Penn Medicine
Abramson Cancer Center
Leukemia Program, Abramson Cancer Center

Targeting FLT3: how to choose among inhibitors?

New Drugs in Hematology

Bologna, IT

May 18th, 2026

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Disclosures of Alexander Perl

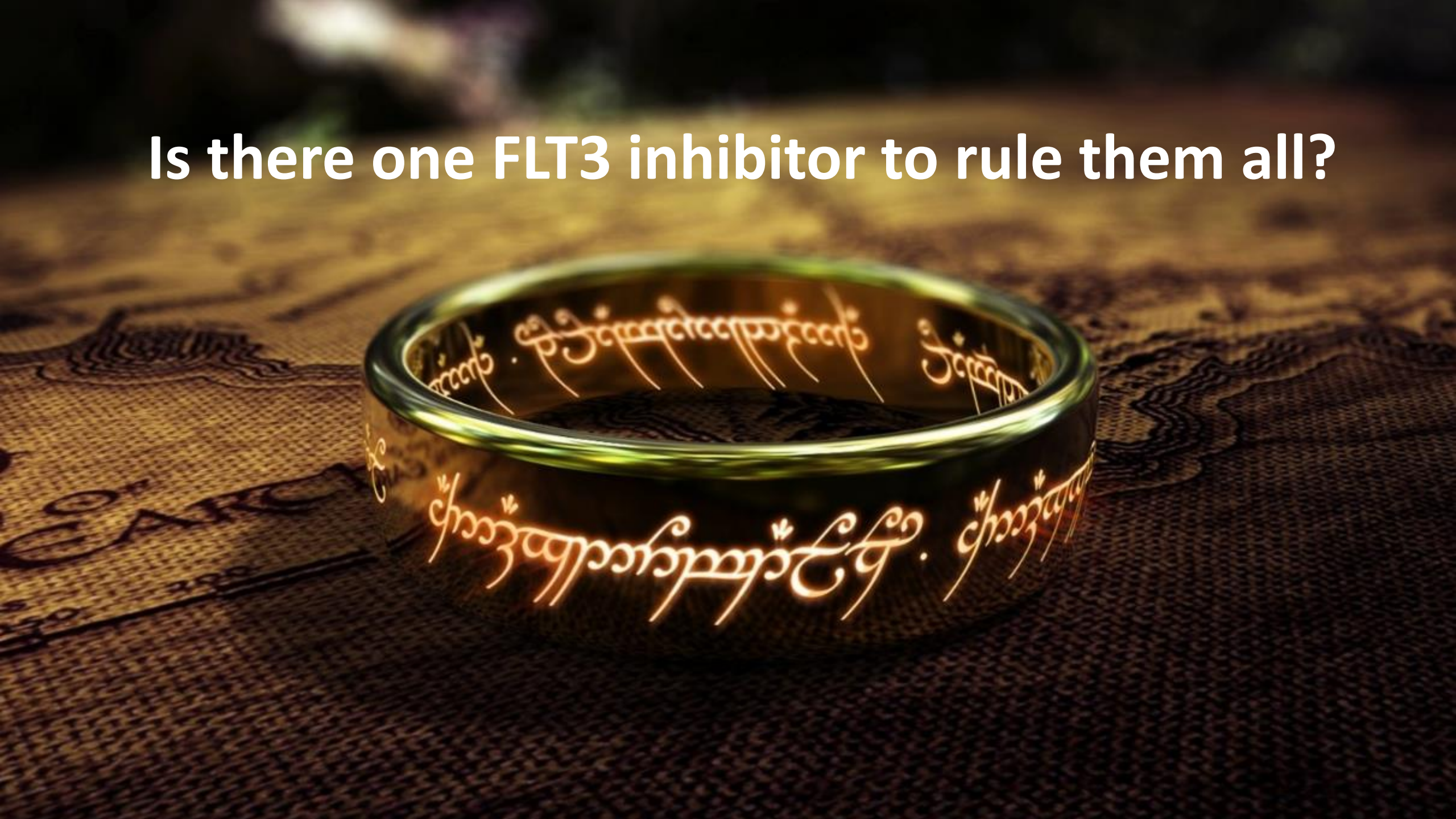
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	x		x				
Astellas	x		x			x	
Daiichi Sankyo	x		x			x	
Foghorn							DSMB
Syndax	x		x			x	
Johnson & Johnson						x	
Kura						x	
Stemline						x	

25 years of targeted therapy of leukemia!

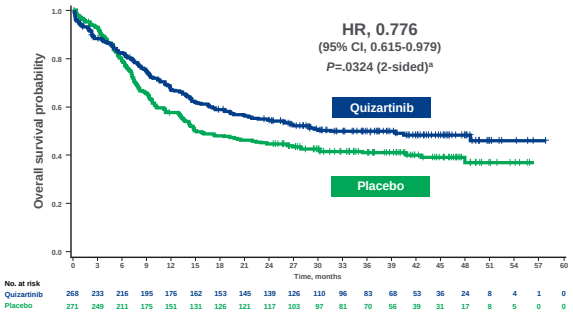
5/10/2001: FDA approval of imatinib for CML
An additional 5 TKIs have since been approved

www.wikipedia.org

Is there one FLT3 inhibitor to rule them all?



The current treatment approach for *FLT3*$^{mut+}$ AML



TKI on days 8-21

fit
FLT3^{mut+}

AML diagnosis

"unfit"
FLT3^{mut+}

cytarabine/anthracycline-based induction (7&3) + TKI

midostaurin
quizartinib

low intensity (VEN + HMA)

genetic risk profile
+
MRD

lower risk

higher risk

midostaurin
quizartinib

cytarabine-based consolidation (HiDAC) + TKI

hematopoietic stem cell transplant (HSCT)

midostaurin
quizartinib

TKI maintenance

MRD+

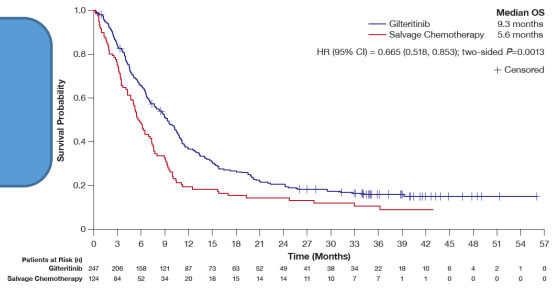
gilteritinib
(off label)

relapse
or refractory

after response

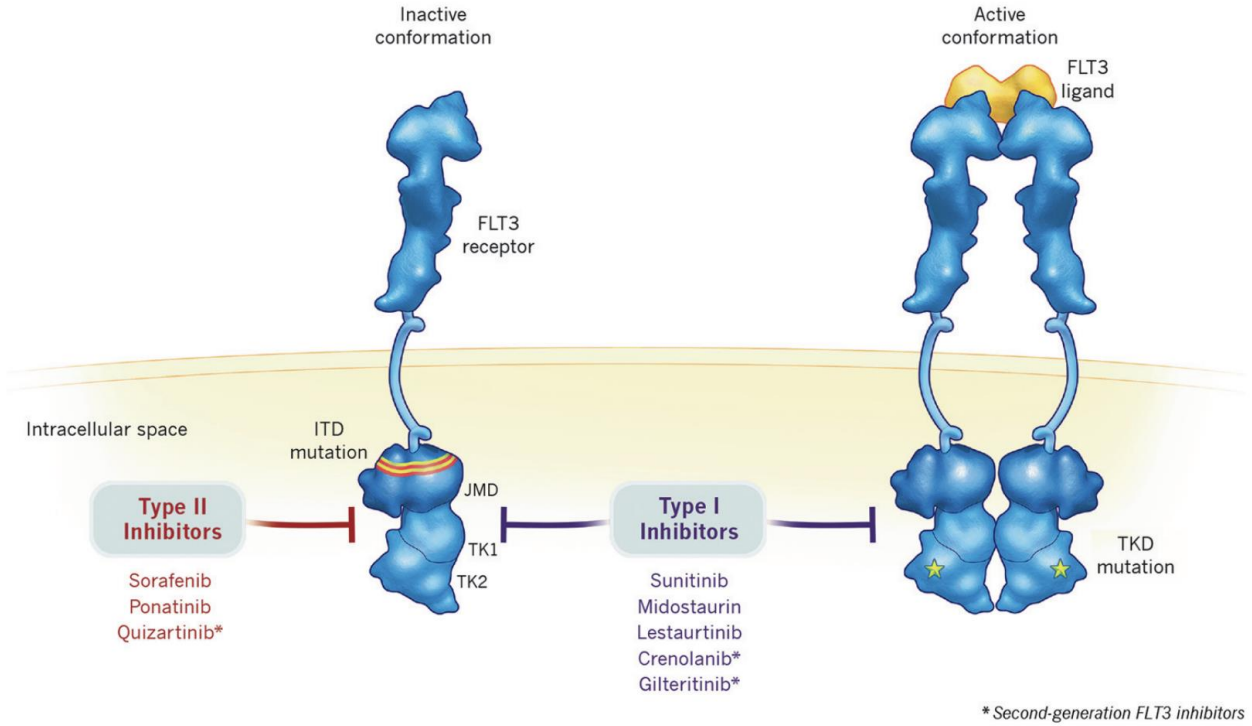
TKI
+/- other agents

gilteritinib



Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583
Perl AE, et al. *Blood* 2022. Jun 9;139(23):3366-3375

