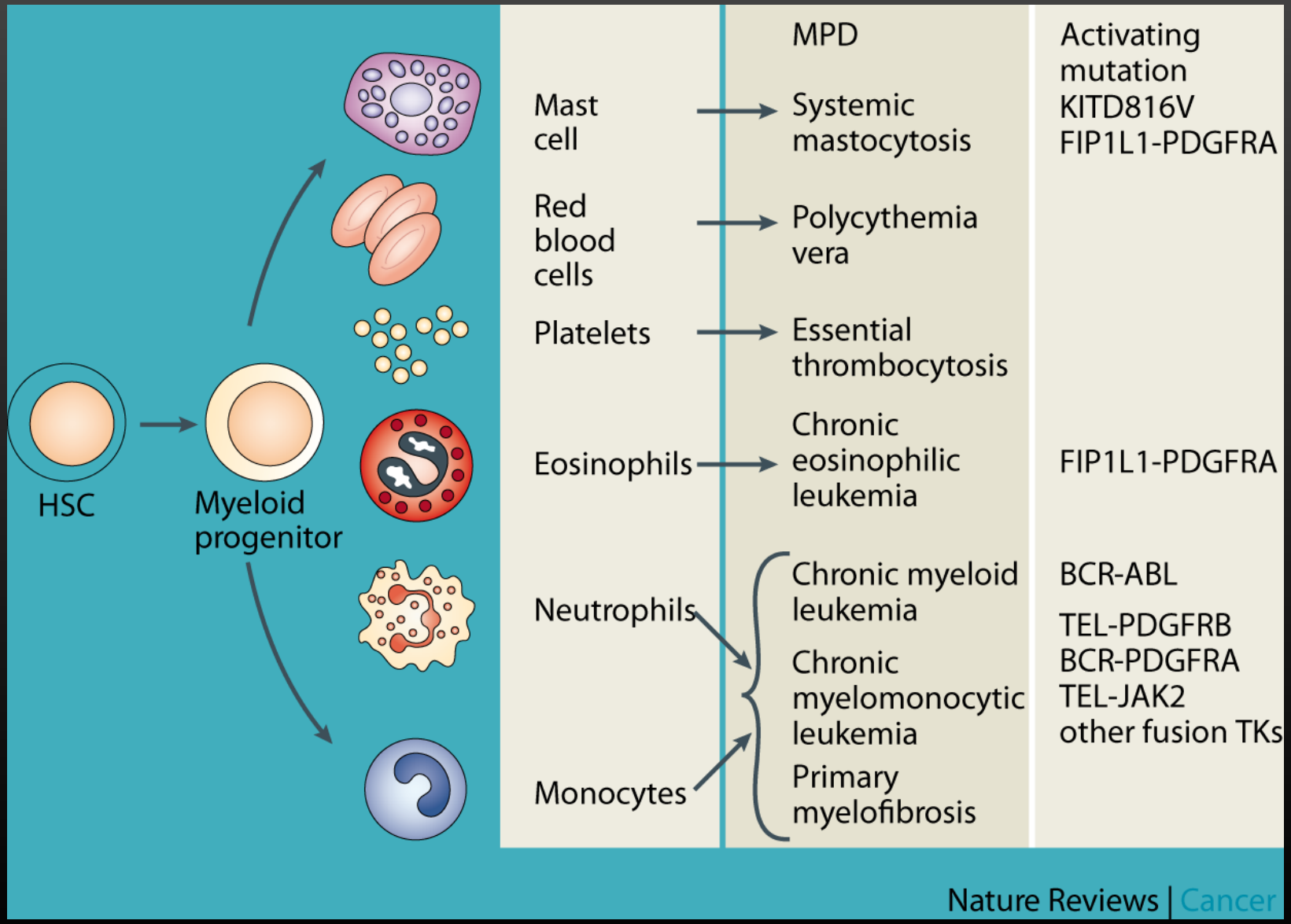
MYELOPROLIFERATIVE NEOPLASMS

Jonathan Abbas, MD

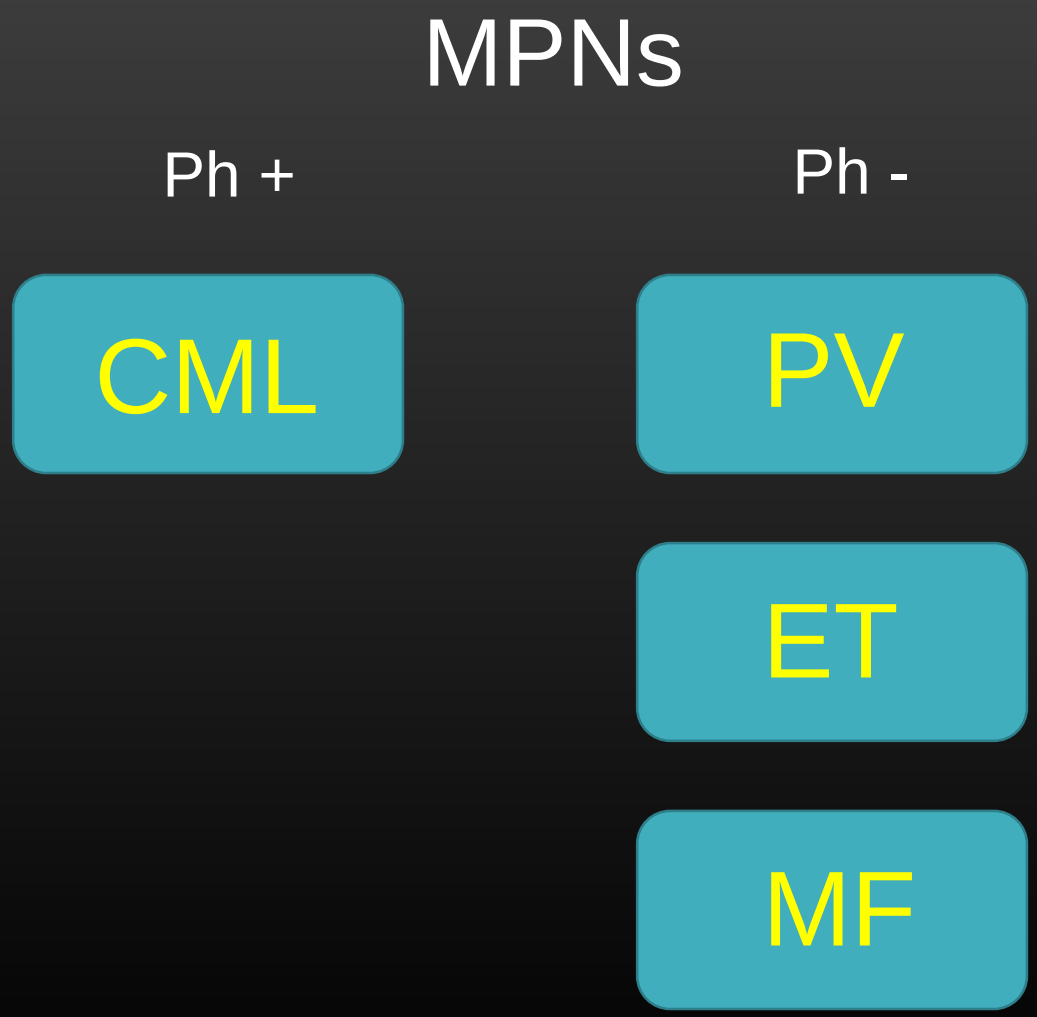
September 25, 2018

Myeloproliferative Disorders



Overview

- Chronic Myeloid Leukemia
- Polycythemia Vera
- Essential Thrombocythemia
- Myelofibrosis

