Less is More in Childhood B-ALL: Targeted Immunotherapies, MRD by HTS, and De-escalation of Therapy in COG Trials AALL1731/AALL1732

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COG Educational Track at APHON 2020

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Disclosure

- Sue Zupanec and Christine Yun have no industry relationships.
- Off label use will be discussed.

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Pediatric B-ALL Survival

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How did we improve pediatric B-ALL survival?

- How did we get here?
  - Clinical Trials!
- What led to the improved survival in pediatric ALL over the last few decades?
  - Improved risk stratification
  - Identifying groups who need intensified therapy and/or targeted therapies
- Can we do even better?
  - Yes - we can further define risk groups
    - Are there groups still at high risk for relapse that we can identify?
  - Can we further prevent relapse with immunotherapy?

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Who's Cutting to the Front of the Line, and Why?

- Blinatumomab
- Inotuzumab

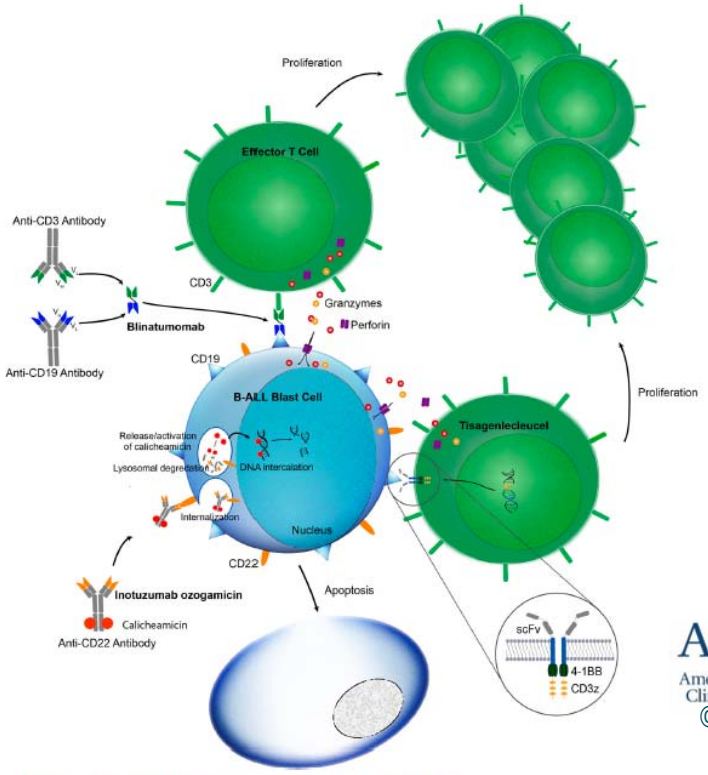

FIGURE 1. Mechanisms of Action of Blinatumomab, Inotuzumab Ozogamicin, and Tisagenlecleucel

McNeer, J et al. ASCO Educational Book 2020

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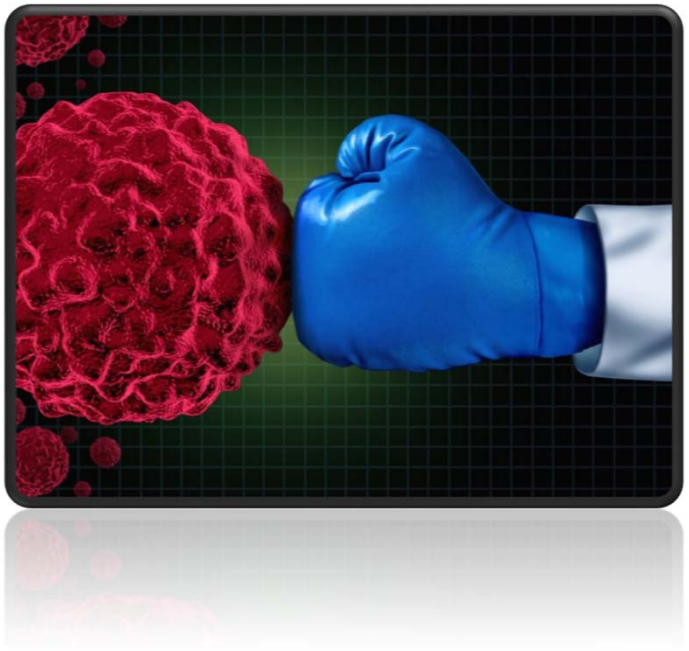
Why Immunotherapy?

- Intensification of chemotherapy was not successful
- Immunotherapy!
  - Improved OS on AALL1331
  - AALL1621 – Primary aim successful



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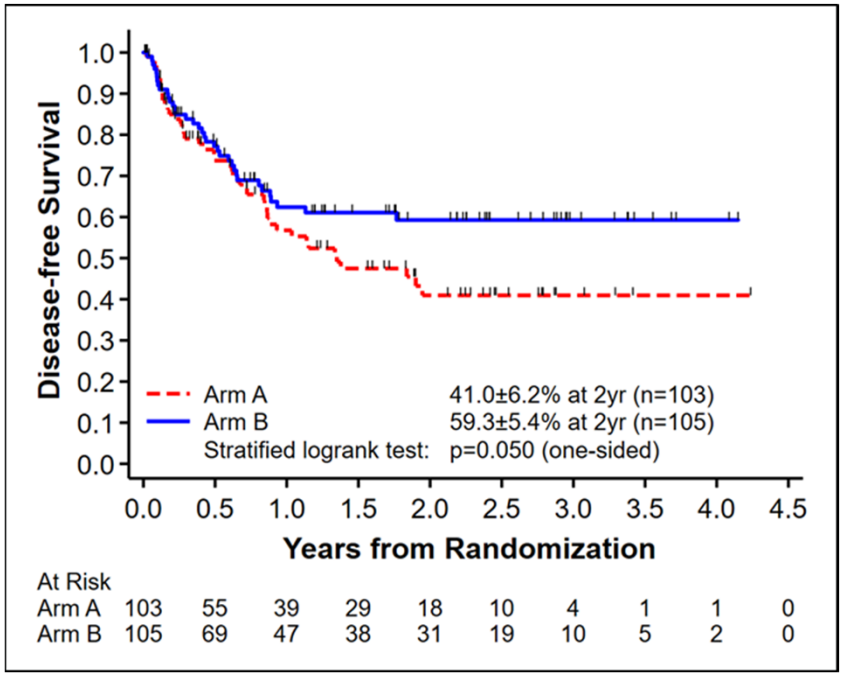
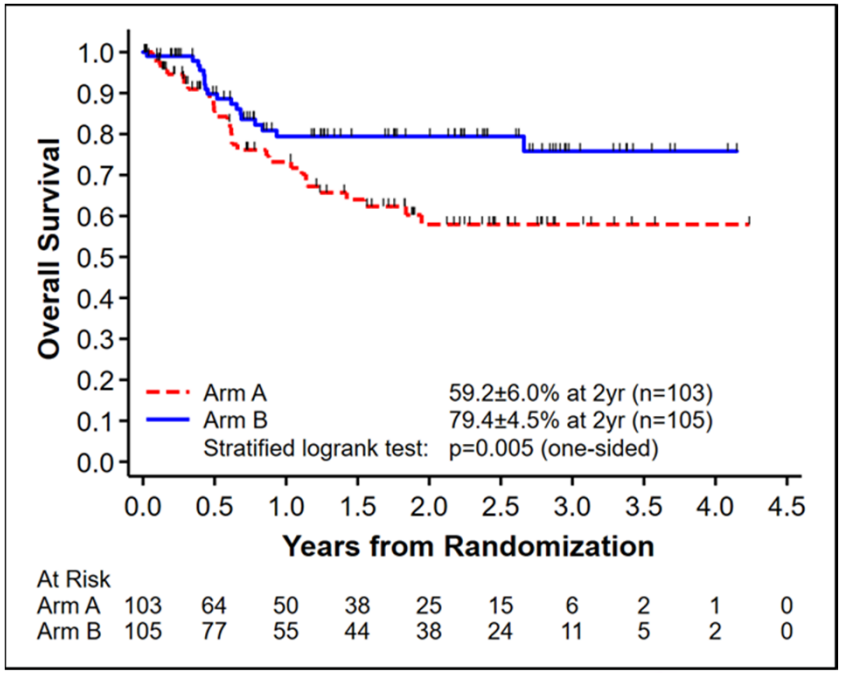
ALL1331 HR and IR Results





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Brown, P. Abstract #LBA-1. Presented at the 2019 ASH Annual Meeting, December 10, 2019; Orlando, FL.

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AALL1621 ASH Abstract 2019 – Primary Aim Outcomes

- AALL1621: A Phase 2 Trial of Inotuzumab Ozogamicin (InO) in Children and Young Adults with Relapsed or Refractory CD22+ ALL
  - InO demonstrated a CR or CRi in 58% of patients
  - Minimal hepatic toxicity observed during InO cycles
  - SOS occurred in 26% of patients who underwent subsequent HCT

O'Brien, M. 61st American Society of Hematology (ASH) Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Abstract 741

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AALL1621

- Trial expansion in development

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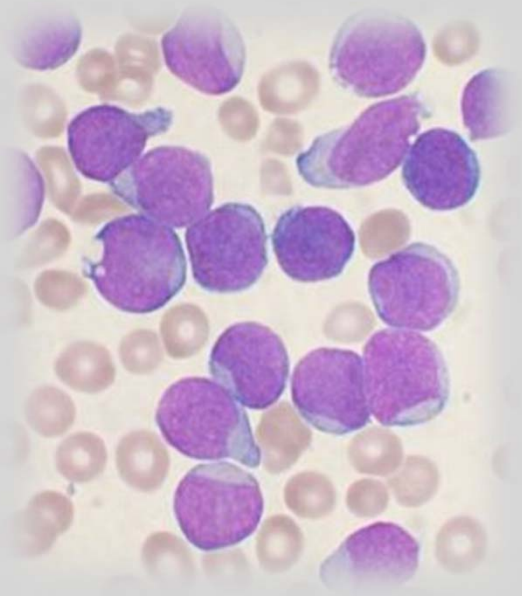
What we did learn from the biology samples and MRD on previous ALL trials?



