Lymphoblastic leukemia with a kinase-activating alteration

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Patient – 59 female who presented with persistent B-lymphoblastic leukemia

- First diagnosis - 5 months prior, WBC 92.6 x 10^9/L,
  Initial CSF analysis was positive for blasts

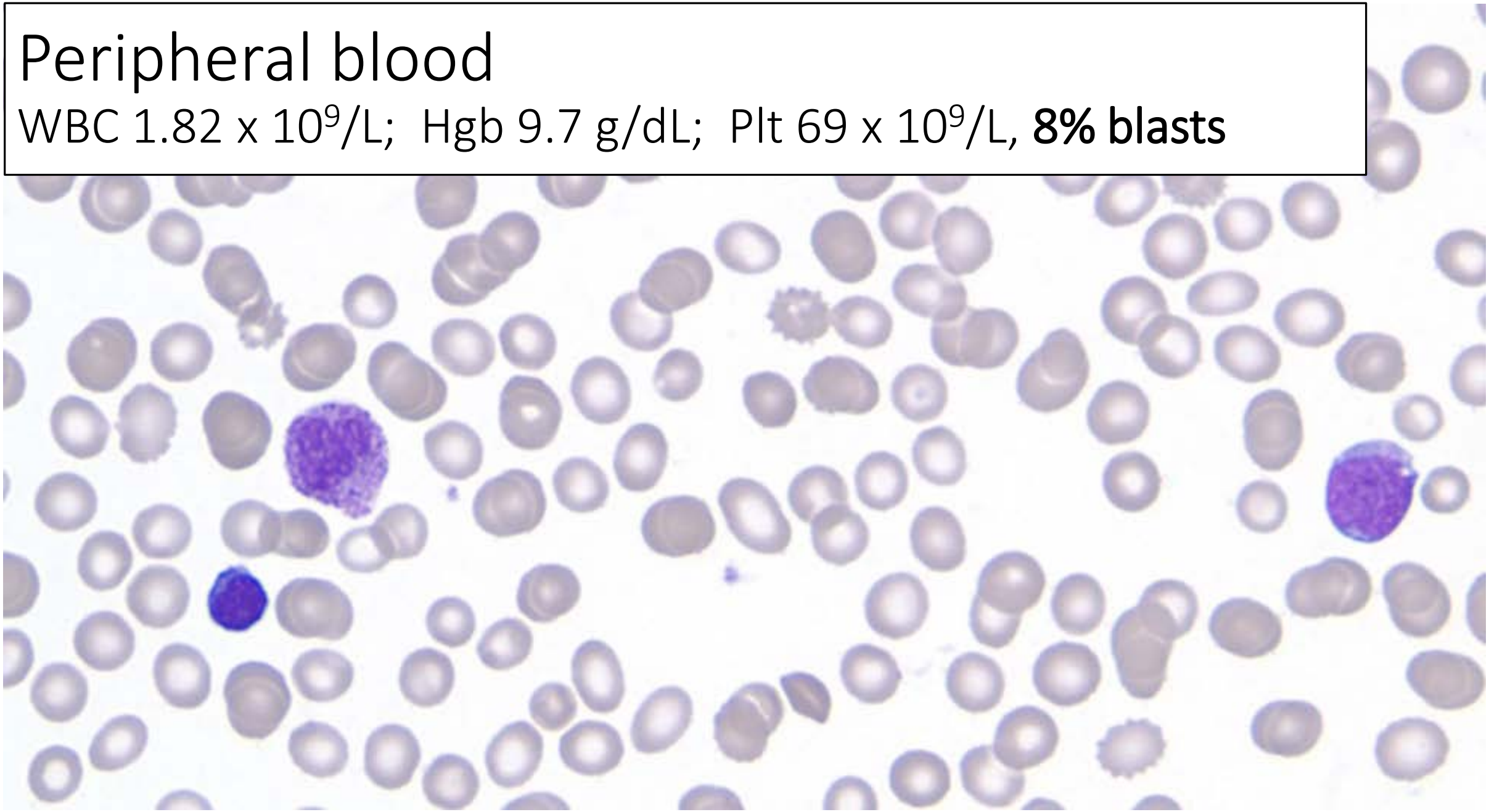
- Therapy included hyper-CVAD through cycle 2A, blinatumumab, and two cycles of ICE, plus five intrathecal treatments

- In the five months since diagnosis she maintained 40-60% blasts in the bone marrow over five subsequent biopsies

