2nd edition
Unmet challenges in high risk hematological malignancies: from benchside to clinical practice
Turin, September 13-14, 2021

How I Treat High Risk Acute Lymphoblastic Leukemia in First Line

Renato Bassan
UOC Ematologia, Ospedale dell'Angelo, Mestre – Venezia, Italy

2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2021

Starhotels Majestic

Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)

Disclosures of RENATO BASSAN

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						+	+
Servier						+	+
Incyte							+
Pfizer							+
Jazz							+

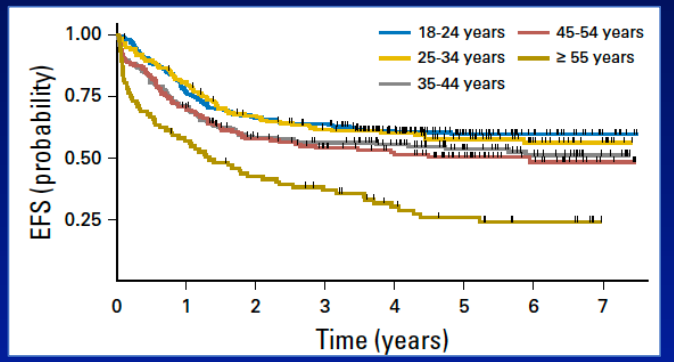
First Line Therapy Results in Adult Ph- ALL

Adult Ph- ALL

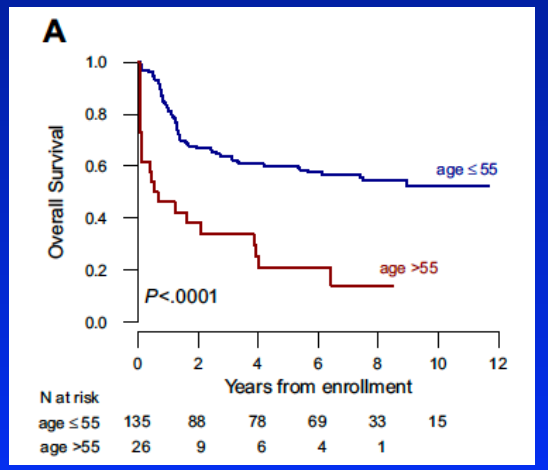
- *Cure rate approx. 60% <55 vs. 20% >55 Y*

Study	Age (Y)	No.	OS (%)	RFS (%)	EFS (%)	Estimates @ (Y)
GMALL 07/03	35 (15-55)	1226	60-67	-	-	3-Y
RALL 2009	30 (15-60)	250	66	69	-	4-Y
GRAALL 2003	36 (18-59)	225	60	59	55	3.5-Y
GRAALL 2005	37 (18-60)	787	59	-	52	4-Y
Toronto/DFCI	37 (18-60)	85	63	71	-	5-Y
PETHEMA HR-11	40 (15-60)	348	40	-	40	5-Y
JALSG 202-O	40 (24-65)	115	64	58	-	5-Y
GIMEMA 1913	40 (18-65)	203	67	63	-	3-Y
NILG 10/07	41 (18-65)	161	52	53	46	5-Y

Modified after Tosi M et al, *Cancers* 2021



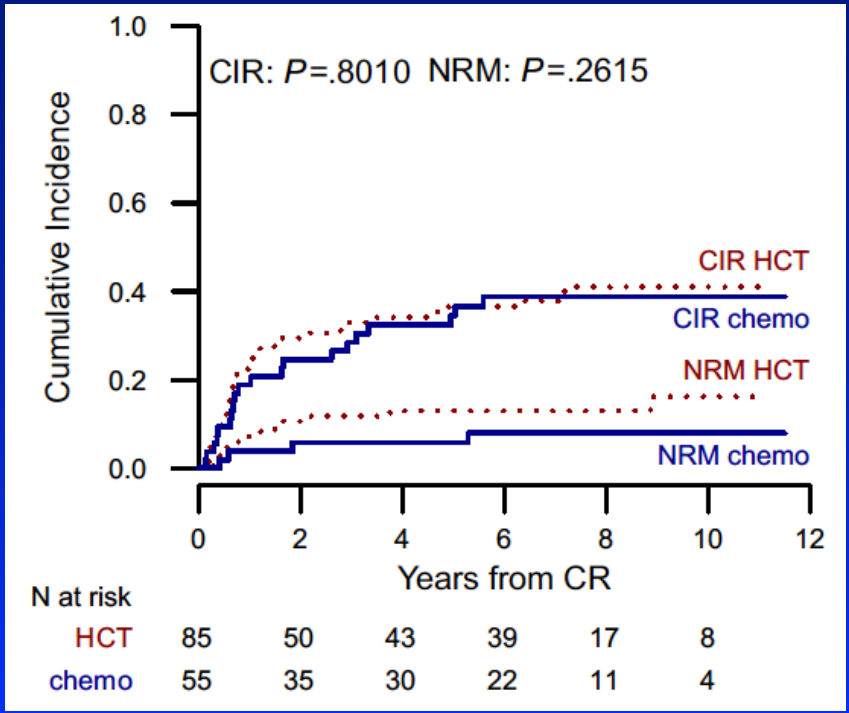
Huguet F et al, *J Clin Oncol* 2018



Bassan R et al, *Blood Cancer J* 2020

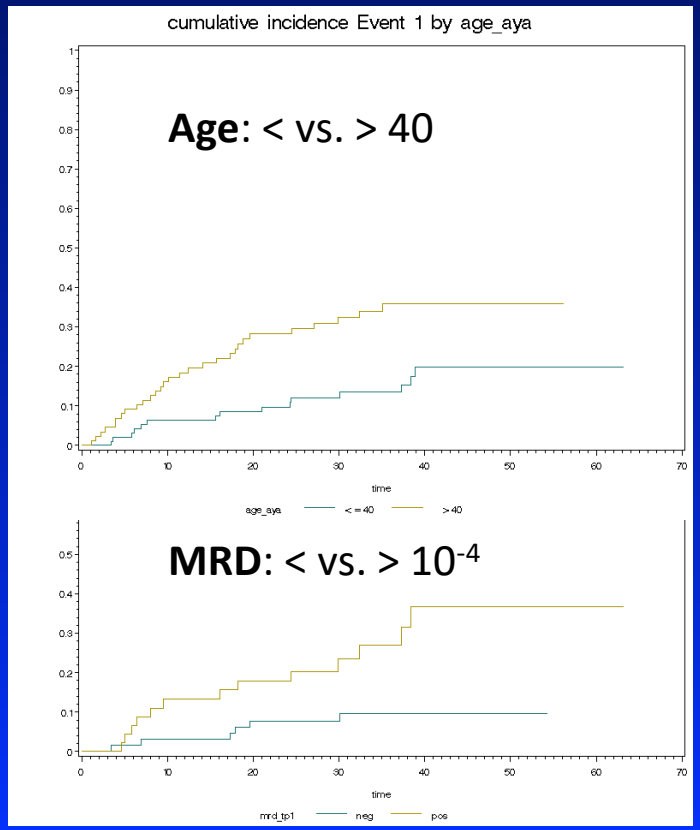
Relapse Risk by Selected Risk Characteristics in Adult Ph- ALL (Italian Risk-Oriented Trials, Age 18-65)

