



Advances in Cancer Immunotherapy™

Monoclonal Antibodies and Antibody-Drug Conjugates: Pediatric Update

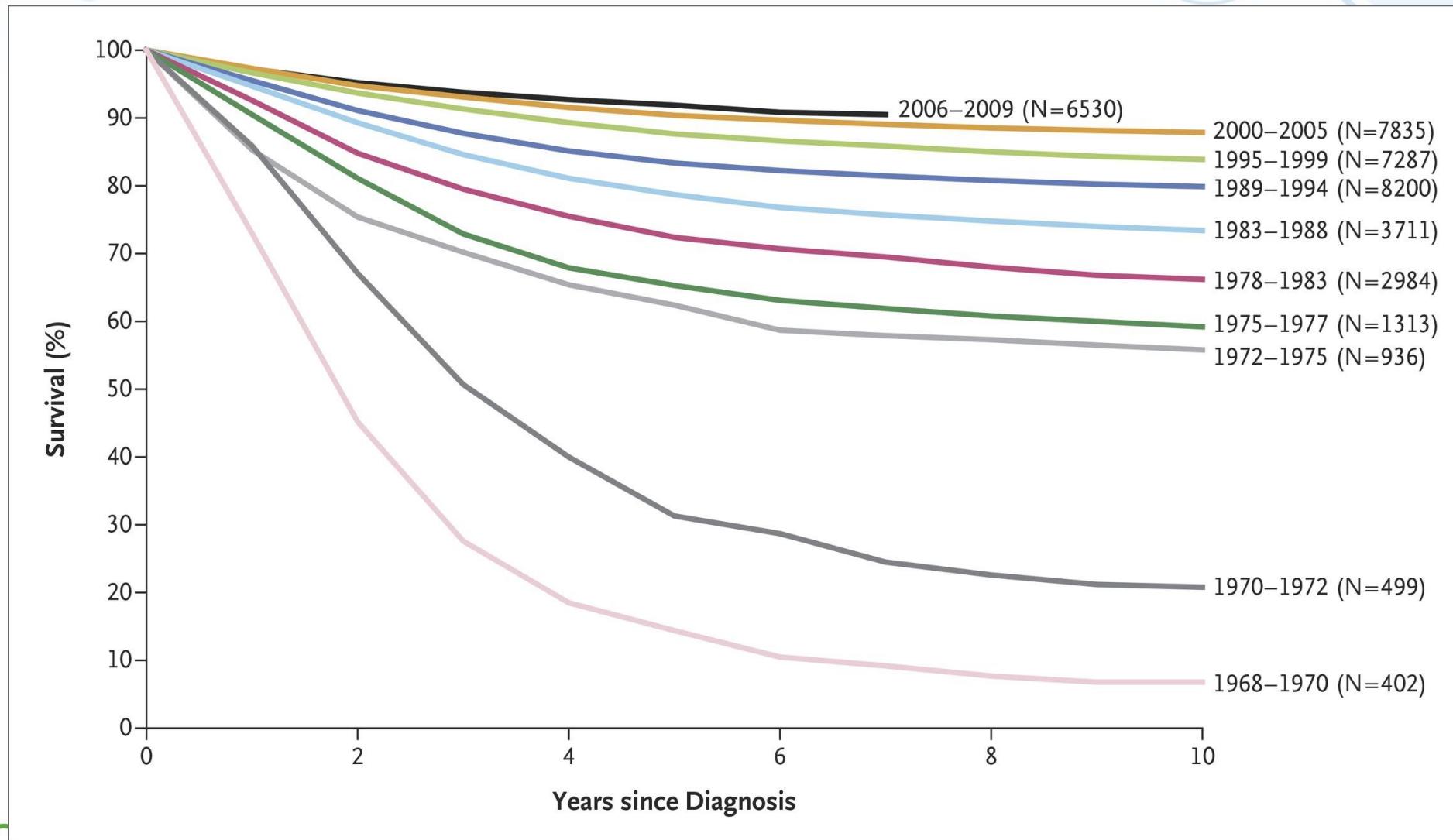
Patrick Brown, MD
Professor of Oncology and Pediatrics
Director, Pediatric Heme Malignancies Program
Johns Hopkins University

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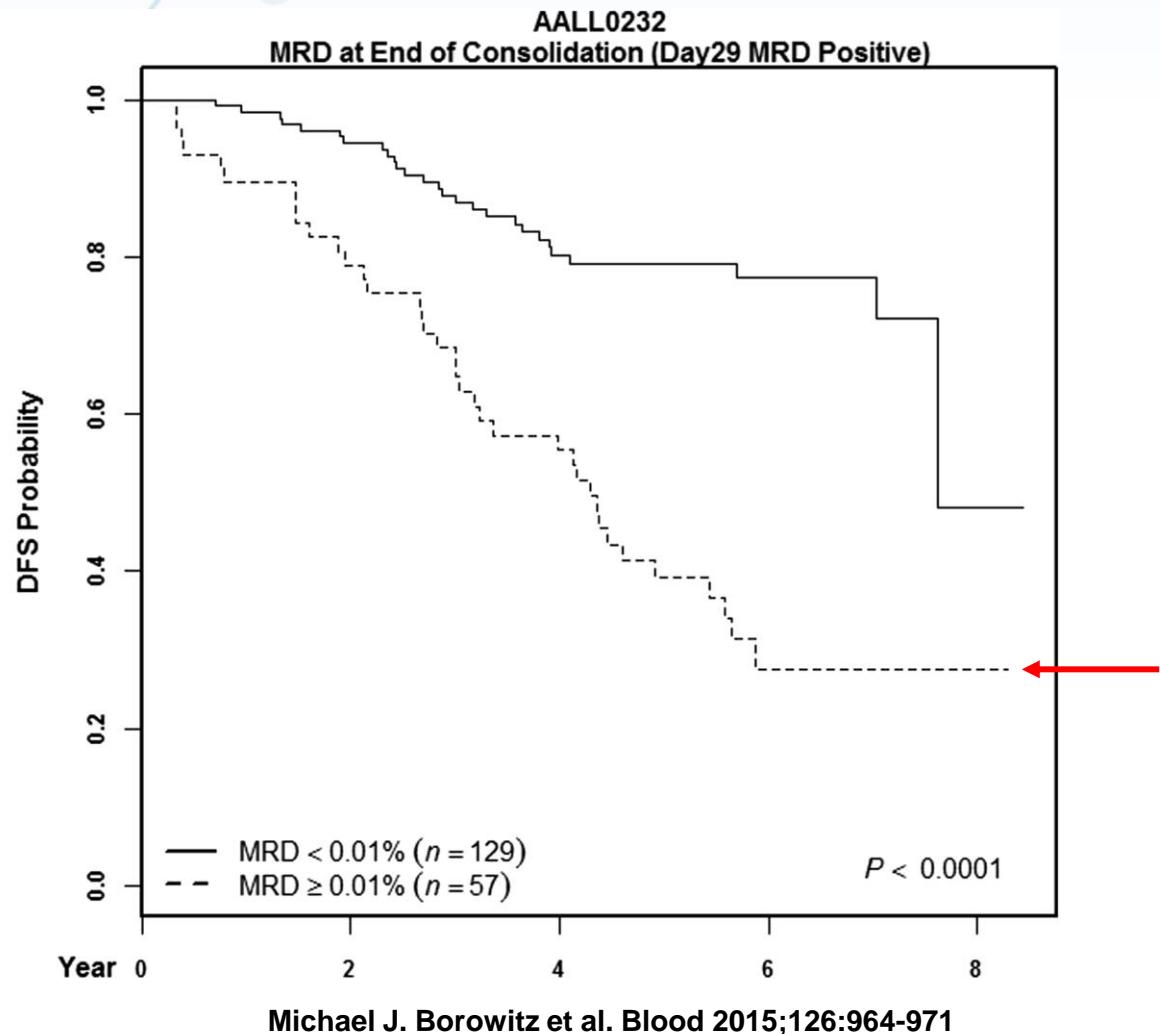
Disclosures

- Consulting Fees: Novartis Pharmaceuticals Corp; Takeda Pharmaceuticals North America, Inc.; Amgen Inc; Kura Oncology, Inc.; Kite Pharma
- I will be discussing non-FDA approved indications during my presentation.

Newly Diagnosed Pediatric ALL



High Risk Subsets of Pediatric ALL



MRD determined by multi-parameter flow cytometry

5-year DFS by EOC MRD

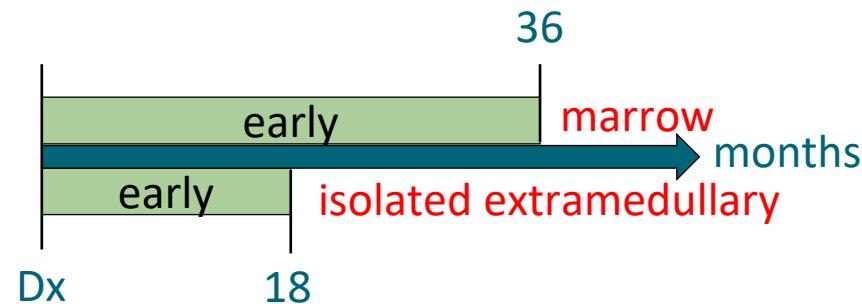
MRD <0.01%: 79% ± 5%

MRD ≥0.01%: 39% ± 7%

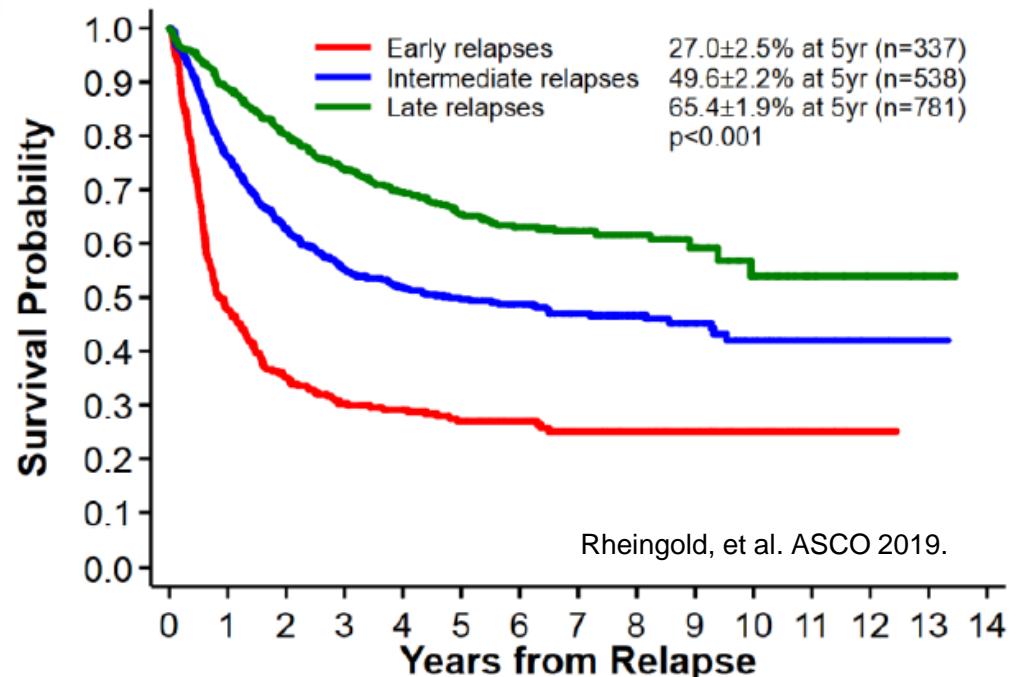
Other very high risk CR1:

- *HR genetics (hypo, KMT2A-r, iAMP21) with EOI MRD+*
- *Infants with KMT2A-r*

Poor survival for 1st relapse B-ALL,
especially early relapses

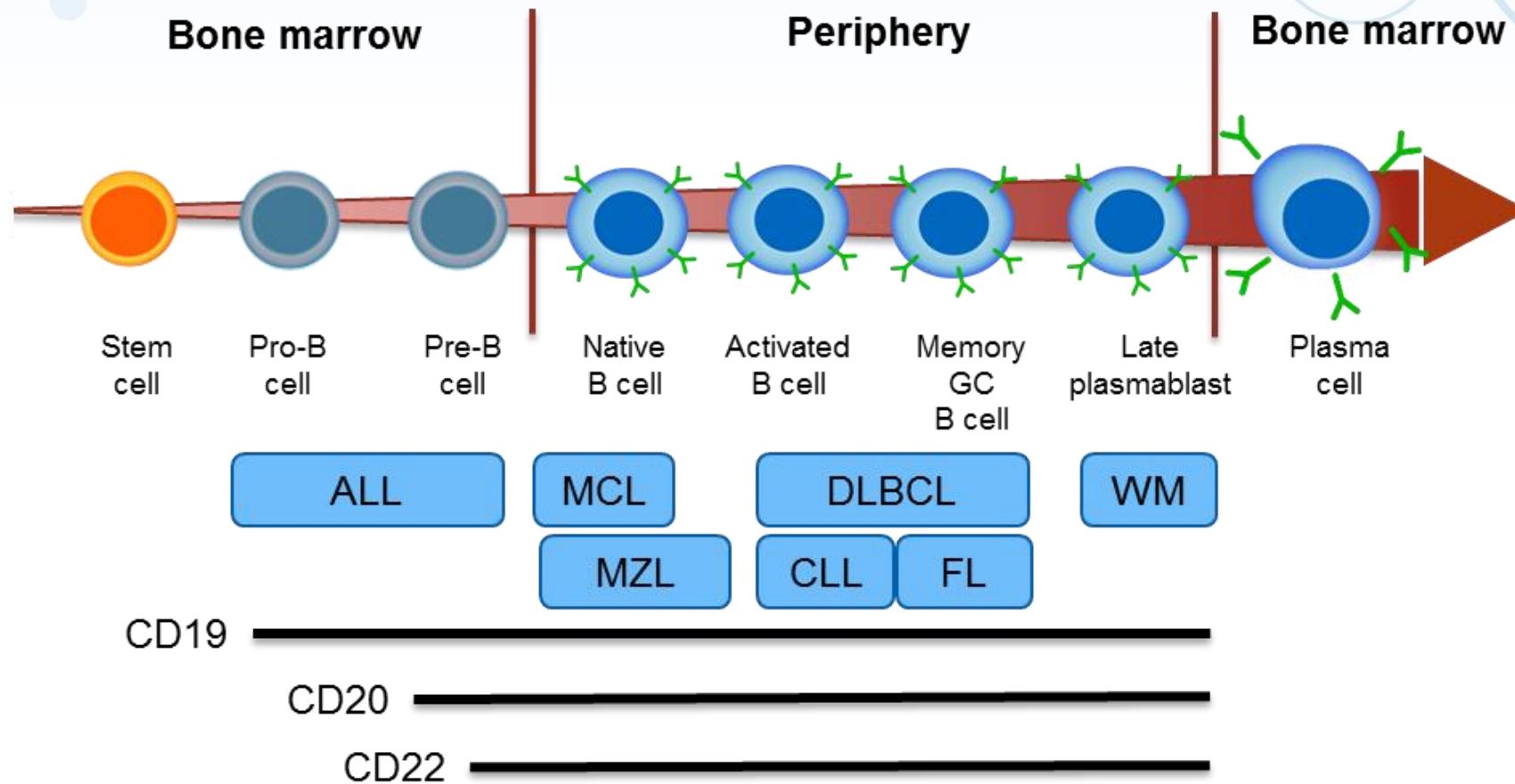


Relapsed Pediatric/AYA ALL



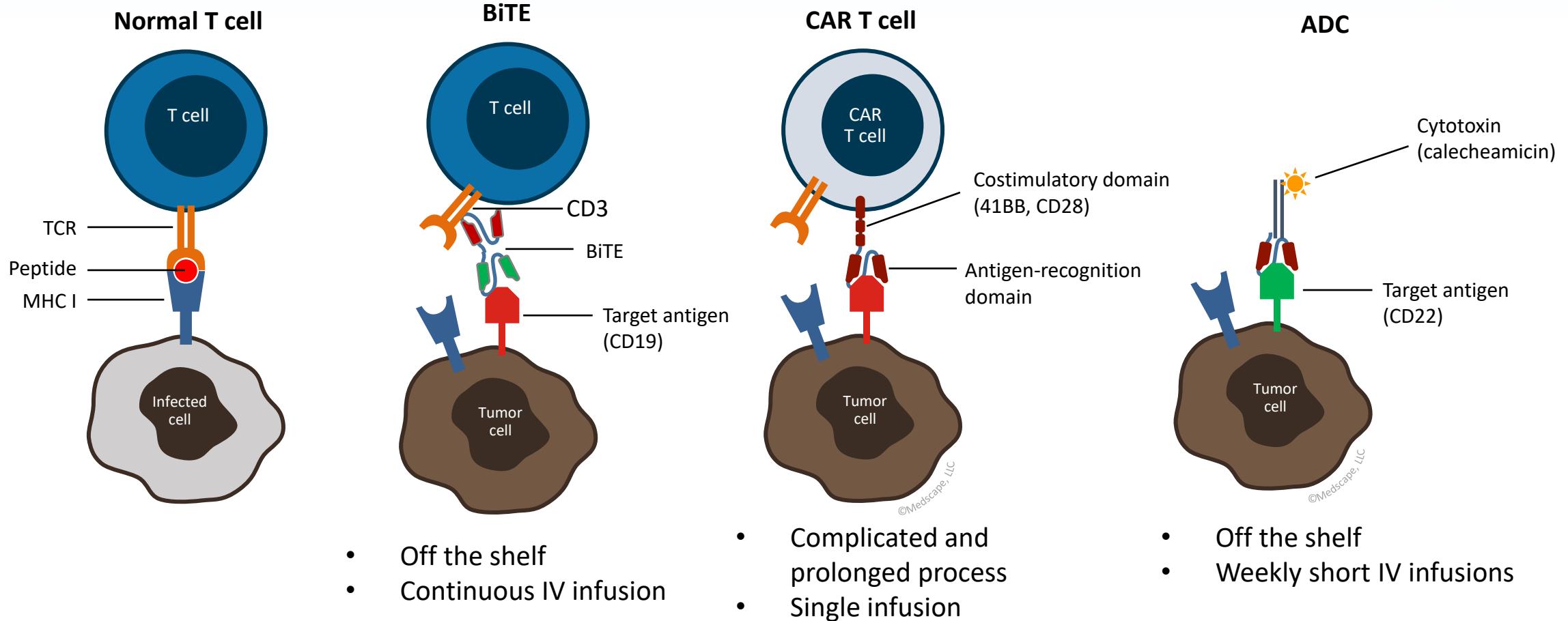
How can we improve on this “standard”?

CD19, CD20, CD22: Rational Targets for Therapy



- CD19, CD20 and CD22 are not expressed on bone marrow stem cells or other tissues
- The complete loss of normal B-cells is, at least for limited period, tolerable

Mechanism: Normal vs. BiTE vs. CAR vs. ADC



Response Rates and Survival in Relapsed/Refractory B-ALL

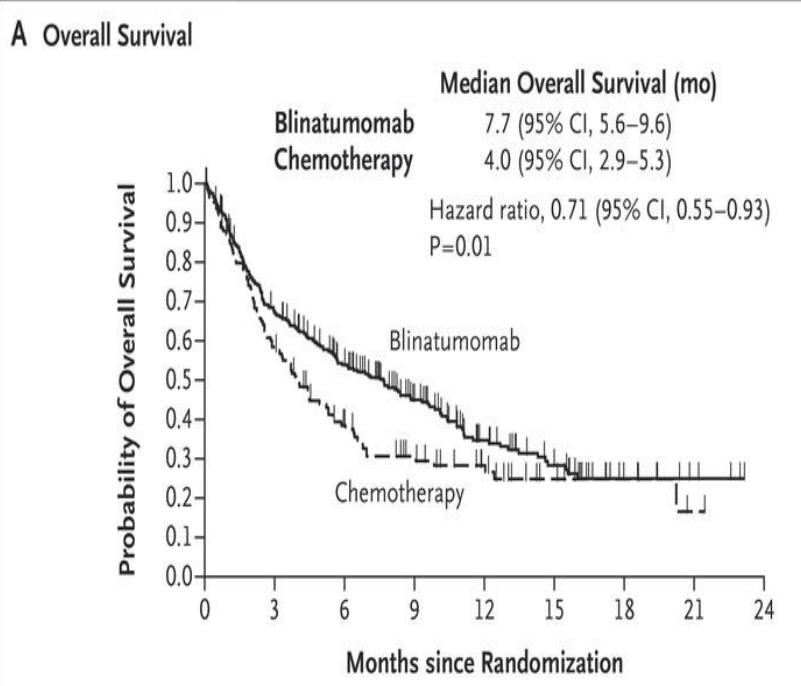
Agent	Type	Target	Responses (CR / MRD-)	Toxicities	FDA indication	Cost
Blinatumomab ^{1,2}	BiTE	CD19	42-44% / 22-33%	CRS, neurotoxicity	Adult and pediatric R/R B-ALL, MRD+	\$180K
Inotuzumab ^{3,4}	Immuno-conjugate	CD22	58-81% / 38-63%	Hepatotoxicity	Adult R/R B-ALL	\$168K
Tisagenlecleucel ⁵	CAR T cell	CD19	81% / 81%	CRS, neurotoxicity	Refractory or 2 nd /greater relapse; age up to 26 years	\$475K

1. Kantarjian H, et al. N Engl J Med. 2017;376:836-847; 2. von Stackelberg, et al. J Clin Oncol. 2016;34:4381-4389 3. Kantarjian H, et al. N Engl J Med. 2016;375:740-753; 4. O'Brien, et al. Blood . 2019;134:741; 5. Maude SL, et al. N Engl J Med. 2018;378:439-448.

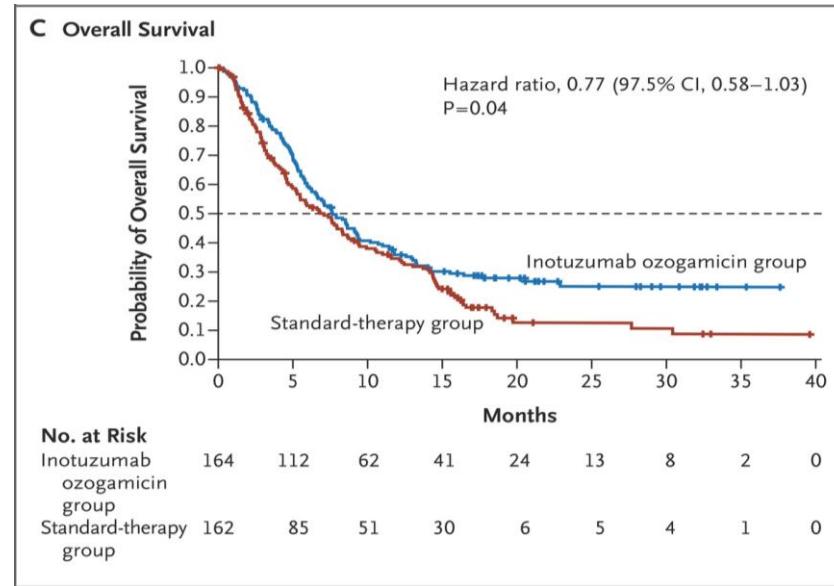
Unprecedented initial response rates . . . BUT . . .

