Il futuro dello scenario terapeutico della LAL

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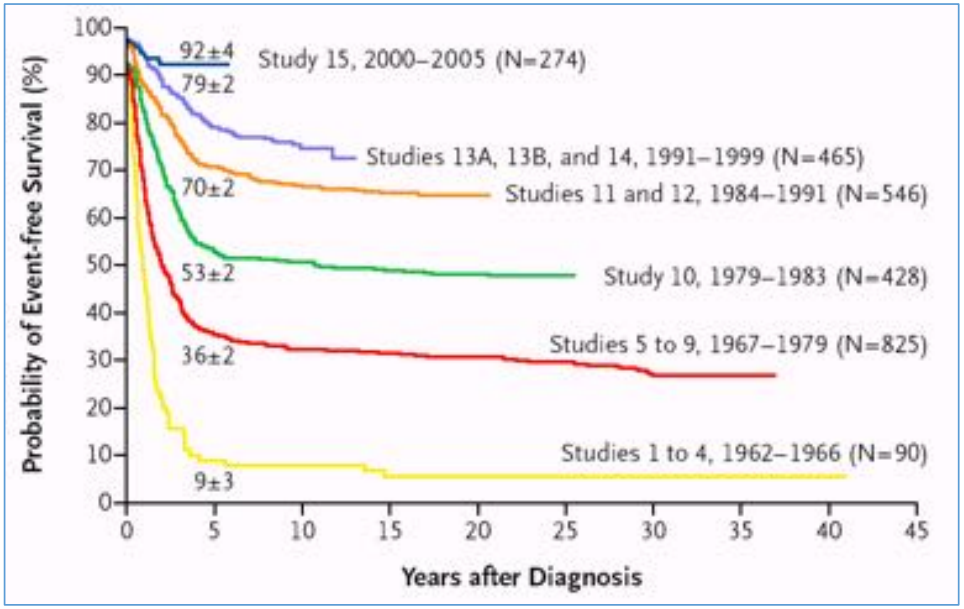
There was a future …

