Acute Leukemia – From Precision Medicine to ImmunoRx

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Disclosures

Hagop M. Kantarjian, MD, has affiliations with Amgen, ARIAD, Astex, BMS Novartis, Pfizer *(Contracted Research)*; AbbVie, Amgen ARIAD, BMS, Immunogen, Orsinex, Pfizer *(Other Honoraria)*.

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Acute Leukemia - Exciting Trends

- AML – Monoclonal antibodies and bispecific antibody constructs targeting CD33 and CD123
  - FLT3 inhibitors
  - IDH1/2 inhibitors
  - venetoclax
- ALL – BCR-ABL TKIs in Ph+ ALL
  - Monoclonal antibodies and bispecific antibody products targeting CD20,CD19, CD22 and CD123 (rituximab, inotuzumab, blinatumomab)
  - CART

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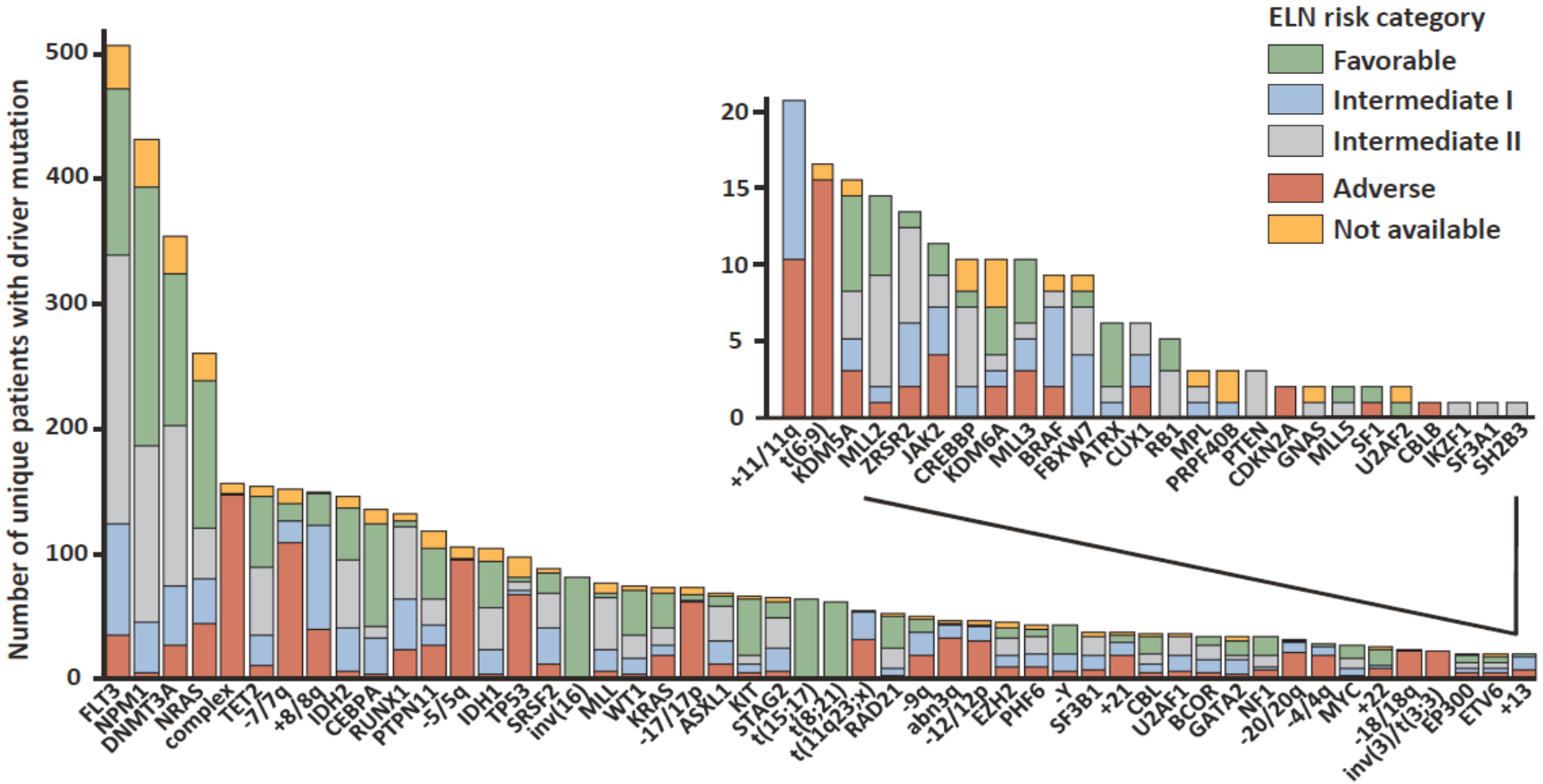
Genomic Landscape of AML



- Targeted resequencing of 111 myeloid cancer genes (combined with cytogenetic profiles) in 1540 AML
- 5236 driver mutations (i.e., fusion genes, copy number alterations, gene mutations) involving 77 loci
- 6 genes mutated in >10% pts; 13 genes 5–10% pts; 24 genes 2–5% pts; 37 genes <2% pts

Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221.

Clinical Applications of Molecular Studies in AML

- **FLT3-ITD mutations**: Add FLT3 inhibitor (midostaurin, sorafenib, quizartinib), 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
- **TP53 mutation**: Consider decitabine 10 days ± others (GO, venetoclax); refer to allo-SCT

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NCCN Guidelines. Acute Myeloid Leukemia; v2.2018.
https://www.nccn.org/patients/guidelines/aml/4/. Accessed October 29, 2018.

And, Suddenly in 2017 to 2018, FDA Approvals….

- **Midostaurin** (RYDAPT®) for de novo younger AML (< or = 60 yrs), FLT3 mutation - April 2017
- **Enasidenib** (AG-221; IDHIFA®) for R-R AML and IDH2 mutation - August 2017
- **Ivosidenib** (AG-221) for R-R AML - August 2018
- **CPX 351** (VYXEOS™) for newly Dx Rx-related AML and post MDS AML - August 2017
- **Gemtuzumab ozogamycin** revival for frontline AML Rx - August 2017
- **Venetoclax (VENCLEXTA®) combo with AZA, DAC, LDAC and Glasdegib (DAURISMO™) combo with LDAC for frontline elderly AML- November 2018**
- **Giteritenib (FLT3 inhibitor) for FLT mut. R-R AML**
- Data + with another FLT3 inhibitors: **quizartinib**

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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 x 1 if WBC> 10 x 10^9/L
- **Maintenance**
  - ATRA 45 mg/m^2/d x 2 wks Q mo x 6
  - As_2O_3 0.15/kg/d x 4 wks Q2 mo x 3
  - GO in PCR+

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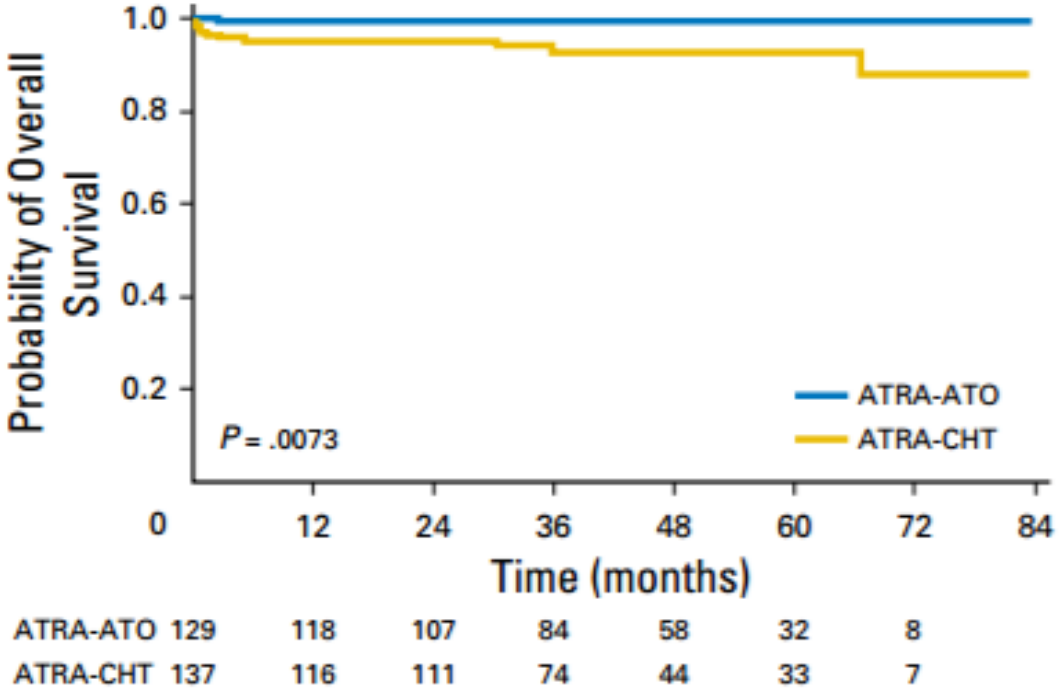
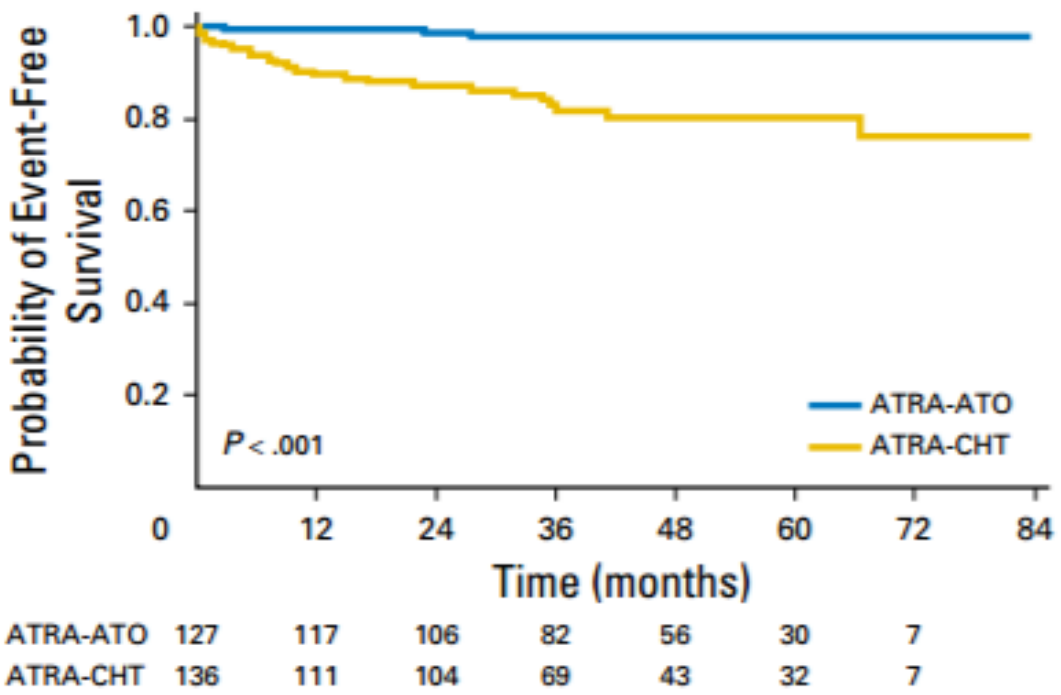
Ravandi F, et al. *J Clin Oncol*. 2009;27(4):504-510.

APL: Outcome with ATRA + AS_2O_3 versus AIDA





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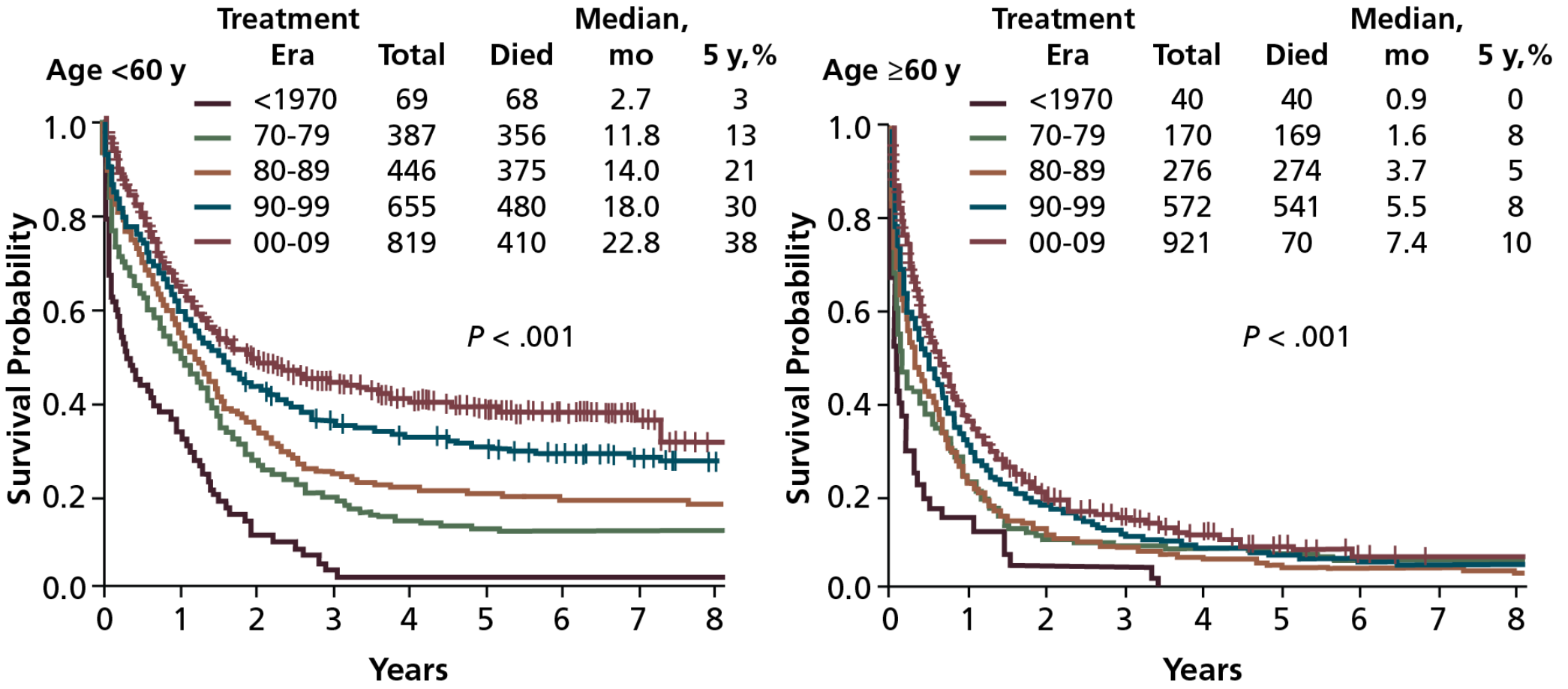
Platzbecker U, et al. *J Clin Oncol*. 2016;35(6):605-612.