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Looking back at MRD

- Banked samples
- 9900 series ALL

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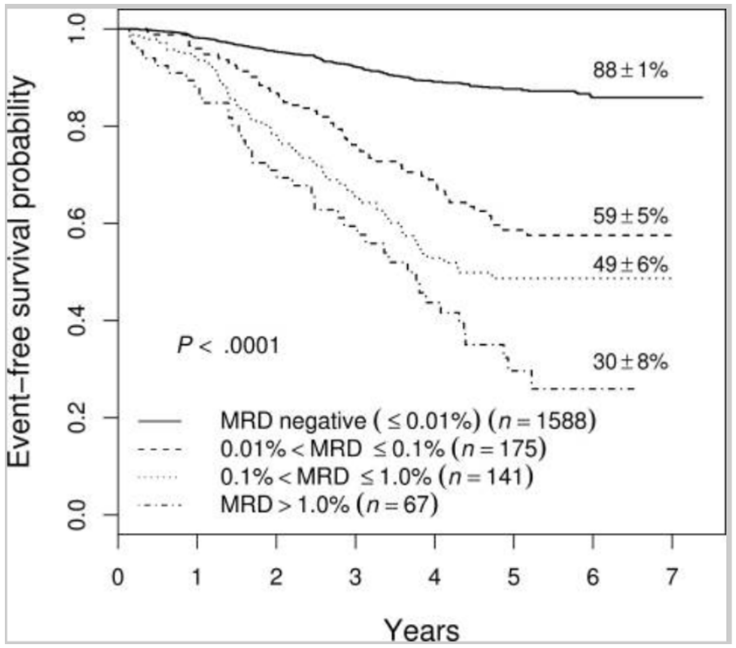
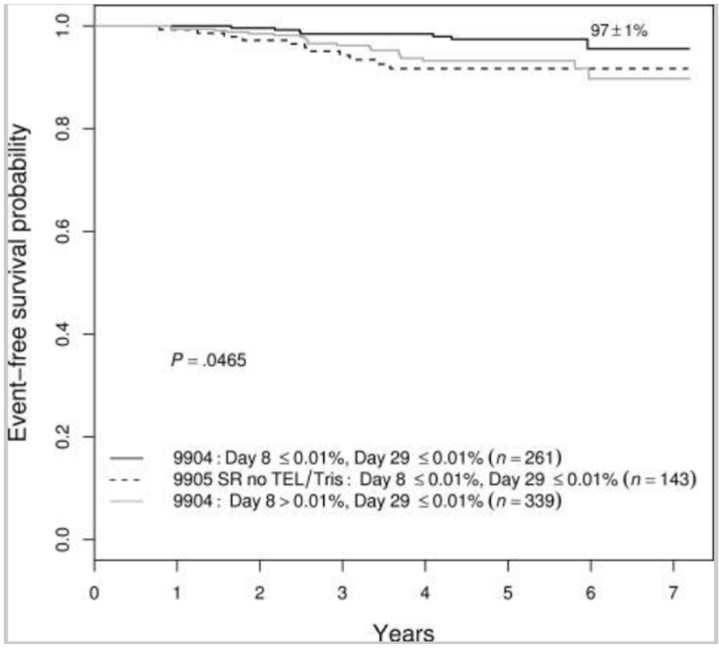
MRD and EFS 9900 Series Trials





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blood

Borowitz, M. (2008), Blood

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HTS – why might it help us with risk stratification?

- MRD currently measured by flow cytometry, which can detect down to 1/10,000 leukemia cells
- The new "High Throughput Sequencing" (HTS) is much more sensitive and can detect to a level of 1/1,000,000
- Retrospective data shows that patients who are flow MRD negative can still have detectable disease by HTS MRD (predicted up to 42%)
- Patients with HTS MRD negative EOI results have excellent survival!

Negative EOI FLOW MRD but Positive HTS MRD Evidence of Resistant Disease

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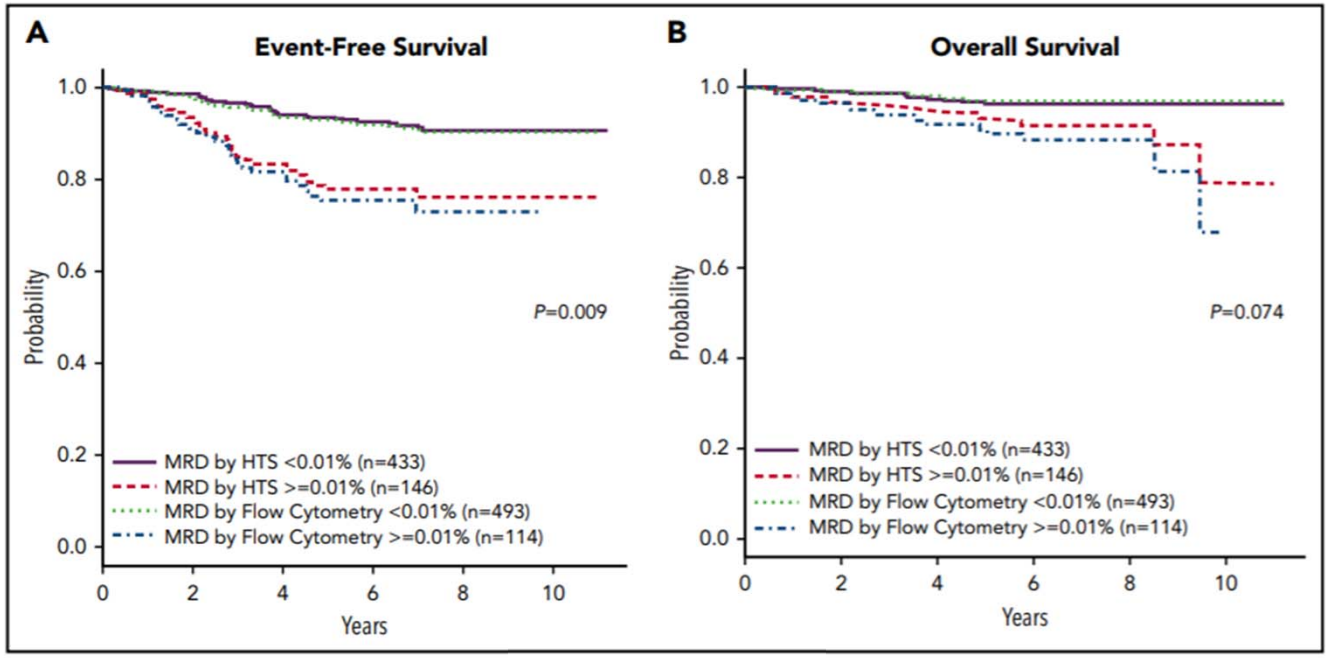
Looking back - HTS MRD Survival on AALL0331/0232



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blood

Wood, D. et al. (Blood) 2017

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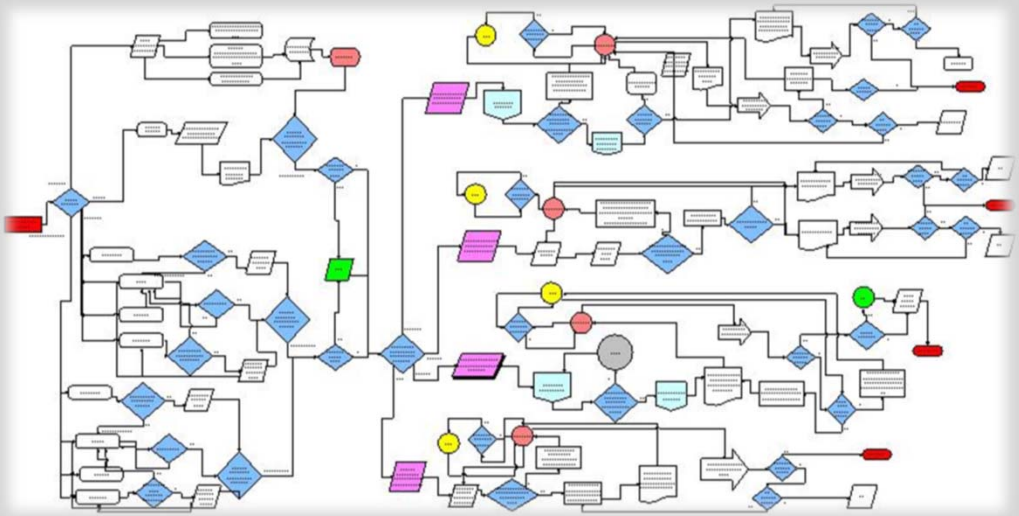
Improved Risk Stratification has led to better outcomes but, has become very complex…



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Increasing Complexity = Improved Survival

9900 Series

- 9904 Low Risk
- 9905 Standard Risk
- 9906 High Risk

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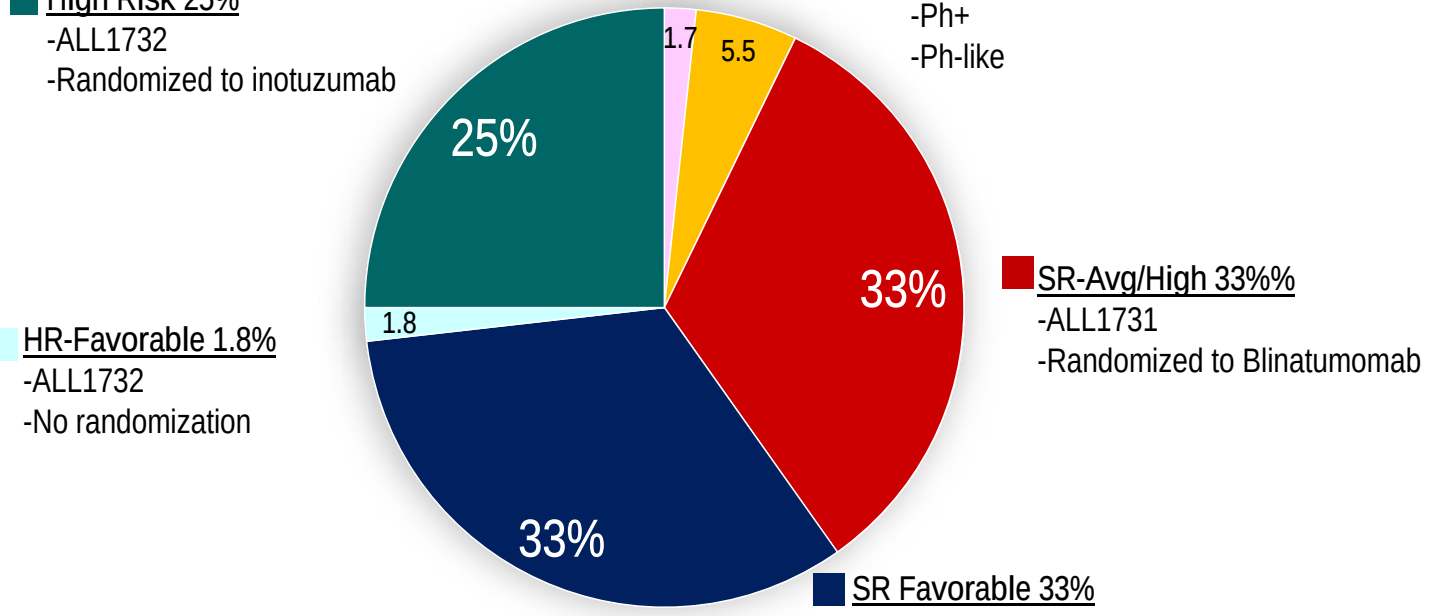
B-ALL Frontline Trials 2019



