

Chronic myeloid leukemia

Molecular basis • diagnostic morphology • disease evolution

BCR::ABL → constitutive ABL kinase signaling

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A pathology lecture grounded in Robbins, Cotran & Kumar

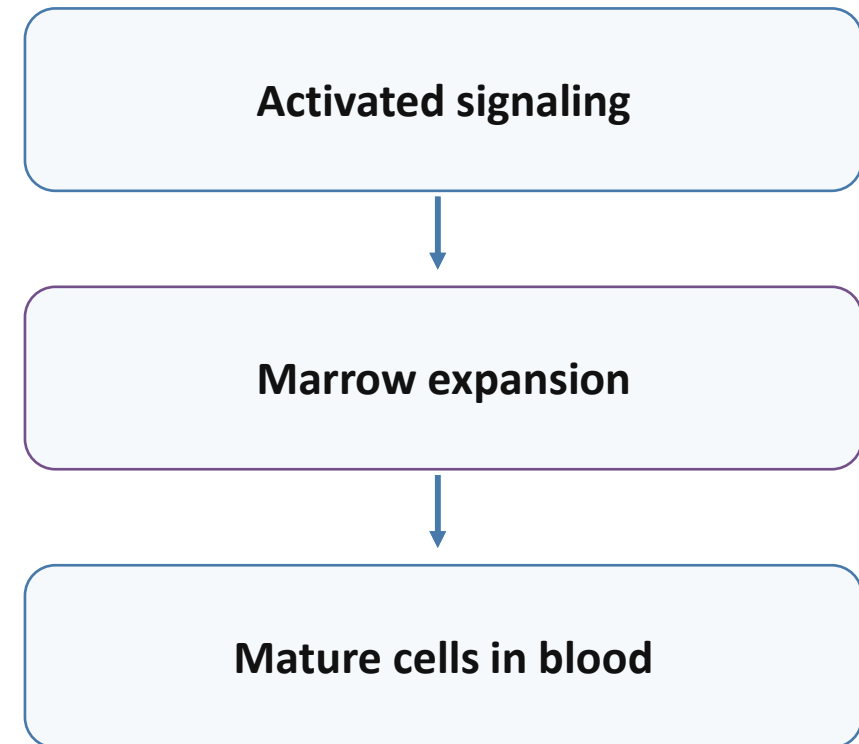
Learning outcomes

- Trace the t(9;22) rearrangement to constitutive BCR-ABL signaling.
- Explain the characteristic peripheral blood, marrow, and splenic findings.
- Select tests that establish the molecular identity of CML.
- Relate clonal evolution and kinase inhibition to the disease course.

Mechanism → morphology → diagnosis → clinical outcome

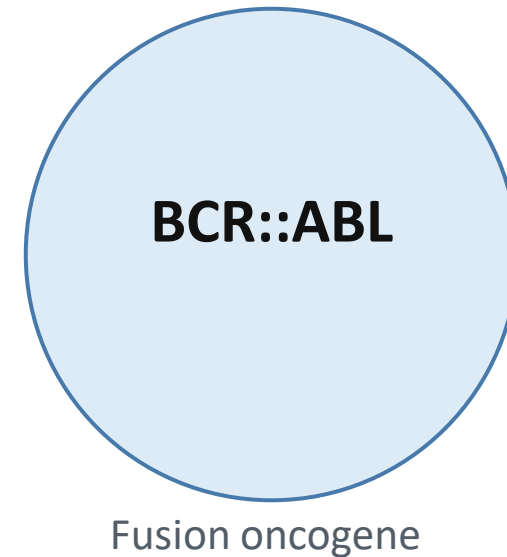
CML belongs to the myeloproliferative neoplasms

- MPNs are clonal expansions driven by aberrant growth and survival signaling.
- They commonly overproduce differentiated blood cells.
- CML is distinguished by a specific BCR::ABL gene fusion.



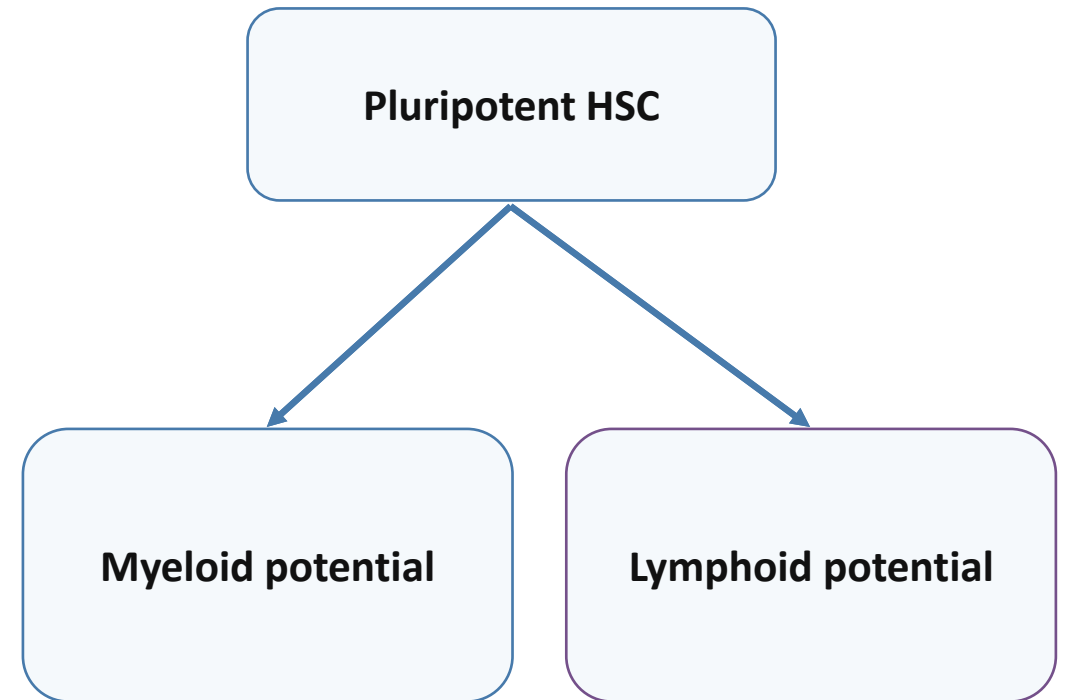
CML has a defining molecular lesion

- The characteristic lesion combines sequences from BCR on chromosome 22 and ABL on chromosome 9.
- The resulting fusion encodes a constitutively active tyrosine kinase.
- A molecular test can therefore identify the disease, not merely support a morphologic impression.



Stem-cell origin explains multilineage potential

- The initiating neoplastic cell is a pluripotent hematopoietic stem cell.
- Its descendants expand especially in granulocytic and megakaryocytic compartments.
- Both myeloid and lymphoid blast crises are possible after progression.



Proliferation increases without a maturation block

- The founding BCR-ABL kinase promotes proliferation and survival.
- It does not, by itself, prevent differentiation.
- Consequently, chronic-phase blood contains many maturing and mature granulocytes.

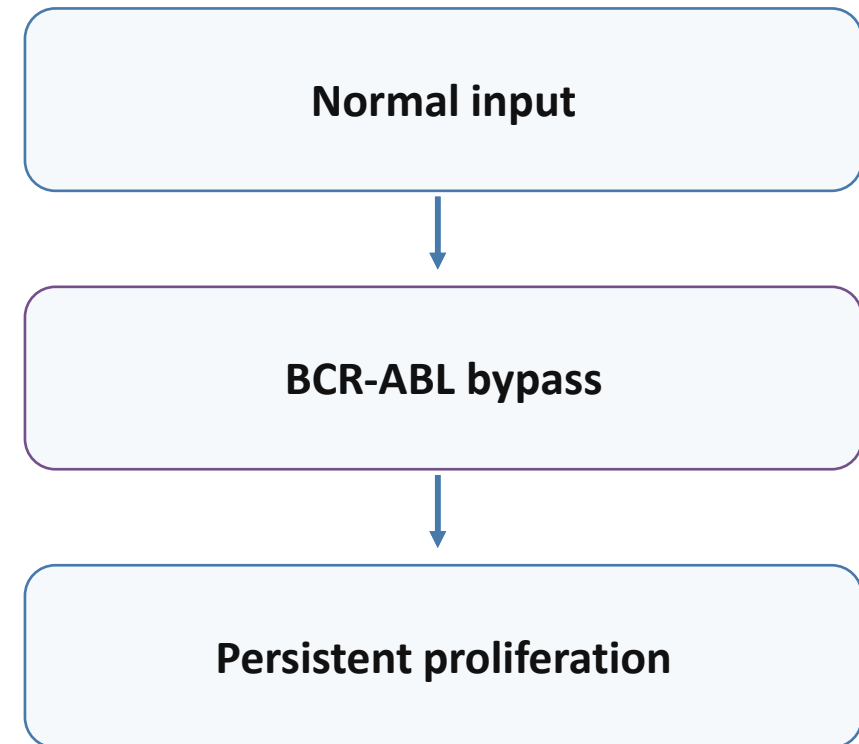
**CML: Expansion +
maturation**

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**Acute leukemia:
Blast accumulation**

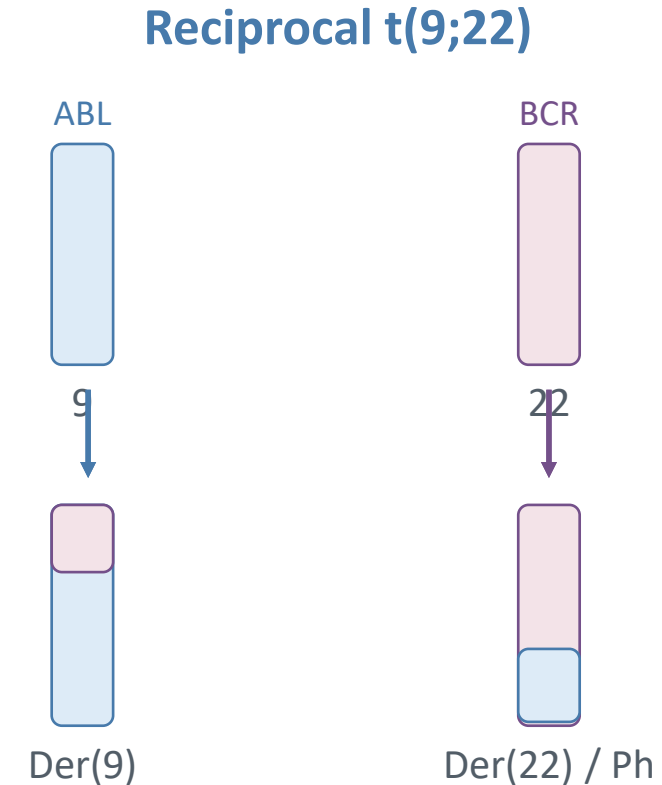
Growth-factor independence: The central MPN principle

- Normal growth factors regulate tyrosine kinase signaling.
- Oncogenic signaling allows progenitors to proliferate with reduced dependence on these controls.
- In CML, the BCR-ABL fusion protein provides this abnormal signal.



The Philadelphia rearrangement involves 9 and 22

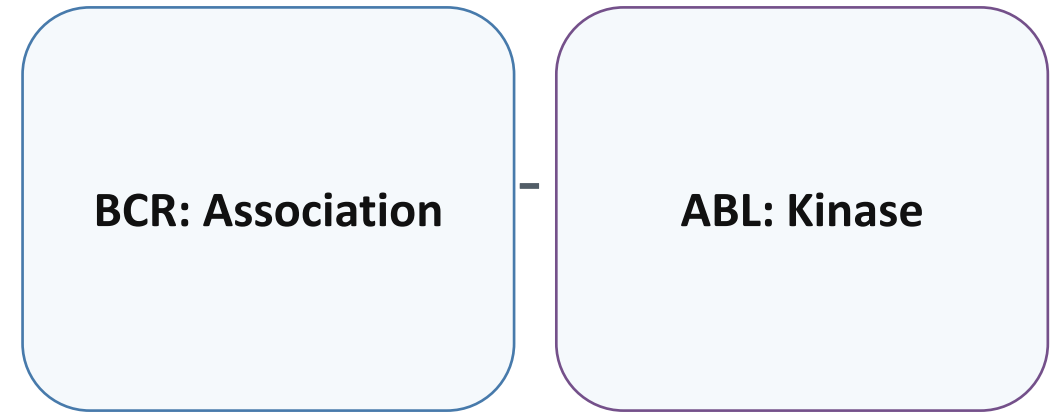
- The usual cytogenetic event is reciprocal $t(9;22)(q34;q11)$.
- A derivative chromosome 22 carries the BCR::ABL fusion.
- The rearrangement is conventionally called the Philadelphia chromosome.



