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A horizontal band containing a microscopic image of blood cells, likely showing a large white blood cell with a prominent nucleus and surrounding red blood cells.

# Acute Lymphoblastic Leukemia

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Cincinnati, OH

# Disclosures

*In compliance with ACCME policy, ASH requires disclosures to the session audience:*

## Speaker

Emily Curran, MD

## Disclosures

**Consultancy:** Amgen; Incyte; Kite Pharma; Tempus

**Honoraria:** Clinical Care Options; Servier; Tempus

**Membership on a Board or Advisory Committee:** Amgen;  
Incyte; Kite Pharma; Tempus

**Discussion of off-label drug use:** Not applicable



# Learning Objectives

Upon participation in this activity, attendees will be able to:

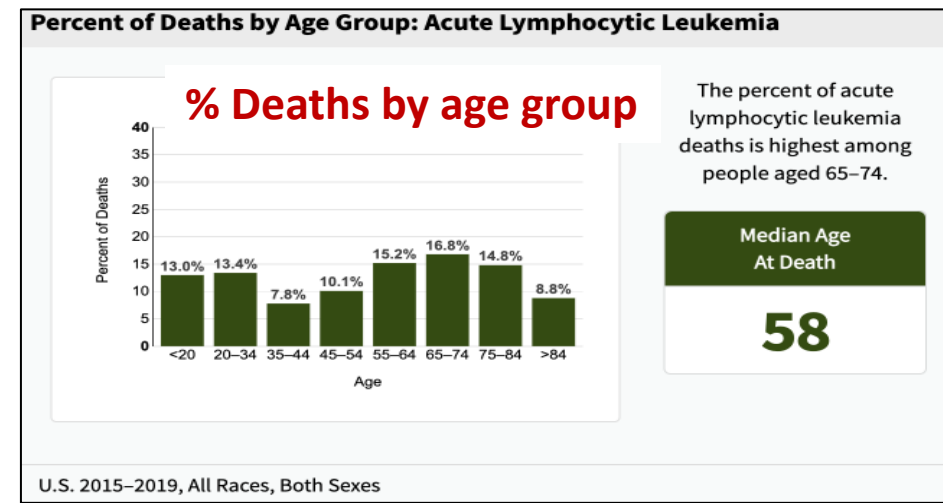
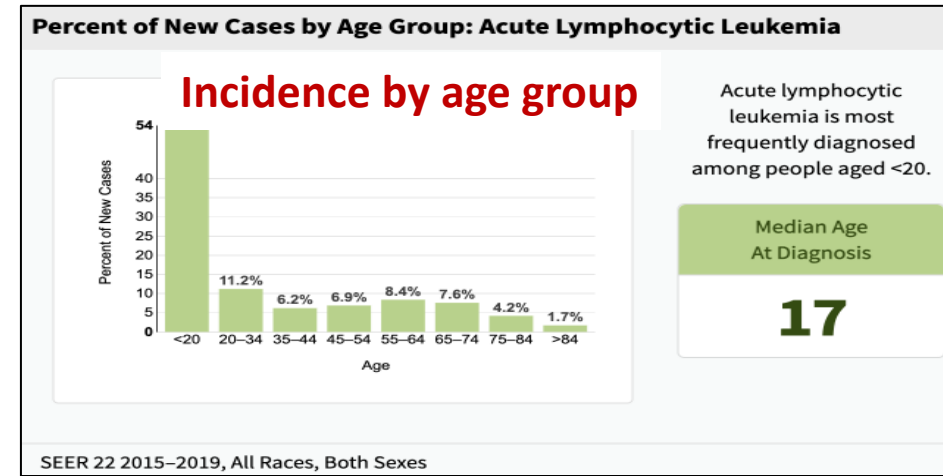
- Describe the difficulties in treating older patients with ALL and novel approaches to improve outcomes.
- Summarize the results of trial incorporating blinatumomab in post-remission therapy for Ph-negative ALL.
- Understand the growing data for chemotherapy-free approaches for front-line treatment of Ph-positive ALL.
- Discuss challenges in treatment approaches for relapsed or refractory T-ALL.



# Acute lymphoblastic leukemia in adults

Estimated New Cases in 2022	6,660
% of All New Cancer Cases	0.3%

- Most common leukemia in children.
- Adults: ~50% of diagnoses, but majority of relapses and deaths.
- Risk factors: Down syndrome, prior chemo/radiation (myeloma).



# Case 1

- 63-year-old man presents with dyspnea to his PCP
- **CBC:** WBC 55 K/uL, 90% blasts, Hg 6.5 g/dL, Plt 87 K/uL
- **Flow cytometry:** lymphoblasts, B-lineage, CD34+, TdT+, CD10+, CD19+, CD22+, no T-cell or myeloid markers.
- **Karyotype:** 46,XY [20]
- **PMH:** GERD, obesity, HL, arthritis
- Treatment approach for an older adult with B-ALL?



# Section 1: ASH 2022 updates on treating (older) adults with Ph-neg ALL

Older adults have poor outcomes when treated with conventional chemotherapy

	Age	CR (%)	Early Death (%)	OS (%)
<b>Adult trials, older adult cohorts (dose modifications employed)</b>				
CALGB 9111	≥60	77	17	17 (3 yr)
ECOG 2993 / UKALL XII	55-65	73	18	21 (5 yr)
Hyper CVAD	≥60	84	10	20 (5 yr)
<b>Older adult trials</b>				
Dana-Farber/Harvard	>50	67	13	52 (2 yr)
GMALL	≥55	76	14	23 (5 yr)
PETHEMA ALLOLD07	>55	74	13	12.4 mo med

## Resistant disease

- Lower CR rate/refractory
- Relapse

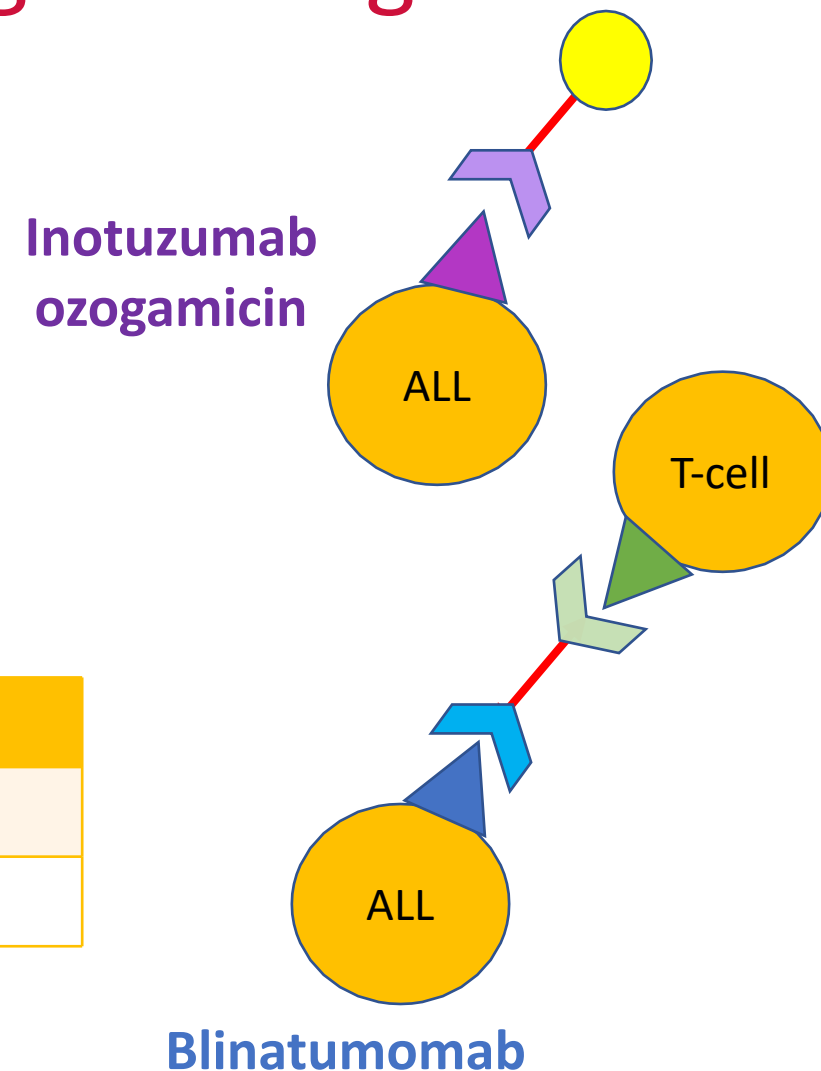
## Toxicity

- High early death (10–20%)
- Death in CR

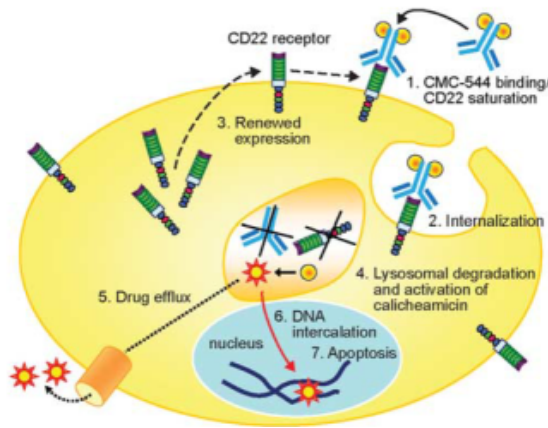
# Ph-neg ALL in older adults: Novel Agent Integration

- Until recently, relied on conventional chemotherapy.
- Can optimize chemo, but benefit ceiling - can decrease mortality, but trade-off is increased relapse (**ASH 2022: Boissel #50; Goekbuget #212**)
- **Blinatumomab (2015) and inotuzumab ozogamicin (2017)** approved for relapsed or refractory B-ALL.

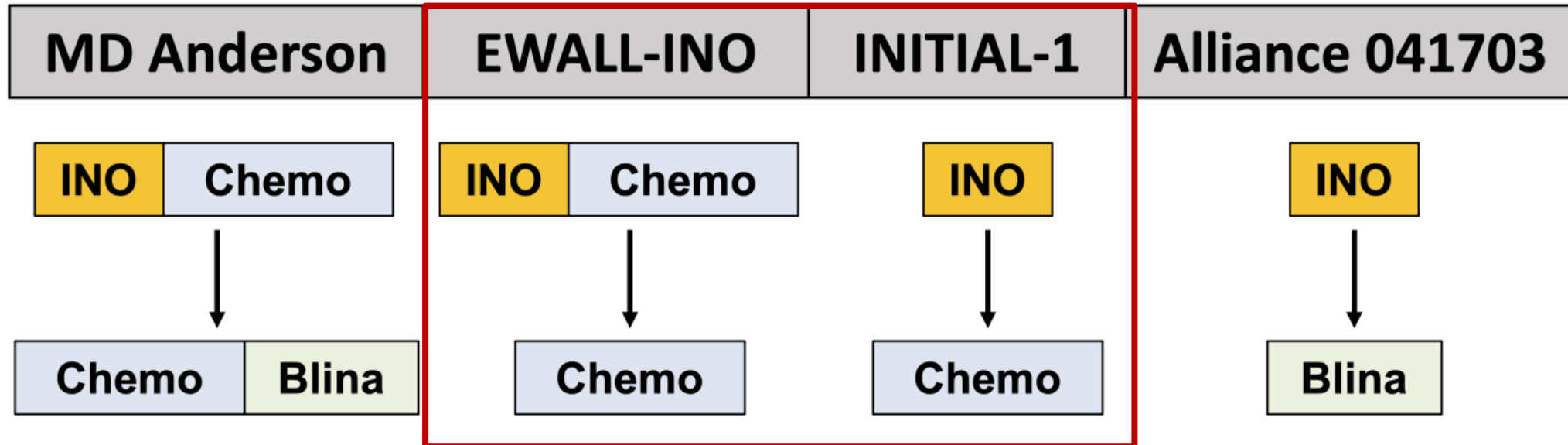
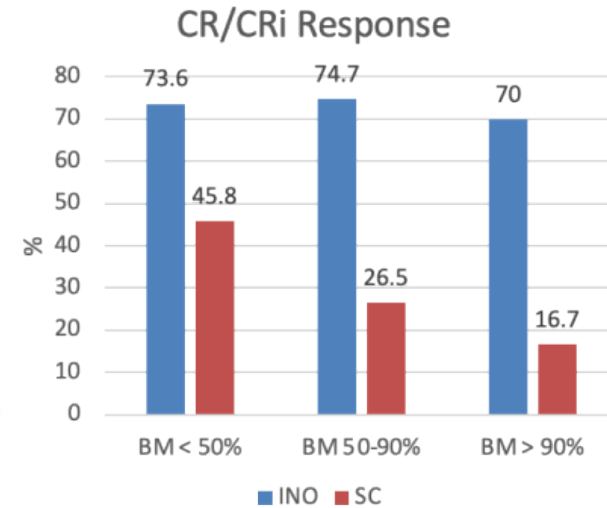
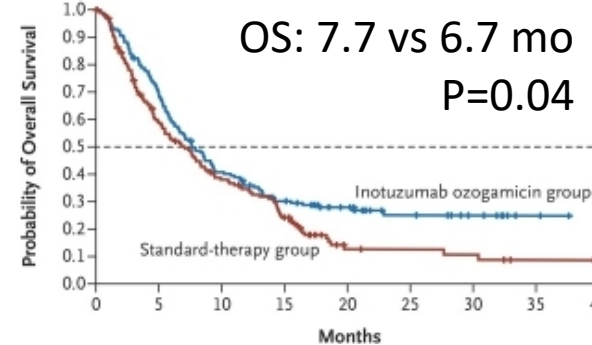
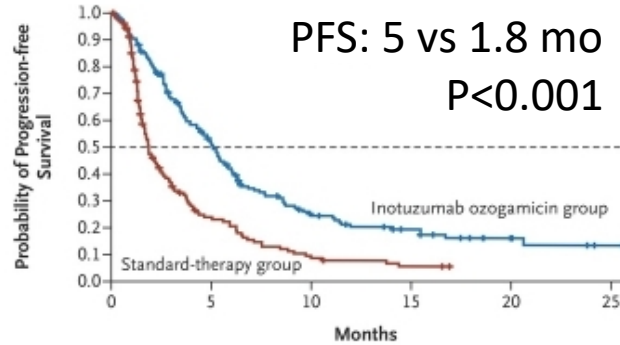
Goals	Approach
Better efficacy	Add novel agents
Less toxicity	Reduce/omit conventional chemotherapy