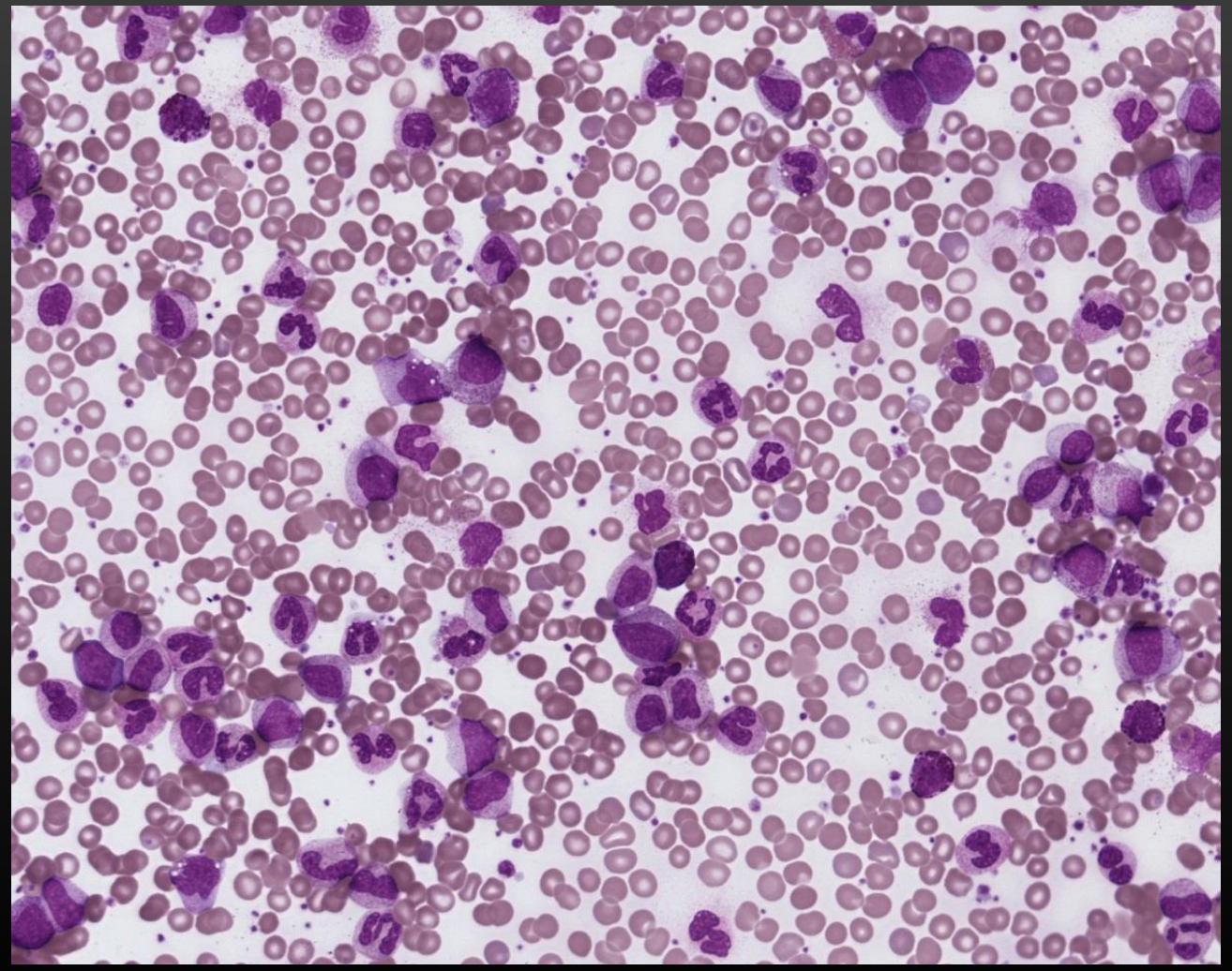


Chronic Myeloid Leukemia

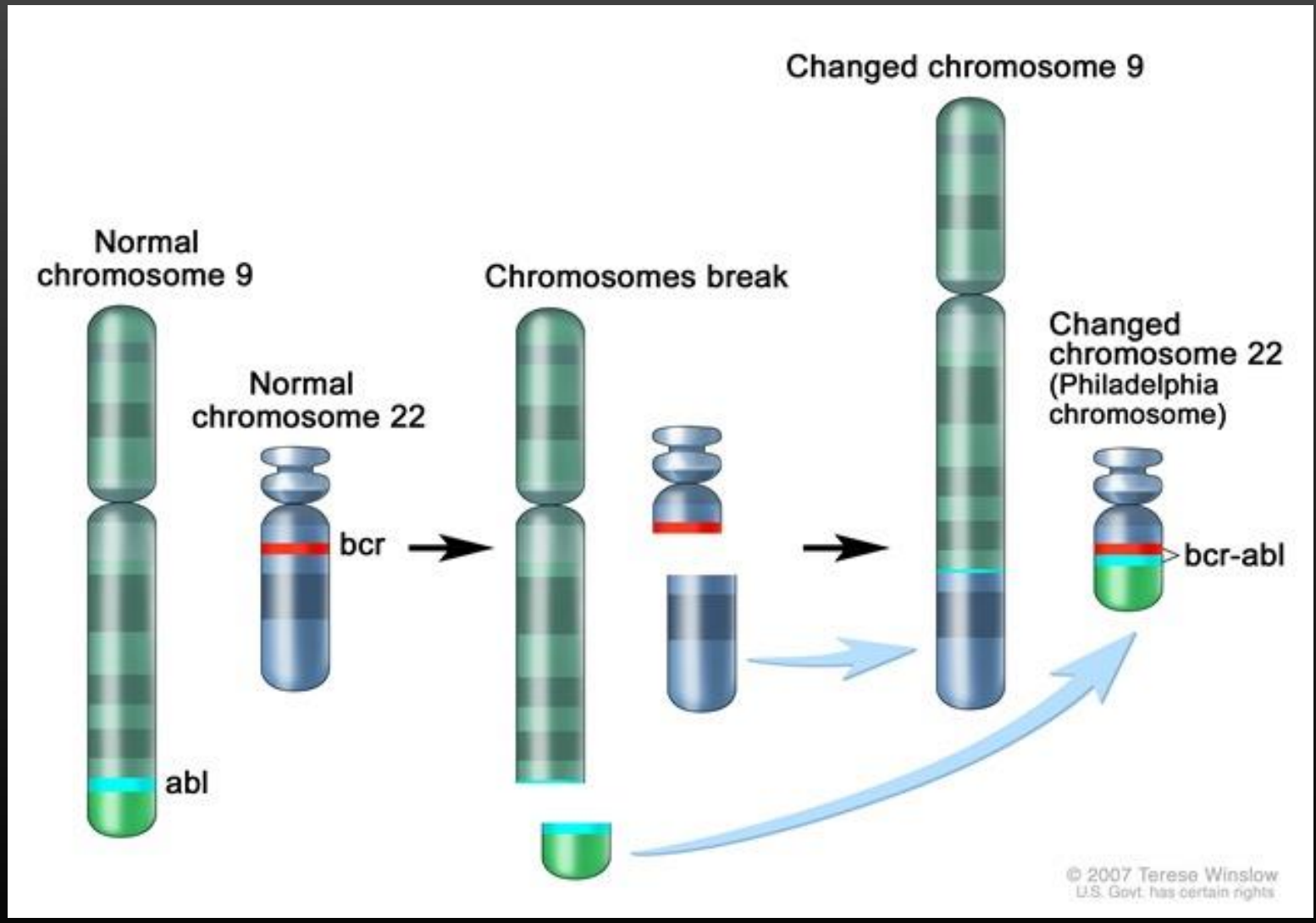
- 6000 new cases in 2013
- 15% of adult leukemias
- Median age 67
- Seen in all age groups
- Defined by t(9;22)
  Philadelphia chromosome

