

# Long-term outcomes in *FLT3*-mutated acute myeloid leukemia after frontline hypomethylating agent, venetoclax and a *FLT3* inhibitor

Nicholas J. Short,<sup>1\*</sup> Sanam Loghavi,<sup>2\*</sup> Musa Yilmaz,<sup>1</sup> Omer Karrar,<sup>1</sup> Kunhwa Kim,<sup>1</sup> Courtney D. DiNardo,<sup>1</sup> Tapan M. Kadia,<sup>1</sup> Manuel Maroun,<sup>1</sup> Gautam Borthakur,<sup>1</sup> Ghayas C. Issa,<sup>1</sup> Joseph Jabbour,<sup>1</sup> Betul Oran,<sup>3</sup> Elizabeth J. Shpall,<sup>3</sup> Uday Popat,<sup>3</sup> Keyur P. Patel,<sup>2</sup> Mark Routbort,<sup>2</sup> Marina Konopleva,<sup>4</sup> Farhad Ravandi,<sup>1</sup> Hagop Kantarjian<sup>1</sup> and Naval Daver<sup>1</sup>

<sup>1</sup>Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX;

<sup>2</sup>Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX; <sup>3</sup>Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX and <sup>4</sup>Department of Oncology, Montefiore Einstein Cancer Center & Albert Einstein College of Medicine, New York, NY, USA

*\*NJS and SL contributed equally as first authors.*

**Correspondence:** N.J. Short  
[nshort@mdanderson.org](mailto:nshort@mdanderson.org)

N. Daver  
[ndaver@mdanderson.org](mailto:ndaver@mdanderson.org)

**Received:** June 24, 2025.  
**Accepted:** September 24, 2025.  
**Early view:** October 2, 2025.

<https://doi.org/10.3324/haematol.2025.288553>

©2026 Ferrata Storti Foundation  
Published under a CC BY-NC license



**Title:** Long-term outcomes in *FLT3*-mutated acute myeloid leukemia after frontline hypomethylating agent, venetoclax and a *FLT3* inhibitor

**Running title:** Outcomes of triplet regimens in *FLT3*-mutated AML

**Supplemental Table 1:** Mutations included in the 81-gene targeted sequencing panel

**Supplemental Table 2:** Hematologic responses

**Supplemental Table 3:** Baseline characteristics of patients evaluated for the landmark analysis

**Supplemental Table 4:** Cytogenetic and molecular clonal evolution at time of relapse.

**Supplemental Figure 1:** Patient disposition

**Supplemental Figure 2:** Outcomes of the study cohort (A) Relapse-free survival, and (B) Overall survival

**Supplemental Figure 3:** Outcomes of the study cohort, stratified by age

**Supplemental Figure 4:** Impact of *FLT3* mutations on overall survival, stratified by age. (A) *FLT3-ITD* mutation, and (B) *FLT3-TKD* mutation

**Supplemental Figure 5:** Overall survival by subgroup. (A) *NPM1* co-mutation status, and (B) ELN 2022 risk stratification

**Supplemental Figure 6:** Overall survival stratified by *FLT3-ITD*, *NPM1*, and *DNMT3A* co-mutations status

**Supplemental Figure 7:** Overall survival stratified by receipt of hematopoietic stem cell transplantation (landmark analysis)

**Supplemental Figure 8:** Overall survival stratified by receipt of hematopoietic stem cell transplantation in patients <75 years of age (landmark analysis)

**Supplemental Figure 9:** Overall survival stratified by receipt of hematopoietic stem cell transplantation in patients with *FLT3-ITD* mutation (landmark analysis)

**Supplemental Figure 10:** Overall survival stratified by receipt of hematopoietic stem cell transplantation in patients with ELN adverse risk disease (landmark analysis)

**Supplemental Figure 11:** Overall survival after relapse

**Supplemental Figure 12:** Overall survival after relapse, stratified by *FLT3* mutation status by PCR at time of relapse

**Supplemental Table 1.** Mutations included in the 81-gene targeted sequencing panel

<i>ANKRD26</i>	<i>CBLB</i>	<i>EED</i>	<i>GFI1</i>	<i>JAK1</i>	<i>NF1</i>	<i>PTEN</i>	<i>SH2B3</i>	<i>SUZ12</i>
<i>ASXL1</i>	<i>CBLC</i>	<i>ELANE</i>	<i>GNAS</i>	<i>JAK2</i>	<i>NOTCH1</i>	<i>PTPN11</i>	<i>SMC1A</i>	<i>TERC</i>
<i>ASXL2</i>	<i>CEBPA</i>	<i>ETNK1</i>	<i>HNRNPk</i>	<i>JAK3</i>	<i>NPM1</i>	<i>RAD21</i>	<i>SMC3</i>	<i>TERT</i>
<i>BCOR</i>	<i>CREBBP</i>	<i>ETV6</i>	<i>HRAS</i>	<i>KDM6A</i>	<i>NRAS</i>	<i>RARA</i>	<i>SRSF2</i>	<i>TET2</i>
<i>BCORL1</i>	<i>CRLF2</i>	<i>EZH2</i>	<i>IDH1</i>	<i>KIT</i>	<i>PAX5</i>	<i>RUNX1</i>	<i>STAG1</i>	<i>TP53</i>
<i>BRAF</i>	<i>CSF3R</i>	<i>FBXW7</i>	<i>IDH2</i>	<i>KMT2A</i>	<i>PHF6</i>	<i>SETBP1</i>	<i>STAG2</i>	<i>U2AF1</i>
<i>BRINP3</i>	<i>CUX1</i>	<i>FLT3</i>	<i>IKZF1</i>	<i>KRAS</i>	<i>PIGA</i>	<i>SF1</i>	<i>STAT3</i>	<i>U2AF2</i>
<i>CALR</i>	<i>DDX41</i>	<i>GATA1</i>	<i>IL2RG</i>	<i>MAP2K1</i>	<i>PML</i>	<i>SF3A1</i>	<i>STAT5A</i>	<i>WT1</i>
<i>CBL</i>	<i>DNMT3A</i>	<i>GATA2</i>	<i>IL7R</i>	<i>MPL</i>	<i>PRPF40B</i>	<i>SF3B1</i>	<i>STAT5B</i>	<i>ZRSR2</i>

