Case SH2017-0119: A 22-year-old male with a Ph-like mixed phenotype acute leukemia (B/myeloid)

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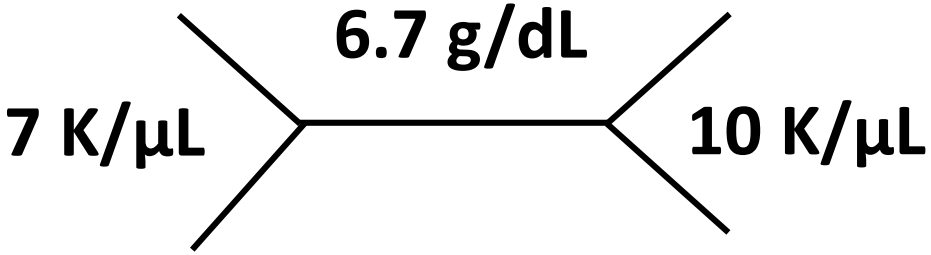
Clinical history

- A 22-year-old male with a one-month history of worsening dyspnea on exertion and subsequent headaches, oral lesions, and gingival bleeding.

Laboratory findings



- Peripheral blood differential count:

Blasts 41%

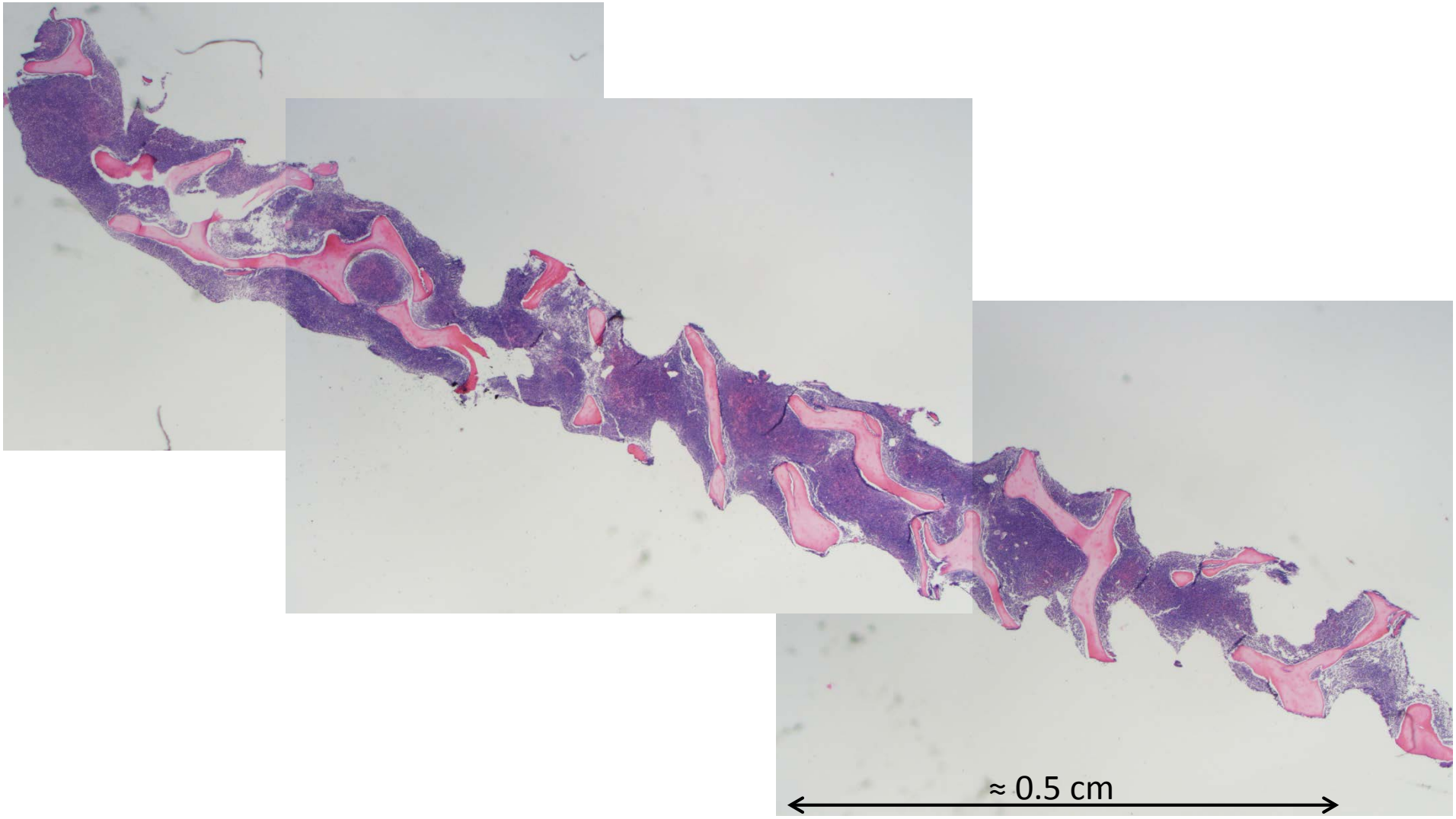
Neutrophils 19%

Lymphocytes 36%

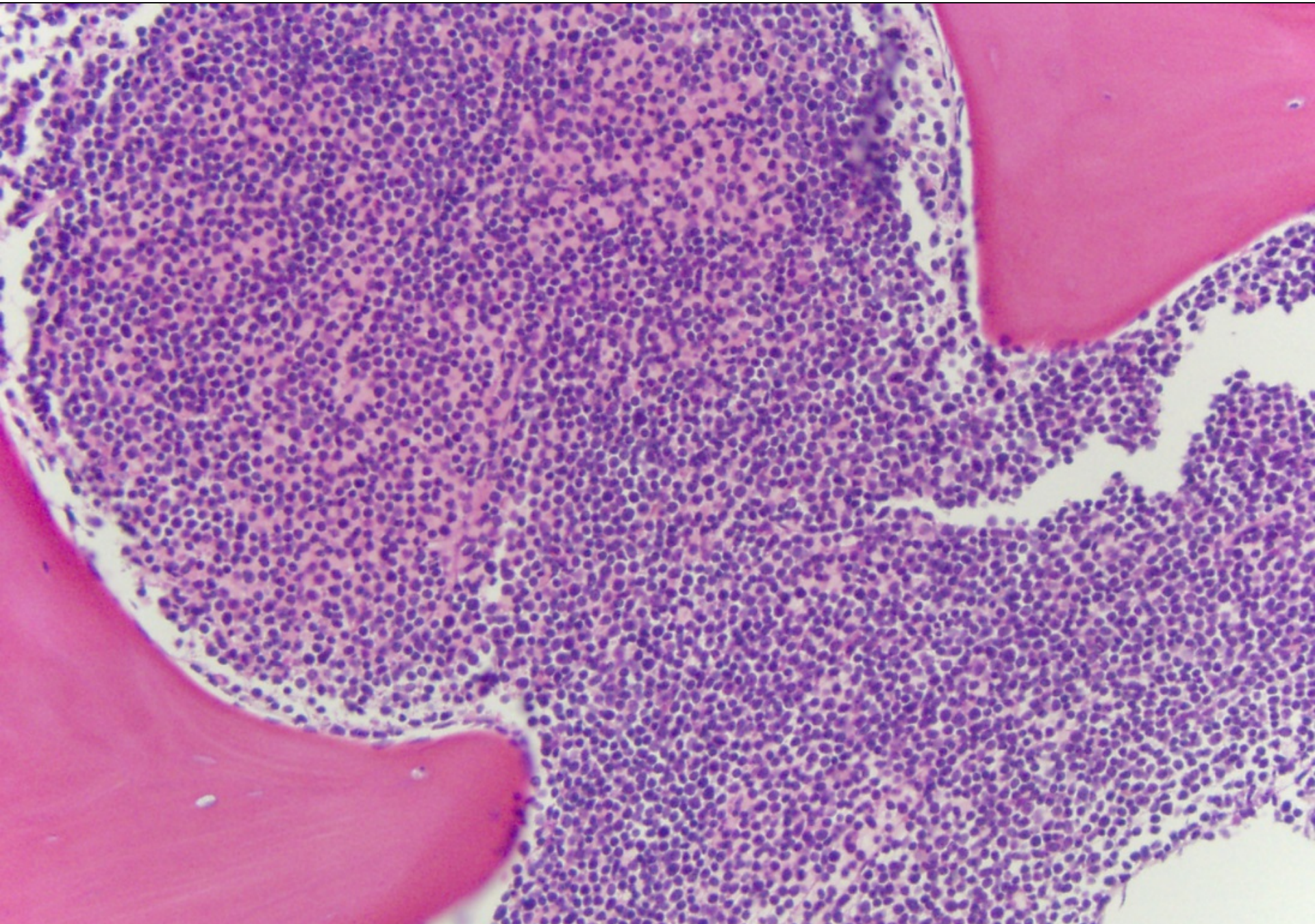
Monocytes 3%

Eosinophils 1%

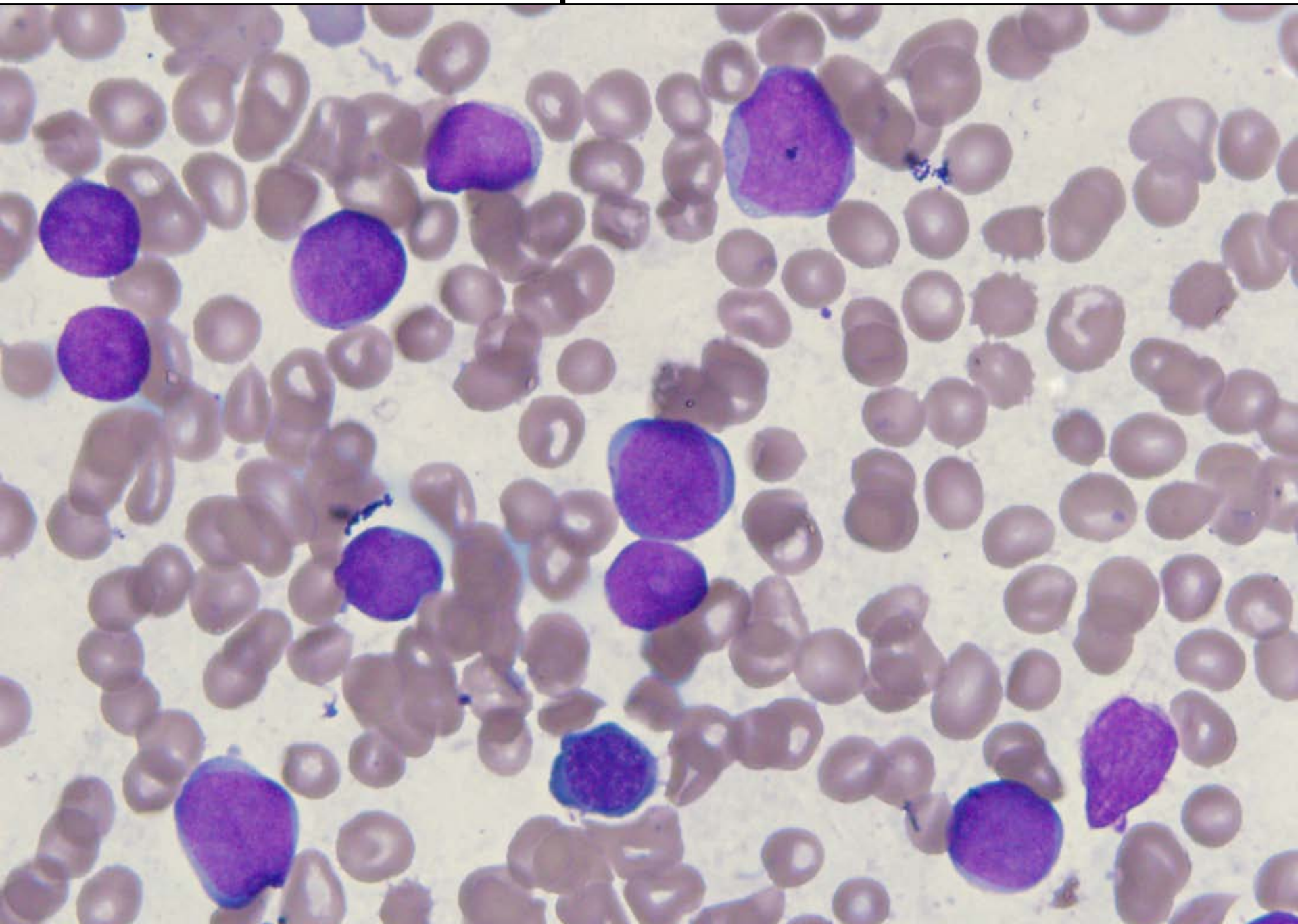
Core biopsy



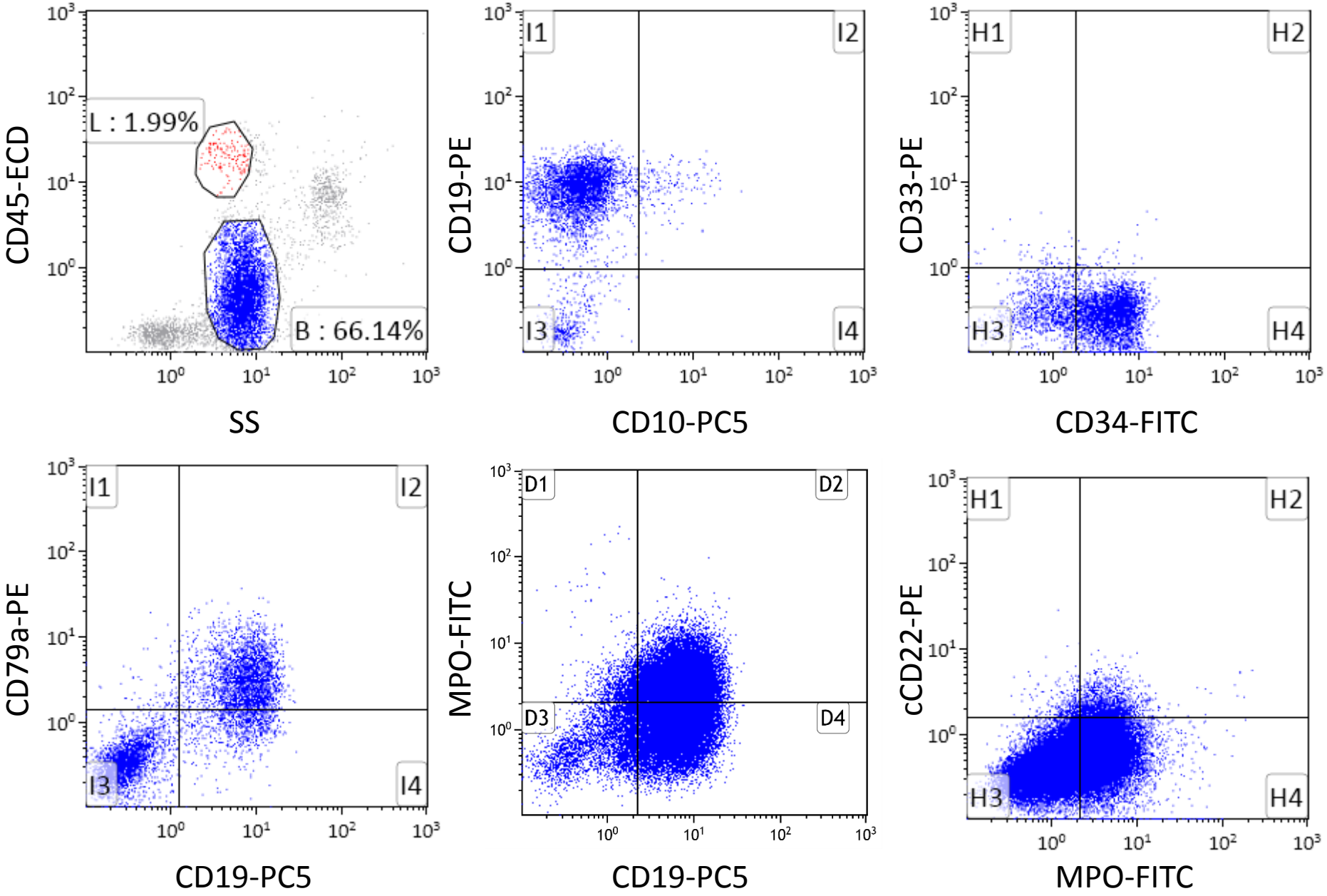
Core biopsy



Aspirate smear



Flow cytometry



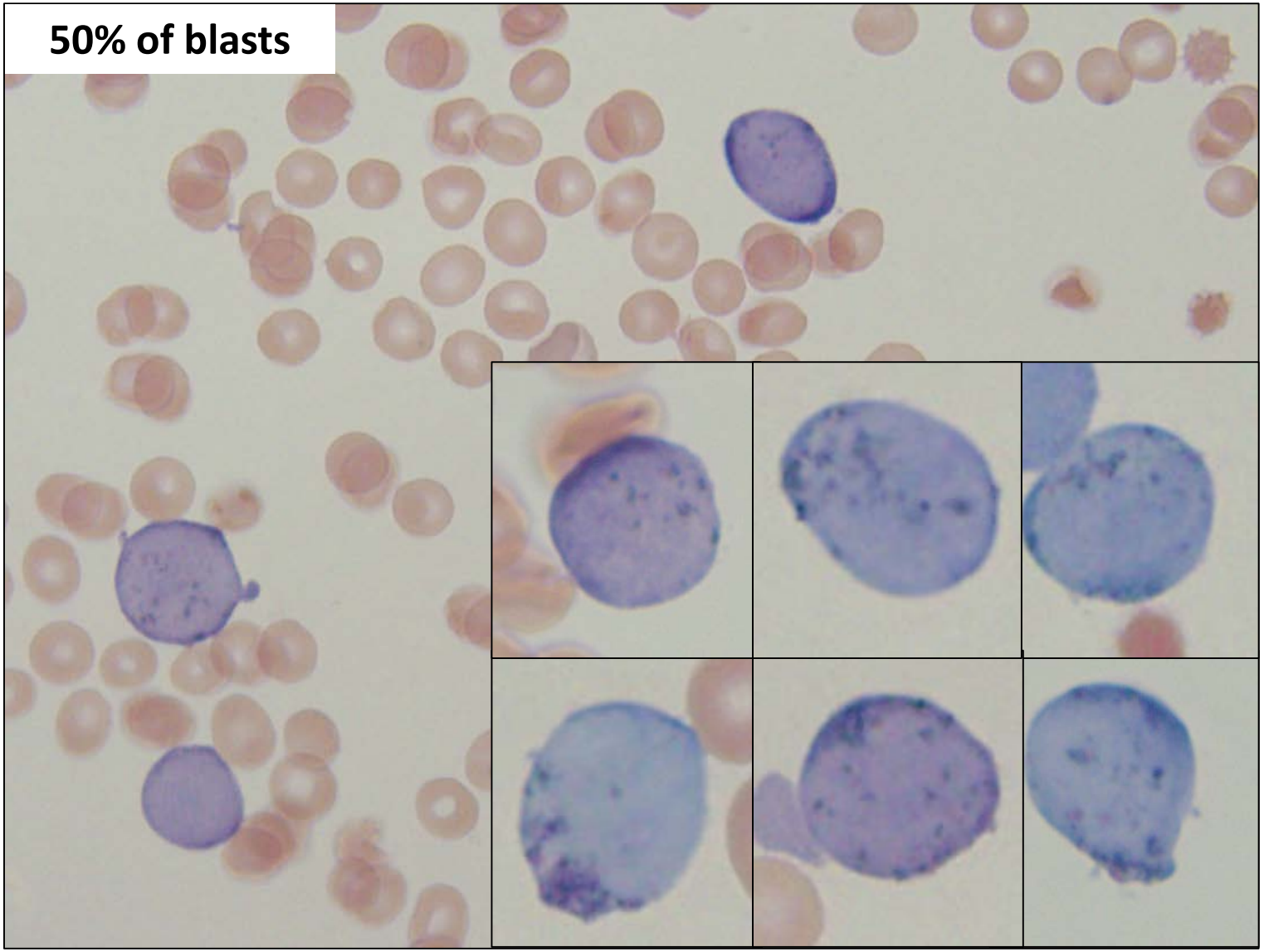
Immunophenotypic summary

Blasts (positive flow cytometry markers)