Survival in R/R ALL

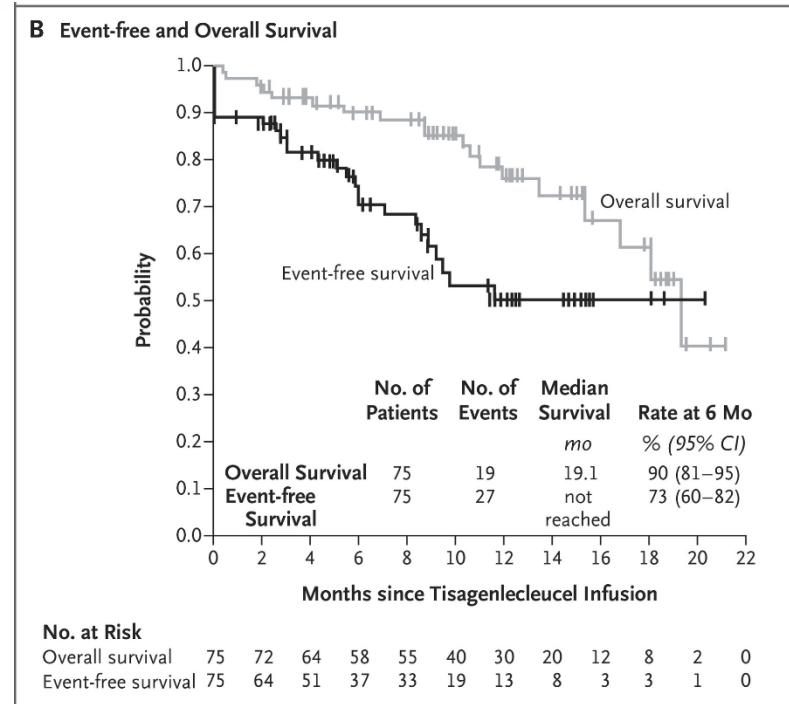
Blinatumomab¹



Inotuzumab Ozogamicin²



Tisagenlecleucel³



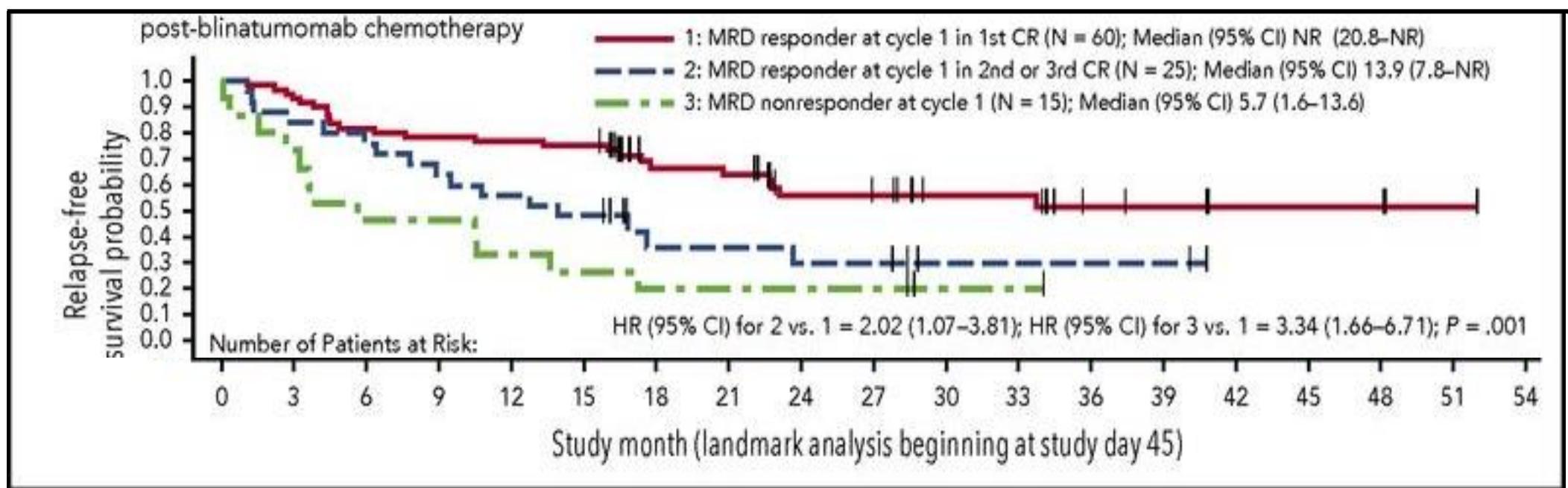
Blina: Improved survival initially, but not durable

Ino: Improved survival initially, but not durable

Tisa: Durable survival improvement, but long-term EFS ~50%

Blinatumomab in MRD+ B-ALL (Adults)

- N = 116 adults, international multicenter single-arm Ph 2 (BLAST trial)
- MRD+ ($>10^{-3}$); 65% in CR1 (rest CR2+)
- MRD cleared in 78%; most proceeded to HSCT
- ~60% RFS in CR1
- Compared to ~30% in historical control

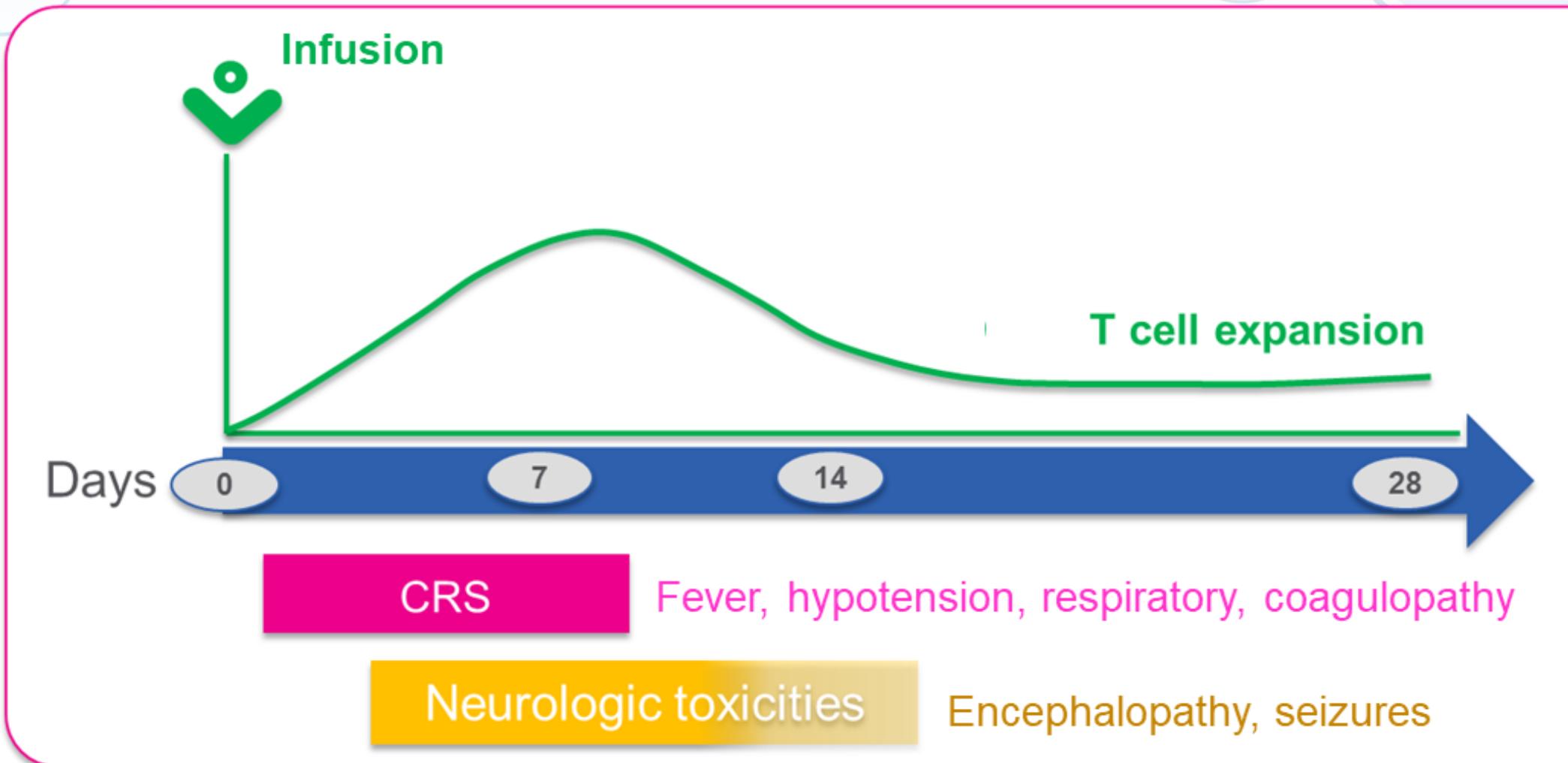


Adverse Events in Relapsed/Refractory B-ALL

Agent	Type	Target	Responses (CR / MRD-)	Toxicities	FDA indication	Cost
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AEs After Blinatumomab and CAR T Cells

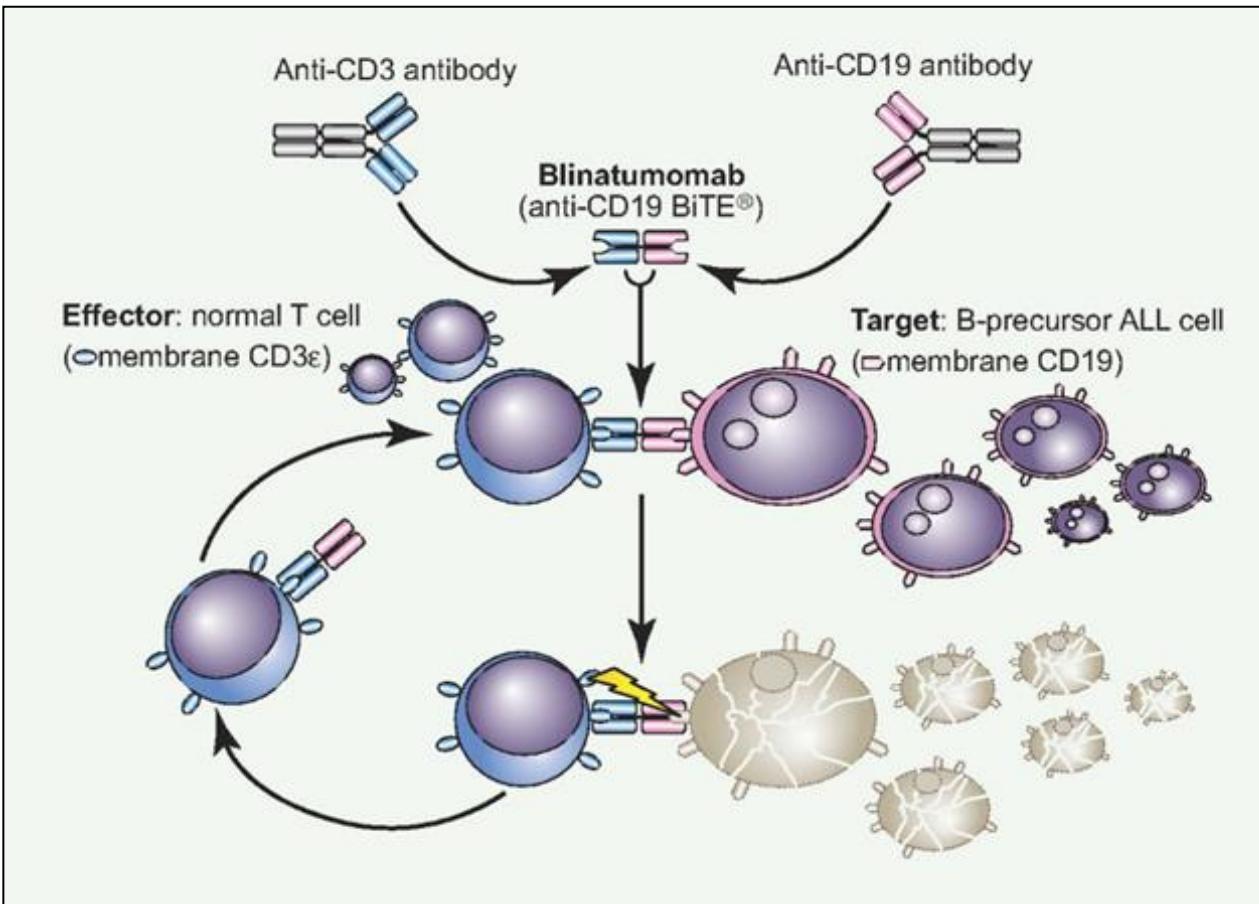


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Figure adapted from/courtesy of Novartis.