**Supplemental Table 2.** Hematologic responses

<b>Response, N (%)</b>	<b>N=73</b>
<b>CRc (CR+CRi)</b>	68 (93)
<i>CR</i>	60 (82)
<i>CRi</i>	8 (11)
<i>MLFS</i>	4 (6)
<b>ORR (CR + CRi + MLFS)</b>	72 (99)
<b>Early death</b>	1 (1)

Abbreviations: CRc, composite complete remission; CR, complete remission; CRi, complete remission with incomplete count recovery; MLFS, morphologic leukemia-free state; ORR, overall response rate

**Supplemental Table 3.** Baseline characteristics of patients evaluated for the landmark analysis

<b>Characteristic<sup>1</sup></b>	<b>Transplanted cohort (N=30)</b>	<b>Non-transplanted cohort (N=32)</b>	<b>Univariate p-value</b>
<b>Age, years</b>			
<i>Median [range]</i>	67 [18-75]	72 [61-88]	<b>0.001</b>
≥75 years	1 (3)	14 (44)	<b>0.0002</b>
<b>Cytogenetics</b>			
<i>Diploid</i>	15 (60)	13 (41)	0.57
<i>Adverse</i>	6 (20)	4 (13)	
<i>Others</i>	7 (23)	12 (38)	
<i>Insufficient</i>	2 (7)	3 (22)	
<b>ELN 2022 risk stratification</b>			
<i>Favorable</i>	5 (17)	3 (9)	0.63
<i>Intermediate</i>	9 (30)	12 (38)	
<i>Adverse</i>	16 (53)	17 (53)	
<b>FLT3 subtype</b>			
<i>ITD</i>	26 (87)	24 (75)	0.41
<i>TKD</i>	4 (13)	7 (22)	
<i>ITD+TKD</i>	0	1 (3)	
<b>FLT3 variant allelic frequency</b>			
<i>ITD</i>	18 [1-53]	25 [3-75]	0.1
<i>TKD</i>	34 [26-57]	14 [13-51]	0.07
<b>FLT3 inhibitor</b>			
<i>Gilteritinib</i>	21 (70)	21 (66)	0.88
<i>Quizartinib</i>	6 (20)	8 (25)	
<i>Sorafenib</i>	3 (10)	2 (6)	
<i>Midostaurin</i>	0	1 (3)	
<b>Hypomethylating agent</b>			
<i>Azacitidine</i>	15 (50)	16 (50)	0.99
<i>Decitabine</i>	15 (50)	16 (50)	
<b>Mutations<sup>2</sup></b>			
<i>NPM1</i>	13 (43)	15 (47)	0.78
<i>DNMT3A</i>	11 (37)	16 (50)	0.29
<i>WT1</i>	8 (27)	4 (13)	0.21
<i>RUNX1</i>	7 (23)	8 (25)	0.88
<i>BCOR</i>	5 (17)	5 (16)	0.91
<i>IDH1</i>	5 (17)	0	<b>0.01</b>

<i>IDH2</i>	4 (13)	5 (16)	0.99
<i>TET2</i>	3 (10)	10 (31)	0.06
<i>ASXL1</i>	3 (10)	2 (6)	0.79
<i>NF1</i>	3 (10)	0	0.06
<i>RAD21</i>	3 (10)	2 (6)	0.58
<i>U2AF1</i>	3 (10)	3 (9)	0.93
<i>BCORL1</i>	2 (7)	3 (9)	0.69
<i>NRAS</i>	2 (7)	1 (3)	0.51
<i>PTPN11</i>	2 (7)	3 (9)	0.69
<i>SF3B1</i>	2 (7)	2 (6)	0.94
<i>SRSF2</i>	2 (7)	5 (16)	0.26
<i>STAG2</i>	2 (7)	3 (9)	0.69
<i>CEBPA</i>	1 (3)	5 (16)	0.10
<b>RAS pathway mutation<sup>3</sup></b>	9 (30)	6 (19)	0.30

<sup>1</sup> Values are listed as median [range] or n (%)

<sup>2</sup> Mutations detected in ≥5% of the study cohort

<sup>3</sup> Includes *KRAS*, *NRAS*, *PTPN11*, *CBL*, *NF1* and/or *BRAF* mutations

Abbreviations: ELN, European LeukemiaNet; ITD, internal tandem duplication; TKD, tyrosine kinase domain

**Supplemental Table 4.** Cytogenetic and molecular clonal evolution at time of relapse.

Patient	Regimen	Cytogenetics at diagnosis	Cytogenetics at relapse	Cytogenetic evolution	Mutation(s) at diagnosis	Mutation(s) at relapse	Mutational evolution
#1	Azacitidine + venetoclax + gilteritinib	46,XX,t(7;11)(p15; p15)[20]	46,XX,t(7;11)(p15; p15)[17]/46XX[3]	No	<b>FLT3 ITD</b> RUNX1 F163fs KRAS Q22K	RUNX1 F163fs <b>NRAS G12A</b> <b>NRAS G13R</b> <b>GATA2 A372T</b>	Yes
#2	Azacitidine + venetoclax + gilteritinib	47,XY,+11[20]	47,XY,+11[8]/ <b>49,idem,+14,+18[4]</b> /46,XY[8]	Yes	<b>FLT3 D835Y</b> <b>SF3B1 K700E</b> <b>SMC1A I9T</b> <b>NRAS G13C</b> DNMT3A R882H TET2 N1156Y <b>STAG2 K493fs</b>	DNMT3A R882H TET2 N1156Y <b>TET2 L1101fs</b> <b>ZRSR2 C326G</b> <b>GATA2 R307Q (11)</b>	Yes
#3	Azacitidine + venetoclax + gilteritinib	N/A	N/A	N/A	FLT3 ITD NPM1 W288fs IDH2 R140Q DNMT3A Splice	N/A	N/A
#4	Azacitidine + venetoclax + gilteritinib	N/A	N/A	N/A	<b>FLT3 ITD</b> U2AF1 S34F DNMT3A R882H TET2 Y1148fs BCOR R1480* <b>BCORL1 P334fs</b> PTPN11 N58Y	<b>FLT3 TKD</b> U2AF1 S34F DNMT3A R882H TET2 Y1148fs TET2 Q531* BCOR R1480* PTPN11 N58Y	Yes
#5	Azacitidine + venetoclax + gilteritinib	46, XY[20]	N/A	N/A	FLT3 ITD NPM1 p.W288fs IDH1 R132H DNMT3A R882	N/A	N/A
#6	Azacitidine + venetoclax + gilteritinib	46,XY,del(12)(p13 p12)[13]/46,XY[7]	46,XY,del(12)(p13 p12)[3]/ <b>47,idem,+21[1]</b> /46,XY[6]	Yes	FLT3 D835E RUNX1 splice DNMT3 I705T	FLT3 D835E RUNX1 splice DNMT3 I705T <b>IKZF1 p.N159S</b>	Yes

