Quizartinib in Combination with Decitabine and Venetoclax in *FLT3-ITD* Mutated AML

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Key Takeaway Points/Conclusions

In older patients with newly diagnosed *FLT3-ITD*–mutated AML, outcomes are poor (median OS ~10 months).

Quizartinib, decitabine and venetoclax (triplet) improves OS (median 36m) in older patients with newly diagnosed *FLT3-ITD* AML.

Myelosuppression (common AE) can be mitigated with appropriate dose adjustments.

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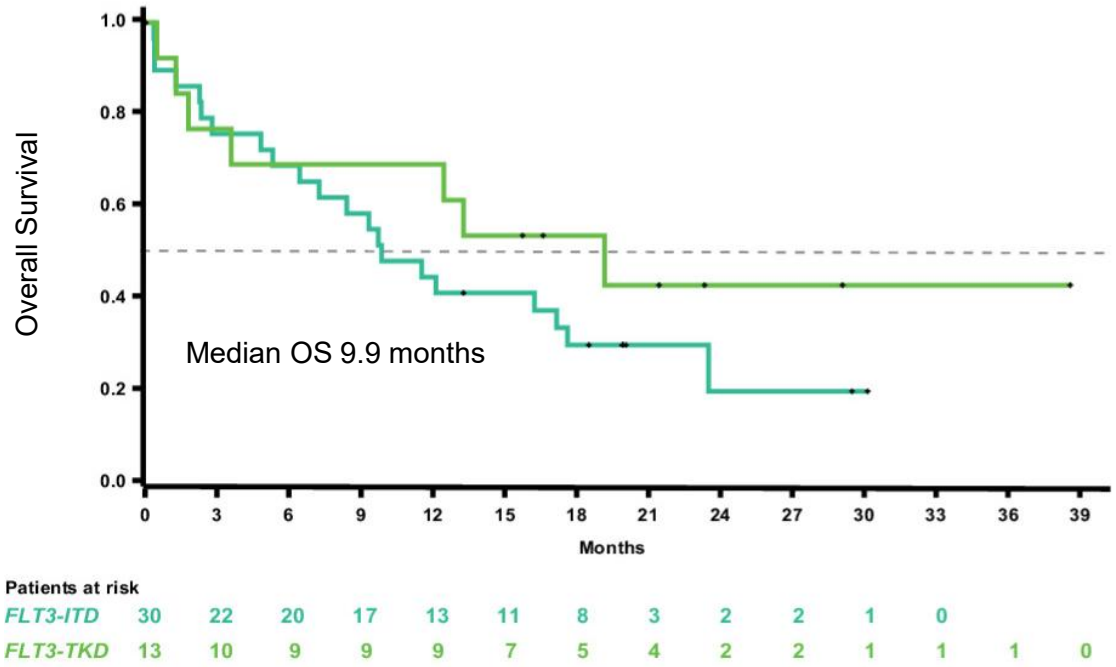
Background

- FLT3 (ITD + TKD) mutations detected in 20-30% of pts with AML[1]
- FLT3-ITD mutations - ↑ risk of relapse, ↓ OS
- Older/unfit pts with newly diagnosed FLT3m AML – poor outcomes
  - AZA + Venetoclax – median OS of 9.9 months[2]
- Quizartinib – potent 2nd generation FLT3i
  - ↑ OS in FLT3m in R/R as monotherapy in randomized PIII study[3]
  - Approved (FDA) in combination with 7+3 in pts who are fit for intensive chemotherapy in frontline[4]
- In this study, we investigated the safety and efficacy of quizartinib in combination with decitabine and venetoclax in FLT3-ITDm AML.

OS in Frontline *FLT3m* AML with Azacitidine and Venetoclax[2]

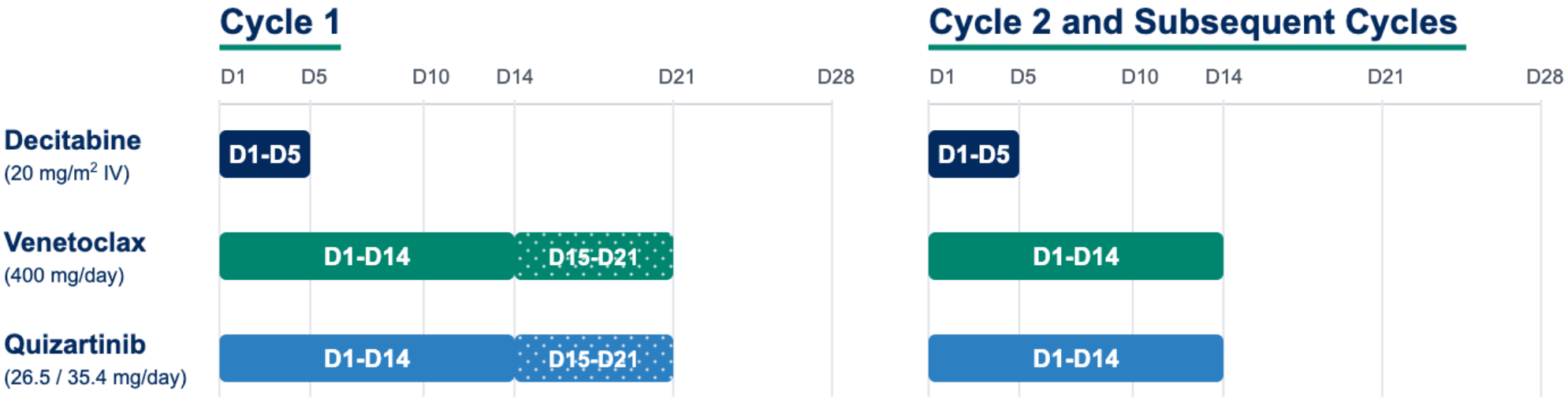


1-Kottaridis et al. *Leuk Lymphoma*. 2003;44:369-73.
2-Konopleva et al. *Cancer Discov*. 2022;12:1262-79.
3-Cortes et al. *Lancet Oncol*. 2019;20:984-97.
4-Erba et al. *Lancet*. 2023;401:1571-83

Methods

Patients;
R/R *FLT3 ITD*-mutated AML or high-risk MDS (≥10% blasts)
or newly diagnosed *FLT3 ITD*-mutated AML unfit for IC

Key Eligibility: Unfit for Intensive Induction
Age ≥75 y, or age <75 y with ≥1: ECOG 2-3;
LVEF ≤50%; DLCO/FEV1 ≤65%; angina/CHF on meds;
AST/ALT >3× ULN; anthracycline contraindication; other comorbidity



Primary Objectives: Phase I: determine MTD. Phase II: evaluate safety and efficacy (modified CRc [mCRc]); mCRc = CR + CRi + MLFS.

