Ph+ ALL: perché rinviare il trapianto?

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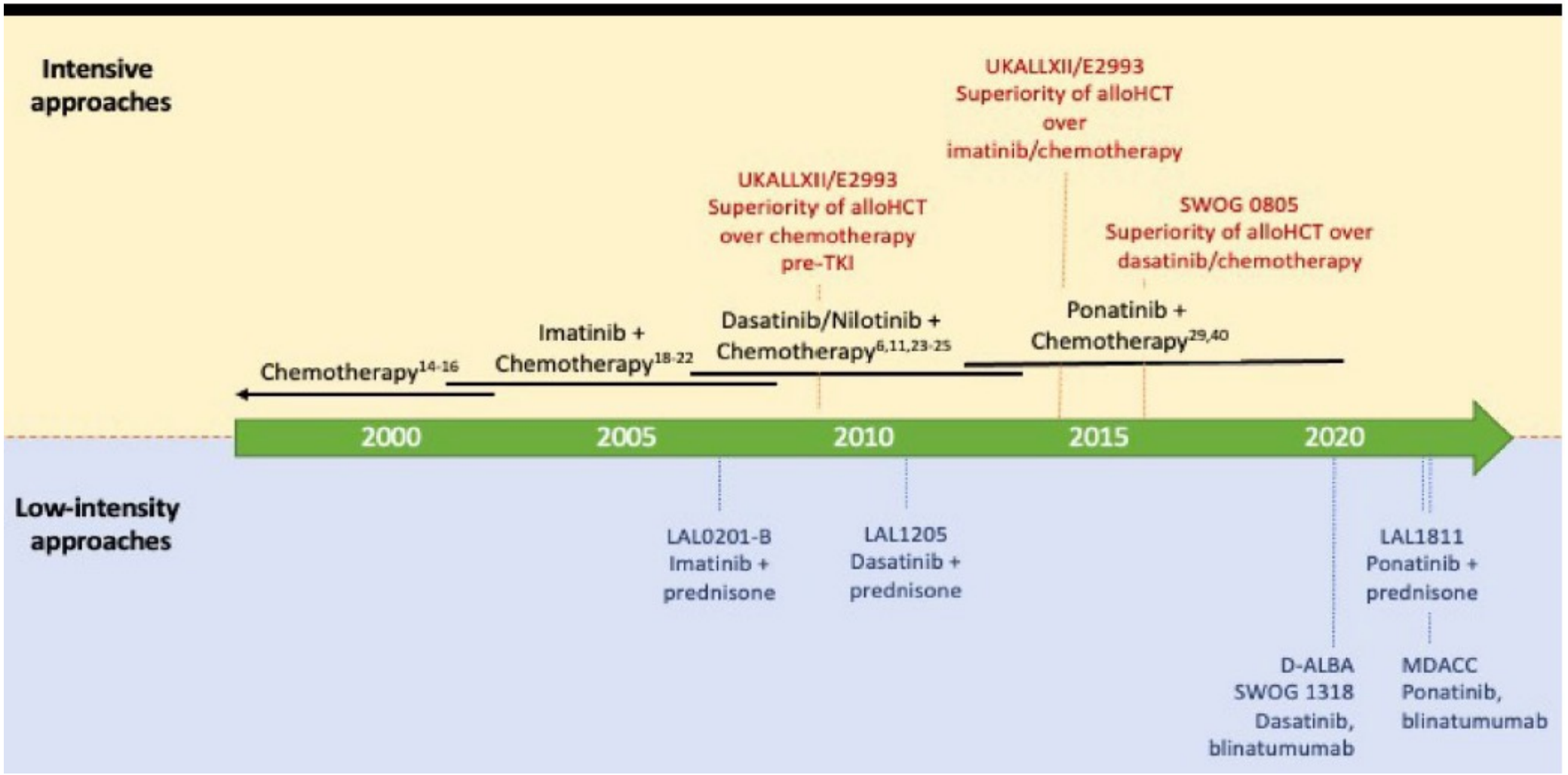
Disclosures of CRISTINA PAPAYANNIDIS

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie						X	X
Astellas						X	X
Servier							X
Menarini							X
BMS							X
Pfizer						X	X
Amgen							X
Janssen						X	
GSK						X	
Blueprint						X	
Incyte						X	X
Paladin Labs Inc							X
Jazz pharmaceuticals						X	
Novartis						X	
Delbert Laboratoires						X	

Milestones in the treatment of Ph+ ALL



First and second generation TKI

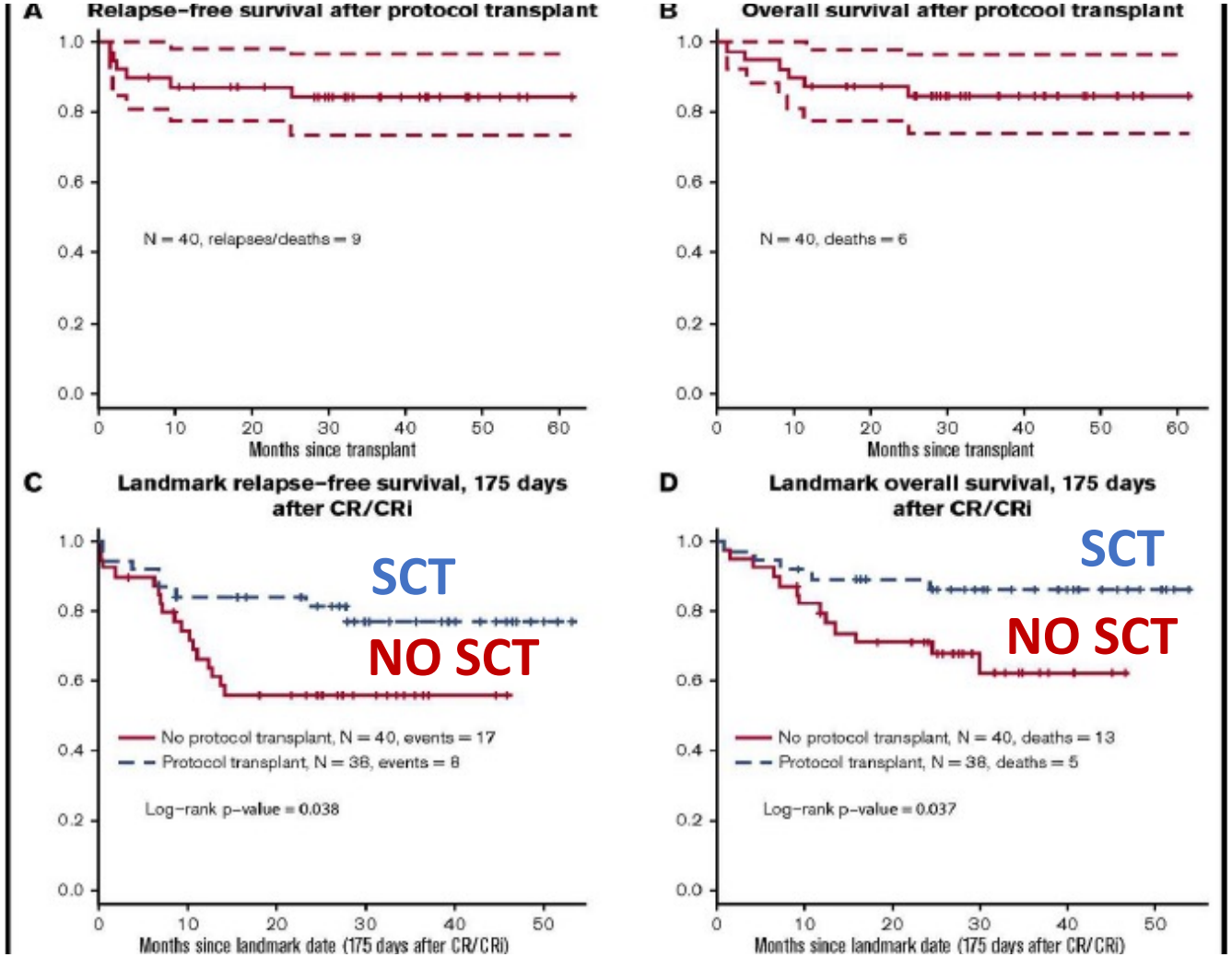
Superiority of alloHSCT over TKI+ chemo

Similar outcomes after AlloHSCT with imatinib and dasatinib

US Intergroup study of chemotherapy+Dasatinib and alloHSCT in Ph+ ALL

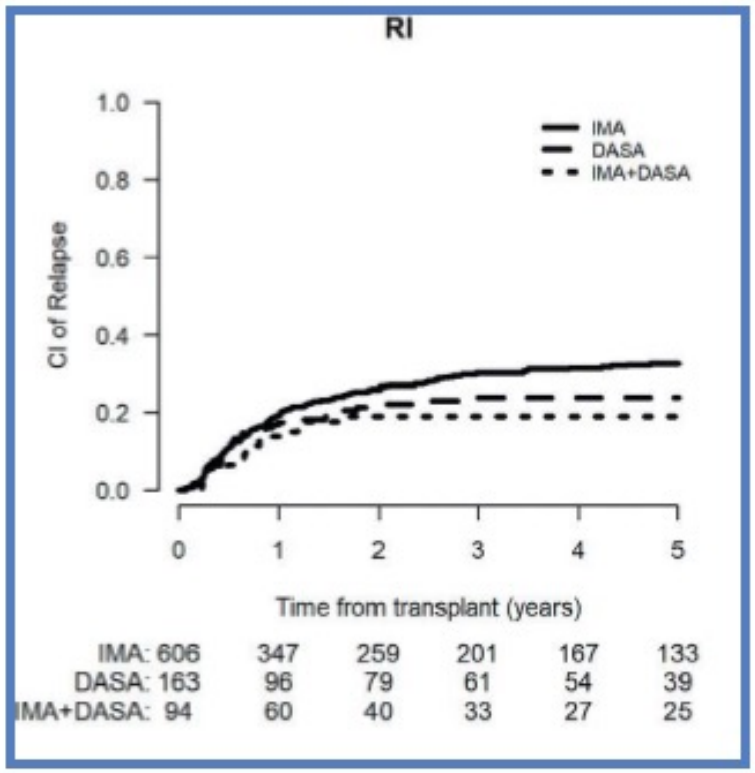
N=94
Median age 44 y (20-60)

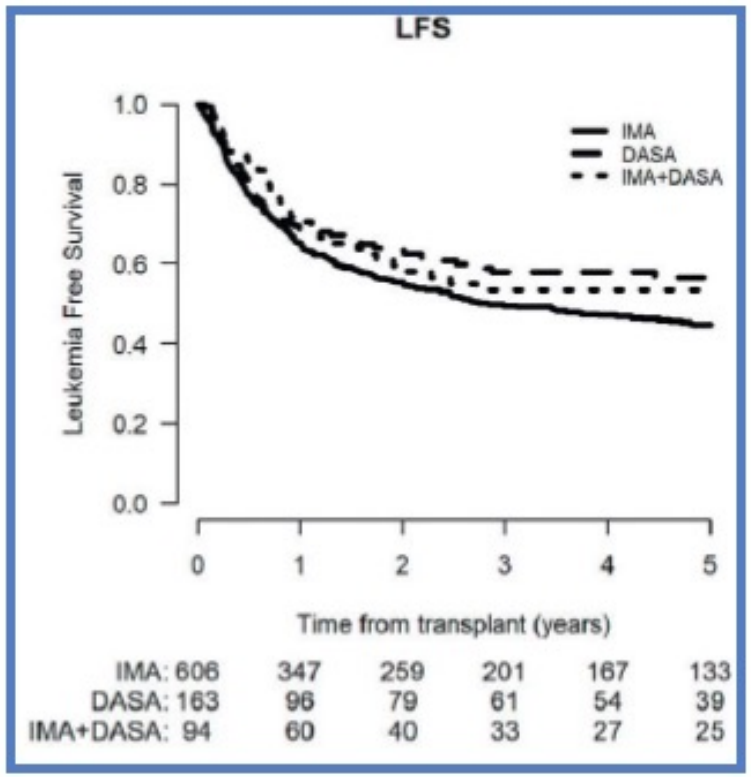
Landmark comparison, non randomized !

