Biology of High-Risk Acute Lymphoblastic Leukaemia (in Children and Young Adults)

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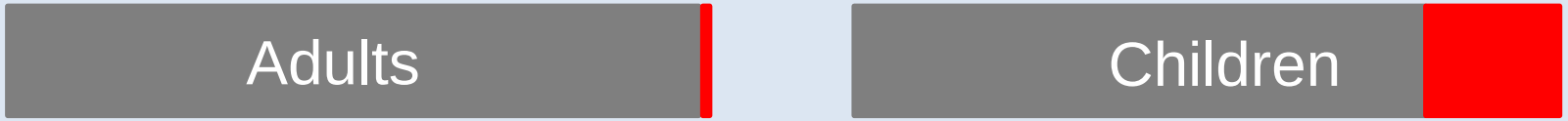
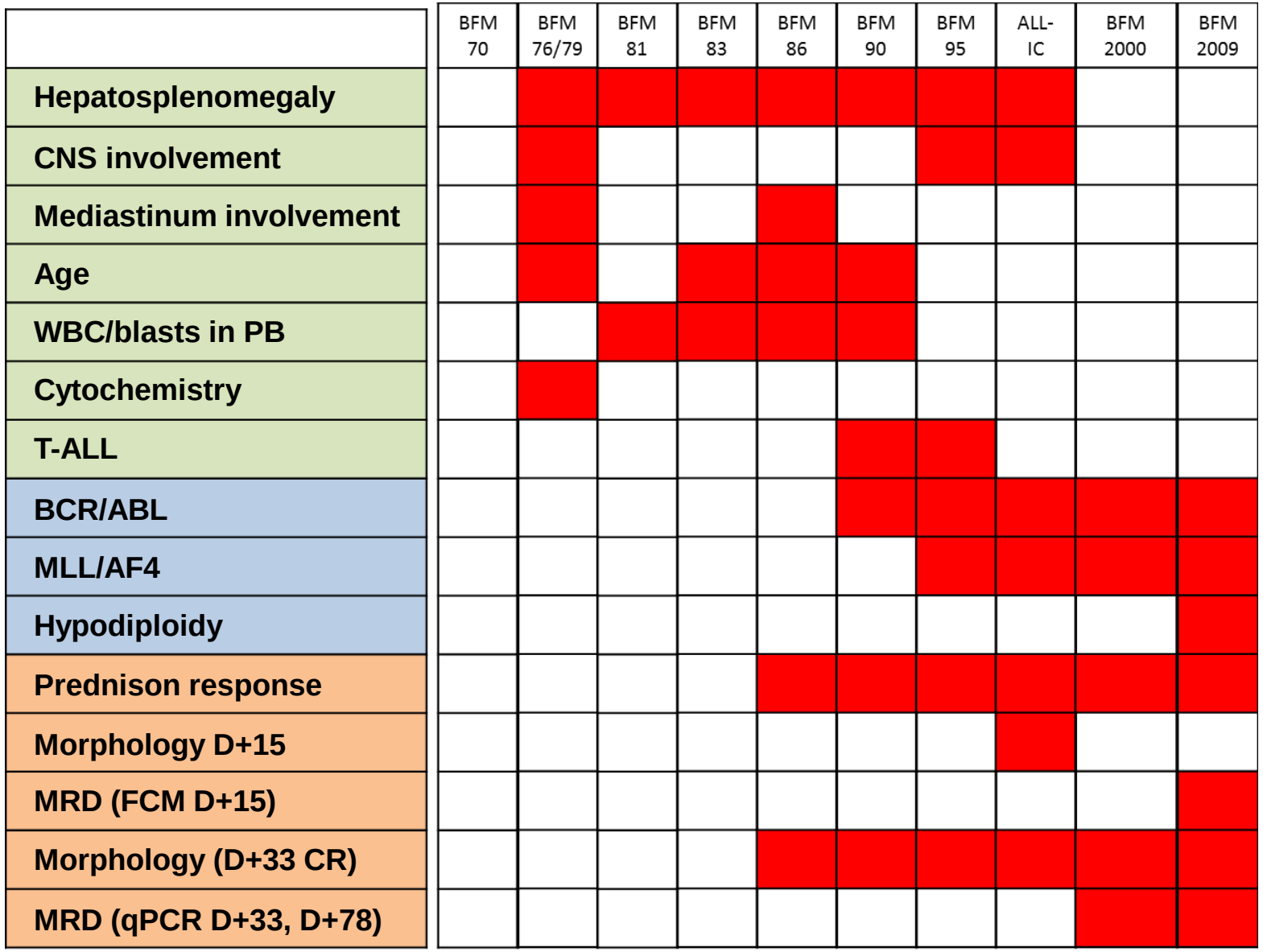
ALL: genetics defines prognosis

- rarer in adults,
  the most frequent malignant diseases in children:
  representation among malignancies



- **genetic aberrations**: key role in pathogenesis
- **heterogeneous biological nature** → ALL subtypes
- **excellent prognosis** on modern therapy (children, AYA)
- **significant improvement of treatment results**: new schemes and adjustment of treatment by **risk stratification**

ALL risk stratification – AIEOP/BFM evolution



Genetics

Early response to treament (MRD)

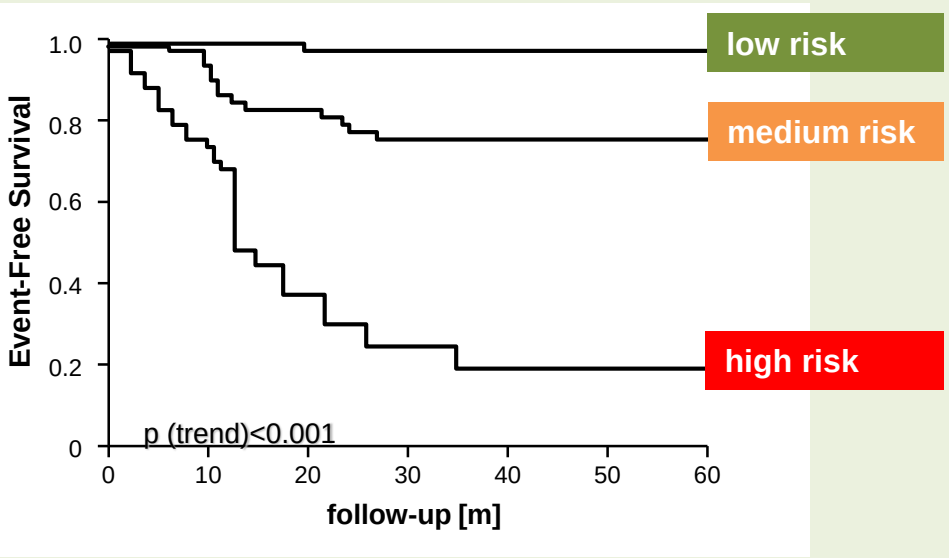
How to identify **High-Risk ALL**

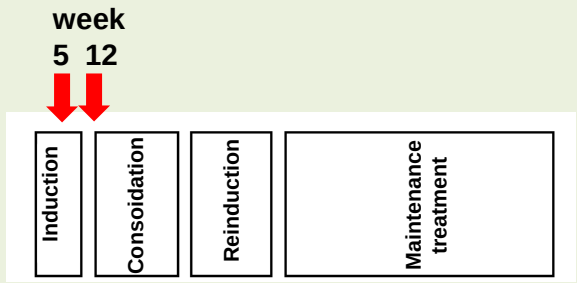
Genetically-defined groups with empirically known poor overall outcome

High Minimal Residual Disease during (early) phase of treatment predicts poor overall outcome

