# LEUKEMIA2020-2021

ASSOCIAZIONE ITALIANA CONTRO LE LEUCEMIE-LINFOMI E MIELOMA ONLUS

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# Current treatment strategies in T-ALL



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GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

SIE - Società Italiana di Ematologia

# Disclosures

- Current presentation: nothing to disclose
- Other: Amgen, Pfizer, Incyte, Novartis, Jazz, Servier

# T-ALL

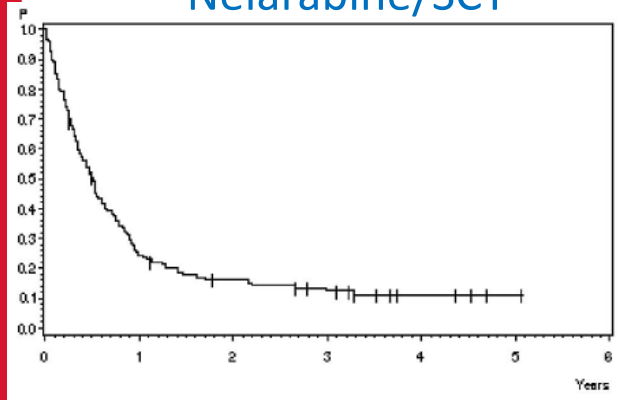
- In adults: 20% of all cases
- The «forgotten» ALL subset ?
  - At diagnosis (vs. B-ALL)
    - Younger age, male gender
    - Higher WBC
    - Better Hb and PTL
    - Mediastinum
  - **Prognosis: equal or better**

# A note of caution

- Cure upfront, avoid resistance/relapse (R/R)
- Reported strategies for R/R T-ALL[1-3]

**GMALL (Germany)**

Nelarabine/SCT

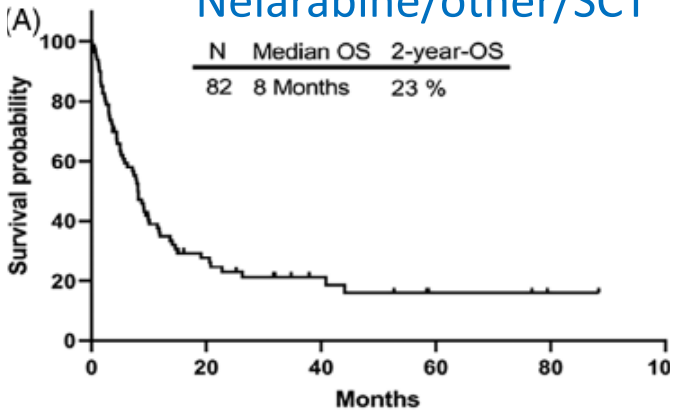



**126 patients**

Survival 12% at 3 years

**MD Anderson Cancer Ctr (USA)**

Nelarabine/other/SCT

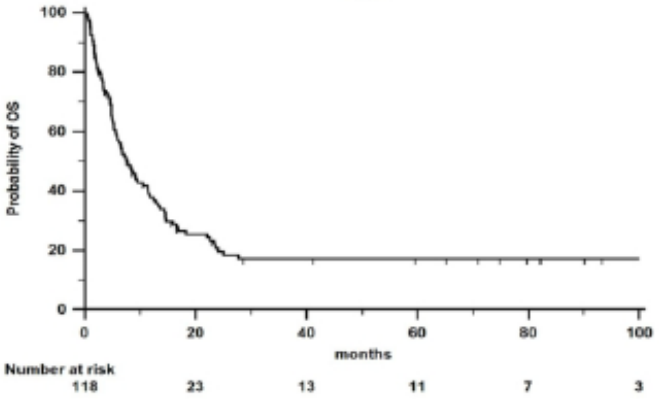



**82 patients**

Survival 23% at 2 years

**Italy**

Nelarabine/SCT




**118 patients**

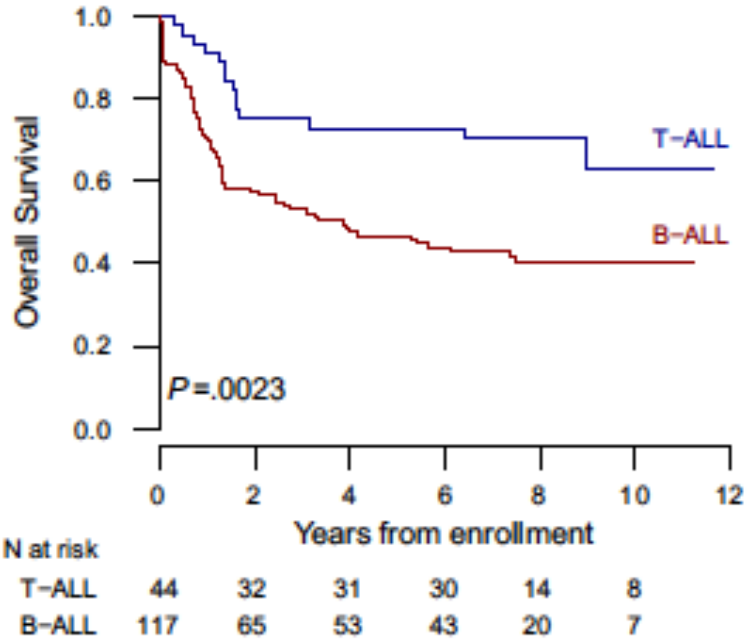
Survival 18% at 5 years

[1]Goekbuget N et al, *Blood* 2011; [2]Samra B et al, *Am J Hematol* 2020; [3]Candoni A et al, *Am J Hematol* 2020

