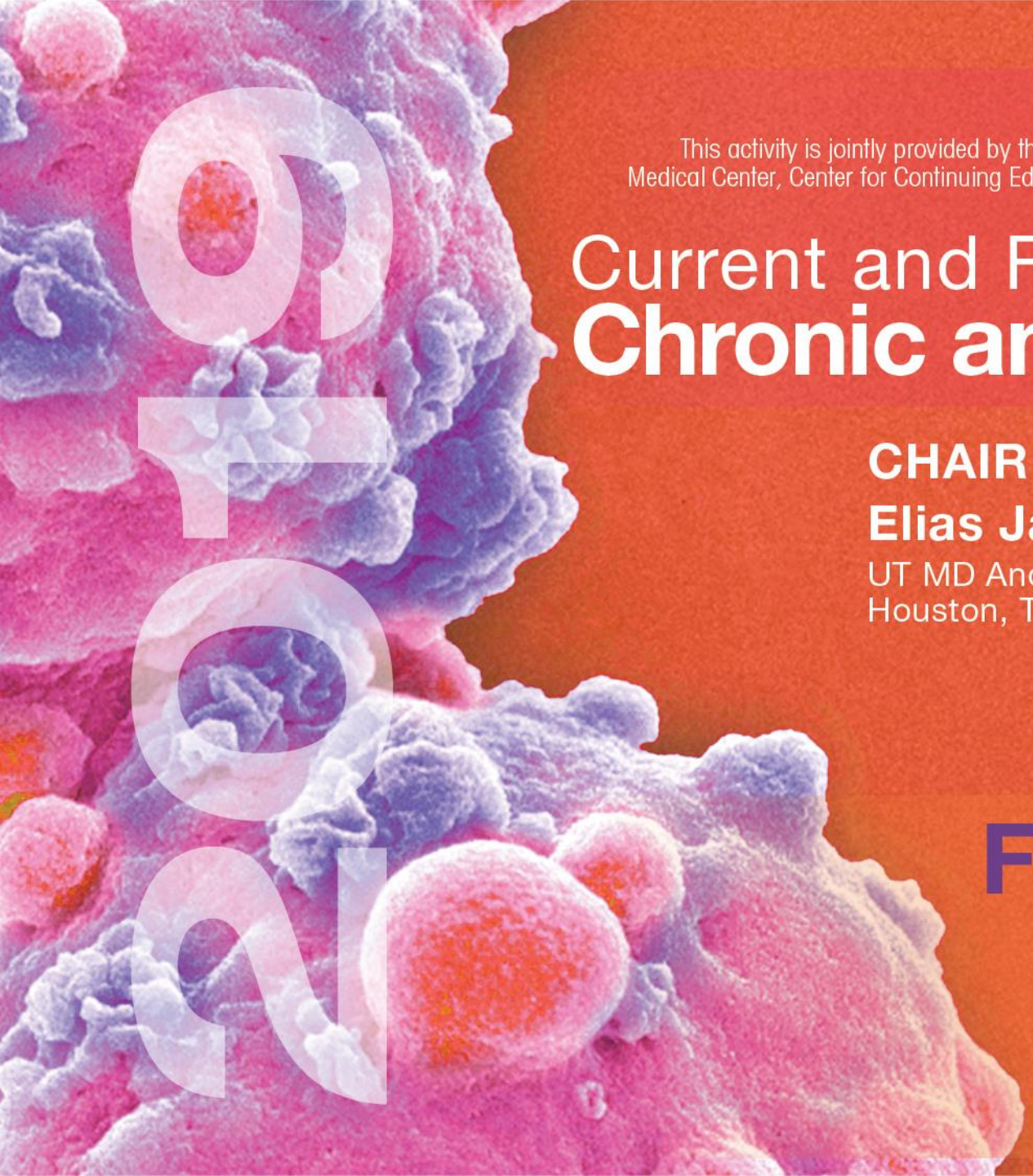

This activity is jointly provided by the University of Nebraska Medical Center, Center for Continuing Education and Bio Ascend.

UNIVERSITY OF NEBRASKA MEDICAL CENTER
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Bio Ascend

Current and Future Directions in **Chronic and Acute Leukemias**

CHAIR

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FACULTY

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Irvine, California

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UT MD Anderson Cancer Center
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Friday, September 13
6:00 AM – 7:45 AM

This activity is supported by an independent educational grant from Pfizer Inc.

Relapsed ALL

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Disclosure Information

Susan O'Brien, MD

I have the following financial relationships to disclose

Sponsor/Company	Affiliation(s)
Amgen	Consultant
Astellas	Consultant
Celgene	Consultant
GlaxoSmithKline	Consultant
Janssen Oncology	Consultant
Aptose Biosciences Inc.	Consultant
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Pharmacyclics	Consultant/Research Support
TG Therapeutics	Consultant/Research Support
Pfizer	Consultant/Research Support
Sunesis	Consultant/Research Support

ALL Salvage Standards of Care in 2019

- Pre-B ALL
  - Blinatumomab (FDA approval 12/2014)
  - Inotuzumab (FDA approval 8/2017)
  - 2 CAR T-cell therapies (FDA approvals 8/2017 and 10/2017); neither approved for adult ALL
- T ALL: nelarabine
- Ph-positive ALL — TKIs + chemoRx; blinatumomab
- Refer for investigational therapies — mAb + ChemoRx; CAR T-cell therapy
- ChemoRx: FLAG IDA, HIDAC, hyper-CVAD, augmented HCVAD, and MOAD

Historical Results in R/R ALL

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

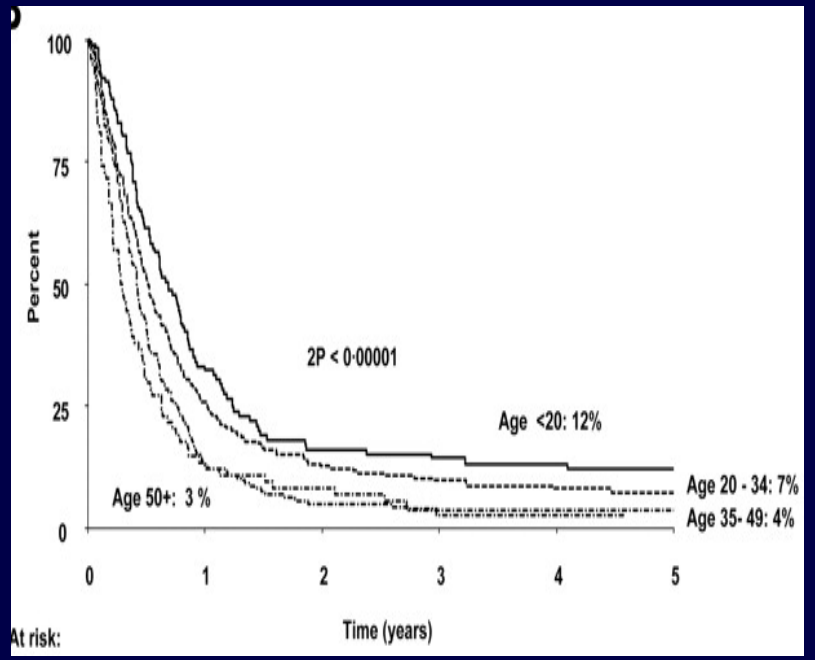
	No Prior Salvage (S1)	1 Prior Salvage (S2)	≥2 Prior Salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

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

ALL — Historical Survival Rates After 1st Relapse

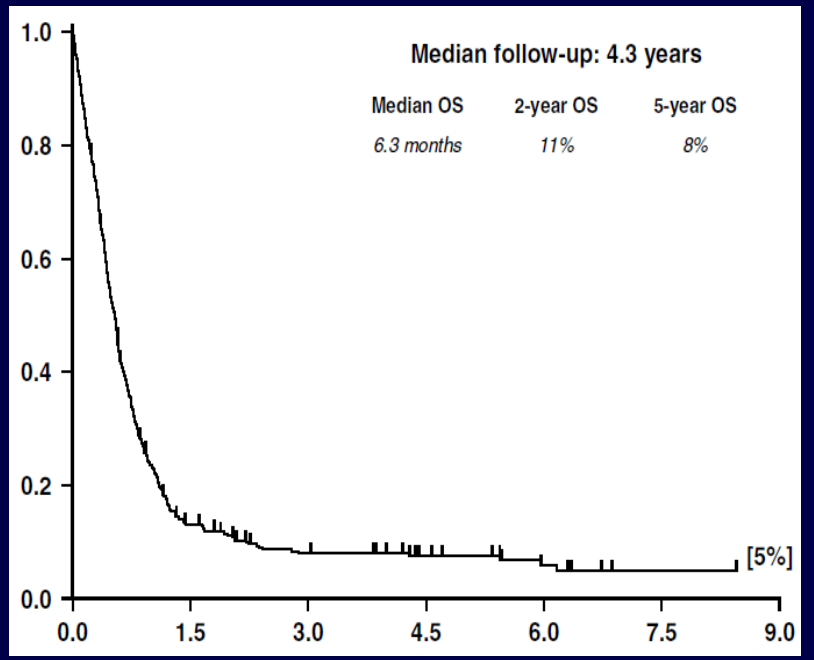
MRC UKALL2/ ECOG2993 Study (n=609)

Outcome of patients after 1st relapse
5-yr OS: 7%



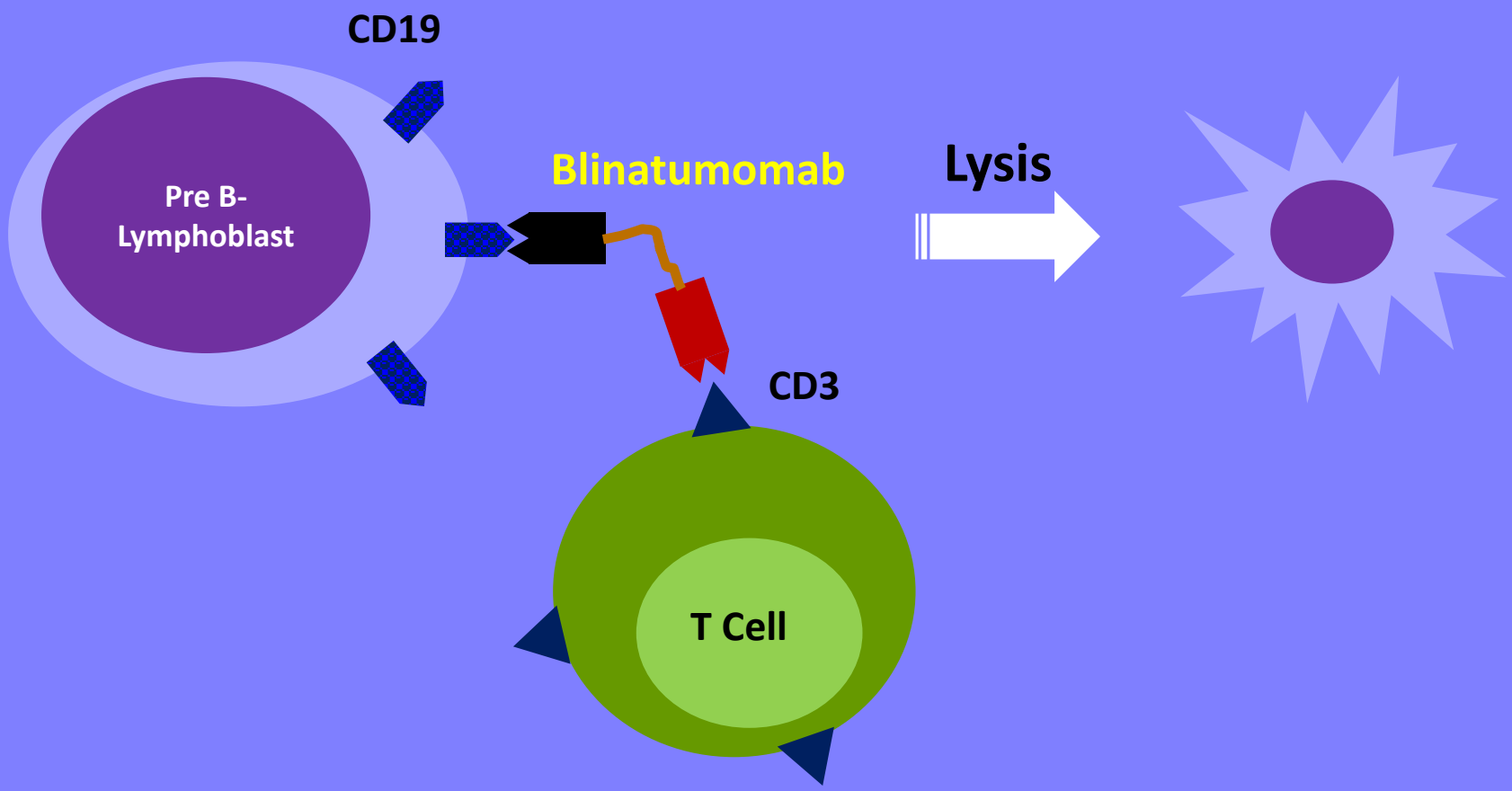
LALA-94 Study (n=421)

