Advances in Treatment of Acute Lymphoblastic Leukemia

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Advances in

- Cytogenetics (Philadelphia like) and Genes sequencing.
- Using Pediatrics Based regimen in adults
- MRD
- Involving Immune mediated therapy (CD20, CD19, CD22) (CD38, CD123)
- Advances in Allogenic transplant (Conditioning regimen), more donor availability.

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ALL is the most common leukemia in children, 23% of all pediatric cancer diagnoses.

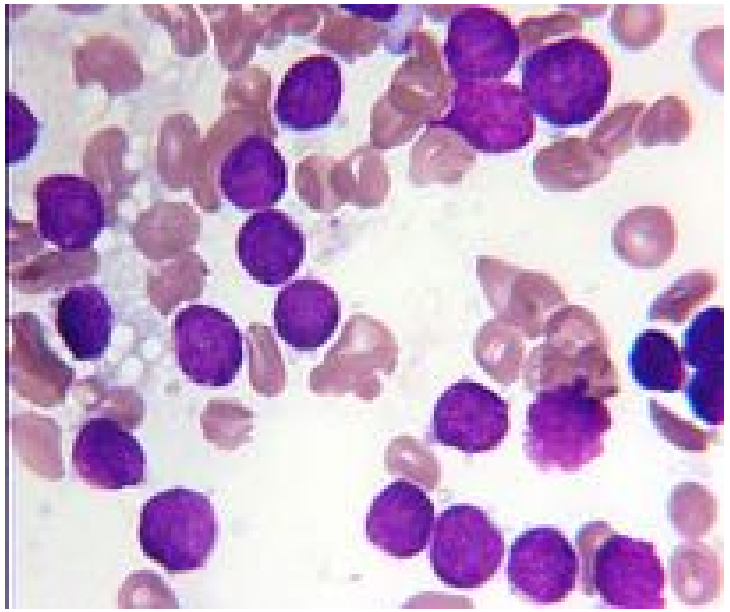
20% of adult acute leukemia, carries devastating outcomes.

> 6500 new cases per year, with over 1400 deaths in US.

Bimodal distribution- first peak in childhood second peak around age of 50.

In adults- B-cell ~75% of cases, while T-cell ALL 25% cases.

Despite a high rate of response to induction chemotherapy, 30–40% of adult patients will achieve long-term remission.



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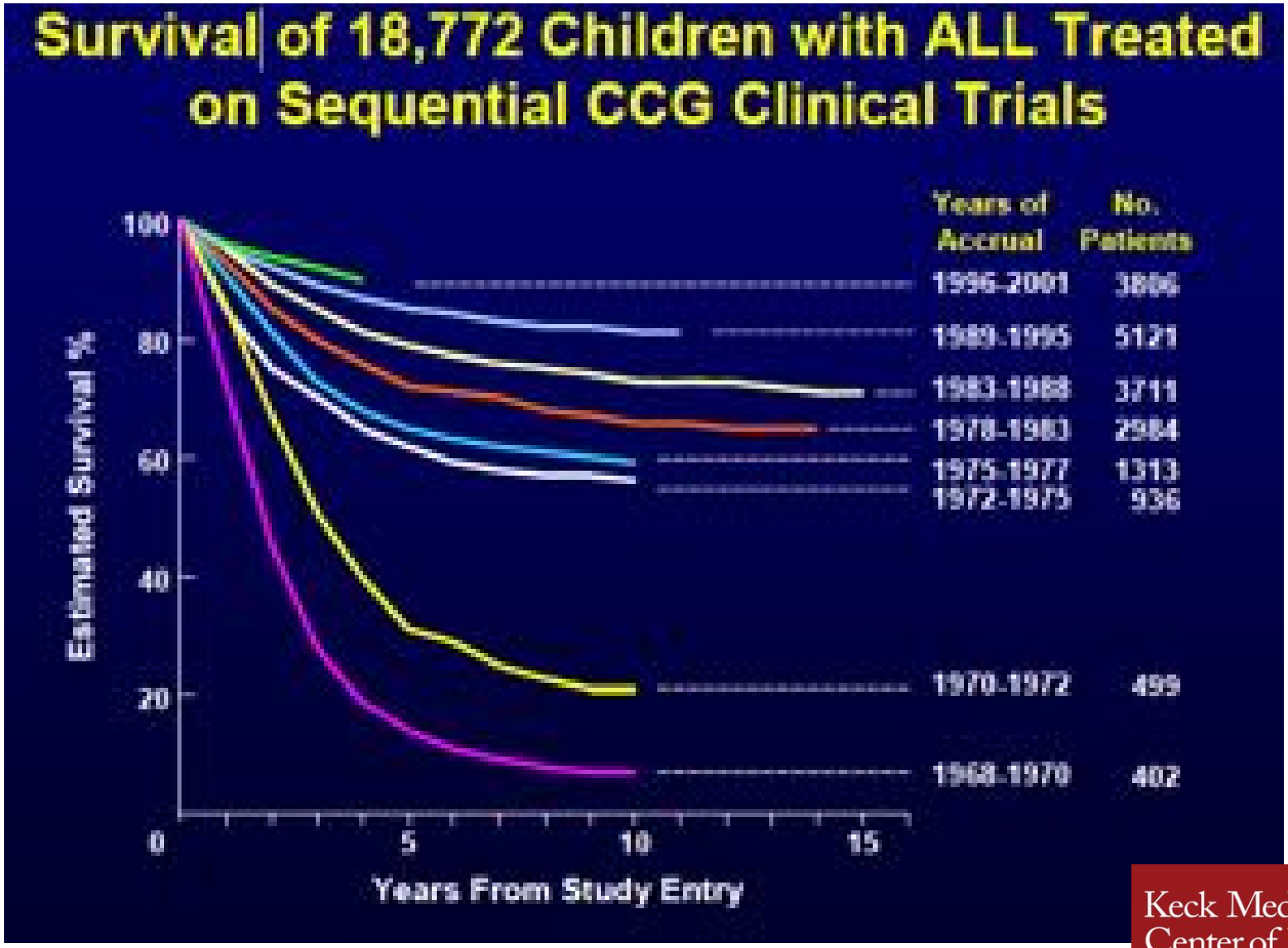
T Terwilliger et al blood cancer journal 2017

ALL outcomes- Children



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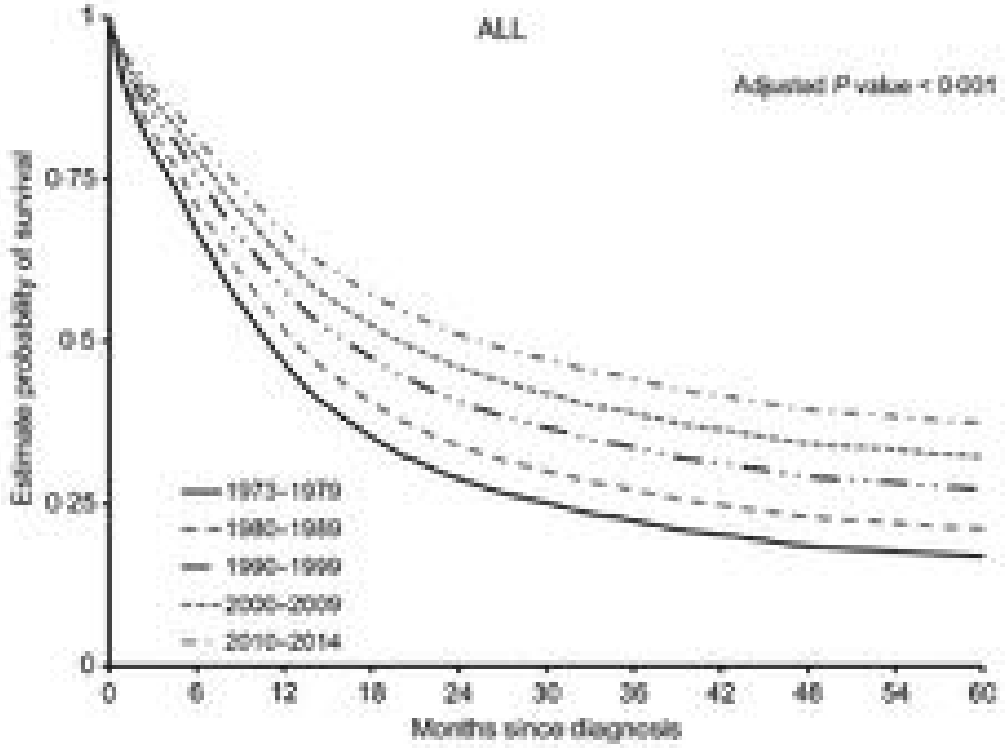
ALL outcomes- Adults

- Igwe J Igwe, Akil Merchant, George Yaghmour,… and Giridharan Ramsingh et al BJH 2017



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Age Matter?

blood 2005 106: 3760-3767
doi:10.1182/blood-2005-04-1623 originally published online August 16, 2005

Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993

Jacob M. Rowe, Georgina Buck, Alan K. Burnett, Raj Chopra, Peter H. Wiernik, Susan M. Richards, Hillard M. Lazarus, Ian M. Franklin, Mark R. Litzow, Niculae Ciobanu, H. Grant Prentice, Jill Durrant, Martin S. Tallman and Anthony H. Goldstone

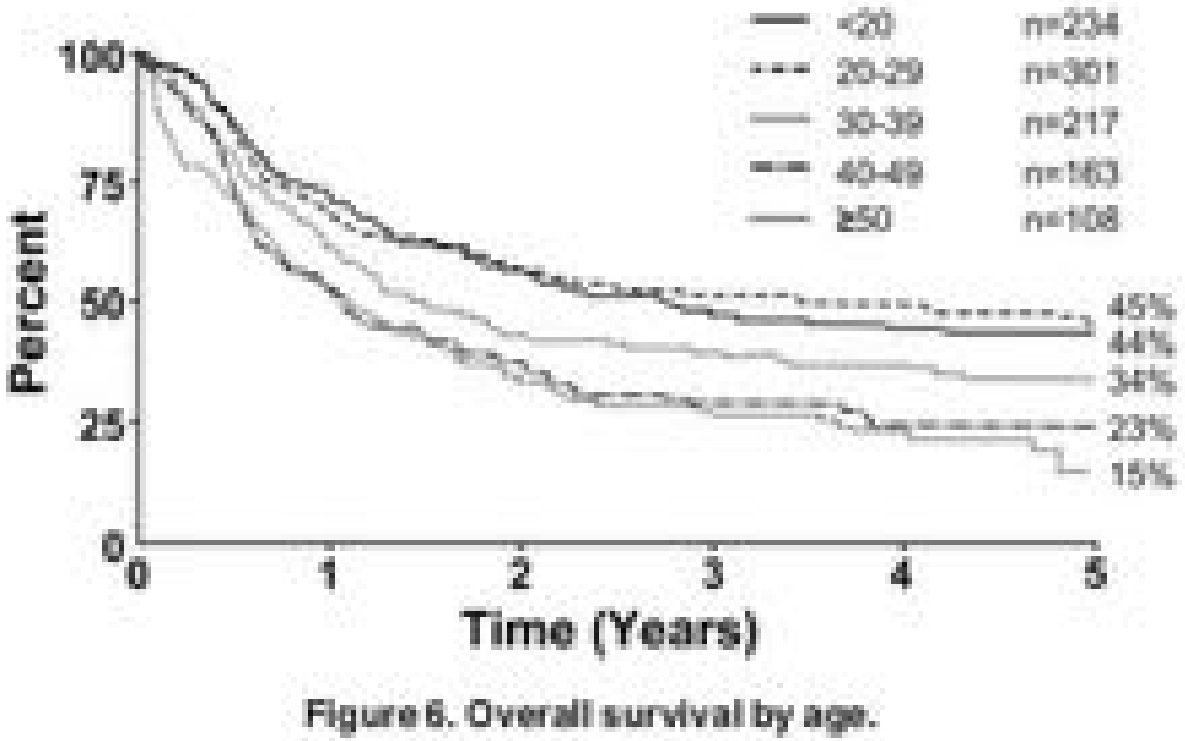
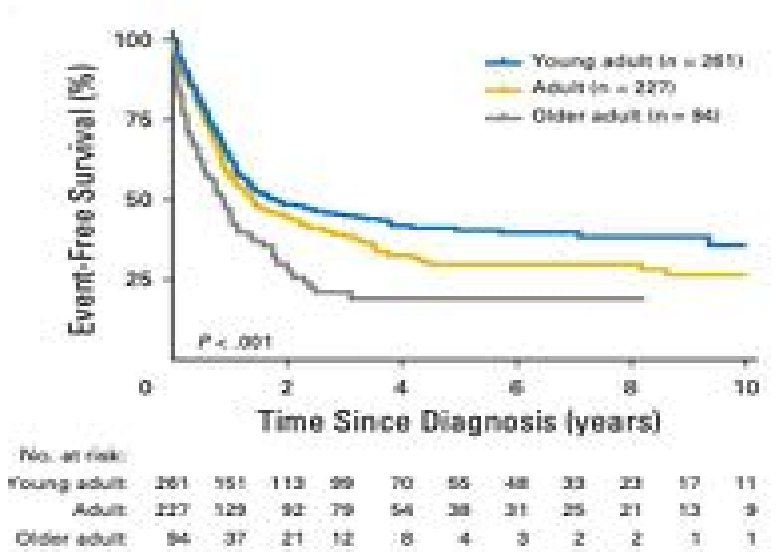
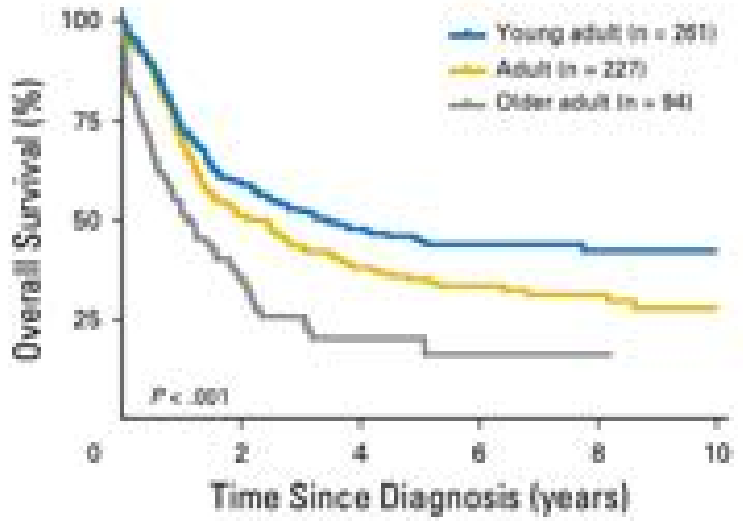


Figure 6. Overall survival by age.

Rowe JM et al blood 2005





Roberts et al, JCO 2017

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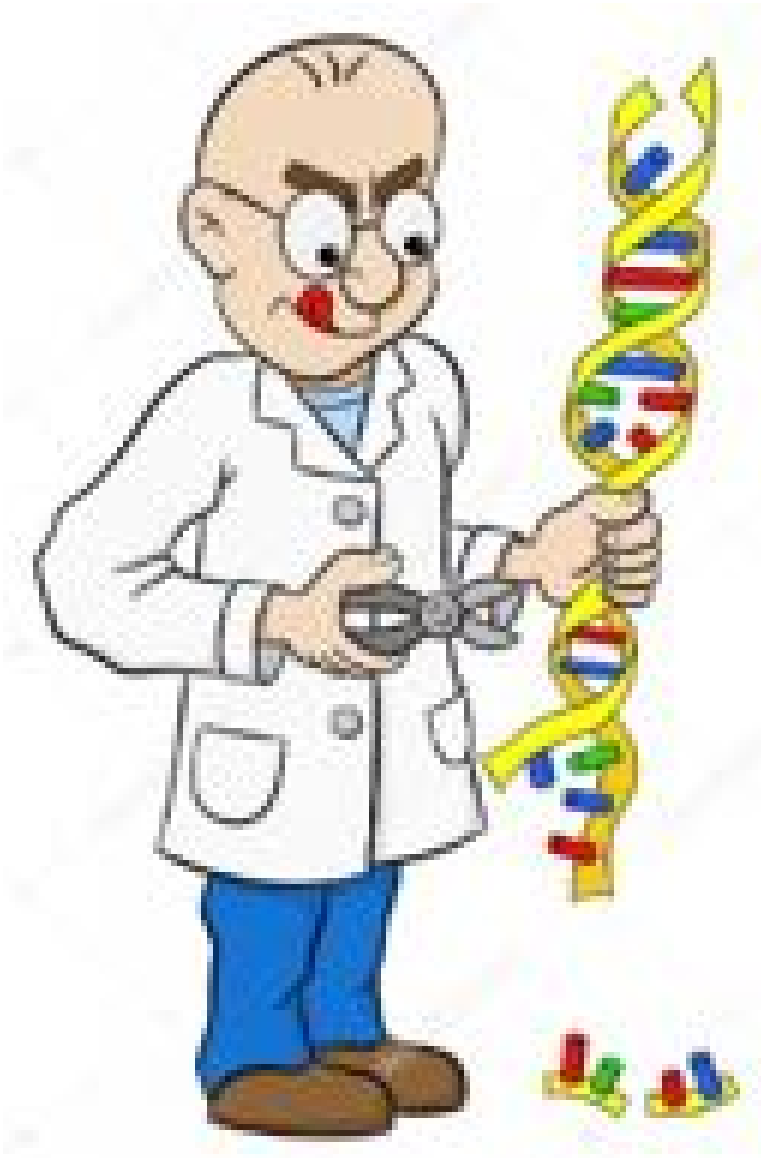
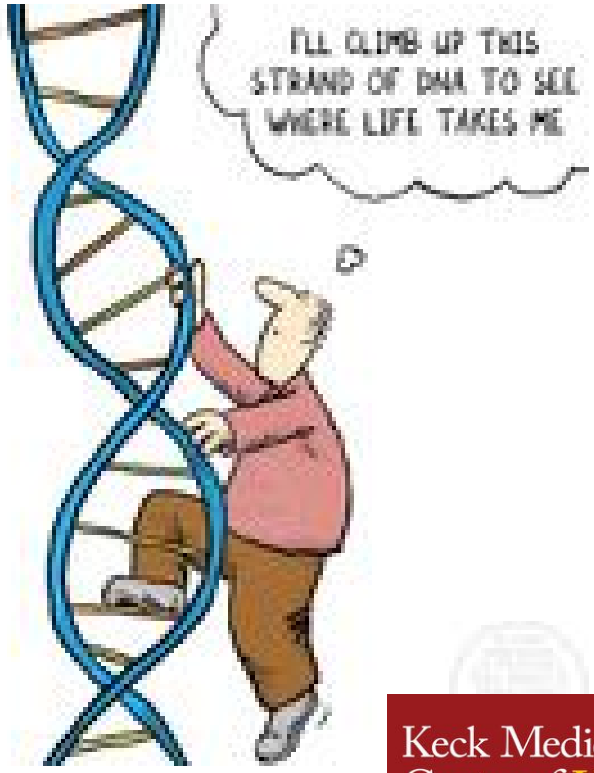
CYTOGENTETICS





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VOLUME 35 · NUMBER 9 · MARCH 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Genetic Basis of Acute Lymphoblastic Leukemia

Ilaria Iacobucci and Charles G. Mullighan

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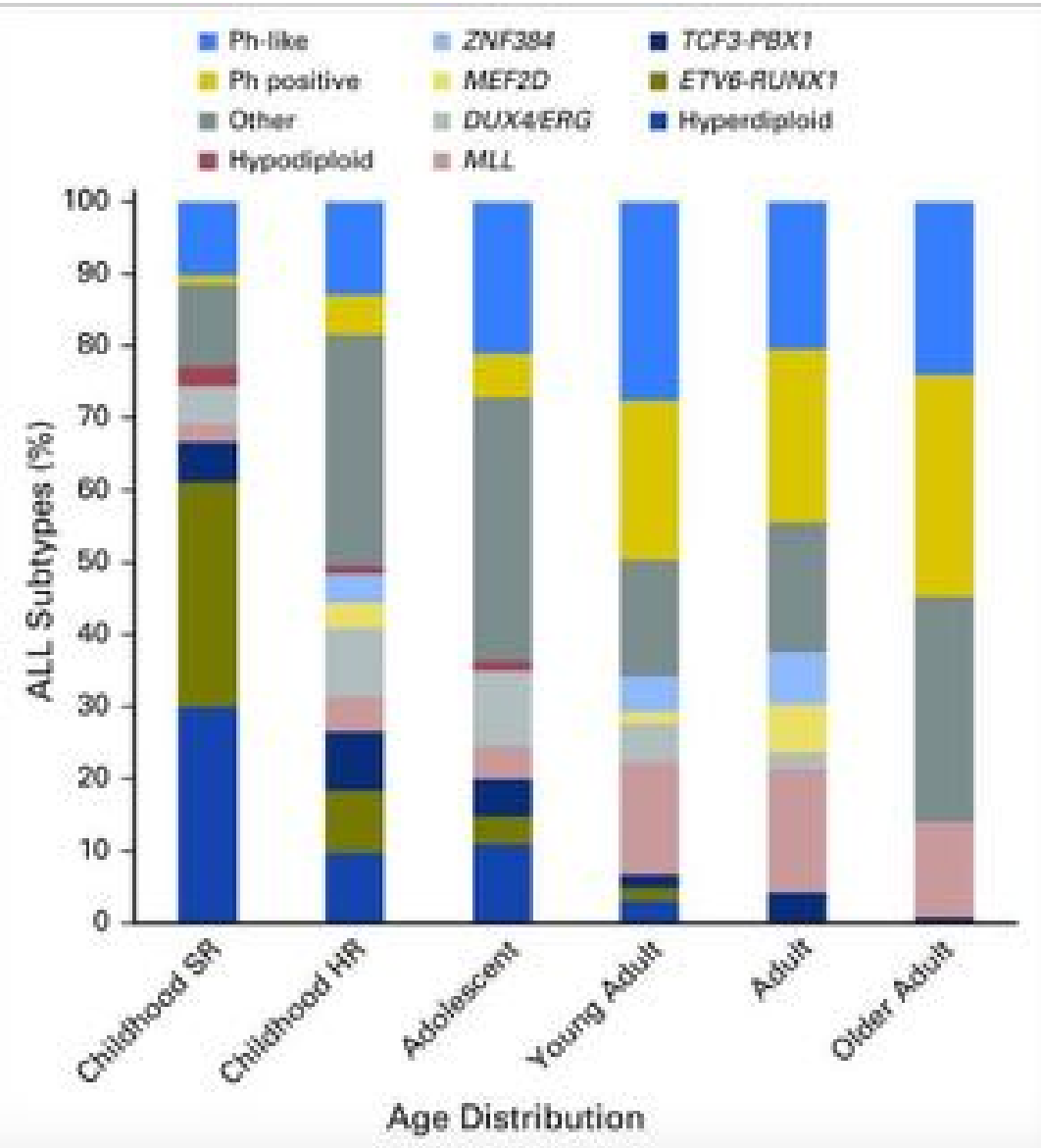
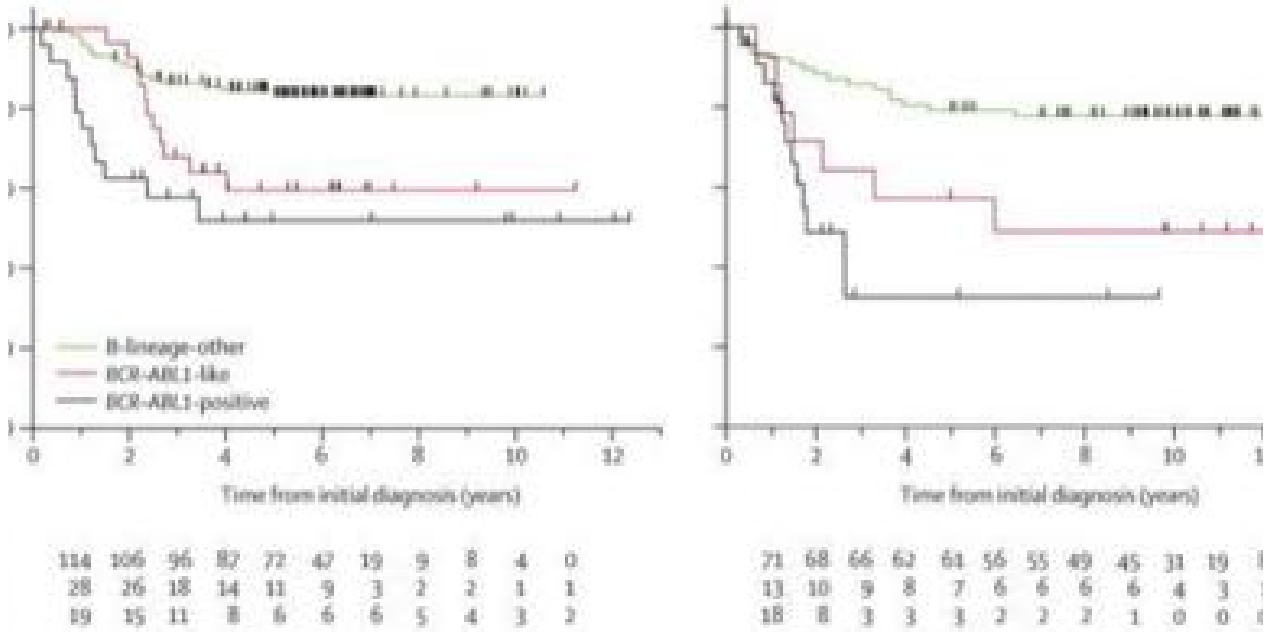
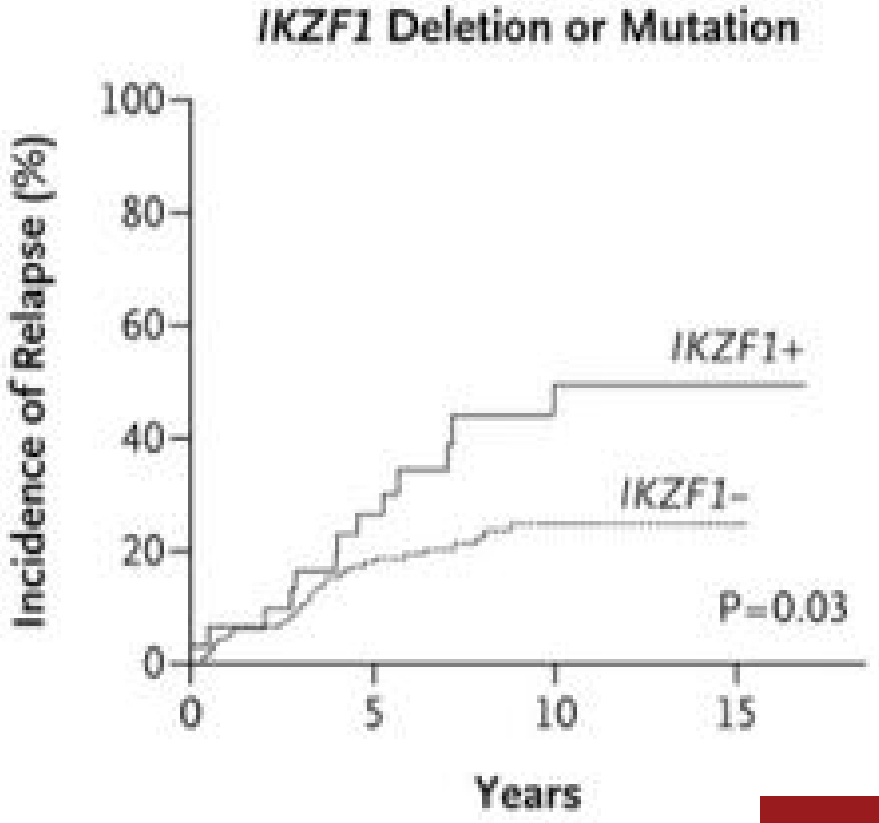


Cytogenetics Matters?



Den Boer et al, Lancet Oncol 2009



Mullighan et al, NEJM 2009

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Risk stratification

NCCN

CYTOGENETIC RISK GROUPS FOR B-ALL

RISK GROUPS	CYTOGENETICS
Good risk	Hyperdiploidy (51–65 chromosomes; cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome); t(12;21)(p13;q22): *ETV6-RUNX1*
Poor risk	Hypodiploidy (<44 chromosomes); *KMT2A* rearranged (t[4;11] or others); t(v;14q32)/IgH; t(9;22)(q34;q11.2): *BCR-ABL1* (defined as high risk in the pre-TKI era); complex karyotype (5 or more chromosomal abnormalities); Ph-like ALL; intrachromosomal amplification of chromosome 21 (iAMP21)

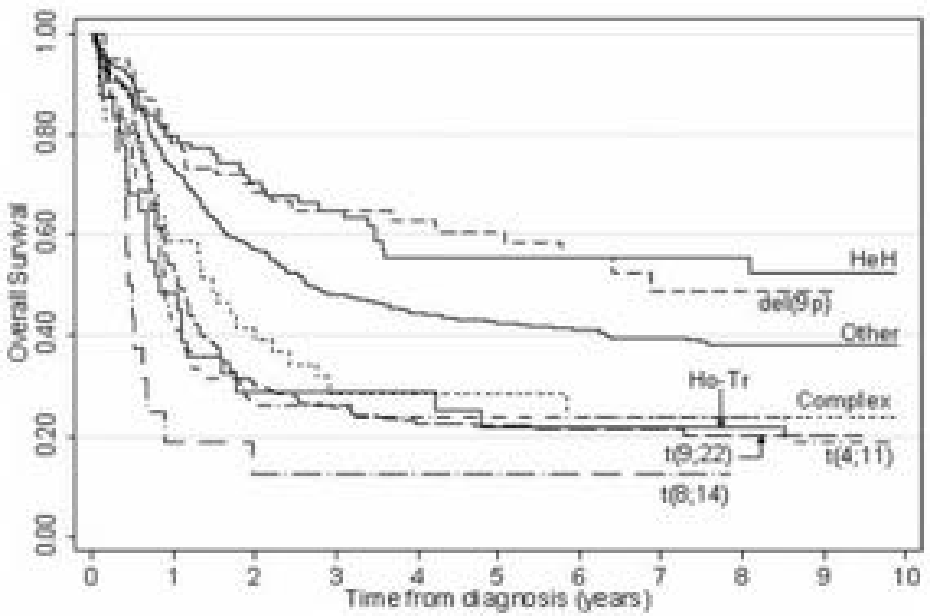


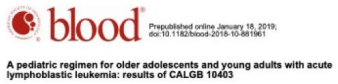
Figure 2. Overall survival by cytogenetic subgroup of patients registered on MRC UKALLXII/ECOG 2993.

blood
2007 109: 3189-3197
doi:10.1182/blood-2006-10-051912 originally published online December 14, 2006

Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial

Anthony V. Moorman, Christine J. Harrison, Georgina A. N. Buck, Sue M. Richards, Lorna M.

