

# **The Gold Standard in the Use of FLT3 and IDH Inhibitors in AML**

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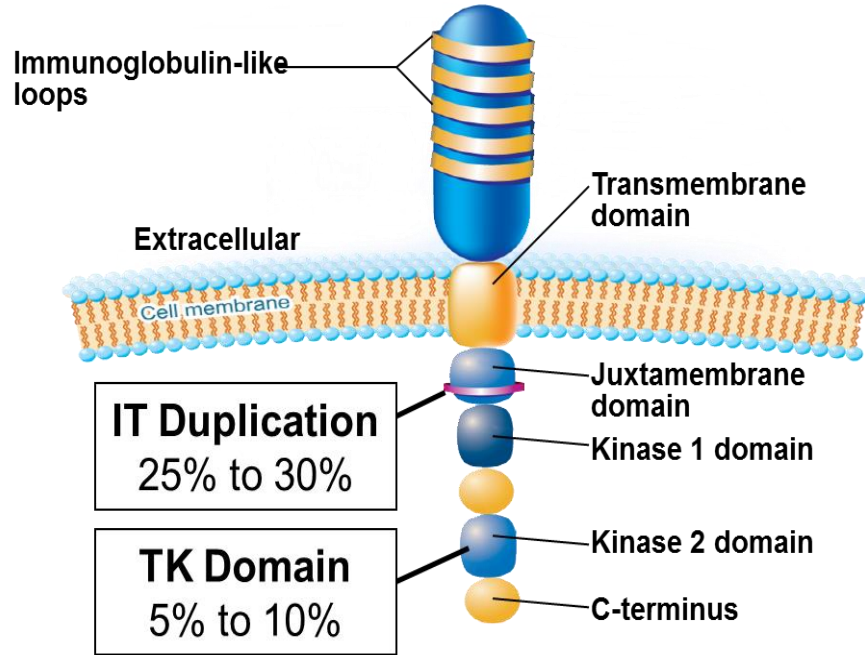
Moffitt Cancer Center

Tampa, FL

# Disclosures

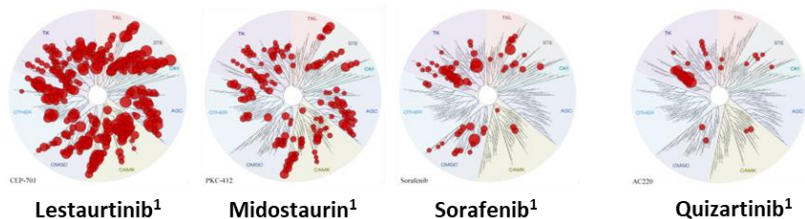
- Consulting: Treadwell Therapeutics, Bristol Myers Squibb, Moderna, AbbVie
- Research Funding: AbbVie

# Activated FLT3 Mutations in AML



Characterized by high relapse rate, poor prognosis

# Selectivity and potency of FLT3 Inhibitors



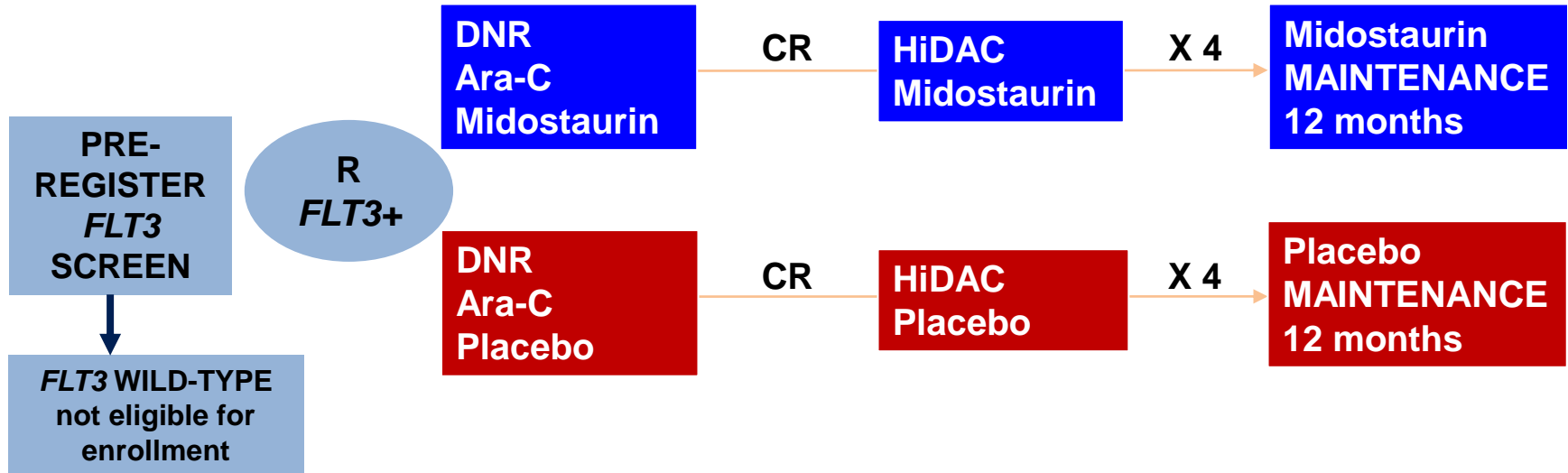
First-generation multikinase inhibitors<sup>2</sup>

Second-generation FLT3 inhibitor<sup>3</sup>

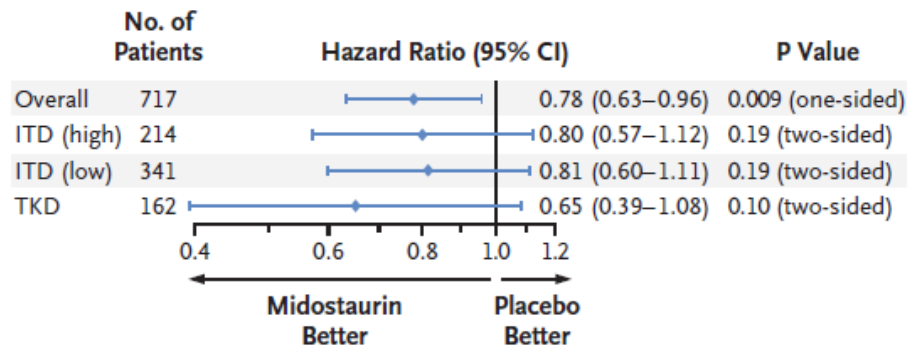
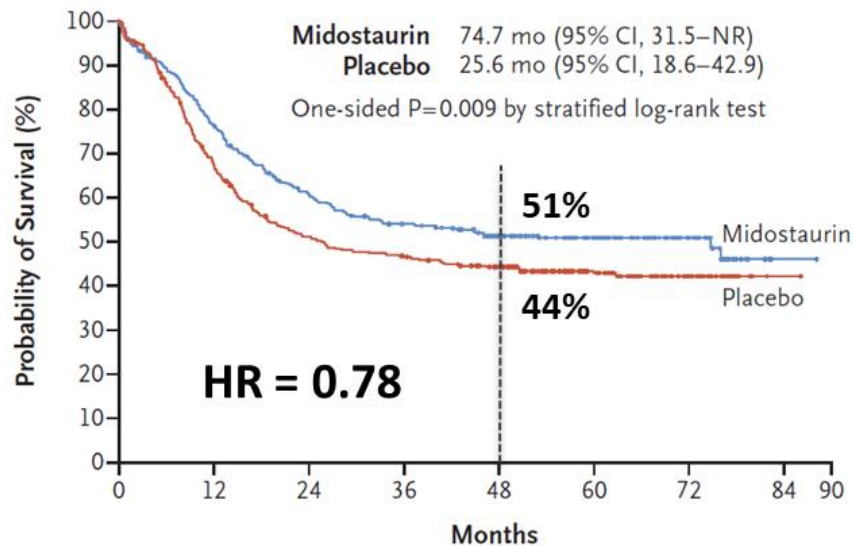
		IC <sub>50</sub> (medium)	IC <sub>50</sub> (plasma)	Single agent clinical activity	Kinase inhibition
1 <sup>st</sup> generation	Lestaurtinib	2 nM	700 nM	-	Type 1
	Midostaurin	6 nM	~1000 nM	-	Type 1
	Sorafenib	3 nM	~265 nM	+/-	Type 2
2 <sup>nd</sup> generation	Quizartinib	1 nM	18 nM	+	Type 2
	Crenolanib	2 nM	48 nM	+	Type 1
	Gilteritinib	3 nM	43 nM	+	Type 1

1. Davis MI, et al. *Nat Biotechnol.* 2011;29:1046-1051.
2. Stone R, et al. *N Engl J Med.* 2017;377:454-464.
3. Zarrinkar P, et al. *Blood.* 2009;114:2984-2992.
4. Cortes JE, et al. *J Clin Oncol.* 2013;31:3681-3687.

