Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

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How I Treat High Risk ALL in First Line

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Risk factors

Patient-related

Age
Performance status
Comorbidity

Disease-related

WBC
Immunophenotype
Cytogenetics/genetics/genomics
Response kinetics (MRD)
Drug sensitivity profiling

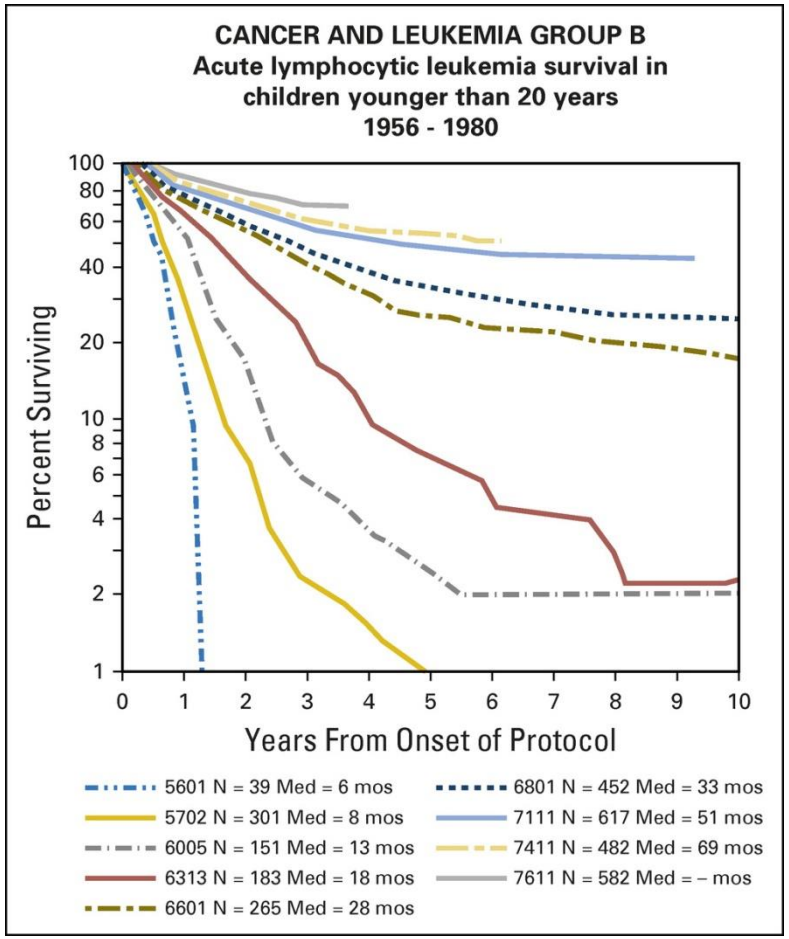
treatment compliance, therapy-related mortality

resistance, relapse

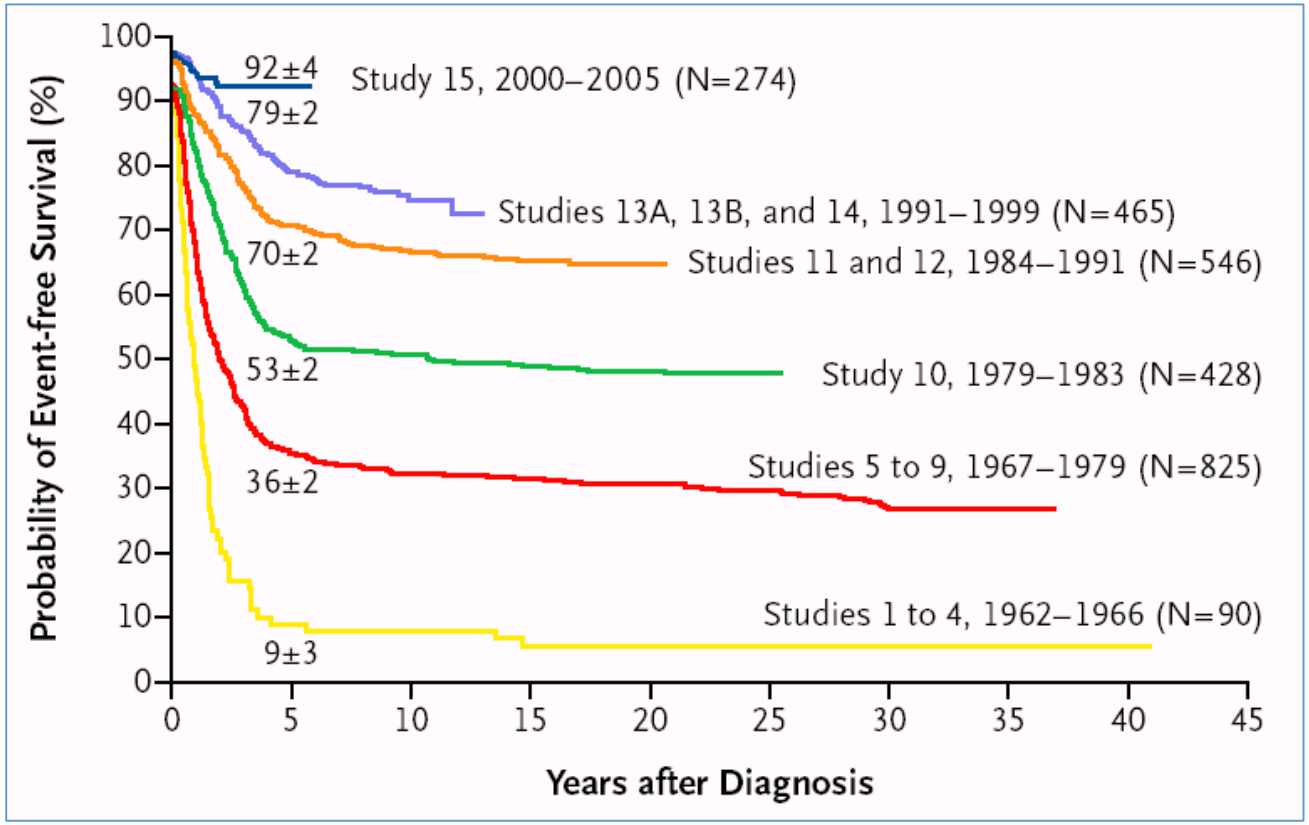
INDIVIDUAL RISK PROFILE: HOW TO TREAT ?

