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Ph-*like* ALL Relapse
- Case Report -

Young male, 12 year-old
1 month with progressive asthenia and pallor

BC: WBC 90000/mcl (N 3400/ul, Ly 85000/ul), Hb 3,4 g/dl, Platelets 45000/ul

Exams	Findings
Cytomorphology PB	L1 FAB blasts
Immunophenotype	CD45low/CD19+/CD34+, CD10+,CD20+, CD38-,CD22+,HLADR+, CD13-,CD11b-,CD7-,CD5-,CD15-, cyCD79a+, cyIgM-, nTDT+, cyMPO-
Karyotype	Not feasible
FISH	Chr. 4 trisomy and chr. 11 monosomy/deletion NO: t(12;21), t(9;22), 11q23 (MLL)
Molecular	no rearrangements
CSF	No infiltration

Common ALL without gene rearrangements

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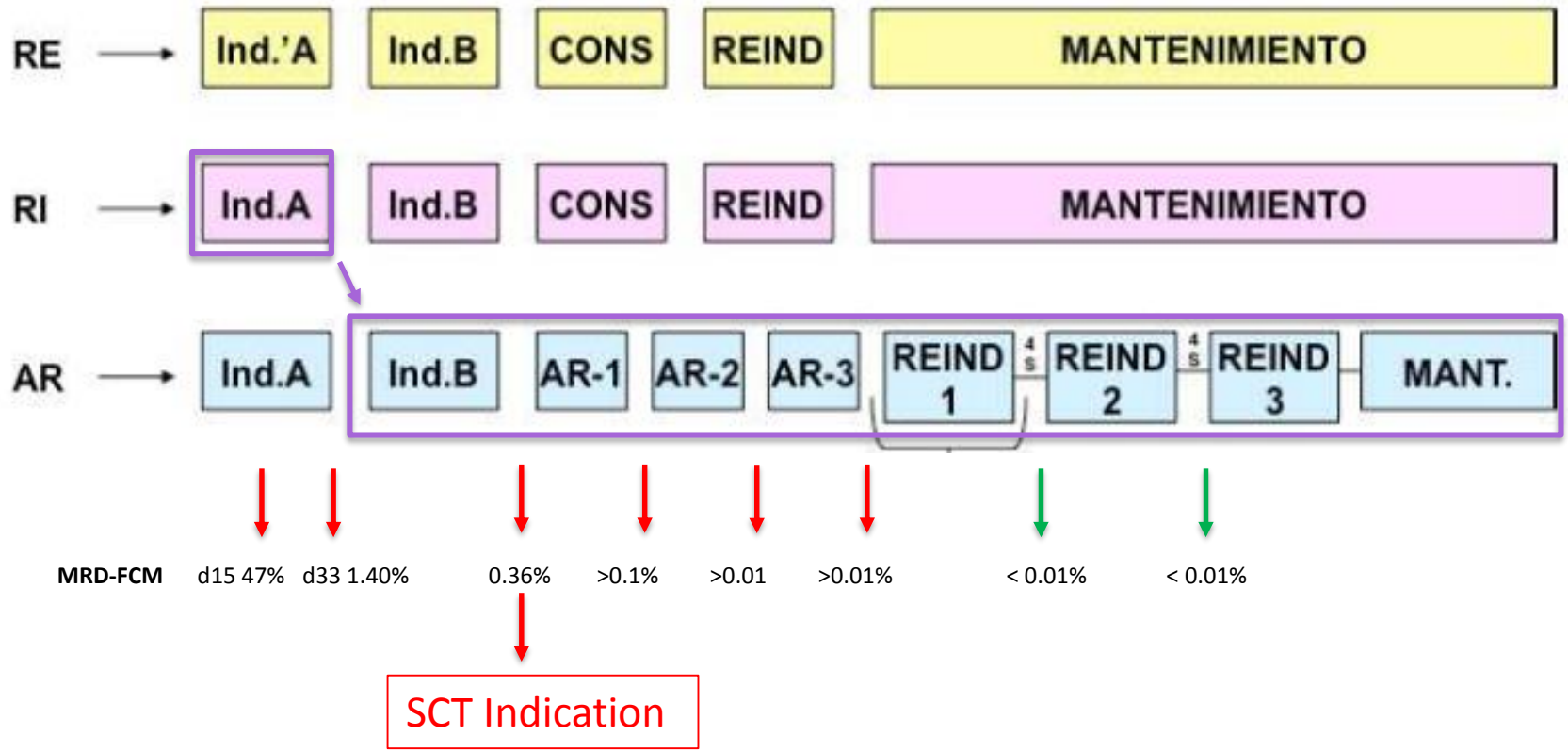
FRONTLINE BFM BACKBONE THERAPY



Family refused HSCT
Persistent positive MRD until Re-Induction Therapy

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Almost 3 years later ….

