4:05–4:45 PM

Fellows Session

MODERATOR

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THE 2nd ANNUAL HemOnc Pulse LIVE AUSTIN 2025

Characteristics and Outcomes of Patients With Acute Myeloid Leukemia (AML) and *FLT3*-Tyrosine Kinase Domain (TKD) Mutations

Presenter

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Background

- *FLT3* tyrosine kinase domain mutations (*FLT3*-TKD) 7%-10% of AML.
- No clear prognostic impact of *FLT3*-TKD.
- Prognostic impact of *FLT3*-TKD may depend on co-mutations:
  - Improved outcomes when co-mutated with *NPM1* (approx. 50%-55% of *FLT3*-TKD AML also have *NPM1*).
  - Worse outcomes when co-mutated with *FLT3*-ITD and *MLL*-PTD.
- Increasing use of FLT3 inhibitors and venetoclax in frontline AML over past 5 years. How this impacts *FLT3*-TKD AML is not well defined.

Daver et al. *Leukemia*. 2019. Boddu et al. *Blood Adv*. 2017. Bacher et al. *Blood*. 2008. Li et al. *Front Oncol*. 2023. Perry et al. *Clin Lymphoma Myeloma Leuk*. 2018.

Methods and Objectives

- Retrospective analysis
- Inclusion : Pts with AML (age ≥18) on frontline Rx at MDACC 1/2012 - 10/2023, with *FLT3*-TKD AML (with or without *NPM1)*
- Exclusion : *FLT3*-ITD AML

- Primary objective: Determine response rates and survival outcomes based on type of frontline Rx.
- Secondary objectives: Determine impact on OS in *FLT3*-TKD AML of :
  - *NPM1* co-mutation
  - VEN- or FLT3i-based frontline Rxs
  - Allogenic stem cell transplantation

Results: *FLT3*-TKD cohort

- 124 pts, median age 65 years (25-89)
- *NPM1* co-mutation in 55 (44%)
- Analyzed based on frontline Rx:
  - Intensive chemo Rx (IC) 54 (44%)
  - Lower intensity (LIT) in 70 (56%)

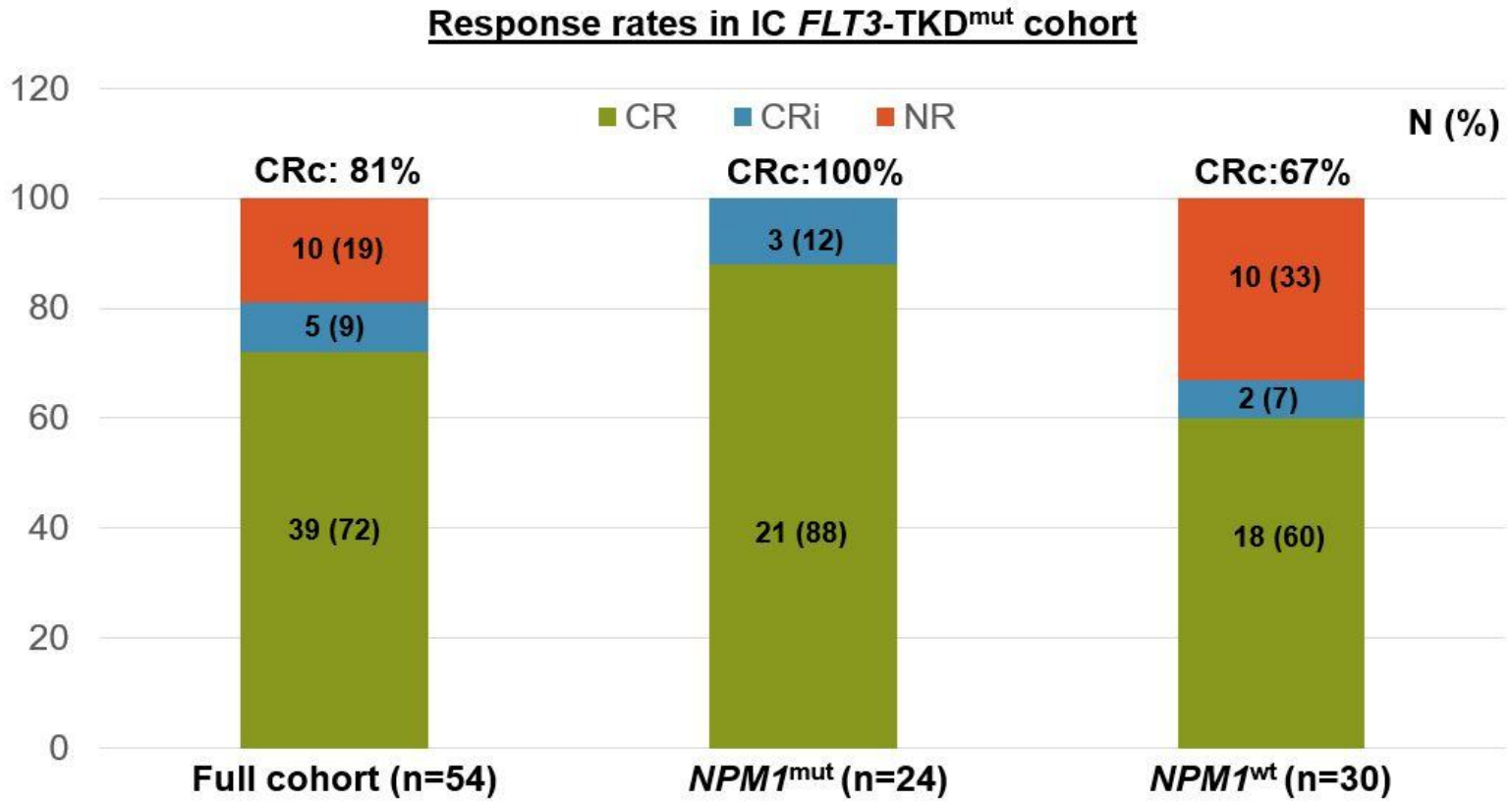
FLT3-TKD domain mutation	N (%)
D835	97 (78)
N676	13 (11)
D839	5 (4)
A680	3 (2)
N841	3 (2)
A848	1 (0.8)
D836	1 (0.8)
S838	1 (0.8)

Results: *FLT3*-TKD IC Cohort (n=54)