THE ULTIMATE PROGNOSTIC FACTOR IS TREATMENT

Same patients, different outcome



JF Holland, J Clin Oncol 1983;1:75-90



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

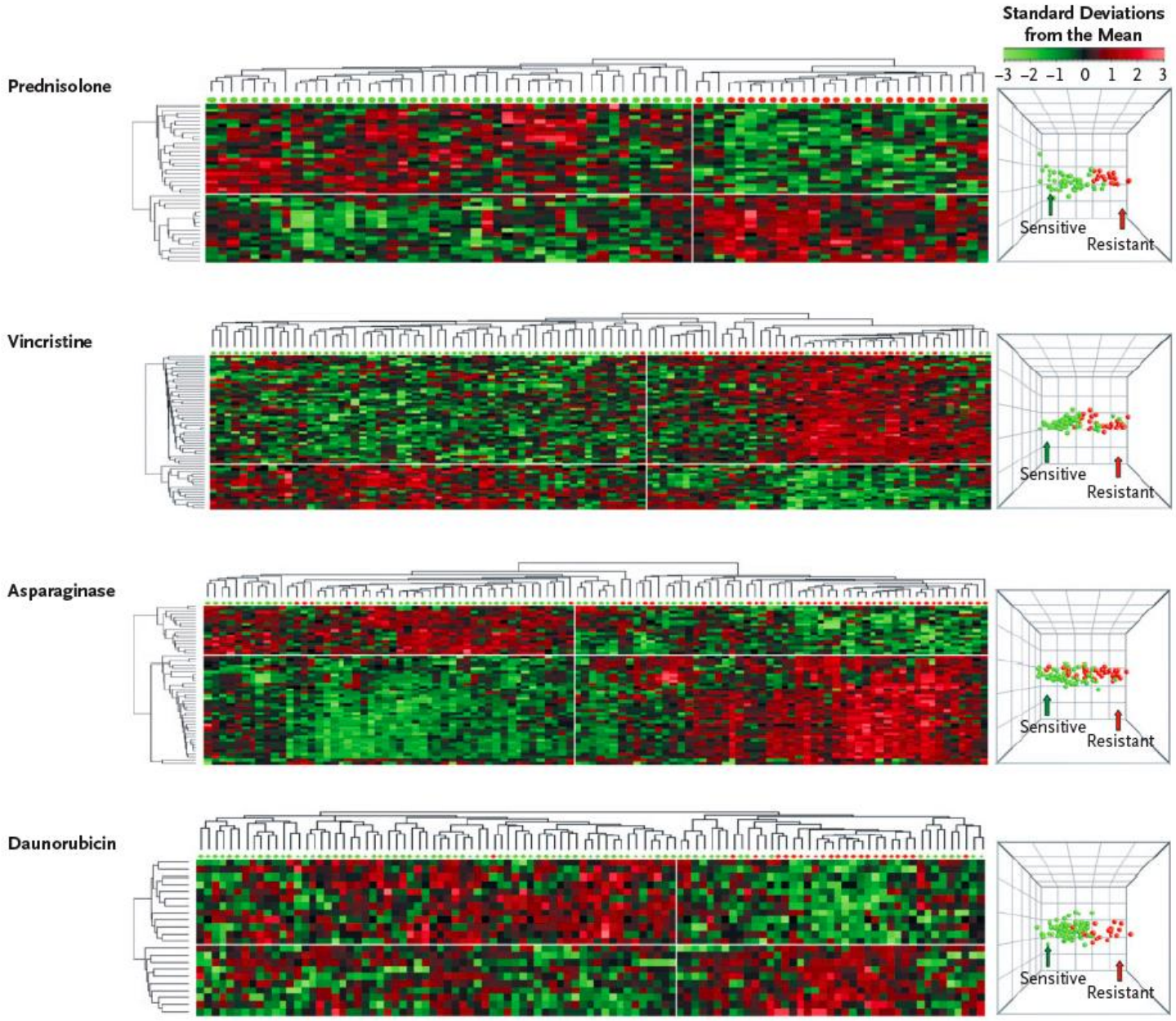
Causes of induction failure

Risk factors*	REFRACTORY	EARLY DEATH
Patient age	-	>55 Y
Disease subset (*v* treatment)	B-lineage (Ph-like), Other (?)	B-lineage (**older pts**) Ph+ (**chemo-associated**)
Complications (*v* supportive care)	-	Infections (**intensive chemo, protocol-specific**)

*vs induction regimens, *see* reccomendations for prevention/management of infections and ASP-related toxicity (**NILG 10/07, GIMEMA LAL 1913/2317**)