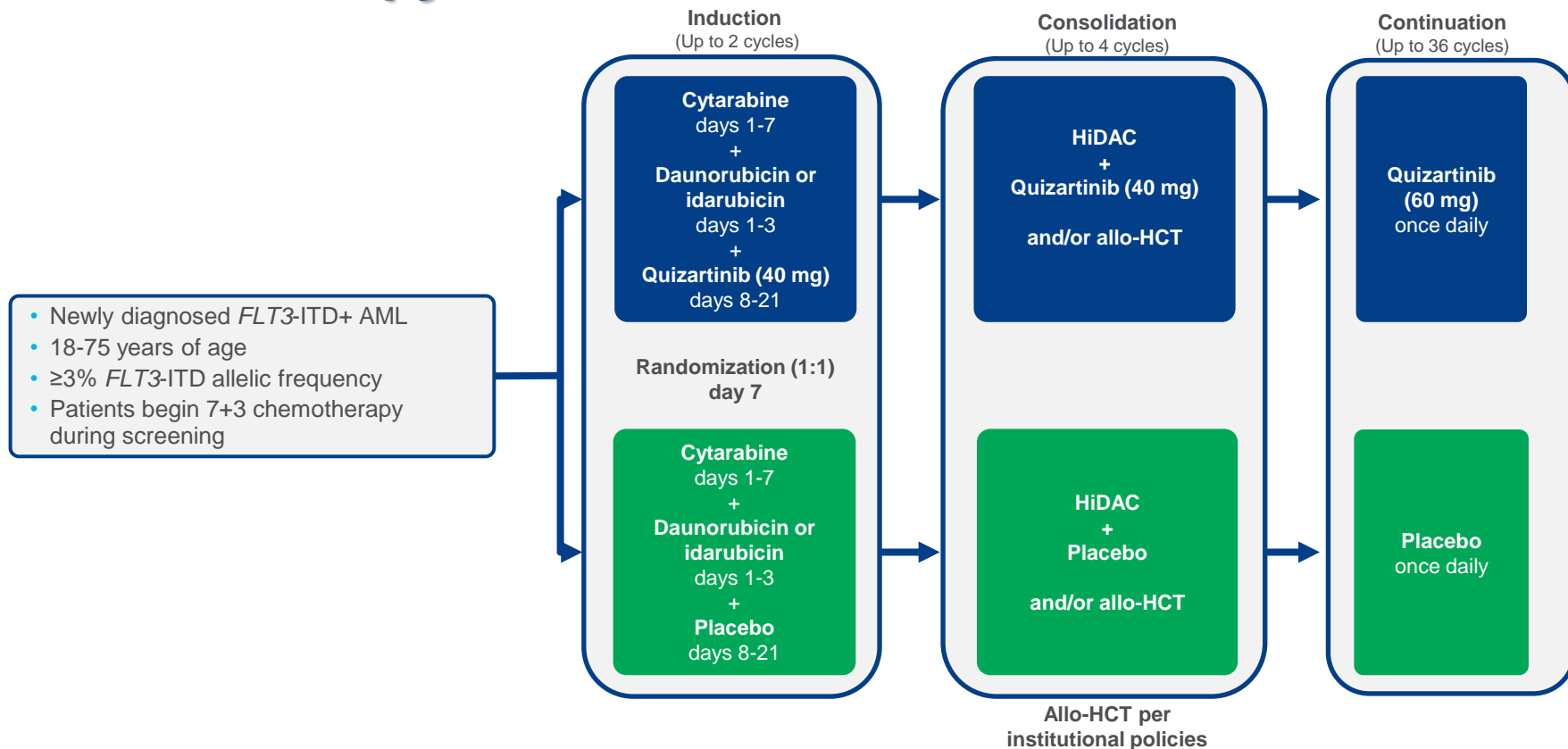
# C10603/RATIFY Schema



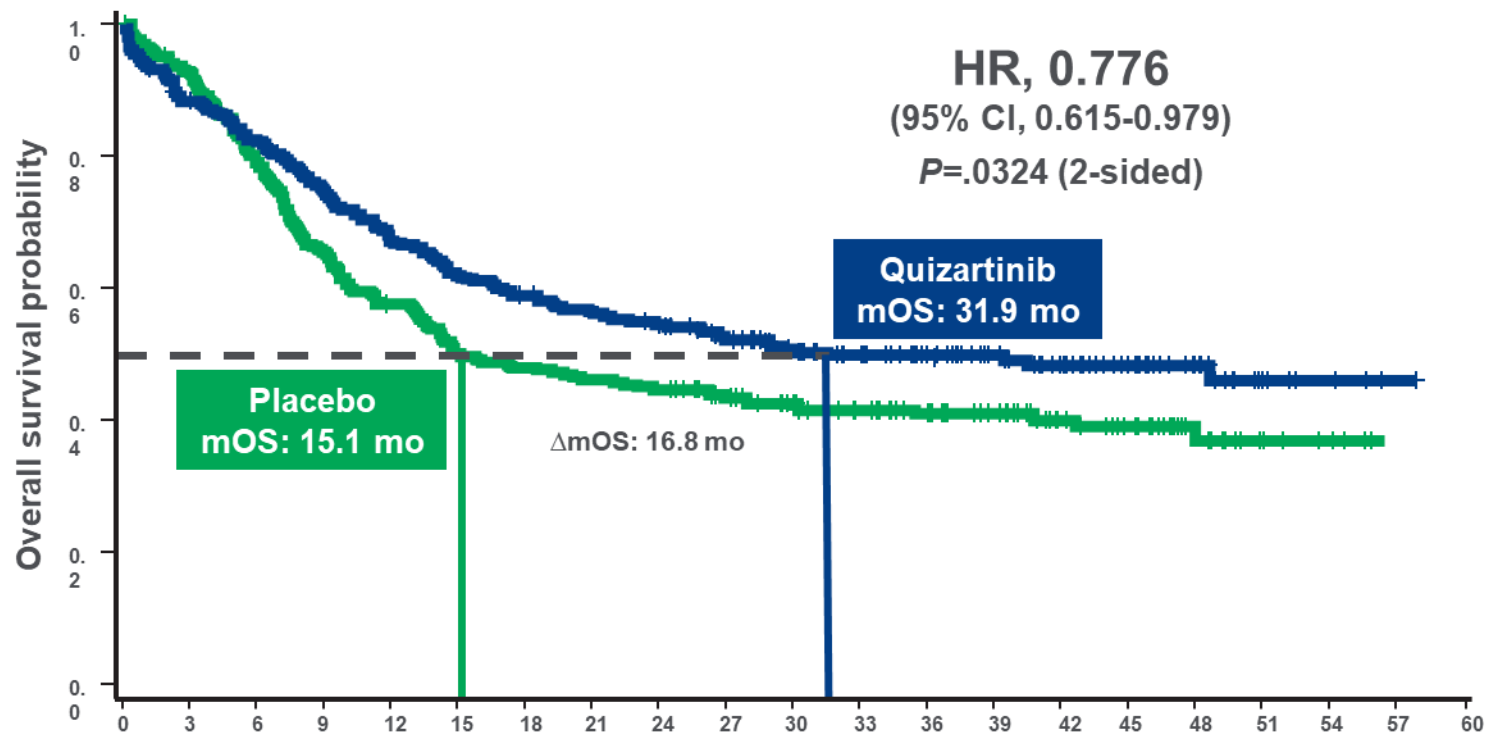
# Overall Survival



# QuANTUM-FIRST Phase 3 Trial: Induction Chemotherapy +/- Quizartinib



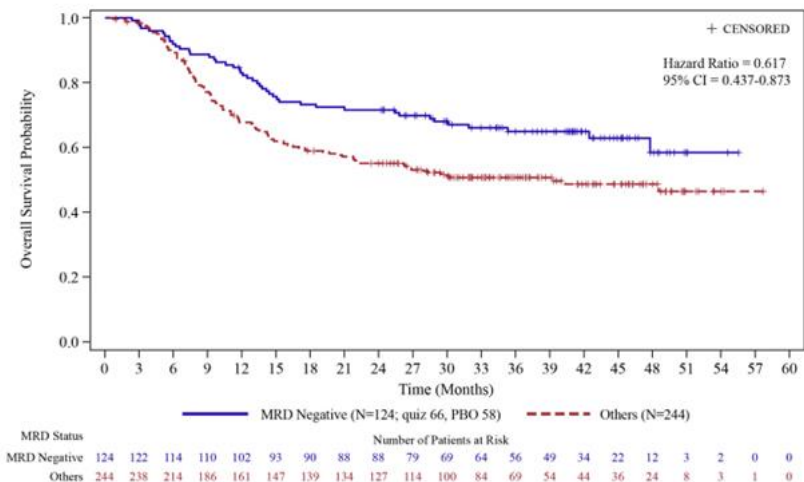
# Overall Survival



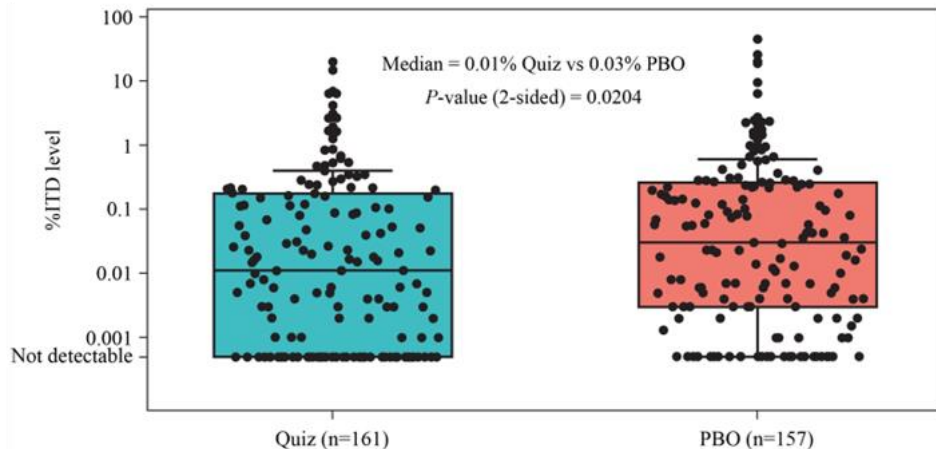


# QuANTUM-First: *FLT3*-ITD–Specific MRD Clearance Is Associated With Improved OS

Percentage of patients in CRc with *FLT3*-ITD MRD of  $<10^{-4}$  was similar across study arms (24.6% quiz vs 21.4% PBO,  $P = 0.385$ )

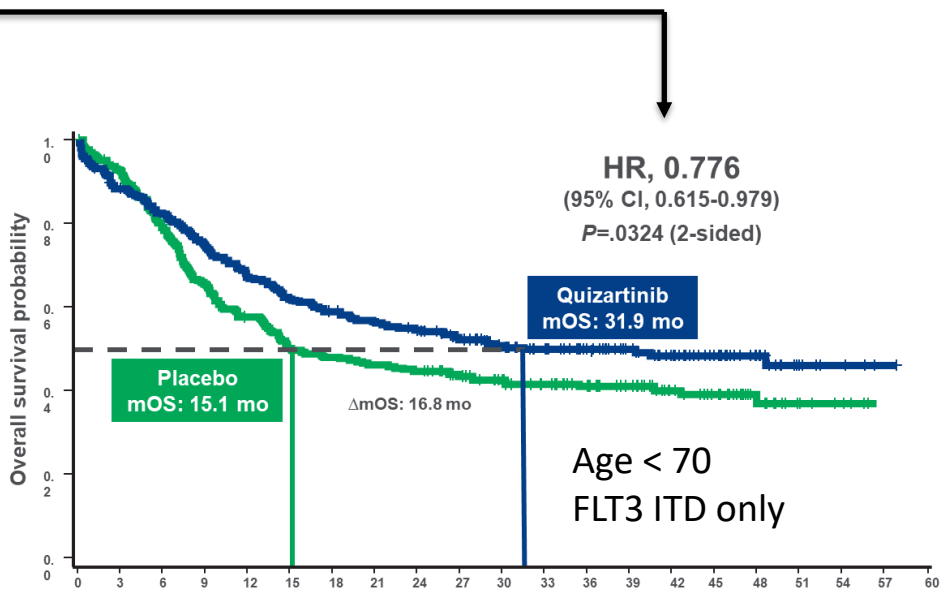
