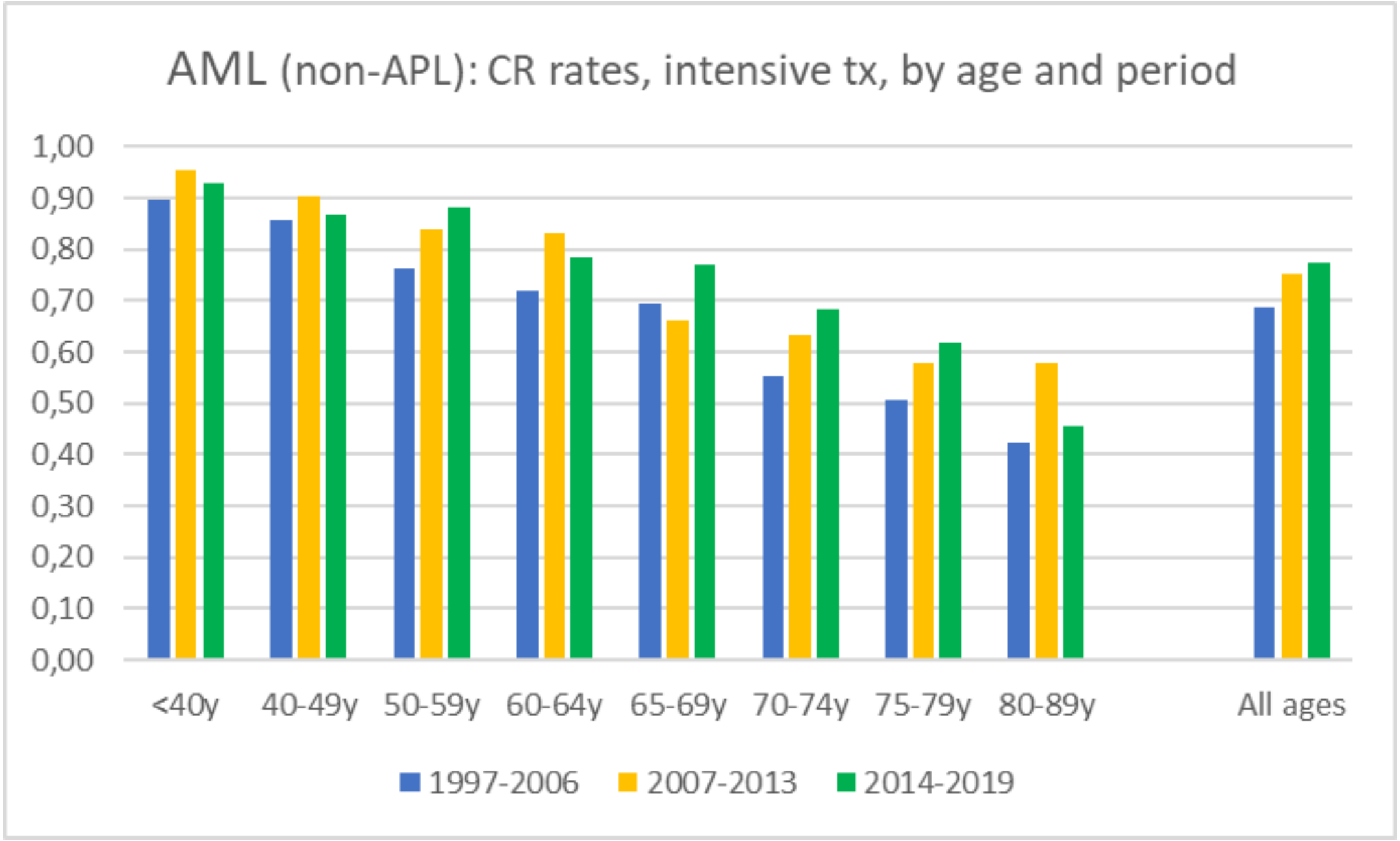
AML - Recidiv

SK-kurs 26-28 April 2021

Gunnar Juliusson


AML (non-APL): CR rates, intensive tx, by age and period
1,00
0,90
0,80
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
<40y
40-49y
50-59y
60-64y
65-69y
70-74y
75-79y
80-89y
All ages
1997-2006
2007-2013
2014-2019

AML Recidiv

Riskfaktorer

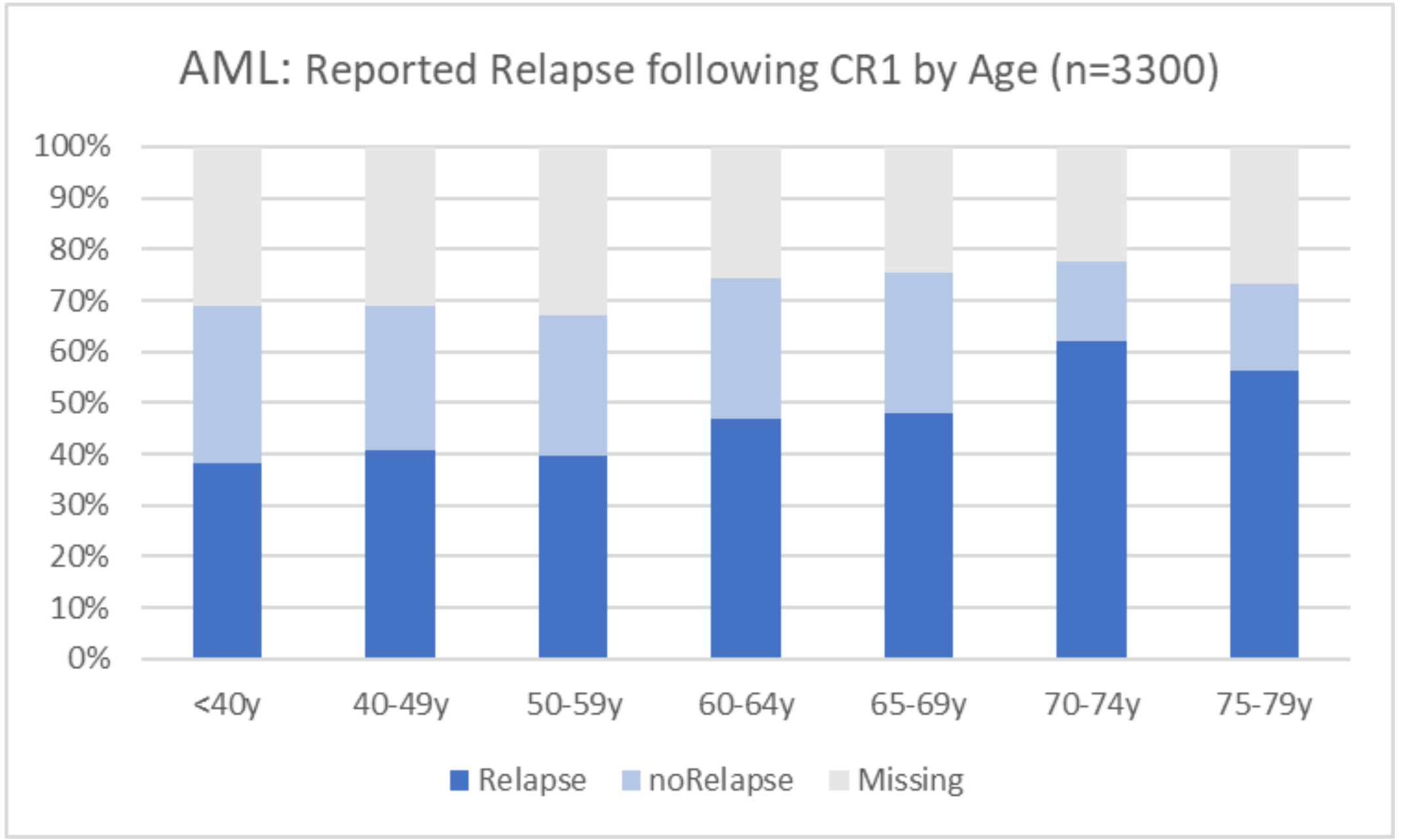
- CR1-duration
- Genetik (CBF - Adverse)
- Ålder
- AlloSCT gjord i CR1
- Möjlighet till AlloSCT i CR2

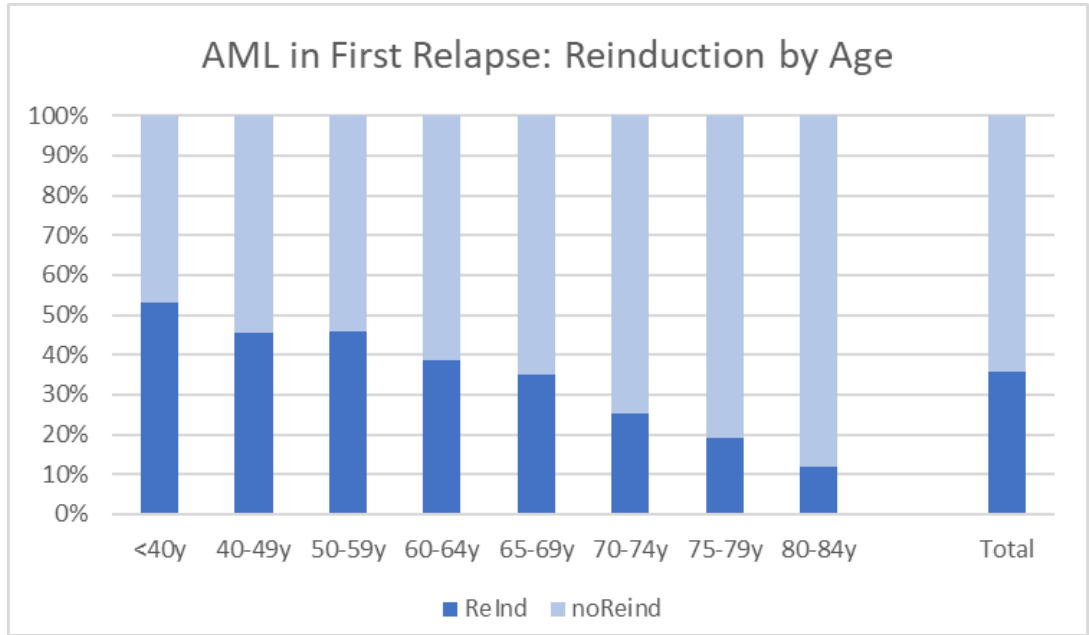
- Klonal evolution
  - samma sjukdom
  - mer aggressiv subklon
    - ex.vis *FLT3*-ITD, *RAS, TP53*
  - ny terapi-inducerad AML

