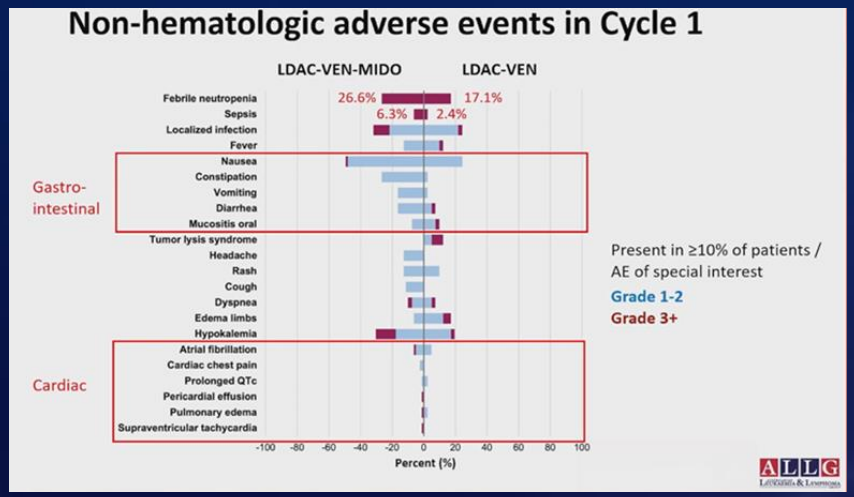
Adverse Events	
Frontline	RR
FN: 33%	45%
Infect: 50%	59%
Dose red: 68%	25%

Short et al. JCO 2024

Management of *FLT3* mutated AML in intensive ineligible

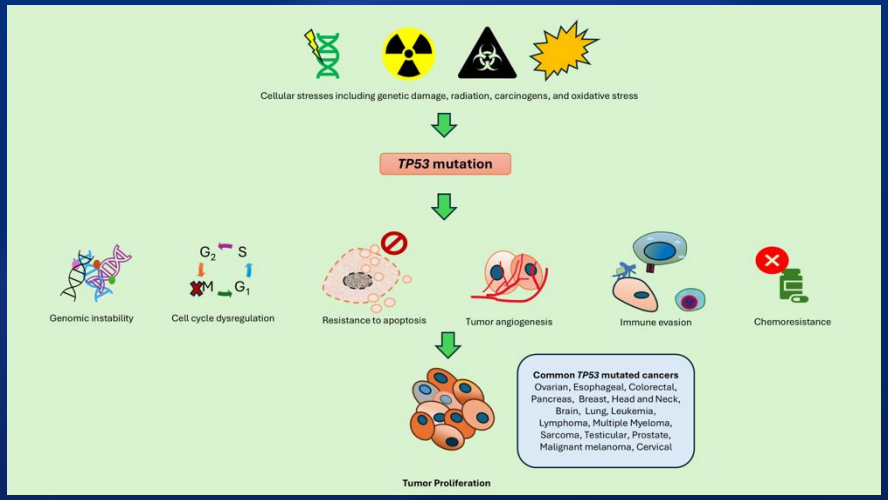


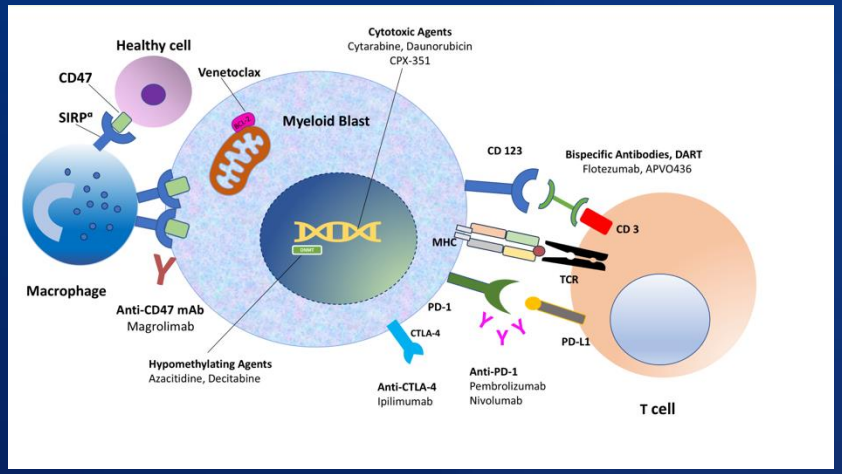




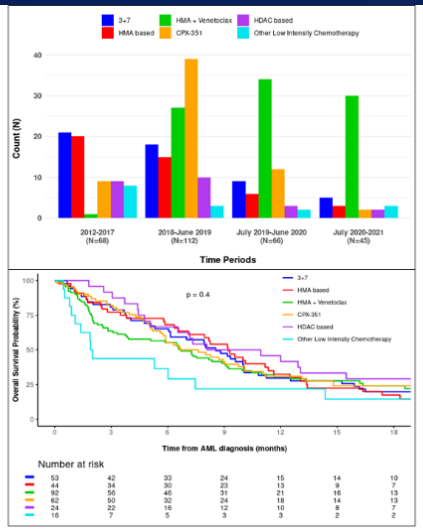
Chyn Chua et al ASH 2024, Abs # 217

How to treat newly diagnosed *TP53*m AML





- Induction strategy for *TP53* mutated AML has evolved over time with more use of hypomethylating agent plus venetoclax based regimens.
- Hypomethylating agent plus venetoclax based regimens demonstrated relatively better complete remission rates but did not translate into better EFS or OS.
- Allogeneic hematopoietic stem cell transplant demonstrated significance for better EFS and OS in multivariate analysis.



Prediction of Complete Response to Induction: Logistic Regression		
	OR (95% CI)	P-value
Induction regimen		
3 + 7	Reference	NA
HMA based	1.43 (0.50, 4.11)	0.50
HMA + Ven	3.06 (1.34, 7.54)	0.010
CPX-351	1.73 (0.70, 4.53)	0.24
HDAC based	2.22 (0.72, 6.86)	0.16
Other Low Intensity chemotherapy	0.89 (0.12, 4.18)	0.89
Age at diagnosis (70 and over)	1.36 (0.77, 2.38)	0.28
Complex CG	0.93 (0.40, 2.36)	0.87
Bone marrow fibrosis	1.20 (0.64, 2.22)	0.57
Extra-medullary disease	0.87 (0.23, 2.63)	0.81
Multiple TP53 mutations	0.79 (0.36, 1.63)	0.55
TP53 VAF > 40%	0.86 (0.46, 1.59)	0.62

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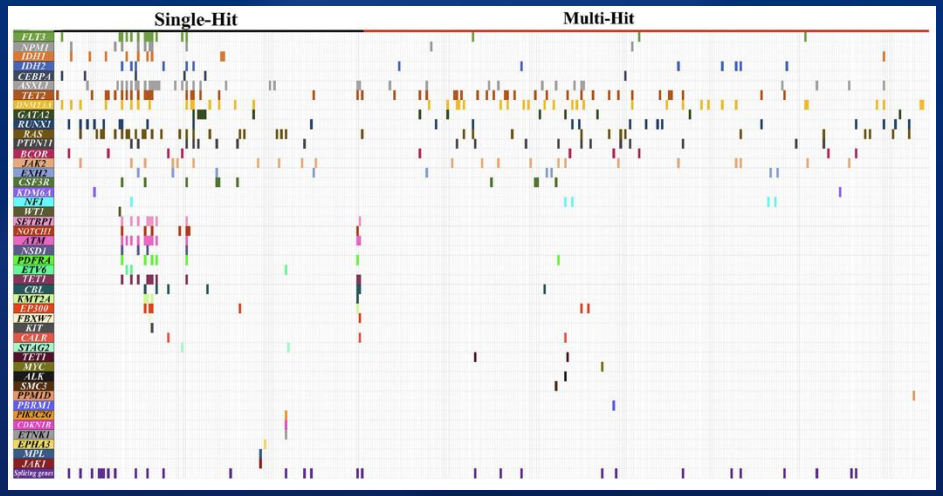
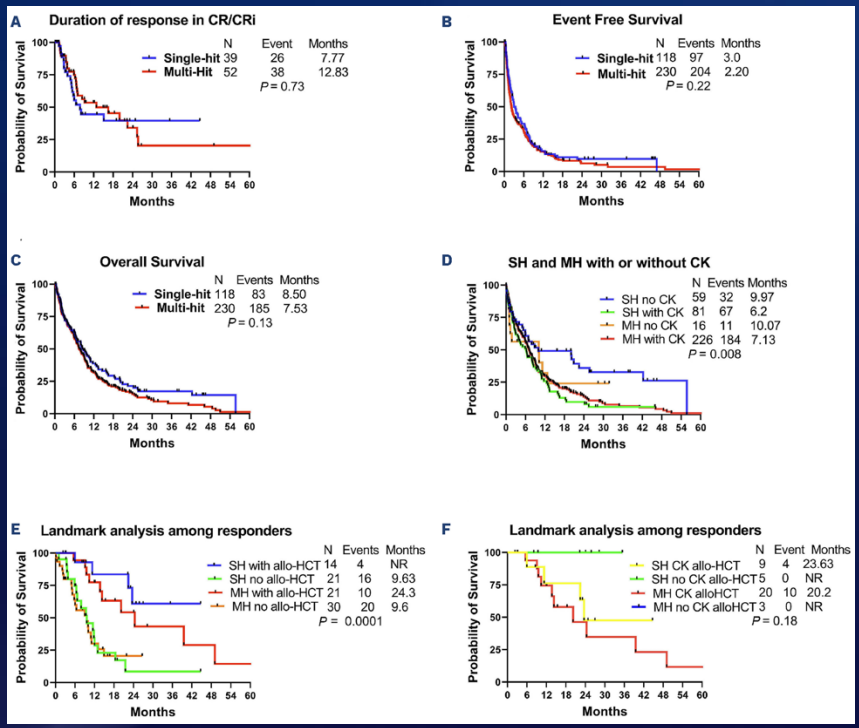
M. Shahzad, …. Badar BCJ 2024, Badar et al. AJH 2022