AML: Survival by Age and Treatment Era



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Kantarjian H, et al. *Cancer*. 2010;116(21):4896-4901.

AML: What Works

- FLT3 inhibitors
- IDH1-2 inhibitors
- CD33 and CD123 antibodies
- Venetoclax
- CPX351

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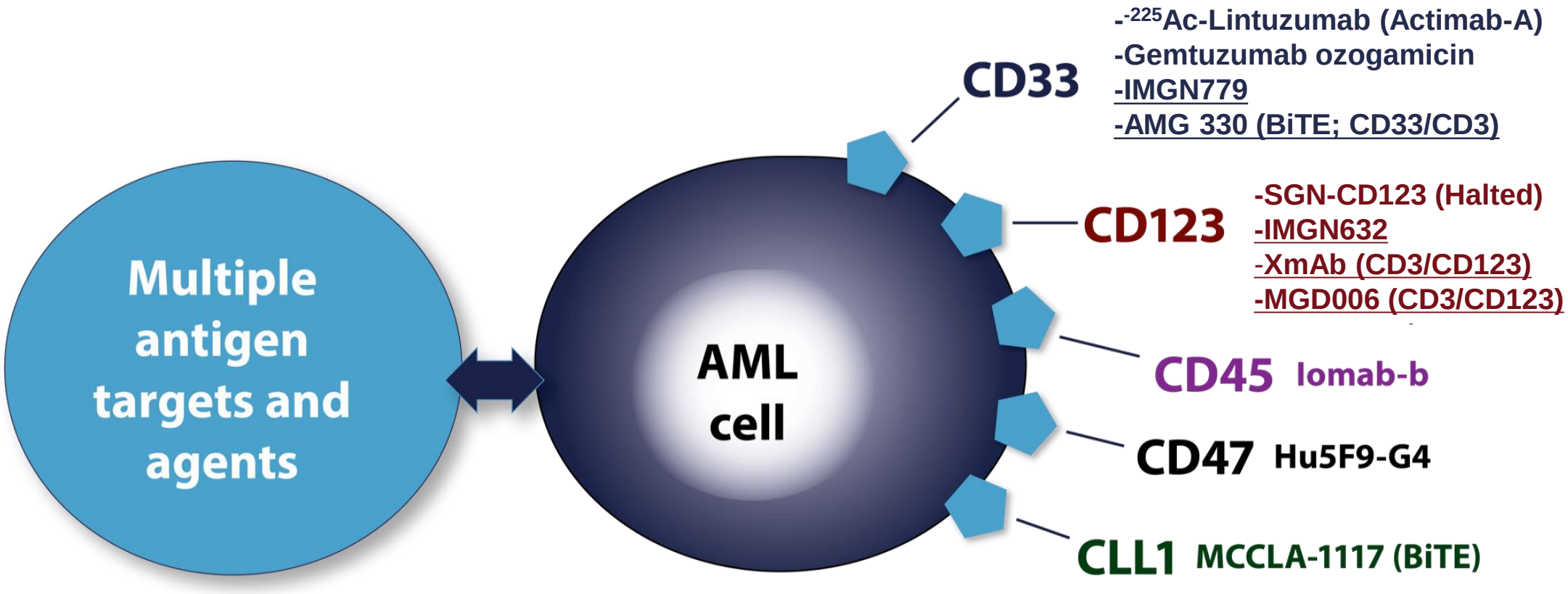
Target Antigens and Novel Antibodies in AML



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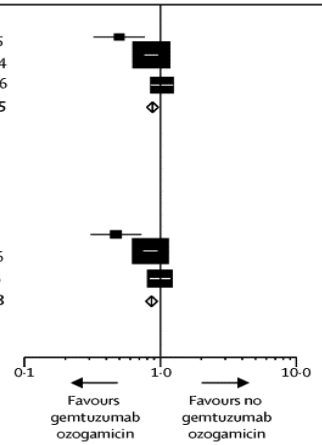
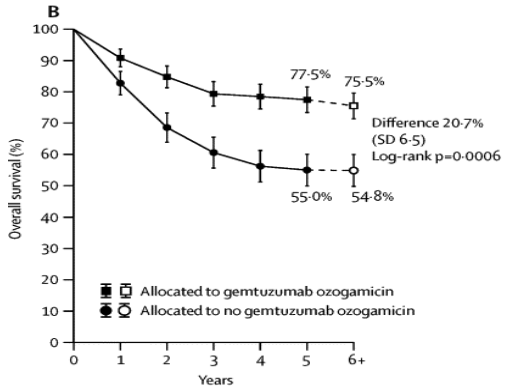
Gemtuzumab Ozogamycin in Induction Therapy Meta-Analysis of 5 Randomized Trials

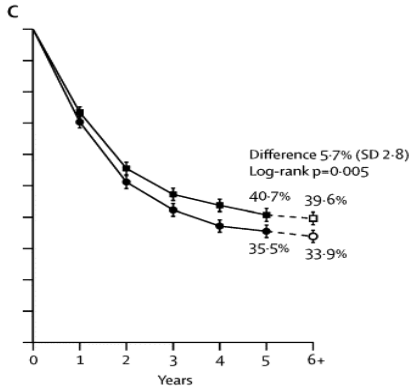
A

	Events/patients: Gemtuzumab ozogamicin group	Events/patients: No gemtuzumab ozogamicin group	o–e	Variance	OR (95% CI)	p value
Original coding						
Favourable	32/125	54/126	−14·3	20·5	0·50 (0·32–0·77)	
Intermediate	549/962	596/964	−44·2	284·4	0·86 (0·76–0·96)	
Adverse	223/261	227/256	3·1	110·6	1·03 (0·85–1·24)	
Subtotal	**804/1348**	**877/1346**	**−55·4**	**415·5**	**0·88 (0·79–0·96)**	**0·007**
Test for heterogeneity between subgroups: χ^2=9·6; p=0·008						
Test for trend between subgroups: χ^2=7·8; p=0·005						
Revised MRC coding[12]						
Favourable	30/122	54/124	−15·5	20·6	0·47 (0·31–0·73)	
Intermediate	506/911	559/916	−45·3	264·6	0·84 (0·75–0·95)	
Adverse	260/299	258/284	−1·2	127·6	0·99 (0·83–1·18)	
Subtotal	**796/1332**	**871/1324**	**−61·9**	**412·8**	**0·86 (0·78–0·95)**	**0·002**
Test for heterogeneity between subgroups: χ^2=10·1; p=0·006						
Test for trend between subgroups: χ^2=7·7; p=0·006						

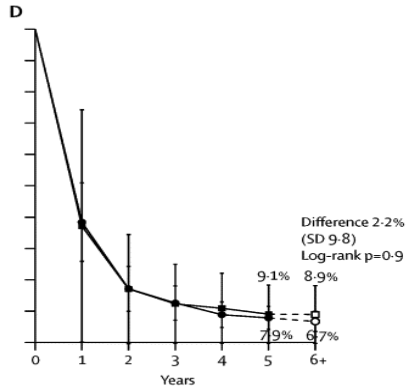




Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0



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

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Hills RK, et al. *Lancet Oncol*. 2014;15(9):986-996.

Current mAb Trials at MDACC

Target	Product	Class	PI	MDACC Protocol
CD33	IMGN-779	ADC (DGN-462)	Cortes	2015 – 1024
	AMG-330	Bispecific CD33 / CD3	Ravandi	2015 – 0296
	AMG-673	Bispecific CD33 / CD3	Ravandi	2017 – 0365
	AMV-564	Tandem Diabody CD33 / CD3	Cortes	2016 – 0646
CD123	SL401	ADC (Diphtheria)	Konopleva	2013 – 0979
	SL401	ADC (Diphtheria)	Pemmaraju	2014 – 0976
	XmAb	Bispecific CD123 / CD3	Ravandi	2016 – 0165
	SGN-123	ADC (PBD)	Ravandi	2016 – 0454
	IMGN-632	ADC (IGN)	Daver	2017 – 0855
CD19	ADCT-402	ADC (PBD)	Jain	2015 – 0985
CD22	ADCT-602	ADC (PBD)	Jain	2017 – 0938
CD25	ADCT-301	ADC (PBD)	Jain	2015 – 0618
FLT3	AGS62P1	ADC (AGL-0185-30)	Cortes	2016 – 0647

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FLT3 Inhibitors Under Development in AML

Phase 2[1-3]

- Crenolanib
- PLX3397
- Dovitinib
- Ponatinib

Phase 3[3-5]

- Quizartinib
- Sorafenib

FDA approved[6]

- MidostaurinG
- Gilteritinib

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01831726. Accessed October 29, 2018.
2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01207440. Accessed October 29, 2018.
3. Wander SA, et al. *Ther Adv Hematol.* 2014;5(3):65-77.
4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02039726. Accessed October 29, 2018.
5. Perl AE, et al. *J Clin Oncol.* 2016;Abstract TPS7072.
6. Rydapt® USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf. Acessed October 29, 2018.

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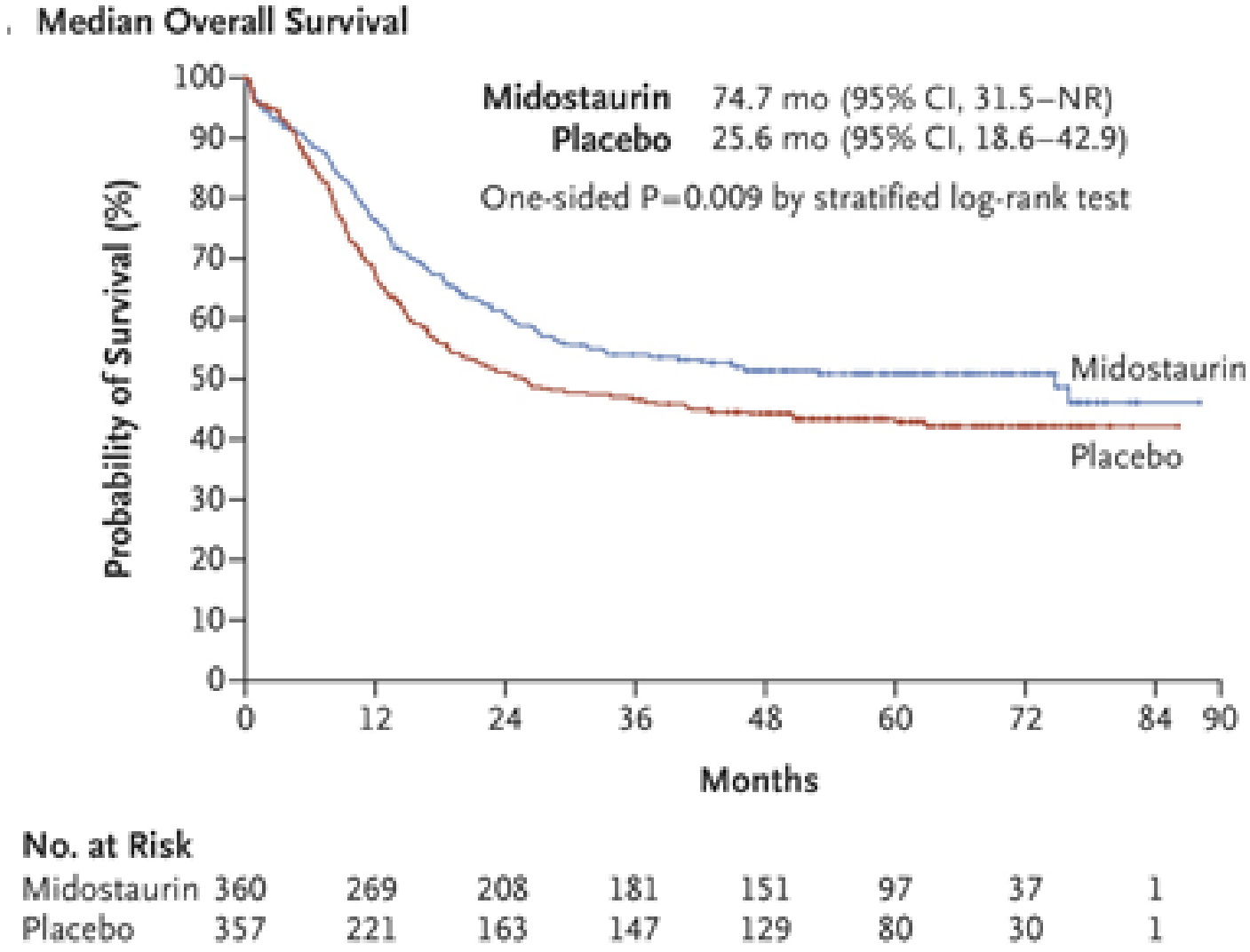
Chemo Rx ± Midostaurin in AML (RATIFY)



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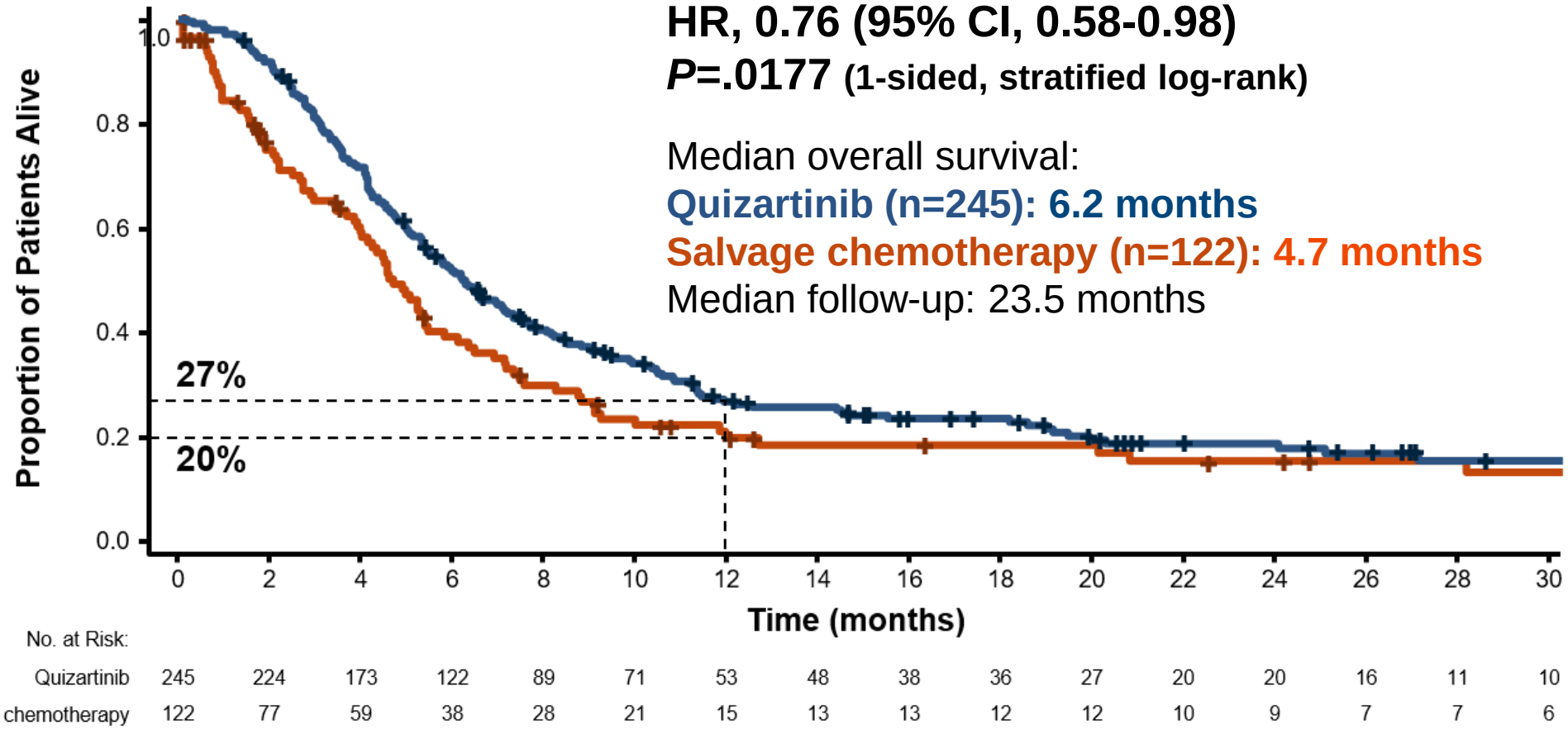
Stone RM, et al. *N Engl J Med*. 2017;377(5):454-464.