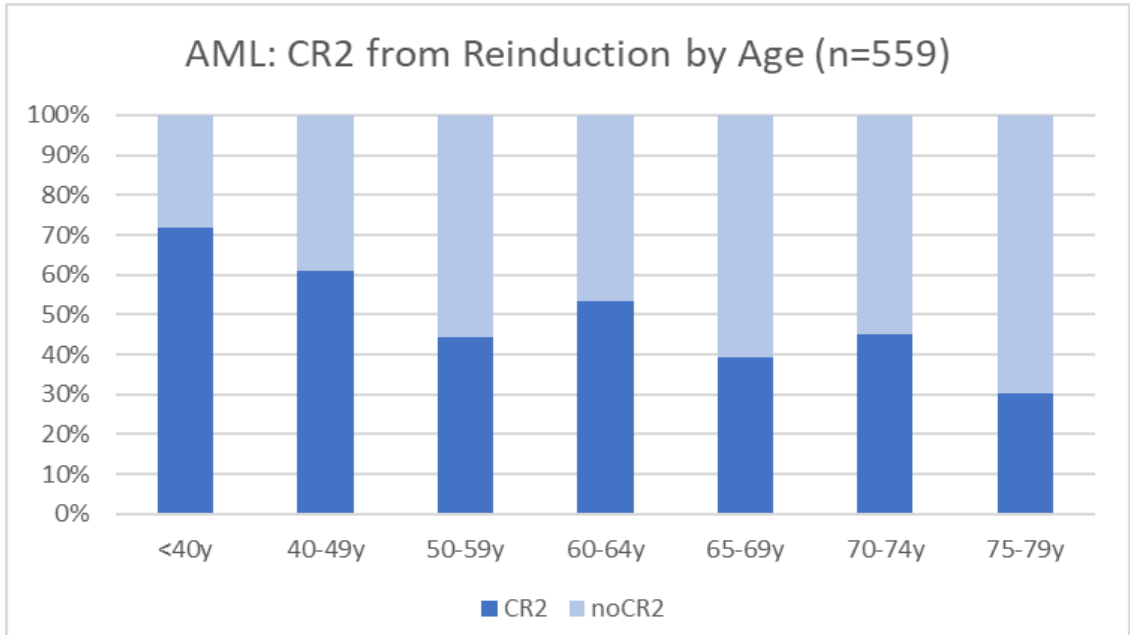
Recidivbehandling

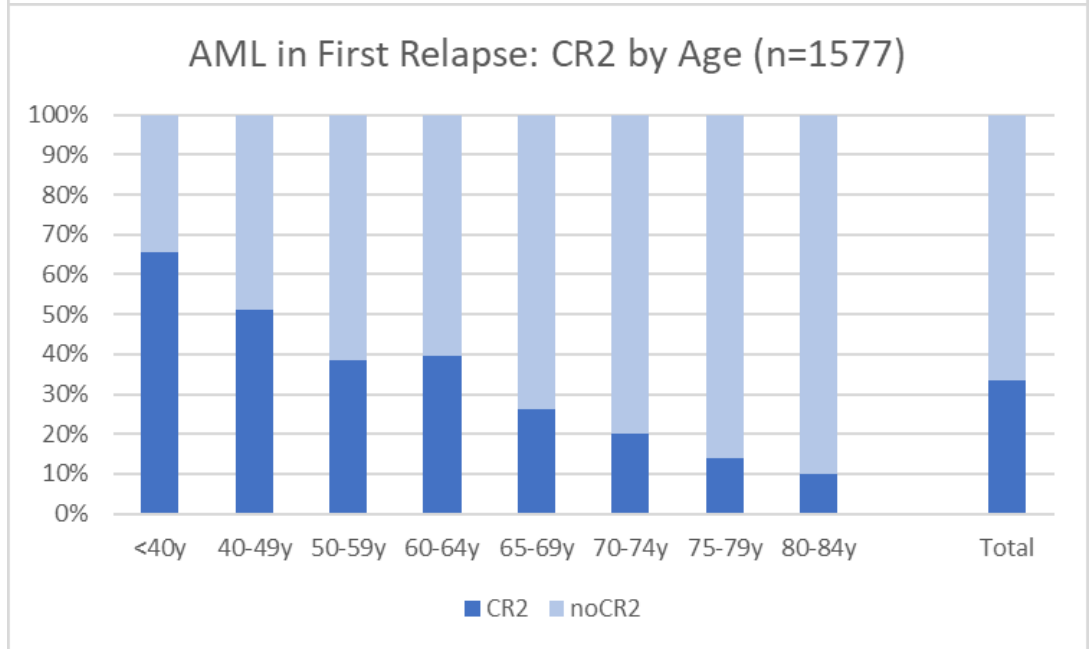
- Byte från primärbehandling
  - tänk på kumulativ antracyklindos
- FLAG-Ida / ACE / MEC
- HD ara-C + Gemtuzumab

- Lågintensiv
  - Aza-baserad
  - Målstyrd
    - *FLT3/IDH*


AML: Reported Relapse following CR1 by Age (n=3300)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
<40y
40-49y
50-59y
60-64y
65-69y
70-74y
75-79y
Relapse
noRelapse
Missing


AML in First Relapse: Reinduction by Age
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
<40y
40-49y
50-59y
60-64y
65-69y
70-74y
75-79y
80-84y
Total
ReInd
noReind


AML: CR2 from Reinduction by Age (n=559)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
<40y
40-49y
50-59y
60-64y
65-69y
70-74y
75-79y
CR2
noCR2


AML in First Relapse: CR2 by Age (n=1577)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
<40y
40-49y
50-59y
60-64y
65-69y
70-74y
75-79y
80-84y
Total
CR2
noCR2

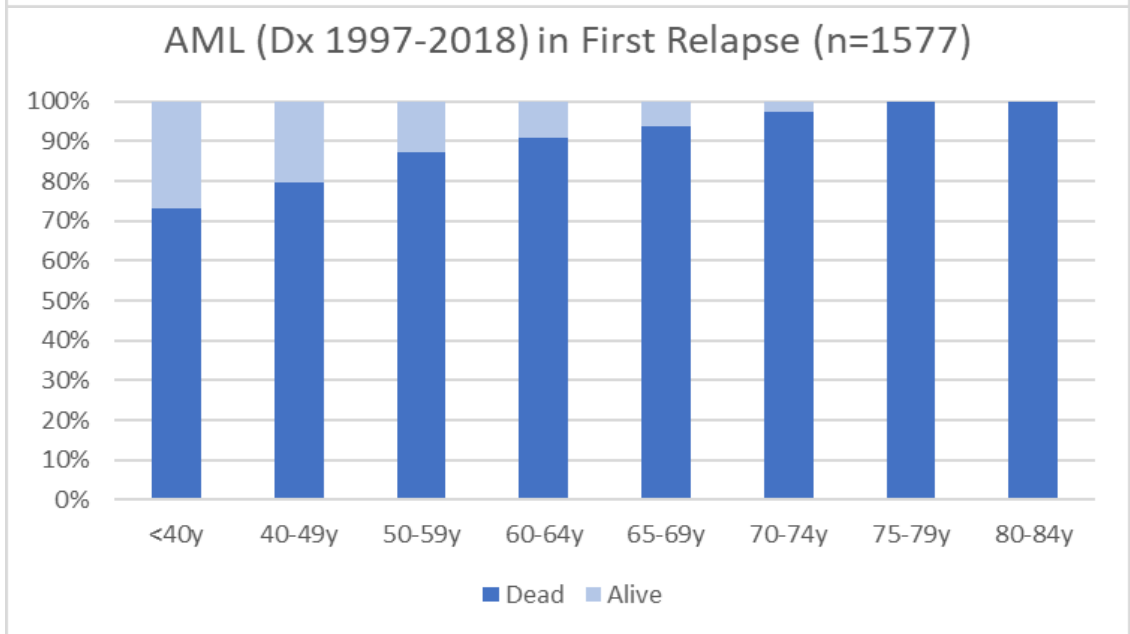

AML (Dx 1997-2018) in First Relapse (n=1577)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
<40y
40-49y
50-59y
60-64y
65-69y
70-74y
75-79y
80-84y
Dead
Alive

Table 1. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission in comparison to autologous stem cell transplantation and chemotherapy.

AML Trial Group	Relapse rate			Overall survival		
	Allo	Auto	Chemo	Allo	Auto	Chemo
EORTC/AML-8	24%	41%	57%	59%	56%	46%
GOELAM	37%	45%	55%	55%	52%	58%
ECOG/CALGB/SWOG	29%	48%	61%	46%	43%	52%
EORTC AML-10	30%	52%		58%	50%	
UK MRC AML-10	36%	52%*		55%	42%*	
HOVON-SAKK	32%	59%*		54%	46%*	

AML: acute myeloid leukemia; ALLO: allogeneic stem cell transplantation; AUTO: autologous stem cell transplantation; CHEMO: chemotherapy. Table modified from Kanate et al.[51]
**No separate data of autoSCT and chemotherapy available.*

Ossenkoppele et al, Haematologica 2016;101(1):20-25

Salvage Therapy Outcomes in a Historical Cohort of Patients With Relapsed or Refractory Acute Myeloid Leukemia

Farhad Ravandi,[1] Sherry Pierce,[1] Guillermo Garcia-Manero,[1] Tapan Kadia,[1] Elias Jabbour,[1] Gautam Borthakur,[1] Courtney D. DiNardo,[1] Naval Daver,[1] Nicholas J. Short,[1] Yesid Alvarado,[1] Jorge Cortes,[1] Christopher Kim,[2] Michael Kelsh,[2] Aaron Katz,[3] Richard Williams,[4] Zhao Yang,[2] Bhakti Mehta,[2] Hagop Kantarjian[1]

Abstract

We examined the outcomes of 818 adult patients with relapsed/refractory acute myeloid leukemia (AML) treated at MD Anderson Cancer Center between 2002 and 2016. Complete remission rates decreased from 14% after first salvage, to 9% after second salvage, and 3% after third salvage treatment. Strategies that improve initial response and decrease the likelihood of relapse are needed to obtain long-term remission for AML.

Table 2 CR Rates in Patients With Disease-Refractory Therapy or Relapsed Disease After Primary Therapy

Salvage Treatment No.		CR		CR + CRi	
	N	n	Proportion	n	Proportion
First	818	115	0.14	160	0.20
<60 years old	371	60	0.16	84	0.23
≥60 years old	447	55	0.12	76	0.17
P			.099		.031
Second	809	71	0.09	129	0.16
<60 years old	414	41	0.10	73	0.18
≥60 years old	395	30	0.08	56	0.14
P			.32		.12
Third	397	12	0.03	30	.08
<60 years old	235	9	0.04	19	.08
≥60 years old	162	3	0.02	11	.07
P			0.26		.71

Abbreviations: CR = complete remission; CRi = CR with incomplete blood count recovery.

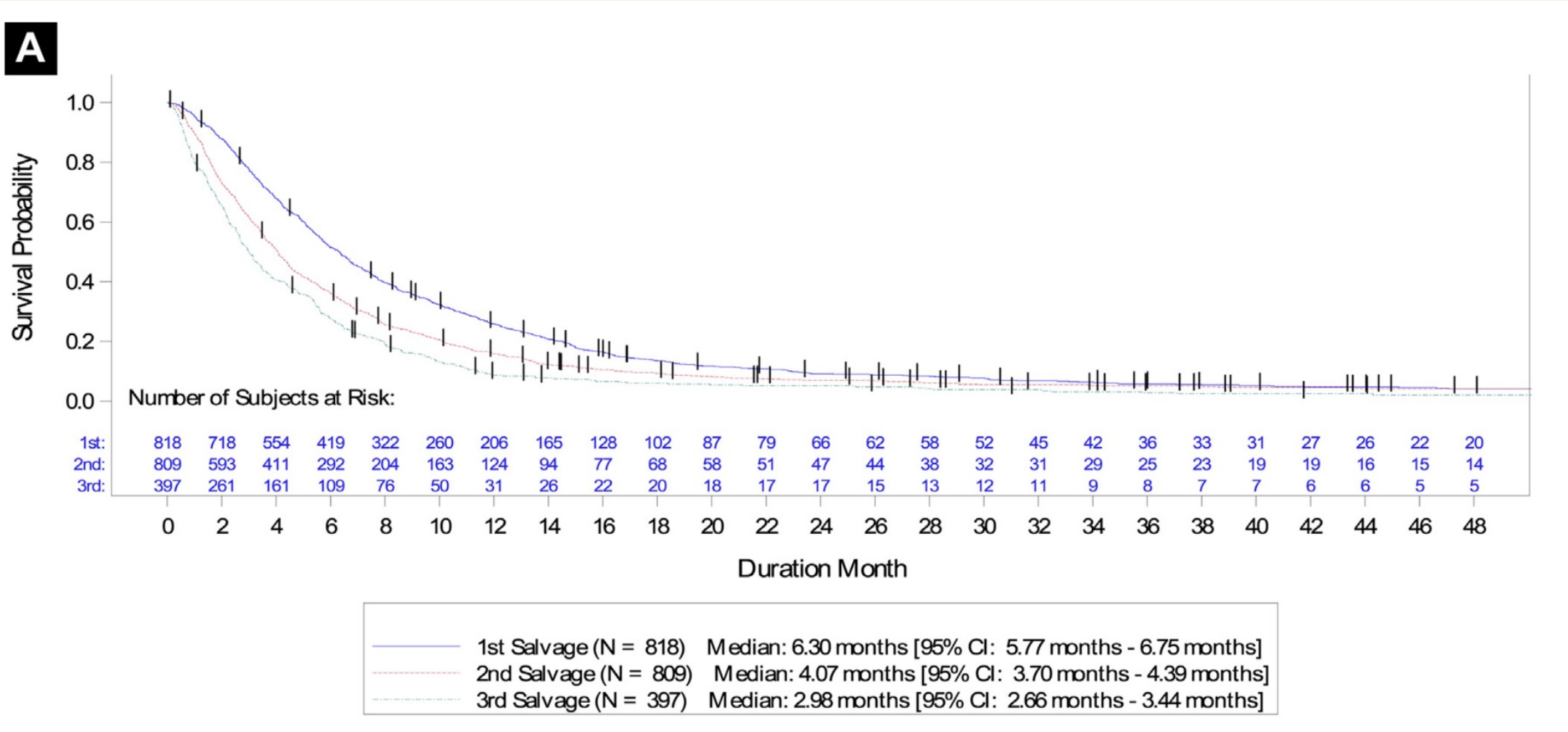
Table 3 CR Rates by Salvage Regimen Type