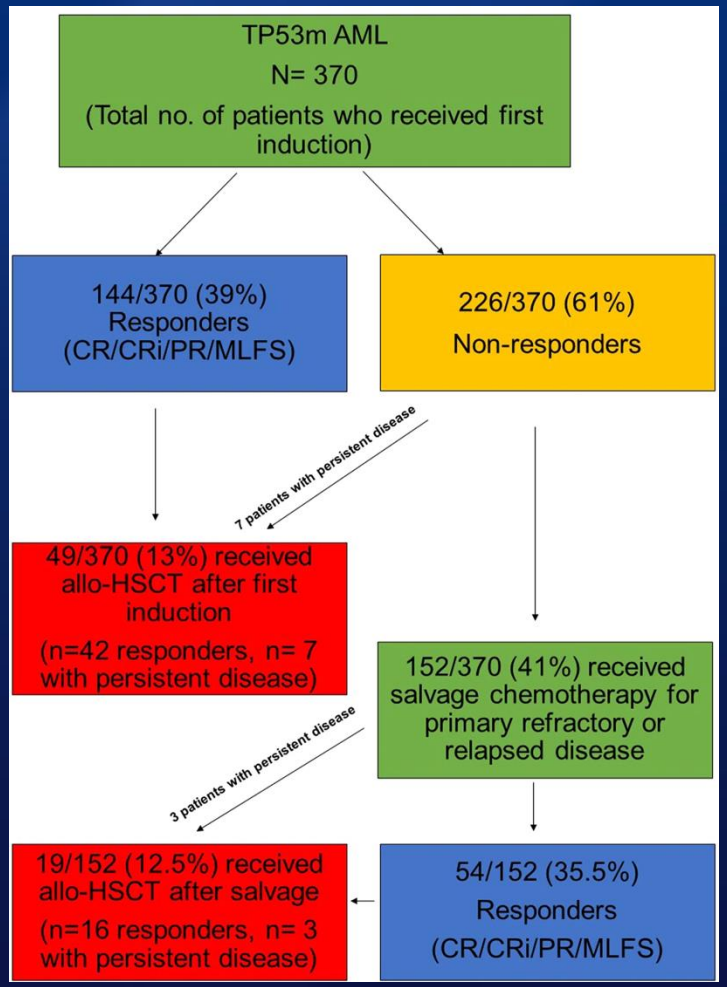
Impact of allelic burden on outcome *TP53*m AML

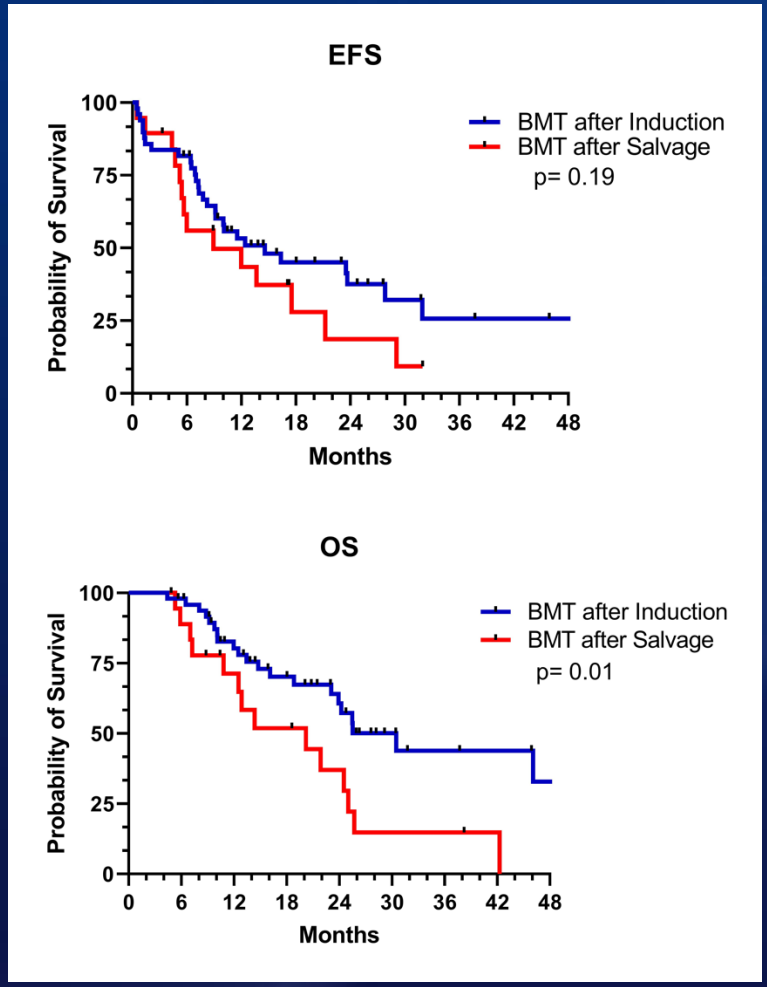




Badar et al. Haematologica 2024

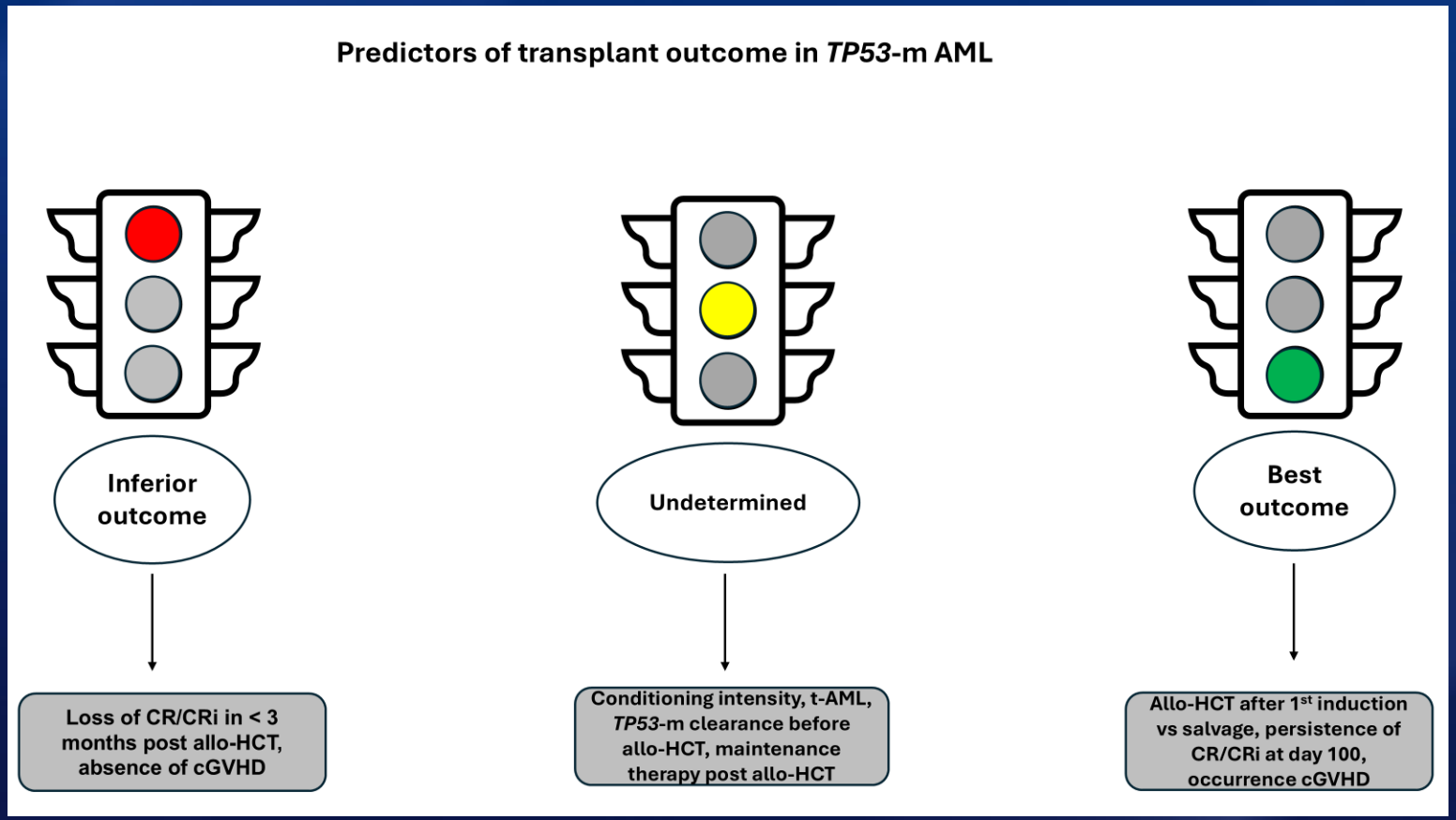
Should we consider alloHCT for TP53m AML





Badar et al. Leukemia 2023

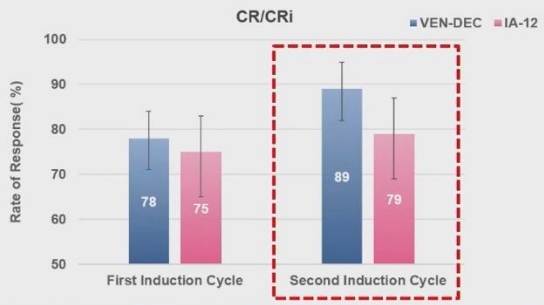
Should we consider alloHCT for TP53m AML



Badar et al. Leukemia 2023, Badar et al Oncotarget 2024

Dec + VEN vs IC in ND AML; Phase 2b trial

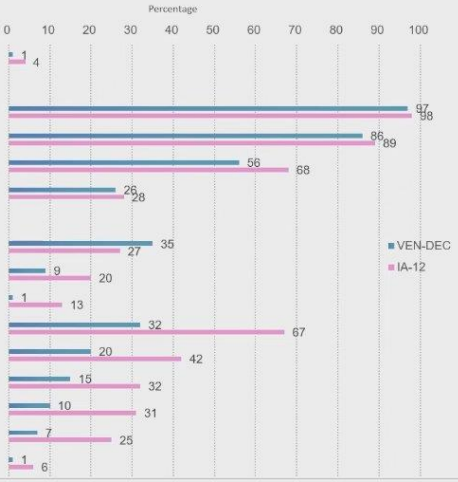
- VEN-DEC proved non-inferior efficacy to IA-12 at 2.5% significance with a 5% non-inferiority margin.