QUANTUM-R : Overall Survival



HR, 0.76 (95% CI, 0.58-0.98)
***P*=.0177 (1-sided, stratified log-rank)**

Median overall survival:
Quizartinib (n=245): 6.2 months
Salvage chemotherapy (n=122): 4.7 months
Median follow-up: 23.5 months

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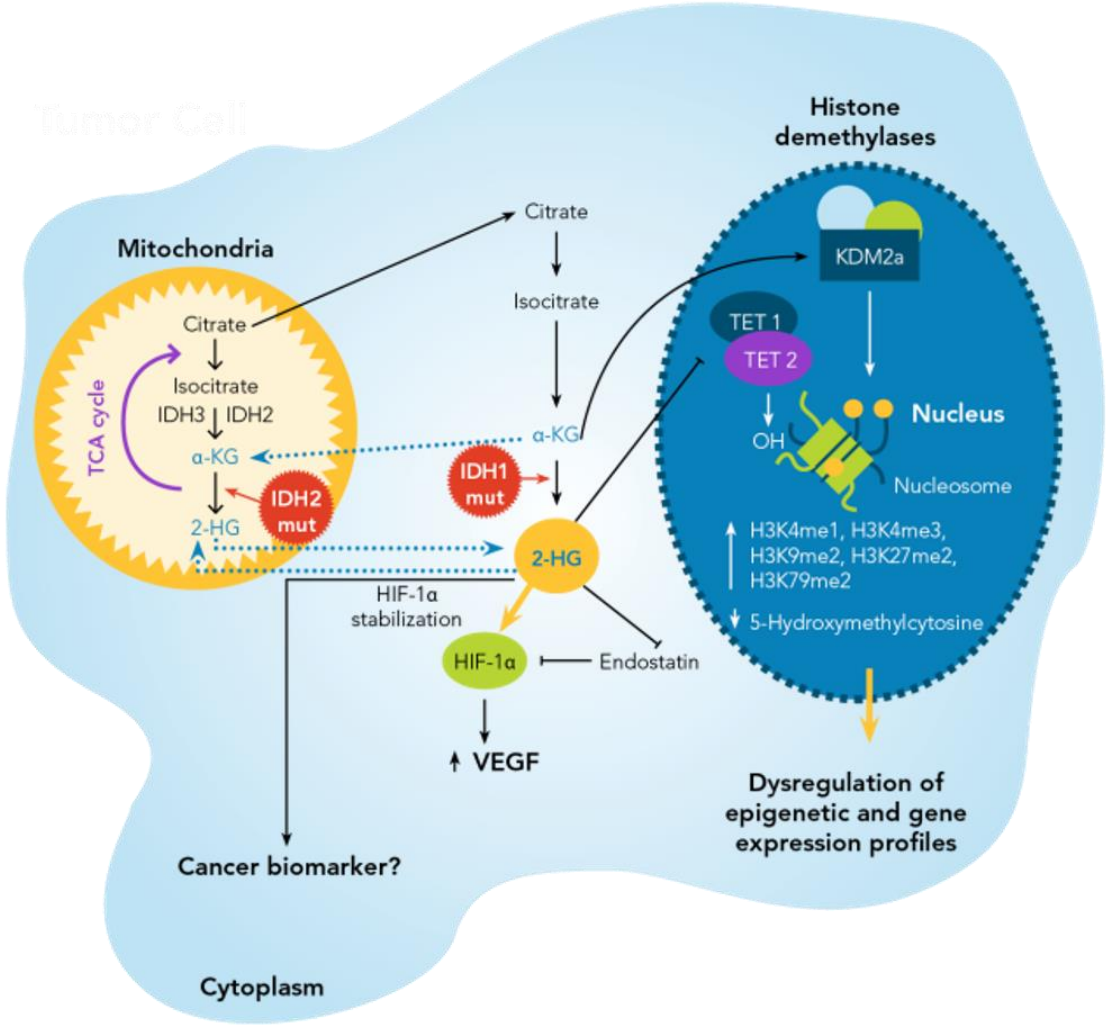
Cortes. EHA: LB2600; 2018

IDH Mutations Represent Important Cancer Metabolism Targets



- IDHwt: catalyzes oxidative decarboxylation of isocitrate to produce CO2 and α-KG
- 3 isoforms exist: IDH1, IDH2, IDH3
  - IDH1: cytoplasm
  - IDH2: mitochondria
- IDH mutations have neomorphic activity:
  - Produce high levels of "oncometabolite" 2-HG (gain of function)
  - 2HG leads to differentiation block via epigenetic alterations

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Adapted from: Prensner JR, et al. *Nat Med*. 2011;17(3):291-293.

Enasidenib (AG221) in R-R AML

- 239 patients Rx with enasidenib 5 to 650 mg orally daily; 153 patients Rx with 100 mg daily in Phase 2
- **ORR 70/239 = 40%;** median RD 5.8 mos; **median OS 9.3 mos**
- CR 19%; median OS 19.7 mos
- Grade 3 to 4 AEs: ↑ bili 12%; differentiation syndrome 7%

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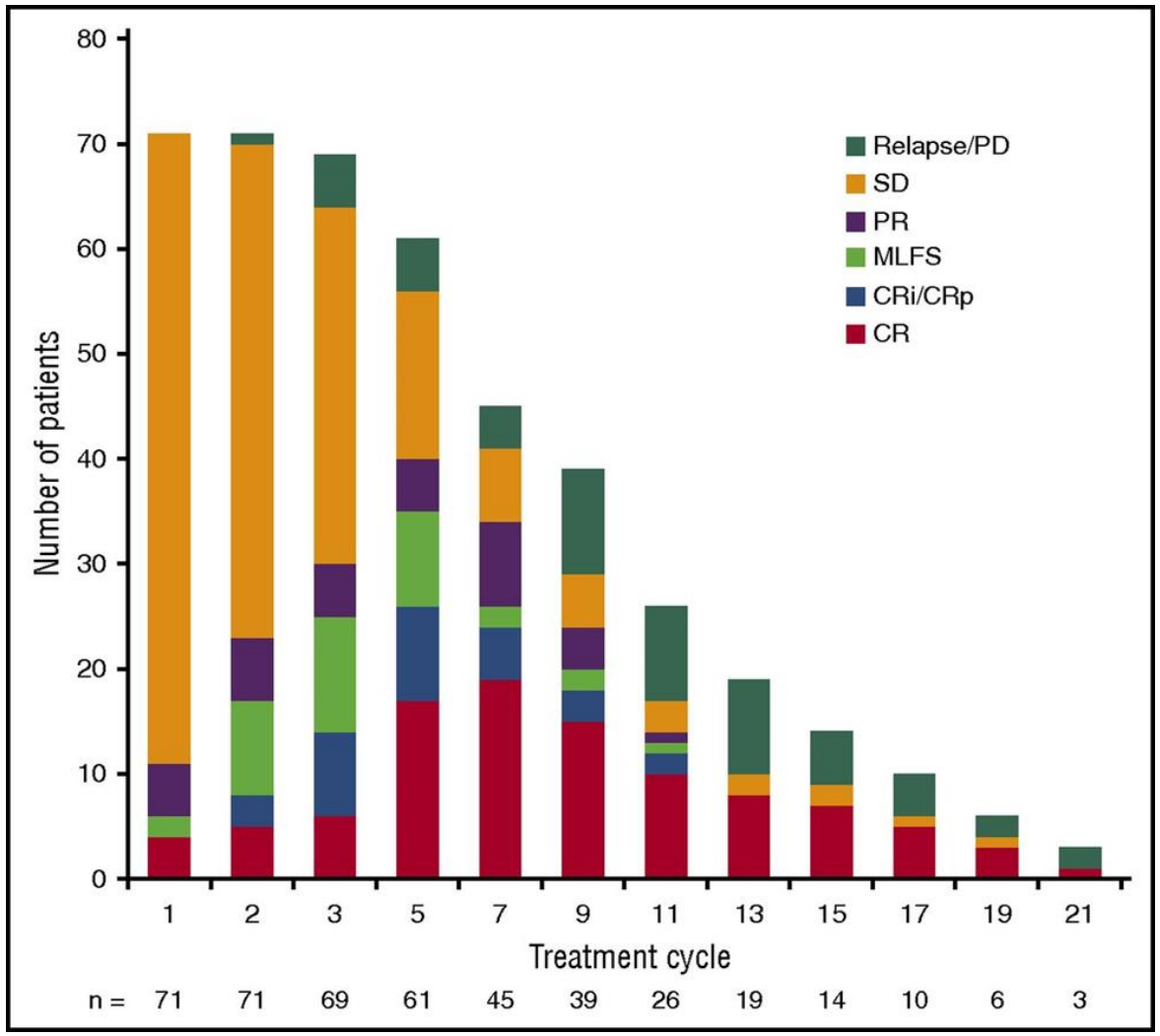
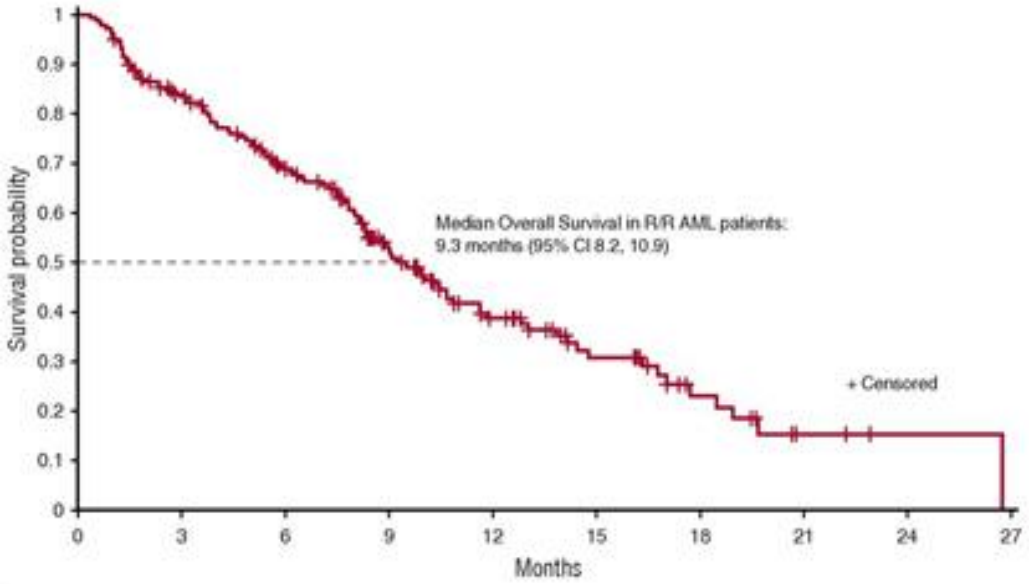
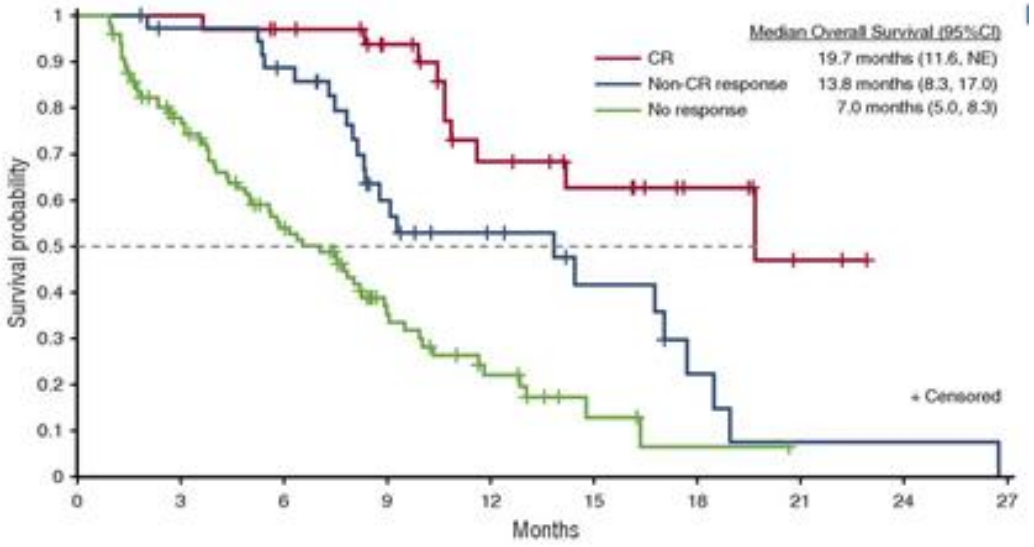
Stein EM, et al. *Blood*. 2017;130(6):722-731.

Enasidenib (AG221) in R-R AML







Stein EM, et al. *Blood*. 2017;130(6):722-731.

