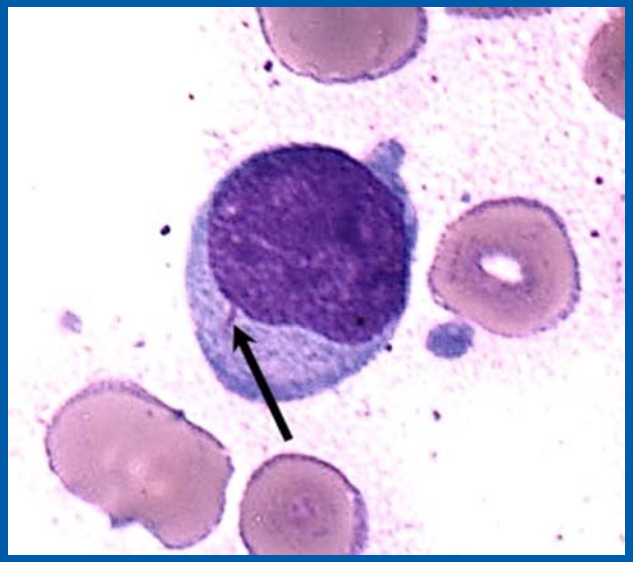
Clinical Decision-Making for Patients Diagnosed with AML and an Actionable Mutation



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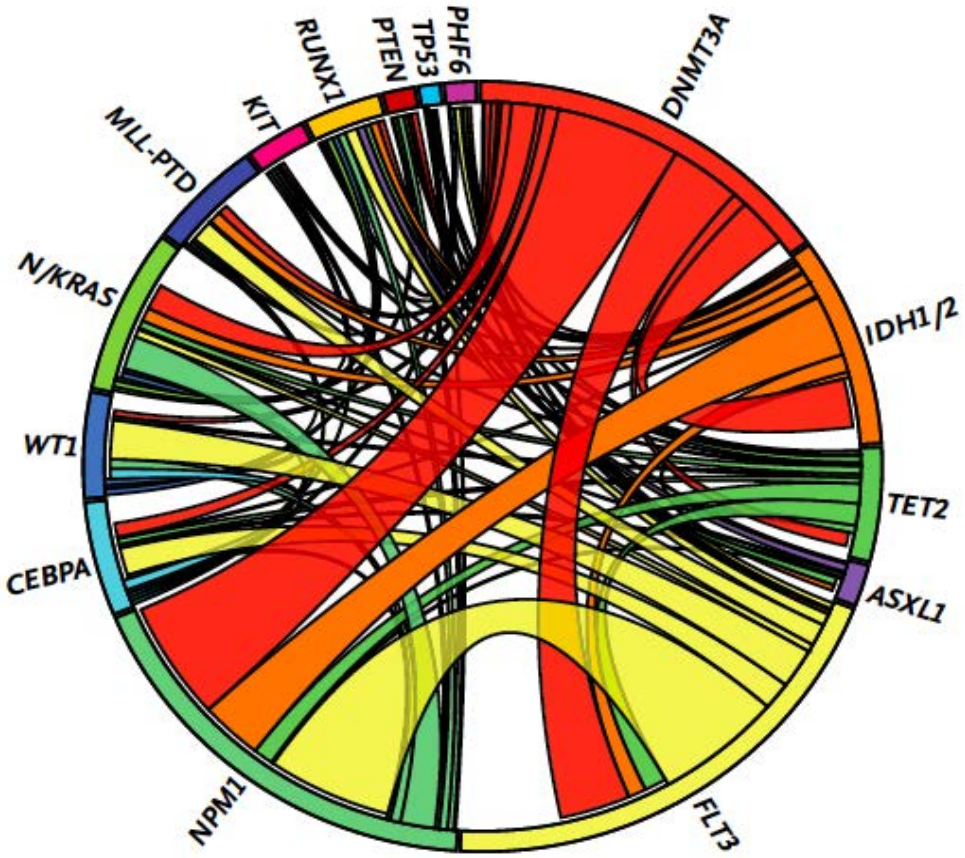
Chief, Leukemia Service

Actionable Mutations in Acute Myeloid Leukemia



Gene	Overall Frequency, %
FLT3 * (ITD, TKD)	37 (30,7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2 *	8
IDH1 *	7
KIT	6

Gene	Overall Frequency, %
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

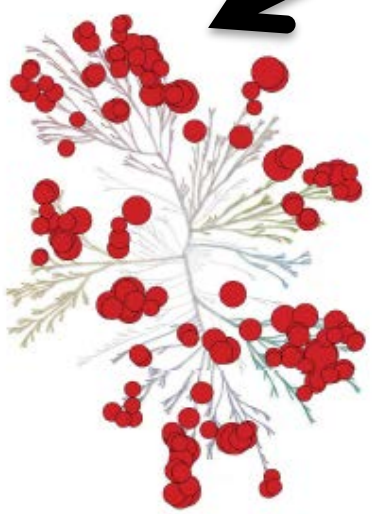
*** Targetable mutation**

FLT3 mutant: Midostaurin, gilteritinib,
IDH1: ivosidenib; IDH2: enasidenib

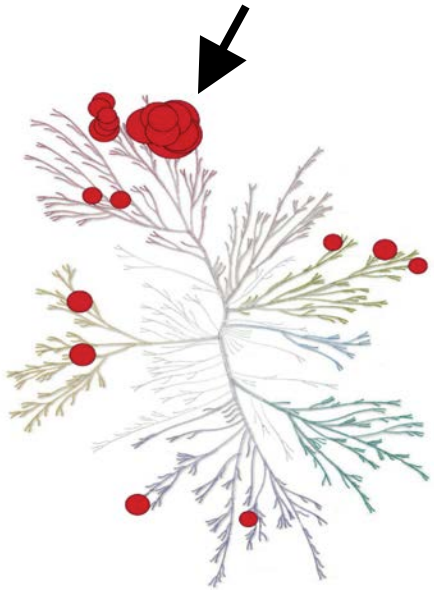
Papaemmanuil E et al NEJM 374(23): 2209-221, 2016

FLT3 tyrosine kinase inhibitors in clinical use

Class 3 RTK's:
FLT3, KIT, CSF1R,
PDGFRA/B



Midostaurin (PKC412)



Quizartinib (AC220)

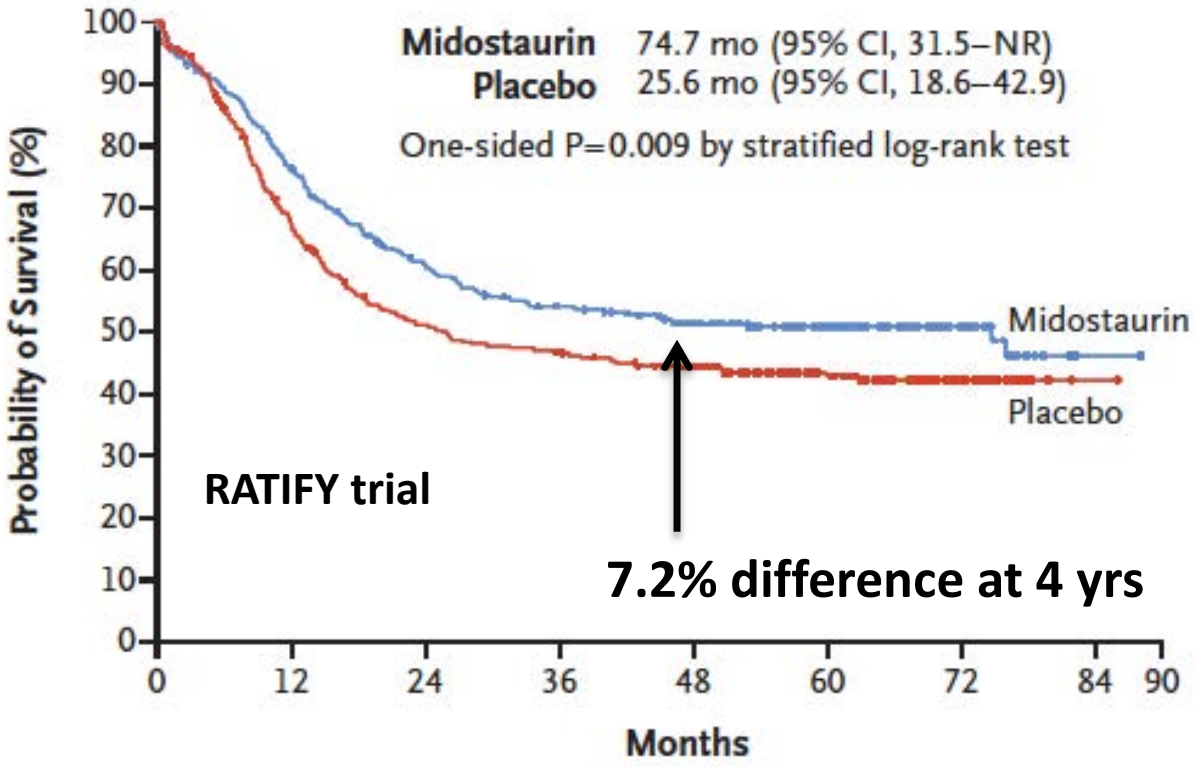
	Other Kinases	IC_{50} (plasma)
Lestaurtinib	JAK2, TrkA	700 nM
Midostaurin	cKIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib	cKIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib	cKIT, PDGFR, RET	18 nM
Crenolanib	PDGFR	48 nM
Gilteritinib	AXL	43 nM

Pratz et al. Blood 2010;115(7):1425 ;Zarrinkar, et al. Blood 2009;114(14):2984-92; Galanis, et al. Blood 2014; Levis MJ, et al. ASCO 2015, #7003

Midostaurin plus 7+3 in patients (18-59 yo)

