Personalized Therapy in Adult Acute Lymphocytic Leukemia: Path to the Cure

Elias Jabbour M.D.

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Disclosures

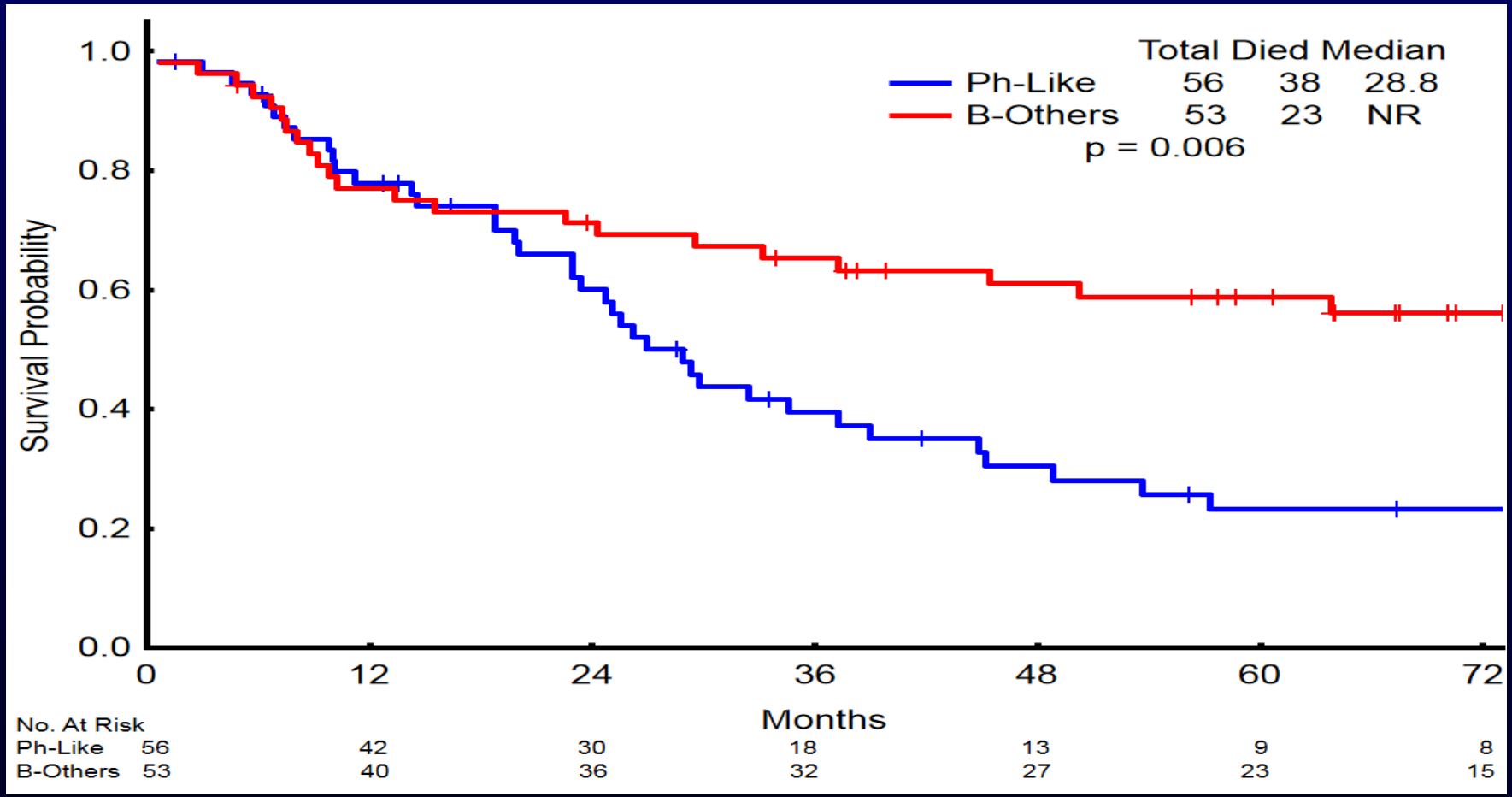
- Elias Jabbour has a financial interest/relationship or affiliation in the form of:
  - Consultant: AbbVie, Amgen, Bristol-Myers Squib, Pfizer Takeda and Teva Pharmaceuticals USA
  - Grant/research support: Abbvie, Amgen, Novartis Pharmaceuticals Corporation, Pfizer, Spectrum, Takeda and Teva Pharmaceuticals USA

The Present…
ALL Therapy or "Personalized Therapy"

Entity	Management	% Cure
Burkitt	HCVAD-R x 8; ITx16; R/O-EPOCH	80-90
Ph-positive ALL	HCVAD + TKI; TKI maintenance; allo SCT in CR1	50+
T-ALL (except ETP-ALL)	Lots of HD CTX, HD ara-C, Asp; nelarabine?	60
CD20 – positive ALL	ALL chemo Rx+ rituximab/ofatumomab	50
if not Ph-like		60-70
AYA	Augmented BFM; HCVAD-R/O	65+
MRD by FCM	Prognosis; need for allo SCT in CR1	--

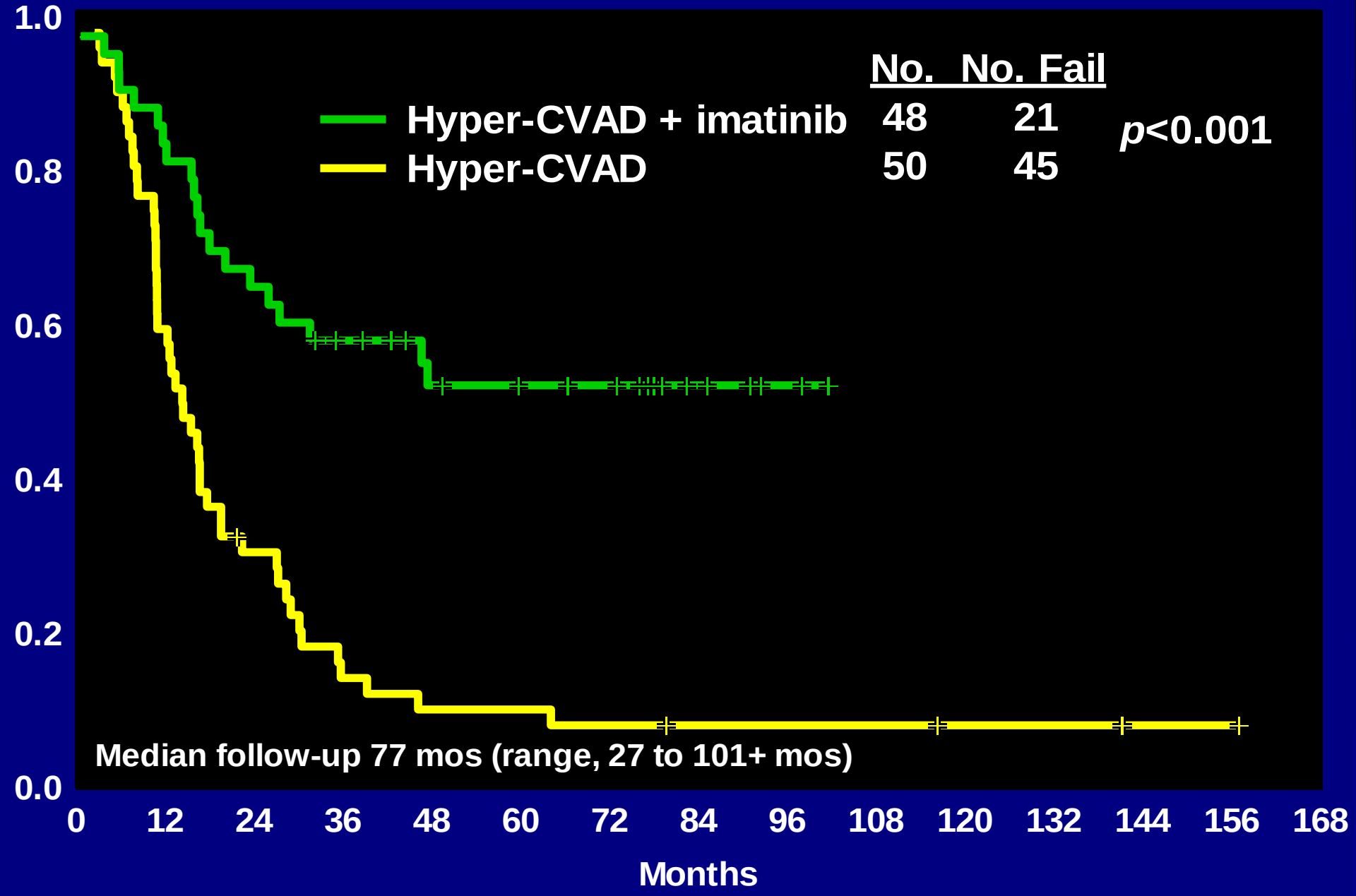
Ph-like ALL: Inferior OS

- Gene expression profile= Similar to Ph-positive ALL
- No Ph chromosome or BCR-ABL1
- 25%-30%; poor prognosis



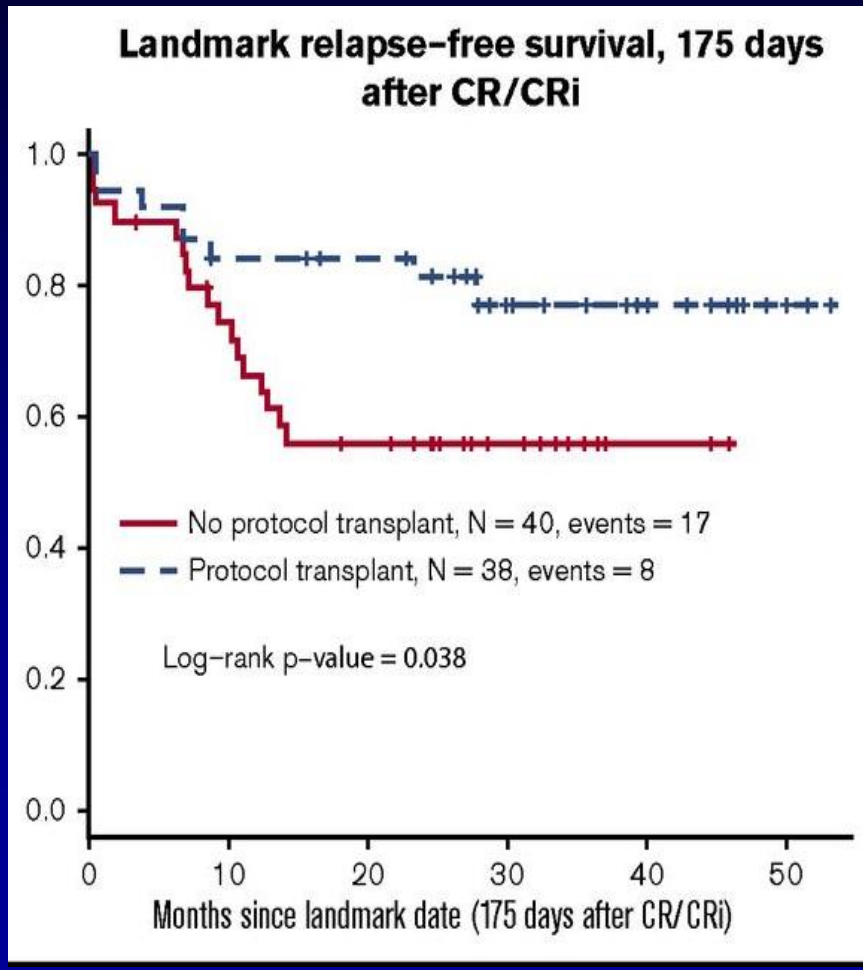
Jain. Blood 2017; 129:572-581

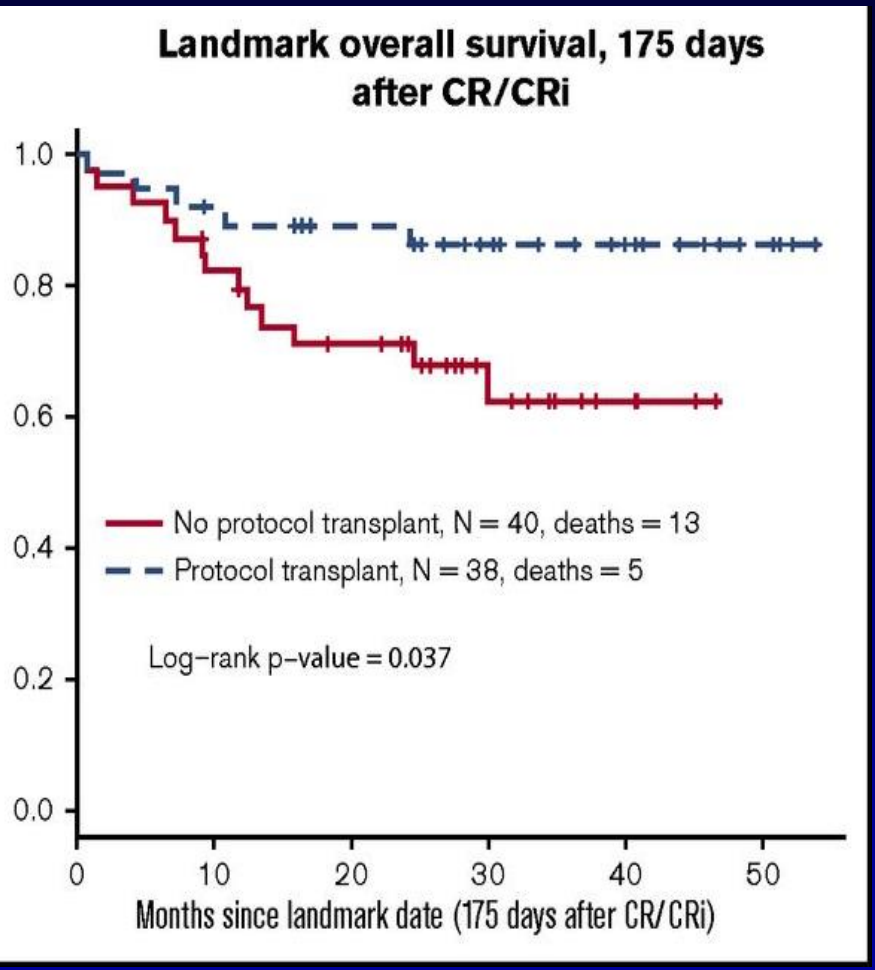
Survival in Ph-ALL by Regimen (Excluding Primary Refractory)



Daver N. Haematologica. 2015;100(5):653-661.

Hyper-CVAD + Dasatinib in Ph+ ALL. Landmark Analysis – No ASCT vs ASCT



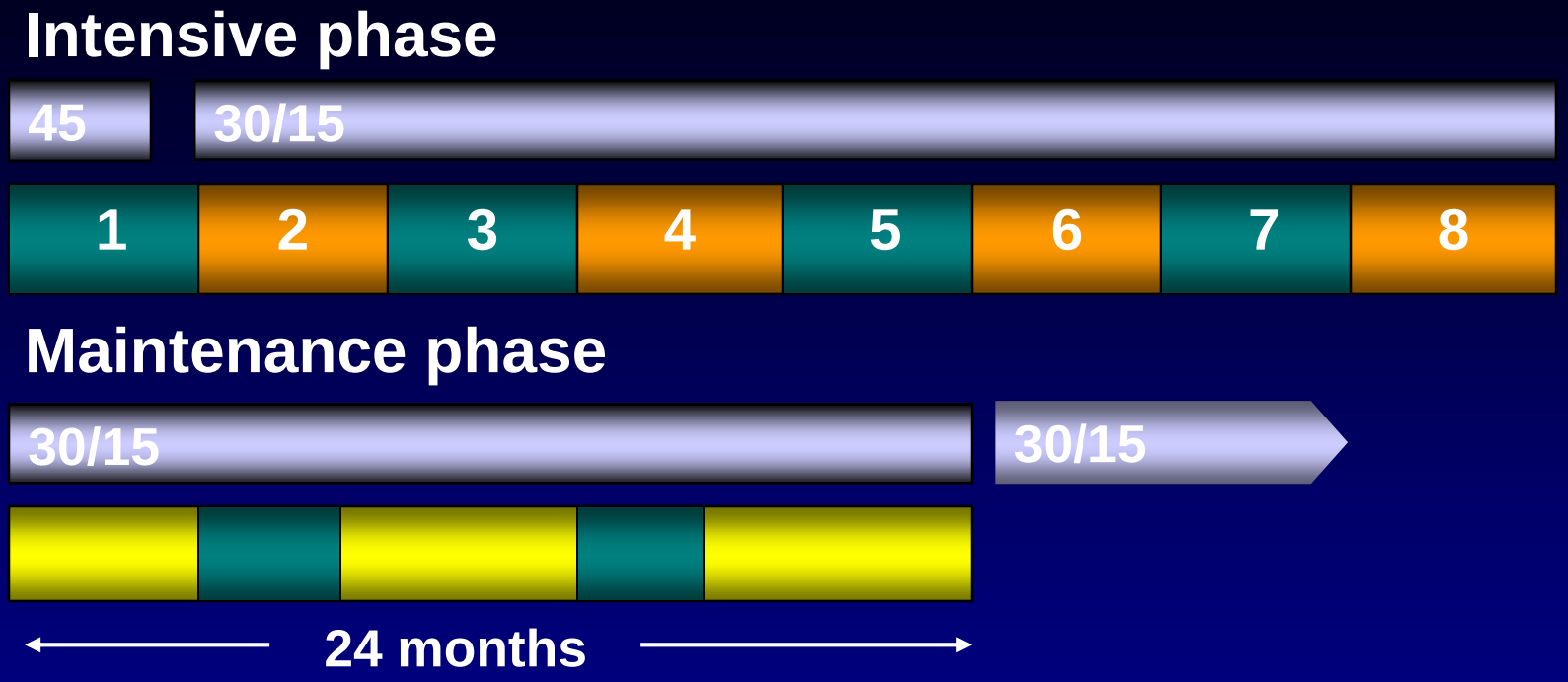


Low-intensity chemo Rx + Dasatinib in Ph + ALL ≥ 55 yrs

- 71 pts (2007-2010); median age 69 yrs (58-83)
- Dasatinib 100-140 mg/D, VCR 1mg Q wk, Dex 20-40 mg/D x 2, Qwk
- Consolidations: dasatinib 100 mg/D; MTX-Asp C1,3,5; ara-C C2,4,6. Maintenance: dasatinib + POMP
- CR 96%; MMR 65%; CMR 24%
- 5-yr survival 36%; EFS 25%
- T315I at Dx 23% by NGS
- 36 relapses; T315I in 75%

Rousselot. Blood 2016;128(6):774-82

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

Jabbour. Lancet Onc. 16:1547;2015

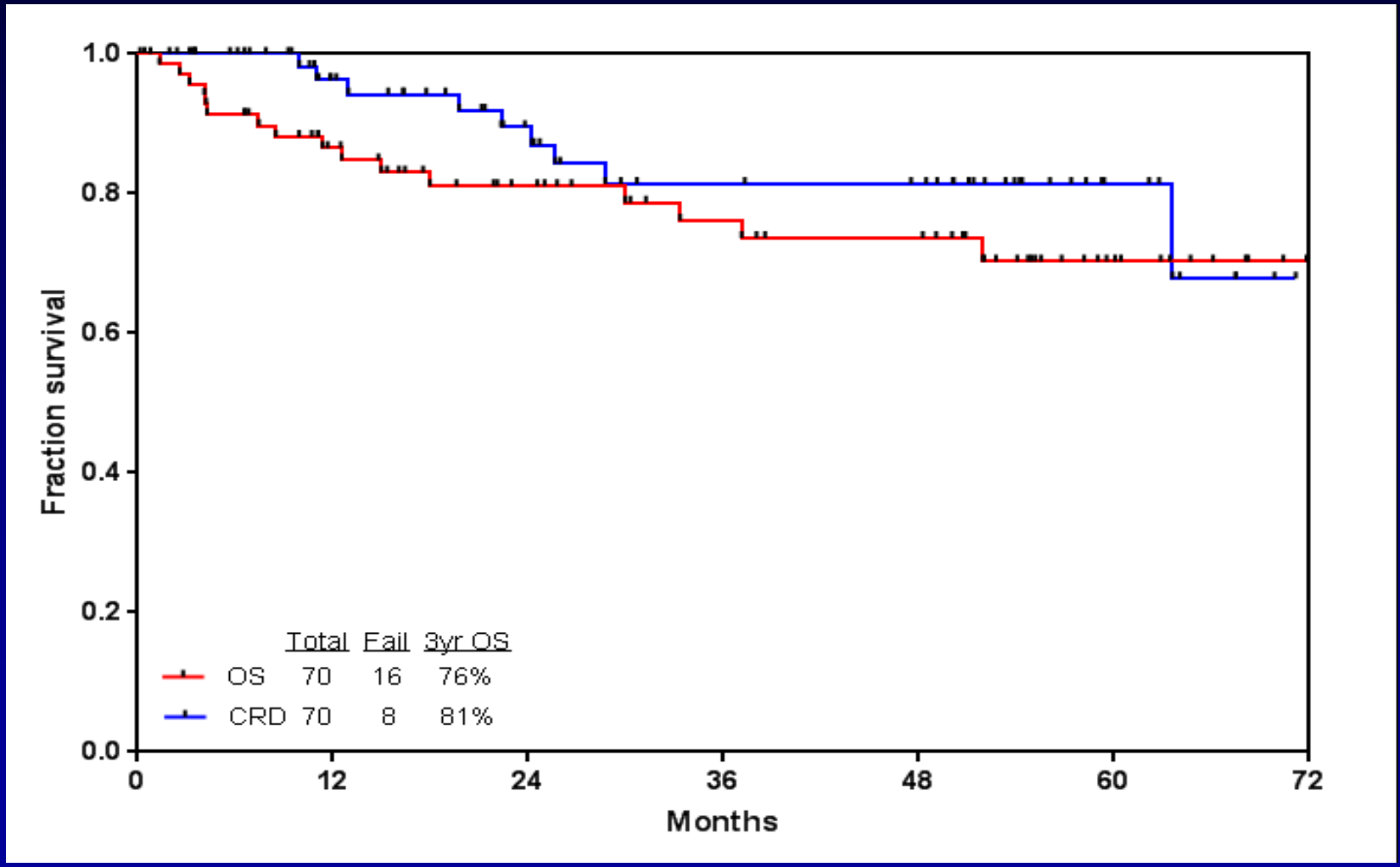
Hyper-CVAD + Ponatinib in Ph-Positive ALL. Overall Results