Anthony V Moorman e al blood 2007



B-ALL CALGB10403

Favorable karyotype

- **Abnormalities involving region 11 of the long arm of chromosome 14 [14q11]; deletions and translocations involving 12p**
- **Balanced rearrangements involving 7p14-15 and 7q34-36**

Intermediate-risk cytogenetic

- Normal karyotype
- Abnormalities in the short arm of chromosome 9 (9p), deletions of the long arm of chromosome 6 [del(6q)] and the long arm of chromosome 13 [del(13q)], trisomy of chromosome 21 (+21),
- high hyperdiploidy with a chromosome number>50, excluding near tetraploidy; deletion of the long arm of chromosome 13 (del[13q])
- t(1;19)(q23;p13.3) a derivative of chromosome 19 resulting from this reciprocal translocation [der(19)t(1;19)(q23;p13.3)].

High-risk cytogenetic:

- **t(9;22)(q34;q11.2 or variants**
- **t(4;11)(q21;q23) or other balanced translocation involving band 11q23**
- **Loss chromosome 7 loss, chromosome 8 gain (+8)**
- **hypodiploidy with a chromosome number<43 with or without a near-triploid (i.e., with near 69 chromosomes) clone (or had a near triploid clone without a hypodiploid one).**

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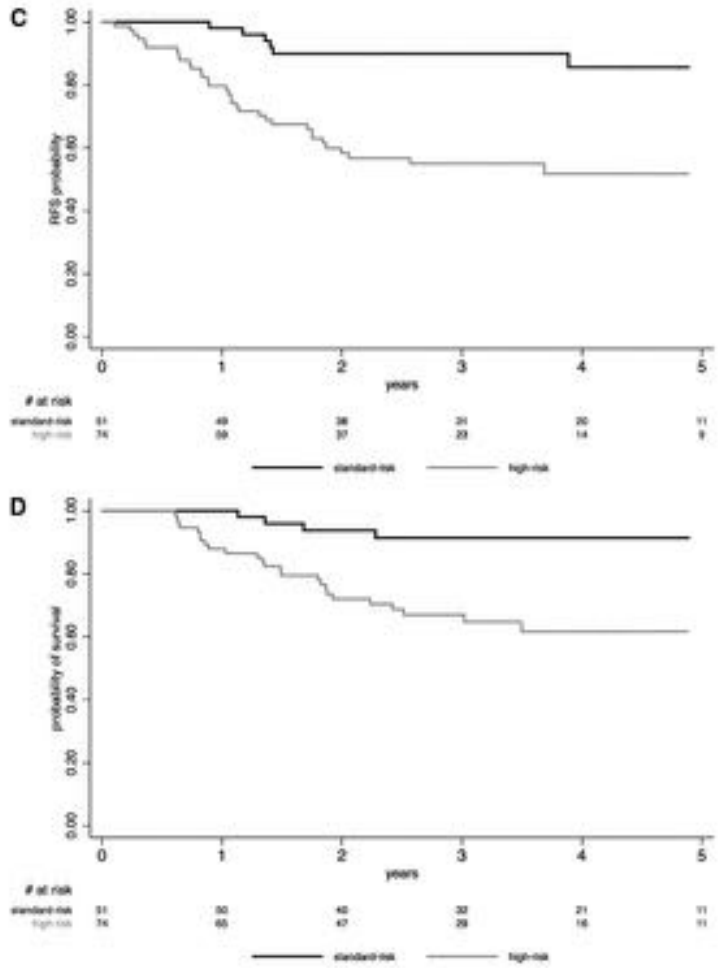
T-ALL

- NOTCH1 or FBXW7 mutations are associated with a favorable prognosis in adult and childhood ALL.

- K-RAS, N-RAS , and PTEN Mutations are associated with a poor prognosis; and the NUP214-ABL1 fusion is responsive to tyrosine kinase inhibition.

- Good prognosis: N/F mutations - without R/P mutation. Poor risk all others.



T Terwilliger et al blood cancer journal 2017

Kheira Beldjord, et al blood 2014

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MRD- strongest Prognostic factor

- PETHEMA ALL-AR-03 trial, a multivariate analysis- persistence of MRD was the only significant prognostic marker for OS and DFS.

- In a large meta analysis, Berry and colleagues assessed the correlation between clinical outcomes and MRD status. In 13,637 pediatric and adult patients with ALL: MRD negativity with higher 10-year EFS rate than MRD positivity (*77% vs. 32% in pediatrics and 64% vs. 21% in adults*).

- It is important to assess MRD status at CR, 3 months, and then every 3 to 6 months thereafter to help guide treatment strategy.

- Gokbuget et al found that the 5-year Cumulative relapse was significantly higher in those with persistent MRD who received alloSCT compared with those who did not (66% vs. 12%; P < .0001).

Brüggemann M et al blood 2006.
Gökbuget N et al blood 2012
Bassan R et al Blood 2009
Berry DA et al JAMA oncol 2017
Ravandi et al blood 2013

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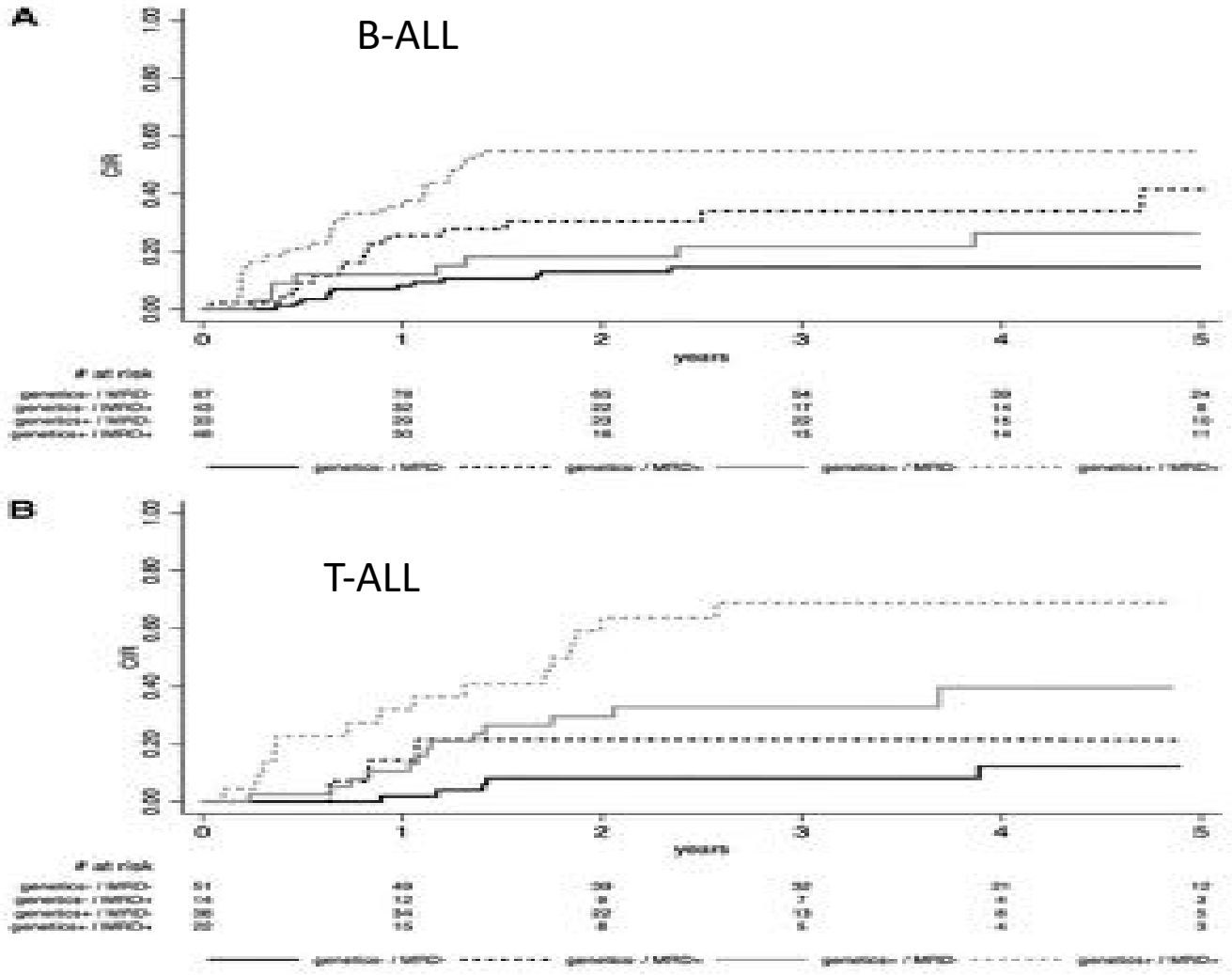
Cytogenetics and MRD?



Kheira Beldjord, et al blood 2014

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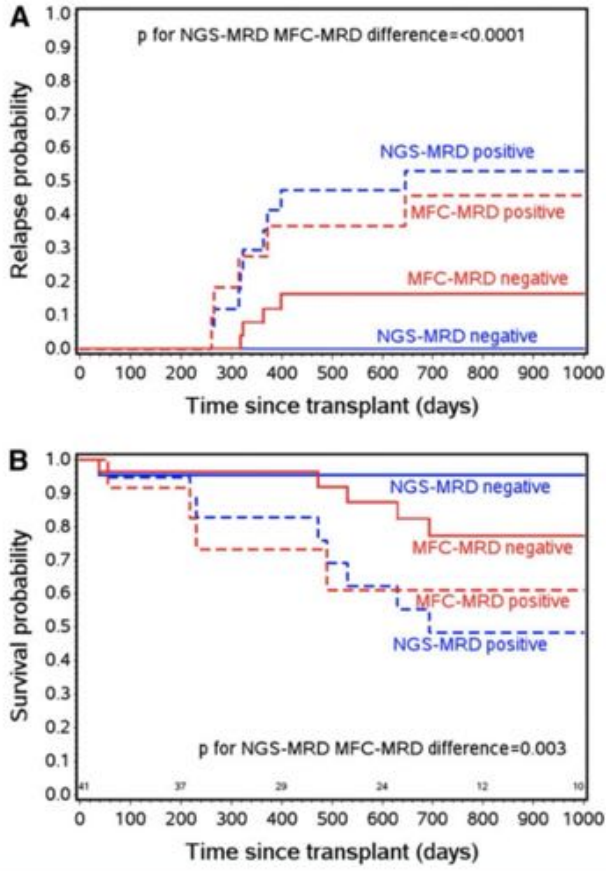
NGS-MRD

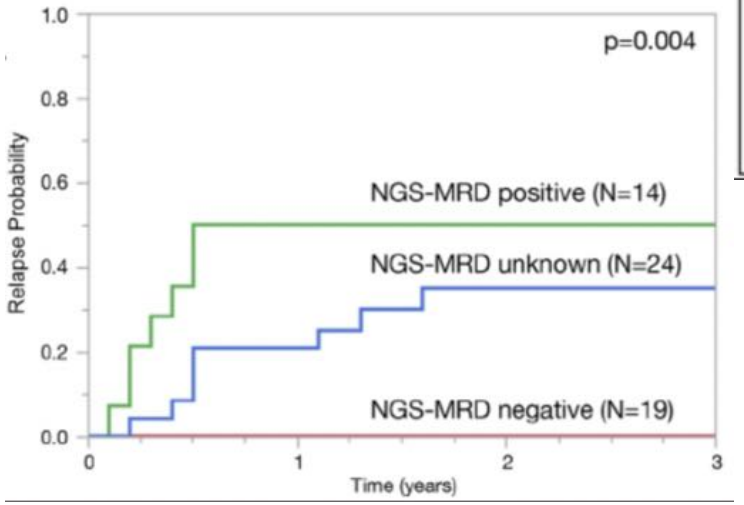
TRANSPLANTATION

IgH-V(D)J NGS-MRD measurement pre- and early post-allotransplant defines very low- and very high-risk ALL patients

Michael A. Pulsipher,[1] Chris Carlson,[2,3] Bryan Langholz,[4] Donna A. Wall,[5] Kirk R. Schultz,[6] Nancy Bunin,[7] Ilan Kirsch,[3] Julie M. Gastier-Foster,[8-10] Michael Borowitz,[11] Cindy Desmarais,[3] David Williamson,[3] Michael Kalos,[12] and Stephan A. Grupp[7,13]



MRD by NGS and relapse- peds and AYA data



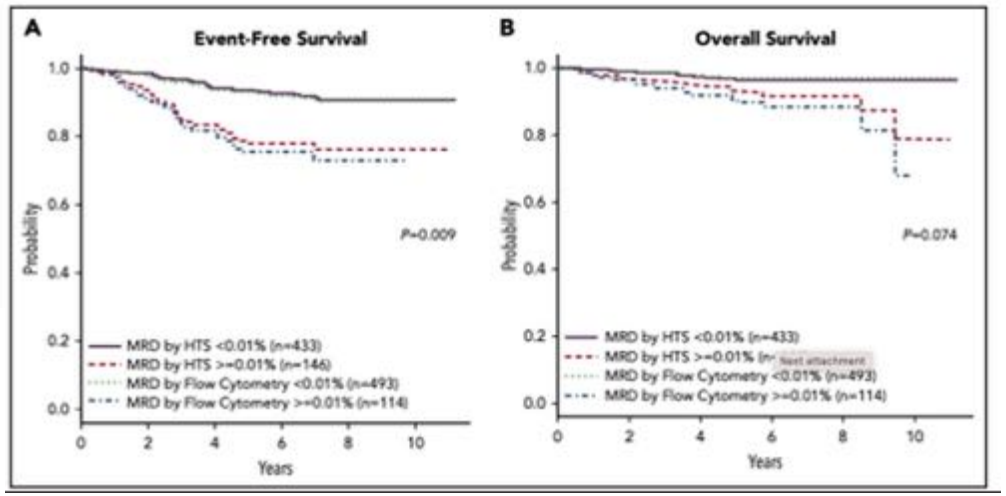
Friend BD, Bailey-Olson M, Melton A, et al. The impact of total body irradiation-based regimens on outcomes in children and young adults with ALL undergoing allogeneic hematopoietic stem cell transplantation. *Pediatr Blood Cancer*. 2020;67:e28079.

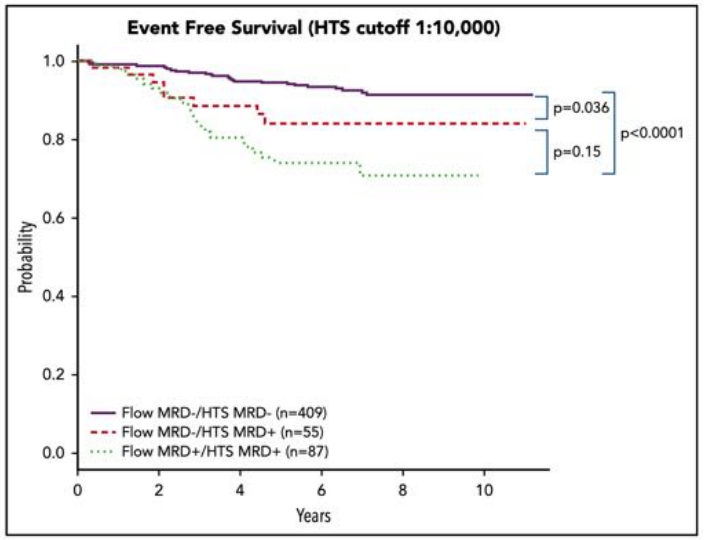
blood Regular Article

LYMPHOID NEOPLASIA

Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL

Brent Wood,[1,*] David Wu,[1,*] Beryl Crossley,[2] Yunfeng Dai,[3] David Williamson,[2] Charles Gawad,[4] Michael J. Borowitz,[4] Meenakshi Devidas,[5] Kelly W. Maloney,[5] Eric Larsen,[6] Naomi Winick,[7] Elizabeth Raetz,[8] William L. Carroll,[9] Stephen P. Hunger,[10] Mignon L. Loh,[11] Harlan Robins,[2,12,†] and Ilan Kirsch[2,†]





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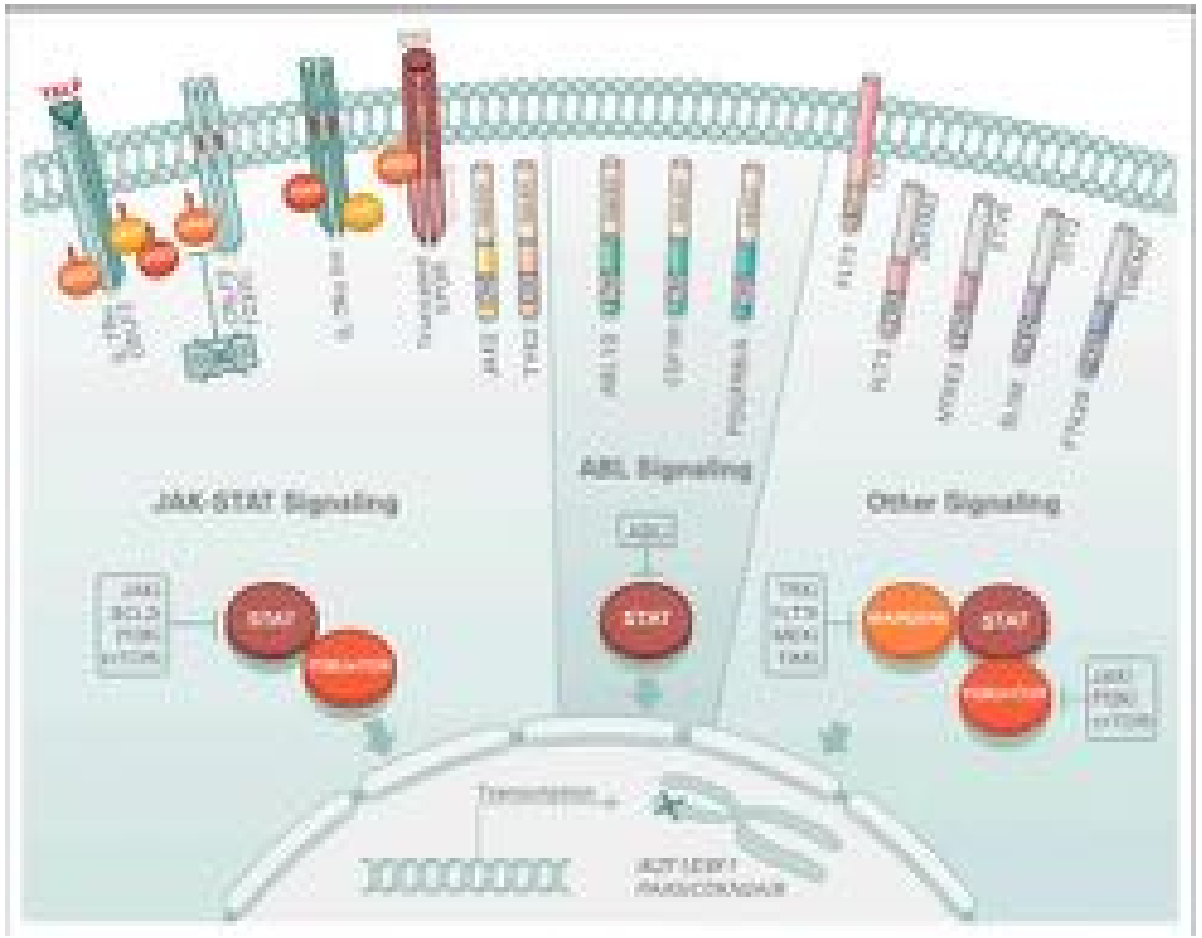
Ph-Like B ALL

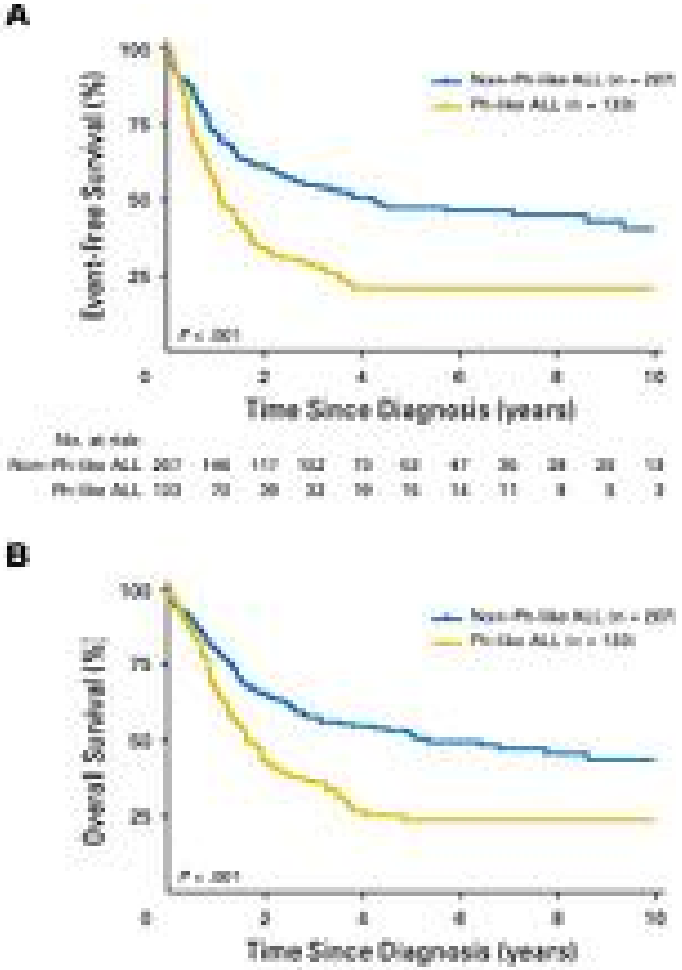
- Genetically, it appears similar to BCR-ABL1 but lacks the fusion protein t(9;22) (q34;q11.2).
- The incidence increases with age and occurs in approximately 10% to 15% of children and 25% to 30% of AYA.
- It also more prevalent among patients of Hispanic descent.
- 50% to 80% of patients with Ph-like ALL have a rearrangement in cytokine receptor-life factor 2 (CRLF2) that encodes for the receptor thymic stromal lymphopoietin.
- Majority of the cases with deletions in key transcription factors involved in B-cell development including: IKAROS family zinc finger 1 (IKZF1), transcription factor 3 (E2A), early B-cell factor 1 (EBF1) and paired box 5 (PAX5).
- Of these cases, 50% have a janus kinase mutation (JAK1 and JAK2) with higher frequency in children than adults.
- In patients who are CRLF2 negative, 10% have a kinase rearrangement (ABL1, ABL2, CSF1R, PDGFRB, PDGFRA, LYN, EPOR). Activating mutations of IL7R and FLT3 and deletion of SH2B3, which encodes the JAK2-negative regulator LNK

Signaling pathways Ph- Like ALL



Ilaria Iacobucci et al JCO 2017

Philadelphia-like outcomes



Roberts et al, JCO 2017

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Treatment improvement

Ph-like ALL remain MRD-positive, and utilizing blinatumomab or inotizumab, CAR-T in the frontline and MRD pos - improve outcomes ?

Treatment with ruxolitinib in JAK2-mutated patients has not shown to improve outcomes

TKIs in ABL-class mutations have demonstrated promising activity with sustained responses and continue to be examined further.

Kobayashi K et al Pediatric blood cancer 2015

Inaba H et al Hematologica 2013

Lengeline E et al, Hematologica 2013

Weston BW et al, JCO 2013

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ALL treatment

- Induction to achieve CR followed with post remission Consolidation/Intensification then maintenance.
- Combination chemotherapy is the primary treatment modality for patients with ALL/LBL.
- Contain vincristine, a corticosteroid (ie, prednisone or dexamethasone), and an anthracycline.
- East Asia, Hispanic- TPMT status , *NUDT15* gene.

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Different regimen

- CALGB study 8811 or 9111 ALL/LBL regimen
- CALGB study 10403 ALL/LBL regimen for adolescents and young adults (AYA)
- Dana Farber Cancer Institute (DFCI) ALL/LBL Consortium study for patients 18 to 50 years old
- Standard or augmented Berlin-Frankfurt-Munster (BFM), which has been used by the Children's Cancer Group for children and adolescents
- (Hyper-CVAD) alternating with high dose methotrexate and cytarabine
- French GRAALL 2003 regimen for younger adults
- French GRAALL 2005 regimen for adults up to 55 years old

Optimal Pediatrics based Regimen

Study	Number	Median age	CR%	Induction death (%)	OS	DFS/EFS
C10403 [47]	296	24 (17–39)	NR	4 (1)	2-yr = 78%	2-yr EFS = 66%
DFCI [38]	92	28 (18–50)	85	1 (1)	4-yr = 67%	4-yr DFS = 69%
USC [37]	51	32 (18–57)	96	0 (0)	7-yr = 51%	7-yr DFS = 58%
PETHEMA [39]	81	20 (15–30)	98	1 (1)	6-yr = 69%	6-yr EFS = 61%
GRAAL-2003 [40]	225	31 (15–60)	94	14 (6)	3.5-yr = 60%	3.5-yr EFS = 55%
HOVON [41]	54	26 (17–39)	91	2 (4)	2-yr = 72%	2-yr EFS = 66%
FRALLE 2000 [45]	89	19 (15–29)	99	NR	5-yr = 66%	5-yr EFS = 61%
MDACC [44]	85	21 (12–39)	94	1 (1)	3-yr = 74%	3-yr CRD = 70%
GMALL 07/03 [149]	1226	35 (15–55)	91%	4–5%	3-yr = 60–67%	NR

CR: complete remission; OS: overall survival; DFS: disease free survival; EFS: ev free survival; NR: not reported.