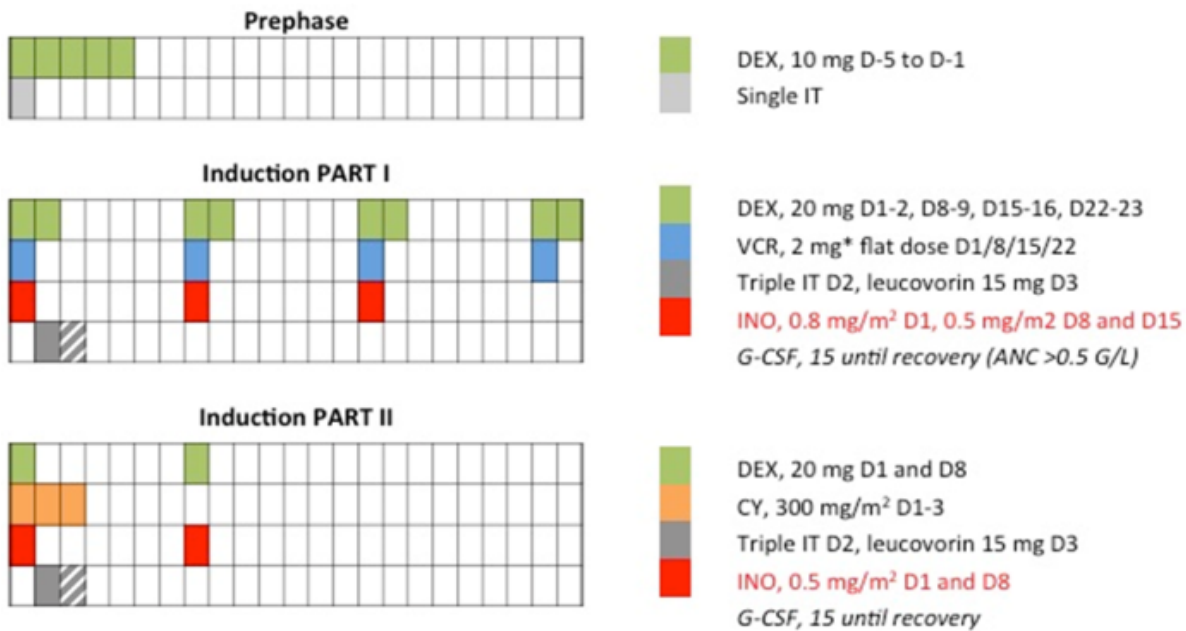


# Inotuzumab ozogamicin (InO) in front line



INO-VATE Study (NCT01564784)





6 consolidations (AraC/MTX/CY), POMP maintenance 18 months

## EWALL-INO (GRAALL)

Single arm, Phase II, age >55, CD22+ B-ALL

**N=131**

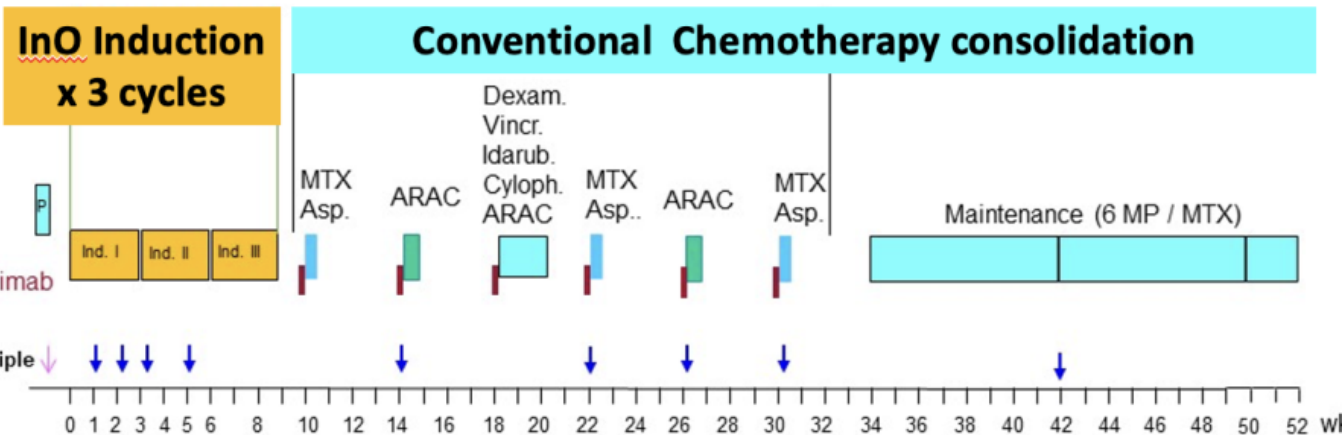
Median age: **69 yrs (55-84)**

**CR/CRp: 90%; MRD-neg: 81%**

Induction death: 3%

3 pts (2.2%) with SOS

Deaths: N= 50 (38.1%); 29 relapse, 21 AEs



## INITIAL-1 (GMALL)

Single arm, Phase II, age >55, CD22+ B-ALL

**N=43**

Median age: **64 yrs (56-80)**

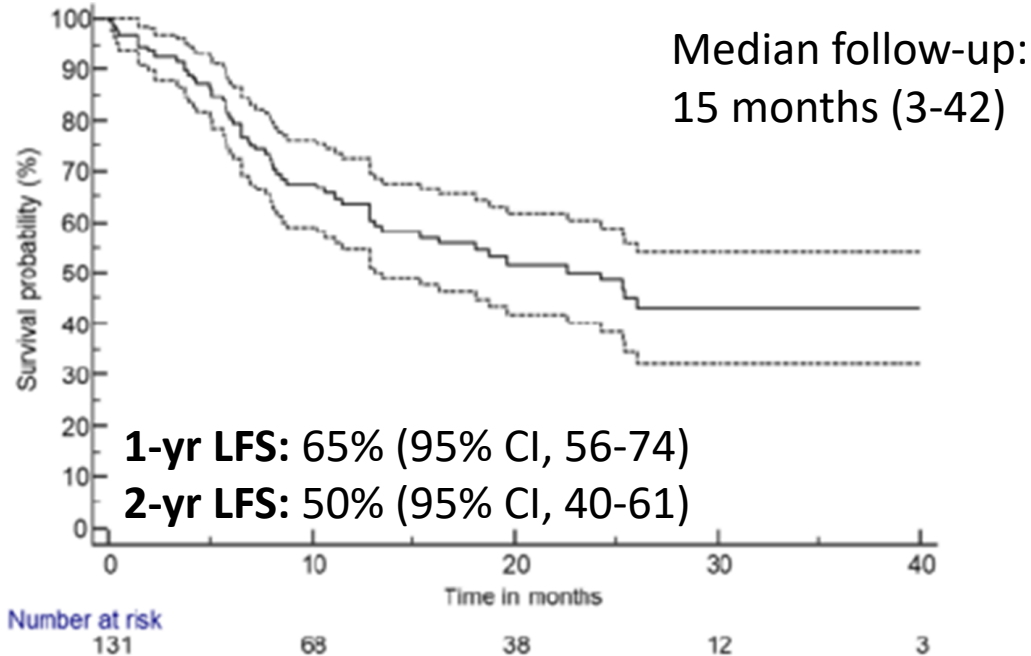
**CR/Cri: 100%; MRD-neg: 74%**

Early deaths (1<sup>st</sup> 6mo): 0%

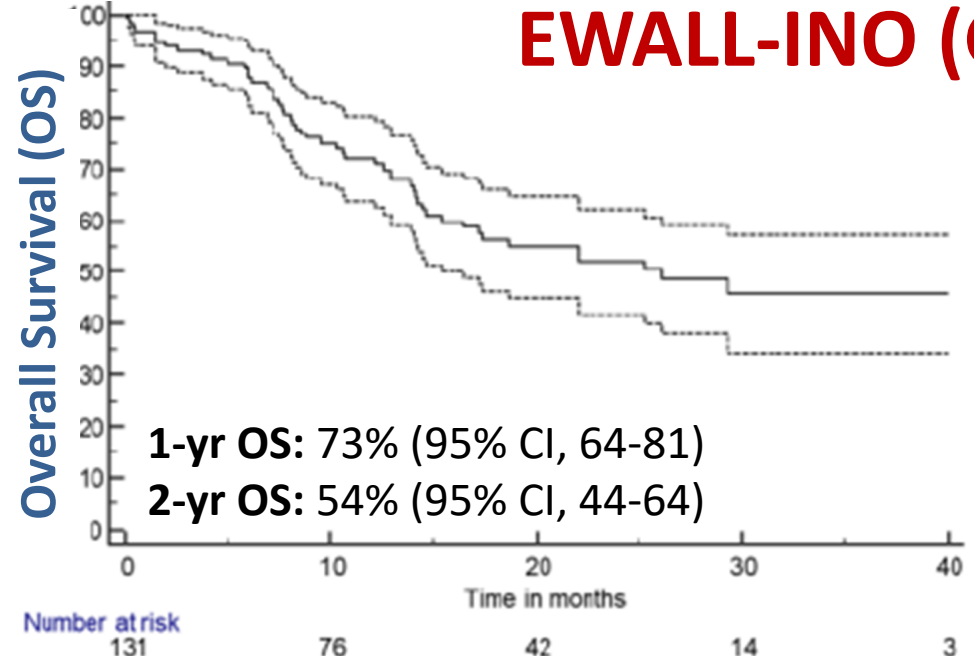
1 suspected VOD/SOS after cycle 2

**Blasts >60% CD22+: 28 pts (65%)**

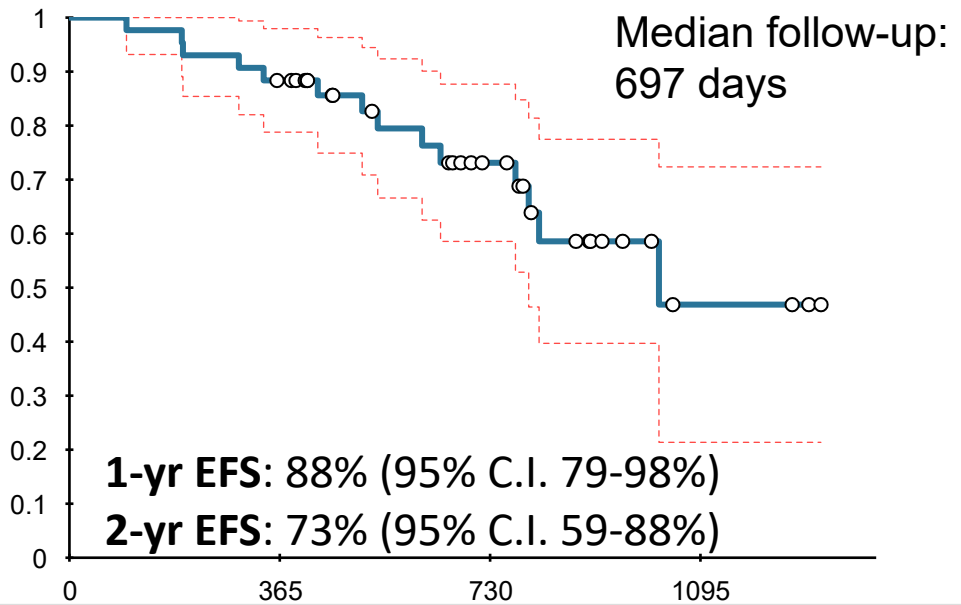
# Leukemia-Free Survival (LFS)



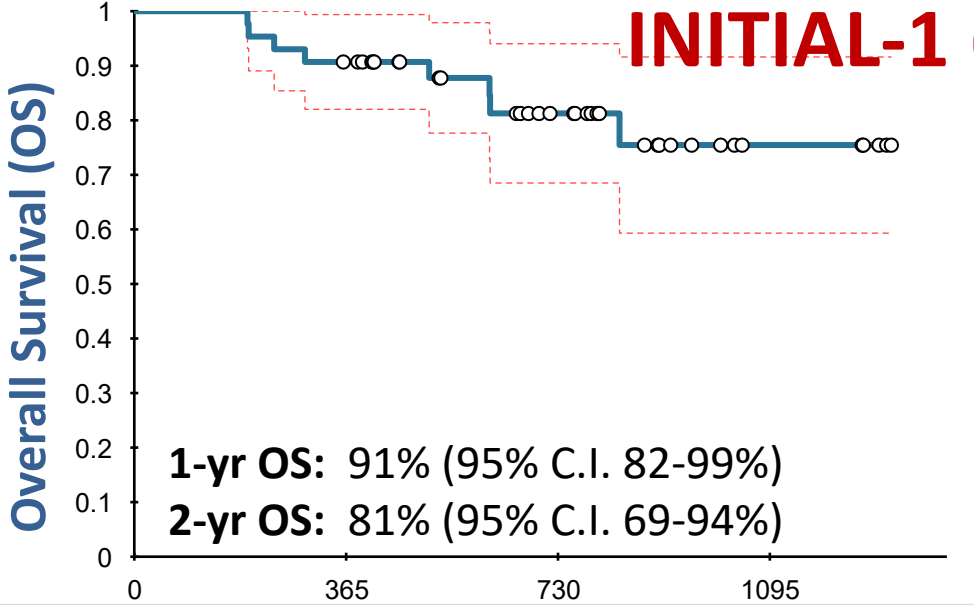
# EWALL-INO (GRAALL)



# Event-Free Survival (EFS)



# INITIAL-1 (GMALL)



# Conclusions – InO for Induction in ALL

- Novel agent-based induction regimens with no or minimal conventional chemotherapy improve early responses → high rates of MRD-negative CR.
- Events are accruing after years 1 and 2 (relapses and death).
- Consolidation approaches based on conventional chemotherapy need improvement as well.