Key Amendments: C1 decitabine D1-D10 to D1-D5; venetoclax/quizartinib stopped at D14 for BM remission (≤5% BM blasts) or hypoplastic BM.

Notes: Consolidation permitted up to 12 cycles or beyond if deriving clinical benefit.

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Baseline Patient Characteristics

Patient Characteristics	Newly Diagnosed Cohort (N=42)	Relapse/Refractory Cohort (N=46)
Age, years		
Median	70 (62-85)	58 (19-86)
≥75 years, No. (%)	14 (33)	5 (11)
Diagnosis, AML, No. (%)		
De novo	25 (60)	34 (74)
Secondary	12 (28)	9 (20)
Therapy related	5 (12)	3 (6)
BM blasts %, median	63 (20-96)	52 (6-92)
Karyotype, No. (%)		
Diploid	26 (62)	18 (40)
Other	11 (26)	14 (30)
Adverse	5 (12)	14 (30)
***FLT3* mutation type, No. (%)**		
ITD	40 (95)	45 (98)
TKD	0	0
ITD + TKD	2 (5)	1 (2)
***FLT3* variant AF %, median**		
ITD	31 (1-90)	33 (1-96)
TKD	8 (4-12)	3

Patient Characteristics	Newly Diagnosed Cohort (N=42)	Relapse/Refractory Cohort (N=46)
Other mutations*, No. (%)		
DNMT3A	18 (43)	20 (44)
NPM1	14 (33)	15 (33)
RUNX1	13 (31)	12 (27)
TET2	10 (24)	10 (22)
WT1	7 (17)	18 (40)
SRSF2	7 (17)	3 (6)
IDH1/2	7 (17)	5 (11)
U2AF1/2	6 (14)	3 (6)
SF3B1	6 (14)	5 (11)
RAS/MAPK	6 (14)	12 (27)
TP53	1 (2)	1 (2)
No. of prior therapies, median	-	3 (1-5)
Any prior FLT3i, No. (%)	-	39 (85)
Prior Gilteritinib, No. (%)	-	35 (76)
Prior HMA + VEN, No. (%)	-	27 (59)
HMA + VEN + FLT3i, No. (%)	-	24 (52)
Prior Allo-SCT , No. (%)	-	17 (37)

