Cellular Therapies in Leukemias

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Dana-Farber Cancer Institute

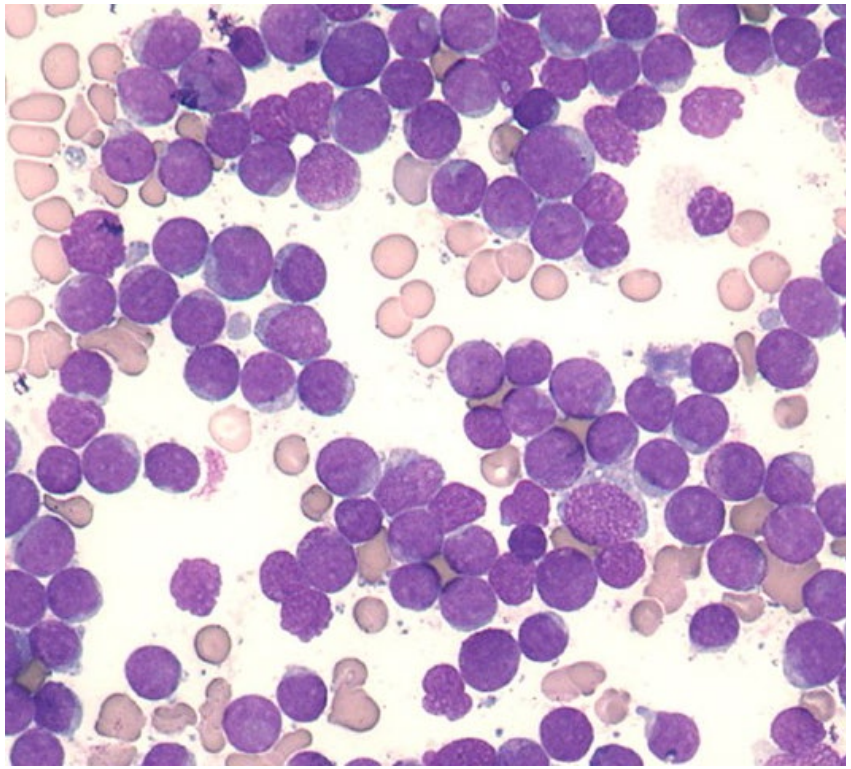
The acute leukemias

Acute Myeloid Leukemia (AML)

~20,000 new cases/year

- Adults > Pediatric

30% 5-year OS



ASH Image Bank, accessed 3/2023

Acute Lymphoblastic Leukemia (ALL)

~6600 new cases/year

- Pediatric > Adults and AYA

70% 5-year OS

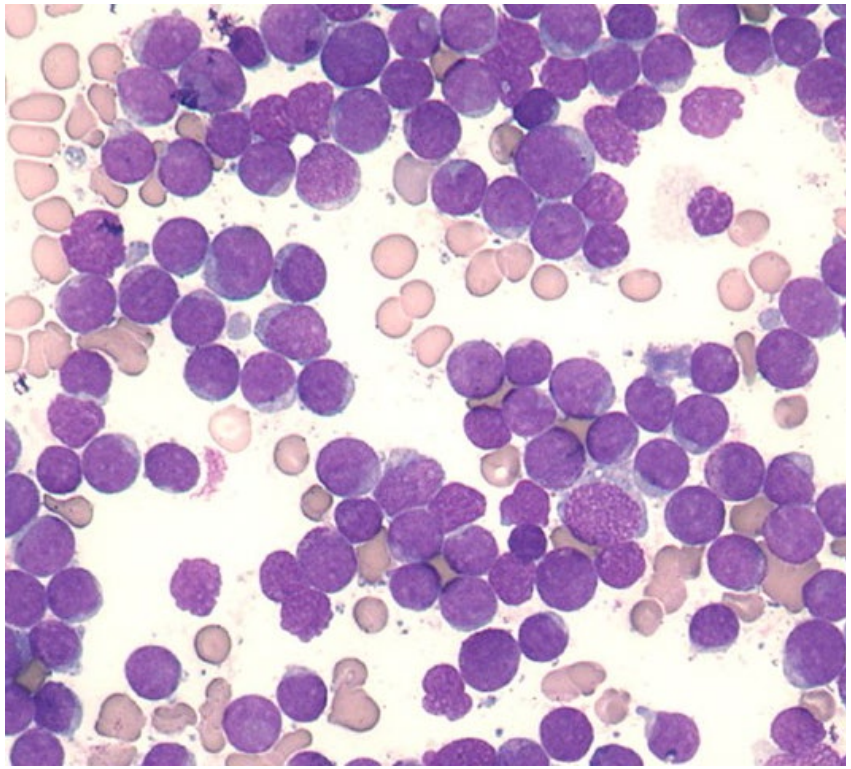
- >90% in children
- 30-40% in adults

SEER Database, accessed 3/2023

The acute leukemias

Acute Myeloid Leukemia (AML)

No approved cellular therapies



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Acute Lymphoblastic Leukemia (ALL)

Bispecific antibody

- Blinatumomab

CAR-T cells

- Tisagenlecleucel
- Brexucabtagene autoleucel

SEER Database, accessed 3/2023

Outline

- Indications and mechanisms
- Major class toxicities
- Efficacy
- Toxicity
- Practical pearls

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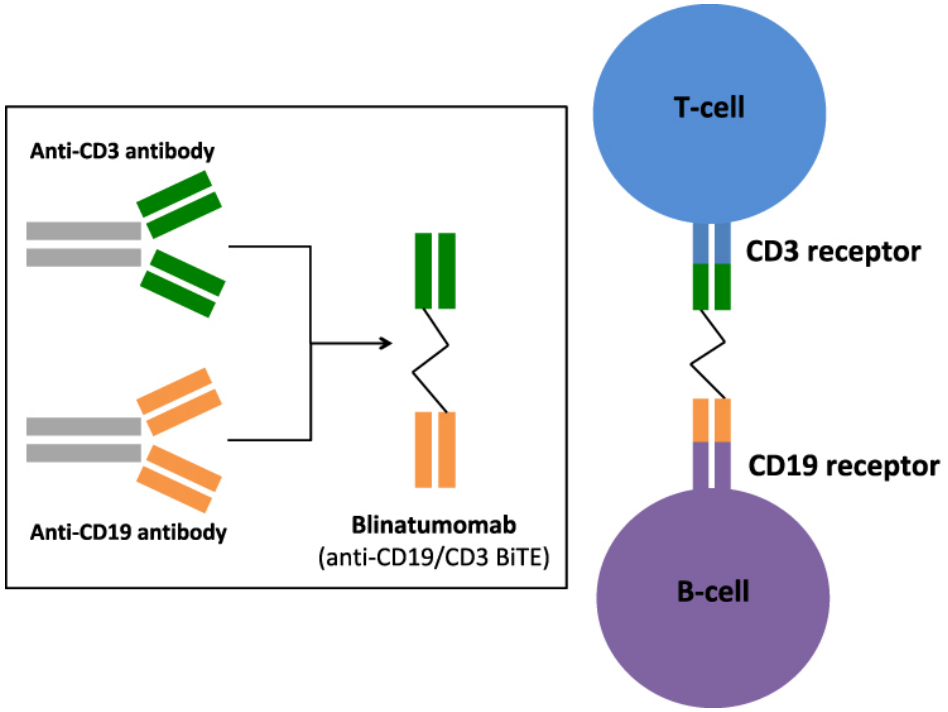
Indications and mechanisms