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Remember to…

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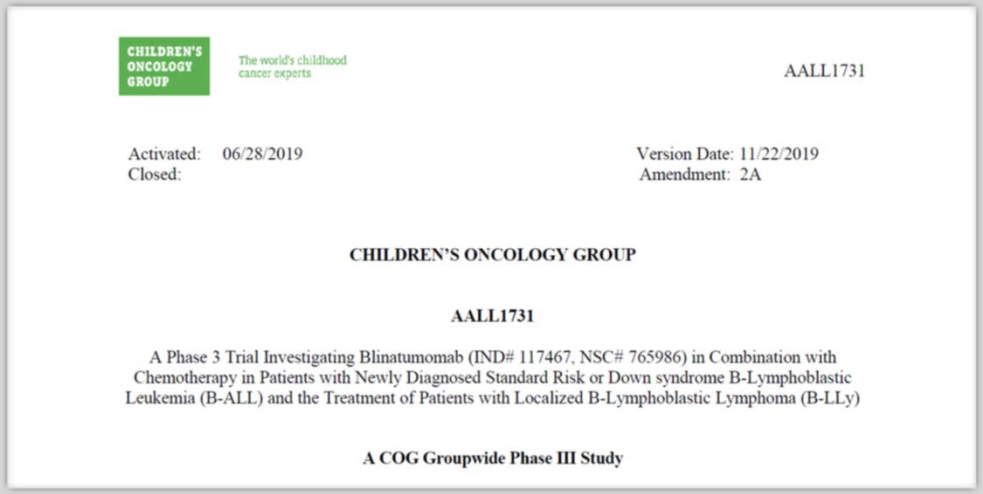
Let's take a look at ALL1731, Standard Risk B Lineage ALL…



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AALL1731

Activated: 06/28/2019
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Amendment: 2A

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AALL1731

A Phase 3 Trial Investigating Blinatumomab (IND# 117467, NSC# 765986) in Combination with Chemotherapy in Patients with Newly Diagnosed Standard Risk or Down syndrome B-Lymphoblastic Leukemia (B-ALL) and the Treatment of Patients with Localized B-Lymphoblastic Lymphoma (B-LLy)

A COG Groupwide Phase III Study

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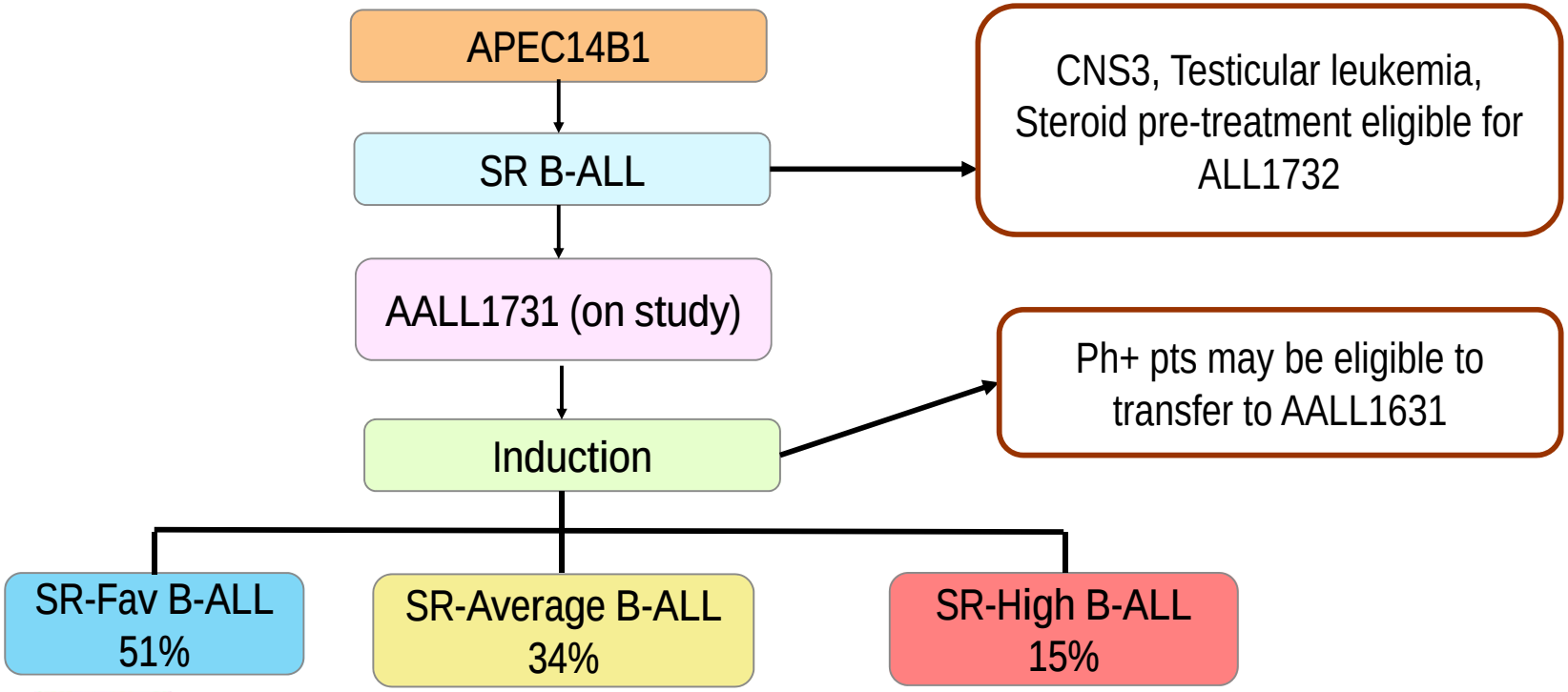
Risk Groups AALL1731



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ALL1731

- All NCI SR patients will enroll on and stay on AALL1731
- There will be an investigational agent – Blinatumomab
  - SR – Avg B ALL: Randomization Blinatumomab
  - SR – High B ALL: Randomization Blinatumomab
- SR – Fav B ALL Arm will NOT be randomized

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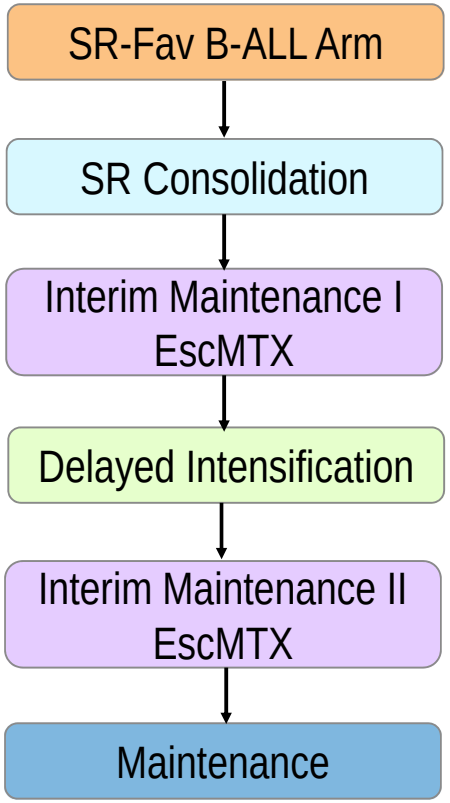
SR-Favorable

- NCI SR (non-DS and DS)
- Favorable cytogenetics (ETV6/RUNX1 or DT)
- Day 8 PB MRD <1%
- EOI BM MRD <0.01%
- CNS 1&2

No Randomization – Predicted EFS 97%



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Down Syndrome DS and ALL

- All patients with B-ALL and DS will remain on AALL1731
  - BOTH NCI SR and HR
  - 3 drug induction – NO day 15 BMA
    - Previously day 15 BMA was used determine escalation of therapy
- Three risk groups:
  - Standard Risk-Favorable (SR-Fav) DS B-ALL
  - Standard Risk-Average (SR-Avg) DS B-ALL
  - DS-High B-ALL

Illustration by Aimee Ermel, 2013

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SR-Average

- NCI SR (non-DS and DS)
  - CNS 1&2, fav cyto, D8 PB MRD >1%, EOI MRD <0.01%
  - CNS1, neutral cyto, EOI MRD <0.01%
  - CNS2, 1&2, DT any Day 8, *EOI MRD 0.01-<0.1%*
- EOI HTS MRD Stratification
  - EOI HTS undetectable
    - Non-random, standard treatment
  - EOI HTS -detectable/indeterminate/unavailable
    - Randomized to chemo +/- Blin

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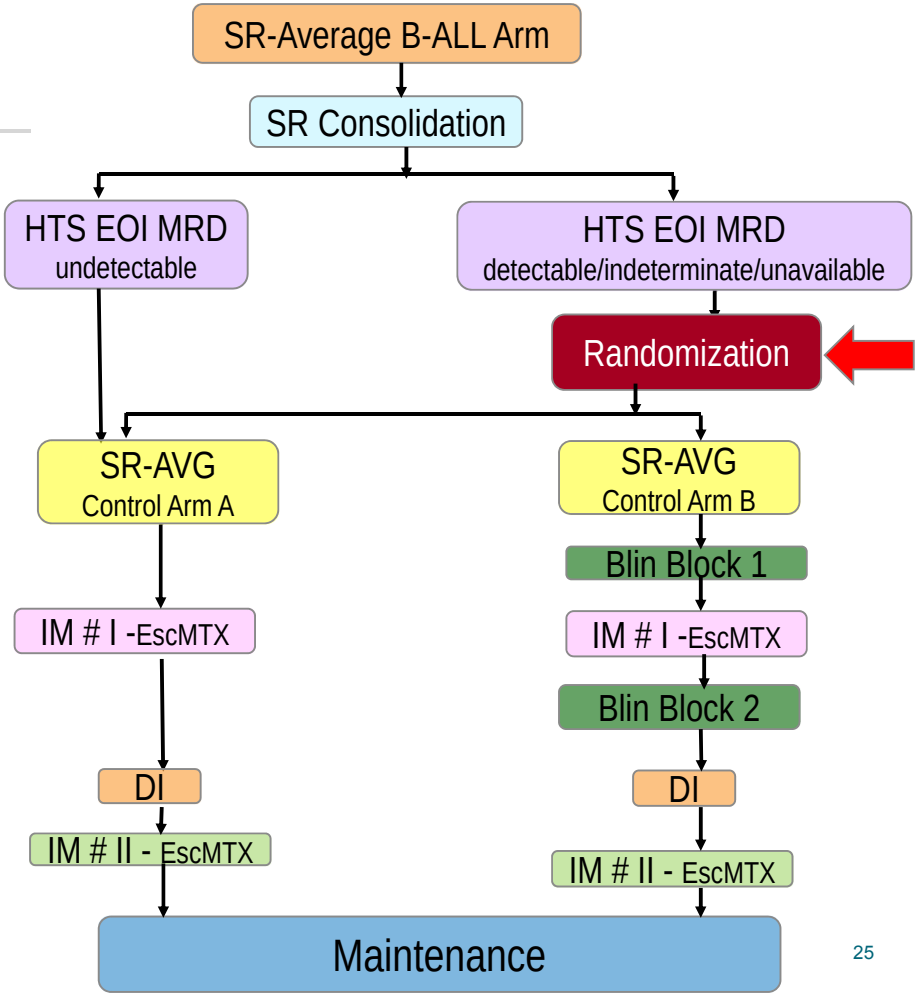

