Addition of Sorafenib to Chemotherapy Improves the Overall Survival of Older Adults with *FLT3*-ITD Mutated Acute Myeloid Leukemia (Alliance C11001)

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FLT3 (FMS-Related Tyrosine Kinase 3)

- Mutations in *FLT3* affect ~25-30% pts with AML
- Two types of activating mutations
  - Internal tandem duplication (ITD)
  - Point mutations tyrosine kinase domain (TKD)
- Associated with higher rates of relapse, worse survival
- Poor prognostic impact of *FLT3* mutations also present in older adults
  - 243 cytogenetically normal older adults on CALGB studies 10201, 9720, 9420

	***FLT3 ITD* (n=72)**	***FLT3* WT (n=147)**	**P**
% CR	67%	70%	.64
1 yr DFS	25%	53%	
1 yr OS	31%	69%	

Whitman *et al.* Blood 2010; 116(18):3622-3626

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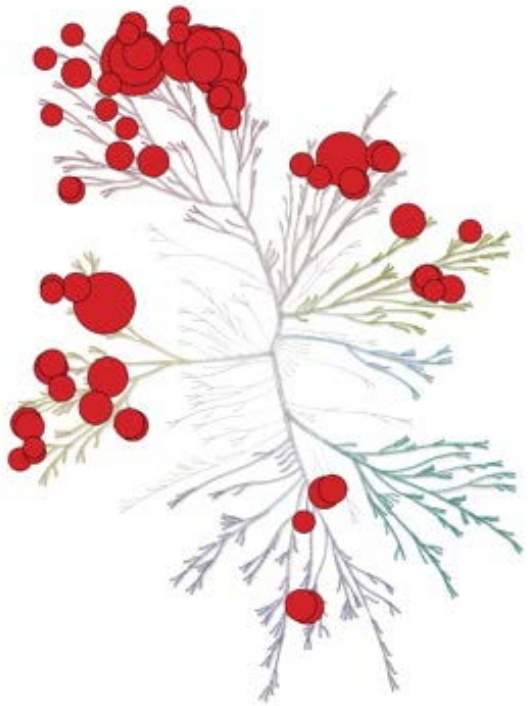
Sorafenib

- Oral small molecule inhibitor of Raf1 (IC50 6 nM)
- FDA approved dosing 400 mg bid (renal & HCC)
- Other kinase targets include FLT3

Biochemical activity	IC_{50}
FLT3-WT	32.6 nM
FLT3-ITD	2.8 nM
FLT3-D835Y	103.5 nM
B-Raf	25 nM
KIT	68 nM
FGFR	580 nM



Sorafenib

Zarinker et al., Blood 2009. 114:2984-2992
Auclair, et al. Leukemia 2007. 21:439–445

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Sorafenib in AML

- MD Anderson Phase I/II Sorafenib + IA (Ravandi)
  - 17/18 pts morph CR/CRp (94%, 95% CI 73-99)
- Compassionate use sorafenib
- SAL > 60 yrs (Serve)
  - Randomized P2 of 201 pts
  - No improvement in EFS or OS with early TRM for sorafenib
- SORAML < 60 yrs (Röllig)
  - Randomized P2 of 276 pts
  - Median EFS of 21 mo (95% CI, 9-32) vs 9 months (4-15) for sorafenib without difference in OS
  - Trend for improved RFS and OS in FLT3-ITD

Ravandi, *et al*. JCO 2010; 28:1856-62.
Metzelder *et al*. Blood.2009; 113: 6567-6571
Serve et al. JCO 2013; 31:3110-3118
Rollig *et al.* Lancet Onc 2015; 16:1691-99

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Study Design

- Multicenter, single-arm phase 2 study
  - Primary endpoint: 1 yr OS for FLT3-ITD pts only
  - H_0: 30% versus H_1: 50%
  - type I error = 10%, power 90%
  - Designed to accrue 39 FLT-ITD pts
- Eligibility Criteria
  - Age ≥ 60 years
  - FLT3 mutation (ITD ***or*** point mutation)
  - No t(15;17), t(8;21) or inv(16)
  - No prior treatment for MDS/AML