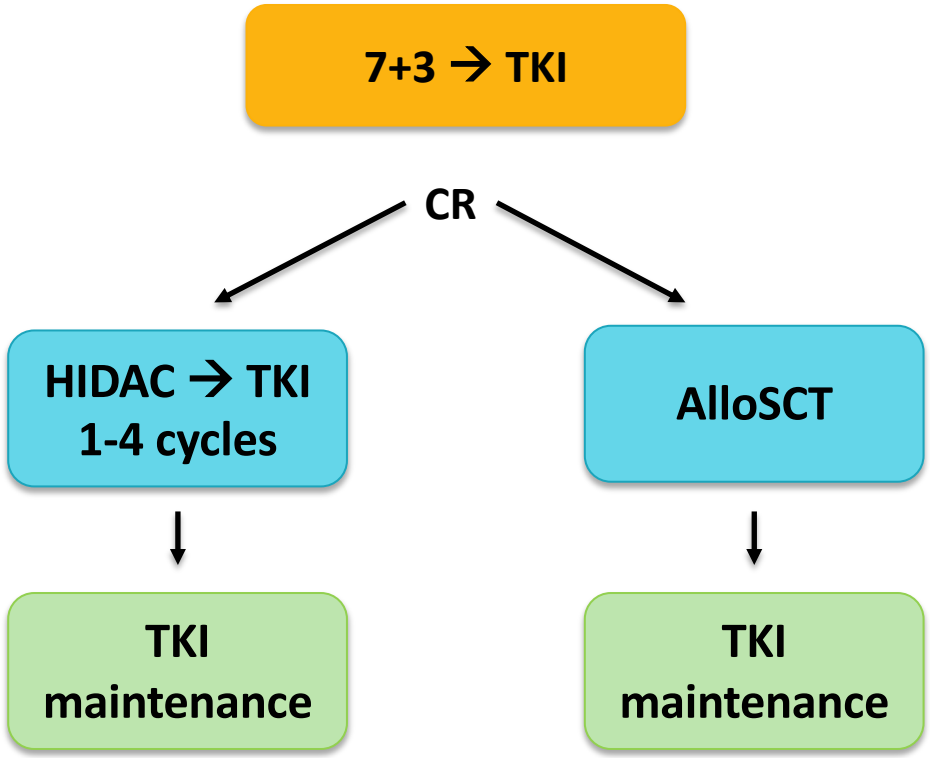
Kinase Profile: cKIT, PKC, PDGFR, VEGFR, FLT3 TKD FLT3 ITD

Midostaurin Group (N=360)	Placebo Group (N=357)	P Value†
212 (59)	191 (54)	0.15



Stone R et al NEJM 2017

FLT3 inhibitor plus 7+3 for fit pts with FLT3^{mut} AML



FLT3 TKI	Pts (phase)	CRCR/CRi/CRh
Midostaurin plus 7+3	717 (ph 3)	**59%**
Quizartinib plus 7+3	16 (ph 1)	**84%**
Crenolanib plus 7+3	38 (ph 2)	**88%**
Gilteritinib plus 7+3	38 (ph 1)	**82%**

Stone R et al NEJM 377(5): 454, 2017; Wang E et al ASH 2017; Altman J et al AJH 93(2): 213, 2018; Pratz K et al ASH 2020

Newly Diagnosed AML: Phase 1b trial of gilteritinib plus 7+3 (n=38)

Duration of response[a]	Disease-free survival[a]	Overall survival[a]	Duration of follow-up[a]
8.0 (4.0–14.7) months	13.3 (4.9–18.7) months	Not reached	35.8 (23.4–37.6)

Clinical Responses (CR/CRp)

Response Parameter at End of Induction,[b] n (%)	Gilteritinib Escalation Cohort (120 mg only) (n=2)	Gilteritinib Expansion Cohort (n=17)	Alternative Anthracycline Schedule: Cohort A (7+3 daunorubicin) (n=6)	Alternative Anthracycline Schedule: Cohort B (7+3 idarubicin) (n=6)	Continuous Gilteritinib Exposure (n=7)	TOTAL *FLT3*[mut+] (N=38)[c]
CR	1 (50.0)	7 (41.2)	2 (33.3)	1 (16.7)	4 (57.1)	**15 (39.5)**
CRp	0	1 (5.9)	0	0	0	1 (2.6)
CRi	1 (50.0)	6 (35.5)	4 (66.7)	3 (50.0)	1 (14.3)	15 (39.5)
PR	0	0	0	0	0	0
NR	0	0	0	2 (33.3)	2 (28.6)	4 (10.5)
CRc[c]	2 (100.0)	14 (82.4)	6 (100.0)	4 (66.7)	5 (71.4)	**31 (81.6)**

Mutational Clearance (FLT3-ITD signal)

- Among patients with *FLT3* ITD-positive AML who received a gilteritinib dose of 120 mg and achieved CRc,[b] high proportions of patients achieved mutational clearance (defined as *FLT3* ITD:total *FLT3* signal ratio $\leq 10^{-4}$)

Mutational Clearance Status	End of Induction (n=12)	Beginning of Consolidation (n=8)	Beginning of Maintenance (n=13)
Cleared[c]	4 (33.3)	3 (37.5)	11 (84.6)
Not cleared[d]	8 (66.7)	5 (62.5)	2 (15.4)

Pratz K et al, ASH 2020 abstract #24

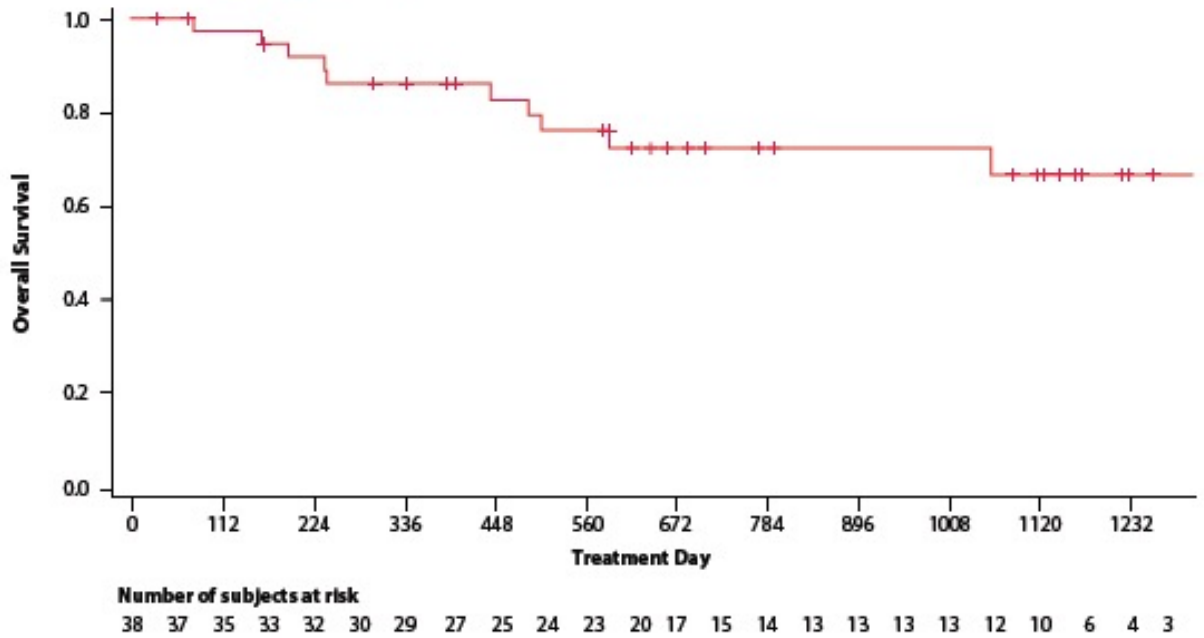
Newly Diagnosed AML: Phase 1b trial of gilteritinib plus 7+3

Conclusions

- Gilteritinib + intensive chemo well tolerated
- Anti-leukemia activity seen in FLT3 mut AML
- Anthracycline type or gilteritinib schedule did not impact on efficacy
- High mutational clearance with Gilt 120 mg in pts who achieved CRc

- **Randomized trials of Gilt + chemo vs Midostaurin + chemo for newly diagnosed FLT3 mutant AML are underway**

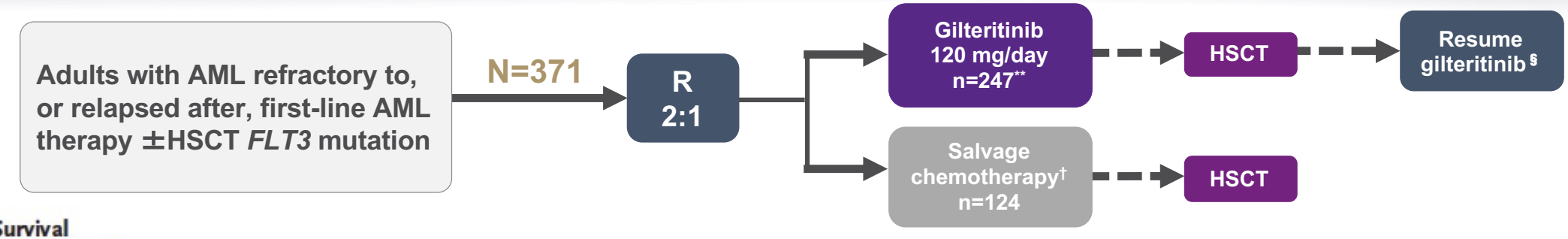
Figure 2. Overall Survival Probability in Patients With *FLT3*$^{mut+}$ AML Who Received Gilteritinib 120 mg/day (N=38)

