open.michigan

Author(s): Dale Bixby, M.D., Ph.D., 2009

Citation Key

for more information see: http://open.umich.edu/wiki/CitationPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

Public Domain – Government: Works that are produced by the U.S. Government. (17 USC § 105)

Public Domain – Expired: Works that are no longer protected due to an expired copyright term.

Public Domain – Self Dedicated: Works that a copyright holder has dedicated to the public domain.

Creative Commons – Zero Waiver

Creative Commons – Attribution License

Creative Commons – Attribution Share Alike License

Creative Commons – Attribution Noncommercial License

Creative Commons – Attribution Noncommercial Share Alike License

GNU – Free Documentation License

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

Public Domain – Ineligible: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

Fair Use: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.

Chronic Myeloid Leukemia and other Myeloproliferative Neoplasms (MPNs)

Dale Bixby, M.D., Ph.D
Clinical Assistant Professor
Assistant Program Director
Division of Hematology and Oncology
Department of Internal Medicine
University of Michigan

Winter 2010

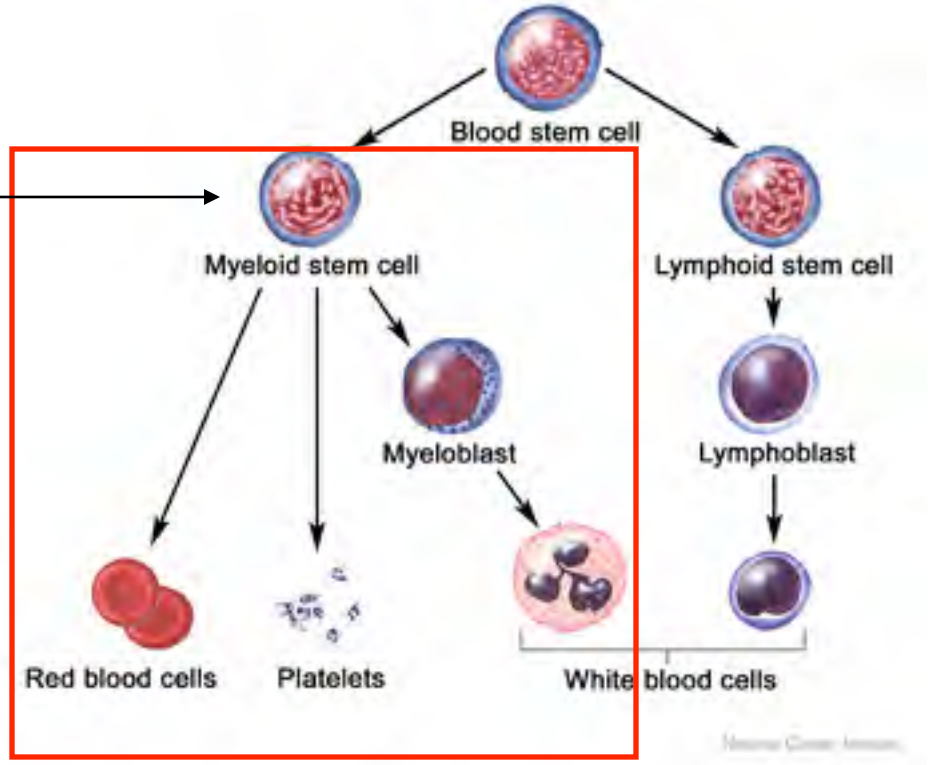
University of Michigan
Medical School

Definitions

Myeloproliferative Neoplasms (MPNs): are a group of clonal myeloid neoplasms in which a genetic alteration occurs in a hematopoietic progenitor cell leading to its proliferation resulting in an increase in the peripheral blood white blood cells (WBCs), red blood cells (RBCs), platelets, or a combination of these cells.

Hematopoietic Progenitors and MPNs

Genetic Mutation



National Cancer Institute

More Definitions

The type of disorder is often based on the predominant cell line that is affected, but because blood counts are often abnormal in more than one cell line, diagnoses based upon blood counts alone may be inaccurate.

Four Main MPNs:

1. Chronic Myelogenous Leukemia (CML)
2. Polycythemia Vera (PV)
3. Essential Thrombocytosis (ET)
4. Primary Myelofibrosis (PMF)

Additional MPNs:

1. Systemic Mastocytosis
2. Hypereosinophilic Syndrome
3. Chronic Myelomonocytic Leukemia
4. Chronic Neutrophilic Leukemia
5. Chronic Eosinophilic Leukemia

MPN overview

In CML, the predominant feature is a leukocytosis with a left shift. A mild anemia, normal to elevated platelet count, and a peripheral blood basophilia is often seen.

In PV, the predominant features are elevated red blood cell indicies (RBC count, hemoglobin, and hematocrit). Patients often also have a mild leukocytosis and thrombocytosis.

In ET, the predominant feature is an elevated platelet count. Patients also often have a mild leukocytosis and polycythemia.

In PMF, the predominant feature is evidence of extramedullary hematopoiesis in the form of hepatomegaly, splenomegaly, and lymphadenopathy. Patients often have a mild anemia, but their WBC and platelet counts can be quite variable. Leukoerythroblastosis (tear drops, nucleated RBCs and early myeloid progenitors (including blasts) are often seen in the peripheral blood.

Clonal Genetic Abnormalities Define Many MPNs

See online at: http://img.medscape.com/fullsize/migrated/563/885/nrc563885.fig1.gif

Original source: Levine et al. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. Nature Reviews – Cancer 2007;7:673-683

Chronic Myeloid Leukemia (CML)

Epidemiology of CML

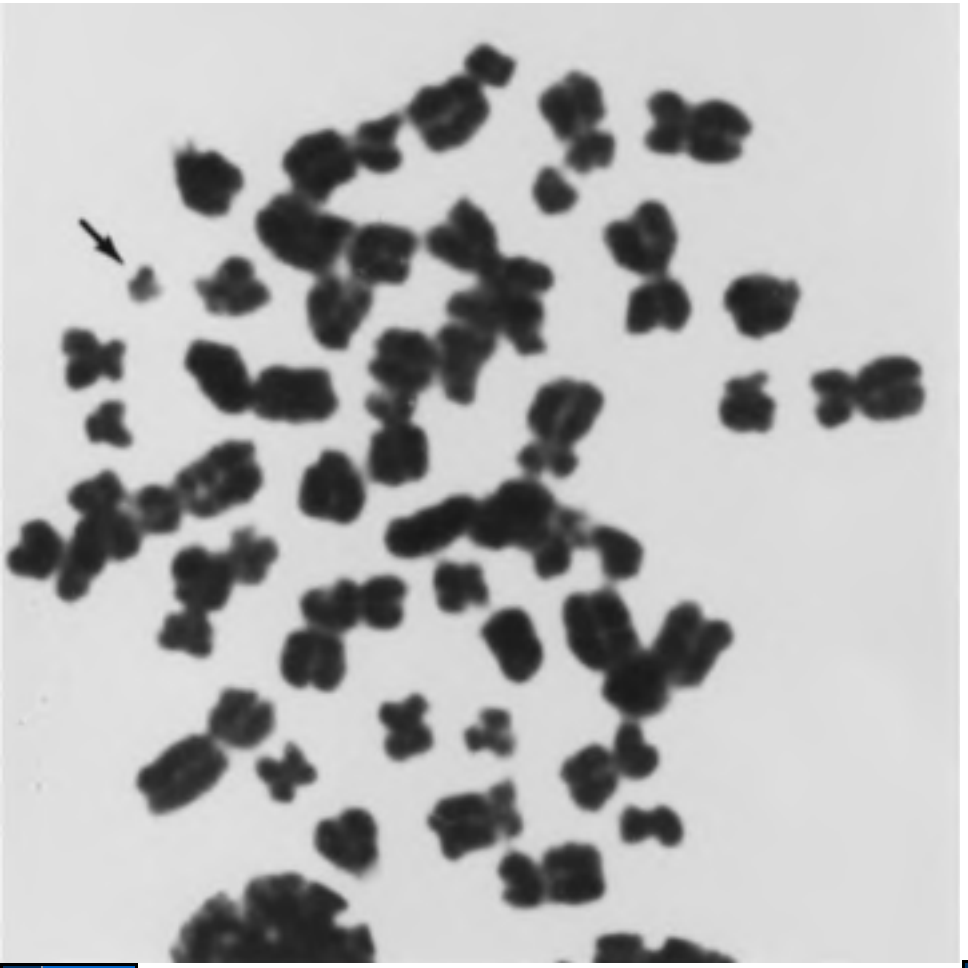
Approximately 5,050 cases in the U.S. in 2009 (11% of all leukemias) with an incidence that increases significantly with age (median age ~ 55)

Risk Factors include:

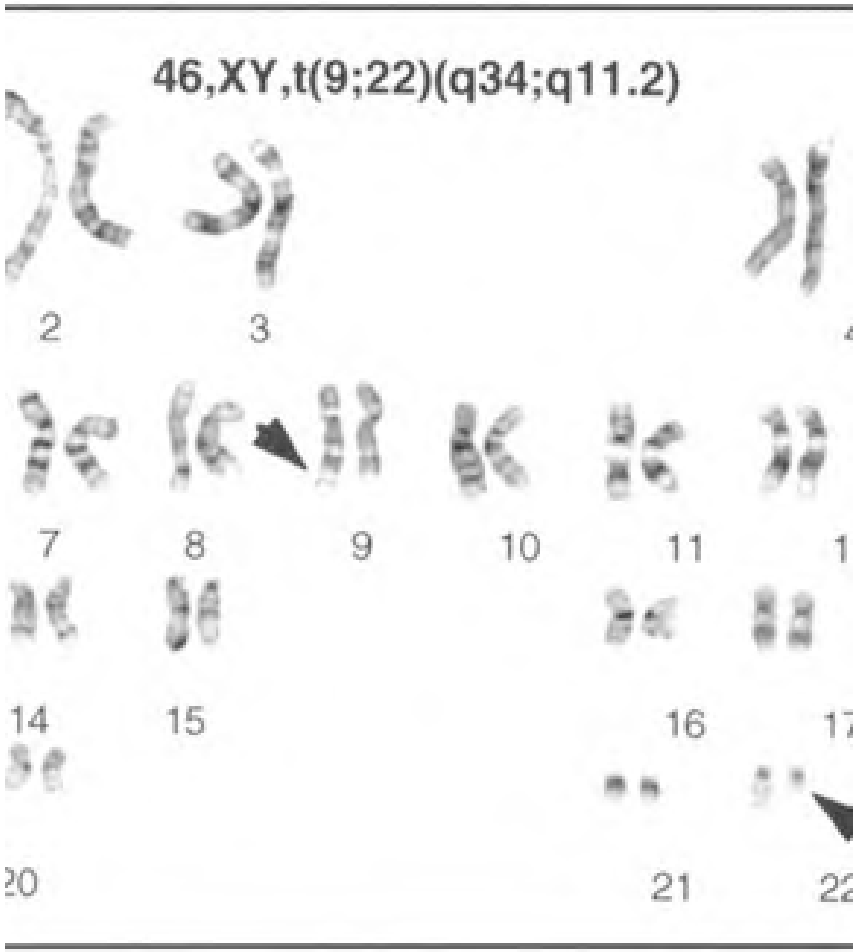
- prior high dose radiation exposure (WW II / Chernobyl / etc…)
- exposure to certain organic solvents (benzene)
- age
- gender (male > female)

A very small percentage (< 0.1%) of individuals can express Bcr-Abl but not develop CML (wrong cell of origin, multiple genetic mutations leading to non-viability, immune surveillance)

