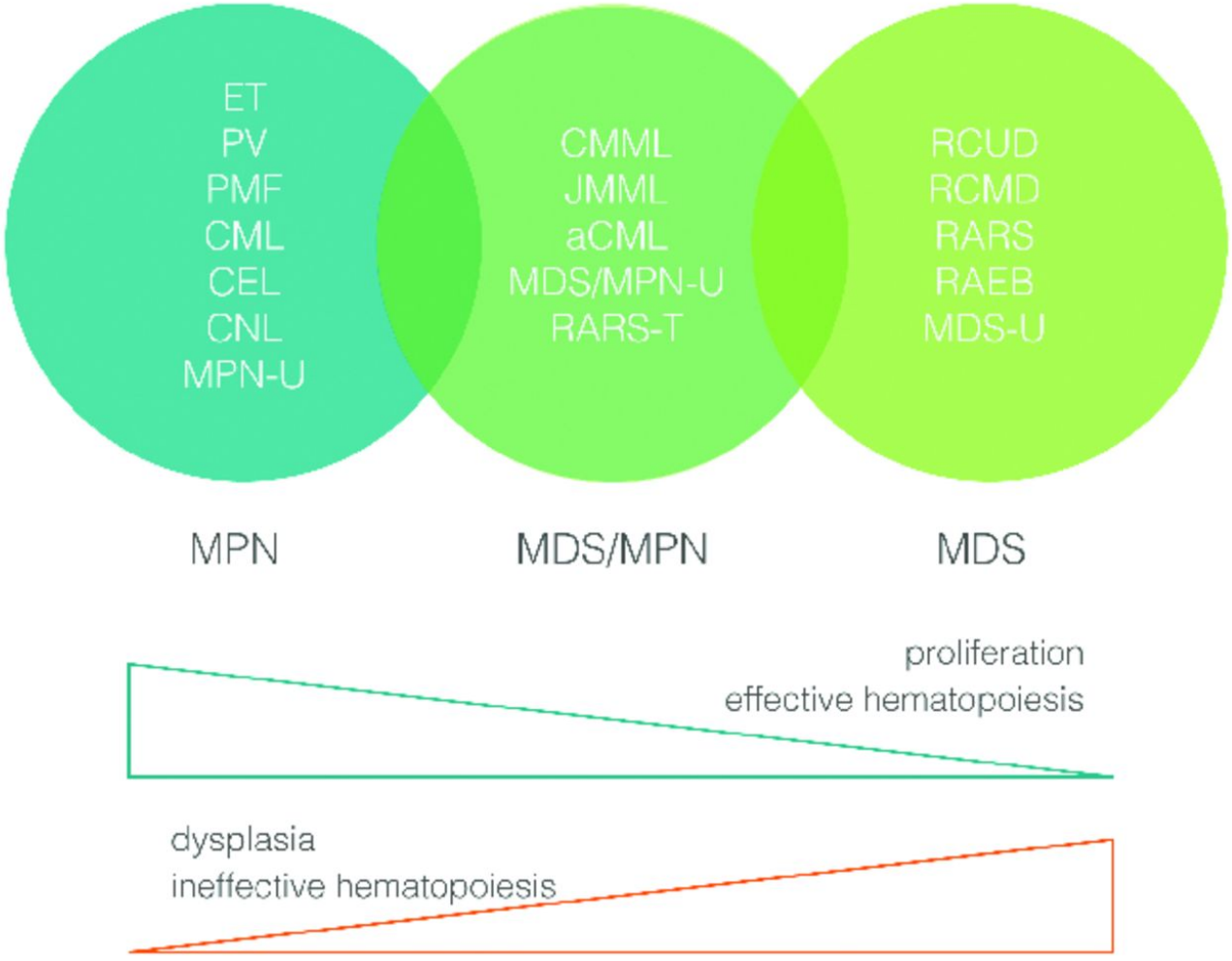
Atypical CML

Lymphoma Tumor Board

June 16, 2017

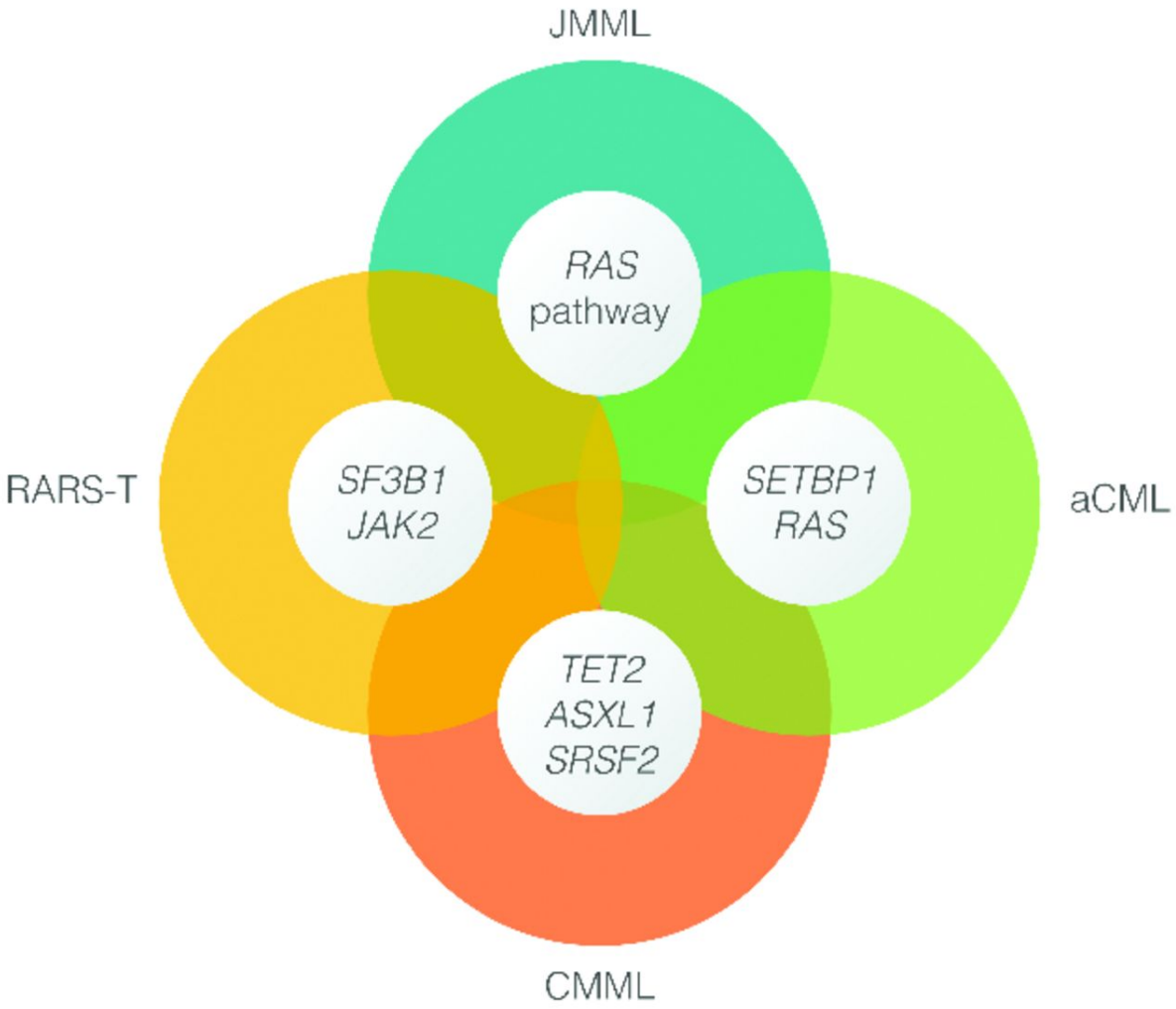
Myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) define a spectrum of pathology



Tariq I. Mughal et al. Haematologica 2015;100:1117-1130

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Emerging molecular fingerprints of MDS and MPN