Morphology

- No leukemic arrest
- Accompanying eosinophilia and basophilia



Philadelphia Chromosome



CML Clinical Presentation

A 36 year old dentist has annual bloodwork done. 2 days later he is called by his PCP and told to go to the ER for abnormal CBC

CBC reveals a WBC of 248,000, Hgb 7.4, Plts 360

Differential is 60% neutrophils, 22% lymphocytes, 8% monocytes, 6% basophils, 4% eosinophils

The patient has had a 20# weight loss and some mild fatigue over the past 3 months

On exam he has marked splenomegaly but no other findings

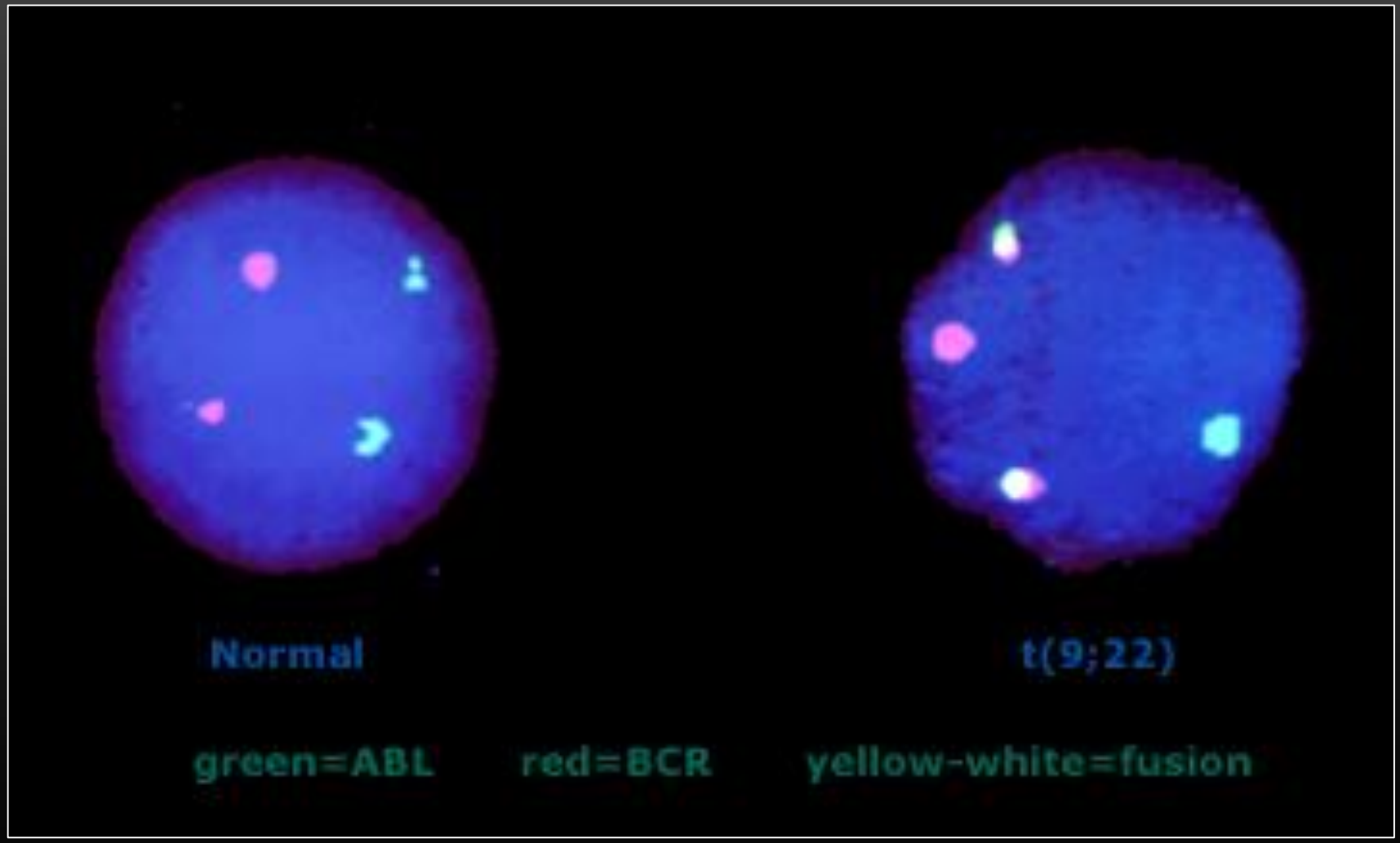
CML Workup

Very high clinical suspicion based on CBCd and peripheral blood smear alone

Bone Marrow Biopsy

- Baseline for further assessments
- Assess percentage of blasts
- Confirm presence of Philadelphia chromosome
- Test for additional cytogenetic abnormalities

CML Diagnosis by FISH for t(9;22)



CML Phases

Chronic Phase

- Most common presentation
- Usually found incidentally on CBC
- Will progress to Accelerated or Blast Phase in 3-5 years if untreated

Accelerated Phase

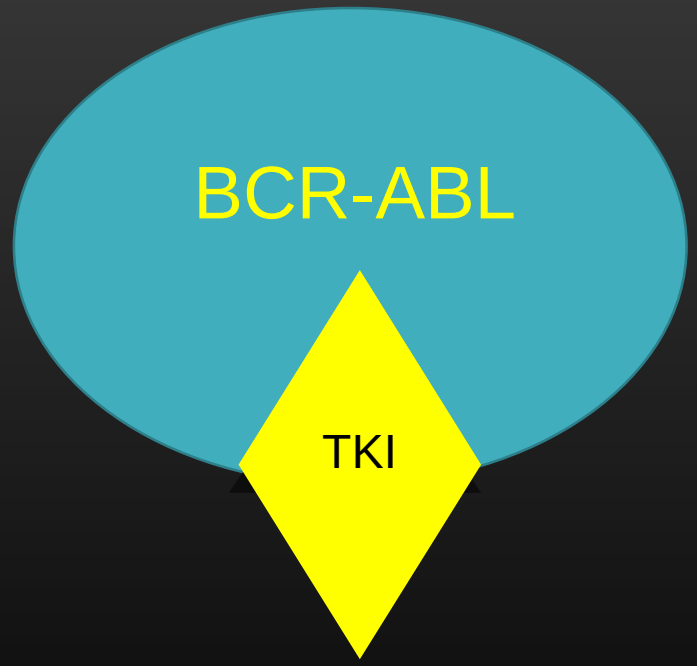
- 10-19% blasts

Blast Phase

- > 20% blasts
- Treated like an acute leukemia (may be myeloid or lymphoid blast crisis)

CML Treatment

Tyrosine Kinase Inhibitors (TKIs) have revolutionized CML treatment



BCR-ABL is the
leukemia ON switch

TKI inhibits BCL-ABL,
turning OFF the ON switch

CML Treatment

Chronic Phase Treatment

- TKI therapy provides durable remission
- *BCR-ABL* PCR < 10% at 3 months is the major predictor of survival