CML – Pathophysiology – the Philadelphia Chromosome

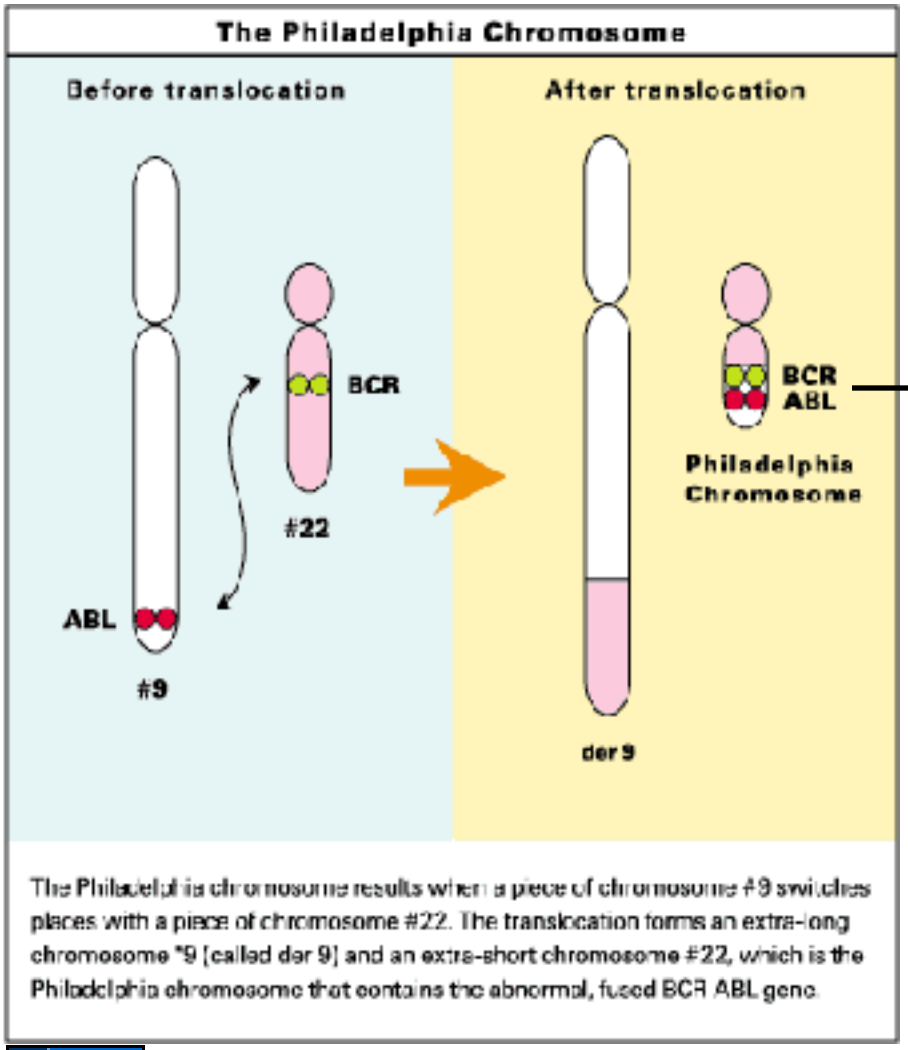


Source Undetermined

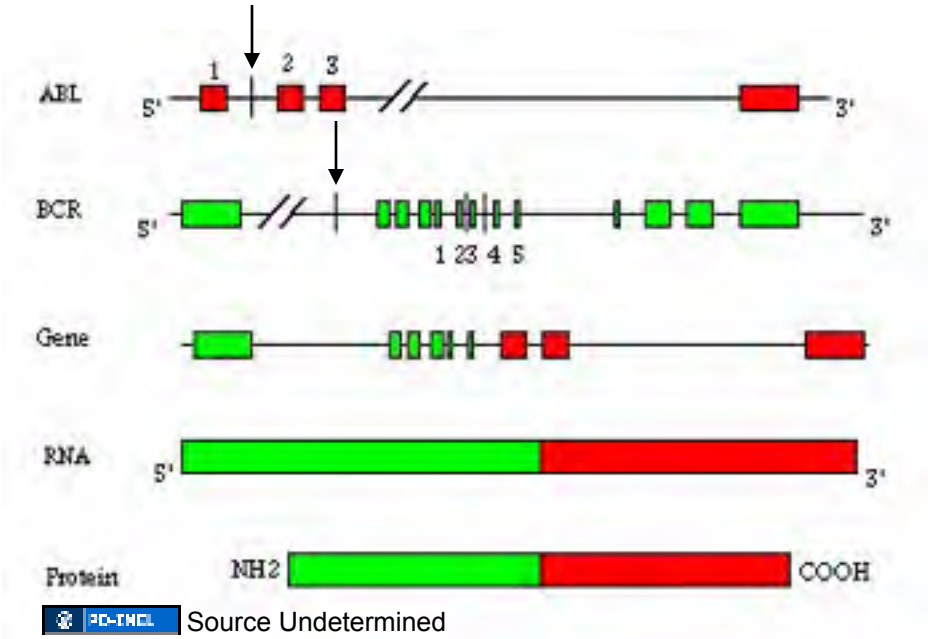


Source Undetermined

Bcr-Abl and CML

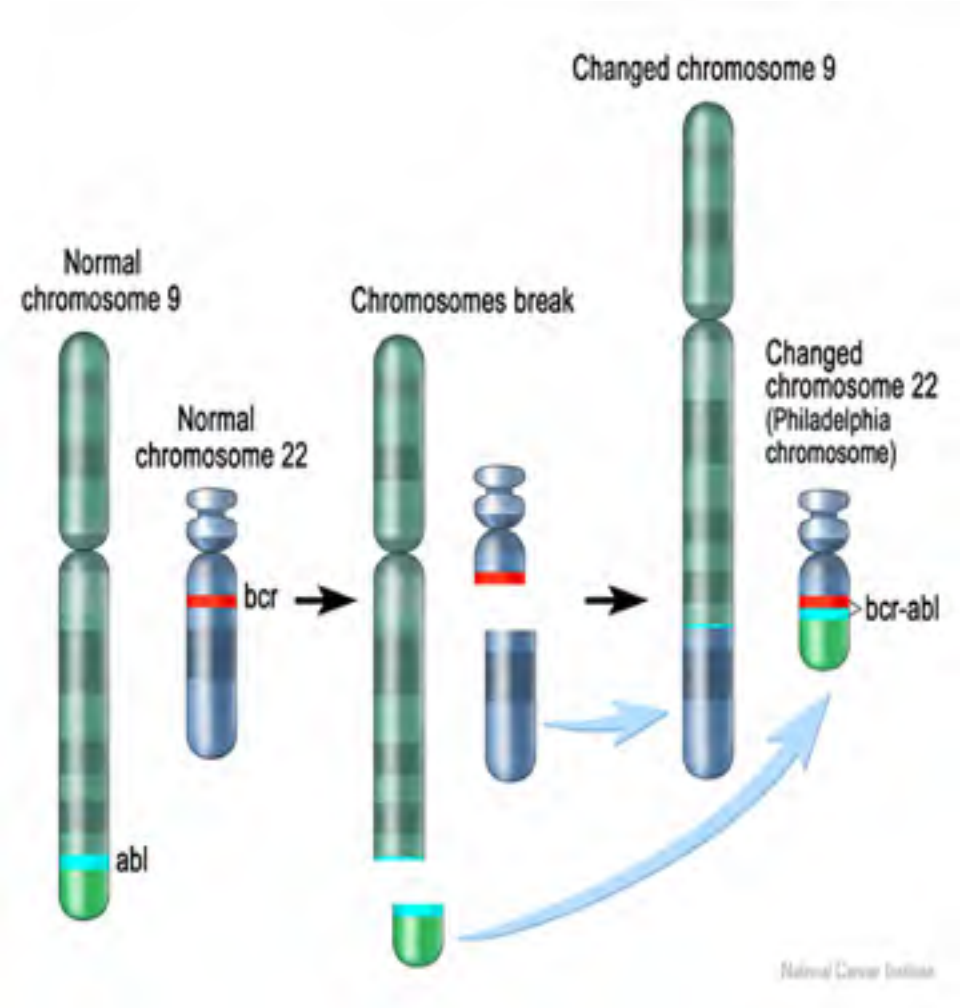


Source Undetermined

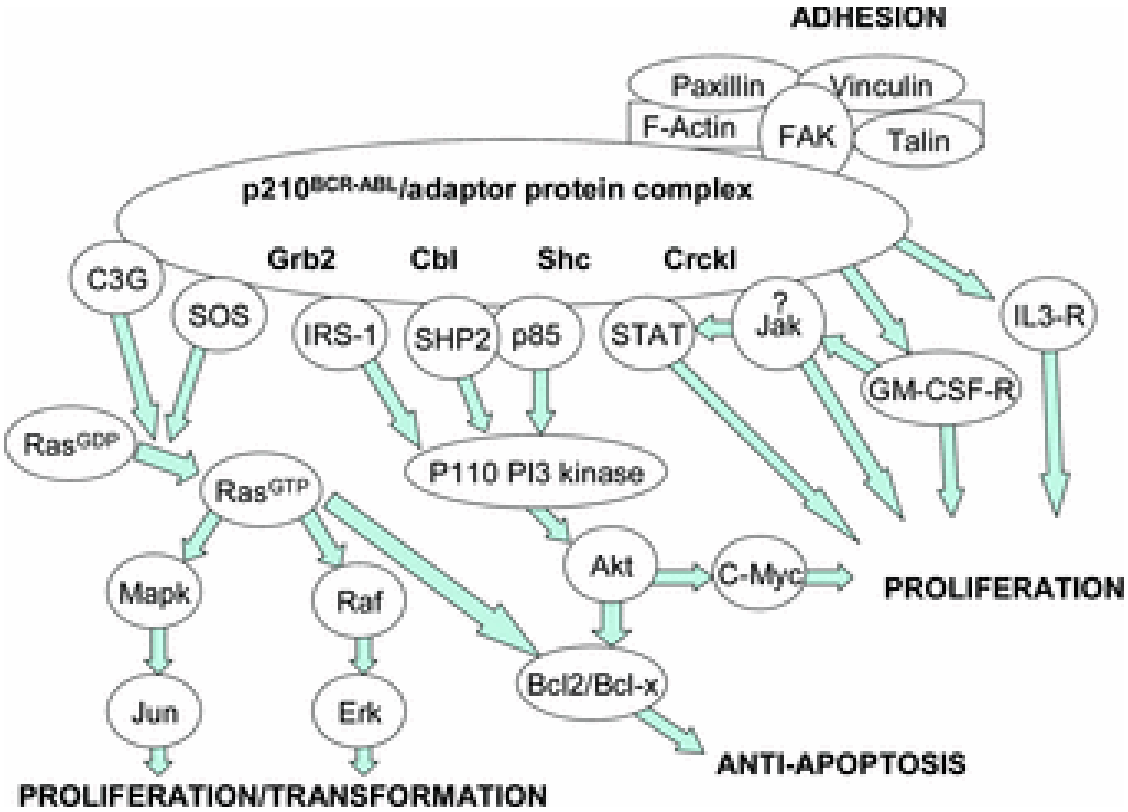


Source Undetermined

Multiple Breakpoints in Bcr-Abl



Pathophysiologic Result of the Expression of Bcr-Abl



Stephen B. Marley and Myrtle Y. Gordon. Chronic myeloid leukaemia: stem cell derived but progenitor cell driven Clinical Science (2005) 109, (13*25)

Bcr-Abl expression **alone** is necessary and sufficient for the development of CML

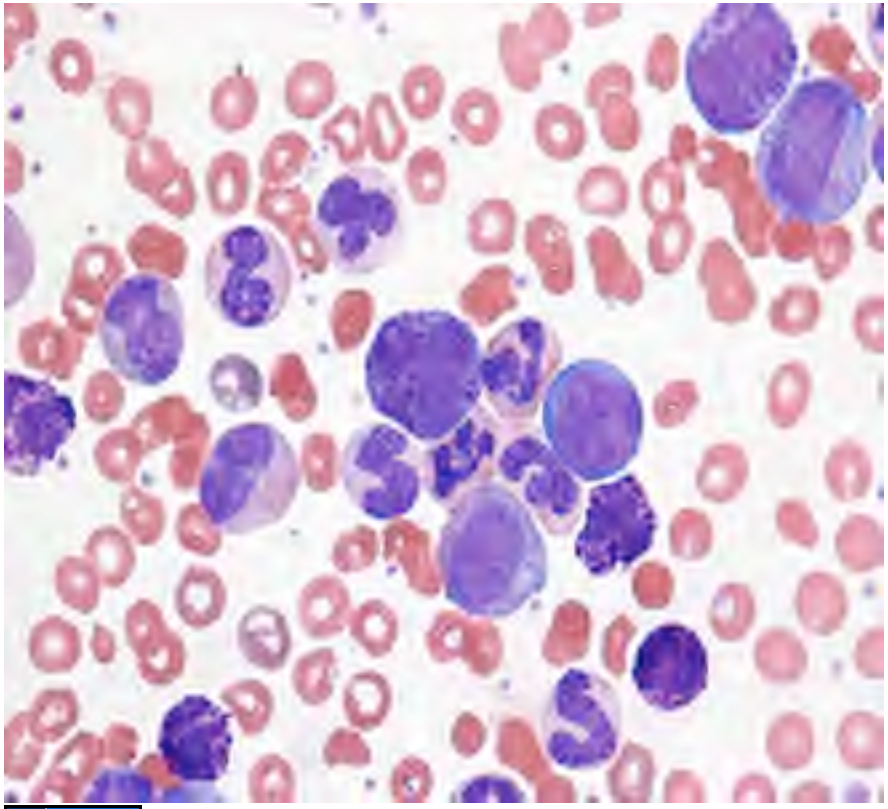
Chronic Myeloid Leukemia
Clinical Presentation

- Asymptomatic (~ 30%)
- Fatigue, weight loss, fever
- Abdominal fullness, pain and/or early satiety due to splenomegaly (~ 50-90%)
- Easy bruising and purpura
- Leukostasis
  - Pulmonary symptoms
  - Neurologic symptoms

CML – Peripheral Blood and BM Findings

Peripheral smear can only give a presumptive diagnosis of CML [you need to confirm the t(9;22)]:

1) leukocytosis with a 'left shift'
2) normocytic anemia
3) thrombocytosis in 50% of pts
4) absolute eosinophilia with a normal % of Eos.
5) absolute and relative increase in basophils
6) LAP score is low (not frequently employed)