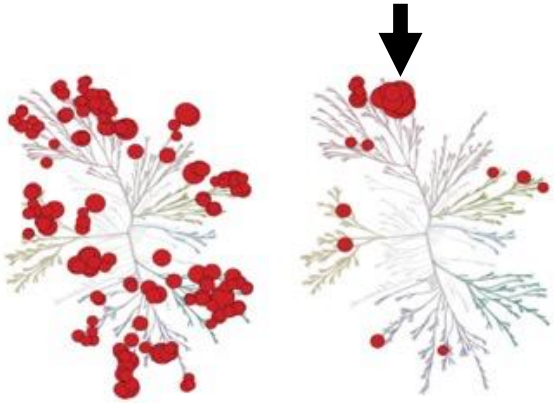
No two FLT3 inhibitors are identical



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

*investigational or off-label

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

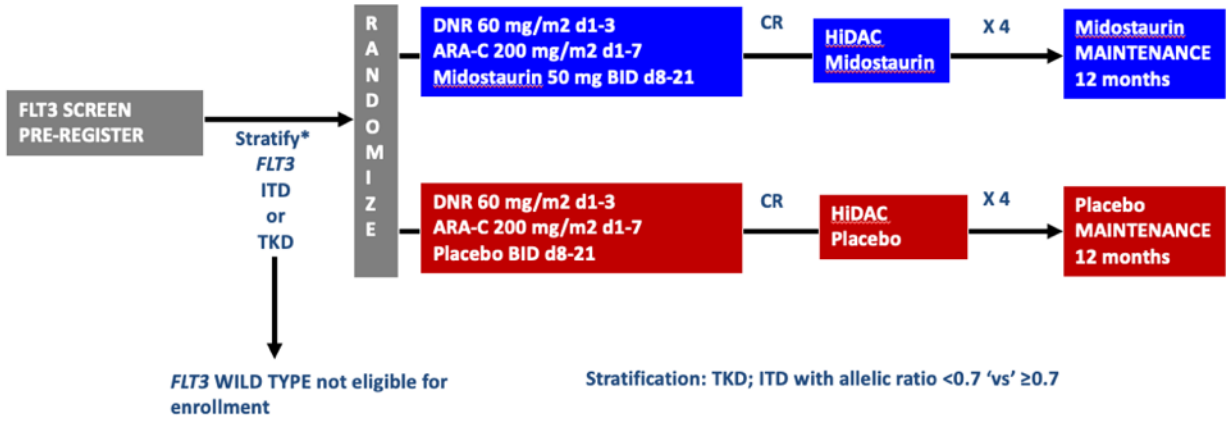


Midostaurin **Quizartinib**

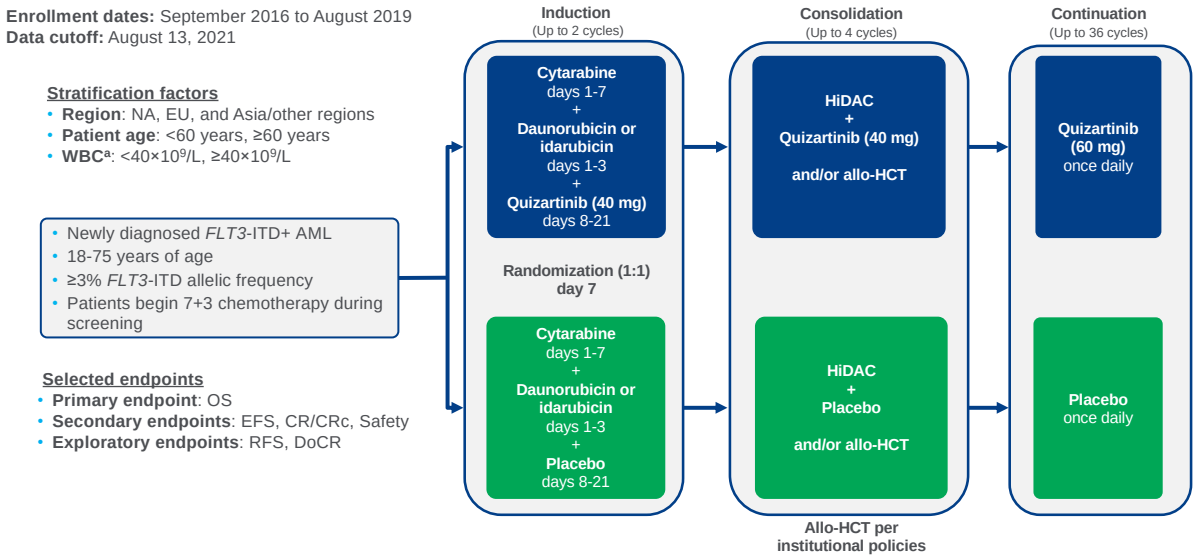
Daver NG, et al. Leukemia. 2019 Feb;33(2):299-312.
Pratz KW, et al. Blood 2010;115(7):1425-32
Zarrinkar PP, et al. Blood. 2009 Oct 1;114(14):2984-92
Galanis A, et al. Blood 2014 Jan 2;123(1):94-100
Levis M, Perl AE. Blood Adv. 2020 Mar 24;4(6):1178-1191
Smith CC, et al. Nature. 2012 Apr 15;485(7397):260-3
Tarver TC, et al. Blood Adv. 2020 Feb 11;4(3):514-524

Comparing Ratify and Quantum-First: design/eligibility

RATIFY/C10603



QuANTUM-First



Primary endpoint: OS

- 3277 patients were screened, 717 were randomized (555 with FLT3-ITD)
- FLT3-ITD and TKD mutations (cutoff >0.05 allelic ratio for either)
- Median age 48 years (range 18-60.9)
- Median follow-up 59 months
- HSCT was an off-protocol therapy
- maintenance given post-consolidation only
- MRD not collected

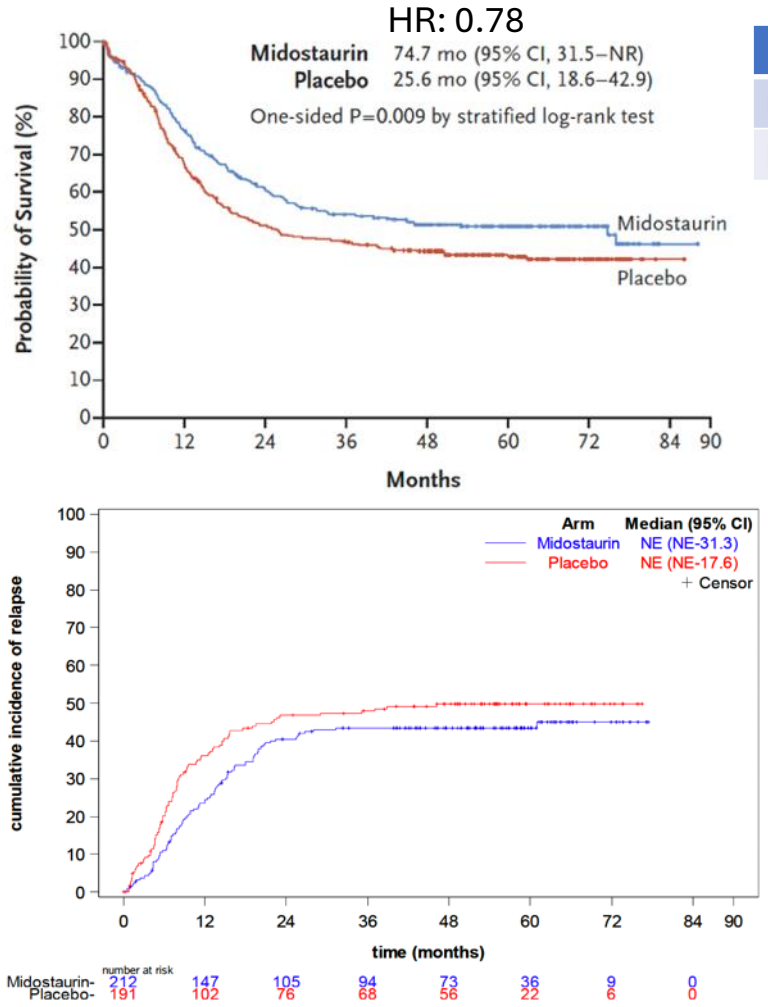
Primary endpoint: OS

- 3468 patients were screened, and 539 with FLT3-ITD were randomized
- FLT3 ITD only (cutoff of 3% VAF)
- Median age 56 (range 20-75)
- Median follow-up 39 months
- HSCT allowed on study
- maintenance given both post-HSCT and post-consolidation
- prospective monitoring of MRD

Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583

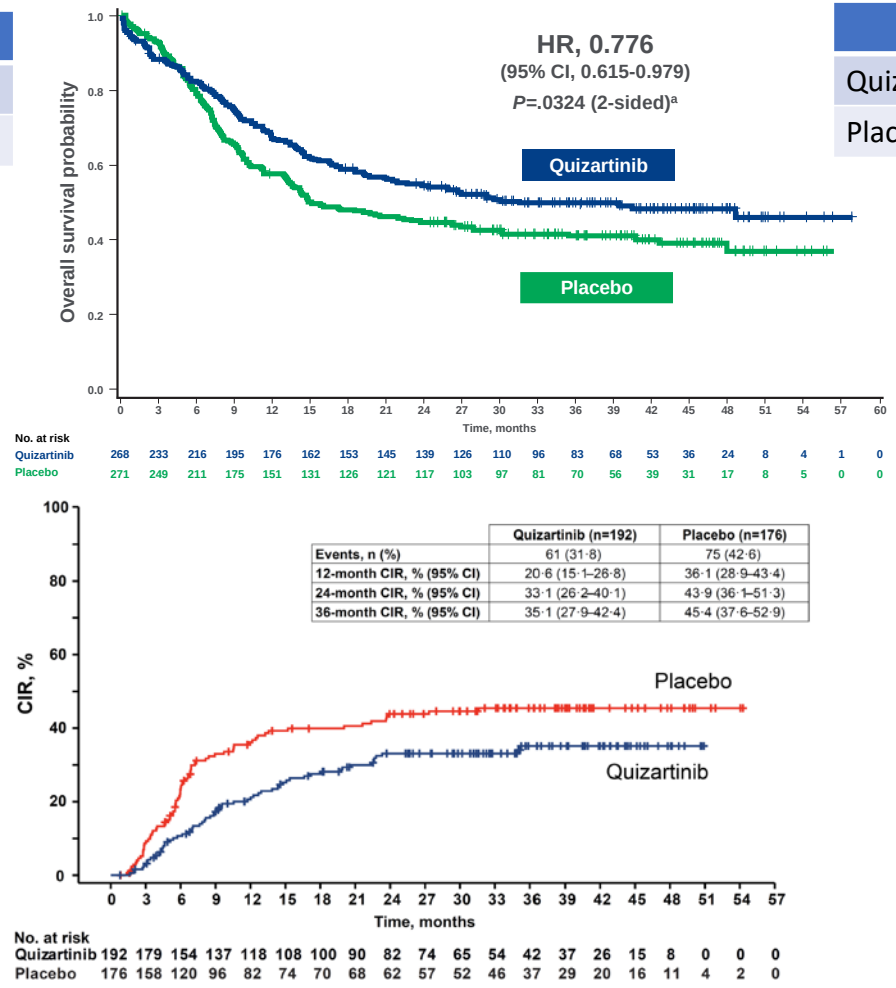
Response, relapse, and survival

RATIFY (midostaurin)



