Optimal Treatment Approaches for AML with Targetable Mutations

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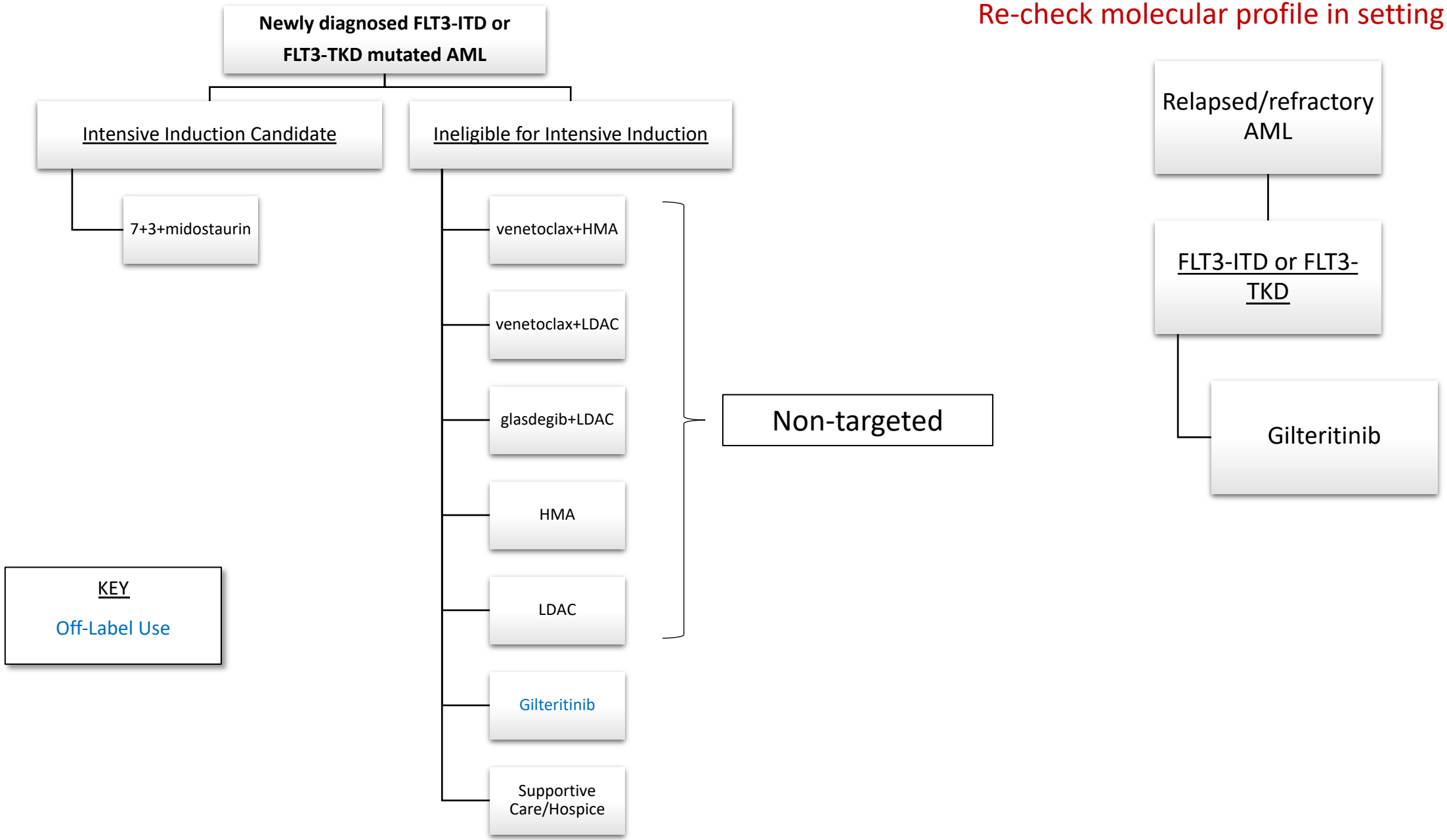
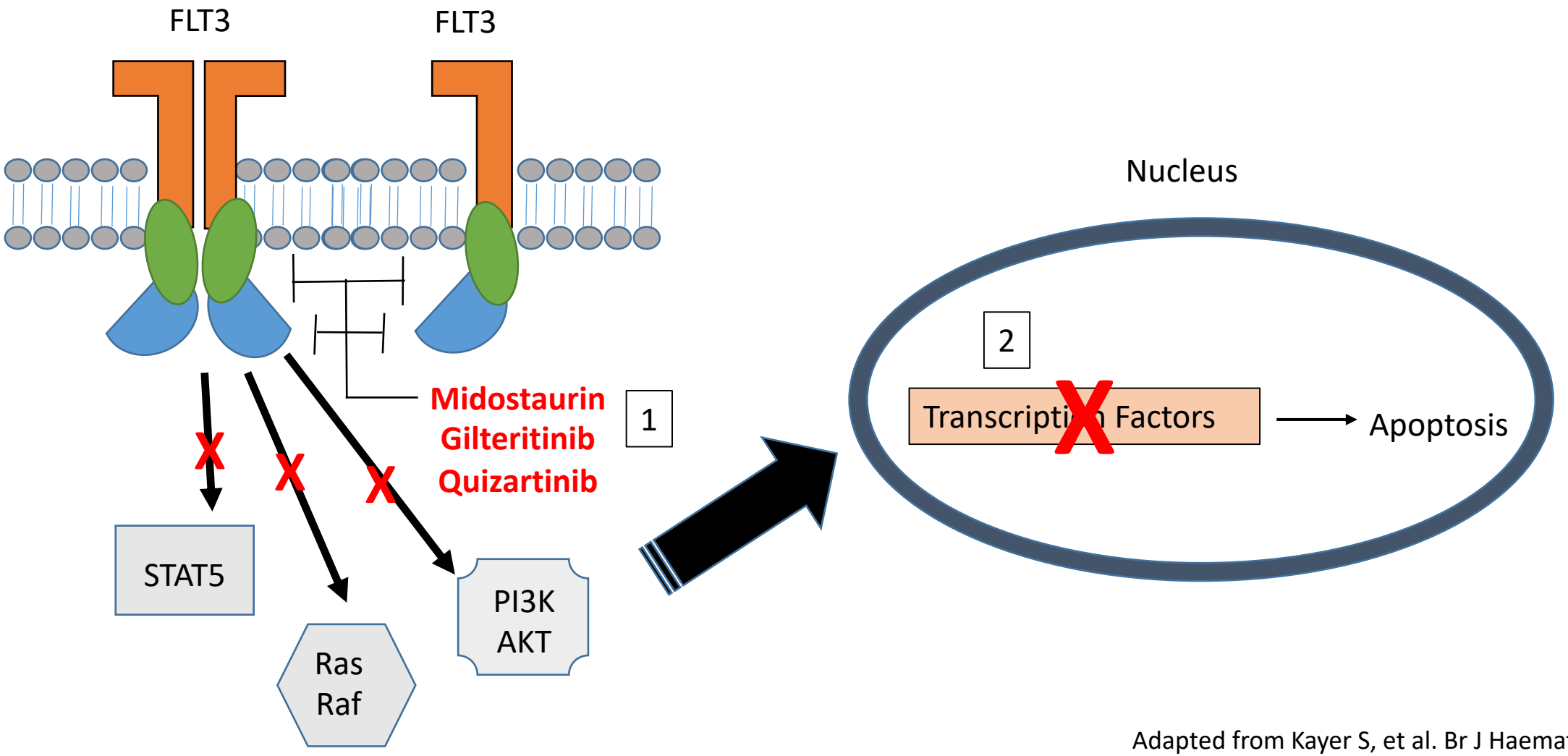
Learning Objectives

- Optimal approaches to the management of newly diagnosed or relapsed/refractory (R/R) AML with a *FLT3* mutation
- Available data with and ongoing clinical trials of investigational FLT3 inhibitors for patients with newly diagnosed and progressive AML
- Optimal integration of ivosidenib into current management paradigms for patients with newly diagnosed and R/R *IDH1*-mutant AML
  - Available and emerging data from the Phase III AGILE study of ivosidenib/azacitidine as front-line therapy
- Long-term data supporting the use of enasidenib in R/R *IDH2*-mutant AML
  - Early data with and ongoing evaluation in patients with newly diagnosed disease
- Efficacy observed with the use of venetoclax-based therapy in patients with *FLT3* or *IDH*1/2 mutations
  - Ongoing research efforts assessing venetoclax in combination with targeted therapy