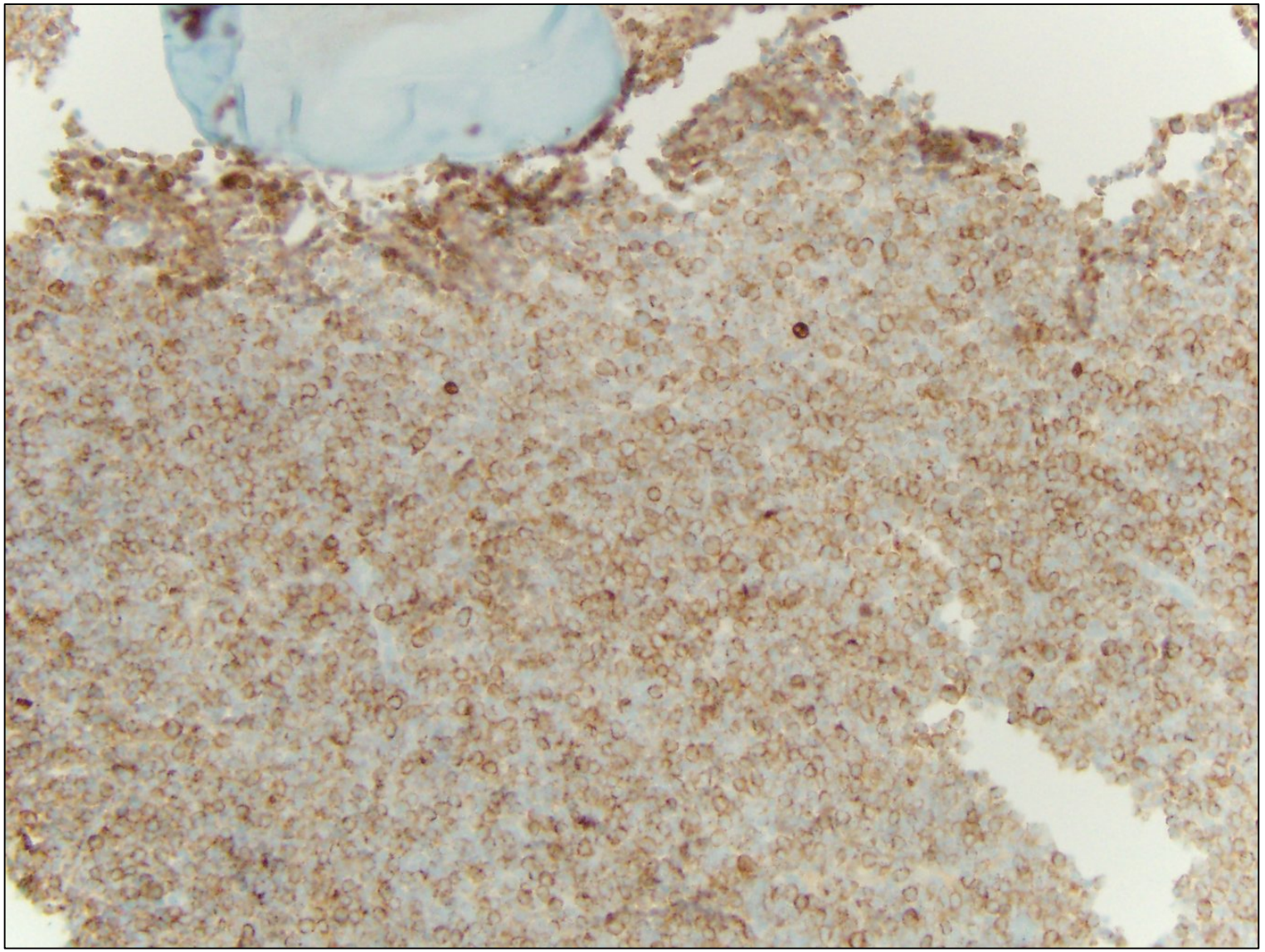
- CD19 (moderate)
- CD79a (moderate)
- CD10 (dim, very minor subset)
- CD20 (dim, minor subset)
- CD22 (surface/cytoplasmic, dim to negative)
- CD34 (dim, subset)
- CD45 (dim to negative)
- TdT (moderate, subset)
- MPO (dim, subset)

Negative: CD11c, CD13, CD14, CD33, CD38, CD56, CD117, T cell markers

Aspirate smear – Myeloperoxidase cytochemistry



Core biopsy – Myeloperoxidase immunohistochemistry



Panel differential diagnosis

Mixed phenotype acute leukemia, B/myeloid

vs.

B-ALL (with isolated MPO expression)

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

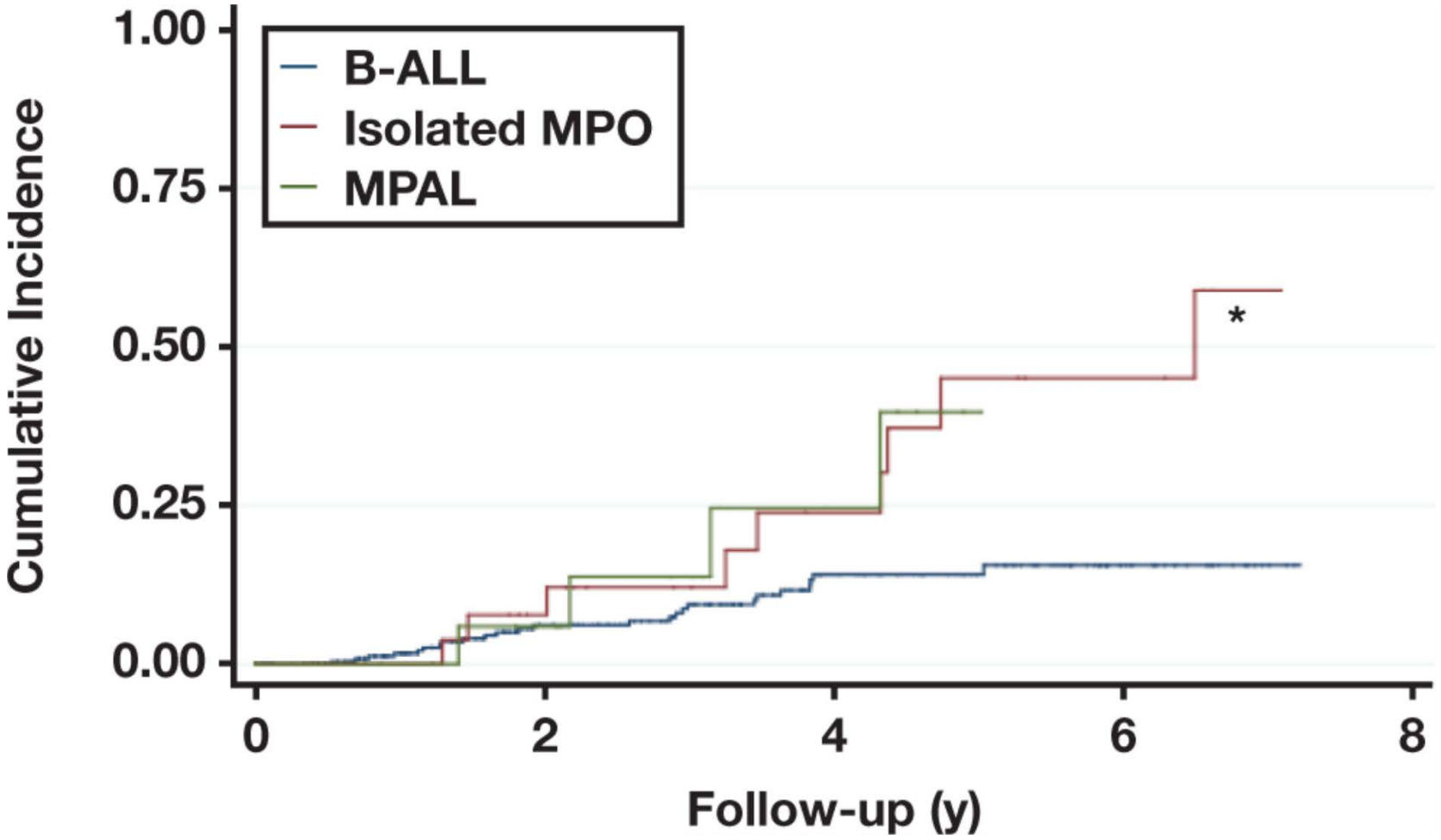
Daniel A. Arber,[1] Attilio Orazi,[2] Robert Hasserjian,[3] Jürgen Thiele,[4] Michael J. Borowitz,[5] Michelle M. Le Beau,[6] Clara D. Bloomfield,[7] Mario Cazzola,[8] and James W. Vardiman[9]

Table 19. Criteria for lineage assignment for a diagnosis of MPAL

ALL, but only for MPAL. It is also now recognized that some cases of otherwise typical B-ALL with homogeneous expression of lymphoid markers on a single blast population may express low-level myeloperoxidase using immunophenotypic methods without other evidence of myeloid differentiation. Because the clinical significance of this finding has not yet been established, it is recommended that care be taken before making a diagnosis of B/myeloid MPAL when low-intensity myeloperoxidase (MPO) is the only myeloid-associated feature. Multiparameter flow cytometry is the method of choice for recognizing MPAL; even when there

