1ST INTERNATIONAL CONFERENCE ON
Ph+ Leukemias

Bologna, Royal Hotel Carlton **September 29-30, 2025**

How should we monitor MRD in Ph+ ALL : *BCR::ABL1* or *IG/TR* ?

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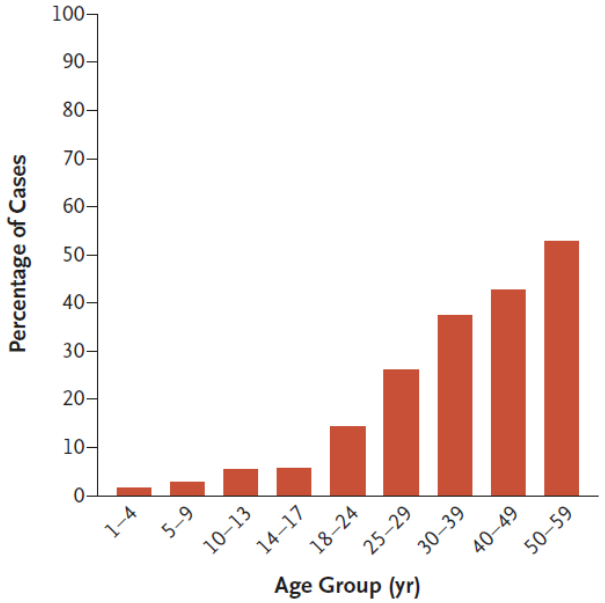
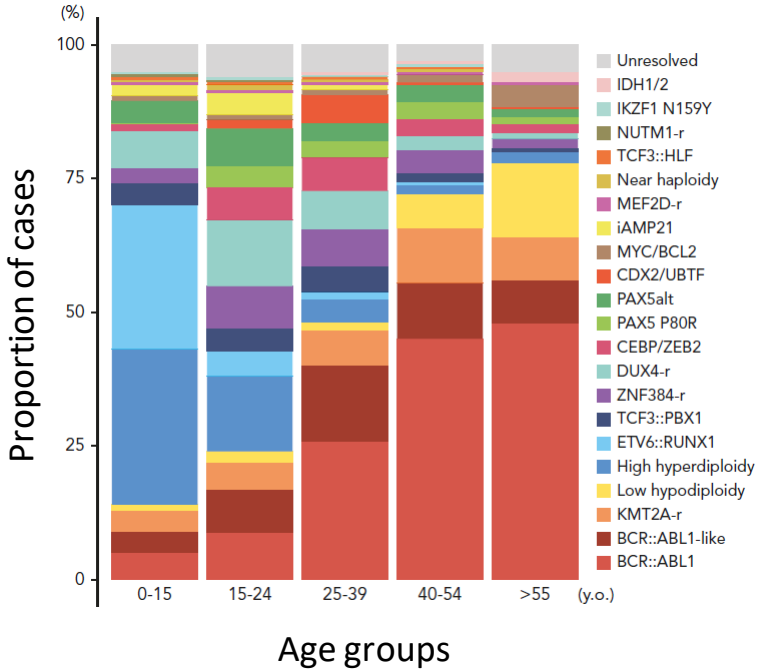
Disclosures Rathana KIM

Nothing to disclose

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)



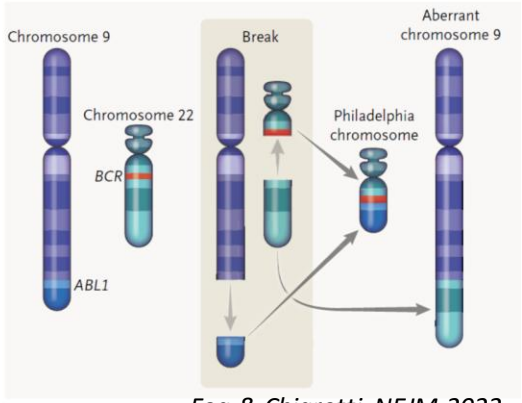
Foà & Chiaretti NEJM 2022



Passet et al. Blood 2025

- The most prevalent B-ALL subtype in adults → ~1/3 cases
- Proportion increase with age → up to 50% B-ALL cases after 55-60 years old

Ph+ ALL : two molecular targets for MRD monitoring



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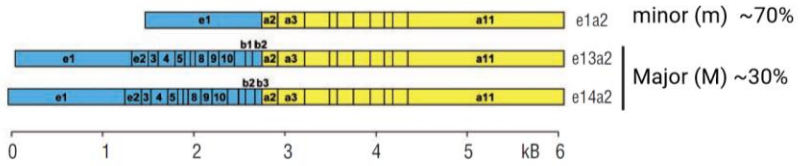
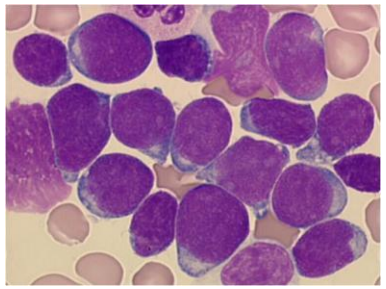