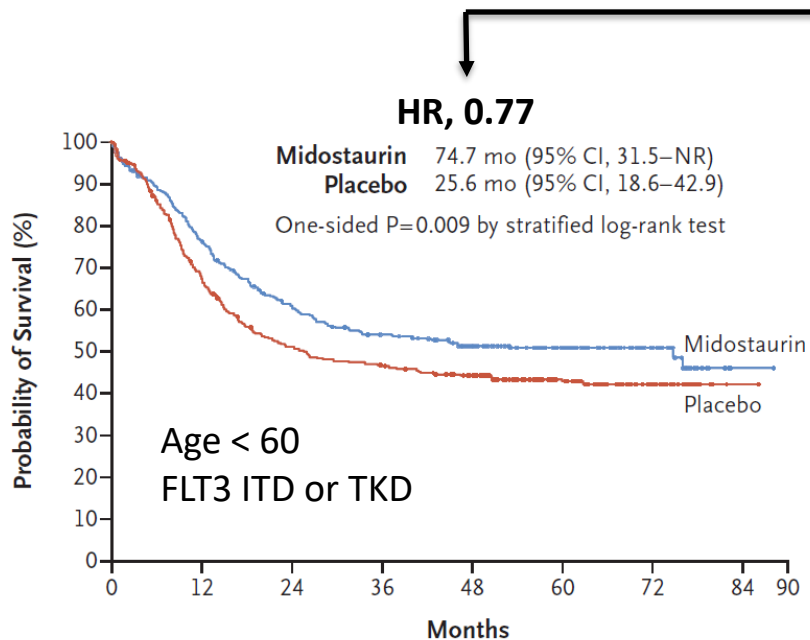


Percentage of patients in CRc with undetectable MRD ( $< 1 \times 10^{-5}$ ) was greater with quizartinib (13.8% vs 7.4%,  $P = 0.017$ ).



Long-term survival benefits conferred by quizartinib in the QuANTUM-First may in part derive from an early and deep reduction of the *FLT3*-ITD+ leukemia burden

# Midostaurin or Quizartinib in Newly Diagnosed FLT3+ AML????



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# No Data Comparing 2<sup>nd</sup> Generation FLT3 Inhibitors vs Midostaurin!