	CR
Midostaurin	68%
Placebo	61%

QuANTUM-First (quizartinib)

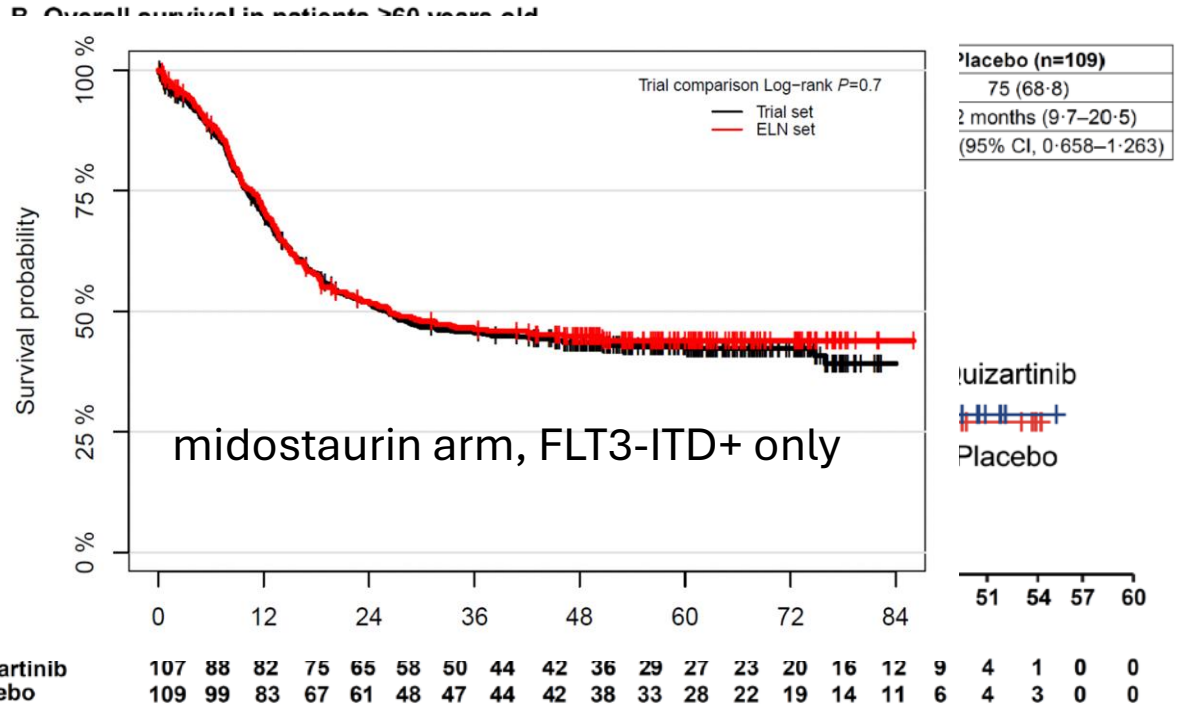


	CR	CR/CRi
Quizartinib	54.9%	71.6
Placebo	55.4%	64.9

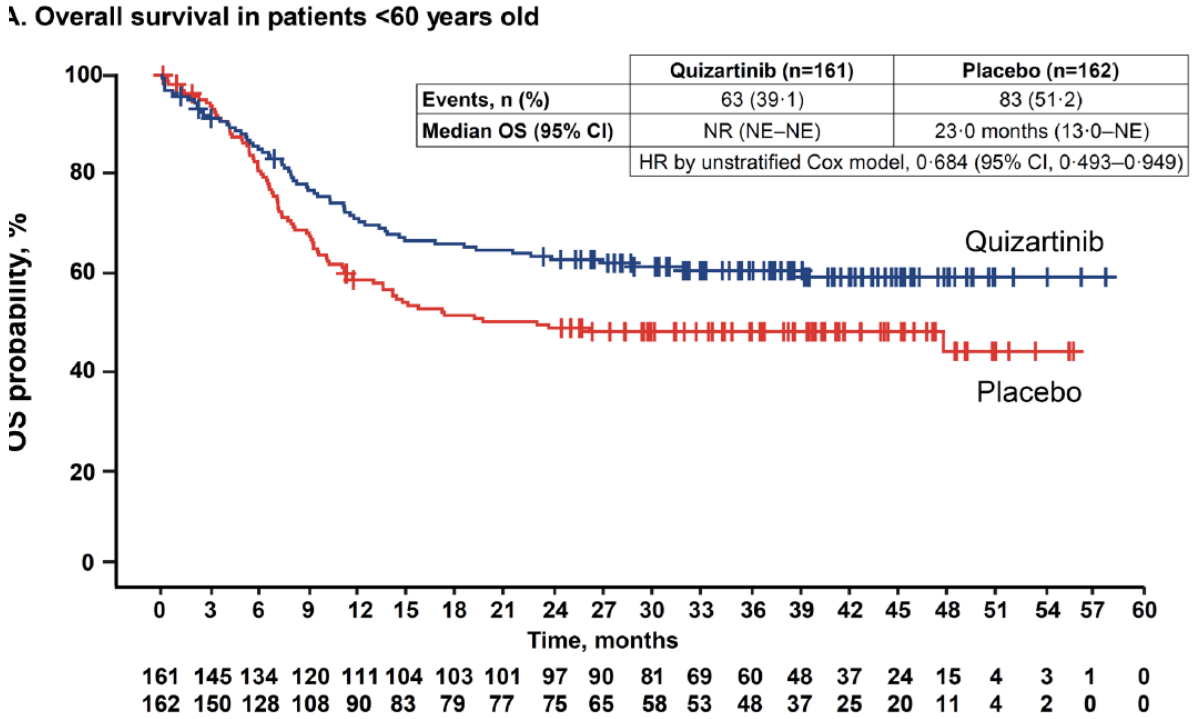
Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583

Younger patients particularly benefit from quizartinib

Quantum First



Quantum First

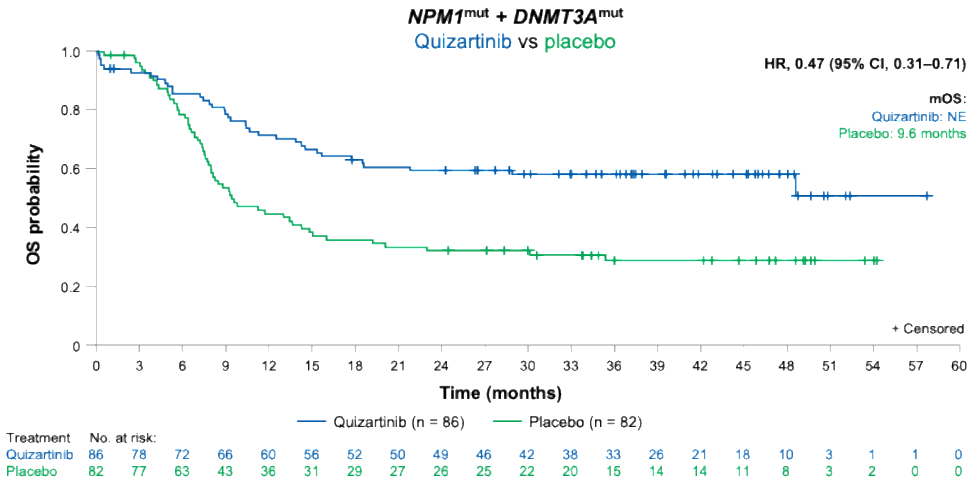


QuANTUM-First 60-day mortality: quizartinib 7.5%, placebo 4.9% (mostly infections)
Median time to ANC >1000 was 36 days, 7 days longer in quiz arm; platelets >100K= 31 days, 2 days longer in quiz arm

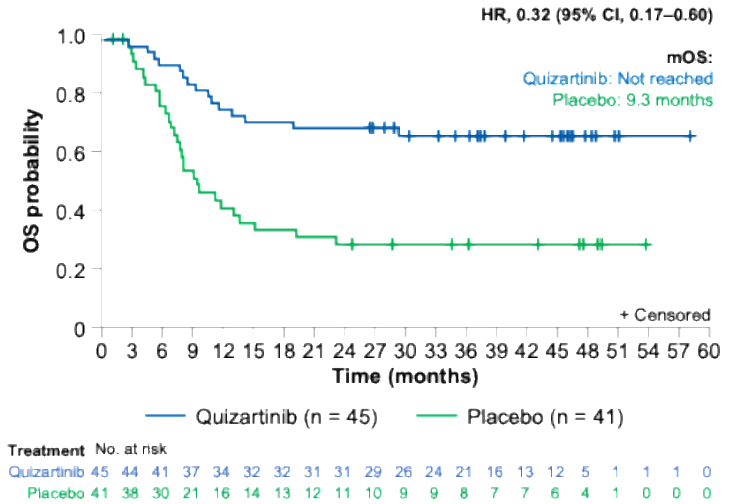
Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583
Döhner K, et al. *Blood*. 2020 Jan 30;135(5):371-380.