NILG 10/07, relapse incidence 35.7%



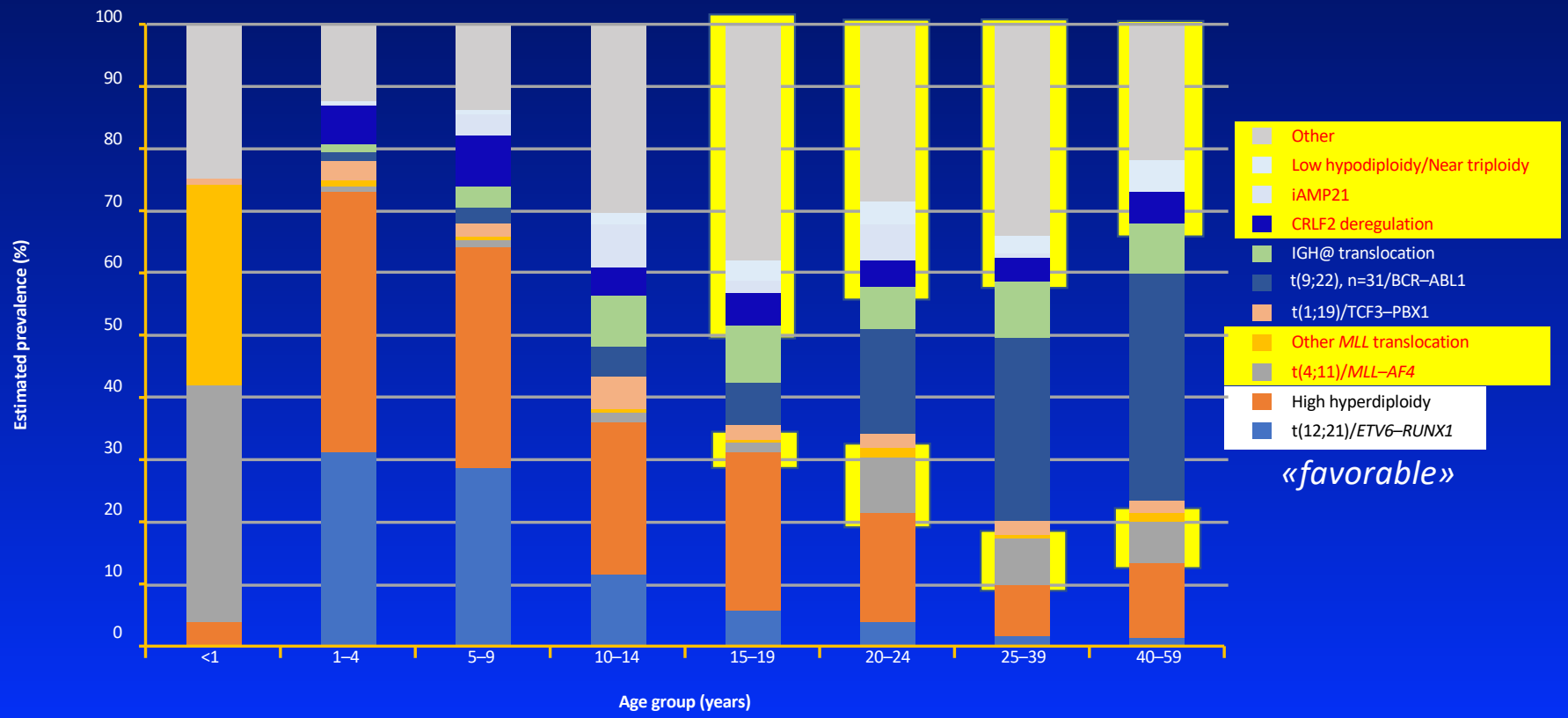
Bassan R et al, *Blood Cancer J* 2020

GIMEMA 1913, relapse incidence 35.9%



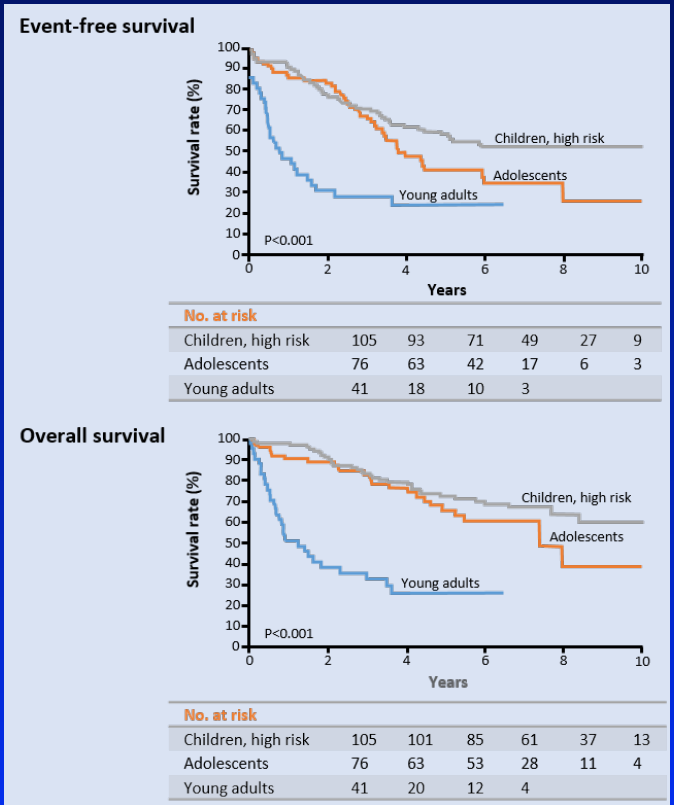
HR Genetic/Cytogenetic Variants

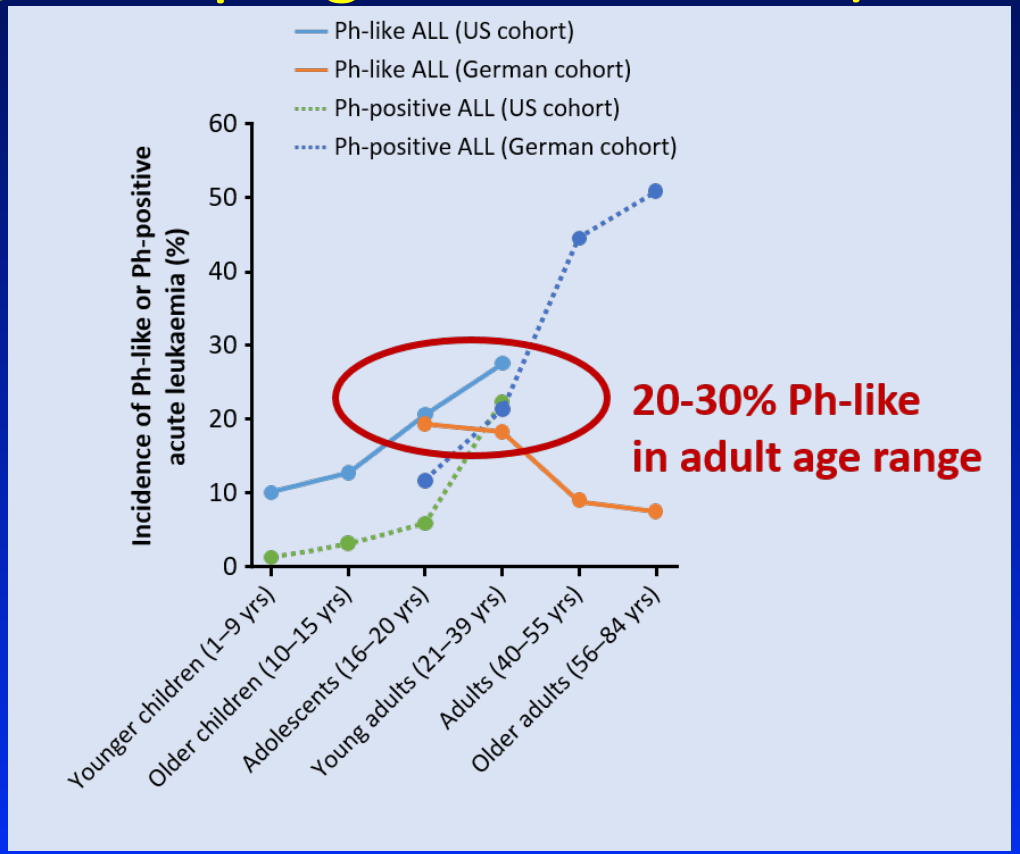
large «other» and HR areas!



Moorman AV. *Blood Rev* 2012; 26:123–135

New Public Enemy No. 1 is Ph-Like ALL
(in «other» genetic area, after progress in Ph+ ALL)