Chemoresistance-I

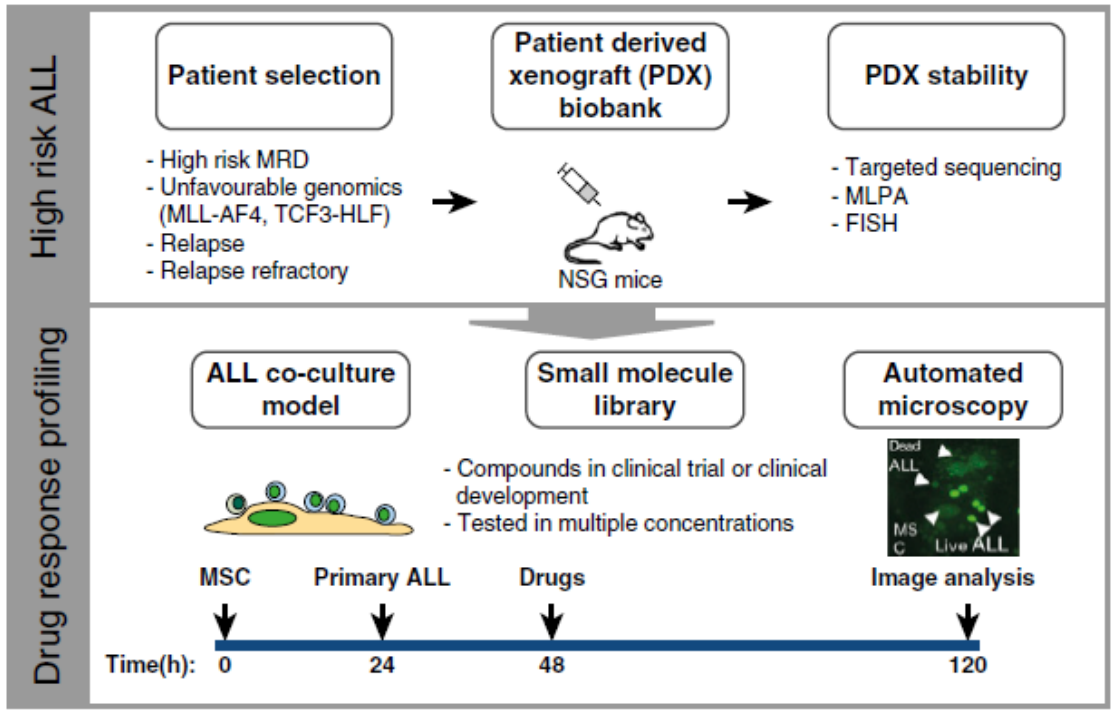
GEP-associated resistance to PDN/VCR/ ASP/DNR in ALL