Prediction of relapse: MRD

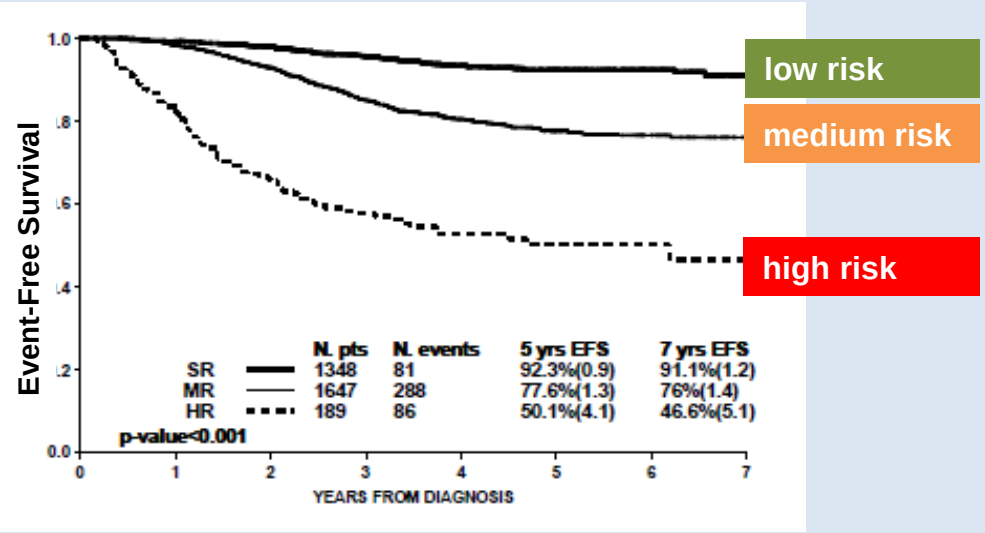
based on MRD in two time-points in initial treatment