# Current standards (Italy)

- Pediatric-inspired chemo and risk/MRD-oriented SCT

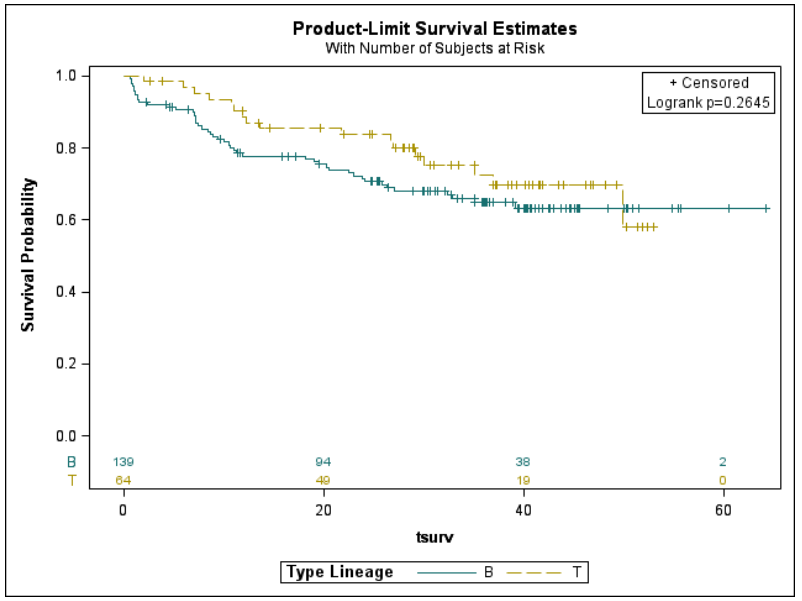
**NILG 10/07[1]**




**44 patients** **CR 98%**

Survival 73% at 5 years

**GIMEMA LAL 1913[2]**



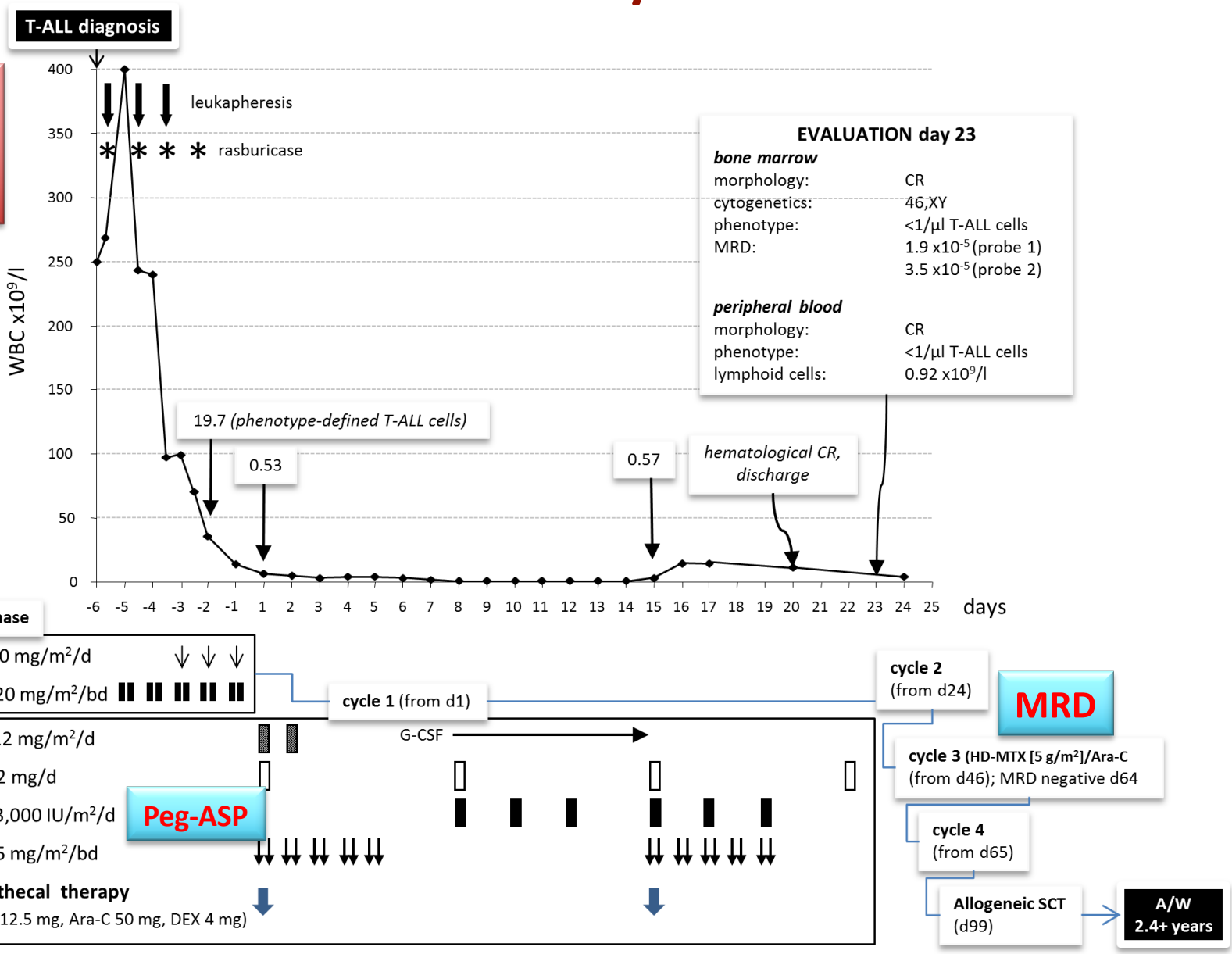

**64 patients** **CR 98%**

Survival 72.6% at 3 years

[1]Bassan R et al, *Blood Cancer J* 2020; [2]Bassan R et al, *HemaSphere* 2018

# Effective induction/consolidation

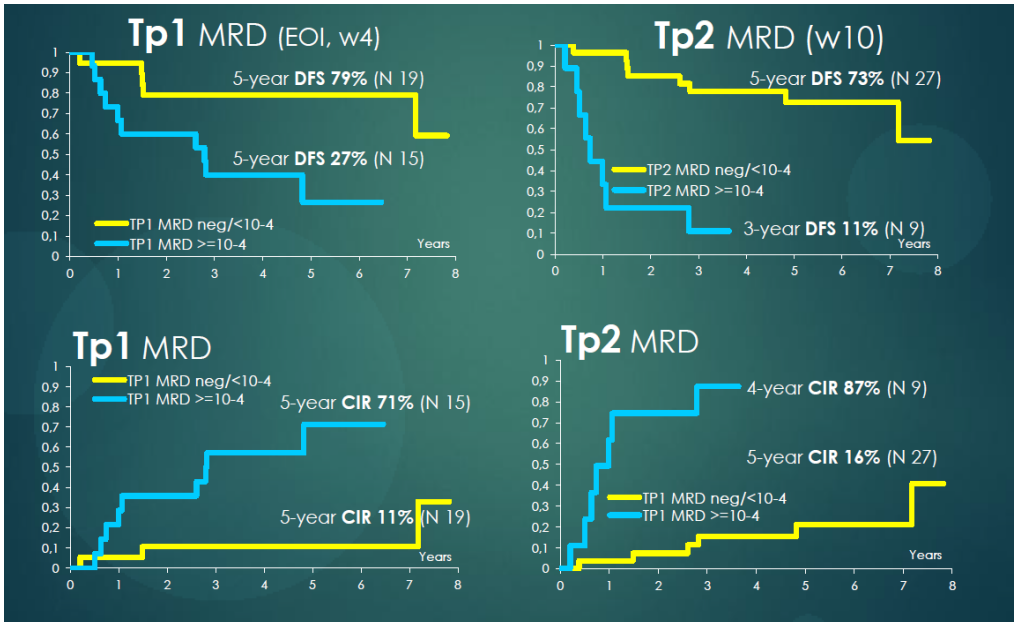