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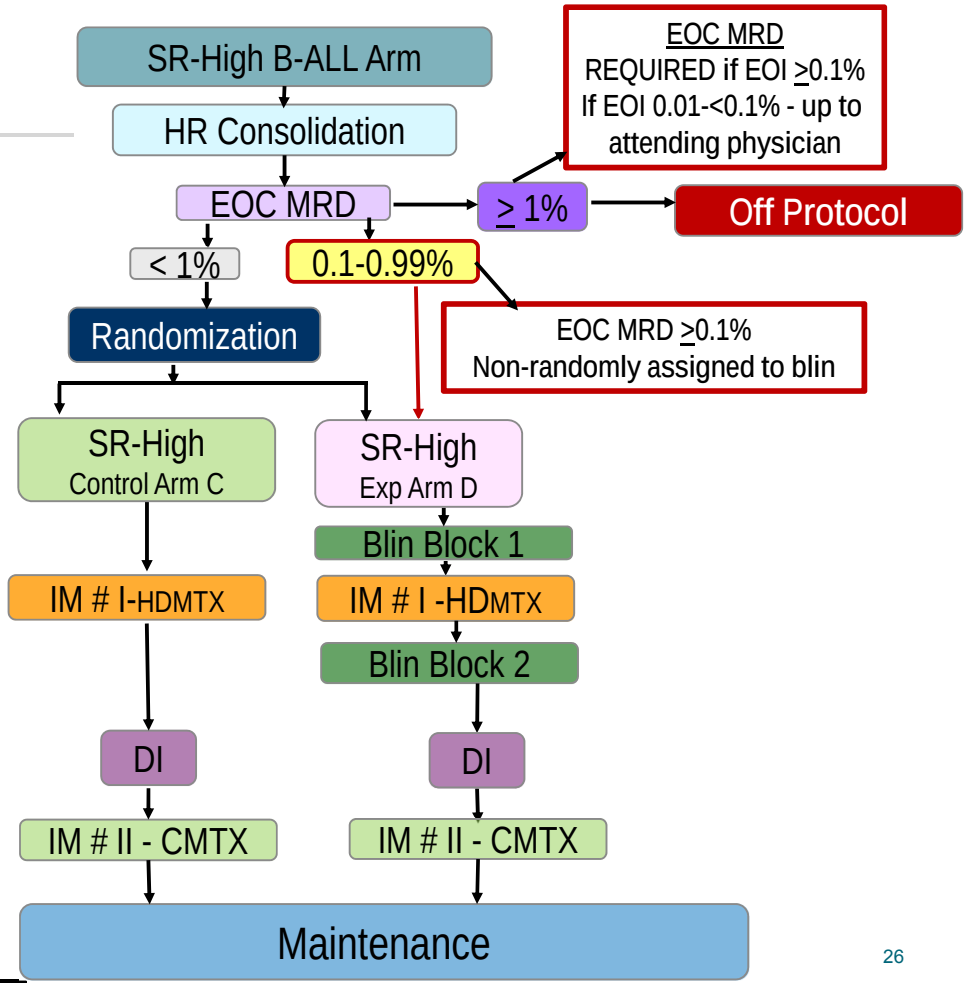
SR-High

- NCI SR (non DS ONLY)
  - EOI MRD ≥0.01% (≥0.1% for DT pts)
  - Unfavorable cytogenetics
  - CNS2 and neutral cytogenetics
- EOI MRD+ SR-High pts: EOC MRD
  - <0.1% - Randomized
  - 0.1-0.99% NON-RANDOM assignment to Experimental Arm D (Blinatumomab)
  - ≥1% = Consolidation failures, off protocol therapy



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Down Syndrome and ALL

- DS patients will follow the same risk classification criteria as non-DS SR patients
- Standard Risk-Fav DS B ALL
  - Standard chemotherapy with no randomization
- Standard Risk-Avg DS B-ALL
  - Eligible for randomization – Blinatumomab

Illustration by Aimee Ermel, 2013

EXCEPTION: DS patient with any HR features – Single Arm Trial

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DS High B-ALL

- DS B-ALL patients with ANY HR features will be non-randomly assigned to:
  - Single arm of SR-high ALL therapy
  - 3 cycles of Blinatumomab
- This arm remains under the SR trial AALL1731

Illustration by Aimee Ermel, 2013

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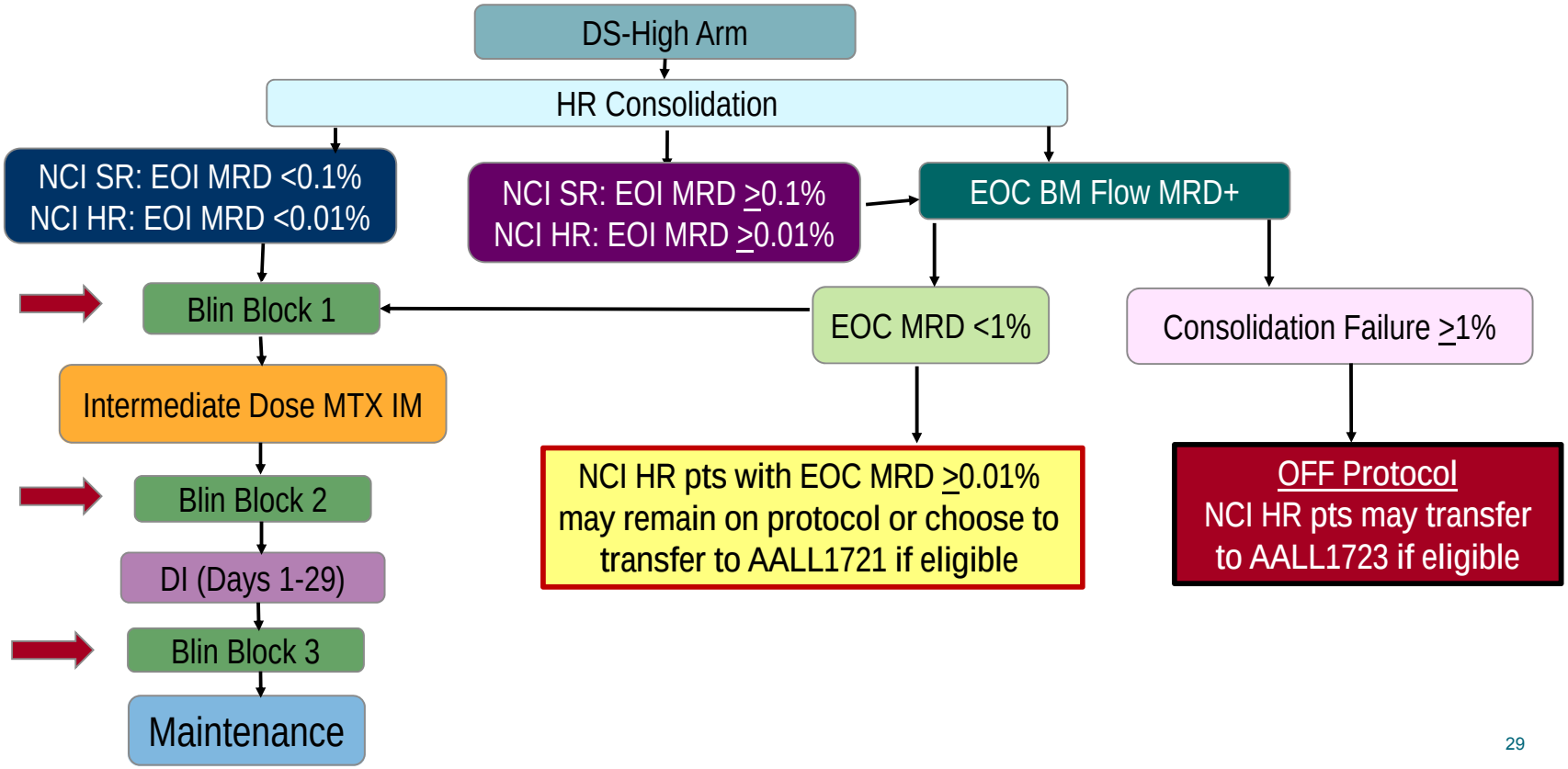
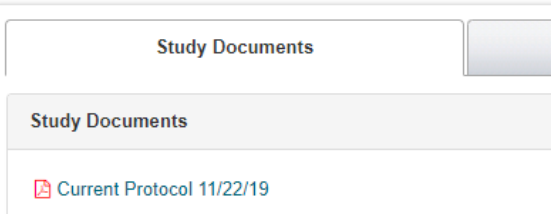
DS High B-ALL Treatment Schema



Blinatumomab

- FAQs
- PORTs



- Adaptive Standard Operating Procedure
- Blinatumomab Administration and Preparation Training
- Blinatumomab Home Health Care Manual
- Blinatumomab FAQ
- Blinatumomab Drug Information Sheet for Patients

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Interruptions of Blinatumomab

- New Protocol Language – **interruptions are unavoidable**
- Dose Clarification – due to unavoidable interruptions for patient care
  - Consideration of PORT care

> ...when the interruption time over 28 days is greater than 24 hours, missed hours of Blin may be added to the overall infusion time…at the discretion of the treating physician….

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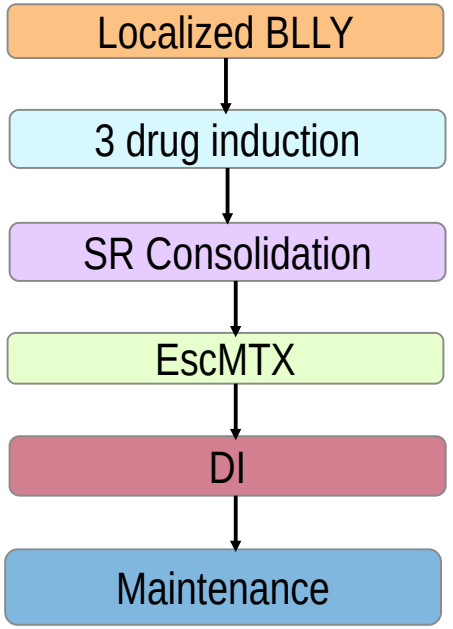
AALL1731 – Localized B-LLy (B Lymphoblastic Lymphoma)

- Current standard of care for these pts remains unknown
- Included on ALL trials within COG since AALL0932
- Rare group – between March 2013-June 2016 only 30 patients with localized B-LLy enrolled on AALL0932
- Therapy will remain consistent from ALL0932 to AALL1731 to increase the number of evaluable patients



GOAL: Define SOC for this sub-group with combined analysis

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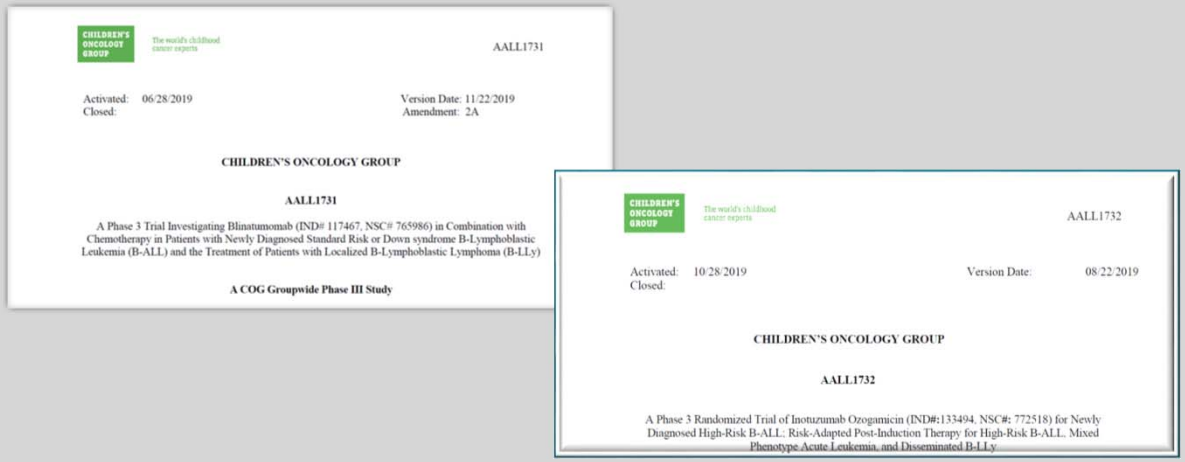
There are a few other changes (hint – less is more) that overlap both protocols, AALL1731 and AALL1732…



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A COG Groupwide Phase III Study

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AALL1732

A Phase 3 Randomized Trial of Inotuzumab Ozogamicin (IND#:133494, NSC#: 772518) for Newly Diagnosed High-Risk B-ALL; Risk-Adapted Post-Induction Therapy for High-Risk B-ALL, Mixed Phenotype Acute Leukemia, and Disseminated B-LLy

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What we have learned from previous frontline high risk B lineage studies…

Perhaps more is not always better…….

