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Emerging and Practical Concepts and Controversies in Leukemias

16 May 2021

Virtual Breakout: Adult Leukemia Patients

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

Elias Jabbour

APTITUDE HEALTH

Meet the Faculty

Elias Jabbour, MD
Professor of Medicine
Department of Leukemia
University of Texas
MD Anderson Cancer Center
USA

Naval Daver, MD
Associate Professor
Department of Leukemia
University of Texas
MD Anderson Cancer Center
USA

Aaron Logan, MD, PhD
UCSF, Helen Diller Family
Comprehensive Cancer Care, USA

José-Maria Ribera, MD
Chief of the Stem Cell Transplantation at University Hospital "Germans Trias I Pujol"
Head of the Clinical Hematology Department for the Catalan Institute of Oncology
Spain

Eunice Wang, MD
Chief of the Leukemia Service
Roswell Park Comprehensive Cancer Center
USA

JPAC Faculty

- **Shaun Fleming, MBBS(Hons), FRACP, FRCPA**
  Alfred Hospital, Australia
- **Chyn Chua, MBBS, BMedSc, FRCAP, FRCPA**
  Alfred Hospital, Australia
- **Sun Loo, MD**
  Alfred Hospital, Australia

Objectives of the Program

- Understand current treatment patterns for leukemia including incorporation of new technologies in ALL and AML
- Uncover when genomic testing is being done and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring leukemias
- Gain insights into antibodies and bispecifics in ALL: what are they? When and how should they be used? Where is the science going?
- Discuss the evolving role of ADC therapies
- Review promising novel and emerging therapies in ALL and AML

Virtual Breakout – Adult Leukemia Patients (Day 2)

Chair: Elias Jabbour

TIME (UTC +9)	TITLE	SPEAKER
11.00 – 11.15	Session open • Educational ARS questions for the audience	Elias Jabbour
11.15 – 11.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation (15 min) • Q&A (5 min)	Aaron Logan
11.35 – 11.55	Current treatment options for relapsed ALL in adult and elderly patients (including COVID-19 and vaccination strategy) • Presentation (15 min) • Q&A (5 min)	José-Maria Ribera
11.55 – 12.30	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in adult and elderly patients Panelists: Elias Jabbour, José-Maria Ribera, Aaron Logan	Shaun Fleming
12.30 – 12.45	Break	
12.45 – 13.05	Personalized induction and maintenance approaches for AML • Presentation (15 min) • Q&A (5 min)	Naval Daver
13.05 – 13.25	Optimizing management of relapsed/refractory AML • Presentation (15 min) • Q&A (5 min)	Eunice Wang
13.25 – 14.15	Case-based panel discussion or questions on regional challenges in AML care	Case 1: Chyn Chua Case 2: Sun Loo
14.15 – 14.30	Session close	Elias Jabbour

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Educational ARS Questions

Elias Jabbour

APTITUDE HEALTH

Q

Question 1

What age group is considered elderly ALL patients?

a) ≥50 years
b) ≥55 years
c) ≥60 years
d) ≥65 years
e) ≥70 years

Q

Question 2

Which of the following is NOT true for treating ALL?

a) Inotuzumab and blinatumomab plus chemotherapy has produced 90% CR rates in salvage therapy and in first line in older patients
b) Blinatumomab and ponatinib can be used as a chemotherapy-free regimen in Ph+ ALL
c) MRD-negative CR does not correlate strongly with outcome
d) Since 1999, median survival for ALL patients older than 60 has been increasing with each successive decade

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Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens

Aaron Logan

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UCSF Helen Diller Family Comprehensive Cancer Center

Optimizing First-Line Therapy in Older Adults With ALL:

Integration of Immunotherapy Into Frontline Regimens

Aaron Logan, MD, PhD, MPhil
UCSF Division of Hematology and
Blood and Marrow Transplantation

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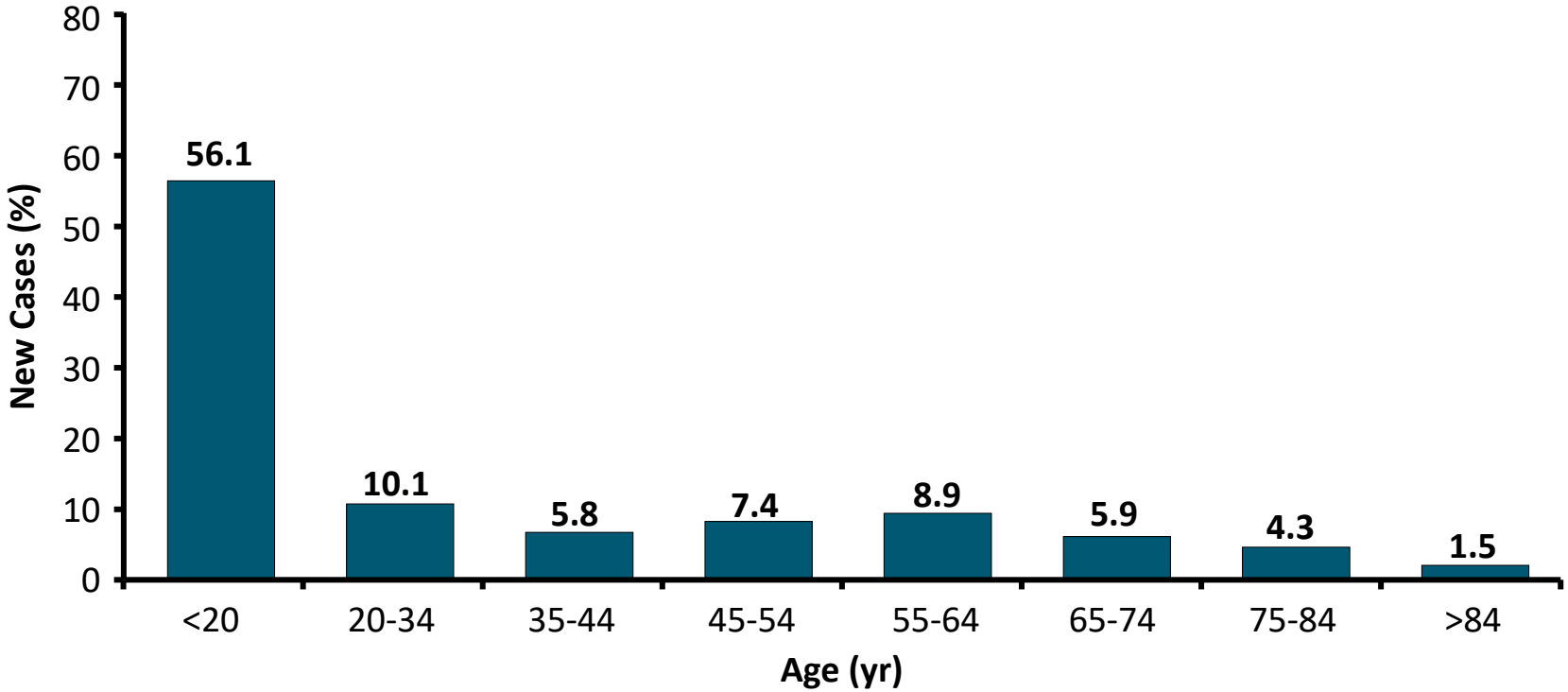
Q

Question 1

Which of the following agents, when added to front-line therapy for adults with ALL, have been shown to improve leukemia-free survival in a randomized clinical trial:

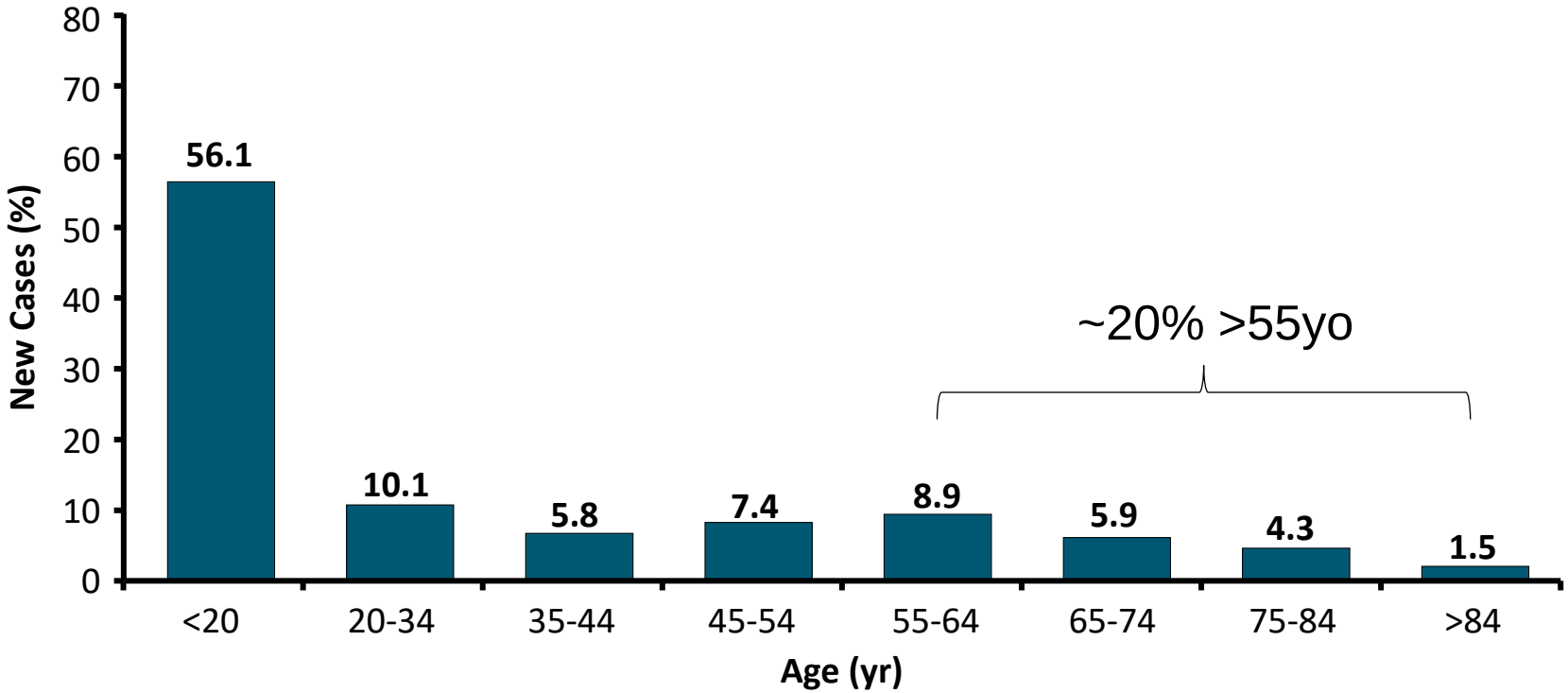
(a) Inotuzumab
(b) Blinatumomab
(c) Rituximab
(d) Ponatinib
(e) Ofatumumab

Incidence of Acute Lymphoblastic Leukemia by Age



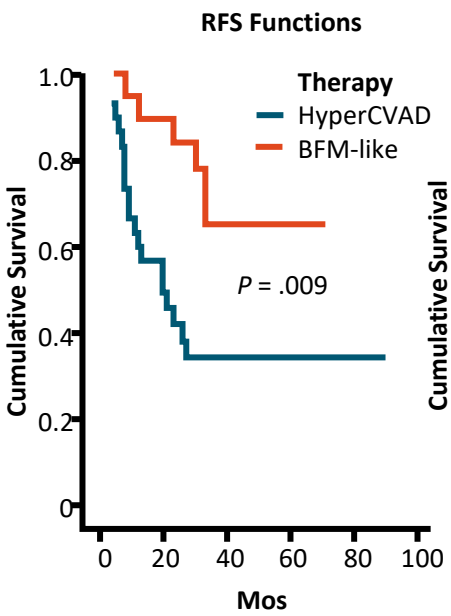
SEER Cancer Statistics Factsheets, 2017.

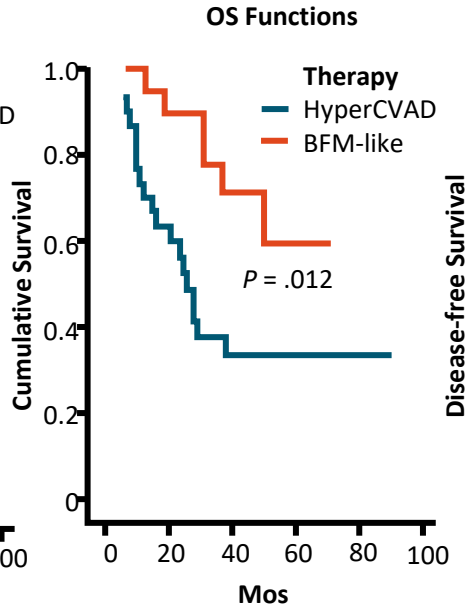
Incidence of Acute Lymphoblastic Leukemia by Age

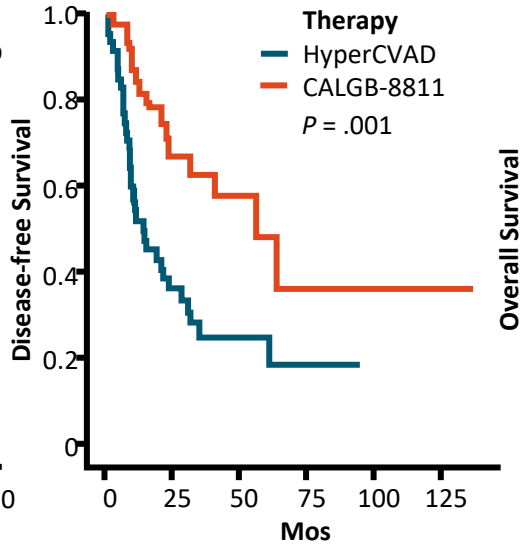


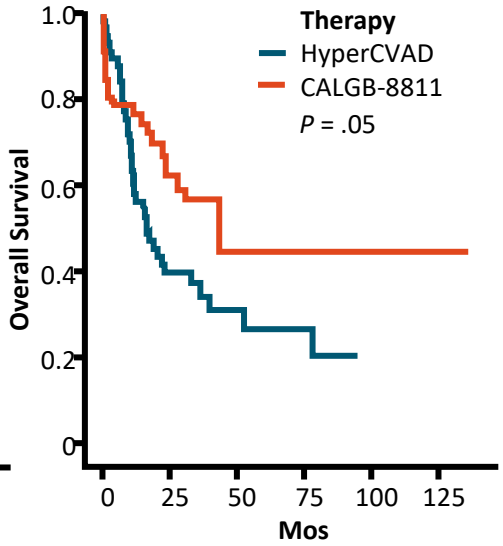
SEER Cancer Statistics Factsheets, 2017.

Pediatric vs Adult Regimens for Adults with ALL





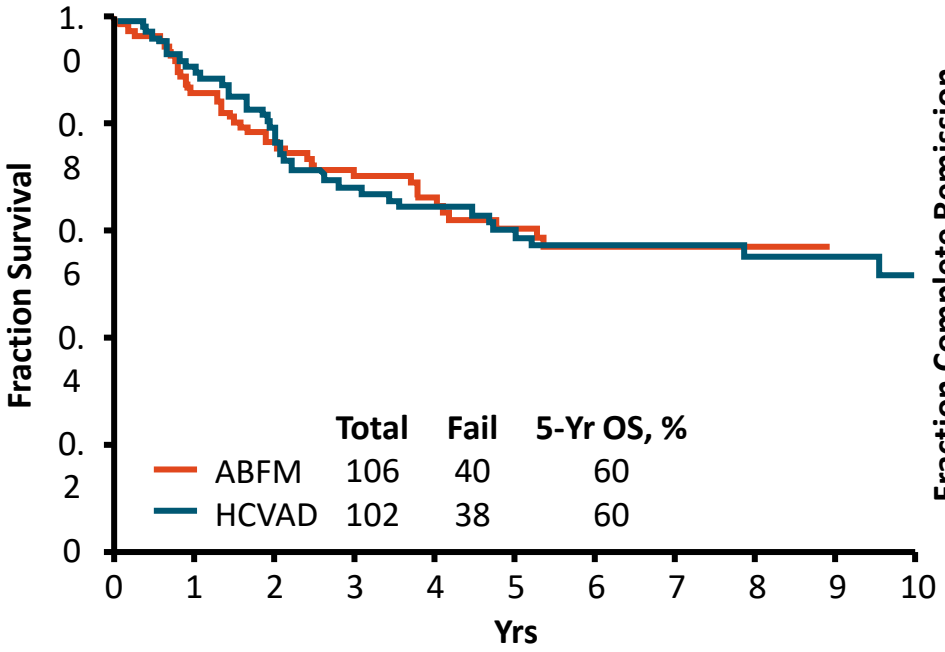


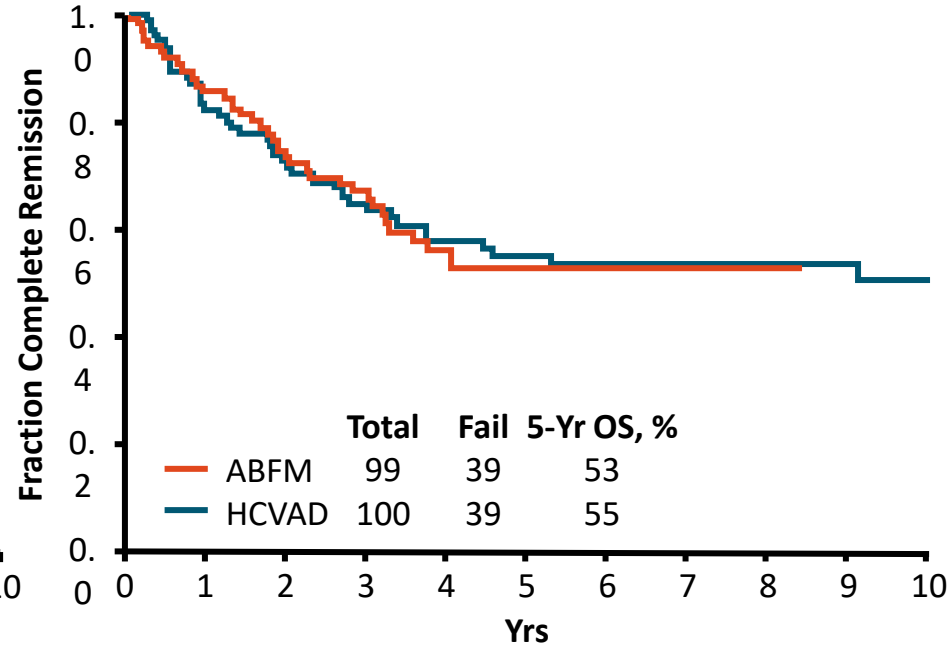


Alacacioglu I, et al. Chemotherapy 2014; 60:219-223.

Buyukasik et al. Acta Haematologica 2013; 130:199-205.

Pediatric vs Adult Regimens for ALL: BFM vs hyper-CVAD





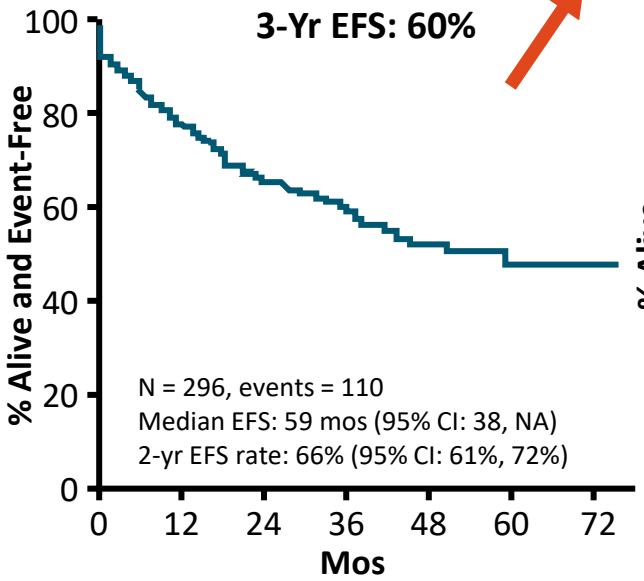
Rytting ME, et al. Am J Hematol 2016; 91:819-823.

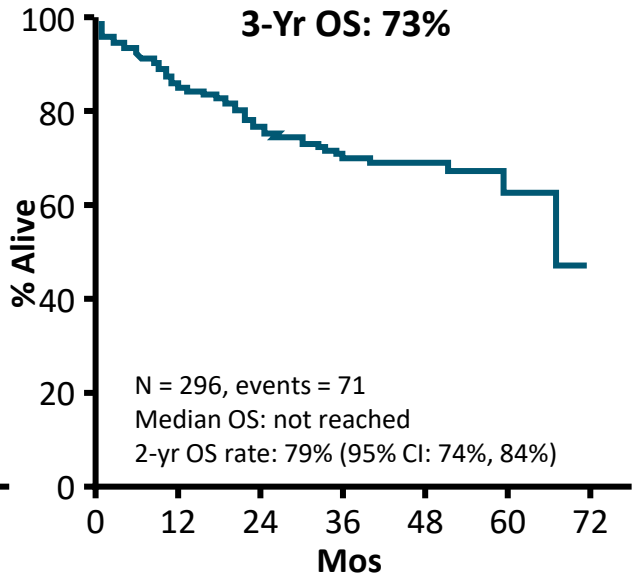
Intergroup C10403: Pediatric-Like Regimen for AYA <40yo

- CALBG historical control event-free survival: 34%

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	

85% if MRD neg by Q-PCR at end of induction

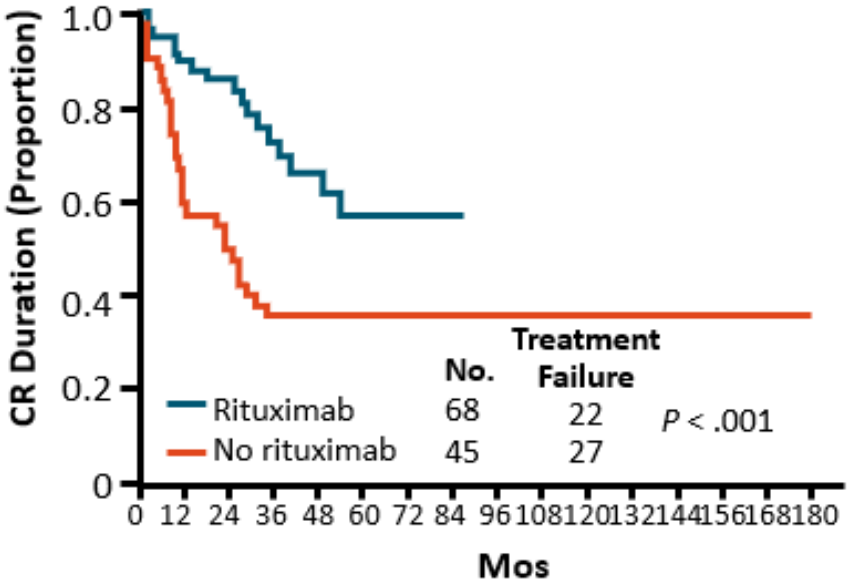


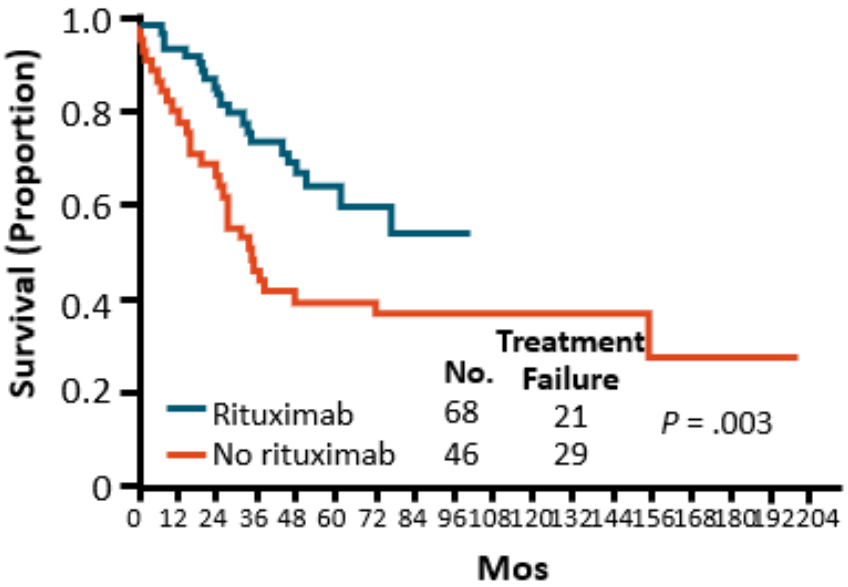


Stock W, et al. Blood 2019; 133(14):1548-1559

Rituximab Improves Outcomes for CD20+ ALL

Rituximab + Hyper-CVAD





Thomas DA, et al. J Clin Oncol. 2010;28:3880-3889.

GRAALL: Rituximab Improves Outcome for CD20+ ALL treated with BFM-like regimen

RCT, n=209, Age 18-59

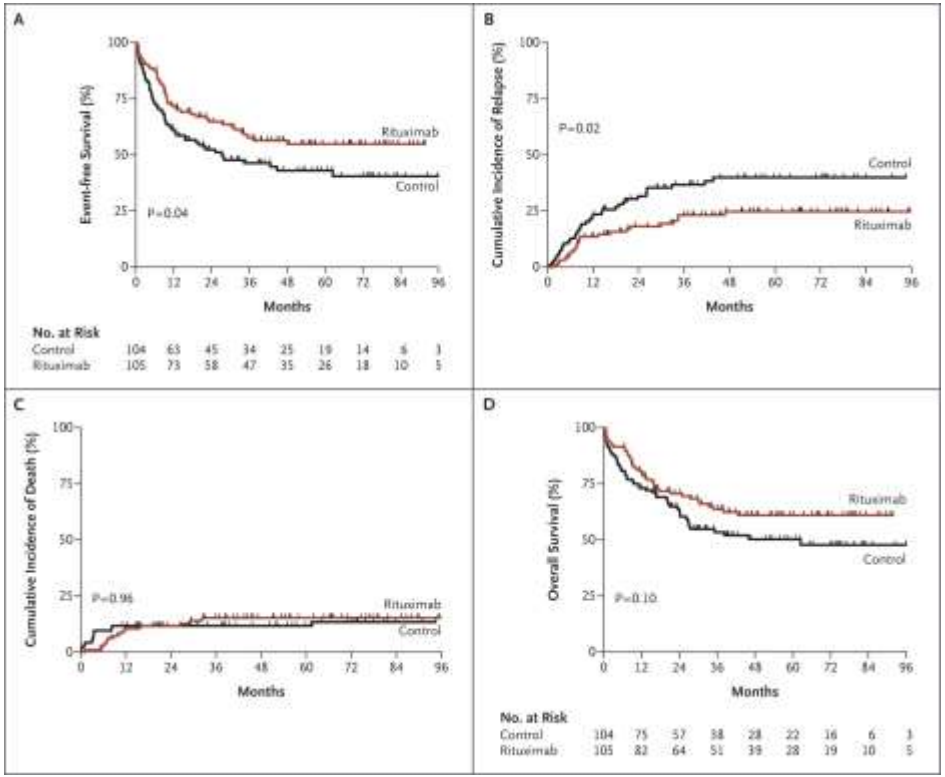


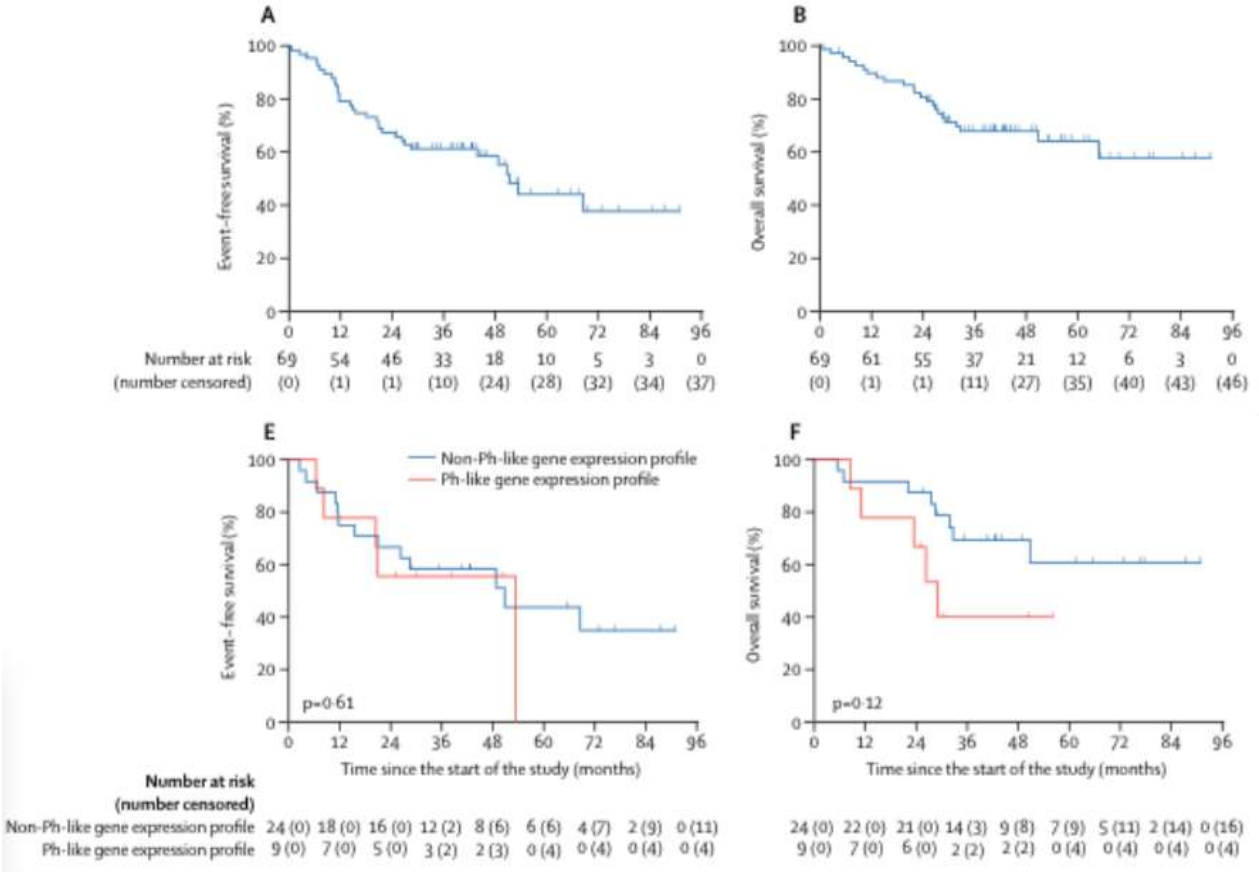
Table 2. Response to Initial Therapy.*

Variable	All Patients (N=209)	Rituximab Group (N=105)	Control Group (N=104)	P Value
Early response to therapy — no. (%)				
Poor peripheral-blood blast clearance	34 (16)	20 (19)	14 (13)	0.35
Poor bone marrow blast clearance	87 (42)	46 (44)	41 (39)	0.58
Response to induction — no. (%)				
Complete remission				
Without salvage reinduction	186 (89)	95 (90)	91 (88)	0.52
With or without salvage reinduction	191 (91)	97 (92)	94 (90)	0.63
Resistant disease	2 (2)	1 (1)	1 (1)	
Death during induction	16 (8)	7 (7)	9 (9)	
MRD $<10^{-4}$ bone marrow blasts — no./total no. (%)				
After first induction course	54/85 (64)	32/49 (65)	22/36 (61)	0.82
After first consolidation phase	70/80 (88)	42/46 (91)	28/34 (82)	0.31
High-risk ALL — no. (%)†	140 (67)	73 (70)	67 (64)	
Allogeneic SCT during first complete remission — no. (%)	57 (27)	36 (34)	21 (20)	

* MRD denotes minimal residual disease, and SCT stem-cell transplantation.
† High-risk acute lymphoblastic leukemia (ALL) was determined according to protocol-specified criteria.

Maury S, et al. NEJM. 2016;375:1044-1053.

Ofatumumab + hyper-CVAD



Thomas DA, et al. J Clin Oncol. 2010;28:3880-3889.

Older ALL Patient Outcomes With Conventional Regimens

Reference	Year	Age (y)	Ph+	Patients (N)	CR rate (%)	Early death	Failure	CCR*	DFS*	OS†
16	1996	60-73 (64)	Yes	22	59	18%	14%	12	9	20% (2 y)
23	1997	55-86 (67)	Yes	40	85	n.r.	n.r.	n.r.	14	16% (2 y)
24	2002	65 (55-81)	Yes	58	43	10%	47%	5	10	n.r.
17	2004	69 (61-79)	Yes	17	76	17%	6%	20	21	38% (2 y)
19	2007	65 (56-77)	No	33	58	36%	6%	46% (2 y)	7	39% (1 y)
20	2008	66 (60-78)	Yes	17	71	29%	0%	82% (1 y)	n.r.	71% (1 y)
25	2008	66 (56-73)	No	54	85	0%	15%	9	n.r.	61% (1 y)
18	2011		No						n.r.	
	Arm 1	68 (55-77)		31	90	7%	3%	32% (2 y)		35% (2 y)
	Arm 2	66 (60-80)		29	72	10%	17%	52% (2 y)		24% (2 y)
14	2012	57 (55-85)	No	268	76	14%	10%	32% (5 y)	n.r.	23% (5 y)
21	2016	58 (51-72)	Yes	30	67	3%	30%	n.r.	52% (2 y)	52% (2 y)
22	2016	66 (56-79)	No	54	74	14%	14%	n.r.	8; 24% (2 y)‡	12; 30% (2 y)‡

Arm 1, continuous infusion doxorubicin; Arm 2, pegylated doxorubicin; CCR, continuous complete remission; DFS, disease-free survival; n.r., not reported; OS, overall survival; Ph+, Ph/BCR–ABL1-positive ALL included yes or no.