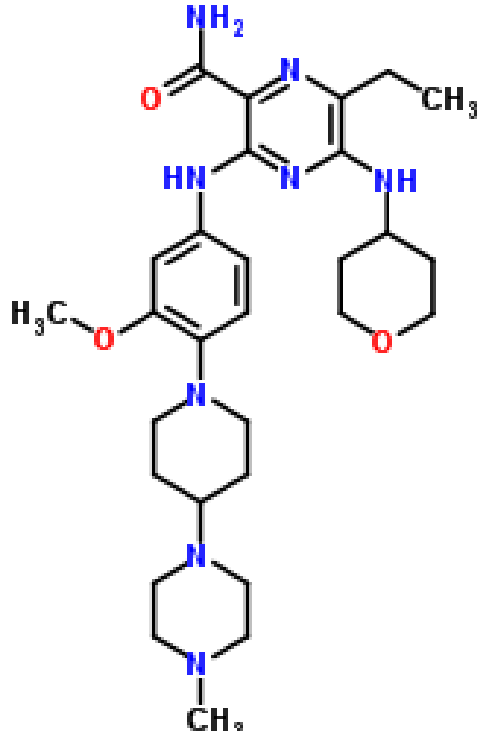
## **HOVON 156 AML Trial: Phase 3, Midostaurin + Induction vs Gilteritinib + Induction**

- Last patient enrolled June 2023 -
- Endpoint analysis expected October 2025

## **Crenolanib versus midostaurin combined with induction and consolidation chemotherapy in newly diagnosed *FLT3* mutated AML**

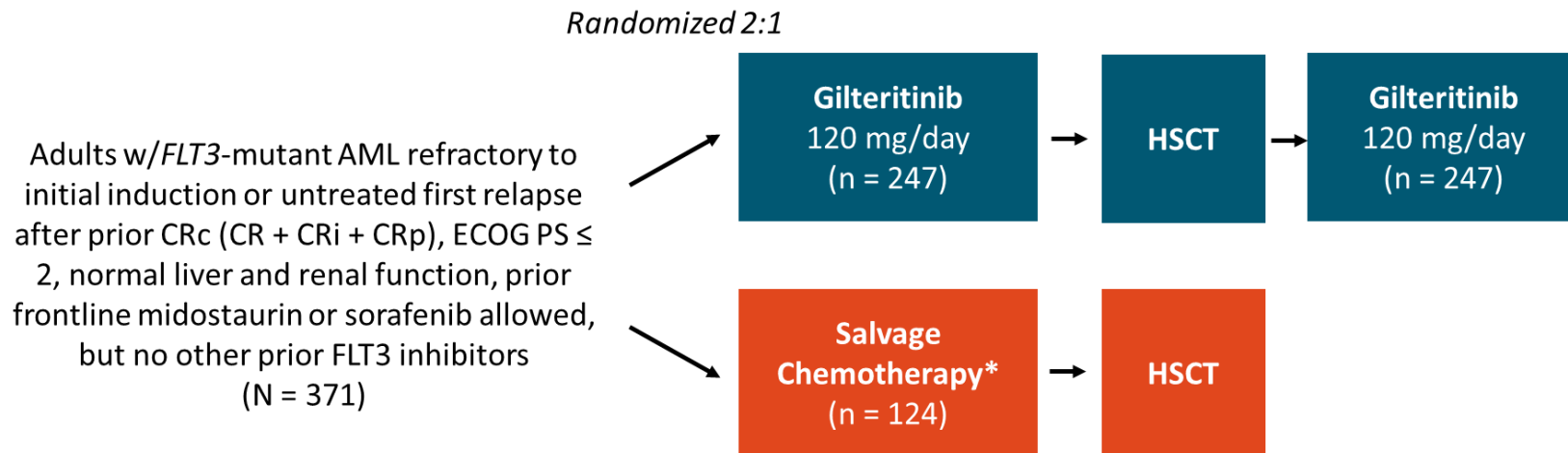
- ON HOLD

# Gilteritinib



- A highly potent, selective FLT3/AXL inhibitor with activity in vitro against FLT3-ITD and FLT3-D835<sup>4-6</sup>

# Phase III ADMIRAL Study: Gilteritinib in *FLT3*-Mutant R/R AML

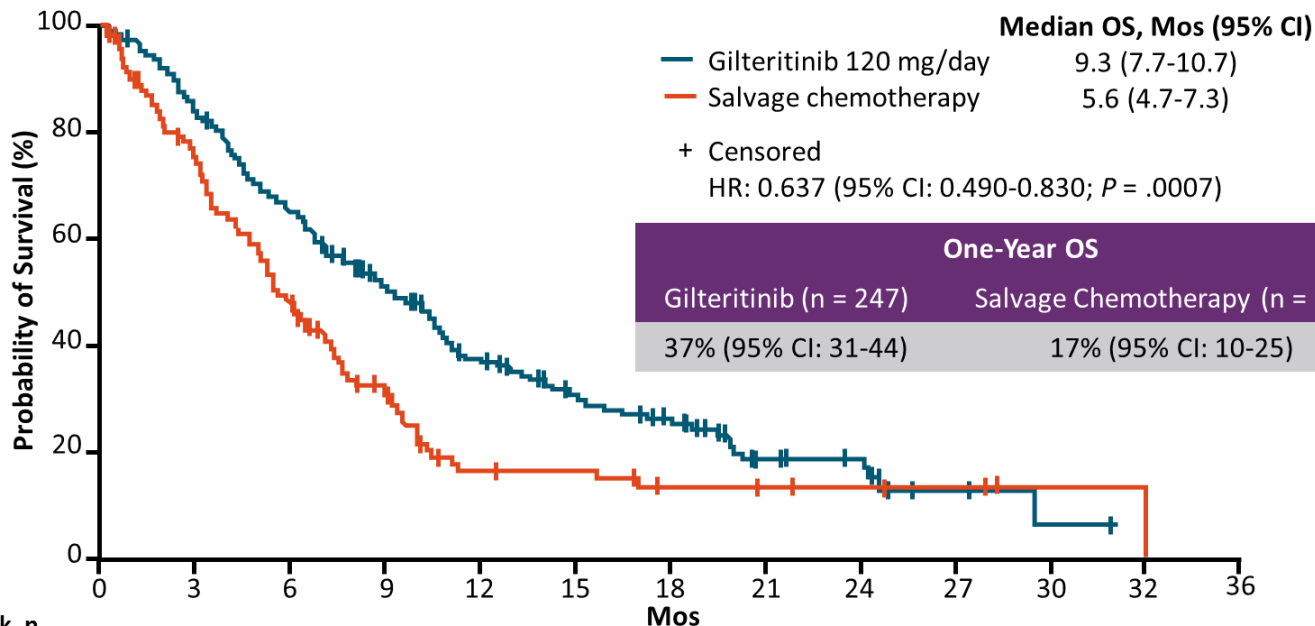


\*Salvage chemotherapy selected prior to randomization: MEC + FLAG-IDA (high intensity) for 1-2 cycles; Low-dose cytarabine + azacytidine (low intensity) administered until disease progression or intolerance

- Primary endpoints: OS, CR/CRh rate
- Secondary endpoints: EFS, CR rate

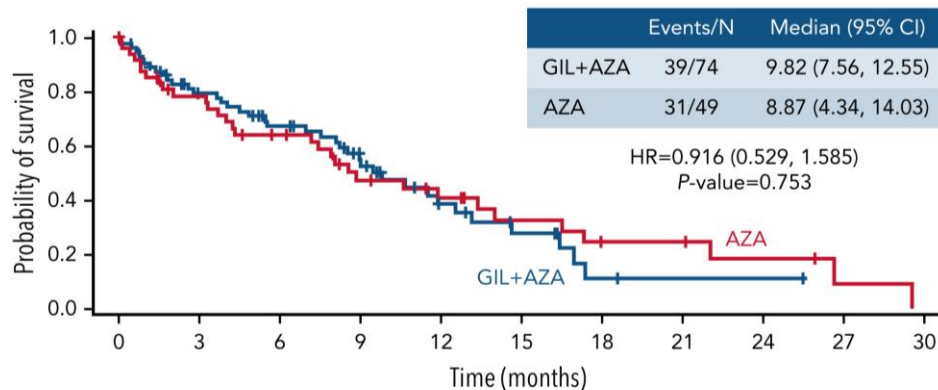
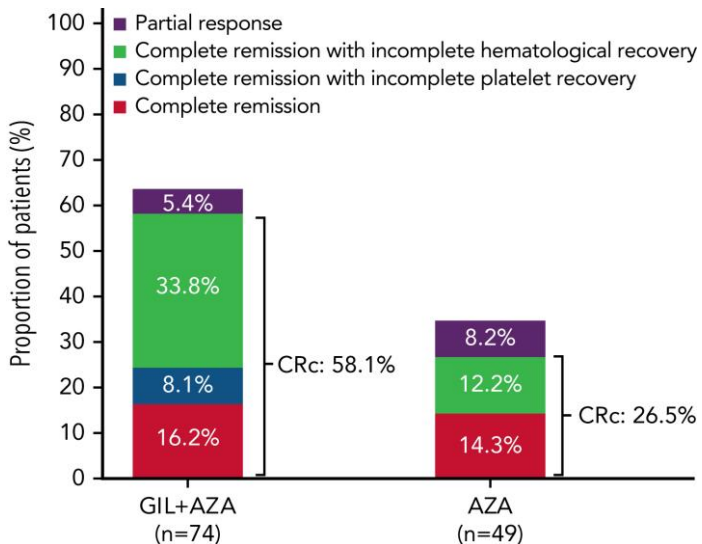
# Gilteritinib Prolongs OS in *FLT3*-Mutant R/R AML