15 year-old, puberty reached **(10 months after end of Manteinace Therapy)**
Both testicles increased size

BC: WBC 15000/mcl (N 2800/ul, Ly 10600/ul), Hb 16,3 g/dl, Platelets 128000/ul

Exams	Findings
Cytomorphology PB	**L1 FAB blasts (60%)**
Immunophenotype	CD19+/-,CD34+, CD10+, CD20+ → **Common ALL**
Karyotype	Not feasible
FISH	**30% JAK2 (9p24) rupture**
Molecular	No pathological findings
CSF	No infiltration
Test. biopsy	**Bilateral leukemic infiltration**

Additional biological studies in first ALL samples:
FISH 50% JAK2 rupture

Late combined relapse of Ph-like ALL

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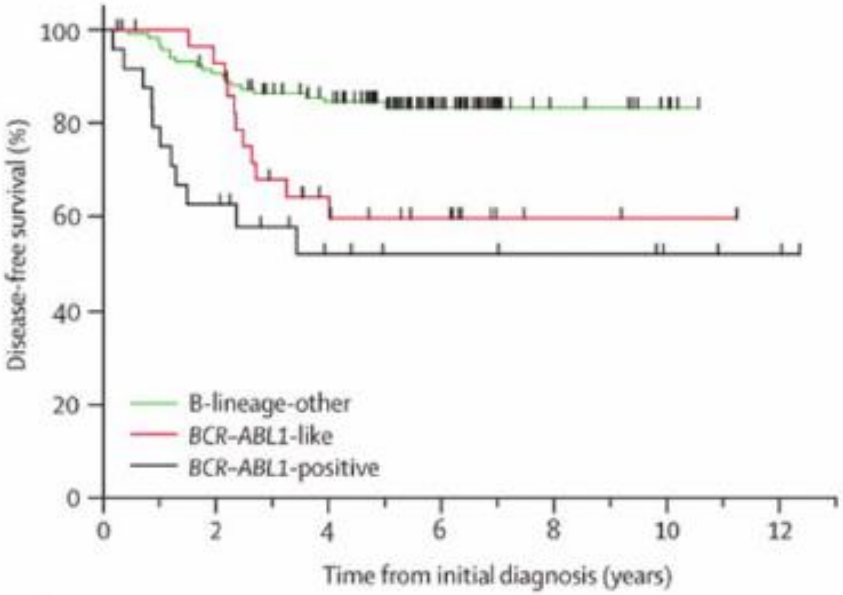
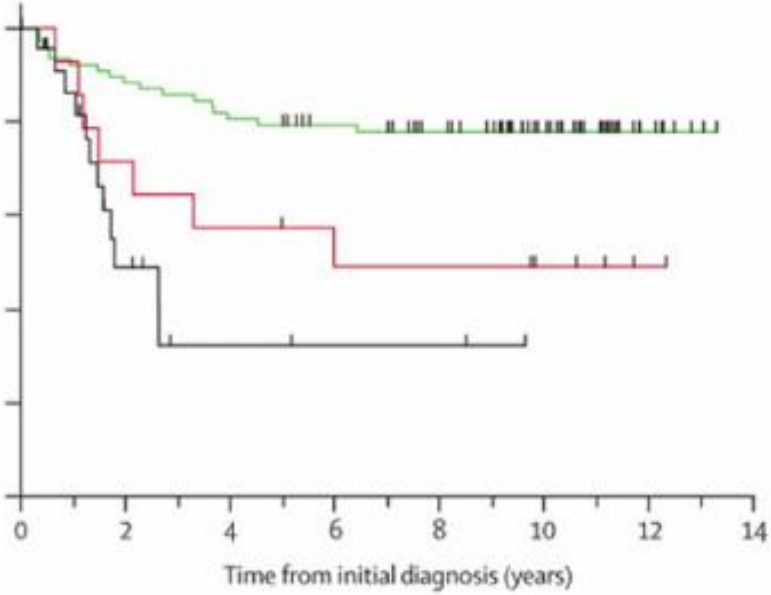
Ph-*like* ALL

A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study

COALL



DCOG



Number at risk																							
B-lineage-other	114	106	96	87	72	47	19	9	8	4	0	71	68	66	62	61	56	55	49	45	31	19	8
BCR-ABL1-like	28	26	18	14	11	9	3	2	2	1	1	13	10	9	8	7	6	6	6	6	4	3	1
BCR-ABL1-positive	19	15	11	8	6	6	6	5	4	3	2	18	8	3	3	3	2	2	2	1	0	0	0

Monique L. Den Boer, Lancet Oncology 2009

pB-ALL HR subset (15-20%): gen expression pattern similar to BCR-ABL positive ALL