# Case 1 Continued

- 63-year-old man presents with dyspnea to his PCP, who checks CBC.
- **Flow cytometry:** CD34+, TdT+, CD10+, CD19+, CD22+, no T-cell or myeloid markers.
- **Karyotype:** 46(X,Y)
- **PMH:** GERD, obesity, HL, arthritis

Treated with intensive chemotherapy-based induction

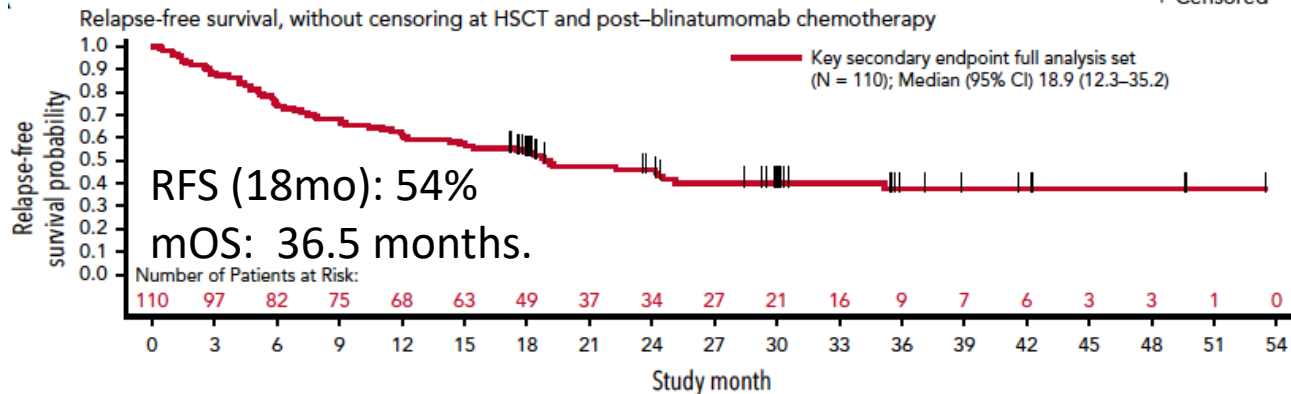
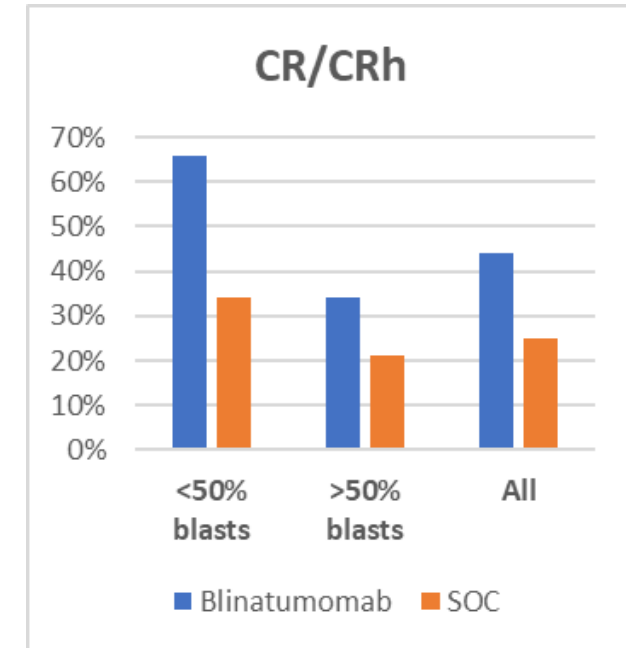
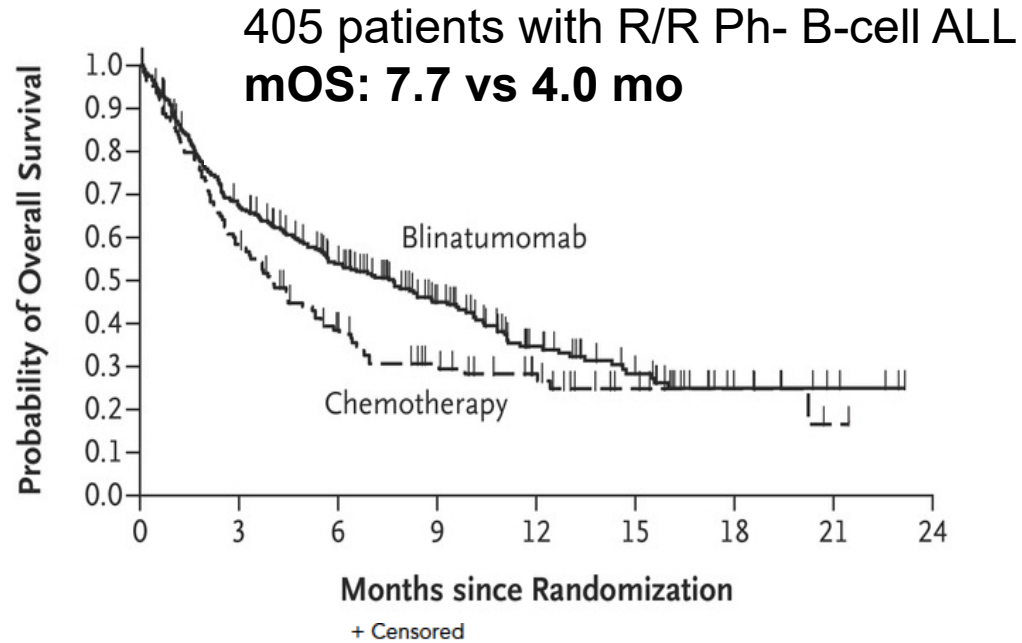
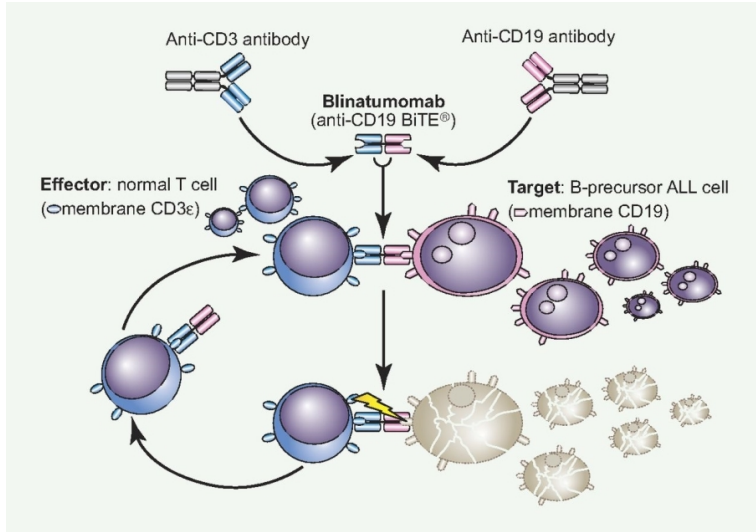
Achieves MRD-negative CR (MRD < 10<sup>-4</sup>)

Next steps?



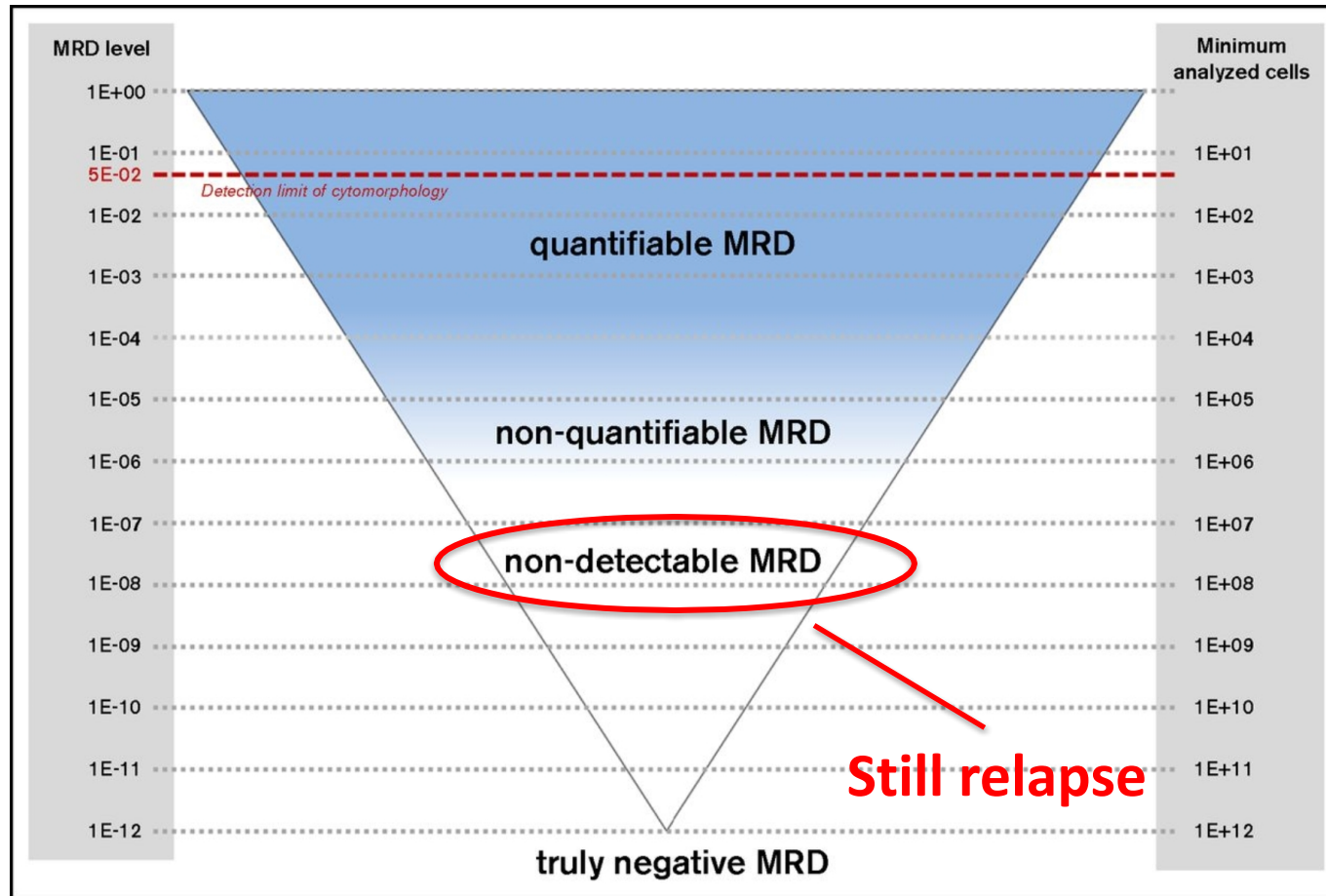
# Section 2: ASH 2022 updates on post-remission therapy for adult patients

# Blinatumomab: R/R and MRD+ disease

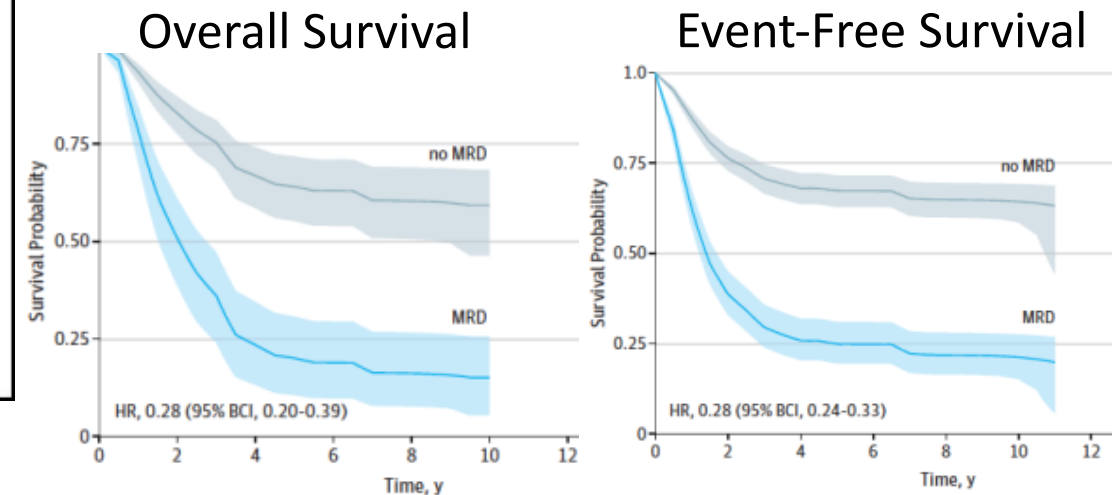


- 116 patients with B-ALL in CR
- Persistent or recurrent  $\text{MRD} \geq 10^{-3}$  after 3+ blocks of chemotherapy
- Received up to 4 cycles of blinatumomab
- **MRD response: 88/113 (78%) after CR1**

# MRD: “Minimal” or “Measurable” Residual Disease



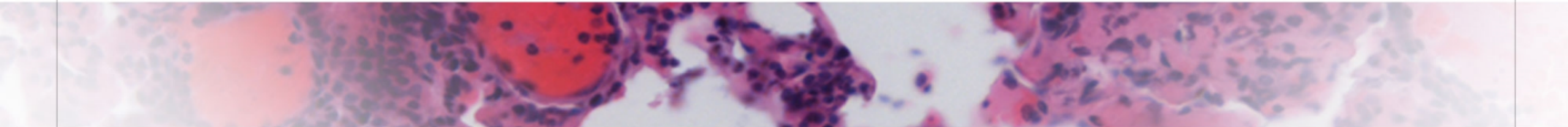
- **Multiparameter Flow Cytometry (MFC):** Sensitivity:  $10^{-4}$
- **Allele-Specific Oligonucleotide PCR (ASO-PCR):** Sensitivity  $10^{-5}$  to  $10^{-6}$
- **Next Generation Sequencing (NGS):** Sensitivity:  $10^{-6}$





