



Measurable residual disease status and FLT3 inhibitor therapy in patients with *FLT3*-ITD mutated AML following allogeneic hematopoietic cell transplantation

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Background

- Measurable residual disease (MRD) is associated with increased risk of relapse and decreased overall survival in AML, even after allogeneic HCT. MRD can be detected by next-generation sequencing (NGS) methods.
- FLT3*-ITD mutations are a poor prognostic factor in AML.
- The SORMAIN trial reported a highly significant relapse-free survival benefit for inhibitor sorafenib as post-HCT maintenance, particularly among patients with detectable MRD following HCT.
- In 2019, we initiated prospective *FLT3*-ITD MRD monitoring by NGS of the peripheral blood or bone marrow throughout the first 3 months following HCT for all patients with *FLT3*-ITD mutated AML undergoing HCT. We encouraged *FLT3* inhibitor use as post-HCT maintenance.

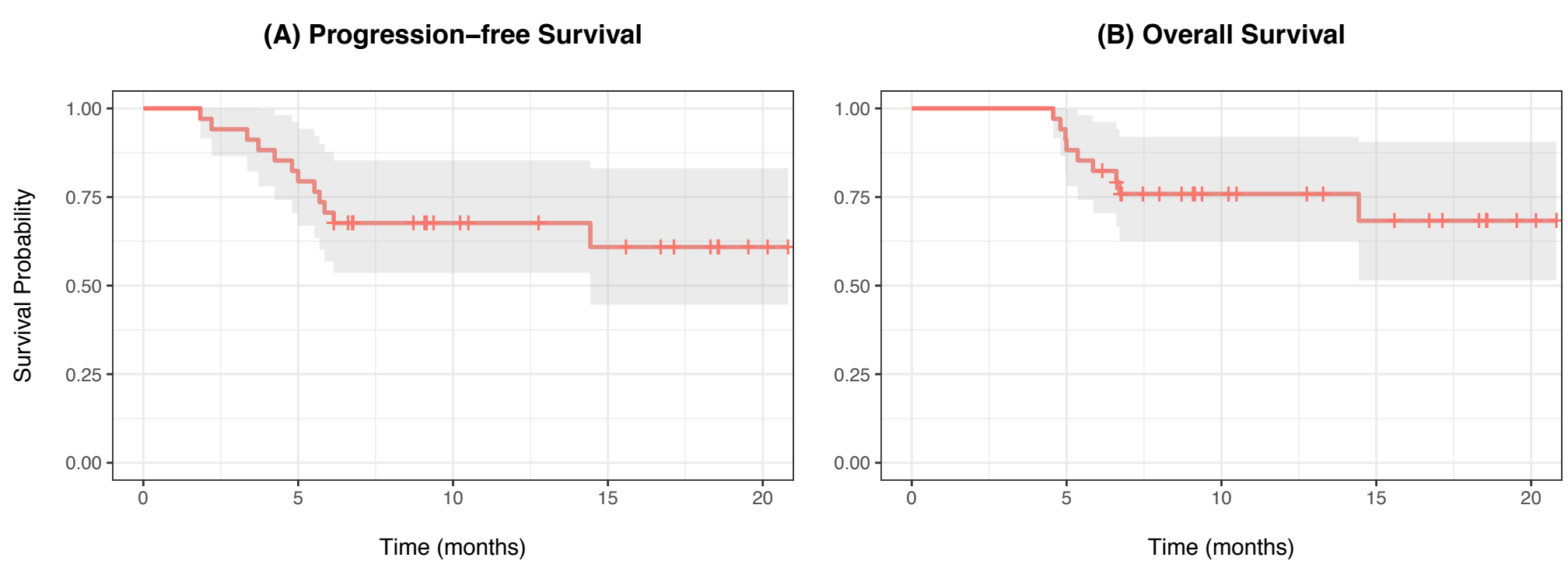
Objective and Study Cohort

- Objective:** To evaluate the impact of post-HCT *FLT3* MRD testing and *FLT3* inhibitor use in a non-clinical trial setting
- Study design:** Observational study of adults with *FLT3*-ITD mutated AML who underwent allogeneic HCT at Stanford University between April 2019 and August 2020
- Study cohort:** Thirty-six adults, 2 of whom were excluded from analyses due to early graft failure and receipt of azacitadine/enasidenib maintenance therapy.
- Nine patients (26%) relapsed at a median of 4.8 months post-HCT (range, 1.8-5.7), and 9 (26%) died, 5 from transplant-related mortality and 4 from progressive AML.
- Ten patients (29%) had detectable MRD within the first 3 months following HCT while 24 (71%) of patients remained MRD-negative. Twenty-four patients (71%) received post-HCT *FLT3* inhibitor maintenance therapy.