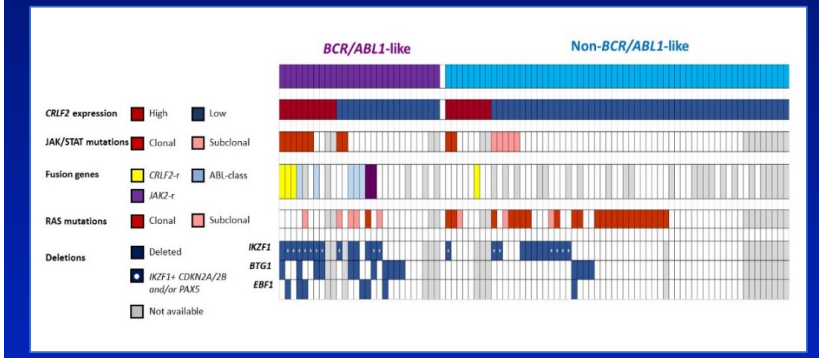




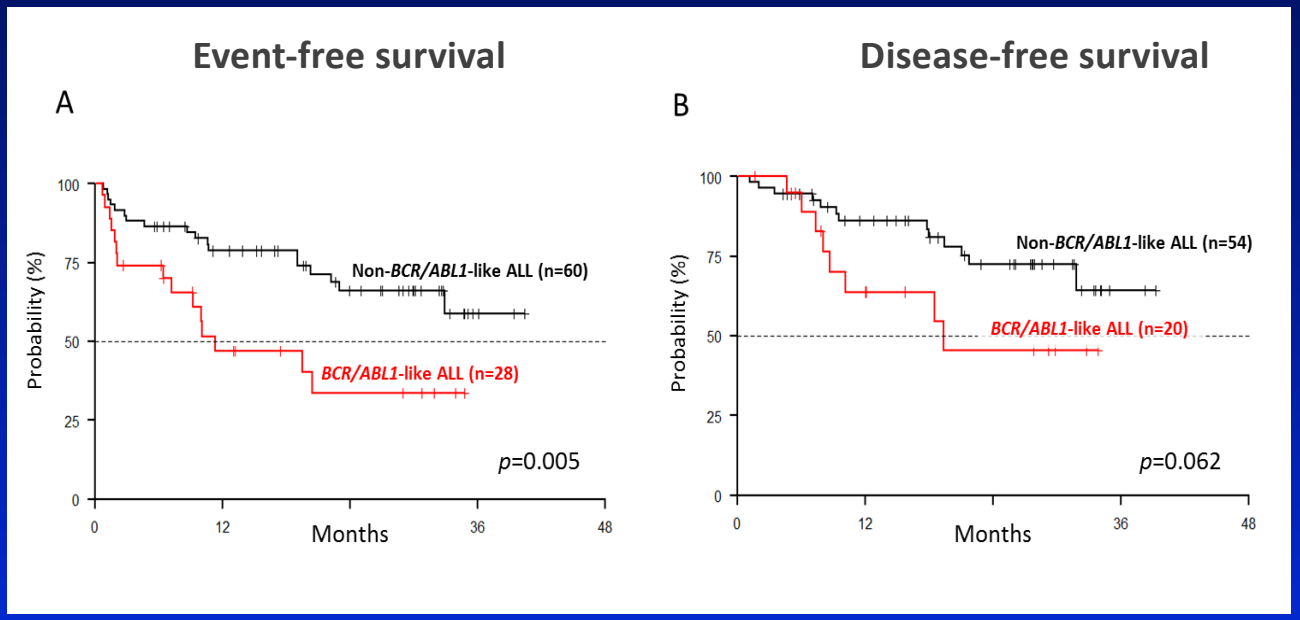
1. Roberts KG, et al. *N Engl J Med* 2014;371:1005–1015;
2. Herold T, et al. *N Engl J Med* 2014;371:2235.

Ph-like ALL, GIMEMA Experience (LAL 1913)

Ph-like or *BCR/ABL1*-like:
molecular diagnostic algorithm



96 'B-other' ALL evaluable
28 Ph-like (29.1%)

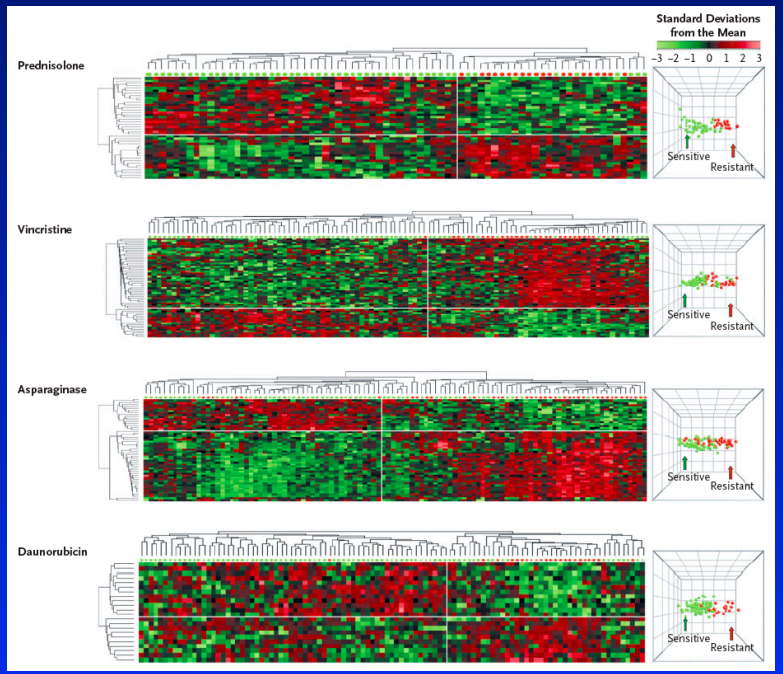


	Non Ph-like	Ph-like
CR rate (%)	91	75 (P .07)
MRD_{neg}/<10^{-4} @ w10 (%)	81.6	47.1 (P .009)

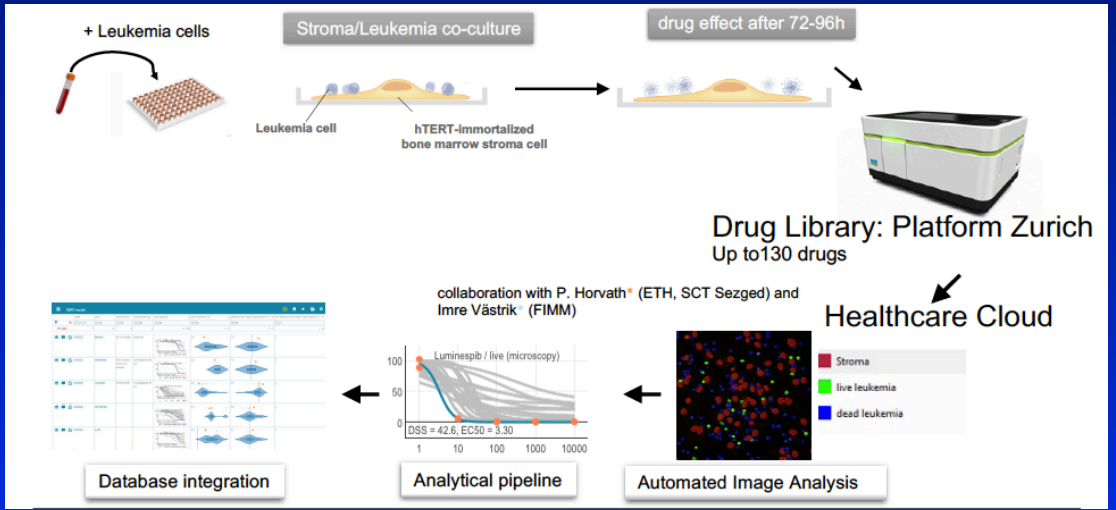
Chiaretti S et al, *Br J Haematol* 2018; Chiaretti S et al, *Haematologica* 2021

Drug Resistant ALL Variants

- **Well known story**



- **Today: rapid drug response profiling for clinical application**



Holleman A et al, *NEJM* 2004

Courtesy Bourquin J-P (Zurich, CH), 2021

Risk Stratification (Age 1-45)

	Standard risk (SR)	Intermediate-low risk (IR-low)	Intermediate-high risk (IR-high)	High risk (HR)
Cytogenetics/ genetics	• No high risk genetics	• *ETV6-RUNX1* with MRD <0.1% • Hyperdiploidy with MRD <0.03% • Good CNA profile: – no deletion *IKZF1*, *CDKN2A/B*, *PAR1*, *BTG1*, *EBF1*, *PAX5*, *ETV6*, *RB1* – isolated deletion *ETV6*, *PAX5*, *BTG1* – *ETV6* deletion with single deletion *BTG1*, *PAX5*, *CDNK2A/B* with MRD <0.05%	• High risk genetics: – t(4;11)/*KMT2A+* – Near haploidy/low hypodiploidy – iAMP21 – Rearranged *ABL1*, *ABL2*, *PDGFRB* and *CSFR1* (except *BCR-ABL1*)	• t(17;19)/*TCF3-HLF*
TP1 MRD *(end of induction)*	• 0%		• > 0% and < 5%	• ≥ 5%
TP2 MRD *(post-consolidation)*	-		• > 0.01% and < 0.05%	• ≥ 0.05%
Miscellaneous	• Testicular CR at TP1 MRD • No CNS3/traumatic lumbar puncture	• < 16 years • No CNS3/traumatic lumbar puncture	• ≥ 16 years • T-ALL • Extramedullary disease at TP2 MRD • Remaining patients	• ≥ 16 years and any high risk criteria
Risk-Oriented Treatment Strategy	• **SR chemo** • **Random 1:** Doxorubicin omission in delayed intensification	• **IR-low chemo** • **Random 2:** Doxorubicin omission in delayed intensification; VCR/Dexa omission in maintenance	• **IR-high chemo** • **Random 3:** Inotuzumab ozogamicin before maintenance; 6TG in maintenance • **TKI** if *ABL*-class fusions	• **HR chemo** • **Allogeneic HCT** • **CAR-T (BCP ALL)** • **Nelarabine (T-ALL)**