Schematic gene exchange — not a karyotype

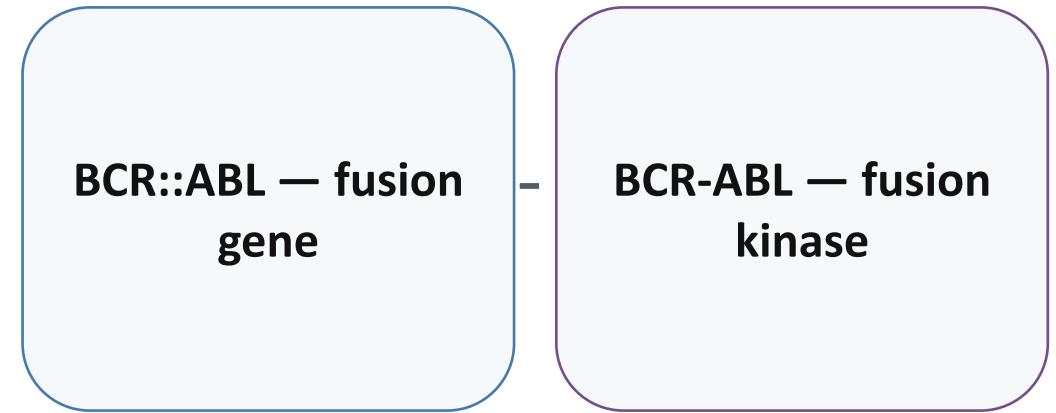
The two partner genes contribute distinct functions

- BCR contributes a self-associating dimerization region.
- ABL supplies the tyrosine kinase catalytic component.
- Their fusion changes the normal control of ABL activity.



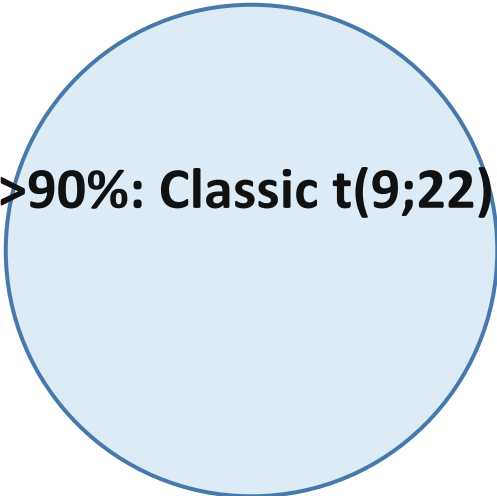
BCR::ABL is the gene; BCR-ABL is its protein

- BCR::ABL denotes the rearranged genetic sequence.
- BCR-ABL denotes the encoded chimeric tyrosine kinase.
- Distinguishing the gene from the protein clarifies diagnostic and therapeutic language.



Most cases show a visible Philadelphia translocation

- More than 90% of cases have the classic reciprocal rearrangement.
- Conventional chromosome analysis can demonstrate t(9;22).
- A minority require molecular methods to reveal a cryptic or complex fusion.

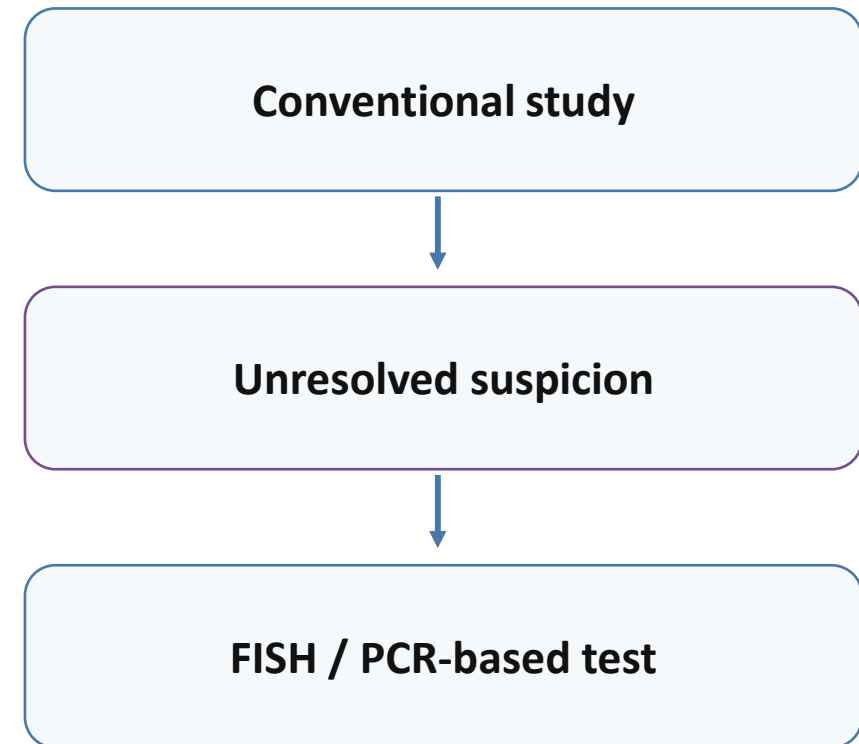


>90%: Classic t(9;22)

Remainder: Cryptic / complex

Cryptic BCR::ABL may escape routine karyotyping

- The fusion can arise through cytogenetically complex or cryptic events.
- Absence of a visibly recognizable Ph chromosome does not exclude BCR::ABL.
- Fluorescence in situ hybridization and PCR-based tests can detect these cases.



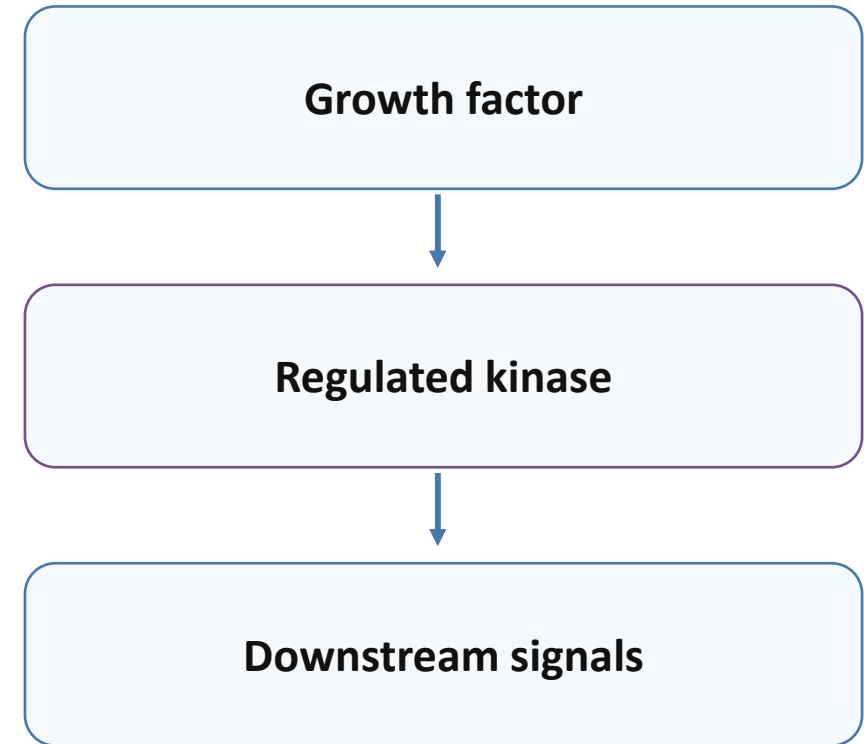
CML usually produces the 210-kDa BCR-ABL protein

- The typical fusion product in CML is about 210 kDa.
- Its biological importance is constitutive ABL kinase activity.
- Protein size is not a substitute for demonstrating the fusion genetically.



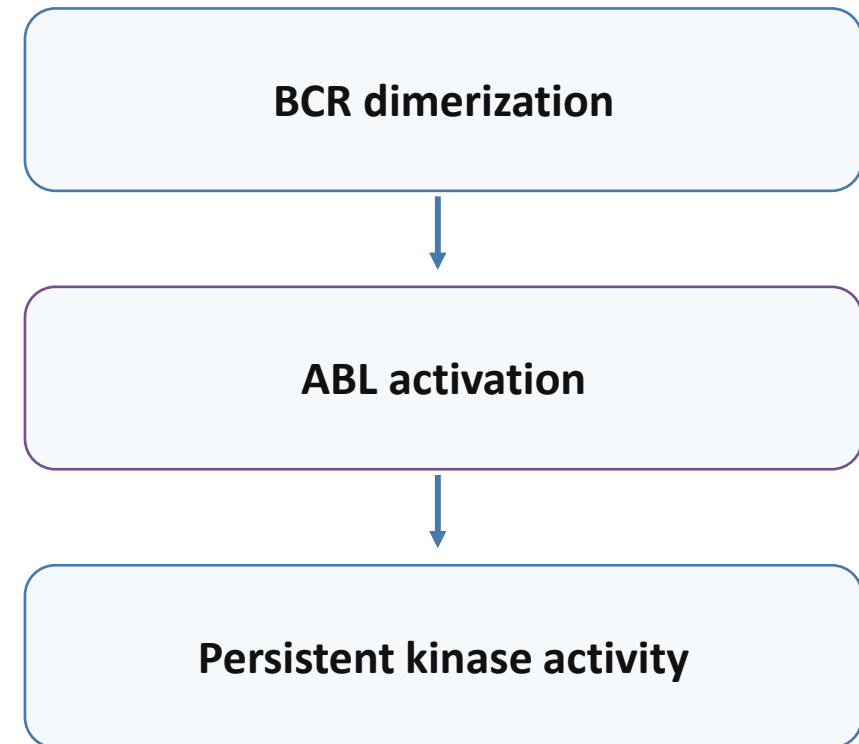
Normal kinase activation is regulated

- Ligand-dependent receptor activation ordinarily promotes dimerization.
- Autophosphorylation initiates signaling through downstream substrates.
- This architecture ties signaling to physiological inputs.



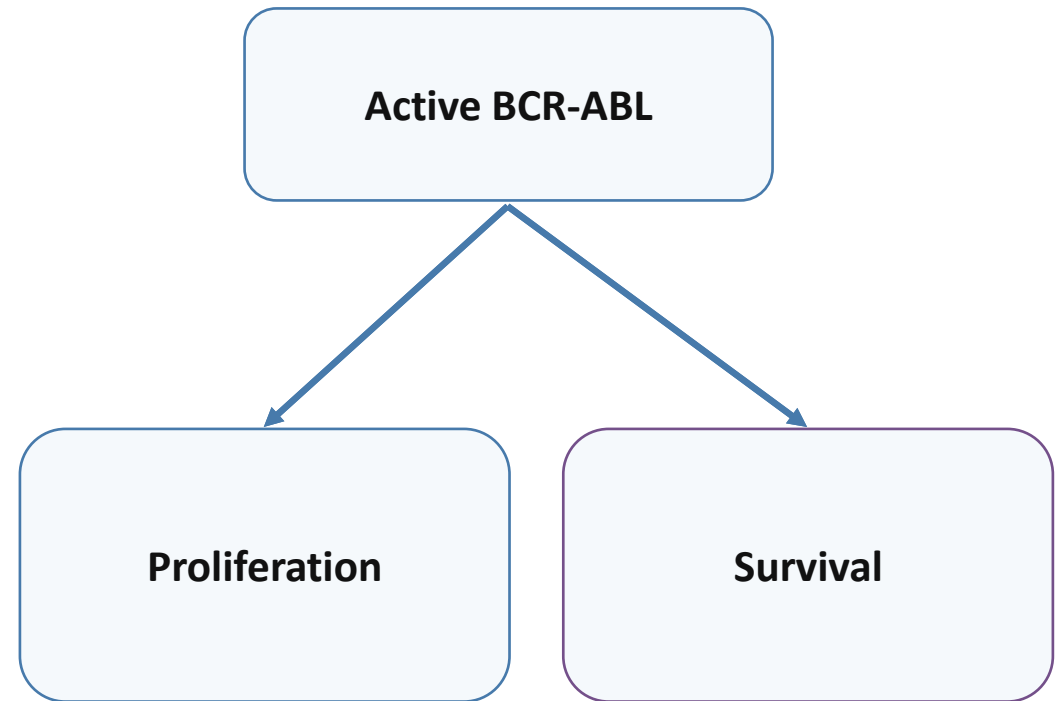
BCR-mediated dimerization switches ABL on

- The BCR region self-associates, bringing fusion proteins together.
- This permits inappropriate ABL kinase activation.
- Signaling persists in the absence of ordinary growth-factor regulation.