Agent	Indications	Mechanism
Blinatumomab (BLINCYTO)	R/R B-ALL B-ALL in MRD+ CR	Bispecific T-cell engager



Sigmund et al, Blood and Lymph Cancer, 2020

Indications and mechanisms

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Blinatumomab (BLINCYTO)	R/R B-ALL B-ALL in MRD+ CR	Bispecific T-cell engager
Tisagenlecleucel (KYMRIAH)	AYA with R/R B-ALL (<26 years, ≥2 relapses)	CAR-T (CD28 co-stimulatory domain)
Brexucabtagene autoleucel (TECARTUS)	Adults with R/R B-ALL	CAR-T (41BB co-stimulatory domain)

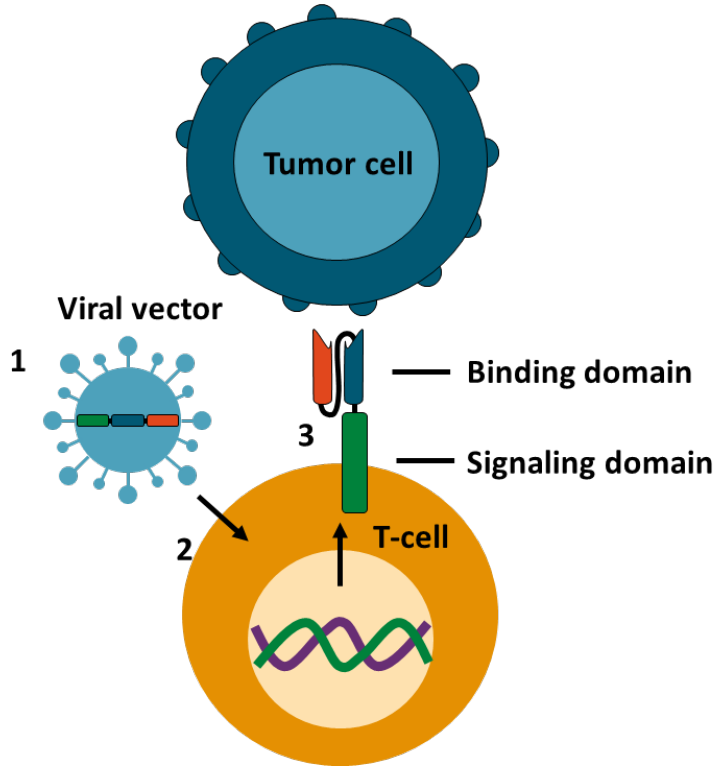

Image credit: clinicaloptions.com

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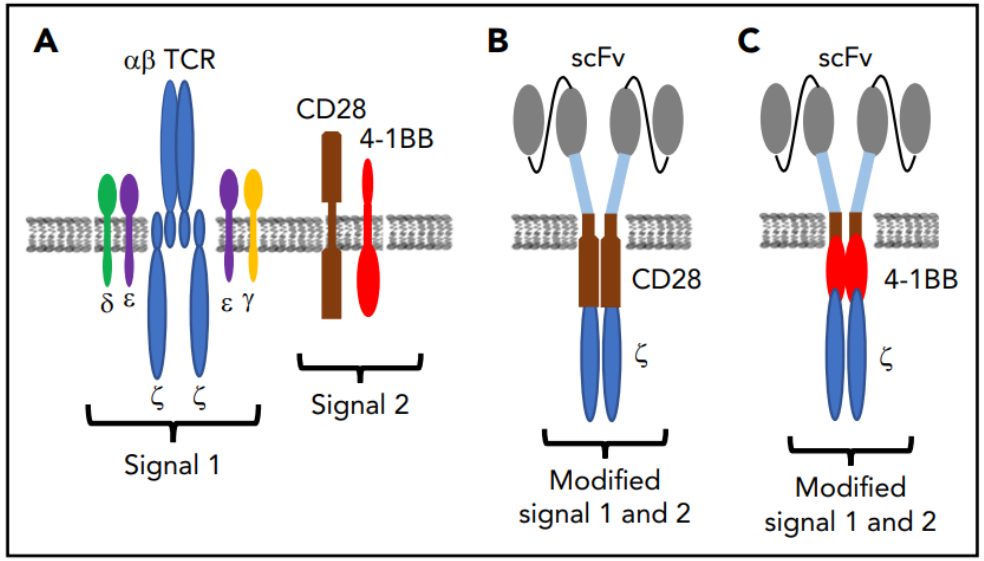

Salter et al, Blood 2018

Outline

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Major toxicities – cytokine release syndrome (CRS)

- Typically within 14 days after infusion, lasts 1-10 days
- Correlates with tumor burden, dose of infused CAR-T cells, malignancy
- Concerns that that steroids may blunt treatment efficacy; tocilizumab is mainstay of treatment

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Lee et al, BBMT 2018

Tocilizumab	X (If not improving)	X	X	X
Steroids		X (If not improving)	X	X
Discontinue infusion (for blinatumomab)			X (restart with dose-reduction once resolved)	X (stop permanently)

Major toxicities – immune effector cell-associated neurotoxicity syndrome (ICANS)

- Onset frequently during/after CRS, late complications can occur
- Headaches, confusion, expressive aphasia >> seizures, cerebral edema
- Corticosteroids are mainstay; prophylaxis with leviteracetam
- Tocilizumab may worsen ICANS; generally use only if concurrent CRS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Lee et al, BBMT 2018

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Motor findings‡	N/A			notor weakness such as hemiparesis or
Elevated ICP/ cerebral edema	N/A			bral edema on neuroimaging; decere- rticate posturing; or cranial nerve VI billedema; or Cushing's triad