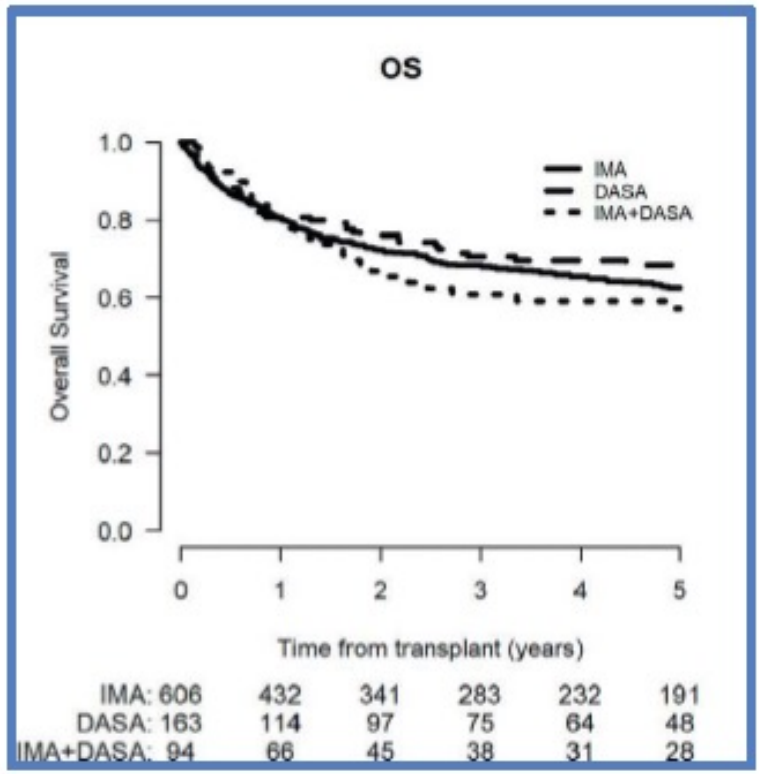


Ravandi F et al, Blood Adv 2016

Similar outcomes after alloHSCT according to Imatinib or Dasatinib before transplant: EBMT data

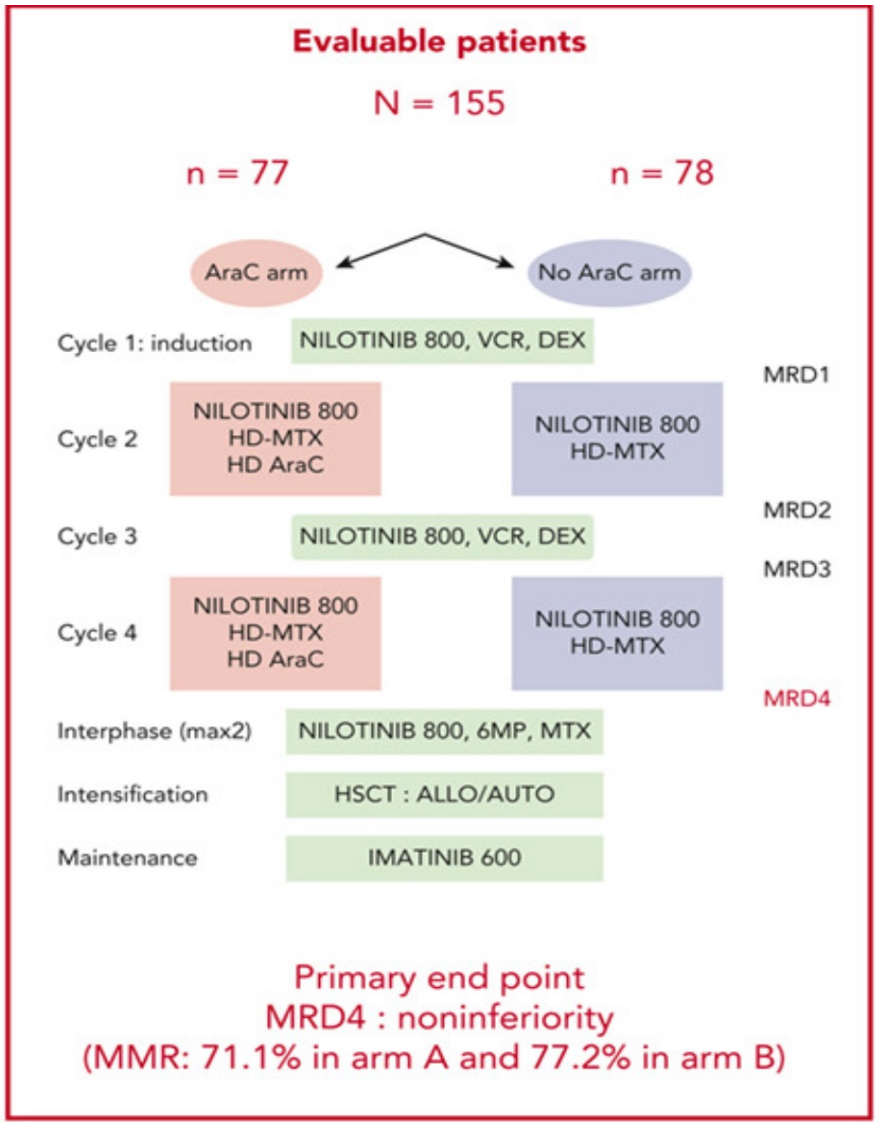






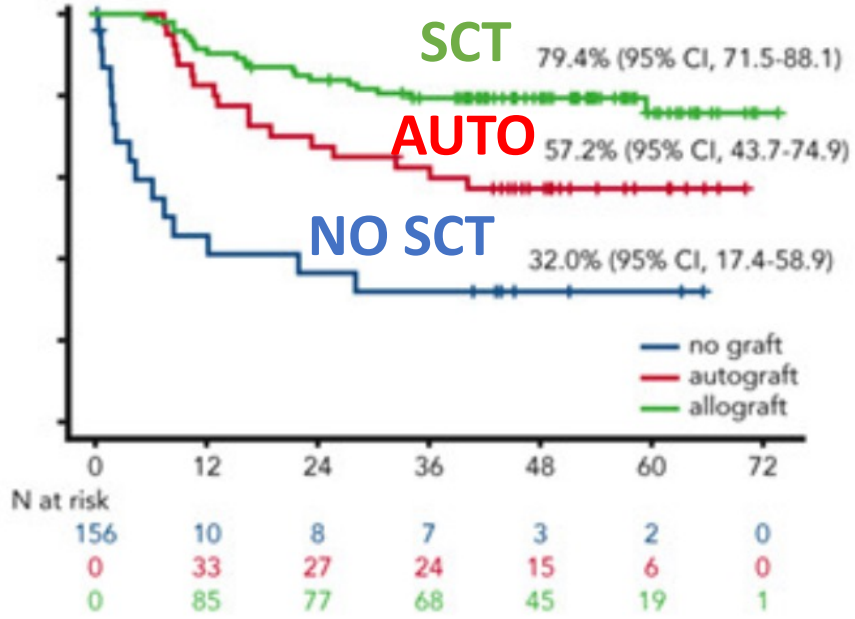
Giebel S et al, Transplant Cell Ther 2024

Nilotinib+chemotherapy: better RFS for pts who proceeded to alloHSCT



Better RFS in allogeneic stem cell transplantation patients

Non randomized comparison



Median age (IQR): 47.1 y (38.8-53.8)

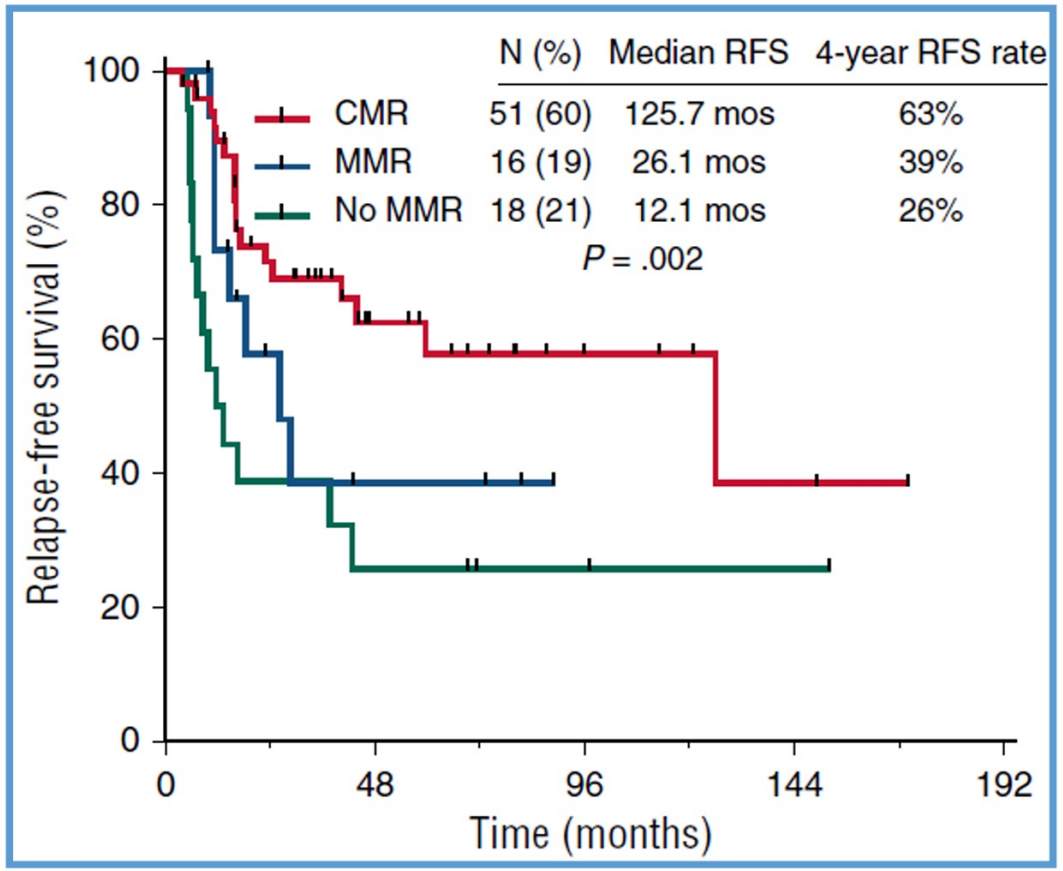
Chalandon Y et al, Blood 2024

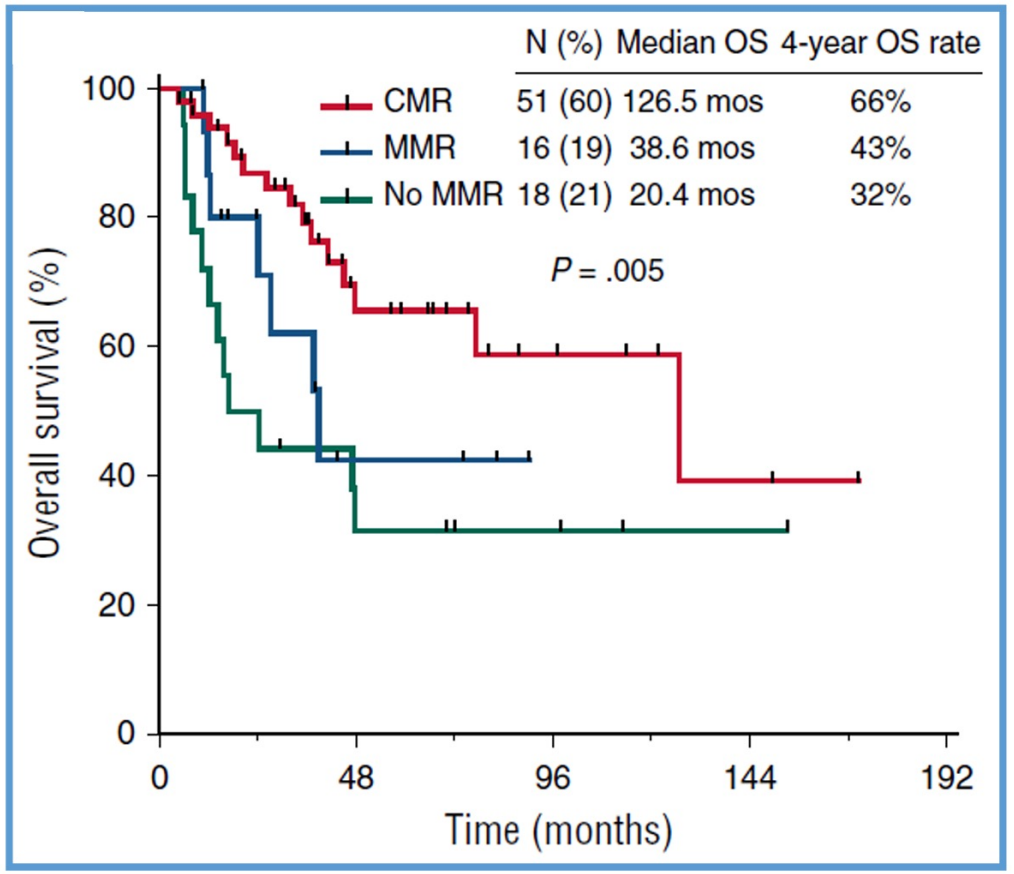
Why might alloSCT no longer be necessary in (a subgroup) of Ph+ ALL?

PERSPECTIVE RANDOMIZED DATA ARE STILL MISSING

- Identification of prognostic factors in Ph+ ALL
- Availability of more effective drugs
- Improvement of biological knowledges