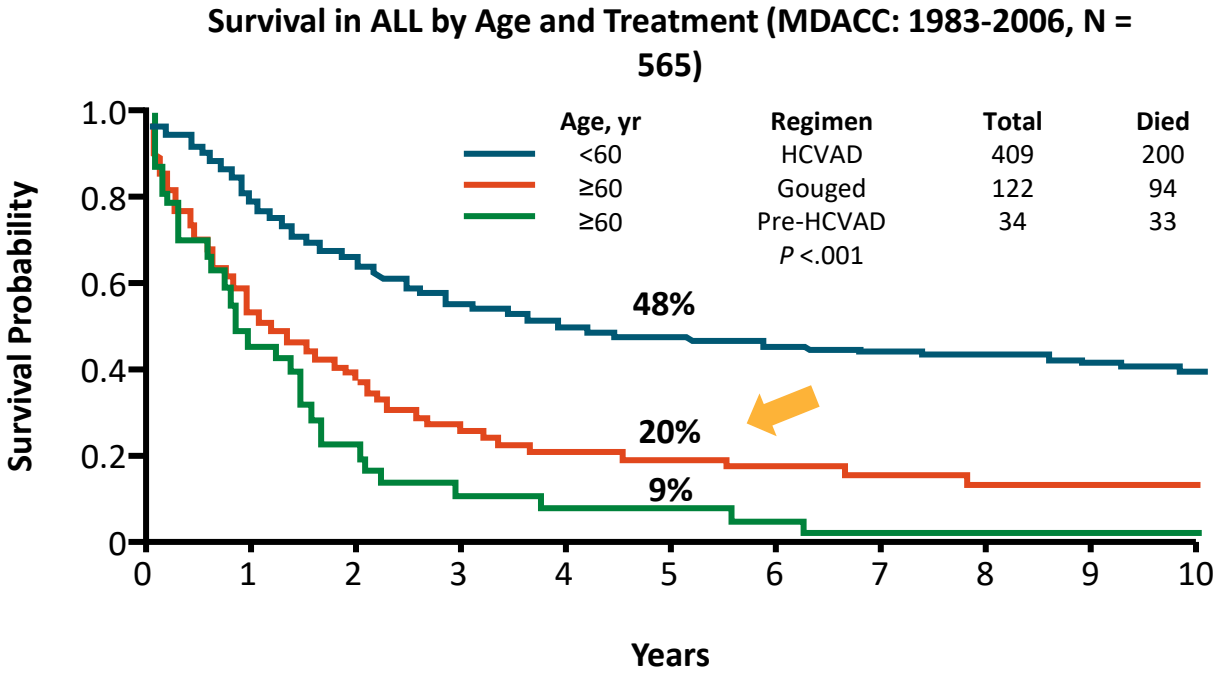
*Median months or probability.

†Probability.

‡Estimated from Kaplan-Meier curve.

Gökbuget N. *Hematol Am Soc Hematol Educ Program.* 2016;2016(1):573-579.

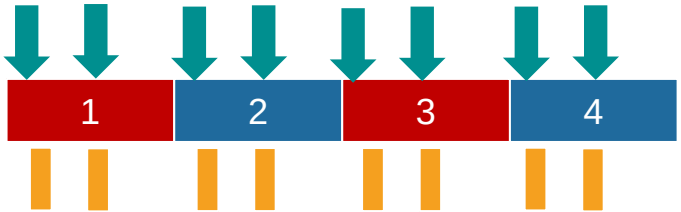
Older ALL Patient Outcomes With Conventional Regimens



O'Brien S, et al. *Cancer*. 2008;113:2097-2101.

Mini-hyperCVD + Inotuzumab +/– Blinatumomab

Intensive phase



Mini-hCVD

Mini-MTX–cytarabine

Blinatumomab

POMP

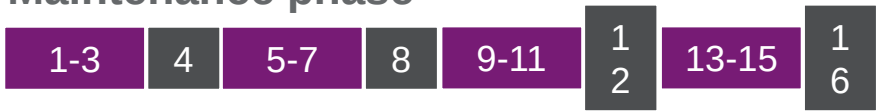
IT MTX/AraC

Consolidation phase

Inotuzumab	Dose per day (mg/m²)
C1	0.6 D1, 0.3 D8
C2-4	0.3 D1 and D8

Total Ino dose = 2.7 mg/m²

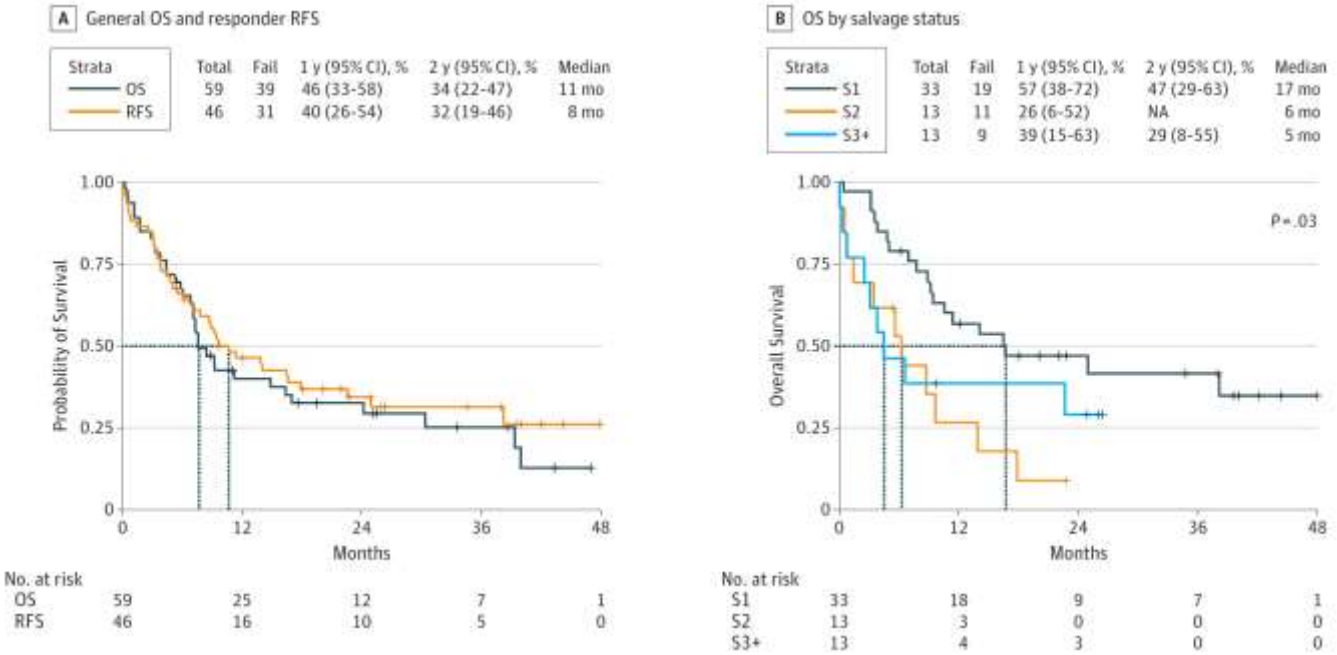
Maintenance phase



Jabbour E, et al. *JAMA Oncol*. 2018;4(2):230-234; Jabbour E, et al. *Cancer*. 2018;124:4044-4055.

Mini-hyperCVD + Low-Dose Inotuzumab: R/R ALL

N = 59; responses: 78% ORR, 59% CR (82% MRD neg in CR)

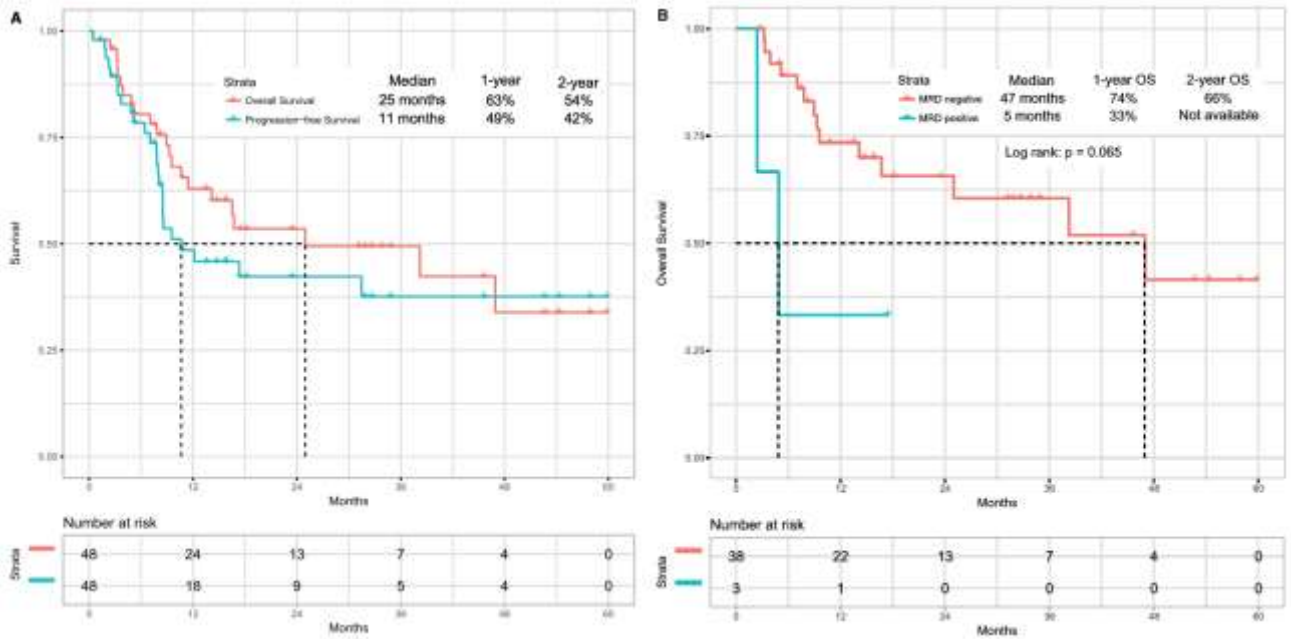


VOD observed in 23% who went to alloHCT, 9% who did not

Jabbour E, et al. *JAMA Oncol*. 2018;4(2):230-234.

Mini-hCVD + Low-Dose Inotuzumab +/– Blin: R/R ALL

N = 48 responses: 92% ORR, 73% CR (93% MRD neg in CR)

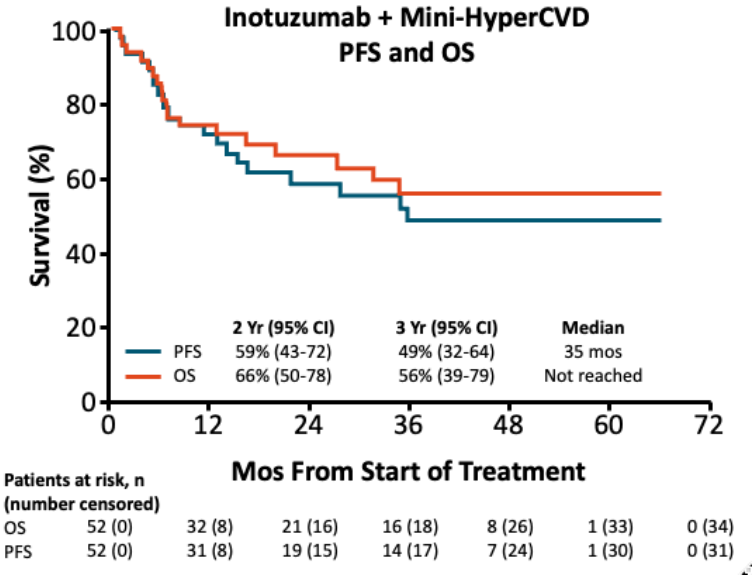


VOD observed in 13% who went to alloHCT (2 grade 5), 8% who did not

Jabbour E, et al. *Cancer*. 2018;124:4044-4055.

Mini-hCVD + Inotuzumab as Frontline Therapy in Patients >60 Years Old

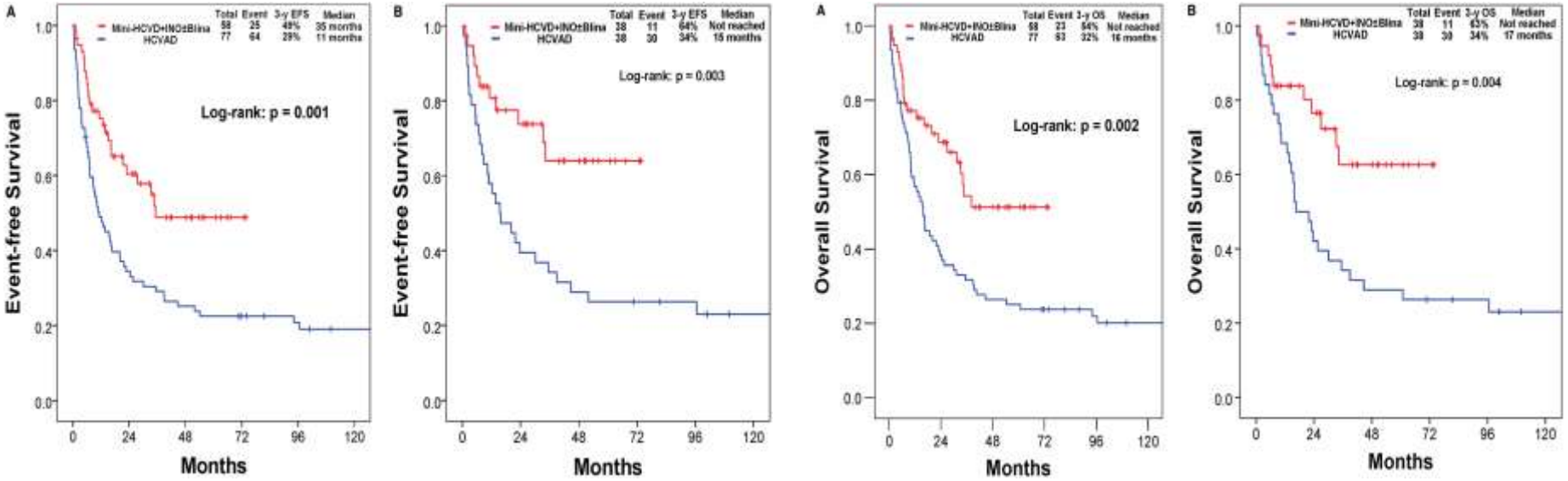
N = 52 responses: 98% ORR, 85% CR/CRi



VOD observed in 8% of patients (Ino 1.8 mg/m^2 in C1, 1.3 mg/m^2 in C2+) ->
No VOD after further dose reduction (Ino 1.3 mg/m^2 in C1, 1 mg/m^2 in C2+)

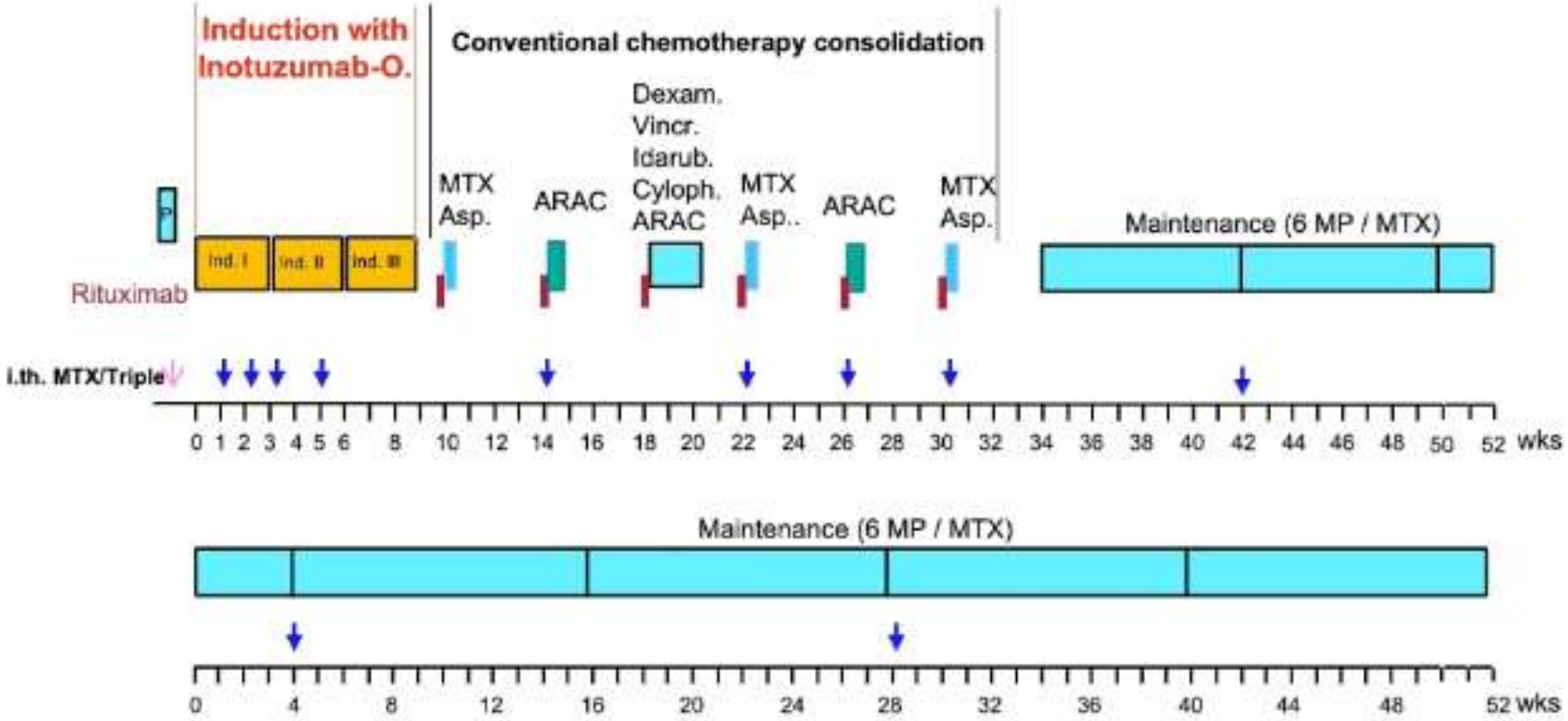
Kantarjian H, et al. *Lancet Oncol*. 2018;19:240-248.

Mini-hCVD + Inotuzumab as Frontline Therapy in Patients >60 Years Old



Jabbour E, et al. *Cancer.* 125(15):2579-2586.

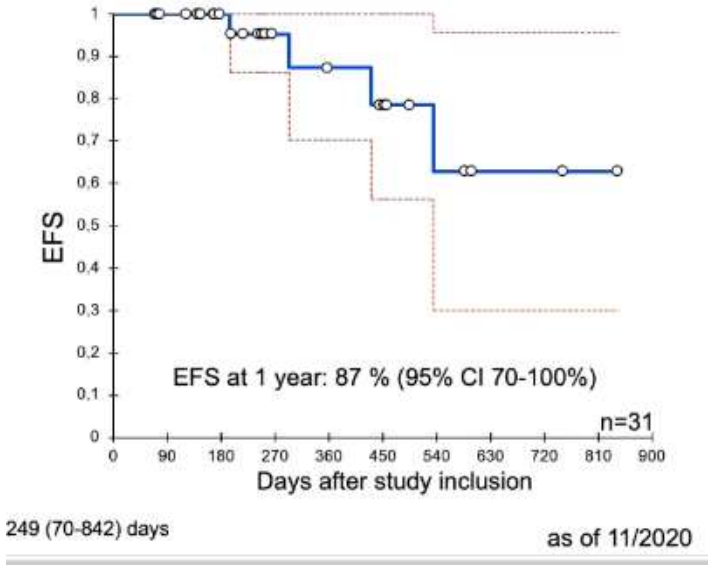
Initial-1: Inotuzumab for Induction Therapy Followed by Conventional Chemo, Age 55+, Phase II (GMALL)



Stelljes C, et al. ASH 2020. Abstract 267.

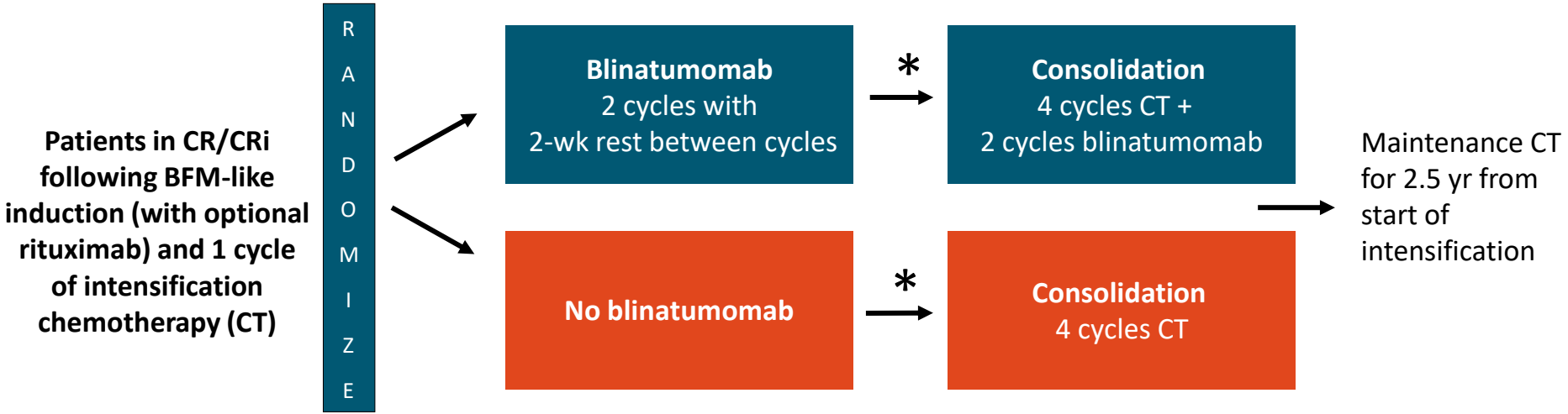
Initial-1: Inotuzumab for Induction Therapy Followed by Conventional Chemo, Age 55+, Phase II

- N = 36, age 56-80
- CR/CRi after ≥1 induction cycle with inotuzumab: 100% (31 evaluable)
- Patients receiving 3 cycles of inotuzumab: 29 (94%)
- MRD-negative remission as best response: 21 (78%)
- Relapses: 3 (2 hematologic, 1 molecular)
- Allogeneic HCT in remission: 3



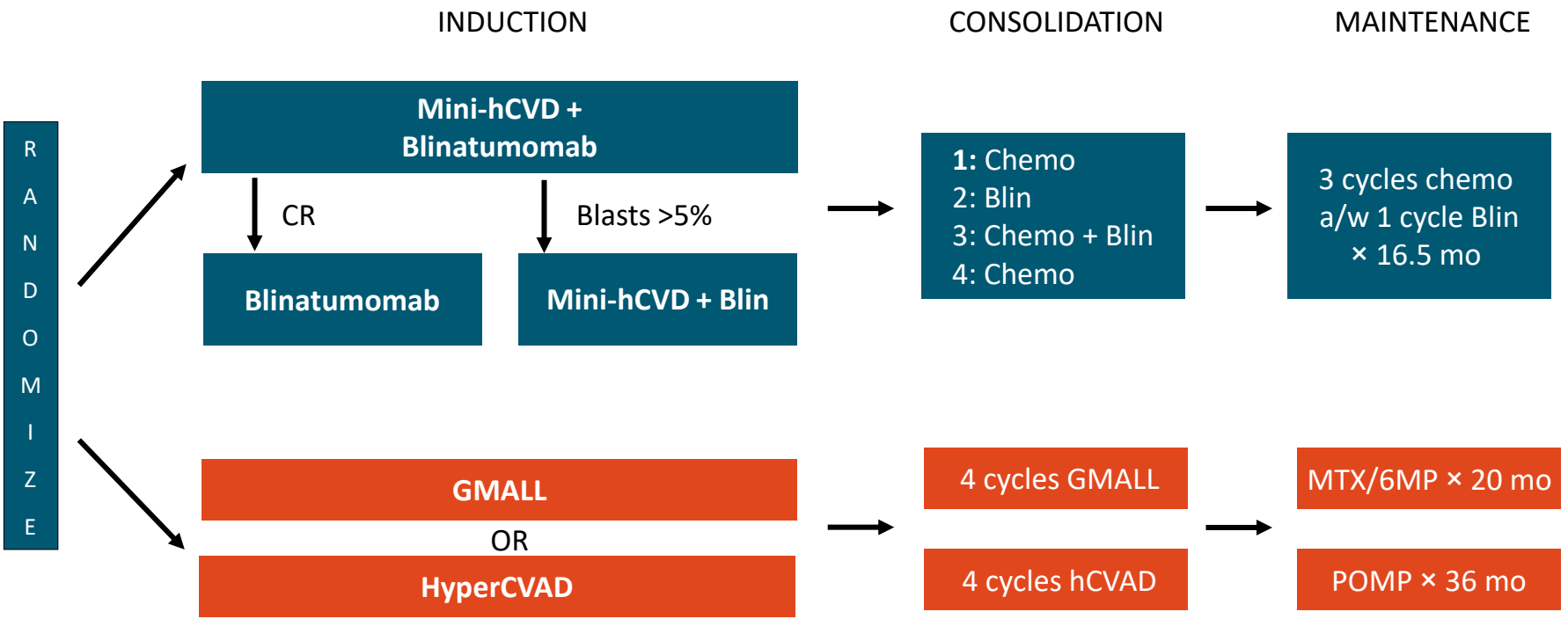
Stelljes C, et al. ASH 2020. Abstract 267.

ECOG 1910: Blinatumomab in Frontline Therapy for Newly Diagnosed Ph-Neg B-ALL (Age 30-70), Phase III RCT

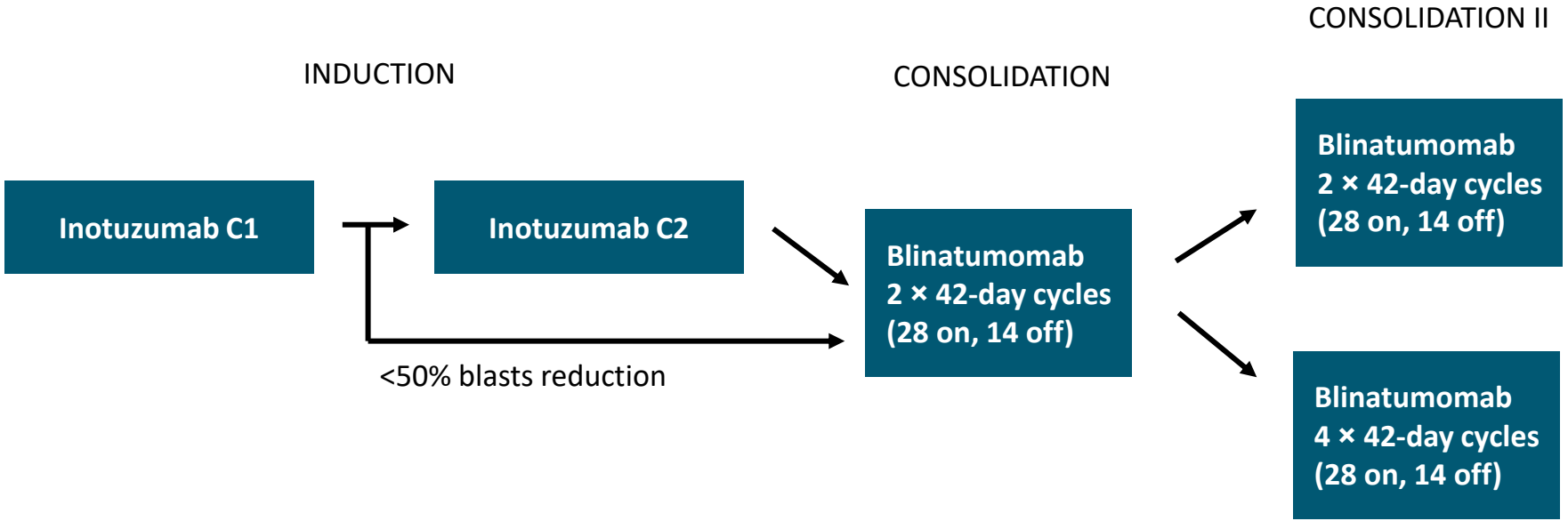


*Patients can proceed to BMT if recommended and suitable donor found.

Blinatumomab in Frontline Therapy for Newly Diagnosed Ph-Neg B-ALL Age 55+, Phase III RCT



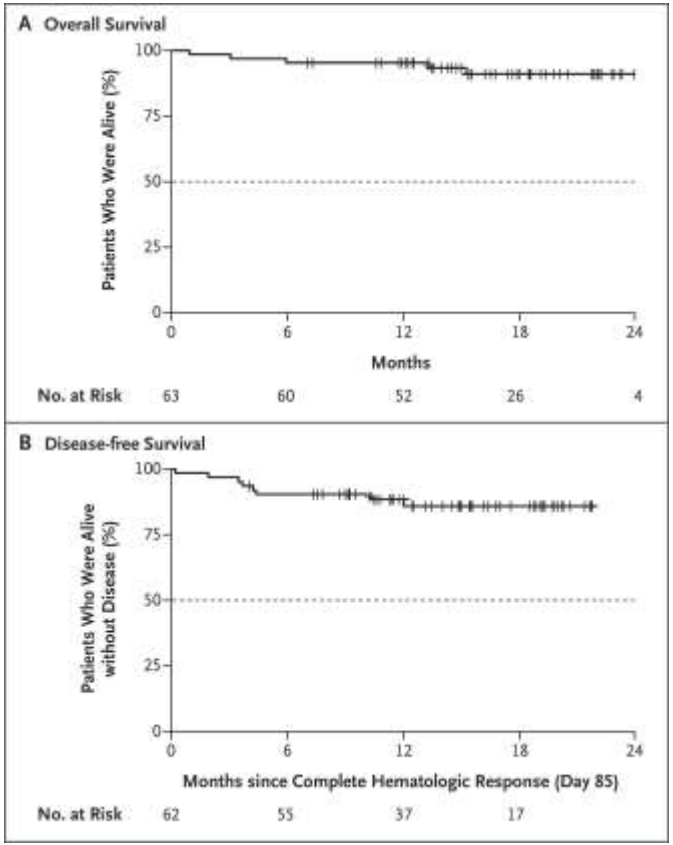
Frontline Inotuzumab Followed by Blinatumomab for Ph-Neg B-ALL in Older Adults, Phase II (Alliance)



Blinatumomab + Dasatinib as Frontline Therapy in Ph+ ALL

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.

Characteristic	Enrolled Patients (N=63)
Age — yr	
Median	54
Range	24–82
Sex — no. (%)	
Male	29 (46)
Female	34 (54)
White-cell count — per mm^3	
Median	13,000
Range	600–88,000
Fusion protein — no. (%)	
p190	41 (65)
p210	17 (27)
p190 and p210	5 (8)



Foa R, et al. *N Engl J Med.* 2020;383:1613-1623.

Adult / Older Adult ALL Summary

- Rituximab improves disease-free survival when added to front-line hyper-CVAD or BFM-like therapy
- Historically, older adults (>55 yr) have done poorly with conventional adult ALL regimens – high toxicity, high early death, low long-term OS
- Mini-hyperCVD + low-dose inotuzumab is well tolerated and achieves 3-yr OS ~50% in age 60+
- Ongoing studies are assessing alternative uses of inotuzumab, blinatumomab, and combinations of Ino-Blin as potential strategies in this patient population

Q

Question 1

Which of the following agents, when added to front-line therapy for adults with ALL, have been shown to improve leukemia-free survival in a randomized clinical trial:

(a) Inotuzumab
(b) Blinatumomab
(c) Rituximab
(d) Ponatinib
(e) Ofatumumab

Global Leukemia Academy

Current treatment options for relapsed ALL in adult and elderly patients (including COVID-19 and vaccination strategy)

José Maria Ribera

APTITUDE HEALTH

Global Leukemia Academy
Virtual Breakout – Adult Leukemia Patients
April 24, 2021

Current Treatment Options for R/R ALL in Adult and Elderly Patients (including COVID-19 and vaccination)

JM Ribera
Clinical Hematology Department
ICO-Hospital Germans Trias i Pujol
Institut de Recerca contra la Leucèmia Josep Carreras
Universitat Autònoma de Barcelona, Spain

Disclosures

- Pfizer: speaker and advisory boards honoraria, clinical trials
- AMGEN: speaker and advisory boards honoraria, research support, clinical trials
- Shire: speaker and advisory boards honoraria
- Ariad: speaker and advisory boards honoraria, clinical trials
- Takeda: speaker and advisory boards honoraria, clinical trials
- Novartis: speaker and advisory boards honoraria

How Can We Improve the Outcome of Elderly Patients With R/R ALL?