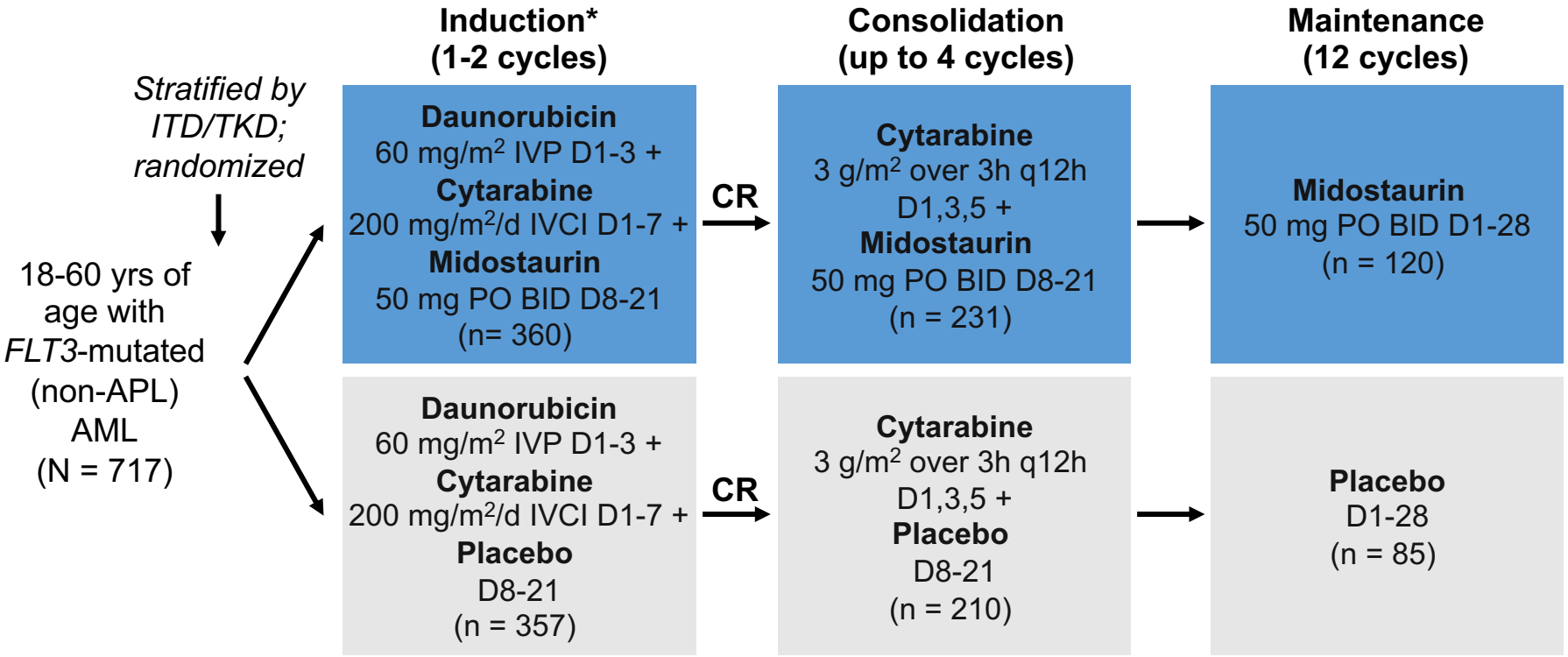

Newly diagnosed FLT3-ITD or FLT3-TKD mutated AML
Intensive Induction Candidate
Ineligible for Intensive Induction
7+3+midostaurin
venetoclax+HMA
venetoclax+LDAC
glasdegib+LDAC
HMA
LDAC
Non-targeted
Gilteritinib
Supportive Care/Hospice
KEY
Off-Label Use
Re-check molecular profile in setting of relapse
Relapsed/refractory AML
FLT3-ITD or FLT3-TKD
Gilteritinib

Mechanism of Action for FLT3 inhibitors (Midostaurin/Gilteritinib/Quizartinib)



Adapted from Kayer S, et al. Br J Haematol 2021

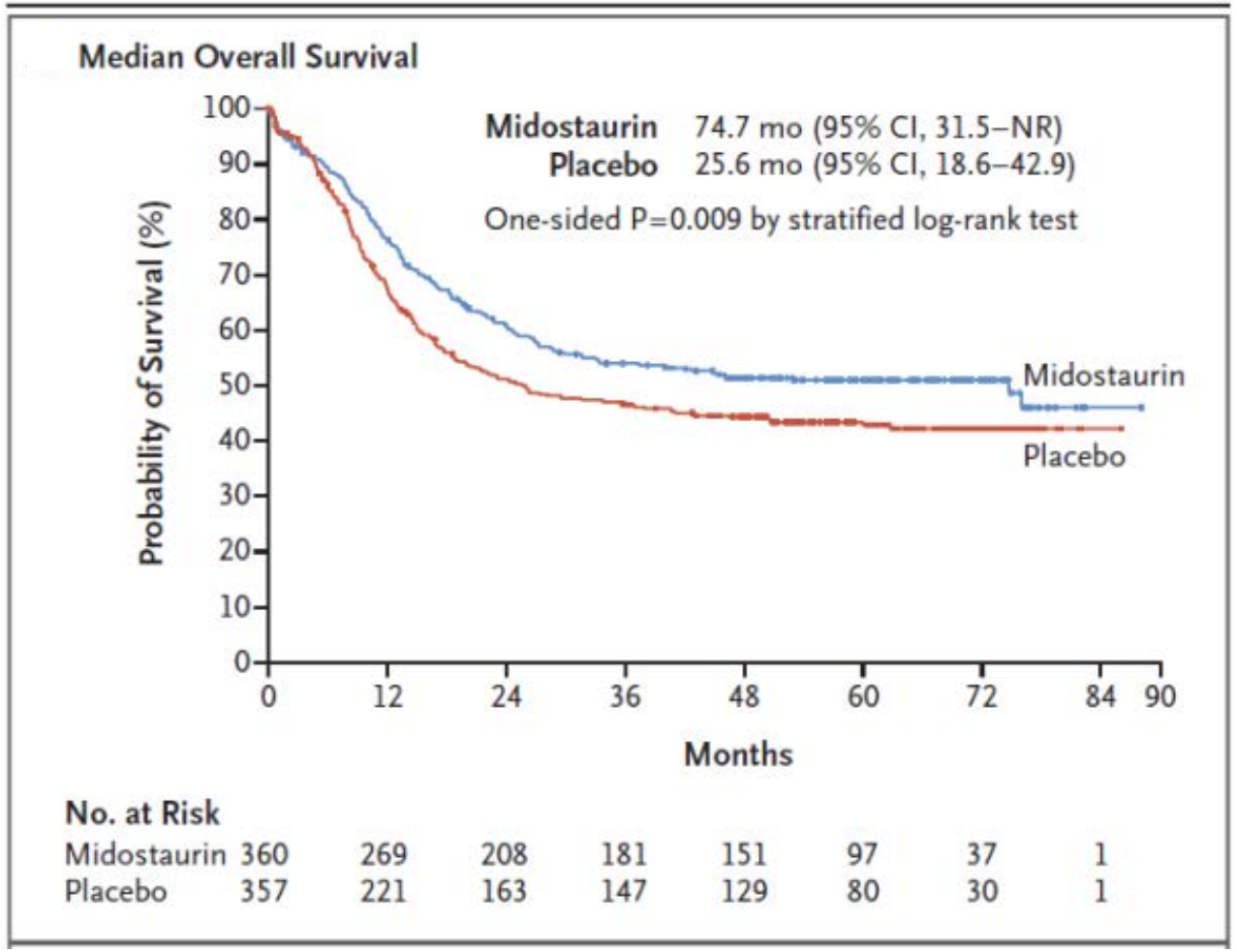
RATIFY: Study Design



- Double-blind, placebo-controlled, randomized phase III study
  - Primary endpoint: OS (not censored for SCT)
  - Secondary endpoint: EFS