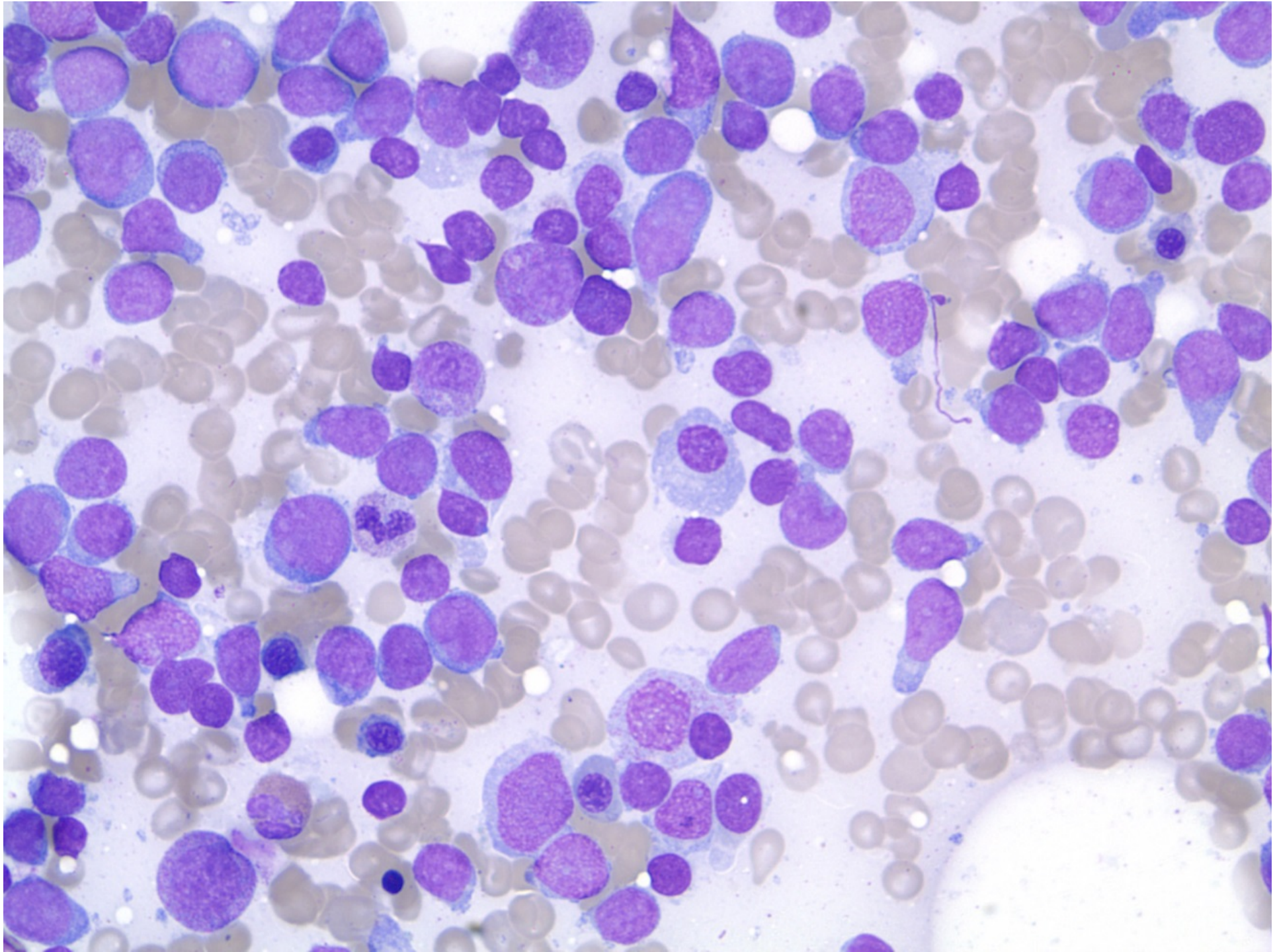
- She came to our institution and was initiated onto a clinical trial (SWOG 1312) with plans underway for allogeneic hematopoietic stem cell transplant

Peripheral blood

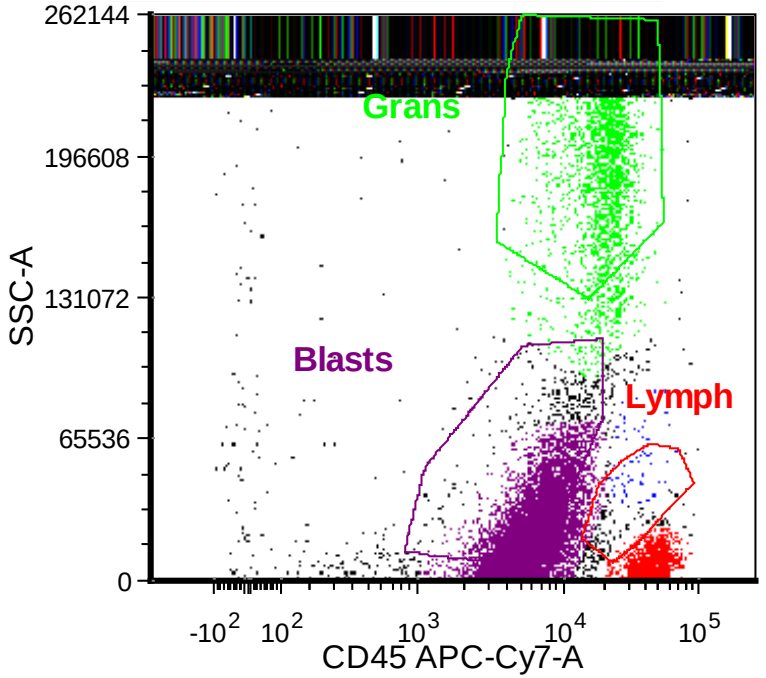
WBC 1.82 x 10^9/L; Hgb 9.7 g/dL; Plt 69 x 10^9/L, **8% blasts**