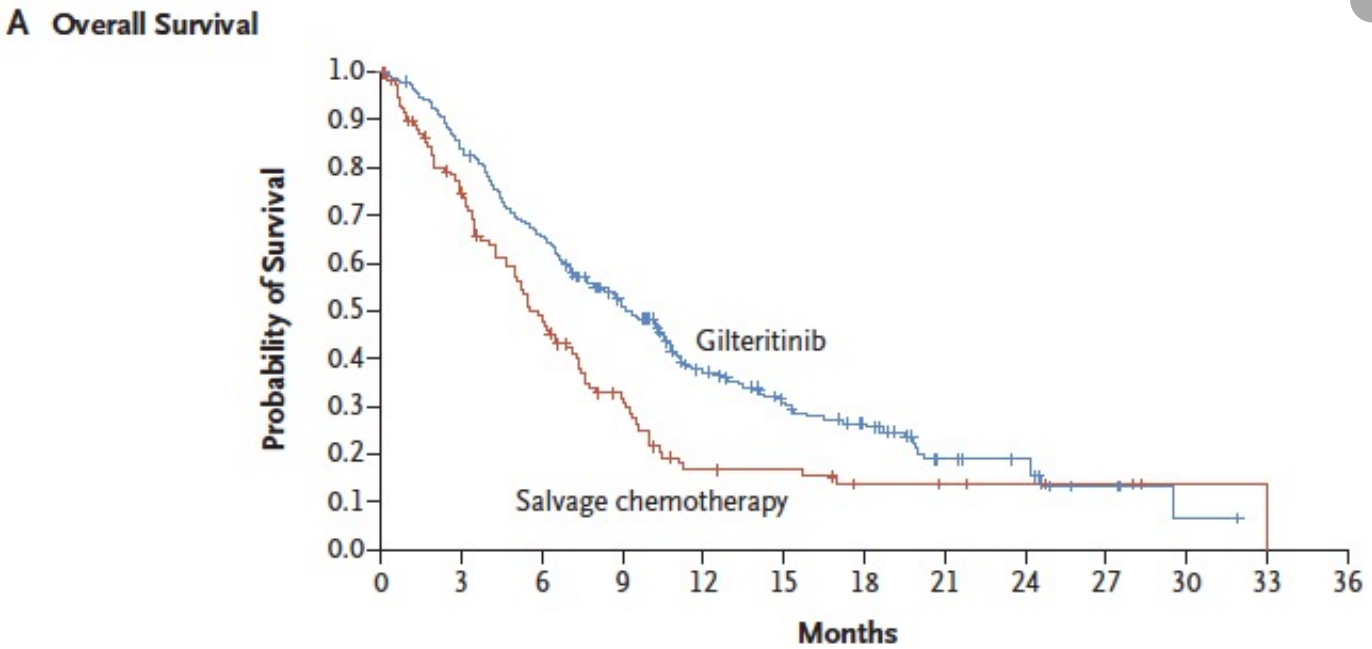


Abbreviations: AML, acute myeloid leukemia; *FLT3*$^{mut+}$, FMS-like tyrosine kinase 3 mutation–positive.

Pratz K et al, ASH 2020 abstract #24

ADMIRAL: Phase 3 gilteritinib vs salvage chemo in RR-AML





No. at Risk													
Gilteritinib	247	206	157	106	64	44	31	14	11	4	1	0	0
Salvage chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

36% reduced risk of death* for gilteritinib

- HR=0.64 (0.49–0.83); two-sided p<0.001

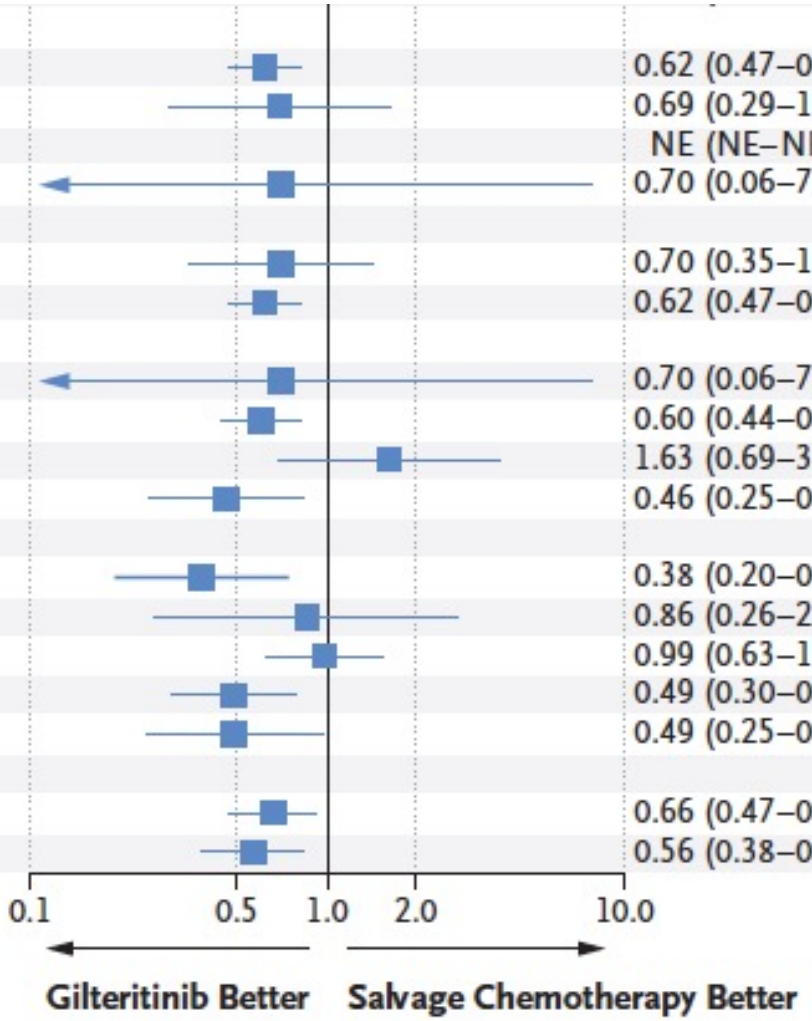
Median OS, months (95% CI)

- **9.3 months** with gilteritinib (7.7–10.7)
- 5.6 with salvage chemotherapy (4.7–7.3)

Perl A et al NEJM 2019

ADMIRAL: Phase 3 gilteritinib vs salvage chemo in RR-AML

FLT3 mutation type			
FLT3 ITD alone	145/215	81/113	0.62 (0.47–0.82)
FLT3 TKD alone	16/21	8/10	0.69 (0.29–1.64)
FLT3 ITD and *FLT3* TKD	6/7	0	NE (NE–NE)
Other	4/4	1/1	0.70 (0.06–7.92)
Previous use of *FLT3* inhibitor			
Yes	26/32	11/14	0.70 (0.35–1.44)
No	145/215	79/110	0.62 (0.47–0.82)
Cytogenetic risk status			
Favorable	3/4	1/1	0.70 (0.06–7.92)
Intermediate	119/182	63/89	0.60 (0.44–0.82)
Unfavorable	22/26	7/11	1.63 (0.69–3.85)
Unknown	27/35	19/23	0.46 (0.25–0.84)
Response to first-line therapy per IRT			
Relapse ≤6 mo after allogeneic HSCT	24/31	16/17	0.38 (0.20–0.75)
Relapse >6 mo after allogeneic HSCT	10/17	4/8	0.86 (0.26–2.80)
Primary refractory disease without HSCT	70/98	28/48	0.99 (0.63–1.55)
Relapse ≤6 mo after composite complete remission and no HSCT	47/67	28/34	0.49 (0.30–0.80)
Relapse >6 mo after composite complete remission and no HSCT	20/34	14/17	0.49 (0.25–0.98)
Preselected chemotherapy per IRT			
High intensity	96/149	52/75	0.66 (0.47–0.93)
Low intensity	75/98	38/49	0.56 (0.38–0.84)



Perl A et al NEJM 2019

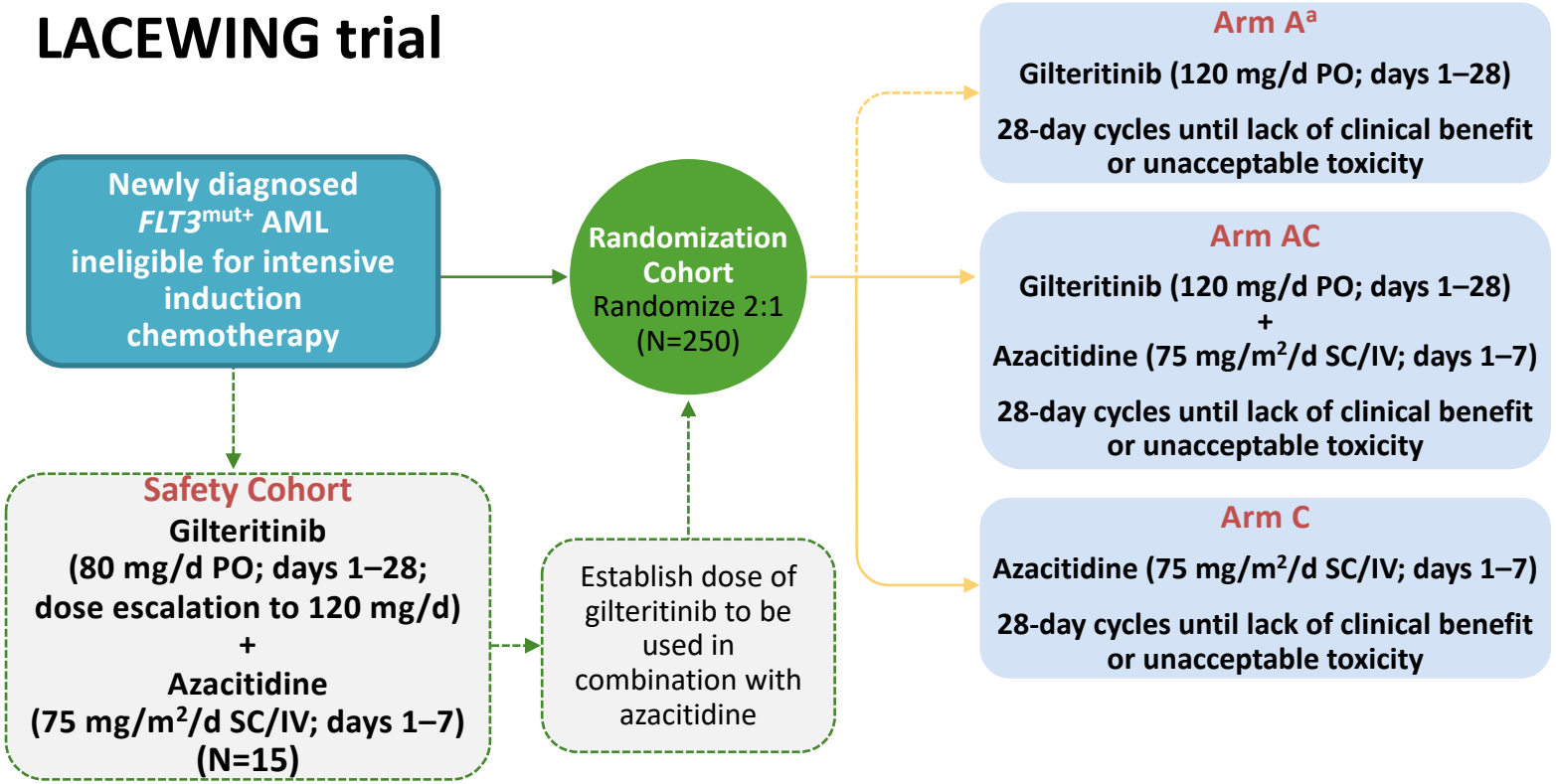
Recommended management of toxicities of gilteritinib