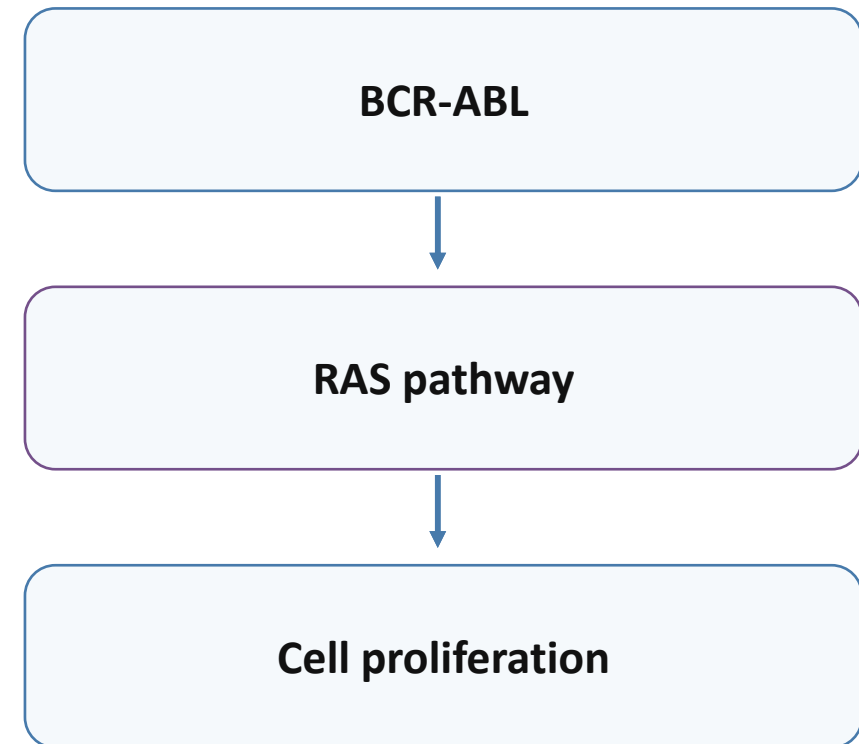
Constitutive signaling drives two main outcomes

- Survival signaling allows expansion of abnormal progenitors.
- Proliferative signaling increases their production of progeny.
- Together these outputs support the highly cellular marrow and leukocytosis.



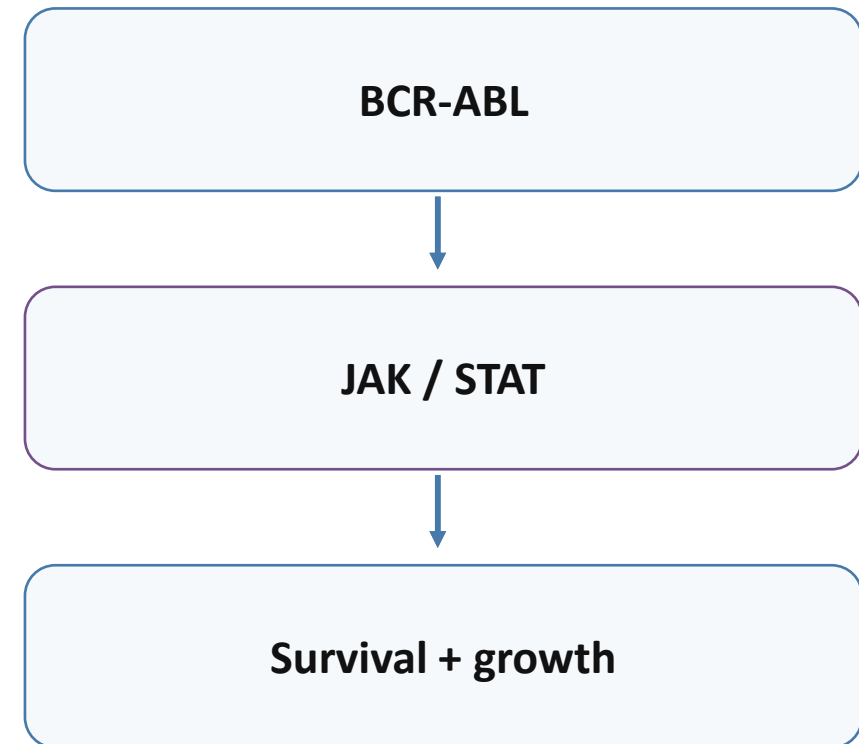
The RAS pathway contributes to growth signals

- BCR-ABL activates downstream pathways that include RAS signaling.
- These pathways normally participate in growth-factor responses.
- Constitutive upstream activity sustains progenitor proliferation.



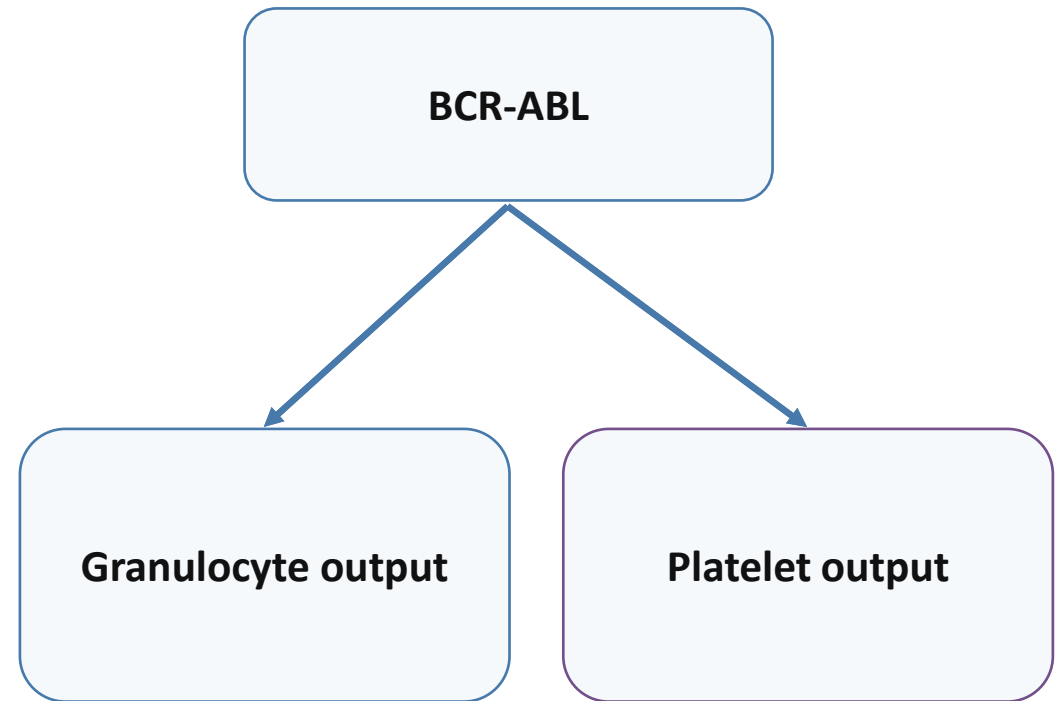
The JAK/STAT pathway supports the neoplastic clone

- BCR-ABL also activates the JAK/STAT pathway.
- Its signaling contributes to prosurvival and progrowth effects.
- The hallmark is inappropriate pathway activation, not an asserted unique pathway dependency.



Multiple signals converge on increased cell output

- The kinase activates more than one downstream effector pathway.
- Granulocytic and megakaryocytic progenitors respond prominently.
- The net result is excess differentiated granulocytes and commonly platelets.



Why those progenitors dominate remains uncertain

- Preferential stimulation of granulocytic and megakaryocytic progenitors.
- The molecular basis for this lineage preference is not established in the source.
- Do not mistake an observed phenotype for a proven lineage-specific mechanism.

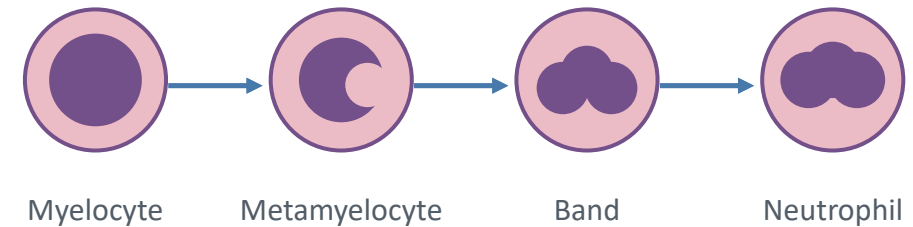
**Established:
Lineage bias**

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**Uncertain: Exact
cause**

Premature release reshapes the blood differential

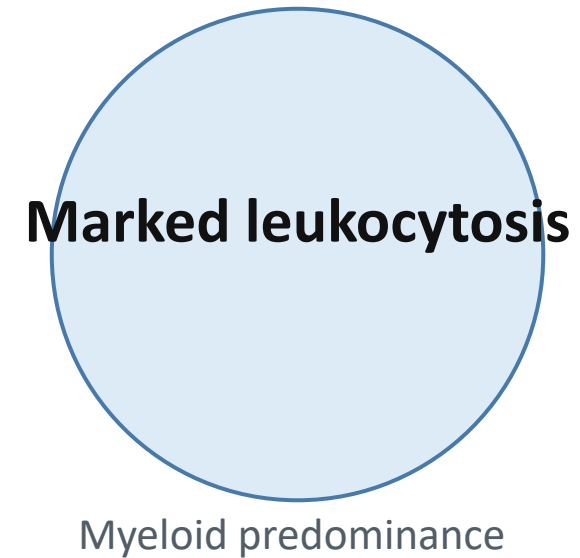
- Immature granulocytic cells appear in circulating blood.
- They accompany, rather than replace, large numbers of mature forms.
- This is a left-shifted granulocytic spectrum associated with CML.



Schematic cell maturation — not a blood film

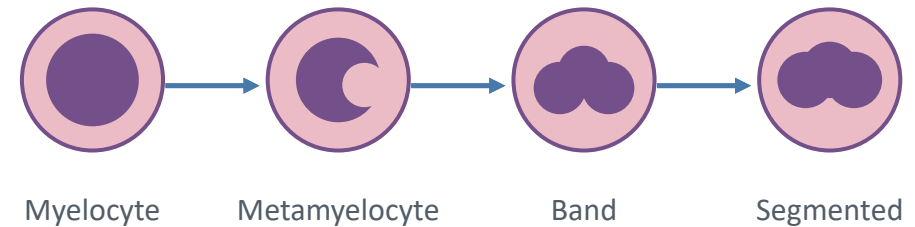
Marked leukocytosis is the central blood finding

- Leukocytes can be strikingly increased at presentation.
- Most circulating cells belong to the neutrophilic granulocytic series.
- Absolute cell count alone cannot establish the genetic diagnosis.



A spectrum of granulocyte maturity is typical

- Circulating cells include myelocytes and metamyelocytes.
- Bands and segmented neutrophils are also numerous.
- The co-occurrence of several maturation stages reflects preserved differentiation.



Schematic cell maturation — not a blood film

Basophils and eosinophils are increased

- Basophilia and eosinophilia accompany the expanded granulocytic compartment.
- These components are diagnostically informative when read with the full differential.
- Neither alone proves BCR::ABL positivity.



Blast cells form a minority during chronic phase

- In the Robbins morphology description, circulating blasts usually account for less than 10%.
- Most leukocytes remain at later stages of maturation.
- Rising blasts raise concern for a change in disease phase.

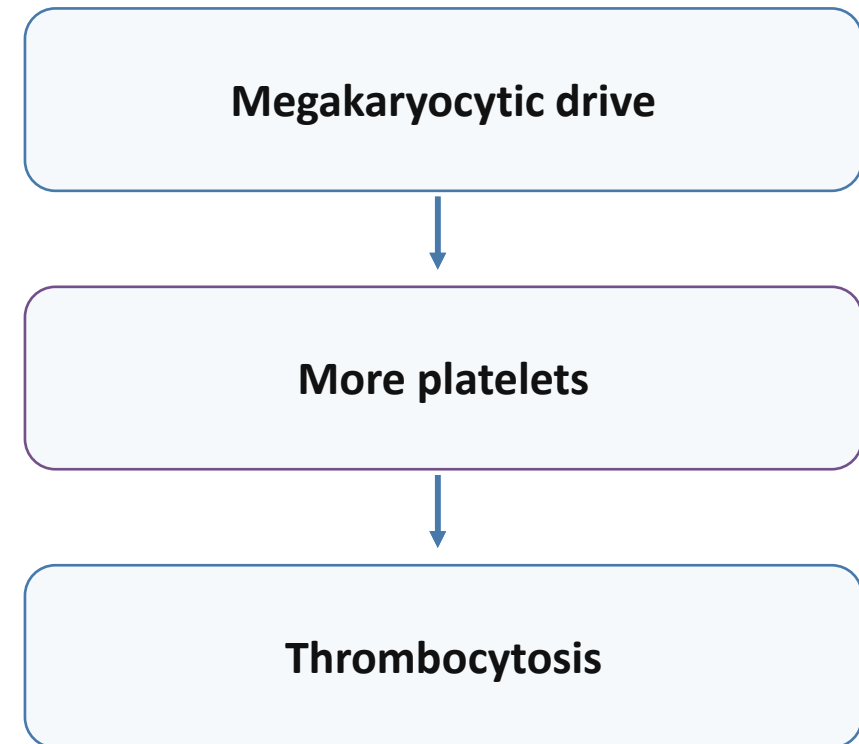
**Chronic: Mature
series dominant**

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**Progression:
Immature cells rise**

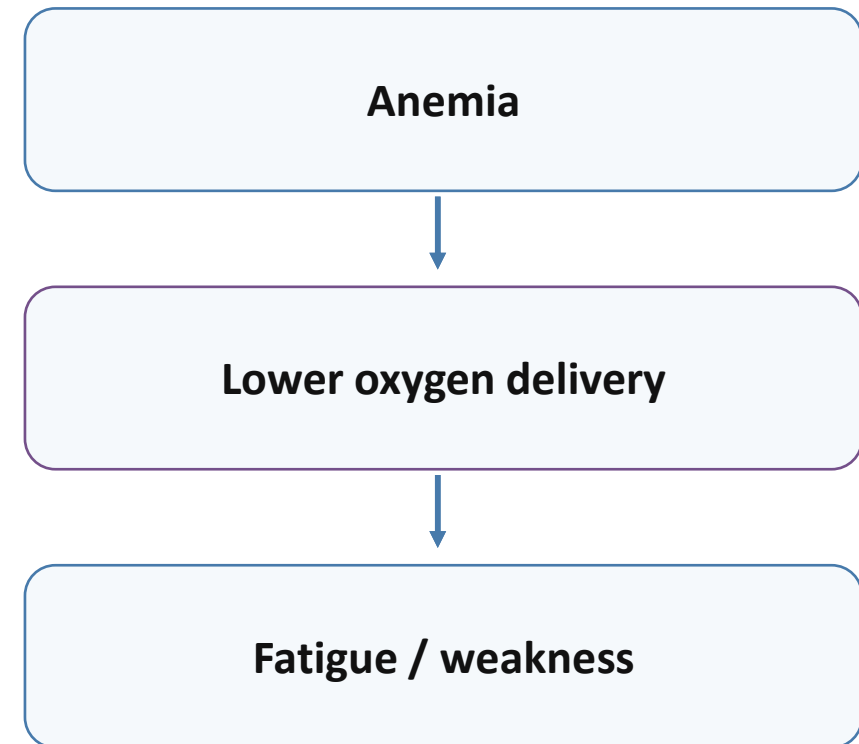
Thrombocytosis often accompanies leukocytosis

- Platelet numbers are commonly elevated.
- In some cases the platelet increase is marked.
- This parallels expansion of megakaryocytic progenitors in the marrow.