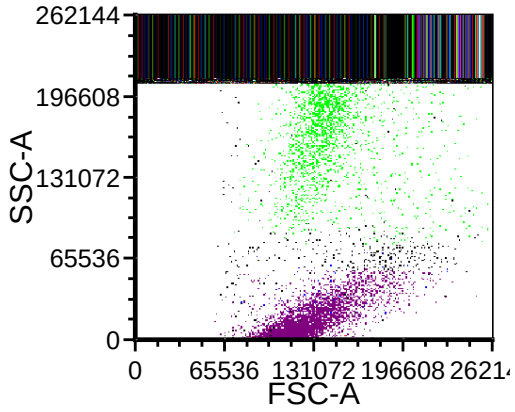


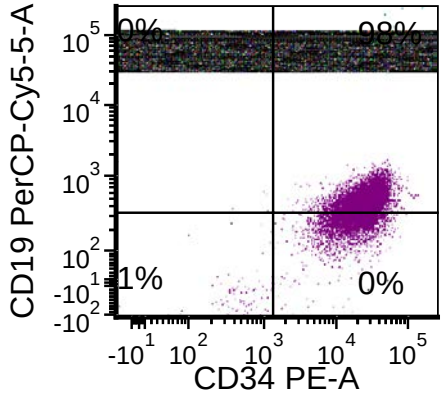
Bone marrow aspirate 71% blasts

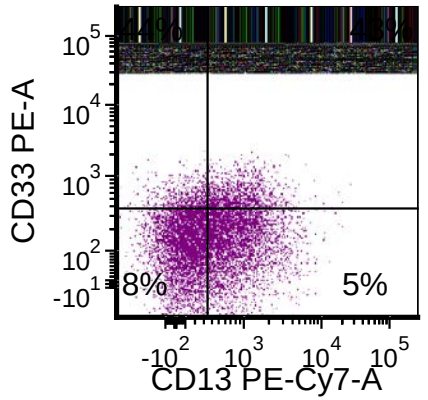


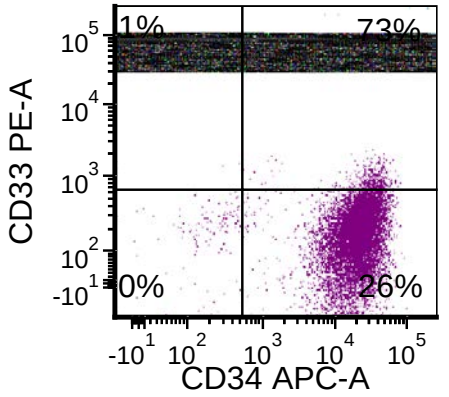
Flow cytometry – bone marrow aspirate

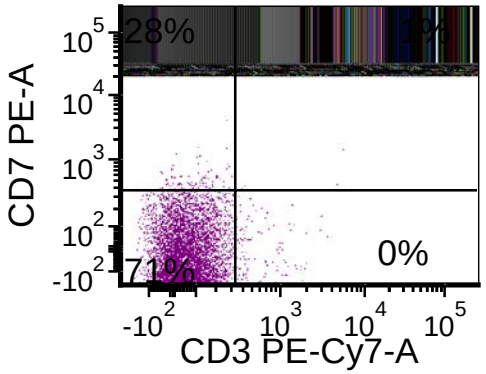


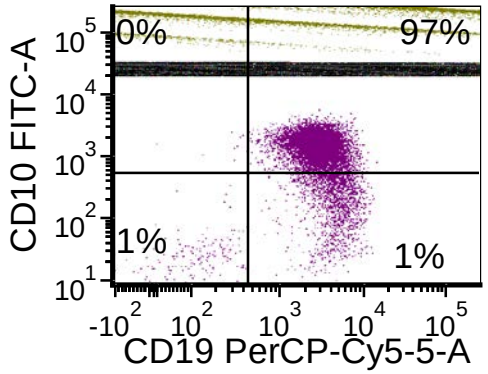


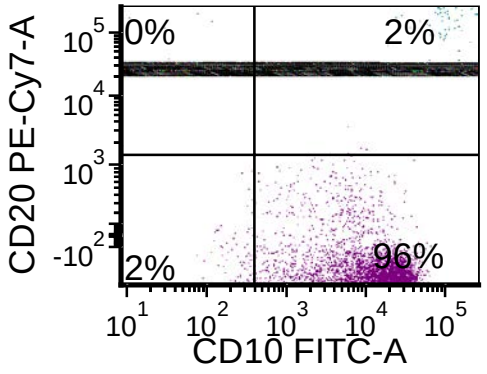


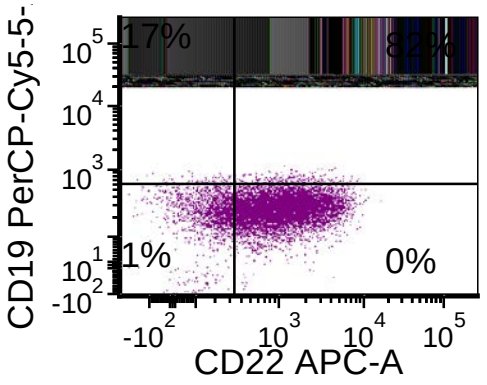


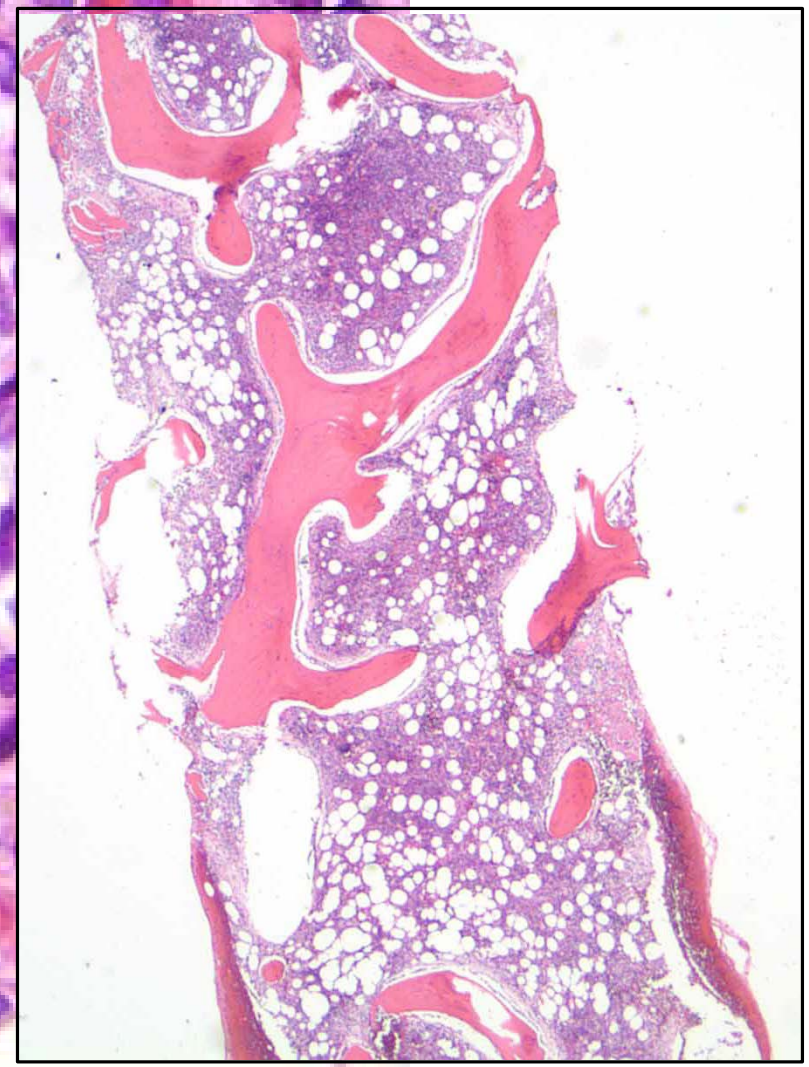


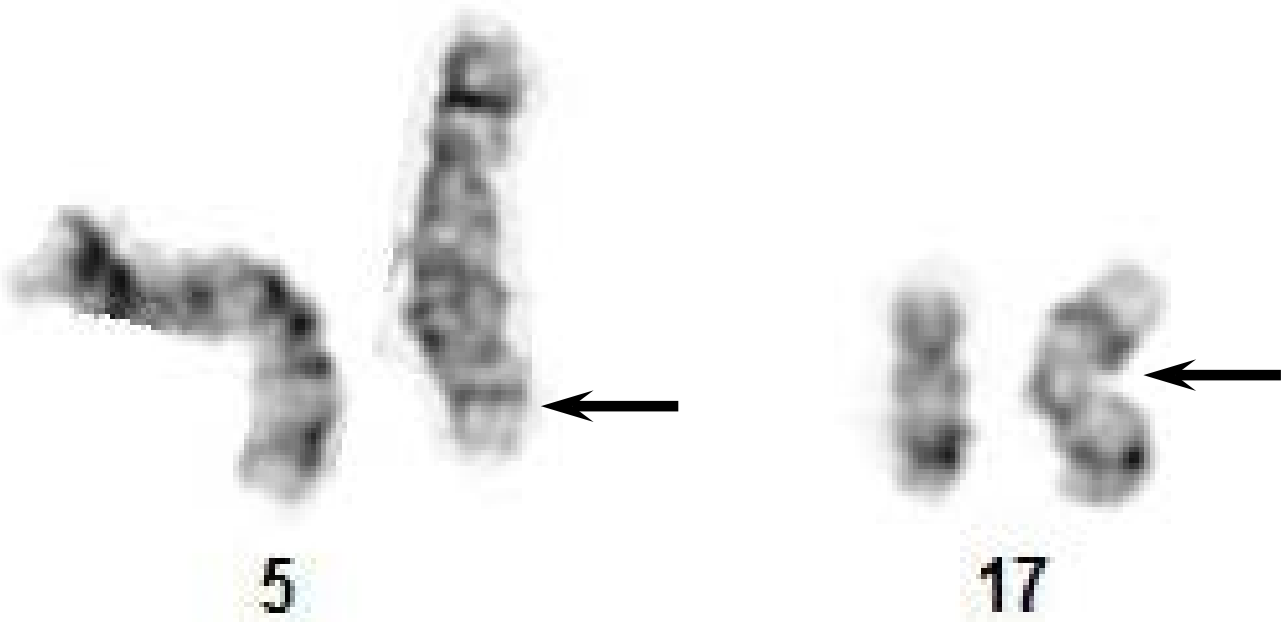




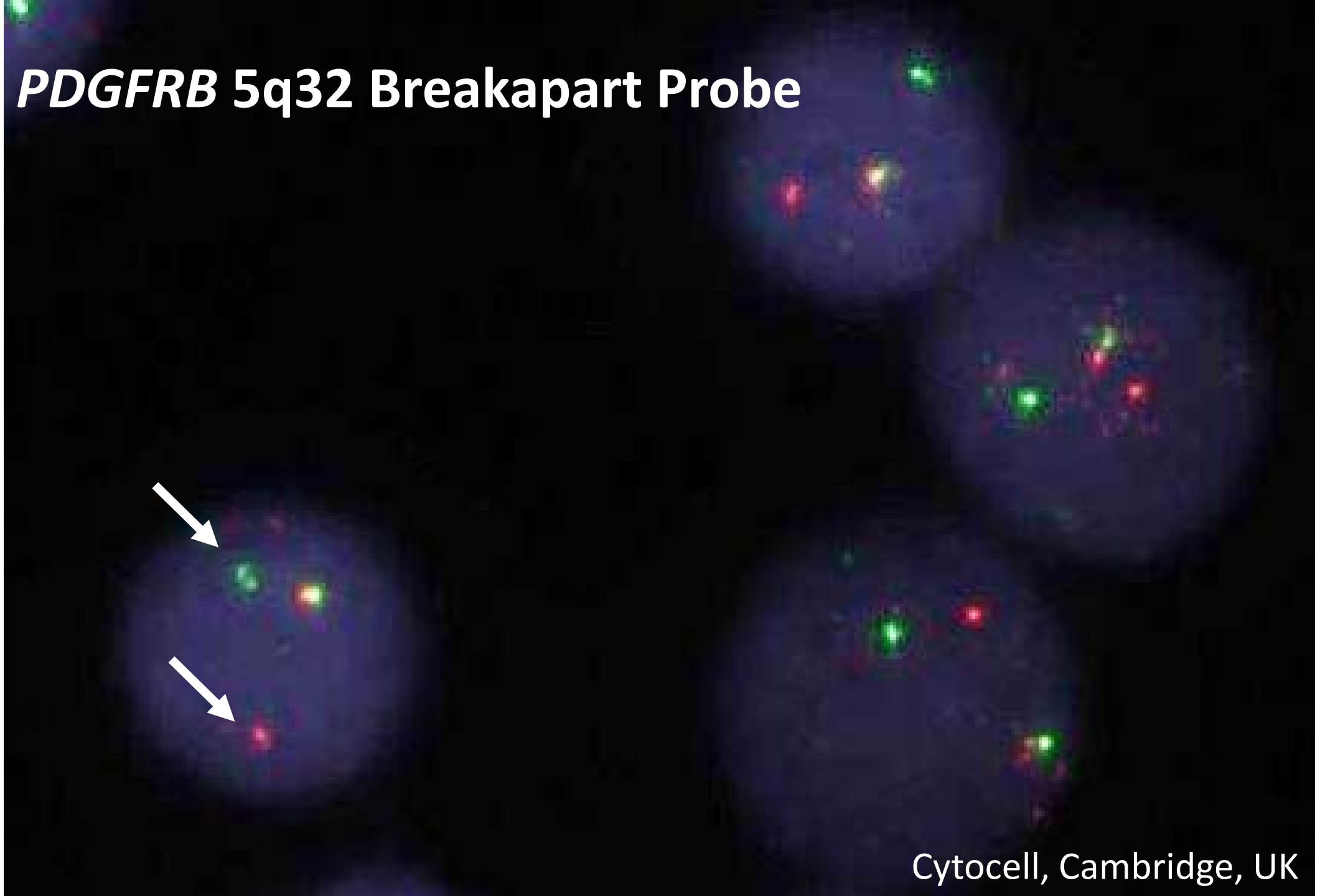








46,XX,t(5;17)(q33;p11.2~13)[7]/45,idem,-7[6]/46,XX[12]


PDGFRB 5q32 Breakapart Probe
Cytocell, Cambridge, UK

46,XX,t(5;17)(q33;p11.2~13)[7]/45,idem,-7[6]/46,XX[12]

- Chr 17 breakpoint – either p11.2 or p13

  - t(5;17) with 17p13 was described in:
    - One case of T-lymphoblastic leukemia with myeloid neoplasm and *PDGFRB* rearranged to *RABEP1*
      (Ondrejka et al, Haematologica 2014)