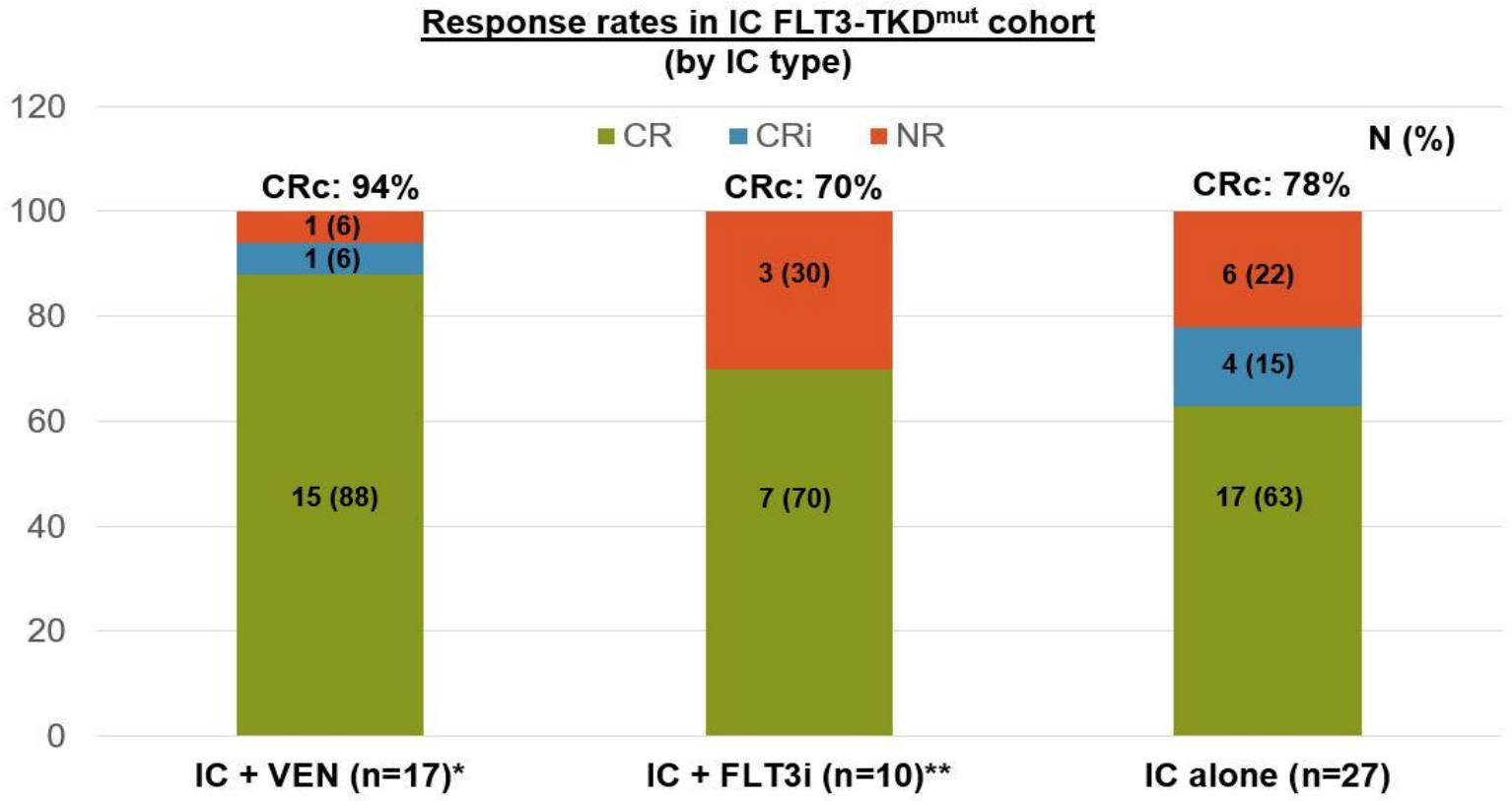
Parameters	*NPM1*^{mut} (n=24; 44%)	NPM1^{wt} (n=30; 56%)	*P* value
	N (%), Median [range]		
Age (years)	54 [28-63]	54 [25-80]	0.9
Females	11 (46)	13 (43)	1
Baseline WBC count (x10^9/L)	7.8 (1.4 - 69.8)	5.6 (0.6 - 184)	0.8
Baseline BM blasts (%)	70 (16 – 92)	60 (21 – 94)	0.9
Secondary AML	0 (0)	6 (20)	0.03
Cytogenetics			
Diploid	20 (83)	12 (40)	0.002
CK	1 (4)	5 (17)	0.2
Isolated -5/5q- or -7/7q-	0 (0)	3 (10)	0.3
11q23 Rearrangement	0 (0)	1 (3)	1
Others	3 (13)*	9 (30)**	0.2
Mutations			
DNMT3A	10/20 (50)	3/21 (14)	0.02
RAS	8/19 (42)	10/22 (46)	1
WT1	1/13 (8)	5/20 (25)	0.4
ASXL1	0/15 (0)	5/23 (22)	0.1
RUNX1	0/12 (0)	4/19 (21)	0.1

*Included +8, -Y, del(4q) **Included +8, +9, +11, -12, del(12p), i(8q), der(3)t(3;8)

Results: *FLT3*-TKD IC Cohort (n=54)



Results: *FLT3*-TKD IC Cohort (n=54)

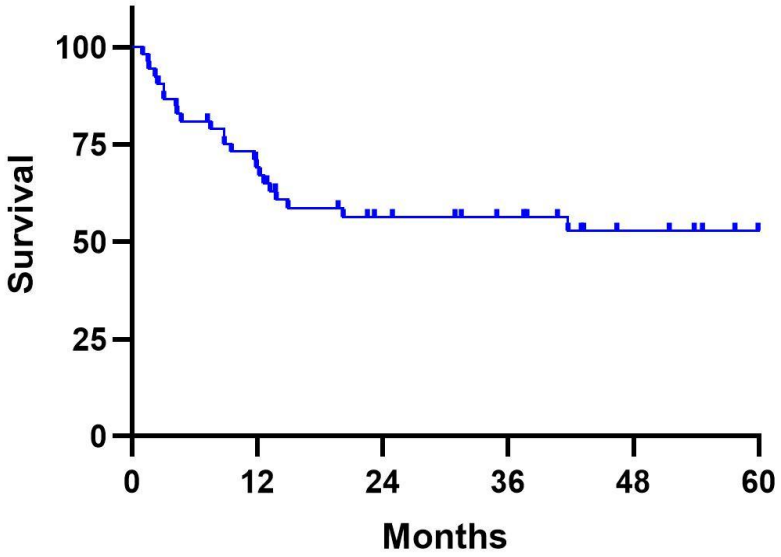


*Included: CLIA + VEN (n=9), FLAG-Ida + VEN (n=7), CPX-351 + VEN (n=1)
**Included: CLIA + Midostaurin (n=6), CLIA + Gilteritinib (n=4)

Results: *FLT3*-TKD IC Cohort (n=54)