- Imatinib (Gleevec): 1st generation TKI
  - Side effects: fluid retention, nausea, vomiting, diarrhea
- Nilotinib (Tasigna): 2nd generation TKI
  - Side effects: QT prolongation, arrhythmias
- Dasatinib (Sprycel): 2nd generation TKI
  - Side effects: cough, pleural effusions

CML Frontline Treatment

Advantages of Nilotinib (2nd gen) vs Imatinib (1st gen)

ENESTnd Study

- Nilotinib at 300mg BID or 400mg BID vs Imatinib at 400mg BID
- Deeper molecular responses
- Fewer progressions to AP/BC on therapy (1% vs 6%)

CML duration of therapy

Until recently, TKIs were considered lifelong treatments

ENESTop Study

- Must have been on nilotinib for at least 2 years with a deep molecular response (log $^{-4.5}$)
- Take 1 additional year of nilotinib, maintaining MMR
- Discontinue treatment
- 50% remained in remission after discontinuation
- 50% progressed, but regained deep remission when restarting nilotinib

3rd generation TKIs

Reserved for failure of 1st and 2nd generation TKIs

Bosutinib (Bosulif)

- Side effect: diarrhea

Ponatinib (Inclusig)

- Most potent TKI
- Black box warning for arterial and venous thrombosis
- Appears to be safe at lower doses

CML Treatment

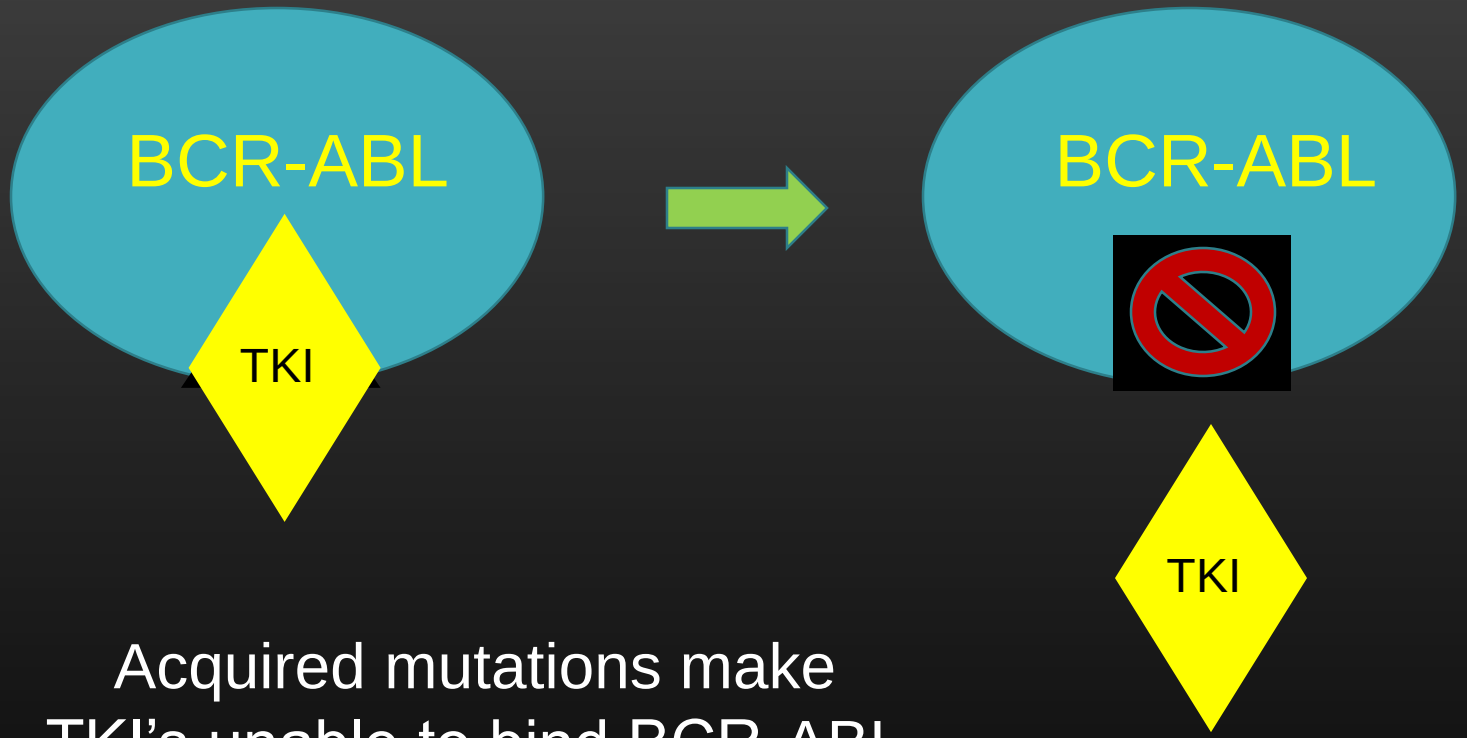
Accelerated Phase Treatment

- TKI therapy alone can return to Chronic Phase

Blast Phase Treatment

- Found on initial presentation or progressed from chronic phase
- Despite being a myeloid leukemia, 40% of Blast Phases are lymphoid blasts
- Induction chemotherapy + TKI
  - Myeloid blast phase: Treat like AML
  - Lymphoid blast phase: Treat like ALL
- Relapse guaranteed without allogeneic stem cell transplant

CML: Why TKI's stop working



Acquired mutations make
TKI's unable to bind BCR-ABL

CML: Stem Cell Transplant

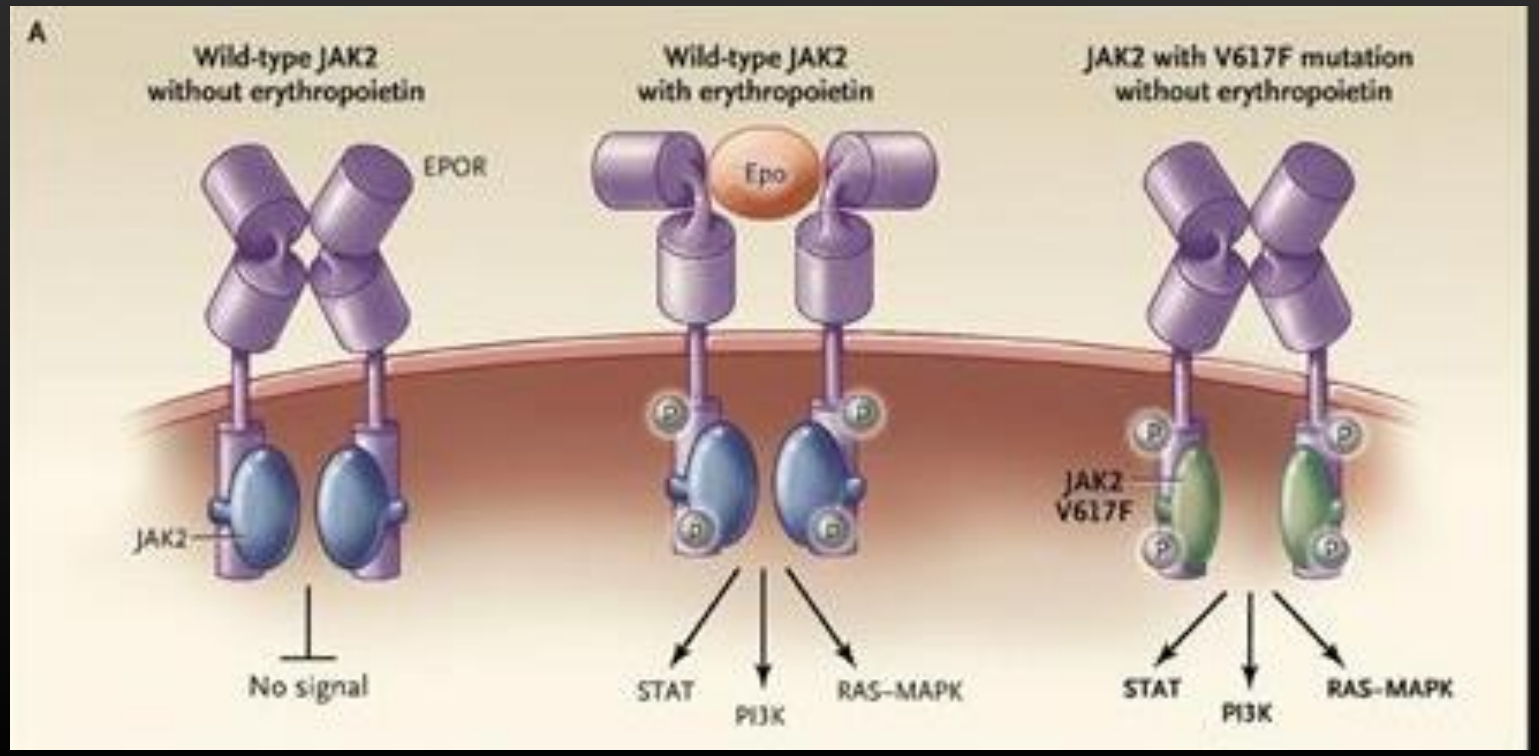
TKIs provide durable remissions and have made transplant for CML rare