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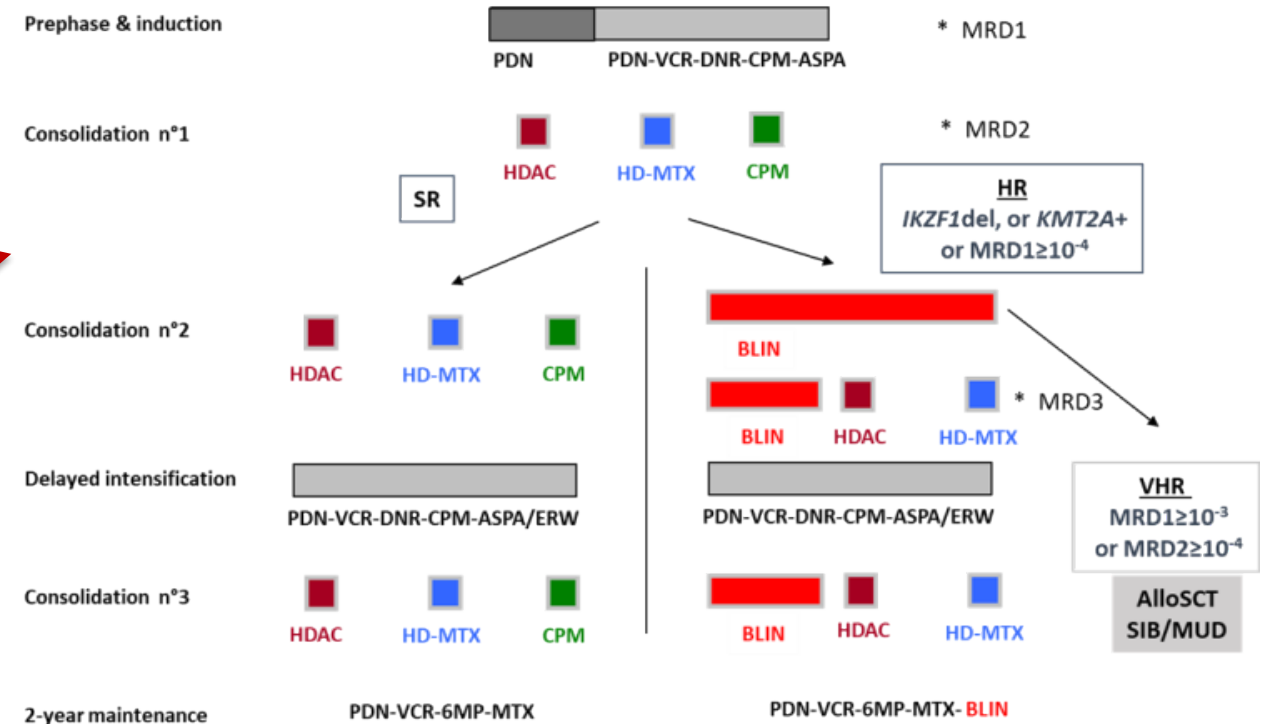
**Blinatumomab During Consolidation in High-risk  
Philadelphia Chromosome-negative B-cell Precursor  
Acute Lymphoblastic Leukemia Adult Patients:  
A Two-cohort Comparison within the GRAALL-2014/B Study**

Nicolas Boissel, Françoise Huguet, Thibaut Leguay, Mathilde Hunault, Rathana Kim, Yosr Hicheri, Patrice Chevallier, Marie Balsat, Sébastien Maury, Anne Thiebaut, Florence van Obbergh, Thomas Cluzeau, Martine Escoffre-Barbe, Nicole Straetmans, Johanna Konopacki, Amine Belhabri, Alban Villate, Florence Pasquier, Ioana Vaida, Laurence Sanhes, Magda Alexis, Mathilde Lamarque, Laure Farnault, Céline Berthon, Véronique Lhéritier, Norbert Ifrah, Carlos Graux, Yves Chalandon, Emmanuelle Clappier, Hervé Dombret

# GRAALL-2014/B QUEST Phase 2 sub-study

## *Blinatumomab during consolidation for high-risk patients*

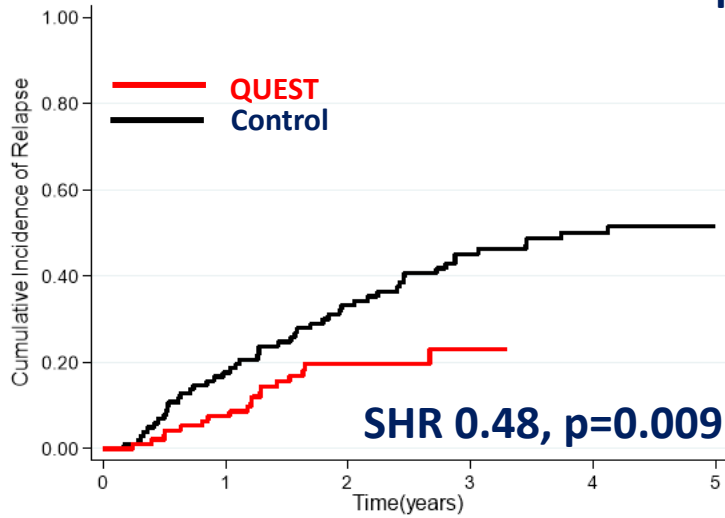
- **GRAALL-2014/B trial (N=489):** Patients with newly diagnosed Ph-negative BCP-ALL enrolled between 12/2015 to 12/2020
- **QUEST sub-study cohort (N=94) – received blinatumomab**
  - Eligibility: HR features: *KMT2A-r*, *IKZF1del* and/or  $MRD1 \geq 10^{-4}$
- **Internal control cohort (N=104) – ineligible if exposed to blinatumomab**
  - Patients enrolled in the GRAALL-2014/B trial with similar eligibility criteria
  - Mostly consisted of patients treated before QUEST activation (n=91)



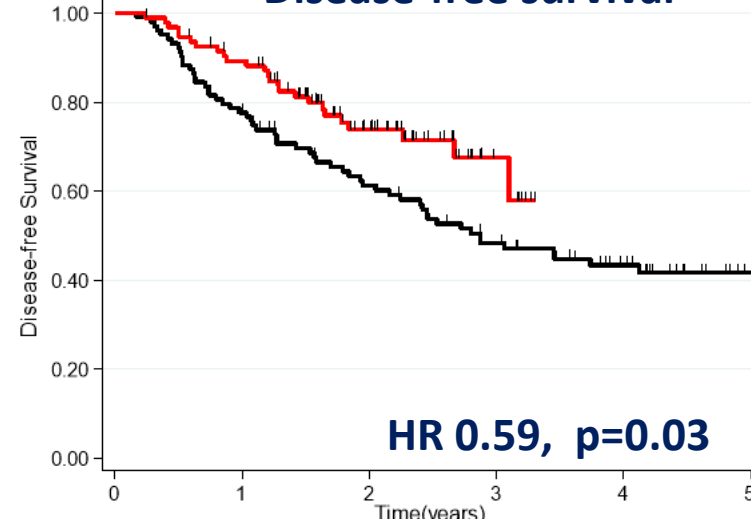
- **In patients eligible for allo-HSCT:**
  - Blinatumomab was given continuously as a bridge to transplant (SIB/MUD)
  - Minimum 4-week exposure to blinatumomab before HSCT

# QUEST vs Control - Results

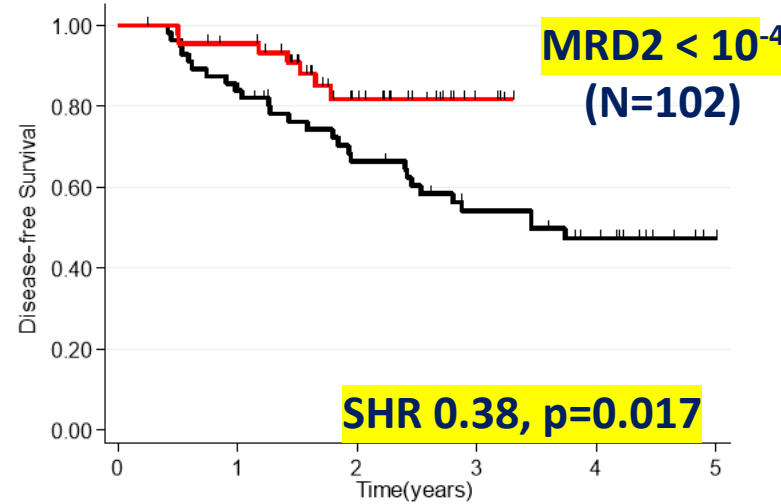
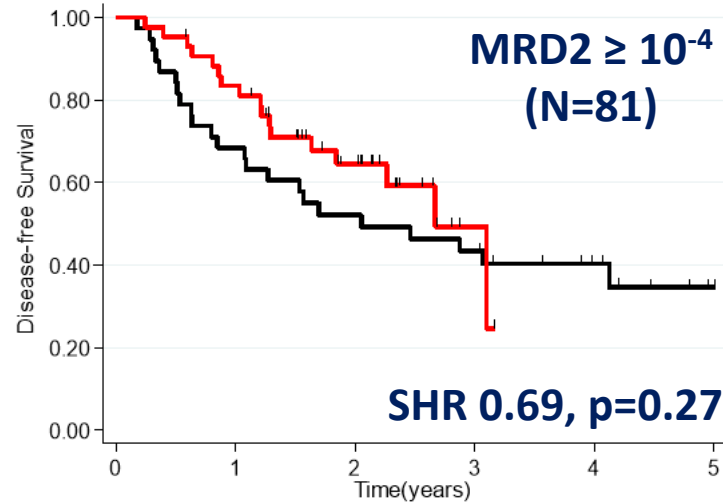
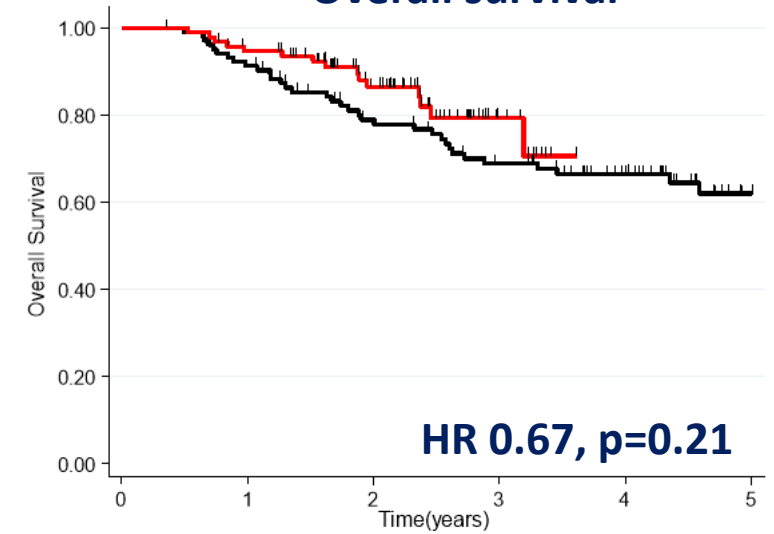
**Cumulative incidence of relapse**



**Disease-free survival**



**Overall survival**



**Blinatumomab during consolidation associated with:**

- Higher MRD response rate
- 52% reduction in CIR
- Prolonged DFS

**Benefit in DFS in particular in pts with MRD response prior to blinatumomab**

Number at risk

Control	38	26	18	15	8	2
QUEST	43	35	18	2	0	0

Number at risk

Control	57	46	34	25	18	6
QUEST	46	42	22	4	0	0



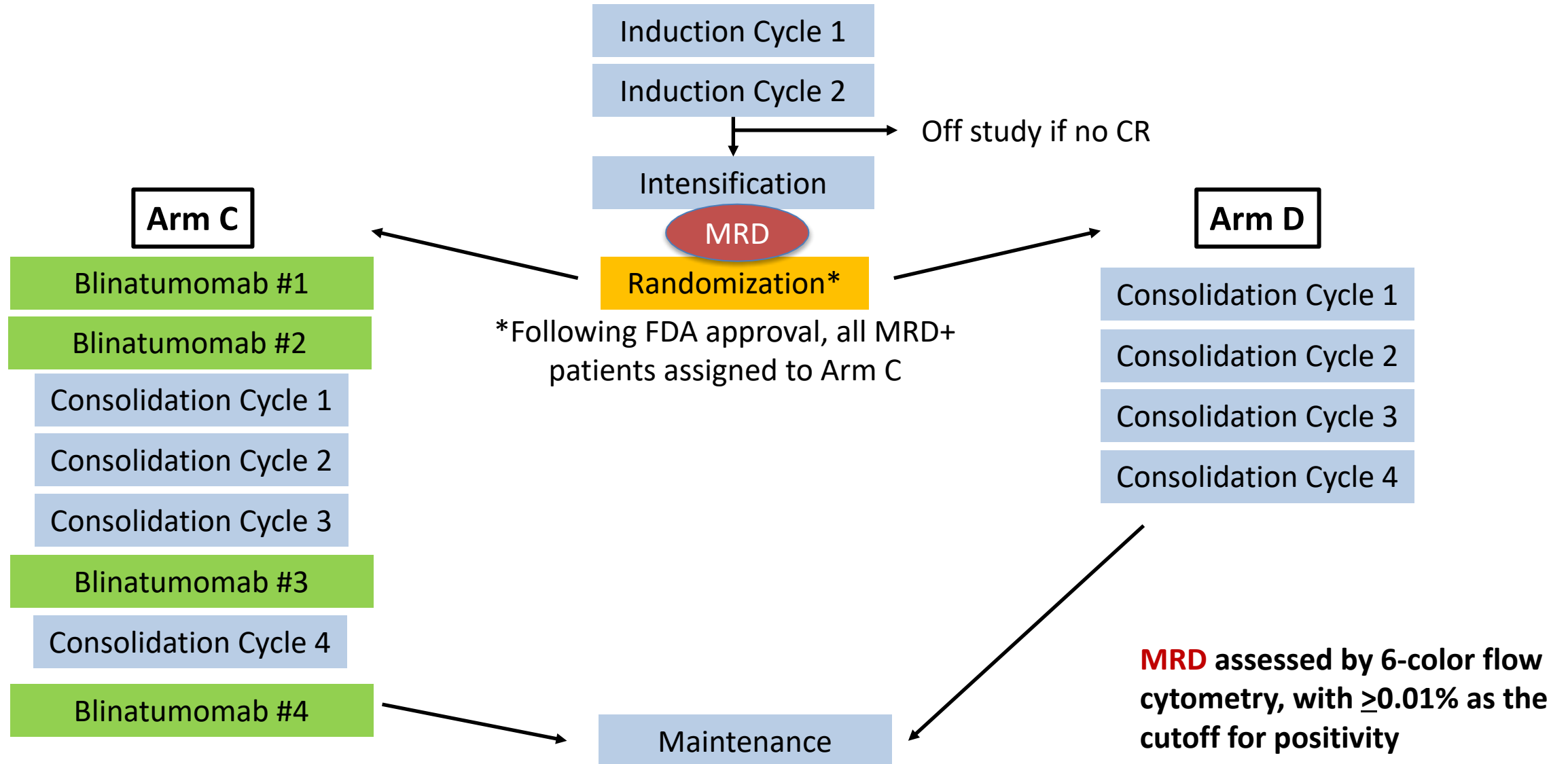
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**ECOG-ACRIN-E1910 NCTN Clinical Trial: A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR::ABL-negative B lineage Acute Lymphoblastic Leukemia in Adults**