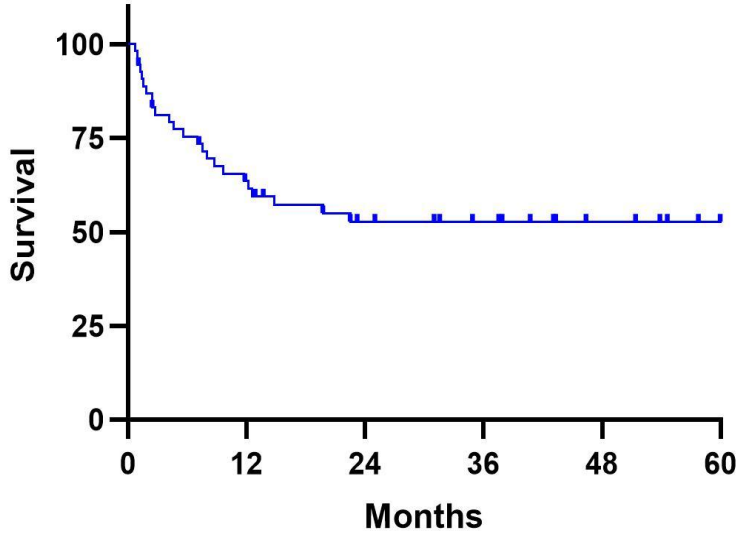
Median Follow-up: 43 mo

Overall Survival IC *FLT3*-TKD^{mut} cohort



N	Events	mOS	3 yr OS
54	23	NR	56%

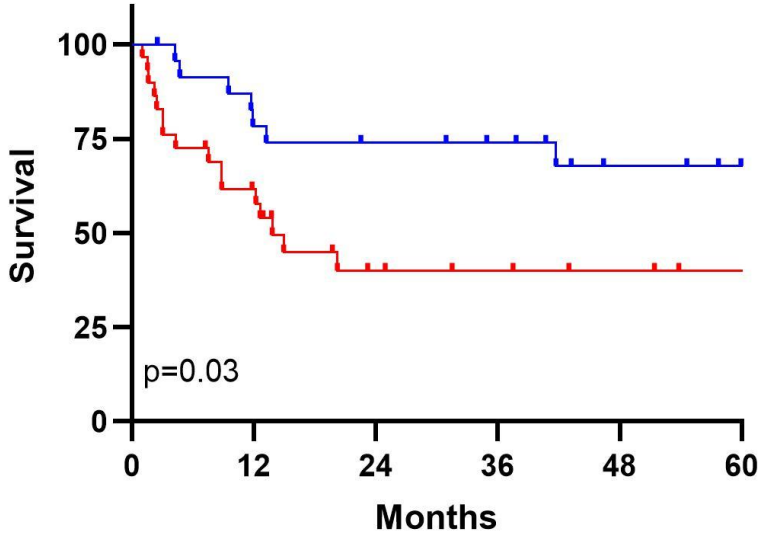
Event Free Survival IC *FLT3*-TKD^{mut} cohort



N	Events	mEFS	3 yr EFS
54	24	NR	53%

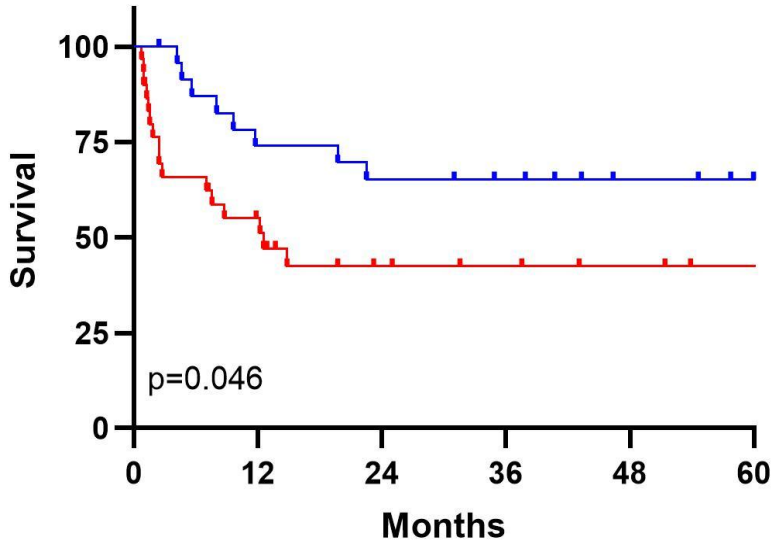
Results: *FLT3*-TKD IC Cohort (n=54)

Overall Survival by *NPM1* status (IC *FLT3*-TKD^{mut} cohort)



	N	Events	mOS	3 yr OS	mF/U
NPM1^{mut}	24	7	NR	74%	55
NPM1^{wt}	30	16	13.8	40%	32

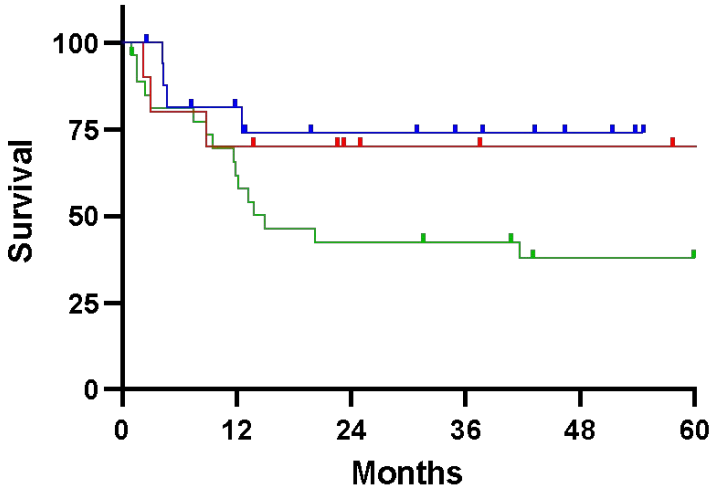
Event Free Survival by *NPM1* status (IC *FLT3*-TKD^{mut} cohort)



	N	Events	mEFS	3 yr EFS	mF/U
NPM1^{mut}	24	8	NR	65%	55
NPM1^{wt}	30	16	12.5	42%	32