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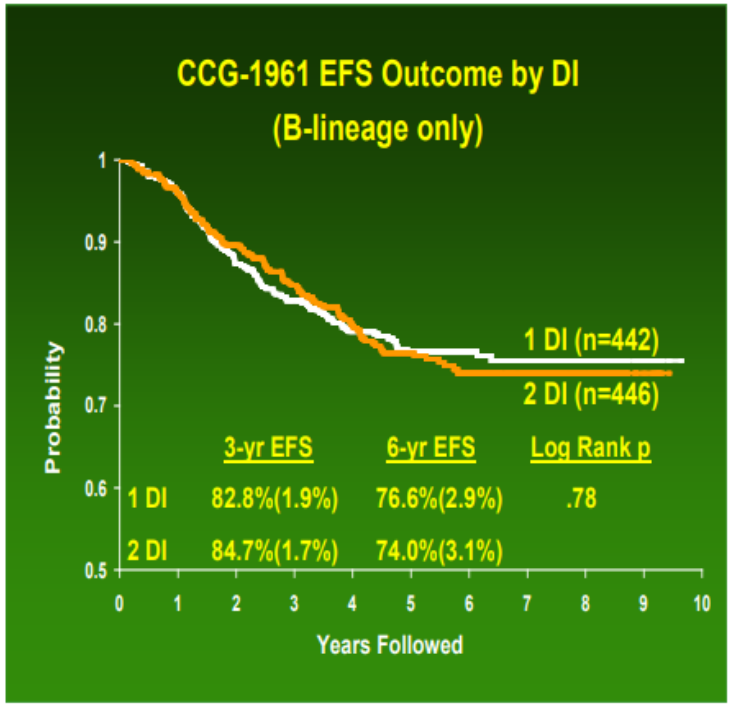
No Advantage of 2nd DI in Rapid Responders



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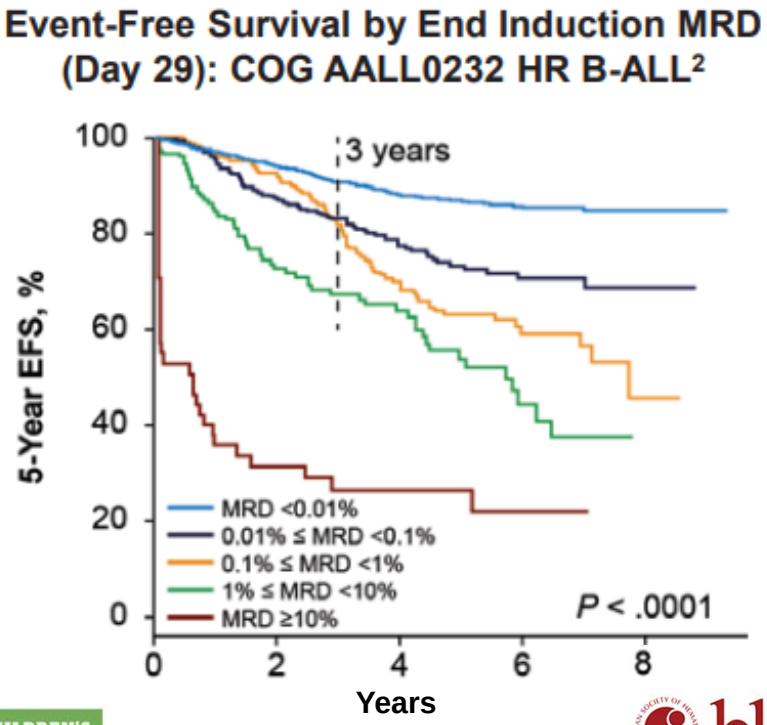
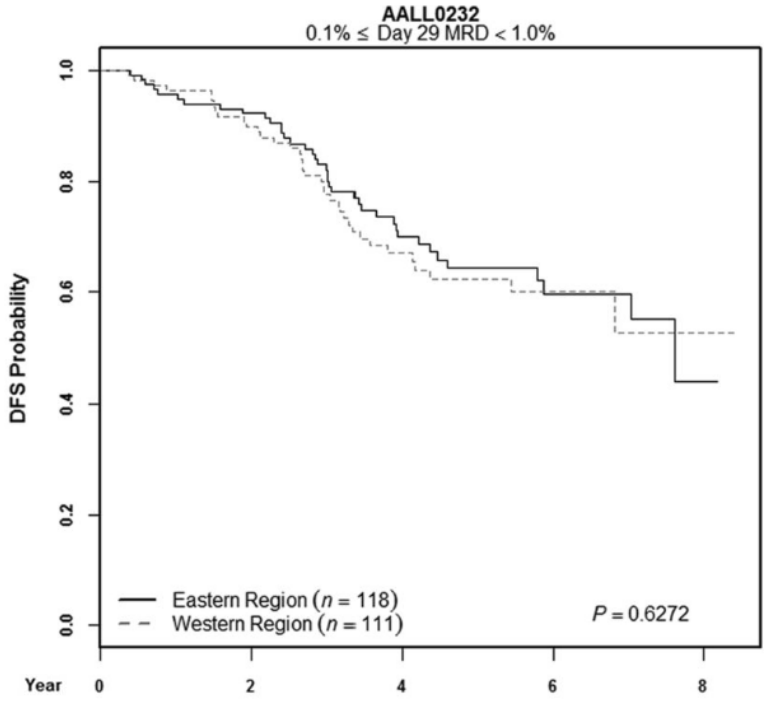
Seibel N et al. *Blood*, 2008 35

Therapies Still Failing a Subset of HR patients





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blood

Borowitz M et al. *Blood* 2015

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Ceiling Effect of Intensifying via Conventional Chemotherapy

Toxicity Associated with Intensive Post-Induction Therapy Incorporating Clofarabine in the Very High Risk Stratum of Patients with Newly Diagnosed High Risk B-Lymphoblastic Leukemia: a Report from the Children's Oncology Group Study AALL1131

Consolidation Part 2		
Control Arm	*Experimental Arm 1*	*Experimental Arm 2*
CPM 1000 mg/m^2 Day 29	CPM 440 mg/m^2 Days 29-33	CPM 440 mg/m^2 Days 29-33
ARAC 75 mg/m^2 Days 29-32, 36-39	ETOP 100 mg/m^2 Days 29-33	ETOP 100 mg/m^2 Days 29-33
MP 60 mg/m^2 Days 29-42		CLOF 30 mg/m^2 Days 29-33 (20 mg/m^2 post amendment)
VCR 1.5 mg/m^2 (2 mg max) Days 43, 50	VCR 1.5 mg/m^2 (2 mg max) Days 43, 50	VCR 1.5 mg/m^2 (2 mg max) Days 43, 50
PEG-ASP 2,500 units/m^2 Day 43	PEG-ASP 2,500 units/m^2 Day 43	PEG-ASP 2,500 units/m^2 Day 43

CLOF as administered with CPM/ETOP on AALL1131 was associated with unacceptable toxicity

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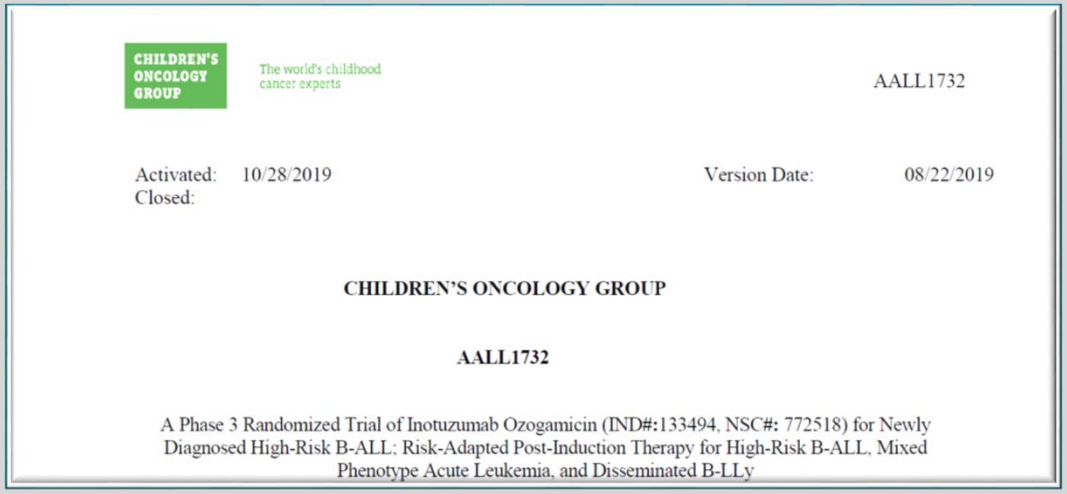
American Cancer Society® Cancer