Tariq I. Mughal et al. Haematologica 2015;100:1117-1130

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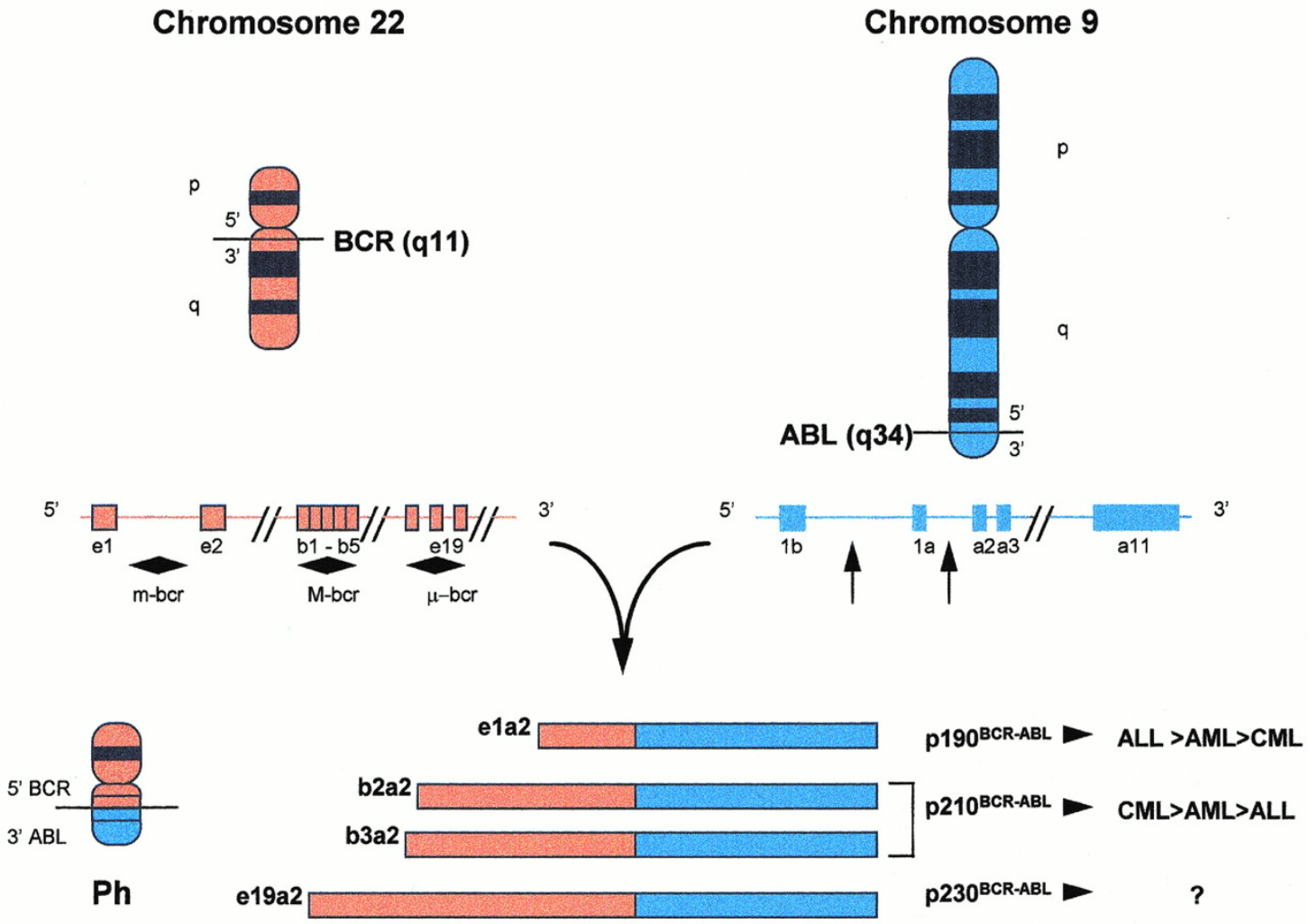
The variety of t(9;22)(q34;q11) breakpoints in CML



Stefan Faderl *et al*. Blood 1998;91:3995-4019

The rare CML variant characterized by the p230 BCR-ABL fusion protein presents as a "neutrophilic" CML

RAPID COMMUNICATION

Neutrophilic-Chronic Myeloid Leukemia: A Distinct Disease With a Specific Molecular Marker (*BCR/ABL* With C3/A2 Junction)

By Fabrizio Pane, Ferdinando Frigeri, Maria Sindona, Luigia Luciano, Felicetto Ferrara, Renato Cimino, Giovanna Meloni, Giuseppe Saglio, Francesco Salvatore, and Bruno Rotoli

Neutrophilic-chronic myeloid leukemia (CML-N) is a rare myeloproliferative disorder that runs a much more benign course than chronic myeloid leukemia, and for which no specific underlying molecular lesion has been described so far. We have analyzed the genomic DNA by Southern blotting and the *BCR/ABL* hybrid gene transcripts by reverse transcriptase-polymerase chain reaction in three patients with clinical findings of CML-N, who did have a t(9;22) chromosomal translocation. In all patients we have found a rare type of *BCR/ABL* rearrangement, with a breakpoint between exons c3 and c4 of the *BCR* gene (corresponding to *BCR* exons 19 and 20). This was confirmed by hybridization with an oligonucleotide probe spanning the c3/a2 region. This type of junction causes almost the entire *BCR* gene to fuse with *ABL*. The junction is in frame and it gives rise to a fusion protein of predicted 230 kD. Our data now provide a molecular diagnostic marker for CML-N, and they are consistent with the notion that the inclusion or exclusion of *BCR* exons in the fusion protein affects dramatically its capacity to derange myeloid proliferation and differentiation, leading to the appearance of different disease phenotypes.

Blood, Vol 88, No 7 (October 1), 1996: pp 2410-2414

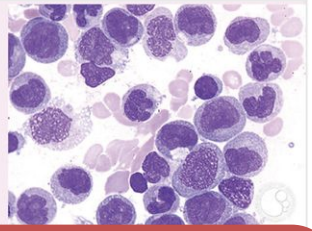
WHO (2008) classification of MDS/MPNs: disease definitions and key molecular features

Key features of myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

Chronic myelomonocytic leukemia (CMML)

Most commonly diagnosed MDS/MPN; splenomegaly is frequent
Defined by:
- Persistent peripheral blood monocytosis (>1 x 10^9/L and ≥10% of leukocytes)
- No *BCR-ABL1* fusion or *PDGFRA/PDGFRB* rearrangement
- <20% myeloblasts + monoblasts/promonocytes in blood and marrow
- Dysplasia in one or more myeloid lineages
  (or a clonal cytogenetic marker, or monocytosis x 3 months and other causes ruled out)

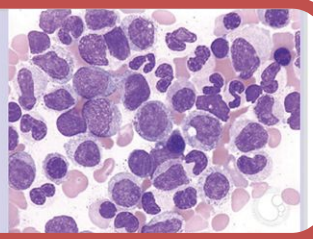
Deregulated GM-CSF and Ras signaling common
Frequently associated mutations: *ASXL1, SRSF2, TET2, KRAS/NRAS, CBL*



Atypical chronic myeloid leukemia (aCML)

Can be mistaken for CML, but dysplasia is more prominent
Defined by:
- Persistent leukocytosis (≥13 x 10^9/L)
- Immature circulating neutrophil precursors (≥ 10% of leukocytes)
- Marked dysgranulopoiesis and hypercellular marrow
- <20% blasts in blood and marrow
- No *BCR-ABL1* fusion or *PDGFRA/PDGFRB* rearrangement
- Absent/minimal monocytosis (<1 x 10^9/L, <10% of leukocytes) and basophilia (usually <2%)

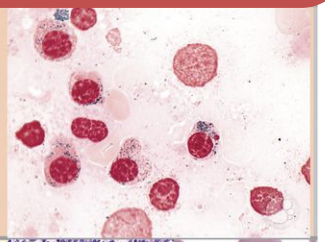
Associated mutations: *SETBP1, CSF3R* in some cases



Refractory anemia with ring sideroblasts and thrombocytosis (RARS-T)

