AMGEN

Global Leukemia Academy

Global Leukemia Academy Virtual Breakout: Pediatric ALL Patients

Emerging and Practical Concepts and Controversies in Leukemias

24 July 2020

APTITUDE HEALTH®

Global Leukemia Academy

Virtual Breakout: Pediatric ALL Patients Session Opening

Patrick Brown

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Meet the Faculty and Panelists

Patrick Brown, MD
Associate Professor of Oncology and Pediatrics, Director of the Pediatric Leukemia Program
Johns Hopkins University
Baltimore, MD, USA

Lia Gore, MD
Professor and Chief of Pediatric Hematology/ Oncology/Bone Marrow Transplant
Children's Hospital Colorado and the University of Colorado School of Medicine

Franco Locatelli
Head of Department of Paediatric Haematology and Oncology, IRCCS Bambino Gesù Children's Hospital, Rome. and Full Professor of Pediatrics at the Sapienza University of Rome, Italy

Oscar González Ramella, MD, PhD
Professor, Physician in Pediatric Oncology and Hematology; Chair of the Bone Marrow Transplantation Unit at Hospital Civil of Guadalajara, Jalisco, Mexico

Adriana Seber, MD
Coordinator of Pediatric Bone Marrow Transplantation Team at Hospital Samaritano Higienópolis, São Paulo, Brazil

Carlos Andrés Portilla, MD
Coordinator of Pediatric Hematology and Oncology Unit, Centro Médico Imbanaco, Cali, Colombia

María Sara Felice, MD, PhD
Director, Acute Leukemia And Lymphoma, Hospital Garrahan, Buenos Aires, Argentina

Objectives of the Program

- Understand current treatment patterns for ALL including incorporation of new technologies
- Uncover when genomic testing is being done for ALL, and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation in ALL as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring ALL
- Gain insights into antibodies and bispecifics in ALL: what are they? When and how should they be used? Where is the science going?
- Discuss the evolving role of ADC therapies in ALL
- Review promising novel and emerging therapies in ALL

Virtual Breakout: Pediatric ALL Patients

Chair: Patrick Brown

TIME UTC-3	TITLE	SPEAKER
17.00 – 17.15	Session opening • Educational ARS questions for the audience	Patrick Brown
17.15 – 17.35	First-line treatment of pediatric ALL • Presentation • Q&A	Lia Gore
17.35 – 17.55	Current treatment options for relapsed ALL in children including HSCT and COVID-19 considerations • Presentation • Q&A	Franco Locatelli
17.55 – 18.15	Bispecific T-cell engagers for pediatric ALL • Presentation • Q&A	Patrick Brown
18.15 – 18.45	Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in pediatric patients Panelists: María Sara Felice (Arg), Oscar González Ramella (Mex), Adriana Seber (Bra), Carlos Andres Portilla (Col)	Maria Sara Felice Carlos Andres Portilla Discussion
18.45 – 19.00	Session close • Educational ARS questions for the audience	Patrick Brown

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Educational ARS Questions

Patrick Brown

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VOTING QUESTION

Educational Questions Pediatric ALL
Question 1: Which assertion is correct for children with ALL?

a) All patients with MLL-rearranged ALL should be transplanted
b) All patients with BCR-ABL-positive ALL should be transplanted
c) No patient with BCR-ABL-positive ALL should be transplanted
d) AlloSCT is part of treatment for children with early relapsed ALL

VOTING QUESTION

Educational Questions Pediatric ALL
Question 2: Which assertion is correct for children with ALL?

a) Blinatumomab and inotuzumab are part of first-line treatment
b) Blinatumomab and inotuzumab cannot be administered sequentially
c) Therapeutic drug monitoring of asparaginase improves outcome
d) Dexamethasone and vincristine are standard components of maintenance therapy

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First-Line Treatment of Pediatric ALL

Lia Gore

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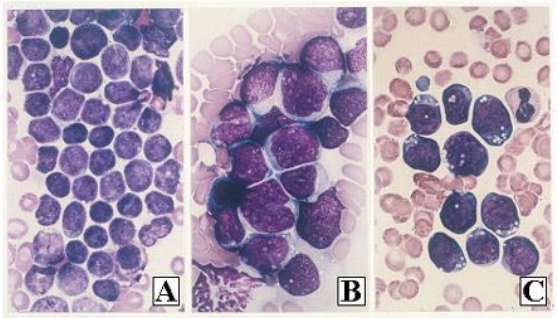
Therapy for Pediatric Acute Lymphoblastic Leukemia in the Front Line



Lia Gore, MD
Chief, Pediatric Hematology/Oncology/Bone Marrow Transplant-Cellular Therapeutics
University of Colorado School of Medicine and Children's Hospital Colorado

Success in Treating the Most Common Childhood Cancer

- 1948 – first case of temporary remission reported by Farber et al
- Successive generations of treatment show improved outcomes
- Current regimens offer survival of 90%–99% for most patients

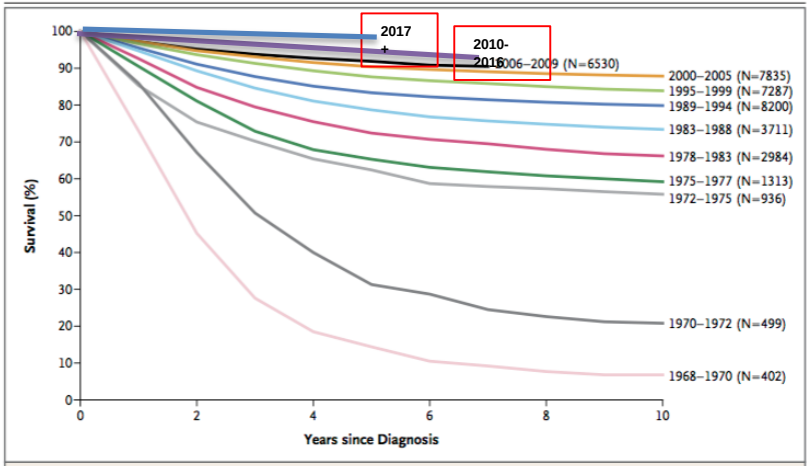


Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.

Mullighan, Hunger. *N Engl J Med.* 2015.

Outcomes for Patients With Favorable Genetics and CNS1 in Current COG Trials

NCI Risk	Day 8 MRD	Day 29 MRD	5-Year EFS	5-Year OS	n
Standard	<1%	<0.01%	95.7%	99.1%	1129
Standard	≥1%	<0.01%	91.7%	99.4%	170
Standard	Any	≥0.01%	88.1%	96.8%	369
High	<1%	<0.01%	94.9%	98.1%	243
High	≥1%	<0.01%	93.6%	95.5%	50
High	Any	≥0.01%	75.4%	90.4%	121

	<10 Yr Old n = 107 (44%)	≥10 Yr Old n = 136 (56%)	*P* Value
5-year EFS	98.0%	92.4%	.126
5-year OS	98.7%	97.8%	.411

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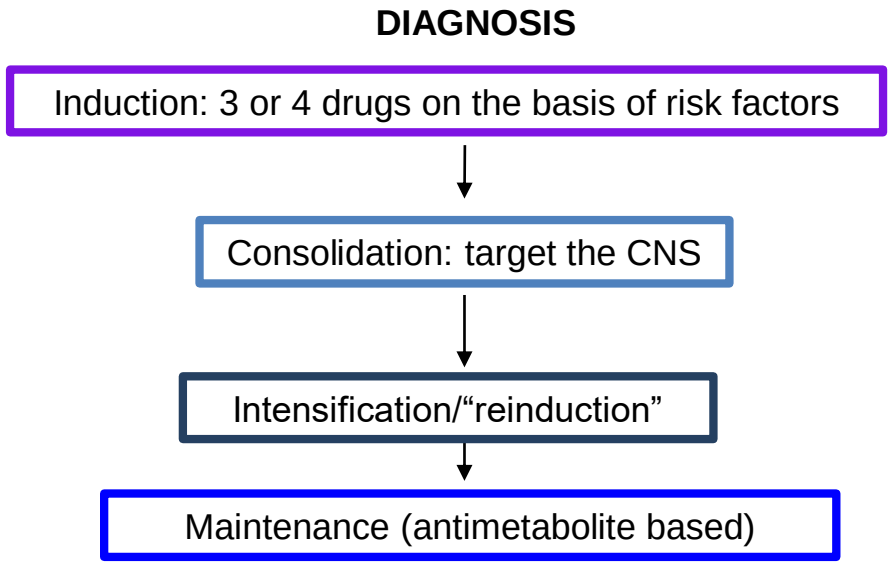
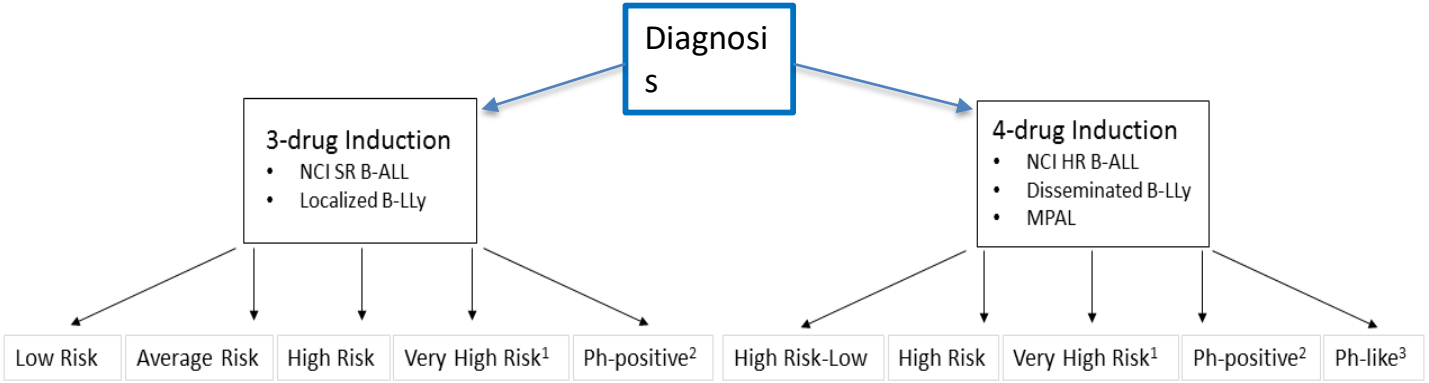
Raetz, et al. ASH 2015.

Simplified Treatment of ALL



Overall Schema of Current ALL Therapy



Risk stratification based on biologic and genetic features at diagnosis and response to induction chemotherapy remain the best predictors of outcome for all patients

Induction

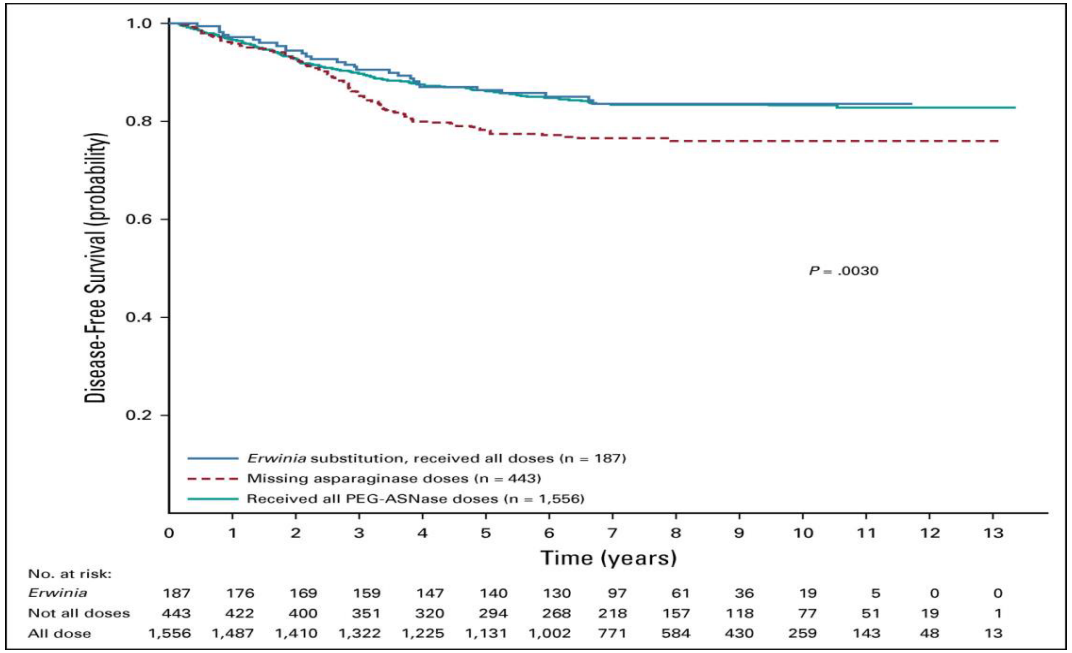
- 3-drug induction = steroid, VCR, ASP
  - NCI standard risk
    - Except CNS3, testicular disease, steroid pretreatment
  - Localized B-lymphoblastic lymphoma (B-LLy)
- 4-drug induction = steroid, VCR, ASP, + daunorubicin
  - NCI high risk
  - NCI standard risk with CNS3, testicular, steroid pretreatment
  - Disseminated B-LLy
  - MPAL

Postinduction risk-stratification is based on response to induction

Observations on the History of Frontline ALL Therapy

- Induction with steroids, vincristine, and asparaginase are key elements that, to date, cannot be removed from therapy
  - Asparaginase intensification improves outcomes in most risk groups: T-, B-, and LLy (multiple iBFM, DFCI, POG, COG trials: Amylon 1999; Silverman 2001; Pession 2005; Pieters 2011; Gupta 2020) but not in SR-low (Mattano 2014), and is not without toxicity
  - Prednisone pre-phase separates out good responders (Schrappe 1998)
- Daunorubicin increases survival for high-risk patients (Gaynon 1988; Nachman 1997, 1998; Veerman 2009)
- Intensified consolidation not needed for excellent outcomes in SR patients (Maloney 2013, 2019)
- Pulses of maintenance therapy cure more patients (HR = 0.54) (Conter 2007; De Moerloose 2010)
  - Dexamethasone vs prednisone matters (Mitchell 2005; Larson 2016)
  - 6-MP and 6-TG are both effective in maintenance (Harms 2003), but 6-TG leads to more VOD/SOS (Stork 2010)
- CNS-directed therapy is essential for cure
  - Intrathecal therapy can replace cranial irradiation (Clarke 2003)
  - 24 Gy is <u>not</u> better than 18 Gy (Steinherz 1989; Schrappe 1998)
  - IT methotrexate can also decrease marrow relapse (Clarke 2003)
- Modern combination regimens equalize outcomes for <u>most</u> patients with B- and T-cell ALL
- TKIs have changed the outcome for Ph+ disease and eliminated HSCT in CR1 for the majority of patients
- Infants with *KMT2A* rearrangements have a dismal prognosis with any regimen tested to date

Asparaginase Intensity but Not Product in HR Patients Affects Outcomes

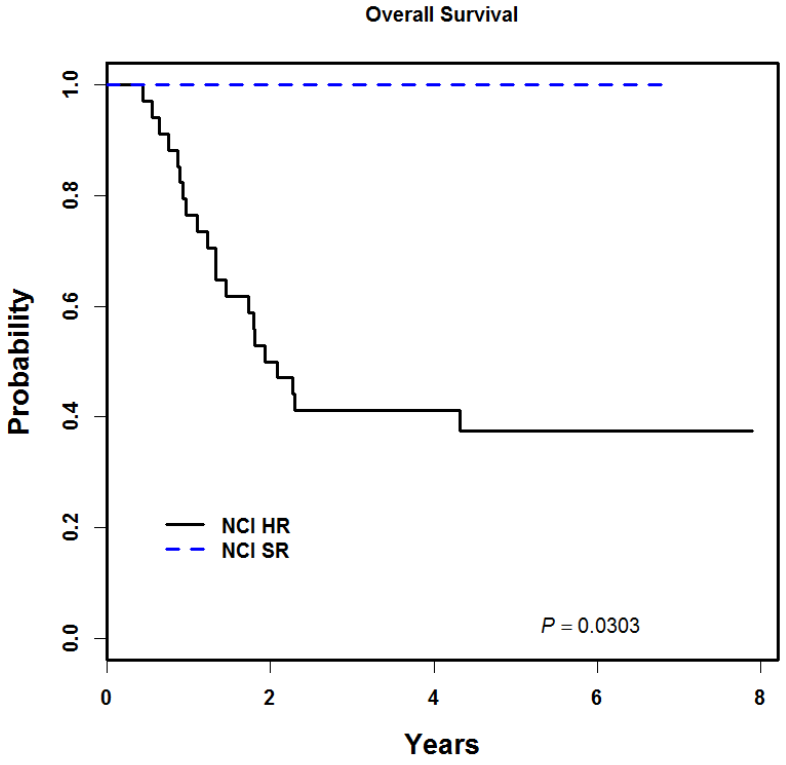


Gupta, et al. *J Clin Oncol.* 2020.

3 vs 4 Drugs: Adding Daunorubicin

Evidence	Study/Trial	Daunorubicin Dose	Additional Information
Standard of care established	1. Veerman (2009)-DCOG-ALL-9 2. Gaynon (1988)-CCG-193P 3. Nachman (1997) 4. Nachman (1998) 5. Buchmann (2003)-POG 8303	25 mg/m^2	1. Dexamethasone. IT during induction. No infant data. HD MTX plus 2 intensification phases 2. Prednisone. CNS prophylaxis given. No infant data 3. Prednisone. IT cytarabine on day 0. No infant data 4. Prednisone. IT cytarabine on day 0. No infant data 5. Prednisone. All patients had initial therapy and developed first relapse. Infant (<1 yr) data (n = 14)
Evidence	**Study/Trial**	**Daunorubicin Dose**	**Additional Information**
Infant data	1. Lauer (1998) POG 8398 2. Reaman (1999) CCG-107/1883 3. Saltzer (2014) 4. Pieters (2019)	1. 0.83 mg/kg IV days 2, 8, 15, 22 2. 12.5 (<3 mo) or 25 mg/m^2 (4-11 mo) IV/week 3. 15 mg/m^2 (<7d); 20 mg/m^2 (7d-<6 mo); 22.5 mg/m^2 (6-12	1. Infants grouped <6 months (60%) and >6 months (40%). CNS prophylaxis given (triples) 2. Infants grouped <3 months, 3-5 months, 6 to <1 year. Given intrathecal Ara-C and MTX 3. IT MTX d1, IT HC/Ara-C d15, IT MTX/HC d29
Evidence	**Study/Trial**	**Daunorubicin Dose**	**Additional Information**
Dex > Pred	Larson (2016)-AALL0232	25 mg/m^2	Dexamethasone had superior outcome in younger children (1-9 yo) compared with prednisone. Older patients had more toxicity with Dex than Pred

Overall Survival After Induction Failure by (M3) Marrow Status



	5-Year OS ± SE
AALL0232 (HR)	37.4% ± 10.5%
AALL0331 (SR)	100%

AALL0232 PI: Eric Larsen, MD
AALL0331 PI: Kelly Maloney, MD

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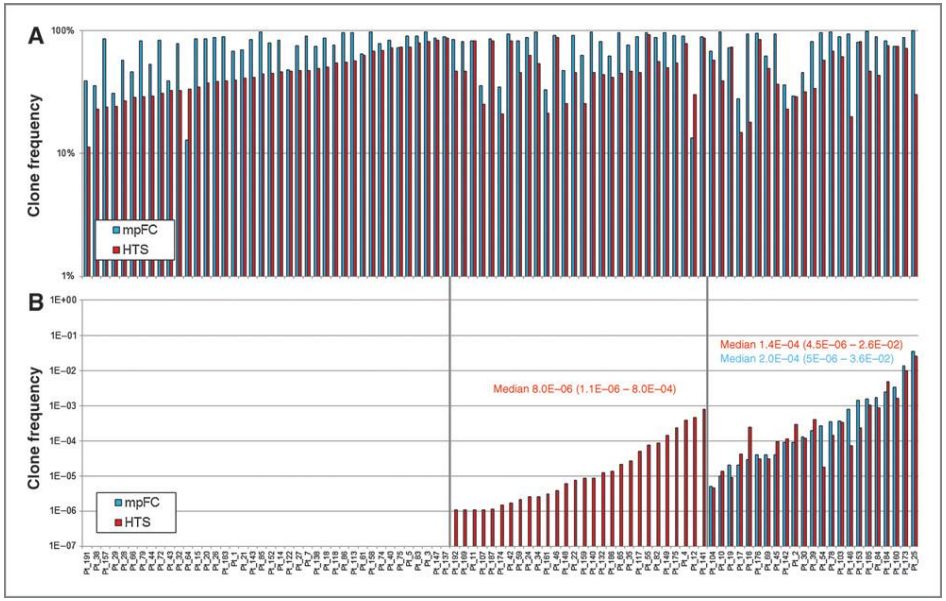
Improving MRD Detection by Next-Generation/ High-Throughput Sequencing (HTS)



Wu, et al. *Clin Cancer Res.* 2014.

- HTS of clonotypic Ig/TCR rearrangements detects MRD at ~1/1,000,000
- Pilot study of ~300 pts from AALL0331 showed that 20% had no detectable residual clonal sequence at any level at day 29
  - HTS-neg pts had a 5-yr EFS of 98.1% and OS 100%
- Includes pts with and without favorable genetics

Kirsch SIOP 2016 and Wood ASH 2016

Observations on the History of Frontline ALL Therapy

- Cytogenetic and molecular abnormalities/variations matter
  - *KMT2A*, Ph+/*BCR-ABL*, Ph-like, *ETV6-RUNX1*, triple trisomy, high hyperdiploidy iAMP21, *TCF-PBX1*, *CRLF2*, and severe hypodiploidy all confer different prognostic implications
    - Impact of advancing technology on treatment and outcomes
    - Changing role of HSCT in the front line
- MRD matters (van Dongen 1998; Coustan-Smith 2000; Borowitz 2008)
  - Lower is better; none is best – but by what method?
- Many patients with ALL can be cured with simple therapy (Kirsch SIOP 2016 and Wood ASH 2016)
  - 4-6 weeks of 3-drug induction
  - Appropriate CNS prophylaxis
  - Pulses of maintenance therapy
- Escalating MTX improves outcomes for some patients
- Addition of rituximab (GRAALL 2005) improves outcomes for adults (Maury 2016); pediatric outcomes unknown
- Adding anthracycline during induction plus 4 weeks of CPM/Ara-C/6-MP consolidation therapy or 8 weeks of delayed intensification (Protocol IIa + IIb) cures another ~10% of patients
- A major cause of morbidity and mortality in children with ALL is treatment-related toxicity and late effects

Role of End-Induction HTS-MRD

- Conservatively estimating true EFS of HTS-MRD–undetectable patients at 96%, and accounting for 20% of AR patients, EFS of patients with detectable HTS-MRD should be ~88%
  - Wood/UW cohort – 87.4% EFS for an approximately equivalent population
- Patients with noninformative HTS had a 5-year EFS of 78.5% (included NCI HR patients)
- From COG 0331 (SR) and 0232 (HR) samples, HTS detected dominant clone in 93.2% of patients
  - Among SR patients, 19.9% had no detectable residual clonal sequence at any level at EOI; these patients had an outstanding EFS of 98.1% +/- 0.2%
- Proportion of undetectable samples did not vary between cytogenetic risk groups (so likely similar among SR/AR patients)

COG Classification Table*

Risk Group	SR-Favorable (SR-Fav)	SR-Average (AR)		HR-Favorable (HR-Fav)	High Risk[1] (HR)					Very-High Risk (VHR)
Projected 5-year EFS	>95%	85-95%		>94%	65-92%					<65%
NCI Risk Group	SR	SR	SR	HR <10yr	SR	SR	SR	HR (except HR-Fav)	HR	HR
CNS[1]	1/2	1/2	1	1	2	Any	Any	Any	Any	Any
Cytogenetics[2]	Fav	Fav	Neut	Fav	Neut	Unfav	Any	Any	Any	Any[3]
Day 8 PB MRD (%)	<1	≥1	Any	n/a	Any	Any	Any	n/a	n/a	n/a
EOI MRD (%)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	≥0.01[4]	<0.01	≥0.01[4]	≥0.01
EOC MRD (%)	n/a	n/a	n/a	n/a	n/a	n/a	Any	n/a	<0.01	≥0.01
Total pt accrual/yr	521	348		38	598					24
Fraction of patients (%)[5]	30	20		2	35					1

*BFM has similar classification categories; efforts to facilitate data comparisons when possible.

What About Lymphoblastic Lymphoma?