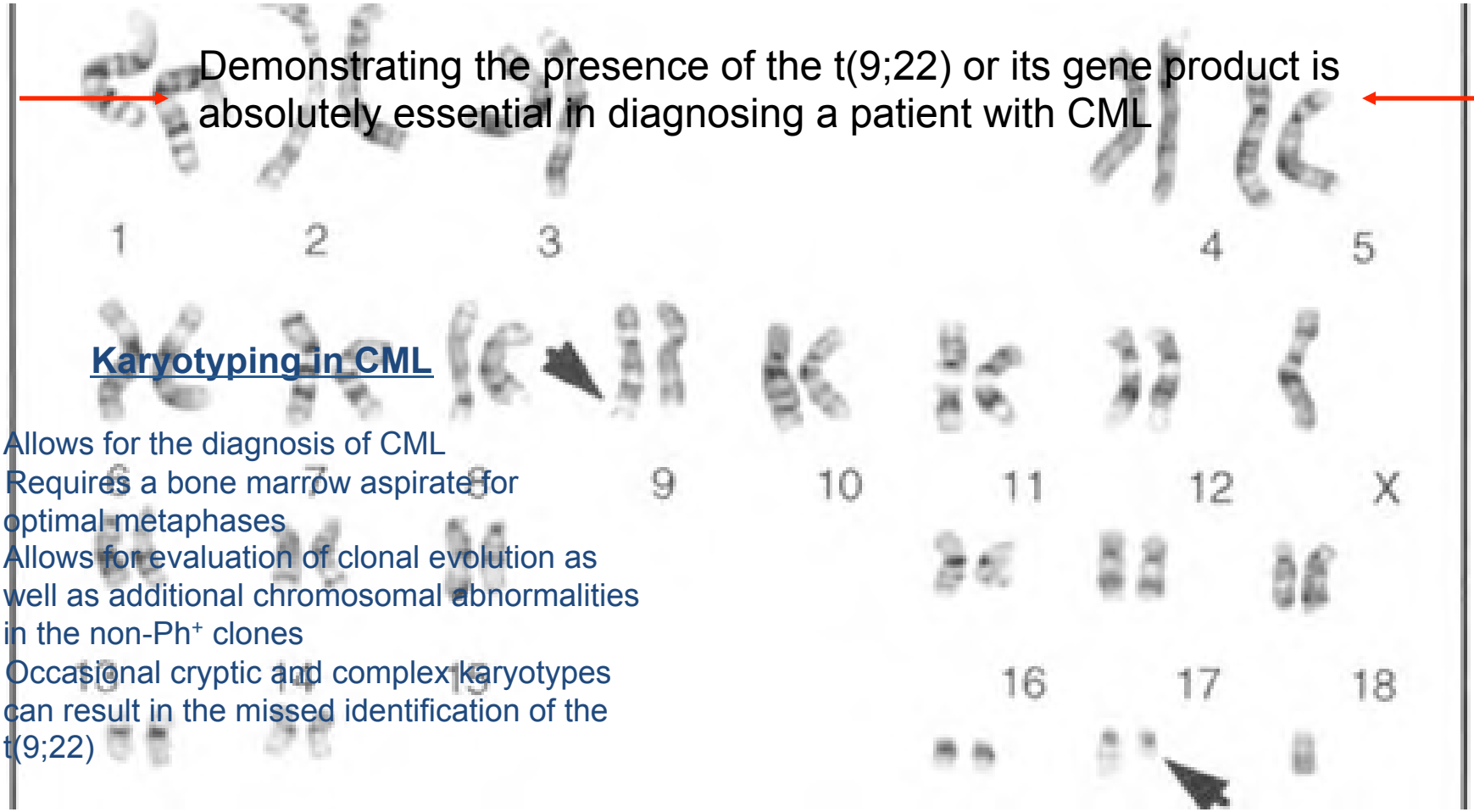


Source Undetermined

Diagnosing Chronic Myeloid Leukemia

Diagnostic Considerations in Chronic Myeloid Leukemia

Demonstrating the presence of the t(9;22) or its gene product is absolutely essential in diagnosing a patient with CML



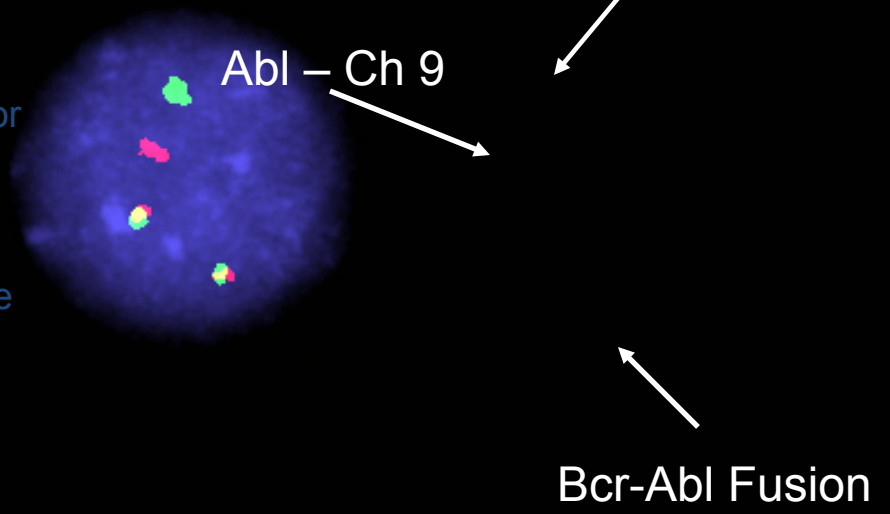
Karyotyping in CML

1) Allows for the diagnosis of CML
2) Requires a bone marrow aspirate for optimal metaphases
3) Allows for evaluation of clonal evolution as well as additional chromosomal abnormalities in the non-Ph^+ clones
4) Occasional cryptic and complex karyotypes can result in the missed identification of the t(9;22)

Diagnostic Considerations in Chronic Myeloid Leukemia

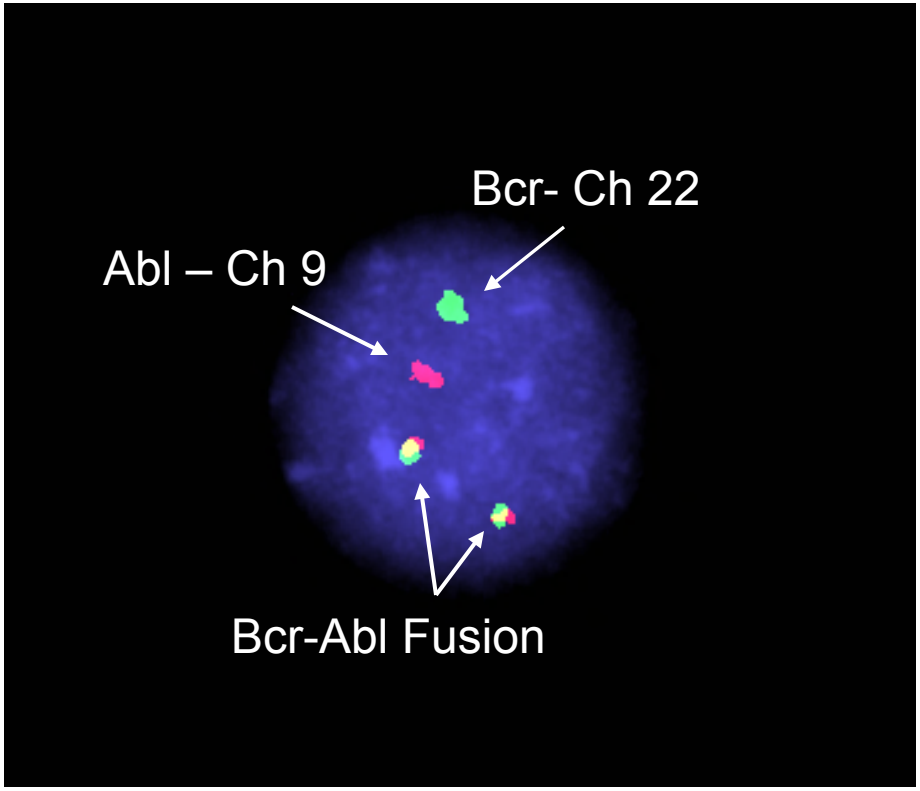
Fluorescence in-situ hybridization (FISH) in CML:

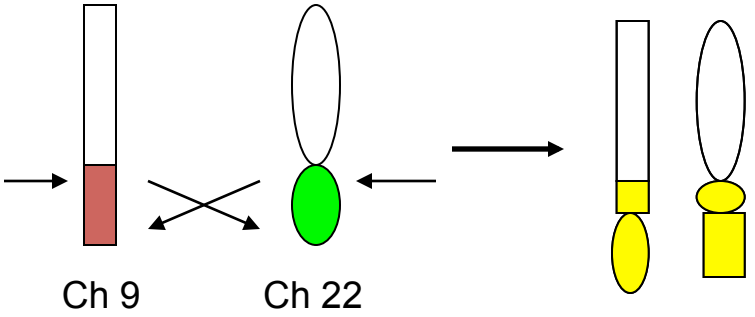
1) Allows for the diagnosis of CML
2) Does not require a bone marrow aspirate for optimal results
3) Allows for the identification of potential duplications of the Ph chromosome
4) Allows for the identification of the loss of the der (9) chromsome
5) Allows for the identification of cryptic translocations involving Bcr-Abl



FISH in CML

PD-TMCL Source Undetermined





PD-TMCL Source Undetermined

Red → Bcr probe

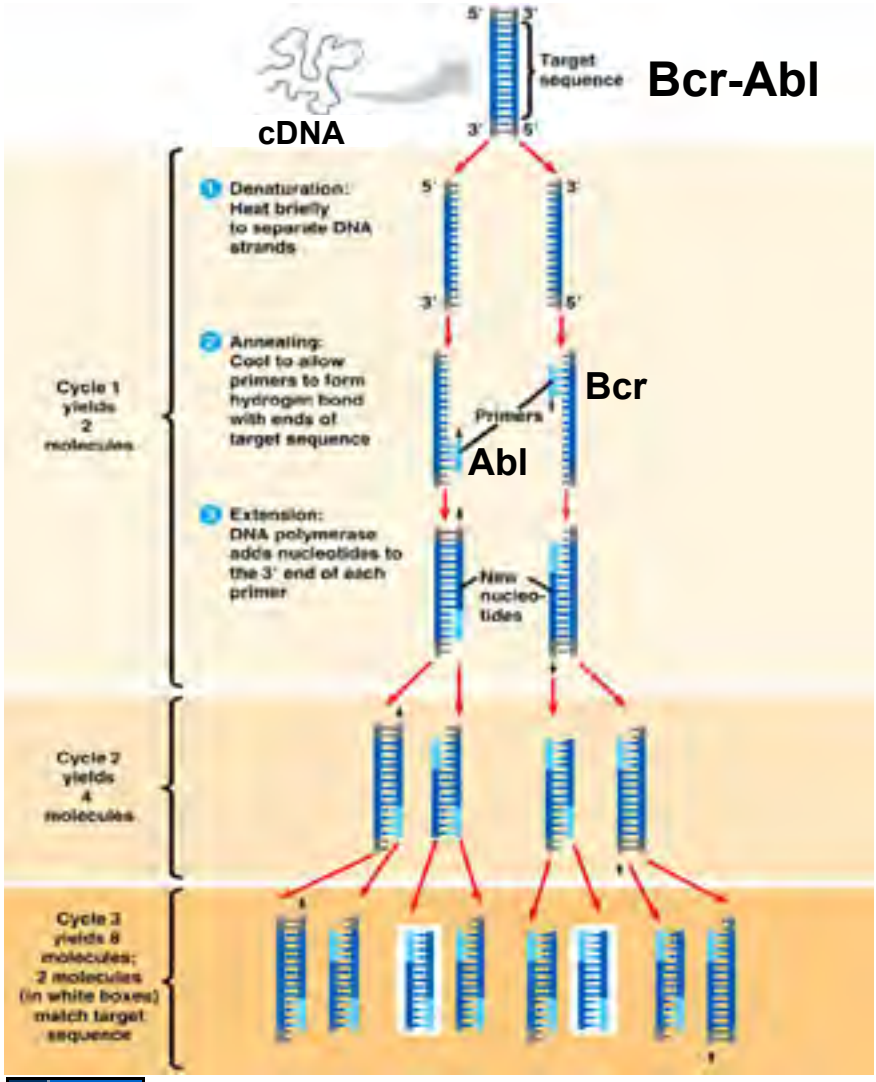
Green → Abl Probe

Yellow → fusion of Bcr and Abl

Diagnostic Considerations in Chronic Myeloid Leukemia

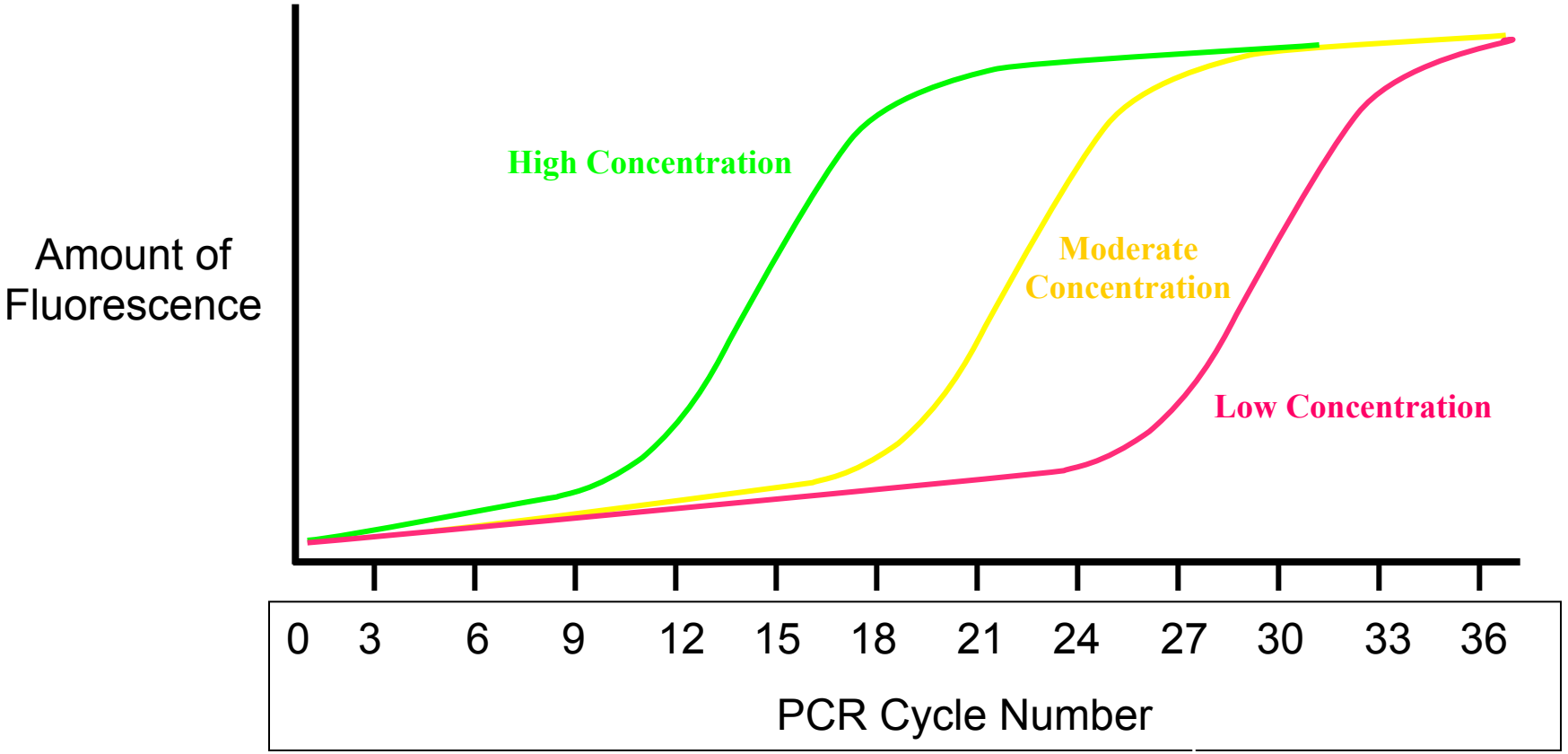
Quantitative RT-PCR for Bcr-Abl in CML

1) Allows for the diagnosis of CML
2) Does not require a bone marrow aspirate for optimal results
3) Can quantify the amount of disease
4) Allows for the identification of cryptic translocations involving Bcr-Abl
5) Many primers sets only detect the p190 and/or the p210 translocation and may miss the p230 or alternative translocations