    - One case of CMML with *PDGFRB-RABEP1*
      (Magnusson et al, Blood 2001)

  - t(5;17) with 17p11.2 was described in:
    - One case of JMML involving *PDGFRB-SPECC*
      (Panarello, Atlas Genet Cytogenet Oncol Haematol 2004)

- Monosomy 7 - present 4-6 % of B-ALL, most often as a secondary anomaly of the t(9;22); the association t(9;22), -7 is present in 16 % of the Ph+ ALL

Send-out multiplex RT-PCR fusion for Ph-like ALL– **Negative** for fusion transcript products

Fusion genes detected in the assay:

- 12 *ABL1* fusions
- 11 *JAK2* fusions
- 15 kinase fusions including: *EBF1-PDGFRB*, *ZEB2-PDGFRB*, *TNIP-PDGFRB*, *ATF7IP-PDGFRB*, *ZMYND8-PDGFRB*, *ETV6-PDGFRB*, *AGGF1-PDGFRB*

Proposed diagnosis:

Ph-like B-lymphoblastic leukemia with PDGFRB translocation

Panel diagnosis:

B-lymphoblastic leukemia, BCR-ABL1-like

Arber DA et al, WHO revision, Blood 2016

Differential diagnosis

- Myeloid and lymphoid neoplasm with eosinophilia and *PDGFRB* rearrangement

  - No evidence of myeloid neoplasm or eosinophilia at diagnosis or in five subsequent marrows.

  - No myeloid neoplasm or eosinophilia upon presentation at our hospital or in a bone marrow biopsy after first cycle of SWOG-1312

Patient follow-up

- Bone marrow biopsy after first cycle on SWOG-1312 was morphologically negative, but there was minimal residual disease detected by flow cytometry (0.062%) and persistence of t(5;17)(q33;p11.2) in 6 metaphase cells.
- She continued therapy for another cycle and proceeded to allogeneic bone marrow transplant at another institution
- A bone marrow biopsy one month after transplant was normocellular with trilineage hematopoiesis and no evidence of B-lymphoblastic leukemia; karyotype //46,XY[20]

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

- Range of genetic alterations that activate cytokine receptor genes and kinase signaling pathways