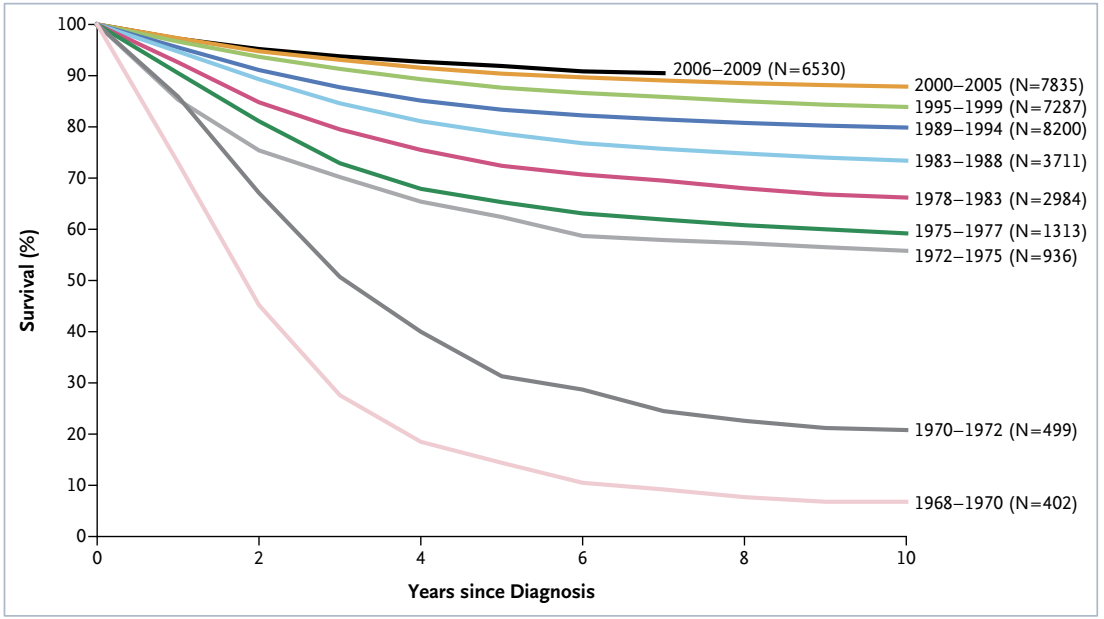
St. Jude's Hospital



2628 children, 6 trials

C-H Pui. *Semin Hematol* 50:185–196. 2013

CCG/COG



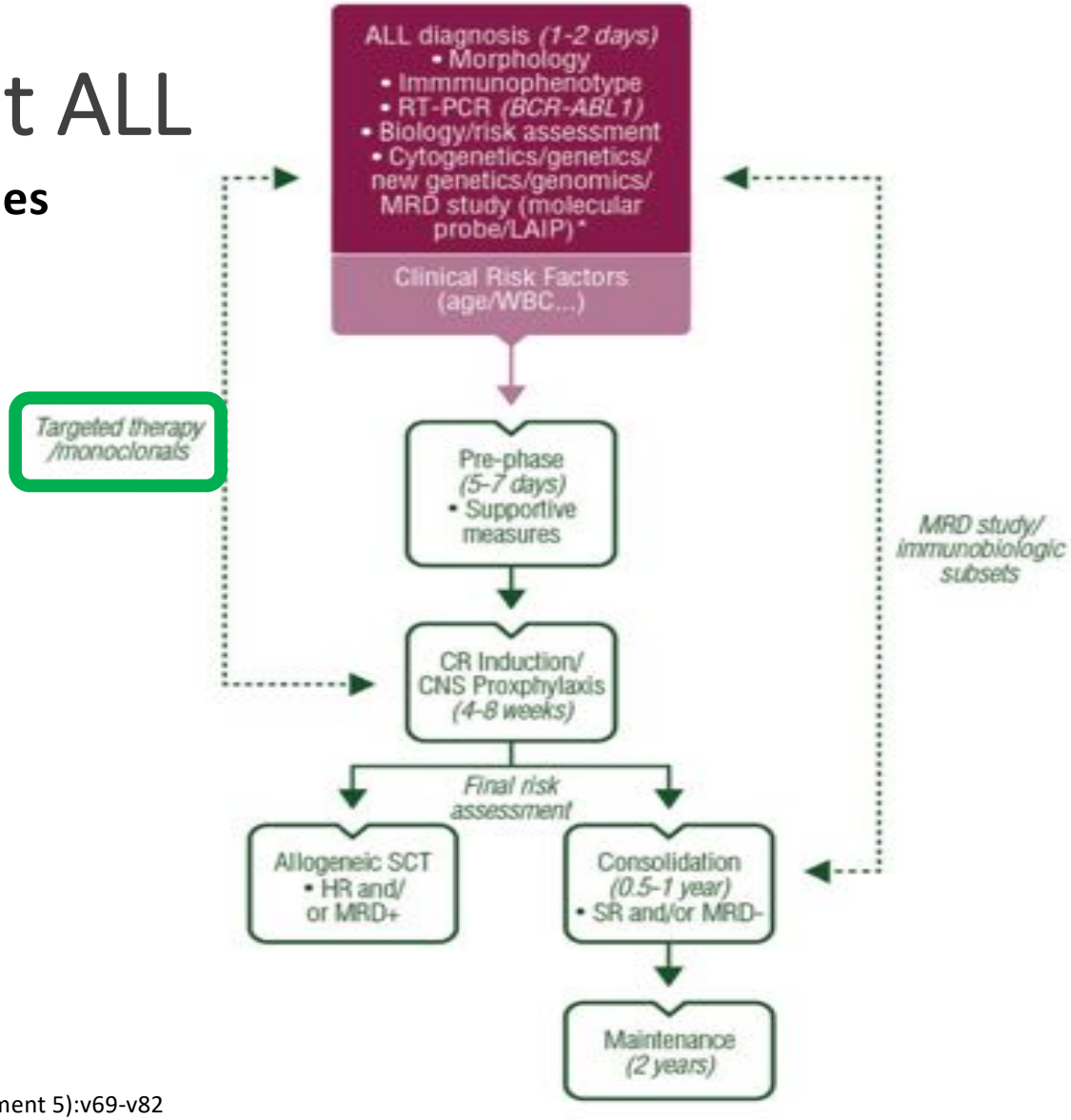
39.697 children, 10 trials

SP Hunger, CG Mullighan. *N Engl J Med* 373:1541-1552. 205

Essential steps in adult ALL

ESMO Clinical Practice Guidelines

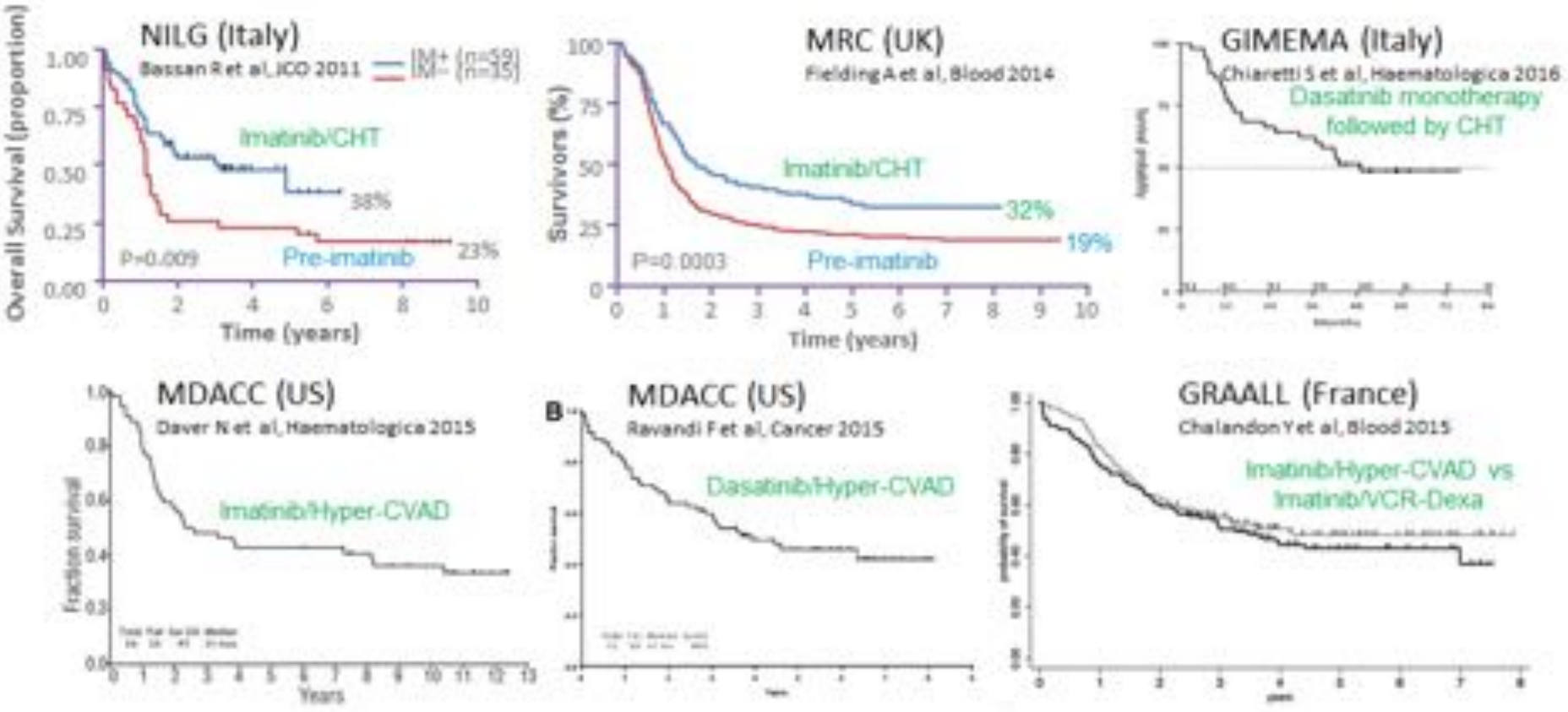
ALL SUBSETS and TARGETS
(TKI [Ph+], monoclonals, …)



Hoelzer D, Bassan R, Dombret H, Fielding, A, Ribera J & Buske A. *Ann Oncol* 2016;27 (Supplement 5):v69-v82
ESMO Gudelines update (D Hoelzer et al) and new **ELN Guidelines** under preparation (N Goekbuget et al)

* available at a later stage

Ph+ ALL: progress with TKI therapy



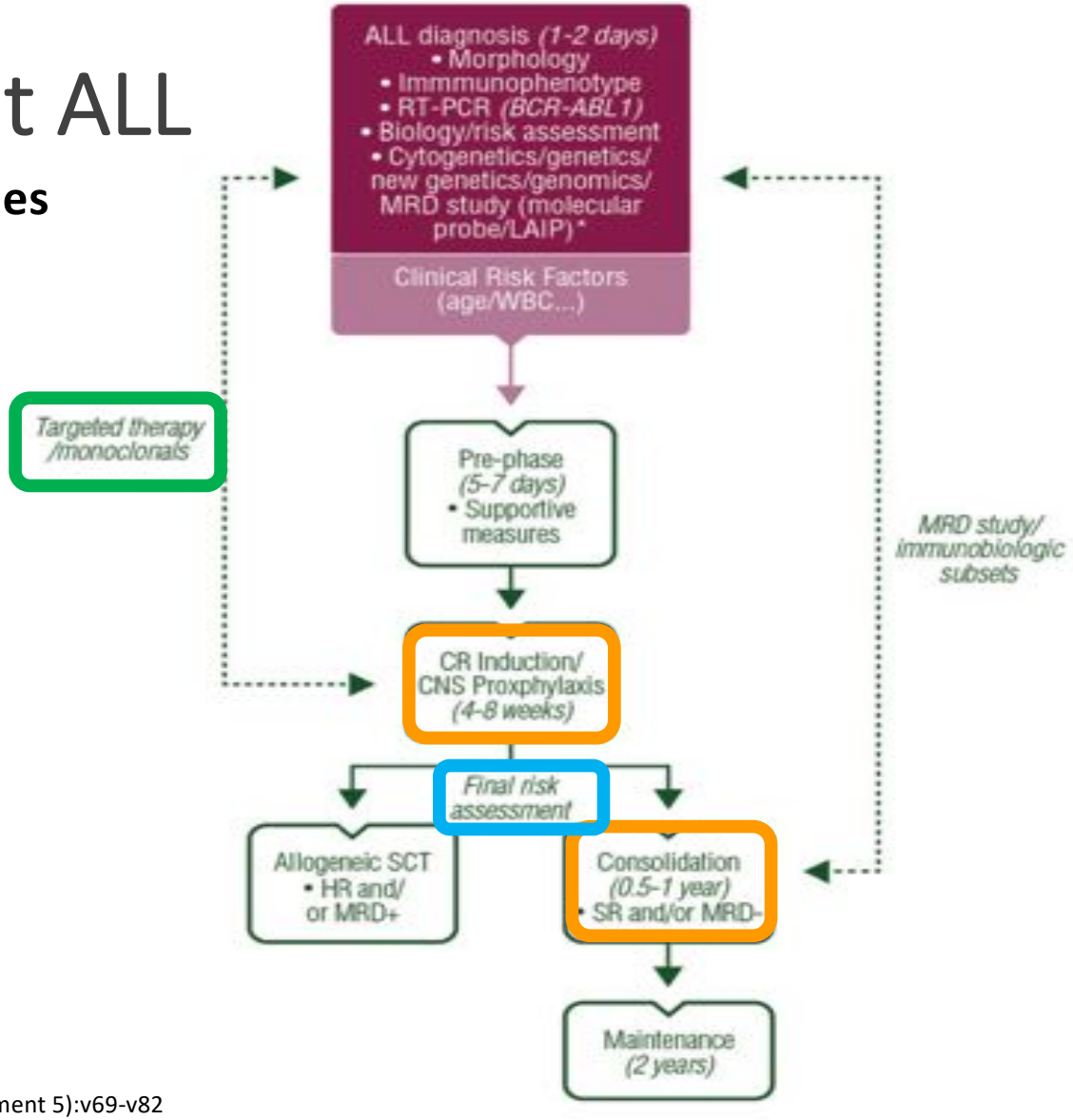
Essential steps in adult ALL

ESMO Clinical Practice Guidelines

ALL SUBSETS and TARGETS
(TKI [Ph+], monoclonals, …)

RISK STRATIFICATION
(MRD and genetics)

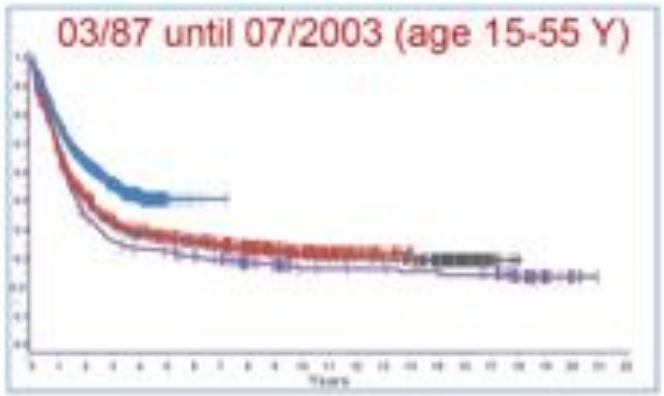
CHEMOTHERAPY
(pediatric-based [Ph-])



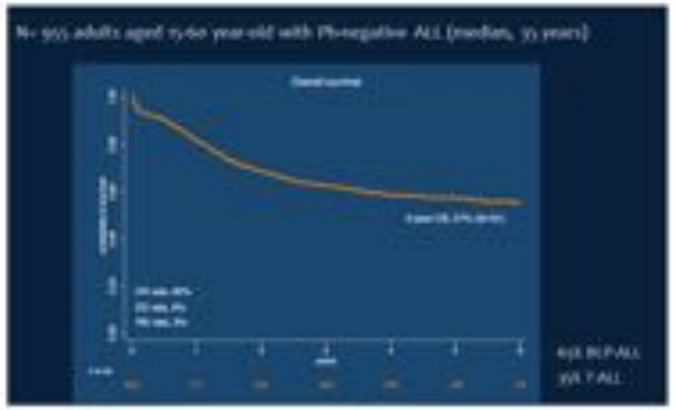
Hoelzer D, Bassan R, Dombret H, Fielding, A, Ribera J & Buske A. *Ann Oncol* 2016;27 (Supplement 5):v69-v82
ESMO Gudelines update (D Hoelzer et al) and new **ELN Guidelines** under preparation (N Goekbuget et al)