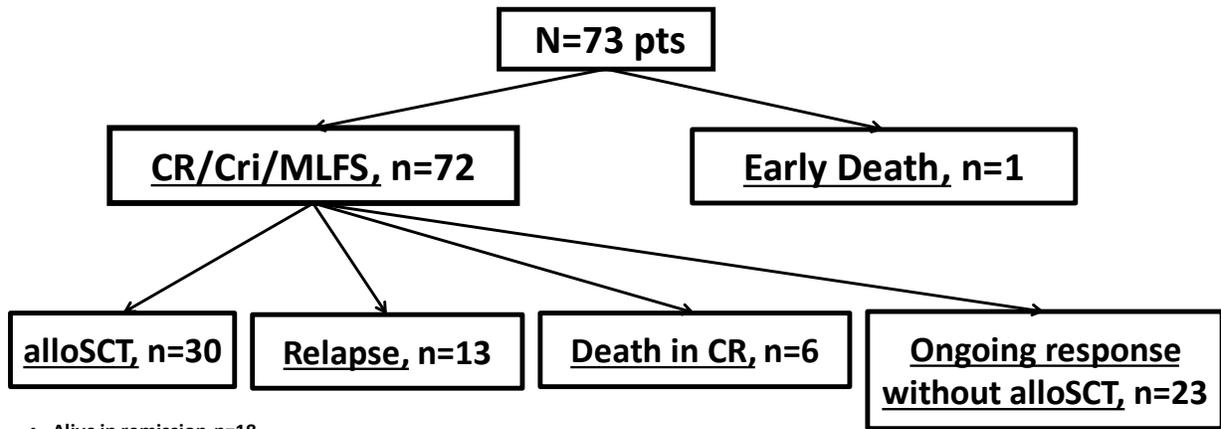
						<b>PTPN11 p.G60R</b>	
<b>#7</b>	Azacitidine + venetoclax + gilteritinib	N/A (FISH pos for KMT2A)	46,XY,t(11;19)(q23;p13.3)[20]	No	<b>FLT3 ITD</b> <b>STAG2 N58fs</b>	None	No
<b>#8</b>	Decitabine + venetoclax + quizartinib	46,XX,inv(3)(p23q26.2)[18]/45,idem,t(4;5)(q21;p15.1),-21[1]/47,XX,add(5)(p15.3),+13[1]	46,XX,inv(3)(p23q26.2)[3]/45, <b>idem</b> ,-7[16]/46,XX[1]	Yes	<b>FLT3 ITD</b> RUNX1 H85fs RUNX1 G412S DNMT3A R882H SRSF2 P95L	DNMT3A R882H SRSF2 P95L <b>IKZF1 p.H163Q</b> <b>IKZF1</b> <b>Y180_A181del</b> <b>IKZF1 N159K</b> RUNX1 H85fs RUNX1 G412S <b>RUNX1 I193N</b> <b>NRAS Q61H</b> <b>NRAS G13D</b>	Yes
<b>#9</b>	Decitabine + venetoclax + quizartinib	46,XX,add(12)(q24.3)[4]/46,XX[16]	46,XX[20]	No	<b>FLT3 ITD</b> SUZ12 F295S <b>RUNX1 R201</b> <b>TET2 R550*</b> TET2 T1554fs SRSF2 P95H PFH6 p.R225 CBL R420Q SH2B3 I446N	CBL R420Q SUZ12 F295S SH2B3 I446N SH2B3 S503fs ET2 R550* TET2 T1554fs SRSF2 P95H PFH6 p.R225 <b>GATA2 L305V</b>	Yes
<b>#10</b>	Decitabine + venetoclax + quizartinib	46,XX,t(4;7)(q21;q32),del(21)(q22)[20]	46,XX,t(4;7)(q21;q32)[5], 46XX[1]	No	FLT3 ITD WT1 T460_C461delinsS	FLT3 ITD WT1 T460_C461delinsS <b>CBL C384Y</b>	Yes
<b>#11</b>	Azacitidine + venetoclax + gilteritinib	46,XY,t(7;11)(p15;p15)[20]	46,XY,t(7;11)(p15;p15)[18]/46,XY[2]	No	<b>FLT3 D835</b> MPL L580fs WT1 R385fs RUNX1 A352fs	MPL L580fs WT1 R385fs RUNX1 A352fs	No