Source Undetermined

Quantitative RT-PCR for Bcr-Abl in CML



Disease Diagnosis and Monitoring in CML

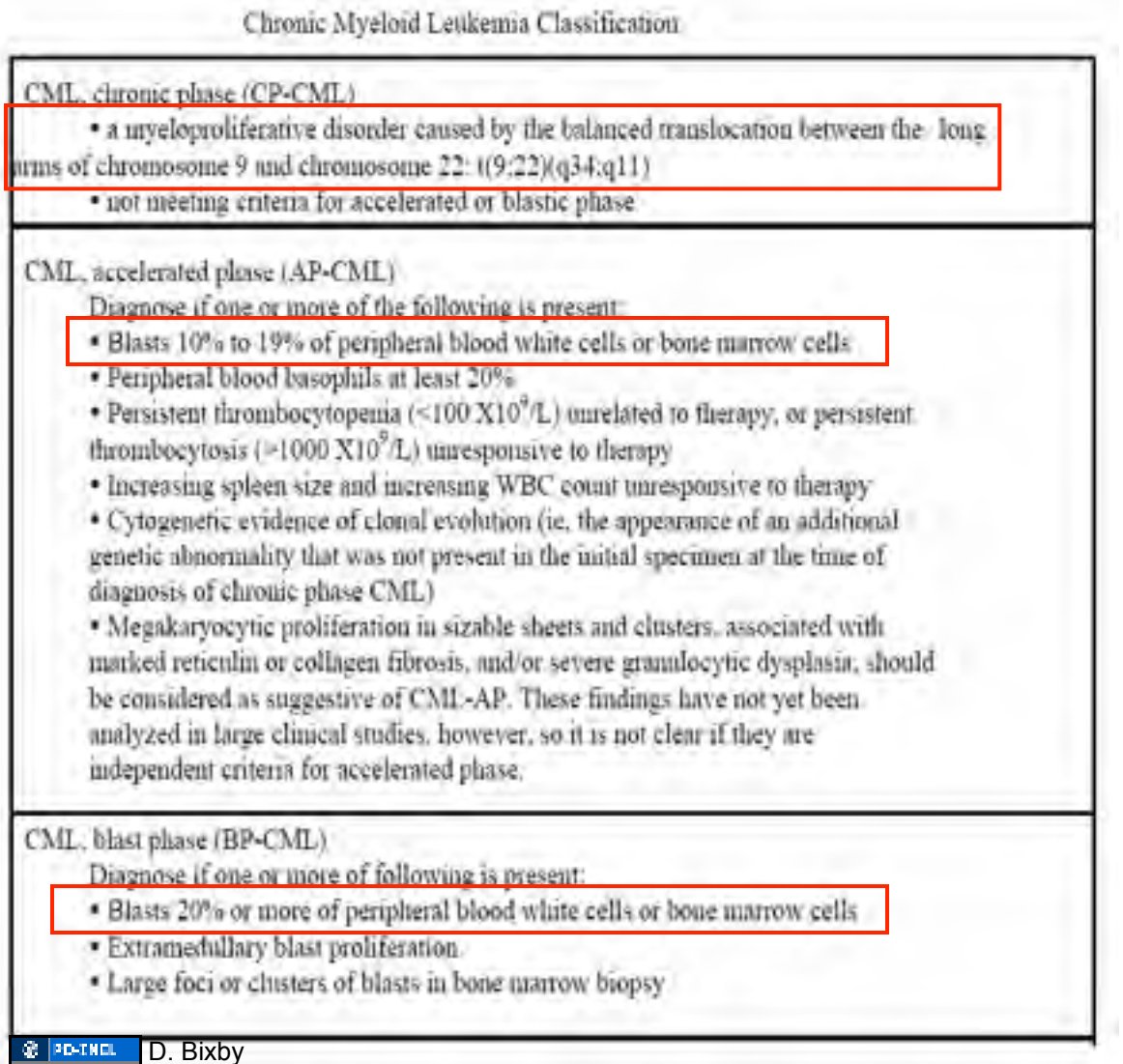
Test	Target	Tissue	Sensitivity (%)*	Use
Cytogenetics	Ph chromosome	BM	1-10	▪ Confirm diagnosis of CML ▪ Evaluate karyotypic abnormalities other than Ph chromosome (ie, clonal evolution)
FISH	Juxtaposition of *bcr* and *abl*	PB/BM	0.5-5	▪ Confirm diagnosis of CML ▪ Routine monitoring of cytogenetic response in clinically stable patients ▪ Routine measurement of MRD
RT-PCR	*bcr-abl* mRNA	PB/BM	0.0001-0.001	▪ Routine measurement of MRD ▪ Determine the breakpoints of the fusion genes

*Number of leukemic cells detectable per 100 cells.

BM = bone marrow; FISH = fluorescence in situ hybridization; PB = peripheral blood; MRD = minimal residual disease; RT-PCR = reverse transcriptase polymerase chain reaction.

Wang et al. *Genes Chromosomes Cancer*. 2001;32:97

Chronic Myeloid Leukemia - Diagnostic Criteria for the 3 Phases of the Disease



Chronic Myeloid Leukemia Classification

CML, chronic phase (CP-CML)

- a myeloproliferative disorder caused by the balanced translocation between the long arms of chromosome 9 and chromosome 22: t(9;22)(q34;q11)
- not meeting criteria for accelerated or blastic phase

CML, accelerated phase (AP-CML)

Diagnose if one or more of the following is present:

- Blasts 10% to 19% of peripheral blood white cells or bone marrow cells
- Peripheral blood basophils at least 20%
- Persistent thrombocytopenia (<100 $X10^9$/L) unrelated to therapy, or persistent thrombocytosis (>1000 $X10^9$/L) unresponsive to therapy
- Increasing spleen size and increasing WBC count unresponsive to therapy
- Cytogenetic evidence of clonal evolution (ie, the appearance of an additional genetic abnormality that was not present in the initial specimen at the time of diagnosis of chronic phase CML)
- Megakaryocytic proliferation in sizable sheets and clusters, associated with marked reticulin or collagen fibrosis, and/or severe granulocytic dysplasia, should be considered as suggestive of CML-AP. These findings have not yet been analyzed in large clinical studies, however, so it is not clear if they are independent criteria for accelerated phase.

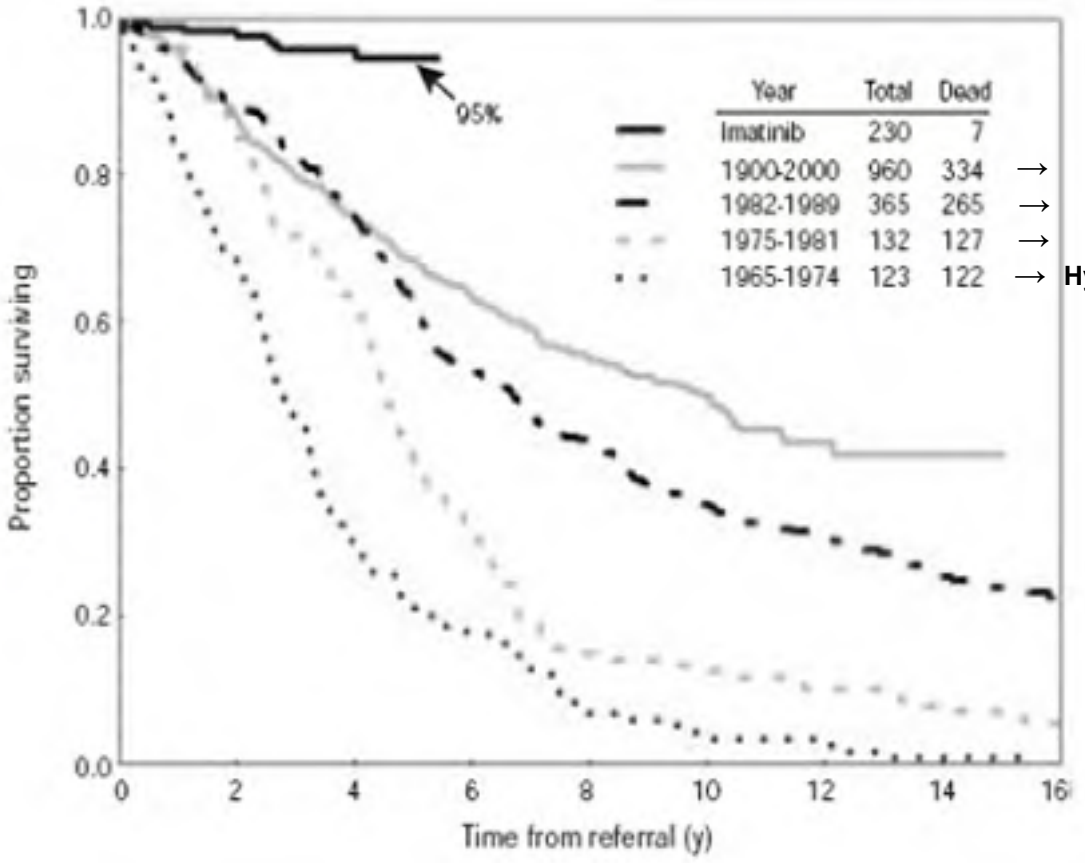
CML, blast phase (BP-CML)

Diagnose if one or more of following is present:

- Blasts 20% or more of peripheral blood white cells or bone marrow cells
- Extramedullary blast proliferation
- Large foci or clusters of blasts in bone marrow biopsy

