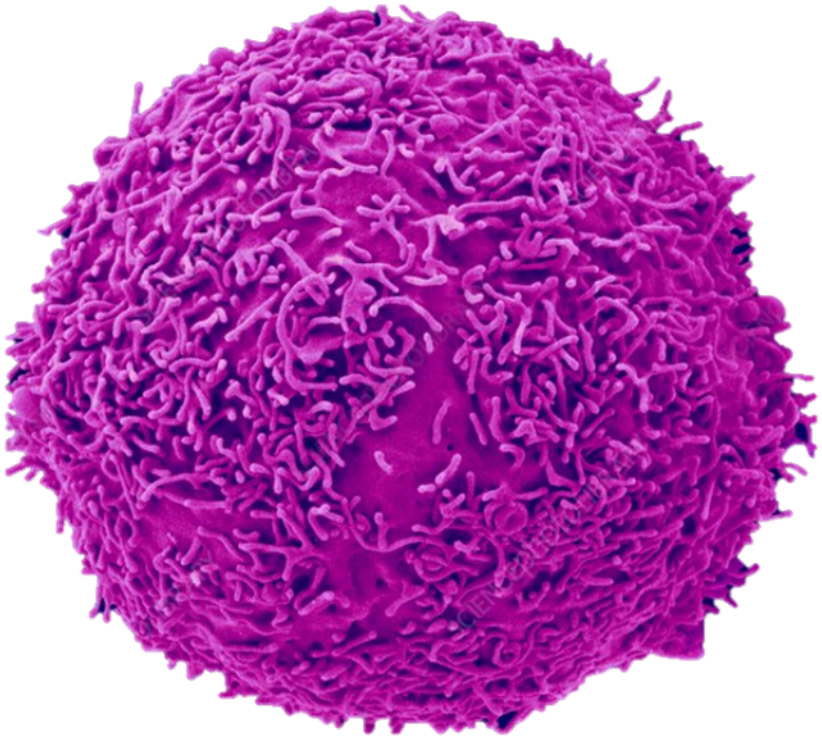
Acute lymphoblastic leukemia

Latest Advances



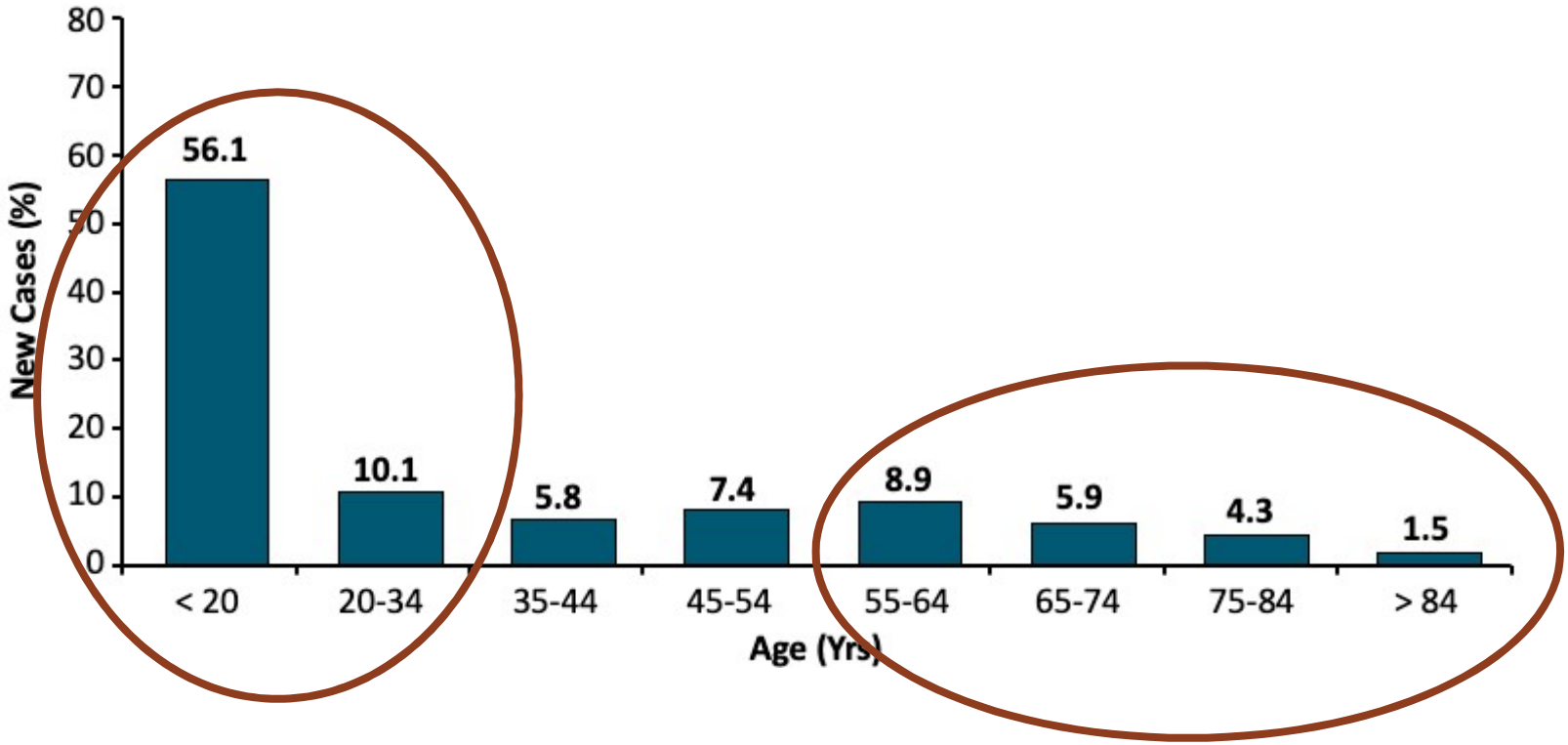
Gabriel N. Mannis, MD
Assistant Professor of Medicine
Division of Hematology
Stanford University

California Cancer Consortium Conference 2019

Stanford University

ALL ADVANCES

INCIDENCE OF ALL BY AGE



SEER Cancer Statistics Fact Sheet, 2011-2015.