from Tosi M et al, *Cancers* 2021

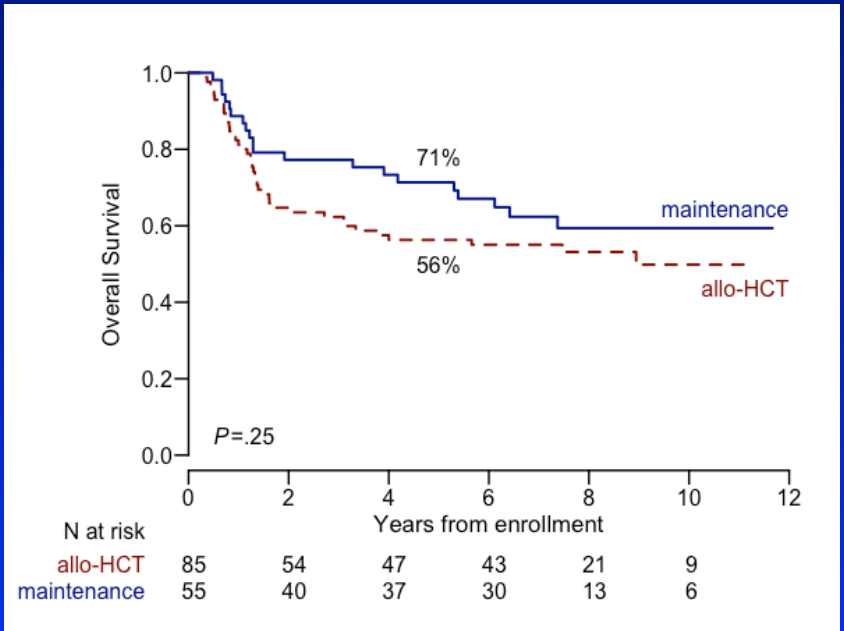
A Treatment Study Protocol of the ALLTogether Consortium for Children and Young Adults (1-45 Years of Age) With Newly Diagnosed Acute Lymphoblastic Leukaemia (ALL): a Pilot Study. ***ClinicalTrials.gov Identifier: NCT03911128.***

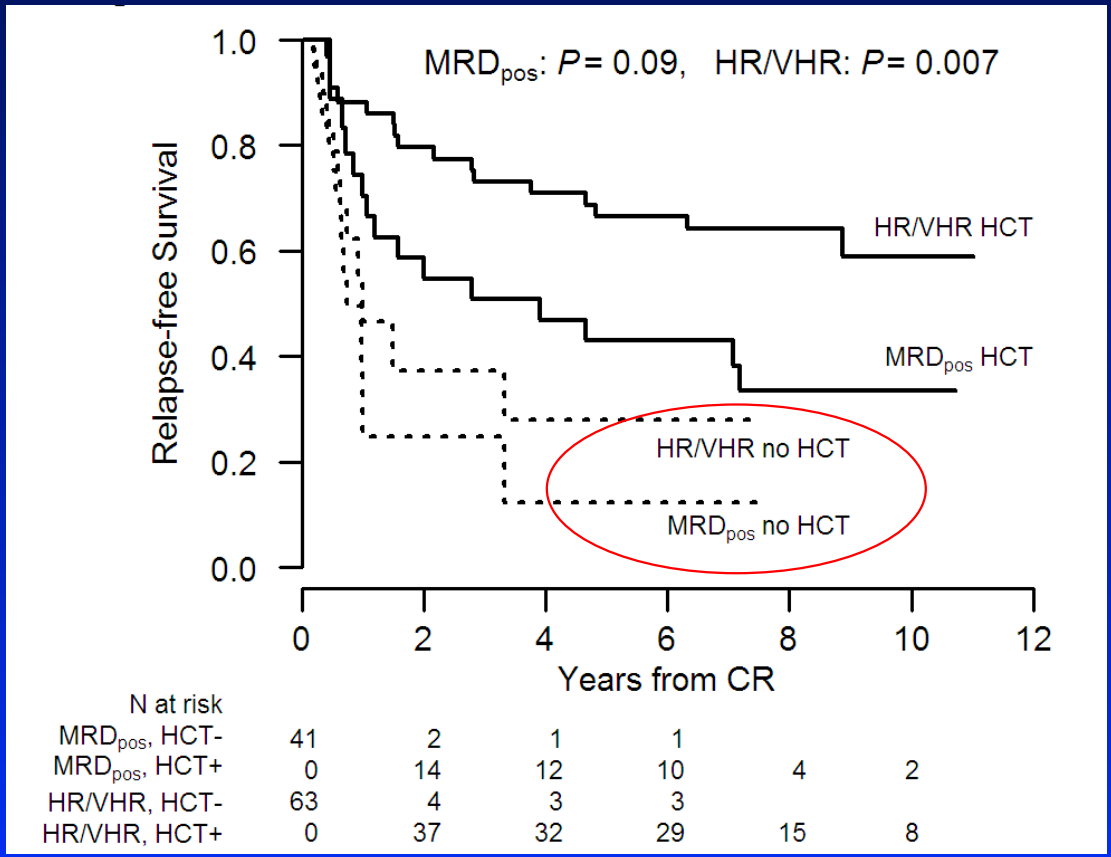
Allo-SCT for Adult HR ALL (Age 18-65)

Time-dependent Simon-Makuch statistics

Survival of remitters by allocation cohort (treatment intention)

RFS comparing HCT vs. no HCT in HR pts. (Simon- Makuch statistics)





Bassan R et al, *Blood Cancer J* 2020

HR/VHR for SCT: WBC >100, high risk genetics, early/mature-T, MRD+, WBC >30/pro-B MRDu/k

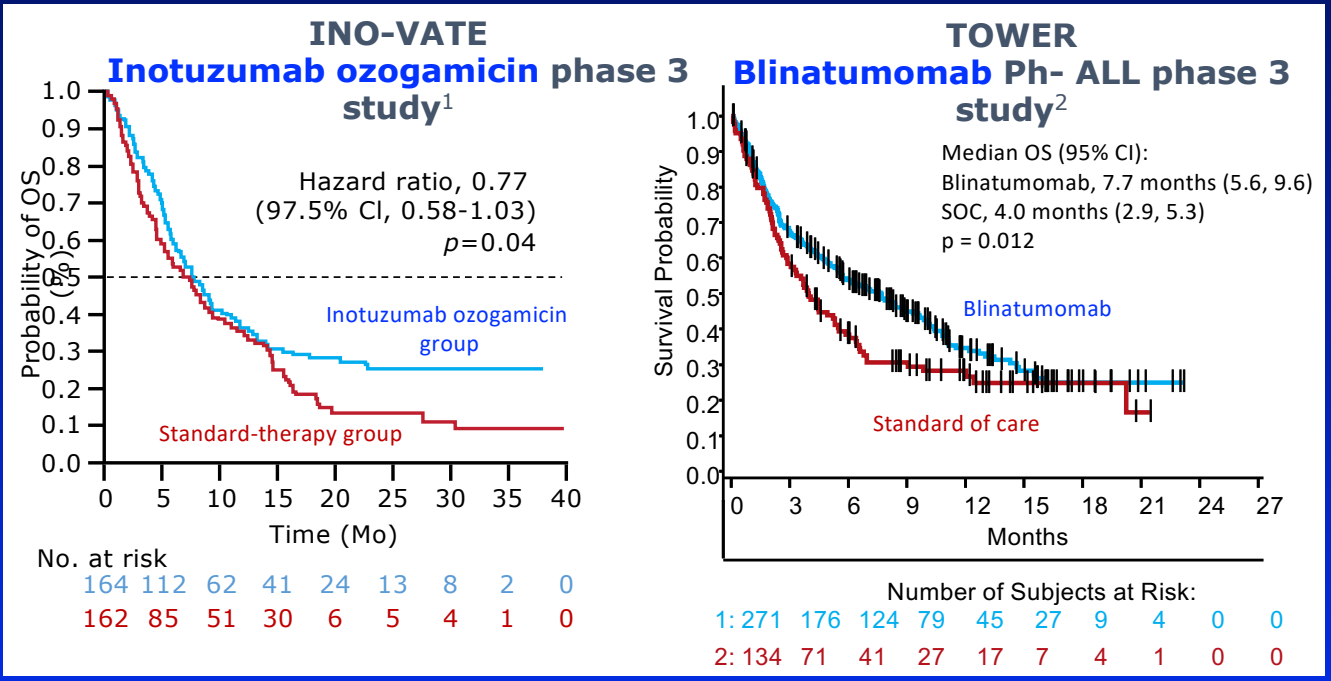
Allo-SCT for MRD+ ALL

Reasons to allograft (trial):
GMALL: HR or SR **MRD+**
NILG: Very HR or SR/HR **MRD+**
PETHEMA: MRD+ or HR late CR
GRAALL: HR **MRD+/-**