Efficacy Response	VEN-DEC n/N [95%CI]	IA-12 n/N [95%CI]	Treatment difference %(95% CI)	Non-inferiority P Value*
First Induction Cycle	73/94 [68-86]	70/94 [64-83]	3.2 (-9.1 to 15.4)	0.095
Second Induction Cycle	84/94 [81-95]	74/94 [69-87]	**10.6 (0.2 to 21.3)**	**0.0021**

Treatment naïve AML, age 18-59 yrs, randomized 1:1. Baseline characteristics were comparable.

Adverse Events	VEN-DEC N=94 n(%)	IA-12 N=94 n(%)	P
100-day mortality	1 (1)	4(4)	0.368
Hematologic adverse events (≥ Grade 3)			
Leukopenia	91 (97)	92 (98)	1.0
Neutropenia	81 (86)	84 (89)	0.657
Thrombocytopenia	53 (56)	64 (68)	0.097
Anemia	24 (26)	26 (28)	0.869
Nonhematologic adverse events			
Nausea/vomiting	33 (35)	25 (27)	0.269
Diarrhea	8 (9)	19 (20)	0.036
Abdominal pain	1 (1)	12 (13)	0.002
Infections (≥ Grade 3)	30 (32)	63 (67)	<0.001
Serious adverse events (≥ Grade 3)	19 (20)	39 (42)	0.003
Pneumonia	14 (15)	30 (32)	0.009
Febrile neutropenia	9 (10)	29 (31)	<0.001
Sepsis	7 (7)	23 (25)	0.002
Septic shock	1 (1)	6 (6)	0.118

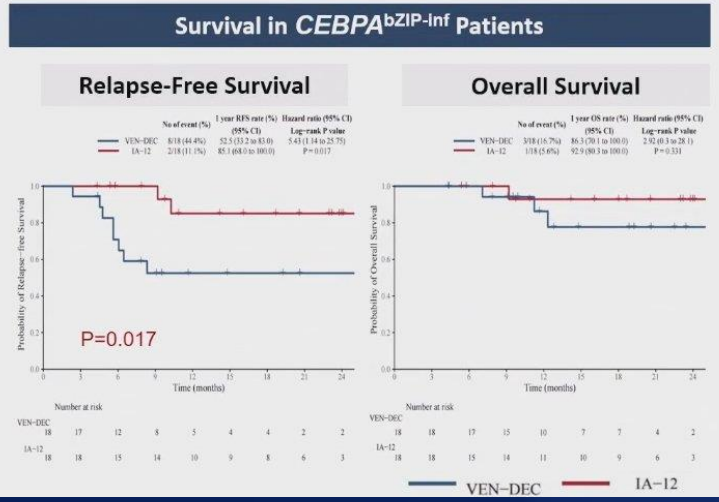


Lu et al ASH 2024, Abs # 970

Survival

- Deaths in VEN-DEC were mostly from progression (12%), in IA-12 (9%) from treatment-related SAEs.
- CEBPA$^{bZIP\text{-}inf}$ mutations lead to lower 1-year RFS in VEN-DEC-treated patients, potentially affecting OS.

	VEN-DEC (N=94), n (%)	IA-12 (N=94), n (%)
Total number of patient death	16 (17)	14 (15)
Due to disease progression	11 (12)	3 (3)
Due to treatment-related SAE	5 (5)	8 (9)
Due to transplantation-related SAE	0	3 (3)



- At a median follow-up of 12.1 months (R, 0.33 to 26.5), the median survival time was not reached in either group, with no significant difference in EFS (hazard ratio, HR=0.91, p=0.714) or OS (HR=1.15, p=0.705).

- VEN-DEC group, patients with CEBPAbZIP had a 1-year RFS rate of 52.5% (95% CI 33.2 to 83.0), significantly lower than 85.1% (95% CI 68.0 to 100) in the IA-12 group (HR for relapse or death, 5.43; 95% CI 1.14 to 25.75; p=0.017).

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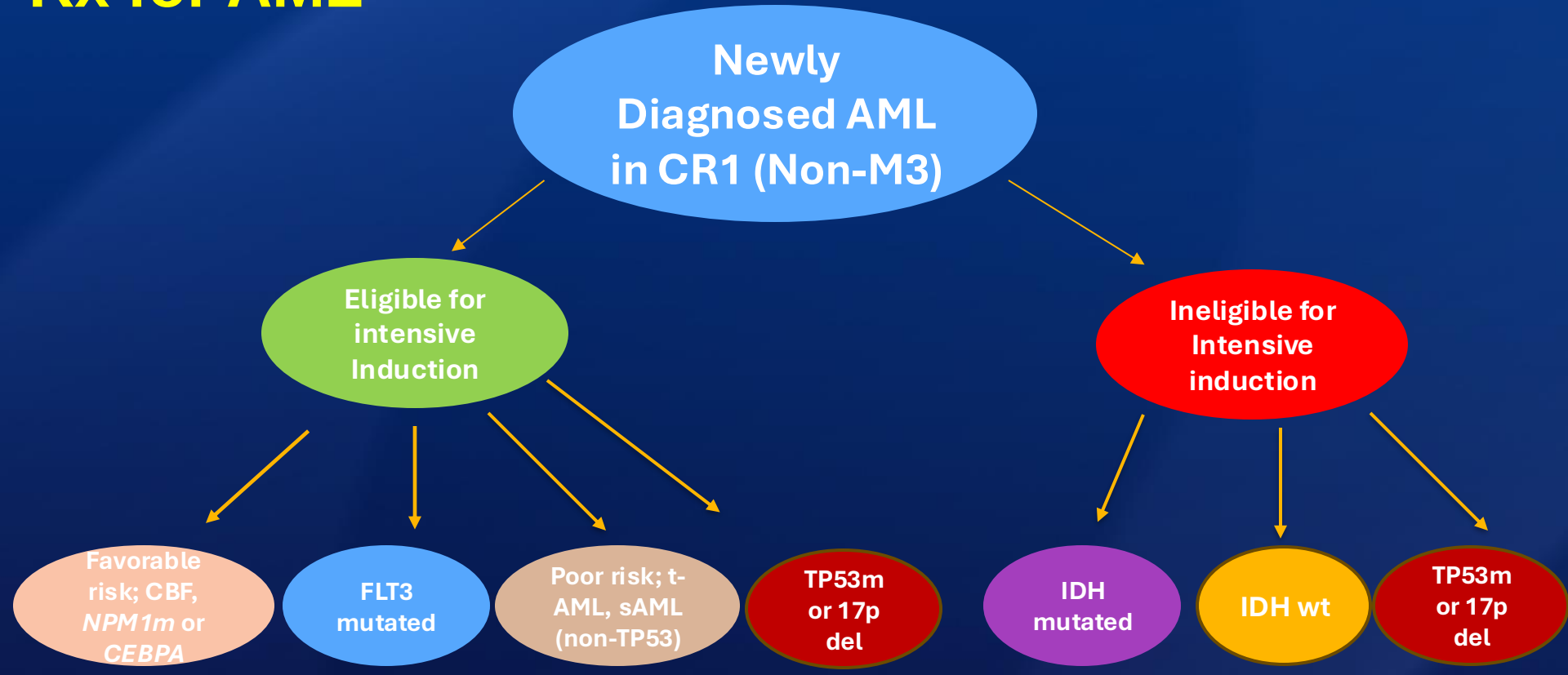
Consolidation Rx for AML



Consolidation

- Cytarabine or Cytarabine+GO (if given during induction)
- **<u>If MRD –ve by C2, no benefit of AlloHCT for OS.</u>**
- Consider allo-HCT in pts with MRD+ after **C2**
- HMA maintenance if allo-HCT not planned

Consolidation

- Cytarabine + Midostaurin (FLT3 ITD or TKD)
- Cytarabine plus Quizartinib (FLT3 ITD only)
- Allo-HCT
- Sorafenib maintenance post allo-HCT (FLT3 ITD)
- Gilteritinib or Quizartinib for MRD+ve post allo-HCT

Consolidation

- Allo-HCT recommended
- Cytarabine, CPX-351, FLAG or HMA +Ven as per induction
- No strong evidence to support maintenance therapy post AlloHCT.

Consolidation

- Continue therapy used during induction.
- Allo-HCT in eligible pts.
- Oral azacitidine maintenance if AlloHCT not planned.
- Post AlloHCT FLT3 inhibitor maintenance.

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Unsettled issues regarding consolidation for AML in CR1

Duration of Venetoclax plus HMA therapy; ineligible for AlloHCT.

Maintenance therapy post AlloHCT in high-risk AML

Utility of MRD for AlloHCT decision in NPM1m AML, co-mutated with adverse risk molecular aberrations.