Therapeutic Options in Chronic Myeloid Leukemia

History of CP-CML Therapies



→ Interferon – α +/- AraC

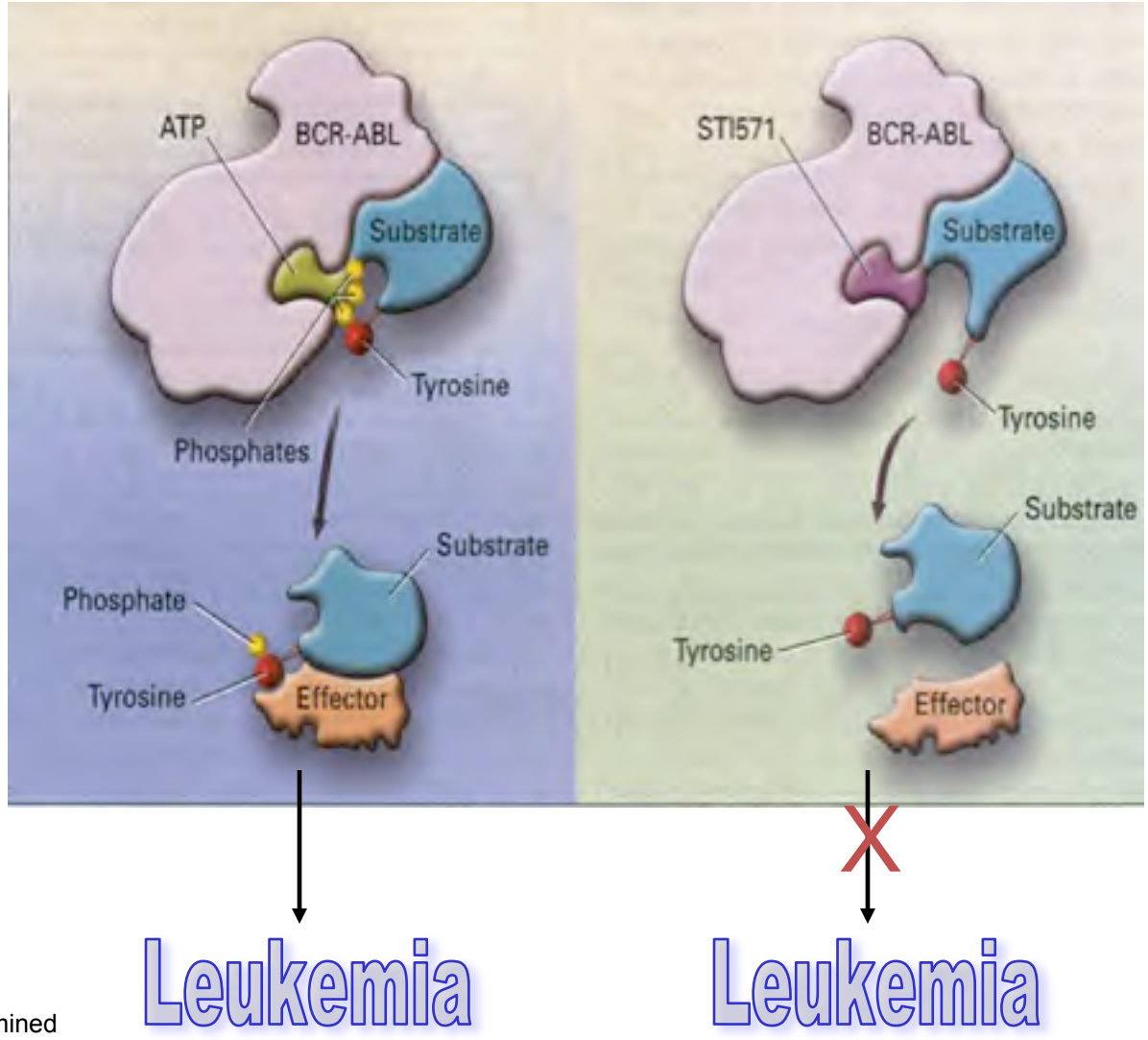
→ early Interferon – α trials

→ intensive chemotherapy

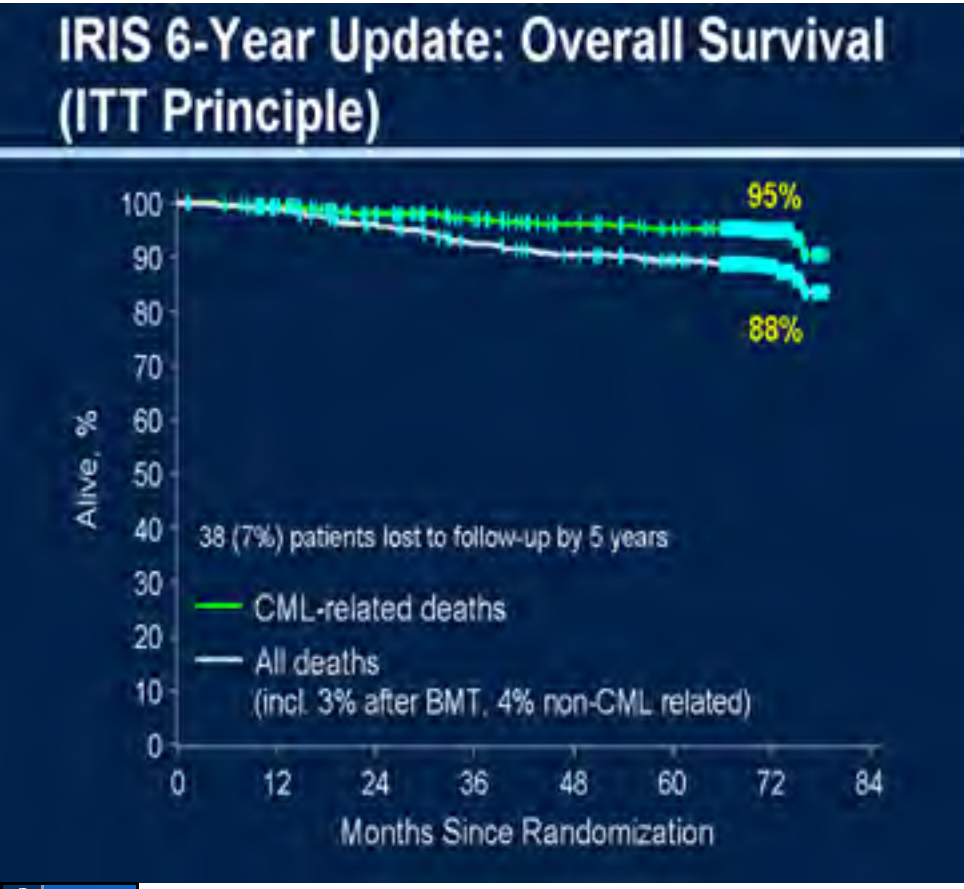
→ Hydrea, or radiation therapy or Busulphan

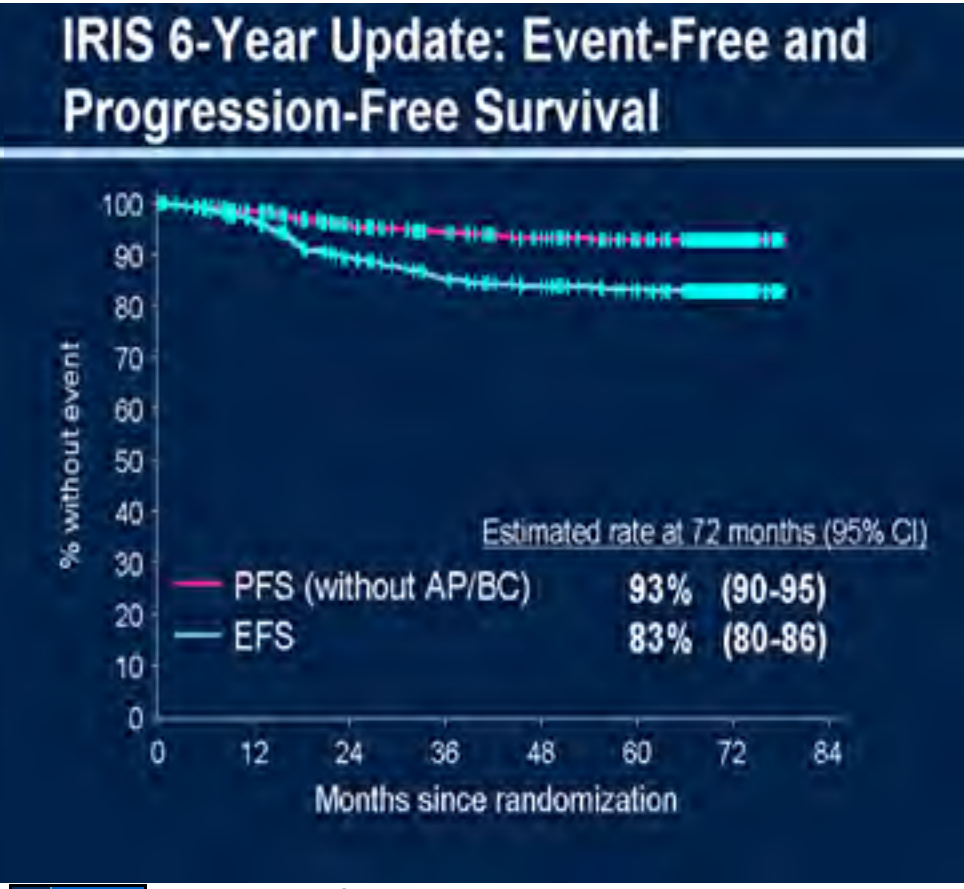
Quintas-Cardama et al. Mayo Clin Proc 2006; 81(7):973-988

Imatinib (Gleevec, Novartis)
a small molecule tyrosine kinase inhibitor



Frontline Therapy in Chronic Phase - Chronic Myeloid Leukemia



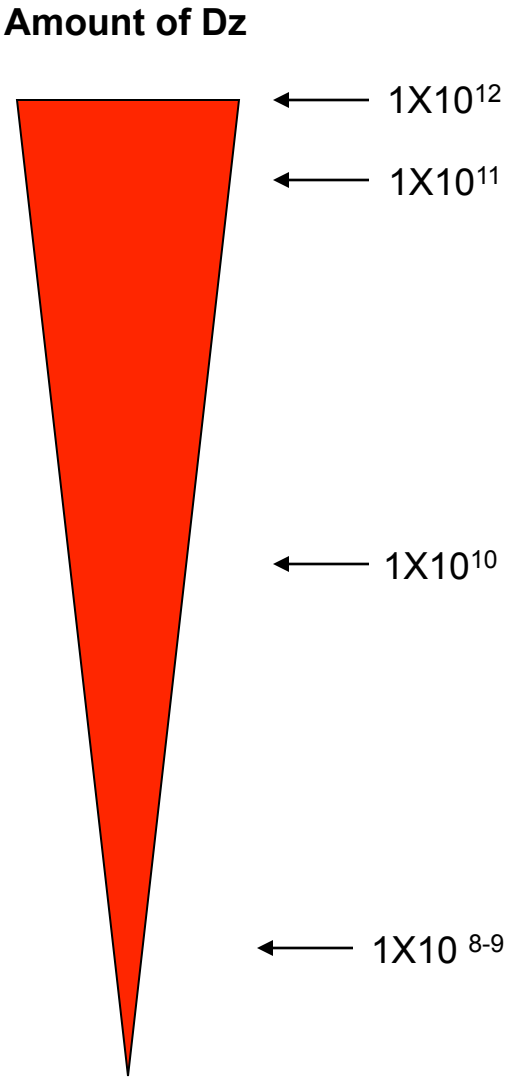


Hochhaus A, Druker B, Larson R, et al. Blood (ASH Annual Meeting Abstracts), Nov 2007; 110: 25.

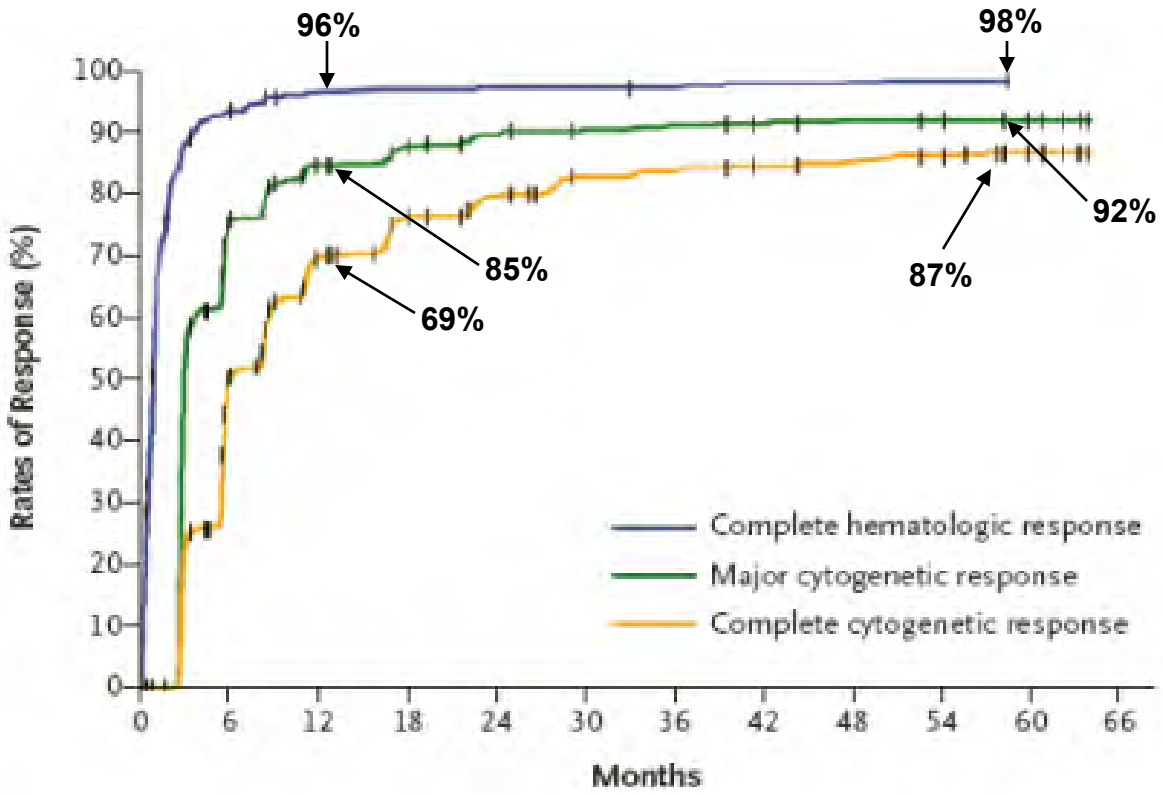
Hochhaus A, O' Brien S, Guilhot F, et al., Leukemia (2009) 23, 1054–1061.

Treatment Milestones for CML

Definitions of Responses to Treatments
Hematologic Response
Complete Hematologic response
1) Normal PB counts (WBC < 10 and plt < 450)
2) Normal WBC differential
3) No Dz symptoms
4) Normalization of the size of the liver and spleen
Cytogenetic Responses: Ph^+ Metaphases
1) complete: 0%
2) partial: 1% - 35%
3) minor: 36% - 65%
4) minimal: 66% - 95%
5) none: 96% - 100%
Molecular Responses: ratio of Bcr-Abl/Abl
Major Molecular Response
3-$\log_{10}$ reduction from initial diagnosis sample (i.e. 25 →0.025)



Imatinib has Revolutionized the Treatment of CML – IRIS Trial[1]



1. Newly diagnosed CML patients were randomized to receive either Imatinib 400 mg daily or Interferon-α at approximately $5X10^6$ U/day as well as Ara-C 20 mg/m^2 d1-10 q 8 days. Graph shows outcomes of 553 pts randomized to Imatinib.

Druker et al. N Engl J Med 2006; 355(23): 2408-2417.

2009 ELN Recommendations for Response Assessment for Treatment

Evaluation Time, Months	Response			Warnings
	Optimal	Suboptimal	Failure	
Baseline	NA	NA	NA	High risk; CCA/Ph+*
3	CHR and at least minor CgR (Ph+ ≤ 65%)	No CgR (Ph+ > 95%)	Less than CHR	NA
6	At least PCgR (Ph+ ≤ 35%)	Less than PCgR (Ph+ > 35%)	No CgR (Ph− > 95%)	NA
12	CCgR	PCgR (Ph− 1% to 35%)	Less than PCgR (Ph+ > 35%)	Less than MMolRt
18	MMolRt	Less than MMolRt	Less than CCgR	NA
Any time during treatment	Stable or improving MMolRt	Loss of MMolRt; mutations†	Loss of CHR; loss of CCgR; mutations‡; CCA/Ph+	Increase in transcript levels‖; CCA/Ph−

Baccarani M, Cortes J, Pane F, et al., J Clin Oncol. 2009 Dec 10;27(35):6041-51.