CMR at 3 months: the best prognostic factor in Ph+ ALL

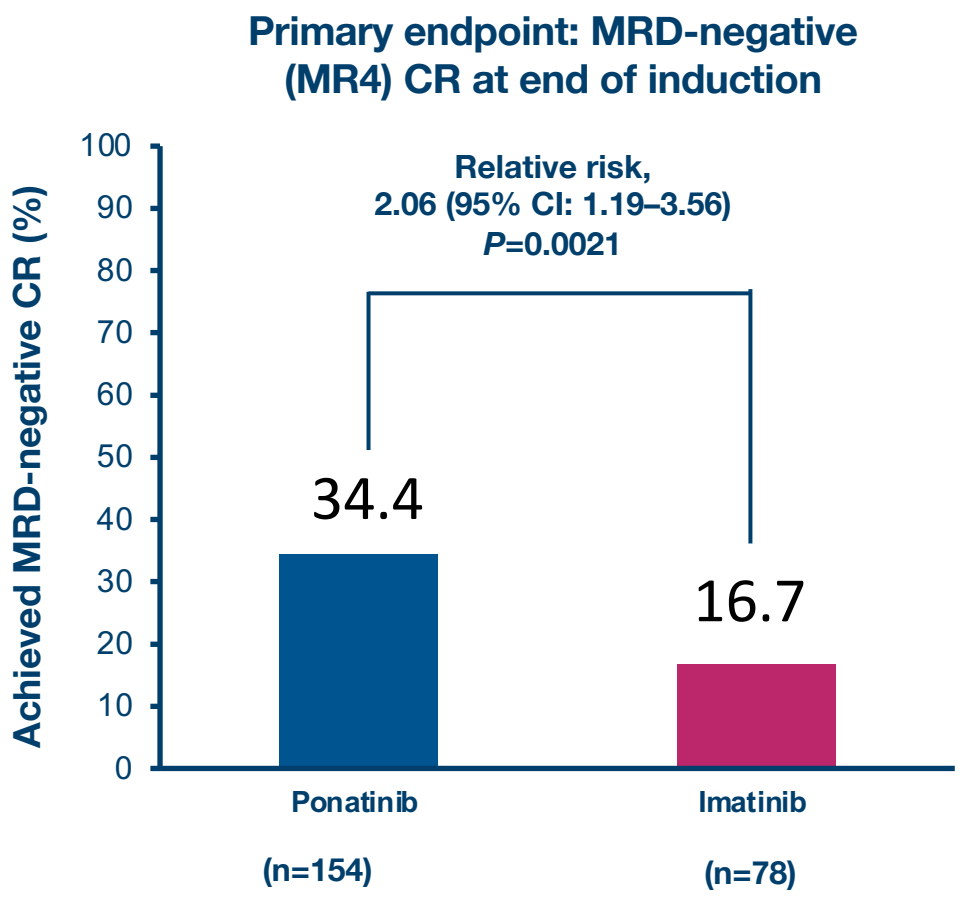


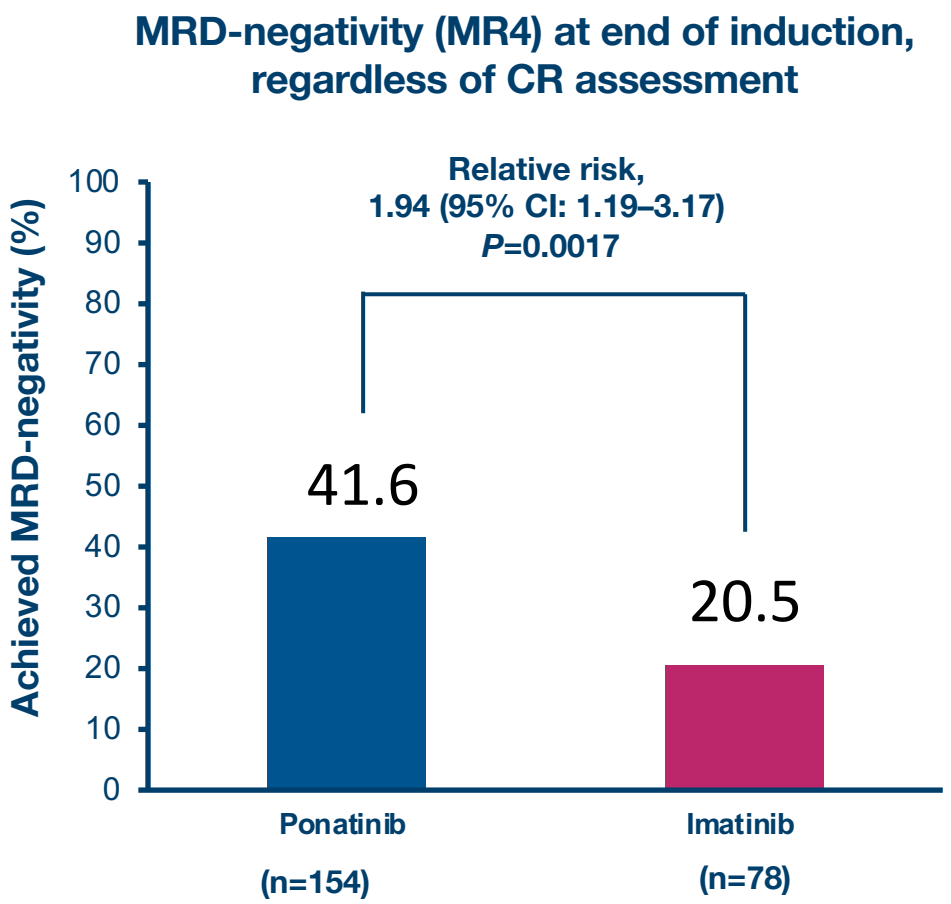


Short NJ et al, Blood 2016

Ponatinib+low intensity chemotherapy is superior to Imatinib+low intensity chemotherapy: phase III PhALLCON trial

FDA APPROVED





Jabbour E et al, JAMA 2024

The type of TKI we use matters

TKI+steroids (+/-low chemo)

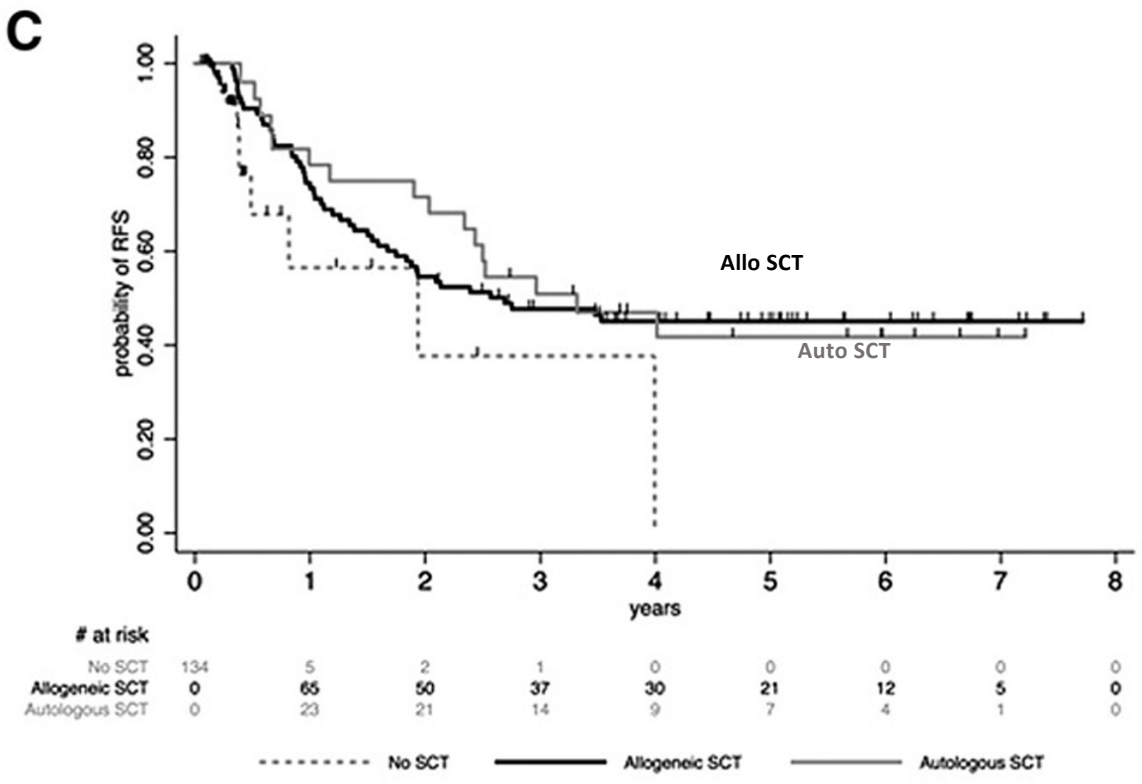
	CMR@3 months
Dasatinib+steroids (Chiaretti S et al, Haematologica 2021)	19.3%
Ponatinib+steroids (Martinelli G et al, Blood Adv 2021)	47.7%

TKI+chemotherapy

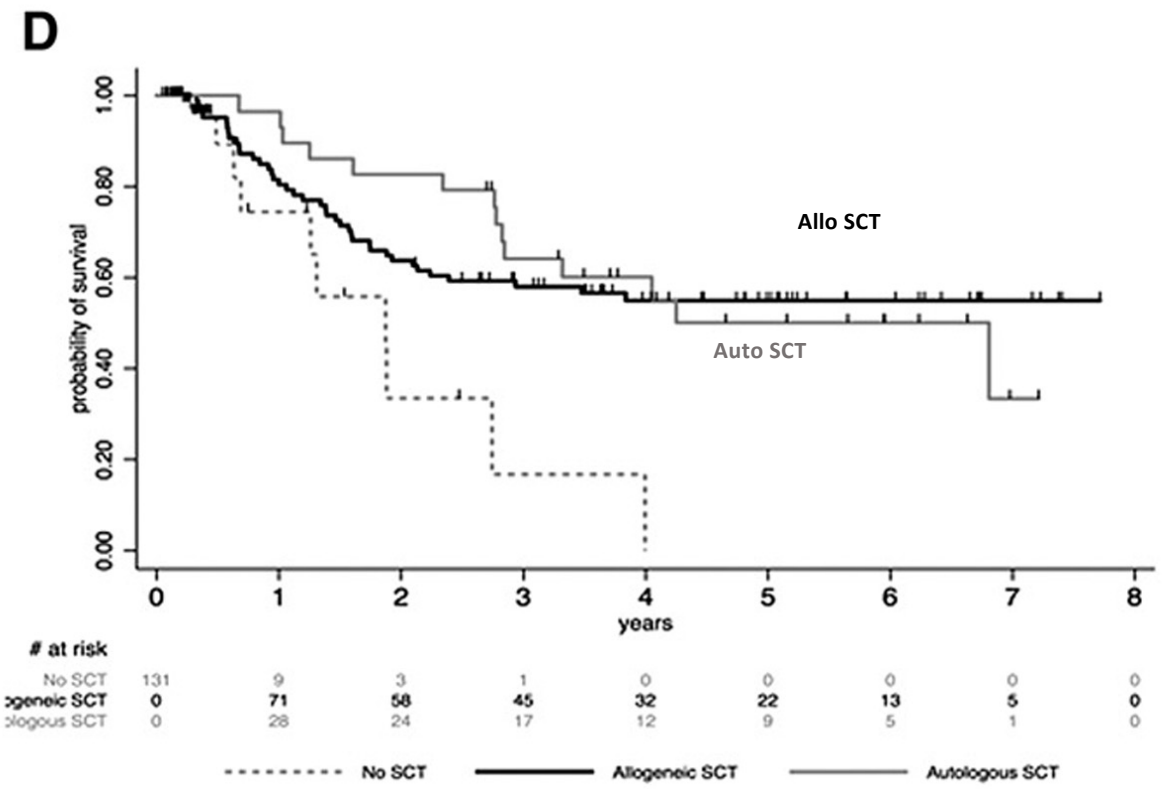
	CMR@3 months
Hypercvad+Dasatinib (Ravandi F et al, Blood 2010)	33%
Hypercvad+Ponatinib (Jabbour E et al, Lancet Haematol 2018)	64%

In patients achieving MMolR outcome is similar after autologous and allogeneic transplantation

RELAPSE FREE SURVIVAL



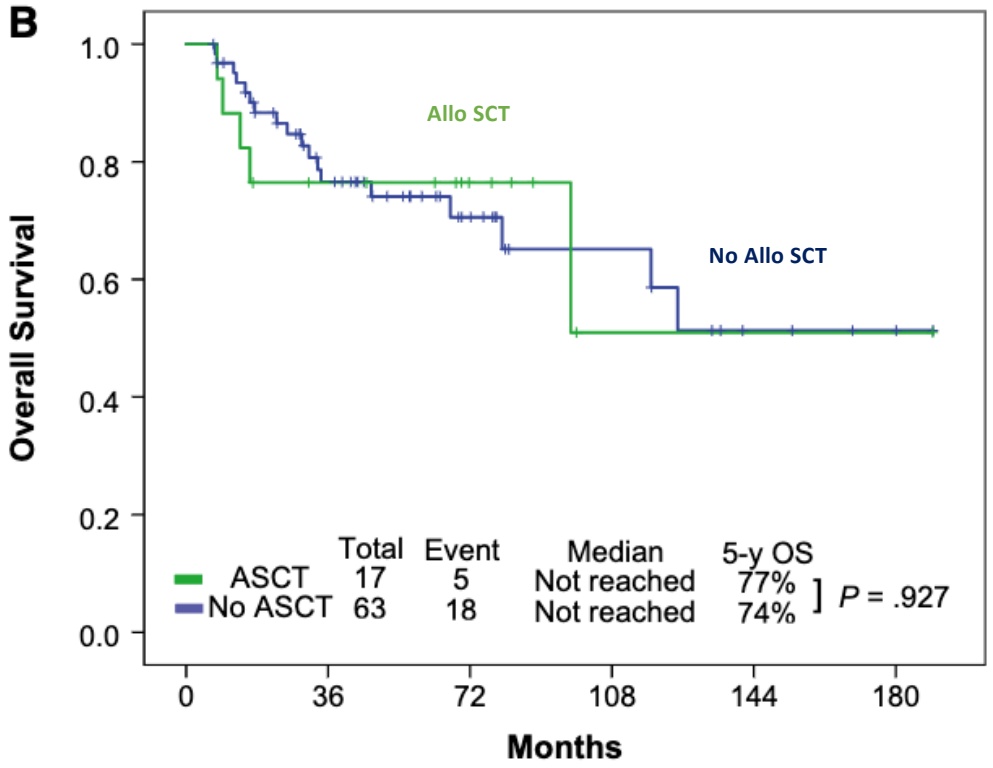
OVERALL SURVIVAL

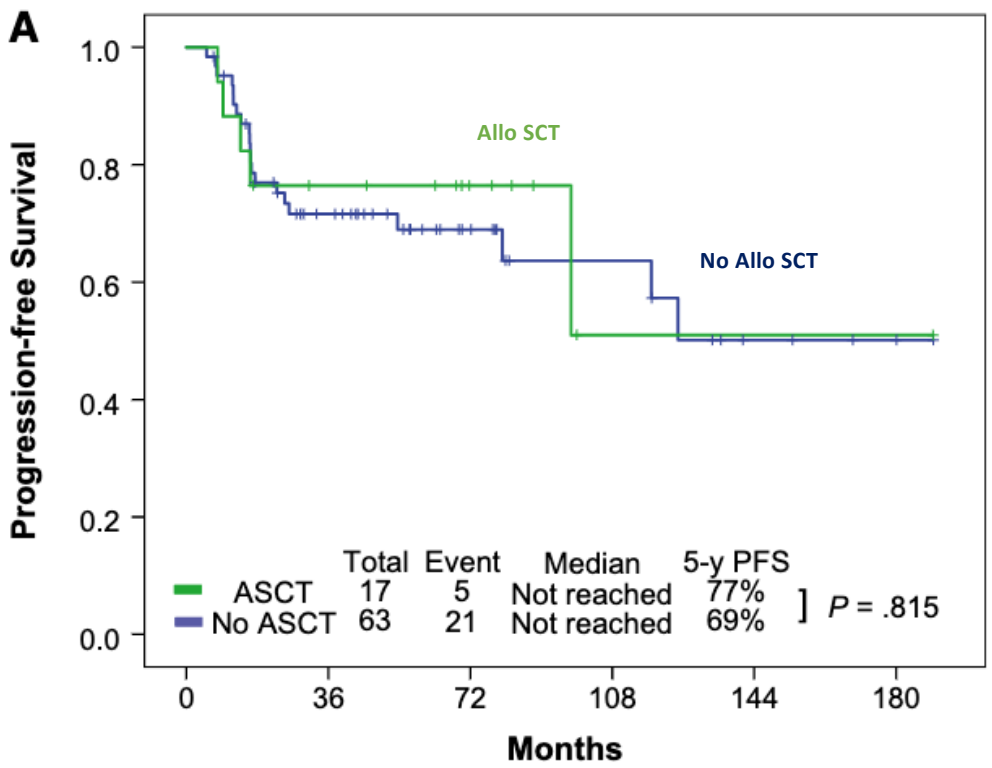


Chalandon Y et al, Blood 2015

Allogeneic transplantation does not improve outcome once a 3-month CMR is achieved