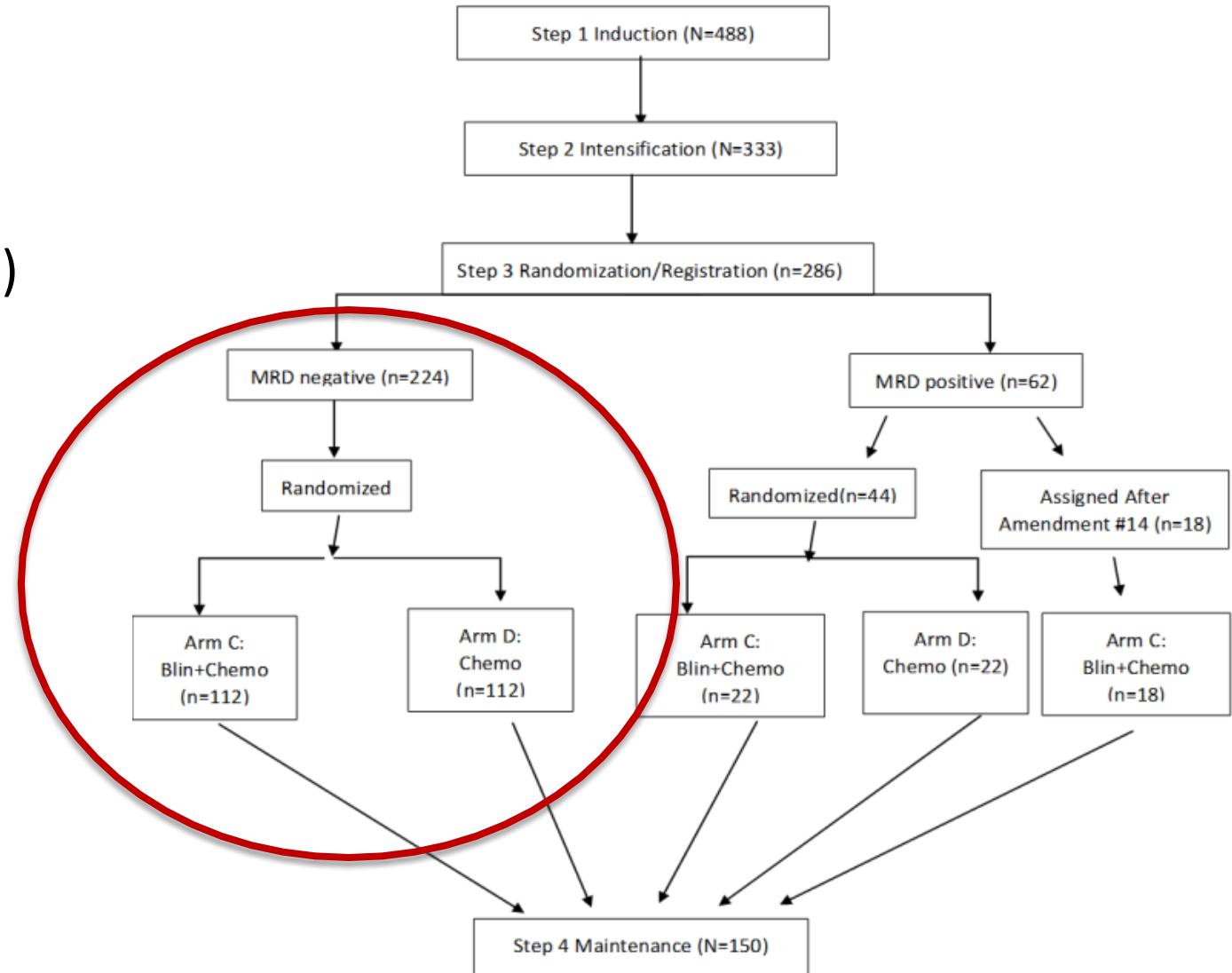
Mark R. Litzow, Zhuoxin Sun, Elisabeth Paietta, Ryan Mattison, Hillard Lazarus, Jacob Rowe, Daniel Arber, Charles Mullighan, Cheryl Willman, Yanming Zhang, Matthew Wieduwilt, Michaela Liedtke, Julie Bergeron, Keith Pratz, Shira Dinner, Noelle Frey, Steven Gore, Bhavana Bhatnagar, Ehab Atallah, Geoffrey Uy, Deepa Jeyakumar, Tara Lin, Daniel DeAngelo, Richard Stone, Harry Erba, Richard Little, Selina Luger, Martin Tallman

# E1910: Randomized Adult Frontline ALL



# E1910 Results

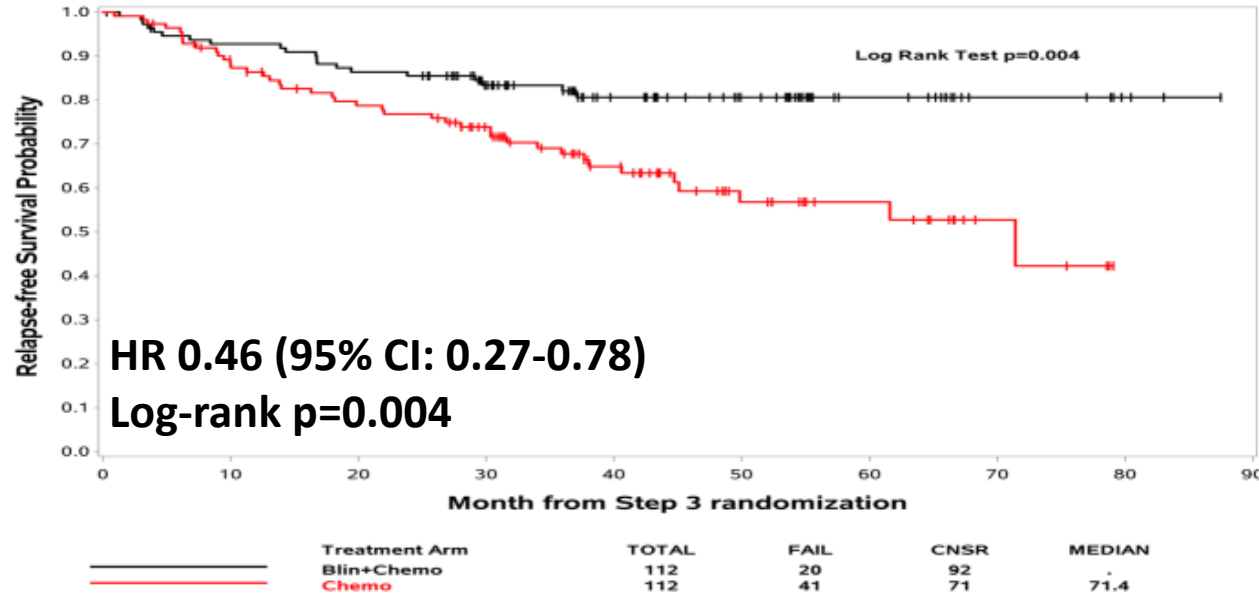
- 488 pts enrolled
- Median age: 51yrs (range 30-70yrs)
- Median follow-up 3.6 yrs
- CR/CRi rate 81% (395/488 pts)
  - CR 75% (364 pts)
  - CRi 6% (31 pts)
- Among MRD-neg, 22 patients in each arm underwent alloHSCT
- 80% of pts received  $\geq 2$  cycles of blinatumomab



# E1910: MRD-neg patients

Median follow-up 3.6 yrs

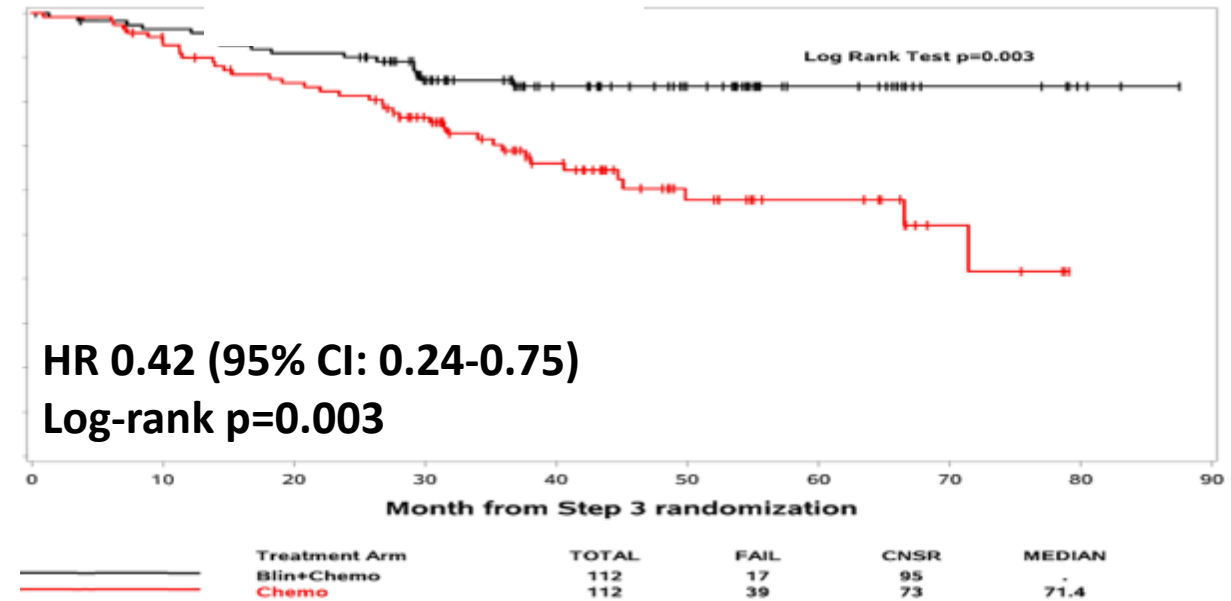
## Event-Free Survival



### Median RFS:

- Blina + Chemo (arm C): not reached
- Chemo alone (arm D): 22.4 mos

## Overall Survival



### Median OS:

- Blina + Chemo (arm C): not reached
- Chemo alone (arm D): 71.4 mos

Deaths on Blin+Chemo Arm=17 (2° to ALL=8, NRM=9), Chemo Arm=39 (2° to ALL=20, NRM=17, Unknown=2)

# Conclusions – Blinatumomab as consolidation for ALL

- Addition of blinatumomab to chemotherapy consolidation in adult patients with newly diagnosed MRD-neg ALL appears to improve EFS and OS

## Unanswered questions

- Role of transplant?
- Subtype analysis?
- Level of MRD-negativity?
- Extrapolation to other regimens?



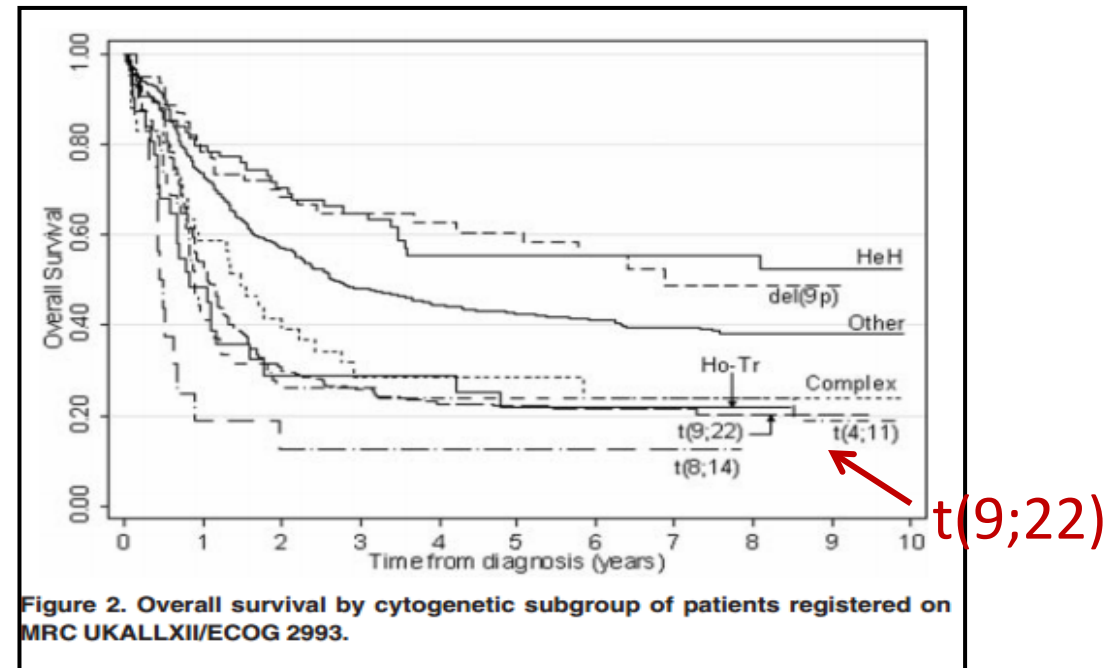
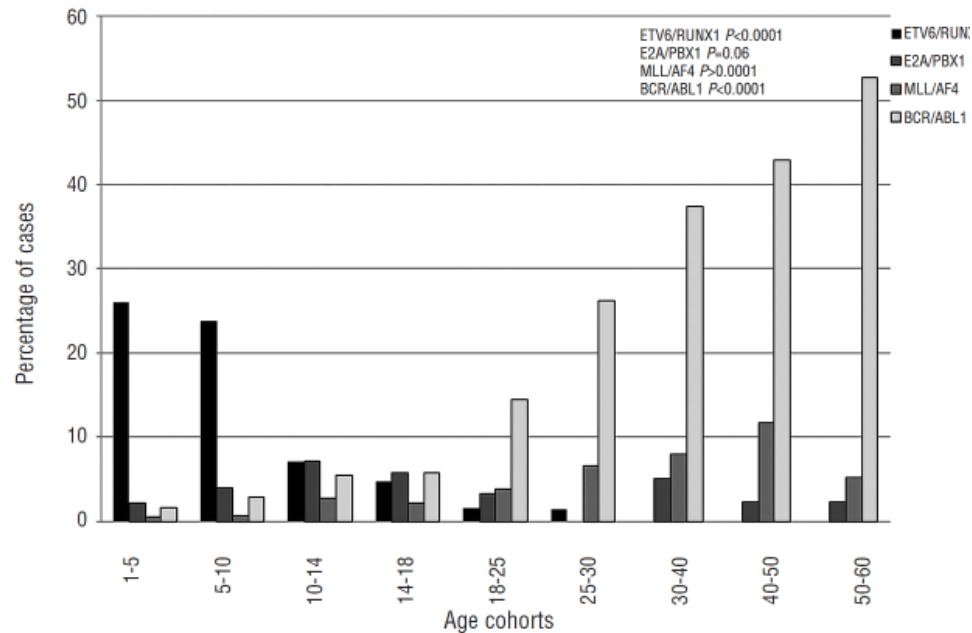
## Case 2

- 54-year-old woman presents with fatigue to her PCP, who checks a CBC.
- **CBC:** WBC 35 K/uL, 80% blasts, Hg 7.0 g/dL, Plt 35 K/uL
- **Flow:** Blasts = lymphoblasts, B-lineage by flow cytometry.
- **Genetics:** t(9;22)(q34;q11.2); *BCR-ABL1* QPCR: p190 transcript
- **PMH:** hyperlipidemia, obesity, BMI 36; no history of MI or stroke.