2nd generation FLT3 inhibitors may particularly benefit *FLT3*-ITD+ AML With *NPM1*^{mut} & *DNMT3A*^{mut} co-mutation

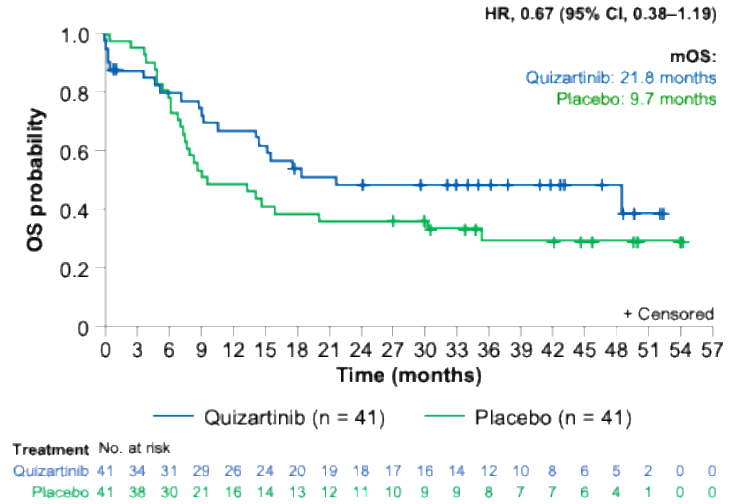
QuANTUM-FIRST:



Age <60



Age ≥60



Levis MJ, et al. EHA 2025 Annual Congress, abstract S140

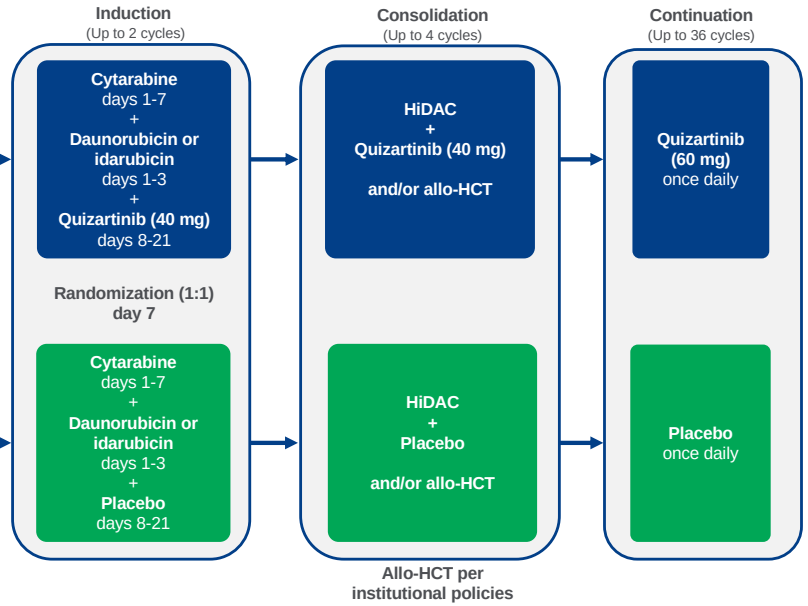
QuANTUM First: Achievement of CRc with MRD Negativity (<10^{-4} Cutoff) by the End of Induction Correlated with Longer OS, Regardless of Treatment Arm

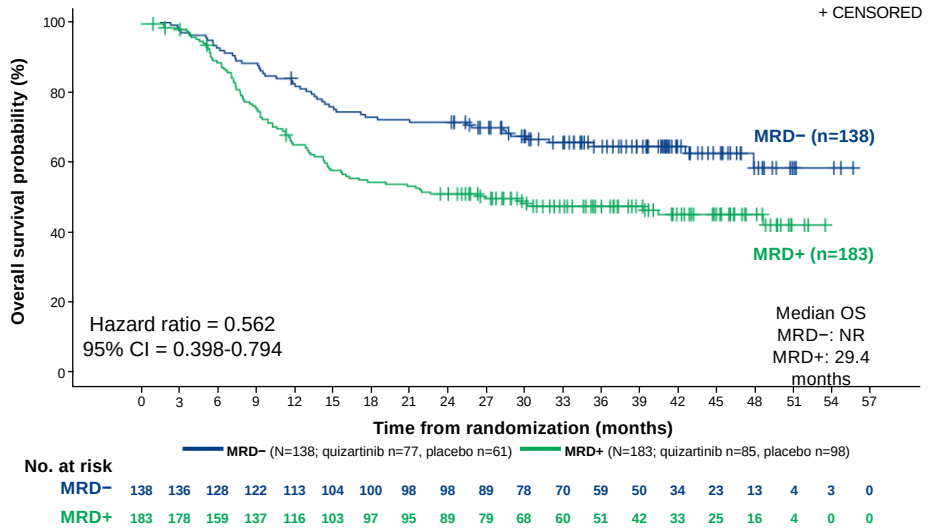
Enrollment dates: September 2016 to August 2019
Data cutoff: August 13, 2021

Stratification factors
- **Region**: NA, EU, and Asia/other regions
- **Patient age**: <60 years, ≥60 years
- **WBC**[a]: <40×10^9/L, ≥40×10^9/L

- Newly diagnosed *FLT3*-ITD+ AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency
- Patients begin 7+3 chemotherapy during screening

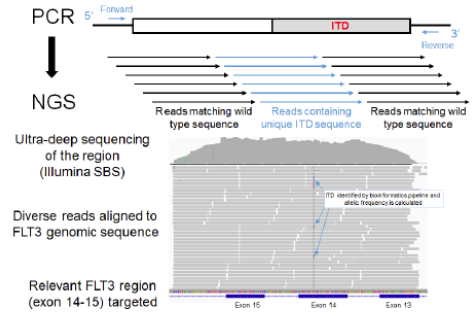
Selected endpoints
- **Primary endpoint**: OS
- **Secondary endpoints**: EFS, CR/CRc, Safety
- **Exploratory endpoints**: RFS, DoCR

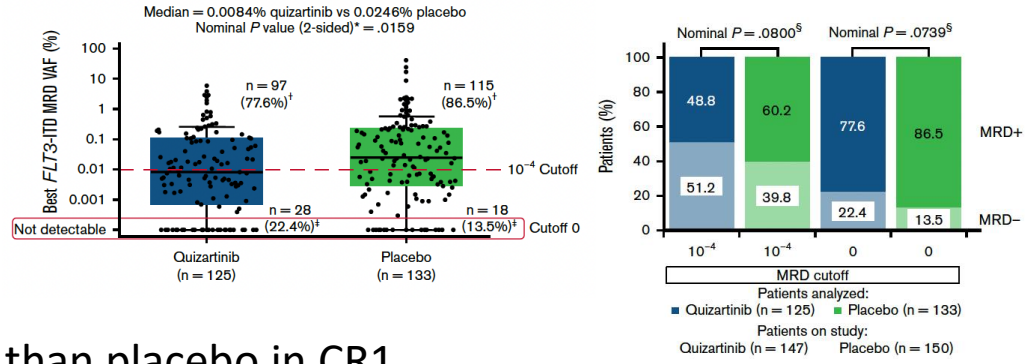




UHS NGS MRD assay for FLT3-ITD

- quantitative to 1 x 10^{-4}
- limit of ITD detection: 2 x 10^{-6}



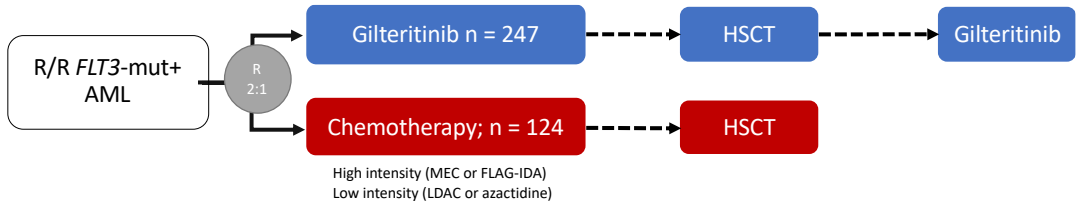


Quizartinib led to more frequent MRD(-) and deeper MRD responses than placebo in CR1

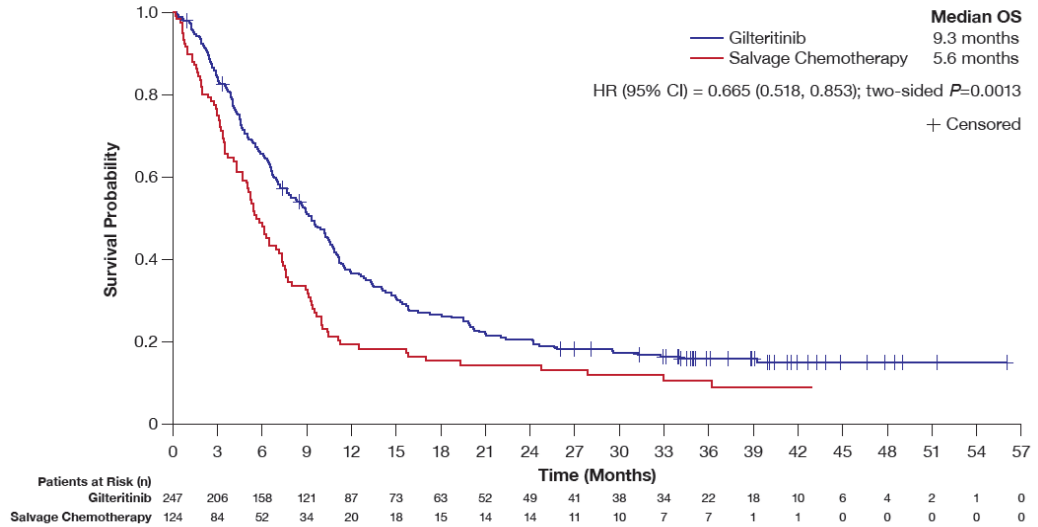
Levis MJ, et al. *Blood*. 2020 Jan 2;135(1):75-78
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583
Levis MJ, et al. Blood Adv. 2026 Feb 10;10(3):917-928