independent of:
age
WBC
immunophenotype

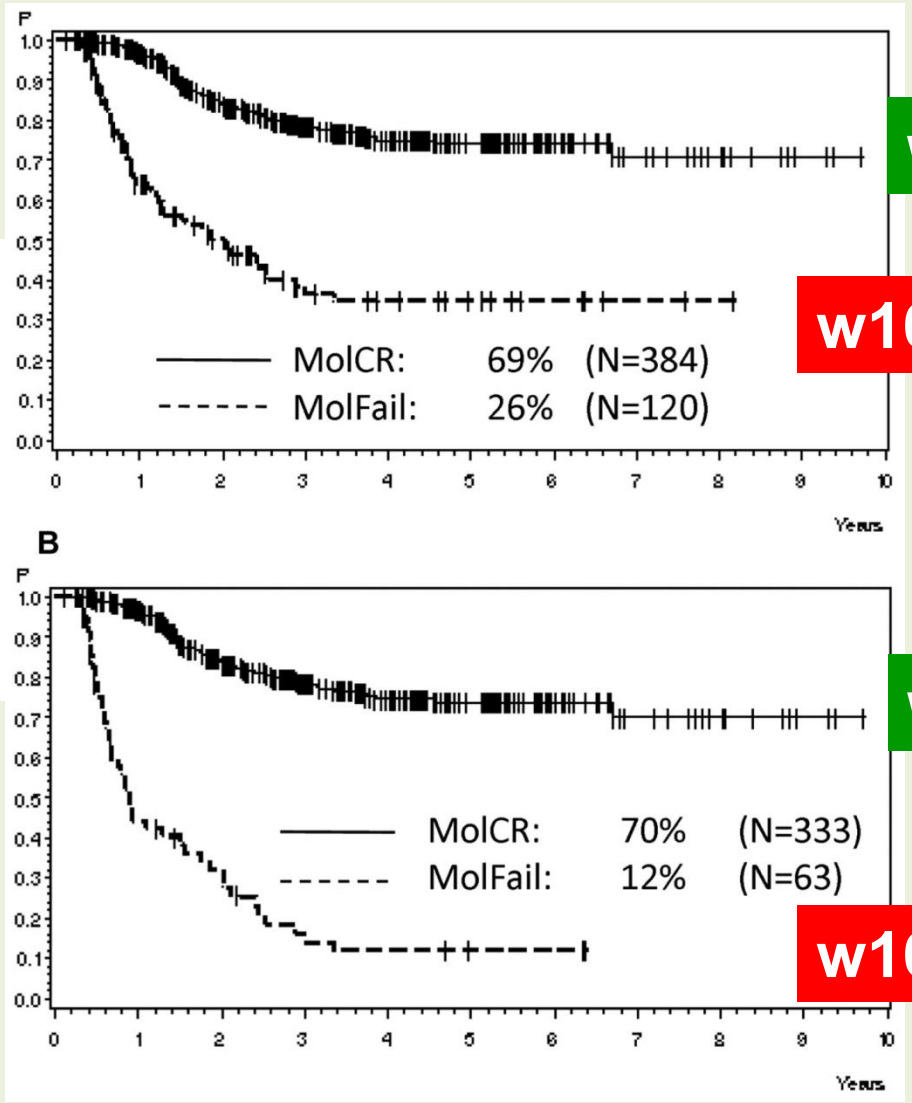
van Dongen et al, Lancet 1998



independent of:
age
WBC
Prednison response

Conter et al, Blood 2010

MRD after consolidation strongly predicts prognosis in adult ALL



w16 MRD negative **"molecular remission"**

w16 MRD ≥ 10^{-4} **"molecular failure"**

57 (47%) SCT in 1st CR: CCR 66%

w16 MRD negative

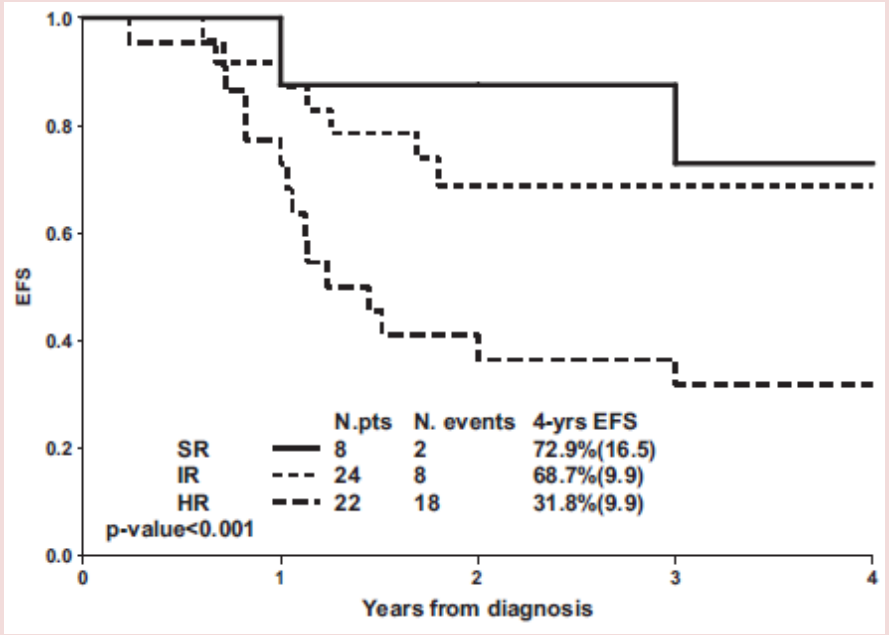
SCT in 1st CCR excluded

w16 MRD ≥ 10^{-4}

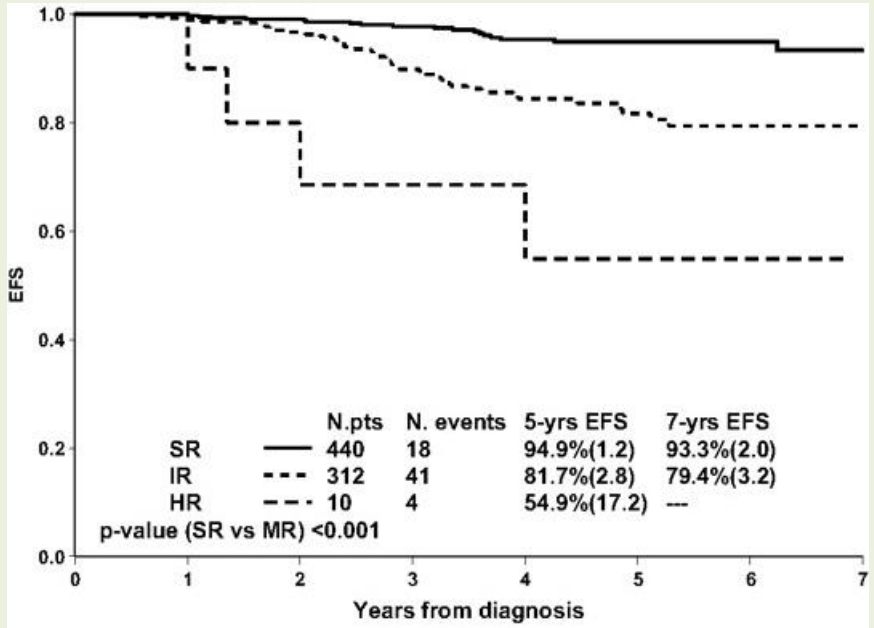
Gokbuget et al, Blood 2012

MRD predicts prognosis independently of genetic subtypes

BCR/ABL1+ ALL



ETV6/RUNX1+ ALL

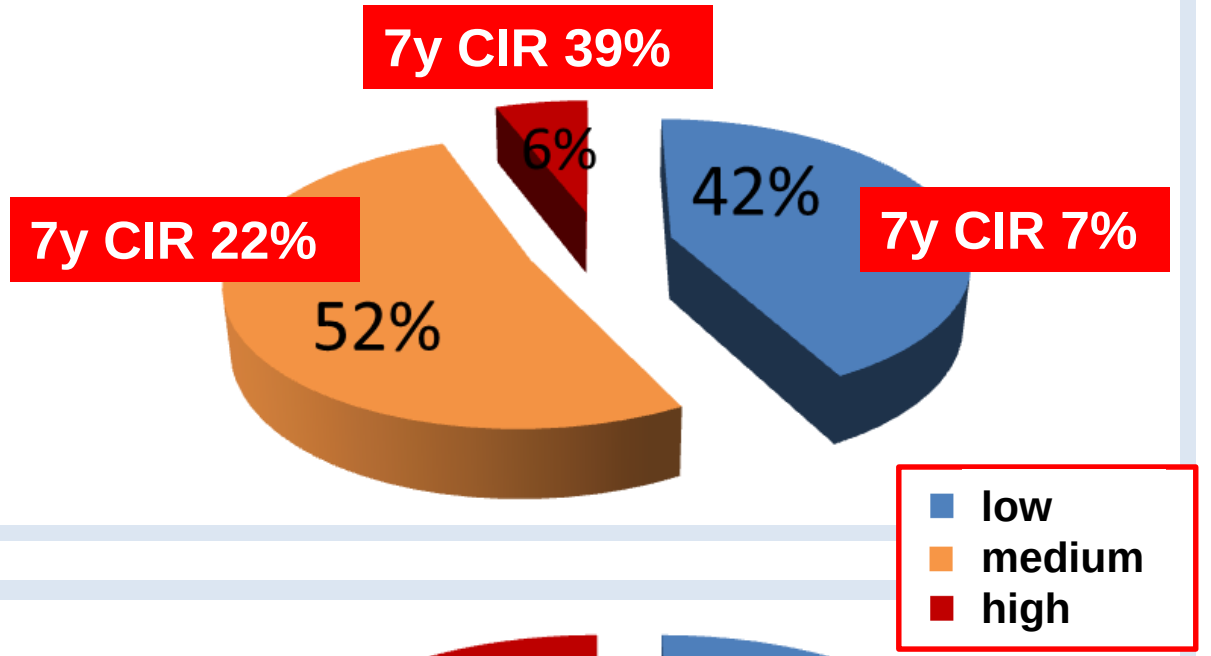


Conter et al, Blood 2010

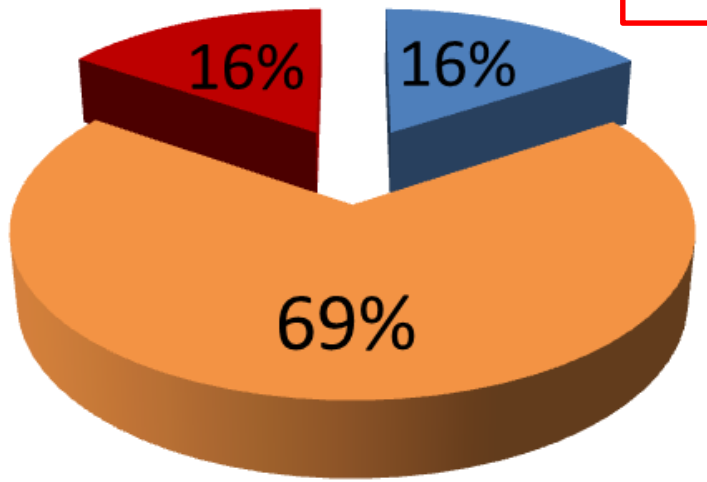
MRD = most important predictor of outcome in both childhood and adult ALL