Indications for Allogeneic Stem Cell Transplant in CML

- Presents in Blast Phase
- Failure to convert Accelerated Phase to Chronic Phase with TKI
- Fails TKI Therapy
  - Acquired mutations making TKIs ineffective
  - Intolerance

Polycythemia Vera

- MPN characterized by increased proliferation of erythroid, megakaryocyte, and granulocyte precursors
- Most clinical signs seen due to high RBC production
- Defined by the V617F Jak2 mutation (95% of PV)
- Average age 63
- Most patients live a normal lifespan



PV case presentation

A 68 year old man presents to his PCP for profound itching and flushing, worse after showering. A CBC reveals a Hgb of 19. EPO level is low at 5

Good questions to ask:

1. How many packs a day do you smoke?

2. Do you spend a lot of time at a mountain house outside Denver?

3. Are you on the US men's cycling team?

With the answer to all 3 being no, a Jak2 mutation test is ordered and is positive

PV Diagnostic Criteria

Defined with 3 major or first 2 major and minor

Major Criteria

- Hgb > 16.5 in men or 16 in women
- BM morphology showing hypercellularity with trilineage hyperproliferation
- Jak2 mutation positive

Minor criteria

- Low EPO level

PV Treatment

Goals of therapy: Reduce thrombotic risk and vasomotor symptoms

Aspirin

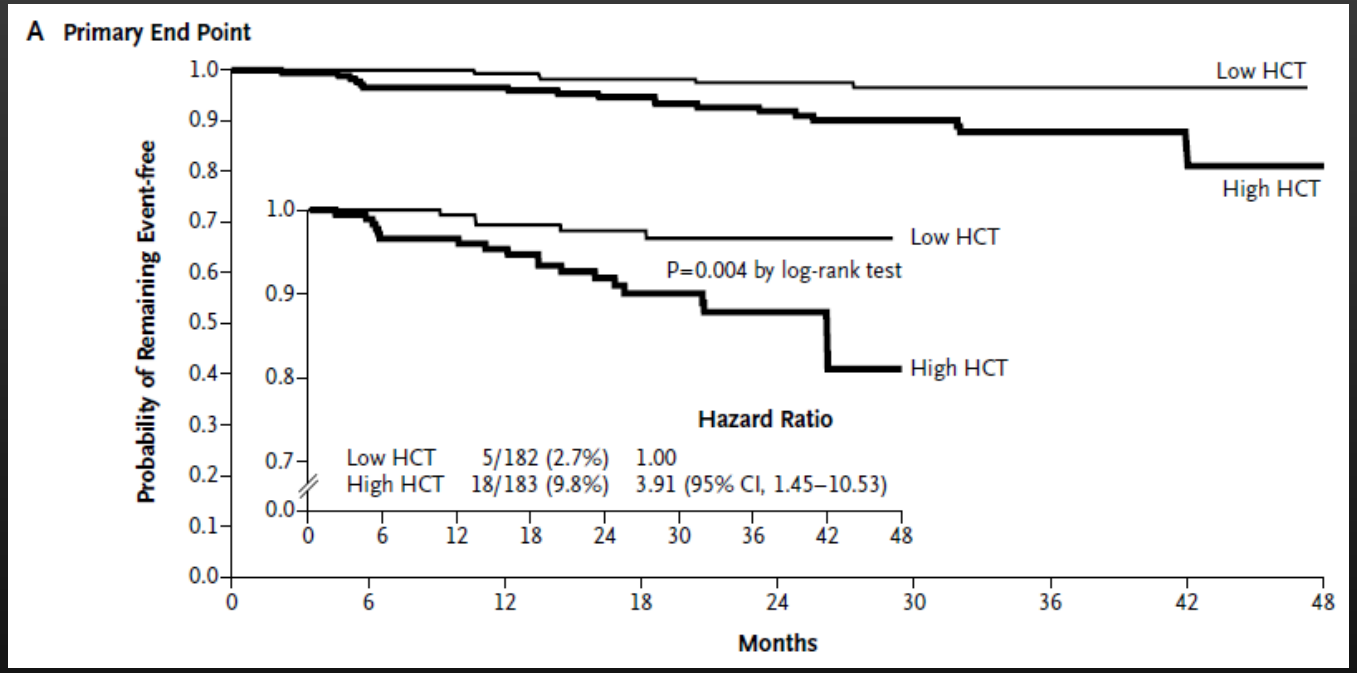
Reduces thrombotic risk and vasomotor symptoms