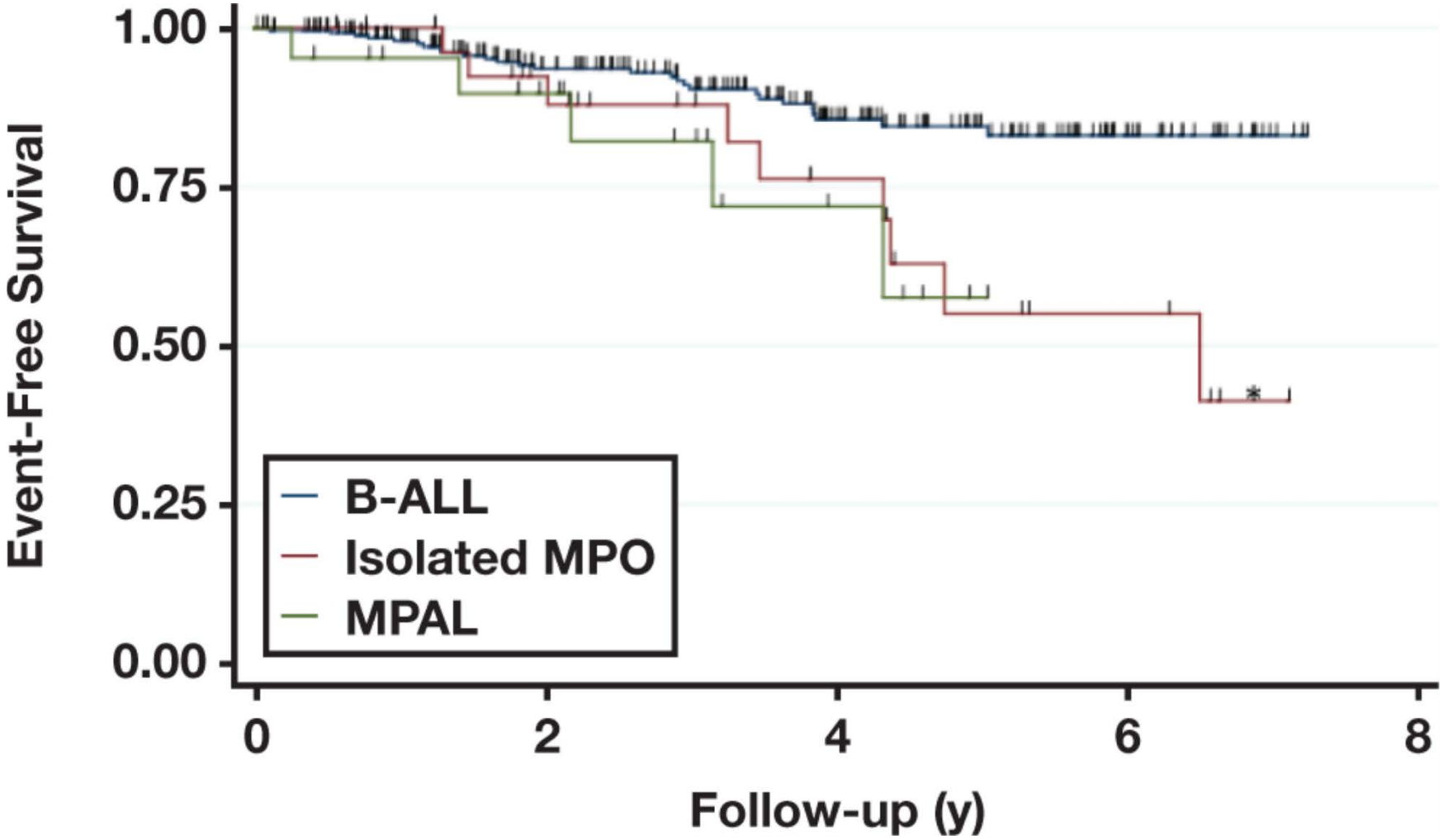
cytoplasmic CD22, or CD10

B-ALL with isolated MPO expression shows higher cumulative incidence of relapse



Oberley et al. *American Journal of Clinical Pathology*, Volume 147, Issue 4, 1 April 2017, Pages 374–381

B-ALL with isolated MPO expression shows worse event-free survival



Oberley et al. *American Journal of Clinical Pathology*, Volume 147, Issue 4, 1 April 2017, Pages 374–381

Cytogenetics/Molecular analysis

Karyotype:

46,XY[20] (normal male karyotype)

FISH:

Negative for *BCR/ABL1* fusion and *KMT2A* (*MLL*) rearrangement.

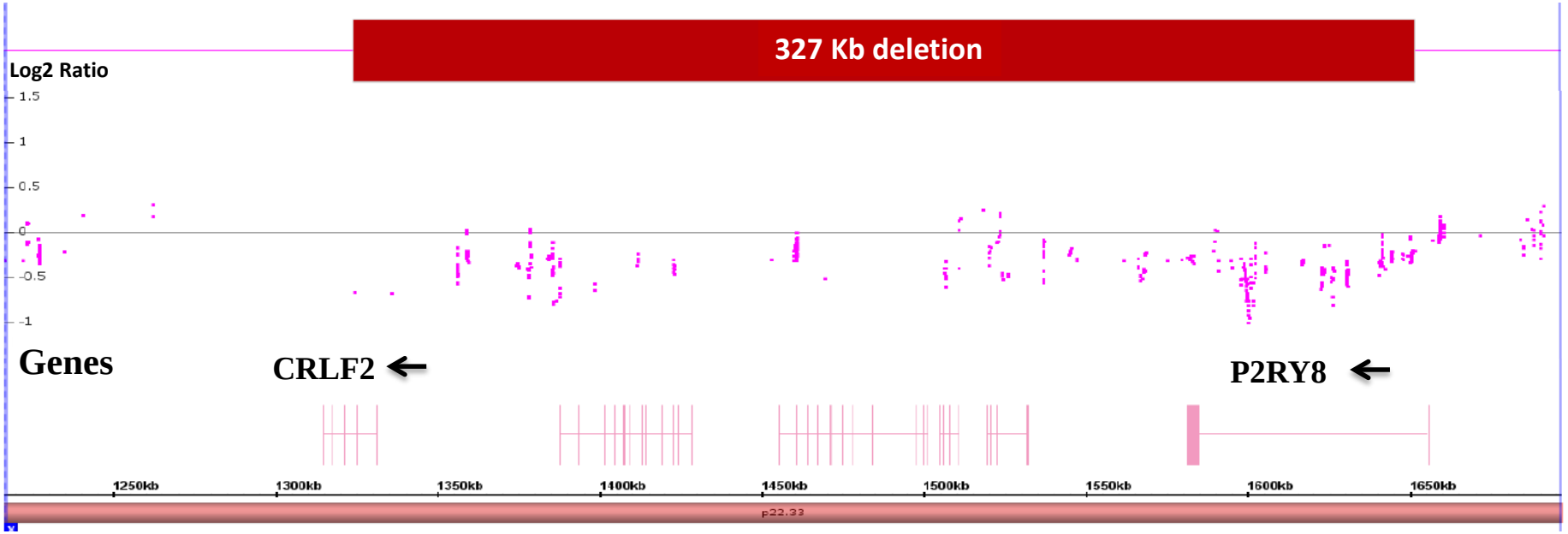
Molecular genetics:

Negative for *JAK2* V617F mutation.

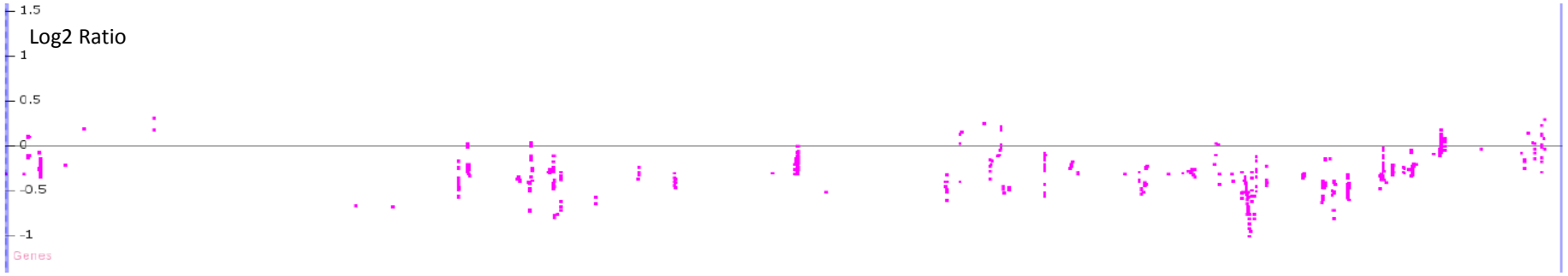
Positive for JAK1 c.1972G>T;p.V658F mutation.

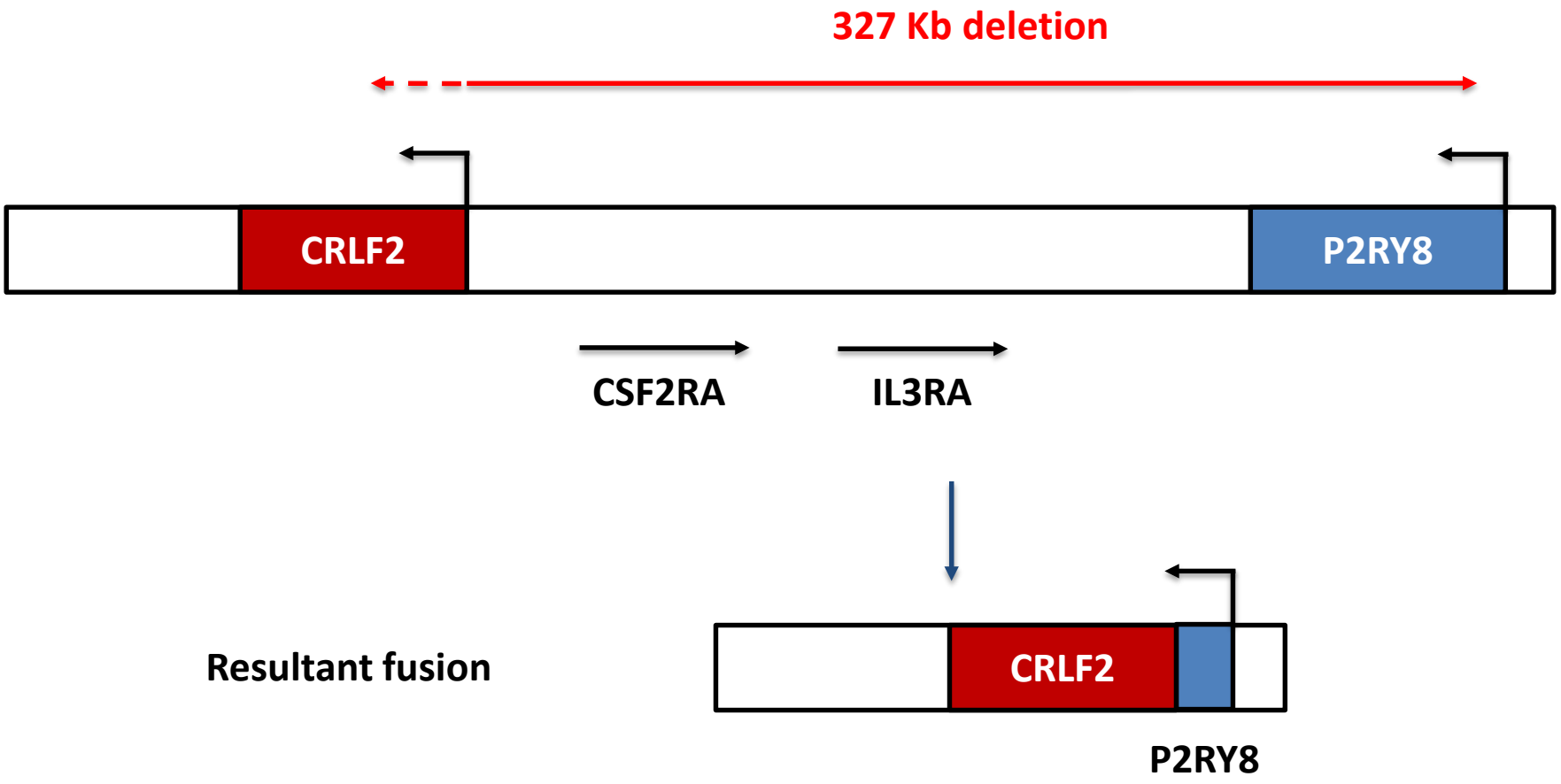
Positive for CDKN2A c.151-6delTinsCCAGGGG mutation.

