



# Leukemia for the Primary Care Physician (Non-CLL)

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WEXNER MEDICAL CENTER

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## OBJECTIVES:

- Presenting symptoms
- Context and basic biology
- Diagnostics
- Prognostics
- Therapeutics



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## CASE 1

- Your longtime patient Mr. Smith, a 57-year-old man who works on his farm, presents with progressive fatigue and dyspnea on exertion over the last two weeks.
- He has shortness of breath with minimal activity and chest pain with climbing stairs, one month ago he was carrying 50lbs without any difficulty. He notes a headache that has been constant for the past day.
- He is able to sleep while laying flat on one pillow



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## CASE 1, CONTINUED

PMH:

HTN, HLD, Rheumatoid Arthritis

SH:

20pk/year smoking history, 1-2 drinks a few times a week, he lives on his farm with his wife and they have a large dog and 2 cats, 3 children whom are grown

FH:

CAD, prostate CA

Meds: lisinopril, simvastatin, methotrexate

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## CASE 1, CONTINUED

- Physical examination
  - Pale but not ill-appearing, with rapid heart rate; not short of breath at rest
  - Hypertrophied gums with areas of bleeding
  - No pitting edema, lungs are clear
  - No lymphadenopathy
  - +Ecchymoses on arms and legs



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## CASE 1, CONTINUED

- Complete blood count
  - WBC count: 55,000 cells/ $\mu$ L
  - Hemoglobin: 6 g/dL
  - Platelet count: 15,000 cells/ $\mu$ L
- CMP
  - Creatinine 1.5 (baseline 1.1), otherwise WNL
  - AST/ALT minimally elevated



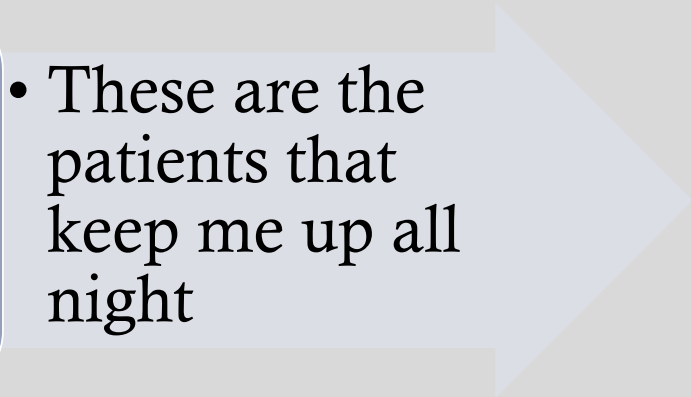
**WHAT DOES THE HEMATOLOGIST WANT TO KNOW?**

- What are his coags? PT/PTT/INR AND Fibrinogen
- Uric Acid
- Has he had any fevers?
- Any headaches? Vision changes? Difficulty breathing or hypoxemia? Any chest pain?

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**WHAT ARE THE IMMEDIATE NEXT STEPS?**

Report to the closest ER  
(acute leukemia treating center if possible)

- These are the patients that keep me up all night
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## ACUTE LEUKEMIA PRESENTING SYMPTOMS

- Cytopenias
- Hyperleukocytosis → leukostasis
- Extramedullary disease
- Tumor lysis syndrome
- Disseminated Intravascular Coagulation



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## CASE 2

- Your longtime patient Mr. Habib, a 57-year-old man who works on his farm, presents with progressive fatigue and early satiety over the past several months.
- He denies any shortness of breath with minimal activity but notes some discomfort with deep inspiration and frequent sharp pains on his left side.
- He has been sleeping well and doesn't understand why he's feeling so fatigued



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## CASE 2, CONTINUED

- PMH: HTN, HLD
- SH: 20pk/year smoking history, 1-2 drinks a few times a week, he lives on his farm with his wife and they have a small dog and 2 hamsters, 2 children whom are grown
- FH:CAD, prostate CA
- Meds: lisinopril, simvastatin



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## CASE 2, CONTINUED

- Physical examination
  - Appears well, non-toxic, normal vitals
  - Cardiac exam unremarkable
  - No pitting edema, lungs are clear
  - No lymphadenopathy, but spleen is palpable 4 cm below left costal margin
  - No rashes or bruises



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## CASE 2, CONTINUED

- Complete blood count
  - WBC count: 55,000 cells/ $\mu$ L
  - Hemoglobin: 10 g/dL
  - Platelet count: 325,000 cells/ $\mu$ L
- CMP
  - Creatinine 1.2 (baseline 1.1), otherwise WNL
  - AST/ALT normal



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## WHAT DOES THE HEMATOLOGIST WANT TO KNOW?

- What does his PB smear look like?
  - Uric acid
  - When was his last CBC and what did it look like?
-

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## WHAT ARE THE IMMEDIATE NEXT STEPS?