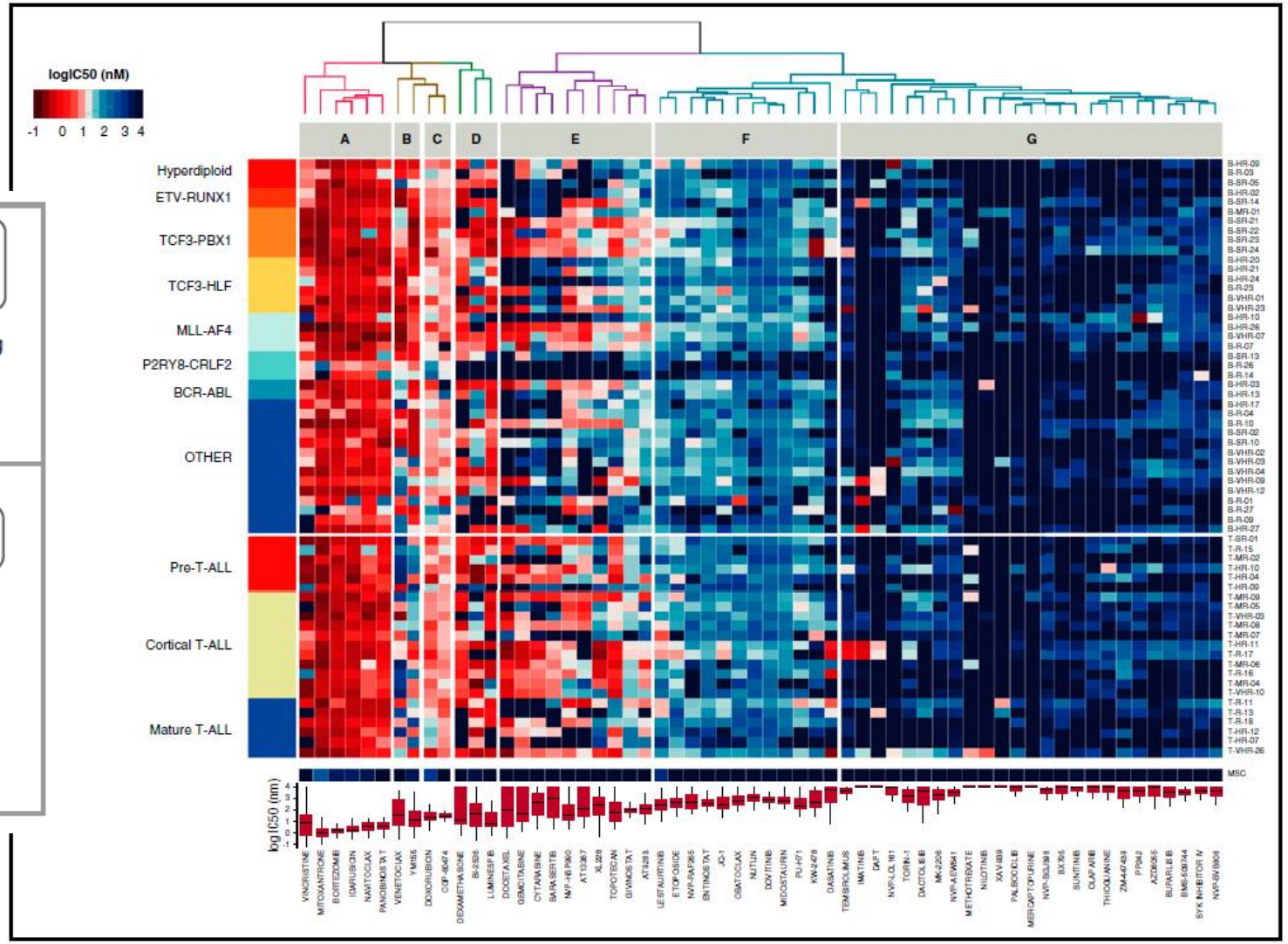


Holleman et al, NEJM 2004; 351: 533

Chemoresistance-II

Predictive tools in known molecular ALL subsets and molecularly unclustered ALL





Frismantas V et al, Blood 2017
Snijder B et al, Lancet Haematol 2017
Bassan R, Bourquin J-P, DeAngelo DJ, Chiaretti S, J Clin Oncol (*in press*)

Induction mortality-I: Ph+ ALL

- High CR rate (CR 90-100%) with TKI-based therapy
- **Variable induction mortality**

Trial (1° author and reference)	Patient no.	Induction regimen and TKI	Early death rate, no. (%)	
Intensive chemo + TKI				
Ravandi F, Blood 2010	35	MDACC HyperCVAD + DASATINIB	2 (6)	4-8.8
Bassan R, J Clin Oncol 2010	53	NILG 09/00 + IMATINIB	2 (4)	
Kim D-Y, Blood 2015	90	Intensive multiagent + NILOTINIB	8 (8.8)	
Chalandon Y, Blood 2015 ▶	133	HyperCVAD + IMATINIB (arm B)	9 (6.7)	
Non-intensive chemo + TKI				
Bassan, J Clin Oncol 2010*	67	NILG 09/00 "low-intensity" + IMATINIB	0	0-4.2
Rousselot P, Blood 2016 ▶	71		3 (4.2)	
Chalandon Y, Blood 2015 ▶	135	EWALL VCR/Dexa + DASATINIB	1 (0.7)	P .010
		VCR/Dexa + IMATINIB (arm A)		
TKI (with steroids), without chemo				
Vignetti M, Blood 2007 ▶	29	GIMEMA IMATINIB	0	0
Foà R, Blood 2011	53	GIMEMA DASATINIB	0	
Martinelli G, Blood 2017 (abstr) ▶	42	GIMEMA PONATINIB	0	

*updated experience (NILG 09/00 Registry)

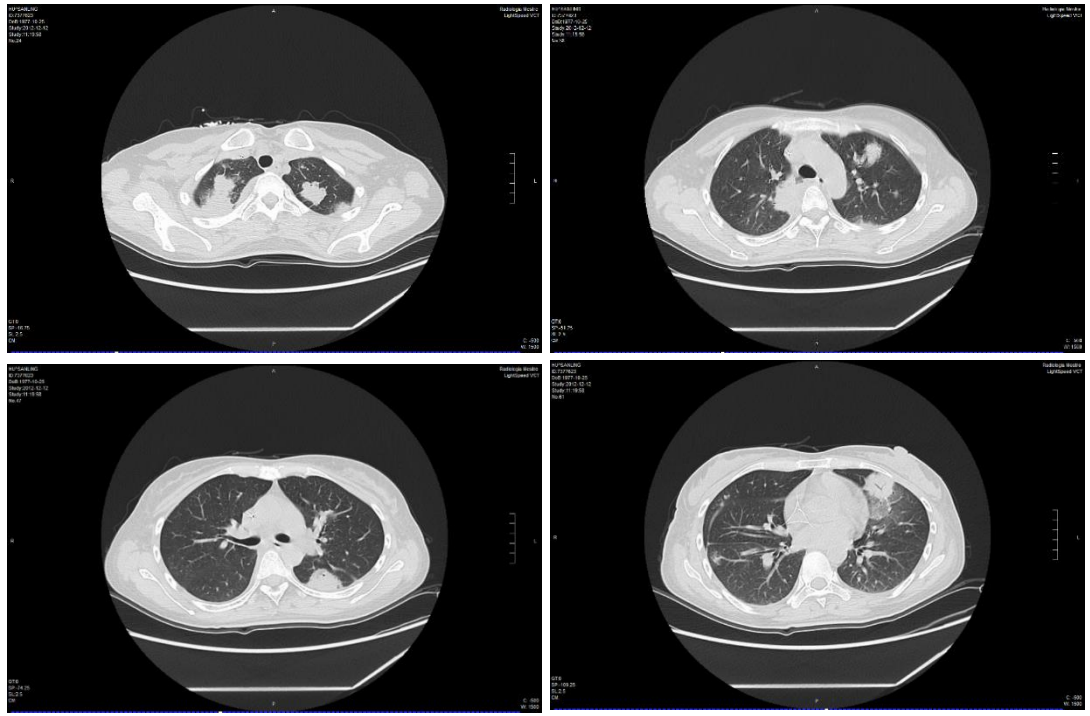
▶ GRAAPH 2005 phase III trial

▶ Unfit adult or elderly patients

CR, complete remission; TKI, tyrosine kinase inhibitor.