Ph+ ALL

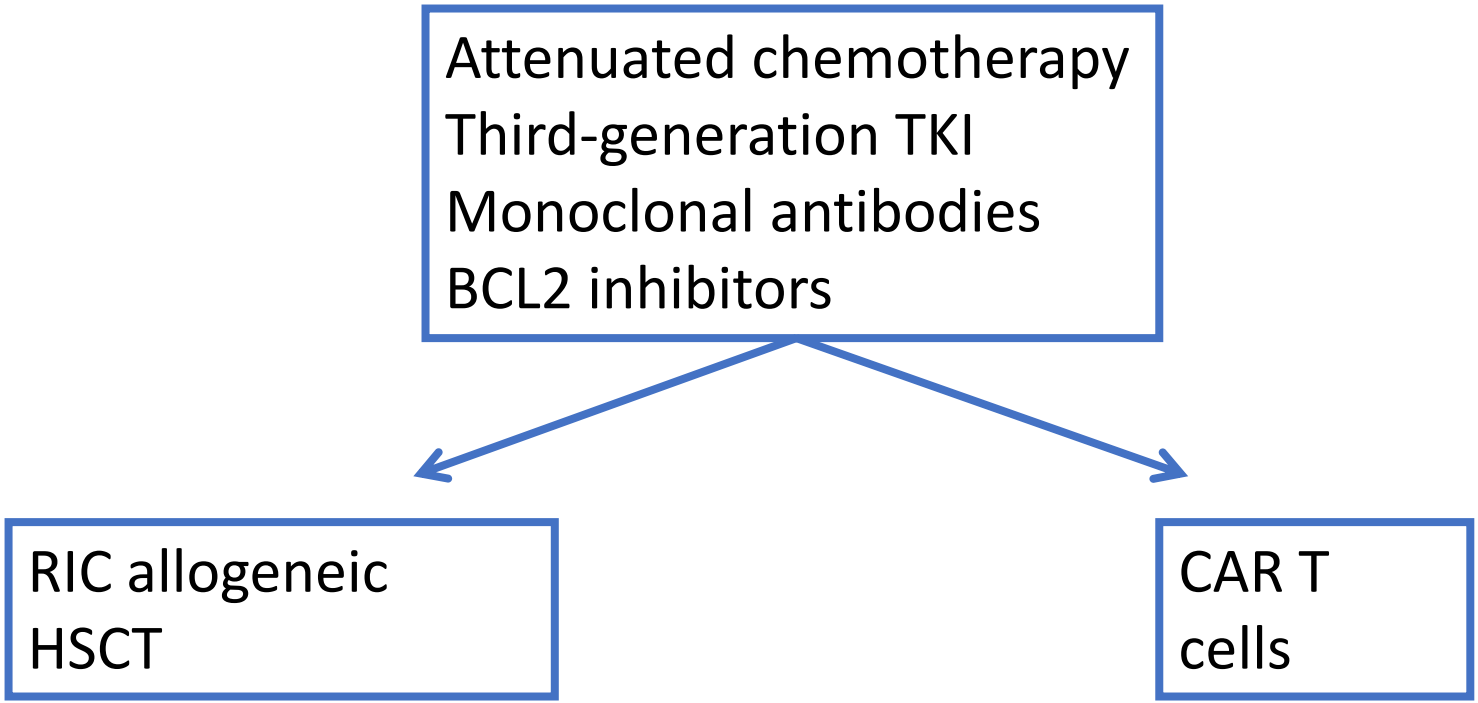
Ph– ALL

Prospective Trials in Older Patients With Newly Diagnosed Ph+ ALL

Author	Year	N	Age (median)	Induction	Post-induction	CR (%)	OS (%)
Vignetti	2007	29	69	IM + PRED	IM + physician's choice	100	74 (1 y)
Foa*	2011	53	54	DASA + PRED	DASA + physician's choice	100	69 (1.5 y)
Pfeifer	2012	121	66	IM ± CHT	IM + CHT	88	22 (5 y)
Ottmann	2014	47	66	NILO + CHT	NILO + CHT	97	-
Ribera	2016	53	66	IM + CHT	IM + CHT	87	41 (5 y)
Rousselot	2016	71	69	DASA + CHT	DAS + CHT	96	36 (5 y)
Ottmann	2017	72	66	NILO + CHT	NILO + CHT	94	40 (5 y)
Jabbour*	2018	68	46 (>60: 20)	**PONA** + CHT	PONA + CHT	100	74 (5 y)
Martinelli	2017	44	68	**PONA**	**PONA**	90	89 (1 y)
Foa*	2020	63	54	DASA	DASA + **BLINA**	98	87 (2 y)
Jabbour*	2020	27		**PONA + BLINA**	**PONA + BLINA**	100	100 (1 y)

*Not specifically designed for elderly patients.

Strategies Potentially Useful in R/R Ph+ ALL in Elderly



Inotuzumab as Single Drug for R/R Ph+ ALL: INO-VATE (n = 22) + Phase I/II Trial (n = 16)

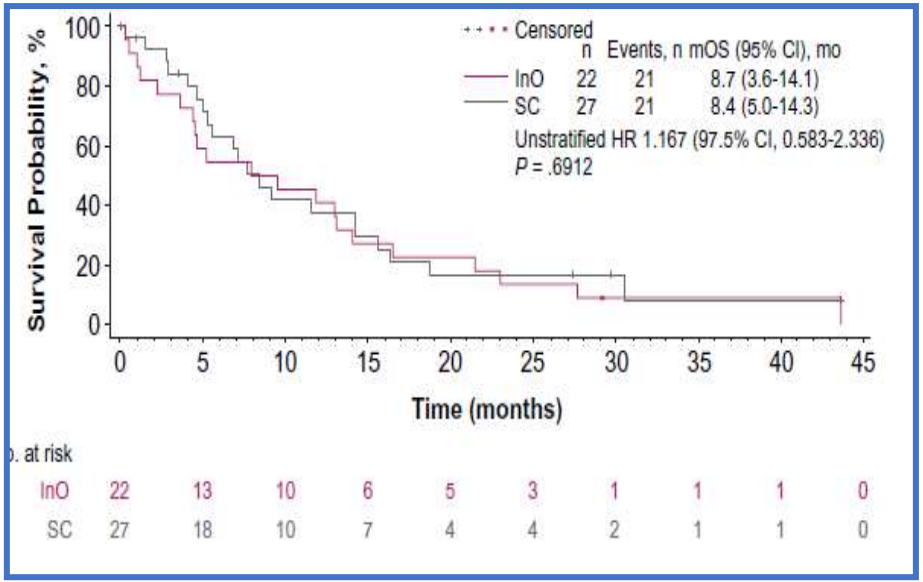
Efficacy Endpoints	Study 1022			Study 1010
	InO (n = 22)	SC (n = 27)	*P*	InO (n = 16)
CR/CRi, n (% [95% CI])	16 (72.7 [49.8-89.3])	15 (55.6 [35.3-74.5])	.1075	9 (56.3 [29.9-80.3])
CR, n (% [95% CI])	10 (45.5 [24.4-67.8])	8 (29.6 [13.8-50.2])	.1265	4 (25.0)
CRi, n (% [95% CI])	6 (27.3 [10.7-50.2])	7 (25.9 [11.1-46.3])	.4577	5 (31.3)
MRD negativity, n (% [95% CI])[a]	13 (81.3 [54.4-96.0])	5 (33.3 [11.8-61.6])	.009	9 (100.0 [66.4-100.0])
OS				
Median, mo (95% CI)	8.7 (3.6-14.1)	8.4 (5.0-14.3)		7.4 (4.3-11.3)
HR (95% CI)	1.17 (0.64-2.14)		.6912	—
PFS				
Median, mo (95% CI)	3.9 (2.1-9.2)	3.1 (1.1-6.2)		4.4 (1.8-5.9)
HR (95% CI)	0.65 (0.34-1.25)		.0963	—

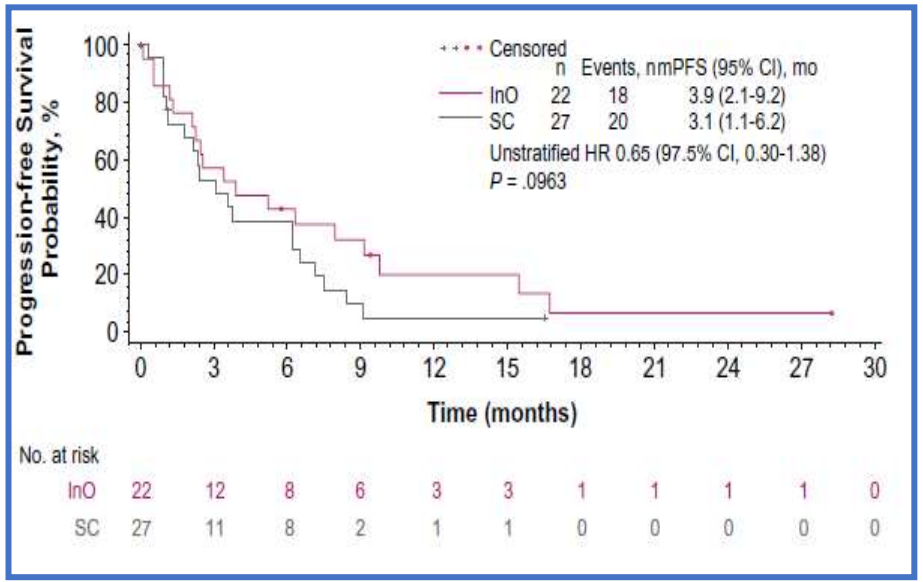
TABLE 2. Efficacy Endpoints Stratified According to Whether Ph+ Patients Received Follow-up HSCT

	Study 1022				Study 1010	
	+ Follow-up HSCT		No Follow-up HSCT		+ Follow-up HSCT	No Follow-up HSCT
	InO (n = 9)	SC (n = 5)	InO (n = 13)	SC (n = 22)	InO (n = 3)	InO (n = 13)
PFS, mo, median (95% CI)	9.2 (1.3-NE)	6.5 (2.2-NE)	2.4 (0.6-6.3)	2.4 (1.0-6.2)	5.4 (4.3-NE)	3.5 (1.7-5.9)
OS, mo, median (95% CI)	16.5 (4.7-43.6)	16.4 (11.6-30.6)	4.4 (1.1-8.0)	6.9 (4.1-9.1)	11.3 (4.3-NE)	7.4 (3.5-11.3)

Stock SW, et al. *Cancer.* 2021;127:905-913.

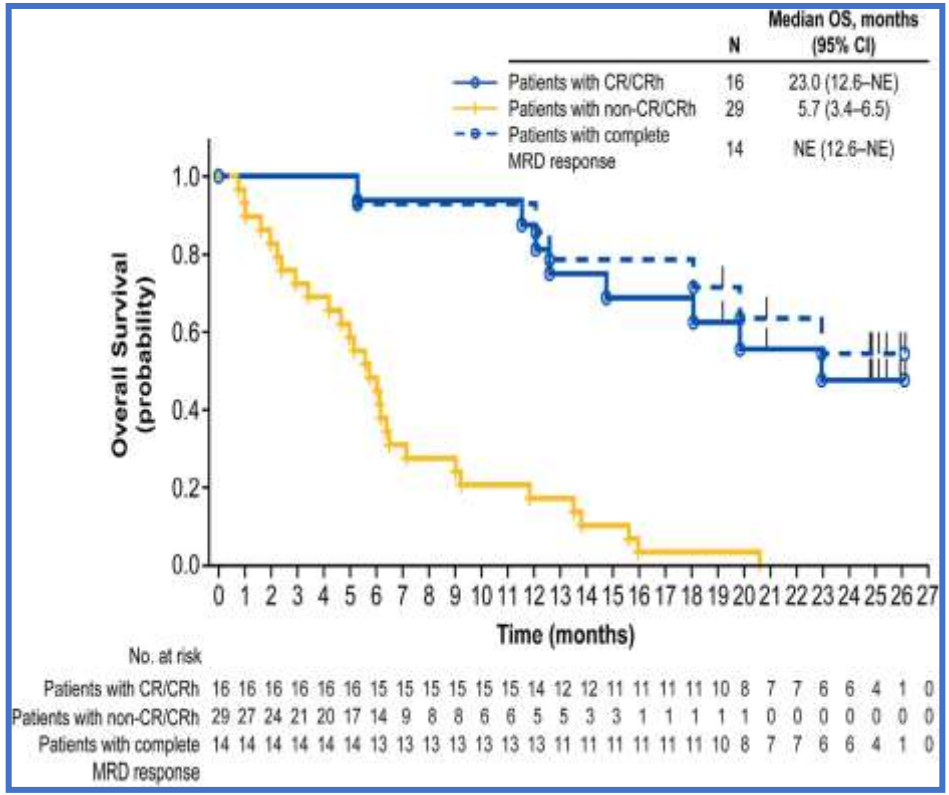
Inotuzumab as Single Drug for R/R Ph+ ALL: Outcomes From INO-VATE Trial





Blinatumomab in R/R Ph+ ALL

Outcome	Responders/ Evaluable	%
CR/CRh	16/45	36
T315I mutation	4/10	40
2 prior therapies	7/21	33
≥3 prior TKI therapies	8/17	47
Prior ponatinib	8/23	35
Prior alloSCT	5/20	25
Best response during the first 2 cycles: CR	14/45	31
CRh	2/45	4
Complete MRD response	14/16	88
Proceed to alloHSCT	4/16	25



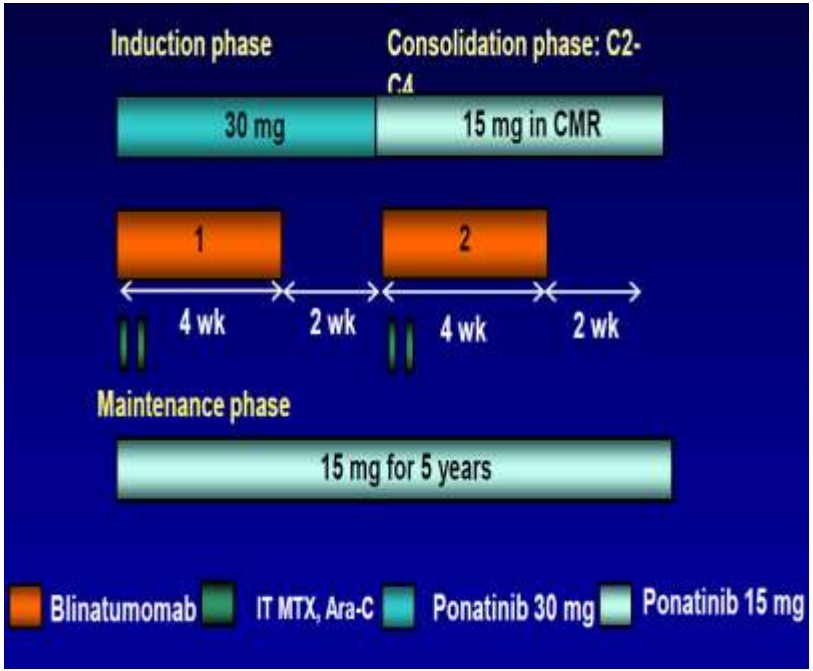
Martinelli G, et al. *Cancer*. 2021;146:107-114.

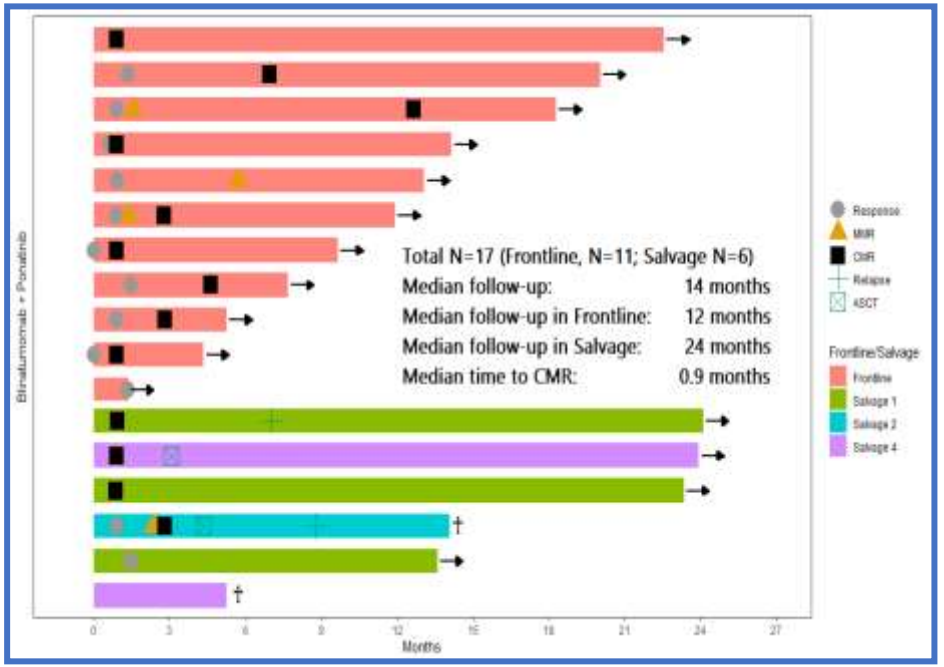
Blinatumomab and Inotuzumab in R/R Ph+ ALL

Parameter	Blinatumomab	Inotuzumab
No. Rx	45	38
No. CR/marrow CR (%)	16 (36)	25 (66)
MRD negative in CR, %	88	63
Median OS (mo)	7.1	8.1
Later alloSCT, %	44	32

Martinelli G, et al. *J Clin Oncol*. 2017;35:1795-1802; Stock W, et al. ASCO 2018. Abstract 7030.

Blinatumomab + Ponatinib Swimmer Plot (N = 17)





Personal communication from Dr Jabbour.

Ponatinib-Venetoclax for R/R Ph+ ALL

Ponatinib
- 45 mg/d
- 30 mg/d if CR/CRi
- 15 mg/d if CMR

Dex 40 mg 4 days/cycle

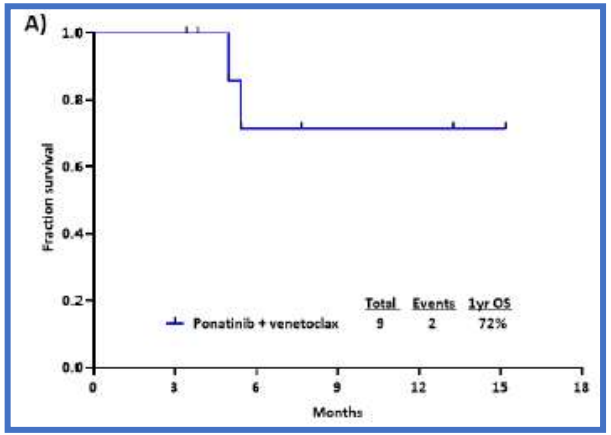
Venetoclax 400-800 mg

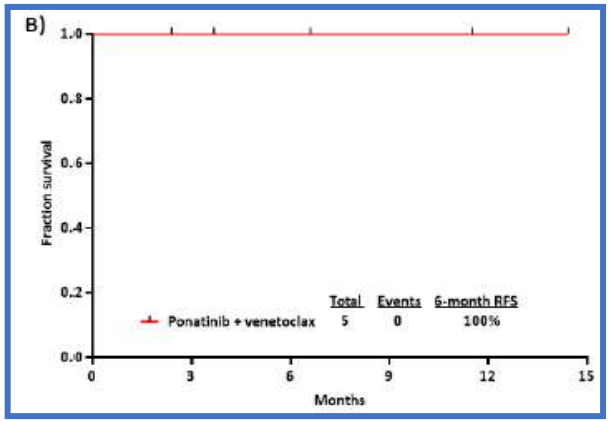
9 pts; *T315I* (4/8); prior therapies 3 (2-4)

CR/CRi: 56%

CMR: 44%

1-yr OS: 72% (2 deaths)





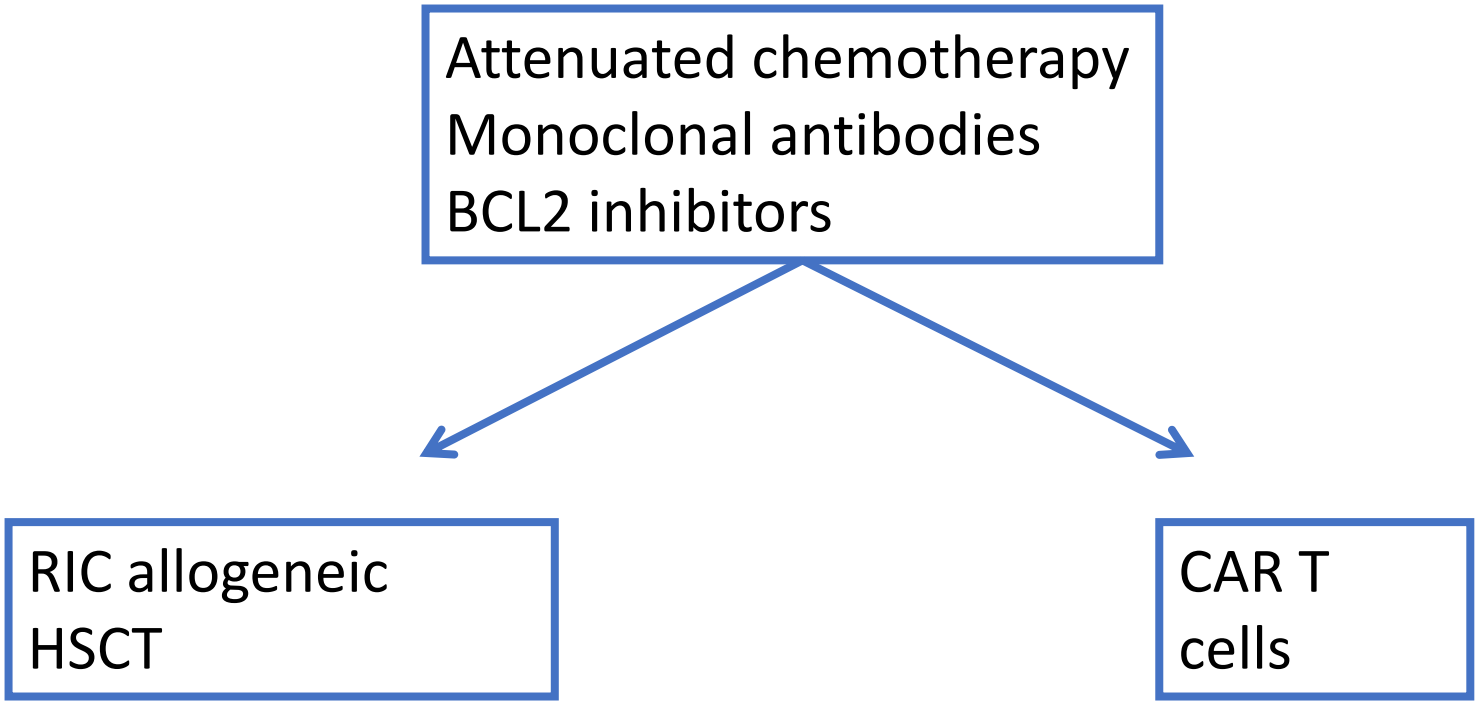
Short NJ, et al. *Am J Hematol*. 2021. doi: 10.1002/ajh.26175.

How Can We Improve the Outcome of Elderly Patients With R/R ALL?

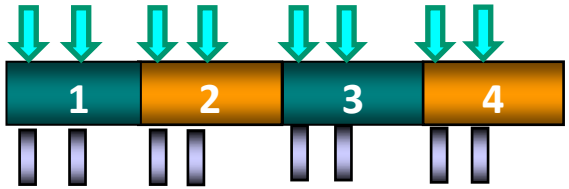
Ph+ ALL

Ph– ALL

Strategies Potentially Useful in R/R Ph– ALL in Elderly



Mini-HCVD + INO ± Blina in Salvage ALL and Frontline Older ALL: Modified Design (Pts #50+)



Mini-HCVD

Mini-MTX–cytarabine

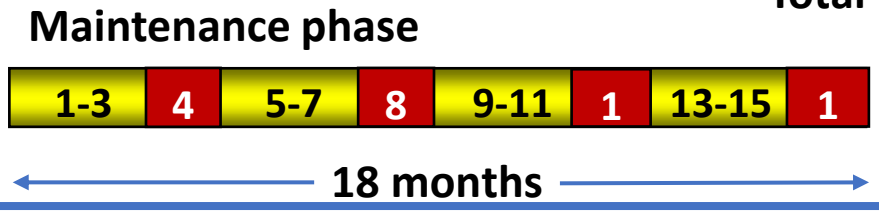
MTX

Blinatumomab

POMP

INO	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2-4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²



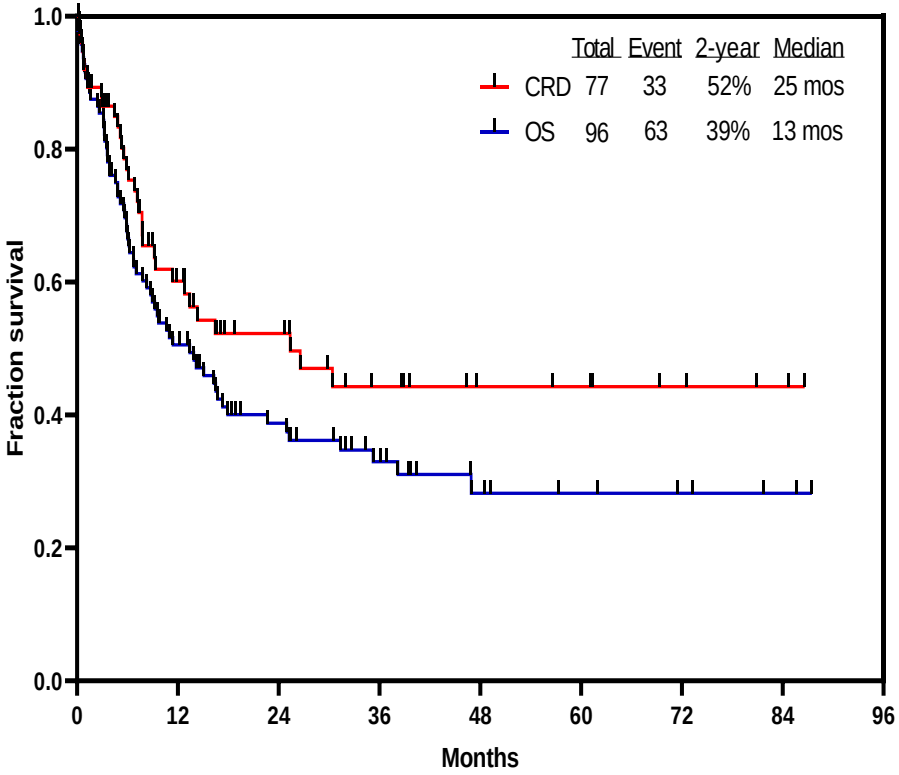
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Short N, et al. ASH 2018. Abstract 36.

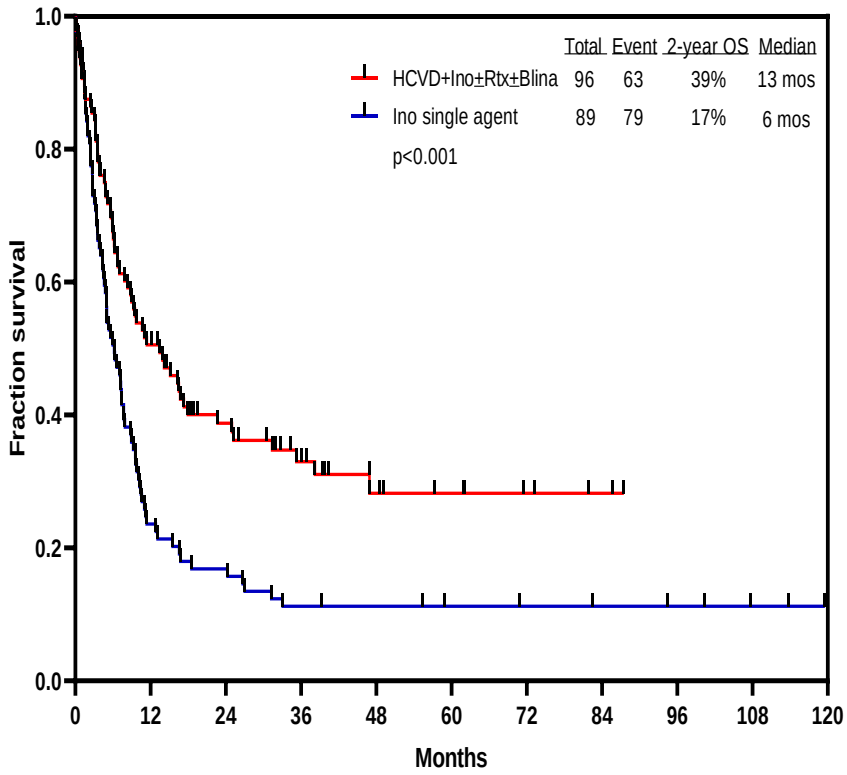
Mini-HCVD + INO ± Blinatumomab in R/R ALL: Response by Salvage (N = 96)

Response	N	Percentage
Salvage 1	58/64	**91**
S1, primary refractory	8	100
S1, CRD1 <12 mo	21	84
S1, CRD1 ≥12 mo	29	94
Salvage 2	11	61
Salvage ≥3	8	57
Overall	77	80
MRD negativity	62/75	83
Salvage 1	50/56	**89**
Salvage ≥2	12/19	63
Early death	7	7

Jabbour E, et al. *JAMA Oncol*. 2018;4:230-234.

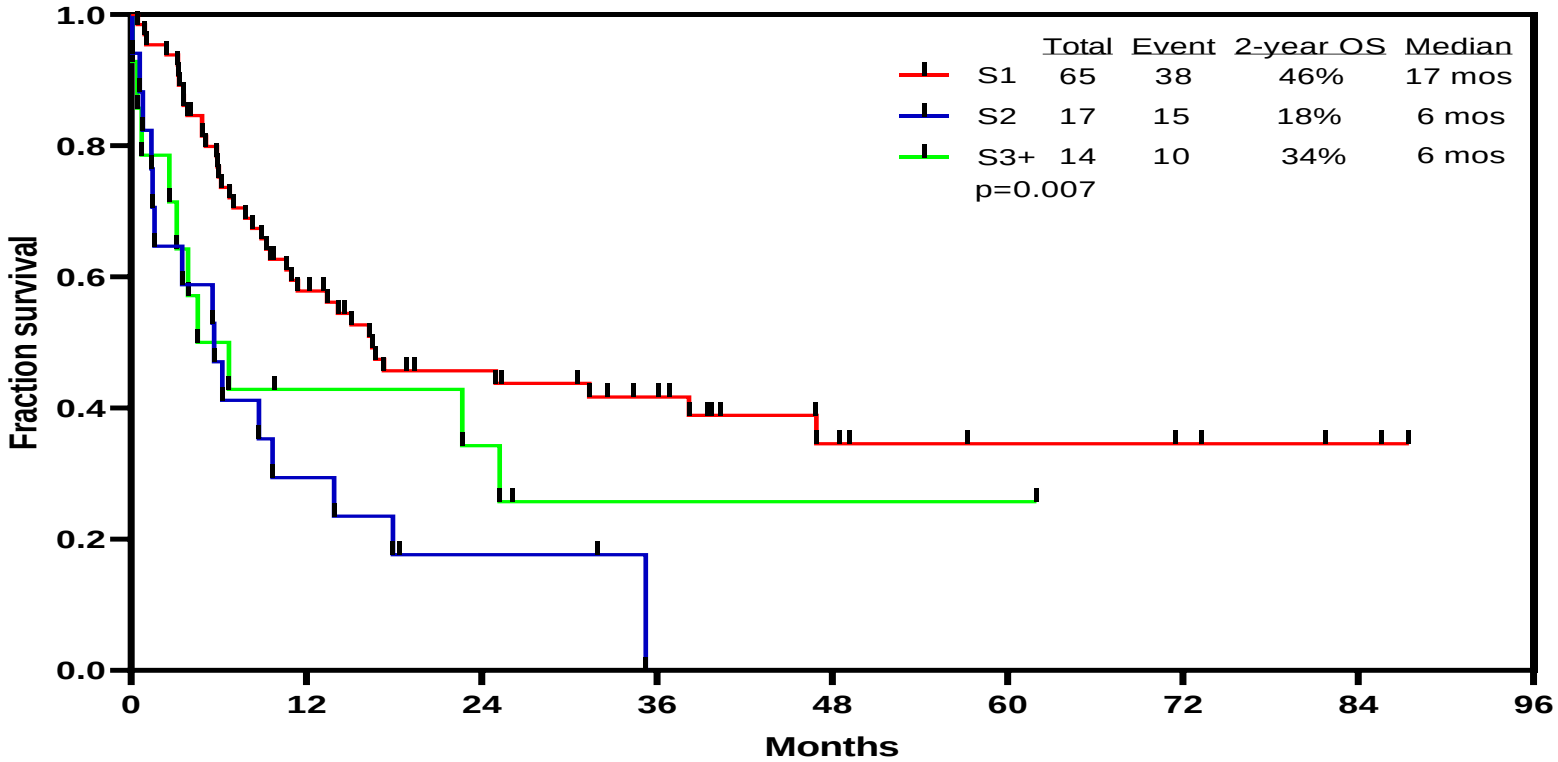
Mini-HCVD + Inotuzumab/Blinatumomab in R/R ALL





Jabbour E, et al. *JAMA Oncol*. 2018;4:230-234.

Mini-HCVD + INO ± Blinatumomab in R/R ALL: OS by Salvage Status



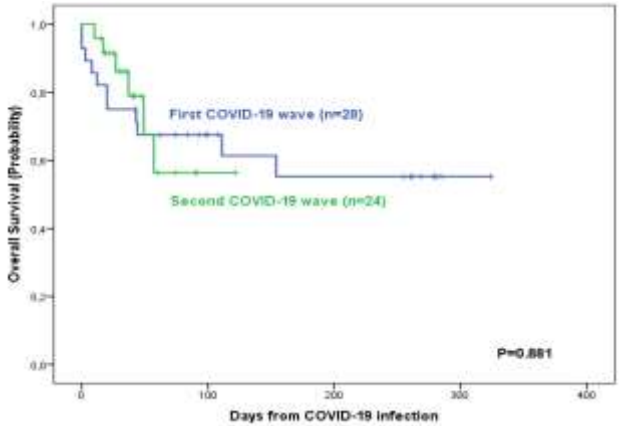
Sasaki K, et al. ASH 2018. Abstract 553; Jabbour E, et al. *JAMA Oncol*. 2018;4:230-234.