Gilteritinib is the only FLT3 inhibitor that consistently leads to CR as a single agent and improves OS in R/R *FLT3*mut+ AML

ADMIRAL



Ph3: 1st salvage of Relapsed/refractory, *FLT3*$^{mut+}$ AML
2:1 randomization of Gilteritinib vs. investigator's choice salvage chemo (SC)
2:1 randomization
co-primary endpoints: CR/CRh and OS
n=371



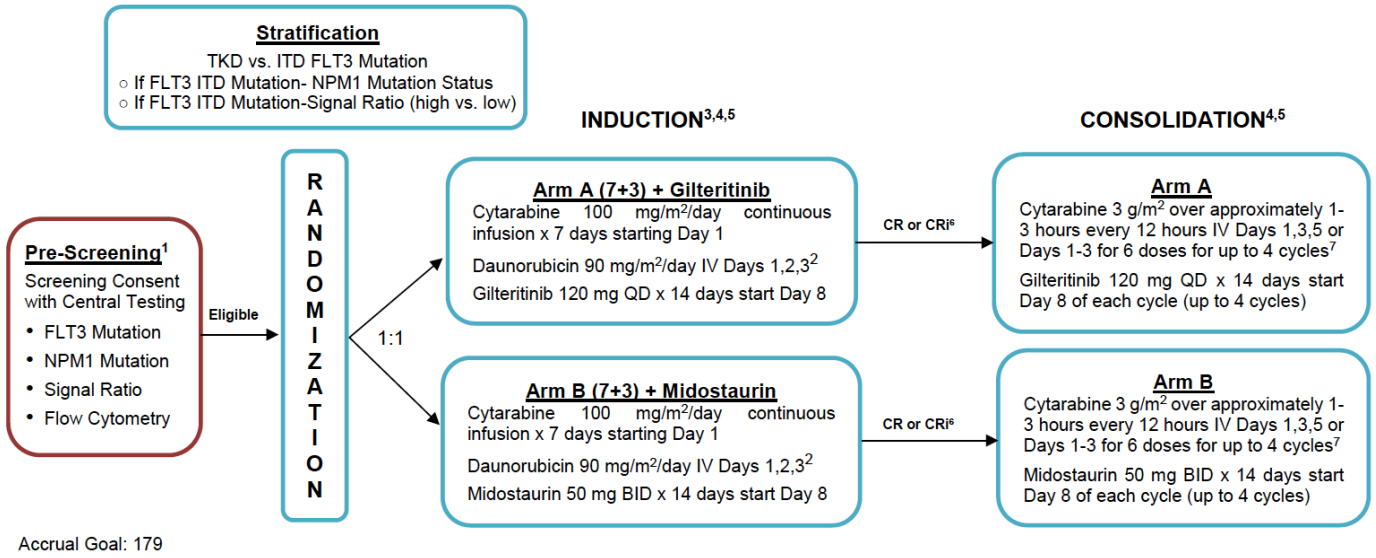
CR/CRh= 34% gilteritinib vs. SC 15.3%
CR= gilteritinib 21.1% vs. SC 10.5%
Median OS: gilteritinib 9.6 mo vs. 5.6 mo. (HR 0.64; 95% CI 0.49-0.83; P<0.001)
Common AEs: myelousppression, Gr1/2 N/V, LFT abnormalities, modest QT prolongation

- Single agent Quizartinib also improved OS in first salvage, but had a full CR rate of only 4% (only approved in Japan for R/R FLT3-ITD+ AML
- Midostaurin CR= 0% during phase 1/2 in R/R AML

Perl AE, et al. N Engl J Med. 2019 Oct 31;381(18):1728-1740
Perl AE, et al. Blood. 2022 Jun 9;139(23):3366-3375
Cortes JE, et al. Lancet Oncol. Lancet Oncol. 2019 Jul;20(7):984-997.
Fischer T, et al. J Clin Oncol. 2010 Oct 1;28(28):4339-45

Randomized gilteritinib vs. midostaurin + IC

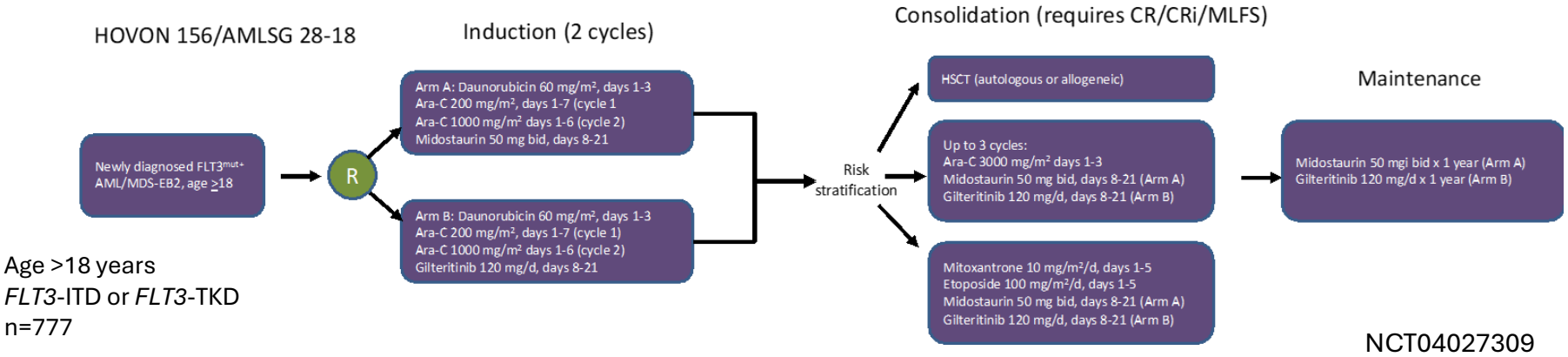
PrECOG 0905



NCT03836209

Primary endpoint: *FLT3*mut(-) CRc rate for each arm (Ultra-high sensitivity-NGS for *FLT3*-ITD, PCR for *FLT3*-TKD)

PASHA

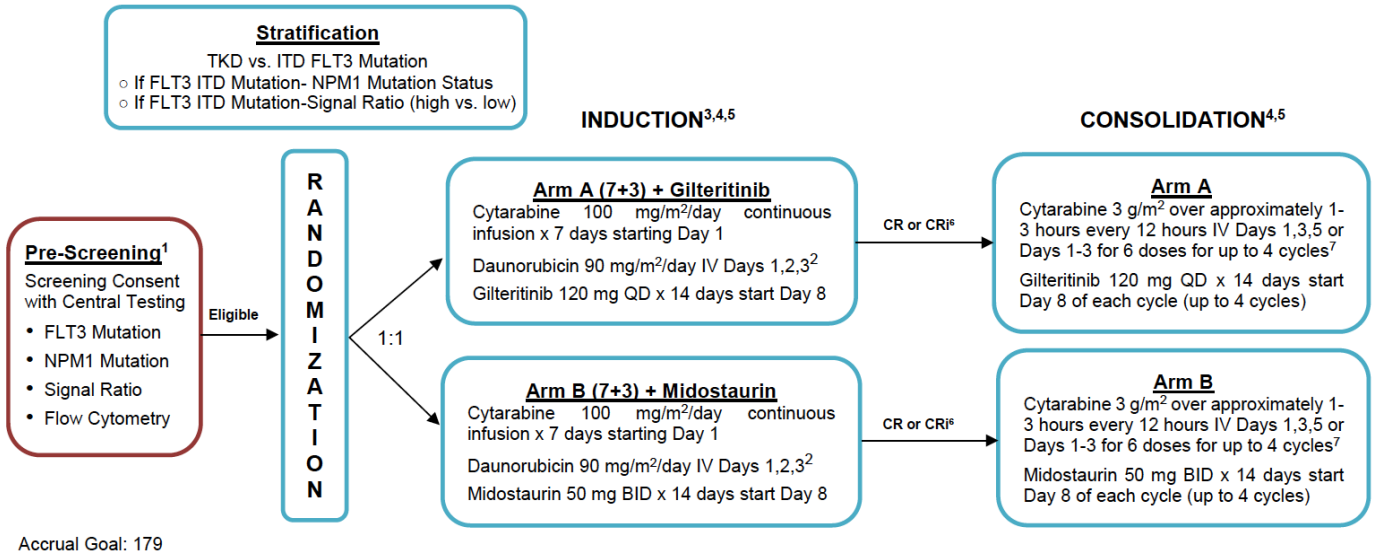


NCT04027309

Primary endpoint: OS (MRD is a secondary endpoint, measured after two intensive cycles)
crenolanib phase 3 (ARO-021) had similar design—trial suspended enrollment in 2023

Randomized gilteritinib vs. midostaurin + IC

PrECOG 0905



NCT03836209

Primary endpoint: *FLT3*mut(-) CRc rate for each arm (Ultra-high sensitivity-NGS for *FLT3*-ITD, PCR for *FLT3*-TKD)