ALL ADVANCES

OUTLINE

- UPDATES IN THE AYA POPULATION
- UPDATES IN THE ELDERLY POPULATION
- UPDATES IN PH+ AND PH- DISEASE
- UPDATES IN RELAPSED/REFRACTORY DISEASE

ALL ADVANCES

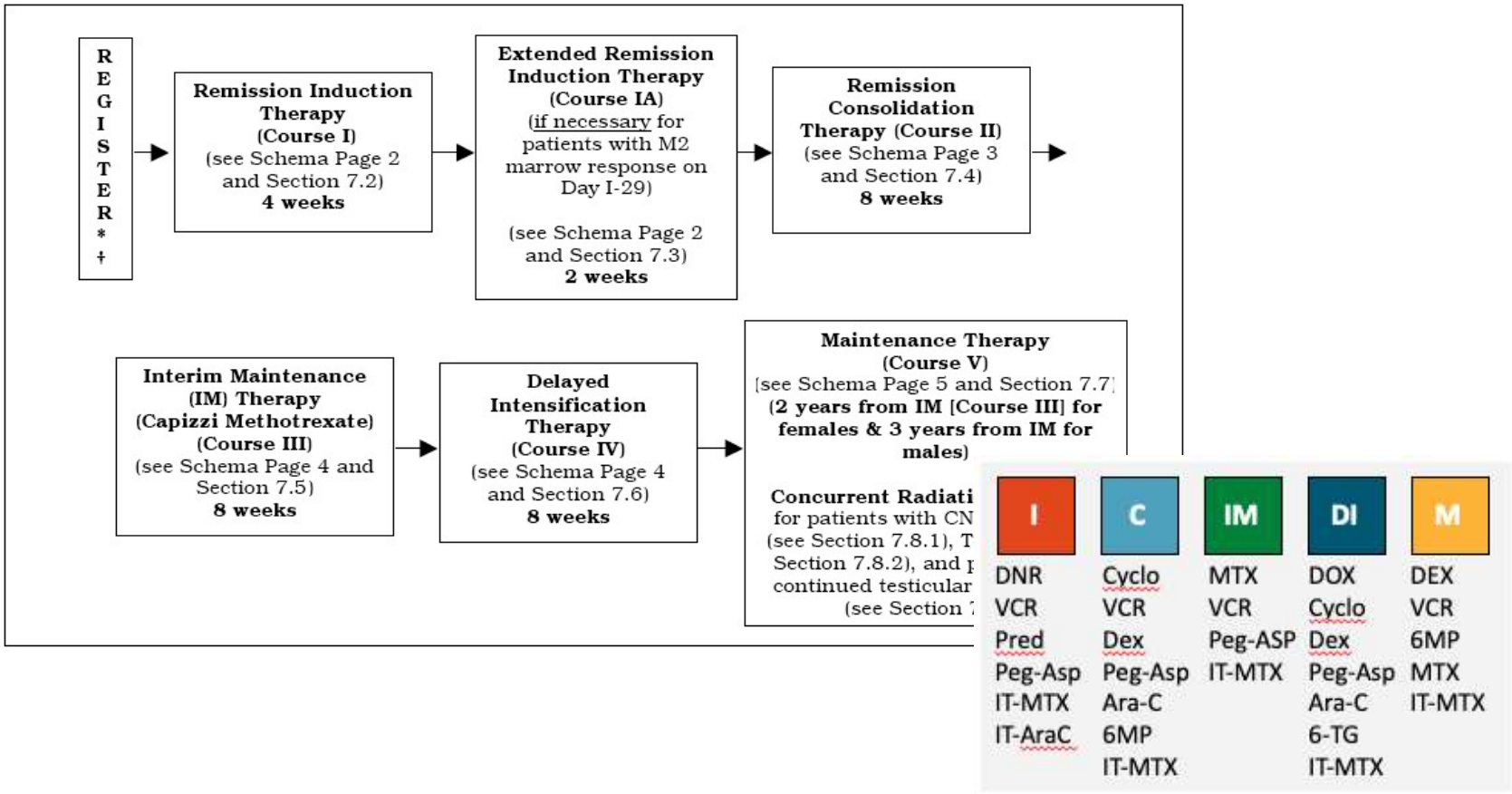
AYA PATIENTS

- KEY DIFFERENCES BETWEEN ADULT AND PEDIATRIC REGIMENS
  - Multiple cycles of non-cross-resistant agents
  - Less myelosuppression
  - Early and frequent CNS prophylaxis
  - Repeated doses of asparaginase
  - Higher cumulative doses of active agents
  - Prolonged maintenance

ALL ADVANCES

AYA PATIENTS

CALGB 10403

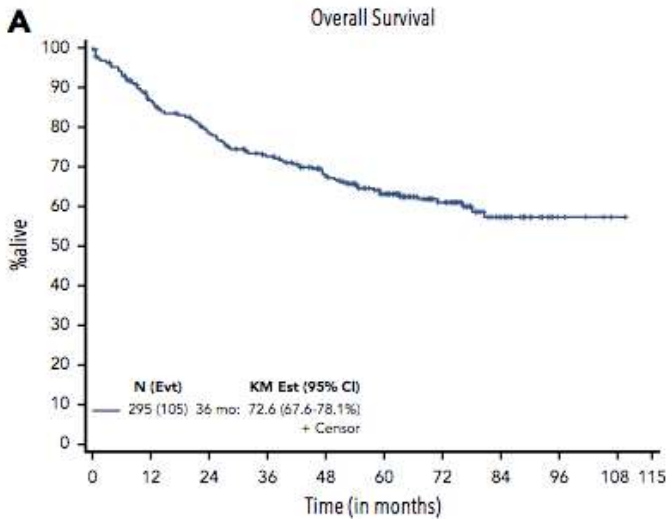


Stock et al, *Blood* 2019

ALL ADVANCES

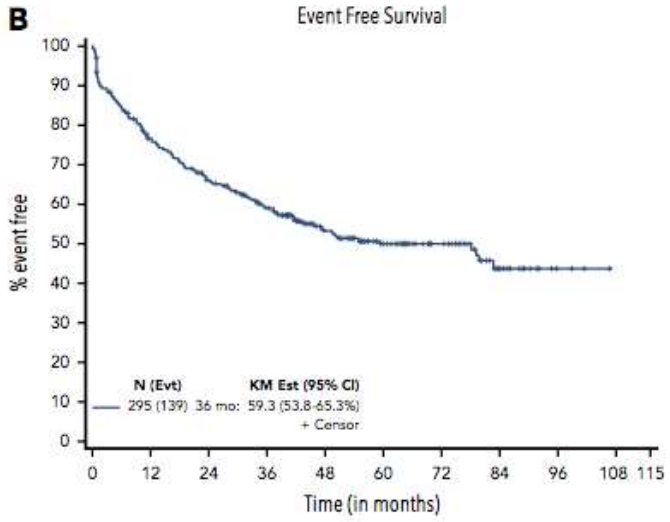
AYA PATIENTS

CALGB 10403 improved survival for AYA patients



3-year OS: 73%

(Historical Control: 58%)