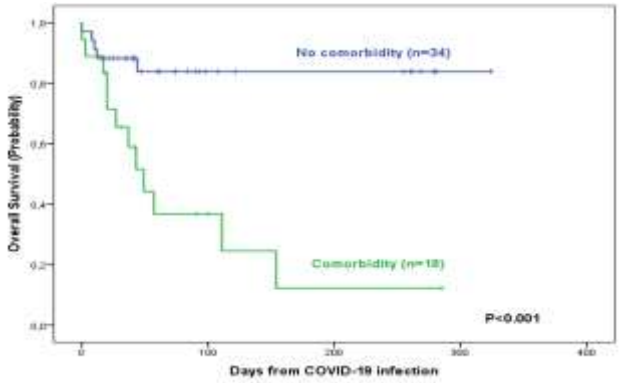
Conclusion

- Treatment of R/R elderly patients with ALL: unmet need
- Better approach for salvage therapy
  - Ph– ALL: attenuated chemotherapy + immunotherapy (INO, Blina)
  - Ph+ ALL
    - Third-generation TKI + immunotherapy
    - Third-generation TKI + BCL2 inhibitors
- Do not forget cell therapy
  - RIC alloHSCT
  - CAR T

Spanish Registry of ALL and COVID-19 Infection: Outcomes in First vs Second Pandemic Wave

	Overall (n = 52)	First COVID-19 Wave (n = 28)	Second COVID-19 Wave (n = 24)	*P* Value
COVID-19 infection resolution	36 (69)	18 (64)	18 (75)	.404
Infection onset-clinical recovery interval, days, median (range)	14 (2-47)	17 (2-47)	12.5 (5-39)	.095
Alive patients at close of follow-up	35 (67)	17 (61)	18 (75)	.274
Causes of death (n = 17)				
COVID-19 infection	10	6	4	
Pseudomonas sepsis and COVID-19 infection	3	2	1	
Leukemia progression and COVID-19 infection	2	2	0	.467
Leukemia progression	1	1	0	
ALL treatment-related mortality	1	0	1	
Infection onset-death interval, days, median (range)	20 (0-154)	20 (0-154)	32 (10-57)	.335





Ribera JM, et al. (submitted).

Spanish Society of Hematology: Recommendations for Vaccination in ALL

1) Patients under conventional chemotherapy

1) Once CR is obtained
2) Between consolidation cycles
3) At any time during maintenance

2) Patients treated with monoclonal antibodies (mAbs)

1) Anti-CD20: Delay vaccination until at least 3 months after the last dose
2) Bispecific monoclonal antibodies: Vaccination indicated due to vulnerability of these patients. Avoid overlapping with continuous infusion of blinatumomab
3) Immunoconjugated mAb: Priority for vaccination due to vulnerability of these patients

3) Patients treated with tyrosine kinase inhibitors: As other ALL patients

4) Patients in complete remission without active treatment

1) Vaccination as soon as possible

Manuscript in preparation.

Q

Question #1

The best approach to date in treatment of R/R Ph– ALL in elderly has been:

A. Inotuzumab as single drug
B. Blinatumomab as single drug
C. Attenuated chemotherapy + inotuzumab
D. Attenuated chemotherapy + ofatumumab
E. Allogeneic HSCT upfront

Q

Question #2

Venetoclax has demonstrated activity in:

A. Ph+ ALL only
B. Ph– ALL only
C. Ph+ and Ph– ALL
D. T-ALL
E. C and D answers are correct

Global Leukemia Academy

Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in adult and elderly patients

Presenter: Shaun Fleming

Panelists: Elias Jabbour, Shaun Fleming, Aaron Logan, and José Maria Ribera

APTITUDE HEALTH

Case – Mr G.L.

Mr G.L. – introduction

- Mr G.L. is a 39-year-old man presenting with newly diagnosed Ph– B-precursor acute lymphoblastic leukaemia
- Background history of moderate obesity
- Received induction with the FRALLE93 protocol (a paediatric-inspired regimen)
- Attains a complete remission – however, at the end of consolidation phase he is MRD+ at a level of 0.15%
- Has an unrelated donor available to him

Q

Therapeutic options?

- Proceed immediately to allogeneic stem cell transplant?
- Continue chemotherapy with the FRALLE93 protocol?
- Switch to salvage with FLAG + Ida?
- Blinatumomab?

Approaches to MRD+ disease – the GMALL experience

- Review of treated patients with either molecular failure or relapse on the GMALL 07/03 protocol
  - Poor response to chemotherapy as molecular salvage
  - AlloHSCT able to rescue a proportion of patients
    - Survival better in patients who had "MRD-directed" therapy pre-alloHSCT
      - 63% vs 34% (*P* = .002)
  - Blinatumomab had a very high MRD response rate
    - Relatively early data with few patients treated
- Targeted therapies should be delivered early to avoid cytologic relapse
- Current GMALL protocols amended for early administration of MRD-directed therapy

Table: Molecular Response in MolF Pts with MolF after Different Consolidation Cycles and Immediate SCT

Therapy	B-precursor				T-ALL			
	N	MolCR	MolF	Cytologic Relapse	N	MolCR	MolF	Cytologic Relapse
Molecular Failure								
MTX/PEG-ASP	**49**	**12** (24%)	**32** (65%)	**5** (10%)	**14**	**7** (50%)	**5** (36%)	**2** (14%)
Other Chemo	**7**	**1** (n.c.)	**4** (n.c.)	**2** (n.c.)	**3** (n.c.)	**0** (n.c.)	**2** (n.c.)	**1** (n.c.)
Nelarabine	0	0	0	0	**6** (n.c.)	**3** (n.c.)	**3** (n.c.)	**0** (n.c.)
Blinatumomab	**11**	**10** (91%)	**1** (9%)	**0** (0%)	0	0	0	0
Total Non SCT	**67**	**23** (34%)	**37** (55%)	**7** (10%)	**23**	**10** (43%)	**10** (43%)	**3** (13%)
SCT	**28**	**21** (75%)	**6** (21%)	**1** (4%)	**24**	**17** (71%)	**7** (29%)	**0** (0%)
Molecular Relapse								
Other Chemo	**26**	**11** (42%)	**12** (46%)	**3** (11%)	**8** (n.c.)	**2** (n.c.)	**4** (n.c.)	**2** (n.c.)
Blinatumomab	**15**	**15** (100%)	**0** (0%)	**0** (0%)				
Nelarabine					**6** (n.c.)	**3** (n.c.)	**3** (n.c.)	**0** (n.c.)

n.c. : Percentages not calculated in cohorts of N=10 and lower.

Definitions

MolCR: No MRD detection with minimum sensitivity of 10^{-4}

MolF: MRD positive $>10^{-4}$

MRDneg: No MRD detection but insufficient sensitivity

MRDpos: MRD detection $< 10^{-4}$ or non quantifiable MRD

MolR: Reoccurence of MRD $>10^{-4}$ beyond wk 16 after prior molCR

Goekbuget N, et al. ASH 2017.

Is transplant still required after blinatumomab for MRD eradication?

- While overall survival appeared similar irrespective of whether patients went to transplant or not, the devil is in the details

Outcome for HSCT was better in those who attained MRD response (median OS NR vs 16.1 months)

The majority of long-term survivors who did not receive an alloHSCT post-blinatumomab received an alloHSCT with later relapse

Overall survival was better with alloHSCT in younger patients (<39 years) following MRD-directed therapy

Goekbuget N, et al. ASH 2018.

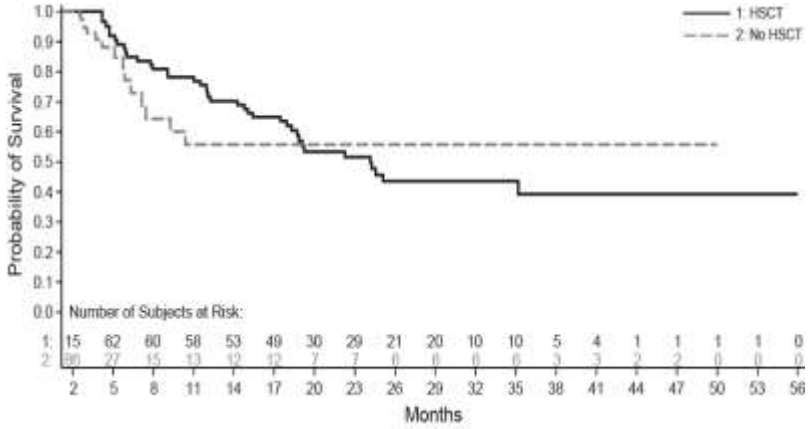
Mr G.L. (continued)

- Received his first cycle of blinatumomab
- Achieved MRD negativity
- Admitted for a second cycle
- Planned for unrelated donor transplant . . .

“I feel great now, much better than when I had chemotherapy. I don’t want a transplant"

Can he avoid transplant?

Figure S5. Simon-Makuch plot of relapse-free survival among all patients in the full analysis set by HSCT status



- Maybe
- Transplant would be high-risk in G.L.’s case, given his obesity
- Most relapses are early if they do occur

Approach to G.L.

- Discussed the pros and cons of transplantation in this setting
- Decided not to proceed to transplant in CR1
- Completed 4 cycles of blinatumomab
- Maintenance therapy with POMP for 2 years
  - Three monthly bone marrow aspirates for MRD assessment
- Now completed maintenance and off all therapy for 1 year – remains in ongoing remission

Global Leukemia Academy

Educational ARS Questions

Elias Jabbour

APTITUDE HEALTH

Q

Question 1

What age group is considered elderly ALL patients?

a) ≥50 years
b) ≥55 years
c) ≥60 years
d) ≥65 years
e) ≥70 years

Q

Question 2

Which of the following is NOT true for treating ALL?

a) Inotuzumab and blinatumomab plus chemotherapy has produced 90% CR rates in salvage therapy and in first line in older patients
b) Blinatumomab and ponatinib can be used as a chemotherapy-free regimen in Ph+ ALL
c) MRD-negative CR does not correlate strongly with outcome
d) Since 1999, median survival for ALL patients older than 60 has been increasing with each successive decade

Global Leukemia Academy

Break

APTITUDE HEALTH

Global Leukemia Academy

Educational ARS Questions

Naval Daver

APTITUDE HEALTH

Q

Question 1 (AML)

Which patients were not included in the VIALE-A study:

a) Patients >75 years of age
b) Patients <75 years of age with ECOG PS 3
c) Patients <75 years of age with significant cardiac co-morbidity
d) Patients <75 years of age with significant pulmonary comorbidities
e) Patients <75 years of age with adverse cytogenetics

Q

Question 2 (AML)

Which of the following is not true regarding HMA + venetoclax in AML:

a) The CR/CRi with HMA+VEN in the VIALE-A was >65%
b) HMA+VEN improved median OS compared with HMA alone
c) Lab or clinical TLS is not seen with HMA+VEN in AML
d) The recommended daily dose of venetoclax (without azoles) was 400mg PO Qday in VIALE-A study
e) Neutropenia is commonly seen with HMA+VEN regimen

Global Leukemia Academy

Personalized induction and maintenance approaches for AML

Naval Daver

APTITUDE HEALTH

Personalized induction and maintenance approaches for AML

APRIL 2021

Naval Daver, MD
Director, Leukemia Research Alliance Program,
Associate Professor
Department of Leukemia
MD Anderson Cancer Center

Clinical Applications of Molecular Studies in AML

- ***FLT3* mutations – add *FLT3* inhibitor (midostaurin, sorafenib, quizartinib, gilteritinib), consider allo-SCT**
- ***IDH1-2* mutations – add *IDH* inhibitor: enasidenib (AG-221/IDH2 inhibitor), ivosidenib (AG-120/IDH1 inhibitor)**
- ***NPM1* mutation in diploid CG – Ara-C sensitivity, VEN sensitivity**
- ***TP53* mutation – consider decitabine 10 days ± others (GO, venetoclax); new agents (APR, CD47) refer to allo-SCT**
- ***RAS* mutations – no targetable therapies in AML, common resistance to VEN, FLT3i, IDHi; consider clinical trials**

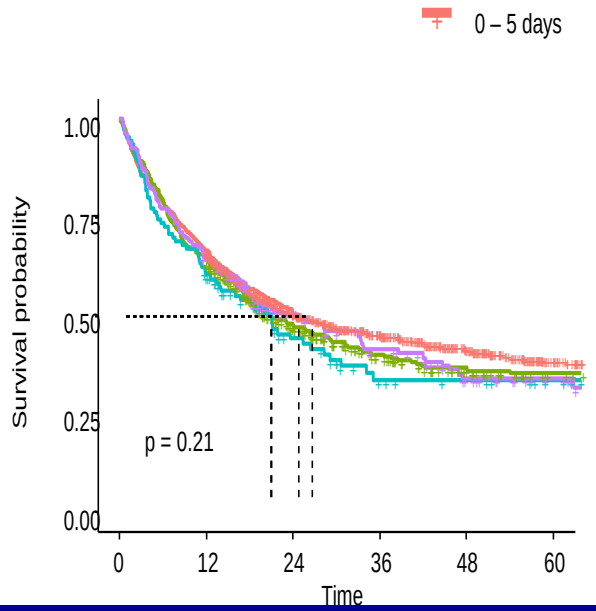
National Comprehensive Cancer Network. NCCN Guidelines. Acute Myeloid Leukemia v2.2018.

Time from diagnosis to treatment does not affect outcome in intensively treated patients with newly diagnosed acute myeloid leukemia

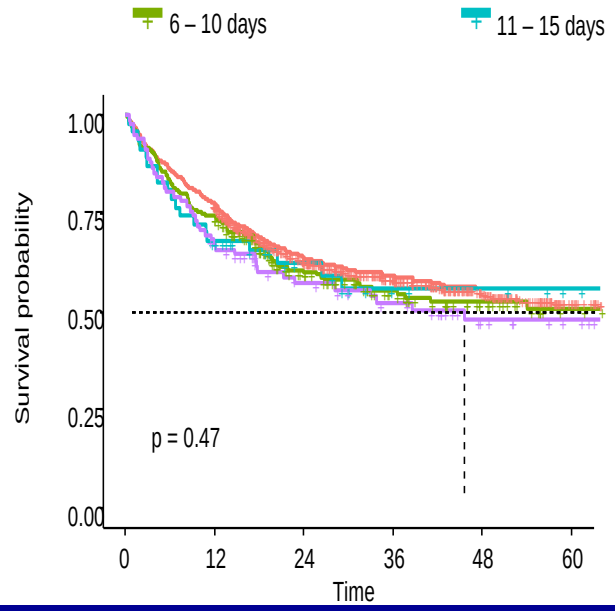
Röllig C, Kramer M, Schliemann C, Mikesch JH, Steffen B, Krämer A, Sauer T, Hänel M, Herbst R, Schäfer-Eckart K, Noppeney R, Jost E, Brümmendorf TH, Krause S, Kunzmann V, Einsele H, Scholl S, Hochhaus A, Fransecky L, Kaufmann M, Neubauer A, Niemann D, Schaich M, Frickhofen N, Kiani A, Heits F, Krümpelmann U, Kaiser U, Kullmer J, Wass M, Klein S, Stölzel F, von Bonin M, Middeke JM, Thiede C, Schetelig J, Ehninger GE, Baldus CD, Müller-Tidow C, Platzbecker U, Serve H, Bornhäuser M

TDT Groups: Overall Survival

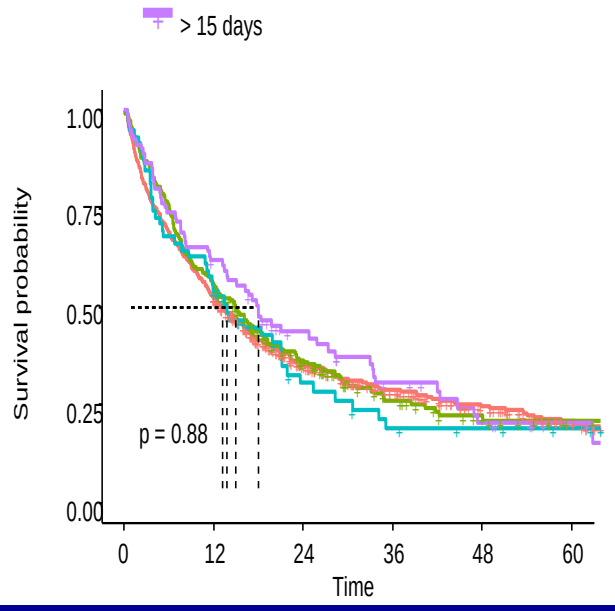
All ages



≤60 years



>60 years



No impact of TDT on CR, early death, and OS in multivariable models.
In practice, would avoid delays >5–7 days if possible.

1. APL: ATRA + As_2O_3 Without Chemotherapy in APL: MD Anderson Experience

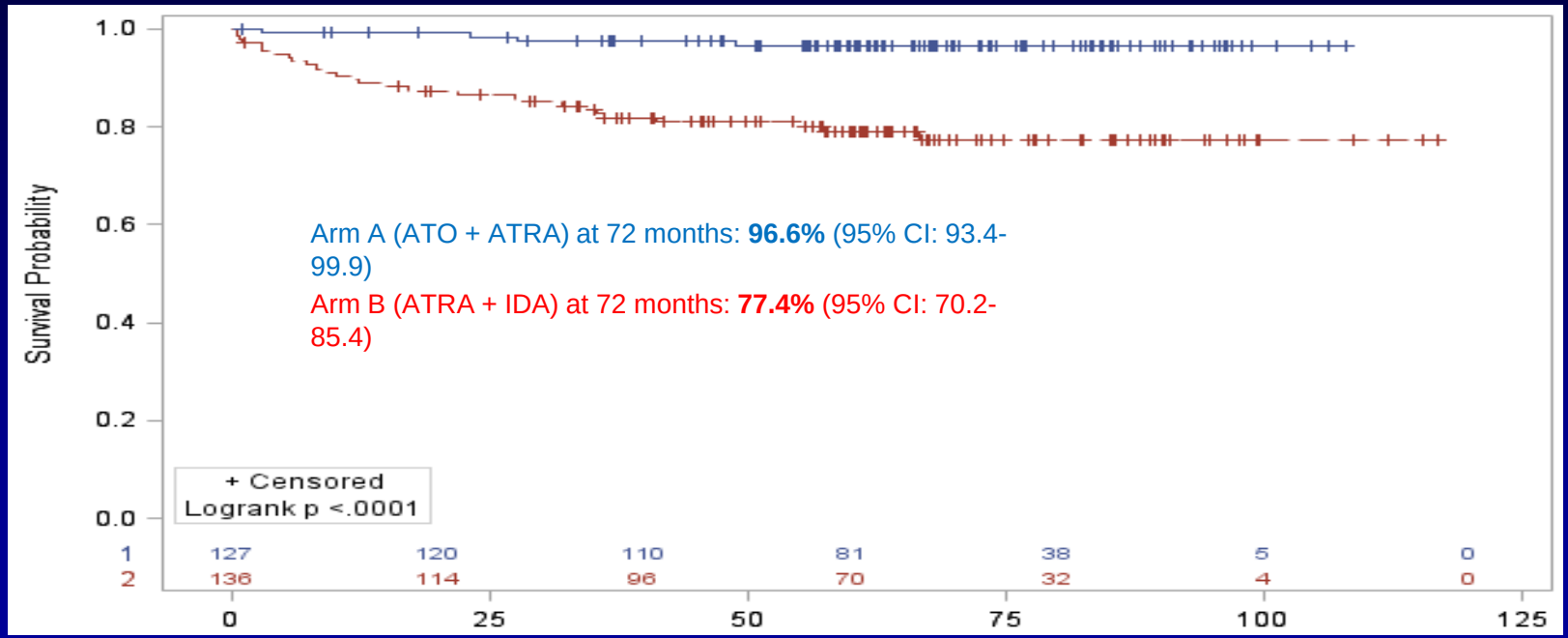
- **Induction**
  - ATRA 45 mg/m^2/D until CR
  - As_2O_3 0.15 mg/kg/D until CR
  - Gemtuzumab (GO) 9 mg/m^2 × 1 if WBC >10 × 10^9/L
- **Maintenance**
  - ATRA 45 mg/m^2/D × 2 wk Q mo × 6
  - As_2O_3 0.15/kg/D × 4 wk Q2 mo × 3
  - GO in PCR+

Ravandi F, et al. *J Clin Oncol*. 2009;27:504-510.

APL0406: Updated Event-Free Survival

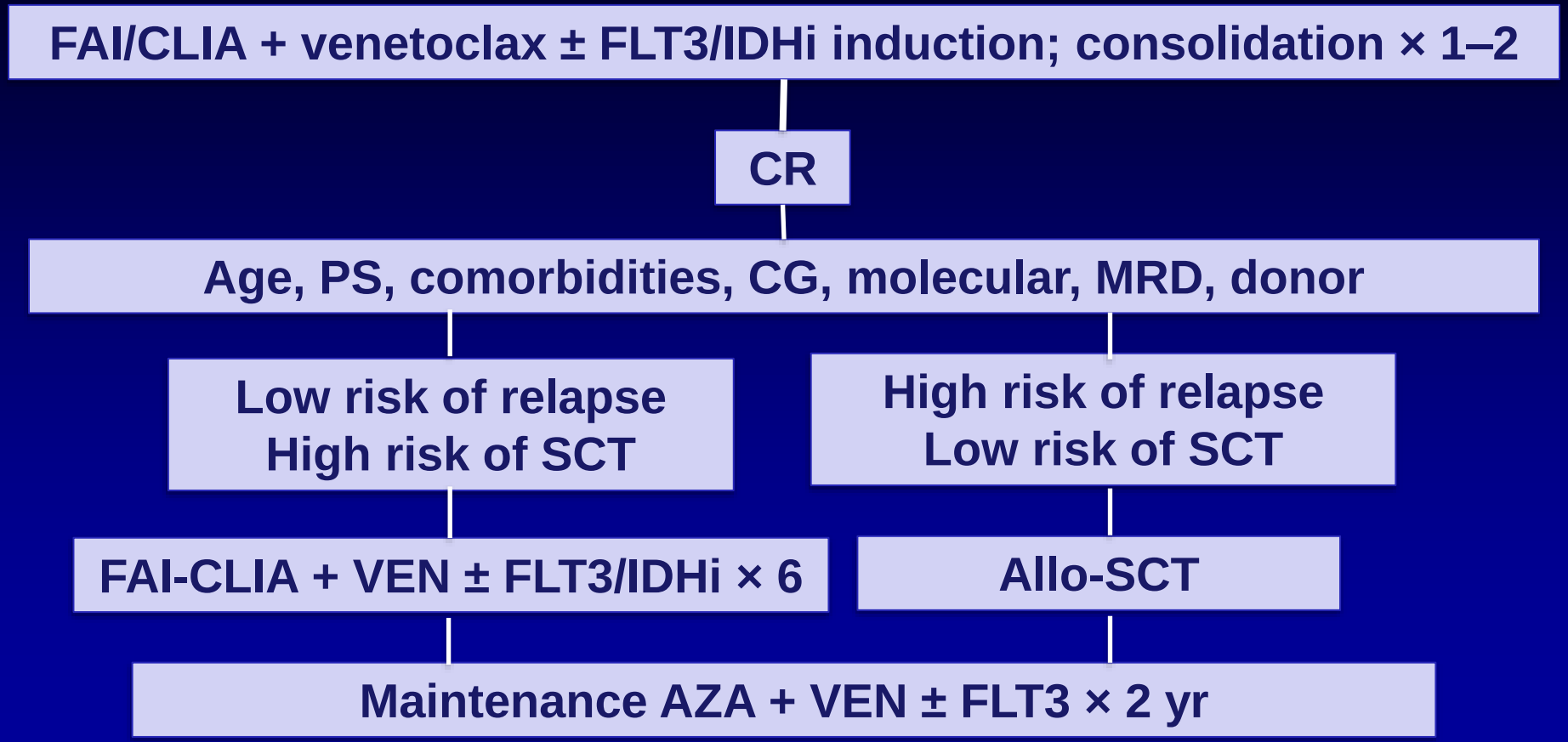
276 pts; follow-up 67 months

Event-free survival

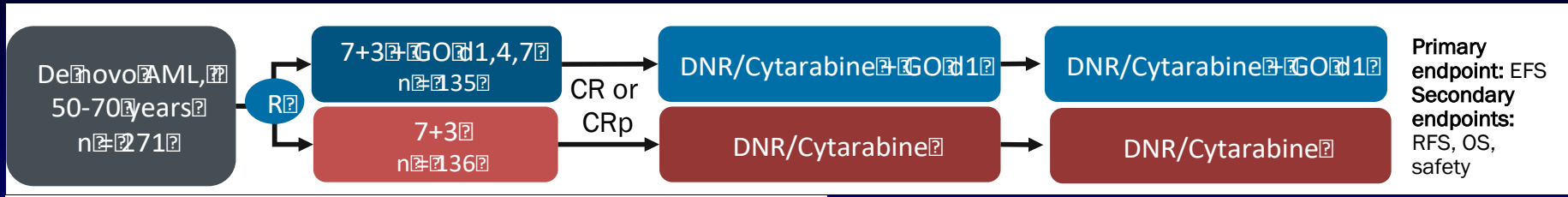


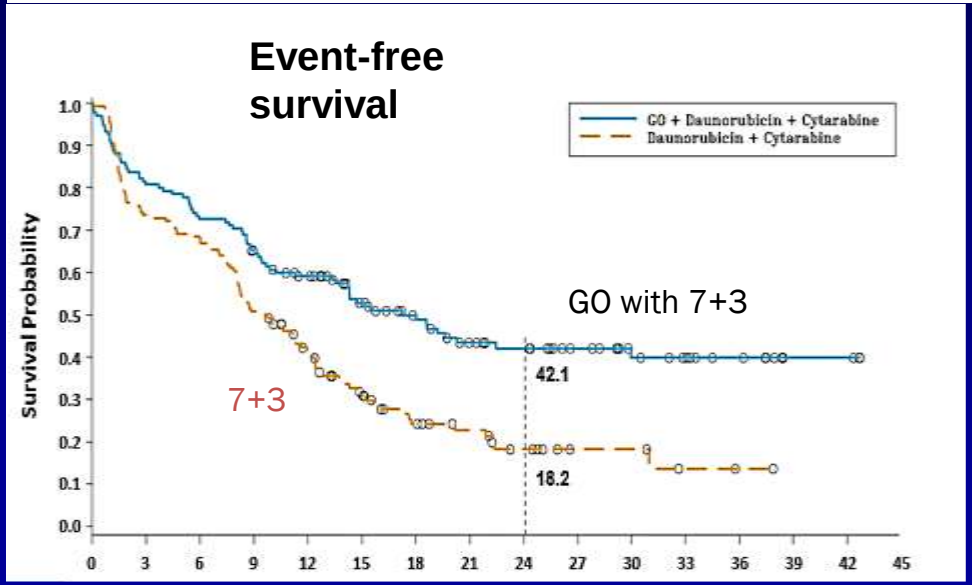
Intl Symposium on APL, Rome, Sept 2017 (unpublished)

Since 2009: Therapy of Younger AML at MD Anderson in 2020+



2. CD33-Targeted Therapy – Gemtuzumab Ozogamicin
ALFA-0701: Phase III Trial of GO Plus 7+3 vs 7+3



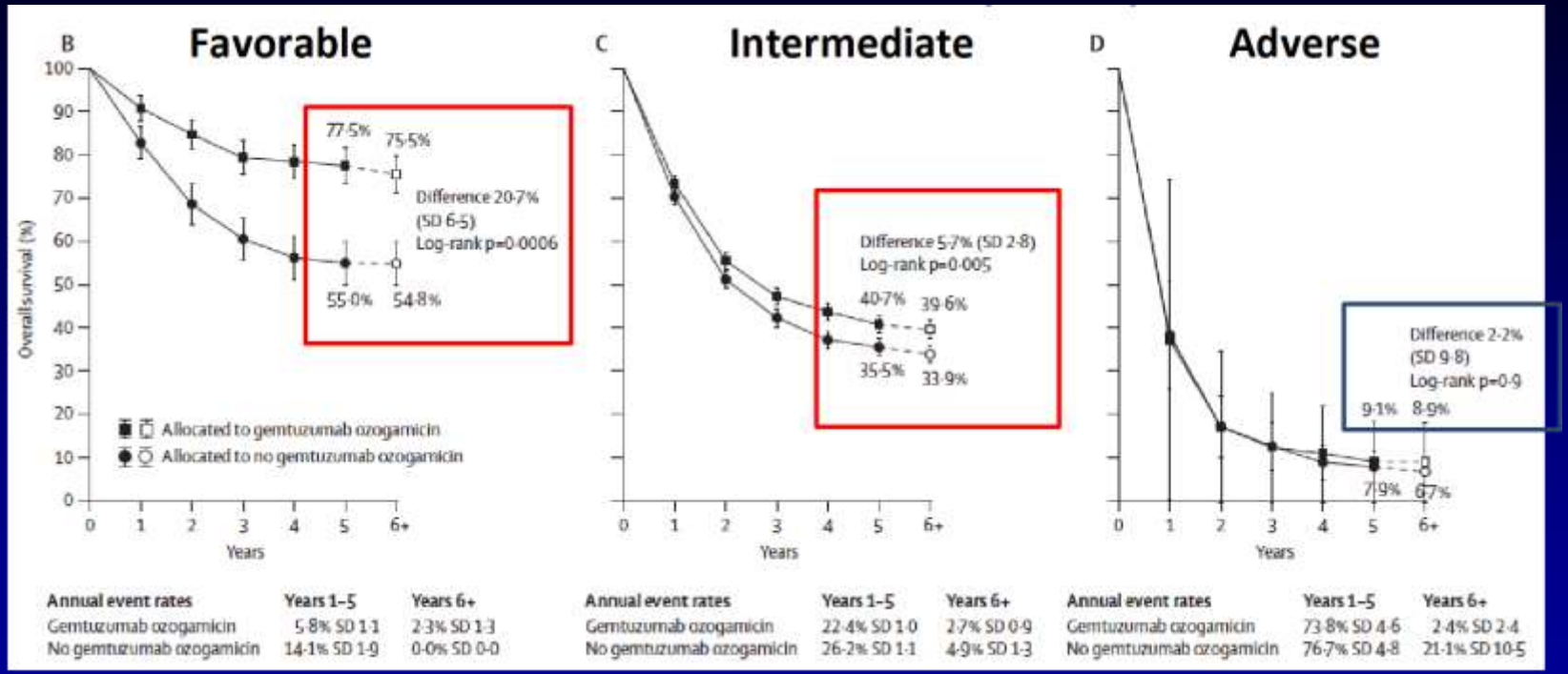


- GO better for favorable/intermediate risk

- Increased grade 3 hemorrhage
- Prolonged thrombocytopenia
- No increase in early mortality (3.8% vs 2.2%) with GO
- VOD 4.6% (GO/7+3) vs 1.5% (7+3)

Lambert J, et al. *Haematologica.* 2019;104(1):113-119.