Adverse event	Signs/Symptoms	%	Recommendation
Differentiation syndrome	Fever, dyspnea, pleural/pericardial effusions, weight gain, rash, renal issues	3%	Dexamethasone 10 mg IV BID x 3 days and until asymptomatic; Hold drug if sx not improved within 48hr on steroids; resume when improved
Posterior Reversible Enceph-alopathy Syndrome (PRES)	Seizure, altered mental status, headache, vision changes	1%	Confirm with MRI and discontinue drug therapy
QTc interval >500 msec	ECG finding	1%	Check ECG prior to, days 8 and 15, and prior to start of next 2 cycles; stop drug & resume at 80 mg when QTc ≤ 480 msec
QTc interval increase >30 msec on day 8	ECG finding	7%	Confirm with ECG on day 9 Dose reduce to 80 mg daily
Pancreatitis or any ≥ Gr 3	Abdominal pain	4%	Interrupt drug and resume at 80 mg

Perl A et al NEJM 2019

Phase 3 trial of Gilteritinib + Aza vs Aza in unfit AML

LACEWING trial



Post-ASH press release reported that trial failed to meet primary endpoint

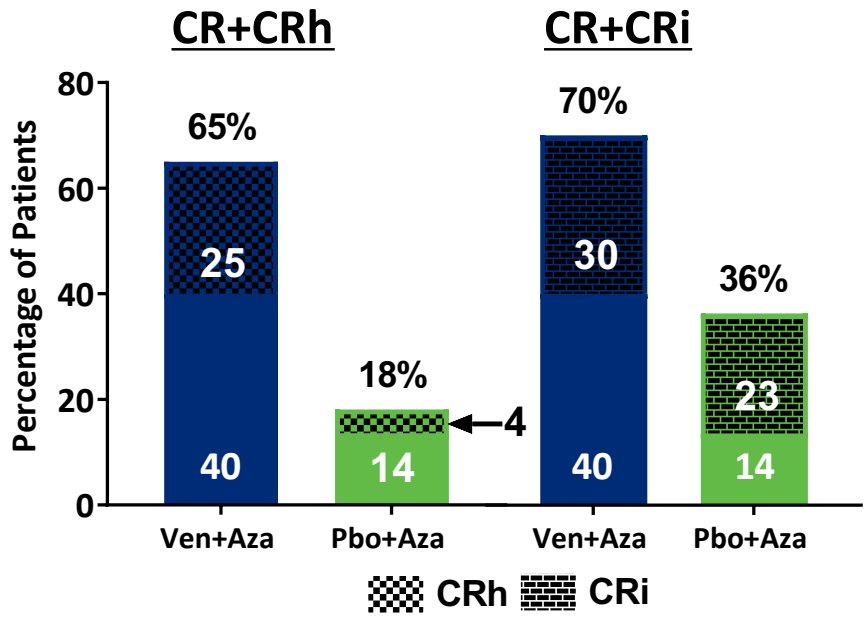
Characteristic	Safety Cohort (N=15)
Age, y	
Median (range)	75 (65–86)
≥75, n (%)	9 (60)
FLT3 status, n (%)	
ITD alone	10 (67)
TKD alone	3 (20)
ITD/TKD	1 (7)
Wild type	1 (7)
ECOG PS ≤1, n (%)	6 (40)
CR	**5/15 (33)**
CRc	**10/15 (67)**
DOR (n=10	**10.4 mo**

Wang E, et al. ASH 2020. Abstract 27.

Outcomes of Ven + Aza in FLT3 mutant AML

Protocol (NCT02993523/NCT02203773)

- **Pooled data from phase 3 of Ven+AZA vs Pbo+AZA and phase 1b of Ven+AZA**
- Ven 400 mg daily (days 1–28) + AZA (75 mg/m^2; days 1–7/28-day cycle)
- Disease assessments per modified IWG response criteria for AML

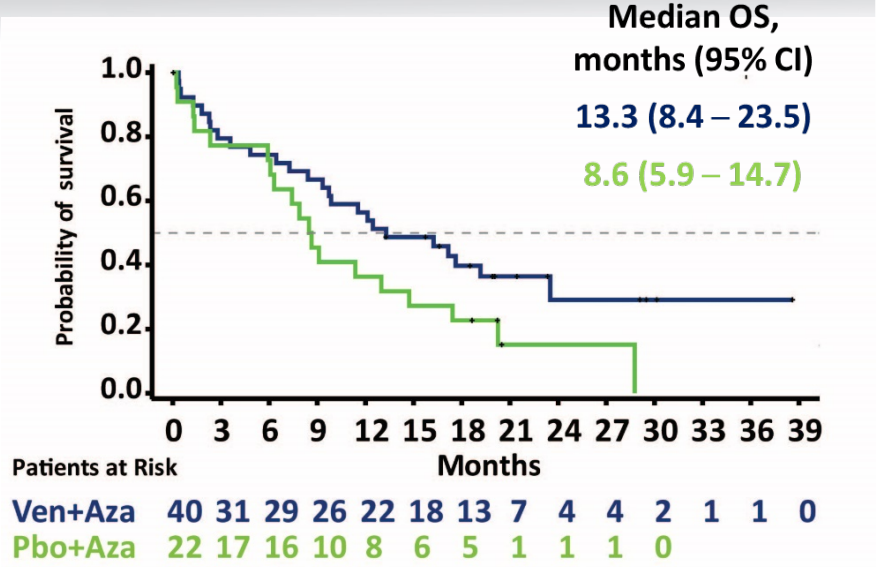


	Ven+Aza (n=40)	Pbo+Aza (n=22)
Median treatment duration, cycles (range)	7.0 (1.0 — 31.0)	5.0 (1.0 — 21.0)
Median time to CR/CRh, months (range)	1.0 (0.8 — 4.8)	3.2 (1.8 — 3.6)
Median time to CR/CRi, months (range)	1.2 (0.8 – 7.7)	2.8 (1.0 – 11.2)

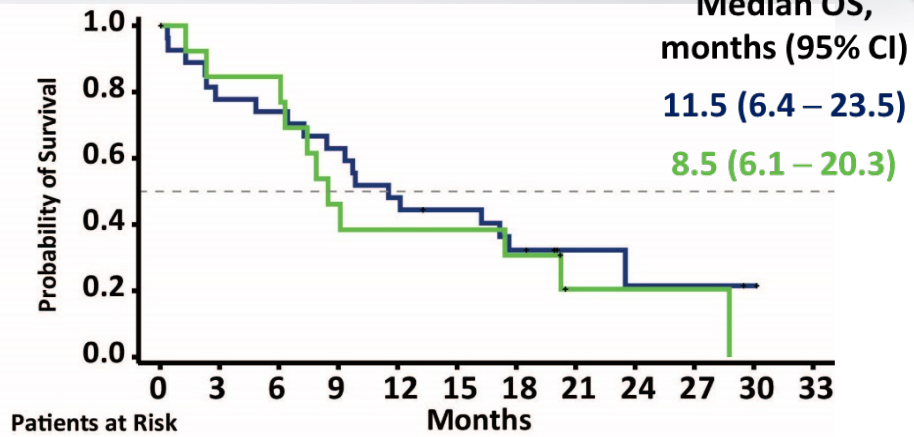
Konopleva M et al, ASH 2020 abstract #1904

Pooled Analysis: Outcomes of Ven + Aza in FLT3 mutant AML

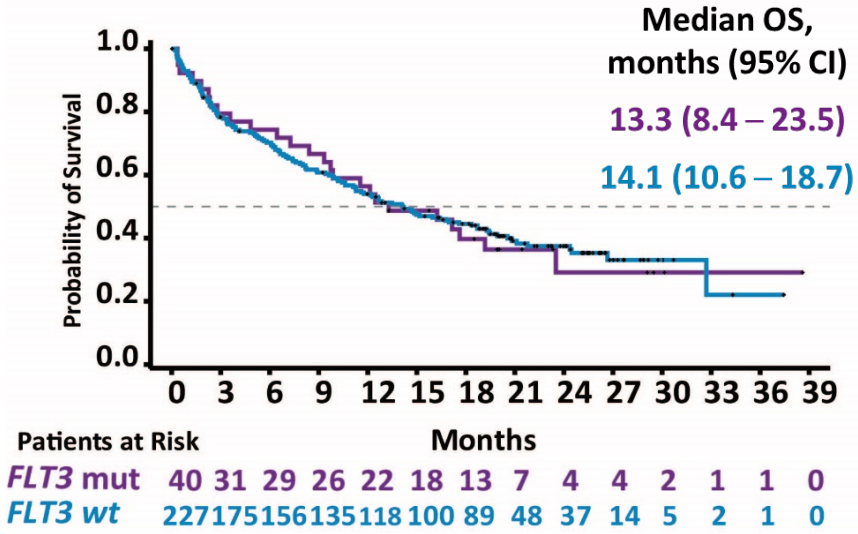
A. FLT3mut



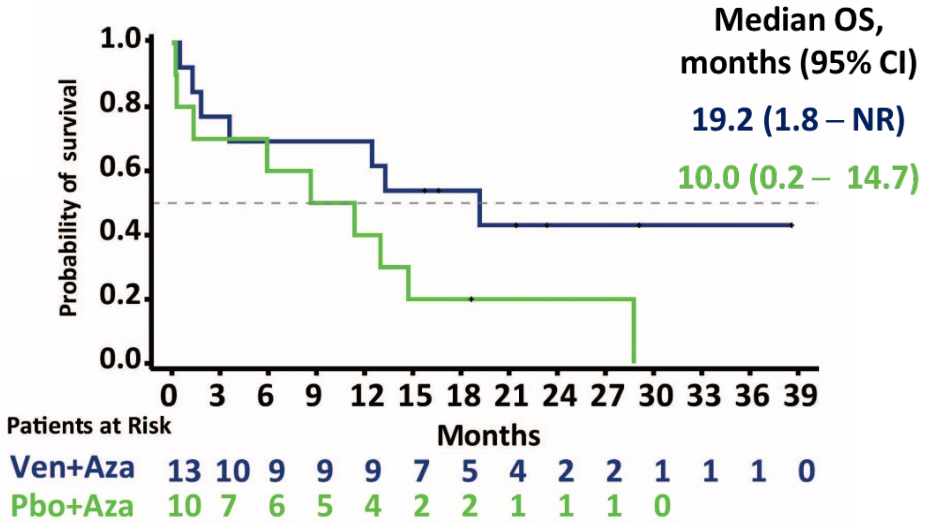
C. FLT3-ITD



B. FLT3mut vs. wt in Ven+Aza



D. FLT3-TKD



Konopleva M et al, ASH 2020 abst #1904

Phase 1b trial of Venetoclax + Gilteritinib in RR-AML

Key Eligibility Criteria

- R/R AML
- WT or *FLT3*$^{mut+}$ (dose escalation) and *FLT3*$^{mut+}$ (dose expansion)
- ≥1 prior line of therapy[a]
- WBC count ≤ 25 x 10^9 /L at start of study drug
- ECOG PS 0–2