Cytogenomic array:



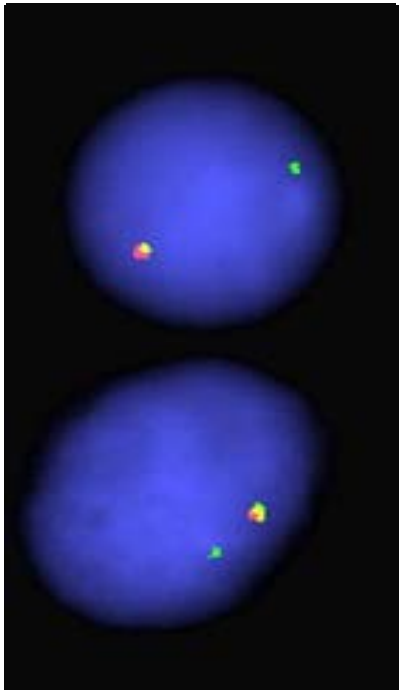
Formation of *P2RY8-CRLF2* fusion in pseudoautosomal region 1 (PAR1)

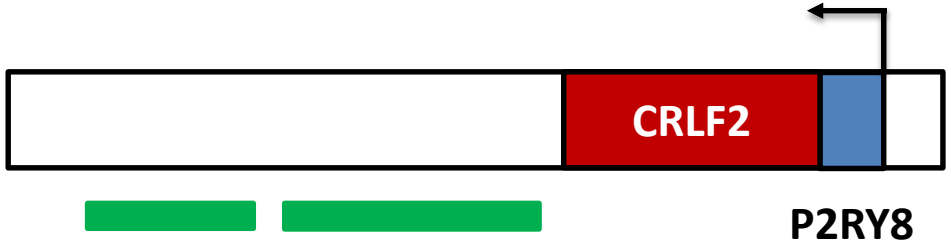




Formation of *P2RY8-CRLF2* fusion in pseudoautosomal region 1 (PAR1)

FISH *CRLF2* breakapart probe





Loss of red-orange signal

Historical context of BCR-ABL1-like vs. Ph-like B-ALL

Den Boer et al, The Lancet February 2009 Vol 10

COALL discovery cohort
DCOG validation cohort

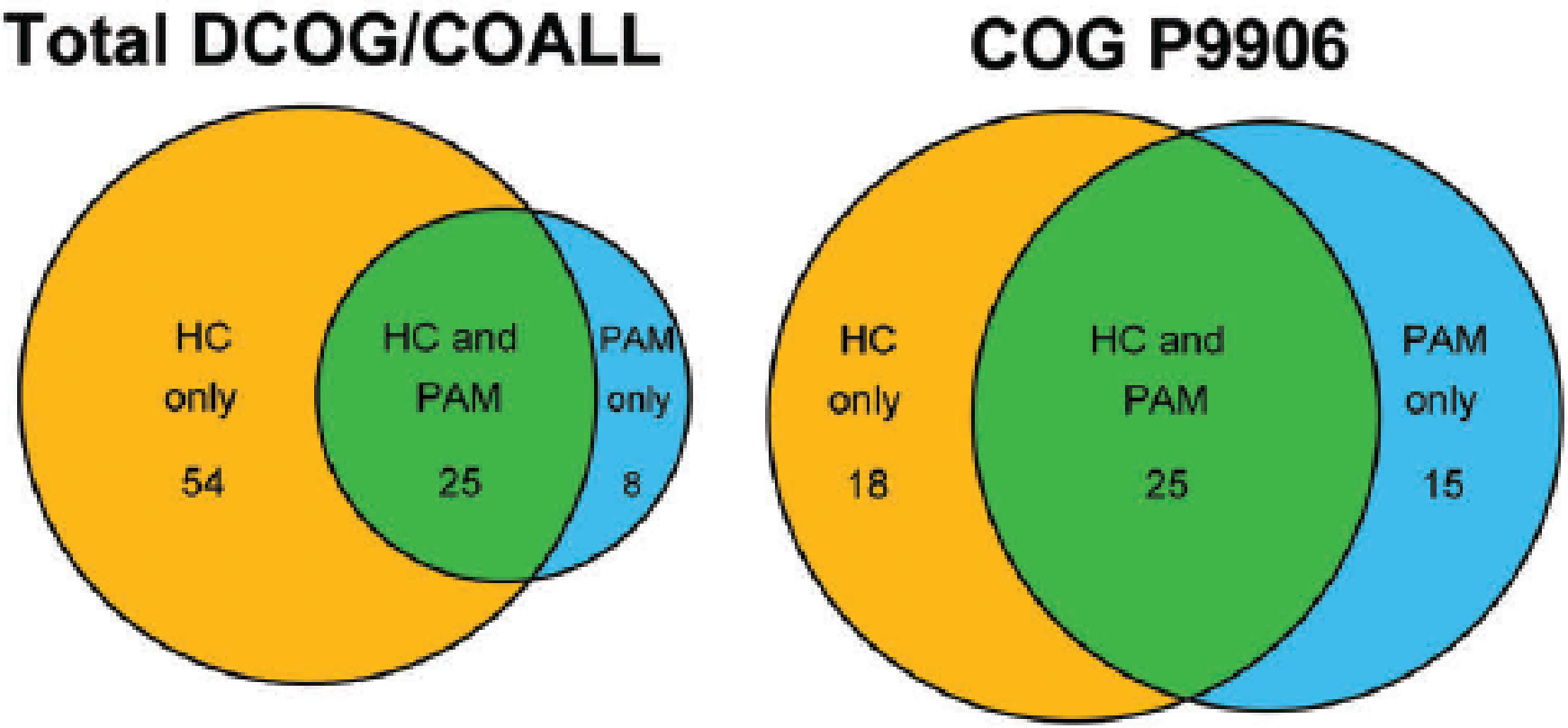
Hierarchical clustering (HC) of 110 gene probe sets identified to predict the major pediatric ALL subtypes (T-cell ALL, *ETV6-RUNX1*, high-hyperdiploidy, *TCF3* or *MLL*-rearranged, *BCR-ABL1*). "*BCR-ABL1*-like"

Mullighan et al, N Engl J Med 2009; 360:470-480

COG P9906 discovery cohort
St. Jude validation cohort

"Ph-like signature" is based on the **prediction analysis of microarrays (PAM)** classifier consisting of 257 gene probe sets trained on *BCR-ABL1*-positive cases.

BCR-ABL1-like cases in pediatric acute lymphoblastic leukemia: a comparison between DCOG/Erasmus MC and COG/St. Jude signatures



Haematologica 2015; 100:e354

CLINICA

The NEW ENGLAND JOURNAL of MEDICINE

Ph-like adults

Brief

ORIGINAL ARTICLE

Regu

blood

LYMPHO

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

K.G. Roberts, Y. Li, D. Payne-Turner, R.C. Harvey, Y.-L. Yang, D. Pei, K. McCastlain, L. Ding, C. Lu, G. Song, J. Ma, J. Becksfort, M. Rusch, S.-C. Chen, J. Easton, J. Cheng, K. Boggs, N. Santiago-Morales, I. Iacobucci, R.S. Fulton, J. Wen, M. Valentine, C. Cheng