**t(8;14)/ *MYC*+ T-ALL**




Parolini M et al, *Blood Cancer J* 2013

# MRD and genetics

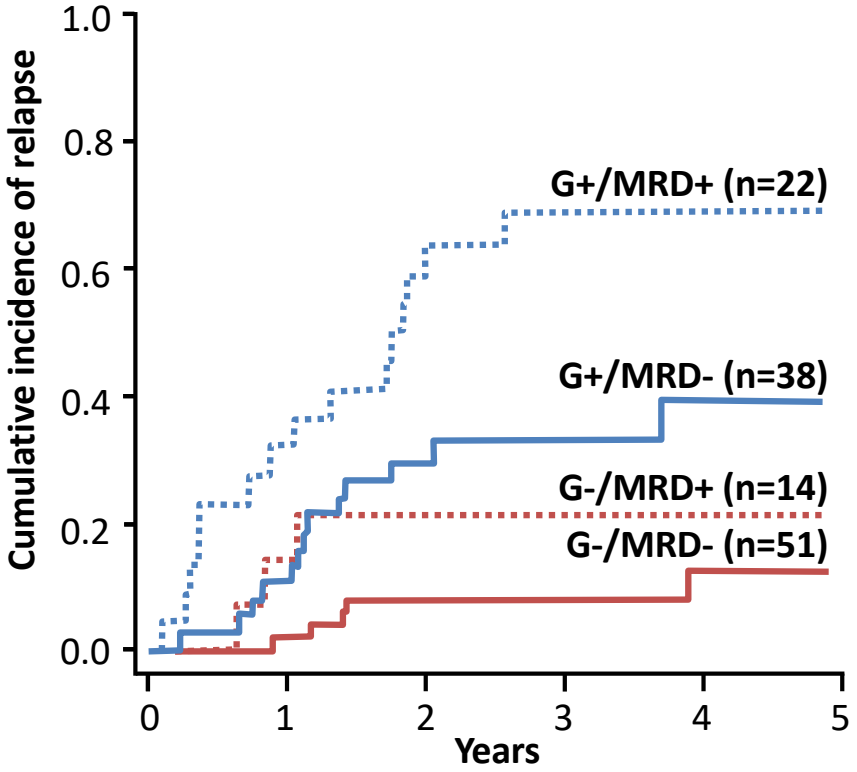
## NILG 10/07[1]




*FAVORABLE:*

**MRD <$10^{-4}$ at w4 and w10**

## GRAALL 2003-2005[2]




*FAVORABLE:*

**MRD <$10^{-4}$ at w6**

**4-gene classifier**: NOTCH1/FBXW7 mutated, no RAS/PTEN alteration

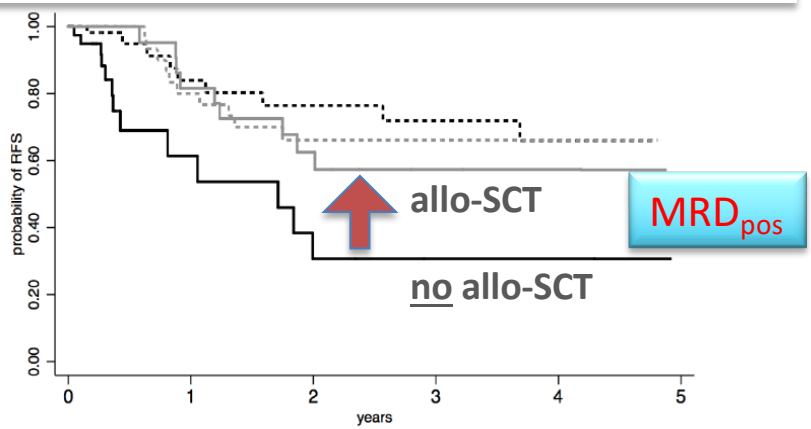
[1]Bassan R et al, *Blood Cancer J* 2020; [2]Beldjord K, et al *Blood* 2014