Study	SCT eligible, (no.)	SCT, no. (%)	5-year OS	
			SCT	No SCT
GMALL 07/03[1,2]	196	121 (62.0) Y 2003–9 (54.0) Y 2010–6 (72.0)	53%	28% (P<0.0001)
	102 (MRD relapse)	38 (37.2)	71%	37% (P=0.001)
NILG 09/00[3,4]	60	26 (43.3)	-	-
NILG 10/07[5]	87	53 (60.9)	58%	-
PETHEMA AR-03[6]	24	24 (100)	31%	-
PETHEMA HR-11[7]	103	58 (56.0)	41%	
GRAALL 2003–5[8]	105	46 (43.8)	~63%	<30% (P=0.002)

1. Gökbuget N, et al. *Blood* 2012;120:1868–76; 2. Gökbuget N, et al. *Blood* 2017;130:139 (abstr); 3. Bassan R, et al. *Blood* 2009;113:4153–62; 4. Bassan R, et al. *Blood Cancer J* 2014;4:e225; 5. Bassan R, et al. *Blood* 2016;128:176 (abstr); 6. Ribera JM, et al. *J Clin Oncol* 2014;32:1595–604; 7. Ribera JM, et al. *Blood* 2019;134:826 (abstr); 8. Dhèdin N, et al. *Blood* 2015;125:2486–96.

Targeting MRD



	Phase 3 (study drug vs. SOC)	
***Patients** (%)	**TOWER**	**INO-VATE**
>1 salvage	57.9	33
Refractory	42.4	16
Previous SCT	34.7	16
CR (%)	44 vs. 25 (P <0.001)	80.7 vs. 29.4 (P <0.001)
MRDneg (%)	76 vs. 46	78.4 vs. 28.1

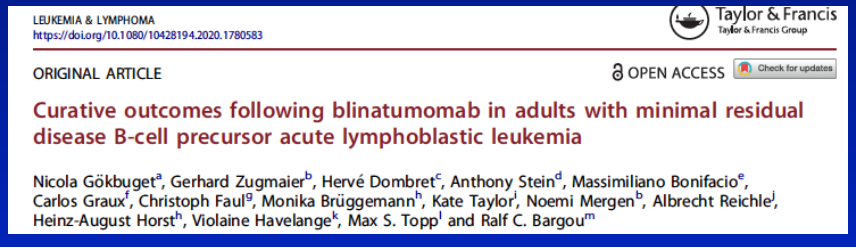
Improved survival in patients achieving MRDneg status (+/- SCT)[3-5]

[1]Kantarjian HM, et al. *N Engl J Med* 2016; [2]Kantarjian HM, et al. *N Engl J Med* 2017; [3]Jabbour EJ et al, *Leuk Res* 2020; [4]Jabbour EJ et al, *Cancer* 2019; [5]Rambaldi A et al, *Blood Adv* 2020

MRDpos: Phase 2 BLAST Trial (Blinatumomab)

Blinatumomab to:

- Patients in first CR with **MRD ≥10^{-3}**
- **Complete MRD response (efficacy set): 80%** (82/103)[1,2]



LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2020.1780583

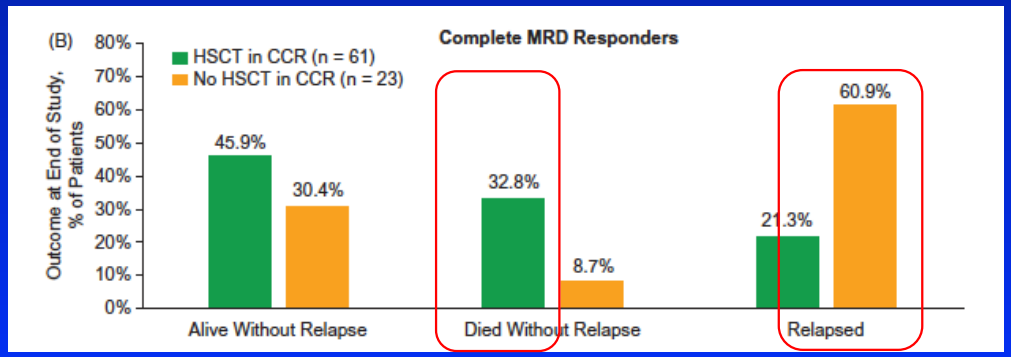
Taylor & Francis
Taylor & Francis Group

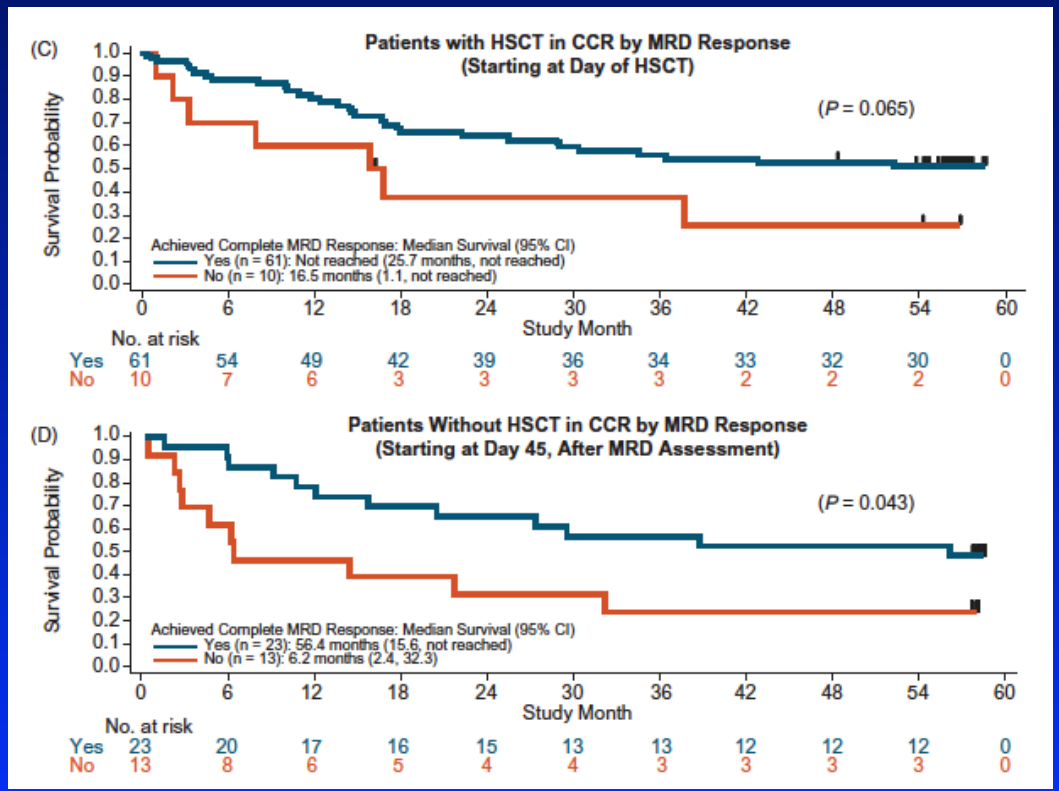
ORIGINAL ARTICLE

OPEN ACCESS Check for updates

Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia

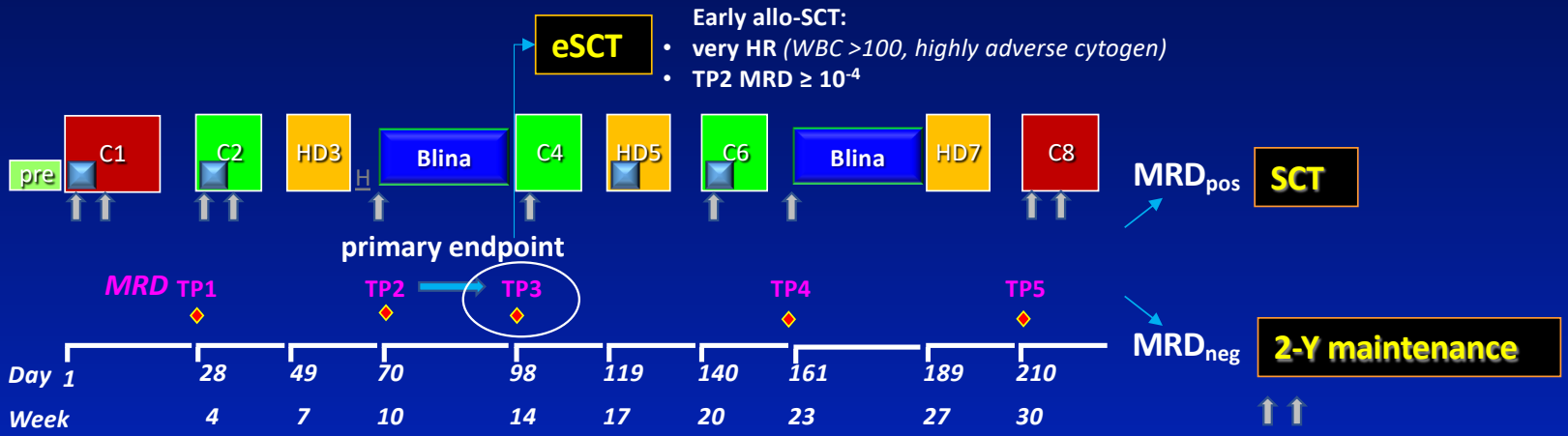
Nicola Gökbuget[a], Gerhard Zugmaier[b], Hervé Dombret[c], Anthony Stein[d], Massimiliano Bonifacio[e], Carlos Graux[f], Christoph Faul[g], Monika Brüggemann[h], Kate Taylor[i], Noemi Mergen[b], Albrecht Reichle[j], Heinz-August Horst[h], Violaine Havelange[k], Max S. Topp[l] and Ralf C. Bargou[m]