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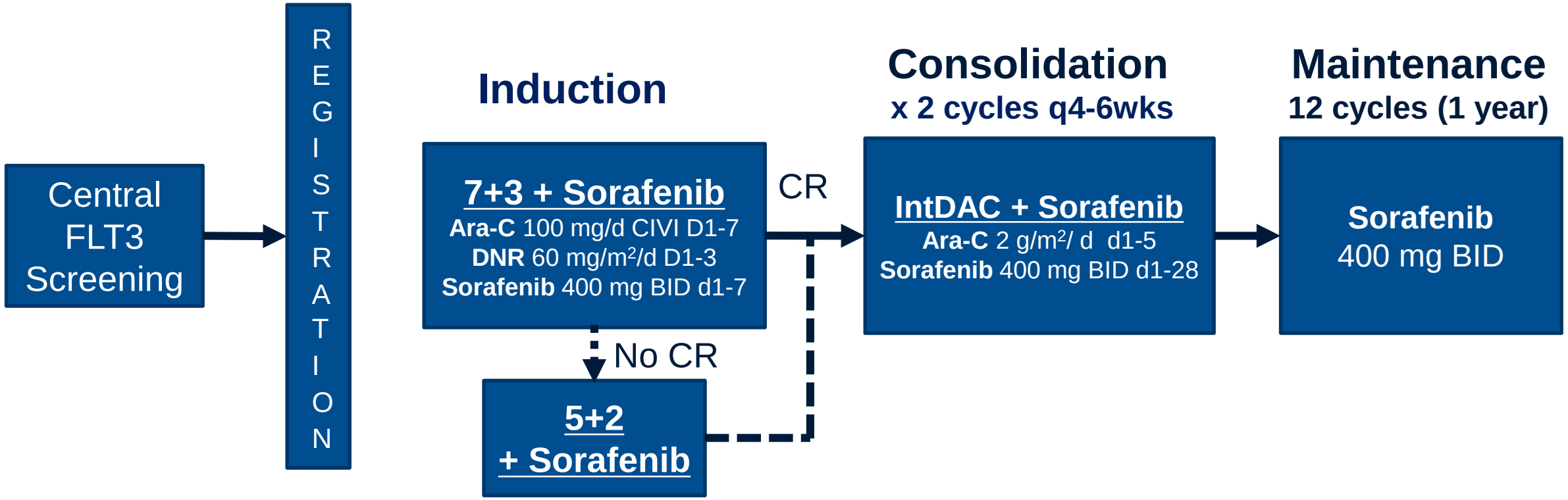
Schema



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FLT3 Screening

- Central FLT3 Screening conducted at Ohio State
- Median turn-around 46 hours with 99.1% cases in 48 hrs

***FLT3* status**	**Frequency**	**Percent**	**Not Enrolled**	**Enrolled**	**% Enrolled**
FLT3-ITD	62	13.08%	23	39	62.9 %
FLT3-TKD	20	4.22%	5	15	75 %
Both	1	0.21%	1	0	0 %
***FLT3* WT**	391	82.49%			
TOTALS	**474**		**29**	**54**	**11.9 %**

Screened 12 patients for every FLT-3 ITD accrual

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Patient Characteristics

	FLT3-ITD (N=39)	FLT3-TKD (N=15)	Total (N=54)
Age, Median (range)	67.6 (60-82)	65.4 (60-82)	67.4 (60-82)
> 70 years	17 (44%)	3 (20%)	20 (37%)
Gender, male	20 (51%)	10 (67%)	30 (56%)
Onset of AML			
De novo	32 (82%)	14 (93%)	46 (85%)
Secondary	7 (18%)	1 (7%)	8 (15%)
Cytogenetics			
CN-AML	21 (54%)	6 (40%)	27 (50%)
Intermediate II	12 (31%)	5 (33%)	17 (31.5%)
Adverse	1 (3%)	2 (13%)	3 (5.6%)
Rejected cyto	5 (13%)	2 (13%)	7 (13%)
WBC, Median (range)	21.9 (0.8-343)	16.3 (0.7-60.1)	18 (0.7-343)

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Remission Induction

	FLT3-ITD (N=39)	FLT3-TKD (N=15)	Total (N=54)
CR % (95% CI)	74% (58-87%)	73% (45-92)	74% (60-85)