# Allogeneic SCT for high-risk/MRD$_{pos}$ T-ALL

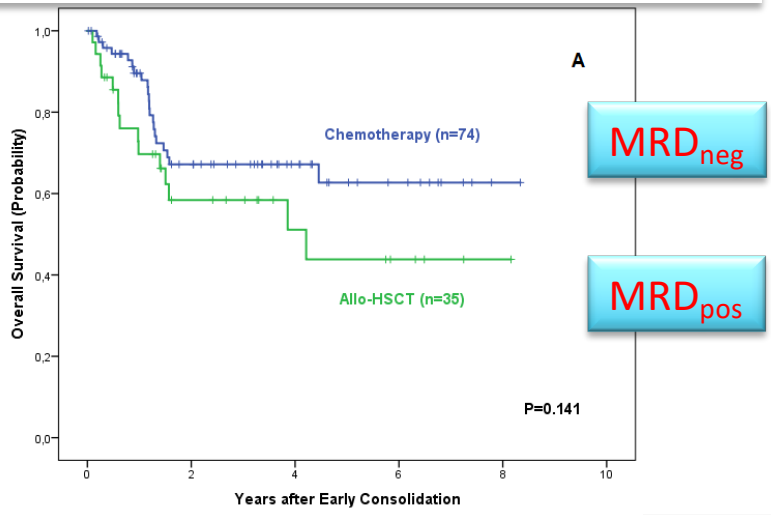
## Risk stratification, NILG/GIMEMA

| Standard risk (allocation to chemotherapy) | High risk (allocation to allogeneic SCT) |
|---|---|
| Cortical/thymic | Pro/pre, mature ETP |
| WBC <100 | WBC >100 |
| MRD$_{neg}$ | MRD$_{pos}$ |
| | adverse cytogenetics |

## Allo-SCT for MRD$_{pos}$, GRAALL[1]



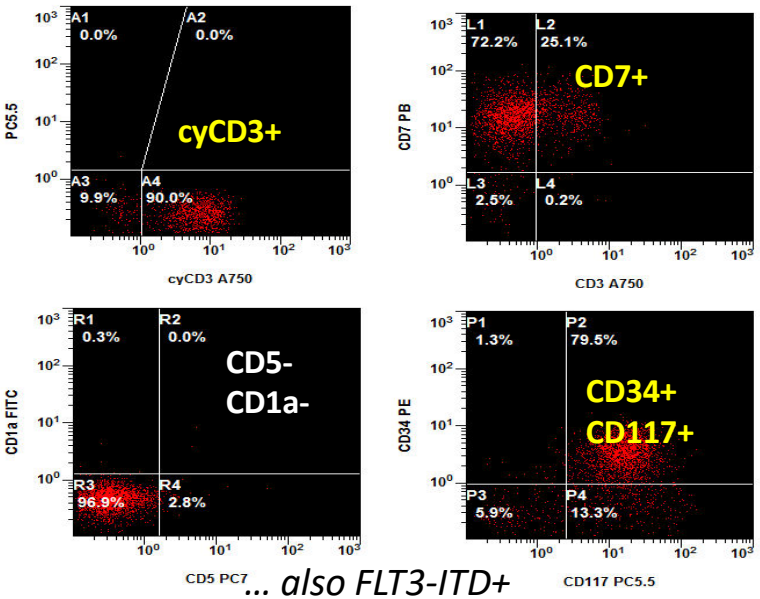

## SCT for MRD$_{pos}$, PETHEMA[2]




[1]Dhèdin N et al, *Blood* 2015; [2]Barba P et al, *Leuk Res* 2018

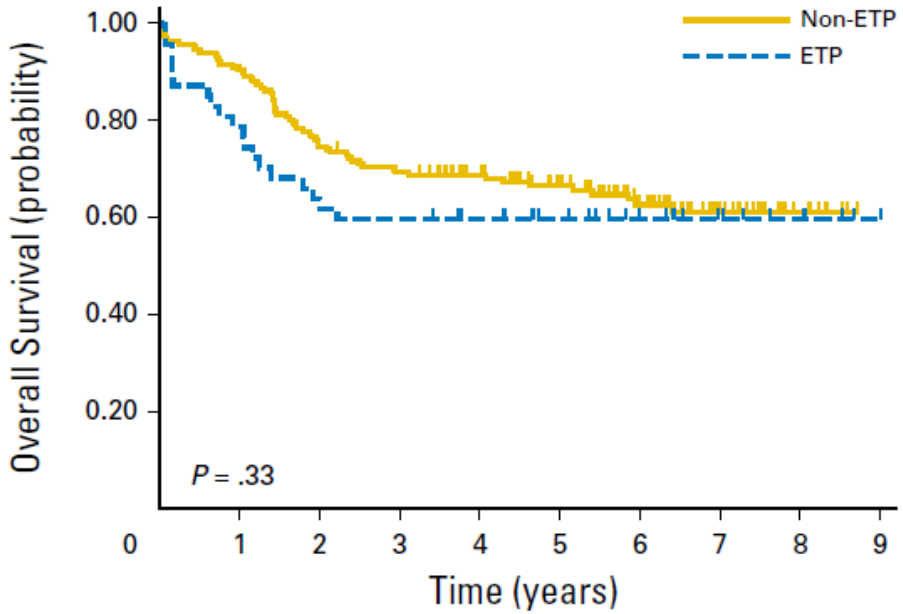
# Early thymic precursor (ETP) ALL

- **Immunophenotype**
  - Early-T CD5- CD1a- My+
- **Gene Expression Profile**
  similarities to stem/myeloid cells
- **Molecular profile**
  - **lower incidence** NOTCH1/CDKN1/2 mutations
  - **frequent** RUNX1/ETV6/GATA3/FLT3/DNMT3A /RAS/ IDH1/IDH2 mutations
- **JAK/STAT pathway activation**