Meta-analysis of Gemtuzumab Ozogamicin Plus 7+3



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Meta-analysis of overall survival of 3325 AML patients stratified by cytogenetic risk

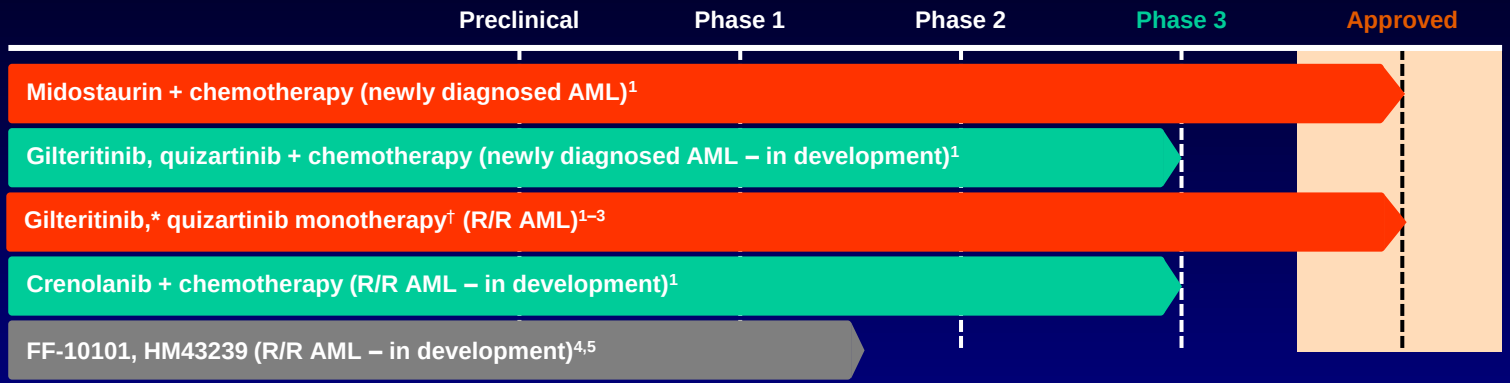
Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

MDACC: FLAG-GO in CBF AML

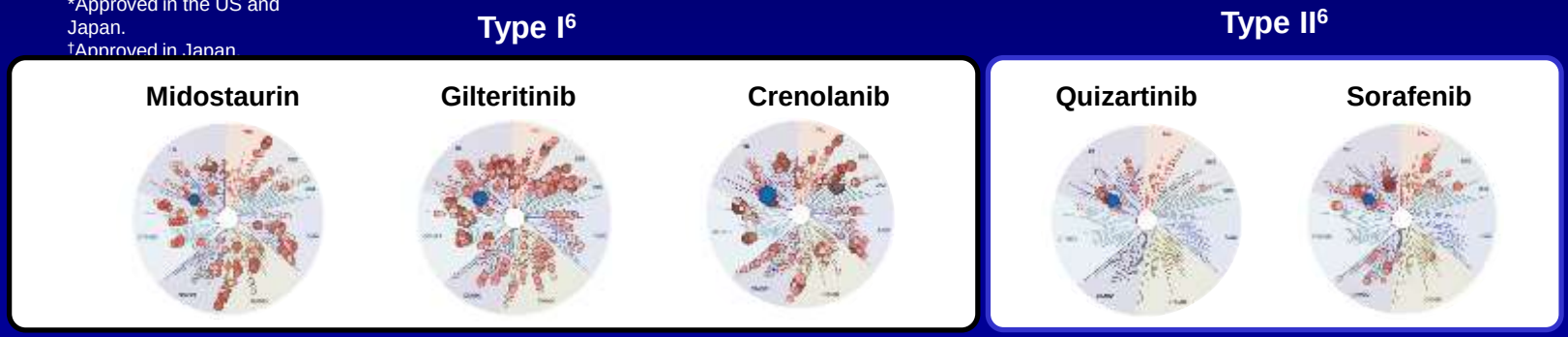
- Induction: fludarabine (FL) 30 mg/m^2 days 1–5; cytarabine (A) 2 g/m^2 IV days 1–5; gemtuzumab ozogamicin (GO) 3 mg/m^2 day 1; G-CSF (G) 5 μg/kg day –1 until neutrophil recovery (can use peg-filgrastim 6 mg × 1 day 4)
- Consolidation: FL and A for 4 (amended to 3) days, GO (in cycle 2/3 and 5/6) and G as in induction for 6 cycles
- Peg–G-CSF instead of G-CSF allowed beyond day 5 (induction) or day 4 (consolidation)

Replaced GO with low-dose idarubicin 6 mg/m^2 days 3 and 4 after patient 50

3. Current and Future Induction Approaches for *FLT3*-Positive AML

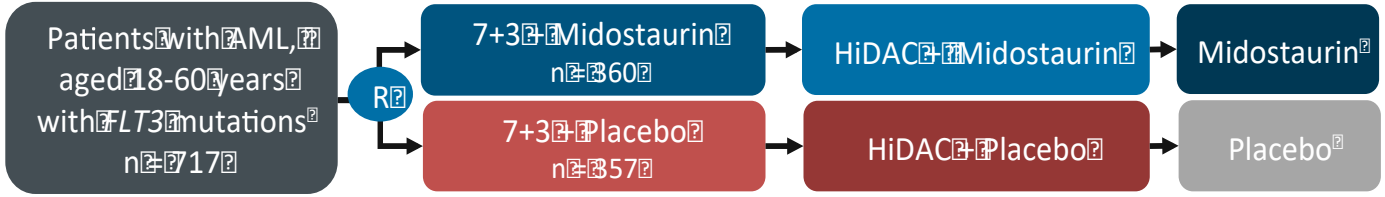


*Approved in the US and Japan.
†Approved in Japan

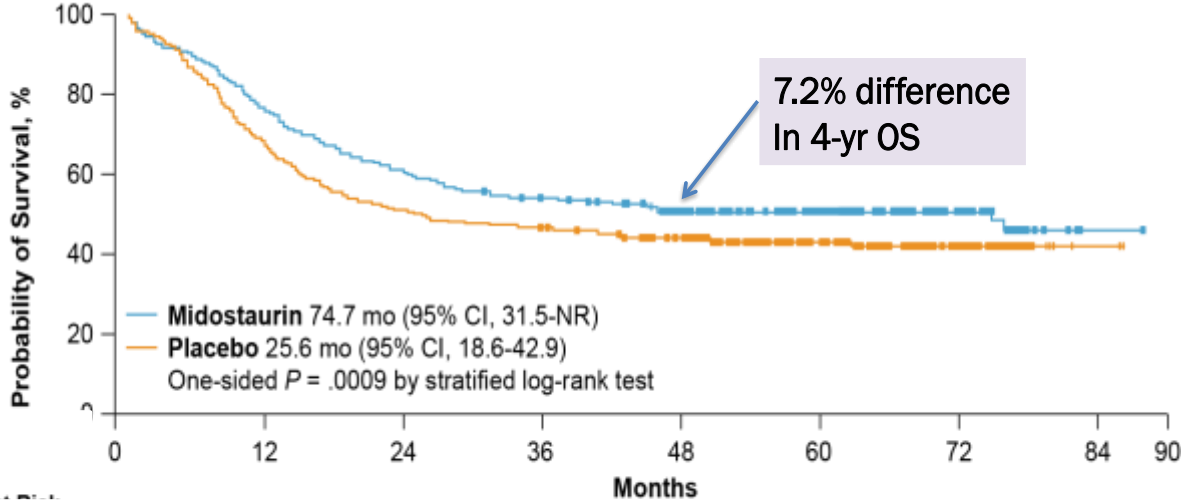


1. Short NJ, et al. *Ther Adv Hematol.* 2019;10:2040620719827310; 2. Daiichi Sankyo. Press release. Available at: https://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/007030.html; 3. Astellas. Press release. Available at: https://www.astellas.com/en/news/14271; 4. ClinicalTrials.gov. NCT03194685. Available from: https://clinicaltrials.gov/ct2/show/NCT03194685; 5. ClinicalTrials.gov. NCT03850574. Available from: https://clinicaltrials.gov/ct2/show/NCT03850574; 6. Aikawa T, et al. Presented at the 2019 Annual Meeting of the AACR; March 29–April 03, 2019; Atlanta, GA. Abstract 131.8

Midostaurin Plus 7+3 vs 7+3 in De Novo *FLT3*-Mutant AML

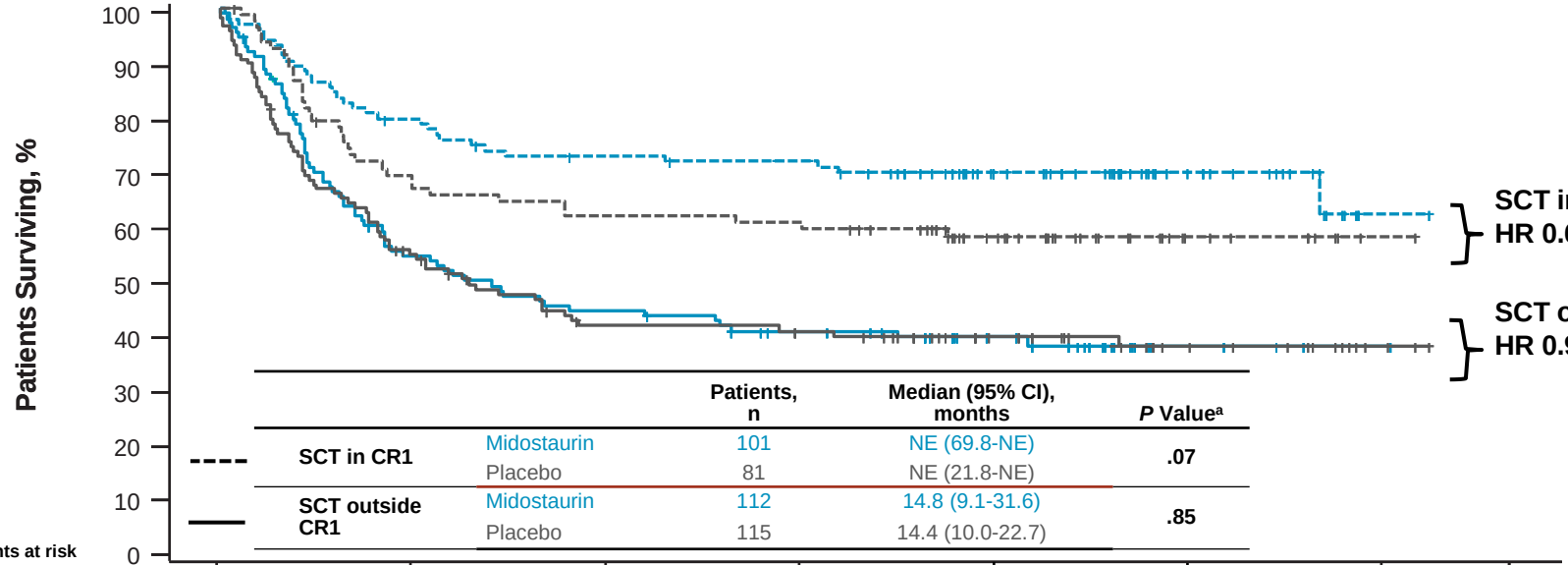


Primary endpoint: OS
Secondary endpoints: EFS, OS, CR, DFS



Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

OS, Posttransplant With 3+7 Plus Mido vs 3+7 Plus Placebo



		Patients, n	Median (95% CI), months	*P* Value[a]
SCT in CR1	Midostaurin	101	NE (69.8-NE)	.07
	Placebo	81	NE (21.8-NE)	
SCT outside CR1	Midostaurin	112	14.8 (9.1-31.6)	.85
	Placebo	115	14.4 (10.0-22.7)	

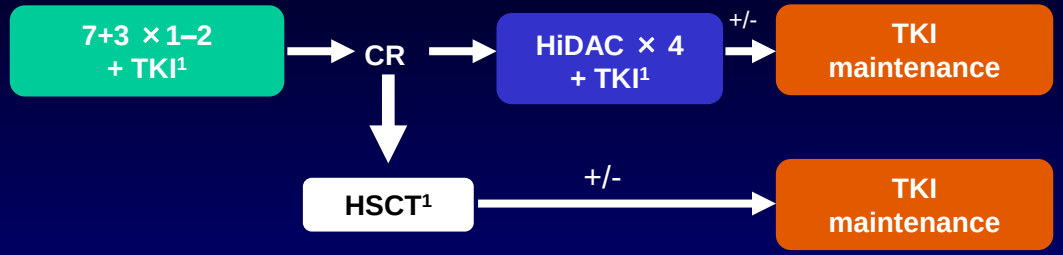
Patients at risk

SCT in CR1					
Midostaurin	101	71	63	21	0
Placebo	81	50	45	12	0
SCT outside CR1					
Midostaurin	112	49	36	5	0
Placebo	115	47	37	13	0

*Stratified on *FLT3* subtype; two-sided, long-rank *P* value.

Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

Combining FLT3 Inhibitors With Standard Therapies
Frontline Intensive Chemotherapy Plus FLT3 Inhibitor

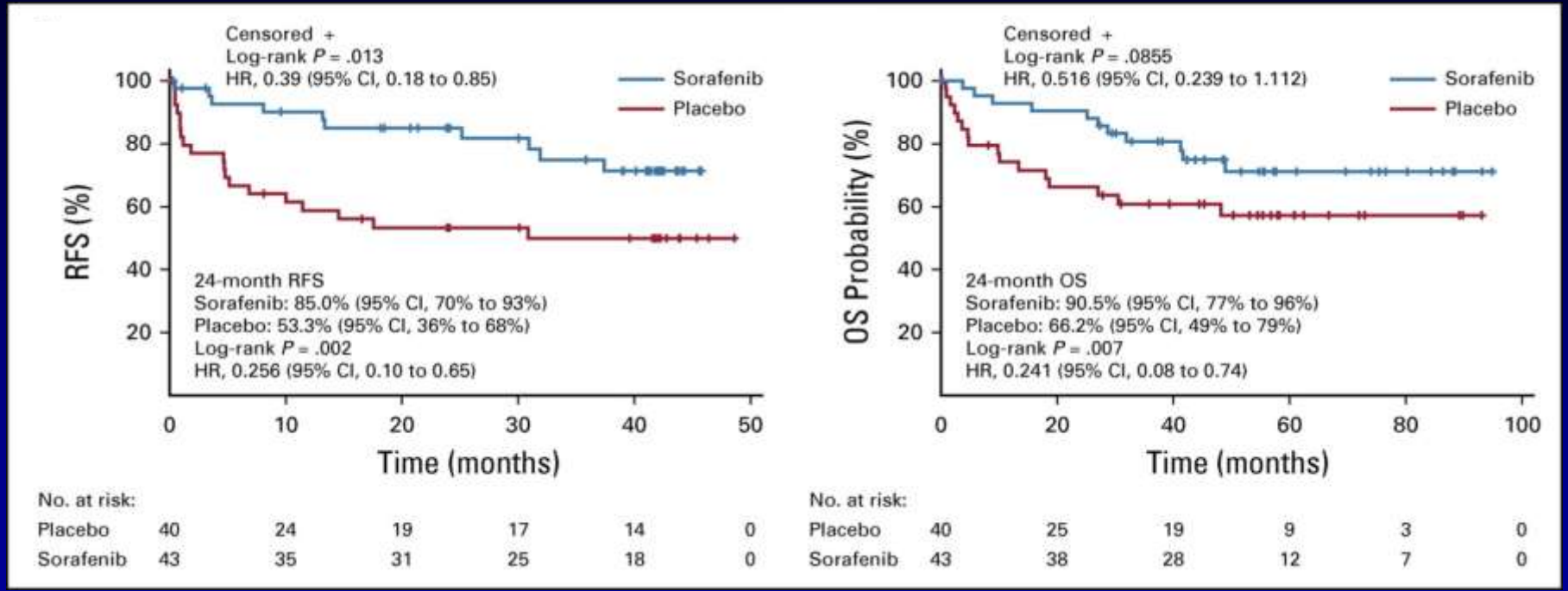


RATIFY[2]	Midostaurin (n = 360)	Placebo (n = 357)	*P* Value*
CR by day 60, n (%)	212 (59)	191 (53)	.15
CR in induction/ consolidation, n (%)	**239 (66)**	211 (59)	.045
Days to CR, median (range)	37 (20–99)	36 (20–112)	

Second-Generation FLT3 Inhibitor	CRc Rate, n (%)
Gilteritinib plus 7+3[3]	31/33 (94)
Crenolanib plus 7+3[4]	24/25 (96)
Quizartinib plus 7+3[5]	16/19 (84)†

*_P_ value is 2-sided and was calculated with the use of Fisher's exact test; †Includes CRc/MLFS.
CR, complete remission; HiDAC, high-dose cytarabine; HSCT, hematopoietic stem cell transplantation; TKI, tyrosine kinase inhibitor.
1. American Cancer Society. Treatment of AML. Available at: https://www.cancer.org/cancer/acute-myeloid-leukemia/treating/typical-treatment-of-aml.html. Accessed October 2019; 2. Stone RM, et al. *Blood.* 2015;126:abstract 6; 3. Pratz K, et al. ASH 2017. Abstract 722; 4. Wang ES, et al. ASH 2016. Abstract 1071; 5. Altman JK, et al. *Am J Hematol.* 2018;93:213-221.

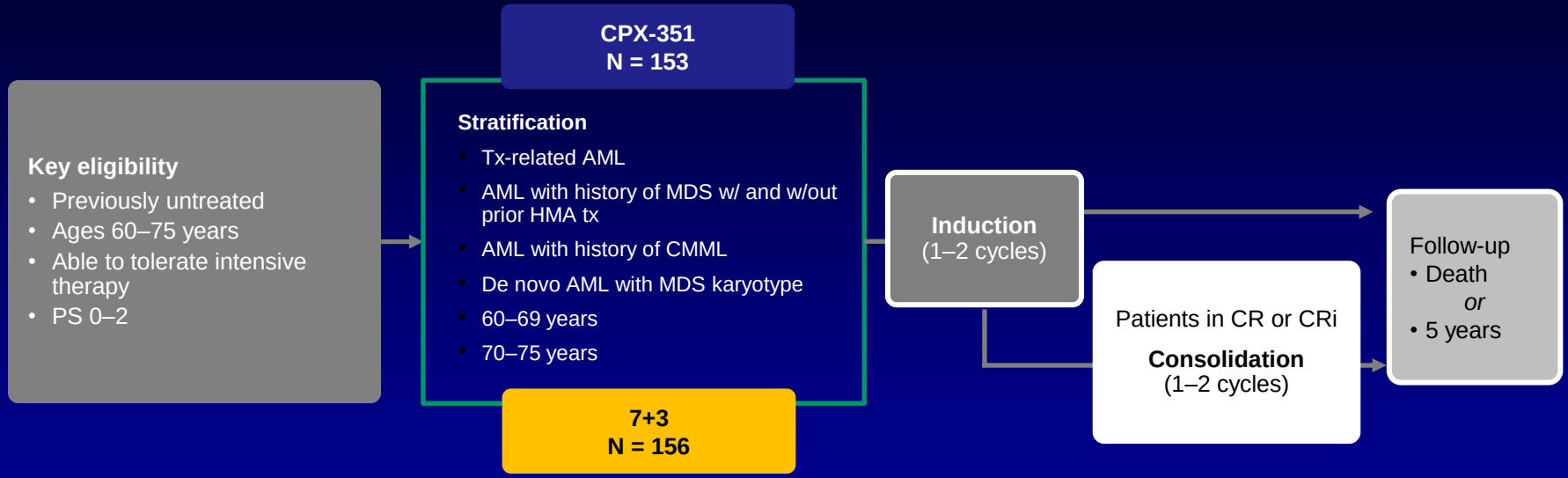
RFS and OS in FLT3+ AML in CR After HCT Treated With Sorafenib vs Placebo (SORMAIN)



Burchert A, et al. *J Clin Oncol.* 2020;38:2993-3002.

4. AML With Myelodysplasia-Related Changes (AML-MRC)

Phase III Study of CPX-351 vs 7+3 in Older Patients With Newly Diagnosed High-Risk AML

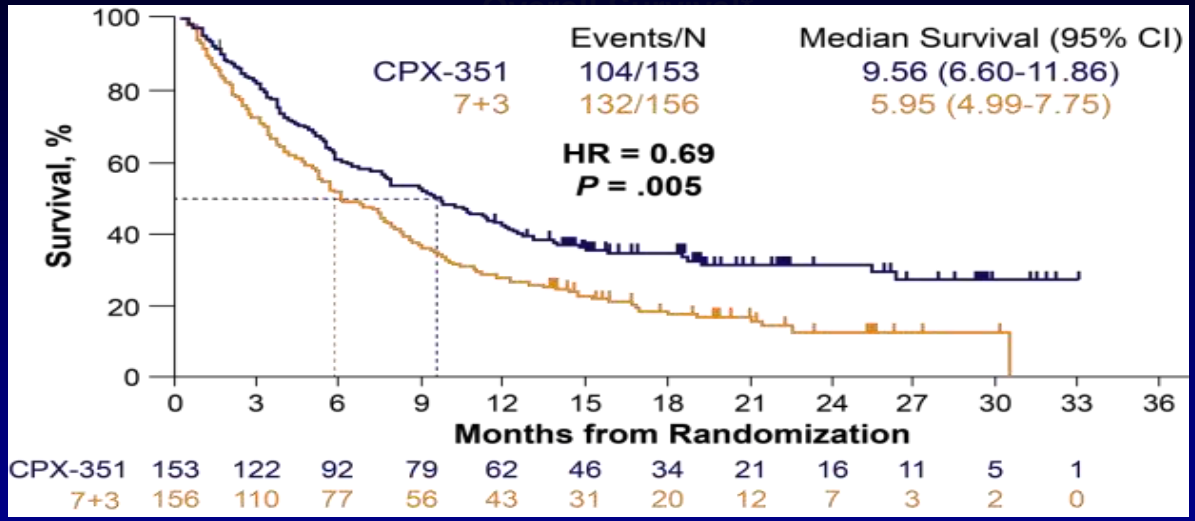


Primary endpoint: overall survival

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete remission; Cri, complete remission with incomplete platelet recovery; HMA, hypomethylating agents; MDS, myelodysplastic syndromes; PS, patient performance status; Tx, therapy.

Lancet J, et al. ASCO 2016. Abstract 7000.

CPX-351 vs 7+3 in Newly Diagnosed Secondary AML: Clinical Outcomes

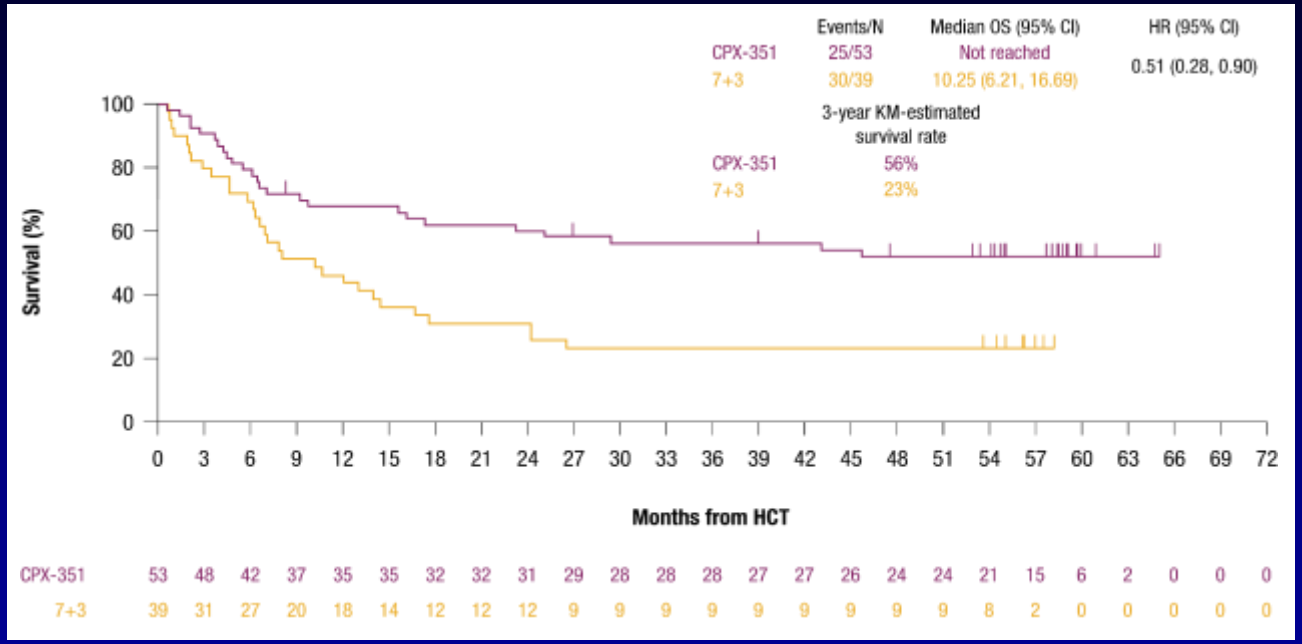


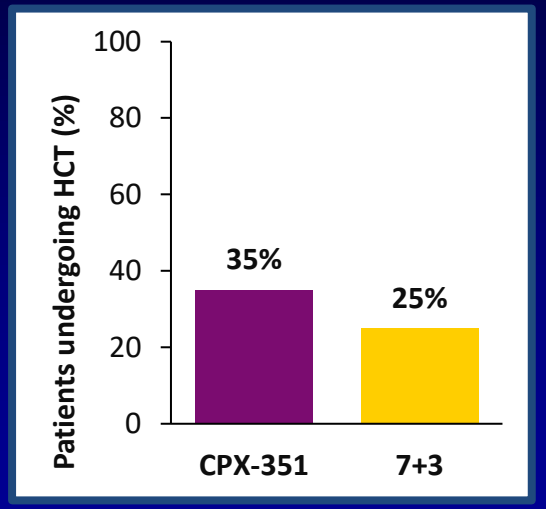
	CPX-351 (n = 153)	7+3 (n = 156)	Odds Ratio	*P* Value
CR + CRi	**47.7%**	**33.3%**	**1.77 (1.11, 2.81)**	**.016**
HCT rate	34.0%	25.0%	1.54 (0.92, 2.56)	.098
Deaths ≤60 days*	**13.8%**	**21.8%**		

*Kaplan-Meier estimate.

Medeiros BC, et al. ASH 2016; Abstract 902.

Overall Survival Landmarked From the HCT Date (long-term follow-up of CPX351 vs 3+7 phase III)





Kaplan-Meier–estimated survival rate landmarked from the date of HCT was >50% at 3 and 5 years for patients treated with CPX-351

Lancet J, et al. ASH 2020. Abstract 635.

5. Novel Intensive Therapy Approaches: Nonmolecular or Cytogenetic Targeted Groups – FLAG-IDA-VEN: Study Cohorts and Treatment Schedule

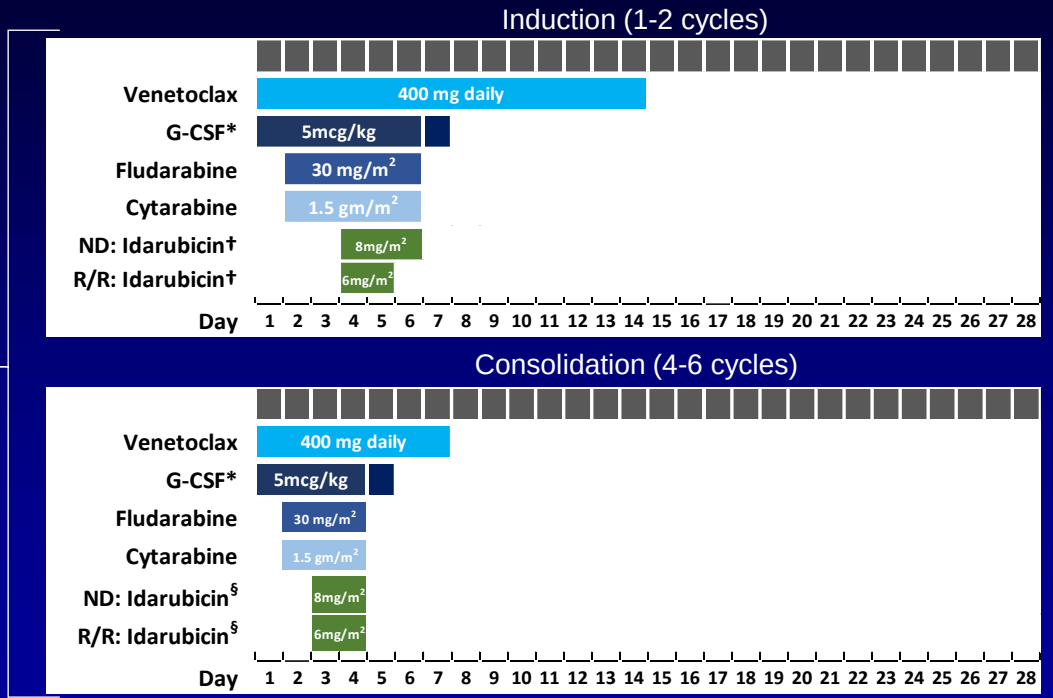
Phase 1b	Phase 2A	Phase 2B
R/R AML	ND AML	R/R AML
N = 16	N = 29	N = 23

Induction	Consolidation
Venetoclax 400 mg D1-14	Venetoclax 400 D1-7
G-CSF D1-6	G-CSF D1-4
Pegfilgrastim or biosimilar D7	Pegfilgrastim or biosimilar D5
Fludarabine 30 mg/m^2 D2-6	Fludarabine 30 mg/m^2 D2-4
Cytarabine 1.5 gm/m^2 D2-6	Cytarabine 1.5 gm/m^2 D2-4
ND: Idarubicin 8 mg/m^2 D4-6	ND: Idarubicin 8 mg/m^2 D3-4
R/R: Idarubicin 6 mg/m^2 D4-5	R/R: Idarubicin 6 mg/m^2 D3-4

Phase 1b		Phase 2
Cytarabine 2 gm/m^2	RP2D*	**Cytarabine 1.5 gm/m^2**
Venetoclax D1-21		**Venetoclax D1-14**

*5/6 initially enrolled phase Ib patients developed bacteremia/sepsis with phase Ib dosing

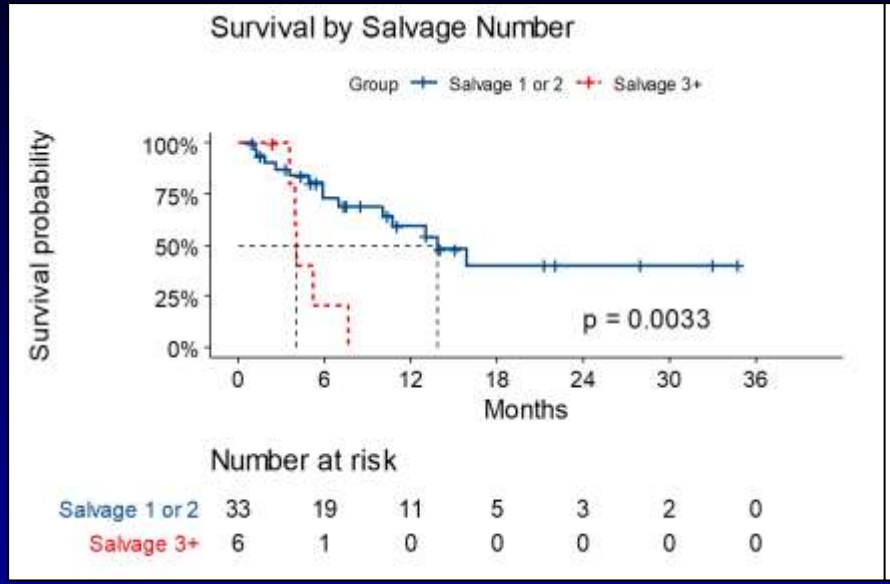
Phase 2 Induction/Consolidation Schedule

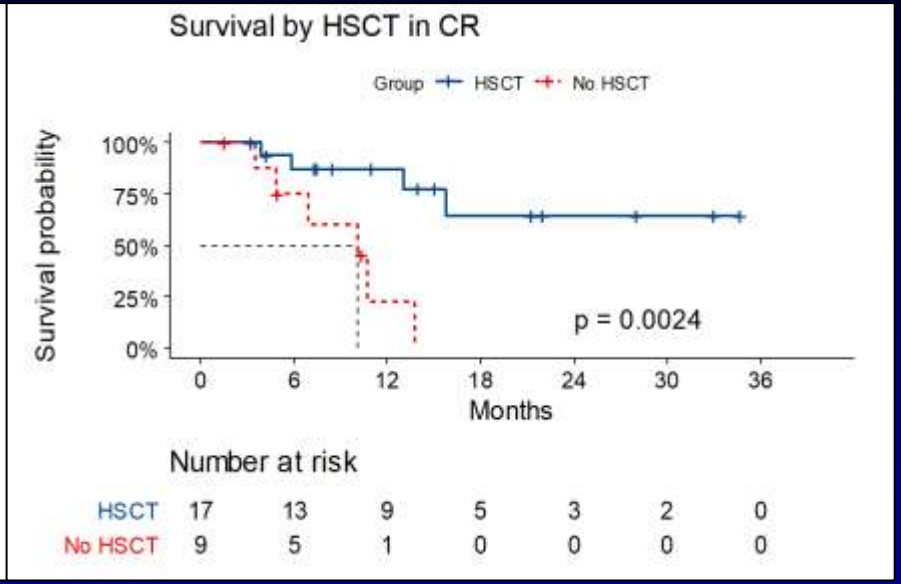


*G-CSF: 5 mcg/kg the day prior to and days of IV chemotherapy followed by 1 dose of pegfilgrastim or biosimilar each 28 D cycle.
†Induction: ND AML = Idarubicin 8 mg/m^2 days 4–6; R/R AML = Idarubicin 6 mg/m^2 days 4 and 5.
§Consolidation: Idarubicin permitted on days 3 and 4 in 2 postremission cycles (ie, C2 or C3 and C5 or C6) at physician discretion.

Lachowiez C, et al. ASH 2020. Abstract 332.

FLAG-IDA-VEN: R/R AML Outcomes

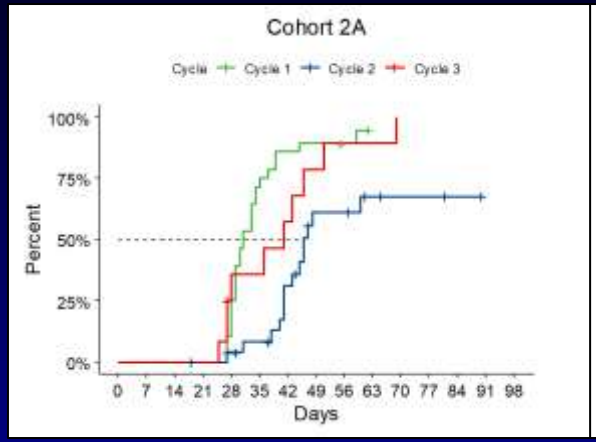


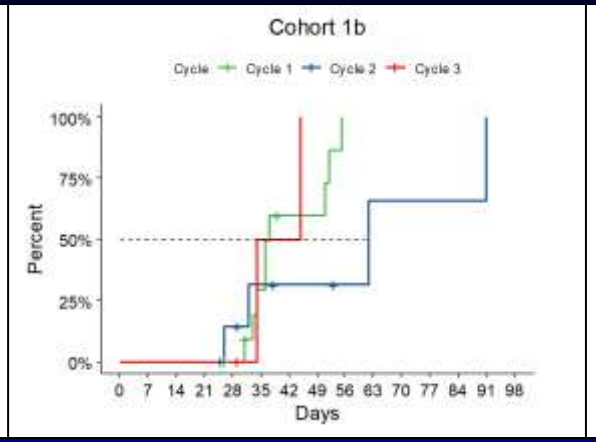


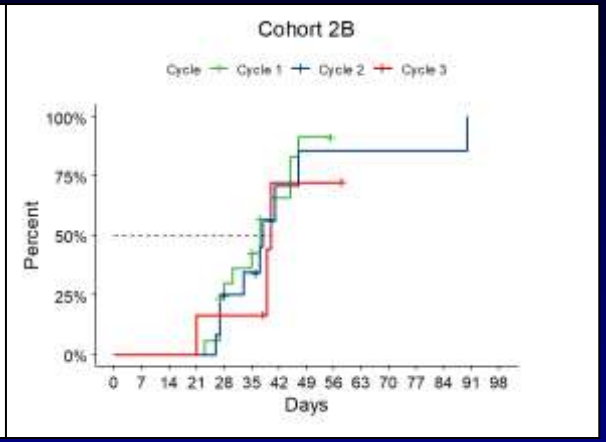
Variable	Salvage #1	Salvage #2	Salvage #3	CRc	HSCT
Event-Free Survival	11 (5-NE)	10 (7-NE)	-	11 (9-NE)	NR (16-NE)
Overall Survival	16 (7-NE)	14 (11-NE)	4 (3.8-NE)	16 (11-NE)	NR (16-NE)

Lachowiez C, et al. ASH 2020. Abstract 332.