Ph- ALL: progress with ‘pediatric’-based and risk-oriented therapy

Germany: GMALL trials 03 - 07

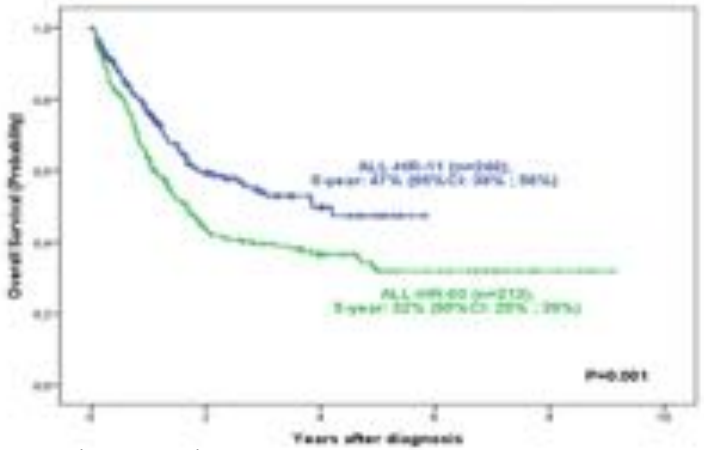


France: GRAALL trials 2003 - 2005



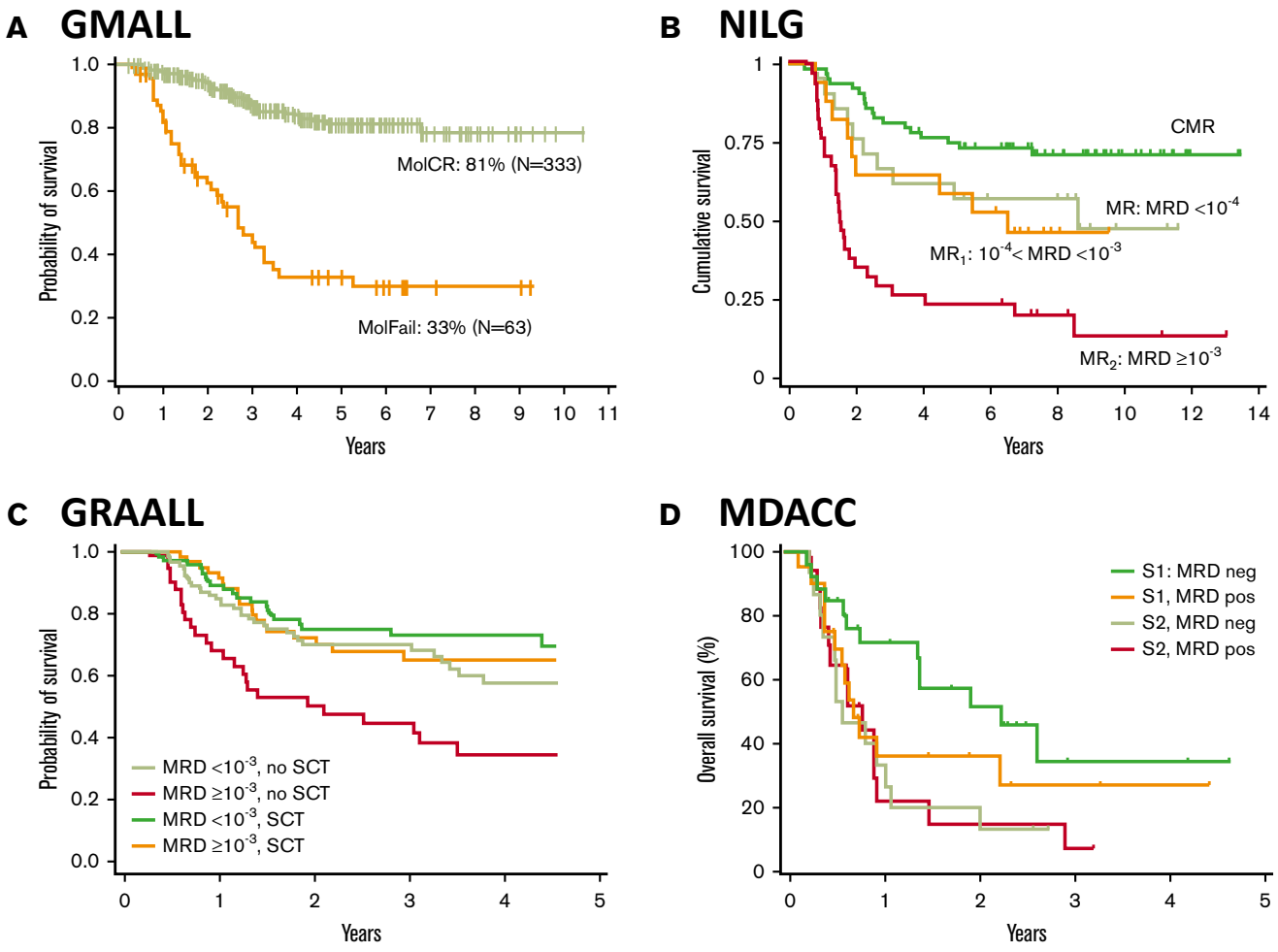
Italy: NILG trials 09/00 – 10/07

Spain: PETHEMA trials HR-03 - HR-11



Hoelzer D, 2010 (GMALL); Dombret H, *EHA 2014* (GRAALL); Bassan R et al, *ASH 2016* (NILG); Ribera J et al, *ASH 2015* (PETHEMA)

Risk stratification for risk-oriented therapy: MRD



These and other studies:

- **MRD most/only significant risk factor in M/V analysis**
- **MRD- pts do better**
  - can do without allo-SCT
- **MRD+ pts do worse**
  (both CR1 and salvage 1)
  - benefit from allo-SCT
  - MRD ≥ 10^{-3} is the worst

reviewed in:

Bruggemann M and Kotrova M, *Blood Adv* 2017

see also:

Goekbuget N et al, *Blood* 2017 (abstr)

Bassan R et al, *Clin Lymph Myeloma Leuk* 2017

Berry DA et al, *JAMA Oncol* 2017

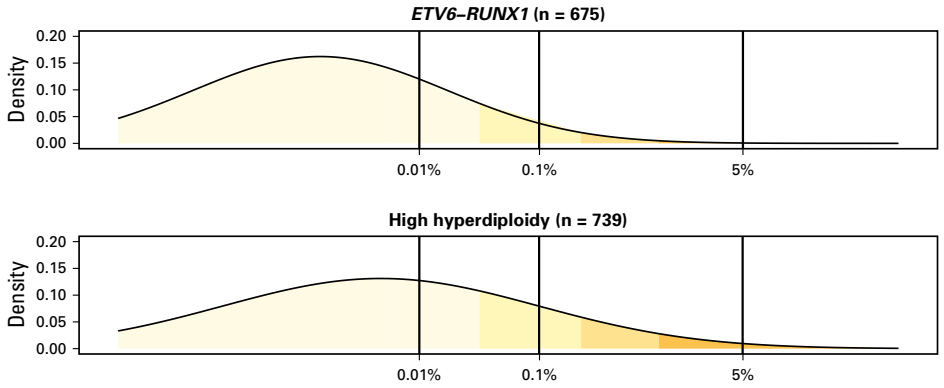
Bassan R, Bruggemann M et al, *Haematologica* 2019

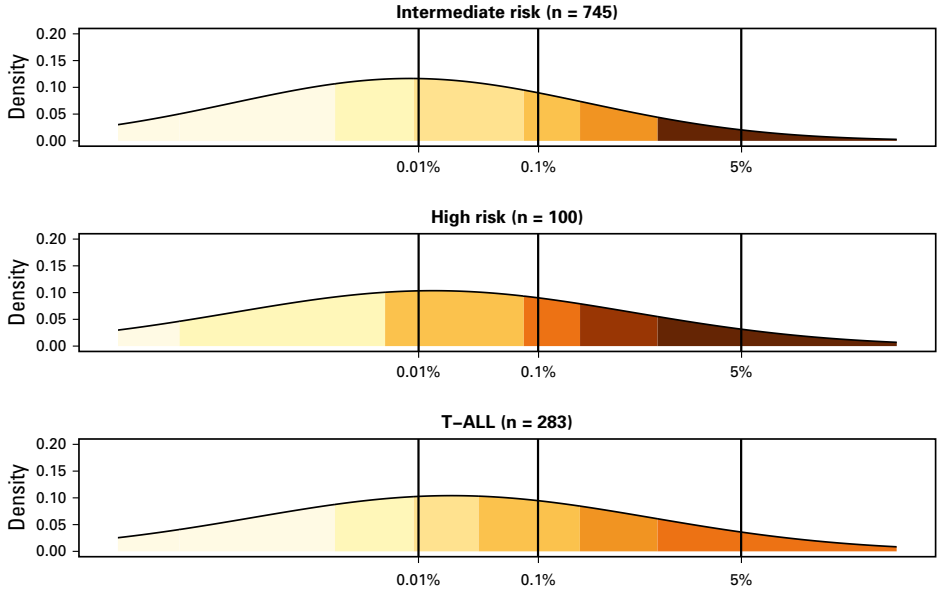
Mixed genetic/MRD pediatric risk model

(O'Connor D et al, *J Clin Oncol* 2018)