Choice of FLT3i for maintenance therapy post AlloHCT

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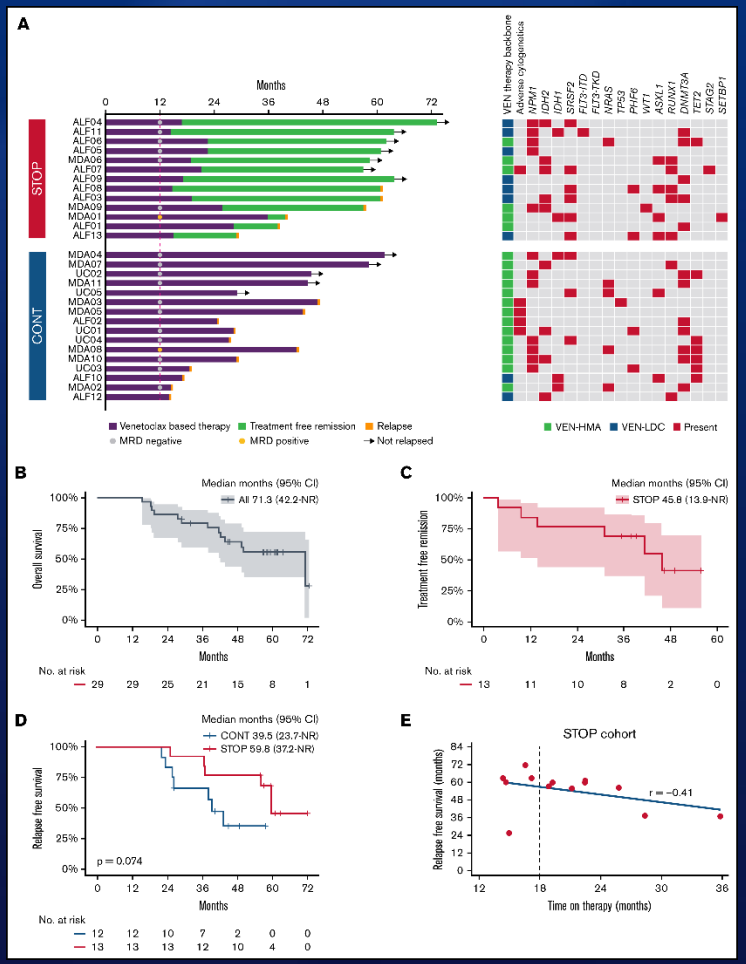
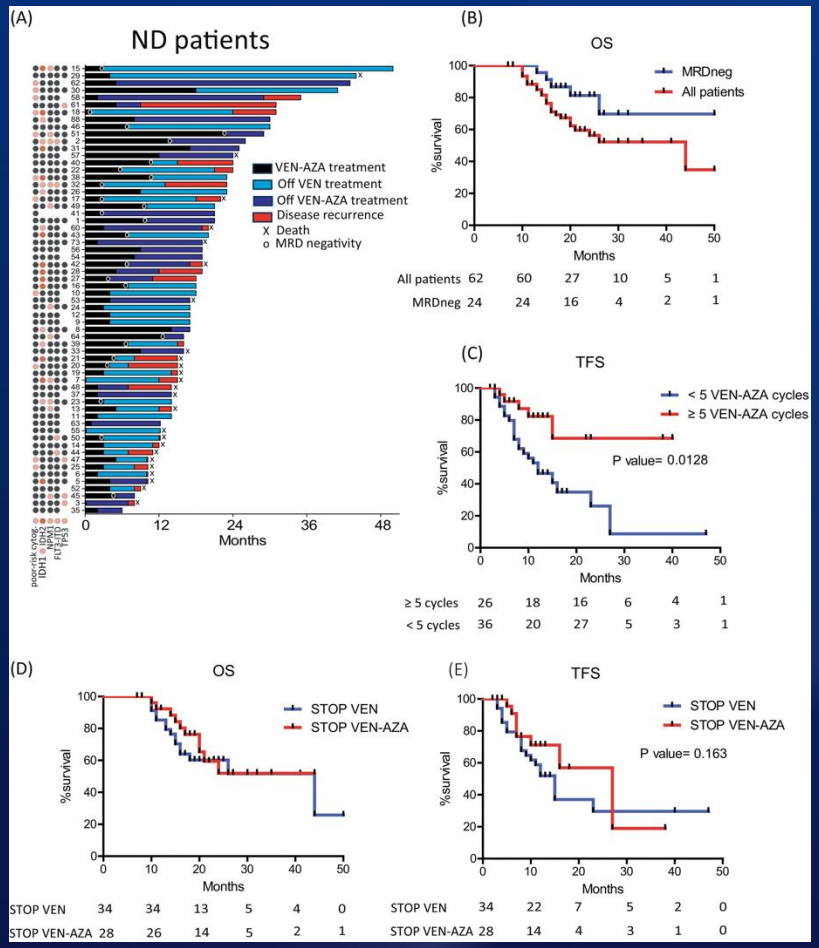
Duration of Venetoclax plus HMA therapy; ineligible for AlloHCT





Subset of pts had durable TFR after being on VEN+HMA for > 12 mo

MRD –ve CR: 2 yr TFR 80%. Outcome were inf with < 5 cycles. No diff with stopping AZA or AZA +VEN

Chua et al. Blood Adv 2022, Garciaz et al AJH 2024

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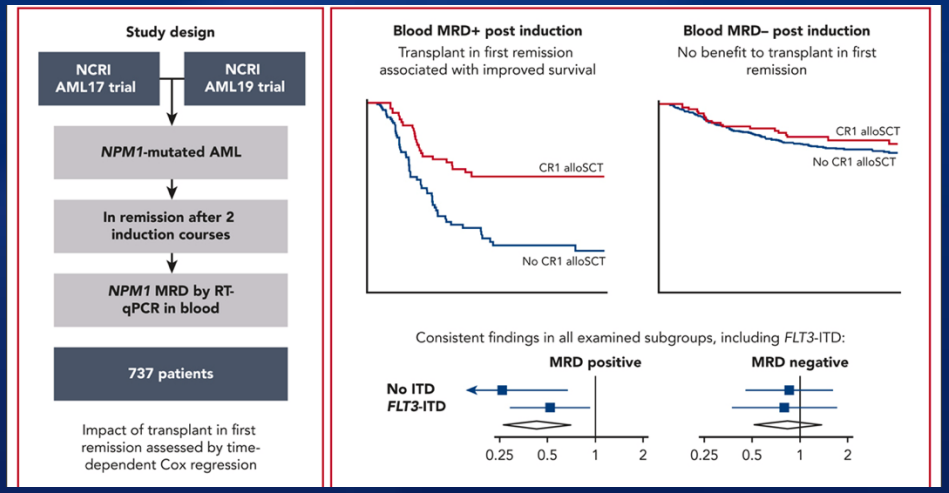
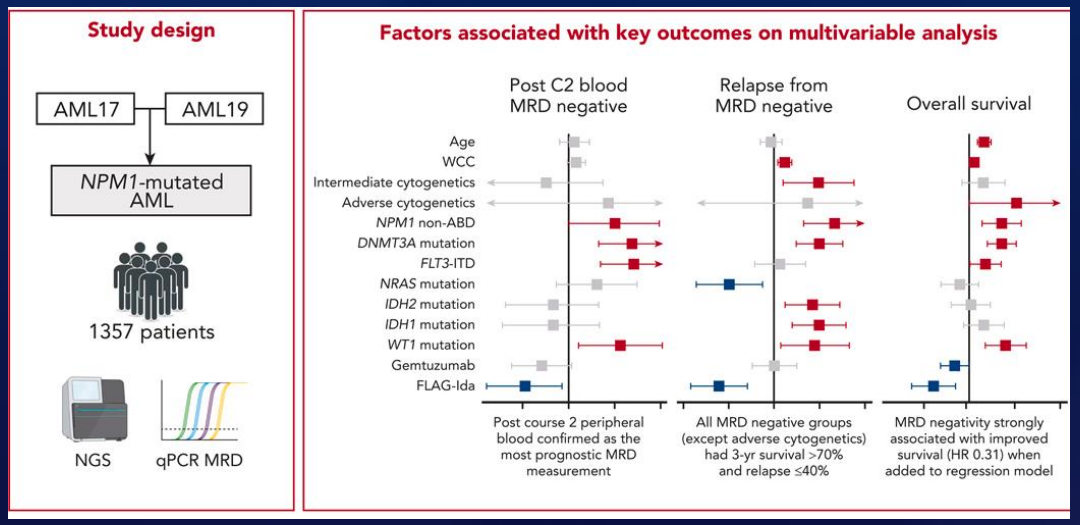
Utility of MRD for AlloHCT decision in NPM1m AML, co-mutated with adverse risk mutations



NPM1-mutated AML achieving MRD negative after 2nd induction, showed no survival benefit with transplant in 1st remission, even if FLT3m



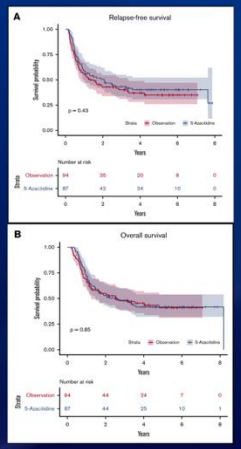
Even in pts with co-existent adverse risk mutation, MRD – remains determinant of OS.

Othman et al. Blood 2024

Benefit of maintenance therapy post AlloHCT in high-risk AML (marker-agnostic)

HMA as a maintenance therapy post allo-HCT

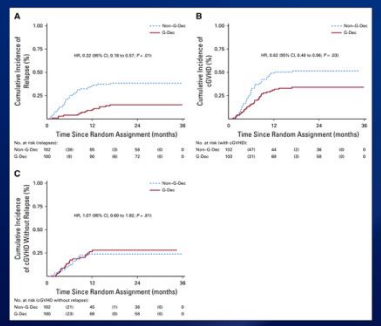
- Initial reports suggest encouraging results with mod. doses of HMA.[1,2]
- Later PIII study was conducted, 187 HR MDS/AML randomized, 87 received AZA (32 mg/m2) maintenance.[3]
- RFS: 2.07 vs 1.28 yrs (p = .43).
- OS: 2.52 vs 2.56 (p = .85)



Pusic et al BBMT 2015[1], de Lima et al. Cancer 2010[2], Oran et al Blood Adv 2023[3]

Low dose decitabine + G-CSF post allo-HCT for HR AML MRD-ve

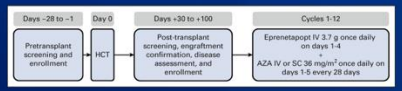
- PII, randomized study in 204 pts with HR-AML MRD-ve post allo-HCT.
- G-CSF 100 ug/m2 D0-5, Dec 5 mg/m2 D1-5.
- PE: RFS
- 2-year CIR; G-Dec gp 15.0% vs 38.3% (HR 0.32 [95% CI, 0.18-0.57]; p< .01).

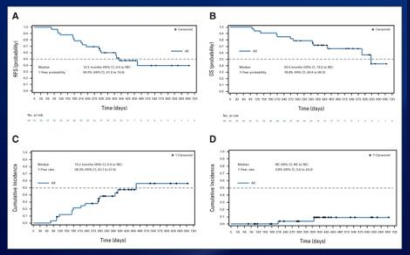


Gao et al. JCO 2020

Eprenetapopt (APR-246) + AZA after allo-HCT in *TP53*m MDS/AML.