Table 1. Demographics of study cohort

Characteristic		n = 36 (%)
Age at transplant, median, years (range)		55 (26-74)
Male		16 (44)
Race/ethnicity	White	20 (56)
	Hispanic or Latino	6 (17)
	Black	1 (3)
	Asian	7 (19)
	Other	2 (6)
<i>NPM1</i> mutation		18 (50)
First-line induction therapy for new or relapsed AML	7 + 3 (including liposomal)	22 (61)
	HMA/venetoclax	8 (22)
	Other	6 (17)
Consolidation regimen	HiDAC	17 (47)
	HMA/venetoclax or HMA-only	6 (17)
	HyperCVAD	1 (3)
	None	10 (28)
Salvage therapy (n = 10)	7 + 3 (including liposomal)	4 (40)
	HMA/venetoclax or HMA-only	4 (40)
	Gilteritinib	2 (20)
	None	7 (19)
Pre-transplant <i>FLT3</i> inhibitor	Midostaurin	24 (56)
	Gilteritinib	9 (25)
	None	7 (19)
Pre-transplant disease status	CR1	27 (75)
	CR2	4 (11)
	CRi1	1 (3)
	Active disease	4 (11)
Donor	Matched related donor	6 (17)
	Matched unrelated donor	14 (39)
	Mismatched unrelated donor	2 (6)
	Haploidentical	9 (25)
	Umbilical cord blood	5 (14)
	Myeloablative	20 (56)
Transplant conditioning regimen	Myeloablative	20 (56)
	Reduced intensity	16 (44)

Figure 1. Progression-free survival (PFS) and overall survival (OS) of cohort..



Results

Figure 2. A) PFS and B) OS by MRD status by day 90. C) PFS and D) OS by use of *FLT3* inhibitor as maintenance therapy. E) PFS and F) OS by MRD status by day 90 and use of *FLT3* inhibitor as maintenance therapy.