Dose escalation phase
WT and *FLT3*$^{mut+}$

Ven 400 mg + Gilt 80 mg (n=7)

Ven 400 mg + Gilt 120 mg (n=16)

DLT monitoring[b]

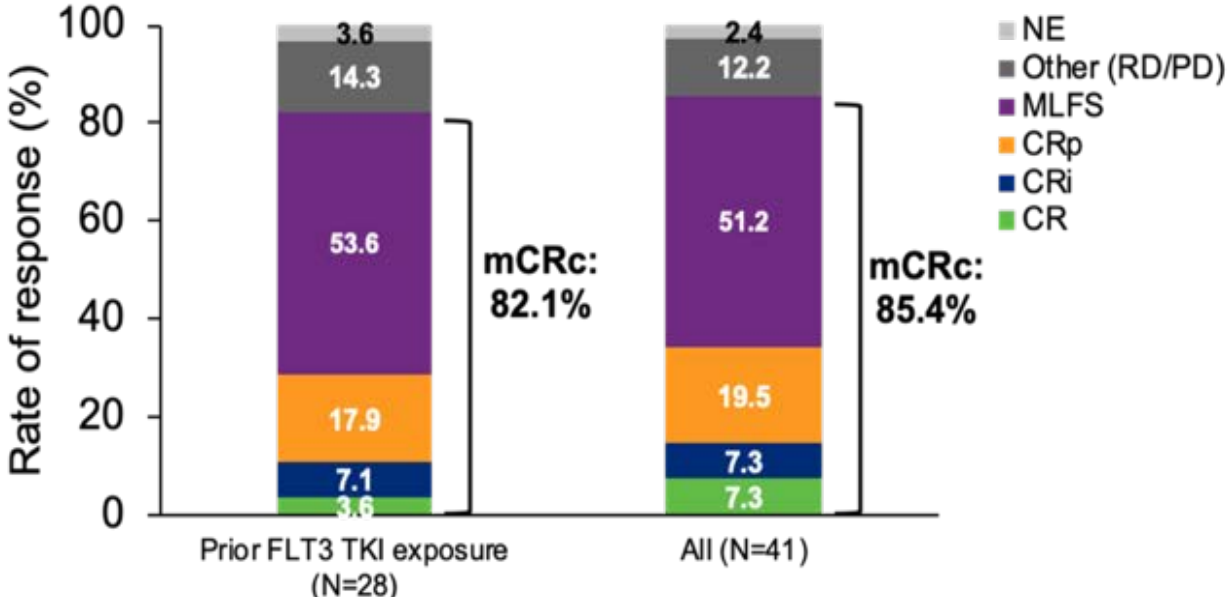
Dose expansion
FLT3^{mut+} only

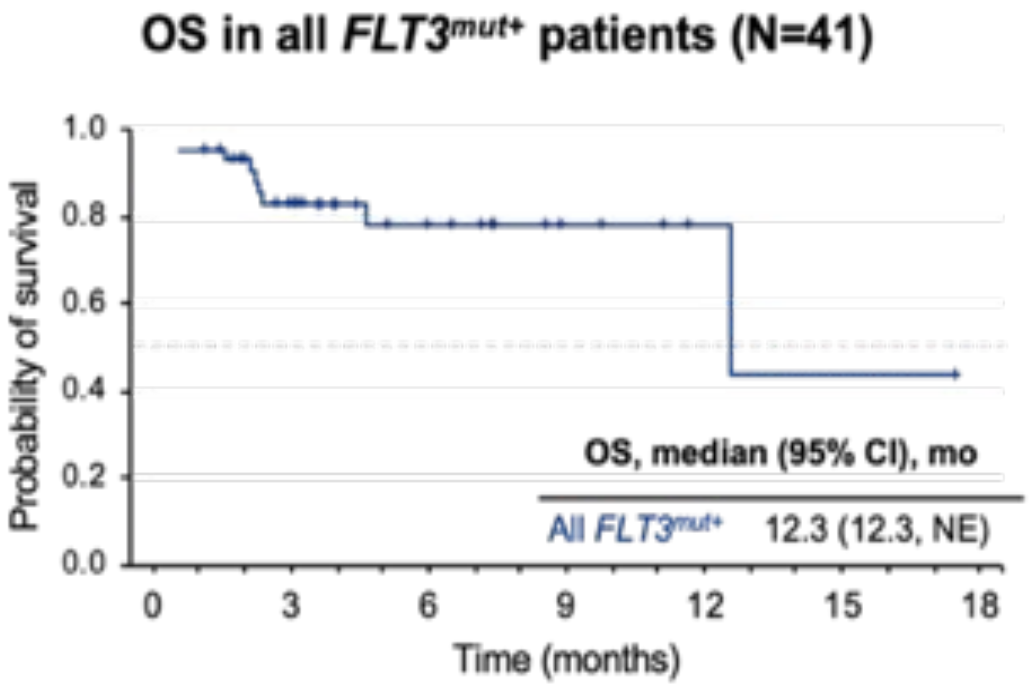
Ven 400 mg + Gilt 120 mg (RP2D) (n=46)[c]

DLT monitoring[b]

Follow-up

- Post-treatment follow-up monthly for up to 1 year, following last dose of study drug





Daver N et al ASH 2020 abstract #335

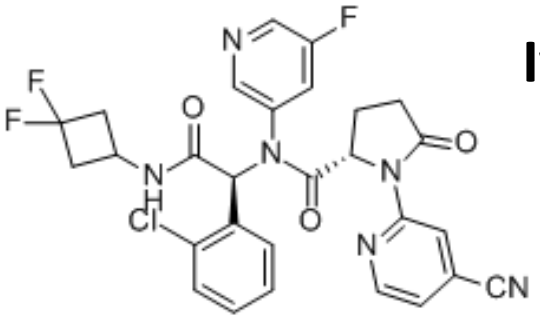
Select Ongoing Phase III Trials of Venetoclax-Based Regimens in AML

Trial Name/NCT#	N	Setting	Treatment arms	Estimated 1º Completion
VIALE-M (NCT04102020)	360	Maintenance for pts in 1st remission after conventional chemo	• Ven + Aza + BSC • Ven + CC-486 + BSC • BSC	November 2026
VIALE-T (NCT04161885)	424	After Allogeneic SCT (ASCT)	• Ven + Aza + BSC • BSC	June 2024
ENHANCE-2 (NCT04778397)	346	Previously untreated with TP53-mutant disease	• Magrolimab + Aza • Venetoclax + Aza • 7+3 chemotherapy	September 2023
SIERRA (NCT02665065)	150	Prior to ASCT in older pts with active R/R disease	• IOMAB-B + RIC • Conventional care	December 2021

RIC = Reduced intensity conditioning; BSC = best supportive care

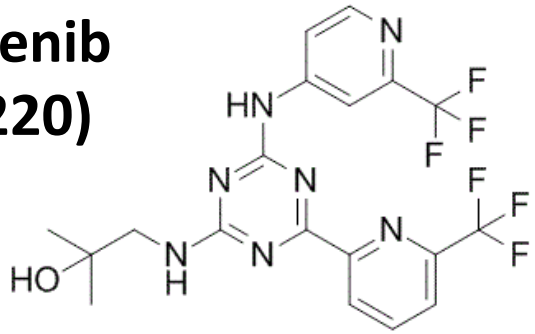
Clinicaltrials.gov; Accessed in July 2021.

IDH1/2 inhibitors in IDH1/2 mutant RR-AML



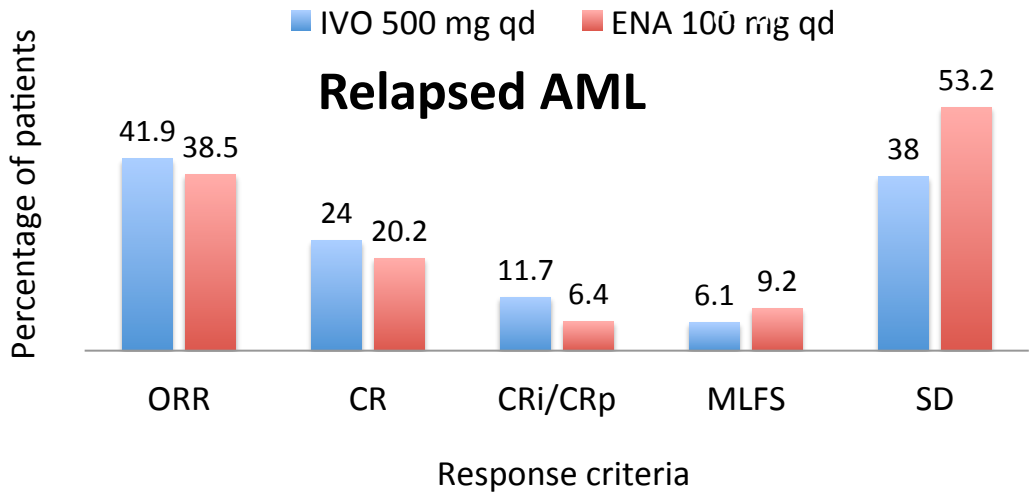
Ivosidenib (AG-120)

Enasidenib (AG-220)