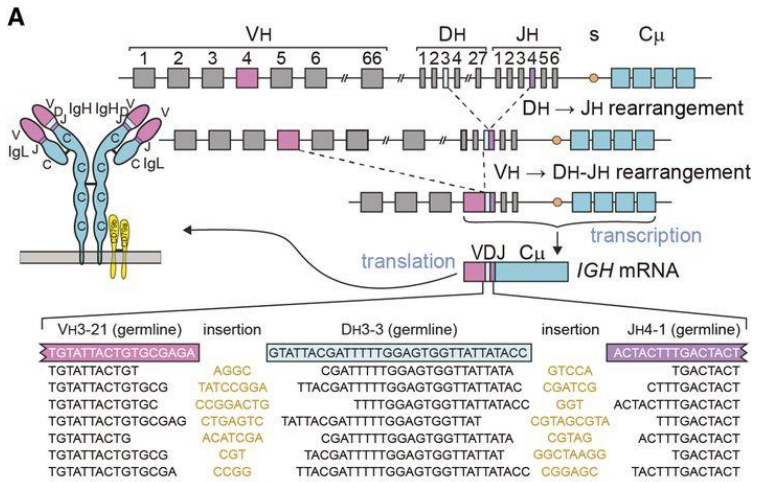
Burmeister et al. Haematologica 2007

BCR::ABL1

Oncogenic fusion



Proliferation of malignant B-cell lymphoblasts in the bone marrow

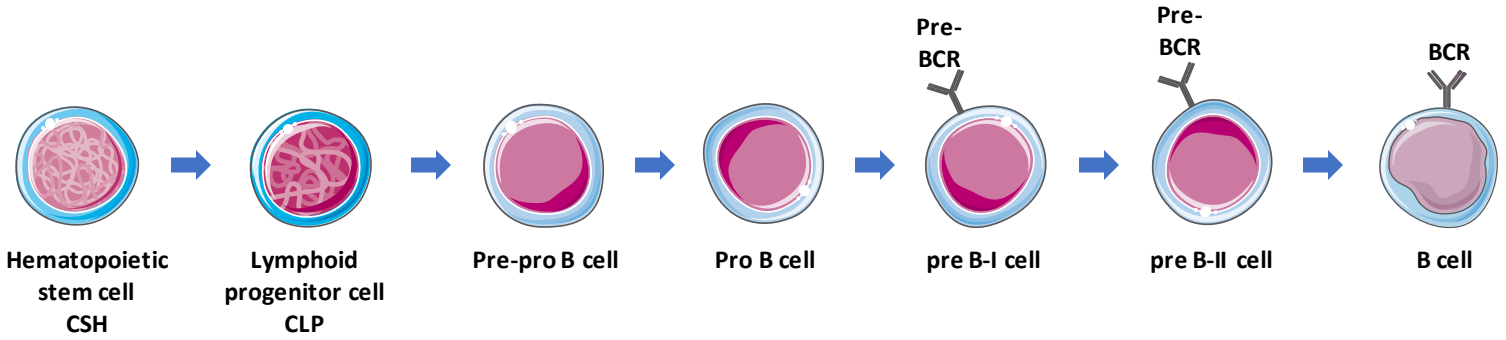


van Dongen et al. Blood 2015

Lymphoid specific markers

Immunoglobulin/T-cell receptor (IG/TR) gene rearrangements

Novel insights in Ph+ ALL pathophysiology revealed by MRD monitoring



BCR::ABL1 fusion

RAG mediated recombinations (IG/TR and others targets)

Until recently

***De novo* Ph+ ALL was defined by the acquisition of BCR::ABL1 fusion in committed B-cell precursors**

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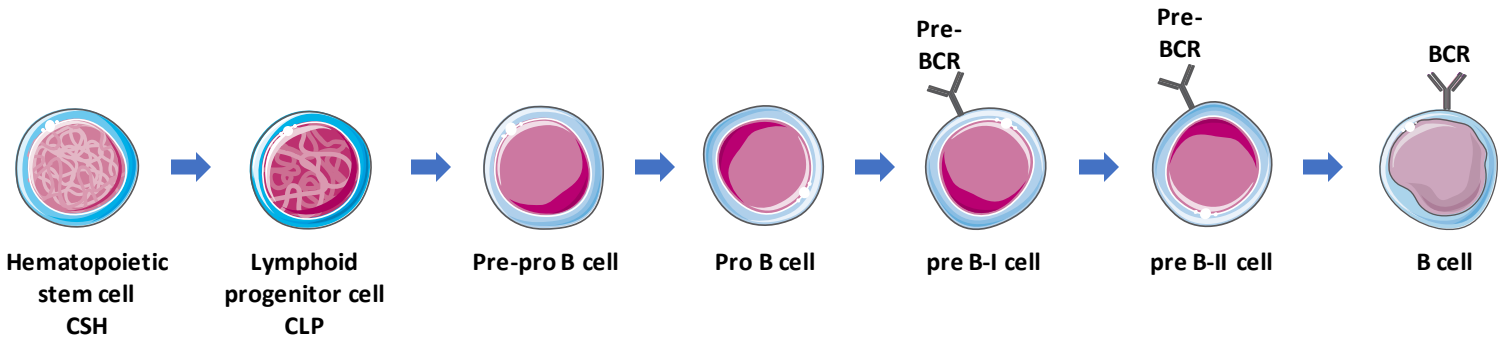

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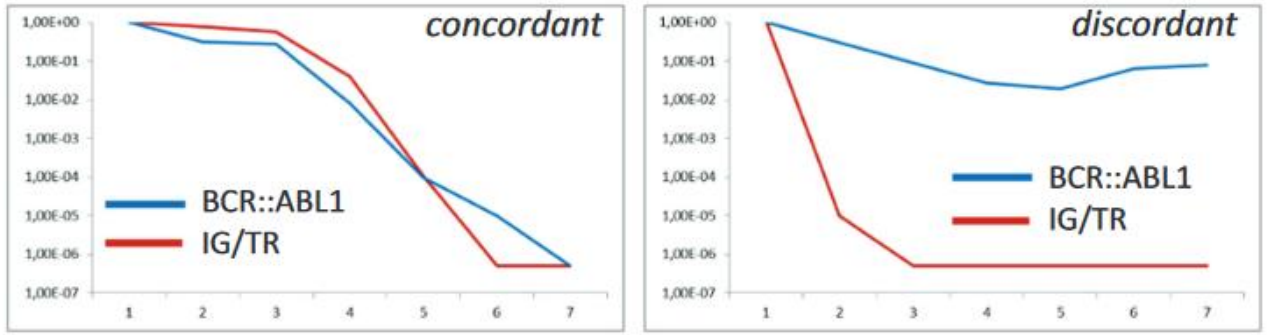

MRD monitoring of two illustrative cases

Zuna et al. Leukemia 2022
Kim et al. JCO 2024

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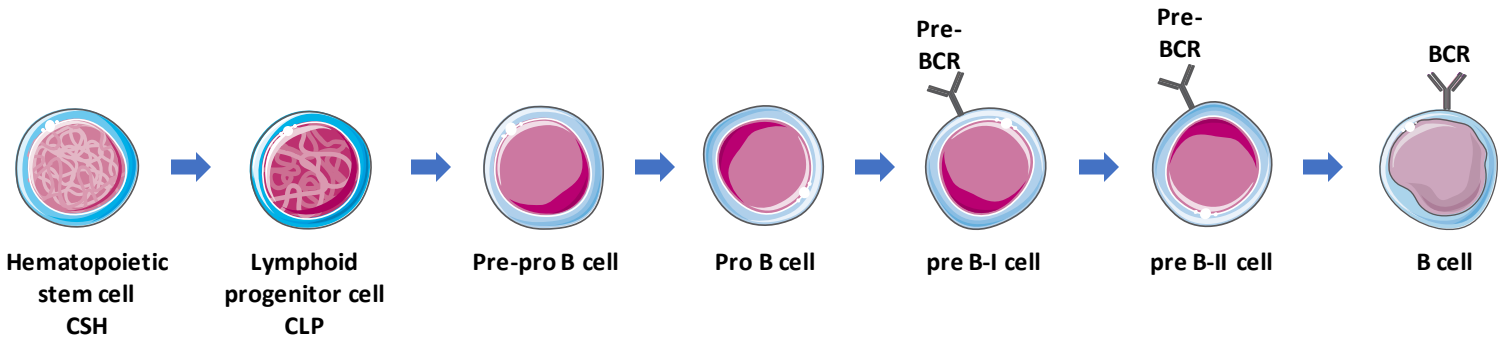

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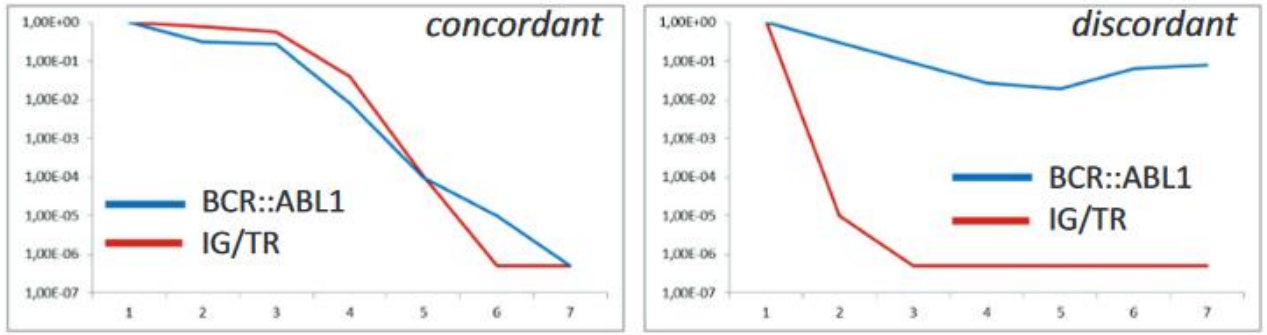