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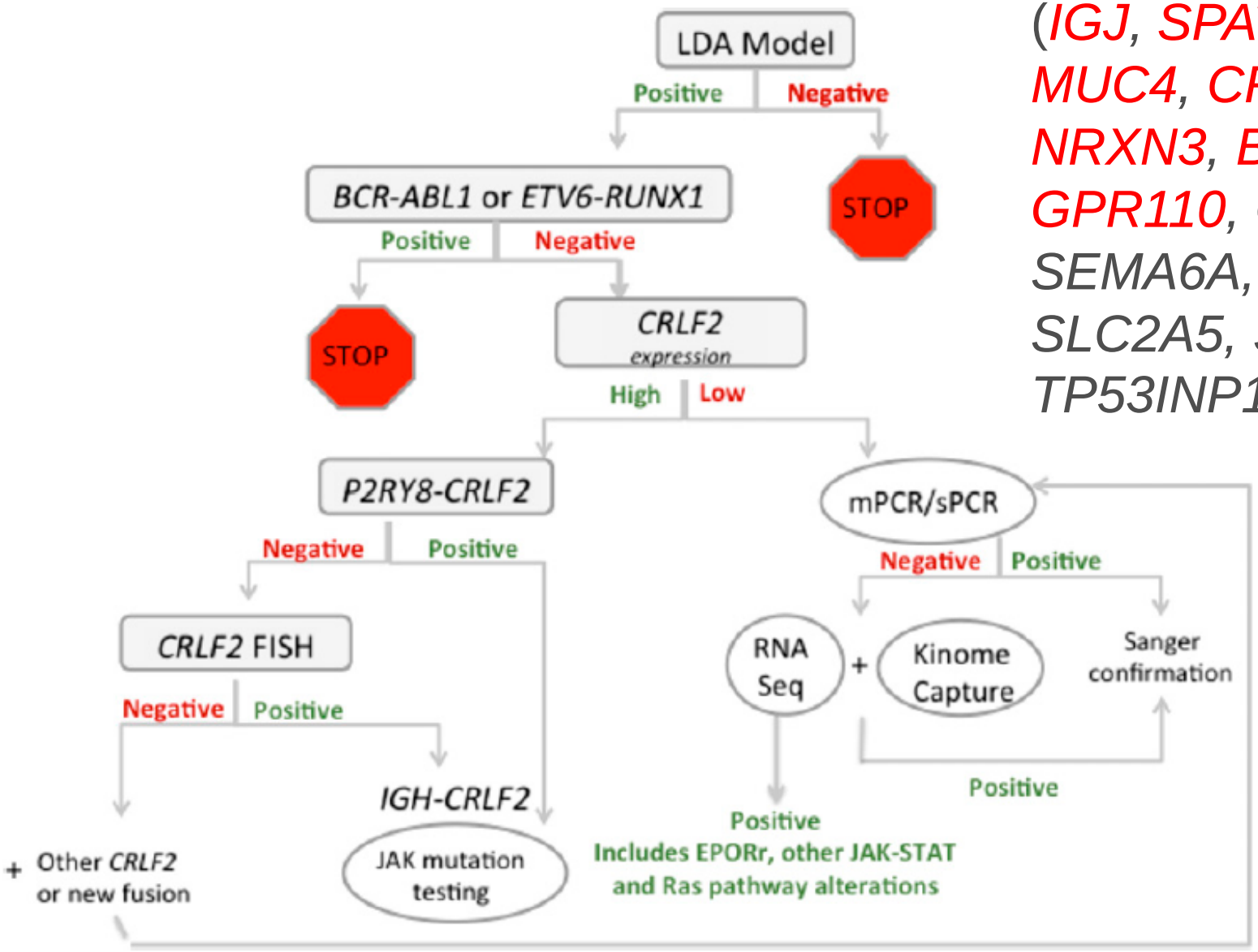
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

High Frequency and Poor Outcome of Philadelphia Chromosome–Like Acute Lymphoblastic Leukemia in Adults

Kathryn G. Roberts, Zhaohui Gu, Debbie Payne-Turner, Kelly McCastlain, Richard C. Harvey, I-Ming Chen, Deqing Pei, Ilaria Iacobucci, Marcus Valentine, Stanley B. Pounds, Lei Shi, Yongjin Li, Jinghui Zhang, Cheng Cheng, Alessandro Rambaldi, Manuela Tosi, Orietta Spinelli, Jerald P. Radich, Mark D. Minden, Jacob M. Rowe, Selina Luger, Mark R. Litzow, Martin S. Tallman, Peter H. Wiernik, Ravi Bhatia, Ibrahim Aldoss, Jessica Kohlschmidt, Krzysztof Mrózek, Guido Marcucci, Clara D. Bloomfield, Wendy Stock, Stephen Kornblau, Hagop M. Kantarjian, Marina Konopleva, Elisabeth Paietta, Cheryl L. Willman, and Charles G. Mullighan

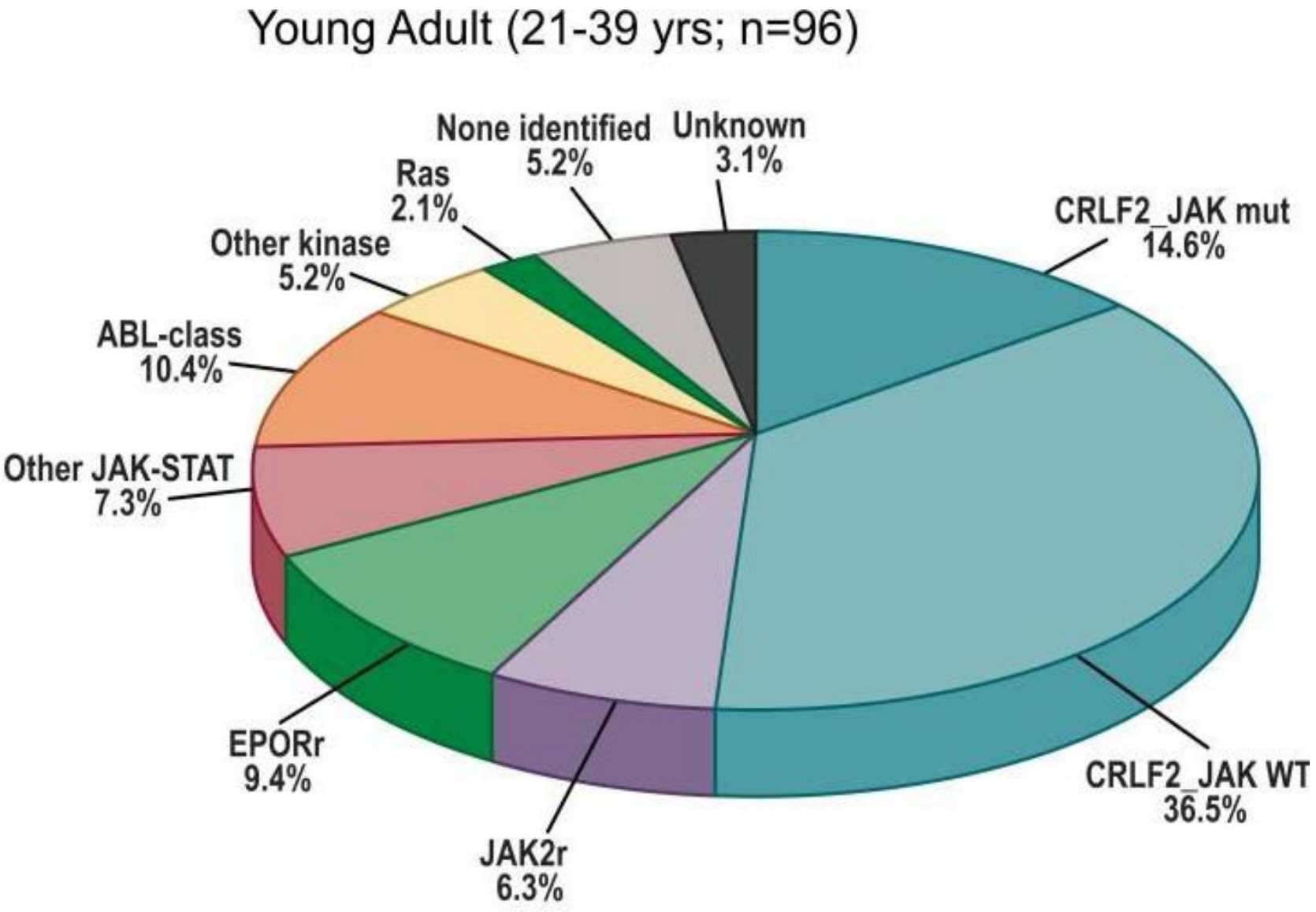
Testing algorithm for Ph-like ALL in COG trials



(*IGJ*, *SPATS2L*, *MUC4*, *CRLF2*, *CA6*, *NRXN3*, *BMPR1B*, *GPR110*, *CHN2*, *SEMA6A*, *PON2*, *SLC2A5*, *S100Z*, *TP53INP1*, *IFITM1*).

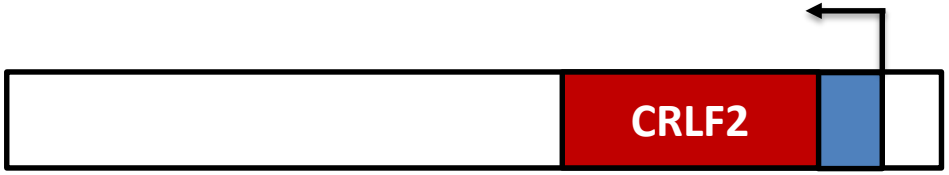
Courtesy of Shalini Reshmi, National Children's Hospital, Columbus OH. Tran and Loh. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):561-566.