Anemia contributes to the presenting symptoms

- CML may have mild-to-moderate anemia.
- Anemia contributes to fatigue and weakness.
- The clinical picture also reflects increased metabolic demand from accelerated turnover.



Bone marrow is markedly hypercellular

- Maturing granulocytic precursors occupy much of the marrow.
- The intense proliferative drive reduces the relative space available to other elements.
- Hypercellularity is a tissue manifestation of the kinase-driven clone.

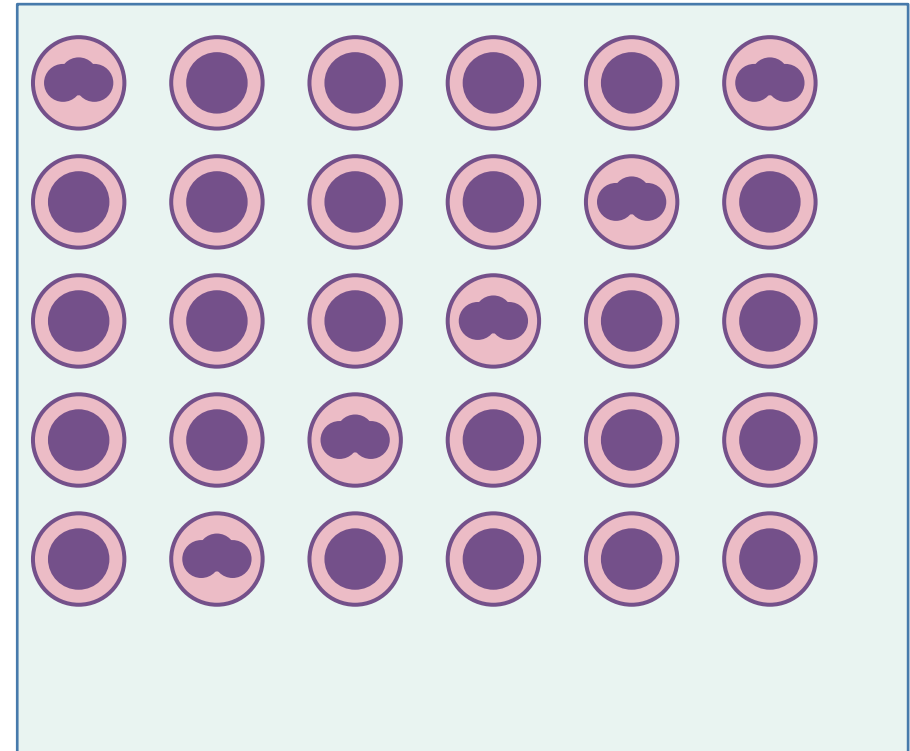
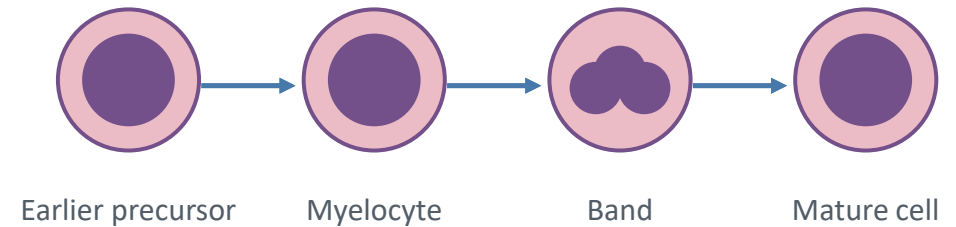


Illustration of increased cellularity — not histology

Myeloid maturation remains evident in marrow

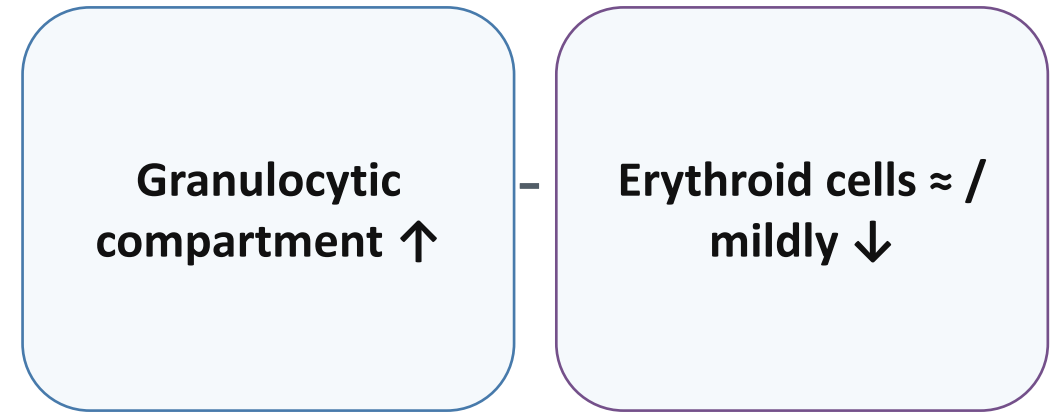
- Granulocytic precursors occur at multiple stages.
- Neutrophilic differentiation remains conspicuous.
- The expanded maturing series explains the left-shifted peripheral blood picture.



Schematic cell maturation — not a blood film

Erythroid progenitors are relatively preserved

- Erythroid progenitors as normal or mildly decreased in number.
- The dramatic feature is disproportionate granulocytic expansion.
- Do not equate a lower relative erythroid proportion with complete erythroid aplasia.



Megakaryocytes include small abnormal forms

- Megakaryocyte numbers are increased.
- Small, dysplastic megakaryocytes are a characteristic component.
- This observation links tissue morphology to platelet overproduction.

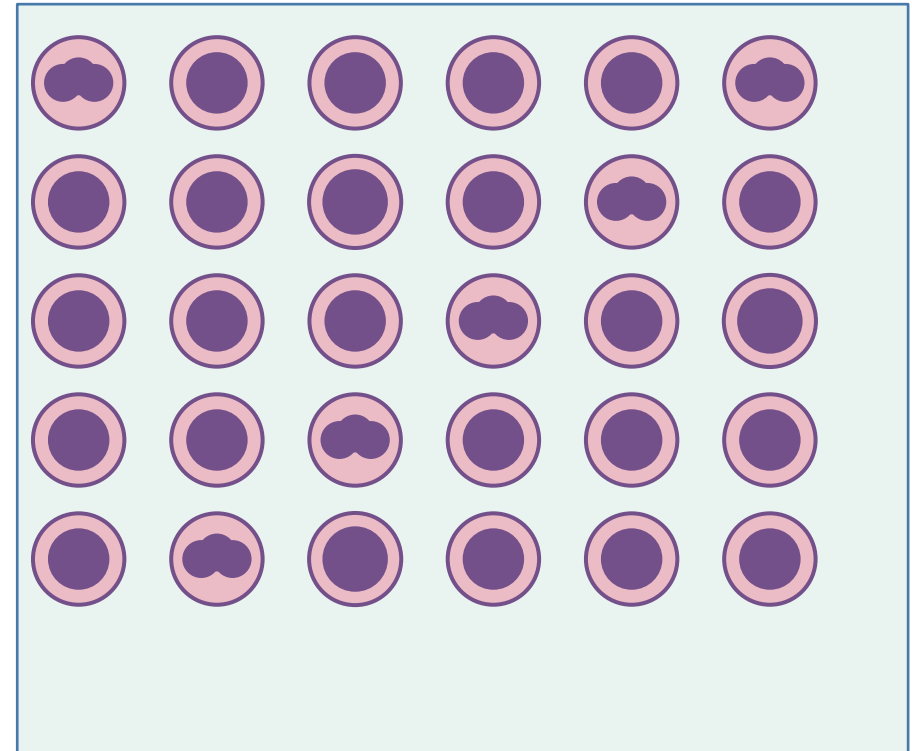


Illustration of increased cellularity — not histology

Sea-blue histiocytes reflect accelerated turnover

- Scattered marrow macrophages may show wrinkled green-blue cytoplasm.
- These are described as “sea-blue histiocytes.”
- They are an associated morphologic clue, not the defining genetic lesion.



Reticulin increase is not synonymous with fibrosis

- Increased reticulin deposition is typical.
- Overt marrow fibrosis is uncommon in ordinary chronic-phase CML.
- The two findings should not be conflated during morphologic description.

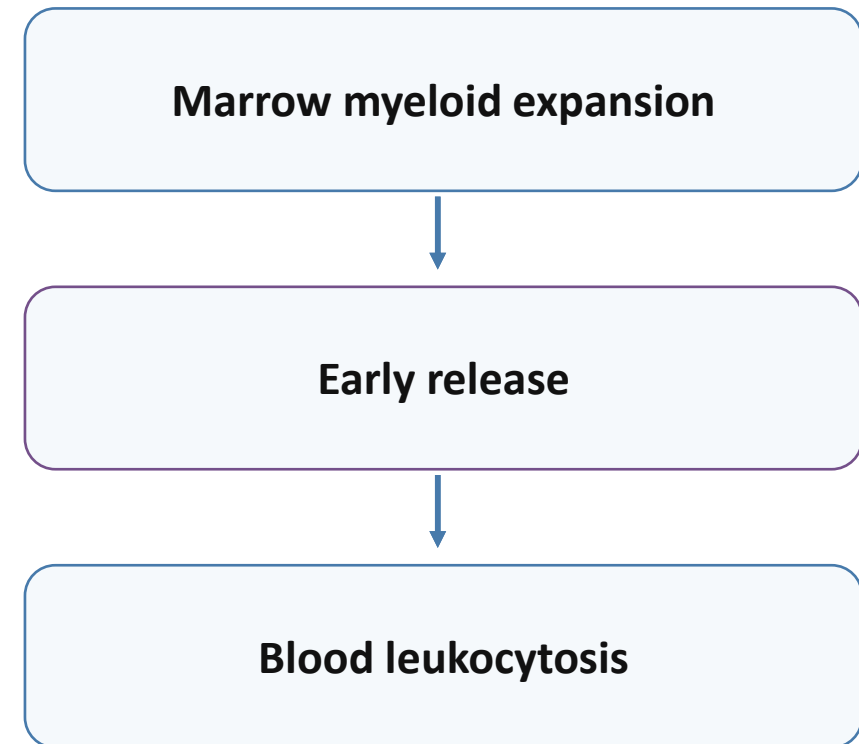
**Reticulin: Often
increased**

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**Overt fibrosis:
Uncommon**

Marrow-to-blood relationship in one view

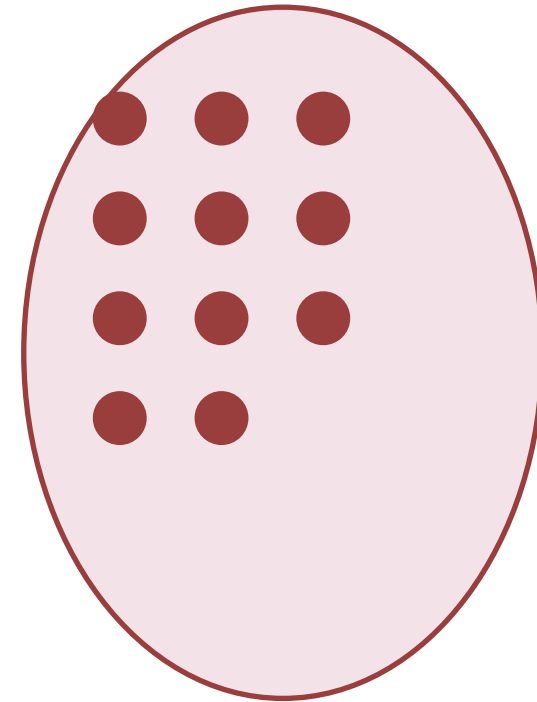
- The hypercellular marrow releases many maturing granulocytes.
- The blood becomes dominated by neutrophilic forms with a left shift.
- Both changes share a BCR-ABL-driven proliferative mechanism.