Induction mortality-II: invasive fungal infections in Ph- ALL

- **All risk factors** (intensive «pediatric»-type chemo*, **long neutropenia (>10 dd)**, mucositis, indwelling catheters, environmental/occupational, age, BPCO …)
- **PLUS** high dose **corticosteroids***
- **PLUS** **VCR** (difficult triazole administration)



The perfect storm

Young Chinese woman (35 yo)
died in ICU (Dec 2012)

*classified **high-risk** condition for fungal infections
(Pagano L et al [SEIFEM], Blood Rev 2017)

Protocol reccomendation (G LAL 2317)

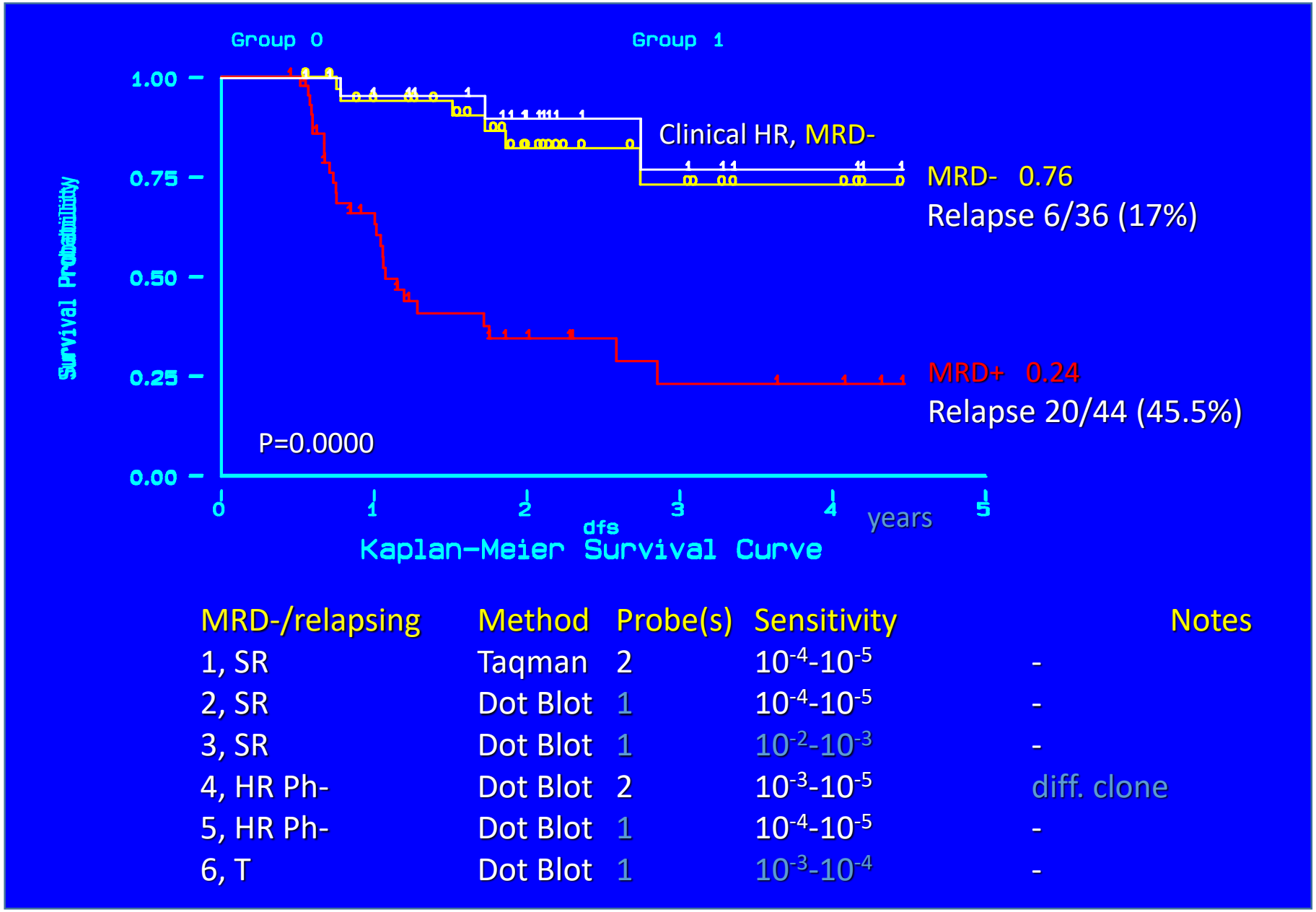
- **Anti-fungal prophylaxis**

- In this setting … suitable alternatives for patients with contraindications to triazoles, according to the 2014 guidelines of the European Society of Clinical Microbiology and Infectious Diseases/Fungal Infection Study Group, are **IV low-dose liposomal amphotericin-B** or **micafungin***.

- Whatever the choice about prophylaxis, early detection and treatment of an invasive fungal infection is mandatory.