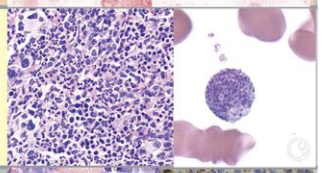
Considered a provisional entity and subset of MDS/MPN-U in WHO 2008, but a real disorder
Defined by:
- Diagnostic features of RARS (anemia, ≥15% ring sideroblasts, erythroid dysplasia)
- Persistent unexplained elevation in platelet count >450 x 10^9/L
- Other causes of thrombocytosis must be ruled out
- Megakaryocyte hyperplasia similar to that seen in essential thrombocythemia, but dissimilar to myelofibrosis
- <5% marrow blasts

Frequently has splicing mutations including *SF3B1*, and proliferative driver mutations (*JAK2*, *MPL*, or rarely *CALR*)



Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U)

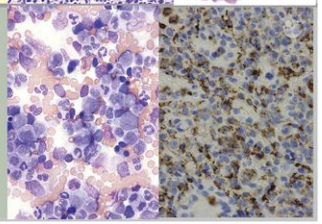
Diverse group of disorders with both MDS and MPN features that do not fit anywhere else
Defined by:
- No history of MDS or MPN and no recent therapy that might alter morphology
- No *BCR-ABL1* fusion or *PDGFRA/PDGFRB* rearrangement or isolated del(5q) or chr. 3q21q26 rearrangement
- De novo disease that does not meet criteria for CMML, aCML or other WHO-defined disorders



Juvenile myelomonocytic leukemia (JMML)

Rare, aggressive pediatric neoplasm that usually presents before age 5; more common in boys
Defined by:
- Persistent peripheral blood monocytosis (>1 x 10^9/L)
- No *BCR-ABL1*
- <20% myeloblasts + monoblasts/promonocytes in blood or marrow
- Minor criteria (at least 2 must be present): elevated Hb F, WBC >10 x 10^9/L, GM-CSF hypersensitivity, leukoerythroblastic blood smear, clonal cytogenetic abnormalities (esp. monosomy 7)

Frequently associated with mutations of *PTPN11, NF1* (germline) , Ras pathway members



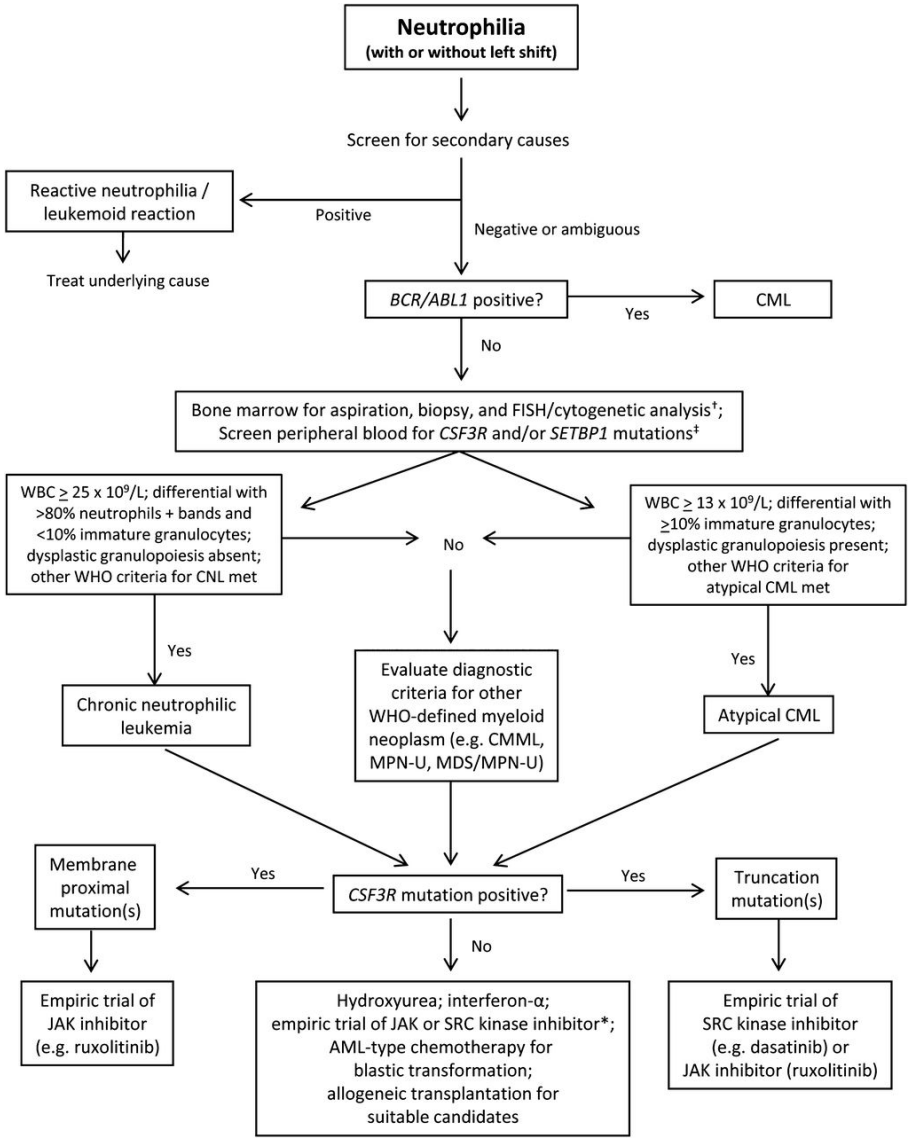
David P. Steensma Blood 2015;125:1849-1851

blood

Atypical Chronic Myeloid Leukemia (aCML)

- Heterogeneous disorder belonging to the group of myelodysplastic/myeloproliferative (MDS/MPN) syndromes
- Clinical features include the following:
  - Splenomegaly
  - Myeloid predominance in the bone marrow – some dysplastic features but without a differentiation block
- Laboratory abnormalities include:
  - Myeloid proliferation
  - Low leukocyte alkaline phosphatase values
  - Lack of the pathognomonic Philadelphia chromosome and *BCR-ABL1* fusion gene
- Median survival is 37 months
- *SETBP1* was identified as a novel aCML-related oncogene in 2012
- Frequent causes of death are intracranial hemorrhage, progressive disease/blastic transformation, and regimen-related toxicity from induction chemotherapy or transplantation

Provisional diagnostic algorithm for neutrophilia and genetically informed treatment options