Intermediate risk, High risk

Good risk



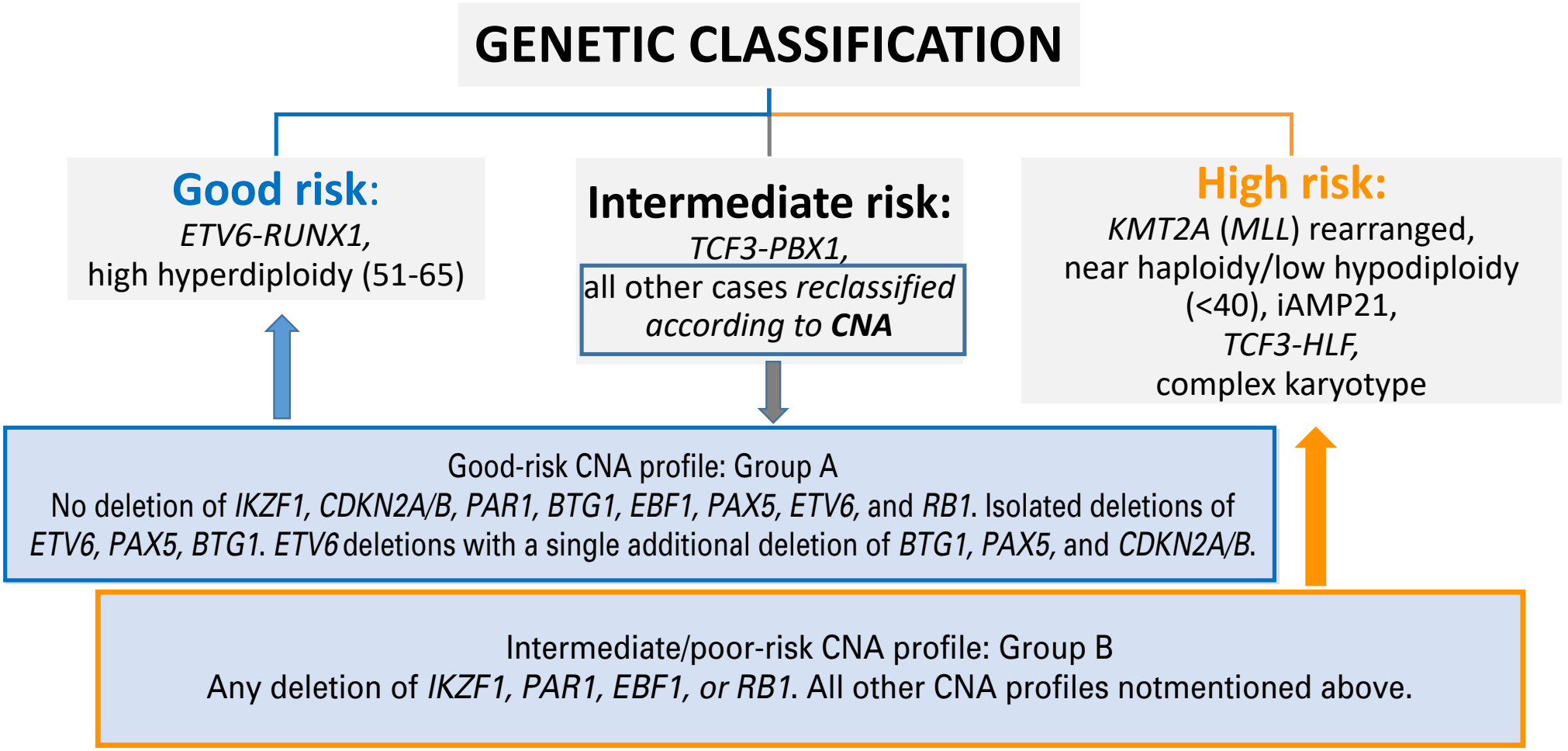


T-ALL

Increasing Relapse Rate at 5 Years (1%–45%)

Genetic risk classification: UKALL14 adult trial

(also pediatric UKALL, DCOG, NOPHO, CoALL etc. [*ALL-together project, age 1-45 Y*])



Risk stratification (PI_{UKALL} score)

TWO WEIGHTED LOG-TRANSFORMED CONTINUOUS VARIABLES

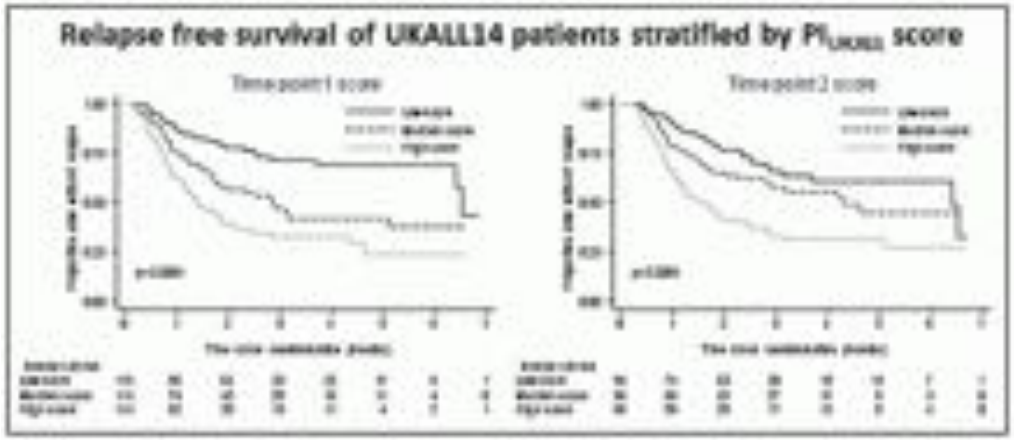
- **WBC**
- **End of induction MRD (PI1, PI2)**

TWO WEIGHTED BINARY VARIABLES

- **High risk genetics**
- **Good risk genetics**

High relapse risk with MAC SCT (N=53, RR 42%)

Excellent outcome on chemo (N=51, EFS 90%)

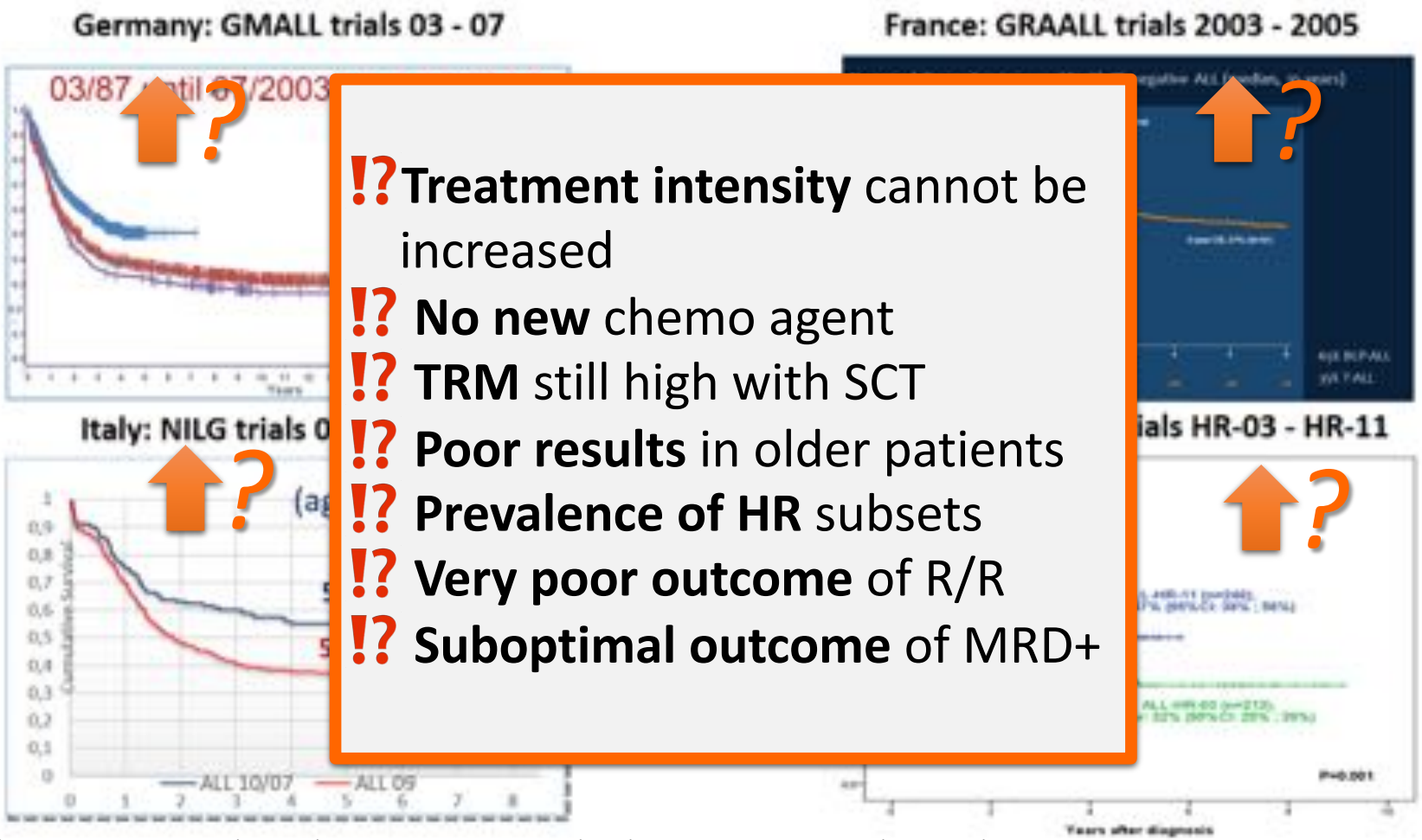


Selected examples of how PI_{UKALL} can be used to identify patients on the same treatment pathway who have differential outcomes

	Hazard ratio (95% CI)	3 years rates (95% CI)	p value
Risk of relapse after myeloablative alloSCT (n=53)			
PI2 score ≤ -1.5	1	5% (1-19)	0.006
PI2 score > -1.5	11.1 (2-62)	42% (18-78)	
Event free survival (EFS) after RIC alloSCT (n=105)			
PI2 score ≤ -2.0	1	62% (45-75)	0.004
PI2 score > -2.0	2.3 (1.3-4.1)	31% (17-46)	
EFS of standard risk patients after maintenance chemotherapy (n=51)			
PI1 score ≤ -2.25	1	90% (66-98)	0.041
PI1 score > -2.25	5.1 (1.1-24.3)	71% (45-86)	

[2]Moorman A et al, *HemaSphere* 2019;3(S1):748-9 (abstr #S1621)

What about the future?