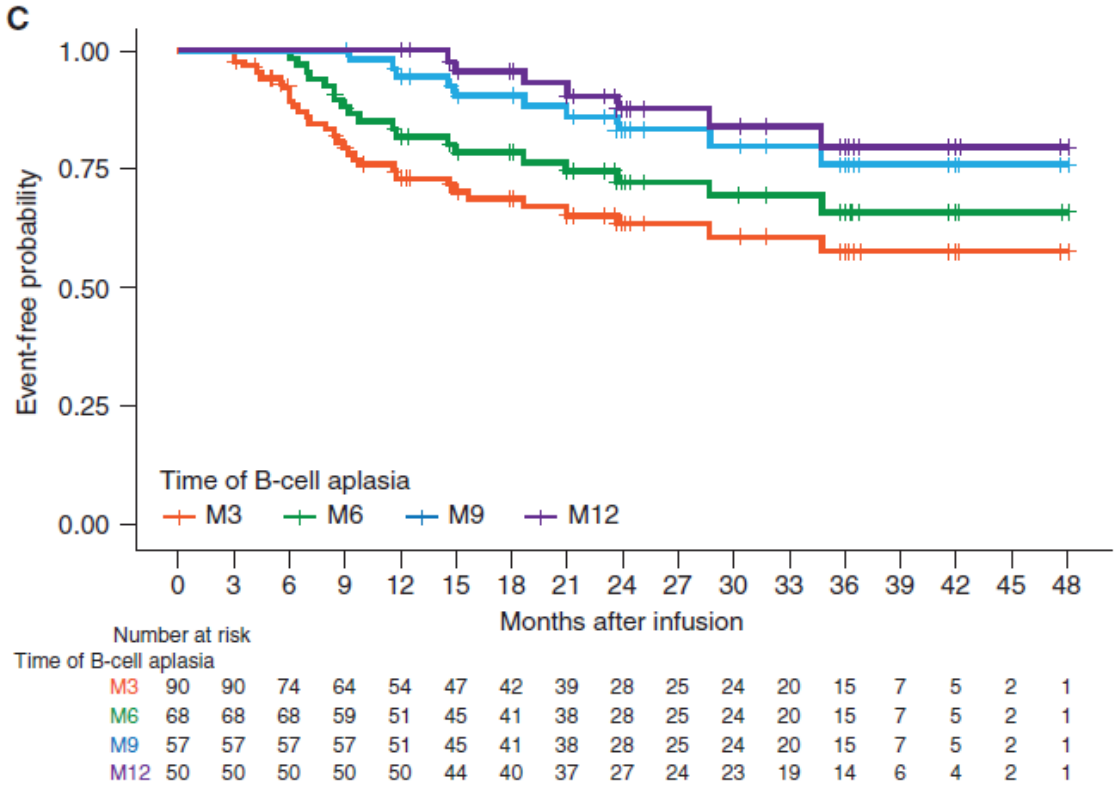
ICE

- **Orientation:** orientation to year, month, city, hospital: 4 points
- **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
- **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
- **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
- **Attention:** ability to count backwards from 100 by 10: 1 point

Lee et al, BBMT 2018

Major toxicities – B-cell aplasia

- On-target, off-tumor toxicity, results in hypogammaglobulinemia
- Increased risk of sinus/pulmonary infections, especially encapsulated
- IgG replacement (thresholds vary, minimum ≥400mg/dL)
- Correlates with disease response and functional persistence of CAR-T cells (Maude, NEJM 2014)



Pulsipher et al, Blood Cancer Disc 2022

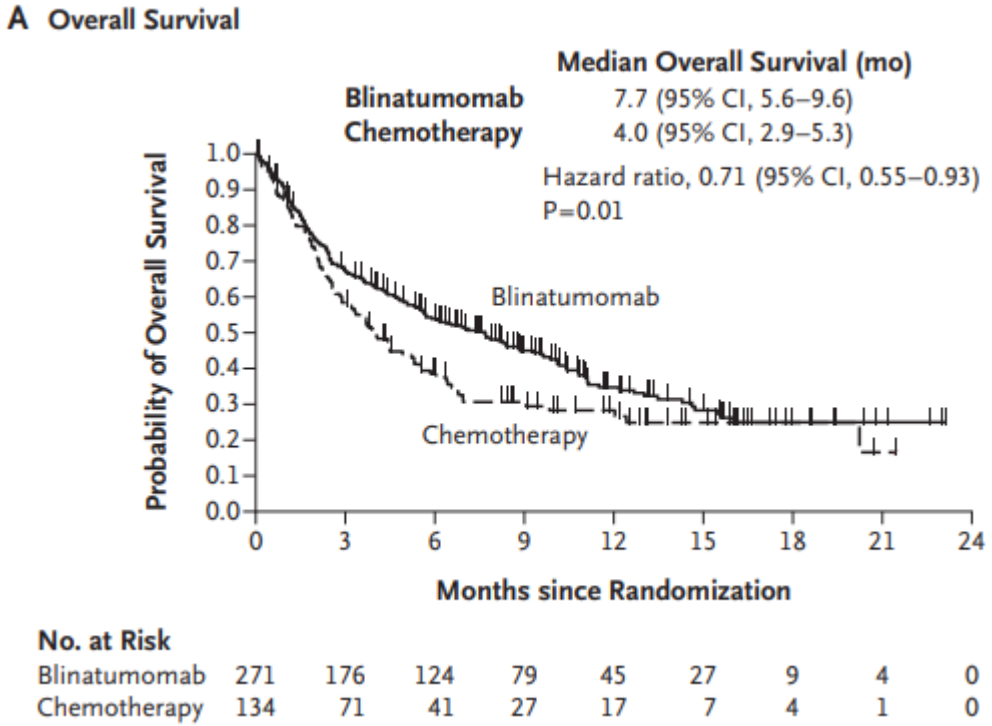
Outline

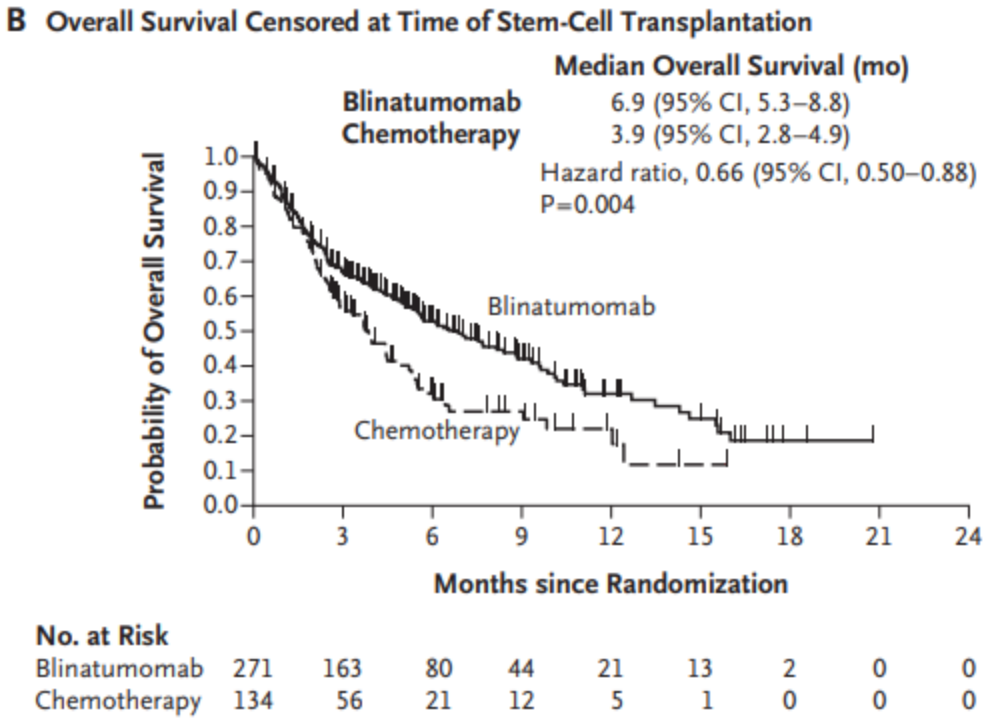
- Indications and mechanisms
- Major class toxicities
- Efficacy
- Toxicity
- Practical pearls