CRLF2 is a frequent rearrangement seen in Ph-like B-ALL



Roberts et al. Journal of Clinical Oncology. Vol 35. No 4. February 1, 2017

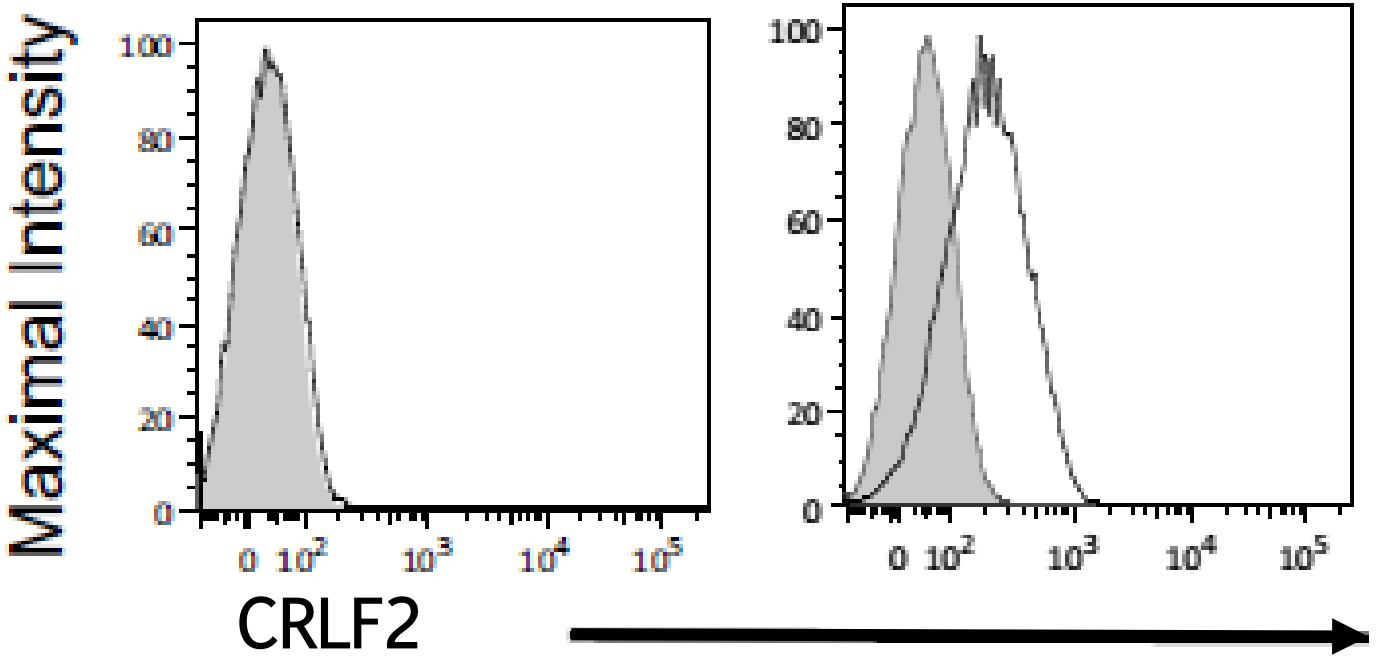
P2RY8-CRLF2 fusion leads to CRLF2 overexpression



P2RY8

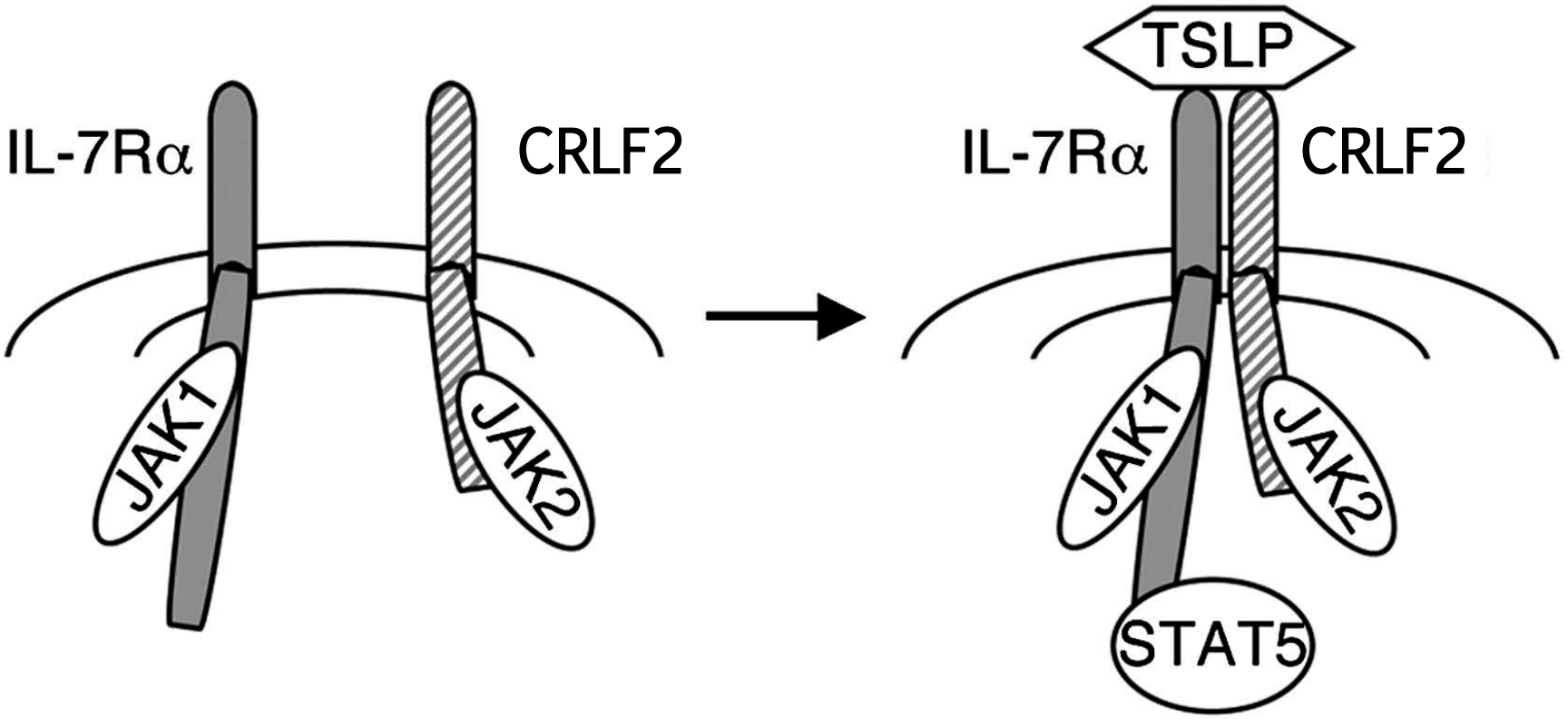
CRLF2 wild-type

IGH@-CRLF2



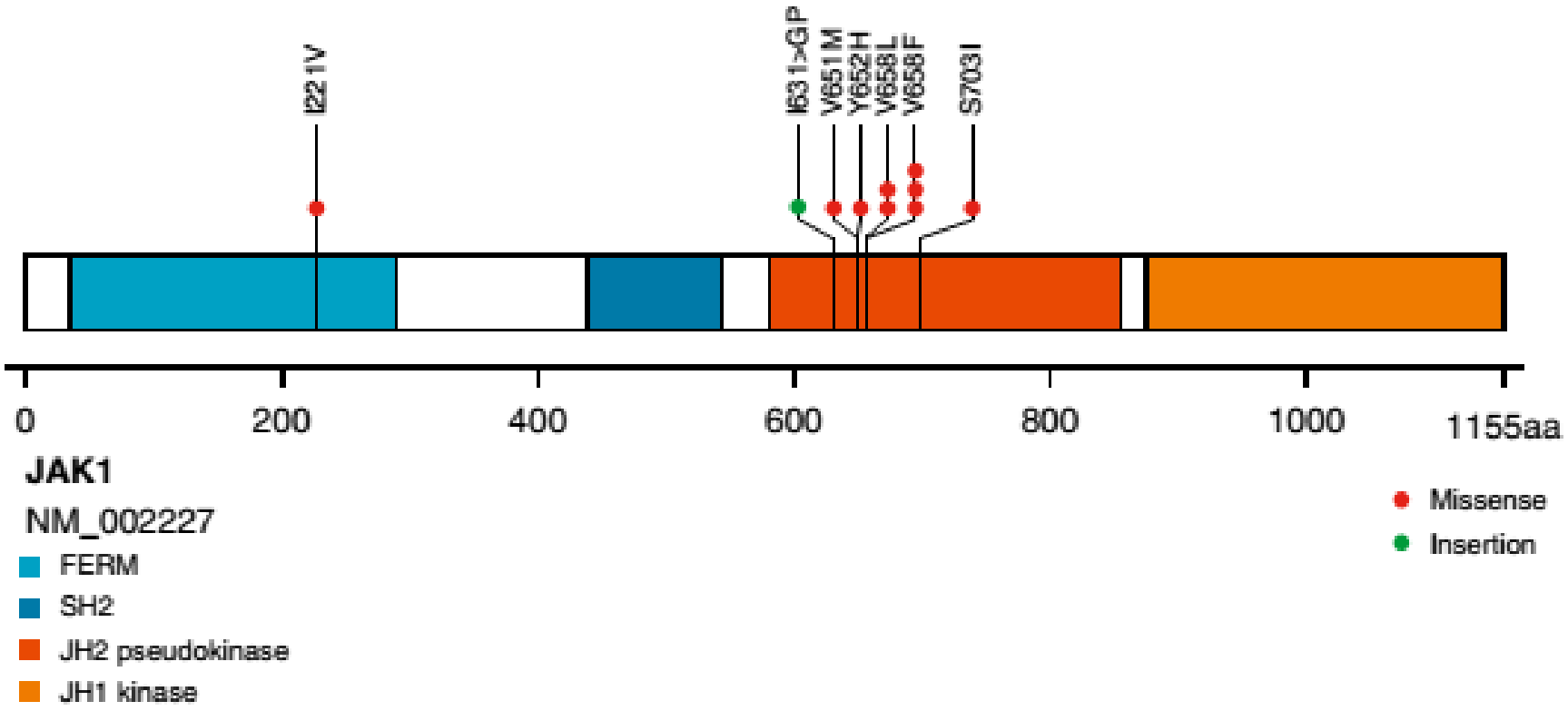
Adapted from Tasian et al. Blood, Jul 26, 2012, Vol. 120, No 4.