FLAG-IDA-VEN: Median Time to Count Recovery*





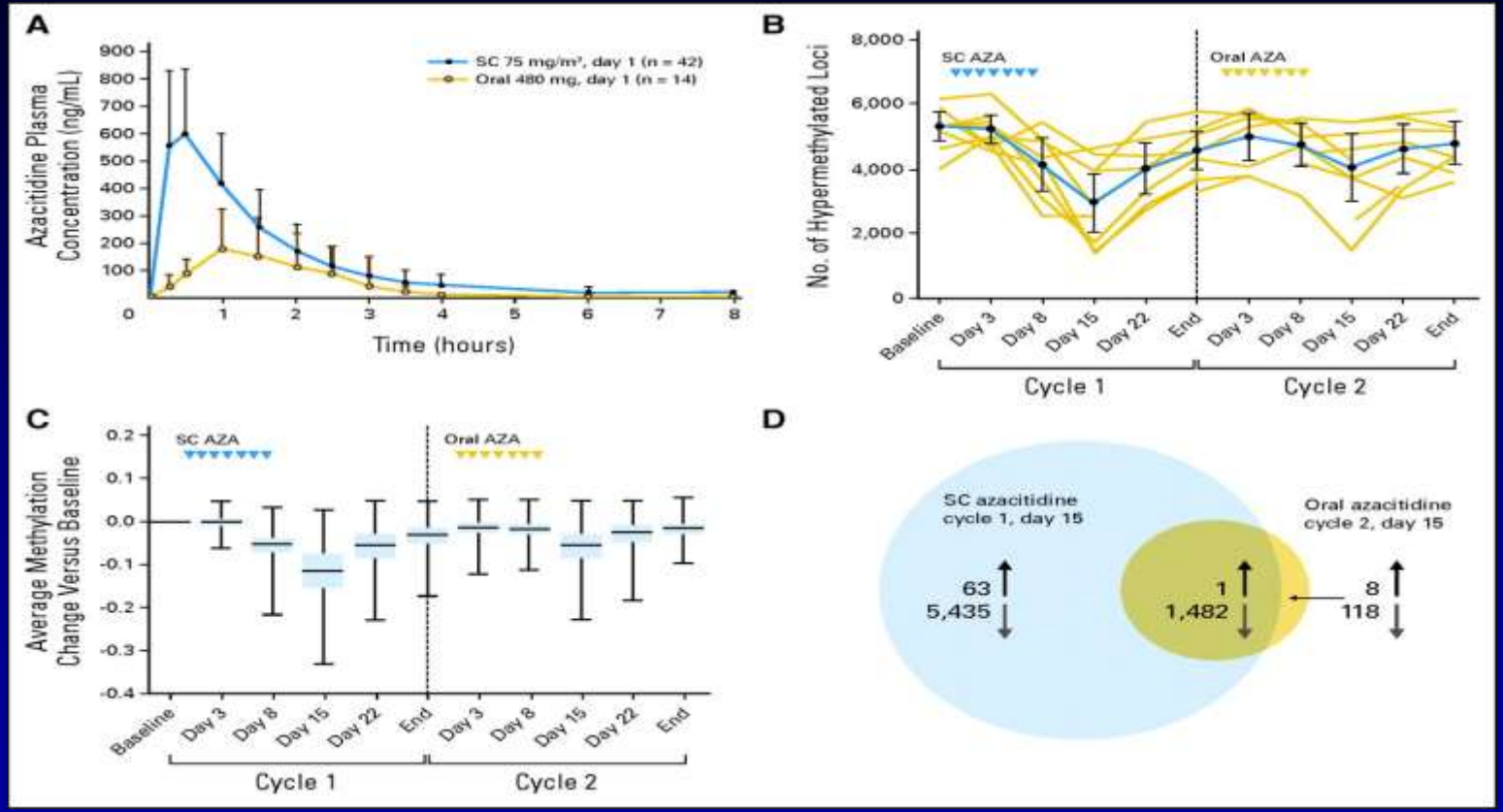


	Phase 2A ND AML (N = 29)	Phase Ib (Dose Finding) R/R AML (N = 16)	Phase 2B (Expansion) R/R AML (N = 23)
Cycle #1	31 days	37 days	37 days
Cycle #2	46 days	62 days	38 days
Cycle #3	41 days	40 days	40 days

*Count recovery: ANC ≥500 and platelet count ≥ 50,000 /µL

Lachowiez C, et al. ASH 2020. Abstract 332.

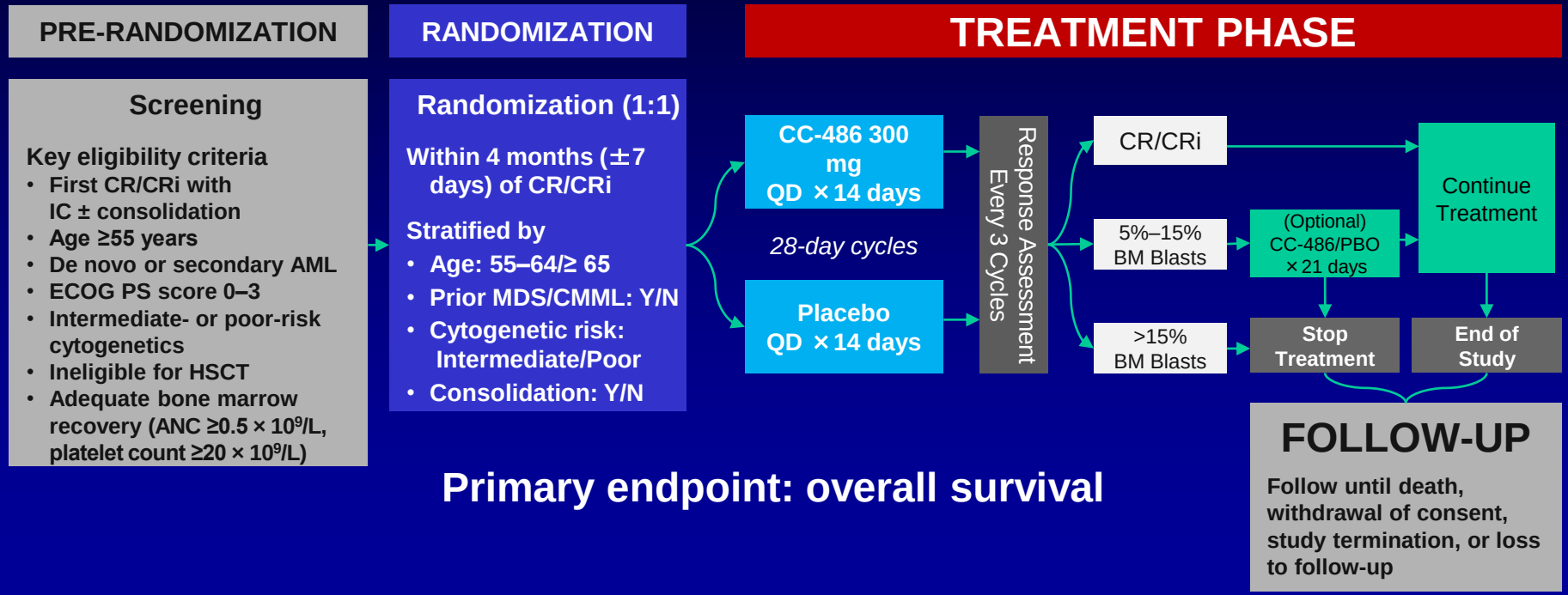
Maintenance: CC486 in MDS and AML



Garcia-Manero G, et al. *J Clin Oncol.* 2011;29(18):2521.

QUAZAR AML-001: Study Design

- International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)

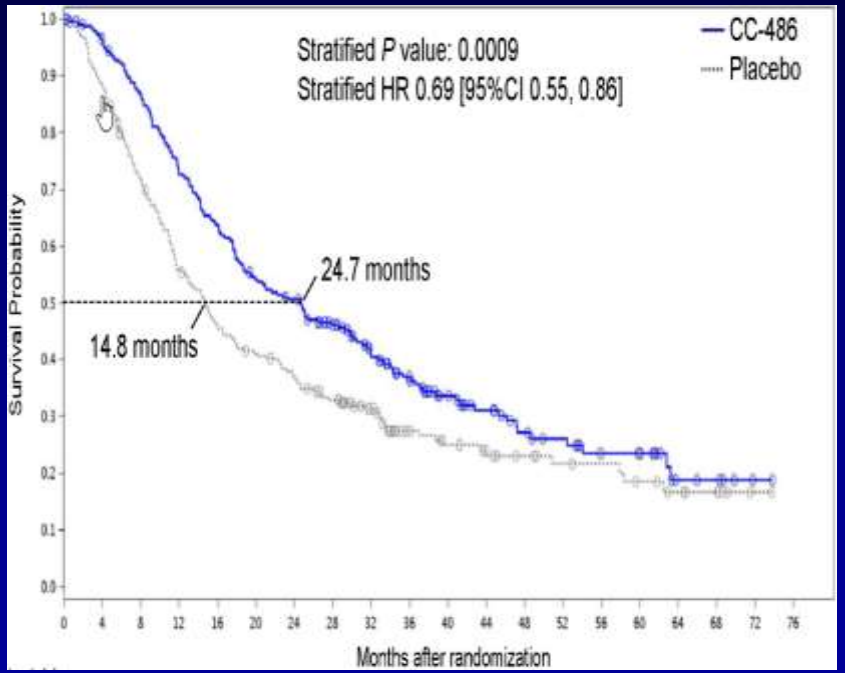


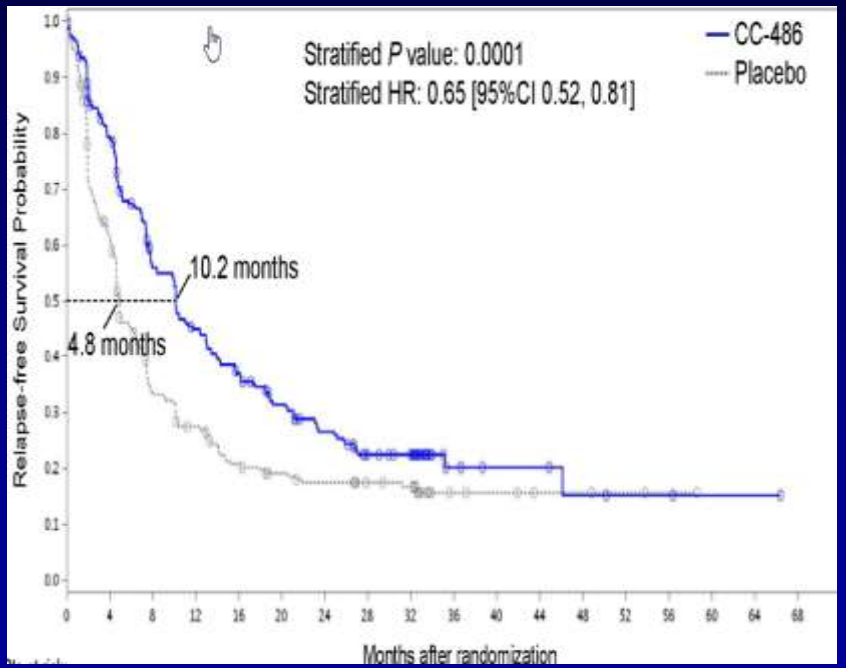
Primary endpoint: overall survival

Wei AH, et al. *Blood.* 2019;134: LBA 3.

Phase III Study of Oral Azacitidine vs Placebo as Maintenance in AML (QUAZAR-AML-001)

- 472 pts 55+ yr (median age 68 yr) with AML in CR-Cri <4 mo randomized to CC-486 300 mg/ daily × 14 Q mo (n = 238) or PBO (n = 234)

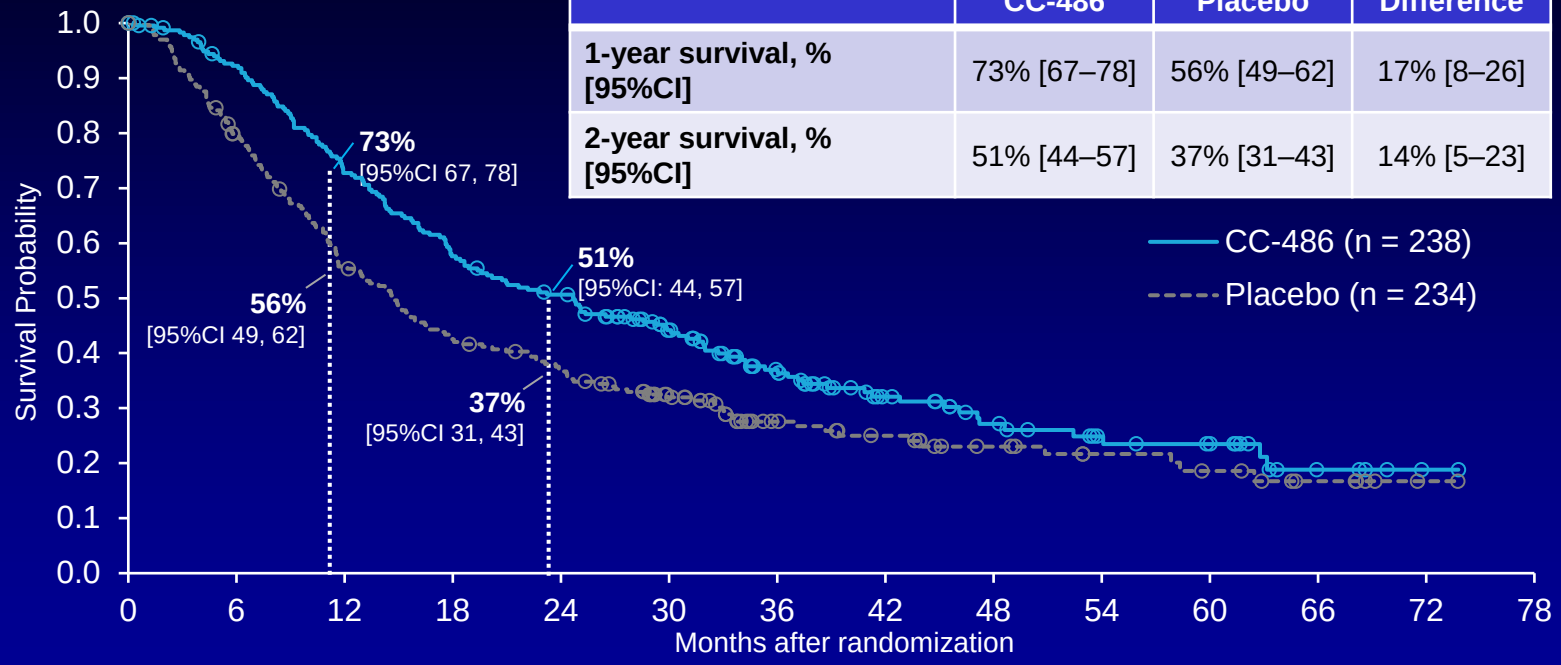




Wei AH, et al. *Blood.* 2019;134: LBA 3.

One-Year and 2-Year Survival

	CC-486	Placebo	Difference
1-year survival, % [95%CI]	73% [67–78]	56% [49–62]	17% [8–26]
2-year survival, % [95%CI]	51% [44–57]	37% [31–43]	14% [5–23]



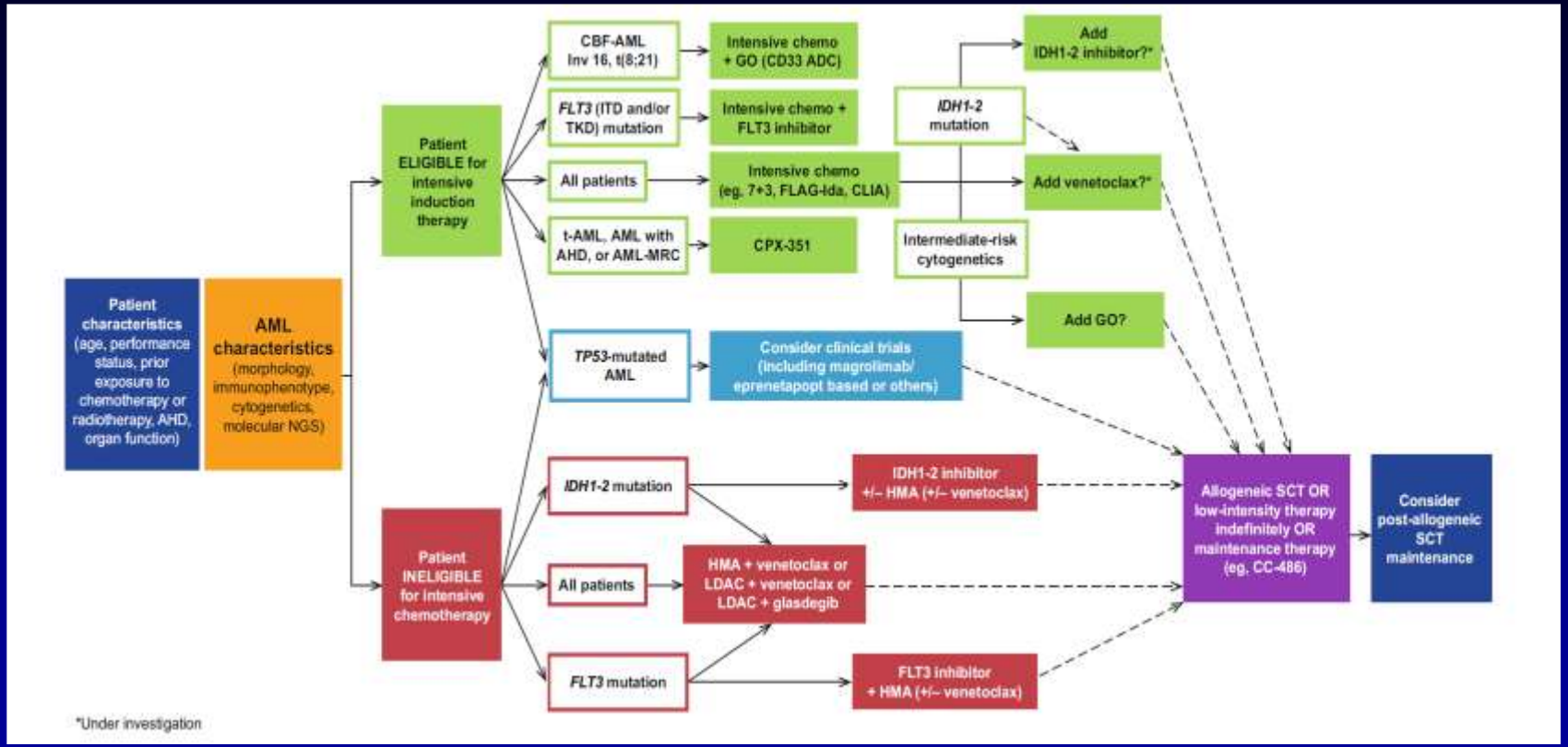
Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Data cutoff: July 15, 2019.

OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 vs placebo by stratified log-rank test. Hazard ratios (HRs) and 95% CIs were generated using a stratified Cox proportional hazards model.

Evolving Diagnostic and Treatment Paradigm for Newly Dx AML



Daver N, et al. *Blood Cancer J.* 2020;10(10):107.

Questions: ndaver@mdanderson.org

Global Leukemia Academy

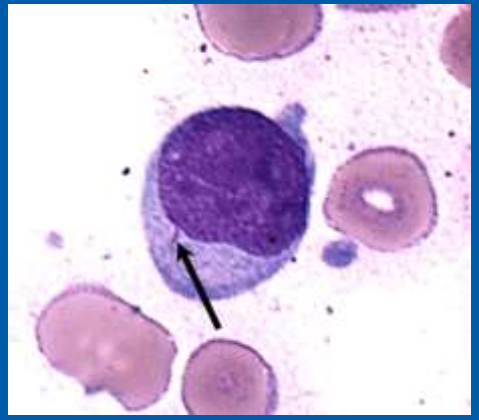
Optimizing management of relapsed/refractory AML

Eunice Wang

APTITUDE HEALTH

Optimizing management of relapsed/refractory AML

Global Leukemia Academy



ROSWELL PARK COMPREHENSIVE CANCER CENTER

Eunice S. Wang, MD
Chief, Leukemia Service
Professor of Oncology

Disclosures: Eunice Wang, MD

- Advisory board: AbbVie, Astellas, BMS/Celgene, Genentech, GlaxoSmithKline, Jazz, Kite Pharmaceuticals, Kura Oncology, Novartis, Pfizer, Stemline, Takeda
- Consulting: Mana Therapeutics
- Speaker role: Stemline, Kura, Pfizer, DAVA Oncology
- Data monitoring committees: AbbVie, Rafael Pharmaceuticals

Cytotoxic Chemotherapy for R/R AML[1-5]

Chemotherapy

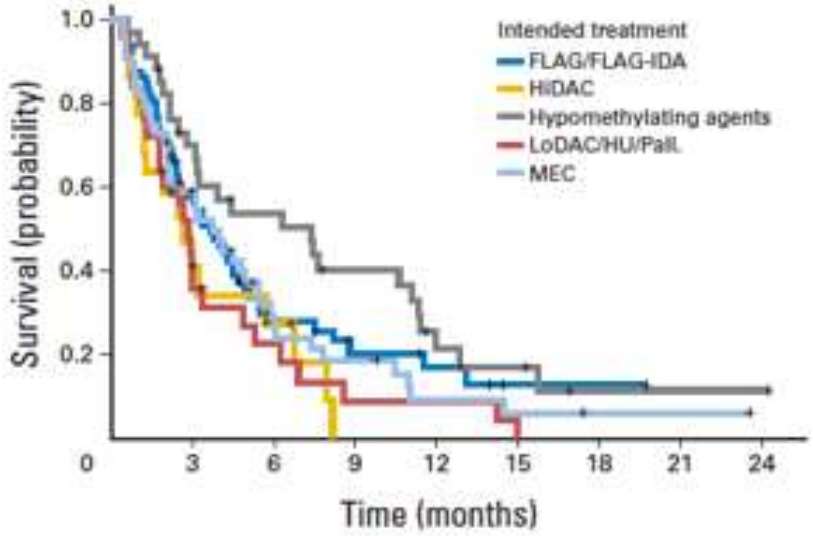
Less aggressive

- Low dose AraC
- HMA (aza, dec)
- Venetoclax + LDAC or HMA

Aggressive

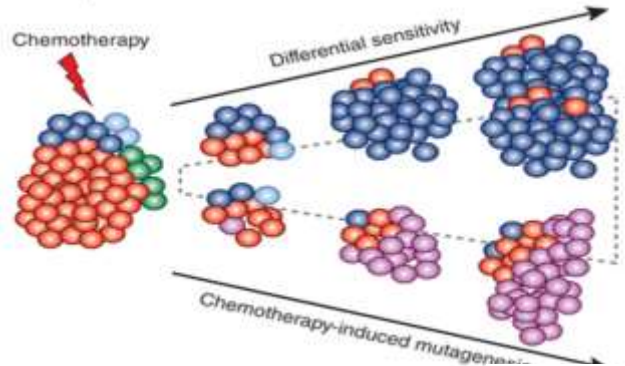
- CLAG + Ida/Mito
- HIDAC + Ida/Daun/Mito
- FLAG + Ida
- Etop/AraC/Mito
- Clof+AraC+Ida

Overall survival



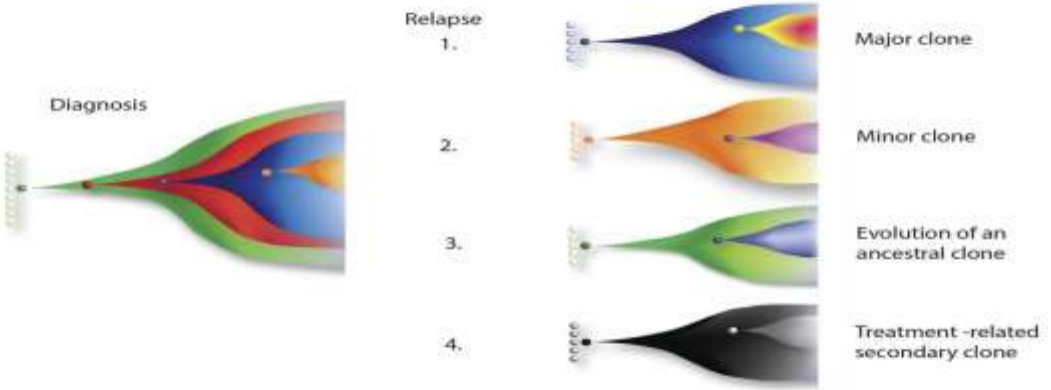
1. Roboz GJ, et al. *J Clin Oncol.* 2014;32(18)1919-1926; 2. Stein EM, et al. *Blood.* 2017;130(6):722-731; 3. DiNardo CD. *N Engl J Med.* 2019;379(12):1186; 3. Taskin AL, et al. *Leukemia*. 2007;21(1):66-71; 5. Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

Clonal Evolution and Therapy Resistance at Relapse



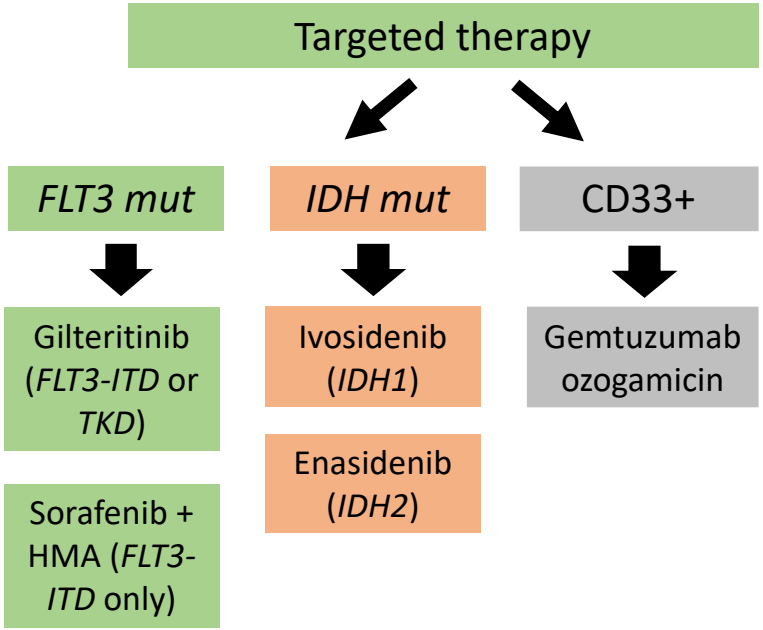
Leukemia is not a static condition!

Repeat genomic analysis at relapse is necessary



Kleppe M, Levine RL. Nat *Med*. 2014;20(4):342;Grimwade D, et al. *Blood*. 2016;127(1):29-41.

Targeted Therapy for R/R AML



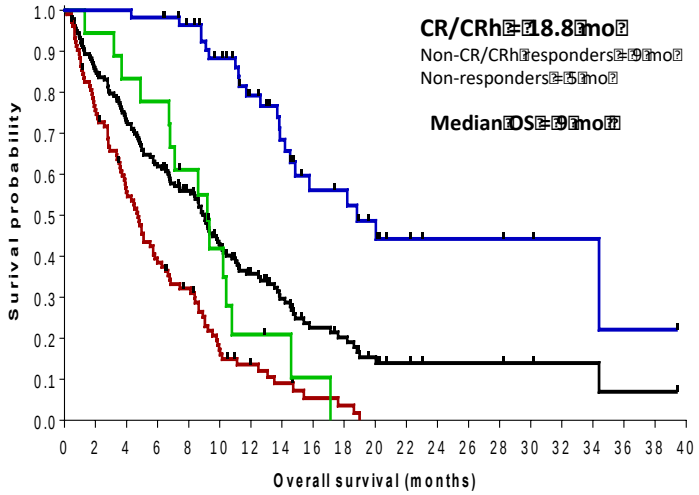
Outcomes of clinical trials

Drug Name	AML Subset	ORR	Median OS
Enasidenib[2]	*IDH2* mutant	40.3%	9.3 mos
Ivosidenib[3]	*IDH1* mutant	41.6%	8.8 mos
GO[4]	CD33+ AML	26%	11.6 mos
Gilteritinib[5]	*FLT3* mutant	34%	9.3 mos

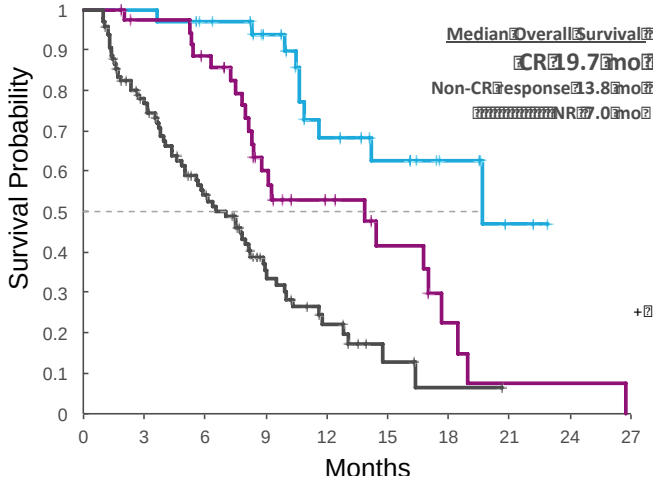
Stein EM, et al. *Blood*. 2017;130(6):722-731; DiNardo CD. *N Engl J Med*. 2019;379(12):1186; Taskin AL, et al. *Leukemia*. 2007;21(1):66-71; Perl AE, et al. *N Engl J Med*. 2019;381(18):1728-1740.

IDH1/2 Inhibitors for *IDH*-Mutant R/R AML

Ivosidenib (*IDH1*): R/R AML



Enasidenib (*IDH2*): R/R AML



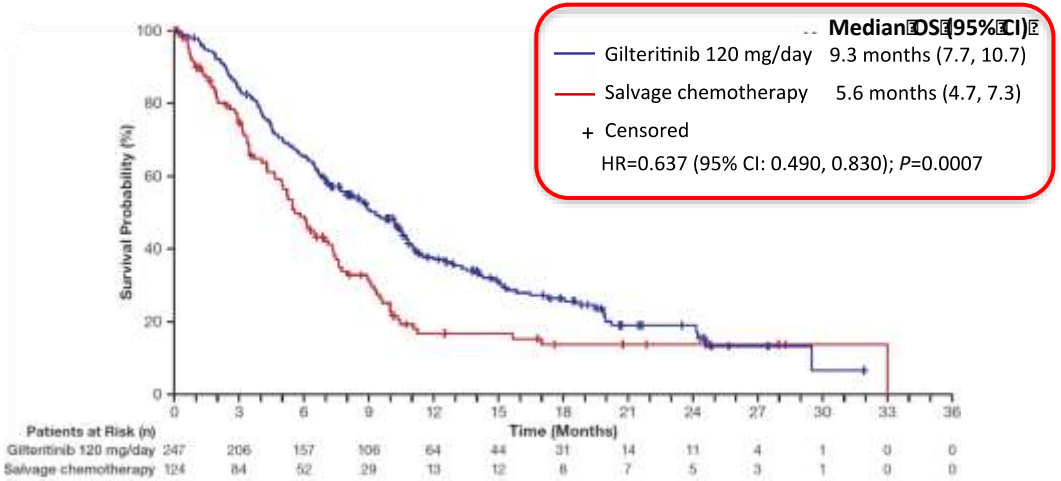
Mechanisms of resistance: Mutant isoform switch (m*IDH1* <-> m*IDH2*), *IDH2* mutations (trans or cis), presence or development of co-mutations (ie, *RAS, FLT3*)

DiNardo CD, et al. *N Engl J Med.* 2018;378(25):2386; Stein EM, et al. *Blood*. 2017;130(6):722-731.