- APR-246 (p53 reactivator) + AZA was evaluated in a PII study, enrolling (33/84) allografted *TP53*m MDS/AML pts.
- PE: RFS
- RFS:12.5 mo (9.6-NE)
- OS: 20.6 mo (14.2-NE)
- Most significant G3 AE's were cytopenia.

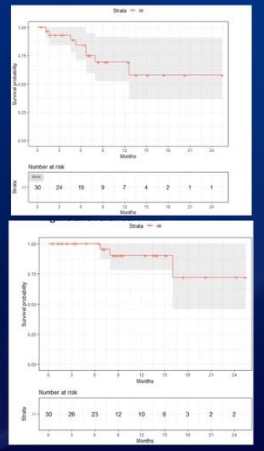




Mishra et al. JCO 2022

Venetoclax (VEN) + AZA maintenance post allo-HCT for AML/ALL/mixed phenotypic leukemia

- PII study on 30 pts VEN (100 mg D1-7) + AZA (32 mg/m2 D1-5) as maintenance therapy post allo-HCT for 12 mo.
- After 11 pts, VEN dose reduced to 50 mg.
- PE: RFS
- The median fu was 8.67 mo; estimates of RFS and OS at 1-year were 69.2% (52.1%-91.8%) and 90.2% (78%-100%), respectively



Oran et al. ASH abstract 2022

Conclusion: HMA maintenance therapy

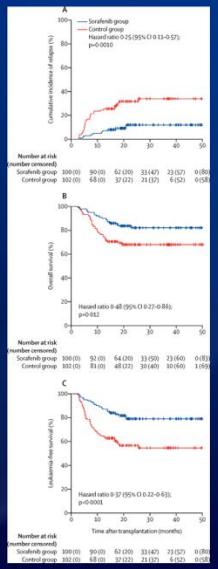
- It is important to identify, who will benefit most.
- Use homogenous pt population to conduct trials.
- HMA combination therapies? (HMA+VEN [PIII]; NCT04161885, NCT04102020)
- Utilize pre-emptive strategy, initiating HMA based on MRD (RELAZA2).[1]

Platzbecker et al. Lancet Onc 2018[1]

Maintenance therapy for FLT3 mutated AML

PIII study of sorafenib maintenance post allo-HCT in *FLT3*-ITD mutated AML

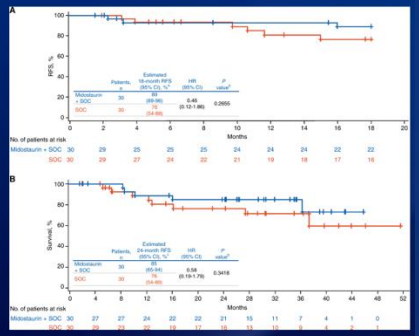
- Pts 18-60 yrs, in cCR pre and post allo-HCT and had count recovery at D60.
- Randomized to receive sorafenib (n=100) for 6 mo or control (n=102).
- PE: 1-yr cumulative incidence of relapse was met: HR 0.25 (95% CI, 0.11-0.57, p= 0.0010).



Xuan et al. Lancet Oncology 2020

RADIUS trial: Midostaurin post allo-HCT in *FLT3*-ITD mutated AML

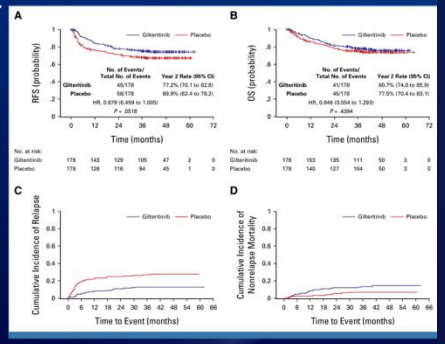
- Randomized PII study on 60 *FLT3*-ITDm AML pts in CR1 pre allo-HCT, assigned midostaurin (n=30) or control (n=30) for 12 mo.
- PE: RFS was not met



Maziarz et al BMT 2020

MORPHO trial: Gilteritinib post allo-HCT in *FLT3*-ITD mutated AML

- PIII study on 356 *FLT3*-ITDm AML pts in CR1 pre allo-HCT, free of GVHD assigned gilteritinib (n=178) or control (n=178) for 24 mo.
- PE; RFS, SE; OS and impact of MRD pre- & post allo-HCT on RFS/OS.



Levis et al. JCO 2024

MORPHO trial: Gilteritinib post allo-HCT in *FLT3*-ITD mutated AML

Secondary analysis

- Impact of molecular MRD (PCR-NGS) at a level of ≥ 1 x10^{-6} pre- or post-HCT.
- Gilteritinib showed benefit for RFS in MRD+.
- Significant AEs were mainly myelosuppression.

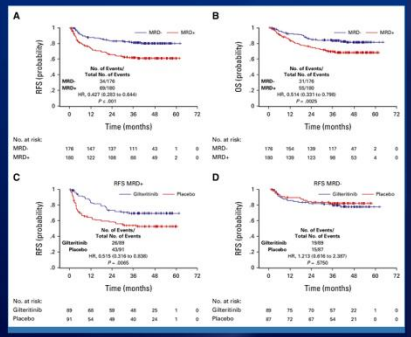


Fig A/B; MRD peri-HCT irrespective of Rx arm, Fig C/D MRD peri-HCT based on Rx.

Levis et al. JCO 2024

Conclusion: FLT3i maintenance post allo-HCT

- Data is heterogeneous; (a) assessment of MRD, (b) use of FLT3i during induction (c) concurrent mutation analysis/data was not available on most studies which could impact benefit with FLT3i.
- Duration of FLT3i post allo-HCT: Sorafenib showed benefit; whether 6 mo or 24 mo post allo-HCT?
- More potent FLT3i only showed benefit on subset of pts with MRD, did the benefit with Sorafenib driven by multi-kinase activity?

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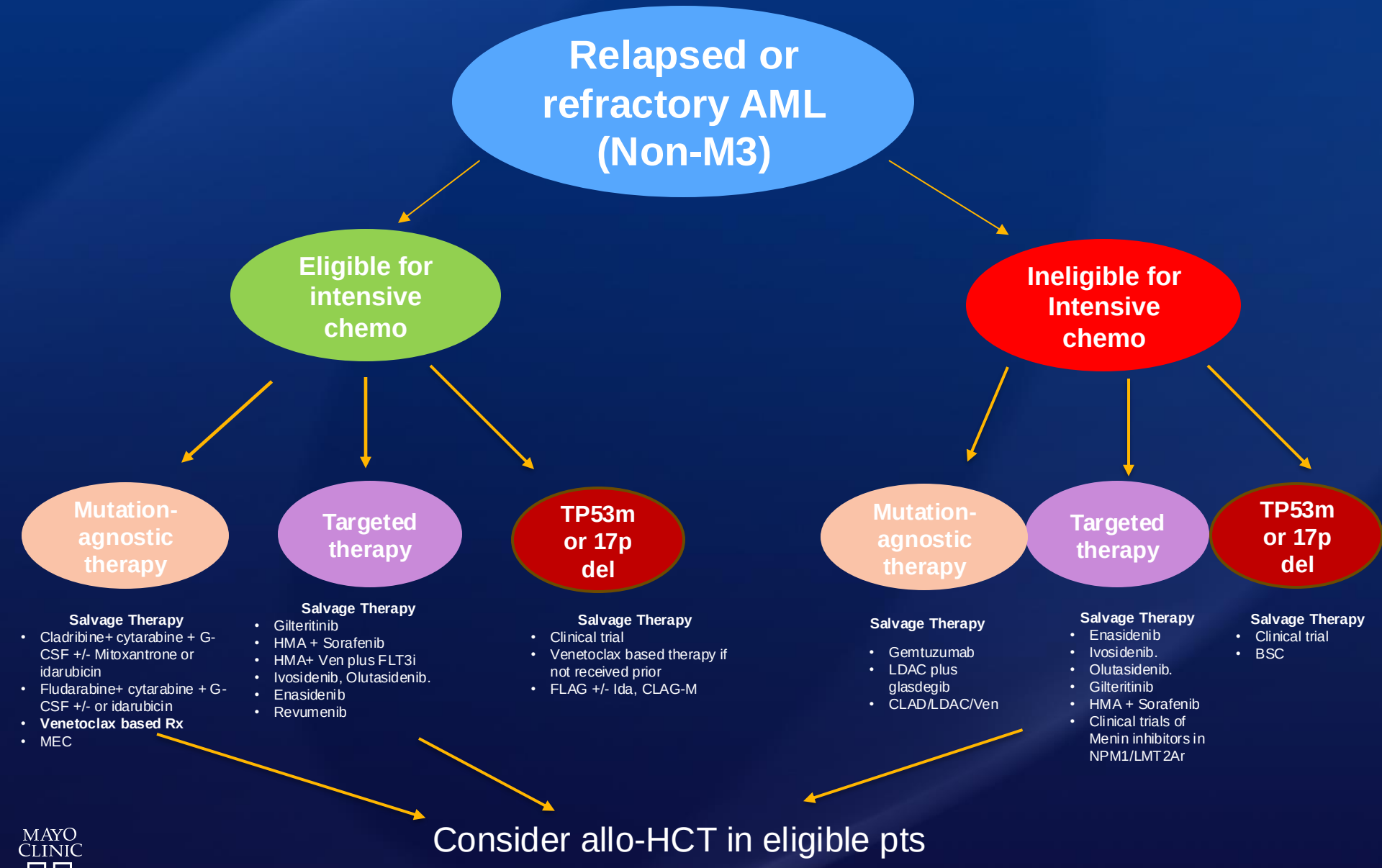
Rx for R/R AML



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Issues needs to be addressed in RR AML

How to best manage RR AML post venetoclax failure

How to best manage RR *TP53*m AML: BSC vs life prolonging therapies.

Effectiveness of T-cell based immunotherapies; bispecific/CAR T-cell/dual-affinity re-targeting antibodies.