Phlebotomy

Goal is to maintain Hct < 45%

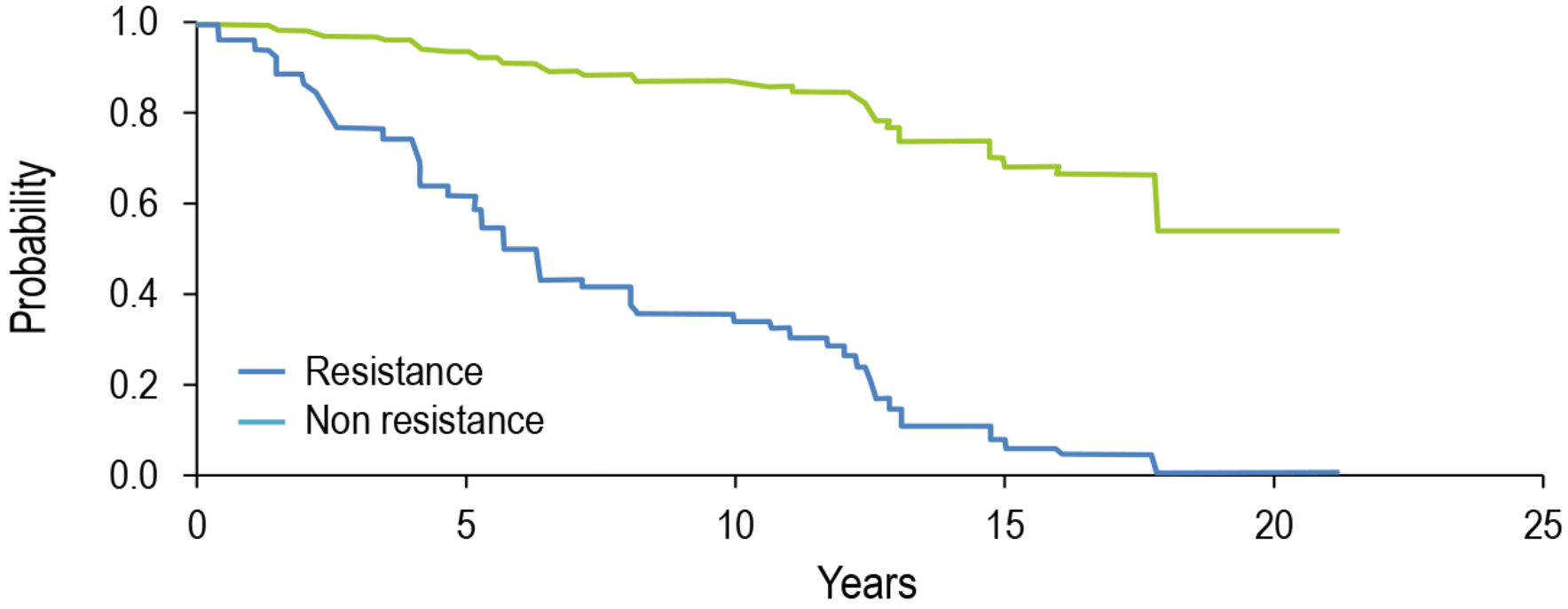
Hydroxyurea

Often used to supplement phlebotomy or when phlebotomy becoming more frequent



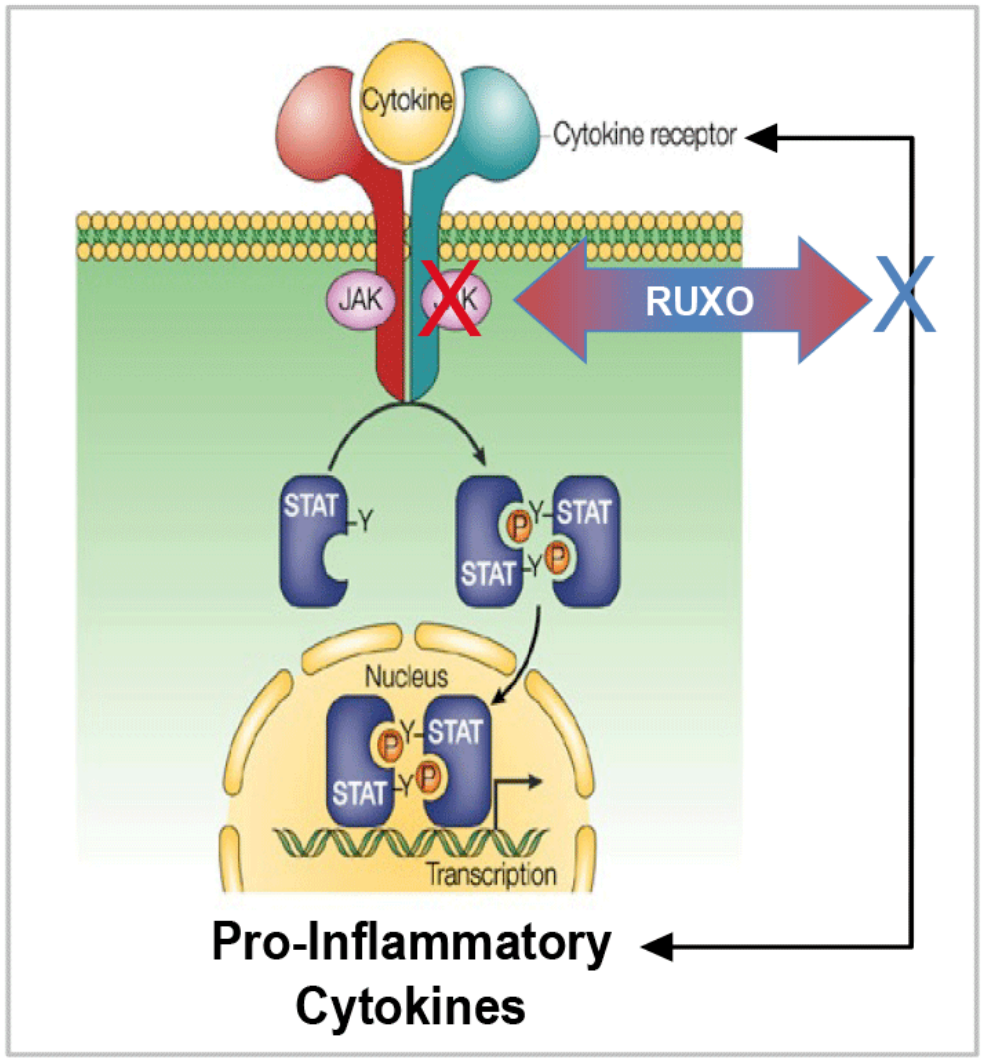
Targeting Hct 45% vs 50% reduces thrombotic risk

Hydroxyurea Resistance



- Resistance to hydroxyurea was associated with higher risk of:
  - Death (HR, 5.6; 95% CI, 2.7%-11.9%; P < .001)

Ruxolitinib (Jakafi)



Inhibitor of Jak2 approved for PV that is refractory to phlebotomy and hydrea

RESPONSE Trial: Jakafi vs BAT

- Spleen size reduction
- Improved Hct
- Improved QOL

Essential Thrombocythemia

- MPN characterized by increased proliferation of megakaryopoiesis without erythroid or neutrophil proliferation
- Clinical symptoms related to high platelet count
- 50-60% have Jak2 mutation, CALR and MPL mutations may be present
- Average age 55 yo, may present in teens
- Rarest of MPNs
- Longest life expectancy

ET Presentation

A 16 year old high school junior is having worsening grades due to an inability to concentrate. On further questioning she admits to blurry vision, headaches, and hot flashes, often triggered by stress

Her PCP checks a CBC and finds a normal WBC and Hgb but a Plt count of 580,000

Jak2 mutation is negative

ET Diagnostic Criteria

Defined with 4 major or first 3 major and minor

Major Criteria

- Plt > 450
- BM morphology showing megakaryocyte hyperproliferation without erythroid or granulocytic proliferation
- Not meeting criteria for CML, PV, MF, or MDS
- Jak2, CALR, or MPL mutation

Minor criteria

- No evidence of reactive thrombocytosis

ET treatment

Goal: Reduce vasomotor symptoms, decrease bleeding risk, decrease thrombotic risk