NRM 23% in alloSCT pts





Sasaki K et al, Cancer 2021

No benefit of alloHSCT in pts with Ph+ ALL who achieve CMR from day 90: retrospective study (n=230)

Patients: 230, from 5 US transplant centers

Criteria:

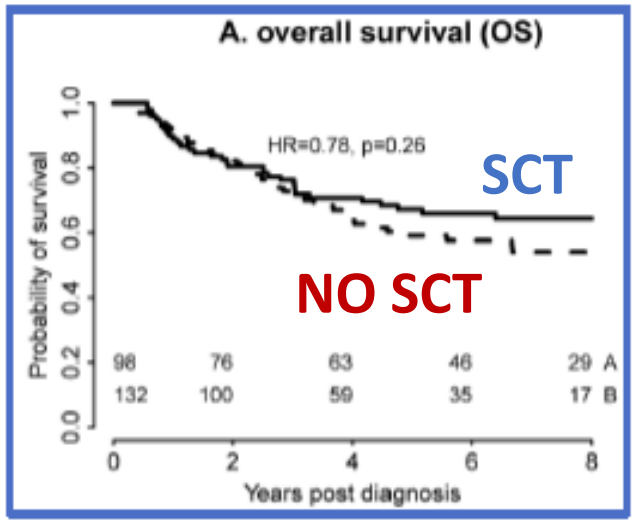
Age≥ 18y, Dx: 2001-2018

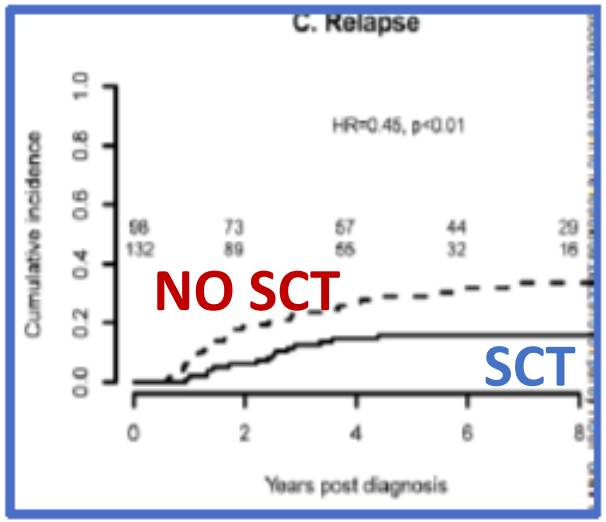
Persistent CMR from d90 (RQ PCR *BCR::ABL*< 10^{-4})

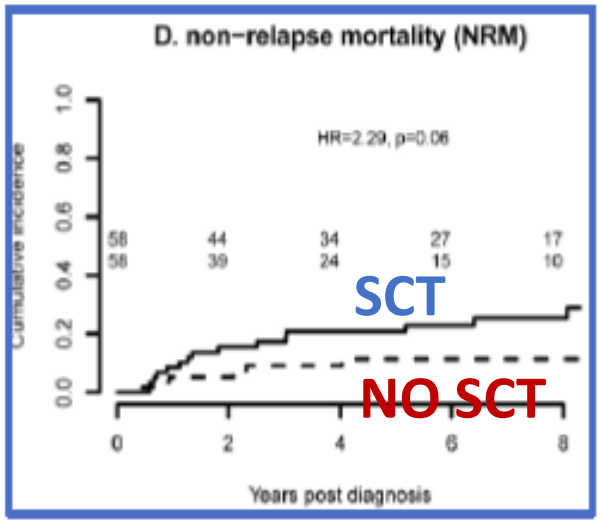
Cohorts

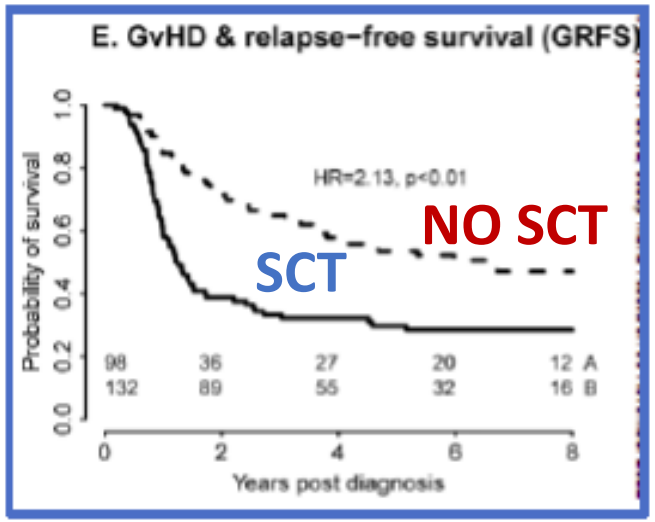
AlloHSCT (n=98), Non HSCT (n=132)

- AlloHSCT in CR1 does not improve survival for patients achieving a deep molecular remission
- AlloHSCT in CR1: lower incidence of relapse but increased treatment-related mortality









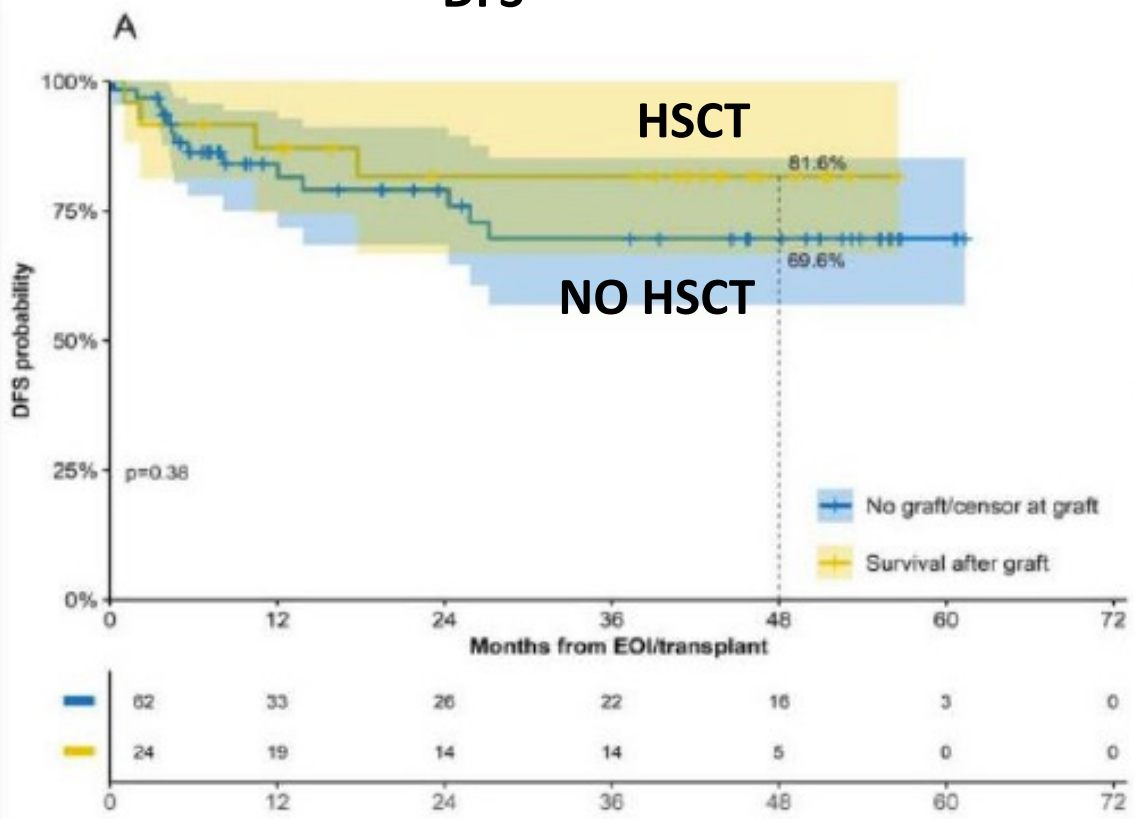
Ghobaldi A et al, Blood 2022

2nd or 3rd generation TKI + Blinatumomab

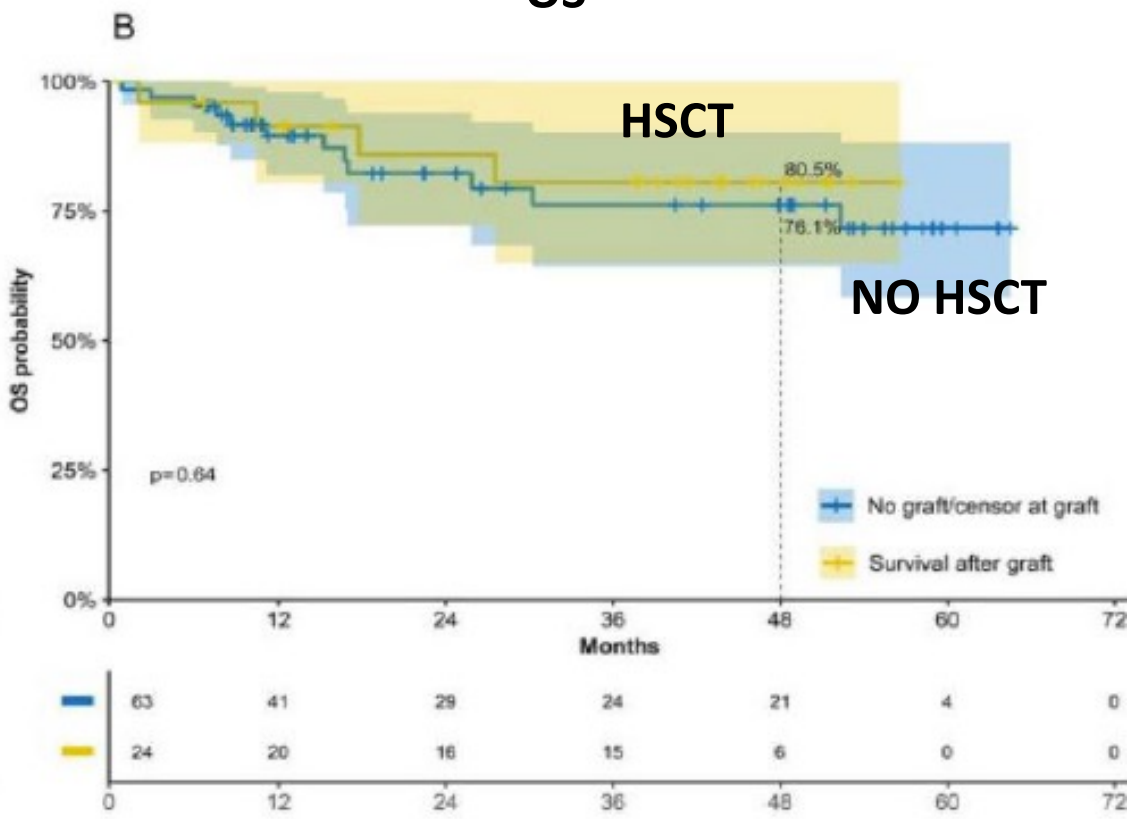
Role of allo HSCT?

Dasatinib+ Blinatumomab: role of HSCT

DFS



OS



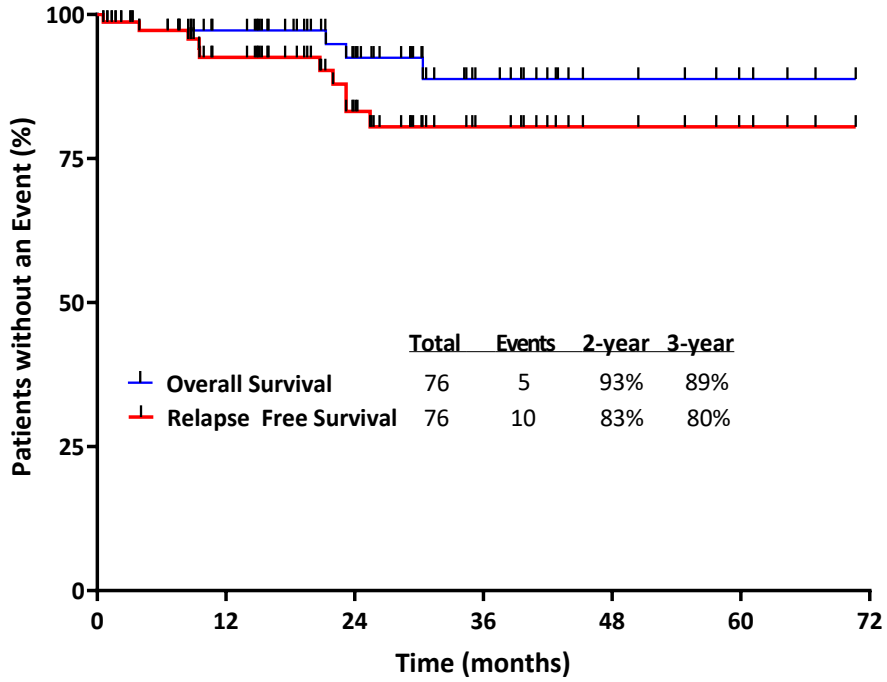
24 pts transplanted in CR1, 29 non transplanted
Transplanted group enriched in MRD+ patients
Transplant-related mortality: 12%

Foà R et al. J Clin Oncol. 2024 ;42(8):881-885.