# Section 3: ASH 2022 updates treating Ph+ ALL

## Ph+ ALL, Historically Adverse Outcomes

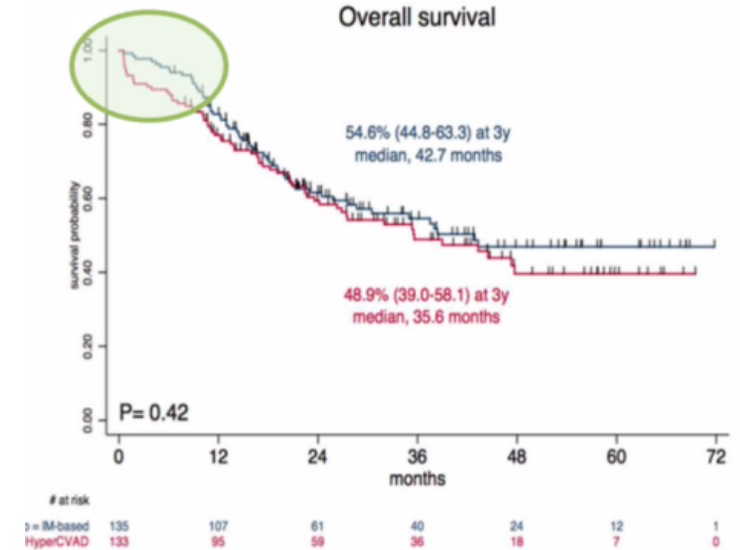
- Philadelphia chromosome/BCR-ABL1 fusion present in ~1/3 of ALL cases.
- Prevalence increases with age (>50% in patients >50 years).
- Historically adverse prognosis prior to 2<sup>nd</sup> and 3<sup>rd</sup> generation TKIs.



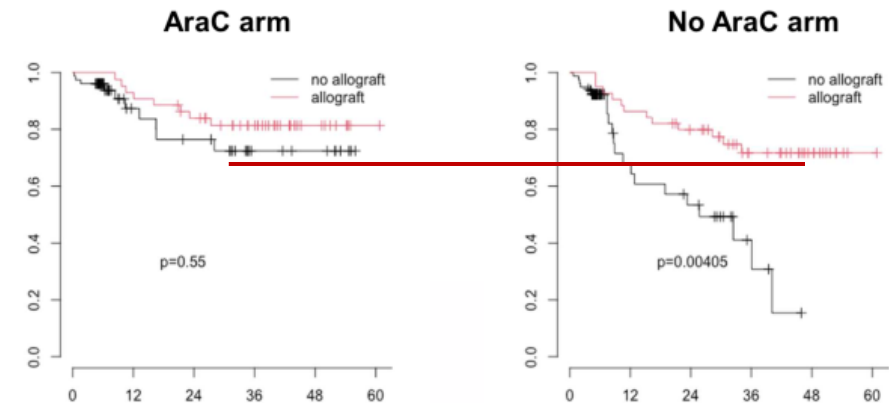
# Ph+ ALL, recent context

- **GRAAPH 2005 (IMATINIB)** → IM + VCR/Dex: ↑CR rate and ↓mortality compared to IM + hyperCVAD (**lesson: reduce chemo in induction**)
- **GIMEMA** → “chemotherapy-free” induction (imatinib LAL 0201-B; dasatinib LAL 1205, ponatinib LAL 1811).
  - High CR rates (>90%); (**lesson: 2G/3G TKIs - Deeper and more durable**); minimal toxicity
- **GRAAPH-2014 (NILETINIB)** → Omission of HiDAC consolidation associated with more relapse in non-transplanted patients (**lesson: still need intensive conventional chemo or BMT in context of 2G TKI**)

## GRAAPH 2005



## GRAAPH 2014

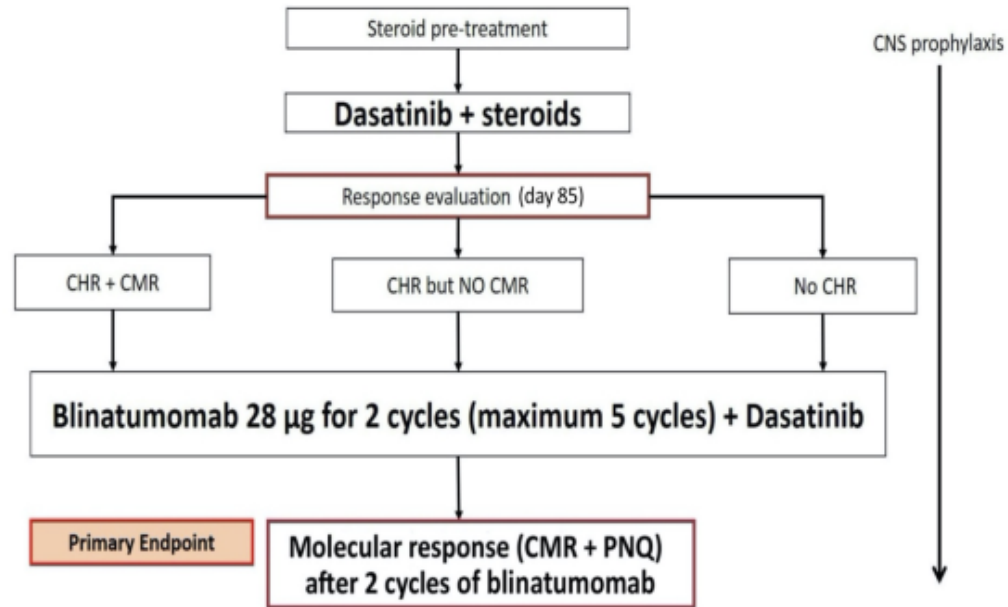


# T315 drives most relapses after 2<sup>nd</sup> generation TKIs, role for novel agents and ponatinib?

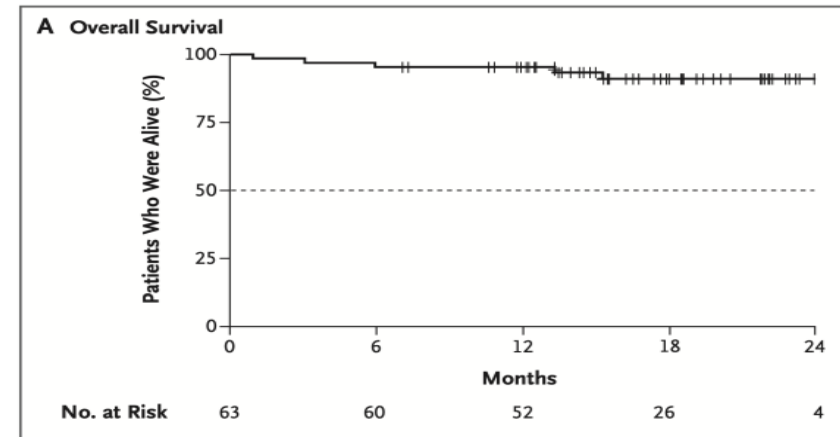
- *BCR::ABL1* T315I KD mutation common at relapse after dasatinib (~70-75%).
- Ponatinib is a 3<sup>rd</sup> gen TKI active against T315I.
- Ponatinib associated with serious arterial thrombotic events, hepatotoxicity, and pancreatitis (unrandomized).
- **Additional therapy needed to limit relapse further – is there a “best” post remission strategy?**



# Dasatinib + blinatumomab (D-ALBA)



- Day 85 – 29% Molecular Response
- Blina C2 (n=55) – 60% Molecular Response
- Blina C4 – 81% Molecular Response



N=63, median age 54 (range 24-82) yrs  
**Note:** Approximately half transplanted

- 18-mo DFS was 88%
- Worse outcomes in *IKZF1* deletion
- T315I in 5/6 relapses tested

# Abstract 213 (Short et al.) – Ponatinib/Blinatumomab for Newly-diagnosed Ph+ ALL

## Eligibility

Adults

Newly-diagnosed Ph+ ALL

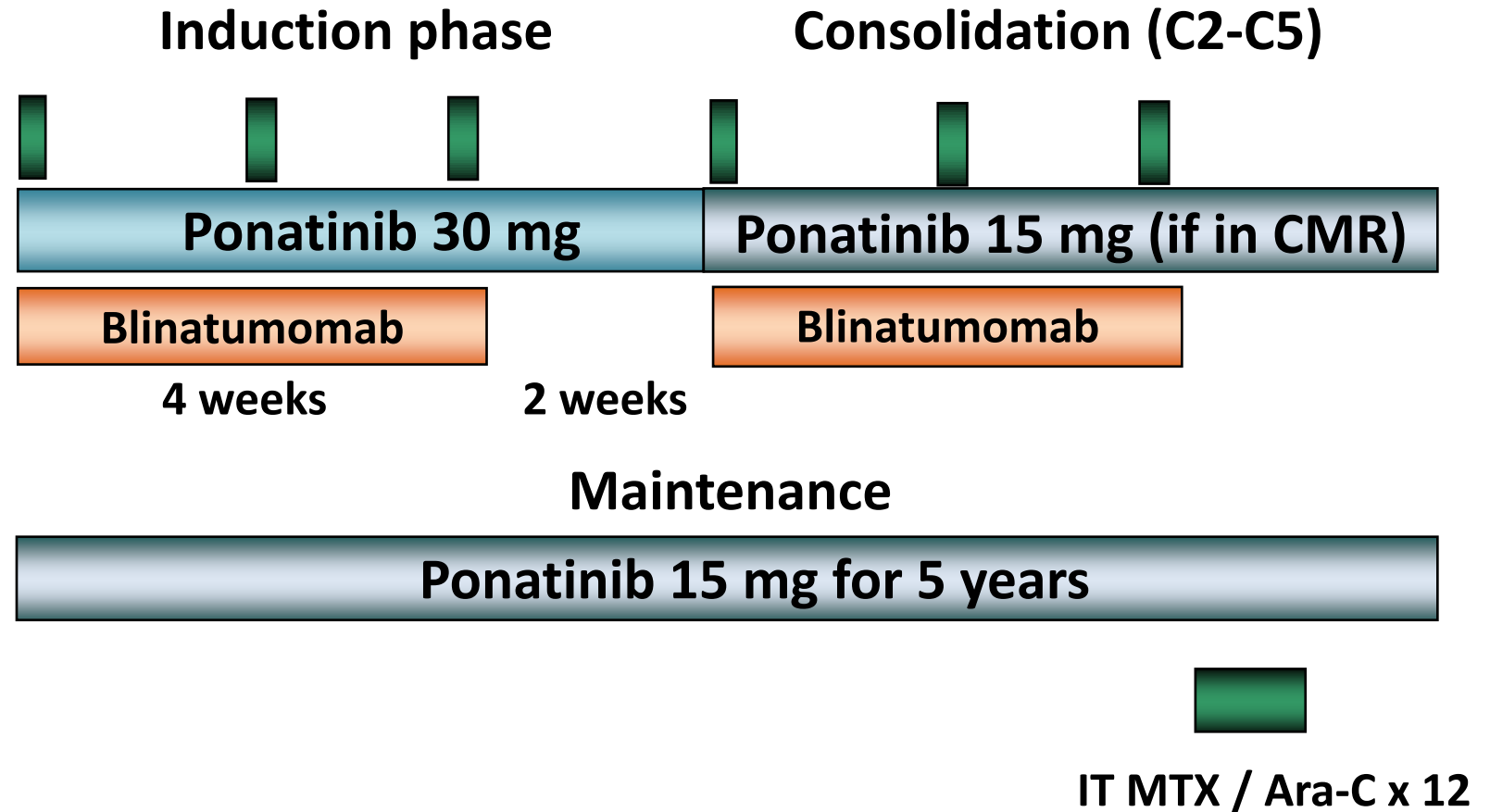
ECOG PS 0-2

No active CV disease

No CNS pathology

## Primary endpoint

CMR rate



# Ponatinib + Blinatumomab in Ph+ ALL: Results

Age (yrs) 57 [20-83]  
 >1 CV risk factor 24/40 (60%)  
 CNS involvement 2/40 (6%)

CR/CRi\* 27/28 (96%)  
 CMR\*\* 33/38 (87%)  
 NGS MRD-neg 22/25 (88%)

**N=40 pts**

**Death in CR, n=1**

Post-procedural bleeding

**Ongoing response without HCT, n=35**

**Relapse, n=2**

- Also, with *IGH::CRLF2*, extramedullary-only (peritoneal and lymphomatous) **Ph-negative relapse** (*MYC* rearranged) after 9 months
- **CNS-only relapse** after 23 months