[1]Gökbuget N, et al. *Blood* 2018;131:1522–31; [2]Gökbuget N, et al. *Eur J Haematol* 2019; doi.101111/EJH.13375 [Epub]

New First Line Trial: GIMEMA LAL 2317 (Chemo-Blinatumomab Sequence)



Treatment elements/strategy

Induction/reinduction (**pre**: CY/PDN; **Ind:** VCR/Dex/IDR/Peg-ASP [C1])

SD consolidation (IDR/CY/DXM/6MP/Ara-C/Peg-ASP [C2,5])

HD consolidation (MTX 2.5 g/m^2 and Ara-C [HD3,7] or Peg-ASP/6MP [HD5]; MTX 1.5 g/m^2 >55 y)

CNS prophylaxis (TIT)

H Stem cell harvest

Blinatumomab 28 mcg/d CIV dd 1-28

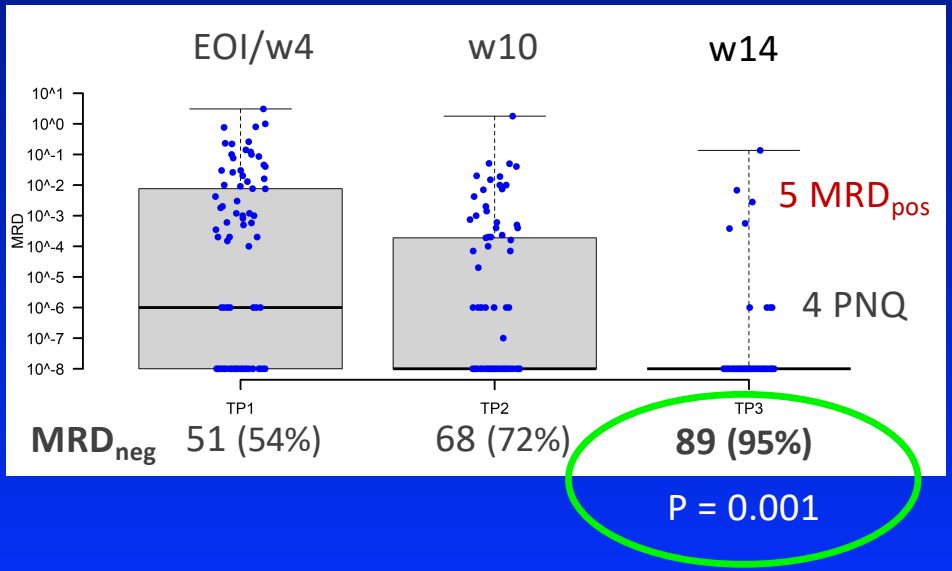
Risk/MRD-specific therapy

ClinicalTrials.gov ID NCT03367299

First Results

Presented EHA, 2021

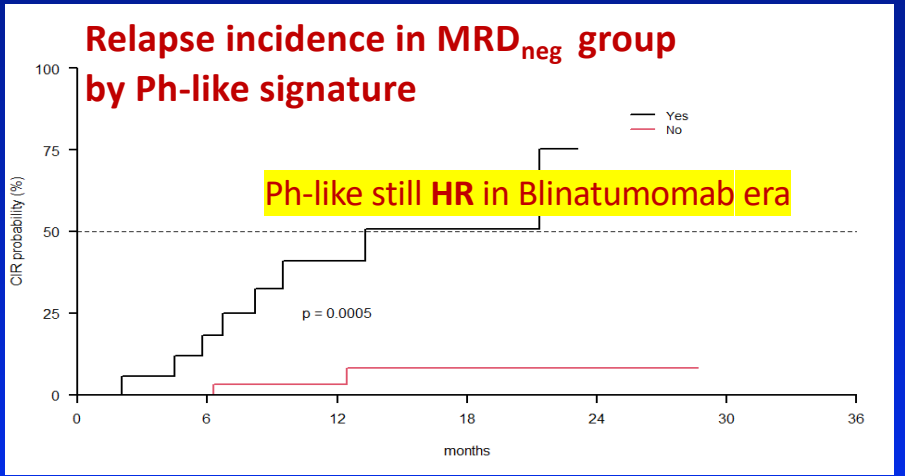
- *Study closed Aug 2020*
- ***94 MRD-evaluable CR patients with paired MRD samples w10 – w14***



1-year relapse rate

Ph-like 40.1 %

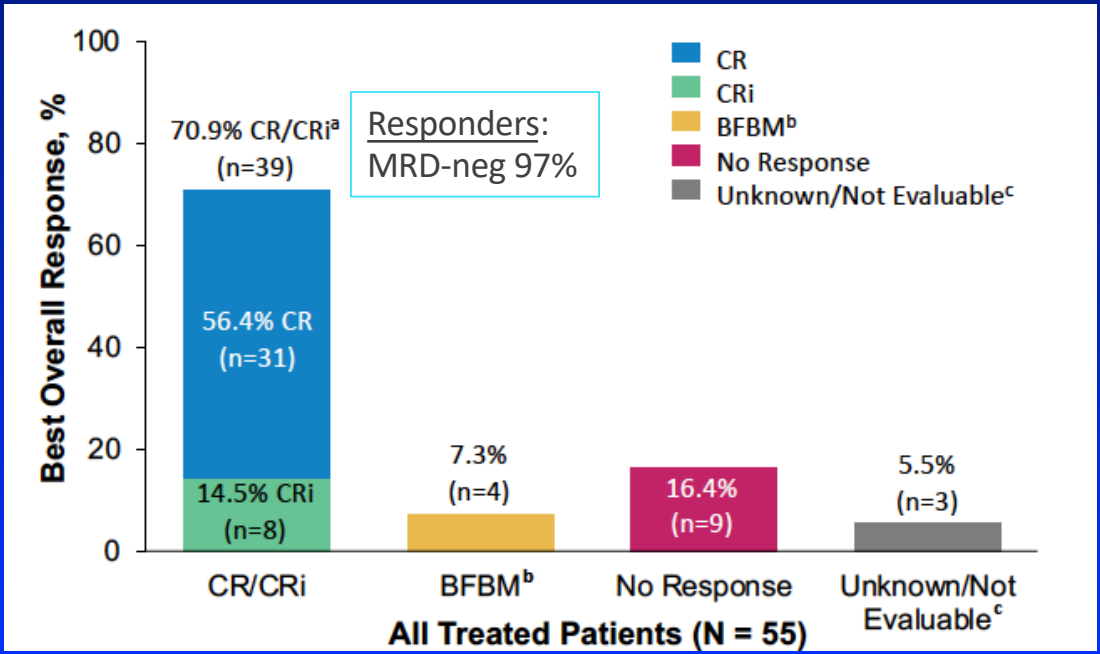
No Ph-like 3.2 % P=0.0005



CAR-T for Very HR ALL

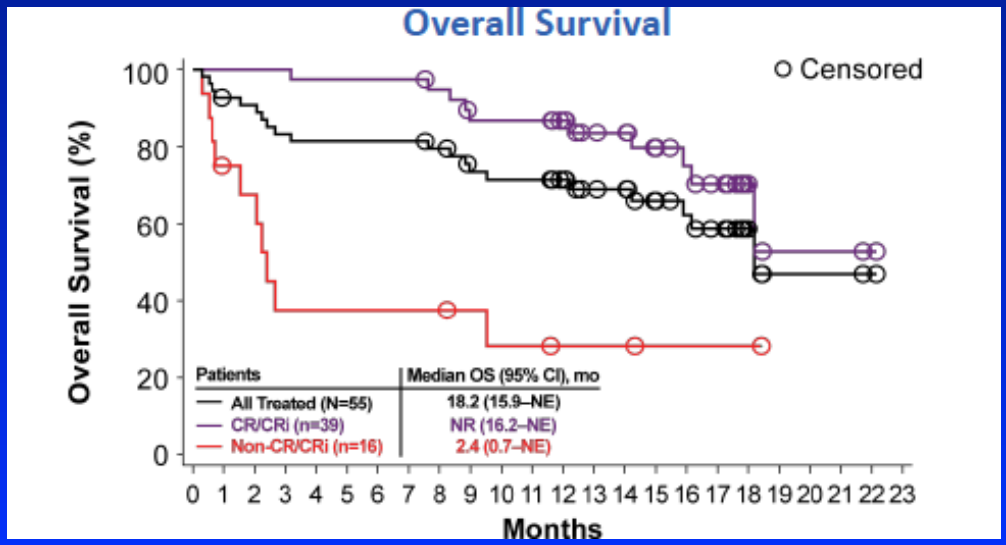
Phase 2 ZUMA-3 Study Evaluating KTE-X19 in Adult Patients With Relapsed/Refractory B-Cell ALL (Shah BD et al, *ASCO* 2021 and *Lancet Oncol* 2021)