ALL-focused regimens are often used to treat HR B-cell or T-cell ALL and lymphoblastic lymphoma – often on the same protocol or on an arm of an ALL protocol

- Several trials have compared various ALL or lymphoma regimens
  1. LSA212 v COMP (non-daunorubicin regimen)
  2. LSA212 v A-COP+ (adriamycin)
  3. Daunorubicin in NHL-BFM-86 was the same in both arms

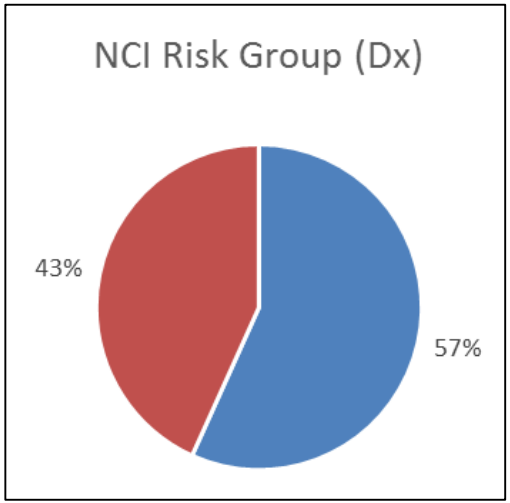
Regimen Used	Daunorubicin Dose (Regimen)	Other Drugs Used During Induction (Regimen)
1. NHL-BFM-86	1. 30 mg/m^2 weekly	1. Prednisone, vincristine, L-asparagine with MTX
2. NHL-BFM-95	2. 30 mg/m^2 weekly	2. Prednisone, vincristine, L-asparagine with MTX, 6-MP, Ara-C, cyclophosphamide
3. UKCCSG 86	3. 45 mg/m^2 days 1, 2 (weekly)	3. Prednisone, vincristine, L-asparagine with MTX
4. LSA212	4. 60 mg/m^2 days 12, 13	4. Prednisone, vincristine, L-asparagine with Ara-C and cyclophosphamide

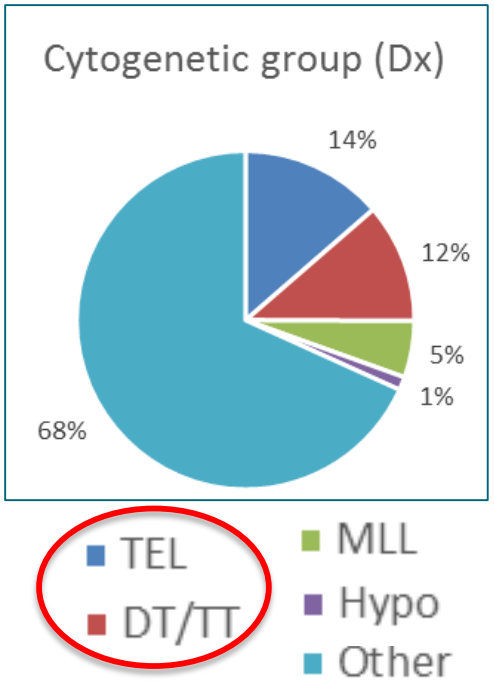
- Many study investigators anticipate that the LLy arm will not achieve statistical significance for an endpoint, but data are gathered and reported in final outcomes
- Data collected and reported on these trials support the findings of ALL outcomes with some differences
  - To date, there is no equivalent to MRD as a prognostic indicator in ALL
  - Most patients with LLy do quite well with combination regimens as above

Continued Need to Improve AR/SR ALL Outcomes

- ~600 NCI HR and ~1200 NCI SR patients enroll on COG trials each year
- Despite better outcome, SR pts contribute about half of treatment failures
  - 5-year EFS rate 77% for HR ALL (AALL0232) and 89% for SR ALL (AALL0331)
  - For every 1000 B-ALL patients, there are ~77 events among HR patients and ~73 events among SR patients
- Improving EFS for SR (and particularly AR) patients will therefore significantly reduce the overall burden of relapse in ALL

Standard- and Low-Risk ALL Remain Major Contributors to Relapse





Brown et al. on COG AALL1331.

Status of Immunotherapy for ALL

- Various immunotherapy approaches are available for patients with B-ALL – primarily in use for relapsed disease
  1) Monoclonal antibodies
  2) Antibody-drug conjugates (ADCs)
  3) Bispecific T-cell engagers (BiTEs)
  4) Cellular immunotherapies (CAR T cells, NK cells)
  5) Experimental: Trispecific T-cell engagers (TriTEs), dual-affinity retargeting antibodies (DARTs), and simultaneous multiple interaction T-cell engagers (SMITEs)
- Immunotherapies for T-cell disease have lagged behind but are gaining
- Early access to novel agents for pediatrics has been revolutionary for patients with relapsed and refractory ALL – could it be for newly diagnosed patients? Those with excess morbidity and mortality from current approaches?

Status of Immunotherapy for ALL in the Front Line

- Cooperative groups worldwide are now introducing various immunotherapy constructs into frontline clinical trials
- Coordination of findings and development of future studies depend on cooperation among investigators and pharmaceutical sponsors globally
- Further implications for
  - Risk stratification
  - Biologic and genetic features of leukemia cells
  - Response kinetics
  - Surrogate and biomarkers of efficacy

Clinical Trial Questions in COG: Introduction of Molecularly or Immunologically Targeted Therapy in B-ALL

	Risk Group	Projected 5-yr DFS	Therapeutic Question	COG Study Number
33%	SR-Favorable	>95%	Standard therapy with 2-year duration of maintenance therapy for boys and girls	AALL1731 and AALL1732
2%	HR-Favorable	>94%		
32%	SR-Avg & High	~89%	Blinatumomab } Randomized	AALL1731
27%	High Risk	~80%	Inotuzumab } Randomized	AALL1732
2%	Very High Risk	<50%	CAR T-cell therapy	AALL1721
5%	Ph+, Ph-like	60%–85%	Molecularly targeted therapy	AALL1631 and 1521

- All patients on AALL1731 and AALL1732 will receive q 12 week pulses of VCR/steroid
- All boys and girls on AALL1731 and AALL1732 will receive therapy for 2 years from the phase that starts after consolidation

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Current/Recent Trials for ALL – Frontline and Relapse

	Trial	Disease	Primary Objective	Status
B-ALL	AALL1731	Newly diagnosed SR B-ALL	Randomized trial of blinatumomab added to standard chemotherapy	Open
	AALL1732	Newly diagnosed HR B-ALL	Randomized trial of inotuzumab added to standard chemotherapy	Open
	AALL1721	Newly diagnosed VHR B-ALL	Efficacy of CAR T in CR1	Open
Ph+/like	AALL1631	Newly diagnosed Ph+ ALL (to add Ph-like B-ALL with ABL1-class alterations)	Randomized trial of imatinib added to AALL0232 vs EsPhALL backbone	Open
	AALL1521	Newly diagnosed Ph-like B-ALL with JAK-STAT pathway alterations	Safety/efficacy of adding ruxolitinib to AALL1131 chemotherapy	Open
Infant	AALL15P1	Newly diagnosed infants with KMT2A-rearranged ALL	Safety of adding azacitidine to Interfant backbone	Recently completed*
T-ALL	AALL1231	Newly diagnosed T-ALL/LLy	Randomized trial of bortezomib	Closed*
Relapse	AALL1331	First relapse B-ALL	Randomized trial of blinatumomab vs chemotherapy	Recently completed*
	AALL1621	2nd/greater relapse B-ALL	Safety and efficacy of inotuzumab	Under amendment
	AINV18P1	1st relapse T-ALL/Lly and 2nd/greater relapse B-ALL	Safety of palbociclib	Open

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*New successor studies in development

International Cooperation Is Essential


Cancer Center
UNIVERSITY OF COLORADO

Global Leukemia Academy

Q&A

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Current Treatment Options for Relapsed ALL in Children Including HSCT and COVID-19 Considerations

Franco Locatelli

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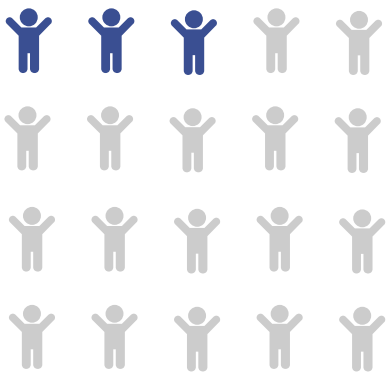
Current treatment options for relapsed ALL in children, including HSCT

Franco Locatelli, MD
Università Sapienza, Roma
Depart. Pediatric Hematology/Oncology and Cell/Gene Therapy
IRCCS Ospedale Bambino Gesù, Roma, Italy

Disclosures

Company name	Disclosure
Amgen	Honoraria, Speakers' bureau, Consultancy and Travel support
Novartis	Consultancy
Medac	Speakers' bureau
Miltenyi	Speakers' bureau
Jazz Pharmaceuticals	Honoraria, Speakers' bureau
Bluebird bio	Speakers' bureau and Consultancy
SOBI	Consultancy

Background



RELAPSE RATE:

Approximately 15-20% of children with ALL relapse after standard treatment[1]

PROGNOSIS OF RELAPSED ALL LARGELY DEPENDS ON[2-6]

- ✓ Time from diagnosis to relapse
- ✓ Site of relapse
- ✓ Blast immune-phenotype

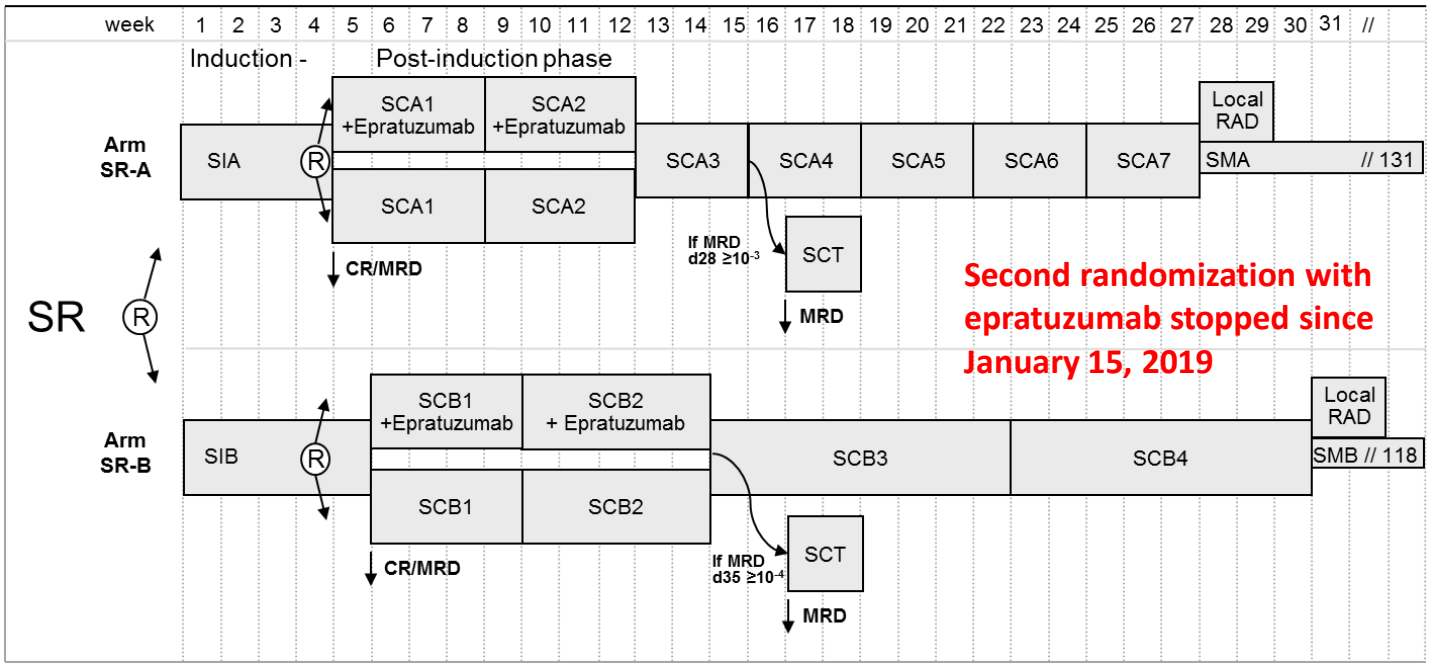
Almost all children with relapsed T-ALL and 2/3 of those with BCP-ALL are candidates for alloHSCT after a second morphological complete remission (M1 marrow) is achieved[7-8]

BCP-ALL; B-cell precursor acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplant.

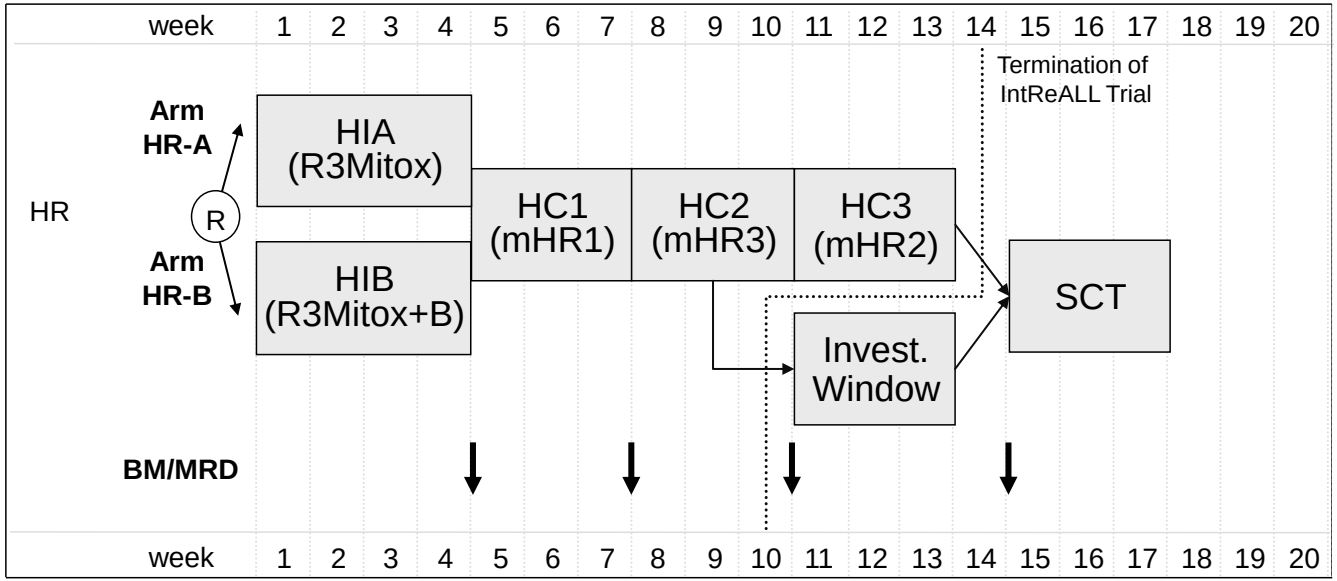
1. Hunger SP, Mullighan CG. *N Engl J Med.* 2015;373:1541-1552. 2. Chessells JM, et al. *Br J Haematol*. 2003;123:396-405. 3. Irving JA, et al. *Blood.* 2016;128:911-922. 4. Krentz S, et al. *Leukemia.* 2013;27:295-304. 5. Malempati S, et al. *J Clin Oncol.* 2007;25:5800-7. 6. Schrappe et al. *N Engl J Med.* 2012;366:1371-1381. 7. Locatelli F, et al. *Blood.* 2012;120:2807-16. 8. Peters C, et al. *J Clin Oncol.* 2015;33:1265-1274.

Immuno-phenotype	B-cell precursor			(pre) T		
Time-Point/Site	Extra-med. Isolated	Bone marrow combined	Bone marrow isolated	Extra-med. isolated	Bone marrow combined	Bone marrow isolated
Very early	**HR**	**HR**	**HR**	**HR**	**HR**	**HR**
Early	**SR**	**SR**	**HR**	**SR**	**HR**	**HR**
Late	**SR**	**SR**	**SR**	**SR**	**HR**	**HR**

Late defined as: >6 months after cessation of frontline therapy, ie, >30 month after initial diagnosis



Arrow down (↓), bone marrow puncture with CR/MRD assessment; MRD, minimal residual disease; ®, randomisation; RAD, irradiation, if indicated; SCA/B, SR consolidation arm A/B; SCT, stem-cell transplantation; SIA/B, SR induction arm A/B; SMA/B, SR maintenance arm A/B; SR, standard risk group;


week
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Termination of IntReALL Trial
Arm HR-A
HIA (R3Mitox)
HR
R
Arm HR-B
HIB (R3Mitox+B)
HC1 (mHR1)
HC2 (mHR3)
HC3 (mHR2)
SCT
Invest. Window
BM/MRD
week
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

IntReALL-BCP 2020 – New risk stratification

VHR (15%)

- **TP53 alteration**
- **Hypodiploidy**
- **T(1;19)/(17;19)**
- **MLL/AF4**
- **Very early relapse (<18 mo)**

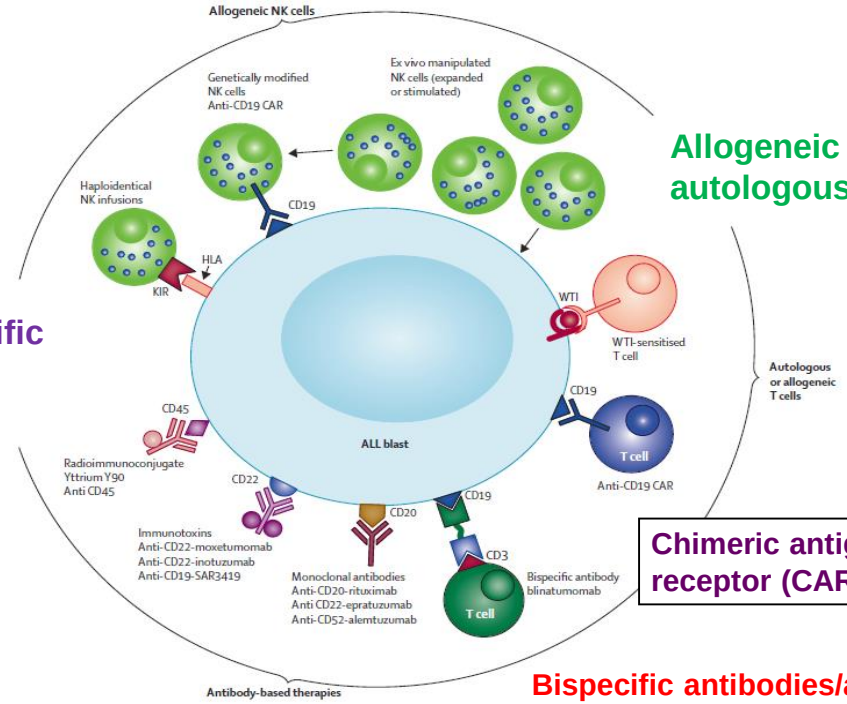
SR (60%)

- Late isolated or combined medullary/extramedullary relapse (HSCT depending on MRD response)

HR (25%)

- Early isolated or combined medullary/extramedullary relapse

New immunological approaches under investigation in childhood ALL



Allogeneic and autologous NK cells

Immunotoxin-specific antibodies

Chimeric antigen receptor (CAR) T cells

Bispecific antibodies/antibody constructs

Adapted from Bhojwani D, Pui CH. *Lancet Oncol.* 2013;14:e205-e217.

A phase I/II study of inotuzumab ozogamicin as a single agent and in combination with chemotherapy for pediatric CD22-positive relapsed/refractory ALL, ITCC-059 study

Patient population and study design

Stratum 1: R/R CD22 positive BCP-ALL patients, aged 1-18 years

- ***Stratum 1A*** Single agent InO — Enrolment completed
- ***Phase 2*** InO to determine preliminary activity — Open at DL2
- ***Stratum 1B*** InO in combination with adjusted R3 block — Not yet open

Stratum 2: Other CD22 positive B-cell malignancies

- ***Stratum 2*** Explorative cohort — Open at DL2

Dose level 2: 1.8 mg/m^2 in course 1

- C1D1: 0.8 mg/m^2
- C1D8 and C1D15 (and next doses): 0.5 mg/m^2

Patient characteristics

	N=25
Age, median (range), y	11 (1.7-16.9)
Disease Status	Refractory, 3 (12%) ≥2nd relapsed ALL, 15 (60%) and 1st relapse post-HSCT, 7 (28%)
Prior treatment regimens, median, range	2 (2-7)
Previous HSCT	11 (44%)
WBC, median $x10^9$/L	3.5 $x10^9$/L (range 0.2-8.6)

- **Toxicity: Febrile neutropenia/infections and Gr 3-4 transaminases elevation related to InO**
- **2 cases of VODs (gr 3-4) were reported after InO, both after further chemotherapy (including HD-MTX) for R/R disease. None of these pts received any HSCT**

Brivio E, et al. ASH Annual Meeting 2019.

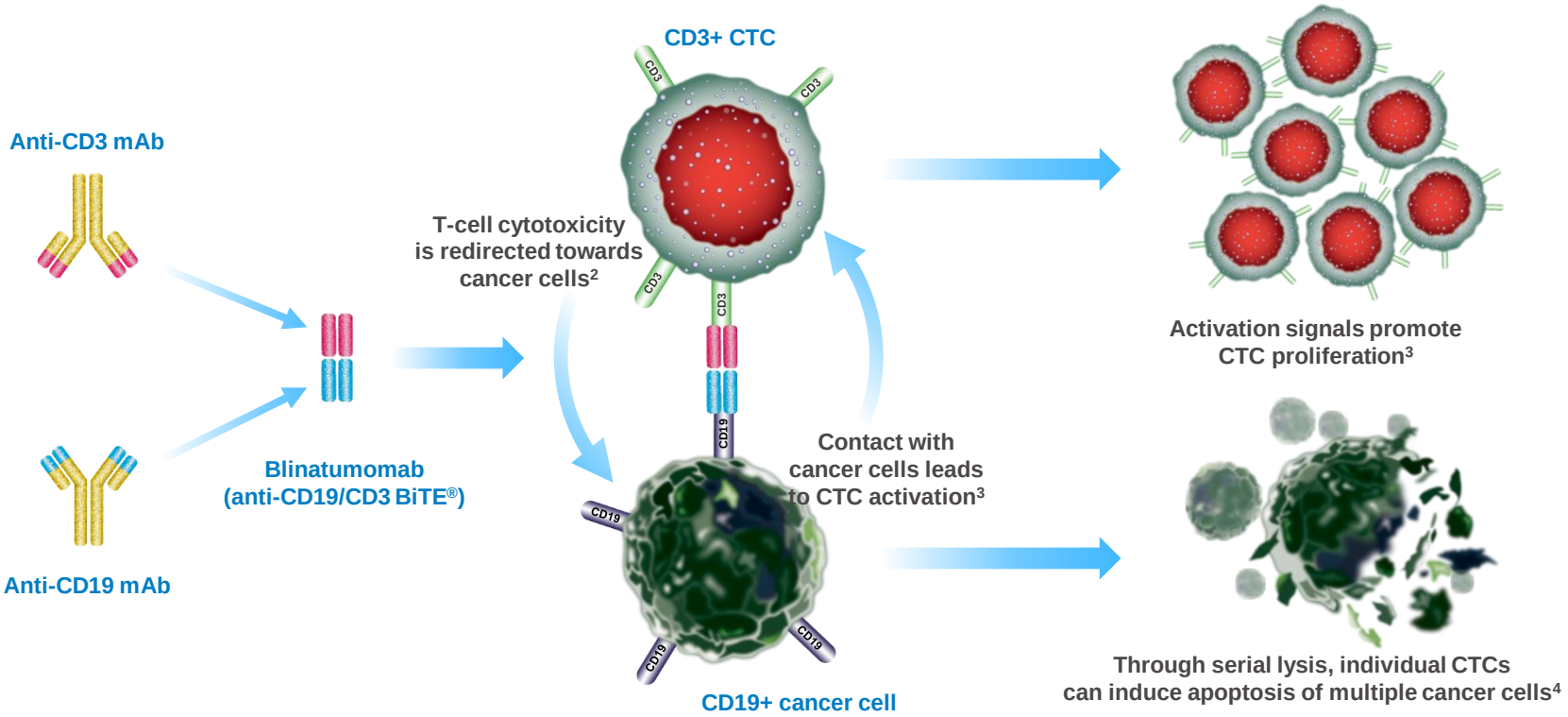
Results, n = 20

ORR after 1 course	80% 75% at DL1 85% at DL2 (CR n = 15, CRp n = 1, CRi n = 4)
Achievement of MRD neg	79% (n = 15)
Median FU	13.3 months (range 1.1–14.0)
Median duration of response	8 months (range 1.1–14.0)
6-m EFS/OS	63.3% (95% CI: 45.8–87.6) 66.7% (95% CI 47.9-93.0)
12 m EFS/OS	33.4% (95% CI: 16.5–67.4) 38.7% (95% CI: 21.3–70.4)

- 8 patients received a consolidation treatment with HSCT (n = 6) or CAR T cells (n = 2) (median of 61 days [range 23-125] after the last InO dose)
- 2/13 patients with available samples showed CD22-negativity at relapse

Brivio E, et al. ASH Annual Meeting 2019.

The BiTE® blinatumomab: Designed to bridge cytotoxic T cells (CTCs) to CD19-expressing cancer cells, resulting in cancer cell death[1]



BiTE®, bispecific T-cell engager; mAb, monoclonal antibody.