- Daunorubicin dose was 90 mg/m2/d
- Transplant was off-study therapy, no maintenance post-consolidation or post-HSCT on study
- Primary endpoint = MRD was measured at documentation of remission (1-2 cycles of chemo)
- Ultra-high sensitivity MRD was only done on *FLT3*-ITD patients
  - *FLT3*-ITD <1 x 10^{-4} = MRD(-)
  - *FLT3*-TKD <1% (1 x 10-2) = MRD(-)

PrECOG 0905 remission rate by arm

	Gilteritinib (n=90)	Midostaurin (n=87)	Overall (n=177)
CR	68 (75.6%)	57 (65.5%)	125 (70.6%)
CRi	9 (10%)	6 (6.9%)	15 (8.5%)
CRc	77 (85.6%)	63 (72.4%)	137 (79.3%)
No Response	13 (14.4%)	24 (27.6%)	37 (20.9%)

- 177 eligible and treated (median age = 54); 81% *FLT3*-ITD+, 21% *FLT3*-TKD (without ITD)
  - Pts who needed 2 induction cycles to reach CRc: Gilteritinib 5 (5.6%), Midostaurin 6 (6.9%)

- CRc and CR1 transplantation rates were higher for gilteritinib
  - **CRc: Gilteritinib 85.6% vs 72.4% (Midostaurin), p=0.042**
  - CR1 transplant: Gilteritinib 54 (60%), Midostaurin 40 (45.9%), overall 94 (53.1%)

Luger SM, et al. ASH 2024 Abstract #221

PrECOG 0905 *FLT3* mutation MRD post induction

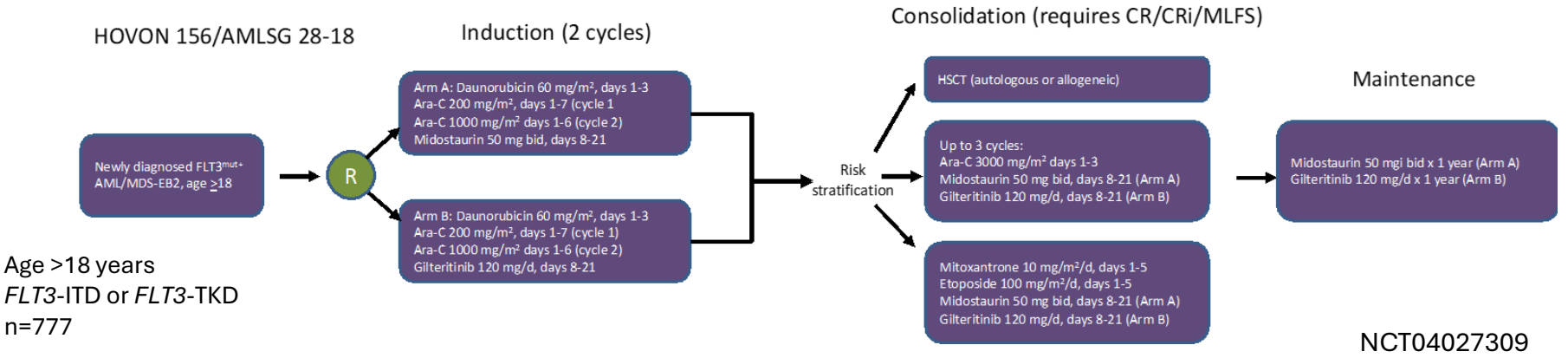
MRD regardless of remission status	Gilterinib N=90	Midostaurin N=87	Overall N=177
MRD negative	36 (40.0%)	46 (52.9%)	82 (46.3%)
MRD positive	39 (43.3%)	28 (32.3%)	67 (37.9%)
Dropped Out/Unknown	15 (16.7%)	13 (14.9%)	28 (15.8%)

- ***FLT3*mut (-) CRc post induction by *FLT3-ITD* UHS-NGS or PCR did not differ by arm:**
  - **40% Gilteritinib vs 47.1% Midostaurin, p=0.366**
  - flow MRD (<1 x 10^{-4}) CRc: 64.4% Gilteritinib vs. 59.8% Midostaurin
- Higher CRc and CR1 HCT rate for gilt among *NPM1+/DNMT3A+/FLT3-ITD+ subset* (n=40)
  - CRc: Gilteritinib 96% (21/22); Midostaurin 72% (13/18)
  - FLT3-ITD <10^{-4}: Gilteritinib 50% (11/22), Midostaurin 33% (6/18)
- PRECOG 0905 questions: what would uniform post-C2 MRD data look like?

Luger SM, et al. ASH 2024 Abstract #221

Randomized gilteritinib vs. midostaurin + IC

PASHA



Primary endpoint: OS (MRD is a secondary endpoint, measured after two intensive cycles)

NOTE:

- Initial design was an EFS primary endpoint, but changed during trial (similar to QuantumFirst)
- Daunorubicin dose was 60 mg/m2/d; double induction design
- Includes 1 year of maintenance post-consolidation AND post-HSCT
- MRD after 2 intensive cycles matches ELN MRD working group guidance
- both Flow MRD and UHS *FLT3*-ITD MRD to be assessed

The JOURNAL of PRESS RELEASES

ESTABLISHED IN 1970 MAR. 9, 2026 VOL. 123 NO. 12

Astellas and Hovon Confirm Phase 3 Study Did not Meet its Primary Endpoint of Overall Survival in Patients with Newly Diagnosed *FLT3*m+ AML

TOKYO AND ROTTERDAM, March 9, 2026 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas") and HOVON Foundation (Rotterdam, The Netherlands) today announced that the Phase 3 HOVON 156 / AMLSG 28-18 / PASHA study investigating XOSPATA™ (gilteritinib) versus midostaurin-based treatment in patients with newly diagnosed *FLT3*-mutated acute myeloid leukemia *(FLT3*m+ AML*)* eligible for intensive chemotherapy did not meet its primary endpoint of overall survival (OS) at the primary analysis.

While the study did not meet its primary endpoint of OS, gilteritinib showed a comparable OS benefit to midostaurin-based treatment in newly diagnosed *FLT3*m+ AML. The rates of treatment emergent adverse events and grade 3 or higher adverse events were similar between both treatment arms. Astellas and HOVON will complete a full evaluation of the data from HOVON 156 / AMLSG 28-18 / PASHA, including secondary endpoints, subgroup analysis and the safety of gilteritinib in combination with chemotherapy, and work with investigators on the future dissemination of the results.

Exactly 3 years earlier, the MORPHO study of post-transplant gilteritinib also did not reach its primary endpoint.
However, this study showed a clear leukemia-free survival benefit for patients who were MRD+ peri-HSCT

HOVON 156/PASHA questions:

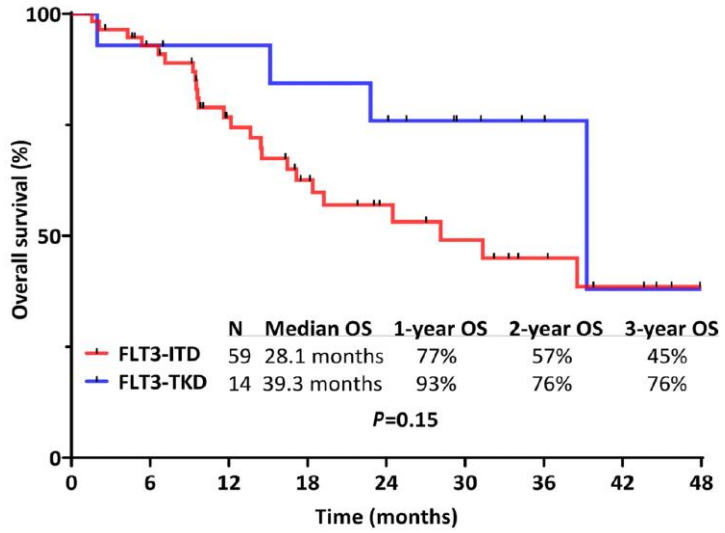
- Was OS the right endpoint if gilteritinib improves OS in 2nd line?
- Will high rates of transplant and post-HSCT maintenance eliminate any impact of initial TKI choice?
- Will MRD levels differ between the drugs? Will this be a function of various co-mutations?
- How will the PrECOG 0905 OS data compare once released?

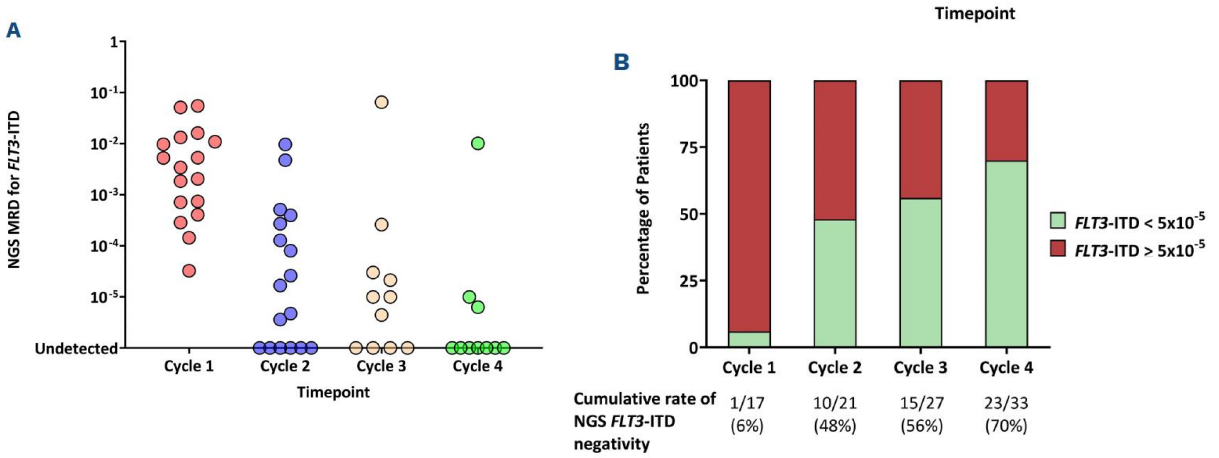
https://www.astellas.com/en/news March 9, 2026

