# Novel FLT3 inhibitors

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# Disclosures of Mark Levis

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Abbvie | | | | | | X | |
| Astellas | X | | | | | X | |
| BMS | | | | | | X | |
| Daiichi-Sankyo | | | | | | X | |
| GSK | | | | | | X | |
| Pfizer | | | | | | X | |
| Syndax | | | | | | X | |
| Takeda | | | | | | X | |

# AML therapy in ancient times (e.g., year ~2000)

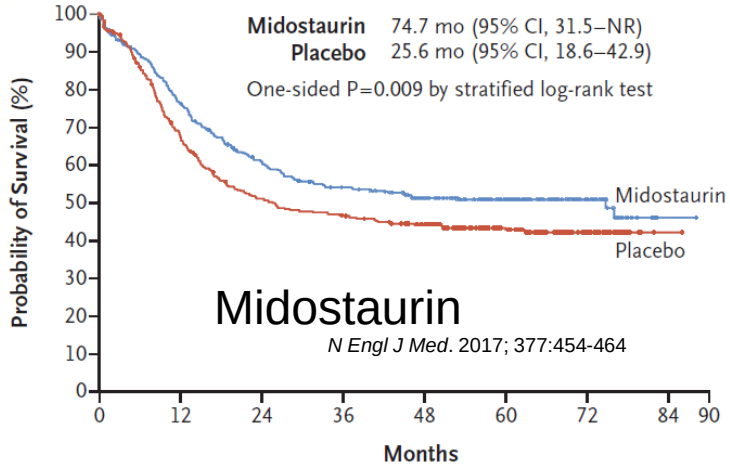
- Treat all AML as the same
- Try to pound the disease (and patient) with chemotherapy
  - Non-targeted
  - 7+3, etc…
- Outcomes: dismal

# AML therapy today

- Identify potential molecular targets
- Incorporate targeted therapy into treatment
  - FLT3 inhibition
  - Bcl-2 inhibition
  - IDH1/2 inhibition
- Use Measurable Residual Disease (MRD) to refine prognosis

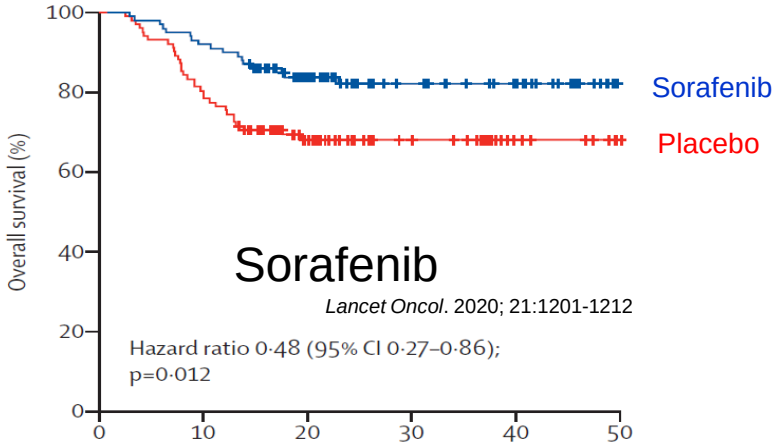
# Next steps in AML therapy

- How to better incorporate targeted therapy into chemotherapy regimens
- How to better combine targeted therapies
- How to use MRD to personalize targeted therapy



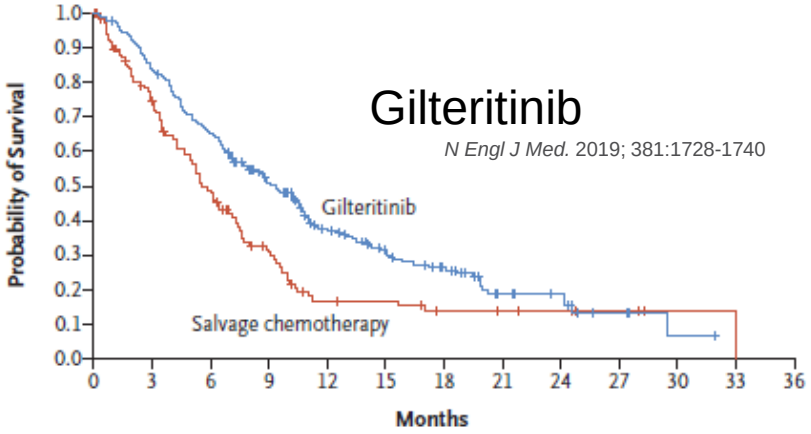

## Midostaurin

*N Engl J Med*. 2017; 377:454-464



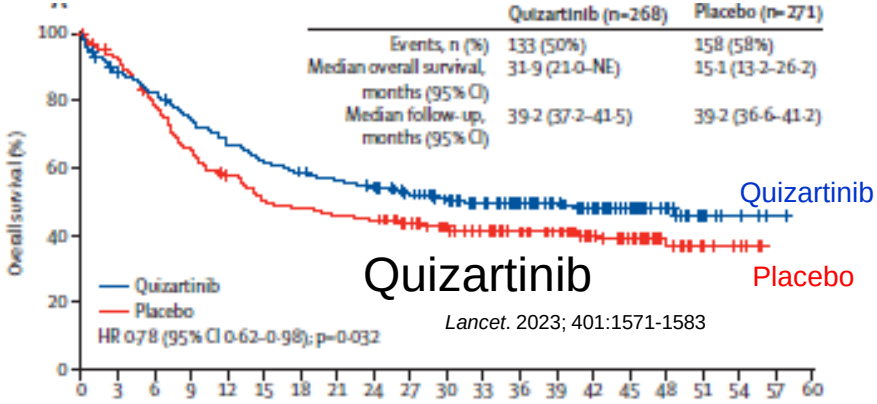

## Sorafenib

*Lancet Oncol*. 2020; 21:1201-1212




## Gilteritinib

*N Engl J Med*. 2019; 381:1728-1740



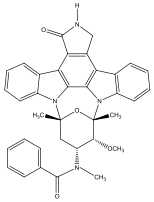

## Quizartinib

*Lancet*. 2023; 401:1571-1583

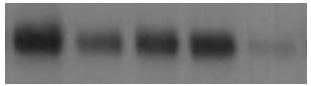
# FLT3 inhibitors



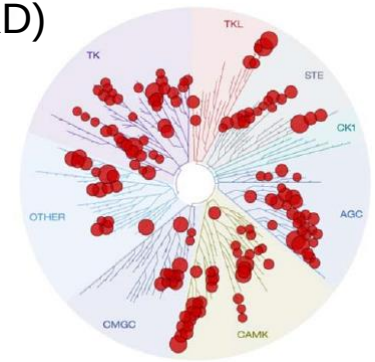
Lowest *in vivo* potency
Type I inhibitor (ITD and TKD)



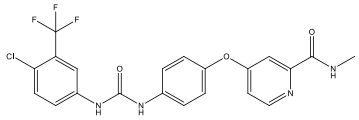
Base.
Treatment



Midostaurin




Intermediate *in vivo* potency
Type II inhibitor (ITD only)