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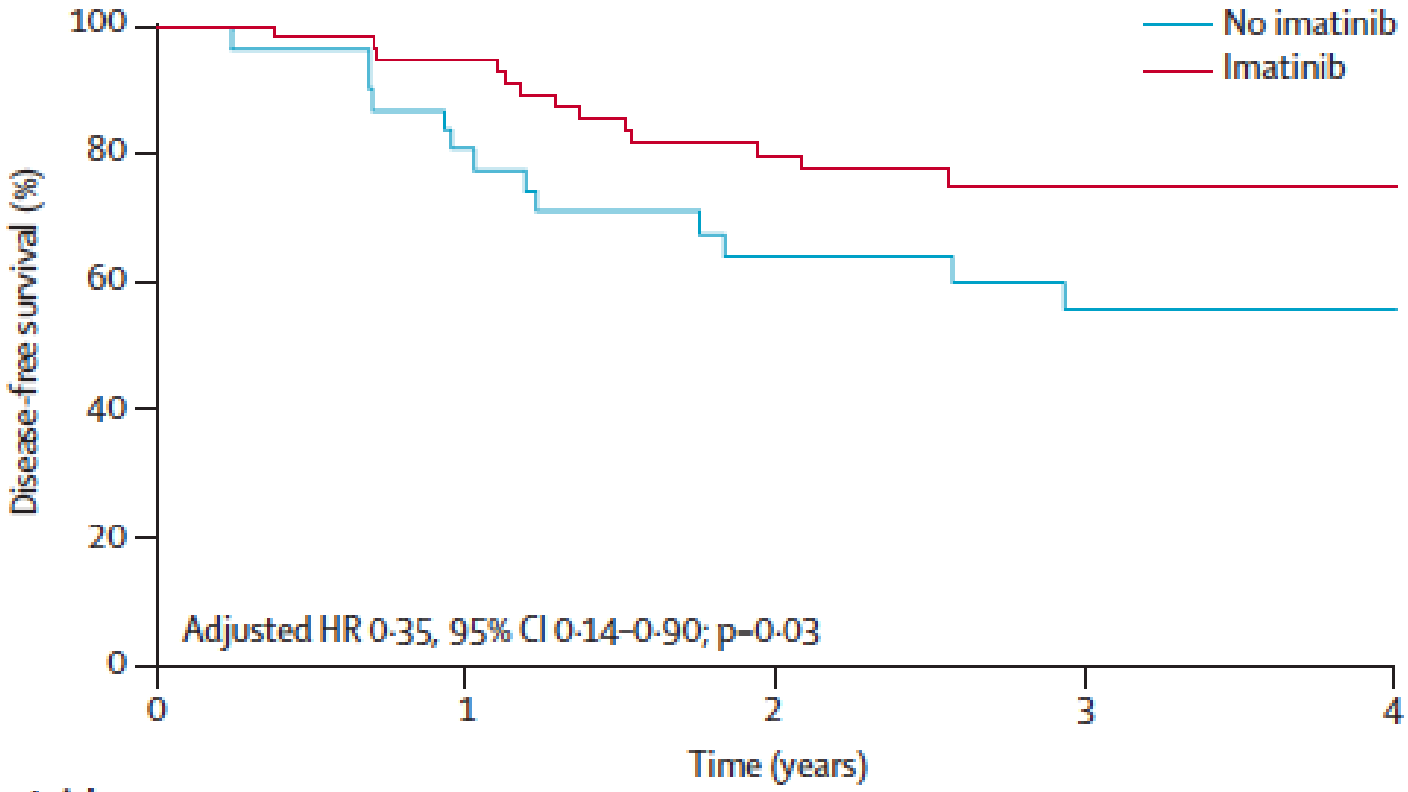
Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study

Andrea Biondi, Martin Schrappe, Paola De Lorenzo, Anders Castor, Giovanna Lucchini, Virginie Gandemer, Rob Pieters, Jan Stary, Gabriele Escherich, Myriam Campbell, Chi-Kong Li, Ajay Vora, Maurizio Aricò, Silja Röttgers, Vaskar Saha, Maria Grazia Valsecchi



Number at risk

No imatinib	31	30	27	25	21	21	17	15	10
Imatinib	58	57	53	50	41	37	28	19	15

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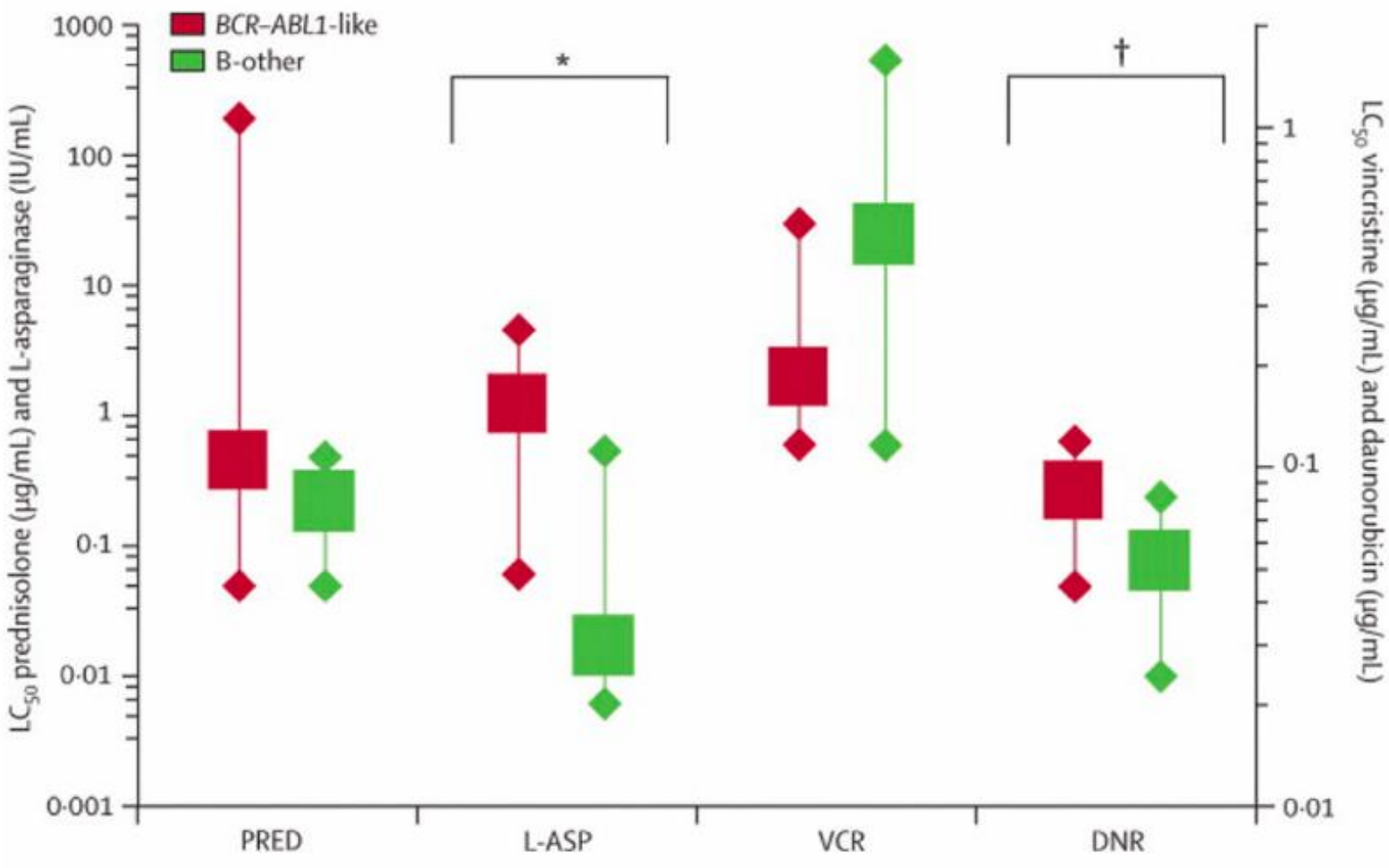
Ph-*like* ALL