Aspirin

81mg daily or BID usually controls vasomotor symptoms

Bleeding Risk

Platelet counts > 1,000,000 are an *increased* risk of bleeding

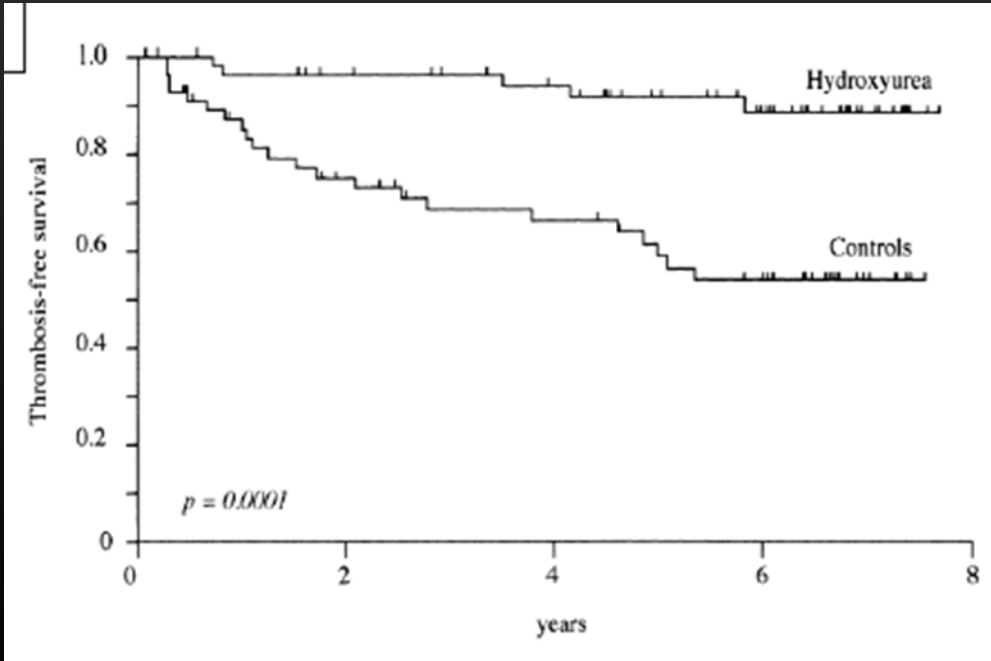
Platelet aggregation causes VWF sequestration leaving inadequate VWF for platelet adhesion

ET treatment

Hydroxyurea

Cytoreduction decreases clotting risk in high risk patients

Patients > 60 with history of thrombosis randomized to hydroxyurea vs placebo



	Age <60yo	Age >60yo
No prior Thrombosis	NO CYTOREDUCTION	Cytoreduce
Prior Thrombosis*	Cytoreduce	Cytoreduce

Myelofibrosis

MPN characterized by hyperproliferation of marrow with *secondary* collagen fibrosis and resulting cytopenias

Median age at diagnosis 65

Clinical presentation includes pruritis, bone pain, splenomegaly, anorexia, cytopenias

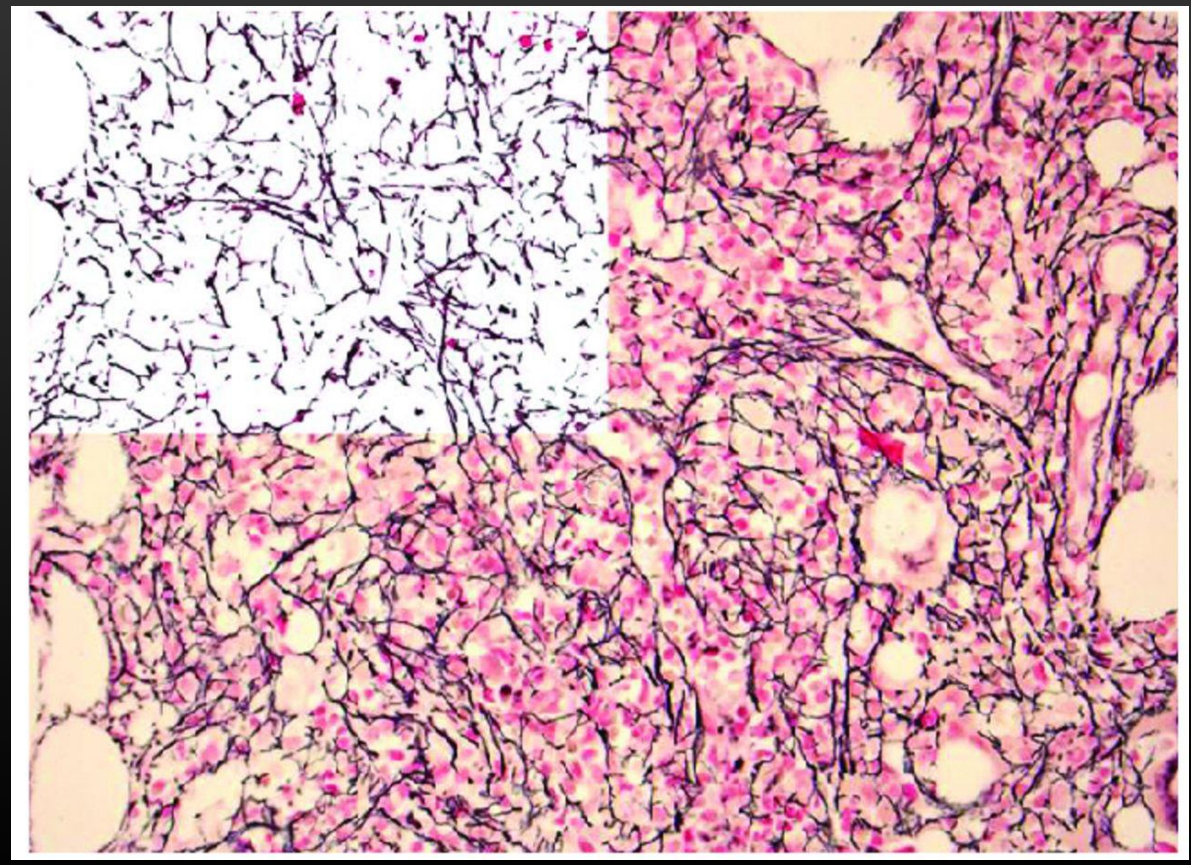
Presence of molecular mutations dictate disease course and prognosis

Variable life expectancy from median 2 to 11 years, based on risk of transformation to acute myeloid leukemia (AML)