Parameter	N (%)
CR*	61/61 (100)
CCyR**	52/52 (100)
MMR	68/70 (97)
CMR	55/70 (79)
Flow negativity***	68/69 (99)
Early death	0 (0)

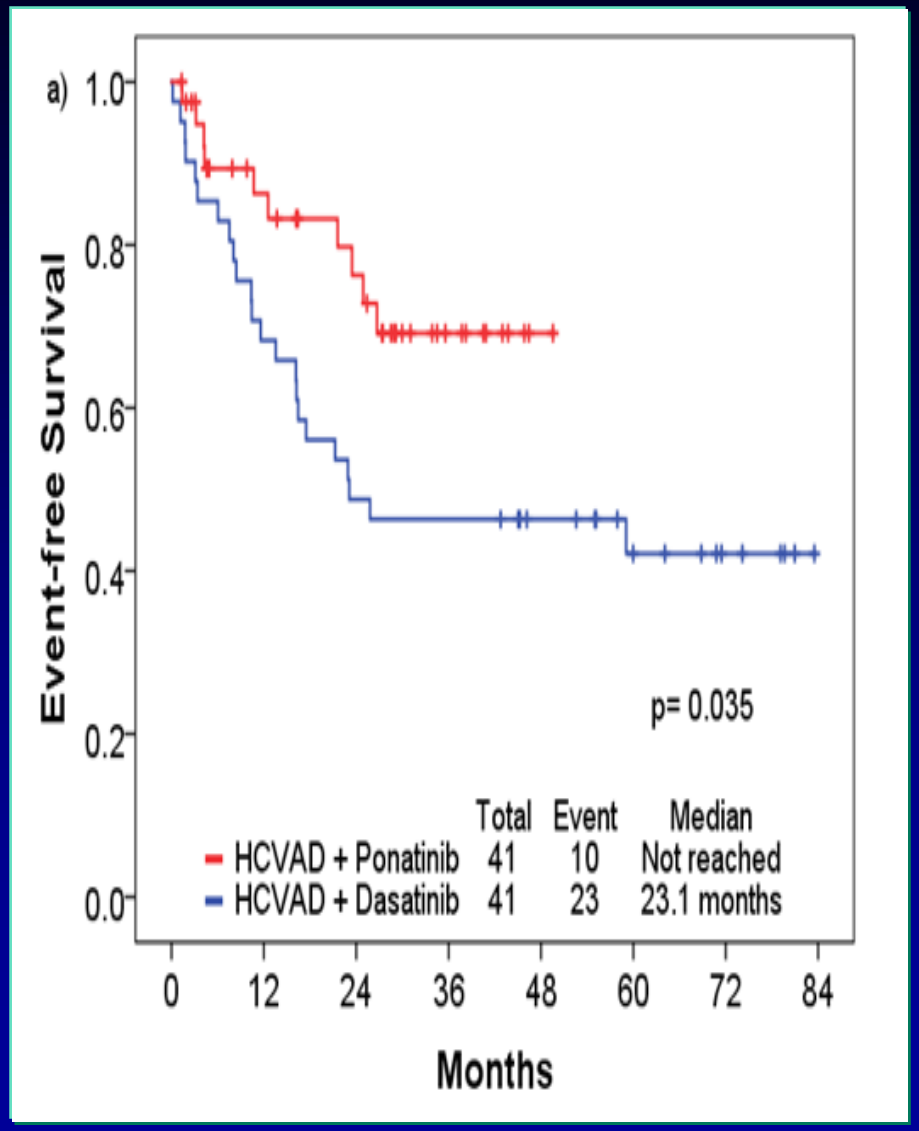
- * 9 pts in CR at start
- ** 18 pts diploid by CG at start
- *** 1 pts had no sample sent for flow

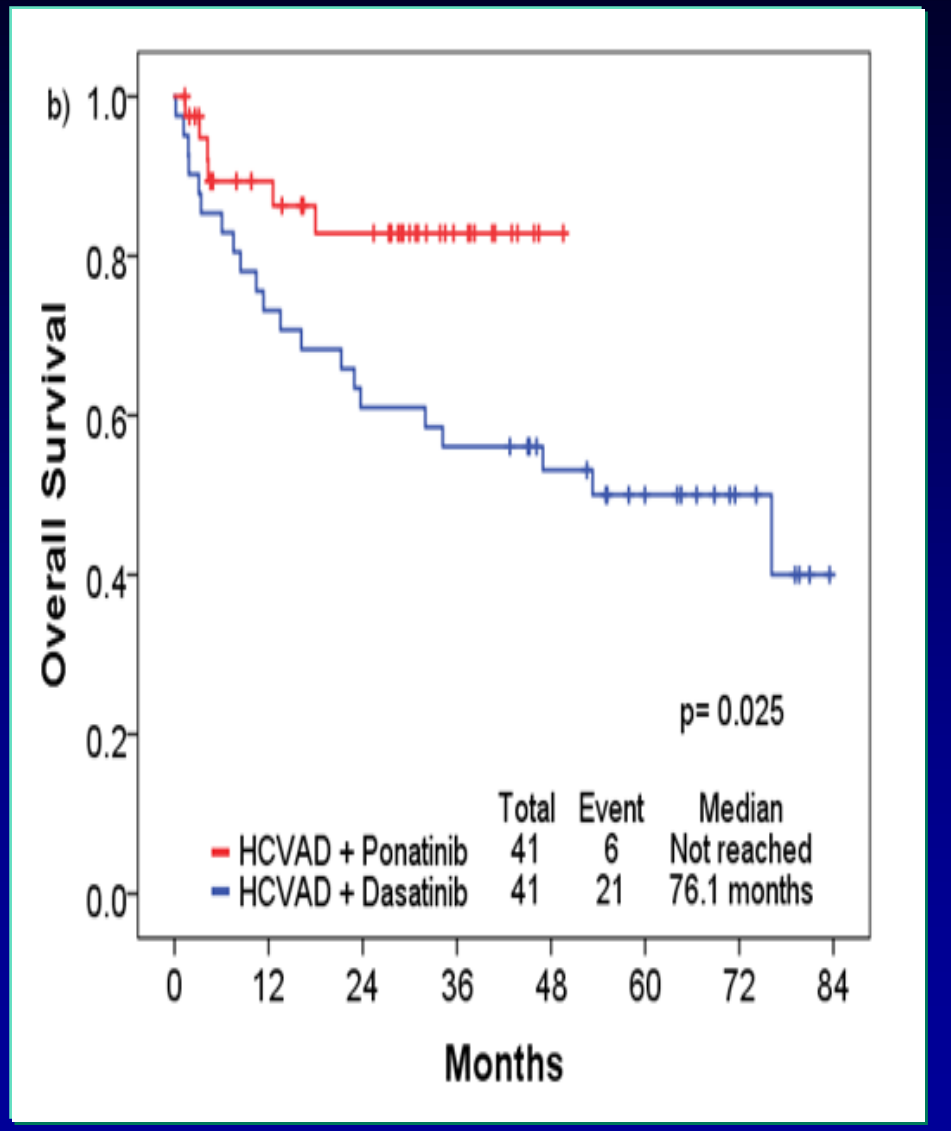
Hyper-CVAD + Ponatinib in Ph-Positive ALL. Survival

- Median follow up of 38 months (<1-72)



Propensity Score Analysis: HCVAD + Ponatinib vs HCVAD + Dasatinib in Ph-Positive ALL.

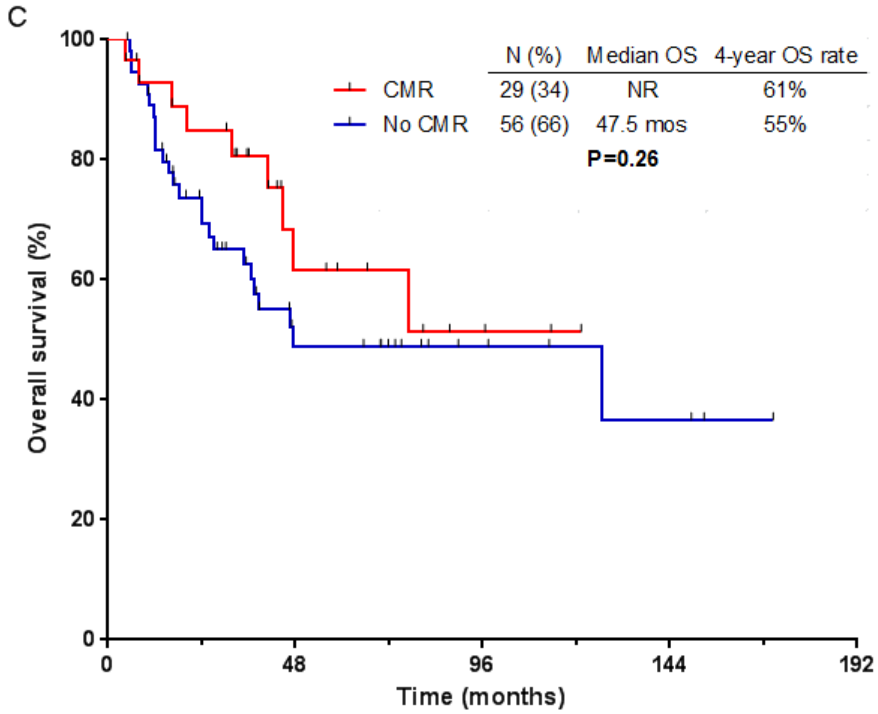




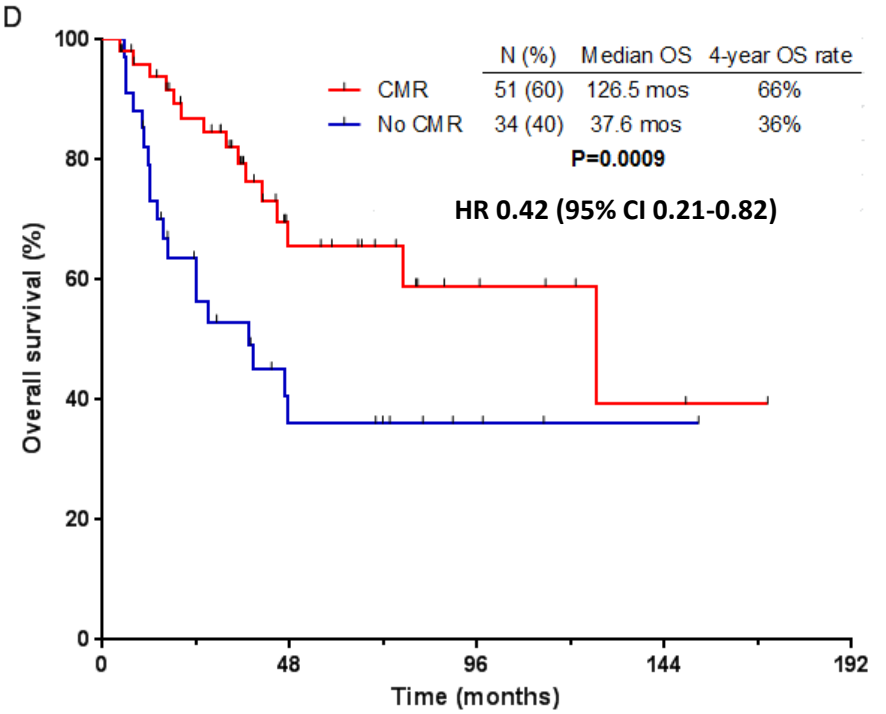
Sasaki. Cancer. 2016; 122(23):3650-3656

CMR in Ph-Positive ALL. OS for CMR vs. others

At CR



At 3 months



- **MVA for OS**

  CMR at 3 months (HR 0.42 [95% CI 0.21-0.82], P=0.01)

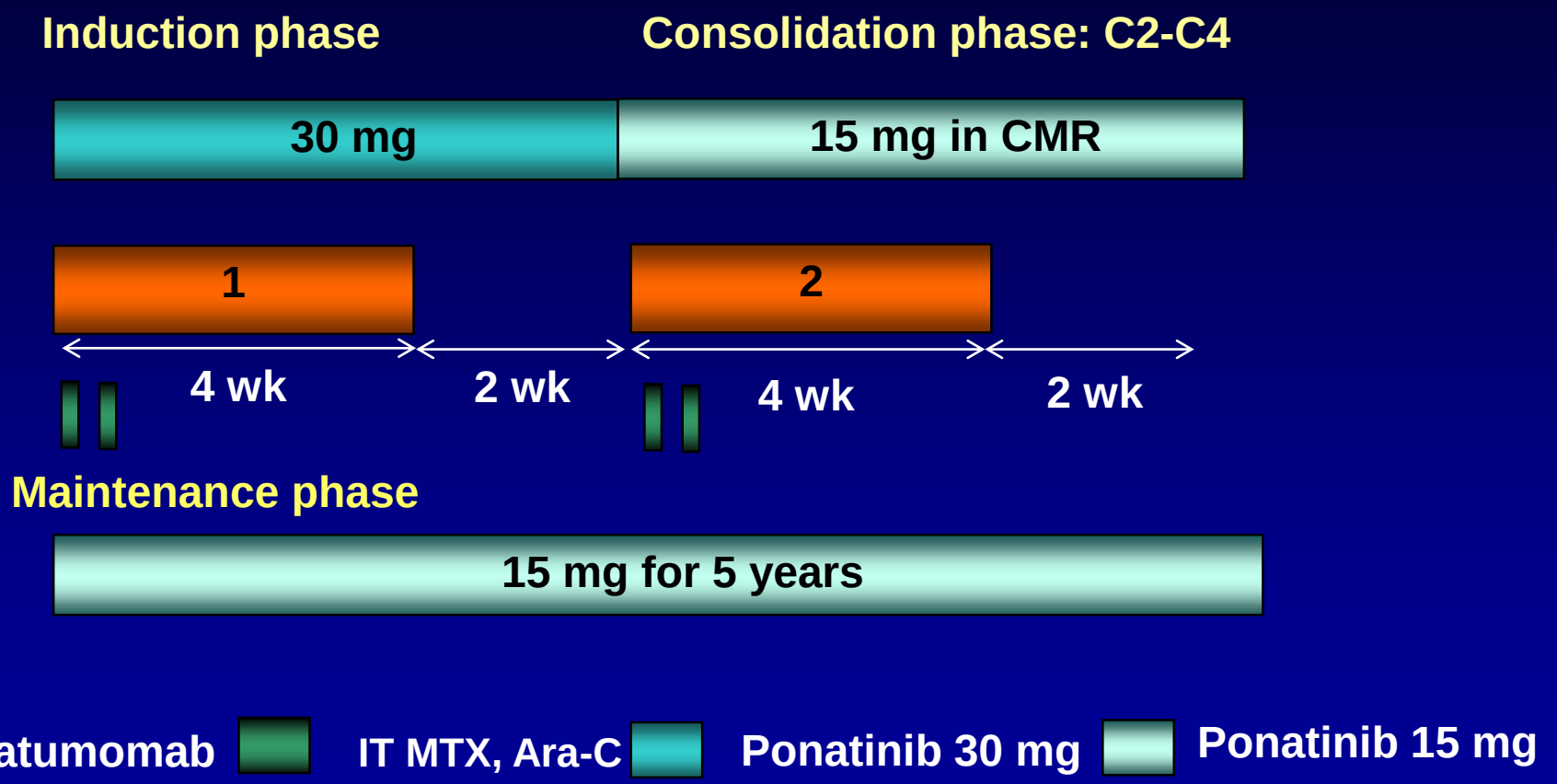
Short. Blood. 2016;128(4):504-7

Blinatumomab in Ph-positive ALL

- Single agent blinatumomab
- R/R Ph+ ALL to 2+ generation TKI (n=45)
- T3151 (n=10); ≥ 2 TKI (n=27); prior ponatinib (n=23)
- Primary endpoint **CR/CRh 16/45=36%**
- Secondary endpoints
  - Complete MRD response in CR: 88%
  - Proceed to alloHSCT: 44%
  - Median RFS 6.7 mo
  - **Median OS 7.1 mo**

Martinelli. JCO 35: 1795; 2017

Blinatumomab-ponatinib in Ph-Positive ALL



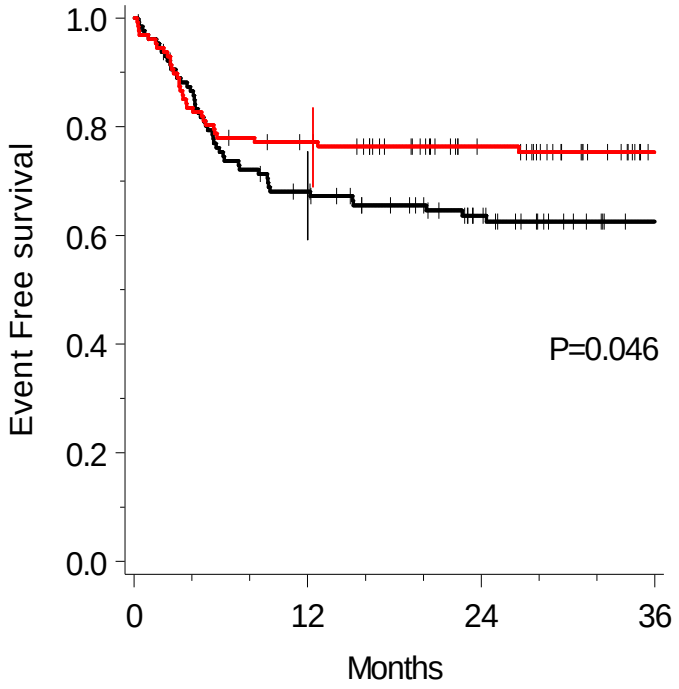
Assi. Clin Lymphoma Myeloma Leuk. 2017;17(12):897-901

Future Questions in Ph-positive ALL

- Do we need allo SCT? --not always; never?
- Which patients can be cured without allo SCT? --if PCR-negative
- How much chemoRx-- low-Intensity versus intensive chemo Rx?
- Can we cure Ph-positive ALL without chemoRx or allo SCT?-- ponatinib+blinatumomab/CAR-T

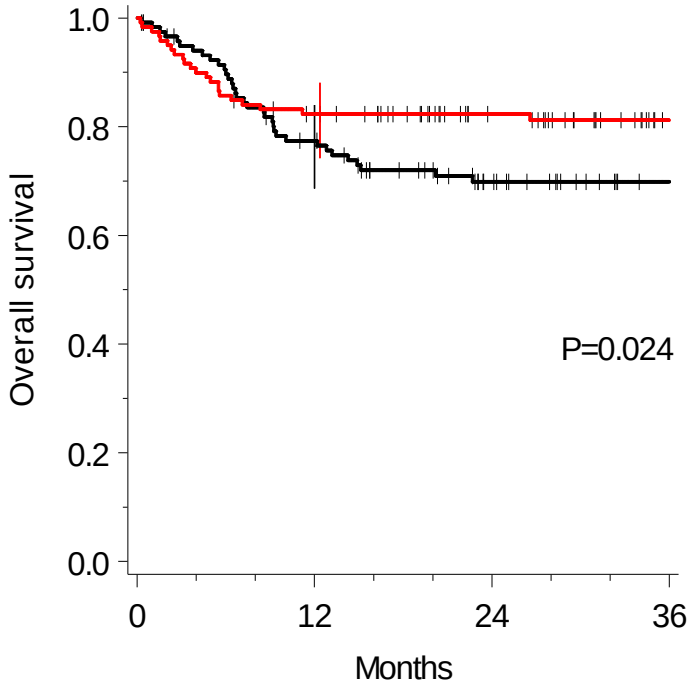
Results of the Randomized Intergroup (GRAALL-Lysa) LMBA02 Study