Monique L. Den Boer, Lancet 2009

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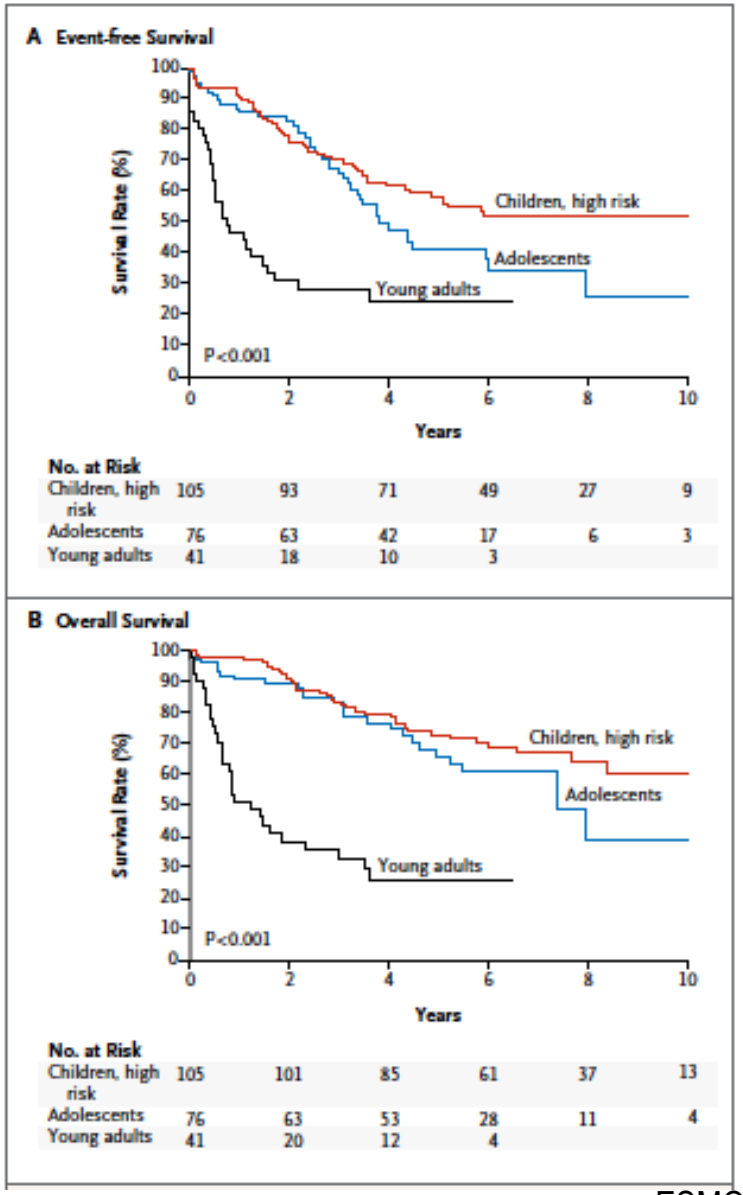
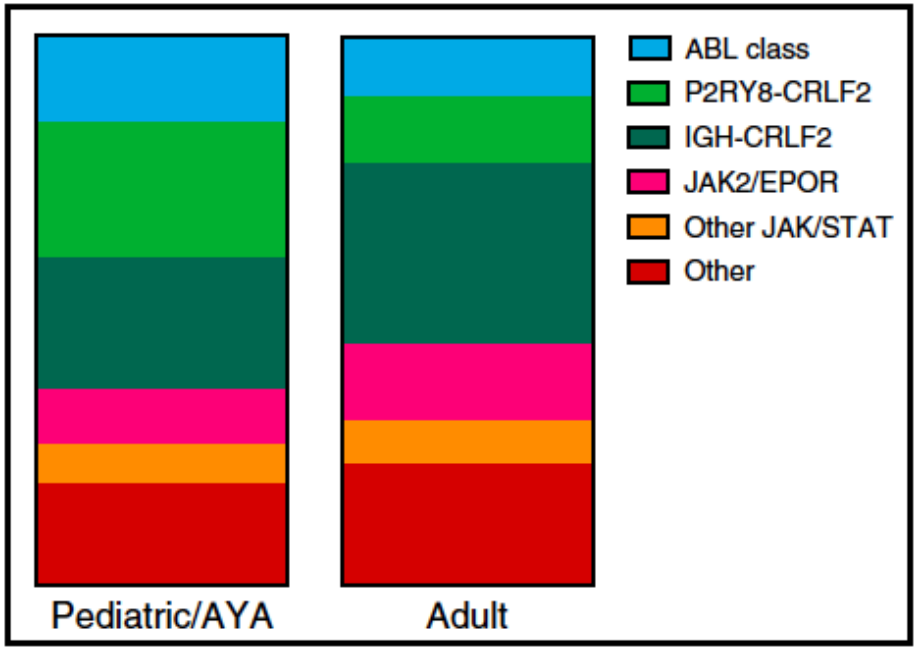
Ph-*like* ALL