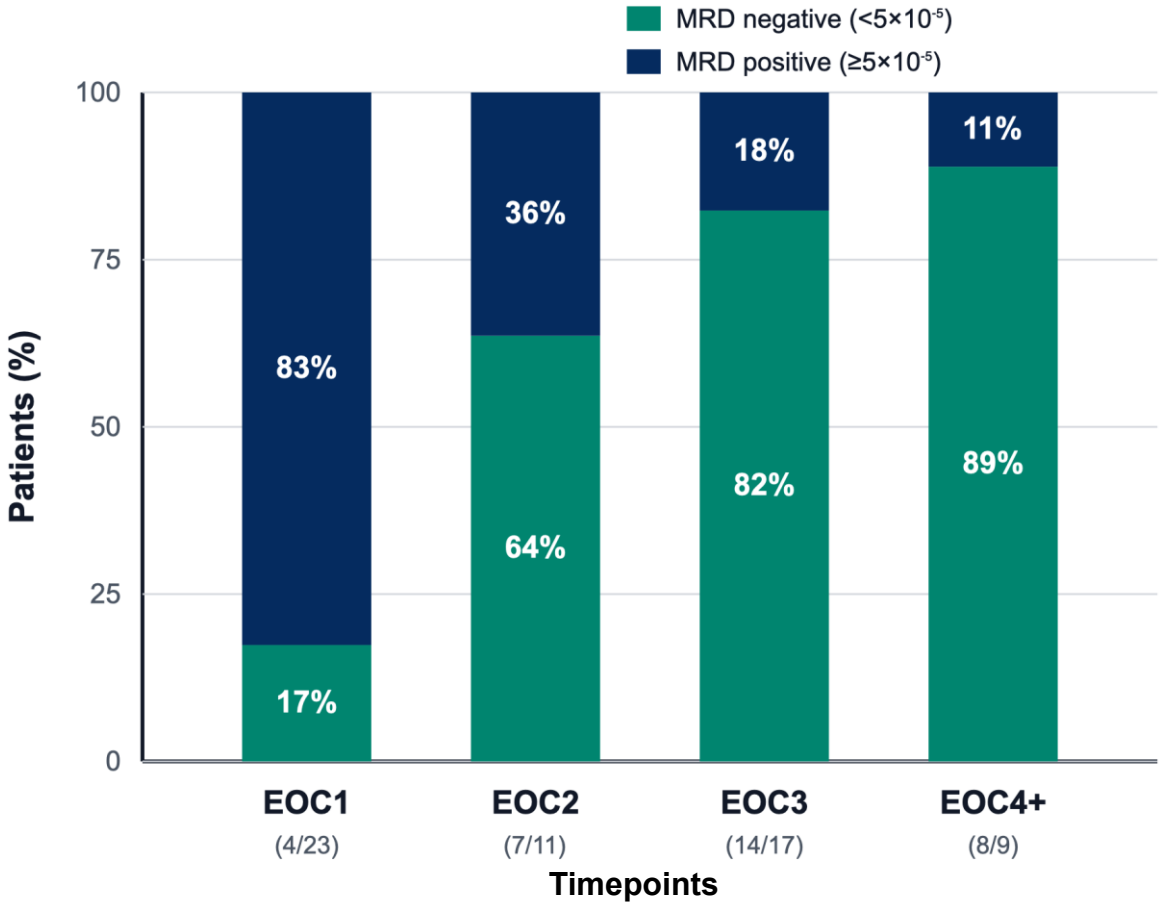
Phase 1 Safety

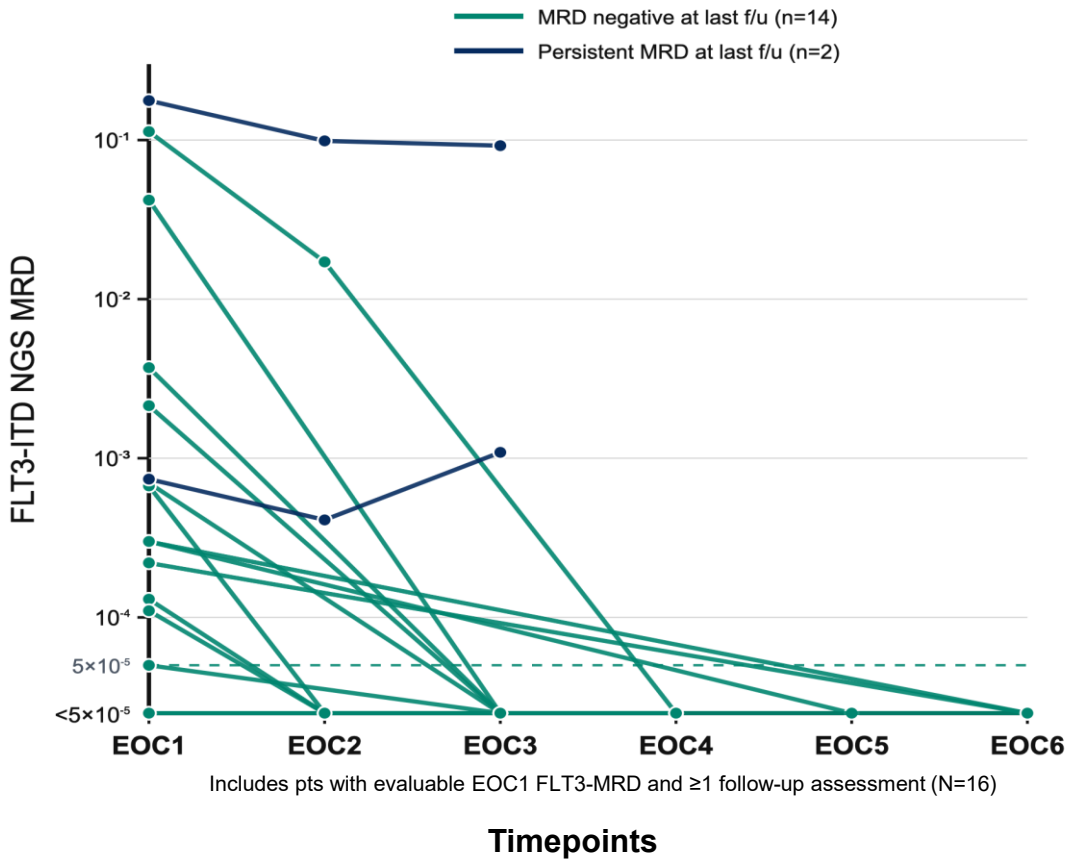
- 11 FLT3-ITD mutated AML pts treated in Phase I cohort
  - Quizartinib 26.5 mg daily in 9 pts (3 DLT non-evaluable + 6 DLT evaluable)
  - Quizartinib 35.4 mg daily in 2 pts
- Hematologic DLTs noted with quizartinib at higher dose level
  - 0/6 DLTs at 26.5 mg dosing
  - 2/2 DLT at 35.4 mg (both were **grade 4 myelosuppression**): further enrollment to quizartinib 35.4 mg triplet stopped.
  - **Quizartinib 26.5 mg chosen as RP2D**

Response Rates

Response*, N (%)	Newly Diagnosed Cohort (N=42)	Relapse/Refractory Cohort (N=46)
Hematologic Response		
mCRc	**38 (91)**	28 (61)
CR	**30 (72)**	5 (10)
CRi	7 (17)	8 (18)
MLFS	1 (2)	15 (33)
No response	3 (7)	17 (37)
Induction death	1 (2)	1 (2)
MRD at the end of cycle 1, N (%)		
Flow Cytometry Negative	19/31 (61)	3/25 (12)
FLT3 PCR Negative	11/18 (61)	7/25 (28)
FLT3-ITD NGS *Negative* ($< 5 \times 10^{-5}$)	**4/23 (17)**	-
MRD at the end of cycle ≥2 (best), N (%)		
Flow Cytometry Negative	22/31 (71)	7/26 (27)
FLT3-ITD PCR negative	19/22 (86)	10/26 (38)
FLT3-ITD NGS Negative ($< 5 \times 10^{-5}$)	**23/27 (85)**	-
Bridge to bone marrow transplant	15 (36)	17 (37)