- ⁉ **Treatment intensity** cannot be increased
- ⁉ **No new** chemo agent
- ⁉ **TRM** still high with SCT
- ⁉ **Poor results** in older patients
- ⁉ **Prevalence of HR** subsets
- ⁉ **Very poor outcome** of R/R
- ⁉ **Suboptimal outcome** of MRD+

Hoelzer D, 2010 (GMALL); Dombret H, *EHA 2014* (GRAALL); Bassan R et al, *ASH 2016* (NILG); Ribera J et al, *ASH 2015* (PETHEMA)

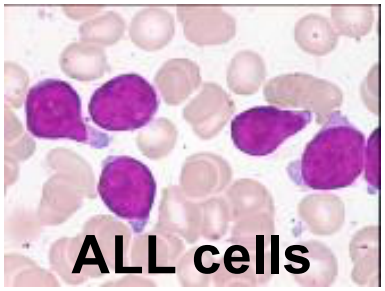
Approach: new targeted therapy frontline

Targeting B-/T-cell membrane antigens

- **Monoclonal antibodies and derivatives** (e.g. *rituximab [CD20], inotuzumab ozogamicin [CD22], blinatumomab [CD19 x CD3]*)
- **Chimeric antigen receptor T-cells and NK-cells** (*CD19, CD20, CD22; CD5, CD7*)
- **Checkpoint inhibitors** (e.g. *nivolumab, pembrolizumab [PD1, PD-L1]*)

Targeting proliferation, apoptosis and differentiation pathways

- **Inhibitors** (*TKI, NOTCH1, BCL2/BCX, BCL6, JAK/STAT, HDAC, MYC, mTOR, PI3K, SYK, MEK, MDM2…)*
- **Agonists** *(P53, SMAC-mimetics, …)*
- **Differentiating agents** *(IL-3, M-/GM-CSF)*



- **Inhibitors** (*CXCR/CXCL, NOTCH3/4*)

Targeting the permissive marrow niche

Dysfunctions related to abnormal ALL genetics and CNA

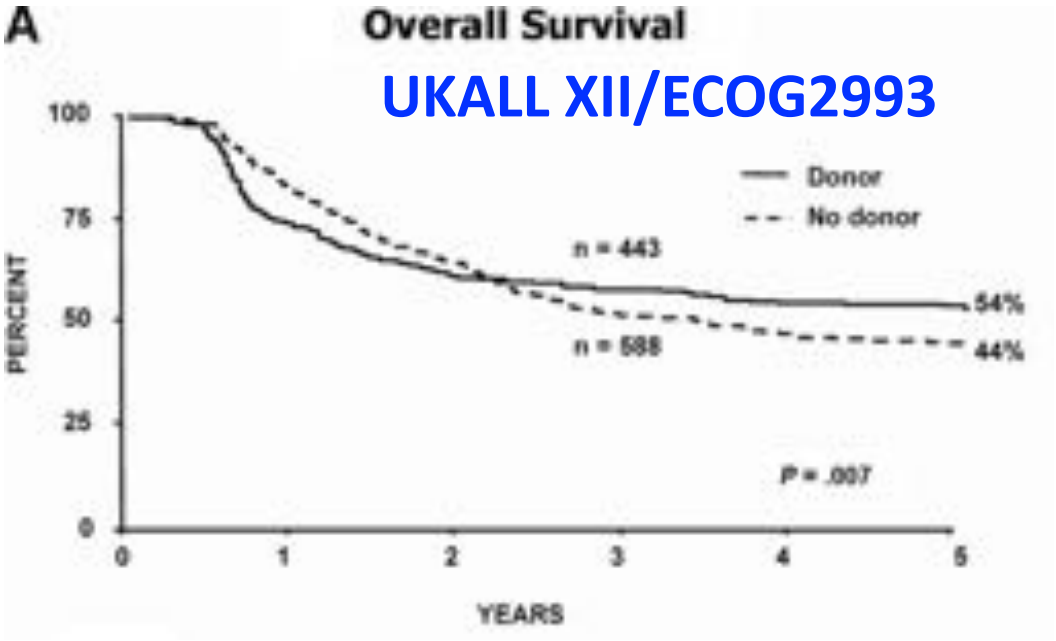
Molecular profiling
- **Actionable targets**

New drug profiling, PDX models
- **Drug sensitivity**
- **Drug combinations**

Bassan R, Bourquin J-P, DeAngelo DJ, Chiaretti S. *J Clin Oncol* 2018 (REVIEW)

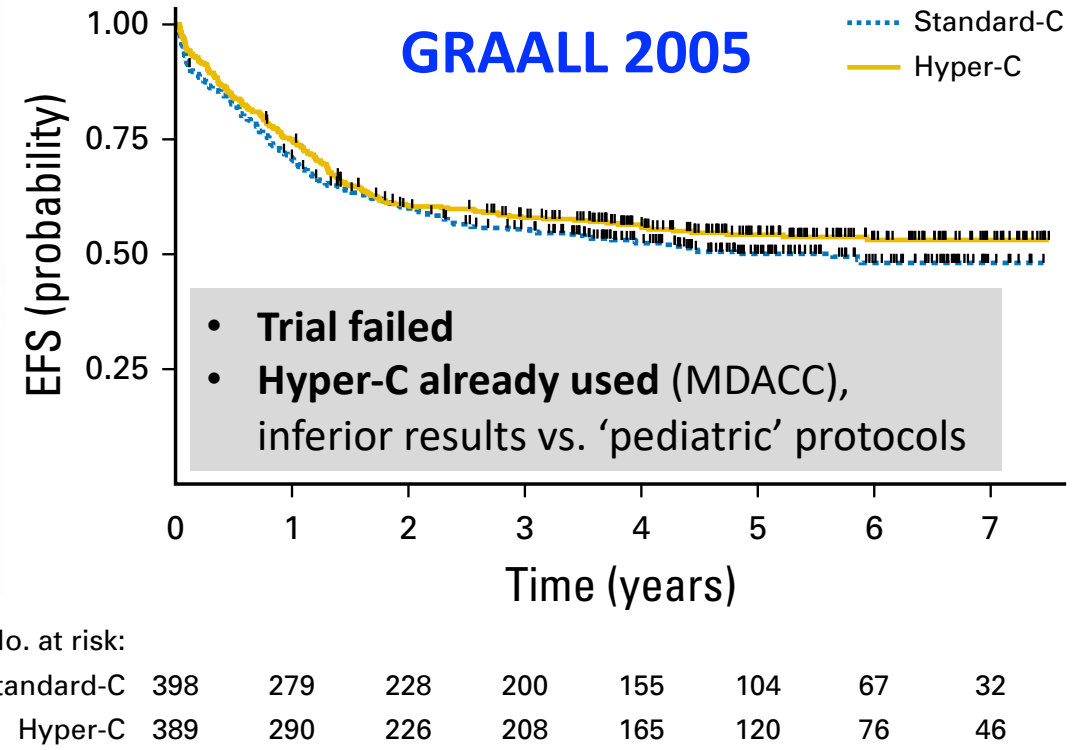
See also: Wolach O et al, *Br J Haematol* 2017; Jabbour E et al, *JAMA Oncol* 2018 (REVIEWS)

Questions about randomized trials



- **Superiority of allo-SCT in SR ALL**
- **Allo-SCT abandoned in SR ALL** (MRD-based), applied in HR ALL (not UKALL-ECOG defined)

N = **1.031**; 1993 → 2008 (**13 Y**)



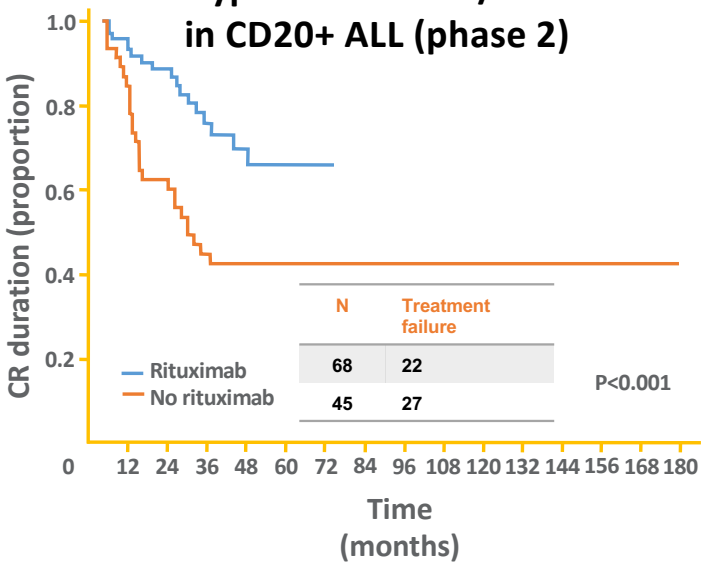
- **Trial failed**
- **Hyper-C already used** (MDACC), inferior results vs. 'pediatric' protocols

N = **787**; 2005 → 2018 (**13 Y**)

Targeting CD20+ ALL (rituximab)

M.D. Anderson Cancer Center (U.S.)