Ponatinib+ Blinatumomab in Ph+ ALL

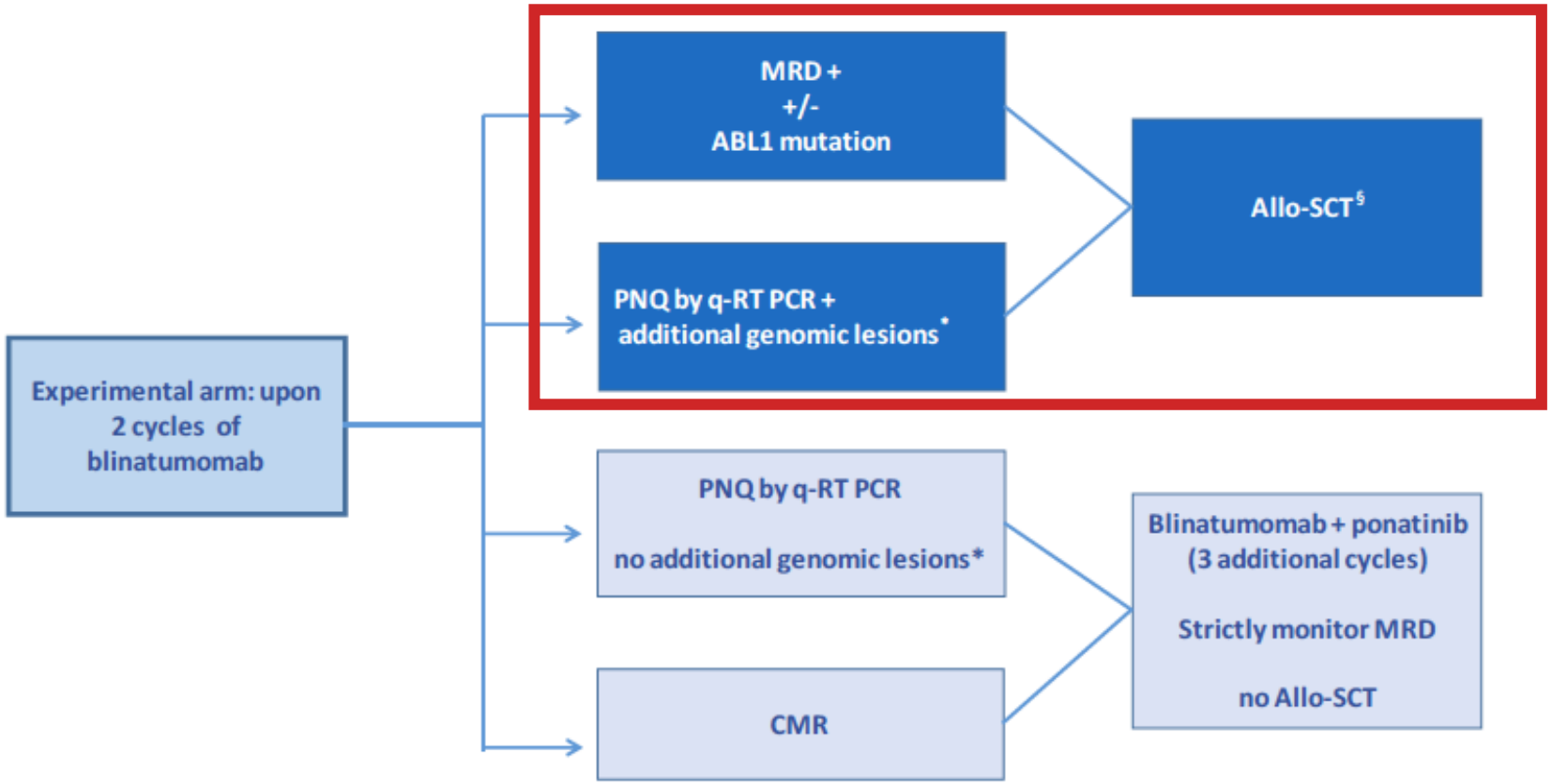
- 76 pts Rx with simultaneous ponatinib 30-15mg/D and blinatumomab x 5 courses. 12-15 ITs
- **Only 2 pts had SCT**(3%)
- Median F/U 24 months. 3-yr EFS 80%, OS 89%
- 7 relapses (all p190): 4 CNS, 1 CRLF2+ (Ph-), 2 systemic. 3-yr cumulative relapse 15%; 5/7 high WBC