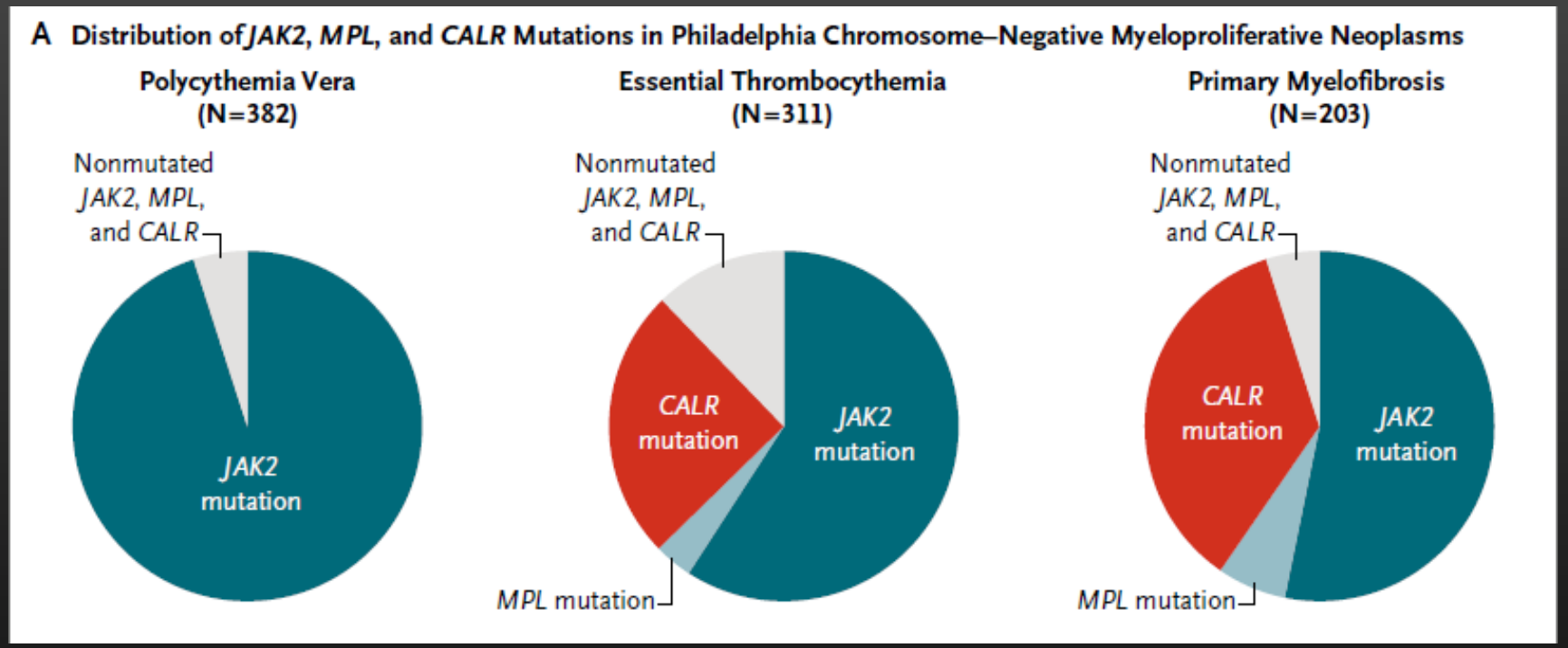
Myelofibrosis presentation

65 year old man presents to ER with 6 weeks of progressive weight loss and new onset abdominal pain. CT scan shows massive splenomegaly and inflamed diverticuli. CBC shows WBC 2.4, ANC 0.8, Hgb 7.8, Plts 110

While being treated inpatient for diverticulitis a hematology consult is obtained, and a BM biopsy reveals the following



Additional mutations in MPNs



Myelofibrosis Prognosis by Mutation

- CALR mutation: Median survival 17.5 years
- “Triple Negative”: Median survival 1.2 years (high risk AML transformation)

Myelofibrosis treatment

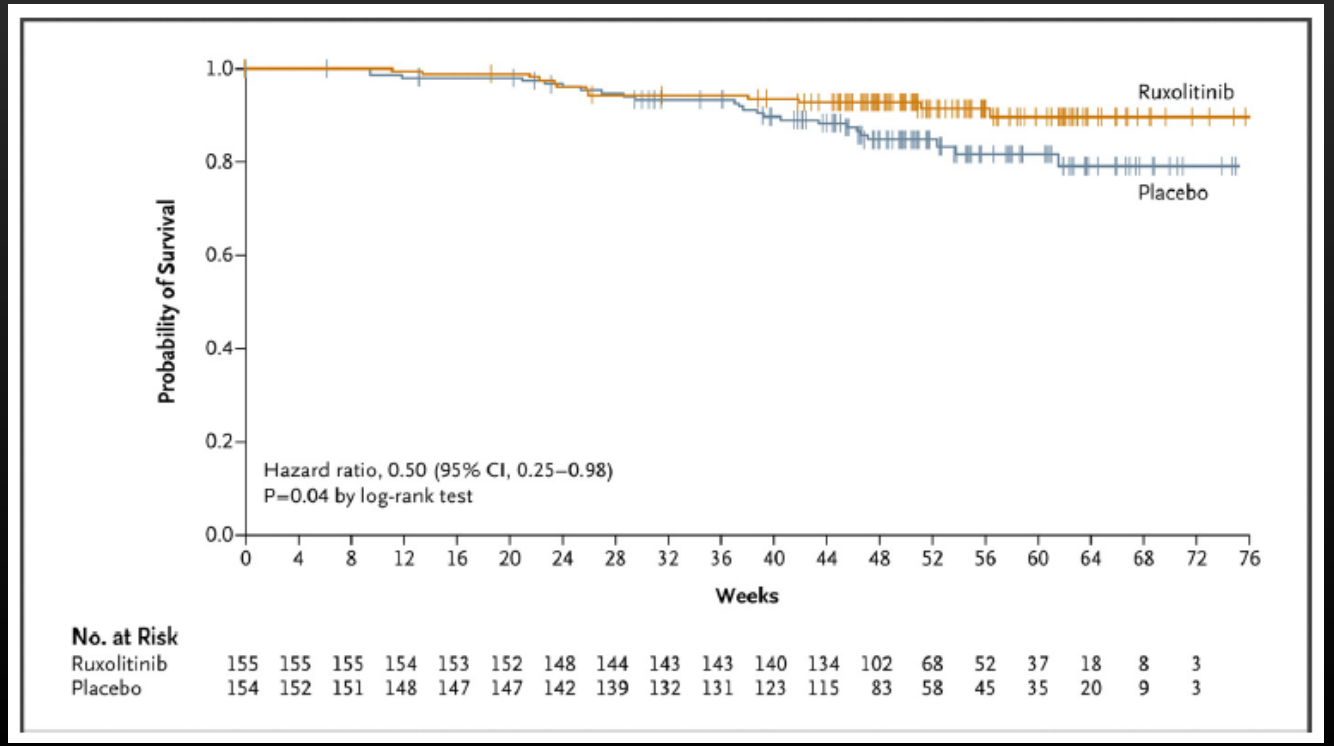
COMFORT I and II trials

Jakafi vs Placebo and Jakafi vs BAT

Endpoints of reduction in spleen size, QOL were met

COMFORT I long term follow up showed overall survival advantage for Jakafi

Implies modifying disease course, not merely improving symptoms



When good diseases behave badly

A 66 year old with JAK2-negative ET well controlled on 500mg hydroxyuea for the past 6 years goes in for a routine 3 month follow up with her hematologist

She has lost 10 pounds since last visit and has been using ibuprofen regularly for diffuse body aches

CBC reveals WBC 3.2, Hgb 8.2, Plts 110

What are you worried about and what's the next step?

When good diseases behave badly

A BM biopsy reveals Grade 3 fibrosis with 6% blasts noted, and mutational analysis is negative for Jak2, MPL, and CALR

Diagnosis?

Post-Polycythemia Vera Myelofibrosis

Risk stratification per molecular mutations?

Very high risk (triple negative mutations)

Treatment plan?

Start Jakafi, refer for allogeneic stem cell transplant

Post-PV and Post-ET Myelofibrosis

15% of PV and ET over a 10 year span will transform into Myelofibrosis

Requires immediate restaging for risk of AML transformation and if appropriate referral for allogeneic stem cell transplant

Even if symptoms are minimal, Jakafi has been shown to improve post-SCT outcomes, so patients are usually started on it as a bridge while a donor is identified

Summary

CML

- MPN defined by t(9;22) Philadelphia chromosome
- Treatment has been revolutionized with TKI therapy
- Future directions include optimizing ways to shorten duration of therapy

PV and ET

- MPNs with long life expectancy
- Treatment emphasis on controlling vasomotor symptoms and thrombotic risk
- Aspirin, Hydroxyurea, Phlebotomy (PV) ,and Jakafi (PV) mainstays of therapy
- Always be wary of PV/ET with new cytopenias as could be transformation to MF

MF

- MPN with short life expectancy due to high risk of AML transformation
- Risk stratification based on molecular mutations
- Jakafi is the primary treatment with allogeneic stem cell transplant as only cure

Thank You !

Jonathan.abbas@bannerhealth.com

(706) 495-6178