CR Rates by Age

Age Group	FLT3-ITD	FLT3-TKD
60-64	8/9 (89%)	6/7 (86%)
65-69	11/13 (85%)	2/5 (40%)
70-74	7/10 (70%)	1/1 (100%)
75-79	3/5 (60%)	1/1 (100%)
80-85	0/2 (0%)	1/1 (100%)

30/60 Day induction mortality
5/54 (9%)

All deaths occurred in individuals ≥ 70 years of age

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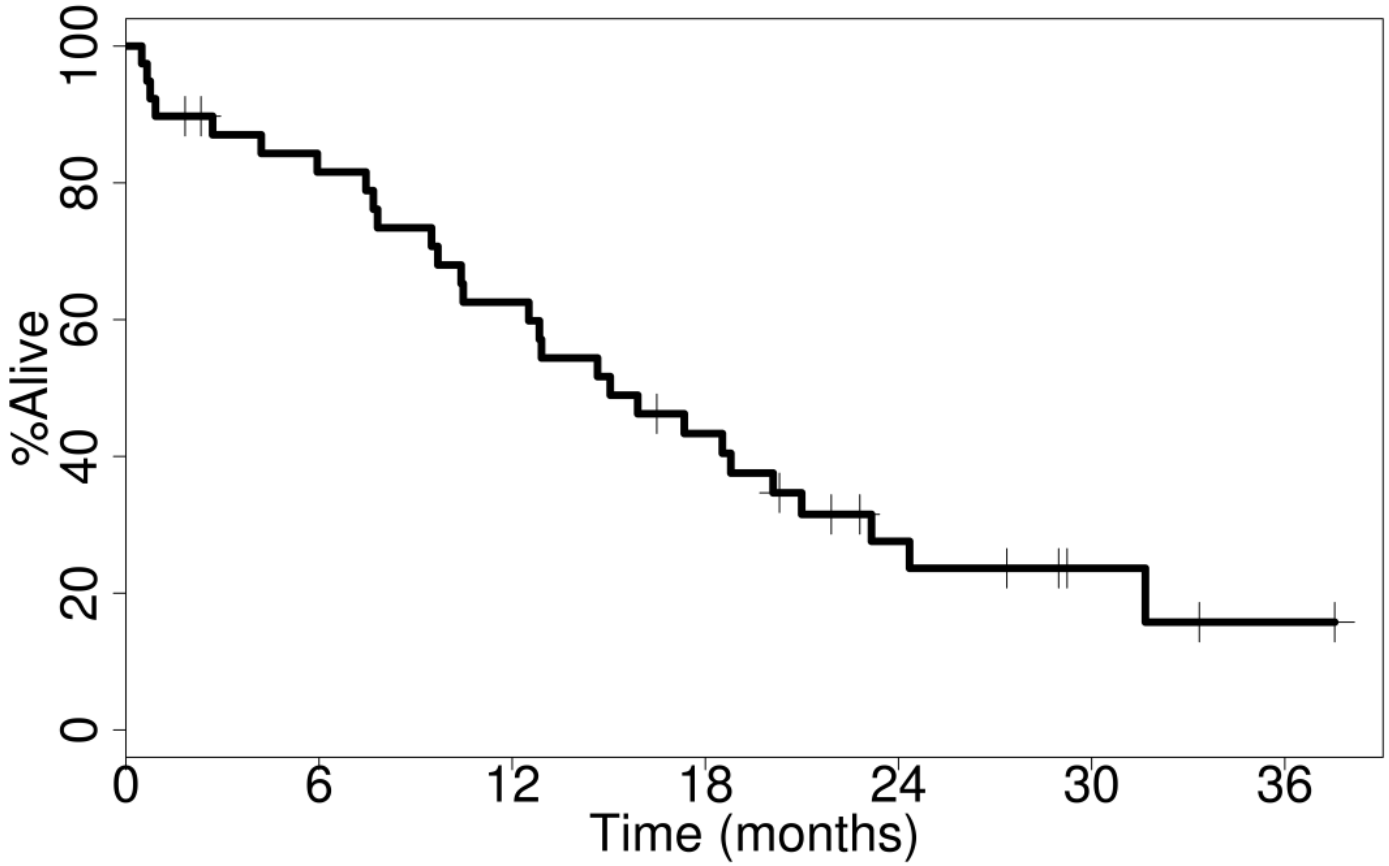
Overall Survival for *FLT3-ITD*