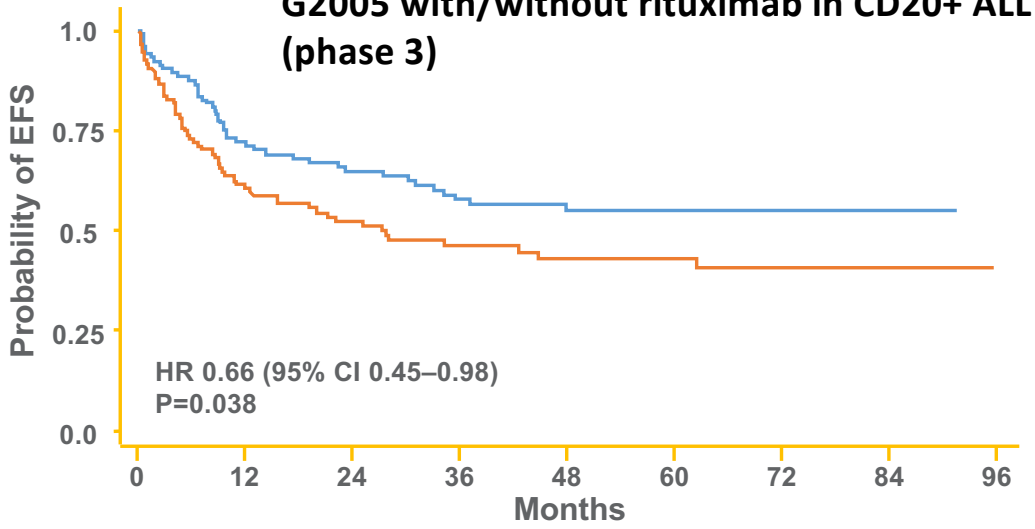
Hyper-CVAD with/without rituximab in CD20+ ALL (phase 2)



Thomas DA. *J Clin Oncol* 2010;28:3880

GRAALL (France/Belgium/Switzerland)

G2005 with/without rituximab in CD20+ ALL (phase 3)

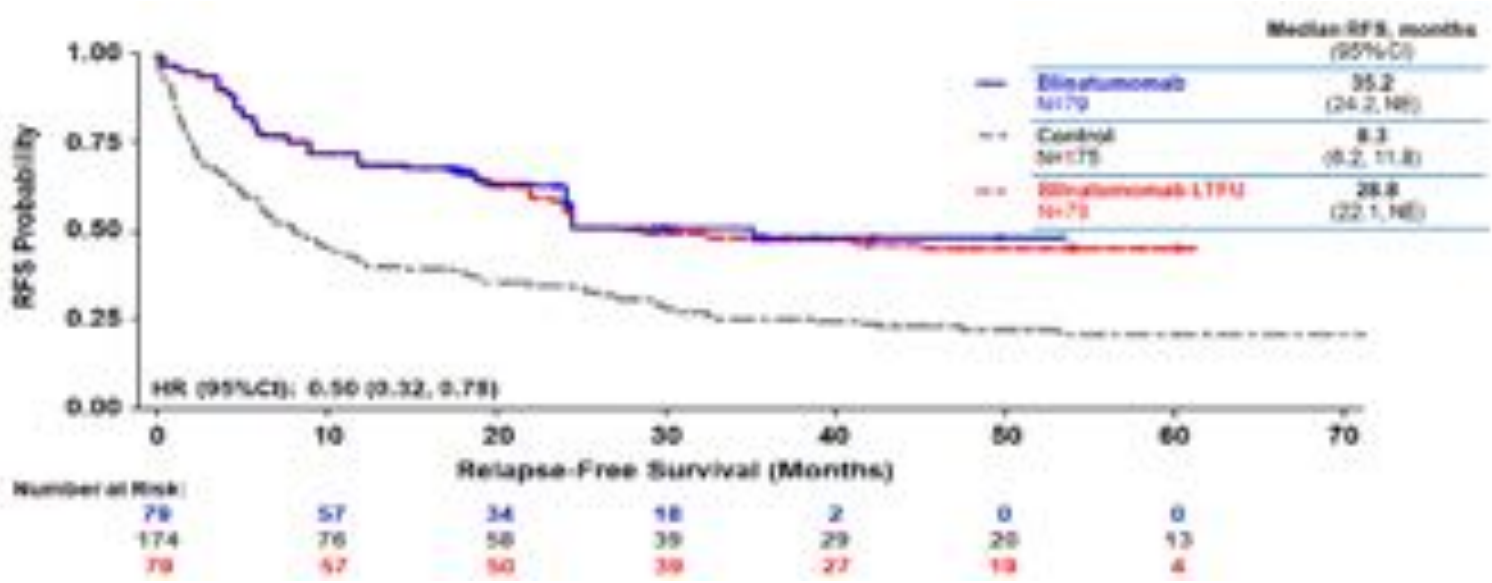


Maury S et al. N Engl J Med. 2016 Sep 15;375(11):1044-53

Blinatumomab for MRD+ Ph-neg BCP-ALL*

Blinatumomab (#79) compared to historical SOC (#175)

- Patients in first CR with **MRD ≥10^{-3}**: **79% MRD negative with blinatumomab**
- Kaplan–Meier curve of RFS after propensity score adjustment using stabilized inverse probability of treatment weighting (IPTW)



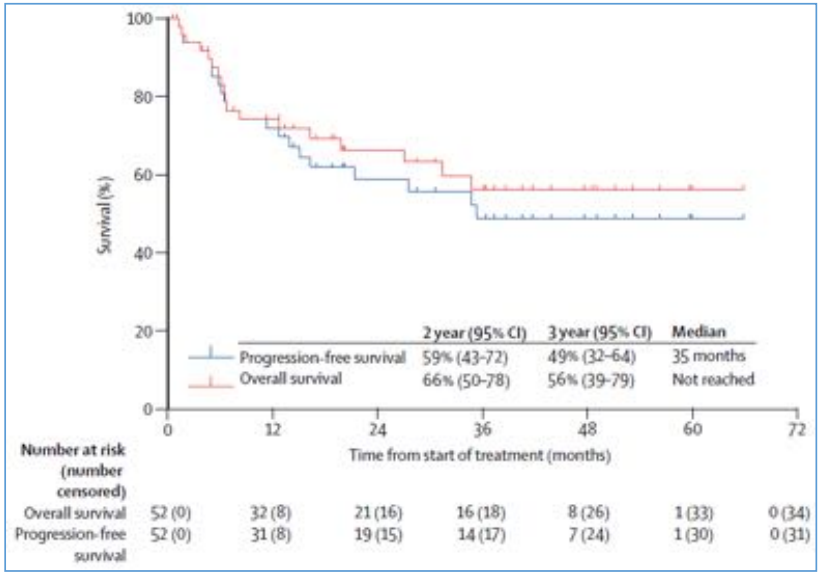
***LARGER TRIAL («Blast») IN MRD+ ALL vs. international reference set MRD+ ≥10^{-3}**

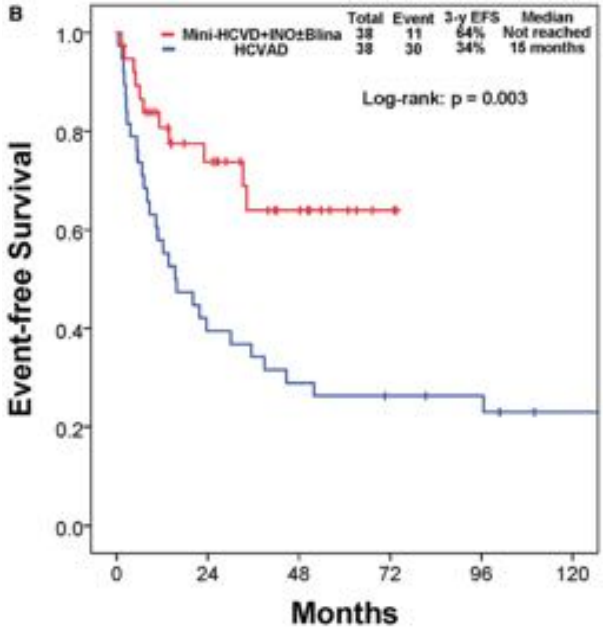
Goekbuget N et al, *ASH* 2015; *Blood* 2017; *Hematology* 2019; (submitted 2019)

Inotuzumab ozogamicin with/without blitamumomab and rituximab in elderly ALL

Attenuated CVD/InO/rituximab	
N	52
Age (Y)	**68** (64-72)
CR	**98%**
MRD neg	**96%**

Attenuated CVD/InO/blina/ritux	
N	58
Age (Y)	**68** (60-81)
CR	**98%**
MRD neg	-





Kantarajian HM et al, *Lancet Oncol* 2018; Jabbour EJ et al, *Cancer* 2019

Platform for drug sensitivity screening

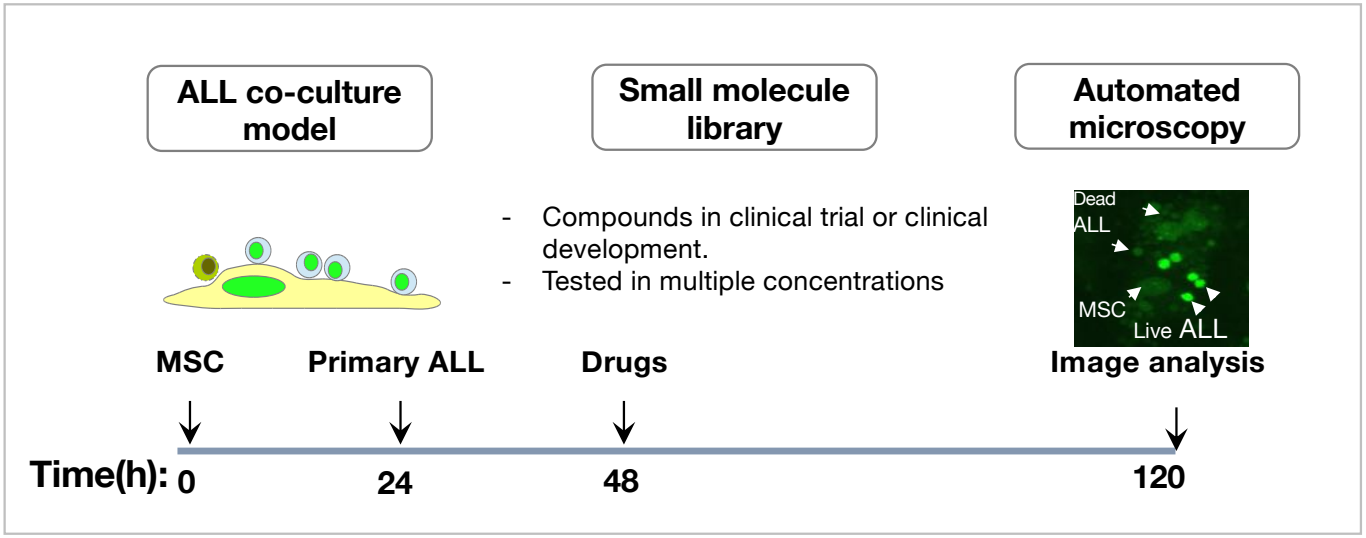
Primary ALL sample (patient)