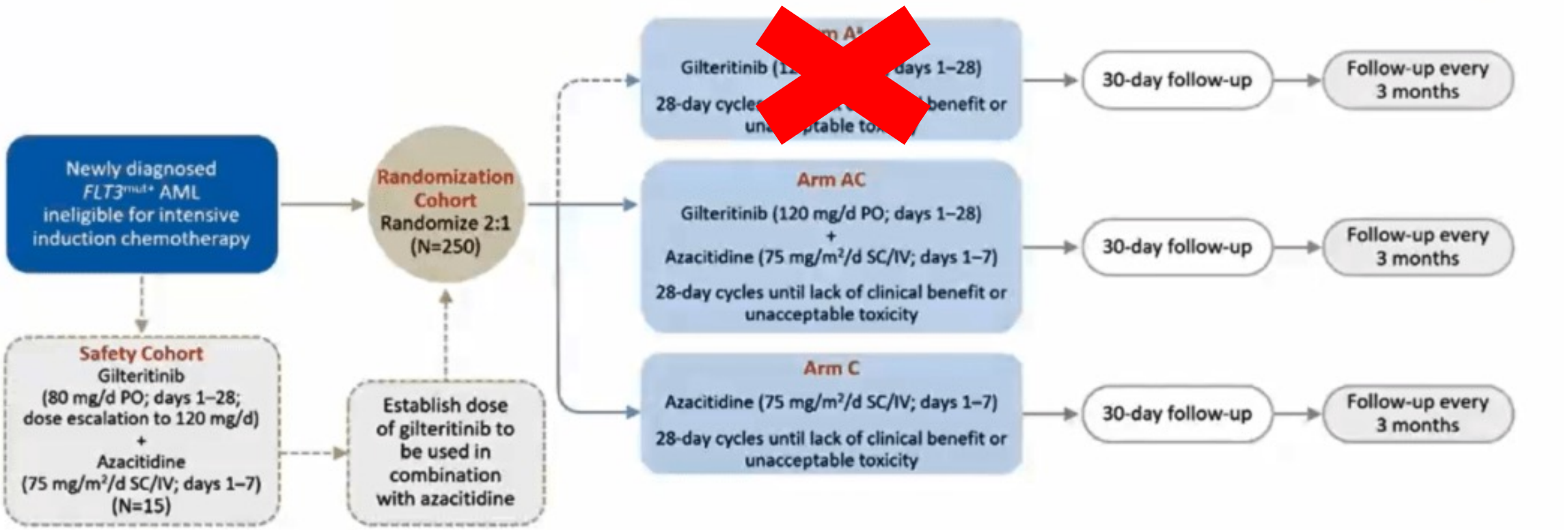
Stone R, et al. N Engl J Med 2017

RATIFY Study: Overall Survival (Primary ITT Analysis)



Stone R, et al. N Engl J Med 2017

LACEWING Study Design



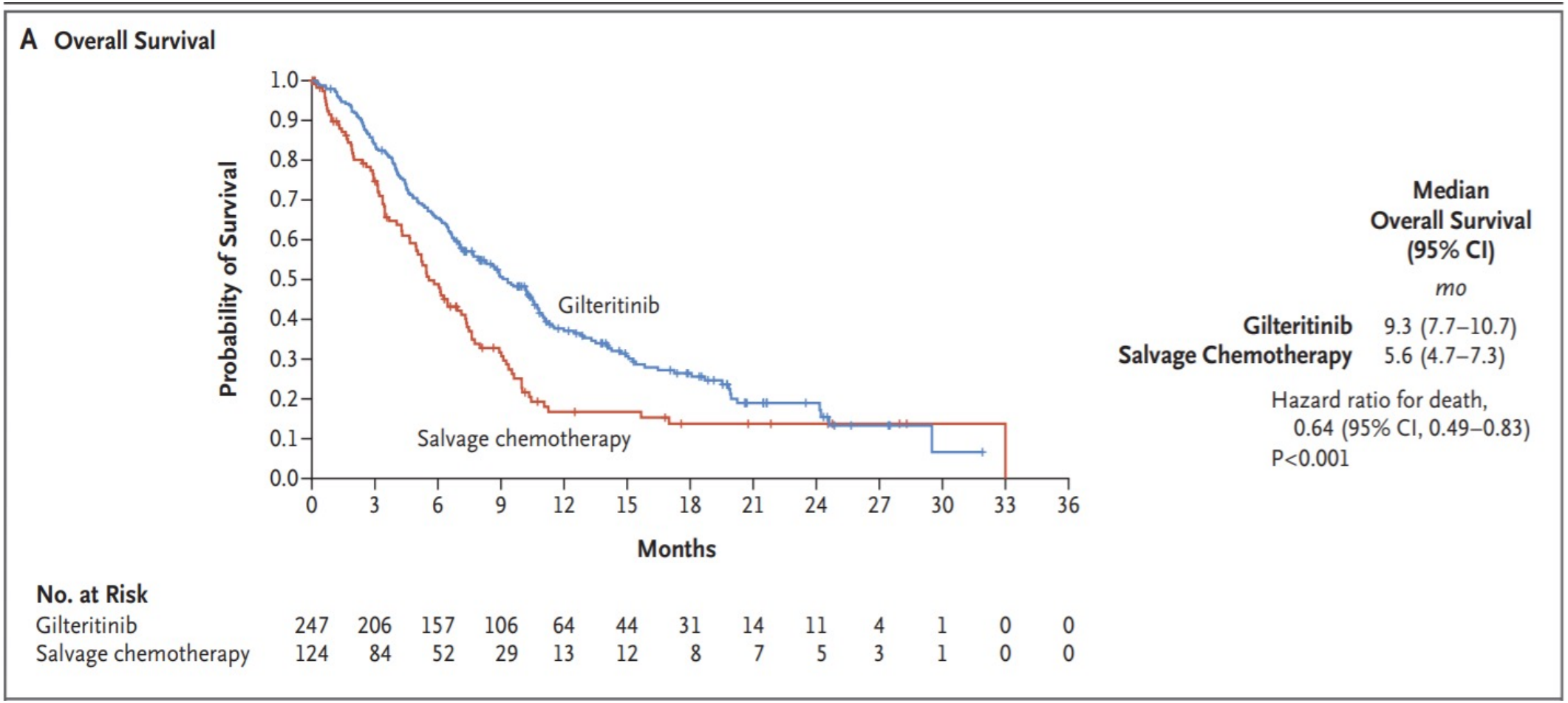
Wang E, et al. ASH 2020 Abstract 27
ASH 2021 Abstracts 696 and 1277

ADMIRAL Study - Efficacy

	Gilteritinib N=247	Salvage Chemotherapy N=124	Hazard Ratio or Risk Difference (95% CI)
Response – n(%)			
CR	52 (21.1)	13 (10.5)	10.6 (2.8-18.4)
CR or CRp	84 (34.0)	19 (15.3)	18.6 (9.8-27.4)
CRp	32 (13.0)	6 (4.8)	ND
CRi	63 (25.5)	14 (11.3)	ND
CR with incomplete platelet recovery	19 (7.7)	0	ND
Partial Remission	33 (13.4)	5 (4.0)	ND
No response	66 (26.7)	43 (34.7)	ND
Composite CR	134 (54.3)	27 (21.8)	ND
Overall response	167 (67.6)	32 (25.8)	32.5 (22.3-42.6)
Median duration of remission (95% CI) –mo	11.0 (4.6 – NE)	NE (NE-NE)	NE
Time to composite CR - mo	2.3 +/- 1.9	1.3+/-0.5	NA