Parameter	%
CR-CRi	98
% CMR	80
% NGS-MRD negative	99
% 3-yr OS	89



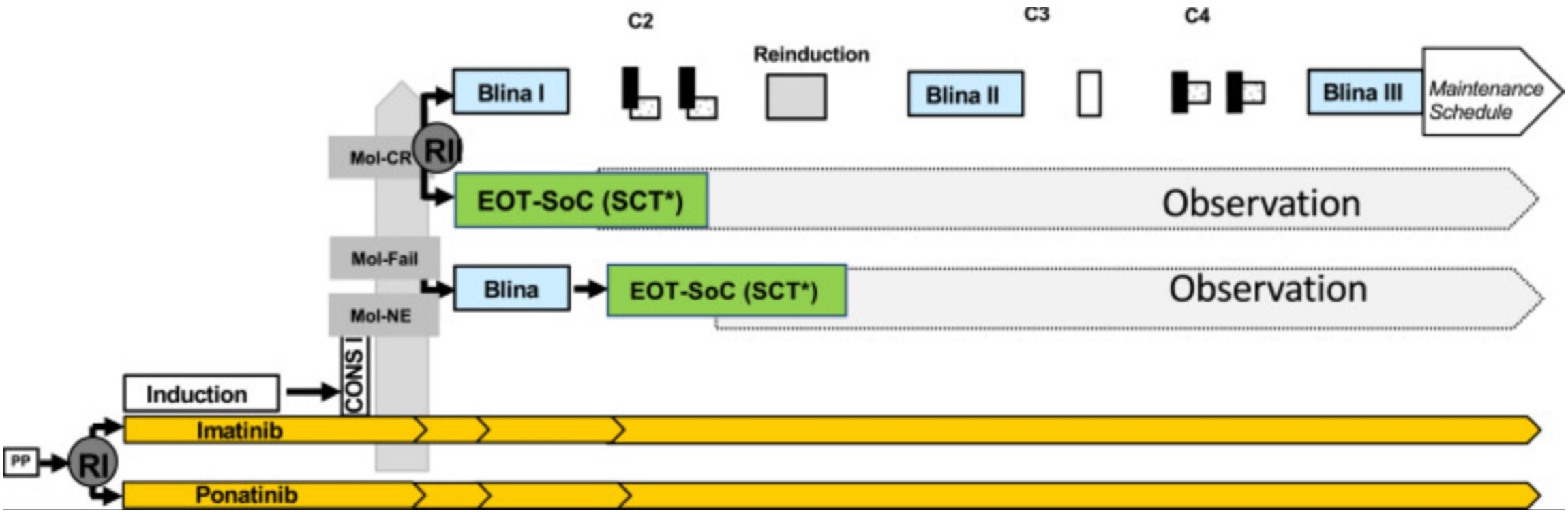
Kantarjian H et al, JCO 2024

Ongoing GIMEMA 2820 clinical trial: alloSCT not for all

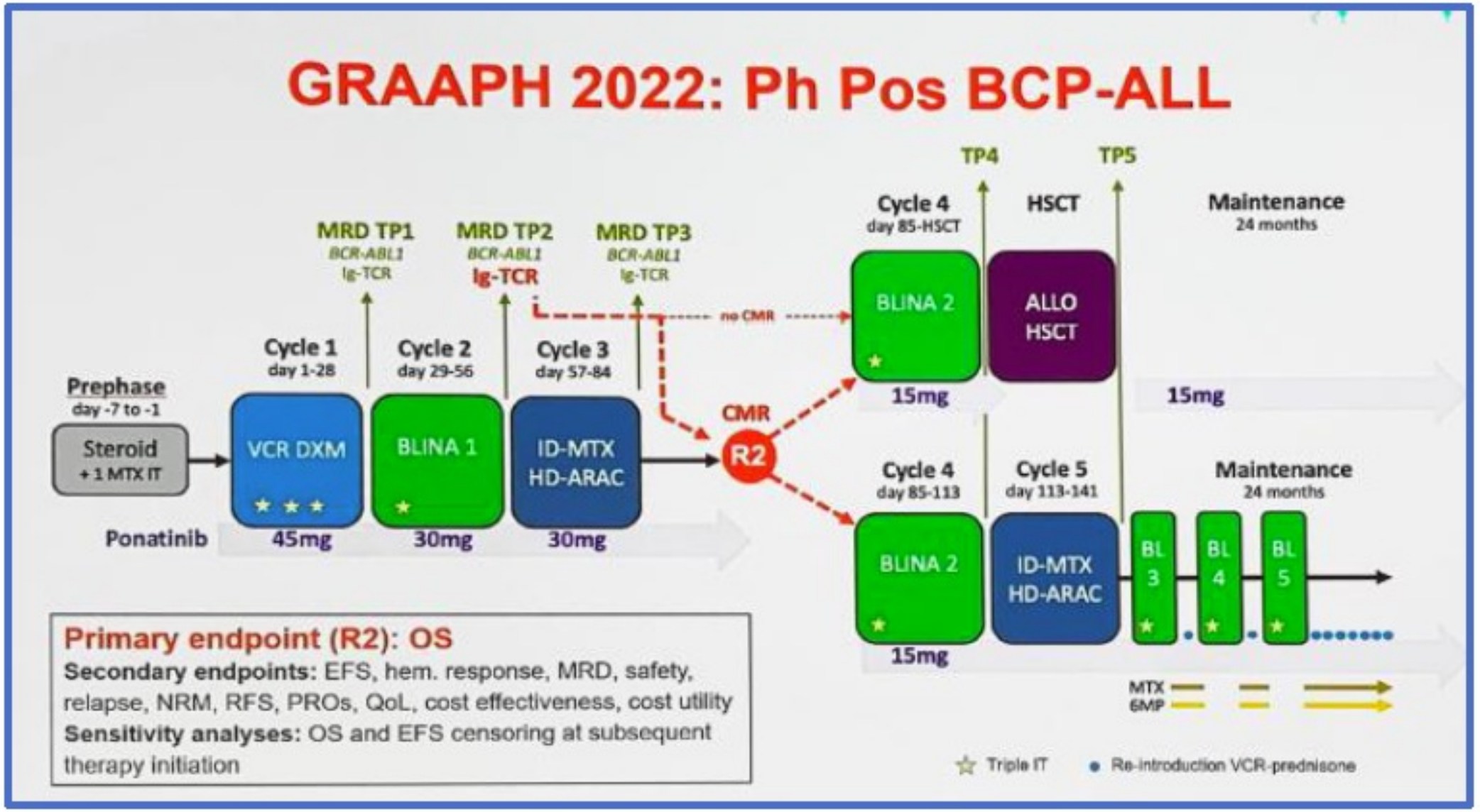


GIMEMA Gruppo Italiano Malattie EMatologiche dell'Adulto

GMALL EVOLVE trial



Lang F et al, Oncol Res Treat 2024

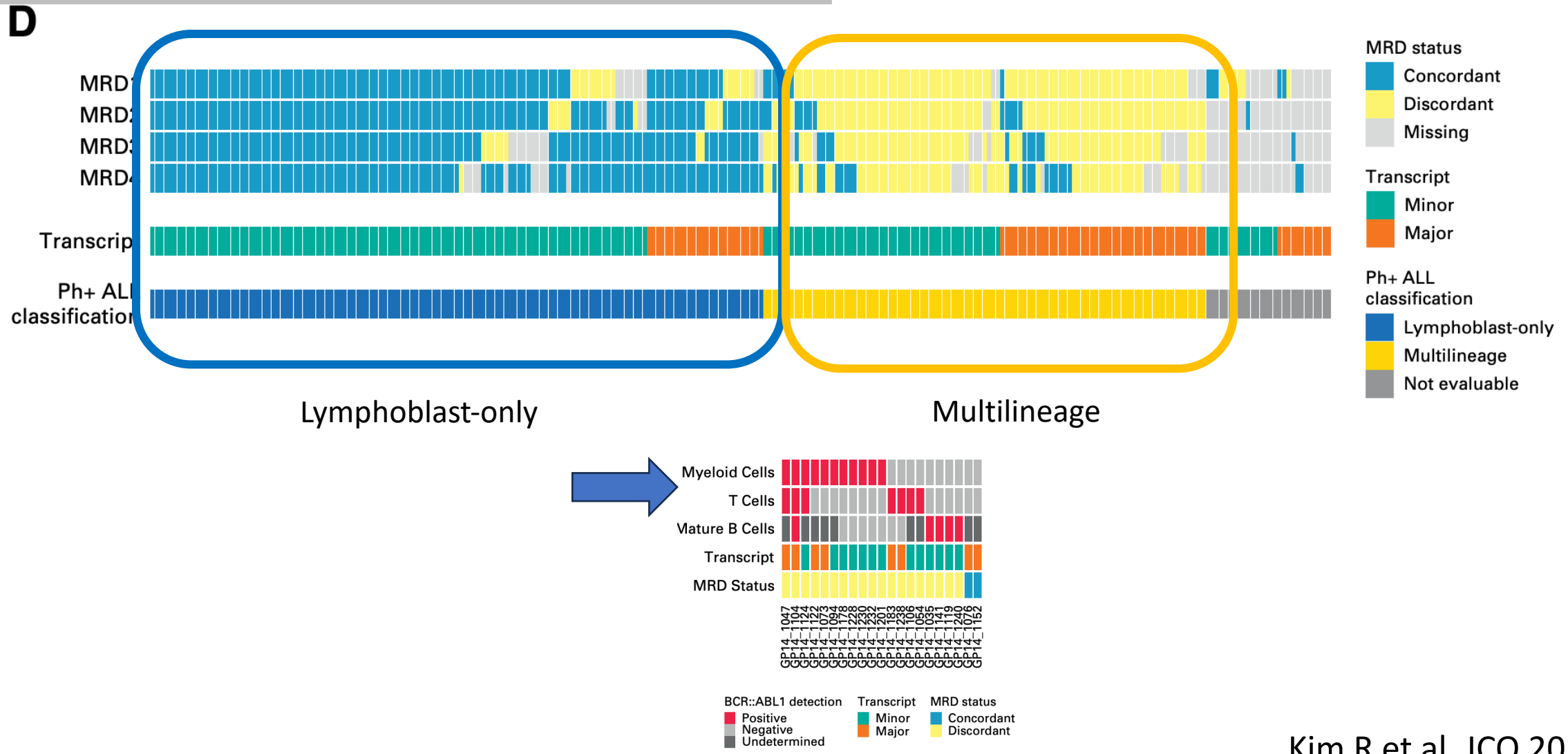

GRAAPH 2022: Ph Pos BCP-ALL
Prephase
day -7 to -1
Steroid
+ 1 MTX IT
Cycle 1
day 1-28
VCR DXM
Cycle 2
day 29-56
BLINA 1
Cycle 3
day 57-84
ID-MTX
HD-ARAC
Ponatinib
45mg
30mg
30mg
MRD TP1
BCR-ABL1
Ig-TCR
MRD TP2
BCR-ABL1
Ig-TCR
MRD TP3
BCR-ABL1
Ig-TCR
no CMR
CMR
R2
TP4
TP5
Cycle 4
day 85-HSCT
BLINA 2
15mg
HSCT
ALLO
HSCT
Maintenance
24 months
15mg
Cycle 4
day 85-113
BLINA 2
15mg
Cycle 5
day 113-141
ID-MTX
HD-ARAC
Maintenance
24 months
BL
3
BL
4
BL
5
MTX
6MP
Primary endpoint (R2): OS
Secondary endpoints: EFS, hem. response, MRD, safety, relapse, NRM, RFS, PROs, QoL, cost effectiveness, cost utility
Sensitivity analyses: OS and EFS censoring at subsequent therapy initiation
Triple IT
Re-introduction VCR-prednisone

Ph+ ALL is not genetically homogeneous

MRD and genetics as decision tools

IgH/TCR
BCR::ABL

MRD discrepancies (BCR::ABL vs IgH/TCR) identifies two patients subgroups



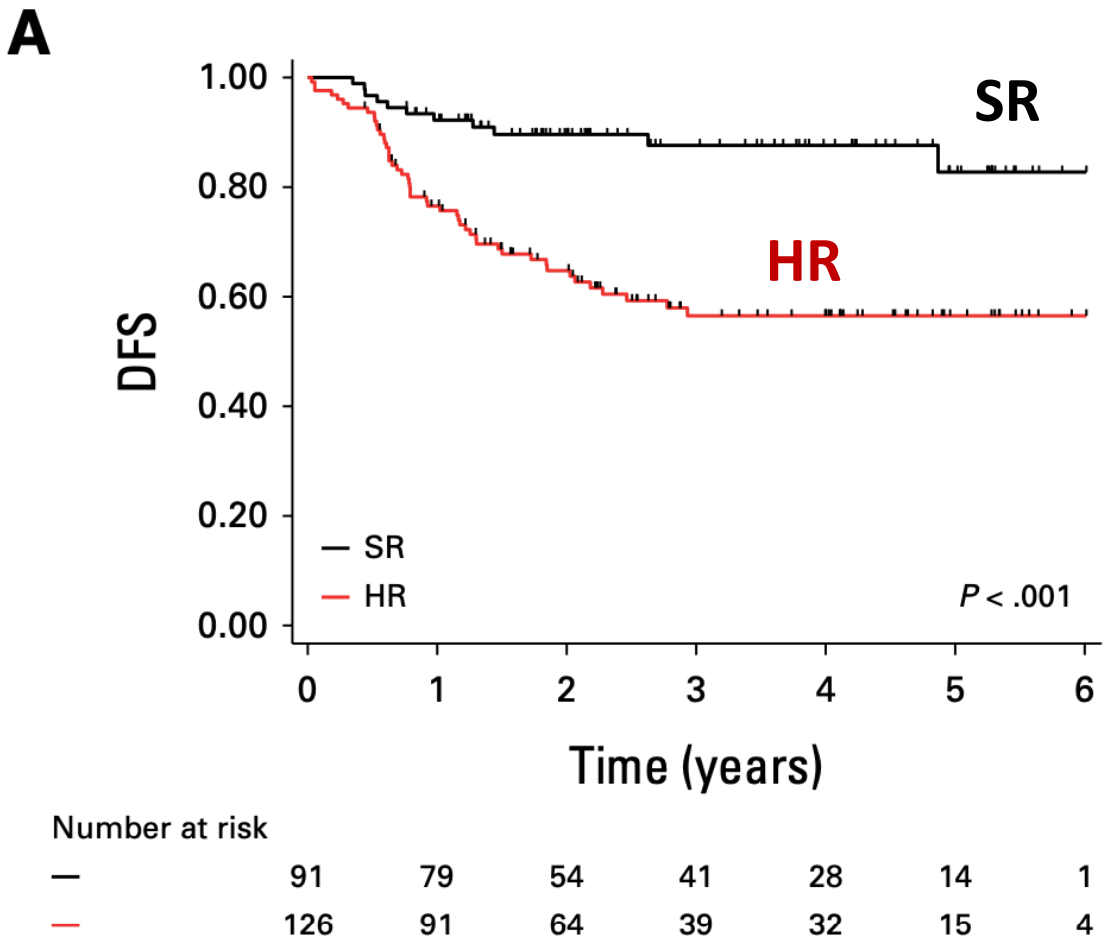
Kim R et al, JCO 2024

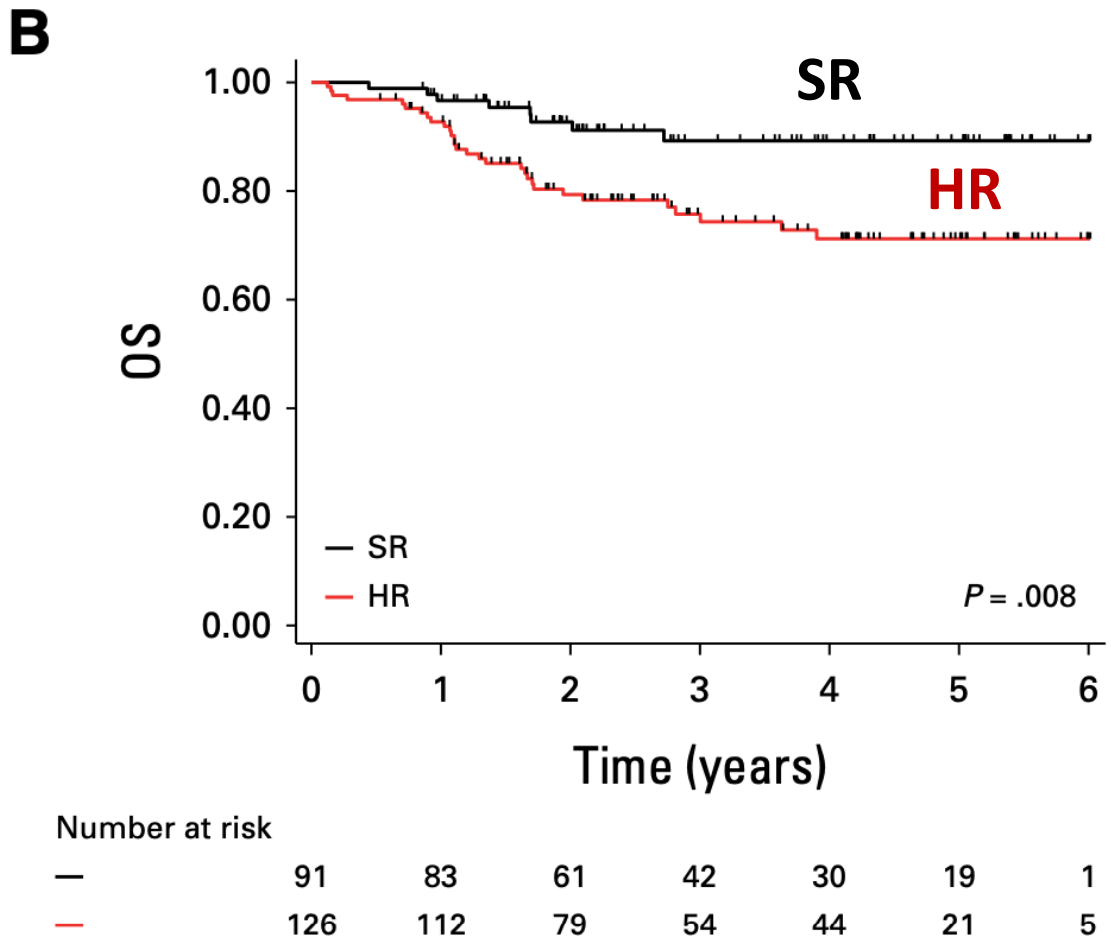
IgH/TCR positivity at TP2 and high WBC predict poor DFS

Characteristic	No.	Univariable HR (95% CI)	Univariable *P*	Multivariable[a] HR (95% CI)	Multivariable[a] *P*
Age[b]	259	0.99 (0.98 to 1.02)	.70	0.99 (0.97 to 1.03)	.84
Log (WBC)[b]	259	1.23 (1.05 to 1.44)	.01	—	—
WBC ≥30 × 10^9/L	259	1.84 (1.17 to 2.89)	.008	2.95 (1.44 to 6.03)	.003
CNS involvement	248	1.16 (0.89 to 1.50)	.27	1.17 (0.92 to 1.49)	.21
m- *v* M-BCR breakpoint	259	1.05 (0.64 to 1.72)	.84	1.69 (0.79 to 3.57)	.17
Favorable prednisone response	259	0.90 (0.75 to 1.09)	.28	1.02 (0.50 to 2.05)	.97
Multilineage *v* lymphoblast-only[a]	228	0.83 (0.49 to 1.41)	.50	0.77 (0.40 to 1.50)	.44
IG/TR MRD2 ≥0.01%	193	2.49 (1.40;4.40)	.002	2.58 (1.34 to 4.96)	.004
Experimental no-cytarabine arm	259	1.59 (1.00;2.51)	.049	1.61 (0.86 to 3.02)	.14

Kim R et al, JCO 2024

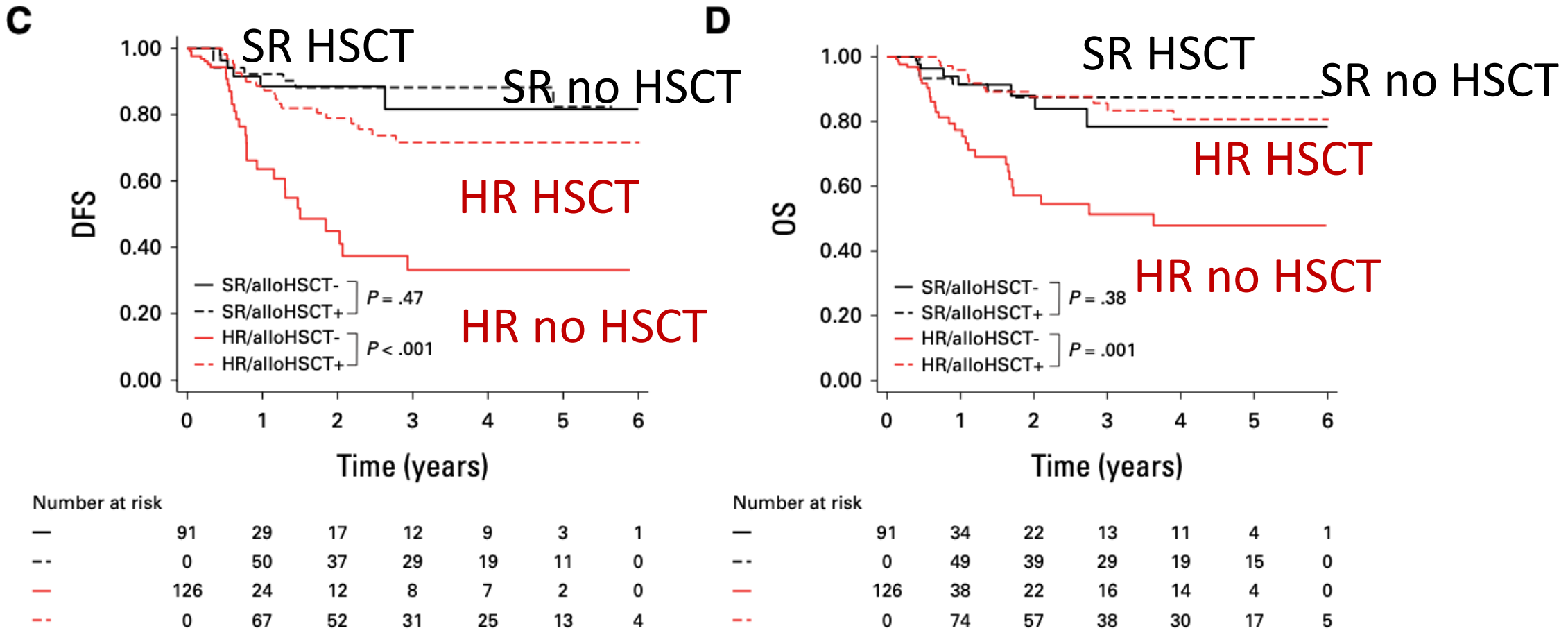
…and identify 2 patients subgroups





Kim R et al, JCO 2024

In HR patients HSCT is beneficial



HR: Ig/TCR MRD >0.01% and/or WBC ≥30 x10^9/L, 58% of pts
SR: remaining

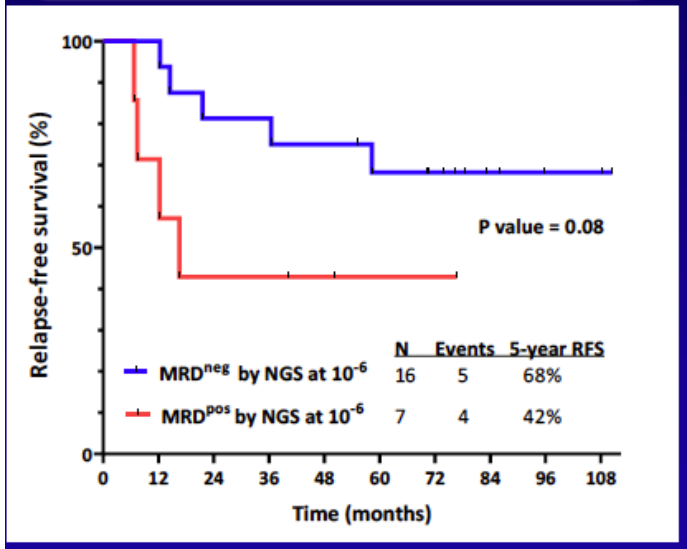
Kim R et al, JCO 2024

MRD in Ph+ ALL: NGS?