Ivosidenib (AG120; IDH1 Inhibitor) in R-R AML

- 258 patients Rx with ivosidenib 500 mg/d; 125 R-R AML
- CR 22%, CRh 9% - **CR + CRh 30%**
- Median OR duration 8.2 mos; median CRD 9.3 mos
- Differentiation syndrome 11%; grade 3 to 4 5%

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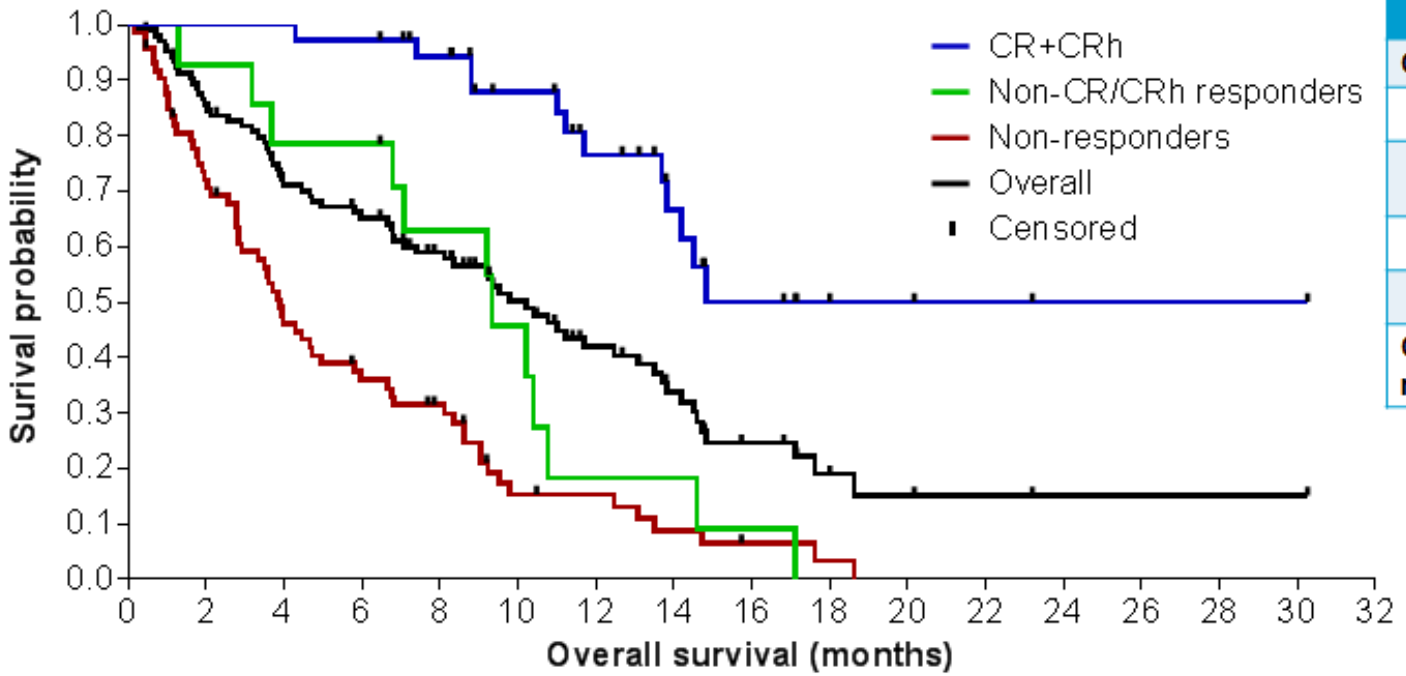
DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398.

Overall Survival by Best Response in R/R AML (n=125)



	Months
Overall Survival, median [95% CI]	
CR+CRh	NE [13.8, NE]
Non-CR/CRh responders	9.3 [3.7, 10.8]
Non-responders	3.9 [2.8, 5.8]
All	8.8 [6.7, 10.2]
Overall follow-up, median (range)	14.8 (0.2–30.3)

Number of patients at risk:

38	38	38	37	32	25	19	13	8	5	4	3	1	1	1	1	CR+CRh
14	13	11	11	8	5	2	2	1	0							Non-CR/CRh responders
73	51	32	24	19	8	7	4	2	1	0						Non-responders

Non-responders = all others including those with best responses of SD, PD or not evaluable

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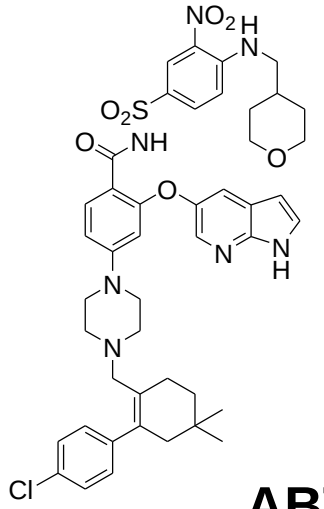
DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398.

Venetoclax (ABT-199): Potent, Selective BCL-2 Inhibitor

- High affinity for BCL-2
- Lower affinity for BCL-X_L, MCL-1
- >100-fold improved functional selectivity
- Orally bioavailable



ABT-199

	Binding Affinity				Cellular Efficacy, EC_{50} (nM)				
	TR FRET K_i (nM)				Engineered cell lines			Tumor cell lines	
Agents	BCL-2	BCL-X_L	BCL-w	MCL-1	BCL-2	BCL-X_L	Functional Selectivity	RS4;11 (BCL-2)	H146 (BCL-X_L)
ABT-263	0.04	0.05	7	>224	20	13	0.6	110	75
ABT-199	< 0.01	48	21	>440	4	261	87	12	3600

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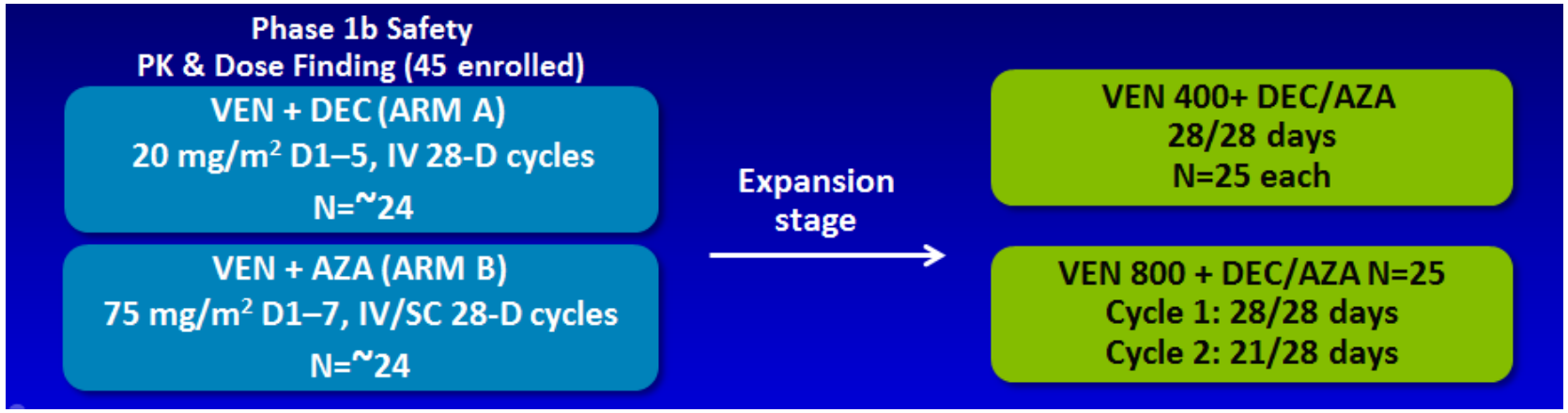
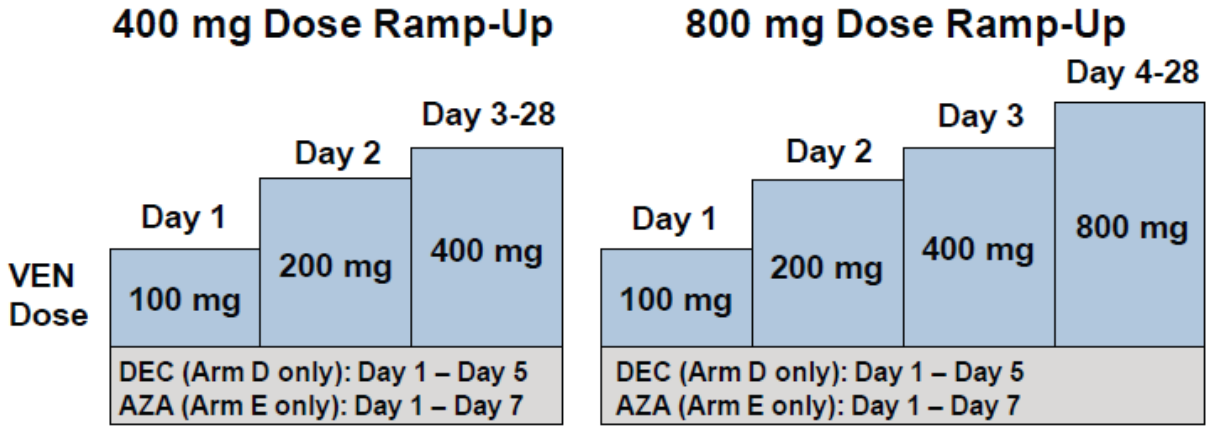
Souers AJ, et al. *Nat Med*. 2013;19(2):202-208.

Frontline AZA or DAC + Venetoclax in UnRx AML





AZA=azacitidine; D=Day; DEC=decitabine; HMA=hypomethylating agent; IV=intravenous; PK, pharmacokinetics; PO=per os; POS= posaconazole; RP2D=recommended phase 2 dose; SC=subcutaneous.

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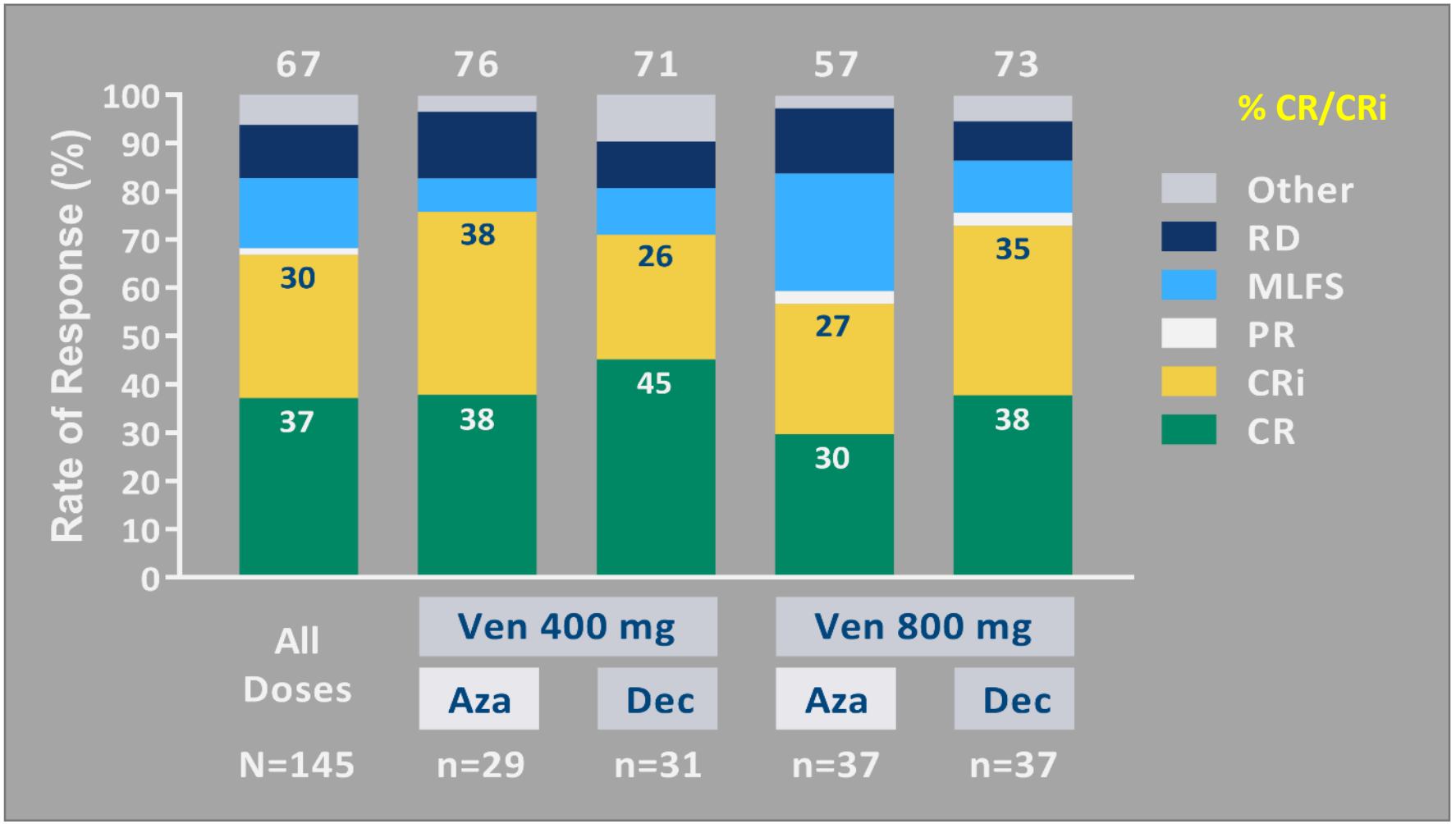
DiNardo CD, et al. *Blood*. 2017;130:2628 (poster presentation); DiNardo CD, et al. *J Clin Oncol* 2018;36:7010 (oral presentation); DiNardo CD, et al. *Lancet Oncol*. 2018;19(2):216-228 (including supplement).

Venetoclax in UnRx Elderly AML: Response by Cohort



DiNardo CD, et al. *J Clin Oncol* 2018; 36:7010 (oral presentation); DiNardo CD, et al. *Lancet Oncol*. 2018;19(2):216-228 (including supplement).