Look at PB smear



Send BCR/ABL

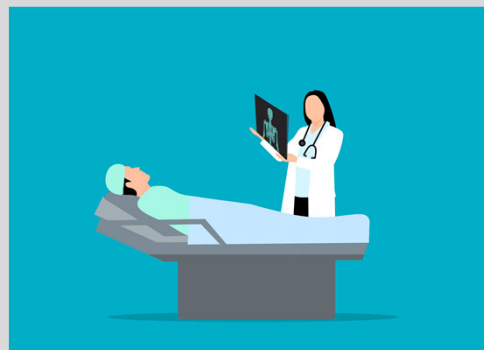


Can follow up in clinic

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## CML PRESENTING SYMPTOMS

- Mild Anemia, thrombocytosis
- Hyperleukocytosis
- Splenomegaly, +/- infarcts
- Hyperuricemia





# WHAT IS LEUKEMIA?

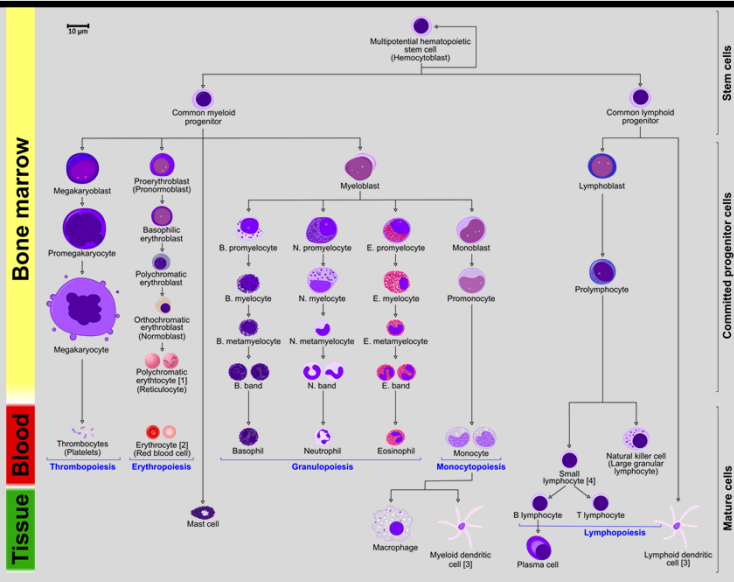


Image courtesy of wikipedia

# WHAT IS LEUKEMIA?

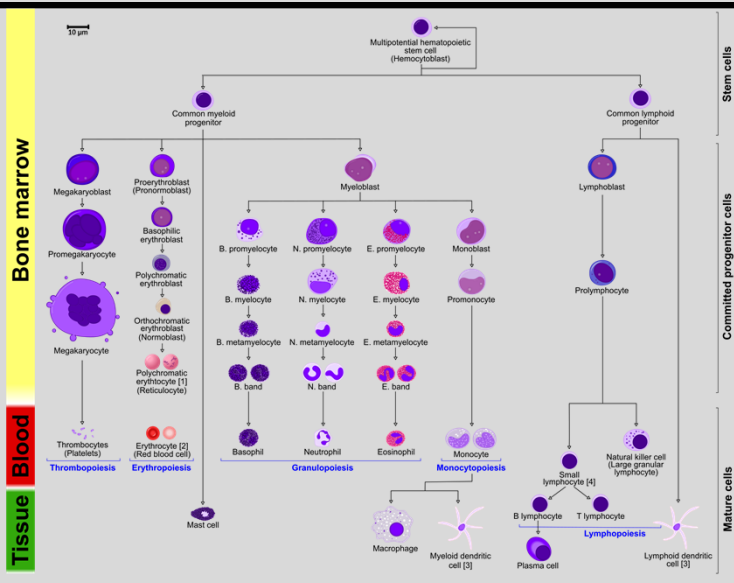
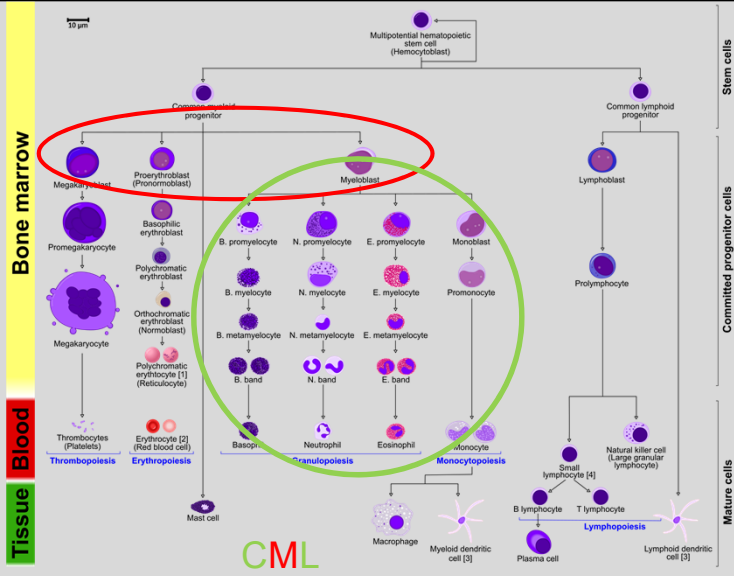