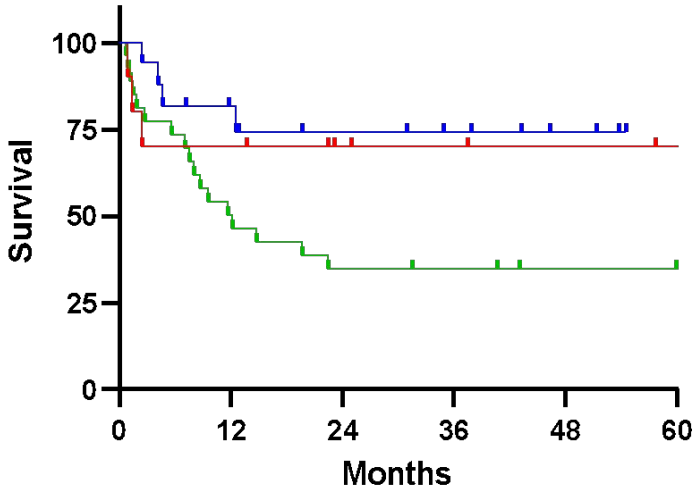
Results: *FLT3*-TKD IC Cohort (n=54)

Overall Survival IC *FLT3*-TKD^{mut} cohort (stratified by type of IC)



	N	Events	mOS	3 yr OS	p	mF/U
IC + VEN	17	4	NR	74%	0.07	35
IC + FLT3i	10	3	NR	70%	0.2	25
IC only	27	16	14.9	42%	ref	60

Event Free Survival IC *FLT3*-TKD^{mut} cohort (stratified by type of IC)



	N	Events	mEFS	3 yr EFS	p	mF/U
IC + VEN	17	4	NR	74%	**0.03**	35
IC + FLT3i	10	3	NR	70%	0.2	25
IC only	27	17	12.2	35%	ref	60

Results: *FLT3*-TKD IC Cohort: Role of Allo-SCT in CR1

Control (non-SCT) group for landmark analysis only included patients with age ≤ 70 years at induction who attained CRc and were alive at landmark.

FLT3-TKD IC full cohort (n=54)

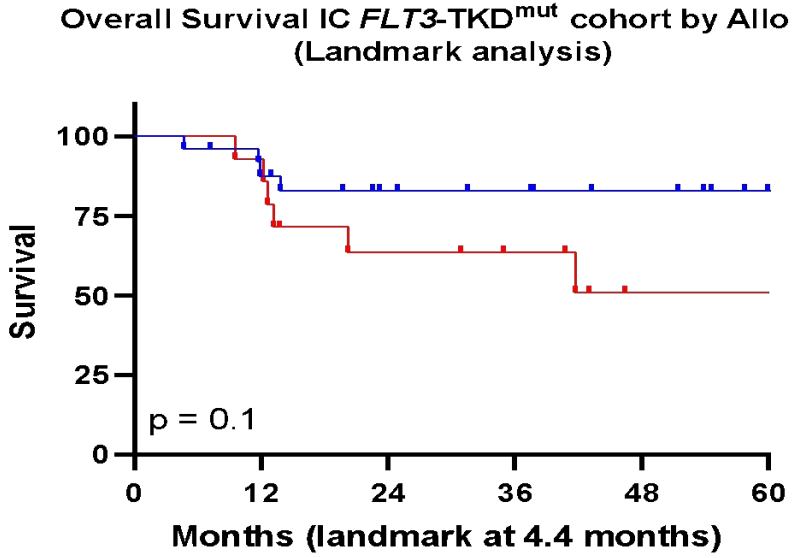
- Allo-SCT in CR1: 25 (46%)
- Median time to allo-SCT: 4.4 mo (2.1-14.2)

FLT3-TKD *NPM1*^{mut} IC full cohort (n=24)

- Allo-SCT in CR1: 13 (54%)
- Median time to allo-SCT: 4.1 mo (3.1-10.2)

FLT3-TKD *NPM1*^{wt} IC full cohort (n=30)

- Allo-SCT in CR1: 12 (40%)
- Median time to allo-SCT: 4.4 mo (2.1-14.2)



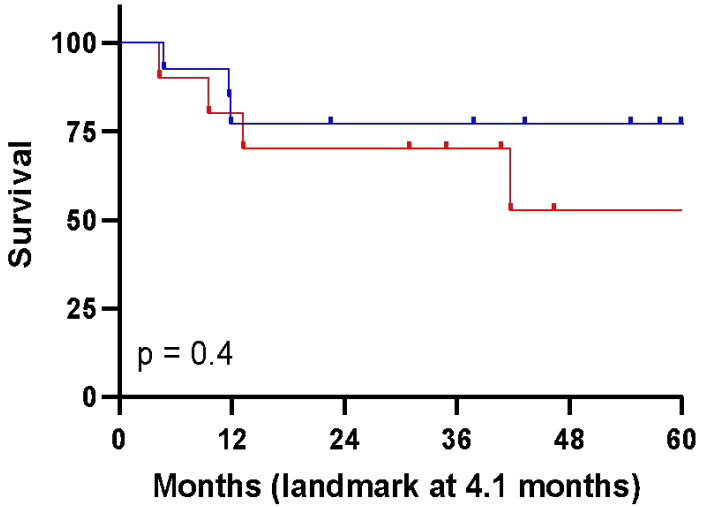
	N	Events	mOS	3 yr OS	mF/U
SCT	25	4	NR	83%	43
No SCT	14	6	NR	64%	43

Median Age:- SCT: 47 yrs (25 – 63) , Non-SCT: 48 yrs (30 – 63)

Results: *FLT3*-TKD IC Cohort: Role of Allo-SCT in CR1

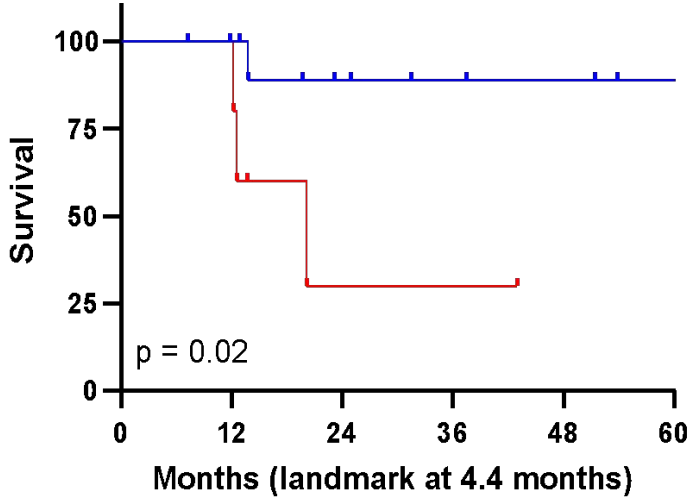
Control (non-SCT) group for landmark analysis only included patients with age ≤ 70 years at induction who attained CRc and were alive at landmark.