Blinatumomab (CD19 BiTE)



Adapted from Brown P. *Blood*. 2018; 131: 1497–1498

- In multiple relapsed/refractory setting (peds and adults)
 - CR 40-45%
 - MRD-negative CR 20%–35%
 - Early survival benefit (adults)

Kantarjian H, et al. *N Engl J Med*. 2017;376:836-847
von Stackelberg et al. *JCO*. 2016; 34:4381-4389

- In MRD+ setting (adults)
 - 80% MRD clearance
 - 60% subsequent DFS (bridge to HSCT)

Gokbuget et al. *Blood*. 2018; 131: 1522-1531

Objective of COG AALL1331:
To determine if substituting blinatumomab for intensive consolidation chemotherapy improves survival in 1st relapse of childhood/AYA B-ALL

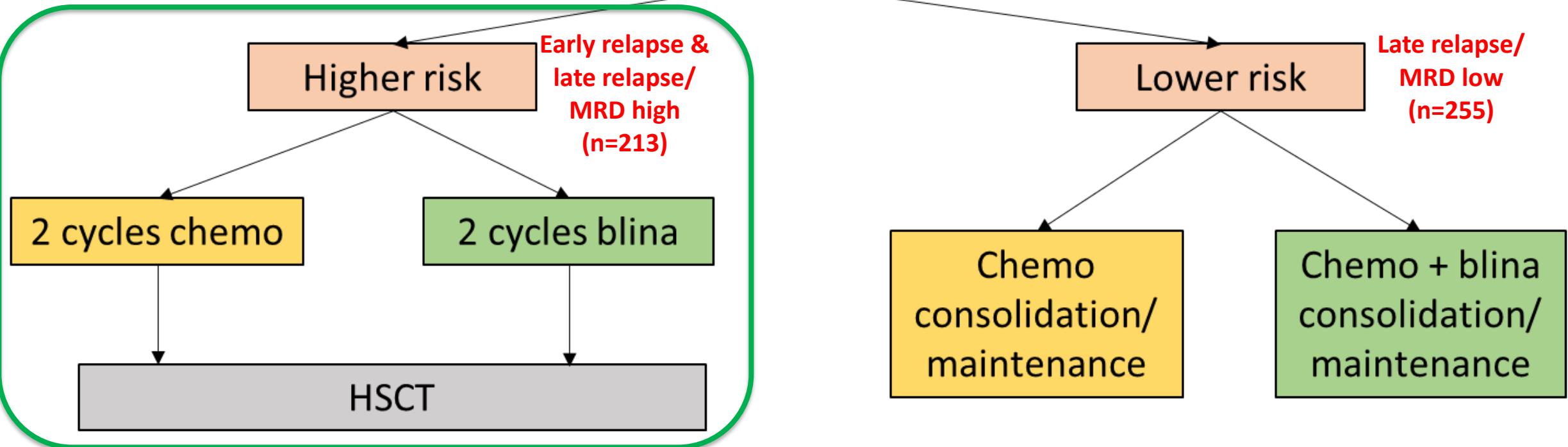
AALL1331: “Big Picture”

- All first relapse (any CR1 duration, any site)
- Ages 1-30
- Major exclusions: Down syndrome, Ph+, prior HSCT, prior blinatumomab

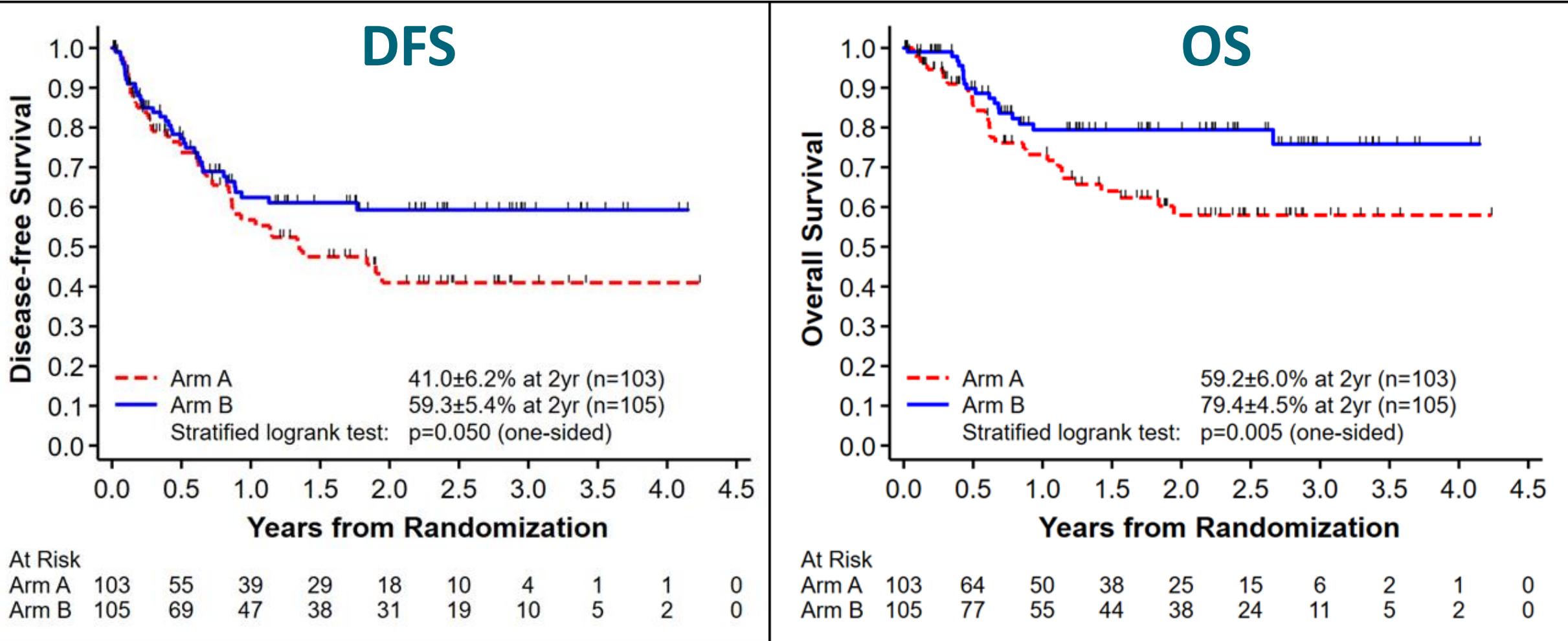
UKALLR3, Mitoxantrone Arm*

- DEX 20 mg/m²/day Days 1-5, 15-19
- VCR 1.5 mg/m² Days 1, 8, 15, 22
- PEG 2500 IU/m² Days 3, 17
- Mitoxantrone 10 mg/m² Days 1, 2
- IT MTX Day 1, then IT MTX or ITT

Chemo
reinduction



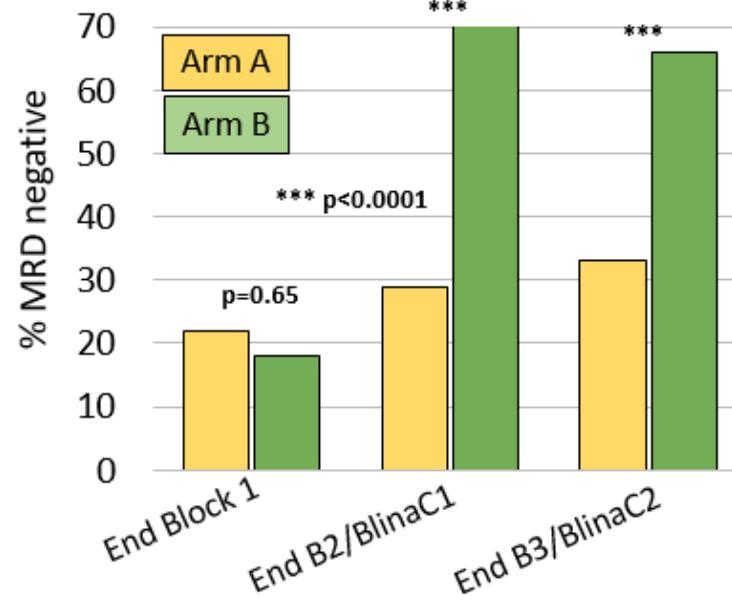
Survival: Arm A (chemotherapy) vs Arm B (blinatumomab)