*suggested effective (Lee C-H et al, Plos ONE 2017)

Failure due to relapse: the example of MRD

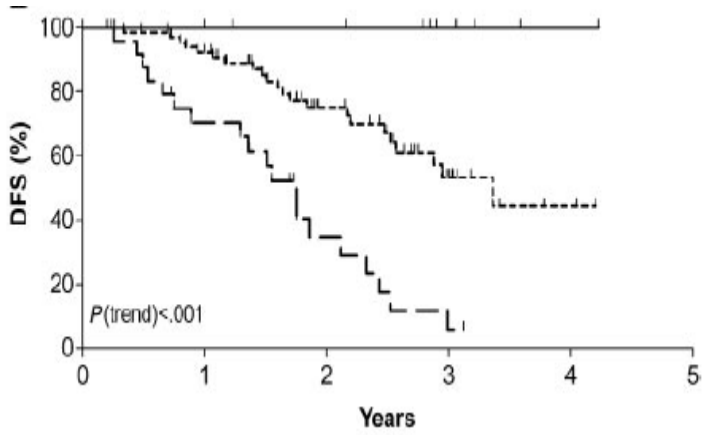


MRD-/relapsing	Method	Probe(s)	Sensitivity	Notes
1, SR	Taqman	2	10^{-4}-10^{-5}	-
2, SR	Dot Blot	1	10^{-4}-10^{-5}	-
3, SR	Dot Blot	1	10^{-2}-10^{-3}	-
4, HR Ph-	Dot Blot	2	10^{-3}-10^{-5}	diff. clone
5, HR Ph-	Dot Blot	1	10^{-4}-10^{-5}	-
6, T	Dot Blot	1	10^{-3}-10^{-4}	-

Early MRD response

Though MRD «negativity» can progressively increase,
END OF INDUCTION MRD may identify the best patients (**small subsets**)

MRD $<10^{-4}$/negative d +11 (n=11)



GMALL 09/00 (Adult, SR)

M Bruggemann et al, Blood 2006

MRD negative d +28 (n=22)

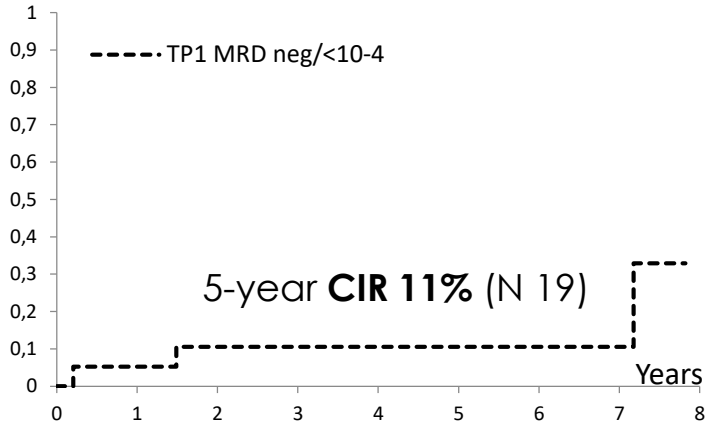
absence of detectable MRD in 22/58 [38%] pts at **day 28 of induction:**

100% 2-year EFS (p=0.0006)

U.S. Intergroup Trial C10403 (AYA 15-39 yrs)

W Stock et al, Blood 2014 (ASH abstr)

MRD $<10^{-4}$/negative d +28 (n=19)



NILG 10/07 (Adult, T-ALL)

R Bassan, EHA 2016 (SWG EWALL)

Allogeneic SCT for HR ALL in national trials

Study Group*	Pt. age (Y)	MRD+	High WBC (subsets)	HR gen/ cytogen (subsets)	HR pheno (subsets)	Late CR	CNS+
CELL	<65	■					
FALL	<45	■	■	■		■	
GIMEMA	<65	■	■	■	■		
GMALL	<55	■	■	■	■	■	
GRAALL	<60	■					
HOVON	<40	■	■	■		■	
PALG	<55	■	■	■			■
PETHEMA	<60	■					
RALL	<55		■	■			

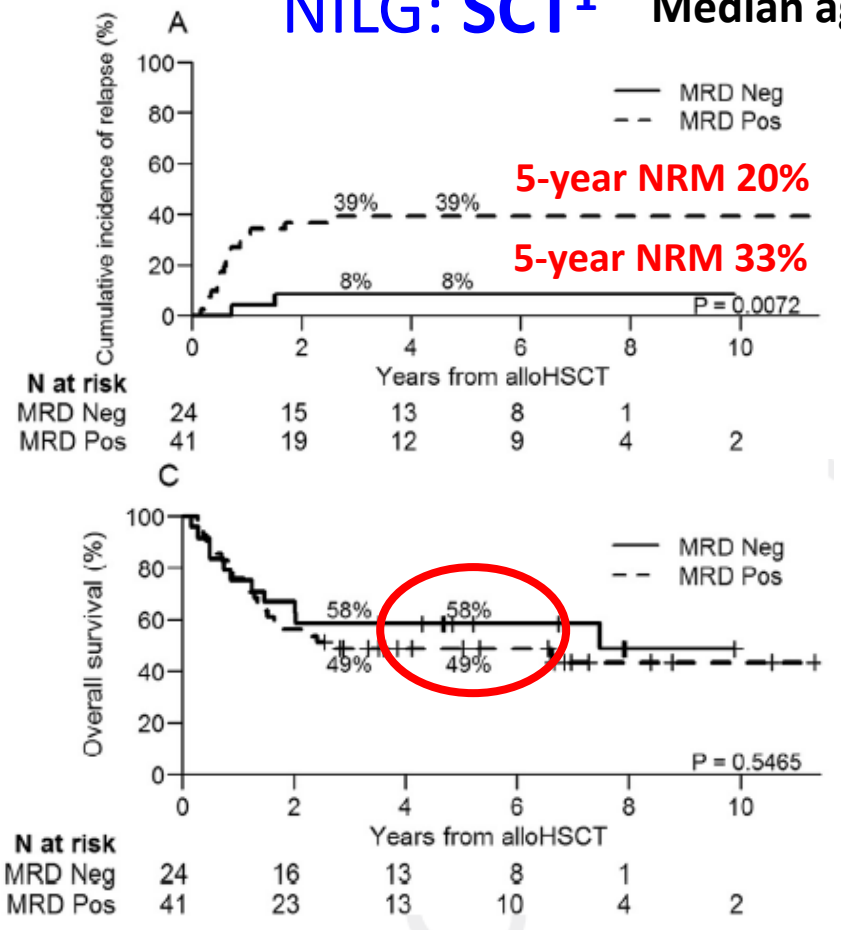
*Czechia, Finland, Italy, Germany, France/Belgium/Switzerland, Netherlands, Poland, Spain, Russia