MRD monitoring of two illustrative cases

Evidence for multilineage involvement in de novo Ph+ ALL revealed by MRD assessed on both targets

~35-40% of patients

Zuna et al. Leukemia 2022
Kim et al. JCO 2024

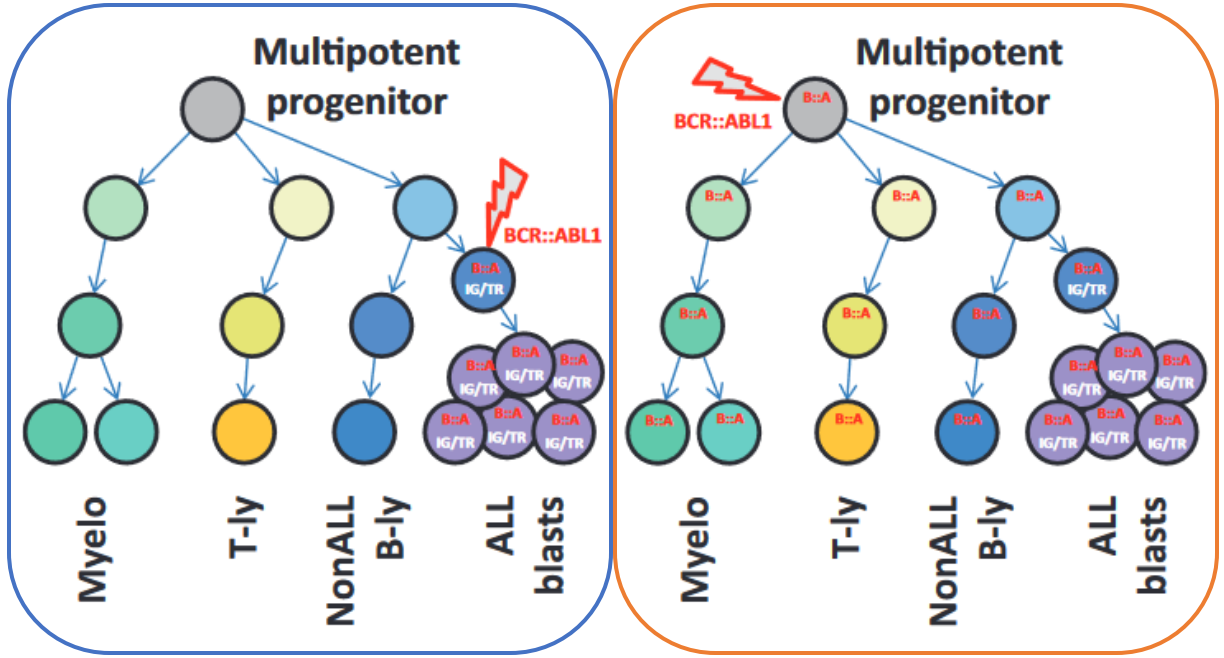
New pathophysiology model of Ph+ ALL

2022 ICC classification

B-ALLwith t(9;22)(q34.1;q11.2)/*BCR::ABL1*

with lymphoid only involvement

with multilineage involvement



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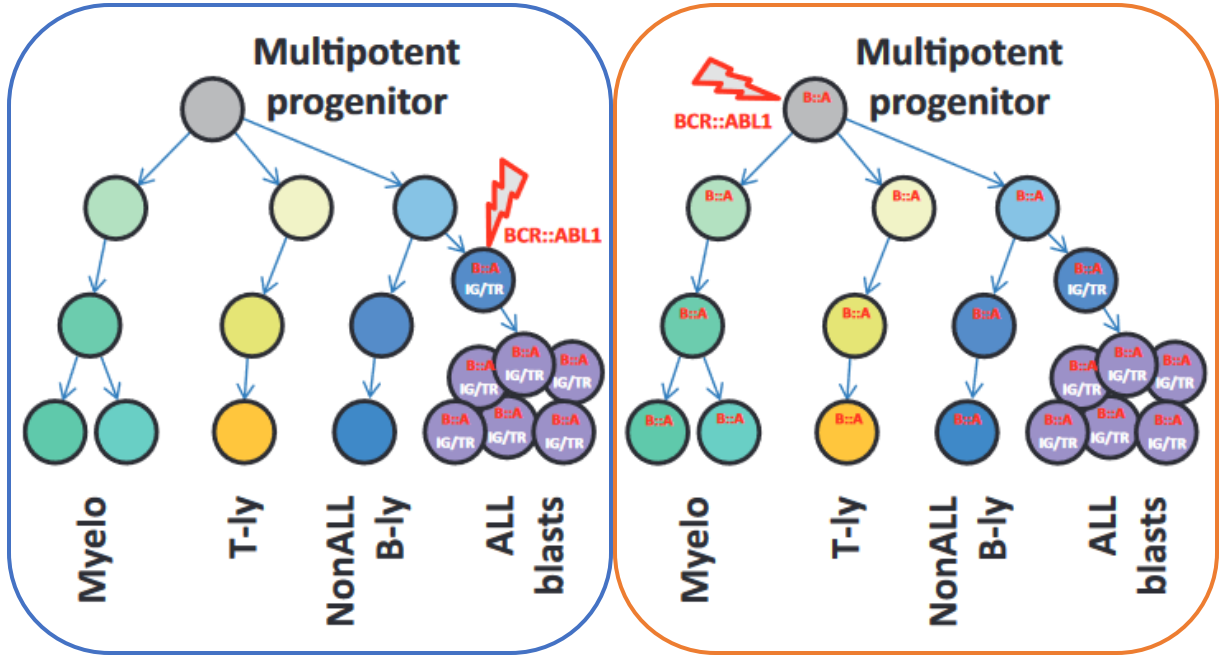

New clinical questions

- ***Which MRD target is the most clinically relevant?***
- ***Impact on new therapeutic strategies?***