Rearrangements of *CRLF2* +/- JAK mutation

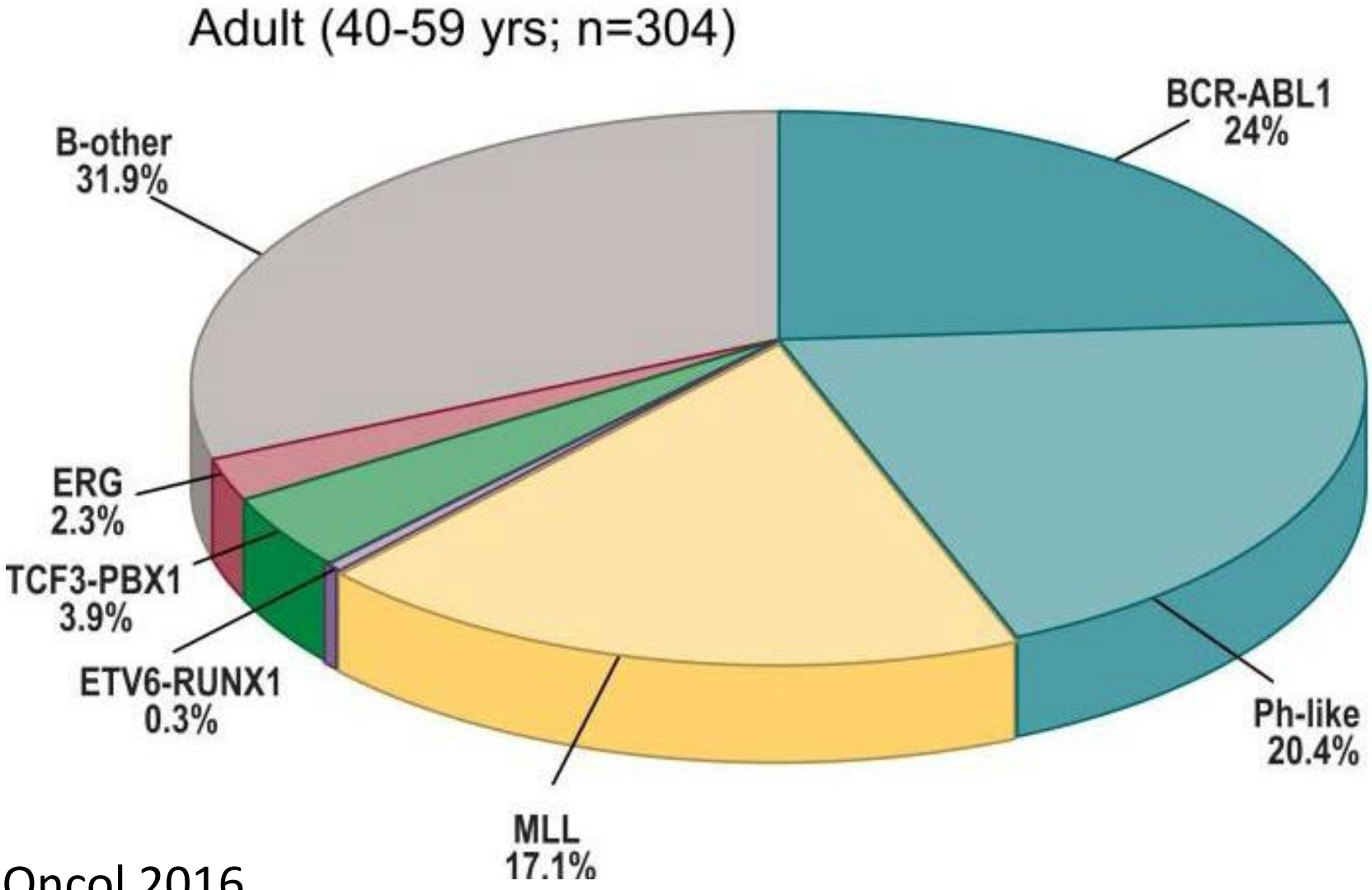
JAK2 and *EPOR* rearrangements

ABL-class gene rearrangements

JAK-STAT alterations

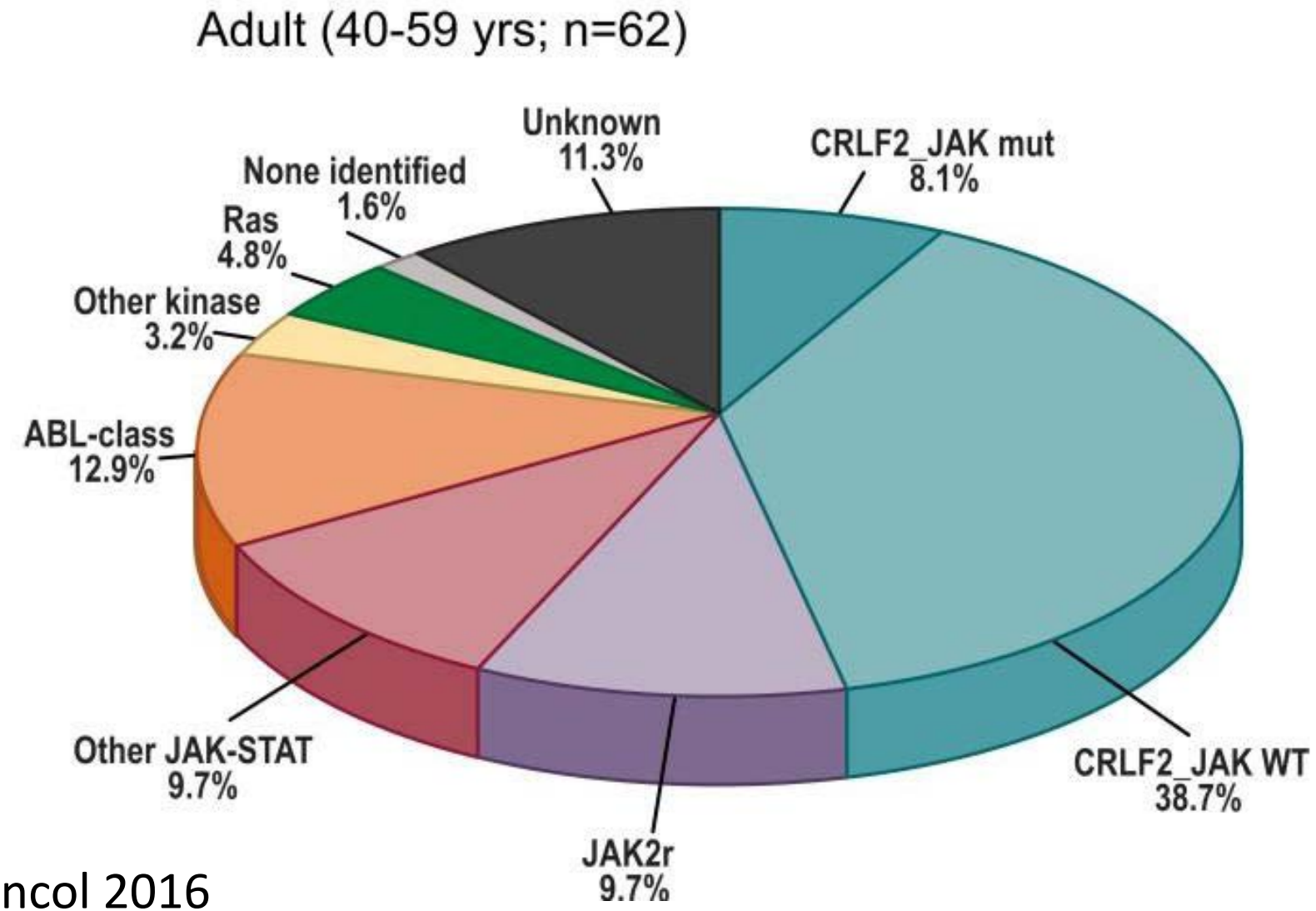
Other rare kinase alterations (ie *NTRK3*)