Xenograft model (PDX)

Stable disease geno- and phenotype

Functional "Omics"
In vivo drug activity

Blood 2011, 2013
Science Translational Medicine 2016

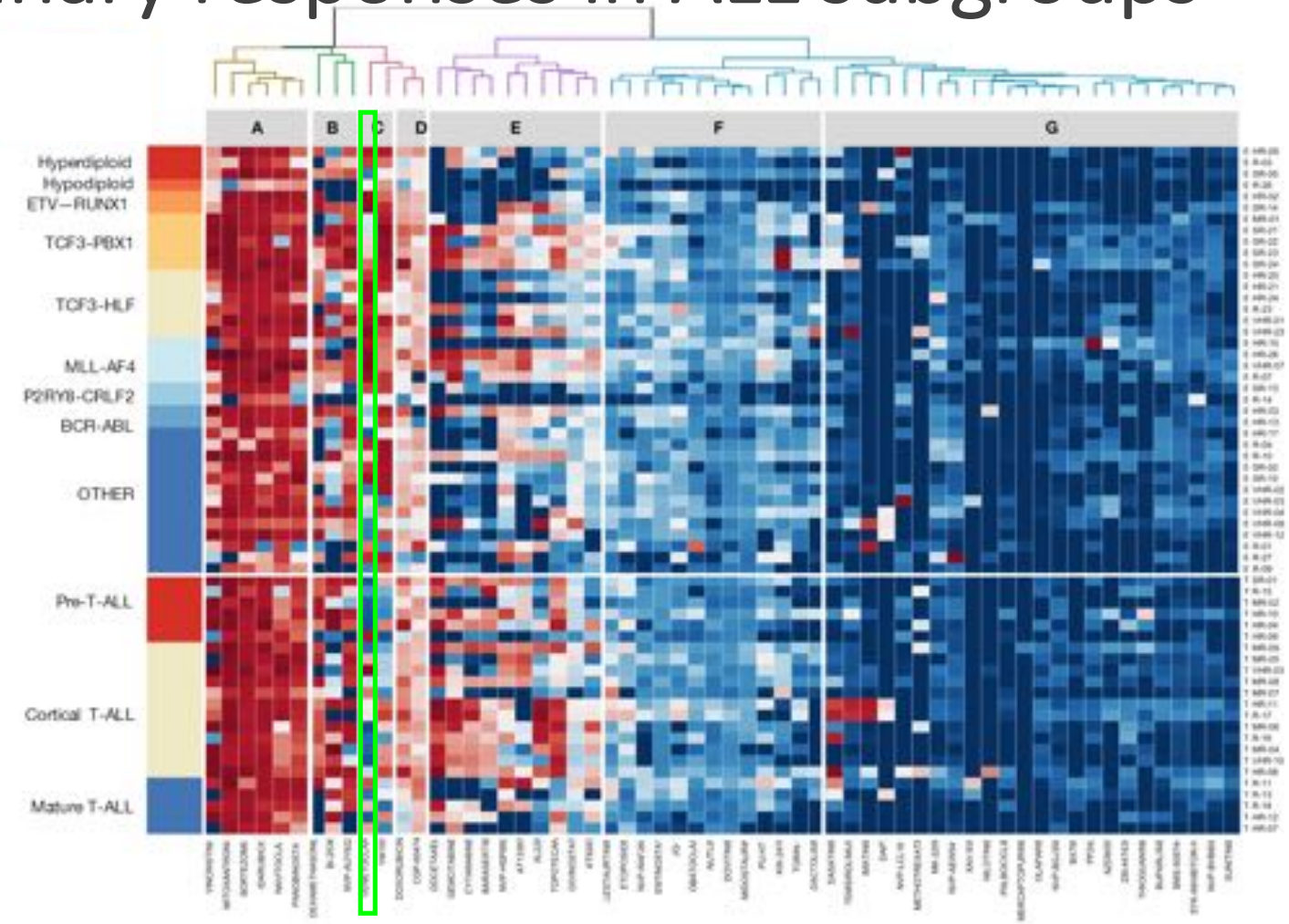


Drug response phenotypes

Oncotarget 2014, Blood 2017, *Nature Genetics* 2016

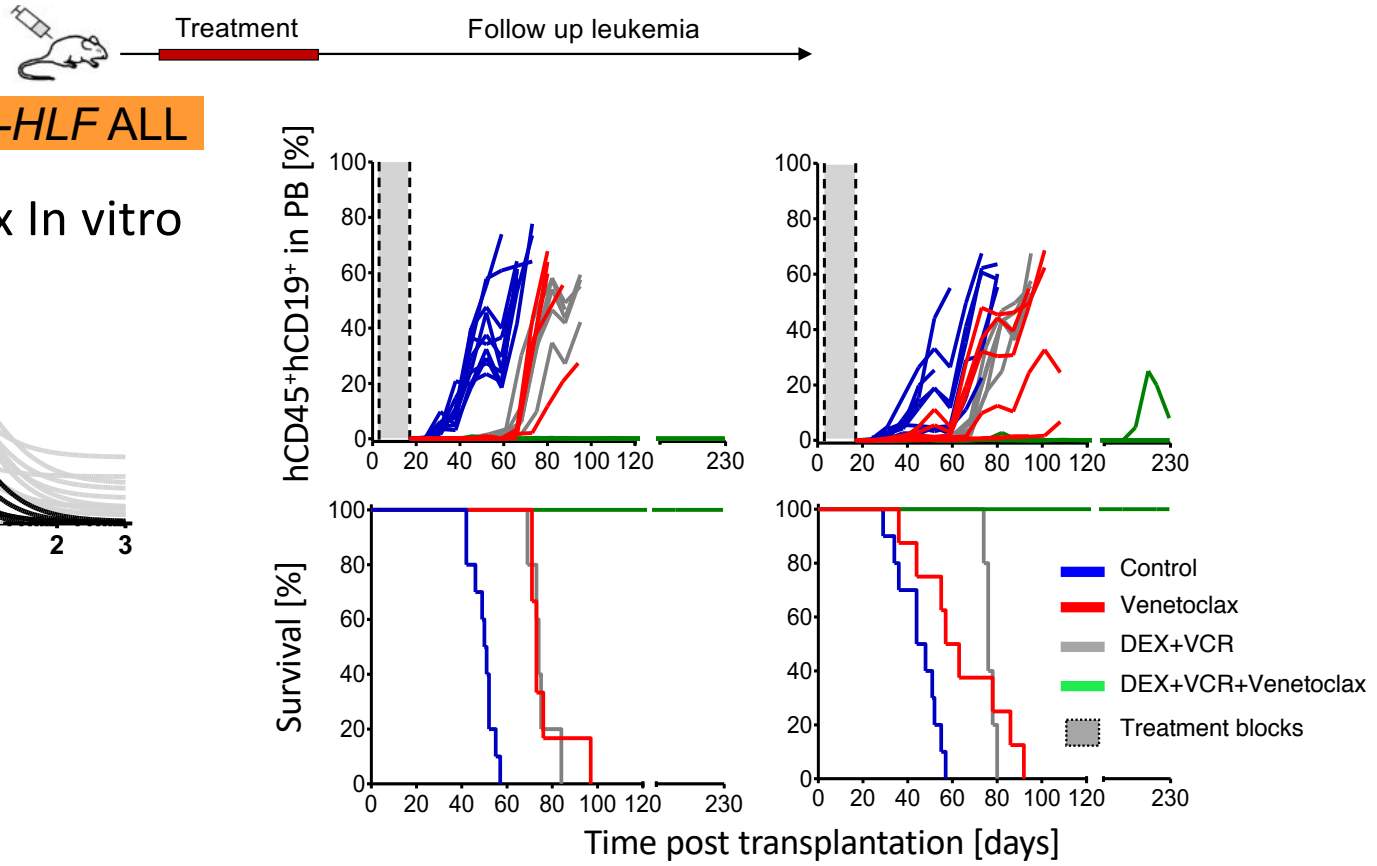
Courtesy
J-P Bourquin

Extraordinary responses in ALL subgroups



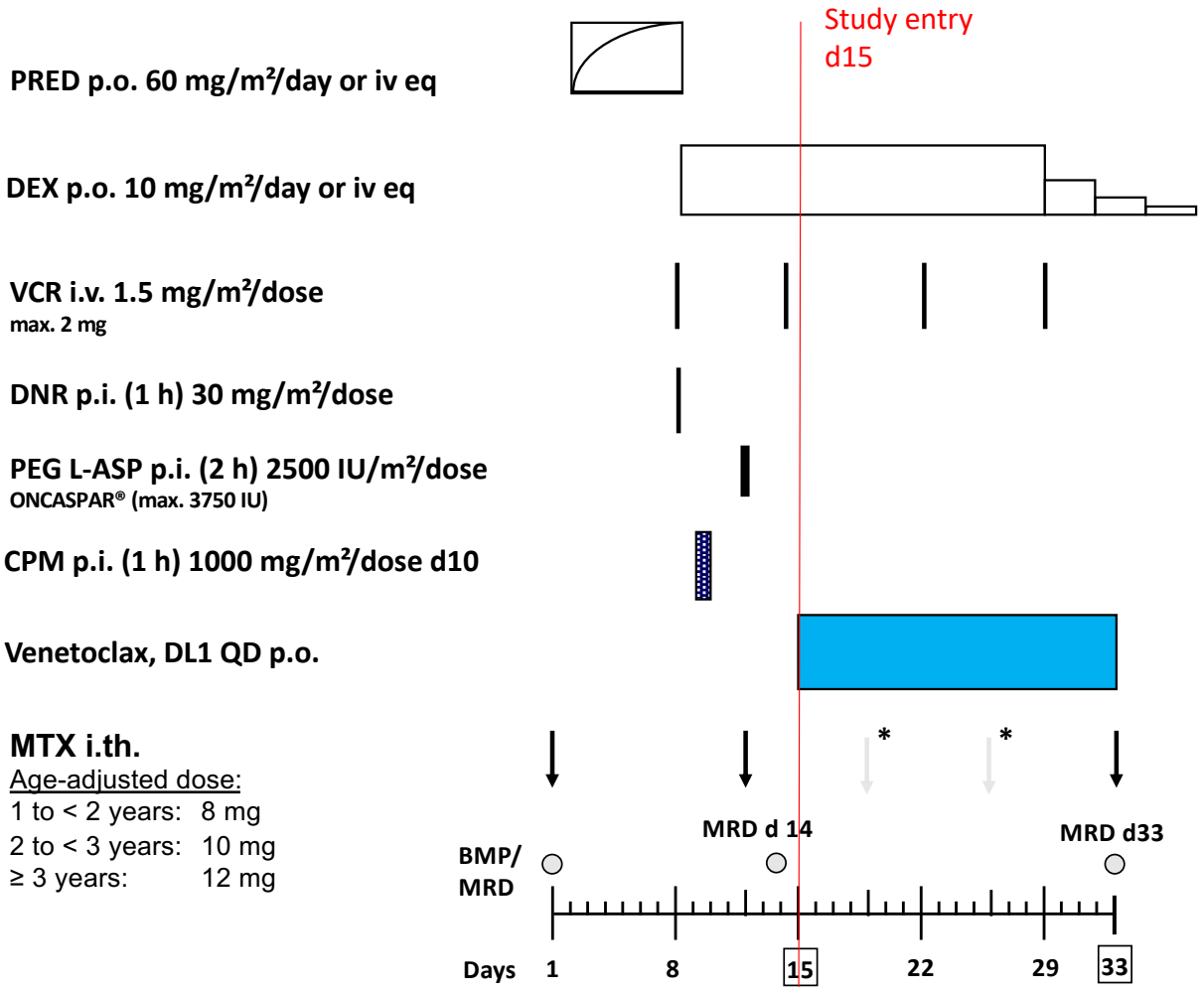
BCL2 inhibitor venetoclax

Venetoclax eliminates ALL in combination with chemotherapy



V. Frismantas et al, *Blood* 2017; Fischer et al, *Nature Genetics* 2015,

Concept for TCF3-HLF ALL



Shaping the future

From preclinical testing to the clinics

Any ALL subset*

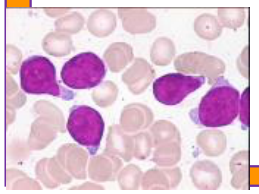
**by trial eligibility*

MoAb's: PBD-conjugated (CD25)

Inhibitors: proteasome (bortezomib/ ixazomib), TKI, mTOR, DRD2, MDM2, PARP, MEK1/2, PI3K, SYK, hedgehog, CXCR-4, PD-L1

Agonists: *GLIPR1* (p53)

Inhibitors: multiple kinase/other inhibitors *(molecular profiling)*



BCP ALL (unselected)

MoAb's: rituximab/ ofatumumab (CD20), inotuzumab (CD22), blinatumomab (CD19), others (CD123)

CAR T/NK cells: CD19, CD20, CD22, ROR1

Inhibitors: TKI, BCR (ibrutinib), CD4/6, CTLA-4, proteasome (carfilzomib), HDAC, PD-1/PD-L1, FLT3, BCL2

Inhibitors: multiple kinase/other inhibitors *(molecular profiling)*