Outcome of patients after 1st relapse
2-yr OS: 11% & 5-yr OS: 8%

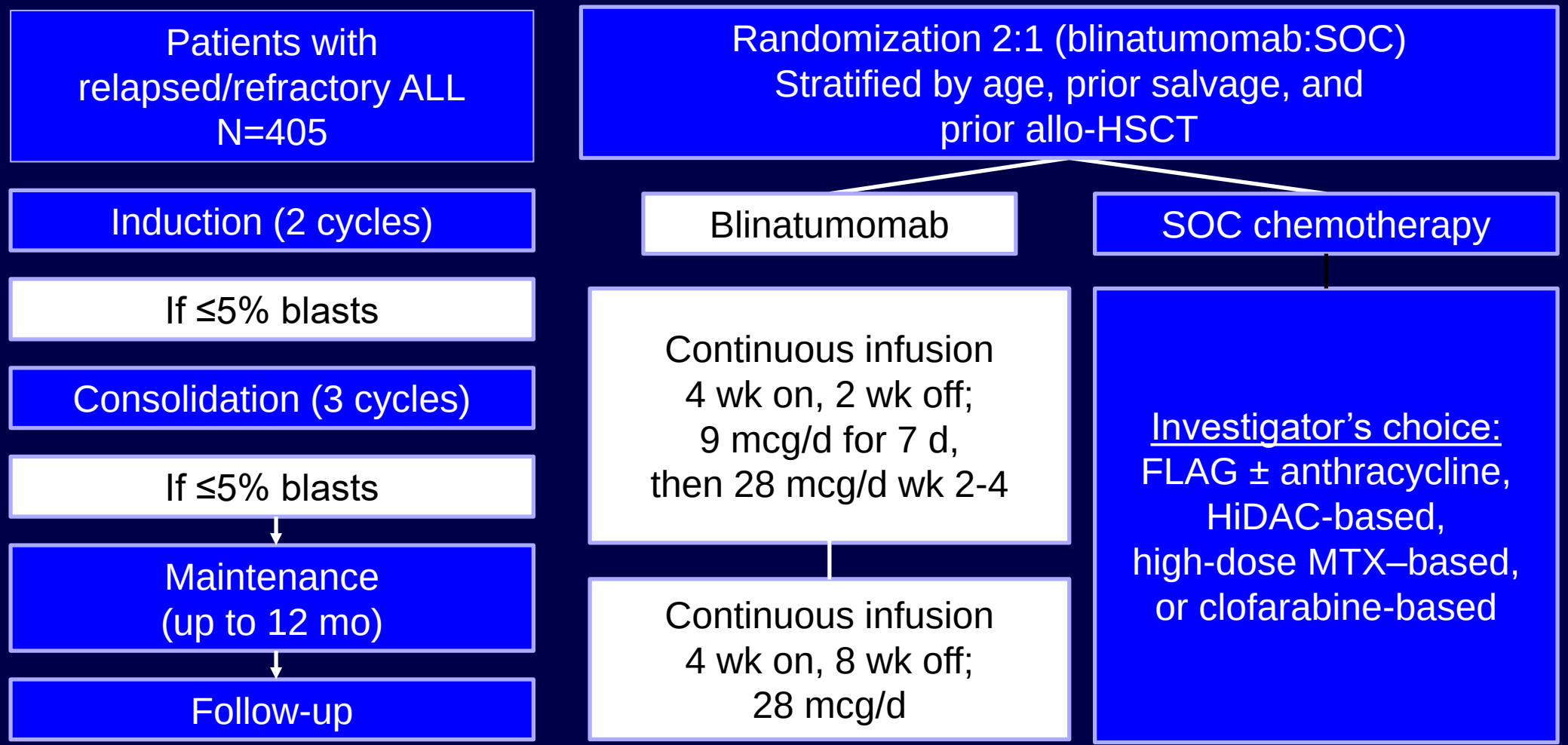


Fielding, et al *Blood*. 2007;109:944-950.
Tavernier E, et al. *Leukemia* 2007;21:1907-1914.

Blinatumomab: A “Serial Killer”



Phase 3 TOWER Study: Randomization and Dosing



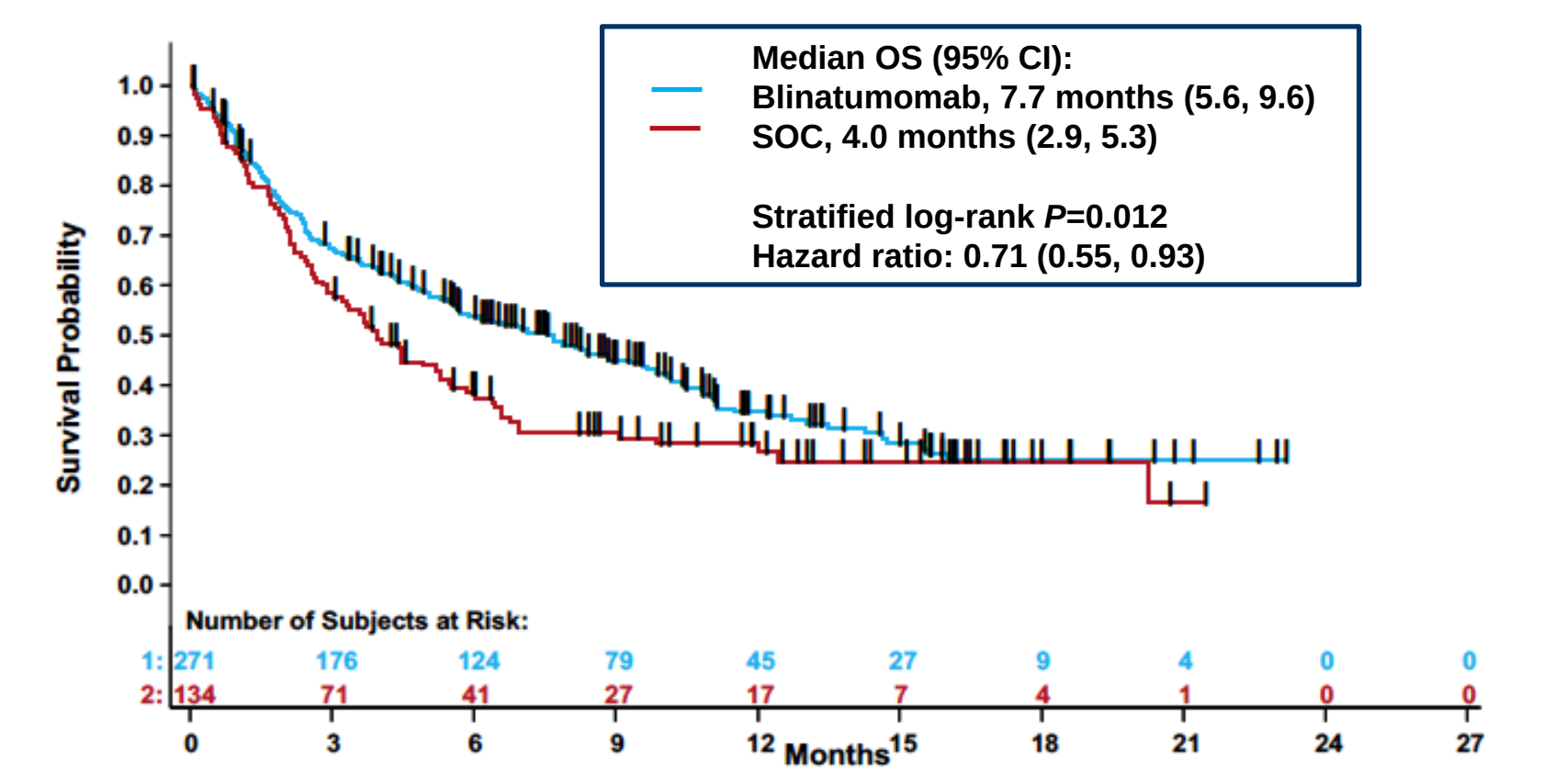
Kantarjian. *N Engl J Med.* 2017;376:836-47.

Blinatumomab vs ChemoRx in R/R ALL (Phase 3 TOWER)

Parameter	Blinatumomab	Chemo Rx	*P* value
CR, %	34	16	<0.001
Marrow CR, %	44	25	<0.001
MRD negative in CR, %	76	48	--
Median OS (mo)	7.7	4.0	0.01
Safety profile	CRS/NE++		

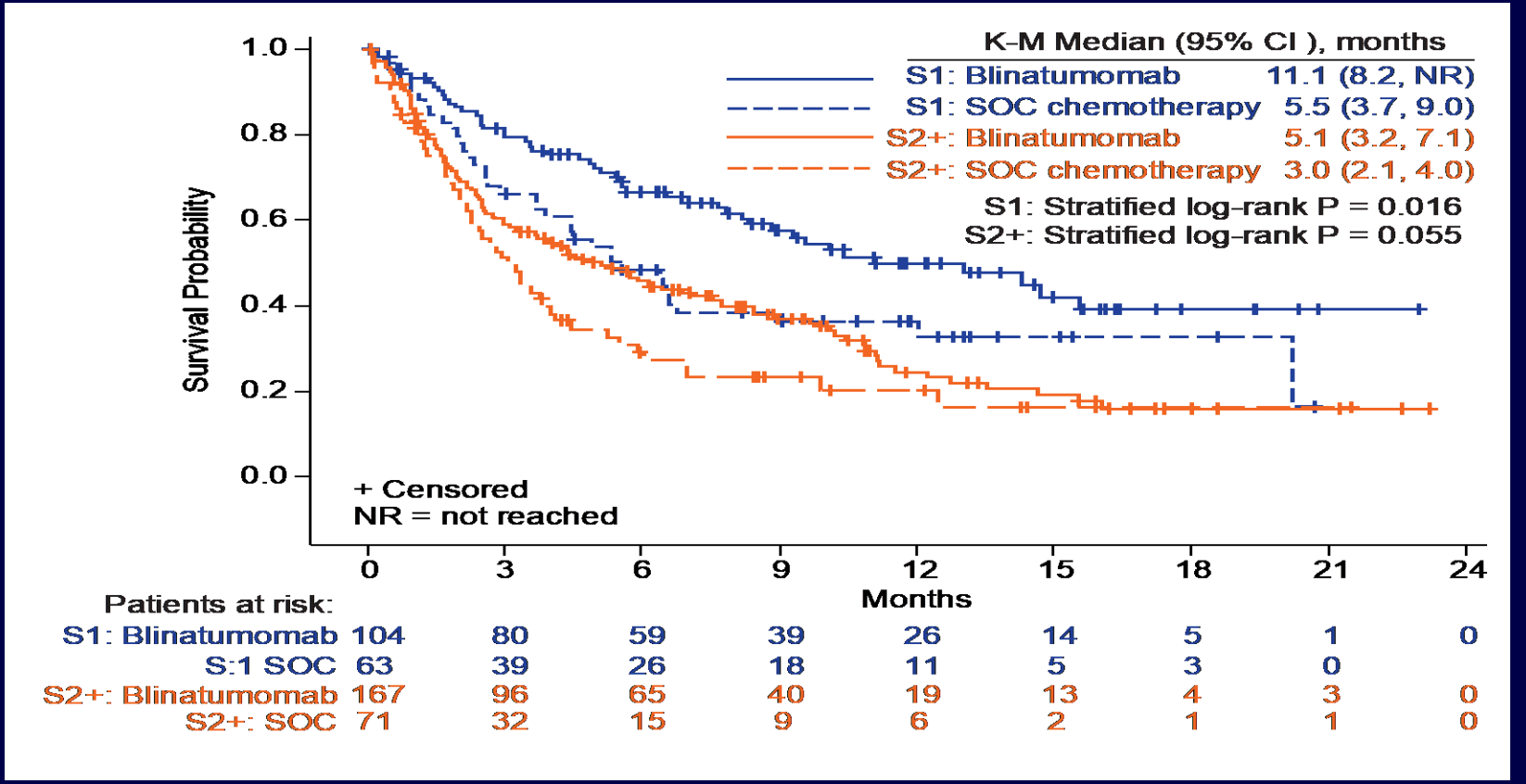
Kantarjian. *N Engl J Med.* 2017;376:836-47.