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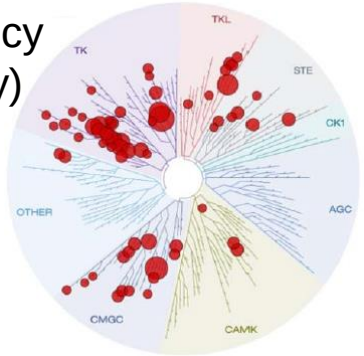


Sorafenib

Gilteritinib

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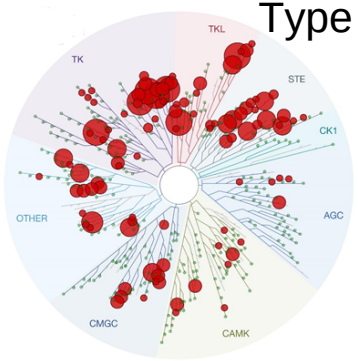


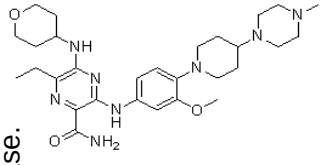

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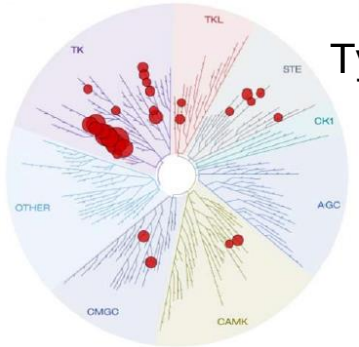
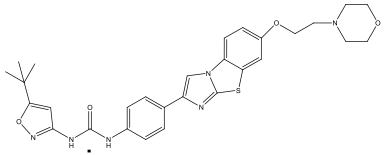



Quizartinib

Highest *in vivo* potency
Type II inhibitor (ITD only)



Base.
Treatment

# Three recent clinical trials

## Phase 1B study

Chemotherapy
+ gilteritinib

Newly-diagnosed
AML

*J Clin Oncol.* 2023;41:4236-4246

## QuANTUM-First

Chemotherapy
+/- quizartinib

Newly-diagnosed
FLT3-ITD AML

*Lancet*. 2023; 401:1571-1583

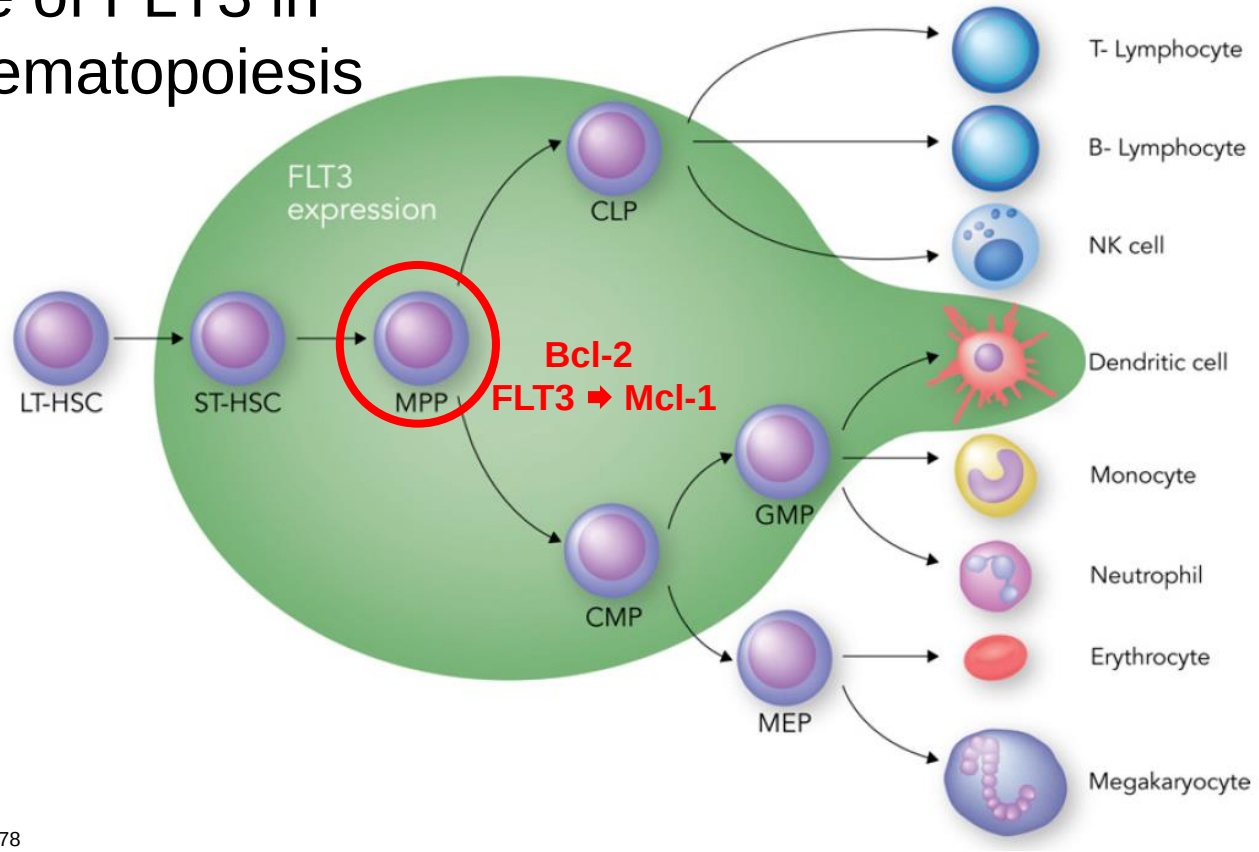
## MORPHO

Post-transplant
maintenance
with gilteritinib

Newly-diagnosed
FLT3-ITD AML

*J Clin Oncol.* 2024; (*In Press*)

# The role of FLT3 in normal hematopoiesis




*Cell Stem Cell* 2011; 9:64.

*Cell Reports 2013;* 3:1766.

*Blood Advances* 2020; 4:1178

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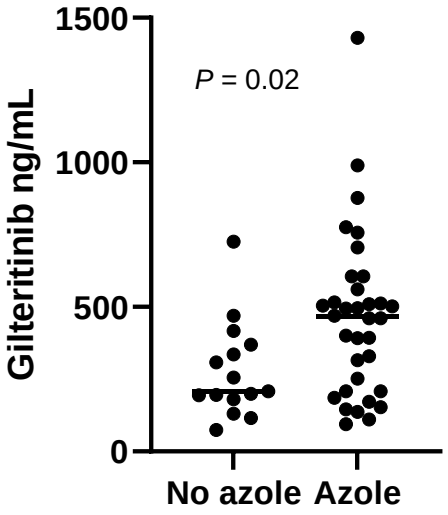
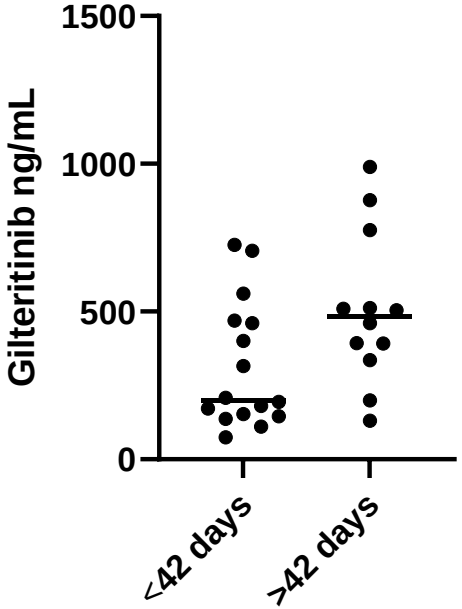