**Early Death, n=1**

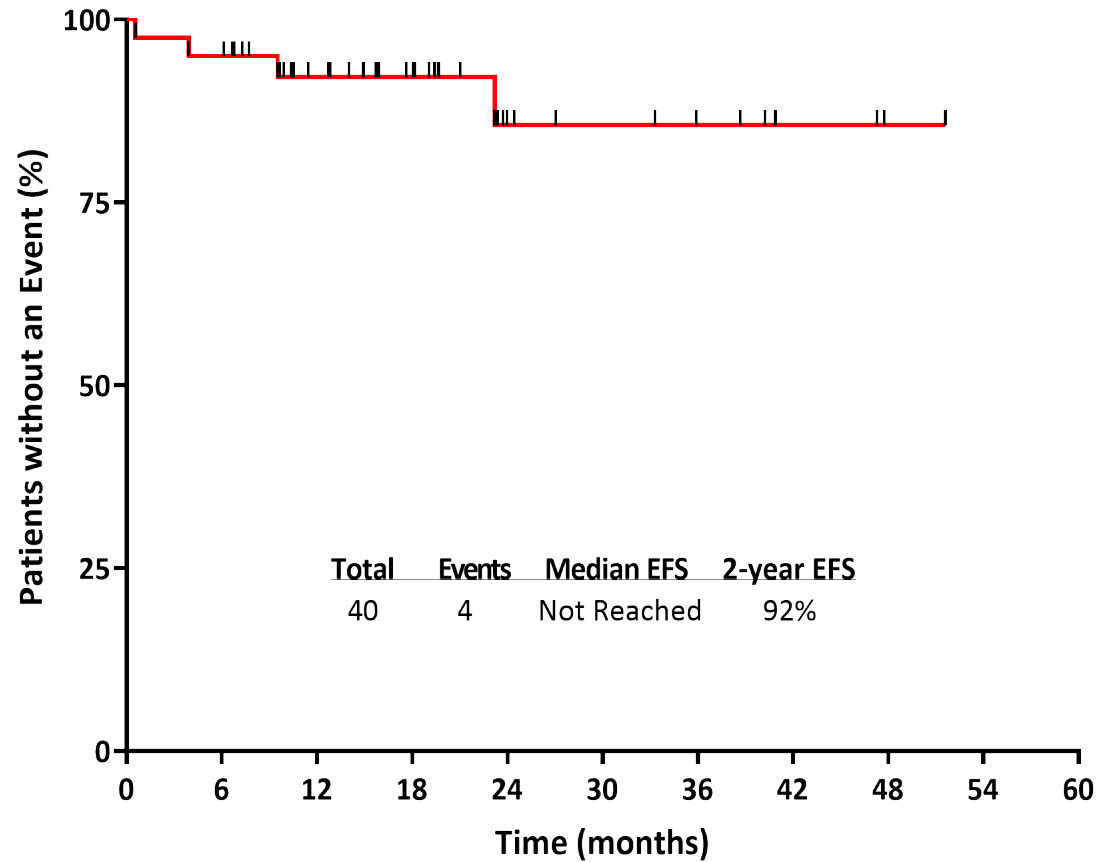
Intracranial hemorrhage

**HCT in CR1, n=1**

# Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes

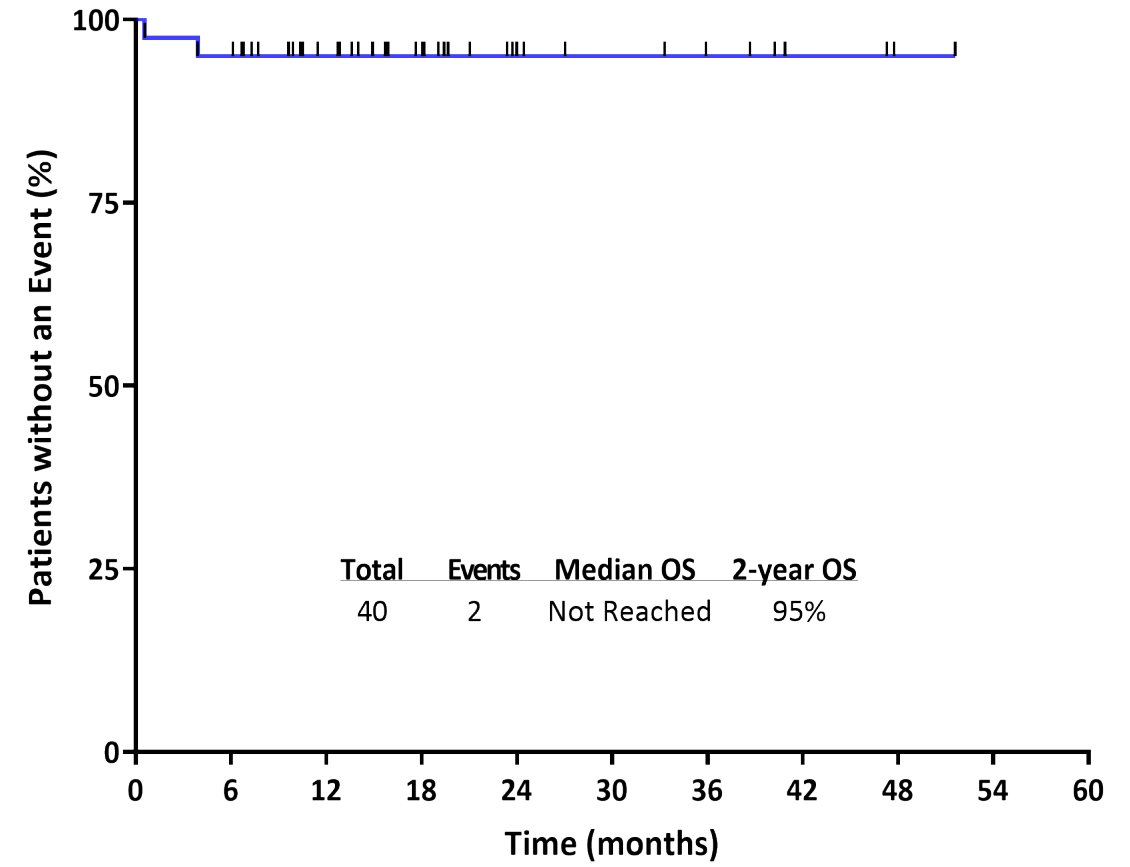
Median follow-up: 18 months (range, 6-52+)

## Event-Free Survival



No. at Risk 40 39 28 21 11 9 7 4 2 0 0

## Overall Survival



No. at Risk 40 39 29 21 12 9 7 4 2 0 0

# Abstract 213 (Short et al.) – Ponatinib/Blinatumomab for Newly-diagnosed Ph+ ALL

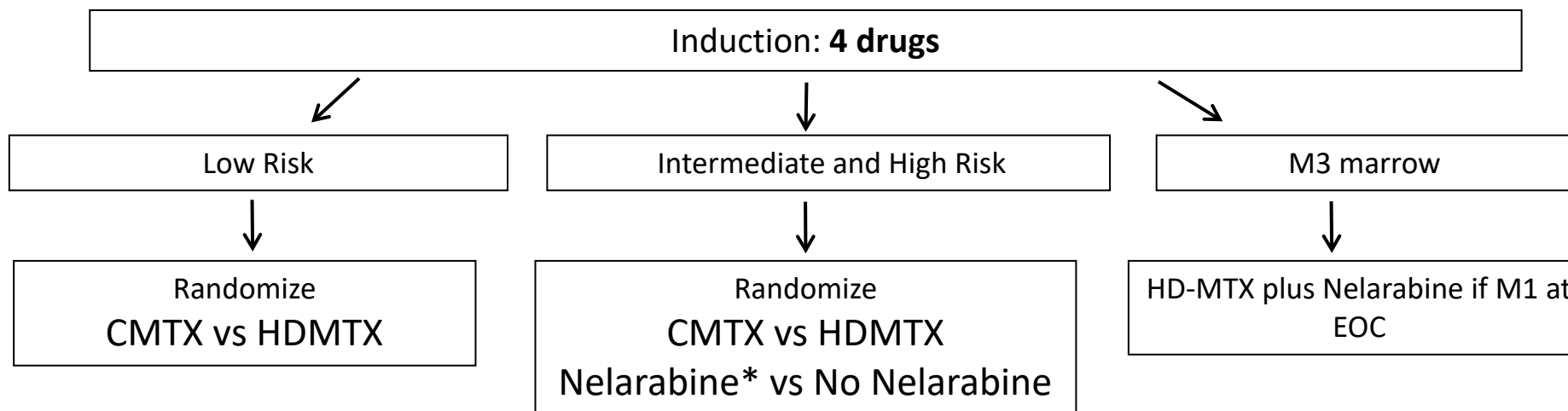
- Ponatinib + blinatumomab is safe and effective in newly-diagnosed Ph+ ALL.
- Deep, rapid, and durable responses without allogeneic HCT.
- 2 relapses to date (isolated CNS, Ph-negative extramedullary).
- The combination of ponatinib + blinatumomab is a promising chemotherapy-free, HCT-sparing regimen for Ph+ ALL

# Case 3

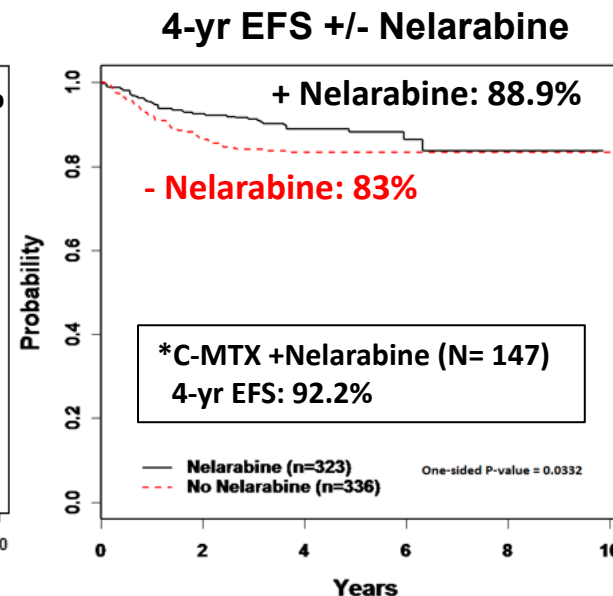
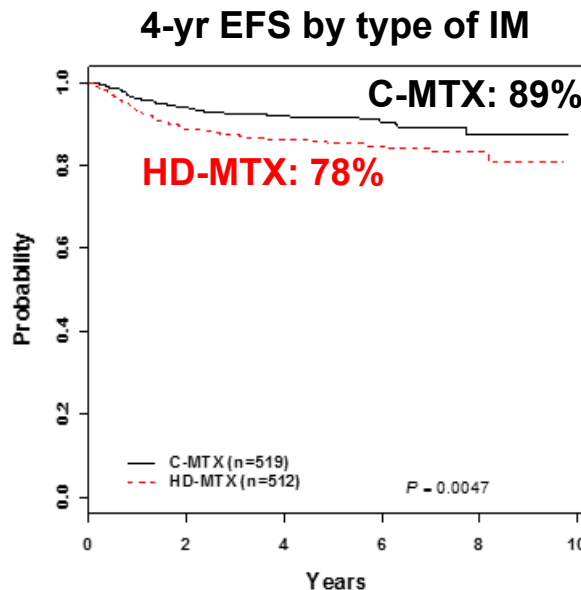
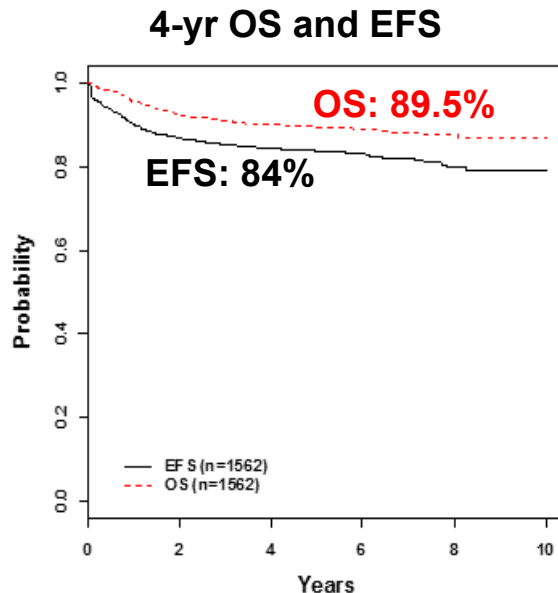
- 32 year-old woman who was 3 months post-partum presented to her primary physician with progressive b/l cervical LAD with joint pain and swelling
- WBC  $8.4 \times 10^9/L$ ; Hgb 11.3 g/dL; HCT 33%; Platelets  $140 \times 10^9/L$ ; ANC,  $1.9 \times 10^9/L$ , 61% blasts
- CT scan of the neck/chest/AP revealed b/l cervical and supraclavicular LAD
- A bone marrow biopsy revealed early T-cell precursor ALL (ETP-ALL)
- **Treatment approach?**



# Children's Oncology Group: AALL0434



\* Six 5-day courses of Nel 650 mg/m<sup>2</sup>/day



- 20-30 year old patients (7%) had same EFS as younger cohort
- Improvement in DFS due to reduction in CNS relapse (1 vs 14)



# Results of the Risk-Adapted, MRD-Stratified GMALL Trial 08/2013 in 281 T ALL/LBL Patients: Excellent Outcome of Standard Risk Thymic T-ALL

Adults 18-55 years old with newly diagnosed ALL, 281 T-lineage recruited over 6 years

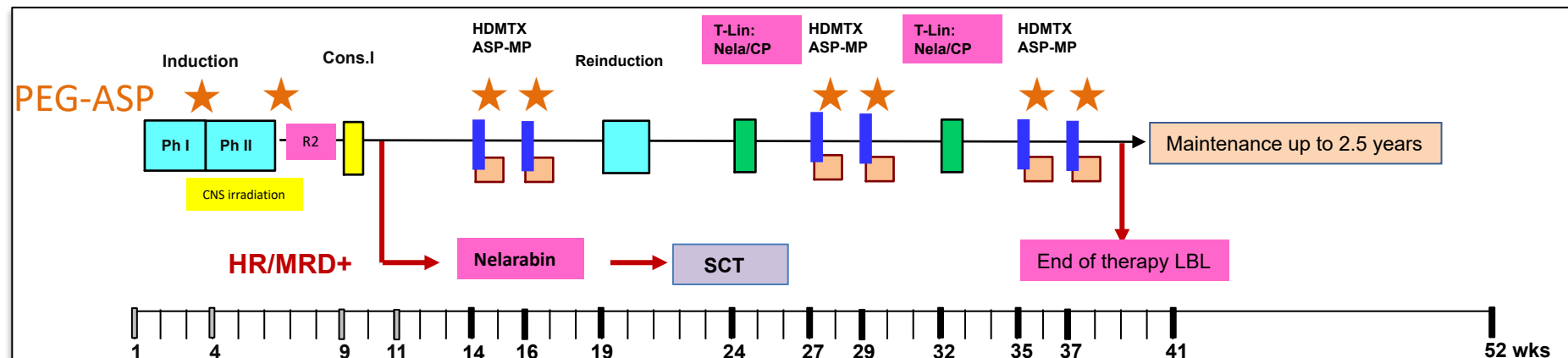
Goal to improve outcomes for T-cell ALL/LL with attention to high-risk subtypes, early and mature T-ALL