CR + CRi + CRp = 52% in prior TKI



Patients at Risk, n	Mos													
	0	3	6	9	12	15	18	21	24	27	30	32	36	
Gilteritinib 120 mg/day	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	

# Phase 3 Trial of Gilteritinib + Azacitidine versus Azacitidine for Newly Diagnosed *FLTm+* AML Ineligible for Intensive Chemotherapy



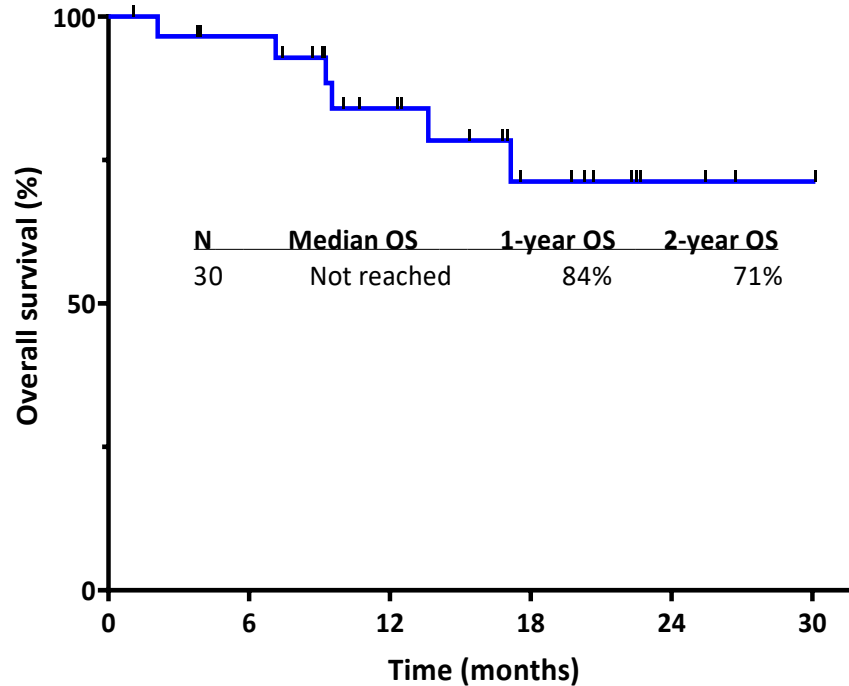
	Patients at risk (n)										
GIL+AZA	74	47	36	25	12	7	2	1	1	0	0
AZA	49	33	25	16	12	8	5	5	3	1	0

Baseline <i>FLT3</i> mutation type	ITD alone	TKD (D835/1836) alone	ITD with TKD (D835/1836)	ITD allelic ratio <0.5	ITD allelic ratio ≥0.5	TKD
	28/58 (48.3)	10/14 (71.4)	1/2 (50.0)	11/25 (44.0)	18/35 (51.4)	10/14 (71.4)
	26/40 (65.0)	4/7 (57.1)	1/2 (50.0)	13/18 (72.2)	14/24 (58.3)	4/7 (57.1)
	0.709 (0.412, 1.222)	2.504 (0.746, 8.411)	>999 (<0.001, NE)	1.279 (0.526, 3.107)	0.580 (0.285, 1.182)	2.504 (0.746, 8.411)
	0.216	0.138	1.000	0.587	0.134	0.138

Wang ES, et al. *Blood* 2022; 140(17): 1845-1857.

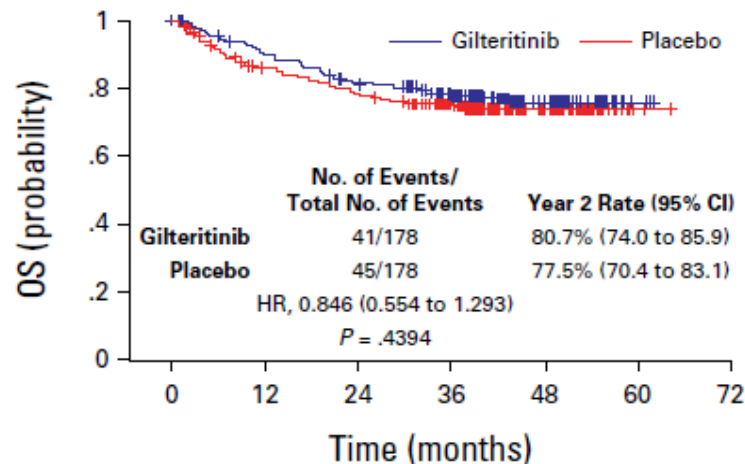
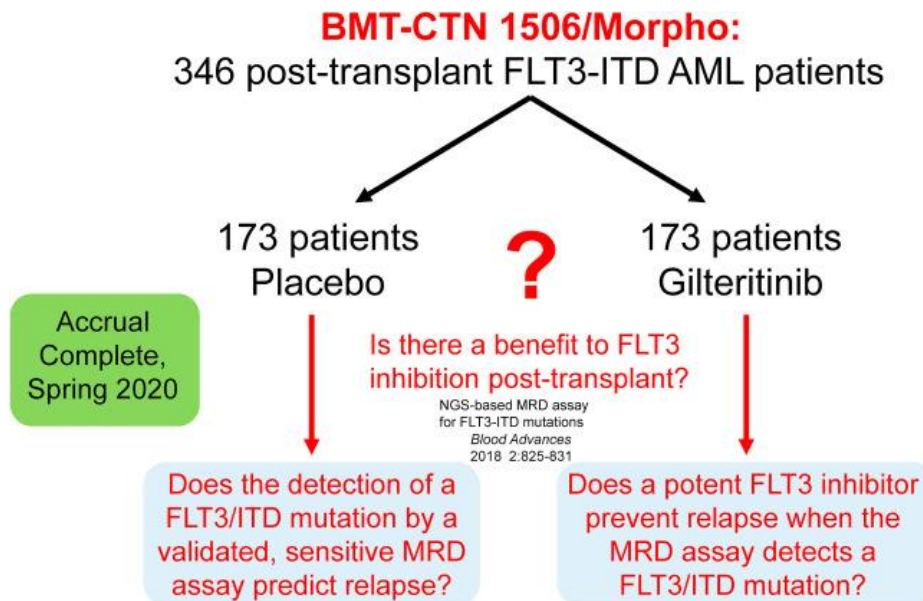
Favors GIL+AZA ← | → Favors AZA