*... also FLT3-ITD+*

## Pediatric-inspired GRAALL regimens




No. at risk:

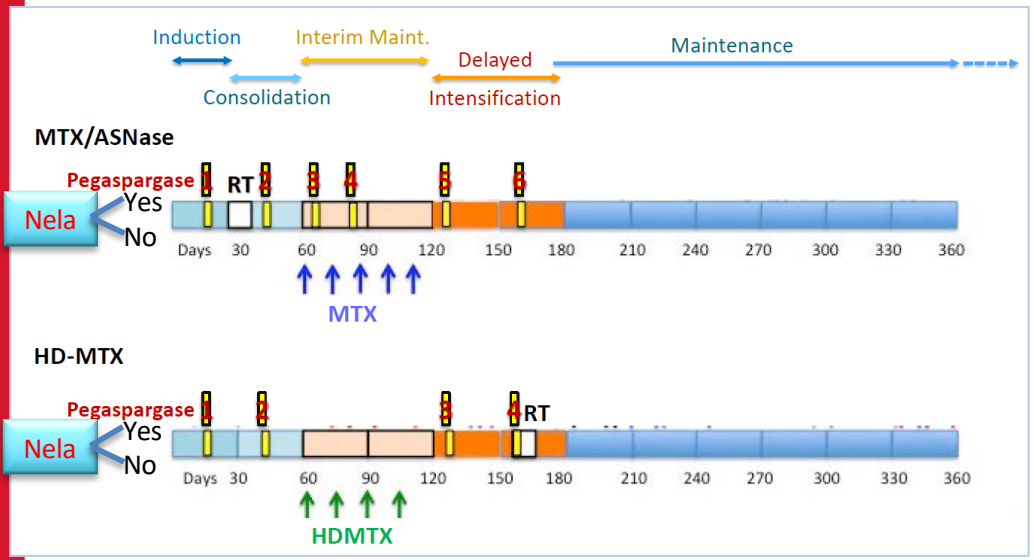
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Non-ETP | 166 | 150 | 124 | 114 | 102 | 82 | 52 | 26 | 8 | 0 |
| ETP | 47 | 37 | 30 | 28 | 25 | 19 | 13 | 8 | 5 | 0 |

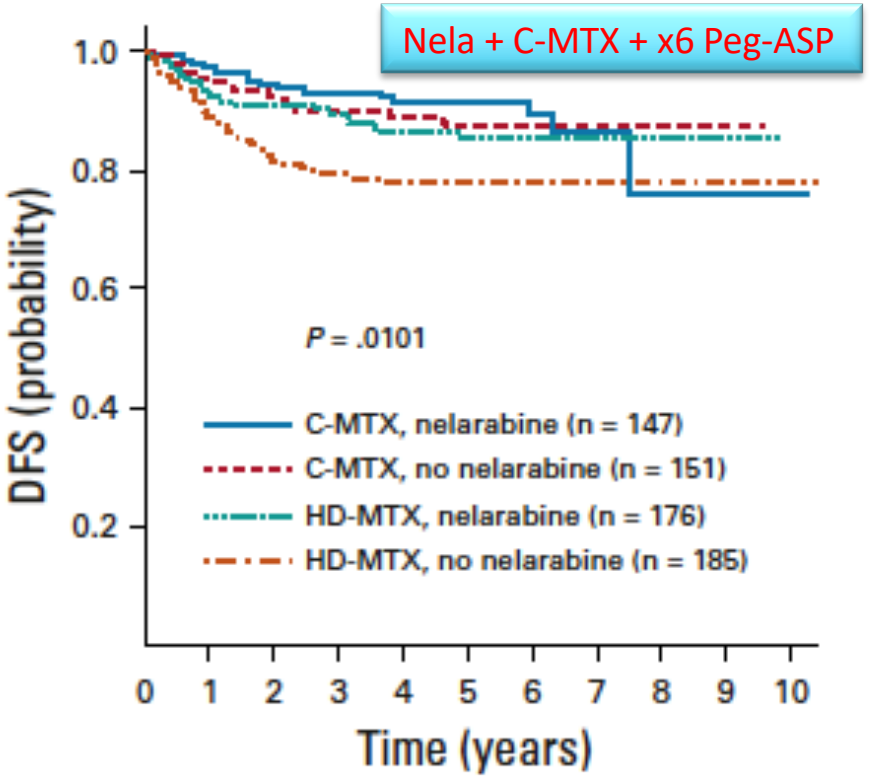
**ETP ALL** more frequently $MRD_{pos}$
more frequent allogeneic SCT