Targetable Kinase-Activating Lesions in Ph-like Acute Lymphoblastic Leukemia



K.G. Roberts et al, nejm 2014



Tasia et al, blood 2017

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Ph-*like* ALL

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Daniel A. Arber,[1] Attilio Orazi,[2] Robert Hasserjian,[3] Jürgen Thiele,[4] Michael J. Borowitz,[5] Michelle M. Le Beau,[6] Clara D. Bloomfield,[7] Mario Cazzola,[8] and James W. Vardiman[9]

BLOOD, 19 MAY 2016 • VOLUME 127, NUMBER 20

Ph-like provisional entity

Table 1. Kinase fusions identified in Ph-like ALL

Kinase gene	TKI	Fusion partners identified to date, n	5′ Fusion partners
ABL1	Imatinib/dasatinib	13	*CENPC, ETV6, FOXP1, LSM14A, NUP153, NUP214, RANBP2, RCSD1, SFPQ, SNX1, SNX2, SPTNA1, ZMIZ1*
ABL2	Imatinib/dasatinib	3	*PAG1, RCSD1, ZC3HAV1*
CSF1R	Imatinib/dasatinib	3	*MEF2D, SSBP2, TBL1XR1*
PDGFRA	Imatinib/dasatinib	1	*FIP1L1*
PDGFRB	Imatinib/dasatinib	8	*ATF7IP, EBF1, ETV6, SNX29, SSBP2, TNIP1, ZEB2, ZMYND8*
LYN	Imatinib/dasatinib	2	*GATAD2A, NCOR1*
CRLF2	JAK2 inhibitor	3	*CSF2RA, IGH, P2RY8*
JAK2	JAK2 inhibitor	21	*ATF7IP, BCR, EBF1, ETV6, GOLGA5, HMBOX1, OFD1, PAX5, PCM1, PPFIBP1, RFX3, SMU1, SNX29, SSBP2, STRN3, TERF2, TPR, USP25, ZBTB46, ZNF274, ZNF340*
EPOR	JAK2 inhibitor	4	*IGH, IGK, LAIR1, THADA*
TSLP	JAK2 inhibitor	1	*IQGAP2*
TYK2	TYK2 inhibitor	3	*MYB, SMARCA4, ZNF340*
IL2RB	JAK1/JAK3 inhibitor	1	*MYH9*
NTRK3	TRK inhibitor	1	*ETV6*
PTK2B	FAK inhibitor	3	*KDM6A, STAG2, TMEM2*
FGFR1	Ponatinib	1	*BCR*
FLT3	FLT3 inhibitor	1	*ZMYM2*
DGKH		1	*ZFAND3*
BLNK		1	*DNTT*
CBL		1	*KANK1*