Zuna et al. Leukemia 2022
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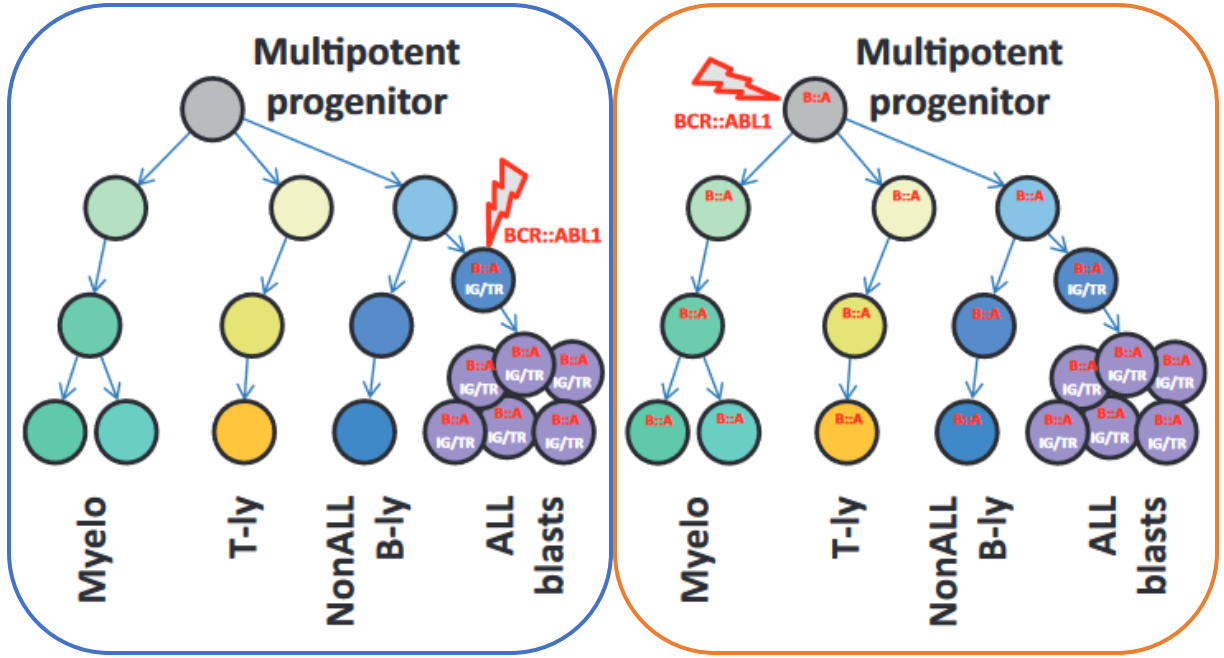

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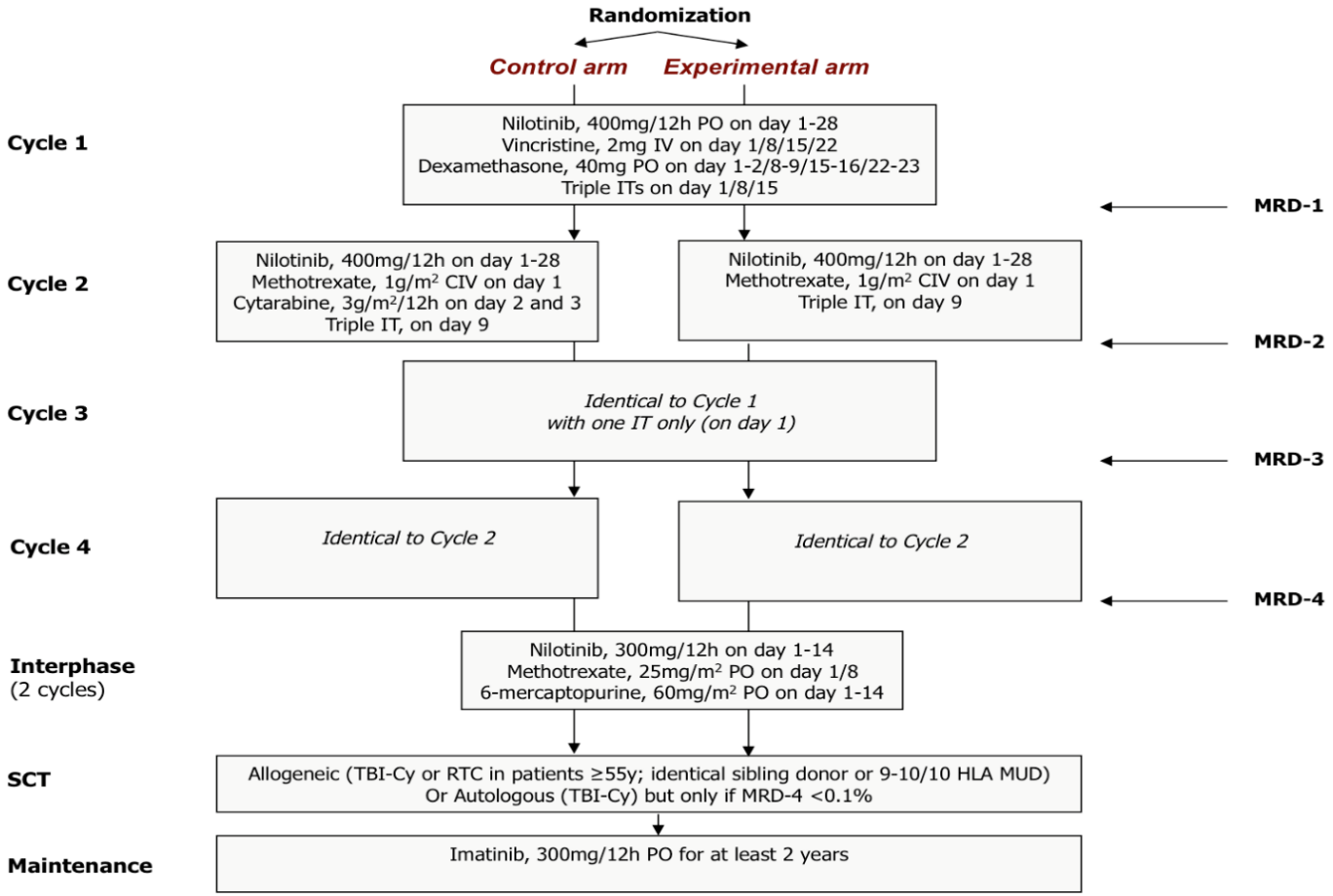
Zuna et al. Leukemia 2022
Kim et al. JCO 2024
Arber et al., Blood 2022

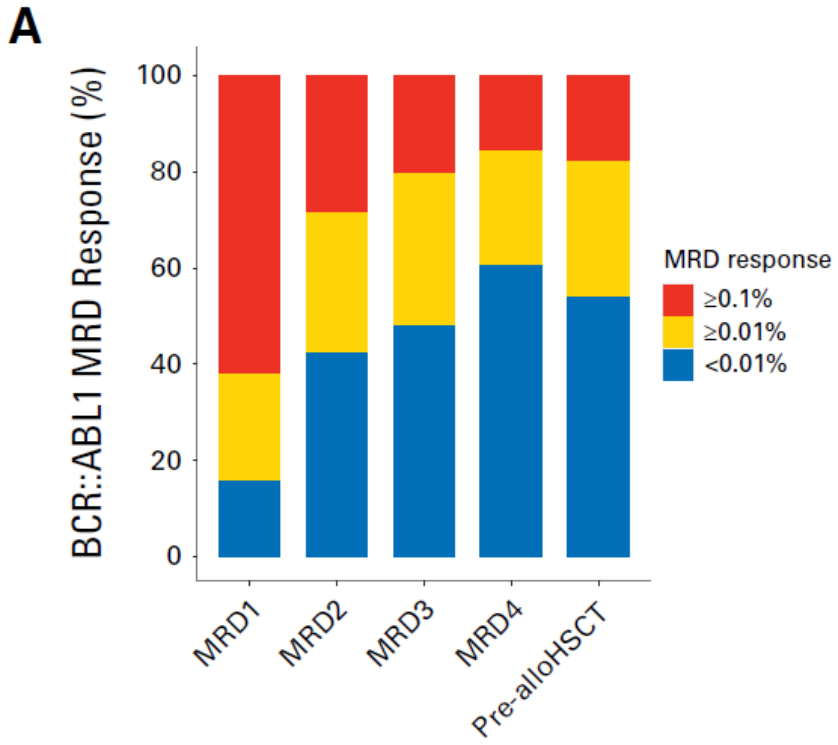
The GRAAPH-2014 study

Nilotinib combined with lower-intensity chemotherapy for front-line treatment of younger adults (18-59 years) with Ph+ ALL