Bond J et al, *J Clin Oncol* 2017

# Ways to improve

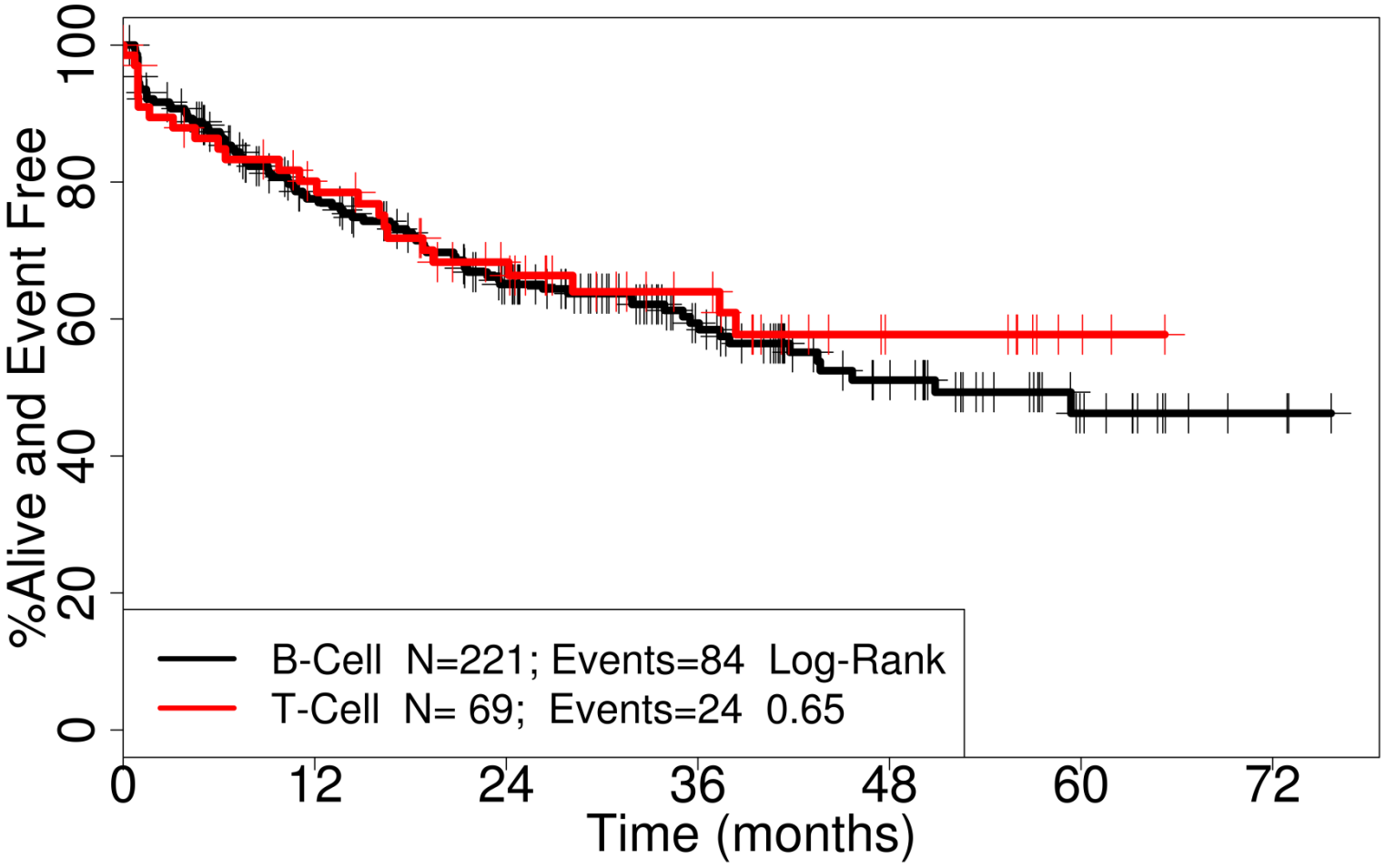
- **Upfront nelarabine** (**COG 0434**, 1-30 years, n=1,562)
  - 4x HDMTX/Peg-ASP vs. 5x Capizzi MTX/6x Peg-ASP and Nelarabine vs. no nelarabine
  - **BETTER ARM:** Capizzi MTX + nelarabine
  - **ETP ALL:** no worse




Dunsmore KP, *JCO* 2020

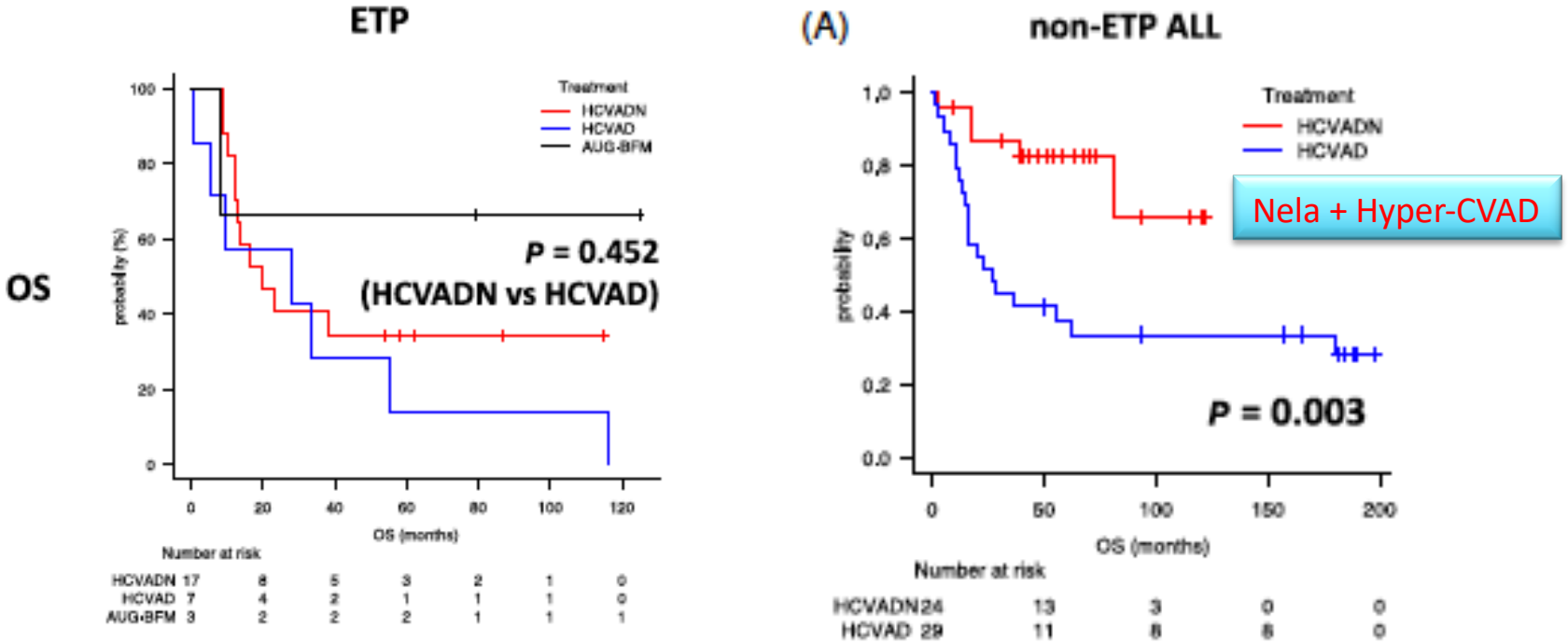
# US COG 0434-Alliance (x6 Peg-ASP/C-MTX/no nelarabine) in AYAs 17-39 years