Event Free Survival



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

Overall Survival

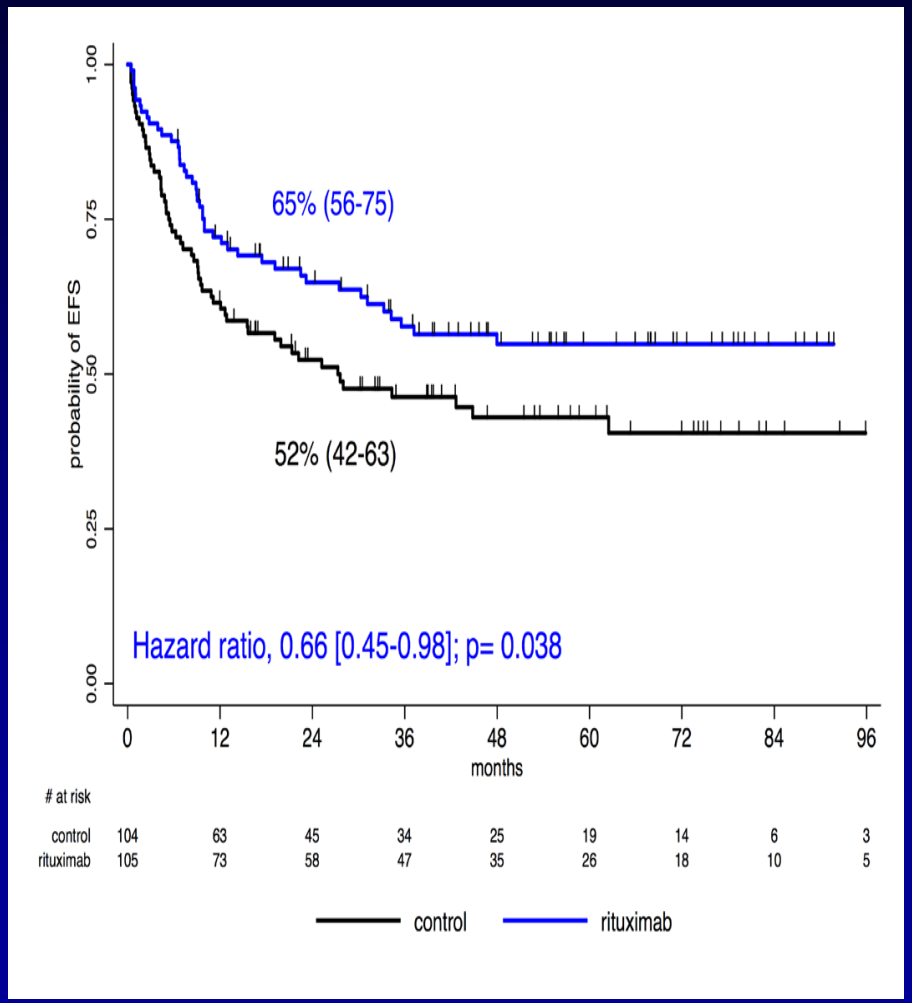


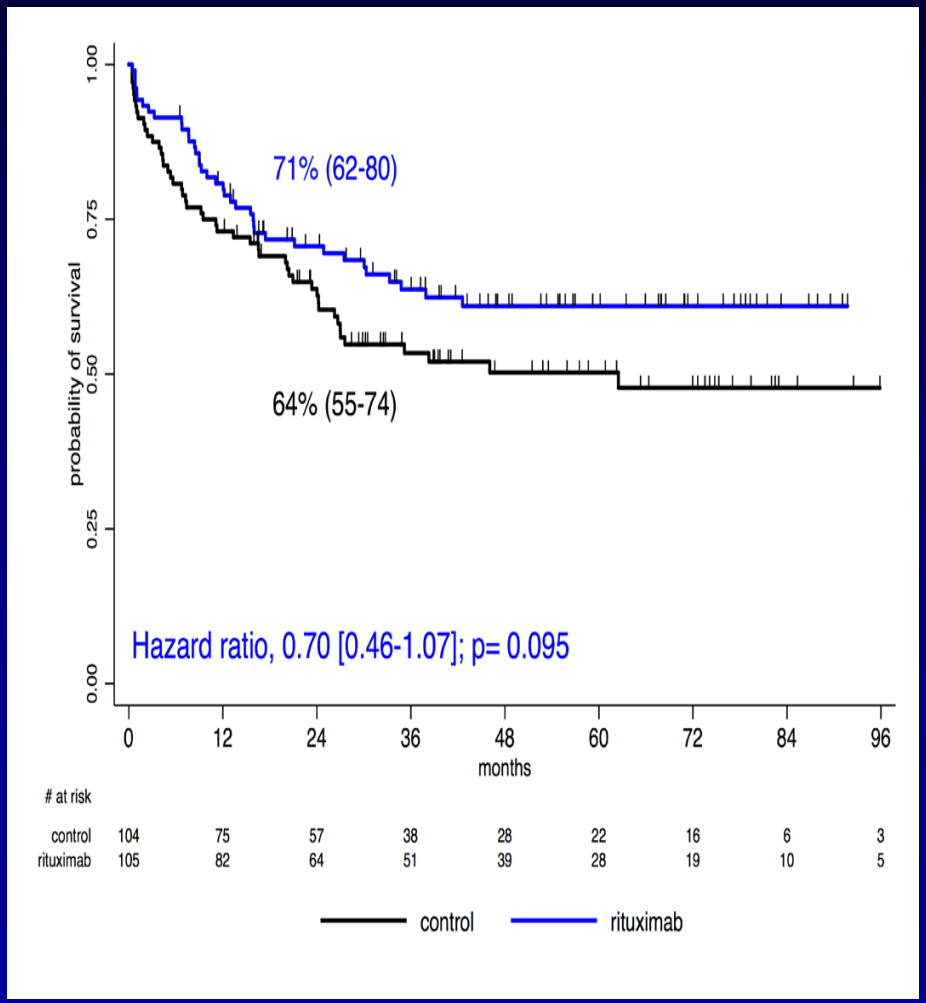
Treatment arm	Patients at risk			
No Rituximab	119	87	60	44
Rituximab	120	95	73	50

Ribrag. Lancet. 2016;387:2402-11.

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

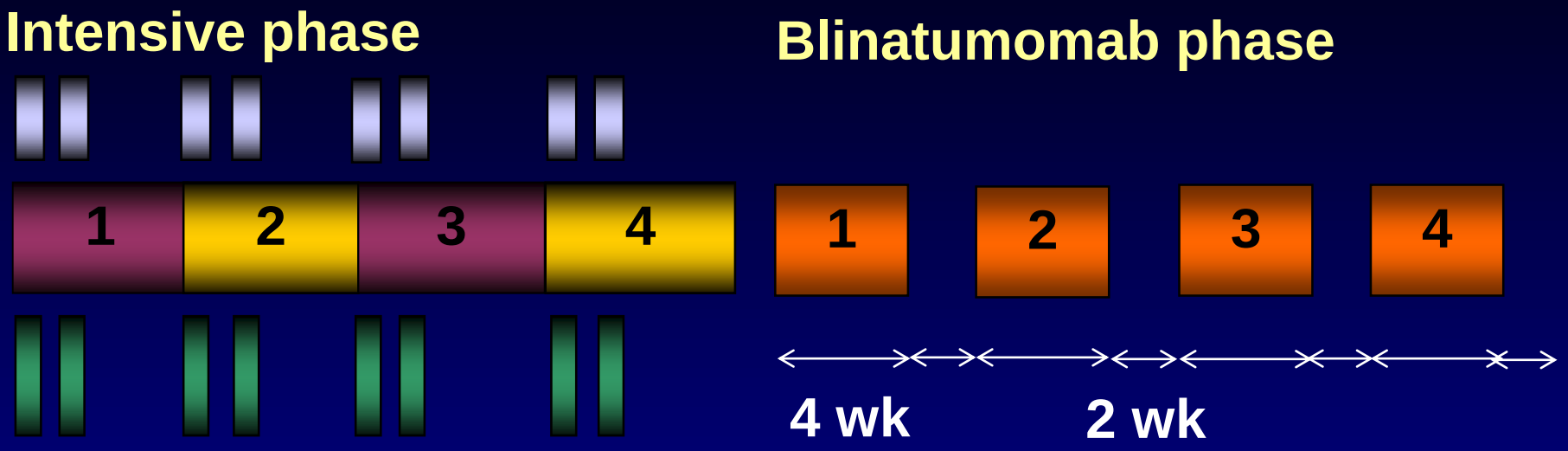
- Median follow-up 30 months





Maury. N Engl J Med. 2016;375:1044-53

Hyper-CVAD + Blinatumomab in B-ALL (Ph-negative B-ALL < 60 years)



Hyper-CVAD

Rituximab or Ofatumumab

MTX-Ara-C

IT MTX, Ara-C

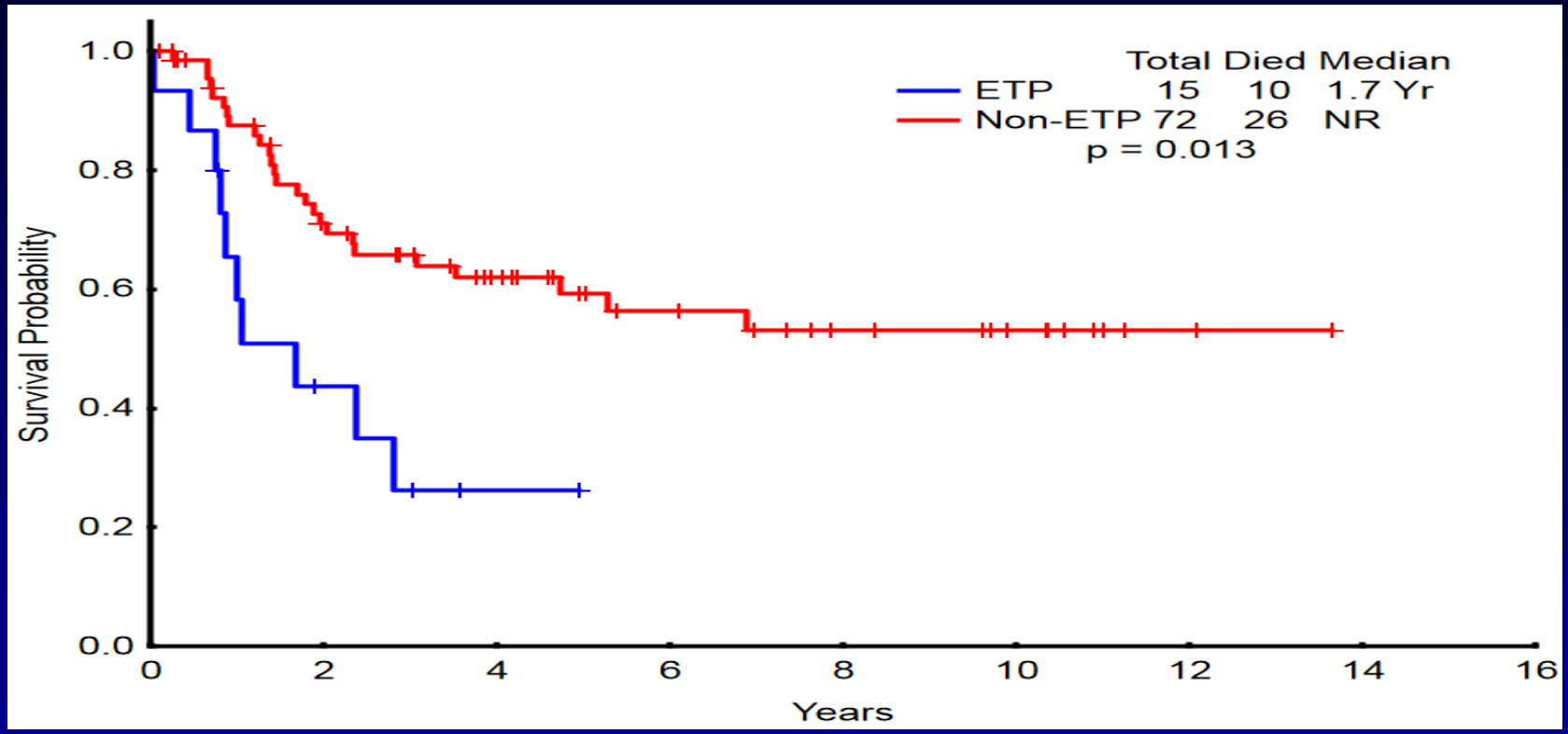
POMP

Blinatumomab

Blina to be administered after C2 in pts with HR disease: T(4;11); Ph-like; Ho-Tr

Overall Survival in T-ALL by Subtype

- CD1a(-), CD8(-), CD5(-/dim), and positivity for one or more stem cell or myeloid antigens

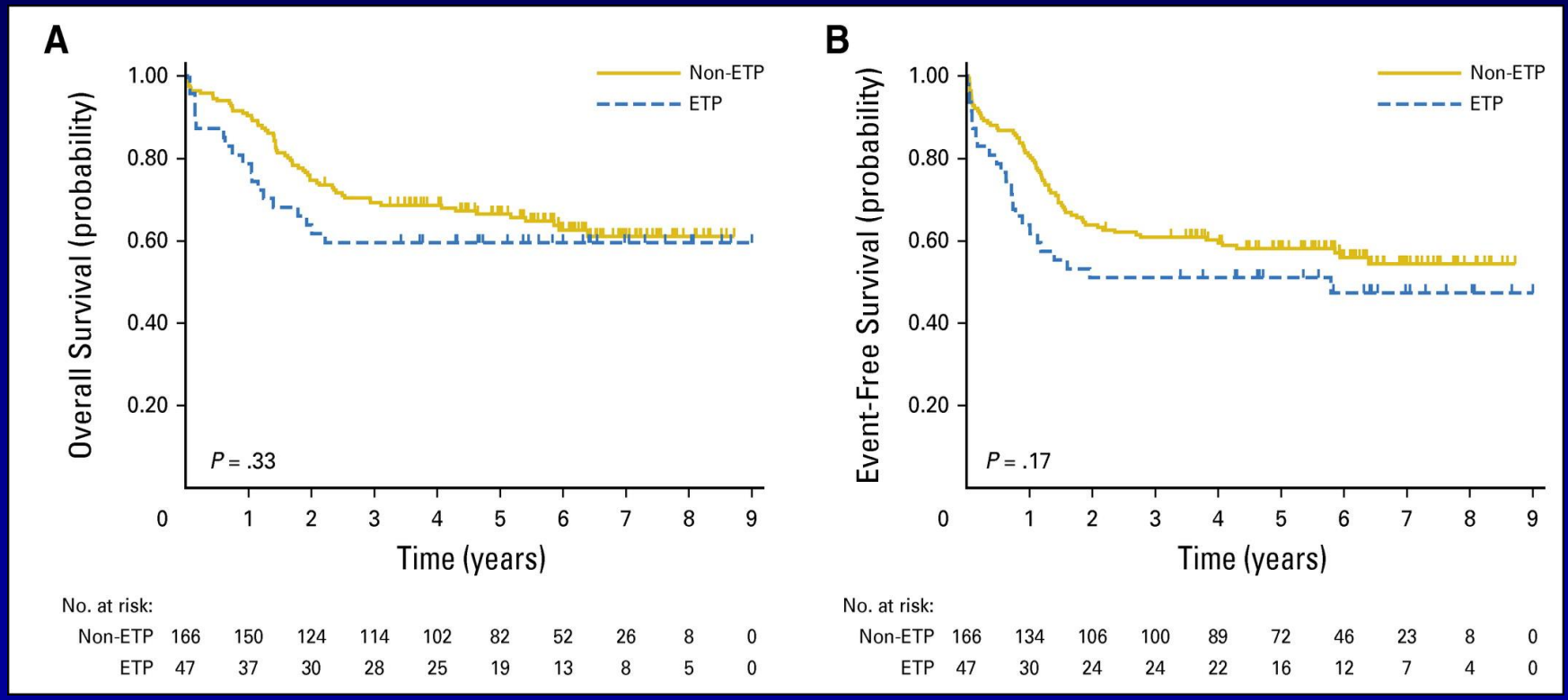


- Low frequency of NOTCH1 mutations; harbors at least one lesion in DNMT3A, IDH1, IDH2, ETV6; hyperactivation of JAK-STAT pathway

Coustan-Smith. Lancet Oncology 2009;10:147-56; Jain. Blood. 2016;127:1863-1869; Neumann. Blood. 2013; 121:4749-52; Zhang. Nature. 2012;481:157-63

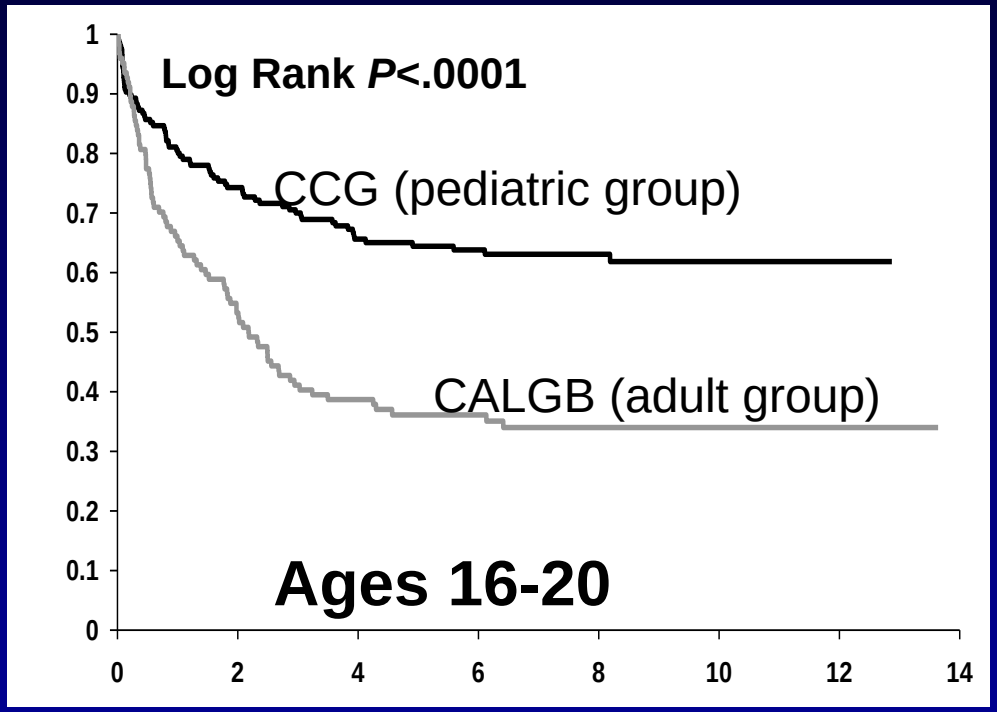
Overall Survival in T-ALL by Subtype. GRAALL Experience

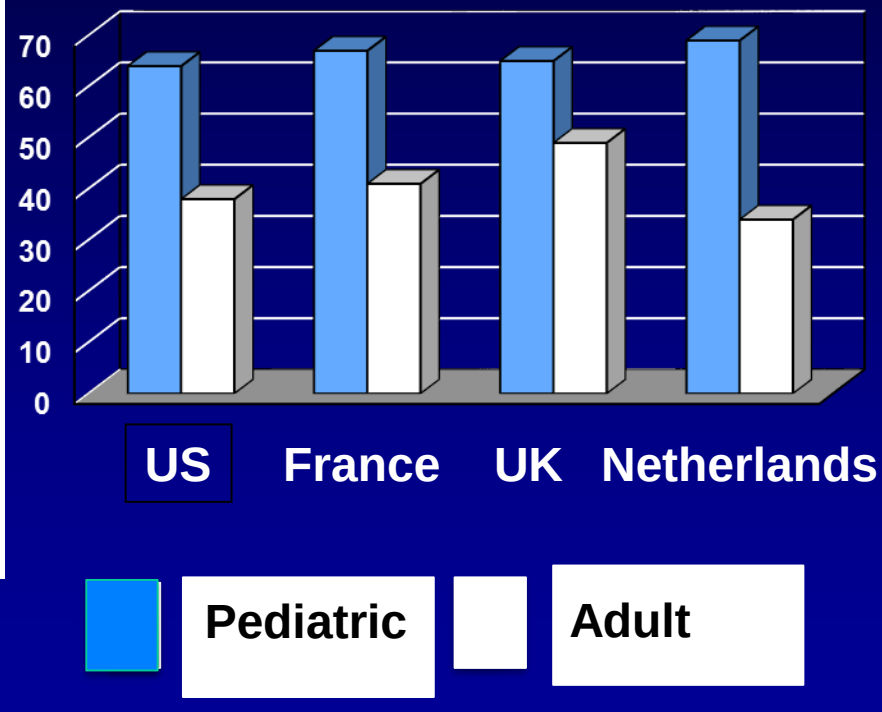
- 213 ALL (47 ETP; 22%)
- MRD positivity post induction 20% vs 70% (non ETP)
- ASCT in CR1 in 49% of ETP-ALL
- 5-yr OS rates 60% (ETP) vs 66% (non-ETP)



Bond. JCO. 2017;35;2683-91

Pediatric vs Adult ALL Regimens in AYA

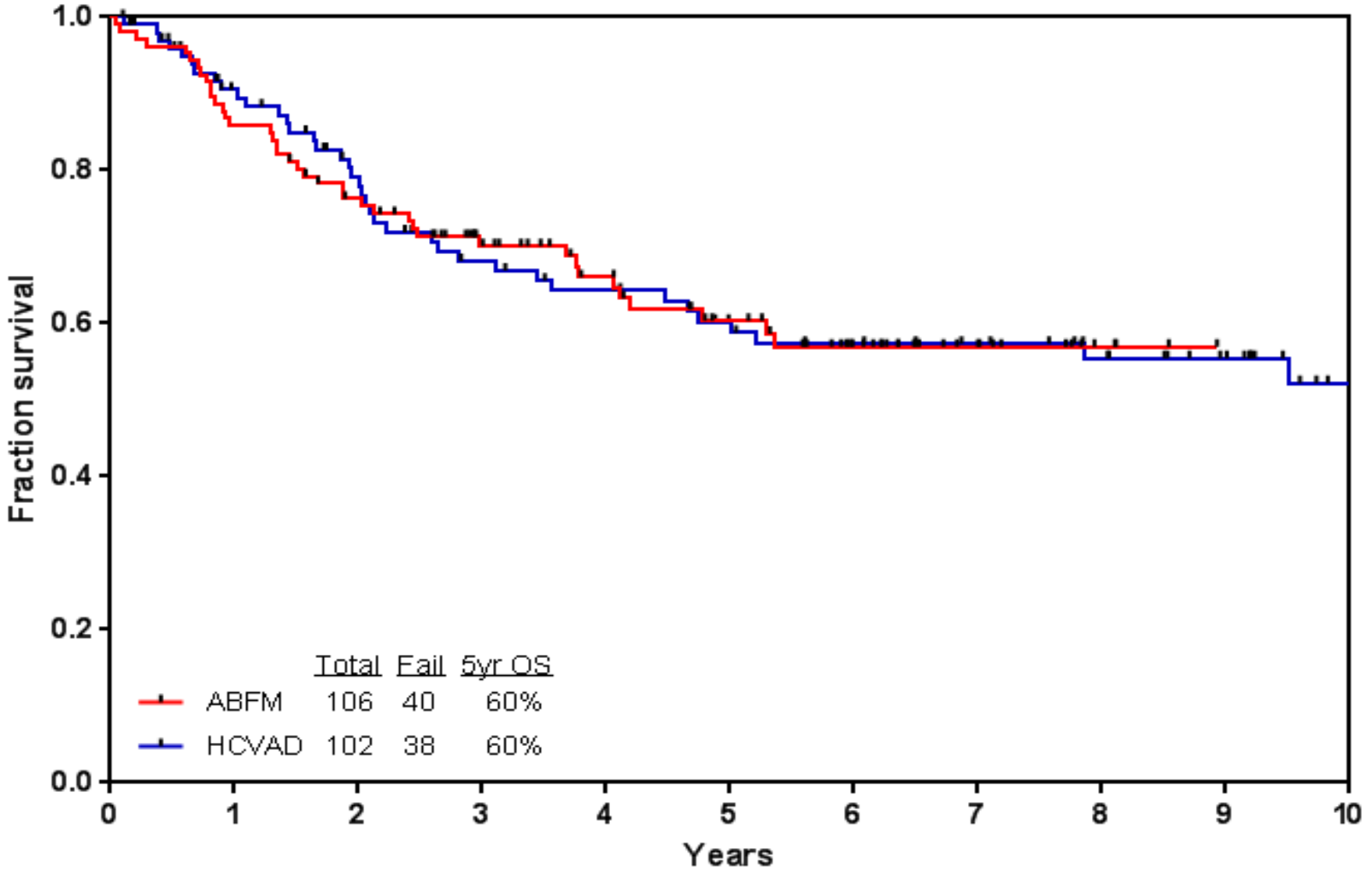




Survival of adolescents/young adults (AYA), ages 16-20 years

Stock W, et al. *Blood.* 2008;112(5):1646-1654. Stock W, et al. *Blood.* 2014;124: Abstract 796.