Concomitant azole use
=
Higher gilteritinib levels




Higher gilteritinib levels
=
Delayed count recovery

Phase 1B study

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*J Clin Oncol.* 2023;41:4236-4246

Induction therapy + gilteritinib:

Safe and well-tolerated
High response rate

<u>Delayed count recovery</u>

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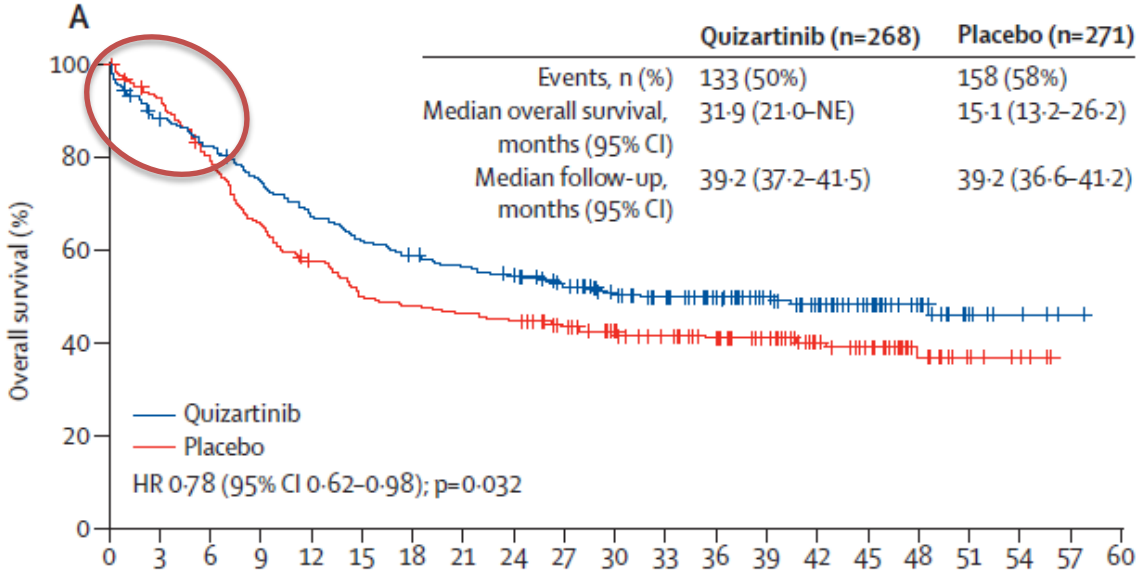


No benefit of quizartinib in pts > age 60

*Lancet*. 2023; 401:1571-1583

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+/- quizartinib

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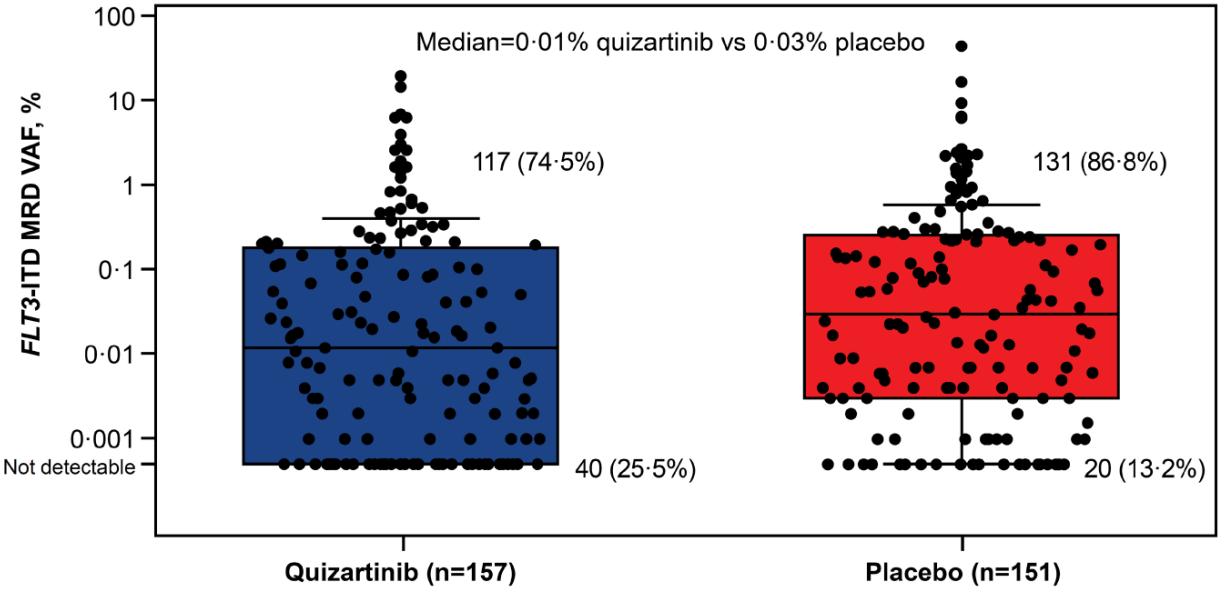
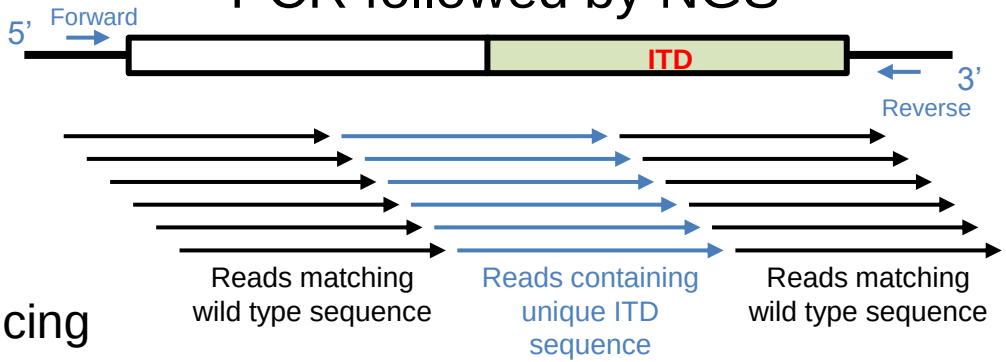
FLT3-ITD AML




FLT3-ITD MRD assay:
Quizartinib added to induction chemotherapy leads to deeper remissions