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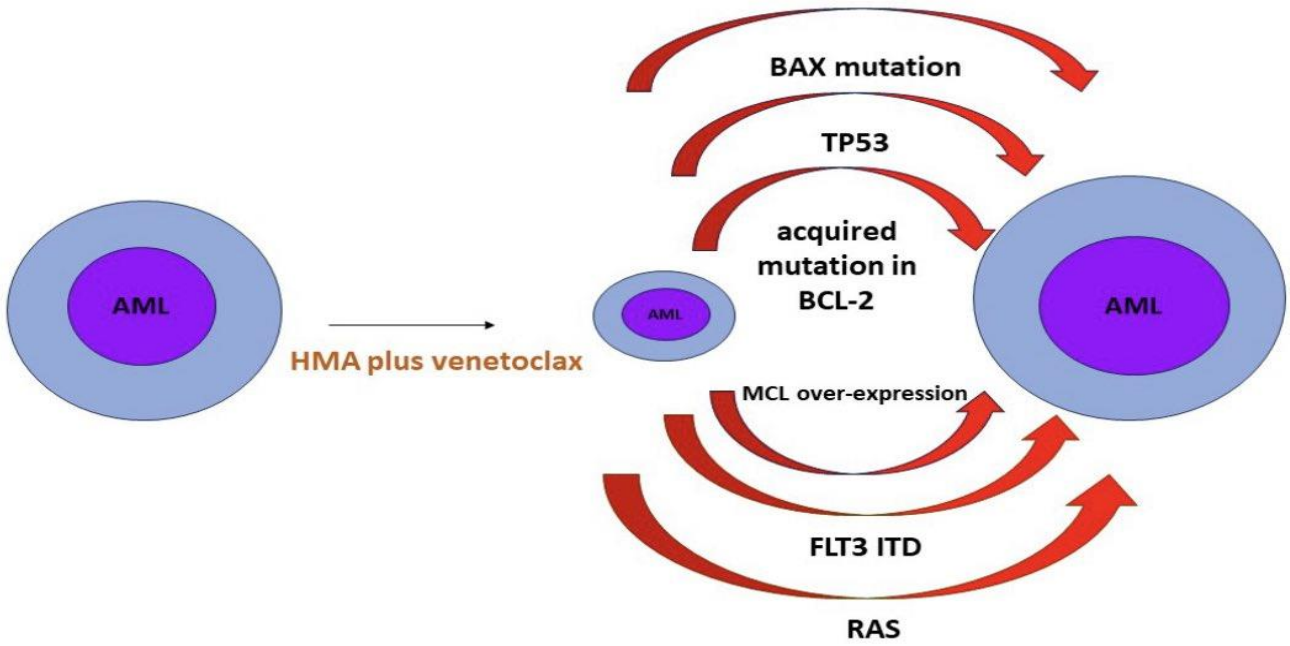
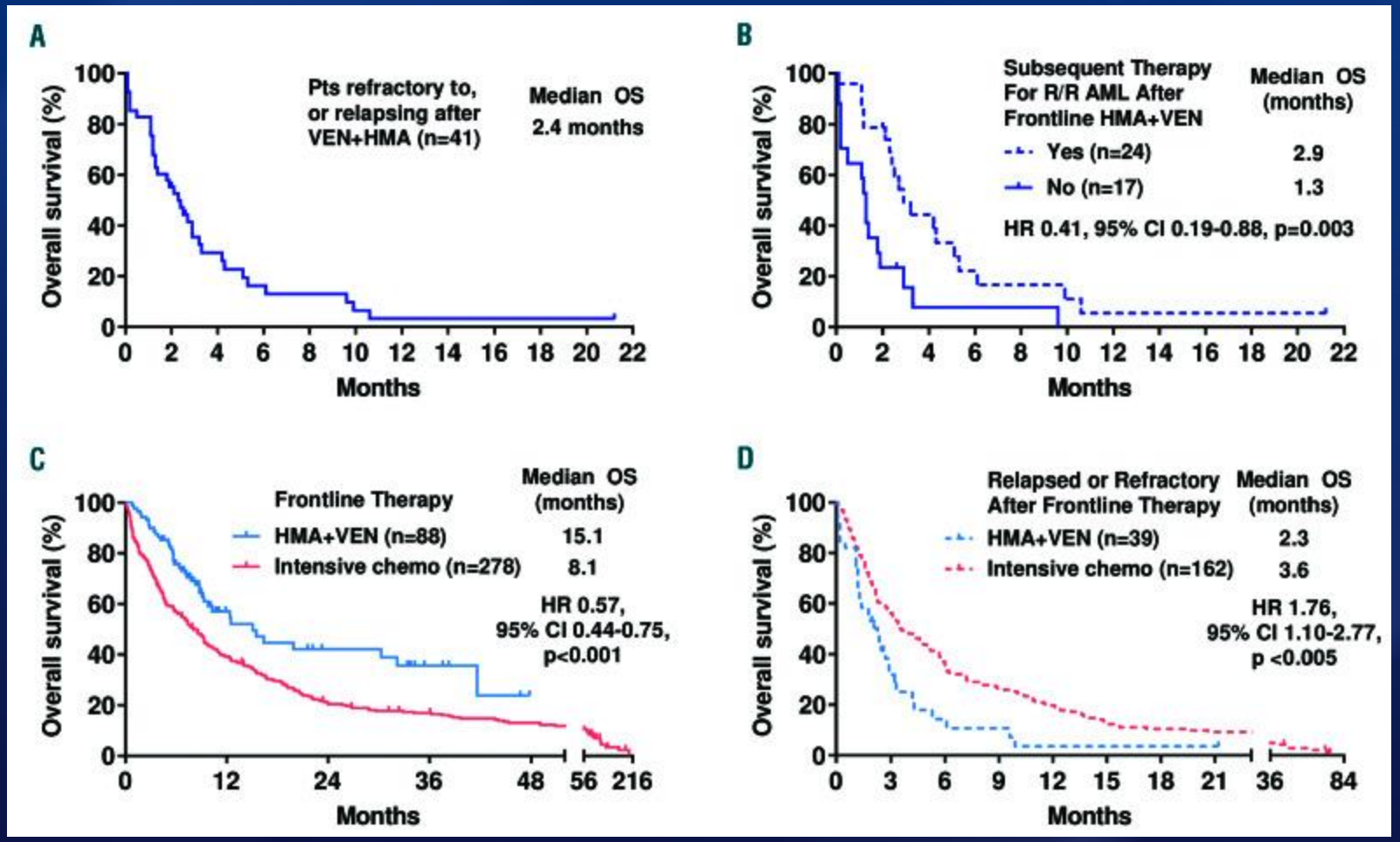
How to best manage RR AML post venetoclax failure