3-year EFS: 59%

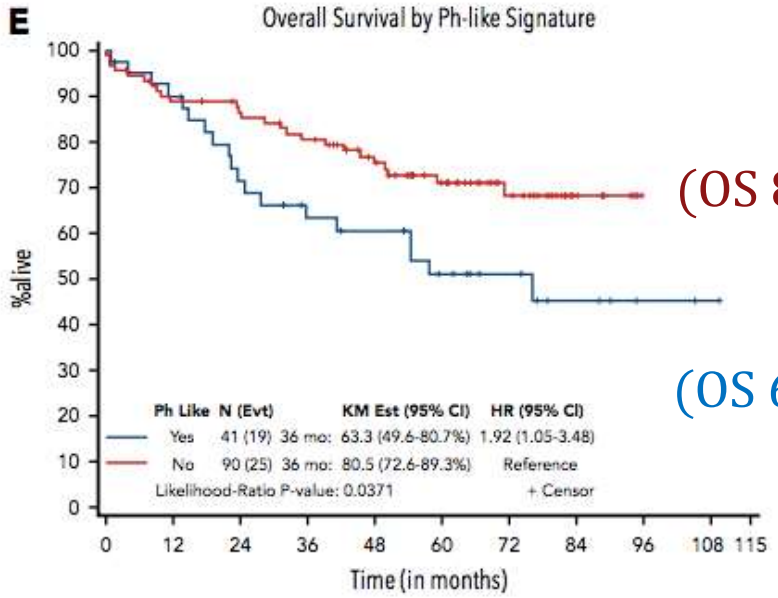
(Historical Control: 34%)

Stock et al, *Blood* 2019

ALL ADVANCES

AYA PATIENTS

- PREDICTORS OF POOR SURVIVAL IN CALGB 10403:
  - MRD positivity
  - Ph-like disease
  - Obesity



Not Ph-like
(OS 81% at 3 years)

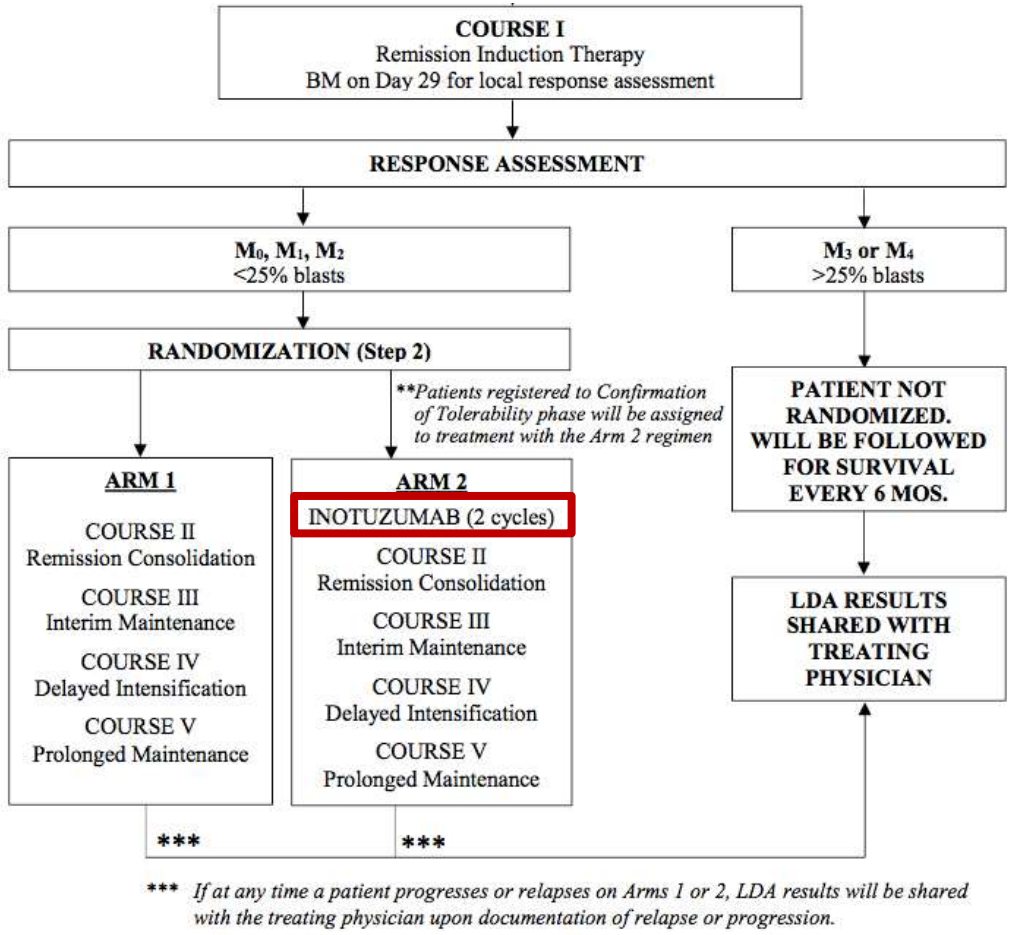
Ph-like
(OS 63% at 3 years)

Stock et al, *Blood* 2019

ALL ADVANCES

AYA PATIENTS

A041501: AYA PROTOCOL +/- INOTUZUMAB



ALL ADVANCES

AYA PATIENTS

- CURRENT/FUTURE DIRECTIONS
  - Focus on eradication of measurable residual disease (MRD)
  - Expanded uptake of testing for Ph-like gene signature and use in risk stratification
  - Novel therapeutic approaches aimed at treating recurrent gene fusions in Ph-like disease