1. Baeuerle PA, Reinhardt C. *Cancer Res.* 2009;69:4941-4944; 2. Bargou R, et al. *Science.* 2008;321:974-977; 3. Klinger M, et al. *Blood.* 2012;119:6226-6233; 4. Hoffmann P, et al. *Int J Cancer.* 2005;115:98-104.

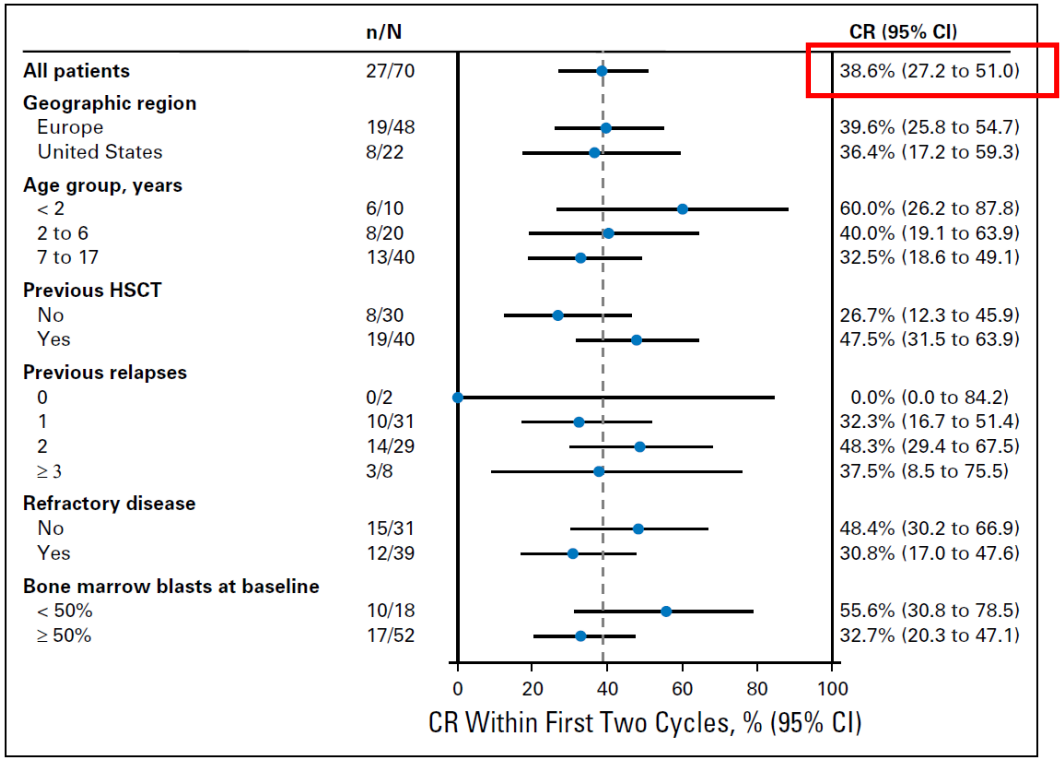
Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

Arend von Stackelberg,[1] Franco Locatelli,[2] Gerhard Zugmaier,[3] Rupert Handgretinger,[4] Tanya M. Trippett,[5] Carmelo Rizzari,[6] Peter Bader,[7] Maureen M. O'Brien,[8] Benoît Brethon,[9] Deepa Bhojwani,[10] Paul Gerhardt Schlegel,[11] Arndt Borkhardt,[12] Susan R. Rheingold,[13] Todd Michael Cooper,[14] Christian M. Zwaan,[15] Phillip Barnette,[16] Chiara Messina,[17] Gérard Michel,[18] Steven G. DuBois,[19] Kuolung Hu,[20] Min Zhu,[20] James A. Whitlock,[21] and Lia Gore[22]

[1]Charité Campus Virchow, Berlin; [2]Ospedale Pediatrico Bambino Gesù, Rome, University of Pavia, Pavia; [3]Amgen Research (Munich) GmbH, Munich, Germany; [4]University of Tübingen, Tübingen; [5]Memorial Sloan Kettering Cancer Center, New York, NY; [6]San Gerardo Hospital, University of Milano-Bicocca, Monza; [7]Hospital for Children and Adolescents III, University of Frankfurt, Frankfurt; [8]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [9]Hôpital Robert Debré, Service Hématologie-Immunologie Pédiatrique, Paris; [10]Children's Hospital of Los Angeles; [11]University Children's Hospital Würzburg, Würzburg; [12]University of Düsseldorf Medical Faculty, Düsseldorf, Germany; [13]Children's Hospital of Philadelphia, Philadelphia, PA; [14]Seattle Children's Hospital, Seattle, WA; [15]Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, Netherlands; [16]Primary Children's Medical Center, Salt Lake City, UT; [17]Clinica di Oncoematologia Pediatrica, Università degli Studi di Padova, Padova, Italy; [18]Hôpital de la Timone, Marseille, France; [19]Dana-Farber/Boston Children's Cancer and Blood Disorders Center and Harvard Medical School, Boston, MA; [20]Amgen, Thousand Oaks, CA; [21]University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada; [22]University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO.

von Stackelberg A, et al. *J Clin Oncol.* 2016;25:181-184.

Blinatumomab antileukaemic activity across different groups



CR, complete response; HSCT, hematopoietic stem-cell transplant.

von Stackelberg A, et al. *J Clin Oncol.* 2016;25:181-184.

High Remission Rates In Pediatric Patients With Resistant Acute Lymphoblastic Leukemia Treated With Blinatumomab: Updated Analysis Of An Expanded Access Study (RIALTO)

Franco Locatelli[1], Gerhard Zugmaier[2], Peter Bader[3], Sima Jeha[4], Paul-Gerhardt Schlegel[5], Jean-Pierre Bourquin[6], Rupert Handgretinger[7], Benoit Brethon[8], Claudia Rossig[9], Christiane Chen-Santel[10]

[1]Department of Hematology and Oncology, IRCCS Bambino Gesù Children's Hospital, Sapienza, University of Rome, Italy;[2]Amgen Research (Munich) GmbH, Munich, Germany; [3]Department for Children and Adolescents, University Hospital Frankfurt, Frankfurt, Germany; [4]St Jude Children's Research Hospital, Memphis, TN; [5]University Children's Hospital Würzburg, Würzburg, Germany; [6]Department of Pediatric Oncology, Children's Research Centre, University Children's Hospital Zurich, Zurich, Switzerland; [7]Hematology/Oncology, University Children's Hospital Tübingen, Tübingen, Germany; [8]Pediatric Hematology and Immunology Department, Robert Debré Hospital, APHP, Paris, France; [9]University Children's Hospital Münster, Münster, Germany; [10]Charité University Medicine Berlin, Berlin, Germany

Locatelli F, et al. *Blood Cancer J.* 2020, *in press*.

Patient eligibility

Key inclusion criteria	• Age >28 days and <18 years • CD19-positive B-precursor ALL with ≥5% blasts in the bone marrow, or <5% blasts but with minimal residual disease (MRD) level ≥10^{-3} • Relapsed/refractory disease defined as – ≥2 relapses – Relapse after alloHSCT – Refractory to prior treatments • Prior treatment with blinatumomab was allowed, provided the patient was not blinatumomab-refractory or intolerant, and leukemic cells were CD19 positive
Key exclusion criteria	• Clinically relevant CNS pathology • Chemotherapy within 2 weeks, radiotherapy within 4 weeks, or immunotherapy within 6 weeks • Grade 2–4 acute GvHD or active chronic GvHD • Immunosuppressive agents to prevent or treat GvHD within 2 weeks

CNS, central nervous system; GvHD, graft-versus-host disease; alloHSCT, allogeneic haematopoietic stem cell transplantation.
Locatelli F, et al. *Blood Cancer J.* 2020, *in press*.

Best response during first 2 cycles of blinatumomab

Response	Patients with ≥5% blasts at baseline (N = 98)	
	n (%)	95% CI
CR in first 2 cycles, n (%)	58 (59)	48.8–69.0
CR with full recovery of peripheral blood counts	39 (67)	30.0–50.2
CR with incomplete recovery of peripheral blood counts	6 (10)	2.3–12.9
CR without recovery of peripheral blood counts	13 (22)	7.3–21.6
MRD response	46 (47)	36.8–57.3
MRD non-responsive	19 (19)	21.1–28.6
Proceeded to HSCT, n (%)	36 (62)	48.4–74.5
Hypoplastic or acellular bone marrow	1 (1)	0.0–5.6
Partial remission	0	0.0–3.7
Non-CR		
Stable disease	5 (5)	1.7–11.5
Progressive disease	20 (20)	12.9–29.7
Not evaluable	1 (1)	0.0–5.6
No response data	13 (13)	7.3–21.6
Prior HSCT	45 (46)	35.9–56.3
Genetic abnormality	30 (31)	21.9–40.9

Locatelli F, et al. *Blood Cancer J.* 2020, *in press*.

Response within first 2 cycles of blinatumomab

Patient Subgroup	CR		CR with full haematological recovery		MRD	
	n/N1	%	n/N1	%	n/N1	%
Baseline blast category						
<5%	11/12	92	3/12	25	11/12	92
5-49%	39/55	71	26/55	47	33/55	60
≥50%	19/42	45	13/42	31	13/42	31
Genetic abnormality						
Yes	17/32	53	11/32	34	11/32	34
No	52/78	67	31/78	40	46/78	59
t(17;19)	2/2	100	2/2	100	2/2	100
Down syndrome	4/4	100	2/4	50	4/4	100
Prior HSCT						
Yes	28/45	62	19/45	42	22/45	49
No	41/65	63	23/65	35	35/65	54
Prior blinatumomab	4/4	100	4/4	100	3/4	75
Prior relapses						
1	17/30	57	12/30	40	13/30	43
≥2	42/63	67	24/63	38	36/63	57

alloHSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; MRD, minimal residual disease. n/N1, number of responders/total number of patients with evaluable data under each category.

Locatelli F, et al. *Blood Cancer J.* 2020, *in press*.

Superior Event-free Survival With Blinatumomab Versus Chemotherapy in Children With High-risk First Relapse of B-cell Precursor Acute Lymphoblastic Leukemia: A Randomized, Controlled Phase 3 Trial

Franco Locatelli, Gerhard Zugmaier, Carmelo Rizzari, Joan Morris, Bernd Gruhn, Thomas Klingebiel, Rosanna Parasole, Christin Linderkamp, Christian Flotho, Arnaud Petit, Concetta Micalizzi, Noemi Mergen, Abeera Mohammad, Cornelia Eckert, Anja Moericke, Mary Sartor, Ondrej Hrusak, Christina Peters, Vaskar Saha, and Arend von Stackelberg

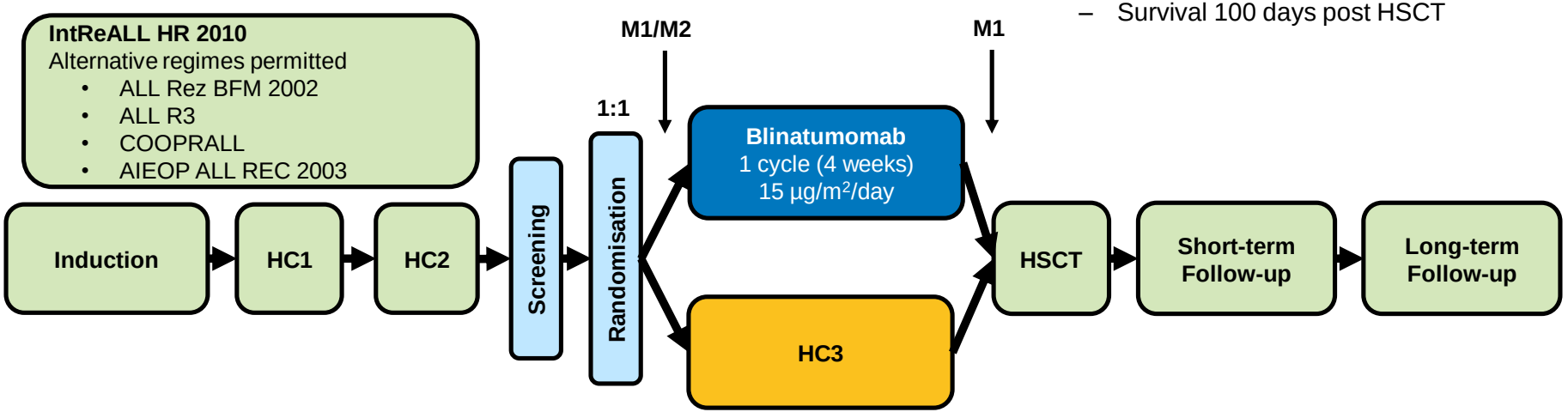
Locatelli F, et al. EBMT 2020; Abstract GS2-5 and oral presentation.

Open-label, randomised, phase III trial: 47 centres, 13 countries

Key eligibility criteria
- Age >28 days <18 years
- HR 1st relapse Ph– BCP-ALL
- M1 or M2 marrow at randomisation
- No CNS disease, unless treated before enrolment
- No clinically relevant CNS pathology

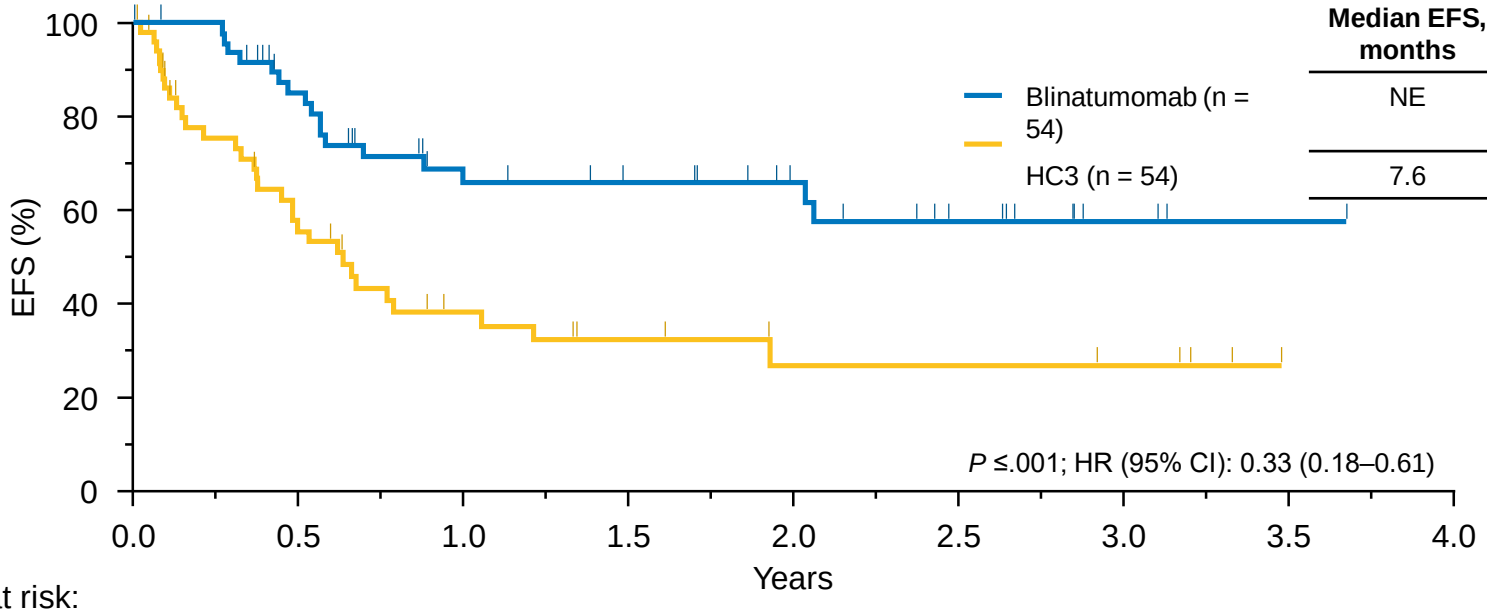
Stratification
- Age: <1 year, 1 to 9 years, >9 years
- BM status at end of HC2
  - M1 with MRD >10^{-3}
  - M1 with MRD <10^{-3}
  - M2

Endpoints
- Primary: EFS
- Secondary
  - OS
  - MRD response (end of blinatumomab or HC3)
  - Cumulative incidence of relapse
  - Incidence of AEs
  - Survival 100 days post HSCT



BCP, B-cell precursor; EFS, event-free survival; HC, high-risk consolidation.
Locatelli F, et al. EBMT 2020; Abstract GS2-5.

Superior EFS in the blinatumomab arm



	Median EFS, months	95% CI
Blinatumomab (n = 54)	NE	24.4–NE
HC3 (n = 54)	7.6	4.5–12.7

Subjects at risk:

Blinatumomab	54	50	38	29	24	23	21	19	16	13	10	7	4	1	1	0
HC3	54	35	25	17	13	11	9	8	5	5	5	5	4	2	0	

P, stratified log rank P-value; HR, hazard ratio from stratified Cox regression.
Adapted from Locatelli F, et al. EBMT 2020; Abstract GS2-5 and oral presentation.

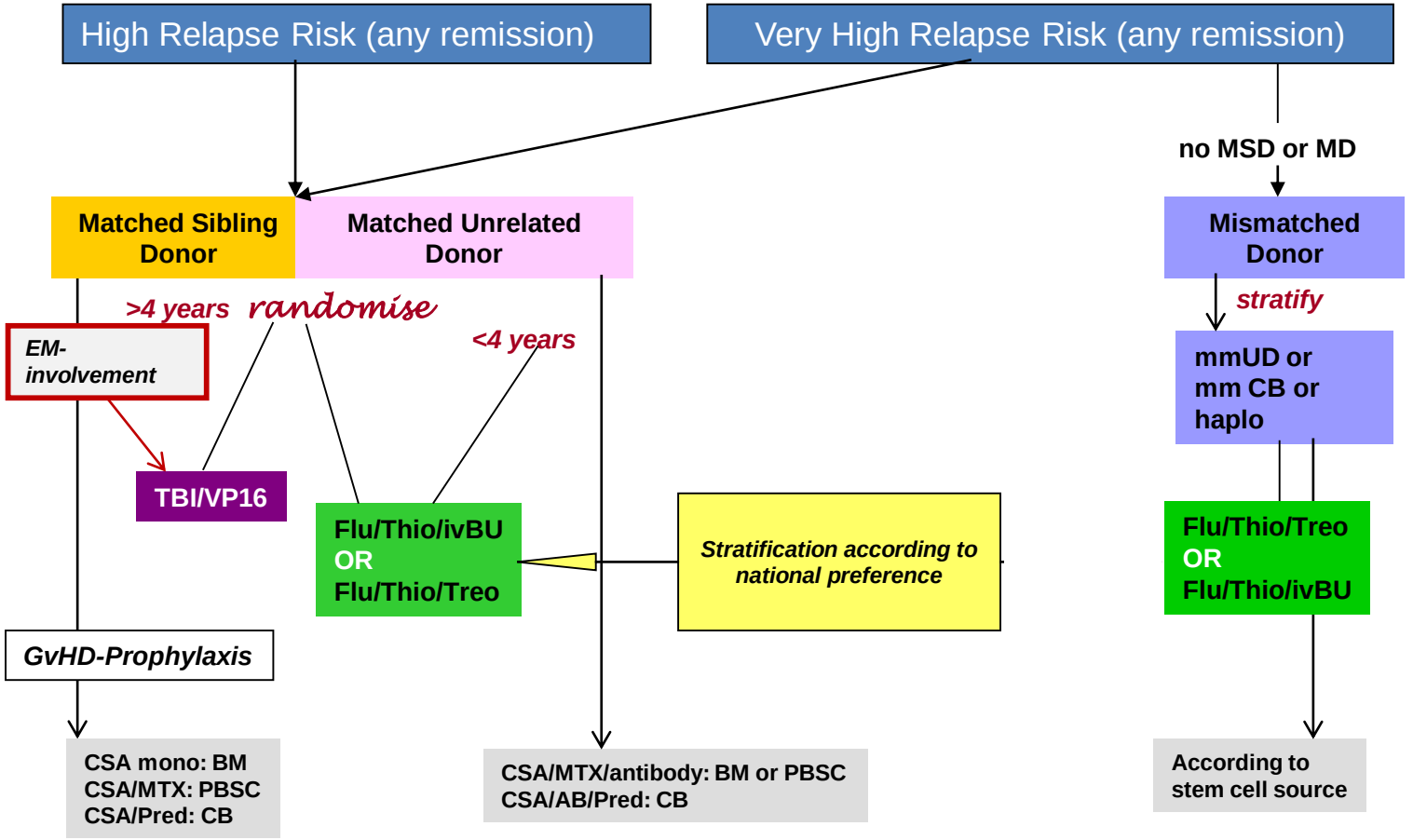
TBI or Chemotherapy-Based Conditioning for Children and Adolescents with ALL: the **FORUM** Trial on Behalf of the AIEOP-BFM-ALL SG, IBFM-SG, INTREALL-SG and EBMT-PD WP

Christina Peters

Vienna, Austria

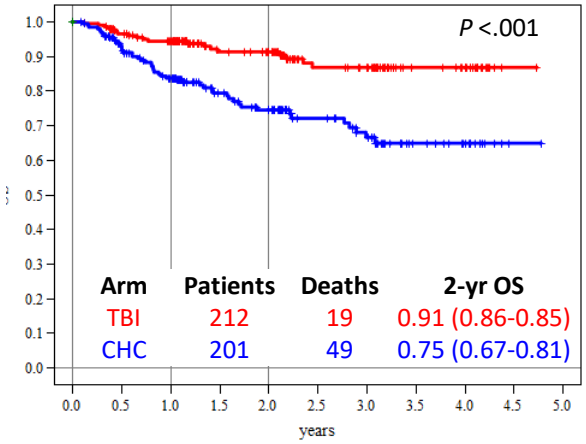
Date: June 12, 15.00 – 17.00
Program section: Presidential Symposium

Study Design ALL SCTped FORUM

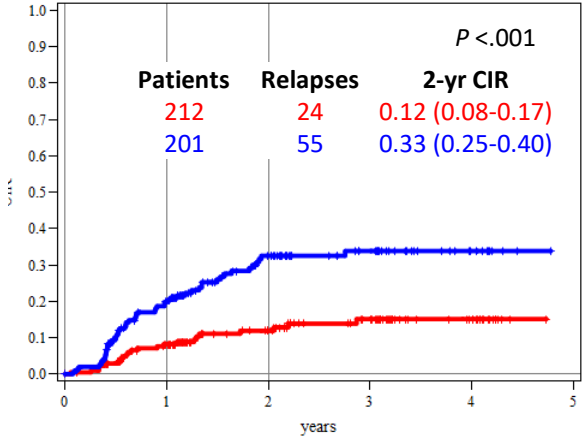


Results: Intention to treat

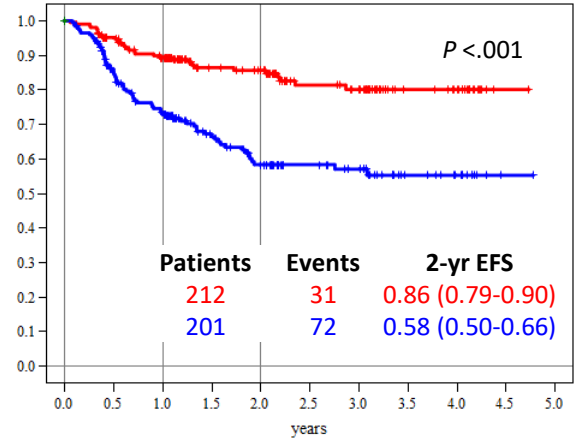
Overall Survival



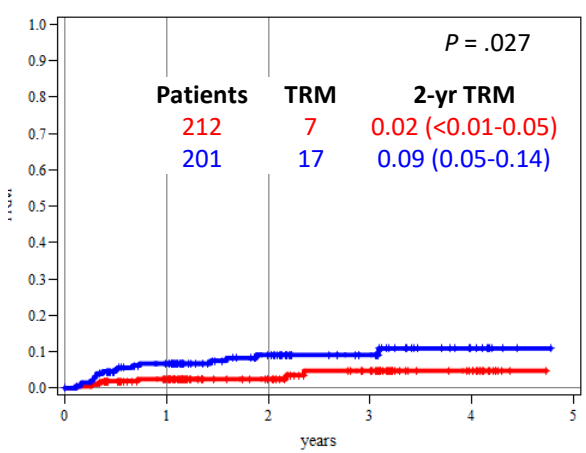
Relapses (CIR)