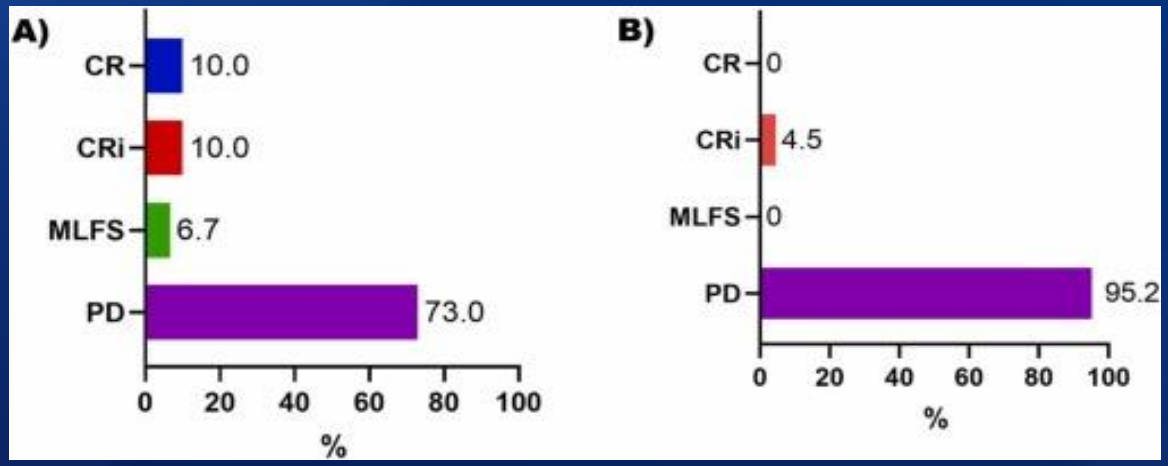


Dismal outcome post venetoclax based therapies

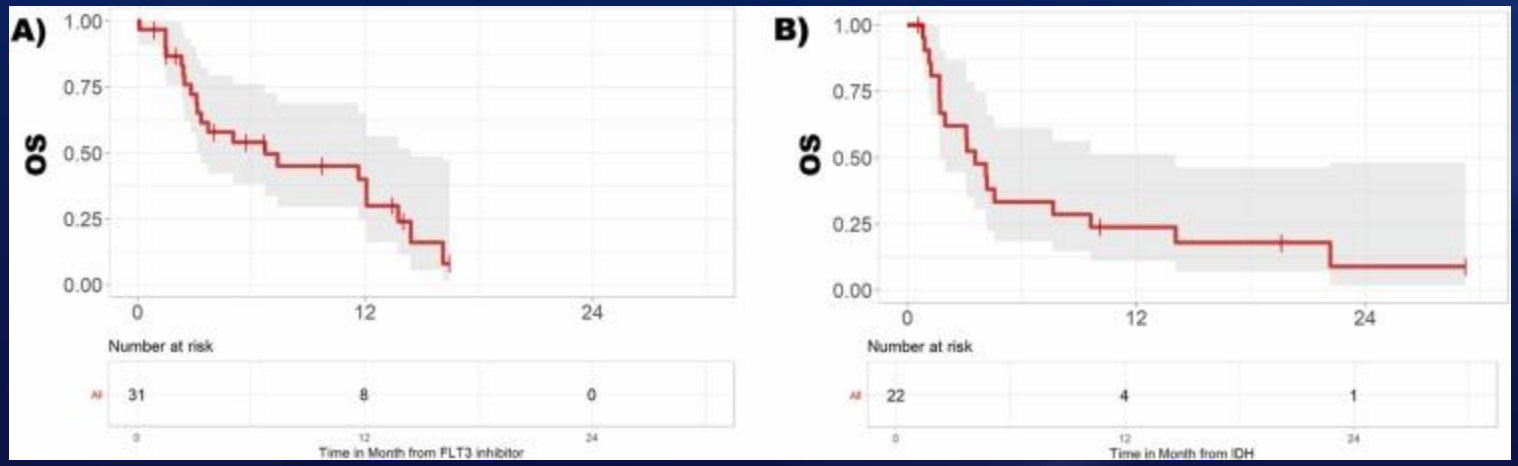


Maiti et al. Haematologica 2020

IDH and FLT3 targeted therapy after venetoclax



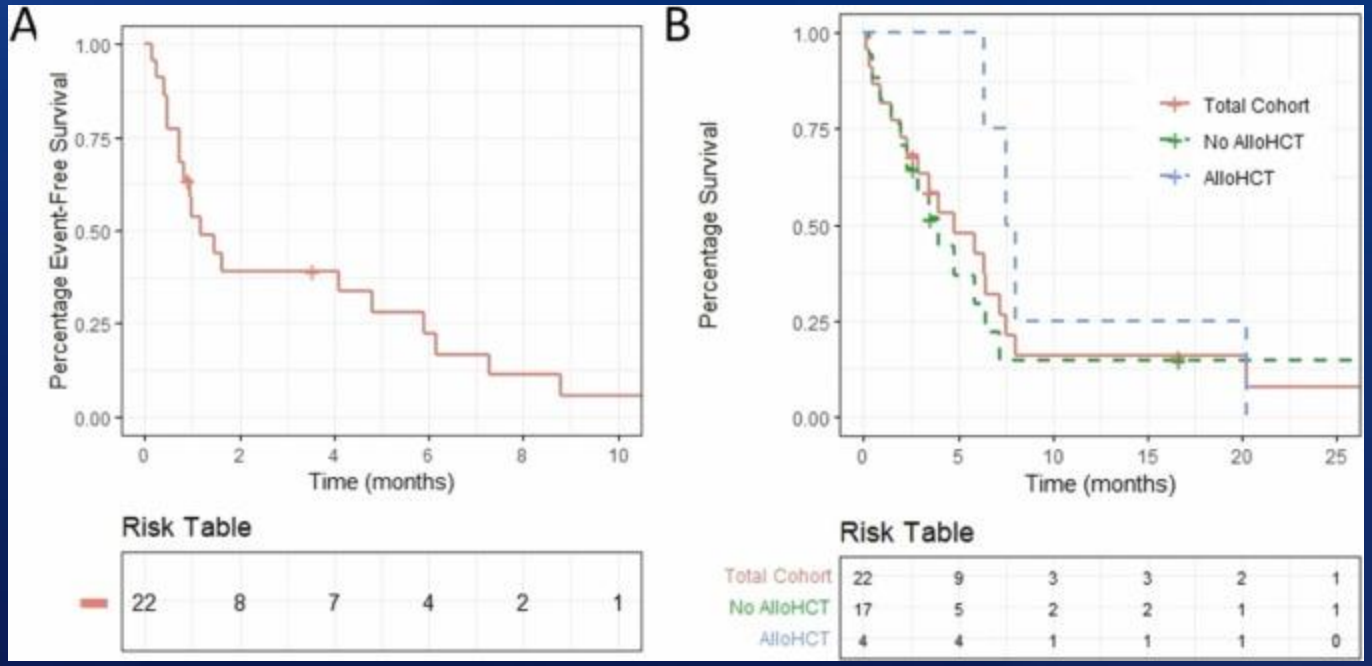
Response with FLT3i **Response with IDHi**



OS with IDHi; median 3.6 mo **OS with FLT3i; median 6.7 mo**

Bewersdorf et al. Leuk Res 2022

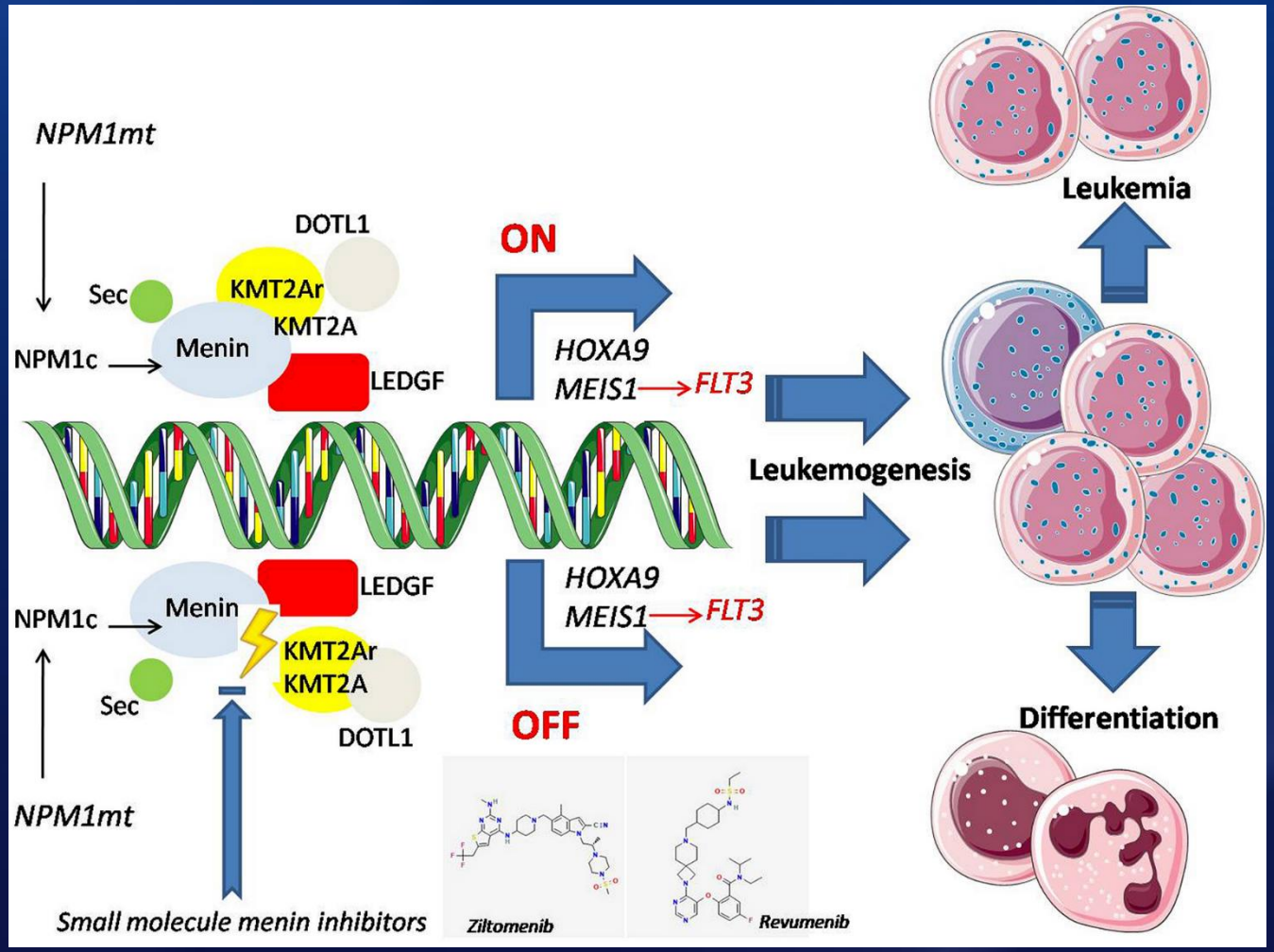
Intensive chemotherapy after venetoclax



Median OS 4.8 months, ELN adverse risk or transplant ineligible have poorer outcome