Image courtesy of wikipedia  
 Image courtesy of wikipedia

# WHAT IS LEUKEMIA?

AML

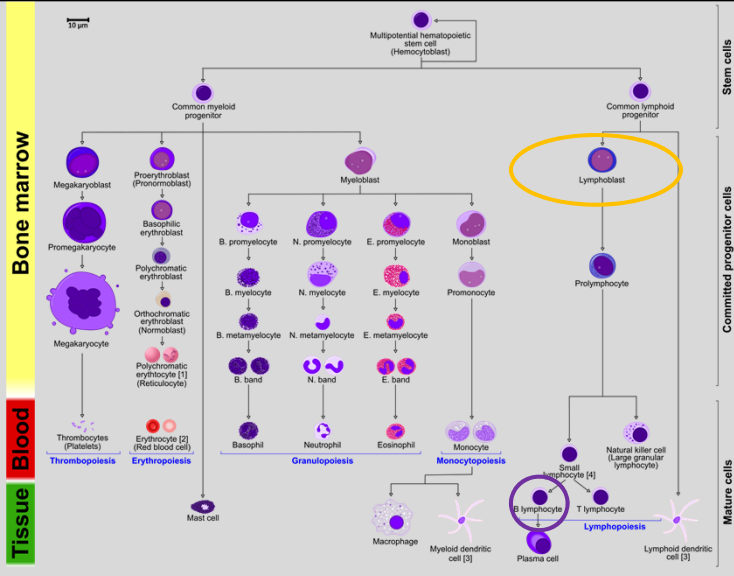


CML

Image courtesy of wikipedia  
Image courtesy of wikipedia

# WHAT IS LEUKEMIA?

ALL



CLL

Image courtesy of wikipedia  
Image courtesy of wikipedia

## WHAT IS LEUKEMIA?

### AMBIGUOUS LINEAGE ACUTE LEUKEMIA

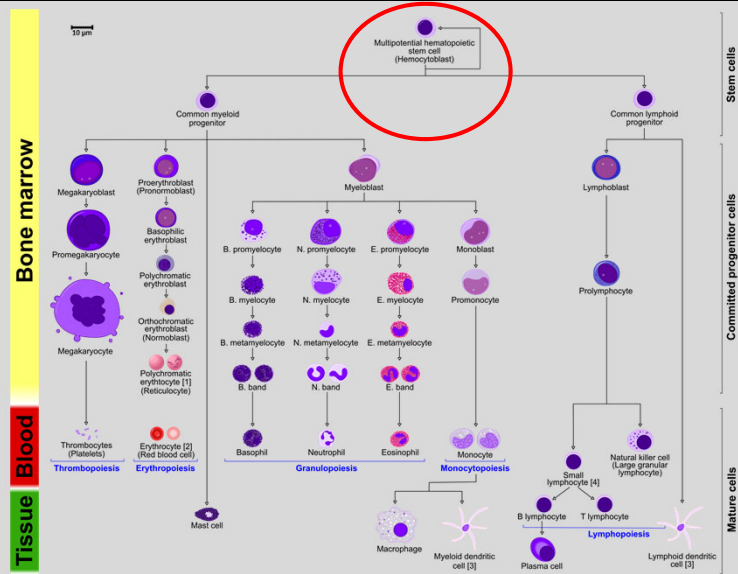
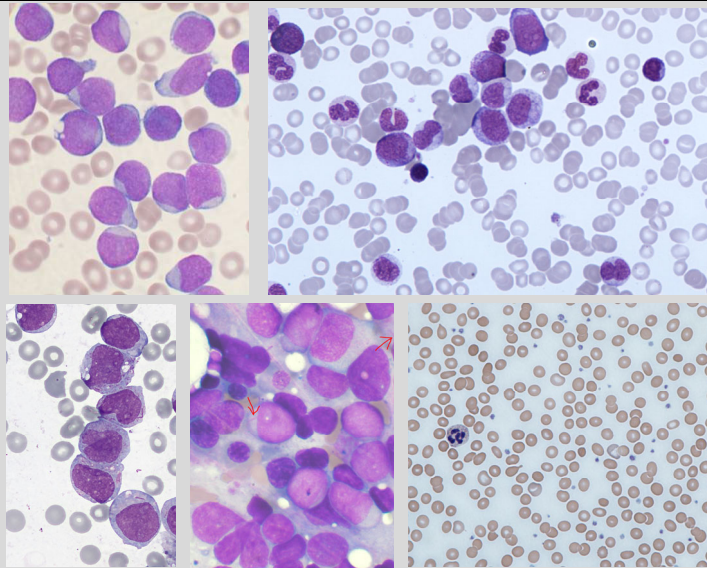