■ = allogeneic SCT criteria (any)

Source: EWALL/EBMT recommendations, S Giebel et al *(manuscript)*

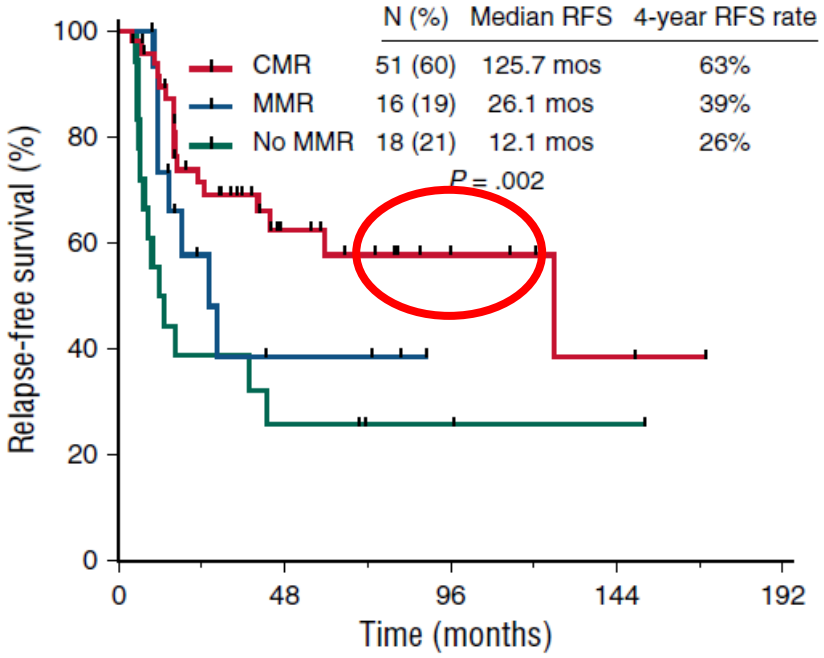
Failure due to treatment-related mortality (SCT for Ph+ ALL?)

NILG: **SCT**[1] **Median age: 44 Y**



MDACC: **TKI/chemo**[2]

PCR negative @ 3 mos.



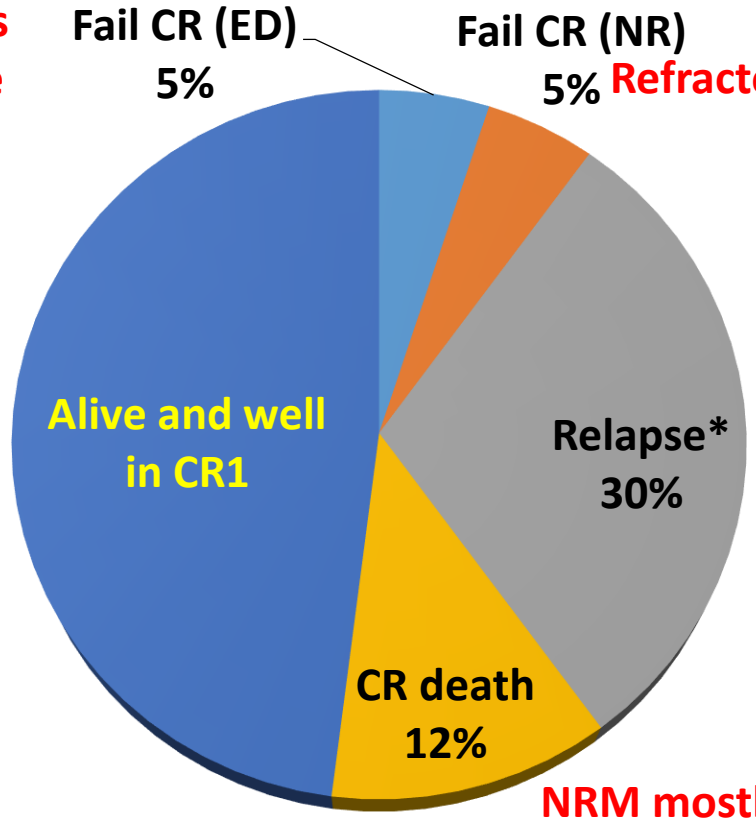
[1]Lussana F et al, *Biol Blood Bone Marrow Transpl* 2016;22:1983-7; [2]Short NJ et al, *Blood* 2016;128:504-7