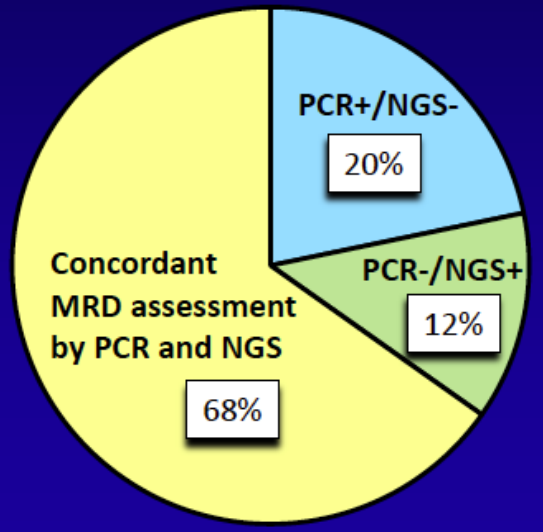
Adults with Ph+ ALL undergoing frontline therapy
(n=44 in retrospective cohort)
(n=74 in validation cohort)

→ **Comparison of MRD assessment by RT-PCR for *BCR::ABL1* and next-generation sequencing for IG/TR (sensitivity 10^{-6})**

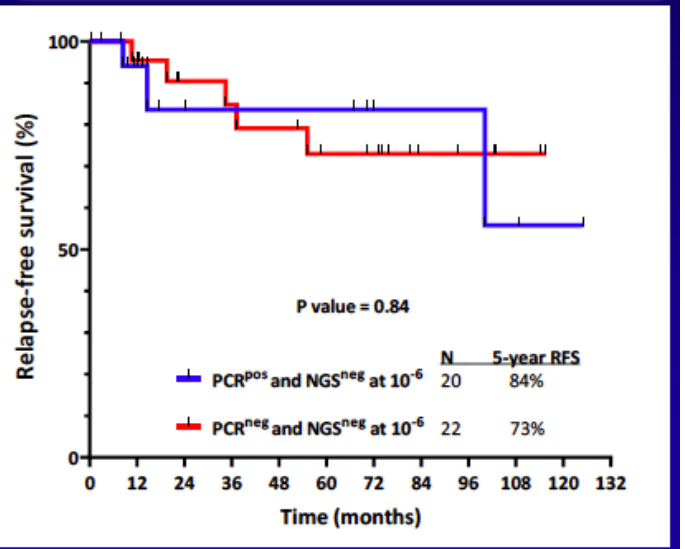
NGS MRD in first 6 months of treatment is prognostic for RFS and OS



Discordance between MRD assessment by PCR and NGS is relatively common

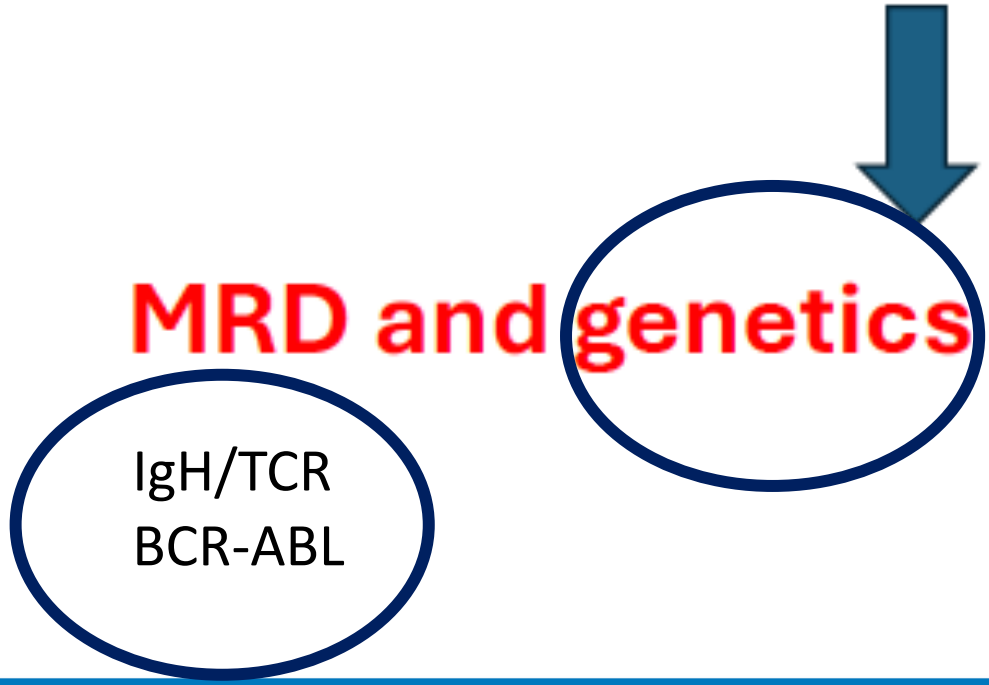


RT-PCR for *BCR::ABL1* is not prognostic in patients who achieve NGS MRD negativity



Short N et al, Am J Hematol 2023

Ph+ ALL is not genetically homogeneous

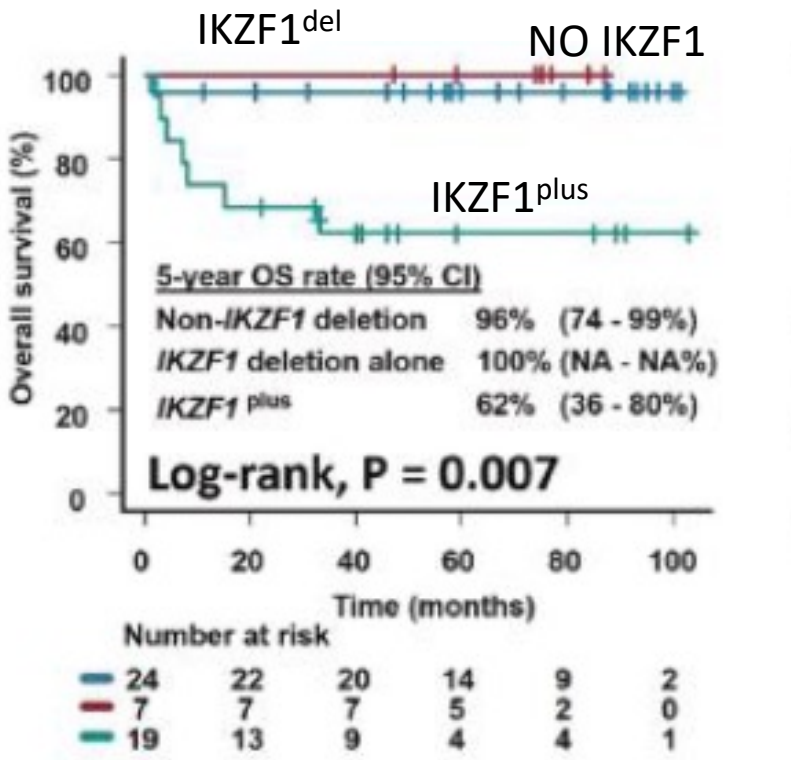


MRD and genetics as decision tools

IgH/TCR
BCR-ABL

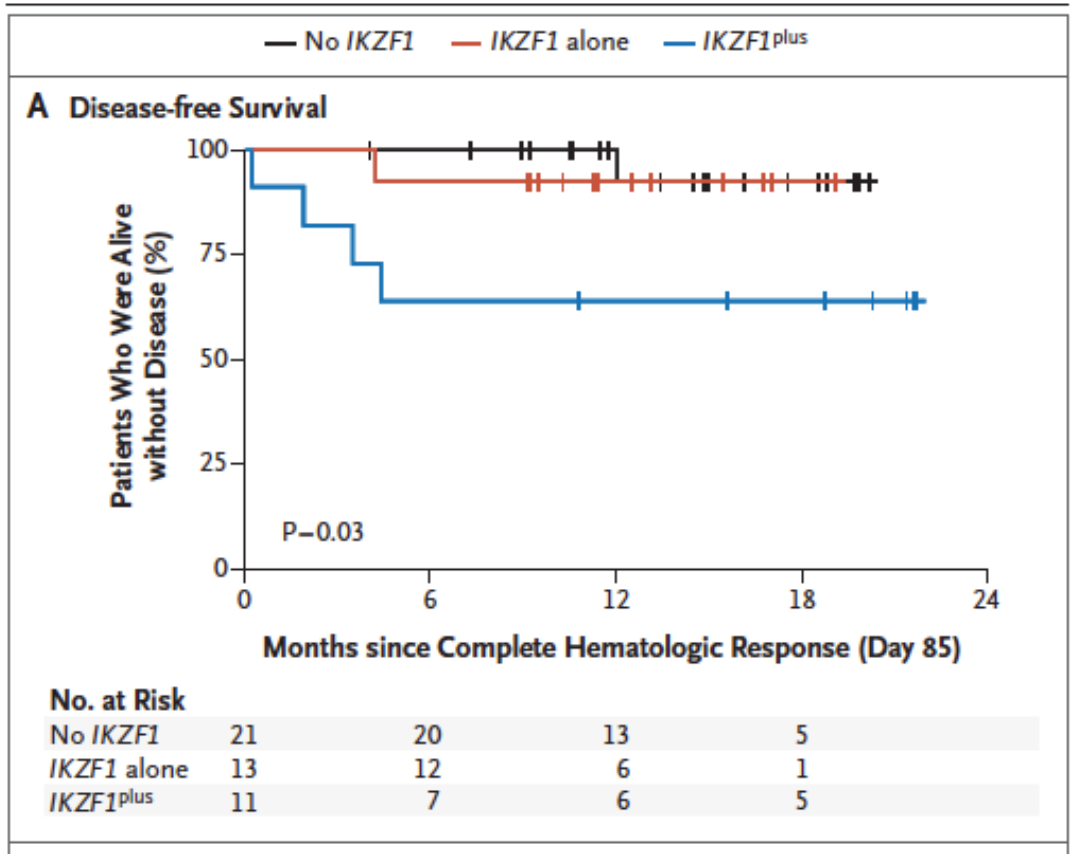
Prognostic role of IKZF1^{plus}

HYPERCVAD+PONATINIB



Sasaki Y et al, Leukemia 2022

DASATINIB+BLINATUMOMAB



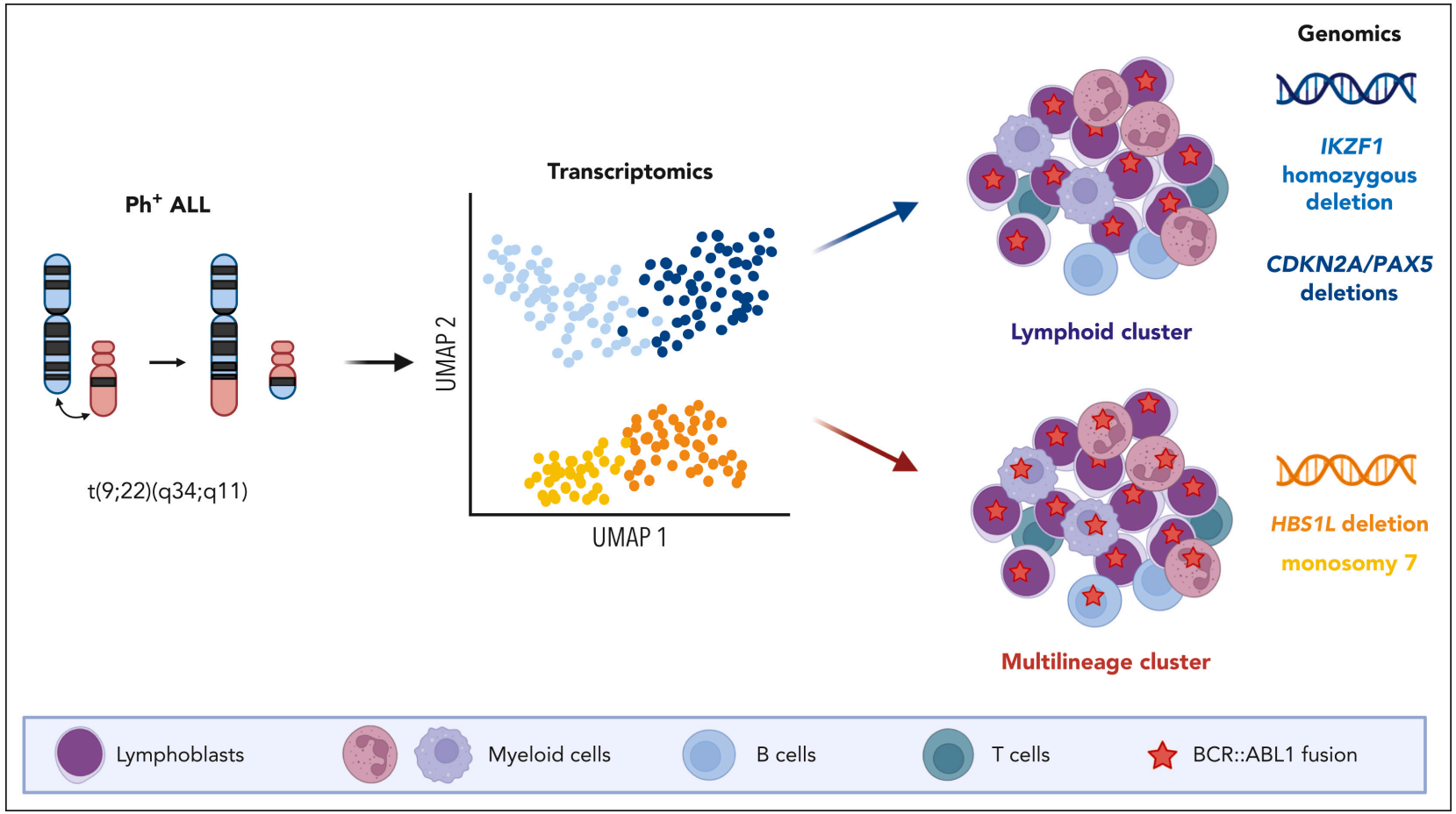
Foà R et al, NEJM 2020

What about Ponatinib+ Blinatumomab?