De novo AML

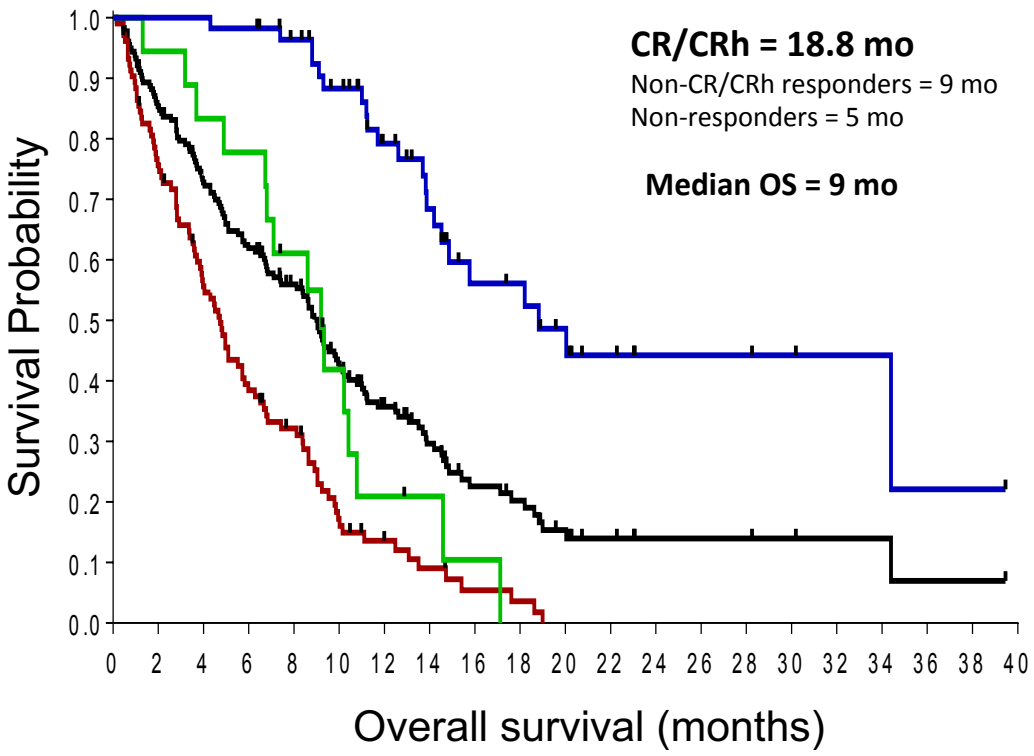
Single agent	IVO 500 mg qd (N=33)	ENA 100 mg qd (N=39)
CR/CRh	14 (42.4%)	12 (30.8%)
Median OS	12.6 mos	11.3 mos



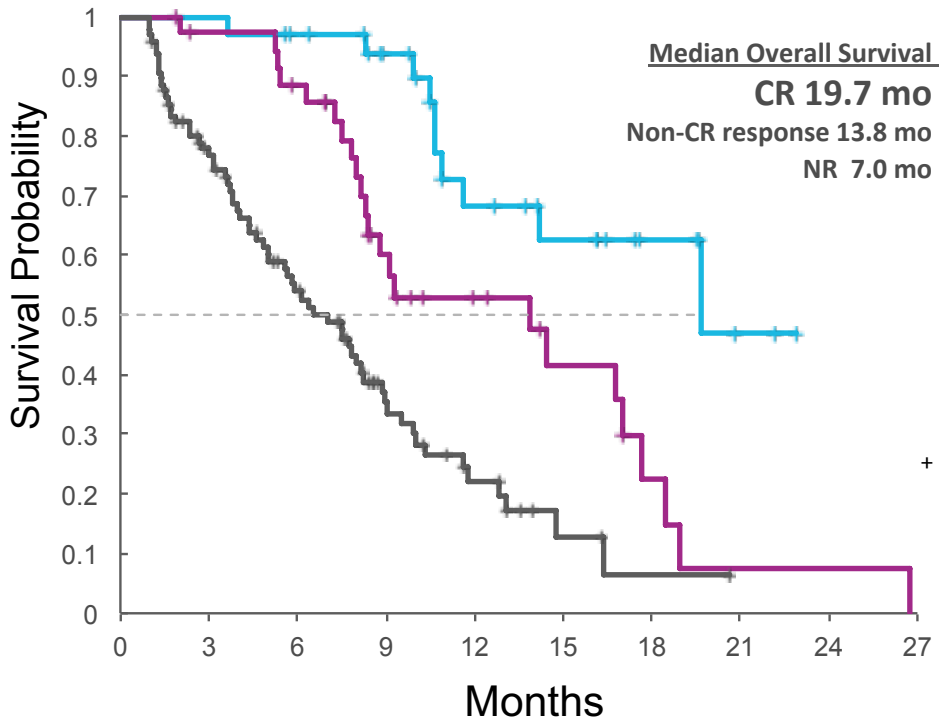
DiNardo CD, et al. NEJM. 2018;378(25):2386; Stein EM, et al. Blood. 2017;130(6):722

IDH1/2 Inhibitors for IDH-mutant RR-AML

Ivosidenib (IDH1 inhibitor)



Enasidenib (IDH2 inhibitor)

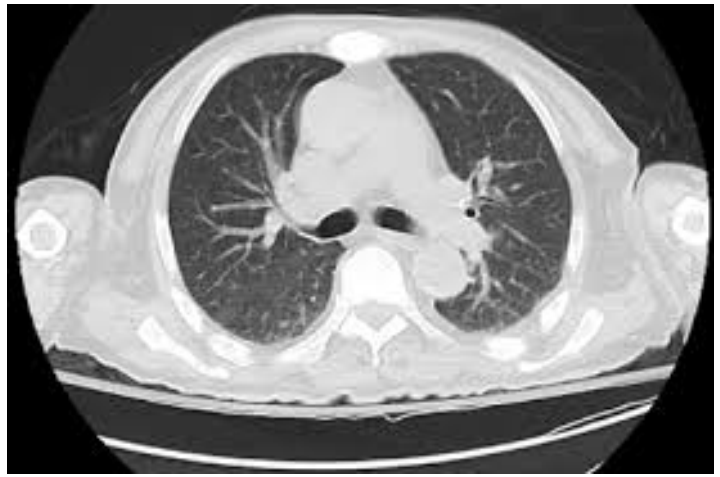


DiNardo CD, et al. N Engl J Med. 2018;378(25):2386.; Stein EM, et al. Blood. 2017;130(6):722-731.

Adverse events associated with IDH inhibitors

Ivosidenib – Adverse Events	Grade ≥ 3
Prolonged QT interval	7.8%
IDH differentiation syndrome	3.9%
Anemia	2.2%
Thrombocytopenia	1.7%
Leukocytosis	1.7%
Decreased platelet count	1.7%
Hypoxia	1.1%

Enasidenib – Adverse Events	Grade 3 or 4
Hyperbilirubinemia	8%
IDH differentiation syndrome	7%
Anemia	7%
Thrombocytopenia	5%
Tumor lysis syndrome	3%
Decreased appetite	2%



Differentiation Syndrome

New onset or worsening fever, rapid weight gain, swelling in legs, respiratory symptoms, effusions (pericardial/pleural), hypotension, renal issues;
Can occur up to 100 days after treatment initiation

DiNardo CD, et al. NEJM 2018; Stein EM, et al. Blood. 2017;130(6):722

Management of IDH Inhibitor Differentiation Syndrome (4-9%)

Suspicion of IDH-DS

New onset or worsening of characteristic symptoms of unexplained etiology, incl. fever, rapid weight gain or edema, respiratory symptoms (regardless of infiltrates), pleural or pericardial effusions, hypotension, and acute renal failure*

→

Initiate treatment with dexamethasone (10 mg BID), as indicated

- Empiric therapy for other possible causes (eg, anti-infective agents)
- Hydroxyurea for co-occurring leukocytosis
- Hyperuricemia agents for co-occurring tumor lysis syndrome

→ Hospitalization indicated in setting of rapidly progressing symptoms (esp. respiratory), development of hypoxia, renal failure, rising WBC count, DIC

- Stop/interrupt enasidenib treatment†

→ Improvement of IDH-DS signs/symptoms → Continue dexamethasone until significant improvement or resolution of signs/symptoms, then taper per institutional guidelines

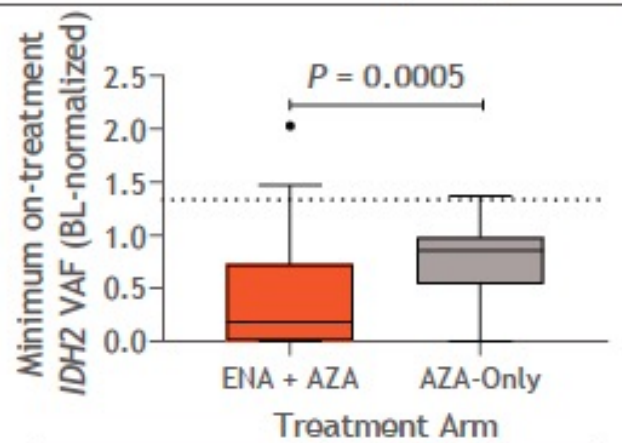
*Typical onset is between 7-10 days and 5 months from initiation/reinitiation of enasidenib

†Treatment may not immediately reverse symptoms, as enasidenib has a long half-life

Fathi A et al JAMA Oncology 2018: 4, 110

AG-221-AML-005 Trial: Enasidenib + Aza in newly diagnosed IDH2-mutant AML

Figure 5. Maximum reductions from baseline in *IDH2* variant allele frequency on-study