Mechanisms of Imatinib Resistance

Primary resistance

- failure to achieve preset hematologic and/or cytogenetic milestones

- IRIS data indicates a rate of ~ 15% by failing to a achieve a PCyR at 12 months and 24% by failing to achieve a CCyr by 18 months of therapy.

- rates higher in accelerated and blast phase disease

Secondary resistance

- loss of a previously achieved hematologic or cytogenetic milestone

- rates may be 10-15% on Imatinib, but become rarer as time on therapy progresses

- rates higher in accelerated and blast phase disease

Resistance Mechanisms

1) Bcr-Abl Kinase mutations
   - > 50 known mutations within Abl sequence which inhibits Imatinib from binding
   - mutations identified in 30-80% of individuals with resistant disease
2) Bcr-Abl duplication

   duplication of the *Bcr-Abl* sequence has been identified in cell lines with Im resistance
3) Pgp over-expression

   export pump of many chemotherapeuticsleading to lower intracellular Im concentration
4) hOct-1 under-expression

   import pump for Im which may lead to lower intracellular levels of IM
5) Src-Family kinase (SFK) expression

   activation may circumnavigate the Bcr-Abl 'addiction' of the transformed cell

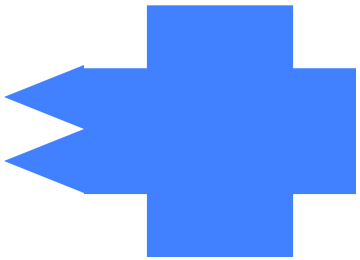
Bcr-Abl

imatinib

Mut. Bcr-Abl

imatinib

Mut. Bcr-Abl



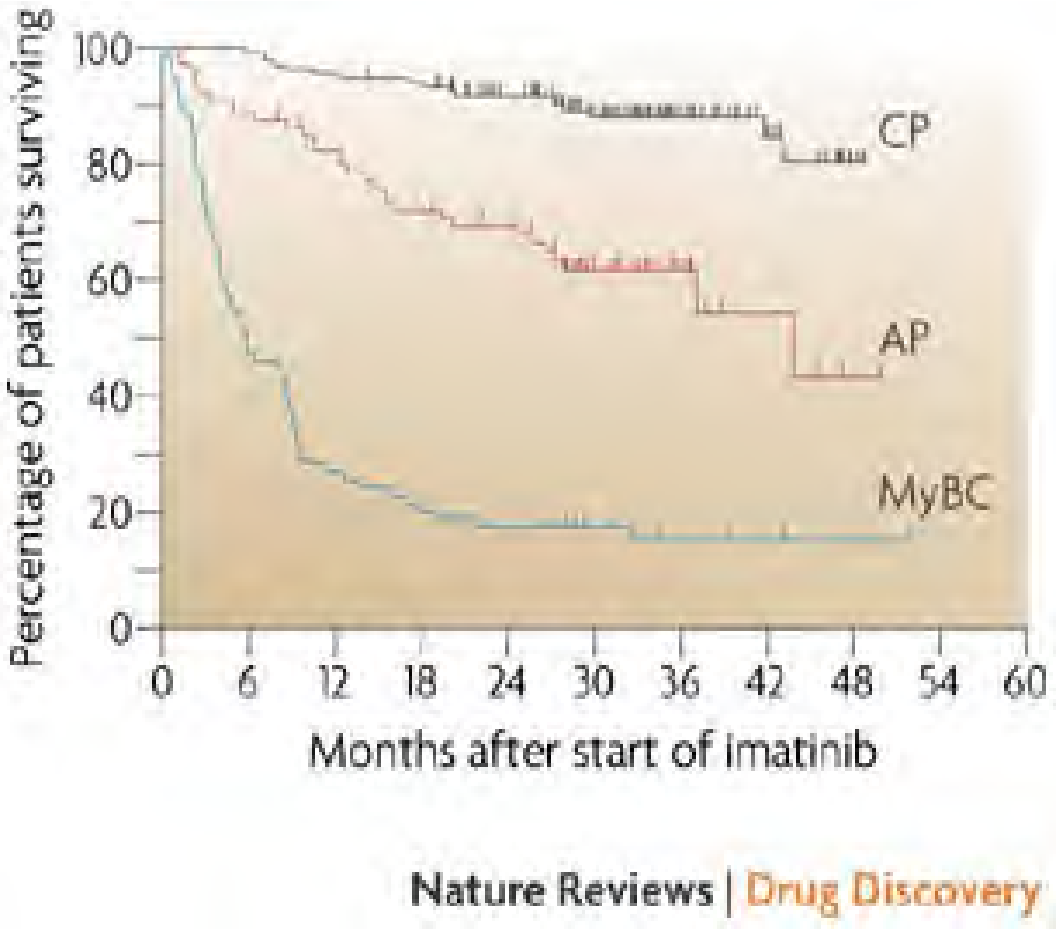
dasatinib

	Parental	38.31	10.78	> 50	38.43
	WT	1	1	1	1
P-LOOP	L248V	2.97	3.54	5.11	2.80
	G250E	4.31	6.86	4.45	4.56
	Q252H	0.81	1.39	3.05	2.64
	Y253F	0.96	3.58	1.58	3.23
	E255K	9.47	6.02	5.61	6.69
	E255V	5.53	16.99	3.44	10.31
C-Helix	D276G	0.60	2.18	1.44	2.00
	E279K	0.95	3.55	1.64	2.05
ATP binding region (drug contact sites)	V299L	76.10	1.54	8.65	1.34
	T315I	45.42	17.50	75.08	39.41
	F317L	2.42	2.60	4.46	2.22
SH2-contact	M351T	0.70	1.76	0.88	0.44
Substrate binding region (drug contact sites)	F359V	0.93	2.86	1.49	5.16
A-LOOP	L384M	0.47	1.28	2.21	2.33
	H396P	0.43	2.43	1.07	2.41
	H396R	0.81	3.91	1.63	3.10
	G398R	1.16	0.35	0.69	0.49
C terminal lobe	F486S	2.31	8.10	3.04	1.85

Sensitive	≤ 2

PD-INCL Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009;27(3):469-471, PMID: 19075254.

Imatinib Poorly Control Advanced Phase Disease



Kamb et al. The value of early detection, the right drug and the right patient population. Nature Reviews Drug Discovery 2007; 6: 115-120.

Treatment Options for Resistant Disease

1) Dose Escalation of imatinib

2) Second Generation TKIs

3) Bone Marrow Transplant

4) Clinical Trial Participation

Dose Escalation of imatinib
START-R Trial[1]

Patients resistant to 400mg-600 mg of imaitnib were treated with either 70 mg BID of dasatinib or 800 mg of imaitnib

- primary endpoint of the trial was the rate of MCyR at 12 weeks and this was equal (D=36%; IM=29%; p=.40)
- At a minimum follow-up of 2 years, dasatinib demonstrated higher rates of:
  - complete hematologic response (93% vs 82%; *P* = .034)
  - major cytogenetic response (MCyR) (53% vs 33%; *P* = .017)
  - complete cytogenetic response (44% vs 18%; *P* = .0025)

The depth of the previous response to imatinib may be associated with the proportion of patients responding to dose escalation. Patients having achieved a prior major cytogenetic response (MCyR) with imatinib reported a greater than 50% chance of re achieving that response with high-dose imaitnib, yet only 7% of patients who did not achieve any cytogenetic response on standard dose imatinib were able to achieve a MCyR.

Kantarjian H, Pasquini R, Levy V, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). Cancer. 2009.

Second Generation Tyrosine Kinase Inhibitors (TKIs)

The FDA has approved 2 additional oral TKIs for the treatment of imatinib relapsed/refractory or imatinib intolerant CML

dasatinib (Sprycel – BMS)

- oral multi-kinase inhibitor
- ~ 325 times more potent than IM
- active against the ‘open’ and ‘closed confirmation of Bcr-Abl
- active against many of the identified kinase domain (KD) mutations
- active against the SFKs
- may not be a substraight for Pgp or hOct-1

nilotinib (Tasigna – Novartis)

- oral multi-kinase inhibitor
- ~ 30 times more potent than IM
- active against only the closed confirmation of Bcr-Abl
- active against many of the KD mutations
- not active against the SKFs
- may not be a substraight for hOct-1

Bone Marrow Transplantation

Allogeneic bone marrow transplant remains the only known curative option in CML

Associated with an increased morbidity and mortality (TRM -10%-30%)

Therefore, not typically applied for upfront therapy for CML

- considered only in cases of matched-related Txp for extremely young pts (pediatrics)

However, often considered in those with relapsed/refractory disease to TKI based therapies

- efficacy of the transplant dependent upon the phase of the disease at the time of the transplant: CP>AP>BP

Clinical Trial Options in CML

				INNO-406
(NS-187)	CytRx	CML, Ph+ ALL	ABL, KIT, LYN, PDGFR	Phase I/II NCT00352677 (c)
AP24534*	Ariad	CML, advanced hematologic malignancies	ABL, FGFR1, FLT3, KIT, VEGFR	Phase I NCT00660920
XL228* →	Exelixis	CML, Ph+ ALL, lymphoma, myeloma, solid tumors	ABL, Aurora A, FGFR1-3, IGF1R, SRC	Phase I NCT00464113
AT9283 →	Astex Therapeutics	CML, AML, ALL, MDS, myelofibrosis, NHL, solid cancers	ABL, Aurora A&B, FLT3, JAK2, JAK3	Phase I/II NCT00522990
PHA739358*	Nerviano Medical Sciences	CML, myeloma, prostate	ABL, Aurora A&B, FGFR1, RET, TRK	Phase II NCT00335868
KW-2449*	Kyowa Hakko Kirin Pharma	CML, AML	ABL, Aurora A, FGFR1, FLT3	Phase I NCT00346632(i) Phase I/II NCT00779480
MK-0457*	Merck	CML, ALL, MDS	ABL, Aurora A&B, FLT3, JAK2	Phase I/II NCT00111683(c)
Homoharringtonine (HHT)*	ChemGenex	CML	cytochrome C, MCL-1	Phase II NCT00375219 NCT00462943 NCT00114959 (c)
DCC2036* →	Deciphera	CML, Ph+ ALL	ABL, FLT3, KDR SFK, TIE2	Phase I NCT00827138

ABL indicates Bcr-Abl (Abelson) kinase; SFK, Src family kinase; KIT, CD117; TEC, Tec protein kinase; STE20, serine/threonine 20 kinase; CAMK2G, calcium/calmodulin-dependent protein kinase (CaM kinase) II gamma kinase; PDGFR, platelet-derived growth factor receptor; FGFR1, fibroblast growth factor receptor 1; IGF1R, insulin like growth factor receptor; JAK, Janus kinase; FLT3, fms-like tyrosine kinase

Polycythemia Vera (PV)

Polycythemia

A hematocrit greater than 48%(♀) or 52 % (♂) constitutes polycythemia

Likewise, a hemoglobin of >16.5 g/dL (♀) or >18.5 g/dL (♂) raises the suspicion for polycythemia

Absolute polycythemia is characterized by an increase in red blood cell (RBC) mass

- Five common causes include: 1) primary polycythemia, 2) hypoxia, 3) carboxyhemoglobinemia, 4) cushing's syndrome or corticosteroids, and 5) erythropoietin-secreting tumors

Relative polycythemia is characterized by a decrease in plasma volume.

Two common causes:

- Dehydration (e.g., from vomiting, diarrhea, excessive sweating, or diuretics) can deplete plasma volume, leading to a relative polycythemia.
- Stress erythrocytosis (Gaisböck's polycythemia) actually results from contraction of the plasma volume and is therefore a misnomer. This benign disorder is seen most often in hypertensive, obese men.

Red Blood Cell Mass Assay:

- used to distinguish an absolute versus a relative polycythemia
- does not subclassify absolute polycythemias

Clinical Presentation of Primary PV

Symptoms:

- non-specific complaints: headache, weakness, dizziness, and excessive sweating
- pruritus, especially following a warm bath or shower
- erythromelalgia, or burning pain in the feet or hands accompanied by erythema, pallor, or cyanosis
- symptoms related to either an arterial or venous thrombosis (CVA, MI, DVT, Budd Chiari syndrome or other portal venous thrombosis)

Signs:

- facial plethora (ruddy cyanosis)
- splenomegaly
- hepatomegaly
- gouty arthritis and tophi

Diagnostic Criteria for Primary PV

Polycythemia Vera Study Group (PVSG) Criteria for PV

Major Criteria

- Elevated RBC mass
  - >36 cc/kg in men
  - >32 cc/kg in women
- Oxygen saturation >92%
- Splenomegaly

Minor Criteria

- Plt count > 400,000
- WBC > 12,000
- Elevated LAP score (>100)
- Serum vitamin B12 >900 pg/mL **or** serum unbound B12 binding capacity >2,200 pg/mL

→ All 3 major criteria OR the first 2 major and any 2 minor criteria ←

2008 WHO Diagnostic Criteria for Primary Polycythemia Vera

Major Criteria

1) Hgb > 18.5g/dl (♂) or 16.5g/dl (♀)
   or
   Hgb or Hct > 99%
   or
   Hgb > 17g/dl (♂) or 15 g/dl (♀) and a documented increase of 2 g/dl
   or
   RBC mass > 25% of mean normal

2) Presence of a JAK2 V617F or similar mutation

Minor Criteria

1) Bone marrow trilineage expansion
2) Subnormal EPO level
3) Endogenous erytyhroid colony growth