	***FLT3-ITD* (N=39)**
Median OS, mo (95% CI)	15.0 (10.4-20.1)
1-yr OS	63% (49-80) p < 0.0001
2-yr OS	27% (16-48)

Median follow-up 27.4 months

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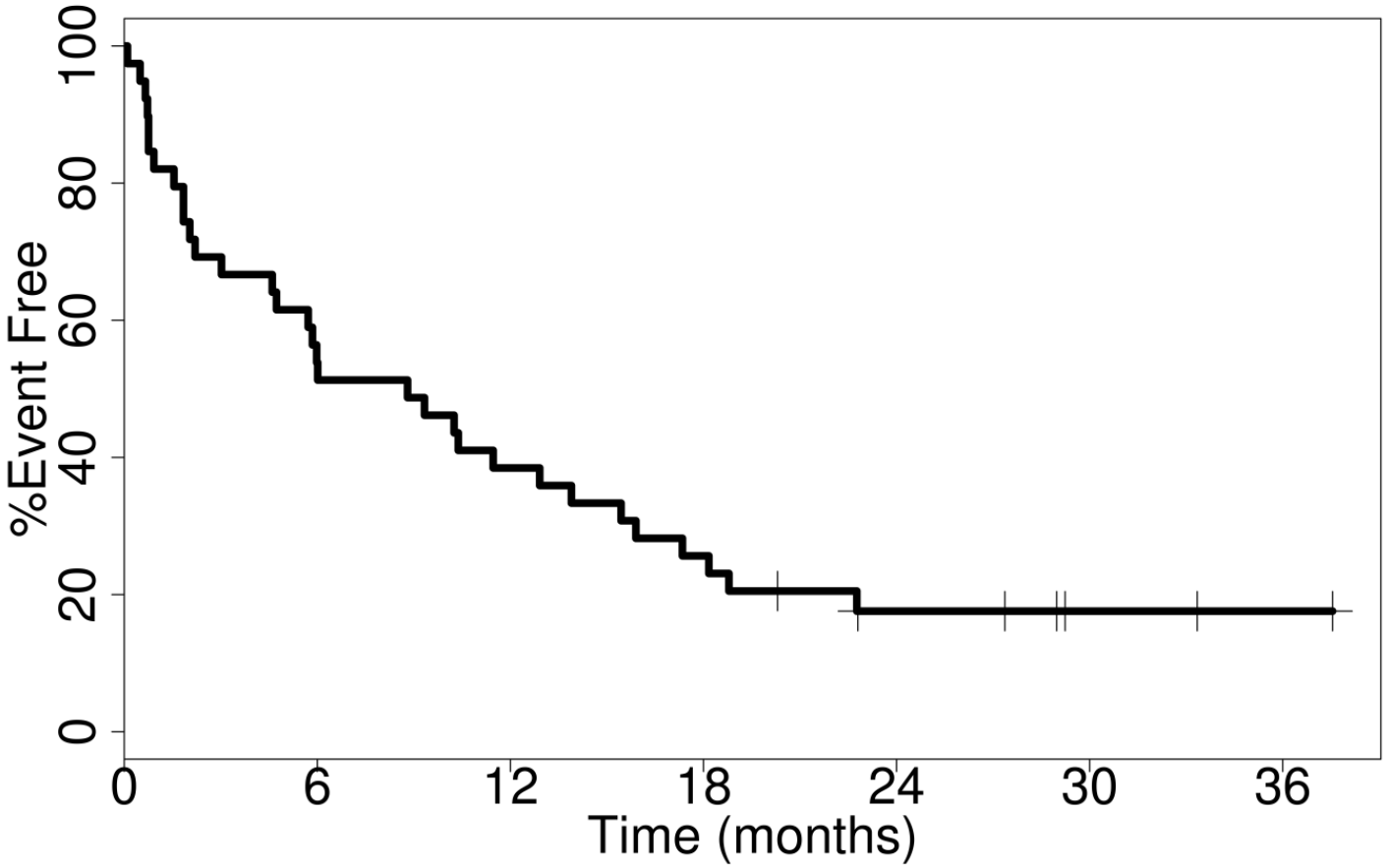
Event-Free Survival for *FLT3-ITD*