# Azacitidine, Venetoclax, and Gilteritinib in Newly Diagnosed FLT3+ AML

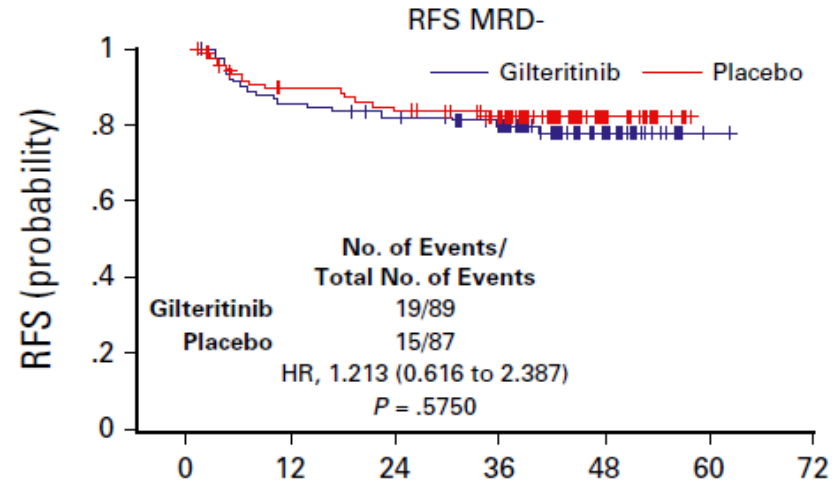
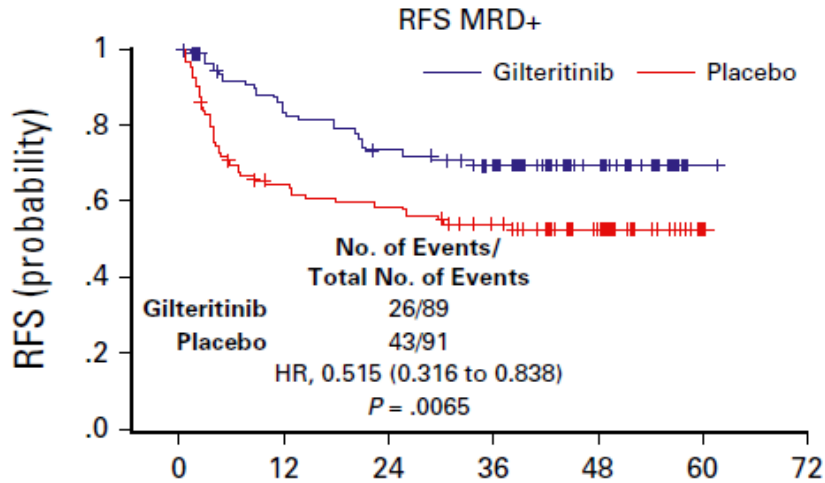




# FLT3 Inhibitors Post Transplant – BMT-CTN 1506/Morpho Study



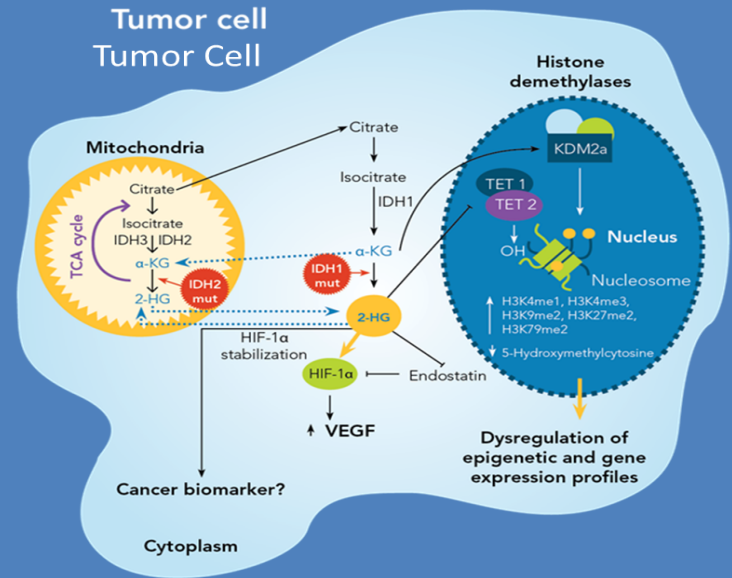
# FLT3 Inhibitors Post Transplant – BMT-CTN 1506/Morpho Study



MRD-positive = MRD  $\geq 10^{-6}$  pre-transplant and/or day 30-90 post-transplant

# Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

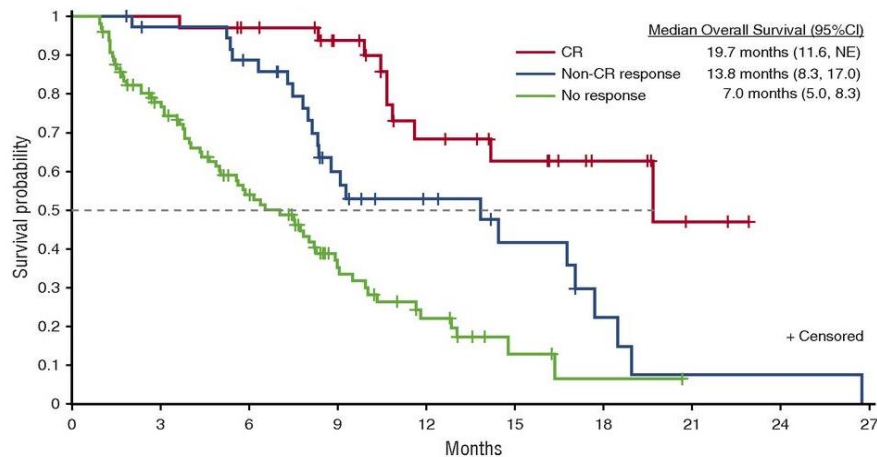
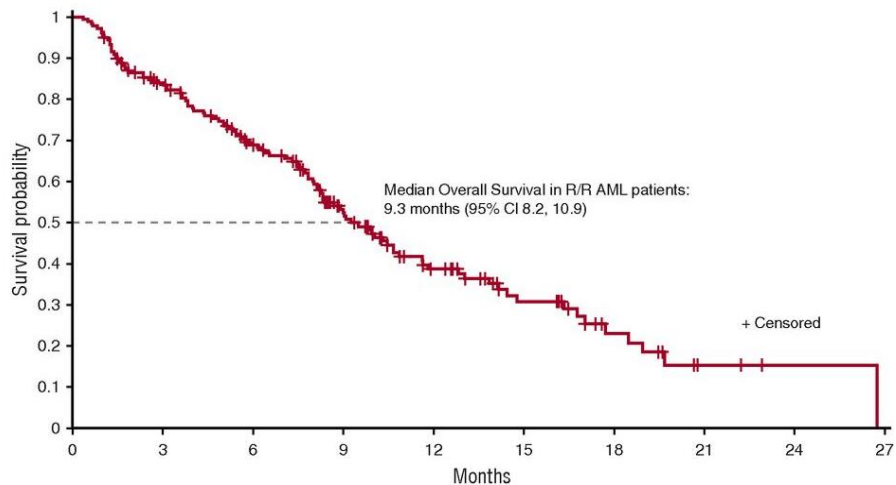
- IDH is an enzyme of the citric acid cycle
- Mutant *IDH2* produces 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation
- AG-221 (CC-90007) is a selective, oral, potent inhibitor of the mutant *IDH2* (*mIDH2*) enzyme



AML, acute myeloid leukemia; IDH, isocitrate dehydrogenase; 2-HG, 2-hydroxyglutarate; *mIDH2*, mutated IDH2