Splenomegaly results from extramedullary hematopoiesis

- The spleen can become massively enlarged.
- Extensive hematopoietic activity develops outside the marrow.
- The enlarged organ may become the most obvious clinical abnormality.

Schematic enlarged spleen (not a specimen)

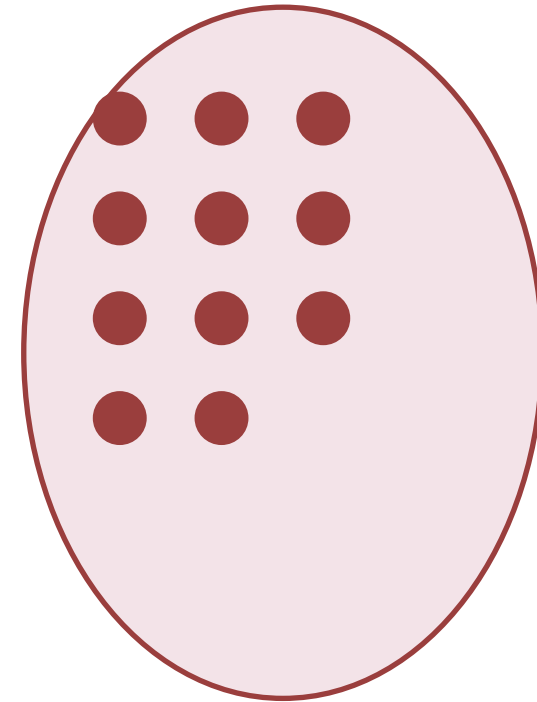


Extramedullary hematopoiesis

Splenic infarcts can complicate enlargement

- Infarcts of varying ages are described in enlarged CML spleens.
- An infarct may present with acute left upper-quadrant pain.
- This differs from the chronic dragging abdominal sensation of splenomegaly.

Schematic enlarged spleen (not a specimen)

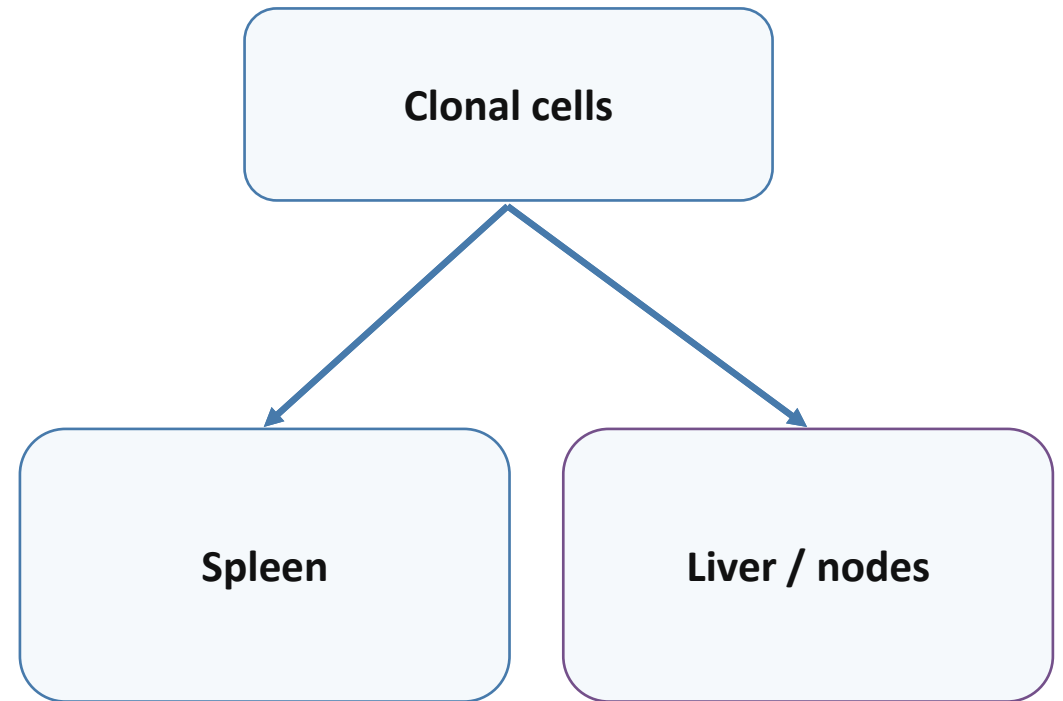


Enlargement

Possible infarct

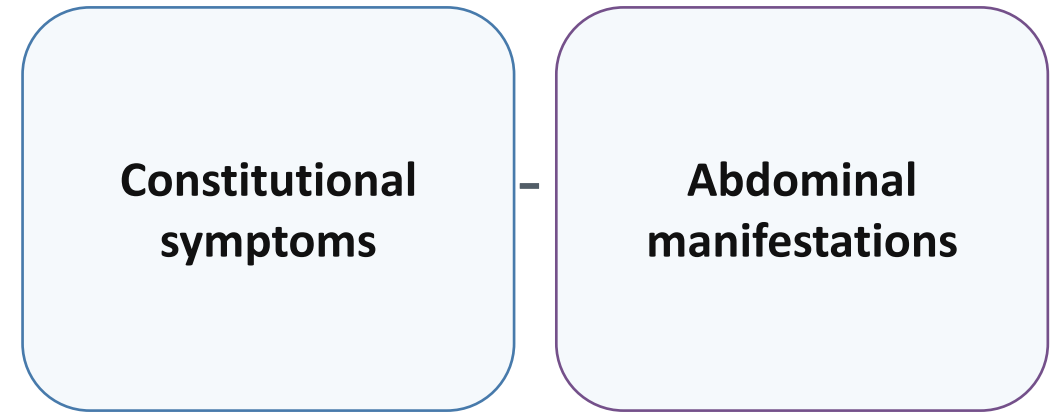
Extramedullary hematopoiesis may involve other sites

- The liver may enlarge mildly.
- Lymphadenopathy can accompany extramedullary hematopoiesis.
- These findings are usually secondary to the systemic hematopoietic clone.



CML commonly has an insidious presentation

- The onset is often gradual.
- Fatigue, weakness, weight loss, and anorexia may develop.
- Some patients present because of splenic discomfort.



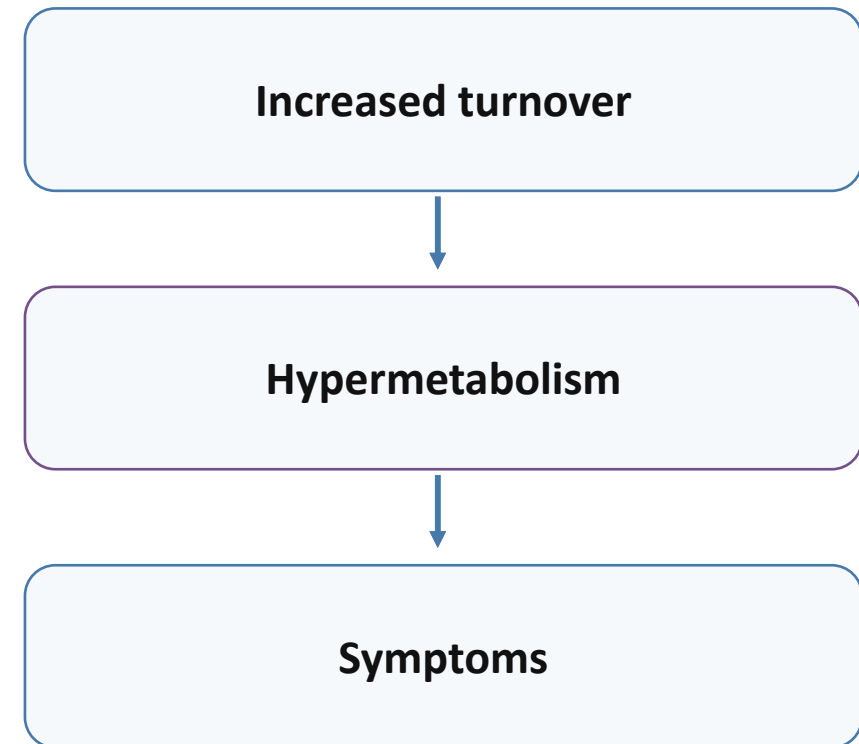
Age profile: Primarily an adult disease

- The peak incidence is in the fifth to sixth decades.
- Children and adolescents can also be affected.
- Age alone must not be used to include or exclude CML.



High cell turnover drives constitutional symptoms

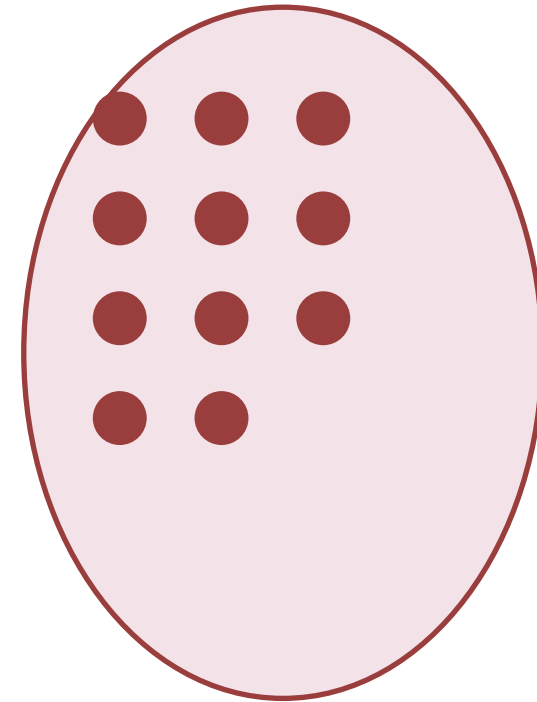
- Excessive hematopoietic activity is metabolically demanding.
- Hypermetabolism contributes to weight loss and reduced appetite.
- Fatigue and weakness reflect a combination of anemia and turnover.



Splenic size explains characteristic discomfort

- Marked splenomegaly can cause abdominal dragging or fullness.
- Acute pain may indicate splenic infarction.
- Symptoms should be interpreted alongside examination and blood findings.

Schematic enlarged spleen (not a specimen)

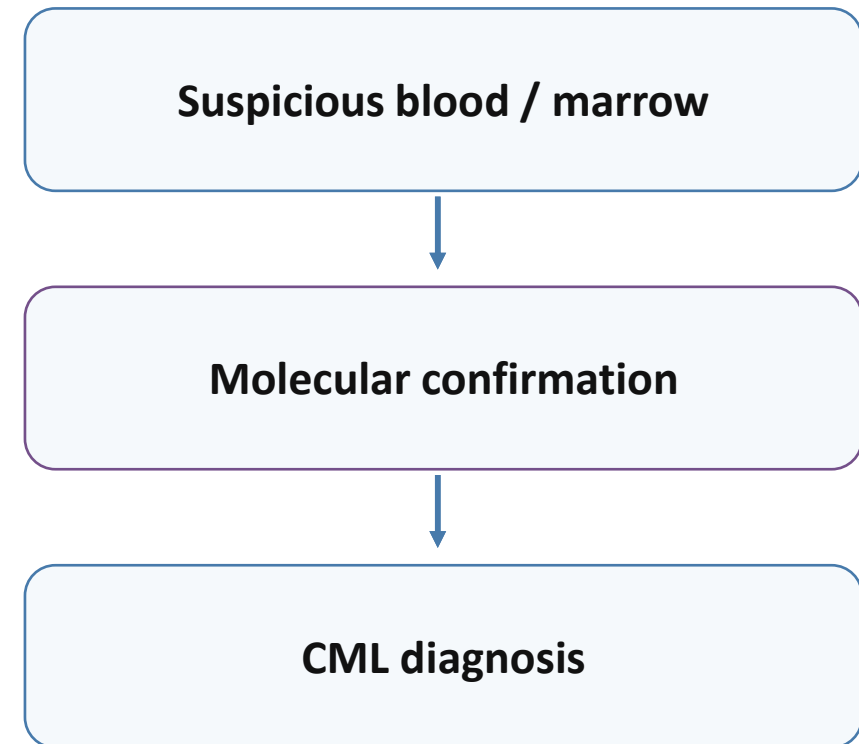


Mass effect

Infarction pain

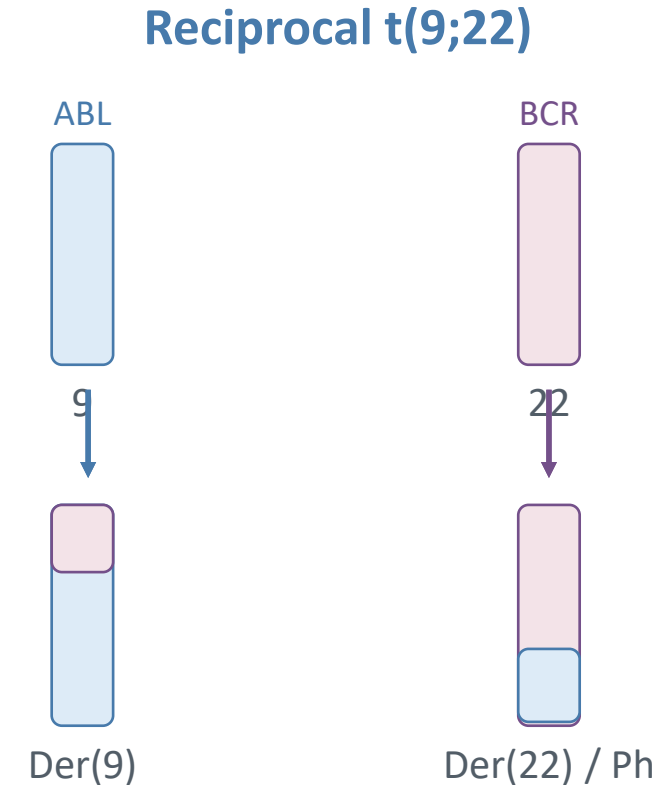
The morphologic pattern raises suspicion; Fusion proves it

- Granulocytic leukocytosis, left shift, basophilia, and marrow hypercellularity suggest CML.
- These findings overlap with other proliferative states.
- Demonstration of BCR::ABL establishes the disease-specific molecular identity.