→ two major or first major and two minor criteria ←

Tefferi et al. Leukemia (2008) 22, 14–22

JAK2 Mutations Seen in Three Different MPNs

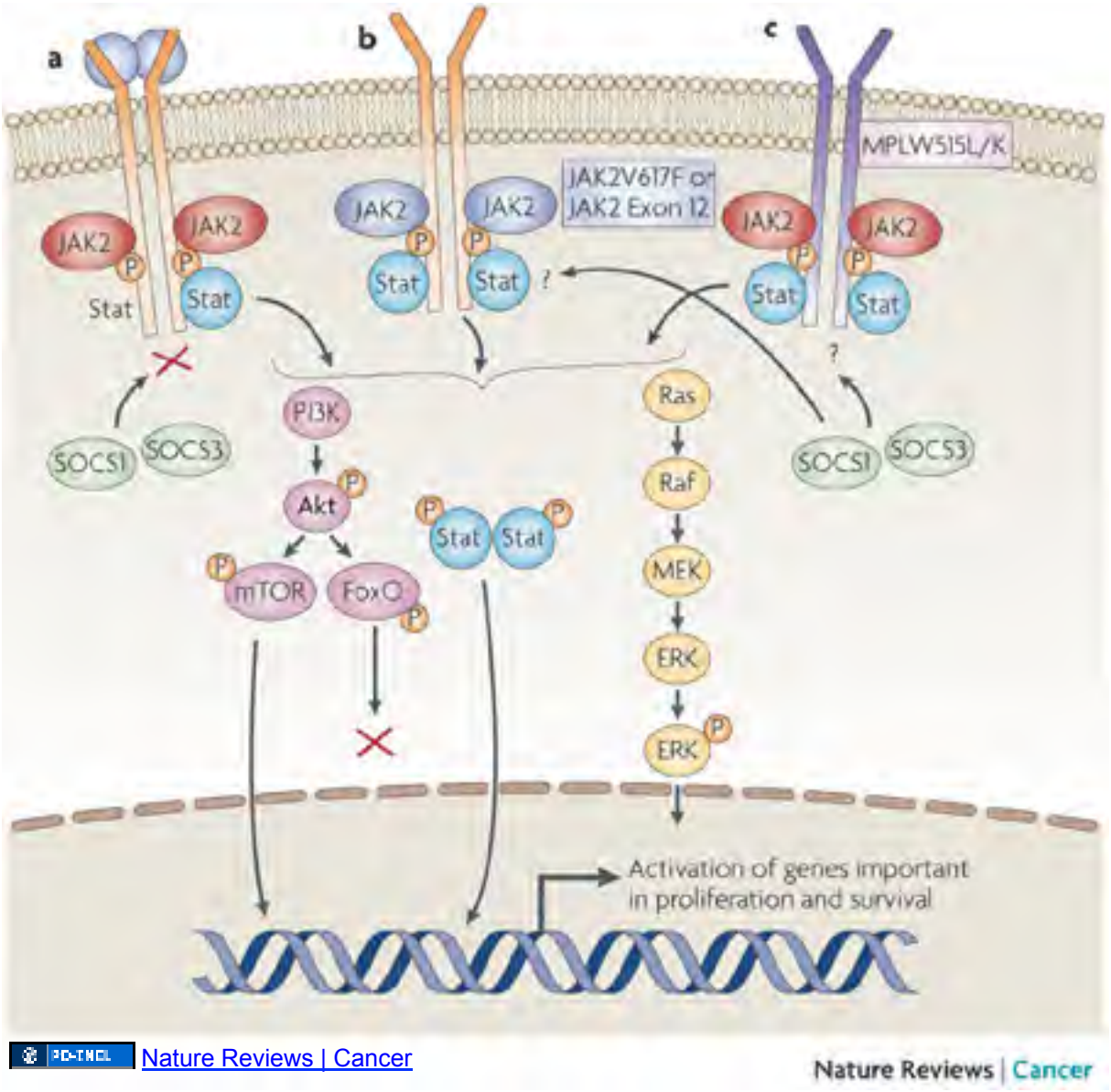
See online at: http://img.medscape.com/fullsize/migrated/563/885/nrc563885.fig1.gif

Original source: Levine et al. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. Nature Reviews – Cancer 2007;7:673-683

JAK2 Mutations and MPNs

- Receptor Tyrosine Kinase - maps to chromosome 9p
- Valine to phenylalanine substitution at amino acid 617 (V617F) in pseudokinase domain of *JAK2* allows for the constitutive activation of the receptor
- Somatic acquired mutation
- High incidence in PCV (~95%)
  - Not present in every patient with PCV
- Lower incidence in ET (~50%) and PMF (~50%)

JAK2 Mediated Signaling



Outcomes and Treatment of PV

Survival outcomes in PV are affected by:

1) hyperviscosity and associated ischemic sequela
2) thromboses independent of hyperviscosity
3) transformation to myelofibrosis or acute myeloid leukemia (~3%-10%)

Therapeutic Options in PV:

1) **Low Risk**: phlebotomy (to an Hct of <45 in ♂ and <42 in ♀) + low dose aspirin (81 mg daily) – decreases risk of thrombosis
2) **High Risk**: phlebotomy + ASA + hydroxyurea

<u>High Risk for Thrombosis:</u>

- age over 70
- prior thrombosis
- platelet count >1,500,000/µl
- presence of cardiovascular risk factors

JAK2 Inhibitors in MPNs

A number of inhibitors of the JAK2 kinase have been developed and inhibit the proliferation and survival of JAK2 V617F transformed cell lines in-vitro

Clinical studies (Phase I and Phase II) have been initiated and demonstrate some symptomatic improvement as well as improvement in splenomegaly in a number of patients, but unlike CML, the percentage of $JAK2^{+}$ progenitor cells have not been significantly altered. However, a large number of trials continue at this time.

Leads to speculation that JAK2 may not be sufficient for the development of MPNs and there may be an earlier genetic mutation that is driving the phenotype.

Essential Thrombocythemia (ET)

Thrombocytosis

Definition: thrombocytosis is defined as a platelet count > 450,000 cells/μL

Etiology of Thrombocytosis

Primary - if the thrombocytosis is caused by a myeloproliferative neoplasm, the platelets are frequently abnormal and the patient may be prone to both bleeding and clotting events.

Secondary - if thrombocytosis is secondary to another disorder (reactive), even patients with extremely high platelet counts (e.g., > 1,000,000 cells/μl) are usually asymptomatic.

Differential Diagnosis of secondary thrombocytosis:

1. Malignancies
2. Infections and inflammatory disorders (e.g., Crohn's disease)
3. Post surgical status
4. Connective tissue disorders
5. Iron deficiency anemia
6. Splenectomy
7. Recovery of the bone marrow from a stress (chemotherapy or alcohol)
8. Essential Thrombocythemia

Clinical Presentation of Essential Thrombocythemia (ET)

Asymptomatic (~ 30-50%)

Vasomotor symptoms including headache, syncope, atypical chest pain, acral paresthesia, livedo reticularis, and erythromelalgia

Thrombosis and hemorrhage occur to various degrees in 5%-25% of patients

Early satiety and abdominal bloating due to splenomegaly

JAK 2^{+} (V617F) in approximately 50% of patients

Diagnostic Criteria for ET

2008 WHO Diagnostic Criteria for Essential Thrombocytosis

1. Platelet count > 450,000
2. Megakaryocytic proliferation with large, mature morphology and with little granulocytic or erythroid expansion
3. Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm
4. Demonstration of the JAK2V617F or other clonal marker or lack of evidence of a secondary (reactive thrombocytosis)

→ Diagnosis of essential thrombocythemia requires meeting all four major criteria ←

Teferri et al. Leukemia (2008) 22, 14–22

Outcomes in ET

Most patients with ET enjoy a normal life expectancy

Like PV, the major risks are secondary to thrombosis and disease transformation:

- 15-year cumulative risks:
  - thrombosis - 17% risk
  - clonal evolution into either myelofibrosis (4%) or AML (2%)

High risk for thrombosis:

- age ≥ 60
- prior thrombosis
- long-term exposure to a plt count of > 1,000,000

Treatment of ET

Low Risk:

- Age <60 years
- No previous history of thrombosis
- Platelet count <1 million/μl

→ aspirin (81 mg daily) if vasomotor Sx or other medical need for ASA

→ if otherwise low risk and plt >1.5 X 10^6, screen for an acquired von Willebrand disease before instituting ASA

High Risk:

- Age ≥60 years
- A previous history of thrombosis

→ hydroxyurea + aspirin (81 mg daily)

→ if plt >1.5 X 10^6, screen for an acquired von Willebrand disease before instituting ASA

→ anagrelide is an option, but when c/w hydroxyurea, it was assn with an increased risk of arterial thrombosis, venous thrombosis, serious hemorrhage, or death from vascular causes

Primary Myelofibrosis (PMF)

Primary Myelofibrosis
(Chronic Idiopathic Myelofibrosis)

Signs and Symptoms:

- asymptomatic (15% - 30%)
- severe fatigue
- splenomegaly
- hepatomegaly
- fever and night sweats
- signs or symptoms of anemia or thrombocytopenia
- foci of extramedullary hematopoiesis may occur in almost any organ
- bone or joint involvement

CBC Findings:

- anemia (hgb<10 in 50% of pts); anisocytosis, poikilocytosis, teardrop-shaped red blood cells (dacrocytes), and nucleated red blood cells
- leukoerythroblastosis (increased presence of immature myeloid cells and nucleated erythrocytes in the circulating blood.
- WBC and Plt counts are variable (ranging from low to high) with increased circulating $CD34^+$ precursor cells
- BM Biopsy shows increased fibrosis (reticulin fibers or mature collagen)
- $JAK2^+$ (V617F) in approximately 50% of cases

Diagnostic Criteria for PMF

2008 WHO Diagnostic Criteria for Primary Myelofibrosis

Major:

1. Megakaryocytic proliferation and atypia with either reticulin or collagen fibrosis
   or
   If no fibrosis, mekakaryocytic expansion must be assn. w/ increased BM cellularity
2. Does not meet WHO criteria for CML, PV, MDS, or other myeloid neoplasm
3. Demonstration of the JAK2 V617F mutation or other cloanl marker
   or
   no other evidence of a reactive marrow fibrosis

Minor:

1. Leukoerythroblastosis (immature RBCs and WBCs in the PB)
2. Increased LDH
3. Anemia
4. splenomegaly

→ Diagnosis of primary myelofibrosis (PMF) requires meeting all three major criteria and two minor criteria ←

Teferri et al. Leukemia (2008) 22, 14–22

DDx of Myelofibrosis

Myeloid Neoplasms
PMF
CML
ET
PV
MDS
Acute myelofibrosis (potentially assn. w/ FAB M7 AML)
AML
Mast Cell Disease
Lymphoid Neoplasms
lymphoma
Hairy Cell Leukemia
Multiple Myeloma
Non-Hematologic Disorders
Metastatic cancer
Connective tissue diseases
Rickets
Infections
Renal Osteodystrophy

Source Undetermined

Outcomes in PMF

As fibrosis progresses, cytopenias worsen leading to a transfusion dependency

- symptoms related to extrmedullary hematopoiesis increase (worsening splenomegaly and ‘B’ symptoms) also are frequently identified

Rarely do patients transform to Acute Leukemia (~ 4%)

- clonal evolution was common in these patients
- some evidence that in all MPNs, cases of JAK2 $^{(-)}$ Acute Leukemia arise out of a JAK^{+} MPN, causing speculation that there are additional genetic changes that either initiate and/or propagate these diseases

Despite the lack of transformation to leukemia, three-year survival rate is approximately 52%

Risk Assessment in PMF

Mayo Scoring System (pts age < 60)	
Score	Median Survival
0	173 mo
1	61 mo
≥ 2	26 mo

Risk Factors: Hemoglobin <10 g/dL
White blood cell count <4000/µl or >30,000/ µl
Absolute monocyte count >1000 µL
Platelet count <100,000/ µL

Elliott et al. Leuk Res. 2007;31(11):1503-9.

Transplant Scoring System (pts age < 55)	
Score	Median Survival
0 or 1	15 yrs
≥ 2	3 yrs

Risk factors: Hemoglobin <10 g/dL
'B' symptoms present (eg, fever, NS, weight loss)
Circulating blasts >1 percent

Dupriez et al. Blood 1996 Aug 1;88(3):1013-8.