	***FLT3-ITD* (N=39)**
Median EFS, mo (95% CI)	8.8 (3.0-13.9)
1-yr EFS	39% (26-57)
2-yr EFS	18% (9-35)

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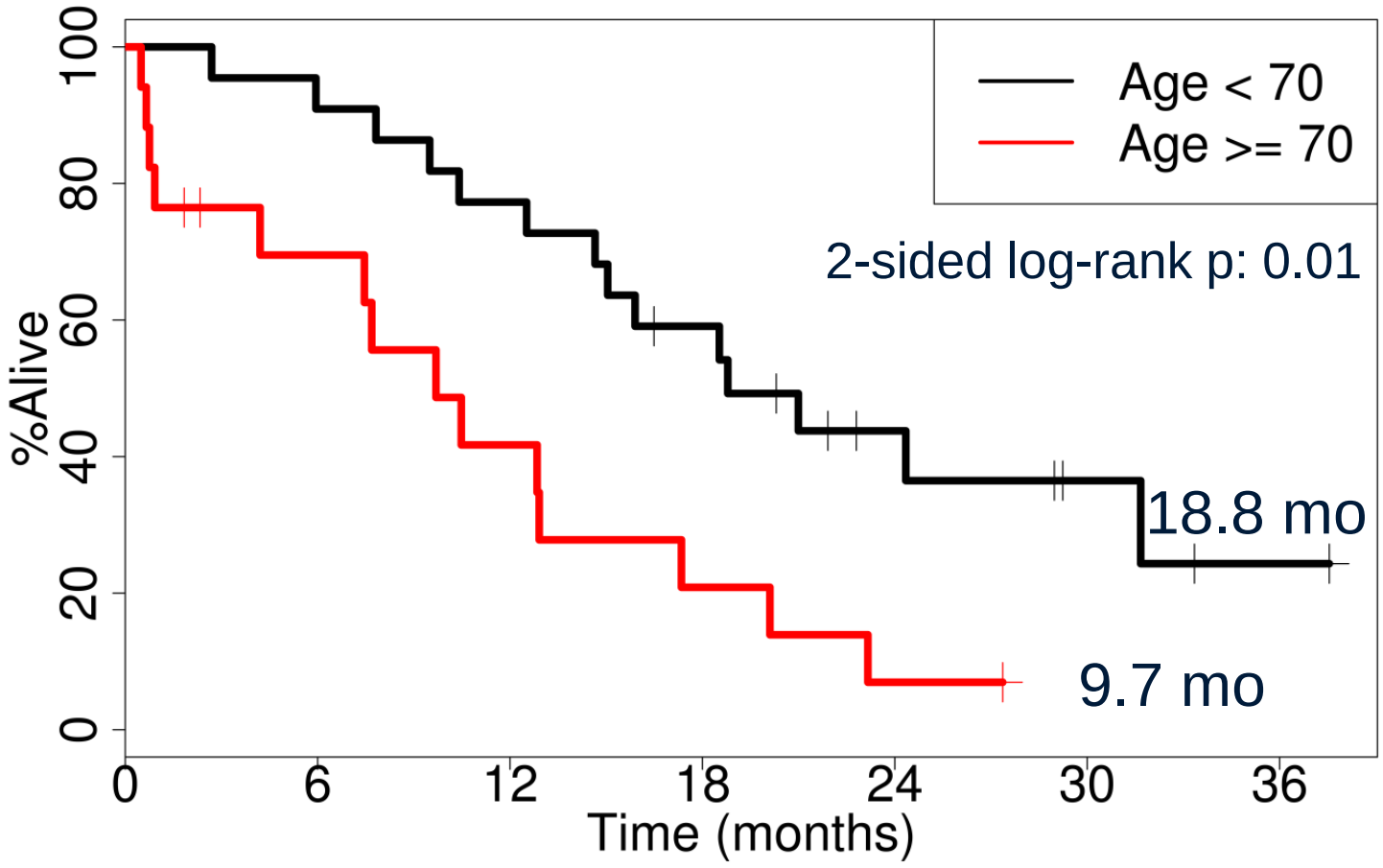
Overall Survival by Age