Jason Gotlib et al. Blood 2013;122:1707-1711

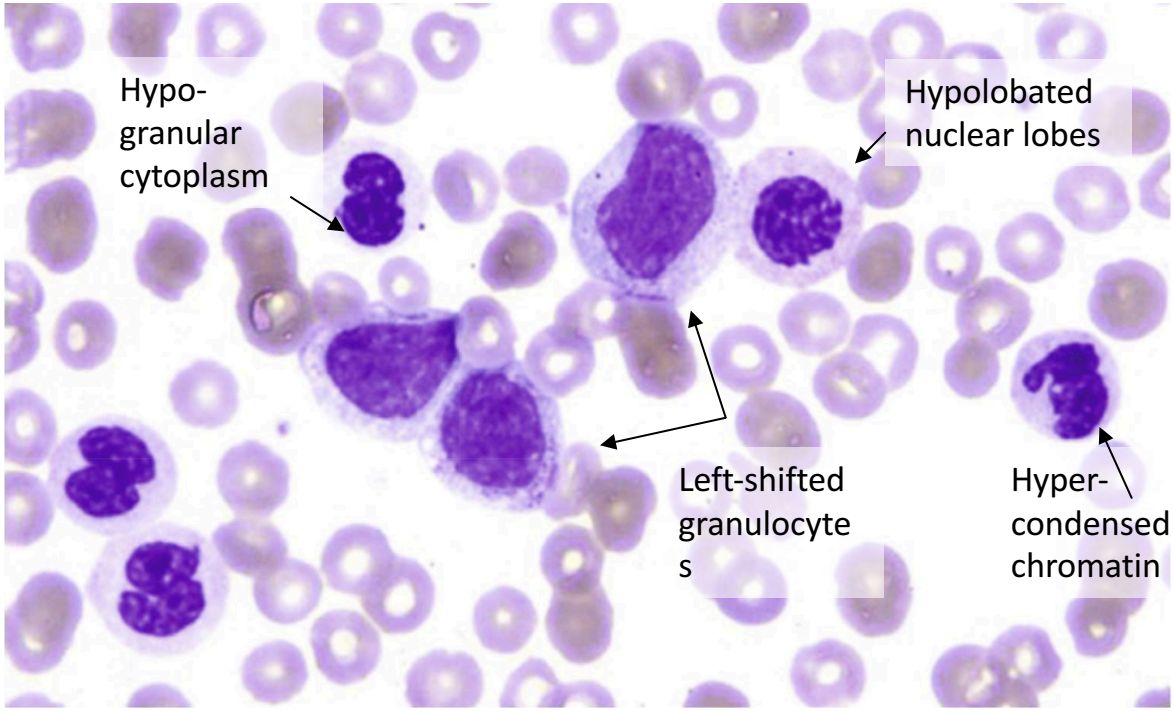
blood

Diagnostic criteria for chronic neutrophilic leukemia (CNL) and atypical CML

	CNL	aCML
Peripheral Blood Leukocytes	≥ 25 x 10^9/L	≥ 13 x 10^9/L
Neutrophils/bands	> 80%	
Immature granulocytes	< 10%	≥10%
Blasts	< 1% (PB) < 5% (BM)	< 20%
Granulocytic Dysplasia	No	Yes
Other dysplasia or laboratory findings	No myelodysplasia in other lineages; monocytes <1 x 10^9/L	Variable dysplasia; Basophils <2%; Monocytes <10%
Hepatosplenomegaly	Yes	Often
BCR-ABL, *PDGFRA/B*	Absent	Absent

Summarized from: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues

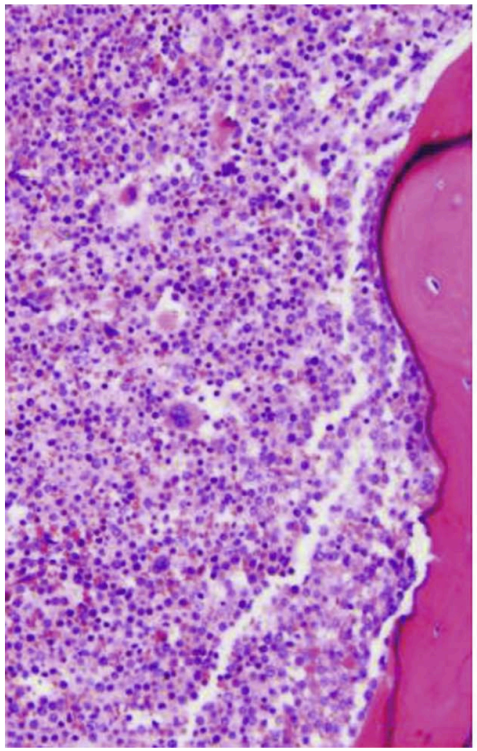
Peripheral blood in atypical CML

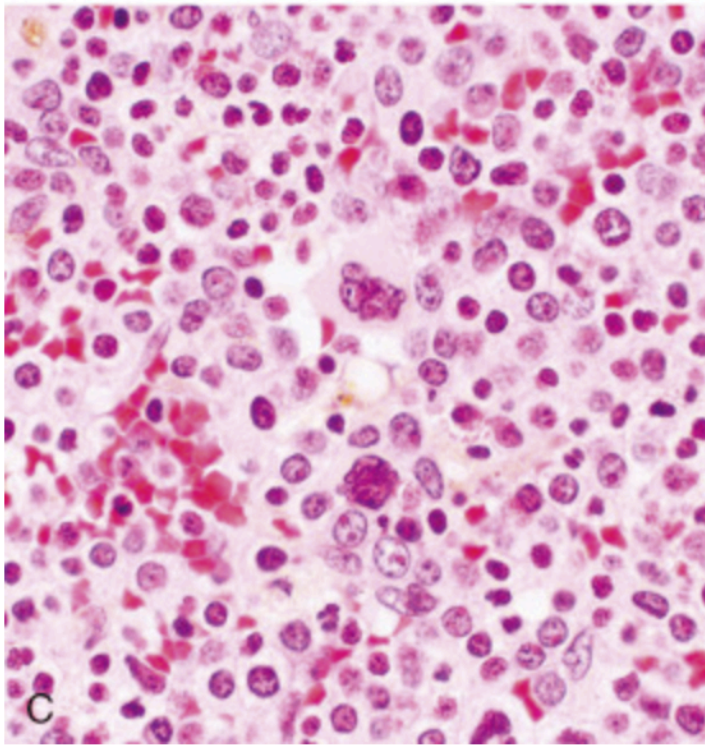


- Leukocytosis > 35K
- Granulocytosis with mild left-shift
- Monocytes < 10%
- **Marked granulocytic dysplasia**
  - Hypercondensed chromatin
  - Hypolobated nuclei
  - Hypogranular cytoplasm

Hsi E et al (ed.) Hematopathology: A Volume in the Series Foundations in Diagnostic Pathology. 2012
Jaffe E et al (ed.) Hematopathology. 2017

Bone marrow in atypical CML

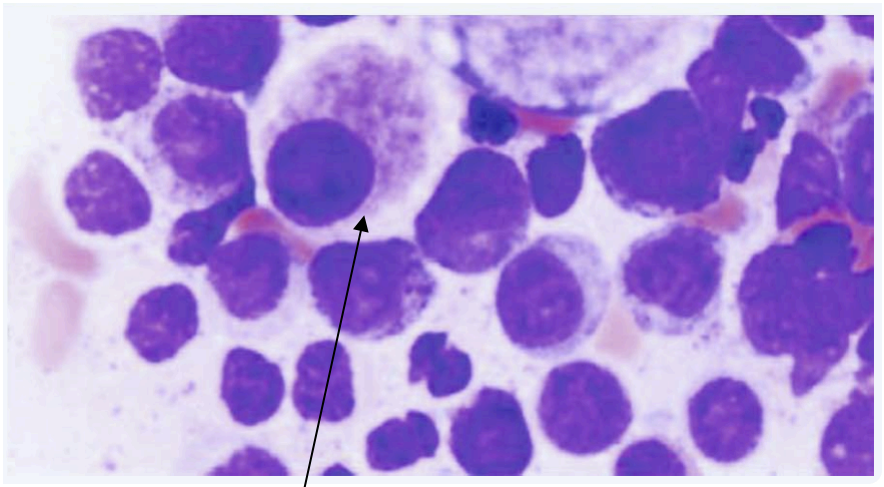




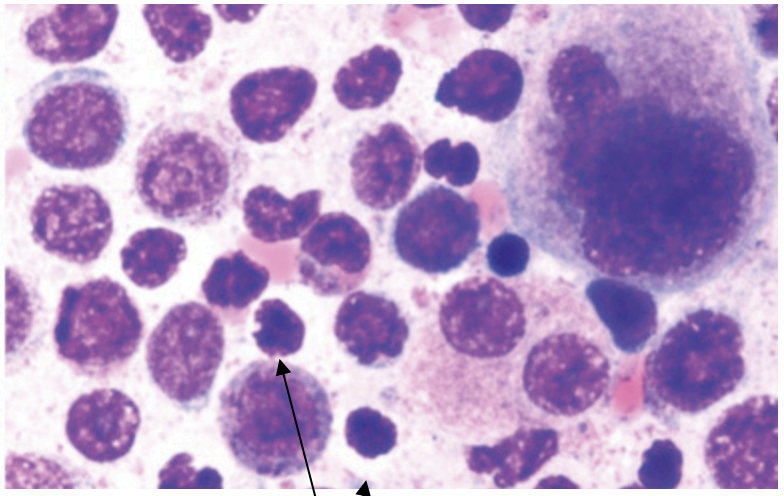
- Hypercellular marrow
- Increased M:E ratio
- Blasts are increased, but < 20%

Hsi E et al (ed.) Hematopathology: A Volume in the Series Foundations in Diagnostic Pathology. 2012
Jaffe E et al (ed.) Hematopathology. 2017

Dysplasia in atypical CML



Dysplastic megakaryocyte



Dysplastic granulocytes

Multilineage dysplasia with prominent granulocytic dysplasia

Hsi E et al (ed.) Hematopathology: A Volume in the Series Foundations in Diagnostic Pathology. 2012
Jaffe E et al (ed.) Hematopathology. 2017