MRD responses during the early phases of treatment

BCR::ABL1



BCR::ABL1 MRD response reaches a plateau

Kim et al. JCO 2024

MRD responses during the early phases of treatment

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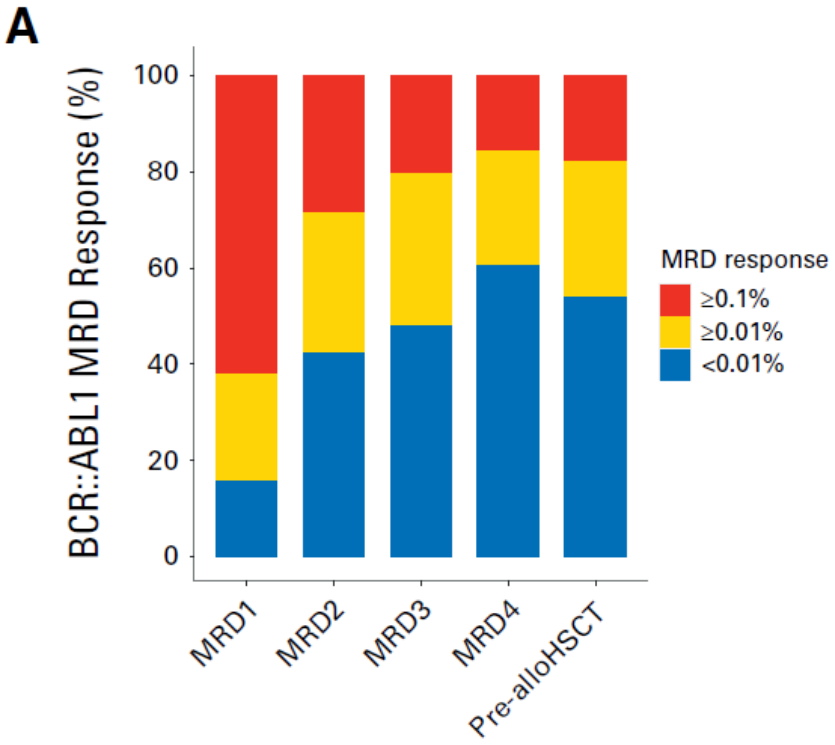
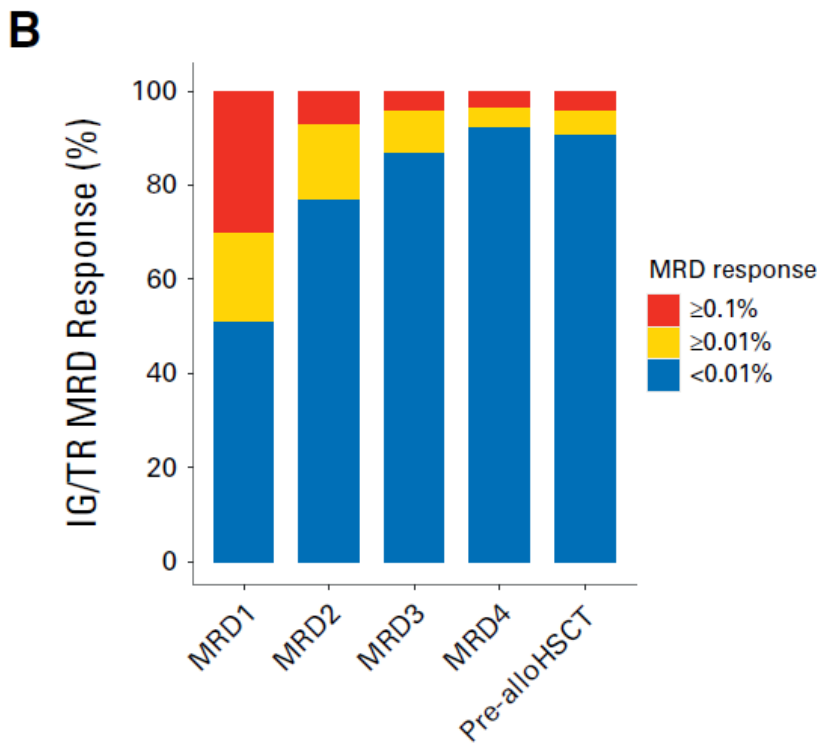


IG/TR



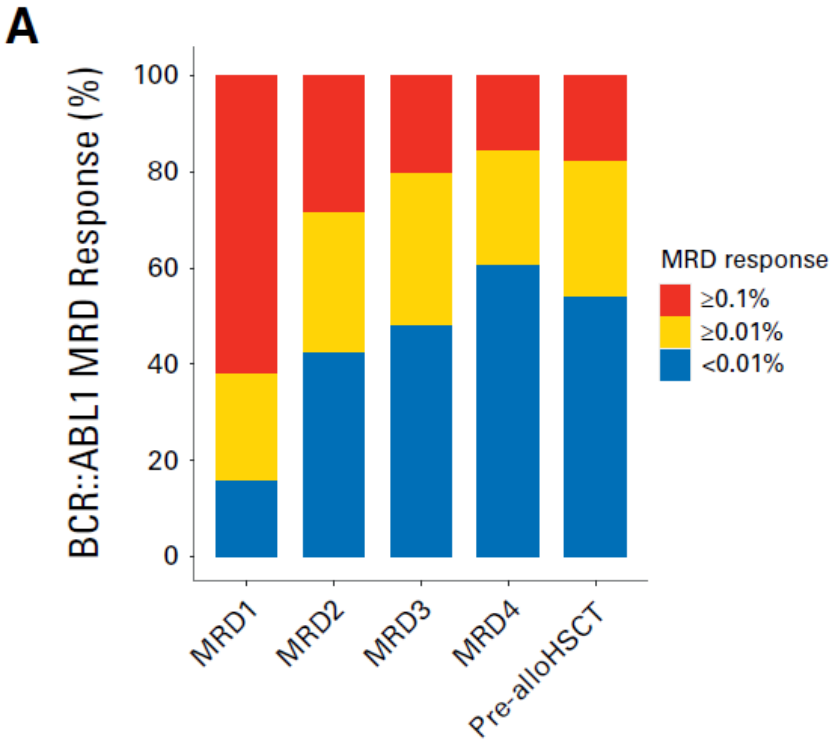
BCR::ABL1 MRD response reaches a plateau

Better proportion of IG/TR MRD clearance during early phase of treatment

Kim et al. JCO 2024

MRD responses during the early phases of treatment

BCR::ABL1



Blinatumomab + Dasatinib
D-ALBA study

Table 2. Molecular Responses during Induction Therapy, at the End of Induction Therapy (Day 85), and after Each Blinatumomab Cycle.