Ibrahim Aldoss et al Leukemia & lymphoma 2018

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Remission Induction (Course I)

- **Allopurinol** –300 mg/day (unless allergic), to continue until peripheral blasts and extramedullary disease are reduced
- **IT-Ara-C** – Ara-C 70 mg IT on D 1
- **Pred** –60 mg/m^2/day PO or IV in two divided doses on D1-28
- **VCR** –1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 8, 15, and 22
- **DNR** –25 mg/m^2 IV on D 1, 8, 15, and 22
- **PEG** –2500 IU/m^2 IM or IV D 4
- **IT-MTX** - 15 mg IT on D 8 & D 29 (also administered on D 15 and 22 for CNS3 patient)

Extended Remission Induction (If required)(Course IA)

- **Pred** –60 mg/m^2/day PO or IV (methylprednisolone) in two divided doses on D 1-14
- **DNR** –25 mg/m^2 IV on D 1
- **VCR** – Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on D 1 and 8
- **PEG** –2500 IU/m^2 IM or IV D 4

Remission Consolidation (Course II)

- **CTX** –1000 mg/m^2 IV on D 1 & 29
- **Ara-C** –75 mg/m^2 IV or SC on D 1-4, 8-11, 29-32, and 36-39
- **6-MP** –60 mg/m^2 PO on D 1-14 and 29-42
- **VCR** –1.5 mg/m^2 (maximum 2 mg) IV on D 15, 22, 43 and 50
- **PEG** –2500 IU/m^2 IM or IV on D 15 and 43
- **IT-MTX** – 15 mg IT on D 1, 8, 15 and 22 (omit doses on D 15 & 22 for CNS3 patients)

Interim Maintenance (Course III)

- **IV-MTX** –starting dose 100 mg/m^2 IV escalate by 50 mg/m^2 dose on D 1, 11, 21, 31 and 41
- **PEG** –2500 IU/m^2 IM or IV on D 2 and 22
- **IT-MTX** - 15 mg IT on D 1 and 31

Delayed Intensification (Course IV)

- **VCR** – 1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 8, 43, and 50
- **DEX** – 10 mg/m^2 PO (or IV) divided BID on D 1-7 and 15-21
- **PEG** – 2500 IU/m^2 IM or IV D 4 (OR D 5 OR D 6) and D 43
- **CTX** – 1000 mg/m^2 IV on D 29
- **Ara-C** – 75 mg/m^2 IV or SC on D 29-32 and 36-39
- **6-TG** – 60 mg/m^2/day PO on D 29-42
- **IT-MTX** – 15 mg IT on D 1, 29, & 36

Maintenance (Course V)

- **VCR**–1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 29, and 57
- **DEX**– 6 mg/m^2/day PO (or IV) in 2 divided doses every 4 weeks on D 1-5, 29-33, and 57-61
- **6-MP**– 75mg/m^2/day PO on D 1-84
- **IT-MTX** – 15 mg IT on D 1 (also is given on D 29 of the first 6 courses of maintenance)

blood
Prepublished online January 18, 2019;
doi:10.1182/blood-2018-10-881961

A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403

CALGB10403

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	Overall	Historical Controls
Months of follow-up, for surviving patients, median (Range)	64.2 (0.4-109.5)	
Induction death rate	9 (3%)	
Response/progression		
M-status complete response* N (%) (95% Exact CI)	263 (89%) (85-93%))	
Overall survival	N=295, Events=105	
Median (months (95%CI)	NE	61 (39-89)
At 3 yrs (% (95%CI)	73% (68-78%)	58% (52-64%)
Event-free survival	N=295, Events=139	
Median (months (95%CI)	78.1 (41.8-NE)	30 (22-38)
At 3 yrs (% (95%CI)	59% (54 – 65%)	
Disease-free survival	N=263, Events=107	
Median (months (95%CI)	81.7 (58.4-NE)	34 (28-50)
At 3 yrs (% (95%CI)	66% (60-72%)	48% (41-55%)

blood Prepublished online January 18, 2019; doi:10.1182/blood-2018-10-881961

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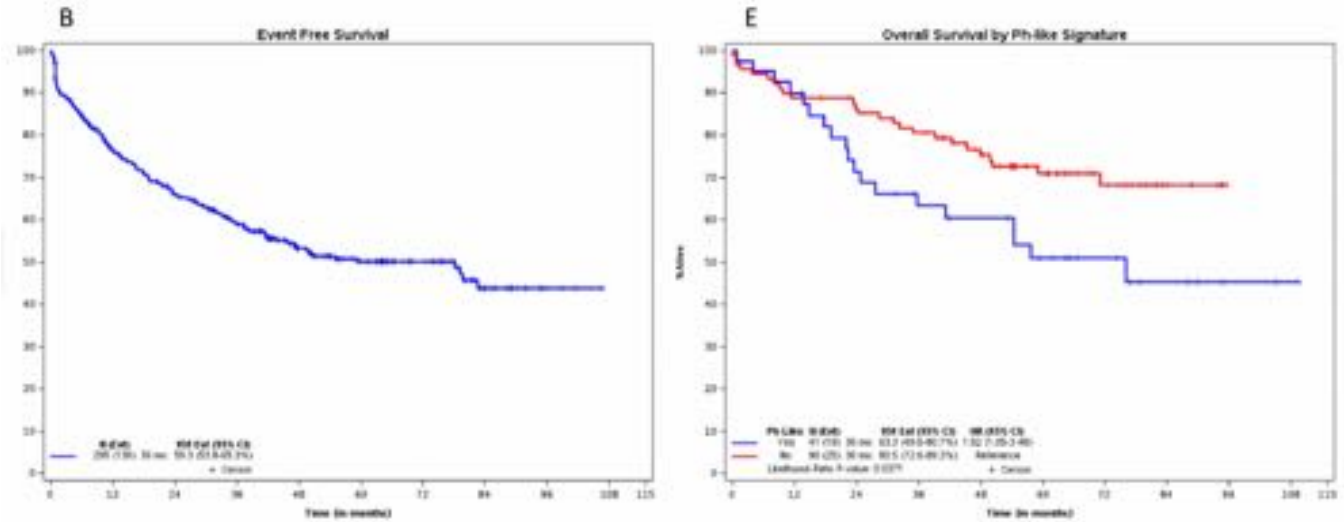

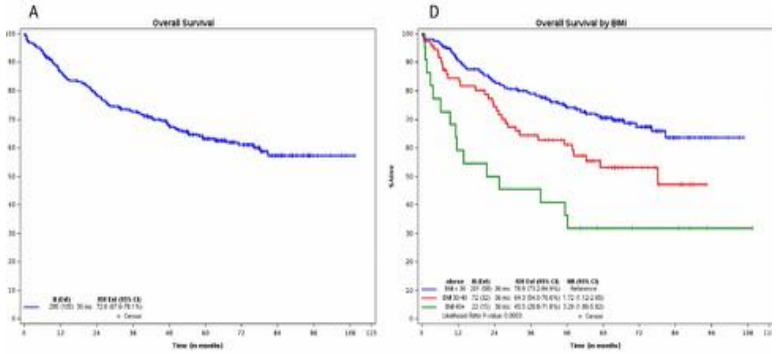

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A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403

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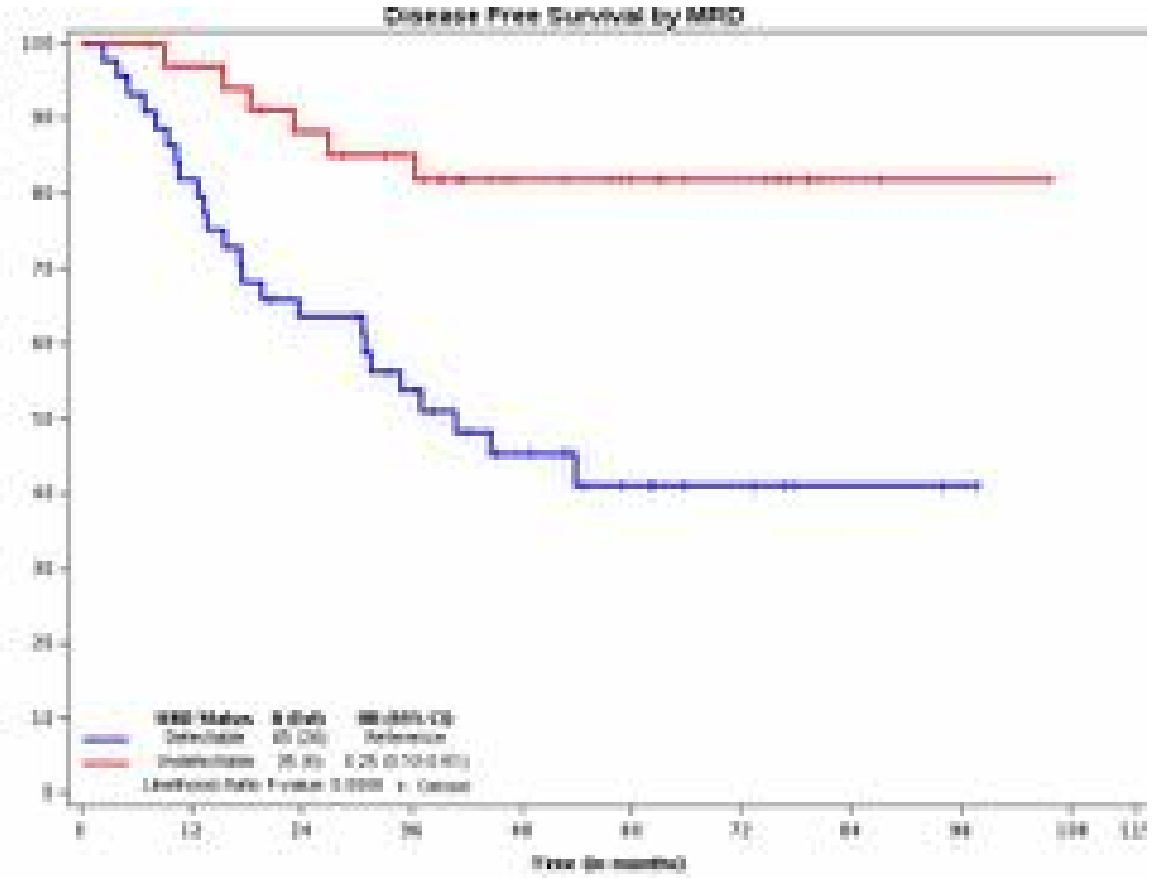
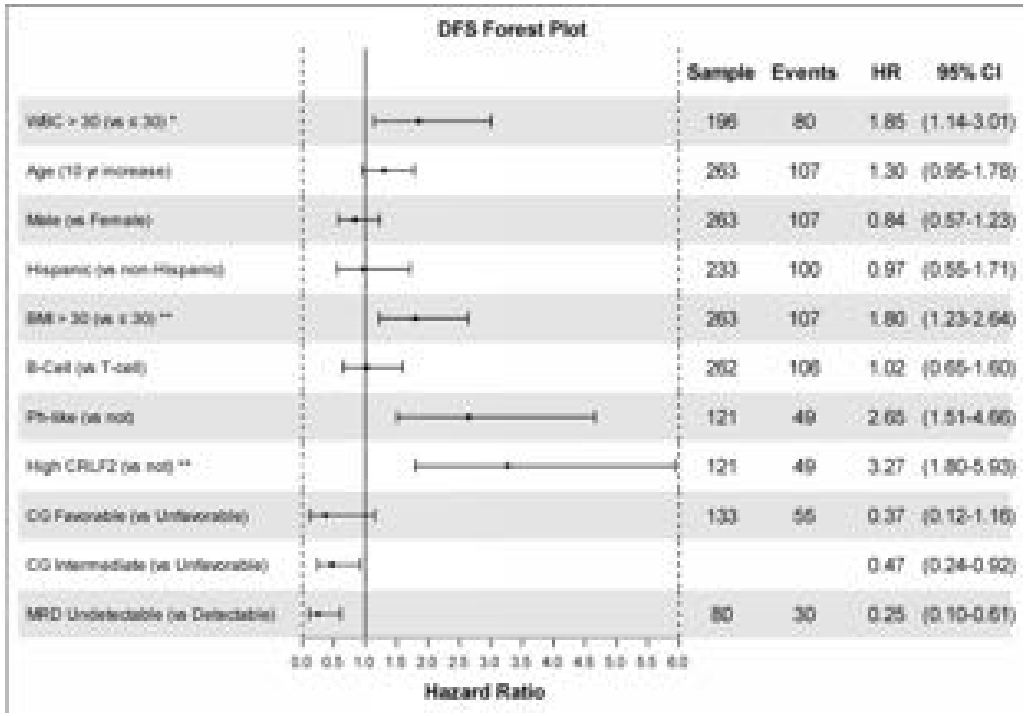
MRD and OS





blood®
Prepublished online January 18, 2019;
doi:10.1182/blood-2018-10-881961

A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403

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Asparaginase

Deprivation of ALL blasts from circulating asparagine

- *Erwinia* asparaginase – Half-life 14 hours

- Pegylated *Escherichia coli* asparaginase – Half-life 6 days. peg asp 2000 units/m^2 given every two weeks or 1000 units/m^2 given weekly-> These doses should result in asparagine depletion in the vast majority of adults for a two-week period.

- Calaspargase pegol was approved by the US Food and Drug Administration for treatment of ALL/LBL in pediatric and young adult patients age 1 month to 21 years based on achievement and maintenance of nadir serum **asparaginase activity >0.1 units/mL** when using calaspargase pegol 2500 units/m^2 IV every three weeks.

- Asparaginase activity measure 7 and 14 days after the first dose during induction and 7 days after every reintroduction after a break in asparaginase treatment . A level below 0.1 international units (IU)/mL on day 7 and/or undetectable levels on day 14 are consistent with silent inactivation.

Van der Sluis IM et al Hematologica 2016

Malgorzata Cet al, BioMed research International 2014

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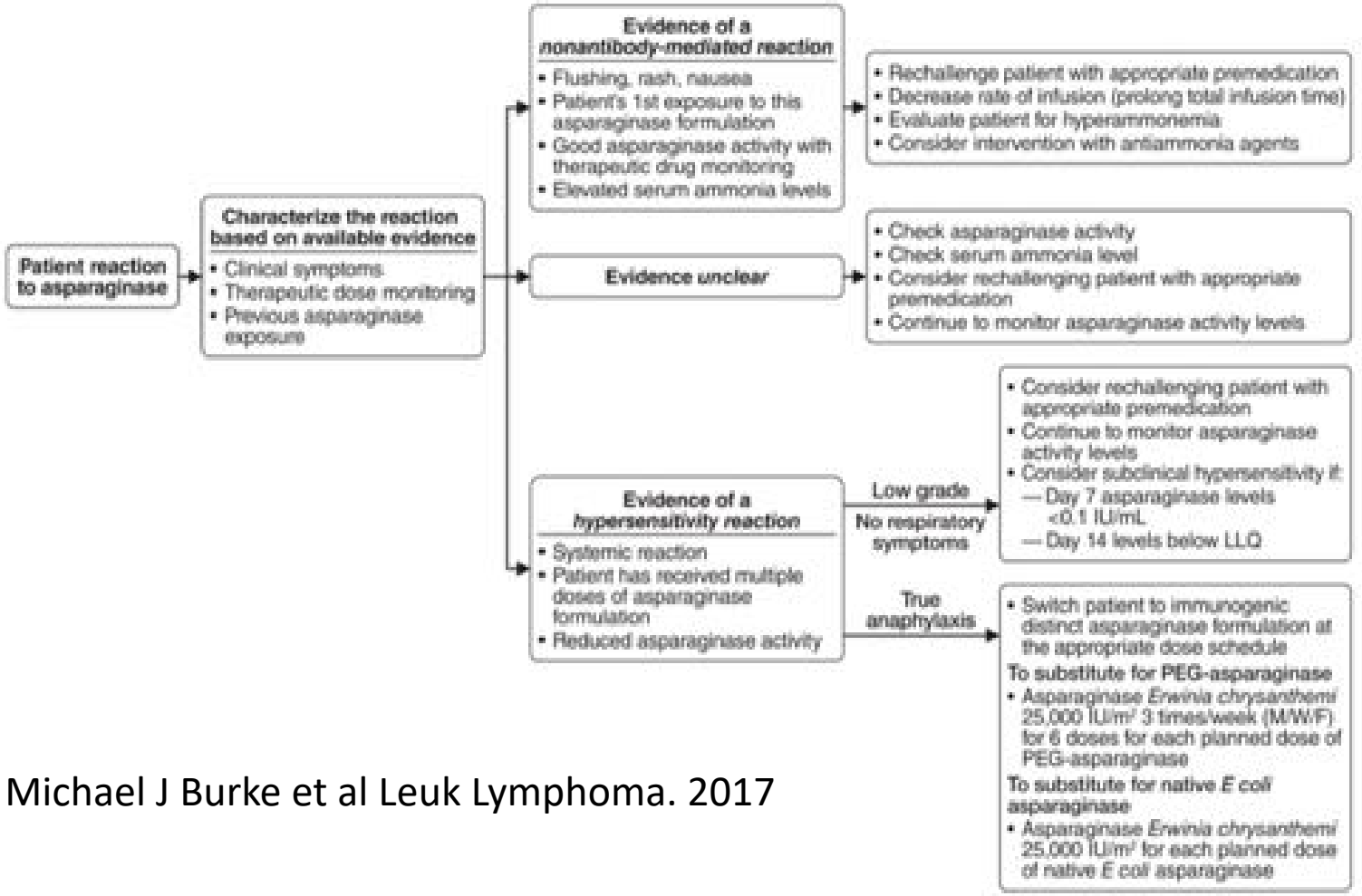
Transfusion reaction VS Hypersensitivity reaction

Amonia level, reaction type, and Asparaginase activity.



Michael J Burke et al Leuk Lymphoma. 2017

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Table 2. Asparaginase toxicities and management [42,43].

Toxicity	Grade III–V	Notes
Hyperbilirubinemia	14–24%	Reversible. Not an indication to hold subsequent asparaginase therapy
Transaminases	36–54%	Reversible. Not an indication to hold subsequent asparaginase therapy
Thrombosis	8–11%	Start anticoagulation. Asparaginase can be resumed while the patient remains on anticoagulation for non-life-threatening thrombosis cases
Bleeding	<1%	Rare
Hypertriglyceridemia	31%	Reversible. No relation to clinical pancreatitis
Pancreatitis	5–13%	Permanent discontinuation of asparaginase due to high risk of recurrent pancreatitis if rechallenged. Chemical pancreatitis is not an indication to hold subsequent doses of asparaginase
Allergy	1–7%	Replace with Erwinia asparaginase
Hypofibrinogenemia (<100)	16–48%	Avoid replacement with cryoprecipitate due to high risk of thrombosis

Aldoss I, Douer D et al
Eur J Haematol. 2016

Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma. 2011.

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Pegsparaginase Toxicity and management in adults summary

- Hypersensitivity prevention
  - Hydrocortisone premedication

- Clinical hypersensitivity and silent inactivation
- switch to Erwina asparaginase.

- Liver toxicity
- continue when recovers without dose changes

- Thrombosis treatment:
- LMWH without dose change.
- Continue except sagittal venous thronbosis

Stock W et al. Leukemia Lymphoma 2011, NCCN guidlines

Pancreatitis
- Early diagnosis and immediate treatment
- permanently discontinue if severe.

Hypertriglyceridemia
- Continue without dose changes
- Add lipid lowering sgent.

dose recommendation:
Full adult dose ages 18-55-2000 IU/m2
Dose reduction, IU/m2
56 to 70 y 1000
71 to 75y 500
BMI>35 1000

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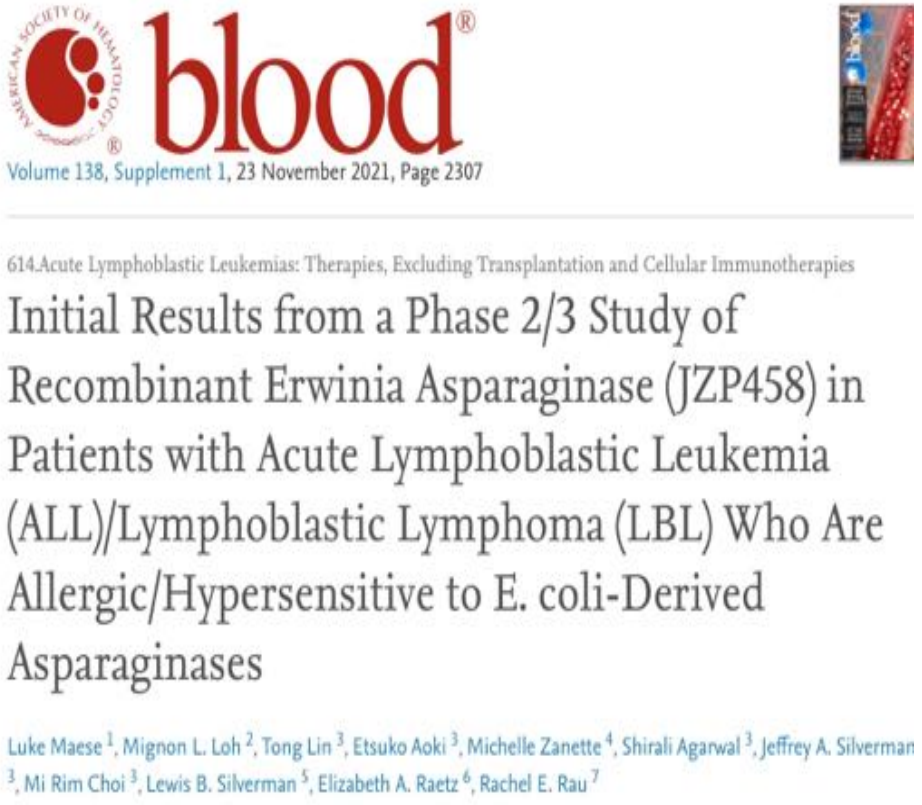
JZP458 Recombinant Erwinia Asparaginase Chrysanthemi

- 102 patients ages 1 to 24 with ALL and hypersensitivity to E. coli-derived asparaginase within a chemotherapy regimen.
- Asparaginase Erwinia chrysanthemi was administered intramuscularly at various dosages. The primary endpoint of the study was the achievement and maintenance of nadir serum asparaginase activity above 0.1 U/mL.
- At a dosage of 25 mg/m^2, 93.6% of patients achieved the primary endpoint at 48 hours after administration.
- The JZP458 IM dosing regimen of 25 mg/m ^{2} M and W, and 50 mg/m ^{2}F demonstrates a positive benefit:risk profile, achieving SAA levels ≥0.1 IU/mL in >90% of patients studied at both 48- and 72-hrs and a safety profile that is consistent with what has been observed in published literature on asparaginases.



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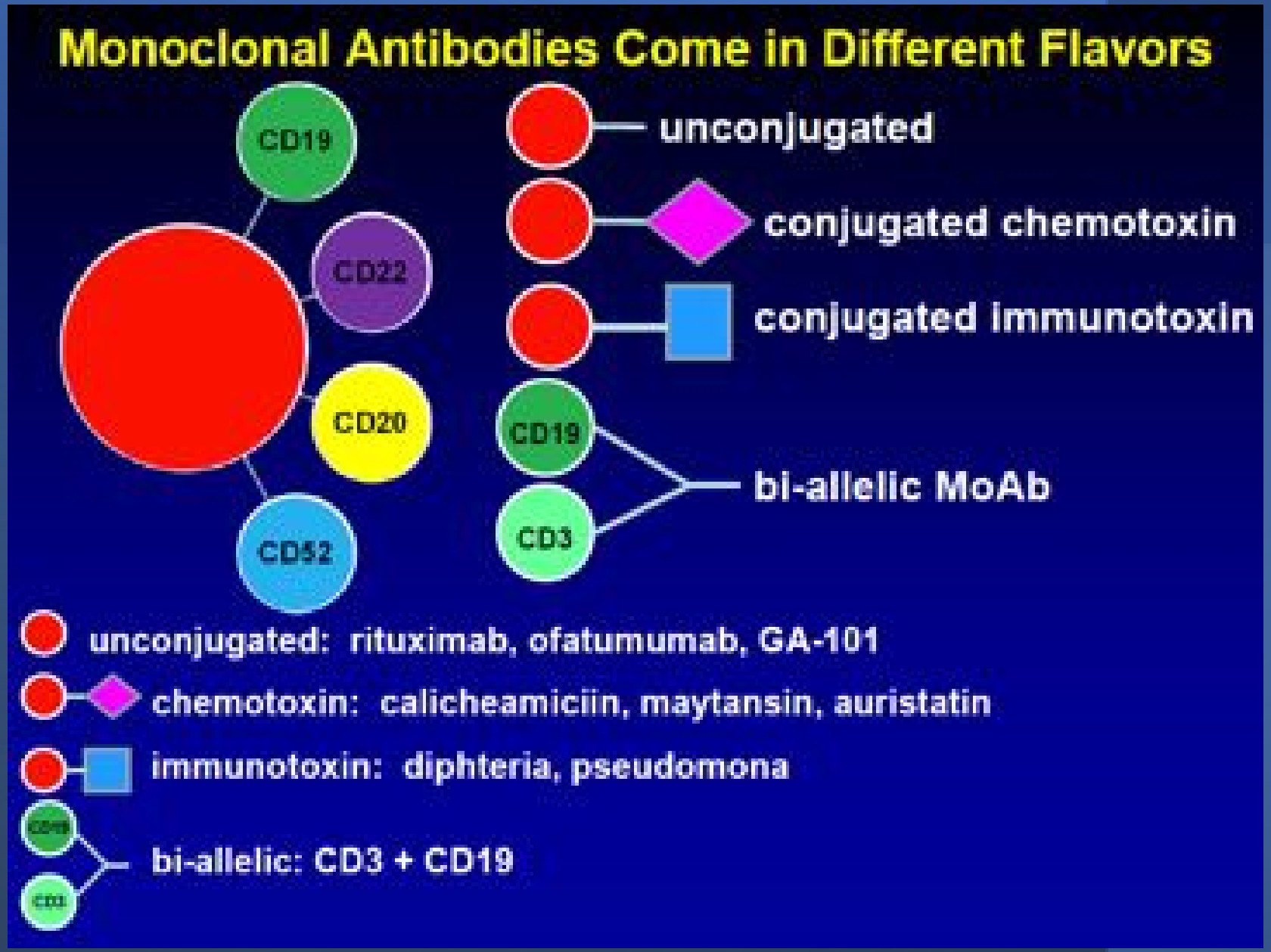

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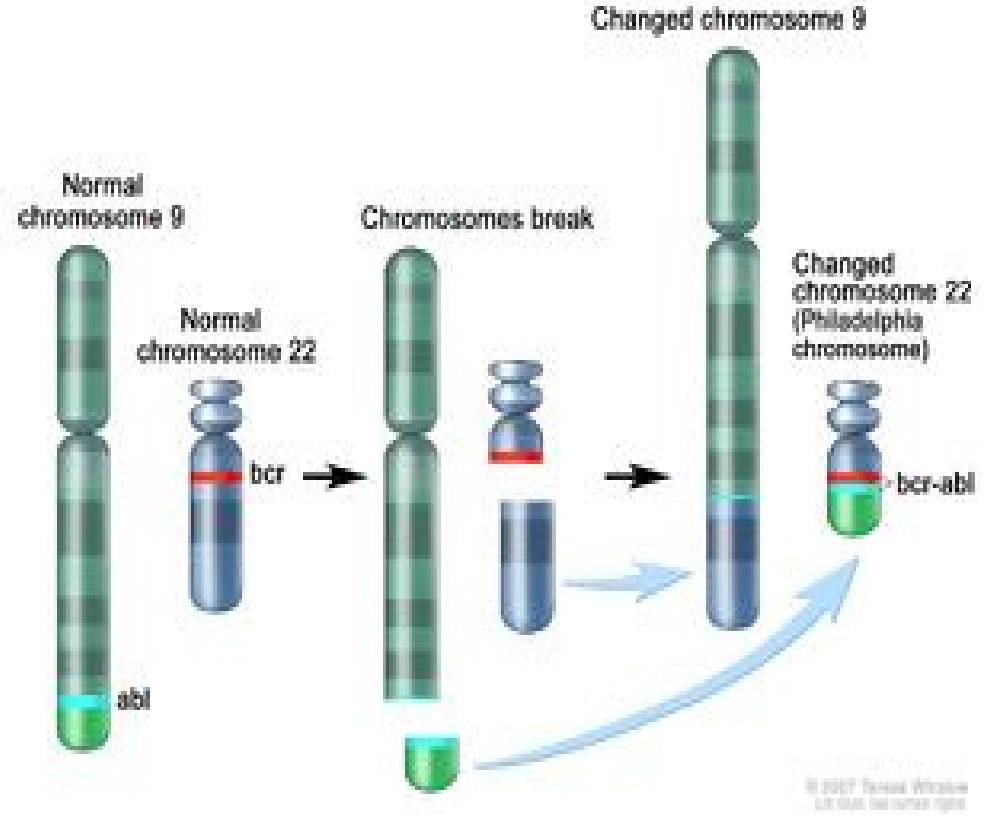
Philadelphia Positive ALL

- 25% of patients with pre-B ALL.
- Increases with age; 50% of pre-BALL patients over 50 years are Ph+
- Poor prognosis, ***5-year OS of 20%***.
- Chemotherapy with TKIs is the standard of care, significantly improved outcomes, with 5-year OS of 60% to 70%.