N = 71; median age 40 (19-84)
prior Blina 45%, prior InO 22%, prior SCT 42%



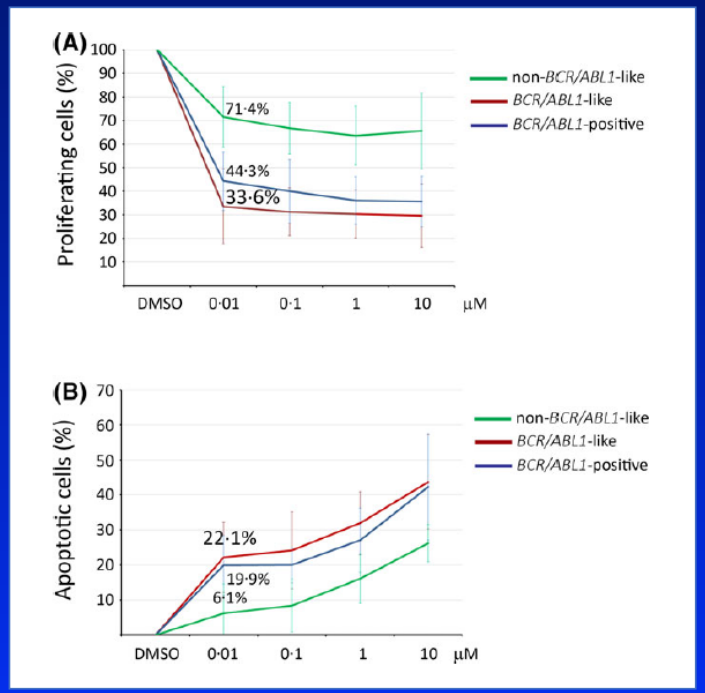
RESPONDERS (N = 39*)
Median OS NR, Median RFS 14.2 mos.

**9 to alloSCT, 5 to other, 12 relapsed, 1 died*



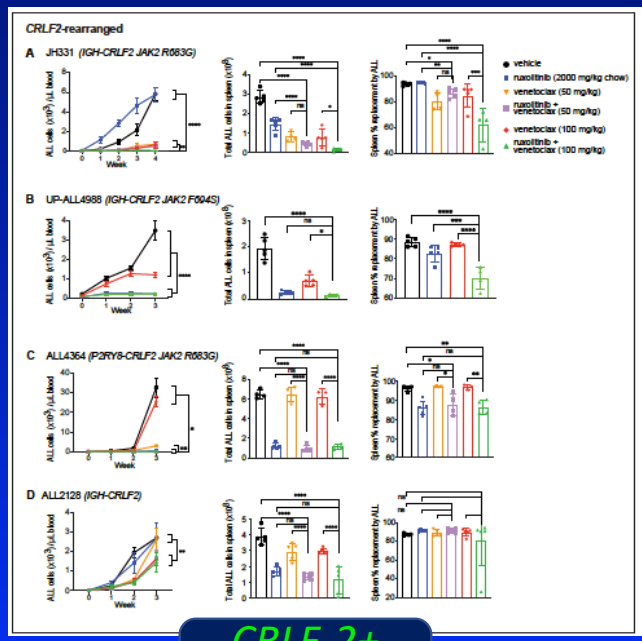
Drug Response Profiling for Ph-Like ALL

Ponatinib efficient killing of Ph-like ALL *(supporting new GIMEMA clinical trial)*

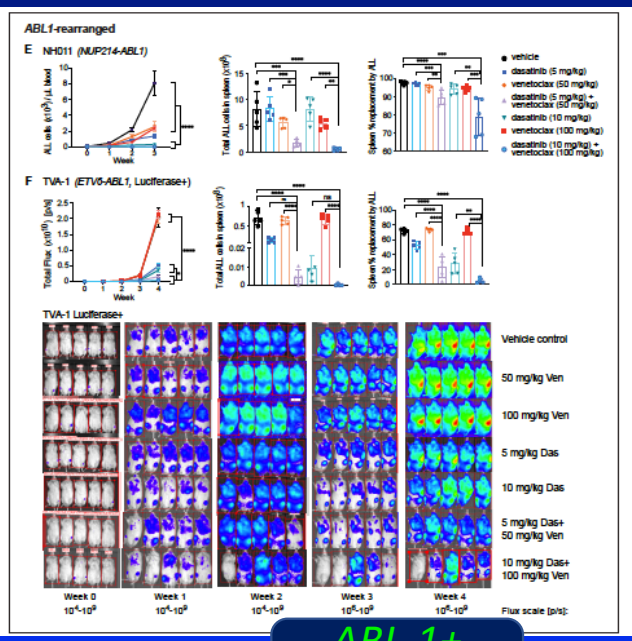


Chiaretti S et al, *Br J Haematol* 2018

Combinatorial drug discovery (venetoclax with dasatinib *or* ruxolitinib) based on systematic interrogation of synergistic vulnerability pathways with pharmacologic inhibitor validation in preclinical human leukemia models



CRLF-2+
VEN-RUX



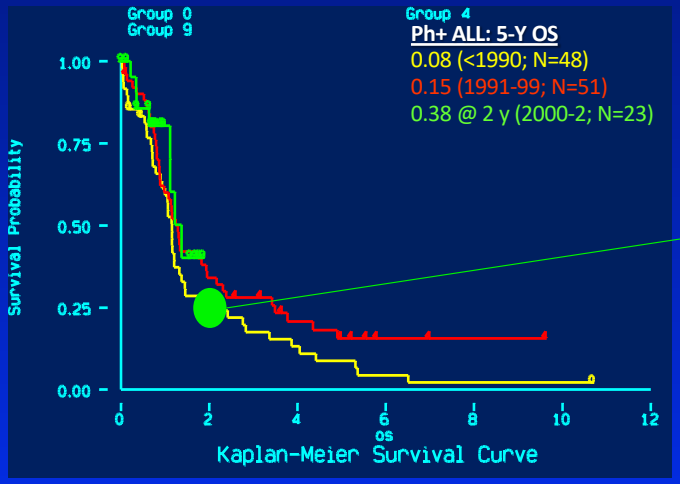
ABL-1+
VEN-DAS

Ding Y-Y et al. *Clin Cancer Res* 2021

Former Very HR subset: Ph+ ALL

NO Targeted Therapy

Chemo / Some transplants

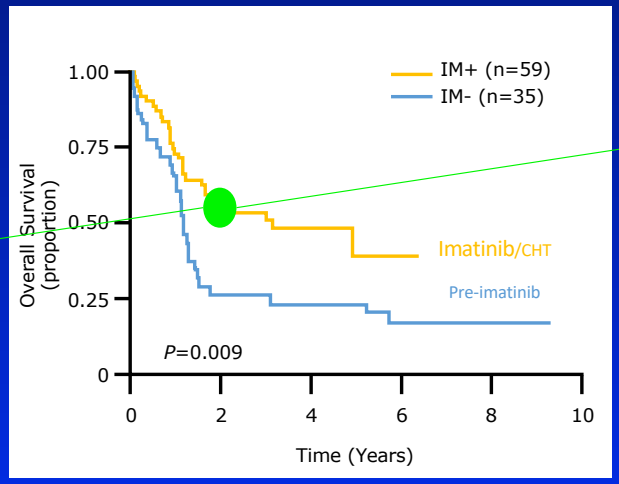


2-Y OS: 25%

Data on file (NILG data base);
Bassan R et al, *Hematology J* 2000

Targeted Therapy (imatinib)