Hyper-CVAD vs. ABFM.Overall Survival



Rytting. Cancer 120: 3660-8; 2014 . Rytting. AJH 91: 819; 2016

ABFM vs HyperCVAD. Severe Toxicities

% Toxicity	ABFM (n=106)	Hyper-CVAD (n=102)	p value
Asparaginase allergy	19	N/A	NS
Hypofibrinogenemia	35	14	<0.001
Pancreatitis	11	3	0.02
↑LFTs	41	44	0.60
↑ Bili	38	18	0.001
Osteonecrosis	9	8	0.68
Thrombosis	19	12	0.16
Stroke	3	0	0.09
Induction infections	22	45	<0.001
Induction bleeding	1	5	0.09
Infections in CR first 60 days	30	60	<0.001
Bleeding in CR first 60 days	1	5	0.09
Deaths in CR	8	7	.85

Rytting. Cancer 120: 3660-8; 2014 .AJH 91: 819; 2016

Historical Results in R/R ALL

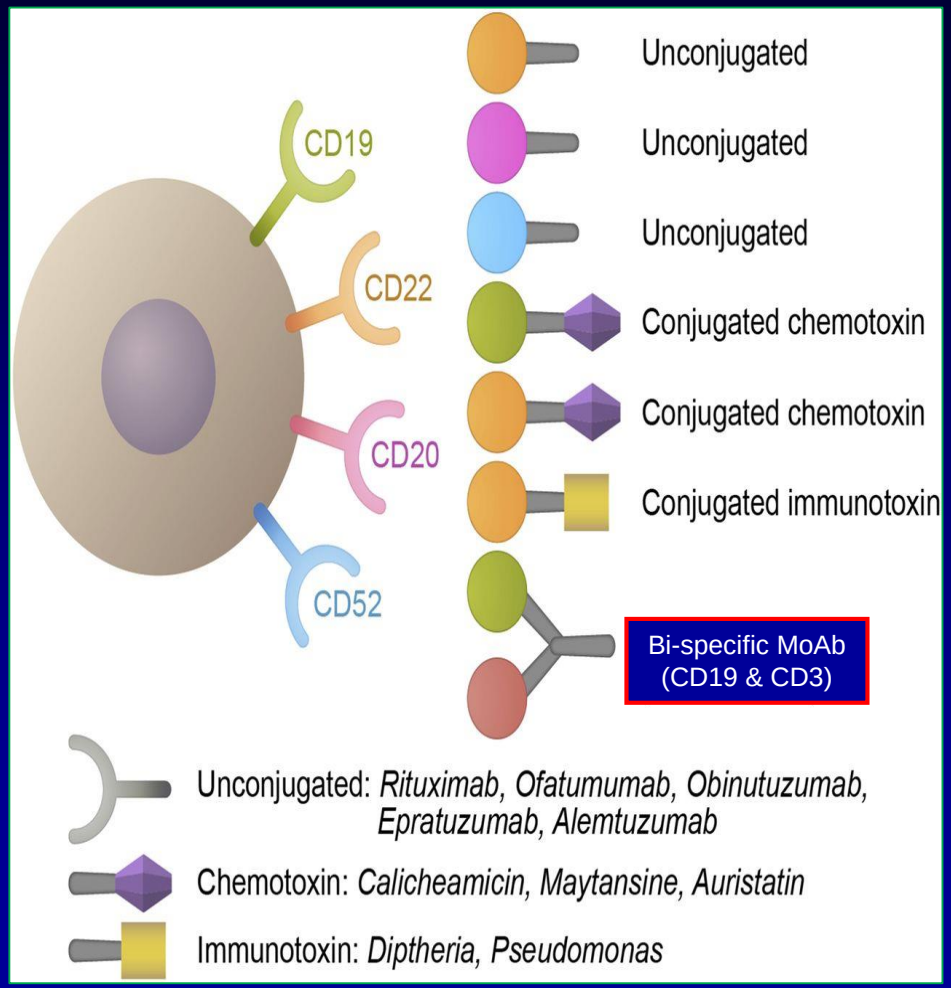
- Poor prognosis in R-R ALL Rx with standard of care (SOC) chemotherapy

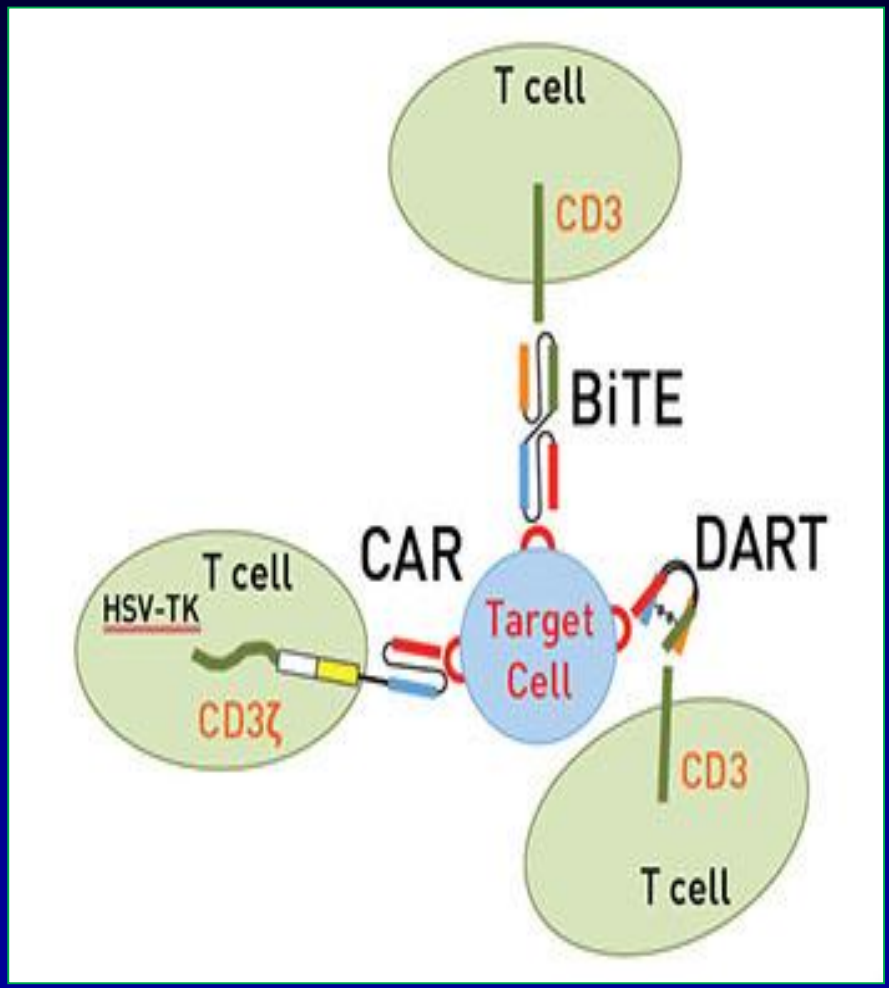
Rate (95% CI)	No prior salvage (S1)	One prior salvage (S2)	≥2 prior salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

Gökbuget N, et al. *Haematologica*. 2016;101:1524–33.

Immuno-oncology in ALL

- **Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR-T cells**



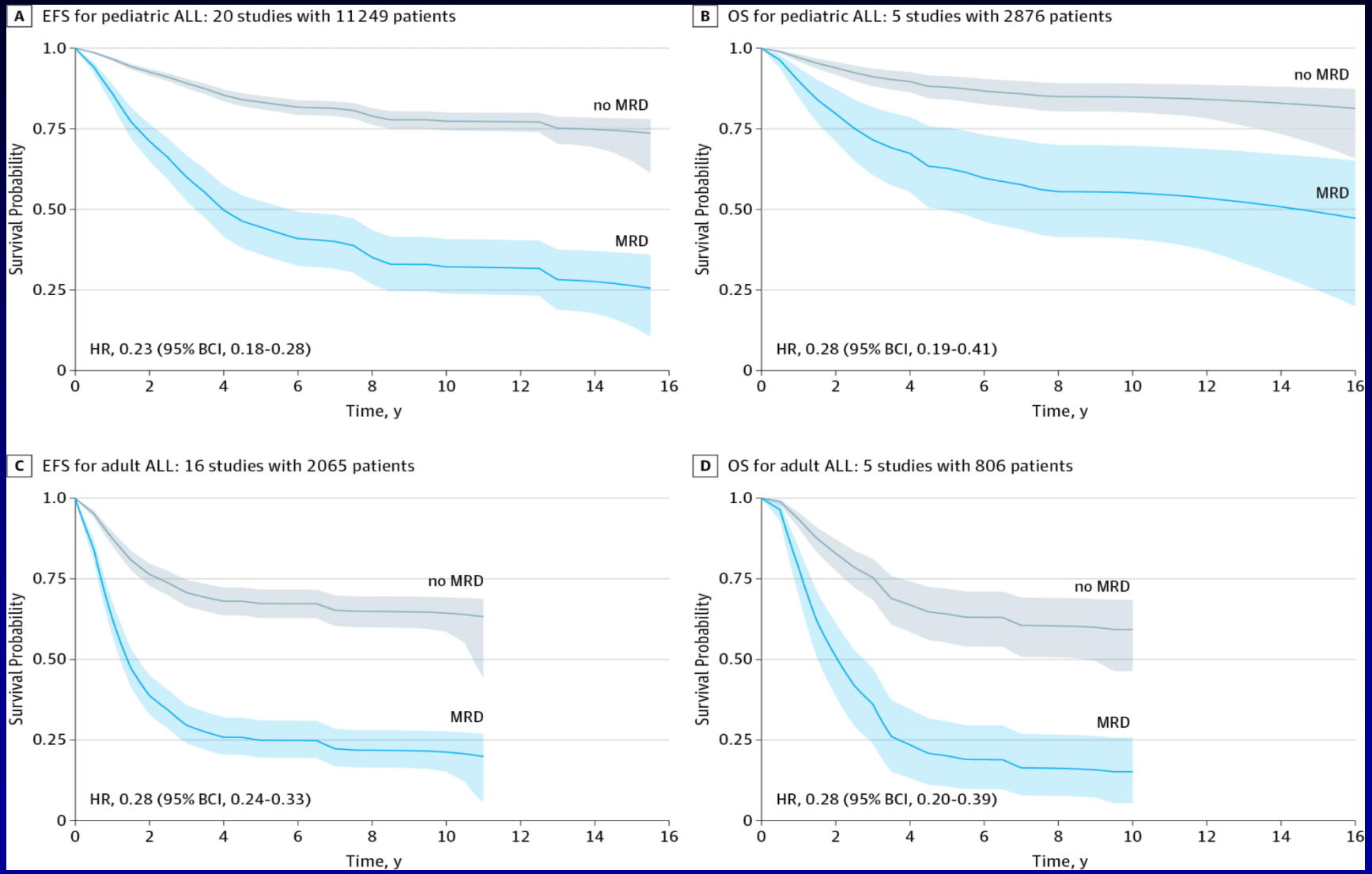


Jabbour E. Blood 125: 4010; 2015

ALL Salvage Standards of Care in 2018

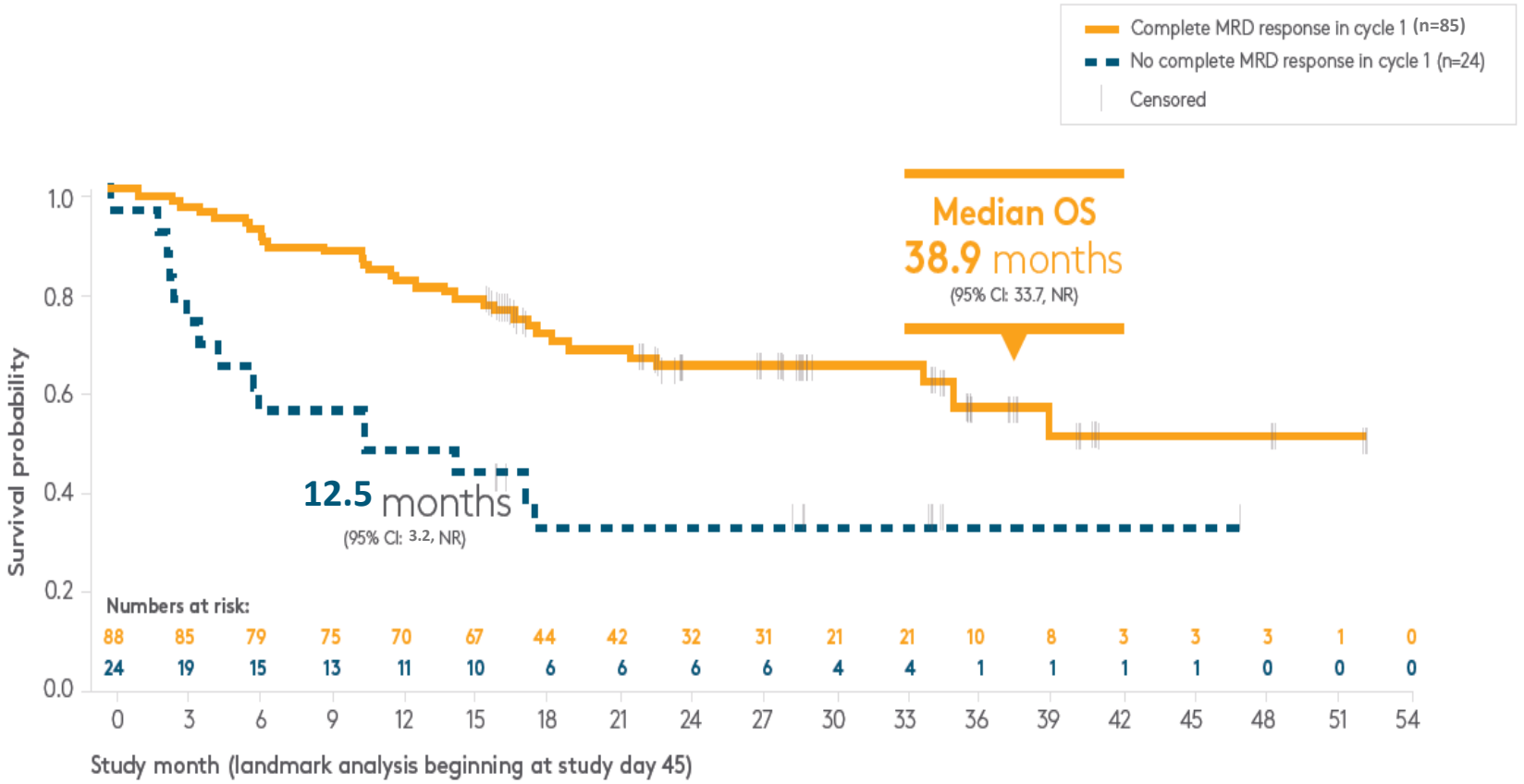
- Refer for investigational therapies-- MoAb + ChemoRx; CAR-T
- Ph-positive ALL-- TKIs+ chemoRx; blinatumomab
- Pre-B ALL--
  - Blinatumomab (FDA approval 12.2014)
  - Inotuzumab (FDA approval 8.2017)
  - CART (FDA approval 8.2017)
- T ALL: nelarabine
- ChemoRx: FLAG IDA, Hyper CVAD, augmented HCVAD, MOAD