Chromosome analysis demonstrates the classic event

- Conventional karyotyping can detect $t(9;22)(q34;q11)$.
- It documents the cytogenetic rearrangement in typical cases.
- A negative routine karyotype may require further fusion testing.



Schematic gene exchange — not a karyotype

FISH can detect a cryptic fusion

- Fluorescence in situ hybridization can reveal BCR::ABL despite a cryptic rearrangement.
- Its role is particularly important when routine cytogenetics are non-diagnostic.
- The biological target is still the BCR::ABL fusion.

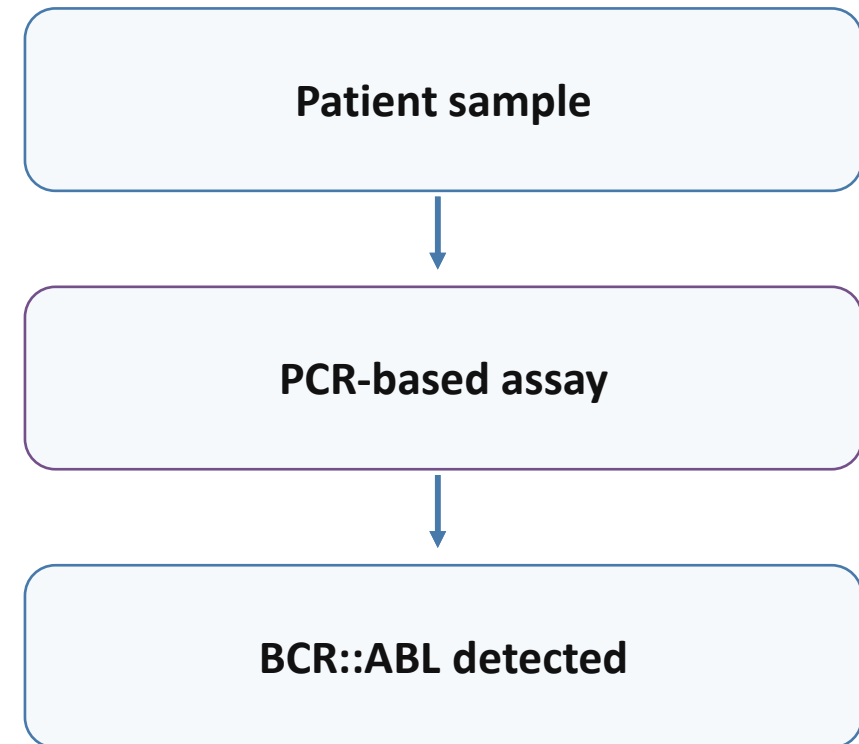
**Cytogenetically
visible**

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**Cryptic fusion by
FISH**

PCR-based testing identifies the fusion sequence

- PCR-based detection as an alternative to chromosome analysis.
- The fusion is molecularly specific even when the chromosome event is complex.
- Sensitive molecular assays also support later surveillance for recurrence.



Three methods interrogate different features

- Karyotype: Visible chromosomal architecture.
- FISH: Physical colocalization of gene sequences.
- PCR-based analysis: Fusion sequence detection.

Karyotype

Chromosome rearrangement

FISH

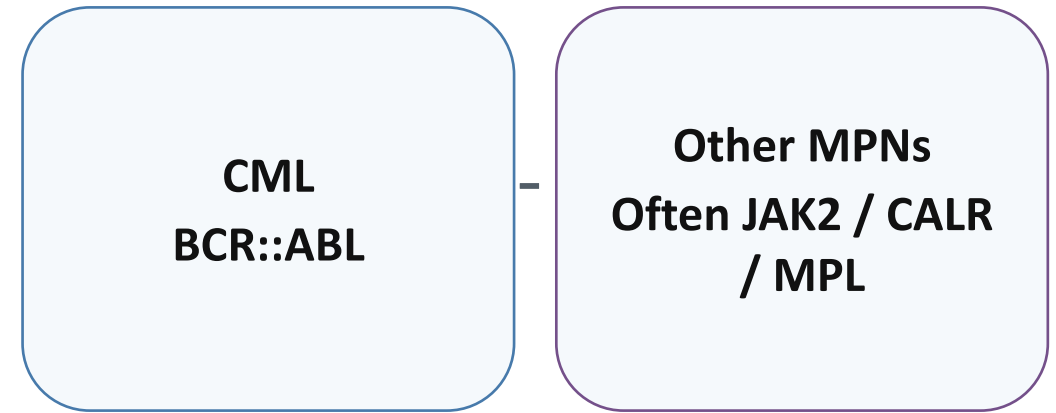
Fusion locus

**PCR-based
test**

Fusion sequence

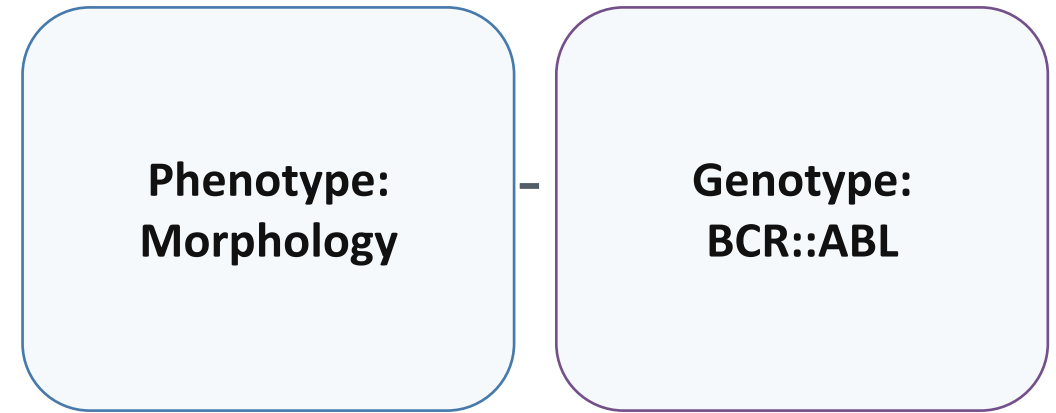
CML differs molecularly from other common MPNs

- CML is linked to BCR::ABL-mediated ABL signaling.
- Other common MPNs often carry JAK2, CALR, or MPL pathway lesions.
- The presence of BCR::ABL is therefore more discriminating than clinical overlap.



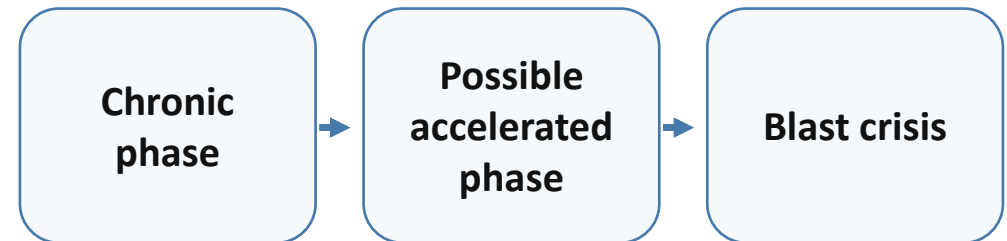
Morphology and molecular testing are complementary

- Morphology shows the tissue response and degree of maturation.
- Molecular testing identifies the causal driver.
- Neither clinical symptoms nor a high leukocyte count alone is sufficient for subtype assignment.



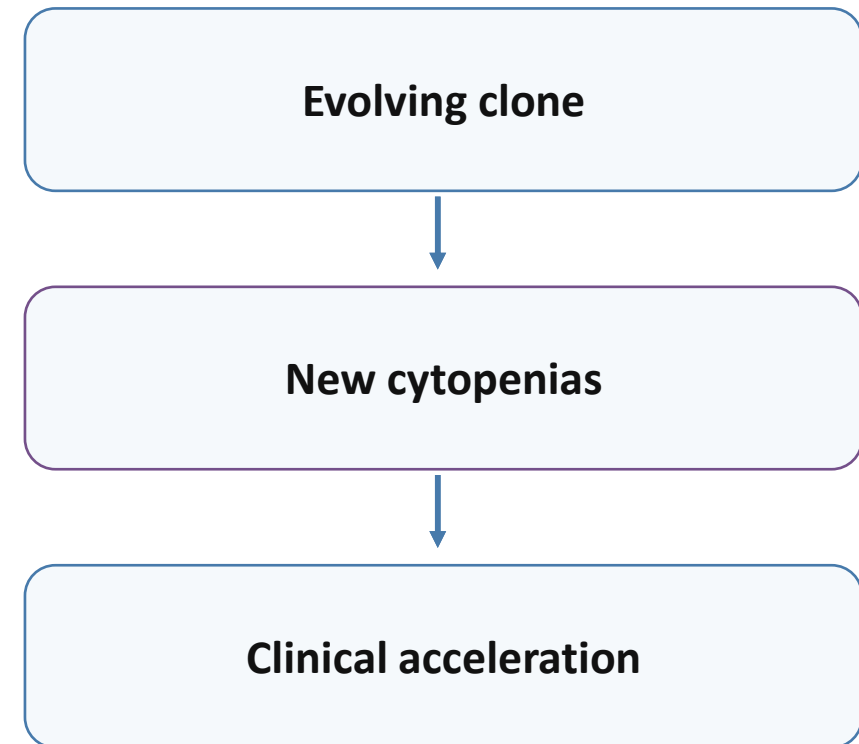
Untreated CML follows a progressively unstable course

- Chronic-phase disease typically progresses gradually without therapy.
- Historical median survival of about 3 years without treatment.
- That value must not be presented as the prognosis of modern treated CML.



The accelerated phase reflects clonal evolution

- About half of historically untreated patients passed through an accelerated phase.
- Anemia and thrombocytopenia become more prominent.
- Blood basophils may increase further.



Additional chromosome abnormalities accompany progression

- Examples include trisomy 8.
- Isochromosome 17q can emerge.
- An additional copy of the Philadelphia chromosome may appear.