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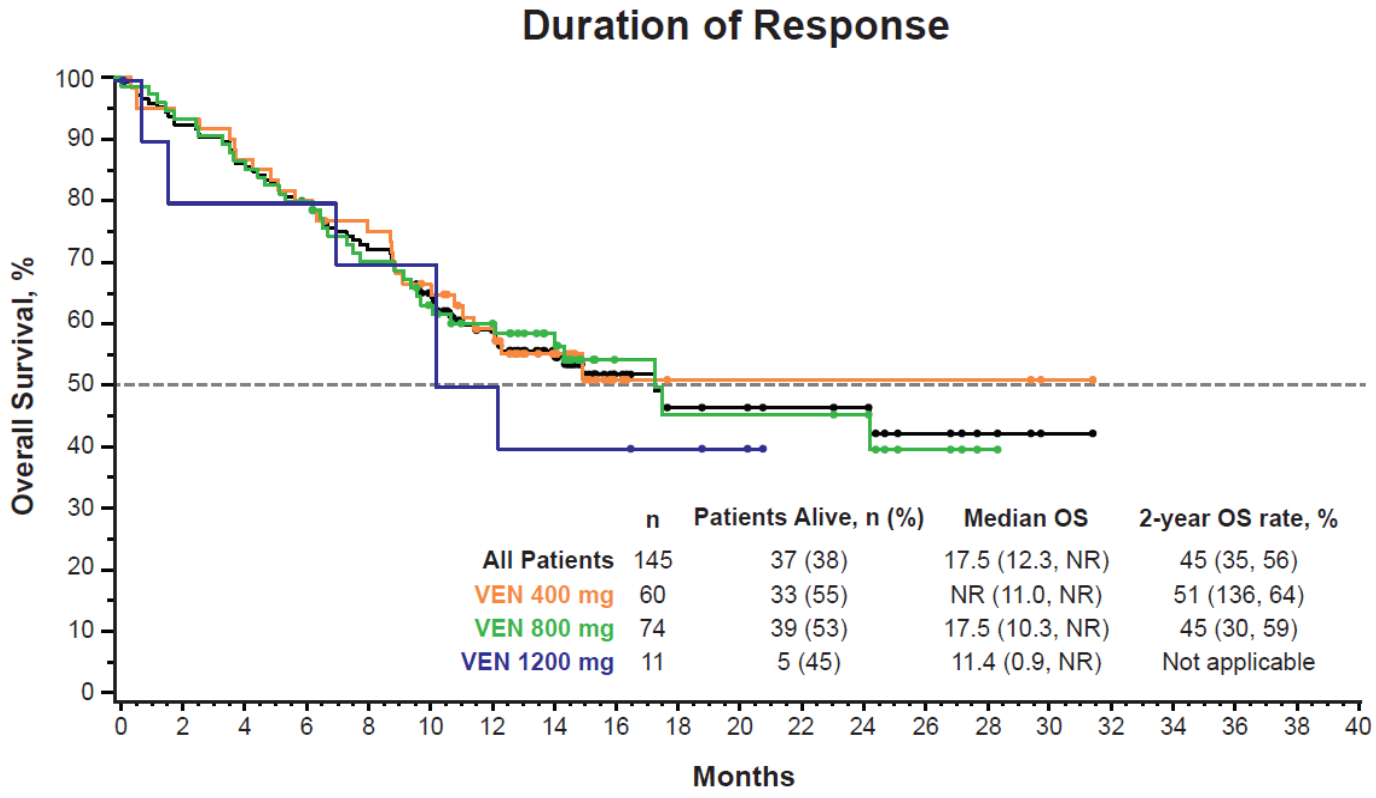
Venetoclax in UnRx Elderly AML: Survival



Patients at risk

All patients	145	133	124	115	102	89	73	53	25	16	15	13	12	7	4	2
VEN 400 mg	60	56	52	48	45	38	30	20	8	3	3	3	3	3	3	2
VEN 800 mg	74	69	64	59	50	44	38	29	13	10	10	10	9	4	1	
VEN 1200 mg	11	8	8	8	7	7	5	4	4	3	2					

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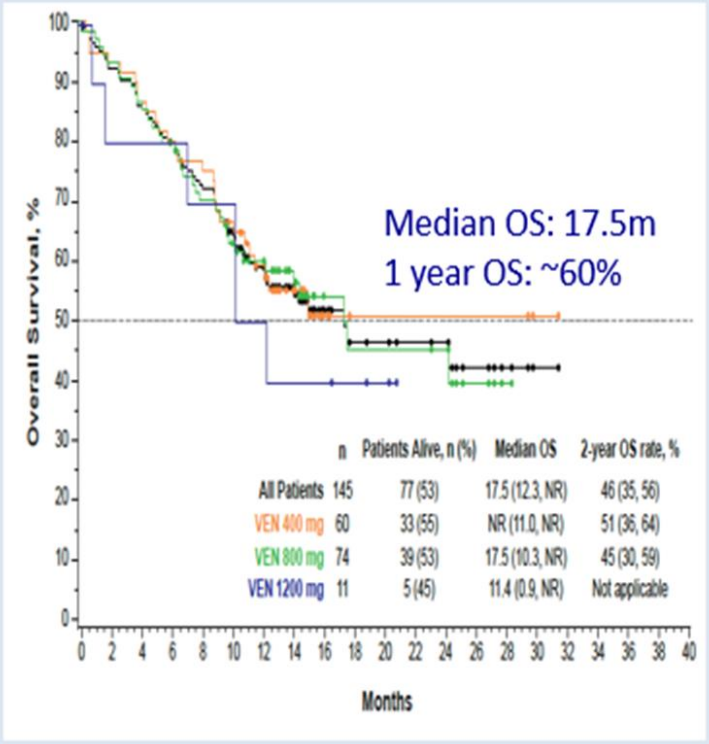
DiNardo CD, et al. *Blood*. 2017;130:2628 (poster presentation); DiNardo CD, et al. *Lancet Oncol*. 2018;19(2):216-228 (including supplement).

Venetoclax in UnRx Elderly AML: AZA/DAC ± Venetoclax

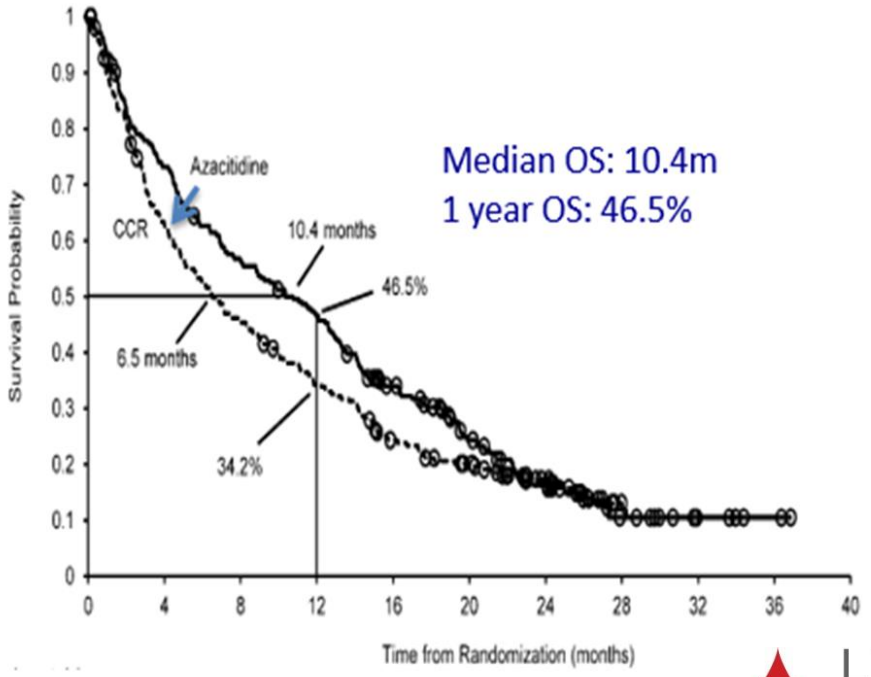
VEN/HMA CR/CRi 67%

N=145, median age 73



AZA CR/CRi 28%

N=241, median age 75



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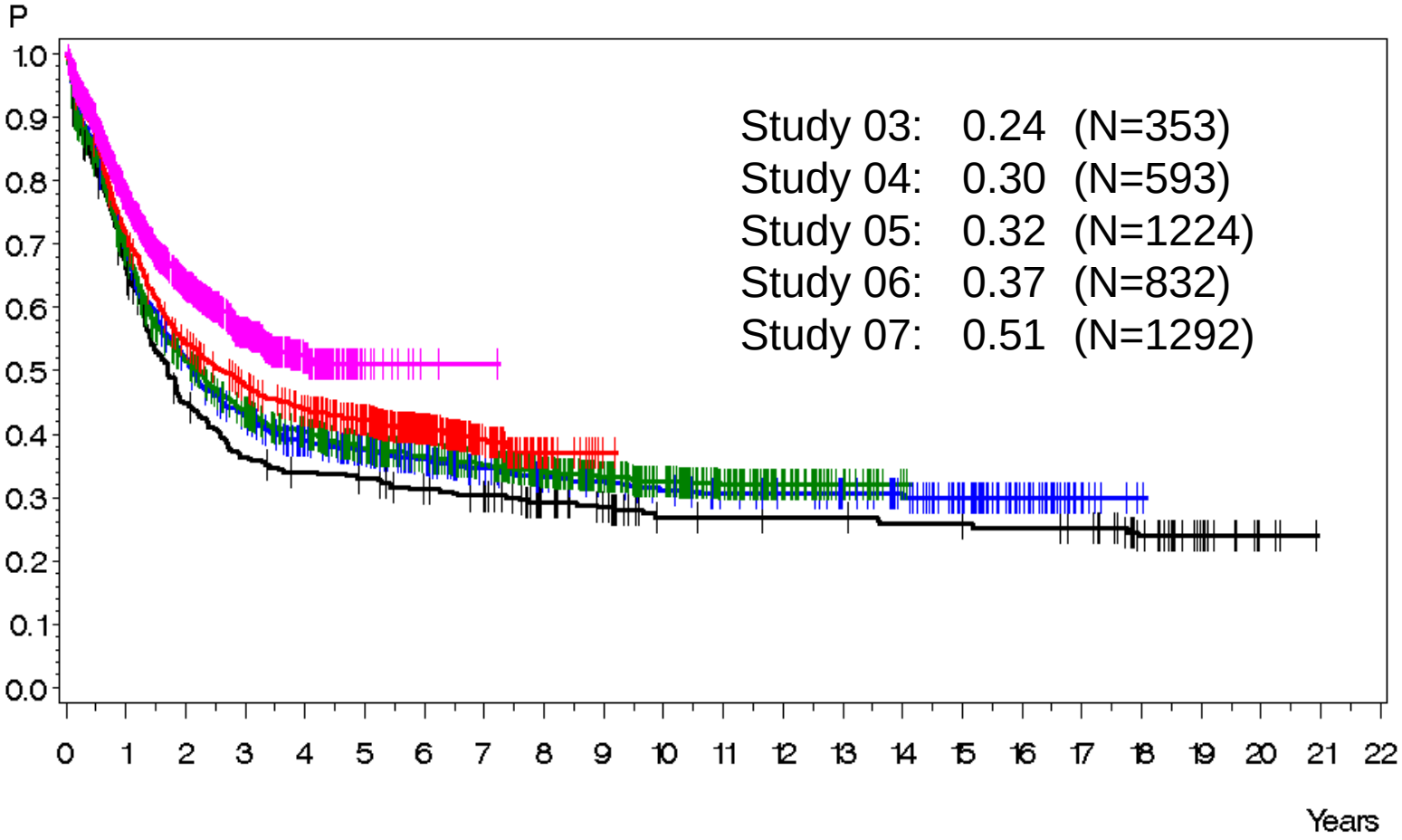
DiNardo CD, et al. *Blood*. 2017;130:2628 (poster presentation); Dombret H, et al. *Blood*. 2015;126(3):291-299.

Overall Survival: Comparison of the GMALL Studies (03/87 until 07/2003)



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Reasons for Recent Success in Adult ALL Rx

- Addition of TKIs to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- **Potential benefit of addition of CD19 bispecific antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx**
- **CAR-T**

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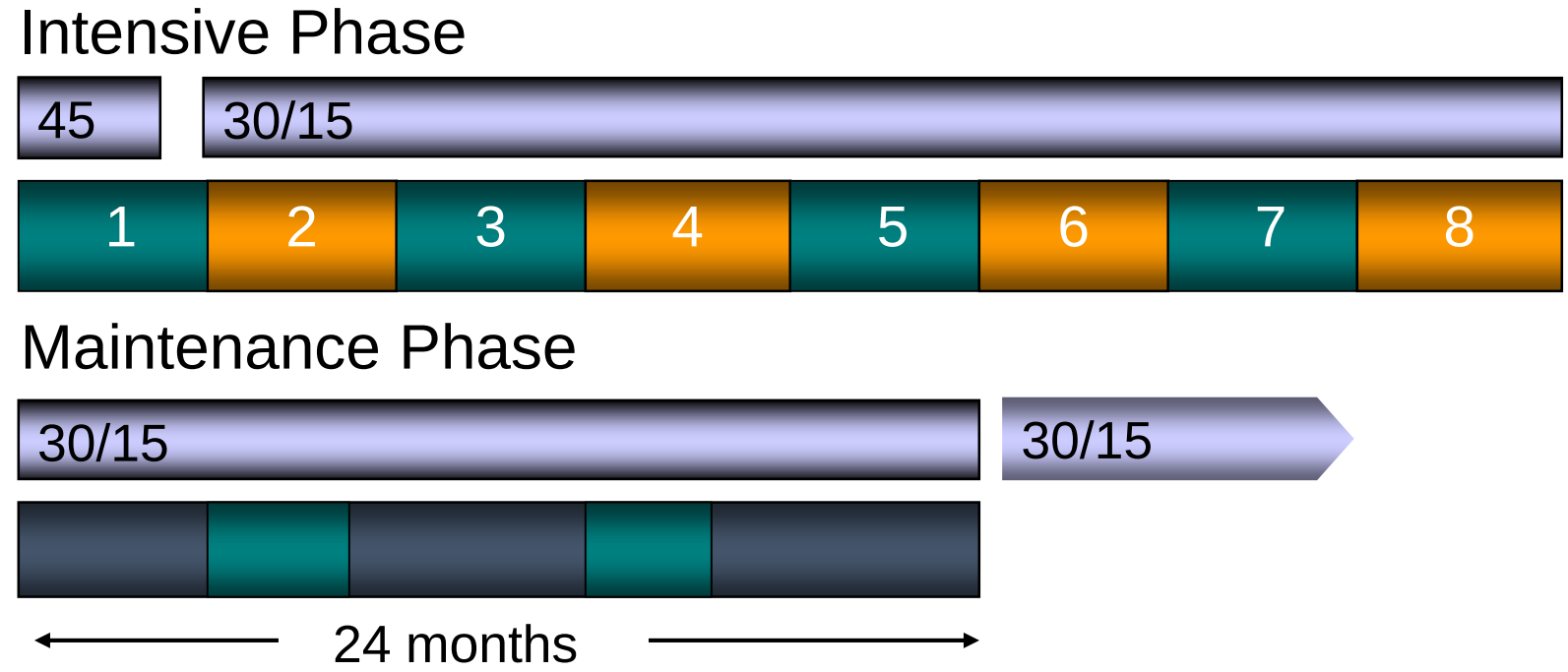
Hyper-CVAD + Ponatinib Design



- After the emergence of vascular toxicity, protocol was amended:
  Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