MRD in ALL



Berry DA. JAMA Oncol. 2017 Jul 13;3(7):e170580

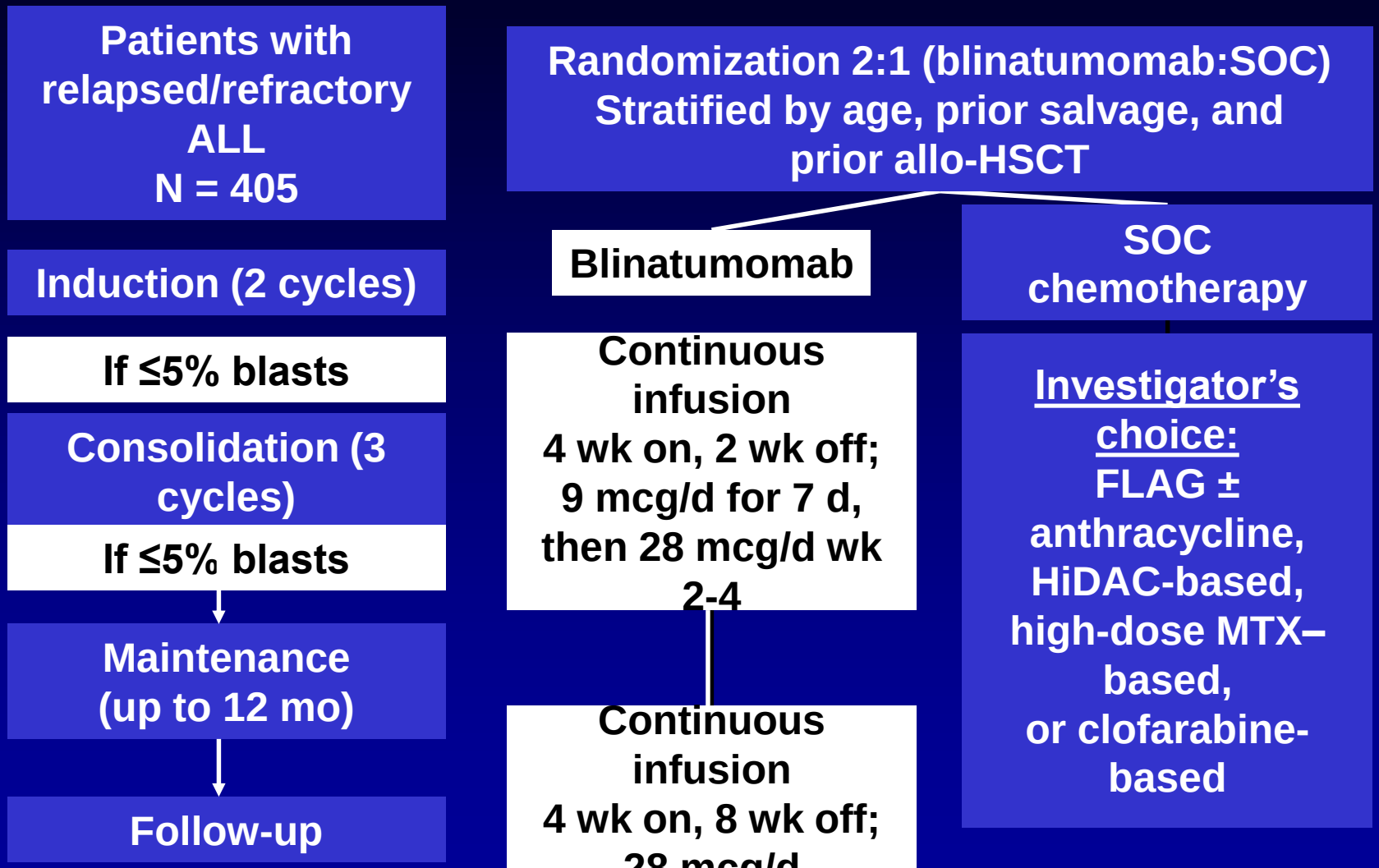
Blinatumomab in ALL MRD-positive



- Median OS in pts with CR2+ MRD- is 12 mos

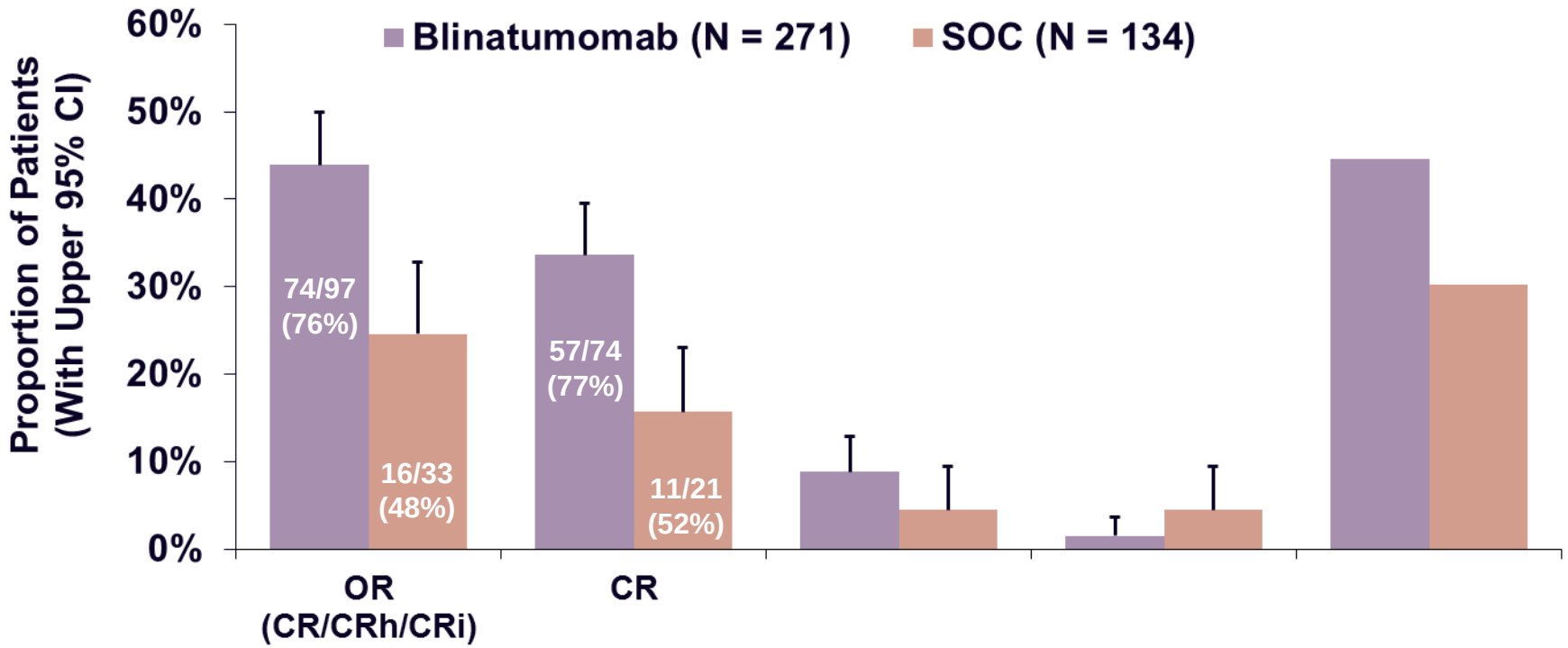
Gokbuget. Blood. 2018; In press

Phase 3 TOWER Study: Randomization and Dosing



Kantarjian. NEJM. 376: 836-47; 2017

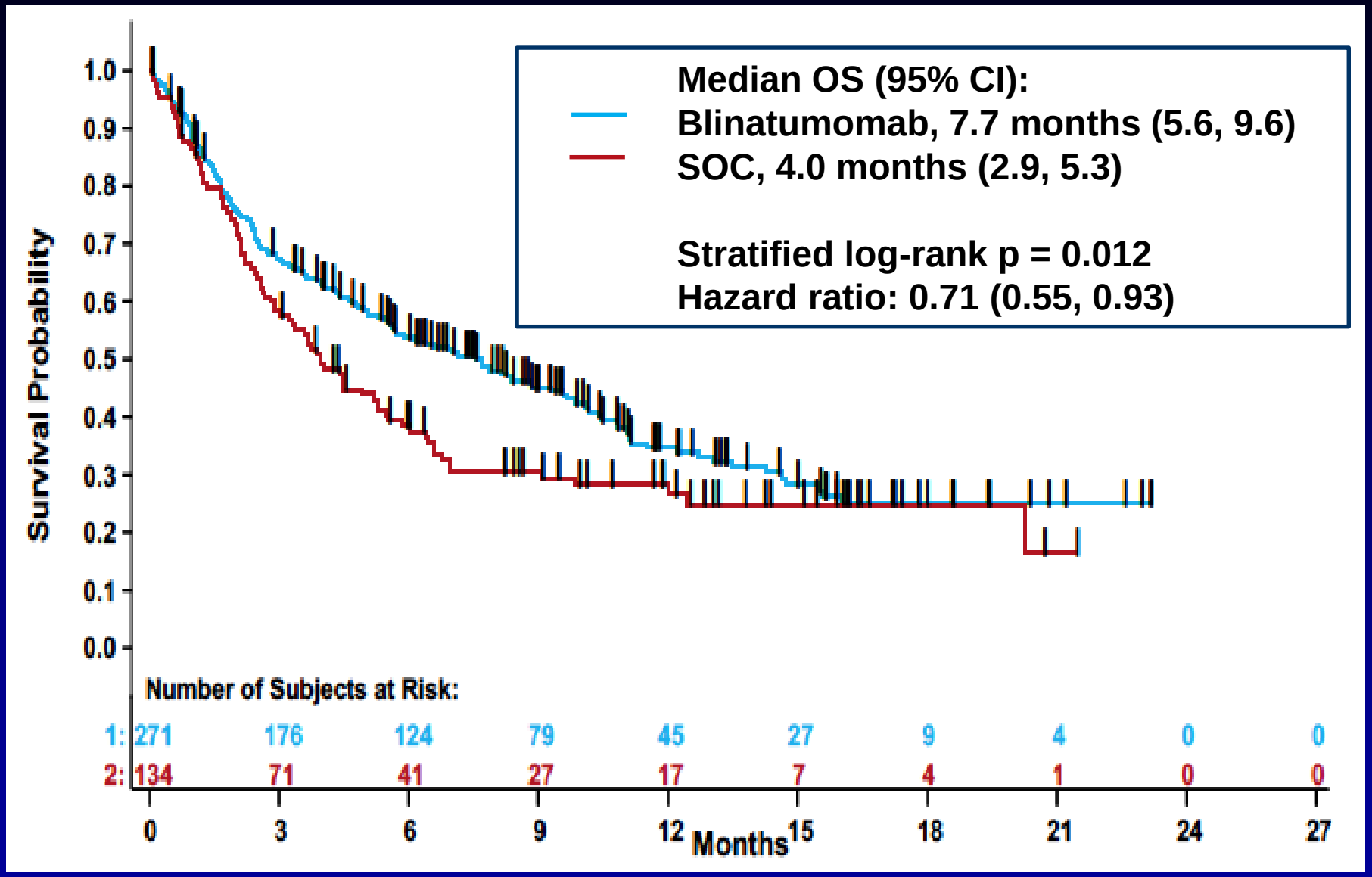
Phase 3 TOWER Study: Molecular Response



Molecular remission was defined as $<10^{-4}$ blasts in the first 12 weeks

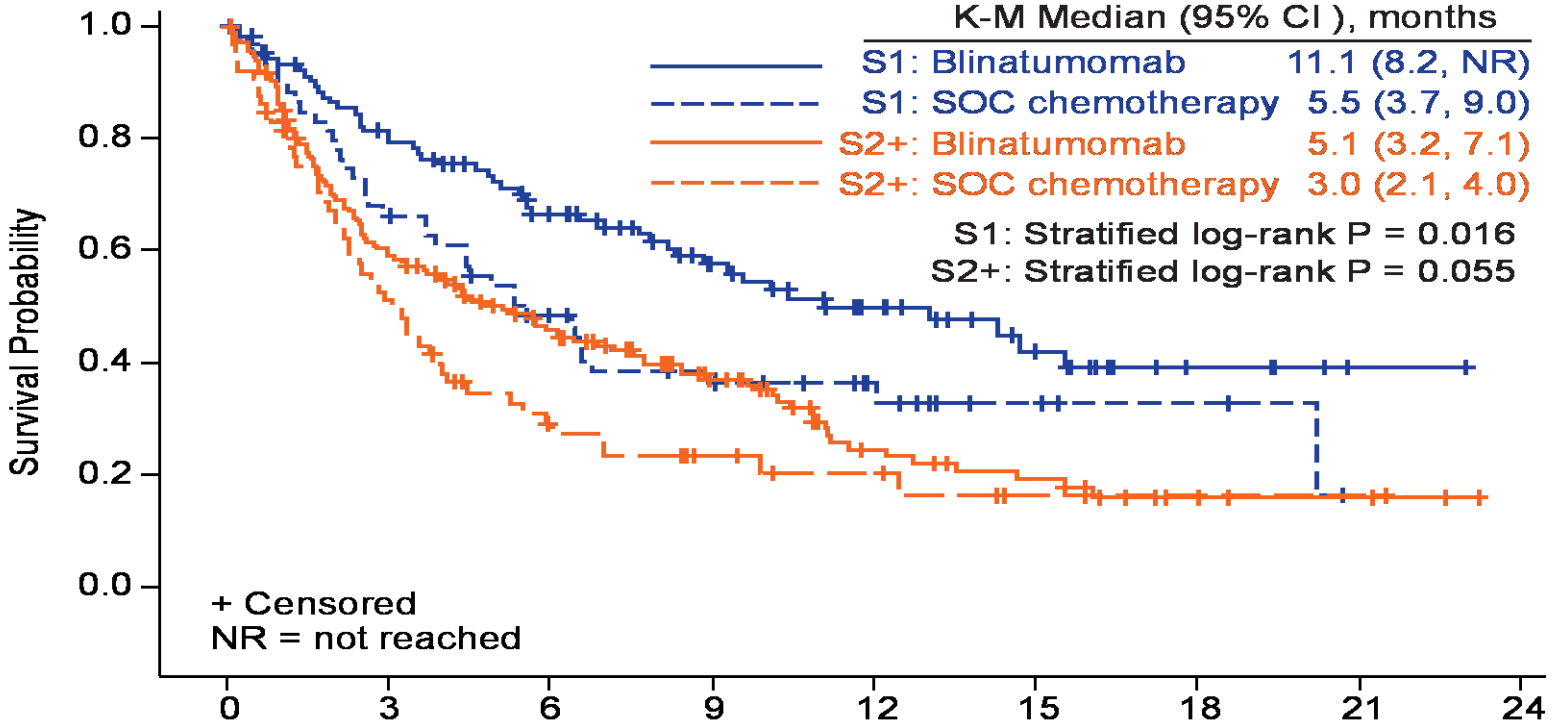
Kantarjian. NEJM. 376: 836-47; 2017

Blinatumomab vs Chemotherapy in R.R. ALL



Kantarjian. NEJM. 376: 836-47; 2017

Phase 3 TOWER Study: Survival by Salvage



Patients at risk:									
S1: Blinatumomab	104	80	59	39	26	14	5	1	0
S:1 SOC	63	39	26	18	11	5	3	0	
S2+: Blinatumomab	167	96	65	40	19	13	4	3	0
S2+: SOC	71	32	15	9	6	2	1	1	0

Dombret H, et al. *Haematologica.* 2017;102(s2):179. Abstract S478

Inotuzumab vs ChemoRx in R-R ALL. Design

- Open-label, phase 3 study; 326 pts randomized at 117 sites in 19 countries

- R/R CD22+ ALL
- Salvage 1 or 2
- Ph– or Ph+

1:1 Randomization (N=326)

Stratifications:

- Duration of 1st CR ≥12 vs <12 mo
- Salvage 2 vs 1
- Aged ≥55 y vs <55 y

InO

- Starting dose 1.8 mg/m^2/cycle[a]
- 0.8 mg/m^2 Day 1; 0.5 mg/m^2 Days 8 and 15 of a 21–28 Day cycle (≤6 cycles)

Standard of Care (SOC)

- FLAG or
- Ara-C plus mitoxantrone or
- HIDAC
- ≤4 cycles

[a]InO dose reduced to 1.5 mg/m^2/cycle once patient achieved CR/CRi.

Kantarjian. NEJM. 375: 740; 2016

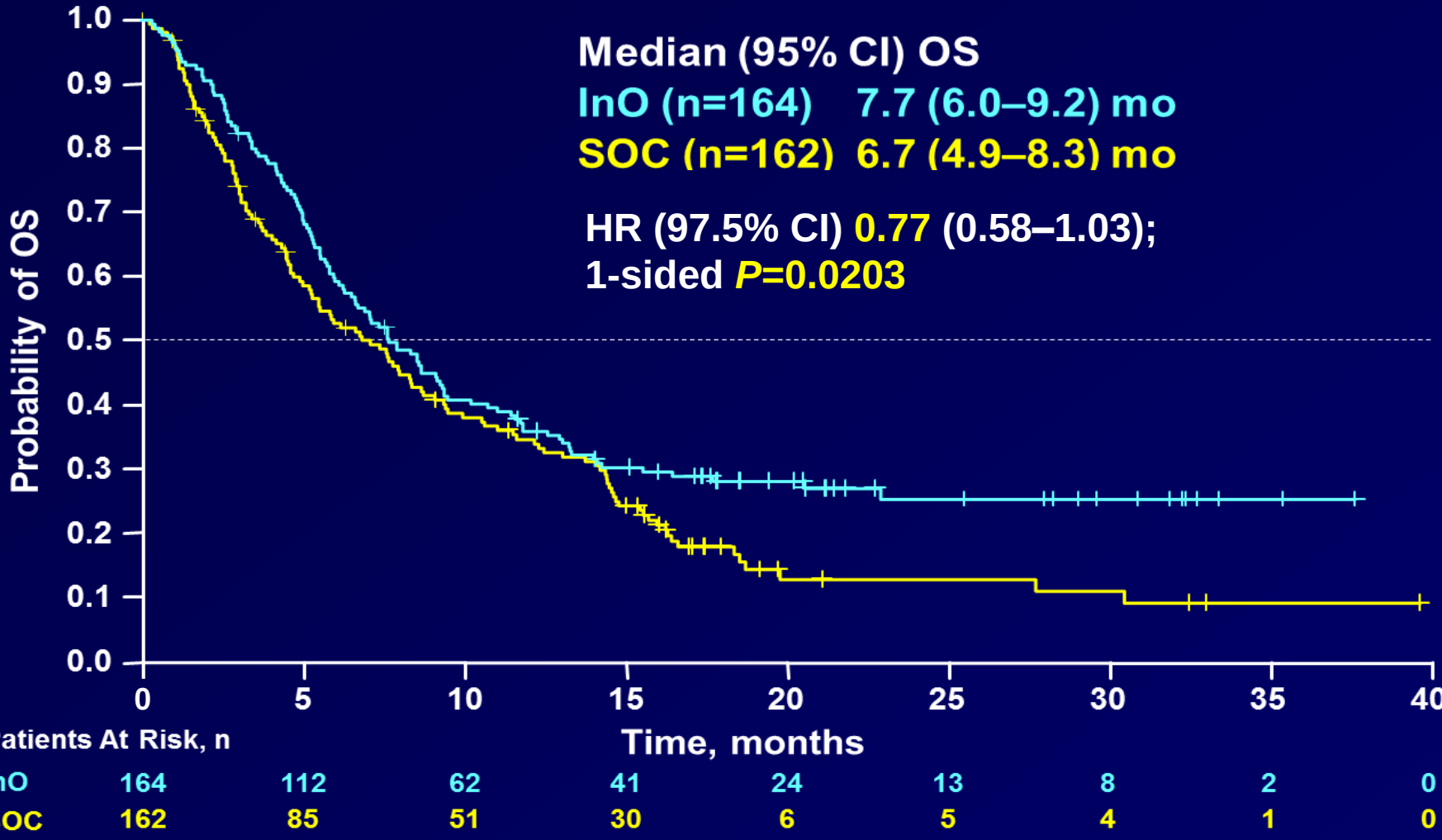
Inotuzumab vs ChemoRx in R-R ALL. Responses

Response,[a] n (%) [95% CI]	InO (n=109)	SOC (n=109)	1-sided *P* Value
CR/CRi	88 (80.7) [72−88]	32 (29.4) [21−39]	<0.0001
MRD neg[b]	69/88 (78.4) [68−87]	9/32 (28.1) [14−47]	<0.0001

- Among the first 218 pts randomized, over 4X more achieved CR/CRi and proceeded directly to SCT after CR/CRi with InO vs SOC (n=41/109 vs n=10/109; *P*<0.0001)[c]

Kantarjian. NEJM. 375: 740; 2016

Overall Survival



- Primary objective to demonstrate significantly improved OS with InO at the prespecified boundary of *P*=0.0104 not met

Kantarjian. NEJM. 375: 740; 2016

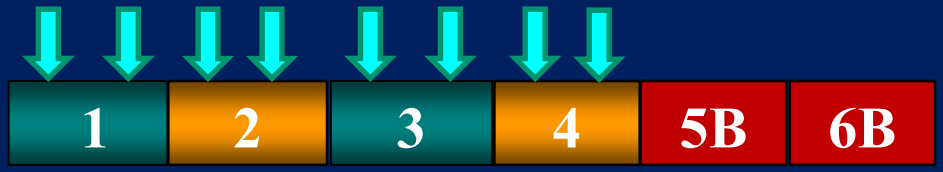
MiniHCVD-INO in ALL. Design

- Dose reduced HyperCVD for 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)**
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- POMP maintenance for 3 years

Jabbour. JAMA Oncology; 2017 (In press)

MiniHCVD-INO-Blina in ALL.

Intensive Phase



Consolidative Phase

Maintenance phase

MiniHCVD

Mini-MTX-cytarabine

Blinatumomab

POMP Maintenance

Inotuzumab

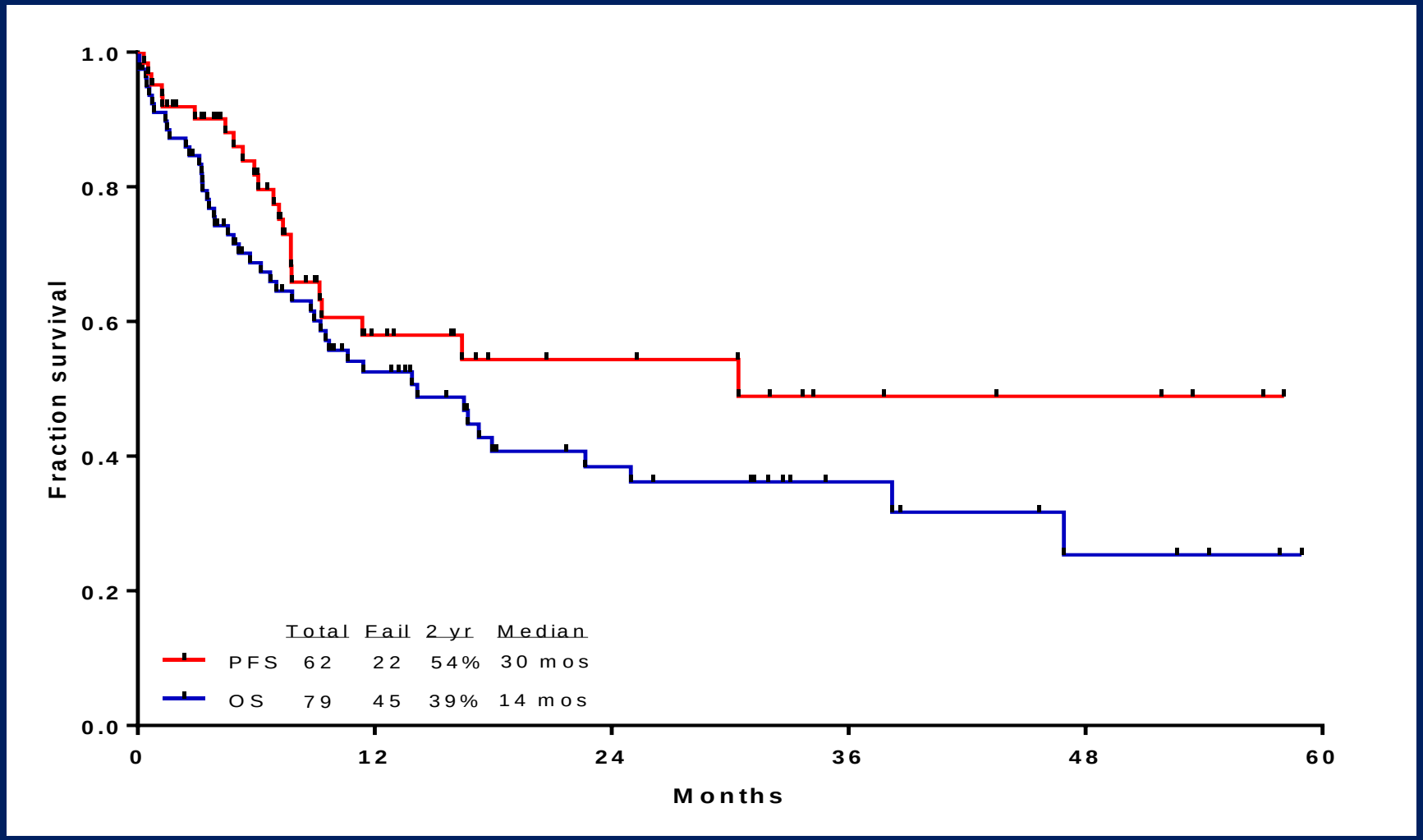
	Total dose	Dose per day
C 1 (mg/m^2)	0.9	0.6 D2 & 0.3 D8
C 2- 4 (mg/m^2)	0.6	0.3 D2 & D8

MiniHCVD-INO in R/R ALL. Response By Salvage (N=78)