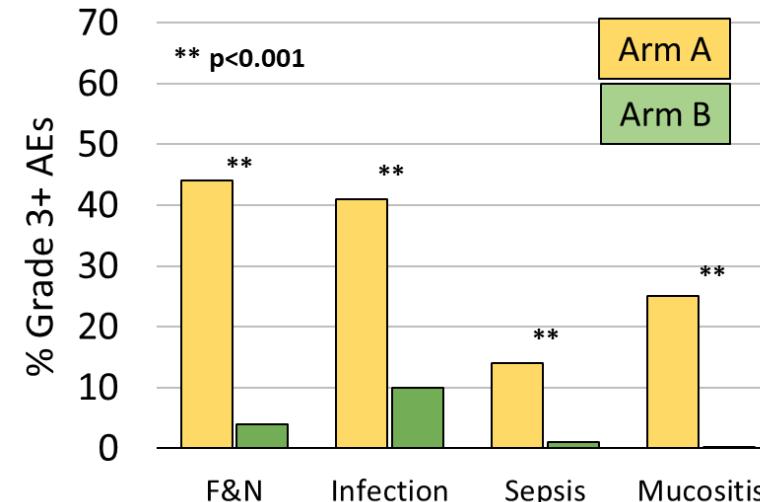
Median follow up 2.9 years

Other Endpoints: MRD, AEs, HSCT bridging

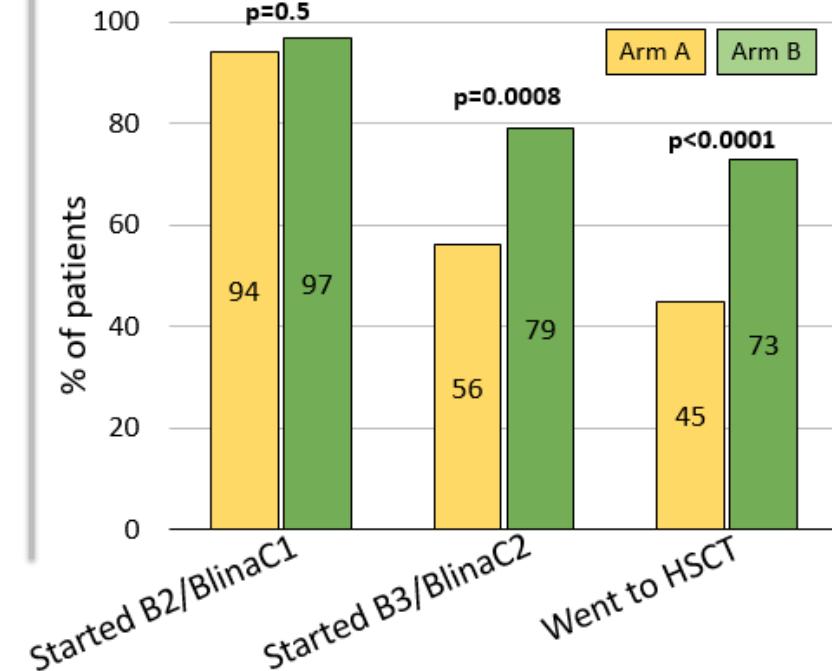
MRD Clearance



Adverse Events

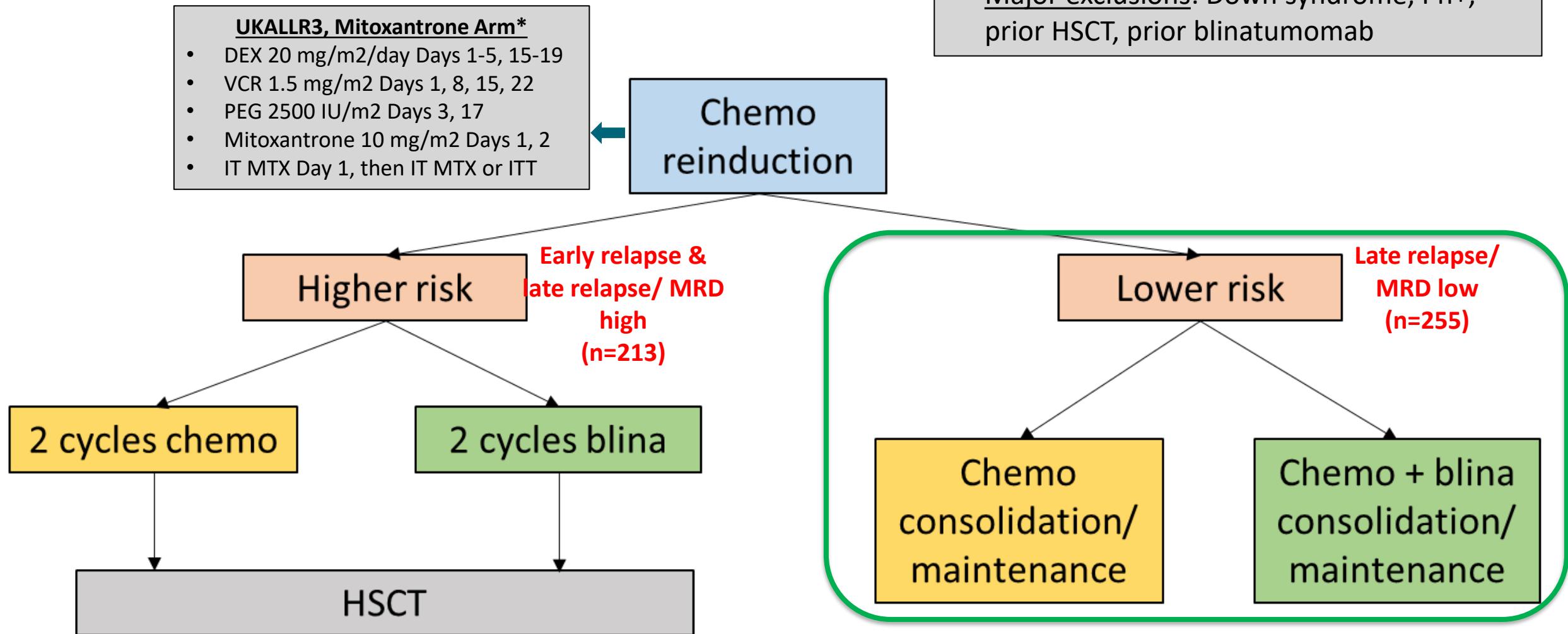


Bridge to Transplant

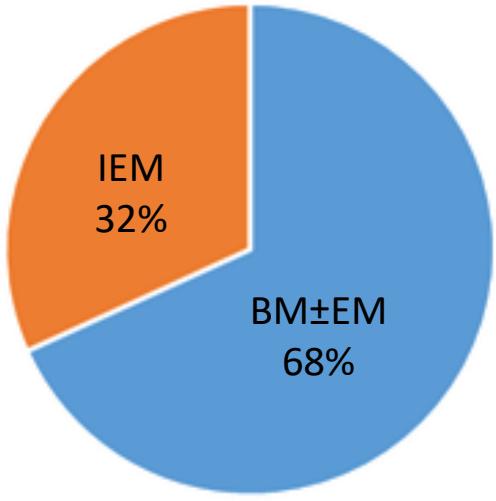


Significant contributors to the improved outcomes for Arm B (blina) vs. Arm A (chemo) in HR/IR relapses may include better **MRD clearance, less toxicity and greater ability to successfully bridge to HSCT**

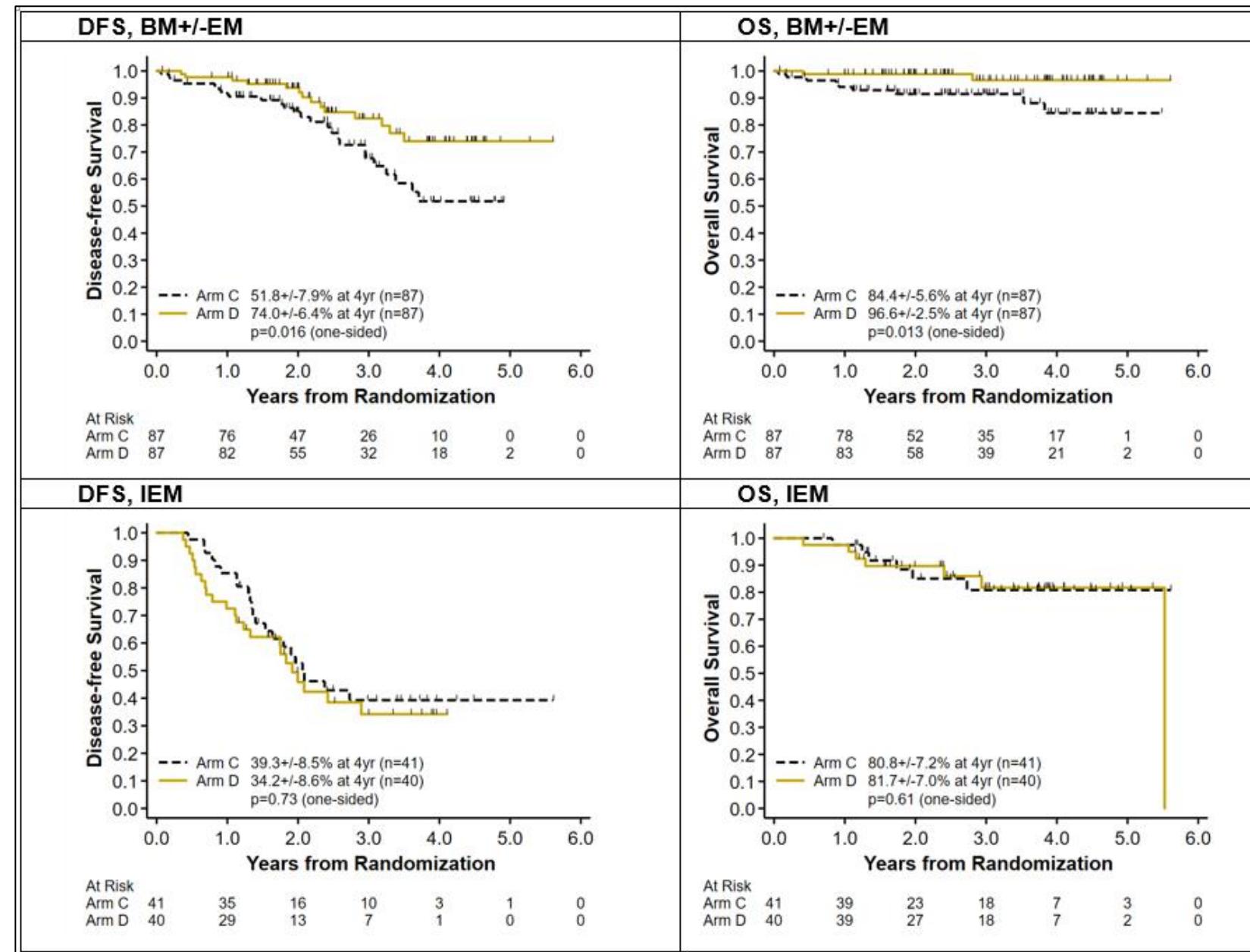
AALL1331: “Big Picture”



DFS/OS by site of 1st relapse



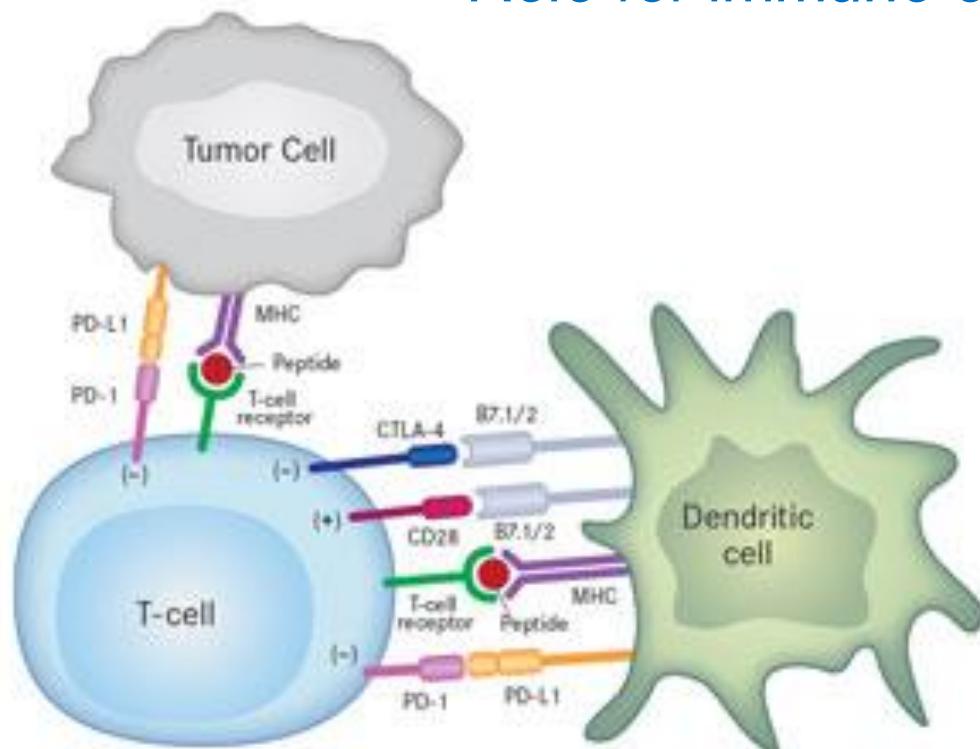
Brown P, et al. ASH 2021 Oral Presentation



Rationale for Blina/CPI Combination?

- Endogenous T-cell “exhaustion”

Role for immune checkpoint inhibitors (anti-PD1, e.g.)?

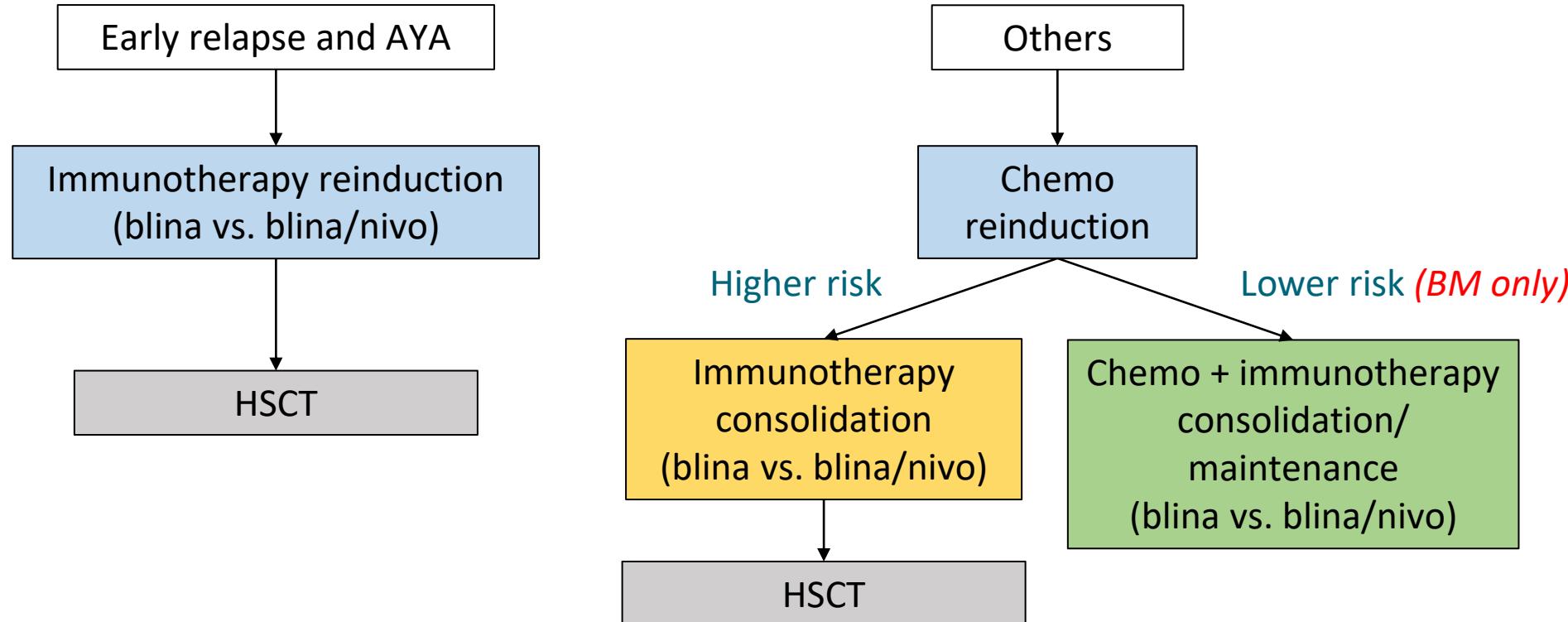


PD-1	PD-L1	CTLA-4
Nivolumab	Atezolizumab	Ipilimumab
Pembrolizumab*	Avelumab	
	Durvalumab	