Measurable residual disease (MRD) negativity (by NGS) improved over time





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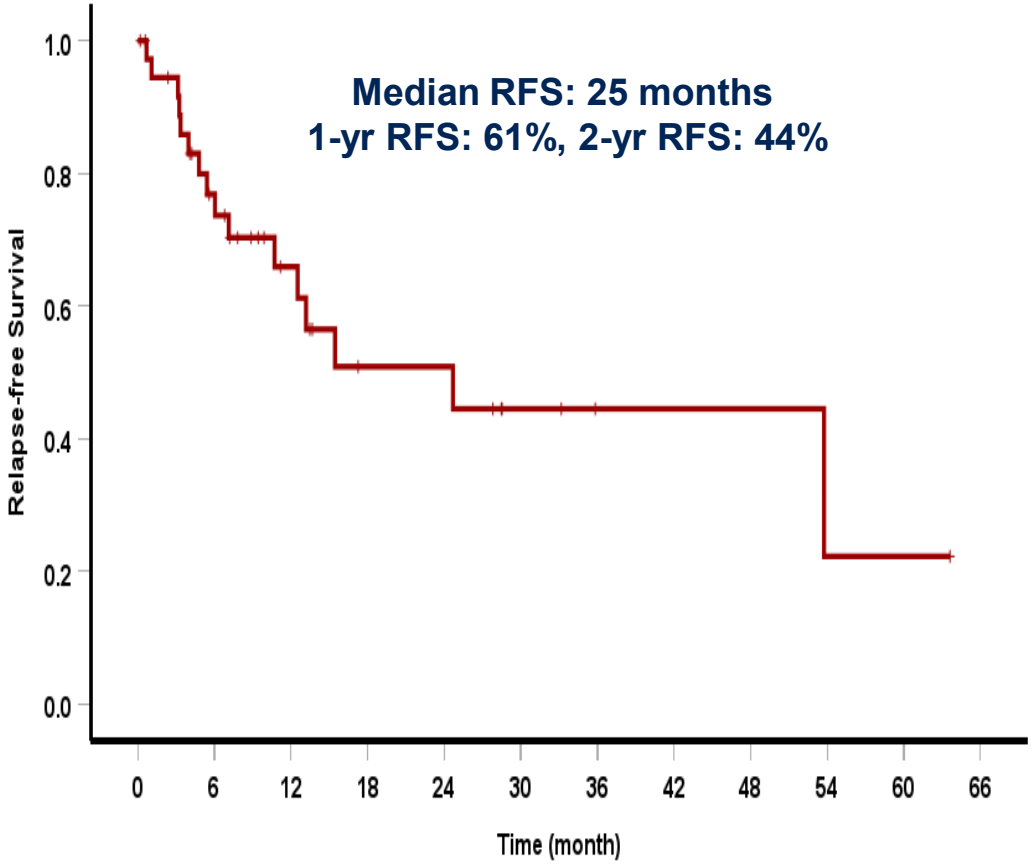
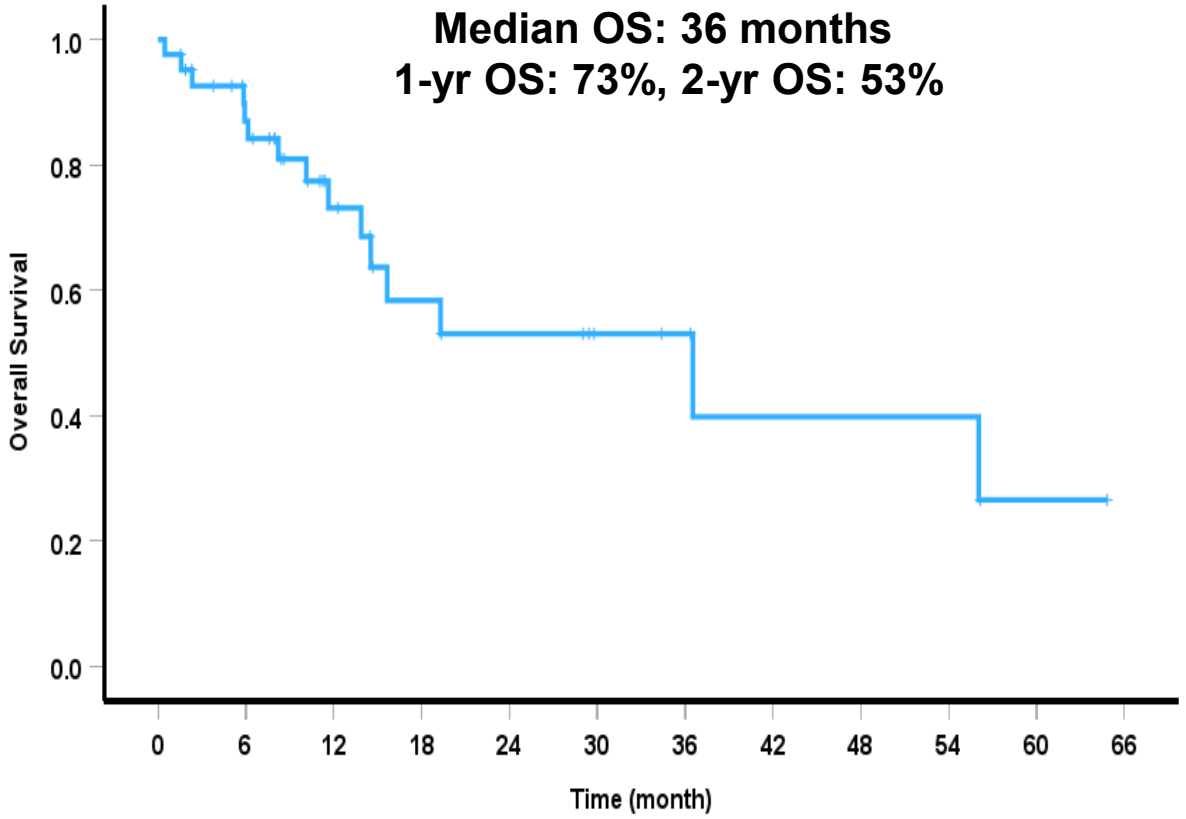
Overall Survival Improved in Newly Diagnosed Pts