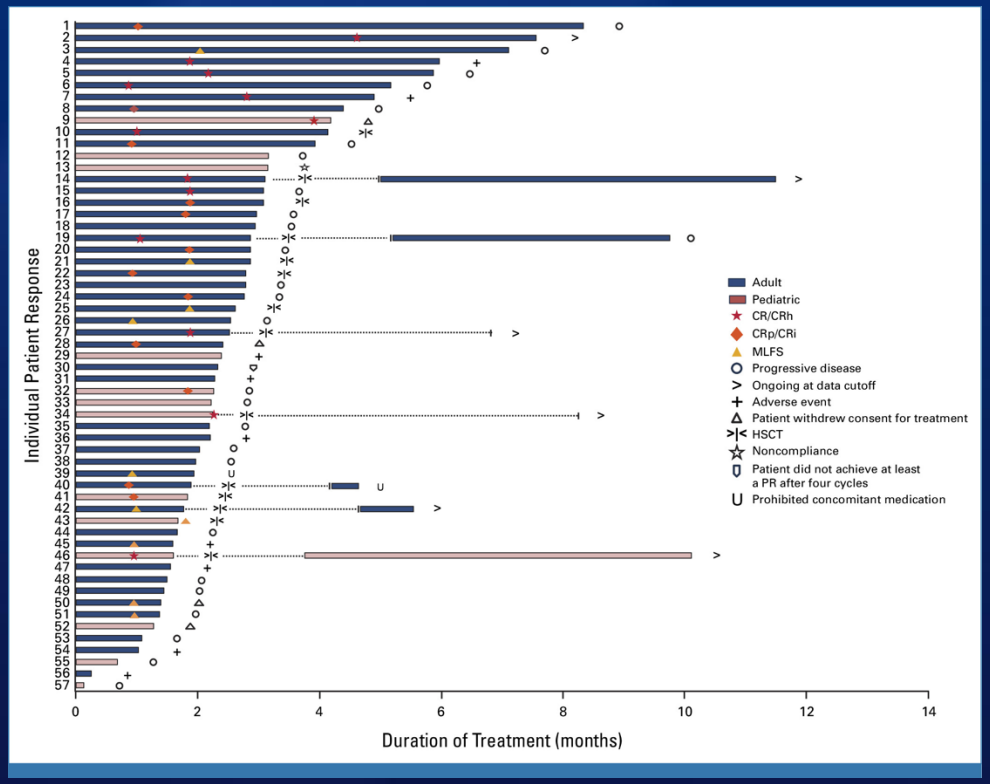
Achar et al Leuk Res 2024

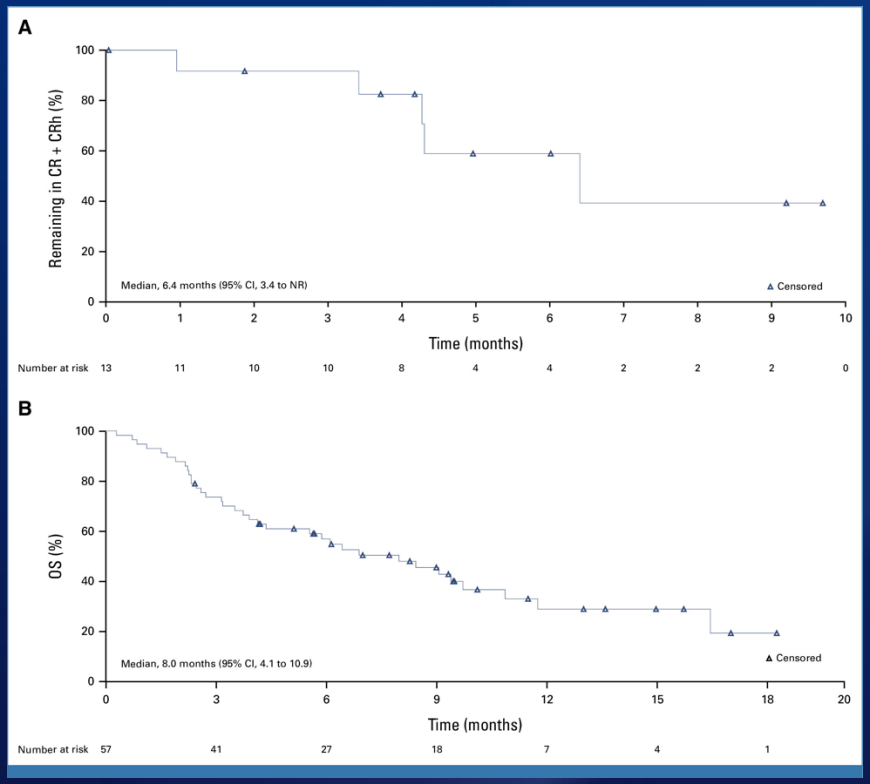
Menin inhibitors for acute leukemia



Xavier Thomas, Oncology & Therapy 2024

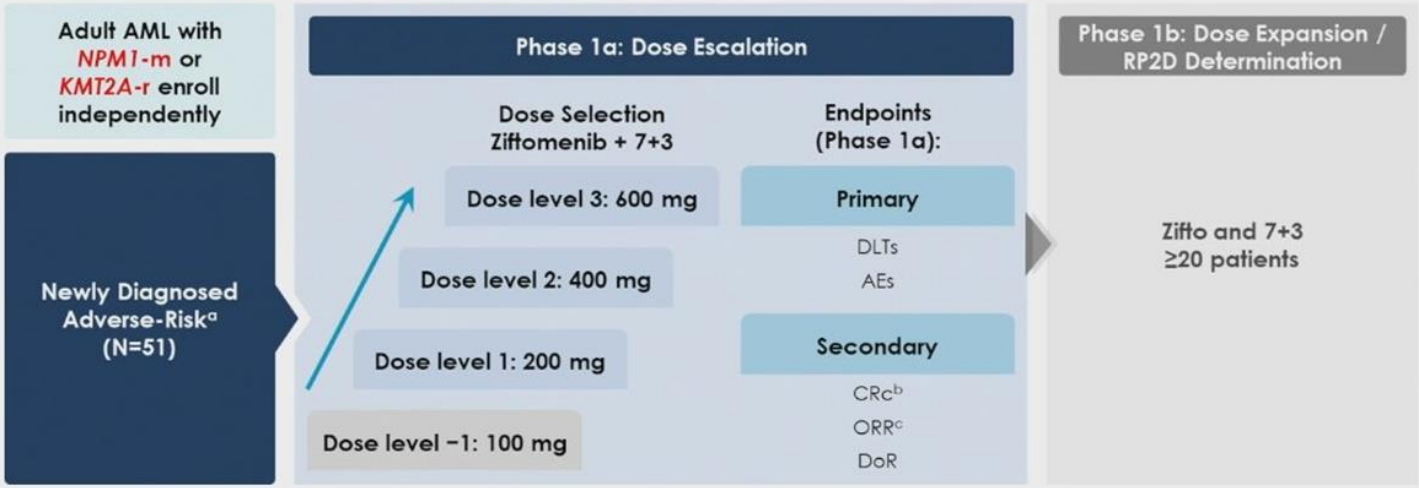
Revumenib for RR Acute Leukemia with KMT2A-r: AUGMENT 101





Issa et al, JCO 2024

Ziftomenib + Intensive induction in *NPM1*m or KMT2Ar AML (KOMET-007)



- Ziftomenib started on Cycle 1 Day 8 and administered continuously thereafter. Cytarabine administered on Cycle 1 Days 1–7; daunorubicin on Cycle 1 Days 1–3; re-induction cycles allowed based on bone marrow biopsy results
- Here, we present data from the dose escalation (Phase 1a) in patients with Adverse-Risk[a] AML (data cutoff: Oct 1, 2024)
- Dose expansion (Phase 1b) is ongoing and includes all newly diagnosed *NPM1*-m and *KMT2A*-r AML patients, with or without adverse-risk

[a]Adverse-risk *NPM1*-m AML defined as having high-risk cytogenetics per ELN criteria, age ≥60 yrs and/or treatment-related *NPM1*-m/*KMT2A*-r AML regardless of age. [b]CR, CRh, or CRi. [c]CRc or MLFS.
AE, adverse event; CRc, composite complete remission; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete hematological recovery; DLT, dose limiting toxicity; DoR, duration of response; MLFS, morphologic leukemia-free state; RP2D, recommended phase 2 dose.

Zeidan et al. ASH 2024, Abs# 214

KOMET-007: Safety and efficacy

Safety and Tolerability of Ziftomenib in Combination with 7+3 in 1L AML (N=51)

TEAEs in ≥30% of All Patients

TEAEs, n (%)	All Patients (N=51)	*NPM1*-m 200 mg (n=8)	*NPM1*-m 400 mg (n=7)	*NPM1*-m 600 mg (n=9)	*NPM1*-m Total (n=24)	*KMT2A*-r 200 mg (n=10)	*KMT2A*-r 400 mg (n=9)	*KMT2A*-r 600 mg (n=8)	*KMT2A*-r Total (n=27)
Any Grade	**48 (94)**	8 (100)	6 (86)	8 (89)	22 (92)	10 (100)	9 (100)	7 (88)	26 (96)
Febrile neutropenia	**34 (67)**	5 (63)	4 (57)	8 (89)	17 (71)	8 (80)	4 (44)	5 (63)	17 (63)
Diarrhea	**27 (53)**	4 (50)	4 (57)	4 (44)	12 (50)	6 (60)	7 (78)	2 (25)	15 (56)
Platelet count decreased	**22 (43)**	7 (88)	4 (57)	4 (44)	15 (63)	3 (30)	2 (22)	2 (25)	7 (26)
Anemia	**19 (37)**	4 (50)	2 (29)	4 (44)	10 (42)	4 (40)	3 (33)	2 (25)	9 (33)
Nausea	**19 (37)**	4 (50)	3 (43)	3 (33)	10 (42)	4 (40)	2 (22)	3 (38)	9 (33)
Neutrophil count decreased	**18 (35)**	6 (75)	3 (43)	3 (33)	12 (50)	3 (30)	2 (22)	1 (13)	6 (22)
Constipation	**18 (35)**	5 (63)	2 (29)	2 (22)	9 (38)	5 (50)	2 (22)	2 (25)	9 (33)

- Safety profile of ziftomenib in combination with intensive chemotherapy was similar to that reported for newly diagnosed AML patients treated with 7+3 alone[1]
- Rate of TEAEs was consistent across escalating doses of ziftomenib

Clinical Activity in All Response-Evaluable[a] 1L Patients (N=46)

- Historically, only 33% of 7+3 treated newly diagnosed Adverse-Risk AML patients achieve CRc, with a median overall survival of ~6 months[1-2]

Response, n (%)	All Patients (N=46)	*NPM1*-m 200 mg (n=8)	*NPM1*-m 400 mg (n=7)	*NPM1*-m 600 mg (n=8)	*NPM1*-m Total (n=23)	*KMT2A*-r 200 mg (n=10)	*KMT2A*-r 400 mg (n=9)	*KMT2A*-r 600 mg (n=4)	*KMT2A*-r Total (n=23)
CRc	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
ORR	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
CR	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
CRh	0	0	0	0	0	0	0	0	0
CRi	0	0	0	0	0	0	0	0	0
MLFS	0	0	0	0	0	0	0	0	0
PR	0	0	0	0	0	0	0	0	0
NR	3 (7)	0	0	0	0	0	3 (33)	0	3 (13)
NE	1 (2)	0	0	0	0	1 (10)	0	0	1 (4)
MRD negativity, n/N[b]	**28/37 (76)**	8/8 (100)	4/6 (67)	4/7 (57)	**16/21 (76)**	5/8 (63)	5/6 (83)	2/2 (100)	**12/16 (75)**

[a]Patients who have ≥1 response assessment or who had died.
[b]Among CRc responders tested for MRD per local assay (NGS, RT-qPCR, FISH, flow cytometry).

Zeidan et al. ASH 2024, Abs# 214

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Summary

- Progress has been made in improving outcome of AML, especially in young; eligible for IC.
- Elderly AML, those enriched with adverse risk mutation continues to have sub-optimal outcome.
- More sensitive MRD assesment techniques are evolving end favorably shaping consolidation strategies in AML.

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Thank you