Blinatumomab vs Chemotherapy in R/R ALL



Kantarjian. *N Engl J Med.* 2017;376:836-47.

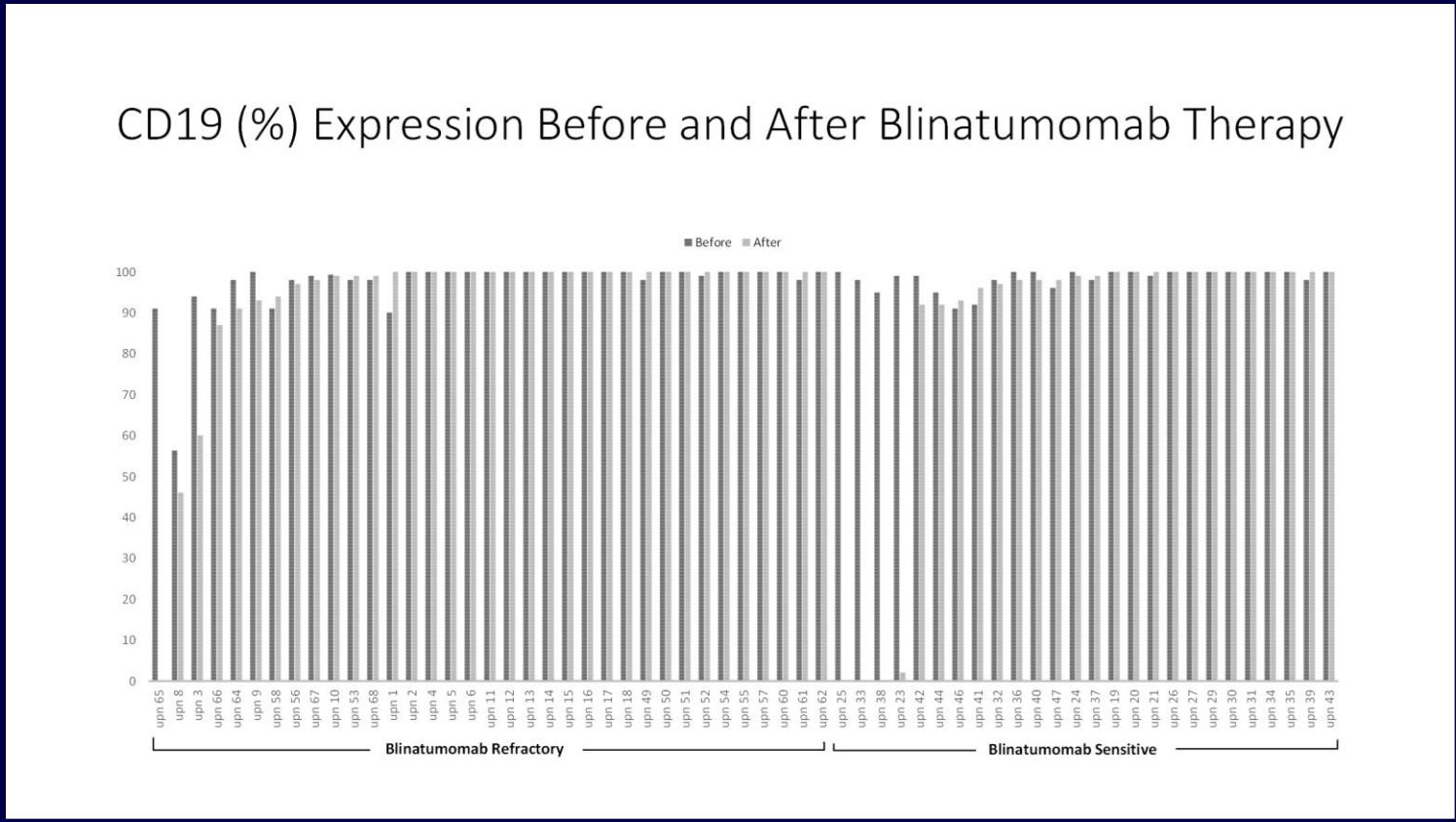
Phase 3 TOWER Study: Survival by Salvage



Dombret. *Leuk Lymphoma*. April 2019.

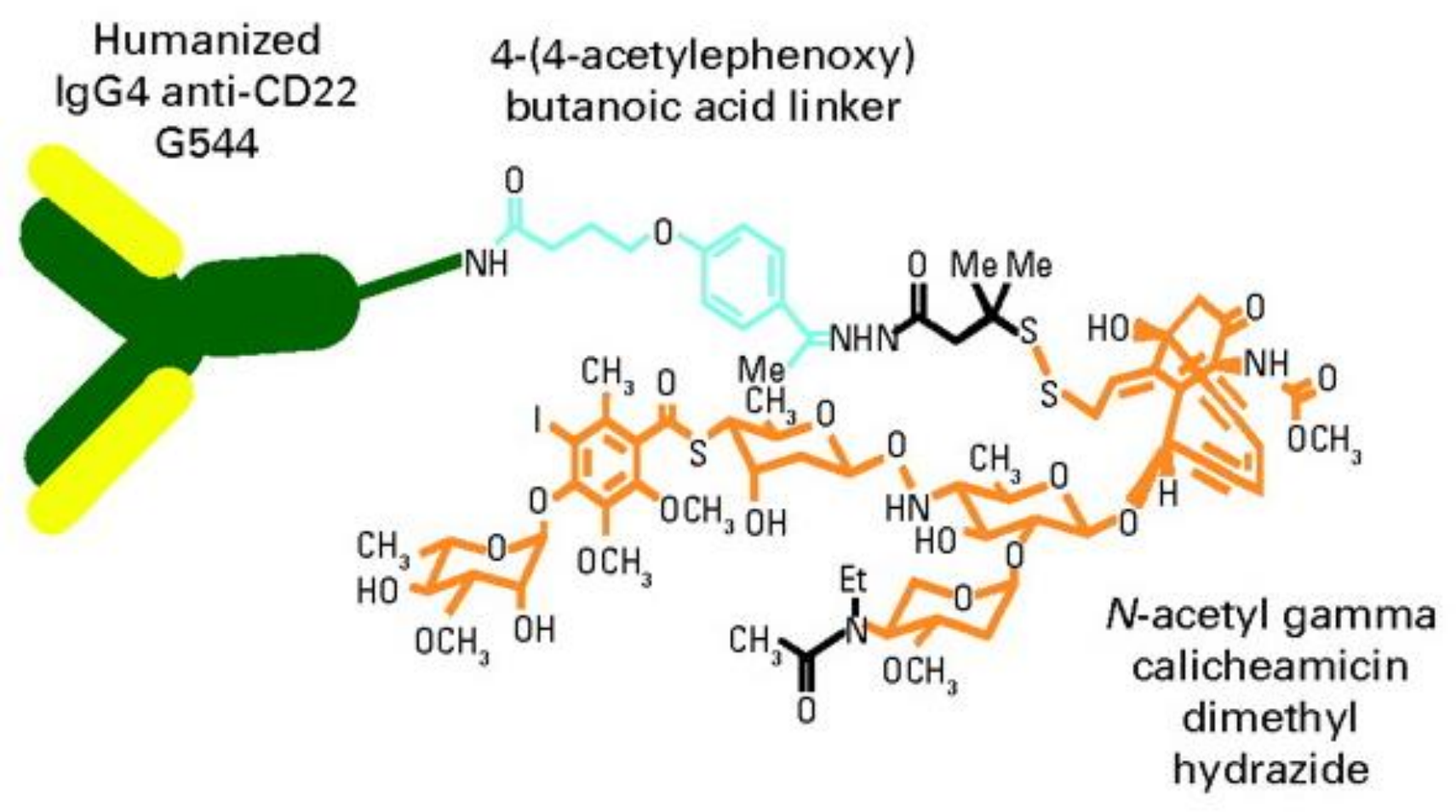
CD19 (%) Expression Before and After Blinatumomab Therapy

- 61 patients evaluated for immunophenotype, 56 (92%) had CD19-positive disease
  - 5 (8%) had ALL recurrence with CD19-negative disease
  - 2 patients progressed with lower CD19-positive disease



Jabbour. *Am J Hematol.* 2018;376:836-47.

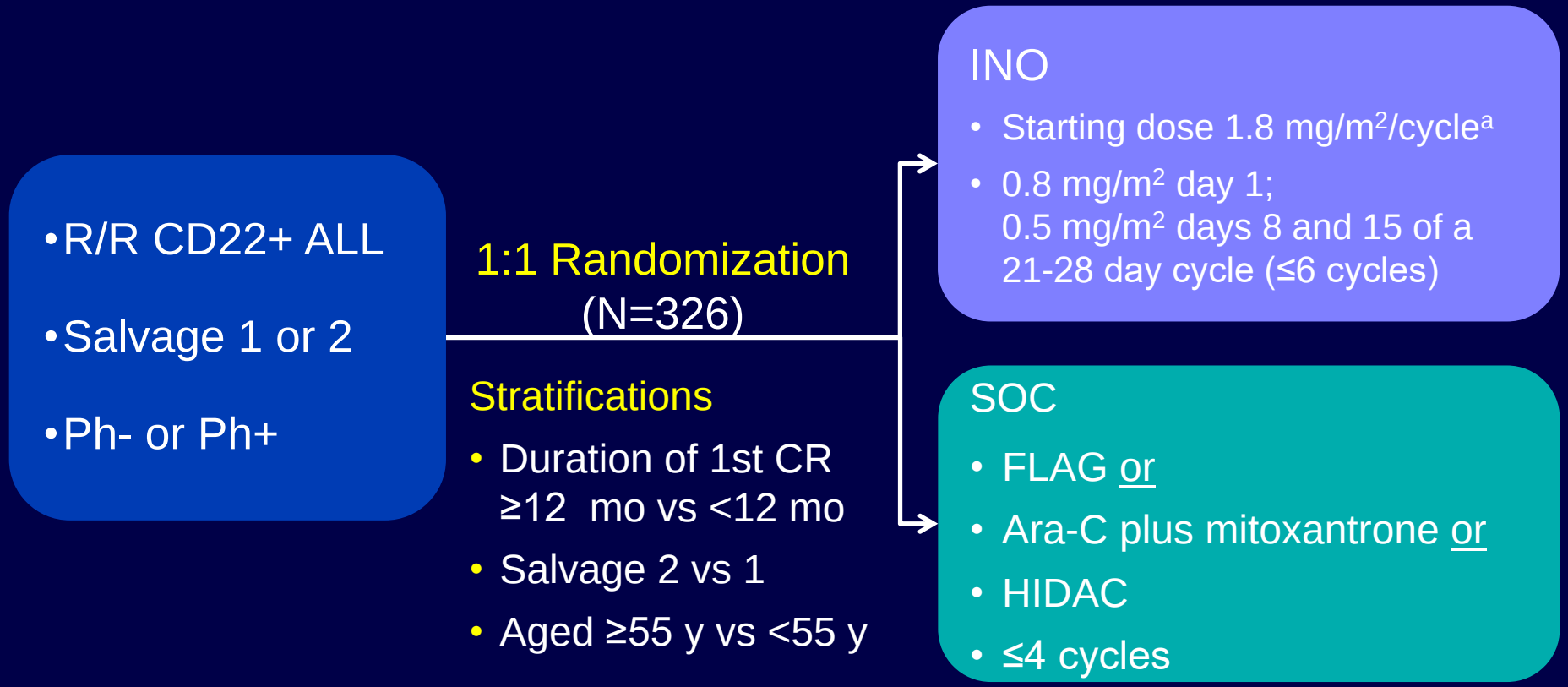
Inotuzumab Ozogamicin



Advani, et al. *J Clin Oncol.* 2010.