Puiet al,2004
Ravandi & Kebri-aei, 2009
Shilpa Paul et al Clinical lymphoma, Myeloma, & leukemia 2019

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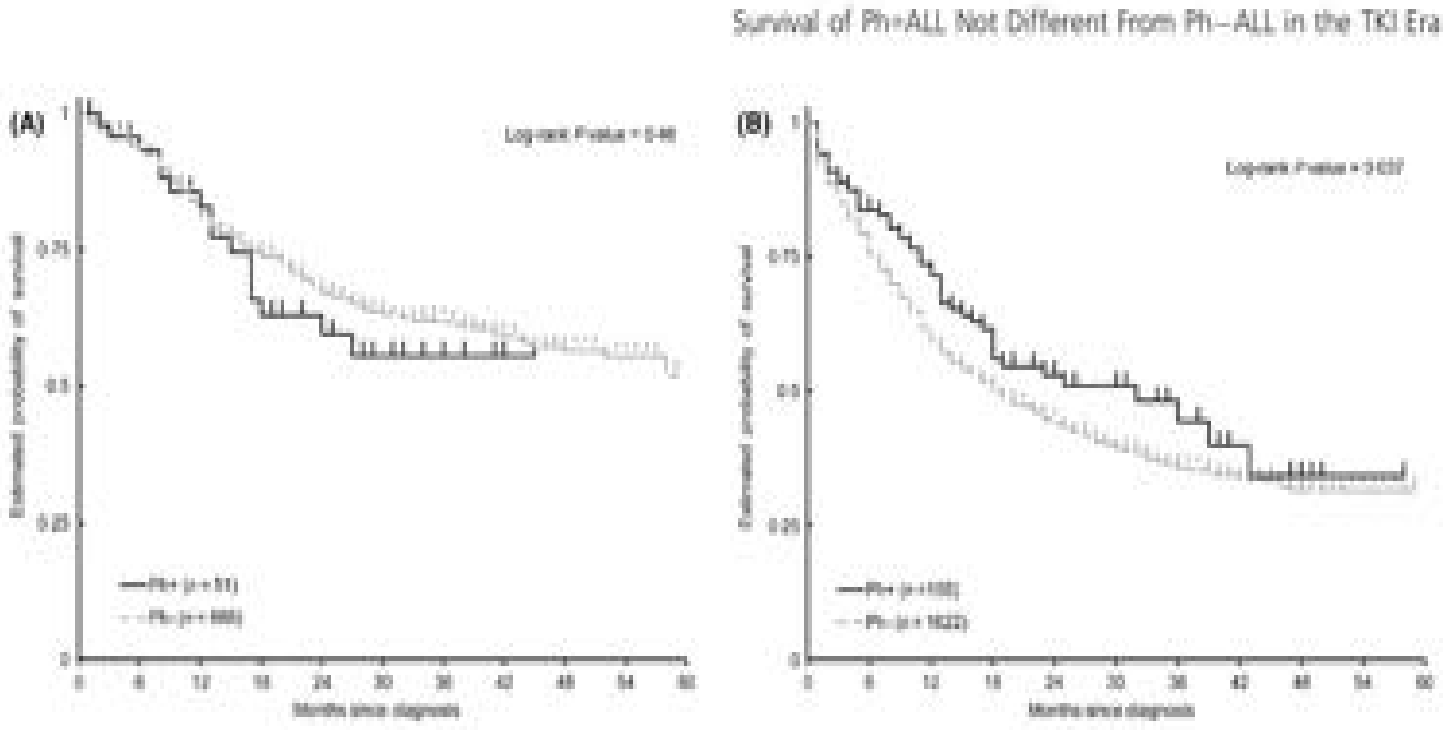
bjh research paper

The presence of Philadelphia chromosome does not confer poor prognosis in adult pre-B acute lymphoblastic leukaemia in the tyrosine kinase inhibitor era – a surveillance, epidemiology, and end results database analysis

Igwe J. Igwe,[1] Dongyun Yang,[2]
Akil Merchant,[1] Noah Merin,[3]
George Yaghmour,[1] Kevin Kelly[1]
Giridharan Ramsingh[1]
[1]Jane Anne Nohl Division of Hematology



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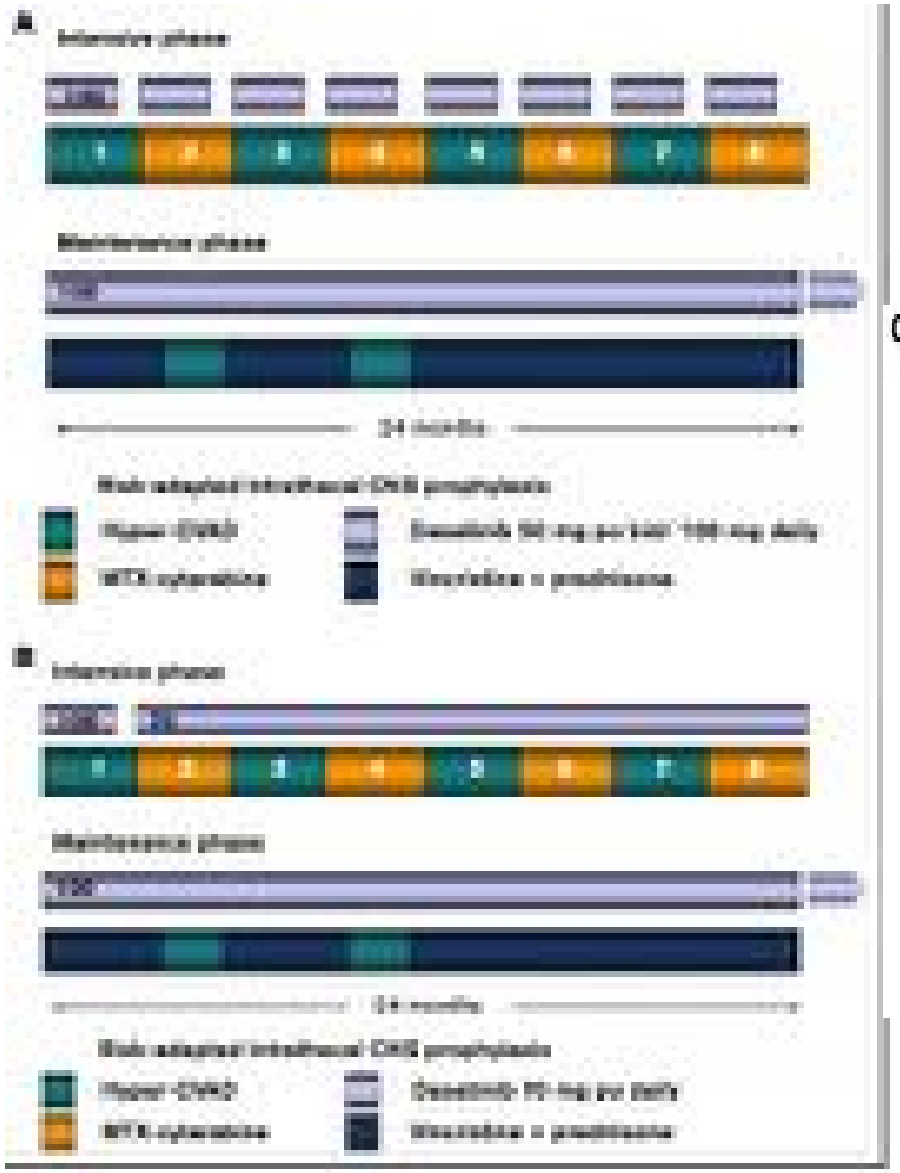
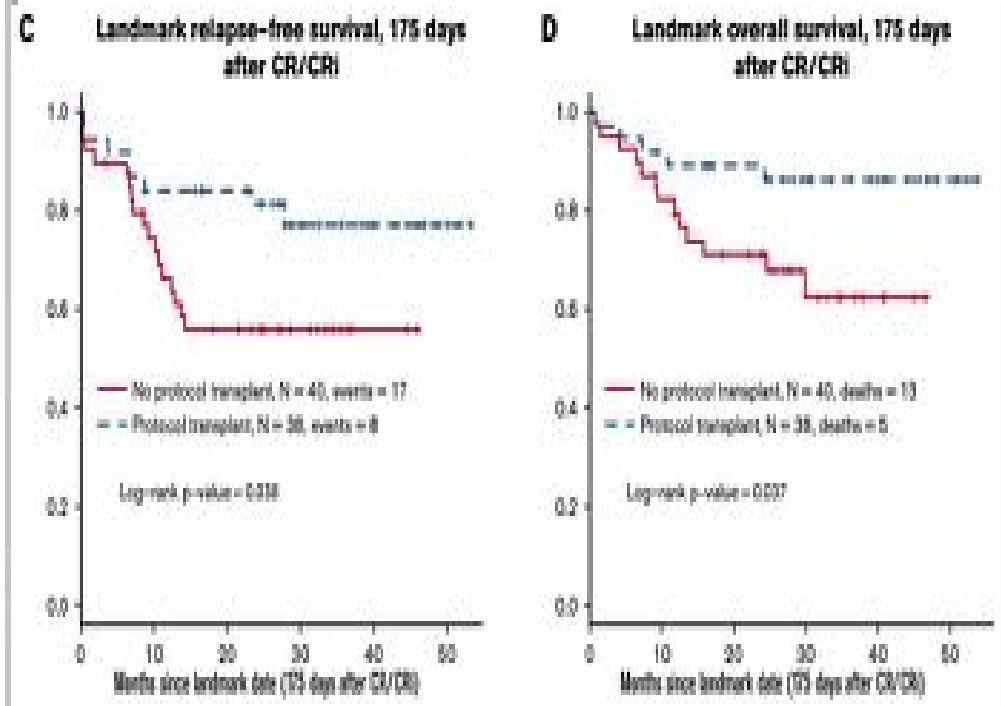
SWOG Hyper-CVAD with Dasatinib





CR/Cri 88%, CMR 65%.
3- year OS 71%, event-free survival 54%,

F Ravandi et al blood advance 2016

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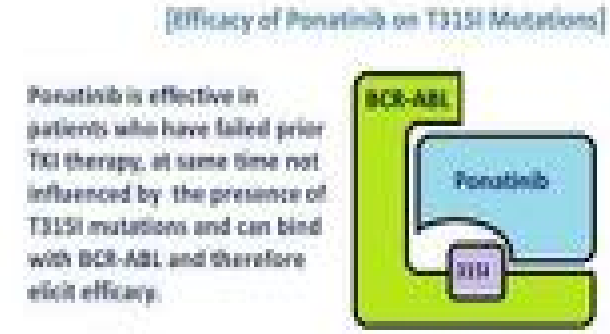
T315I ABL1 kinase mutation



- 60% R/R patients on treatment with first- or second-generation TKIs.

Elderly 23% present with T315I mutation, who relapsed 75% with T315I mutation

Ponatinib is a third-generation TKI overcome resistance to the T315I ABL1 kinase mutation

Phase 2 HyperCVAD- ponatinib –CMR 83%, **3-year OS 76%**

Ponatinib + hyperCVAD VS dasatinib+ hyperCVAD propensity score analysis: The 3-month CMR 82% vs 65% ($P < .03$)

3-year OS 83% versus 56% ($P < .03$)

Jabbour E et al Lancet oncology 2015
Jabbour E et Lancet Hematol 2018
Sasaki K et al Cancer 2016
Rousselot et al blood 2016

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Low intensity regimen with TKI

- Chiaretti S et al blood 2015- Dasatinib 140 mg daily and corticosteroids for the first 3 months- CR 97%. 3-yr OS and 58%, 3-yr DFS 49%. 3-month CMR was an independent factor for improved survival.

- Ottmann OG et al Blood 2018 – Nilotinib- The CR rate 94%, 4-year EFS was 42%, and the OS rate was 47%, respectively. 32% percent of patients underwent alloSCT, 4-year OS of transplanted patients was 61%

- Martinelli G et al Blood 2017 Gimema LAL ponatinib with steroids. ponatinib 45 mg daily continuously for 8 cycles of 6 weeks. Steroids were given for 2 weeks starting on day 14 of the first cycle: CR in 95% after the first cycle and 91% after 8 cycles. The CMR was 46%, and the 2-year OS was 60%.

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Factors influencing survival

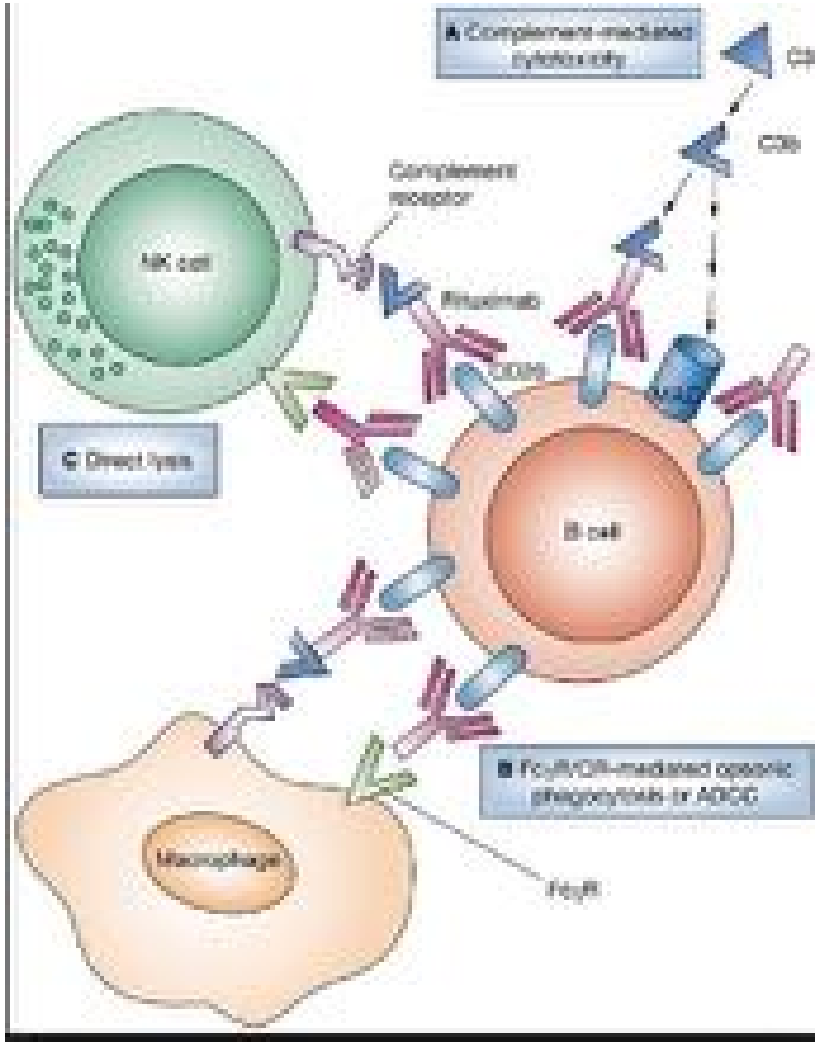
- Primary refractory
- MRD after initial therapy for 9-12 weeks
- Genetics markers
- Relapsed patients - relapse within 2-3 years

Hunger sp et al JCO 2012

Nguyen K et al leukemia 2008.

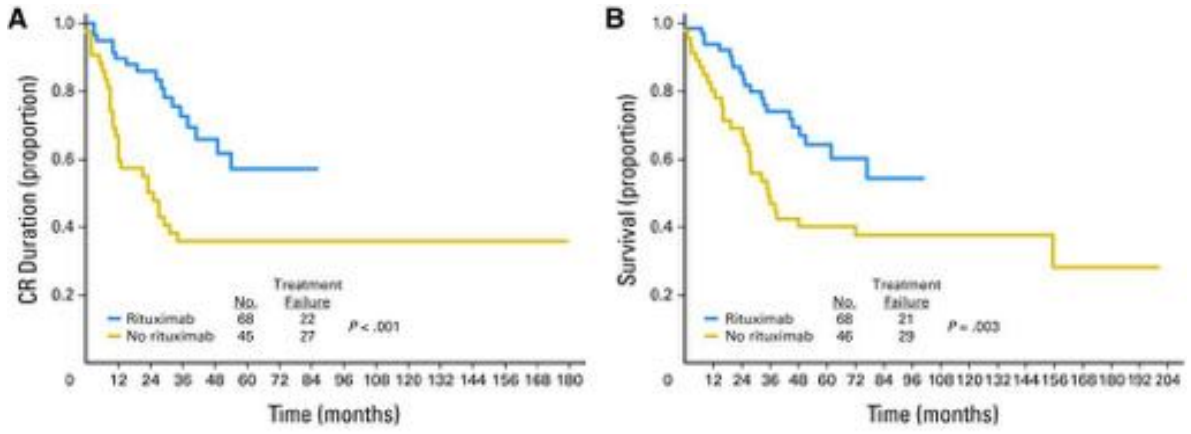
Targeting CD20 (Rituximab, Ofatumumab

- 30-50% of precursors B ALL express CD20.
- CD20 positivity associated with worse outcomes
- Expression up regulated after chemotherapy/Steroids



Raponi et al Leuk Lymphoma 2011
Maury S et al Hematologica 2010
Thomas DA et al Blood 2009
Dworzal et al blood 2008

Rituximab for CD20+ ALL



- 3-year CR rates from 38 to 70% ($p < .001$)
- 3-yr OS rates from 47 to 75% ($p < .003$

Thomas DA et al JCO 2010

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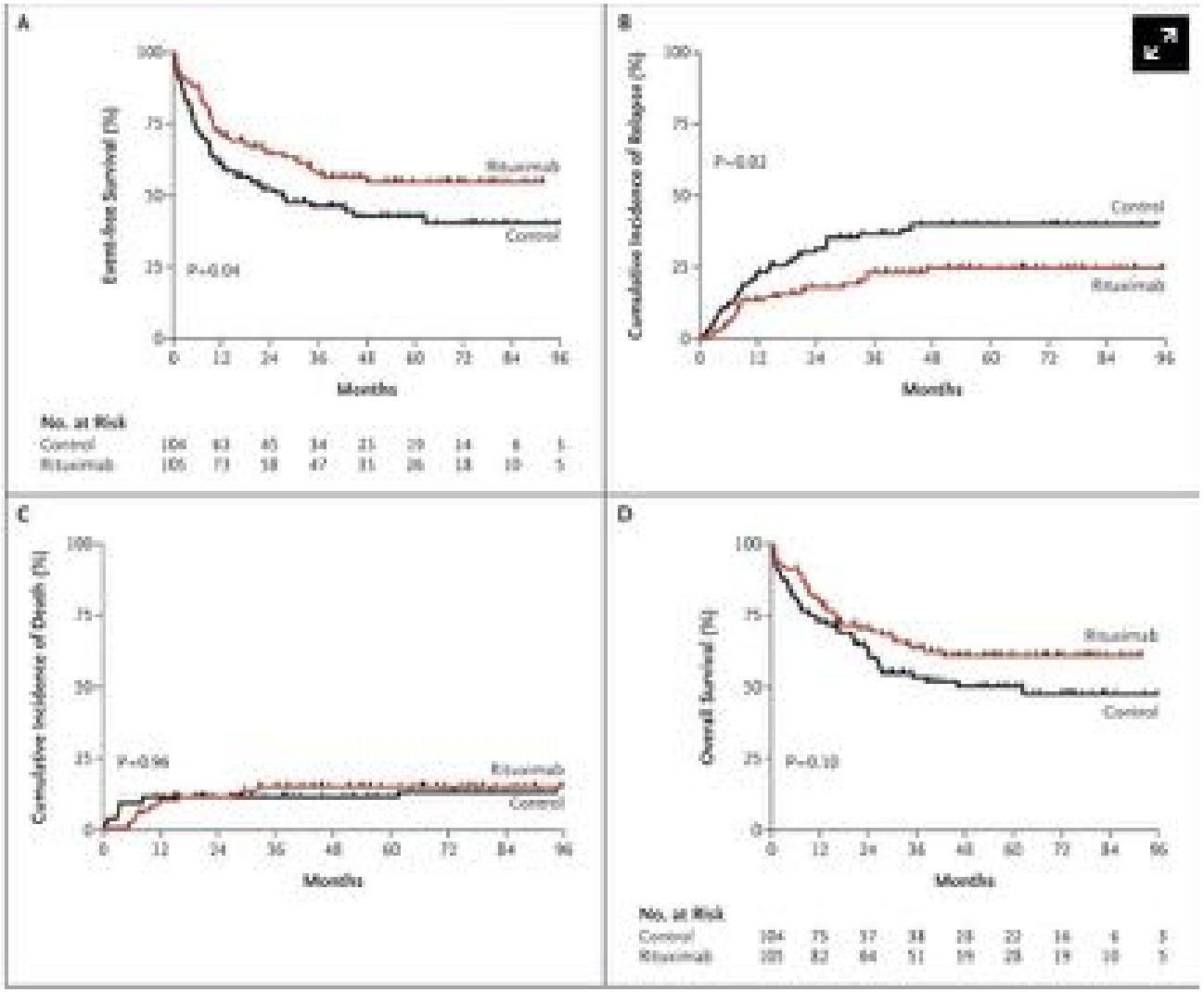
Rituximab-GRALL study



Maury S et al NEJM 2016

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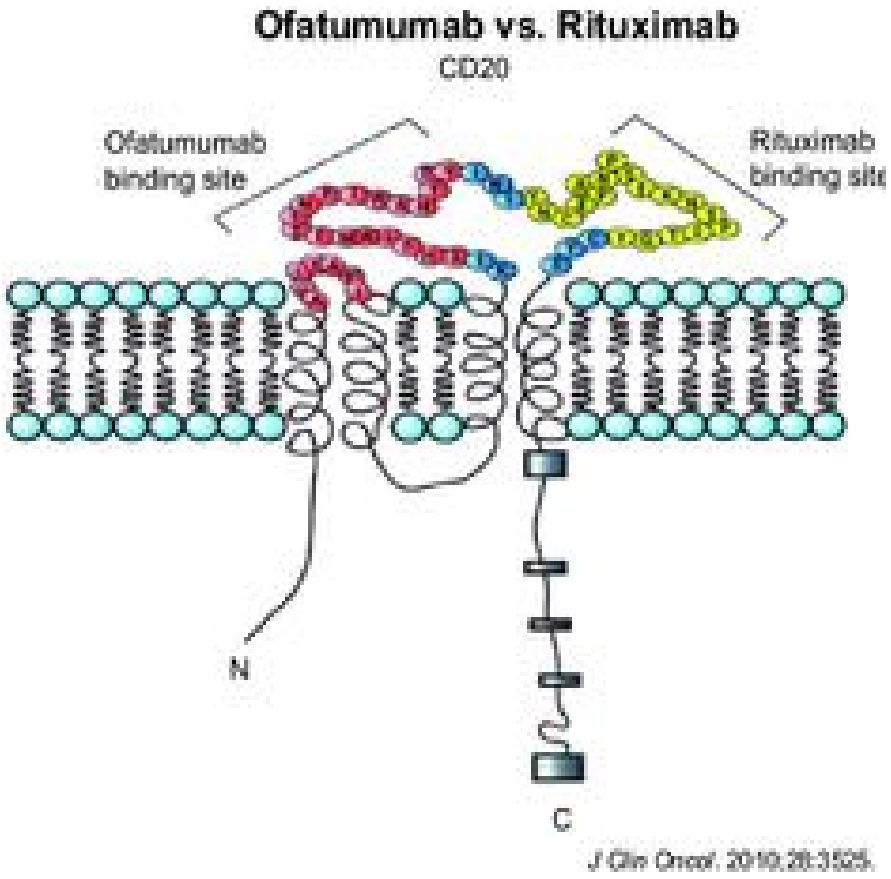
Ofatumumab

- 2nd generation anti-CD20.
- More potent than rituximab - slower dissociation rate and stronger binding
- Maintain efficacy with < 20% CD20 expression.
- CR rate was 98%
- 93% of patients achieved MRD neg.
- The estimated 3-year OS was 70%, and the survival benefit was equal regardless of CD20 expression



Sasaki K et al Blood 2016

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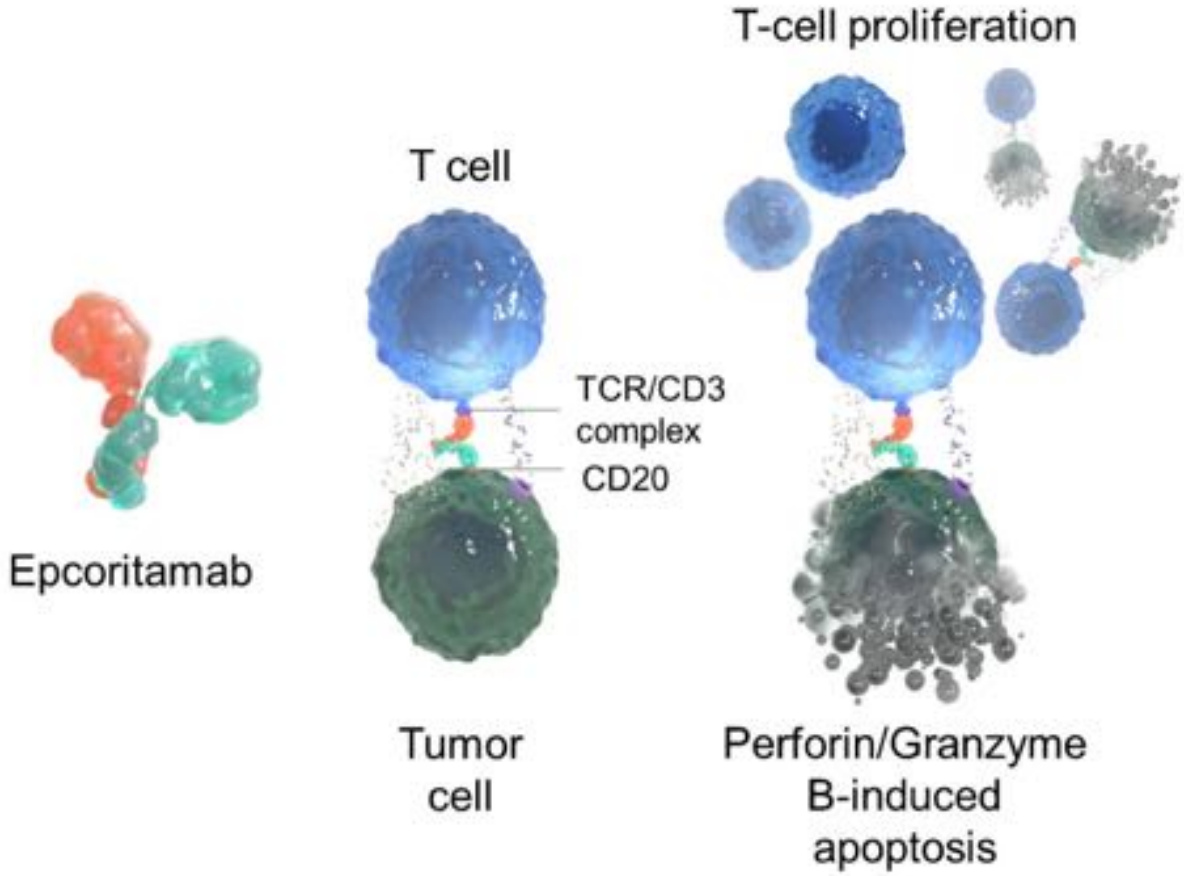
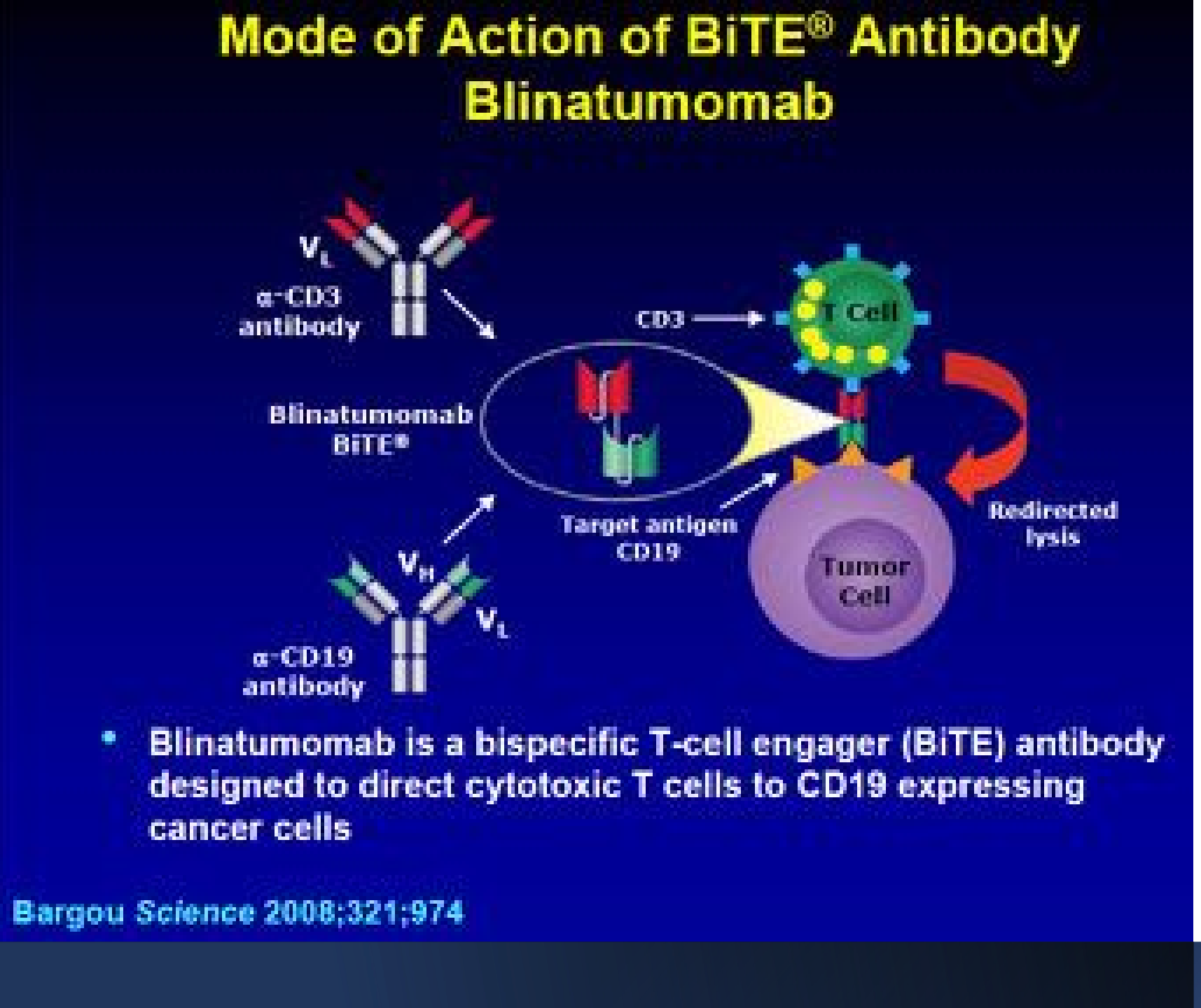
Epcoritamab

CD3xCD20 Bite





Blinatumomab

- Topp MS et al JCO 2011
- Topp MS et al Blood 2012
- Topp MS et al Lancet Oncology 2015
- Gokbuget N et al Hematologica 2017- MRD
- Gokbuget N et al Blood 2018- MRD
- Kantarjian H et al NEJM 2017
- Martinelli G et al JCO 2017

Blinotimumab

Table 1 Blinatumomab Clinical Trial Results

Clinical Trial	Patient Population	Response	MRD Negativity	Median Overall Survival, mo
ALCANTARA	R/R Ph^+ ALL (N = 45)	ORR: 35% CR: 31% CRh: 4%	88%[b]	7.1
TOWER[c]	R/R Ph^- ALL (N = 237)	ORR: 44% CR: 34% CRh: 10%	76%	7.7
BLAST	MRD^+ ALL (N = 116)	N/A	78%[a]	36.5

Table 4. Blinatumomab studies.