Treatment of PMF

Risk stratification is critical in deciding on therapeutic options
(see previous scoring systems)

'Low Risk' without symptoms – expectant management

'Low Risk' with symptoms – hydroxyurea
androgenic and corticosteroids
splenectomy if adequate BM hematopoiesis
splenic irradiation
thalidomide or lenalidomide

'High Risk' and age < 55(?) – consider a reduced intensity allogeneic BMT

One Genetic Abnormality and Three Diseases Possible Role of Allele Burden

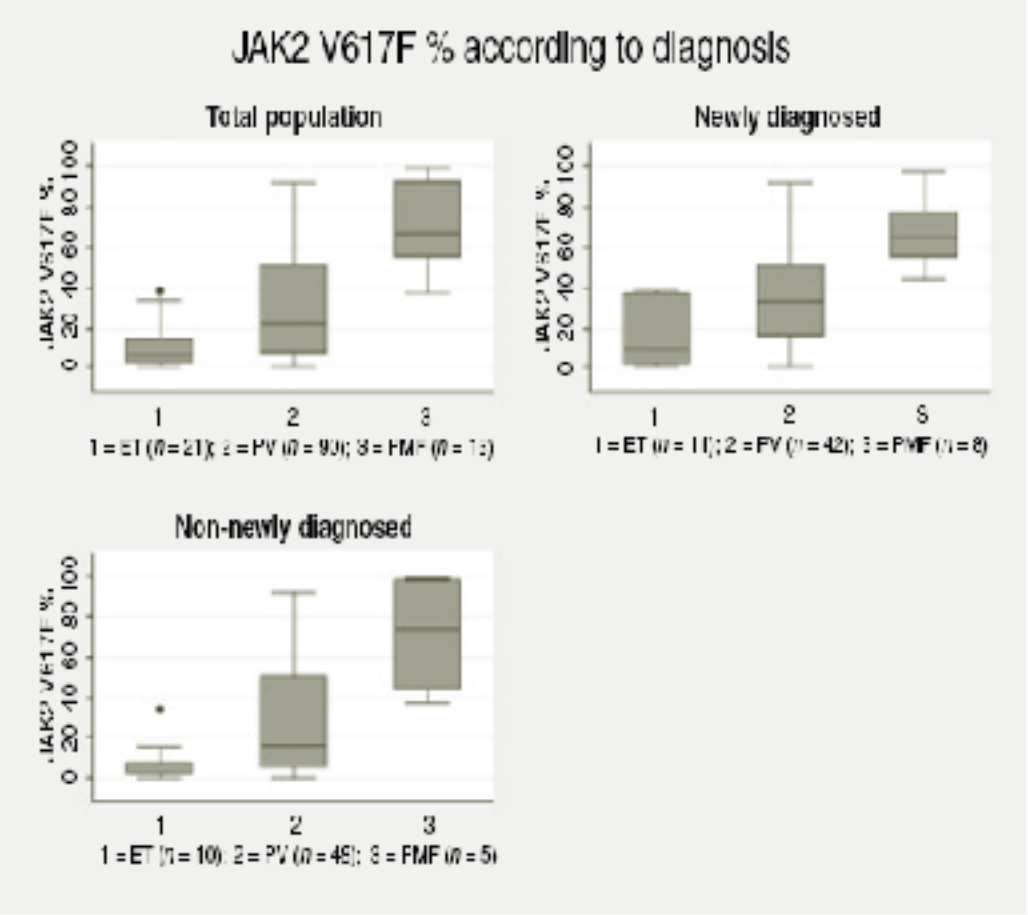


Figure 1 Box-plots showing the JAK2 V617F allele percentage in essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF) for (upper left) the total JAK2 V617F positive population analysed with qPCR ($n = 124$). The difference in JAK2 V617F allele burden was highly significant between the disease entities (ET vs. PV $P = 0.001$ and PV vs. PMF $P < 0.00001$); Upper right: newly diagnosed patients ($n = 61$) (ET vs. PV $P = 0.02$ and PV vs. PMF $P = 0.0008$). Lower left: non-newly diagnosed patients ($n = 63$).

PO-INCL Larsen et al. Eur J Hemeatology 2007; 79: 508-515

Review Question # 1

42 yo woman with no past medical Hx presented to her PCP for an annual health maintenance examination. Physical exam was normal. A CBC was drawn and revealed a WBC of 14.2 (normal differential), Hbg of 13.5 and a plt count of 752,000.

Her diagnosis is:

A) Polycythemia Vera (PV)

B) Essential Thrombocythema (ET)

C) Chronic Myeloid Leukemia (CML)

D) Reactive Thrombocytosis

E) Not sure – need more data

Review Question #1 (cont)

Iron studies are normal and there was no evidence of inflammation on history or examination. There was no history of recurrent infections or connective tissue diseases. Further blood testing demonstrated no evidence of the JAK2 V617F mutation by gene sequencing.

Her diagnosis is:

A) Polycythemia Vera (PV)

B) Essential Thrombocythema (ET)

C) Chronic Myeloid Leukemia (CML)

D) Reactive Thrombocytosis

E) Not sure – need more data

Review Question #1 (cont)

Additional testing of her peripheral blood demonstrated a negative RT-PCR for the *Bcr-Abl* p210 and p190 gene products but the peripheral blood FISH for the *Bcr-Abl* translocation was positive in 72% of cells. Repeat testing confirmed both of these findings.

Her diagnosis is:

A) Polycythemia Vera (PV)

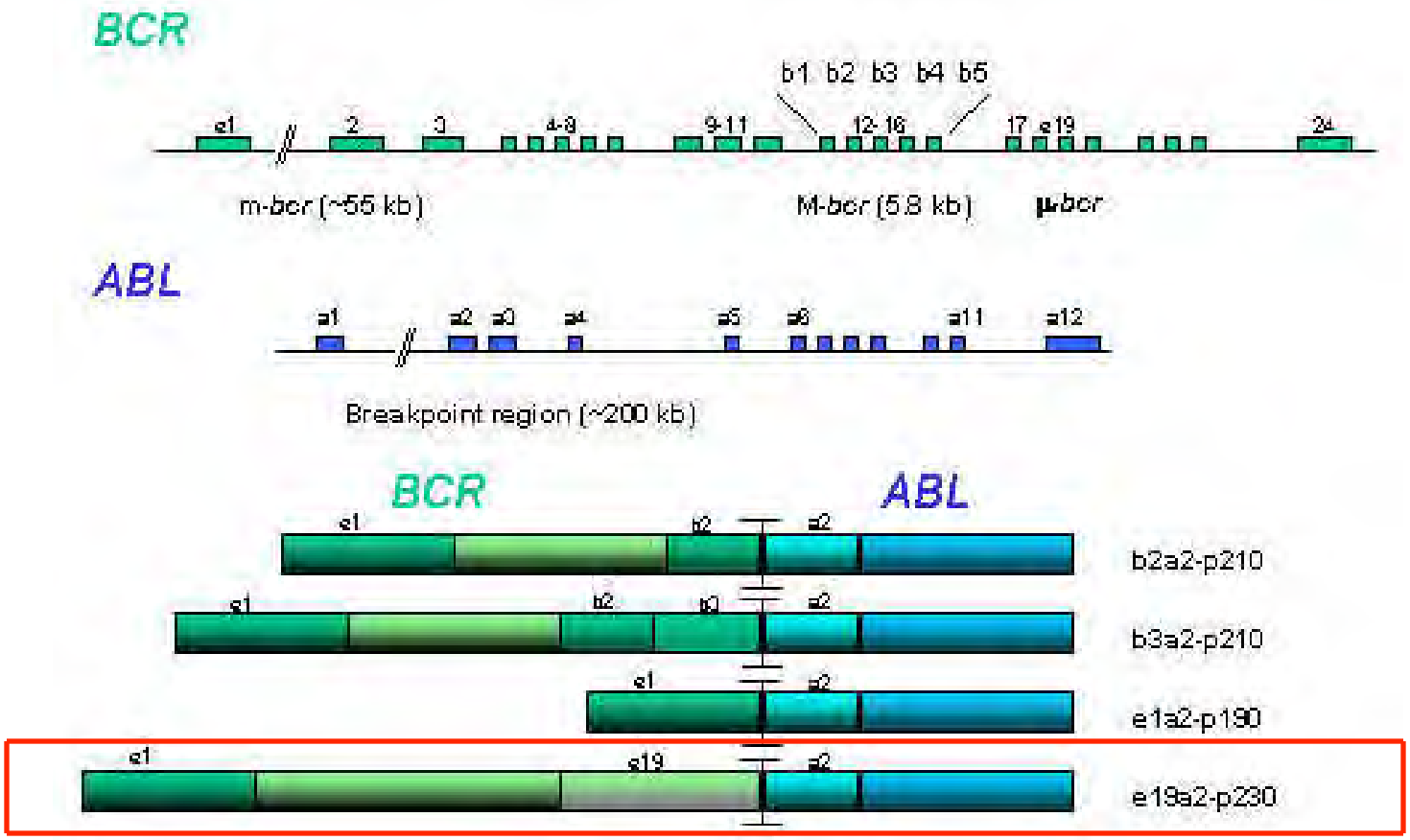
B) Essential Thrombocythema (ET)

C) Chronic Myeloid Leukemia (CML)

D) Reactive Thrombocytosis

E) Not sure – need more data

Review Question #1 (cont)



Review Question #2

A 34 yo woman presents for her annual HME and a CBC reveals a WBC count of 11.2, hgb of 17.1 and a platelet count of 390,000. Peripheral blood was sent to evaluate for the JAK2 mutation and was negative. What is the most appropriate next step in the evaluation of the patient?

A) Bone marrow biopsy to evaluate for a myeloproliferative neoplasm
B) Repeat CBC in 3 months
C) Repeat JAK2 testing to ensure laboratory accuracy
D) Red cell mass assay to determine a primary versus a seconday erythrocytosis
E) Referral to hematology

Review Question#2 (cont)

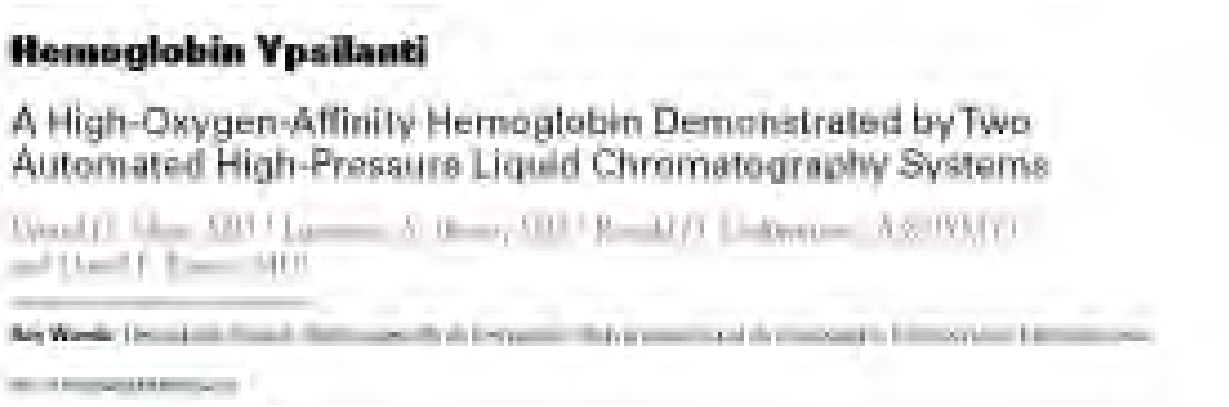
The patient underwent a red cell mass assay that demonstrated a true erythrocytosis (increased red cell mass). Upon further questioning, she states that she was previously treated with phlebotomy for the elevated Hgb and felt horrible for 3-4 weeks. She also indicates that her brother has a similar condition as did her mother and her mothers sister, but no one has been able to find a cause. What is the most appropriate next step in the management of this patient.

A) Repeat phlebotomy, but take only 250 cc/session

B) Initiate treatment with low dose aspirin (81 mg/day) and hydroxyurea

C) Repeat phlebotomy, but take only 250 cc/session and also treat with low dose aspirin (81 mg/day)

D) Evaluate for an inherited cause of polycythemia



Hemoglobin Ypsilanti

A High-Oxygen-Affinity Hemoglobin Demonstrated by Two Automated High-Pressure Liquid Chromatography Systems

Hemoglobin (Hb) Ypsilanti is a rare, high-oxygen-affinity hemoglobin first described in 1967 and named for the Michigan city in which the index family resided.[1-3]

Like other high-oxygen-affinity hemoglobins, of which there are now substantially more than 100 described, Hb Ypsilanti manifests as a true erythrocytosis.

Phlebotomy in individuals with an appropriate erythrocytosis (high affinity Hgb, CO poisoning, living at altitude, sleep apnea) will increase symptoms because the erythrocytosis is an appropriate correction for the primary disorder.

1. Rucknagel DL, Glynn KP, Smith JR. Hemoglobin Ypsilanti, characterized by increased oxygen affinity, abnormal polymerization, and erythremia [abstract]. *Clin Res.* 1967;15:270.
2. Glynn KP, Penner JA, Smith JR, et al. Familial erythrocytosis: a description of three families, one with hemoglobin Ypsilanti. *Ann Intern Med.* 1968;69:769-776.
3. **Mais DD**, **Boxer LA**, **Gulbranson RD**, **Keren DF**. Hemoglobin Ypsilanti: a high-oxygen-affinity hemoglobin demonstrated by two automated high-pressure liquid chromatography systems. Am J Clin Pathol. 2007 Nov;128(5):850-3.

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 5: National Cancer Institute, http://www.cancer.gov/

Slide 11: Sources Undetermined

Slide 12: Sources Undetermined

Slide 13: Sources Undetermined

Slide 14: Stephen B. Marley and Myrtle Y. Gordon. Chronic myeloid leukaemia: stem cell derived but progenitor cell driven Clinical Science (2005) 109, (13*25)

Slide 16: Source Undetermined

Slide 18: Source Undetermined

Slide 19: Source Undetermined

Slide 20: Sources Undetermined

Slide 21: Source Undetermined

Slide 22: Dale Bixby

Slide 23: Wang et al. *Genes Chromosomes Cancer*. 2001;32:97

Slide 24: Dale Bixby

Slide 26: Quintas-Cardama et al. Mayo Clin Proc 2006; 81(7):973-988

Slide 27: Source Undetermined

Slide 28: Hochhaus A, Druker B, Larson R, et al. Blood (ASH Annual Meeting Abstracts), Nov 2007; 110: 25.; Hochhaus A, O'Brien S, Guilhot F, et al., Leukemia (2009) 23, 1054–1061.

Slide 29: Dale Bixby

Slide 30: Druker et al. N Engl J Med 2006; 355(23): 2408-2417.

Slide 31: Baccarani M, Cortes J, Pane F, et al., J Clin Oncol. 2009 Dec 10;27(35):6041-51.

Slide 33: Dale Bixby

Slide 34: Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009;27(3):469-471, PMID: 19075254.

Slide 35: Kamb et al. The value of early detection, the right drug and the right patient population. Nature Reviews Drug Discovery 2007; 6: 115-120.

Slide 40: Dale Bixby

Slide 47: Nature Reviews | Cancer, http://www.nature.com/nrc/journal/v7/n9/images/nrc2210-f2.jpg

Slide 59: Source Undetermined

Slide 61: Elliott et al. Leuk Res. 2007;31(11):1503-9.; Dupriez et al. Blood 1996 Aug 1;88(3):1013-8.

Slide 63: Larsen et al. Eur J Hemeatology 2007; 79: 508-515

Slide 67: Source Undetermined