Blinatumomab – two indications

Indication	Reference	Intervention	OS	CR	CR/CRi/CRh	MRD-neg	Bridged to HCT
R/R B-ALL	*Kantarjian, NEJM 2017* Phase 3 "TOWER"	Blinatumomab (N=271)	7.7mo*	34%*	44%*	76%*	24%
		Chemotherapy (N=134)	4.0mo*	16%*	25%*	48%*	24%

* = Statistically significant difference





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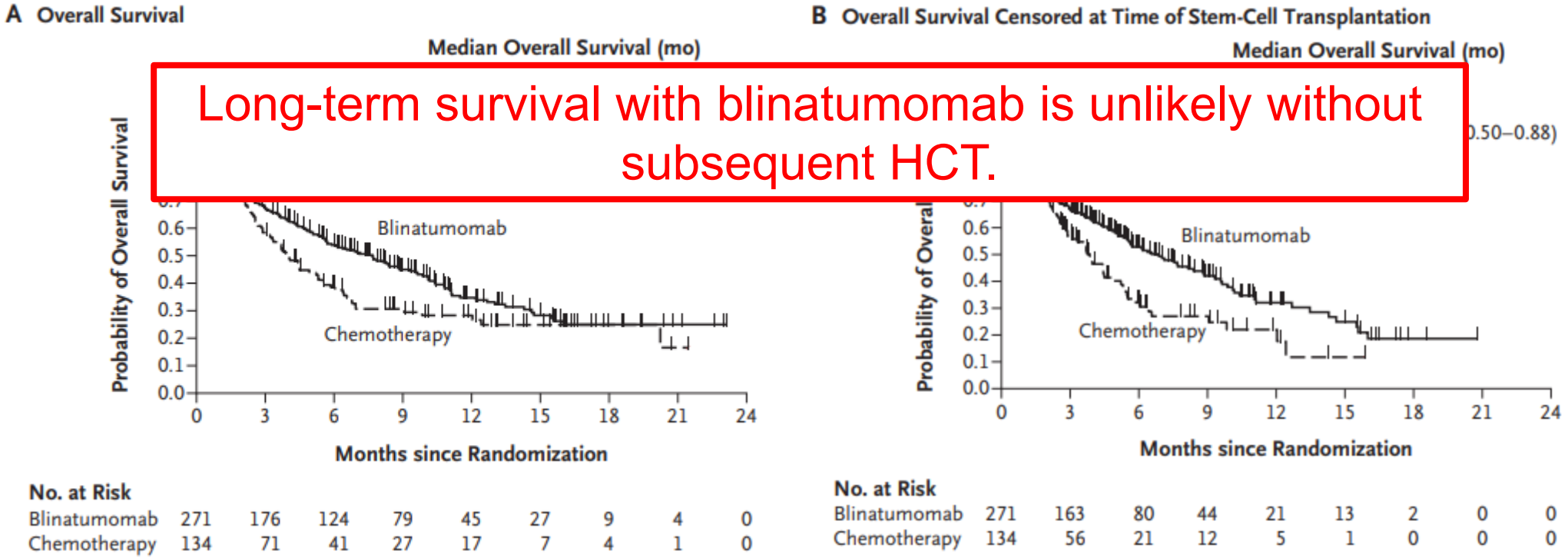
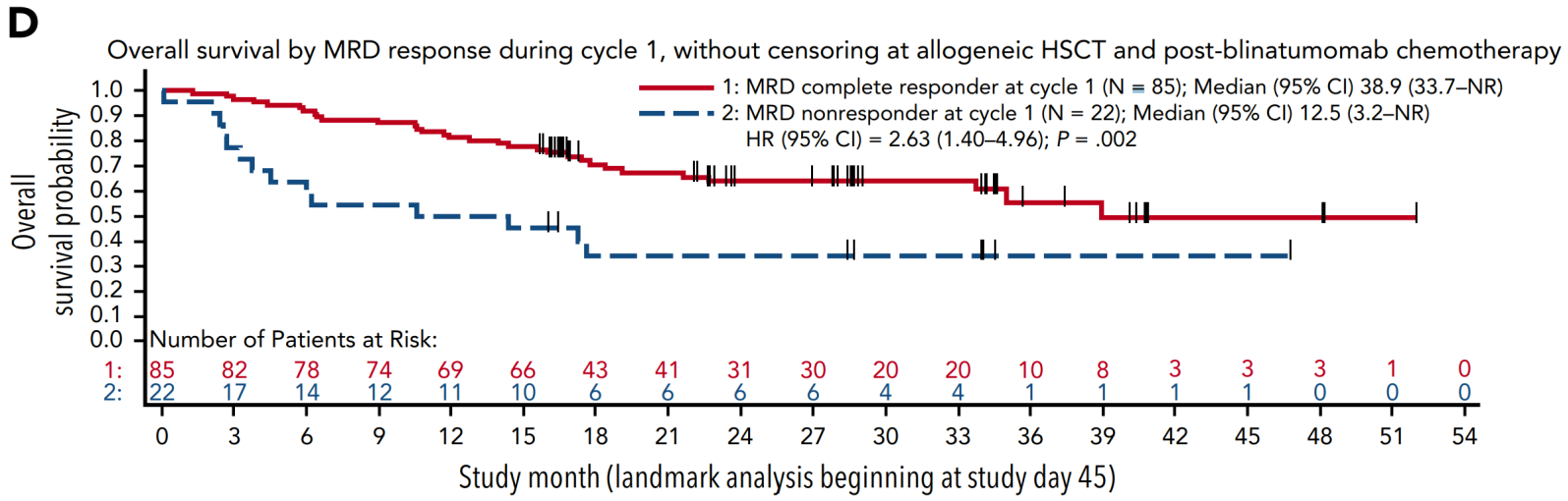
Long-term survival with blinatumomab is unlikely without subsequent HCT.



Blinatumomab – two indications

Indication	Reference	Intervention	OS	MRD-neg	Bridged to HCT
B-ALL in MRD+ CR	*Gökbuget, Blood 2018* Single-arm Phase 2 Patients with MRD+ CR after 3 blocks of intensive chemo	Blinatumomab (N=116, 111 were Ph-neg)	36.5mo If MRD-neg after cycle 1: 38.9mo If MRD-pos after cycle 1: 12.5mo	78% (after cycle 1)	67%