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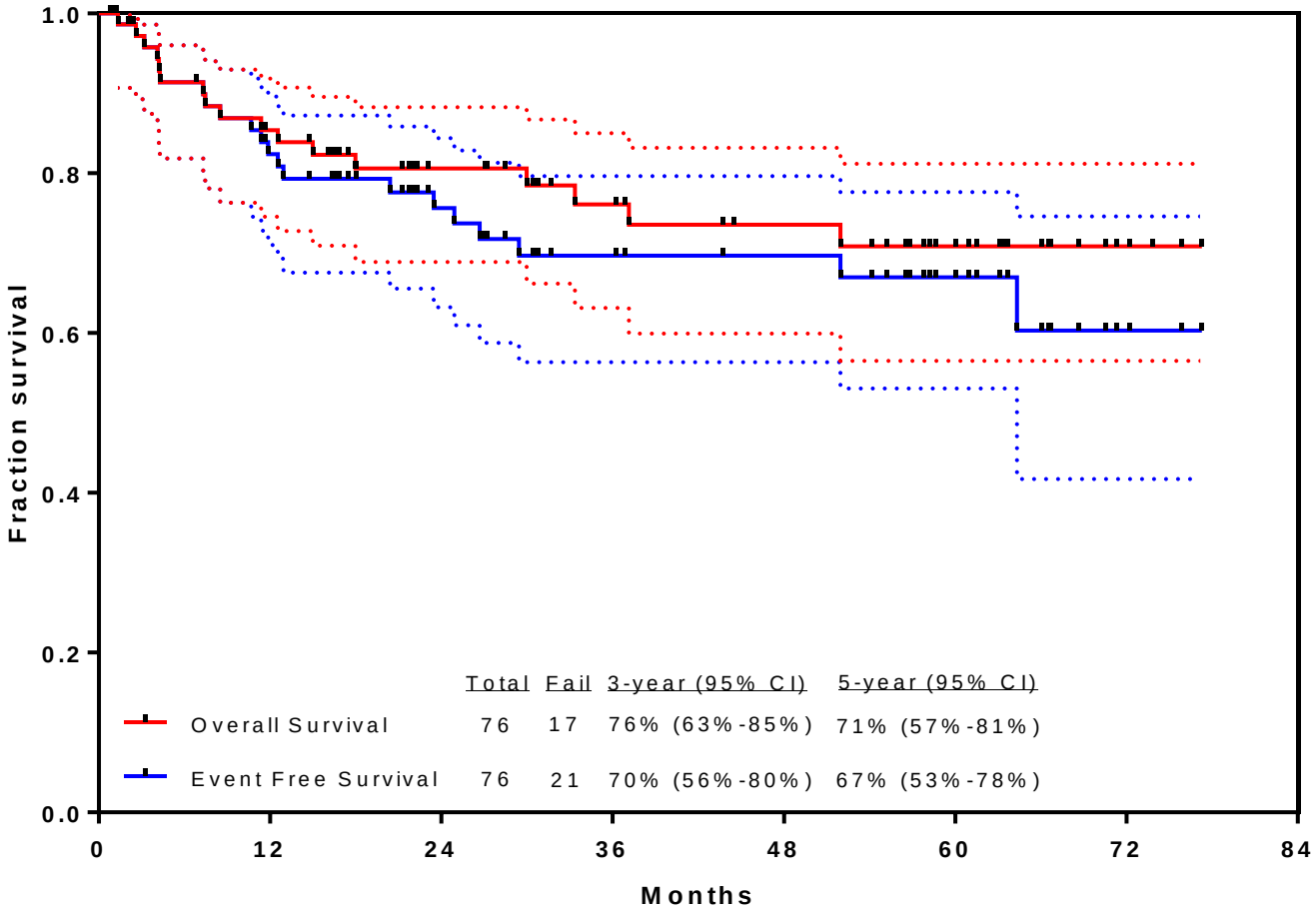
Jabbour E, et al. *Lancet Oncol.* 2015;16(15):1547-1555.

Hyper-CVAD + Ponatinib in Ph-Positive ALL: Survival



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Blinatumomab and Inotuzumab in R-R Ph-positive ALL

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

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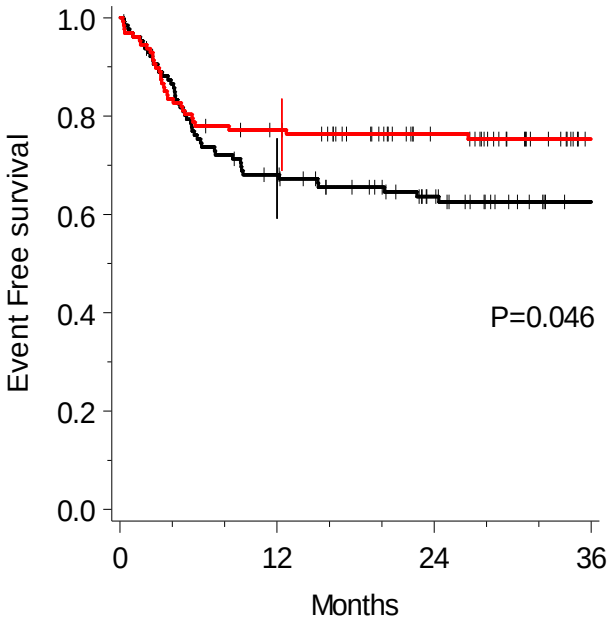
Martinelli G, et al. *J Clin Oncol*. 2017;35(16):1795-1802.

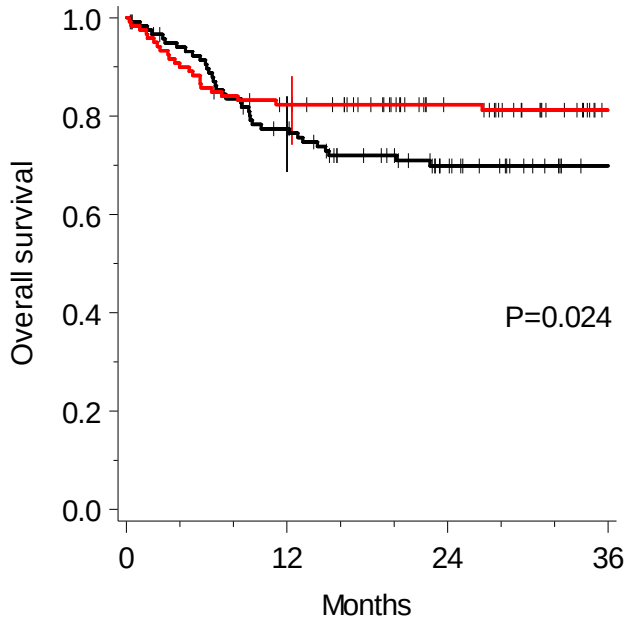
ChemoRx ± Rituximab in Burkitt Disease: Results of the Randomized Intergroup (GRAALL-Lysa) LMBA02 Study

Event-Free Survival



Treatment arm	Patients at risk			
No Rituximab	129	83	61	43
Rituximab	128	95	74	50

Overall Survival



Treatment arm	Patients at risk			
No Rituximab	119	87	60	44
Rituximab	120	95	73	50

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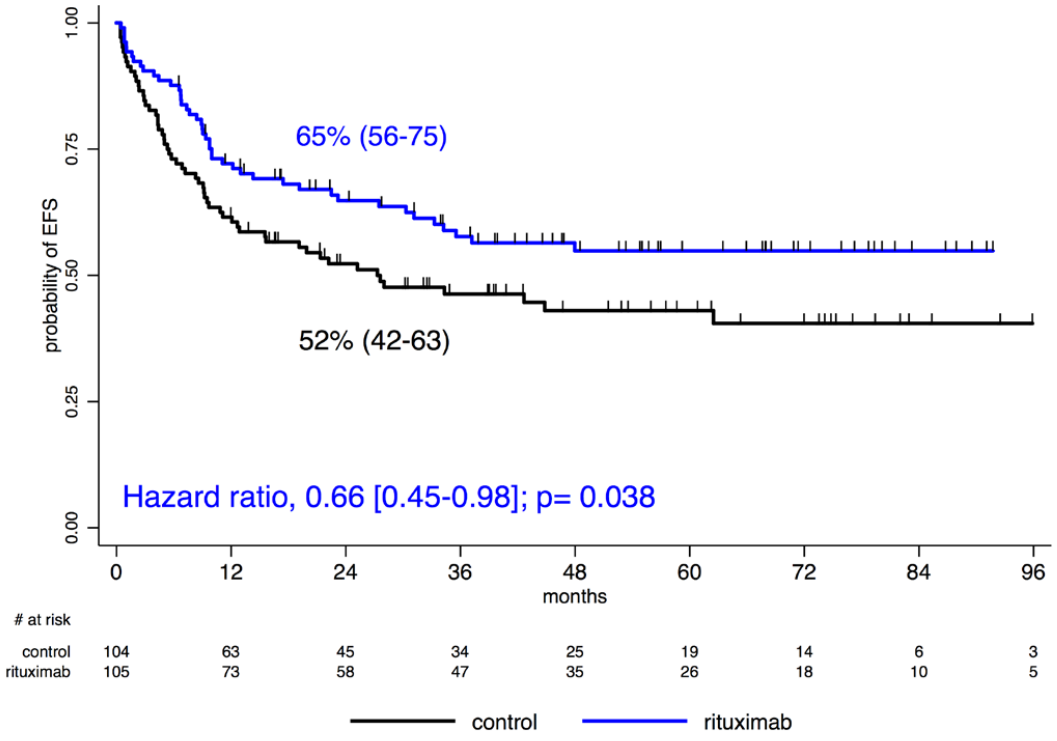
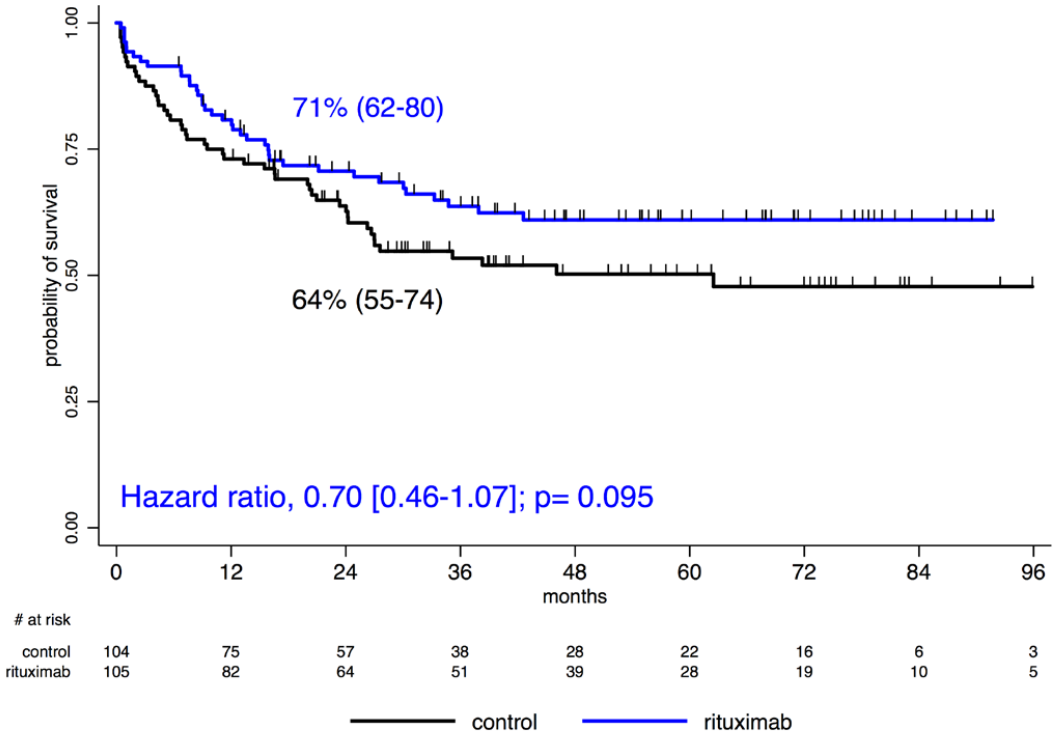
Ribrag V, et al. *Lancet*. 2016;387(10036):2402-2411.