Tasian et al, blood 2017

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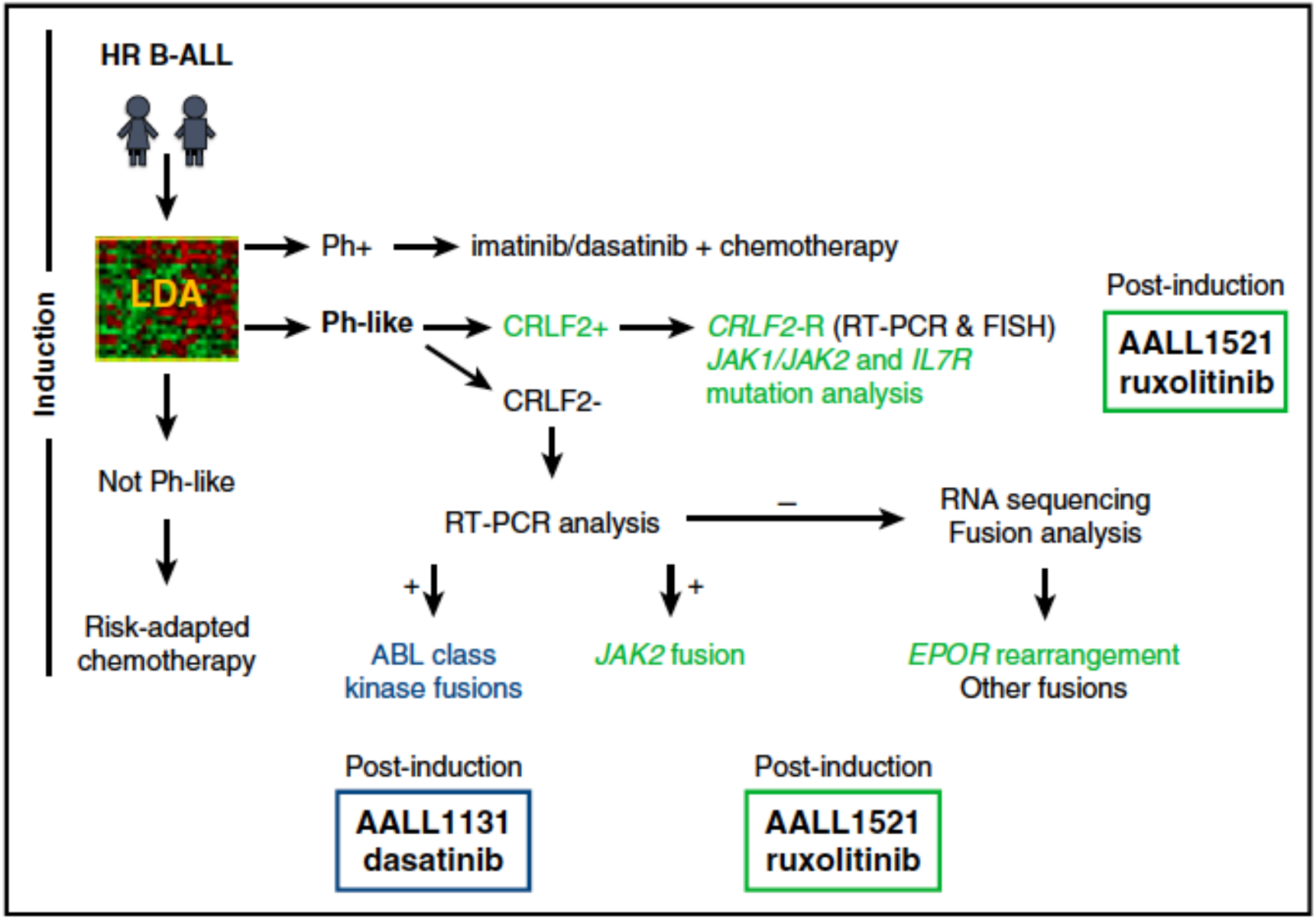
Ph-*like* ALL