ALL ADVANCES

ELDERLY PATIENTS

Chemoimmunotherapy with Inotuzumab Ozogamicin Combined with mini-hyper-CVD, with or without Blinatumomab, for Newly Diagnosed Older Patients with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: Results from a Phase II Study

NJ Short, E Jabbour, F Ravandi, X Huang, N Jain, K Sasaki, N Daver, N Pemmaraju, JD Khoury, J Jorgensen, Y Alvarado, M Konopleva, G Garcia-Manero, T Kadia, M Yilmaz, G Borthakur, J Burger, S Kornblau, W Wierda, C DiNardo, A Ferrajoli, J Jacob, R Garris, S O'Brien, H Kantarjian

Department of Leukemia
The University of Texas MD Anderson Cancer Center

ALL ADVANCES

ELDERLY PATIENTS

Mini-HCVD + INO ± Blina in Older ALL: Original Design

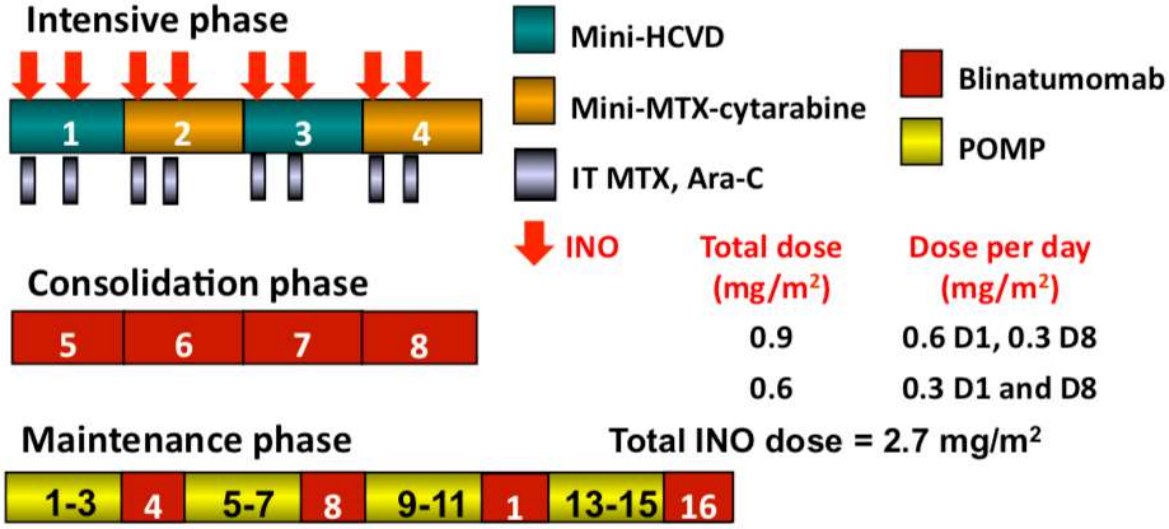
- **Dose-reduced, modified hyper-CVAD x 8 courses**
  - **Cyclophosphamide (150 mg/m^2 x 6) 50% dose reduction**
  - **Dexamethasone (20 mg) 50% dose reduction**
  - **No anthracycline**
  - **Methotrexate (250 mg/m^2) 75% dose reduction**
  - **Cytarabine (0.5 g/m^2 x 4) 83% dose reduction**
- **INO on day 3 (first 4 courses)**
- **Rituximab days 2 and 8 (first 4 courses) if CD20+**
- **IT chemotherapy days 2 and 8 (first 4 courses)**
- **POMP maintenance x 3 years**

Short et al, ASH 2018, #36

ALL ADVANCES

ELDERLY PATIENTS

Mini-HCVD + INO ± Blinatumomab in older ALL:
Modified Design



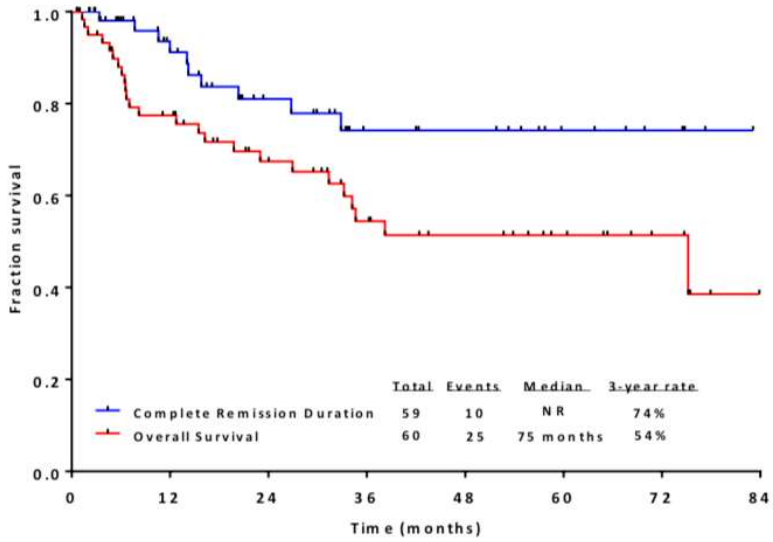
- From pt # 50 and onwards:
  - Blinatumomab 4C at consolidation; 4C at maintenance
  - Total INO dose: 2.7 mg/m² for 4 courses

Short et al, ASH 2018, #36

ALL ADVANCES

ELDERLY PATIENTS

Mini-HCVD + INO± Blina in Older ALL: CRD and OS (Entire Cohort)



n=60

Median Age: 68 (Range 60-81)

Median CR duration: NR (74% at 3 years)