Chemo Rx ± Rituximab: Results of the Randomized GRAALL-R 2005 in Pre B-ALL

- Median follow-up: 30 months





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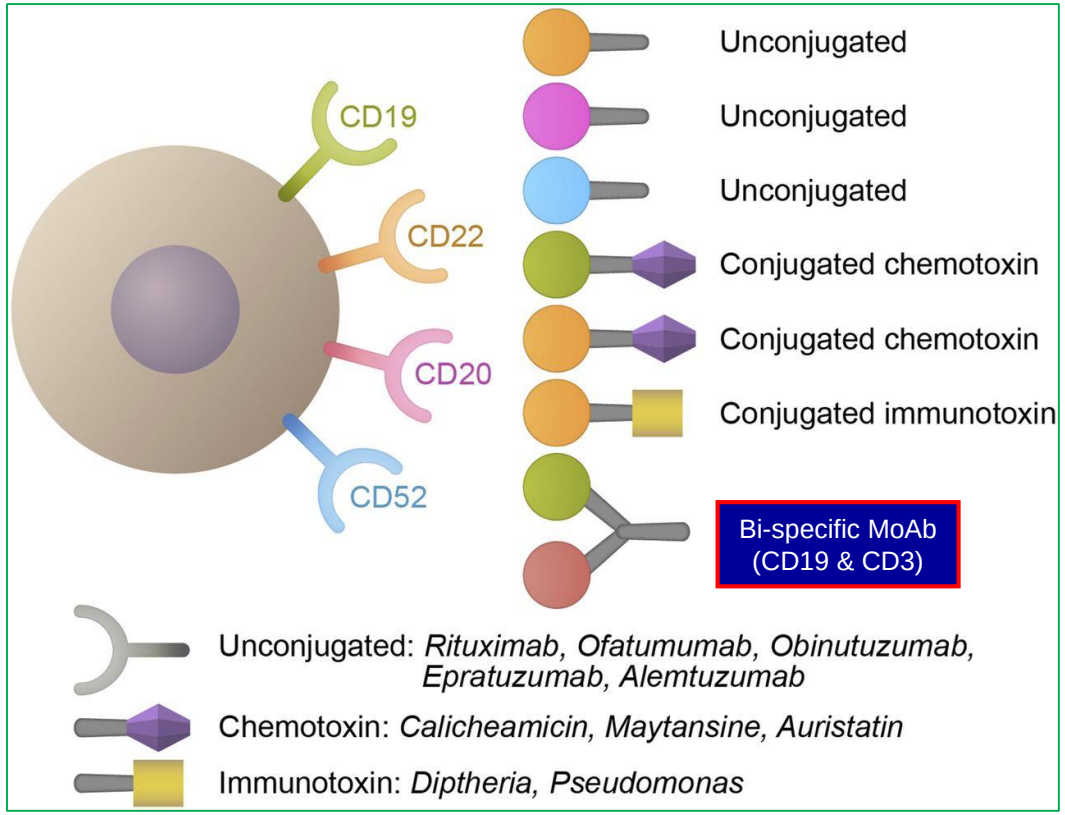
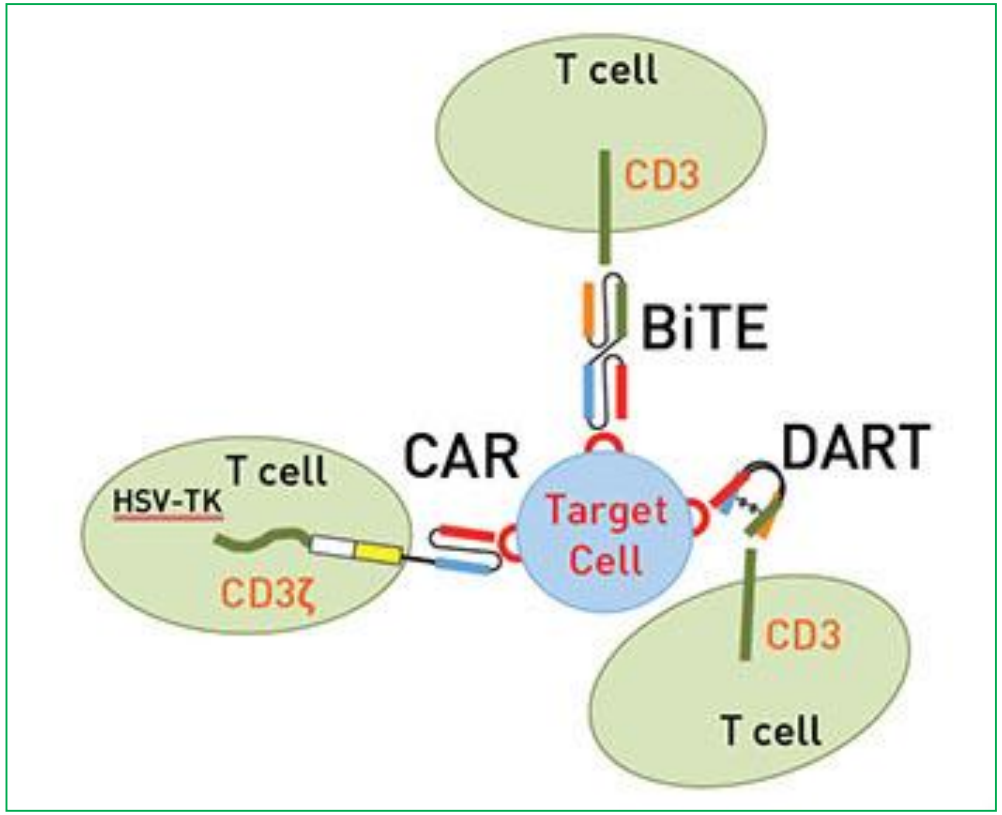
Maury S, et al. *N Engl J Med*. 2016;375(11):1044-1053.

Immuno-oncology in ALL

- Antibodies, ADCs, Immunotoxins, BiTEs, DARTs, CAR-T Cells





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Jabbour E, et al. *Blood*. 2015;125(26):4010-4016.

Blinatumomab/Inotuzumab in R-R ALL

Therapy	% Marrow CR	% MRD-negative
Blinatumomab	44	76
SOC	25	48
Inotuzumab	81	78
SOC	29	28

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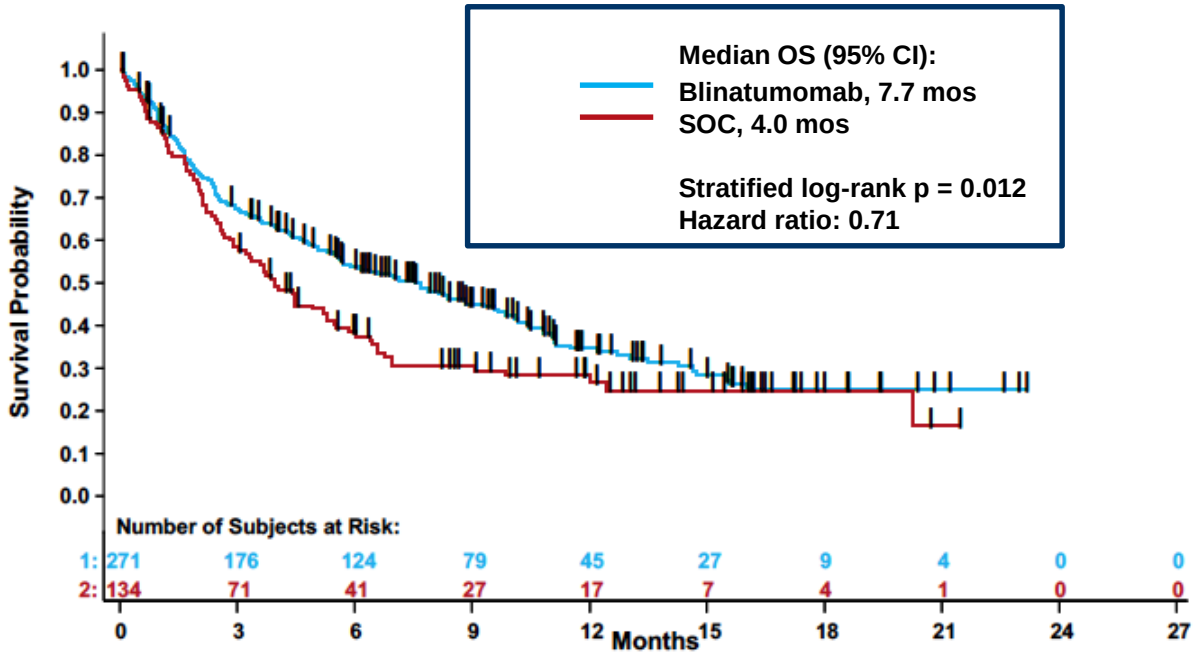
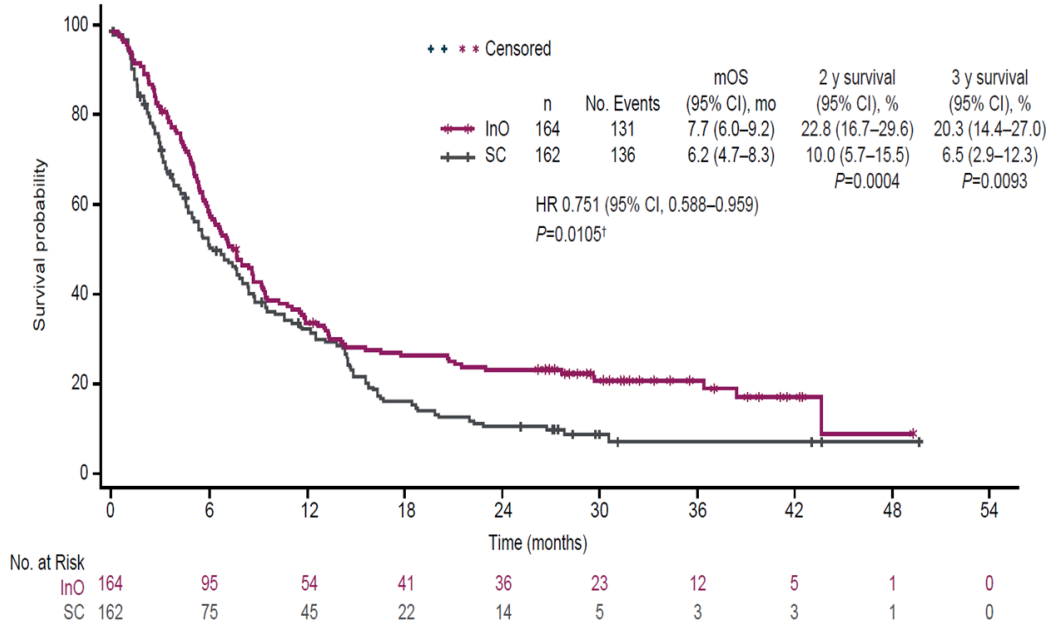
Kantarjian. NEJM. 375: 740; 2016

Kantarjian. Blood. 130: abst 1099; 2017

Blinatumomab/Inotuzumab versus ChemoRx in R-R ALL





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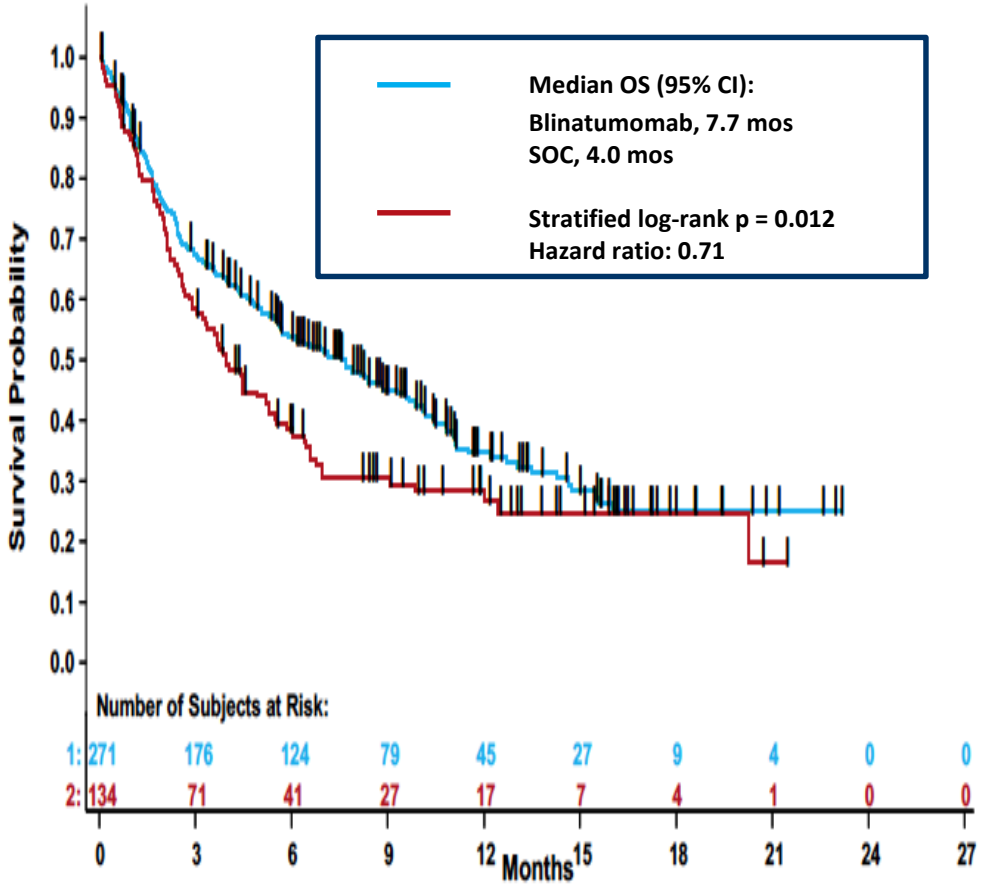
Kantarjian H, et al. *N Engl J Med*. 2017;376(9):836-847; Kantarjian HM, et al. *N Engl J Med*. 2016;375(8):740-753;

Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

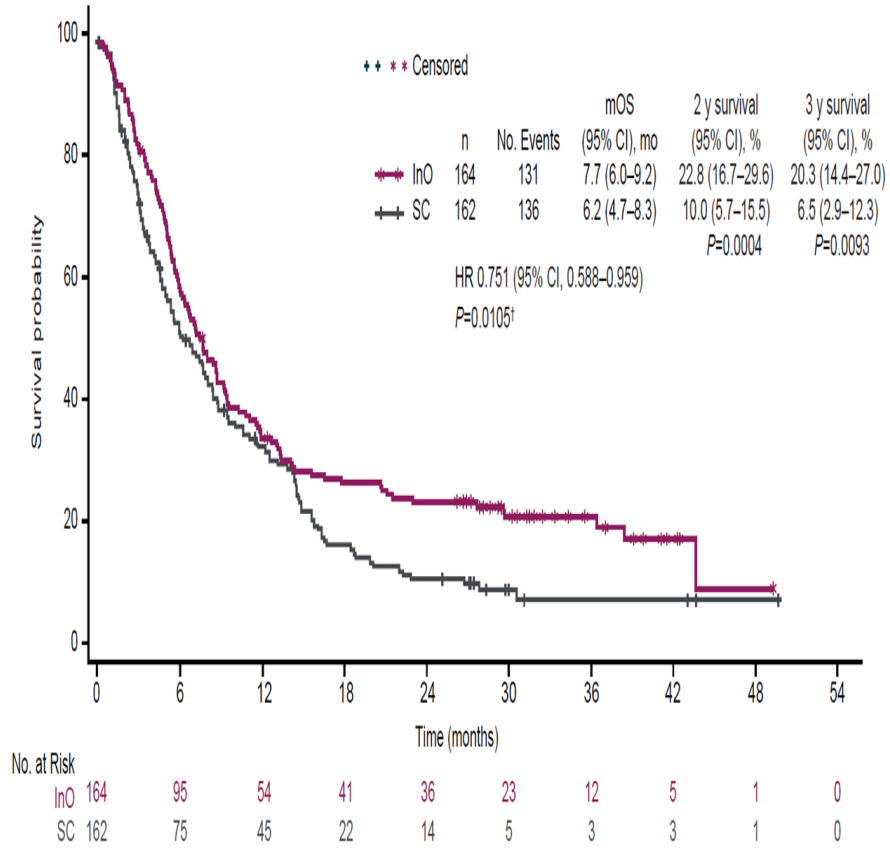
- Marrow CR

Blina vs SOC: 44% vs 25%



Kantarjian. NEJM. 376: 836-47; 2017

Ino vs SOC: 81% 29%



Kantarjian. NEJM. 375: 740; 2016

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MiniHCVD-INO-Blina in ALL: Design

- Dose reduced HyperCVD for 4 to 8 courses
  - Cyclophosphamide (150 mg/m^2 x 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 x 4) 83% dose reduction
- **Inotuzumab on D3 (first 4 courses)**
  - **Modified to 0.9 mg/m^2 C1 (0.6 and 0.3 on D1&8) and 0.6 mg/m^2 C2 - C4 (0.3 and 0.3 on D1&8)**
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- **Blinatumomab 4 courses and 3 courses during maintenance**
- POMP maintenance for 3 years, reduced to 1 year

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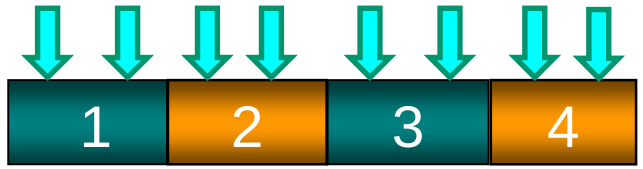
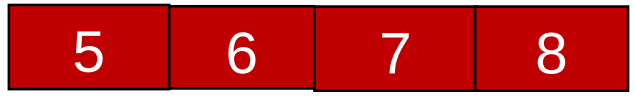
MiniHCVD-INO-Blina in ALL