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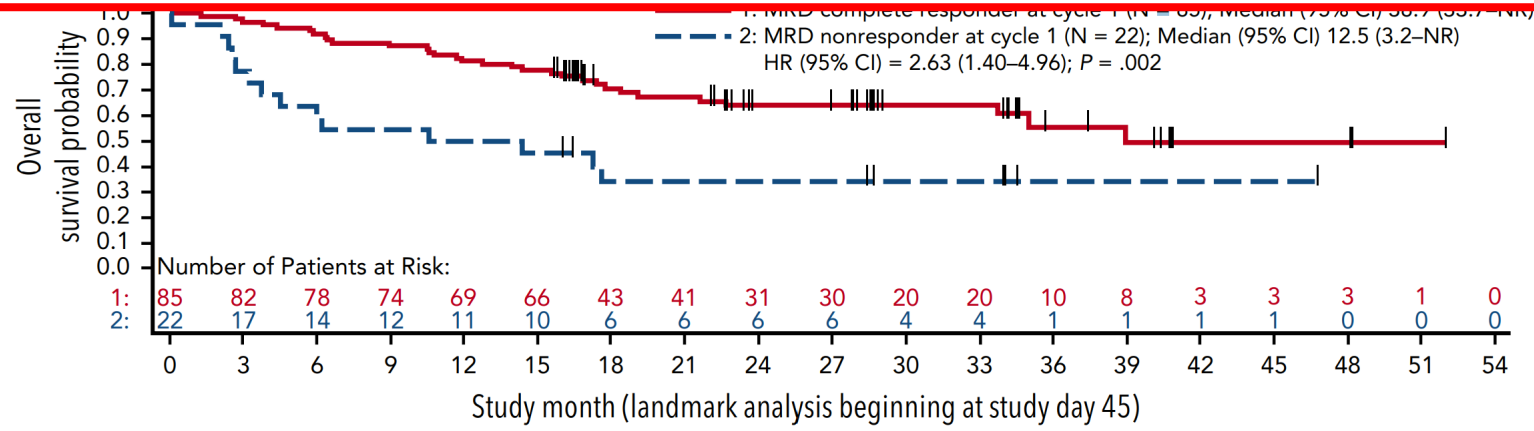
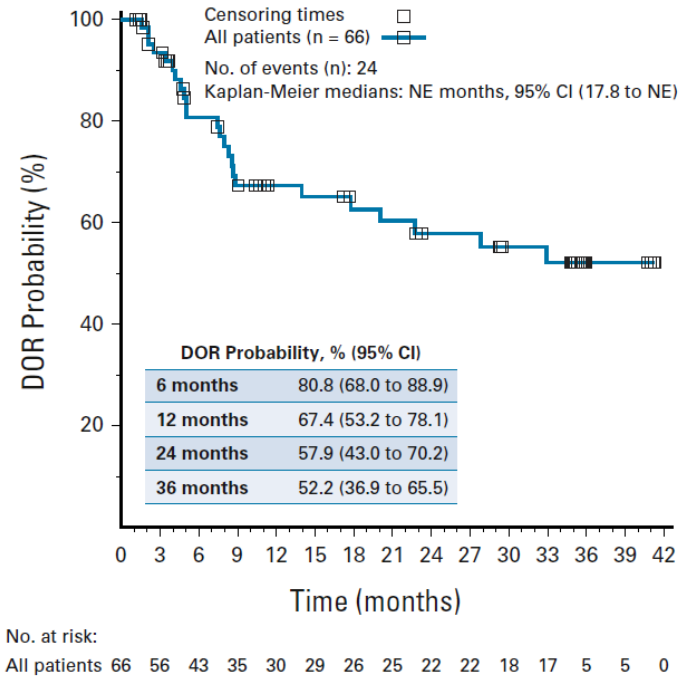
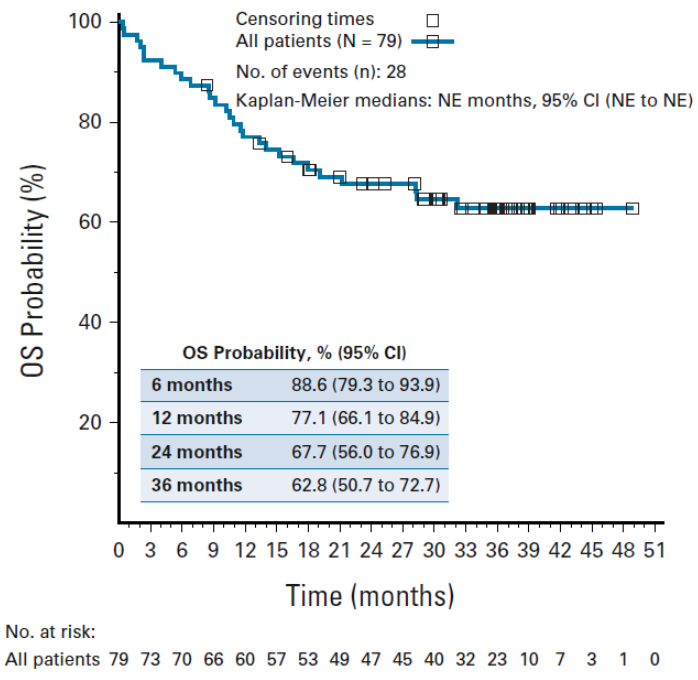
Blinatumomab is an excellent MRD "eraser." Facilitates bridging to HCT for long term survival.



CAR-T – two indications

Indication	Reference	Intervention	OS	CR/CRi	MRD-neg	Median DOR	CAR-T persistence	Bridged to HCT
AYA with R/R B-ALL (<26 years, ≥2 relapses)	*Maude, NEJM 2018* *Laetsch, JCO 2022* Phase 2 "ELIANA" Patients aged 3-21. No prior anti-CD19 therapy	Tisagenlecluecel (41BB co-stim) (N=75)	76% (@12 mo) 63% (@36 mo)	82% (@3 mo)	100%	Not reached	Median 168 days (range 20-617)	24%