Overall Survival IC *FLT3*-TKD^{mut} *NPM1*^{mut}cohort by Allo SCT (Landmark analysis)



	N	Events	mOS	3 yr OS	mF/U
SCT	13	3	NR	77%	59
No SCT	10	4	NR	70%	46

Overall Survival IC *FLT3*-TKD^{mut} *NPM1*^{wt}cohort by Allo SCT (Landmark analysis)



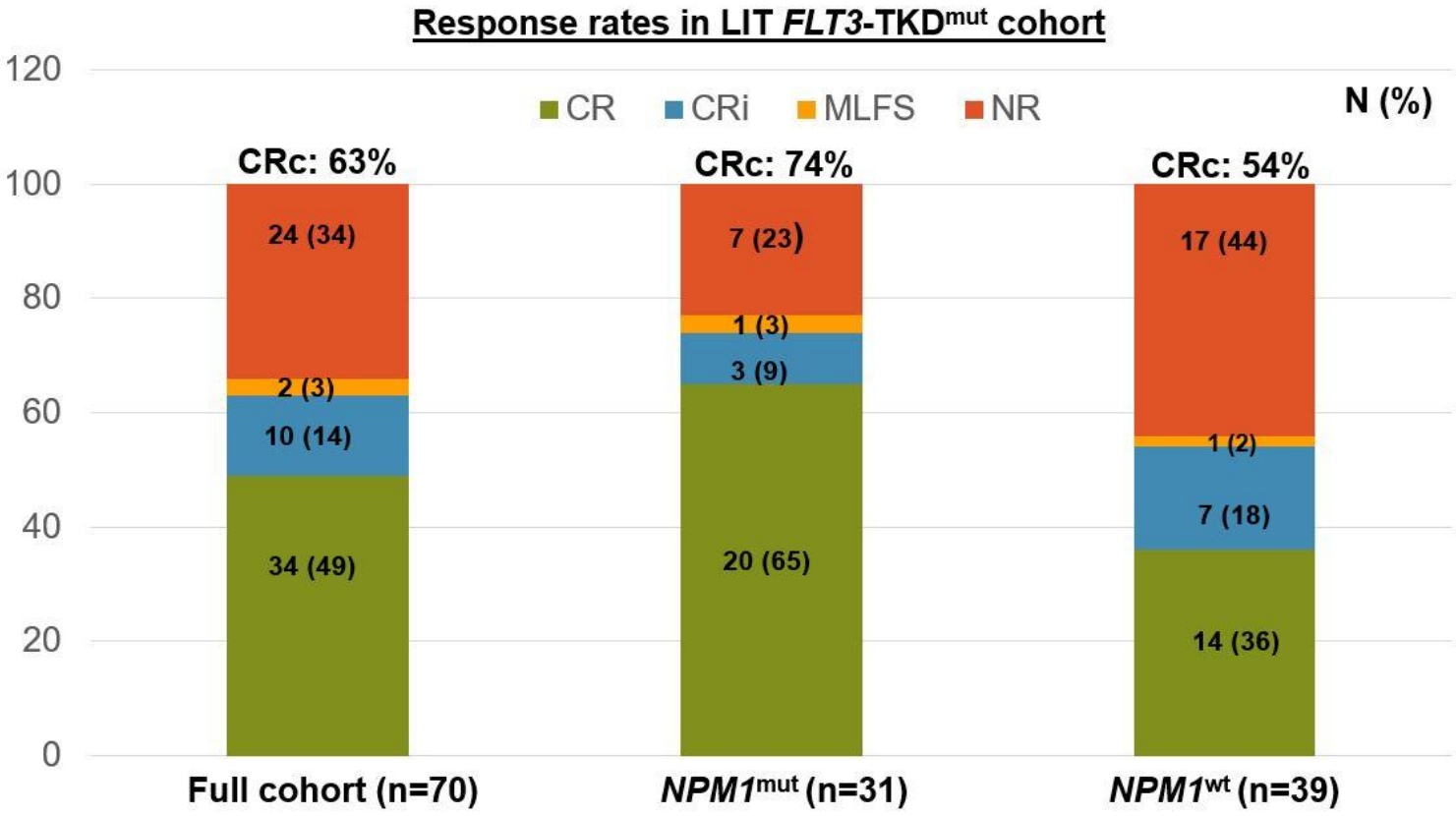
	N	Events	mOS	3 yr OS	mF/U
SCT	12	1	NR	89%	25
No SCT	5	3	20.2	30%	43

Results: *FLT3*-TKD LIT Cohort (n=70)