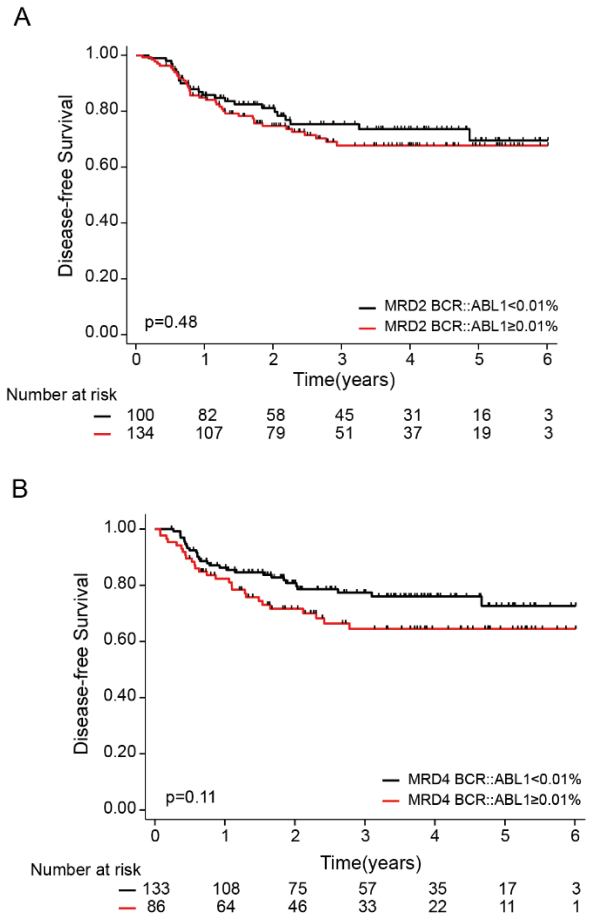
Assessment	No Molecular Response	Complete Molecular Response	Positive Nonquantifiable Response	Overall Molecular Response
	number of patients/total number (percent)			
Induction period				
Day 22	48/58 (83)	3/58 (5)	7/58 (12)	10/58 (17)
Day 45	43/60 (72)	9/60 (15)	8/60 (13)	17/60 (28)
Day 57	38/56 (68)	11/56 (20)	7/56 (12)	18/56 (32)
Day 85	42/59 (71)	6/59 (10)	11/59 (19)	17/59 (29)
Blinatumomab cycle				
After cycle 1	20/55 (36)	19/55 (35)	16/55 (29)	35/55 (64)
After cycle 2	22/55 (40)	23/55 (42)	10/55 (18)	33/55 (60)
After cycle 3	12/40 (30)	20/40 (50)	8/40 (20)	28/40 (70)
After cycle 4	7/36 (19)	17/36 (47)	12/36 (33)	29/36 (81)
After cycle 5	8/29 (28)	16/29 (55)	5/29 (17)	21/29 (72)

BCR::ABL1 MRD response reaches a plateau
Similar findings in immunotherapy + TKI combination (D-ALBA study)

Kim et al. JCO 2024
Foà et al., NEJM 2020

Prognostic impact of MRD

BCR::ABL1

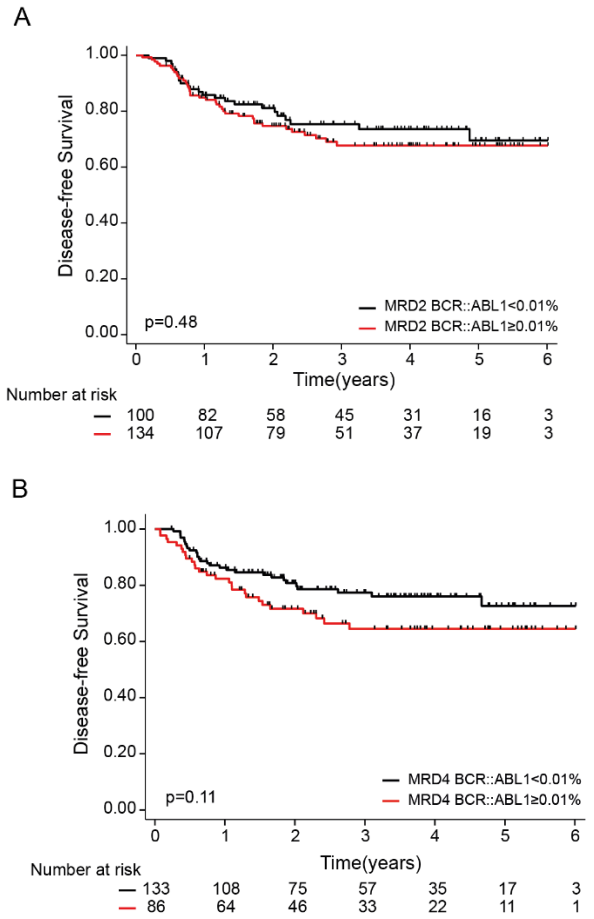


No prognosis value of BCR::ABL1 in a chemotherapy + TKI + alloHSCT regimen (GRAAPH-2014 study)