FLT3 Inhibitors for *FLT3*-Mutant R/R AML

	Other Kinases	IC_{50} (Plasma)
Lestaurtinib	JAK2, TrkA	700 nM
Midostaurin	cKIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib	cKIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib	cKIT, PDGFR, RET	18 nM
Crenolanib	PDGFR	48 nM
Gilteritinib	AXL	43 nM

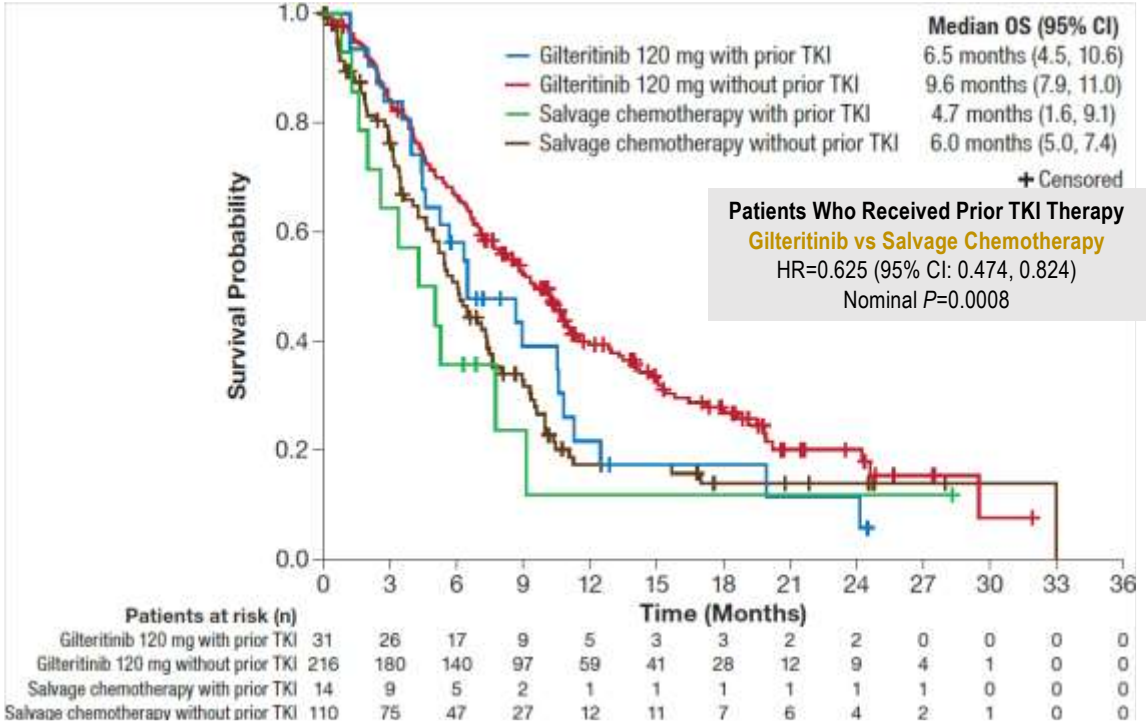
Gilteritinib vs salvage chemo in *FLT*^{mut} R/R AML



Pratz KW, et al. *Blood.* 2010;115(7):1425-1432;
Zarrinkar PP, et al. *Blood.* 2009;114(14):2984-2992;
Galanis A, et al. *Blood.* 2014;123(1):94-100;
Levis MJ, et al. *J Clin Oncol.* 2015;33(15_suppl): abstract 7003.

Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

FLT3-Mutant AML: Gilteritinib vs Chemotherapy

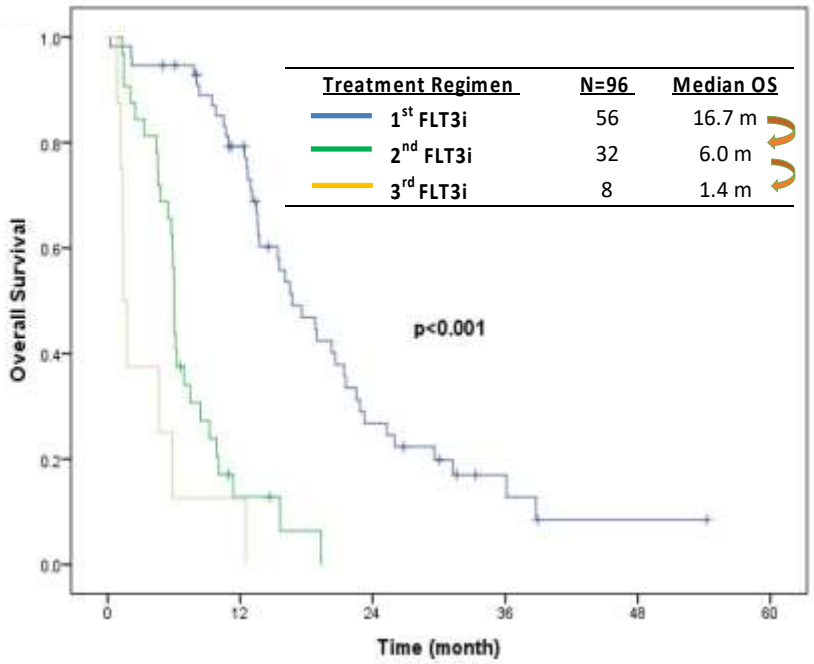


Median OS, mos (95% CI)	Gilteritinib	
	Prior TKI	No Prior TKI
***FLT3* Mutation Type**		
FLT3-ITD	6.5 (4.4, 10.8)	10.2 (7.7, 11.1)
FLT3-TKD	4.6 (1.2, 24.1)	8.0 (3.0, 24.6)
FLT3-ITD and -TKD	13.2 (4.0, NE)	10.2 (8.9, 20.2)
Relapsed or Refractory Status		
Relapsed	6.5 (4.0, 11.3)	8.9 (6.7, 10.8)
Refractory	10.5 (2.4, 24.1)	10.3 (7.9, 13.5)

Perl AE, et al. ASH 2020. Abstract 262.

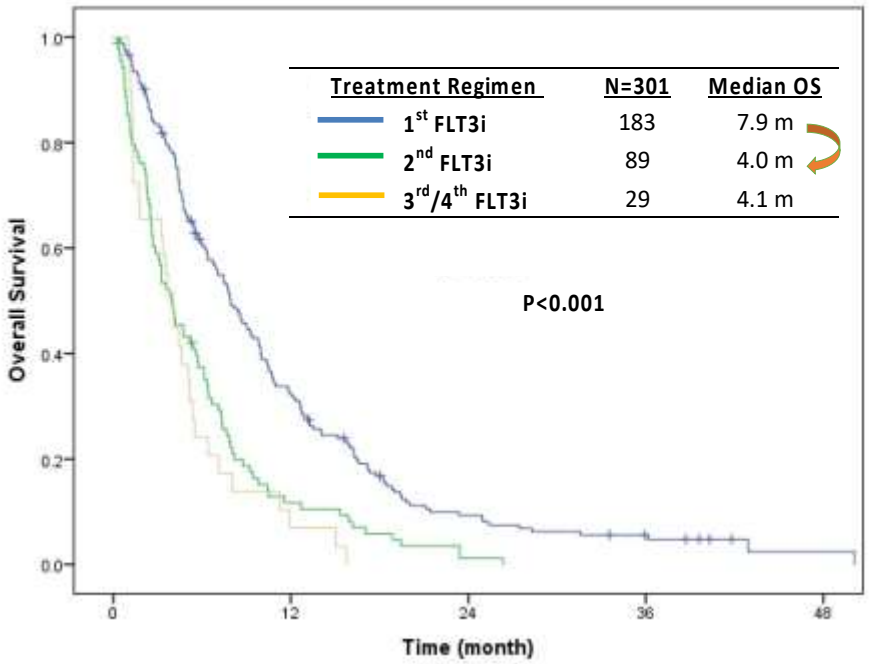
Sequential FLT3 Inhibitor Therapy for R/R AML

Frontline Cohort (n=96)



Treatment Regimen	N=96	Median OS
1st FLT3i	56	16.7 m
2nd FLT3i	32	6.0 m
3rd FLT3i	8	1.4 m

Salvage Cohort (n=301)

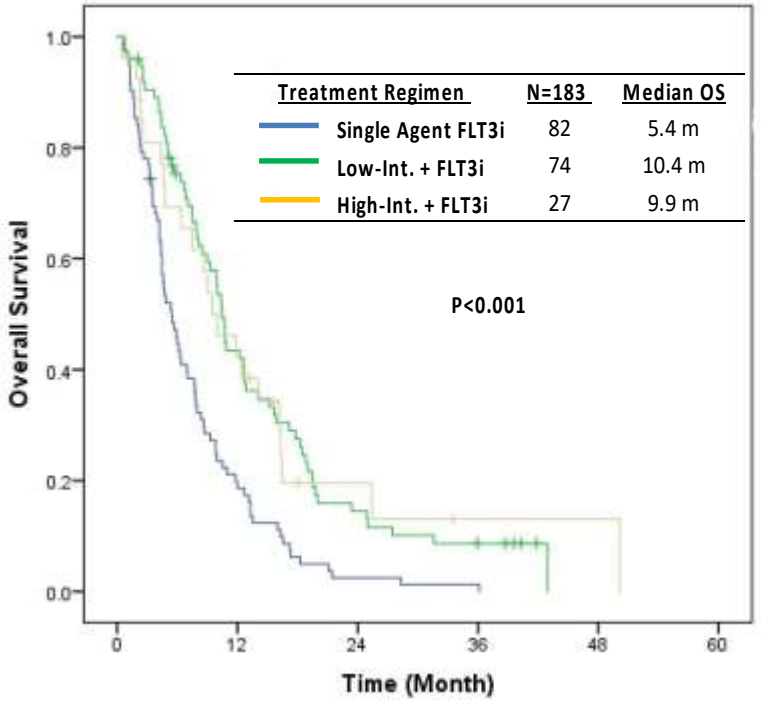


Treatment Regimen	N=301	Median OS
1st FLT3i	183	7.9 m
2nd FLT3i	89	4.0 m
3rd/4th FLT3i	29	4.1 m

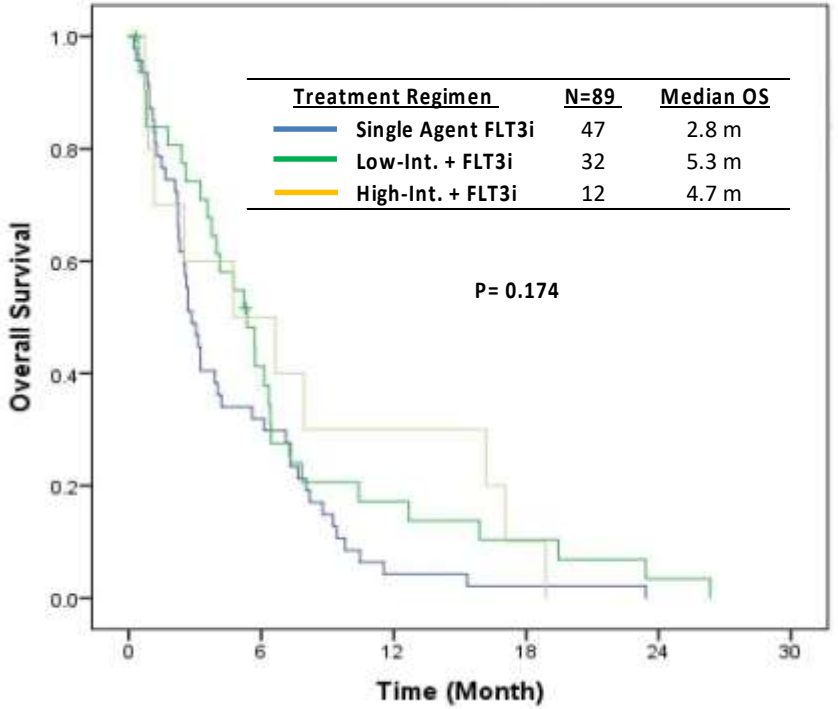
Yilmaz M, et al. ASH 2020. Abstract 29.

Combination vs Single-Agent FLT3 Inhibitor Salvage

1st FLT3i exposure (n=183)



2nd FLT3i exposure



Yilmaz M, et al. ASH 2020. Abstract 29.

FLT3-Mutant R/R AML: Venetoclax + Gilteritinib

Key Eligibility Criteria

- R/R AML
- WT or *FLT3*$^{mut+}$ (dose escalation) and *FLT3*$^{mut+}$ (dose expansion)
- ≥1 prior line of therapy[a]
- WBC count ≤ 25 x 10^9 /L at start of study drug
- ECOG PS 0–2

Dose escalation phase
WT and *FLT3*$^{mut+}$

Ven 400 mg + Gilt 80 mg (n=7)

Ven 400 mg + Gilt 120 mg (n=16)

DLT monitoring[b]

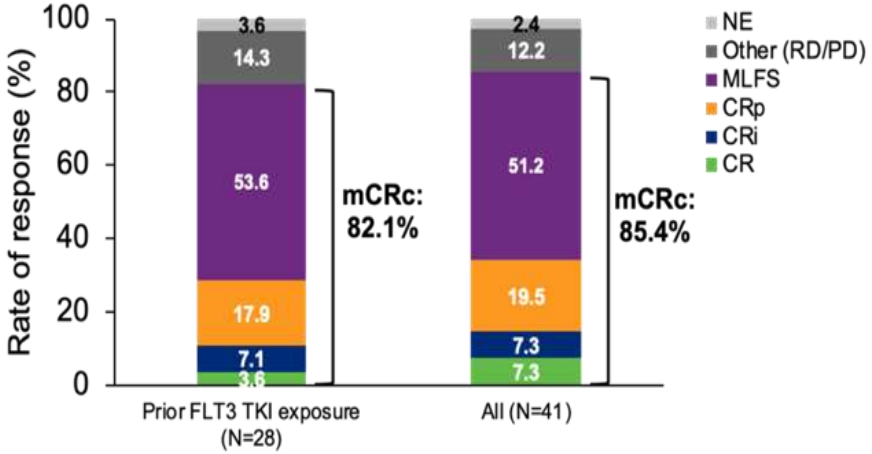
Dose expansion
FLT3^{mut+} only

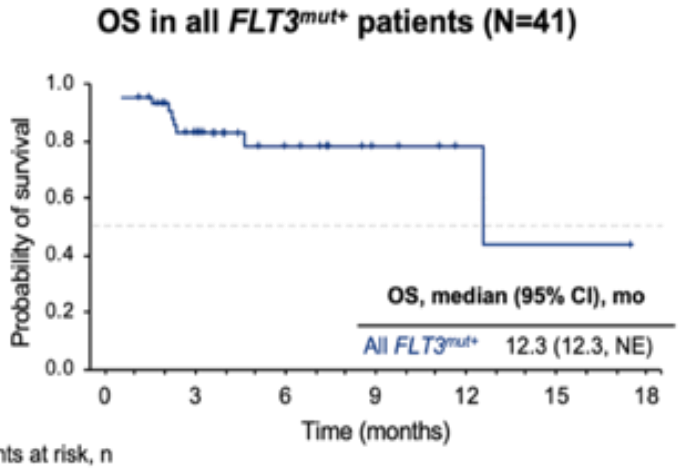
Ven 400 mg + Gilt 120 mg (RP2D) (n=46)[c]

DLT monitoring[b]

Follow-up

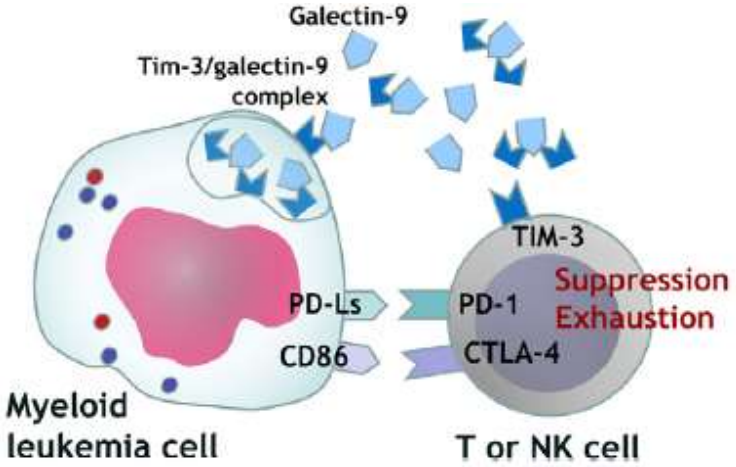
- Post-treatment follow-up monthly for up to 1 year, following last dose of study drug

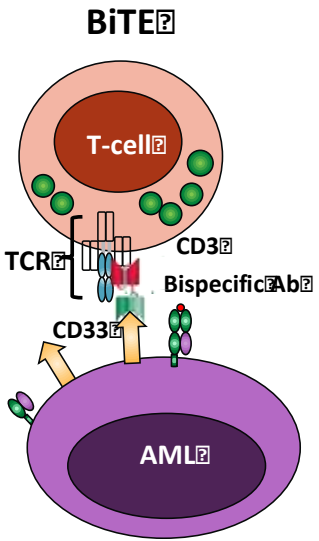


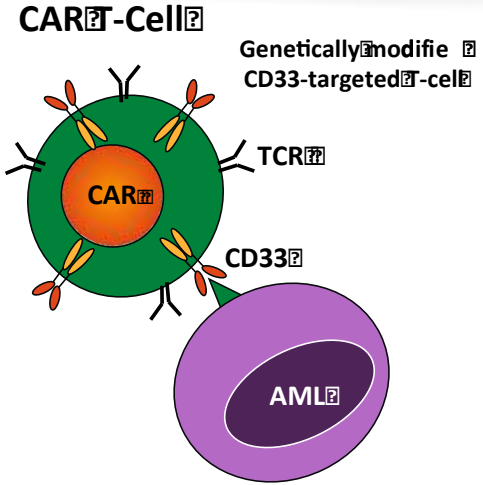


Daver N, et al. ASH 2020. Abstract 335.

Immunotherapeutic Approaches for R/R AML







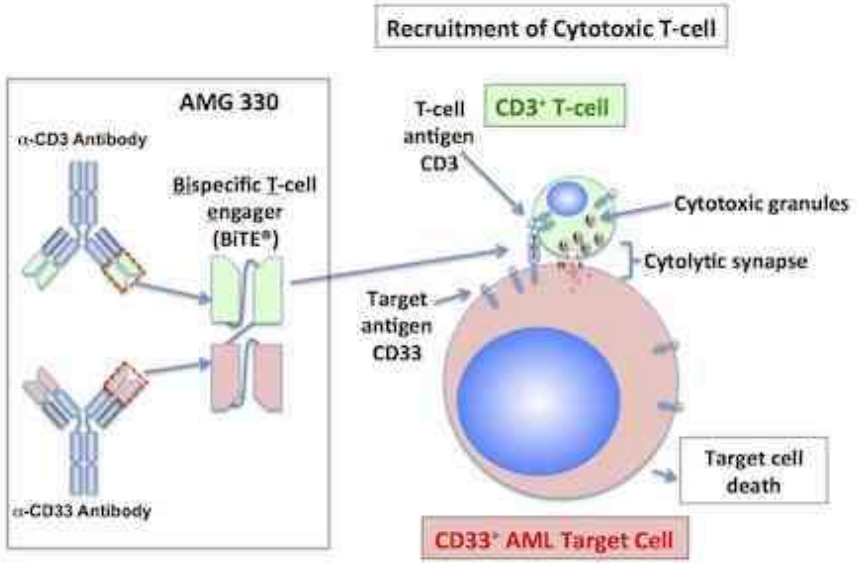
Targeting immune checkpoints

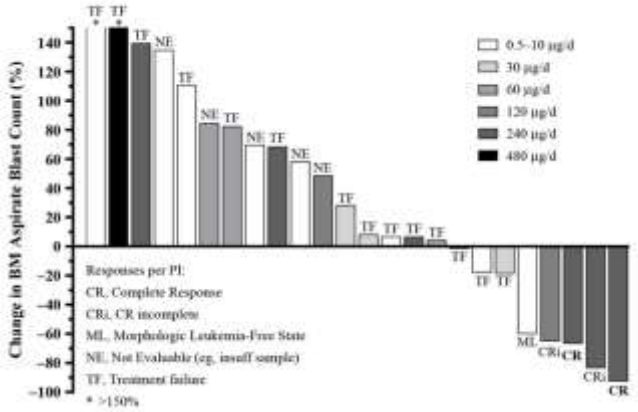
- Ipilimumab (anti–CTLA-4 ab)
- Magrolimab (anti-CD47 ab)
- MBG453 (anti-TIM3 ab)

AML cell antigens

- **CD33**
- **CD123**
- Folate Rc β
- **CLL1**
- **Wildtype FLT3**
- Lewis Y

AMG 330: CD33/CD3 Bispecific Antibody



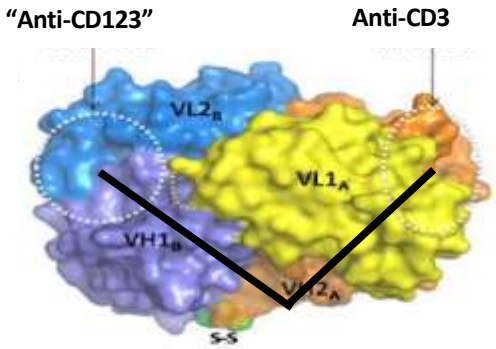


35 pts on 12 dose cohorts (40% prior alloSCT)
DLTs grade 2 CRS, grade 4 VF
Target dose = 240 µg/day
Responses: 2 CR, 2 CRi at 120–240-µg/day dosing
CRs seen after 1 cycle of therapy

Laszlo GS, et al. *Blood*. 2014;123(4):554-561; Harrington KH, et al. *PLOS One*. 2015;10(8):e0135945; Ravandi F, et al. ASH 2018. Abstract 25.

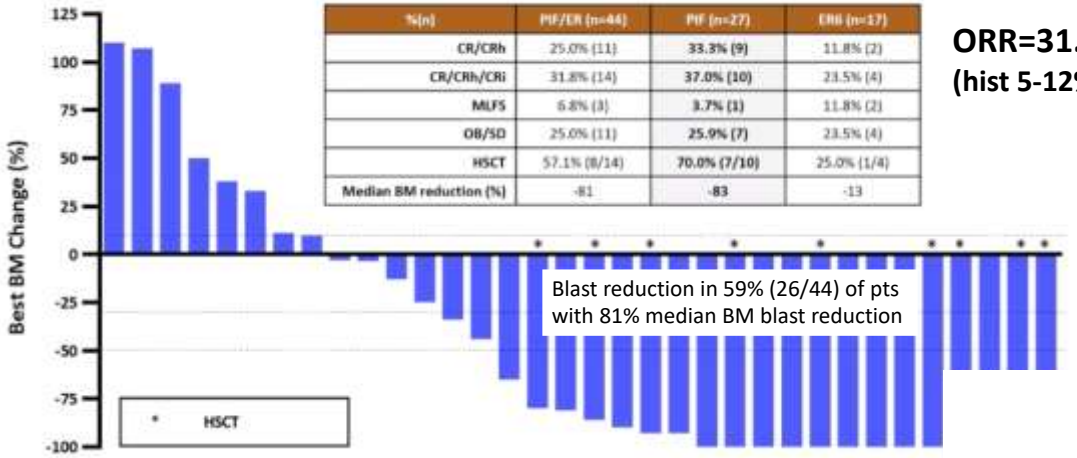
Flotetuzumab: Primary Induction Failure/Early Relapse

- Flotetuzumab (MGD006/S80880) redirects T-cell killing of CD123+ Cells



Root, et al. Antibodies 2016, 5, 6
Chichili, et al. Sci Transl Med. 2015 May 27;7(289)

Responses to therapy in PIF/ER AML pts



%(n)	PIF/ER (n=44)	PIF (n=27)	ERi (n=17)
CR/CRh	25.0% (11)	33.3% (9)	11.8% (2)
CR/CRh/CRi	31.8% (14)	37.0% (10)	23.5% (4)
MLFS	6.8% (3)	3.7% (1)	11.8% (2)
OB/SD	25.0% (11)	25.9% (7)	23.5% (4)
HSCT	57.1% (8/14)	70.0% (7/10)	25.0% (1/4)
Median BM reduction (%)	-81	-83	-13

ORR=31.8%
(hist 5-12%)

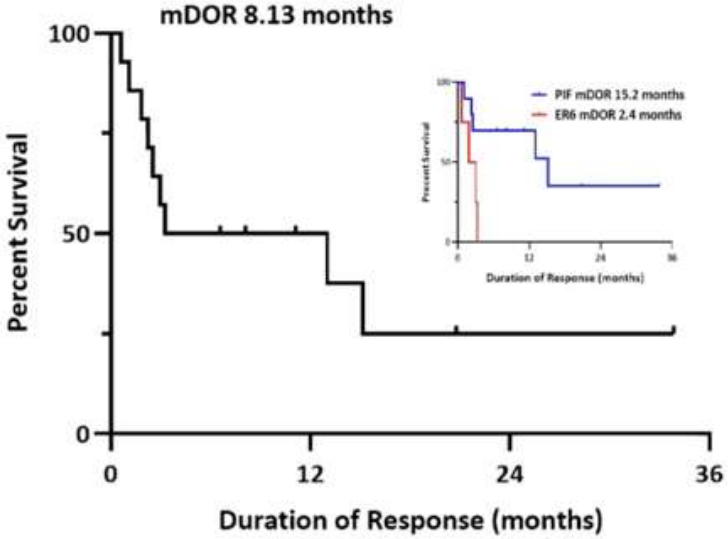
Need for <u>hospitalization (min 8 d) in all patients</u>
100% infusion reaction/cytokine release
Outpatient dosing after day 8 feasible

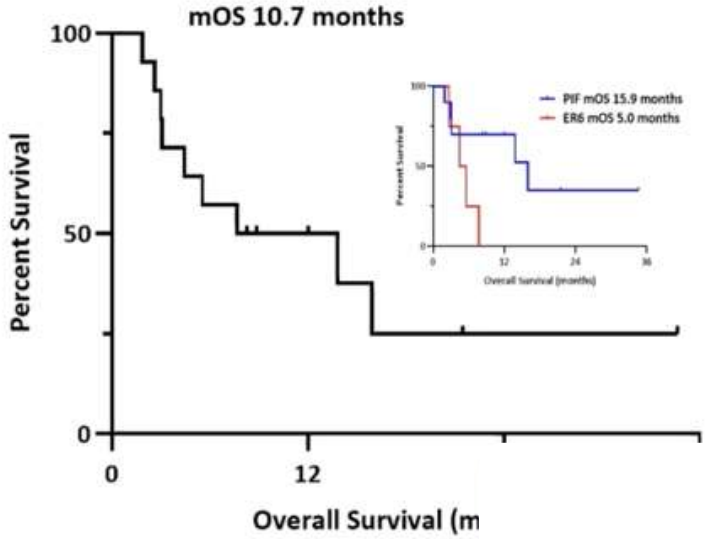
Aldoss I, et al. ASH 2020. Abstract 331.

Flotetuzumab in Primary Induction Failure/Early Relapse

Primary refractory (PIF): Refractory to up to 2 cycles of cytarabine-based chemotherapy
Or ≥2 but ≤4 bcl-2 inhibitor-based combinations or gemtuzumab ozogamicin

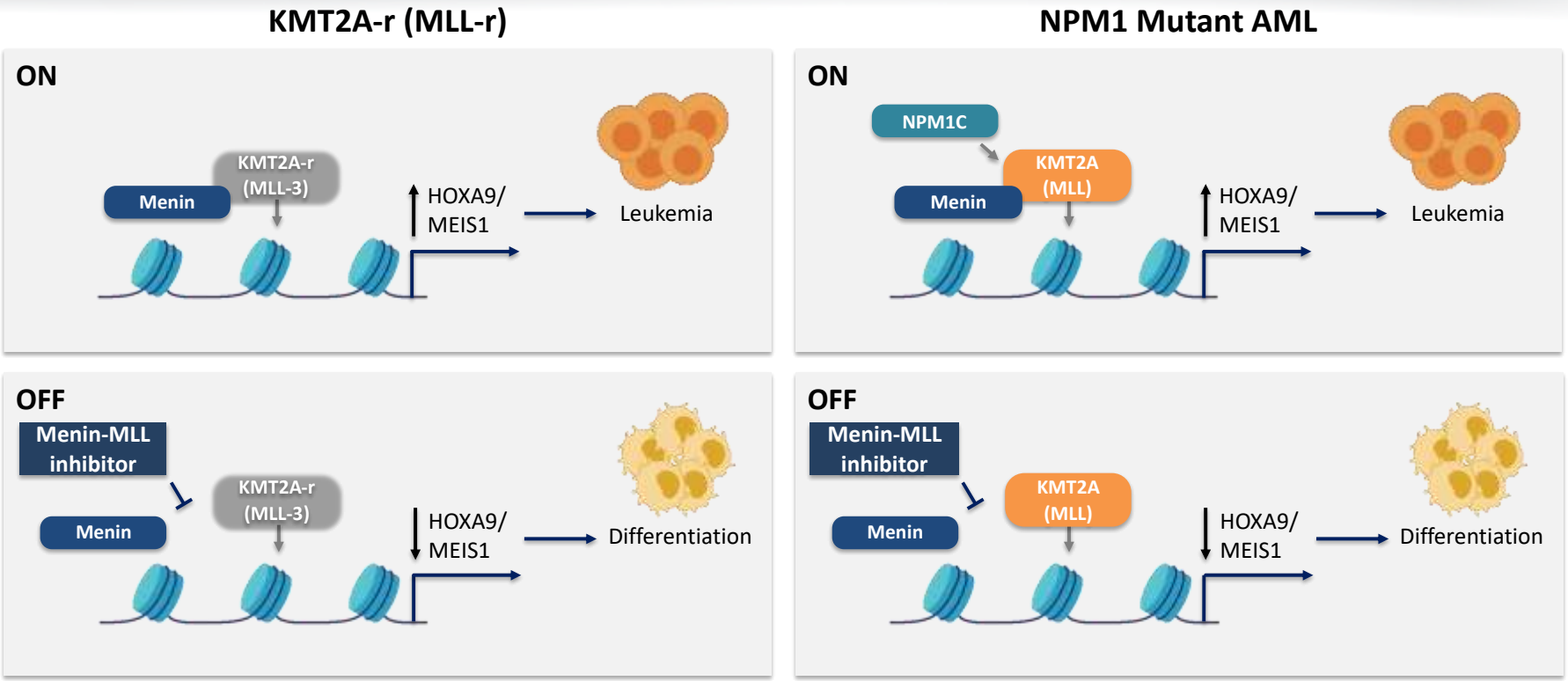
Early relapse (ER6): First relapse with initial CR duration of <6 months





Aldoss I, et al. ASH 2020. Abstract 331.

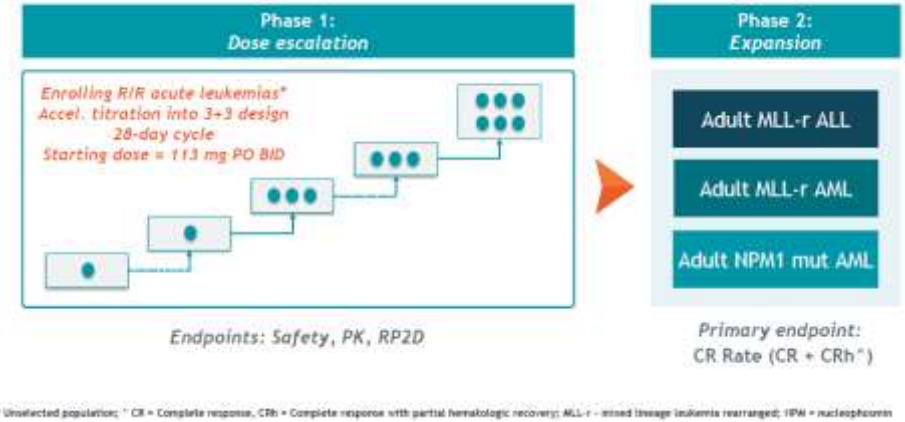
KMT2A-r and *NPM1*-Mutant AML: Menin Inhibition



Wang ES, et al. ASH 2020. Abstract 1015.