VEN + HMA + FLT3 inhibitor triplets

MDACC experience:

- 73 newly diagnosed pts, *FLT3*-ITD (81%) or TKD+ (19%), unfit
- median age 70 (range 18-88)
  - ELN Risk: Favorable 12%, Intermediate 38%, Adverse 49%
- median follow up= 26 months
- FLT3 inhibitor
  - gilteritinib 67%
  - quizartinib 25%
  - sorafenib 7%
  - midostaurin 1%
- Myelosuppression was the major toxicity
  - early death in 1/73= 1%
  - median time to ANC >500 = 37 days
  - median time to Platelets >50K = 25 days
- CR/CRi= 93%
  - no patients were refractory (all had MLFS or better)

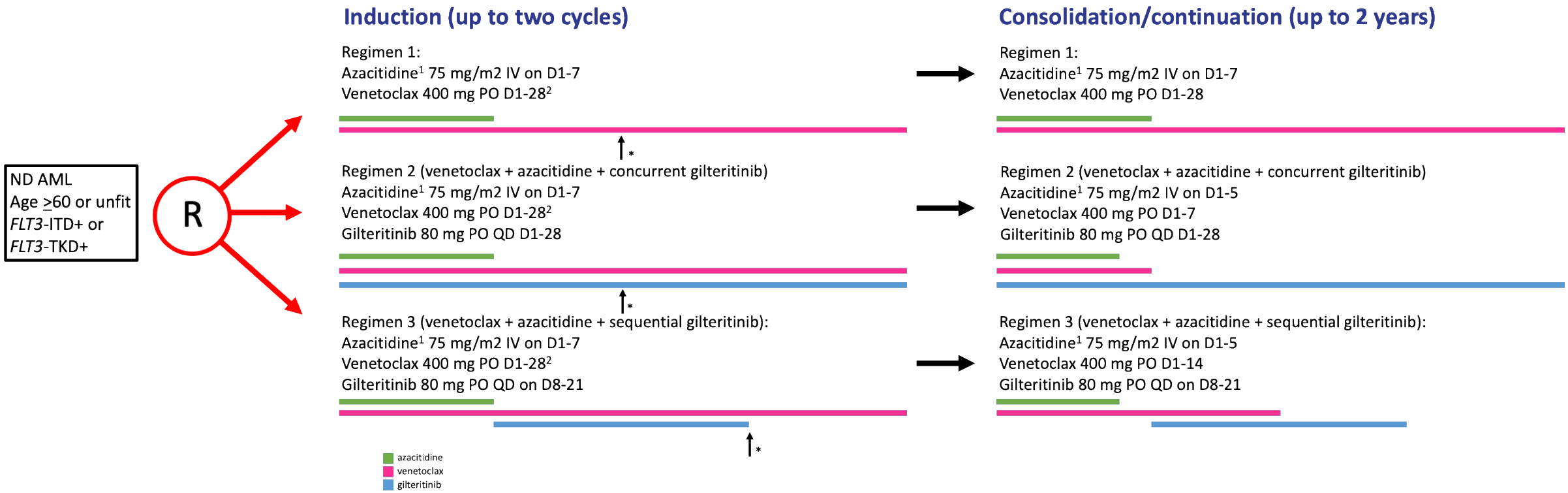




A separate, multi-center study of ven/aza/gilt had similar CRc rate, MRD(-) rates, and OS (albeit shorter follow up)

Short NJ, et al. Haematologica. 2026 Apr 1;111(4):1246-1253.
Short NJ, et al. J Clin Oncol. 2024;42(13):1499-1508
Altman JK, et al. ASH 2025, #654

MyeloMATCH MM1OA-EA02 study



*chemotherapy is withheld during induction until count recovery if no evidence of leukemia is seen at the time of a mid-cycle marrow biopsy (vertical arrow)
consolidation begins after count recovery to ANC>500 and platelets >50K
marrow biopsies for flow MRD are done after cycles 2 and 4 to measure the primary endpoint

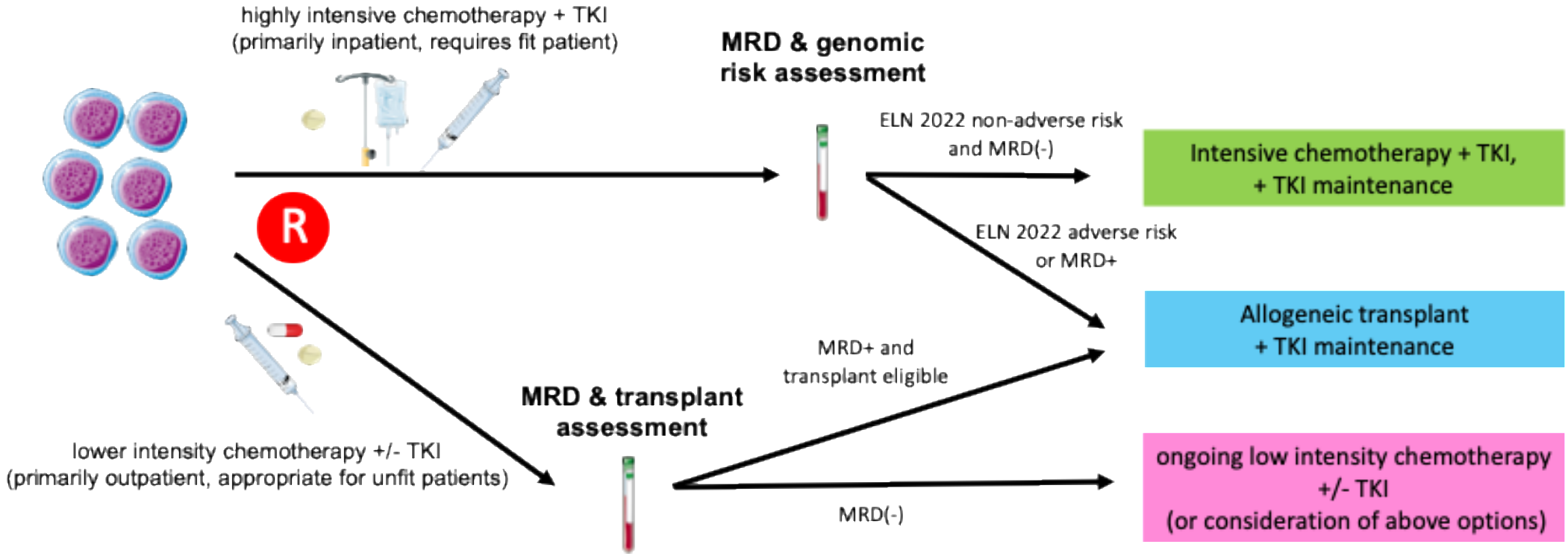
ND= newly diagnosed; AML= acute myeloid leukemia; FLT3= FMS-like tyrosine kinase 3; ITD= internal tandem duplication; TKD= tyrosine kinase domain (D835 or I836del); MRD= measurable residual disease

NCT06317649

Primary endpoint: MRD(-) CR after up to 4 cycles

Altman JK, Perl AE, et al. ASH Annual Meeting 2024 #2907.1

Following on the success of Paradigm…



- Patients with FLT3 mutations were **excluded** from PARADIGM

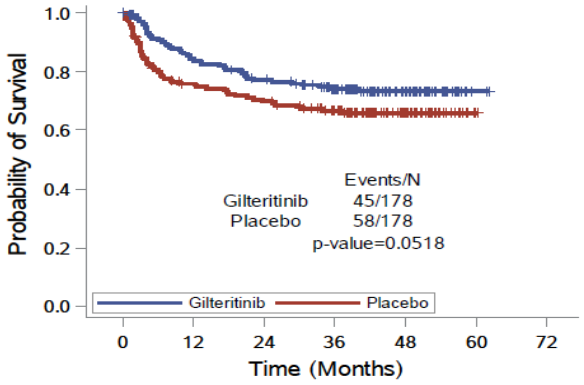
- The next frontier:
  - In fit *FLT3*mut+ patients, should the backbone regimen to which we add FLT3 inhibitors be 7+3 or AZA/VEN?