Stock W, et al *Blood* 2019
Data courtesy of Wendy Stock (Chicago, IL)

# Frontline nelarabine in adult T-ALL

- UKALL Phase 3 and GRAALL Phase 2 (results awaited)
- GMALL $MRD_{pos}$ (6/12 turning $MRD_{neg}$, 50%)[1]
- MDACC Hyper-CVAD[2]



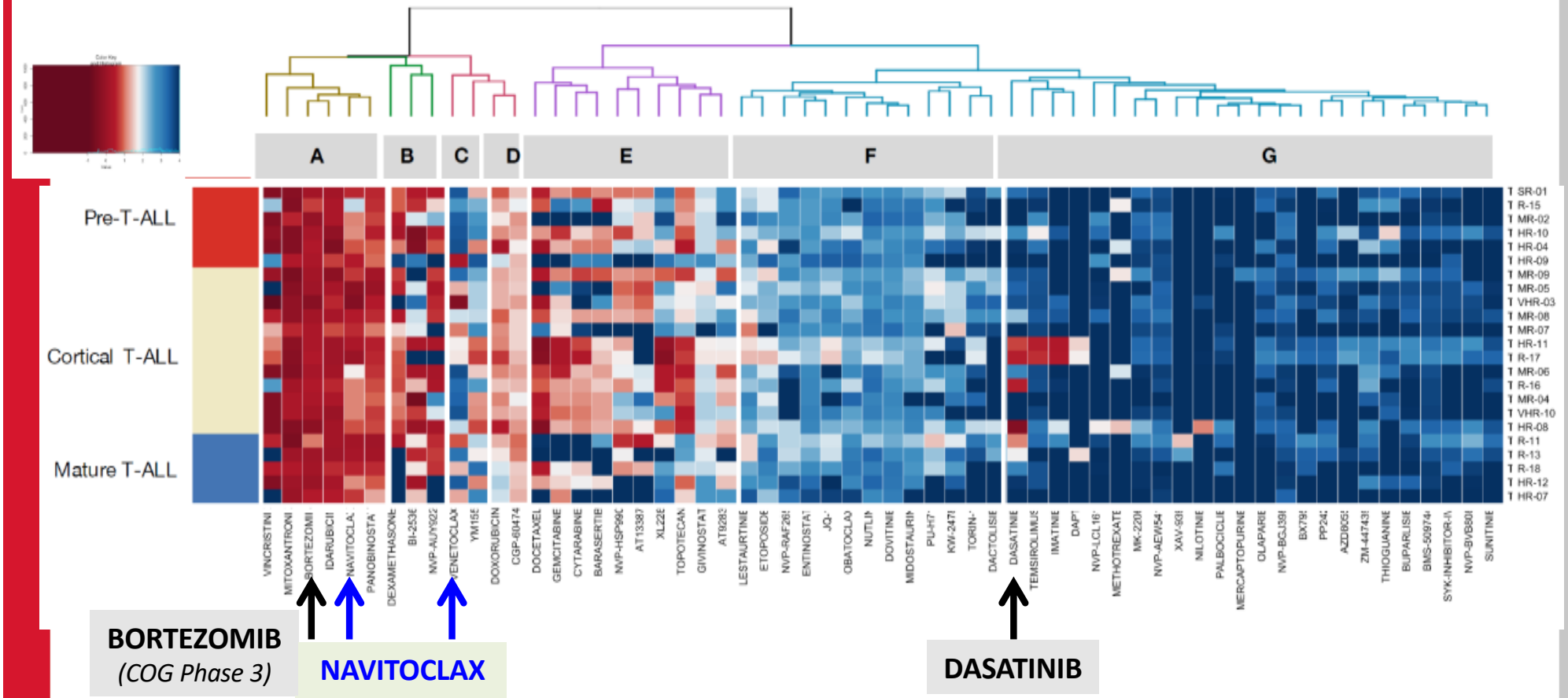

[1]Goekbuget N et al, *ASH* 2017; [2]Morita K et al, *Am J Hematol* 2021

# The future

- Better results with targeted therapy ?
  - Molecular screening for target identification
  - Drug sensitivity screening

- **Immunotherapy**
  - **CAR-T** CD2, CD5, CD7, CD38
  - **Monoclonals** CD25-basiliximab, CD38-**daratumumab**/isatuximab
- **Targeting agents**
  - **IL7–JAK/STAT** **ruxolitinib** …
  - **PI3K/AKT/mTOR** idelalisib, sirolimus …
  - **Cell cycle regulation** palbociclib
  - **Proteasome** **bortezomib** …
  - **MAPK–RAS** trametinib …
  - **Notch receptors** BMS906024 …
  - **Apoptotic machinery** **venetoclax, navitoclax, idasanutlin**
  - **Epigenetic** hypomethylating agents, HDA and DOT1-L inhibitors
  - **Tyrosine kinase** **dasatinib** …