Inotuzumab vs ChemoRx in R/R ALL: Design

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



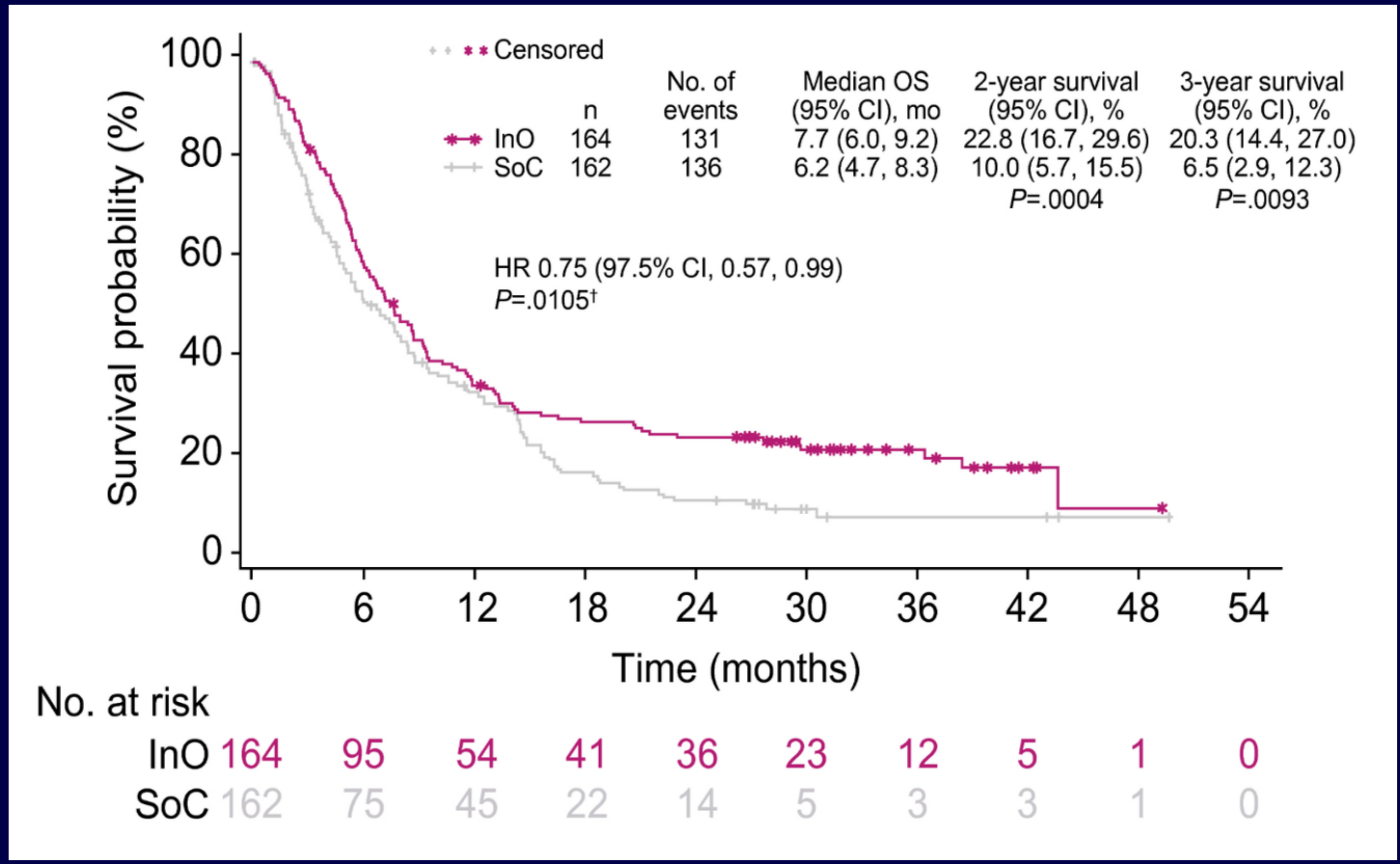
[a]INO dose reduced to 1.5 mg/m^2/cycle once patient achieved CR/CRi.

Kantarjian. *N Engl J Med.* 2016;375:740.

Inotuzumab vs Chemo Rx in R/R ALL (Phase 3 INO-VATE)

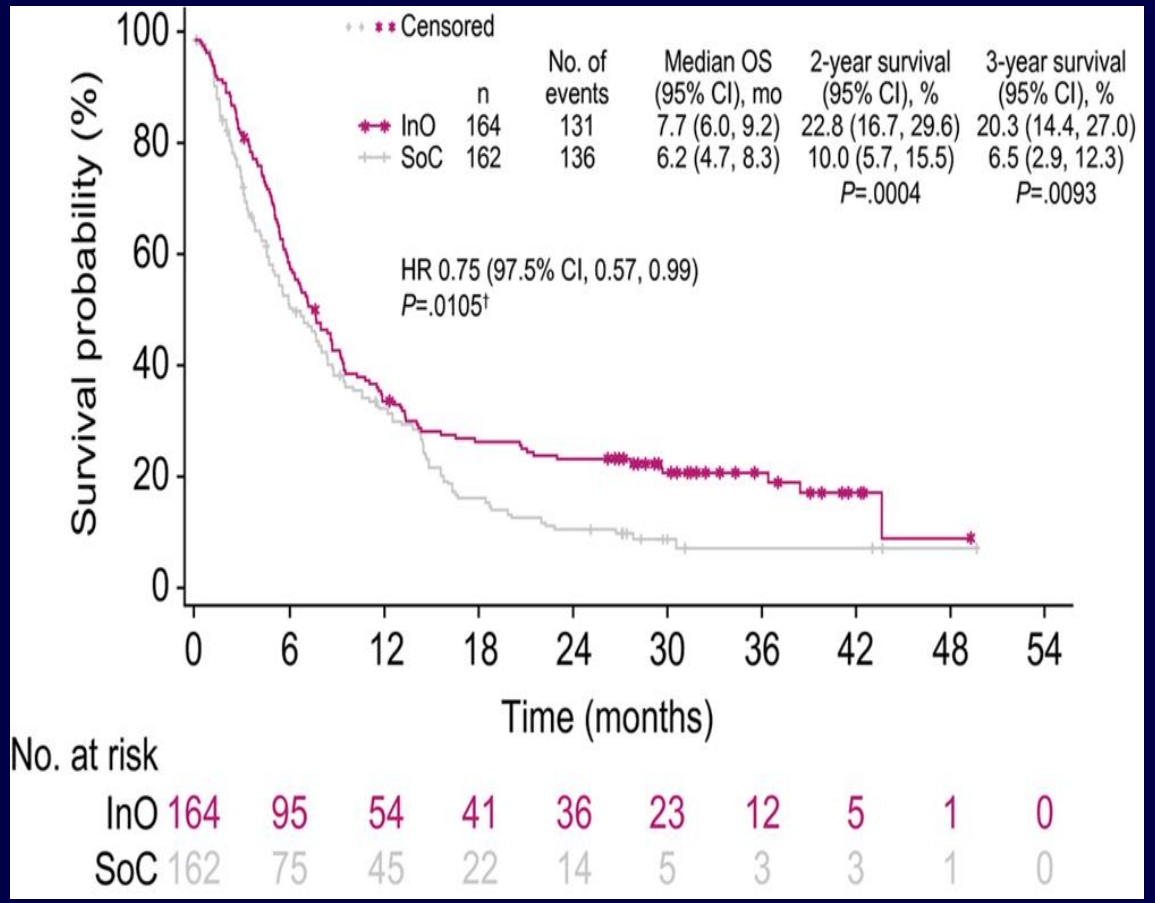
- 326 pts with R/R ALL randomized 1:1 to INO vs Chemo Rx

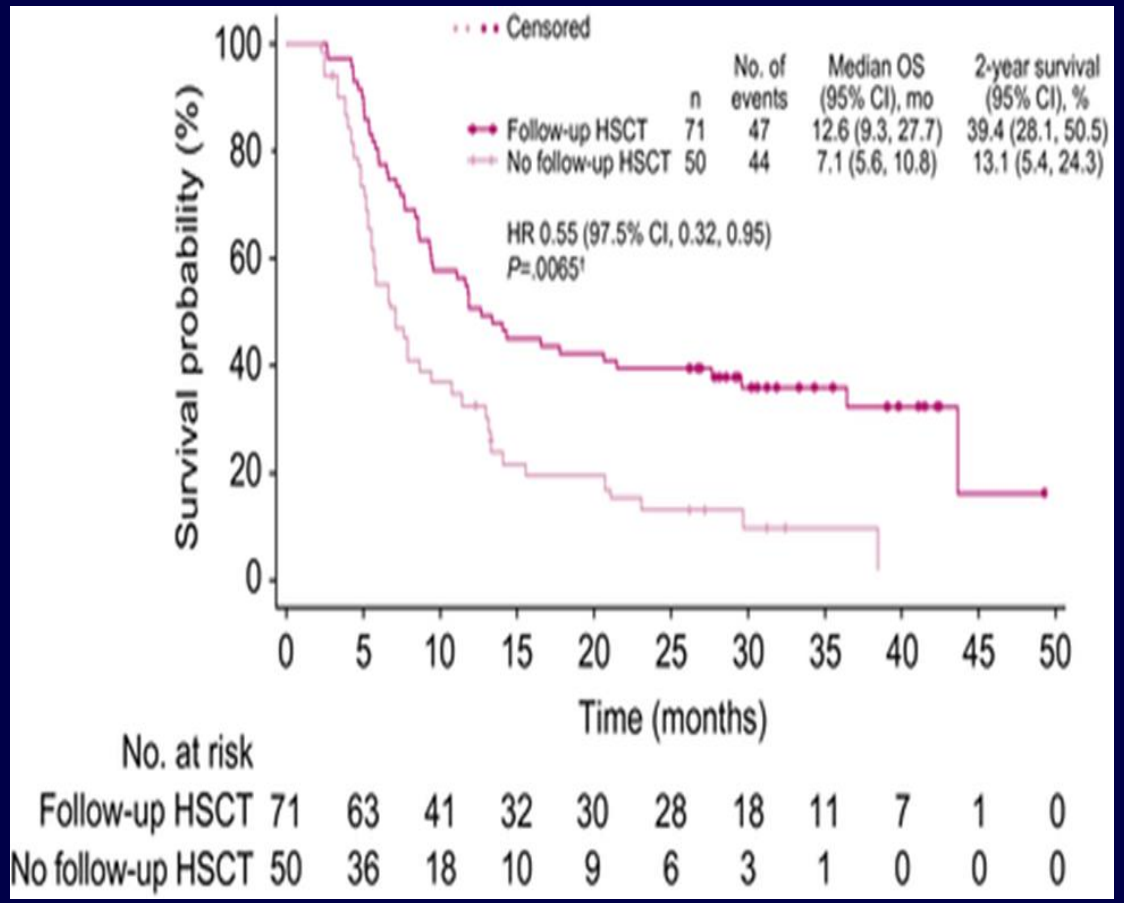
Parameter	INO	Chemo
CR-Cri, %	74	31
MRD neg. in CR, %	78	28
Allo SCT, %	40	10
VOD, %	14	2
Median OS, mo	7.7	6.2
2-yr OS, %	23	10



Kantarjian. *N Engl J Med.* 2016;375:740.
Cancer. May 2019.