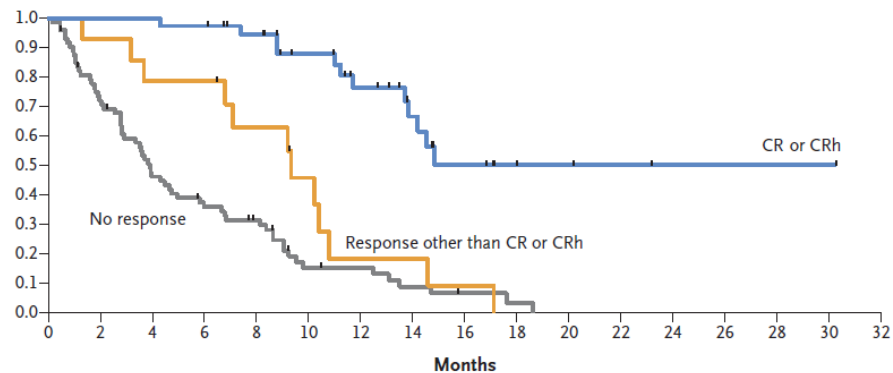
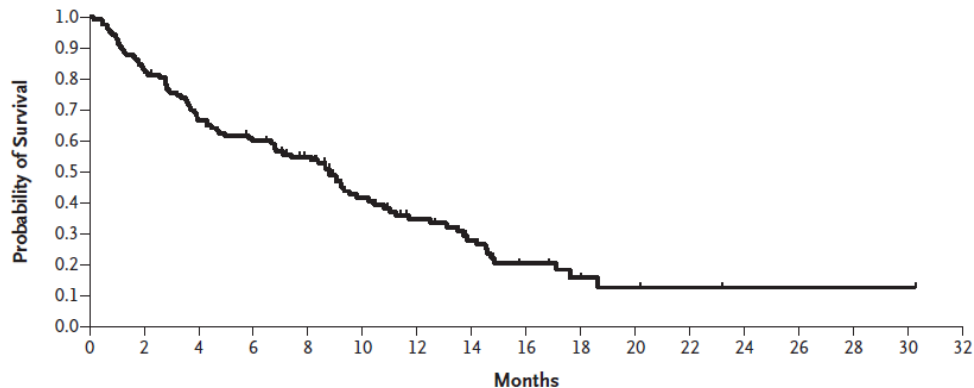
# Enasidenib (IDH2 inhibitor) in Relapsed/Refractory AML

Overall response rate = 38.8%  
CR + CRi/CRp = 29%



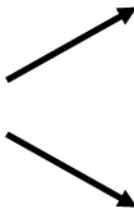
# Ivosidenib (IDH1 Inhibitor) in Relapsed/Refractory AML

Overall response rate = 41.6%  
CR + CRi/CRp = 30%



# AGILE: Phase 3 Azacitidine +/- Ivosidenib in Newly Diagnosed *IDH1* mutated AML

Patients with untreated AML (WHO criteria); centrally confirmed *IDH1* mutation status; ineligible for IC; ECOG PS 0-2 (planned N = 200)



The diagram shows two arrows originating from the eligibility criteria text. The top arrow points to the Ivosidenib treatment arm, and the bottom arrow points to the Placebo treatment arm.

Ivosidenib 500 mg PO QD +  
Azacitidine 75 mg/m<sup>2</sup> SC or IV  
(n = 72)\*

Placebo PO QD +  
Azacitidine 75 mg/m<sup>2</sup> SC or IV  
(n = 74)\*

\*Enrollment at time of data cutoff (May 18, 2021).

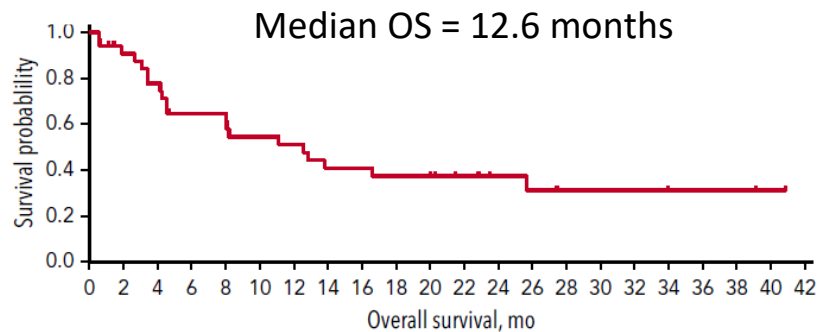
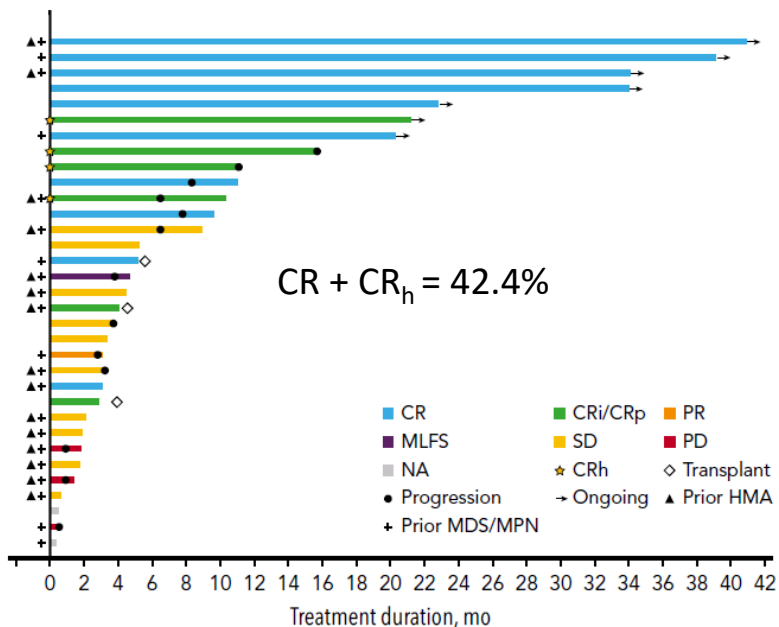
- Enrollment halted based on efficacy as of May 12, 2021 (N = 148)
- **Primary endpoint:** EFS with ~173 events (52 mo)
- **Secondary endpoints:** CRR, OS, CR + CRh rate, ORR

# AGILE: Phase 3 Azacitidine +/- Ivosidenib in Newly Diagnosed *IDH1* mutated AML

Survival Outcome	IVO + AZA	PBO + AZA	HR (95% CI)	P Value
Median EFS in ITT population	NR	NR	0.33 (0.16-0.69)	.0011
Median EFS in patients achieving CR by Wk 24, mo (95% CI)	NE (14.8-NE)	17.8 (9.3-NE)	NR	NR
Median OS, mo	24.0	7.9	0.44 (0.27-0.73)	.0005

Response rates, % (95% CI)	IVO + AZA	PBO + AZA
Overall Response	62.5 (50.3-73.6)	18.9 (10.7-29.7)
Complete Response	47.2 (35.3-59.3)	14.9 (7.7-25.0)

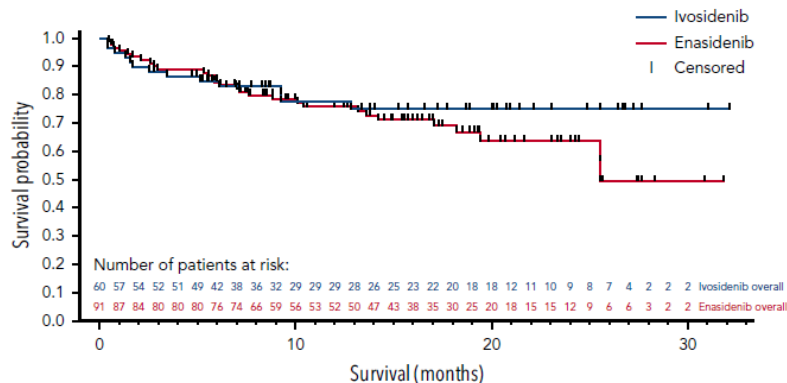
# Ivosidenib Monotherapy in Newly Diagnosed AML