Image courtesy of wikipedia

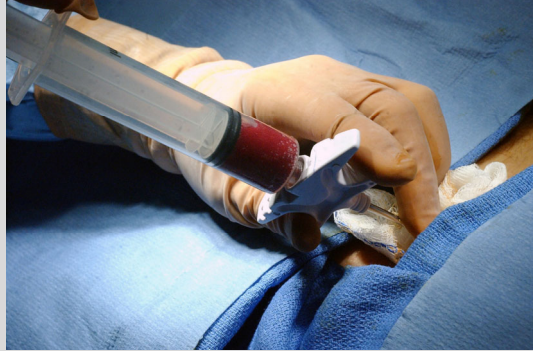
## LEUKEMIA UNDER THE MICROSCOPE



• Images courtesy of Wikipedia

## TESTING: BONE MARROW BIOPSIES

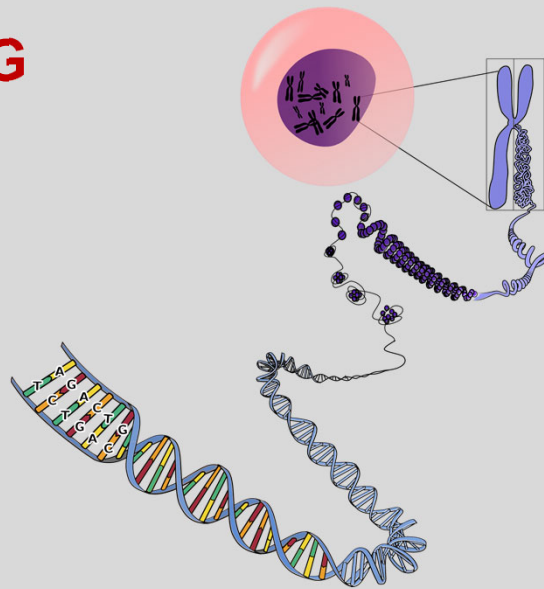
- Morphology
- Flow cytometry  
(immunophenotype)
- Cytogenetics
- Molecular genetics



By Photographer's Mate 2nd Class Chad McNeeley - Navy News Service, 021204-N-0696M-180,  
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## GENETIC TESTING

- Karyotyping
- Fluorescence in situ hybridization (FISH)
- Molecular genetics  
(next generation sequencing, NGS)



## OTHER USEFUL TESTS/PROCEDURES

Testing	AML	ALL	CML
Lumbar puncture	If high suspicion	Multiple	No
PET or CT scans	Myeloid sarcoma	Presenting with LAD or masses	No
Tuneled line	Yes	Yes	No

## LEUKEMIA ACUTE VS. CHRONIC

In terms of:

Prevalance

Curability

Acuity/Severity

Treatment



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## EPIDEMIOLOGY

### AML

- ~20,000 new cases yearly in US
  - > 11,000 deaths/year
- Median age: 68 years
- 5yr survival 30.5%

### ALL

- ~ 6,600 new cases yearly in US
  - > 1,500 deaths/year
- Median age: 17 years
- 5 yr survival 70.8%

### CML

- ~8,800 new cases yearly in US
  - > 1,200 deaths/year
- Median age: 65 years
- 5yr survival 70.4%

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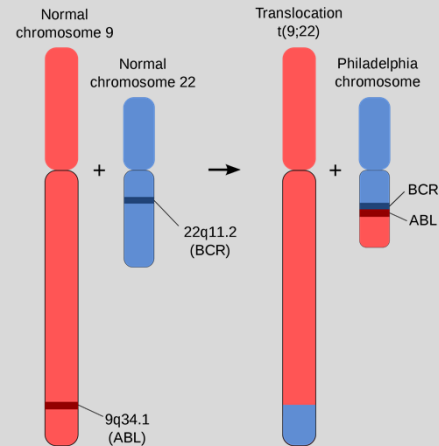
SEER data. Cancer.gov

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# CHRONIC MYELOGENOUS LEUKEMIA

## DIAGNOSING CML

- Clinical History
- Physical Exam
- Labs
- BCR-ABL
- BM Biopsy



## SYMPTOMS

Up to 50% of patients asymptomatic

46-76% p/w splenomegaly

Fatigue, night sweats

Symptoms of anemia, bleeding d/t platelet dysfunction

<5% p/w hyperviscosity symptoms (usually WBC >250,000)

## CBC AND PERIPHERAL SMEAR

Absolute leukocytosis (median 100,000)

Left shift

Myelocytes outnumber mature metamyelocytes on PB smear

Blasts usually <2%

Absolute basophilia (100%)

Absolute eosinophilia (90%)

Platelet count usually normal or elevated

Thrombocytopenia= alternative dx OR advanced stage CML

## CML PHASES

### Chronic

- most patients present in early phase

### Accelerated

- more aggressive disease, less likely to respond as well to therapy
- most commonly seen after treatment failure

### Blast

- AML or ALL



## CML RISK SCORES

Sokal

Hasford

European  
Treatment and  
Outcome Study  
(EUTOS)