Salvage Regimen	First					Second					Third				
		CR		CR + CRi			CR		CR + CRi			CR		CR + CRi	
	N	n	Prop	n	Prop	N	n	Prop	n	Prop	N	n	Prop	n	Prop
HD cytarabine based	297	56	0.19	73	0.25	194	29	0.15	39	0.20	80	4	0.05	8	0.10
HD cytarabine based + FLT3	15	5	0.33	5	0.33	9	3	0.33	4	0.44	7	0	0.00	1	0.14
Cytarabine based	25	5	0.20	5	0.20	25	0	0.00	1	0.04	15	0	0.00	1	0.07
LD cytarabine based	21	5	0.24	5	0.24	15	3	0.20	3	0.20	5	1	0.20	1	0.20
LD cytarabine based + FLT3[a]	2	0	0.00	0	0.00	2	1	0.50	1	0.50	1	0	0.00	0	0.00
Hypomethylating	64	7	0.11	10	0.16	58	4	0.07	12	0.21	34	2	0.06	3	0.09
Hypomethylating + FLT3	22	1	0.05	6	0.27	33	1	0.03	14	0.27	10	0	0.00	1	0.10
Investigational	243	13	0.05	27	0.11	314	15	0.05	28	0.11	173	0	0.00	3	0.02
Gemtuzumab based	51	10	0.20	11	0.20	52	4	0.08	9	0.10	20	1	0.05	3	0.15
Molecular target based (eg, FLT3, IDH1, IDH2 inhibitors)	31	5	0.16	9	0.29	66	3	0.05	5	0.20	30	2	0.07	5	0.17
Other chemotherapy	47	8	0.17	9	0.19	41	8	0.20	13	0.22	22	2	0.09	4	0.18

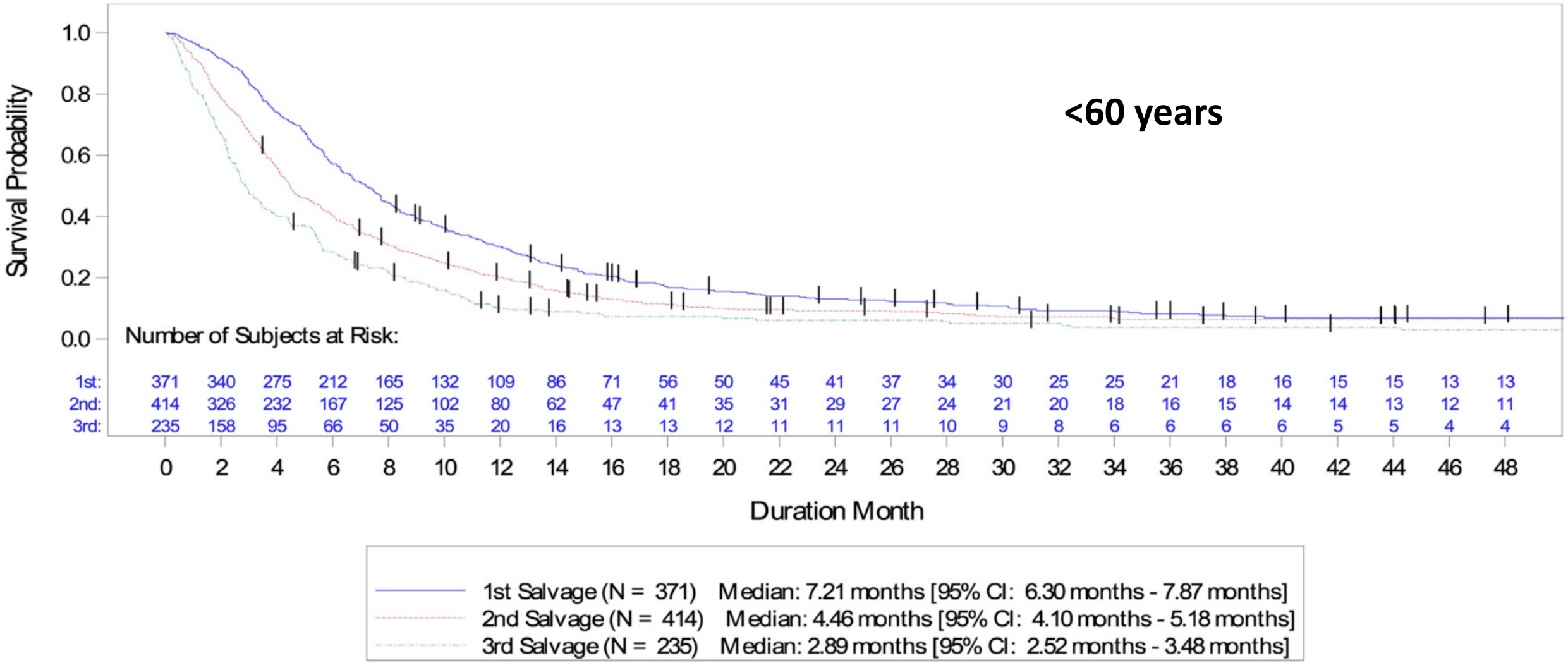
N indicates total evaluable patients in group; n, total number of patients with event.
Abbreviations: CR = complete remission; CRi = CR with incomplete blood count recovery; FLT3 = FMS-like tyrosine kinase 3; HD = high dose; IDH = isocitrate dehydrogenase; LD = low dose; Prop = proportion.
[a]Results from this group were not considered when comparing regimens because sample size was too small.

Salvage Therapy Outcomes in AML

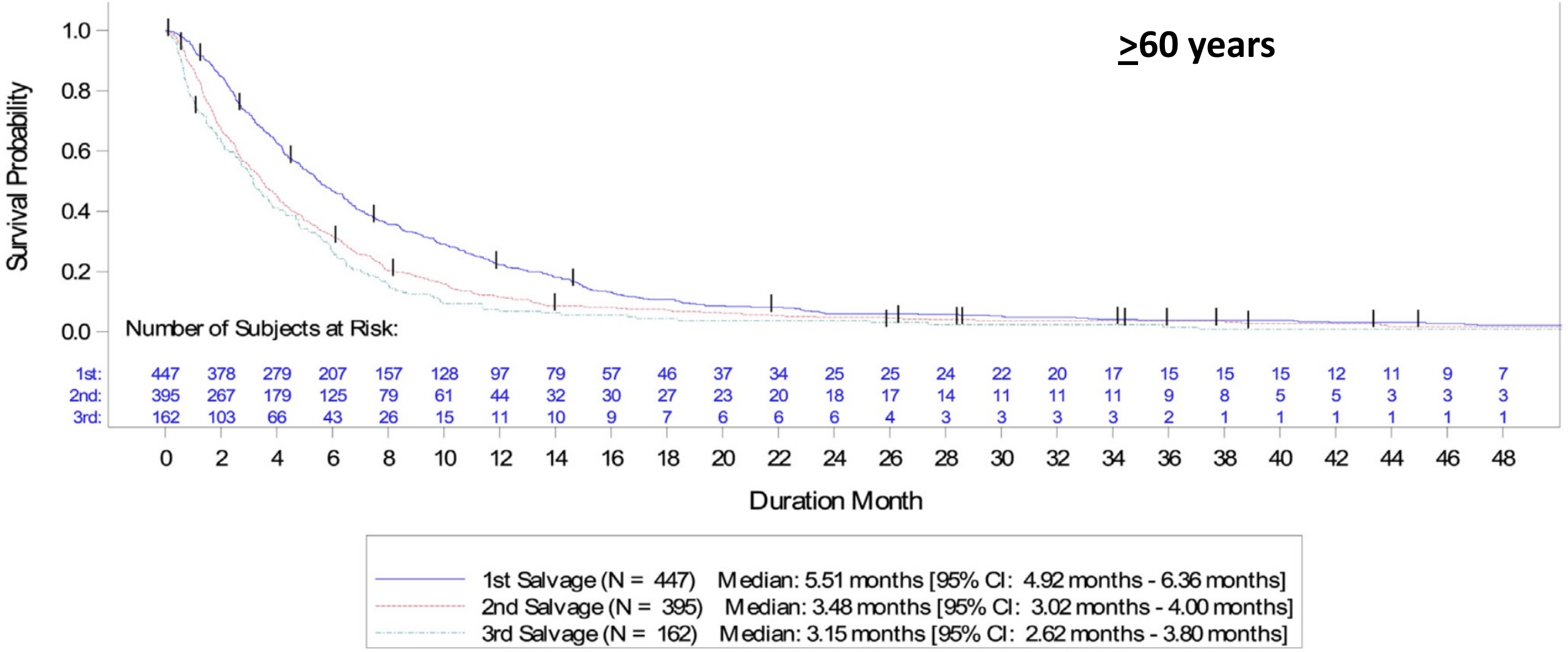
Figure 1 (A) Kaplan-Meier Curve of OS, (B) OS for Patients Aged Less Than 60 Years, and (C) OS for Patients Aged 60 Years or