# *Ex vivo* drug vulnerability




**BORTEZOMIB**
*(COG Phase 3)*

**NAVITOCLAX**

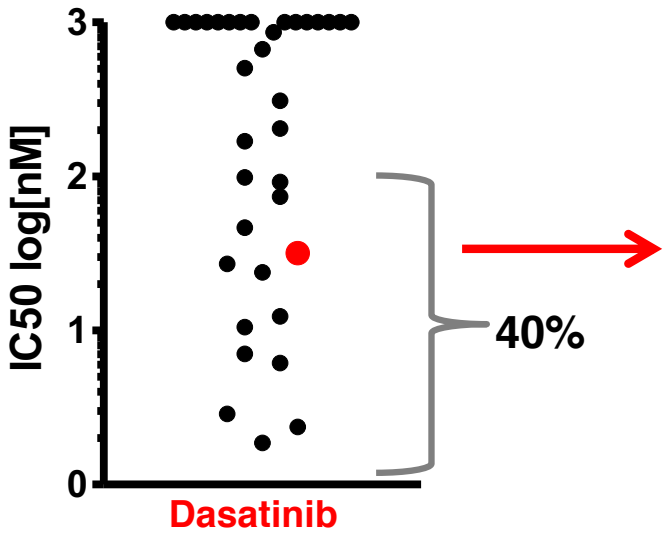
**VENETOCLAX**
*(R/R Phase 1-2s)*

**DASATINIB**

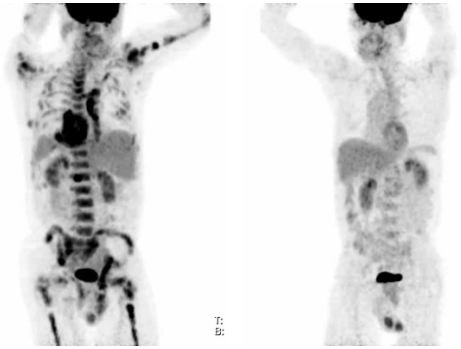
**Navitoclax-venetoclax** induced CR in 6/16 R/R T-ALL, with $MRD_{neg}$ in 4 (Jabbour E et al, *HemaSphere* 2020)

Courtesy JP Bourquin, Zurich (CH)

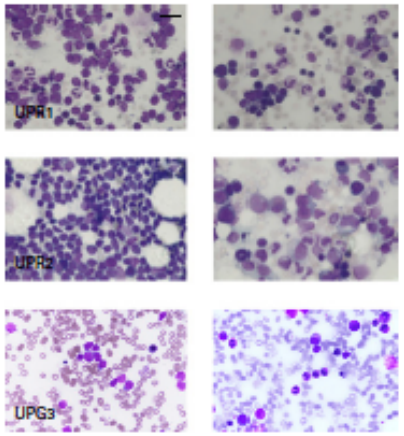
# The turning point

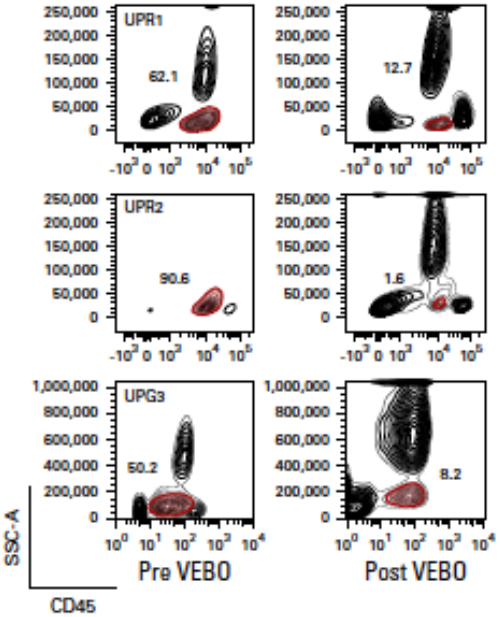



Refractory T-ALL patient
Dasatinib + Asparaginase

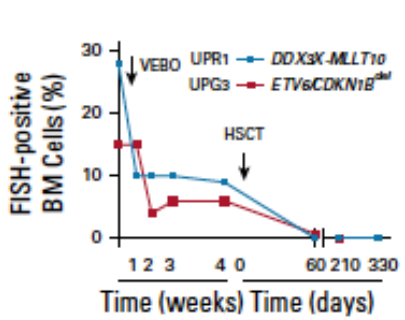



Frismantas V et al, *Blood* 2017




| | UPR1 | UPR2 | UPG3 | |
|---|---|---|---|---|
| Days | +320 | +56 | +239 | |
| RBC | 4010 | 3170 | 4720 | ×10^6 / uL |
| Hb | 13.5 | 9.8 | 9.7 | g/dL |
| MCV | 99 | 91 | 103 | fL |
| WBC | 5030 | 3750 | 4720 | ×10^3 / uL |
| N | 3280 | 2720 | 3870 | ×10^3 / uL |
| L | 1280 | 540 | 425 | ×10^3 / uL |
| PLT | 170 | 210 | 110 | ×10^3 / uL |




Refractory ETP-ALL patients
Venetoclax + Bortezomib

La Starza R et al,
*JCO Precision Oncol* 2019

# Conclusions

- T-ALL no longer high/higher risk subset, cure ≥ 60% in adults
- *State-of-the-art*: Pediatric-based and risk-oriented regimens
- Therapeutic progress
  - Upfront nelarabine
  - Precision medicine: from R/R to frontline therapy