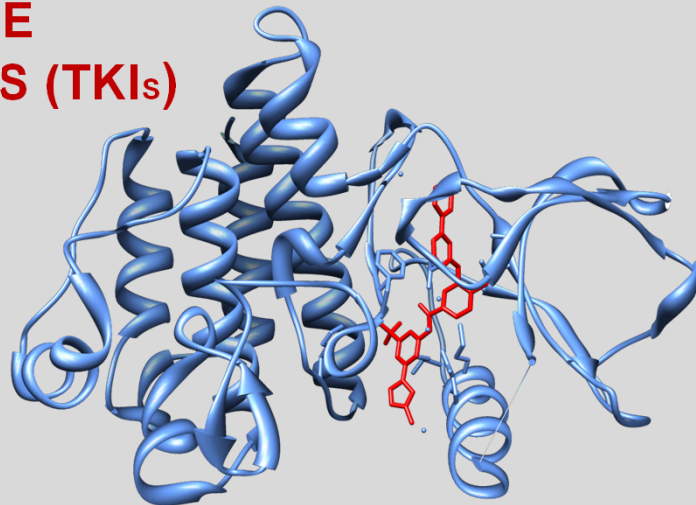
- Spleen size
- Cell counts
- +/- Age



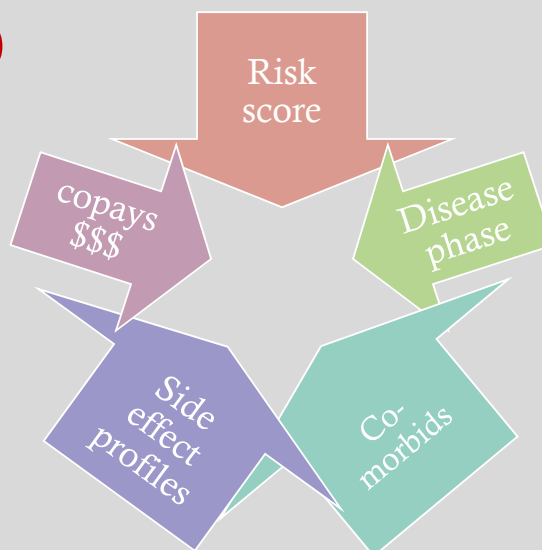
- Low
- intermediate
- high

## BCR-ABL TYROSINE KINASE INHIBITORS (TKIs)

- **Imatinib (1998)**
- Dasatinib
- Nilotinib
- Bosutinib
- Ponatinib
- Asciminib



## WHICH TKI TO CHOOSE?



## MONITORING WHILE ON TKI THERAPY

CBCs --> complete hematologic response

Quantitative PCR for BCR-ABL transcript q3 months

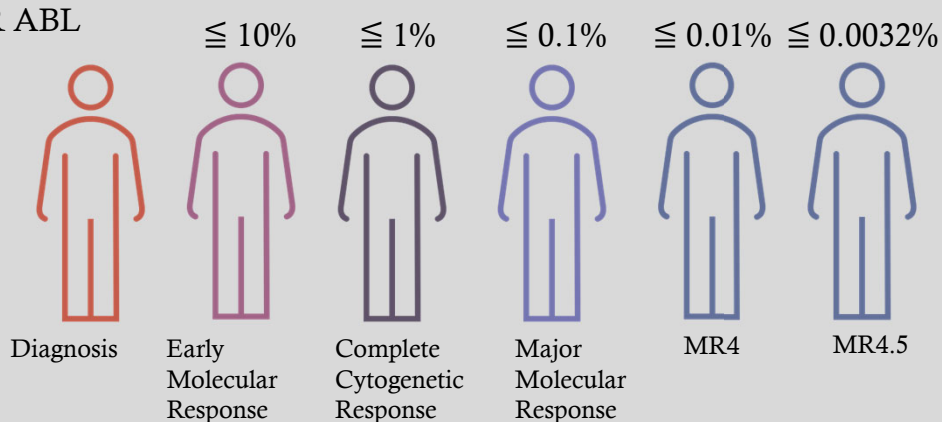
Exams/labs focused on side effect profiles

- Pleural effusions, pericardial effusions
- Pancreatitis
- CAD

“intolerable side effects”

## MOLECULAR RESPONSE DEFINITIONS

BCR ABL



## INTOLERANCE TO TKI

Side effects

Can be numerous

Often resolve with time

Often managed with good supportive care

Can require dose reductions or dose interruptions especially in the beginning

Severity of some reactions can require permanent drug discontinuation

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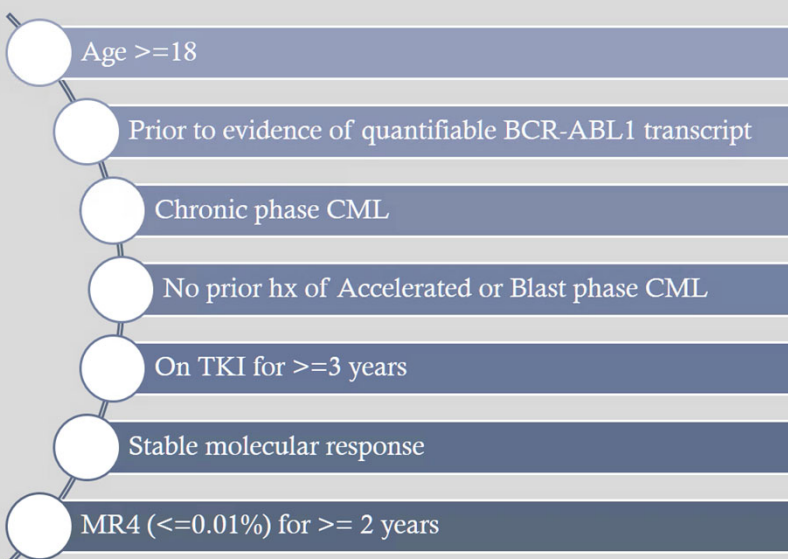
## LOSS OF RESPONSE TO TKI

- Adherence
  - Adherence
  - Adherence
  - Taking correctly (PPIs, food)
  - Check TKI resistance panel
    - BCR-ABL kinase domain mutational analysis
- 