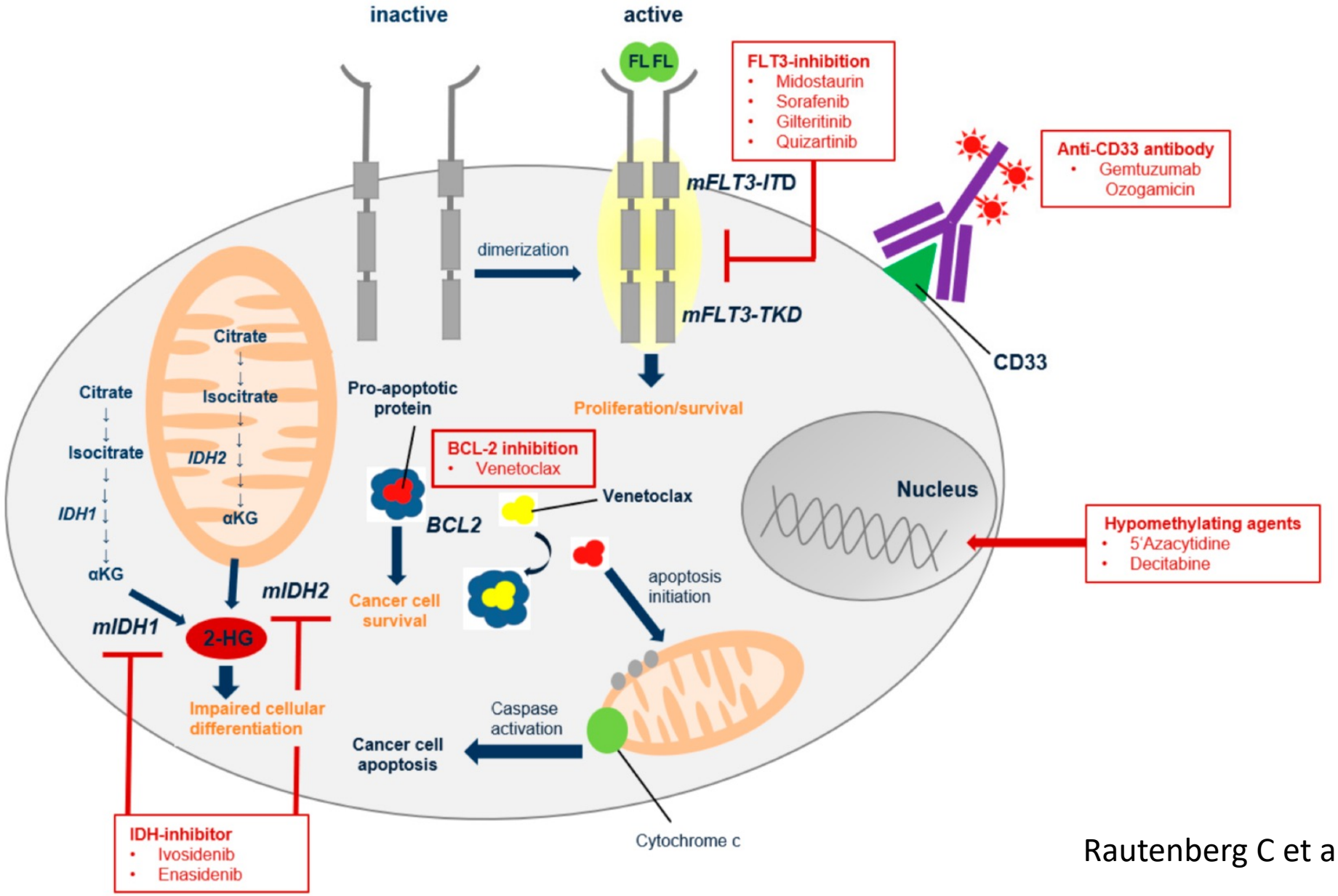


B


<60 years
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Number of Subjects at Risk:
1st: 371 340 275 212 165 132 109 86 71 56 50 45 41 37 34 30 25 25 21 18 16 15 15 13 13
2nd: 414 326 232 167 125 102 80 62 47 41 35 31 29 27 24 21 20 18 16 15 14 14 13 12 11
3rd: 235 158 95 66 50 35 20 16 13 13 12 11 11 11 10 9 8 6 6 6 6 5 5 4 4
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
Duration Month
1st Salvage (N = 371) Median: 7.21 months [95% CI: 6.30 months - 7.87 months]
2nd Salvage (N = 414) Median: 4.46 months [95% CI: 4.10 months - 5.18 months]
3rd Salvage (N = 235) Median: 2.89 months [95% CI: 2.52 months - 3.48 months]

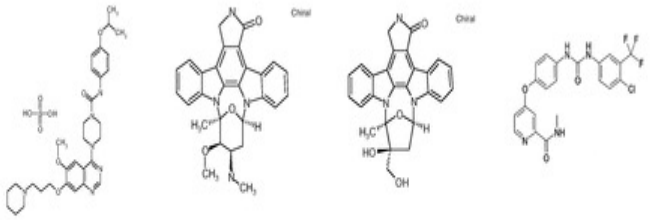
C

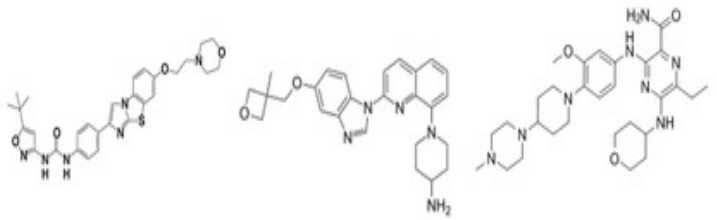
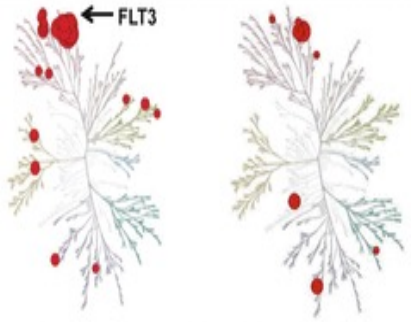

≥60 years
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Number of Subjects at Risk:
1st: 447 378 279 207 157 128 97 79 57 46 37 34 25 25 24 22 20 17 15 15 15 12 11 9 7
2nd: 395 267 179 125 79 61 44 32 30 27 23 20 18 17 14 11 11 11 9 8 5 5 3 3 3
3rd: 162 103 66 43 26 15 11 10 9 7 6 6 6 4 3 3 3 3 2 1 1 1 1 1 1
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
Duration Month
1st Salvage (N = 447) Median: 5.51 months [95% CI: 4.92 months - 6.36 months]
2nd Salvage (N = 395) Median: 3.48 months [95% CI: 3.02 months - 4.00 months]
3rd Salvage (N = 162) Median: 3.15 months [95% CI: 2.62 months - 3.80 months]



Rautenberg C et al, 2019

FLT3/kinas-inhibitorer

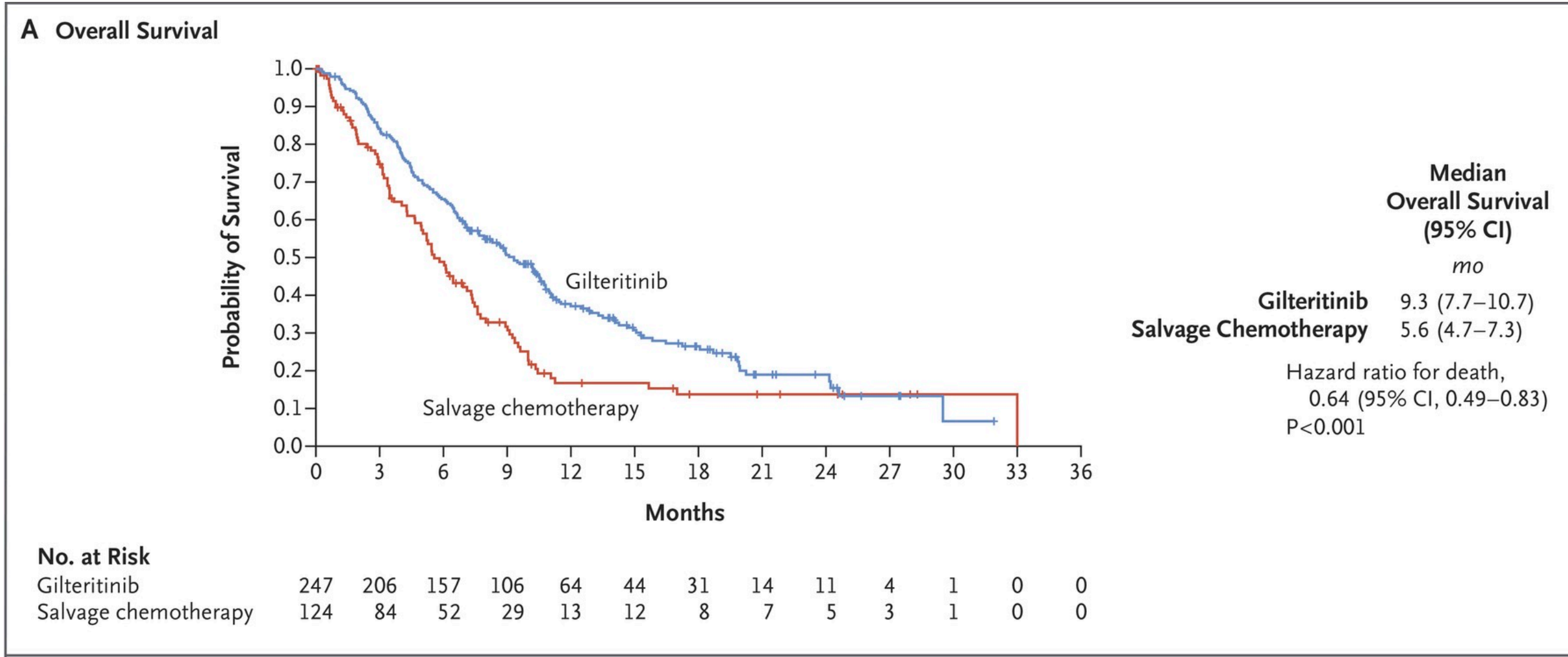
Inhibitor	Tandutinib	Lestaurtinib	Midostaurin	Sorafenib
IC_{50} against FLT3 (nM)	220	3	<10	58
Structure				
Kinase dendrogram				

Inhibitor	Quizartinib	Crenolanib	Gilteritinib
IC_{50} against FLT3 (nM)	1.1	1.3	0.29
Structure			
Kinase dendrogram			

Kinase	IC_{50} (nM) (95% CI)
FLT3	0.29 (0.26–0.32)
LTK	0.35 (0.29–0.43)
AXL	0.73 (0.51–1.0)
EML4-ALK	1.2 (0.68–2.0)
c-KIT	230 (190–280)

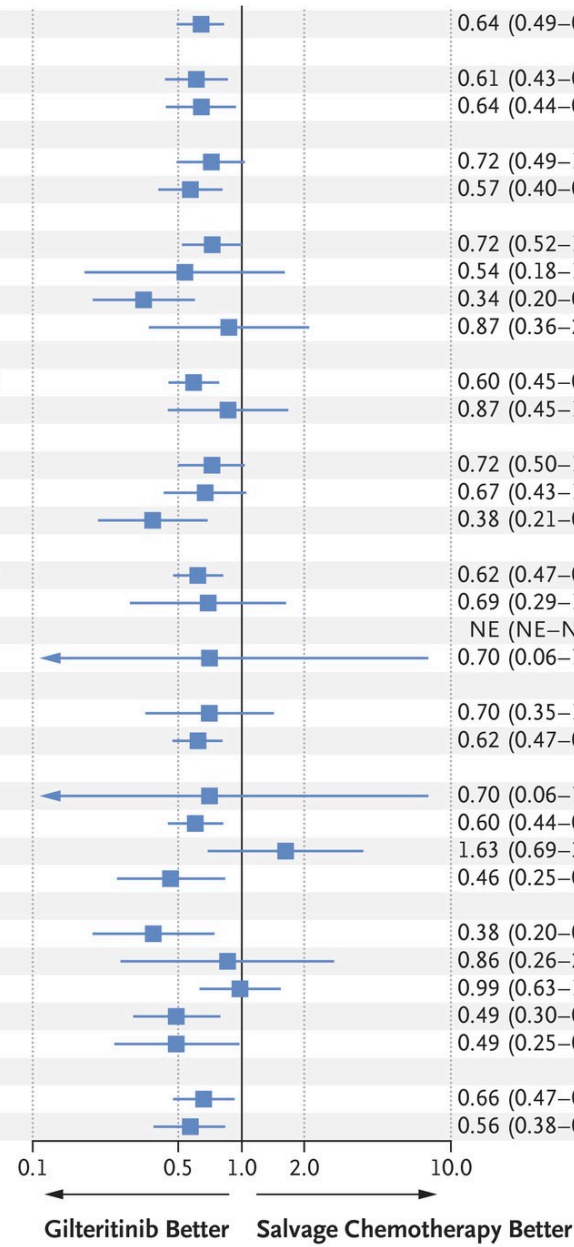
Inhibitory assays for tyrosine kinases were conducted using TK-ELISA, off-chip MSA, or HTRF® KinEASE™-TK. Geometric mean IC_{50} values were deter-