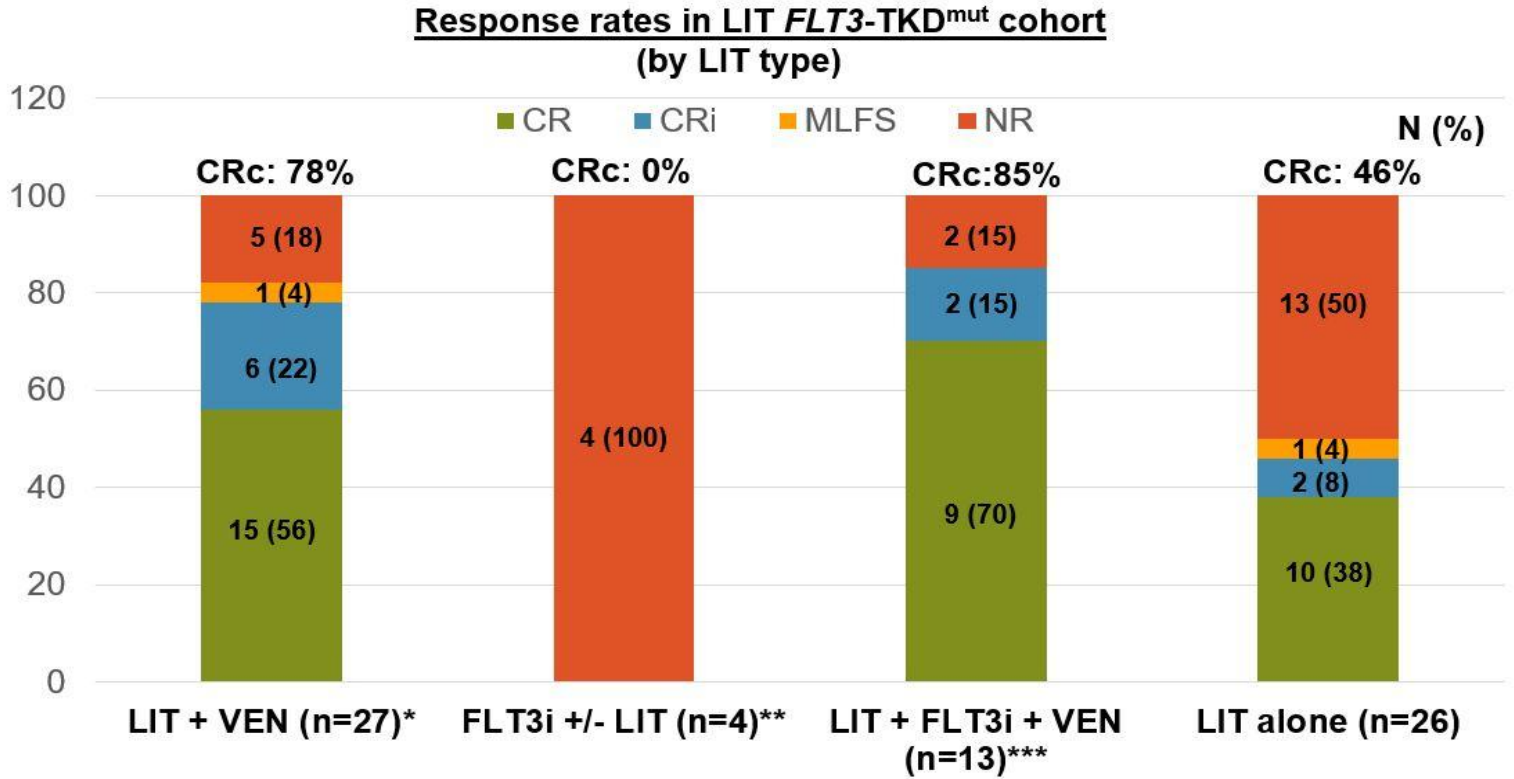
Parameters	$NPM1^{mut}$ (n=31; 44%)	$NPM1^{wt}$ (n=39; 56%)	*P* value
	N (%), Median [range]		
Age (years)	71 [60-89]	70 [50-87]	0.7
Females	13 (42)	18 (46)	0.8
Baseline WBC ($x10^9$/L)	2.7 (0.4-114)	5.85 (0.1-46.1)	0.7
Baseline BM blasts (%)	56 (21-91)	57 (12-92)	1
Secondary AML	5 (16)	21 (54)	0.001
Cytogenetics			
Diploid	19	10	0.004
CK	3	9	0.2
Isolated -5/5q- or -7/7q-	0	3	0.3
11q23 Rearrangement	0	5	0.06
Others	9*	12**	1
Mutations			
DNMT3A	14/26 (54)	7/24 (29)	0.09
ASXL1	1/19 (5)	11/22 (50)	0.002
RAS	8/22 (36)	15/29 (52)	0.4
RUNX1	0/18 (0)	10/36 (39)	0.03
TP53	0/18 (0)	7/25 (28)	0.01

*Included +4, +8, -Y, t(1:22), inv(9), del(9q) **Included +1, +8, +11, +13, +19, + 21, -10, i(17q), del(12p)

Results: *FLT3*-TKD LIT Cohort (n=70)



Results: *FLT3*-TKD LIT Cohort (n=70)

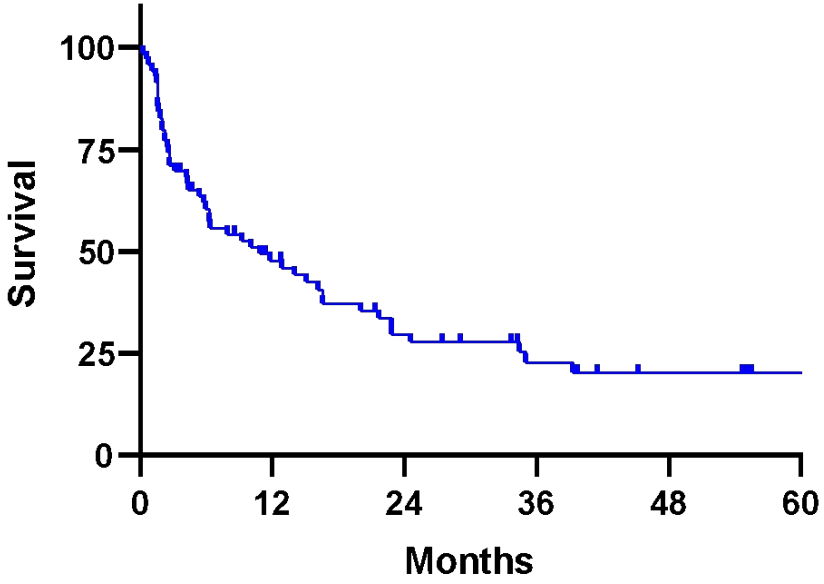


*Included: CLAD + LDAC+ VEN (n=11), DAC + VEN (n=6), AZA + VEN +/- additional non-FLT3i agent (n=5), ASTX727 + VEN (n=4), IVO + VEN (n=1)
**Included: AZA + Crenolanib (n=1), Crenolanib (n=1), Selinexor + Sorafenib (n=1), E6201 (n=1)
***Included: DAC + VEN + Gilteritinib (n=6), AZA + VEN + Gilteritinib (n=4), DAC + VEN + Midostaurin (n=3)

Results: *FLT3*-TKD LIT Cohort (n=70)