Relapse-free Survival



Overall Survival



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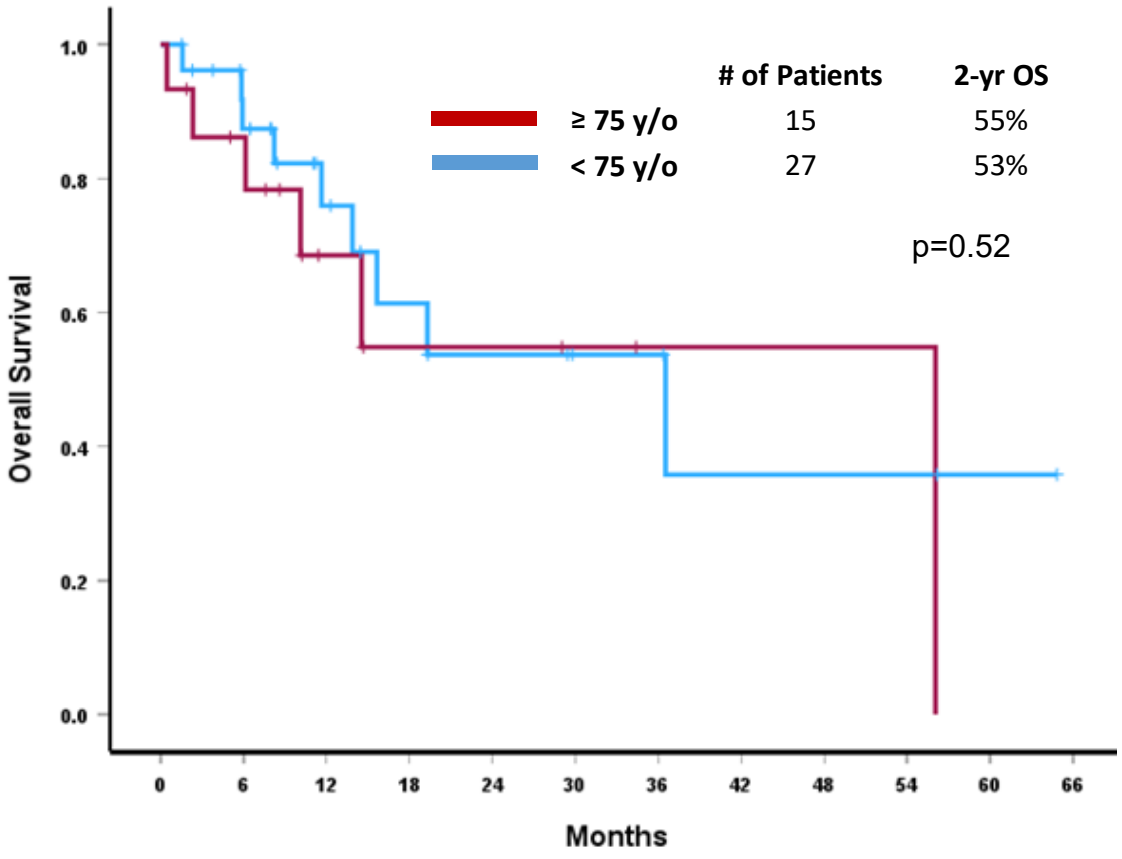
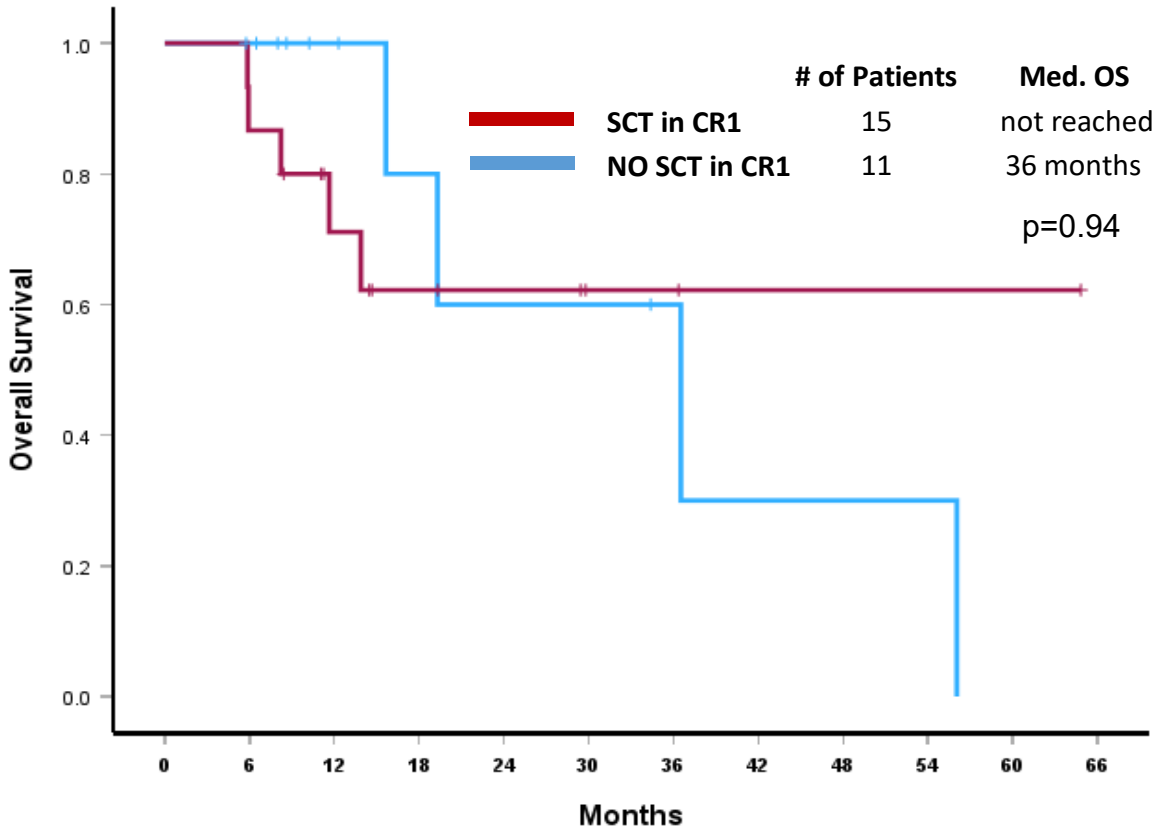
Overall survival in subgroups (Frontline Cohort)