Perl AE, et al. NEJM 2019

ADMIRAL Study - Overall Survival

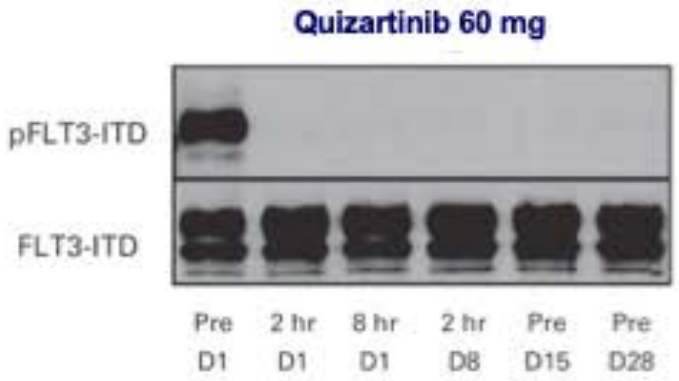


Perl AE, et al. NEJM 2019

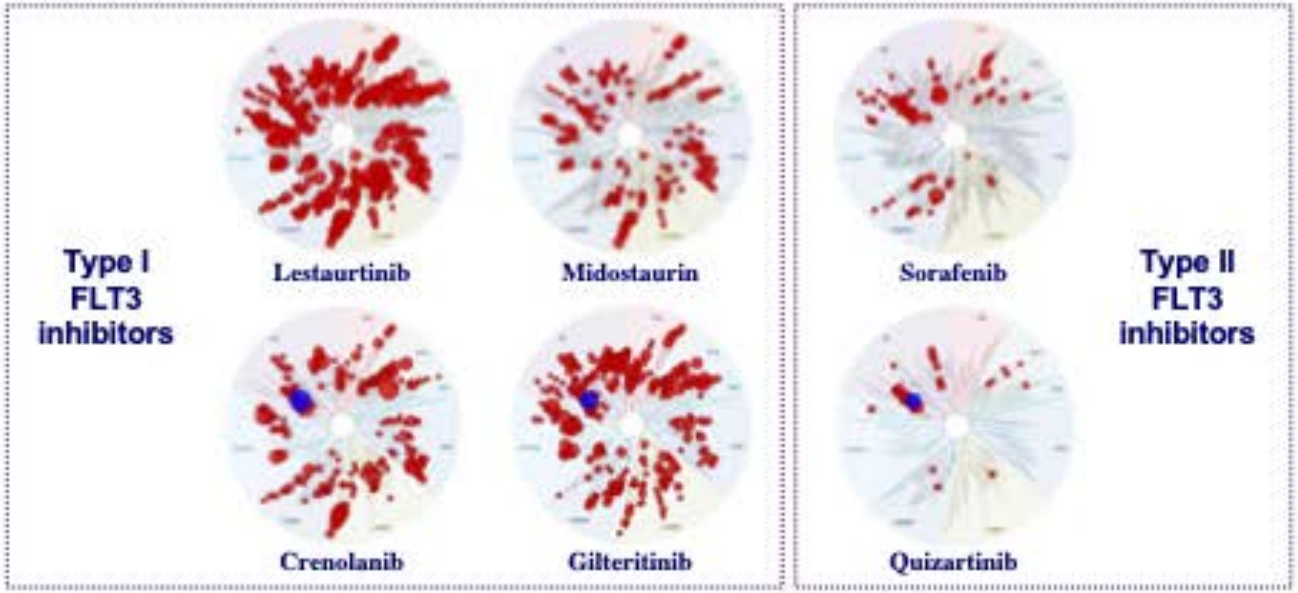
FLT3 Inhibitors and Areas of Investigation (Non-Venetoclax Based Regimens)

- **Gilteritinib**
  - Beat AML: Gilteritinib+Decitabine (Traer E ASH 2021 Abstract 1277)
  - Phase 1 Study in Combination with Induction and Consolidation (Pratz K EHA 2021 Abstract EP437)
    - HOVON 156: Randomized Phase 3 Gilteritinib vs Midostaurin with Induction, Consolidation and Maintenance (NCT04027309)
  - BMT CTN 1506: Post-transplant maintenance (NCT02997202)
- **Quizartinib**
  - QuANTUM-R: Phase 3 Study versus Salvage Chemotherapy (Cortes JE, et al. Lancet Oncol 2019)
  - Phase 1/2: Quizartinib + Aza/LDAC as first salvage or previously untreated older AML (Swaminathan M, et al. Haematologica 2021)
  - QuANTUM-First: Randomized Phase 3 Study in Combination with Induction, Consolidation and Maintenance – Press Release met Primary Endpoint of OS
- **Crenolanib**
  - Randomized Phase 3 Study with Induction and Consolidation and Post-transplant Maintenance (NCT03258931)
  - Randomized Phase 3 Study in Combination with Salvage Chemotherapy vs Salvage Chemotherapy alone (NCT03250338)
- Efficacy Analysis of Different FLT3 Inhibitors in Relapsed/Refractory Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome Patients – a Systematic Review and Meta-Analysis (Swaminathan M, et al ASH 2021 Abstract 1225)

Quizartinib Is a Second-Generation FLT3 Inhibitor



Cortes JE, et al. *J Clin Oncol*. 2013;31(29):3681-3687. Reprinted with permission. © 2013 American Society of Clinical Oncology. All rights reserved.



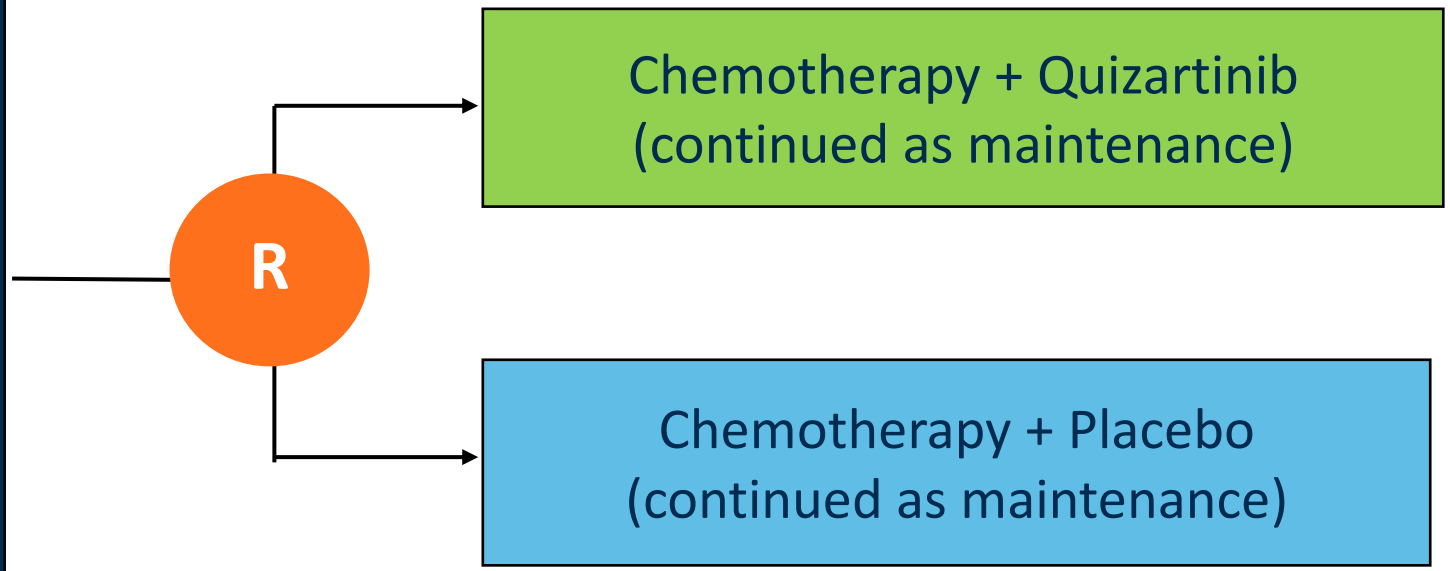
- **Quizartinib is more potent in vivo than any other FLT3 inhibitor to date**
- **FLT3-TKD mutations are an established mechanism of resistance in quizartinib-treated patients**
- **Possible QT prolongation at higher doses**

- **Gilteritinib 'hits' both ITD and TKD subtypes**
- **Well tolerated**
- **Within 10-fold that of FLT3 were closely related RTKs, eg, KIT**

QuANTUM-First Phase III Study Design

Key eligibility criteria

- 18-75 years old
- ECOG PS 0-2
- No history of central nervous system leukemia, significant cardiovascular disease, QTcF >450 msec, active liver disease
- No prior therapy



Primary endpoint: event-free survival based on centrally adjudicated response assessment using local morphology results

Secondary endpoints: OS, CR, CRc (CR + CRi per latest IWG definitions)

www.clinicaltrials.gov. NCT02668653. Accessed December 2021.