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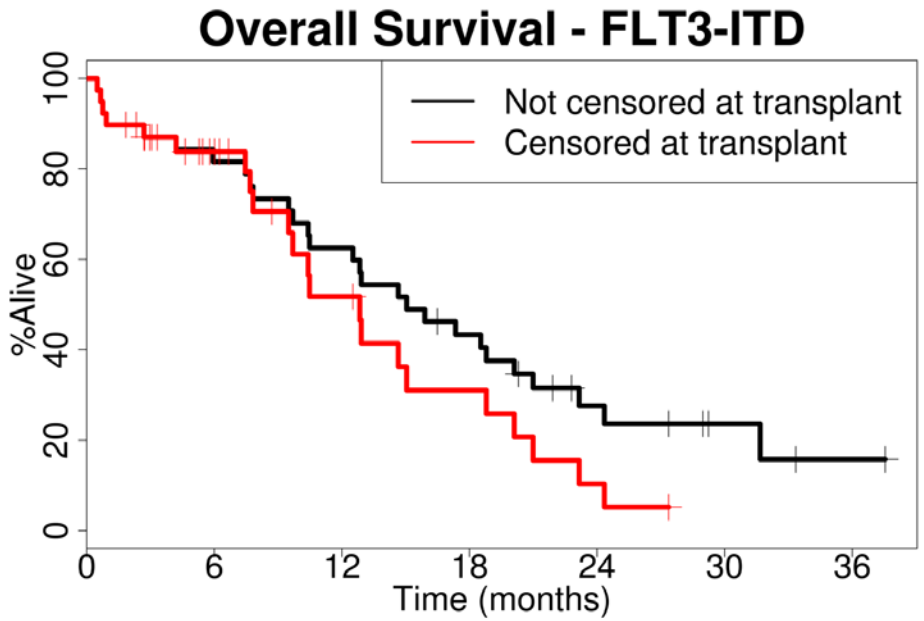
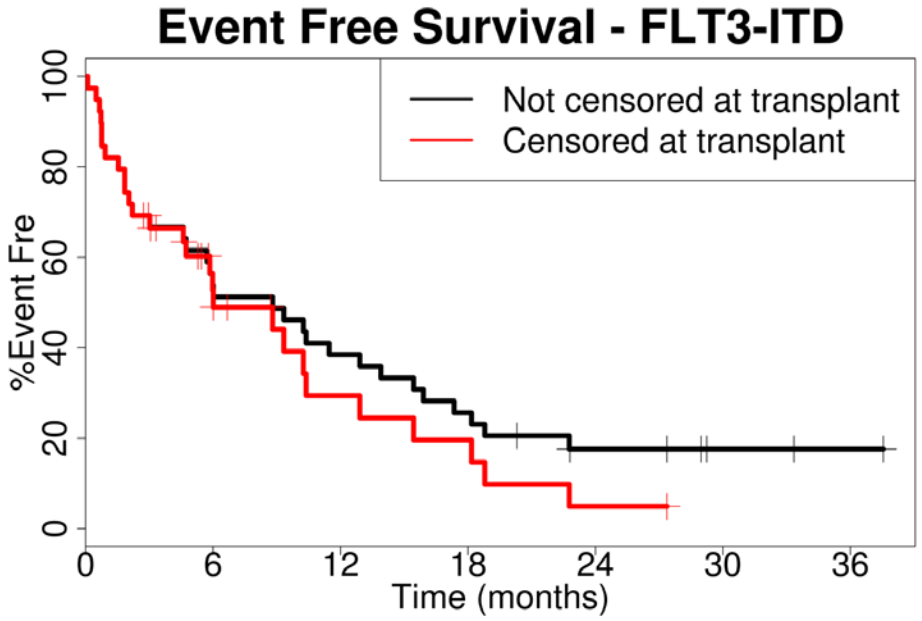
Impact of AlloHCT





	Overall Survival	Event-Free Survival
Median, mo (95% CI)	12.9 (7.8-18.1)	6.0 (3.0-10.4)
1-yr	52% (35-76)	29% (16-54)
2-yr	10% (3-38)	5% (1-33)

FLT3-ITD: 14 (36%) with alloHCT (13 in CR1)