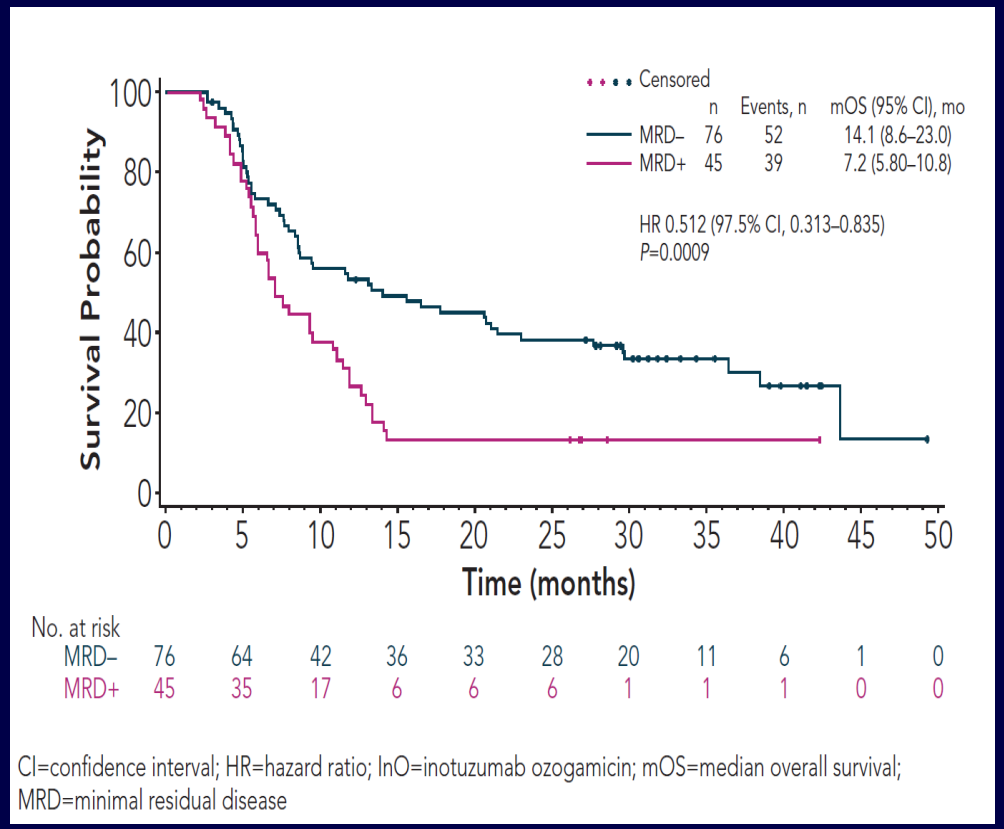
Inotuzumab vs Chemo Rx in R/R ALL — (INO-VATE Phase 3 Final Report)



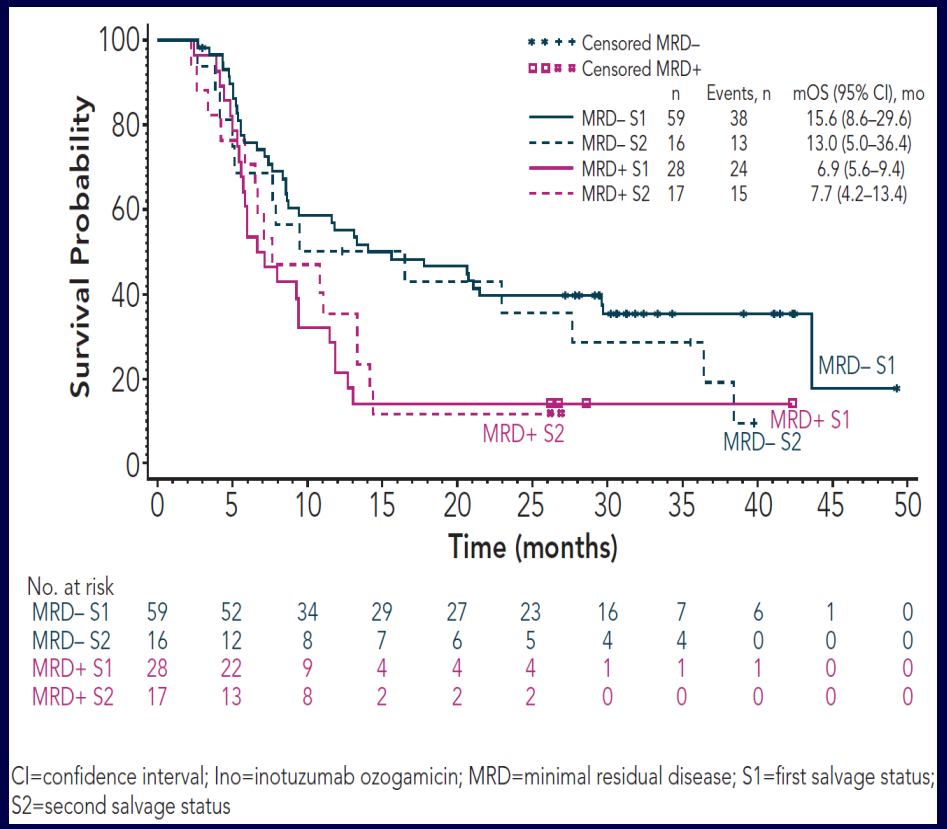


Kantarjian, et al. *Cancer.* 2019 Jul 15;125(14):2474-2487.

Impact of MRD in R/R ALL Rx With INO



CI=confidence interval; HR=hazard ratio; InO=inotuzumab ozogamicin; mOS=median overall survival; MRD=minimal residual disease



CI=confidence interval; Ino=inotuzumab ozogamicin; MRD=minimal residual disease; S1=first salvage status; S2=second salvage status

Jabbour. ASCO 2018: Abstract 7013.

VOD/SOS Among INO-Treated Patients

- VOD incidence: INO, 13% (n=22) vs SOC, 1% (n=1)
- 5 (3%) pts had VOD during study Rx (2 with prestudy SCT)
- 77/164 (47%) on INO had post-study SCT vs 33/162 (20%) in the SOC arm
  - 17/77 (22%) on INO had VOD post-SCT (5/17 also had prestudy SCT)
- Median (range) time to VOD after SCT: 15 (3-57) days

MVA Analysis of Factors Associated With Post-SCT VOD		
Factor	OR (95% CI)	*P* value
Alkylator conditioning (dual vs single)	7.6 (1.7-33.8)	0.008
Age (≥55 y vs <55 y)	4.8 (1.0-22.0)	0.043

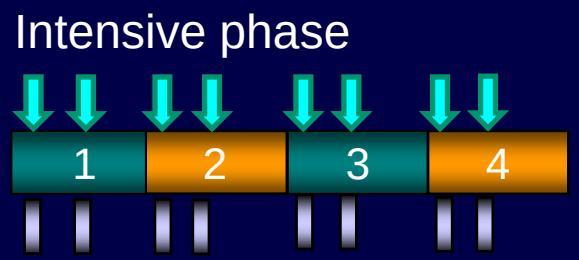
Kantarjian. *N Engl J Med.* 2016;375(8):740-53.
Kantarjian. *Lancet Haematol*. 2017;4:387-98.

MiniHCVD-INO-Blina in ALL: Design

- Dose-reduced hyper-CVD for 4-8 courses
  - Cyclophosphamide (150 mg/m^2 × 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 × 4) 83% dose reduction
- Inotuzumab on day 3 (first 4 courses)
  - Modified to 0.9 mg/m^2 cycle 1 (0.6 and 0.3 on days 1 and 8) and 0.6 mg/m^2 cycles 2-4 (0.3 and 0.3 on days 1 and 8)
- Rituximab days 2 and 8 (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

Jabbour, et al. *Cancer.* 2018 Oct 15;124(20):4044-4055.

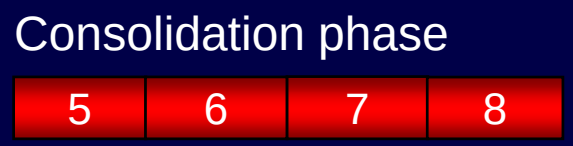
Mini-HCVD + INO ± Blinatumomab in R/R ALL
Modified Design



Mini-HCVD

Mini-MTX -cytarabine

IT MTX, Ara-C



INO

	Total Dose (mg/m^2)	Dose per Day (mg/m^2)
Cycle 1	0.9	0.6 day 1, 0.3 day 8
Cycles 2-4	0.6	0.3 days 1 and 8

Total INO dose = 2.7 mg/m^2

Blinatumomab

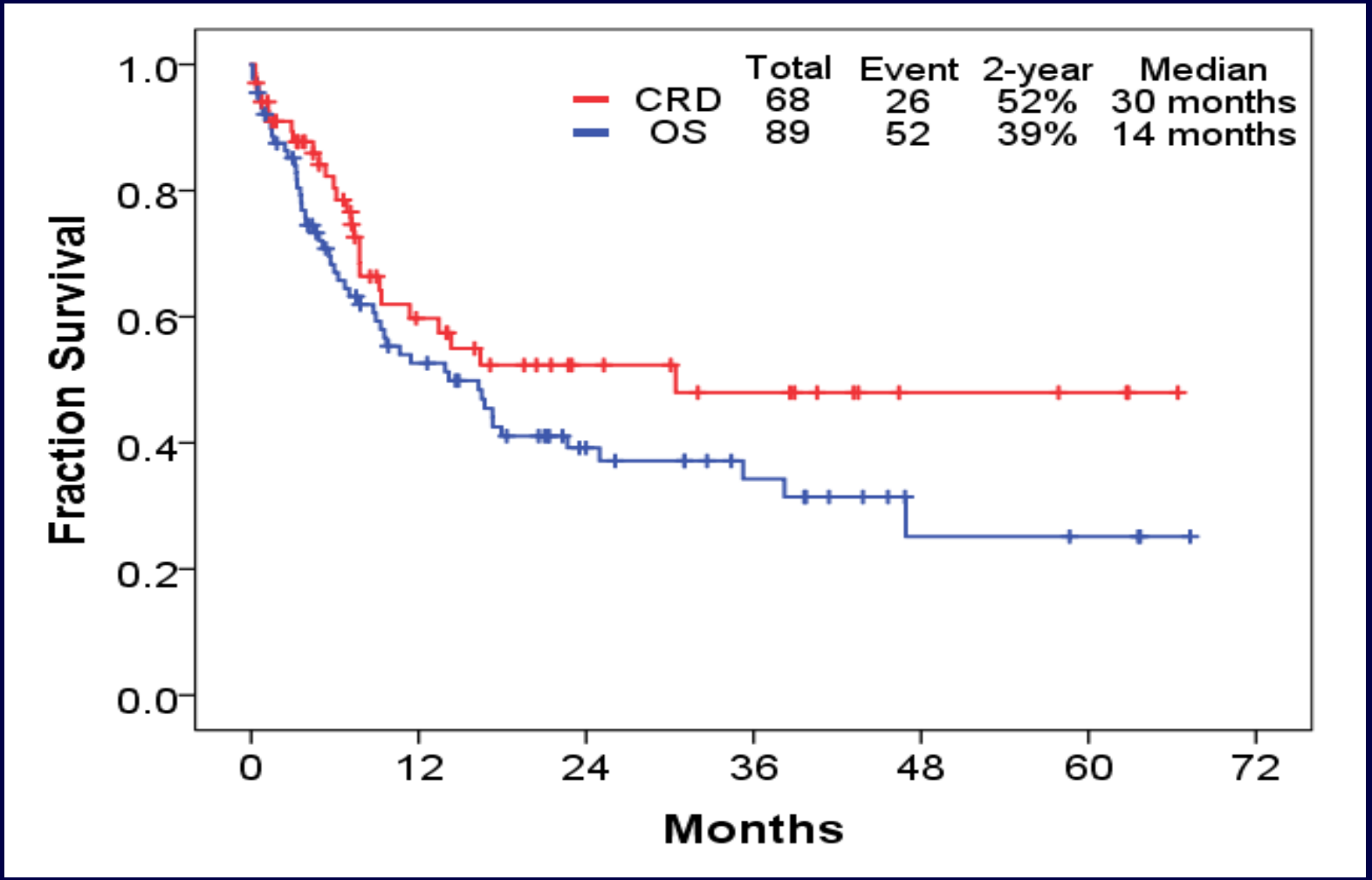
POMP

Jabbour. *Cancer.* 2018 Oct 11.
Sasaki. *Blood.* 2018;132: abst 553.