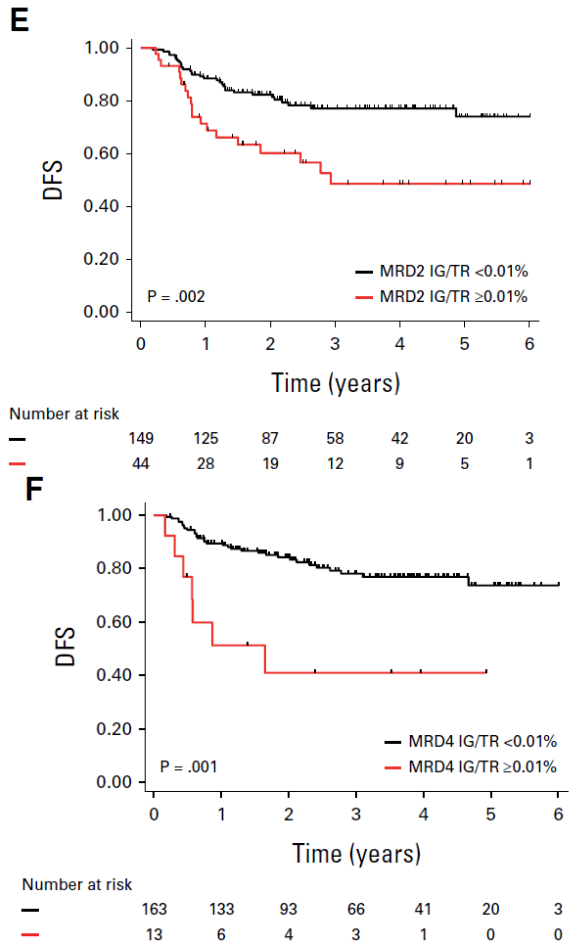
Kim et al. JCO 2024

Prognostic impact of MRD

BCR::ABL1



IG/TR

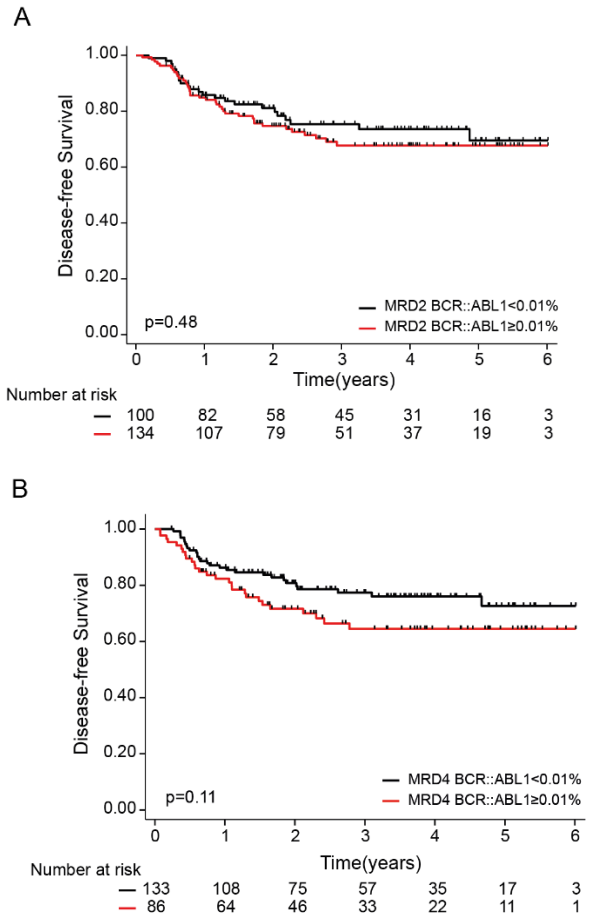


IG/TR MRD is a better predictor of outcome

Kim et al. JCO 2024

Prognostic impact of MRD

BCR::ABL1



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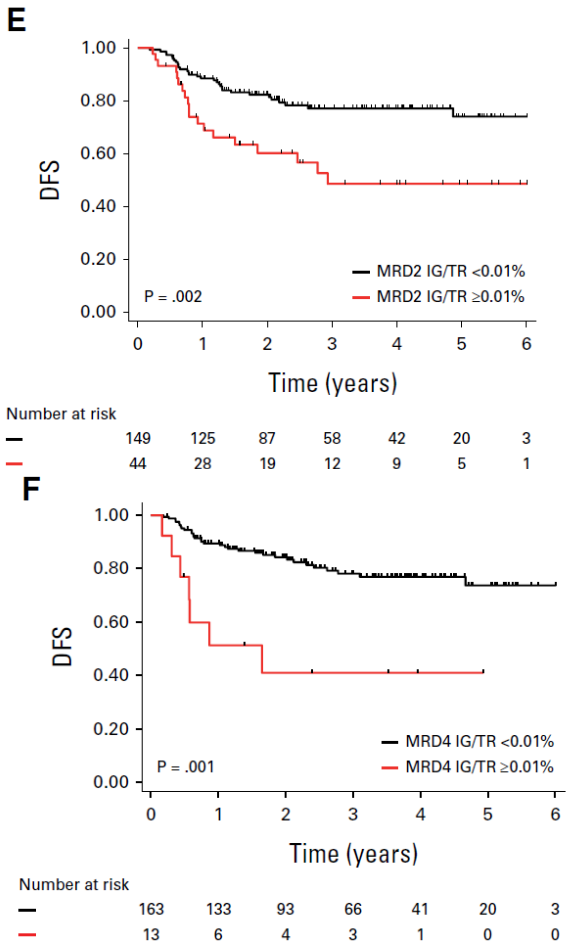
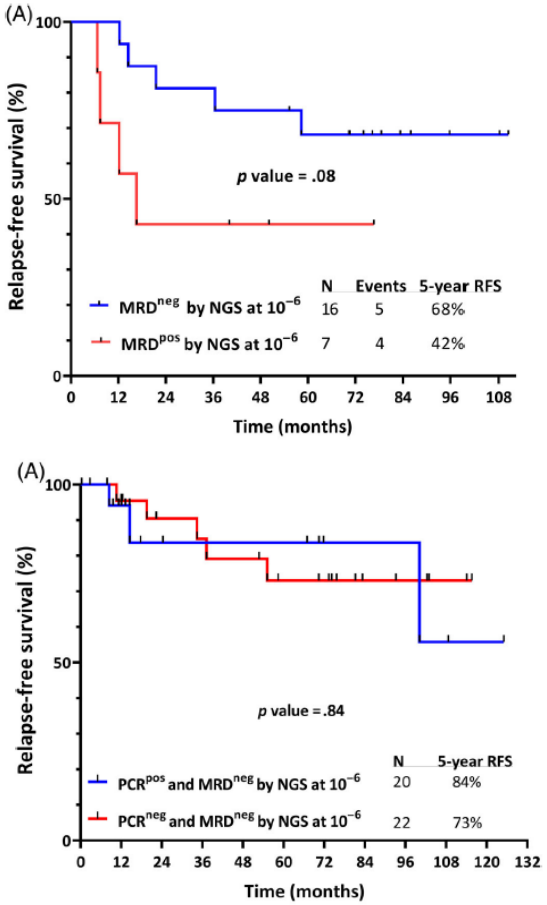


MD Anderson study
IGH MRD by NGS (clonoSEQ)



IG/TR MRD is a better predictor of outcome

Kim et al. JCO 2024
Short et al. Am J Hematol 2023

Incorporating *IG/TR* MRD into a prognostic model

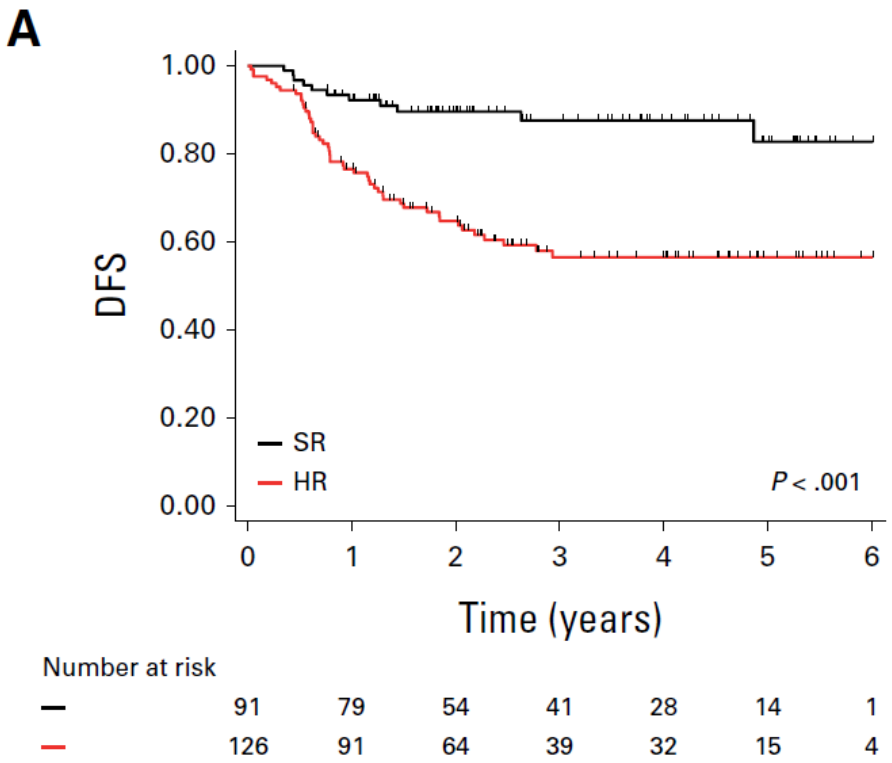
TABLE 3. Univariable and Multivariable Analyses for DFS