Perl AE, *Blood. 2025 Jun 12;145(24):2834-2839.*

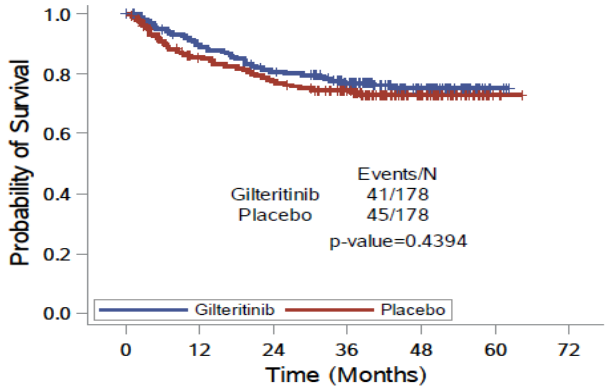
MRD+ *FLT3*-ITD+ patients benefit from post-HCT gilteritinib mainteance

BMT-CTN1506/MORPHO

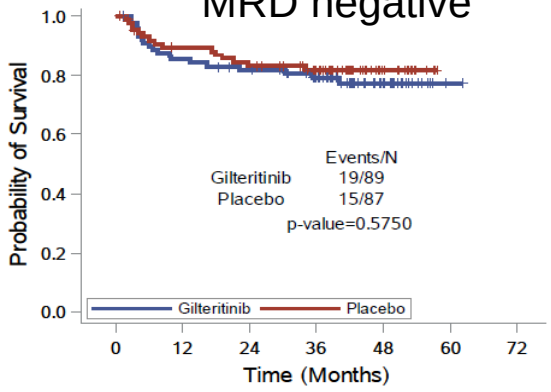
RFS



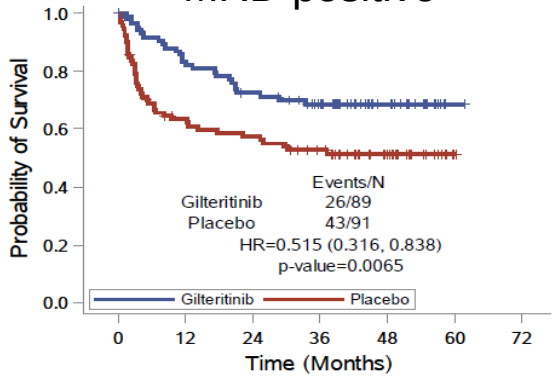
OS



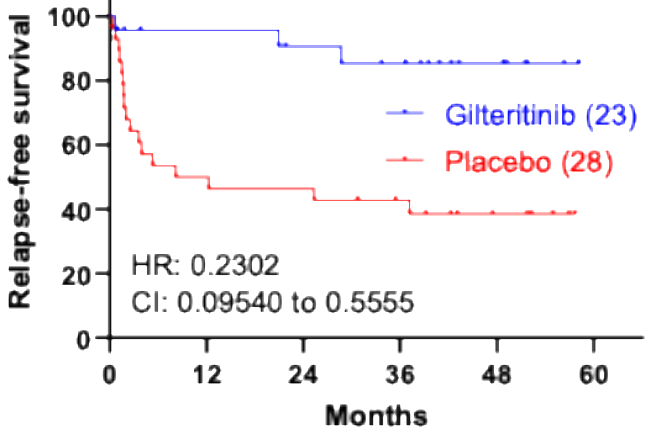
RFS
MRD negative



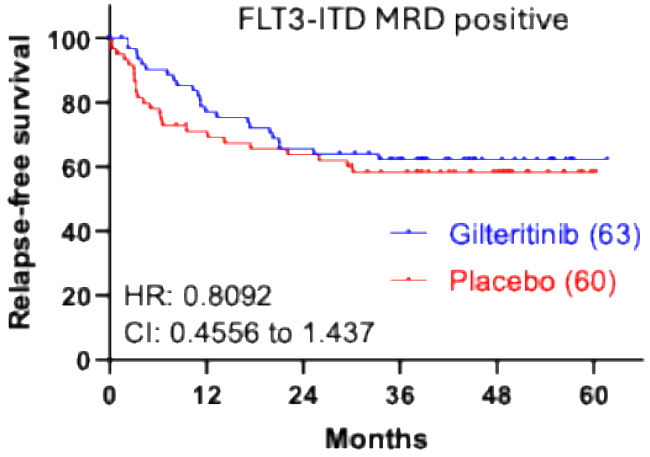
RFS
MRD positive



NPM1-mutated
FLT3-ITD MRD positive



NPM1 wild type
FLT3-ITD MRD positive

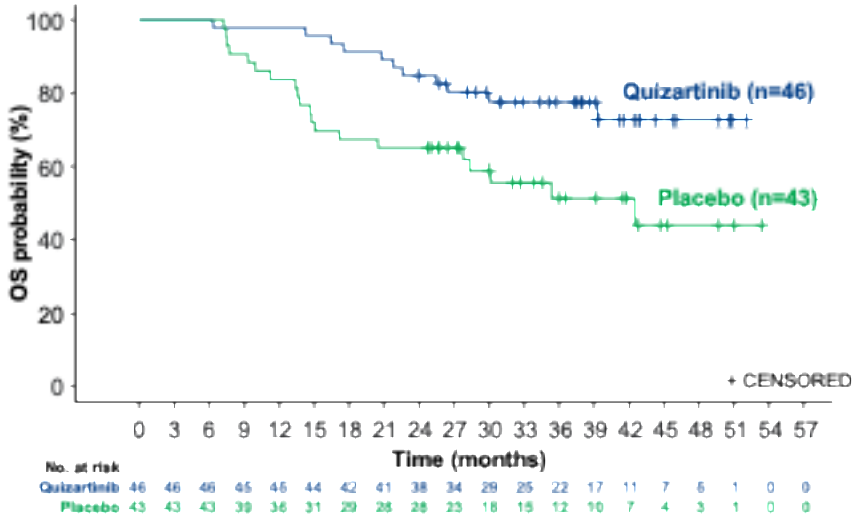


If MRD(-), no RFS benefit for gilteritinib in either *NPM1+ or NPM1*-WT

Levis MJ, et al. J Clin Oncol. 2024 May 20;42(15):1766-1775
Levis MJ, et al. Blood Adv. 2025 Oct 28;9(20):5123-5133

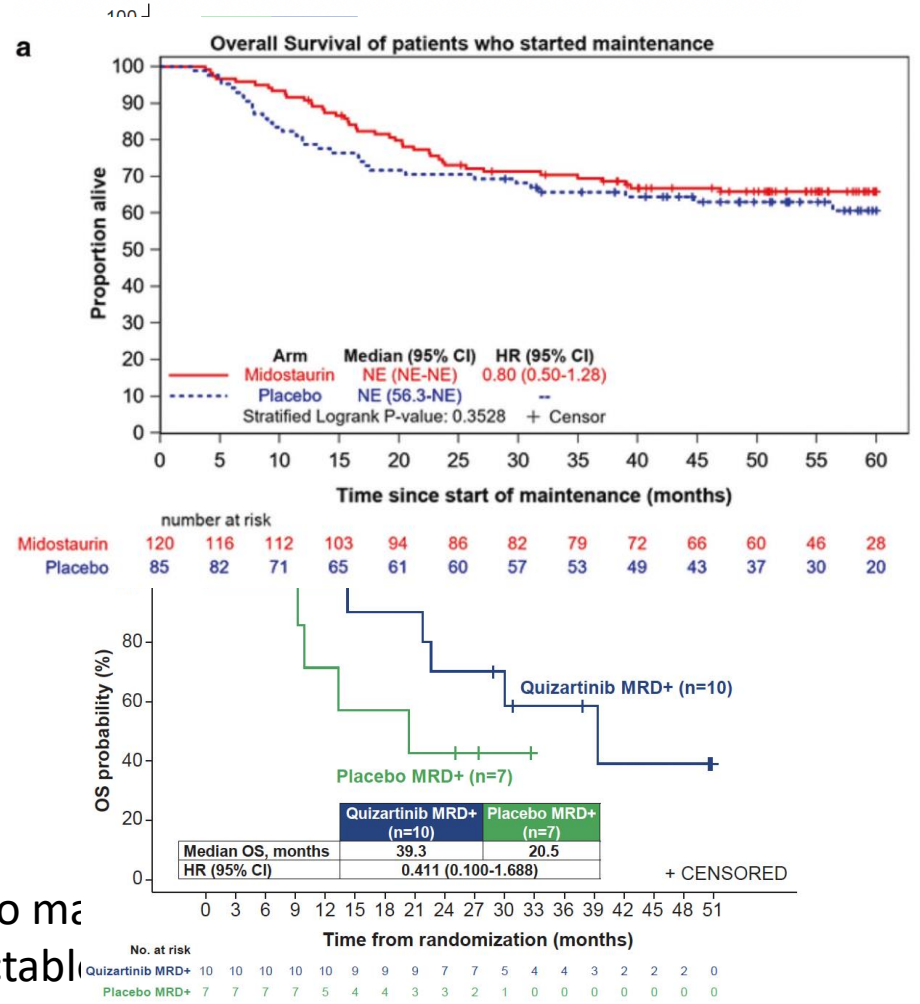
Quizartinib maintenance (Quantum-First)

OS in patients who received quizartinib maintenance without Allo-HCT



	Quizartinib (n=46)	Placebo (n=43)
Median OS, months	NR	42.5
HR (95% CI)	0.401 (0.192-0.838)	

C. OS in MRD− (0 Cutoff) Patients Who Received Maintenance Without Allo-HCT, by Treatment Arm RATIFY study **e with Allo-HCT**



NOTE: post-hoc analysis and no second randomization done prior to ma
only 17% of randomized patients with pre-HSCT samples had detectabl

Levis MJ, et al. Blood Adv. (epub, online)
Larson RA, et al. Leukemia. 2021 Sep;35(9):2539-2551.

Conclusions (aka "How I Treat")

- All 3 approved FLT3 inhibitors work well, are tolerable for 14 days + IC, and improve OS
  - The key question now is not which TKI, but what should be the backbone regimen be for fit patients: AZA/VEN or IC?

- INITIAL TKI CHOICE WITH INTENSIVE CHEMO:
  - For *FLT3*-TKD, midostaurin remains the standard of care
  - I give quizartinib in younger patients (e.g. age <65) and any age if fit and *NPM1c+*
  - I generally use ven/aza +/- gilteritinib in patients >age 60-65 or with comorbidities
  - coming soon: HOVON156/PASHA (?EHA LBA) and retrospective comparison of mido vs. quiz (Lee M, EHA 2026 #S133)
  - combination studies of FLT3i with menin inhibitors for IC or ven/aza backbone are ongoing

- MAINTENANCE TKI:
  - For CR1 post-HSCT, I give gilteritinib to MRD+ patients x 2 years (and longer if >CR1), more evidence base than quiz, better tolerability than sorafenib/midostaurin
  - For *FLT3*-ITD+ post-consolidation I give quizartinib maintenance, for FLT3-TKD+ midostaurin seems reasonable

- RELAPSED/REFRACTORY TKI
  - gilteritinib (especially if single agent)