Molecular findings in atypical CML

NEGATIVE

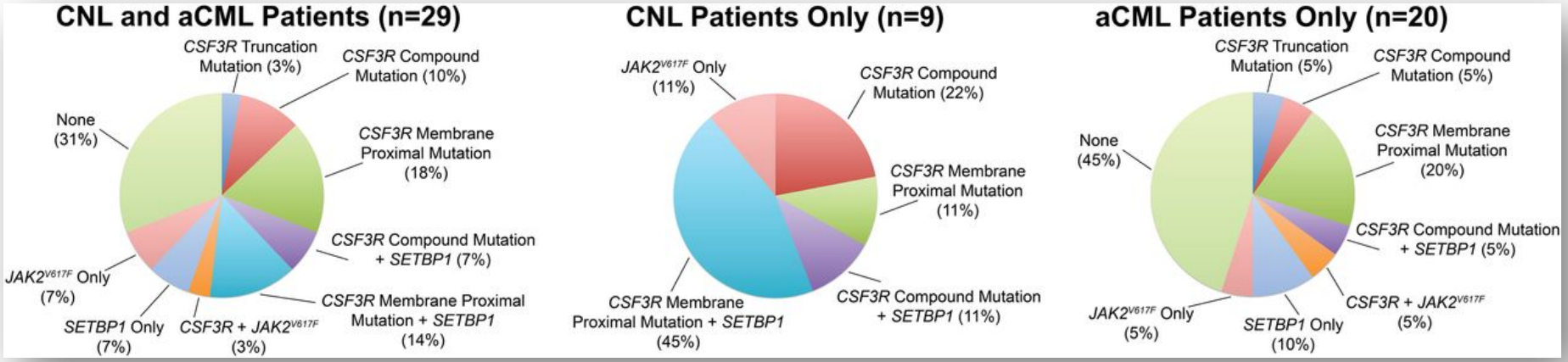
- Must be *BCR-ABL1*/t(9;22) *negative*
- Usually negative for mutations associated with pure MPN: *JAK2, CALR, MPL*
- Usually negative for *CSF3R* (mutation that is common in CNL)

POSITIVE

- 1/3 of cases are positive for *SETBP1* and/or *ETNK1*
- Approximately 80% will have some cytogenetic abnormality; 8+, del(20q) are most common.

Arber DA et al. Blood. 2016; 127(20):2391-2405
Hsi E et al (ed.) Hematopathology: A Volume in the Series Foundations in Diagnostic Pathology. 2012
Jaffe E et al (ed.) Hematopathology. 2017

Mutations in *CSF3R* and *SETBP1* are common in chronic neutrophilic leukemia (CNL) and atypical CML



Jason Gotlib et al. Blood 2013;122:1707-1711

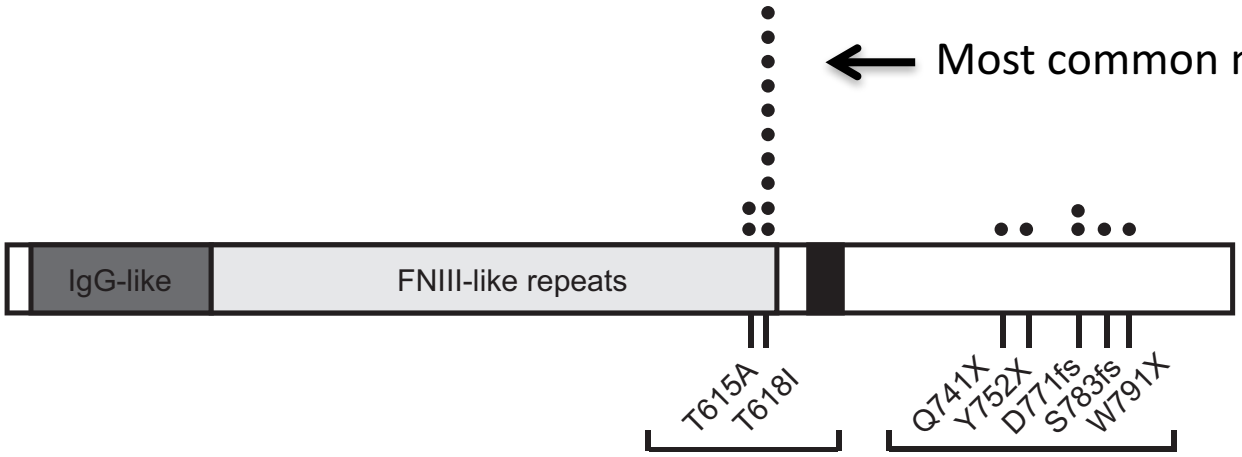
CSF3R mutations are enriched in patients with chronic neutrophilic leukemia (CNL) and atypical CML (2)

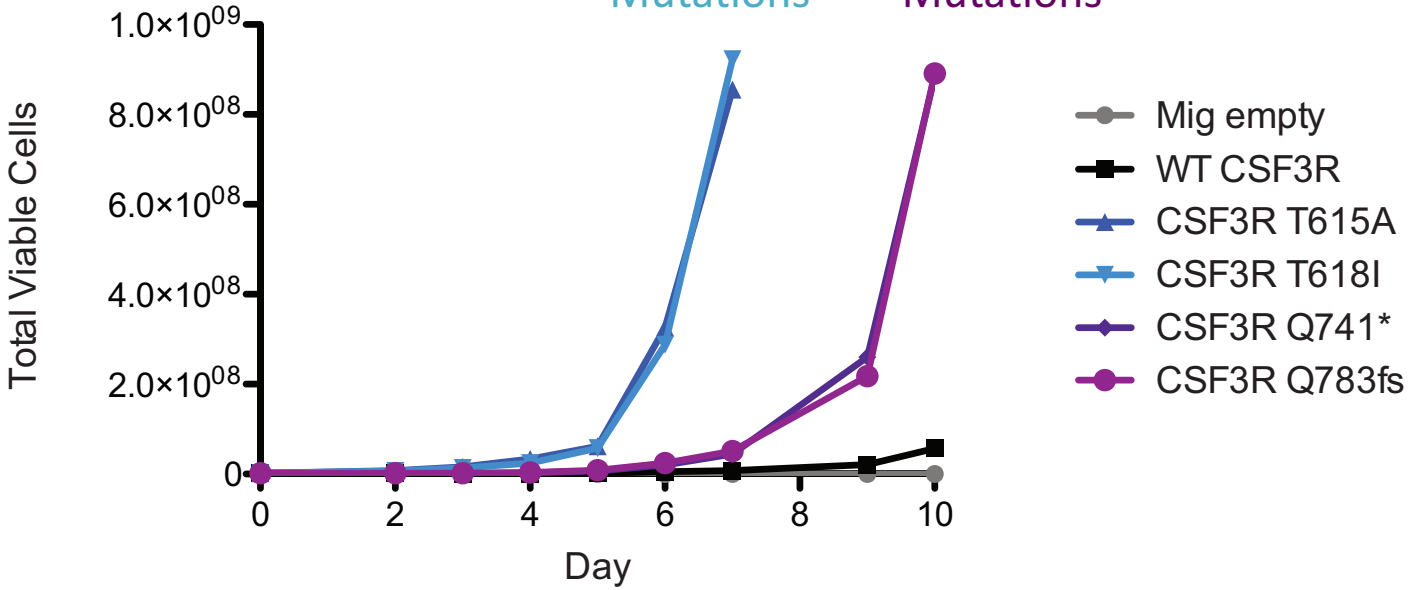
Diagnosis	*CSF3R* Mutation	Estimate of Frequency	Other Cohorts
CNL/aCML	16/27	59%	83% in CNL Pardanani et al, 2013
AML*	3/292	~1%	~0.5% Beekman et al, 2013
ETP-T-ALL	1/3	unknown	
T-ALL	0/8	0	
B-ALL	0/41	0	

*Frequency for AML includes patients from TCGA

Maxson et al, NEJM, 2013.