Chemo / Transplants

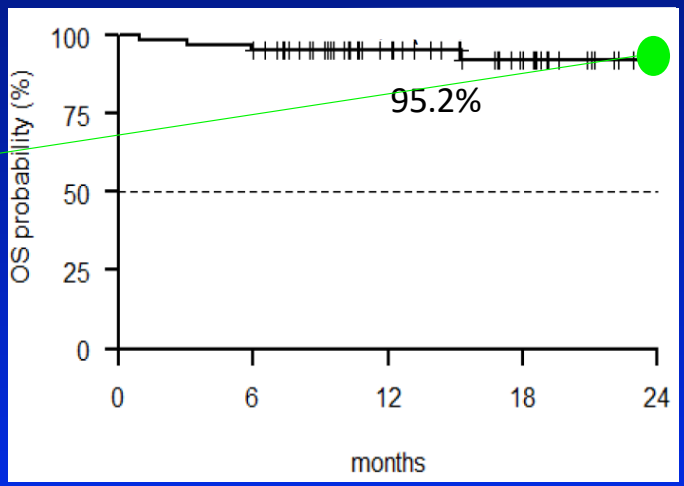


55%

Bassan R et al, *JCO* 2010

Dual Targeted Therapy (dasatinib/blinatumomab)

NO Chemo / LESS Transplants

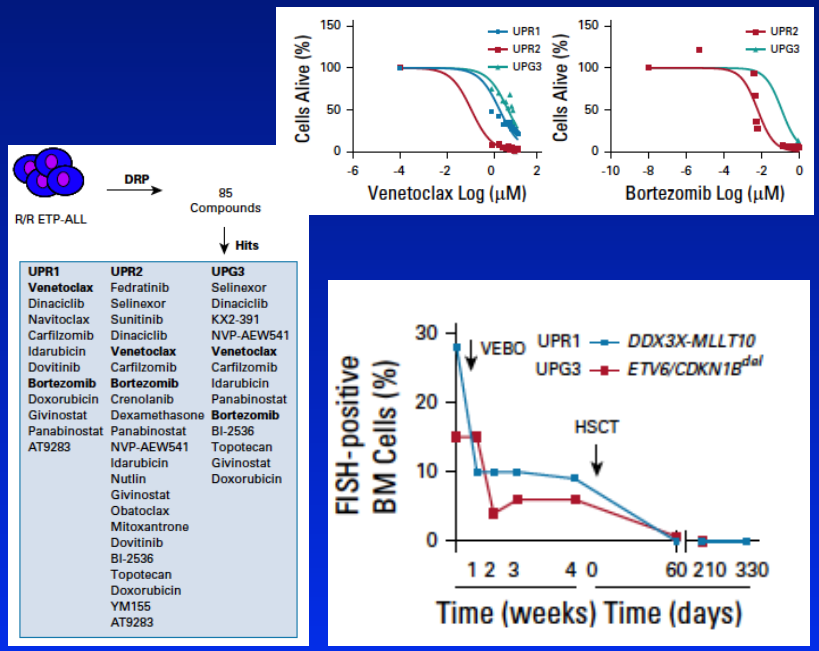


95%

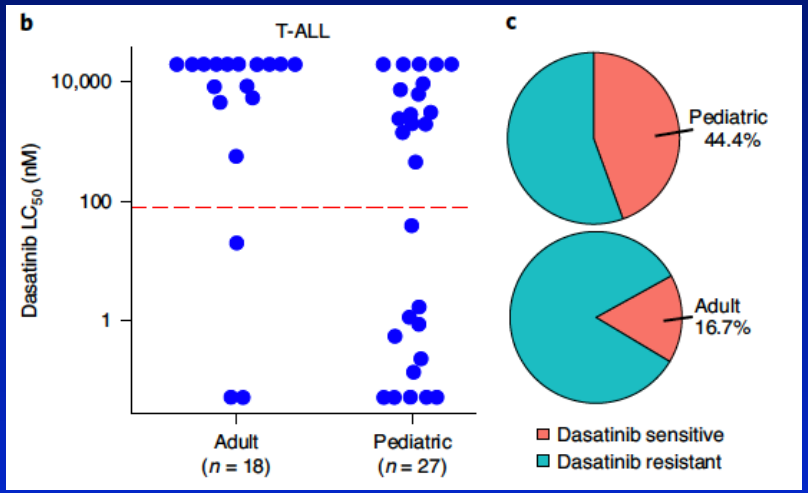
Foà R et al, *NEJM* 2020

Drug Response Profiling for HR T-ALL

- Highly refractory ETP-ALL sensitive to **bortezomib-venetoclax**



- T-ALL subset sensitive to **dasatinib**



Das-sensitive T-ALL

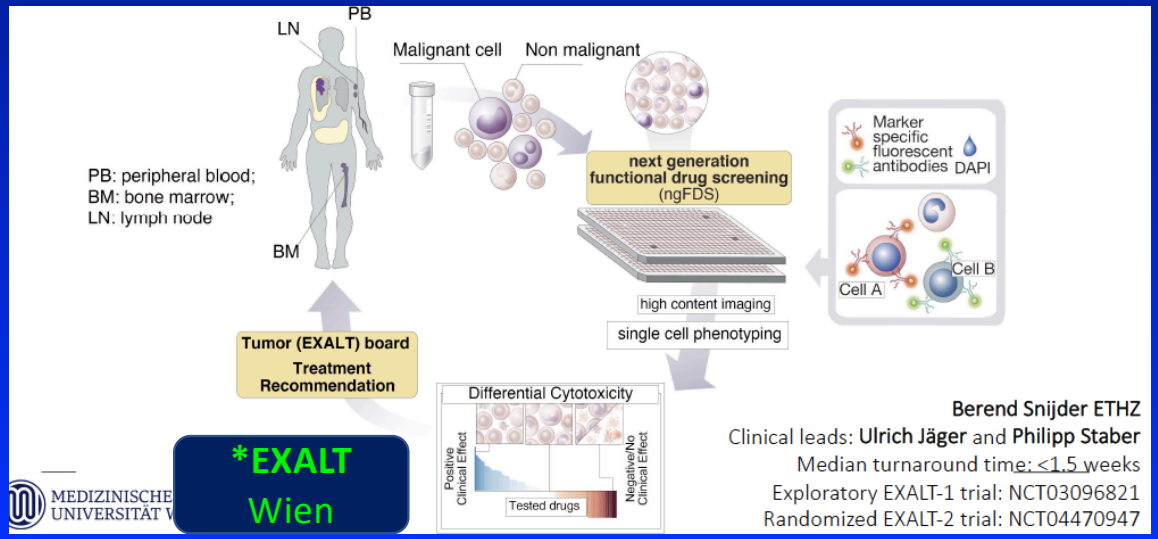
- LCK tyrosine kinase
- High BCL-XL
- Low BCL2
- Venetoclax resistance

La Starza R et al, *Cancer Discov* 2019

Gocho Y et al, *Nat Cancer* 2021

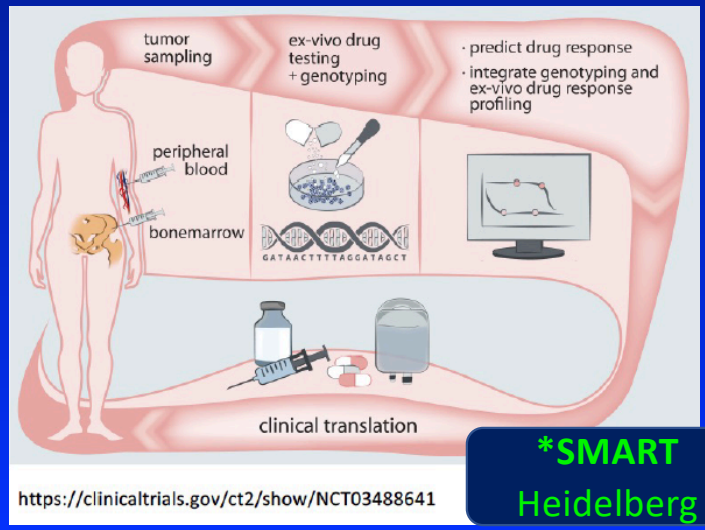
New Options to Expand Drug and Targeting Agent Combination Strategies for HR ALL

- **Highly specific:** Genetics, MRD and drug sensitivity patterns
- **Standard approach:** MRD targeting with Allo-SCT in CR1
- **<u>CHALLENGE:</u>** New targeted therapy integrated with genomics and case/subset-specific drug response profiling (trials: I-BFM pediatric; adult*)



***EXALT**
Wien

Berend Snijder ETHZ
Clinical leads: **Ulrich Jäger** and **Philipp Staber**
Median turnaround time: <1.5 weeks
Exploratory EXALT-1 trial: NCT03096821
Randomized EXALT-2 trial: NCT04470947



***SMART**
Heidelberg