R/R AML med FLT3-mut: Gilteritinib vs Chemo



B Subgroup Analysis of Overall Survival

Subgroup	Gilteritinib	Salvage Chemotherapy	Hazard Ratio for Death (95% CI)
	no. of events/total no. of patients		
All patients	171/247	90/124	0.64 (0.49–0.83)
Age			
<65 yr	91/141	52/75	0.61 (0.43–0.86)
≥65 yr	80/106	38/49	0.64 (0.44–0.95)
Sex			
Male	86/116	40/54	0.72 (0.49–1.05)
Female	85/131	50/70	0.57 (0.40–0.82)
Race			
White	102/145	56/75	0.72 (0.52–1.00)
Black	13/14	6/7	0.54 (0.18–1.63)
Asian	42/69	20/33	0.34 (0.20–0.60)
Other or unknown	14/19	8/9	0.87 (0.36–2.12)
ECOG performance-status score			
0 or 1	138/206	78/105	0.60 (0.45–0.79)
≥2	33/41	12/19	0.87 (0.45–1.69)
Geographic region			
North America	88/114	42/52	0.72 (0.50–1.05)
Europe	43/68	32/43	0.67 (0.43–1.07)
Asia	40/65	16/29	0.38 (0.21–0.69)
FLT3 mutation type			
FLT3 ITD alone	145/215	81/113	0.62 (0.47–0.82)
FLT3 TKD alone	16/21	8/10	0.69 (0.29–1.64)
FLT3 ITD and *FLT3* TKD	6/7	0	NE (NE–NE)
Other	4/4	1/1	0.70 (0.06–7.92)
Previous use of *FLT3* inhibitor			
Yes	26/32	11/14	0.70 (0.35–1.44)
No	145/215	79/110	0.62 (0.47–0.82)
Cytogenetic risk status			
Favorable	3/4	1/1	0.70 (0.06–7.92)
Intermediate	119/182	63/89	0.60 (0.44–0.82)
Unfavorable	22/26	7/11	1.63 (0.69–3.85)
Unknown	27/35	19/23	0.46 (0.25–0.84)
Response to first-line therapy per IRT			
Relapse ≤6 mo after allogeneic HSCT	24/31	16/17	0.38 (0.20–0.75)
Relapse >6 mo after allogeneic HSCT	10/17	4/8	0.86 (0.26–2.80)
Primary refractory disease without HSCT	70/98	28/48	0.99 (0.63–1.55)
Relapse ≤6 mo after composite complete remission and no HSCT	47/67	28/34	0.49 (0.30–0.80)
Relapse >6 mo after composite complete remission and no HSCT	20/34	14/17	0.49 (0.25–0.98)
Preselected chemotherapy per IRT			
High intensity	96/149	52/75	0.66 (0.47–0.93)
Low intensity	75/98	38/49	0.56 (0.38–0.84)



Overall Survival and Response Rates According to Chemotherapy Intensity and Transplantation Status (Intention-to-Treat Population)

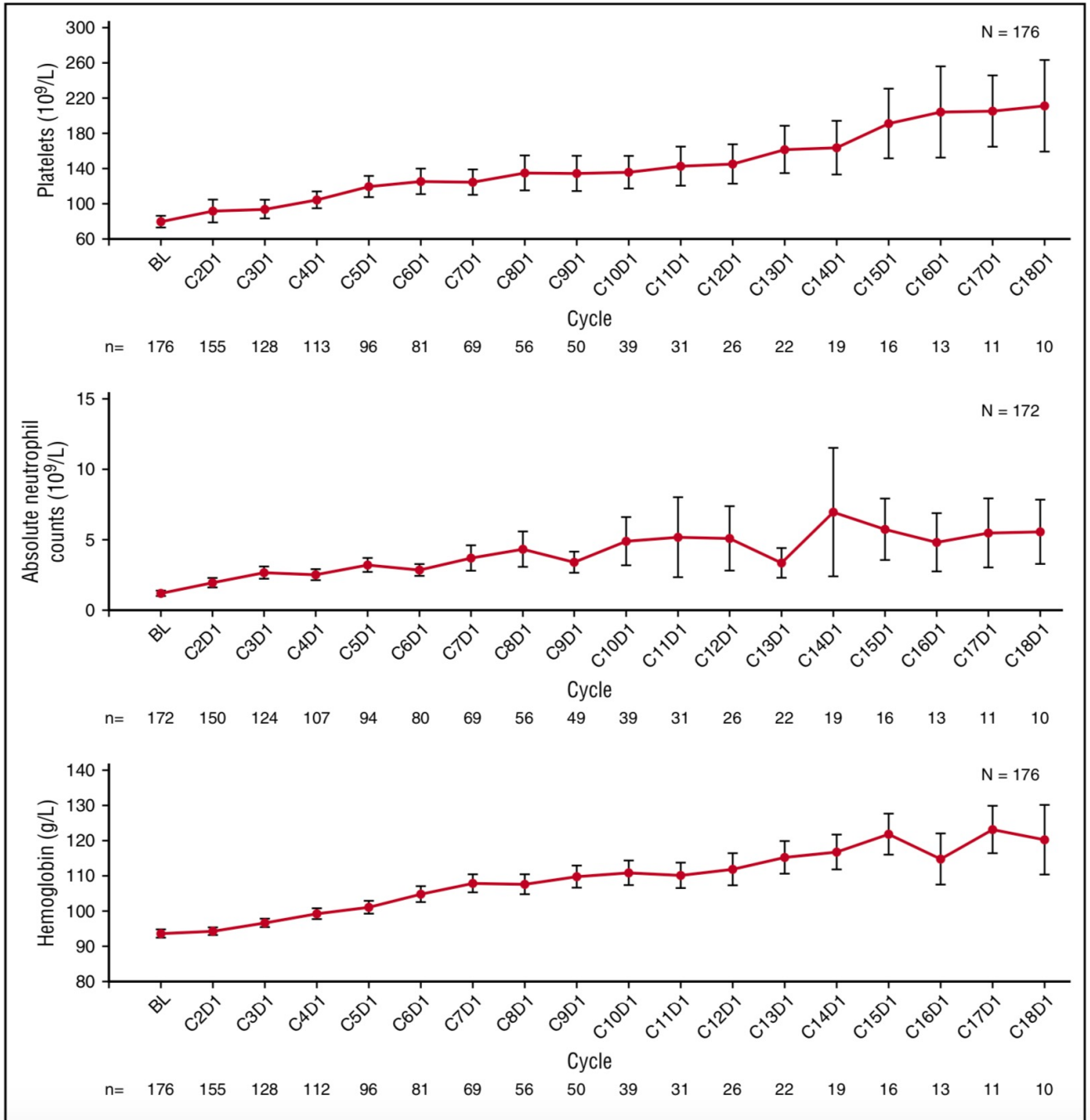
Parameter	Gilteritinib	Salvage Chemotherapy	
Median Overall Survival			Hazard Ratio (95% CI)
High-intensity chemotherapy	10.5 months	6.9 months	0.663 (0.471, 0.932)
Low-intensity chemotherapy	6.4 months	4.7 months	0.563 (0.378, 0.839)
Received prior HSCT	8.3 months	4.0 months	0.480 (0.274, 0.840)
Did not receive prior HSCT	9.6 months	6.0 months	0.684 (0.511, 0.917)
CR Rate, no. (%)			Risk Difference (%) (95% CI)
High-intensity chemotherapy	37/149 (24.8)	12/75 (16.0)	8.8 (–3.0, 20.6)
Low-intensity chemotherapy	15/98 (15.3)	1/49 (2.0)	13.3 (3.6, 22.9)
Received prior HSCT	17/48 (35.4)	3/26 (11.5)	23.9 (2.6, 45.1)
Did not receive prior HSCT	35/199 (17.6)	10/98 (10.2)	7.4 (–1.4, 16.1)
Before on-study HSCT	34/247 (13.8)	13/124 (10.5)	3.3 (–4.0, 10.5)
CR/CRh Rate, no. (%)			Risk Difference (%) (95% CI)
Before on-study HSCT	65/247 (26.3)	19/124 (15.3)	10.9 (2.4, 19.5)

Abbreviations: CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; HSCT, hematopoietic stem cell transplantation.

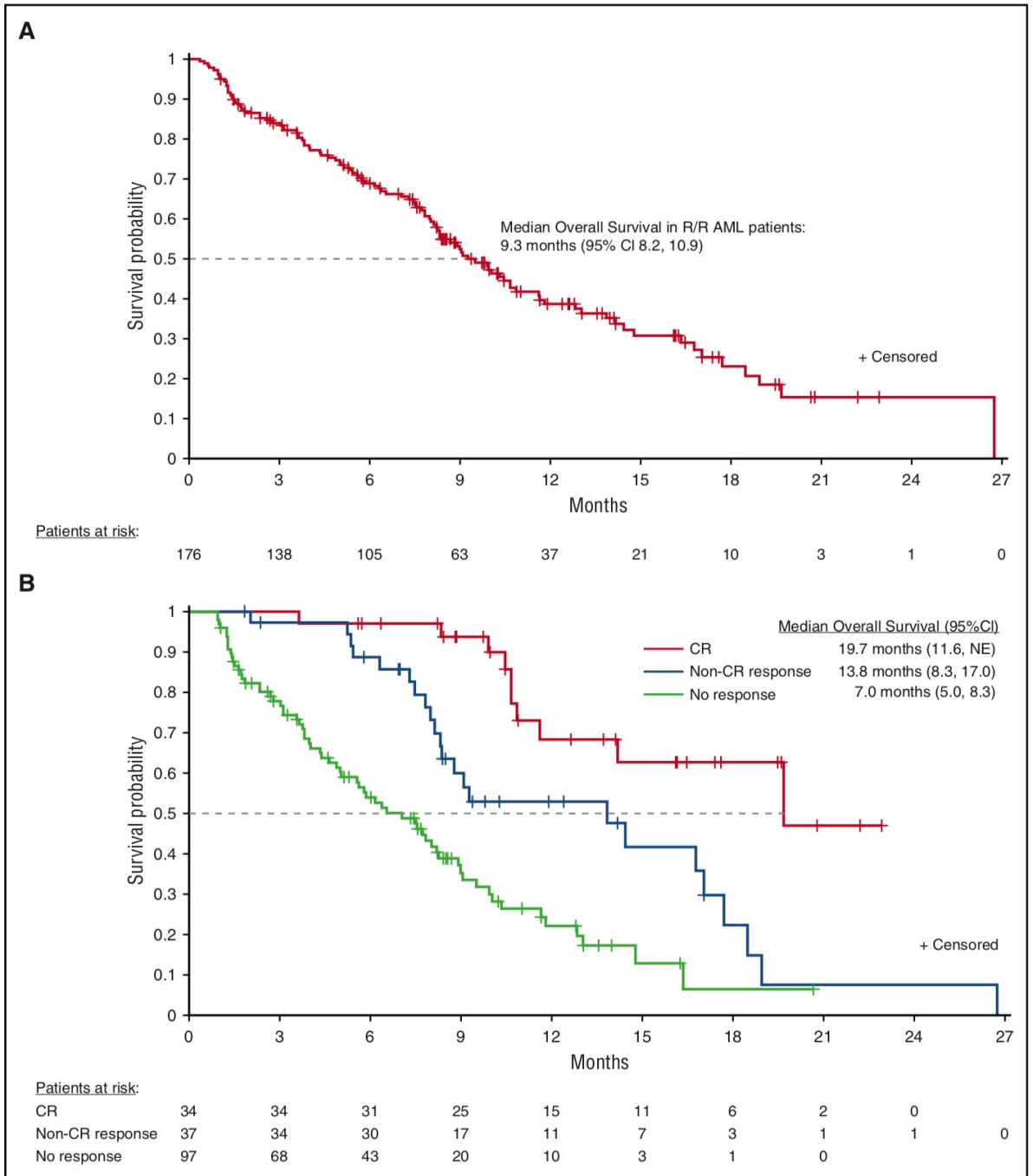
Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia

Eytan M. Stein, Courtney D. DiNardo, Daniel A. Pollyea, …, and Martin S. Tallman

Blood. 2017 Aug 10; 130(6): 722–731.
doi: 10.1182/blood-2017-04-779405
PMCID: PMC5572791 PMID: 28588020



Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia



Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

C.D. DiNardo, E.M. Stein, S. de Botton, G.J. Roboz, J.K. Altman, A.S. Mims, R. Swords, R.H. Collins, G.N. Mannis, D.A. Pollyea, W. Donnellan, A.T. Fathi, A. Pigneux, H.P. Erba, G.T. Prince, A.S. Stein, G.L. Uy, J.M. Foran, E. Traer, R.K. Stuart, M.L. Arellano, J.L. Slack, M.A. Sekeres, C. Willekens, S. Choe, H. Wang, V. Zhang, K.E. Yen, S.M. Kapsalis, H. Yang, D. Dai, B. Fan, M. Goldwasser, H. Liu, S. Agresta, B. Wu, E.C. Attar, M.S. Tallman, R.M. Stone, and H.M. Kantarjian

ABSTRACT

BACKGROUND

Mutations in the gene encoding isocitrate dehydrogenase 1 (*IDH1*) occur in 6 to 10% of patients with acute myeloid leukemia (AML). Ivosidenib (AG-120) is an oral, targeted, small-molecule inhibitor of mutant IDH1.