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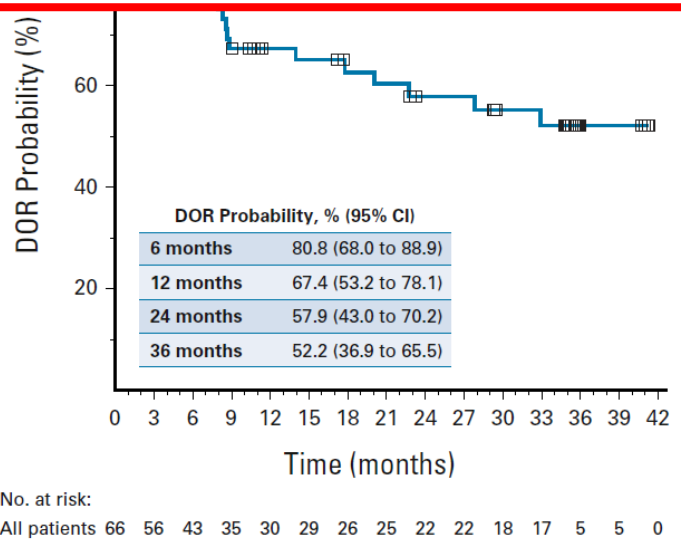
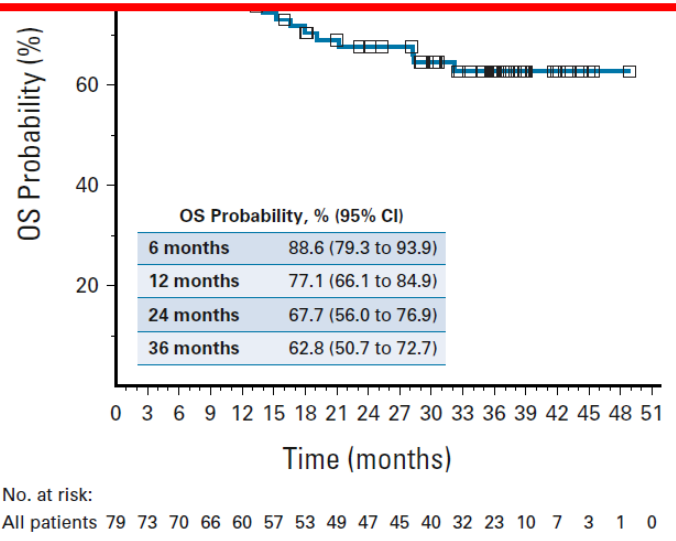
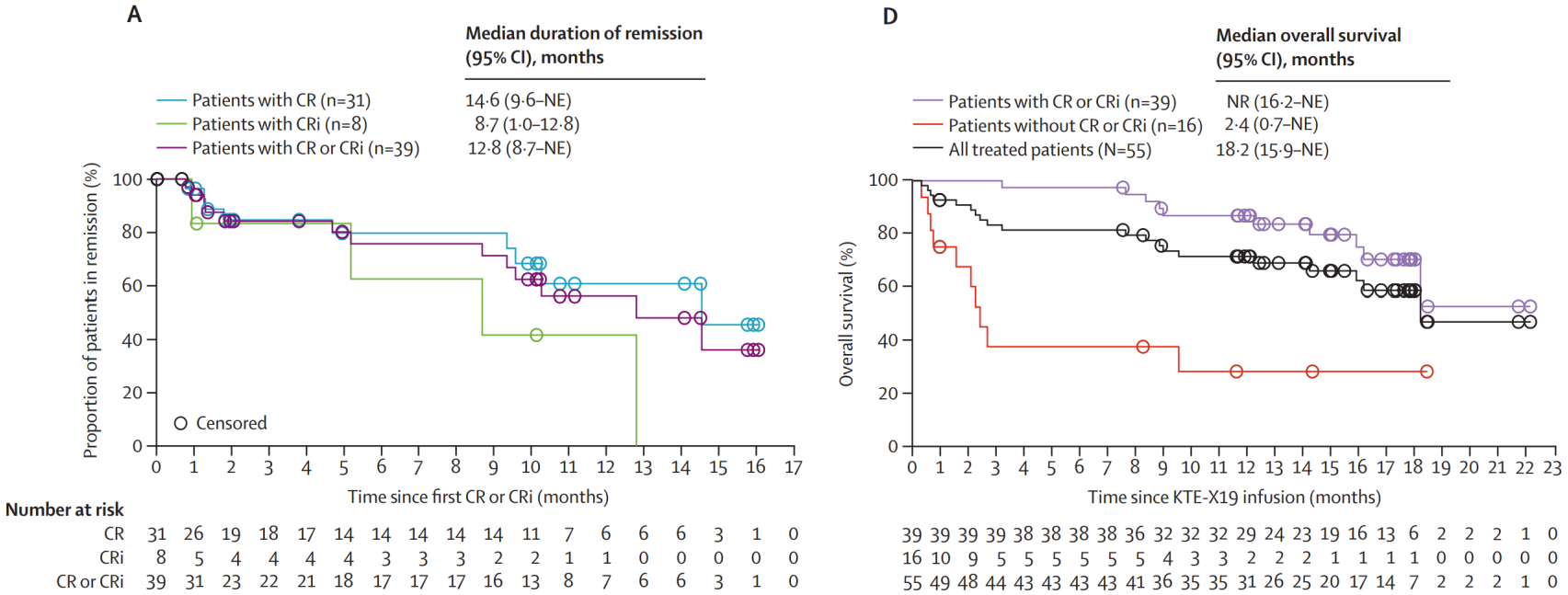
Long-term survival is possible with CAR-T in the absence of subsequent HCT.





CAR-T – two indications

Indication	Reference	Intervention	OS	CR/CRi	MRD-neg	Median DOR	CAR-T persistence	Bridged to HCT
Adults with R/R B-ALL	*Shah, Lancet 2021* Phase 2 “ZUMA 3” Patients aged >18. Prior blinatumomab allowed.	Brexucabtagene autoleucel (CD28 co-stim) (N=55)	18.2mo	71%	97%	12.8mo	21% persisting at 6 months	18%



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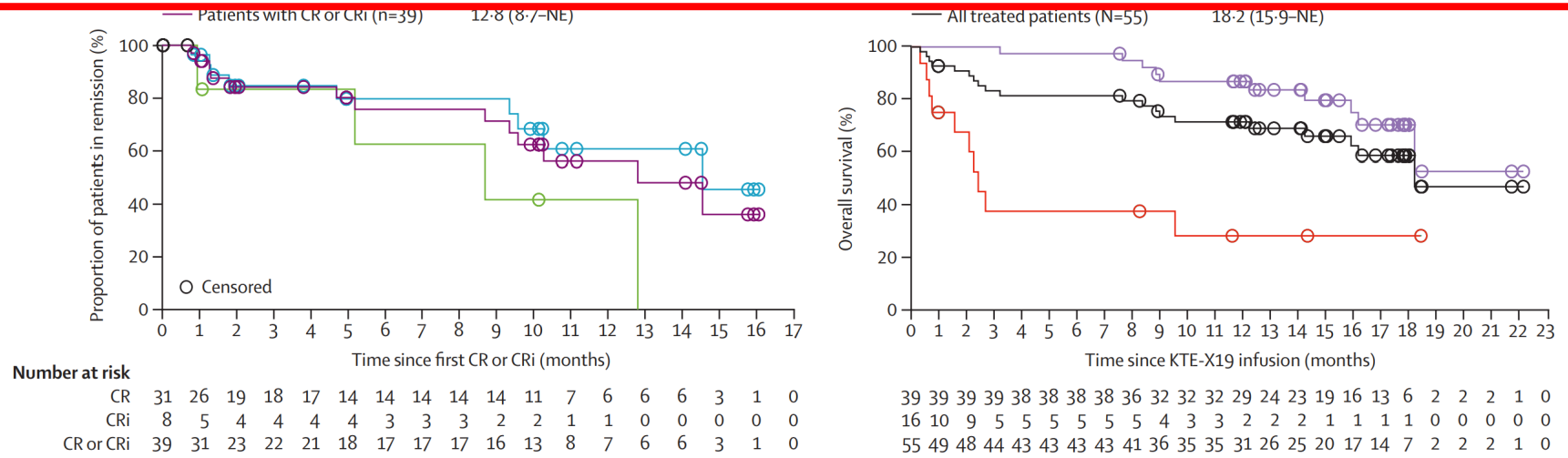
Outcomes are overall worse in the adult population, but long-term survival is still possible in the absence of HCT.