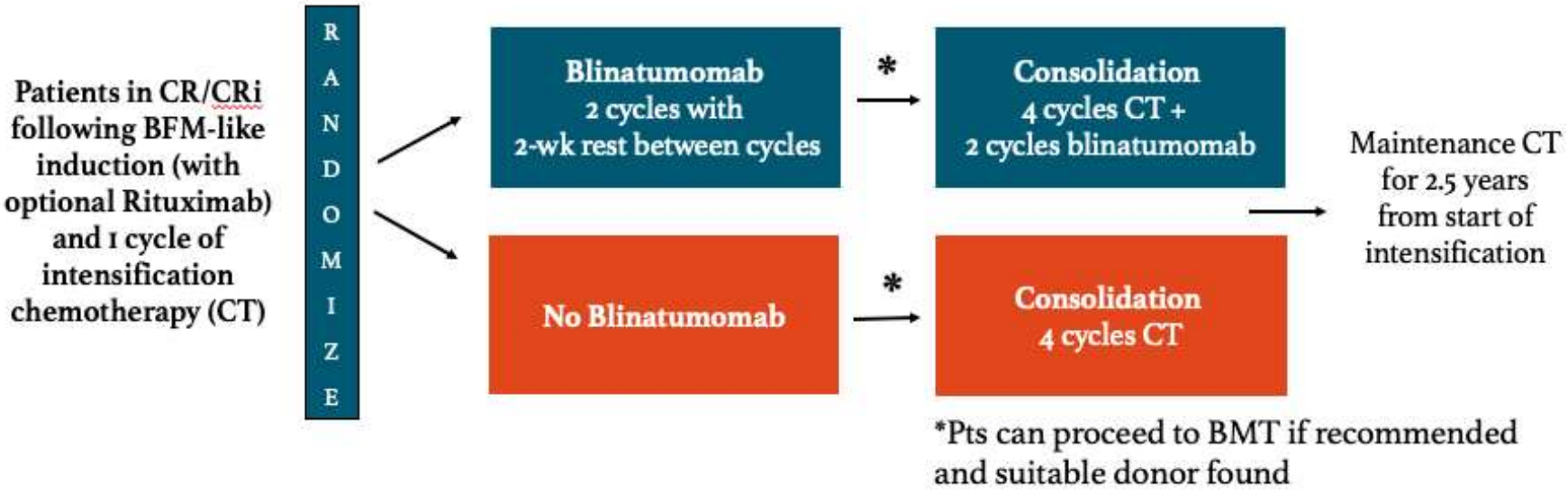
Median OS: 75 months (54% at 3 years)

Short et al, ASH 2018, #36

ALL ADVANCES

PH-NEGATIVE, NEWLY DIAGNOSED

- **E1910: SOC CHEMO +/- BLINATUMOMAB**
  - Phase III RCT
  - Ages 30-70



ALL Advances

Ph-positive, newly diagnosed

A Phase II Study of Dasatinib and Dexamethasone as Primary Therapy Followed by Transplantation for Adults with Newly Diagnosed Ph/*BCR-ABL1*-positive Acute Lymphoblastic Leukemia (Ph+ ALL): Final Results of Alliance/CALGB Study 10701

Matthew J. Wieduwilt, Jun Yin, Meir Wetzler, Geoff Uy, Bayard L. Powell, Jonathan Kolitz, Michaela Liedtke, Wendy Stock, Jan H. Beumer, Ryan J. Mattison, Elizabeth Storrick, Steven Devine, Scott Smith, Richard M. Stone, and Richard A. Larson

Abstract Number: 309

ALL ADVANCES

PH-POSITIVE, NEWLY DIAGNOSED

- **RESPONSE-ADAPTED INTENSIFICATION**
  - Dasatanib + dexamethasone days 1-14
  - If no response by day 15, add vincristine/daunorubicin
  - If no CR/CRi by day 22, add cyclophosphamide and give additional daunorubicin/vincristine
  - Proceed to alloHCT, autoHCT, or dose-intensified chemotherapy

Wieduwilt et al, ASH 2018, #309

ALL ADVANCES

PH-POSITIVE, NEWLY DIAGNOSED

Best hematologic response (N=65)	N	(%)
CR	62	**(95.5)**
CRi	1	(1.5)
CR/CRi*	63	**(97)**
Refractory**	2	(3)
Molecular response end IV (N=40)		
CMR (Undetectable)	17	**(43)**
MMR (Ratio <0.001)	10	(25)
<MMR (Ratio ≥0.001)	13	(32)
Best molecular response (N=52)		
CMR	39	**(75)**
MMR	8	(15)
<MMR	5	(10)

Median Age: 60

Median DFS: 29.7 months

Median OS: Not reached (55% at 3 years)

Wieduwilt et al, ASH 2018, #309

ALL ADVANCES

RELAPSED/REFRACTORY

End of Phase 1 Results of ZUMA-3, a Phase 1/2 Study of KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

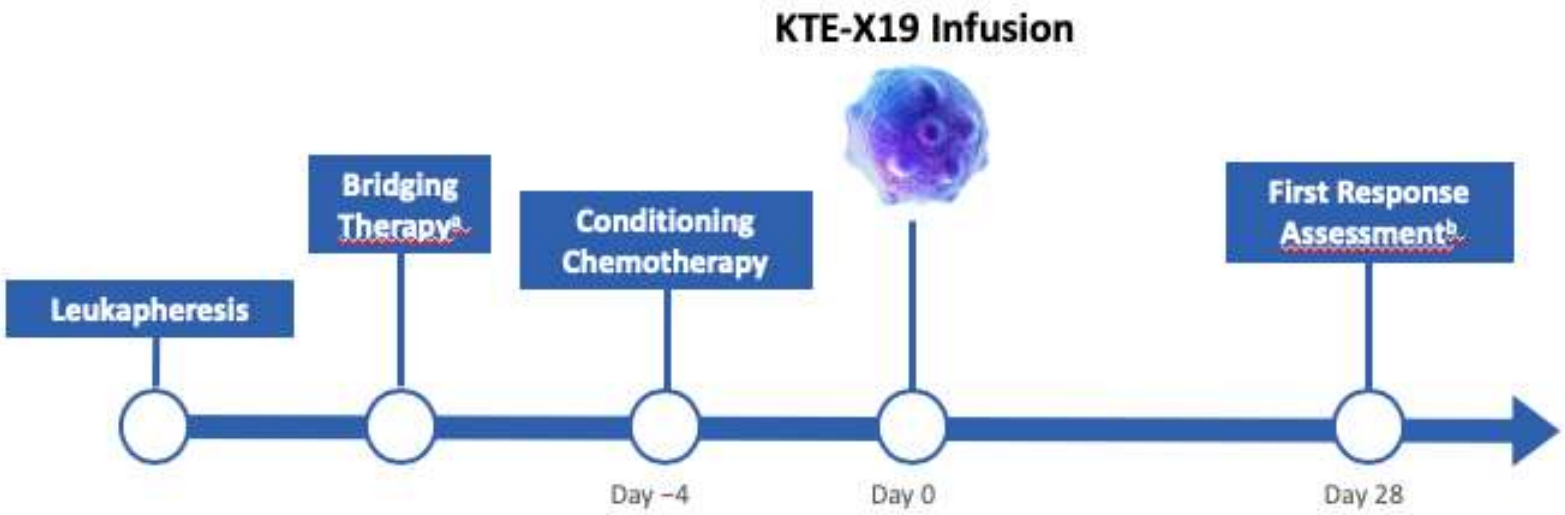
Bijal D. Shah, MD[1]; Michael R. Bishop, MD[2]; Olalekan O. Oluwole, MBBS, MPH[3]; Aaron C. Logan, MD, PhD[4]; Maria R. Baer, MD[5]; William B. Donnellan, MD[6]; Kristen M. O'Dwyer, MD[7]; Houston Holmes, MD, FACP[8]; Martha L. Arellano, MD[9]; Armin Ghobadi, MD[10]; John M. Pagel, MD, PhD[11]; Yi Lin, MD, PhD[12]; Ryan D. Cassaday, MD[13]; Jae H. Park, MD[14]; Armen Mardiros, PhD[15]; Tong Shen, PhD[15]; Lovely Goyal[15]; Remus Vezan, MD, PhD[15]; Rajul K. Jain, MD[15]; and William G. Wierda, MD, PhD[16]