METHODS

We conducted a phase 1 dose-escalation and dose-expansion study of ivosidenib monotherapy in *IDH1*-mutated AML. Safety and efficacy were assessed in all treated patients. The primary efficacy population included patients with relapsed or refractory AML receiving 500 mg of ivosidenib daily with at least 6 months of follow-up.

RESULTS

Overall, 258 patients received ivosidenib and had safety outcomes assessed. Among patients with relapsed or refractory AML (179 patients), treatment-related adverse events of grade 3 or higher that occurred in at least 3 patients were prolongation of

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. DiNardo at the University of Texas M.D. Anderson Cancer Center, Department of Leukemia, 1515 Holcombe Blvd., Unit 0428, Houston, TX 77030, or at cdinardo@mdanderson.org.

Drs. DiNardo, E.M. Stein, and de Botton and Drs. Stone and Kantarjian contributed equally to this article.

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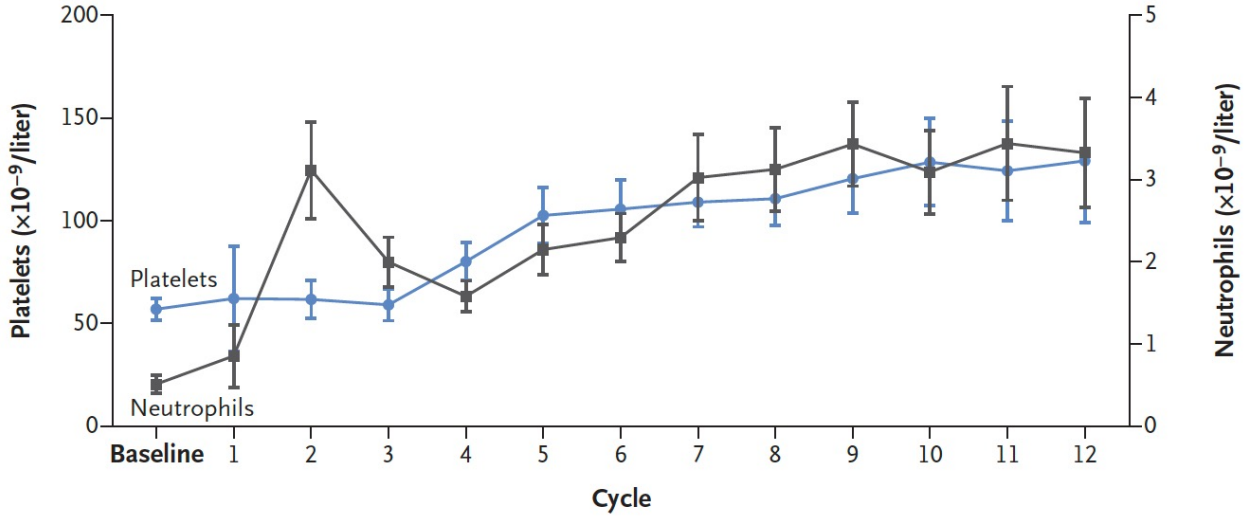
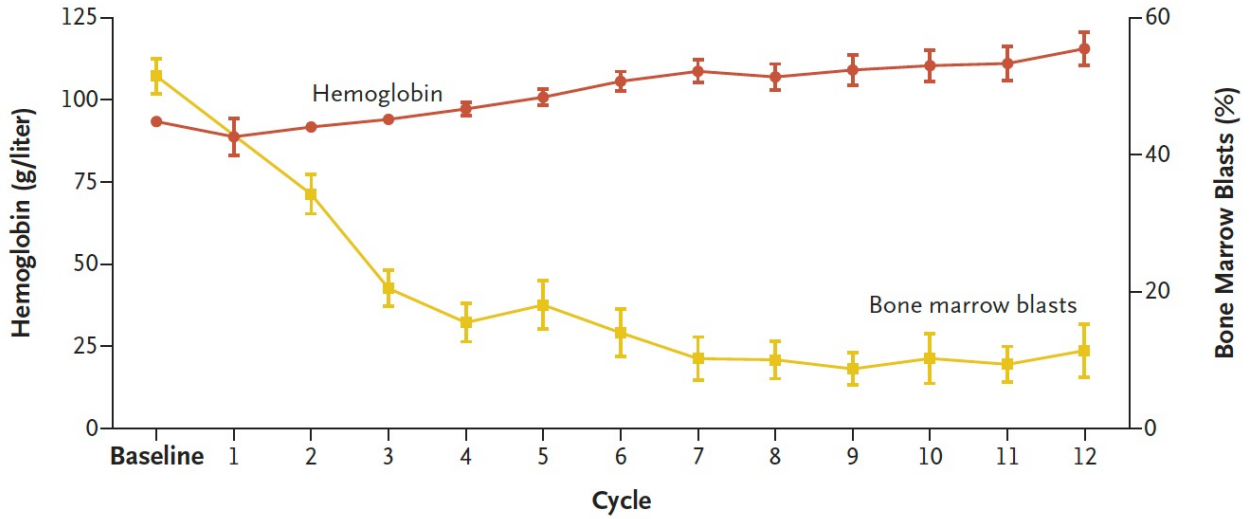
A Platelets and Neutrophils



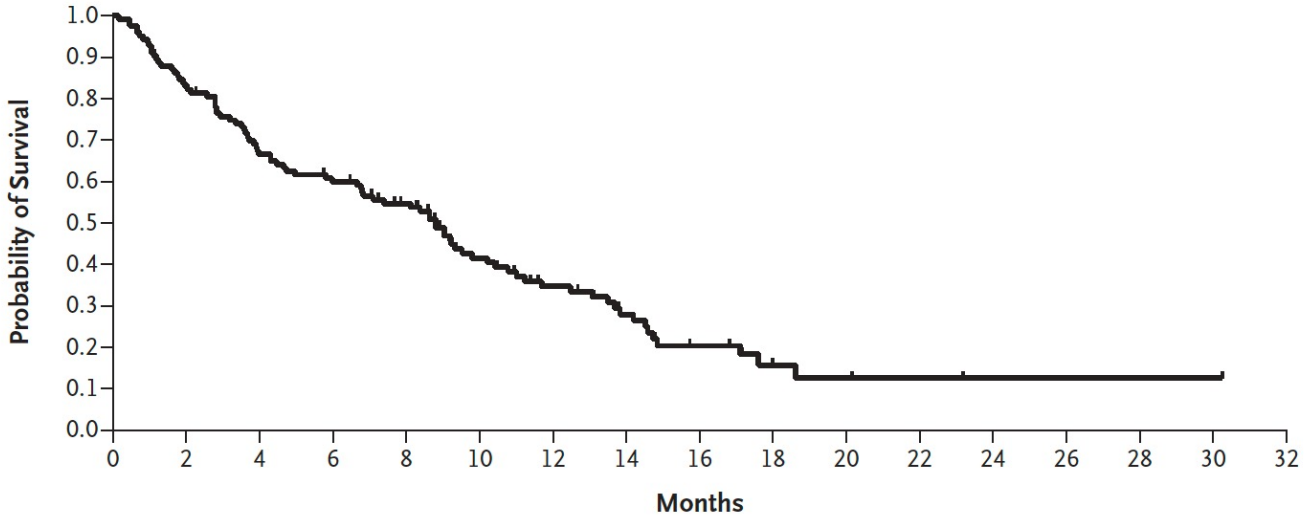
No. of Patients													
Platelets	125	11	101	88	79	67	52	45	42	33	30	21	20
Neutrophils	118	9	97	86	78	66	52	45	42	32	30	22	20

B Hemoglobin and Bone Marrow Blasts



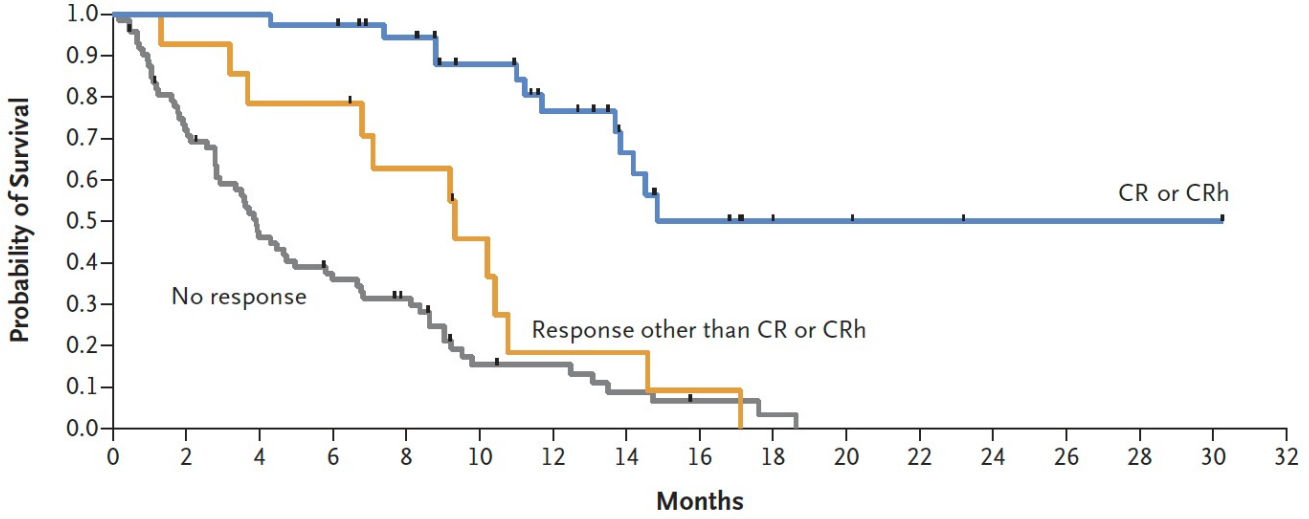
No. of Patients													
Hemoglobin	125	11	101	88	78	66	52	45	42	33	30	22	20
Bone marrow blasts	124		96	81	68	58	45	40	34	29	23	17	14

A Overall Survival



No. at Risk																	
	125	102	81	72	59	38	28	19	11	6	4	3	1	1	1	1	0

B Overall Survival According to Response



No. at Risk																	
CR or CRh	38	38	38	37	32	25	19	13	8	5	4	3	1	1	1	1	0
Response other than CR or CRh	14	13	11	11	8	5	2	2	1	0							
No response	73	51	32	24	19	8	7	4	2	1	0						

VENETOCLAX-BASED COMBINATIONS AS TREATMENT OF RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIAS AND HIGH-RISK MYELODYSPLASTIC SYNDROMES: A FRENCH EXPERIENCE

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INTRODUCTION

Venetoclax has recently been approved by FDA in combination with hypomethylating agents (HMA) as frontline therapy of acute myeloid leukemia (AML) patients ineligible to intensive chemotherapy[1].