Overall Survival (≥ 75 versus <75 y/o)



Impact of Allo-SCT– Landmark analysis*



*excluded non-responders, relapses earlier than 4 months, and patients 80 years-old or older

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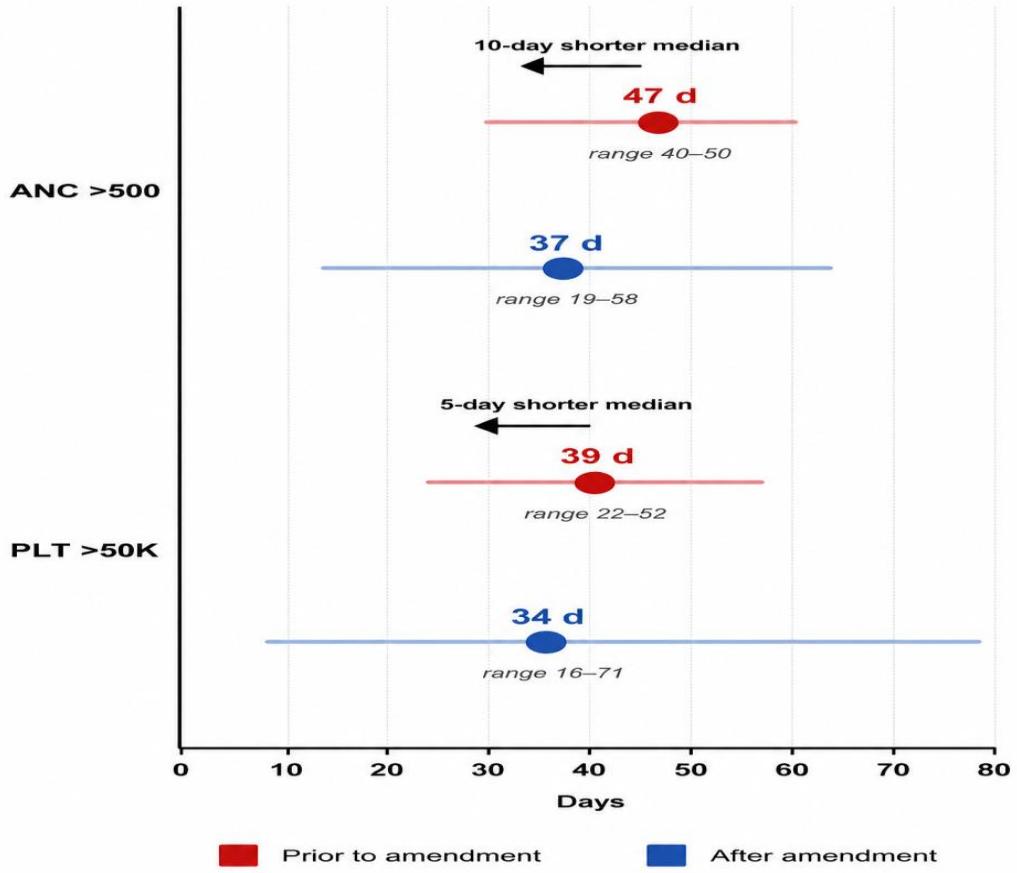
Duration of Treatment and Count Recovery: Frontline Cohort

Rx Cycle	Cycle Length (day)	Quizartinib (day)	Venetoclax (day)	Decitabine (day)
Cycle 1	48 (36.5-57)	15 (14-28)	14 (14-16)	5 (5-8.75)
Cycle 2	44 (41.25-48.75)	14 (10-14)	7 (7-10)	5 (3-5)
Cycle 3	42 (35-51)	10 (10-14)	6 (5-7)	3 (3-5)
Cycle 4	38 (34.5-43)	10 (7.75-14)	5 (3.5-7)	3 (3-3)
Cycle 5	42 (35-47)	10 (7-14)	5 (3-7)	3 (3-3)
Cycles 6-12	41.5 (34-44.75)	10 (7-14)	5 (4.5-7)	3 (3-3)
Cycles 6-39	42 (35.25-48)	7 (7-10)	7 (7-10)	3 (3-3)