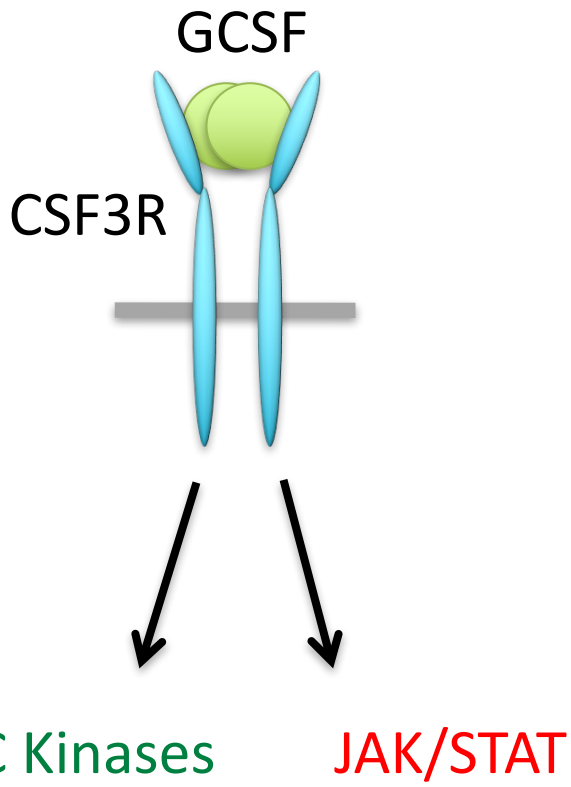
Two classes of *CSF3R* mutations





Maxson et al, NEJM, 2013

CSF3R signals through both SRC and JAK kinases

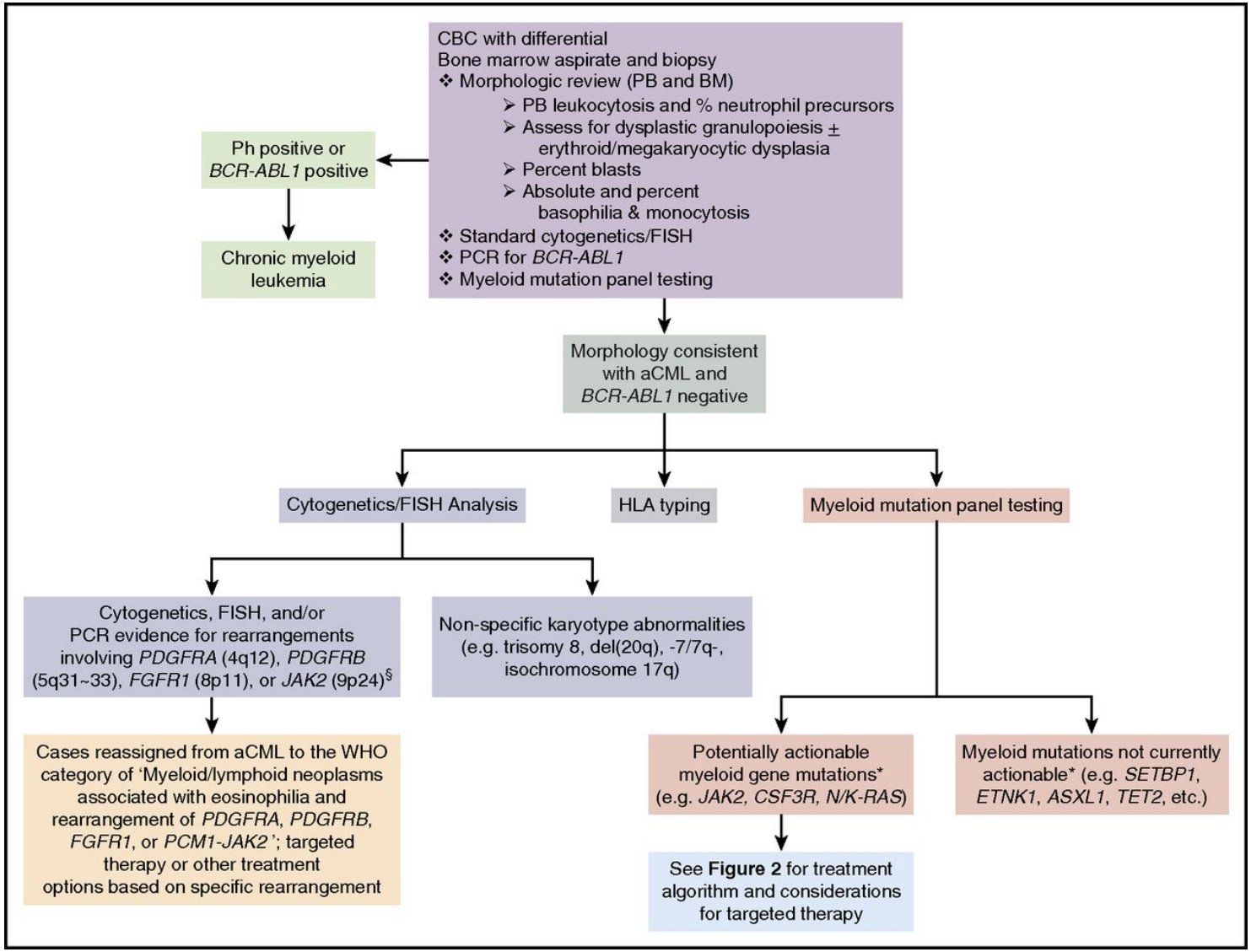


Treatment of atypical CML

- No standard of care exists for aCML
- Current therapy consists of hydroxyurea, oral chemotherapeutics and interferon – α
- These therapies can improve the blood counts, but provide no disease-modifying benefits
- Palliative care can include splenic irradiation and splenectomy to reduce symptoms
- Induction-type chemotherapy for blastic transformation is usually poor with death related to resistant disease or regimen-related toxicities
- Allogeneic transplantation could result in long-term outcomes in select patients
- "In patients for whom the cause of neutrophilia is not easily discernible, the incorporation of *CSF3R* mutation testing can be a useful point-of-care diagnostic to evaluate for the presence of a clonal myeloid disorder, as well as the potential for genetically informed therapy"

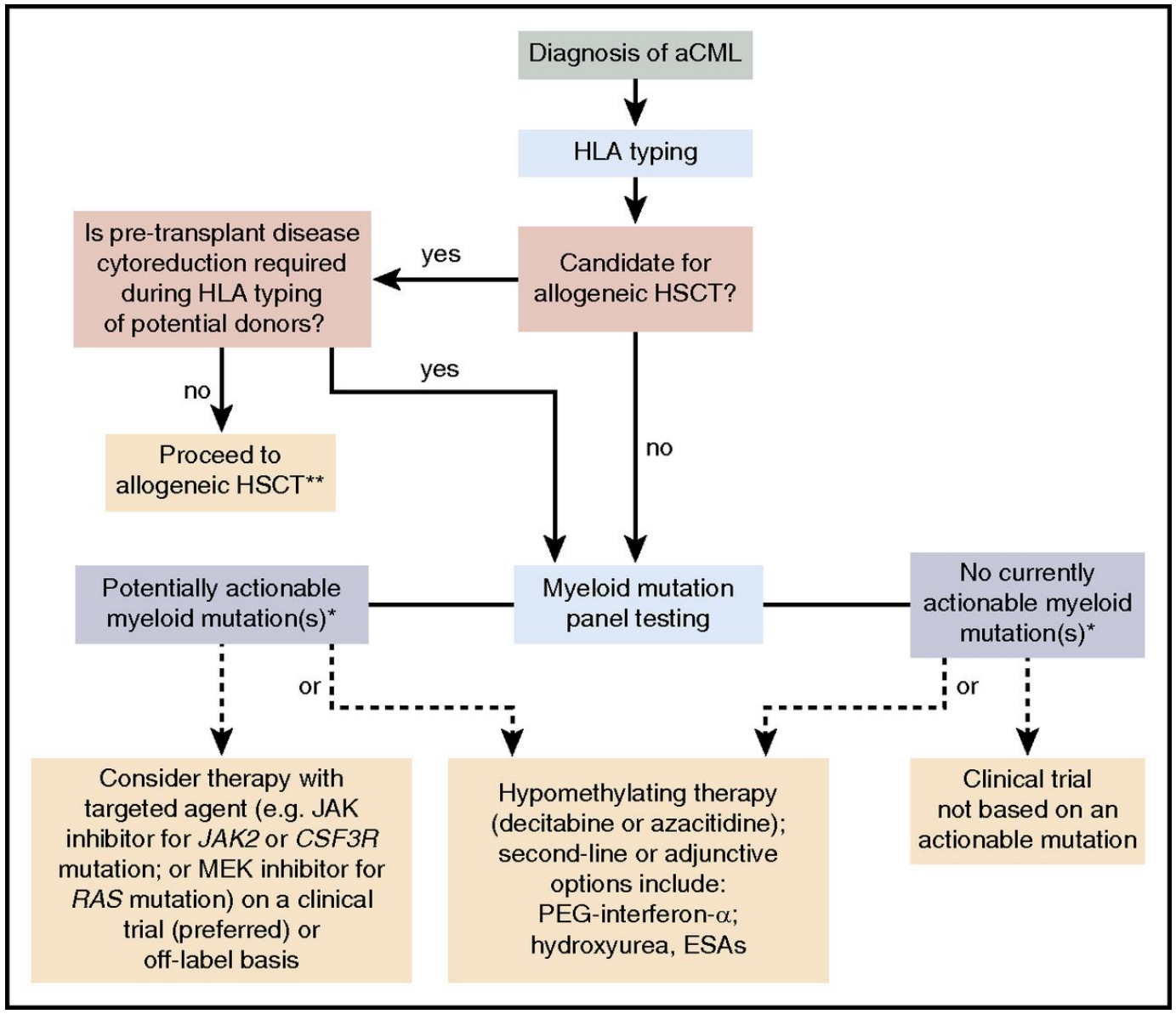
Jason Gotlib et al. Blood 2013;122:1707-1711