Study	ALL setting	N	Prior alloHCT (%)	CR/CRh % (MRD response %)	Median RFS (months)	Median OS (months)
Topp et al. (MRD pilot) [113,114]	MRD^+	21	0 (0)	N/A (80)	61% (at 33 months)	N/A
Goekbuget et al. (BLAST) [115,116]	MRD^+	116	0 (0)	N/A (80)	18.9	36.5
Topp et al. (phase 2 pilot) [117]	r/r Ph^-	36	15 (42)	69 (88)	7.6	9.8
Topp et al. (confirmatory) [112]	r/r Ph^-	189	64 (34)	43 (82)	5.9	6.1
Kantarjian et al. (TOWER) [118]	r/r Ph-	271	94 (35)	44 (76)	6-month EFS = 31%	7.7
Martinelli et al. (ALCANTARA) [150]	r/r Ph^+	45	20 (44)	36 (88)	6.7	7.1

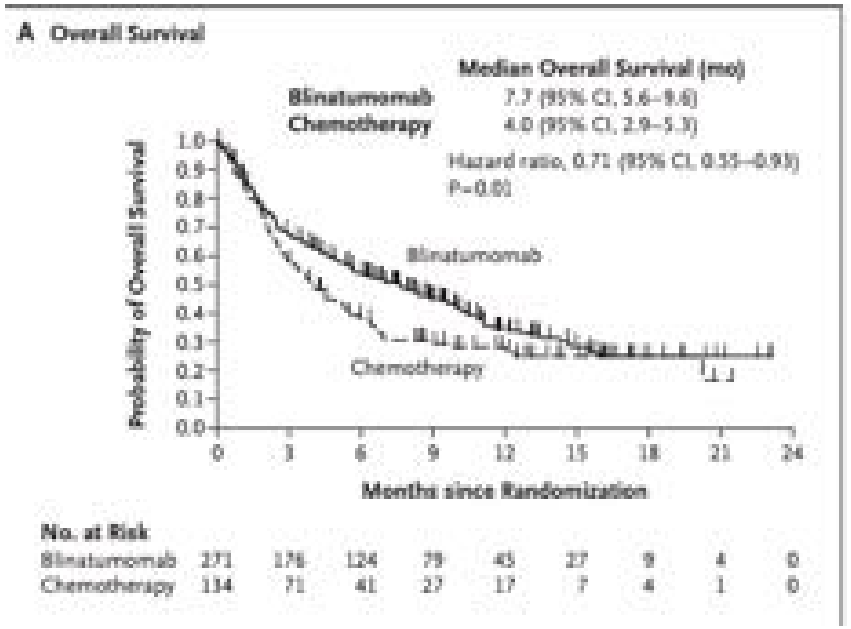
Ibrahim Aldoss et al Leukemia & lymphoma 2018
Shilpa Paul et al Clinical Clinical Lymphoma, Myeloma & Leukemia 2019

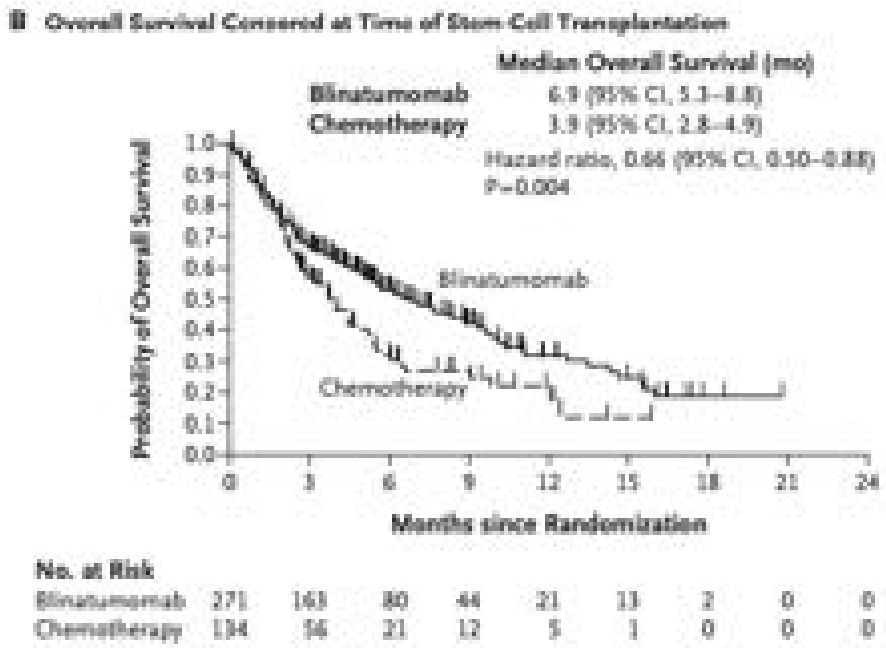
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Hagop Kantarjian, M.D., Anthony Stein, M.D., Nicola Gökbuget, M.D.,
Adele K. Fielding, M.B., B.S., Ph.D., Andre C. Schuh, M.D.





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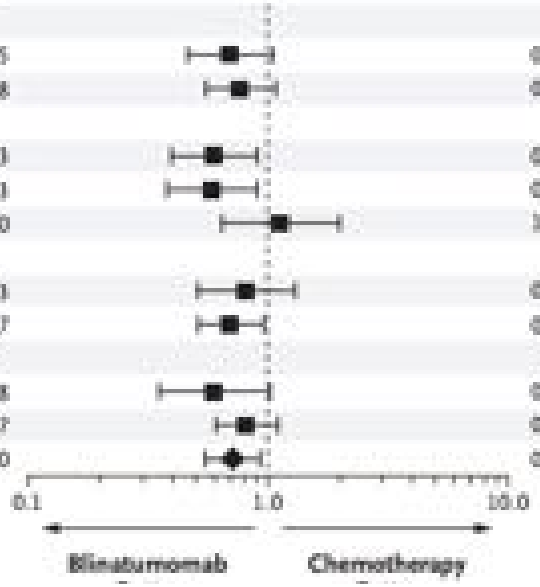
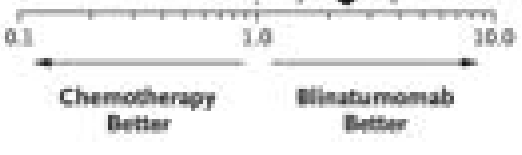
A Prespecified Subgroup Analysis of Overall Survival

Subgroup	Median Survival				Hazard Ratio (95% CI)
	Blinatumomab		Chemotherapy		
	no. of patients	*mo*	*no. of patients*	*mo*	
Age					
<35 yr	123	9.9	60	4.5	0.70 (0.46–1.06)
≥35 yr	148	5.6	74	3.8	0.77 (0.55–1.08)
Salvage-treatment phase					
First	114	11.1	65	5.3	0.60 (0.39–0.91)
Second	91	5.1	43	3.3	0.59 (0.38–0.91)
Third or later	66	3.7	26	3.0	1.13 (0.64–1.99)
Previous allogeneic stem-cell transplantation					
Yes	94	7.7	46	5.3	0.81 (0.51–1.29)
No	177	7.7	88	3.7	0.70 (0.51–0.96)
Bone marrow blasts					
<50%	84	11.5	38	6.8	0.60 (0.35–1.03)
≥50%	18	5.0	96	3.7	0.82 (0.61–1.10)
Overall	271	7.7	134	4.0	0.71 (0.55–0.93)



B Prespecified Subgroup Analysis of Remission Rate

Subgroup	Blinatumomab	Chemotherapy	Odds Ratio (95% CI)
	no. of events/no. of patients (%)		
Age			
<35 yr	53/123 (43.1)	15/60 (25.0)	2.27 (1.15–4.50)
≥35 yr	66/148 (44.6)	18/74 (24.3)	2.50 (1.34–4.66)
Salvage-treatment phase			
First	60/114 (52.6)	23/65 (35.4)	2.03 (1.08–3.80)
Second	36/91 (39.6)	7/43 (16.3)	3.37 (1.35–8.38)
Third or later	23/66 (34.8)	3/26 (11.5)	4.30 (1.11–15.12)
Previous allogeneic stem-cell transplantation			
Yes	38/94 (40.4)	5/46 (10.9)	5.56 (2.02–15.36)
No	81/177 (45.8)	28/88 (31.8)	1.81 (1.06–3.09)
Bone marrow blasts			
<50%	55/84 (65.5)	13/38 (34.2)	3.65 (1.63–8.17)
≥50%	64/186 (34.4)	20/96 (20.8)	1.99 (1.12–3.55)
Overall	119/271 (43.9)	33/134 (24.6)	2.40 (1.51–3.80)



Kantarjian H et al NEJM 2017

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Blin for MRD

blood 2018 131: 1522-1531
doi:10.1182/blood-2017-08-798322 originally published online January 22, 2018

Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia

Nicola Gökbuget, Hervé Dombret, Massimiliano Bonifacio, Albrecht Reichle, Carlos Graux, Christoph Faul, Helmut Diedrich, Max S. Topp, Monika Brüggemann, Heinz-August Horst, Violaine Havelange, Julia Stieglmaier, Hendrik Wessels, Vincent Haddad, Jonathan E. Benjamin, Gerhard Zugmaier, Dirk Nagorsen and Ralf C. Bargou

Figure S2. Overall survival by baseline remission status

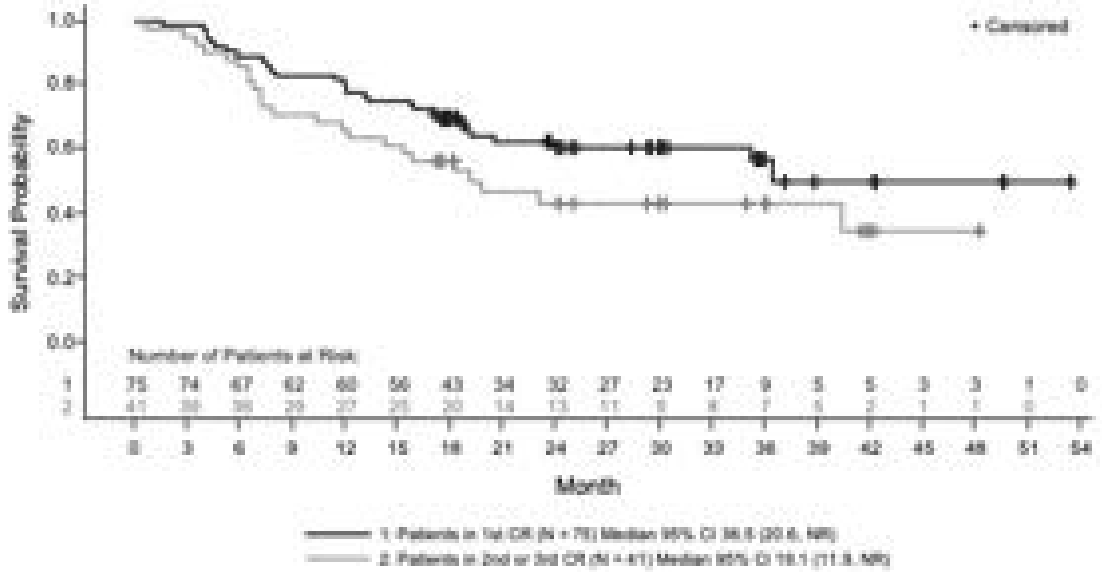
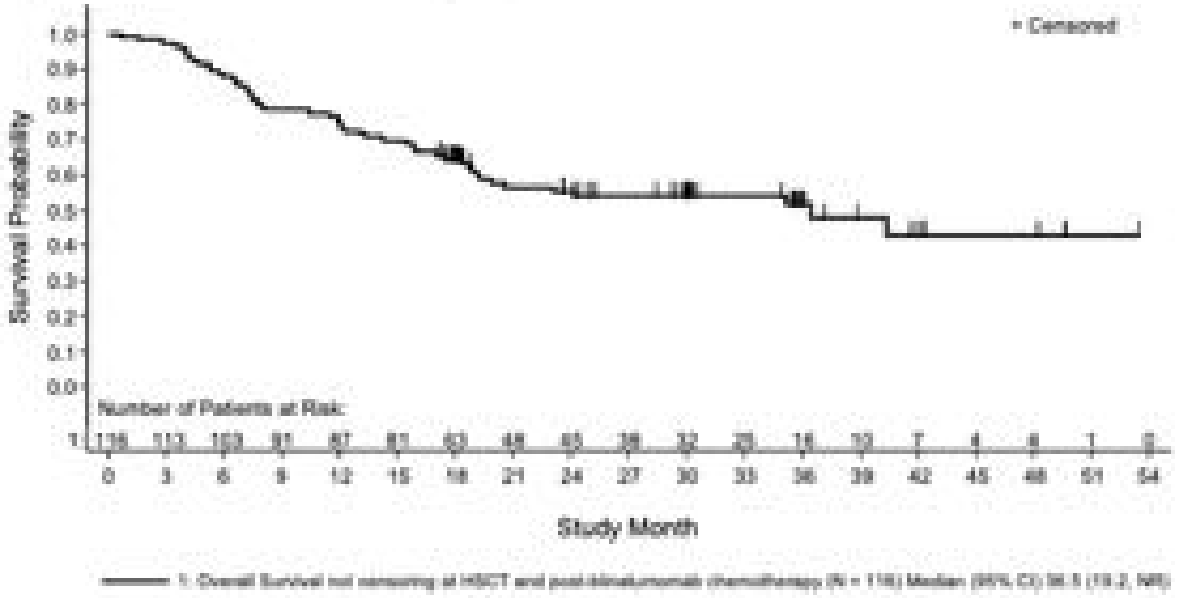


Figure S4. Overall survival among all patients treated



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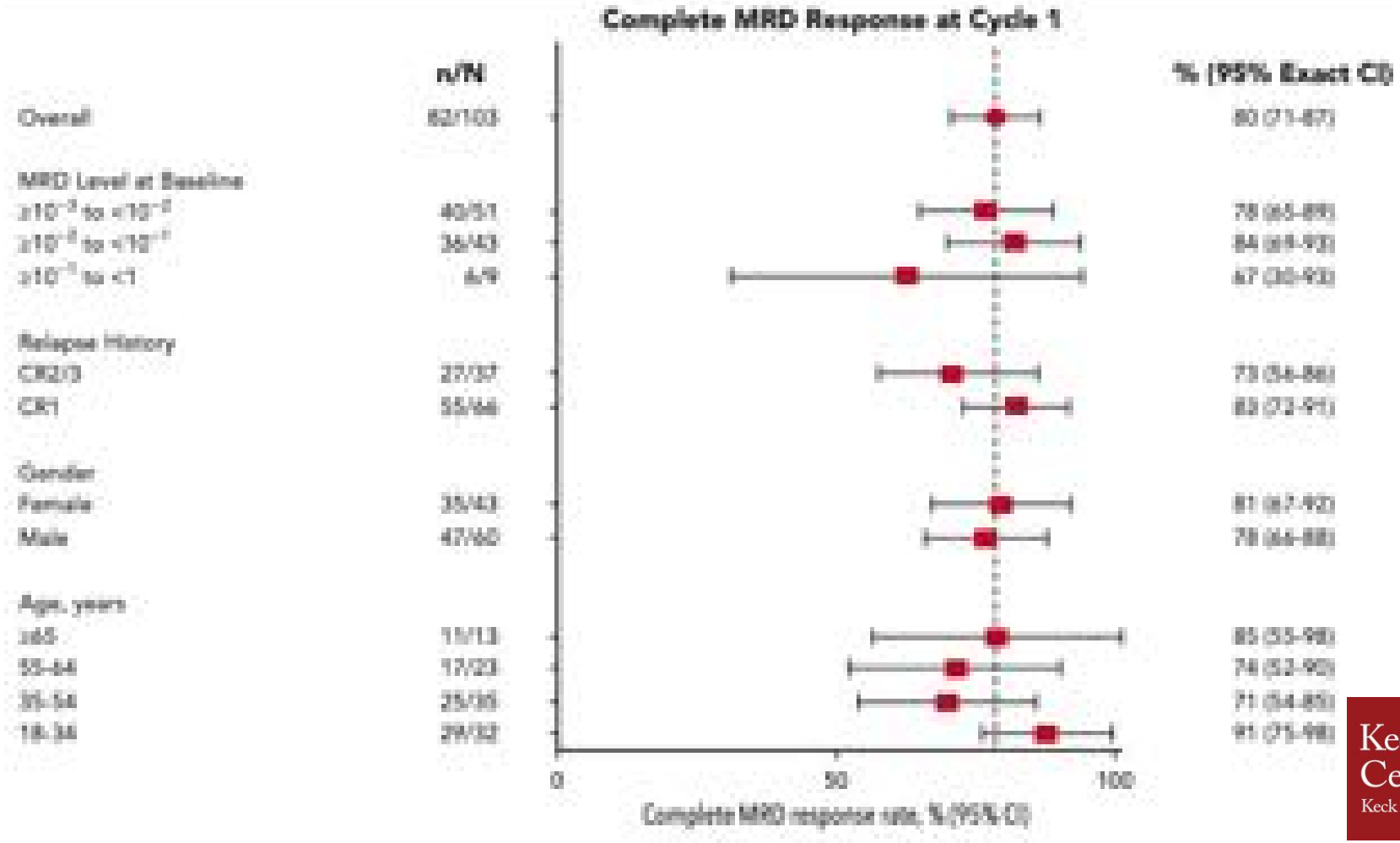

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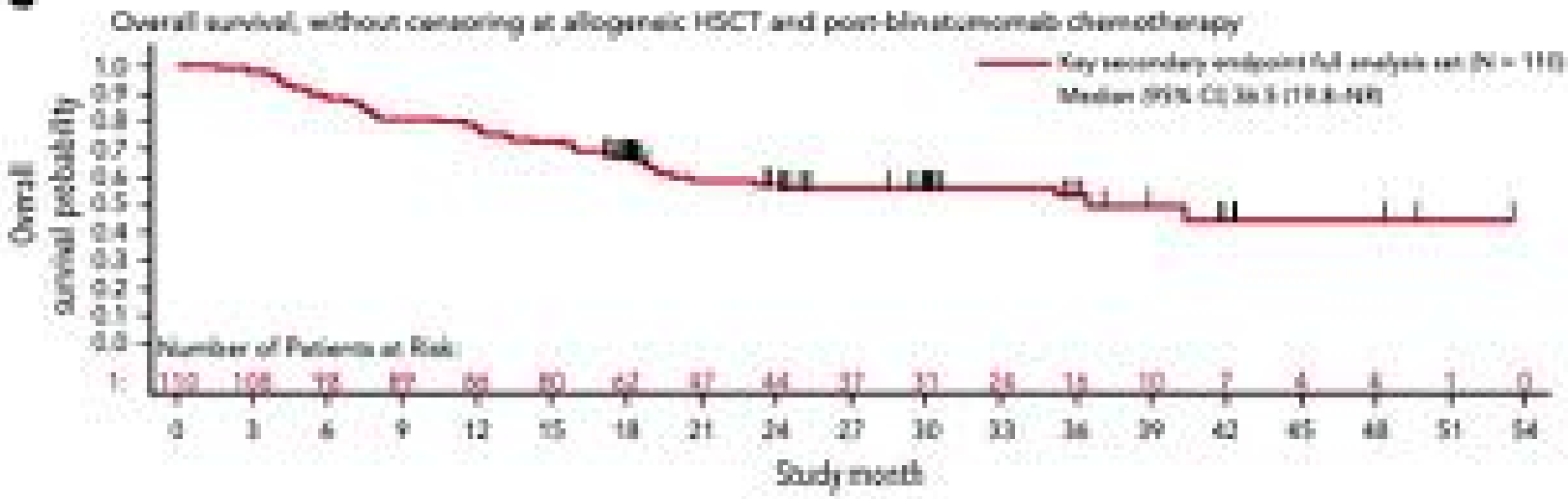

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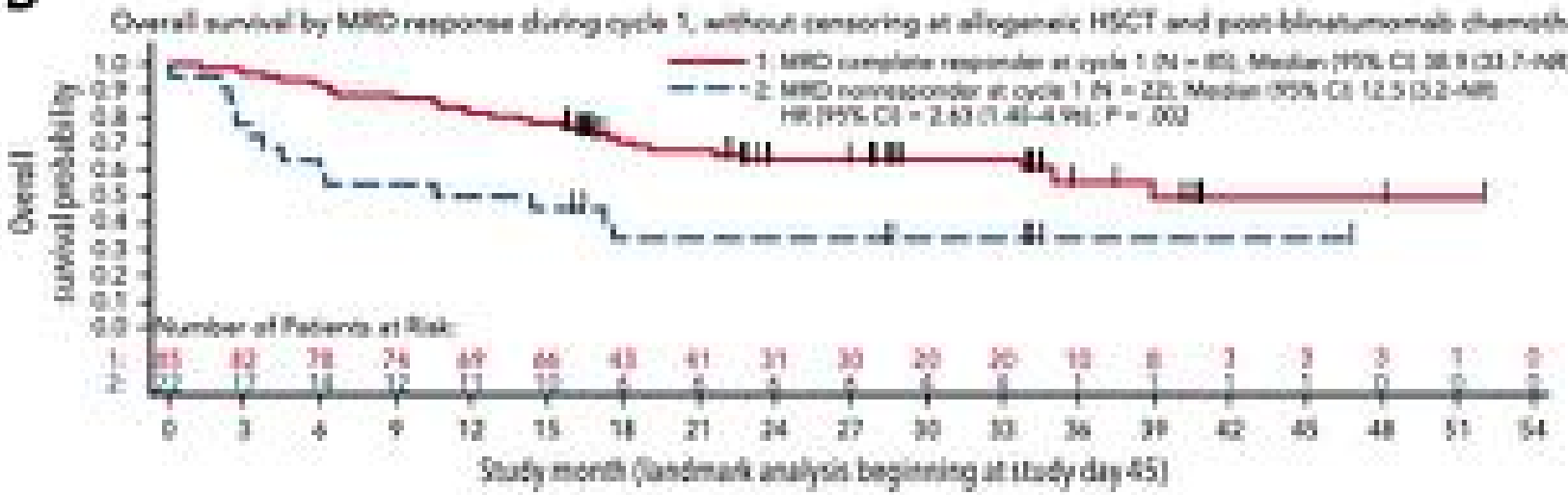

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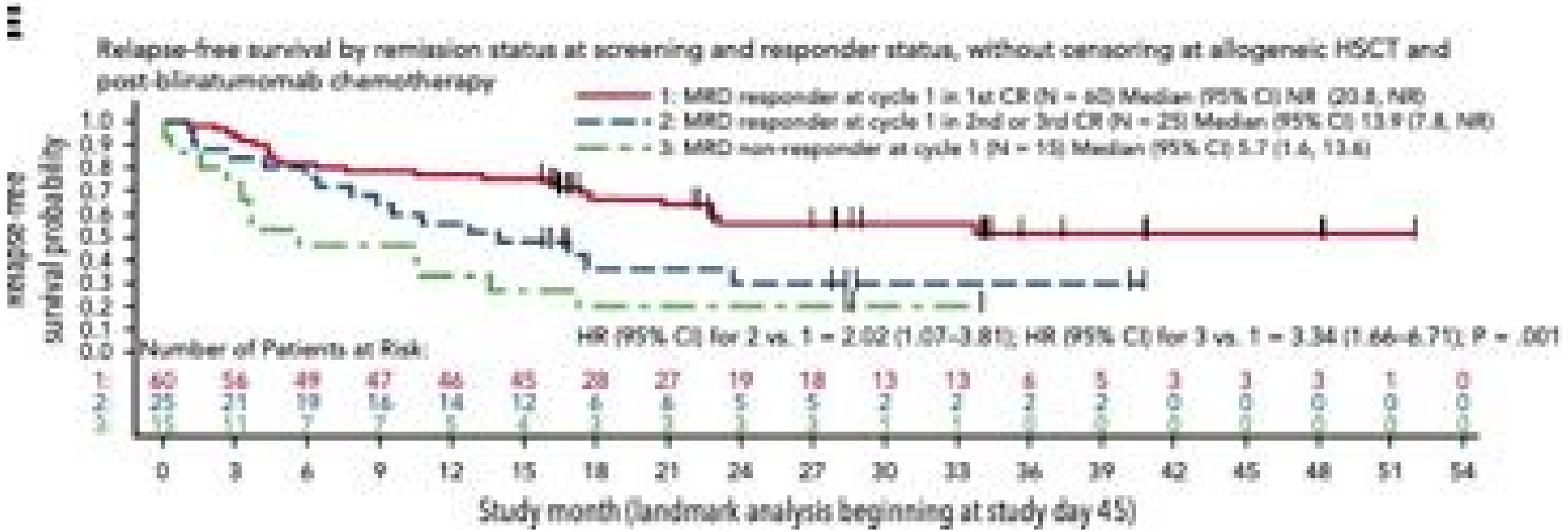

blood
2018 131: 1522-1531
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Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia

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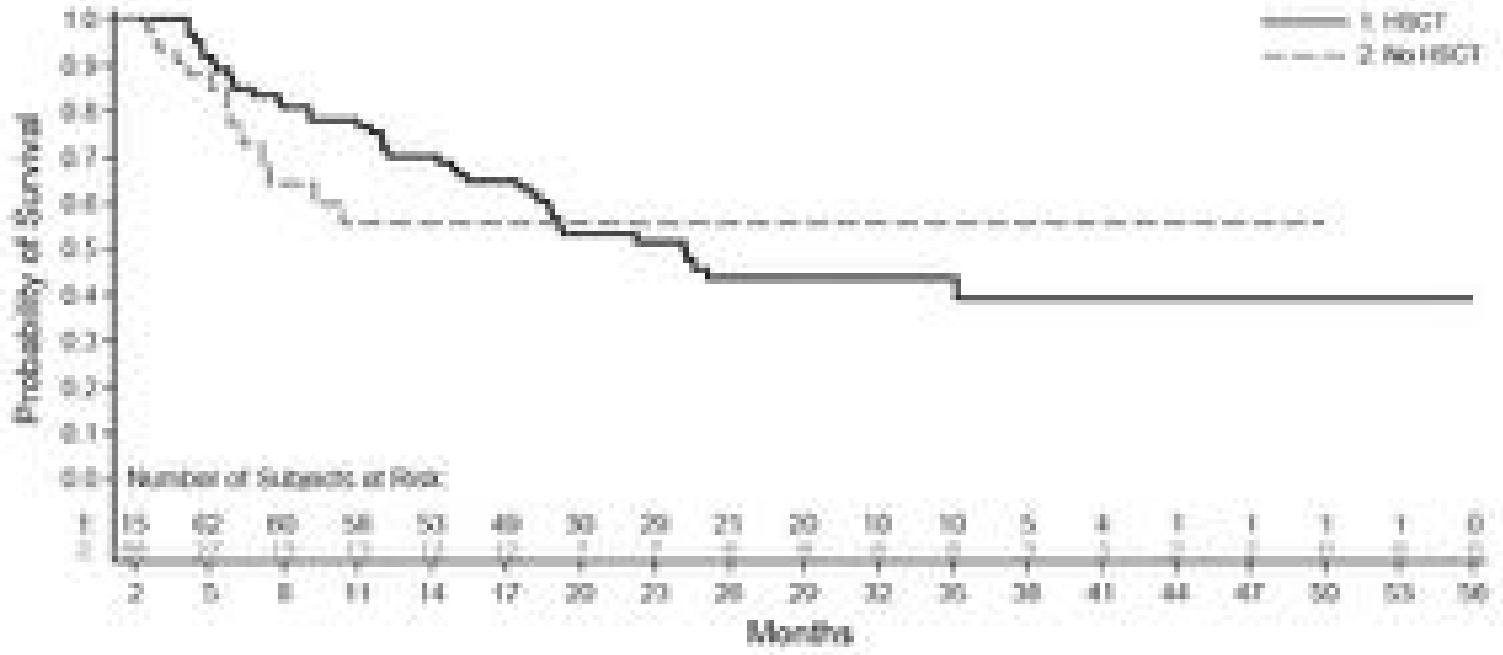
Figure S5. Simon-Makuch plot of relapse-free survival among all patients in the full analysis set by HSCT status



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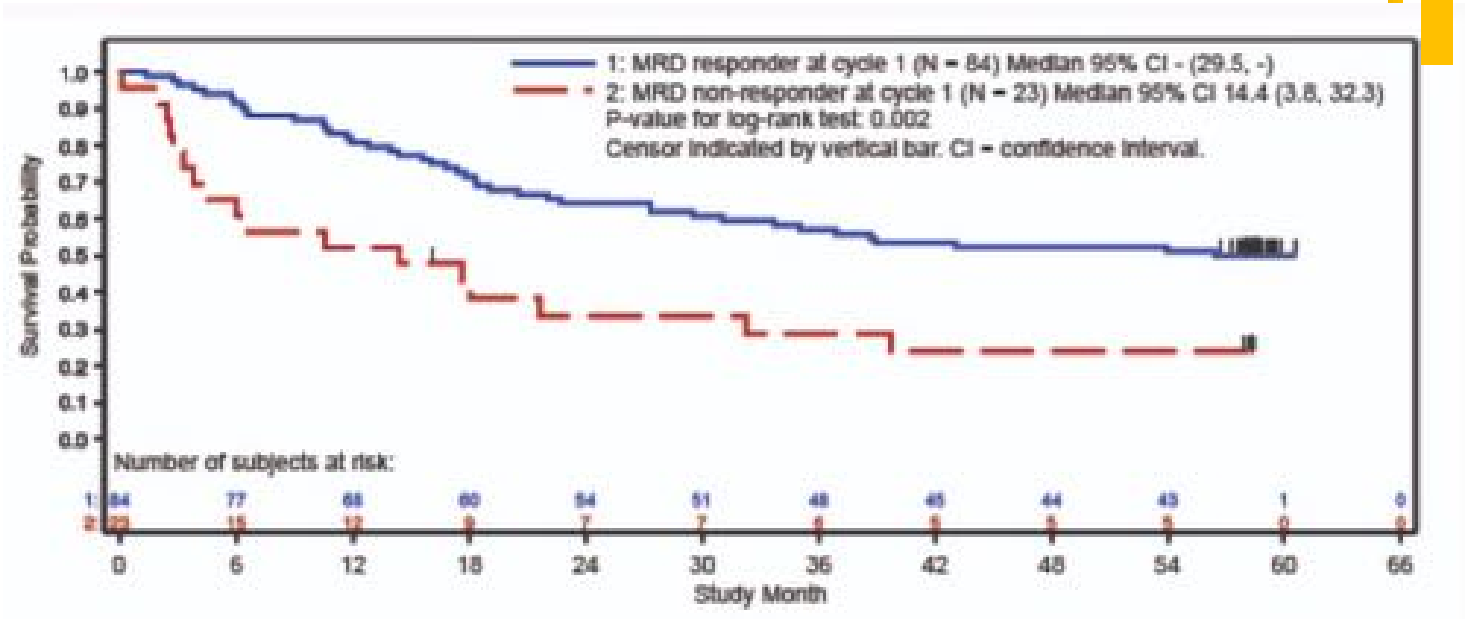
BLINATUMOMAB FOR MINIMAL RESIDUAL DISEASE (MRD) IN ADULTS WITH BCELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (BCPALL): MEDIAN OVERALL SURVIVAL (OS) NOT REACHED AT 5 YEARS FOR COMPLETE MRD RESPONDERS