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## TREATMENT FREE REMISSION



## MONITORING AFTER DISCONTINUATION

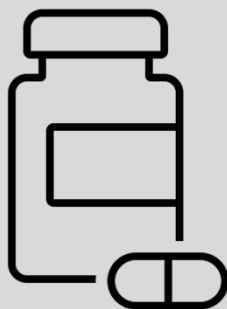
- Enhanced Monitoring off drug

- First 6 months monthly
- Second 6 months decrease to Q2 months
- Forevermore Q3 months

Can continue to hold TKI as long as maintain

MMR ( $\leq 0.1\%$ )

## SUCCESS?



Majority of relapses will occur within 12 months of discontinuation

Roughly ½ patients will maintain a durable remission off of therapy

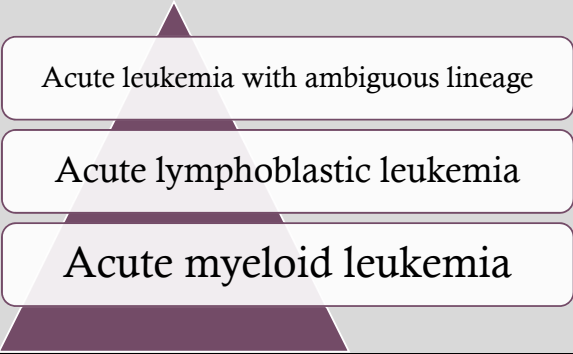
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## CML SUMMARY

- CBC and peripheral smear are very helpful in distinguishing
    - \*Peripheral basophilia
    - PB looks like BM
  - Diagnosis from PB t(9;22) and BM Biopsy establishes stage
  - Multiple TKI treatment options- depends on disease factors/risk score, patient factors
  - Can now consider discontinuing TKI with very close monitoring and follow up
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## ACUTE LEUKEMIAS



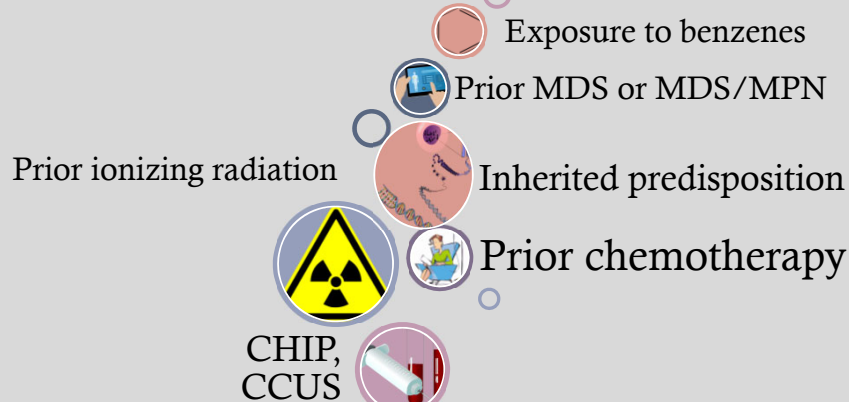
Acute leukemia with ambiguous lineage

Acute lymphoblastic leukemia

Acute myeloid leukemia

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## RISK FACTORS



MDS = myelodysplastic syndrome  
 MPN = myeloproliferative neoplasms  
 CHIP = Clonal Hematopoiesis of Indeterminate Potential  
 CCUS = Clonal Cytopenia of Undetermined Significance

## DIAGNOSING ACUTE LEUKEMIA

Peripheral smear to evaluate CBC differential and morphology

Laboratory tests (LDH, uric acid, comprehensive metabolic panel, coags including fibrinogen), Immunophenotyping

Bone marrow aspirate and biopsy

+/- Lumbar Puncture and Testicular exam/US

Genetic Testing

## SYMPTOMS



- Incredible range
- Fatigue
- Fevers
- Infections
- DIC
- TLS
- hyperleukocytosis
- Bleeding/bruising
- Rash – petechiae, leukemia cutis
- gum hypertrophy
- myeloid sarcoma

## CBC AND PERIPHERAL SMEAR

- Profound cytopenias
- Neutropenia
- Leukocytosis (predominantly blasts)
- possibly dysplastic neutrophils
- Anemia without schistocytes or other abnormal indices
- thrombocytopenia, no clumping



## TREATMENT NOMENCLATURE



### Induction

Ⓢ Intensive chemotherapy for patients with active leukemia (hoping to "induce" remission)



### Consolidation

• Treatment given to "consolidate" or deepen remission (hopefully into a cure)  
 Ⓢ *Chemo only*  
 Ⓢ *Allogeneic stem cell transplant*



### Maintenance

• Therapy given to prevent relapse once in remission

## RESPONSE NOMENCLATURE

- Complete Response (CR)
- Complete Response with incomplete count recovery (CRi)
- Morphologic leukemia free state (MLFS)
- Remission  $\neq$  Cure
- Minimal (Measurable) Residual Disease (MRD)

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# ACUTE LYMPHOBLASTIC LEUKEMIA

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## PROGNOSTICS

T vs. B

Ph+ vs. Ph- vs. "Ph-like"

Cytogenetics

WBC at presentation

Age

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## PROGNOSTICS

T vs. B

Ph+ vs. Ph- vs. "Ph-like"