<b>#12</b>	Decitabine + venetoclax + gilteritinib	46, XX[20]	46,XX[20]	No	<b>FLT3 D835Y</b> WT1 M415fs <b>WT1 A387fs</b> <b>IDH2 R140Q</b> NRAS G13R BRINP3 S592N DNMT3A G413V <b>BCOR V1653A</b>	WT1 M415fs DNMT3A G413V NRAS G13R BRINP3 S592N	No
<b>#13</b>	Decitabine + venetoclax + sorafenib	46,XX,add(2)(q21), add(19)(p13.3)[1]/ 46,XX[19]	46,XX[19], 46,XY[1]	No	<b>FLT3 ITD</b> NPM1 W288fs <b>RAD21 I17N</b> TET2 Q1274fs TET2 V328fs	NPM1 W288fs WT1 G183V TET2 Q1274fs TET2 V328fs	Yes
<b>#14</b>	Decitabine + venetoclax + sorafenib	46,XX,t(3;6)(q26.2 ;q25)[20]	46,XX,t(3;6)(q26.2 ;q25)[9], 46XX[11]	No	<b>FLT3 ITD</b> BCORL1 Q1133 <b>PHF6 G10fs</b> ASXL1 S577*	<b>SF3B1 K666N</b> BCORL1 Q1133 ASXL1 S577*	Yes
<b>#15</b>	Decitabine + venetoclax + sorafenib	46, XX[20]	46,XX,t(4;17)(q12; q25)[15]/46,XX[5]	Yes	<b>FLT3 ITD</b> IDH1 R132C U2AF1 S34F <b>NRAS G12D</b> DNMT3A R882H BCOR Splice	IDH1 R132C U2AF1 S34F DNMT3A R882H BCOR Splice	No
<b>#16</b>	Decitabine + venetoclax + quizartinib	46,XY,t(10;12)(q24 ;p12)[1]/46,XY,del (16)(p11.2)[1]/46, XY[18]	47,XY,+6,add(7)(q 32)[6]/47,idem[cp 2]//46,XX[12]	Yes	FLT3 ITD <b>WT1 Q414fs</b> <b>BCOR Splice</b> BCORL1 R1145* <b>NF1 T1310fs</b>	FLT3 ITD BCORL1 R1145*	No
<b>#17</b>	Oral decitabine + venetoclax + gilteritinib	46, XX[20]	46,XX[20]	No	<b>FLT3 ITD</b> NPM1 W288fs IDH2 R140Q DNMT3 A R882H KIT D816V	NPM1 W288fs IDH2 R140Q DNMT3 A R882H KIT D816V	No

<b>#18</b>	Azacitidine + venetoclax + gilteritinib	46, XX[20]	47,XX, <b>+4</b> [20]	Yes	FLT3 ITD TET2 K1339* TET2 F1287V	FLT3-ITD TET2 K1339* TET2 F1287V	No
<b>#19</b>	Oral decitabine + venetoclax + gilteritinib	46, XY[20]	47,XY, <b>+mar[1]</b> /46,XY[9]	N/A	FLT3 ITD NPM1 W288fs IDH2 R140Q SRSF2 P95L	FLT3-ITD NPM1 W288fs IDH2 R140Q SRSF2 P95L	No

*Bold font indicates changes detected between diagnostic and relapse samples.*

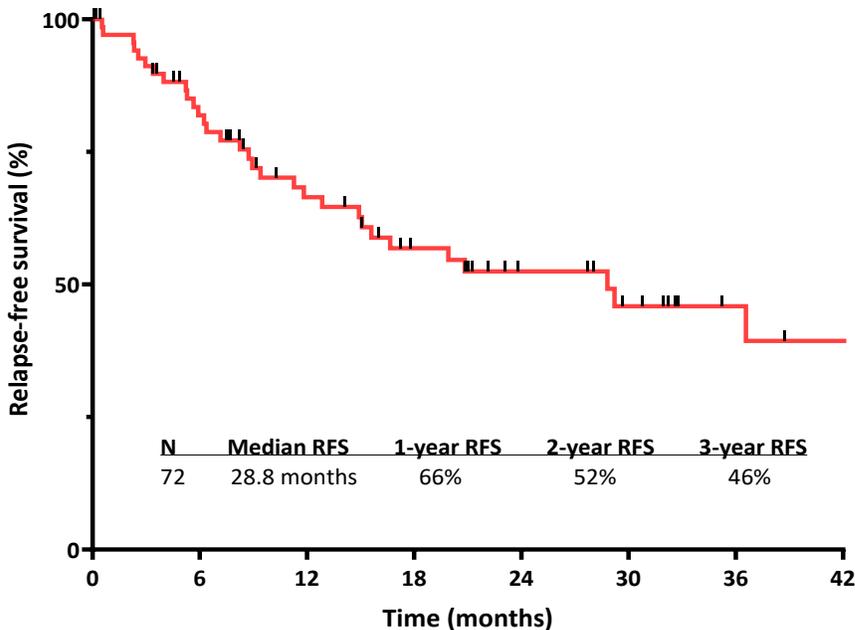
Supplemental Figure 1. Patient disposition



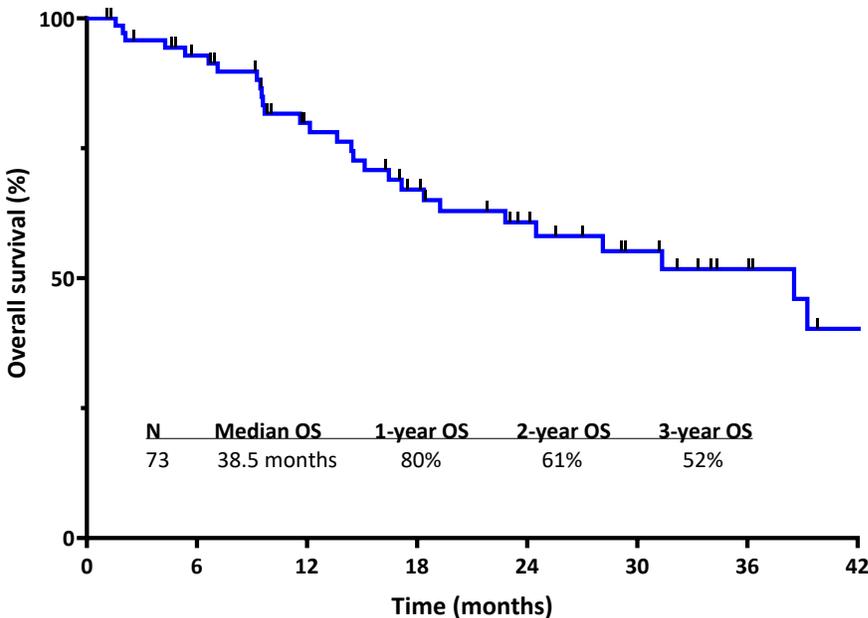
- Alive in remission, n=18
- Died in remission, n=6
- Relapsed → died, n=6