Salzer W and Burke M, *Cancer*, 2018 37

Let's take a look at AALL1732, High Risk B lineage ALL…



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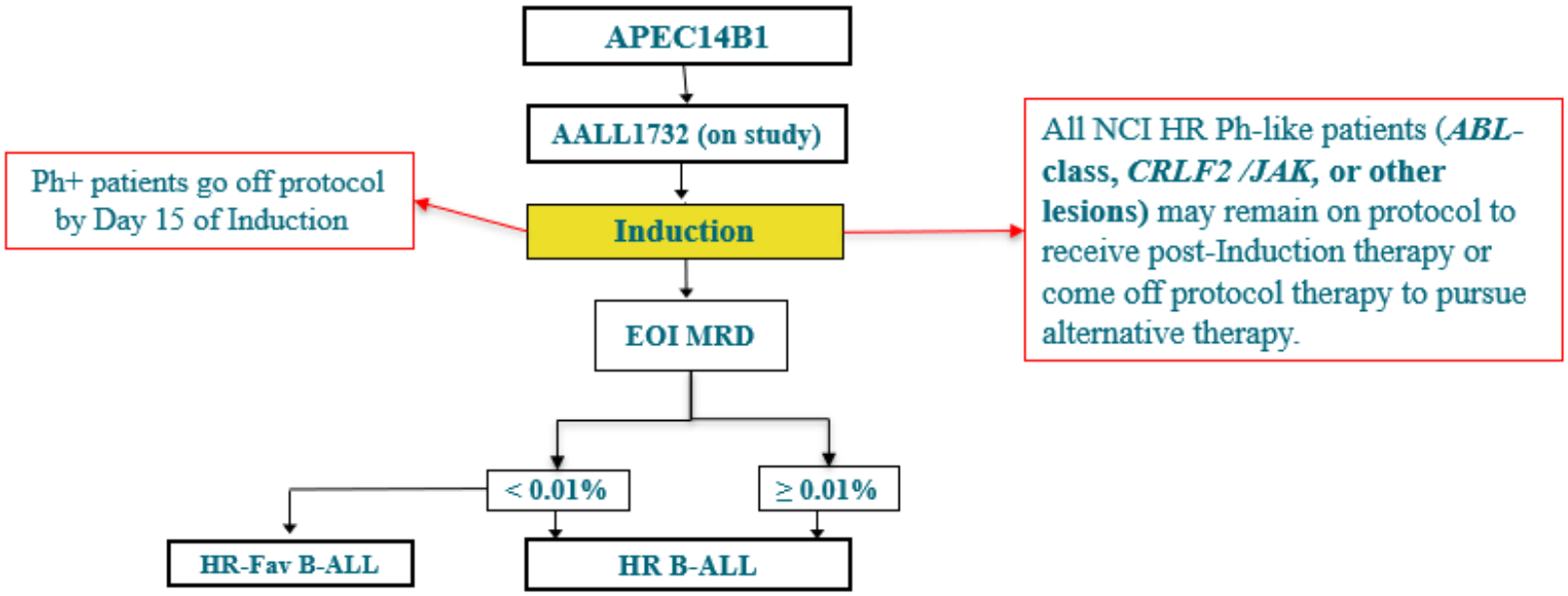
Risk Groups AALL1732



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AALL1732

- ALL NCI HR patients will enroll on and stay on AALL1732
- Subset of NCI SR B-ALL are included
  - With CNS3, testicular leukemia, or steroid pretreatment
- MPAL and HR B-LLy included
- Down syndrome excluded
  - Both NCI-SR and NCI-HR will enroll on AALL1731
- There is an investigational agent – inotuzumab
  - HR B-ALL: Randomization inotuzumab after Consolidation
- HR- Fav B ALL arm will not be randomized

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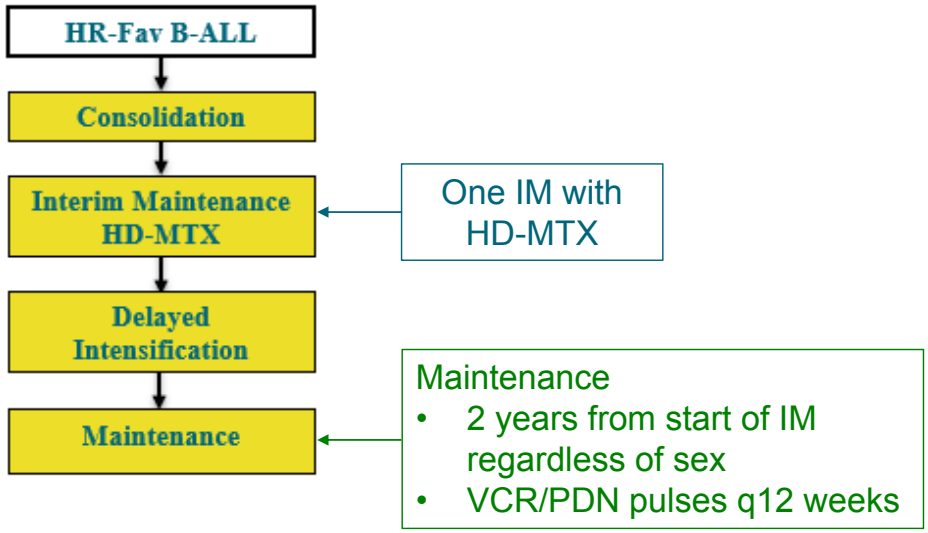
HR-Favorable B-ALL

NCI HR patients with:

- Favorable clinical features:
  - <10 years old but WBC ≥50K/μL at diagnosis
  - CNS1
  - No testicular leukemia
- Favorable cytogenetics:
  - ETV6-RUNX1
  - Trisomy 4 &10
- End of induction MRD < 0.01%



No Randomization – Predicted EFS 94%

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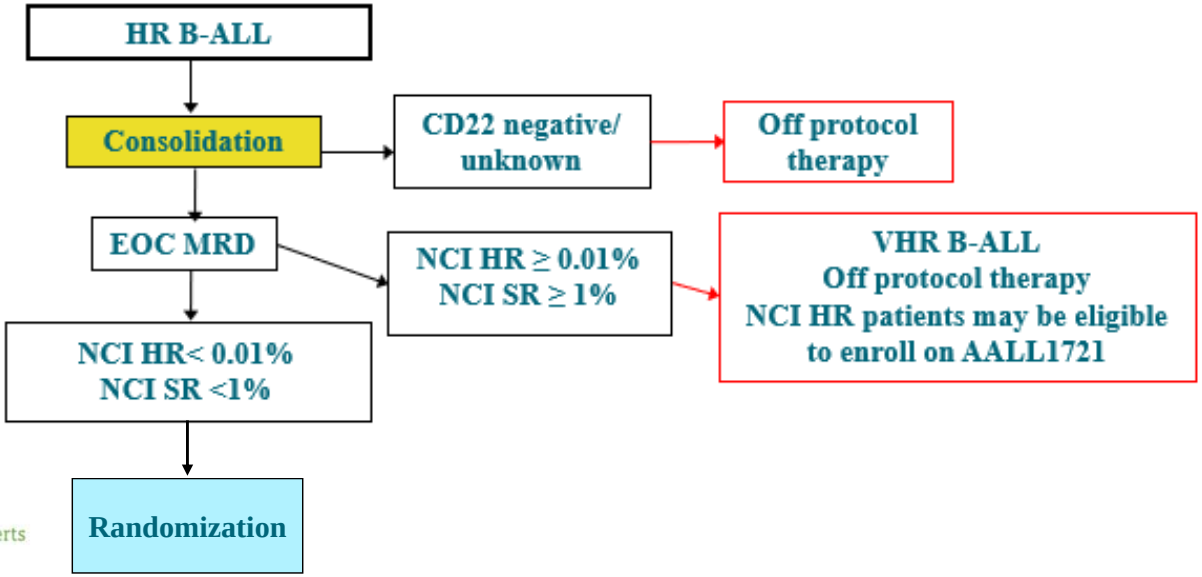
HR B-ALL

- Must have CD22 expression on leukemic blasts ON DIAGNOSTIC SAMPLE
  - NCI HR with EOC MRD <0.01%
  - NCI HR EOC MRD <1%



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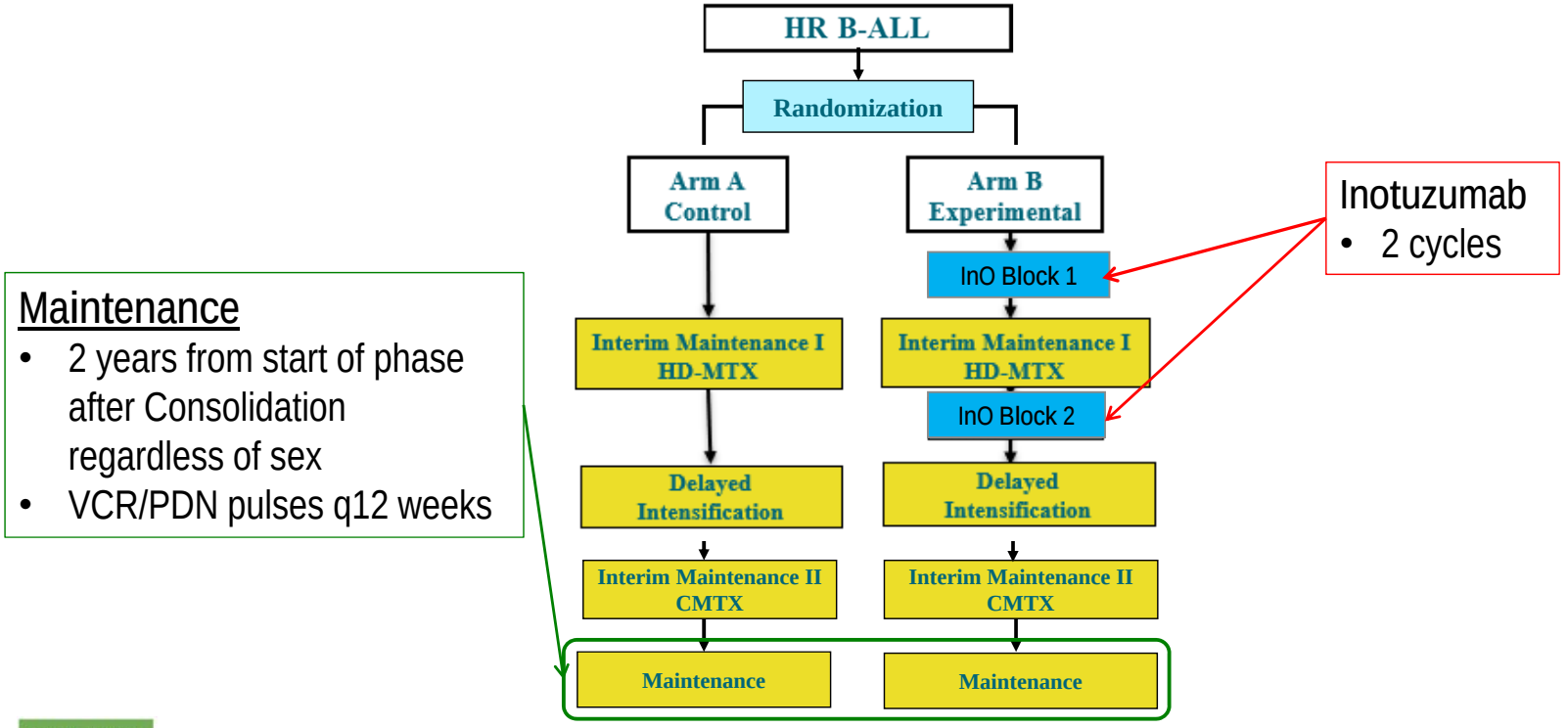
HR B-ALL


HR B-ALL
Randomization
Arm A
Control
Arm B
Experimental
InO Block 1
Interim Maintenance I
HD-MTX
Interim Maintenance I
HD-MTX
InO Block 2
Delayed
Intensification
Delayed
Intensification
Interim Maintenance II
CMTX
Interim Maintenance II
CMTX
Maintenance
Maintenance
Inotuzumab
• 2 cycles
Maintenance
• 2 years from start of phase after Consolidation regardless of sex
• VCR/PDN pulses q12 weeks
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Randomization +/- 2 cycles of Inotuzumab – Predicted EFS 65-90%
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Relationship between InO and hepatic toxicity…