[1]Moffitt Cancer Center, Tampa, FL; [2]The University of Chicago Medicine, Chicago, IL; [3]Vanderbilt-Ingram Cancer Center, Nashville, TN; [4]Helen Diller Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [5]University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD; [6]Sarah Cannon Research Institute, Nashville, TN; [7]University of Rochester, Rochester, NY; [8]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; [9]Winship Cancer Institute of Emory University, Atlanta, GA; [10]Washington University School of Medicine and Siteman Cancer Center, St. Louis, MO; [11]Swedish Cancer Institute, Seattle, WA; [12]Mayo Clinic, Rochester, MN; [13]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; [14]Memorial Sloan Kettering Cancer Center, New York, NY; [15]Kite, a Gilead Company, Santa Monica, CA; [16]The University of Texas MD Anderson Cancer Center, Houston, TX

Shah et al, ASCO 2019, #7006

ALL ADVANCES

RELAPSED/REFRACTORY



Shah et al, ASCO 2019, #7006

ALL ADVANCES

RELAPSED/REFRACTORY

Characteristics	Overall (N = 45)
Age, median (range), y	46 (18 – 77)
Male, n (%)	22 (49)
ECOG, n (%)	
0	15 (33)
1	29 (64)
Philadelphia chromosome-positive	7 (16)
Prior regimens, n (%)	
1	6 (13)
2	9 (20)
≥ 3	30 (67)
Prior blinatumomab, n (%)	19 (42)
Prior inotuzumab ozogamicin, n (%)	6 (13)
Refractory, n (%)	
Primary refractory	16 (36)
First relapse with remission ≤ 12 months	2 (4)
R/R post-alloSCT	13 (29)
BM blasts at screening, median (range), %	61 (5 – 100)
BM blasts preconditioning after bridging, median (range), %	70 (0 – 97)

Shah et al, ASCO 2019, #7006

ALL ADVANCES

RELAPSED/REFRACTORY

Event, %	2×10^6 (n = 6) Any	2×10^6 (n = 6) Grade ≥ 3	1×10^6 (n = 23) Any	1×10^6 (n = 23) Grade ≥ 3	0.5×10^6 (n = 16) Any	0.5×10^6 (n = 16) Grade ≥ 3	Overall (N = 45) Any	Overall (N = 45) Grade ≥ 3
Any CRS[a,b]	**100**	**50**	**100**	**26**	**81**	**25**	**93**	**29**
Pyrexia	100	50	87	39	63	31	80	38
Hypotension	67	50	74	39	50	19	64	33
Sinus tachycardia	33	0	43	4	13	0	31	2
Chills	17	0	39	0	13	0	27	0
Any NE[b]	**83**	**50**	**87**	**43**	**63**	**25**	**78**	**38**
Encephalopathy	67	33	48	26	13	13	38	22
Confusional state	33	17	39	4	31	13	36	9
Tremor	17	0	35	0	25	0	29	0

Two Grade 5 AEs

- Multi-organ failure on day 6 due to CRS
- Stroke on day 7 in context of CRS
- No cerebral edema