**Supplemental Figure 2.** Outcomes of the study cohort (A) Relapse-free survival, and (B) Overall survival

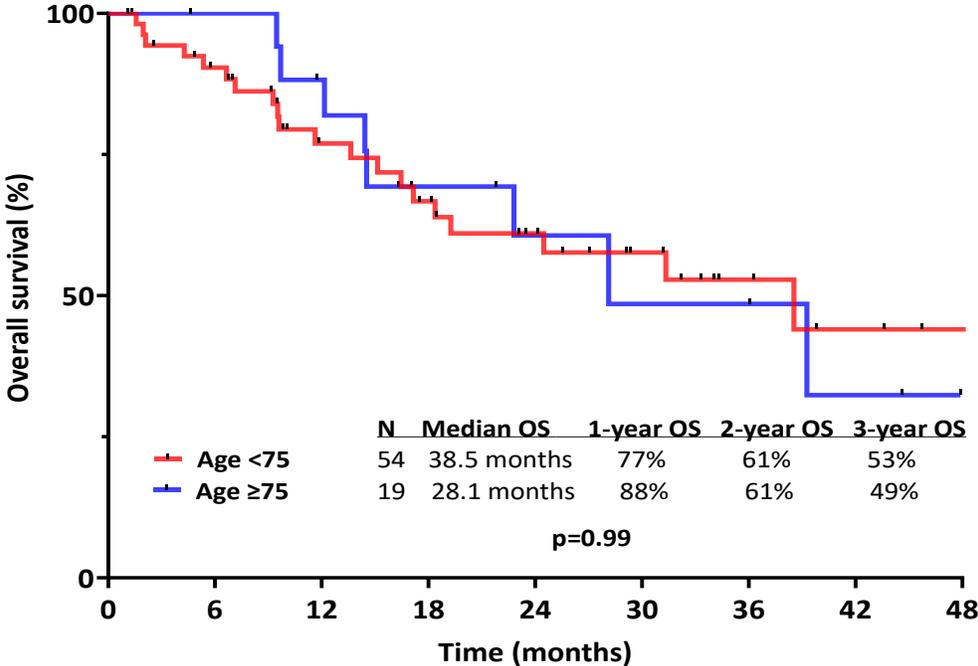
(A)



(B)

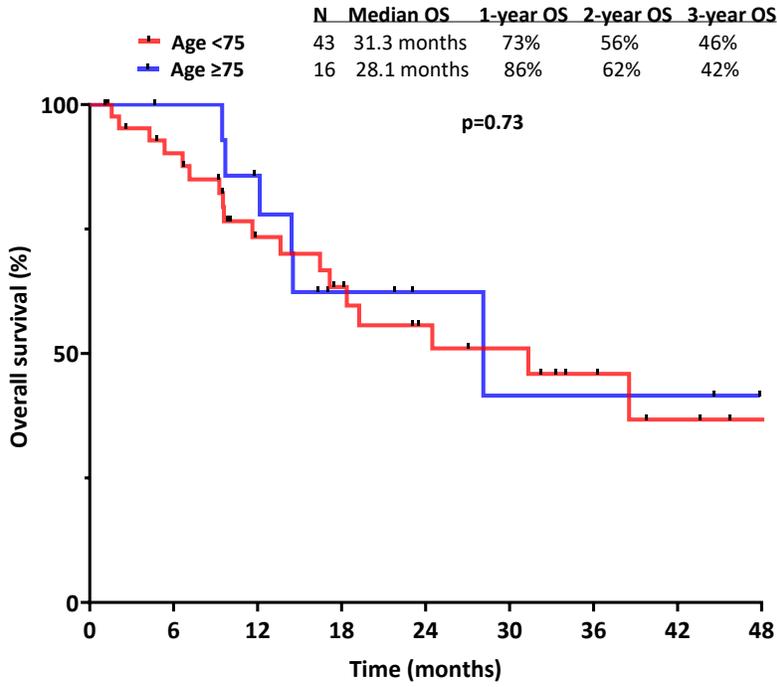


Supplemental Figure 3. Outcomes of the study cohort, stratified by age

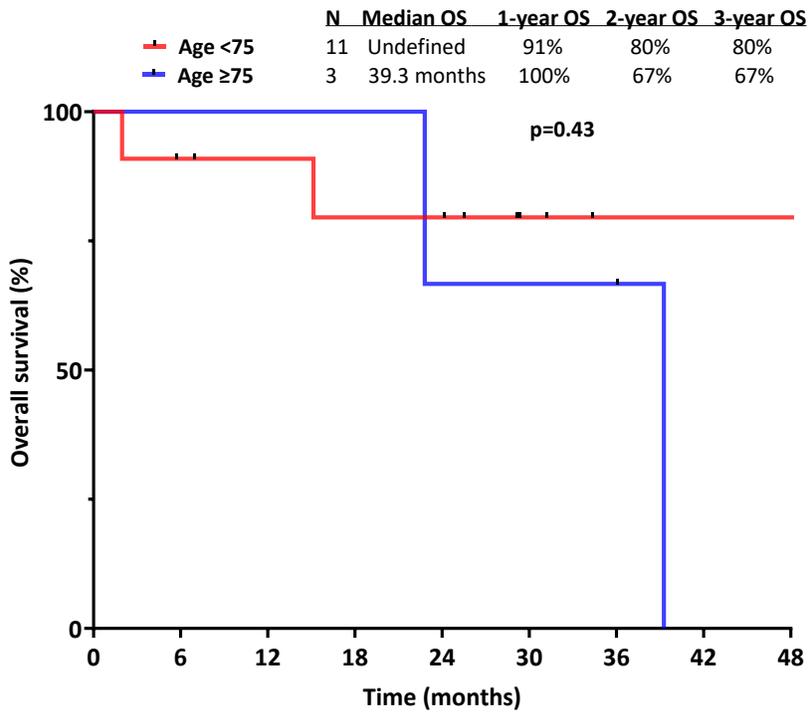


**Supplemental Figure 4.** Impact of *FLT3* mutations on overall survival, stratified by age. (A) *FLT3-ITD* mutation, and (B) *FLT3-TKD* mutation