QuANTUM-First meets primary endpoint for OS

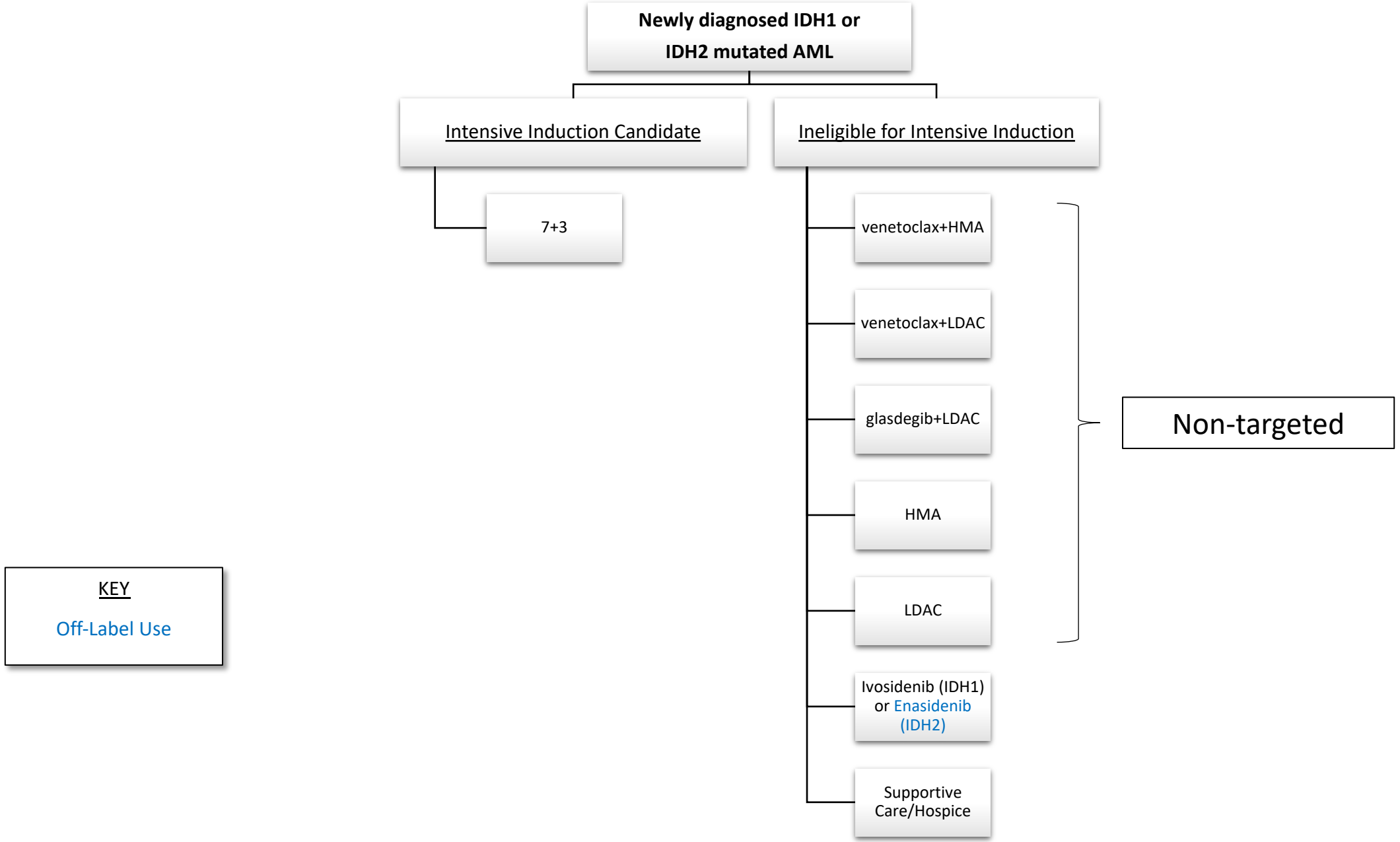
- Investigators announced positive topline results from the global pivotal QuANTUM-First trial evaluating quizartinib, a highly potent and selective FLT3 inhibitor, for patients with newly diagnosed FLT3-ITD-positive acute myeloid leukemia (AML). The trial met the primary endpoint for overall survival.

- QuANTUM-First was a randomized, double-blind, placebo-controlled, multi-center global study evaluating quizartinib in combination with standard induction and consolidation chemotherapy and then continued as single agent therapy. The trial enrolled 539 adult patients (age 18 – 75) with newly diagnosed FLT3-ITD positive AML. Patients were randomized 1:1 into two treatment groups to receive quizartinib or placebo in combination with standard anthracycline and cytarabine-based induction and consolidation regimens. Eligible patients, including those who underwent allogeneic hematopoietic stem cell transplant (HSCT), continued with single agent quizartinib or placebo for up to 36 cycles.

ASH 2021 Abstracts — Quizartinib

- **Abstract 616:** Quizartinib (Quiz) with Decitabine (DAC) and Venetoclax (VEN) Is Highly Active in Patients (pts) with FLT3-ITD Mutated Acute Myeloid Leukemia (AML) — RAS/MAPK Mutations Continue to Drive Primary and Secondary Resistance.

- **Abstract 1536:** Initial Results of Phase I/II Study of Azacitidine in Combination with Quizartinib for Patients with Myelodysplastic Syndrome and Myelodysplastic/Myeloproliferative Neoplasm with *FLT3* or *CBL* Mutations


Newly diagnosed IDH1 or IDH2 mutated AML
Intensive Induction Candidate
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HMA
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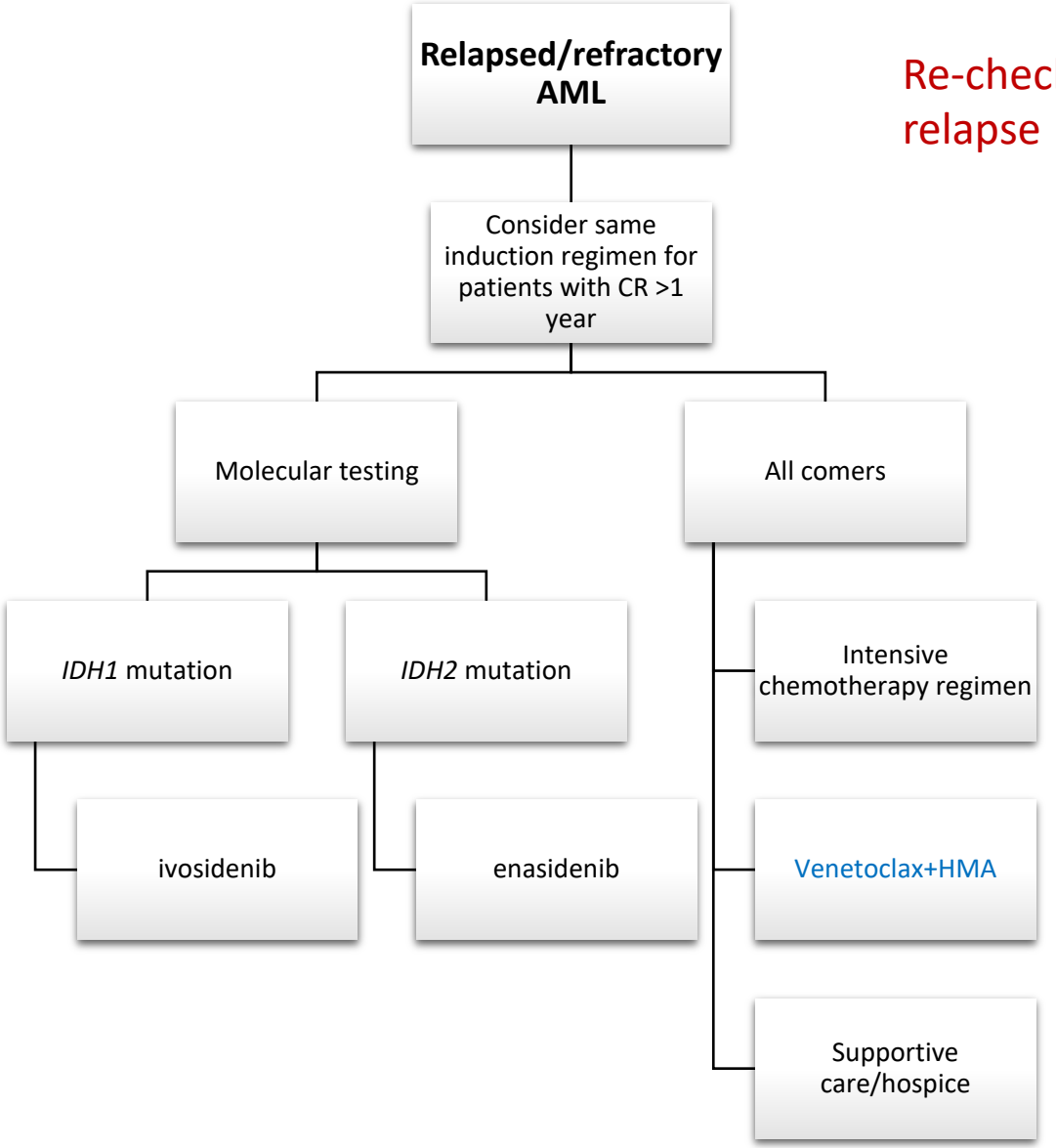
Non-targeted
Ivosidenib (IDH1) or Enasidenib (IDH2)
Supportive Care/Hospice
KEY
Off-Label Use