Tasian et al, blood 2017

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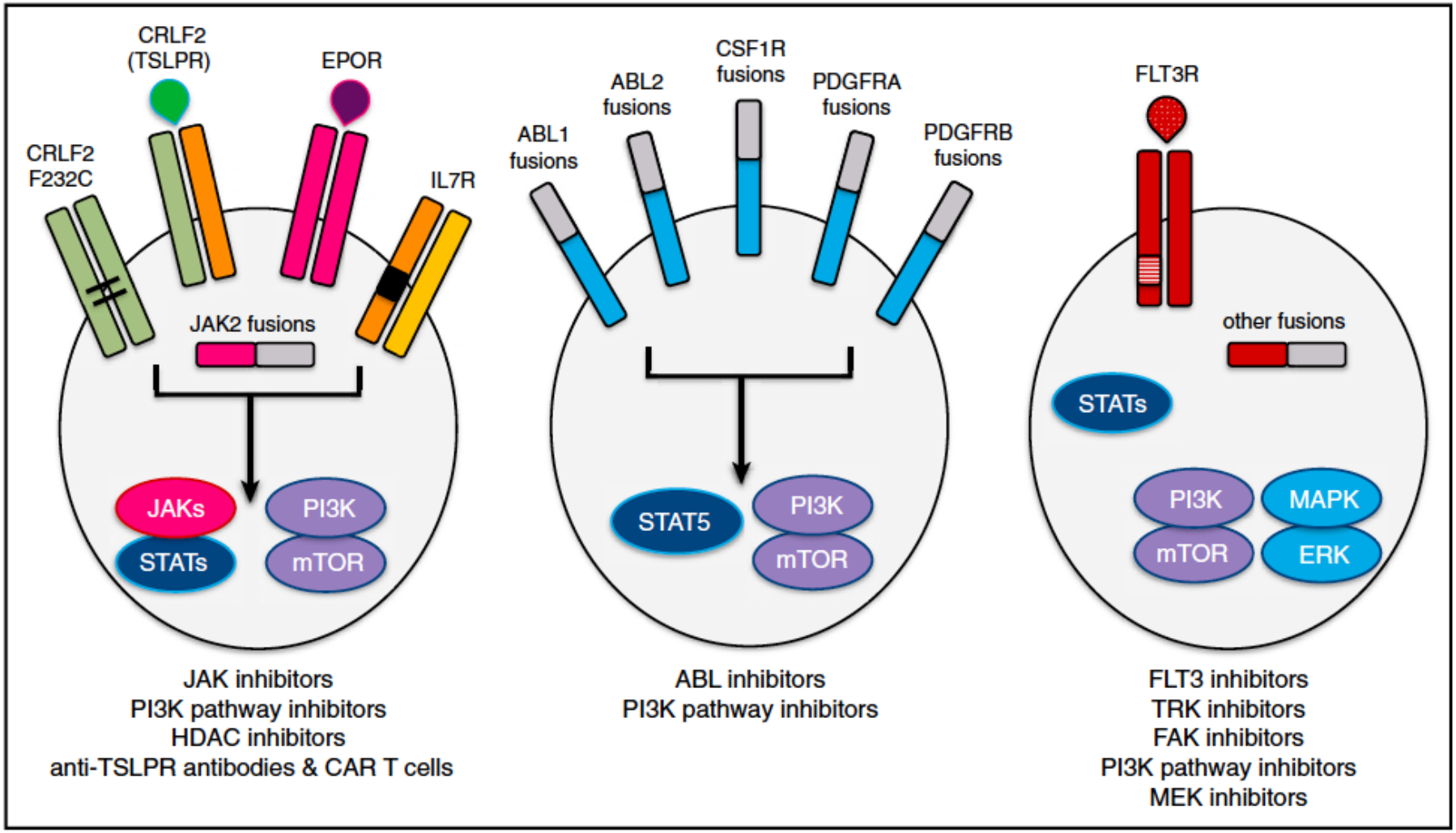
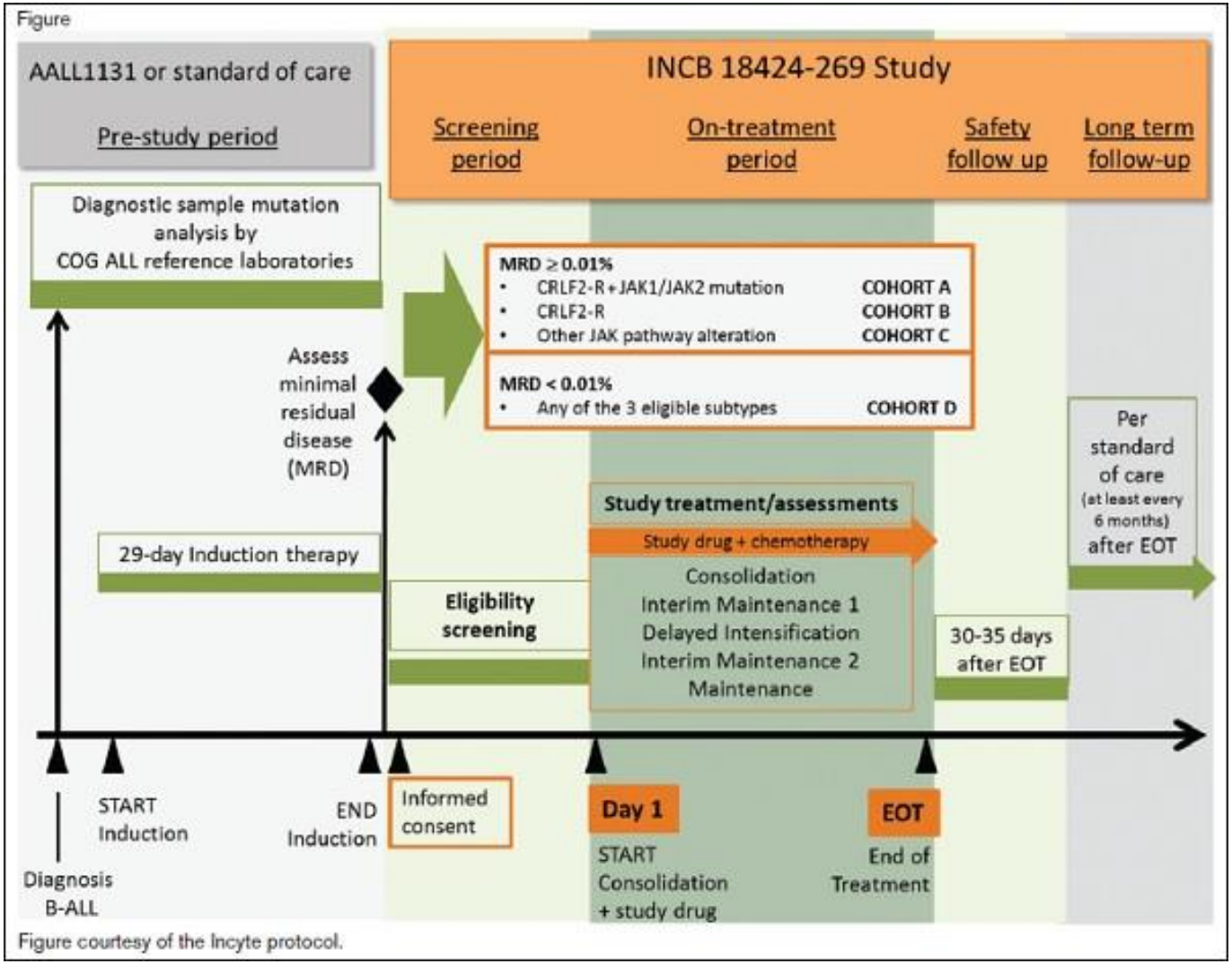


Figure 3. Schema of activated kinase signaling in Ph-like ALL. Kinase fusions and other alterations in Ph-like ALL activate oncogenic signal transduction and may be targetable by specific kinase inhibitors and other therapeutic agents.