(A)

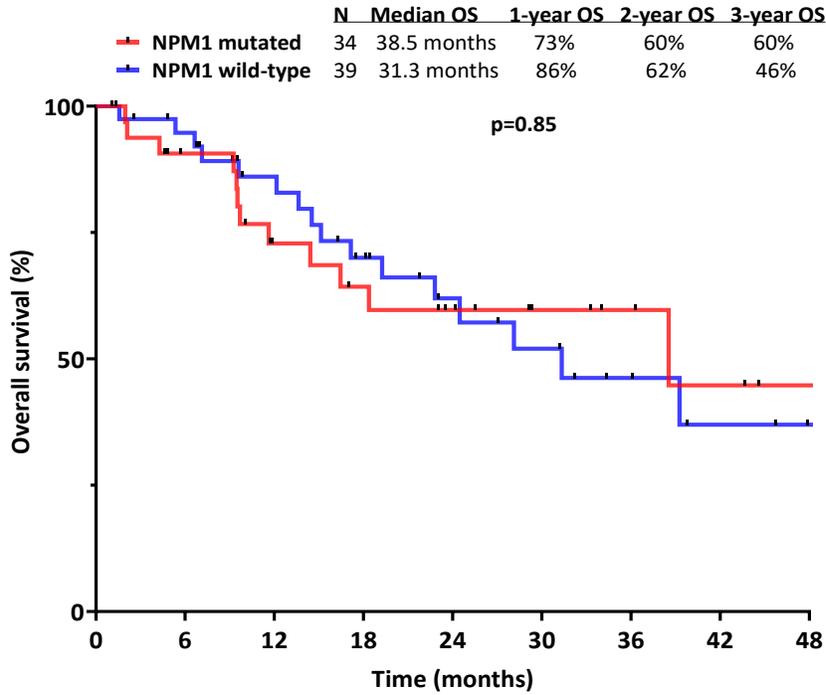


(B)

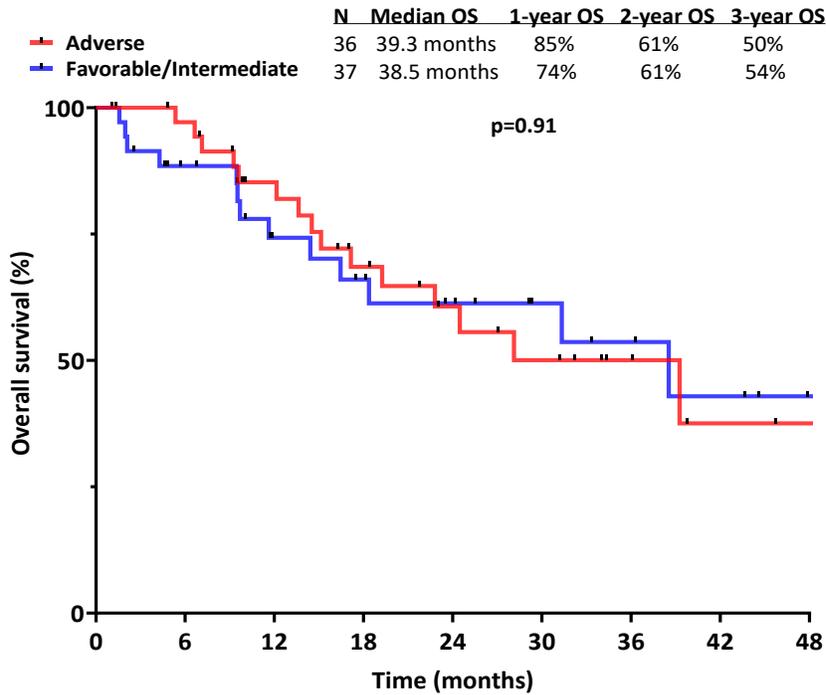


**Supplemental Figure 5.** Overall survival by subgroup. (A) *NPM1* co-mutation status, and (B) ELN 2022 risk stratification

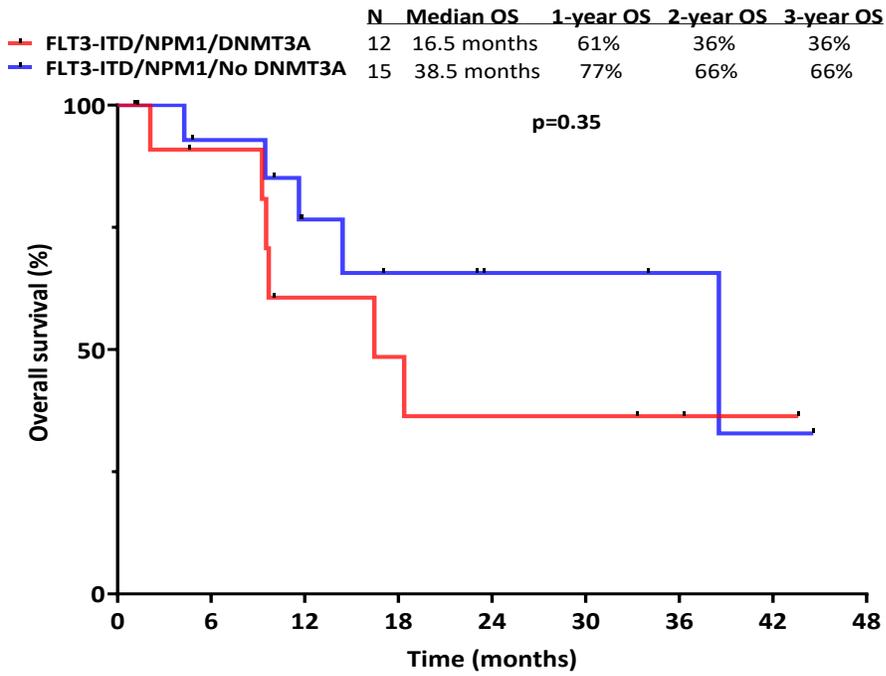
(A)