Whether relapsed patients may benefit from this combination is yet to be confirmed.

OBJECTIVES

Study the efficacy and safety of venetoclax-based combinations in relapsed or refractory AML and high-risk myelodysplastic syndromes (MDS).

METHODS

Retrospective study

66 patients treated with venetoclax-based combinations (table 1)

Relapsed/refractory AML and high-risk MDS

11 French centers

From January 2017 to January 2019

RESULTS

EFFICACY : ORR was 30%

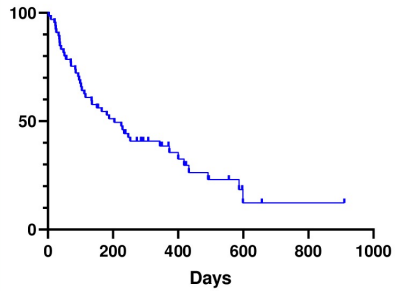
- **18 (27%) patients achieved CR or CRi** and 2 (3%) achieved PR
- Median time to response was 68 days (34-130)
- With a median follow-up of 13.9 months, **overall survival (OS) was 6.7 months (figure 1)**
- **Duration of remission was 7.9 months** (1.8-15.4)
- **8 (12%) patients underwent subsequent alloSCT, including 3 in CR**

- **ELN adverse cytogenetic risk** patients exhibited a **lower response rate** and a **shorter OS (table 2)**
- **TP53** mutation was associated with a **shorter OS (table 2)**
- **TET2 mutation was associated with a higher response rate** without significant impact on survival (table 2)

	N (%) or median (min-max)
Age (y)	62.5 (19.9-86.5)
Male	39 (59)
Delay from diagnosis (d)	264.0 (18-4896)
Previous lines of treatment	1.5 (1-6)
AML	65 (98)
sAML	32 (48)
tAML	3 (5)
MDS	1 (2)
ELN RISK	
Intermediate	32 (48)
Adverse	29 (44)
MUTATIONAL PROFILE	
NPM1	6 (10)
FLT3	6 (10)
DNMT3A	11 (19)
ASXL1	9 (16)
TET2	9 (16)
RUNX1	10 (18)
TP53	7 (12)
PREVIOUS THERAPIES	
Anthracycline	40 (61)
Cytarabine	41 (62)
HMA	41 (62)
Stem-cell transplantation	24 (36)
WBC (G/L)	2.3 (0.1-34.7)
Performance Status	1.0 (0-3)
Molecule association	
Azacitidine	45 (68)
Decitabine	12 (18)
LDAC	9 (14)
CYP3A inhibitor interaction	29 (44)
Dose without CYP3A inhibitors (mg/d)	400 (100-800)
Dose with CYP3A inhibitors (mg/d)	200 (100-400)

Table 1

Fig 1. Overall survival



SAFETY

- Febrile neutropenia occurred in 48 (73%) patients
- Tumor lysis syndrome was reported in 3 (5%) patients
- **4 (20%) patients in CR stopped treatment for hematological toxicity**

	ORR, n (%)	p-value	Median OS (mo)	OR (95CI)	p-value
ELN RISK					
Intermediate	15/32 (53%)	0.010	12.2	1.53 (0.82-2.83)	0.166
Adverse	4/29 (17%)		4.4		
PRIOR TREATMENTS					
Prior HMA	29% vs 32%	>0.999	4.9 vs 13.7	0.56 (0.31-1.02)	0.077
Prior allo-SCT	21% vs 33%	0.398	3.8 vs 7.5	0.66 (0.35-1.25)	0.169
MUTATIONS (mut vs wt)					
NPM1	50% vs 29%	0.359	7.1 vs 5.9	1.09 (0.41-2.87)	0.854
IDH1/2	25% vs 33%	>0.999	16.1 vs 5.9	1.74 (0.75-4.05)	0.313
TET2	67% vs 25%	0.022	11.3 vs 5.4	1.56 (0.73-3.33)	0.304
DNMT3A	18% vs 35%	0.473	3.2 vs 7.5	0.65 (0.26-1.59)	0.268
ASXL1	50% vs 27%	0.258	11.3 vs 6.2	1.52 (0.68-3.43)	0.802
RUNX1	40% vs 30%	0.709	12.2 vs 5.9	2.14 (1.03-4.46)	0.063
TP53	14% vs 34%	0.413	1.2 vs 6.7	0.43 (0.13-1.44)	0.049
MOLECULE					
LDAC	2/9 (22%)	0.712	3.8	0.63 (0.25-1.54)	0.222
HMA	18/57 (32%)		7.5		

Table 2

CONCLUSION

This national multicentric study confirms previous results of venetoclax-based combinations[2] while reflecting the diversity of the management of this molecule in various centers. Venetoclax-based combinations are salvage regimens that allow correct response rates but their very short response duration and high toxicity should be key elements in the therapeutic decision.

REFERENCES

[1]DiNardo et al., Blood 2019
[2]Aldoss et al., Haematologica 2018

E-POSTER – EP575

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Safety and Efficacy: Clinical Experience of Venetoclax in Combination With Hypomethylating Agents in Both Newly Diagnosed and Relapsed/Refractory Advanced Myeloid Malignancies

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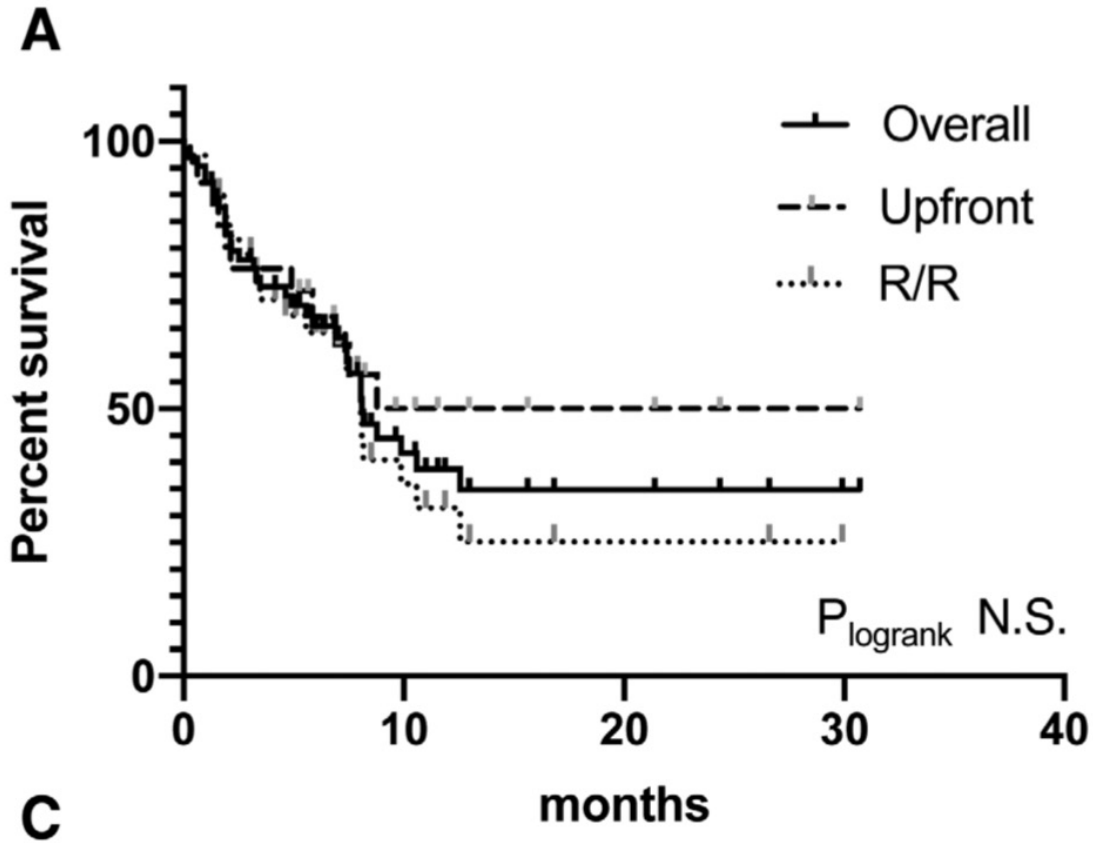
Abstract

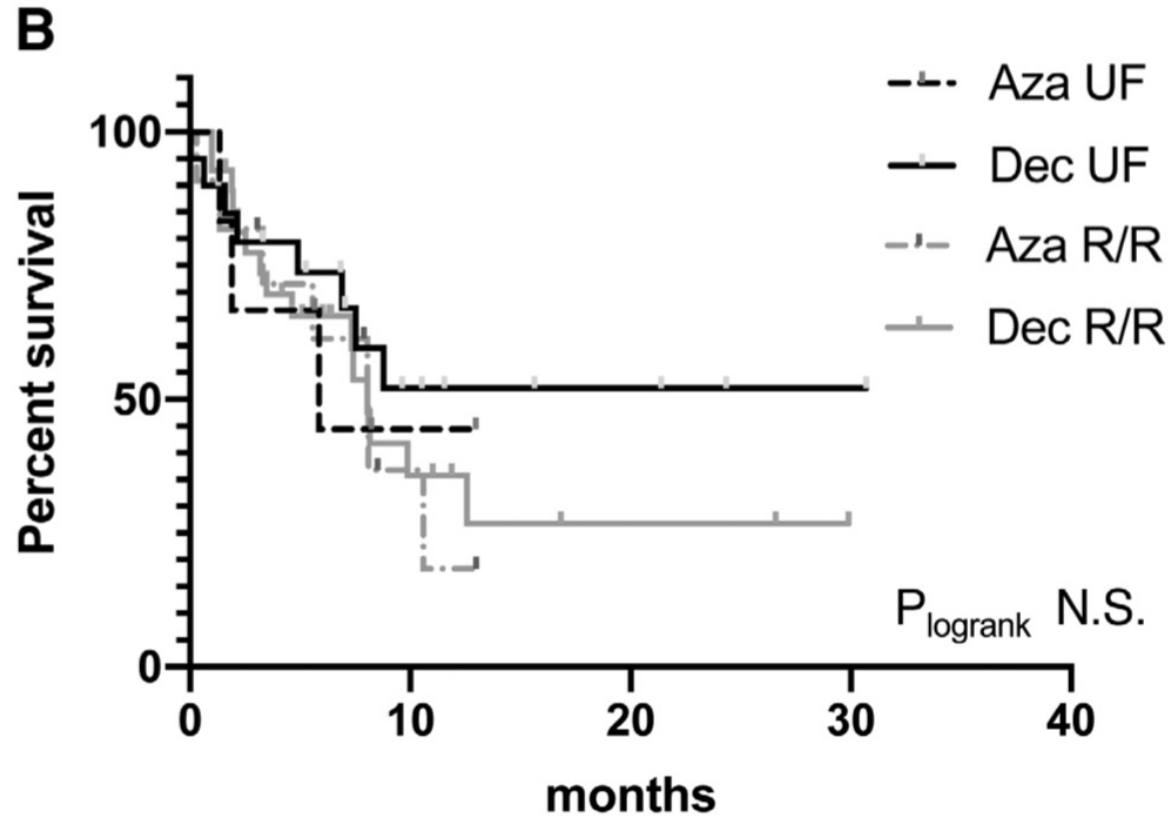
Hypomethylating agents (HMAs) in combination with venetoclax have been widely adopted as the standard of care for patients who cannot tolerate induction chemotherapy and for patients who have relapsed/refractory (R/R) acute myeloid leukemia (AML). This study retrospectively analyzed the outcomes of all patients with AML (n = 65) or myelodysplastic syndrome (n = 7) who received the combination of HMA and venetoclax at our institution. Outcomes measured included complete remission (CR) and CR with incomplete hematologic recovery (CRi) rates, duration of response (DOR), and overall survival (OS). Patient mutational profiles and transfusion requirements were also assessed. Of 26 newly diagnosed AML patients, the CR/CRi rate was 53.8%. The median DOR and OS were 6.9 months and not reached, respectively. Of 39 R/R AML patients, the CR/CRi rate was 38.5%. The median DOR and OS were both 8.1 months. Responders to HMA and venetoclax were enriched for *TET2*, *IDH1*, and *IDH2* mutations, while nonresponders were associated with *FLT3* and *RAS* mutations. Adaptive resistance was observed through various mechanisms including acquired *RAS* pathway mutations. Of transfusion-dependent patients, 12.2% and 15.2% achieved red blood cell (RBC) and platelet transfusion independence, respectively, while 44.8% and 35.1% of RBC and platelet transfusion independent patients, respectively, became transfusion dependent. In total 59.1% of patients developed a ≥grade 3 infection and 46.5% neutropenic fever. HMA + venetoclax can lead to impressive response rates with moderately durable remissions and survival. However, the benefits of this combination are diminished by the significant toxicities from infection, persistent cytopenias, and transfusion requirements.