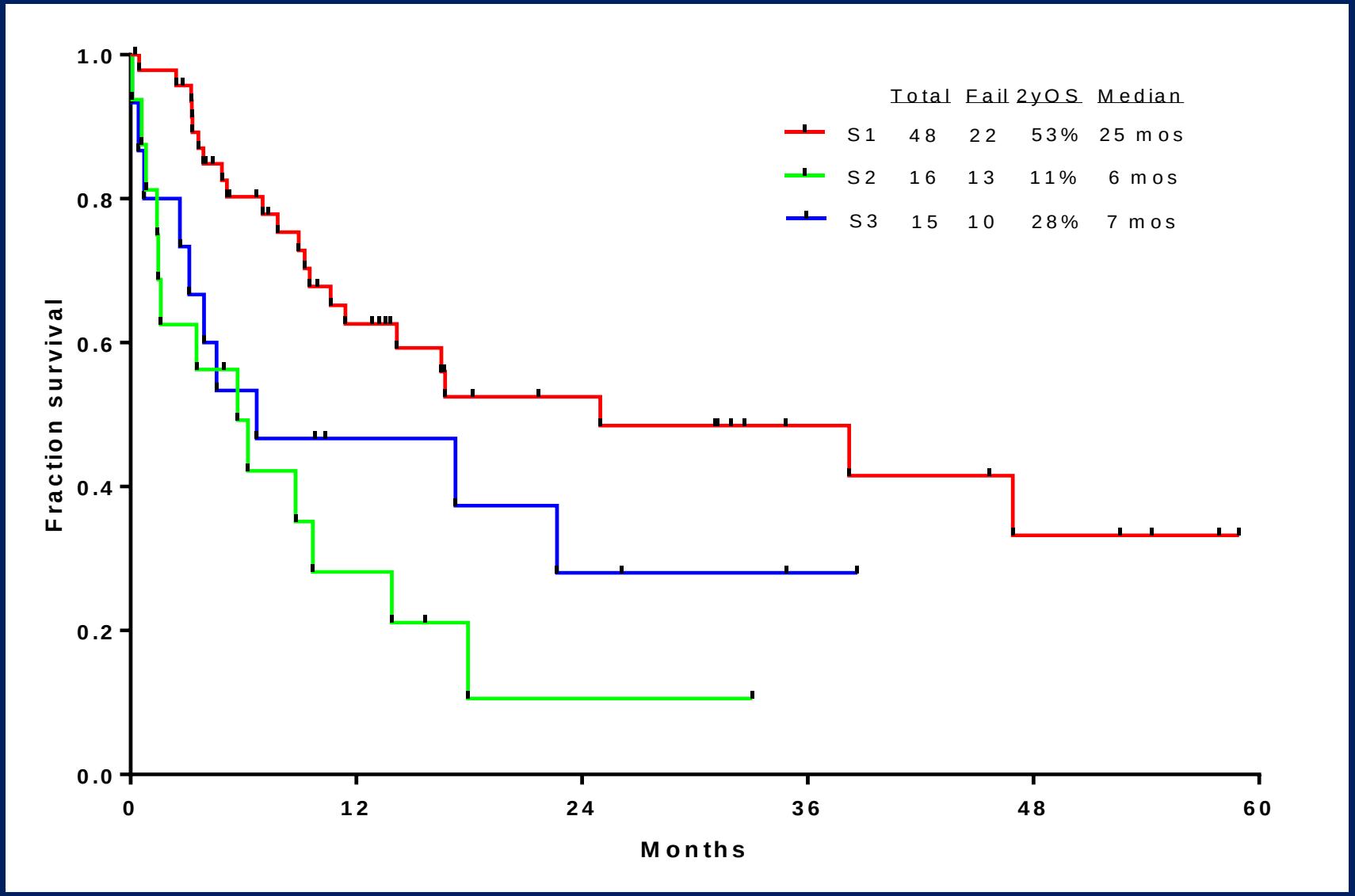
Response	N	(%)
Salvage 1	43/47	91
S1, Primary refractory	5/5	100
S1, CRD1 < 12 mos	15/19	79
S1, CRD1 ≥ 12 mos	23/23	100
Salvage 2	9/16	56
≥ Salvage 3	9/15	60
Overall	61/78	78
MRD negativity	49/59	83
Salvage 1	37/41	90
≥ Salvage 2	12/18	67

MiniHCVD-INO in R/R ALL. Survival

- 2-yr PFS and OS rates 54% and 39%, respectively



MiniHCVD-INO in R/R ALL. Survival by Salvage



Elderly ALL. Historical Results

- MDACC 122 pts ≥ 60 yrs Rx on Hyper CVAD
  - CR 84%; induction mortality 10%; death in CR 34%; Median OS 15 mos; 3-yr OS 20%
- GMALL 268 pts
  - CR 76%; early death rate 14%; death in CR 6%; 5-yr OS 23%
- SEER database among 1675 pts (age ≥60 years) between 1980 and 2011
  - Median survival 4 mos; 3-yr OS 13%
- Medicare database among 727 pts (>65 years) diagnosed between 2007 and 2012
  - Median survival of 10 mos

O'Brien. Cancer 113: 2097, 2008; Gökbuget. Blood. 2013;122:1336; Li S. Blood. 2016;128:3981; Geyer. Blood 2017;129:1878

MiniHCVD-INO in ALL. Response (N=57)

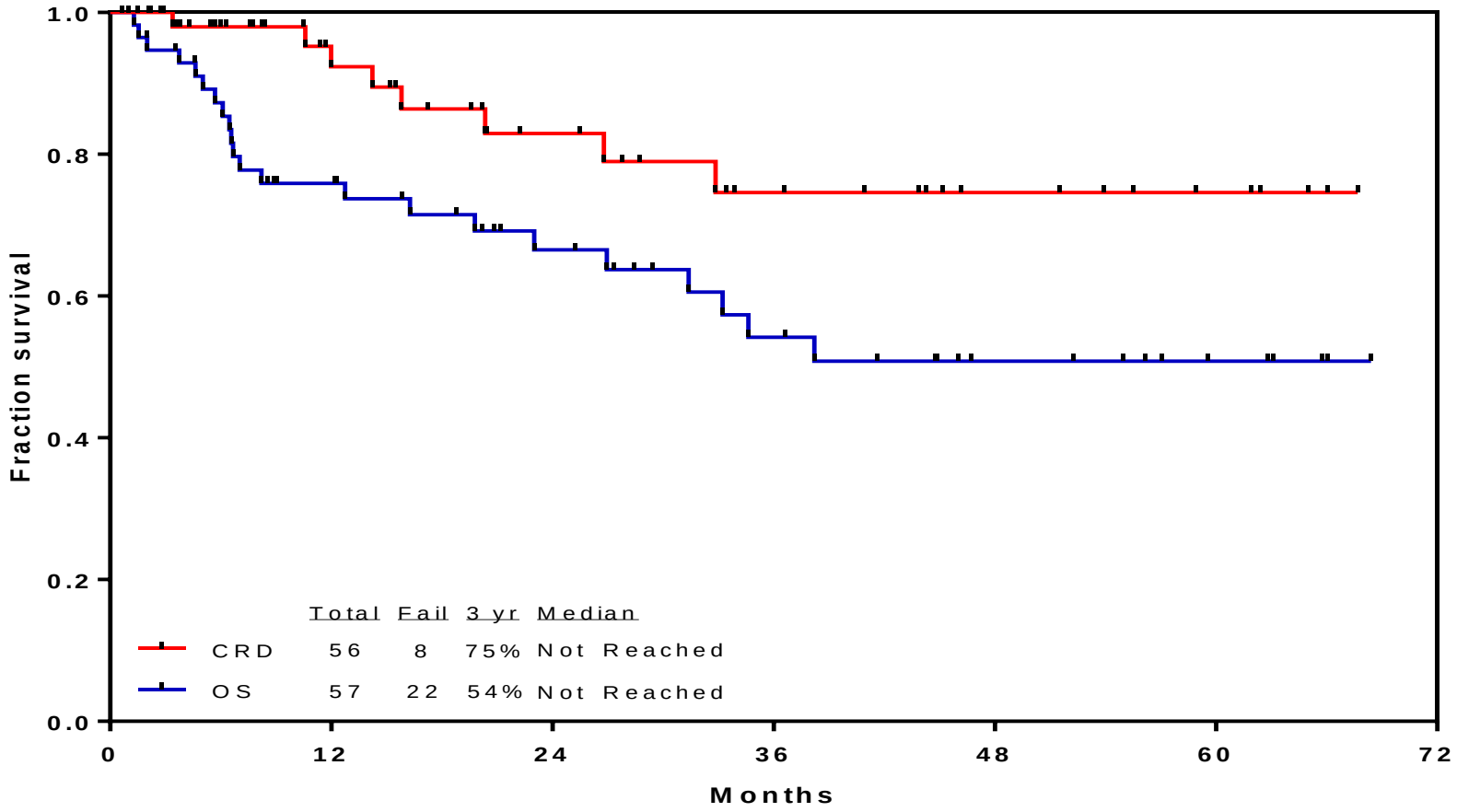
Response	N	(%)
CR	46	(87)
CRp	5	(9)
CRi	1	(2)
ORR	52	(98)
No response	1	(2)
Early death	0	0

- Four patients were enrolled with CR

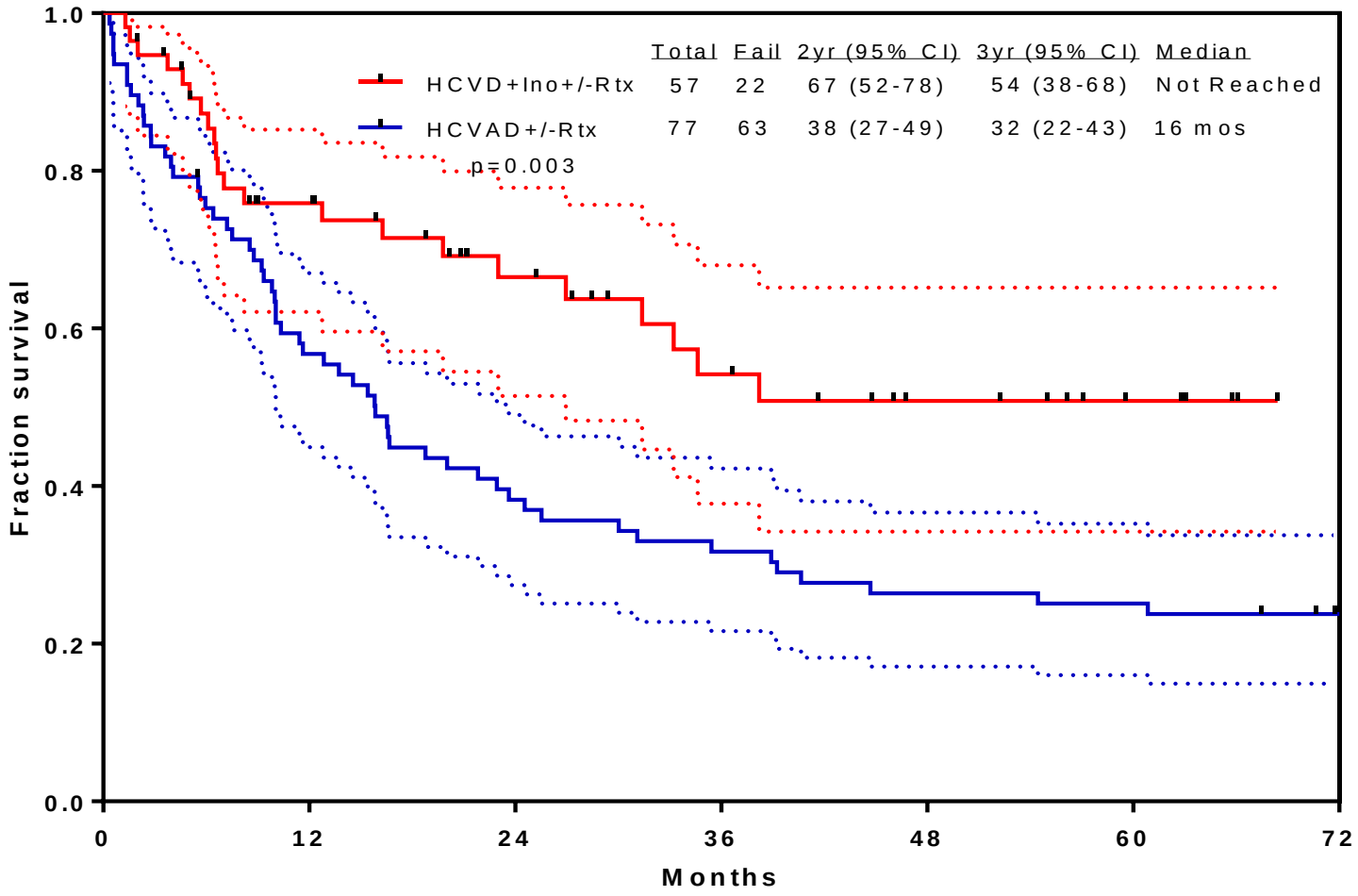
MiniHCVD-INO in ALL. Survival

- Median follow up of 28 months (2-68)

CRD & OS



MiniHCVD-INO vs HCVAD in ALL.

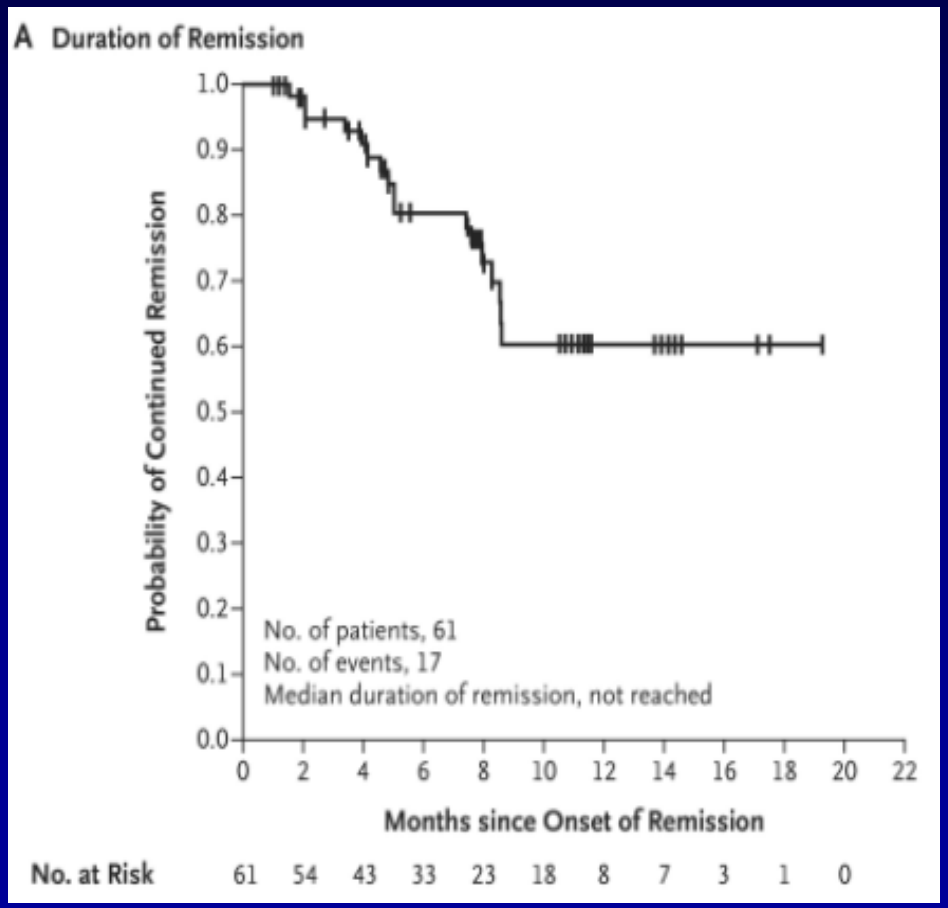


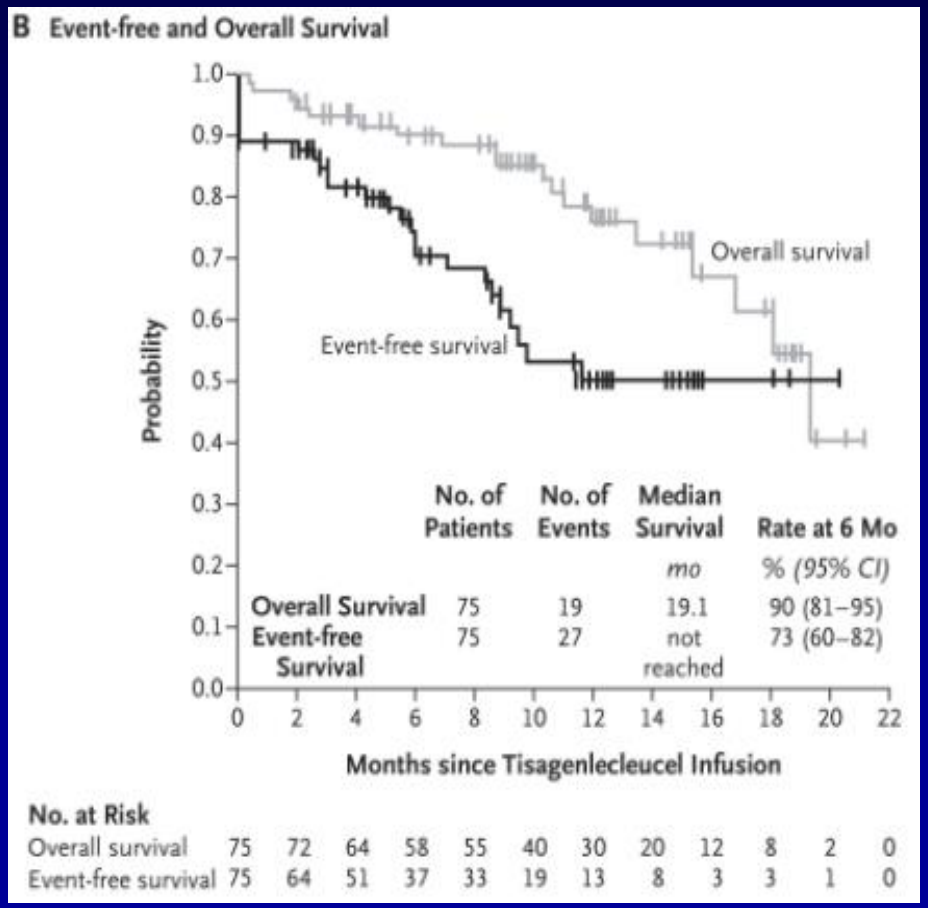
Number at Risk

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

Tisagenlecleucel in ALL

- 107 screened, 92 enrolled, 75 infused-- Lymphodepletion with Flu-CTX; Tisa-Cel 0.1-2.5x 10^8 cells/pt
- OR 61/75 = 81%; CR 44/75 = 60% (or 44/92 = 48%)





Maude. NEJM 378: 439; 2018

CD19-CD28z CAR (MSKCC)

- 53 adults with R/R B-ALL (83 enrolled)
  - 27 BM blasts ≥5%
  - 5 BM blasts <5% + EM disease
  - 21 BM blasts <5% (MRD+ only)

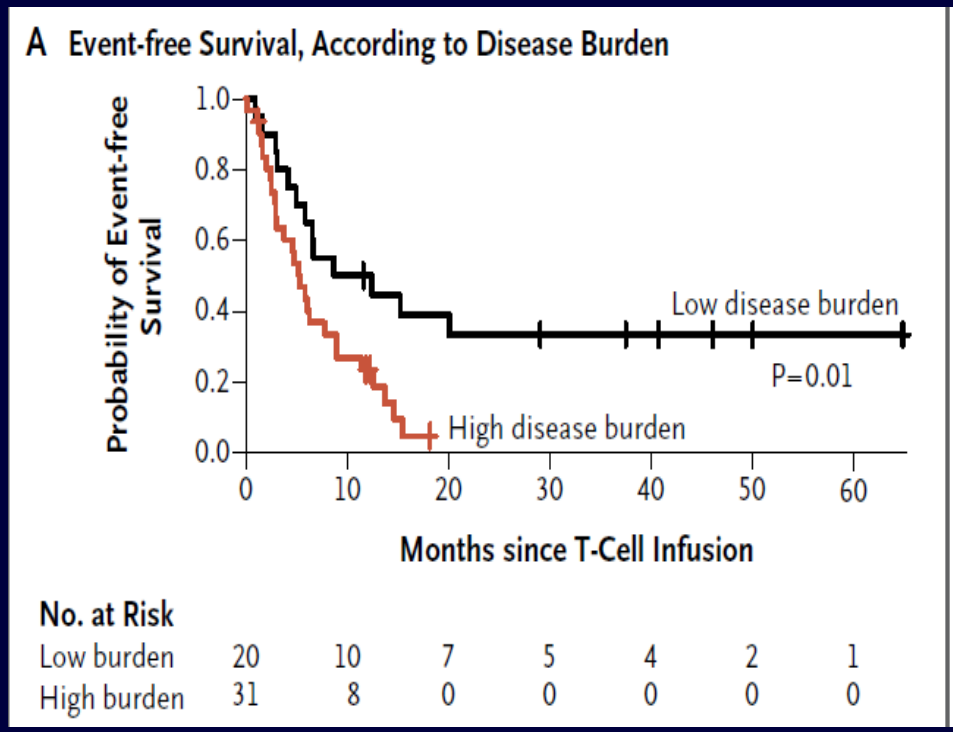
High tumor burden

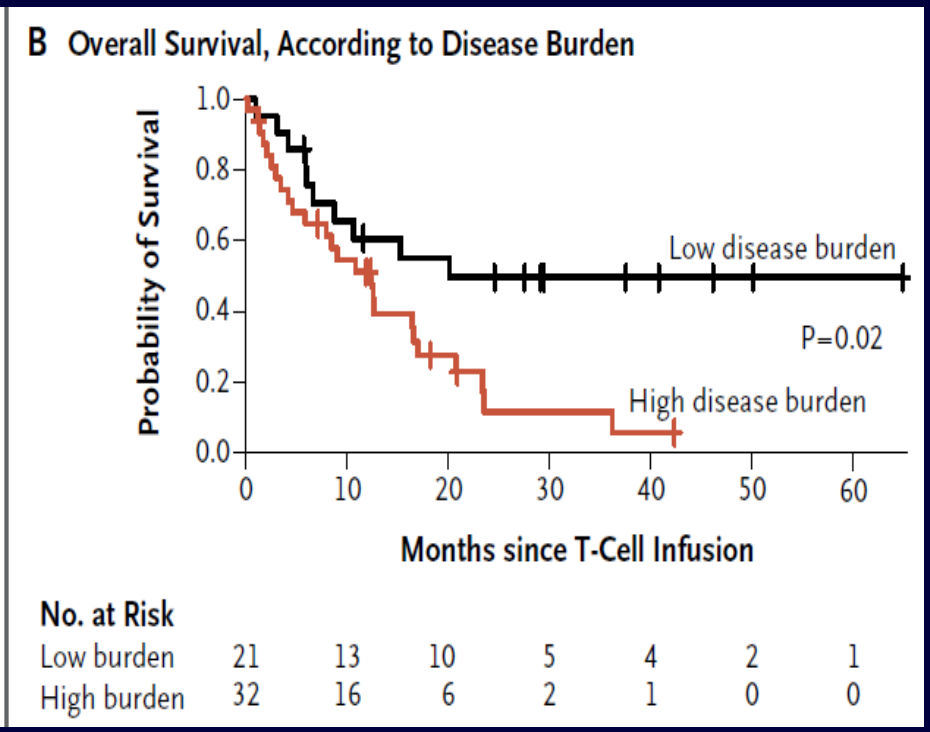
- CR rate 83%; ITT (n=83) CR rate **53%**
  - MRD neg CR rate 60%
- Median EFS 6.1 mos; OS **12.9 mos** (53 pts)
- Grade 3+ CSR 26% and NE 42%