- EHA 2019: Goekbuget N. 06/16/19; 267373; S1619



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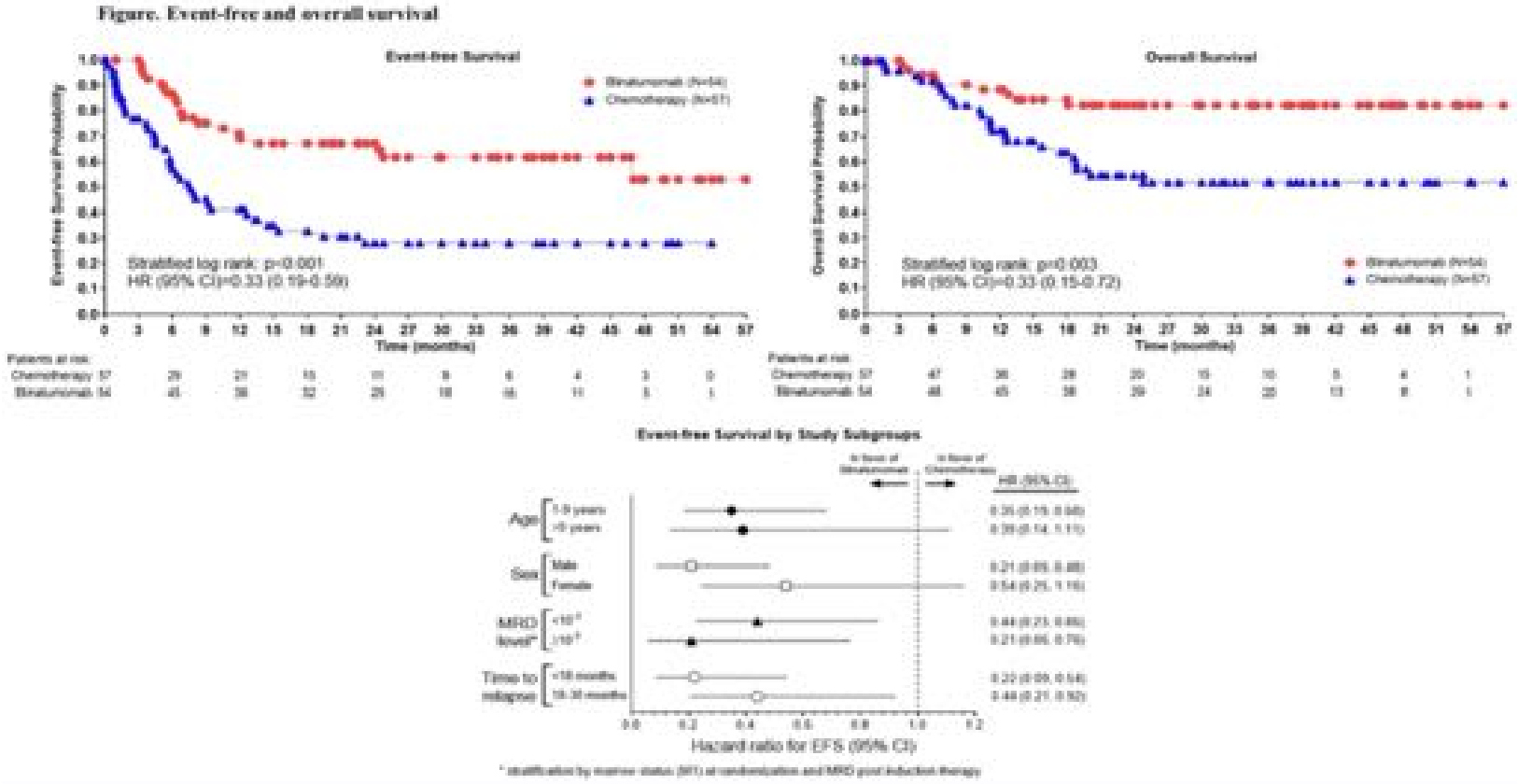
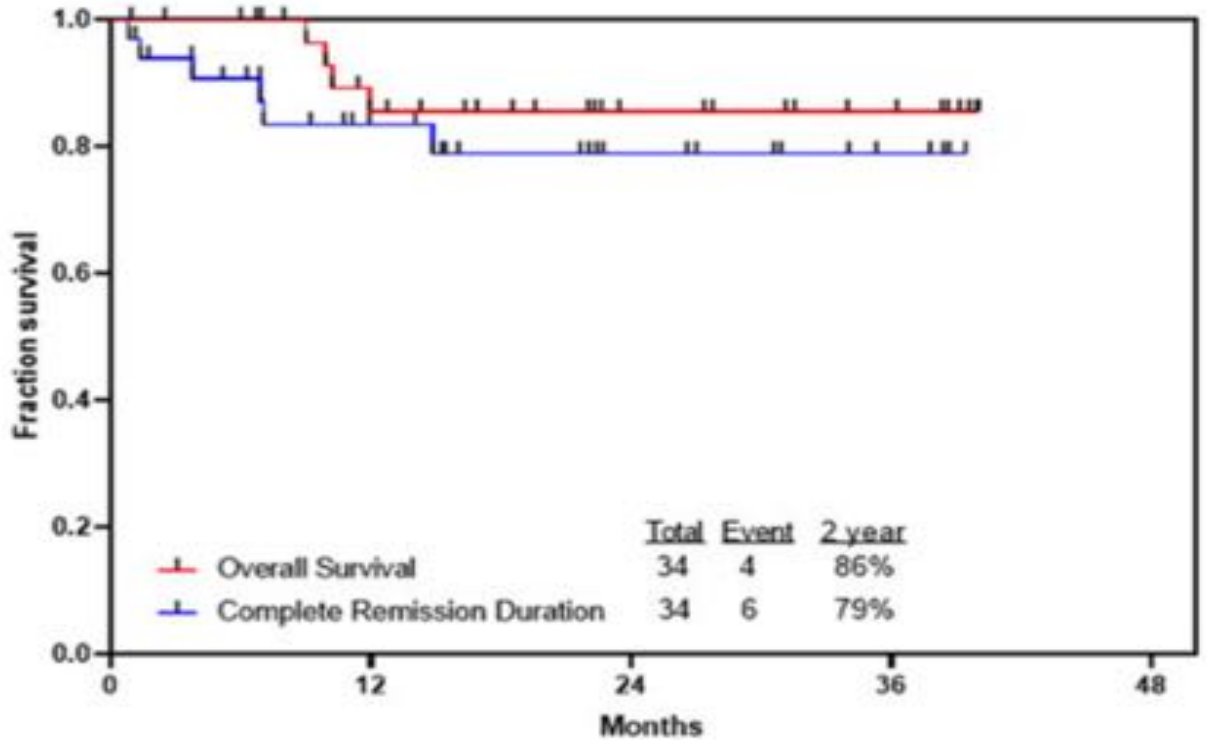
Superior Overall Survival with Blinatumomab Versus Chemotherapy As Pre-Transplant Consolidation Treatment in Children with High-Risk First-Relapse B-Cell Precursor Acute Lymphoblastic Leukemia (B-ALL): Longer Follow-up (FU) of a Phase 3 Randomized Controlled Trial (RCT)



Franco Locatelli,Gerhard Zugmaier,Carmelo Rizzari,Joan D Morris,Bernd Gruhn,Thomas Klingebiel,Rosanna Parasole,Christin Linderkamp,Christian Flotho,Arnaud Petit,Concetta Micalizzi,Yi Zeng,Deepali Dilip Pilankar,William N Kormany,Cornelia Eckert,Anja Moericke,Mary Sartor,Ondrej Hrusak,Christina Peters,Vaskar Saha,Luciana Vinti,Arend von Stackelberg, Superior Overall Survival with Blinatumomab Versus Chemotherapy As Pre-Transplant Consolidation Treatment in Children with High-Risk First-Relapse B-Cell Precursor Acute Lymphoblastic Leukemia (B-ALL): Longer Follow-up (FU) of a Phase 3 Randomized Controlled Trial (RCT), Blood, 2021, Figure 1

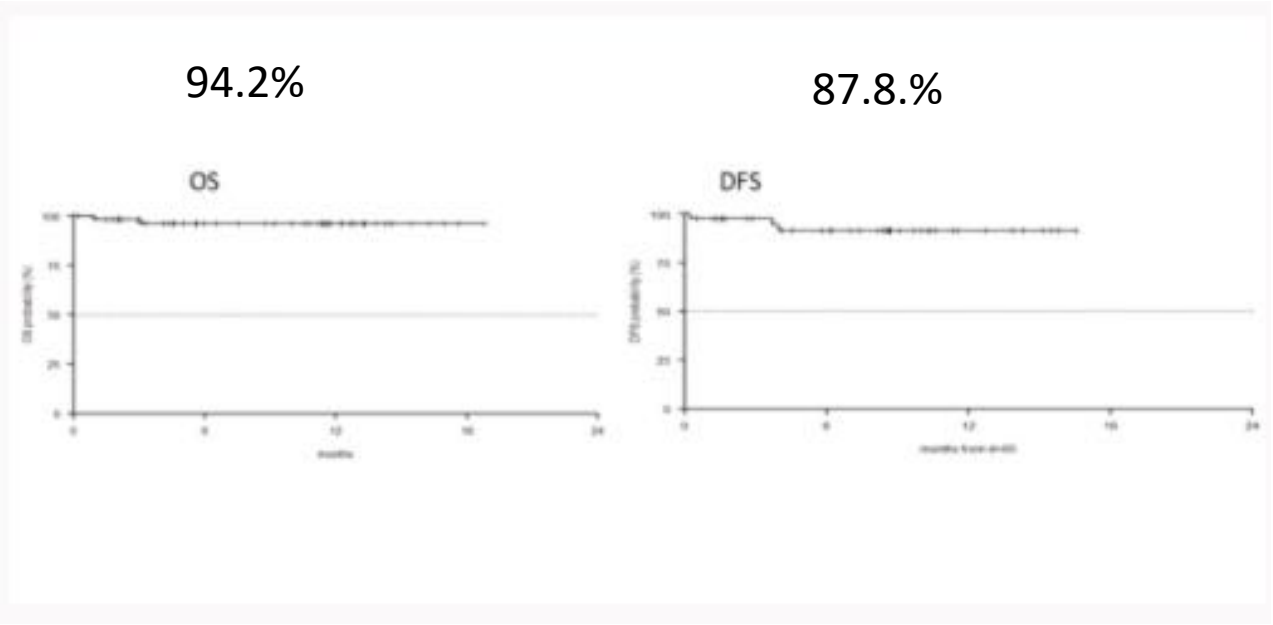
Hyper-CVAD and Sequential Blinatumomab in Adults with Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia: Results from a Phase II Study



Nicholas J. Short, MD,Hagop M. Kantarjian, MD,Farhad Ravandi, MBBS,Xuelin Huang, PhD,Alessandra Ferrajoli, MD,Tapan M. Kadia, MD,Philip A. Thompson, MB, MS,Yesid Alvarado, MD,Nitin Jain, MD,Musa Yilmaz, MD,Joseph D. Khoury, MD,Jeffrey L. Jorgensen, MD PhD,Sa A Wang, MD,Steven M. Kornblau, MD,Marina Konopleva, MD PhD,Guillermo Garcia-Manero, MD,Heather M Schroeder,Monica Kwari, BSN,Shilpa Paul, PharmD,Benjamin Nwakanme,Christopher Loiselle, BS,Rebecca Garris, MSc,Susan M. O'Brien, MD,Elias Jabbour, MD, Hyper-CVAD and Sequential Blinatumomab in Adults with Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia: Results from a Phase II Study, Blood, 2020,

Updated Results of the Gimema LAL2116 D-Alba Trial

- **Dasatinib 140 mg-Blinatumomab Combination for the Front-Line Treatment of Adult Ph+ ALL Patients**
- This is the first chemo-free induction-consolidation protocol for adult Ph+ ALL patients of all ages.
- Pre-phase prednisone 7 days 60 mg/m2 continued till day 24 then tapered down and stopped d32. IT chemo Q 2W during induction (85 days) total 6 doses then once monthly.
- Blin 28mcg/kg consolidation 2 cycles mandatory up to 5 cycles



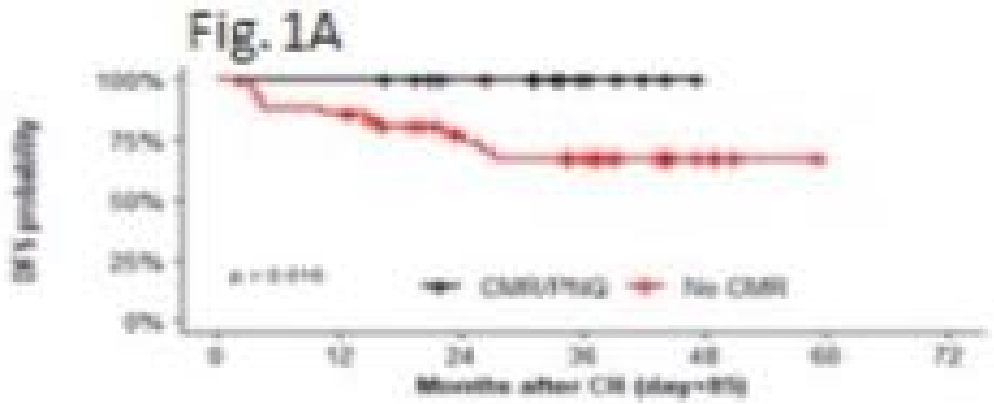
Sabina Chiaretti et al *Blood* (2019) 134 (Supplement_1): 740. https://doi.org/10.1182/blood-2019-128759. Abstract 614

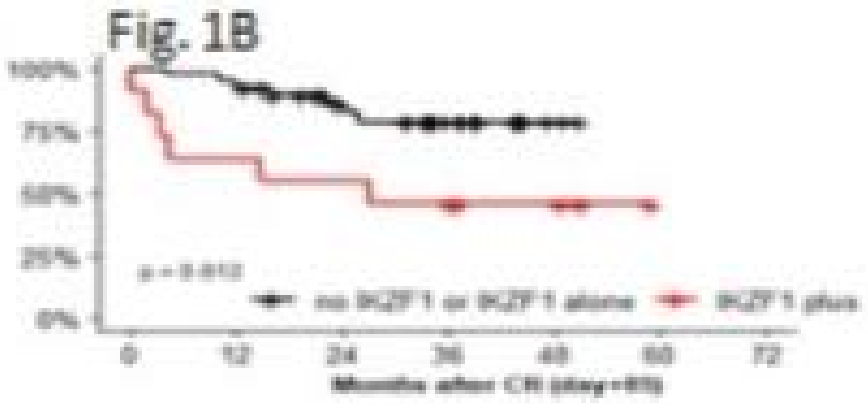
Gimema LAL2116 D-Alba Trial

- *IKZF1* deletion (54%)- 23.9% of patients were thus classified as *IKZF1 +* (i.e. *IKZF1* and/or *PAX5* and/or *CDKN2A/B* deletions).

- A significantly inferior DFS (61.4%, p=0.01) was observed in *IKZF1plus*

FORTY MONTHS UPDATE OF THE GIMEMA LAL2116 (D-ALBA) PROTOCOL AND ANCILLARY LAL2217 STUDY FOR NEWLY DIAGNOSED ADULT PH+ ALL





Sabina Chiaretti,(Abstract release date: 05/12/22) EHA Library. Chiaretti S. 06/10/22; 357216; P353

A phase II trial of a chemotherapy-free combination of ponatinib and blinatumomab in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

- Cycle 1- Ponatinib 30mg daily decreased- 15mg daily once a CMR was achieved.
- Blin up to 5 cycles, after completion of blin, ponatinib was continued for at least 5 years.
- All pts received 12 doses of prophylactic IT chemotherapy.

The 2-year EFS and OS rates in the ND cohort are 93%.

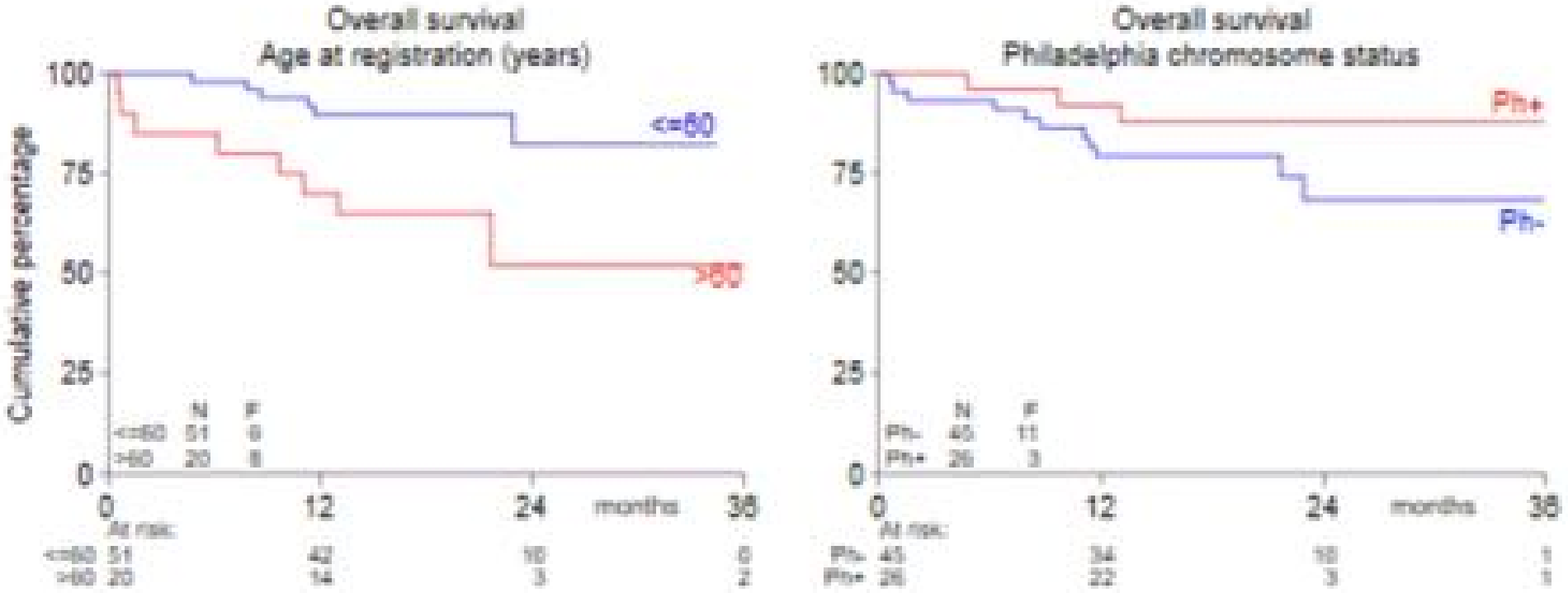
Among the 13 responding pts in the R/R cohort, 6 (46%) underwent SCT. The 2-year EFS and OS rates for the R/R cohort are 42% and 61%, and for the CML-LBP cohort are 33% and 60%, respectively.

55 pts were treated (35 ND, 14 R/R and 6 CML-LBP).

Characteristic N (%) / median [range]	Category	ND Ph+ ALL N = 35	R/R Ph+ ALL N = 14	CML-LBP N=6
Age (years)		57 [22-83]	38 [24-61]	69 [29-82]
CD19 expression		99.8 [74.9-100]	99.9 [98.6-100]	99.7 [98.3-99.9]
BCR-ABL1 transcript	p190 p210	26 (74) 9 (26)	13 (93) 1 (7)	0 6 (100)
Line of therapy	Frontline Primary refractory Salvage 1 Salvage 2+	35 (100) 0 0 0	0 2 (14) 6 (43) 6 (43)	4 (67) 0 1 (17) 1 (17)
Response				
CR		21/23 (91)	11/13 (85)	4/6 (67)
CR/CRi		22/23 (96)	12/13 (92)	5/6 (83)
CMR after 1 cycle		21/33 (64)	10/14 (71)	1/6 (17)
CMR overall		28/33 (85)	11/14 (79)	2/6 (33)

Nicholas James Short, Hagop M. Kantarjian,..., Rebecca Garris, and Elias Jabbour
Journal of Clinical Oncology 2022 40:16_suppl, 7009-7009

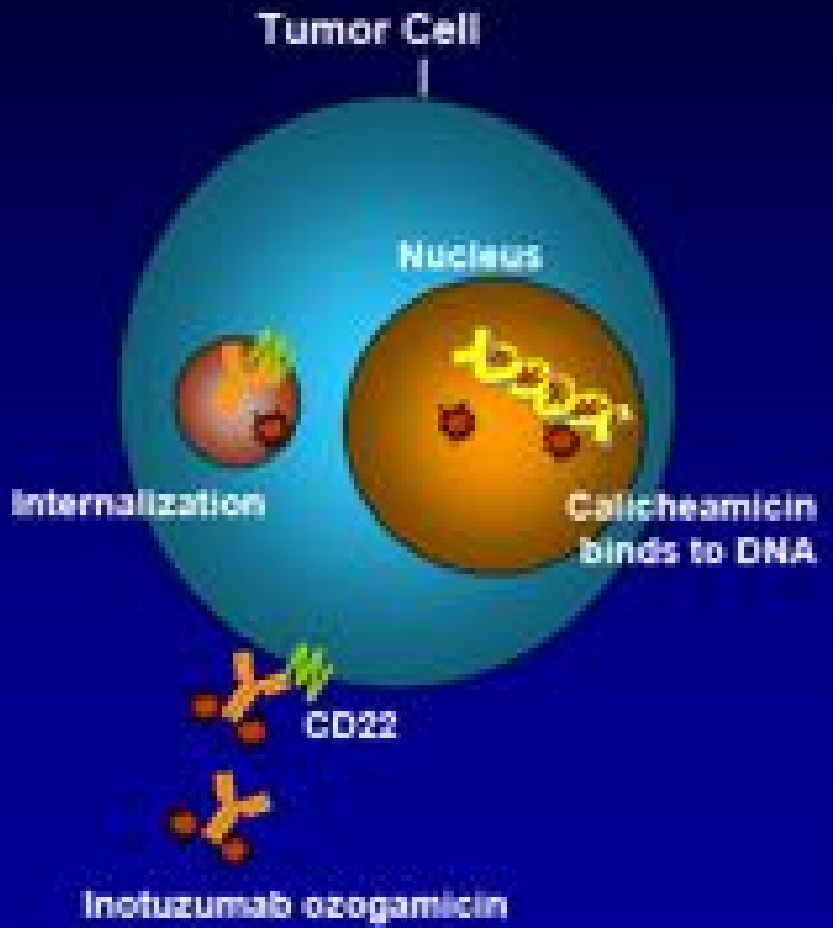
BLINATUMOMAB ADDED TO PREPHASE AND CONSOLIDATION THERAPY IN NEWLY DIAGNOSED PRECURSOR B-ALL IN ADULTS. A PHASE II HOVON TRIAL



Anita Rijneveld, Patrycja Gradowska, Jan Cornelissen
(Abstract release date: 05/12/22) EHA Library. Rijneveld A. 06/10/22; 357229; P366

Inotuzumab in ALL. Mechanisms of Action

- The antibody-antigen complex is rapidly internalized upon binding to CD22
- Calicheamicin is released inside the tumor cell
  - Calicheamicin is more potent than other cytotoxic chemotherapeutic agents
- Calicheamicin binds to DNA, inducing double-stranded DNA breaks
- Development of DNA breaks is followed by apoptosis of the tumor cell



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Inotizumab

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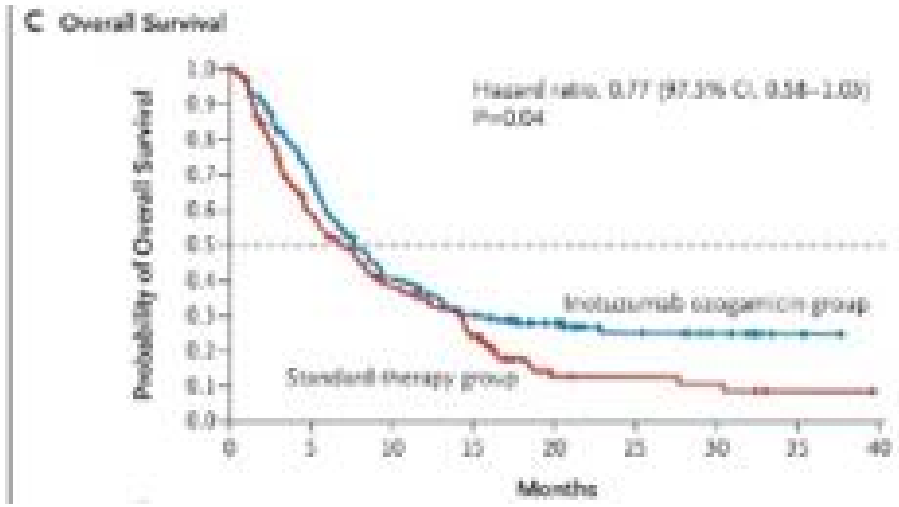
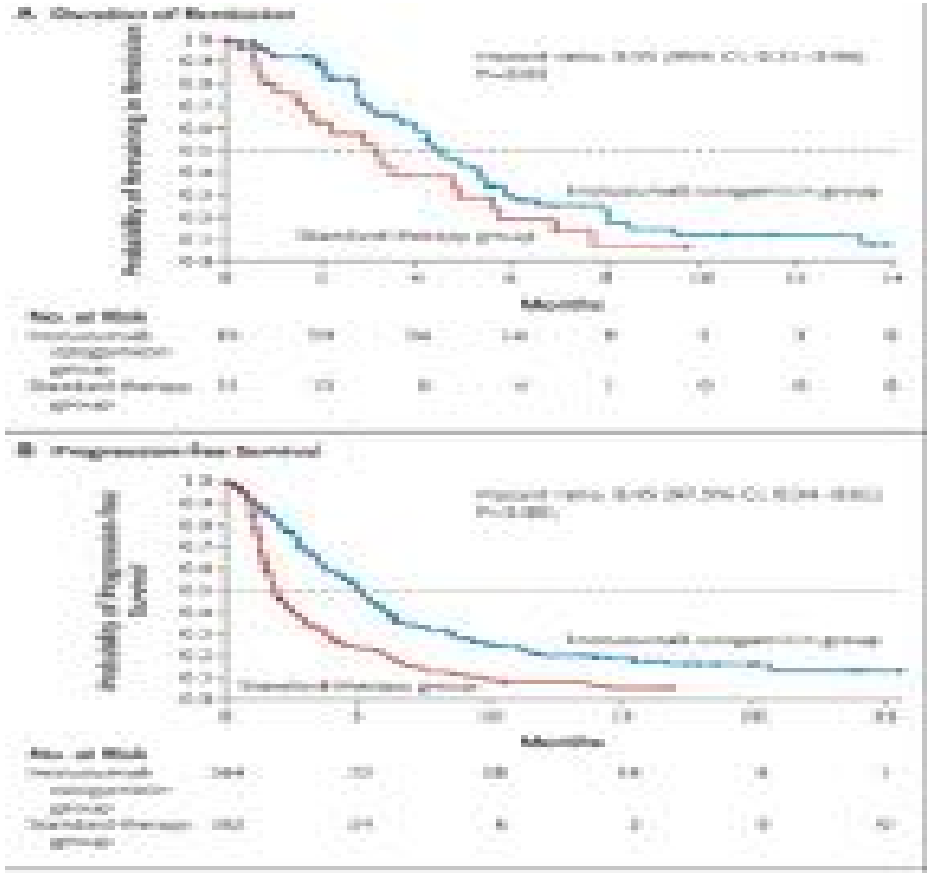
Table 5. Inotuzumab ozogamicin studies.