Table 1

Patient Characteristics Newly Treated and Relapsed/Refractory AML/MDS.

	Newly Diagnosed	R/R
Total (n)	28	44
Age, median (y)	72	61.5
Male/female, N (%)	18/10 (64.3)	29/15 (65.9)
ECOG performance status, N (%)		
0	6 (21.4)	10 (23.3)
1	15 (53.6)	25 (58.1)
2	5 (17.9)	5 (11.6)
3	2 (7.1)	3 (7.0)
AML, (N)	26	39
Subtype, N (%)		
De novo	13 (50.0)	20 (51.3)
Secondary to MDS	3 (11.5)	11 (28.2)
Secondary to MPN	3 (11.5)	7 (17.9)
Secondary to CMML	3 (11.5)	1 (2.6)
Therapy related	4 (15.4)	0
ELN criteria, N (%)		
Favorable	3 (11.5)	4 (10.3)
Intermediate	12 (46.2)	16 (41.0)
Adverse	11 (42.3)	19 (48.7)
MDS, (N)	2	5
IPSS-R very high, N (%)	2 (100)	3 (60)
IPSS-R high, N (%)	0	2 (40)
Cytogenetics, N (%)		
Favorable	1 (3.6)	1 (2.3)
Intermediate	15 (53.6)	26 (59.1)
Adverse	12 (42.9)	17 (38.6)


A
100
50
0
Percent survival
Overall
Upfront
R/R
P logrank N.S.
0
10
20
30
40
months

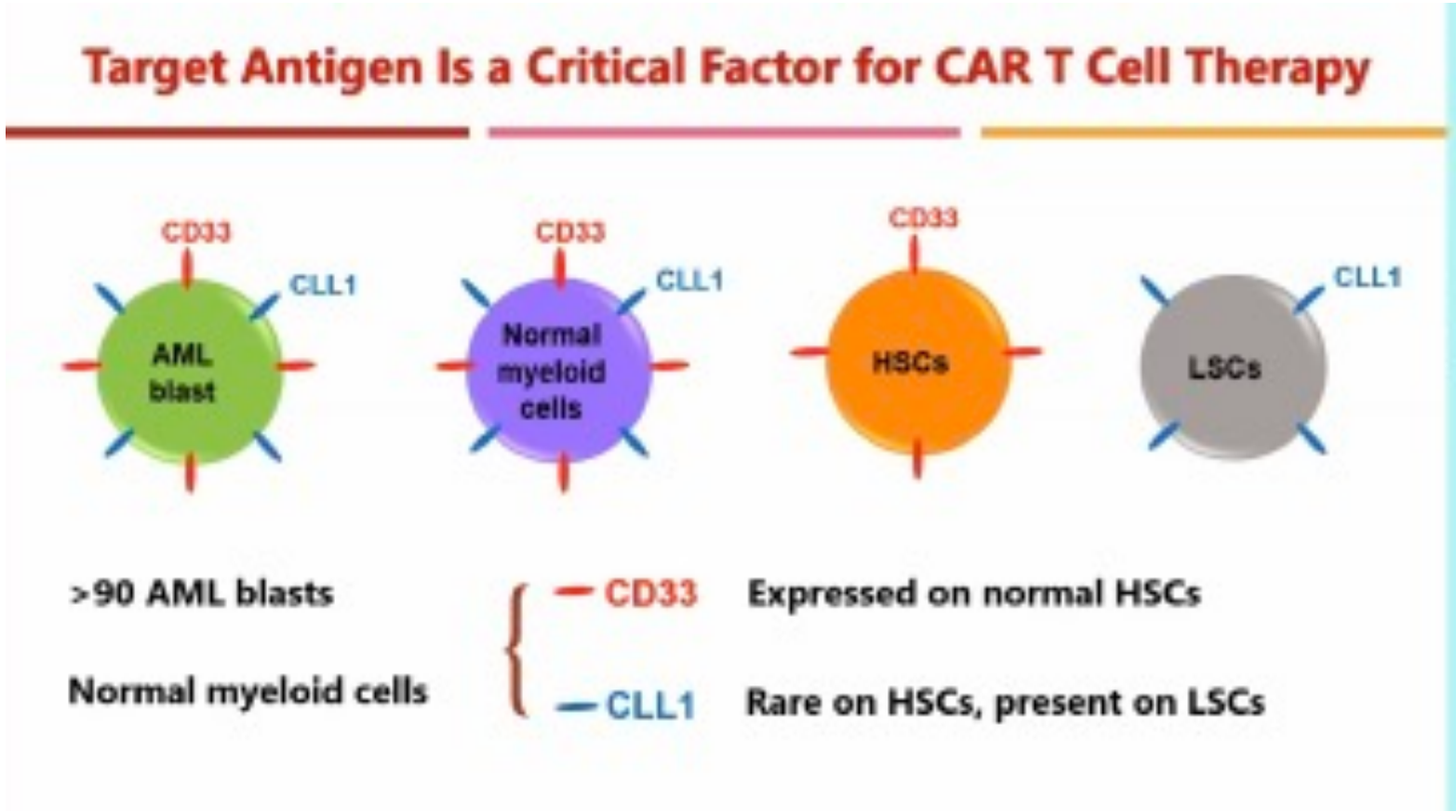

B
100
50
0
Percent survival
Aza UF
Dec UF
Aza R/R
Dec R/R
P logrank N.S.
0
10
20
30
40
months

C

- **S149 First-in-human CLL1-CD33 cCAR T Cell Therapy in R/R AML**

Mouse model

Clinical FIH trial



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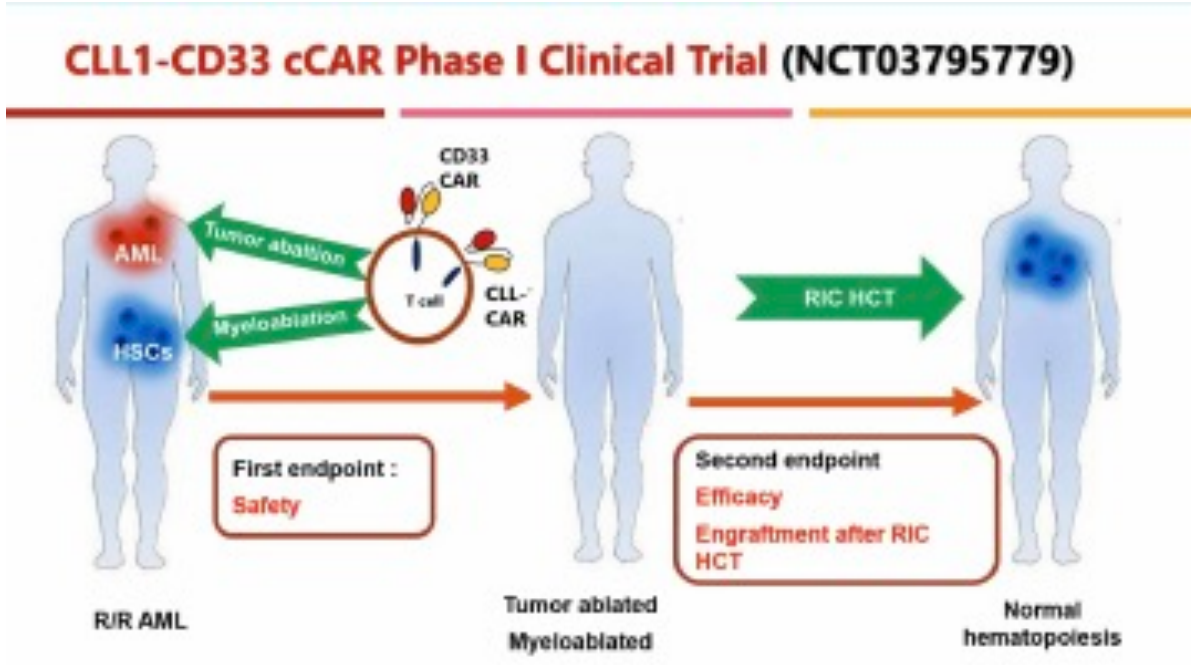
First-in-human CLL1-CD33 cCAR T Cell Therapy in R/R AML



	Age/sex Dx	Prior treatment	BM Blast%	CD33/CLL1 expression	Cytogenetic /molecular	Origin of car-t cells	CAR-T Dose	responses
P1	44/m AML	4 chemo	47%	$CD33^{+}/CLL1^{+}$	ASXL1,TP53	auto	$0.7x10^{6}$/kg	MRD^{-}
P2	6/f JMML-AML	5 chemo	81%	$CD33^{+}/CLL1^{+}$	Complex FLT3-ITD	auto	$2x10^{6}$/kg	MRD^{-}
P3	23/F CML AP	3 TKIs for 5 years	1.63%	$CD33^{+}/CLL1^{+}$	t(9;22) T315mut	auto	$1.1x10^{6}$/kg	MRD^{-}
P4	43/F M2	3 chemo	42%	$CD33^{+}/CLL1^{+}$	NK FLT3-ITD	auto	$2.8x10^{6}$/kg	MRD^{-}
P5	32/F AML	3 chemo	19%	$CD33^{+}/CLL1^{+}$	NK MLL	auto	$2x10^{6}$/kg	MRD^{-}
P6	48/F AML	5 chemo	94%	$CD33^{+}/CLL1^{+}$	t(8;21) AML1/ETO CKIT	auto	$1.3x10^{6}$/kg	MRD^{-}
P7	23/F AML	4 chemo	74%	$CD33^{+}/CLL1^{+}$	t(8;21) AML1/ETO CKIT	auto	$1x10^{6}$/kg	NR
P8	27/F AML	5 chemo	93%	$CD33^{+}/CLL1^{-}$	NA MLL AF9	auto	$2.3x10^{6}$/kg	NR
P9	42/f AML	2 chemo	7%	$CD33^{+}/CLL1+$	T(3;3) RUNX1	MSD donor	$3.7x10^{6}$/kg	MRD^{-}

Sammanfattning

- Återfall
  - fortfarande mycket dålig prognos
  - viktigt med upprepad diagnostik
- Om sent recidiv – ej tidigare SCT – möjlighet till SCT i CR2
  - hyfsade chanser med intensiv kemo + alloSCT
  - Men: inte alla får CR2, inte alla botas av AlloSCT
  - ‘Avstå’ från alloSCT: Gynnsam cytogenetik **och** mutationsstatus **och** MRD-neg?
- Nya målriktade behandlingar
  - mindre toxicitet, lika bra (= dålig) effekt som intensiv kemo
  - sent insättande remission (utom aza+venetoclax), och kort duration
  - vid respons - SCT med pat i bättre allmäntillstånd
  - Snabb kunskapsutveckling, många nya regimer prövas