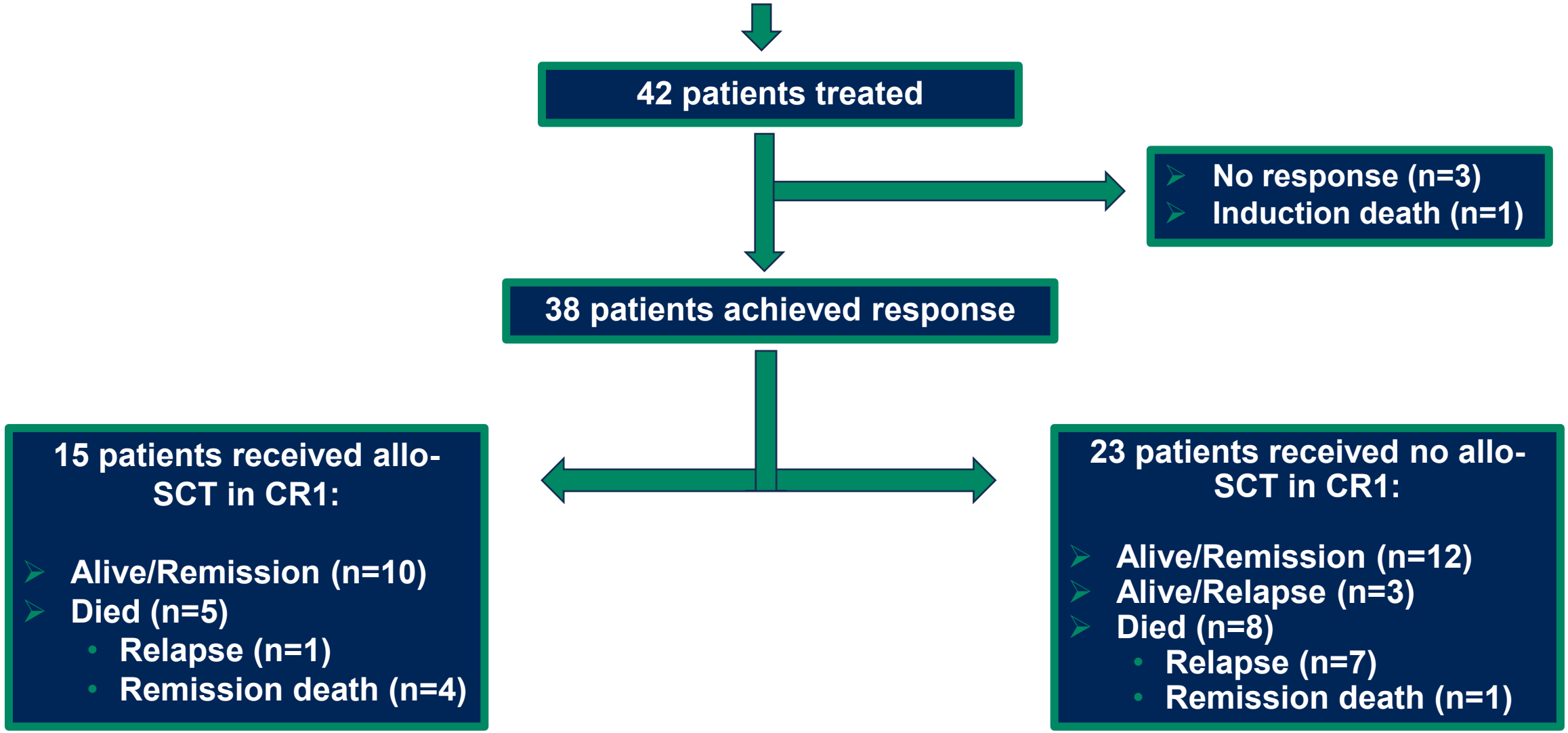
Values represent median days (range) administered per cycle. Color intensity is scaled within each column.

Absolute Neutrophil Count (ANC) and Platelet (PLT) Recovery



Protocol amendment: reduce decitabine to 5 days (from 10), hold both quizartinib and venetoclax on day14.

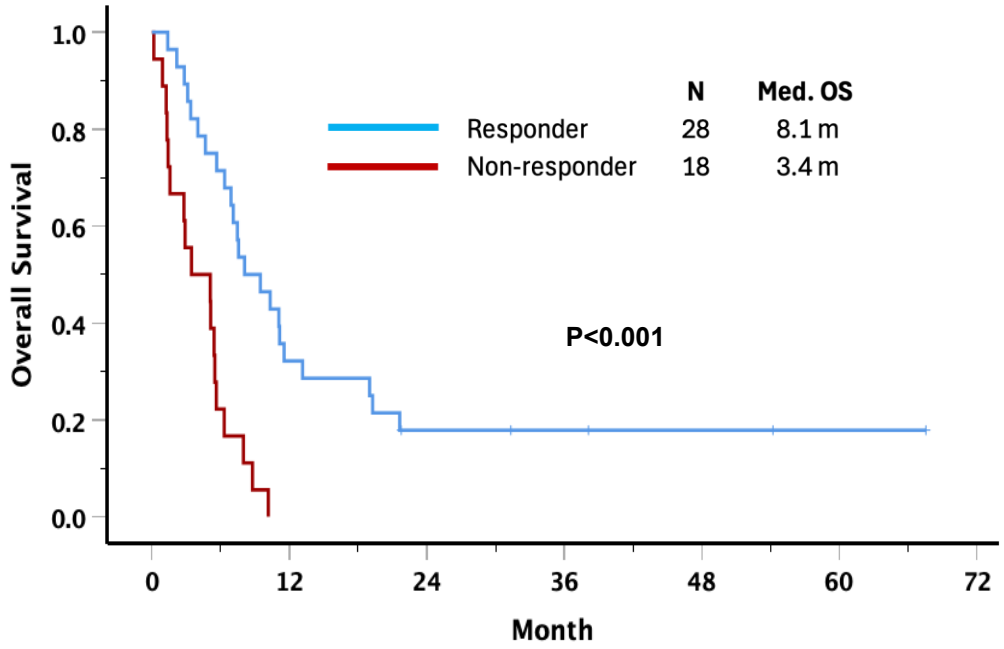
Patient disposition: Frontline Cohort



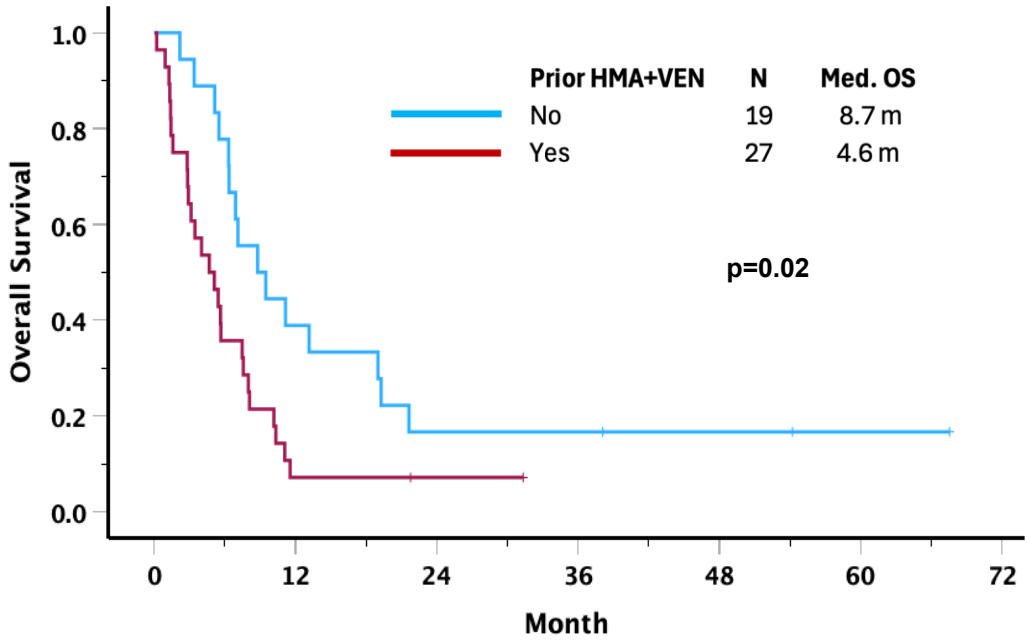
Overall Survival in Relapsed/Refractory Cohort (N=46)