Study	ALL setting	*N*	Prior alloHCT (%)	CR/CRh % (MRD response %)	Median CRD/PFS (months)	Median OS (months)
Kantarjian et al. (Phase II) [126]	r/r Ph+ & Ph−	49	7 (14)	57 (63)	6.3	5.1
Phase II et al. (expansion of phase II) [127]	r/r Ph+ & Ph−	90	10 (11)	58 (72)	7	6.2
Kantarjian et al. (Phase III) [128]	r/r Ph+ & Ph−	109	17 (16)	81 (78)	5	7.7





Kantargian H et Lancet Oncology 2012
Kantargian H et al cancer 2013
Kantarjian HM et al NEJM 2016

Inutuzumab

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Table 2 Inotuzumab Clinical Trial Results

Clinical Trial	Patient Population	Inotuzumab Treatment Schema	Response	MRD Negativity	Median Overall Survival, mo
Inotuzumab monotherapy					
INO-VATE[12]	R/R Ph⁻ ALL (N = 109)	0.8 mg/m² D1 0.5 mg/m² D8,15	ORR: 81% CR: 30% CRi: 45%	78%	7.7
Inotuzumab combinations					
Inotuzumab plus bosutinib	R/R Ph⁺ ALL⁺ (N = 16)	0.8 mg/m² D1 0.5 mg/m² D8, 15,22 1.0 mg/m² D1 cycles 2-6	ORR: 79% CCyR: 81%	NA	10.7
Inotuzumab plus mini-hyperCVD[7]	Treatment naive elderly, Ph⁻ ALL (N = 52)	1.3-1.8 mg/m² cycle 1 1.0-1.3 mg/m² cycles 2-4	ORR: 87% CR: 65% CRp: 10% CRi: 2%	86%	Not reached
Inotuzumab plus mini-hyperCVD[7]	R/R Ph⁻ ALL (N = 58)	1.3-1.8 mg/m² cycle 1 1.0-1.3 mg/m² cycles 2-4	ORR: 78% CR: 59% CRp: 17% CRi: 2%	84%	11
Inotuzumab plus mini-hyperCVD[7] ± blinatumomab	Salvage 1, Ph⁻ ALL (N = 48)	1.3-1.8 mg/m² cycle 1* 1.0-1.3 mg/m² cycles 2-4*	ORR: 92% CR: 73% CRp: 17% CRi: 2%	83%	25

Shilpa Paul et al Clinical lymphoma, Myeloma, & leukemia 2019

Jabbour E et al blood 2017
Kartanjian H Lancet oncol 2018

MiniHCVD-INO in ALL Design

- Dose reduced HyperCVAD for 8 courses
- Cyclophosphamide (150 mg/m2x6) **50% does reduction**.
- Dex 20 mg **50% dose reduction.**
- **No Anthracycline.**
- Methotrexate (250 mg/m^2) **75% does reduction.**
- Cytarabine (0.5g/m^2x4) **83% dose reduction.**
- Inotuzumab on D3 (first 4 courses)
- Rituximab D2,8 for x4 course CD20+
- IT chemotherapy days 2,8 first 4 courses.
- POMP for 3 years.

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Kartanjian H Lancet oncol 2018

Inotuzumab Ozogamicin in Combination With Low-Intensity Chemotherapy (Mini-HCVD) With or Without Blinatumomab Versus Standard Intensive Chemotherapy (HCVAD) as Frontline Therapy for Older Patients With Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Propensity Score Analysis

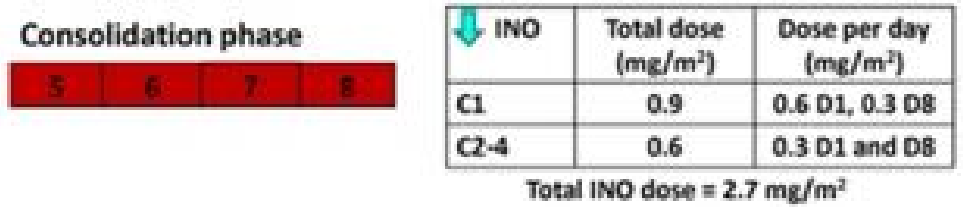


Figure 1. The treatment schedule of mini-hyperfractionated cyclophosphamide, vincristine, and dexamethasone (mini-HCVD) plus inotuzumab ozogamicin (INO) with or without blinatumomab (Blina) is illustrated. Ara-C indicates cytosine arabinoside (cytarabine); C1, cycle 1; C2-4, cycles 2 through 4; D1, day 1; D8, day 8; IT, intrathecal; MTX, methotrexate; POMP, prednisone, vincristine, methotrexate, and 6-mercaptopurine.

Jabbour JE. et al cancer journal August 2019

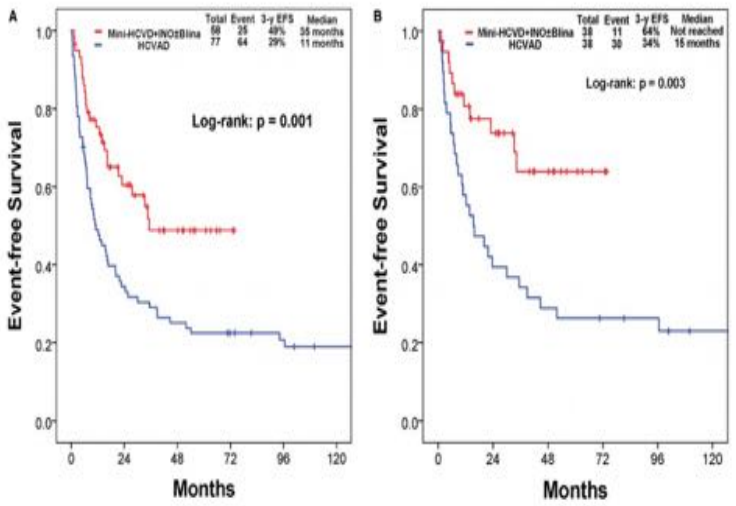
MiniHCVD-INO+-Blin

TABLE 2. Responses and Outcomes Before and After Matching

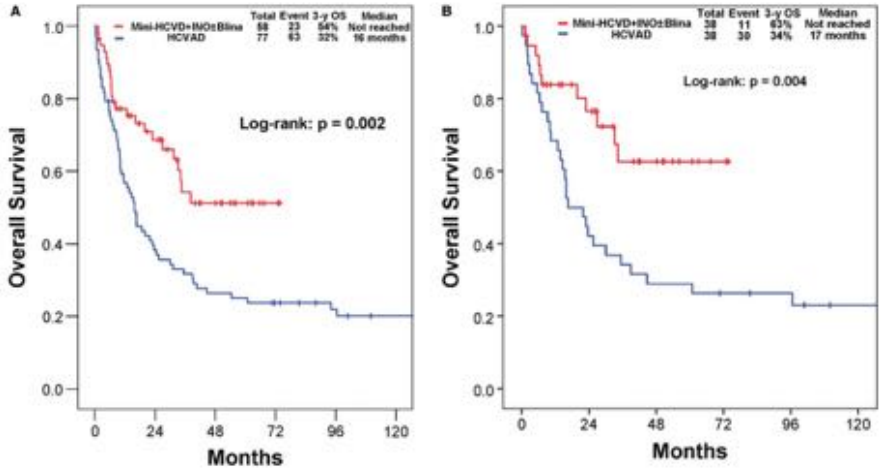
	Prematched Cohorts			Matched Cohorts		
	Mini–HCVD-INO ± Blina, N = 58	HCVAD, N = 77	*P*	Mini–HCVD-INO ± Blina, N = 38	HCVAD, N = 38	*P*
Response: No./Total No. (%)						
CR/CRi/CRp	53/57 (98)	68/77 (88)	.037	33/34 (97)	34/38 (90)	.361
Early death	0 (0)	6 (8)	.030	0	2 (5)	.493
Death in CR within 3 mo	3 (5)	13 (17)	.032	2 (5)	5 (13)	.215

Abbreviations: Blina, blinatumomab; CR, complete response; CRi, complete response without complete hematologic recovery; CRp, complete response without platelet recovery; HCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; INO, inotuzumab ozogamicin; Mini–HCVD, mini–hyperfractionated cyclophosphamide, vincristine, and dexamethasone.

DFS



OS



Jabbour JE. et al cancer journal August 2019

Updated results from a phase II study of mini-hyper-CVD (mini-HCVD) plus inotuzumab ozogamicin (INO), with or without blinatumomab (Blina), in older adults with newly diagnosed Philadelphia chromosome (Ph)-negative B (ALL)

- 73 (99%) responded (CR in 89%). MRD –eg 80% 1 cycle and in 94% overall.
- The 30-day mortality rate was 0%.
- (14%) relapsed, 4 (5%) underwent SCT, 33 (42%) remain in ongoing continuous remission, and 31 (39%) died in remission.
- The 5-year OS

60-69 years without poor-risk cytogenetics (n=37), 69%

60-69 with poor-risk cytogenetics (n=13), 39%

age ≥70 without poor-risk cytogenetics (n=24) 36%

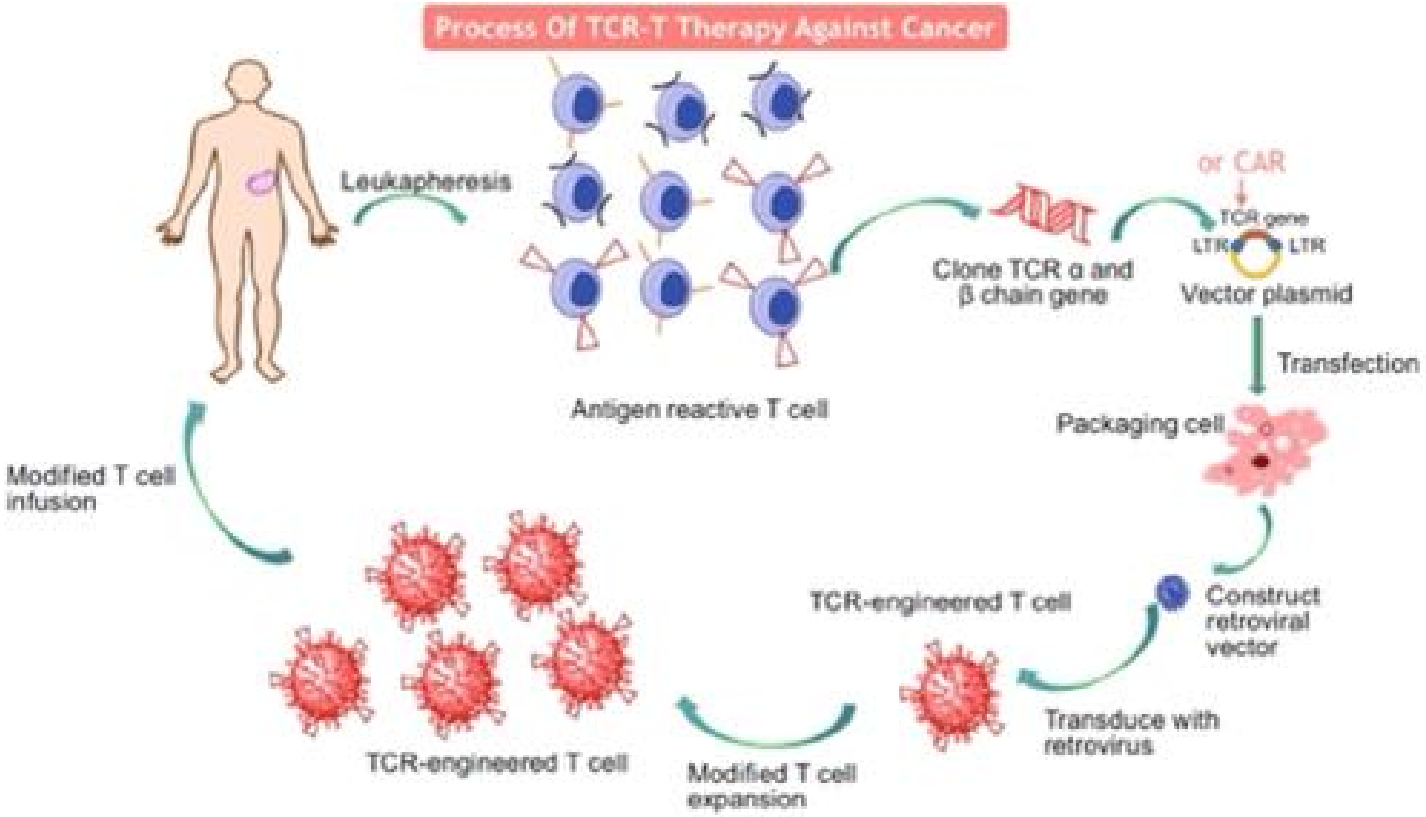
age ≥70 with poor-risk cytogenetics (n=6) 0%.

Characteristic	Category	N (%) / Median [range]
Age (years)		68 [60-87]
	≥70	30 (38)
Karyotype	Diploid	26 (33)
	HeH	5 (6)
	Ho-Tr	12 (15)
	Tetraploidy	3 (4)
	Complex	3 (4)
	t(4;11)	1 (1)
	Misc	15 (19)
	IM/ND	15 (19)
CNS disease at diagnosis		4 (5)
CD19 (%)		99.5 [26-100]
CD22 (%)		96.9 [27-100]
CD20	≥ 20%	44/73 (60)
TP53 mutation		24/61 (39)

Walid Macaron, Hagop M. Kantarjian, , and Elias Jabbour
Journal of Clinical Oncology 2022 40:16_suppl, 7011-7011

CAR T cells/ “a living drug”,

- CD19- targeted Chimeric antigen receptor T cells



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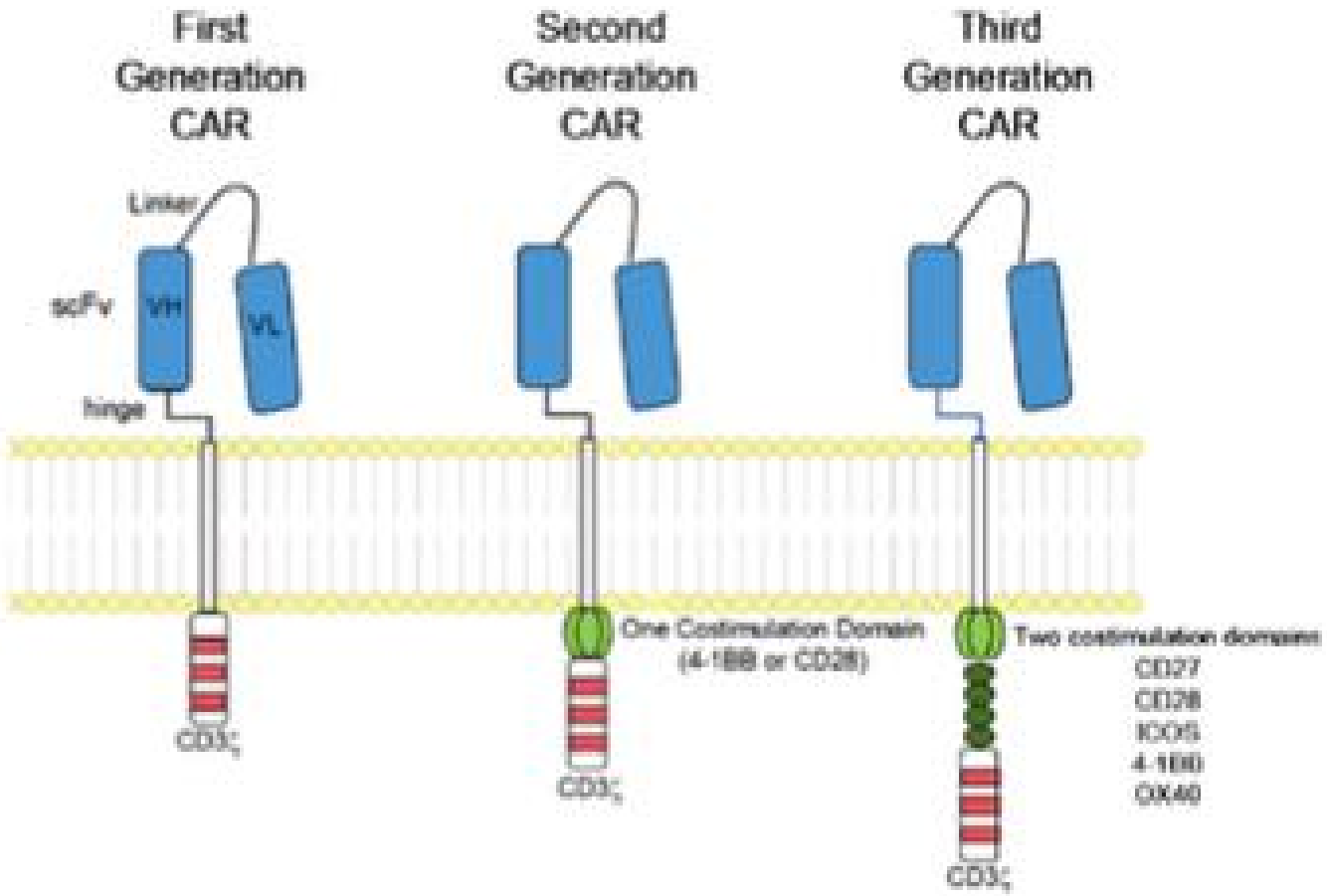

e 1. CAR structure, according to signaling domains. CAR molecules link scFv to intracellular signaling domains. The intracellular component les the CD3ζ alone (first generation) or in combination with 1 (second generation) or 2 (third generation) costimulatory domains. Reprinted with ission.[45]

Maus MV et al blood 2014

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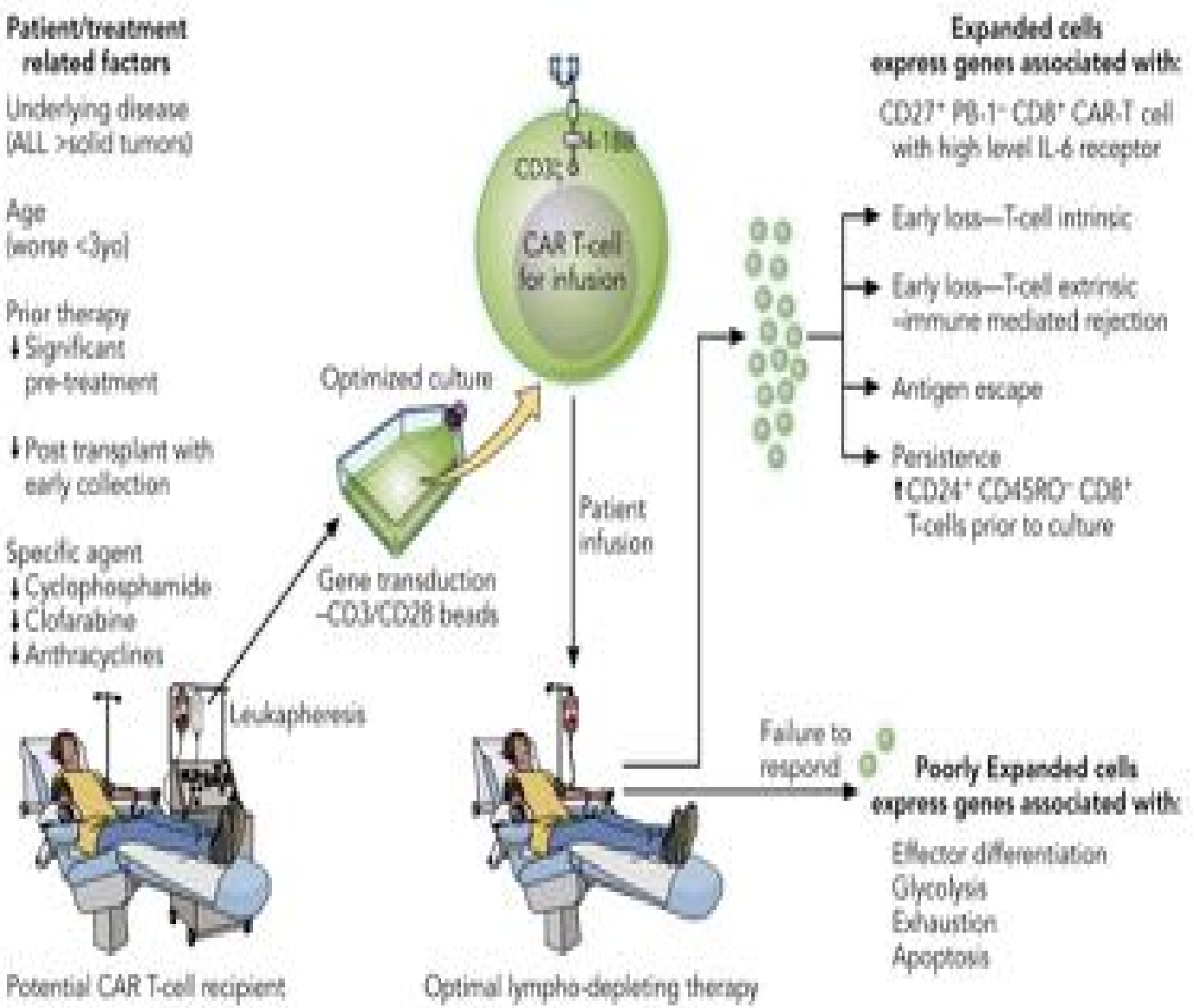

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Table 3 CAR-T Clinical Trial Results

Co-stimulatory Domain	Patient Population	Response	Overall Survival
4-1BB	R/R pediatric and adult ALL (N = 75[a])	CR: 60%	Estimated 12-month: 76%
CD28	R/R adult ALL (N = 53)	CR: 83%	Median: 13 mo

Table 3. CAR T cells studies.

Center	Age group	*N*	Prior alloHCT	CR/Cri % (MRD %)	LFS, RFS, DFS	OS
UPenn/CHOP [97]	Pediatrics/adults	30	15	90 (79)	EFS = 67% (at 6 months)	78% (at 6 months)
MSKCC [98]	Adults	16	4	88 (75)	NR	NR
NCI [99]	Pediatrics/adults	21	8	67 (86)	LFS = 79% (at 4.8 months)	52% (at 6 months)
MDACC [75]	Adults	17	17	–	PFS = 53% (at 1 year)	63% (at 1 year)
FHRCC [100]	Adults	29	11	93 (86)	NR	NR

Reference	Program CAR	Population	Response	CRS	Neurologic toxicity
Maude et al.[4]	CHOP/HUP 4-1BB	N = 30 (r/rALL) Peds & Adults	CR = 90%	100% CRS 27% severe	43% total
Maude et al.[5]	Novartis Multicenter 4-1BB	N = 75 Peds & AYA	CR = 81% MRDNeg = 81%	77% total	13% Gr 3
Park et al.[6]	MSKCC CD28	N = 53 adults	CR = 83% MRDNeg = 67%	85% total 26% severe (1 Gr5)	42% Gr 3-4
Lee et al.[3]	NCI CD28	N = 21 Peds & AYA	CR = 67%	76% CRS 28% severe	29% total
Turtle et al.[7]	Seattle 4-1BB	N = 30 adults	CR = 93%	83% CRS	50% severe
Gardner et al.[2]	Seattle 4-1BB	Peds & AYA N = 45	CR = 93% MRDNeg = 93%	93% CRS 23% severe	49% total 21% Gr 3–4

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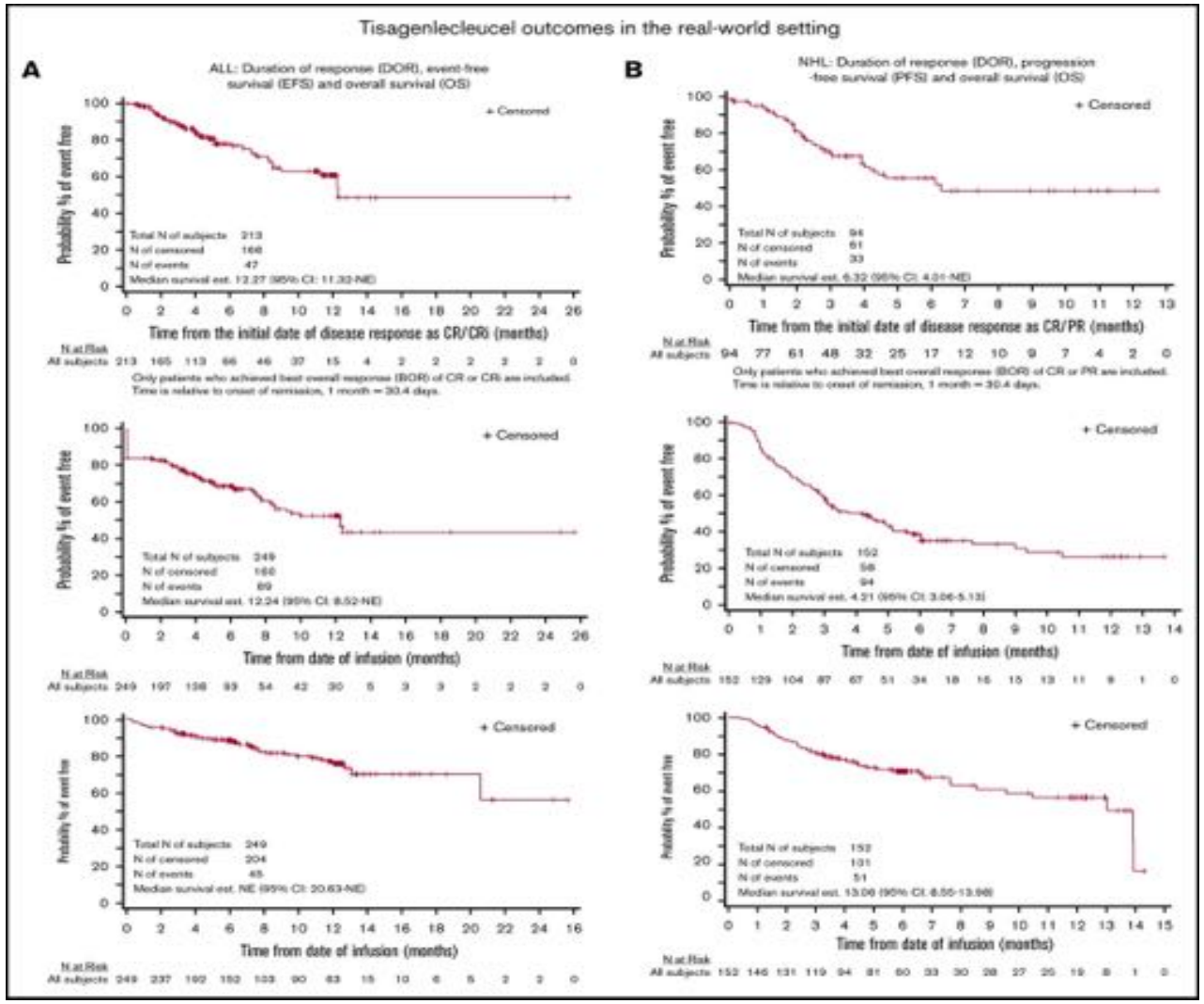
Real-World Outcomes for Pediatric and Young Adult Patients with Relapsed or Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (ALL) Treated with Tisagenlecleucel: Update from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry

Baseline characteristics (all infused patients)	<18y (N=309)	≥18y (N=142)	All patients (N=451)
Median age at infusion, years (range)	10.3 (0.4–17.9)	22.8 (18.0–26.2)	13.9 (0.4–26.2)
Median prior lines of therapy, n	3	4	3
Down syndrome, n (%)	23 (7.4)	2 (1.4)	25 (5.5)
Karnofsky/Lansky score <80, n (%)	37 (12.0)	23 (16.2)	60 (13.3)
Disease status prior to infusion, n (%)			
Relapsed/primary refractory	148 (47.9)/40 (12.9)	89 (62.7)/18 (12.7)	237 (52.5)/58 (12.9)
≥Second relapse	68 (22.0)	46 (32.4)	114 (25.3)
Morphologic CR	120 (38.8)	35 (24.6)	155 (34.4)
MRD negative	58 (18.8)	19 (13.4)	77 (17.1)
MRD positive	59 (19.1)	14 (9.9)	73 (16.2)
Cytogenetics, n (%)			
Abnormal 11q23/MLL rearrangement			
Positive	47 (15.2)	15 (10.6)	62 (13.7)
Ph+ ALL prior to infusion			
Positive	16 (5.2)	15 (10.6)	31 (6.9)
Prior treatment, n (%)			
Allogeneic HCT	84 (27.2)	46 (32.4)	130 (28.8)
Blinatumomab/inotuzumab	42 (13.6)/18 (5.8)	37 (26.1)/27 (19.0)	79 (17.5)/45 (10.0)
CAR-T cell therapy	6 (1.9)	2 (1.4)	8 (1.8)
Dosing			
Median CAR-positive T-cell dose,* n x 10^6 cells/kg (range)	2.0 (0.1–4.6)	1.2 (0.1–3.9)	1.7 (0.1–4.6)
Efficacy outcomes	**N=230**	**N=92**	**N=322**
BOR of CR/CRi % (95% CI)	90.0 (85.4–93.6)	80.4 (70.9–88.0)	87.3 (83.1–90.7)
Median DOR,† months (95% CI)	14.6 (12.2–NE)	23.9 (18.1–NE)	23.9 (12.3–NE)
DOR at Month 12, % (95% CI)	60.6 (51.1–68.7); n=30	69.3 (53.6–80.5); n=12	62.7 (54.8–69.7); n=42
DOR at Month 18, % (95% CI)	47.8 (34.2–60.2); n=13	69.3 (53.6–80.5); n=5	53.7 (42.7–63.5); n=18
Median EFS,‡ months (95% CI)	12.4 (9.8–NE)	18.3 (7.4–NE)	14.0 (9.8–24.8)
EFS at Month 12, % (95% CI)	54.6 (46.5–62.1); n=46	53.1 (40.5–64.2); n=19	54.3 (47.5–60.6); n=65
EFS at Month 18, % (95% CI)	43.0 (31.6–53.9); n=14	53.1 (40.5–64.2); n=8	46.7 (38.0–55.0); n=22
Median RFS,§ months (95% CI)	25.9 (12.2–NE)	18.1 (15.5–24.9)	23.9 (13.0–NE)
RFS at Month 12, % (95% CI)	61.2 (52.7–68.7); n=38	65.3 (50.5–76.6); n=15	62.3 (55.1–68.7); n=53
RFS at Month 18, % (95% CI)	51.6 (40.1–62.0); n=16	55.9 (33.8–73.3); n=5	53.1 (43.1–62.1); n=21
Median OS, months (95% CI)	NE	19.1 (17.1–NE)	NE
OS at Month 12, % (95% CI)	83.3 (77.3–87.8); n=107	70.0 (58.2–79.0); n=34	79.5 (74.2–83.9); n=141
OS at Month 18, % (95% CI)	76.7 (68.2–83.2); n=36	61.1 (44.9–73.9); n=13	72.4 (64.9–78.5); n=49
Safety outcomes, n (%)	**N=275**	**N=125**	**N=400**
AEs of interest <100 days after infusion, n (%)			
CRS	154 (56.0)	78 (62.4)	232 (58.0)
Grade ≥3	49 (17.8)	22 (17.6)	71 (17.8)
Median time to onset, days (range)	6 (1–24)	4 (1–27)	5 (1–27)
Median duration, days (95% CI)	7 (6–7)	7 (5–9)	7 (6–7)
Neurotoxicity	71 (25.8)	38 (30.4)	109 (27.3)
Grade ≥3	27 (9.8)	13 (10.4)	40 (10.0)
Median time to onset, days (range)	7 (2–97)	8 (1–33)	7 (1–97)
Median duration, days (95% CI)	7 (5–10)	7 (4–10)	7 (5–9)
Prolonged neutropenia¶	51 (18.5)	38 (30.4)	89 (22.3)
Prolonged thrombocytopenia¶	47 (17.1)	36 (28.8)	83 (20.8)
CRS intervention, n (%)			
Tocilizumab	69 (25.1)	44 (35.2)	113 (28.3)
Corticosteroids	19 (6.9)	12 (9.6)	31 (7.8)
Neurotoxicity intervention, n (%)			
Tocilizumab	9 (3.3)	8 (6.4)	17 (4.3)
Corticosteroids	14 (5.1)	14 (11.2)	28 (7.0)
Death, n (%)	50 (18.2)	32 (25.6)	82 (20.5)