		Univariable		Multivariable[a]	
Characteristic	No.	HR (95% CI)	*P*	HR (95% CI)	*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

***IG/TR* MRD and high WBC were independently associated with poorer DFS**

Kim et al. JCO 2024

Incorporating *IG/TR* MRD into a prognostic model

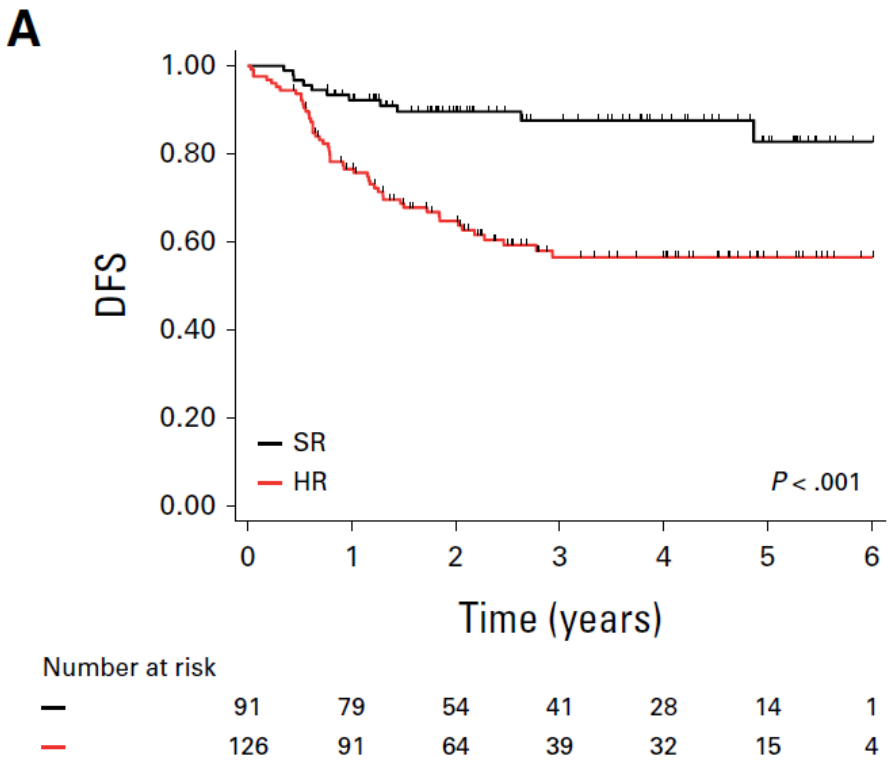


High-risk (HR)
IG/TR MRD ≥ 0.01% or WBC ≥ 30 G/L

Kim et al. JCO 2024

Incorporating *IG/TR* MRD into a prognostic model

Simon-Makush plots



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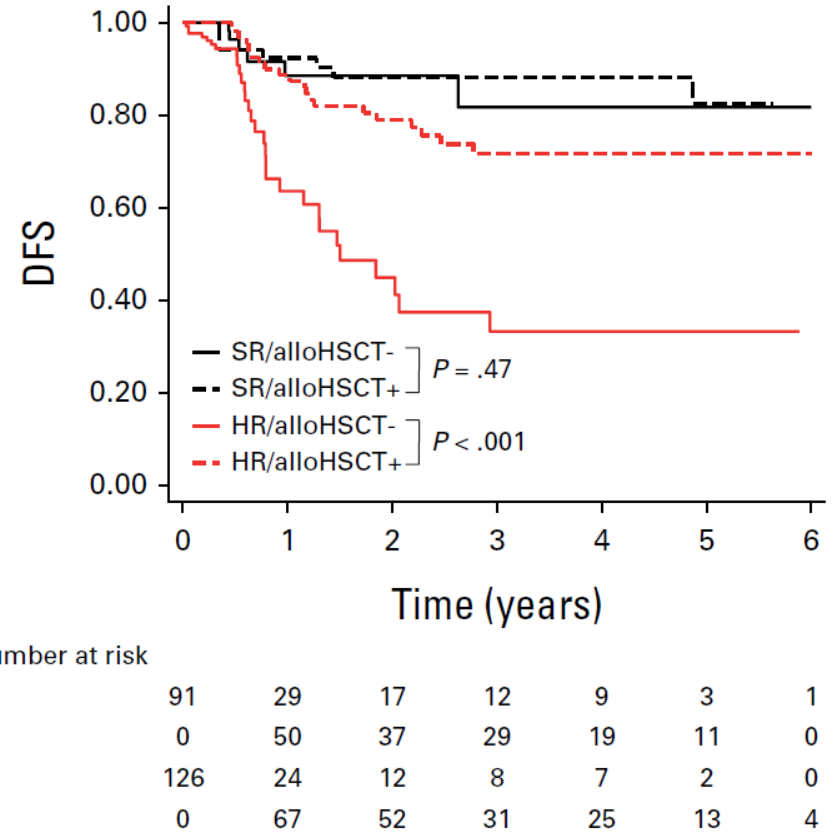

Patients with good *IG/TR* MRD response have excellent outcomes regardless of allo-HSCT

Kim et al. JCO 2024

Summary

- **A large fraction of Ph+ ALL have non-lymphoblastic *BCR::ABL1*-positive cells that persist under treatment**
- ***BCR::ABL1* multilineage involvement and BCR::ABL1 persistence are not associated with poorer outcome**
- ***IG/TR* MRD becomes the new standard for disease monitoring and treatment stratification in Ph+ ALL**

Discussion

Is *BCR::ABL1* still a relevant MRD marker in Ph+ ALL management ?

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Yes !

- ✓ **When no diagnostic sample is available for *IG/TR* target identification**
- ✓ **For *ABL1* TKD mutation screening**

Discussion

Is *BCR::ABL1* still a relevant MRD marker in Ph+ ALL management ?

Yes !

- ✓ **When no diagnostic sample is available for *IG/TR* target identification**
- ✓ **For *ABL1* TKD mutation screening**
- ✓ **In case of MRD negativity with both *IG/TR* and *BCR::ABL1* MRD**

maintenance or post allo-HSCT

Discussion

Is *BCR::ABL1* still a relevant MRD marker in Ph+ ALL management ? **Yes !**

- ✓ **When no diagnostic sample is available for *IG/TR* target identification**
- ✓ **For *ABL1* TKD mutation screening**
- ✓ **In case of MRD negativity with both *IG/TR* and *BCR::ABL1* MRD**

  maintenance or post allo-HSCT

- ✓ **In case of sustained *IG/TR* MRD negativity and stable *BCR::ABL1* MRD ?**

  ***Follow-up stable disease,* indicate marrow aspirate with *IG/TR* MRD if molecular progression**

Perspectives

- ✓ **In the context of increased survival and decreased rates of allo-HSCT on Ph+ ALL, need to assess the long-term significance of persisting BCR::ABL1-positive cells**
  - **May be associated with TKI potency?**
  - **Long-term outcome? potential for CML-like disease or B-ALL recurrence?**
  - **Is treatment-free remission an option for patients with multilineage Ph+ ALL?**

Aknowledgments

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