Shah et al, ASCO 2019, #7006

ALL ADVANCES

RELAPSED/REFRACTORY

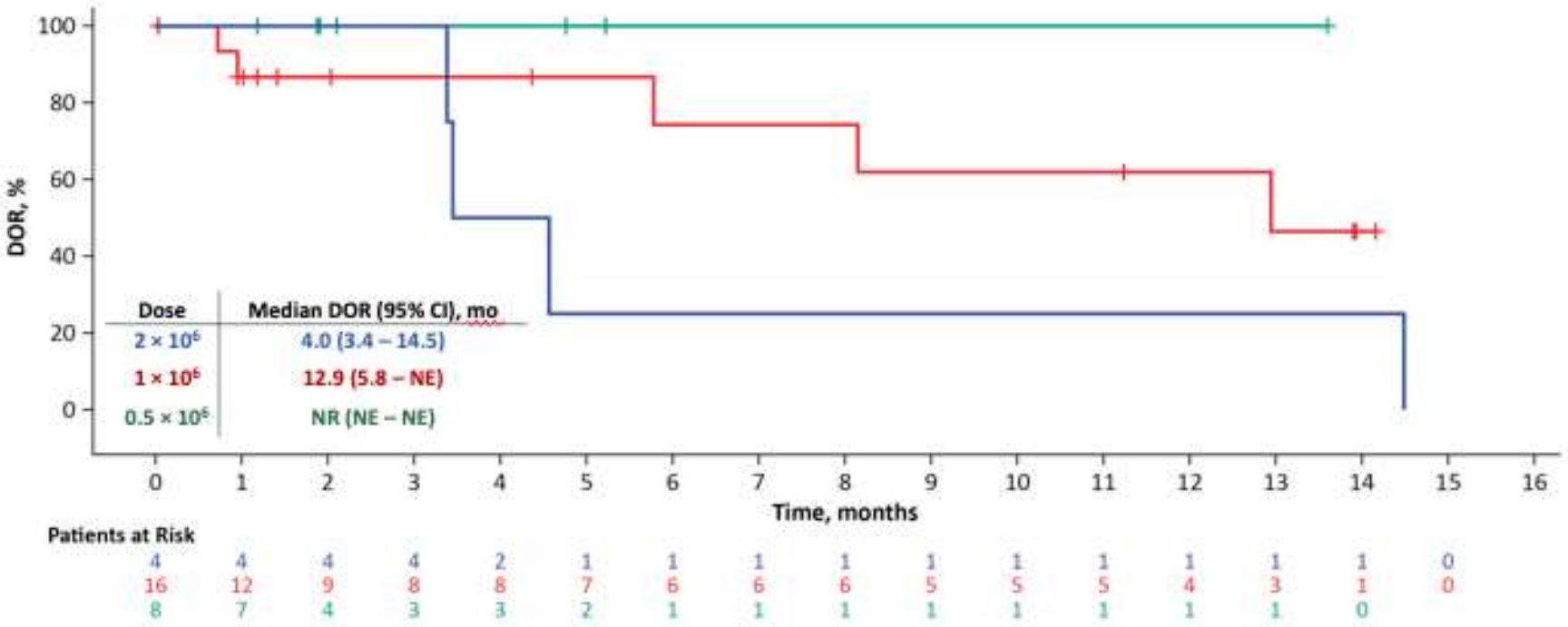
Outcome	2×10^6 Dose (n = 6)	1×10^6 Dose (n = 19)	0.5×10^6 Dose (n = 16)	Overall (n = 41)
CR Rate (CR + CRi), n (%)	4 (67)	16 (84)	8 (50)	28 (68)
CR	3 (50)	13 (68)	6 (38)	22 (54)
CRi	1 (17)	3 (16)	2 (13)	6 (15)
Blast-free hypoplastic/aplastic BM, n (%)	0	1 (5)	1 (6)	2 (5)
PR, n (%)	0	1 (5)	0	1 (2)
PD, n (%)	0	1 (5)	6 (38)	7 (17)

- 100% MRD negativity among evaluable patients with any remission
- Overall response rate consistent across key co-variates (eg. primary refractory, prior HCT)

Shah et al, ASCO 2019, #7006

ALL ADVANCES

RELAPSED/REFRACTORY



- Of 16 patients achieving CR in the 1 x 10^6 cohort, 12 (75%) are ongoing
- Median DOR 12.9 months at RP2D (1 x 10^6/kg)

Shah et al, ASCO 2019, #7006

ALL ADVANCES

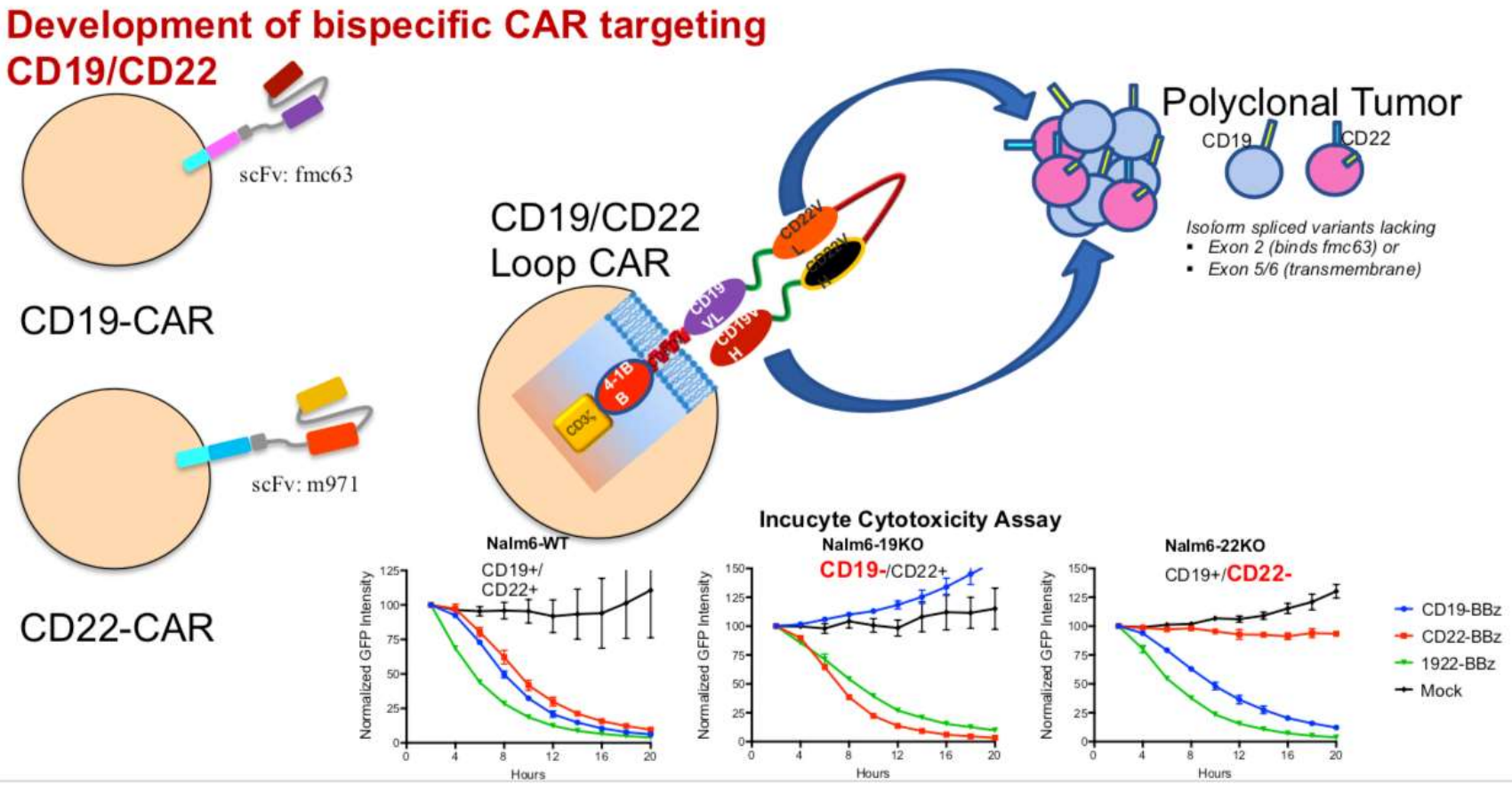
RELAPSED/REFRACTORY

Bispecific CD19/CD22 CAR T cells for the Treatment of Pediatric Relapsed or Refractory ALL