*Lancet*. 2023; 401:1571-1583

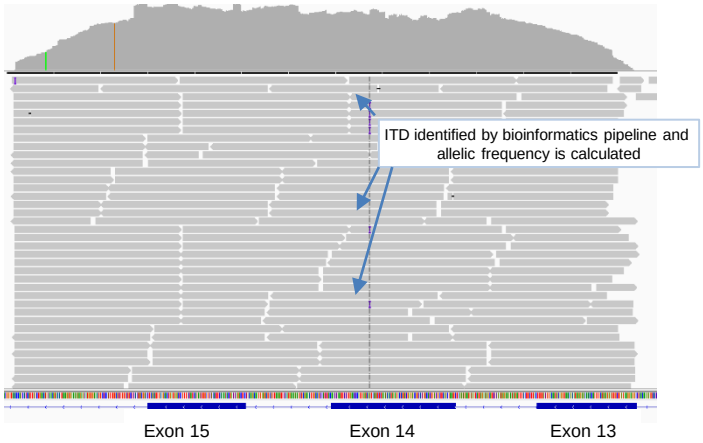
# MRD assay for FLT3-ITD mutations: PCR followed by NGS




Ultra-deep sequencing of the region (Illumina SBS)

Diverse reads aligned to FLT3 genomic sequence

Relevant FLT3 region (exon 14-15) targeted




Detects FLT3-ITD mutations with sensitivity of ~2 x $10^{-6}$

*Blood*. 2020. 135:75-78

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Post-transplant
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FLT3-ITD AML

*J Clin Oncol.* 2024; (*In Press*)

# MORPHO

Post-transplant maintenance with gilteritinib

Newly-diagnosed FLT3-ITD AML

*J Clin Oncol.* 2024; (*In Press*)

- Randomized, double-blind, placebo-controlled
  - Gilteritinib versus placebo as post-HCT maintenance for FLT3-ITD AML
- Global study:
  - 356 pts randomized at 122 centers in 16 countries
  - Accrual from August 2017 to July 2020
- Primary endpoint:
  - Relapse-free survival (RFS)
- Secondary endpoints include:
  - Overall survival (OS)
  - Effect of pre- and post-HCT MRD on RFS and OS

MORPHO

Post-transplant maintenance with gilteritinib

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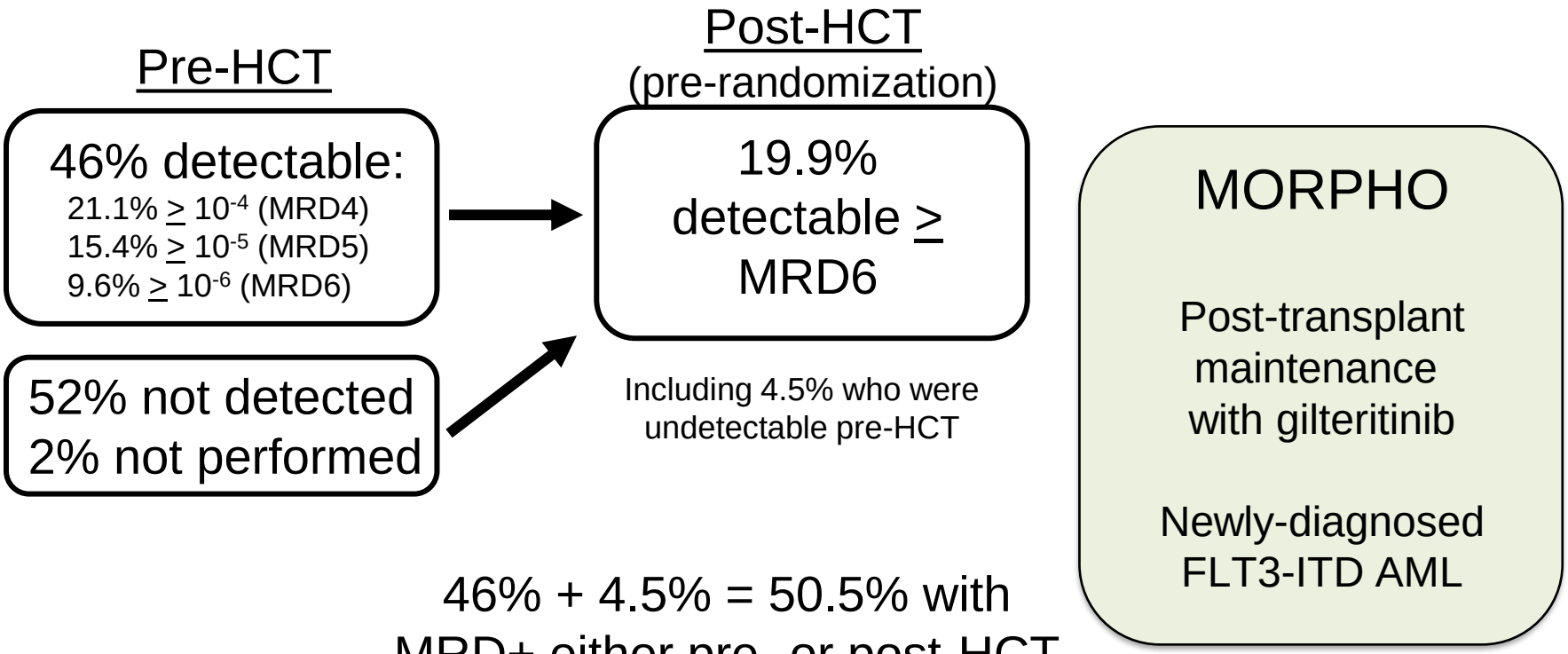
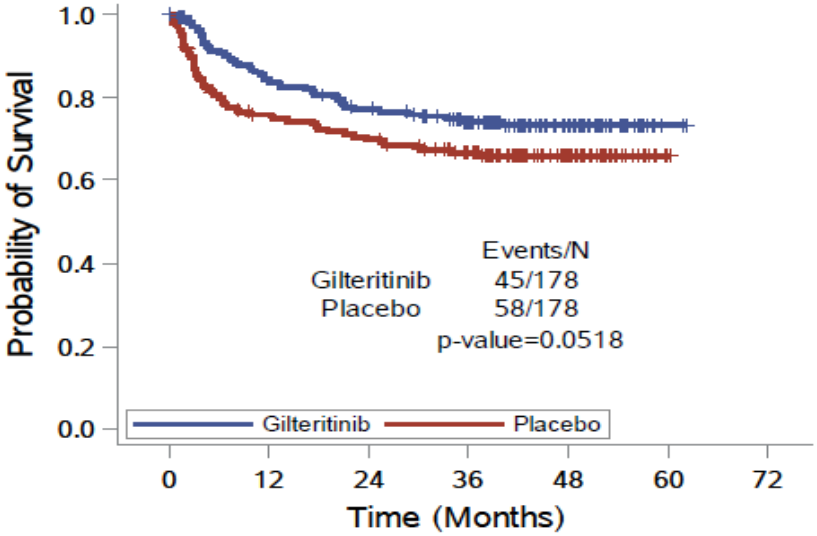
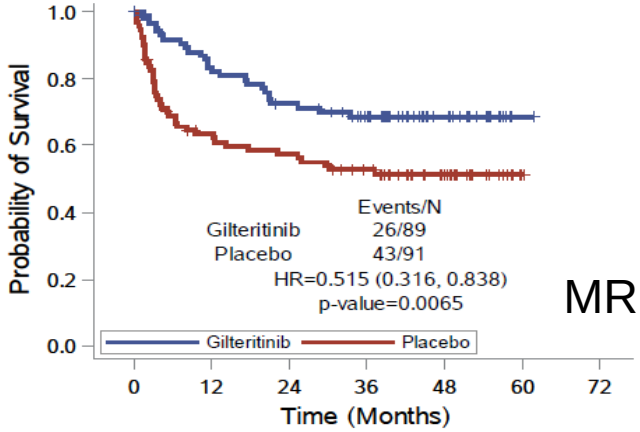