Diagnostic evaluation for atypical CML and identification of opportunities for targeted therapy



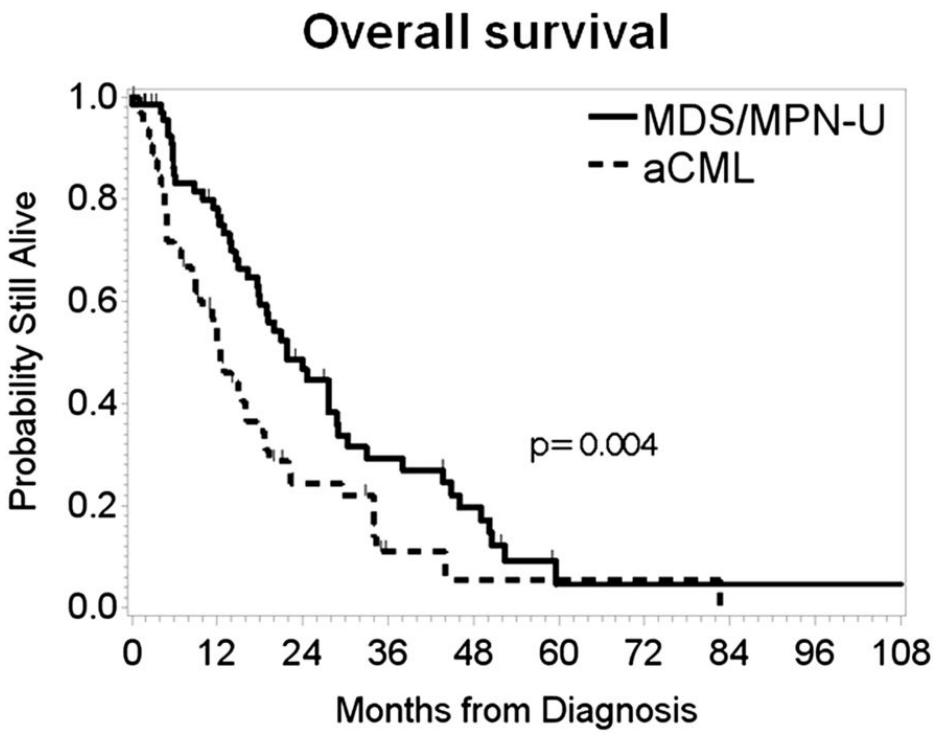
Jason Gotlib Blood 2017;129:838-845

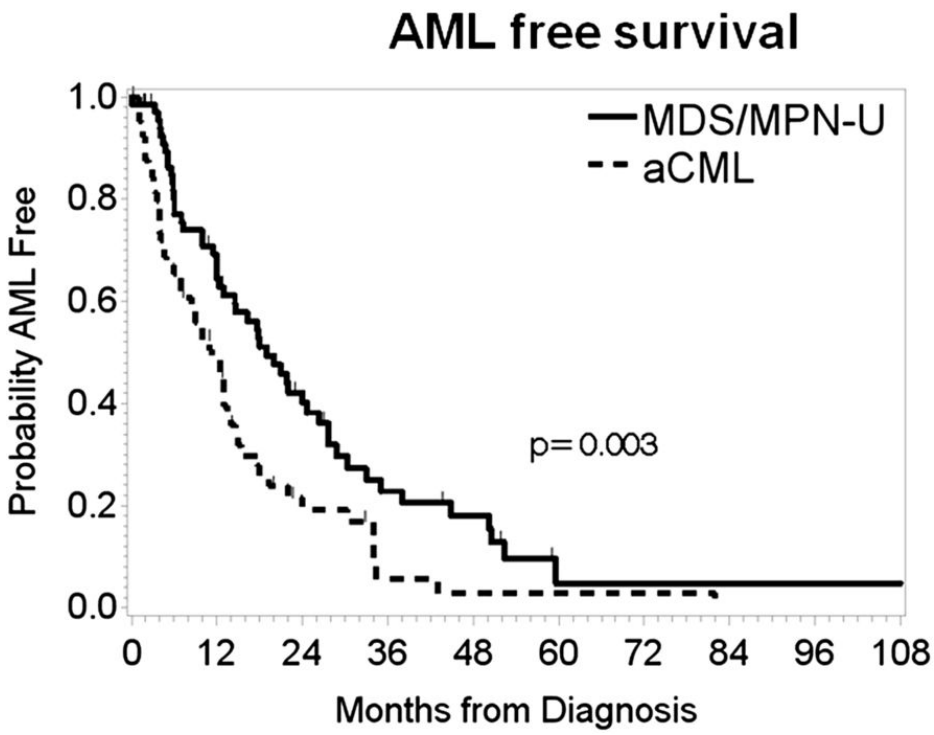
Treatment algorithm for atypical CML



Jason Gotlib Blood 2017;129:838-845

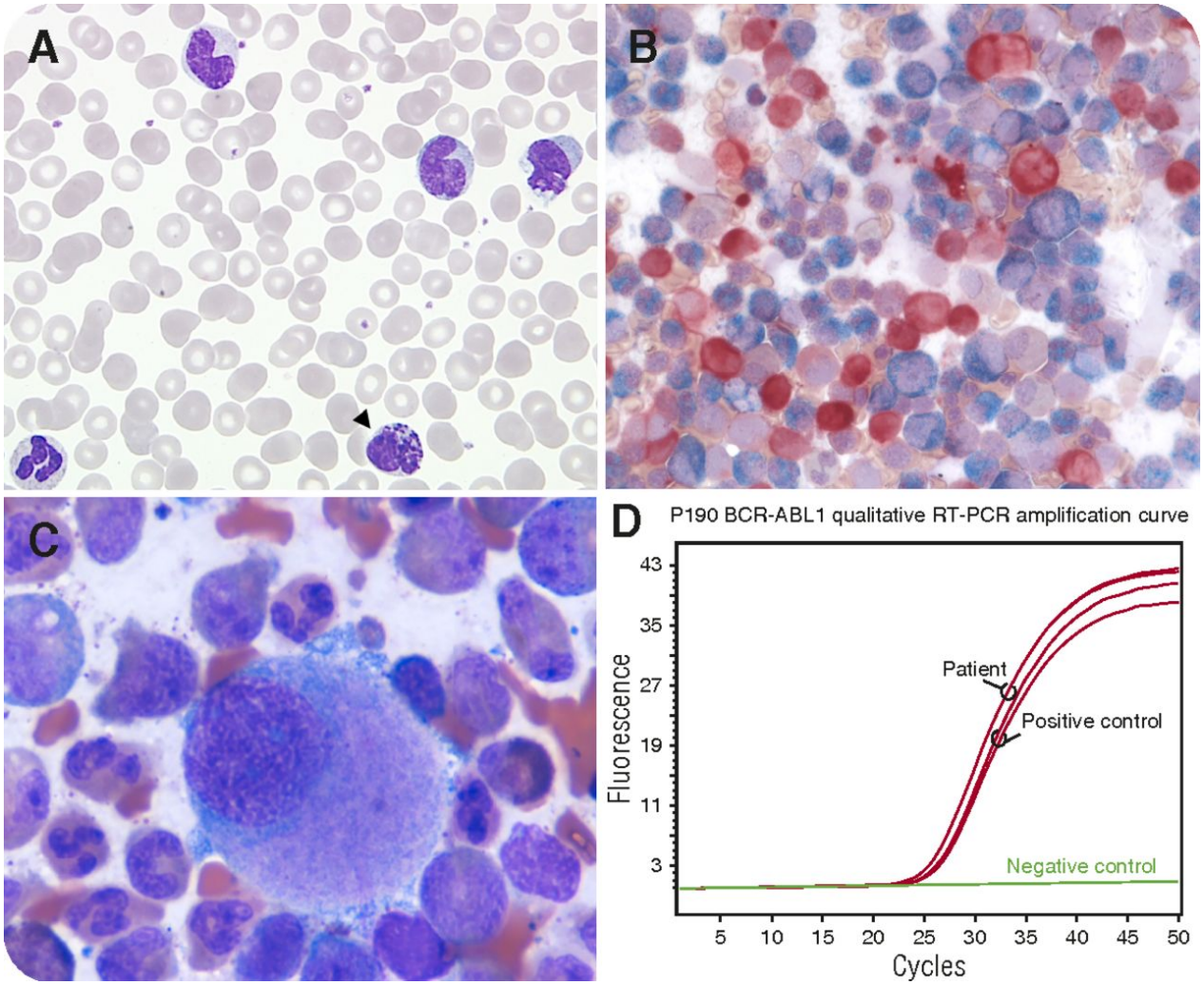
Overall and AML-free survival in atypical CML





Sa A. Wang et al. Blood 2014;123:2645-2651

The thin line between CML and CMML



Megan Parilla, and Girish Venkataraman, Blood 2017;129:2456

A 57-year-old woman with autosomal dominant polycystic kidney disease, after liver/kidney transplant 2 years ago, presented with complaint of isolated left abdominal discomfort. A complete blood count demonstrated isolated leukocytosis (40 200/µL) with normal platelet count (234 000/µL) and hemoglobin. A peripheral blood smear demonstrated absolute monocytosis (6400/µL), neutrophils without significant dysplasia, and rare basophils (panel A, arrowhead indicates basophil; original magnification ×200, Giemsa stain) without circulating blasts. A bone marrow biopsy was hypercellular with marked granulocytic expansion comprising predominantly mature neutrophils and normal megakaryocytes with rare immature small megakaryocytes on