Summary graph

OPTIMIZE THERAPY & SUPPORT

- **G-CSF**
- **Prophylaxis** (bact, fungal)
- **No/low-dose chemo (Ph+)**

Neutropenia
Infections
Older age



Refractory

OPTIMIZE THERAPY

- **TKI (Ph-like)**
- **New agents**

MRD+ & adverse biology

OPTIMIZE THERAPY

- **New agents**

NRM mostly related to SCT

OPTIMIZE THERAPY

- **No SCT & new agents**

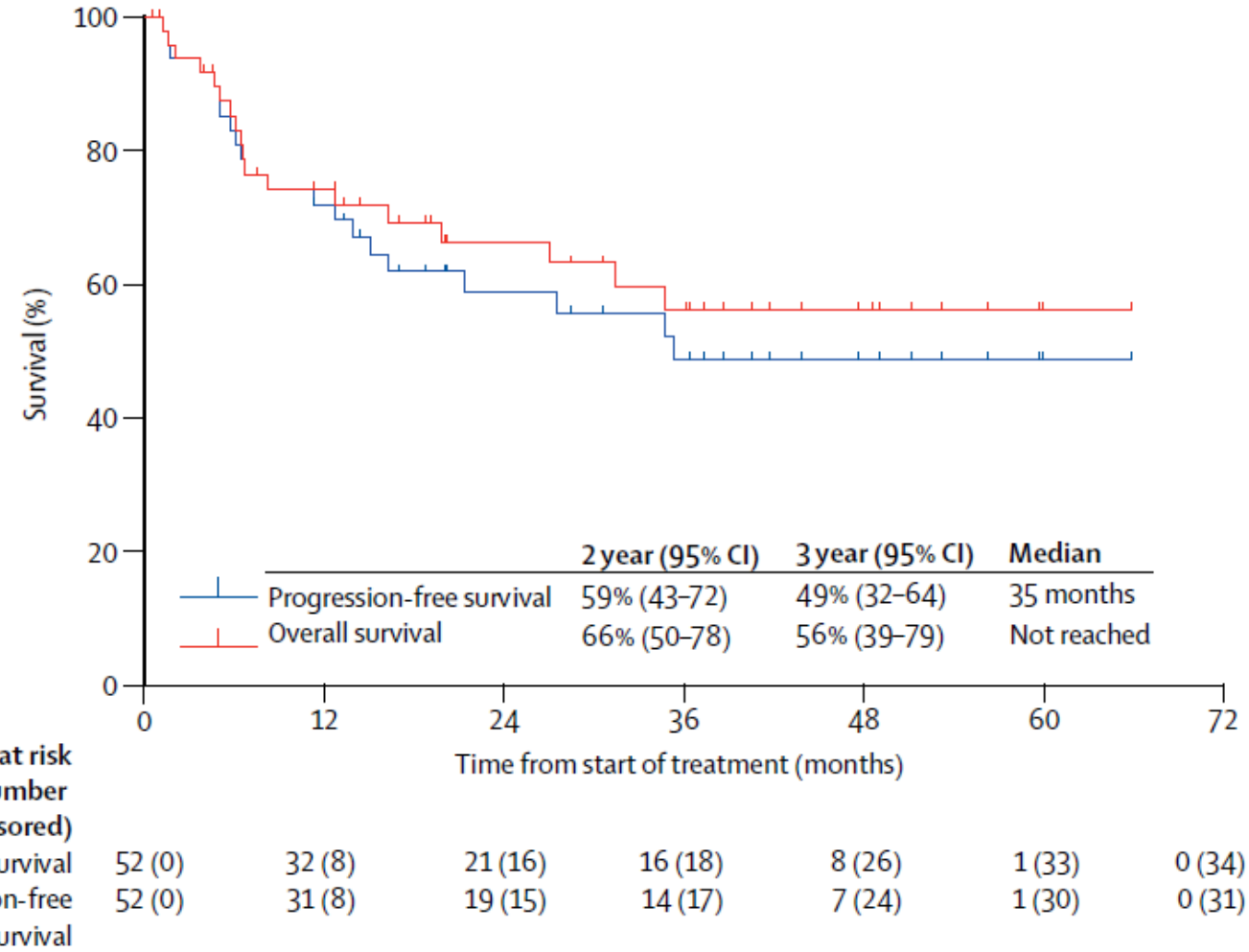
*some rescued by salvage therapy (contributing to 5-year OS rate)

“New agents”: the example of mini-Hyper-CVD plus inotuzumab ozogamicin in elderly ALL

- **Low-dose chemo (BCP Ph-)**
- **New low-toxicity agent(s) (InO ± R*)**

N	52
Untreated	48
Age (Y)	68 (64-72)
CR	47/48 (98%)
MRD negativity	(cycles 1-3) 45/47 (96%)
Allogeneic SCT	3

*rituximab if CD20+



Kantarajian HR et al, Lancet Oncol 2018;19:240-48

How I Treat High Risk ALL

- **HR patient**: Any patient exhibiting any factor associated with risk of failure to achieve or maintain CR on **pediatric-based** and **subset/risk-specific programs**
- **How I Treat (always within protocols)**:
  - **Ph- ALL:** «pediatric-based» regimen; MRD/risk adapted SCT; maximal support in induction

    N10 Ph- «observational» / G LAL 1913 (T) / Blinatumomab-based G LAL 2317 (B)
  - **Ph+ ALL:** TKI + de-intensified/no chemo; transplant-free approach (selected pts, exp.)

    N10 Ph+ «observational» / G D-ALBA

Thanks to NILG and GIMEMA people