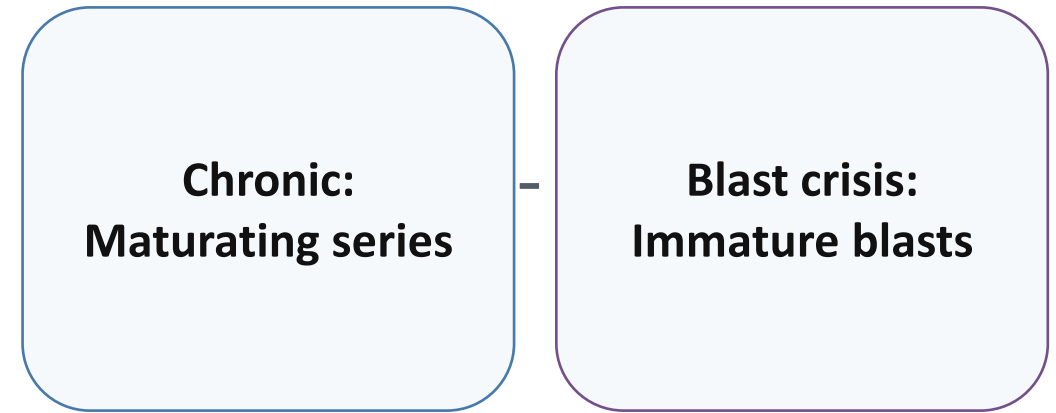
+8

I(17q)

**Additional
Ph**

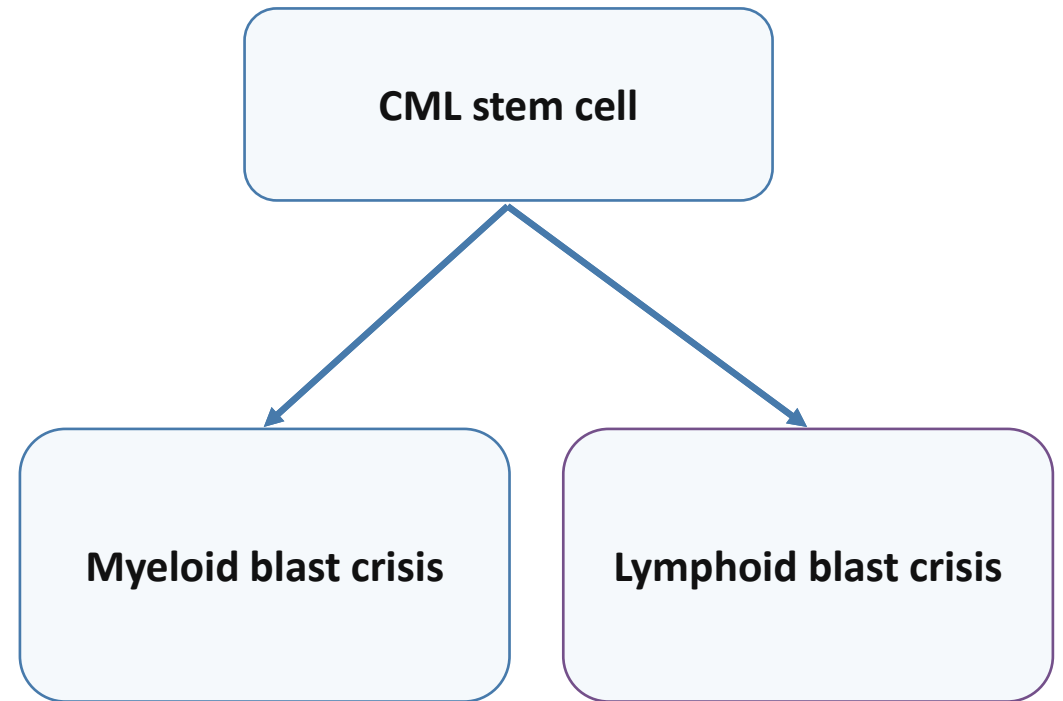
Blast crisis resembles acute leukemia

- The chronic expansion gives way to a high-grade blast population.
- Progression can follow an accelerated phase or occur abruptly.
- A blast crisis changes the clinical behavior of the disease dramatically.



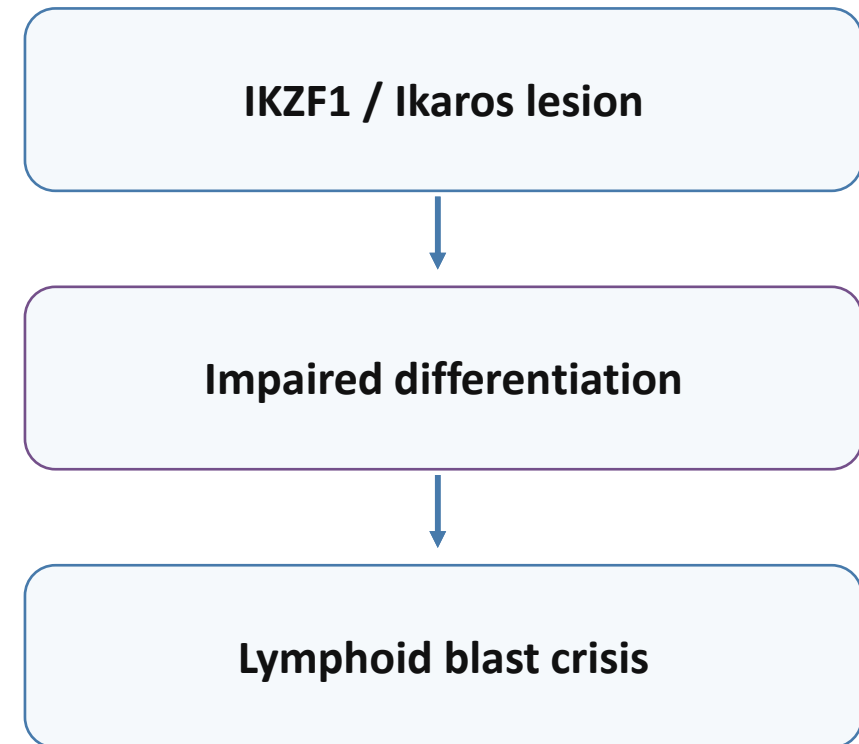
Blast crisis need not be myeloid

- Myeloid blasts in approximately 70% of crises.
- Most remaining crises are of pre-B-cell lymphoid origin.
- This dual potential supports a pluripotent cell of origin.



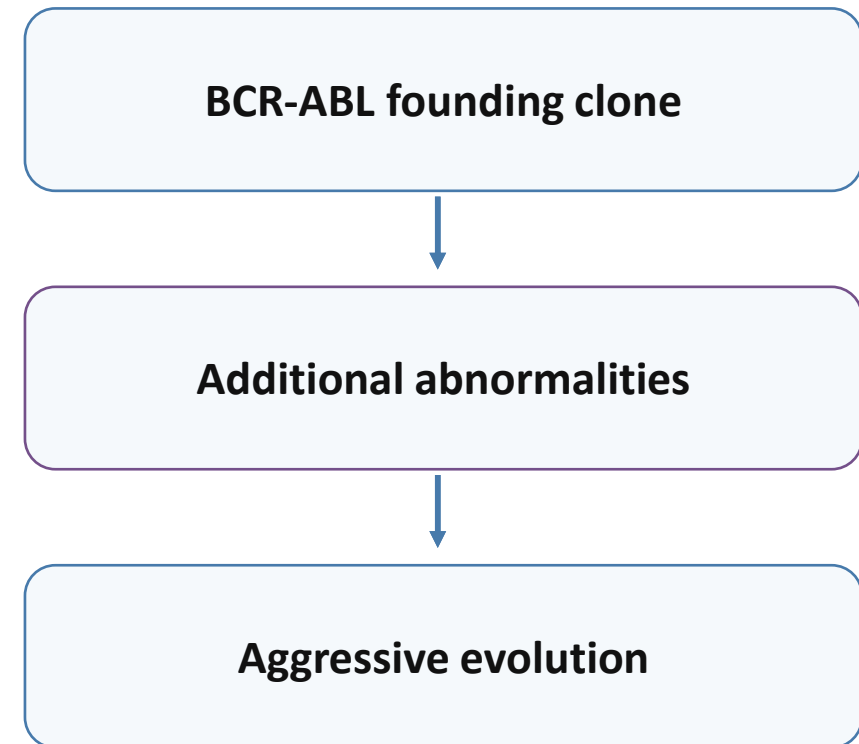
Lymphoid transformation implicates IKZF1

- Ikaros is a transcription factor encoded by IKZF1.
- Alterations impairing Ikaros in most lymphoid blast crises.
- The lesion connects differentiation failure with leukemic transformation.



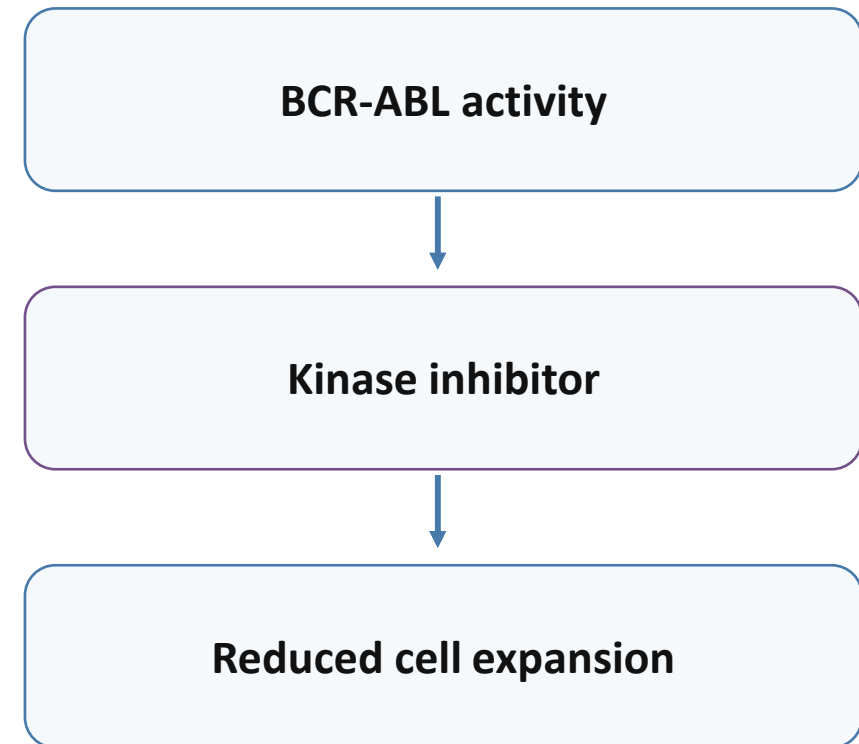
Progression requires more than kinase activation

- BCR-ABL enables persistent clone expansion.
- Additional genetic events can alter differentiation and behavior.
- This multistep interpretation explains the shift toward acute leukemia.



Targeted therapy inhibits the founding kinase

- BCR-ABL-directed tyrosine kinase inhibitors interrupt the driver signal.
- Reduced proliferative drive controls the excess cell production.
- CML is a landmark example of mechanism-based cancer treatment.



Hematologic remission becomes common with TKIs

- Sustained hematologic remissions in more than 90% of patients receiving BCR-ABL inhibitors.
- Blood counts may normalize as the neoplastic output falls.
- Hematologic remission does not necessarily mean every CML stem cell is eradicated.

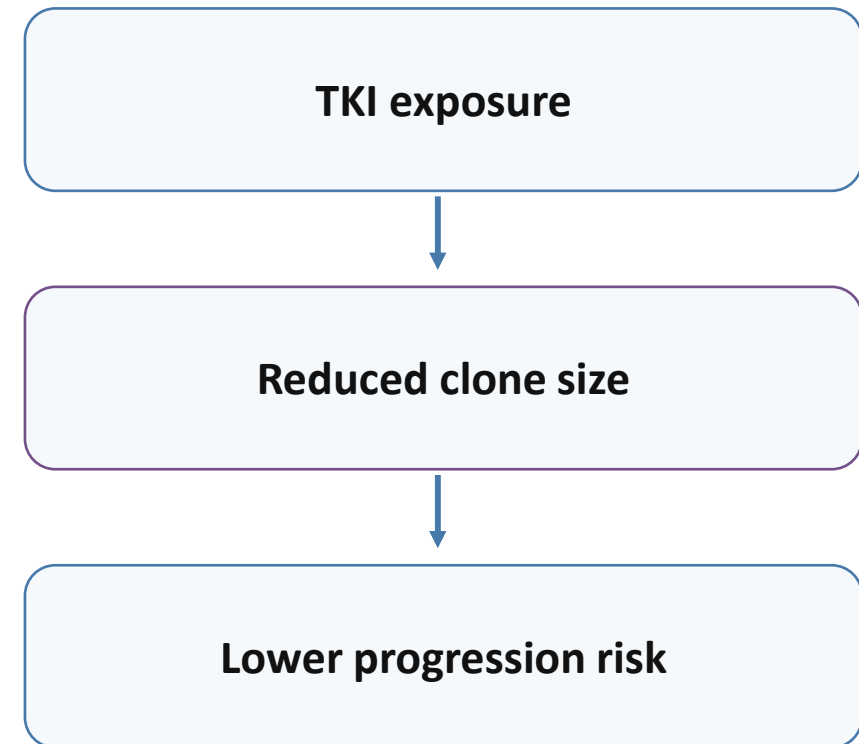
**Remission of blood
counts**

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**Residual clone may
persist**

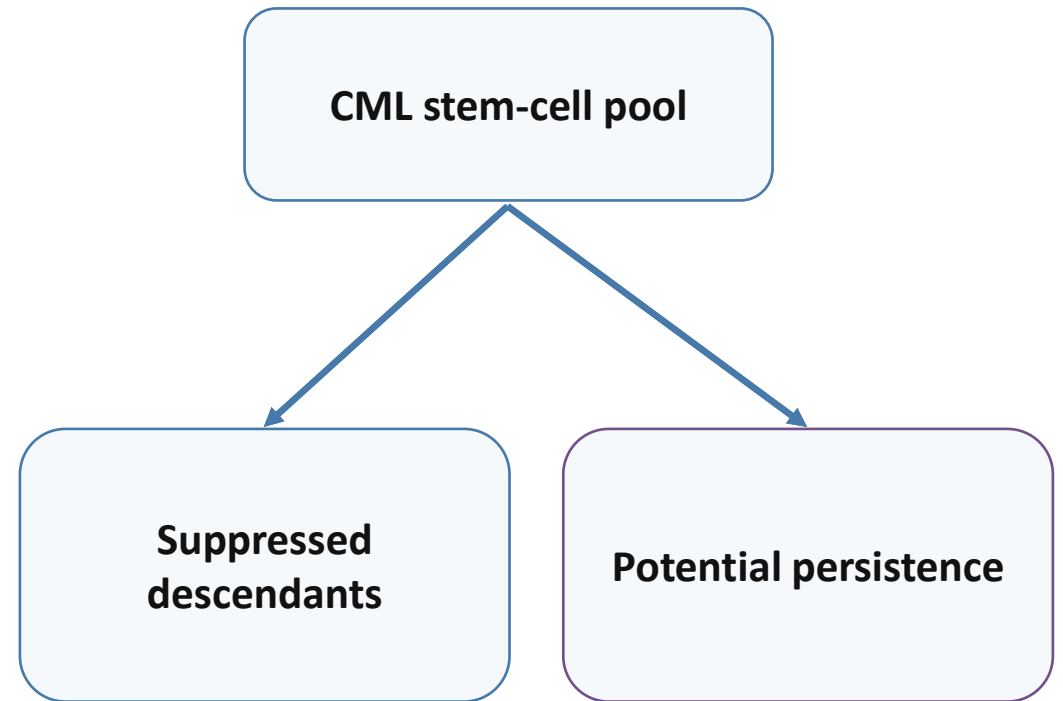
Inhibitors greatly reduce the risk of blast crisis

- Targeted treatment lowers the number of BCR-ABL-positive cells.
- It substantially decreases transition to accelerated and blast phases.
- Reducing proliferation may decrease opportunities for additional oncogenic changes.