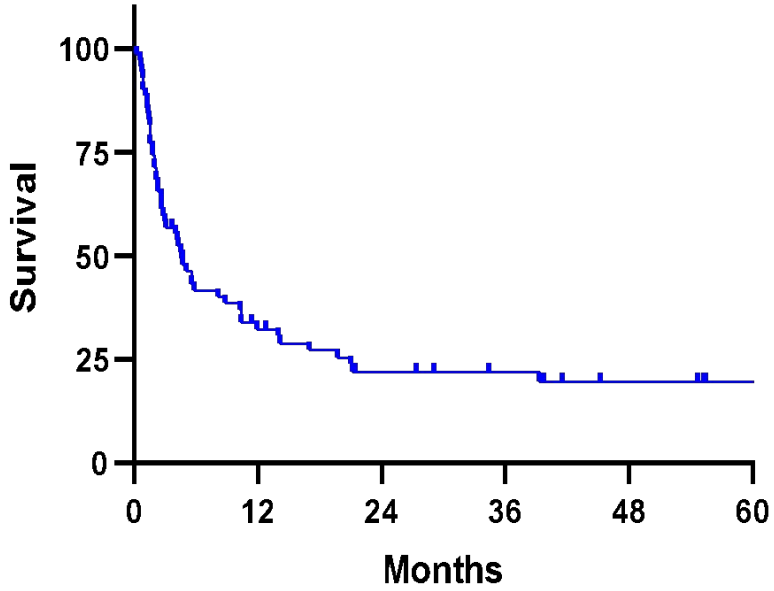
Median Follow-up: 40 mo

Overall Survival LIT *FLT3*-TKD^{mut} cohort



N	Events	mOS	3 yr OS
70	50	10.9	23%

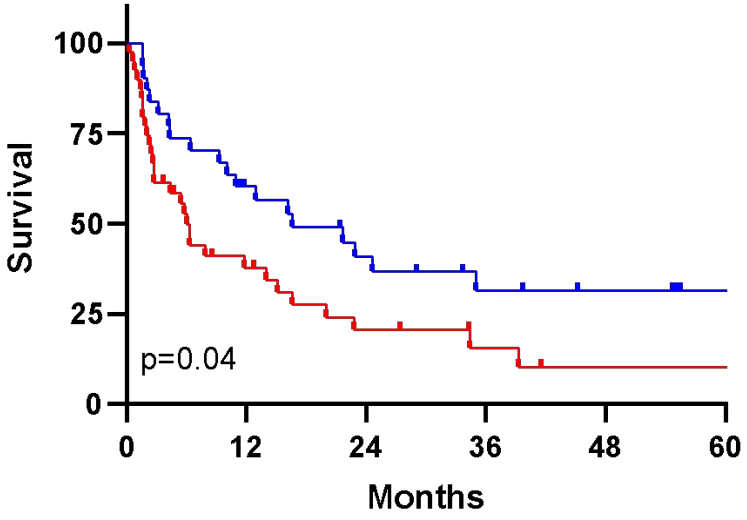
Event Free Survival LIT *FLT3*-TKD^{mut} cohort



N	Events	mEFS	3 yr EFS
70	54	4.6	22%

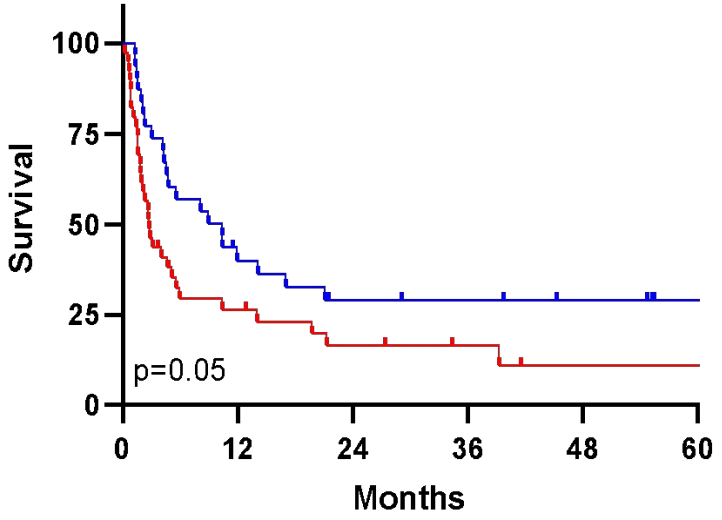
Results: *FLT3*-TKD LIT Cohort (n=70)

Overall Survival by *NPM1* status (LIT *FLT3*-TKD^{mut} cohort)



	N	Events	mOS	3 yr OS	mF/U
NPM1^{mut}	31	20	16.6	32%	45
NPM1^{wt}	39	30	6	16%	34

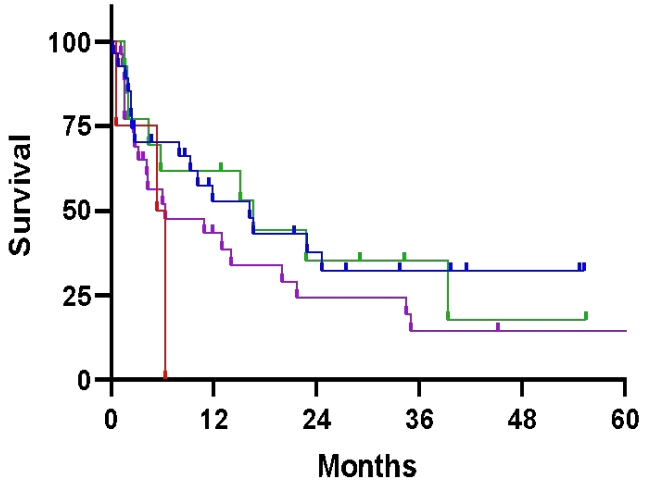
Event Free Survival by *NPM1* status (LIT *FLT3*-TKD^{mut} cohort)



	N	Events	mEFS	3 yr EFS	mF/U
NPM1^{mut}	31	22	10.4	29%	45
NPM1^{wt}	39	32	2.7	17%	34

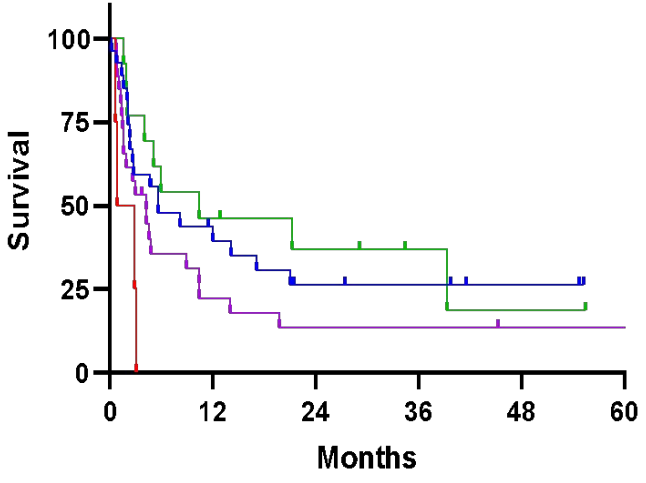
Results: *FLT3*-TKD LIT Cohort (n=70)

Overall Survival LIT *FLT3-TKD*^{mut} cohort
(stratified by type of LIT)



	N	Events	mOS	3 yr OS	p	mF/U
LIT + VEN	27	16	16.2	32%	0.2	34
FLT3i +/- LIT	4	4	5.85	0	0.2	NR
LIT + VEN + FLT3i	13	9	16.6	35%	0.4	34
LIT only	26	21	6.4	14%	ref	100

Event Free Survival LIT *FLT3-TKD*^{mut} cohort
(stratified by type of LIT)



	N	Events	mEFS	3 yr EFS	p	mF/U
LIT + VEN	27	19	5.6	26%	0.2	34
FLT3i +/- LIT	4	4	1.87	0%	**0.04**	NR
LIT + VEN + FLT3i	13	9	10.4	37%	0.1	34
LIT only	26	22	4.23	13%	ref	100

Results: *FLT3*-TKD LIT Cohort: Role of Allo-SCT in CR1

Control (non-SCT) group for landmark analysis only included patients with age ≤ 70 years at induction who attained CRc and were alive at landmark.