Reports of efficacy in patients relapsing after blina/CAR T-cells

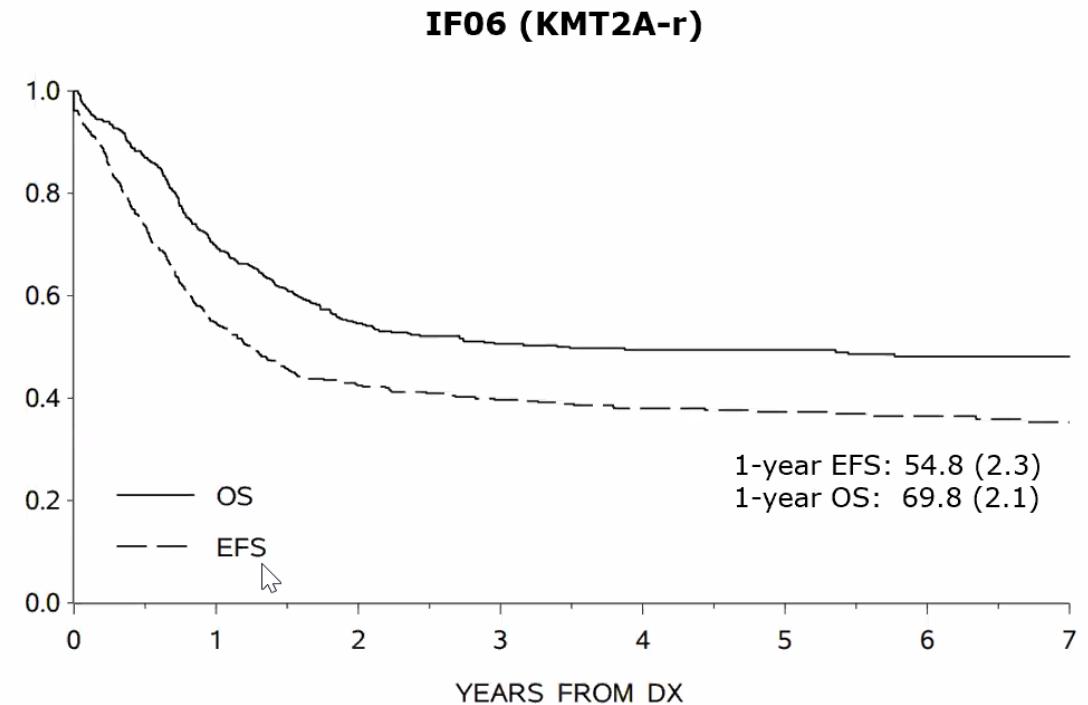
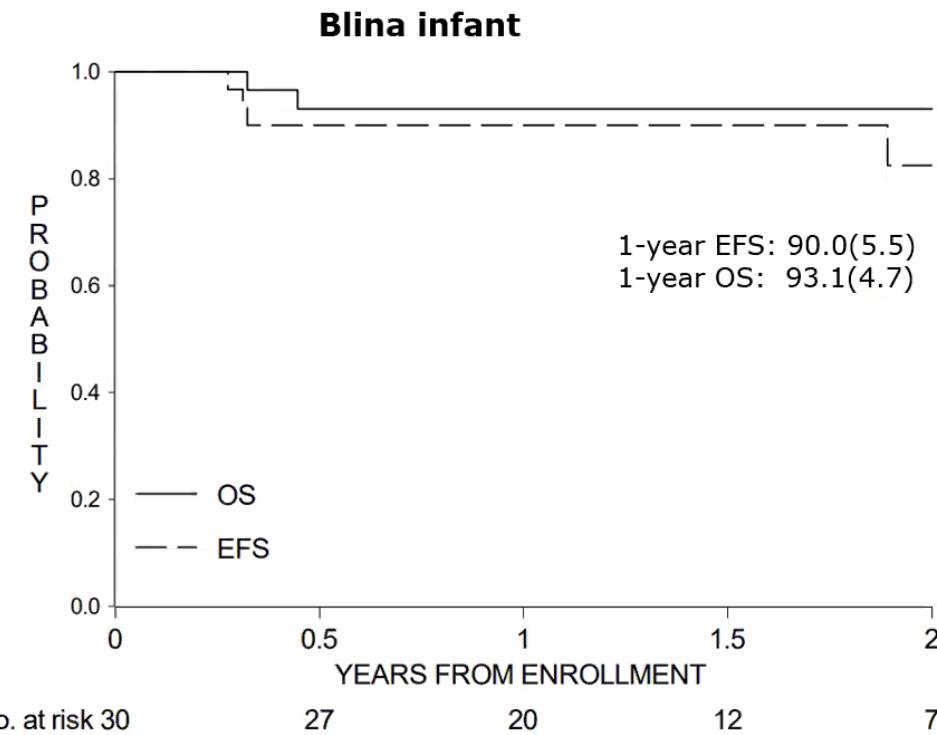
- *Feucht, et al. Oncotarget 2016 Nov 22;7(47):76902-19*

AALL1821: Blinatumomab + Nivolumab



Talking: Inge van der Sluis

EFS and OS

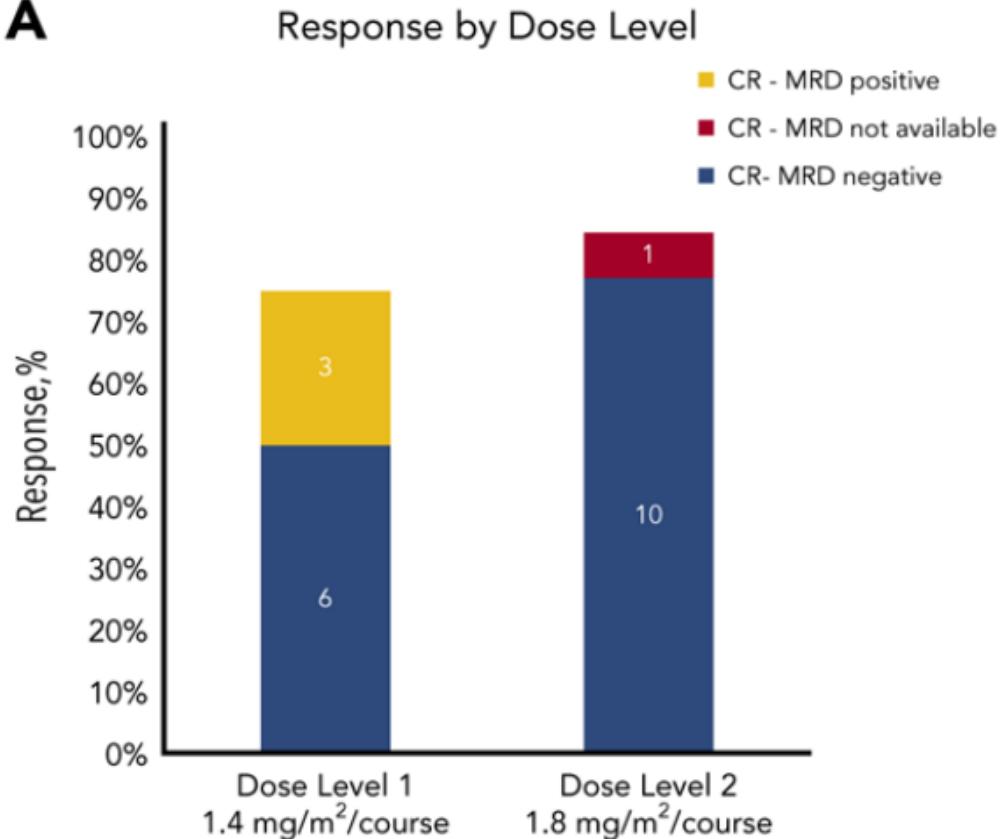


Follow-up (months)
Median: 16.3
Range: 3.3 - 36.7

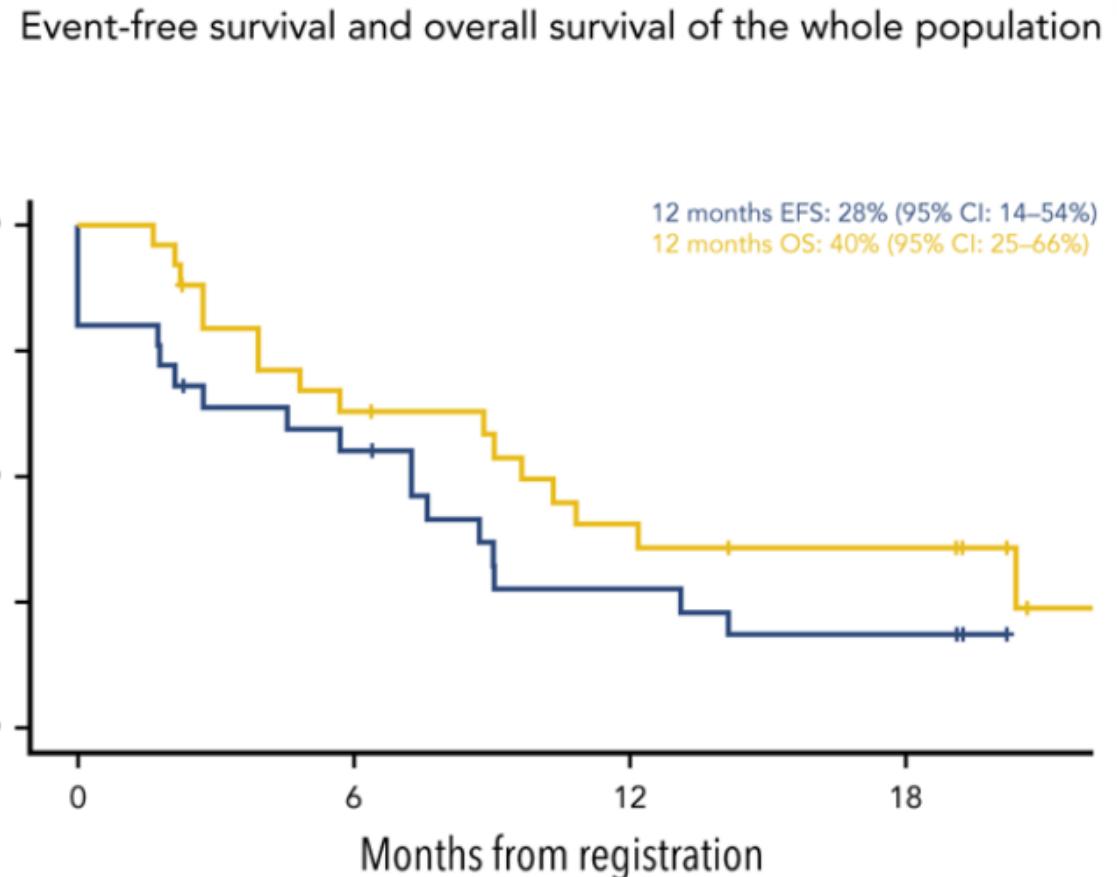
Van Der Sluis et al. Oral Presentation at ASH 2021