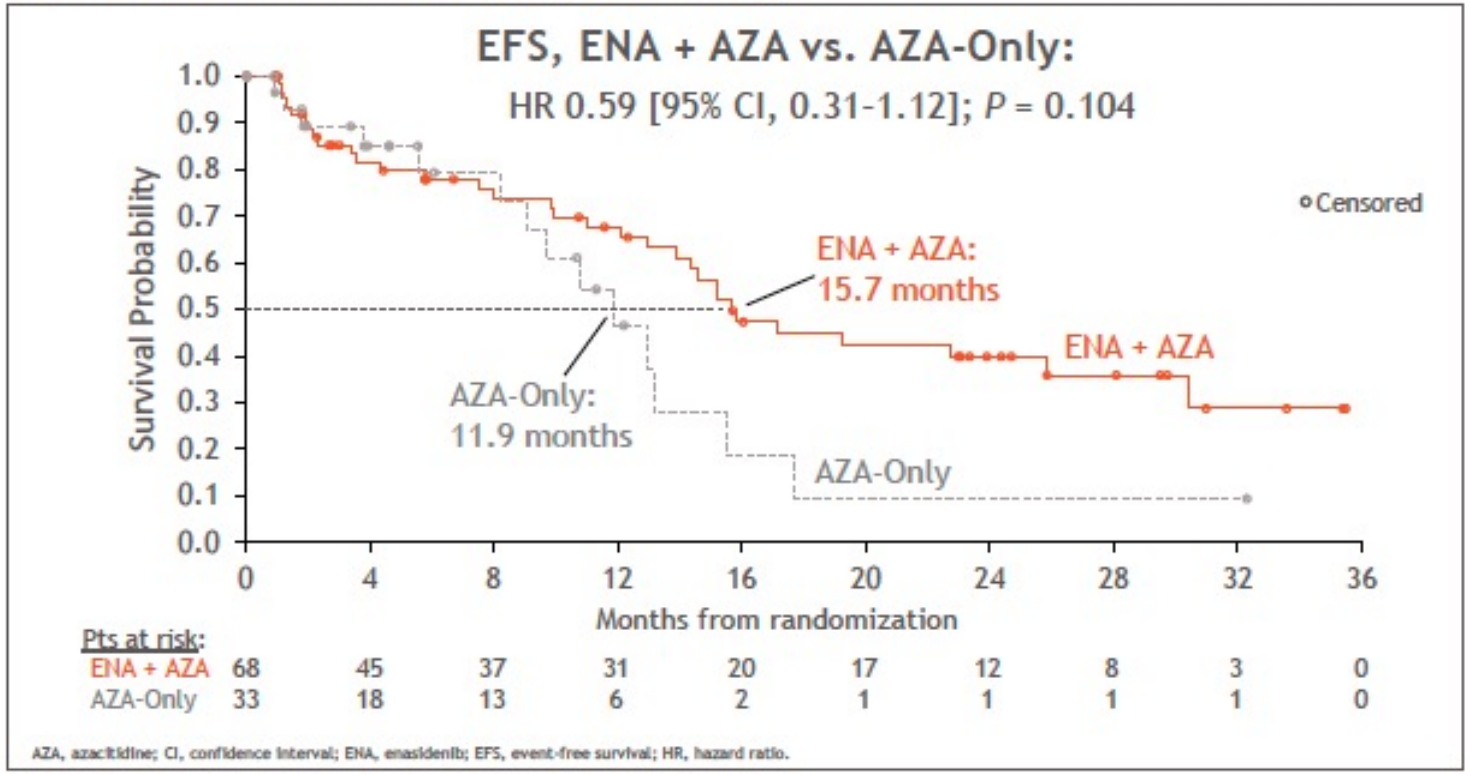


	ENA + AZA	AZA-Only
Count	54	24
Median	0.185	0.860
95% CI	0.060, 0.430	0.550, 0.950
Range	0, 2.030	0, 1.370

Horizontal bars denote median; error bars denote Tukey's range; circles denote outliers. P-value was calculated using Mann-Whitney test.

AZA, azacitidine; BL, baseline; CI, confidence interval; ENA, enasidenib; IDH2, isocitrate dehydrogenase-2; VAF, variant allele frequency.

Figure 7. Event-free survival (Aug 2020 cutoff)



AZA, azacitidine; CI, confidence interval; ENA, enasidenib; EFS, event-free survival; HR, hazard ratio.

DiNardo C et al., 2021 EHA Abstract EP465

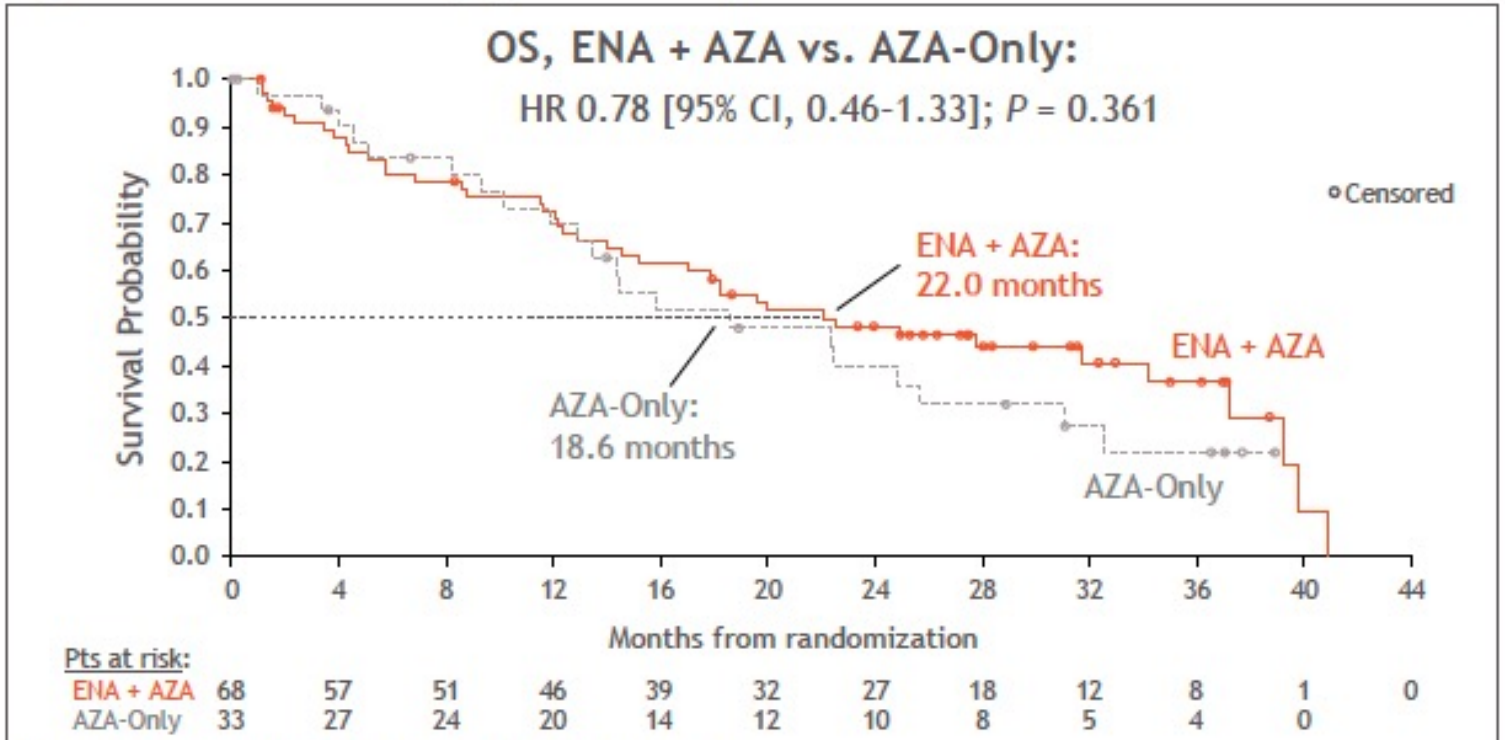
AG-221-AML-005: Enasidenib + Aza in newly diagnosed IDH2-mutant AML

Conclusions

- Overall survival promising
- ENA+AZA reduced 2HG & IDH2 VAF more than AZA alone
- Changes in IDH2 VAF greater in responding patients
- Half of all pts alive at 2 years

- Confounding effects
  - High rate of subsequent AML Rx
  - Commercial use of ENA

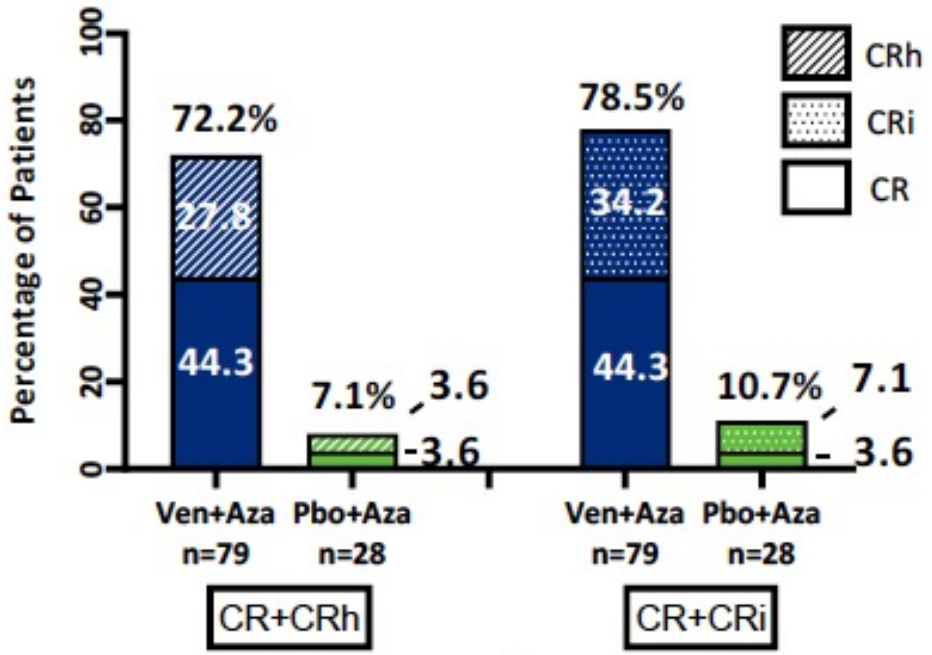
Figure 8. Overall survival (Aug 2020 cutoff)



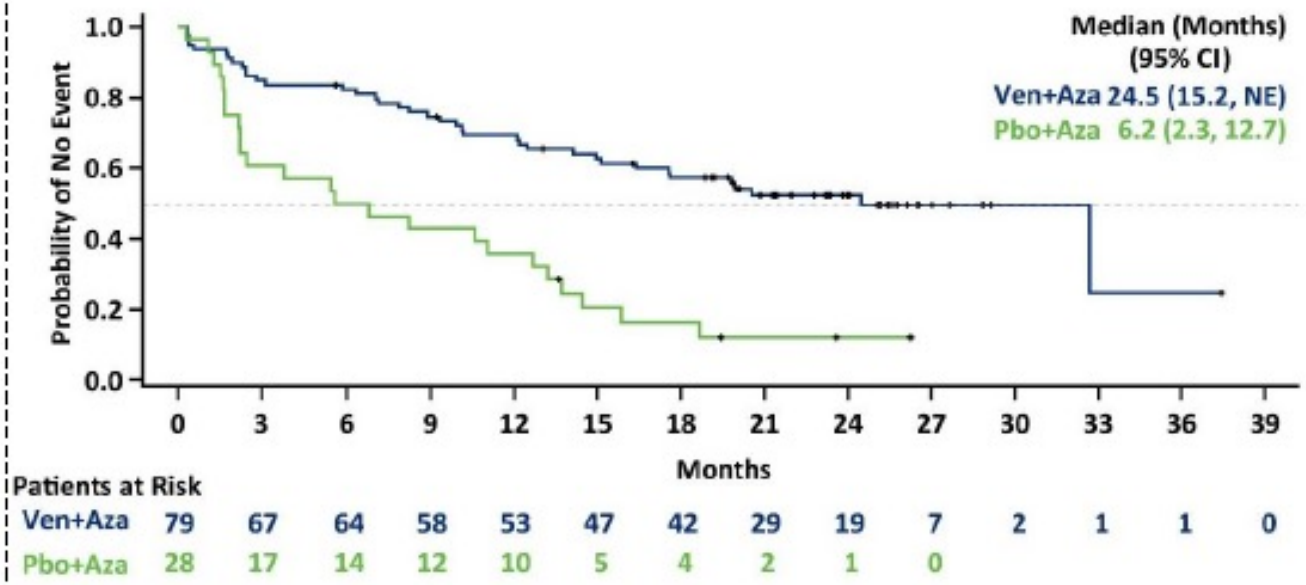
AZA, azacitidine; CI, confidence interval; ENA, enasidenib; HR, hazard ratio; OS, overall survival.