Cytogenetics

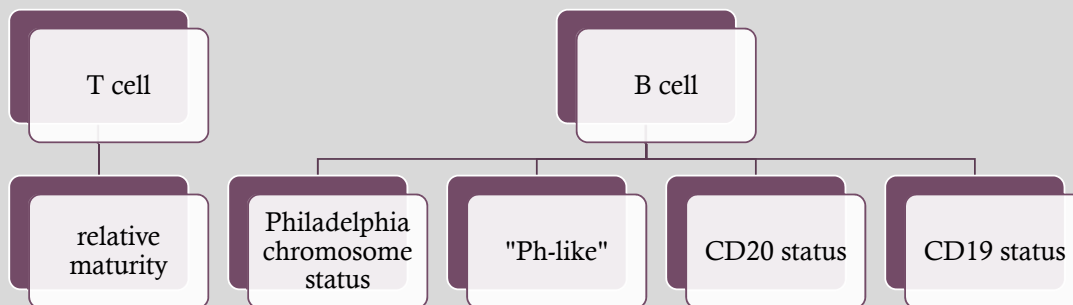
WBC at presentation

Age

# MIRD

## ALL THERAPEUTICS

Origin



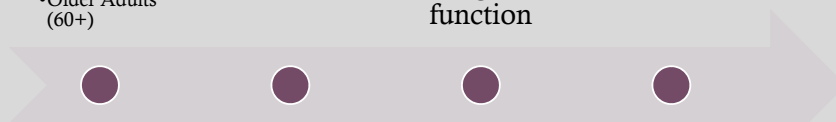
# ALL THERAPEUTICS

## Patient

Age

- AYA (15-39)
- Adult (40-60)
- Older Adults (60+)

Organ  
function



Fitness

Clinical  
Trial  
Eligible?

Multi-agent  
chemotherapy  
regimens

TKIs

Antibody-drug  
Conjugates

Bi-specific  
Antibodies  
CART

# ACUTE MYELOID LEUKEMIA

## PROGNOSTICS: EUROPEAN LEUKEMIANET 2022

### Favorable

- Cure possible with chemo alone

### Intermediate

- Broadest range of outcomes
- Allo SCT generally recommended

### Adverse

- Uniformly poor outcomes
- Allo SCT if possible

## PROGNOSTICS: EUROPEAN LEUKEMIANET 2022

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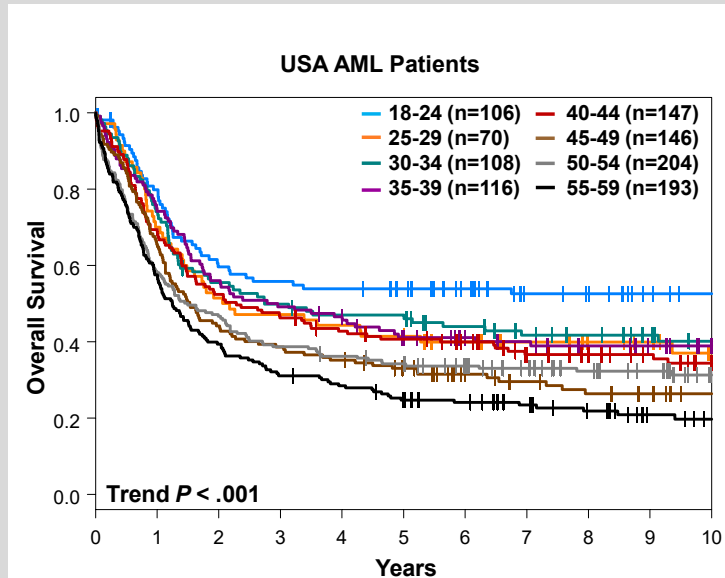
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**MIRD**

# PROGNOSTICS

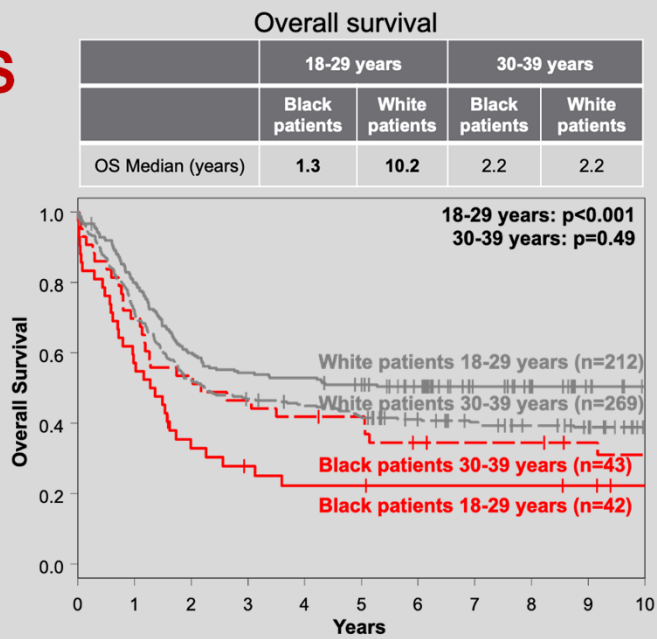
- Age
- Race
- Socioeconomics and other demographic data