CYTOGENETIC AND MOLECULAR PROGNOSTIC RISK STRATIFICATION FOR B-ALL[h]

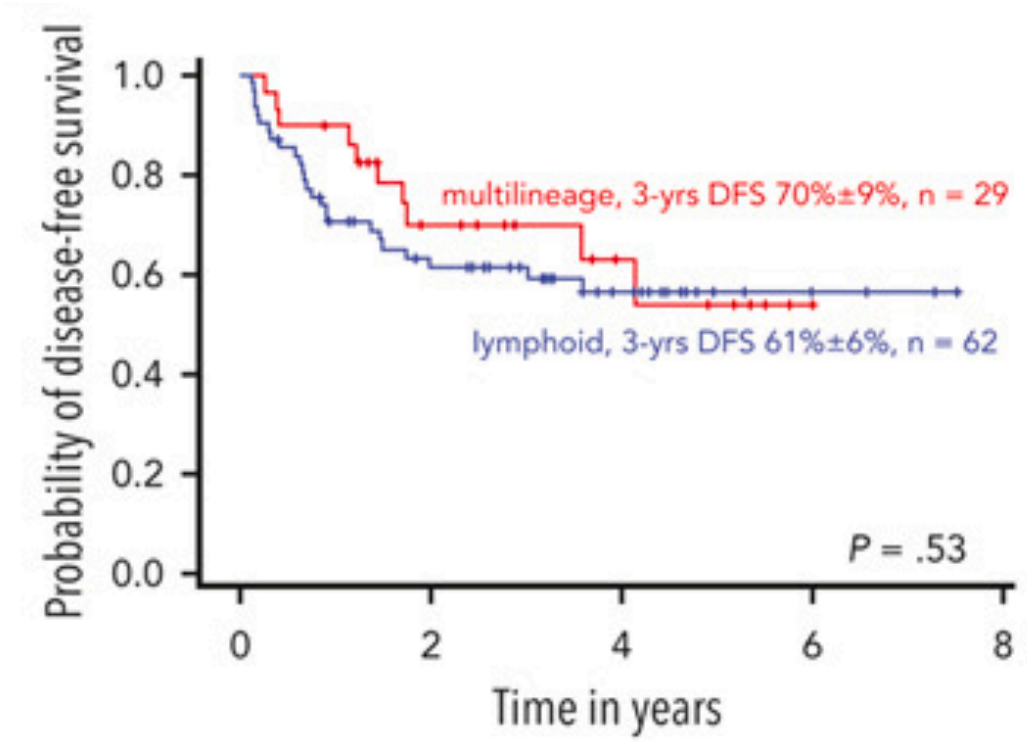
RISK GROUPS	CYTOGENETIC AND MOLECULAR ALTERATIONS
Standard risk	• Hyperdiploidy (51–65 chromosomes) ▸ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome • t(12;21)(p13;q22): *ETV6::RUNX1*[i] • t(1;19)(q23;p13.3): *TCF3::PBX1* • *DUX4* rearranged • *PAX5* P80R • t(9;22)(q34;q11.2): *BCR::ABL1*[j] without *IKZF1* plus[k] and without antecedent chronic myeloid leukemia (CML)
Poor risk	• Hypodiploidy[l,m] (<44 chromosomes) • *TP53* mutation • *KMT2A* rearranged (t[4;11] or others) • *IgH* rearranged[n] • *HLF* rearranged • *ZNF384* rearranged • *MEF2D* rearranged • *MYC* rearranged • *BCR::ABL1*-like (Philadelphia chromosome [Ph]-like) ALL ▸ JAK-STAT (*CRLF2r*,[o] *EPORr*, *JAK1/2/3r*, *TYK2r*, mutations of *SH2B3*, *IL7R*, *JAK1/2/3*) ▸ ABL class (rearrangements of *ABL1*, *ABL2*, *PDGFRA*, *PDGFRB*, *FGFR*) ▸ Other (*NTRKr*, *FLT3r*, *LYNr*, *PTK2Br*) • *PAX5alt* • t(9;22)(q34;q11.2): *BCR::ABL1*[j] with *IKZF1* plus[k] and/or antecedent CML • Intrachromosomal amplification of chromosome 21 (iAMP21) • Alterations of *IKZF1*[k,p,q] • Complex karyotype (5 or more chromosomal abnormalities)

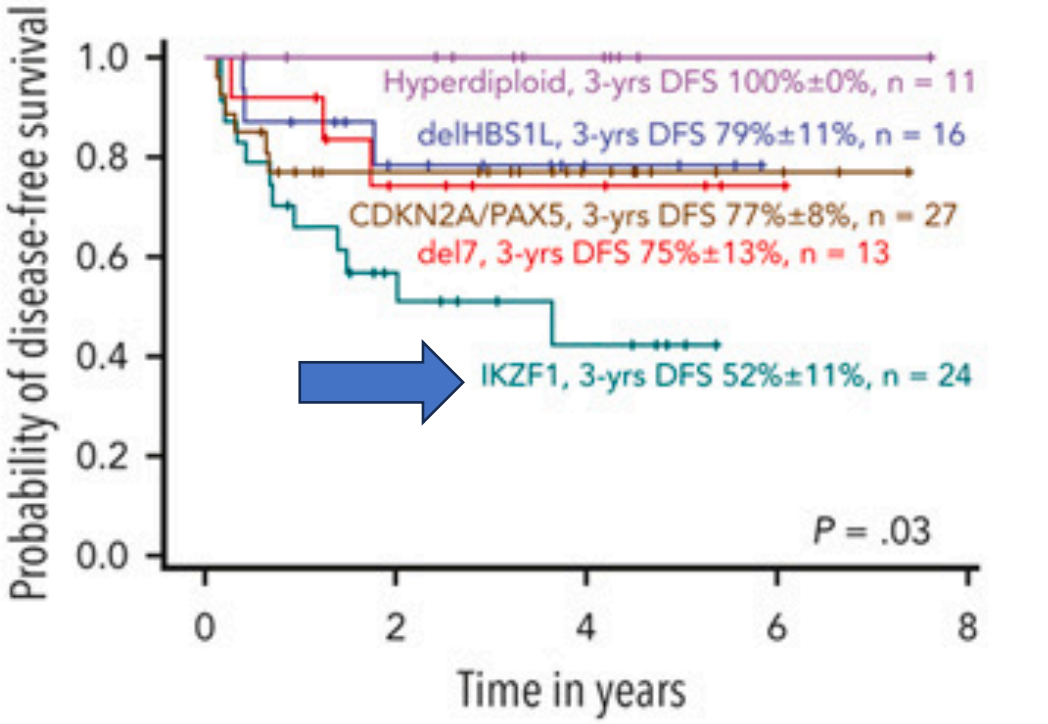
Two transcriptomic clusters with distinct genomic patterns can be identified



Bastian L et al, Blood 2024

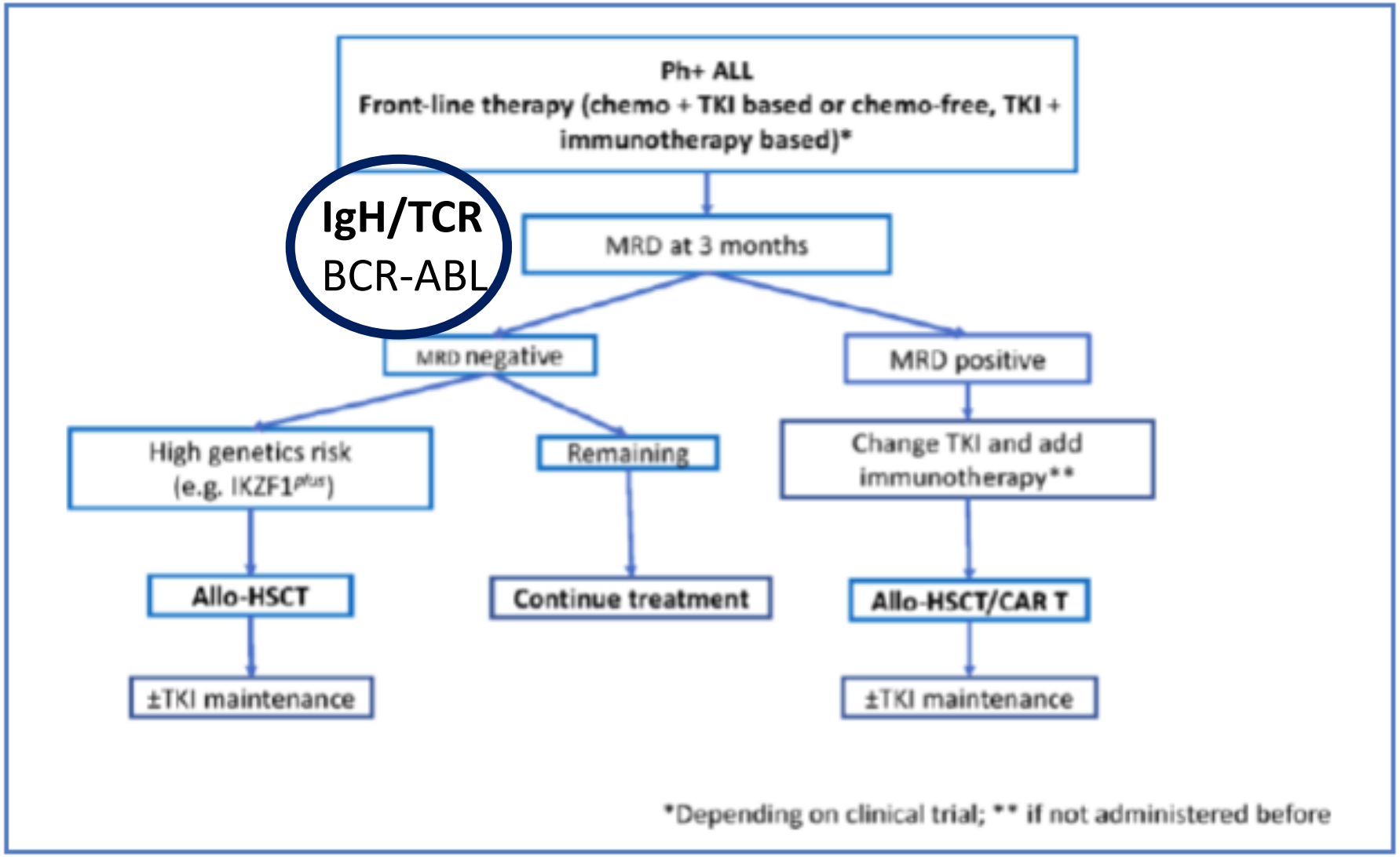
IKZF1 cluster patients have a bad outcome





Bastian L et al, Blood 2024

Flow-chart



Ribera J et al, Cancers 2022

TFR in Ph+ ALL?

- **14 pts** with Ph+ ALL in CR1 and DMR stopped TKI
- Median duration of therapy was 60 months (31-125), **median DMR 46 months** (2-122) prior TKI discontinuation
- **Median follow up 51 months** after discontinuation, **11 pts (79%)remained in TFR, 3 pts (21%) had a molecular relapse**
- All the 3 patients resumed TKI and achieved a DMR
- None of the 8 pts with a DMR>4 years relapsed
- **A clinical trial is required!**

Samra B et al, Acta Haematol 2021

Take home messages

- ✓ Historically, alloHSCT has been **mandatory for all young and fit patients** with Ph+ ALL in CR and, outside clinical trials it's still recommended

- ✓ The introduction of innovative therapeutic approaches (**2nd/3rd generation TKI + immunotherapy**) is showing improved results at the long run, and a large proportion of these patients have not been transplanted

- ✓ Therefore, trying to identify which Ph+ ALL subtypes could benefit from a transplant-free approach, is becoming more and more relevant

- ✓ Patients achieving a **CMR at three months** seem to be the most suitable candidates for a transplant-free treatment

- ✓ **MRD monitoring (BCR::ABL and IgH/TCR, at least within clinical trials) and the integration with genomic data** should be performed to decide which patients need to be allocated to SCT and which ones don't

Thank you!

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