B-lymphoblastic leukemia, in adults



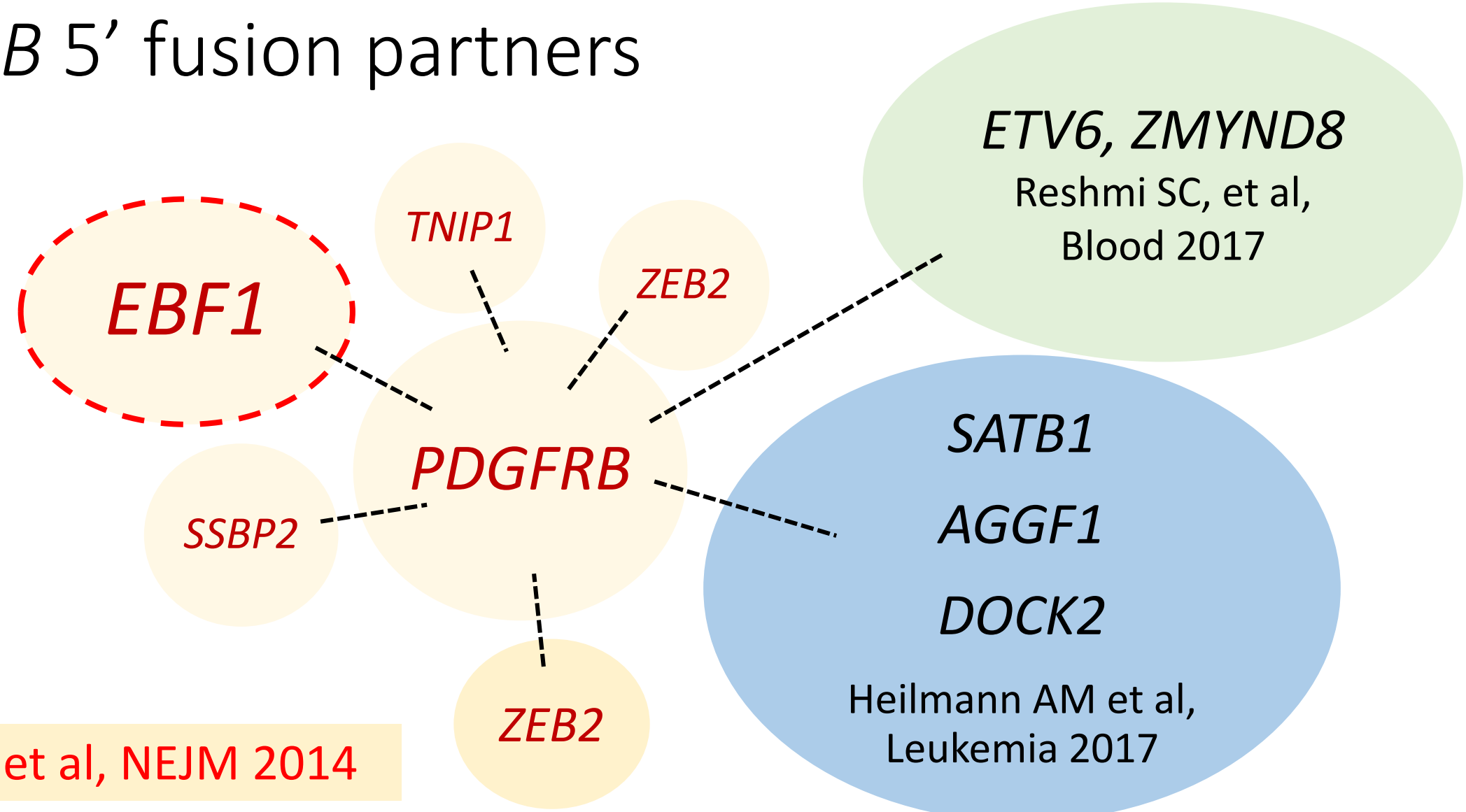
Roberts KG et al, J Clin Oncol 2016

Ph-like lymphoblastic leukemia



Roberts KG et al, J Clin Oncol 2016

PDGFRB 5’ fusion partners



Others: ***SNX29*** Roberts KG et al JCO 2016; ***ATF7IP*** Kobayashi K, Br J Hematol 2015