CRLF2 acts upstream of JAK-STAT signaling



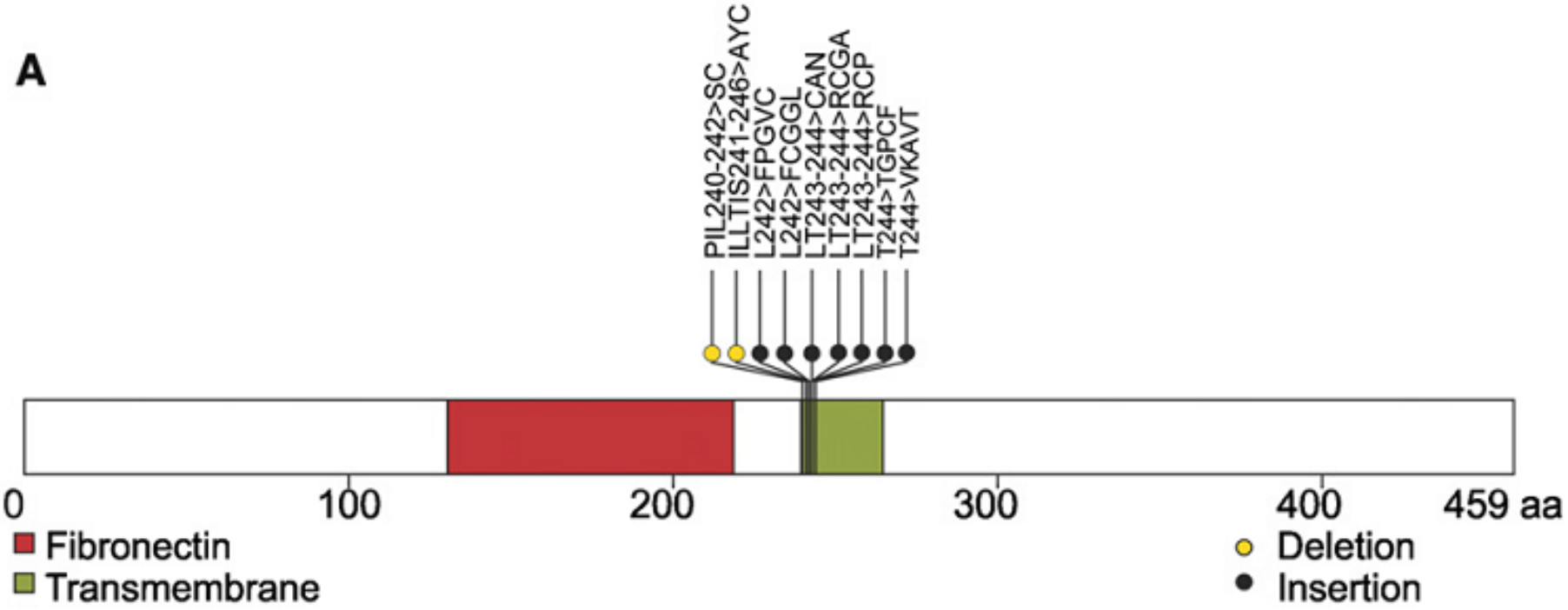
Adapted from Yrina Rochman et al. PNAS 2010;107:19455-19460

CRLF2 rearranged cases have frequent concomitant JAK1 and JAK2 mutations



Reshmi et al. BLOOD, 22 JUNE 2017, VOLUME 129, NUMBER 25

IL-7R transmembrane domain mutations have also been reported in Ph-like B-ALLs



Co-occurrence with *CRLF2* rearrangement and *SH2B3* deletion has been reported.

Roberts et al., Cancer Cell, 22, 153–166, August 14, 2012

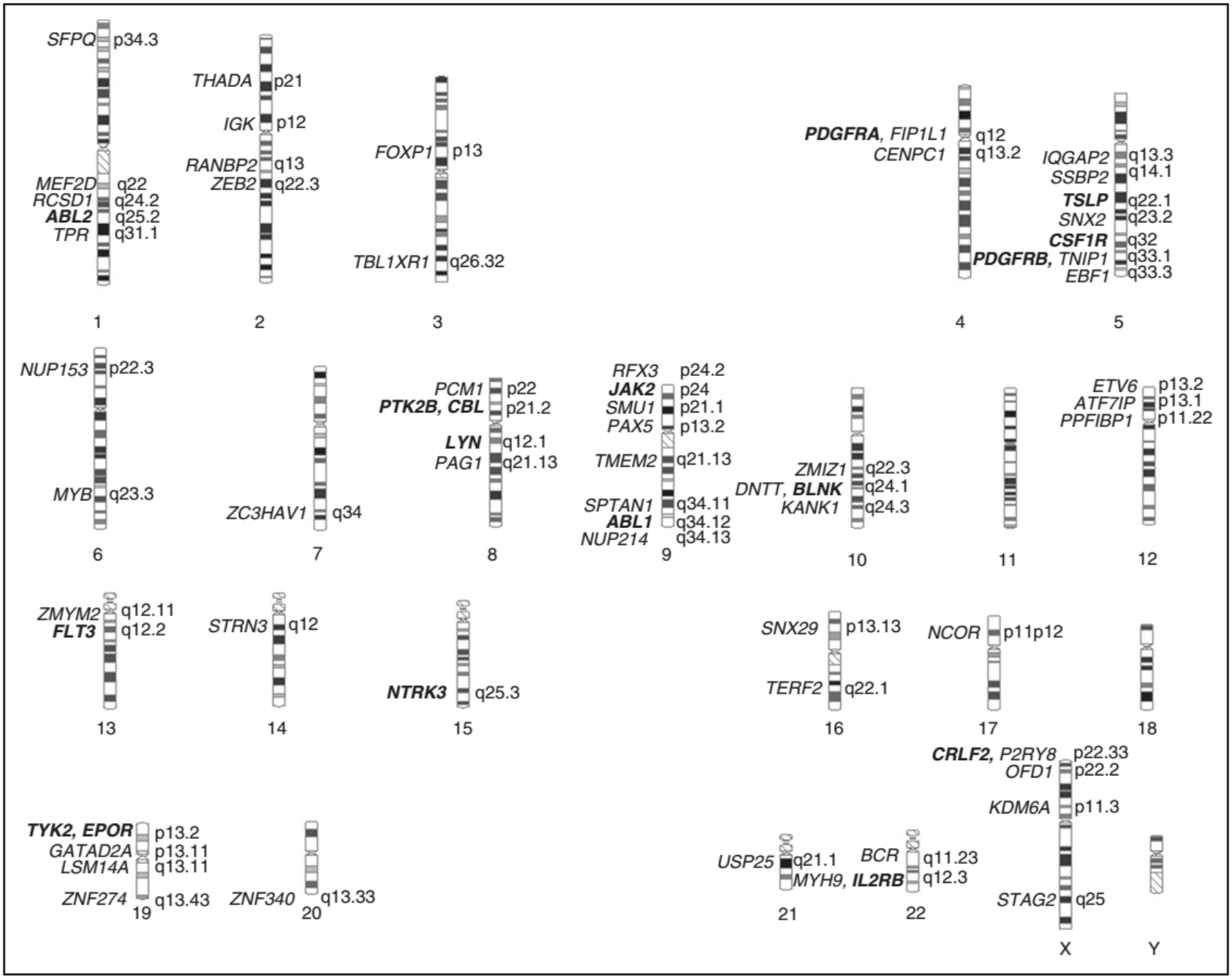
Table 1. Kinase Fusions Identified in Ph-like Acute Lymphoblastic Leukemia.

Kinase Gene	Tyrosine Kinase Inhibitor	Fusion Partners	Patients	5′ Genes
		number		
ABL1	Dasatinib	6	14	*ETV6*,[11] *NUP214*,[11] *RCSD1*,[11] *RANBP2*,[11] *SNX2*,[19] *ZMIZ1*[20]
ABL2	Dasatinib	3	7	*PAG1*,* *RCSD1*,* *ZC3HAV1**
CSF1R	Dasatinib	1	4	*SSBP2**
PDGFRB	Dasatinib	4	11	*EBF1*,[11-13] *SSBP2*,* *TNIP1*,* *ZEB2**
CRLF2	JAK2 inhibitor	2	30	*IGH*,[21] *P2RY8*[22]
JAK2	JAK2 inhibitor	10	19	*ATF7IP*,* *BCR*,[11] *EBF1*,* *ETV6*,[23] *PAX5*,[11] *PPFIBP1*,* *SSBP2*,[24] *STRN3*,[11] *TERF2*,* *TPR**
EPOR	JAK2 inhibitor	2	9	*IGH*,[11] *IGK**
DGKH	Unknown	1	1	*ZFAND3**
IL2RB	JAK1 inhibitor, JAK3 inhibitor, or both	1	1	*MYH9**
NTRK3	Crizotinib	1	1	*ETV6*[25-27]†
PTK2B	FAK inhibitor	2	1	*KDM6A*,* *STAG2**
TSLP	JAK2 inhibitor	1	1	*IQGAP2**
TYK2	TYK2 inhibitor	1	1	*MYB**

* The gene is a previously unreported fusion partner.
† *ETV6–NTRK3* has been reported in multiple cancers, including congenital fibrosarcoma[25,26] and secretory breast carcinoma,[27] but it has not previously been described in acute lymphoblastic leukemia.[28,29]

Roberts KG et al, N Engl J Med 2014; 371:1005-1015

There are MANY “actionable” gene fusions in Ph-like B-ALL



Potential methodologies for identifying Ph-like leukemia

Low density array: currently used primarily in the research setting to initially screen for Ph-like ALL

FISH: breakapart probes for known kinase genes would be simple, cost effective but limited in scope

RT-PCR: can screen for or confirm known fusions

Digital molecular barcoding platform

Capture-based RNA sequencing

Next-generation sequencing

Clinical course and response to therapy

• C8811 (Larson) protocol with rituximab	• Persistent disease (34% blasts)
• 'B' arm of hyperCVAD together with ruxolitinib	• Persistent disease (85% blasts)
• Blinatumomab (1 cycle)	• Persistent disease (96% blasts)
• CLOVE chemotherapy (clofarabine, cyclophosphamide, etoposide).	• Persistent disease (70% blasts)
• Inotuzumab (1 cycle)	• Persistent disease (50% blasts)
• At various time points, considered for clinical trials that either closed, where he did not respond, or he was unable to enroll due to either diagnosis or condition (eg infection).	

Summary

- Ph-like B-ALL with isolated MPO vs “Ph-like” MPAL
  - Potential for further clarification of diagnostic classification

- Ph-like B-ALL is characterized by kinase rearrangements of which *CRLF2* rearrangement is the most prevalent and is often associated with *JAK1/2* mutations.
  - Potential for targeted inhibition of JAK/STAT signaling pathways

- Optimal detection of Ph-like B-ALL? Multiple modalities are possible.

- Need for additional clinical trials investigating therapeutic efficacy of kinase inhibitors and optimization of treatment regimens in Ph-like B-lymphoblastic leukemia
  - Consider inclusion of cases of Ph-like MPAL

Final panel diagnosis:

B-lymphoblastic leukemia, *BCR-ABL1*-like

versus

Mixed phenotype acute leukemia, B/myeloid, not otherwise specified