EFS

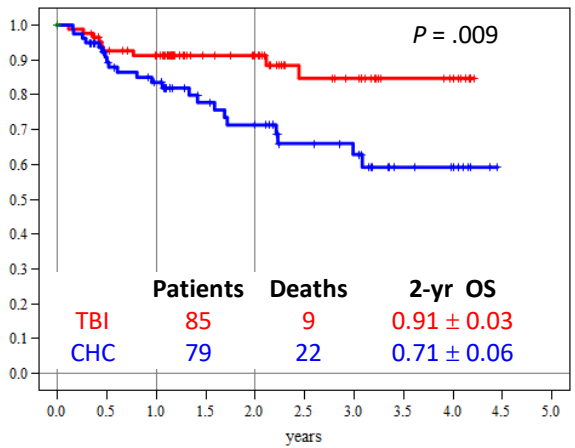


TRM

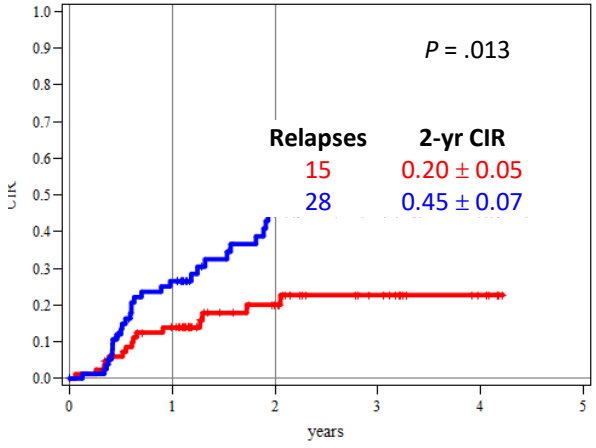


Results: CR2 Intention to treat

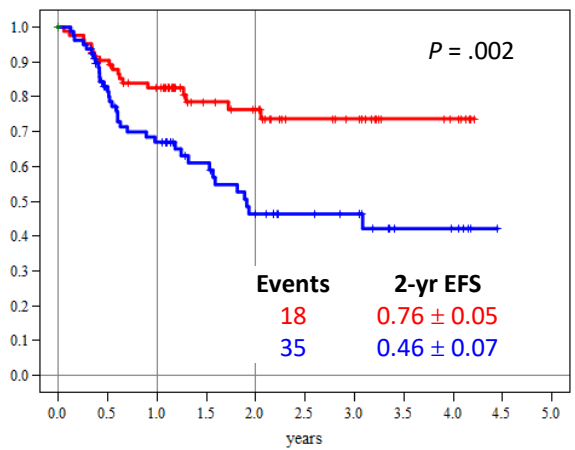
Overall Survival



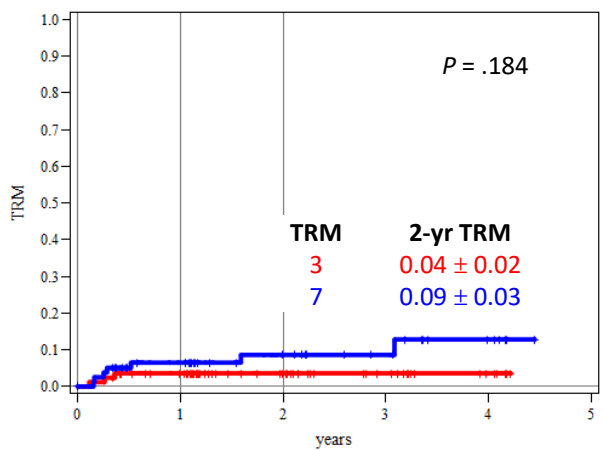
Relapses (CIR)



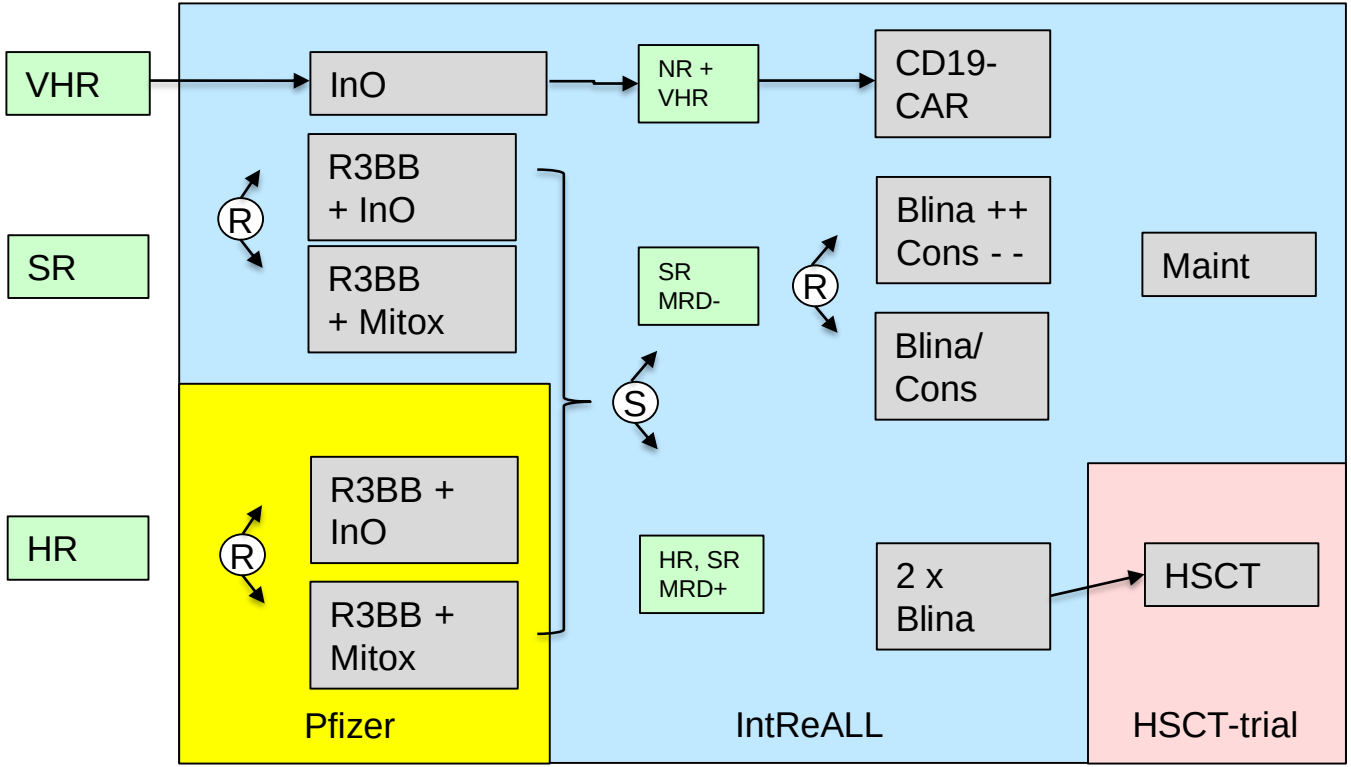
EFS



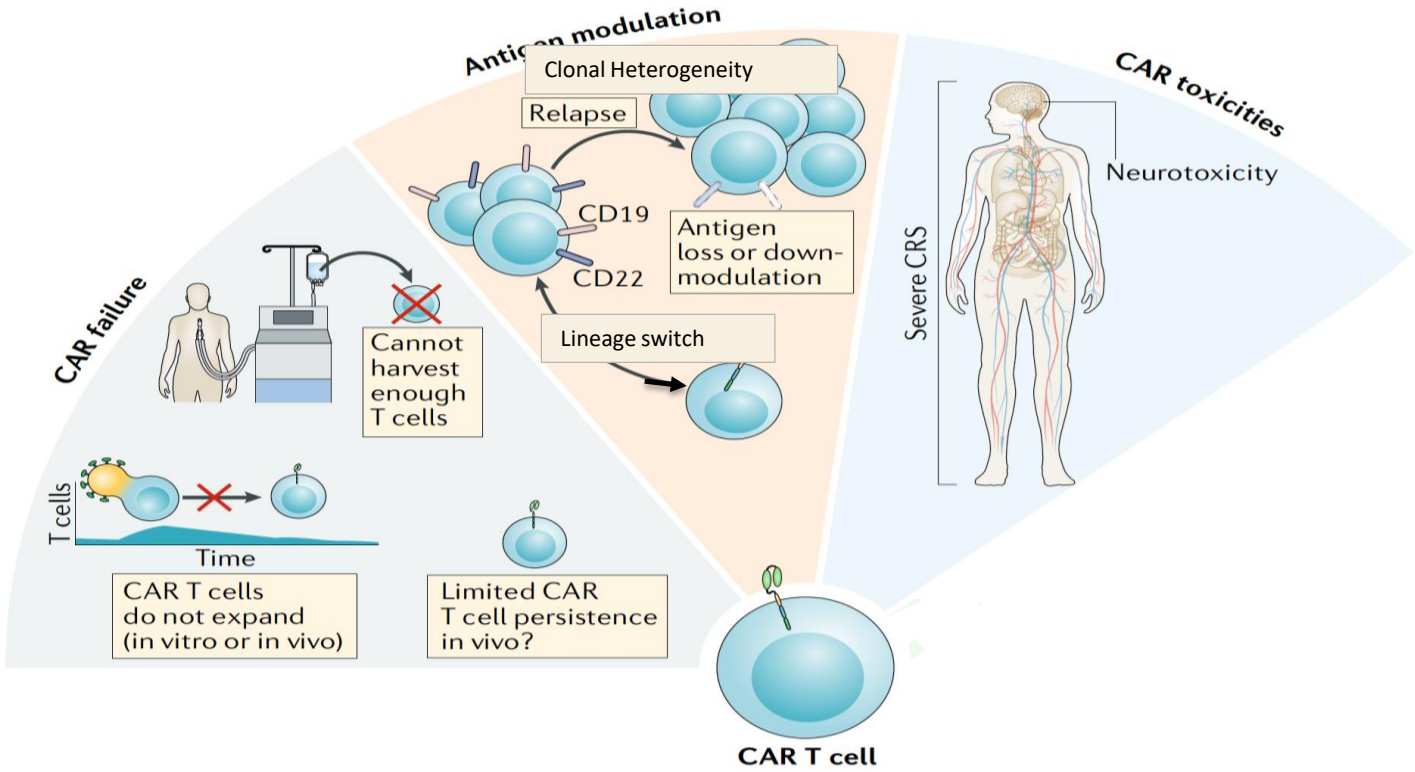
TRM



Design IntReALL-BCP 2020 – Updated 15.11.19



Current limitations of CAR T cells

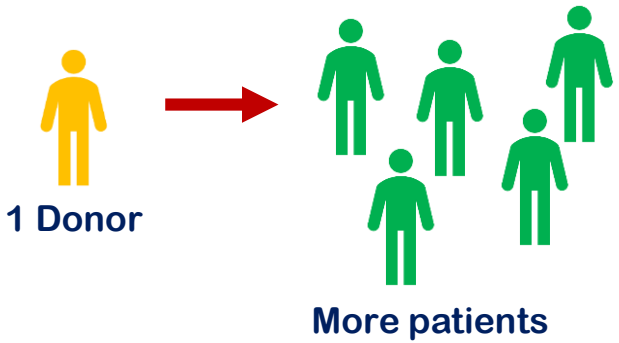


Wayne A, adapted from Shah, Fry. *Nat Rev Clin Oncol.* 2019.

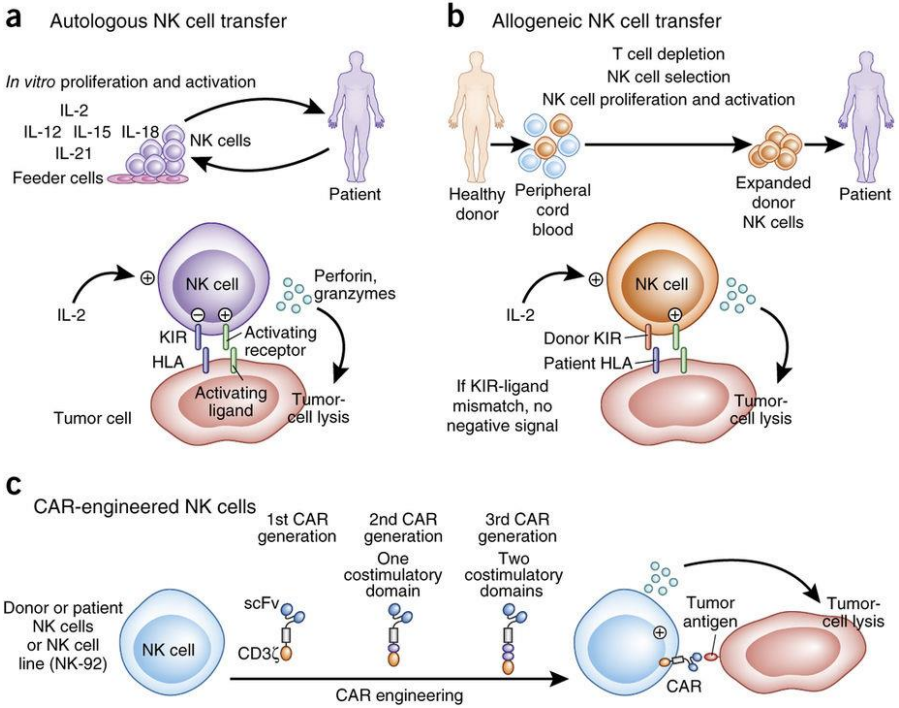
Advantages of NK cells for CAR therapy

CAR-NK CD19

- **Allogenic Product**
  - ✓ ‘Off the shelf’
  - ✓ Potential low cost

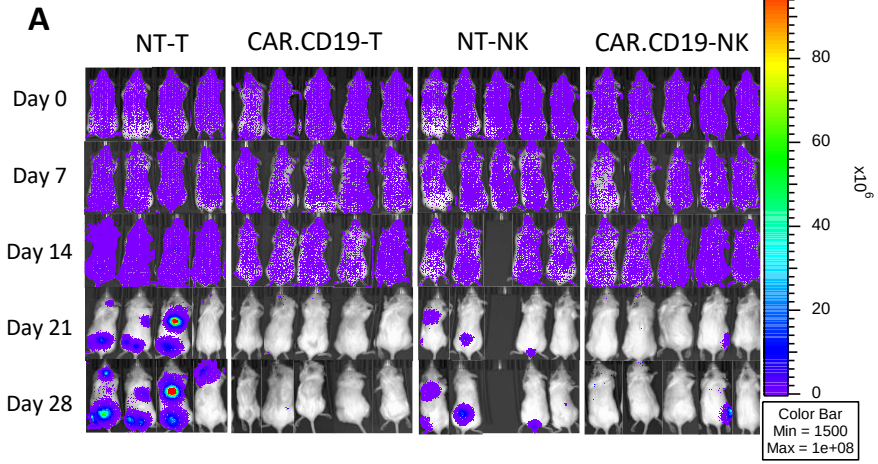


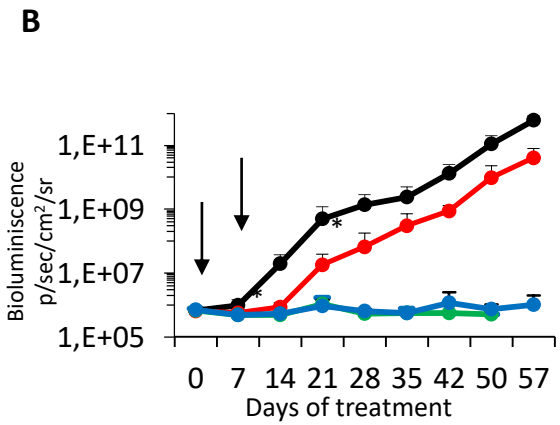
- **Low/Absent GVHD**

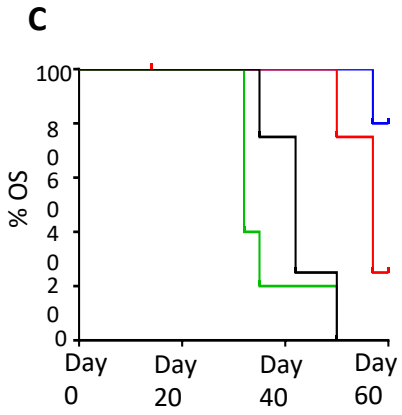


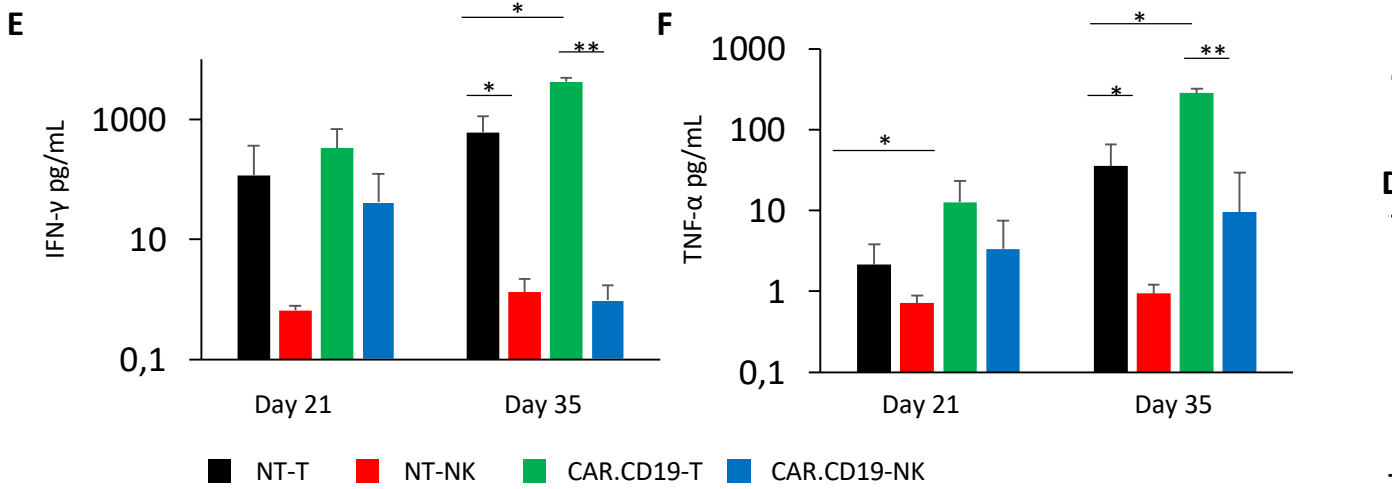
Camille Guillerey, et al. *Nat Immunol.* 2016.

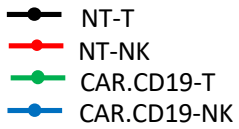
CAR NK cells











D

	P value
NT-T vs NT-NK	.018
NT-T vs CAR.CD19-T	n.s.
NT-NK vs CAR.CD19-NK	n.s.
CAR.CD19-T vs CAR.CD19-NK	.001
NT-T vs CAR.CD19-NK	.003
NT-NK vs CAR.CD19-T	.01

Quintarelli C, et al. *Leukemia*. 2020.

Global Leukemia Academy

Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Bispecific T-Cell Engagers for Pediatric ALL

Patrick Brown

APTITUDE HEALTH®

BiTE Immunotherapy for Pediatric ALL

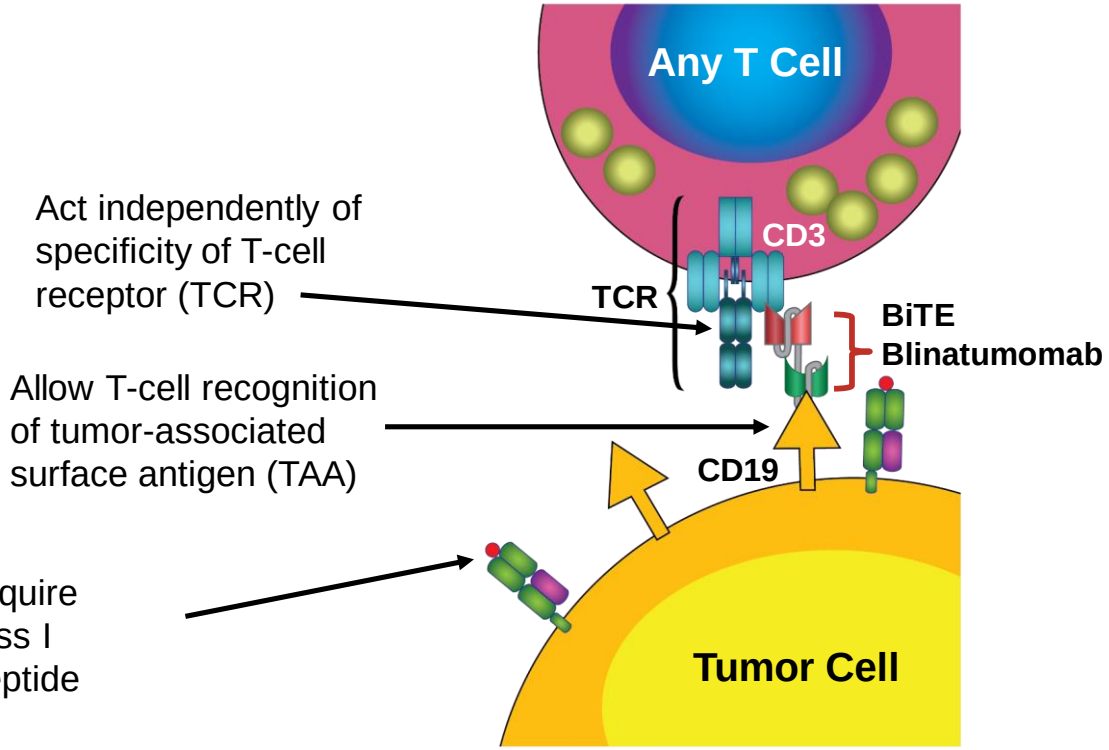
Patrick Brown, MD

Associate Professor of Oncology, Johns Hopkins University
Director, Pediatric Leukemia Program, Sidney Kimmel Comprehensive Cancer Center
Vice Chair for Relapse, COG ALL Committee
Chair, NCCN ALL Guideline Panel

Blinatumomab Mechanism of Action

Bispecific anti-CD19/CD3 BiTE antibody blinatumomab designed to kill autologous tumor cells

Relies on *functional endogenous cytotoxic T-cell response*

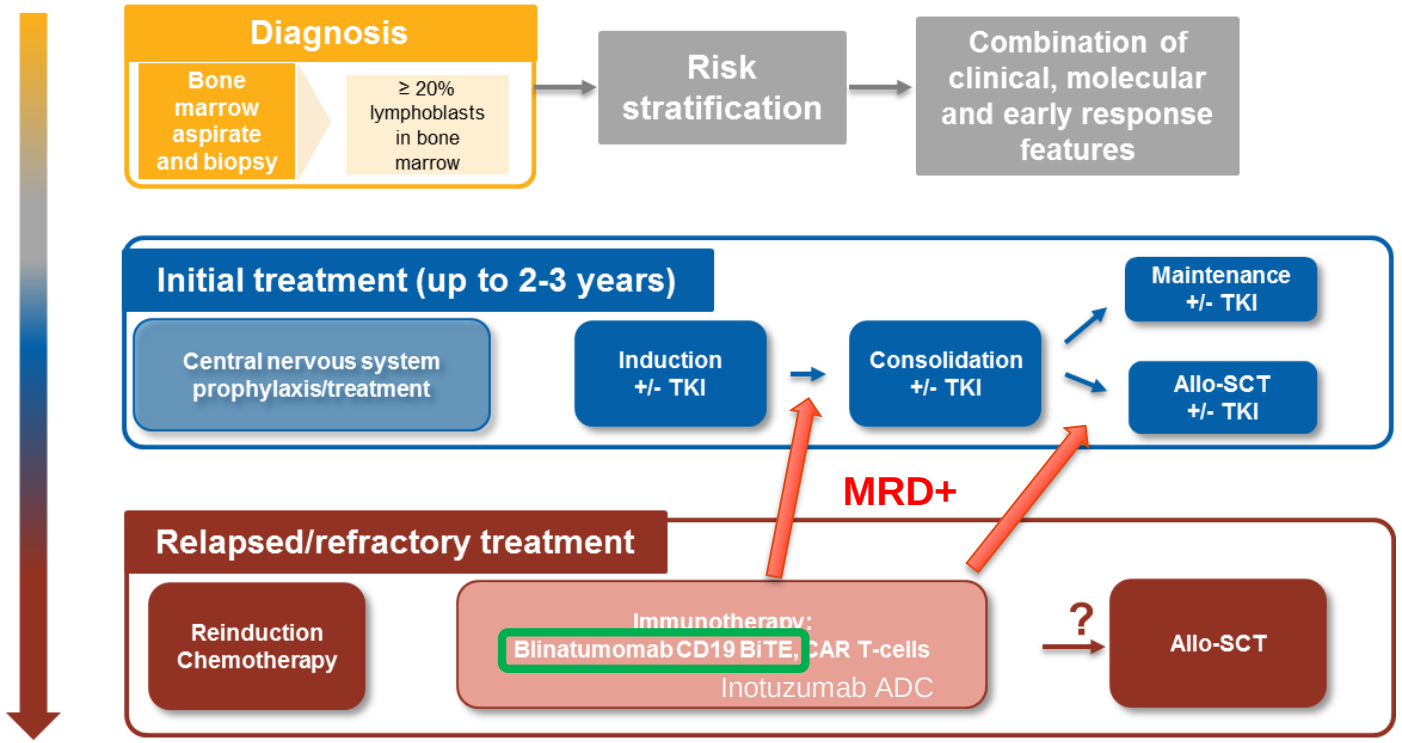


Given as 28-day continuous infusion IV; bag changes q 4-7 days

BiTE, Bispecific T-Cell Engager

Adapted from/courtesy of Amgen.