Data presented by Larkin et al at ASH 2021

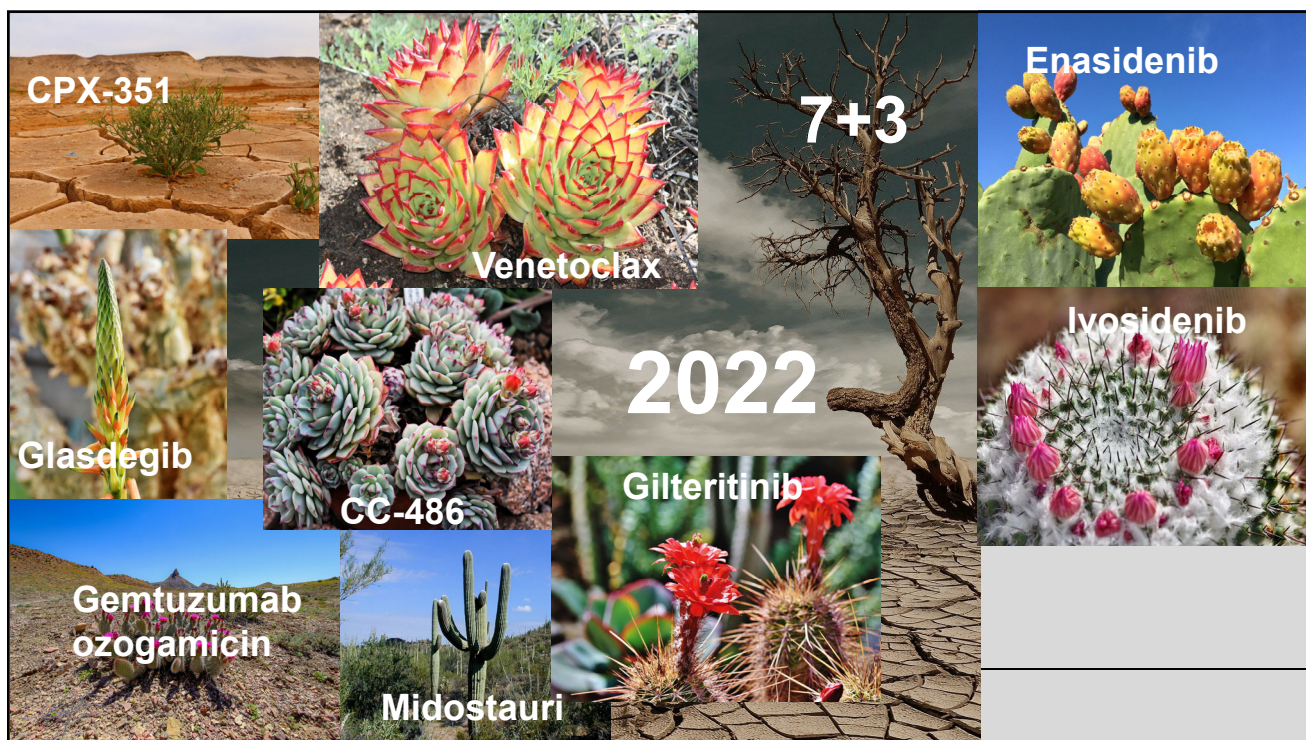
# PROGNOSTICS

- Age
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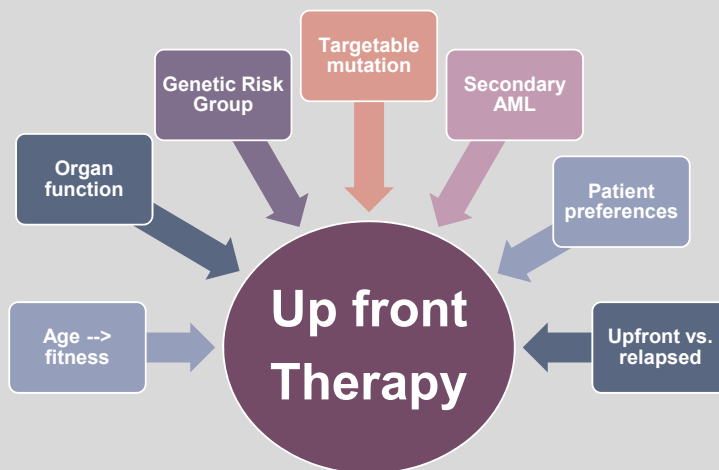


Data presented by Larkin et al at ASH 2021

# AML THERAPEUTICS



## AML THERAPEUTICS



## ADVERSE EFFECTS OF THERAPY

Immediate and prolonged hospitalization\*

Direct toxicity from chemotherapy

Infections due to immunosuppression

Functional decline

Transfusion needs

Psychosocial stressors



## AL SUMMARY

- Onset is typically rapid
- Key historical items can help raise your suspicion in some cases
- CBC and peripheral smear are very helpful in identifying this urgent/emergent disease
- Diagnosis requires multiple specialized tests
- Prognosis depend on multiple factors
- Treatment options are personalized

## HIGH YIELD POINTS

### How do you recognize leukemia?

- Patient presentations vary and sometimes require high degree of clinical suspicion
- CBC is very often enough obvious to direct further work-up

### CML on TKIs

- Characteristic and non-characteristic side effects
- Adherence is key
- There is hope for treatment free remissions albeit in a minority of patients

### Acute Leukemia is a rapidly changing field

- Diagnostics have become more complicated but improved
- Many more tolerable treatment options