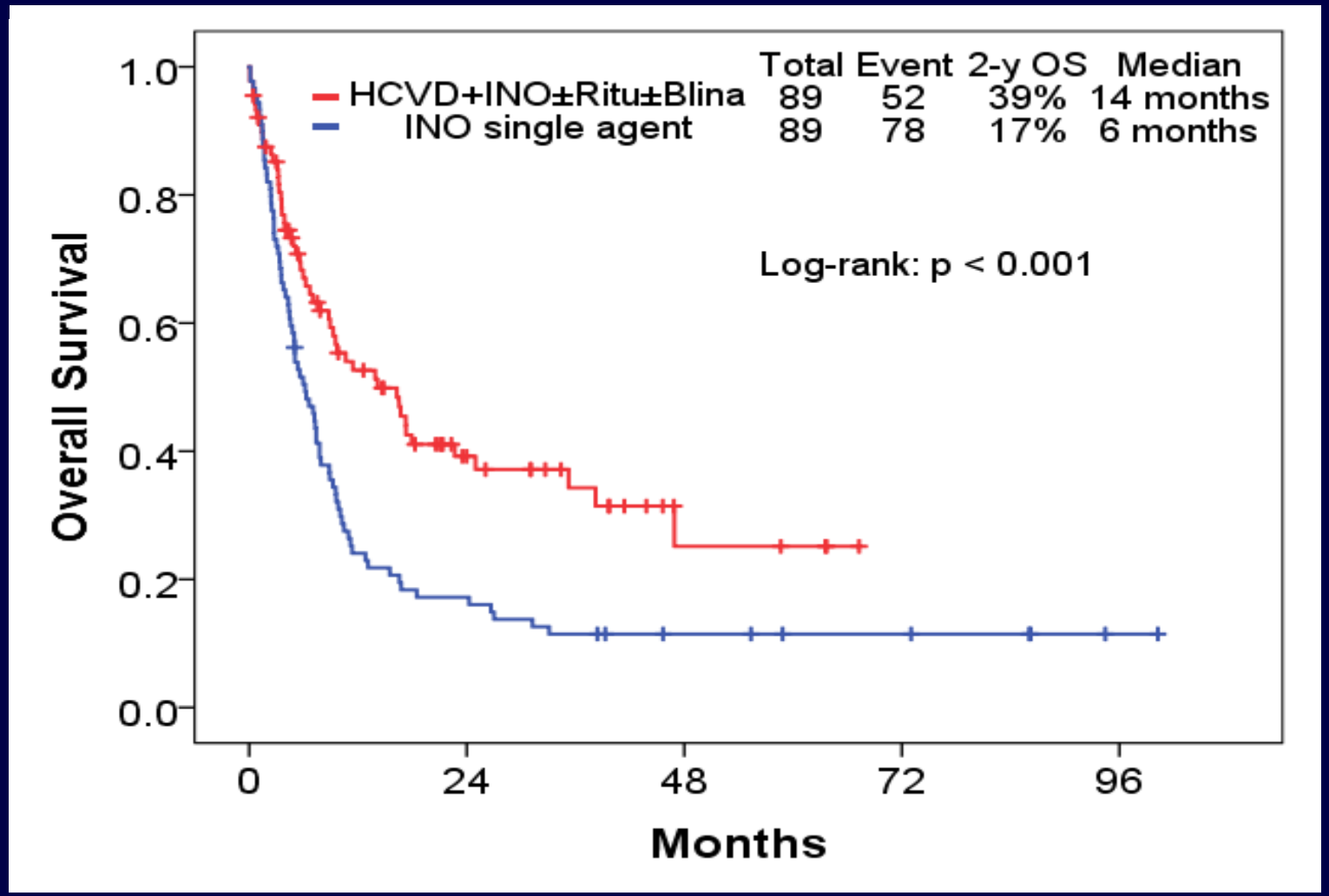
Mini-HCVD + INO ± Blinatumomab in R/R ALL
Response by Salvage (N=89)

Response	N	Percent
Salvage 1	51/56	91
S1, primary refractory	5/5	100
S1, CRD1 <12 mo	19/23	83
S1, CRD1 ≥12 mo	27/28	96
Salvage 2	9/16	56
≥ Salvage 3	9/15	60
Overall	69/87*	79
MRD negativity	55/67	82
Salvage 1	42/49	86
≥ Salvage 2	13/18	72
Early death	7/87	8

Mini-HCVD + INO ± Blinatumomab in R/R ALL CR Duration and OS (Median F/U 31 months)



Mini-HCVD + INO ± Blinatumomab in R/R ALL
Historical Comparison



Optimizing Outcome

- Earlier administration
  - S1 or MRD vs later
- Combination
  - Better efficacy
  - Lower dose
  - Financial benefit (OS 7 vs 14 months)
- Combination and better safety profile
  - Less CRS
  - Less VOD
- Using NGS
  - Compare outcome by NGS
  - NGS vs FCM

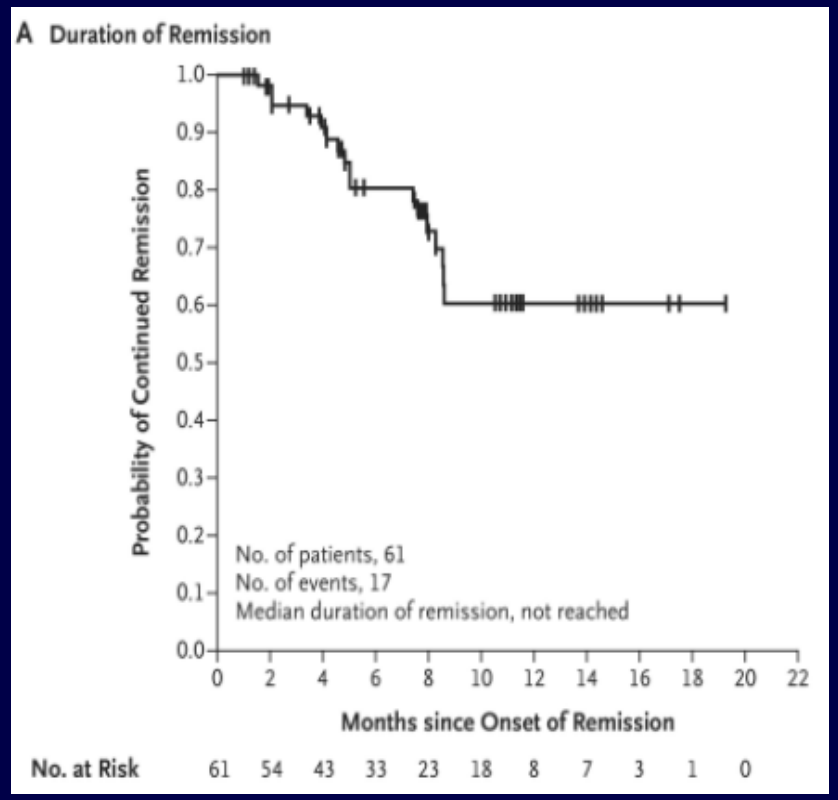
ELIANA: Tisagenlecleucel in Relapsed ALL
Key Patient Characteristics

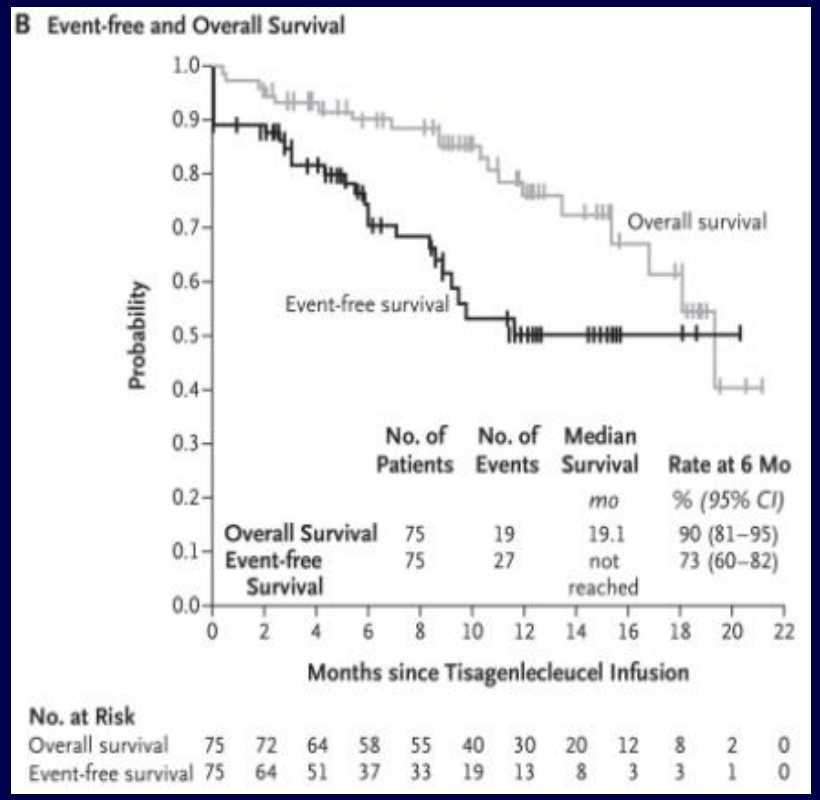
Baseline Characteristics	Patients (N=79)
Median age (range), years	11 (3-24)
Male, %	57
Prior SCT, %	61
Relapse post-SCT in CR1, %	4
Previous lines of therapy, median (range), n	3 (1-8)
Morphologic blast count in bone marrow, median (range), %	74 (5-99)
Disease status, %	
Refractory	8
Relapsed	92
High-risk genetic lesions, %[a]	38
Down syndrome, %	8

[a] *BCR-ABL1*, *MLL* rearrangement, hypoploidy, lesions associated with *BCR-ABL1*–like gene signature, or complex karyotype (≥5 unrelated abnormalities); tumor characterization for cytogenetics/mutations were collected historically based upon local results.
CR1, first complete remission; SCT, hematopoietic stem cell transplant.

ELIANA: Tisagenlecleucel in ALL

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

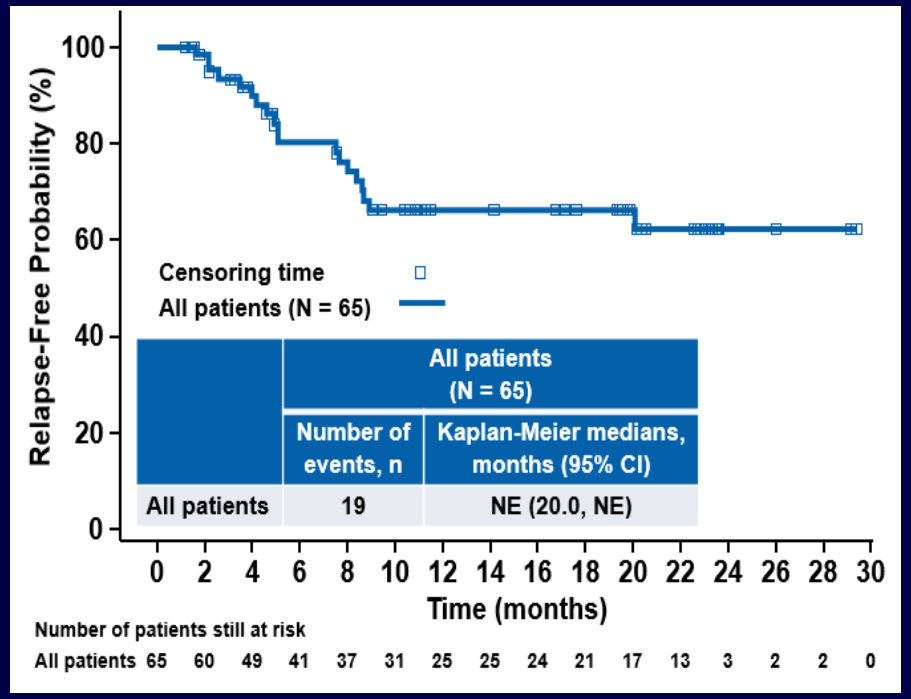


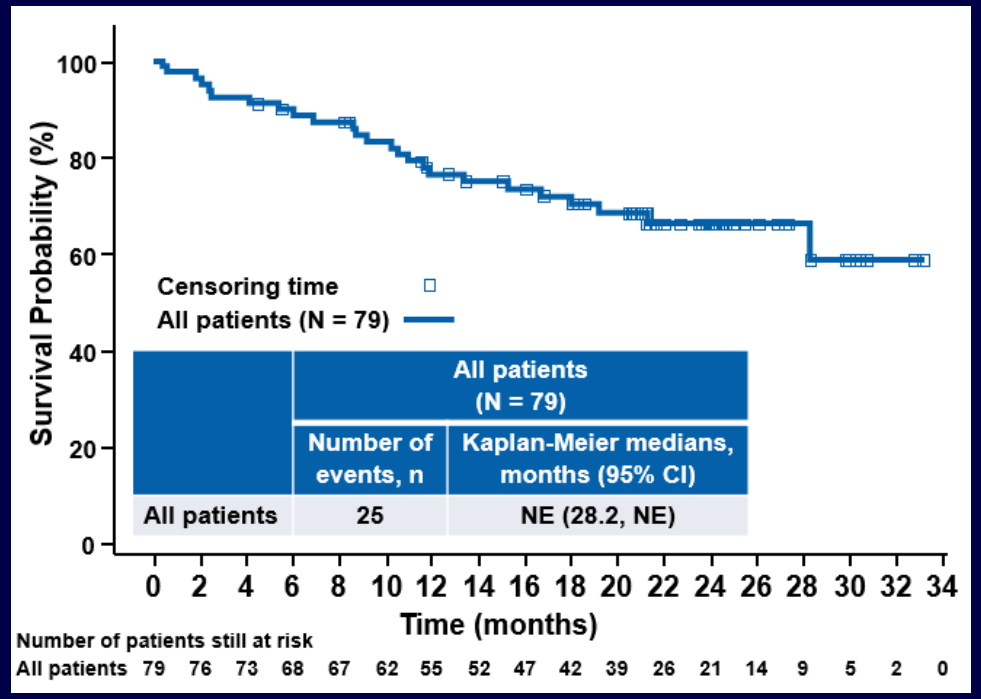


Maude. *N Engl J Med.* 2018;378:439.