*J Clin Oncol.* 2024; (*In Press*)

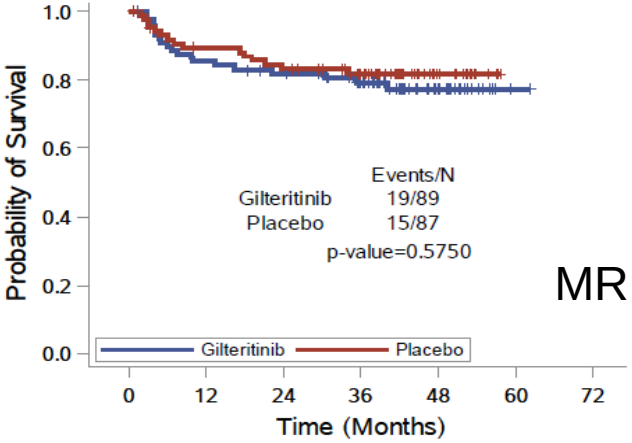
# MORPHO:

Primary objective:
Relapse-free survival (RFS)
HR = 0.679 (0.459-1.005)




RFS
MRD positive




RFS
MRD negative

*J Clin Oncol.* 2024; (*In Press*)

# Safety and tolerability

| Safety Parameter | Gilteritinib (N = 178)* | Placebo (N = 177) |
|---|---|---|
| Treatment emergent acute GVHD[1] grade II-IV | 33 (18.5%) | 36 (20.3%) |
| Treatment emergent chronic GVHD | 93 (52.2%) | 75 (42.4%) |
| Treatment emergent infection grade 3 or greater | 58 (32.6%) | 38 (21.5%) |
| TEAE[2] leading to withdrawal of treatment | 35 (19.7%) | 19 (10.7%) |
| Drug-related TEAE leading to withdrawal of treatment | 27 (15.2%) | 14 (7.9%) |
| Drug-related TEAE leading to drug interruption | 32 (18.0)% | 12 (6.8%) |
| Drug-related grade 3 or higher TEAE | 109 (61.2%) | 45 (25.4%) |

*J Clin Oncol.* 2024; (*In Press*)

# Drug-related Grade 3 or higher treatment emergent adverse events

| Grade 3 or higher Adverse Event, n(%) | Gilteritinib (N=178) | Placebo (N=177) |
|---|---|---|
| **Neutrophil count decreased** | 44 (24.7%) | 14 (7.9%) |
| **Platelet count decreased*** | 27 (15.2%) | 10 (5.6%) |
| **Anemia** | 11 (6.2%) | 3 (1.7%) |
| **Alanine aminotransferase (ALT) increased** | 6 (3.4%) | 4 (2.2%) |
| **Creatine phosphokinase increased** | 12 (6.7%) | 0 (0%) |

*J Clin Oncol.* 2024; (*In Press*)

- MRD level ranged from $3.0 \times 10^{-1}$ to $1.09 \times 10^{-6}$
- 51/164 (31.1%) with pre-HCT MRD had more than a single *FLT3-ITD* mutation
  - "Multiclonal ITDs"- 2 or more *FLT3-ITD* clones detected
- MRD detected post-HCT was often eradicated during follow-up