NOTCH3/4

Agonists: SMAC mimetics, PYST1 (p53)

Ph+ ALL

Dual targeted therapy: TKI + blinatumomab, TKI + inotuzumab, TKI + nivolumab, TKI + ruxolitinib, TKI + ibrutinib

New TKI: ABL001 (ABL1 myristoyl pocket), danusertib (Aurora kinase A/B/C)

Inhibitors: VEGFR (axitinib)

Other: retinoids (*IKZF1*del), cell differentiation promoters (IL-3, M-/GM-CSF)

Ph-like ALL

Inhibitors: dasatinib/other TKI, JAK/STAT (ruxolitinib)

Inhibitors: multiple kinase inhibitors *(molecular profiling)*

KMT2A+ ALL

Inhibitors: CDK4/6

Inhibitors: BCL2/BCL-X_L (venetoclax/ navitoclax), DOT1L, HDAC

pre-BCR+, *TCF3-PBX1*+ and *HLF*+ ALL

Inhibitors: CDK4/6

Inhibitors: TKI, BCR/BCL6 (ibrutinib), *PIK3CD* (idelalisib), BCL2 (venetoclax in *TCF3-HLF*+)

B-mature ALL (Burkitt)

Inhibitors: MYC/BET, CDK7

Inhibitors: mTOR, PI3K, HDAC, Aurora kinase A and B

TCP ALL

MoAb's: isatuximab (CD38)

CAR T/NK cells CD5, CD7

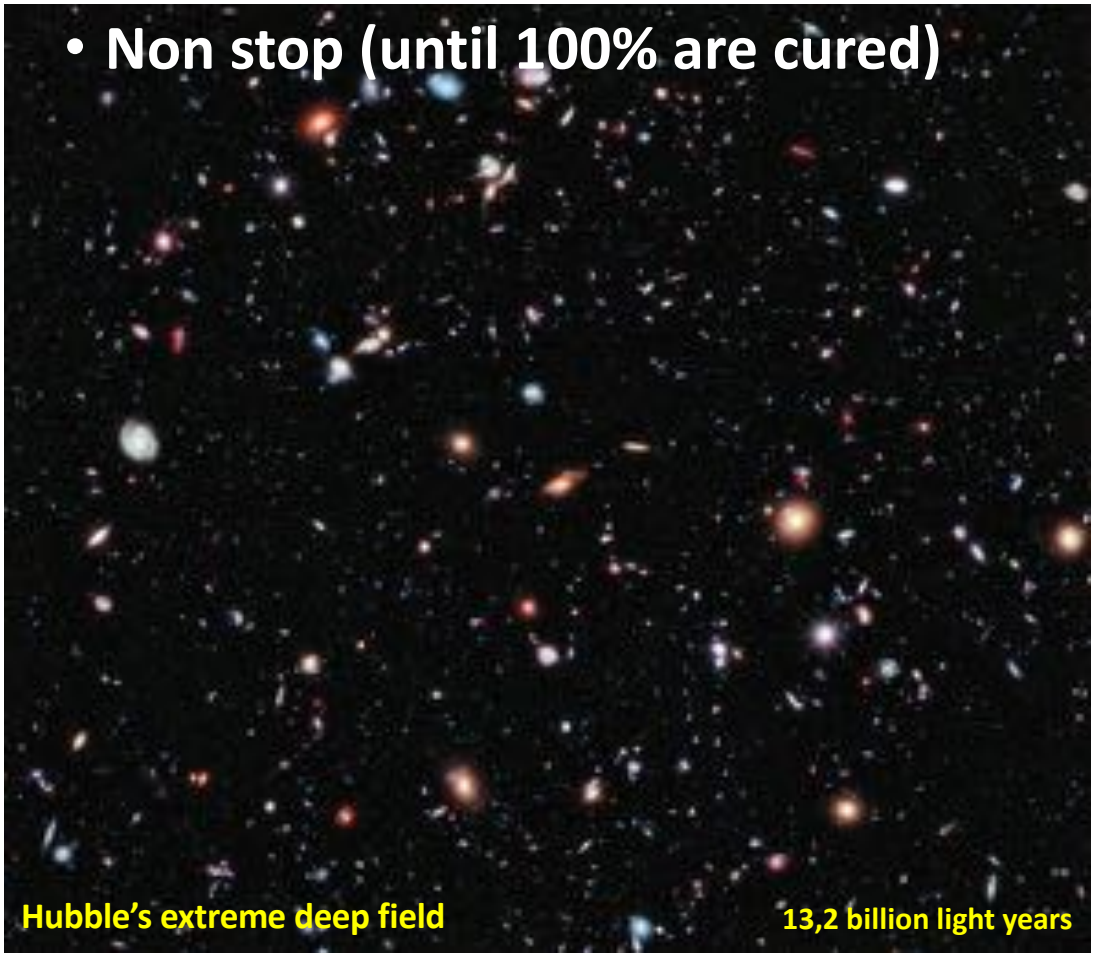
Inhibitors: NOTCH1/GS, CXCR-4, proteasome

MoAb's: anti-CD3/7/30, daratumumab (CD38)

Inhibitors: IL-7R, JAK1, JAK/STAT (ruxolitinib: ETP), FLT3 (ETP),TKI (dasatinib: *NUP-ABL1*+ and *ABL1*- subsets), AKT, GSK-3

Dissecting ALL heterogeneity

Itinerary: today's end



Thank you:

Tiziano Barbui
Alessandro Rambaldi
(*Bergamo*)

Robin Foà
Sabina Chiaretti
(*Roma*)

northernitaly leukemiagroup

GIMEMA