ELIANA Trial Update

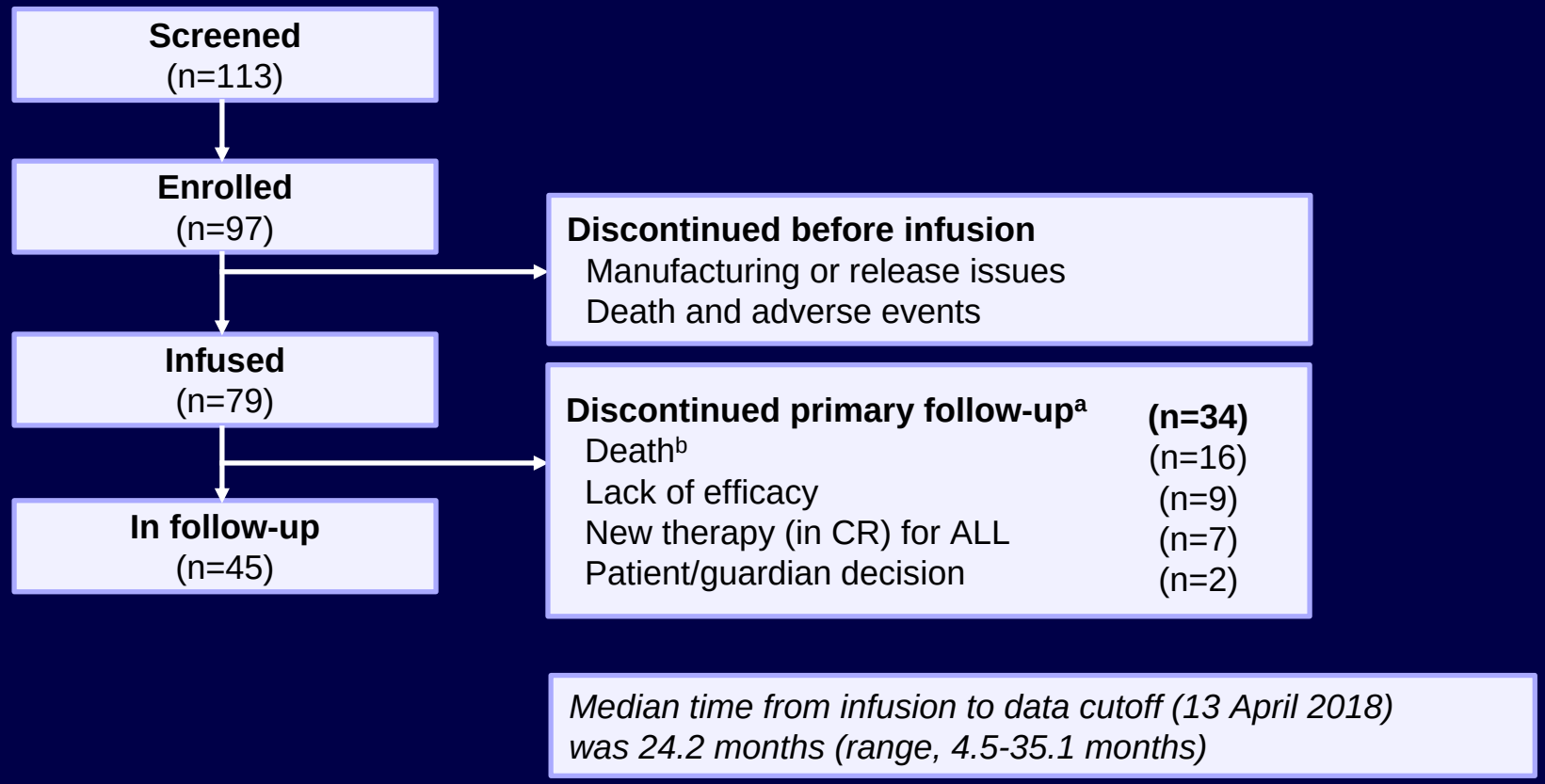
- 113 screened, 97 enrolled, 79 infused
- 3-mo CR 65/79 (82%) or 65/97 (67%)
- 24-mo OS 66%; RFS 62%; grade 3/4 CRS 49%; ICU 48%





Grupp. EHA 2019. Abstract S1618.

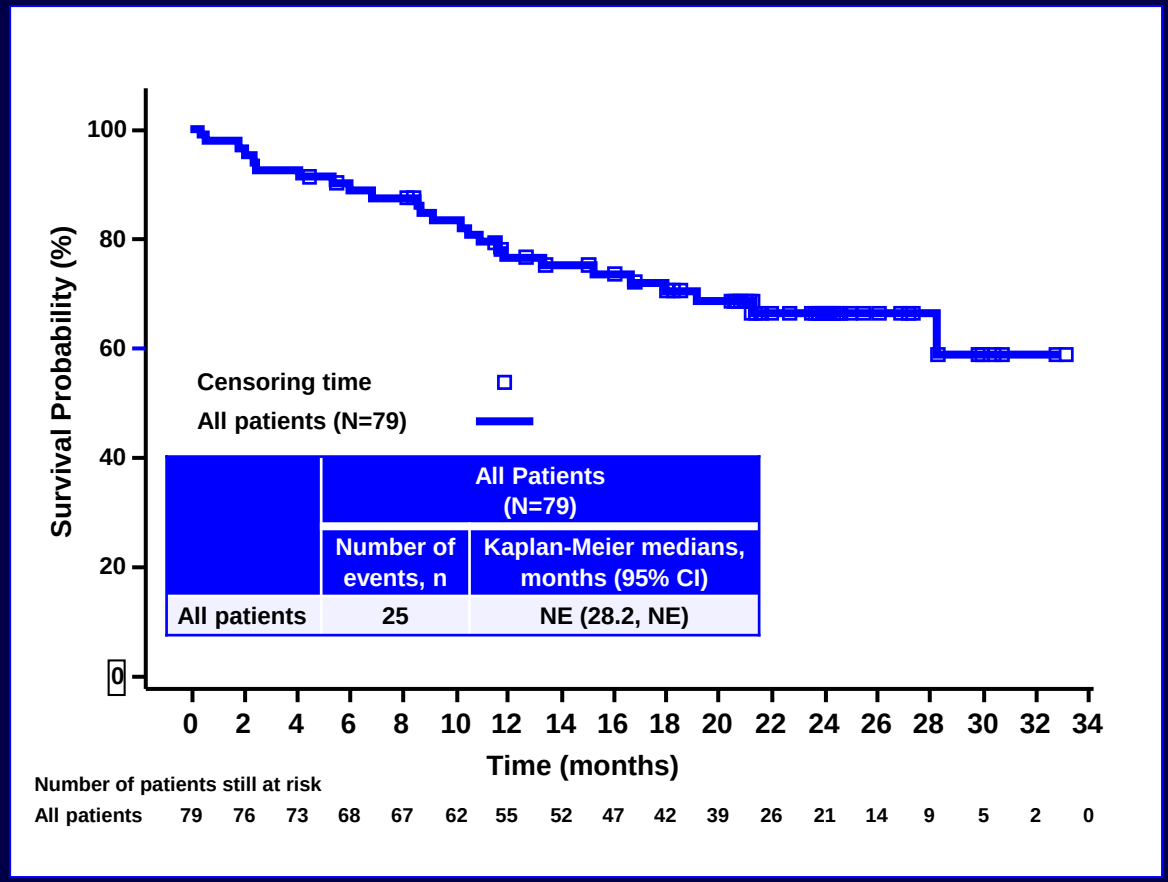
Patient Disposition



[a] Patients followed for survival.
[b] One death occurred while the patient was in remission; other deaths occurred after treatment failure or relapse.

Tisagenlecleucel in Relapsed ALL
Median Overall Survival Not Reached

- Overall survival rates among all infused patients
  - 12-month: 76% (95% CI, 65-85)
  - 18-month: 70% (95% CI, 58-79)
  - 24-month: 66% (95% CI, 54-76)



Note: All patients infused with tisagenlecleucel were included. Time is relative to infusion.
CR, complete remission; CRi, complete remission with incomplete blood count recovery; NE, not estimable.

Overall Safety and AEs of Special Interest Within 8 Weeks After Infusion

AESI[a]	Patients (N=79)		
	All Grades, %	Grade 3, %	Grade 4, %
Cytokine release syndrome[b]	77	22	27
Infections	43	20	4
Cytopenias not resolved by day 28	42	18	18
Neurological events	39	13	0
Tumor lysis syndrome	5	5	0

- Majority of AEs occurred in the first 8 weeks after tisagenlecleucel infusion
- No cases of cerebral edema reported

[a] Occurring within 8 weeks of tisagenlecleucel infusion.
[b] Cytokine release syndrome was graded using the Penn scale.
AESI, adverse events of special interest.

Tisagenlecleucel in Relapsed ALL Cytokine Release Syndrome

	Patients Infused (N=79)
Patients developed CRS, n (%)	61 (77)
Time to onset, median (range), days	3.0 (1-22)
Duration of CRS, median (range), days	8.0 (1-36)
ICU admission, n (%)	38 (48)
Anticytokine therapy, %	31 (39)
Tocilizumab, %	31 (39)
1 dose	18 (23)
2 doses	10 (13)
3 doses	3 (4)
Corticosteroids, %	16 (20)
Hypotension that required intervention, %	42 (53)
High-dose vasopressors, %	19 (24)
Intubation, %	12 (15)
Dialysis, %	8 (10)

CRS was graded using the Penn scale and managed by a protocol-specific algorithm[1]

CRS, cytokine release syndrome; ICU, intensive care unit.

1. Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139.