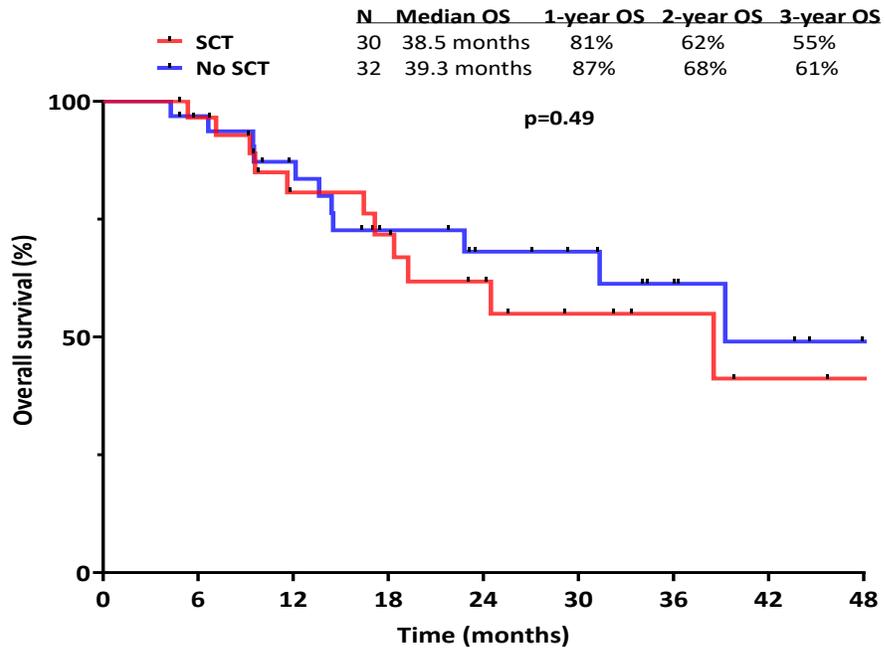
(B)



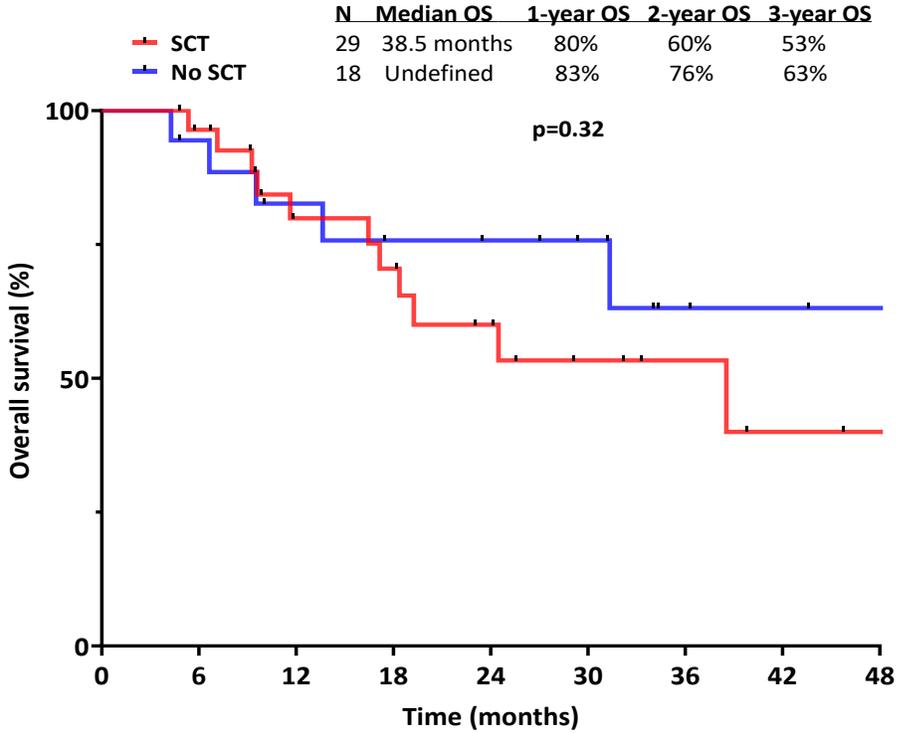
Supplemental Figure 6. Overall survival stratified by *FLT3-ITD*, *NPM1*, and *DNMT3A* co-mutations status



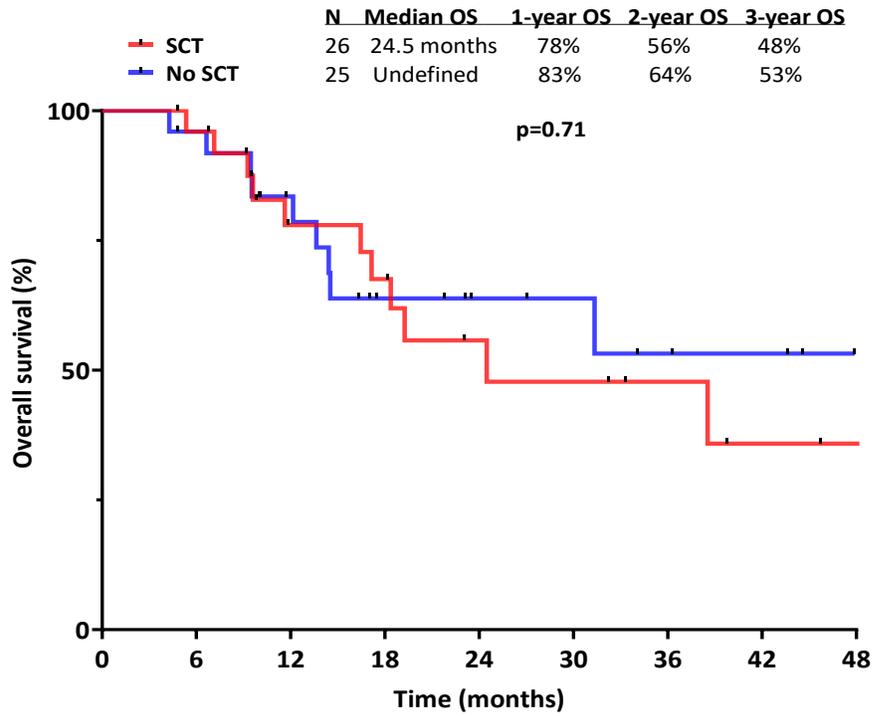
**Supplemental Figure 7.** Overall survival stratified by receipt of hematopoietic stem cell transplantation (landmark analysis)