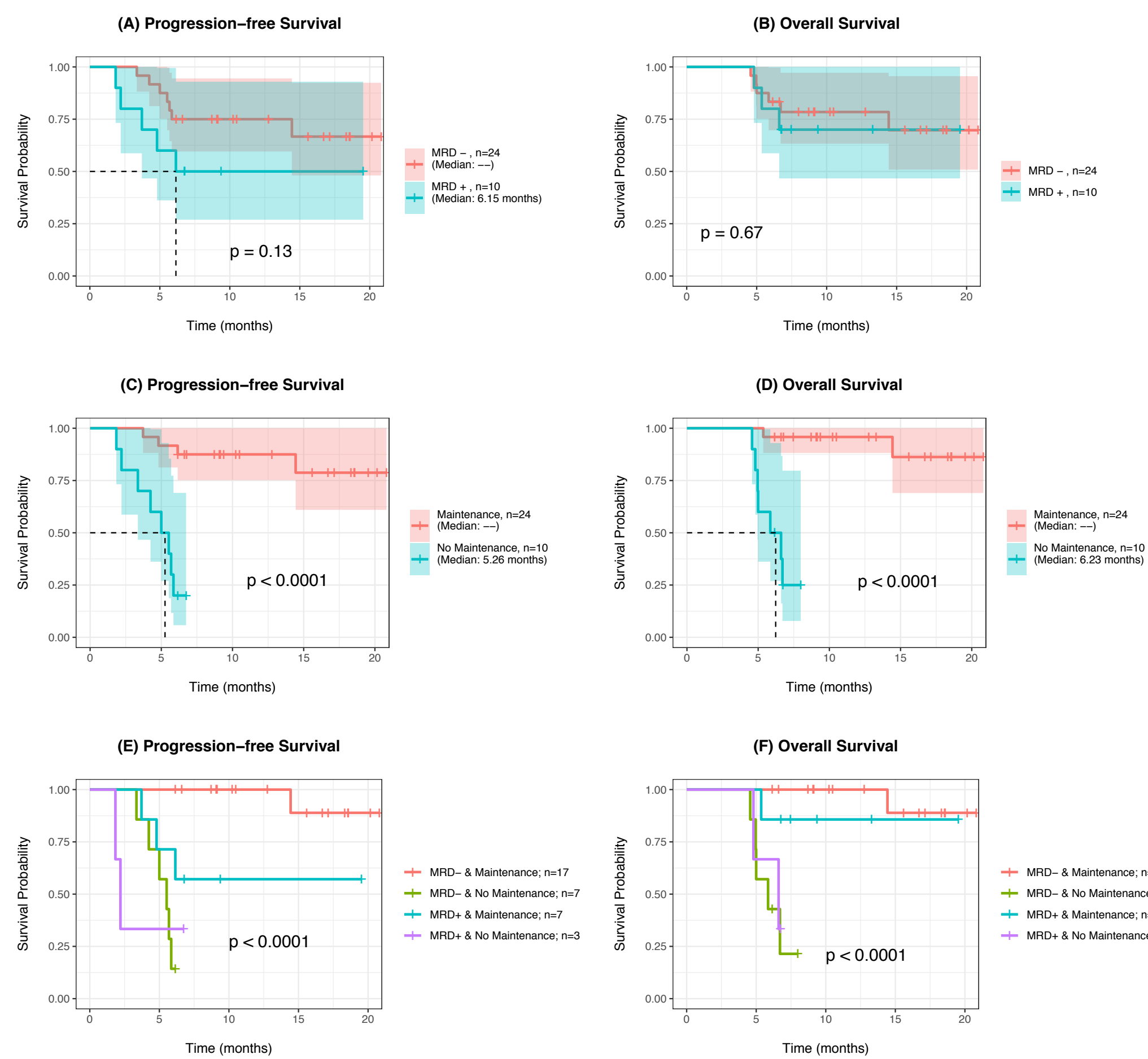
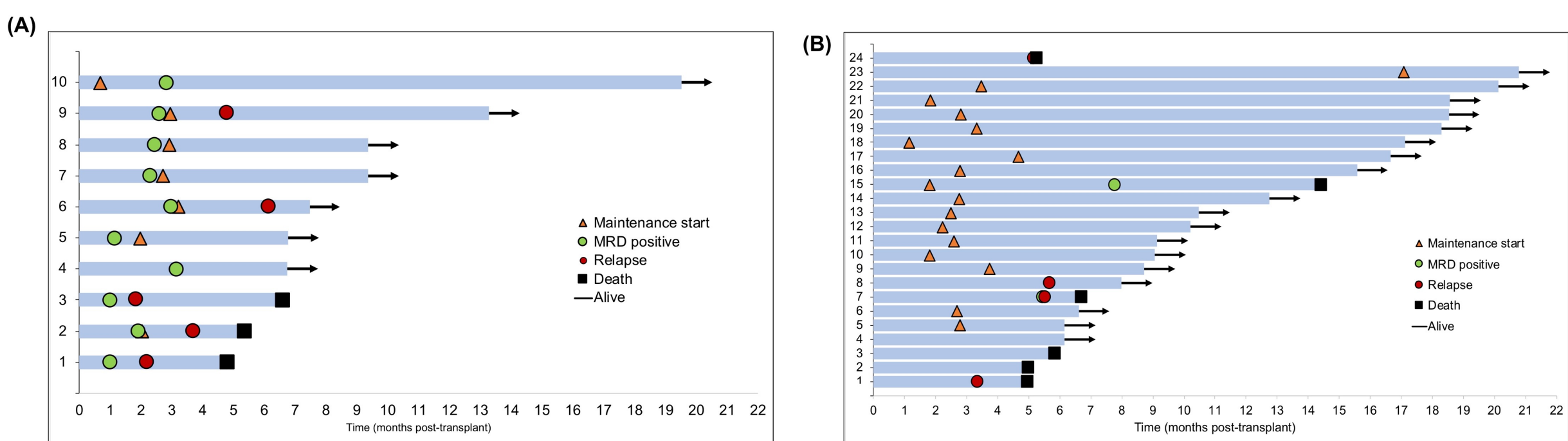


Figure 3. Swimmer plots showing use of *FLT3* maintenance therapy and outcomes for patients who were A) MRD-positive and B) MRD-negative by 90 days post-transplant.



- There was a trend towards inferior PFS for patients with early post-HCT MRD ($p = 0.13$). OS was not significantly impacted by MRD ($p = 0.67$). Of note, among the 4 patients who ultimately relapsed with early post-HCT MRD negativity, only 1 was *FLT3*-negative at time of relapse.
- FLT3* inhibitor maintenance was initiated a median of 2.8 months after HCT (range 0.7-17.1), and the median duration was 6.8 months (range 1.1-18.8). The most common *FLT3* inhibitor was gilteritinib ($n = 14$), followed by midostaurin ($n = 9$) and sorafenib ($n = 6$). Among the 10 patients (29%) who did not receive maintenance therapy, reasons included GVHD ($n = 4$), clinician decision ($n = 3$), cytopenias ($n = 2$), and TMA ($n = 1$).
- The use of maintenance *FLT3* inhibitors led to a significantly superior PFS and OS. It augmented PFS and OS in both MRD-negative and MRD-positive patients, and effectively prevented clinical relapse in 4 patients with post-HCT MRD positivity.

Discussion

- Clinical relapse can be prevented even in patients with detectable post-HCT residual disease using early *FLT3* inhibitor maintenance.
- Real-time sensitive MRD results allowed clinicians to begin early initiation of *FLT3* inhibitor therapy, which appeared to positively affected outcomes in several patients.
- Additional studies are needed to determine the optimal *FLT3* targeting agent for post-transplant use, as well as any subpopulations who may benefit from additional or alternative approaches.