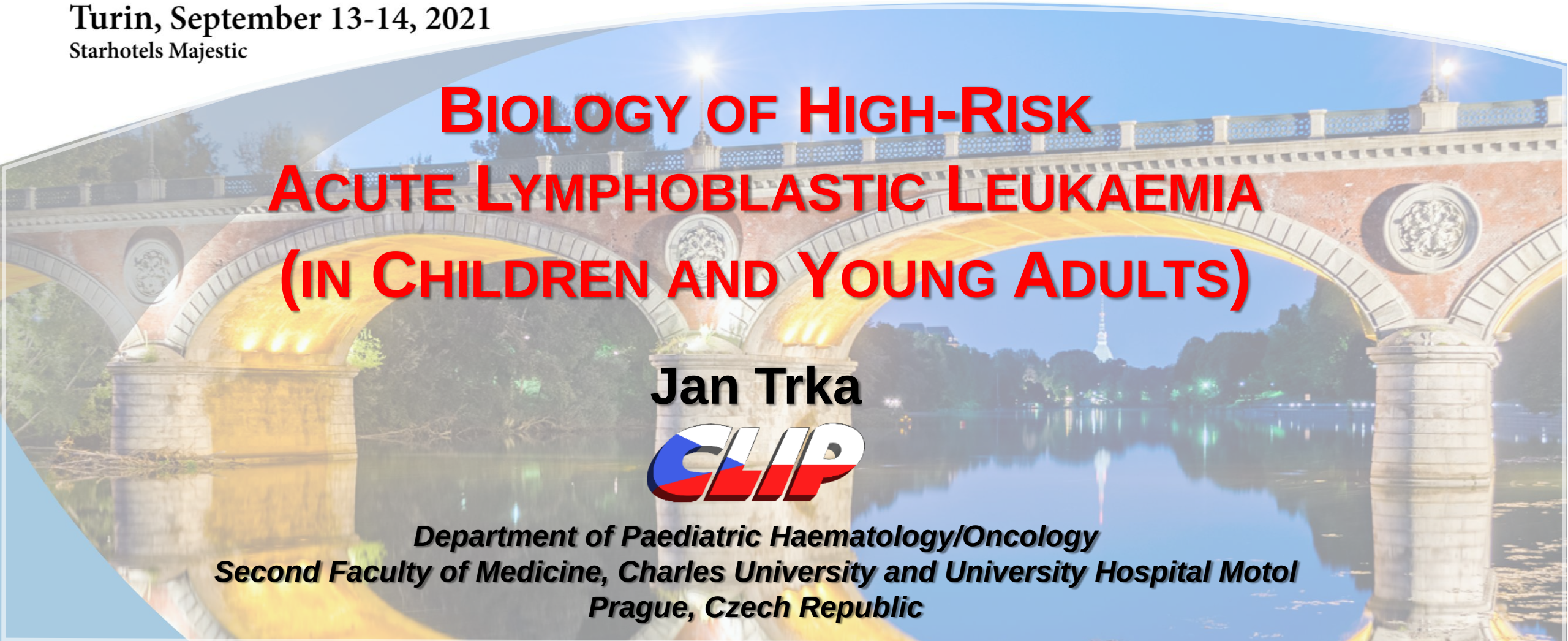
2nd edition

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)



BIOLOGY OF HIGH-RISK ACUTE LYMPHOBLASTIC LEUKAEMIA (IN CHILDREN AND YOUNG ADULTS)

Jan Trka

Department of Paediatric Haematology/Oncology
Second Faculty of Medicine, Charles University and University Hospital Motol
Prague, Czech Republic

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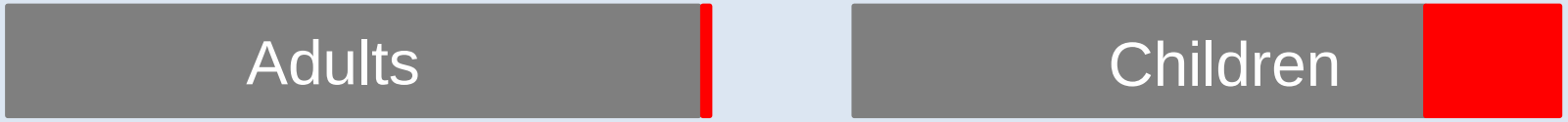
Jan Trka: No relevant conflict of interest

ALL: genetics defines prognosis

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



- **genetic aberrations**: key role in pathogenesis

- **heterogeneous biological nature** → ALL subtypes

- **excellent prognosis** on modern therapy (children, AYA)
  AIEOP/BFM ALL 2000: CR=97.8% EFS=82.4% OS=90.4%

- **significant improvement of treatment results**: new schemes and adjustment of treatment by **risk stratification** plus new therapies

ALL risk stratification – AIEOP/BFM evolution

	BFM 70	BFM 76/79	BFM 81	BFM 83	BFM 86	BFM 90	BFM 95	ALL-IC	BFM 2000	BFM 2009
Hepatosplenomegaly		■	■	■	■	■	■	■		
CNS involvement		■					■	■		
Mediastinum involvement		■			■					
Age		■		■	■	■				
WBC/blasts in PB			■	■	■	■				
Cytochemistry		■								
T-ALL						■	■			
BCR/ABL						■	■	■	■	■
MLL/AF4							■	■	■	■
Hypodiploidy										■
Prednison response					■	■	■	■	■	■
Morphology D+15								■		
MRD (FCM D+15)										■
Morphology (D+33 CR)					■	■	■	■	■	■
MRD (qPCR D+33, D+78)									■	■

Genetics

Early response to treament (MRD)

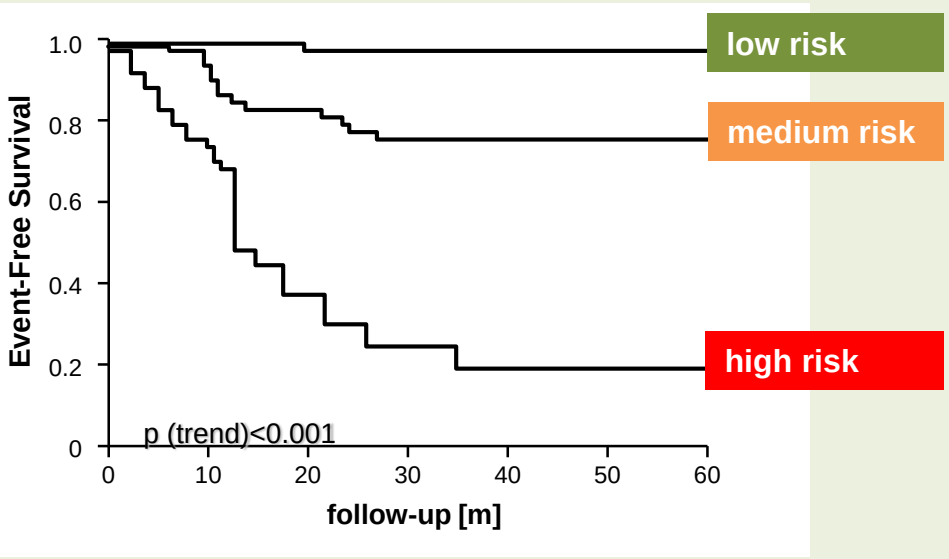
How to identify **High-Risk ALL**

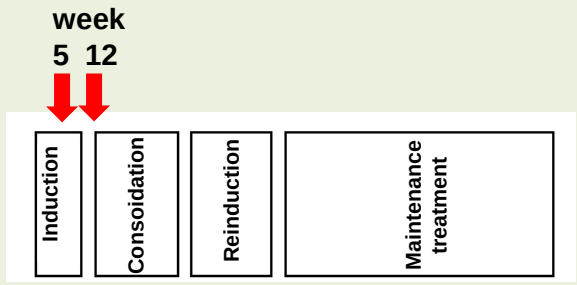
Genetically-defined groups with empirically known poor overall outcome

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

Prediction of relapse: MRD

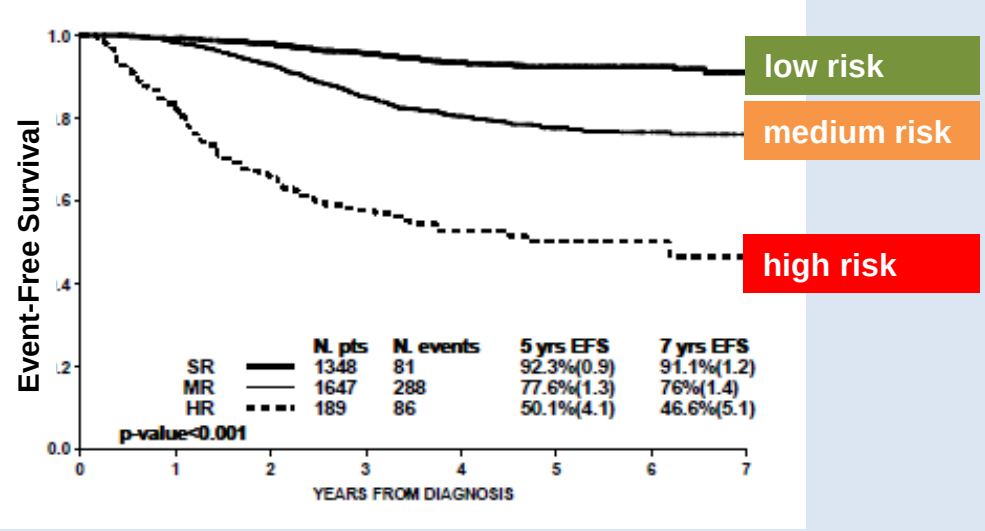
based on MRD in two time-points in initial treatment





independent of:
age
WBC
immunophenotype

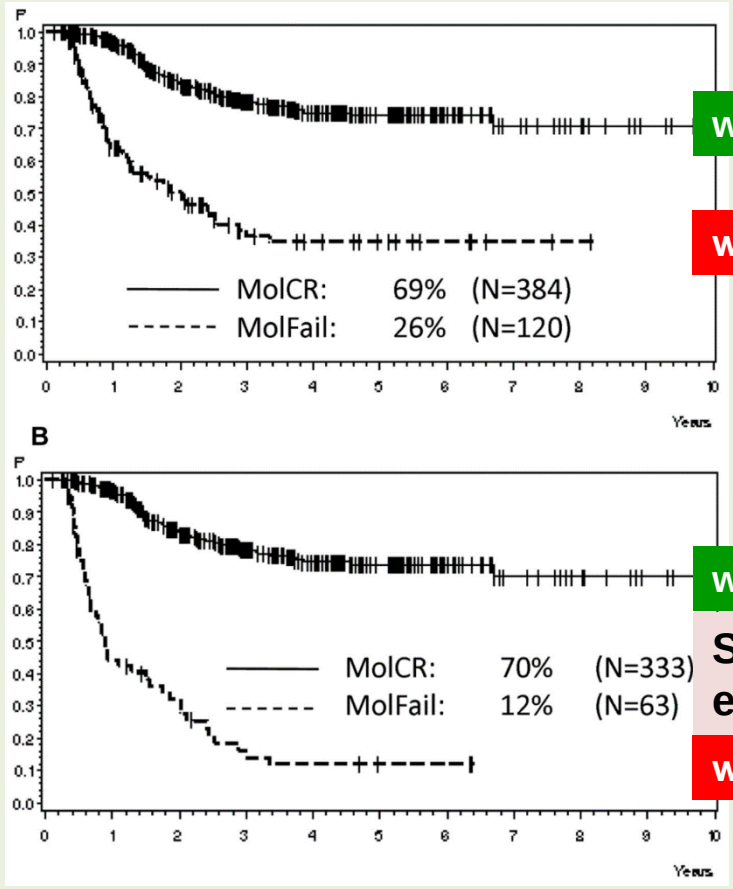
van Dongen et al, Lancet 1998



independent of:
age
WBC
Prednison response

Conter et al, Blood 2010

MRD confers poor prognosis also in adult ALL



w16 MRD negative

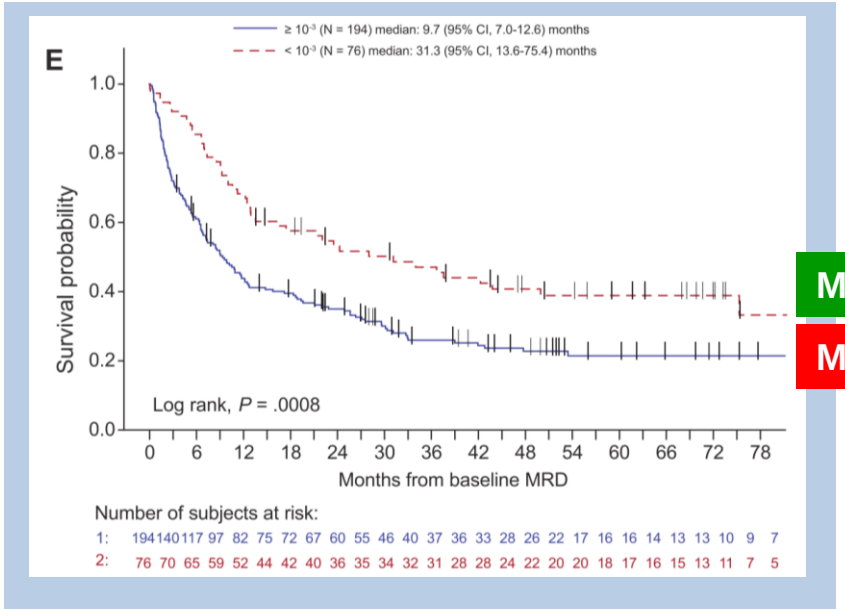
w16 MRD ≥ 10^{-4}

w16 MRD negative

SCT in 1st CCR excluded

w16 MRD ≥ 10^{-4}

Gokbuget et al, Blood 2012



MRD < 10^{-3}

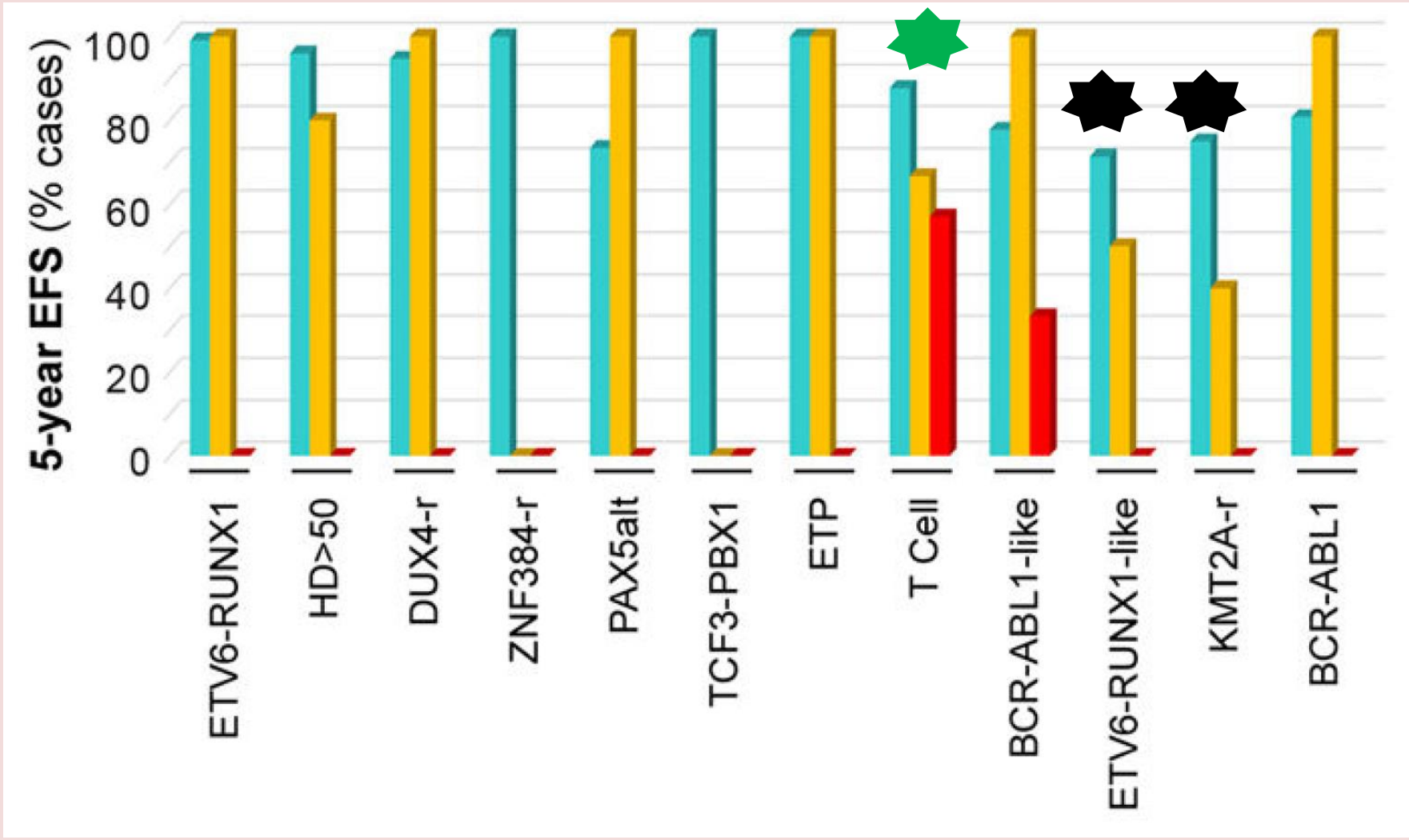
MRD ≥ 10^{-3}

Gokbuget et al, Hematology 2019

Systematic meta-analysis reveals MRD as the strongest predictor of outcome in B-cell adult ALL

Bassan et al, Haematologica 2019

Predictive value of **MRD** differs in subtypes of ALL



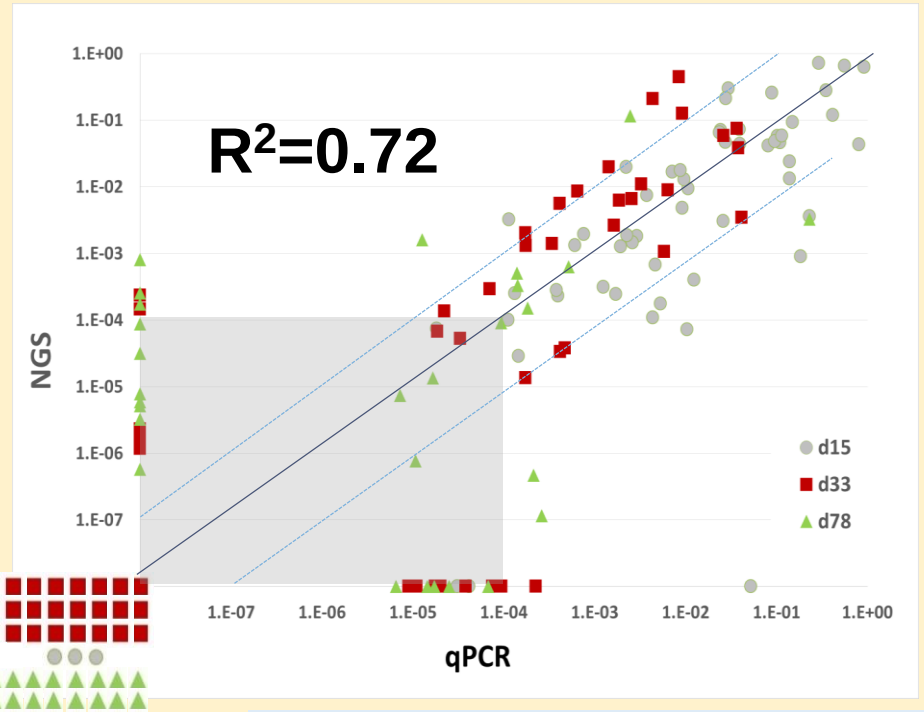
MRD < 10^{-4}

MRD 10^{-4} to <10^{-3}

MRD > 10^{-2}

Jeha et al, Blood Cancer Discov 2021

NGS MRD is equally predictive as qPCR MRD

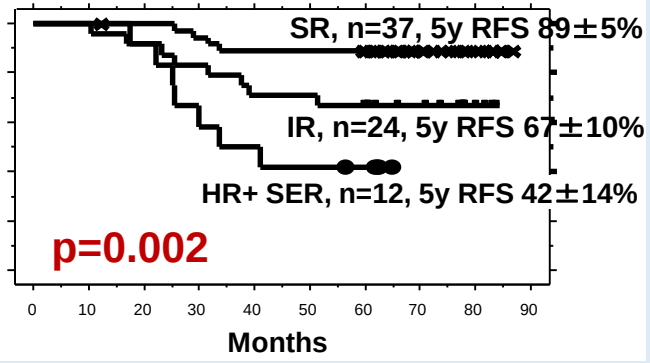


39% double-negative samples

210 samples
76 patients

Kotrova et al, Blood 2015

D+33 and D+78 NGS



CLIP study (unpublished data):
437 consecutive newly diagnoses ALL patients
780 IG/TR MRD markers

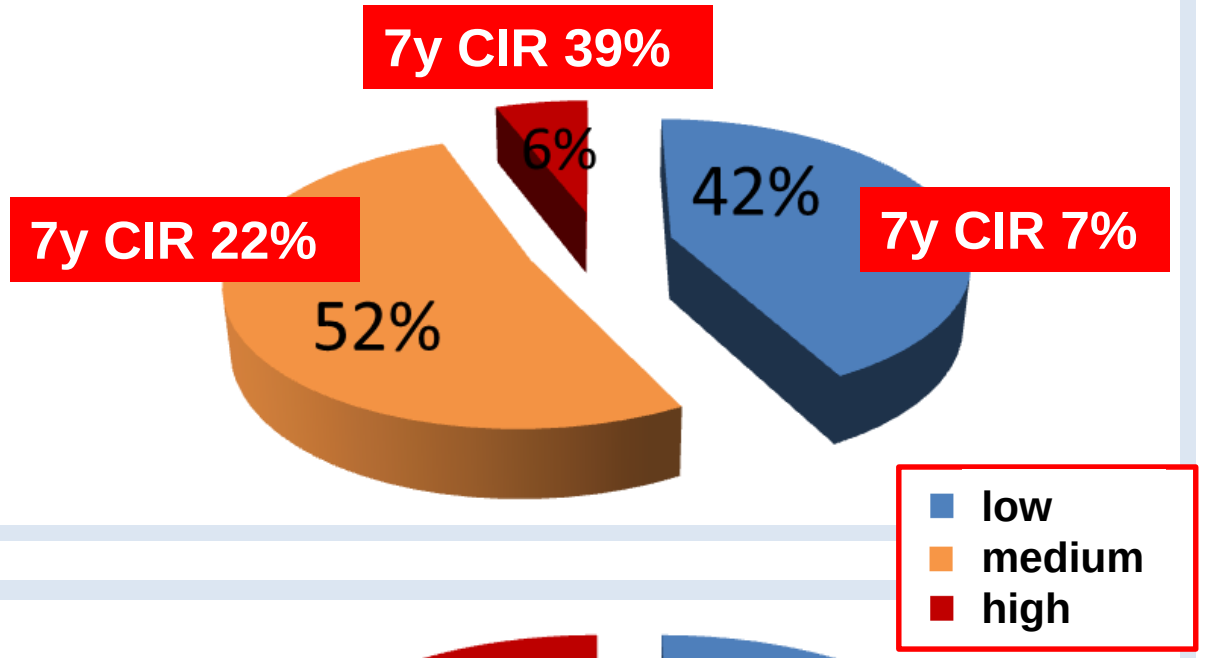
80.6% concordant MRD results
7% (54) markers/results ruled out as false-positive by NGS

10% patients assigned to lower-risk group (based on EoI MRD level)

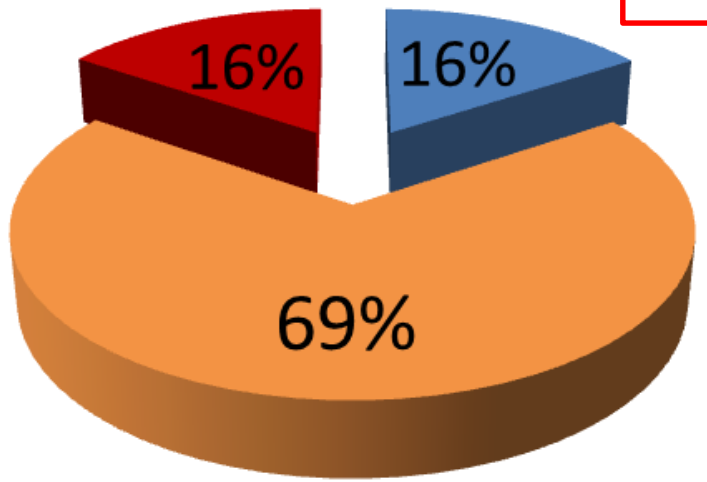
Large datasets of identified and tested **IG/TR rearrangements**:
selecting markers of adequate specificity
(10% of markers selected by traditional technique not enough specific!)

Relapses according to risk groups

MRD risk groups



propotion of MRD risk groups in relapse patients

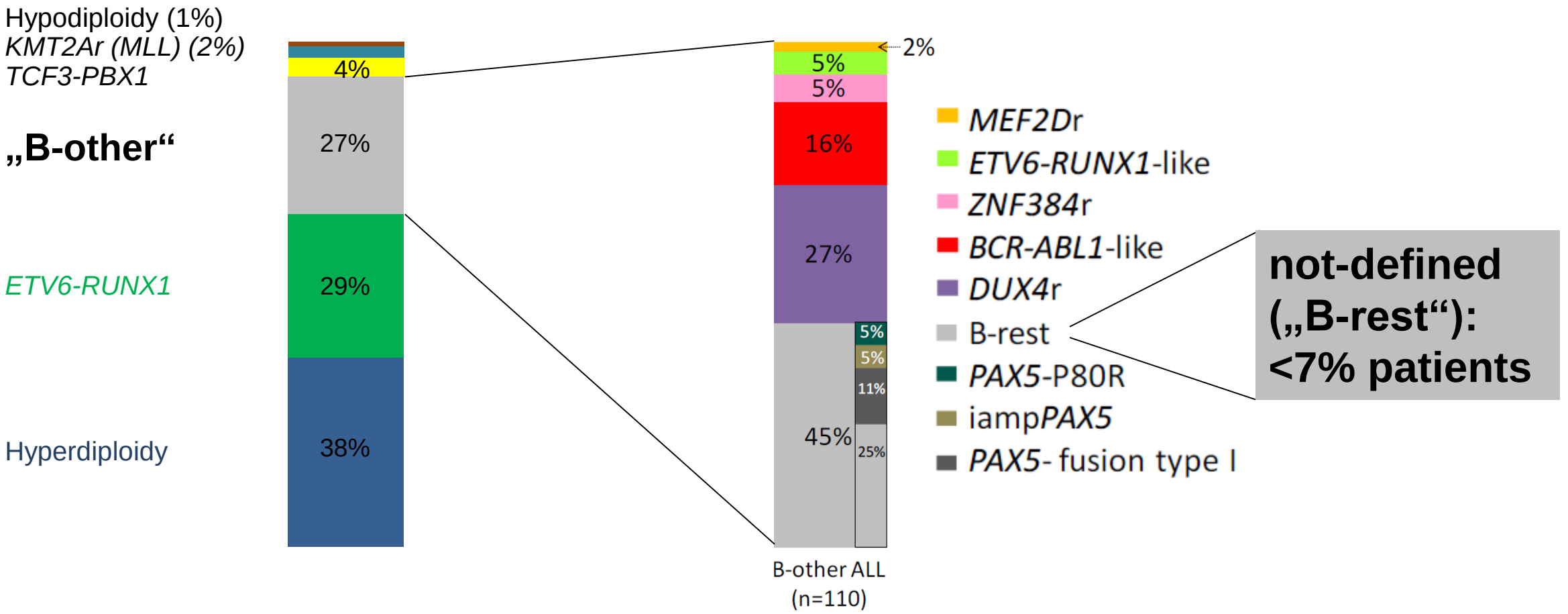


Absolute relapse numbers: most from MEDIUM risk group!

Conter et al, Blood 2010

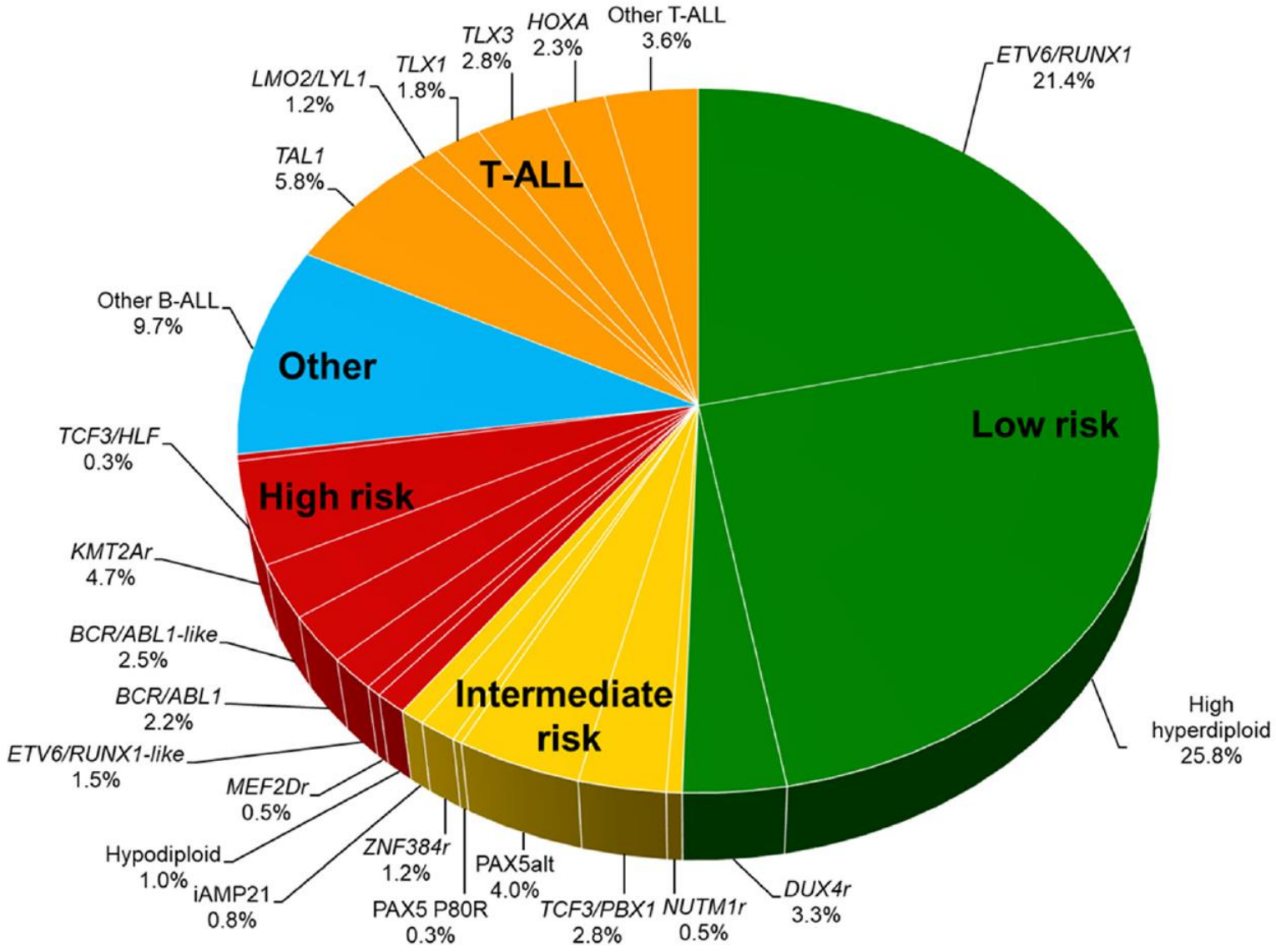
Current genetic subtypes of ALL(Czech BFM ALL 2009)

- heterogeneous group of diseases (‘subtypes’)
- genetic aberrations define biologic features of the cells
- various genotypes have different clinical outcomes



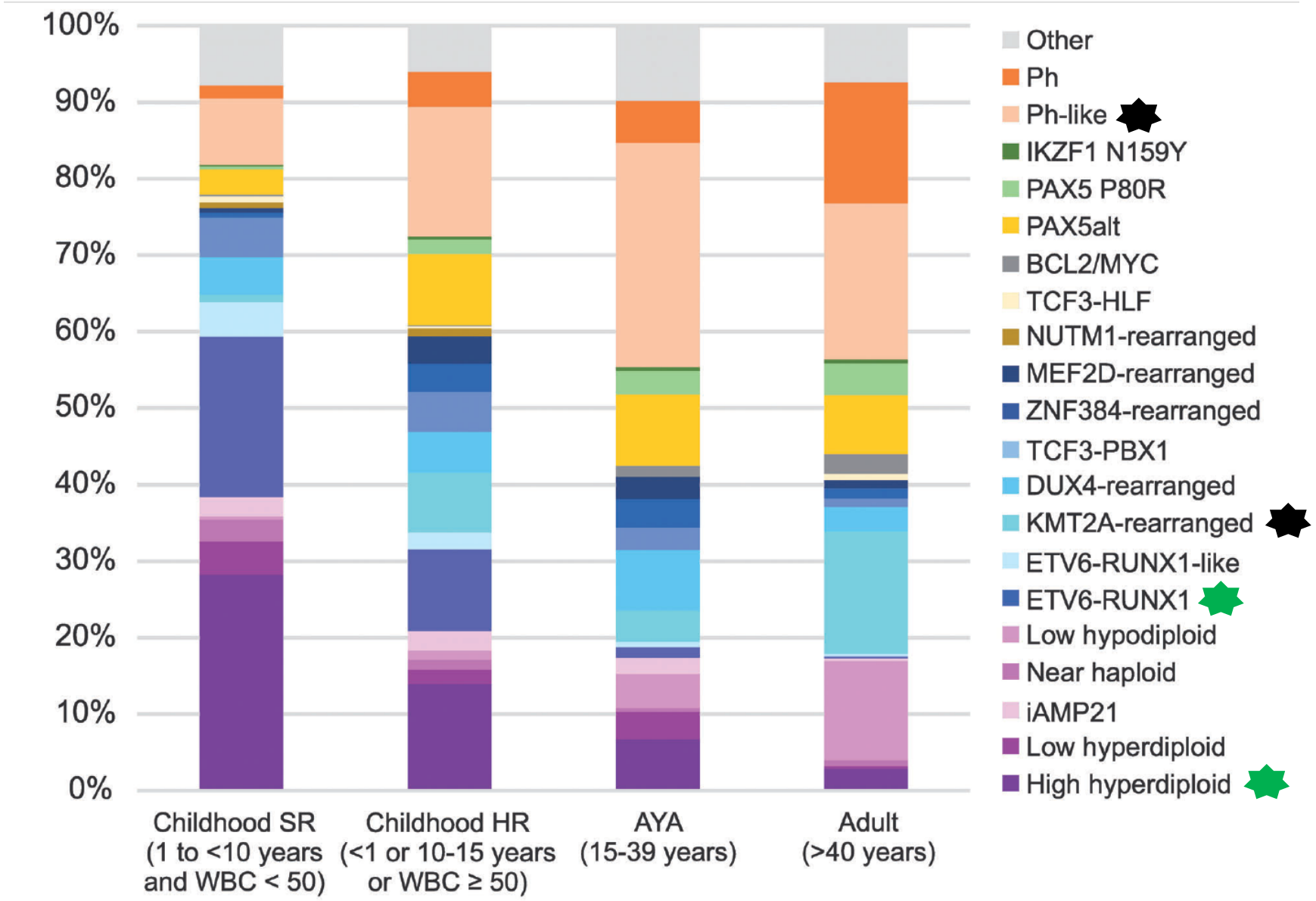
Zaliova et al, Haematologica 2019

Separation of ALL subtypes into risk groups



Inaba & Pui, J Clin Med 2021

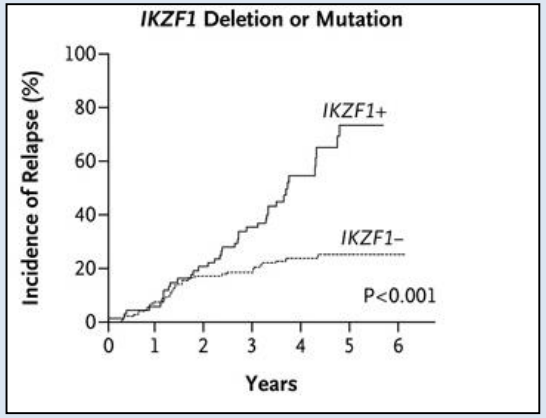
Representation of various genetic aberrations among age groups



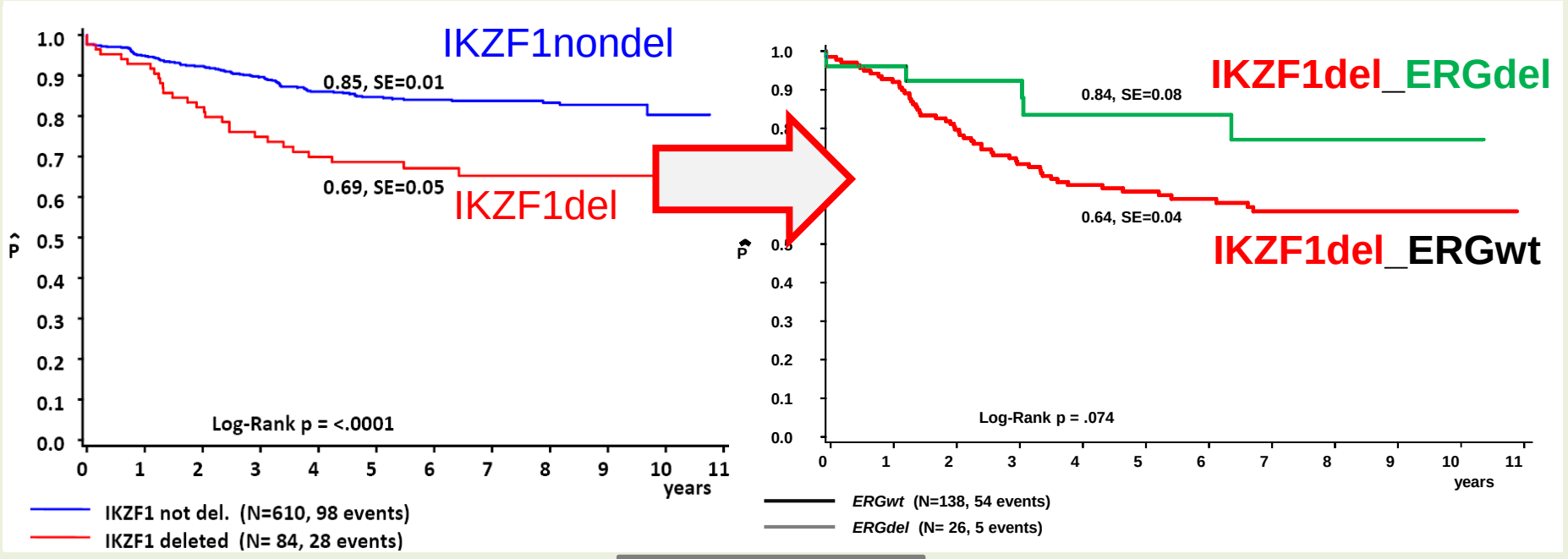
Inaba & Mullighan, Haematologica 2021

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

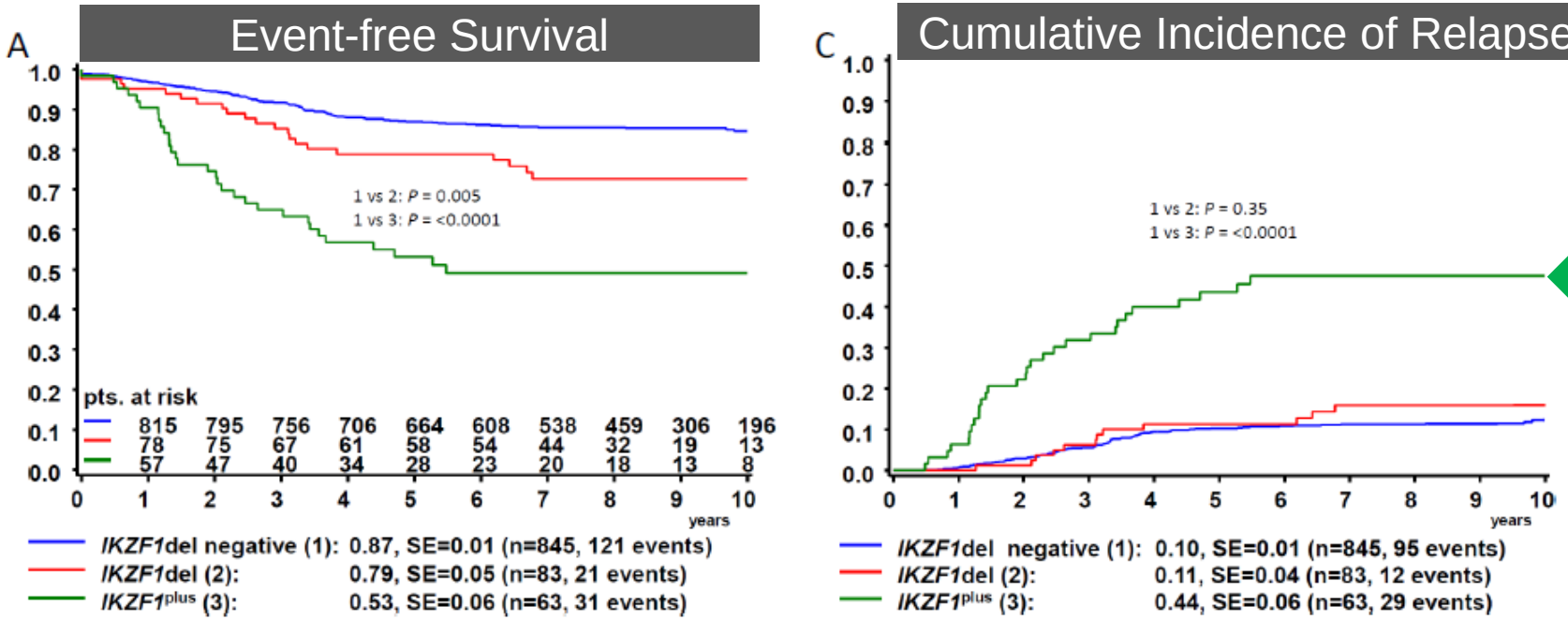


Doerge et al, Haematologica 2013

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%

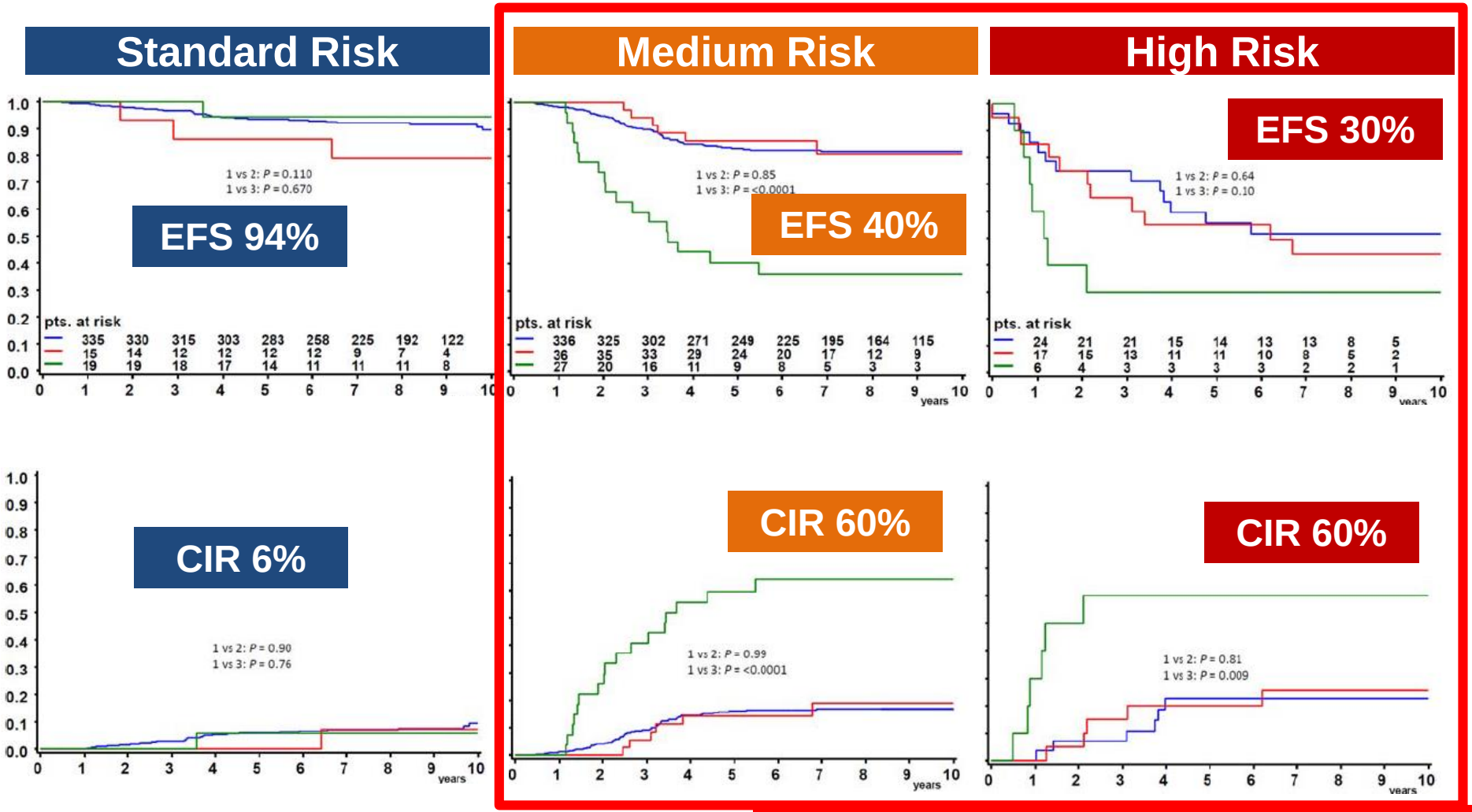
IKZF1^{plus}

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**



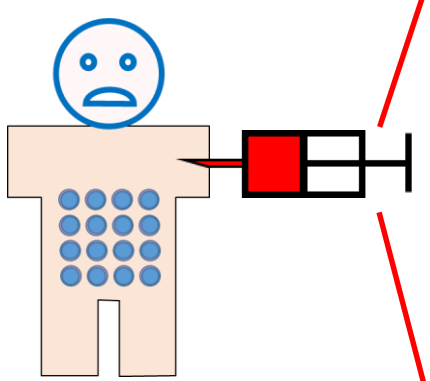
stratification into High-Risk Group with **Blinatumomab** randomisation

Stanulla et al, J Clin Oncol 2018

Case Report: very-high risk ALL

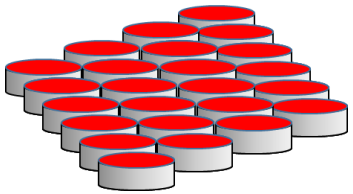
17yo patient
very unsual ALL

CD10+ CD19-
CD22+/-



no response
to standard
Induction
no response
to alternative
regimens

RNAseq:
no targetable aberration



sensitivity testing
to **novel drugs**

more than
100 classical
and novel drugs
JP Bourquin
B Bornhauser

poor efficacy
of traditional
cytostatic

high sensitivity
to inhibitor of
anti-apoptotic
pathway

2 courses of **Venetoclax**
negative MRD
followed by alloSCT

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 small subgroups
- **new methods in diagnostic approaches (NGS- and multiFCM-based)**
  change in diagnostic paradigm: increased analytical and interpretational demand
- **identification of new drugable aberrations?**
  very rare in children x wider use of immunotherapy and/or new therapeutics (Venetoclax)