Diagnosis and Treatment of ALL



Allo-SCT, allogeneic stem cell transplant; FISH, fluorescence in situ hybridization; TKI, tyrosine kinase inhibitor (for BCR-ABL–positive disease)

NCCN Guidelines® for Acute Lymphoblastic Leukemia (Version 2.2015) © 2015 National Comprehensive Cancer Network, Inc. Available at: NCCN.org; 2. Hahn T, et al. *Biol Blood Marrow Transplant*. 2006;12(1):1-30. 3. Raetz EA, et al. *Hematol Am Soc Hematol Educ Program*. 2012;2012:129-136. 4. National Cancer Institute. Childhood acute lymphoblastic leukemia treatment (PDQ®). http://www.cancer.gov/cancertopics/pdq/treatment/childALL/HealthProfessional. Accessed July 10, 2017.

Response Rates and Survival in Relapsed/Refractory B-ALL

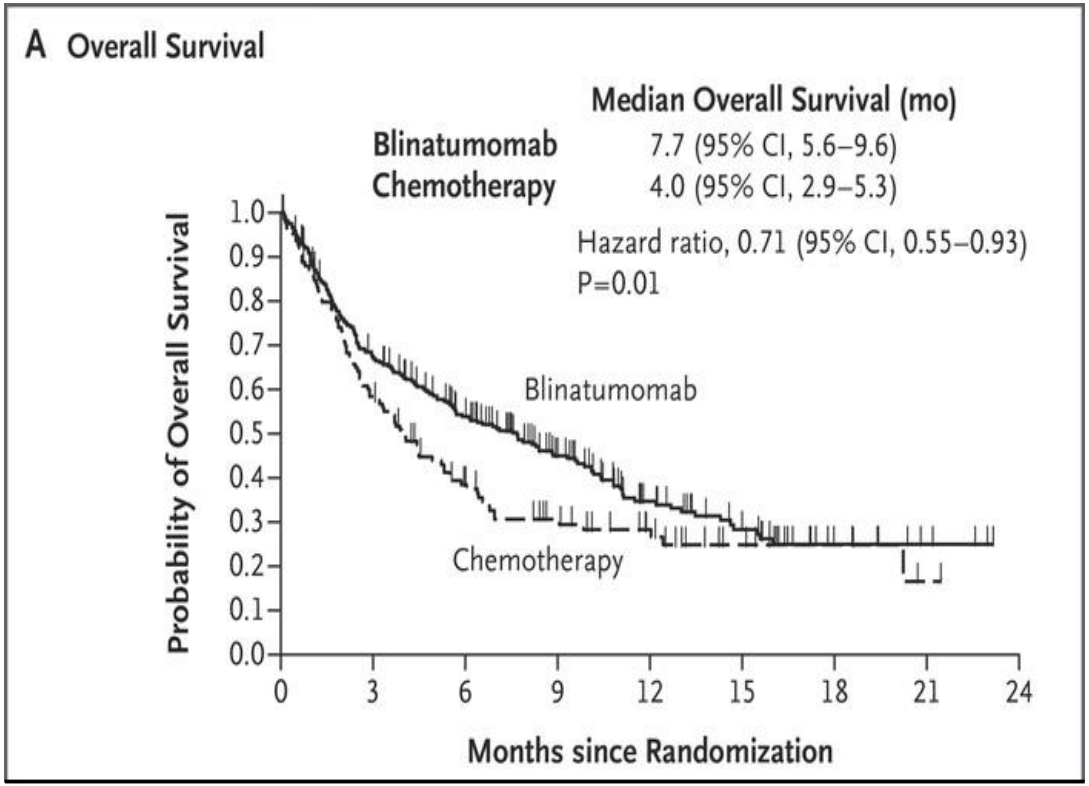
Agent	Type	Target	Responses (CR / MRD–)	Toxicities	FDA indication	Cost
Blinatumomab[1]	BiTE	CD19	44% / 33%	CRS, neurotoxicity	Adult and pediatric R/R B-ALL, MRD+	$180K
Inotuzumab[2]	Immuno-conjugate	CD22	81% / 63%	Hepatotoxicity	Adult R/R B-ALL	$168K
Tisagenlecleucel[3]	CAR T cell	CD19	81% / 81%	CRS,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

Unprecedented initial response rates . . . BUT . . .

1. Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847; 2. Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753; 3. Maude SL, et al. *N Engl J Med.* 2018;378:439-448.

Survival in R/R ALL (adult)

Blinatumomab

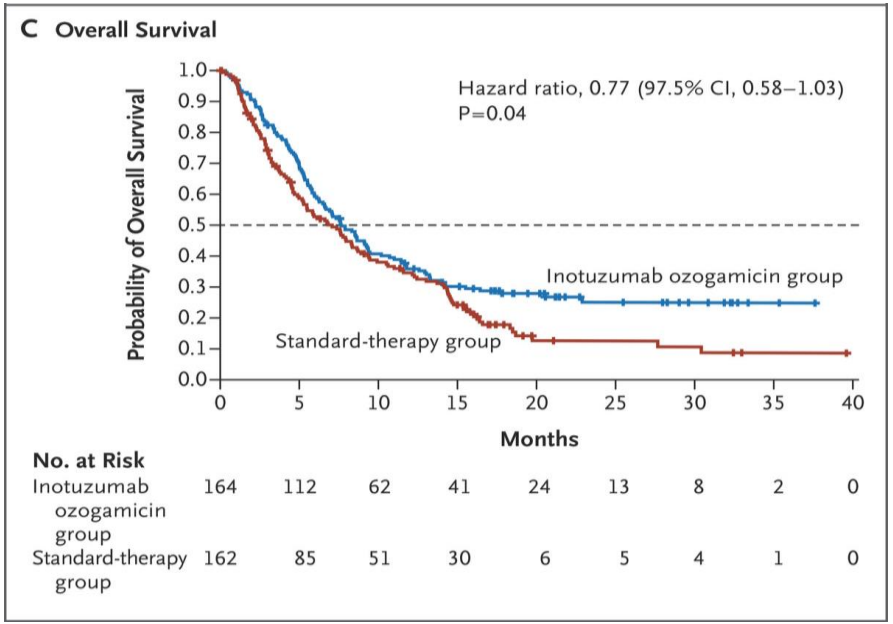


Blina: Improved survival initially, but not durable

Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

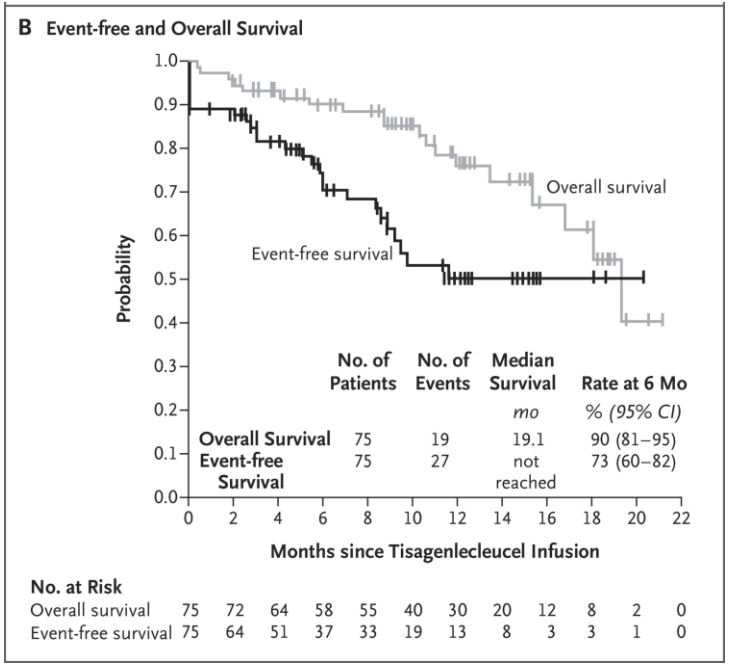
Survival in R/R ALL

Inotuzumab Ozogamicin[1]



Ino: Improved survival initially, but not durable

Tisagenlecleucel[2]



N Engl J Med 2018;378:439-448

Tisa: Durable survival improvement, but long-term EFS is in the 50% range

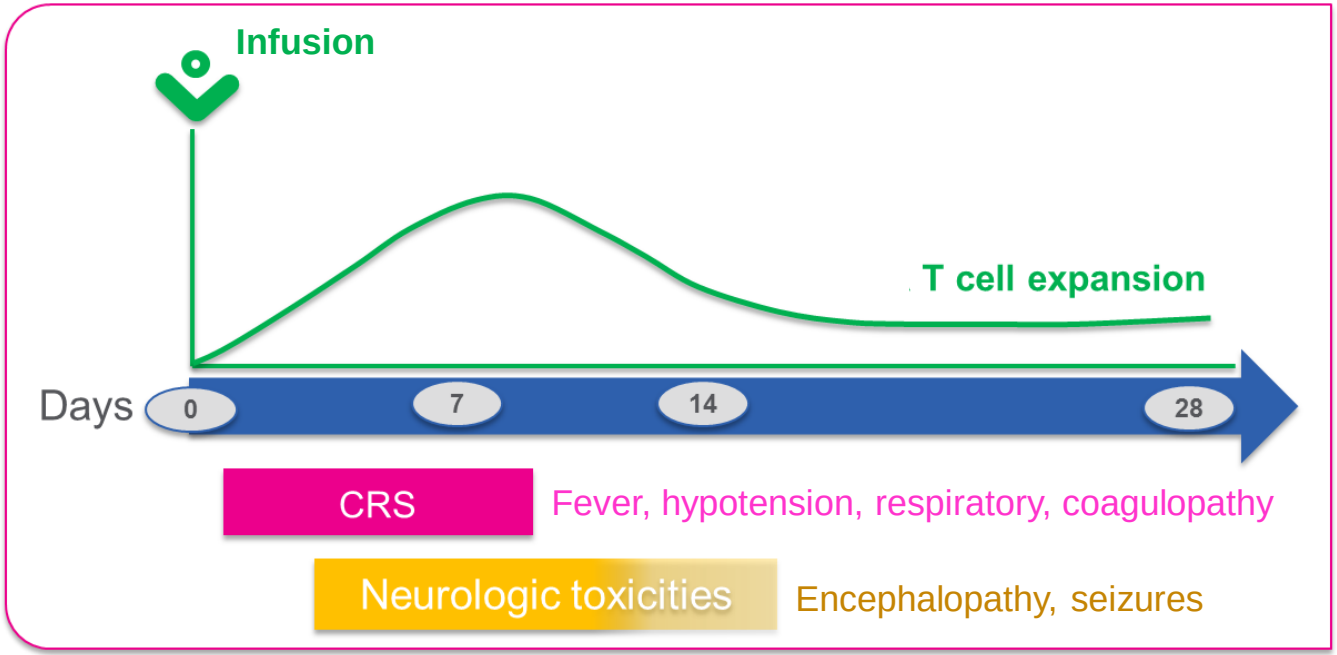
1. Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753; 2. Maude SL, et al. *N Engl J Med.* 2018;378:439-448.

Adverse Events in Relapsed/Refractory B-ALL

Agent	Type	Target	Responses (CR / MRD–)	Toxicities	FDA indication	Cost
Blinatumomab[1]	BiTE	CD19	44% / 33%	CRS, neurotoxicity	Adult and pediatric R/R B-ALL, MRD+	$180K
Tisagenlecleucel[2]	CAR T cell	CD19	81% / 81%	CRS, neurotoxicity	Refractory or 2nd/greater relapse; age up to 26 years	$475K

1. Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753; 2. Maude SL, et al. *N Engl J Med.* 2018;378:439-448.

AEs After Blinatumomab and CAR T Cells



- CRS 40%–80% (20%–40% Gr 3+), Neuro 10%–30% (5%–10% Gr 3+)
- CRS and neuro may **not** correlate
- CRS -> IVF, tocilizumab (anti-IL6R), steroids
- Neuro -> self-limiting, reversible; steroids (toci not effective)

MRD+

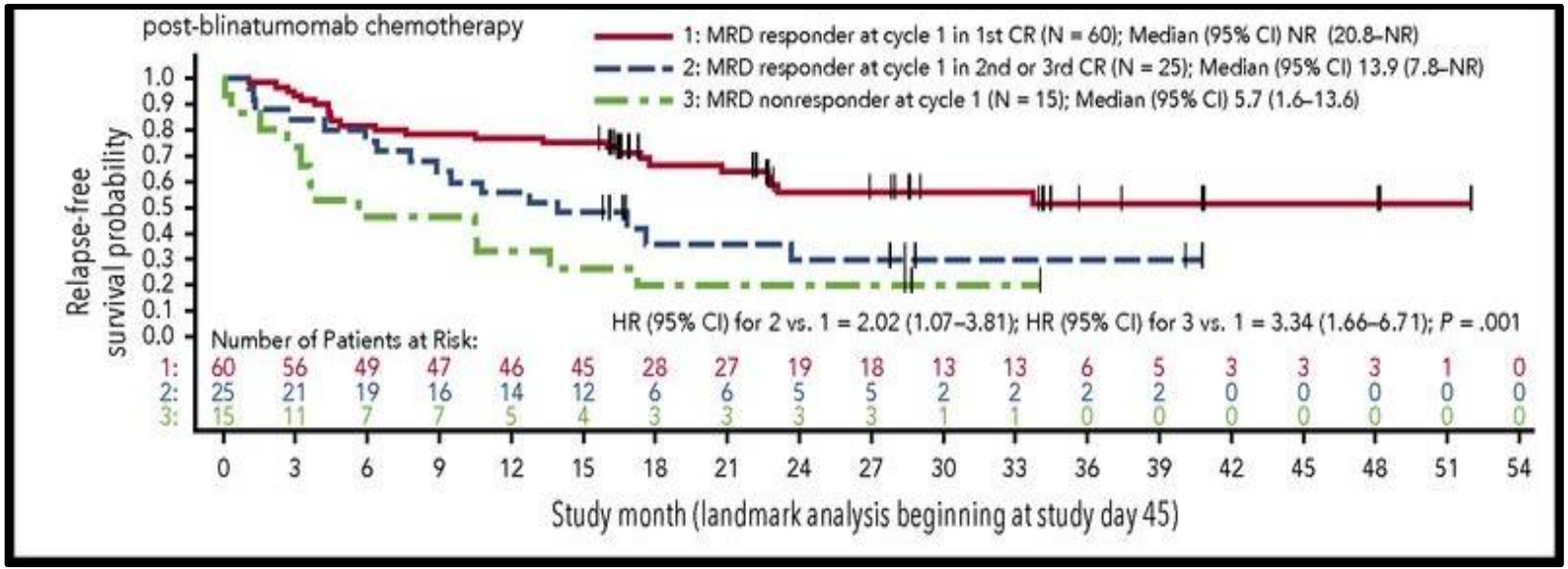
*Incidence of CRS strikingly lower in MRD+ setting; neurotox is similar

Adapted from/courtesy of Novartis.

Response Rates and Survival in MRD+ B-ALL

- N = 116 adults, international multicenter single-arm Ph 2
- MRD+ (>10^{-3})
- 35% MRD+ in CR2+
- MRD cleared in 78% after 1 cycle

- 67% proceeded to HSCT
- Significant percentage of those who did not remain in prolonged remission
- 20 of 74 proceeding to HSCT (27%) died of TRM



Gokbuget N, et al. *Blood.* 2018;131(14):1522-1531.

Stratifications

- Risk group (HR vs IR)
- For HR
  - Site (BM vs iEM)
  - For BM: CR1 duration (<18 vs 18-36 mo)

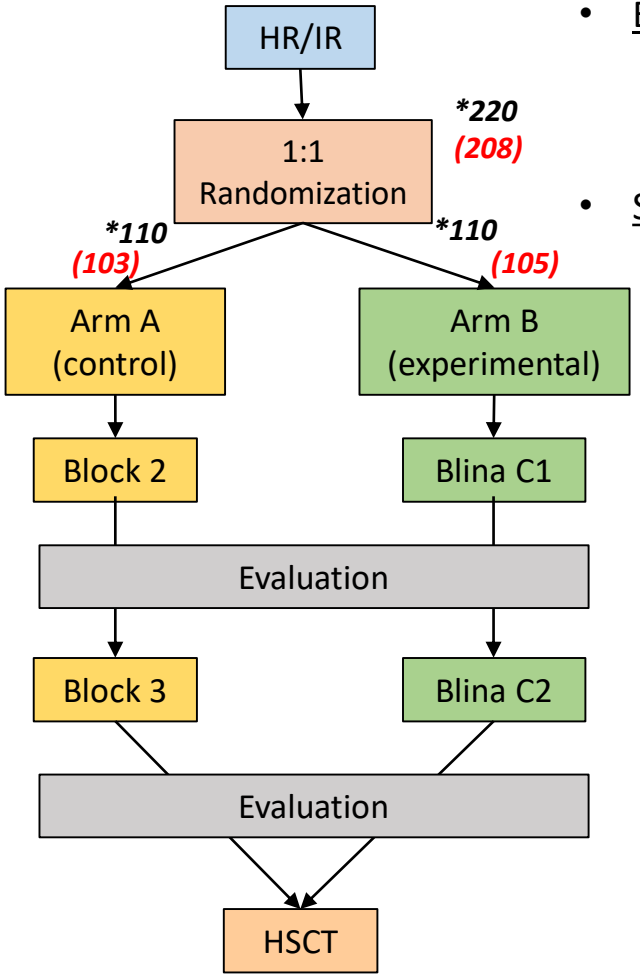
UKALLR3, Block 2*

- VCR, DEX week 1
- ID MTX, PEG week 2
- CPM/ETOP week 3
- IT MTX or ITT

UKALLR3, Block 3*

- VCR, DEX week 1
- HD ARAC, *Erwinia* weeks 1-2
- ID MTX, *Erwinia* week 4
- IT MTX or ITT

*UKALLR3 reference: Parker, et al. *Lancet.* 2010;376:2009-2017.



- Endpoints
  - Primary: DFS
  - Other: OS, MRD response, ability to proceed to HSCT
- Sample size n=220 (110 per arm)
  - Power 85% to detect HR 0.58 with 1-sided α=0.025
  - Increase 2-yr DFS from 45% to 63%

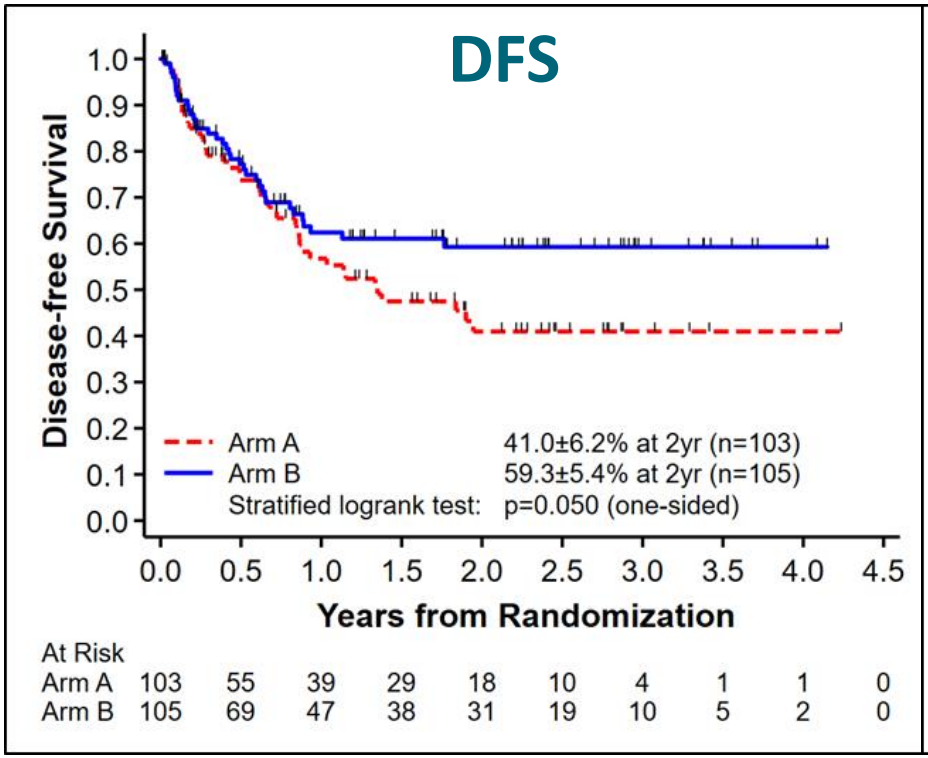
Blina C1 and Blina C2

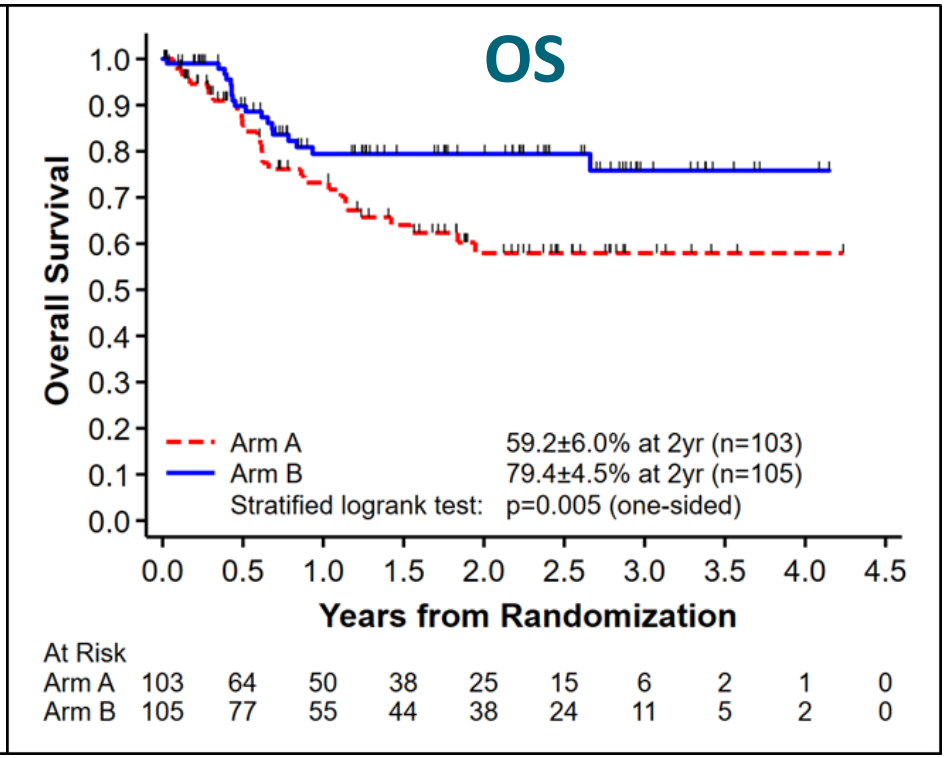
- Blinatumomab 15 µg/m^2/day × 28 days, then 7 days off
- Dex 5 mg/m^2/dose × 1 premed (C1 only)

- ***First patient randomized Jan 2015***
- ***Randomization halted Sep 2019 (95% projected accrual)***

Brown P, et al. *Blood.* 2019;134(suppl_2):LBA-1.

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



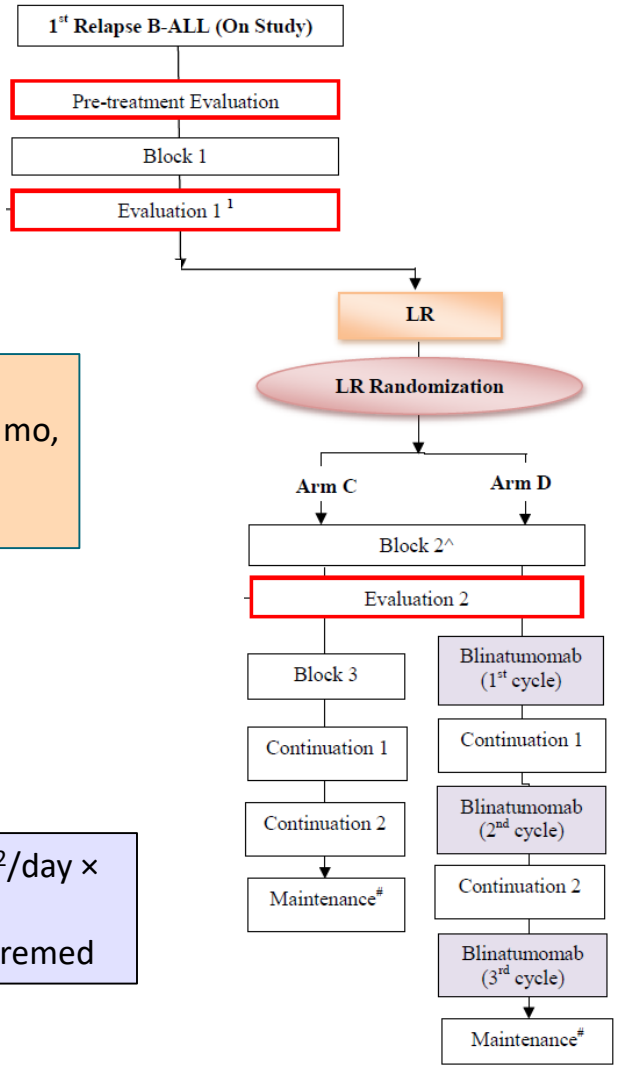


CHILDREN'S ONCOLOGY GROUP

Median follow-up 1.4 years

Brown P, et al. *Blood.* 2019;134(suppl_2):LBA-1.