**Risk stratification for T-ALL: HR:  $\geq$  1 risk factor**

- Early or Mature T
  - No CR after induction
- + Molecular Failure after Consolidation I

BFM-based pediatric regimen  
 Dexamethasone during induction/consolidation I  
 9 x PEG-asparaginase  
 7x HDMTX (1.5 g/m<sup>2</sup>)  
 Reinduction  
 Risk-adapted SCT indication

Randomization 2 for HR pts with MoICR before Cons I: SCT vs Chemo

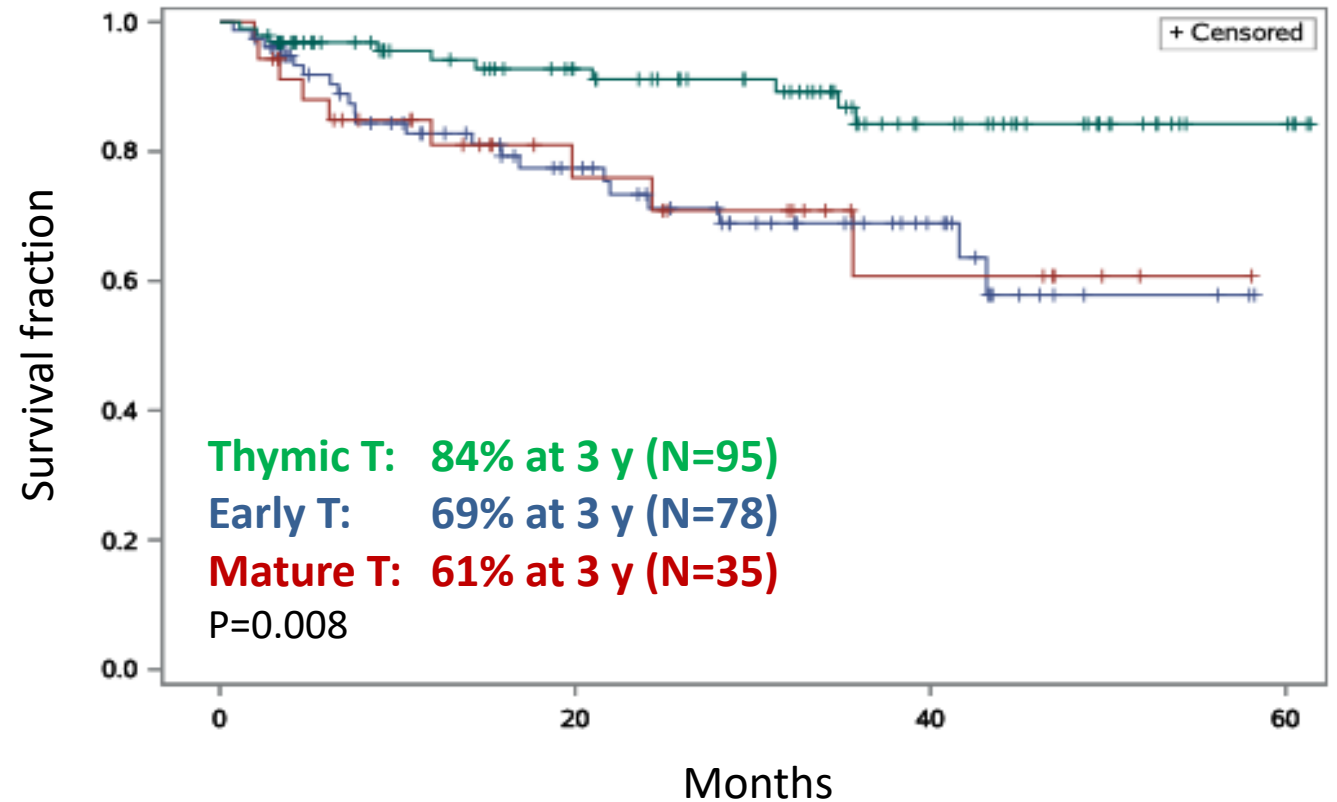


# GMALL 08/2013 – Response and survival by subtype

Overall survival by subtype

T-ALL

	Total	Thymic	Early (HR)	Mature (HR)
CR/CRu	84%	88%	88%	80%
Molecular CR (MRD-neg)	70%	82%	48%	64%
Early death	4%	4%	5%	6%
PR	10%	8%	5%	9%
Failure	2%	0%	1%	3%



# Case 3 (continued)

- Started a four-drug induction regimen, per AALL0434
- Achieves an MRD-neg CR after induction, but relapses in the bone marrow during maintenance therapy.
- **Next steps?**



# Section 4: R/R T-ALL/LL - Unmet Need

- Few effective or novel approaches at relapse
- Nelarabine: purine analog particularly active in T-cell ALL/LL
  - In R/R T-ALL/LL, CR/CRi rate 30-40% (DeAngelo et al., Gokbuget et al.)
  - Improved DFS and decreased CNS relapse in front-line pediatric T-cell ALL (AALL0434, Dunsmore et al.)
- CD38-targeted therapy (daratumumab, isatuximab)
  - Isatuximab wholly ineffective in Phase 2 in R/R T-ALL or T-LL (Boisell et al.)
  - Daratumumab has shown limited activity in extramedullary disease and low burden disease (Cerrano et al.)
  - Ongoing Phase II studies in peds/adults exploring daratumumab further
- Given above, better front-line regimens needed to prevent relapse as well as better therapy for relapse

# Abstract 980 (Zhang et al.) – Anti-CD7 CART

Analysis of 60 Patients with Relapsed or Refractory (R/R) T-cell Acute Lymphoblastic Leukemia (T-ALL) and T-cell Lymphoblastic Lymphoma (T-LBL) Treated with CD7-targeted CAR-T Cell Therapy

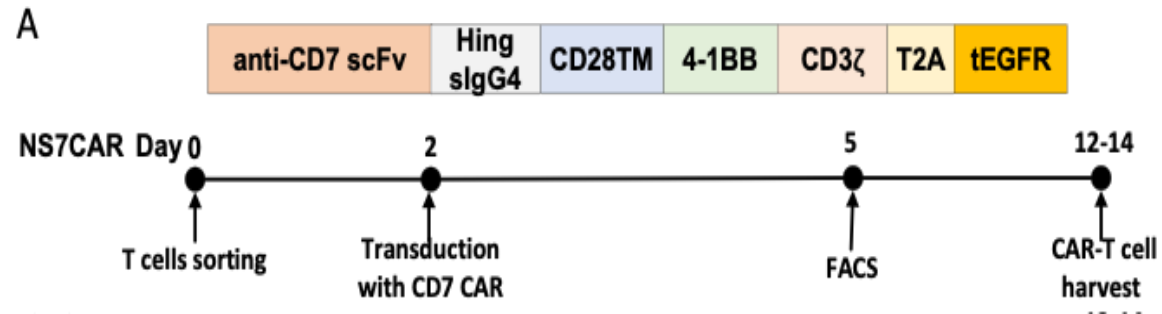
Xian Zhang<sup>1, 2</sup>, Junfang Yang<sup>1, 2</sup>, Jingjing Li<sup>1, 2</sup>, Liyuan Qiu<sup>1</sup>, Jianqiang Li<sup>3</sup>, Peihua Lu<sup>1, 2</sup>

<sup>1</sup>Beijing Lu Daopei Institute of Hematology, Beijing, China;

<sup>2</sup>Hebei Yanda Lu Daopei Hospital, Langfang, China;

<sup>3</sup>Hebei Senlang Biotechnology Co., Ltd., Shijiazhuang, China;

# Abstract 980 (Zhang et al.) – Anti-CD7 CART



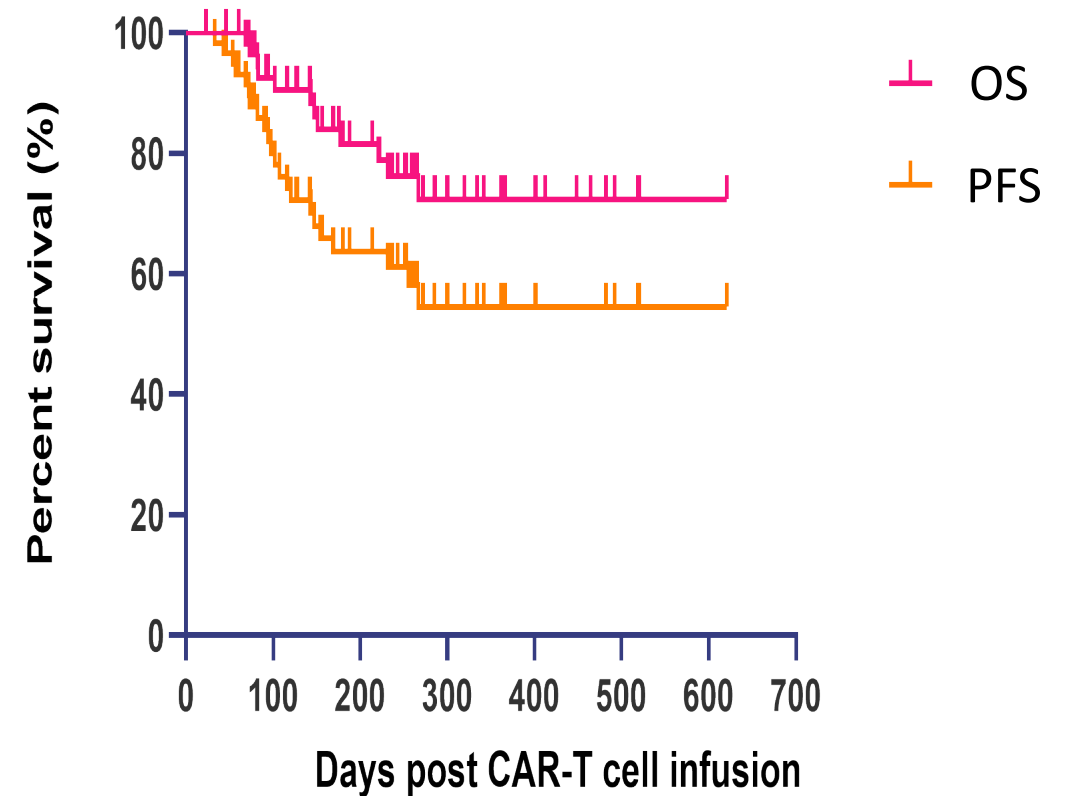
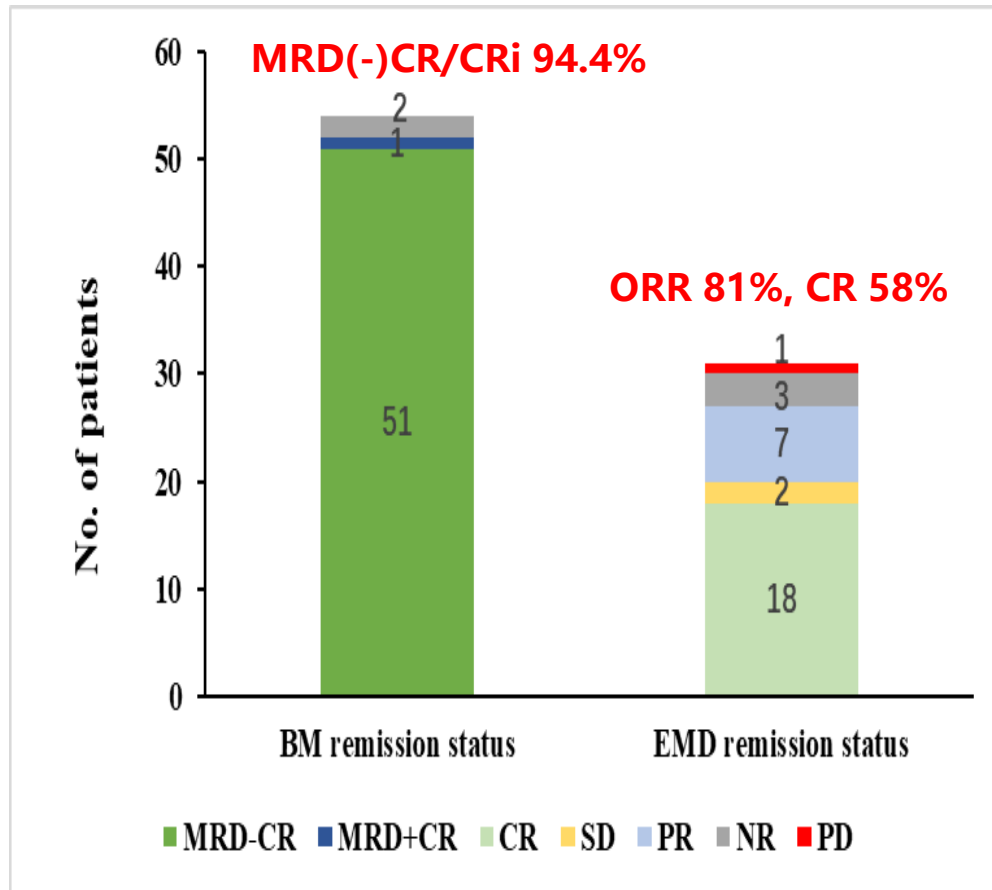
**After transduction, T cells had phenotypic transition from CD7<sup>+</sup>CAR<sup>-</sup> to CD7<sup>-</sup>CAR<sup>+</sup> T cells.**

**CD7 protein and mRNA expression were present.**

**Fratricide resistance achieved by CAR-mediated CD7 epitope masking or by intracellular sequestration of the CD7 protein.**

# Abstract 980 (Zhang et al.) – Anti-CD7 CART

N=60; 35 T-ALL, 25 T-LL



**18-mo PFS improved with alloHCT (61% vs 30%, P=0.0003).**

# Summary

- Older adults with ALL have poor prognosis with conventional chemotherapy approaches, but novel therapies may improve outcomes by minimizing toxicity without increasing relapse rates
- Blinatumomab for consolidation, even in MRD-negative patients appears to be a promising approach
- Chemotherapy-free approaches to Ph+ ALL, using blinatumomab and newer generation TKIs have excellent response rates and survival
- Relapsed/Refractory ALL, particularly T-ALL, remains a challenge



Thank you!!