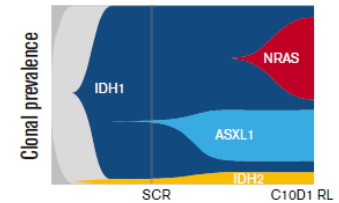
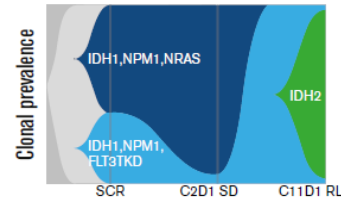
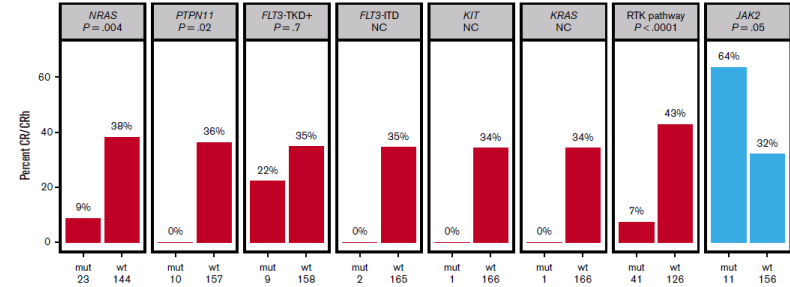
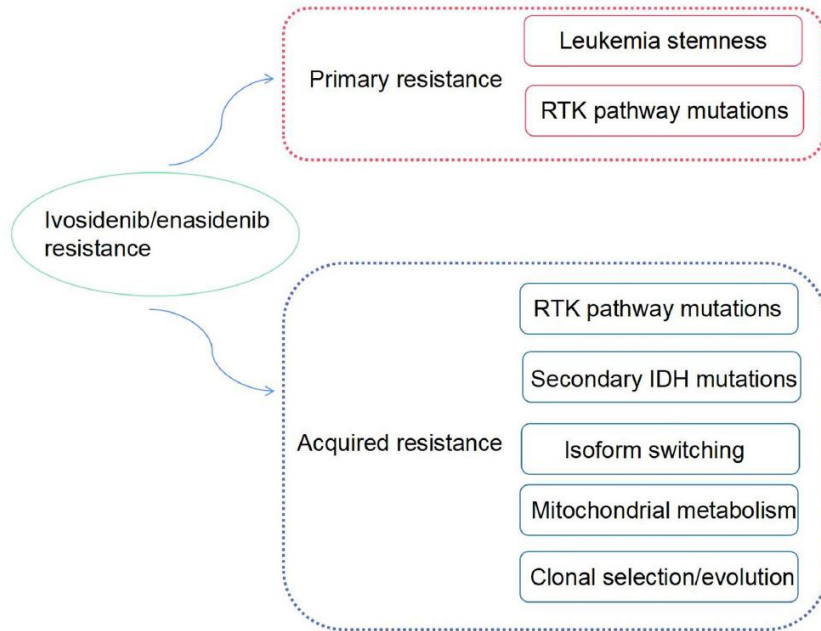


# Combining IDH Inhibitors with Induction Chemotherapy

Response category	Ivosidenib 500 mg + chemotherapy, n (%)			Enasidenib 100 mg + chemotherapy, n (%)		
	All, N = 60	De novo AML, n = 42	Secondary AML, n = 18	All, N = 91*	De novo AML, n = 56	Secondary AML, n = 35
CR/CRi/CRp	46 (77)	37 (88)	9 (50)	67 (74)	45 (80)	22 (63)
CR	41 (68)	32 (76)	9 (50)	50 (55)	36 (64)	14 (40)
CRi/CRp	5 (8)	5 (12)	—	17 (19)	9 (16)	8 (23)
MLFS	4 (7)	3 (7)	1 (6)	10 (11)	5 (9)	5 (14)
PR	2 (3)	—	2 (11)	2 (2)	1 (2)	1 (3)
Treatment failure†	8 (13)	2 (5)	6 (33)	12 (13)	5 (9)	7 (20)



# Resistance to IDH inhibitors



Zhuang, et al. Front Oncol 2022  
 Choe, et al. Blood Adv 2020; 4:1894

# IDH Inhibitor Differentiation Syndrome

- 10-15% patients
- May occur LATE
- High blasts, Higher LDH
  - Higher risk
- Tx: Steroids, support, hold drug
- Consider: Hydrea if high WBC

Table 1. Frequency of Signs and Symptoms Consistent With IDH-DS<sup>a</sup>

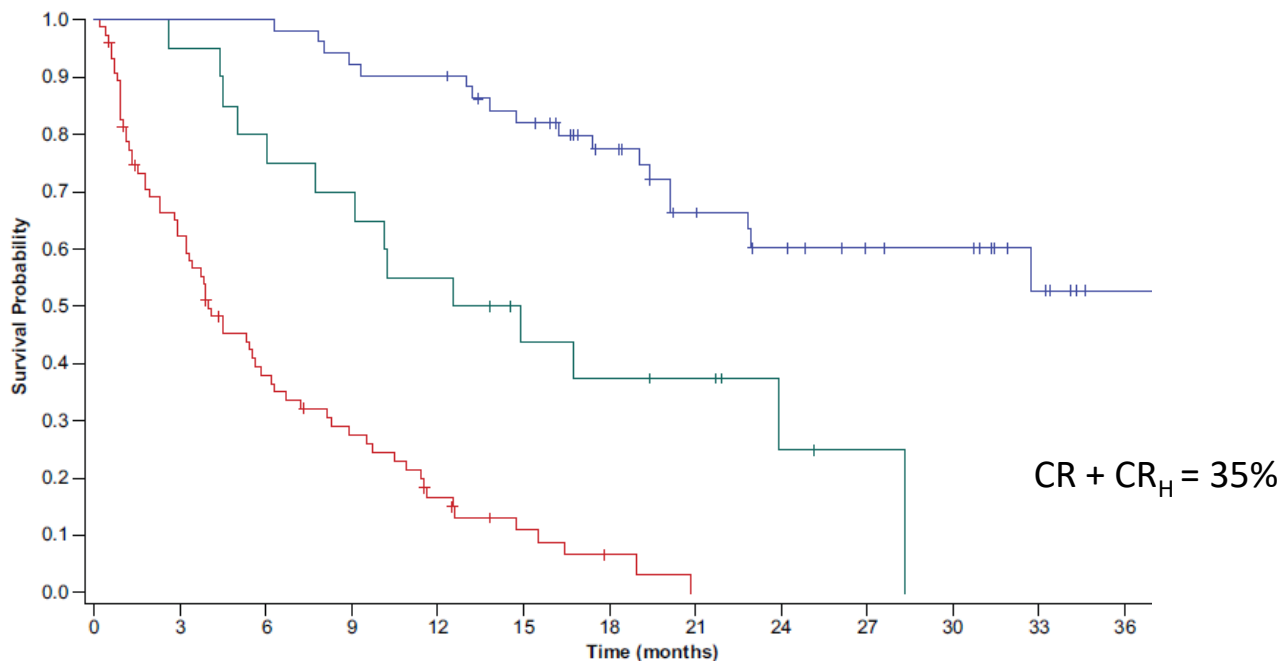
Sign or Symptom	Patients With IDH-DS, No. (%) (n = 33) <sup>b</sup>
Dyspnea	28 (85)
Unexplained fever (body temperature of 38.0°C for 2 d)	26 (79)
Pulmonary infiltrates	24 (73)
Hypoxia	19 (58)
Acute kidney injury (CTCAE grade ≥2)	14 (42)
Pleural effusion	14 (42)
Bone pain or arthralgia	9 (27)
Lymphadenopathy	8 (24)
Rash	8 (24)
Disseminated intravascular coagulopathy	7 (21)
Edema or weight gain of >5 kg from screening	7 (21)
Pericardial effusion	5 (15)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events<sup>14</sup>; IDH-DS, isocitrate dehydrogenase differentiation syndrome.

<sup>a</sup> Signs and symptoms included in this table are based on retrospective differentiation syndrome review committee review of clinical records.

<sup>b</sup> Patients may have had multiple symptoms.

# Olutasidenib: New IDH1 Inhibitor for R/R AML



CR/CR <sub>H</sub> :	51	51	51	47	46	40	31	23	18	14	13	7	1
Other Responders:	20	19	16	14	11	7	6	5	2	1	0	0	0
Non-Responders:	76	45	26	18	10	5	2	0	0	0	0	0	0

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# Summary

- FLT3 and IDH inhibitors are changing the AML landscape
- FLT3 inhibitors combined with induction improve survival in *FLT3m*
  - Role in combination with low intensity therapies still unclear
- Role of FLT3 inhibitors in maintenance therapy remains unclear
- IDH inhibitors have disease modifying capacity as single agents and in combination with HMA/Ven.
- IDH inhibitor resistance is multifactorial
  - High sensitivity and single cell sequencing may be critical to abrogate emergence of resistance

# THANK YOU

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