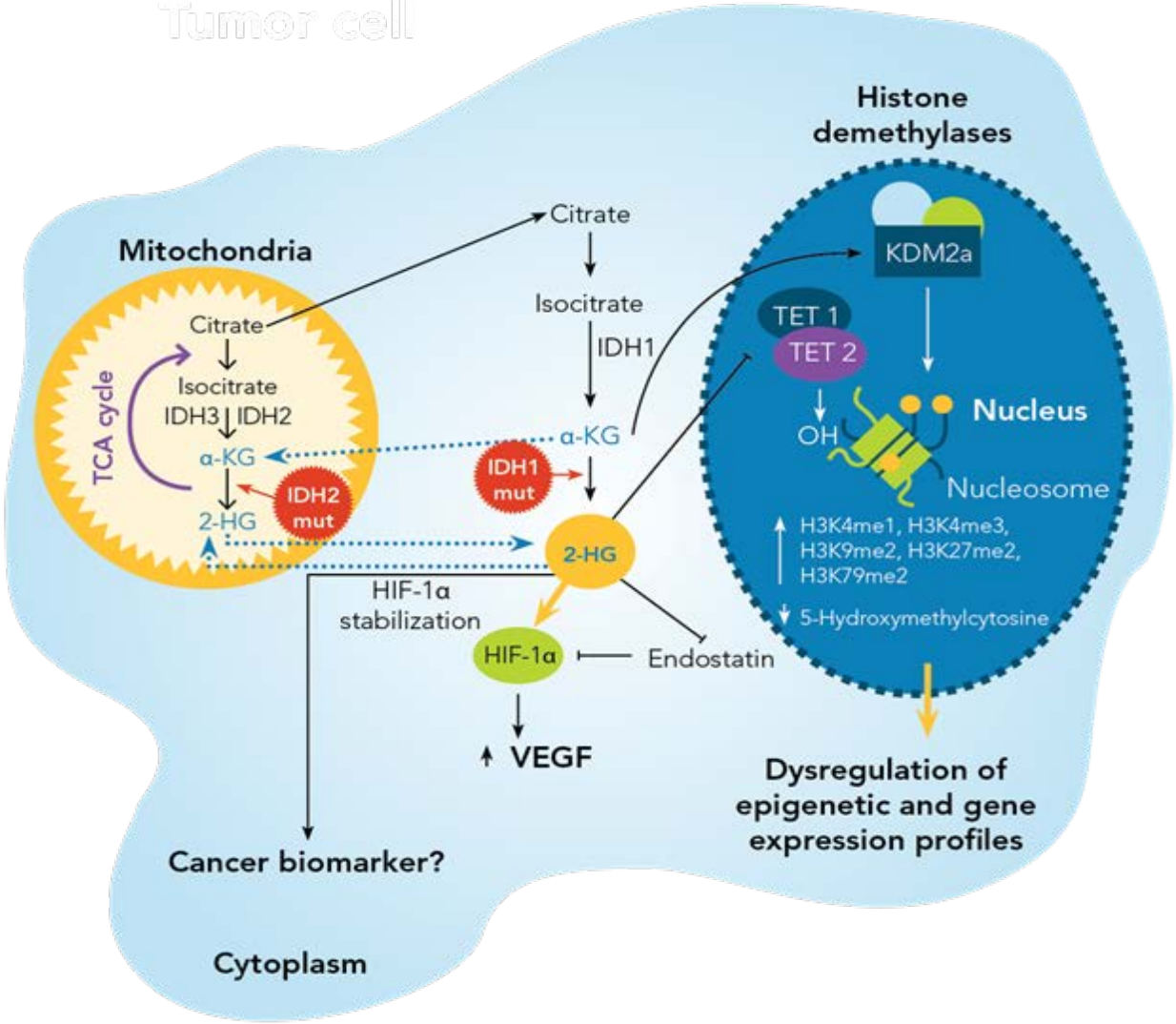
Re-check molecular profile in setting of relapse

KEY

Off-Label Use

Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

- IDH is an enzyme of the citric acid cycle
- Mutant *IDH1* and *IDH2* produce 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation
- *IDH1* mutated 6-10% (Arginine 132)
- *IDH2* mutated 15-20% (Arginine 140 or 172)
- Ivosidenib is a selective, oral, potent inhibitor of the mutant *IDH1* enzyme
- Enasidenib is a selective, oral, potent inhibitor of the mutant *IDH2* enzyme



Prensner and Chinnaiyan. Nature, 2011

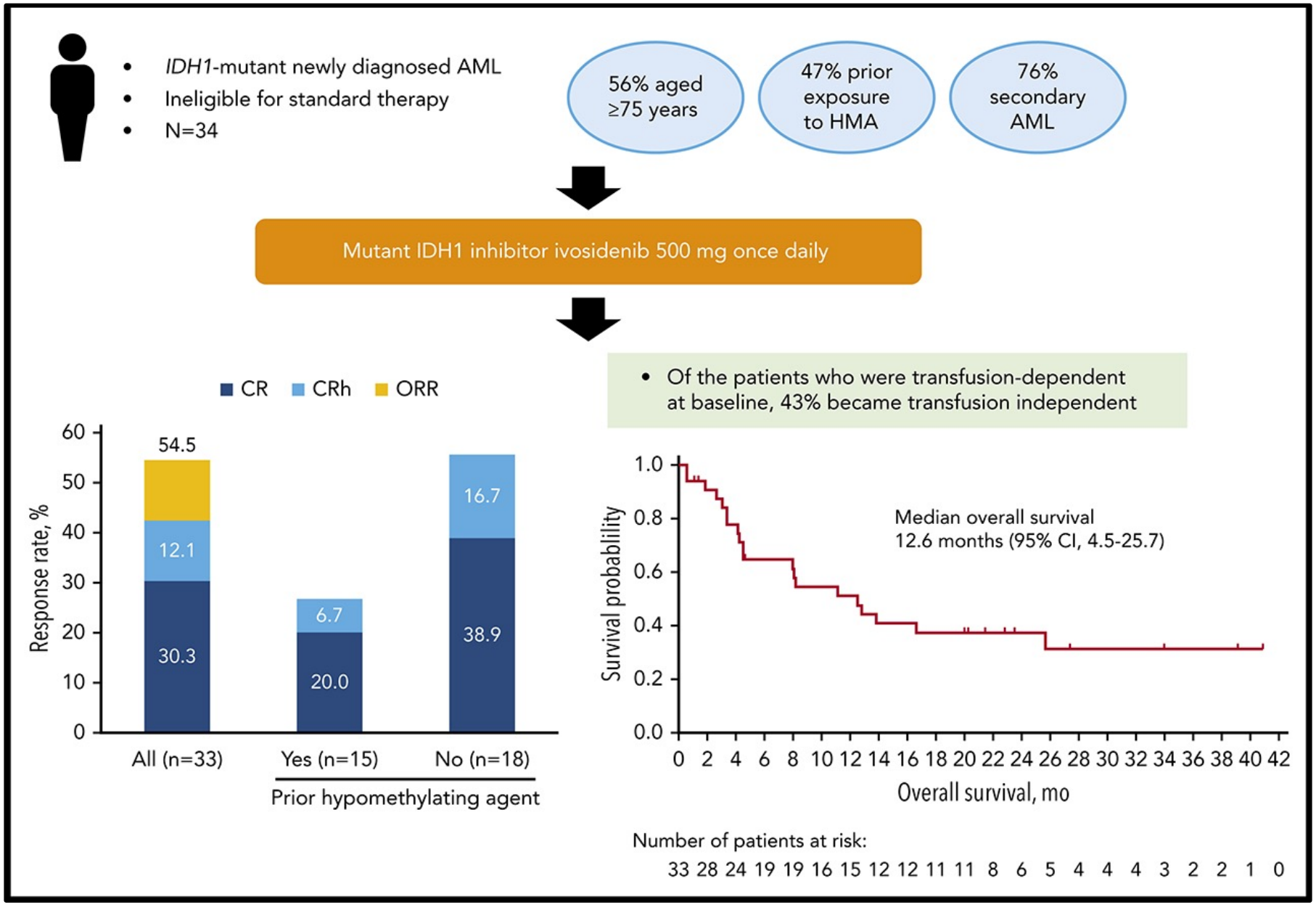
Ivosidenib Response in R/R *IDH1* mutated AML