Relapses according to risk groups

MRD risk groups



propotion of MRD risk groups in relapse patients

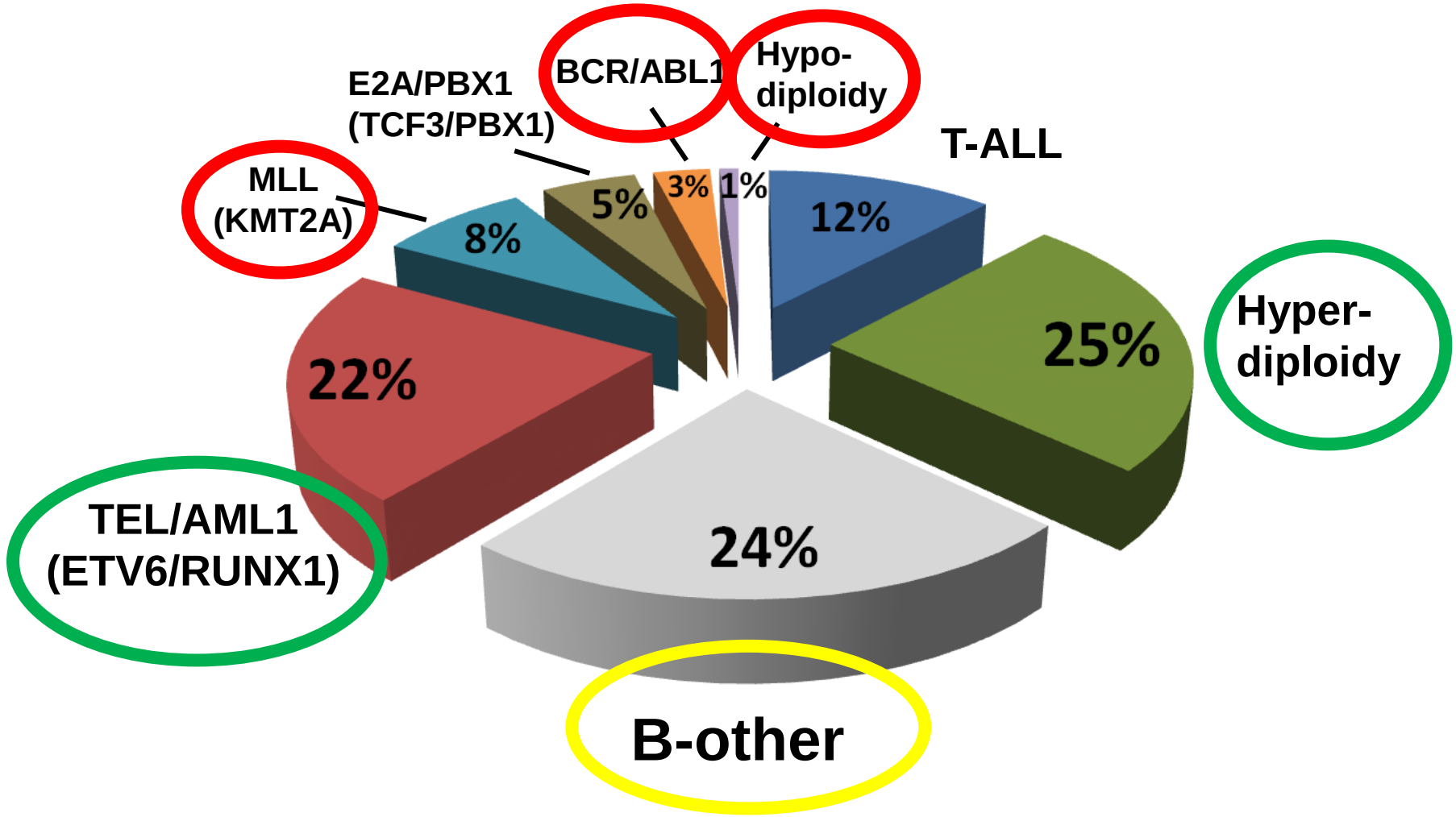


Absolute relapse numbers: most from MEDIUM risk group!

Conter et al, Blood 2010

Genetically-defined prognostic groups: 2004

Immunophenotype + **Primary genetic aberrations**

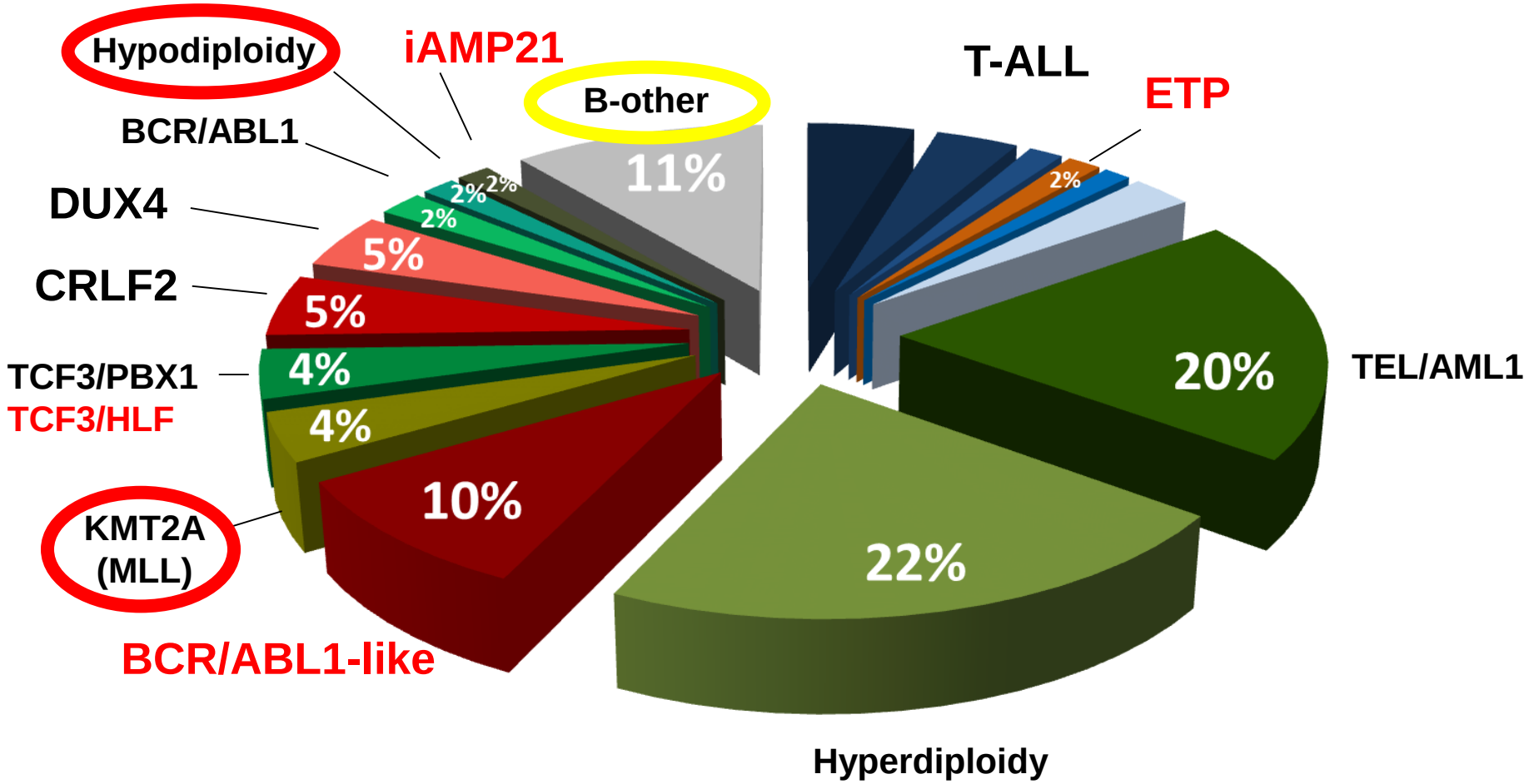


Pui et al, N Engl J Med 2004

Genetically-defined prognostic groups: 2018

Immunophenotype + Primary genetic aberrations

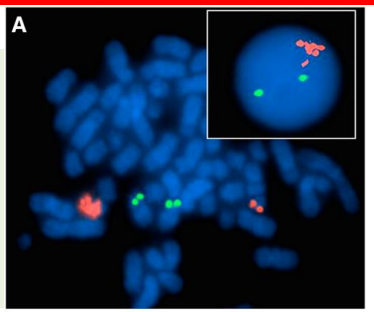
+ Expression profile + Secondary genetic aberrations



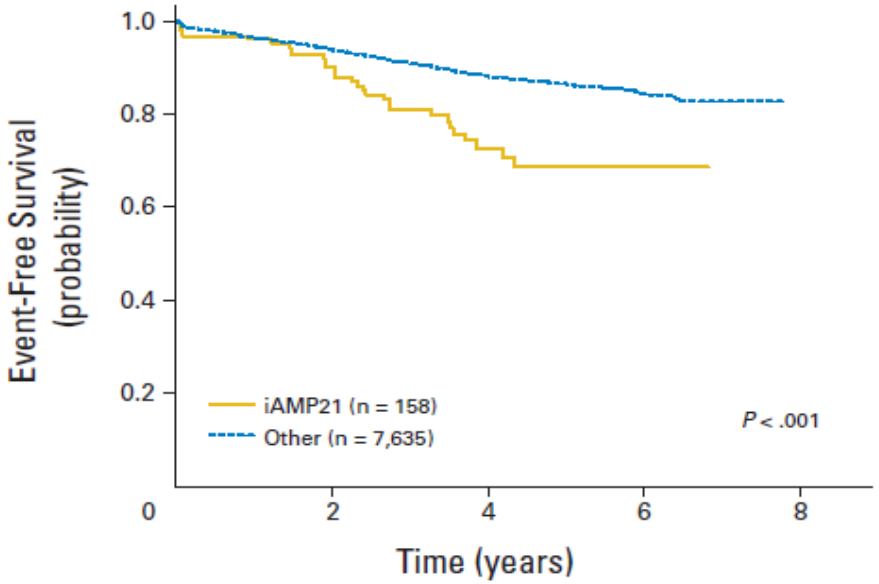
from more sources

iAMP21: poor outcome on standard therapy

Amplification of 47 genes (incl. RUNX1) on chromosome 21
(3 and more extra copies of RUNX1)
Harewood et al, Leukemia 2003; Rand et al, Blood 2011



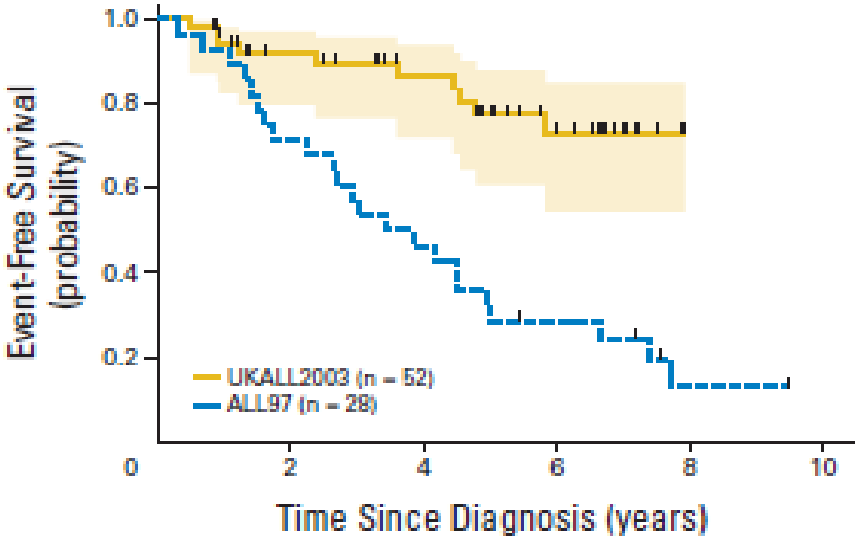
Poor outcome with standard treatment



COG

Heerema et al, JCO 2013

Good outcome with more aggressive CHT



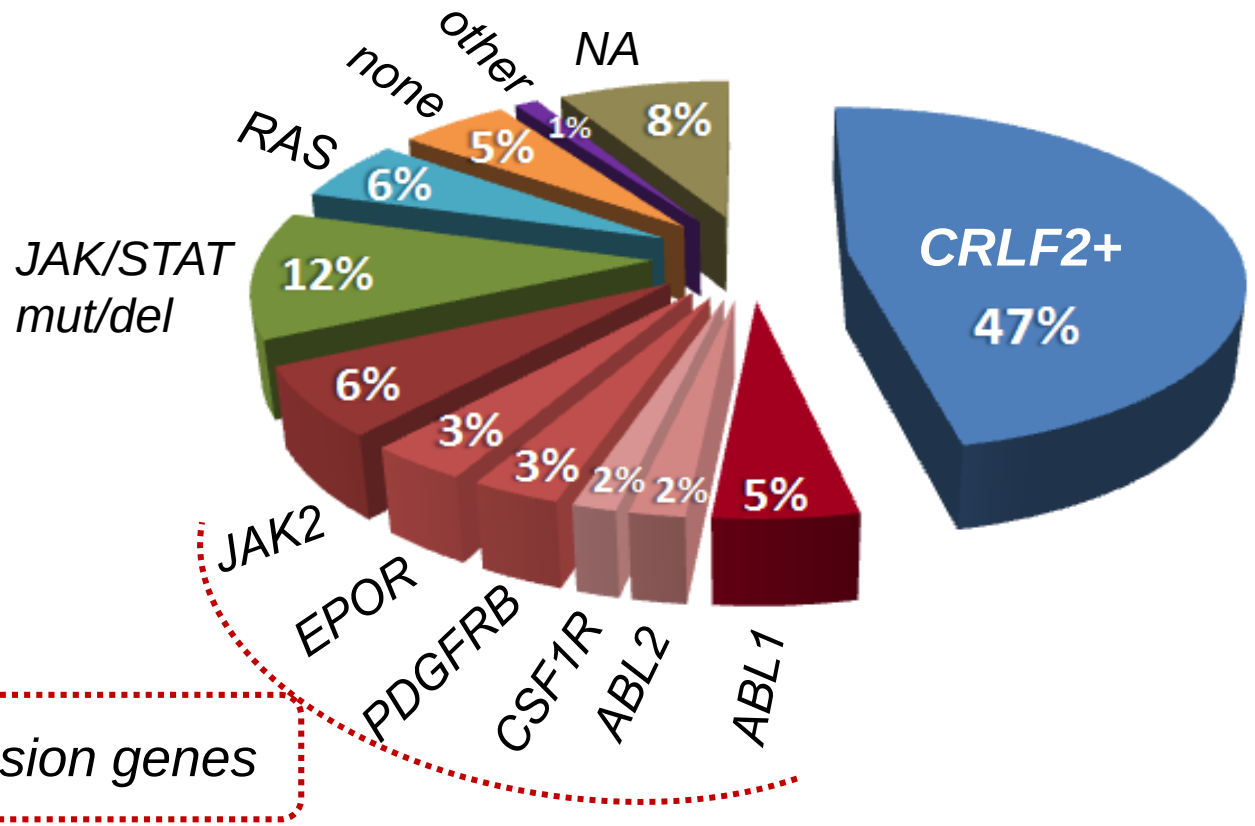
UKALL

Moorman et al., JCO 2013

BCR/ABL1-like ALL: heterogeneous group with kinase activation

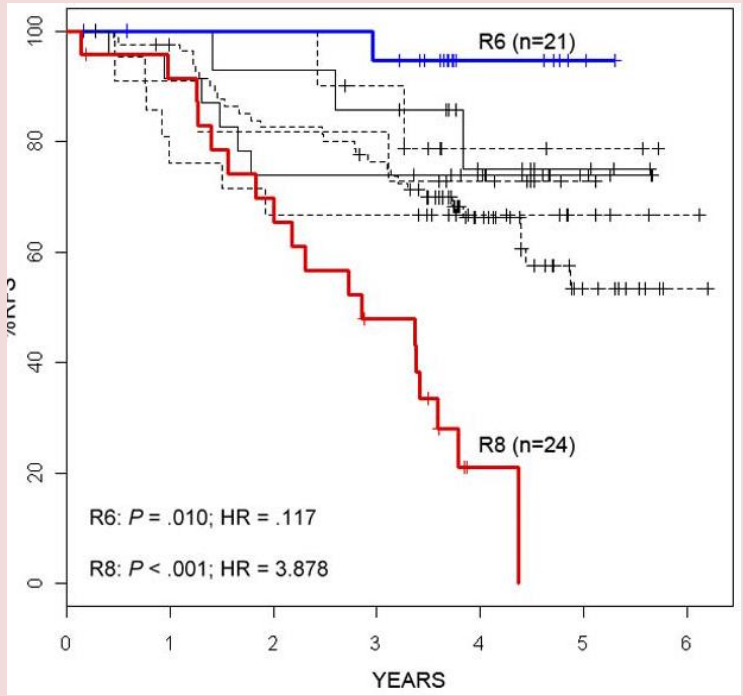
- ***Den Boer et al, Lancet Oncol 2009*** *and* ***Mullighan et al, NEJM 2009***
- without routinely screenable primary genetic alteration
  (x DCOG 18% iAMP21; COG 25% hyperdiploid!)
- classification by GEP, RNAseq, Low Density Array
- in majority of patients alterations activating kinase signalling

Both primary and secondary aberrations!

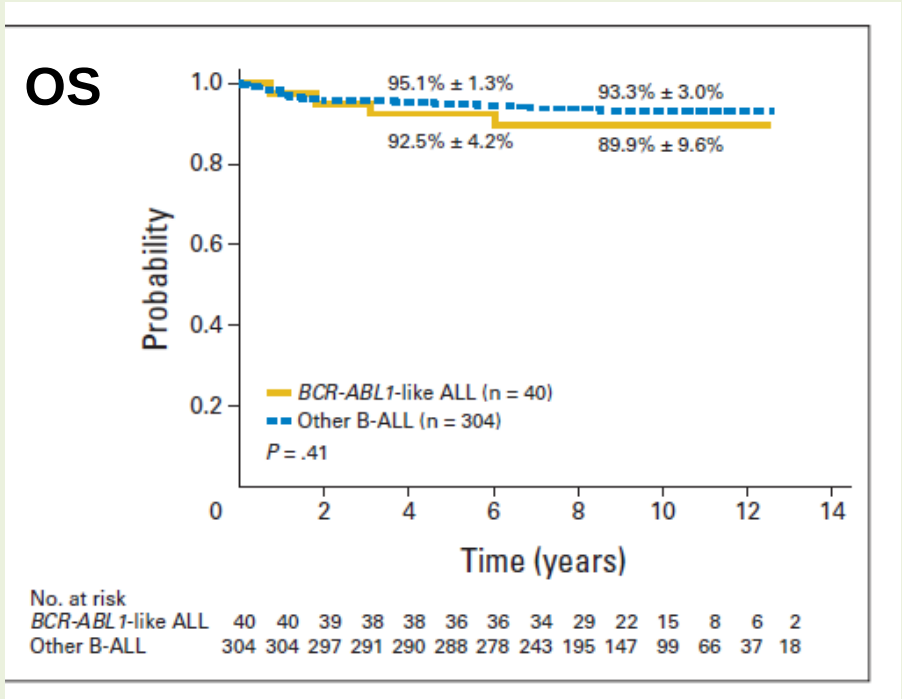


Roberts et al., J Clin Oncol 2014
Boer et al., Haematologica 2015
Roberts et al, N Engl J Med 2014

BCR/ABL1-like ALL: poor outcome?



Harvey et al, Blood 2010



Roberts et al, J Clin Oncol 2014

SJCRH

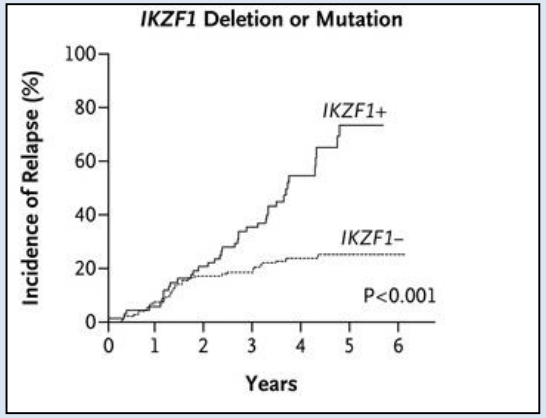
protocol without MRD

risk stratification with MRD

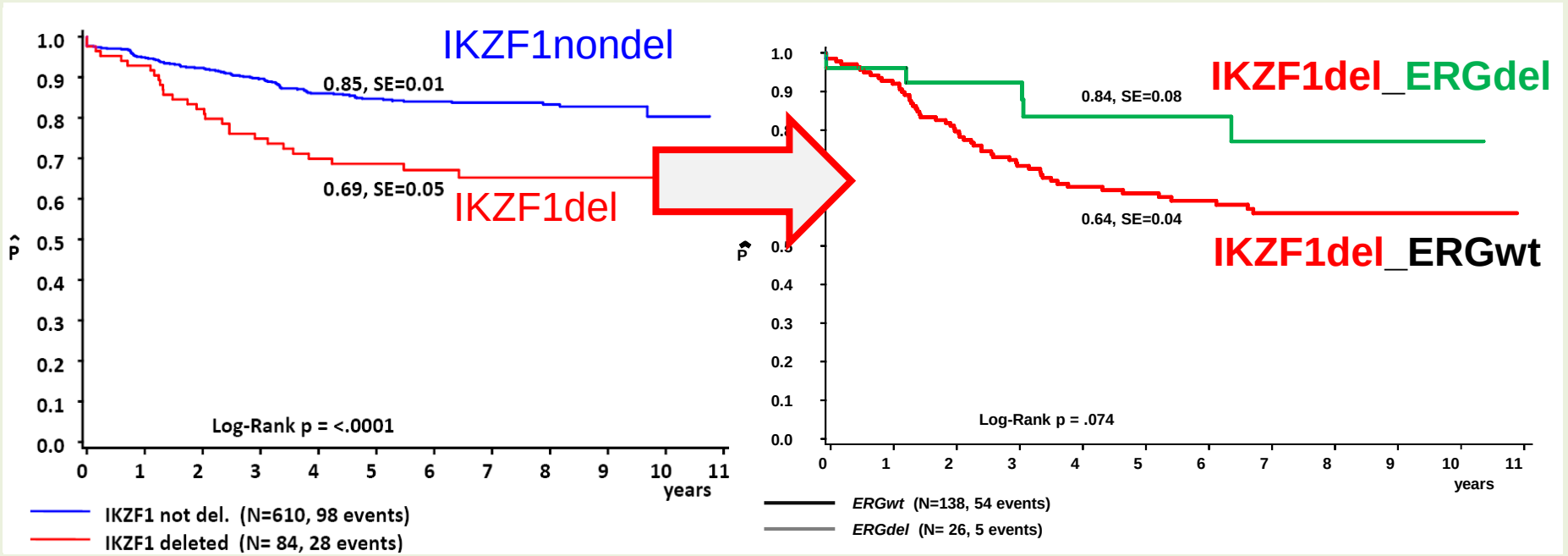
→ hint for targetable kinase aberrations

IKZF1 deletion (… and ERG deletion)

- identified with SNParray ***Mullighan et al, N Engl J Med 2009***
- poor intial response (MRD)
- **secondary aberration** - 29% HR ALL
- **dismal outcome**
- also in Ph+ ALL and BCR/ABL-like ALL
  Roberts et al, N Engl J Med 2014
  van der Veer, Zaliova, Mottadelli et al, Blood 2014



in presence of ERGdel → IKZF1del looses negative prognostic significance

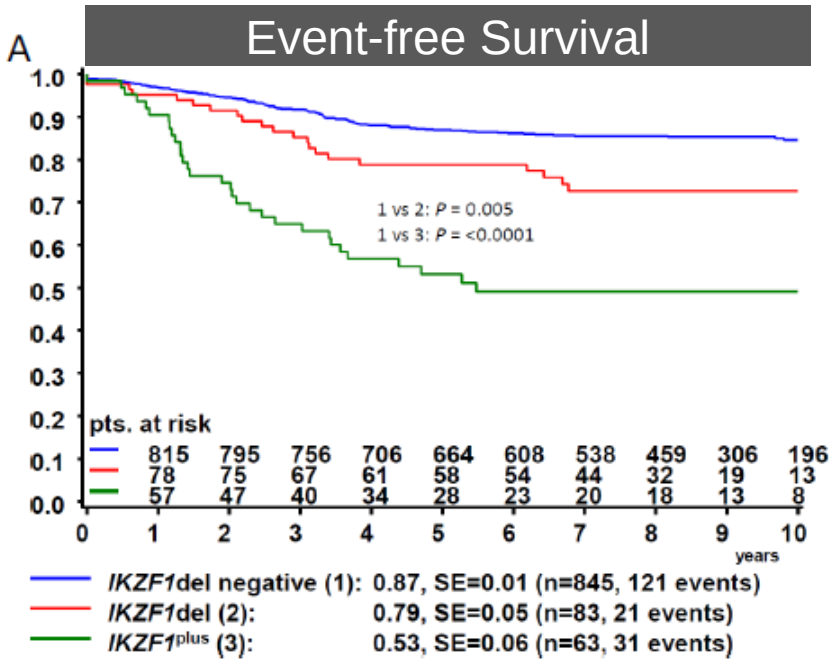


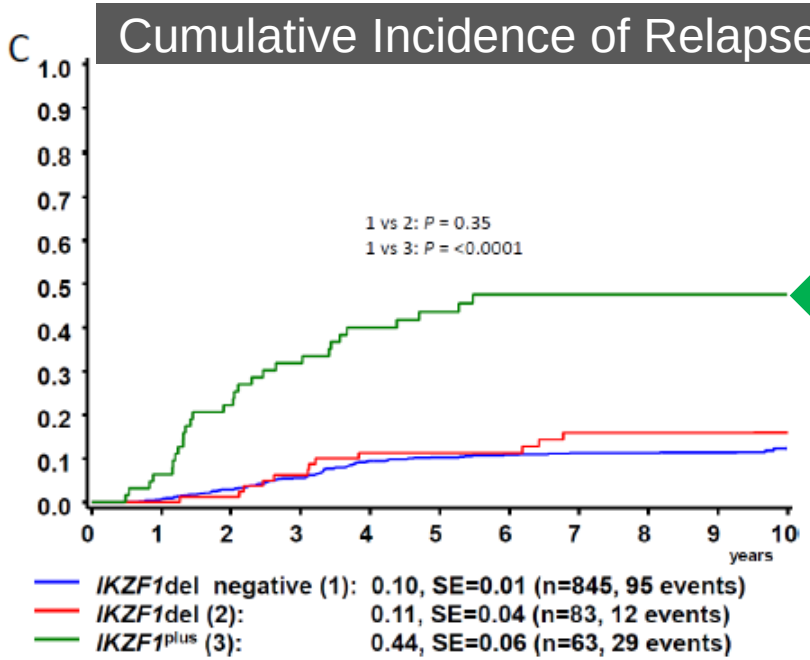
Doerge et al, Haematologica 2013

BFM 2000

Zaliova et al, Leukemia 2014

Negative prognostic impact of IKZF1^{plus}





IKZF1^{plus}

6% BCP-ALL
typically within B-other ALL
rarely ETV6/RUNX1+ / hyperdiploid
5y-EFS 53%
5y-CIR 44%

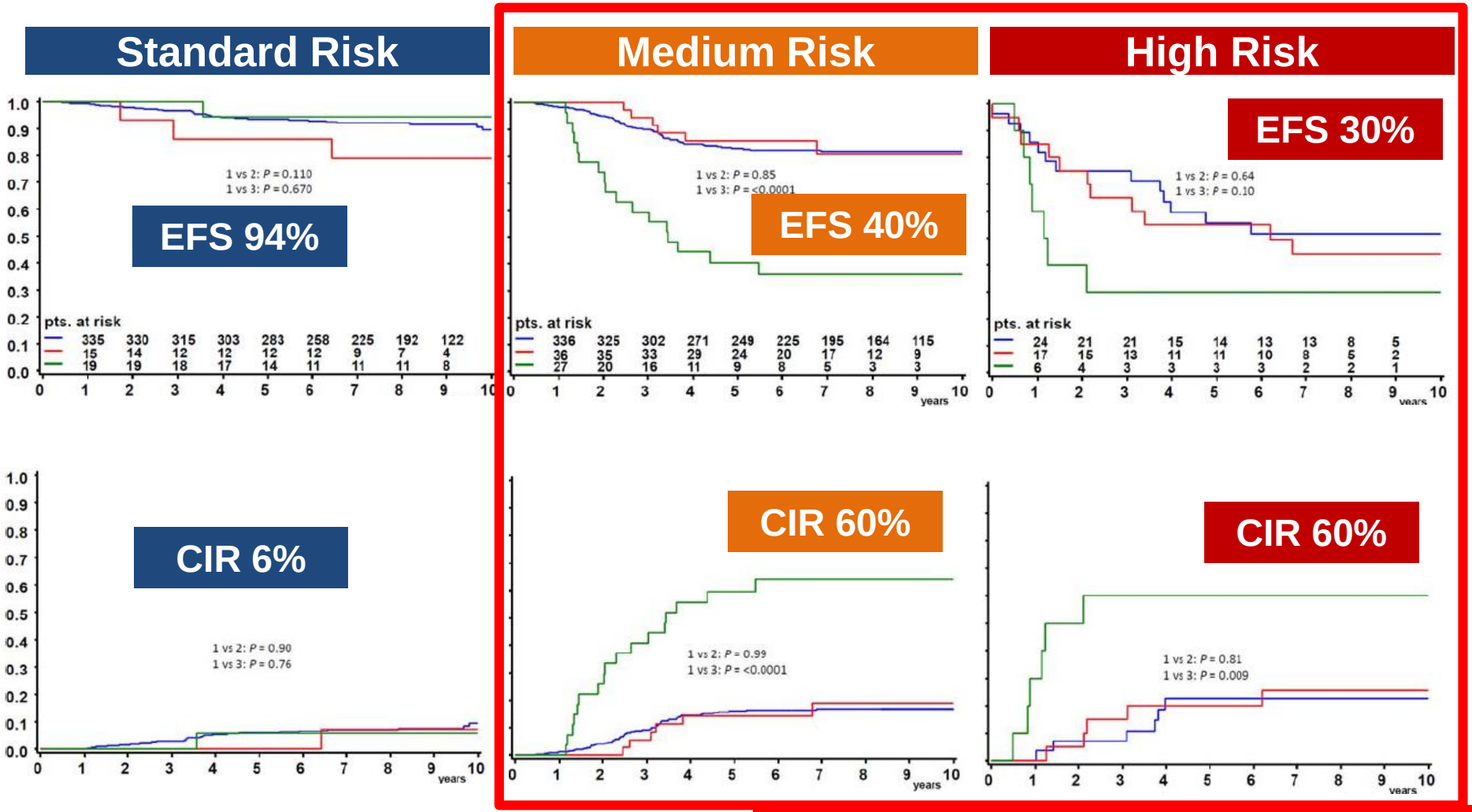
IKZF1^{plus}

deletion IKZF1 **and**

- deletion PAX5 **and/or**
- deletion CDKN2A **and/or**
- deletion CDKN2B **and/or**
- deletion PAR1 (P2RY8-CRLF2)
  and
- (**lack of** ERG deletion)

Stanulla et al, J Clin Oncol 2018

Prognostic impact of **IKZF1^{plus}** depends on **MRD**



stratification into High-Risk Group with **Blinatumomab** randomisation

Stanulla et al, J Clin Oncol 2018

TCF3/HLF-positive ALL: fatal rare subtype

t(1;19)	**TCF3**	**PBX1**	5% childhood ALL, EFS 78-85%
t(17;19)	**TCF3**	**HLF**	<1% childhood ALL, EFS 0%

- *in vitro* relatively sensitive **x** clinically very high resistance
- *in vivo* high sensitivity to **Venetoclax** (Bcl2 inhibitor) → new treatment (incl. induction)

Fischer et al, Nat Genet 2015

B-rest ALL: the „rest“ of B-other

Genetically defined

- (ALL with DUX4 rearrangement) — **RNAseq: GEP, fusions**
- ALL with ZNF384 rearrangement — **RNAseq: fusions, FISH, PCR**
- ALL with MEF2D rearrangement — **RNAseq: fusions, FISH, PCR**
- ALL with PAX5 fusions — **RNAseq: fusions, FISH, PCR**
- ALL with PAX5 amplification — **SNP array**

Defined by GEP

- (BCR/ABL1-like ALL) — **RNAseq: GEP**
- ETV6/RUNX1-like ALL — **RNAseq: GEP**

New categories with potentially **poorer outcome**

TCF3/ZNF384

Children > adults
Low CD10, co-expression of myeloid markers, hybrid leukaemias
Poorer outcome

Liu et al., EBioMedicine 2016
Hirabayashi et al., Haematologica 2017

MEF2D fusions

older children, AYA
Low to negative CD10, CD38++, morphology similar to mature B-ALL
Poorer outcome?

Liu et al., EBioMedicine 2016
Gu et al., Nat Commun 2016

PAX5 amplification

relatively frequent: 3% of B-other
higher incidence of relapses

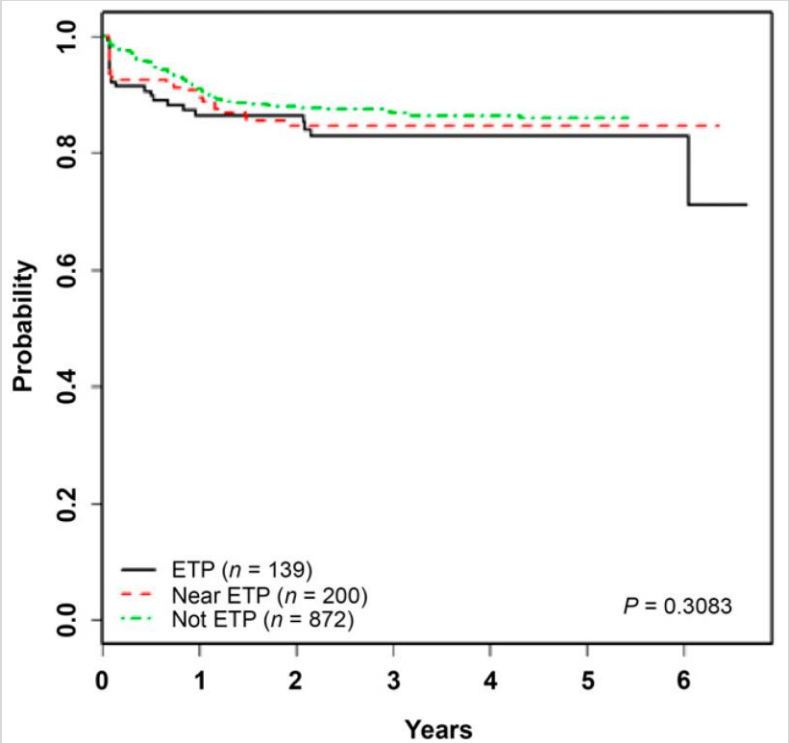
Schwab et al., Blood Advances 2017

Early T-cell Precursor (**ETP**) ALL

cCD31, sCD32, CD1a2, CD21, CD5, dim [<75%+], CD71
and positivity for stem cell and/or myeloid markers, including HLA-DR, CD13, CD33, CD34, or CD117

Coustan-Smith et al, Lancet Oncol 2009

Flow Cytometry



different genomic landscape vs. non-ETP:

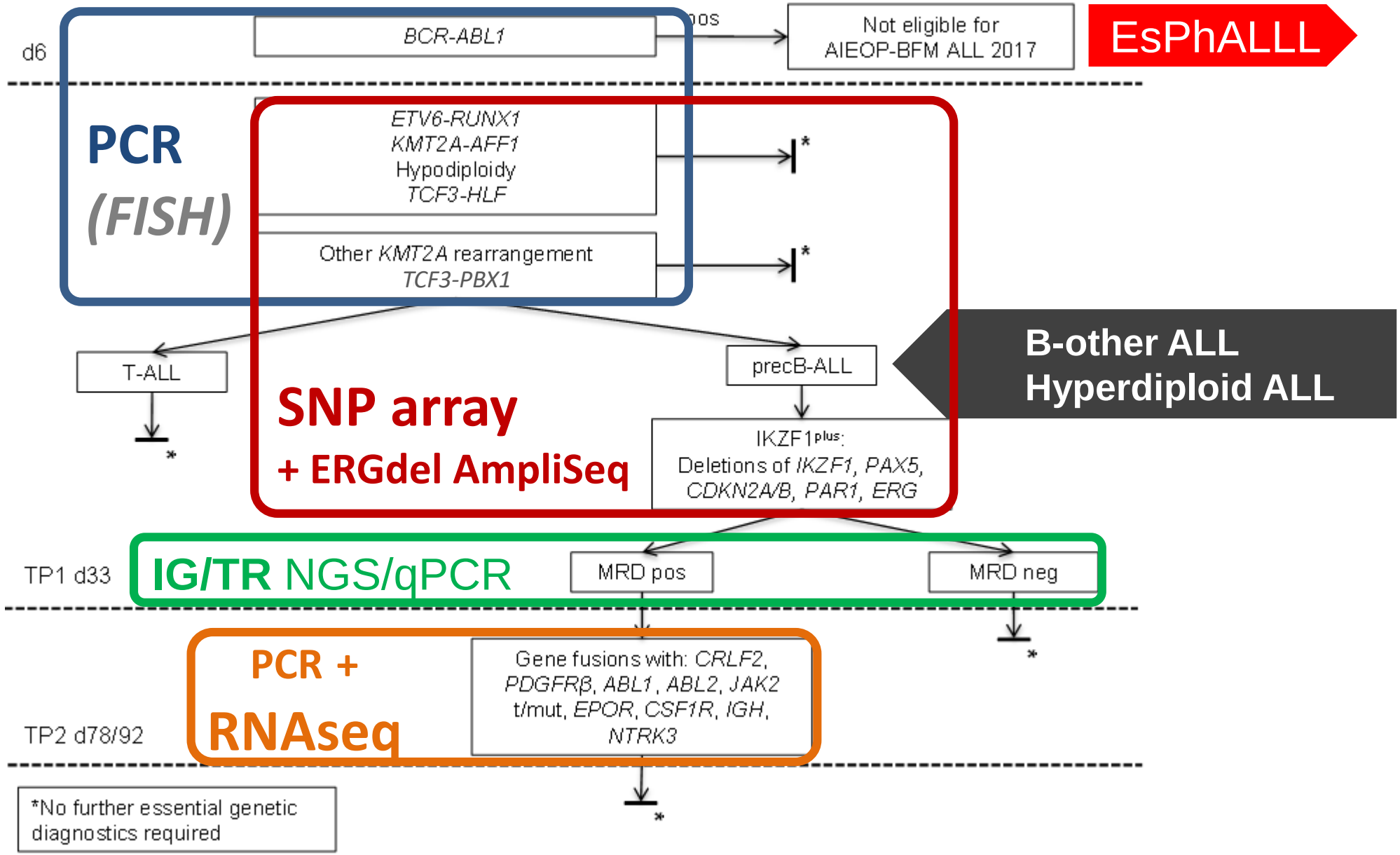
- transcription factors (incl. IKZF1, ETV6, RUNX1)
- MAPK and cytokine receptor signalling (N/KRAS, JAK1/3, IL7R)
- chromatin modifiers

Prognosis: high induction failure 7.8% (vs 1.1% in other T-ALL)

identical EFS/OS on MRD-based regimens

Wood et al, ASH 2014, Patrick et al, Br J Haematol, 2014

Molecular genetic basis of ALL – **diagnostic algorithm**



Summary

- **new subtypes of ALL recently described (incl. High-Risk)**
  less clear definitions, overlaps, different age- and population-based frequencies
- **MRD remains crucial in identification of High-Risk patients**
  time-points specific for particular protocols, most relapses in MRD Medium-Risk group
- **progressive integration of new prognostically relevant genetic subtypes into stratification algorithms**
  specific for particular protocols, MRD as important co-factor, non-randomizable: "N of 1" trials?
- **new methods in diagnostic approaches (NGS- and multiFCM-based)**
  change in diagnostic paradigm: increased analytical and interpretational demand
- **identification of new drugable aberrations**
  validation of new aberrations? difficult standardisation of work with primary samples, time-demanding
- **all approaches of modern genomics / proteomics: diagnostic, discovery or research tools?**

Childhood Leukaemia Investigation Prague

Molecular Genetics

Cytometry

Bioinformatics

Experimental