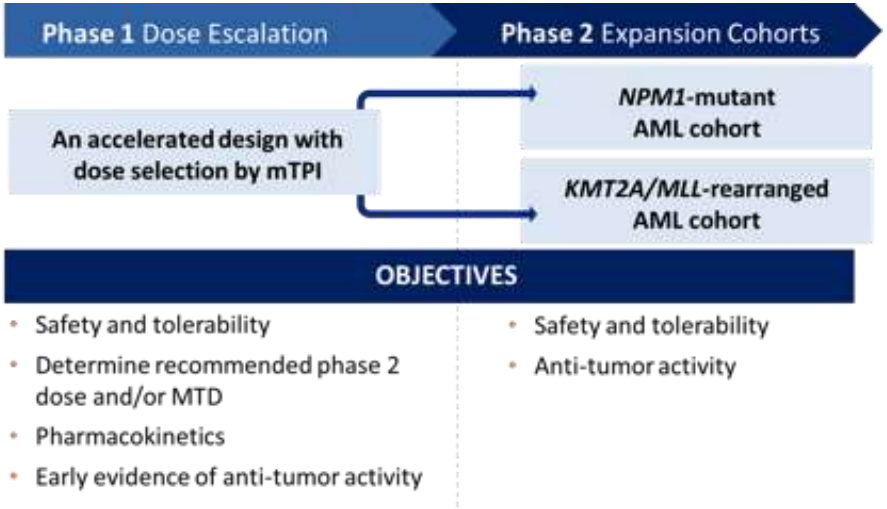
Phase I Clinical Trials for *KMT2A*-r/*NPM1*-Mutant AML

AUGMENT-101 schema: ALL and AML pts



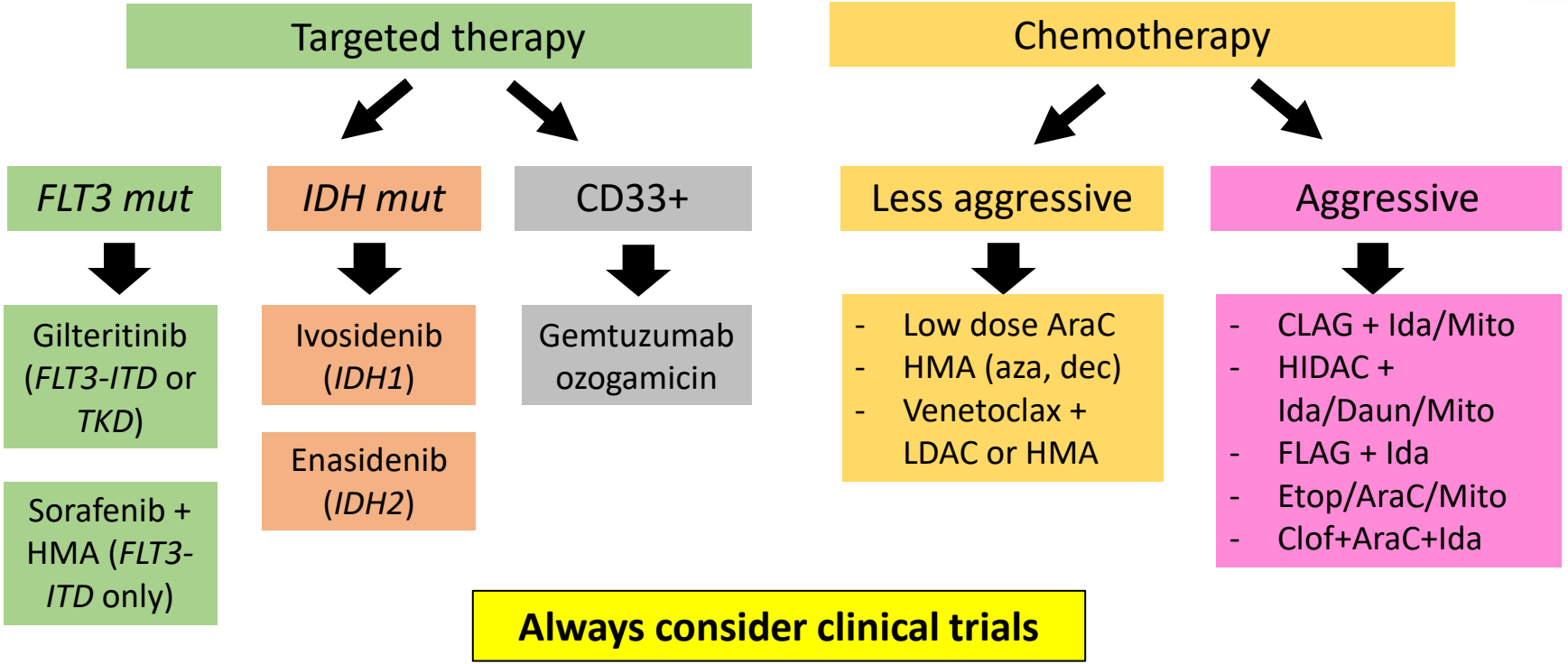
PK: QTC prolongation, interactions with azoles (CYP inhibitors)

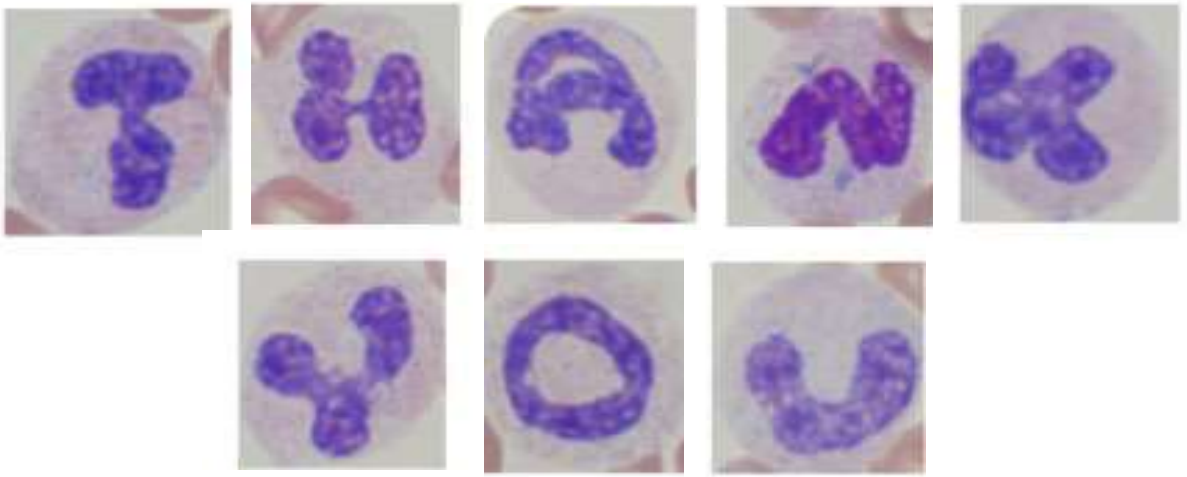
KOMET-001: Phase I/IIA trial



McGeehan J. AACR 2020 meeting; Wang ES, et al. ASH 2020 meeting.

Summary: Optimizing Therapy of R/R AML





Email: Eunice.wang@roswellpark.org

Global Leukemia Academy

Case based panel discussion: regional challenges in AML care

Chyn Chua

APTITUDE HEALTH

AML Clinical Case

Dr Chyn Chua

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Alfred Hospital, Melbourne

Australia

Case: 45-year-old man *(pre-midostaurin era)*

- Presented with leukemia cutis and circulating blasts
- Diagnosed with acute myelomonocytic leukemia
- Cytogenetics: normal karyotype
- Rapid FLT3 testing (capillary electrophoresis): ***FLT3*-ITD** with allelic ratio **(AR) 0.28**
- Further myeloid NGS testing: ***NPM1*** and ***NRAS*** mutations

- Commenced on IDAC-3 induction → CR1 after induction
- Proceeded to IcE consolidation

Favorable risk by ELN 2017

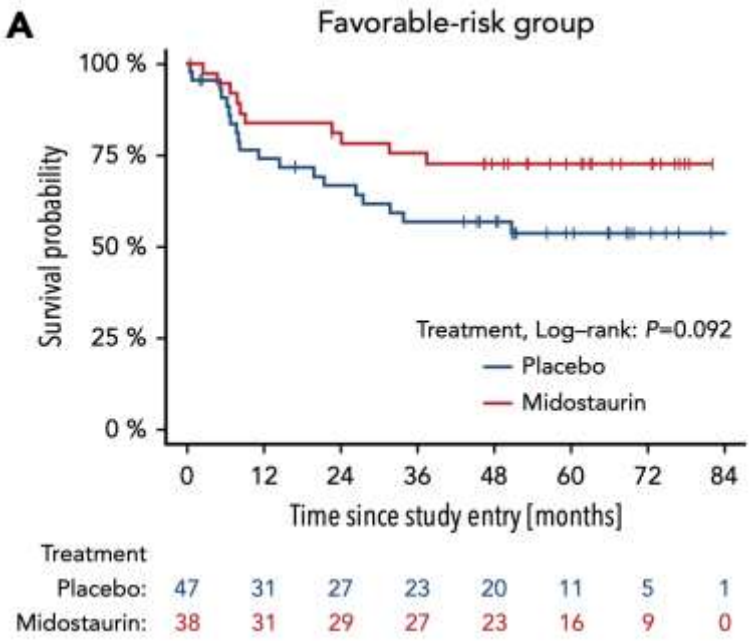
Table 5. 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Döhner H, et al. *Blood*. 2017;129:424-447.

If in the midostaurin era . . .

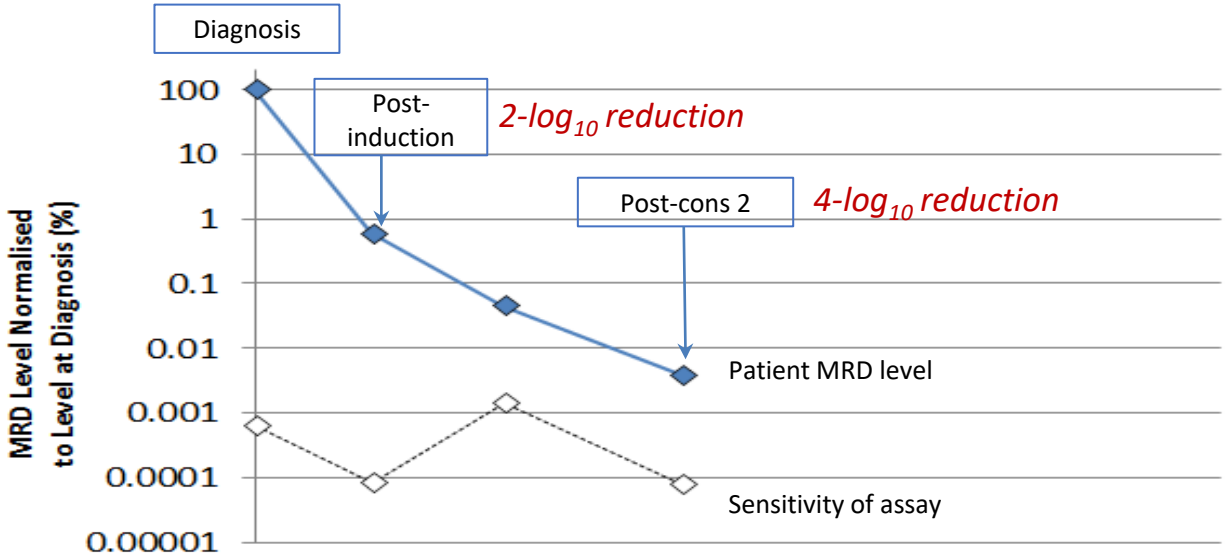
RATIFY study



Döhner K, et al. *Blood*. 2020;135:371-380.

Case: 45-year-old man

- Completed 2 cycles of IcE consolidation → remains in CR
- A sibling donor is identified
- *NPM1* MRD testing by RT-qPCR performed in the bone marrow



Q

FLT3-ITD low-allelic ratio/*NPM1*-mutant AML – CR1 achieved Positive *NPM1* MRD in BM post-consolidation 2

What would you do next?

1. Go directly to allogeneic stem cell transplant if good donor
2. Give salvage chemotherapy (eg, FLAG-Ida) then allogeneic stem cell transplant in CR1
3. Complete 4 cycles of consolidation therapy, commence maintenance therapy (if available), and monitor *NPM1* MRD
4. No further therapy and monitor *NPM1* MRD in PB and BM

FLT3-ITD low-allelic ratio/*NPM1*-mutant AML – CR1 achieved
Positive *NPM1* MRD in BM post-consolidation 2

What would you do next?

1. Go directly to allogeneic stem cell transplant if good donor
2. Give salvage chemotherapy (eg, FLAG-Ida) then allogeneic stem cell transplant in CR1
3. Complete 4 cycles of consolidation therapy, commence maintenance therapy (if available), and monitor *NPM1* MRD
4. No further therapy and monitor *NPM1* MRD in PB and BM

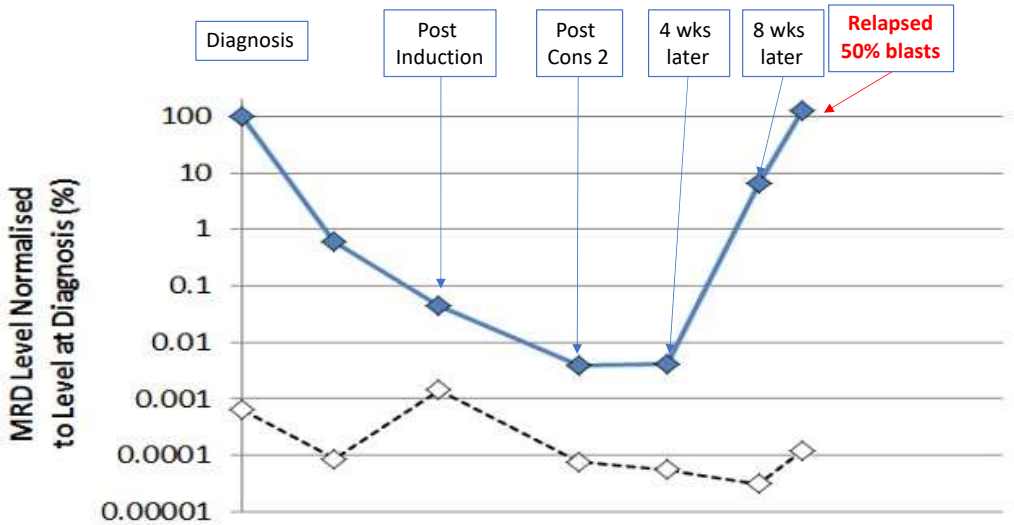
Would your management differ if the patient was receiving midostaurin/FLT3i?

Key questions to the panel

- What is an optimal *NPM1* MRD response?
- What is the conversion rate from *NPM1* MRD positive to MRD negative beyond 3 cycles of intensive chemotherapy?
  - Does that differ between *FLT3*-ITD–mutant vs –wildtype patients?
- How often would you monitor the *NPM1* MRD, and by which source, ie, peripheral blood vs bone marrow?
- What is the role of alloSCT in *FLT3*-ITD_{low}/*NPM1*-mutant patients?

Case: 45-year-old man

- Did not proceed immediately to further consolidation cycles, as had a very tough time during consolidation cycle 2
- *NPM1* MRD repeated 4 and 8 weeks later (2-log rise) → MRD progression
- Morphologic relapse 2 weeks later



Q

Relapsed *FLT3*-ITD low-allelic ratio/*NPM1*-mutant AML

What would you do next?

1. Give salvage intensive chemotherapy (eg, FLAG-Ida) then allogeneic stem cell transplant
2. Commence gilteritinib and then allogeneic SCT if CR2
3. Enroll in a clinical trial if available

ADMIRAL trial: Gilteritinib vs chemotherapy for R/R *FLT3*-mutant AML

Table 2. Antileukemic Responses (Intention-to-Treat Population).*

Variable	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)	Hazard Ratio or Risk Difference (95% CI)†
Median overall survival (95% CI) — mo	9.3 (7.7–10.7)	5.6 (4.7–7.3)	0.64 (0.49–0.83)
Median event-free survival (95% CI) — mo	2.8 (1.4–3.7)	0.7 (0.2–NE)	0.79 (0.58–1.09)
Response — no. (%)			
Complete remission	52 (21.1)	13 (10.5)	10.6 (2.8–18.4)
Complete remission or complete remission with partial hematologic recovery	84 (34.0)	19 (15.3)	18.6 (9.8–27.4)
Complete remission with partial hematologic recovery	32 (13.0)	6 (4.8)	ND
Complete remission with incomplete hematologic recovery	63 (25.5)	14 (11.3)	ND
Complete remission with incomplete platelet recovery	19 (7.7)	0	ND
Partial remission	33 (13.4)	5 (4.0)	ND
No response	66 (26.7)	43 (34.7)	ND
Composite complete remission‡	134 (54.3)	27 (21.8)	32.5 (22.3–42.6)
Overall response	167 (67.6)	32 (25.8)	
Median duration of remission (95% CI) — mo§	11.0 (4.6–NE)	NE (NE–NE)	NE
Time to composite complete remission — mo	2.3±1.9	1.3±0.5	NA
Median leukemia-free survival (95% CI) — mo	4.4 (3.6–5.2)	6.7 (2.1–8.5)	NE

Perl AE, et al. *N Engl J Med*. 2019;381:1728-1740.

Case progress

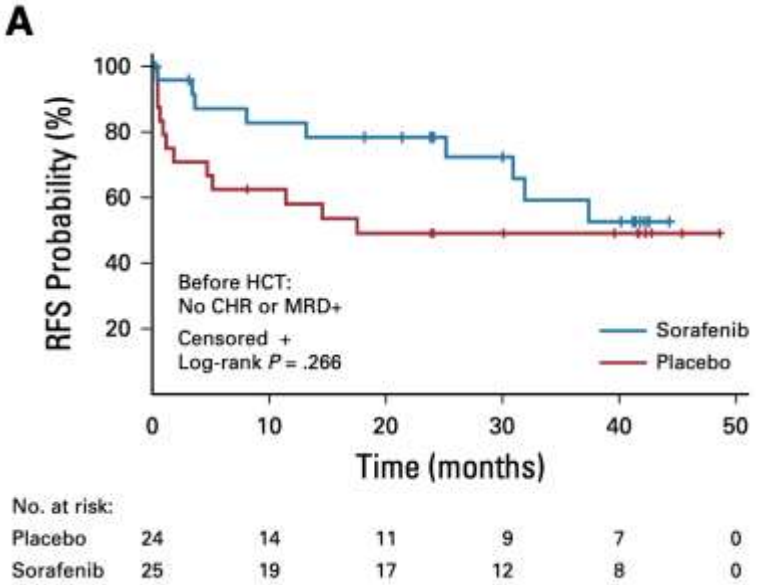
- Received salvage FLAG-amsacrine for morphologic relapse → CR2
  - Gilteritinib was not available then
  - *NPM1* MRD post-salvage 0.47% (212 copies/10^5 ABL)
- Proceeding to myeloablative allogeneic SCT with sibling donor

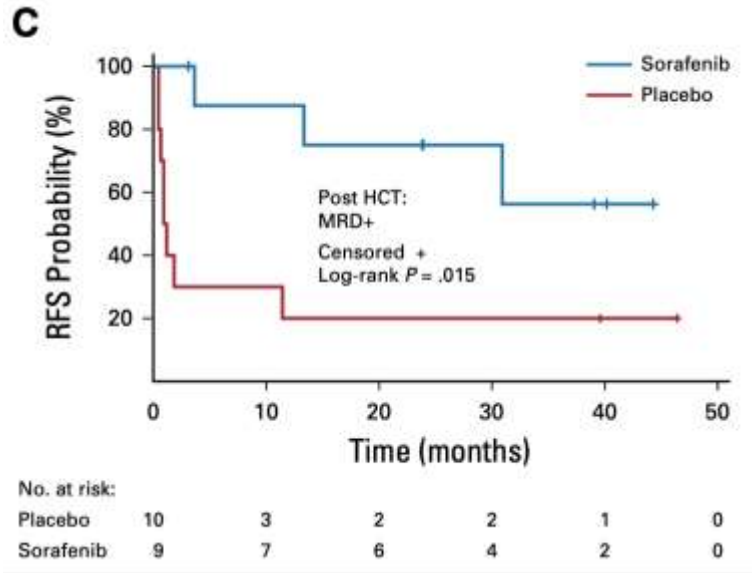
- No GVHD
- Relapsed day +60 post-alloSCT 38% blasts
  - *FLT3*-ITD AR 0.22
  - *NPM1* mutation detected

SORMAIN trial: Sorafenib vs placebo

Starting between day +60 to +100 for 24 months

RFS benefit especially in patients with MRD+ post-HCT





Burchert A, et al. *J Clin Oncol*. 2020;38:2993-3002.

Case progress

- Commenced gilteritinib monotherapy (compassionate access)
  - Best response: MLFS
- Progressive disease with CNS involvement
- Palliative therapy > death

Summary

- Therapeutic landscape is rapidly changing for *FLT3*-mutant AML
- Better strategies are needed to tackle rising MRD
  - *NPM1* MRD monitoring
  - Optimal utilization of *FLT3*-ITD MRD by NGS still being investigated
- Better strategies to salvage relapsed *FLT3*-ITD AML

Global Leukemia Academy

Case based panel discussion: regional challenges in AML care

Sun Loo

APTITUDE HEALTH

GLOBAL LEUKEMIA ACADEMY

AML Clinical Case
16 May 2021

Dr Sun Loo
MBBS, FRACP, FRCPA
Alfred Hospital, Victoria, Australia
Email: s.loo@alfred.org.au

Case presentation

72-year-old male, ECOG 0 with no major comorbidities

History of

- *JAK2* V617F-mutant essential thrombocytosis (ET) since 2015
- Progression to myelofibrosis (MF) in 2020 managed with peg-interferon

14 months later, progression to AML with:
WCC 12 × 10^9/L, platelets 279 × 10^9/L
28% bone marrow blasts
G2-3 reticulin fibrosis with mild osteosclerosis on trephine

Secondary AML: post–ET-MF in blast phase
Cytogenetics: del(7q)
FLT3-ITD, -TKD and *NPM1* negative

Q

Case presentation

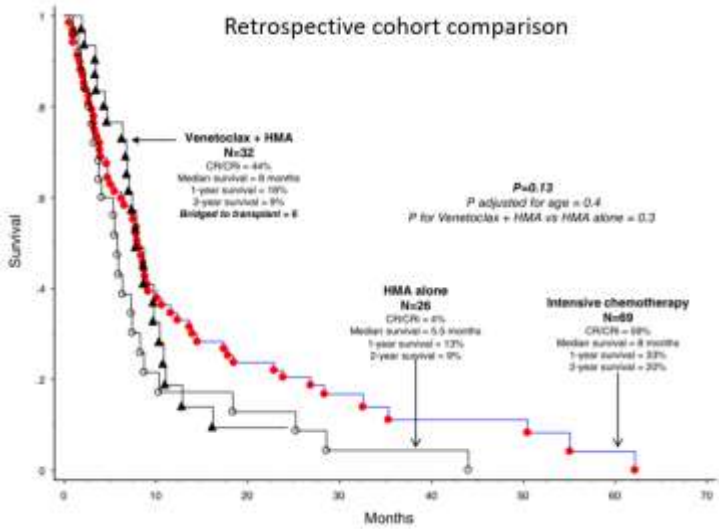
How would you treat this patient?

1. Induction chemotherapy (ie, 7+3 with cytarabine and anthracycline)
2. Venetoclax and azacitidine/low-dose cytarabine
3. Azacitidine monotherapy
4. Azacitidine and ruxolitinib, if accessible
5. Enroll onto a clinical trial
6. Palliation and supportive care

Use of venetoclax combinations in AML transformed from prior myeloproliferative neoplasm described

- Due to rarity, no large prospective studies
- Retrospective cohort comparisons with other agents or case series exist

Regime	Response	Adverse events	References
Venetoclax-azacitidine/decitabine (n = 32) Median VEN dose 200 mg daily	CR/CRi 44%	Febrile neutropenia/sepsis in 31% Degree of pancytopenia not graded	Gangat N, et al. *Am J Hematol*. 2021
Venetoclax-cytarabine (n = 2) VEN dose 600 mg daily	CR in 1 of 2	No major adverse events described	McKay J, et al. *Blood*. 2019 134(Suppl 1): abstract 5140



Question:
Are there any pertinent concerns with using a venetoclax-based regimen in a patient with AML from prior myelofibrosis?

Gangat N, et al. *Am J Hematol*. 2021.

Q

Case presentation

Received induction chemotherapy 7+3
Tolerated chemotherapy well
D28 response = 52% blasts
REFRACTORY

Next step?

1. Venetoclax + HMA/LDAC
2. More extensive mutation testing to identify “druggable” targets
3. Intensive salvage chemotherapy (FLAG-AMSA)
4. Enroll onto clinical trial
5. Palliation and supportive care

Case presentation

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4. Enroll onto clinical trial
5. Palliation and supportive care

Discussion Question:
In this setting, what potential “druggable” targets would you be looking for?

Case presentation

- Myeloid NGS was performed

Mutation	Genotype	Amino acid change	VAF%
JAK2	c.1849G>T	p.Val617Phe	3%
TET2	c.2051_2061del AACAAAGAGCA	p.Gln684ArgfsTer5	38%
CBL	c.1111T>A	p.Tyr371Asn	34%

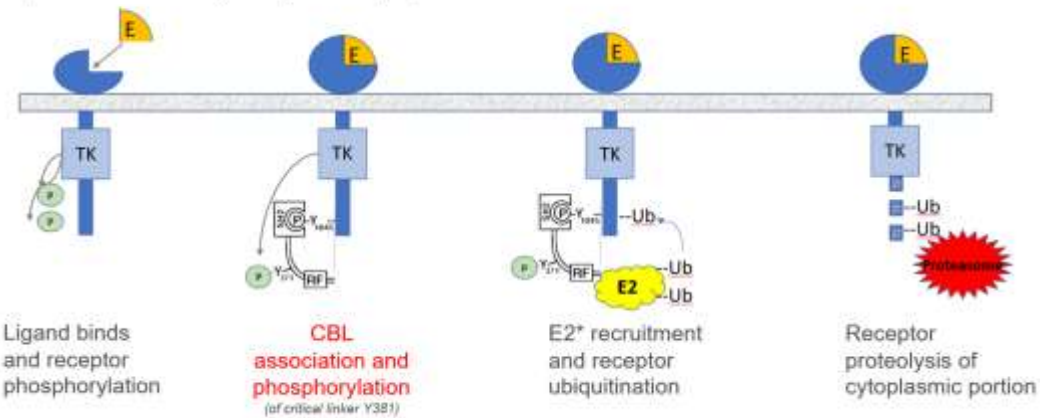
Discussion Question:
Is there a mutation identified above that could be amenable to a targeted inhibitor?

CBL in myeloid neoplasms

- Highest frequency in MDS/MPN overlap disorders (13%–20%)
- Primary myelofibrosis (~5%)
- **In AML, described in** 1.1%–5%
- Frequency in Australian AML population evaluated retrospectively in 90 AML samples with **4.44%** *CBL*-mutant identified

Critical function of CBL: Receptor tyrosine kinase degradation

E3 ligases which ubiquitinate activated RTKs (such as FLT3) and DIRECT their trafficking through endosomal compartments → resulting in degradation by lysosomes



*E2 - ubiquitin conjugating enzyme. This enzyme transfers Ub to TK once cbl RING finger binds to it → recruits proteasome

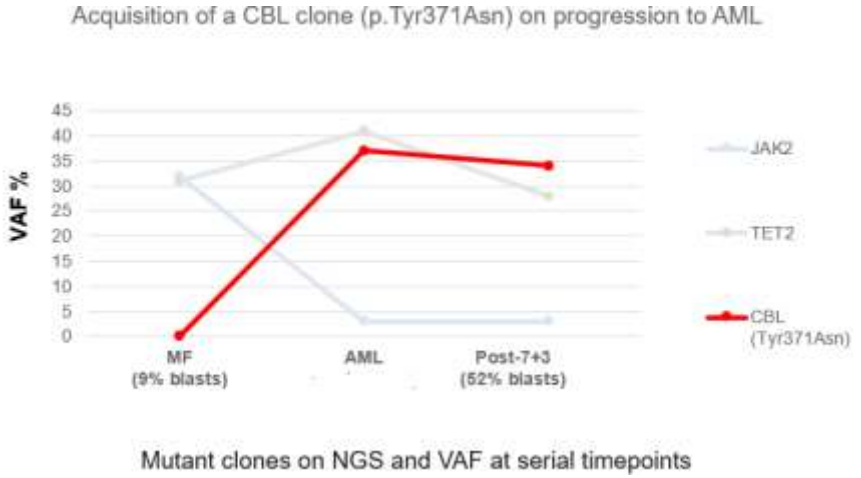
CBL is a **negative regulator of activated tyrosine kinase receptors**

- Functions as E3 ligases that **ubiquitinate** and negatively regulate activated RTKs such as FLT3 receptor
- Directs trafficking through endosomal compartments and degradation by lysosomes
  ***CBL* mutation** → loss of ubiquitin ligase function → **maintenance of signaling function (oncogenic)**

Kohlmann A, et al. *J Clin Oncol*. 2010;28:3858-3865; Tefferi A, et al. *Blood.* 2016;1:105-111; Levkowitz G, et al. *Mol Cell*. 1999;4:1029-1040; Ghassemifar R, et al. *Pathology*. 2011;43:261-265.

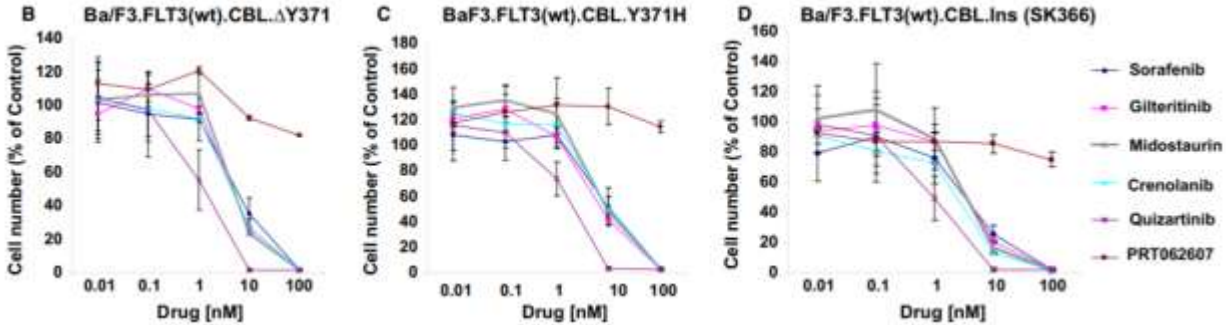
Progress

- Sequencing of prior stored DNA samples from this patient



Mutant clones on NGS and VAF at serial timepoints

- Assessment of preclinical rationale for use of a FLT3 inhibitor in this case



Weisberg E, et al. *J Cell Mol Med*. 2020;24:2145-2156.

- Amendment of protocol to include *CBL*-mutant AML patients into an Australian study primarily evaluating FLT3 inhibitor ponatinib with azacitidine in *FLT3*-ITD AML mutant patients

FLT3-ITD or CBL AML either relapsed or refractory to or unfit for frontline intensive chemotherapy

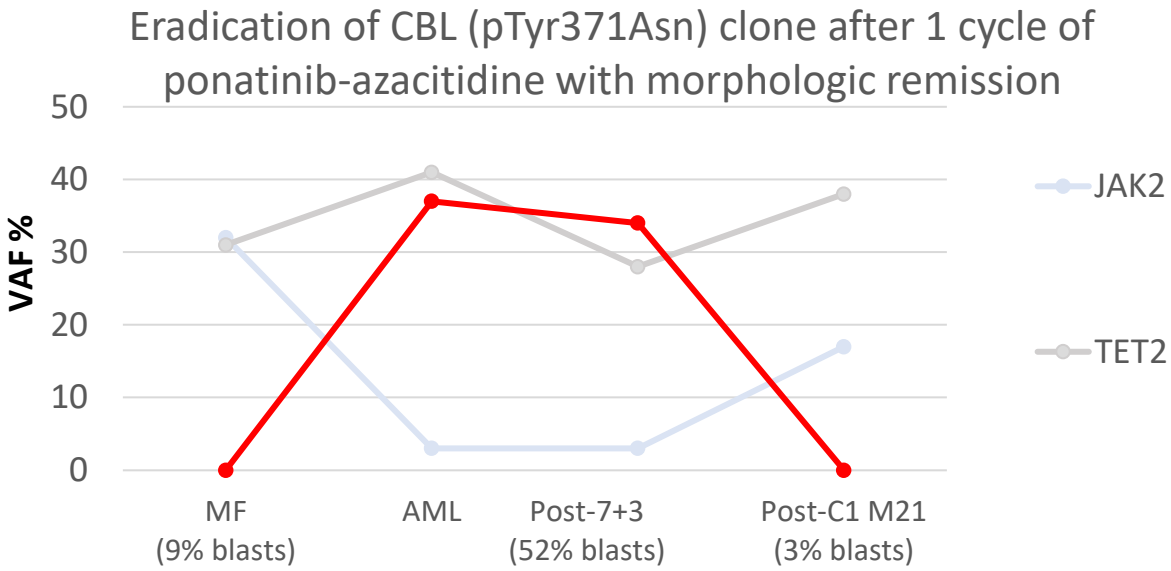
Azacitidine 75 mg/m^2 for 7 days
Oral ponatinib 30 mg from days 5–25
28-day cycles

Challenges include

1. Overall rarity of *CBL*-mutant AML or low frequency of testing in the first place.
2. Identifying other potential combination partners with maximum antileukemic activity.

Back to the case

- Complete remission with incomplete recovery achieved **after 1 cycle** of ponatinib-azacitidine
- **Remains in complete remission at the end of cycle 13** with reversion to MPN disease phenotype



Summary

1. Patients with AML transformed from MPN remain a therapeutic challenge. Variable practice with regard to upfront/relapsed-refractory treatment of AML transformed from prior myelofibrosis.

2. Importance of molecular profiling in these cases (including AML with antecedent CMML) to identify potential option for use of targeted inhibitors.

3. *CBL* mutation is rare, and use of FLT3 inhibitor as a targeted inhibitor is not yet widespread practice beyond clinical trials; however, it is important to document individual/case-series responses in this difficult-to-treat group of patients.

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Panel Discussion

All faculty

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Educational ARS Questions

Naval Daver

APTITUDE HEALTH

Q

Question 1 (AML)

Which patients were not included in the VIALE-A study:

a) Patients >75 years of age
b) Patients <75 years of age with ECOG PS 3
c) Patients <75 years of age with significant cardiac co-morbidity
d) Patients <75 years of age with significant pulmonary comorbidities
e) Patients <75 years of age with adverse cytogenetics

Q

Question 2 (AML)

Which of the following is not true regarding HMA + venetoclax in AML:

a) The CR/CRi with HMA+VEN in the VIALE-A was >65%
b) HMA+VEN improved median OS compared with HMA alone
c) Lab or clinical TLS is not seen with HMA+VEN in AML
d) The recommended daily dose of venetoclax (without azoles) was 400mg PO Qday in VIALE-A study
e) Neutropenia is commonly seen with HMA+VEN regimen

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Closing Remarks

Elias Jabbour

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Thank You!

- Thank you to our sponsors, expert presenters, and to you for your participation
- Please complete the **evaluation link** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the globalleukemiaacademy.com website within a few weeks
- If you have a question for any of our experts that was not answered today, you can submit it through the GLA website in our Ask the Experts section

THANK YOU!

AMGEN

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Emerging and Practical Concepts and Controversies in Leukemias

16 May 2021

Virtual Breakout: Adult Leukemia Patients

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