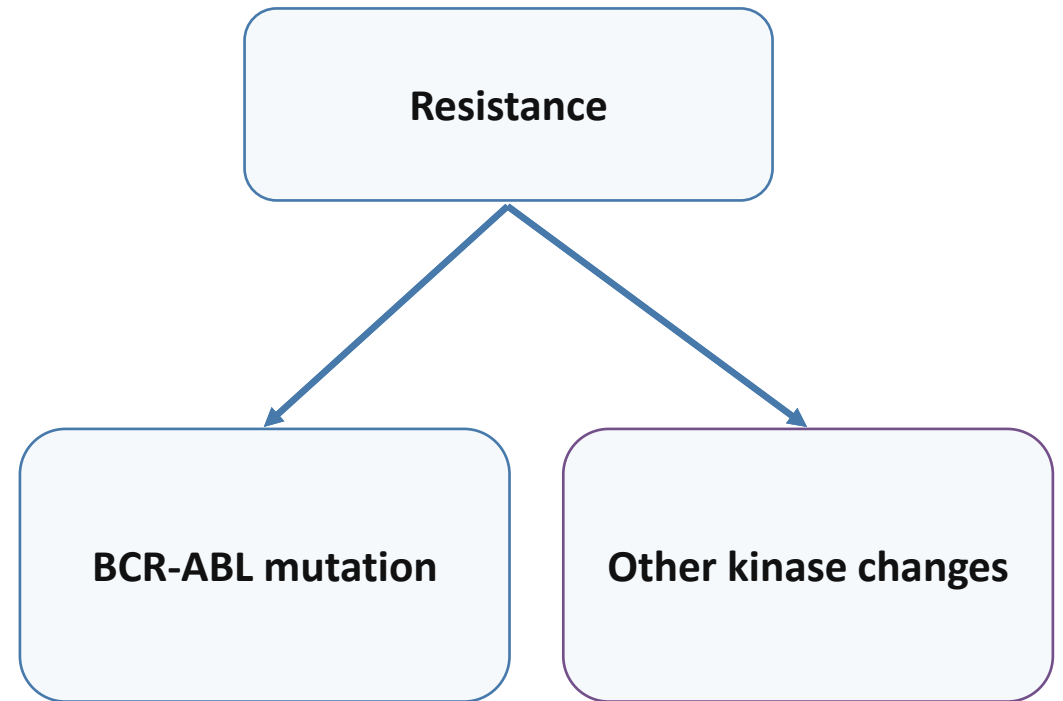
Leukemia stem-cell persistence limits eradication

- A low-level neoplastic stem-cell reservoir can remain.
- This explains why deep suppression and complete elimination are different concepts.
- Sensitive molecular follow-up is relevant even in clinical remission.



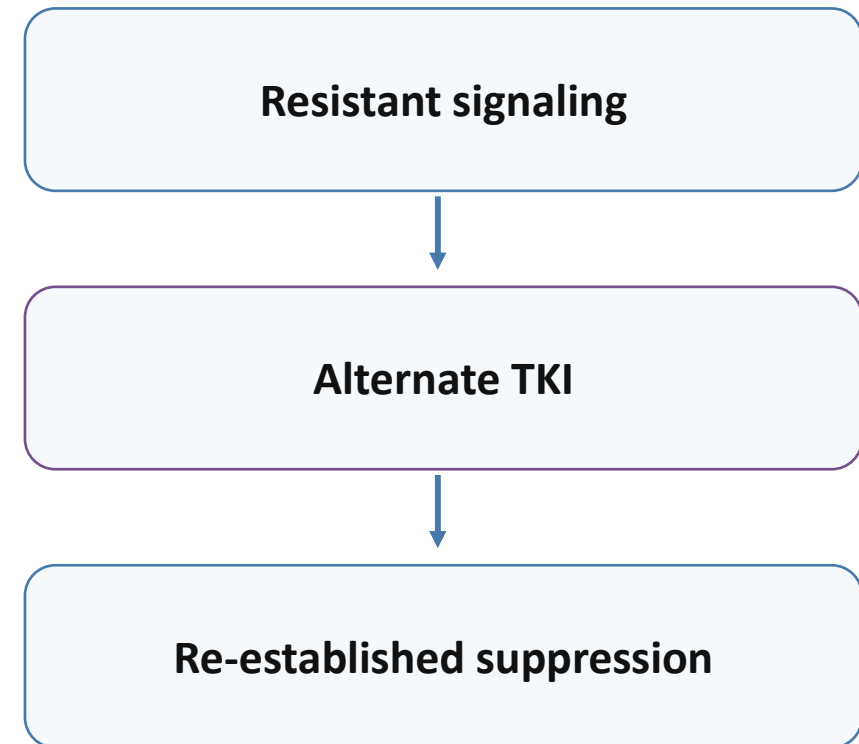
Resistance may develop through kinase alterations

- In about half of resistance to first-generation agents, resistance to BCR-ABL mutations.
- Other kinase alterations account for many remaining cases.
- Mechanistic resistance differs from initial failure to recognize the diagnosis.



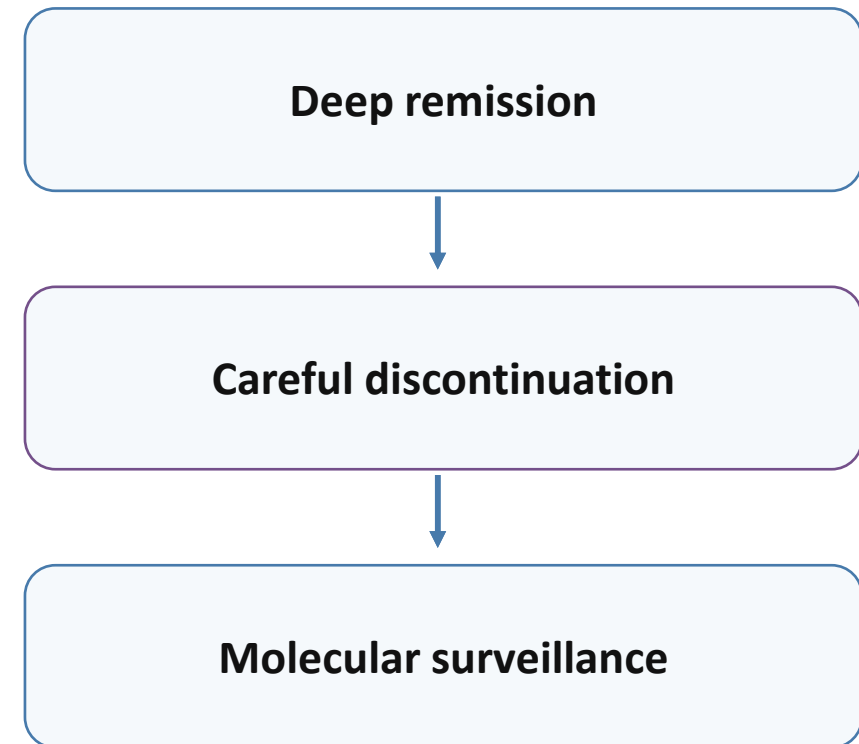
Later-generation inhibitors address some resistance

- Second- and third-generation agents can inhibit certain mutated BCR-ABL forms.
- The choice of inhibitor depends on the resistance context.
- Robbins does not specify a drug-by-mutation treatment matrix in this passage.



Deep molecular remission permits selected treatment stops

- Very sensitive molecular assays can monitor for recurrence.
- Some patients with very deep remissions may discontinue treatment.
- In a subset, remission persists for several years without ongoing therapy.



Transplantation has a restricted modern role

- Hematopoietic stem-cell transplantation is generally reserved for selected patients.
- Otherwise healthy, relatively young patients with suboptimal TKI response.
- The availability of effective kinase inhibitors altered the therapeutic landscape.

TKIs: Usual disease control

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**Transplant:
Selected patients**

Clinicopathologic case: Marked leukocytosis

- An adult reports several months of weakness, weight loss, and fullness in the left upper abdomen.
- Blood film shows granulocytes at multiple maturation stages with basophilia.
- Which molecular lesion should be sought to establish the diagnosis?

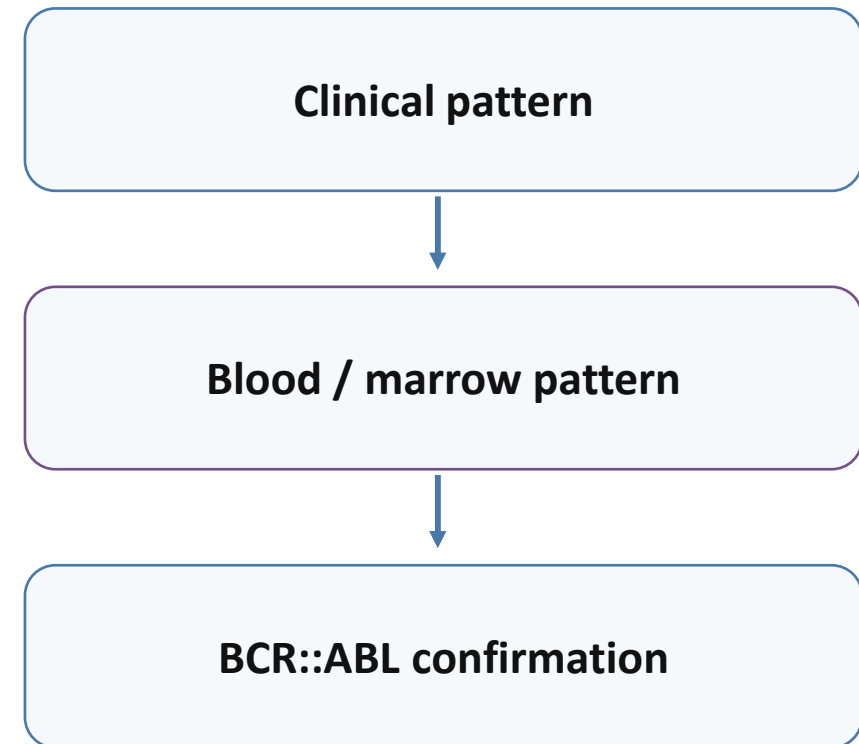
Question



BCR::ABL fusion

Case analysis: Phenotype directs molecular testing

- Symptoms can reflect anemia, hypermetabolism, and splenic enlargement.
- Granulocytic left shift and basophilia raise CML suspicion.
- A BCR::ABL-positive result supplies the defining evidence.



Progression case: Changing cytopenias

- A patient with established CML develops worsening anemia and thrombocytopenia.
- A new cytogenetic abnormality is reported and blasts increase.
- The central interpretation is evolving disease phase, not simply persistent leukocytosis.

New cytopenias



Clonal progression

Diagnostic synthesis

- The driver lesion is BCR::ABL; The effector is constitutively active BCR-ABL kinase.
- The phenotype is hypercellular granulocytic marrow and left-shifted blood leukocytosis.
- The clinical threats are splenic burden, clonal evolution, and blast crisis.
- Targeted kinase inhibition has transformed the expected course.

Driver

Morphology

Progression

Treatment

Reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Primary lecture basis: Chronic Myeloid Leukemia, with the immediately preceding myeloproliferative-neoplasm context.
- Diagnostic morphology here is illustrated by editable teaching schematics, not clinical photomicrographs.