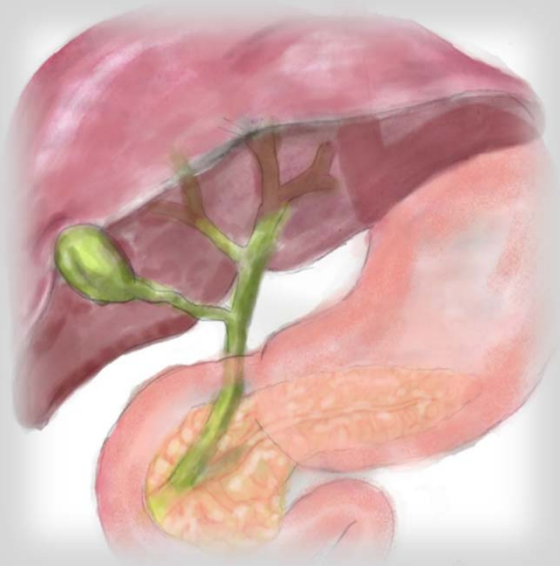

Illustration by Aimee Ermel, 2013

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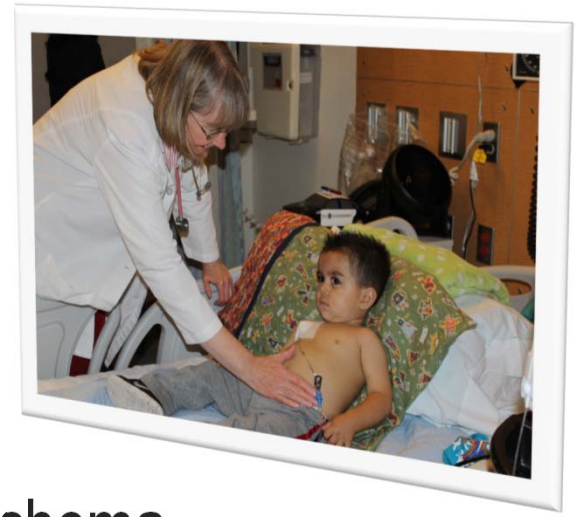
Hepatic Toxicity Assessment

- Monitor for SOS
- Assess d-bili and ALT
  - Prior to each dose of InO in
    - Block 1 and Block 2
- Appendix XV11:
  - InO Dose Modifications for Toxicities Schema



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Hepatic Toxicity Assessment cont'd

- CTCAE guidelines for hepatic toxicity:

Grade	ALT	d-bili
1	> 1-3x ULN	<2 mg/dL
2	>3-5x ULN	2-5 mg/dL
3	>5-20x ULN	>5 mg/dL
4	>20x ULN	

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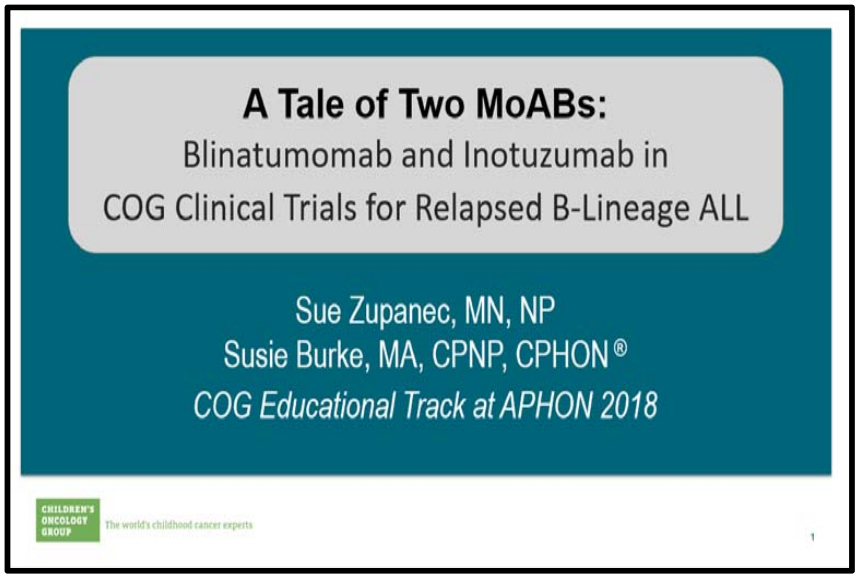
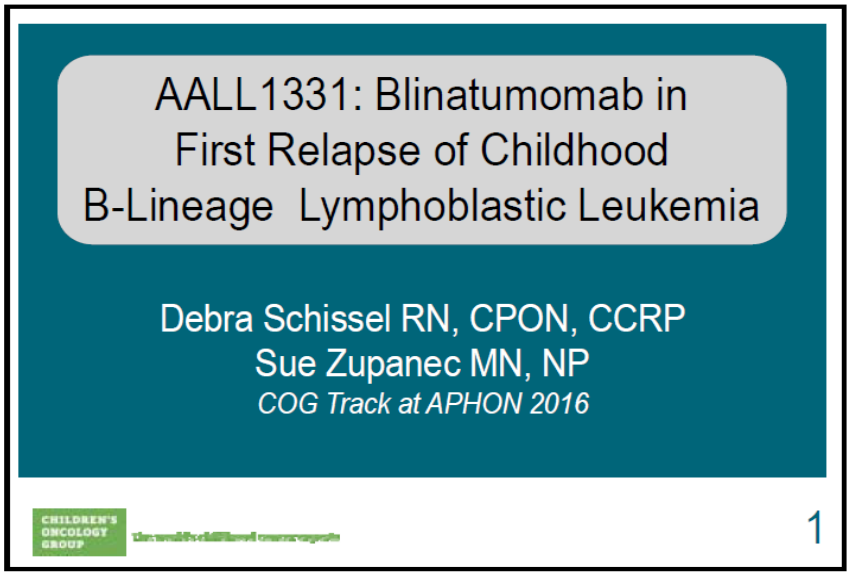
COG Nursing Resources on VIMEO

www.vimeo.com/cognursing





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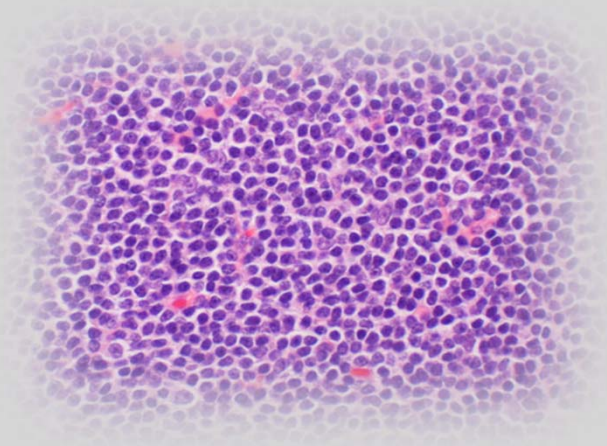
Mixed Phenotype Acute Leukemia (MPAL) and HR B-Lymphoblastic Lymphoma (B- LLy)…



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WHO2016 Definition of MPAL

WHO2016

Table 19. Criteria for lineage assignment for a diagnosis of MPAL

Lineage assignment criteria
Myeloid lineage
MPO* (flow cytometry, immunohistochemistry, or cytochemistry)
or
Monocytic differentiation (at least 2 of the following: nonspecific esterase cytochemistry, CD11c, CD14, CD64, lysozyme)
T-lineage
Strong† cytoplasmic CD3 (with antibodies to CD3 ε chain)
or
Surface CD3
B-lineage
Strong† CD19 with at least 1 of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10
or
Weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10

*See "Acute leukemias of ambiguous lineage" for caveats related to weaker antigen expression, or to expression by immunohistochemistry only.

†Strong defined as equal or brighter than the normal B or T cells in the sample.

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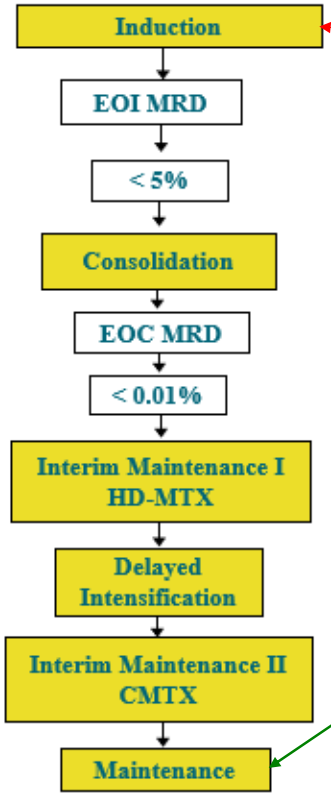
Arber DA et al. *Blood* 2016

MPAL

- Inclusion criteria:
  - Meets WHO2016 criteria
  - Subtypes:
    - B/myeloid
    - T/myeloid
    - B/T myeloid
    - B/T
- Central confirmation required
- No randomizations



Ph+ patients off protocol by Day 15 of Induction

Maintenance:

- 2 years from start of IM1 regardless of sex for all arms
- VCR/PDN pulse q12 weeks

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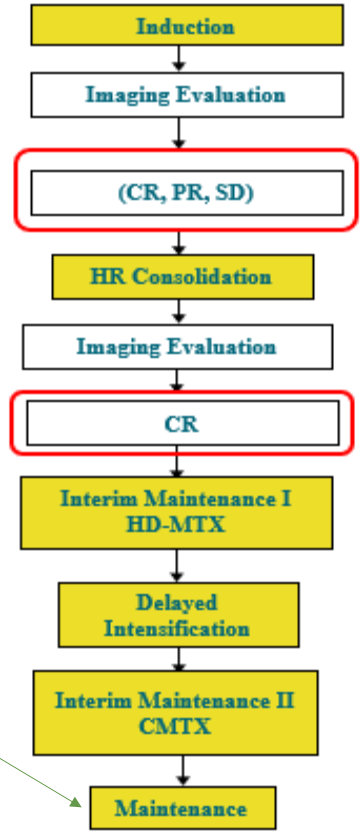
B-LLy

- Inclusion criteria:
  - Murphy Stage III/IV
  - Murphy Stage I/II with steroid pretreatment
    - >48 hours of IV or oral steroids
- Must have CR by EOC to continue protocol therapy
  - By imaging (CT scans, bone scan, +/- PET scan)
- No randomization



Maintenance:

- 2 years from start of IM1 regardless of sex for all arms
- VCR/PDN pulse q12 weeks

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MMD vs. MRD Definitions

- MMD = minimal marrow disease
  - Diagnostic marrow
- MRD = minimal residual disease
  - End of Induction

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How does adherence impact risk of relapse…

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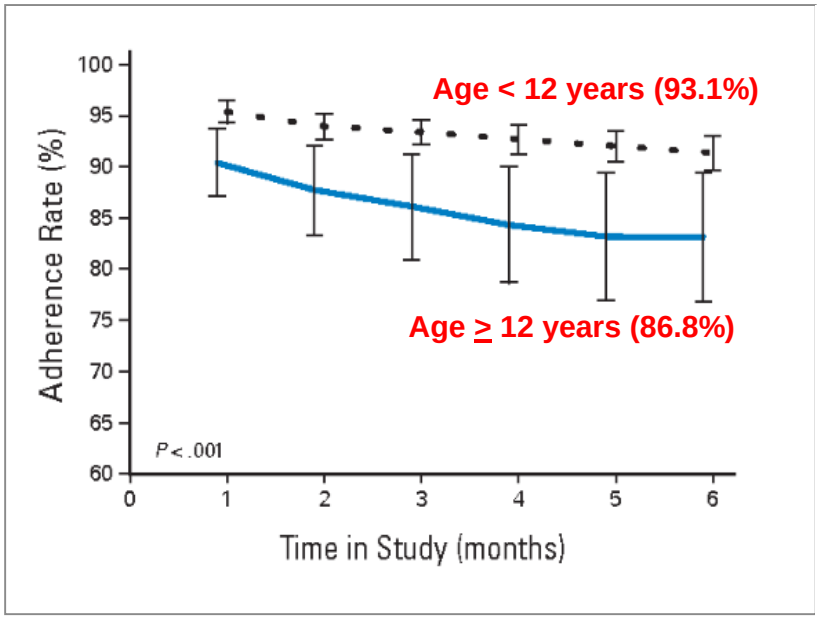
Oral 6-MP Adherence