Tasian et al, blood 2017



A Phase 2 Study of the JAK1/JAK2 Inhibitor Ruxolitinib with Chemotherapy with De Novo High-Risk CRLF2-Rearranged and/or JAK Pathway–Mutant Acute Lymphoblastic Leukemia. NCT02723994. *Patients 1-21 years*

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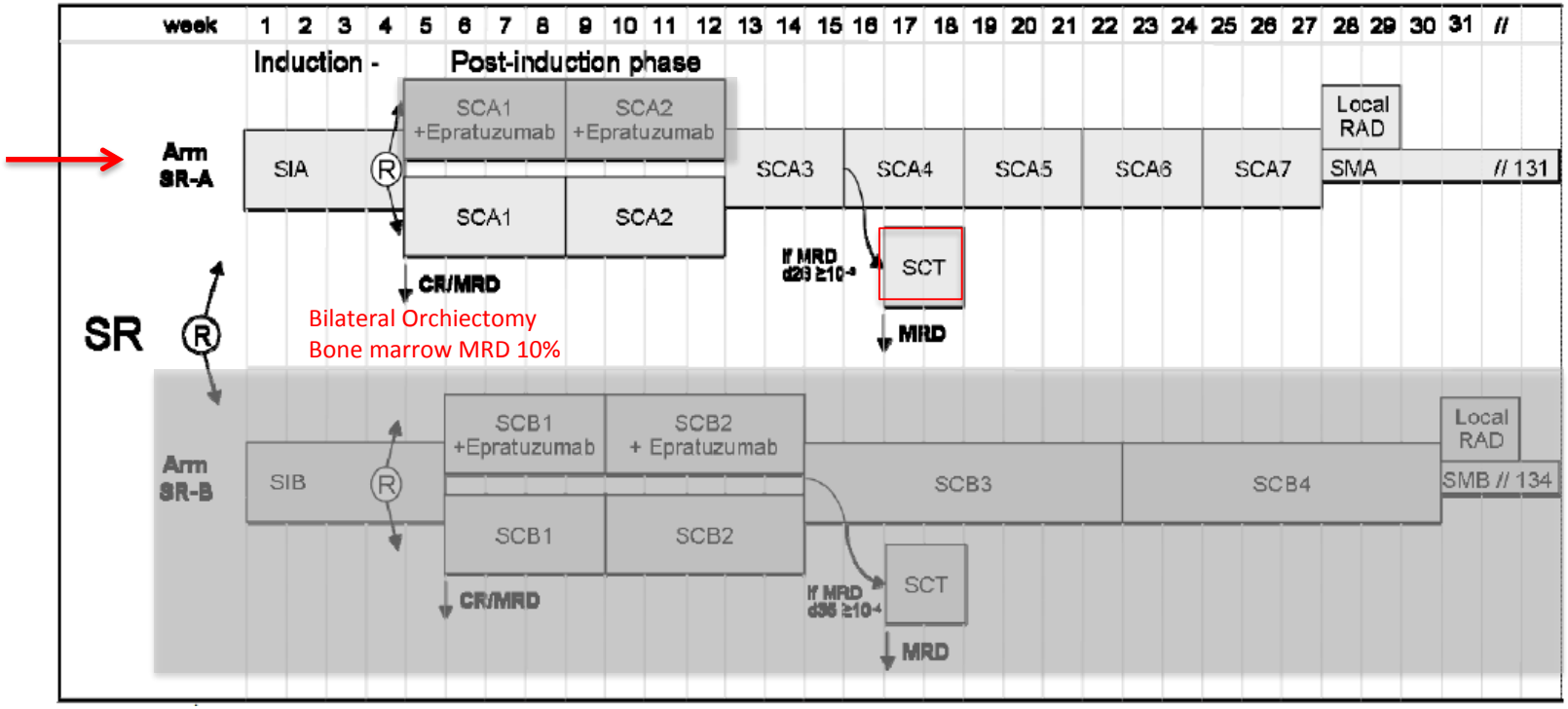
Relapse Therapy: IntReALL 2010 (NCT01802814; inclusion 1-18)

CASE REPORT

Definition of IntReALL SR/HR 2010 risk groups

	Immunophenotype: B-cell precursor			Immunophenotype: (pre) T		
\ Site Time-point \	Extramed. Isolated	Bone marrow combined	Bone marrow isolated	Extramed. isolated	Bone marrow combined	Bone marrow isolated
Very early	HR	HR	HR	HR	HR	HR
Early	SR	SR	HR	SR	HR	HR
Late	SR	SR	SR	SR	HR	HR

2 TREATMENT SCHEDULE INTREALL SR 2010



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DISCUSSION

- Philadelphia-like pB ALL: novel provisional entity (WHO-2016)
- Incidence and poorer outcome increase with age
- Patients could benefit from a more intensive conventional treatment in front-line therapy (HR-therapy +/- SCT)
- Trials indentifying Ph-like ALL and testing efficacy and safety of target therapy are needed
- Inclusion of children and AYA in risk adapted trials recommended

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ESMO Preceptorship Programme

Thank you for your attention!