LR Randomization



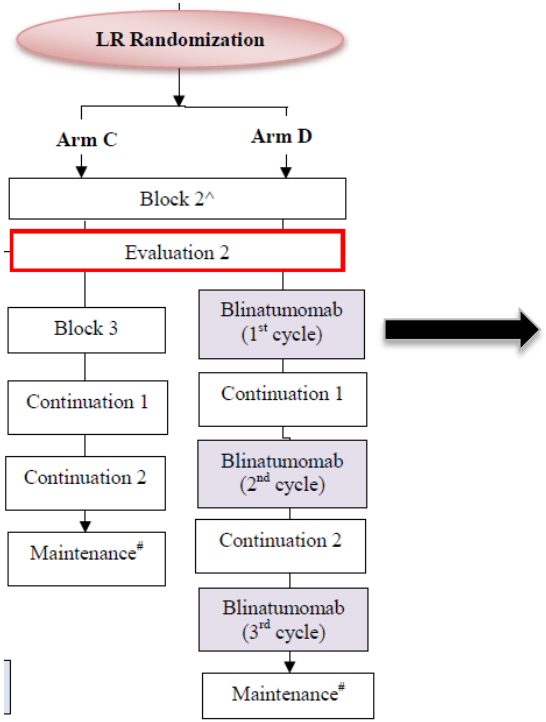
LR

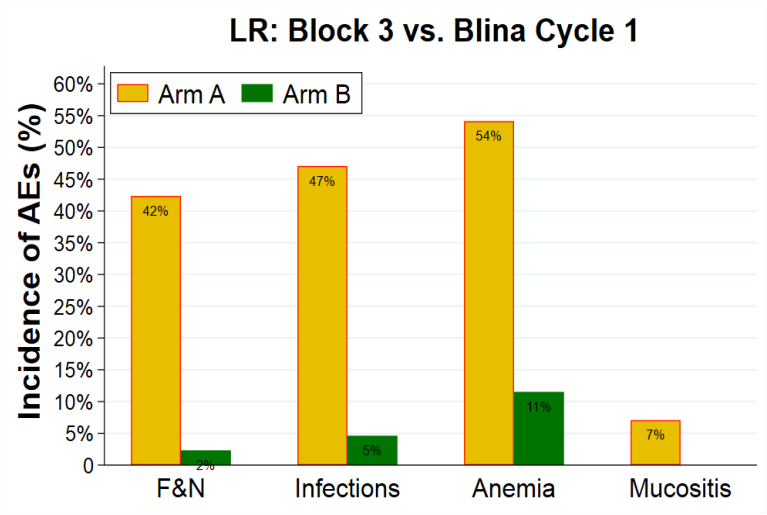
- BM or combined ≥36 mo, MRD <0.01% EOI
- IEM ≥18 mo

- Blinatumomab 15 µg/m^2/day × 28 days, then 7 days off
- Dex 5 mg/m^2/dose × 1 premed

Unpublished data.

Adverse Events: LR (grade 3+)



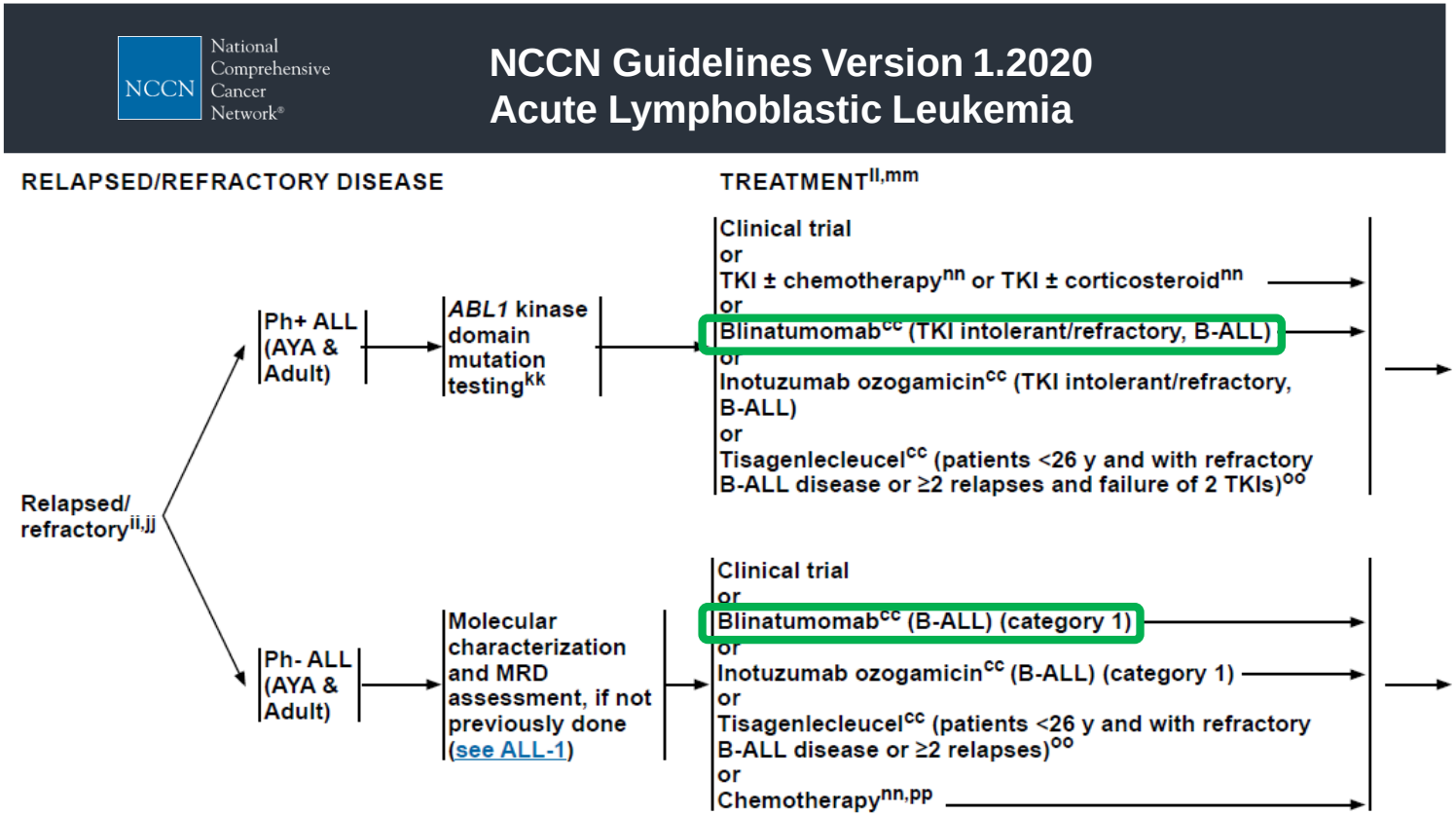


Data cutoff
3/4/19

CHILDREN'S ONCOLOGY GROUP

Unpublished data.

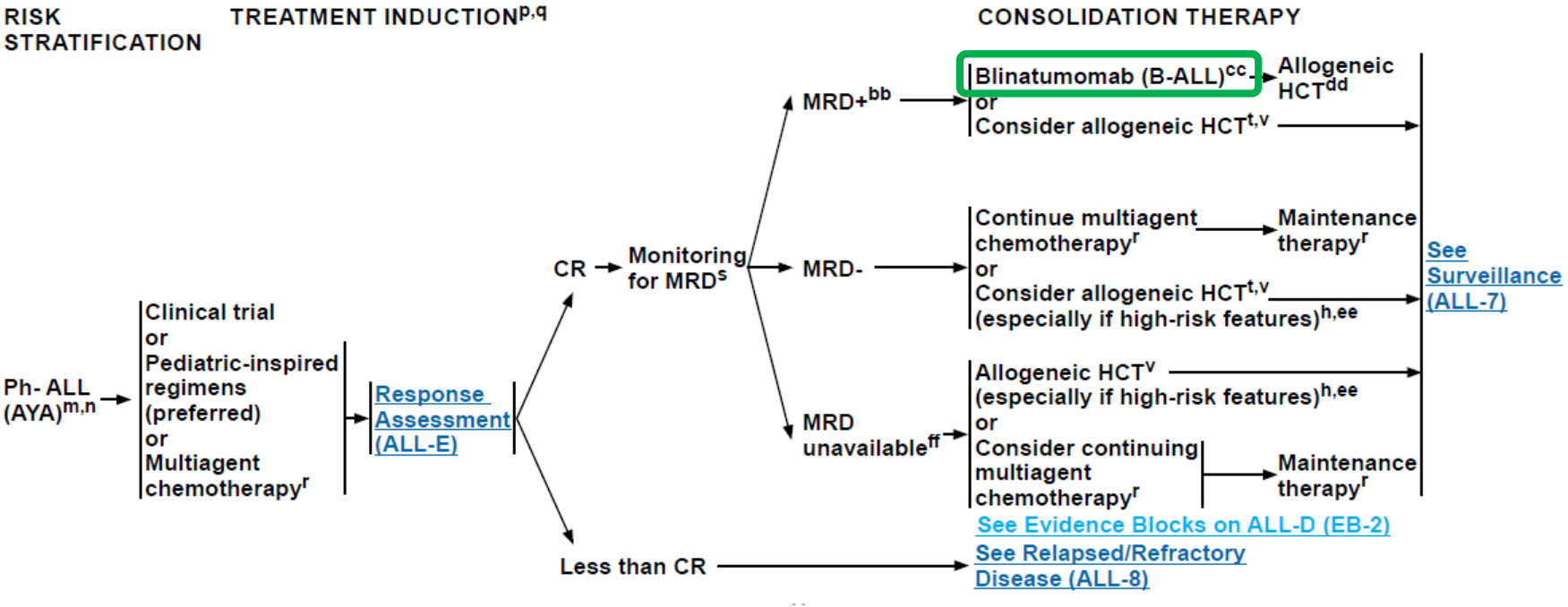
Where Is Blinatumomab in NCCN Adult ALL Guidelines?



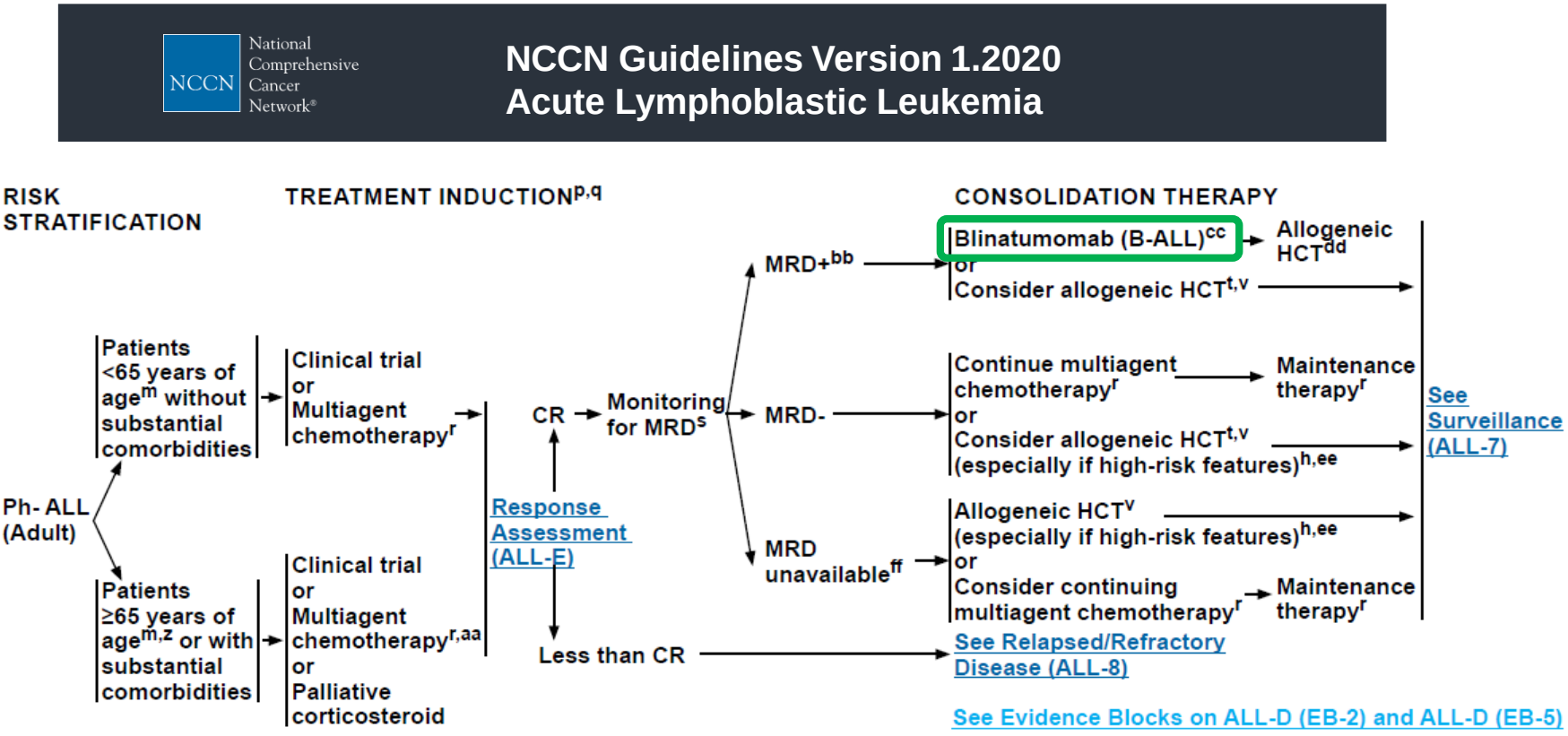
Where Is Blinatumomab in NCCN Adult ALL Guidelines?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Acute Lymphoblastic Leukemia



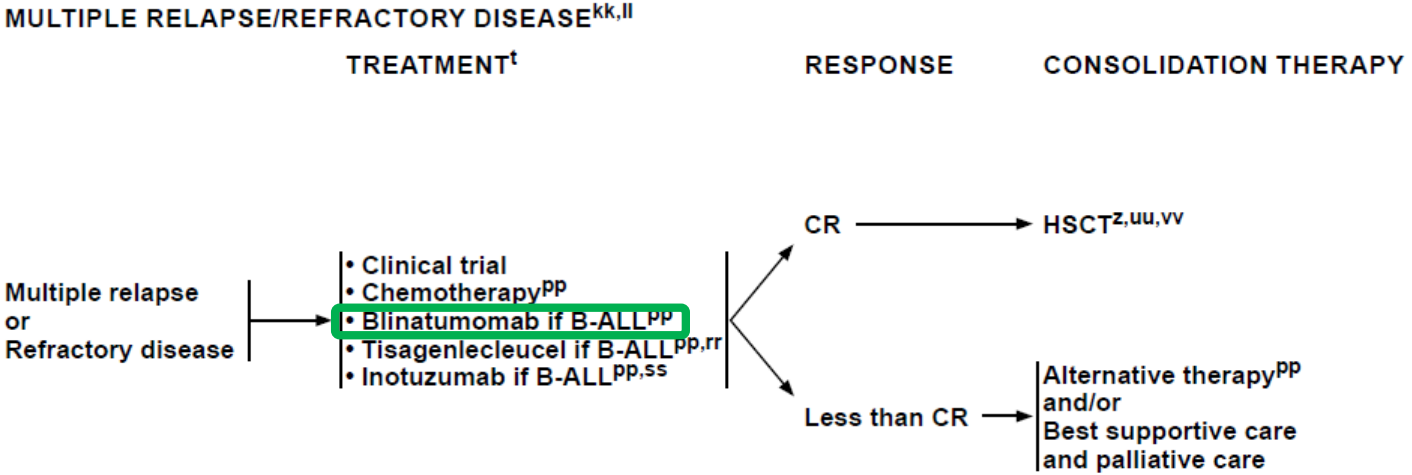
Where Is Blinatumomab in NCCN Adult ALL Guidelines?



Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

National Comprehensive Cancer Network®

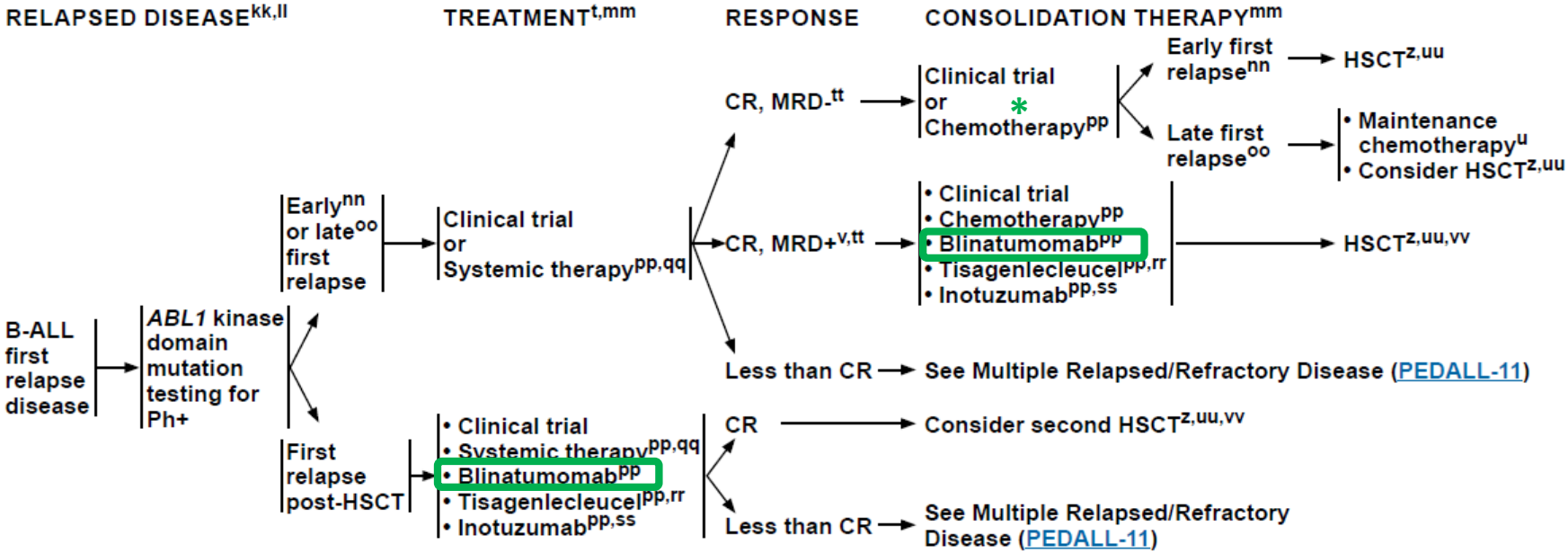
NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

National Comprehensive Cancer Network®

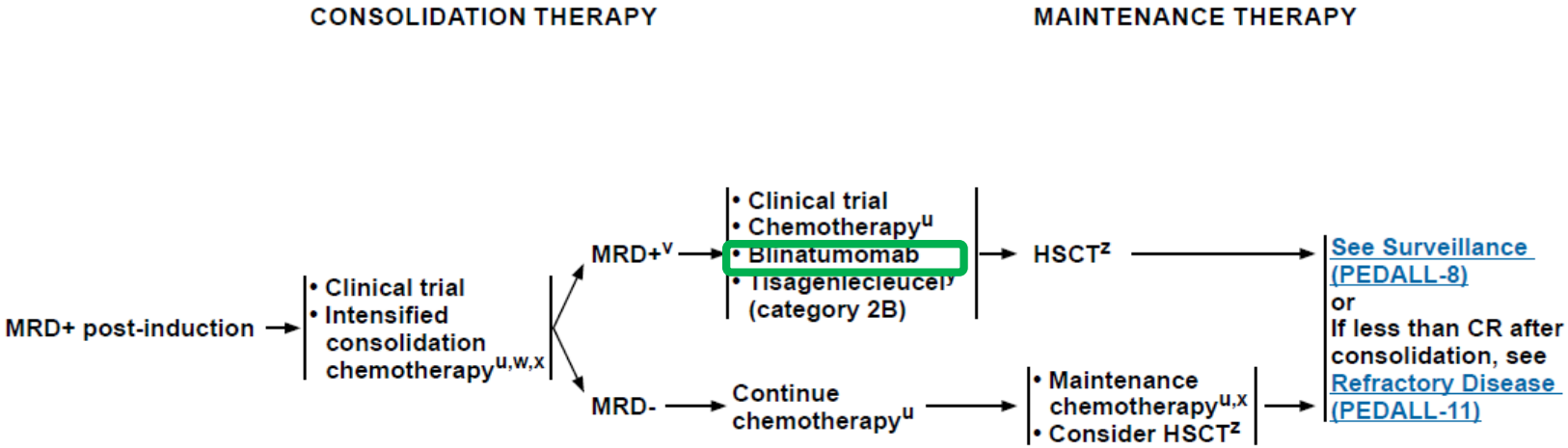
NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

National Comprehensive Cancer Network®

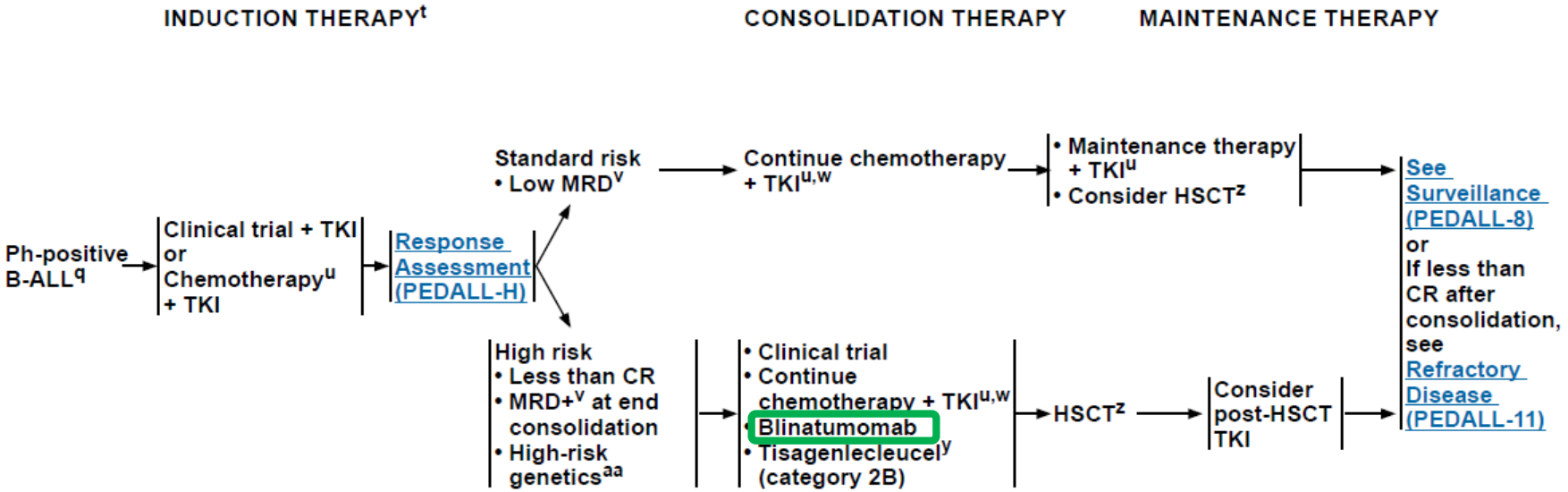
NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

National Comprehensive Cancer Network®

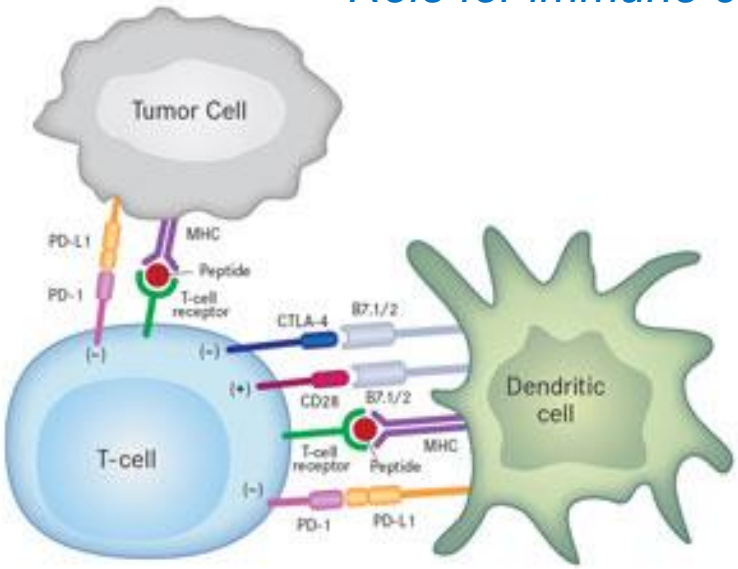
NCCN Guidelines Version 1.2020
Pediatric Acute Lymphoblastic Leukemia



What Happens When Blinatumomab Doesn't Work?