Park. N Engl J Med 2018;378:449-459

CD19-CD28z CAR (MSKCC). Outcome by Tumor Burden

- High tumor burden
  - BM blasts ≥5% (n=27)
  - BM blasts <5% + EM disease (n=5)
- Low tumor burden (MRD+ disease) (n=21)





Median EFS

Low tumor burden (MRD+): 10.6 mos

High tumor burden: 5.3 mos

Median OS

Low tumor burden (MRD+): 20.1 mos

High tumor burden: 12.4 mos

Park. N Engl J Med 2018;378:449-459

ALL. Progress and Future Directions

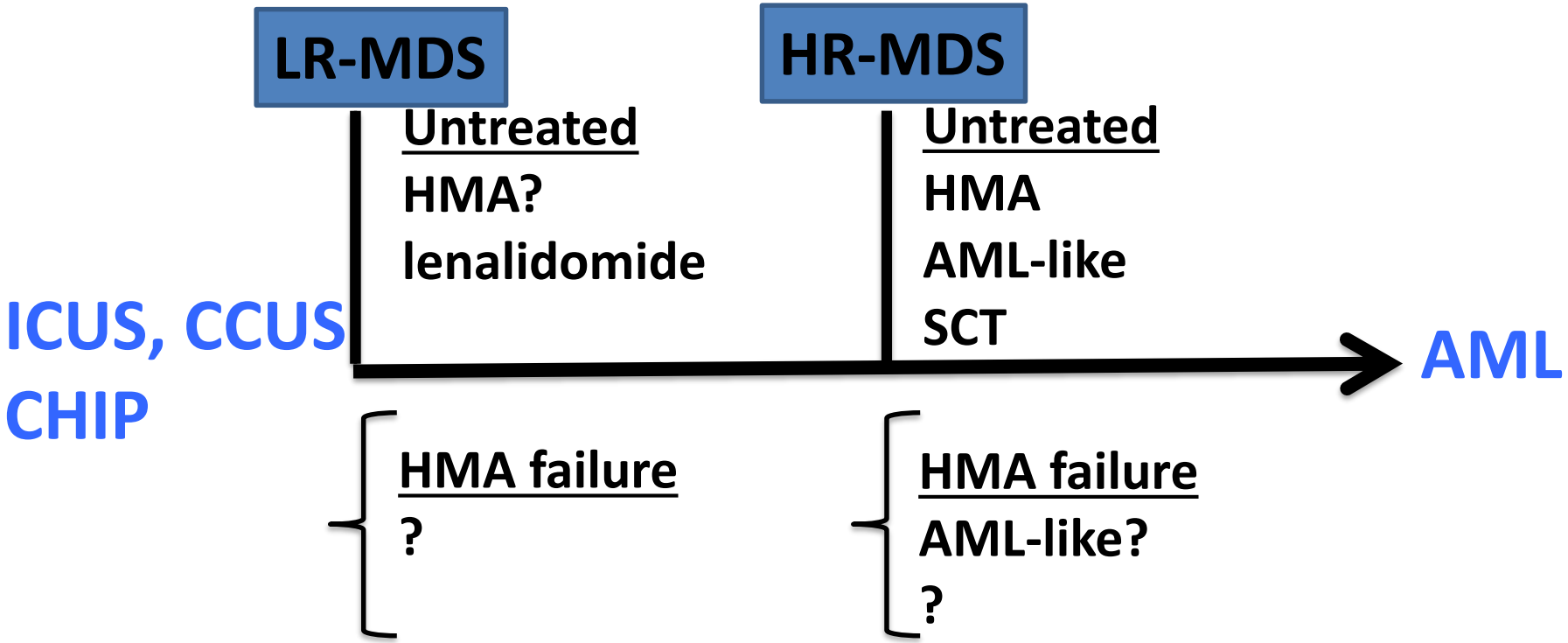
- Burkitt: HCVAD-O/ EPOCH-O
- Adult B-ALL (including Ph-like): HCVAD-Blinatumomab
- Ph-positive ALL:
  - CT + ponatinib
  - Blinatumomab + ponatinib (Chemo free regimen)
- T-cell ALL: CT + ABT199 +/- Neralabine +/- Asparaginase
- Elderly ALL
  - HCVD + Inotuzumab + Blinatumomab
  - HCVD + ABT199
- MRD positive: Blinatumomab; inotuzumab
- Salvage 1: HCVD + Inotuzumab + Blinatumomab (2-yr 50%)
- CAR-T cells Rx (early phases for high-risk patients: MLL, complex CG, etc..)
- Explore venetoclax and other MoAbs targeting CD19, CD22, CD38 and CD123

MDS Update

Elias Jabbour M.D.

3-10-2018

Current practical approach to MDS



HMA lower risk failure survival: 14-17 months
HMA higher risk failure survival: 4-6 months

Jabbour. Cancer 2015; Jabbour. Cancer 2010; Steensma Blood 2015.

Non-del5q- Lower risk MDS

- Phase III CC-486 (oral azacitidine)
- Attenuated schedules of HMA
- Phase III oral decitabine E7727
- Phase III ACE-536
- PD1/PDL1 inhibition
- Splicing inhibitors (H3Bio)
- LSD1 inhibitor
- antiCD38, antiCD123

A Randomized Phase II Study of Low-Dose Decitabine versus Azacitidine in Patients with Low- or Intermediate-1-Risk Myelodysplastic Syndromes

Jabbour E[1], Short N[1], Huang X[1], Maiti A[1], Kadia T[1], Daver N[1], Borthakur G[1], DiNardo C[1], Pemmaraju N[1], Sasaki K[1], Estrov Z[1], Verstovsek S[1], Ravandi F[1], Alvarado Y[1], Sekeres M[2], Komrokji R[3], Steensma D[4], DeZern A[5], Roboz G[6], Kadia T[1], Borthakur G[1], DiNardo C[1], Miller D[1], Dong X[1], Kantarjian H[1], Garcia-Manero G[1]

ASH 2016, Blood 2017

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Cleveland Clinic, Cleveland, OH; [3]Moffitt Cancer Center, Tampa, FL; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Johns Hopkins University, Baltimore, MD; [6]Cornell Medical College, New York, NY

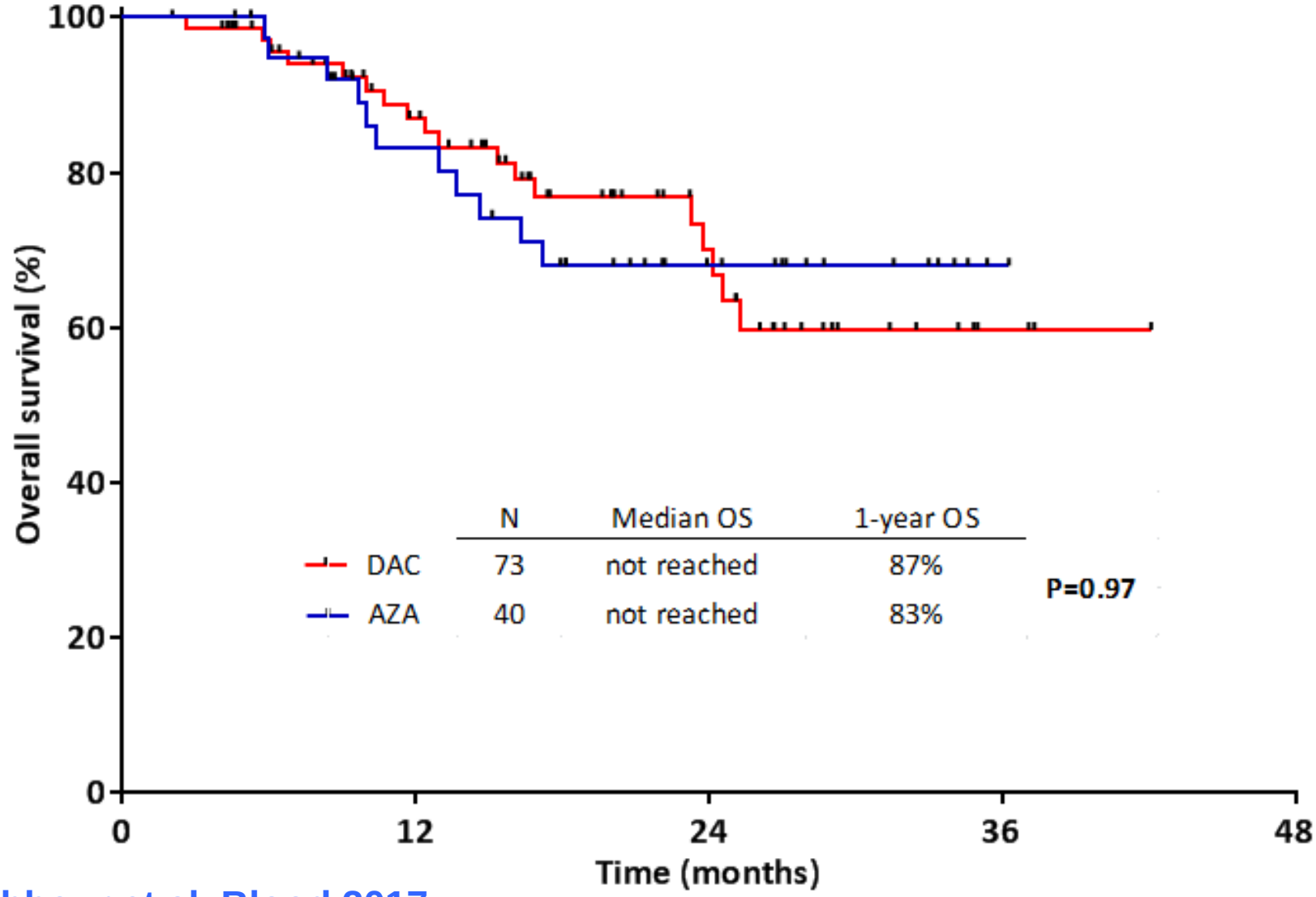
DAC vs. AZA in LR-MDS. Response (IWG)

Response	DAC (N=70) n (%)	AZA (N=39) n (%)	*P*
CR	26 (37)	14 (36)	0.90
mCR	6 (9)	2 (5)	
HI	17 (24)	3 (8)	
ORR	49 (70)	19 (49)	0.03
SD	18 (26)	17 (44)	
PD	3 (4)	3 (8)	

Median number of cycles: 9 (range: 1-41)

Jabbour et al. Blood 2017

DAC vs. AZA in LR-MDS. OS



Jabbour et al. Blood 2017

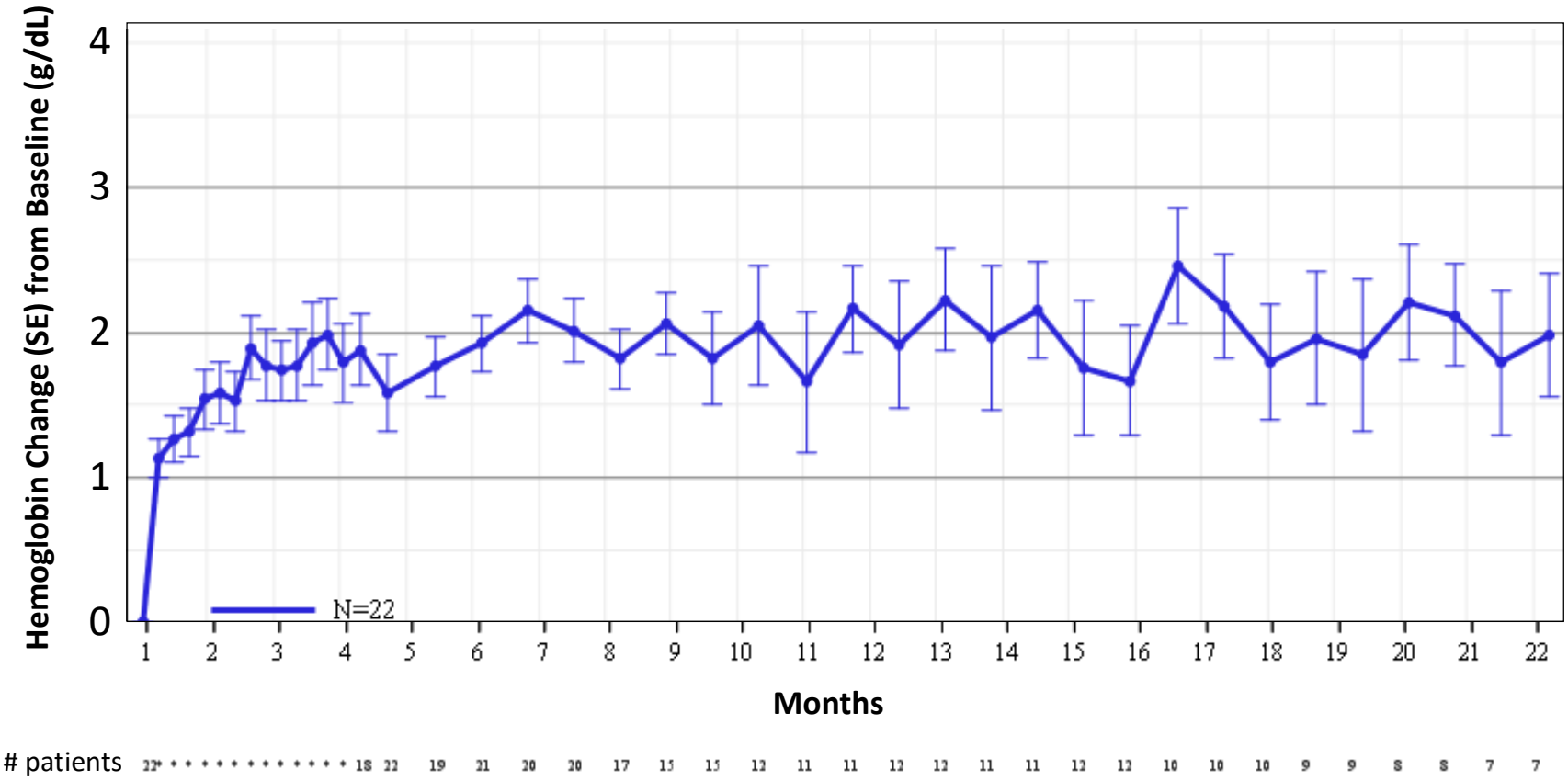
LUSPATERCEPT INCREASES HEMOGLOBIN AND REDUCES TRANSFUSION BURDEN IN PATIENTS WITH LOW-INTERMEDIATE RISK MYELODYSPLASTIC SYNDROMES (MDS): LONG-TERM RESULTS FROM PHASE 2 PACE-MDS STUDY

Uwe Platzbecker, MD[1], Aristoteles Giagounidis, MD, PhD[2], Ulrich Germing, MD[3], Katharina Götze, MD[4], Philipp Kiewe, MD[5], Karin Mayer, MD[6], Joerg Chromik, MD[7], Markus Radsak, MD[8], Thomas Wolff, MD[9], Detlef Haase, MD[10], Monty Hankin[11], Dawn Wilson[11], Xiaosha Zhang[11], Abderrahmane Laadem, MD[12], Matthew L. Sherman, MD[11] and Kenneth M. Attie, MD[11]

[1]Universitätsklinikum Carl Gustav Carus, Dresden, [2]Marien Hospital Düsseldorf, [3]Universitätsklinikum Düsseldorf, [4]Technical University of Munich, [5]Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin, [6]University Hospital Bonn, [7]Universitätsklinikum Frankfurt, Goethe Universitaet, Frankfurt/Main, [8]Johannes Gutenberg-Universität, Mainz, [9]OncoResearch Lerchenfeld UG, Hamburg, [10]Universitätsmedizin Göttingen, Germany; [11]Acceleron Pharma, Cambridge, MA, [12]Celgene Corporation, Summit, NJ, USA

Increase in Mean Hemoglobin in LTB Patients with > 3 Months of Treatment (Extension Study)

- 16/22 (73%) HI-E responders; median time to response: 2.2 months

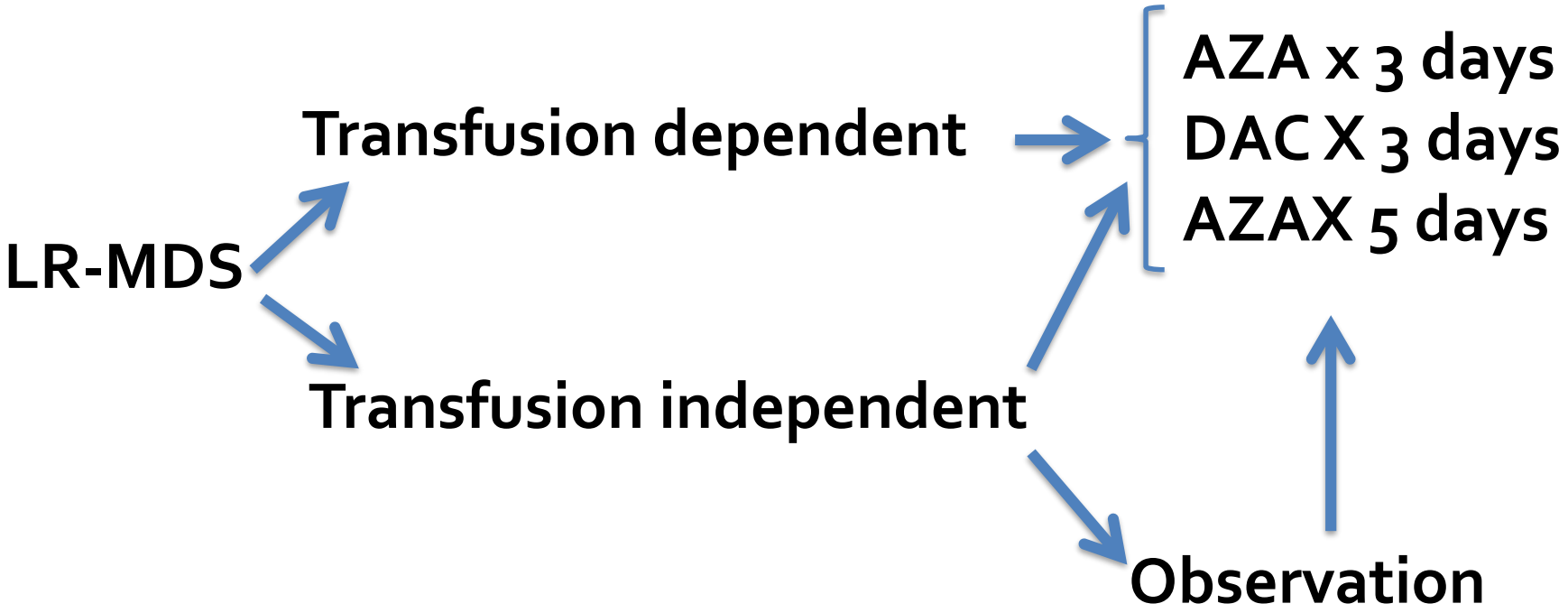


LTB: Low transfusion burden patients (< 4 units/8 wk, Hb <10 g/dL)

Data as of 09 Sep 2016

Early intervention in LR MDS

(US North American MDS Consortium)



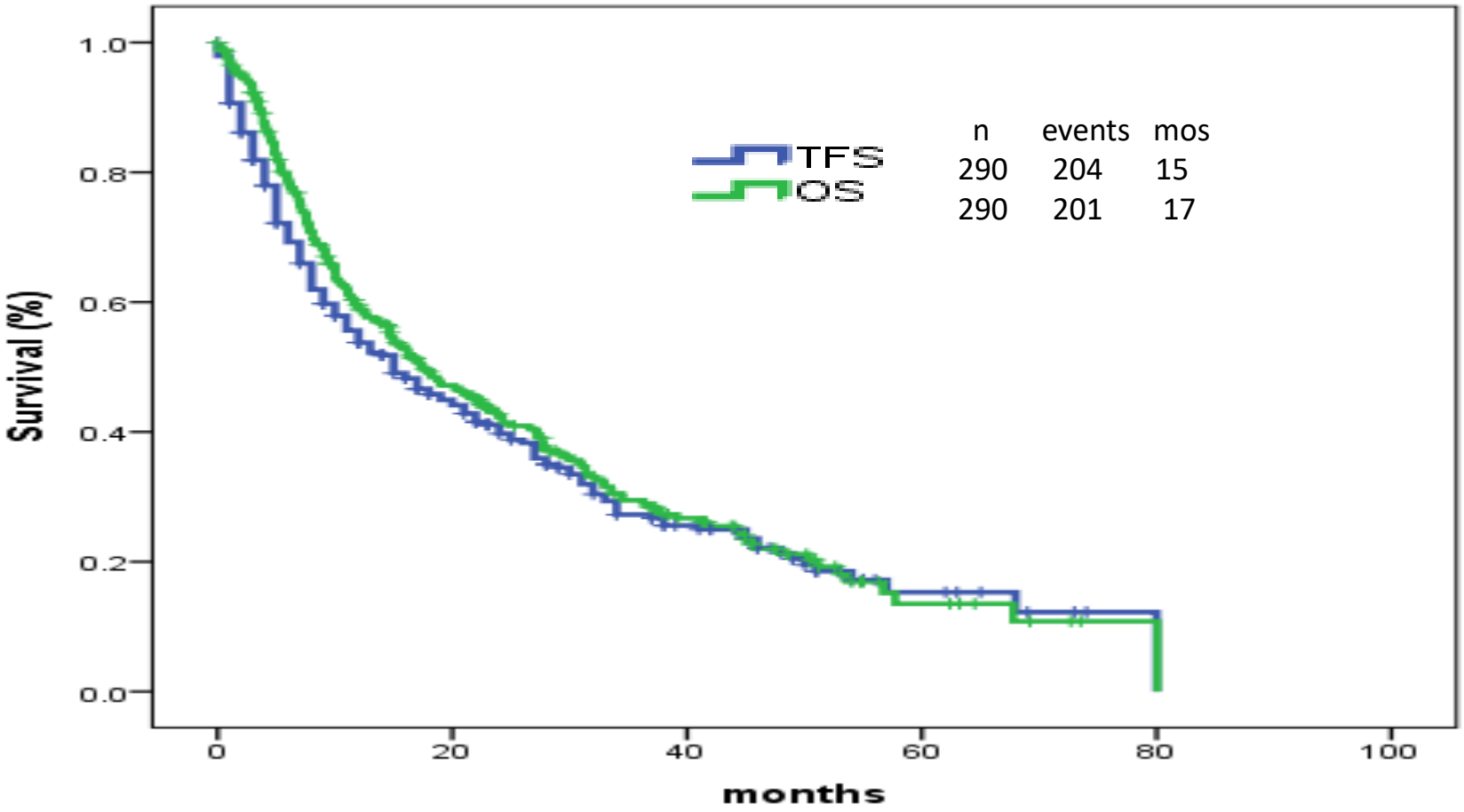
NCT02269280. Funded Edward P Evans Foundation