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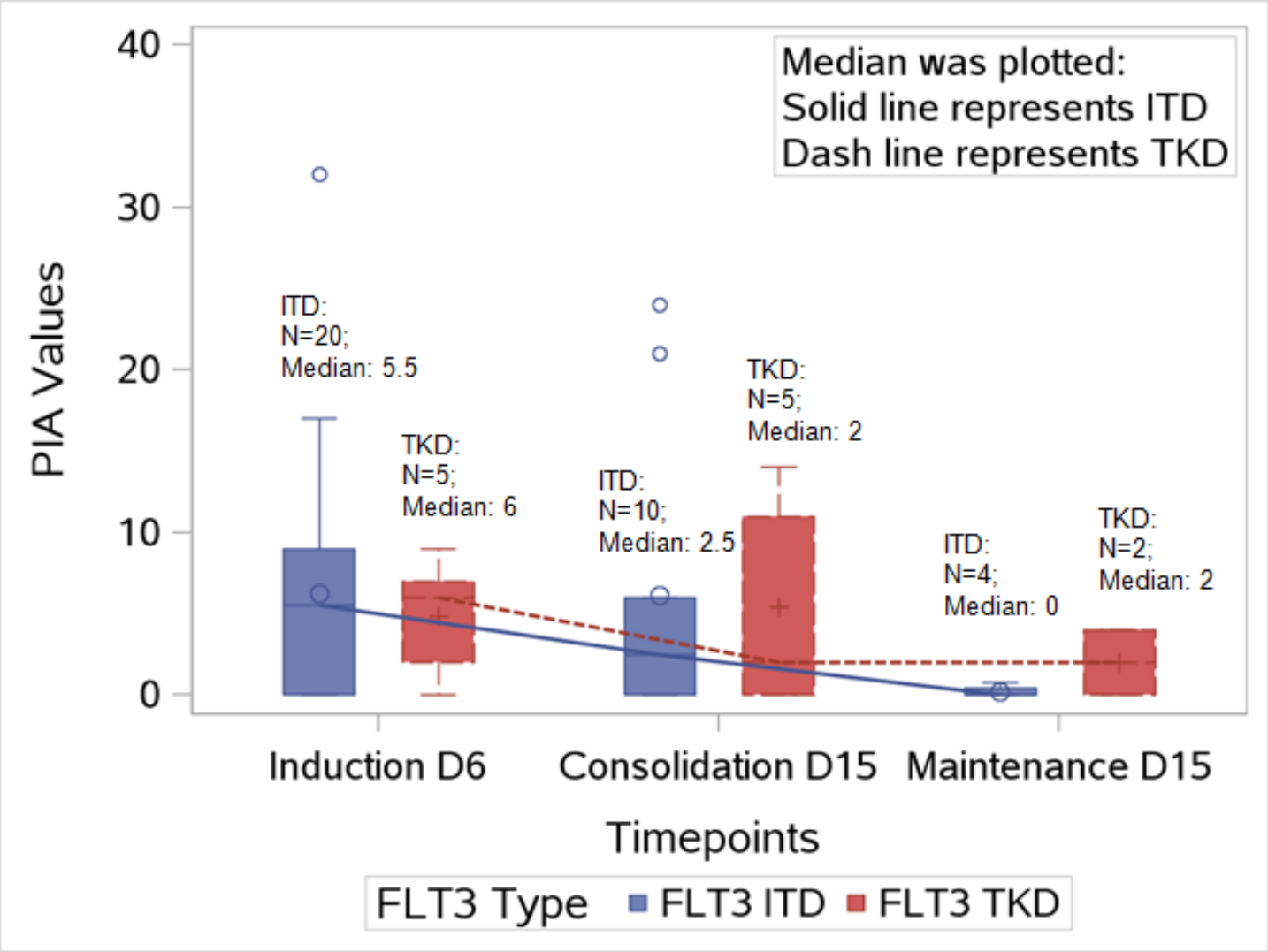
FLT3 Plasma Inhibitory Assays



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Conclusions

- Addition of sorafenib to chemotherapy improves the 1 yr OS of older adults with FLT3-ITD AML compared to historical controls (63% vs 30%)
- Overall survival benefit appears to be independent of allogeneic HCT
- Sorafenib is associated with reduction in FLT3 PIA levels indicating inhibition of FLT3 in vivo
- Benefit of sorafenib observed primarily in 60-69 yr age group

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