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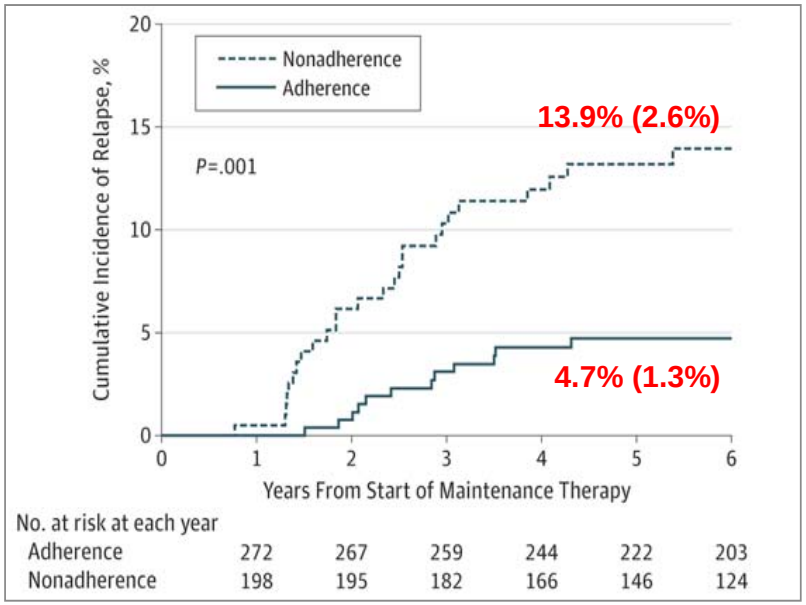

JAMA Oncology
© 2015

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Bhatia et al. *J Clin Oncol* 2012:30-2094-2102 and *JAMA Oncol* 2015; 3:287-295 54

AALL1732 Primary Aim (Adherence Study): *Coming Soon*

- To determine the impact of proposed interventions (IP vs. iIP vs. pIP) on adherence to oral 6 MP in children with HR B-ALL
  - Adherence to oral 6 MP will be measured with the Medication Event Monitoring System (MEMS)

Intervention Components	IP	iIP	pIP
Education (MIPE) (once)	x	x	x
Customized printed 6MP schedule	x	x	x
Oncologist-initiated electronic reminder (one every night)	x		
Oncologist-initiated customized electronic reminder + real-time feed back reminders		x	
Patient/Parent-established reminders			x
Directly supervised therapy	x	x	x

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Slide courtesy of Smita Bhatia, MD

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Take Home Message: Less is More…

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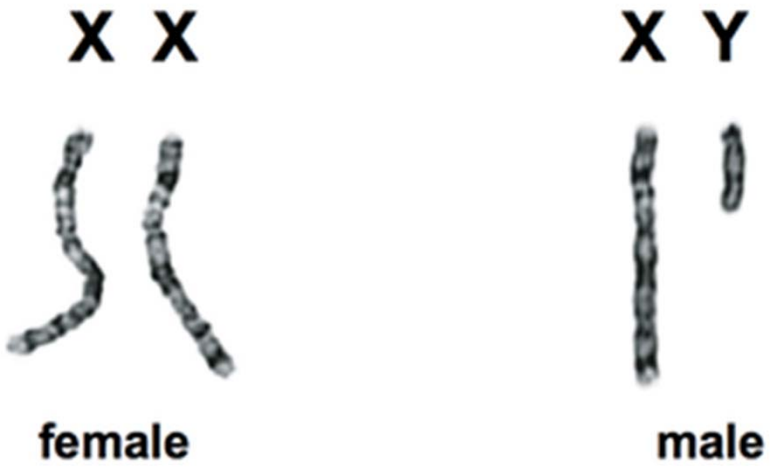
Same length of therapy regardless of biologic sex!



2 years from start of Interim Maintenance, regardless of sex

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Consortium Outcomes for ALL by Sex

Trial Group	Length of Therapy	Gender-based difference?	Outcomes (5 yr EFS)		
			Female*	Male*	Statistically Significant diff in gender ?
BFM-ALL 2000	24 mos from diagnosis	NO	85%	83%	N/S
DFCI 05-001	104 wks post CR	No	86% (95% CI-81-90)	85% (95% CI = 81-89)	N/S in univar analysis
UK ALL 2003	2-3 yrs from beginning of IM	Yes	Haz ratio (female vs male): 0.78 (95% CI 9.54-1.13)		N/S in multivar analysis
DCOG ALL-9	109 wks	No	84.8 ± 2%	78 ± 1.8%	N/S in multivar analysis
NOPHO ALL-2000	2-2.5 yrs post dx	No	81 ± 2%	78 ± 2%	N/S in multivar analysis
St. Jude Total XV	120-146 wks	Yes	88.8 ± 4.3%	83.5 ± 4.1%	N/S in multivar analysis
St. Jude Total XVI	120 wks	No	Ongoing		

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Same length of therapy regardless of sex!

- Both AALL1731 and AALL1732:
  - Length of therapy will NOT be a randomized question
  - Outcomes will be compared to historical trials of similar populations
  - Stopping rules in place to ensure safety

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Reduced VCR/Steroid pulses to every 12 weeks!

Results: AALL0932

Figure 1: DFS by VCR/DEX pulse randomization

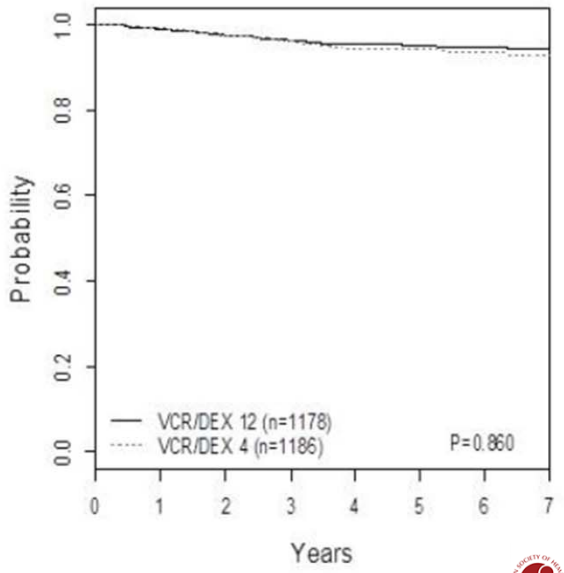
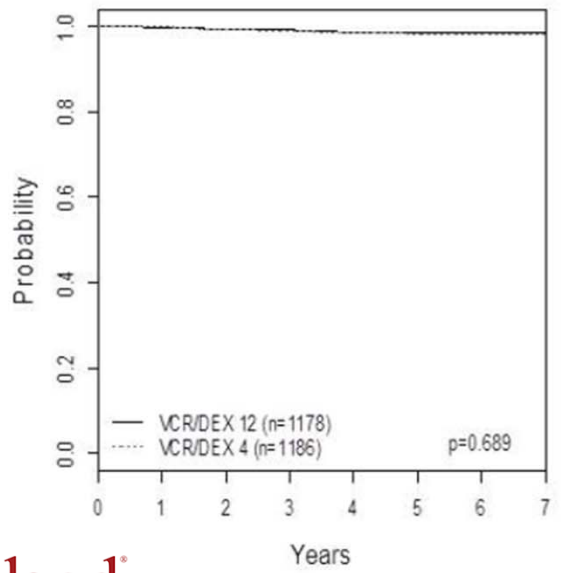


Figure 2: OS by VCR/DEX pulse randomization



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blood

Angiolillo, A. (2019), Blood

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Summary

- ALL treatment has evolved to identify subgroups with outstanding outcomes
- Ceiling effect of intensifying treatment via conventional chemotherapy
- Less acute toxicities with immunotherapy although time will tell with late effects
- Uniform length of Maintenance regardless of sex!
  - 2 years from start of IM#1, Blinatumomab cycle #1, or Inotuzumab cycle #1
- Reduced VCR/Steroid pulses in maintenance to every 12 weeks
  - For both risk groups!

Hence, Less is More!!

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Abbreviations

FULL TERM	ABBREVIATION
Alanine transaminase	ALT
^{18}fluoro-2-deoxy-D-glucose positron emission tomography	FDG-PET
Acute lymphoblastic leukemia	ALL
American Society of Hematology	ASH
Average	Avg
B-cell Acute Lymphoblastic Leuekemiia	B-ALL
Berlin Frankfurt Munster	BFM
Blinatumomab	Blin
B-Lymphoblastic Lymphoma	B-LLy
Bone marrow	BM
Bone marrow aspirate	BMA

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Abbreviations

FULL TERM	ABBREVIATION
Direct bilirubin	d-bili
Down syndrome	DS
End of Induction	EOI
Escalating Methotrexate	EscMTX
Etoposide	ETOP or VP
Event free survival	EFS
Every	q
Favorable	Fav
Frequently asked questions	FAQ(s)
Hazard	Haz
Hematopoietic cell transplant	HCT

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Abbreviations

FULL TERM	ABBREVIATION
High dose methotrexate	HD-MTX
High risk	HR
High-Throughout Sequencing	HTS
Inotuzomab Ozogamicin	InO
Interim maintenance	IM
Intravenous	IV
Janus kinase	JAK
Mercaptopurine	6MP
Minimal Marrow Disease	MMD
Minimal residual disease	MRD
Mixed Phenotype Acute Leukemia	MPAL

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Abbreviations

FULL TERM	ABBREVIATION
Monoclonal antibody/antibodies	MoAb(s)
Multimedia interactive patient/parent education	MIPE
National Cancer Institute	NCI
Nordic Society for Pediatric Hematology and Oncology	NOPHO
Not Significant	N/S
Nurse practitioner(s)	NP(s)
One thousand	K
Overall survival	OS
Partial remission or response	PR
Patient(s)	pt(s)
Peripheral blood	PB

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Abbreviations

FULL TERM	ABBREVIATION
Philadelphia positive	Ph+
Philadelphia-like acute lymphoblastic leukemia	Ph-like ALL
Prednisone	PRED
Project:EveryChild, A Registry, Eligibility Screening, Biology and Outcome Study	APEC14B1
Sinusoidal Obstruction Syndrome	SOS
Stable disease	SD
Standard of care	SOC
Standard risk	SR
Upper Limit of Normal	ULN

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Abbreviations

FULL TERM	ABBREVIATION
Very high risk	VHR
Vincristine	VCR
Week(s)	wk(s)
World health organization	WHO
Year(s)	yr(s)

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