	N=125 (500mg po daily)
Overall response rate, n (%) [95% CI]	52 (41.6) [32.9-50.8]
Median (range) time to first response, months	1.9 (0.8-4.7)
Median [95% CI] duration of response, months	6.5 [4.6-9.3]
Best response, n (%)	
CR	27 (21.6)
CRi or CRp	16 (12.8)
MLFS	9 (7.2)
SD	44 (35.2)
PD	13 (10.4)
NA	16 (12.8)

ORR = CR + CRi + CRp+ MLFS + PR

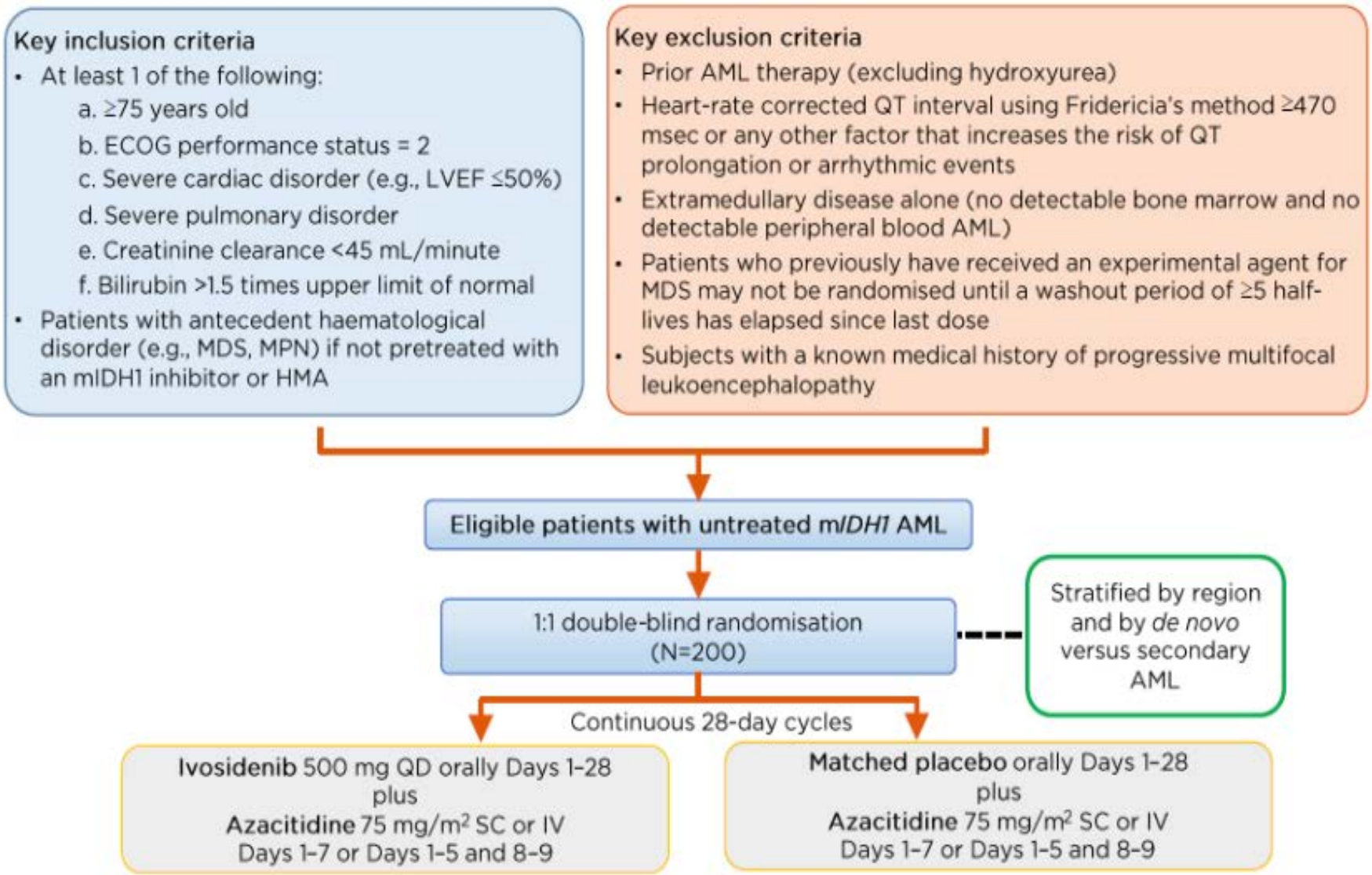
DiNardo CD, et al. N Engl J Med 2018

Ivosidenib Response in Newly Diagnosed *IDH1* mutated AML



Roboz GJ, et al. Blood 2020

AGILE Study: Randomized Phase 3 Study



Montesinos P, et al. EMJ Hematol. 2020
Montesinos P, et al. ASH 2021 Abstract 697

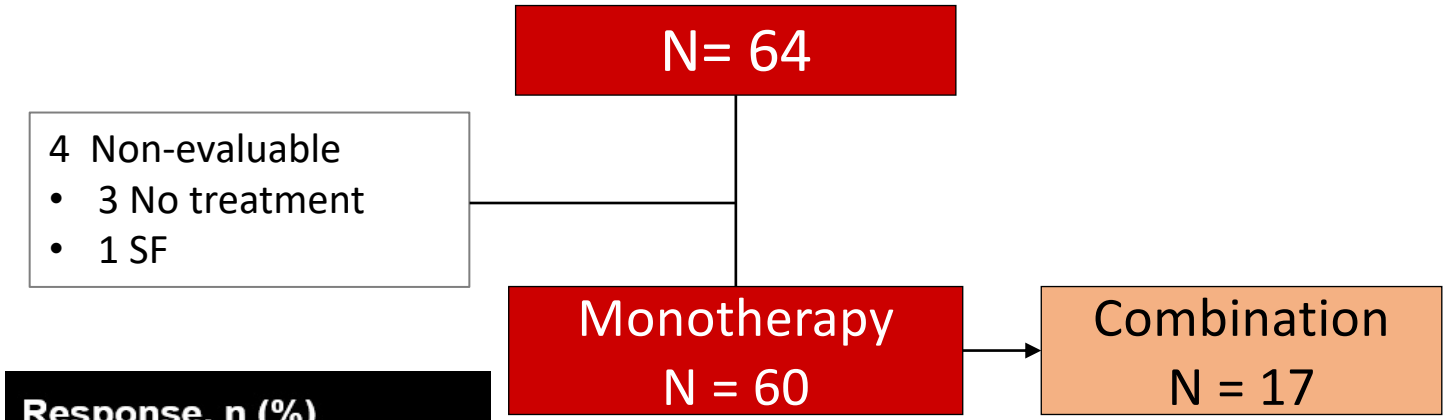
Enasidenib Response in R/R *IDH2* mutated AML

	N=109 (100mg po daily)
Overall response rate, n (%) [95% CI]	42 (38.5) [29.4-48.3]
Median (range) time to first response, months	1.9 (0.5-9.4)
Median [95% CI] duration of response, months	5.6 [3.8-9.7]
Best response, n (%)	
CR	22 (20.2)
CRi or CRp	7 (6.4)
MLFS	10 (9.2)
SD	58 (53.2)
PD	5 (4.6)
NA	2 (1.8)