aspirate (panel C; original magnification ×400, Giemsa stain). Combined esterase cytochemical stain shows marked increase in marrow monocytic cells (panel B, brown; original magnification ×200) with background granulocytic cells (panel B, blue). A concurrently performed peripheral blood BCR-ABL molecular assay (testing simultaneously for both P210 and P190 transcripts) detected the P190 fusion variant (panel D) without P210, whereas conventional karyotype showed the classic t(9;22)(q34.1;q11.2).The chronic myeloid leukemia (CML)-P190 variant often resembles chronic myelomonocytic leukemia (CMML) due to the associated marked monocytosis. However, the lack of granulocytic dysplasia and thrombocytopenia is unusual in CMML. Another rare CML variant with the longer P230 transcript phenotypically presents with neutrophilia and thrombocytosis. In the absence of BCR-ABL fusion, some CMMLs with normal-high platelets counts carry concurrent JAK2 mutations. This case highlights the need to exclude underlying BCR-ABL rearrangements before making a diagnosis of CMML.

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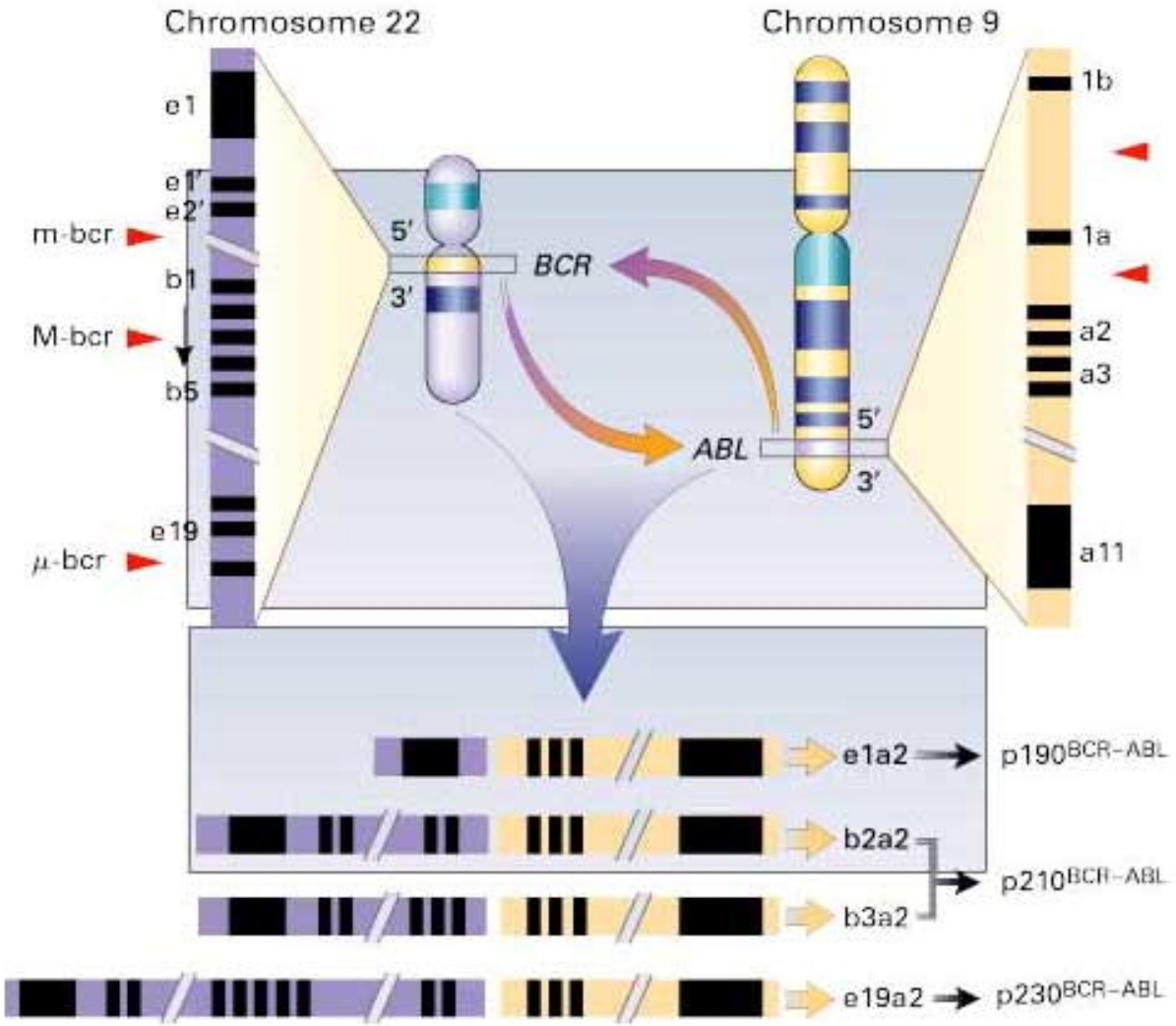
The variety of t(9;22)(q34;q11) breakpoints in CML



Faderl S *et al*. N Engl J Med 1999;341:164-172