Liora Schultz, MD, *Kara Davis, MD, Christina Baggott, RN, PhD, Christie Chaudry, RN, Anne Marcy, RN, Sharon Mavroukakis, Bita Sahaf, Katie Kong, Lori Muffly MD, Stephen Kim, Steven Feldman, Everett H Meyer, MD, PhD, Terry Fry, MD, Nirali Shah, MD, Haiying Qin, PhD, David Miklos, MD, PhD, Crystal Mackall, MD*

ALL ADVANCES

RELAPSED/REFRACTORY



Schultz et al, ASH 2018

ALL ADVANCES

RELAPSED/REFRACTORY

Patient ID	CAR Indication	Disease Status at Infusion	CNS Status at Infusion	Day 28 Morphologic Response	Day 28 MRD Response	Disposition
001	Isolated BM relapse	Flow MRD+ NGS MRD+	CNS1	CR	Flow- NGS-	HCT in CR Alive/MRD-, 1 year post-CAR
002	CNS/BM Relapse	Flow MRD- NGS MRD+	CNS1	CR	Flow- NGS-	HCT in CR Alive/MRD-, 10 mo post-CAR
003	Primary Refractory	Flow MRD+ NGS MRD N/A	CNS1	CR	Flow- NGS N/A	HCT in CR Alive/MRD-, 9 mo post-CAR
004	Isolated BM relapse	Gross Disease (12% Blasts)	CNS1	CR	Flow+ (0.2%) NGS+	HCT with NGS+ disease Alive, 5 mo post-CAR

- **4/4 Patients achieved morphologic complete remissions**
- **3/4 Patients achieved MRD$^-$ CR**

Schultz et al, ASH 2018

ALL ADVANCES

RELAPSED/REFRACTORY

Blinatumomab in Combination with Immune Checkpoint Inhibitors in Relapsed/Refractory CD19+ Leukemias: A Phase I Study

Jonathan Webster[1], Marlise R. Luskin[2], Gabrielle Prince[1], Amy Dezern[1], Daniel J. DeAngelo[2], Mark Levis[1], Amanda Blackford[3], Elad Sharon[4], Howard Streicher[4], Leo Luznik[1], Ivana Gojo[1]

ALL ADVANCES

RELAPSED/REFRACTORY

- **CAUSES OF BLINATUMOMAB FAILURE**
  - Loss of CD19 expression
  - Extramedullary sites inaccessible to blinatumomab
  - Immune dysregulation: Increased checkpoint expression

Dose Level	Dose		
	Blinatumomab[1]	**Nivolumab[2]**	**Ipilimumab[2]**
A1 (-)	9 µg/day IV on D1-7 28 µg/day IV on D8-28	80 mg IV q 2wks	(none)
A1	(same)	240 mg IV q 2wks	(none)
B1 (-)	(same)	80 mg IV q 2wks	1 mg/kg IV q6wks
B1	(same)	240 mg IV q 2wks	1 mg/kg IV q6wks

[1] After cycle 1, blinatumomab is given at 28 µg/day IV on D1-28 of a 42-day cycle
[2] Drug to start day #11 following blinatumomab

Webster et al, ASH 2018

ALL ADVANCES

RELAPSED/REFRACTORY

Pt #	Age	Sex	ECOG PS	Diagnosis	Baseline BM Blast %	Cytogenetics	Disease Status	Prior Rxs	Prior Blina	Prior HSCT
1	31	M	1	Pre-B ALL	90	Hyperdiploid	Relapsed	2	Yes	No
2	54	F	0	Pre-B ALL	45	48, XX, t(6;21), +10, +21	Primary Refractory	1	No	No
3	75	M	2	Pre-B ALL	10	46, XY	Primary Refractory	1	No	No
4	25	F	0	Pre-B ALL	82	47, XX, +4	Relapsed	1	No	No
5	58	F	2	Pre-B ALL	98	46, XX	Relapsed	2	Yes	Yes (+DLI)
6	67	M	2	Pre-B ALL	64	Complex, t(9;22)	Relapsed	3	No	Yes (+DLI)
7	33	F	2	Pre-B ALL	90	46, XX, t(9;22)	Relapsed	3	Yes	Yes x 2
8	56	M	1	Pre-B ALL	10	46, XY, t(9;22)	Relapsed	2	No	Yes

Webster et al, ASH 2018

ALL ADVANCES

RELAPSED/REFRACTORY

	Received Nivolumab (N=6)
Response	
Achieved CR, n (%)	5 (83.3%)
MRD Negative, n (%)	5 (83.3%)
Disposition	
Ongoing Treatment, n (%)	3 (50%)
Discontinued Treatment, n (%)	3 (50%)
Progressive Disease, n (%)	1 (16.7%)
Adverse Event, n (%)	0 (0%)
Bone Marrow Transplant, n (%)	2 (33.3%)
Rx duration in mos, median (range)	3.6 (1.4-11)

Webster et al, ASH 2018

ALL Advances

Summary

- Newer antibodies (blinatumomab, inotuzumab) are increasingly being incorporated into earlier lines of therapy
- For older/less fit patients, combining these antibodies with less intensive chemotherapy appears safe and effective
- For Ph+ patients, it may be possible to risk-adapt therapy with the use of up-front second/third generation tyrosine kinase inhibitors
- Novel cellular therapies and combination immunotherapies continue to advance

ALL ADVANCES

THANKS!