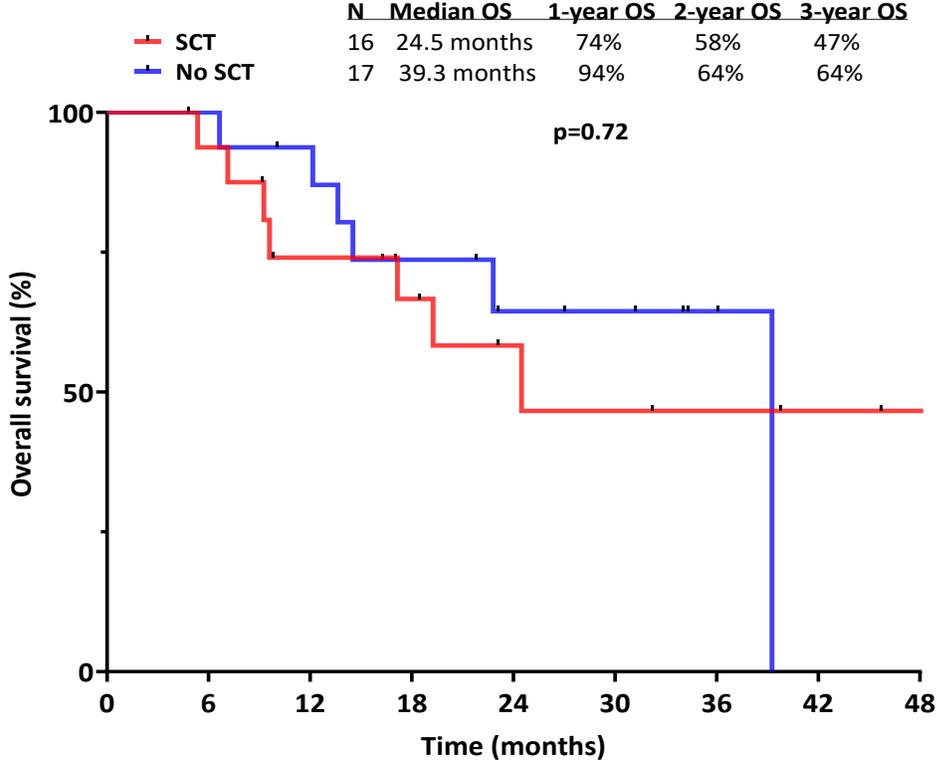
**Supplemental Figure 8.** Overall survival stratified by receipt of hematopoietic stem cell transplantation in patients <75 years of age (landmark analysis)



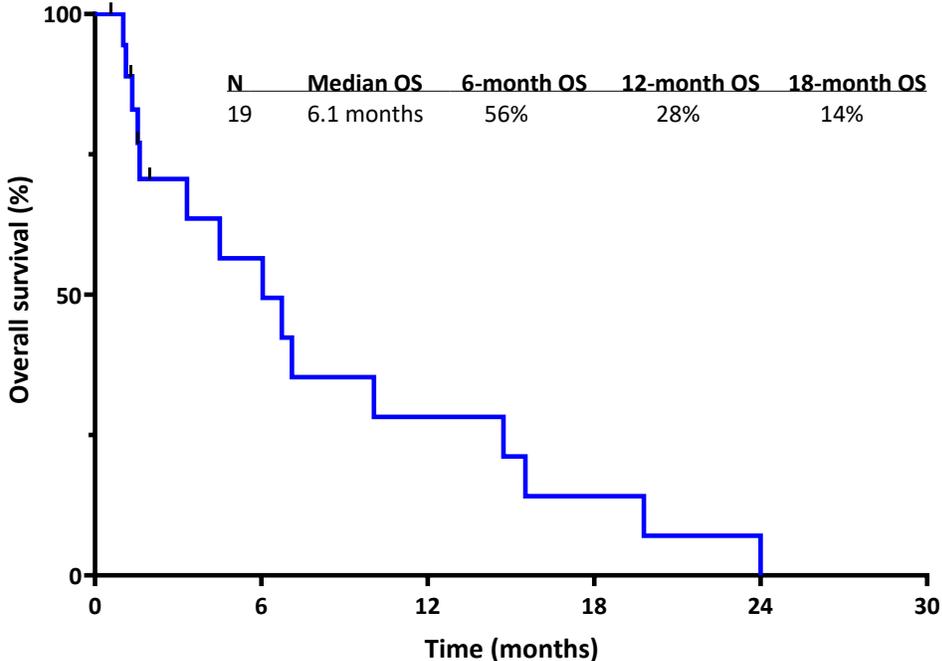
**Supplemental Figure 9.** Overall survival stratified by receipt of hematopoietic stem cell transplantation in patients with *FLT3-ITD* mutation (landmark analysis)



**Supplemental Figure 10.** Overall survival stratified by receipt of hematopoietic stem cell transplantation in patients with ELN adverse risk disease (landmark analysis)



Supplemental Figure 11. Overall survival after relapse



**Supplemental Figure 12.** Overall survival after relapse, stratified by *FLT3* mutation status by PCR at time of relapse