Cleveland Clinic: M. Sekeres; Dana Farber Cancer Center: D. Steensma; Johns Hopkins: A Dezern; MDAnderson: Garcia-Manero; Moffitt Cancer Center: R Komrokji; Weill-Cornell: G Roboz

HMA failure Lower risk MDS

- **PD1/PDL1 inhibition**
- **Toll Like Receptor Inhibition: OPN-305**

LR MDS post HMA Failure. Outcome



- **Median follow-up: 16 (1-80) months**
- **Median TFS and OS: 15 and 17 months**

Jabbour et al; Cancer 2015

Higher risk MDS

- PD1/PDL1 Inhibition
- SGI-110 (Guadecitabine)
- Ph II AZA +/- Durvalumab
- Ph II Aza+Rigosertib
- Ph II Ruxolitinib + AZA
- Aza+Abt-199

Initial results of a Phase 2 Study of Guadecitabine (SGI-110), A Novel Subcutaneous Hypomethylating Agent, for Patients with Previously Untreated Int-2 or High Risk MDS or CMML

Guillermo Montalban-Bravo[1], Prithviraj Bose[1], Yesid Alvarado[1], Naval Daver[1], Farhad Ravandi[1], Gautham Borthakur[1], Koichi Takahashi[1], Michael Andreeff[1], Jorge Cortes[1], Courtney DiNardo[1], Elias Jabbour[1], Tapan Kadia[1], Steven Kornblau[1], Maro Ohanian[1], Ana Alfonso[1], Xuelin Huang[2], Graciela M. Nogueras-Gonzalez[2], Kristy Bodden[1], Kristina Littles[1], Sherry Pierce[1], Carlos Bueso-Ramos[3] and Hagop Kantarjian[1] and Guillermo Garcia-Manero[1]

Departments of Leukemia[1], Biostatistics[2] and Hematopathology[3]
The University of Texas MD Anderson Cancer Center, Houston, TX

Garcia-Manero, ASH 2016 Abstract #346

SGI-110: Response

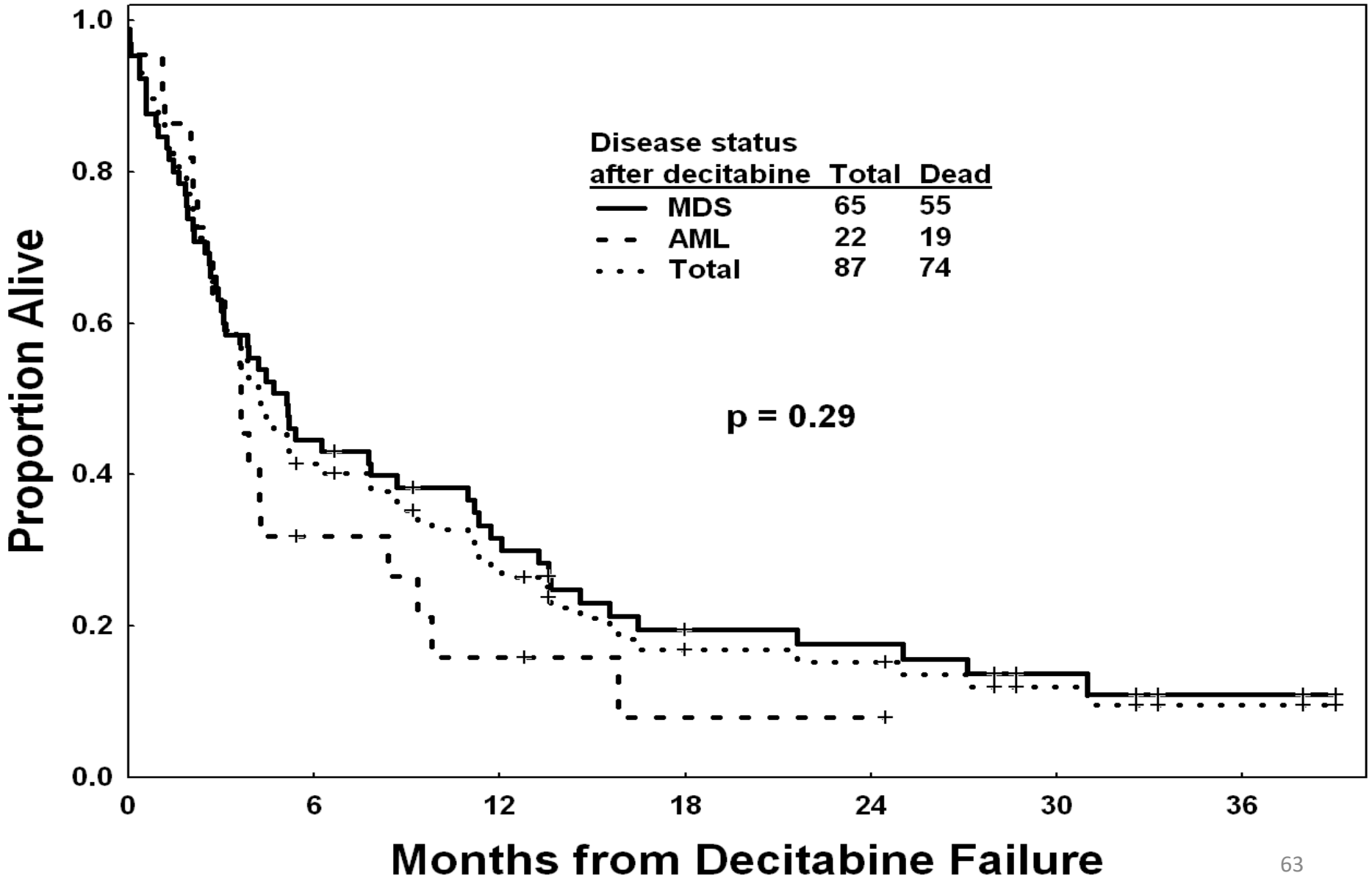
Response Category	Global (n=44) N (%)	MDS (n=38) N (%)	CMML (n=6) N (%)
ORR	31 (71)	26 (68)	5 (83)
CR	14 (32)	12 (32)	2 (33)
mCR	14 (32)	11 (29)	3 (50)
HI	3 (7)	3 (8)	0 (0)
CR+mCR	28 (64)	23 (61)	5 (83)
CCyR	7/33 (21)	7/28 (25)	0 (0)

- Median number of cycles: 6 (range 1-20)
- Median number of cycles to response: 3 (range 1-6)
- Median number of cycles to complete cytogenetic response: 4 (range 1-7)
- Median response duration: 4 cycles (0-14)
- Stopping rule for response not met

Higher risk MDS HMA failure

- Ph III Rigosertib
- PD1/PDL1 inhibition
- Ph II Omacetaxine (Short et al, Abs #2967)
  - ORR 34%
  - 7.6 month median survival
  - 22% 1-year OS
- Ph II CC-486
- Aza+ABT-199 failures
- SGI-110 failures

Targeting Hypomethylating Failure

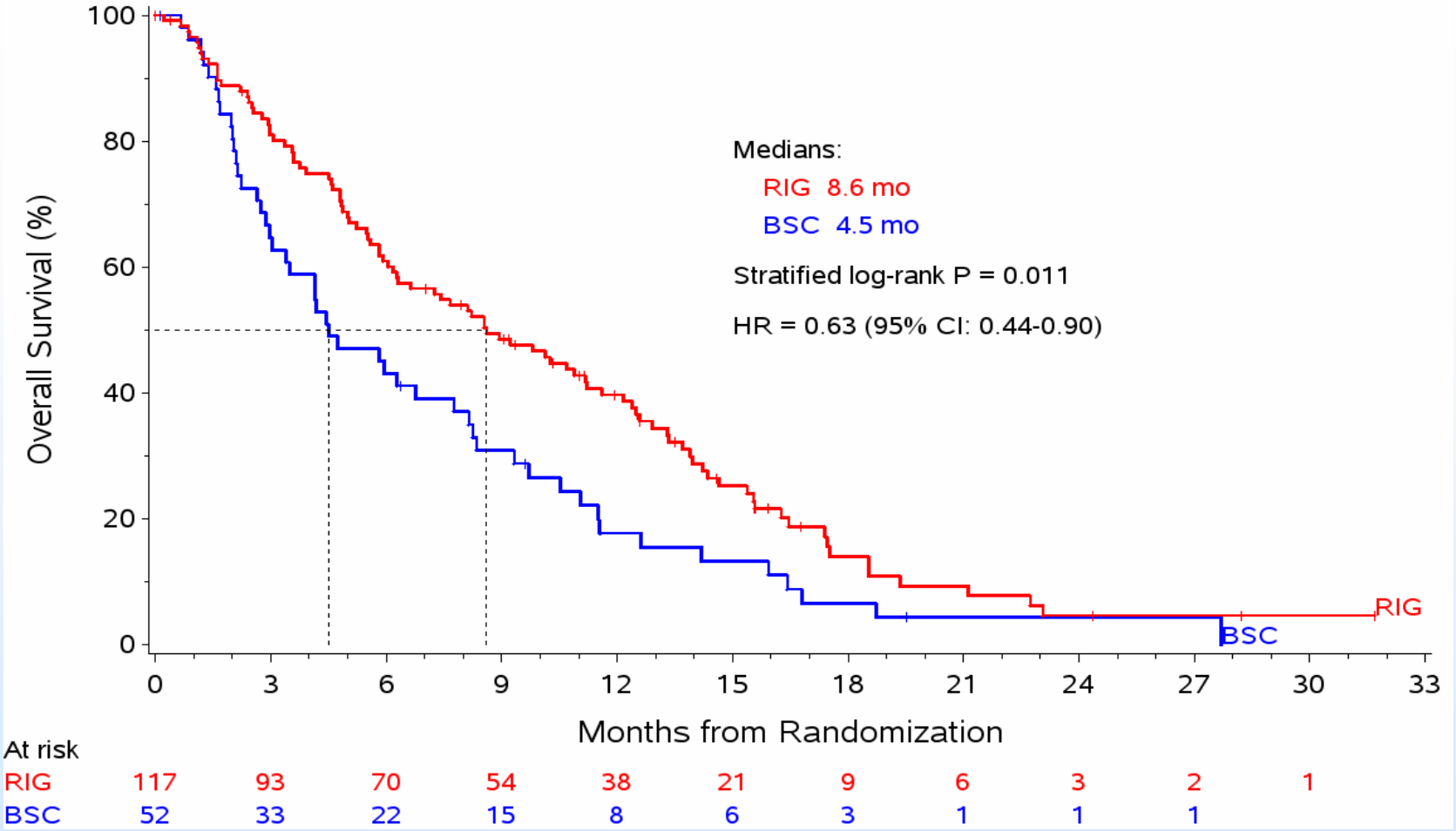


Overall Survival and Subgroup Analysis from a Randomized Phase III Study of Intravenous Rigosertib vs Best Supportive Care in Patients with Higher-risk Myelodysplastic Syndrome After Failure of Hypomethylating Agents (ONTIME Trial of ON 01910)

G. Garcia-Manero, P. Fenaux, A. Al-Kali, M. R. Baer, M. Sekeres, G. Roboz, G. Gaidano, B. Scott, P. Greenberg, U. Platzbecker, D. P. Steensma, S. Kambhampati, L. Godley, R. Collins, E. Atallah, F. Wilhelm, I. Darnis-Wilhelm, N. Azarnia, M. Maniar, L. R. Silverman, for the ONTIME Investigators

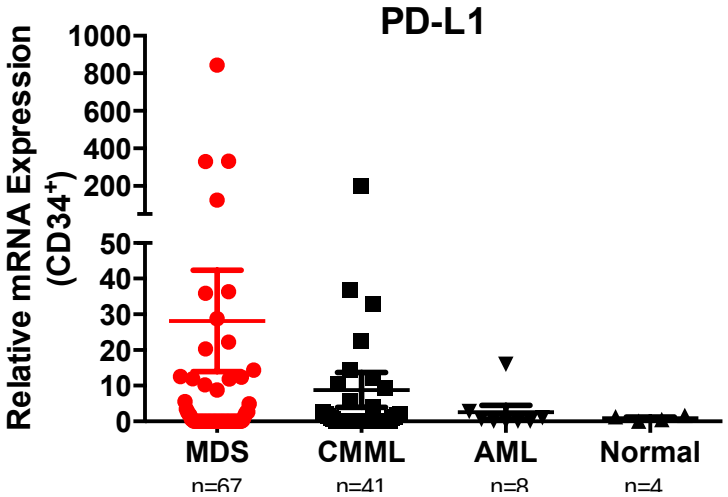
Garcia-Manero. Lancet Oncology 2016

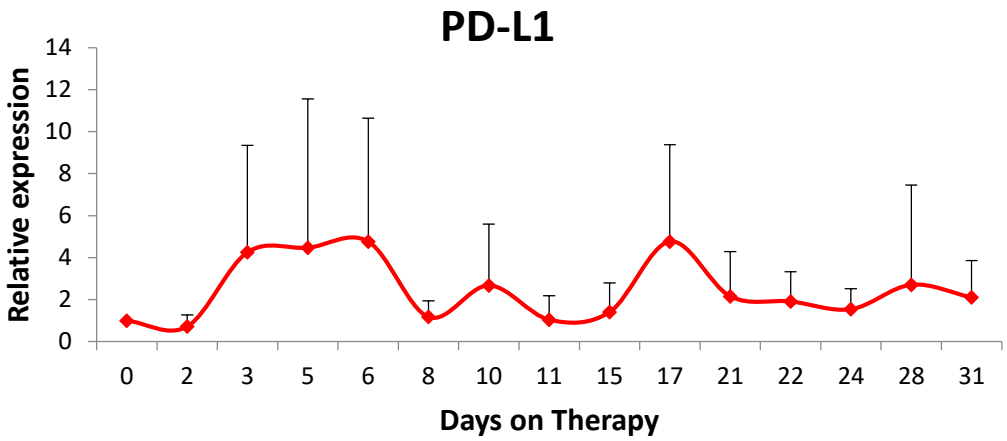
ONTIME Trial: Median Overall Survival for Pts with Primary HMA Failure - Blinded, Centralized Assessment

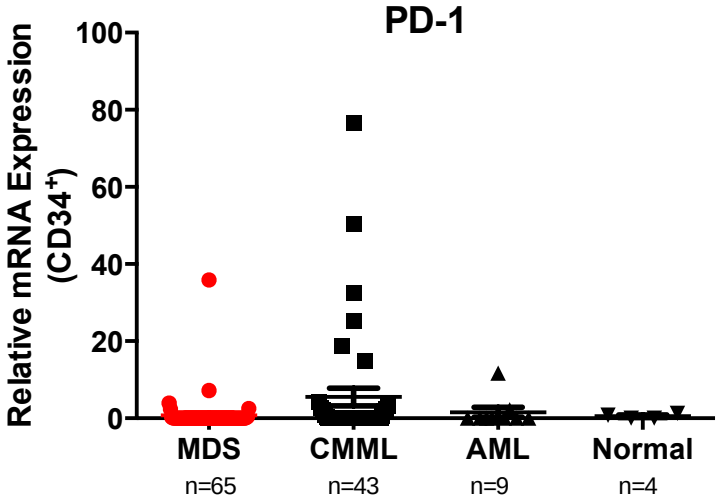


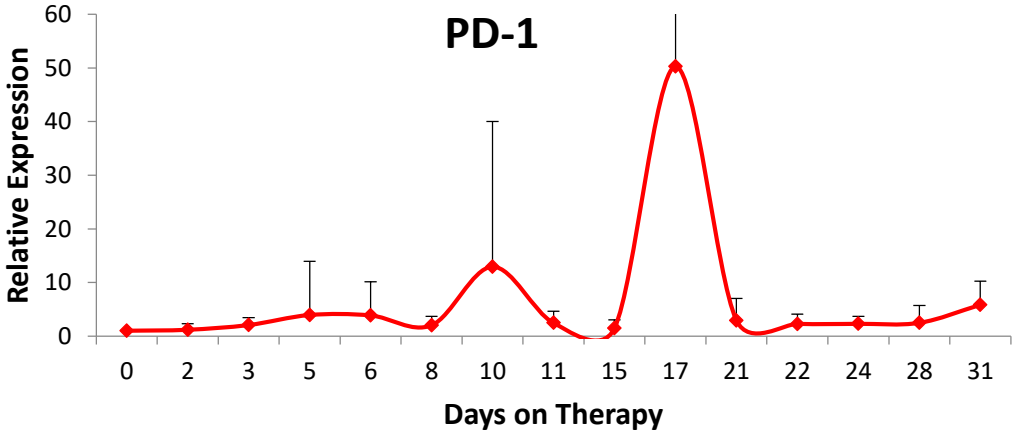
Per Prebet 2011, "Primary HMA Failure" was defined as either no response to or progression during HMA therapy

Sequential PD1/PDL1 activation post HMA



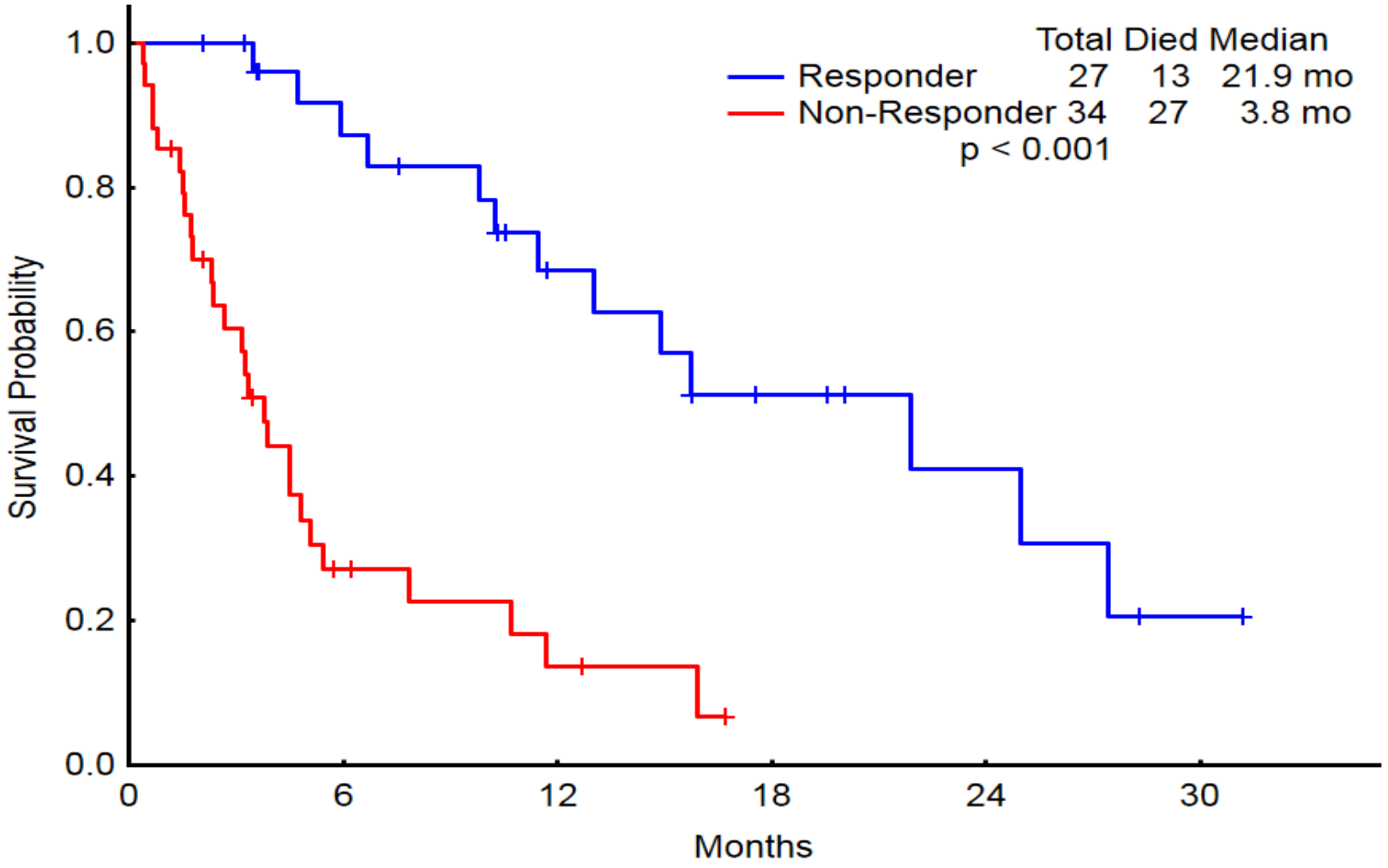






Yang et al, *Leukemia 2014*

CLO and LDAC in HR MDS post HMA. Survival by Response Status



Jabbour et al. Cancer 2017

Conclusion and needs

- Increased role of genomic annotation in MDS
- New targets: CD33, CD123, Bcl-2, TGF-b, TLR, SF3B1,IDH, Flt-3, NPM1
- Lower dose HMAs for lower risk MDS
- Potent oral forms of HMAs: CC-486, ASTX727
- Second generation HMAs: SGI-110
- Combinations: + PD1/PDL1 inhibitors
- 5 ongoing Phase III trials: CC-486, Rigosertib, ACE-536, SGI-110 for failures, ASTX7727
- Need: p53, RAS, transplant integration

Thank You