MORPHO

Post-transplant maintenance with gilteritinib

Newly-diagnosed FLT3-ITD AML

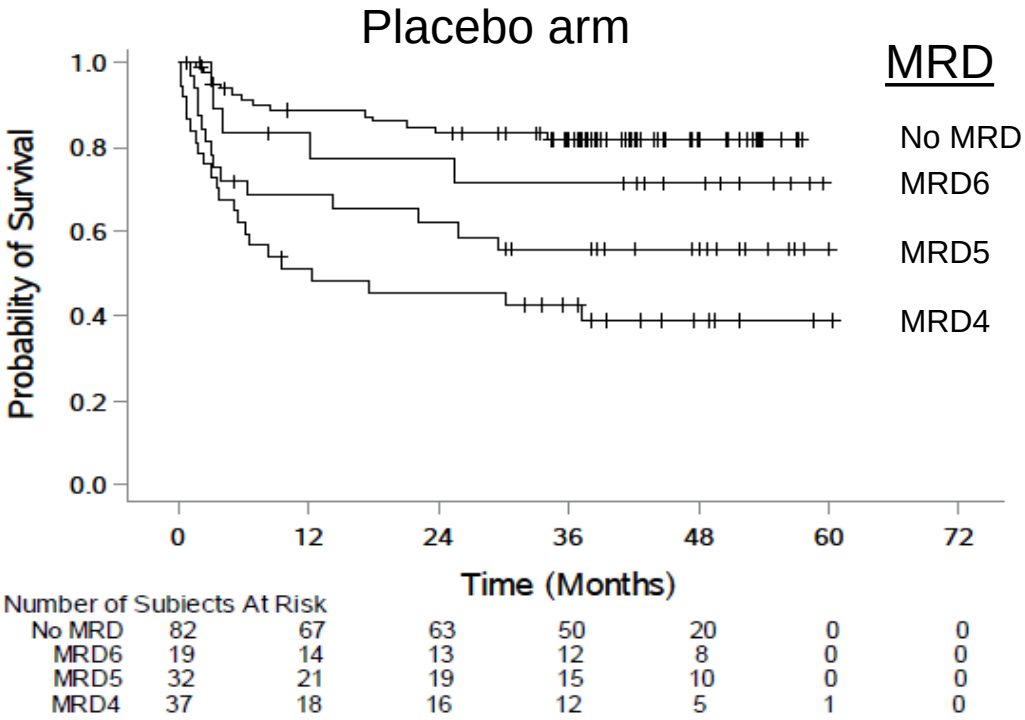
*ASH 2023 abstract #973*

# All levels of detectable MRD impact RFS

$10^{-6} \leq$ MRD6 $< 10^{-5}$

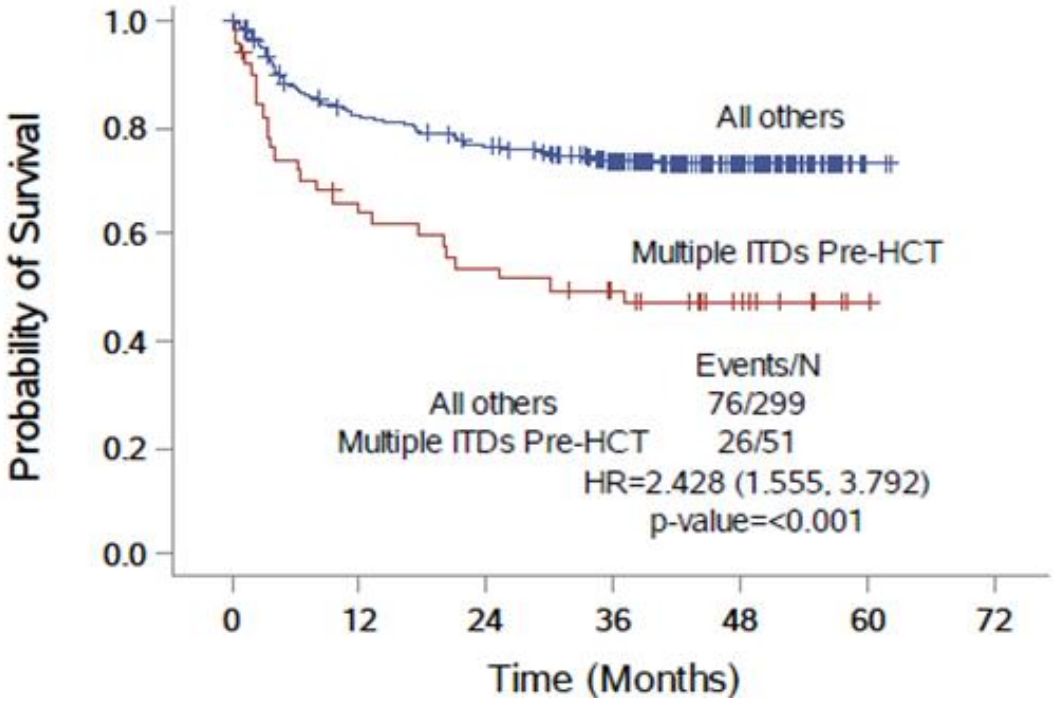
$10^{-5} \leq$ MRD5 $< 10^{-4}$

$10^{-4} \leq$ MRD4




| MRD | Events/N |
|---|---|
| No MRD | 14/82 |
| MRD6 | 5/19 |
| MRD5 | 14/32 |
| MRD4 | 22/37 |

# Multiclonal ITD mutations = worse outcome

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*ASH 2023 abstract #973*

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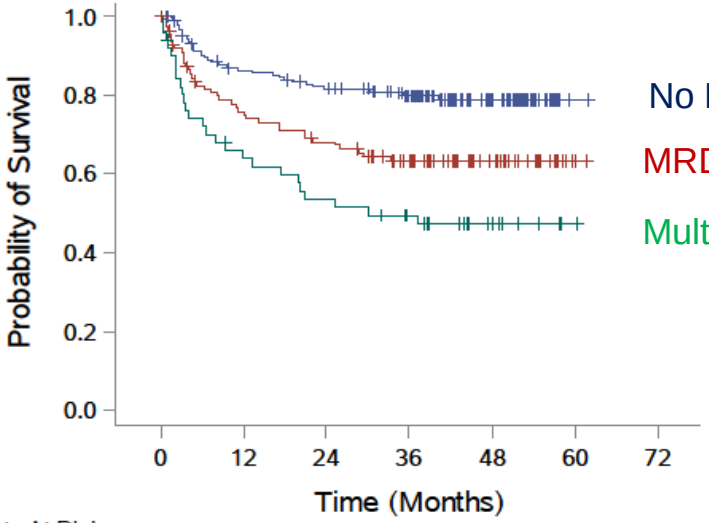



| Number of Subjects At Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| No MRD pre- or post-HCT | 186 | 153 | 143 | 117 | 50 | 1 | 0 |
| MRD positive, no microclones | 113 | 80 | 71 | 56 | 30 | 1 | 0 |
| Microclones | 51 | 31 | 26 | 21 | 11 | 1 | 0 |

No MRD pre- or post-HCT

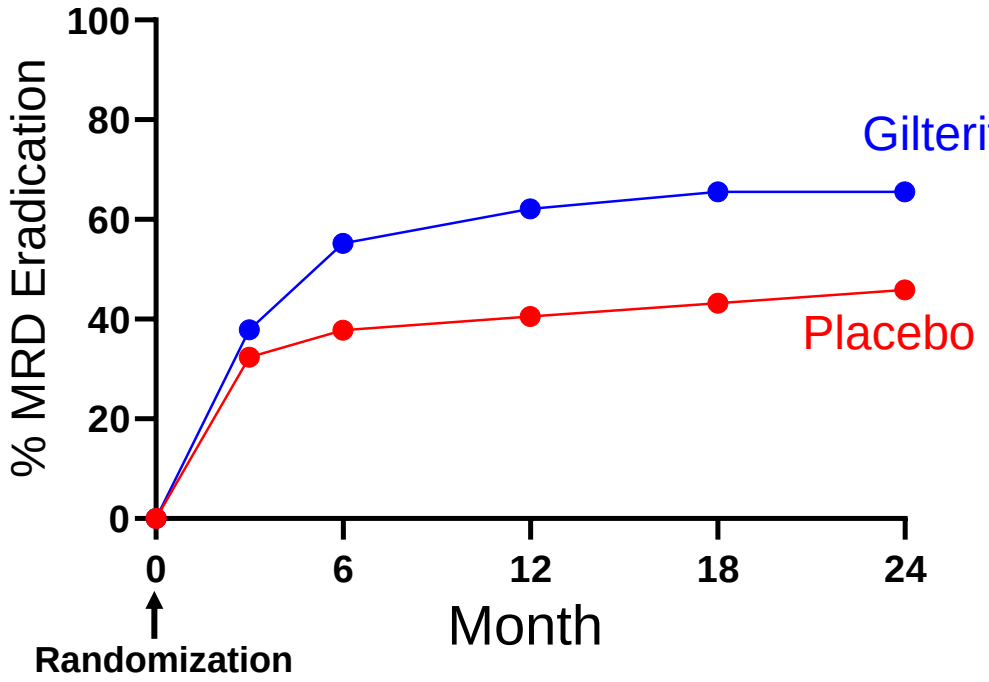
MRD positive, Single ITD clone

Multiclonal ITD mutations

| Events/N | |
|---|---|
| 37/186 | |
| 39/113 | *P* = 0.0023 |
| 26/51 | *P* = 0.0489 |