- EARLY: Endogenous T-cell "exhaustion"

Role for immune checkpoint inhibitors (eg, anti–PD-1)?

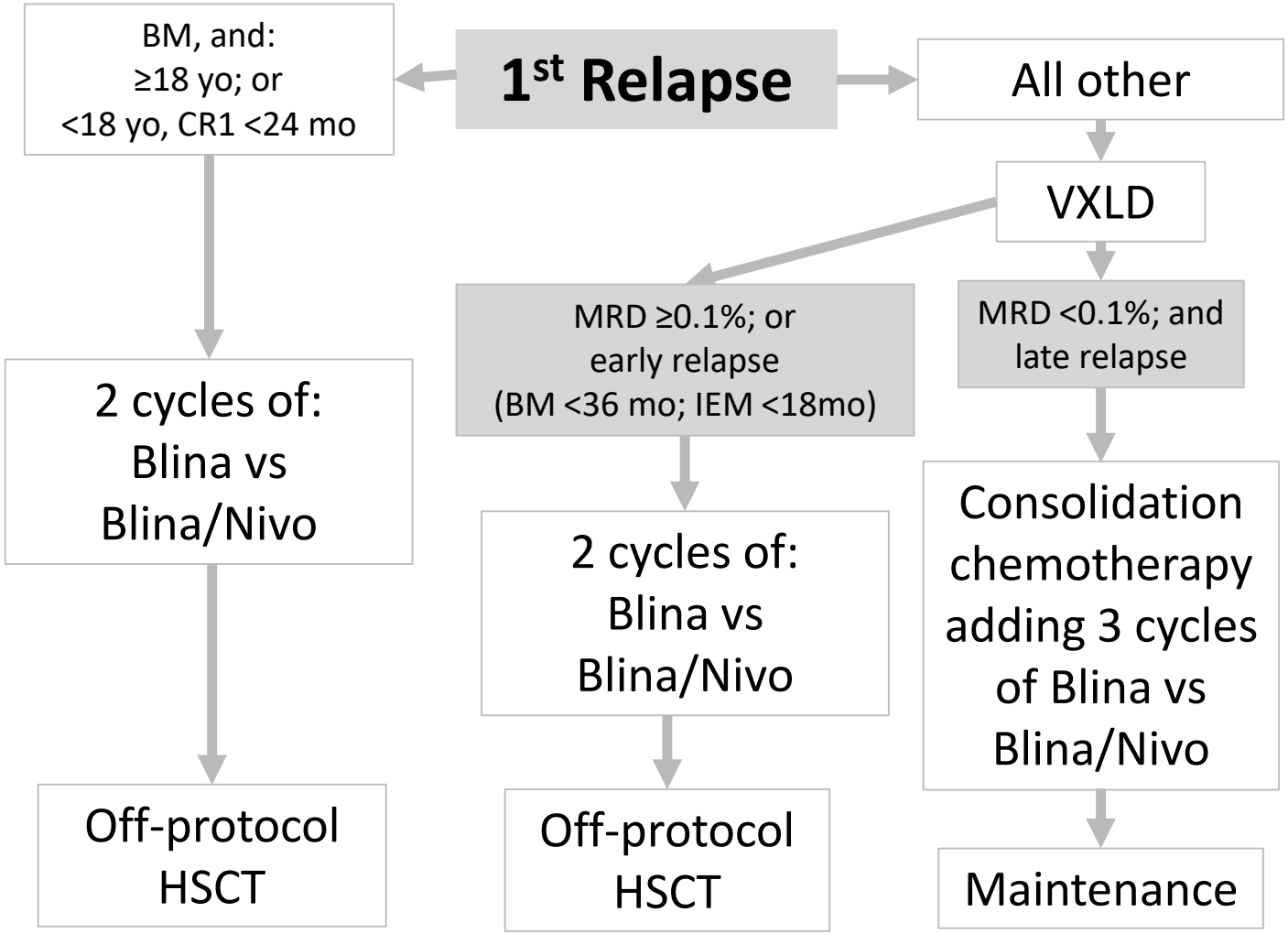


PD-1	PD-L1	CTLA-4
Nivolumab	Atezolizumab	Ipilimumab
Pembrolizumab*	Avelumab	
	Durvalumab	

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

- Feucht, et al. *Oncotarget.* 2016;7(47):76902-76919

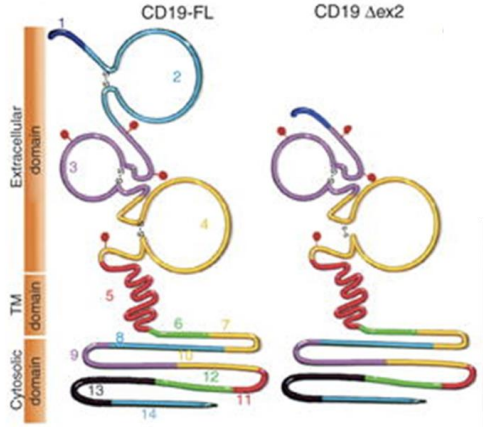
Adapted from Zaravinos A. *Oncotarget.* 2014;5(12):3956-3969.



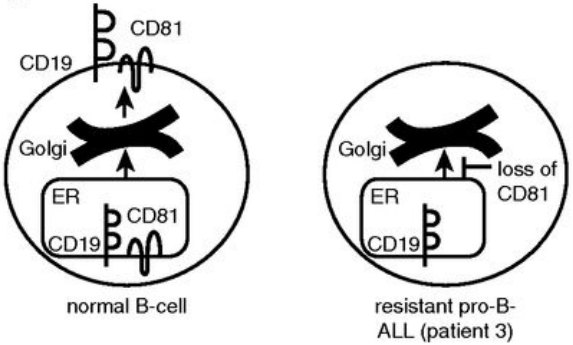
Unpublished data.

Where Is Blinatumomab in NCCN Pediatric ALL Guidelines?

- LATE: Antigen escape
  - CD19 splice variants[1]
  - Defective CD19 membrane trafficking[2]
  - Lineage switching (esp. MLL-r)[3]



Multiantigen targeting?



NOTE: Incidence of CD19 escape lower with blina than with CD19 CAR, likely reflecting less-potent CD19 selection pressure

1. Sotillo, et al. *Cancer Discov*. 2015;5(12):1282-1295; 2. Braig, et al. *Blood*. 2017;129(1):100-104; 3. Gardner, et al. *Blood*. 2016;127(20):2406-2410.

Can We Predict When Blinatumomab Won't Work?

bjh BRITISH JOURNAL OF HAEMATOLOGY

Correspondence | Free Access

Day 15 bone marrow minimal residual disease predicts response to blinatumomab in relapsed/refractory paediatric B-ALL

Patrick Brown, Gerhard Zugmaier, Lia Gore, Catherine A. Tuglus, Arend von Stackelberg

First published: 03 December 2019 | https://doi.org/10.1111/bjh.16306

Brown P, et al. *Br J Haematol.* 2020;188(4):e36-e39.

Efficacy Outcomes in Patients Enrolled in Phase I/II Study

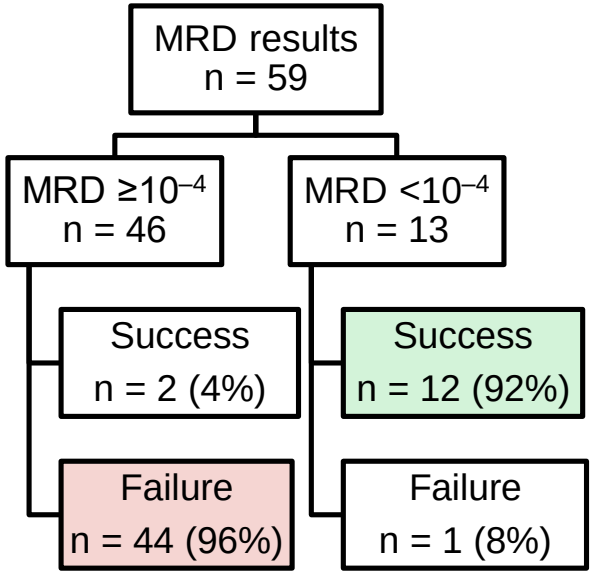
Response	Patients at Recommended Dose Who Had Response Assessment (N = 64)[a]	
	n/N (%)	95% CI
CR within the first 2 cycles	27/64 (42)	30, 55
Non-responders (did not achieve CR)	37/64 (58)	45, 70
Partial remission	4	
Blast-free or aplastic bone marrow	2	
Progressive disease	10	
No response	21	
MRD response in patients who achieved CR within the first 2 cycles		
Complete MRD response	14/27 (52)	32, 71
No MRD response	12/27 (44)	26, 64
No data available	1/27 (4)	

- Study definitions
  - "**Success**" was defined as complete MRD response in CR (n = 14)
  - "**Failure**" was defined as anything other than success (n = 50)

Adapted from von Stackelberg, et al. *J Clin Oncol.* 2016;34:4381-4389.

Biomarkers to Predict Blinatumomab Success/Failure

- Overall, day 15 MRD results predicted best response after 2 cycles with 95% accuracy (correctly in 56 of 59 patients)



Parameter	Accuracy (n/N)	Accuracy (%)
Day 8 PB morphology (clearance of blasts)	19/40	49
Day 15 BM morphology (M1)	54/60	90
Day 29 BM morphology (M1)	42/51	84
Day 15 BM MRD (< 10^{-4})	***56/59***	***95***
Day 29 BM MRD (< 10^{-4})	42/49	86

NOTE: Day 8 PB is an especially poor predictor of subsequent response

- Study definitions
  - "**Success**" was defined as complete MRD response in CR (n = 14)
  - "**Failure**" was defined as anything other than success (n = 50)

As patients with MRD ≥10^{-4} at day 15 could potentially pursue alternative therapies, such as dose escalation or combination therapies, ***day 15 MRD results may allow personalized treatment and improve outcomes in pediatric patients with relapsed/refractory B-ALL***

CR, complete remission; MRD, minimal residual disease.

Brown P, et al. *Br J Haematol.* 2020;188(4):e36-e39.

Blinatumomab: Questions and Discussion

- HSCT after MRD clearance with blinatumomab?
- Ability of checkpoint inhibition to safely enhance blinatumomab response?
- Predictive biomarkers of blinatumomab response?
- Risk of prior blinatumomab exposure and CD19 escape after subsequent CD19 CAR T therapy?

Q.

A 21-year-old male began an infusion of blinatumomab 36 hours ago. He has developed acute onset of fever, hypotension, respiratory distress, hypoxia, and diffuse edema. Which of the following is the most likely explanation?

a. A. Gram-negative bacterial sepsis
b. B. Disseminated adenoviral infection
c. C. Cytokine release syndrome (CRS)
d. D. Macrophage activation syndrome (MAS)
e. E. Hemophagocytic lymphohistiocytosis (HLH)

Q.

True or False: The most effective treatment for blinatumomab-associated neurotoxicity is tocilizumab (anti-IL6R antibody).

a. True
b. False

Global Leukemia Academy

Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Case-Based Panel Discussion: Management of Long- and Short-Term Toxicities and Treatment Selection in Pediatric Patients

Maria Sara Felice

Carlos Andres Portilla

APTITUDE HEALTH®

Global Leukemia Academy

Case-Based Panel Discussion: Case 1

Maria Sara Felice

APTITUDE HEALTH®

Case Report

María Sara Felice, MD, PhD
Hospital de Pediatría Prof Dr Juan P. Garrahan
Buenos Aires, Argentina

Hospital de Pediatría
Garrahan

SAHOP
Sociedad Argentina de Hemato-Oncología Pediátrica

Objectives:

- To present a patient with relapsed ALL, a serious infectious complication, and complex clinical characteristics
- To analyze clinical support measures
- To evaluate the best therapy approach and the opportunity and indication of HSCT

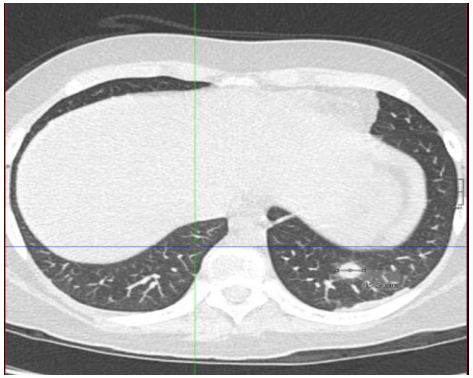
Clinical data

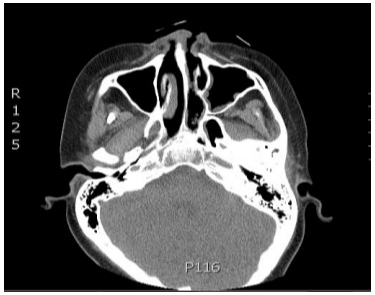
- Male, 14-year-old, referred from Corrientes
- Diagnosis: Pre-B ALL, hyperdyploid, DNA index 1.22, IKZF1 del (not plus) (September 2013)
- ALLIC 2009 protocol, PGR, MRD on day 15: 5.12%, CR on day 33 (MRD 0.027%) → medium risk
- He completed 2 years of treatment without severe toxicity
- Hematological relapse 30 mo from CR (May 2016) → relapse protocol
- First block (REC1) in his province → severe clinical complications (febrile neutropenia, diabetes, neutropenic enteritis, TPN, antibiotic) → referred to our center

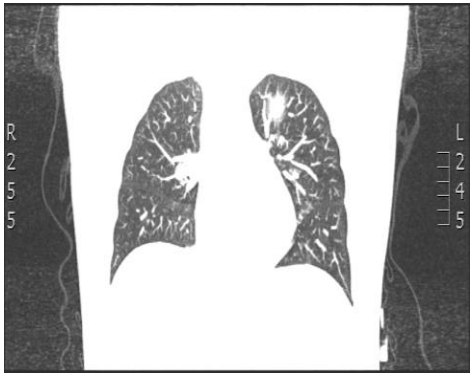
Evaluation at admission

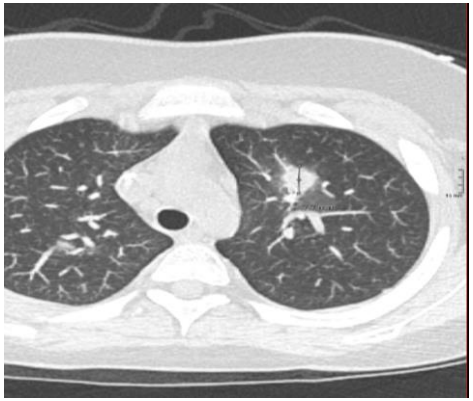
- Bone marrow aspirate: 2nd CR EMR 0.10%
- Severe clinical deterioration: malnourished, febrile neutropenia, diabetes, neutropenic enteritis
- Urine culture: yeasts >100,000 UFC
- Searching for focus of deep fungal infection

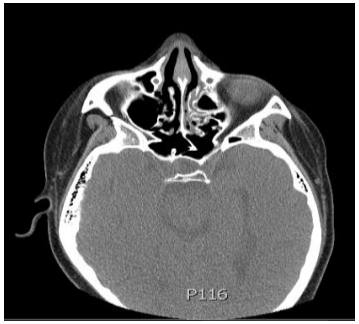
CT scan: lung and paranasal sinus compromise

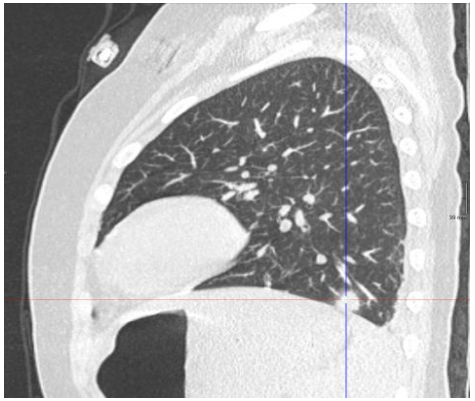












Evaluation at admission

- Bone marrow aspirate: 2nd CR EMR 0.10%
- Severe clinical deterioration: malnourished, febrile neutropenia, diabetes, neutropenic enteritis
- Urine culture: yeasts >100,000 UFC
- Searching of deep fungal focus

- Deep fungal infection was suspected (risk factors: prolonged hospitalization and neutropenia, diabetes, several antibiotic schedules)
- He remained febrile, added epiphora → a specimen from nasal crust was taken → rhinosinusal and lung nodules due to *Aspergillus Flavus* → liposomal amphotericin B 10 mg/kg/day (deteriorated kidney function)

Clinical evolution

- Persistent febrile (10 days)
- Abscess (left thigh with muscle compromise) → surgical drainage → *Aspergillus Flavus* → voriconazole was added

- Distal paresthesia and limitation of dorsiflexion → left limb monoparesis and popliteal sciatic compromise
- IRM cranial and spine

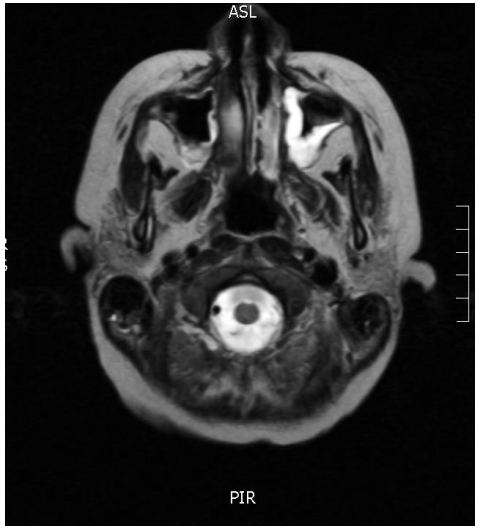
What is your suspected diagnosis?

Q.

a. CNS relapse?

b. Second neoplasm?

c. Collection due to other infection?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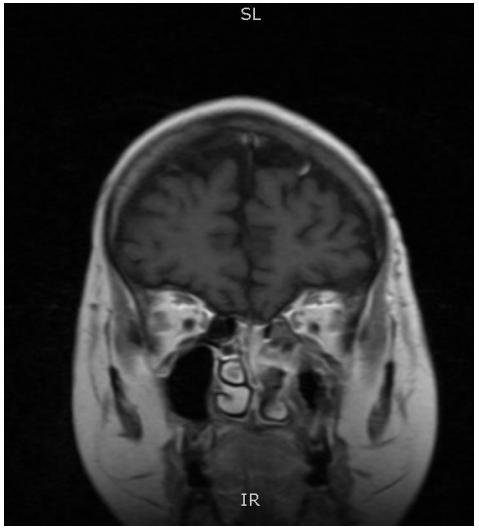
PIR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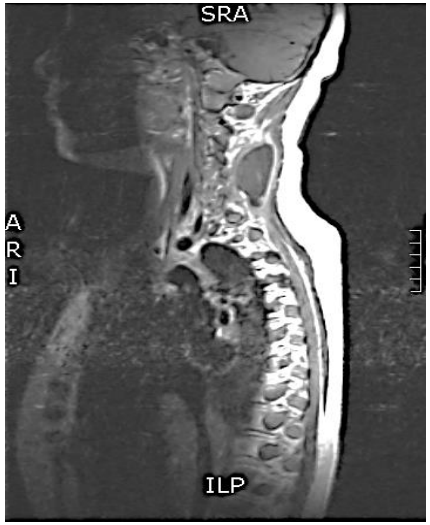
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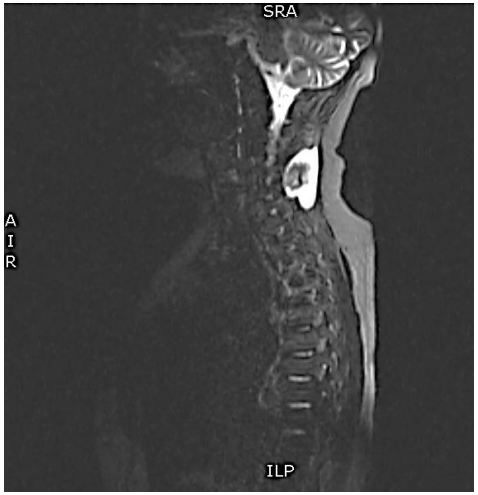
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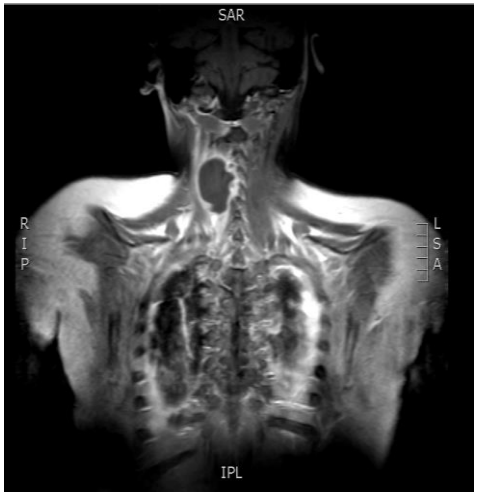
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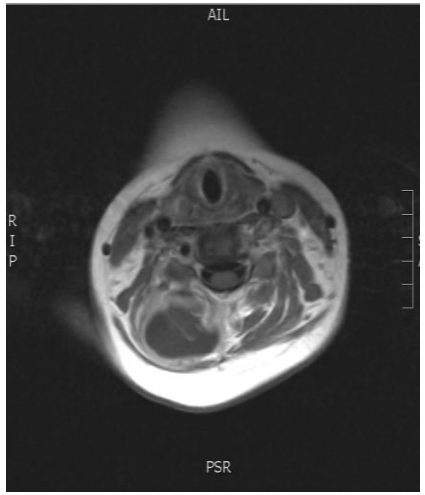
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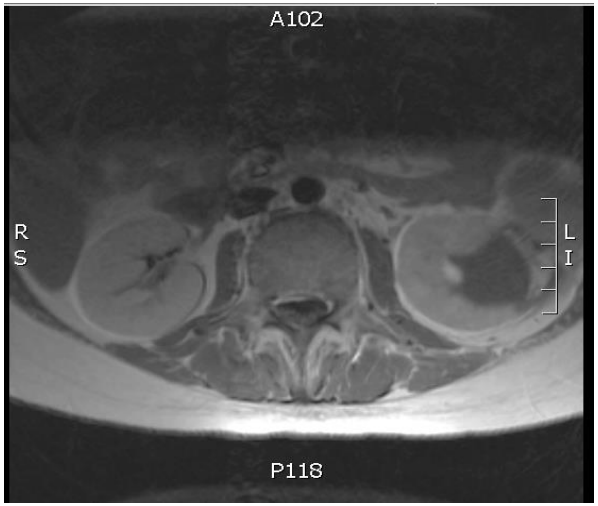
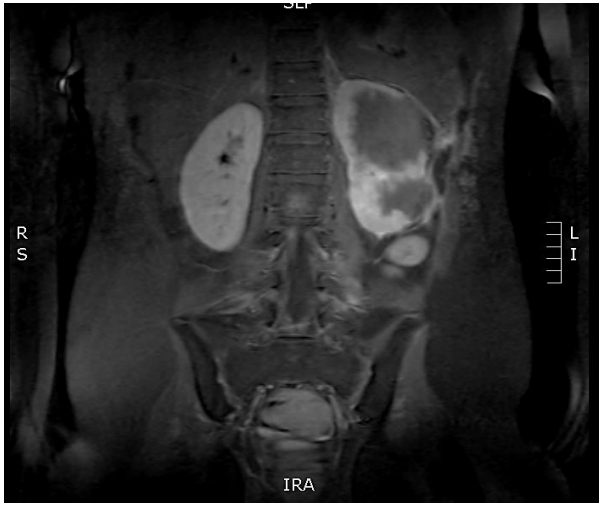


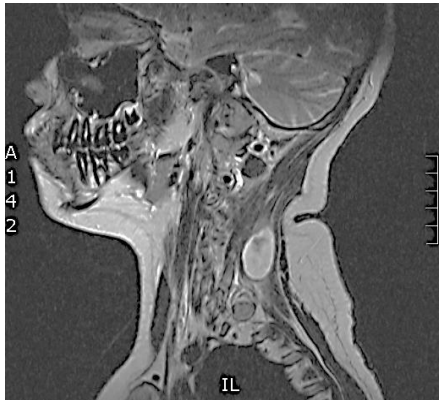


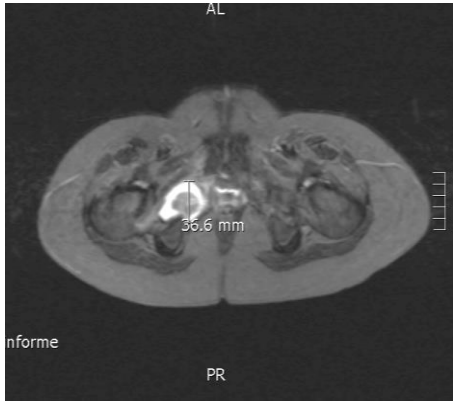
Percutaneous drainage of the cervical, left lumbar, and posterior right thigh collections → fungal elements PAS (+) ***Mucormycosis*** → **voriconazole + amphotericin B**