Inotuzumab in R/R Pediatric ALL

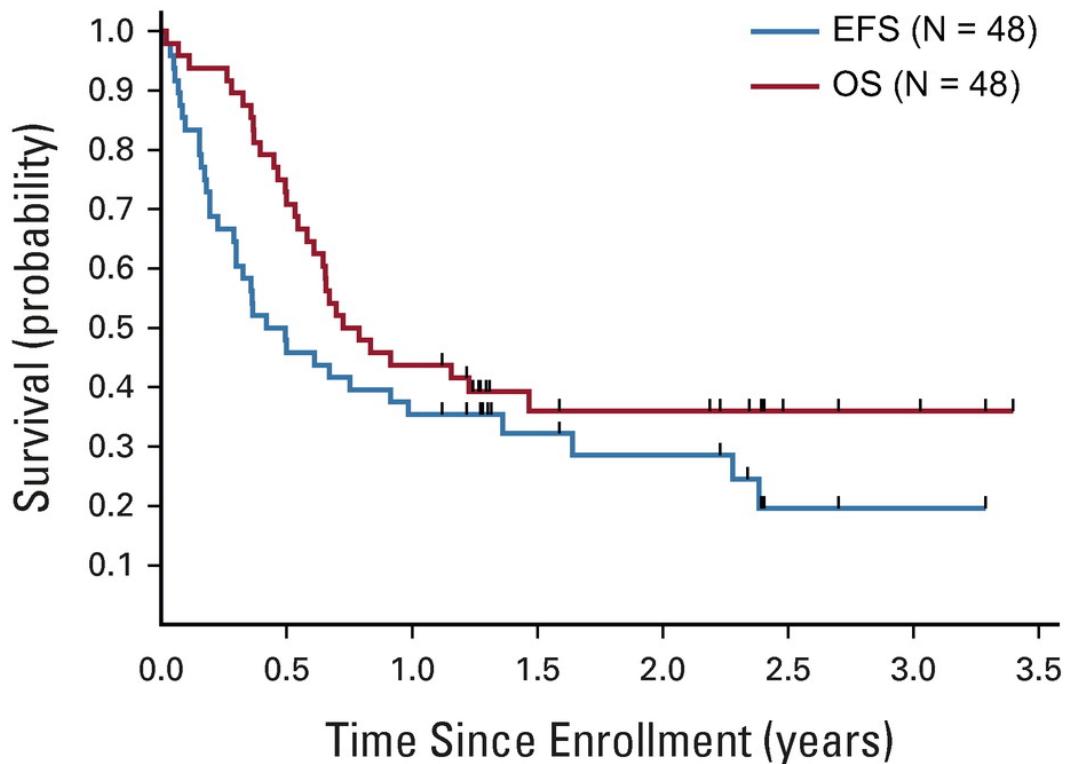
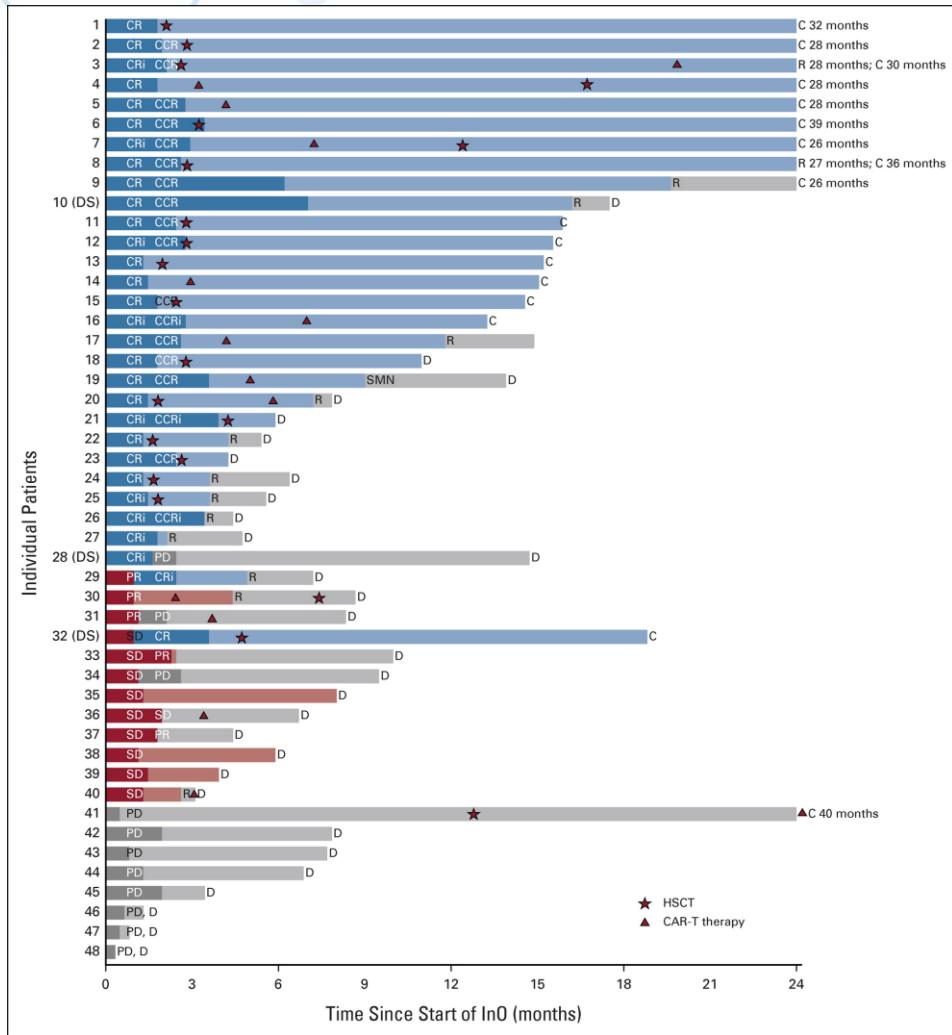
A



B



Inotuzumab in R/R Pediatric ALL

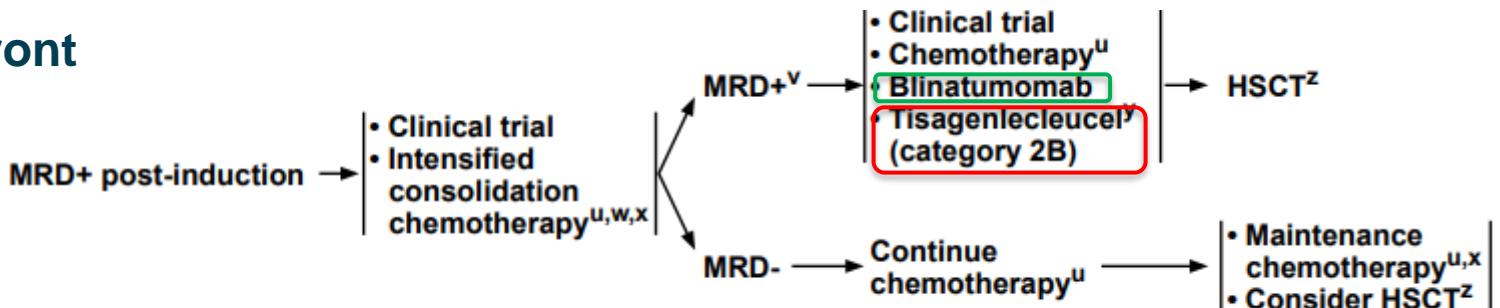


O'Brien et al. J Clin Oncol. 2022 Jan 10. Epub ahead of print.

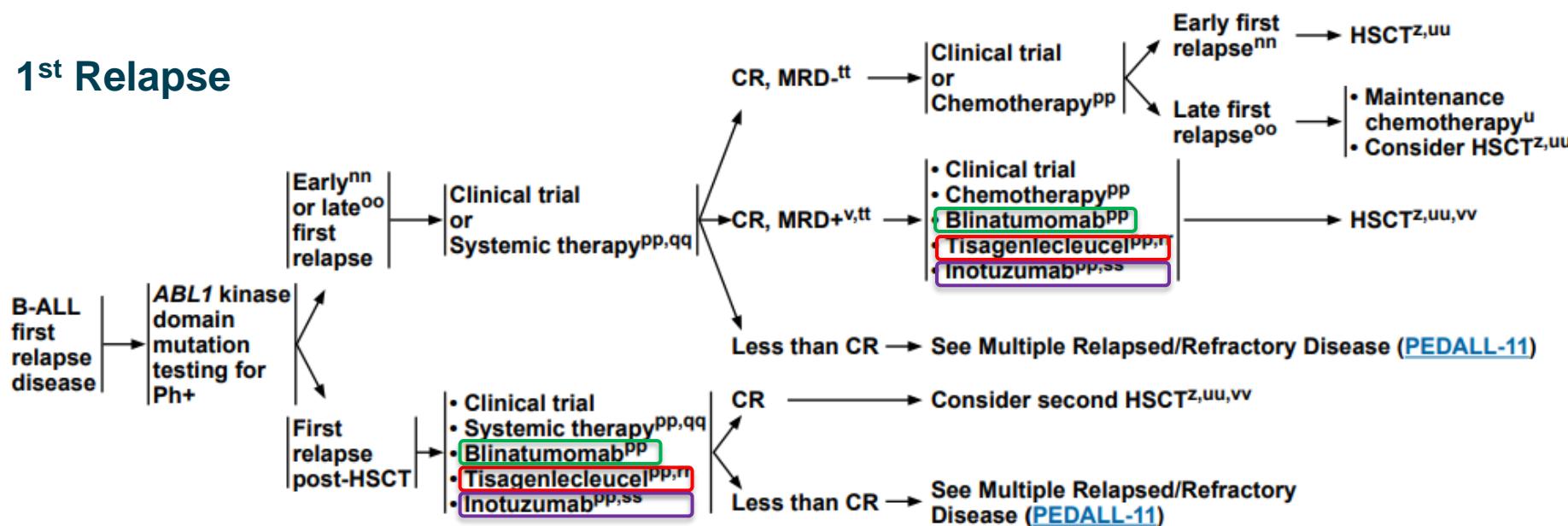
Immunologically Targeted Therapy for Upfront B-ALL

Risk Group	Projected 5-yr DFS	Therapeutic Question
33% SR-Favorable	>95%	Standard therapy with 2 year duration of maintenance therapy for boys and girls
2% HR-Favorable	>94%	
32% SR-Avg & High	~89%	Blinatumomab
27% High Risk	~80%	Inotuzumab } randomized
2% Very High Risk	<50%	Tisagenlecleucel
5% Ph-like	60-85%	Molecularly targeted therapy