ORR = CR + CRi + CRp + MLFS + PR

Stein EM, et al. Blood 2017

Enasidenib Response in Newly Diagnosed *IDH2* mutated AML



Response, n (%)	Monotherapy N = 60	Combination N = 17
CR MRD-	2 (3%)	1 (6%)
CR	20 (33%)	3 (18%)
CRh	6 (10%)	2 (12%)
CRi	1 (2%)	1 (6%)
MLFS	1 (2%)	1 (6%)
No Response	30 (50%)	9 (53%)
Overall Response Rate (CR MRD-/CR/ CRh/CRi)	29 (48%)	7 (41%)

Stein E, et al. ASH 2020 Abstract 636

IDH Inhibitors and Ongoing Areas of Investigation (Non-Venetoclax Based Regimens)

- **Ivosidenib**
  - Phase 2 Ivosidenib+Azacitidine in Newly Diagnosed Older AML (Patel P, et al. ASH 2021 Abstract 875)
  - Post-transplant maintenance: NCT03564821
- **Enasidenib**
  - Phase 1b/Randomized Phase 2: Azacitidine +/- Enasidenib in Newly Diagnosed AML (DiNardo CD, et al. Lancet Oncol 2021)
  - IDHentify Trial: R/R Late Stage AML Enasidenib vs Other Low-Intensive Chemotherapy (DiNardo CD, et al. ASH 2021 Abstract 1243)
  - Post-Transplant Maintenance (Fathi A, et al. ASH 2021 Abstract 2402 - NCT03515512)
    - Actively Enrolling: NCT03728335 and NCT04522895
- **Both Ivosidenib and Enasidenib**
  - Phase 1 IDH inhibitors + Induction/Consolidation in Newly Diagnosed AML (Stein E, et al. Blood 2021 and Update ASH Abstract 1276)
    - Randomized Study HOVON150AML - NCT03839771

VIALE-A: Venetoclax and HMA Responses in Genomic Subgroups

	Aza + Ven (n = 286)	Aza + Pbo (n = 145)	*P* Value
CR + CRi, % (95% CI)	66.4 (60.6-71.9)	28.3 (21.1-36.3)	< .001
CR + CRi by start of cycle 2, % (95% CI)	43.4 (37.5-49.3)	7.6 (3.8-13.2)	< .001
CR rate, % (95% CI)	36.7 (31.1-42.6)	17.9 (12.1-25.2)	< .001
Transfusion independence*, % (95% CI)			
▪ RBC	59.8 (53.9-65.5)	35.2 (27.4-43.5)	< .001
▪ Platelets	68.5 (62.8-73.9)	49.7 (41.3-58.1)	< .001
CR + CRi rate in subgroups, % (95% CI)			
▪ *IDH1/2*	75.4 (62.7-85.5)	10.7 (2.3-28.2)	< .001
▪ *FLT3*	72.4 (52.8-87.3)	36.4 (17.2-59.3)	.021
▪ *NPM1*	66.7 (46.0-83.5)	23.5 (6.8-49.9)	.012
▪ *TP53*	55.3 (38.3-71.4)	0	< .001
EFS, mo (95% CI)	9.8 (8.4-11.8)	7.0 (5.6-9.5)	< .001

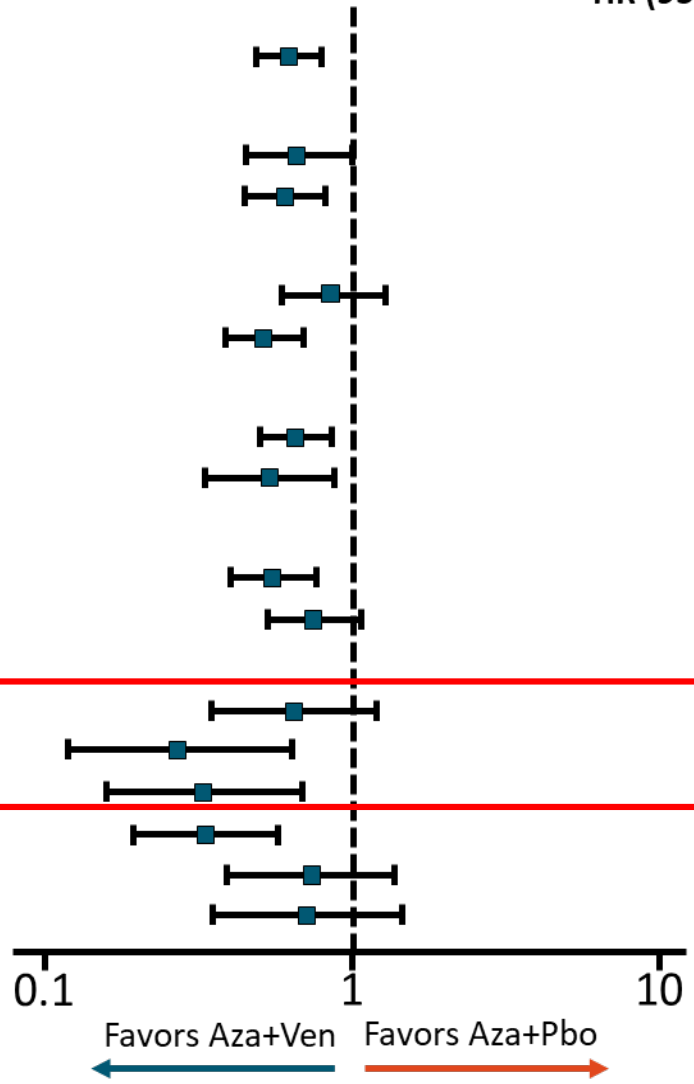
- Median age (range): 76 yrs (49-91)

*≥ 56 days with no RBC or platelet transfusion between first and last day of treatment

DiNardo CD, et al. N Engl J Med 2020

VIALE-A: Overall Survival Subgroup Analysis

	Aza + Ven, n/N (%)	Aza + Pbo, n/N (%)	HR (95% CI) Aza+Ven vs Aza+Pbo
All Subjects	161/286 (56.3)	109/145 (75.2)	0.64 (0.50-0.82)
Gender			
Female	61/114 (53.5)	41/58 (70.7)	0.68 (0.46-1.02)
Male	100/172 (58.1)	68/87 (78.2)	0.62 (0.46-0.85)
Age, Yrs			
< 75	66/112 (58.9)	36/58 (62.1)	0.89 (0.59-1.33)
≥ 75	95/174 (54.6)	73/87 (83.9)	0.54 (0.39-0.73)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51-0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35-0.91)
Cytogenetic Risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41-0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54-1.12)
Molecular Marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35-1.26)
IDH1	15/23 (65.2)	11/11 (100)	0.28 (0.12-0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16-0.71)
IDH1/2	29/61 (47.5)	24/28 (85.7)	0.34 (0.20-0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40-1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36-1.51)



DiNardo CD, et al. N Engl J Med 2020

Ongoing Areas of Investigations: Targeted Therapy Combinations

- **Doublets**
  - Phase 1b/2 Enaven-AML Trial: Enasidenib + Venetoclax in R/R *IDH2* mutated AML and MDS/MPN (ASH 2021 Abstract 1263)
  - Phase 1b/2 Ivosidenib + Venetoclax in R/R *IDH1* mutated AML (NCT04092179)
  - Phase 1 Decitabine/Cedazuridine + Venetoclax or Gilteritinib or Ivosidenib or Enasidenib as Maintenance for AML in CR1 (NCT05010772)
  - Phase 1b Dose Expansion/Escalation: Gilteritinib and Venetoclax in R/R AML (Daver N, et al. ASH 2021 Abstract 691 and ASH 2020 Abstract 333)
- **Triplets**
  - Phase 1b/2 Ivosidenib+Venetoclax +/- Azacitidine (NCT03471260)
  - Phase 1b/2 Decitabine/Cedazuridine + Venetoclax + Enasidenib/Ivosidenib (NCT04774393)
  - Phase 1/2 Gilteritinib + Venetoclax + Azacitidine in R/R and newly diagnosed AML (Short N, et al. ASH 2021 Abstract 696)
  - Phase 1/2 Gilteritinib + Venetoclax + Decitabine in newly diagnosed Older AML (NCT03013998)
  - Phase 1/2 Gilteritinib + Venetoclax + Decitabine/Cedizuridine (NCT05010122)
  - Phase 1 Quizartinib + Venetoclax + Decitabine (Yilmaz M, et al ASH 2021 Abstract 370)

Thank you!


Supermarket
Groceries
FastCare
The James Cancer Hospital and Solove Research Institute
The Ohio State University
Wexner Medical Center