- The median OS – 6.3 months
- Exposure to prior GILT – 6.3 m (prior GILT) vs. 8.0 m (no prior GILT) [p=0.84]

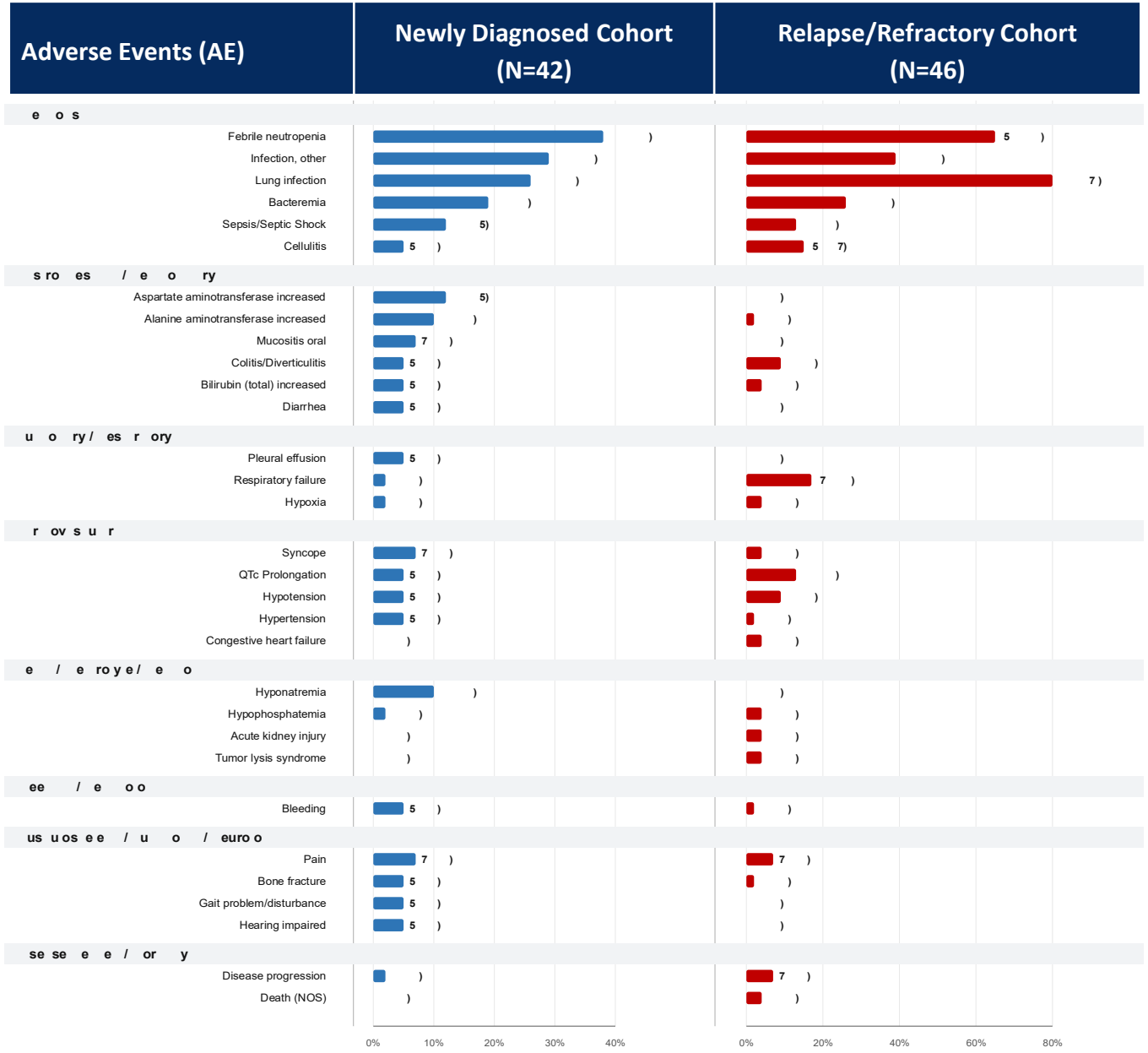
Responders vs. Non-responders



Prior HMA-VEN



Grade 3 or Higher Nonhematologic AEs, Regardless of Causality (>3%*)



*Only grade 3-5 AEs with > 3% frequencies are shown (except overlapping toxicities between groups)

Conclusions

- High remission rates in older patients with newly diagnosed *FLT3-ITD* mutated AML:
  - CRc 91% (CR 72%; CRi 17%; MLFS 2%)
  - *FLT3-ITD* NGS negativity rates improved over time, with a best achieved rate of 85%
  - Median OS 36m, 2-yr OS 53%
- Delayed count recovery may be mitigated by reducing venetoclax and quizartinib to 14 days or less per cycle.
- Infections were the most common grade ≥3 adverse events
- Grade 3 QTcF prolongation was observed, but uncommon (9%)
- This clinical trial continuous to accrue in the frontline setting (NCT03661307)