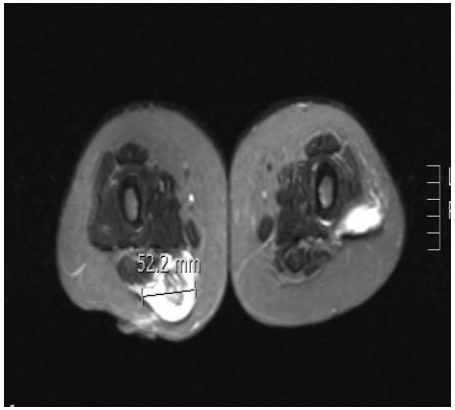
Patient was clinically stable: adaptation of chemo → Protocol IB

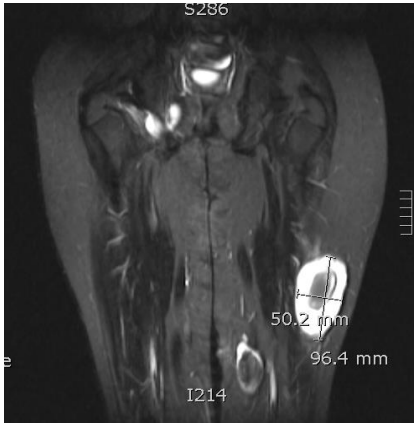
Surgical treatment of collections

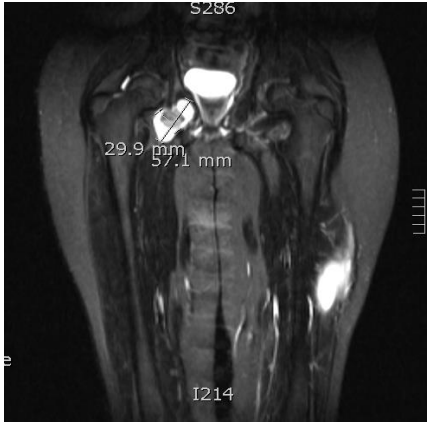
Images for re-evaluation of surgical treatment









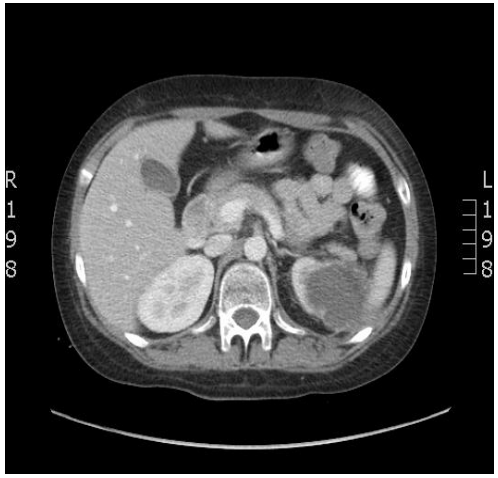


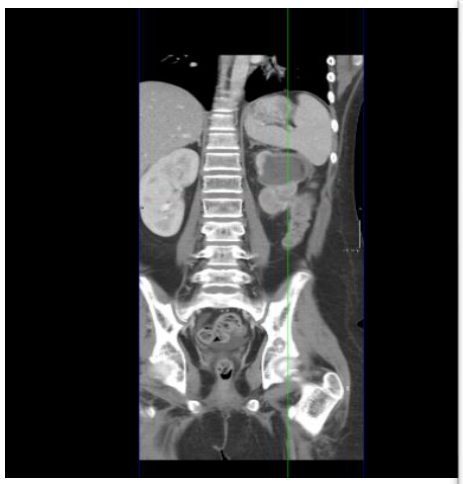
Clinical evolution

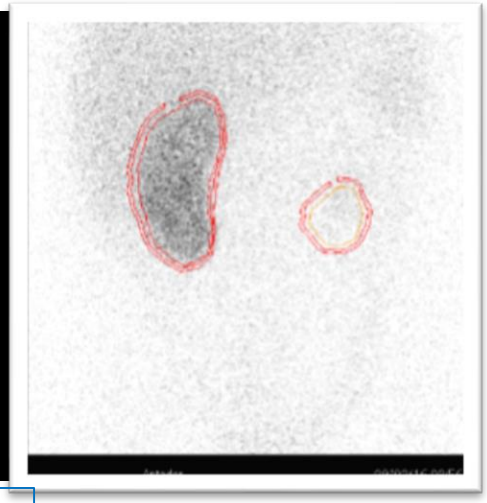
- Joint drainage of bilateral thigh and adductor region
- Bone marrow aspirate → CR2, MRD: 0.004%
- Intensification of chemo (REC 2)

- Drainage was removed

- Septic shock → ICU (72 hrs)→ *Pantoea agglomerans*
- Renal function impairment
- Re-evaluation of images and renal function

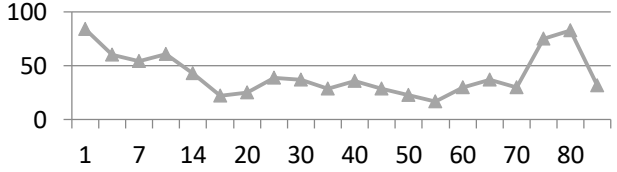


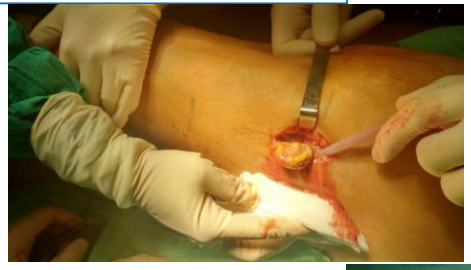




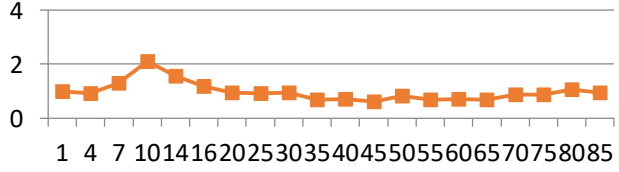
A nephrectomy is decided upon

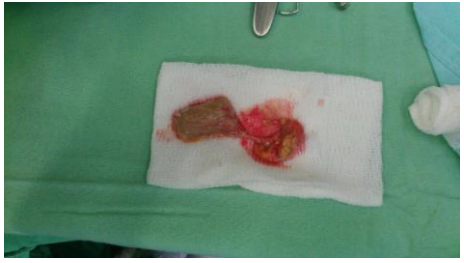
Urea Value





Creatinine Value





What do you consider to be the best option after nephrectomy?

Q.

a. Stop treatment?

b. Continuation of previous therapy?

c. Follow with chemotherapy?

d. Search for an unrelated donor and undergo HSCT?

Summary

- Patient with early relapse ALL, in 2nd CR, MRD +/-, with indication of HSCT
- Severe invasive deep fungal infection: Aspergillus and Mucormycosis
- Impairment of renal function → nephrectomy
- Adapted chemotherapy was administered → REC1 block, IB, REC2, REC3, REC1, REC2, and REC3, followed by preventive cranial radiotherapy and continuation phase
- He is at 49 mo 2nd CR (18 years old and excellent performance status)

Thank you for your attention!!!!

Hospital de Pediatría
Garrahan

SAHOP
Sociedad Argentina de Hemato-Oncología Pediátrica

Global Leukemia Academy

Q&A

APTITUDE HEALTH®

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Case-Based Panel Discussion: Case 2

Carlos Andres Portilla

APTITUDE HEALTH®

Case
Acute Lymphoblastic Leukemia

CARLOS ANDRÉS PORTILLA FIGUEROA

Pediatric Hematologist and Oncologist

Bone Marrow Transplantation

Centro Médico Imbanaco

Universidad del Valle

Cali, Colombia

Diagnostic

- 12-yo 4m male (25/10/2018)
- ALL-B HR (WBC 51310, age)

CNS negative

Karyotype 46 xy der (1)add(1)(q12)[3]/46xy [27]

t(1;19) neg, t(9;22) neg, t(12;21) neg, 11q23 neg

Treatment: Total Therapy XV Modified

Steroid Response	**Good**
MRD day 15	0.01%
MRD end induction	<0.01%
MRD end consolidation	<0.01%

Complications

- **Slow methotrexate depuration**

(Extra folinic acid rescue)

- **Moderated allergic reaction to asparaginase**

(Antibodies suspicious) Ended with Peg-Asp

- **Neutropenic fever**

(2)(Mercaptopurine related – dose adjusted)

- **Tibial osteonecrosis**

(Dexamethasone 50% dose-reduced)

- **Local adverse effect of vincristine**

51-week MRD 0.06% similar to diagnostic (Hematogones)

Delayed Time (Weeks)

1 *Tumoral lysis syndrome*
1 *Change of oncology team*
2 *Neutropenic fever 2 week/each*
>4 *Depression, social and health system barriers* ***(short delays)***

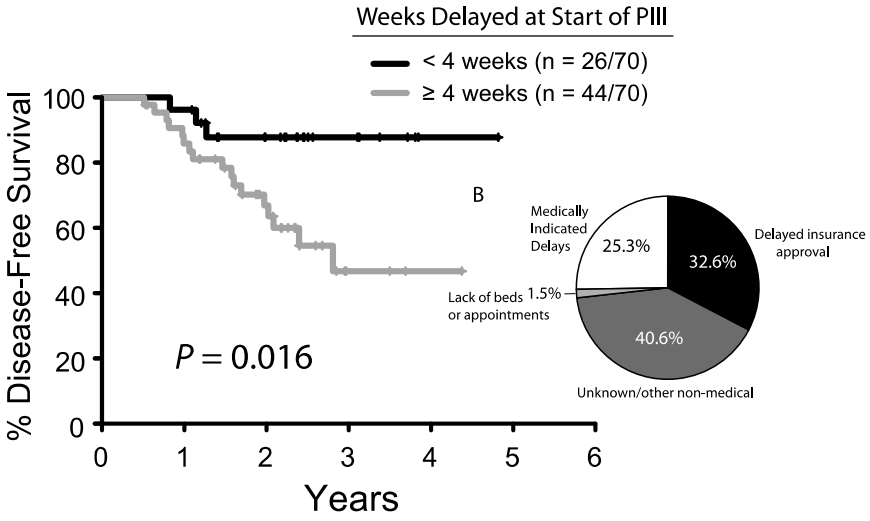
Which one do you think is the most important complication in a Latin American country?

Q.

a. Osteonecrosis
b. L-asparaginase allergy
c. Methotrexate delay depuration
d. Neutropenic fever – mercaptopurine related
e. Delayed treatment

Delayed Treatment

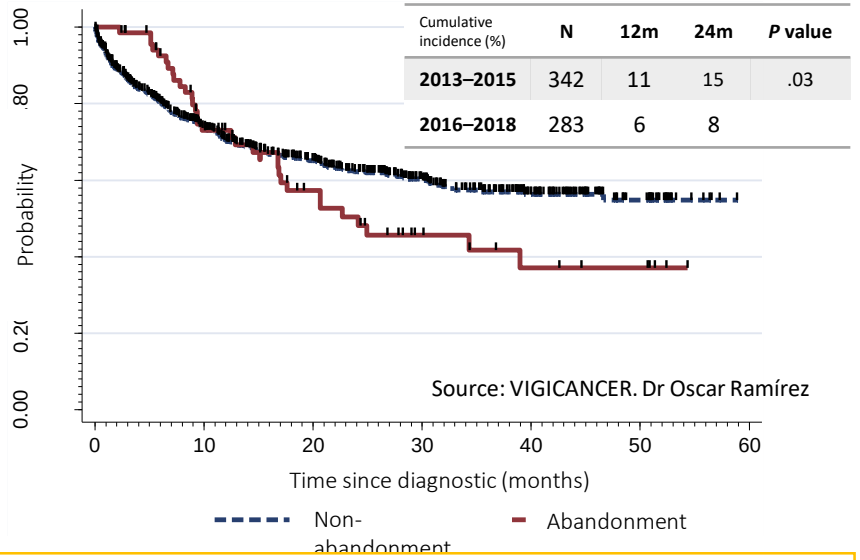
A



<16 years treated in INC (COL). Events: Relapse **2007–2010.**

Abandonment

EFS Pediatric Acute Leukemia, Cali 2009–2014

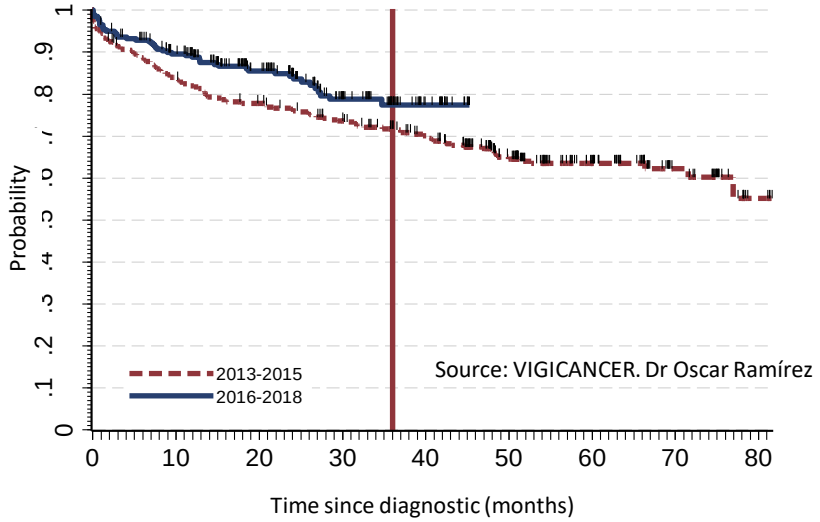


HR for the absence of social support network was 4.9 (95% CI: 1.6–15.3)

Suarez A, Piña M, NichosI-VinuezaD, Lopera J, Rengifo L, Mesa M, Cardenas M, Morrssey L, Veintemilla G, Vizcaino M, Del Toro L, Vicuña V, Fernandez J, Neuberg D, Stevenson K, Gutierrez A. ***Pediatr Blood Cancer.*** **2015;62:1395-1402.**
doi 10.1002/pbc.25510 Epub 2015 March 24

Ospina-Romero M, Portilla CA, Bravo LE, Ramirez O; VIGICANCER working group. Caregivers' Self-Reported Absence of Social Support Networks is Related to Treatment Abandonment in Children With Cancer
Pediatr Blood Cancer. **2016;63(5):825-831.**
doi: 10.1002/pbc.25919. Epub 2016 Feb 12

Overall Survival LLA 2013–2018



Nro. a riesgo

2013-2015	346	255	162	28
2016-2018	283	124	0	0

Forth Cities Cali, Ibagué, Neiva, Pasto: period 2013–2018

Grade 3–4 Toxicities TT.XV Colombia

Population/Events*	No.	%
Total	404 (307)	100 (76)
Osteonecrosis	2	0.6
Pancreatitis	3	1
Diabetes	6	2
Deep mycosis	2	0.6
Renal failure	1	0.3
Asparaginase anaphylaxis	3	1
Thrombosis/thromboembolism	11 (1 PTE)	3.5
Peripheral neuropathy G II-III	12	4

Source: VIGICANCER. Dra Patricia Montenegro and Dr Oscar Ramírez

Relapse

- Week **54** protocol
- BM relapse HR (<18 mo)
- CNS negative
- Karyotype
  46,XY,der(5)t(5;13)(q33;q14),+derder(5)t(5;13)(q33;q14),17[3]/46,XY[27]
- BM cytometry AMO B-ALL blast 91.93%
  cd45+/-, cd10++(62%), cd20+(66%), cd34+(56%), cd19+,nutdt+

Complications

Obesity – insulin resistance
Depression
Vitamin D deficit
Hypertension
Tumoral lysis syndrome
(Rasburicase)

What is the best alternative for treatment?

Q.

a. Blinatumomab
b. Clofarabine
c. CAR T cells
d. Go straight to bone marrow transplant

Rescue #1 CLOVE (clofarabine 40 + etoposide 150 + cyclophosphamide 440)

Height 1.65 m^2 – adjusted weight 59 (93.6) kg BSA 1.6 (2) m^2 (prophylaxis acyclovir, posaconazole, and levofloxacin)

Grade 2 mucositis

Bilirubin high level 1.61 mg/dL

Neutropenic fever

#1 Day 3 (37.7ºC/ANC 100) + abdominal pain (–) cultures

Amikacin (5 d) + vancomycin (3 d)

#2 Day 14 (38.6ºC/ANC 10) + gluteal ulcer

Culture 8 h 37 min SSBL *E. coli* positive (day 17 catheter removal)

Amikacin (1 d) + meropenem (11 d/4 d after negative culture)

Vancomycin (11 d/4 d after negative culture)

#3 Day 28 (37.9ºC/ANC 80) + gluteal abscess

Culture #1 y #2 10 h 54 min SSBL *E. coli* positive, meropenem sensible

Amikacin (4 day) + vancomycin (2 days) // meropenem (10 days) – linezolid (7 days)

Complications

Delay BM recovery (day 40)

GCS-F

MRD <0.001%

Clofarabine-Based Therapy Primary Refractory vs Relapse

- 23 patients (33 cycles)
- 96% B-LLA
- 89% combination CY + VP16 + clofarabine
- 53% after 1 or 2 cycles uMRD (95% CI: 32, 71)
- uMRD 67% induction failure vs 33% relapse
- 19% treatment-related mortality
- 66% transplant

O. Ramirez, C.A. Portilla, M.Quintero, V. Lotero, M.X. Castro, A. Castro, A. Linares, I. Sarmiento. **P-P004.**
Clofarabine-based therapy in children with lymphoblastic leukemia: Primary refractory patients have three times more chance of obtaining undetectable residual disease,compared with those in relapse.
Pediatr Blood Cancer. **DOI10.1002/pbc**

Infectious Complications in Patients With Acute Lymphoblastic Leukemia Receiving Clofarabine

- 21 patients (27 cycles)
- 81% CR
- 46 infectious episodes
  - 1.7 per cycle
  - 52.2% bacterial
  - 10.8% fungal (aspergillosis, mucor)
  - 34.5% viral *5 localized (herpes zoster, herpes simplex, influenza, and adenovirus); 11 invasive (BK virus, adenovirus, and cytomegalovirus)*
- 2 patients had infection-attributable mortality

D. Hernandez, O. Ramirez, C.A. Portilla, M. Quintero, P. Lopez, E. Lopez-Medina. **WSPID-0854** *Clinical Infectious Diseases:*
Infectious complications in patients with acute lymphoblastic leukemia receiving clofarabine.
https://wspid.kenes.com/Documents/WSPID%20All%20Abstracts.pdf

Rescue #2 Blinatumomab (dexamethasone)

14 µg/m²/day

Day 3 Tremor, fever, rash, and bone pain

Day 5 Seizures

- ✓ *Levetiracetam – clobazam – Dexa*
- ✓ *EEG normal*
- ✓ *Lumbar puncture normal*
- ✓ *Brain magnetic resonance imaging: meningeal enhancement*

MRD <0.001%

24-h suspension (48 h 9 µg/kg/day)

CMV reactivation (Ganciclovir)

Ended 28 days

Adverse Events (AEs) in Patients Who Received Blinatumomab

Patients With AEs	All Patients n = 70
AEs grade 3 or 4: anemia 41%, nausea 33%, headache 30%	61 (67%)
Fatal AEs: multiorgan failure (2), sepsis (1), fungal infection (1), respiratory failure (1), thrombocytopenia (1)	6
Cytokine release syndrome (any grade)	8 (11%)
Neurologic/psychiatric events	17 (24)

von Stackelberg A, et al. *J Clin Oncol*. 2016;34;4381-4389.

Bone Marrow Transplant

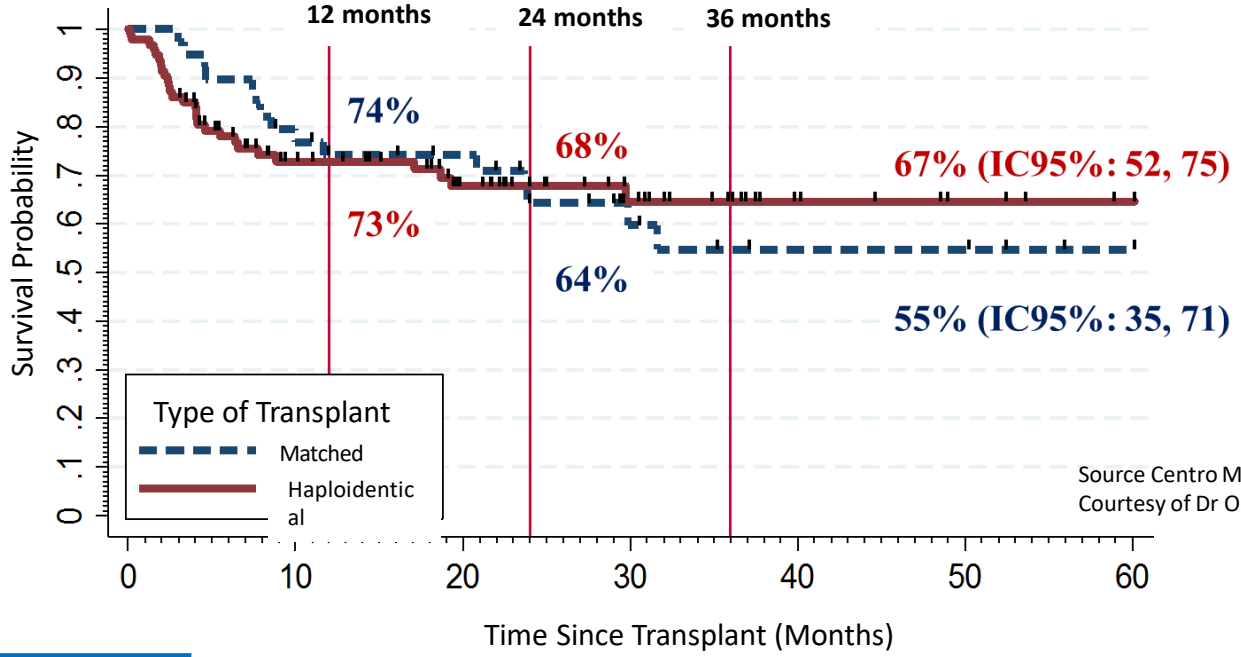
- Related donor allogeneic **(haploidentical)** bone marrow transplant (**7/12**)
- Father 49 yo/peripheral blood
- 5.56 million CD34+/kg weight
- Conditioning regimen: myeloablative – RIC

  FAB *(fludarabine + cytarabine + busulfan [weight adjusted])*
- GVHD prophylaxis ATG + CY post + cyclosporin

Complications

Infusion-related fever
Neutropenic fever
Day +6

Overall Survival Cohort 2012–2018
Haploidentical Donor vs Matched Sibling Donor



Source Centro Médico Imbanaco.
Courtesy of Dr Oscar Ramírez.

Hno Id.	39	24	9	6
Haplo	93	35	8	1

Solo 1er TPH, Exluidos anemia de Fanconi

Unidad de Hematología y Oncología
Centro Médico Imbanaco
Doctors:
Oscar Ramírez
Francy Ortiz
Margarita Quintero
Jesús Ardila
Diana Rendón
Carlos Narváez

Unidad de Trasplante de Médula Ósea Pediátrica

Universidad del Valle – Departamento de Pediatría

¡Gracias!

Tu vida nos inspira

Sistema de Vigilancia de Cáncer Pediátrico de Cali VIGICANCER

Registro Poblacional de Cáncer de Cali

Asociación Colombiana de Hematología y Oncología Pediátrica (ACHOP)

Global Leukemia Academy

Q&A

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Case-Based Panel Discussion: Management of Long- and Short-Term Toxicities

Maria Sara Felice
Oscar Gonzalez Ramella
Adriana Seber
Carlos Andres Portilla
Patrick Brown

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Educational ARS Questions

Patrick Brown

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Educational Questions Pediatric ALL
Question 1: Which assertion is correct for children with ALL?

a) All patients with MLL-rearranged ALL should be transplanted
b) All patients with BCR-ABL-positive ALL should be transplanted
c) No patient with BCR-ABL-positive ALL should be transplanted
d) AlloSCT is part of treatment for children with early relapsed ALL

VOTING QUESTION: please show previous results also from voting in slide 10 and highlighting the correct answer number d after voting

Educational Questions Pediatric ALL
Question 2: Which assertion is correct for children with ALL?

a) Blinatumomab and inotuzumab are part of first-line treatment
b) Blinatumomab and inotuzumab cannot be administered sequentially
c) Therapeutic drug monitoring of asparaginase improves outcome
d) Dexamethasone and vincristine are standard components of maintenance therapy

VOTING QUESTION: please show previous results also from voting in slide 11 and highlighting the correct answer number c.

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Closing Remarks

Patrick Brown

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Emerging and Practical Concepts and Controversies in Leukemias

THANK YOU FOR YOUR PARTICIPATION!

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