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Summary – toxicity

Indication	Reference	Intervention	Any ≥Gr 3	Neutropenia	Infection	LFT	CRS	Neurotoxicity
R/R B-ALL	*Kantarjian, NEJM 2017*	Blinatumomab	70.8%	37.8%	34.1%	12.7%	4.9%	9.4% - 2.9% AMS - 1.5% encephalopathy - 0.7% seizure
		Chemotherapy	79.8%	57.8%	52.3%	14.7%	0%	8.3% - 2.8% seizure - 2.8% headache
B-ALL in MRD+ CR	*Gökbuget, Blood 2018* Patients with MRD+ CR after 3 blocks of intensive chemo	Blinatumomab	60%	16%	0%	~5%	1.7% (all in cycle 1)	13% - 5% encephalopathy - 5% tremor

Indication	Reference	Intervention	Any ≥Gr 3	B-cell aplasia	Infection	CRS	Neurotoxicity
AYA with R/R B-ALL (<26 years, ≥2 relapses)	*Maude, NEJM 2018* Patients aged 3-21. No prior anti-CD19 therapy	Tisagenlecluecel (41BB co-stim)	69% ≤8 wks 17% >8 wks	83% B-cell aplasia at 6 months	24% ≤8 wks	46% ≤8 wks (77% any grade) 0% >8 wks	13% ≤8 wks (40% any grade) - 5% encephalopathy ≤8 wks, 0% >8 wks
Adults with R/R B-ALL	*Shah, Lancet 2021* Patients aged >18. Prior blinatumomab allowed.	Brexucabtagene autoleucel (CD28 co-stim)	95%	10/12 responders recovered at 12 months	25%	24% (89% any grade)	26% (60% any grade) (18% grade 5) - 7% encephalopathy - 4% confusion - 2% tremor

Summary – toxicity

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Toxicity with blinatumomab is much less in the MRD+ setting than in frank relapse.

Indication								icity
AYA with R/R B-ALL (<26 years, ≥2 relapses)	anti-CD19 therapy			months			0% >8 wks	ks grade) - 5% encephalopathy ≤8 wks, 0% >8 wks
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CAR-T products have higher rates of CRS and ICANS than blinatumomab.

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B-ALL in M CR								phalopathy r

Among CAR-T options, 41BB product appears to have greater persistence and lower rates of toxicity (not firmly established).

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Summary – efficacy & toxicity

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R/R B-ALL	*Kantarjian, NEJM 2017*	Blinatumomab	7.7mo	34%	44% (CR/CRi/CRh)	76%	4.9%	9.4%
		Chemotherapy	4.0mo	16%	25% (CR/CRi/CRh)	48%	0%	8.3%
B-ALL in MRD+ CR	*Gökbuget, Blood 2018* Patients with MRD+ CR after 3 blocks of intensive chemo	Blinatumomab	36.5mo	N/A		78% (after cycle 1)	1.7% (all w/in cycle 1)	13%
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Adults with R/R B-ALL	*Shah, Lancet 2021* Patients aged >18. Prior blinatumomab allowed.	Brexucabtagene autoleucel (CD28 co-stim)	22.4mo	56%	71%	97%	24%	26% (18% grade 5)

*CR+CRi+CRh for *Kantarjian, NEJM 2017*. CR+CRi for all other studies

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		Chemotherapy	4.0mo	16%	25% (CR/CRi/CRh)	48%	0%	8.3%
B-ALL in MRD+ CR	*Gökbuget, Blood 2018* Patients with MRD+ CR after 3 blocks of intensive chemo	Blinatumomab	36.5mo	N/A		78% (after cycle 1)	1.7% (all w/in cycle 1)	13%
AYA with R/R B-ALL (<26 years, ≥2 relapses)	*Maude, NEJM 2018* *Laetsch, JCO 2022* Patients aged 3-21. No prior anti-CD19 therapy	Tisagenlecluecel (41BB co-stim)	76% (@12mo) 63% (@36 mo)	60% (@3mo)	82% (@3mo)	100%	46% (w/in 8 wks)	13% (w/in 8 wks)
Adults with R/R B-ALL	*Shah, Lancet 2021* Patients aged >18. Prior blinatumomab allowed.	Brexucabtagene autoleucel (CD28 co-stim)	22.4mo	56%	71%	97%	24%	26% (18% grade 5)

*CR+CRi+CRh for *Kantarjian, NEJM 2017*. CR+CRi for all other studies

Blinatumomab: Less toxicity, long-term survival depends on subsequent HCT.
CAR-T: Greater toxicity, longer survival without needing HCT.

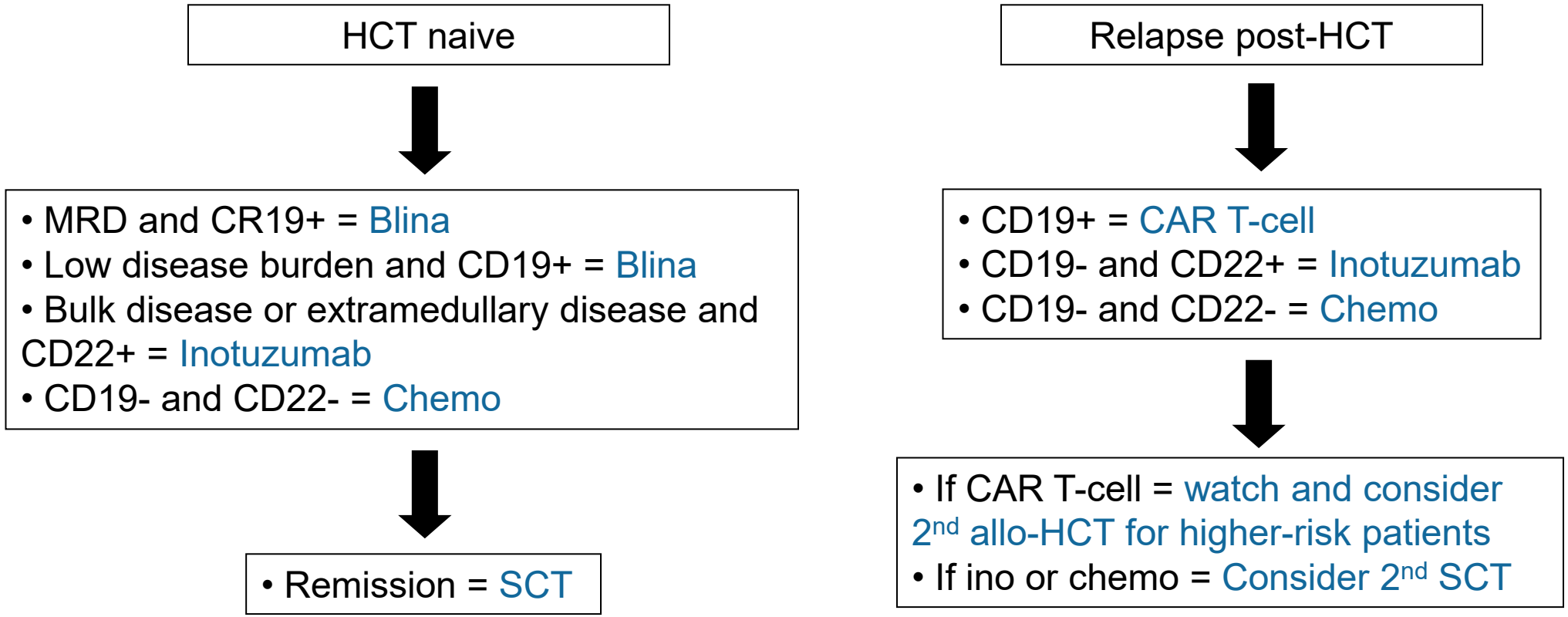
Outline

- Indications and mechanisms
- Major class toxicities
- Efficacy
- Toxicity
- Practical pearls