*ASH 2023 abstract #973*

# Time course of post-HCT MRD eradication: MRD eradicated in 69% of pts on gilteritinib versus 44% on placebo

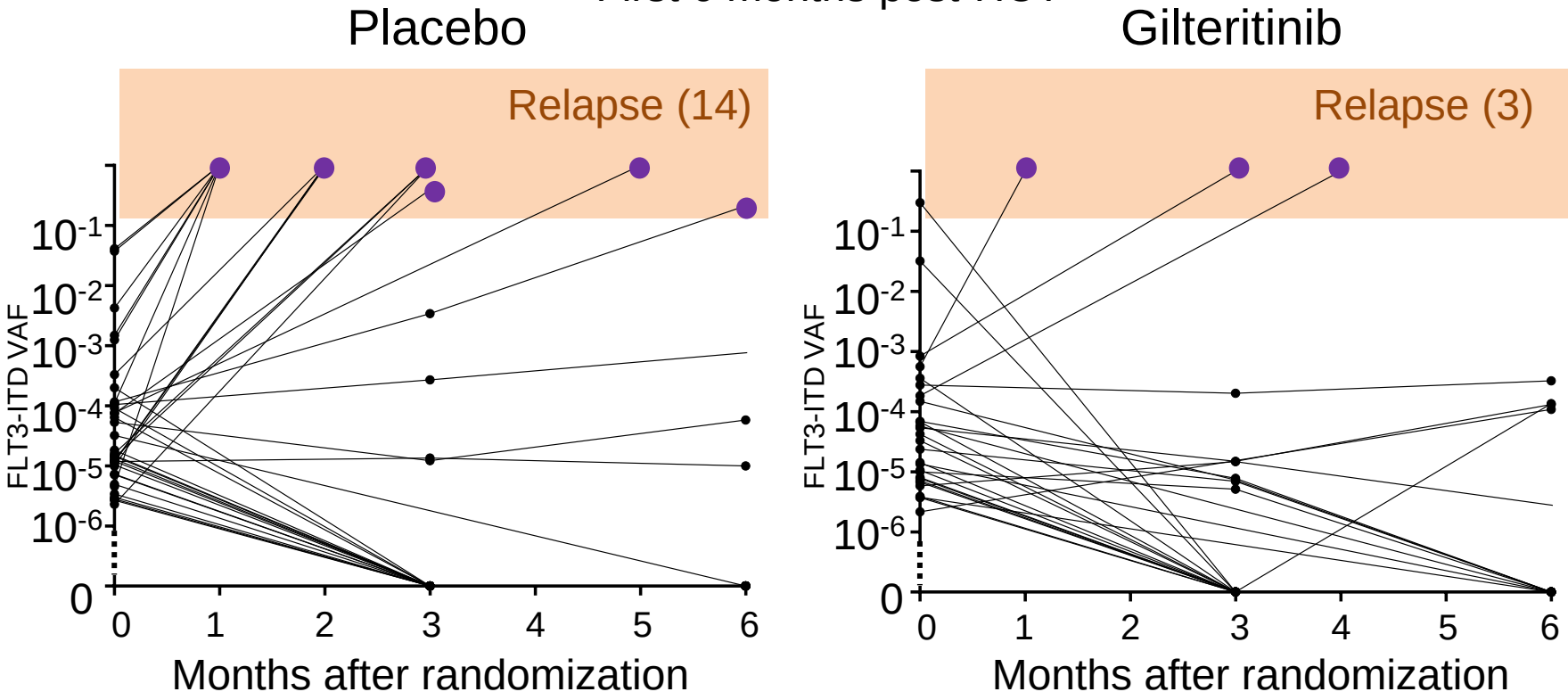



<u>Definition of MRD eradication:</u>

1. FLT3-ITD clone becomes undetectable
2. FLT3-ITD clone does not recur
3. Participant does not relapse

*ASH 2023 abstract #973*

# FLT3-ITD clones detected after transplant, prior to randomization: First 6 months post-HCT

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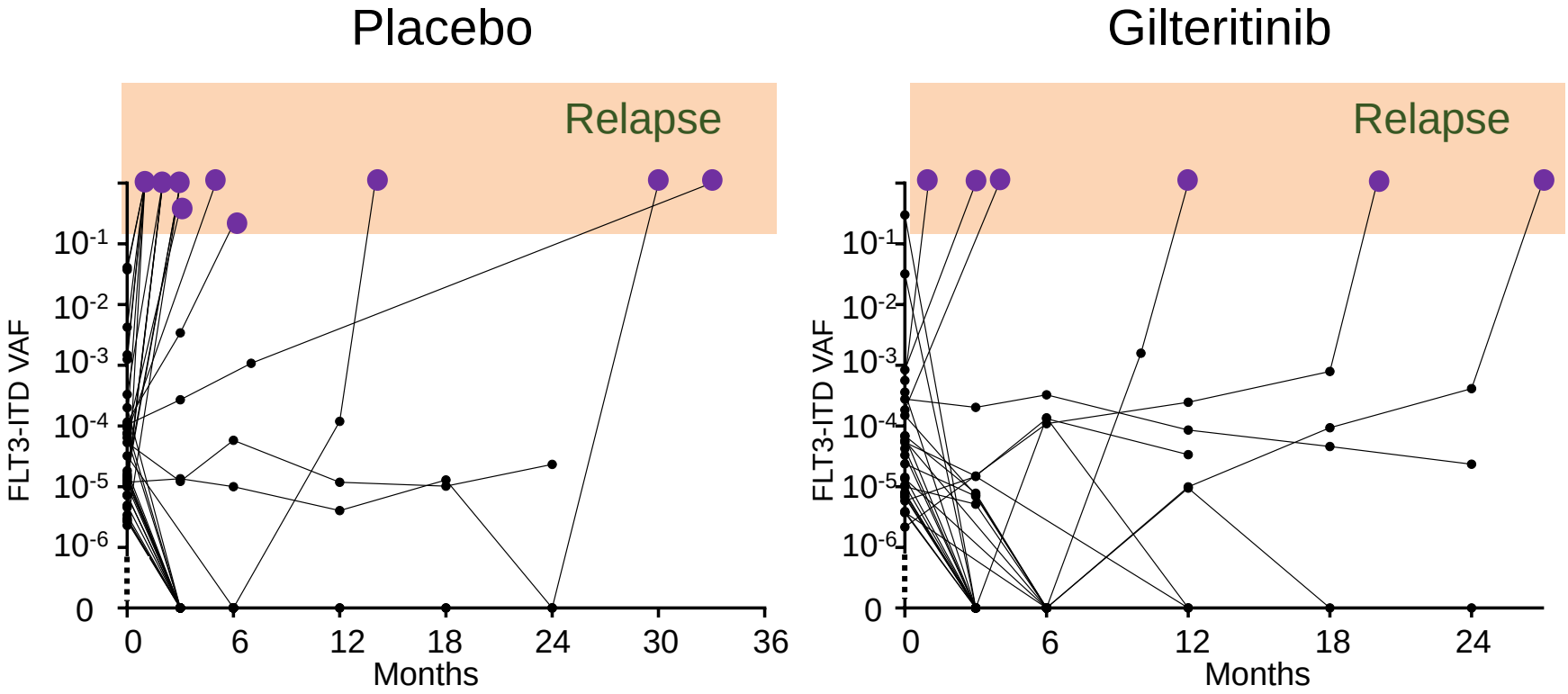
# FLT3-ITD clones detected after transplant, prior to randomization: 24+ months post-HCT