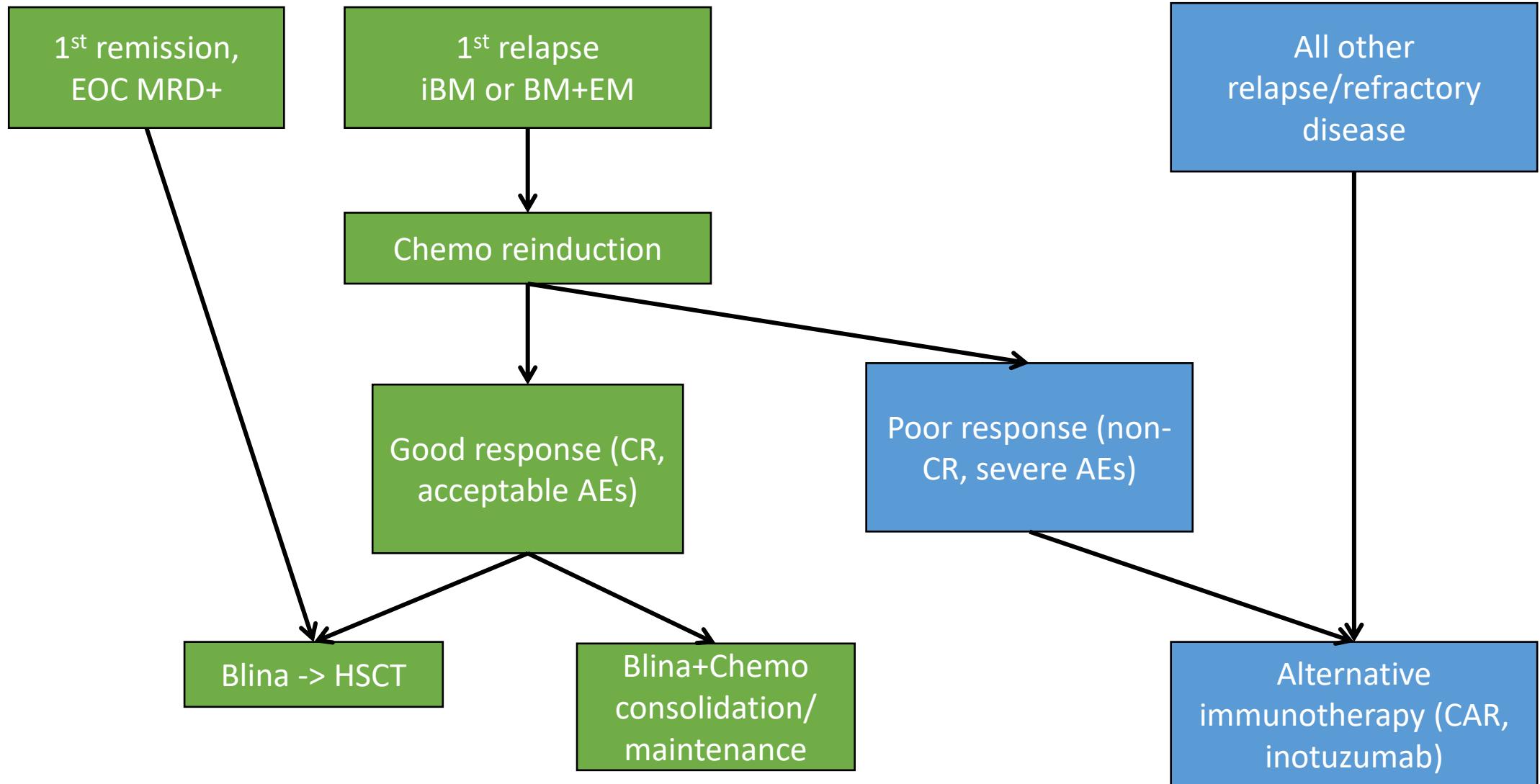
Upfront



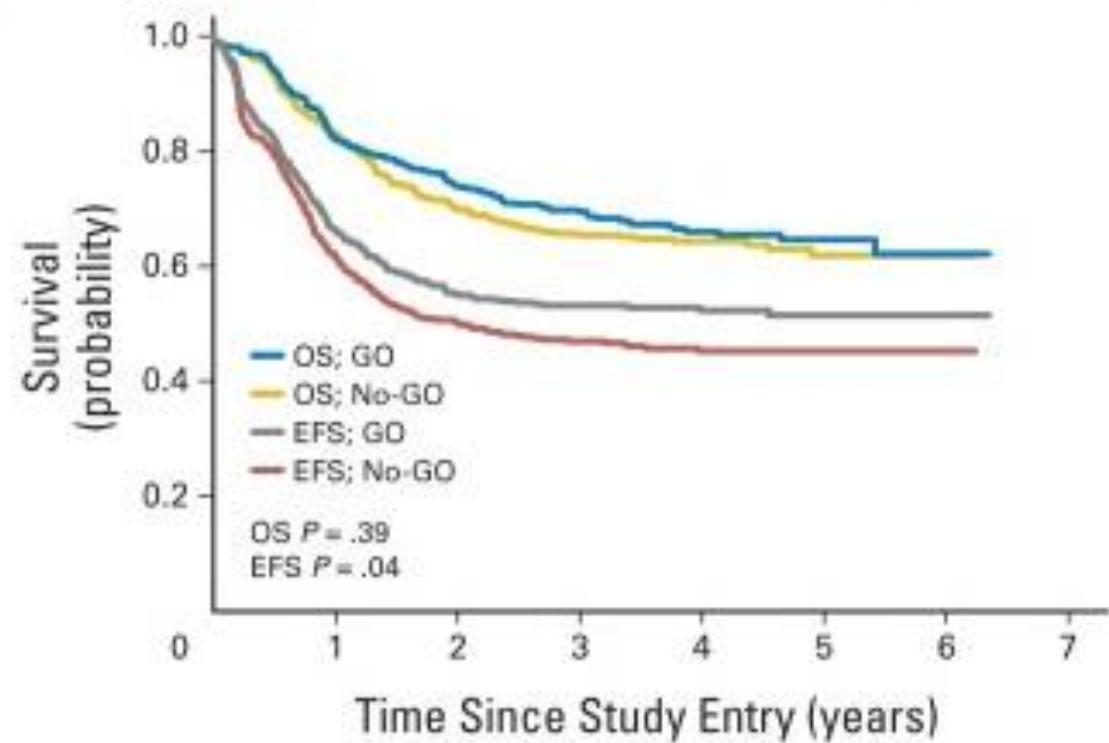
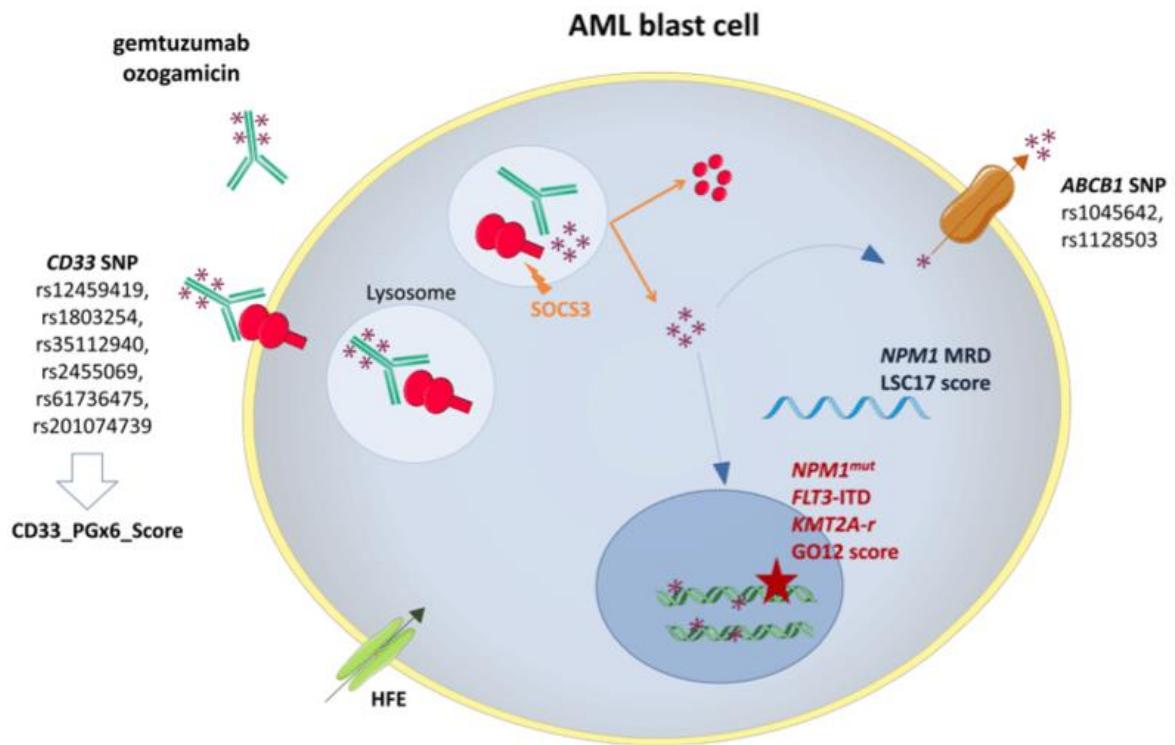
1st Relapse



Summary of My Approach to Relapse/Refractory Peds/AYA B-ALL



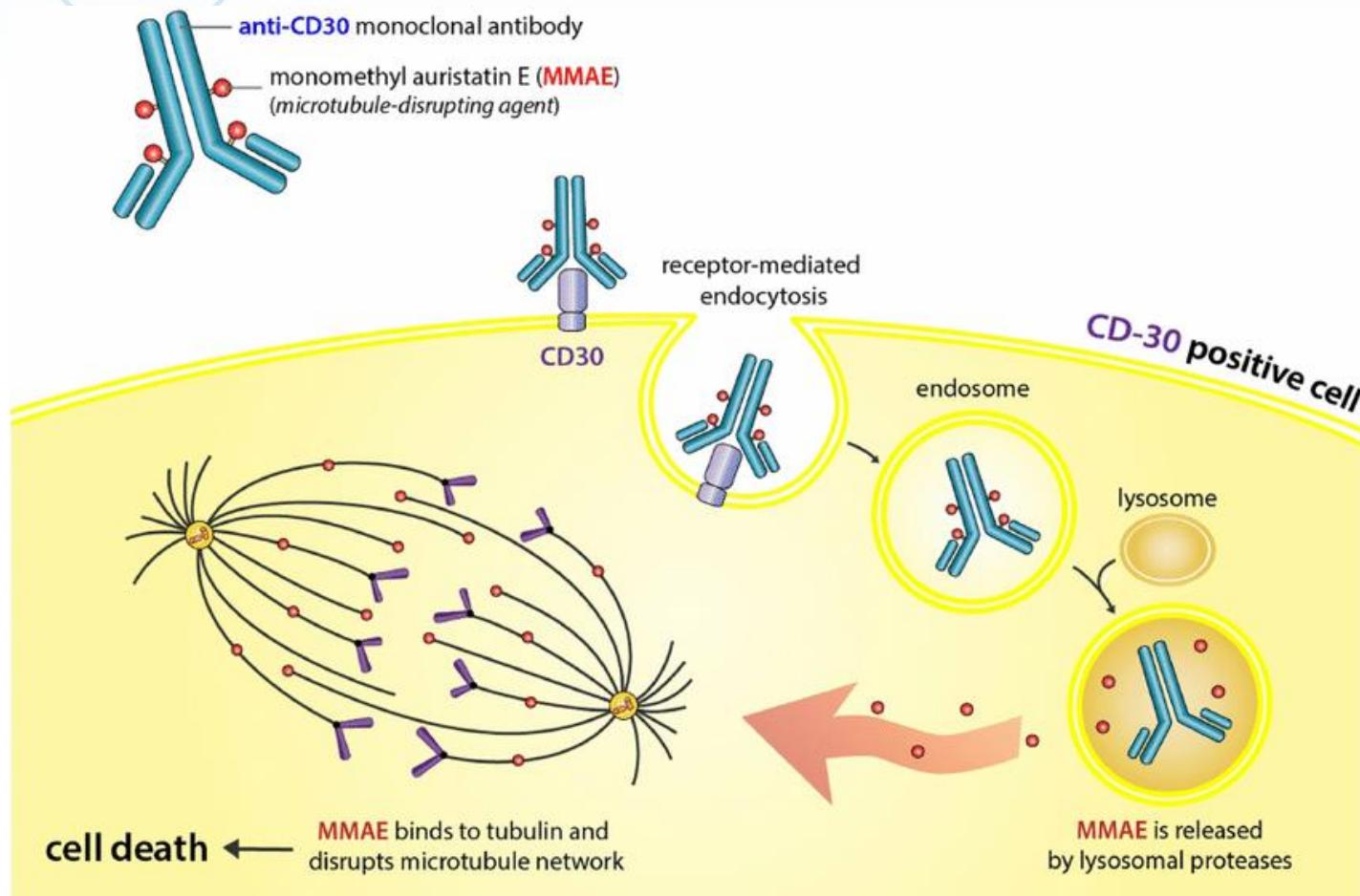
Gemtuzumab: AML



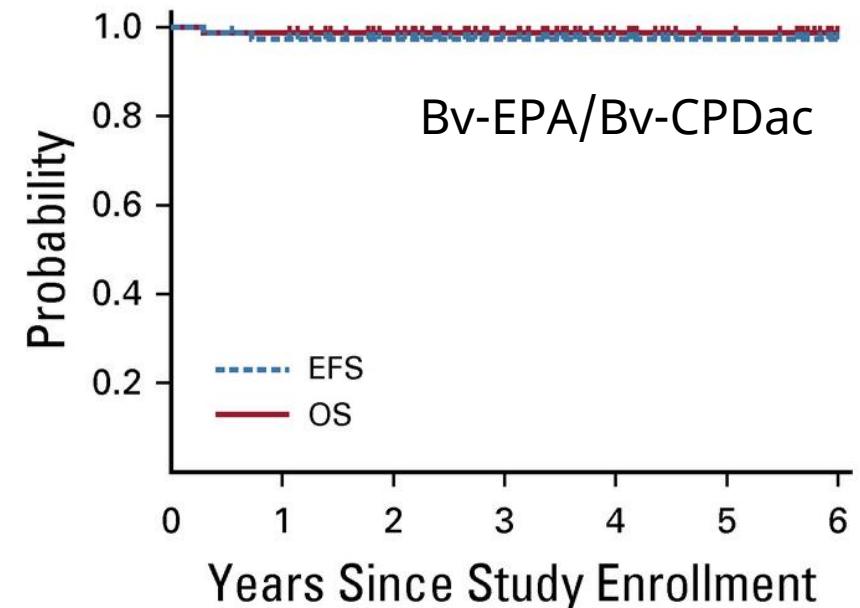
Fenwarth, et al. (2020). International Journal of Molecular Sciences. 21. 5626.

Gamis, et al. J Clin Oncol. 2014;32(27):3021-32

Brentuximab: HR cHD



Collins, et al. 2014. Lymphoma and Chronic Lymphocytic Leukemias. 1. 1-8



Metzger, et al. JCO 2021 39:20, 2276-2283

AHOD1331: Bv-AVEPC arm has superior efficacy with 3-year EFS of 92.1% vs. 3-year EFS of 82.5% with ABVE-PC ($p=0.0002$)

Castellino, et al.
Unpublished

Acknowledgements: AALL1331 Study Committee

- **Chair:** Pat Brown
- **Vice Chair:** Jim Whitlock
- **Stats:** Lingyun Ji, Mini Devidas
- **Heme/Onc:**
 - Lia Gore
 - Laura Hogan
 - Terzah Horton
 - Stevie “Nicks” Hunger
 - Kala Kamdar
 - Mignon Loh
 - Jen McNeer
 - Maureen O’Brien
 - Mike Pulsipher
 - Sue Rheingold
 - Teena Bhatla
 - Sarah Tasian
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 - Julie Gastier-Foster
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- **Pharmacy:**
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 - Olga Militano
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