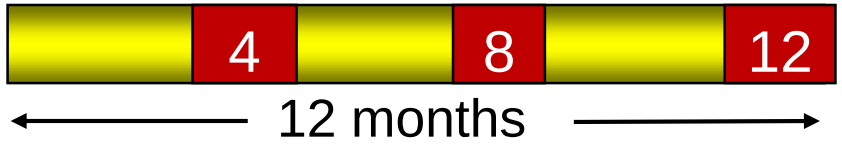
Intensive Phase



Consolidative Phase



Maintenance Phase



- MiniHCVD
- Mini-MTX-cytarabine
- Blinatumomab
- POMP Maintenance

Inotuzumab	Total dose	Dose per day
C 1 (mg/m^2)	0.9	0.6 D2 & 0.3 D8
C2 - C4 (mg/m^2)	0.6	0.3 D2 & D8

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MiniHCVD-INO in R/R ALL. Response By Salvage (N=87)

Response	N	(%)
Salvage 1	**44/48**	**92**
S1, Primary refractory	6/6	100
S1, CRD1 < 12 mos	15/19	79
S1, CRD1 ≥ 12 mos	23/23	100
Salvage 2-3	24/39	**62**
Overall	**68/87**	**78**
MRD negativity	53/65	**82**
Salvage 1	**38/41**	**93**
≥ Salvage 2	12/18	67

Jabbour. JAMA Oncology 4: 230; 2018

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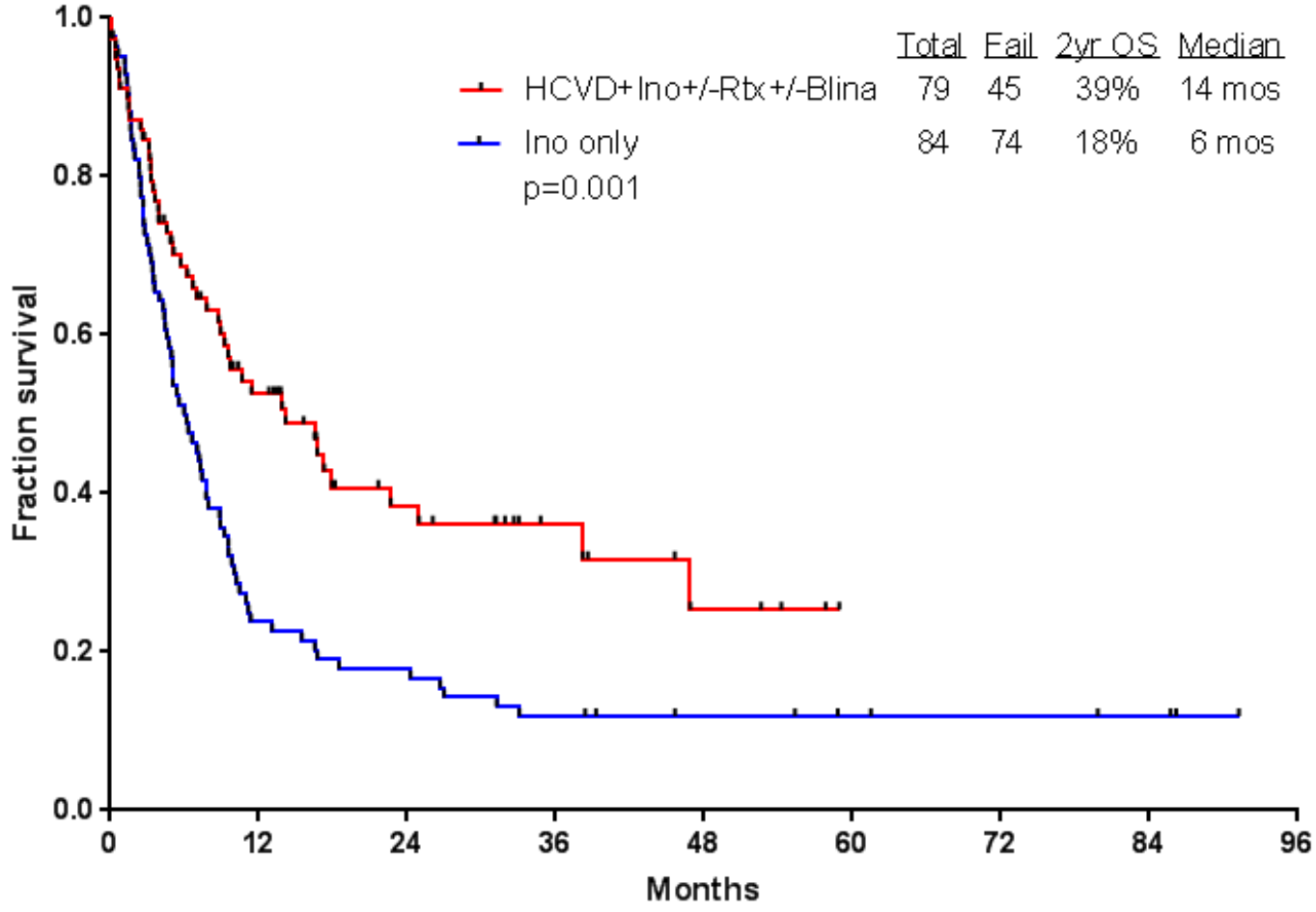
MiniHCVD-INO versus INO in R-R ALL: Survival



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

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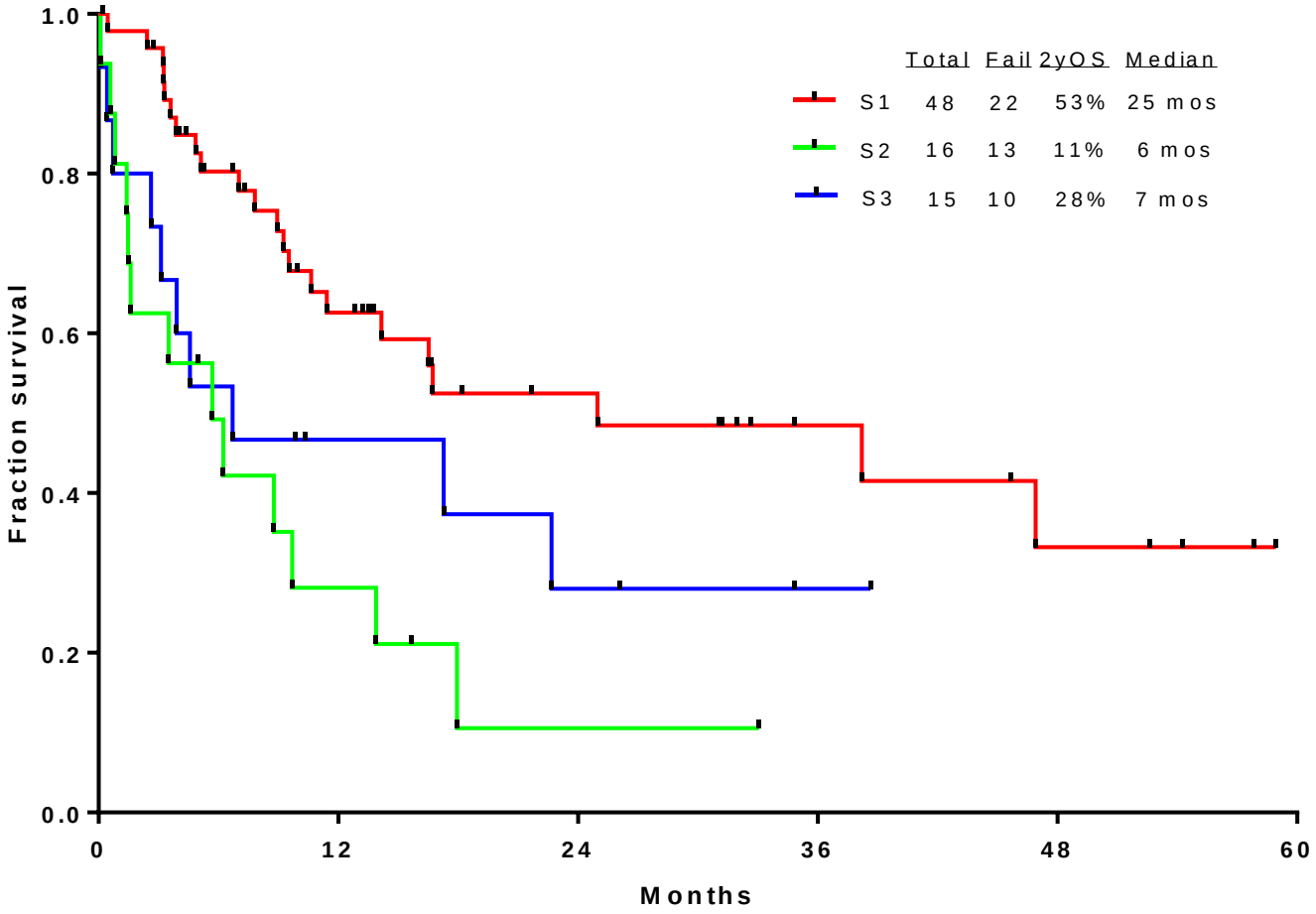
MiniHCVD-INO in R-R ALL: Survival by Salvage



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

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MiniHCVD-INO in Older ALL. Response (N=60)

Response	N	(%)
CR	51	(85)
CRp	6	(10)
CRi	2	(3)
ORR	**59**	**(98)**
No response	1	(2)
Early death	**0**	**0**

- Median age 68yrs (60-81)
- 4 patients were enrolled with CR

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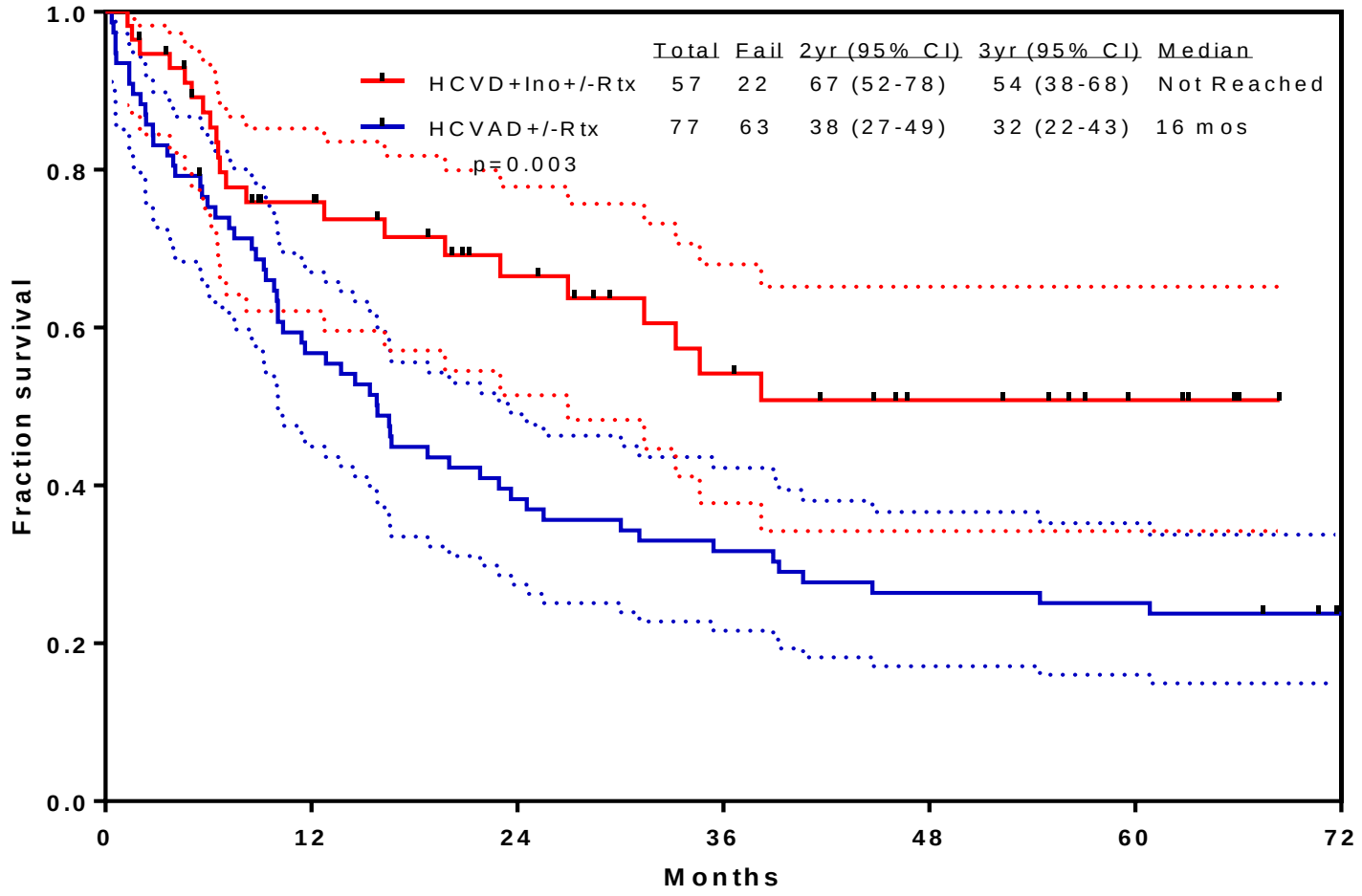
Kantarjian. Lancet Oncology 19: 240; 2018

MiniHCVD-INO versus HCVAD in ALL



Number at Risk							
HCVD+Ino+/-Rtx	57	38	26	18	11	6	0
HCVAD+/-Rtx	77	43	29	24	20	19	15

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Kantarjian H, et al. *Lancet Oncol*. 2018;19(2):240-248.

Future ALL Therapy

- Antibody cocktails targeting CD19, CD22, CD123, (and CD20)
- Much less chemo Rx
- Venetoclax in T ALL
- Second-third generation antibodies with easier delivery (not 4-wk CI) and less toxicity (no VOD)

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How Should targeted Rxs be used in AML and ALL ?

- Very expensive as single agents, with limited /modest response rates and survival prolongation
- FDA approval for many is as single agents, and in R-R disease
- FDA approval may also use historical, perhaps suboptimal dose-schedules – eg midostaurin 2 wks x 2 courses; inotuzumab 1.8mg/m2
- Thus, FDA approved regimens may not offer good “Rx value”; may deliver suboptimal efficacy and excess toxicity
- Studies ongoing to define better dose schedules, combinations with ChemoRx and with cocktails of targeted Rxs
- How should they be used today, in standard of care, until more data?
- I propose use as per peer-reviewed publications, when new data significantly better and safer

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Leukemia Questions?

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