FLT3-TKD LIT full cohort (n=70)

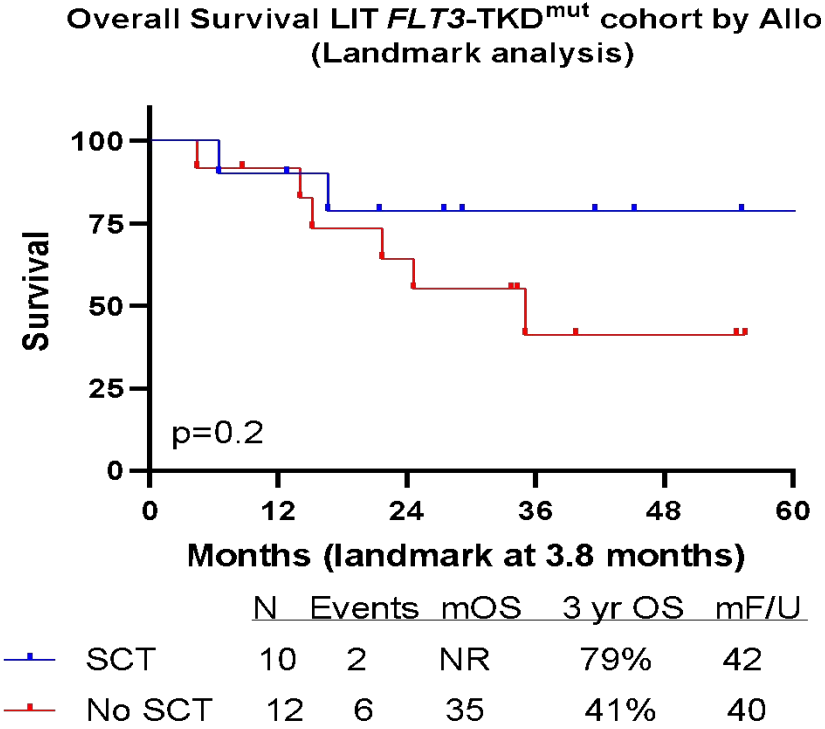
- Allo-SCT in CR1: 10 (14%)
- Median time to allo-SCT: 3.8 mo (2.7-5.5)

FLT3-TKD *NPM1*^{mut} IC full cohort (n=31)

- Allo-SCT in CR1: 5 (16%)
- Median time to allo-SCT: 3.4 mo (2.9-4.8)

FLT3-TKD *NPM1*^{wt} IC full cohort (n=39)

- Allo-SCT in CR1: 5 (13%)
- Median time to allo-SCT: 3.9 mo (2.7-5.5)

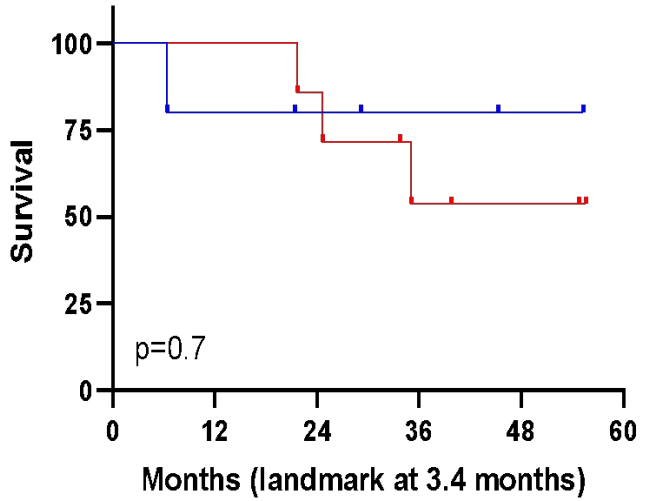


Median age:- SCT: 65.5 years (50-70) , Non-SCT: 67 years (61-70)

Results: *FLT3*-TKD LIT Cohort: Role of Allo-SCT in CR1

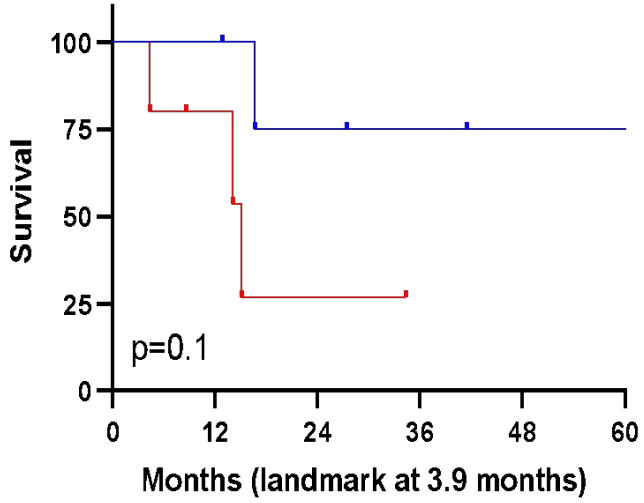
Control (non-SCT) group for landmark analysis only included patients with age ≤ 70 years at induction who attained CRc and were alive at landmark.

Overall Survival LIT *FLT3*-TKD^{mut}*NPM1*^{mut}cohort by Allo SCT (Landmark analysis)



	N	Events	mOS	3 yr OS	mF/U
SCT	5	1	NR	80%	37
No SCT	7	3	NR	54%	55

Overall Survival LIT *FLT3*-TKD^{mut}*NPM1*^{wt} cohort by Allo SCT (Landmark analysis)



	N	Events	mOS	3 yr OS	mF/U
SCT	5	1	NR	75%	42
No SCT	5	3	15.1	27%	34

Conclusions

- *FLT3*-TKD AML commonly harbor *NPM1* co-mutations (44%).
- *FLT3*-TKD and *NPM1* co-mutation = better prognosis:
  - OS : IC-based (mOS NR, 3-year OS 74%), LIT-based (mOS 16.6 mo, 3-year OS 32%)
- *FLT3*-TKD without *NPM1* co-mutation = poor prognosis:
  - OS: IC-based (mOS 13.8 mo, 3-year OS 40%), LIT-based (mOS 6 mo, 3-year OS 16%)
- Frontline IC + VEN (3-year OS 74%) and IC + FLT3i (3-year OS 70%) = trend towards improved OS, compared to IC alone (3-year OS 42%).
- Allo-SCT led to OS benefit with IC and trend to OS benefit with LIT in *FLT3*-TKD AML without *NPM1*^{mut}. No clear benefit with allo-SCT in *FLT3*-TKD + *NPM1* AML.

THANK YOU

PANEL DISCUSSION

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Q & A

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