Samuel John,Michael A. ,Stephan A. Grupp, Real-World Outcomes for Pediatric and Young Adult Patients with Relapsed or Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (ALL) Treated with Tisagenlecleucel: Update from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry, Blood, 2021

Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma



Marcelo C. Pasquini,Zhen-Huan,Stephan Grupp, Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma, Blood Adv, 2020,

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Helping hematologists conquer blood diseases worldwide

KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study

Bijal D Shah, Armin Ghobadi, Olalekan O Oluwole, Aaron C Logan, Nicolas Boissel, Ryan D Cassaday, Thibaut Leguay, Michael R Bishop, Max S Topp, Dimitrios Tzachanis, Kristen M O'Dwyer, Martha L Arellano, Yi Lin, Maria R Baer, Gary J Schiller, Jae H Park, Marion Subklewe, Mehrdad Abedi, Monique C Minnema, William G Wierda, Daniel J DeAngelo, Patrick Stiff, Deepa Jeyakumar, Chaoling Feng, Jinghui Dong, Tong Shen, Francesca Milletti, John M Rossi, Remus Vezan, Behzad Kharabi Masouleh, Roch Houot

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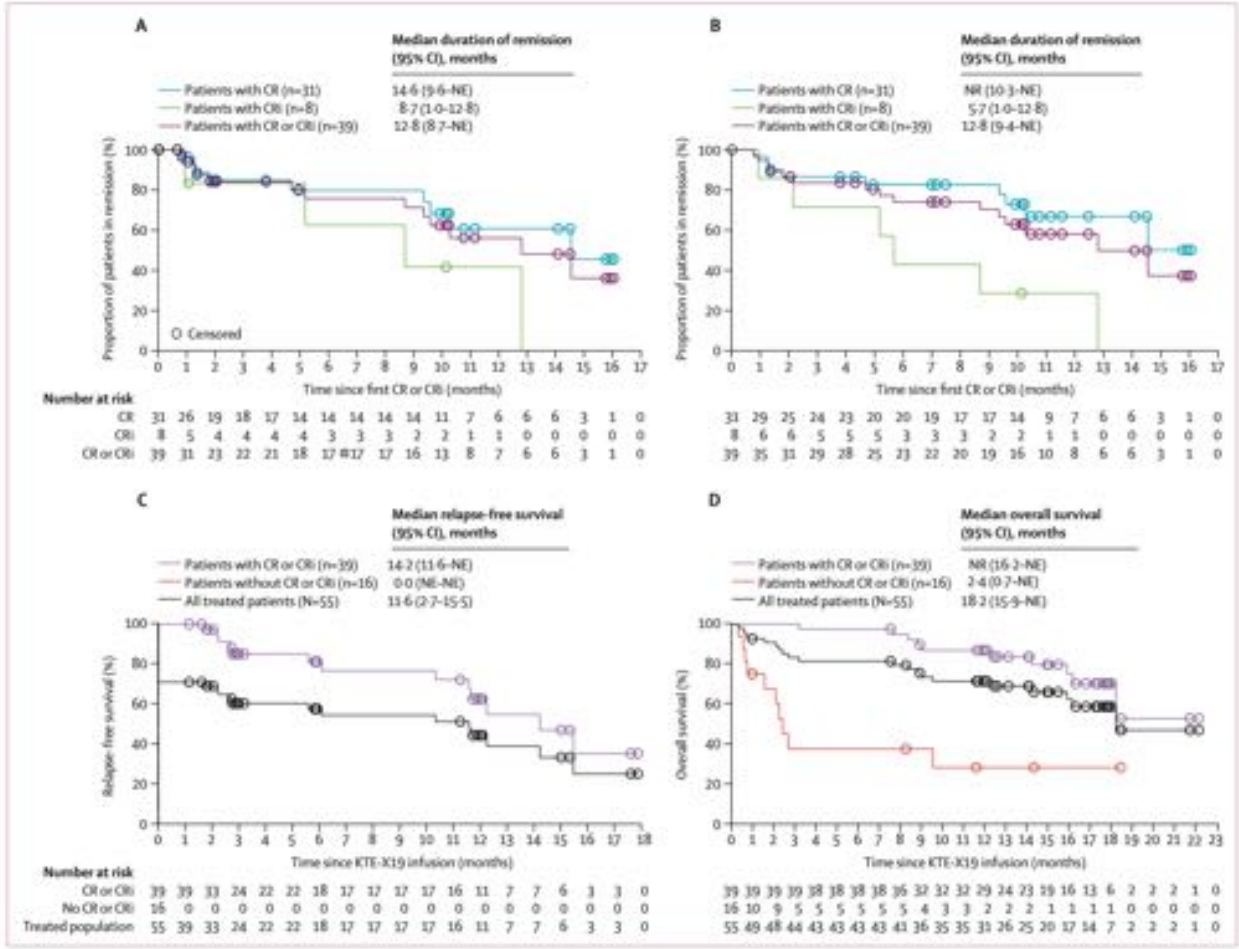
brexucabtagene autoleucel

- 71 pts. KTE-X19 was successfully manufactured for 65 (92%) patients and administered to 55 (77%).
- Median f/u 16·4 months, 39 patients (71%; 95% CI 57–82, p<0·0001) had CR or Cri with 31 (56%) patients reaching complete remission
- Median duration of remission was 12·8 months (95% CI 8·7–not estimable), median relapse-free survival was 11·6 months (2·7–15·5), and median overall survival was 18·2 months (15·9–not estimable)



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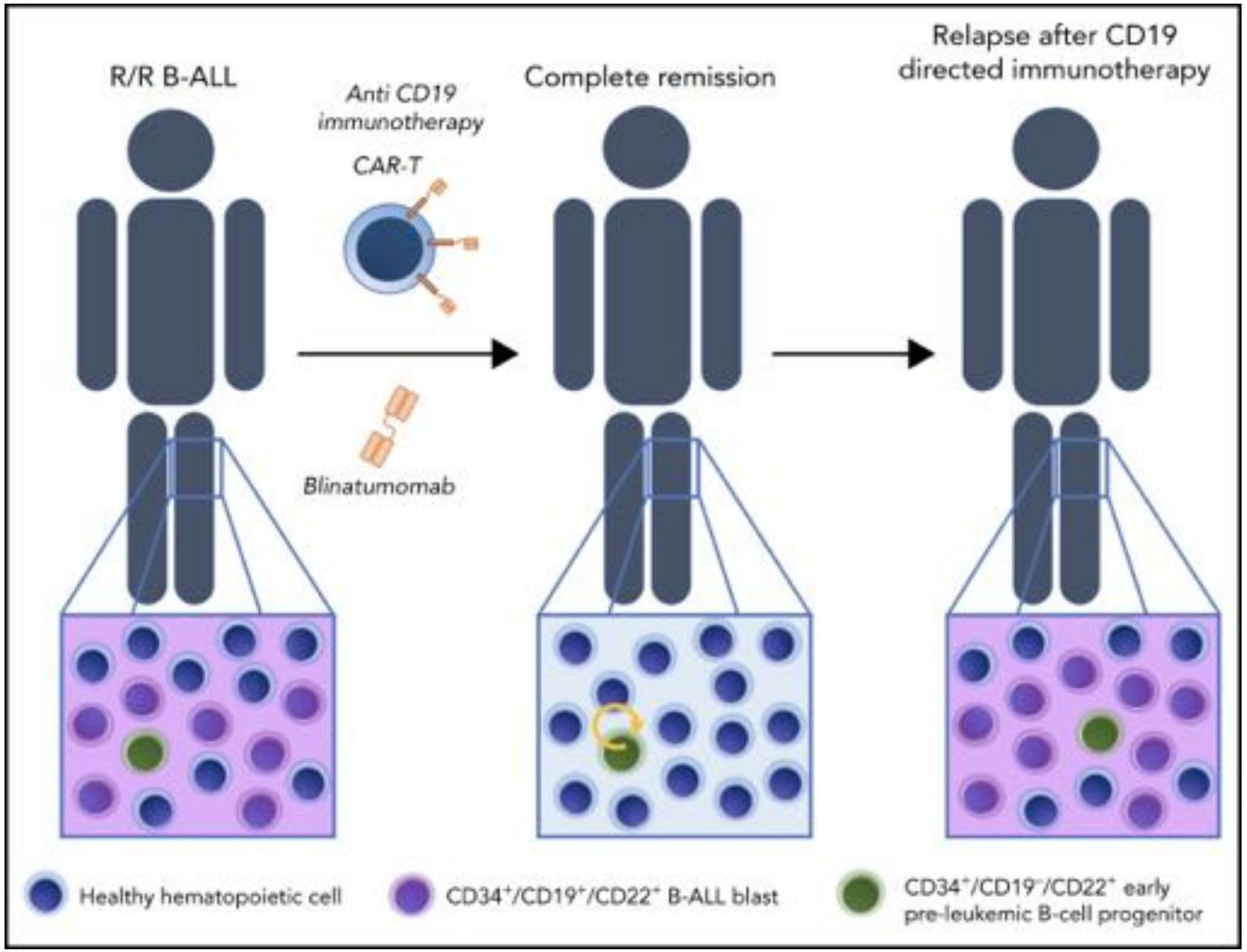
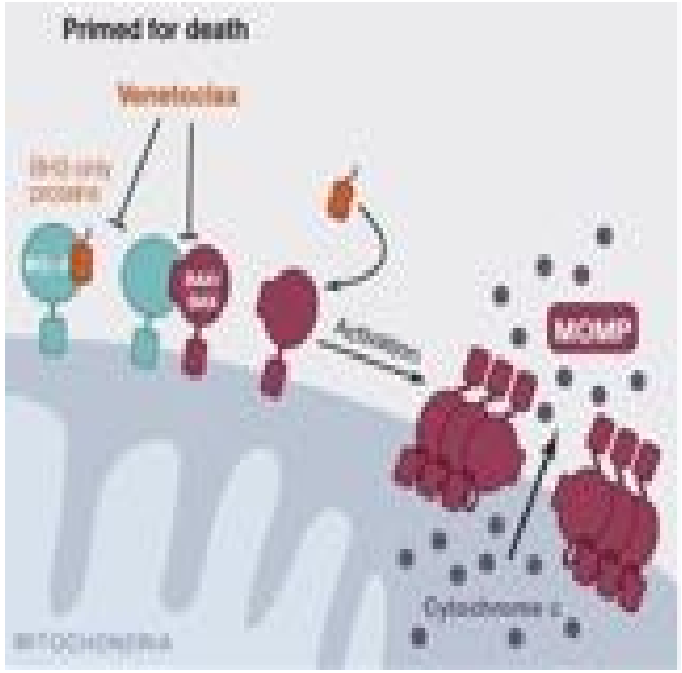
- 14 (25%) patients had infections of grade 3 or higher. Two grade 5 KTE-X19-related events occurred (brain herniation and septic shock). Cytokine release syndrome of grade 3 or higher occurred in 13 (24%) patients and neurological events of grade 3 or higher occurred in 14 (25%) patients.

$CD34^{+}CD19^{-}CD22^{+}$ B-cell progenitors may underlie phenotypic escape in patients treated with CD19-directed therapies



Clara Bueno,Susana Barrera,Alex Bataller,Valentín Ortiz-Maldonado,Natalina Elliot,Sorcha O'Byrne,Guanlin Wang,Montse Rovira,Francisco Gutierrez-Agüera,Juan L. Trincado,María González-González,Mireia Morgades,Marc Sorigué,Paloma Bárcena,Samanta Romina Zanetti,Montse Torrebadell,Nerea Vega-Garcia,Susana Rives,Mar Mallo,Francesc Sole,Adam J. Mead,Irene Roberts,Supat Thongjuea,Bethan Psaila,Manel Juan,Julio Delgado,Alvaro Urbano-Ispizúa,Josep María Ribera,Alberto Orfao,Anindita Roy,Pablo Menendez, $CD34^{+}CD19^{-}CD22^{+}$ B-cell progenitors may underlie phenotypic escape in patients treated with CD19-directed therapies, Blood, 2022,

BH3 Mimetics/BCL2



- Pre-clinical studies have demonstrated activity of the BH3-mimetics venetoclax and navitoclax in B-cell and T-cell ALL cell lines
- Venetoclax showed strong activity in MLL rearranged B-cell ALL
- Both have demonstrated single-agent and synergistic cell killing when combined with chemotherapy owing to the upregulation of BCL-2 in these cell lines.
- A case series of 4 pts with R/R B-cell and T-cell ALL reported a 50% durable CRR for patients receiving venetoclax in combination with asparaginase-based chemotherapy regimens
- The efficacy and safety of venetoclax with navitoclax

- Benito JM et al cell rep 2015
- Khaw SL et al blood 2016
- Frismantas V et al blood 2017
- El-Cheikh J et al clinical lymphoma myeloma leuk 2018

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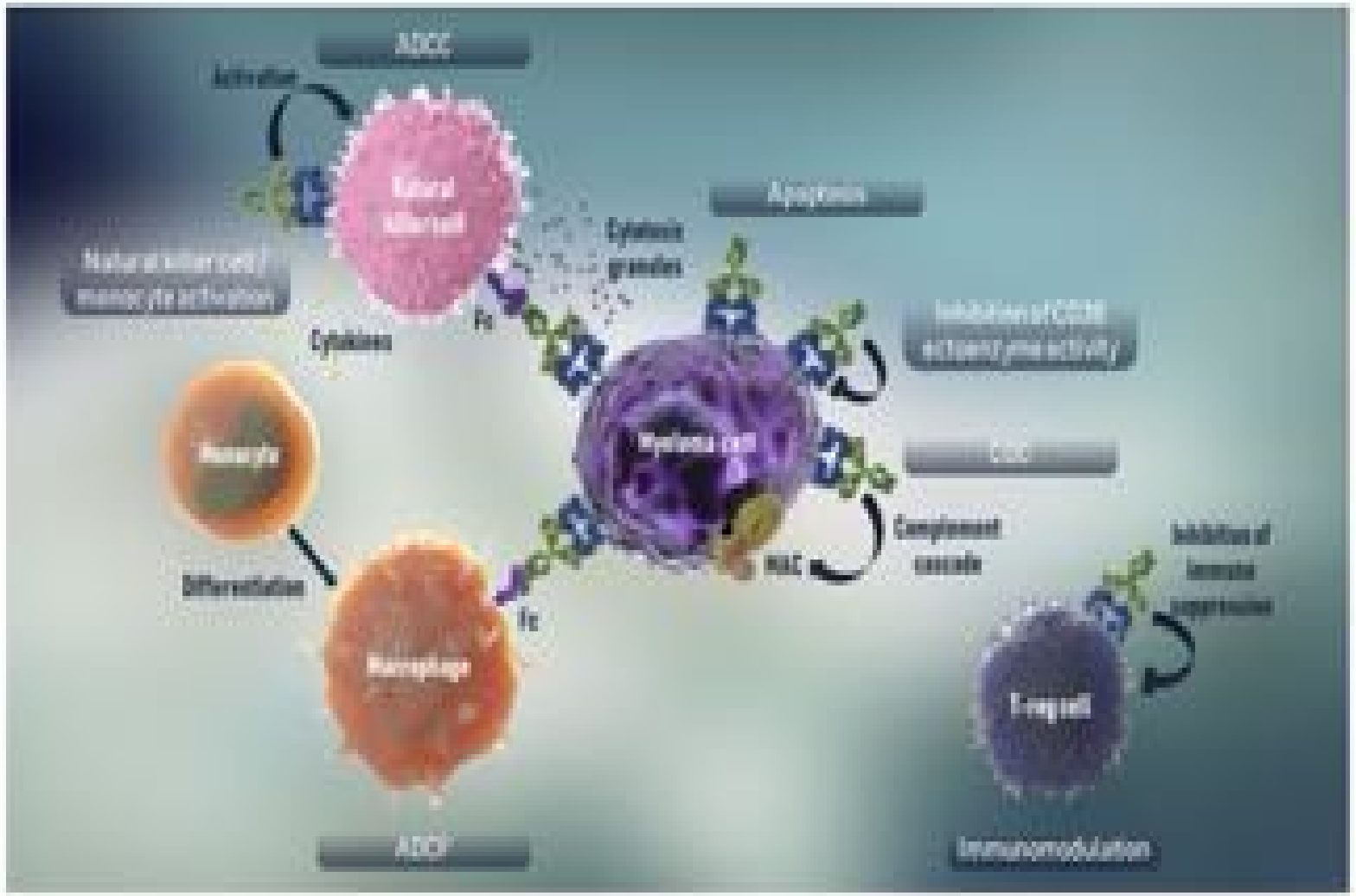
Targeting CD38 with Isatuximab



CD38 functions as a receptor and an ectoenzyme, and is highly and uniformly expressed on multiple myeloma cells[1–5]

Isatuximab is an IgG1 monoclonal antibody that targets a specific epitope on the CD38 transmembrane glycoprotein[6]

Isatuximab has multiple modes of action:[4]

- ADCC, CDC and ADCP
- Inhibition of CD38 ectoenzyme activity
- Immunomodulation
- Direct apoptosis

Isatuximab in Combination with Chemotherapy in Pediatric Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia (ISAKIDS): Interim Analysis

Table

n (%)	B-ALL (n=7)	T-ALL (n=6)	AML (n=4)
Complete response (CR+CRi)	3 (42.9)	2 (33.3)	2 (50.0)
Relapsed/Refractory disease	4 (57.1)	4 (66.6)	2 (50.0)
	B-ALL (n=10)	**T-ALL (n=7)**	**AML (n=7)**
Grade ≥3 TEAE	4 (40.0)	7 (100.0)	6 (85.7)
Any serious treatment-related TEAE*	2 (20.0)	6 (85.7)	5 (71.4)
Patients with any infusion reaction	2 (20.0)	4 (57.1)	3 (42.9)
Grade 5 TEAE (fatal outcome)	1 (10.0)	0	2 (28.6)

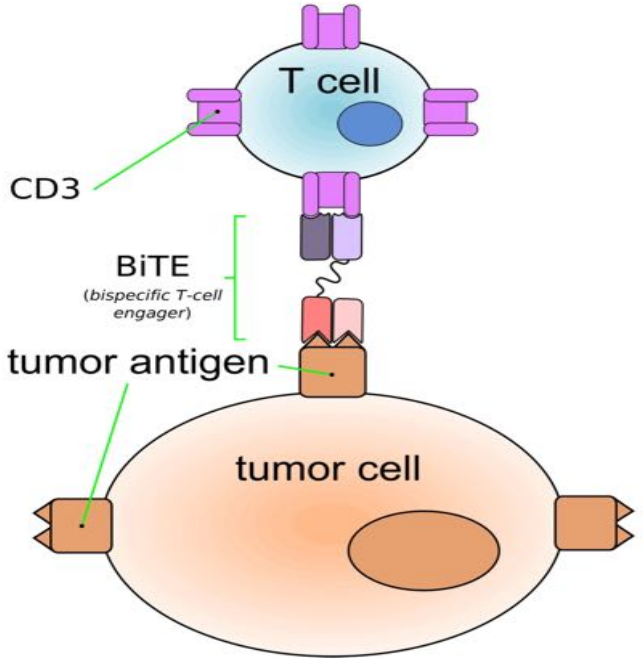
*Serious TEAE is defined as life-threatening, requires hospitalization or prolongation of hospitalization, or results in persistent disability/incapacity or death

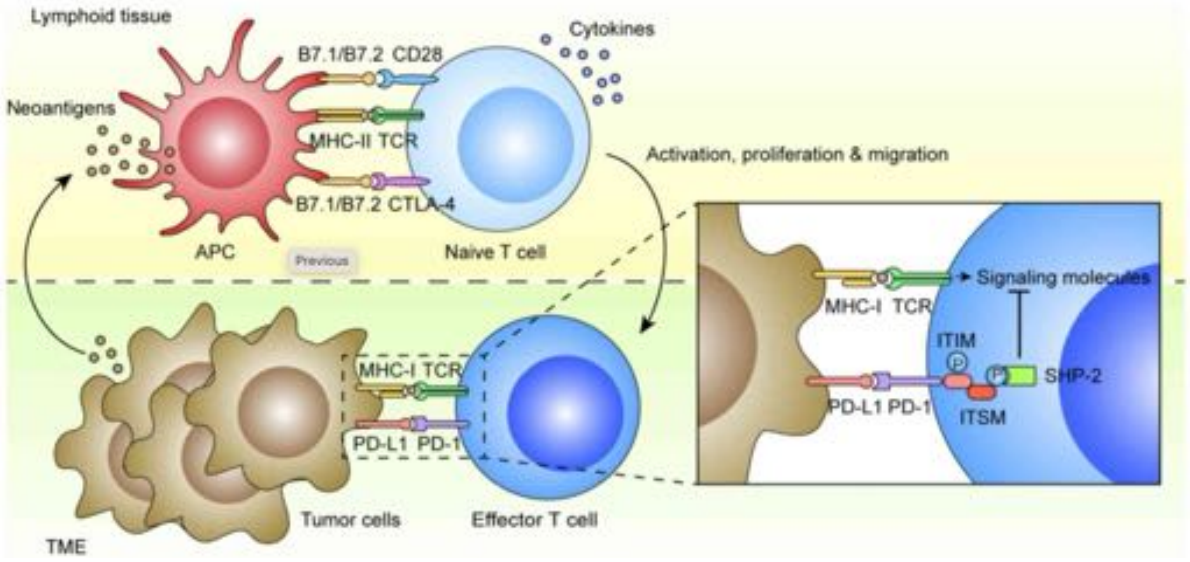
Andre Baruchel,Jonas Abrahamsson,Yves Bertrand,Oscar Gonzalez,Karsten Nysom,Willy Quinones,Carmelo Rizzari,Jochen Buechner,Simone Cesaro,Joaquin Duarte,Franca Fagioli,Hyoung Jin Kang,Antonis Kattamis,Guy Leverger,Kathleen Ludwig,Monica L Makiya,Concetta Micalizzi,Brigitte Nelken,Camilla Tøndel,Keon Hee Yoo,Inna Ivanina,Claire Brillac,Lynn Wang,Corina Oprea,Giovanni Abbadessa,C. Michel Zwaan, Isatuximab in Combination with Chemotherapy in Pediatric Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia (ISAKIDS): Interim Analysis, Blood, 2021, Figure 1

A phase 1b study of blinatumomab with the anti-programmed cell death (PD)-1 antibody AMG 404 in adults with relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL)

Blinatumomab in Combination with Immune Checkpoint Inhibitors of PD-1 and CTLA-4 in Adult Patients with Relapsed/Refractory (R/R) CD19 Positive B-Cell Acute Lymphoblastic Leukemia (ALL): Preliminary Results of a Phase I Study

Jonathan Webster, MD, Marlise R. Luskin, MD, Gabrielle T. Prince, MD, Amy E. DeZern, MD, Daniel J. DeAngelo, MD, Mark J. Levis, MD, Amanda Blackford, Elad Sharon, MD MPH, Howard Streicher, MD, Leo Luznik, MD, Ivana Gojo, MD





T cell ALL

- Poor prognosis especially the early T-cell precursor [ETP]
- Pediatrics based regimen with higher dose MTX 5gm/m2 and Peg Asparaginase multi combined chemotherapy followed with HSCT in CR1. GRALL confirmed
- Nelarabine 1.5 g/m2 /day IV on days 1, 3, and 5 in R/R. The CR 31%. The 1-year OS was 28%.
- Added to Upfront HyperCVAD 650 mg /m2 daily for 5 days. CR 87%.3 yr-OS 65%. ETP ALL OS of 50% VS 29% of HyperCVAD.

DeAngelo DJ et al Blood 2007

Abaza Y et al Am J Hematol 2018- MD Anderson front line nelarabine combined to HyperCVAD

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COG AALL0434: A randomized trial testing nelarabine in newly diagnosed T-cell malignancy.

- ABFM regimen with or without 6 courses of Nel 650 mg/m2 for 5 days.
- 4 arms.
- Int-high risk were randomized 650 mg/m2 for 5 days . All received PPX brain radiation
- Overall 4-yr OS 90%
- 4-year DFS 89%.Nel vs 83%.no Nel
- CMTX 4-yr DFS for Nel 92% VS no Nel 89%
- HDMTX 4-yr DFS for Nel 86% vs 78% no Nel
- Induction failure received HDMTx with Nel 4-yr DFS 54%.

Dunsmore KP et al JCO 2018

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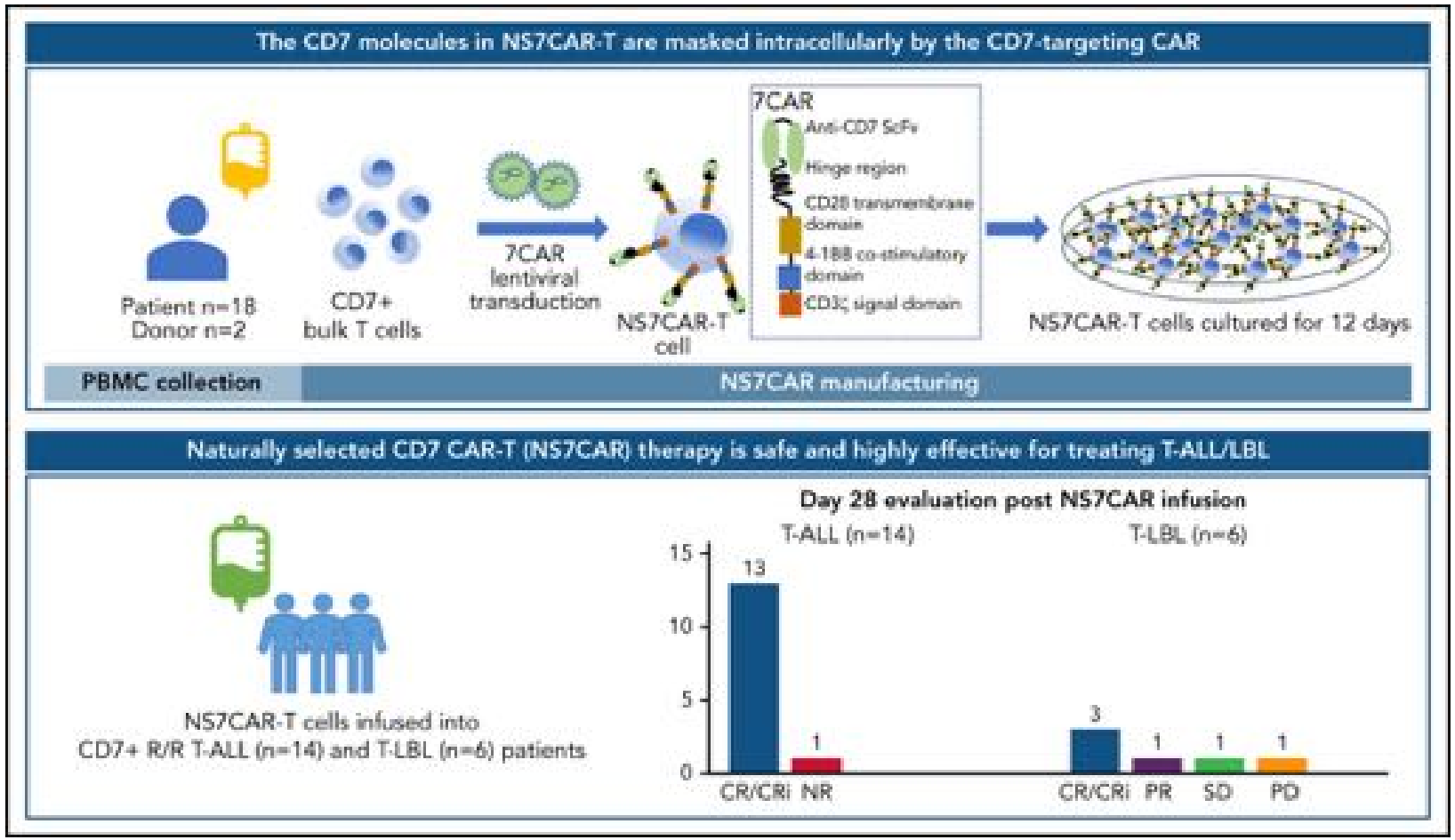
Naturally selected CD7 CAR-T therapy without genetic manipulations for T-ALL/LBL: first-in-human phase 1 clinical trial



Peihua Lu,Ying Liu,Junfang Yang,Xian Zhang,Xiao Yang,Hui Wang,Lin Wang,Qinglong Wang,David Jin,Jianqiang Li,Xiaojun Huang, Naturally selected CD7 CAR-T therapy without genetic manipulations for T-ALL/LBL: first-in-human phase 1 clinical trial, Blood, 2022,

Thank you

Questions