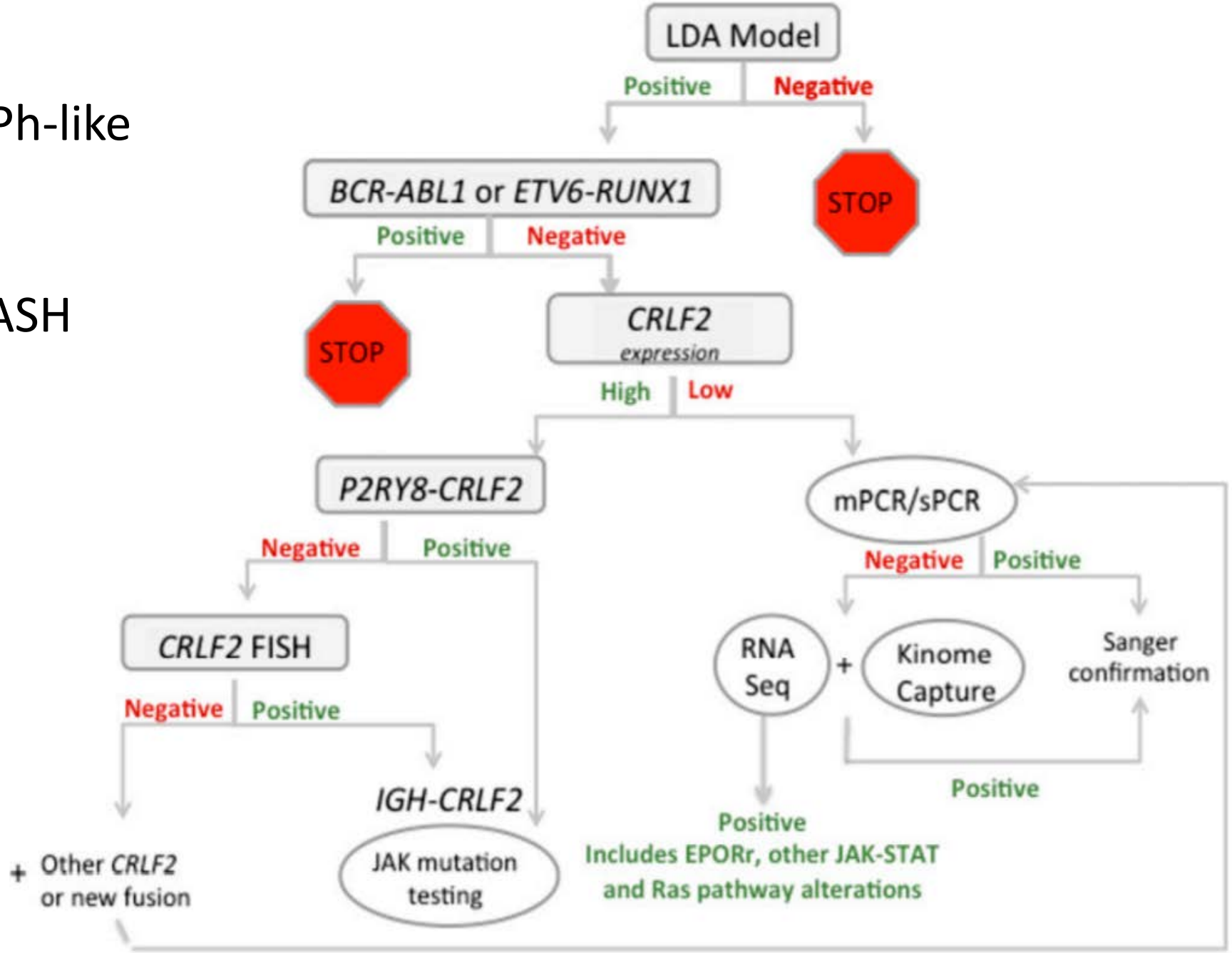
Various ways to test for Ph-like ALL

- Enticing option – targeted capture of RNA (targeted locus amplification) – using the TK gene as a known starting point, followed by NGS. Advantage that novel partner genes will be identified.
- Alternative – focus screening approach on high-risk or induction failure
- Low density array card (TLDA) to screen for the Ph-like gene expression profile – then – Additional genetic testing to identify the kinase lesion

- Goal is to therapeutically target the underlying kinase lesion rather than identify the Ph-like GEP:
  - RT-PCR – for known fusions
  - FISH
  - Phosphoflow signaling
  - NanoString assay

Testing algorithm for Ph-like ALL in COG trials

Tran TH and Loh ML, ASH education book 2016



Therapeutic implications

Rearrangements of *CRLF2* +/- JAK mutation

Ruxolitinib

JAK2 and *EPOR* rearrangements

Ruxolitinib

COG (AALL131) - patients with NCI high-risk Ph-like ALL and ABL-class fusions are eligible to have dasatinib added to backbone chemotherapy

ABL-class gene rearrangements

Dasatinib

JAK-STAT alterations

Ruxolitinib

JAK1/JAK3 inhibitor

Other rare kinase alterations (ie *NTRK3*)

Crizotinib, MEK or FAK inhibitor

Problems in moving forward with Ph-like ALL

- Lots of genetic heterogeneity – difficult to systematically study
- Genetic aberrations are hard to detect by standard diagnostic methods such as karyotyping, FISH or PCR because they are diverse, ever-increasing, and sometimes cryptic.
- Challenging for most laboratories to implement assays that test for these genomic aberrations

Summary / Conclusions

- Patient with Ph-like B-lymphoblastic leukemia with many high risk features – she received allogeneic SCT elsewhere
- Testing for Ph-like alterations in B-lymphoblastic leukemia remains a challenge
- Standardization of screening strategies and cut-offs will help trials evaluating best therapies for these patients

Panel diagnosis:

B-lymphoblastic leukemia, BCR-ABL1-like