Practice pearls

Blinatumomab	CAR-T
Primarily outpatient	Inpatient
“Off-the-shelf”	Requires time and infrastructure for autologous production) Will likely need cytoreductive/bridging chemotherapy during this time
Milder CRS and neurotoxicity	Higher toxicity, 18% grade 5 in ZUMA-3
Bridge to HCT	Durable remissions have been observed without HCT

Current treatment algorithm for R/R B-ALL



On the horizon…

LBA-1 Consolidation Therapy with Blinatumomab Improves Overall Survival in Newly Diagnosed Adult Patients with B-Lineage Acute Lymphoblastic Leukemia in Measurable Residual Disease Negative Remission: Results from the ECOG-ACRIN E1910 Randomized Phase III National Cooperative Clinical Trials Network Trial

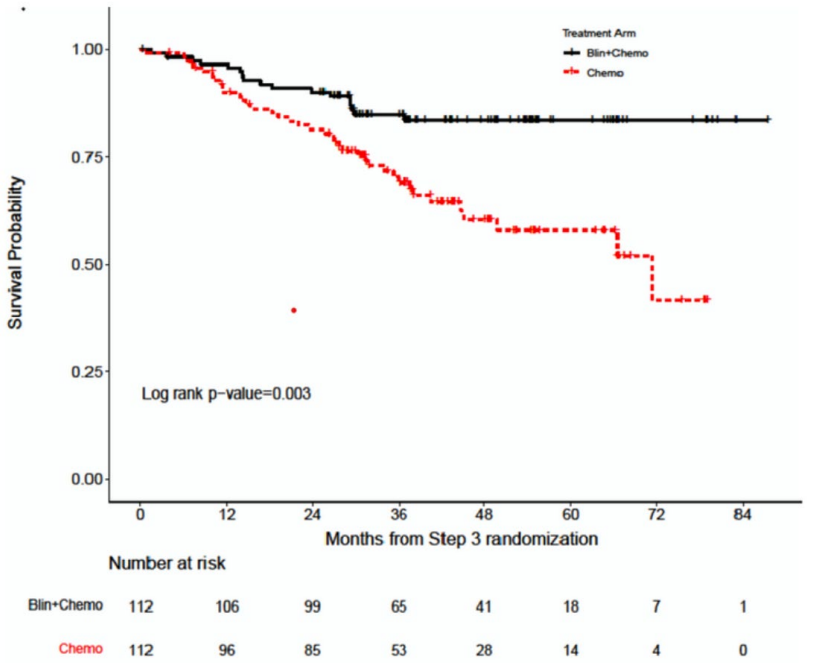
Program: General Sessions
Session: Late-Breaking Abstracts Session
Hematology Disease Topics & Pathways:
ALL, Biological therapies, Lymphoid Leukemias, Clinical Practice (Health Services and Quality), Bispecific Antibody Therapy, Diseases, Therapies, Lymphoid Malignancies

Tuesday, December 13, 2022, 9:00 AM-10:30 AM

Mark R. Litzow, MD[1], *Zhuoxin Sun, PhD*[2*], *Elisabeth Paietta, PhD*[3], *Ryan J. Mattison, MD*[4], *Hillard M Lazarus, MD*[5], *Jacob M. Rowe, MB, BS*[6], *Daniel A. Arber, MD*[7], *Charles G. Mullighan, MBBS, MD*[8], *Cheryl L Willman, MD*[9], *Yanming Zhang, MD*[10], *Matthew Wieduwilt, MD*[11*], *Michaela Liedtke, MD*[12], *Julie Bergeron, MD*[13], *Keith W. Pratz, MD*[14], *Shira Dinner, MD*[15], *Noelle V. Frey, MD, MS*[16], *Steven D. Gore, MD*[17], *Bhavana Bhatnagar, DO*[18], *Ehab L. Atallah, MD*[19], *Geoffrey L. Uy, MD*[20], *Deepa Jeyakumar, MD*[21], *Tara L. Lin, MD*[22], *Richard F. Little, MD, MPH*[23], *Selina M. Luger, MD, FRCPC*[24] *and Martin S. Tallman, MD*[25]

- N=224 pts with MRD-negative (≤ 0.01%) CR/CRi following induction therapy
- Randomized to consolidation chemo or blinatumomab-based consolidation

Figure 2: Overall Survival



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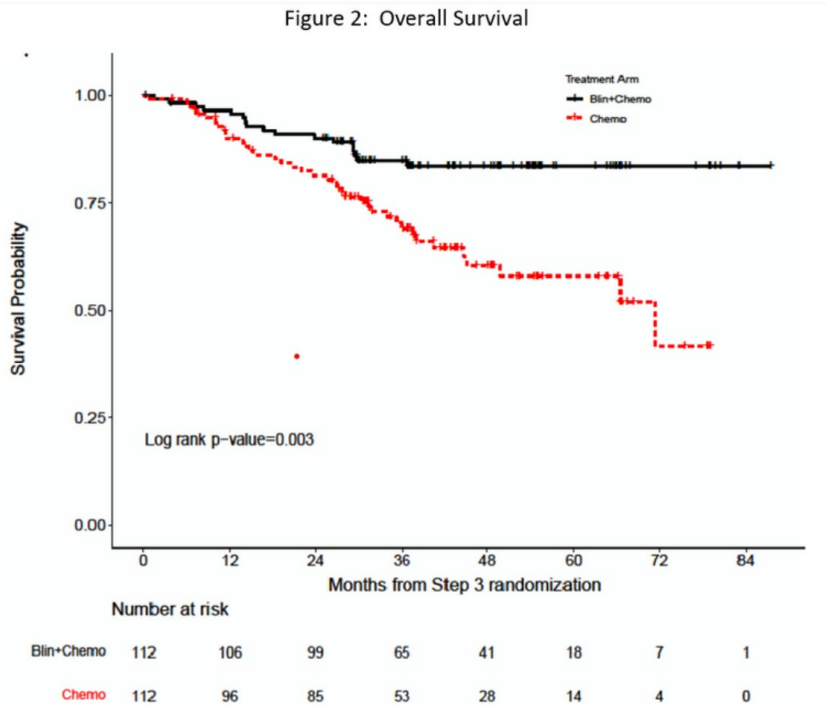
Program: General Sessions
Session: Late-Breaking Abstracts Session
Hematology Disease Topics & Pathways:

Should all CD19+ patients receive blinatumomab in consolidation?
Is HCT still necessary in this context for long-term survival?

- N=224 pts with MRD-negative (≤ 0.01%) CR/CRi following induction therapy
- Randomized to consolidation chemo or blinatumomab-based consolidation



Thank you!

DFCI Adult Leukemia Program

- Daniel DeAngelo, MD, PhD
- Richard Stone, MD
- Martha Wadleigh, MD
- Jacqueline Garcia, MD
- Marlise Luskin, MD
- Eric Winer, MD
- Max Stahl, MD
- Virginia Volpe, MD
- Andy Lane, MD, PhD
- Coleman Lindsley, MD, PhD
- Anthony Letai, MD, PhD
- Rahul Vedula, MD
- Chris Reilly, MD
- Lachelle Weeks, MD
- Ilene Galinsky, NP
- Mary Gerard, PA-C
- Theresa Nguyen, NP
- Ryan Osborn, PA-C
- Donna Neuberg, ScD
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- Robert Soiffer, MD