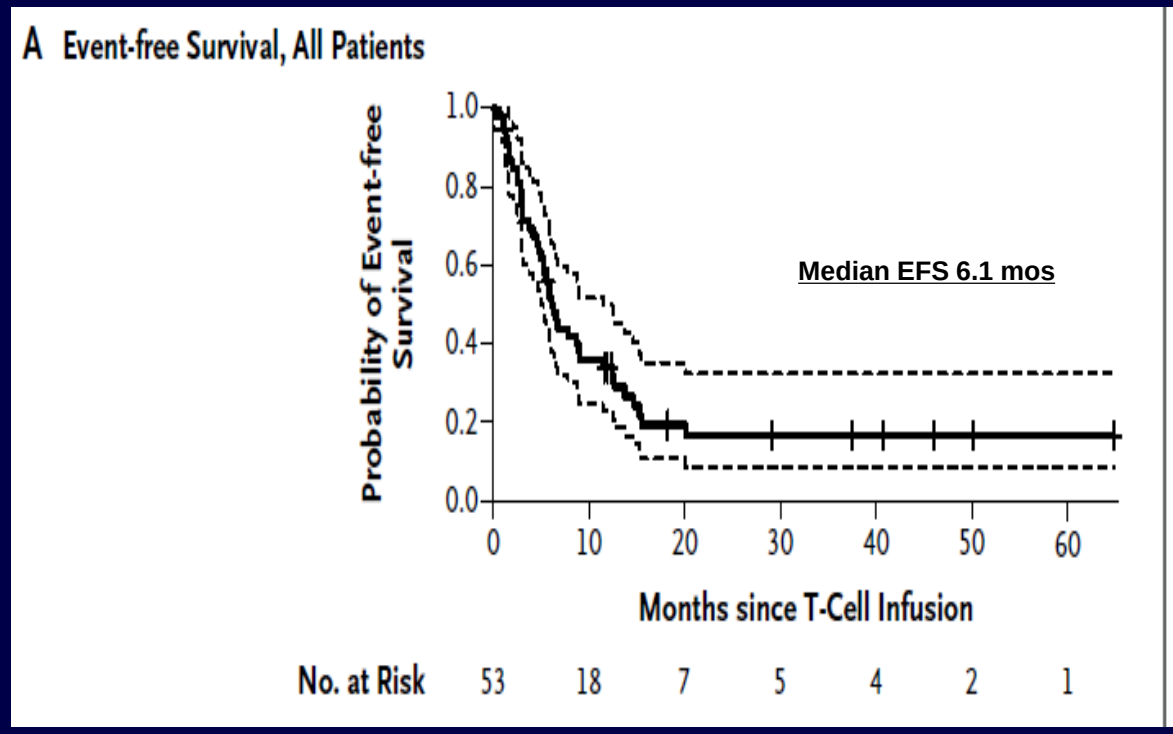
Positive Association of CRS Grade and Neurological Event Grade

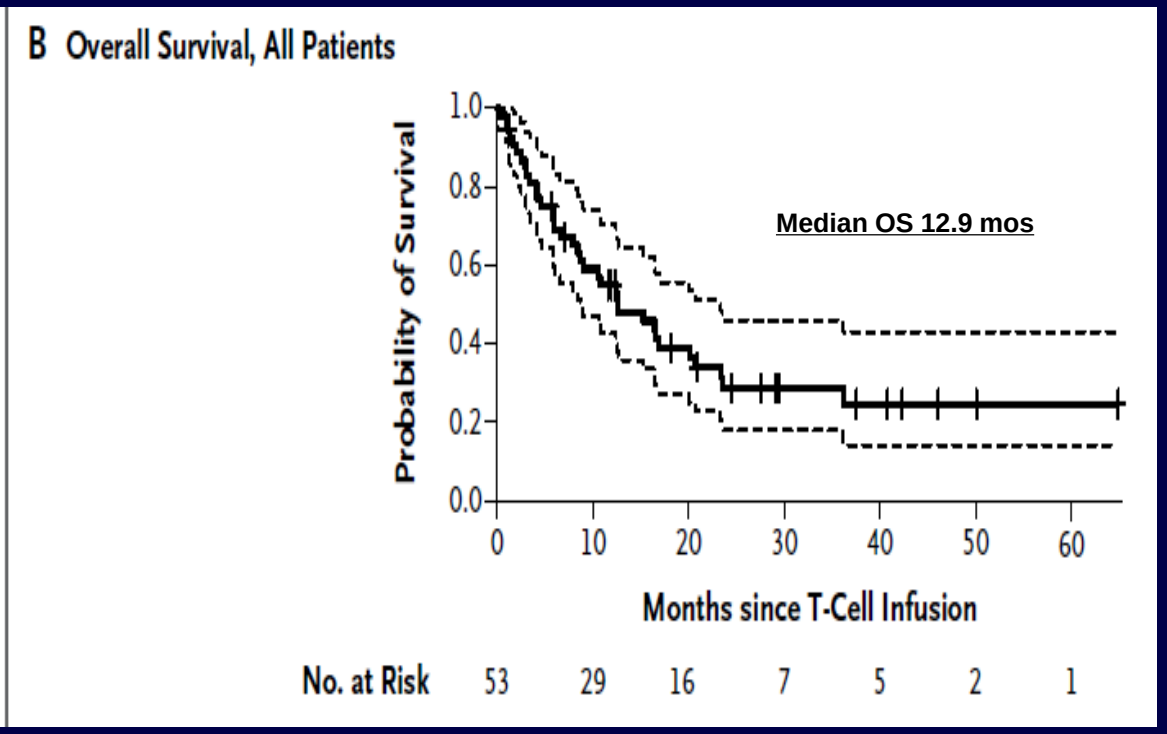
CRS	N	Any-Grade Neurological Events, n (%)	Grade 3 Neurological Events, n (%)
None	18	4 (22)	1 (6)
Grade 1/2	23	7 (30)	1 (4)
Grade 3	17	7 (41)	2 (12)
Grade 4	21	13 (62)	6 (29)

- Grade 3 neurological events were more frequent with grade 4 CRS compared with grades 0-3 CRS (95% CI, –2% to 45%)
- Median onset of any-grade CRS (day 3) preceded median onset of neurological events (day 7)
- Grade 3 or 4 CRS and neurological events occur earlier than grade 1 or 2

MSKCC-Long-Term Data With CD19-CD28z CAR

- CR 44/53 (83%); ITT overall CR 44/78 (56%)
- Response (n=53): CR 83%; MRD- CR 60%



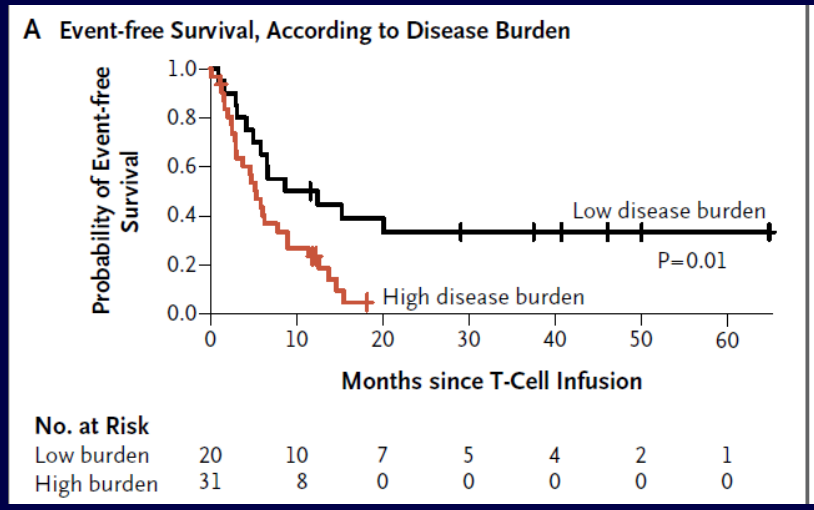


MSKCC: Memorial Sloan Kettering Cancer Center

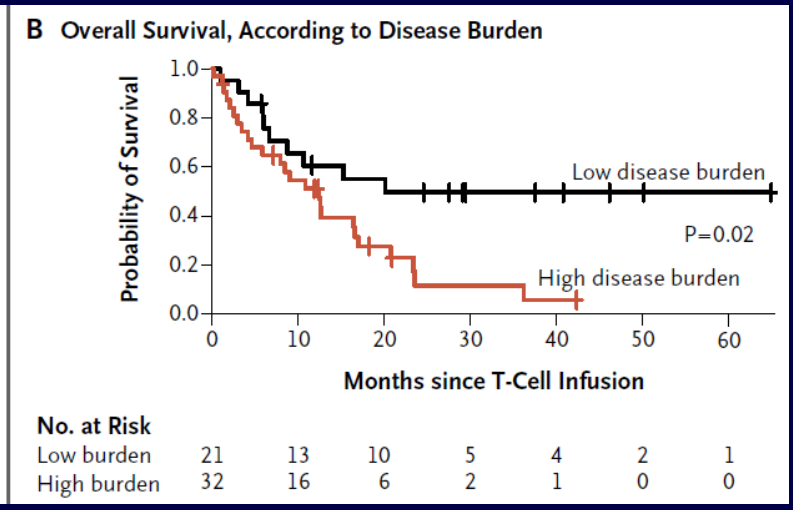
Park. *N Engl J Med.* 2018;378:449.

CD19-CD28z CAR (MSKCC) Outcome by Tumor Burden

- High tumor burden
  - Bone marrow blasts ≥5% (n=27)
  - Bone marrow blasts <5% + extramedullary disease (n=5)
- Low tumor burden (MRD+ disease) (n=21)



Median EFS
Low tumor burden (MRD+): 10.6 mo
High tumor burden: 5.3 mo



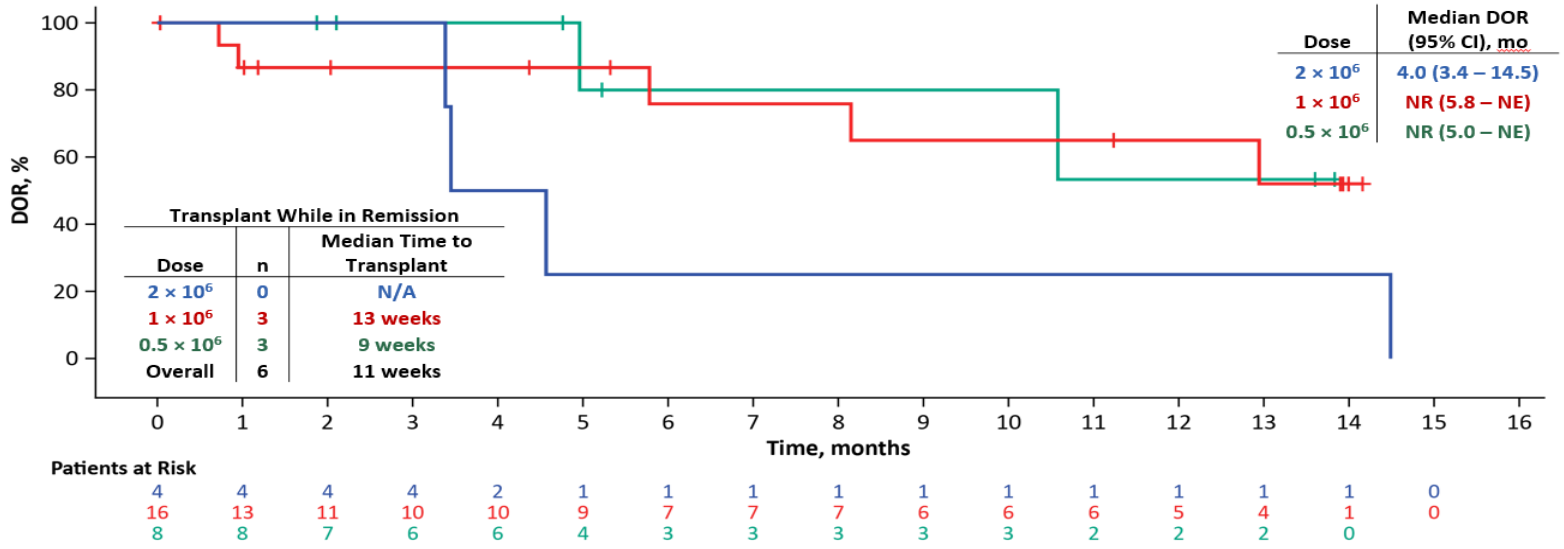
Median OS
Low tumor burden (MRD+): 20.1 mo
High tumor burden: 12.4 mo

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

ZUMA3: KTE-X19 in Refractory/Relapsed ALL

- 54 pts; 45 received CAR T-cell therapy. Median age 46 y (range, 18-77)
- FC→CAR T cells 2 × 10^6/kg; 1o R 16; S1 2; R/R post-allo SCT 13
- CR+CRi (22+6)/41 = 68%; or 28/54 = 52%

Duration of Remission Not Censored at Transplant



- Of the 6 patients who received transplant, 3 have ongoing remission as of the data cutoff

Figure includes all patients who achieved a CR + CRi with at least 2 months of follow up (n = 28) without censoring at transplant. Ticks indicate censored events.
DOR, duration of remission; N/A, not applicable; NE, not evaluable; NR, not reached.

Shah. ASCO 2019. Abstract 7006.

Conclusions: Salvage Therapies in ALL

- Very effective salvage therapy in R/R ALL
  - High MRD negativity rates
  - Best outcome in Salvage 1
- Combination with low dose chemotherapy
  - Safe and effective
  - Median survival 14 months
  - Salvage 1 twenty-four months (2-year OS rate >50%)
- Better control of AEs
  - CRS: debulk with sequential chemotherapy
  - VOD lower doses explored
  - VOD: lower dose INO schedules being explored
- CAR T-cell therapy is very effective for refractory patients
  - Decreasing toxicity is an important goal: CRs decreased with less tumor burden
  - Curative?