DiNardo C et al., 2021 EHA Abstract EP465

VIALE-A: Outcomes of Ven+ Aza in IDH1/2 mutant AML



	Ven + Aza n = 79	Pbo + Aza n = 28
CR+CRh: Median time to first response, mo. (min, max) Median DoR, mo. (95% CI)*	1.0 (0.7, 9.6) 29.6 (16.7, NE)	2.6 (2.1, 3.1) 15.5 (NE)
CR + CRi: Median time to first response, mo. (min, max) Median DoR, mo. (95% CI)*	1.1 (0.7, 8.8) 29.5 (16.7, NE)	3.4 (2.1, 7.1) 9.5 (3.5, 15.5)
Median treatment cycles (min,max)	8.0 (1, 37)	2.5 (1, 18)



Survival Estimate (%) (95% CI)

Month 6	Month 12	Month 24
82.3 (71.9, 89.1)	69.3 (57.8, 78.3)	52.4 (40.4, 63.1)
50.0 (30.6, 66.6)	35.7 (18.9, 53.0)	12.2 (3.2, 27.8)

Pratz K, et al. ASH 2020. Abstract 1944.

Phase I/II Trial of Ivosidenib + Ven ± Aza in IDH1-mutant cancers

Outcome	IVO + VEN400 (n = 6)	IVO + VEN800 (n = 6)	IVO + VEN400 + AZA (n = 13)
CRc, n (%)	4 (67)	6 (100)	11 (85)
▪ CR	3 (50)	3 (50)	7 (54)
▪ CRh	0	2 (33)	0
▪ CRi	1 (17)	1 (17)	4 (31)
MLFS, n (%)	0	0	1 (8)
PR, n (%)	0	0	1 (8)
No remission, n (%)	2 (33)	0	0
12-mo OS rate, % (95% CI)	50 (23-100)	67 (38-100)	83 (65-100)
Median OS, mo (range)	9 (4-NR)	NR (8-NR)	NR
Median event-free survival, mo (range)	9 (0-NR)	9 (7-NR)	NR
Median duration of response, mo (range)	13 (3-NR)	7 (4-NR)	NR

Lachowiez. ASCO 2021. Abstr 7012.

Phase I/II Trial of Ivosidenib + Ven ± Aza in IDH1 mutant cancers

Conclusions

- Ivo + Ven ± Aza well tolerated
- High response rates ± Aza
- 1 yr OS: 76% ND, 50% RR-AML
- ? Longer DOR and OS with triplet
- Small patient numbers (total 25)

- Improved survival (P = .0052) for AML pt achieving MRD-neg status

- MRD-neg pts (n = 9) 12-mo OS: 100%
- MRD-pos pts (n = 6) 12-mo OS: 33%

Outcome	All Patients (N = 25)	ND AML (n = 13)	R/R AML (n = 8)
12-mo OS rate, %	71	76	50
Median OS, mo (range)	NR	NR	9 (8-NR)
Median EFS, mo (range)	NR (9-NR)	NR (8-NR)	6 (4-NR)
Median DOR, mo (range)	NR (13-NR)	NR (7-NR)	NR (5-NR)

Lachowiez. ASCO 2021. Abstr 7012.

Positive Topline Data Announced from the Global Phase 3 AGILE Study of Ivosidenib in Combination with Azacitidine in Patients with Previously Untreated IDH1-mutated AML

- The global Phase 3 double blinded placebo controlled AGILE study of ivosidenib in combination with the chemotherapy azacitidine in adults with previously untreated IDH1-mutated acute myeloid leukemia (AML) met its primary endpoint of event-free survival (EFS)
- Treatment with ivosidenib in combination with azacitidine compared to azacitidine in combination with placebo demonstrated a statistically significant improvement in EFS. Additionally, the trial met all of its key secondary endpoints, including complete remission rate (CR rate), overall survival (OS), CR and complete remission with partial hematologic recovery rate (CRh rate) and objective response rate (ORR).
- The safety profile of ivosidenib in combination with azacitidine was consistent with previously published data.
- The study recently halted further enrollment based on the recommendation of the Independent Data Monitoring Committee (IDMC), as a difference of clinical importance was noted between the treatment groups.

https://www.prnewswire.com/news-releases/servier-announces-positive-topline-data-from-the-global-phase-3-study-of-tibsovo-ivosidenib-tablets-in-combination-with-azacitidine-in-patients-with-previously-untreated-idh1-mutated-acute-myeloid-leukemia-301345783.html

Case 2 presentation (IDH1-mutant AML)

- A 66 year old woman who presented to ER with a sore throat
- Workup revealed a posterior pharyngeal abscess and pancytopenia
- Labs: WBC 0.57, hgb 7.3 gm/dl, platelets 74K, 8% peripheral blasts
- P. smear: 8% blasts

- BMBx: AML with MDS-related changes, 41% blasts

- Cytogenetics: 48 XXder(7), t(1,7)(q21,q36), + 8, + 13
- NGS: **IDH1 R132C**, KRAS G12D, STAT5B, U2AF1
- PCR: FLT3-ITD negative

Case 2 presentation (IDH1-mutant AML) - Continued

Medical course

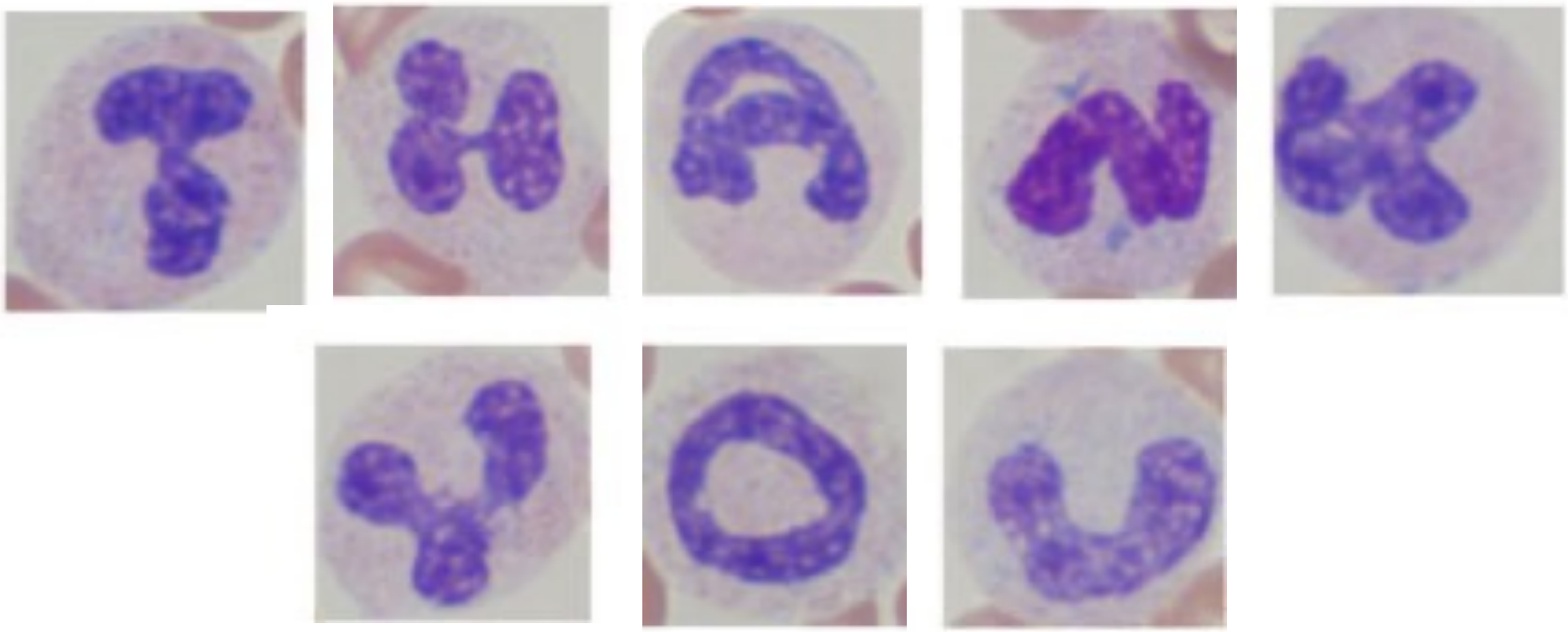
- Started on **venetoclax** (dose reduced for azole) **and azacitidine** induction therapy
- Day 21 BMBx: 40% cellularity, 3% blasts
- Venetoclax stopped, GM-CSF started; patient discharged home with count recovery
- Cycle 2 venetoclax + azacitidine
- BMBx after 2 cycles: Dysplastic marrow with residual AML (4% blasts, 3% promonocytes)

- Patient continued on Ven + Aza for additional 2 cycles with repeat marrow again showing residual AML (8% blasts)
- Cycle 5: Started **ivosidenib + azacitidine** therapy (venetoclax discontinued)

Case 2 presentation (IDH1-mutant AML) - Continued

- Disease continued to progress
- Cycle 7: Triple therapy with **ivosidenib + azacitidine + venetoclax** initiated
- Disease stabilized for an additional 3 cycles
- Repeat BMBx after cycle 10 showed progressive AML with 14% blasts

- Patient admitted for clinical trial of novel immunotherapy
- Unfortunately, patient died shortly thereafter of clinical cytokine release syndrome with respiratory failure



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