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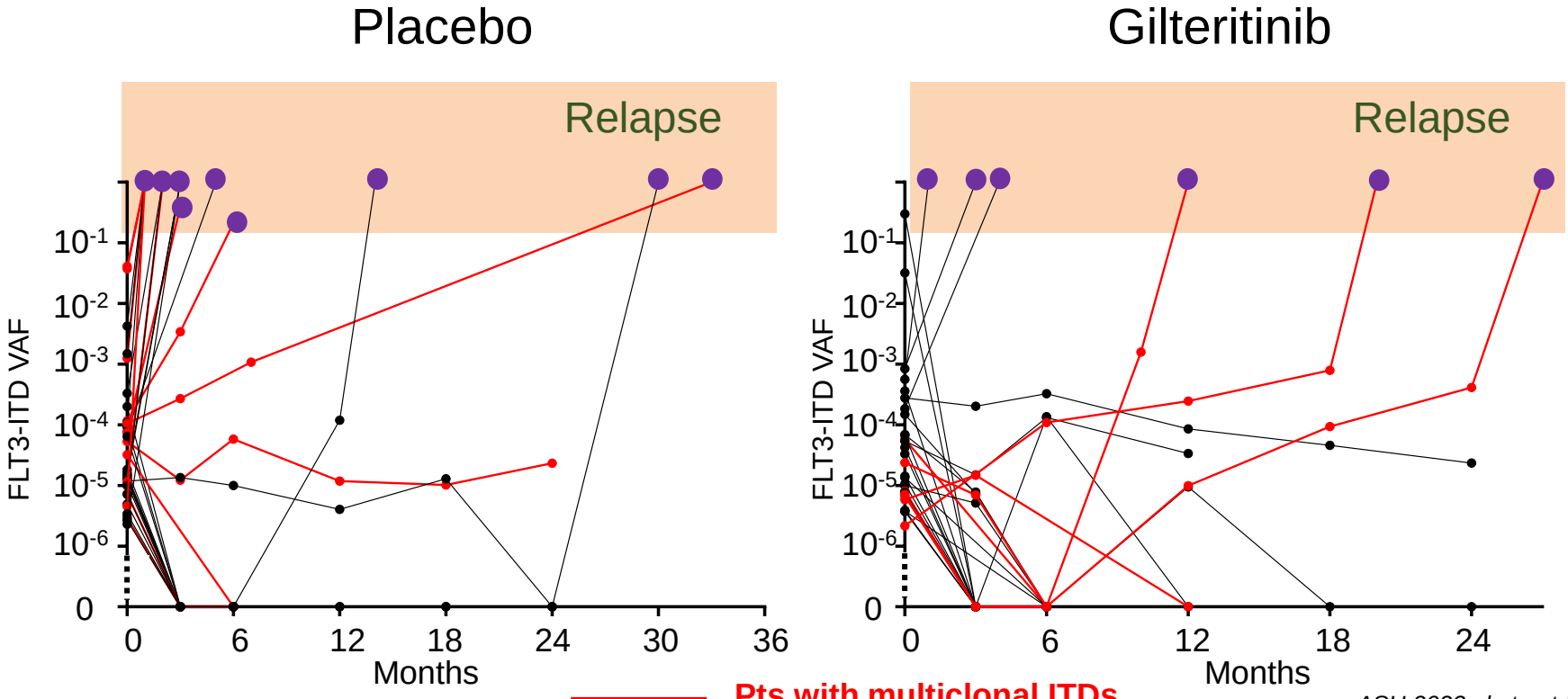


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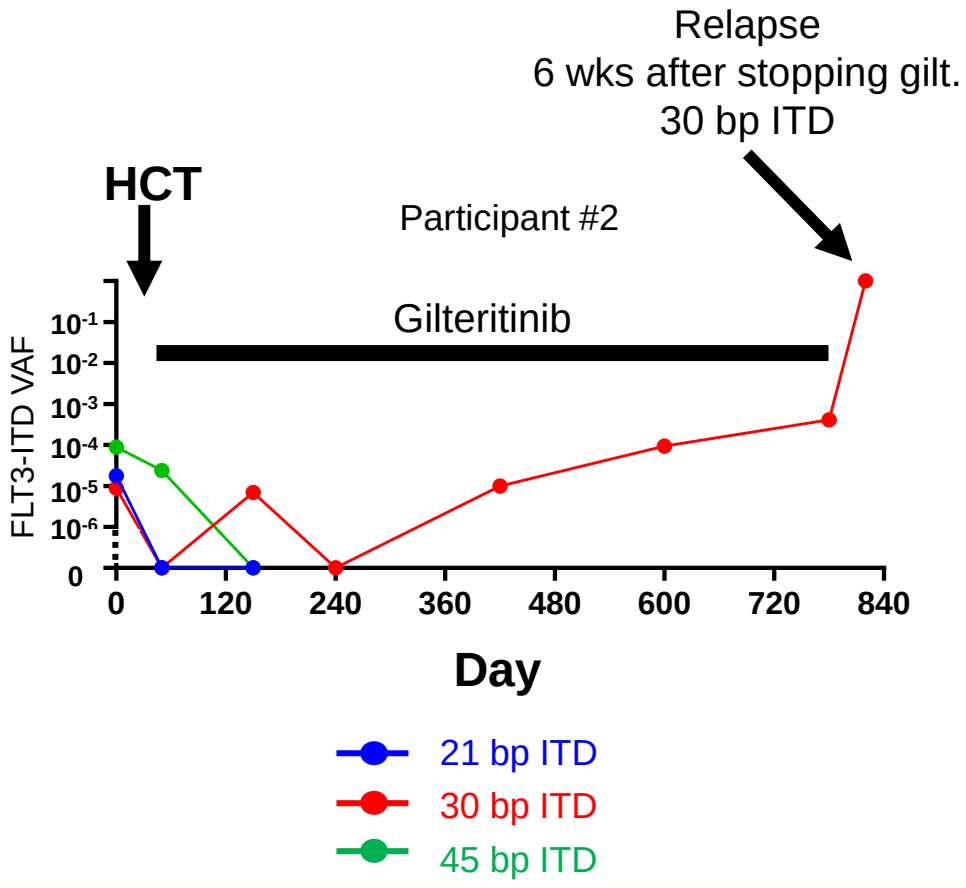
Kinetics of relapse on gilteritinib



# Conclusions

- Potent FLT3 inhibition in the setting of chemotherapy or transplant intensifies and prolongs myelosuppression.
- Not all patients undergoing transplant benefit from post-transplant FLT3
  - MRD is only one factor influencing this…
  - More variables will emerge from MORPHO data set (analysis ongoing)
- Relapse or eradication predominantly occurs during first 6 months post-HCT
- FLT3-ITD MRD is a valuable new tool for clinicians
  - Sensitive and specific
  - Any detectable level is potentially clinically meaningful
  - Can be used to guide duration of maintenance
  - Can identify pts who don't need post-transplant FLT3 inhibition
    - …thereby avoiding unnecessary myelosuppression and GVHD
- The presence of multiple FLT3-ITD clones pre-transplant is associated with a worse survival

Thank you!

JOHNS HOPKINS
MEDICINE
THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER