munotherapy
Hematological
lignancies 2018
CUNEO
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Session V: adoptive immunotherapy: in vivo recruitment

Blinatumomab in ALL and beyond: groundwork and outlook

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Italy

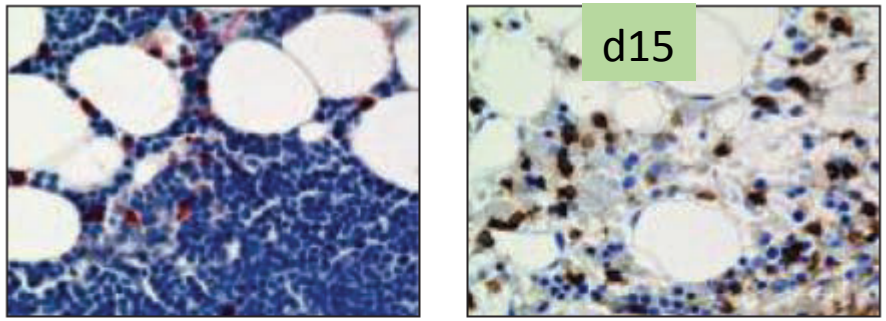
REGIONE DEL VENETO
ULSS3 SERENISSIMA

First evidence in B-cell lymphoma

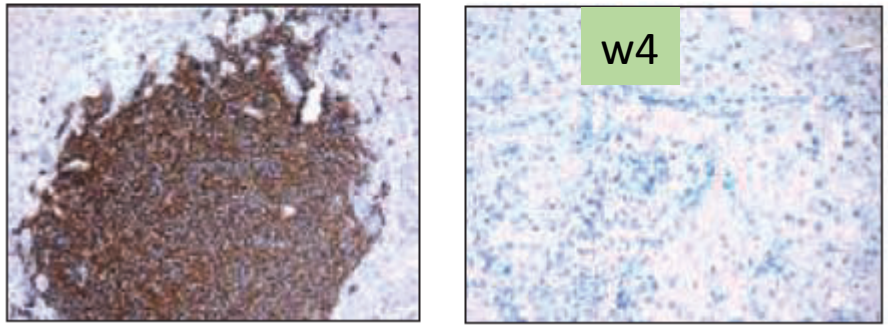
pre **after**

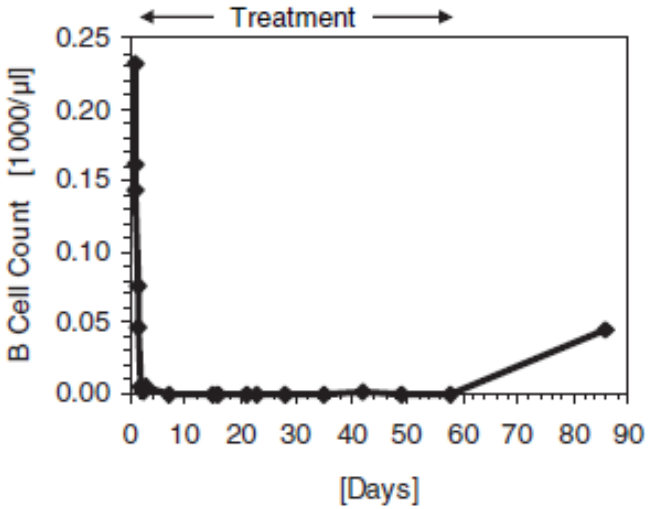
Blinatumomab

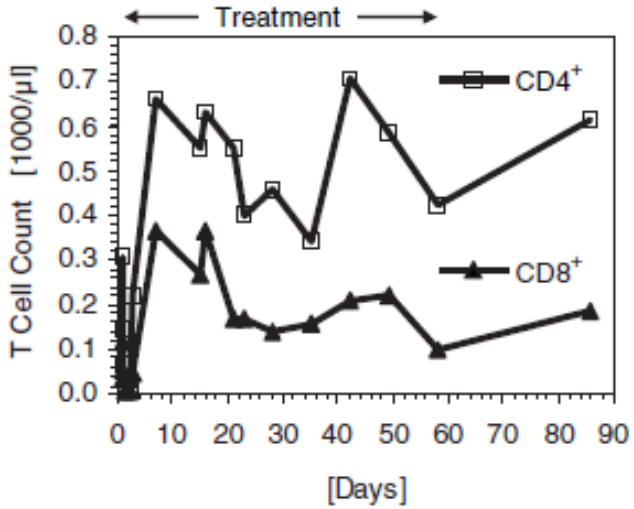
BM



Liver



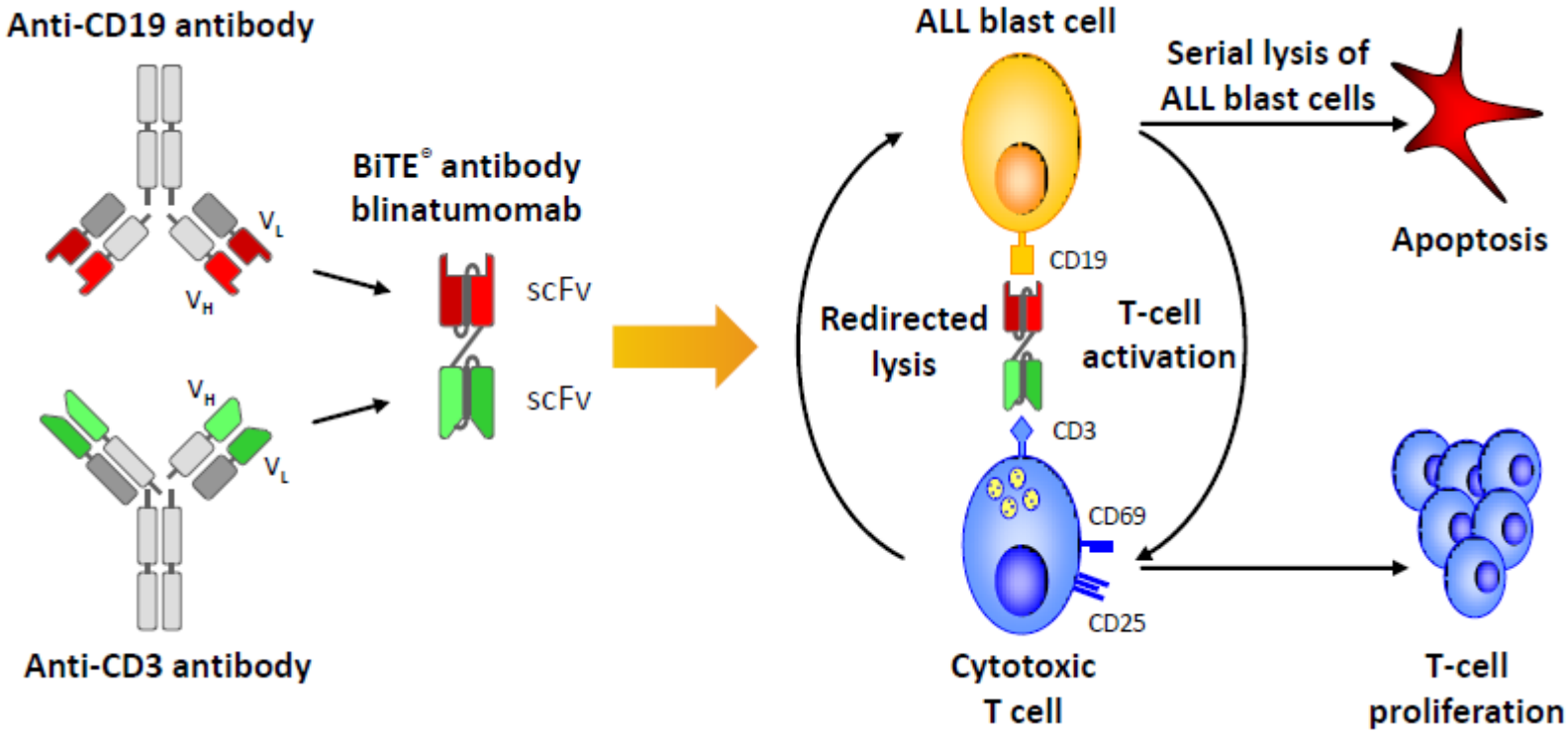




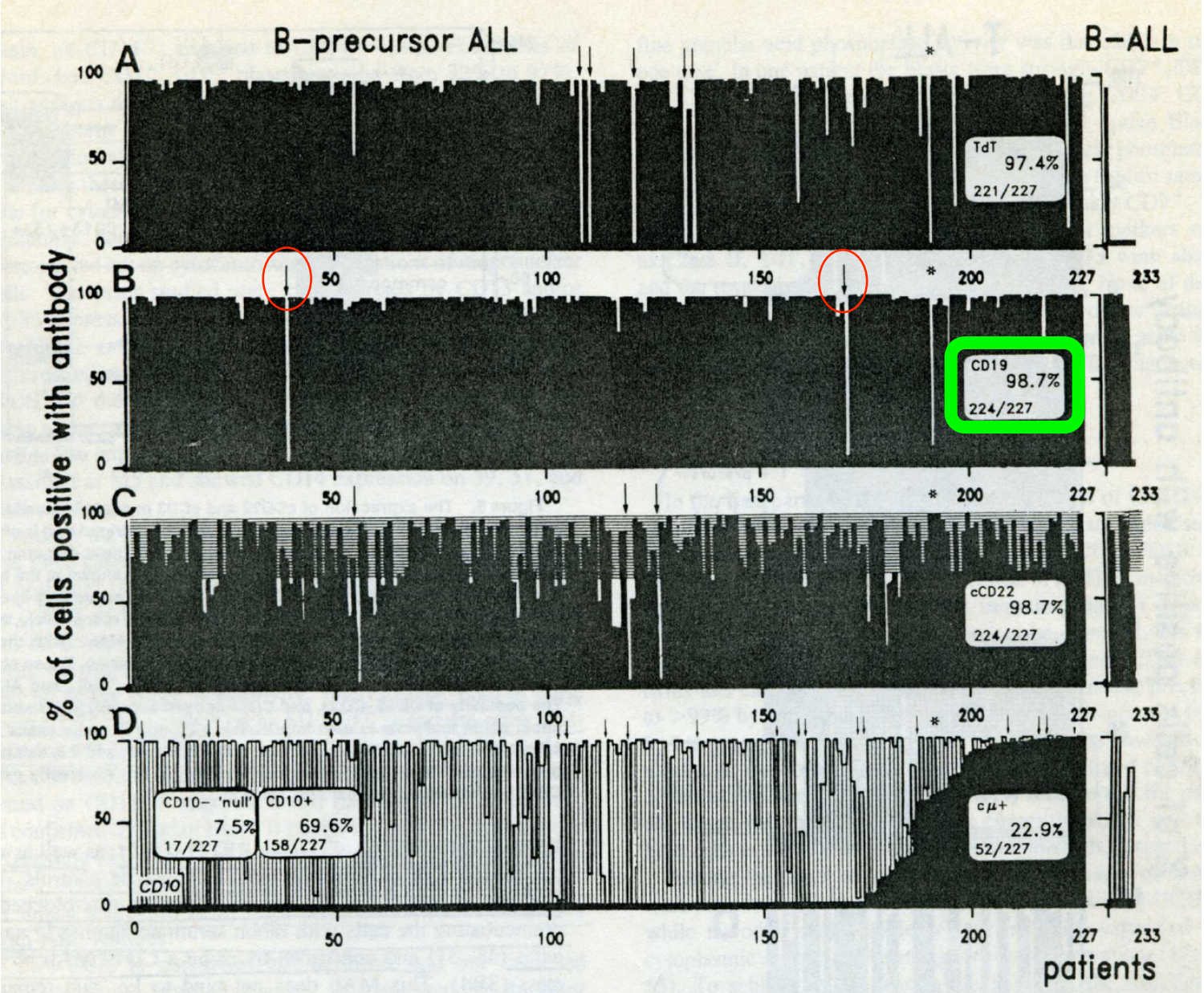
Bargou R et al, **Science** 2008

Blinatumomab (Blincyto)

- **B-lineage anti-tumoral monoclonal antibody construct (by Micromet, then Amgen), a bispecific T-cell engager (BiTE)**



CD19: ideal target in B-precursor ALL



**only 2/227 (0.8
found CD19-**

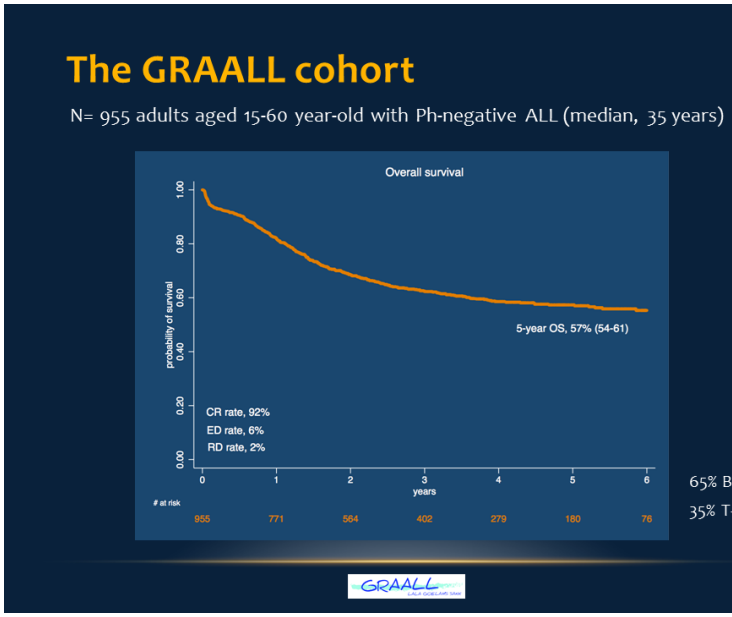
m Janossy G, Coustan-Smith E,
mpana D. Leukemia, 1989

Progress in Ph- ALL (not enough)

ALY: NILG trials 09/00 – 10/07

GERMANY: GMALL trials

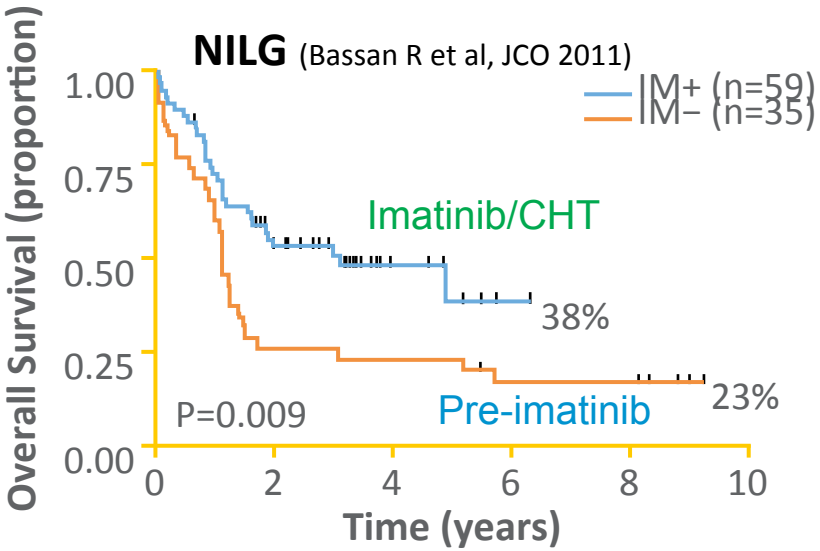
FRANCE: GRAALL trials 2003 - 20

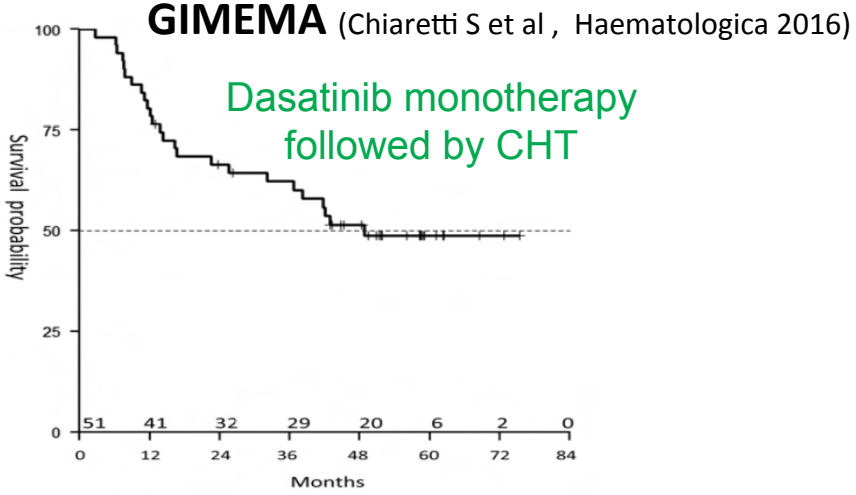


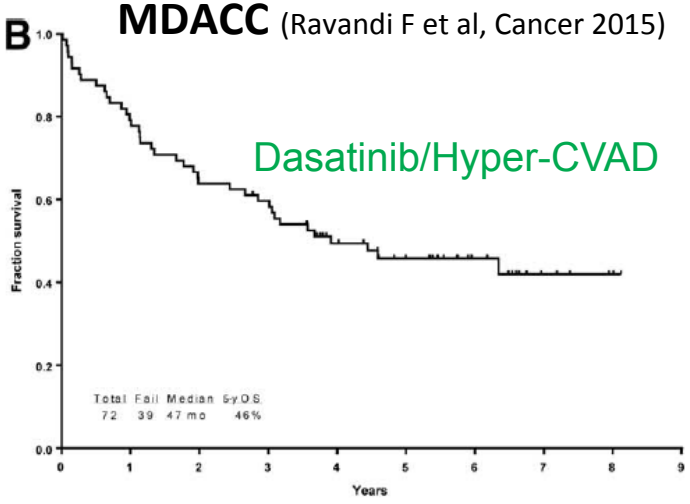
A common language: pediatric-based chemotherapy
nd MRD/risk-oriented allotransplantation strategy

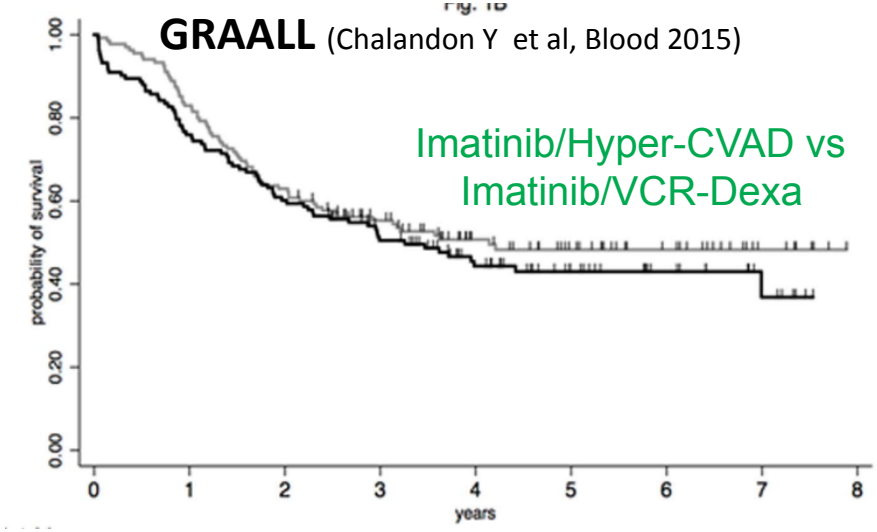
l, ASH 2016; Hoelzer D, 2010; Dombret H, EHA 2014

Progress in Ph+ ALL (not enough)







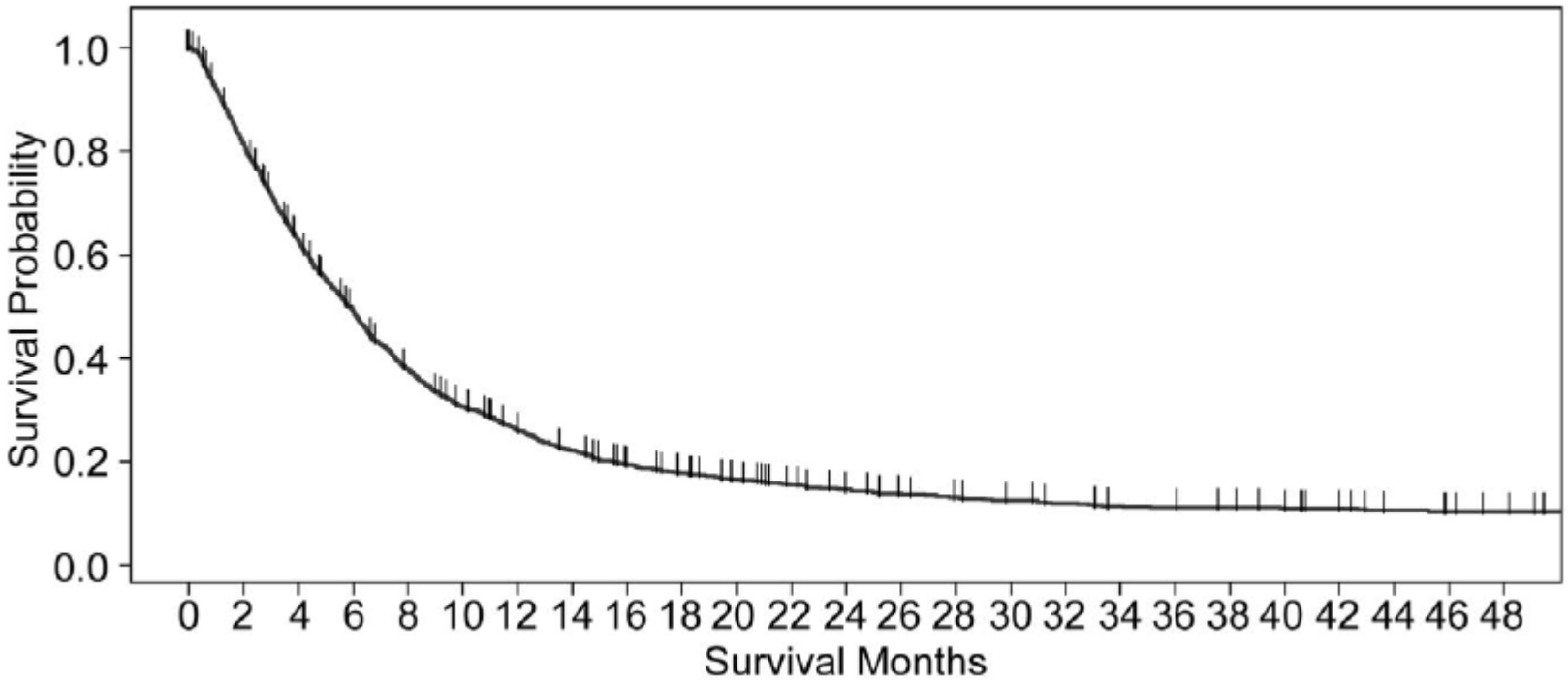


The challenges

- **High risk states**
  - **Adverse biology** subsets
  - **Very poor outcome** of R/R and MRD+
- **Treatment intensity** hard to increase
  - **Few new drugs** for 1st line (Peg-ASP, Nela/Clofa)
  - **TRM** with allo-SCT (15-25%)
  - **Older adults**

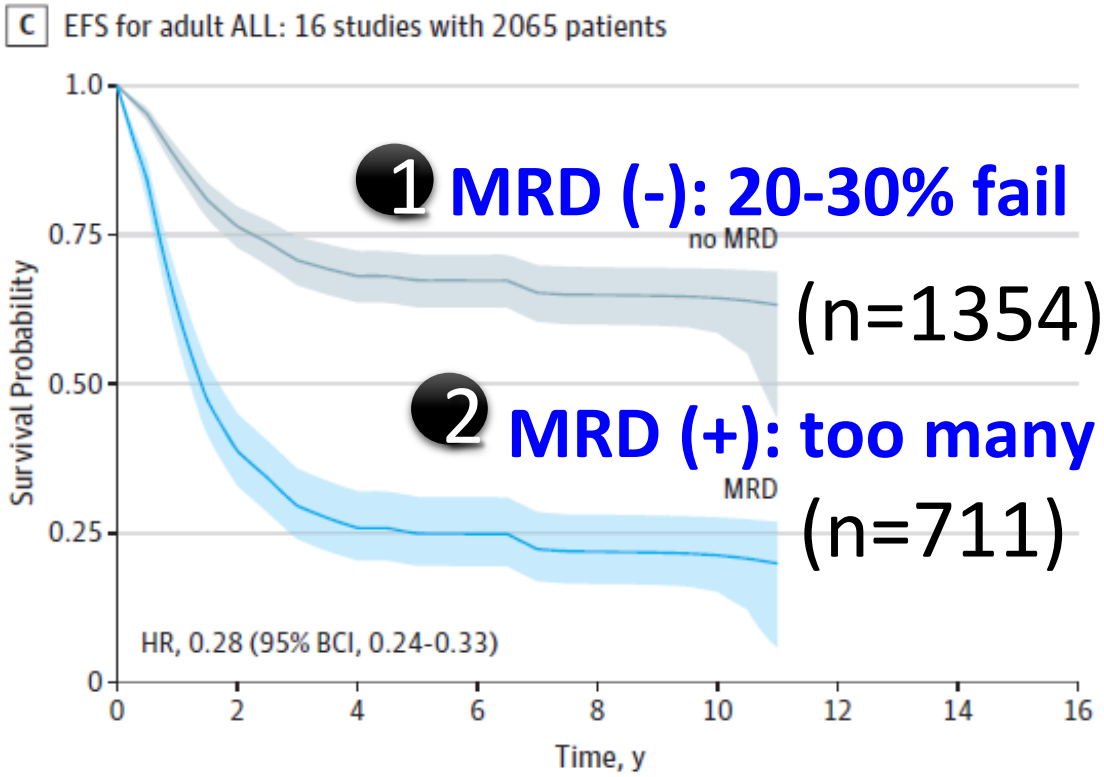
Refractory/relapsed (R/R) ALL

- **R/R Ph- B-precursor ALL**
  (INTERNATIONAL REFERENCE ANALYSIS; N=1706)



Goekbuget N et al, Haematolo

Minimal residual disease

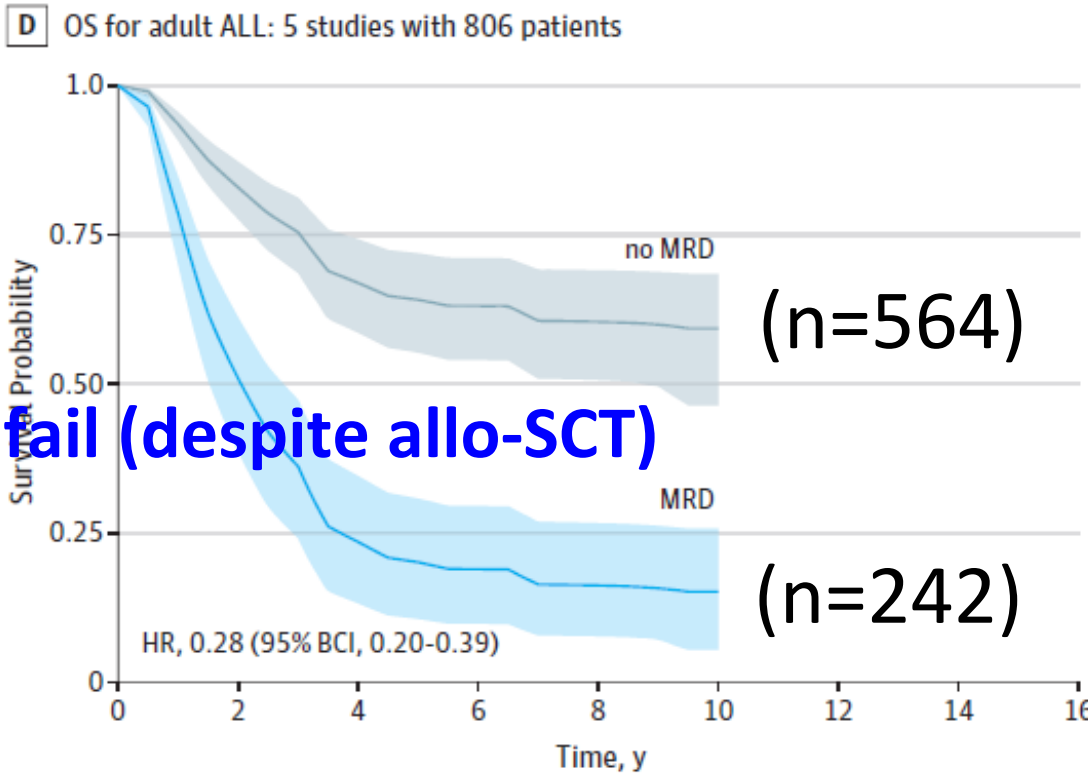


1 MRD (-): 20-30% fail

(n=1354)

2 MRD (+): too many fail (despite allo-SCT)

(n=711)



(n=564)

(n=242)

MRD (+): better outcome with SCT, but …

- Poor SCT realization (NILG, GMALL, GRAALL: 43.3% - 47.5%)
- Risk of subsequent relapse
- TRM

t al, *JAMA Oncology* 2017

Bassan R et al,
Clin Lymphoma Myeloma Leuk

Targeted therapy to improve

Diagnostics/molecular screening and drug sensitivity profiling
- **ACTIONABLE TARGETS**
- **ACTIVE AGENTS and COMBINATIONS**

Targeting
proliferation, apoptosis and cell differentiation pathways

- **Inhibitors**
- **Agonists**
- **Differentiating agents**

Targeting
B- and T-cell membrane antigens

- **Monoclonal antibodies and derivatives *BLINATUMOMAB***
- **Chimeric antigen receptor T cells and NK cells**
- **Checkpoint inhibitors**

Targeting
the supportive marrow microenvironment

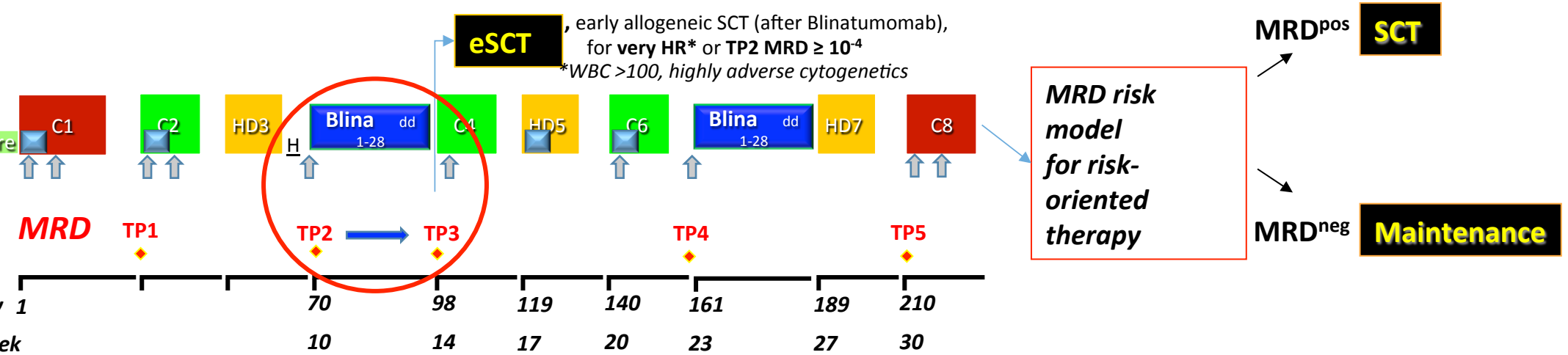
- **Inhibitors**

- ***R/R ALL***
- ***MRD+ ALL*** *(CR1, >CR2)*
- ***first line trials in Ph+ and Ph- ALL***

AL 2317 GIMEMA trial for Ph- CD19+ B-precurso LL (n=149)

nduction/consolidation, Blinatumomab, MRD study and early SCT

B. Final MRD-oriented therapy



Treatment elements

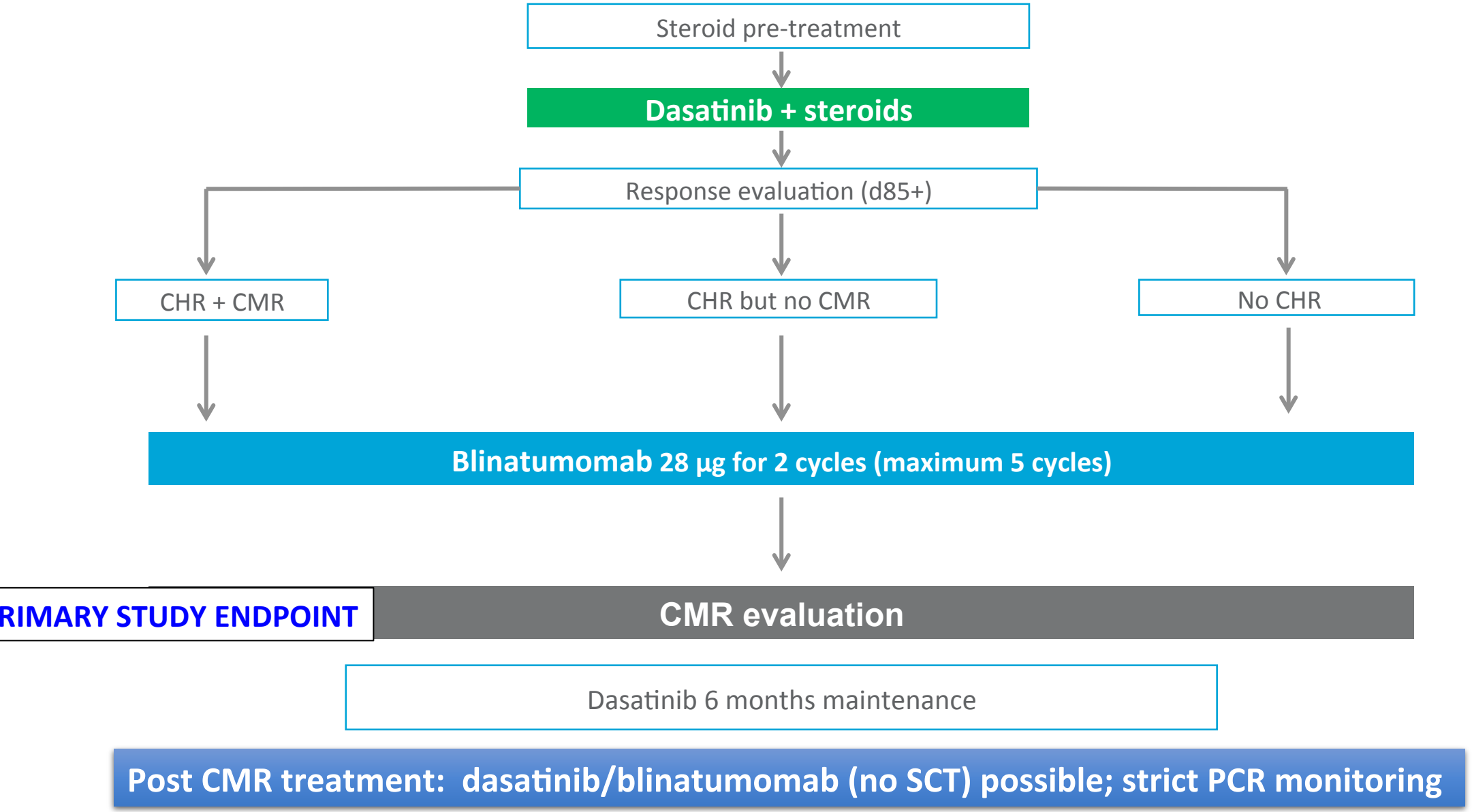
- ADULT -TYPE (pre: CY/PDN; VCR, Dex, IDR)
- TRIPE IT
- Pegylated- ASP
- **BLINATUMOMAB**
- PEDIATRIC-TYPE (IDR-CY-DXM-6MP-AraC)
- PEDIATRIC-TYPE (HD MTX-AraC or HD MTX-ASP-6MP) with lineage-targeted MTX (B: 2.5 g/m²)

PRIMARY STUDY ENDPOINT

MRD negativity rate

after blinatumomab course 1 (TP3 vs TP2)

New GIMEMA trial for Ph+ ALL (D-ALBA)



Conclusions

- Treatment of adult ALL is changing/improving thanks to targeted therapy (associations)
- Targeting agents such as blinatumomab display maximal power in untreated/CR1 patients (trials open worldwide)
- Blinatumomab resistance mechanisms
  - Favorable and unfavorable role of TEM and TREG cells, respectively
  - Expression of co-stimulatory/inhibitory molecules (PD1, PD-L1, …)
  - Loss of CD19 expression & extramedullary relapse