Chronic Leukemia
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Abdallah Abbadi.MD, FRCP, FRCPath

Feras Fararjeh, MD

CLL:- monoclonal profilation of malignant b cells charictrized by this progressive acumulation of these malignant, non functional B lymphocytes

median age: elderly

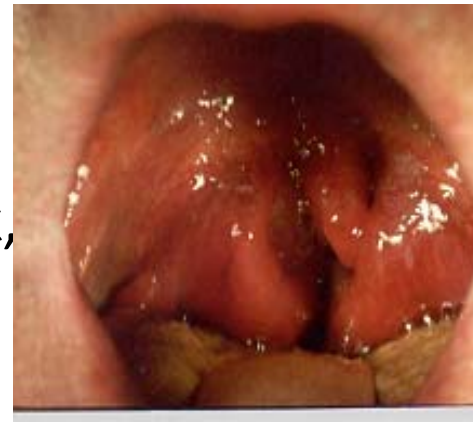
CLL

- main difference chronic Leukemia occure in longer periods of time
- degree of Cytopenia is Usually less

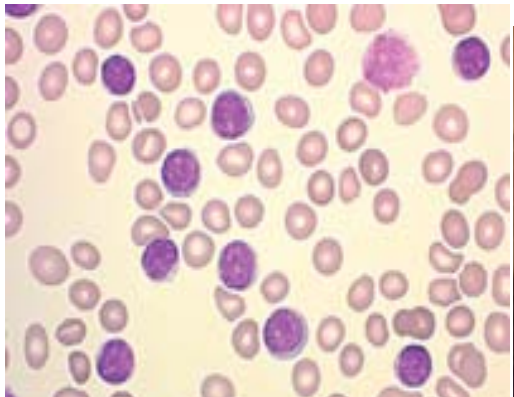
- the person will get infected easly cause this B cells are not contribute to immune normal system

Case 10

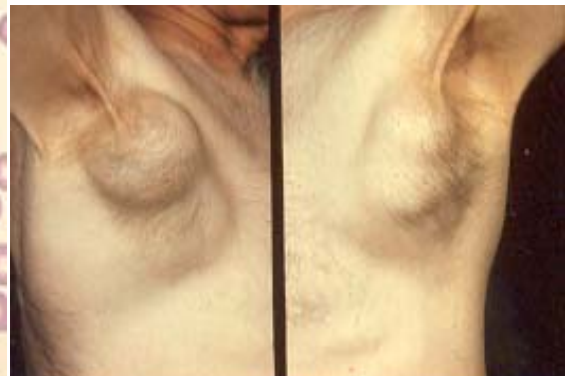
69 yr old man complains of fever and cervical and axillary swellir for several months with recurrent fever and productive purulen cough. P/E Splenomegaly, lymphadenopathy and pallor. Hb 10, MCV 100, Retcs 7%, Ldh 680U/ml, Blood film shown.WBC 123k, Plt 85k, DAT+3, Bilirubin 2, D 0.5

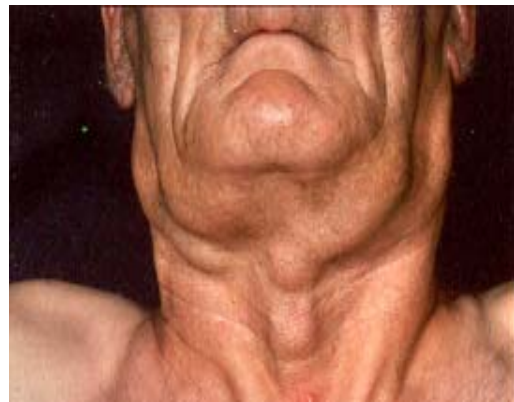


smudge cells



axillary lymph nodes enlargment





Case Ten: Diagnosis and Management

1- Decide the type of lymphocyte

2- Determine the stage

Stage IV Rai, C Binet

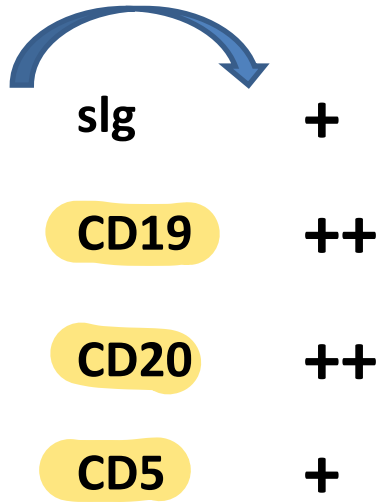
3- Cytogenetics

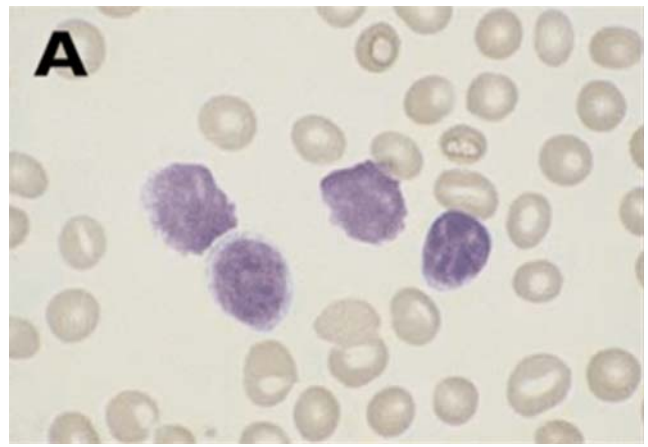
+ 12

3- Decide therapy

5- Decide Prognosis

6- Determine follow-up





CLL Clinical Presentation

- Lymphocytosis
  - Morphologically mature
  - Immunologically immature
  - Accumulation in PB, BM and lymphatic tissues
- Enlarged Lymph nodes
- Splenomegaly
- Hypogammaglobulinaemia

Estimating prognosis

- Clinical staging systems - Rai/Binet
  - (1) – Early - >10 years median survival
  - (2) – Intermediate - 5-7 years median survival
  - (3) – Advanced - 1-3 years median survival
- Heterogeneity of disease

Staging: Rai and Binet staging systems for CLL

Clinical staging systems for CLL

Value	Stage: Rai (5 classes)	Stage: Binet	Median survival
Lymphocytosis (>15,000/mm^3)	0	-	150 months (12.5 years)
Lymphocytosis plus nodal involvement	I	A <3 node groups	101-108 months (8.5-9 years)
Lymphocytosis plus organomegaly	II	B >3 node groups	60-71 months (5-6 years)
Anemia (RBCs)	III Hgb <11 g/dL	C Hgb <10 g/dL	19-24 months (1.5-2 years)
Lymphocytosis plus thrombocytopenia (platelets)	IV PLT <100,000/mm^3	PLT <100,000/mm^3	

Genetic abnormalities in CLL

Genetic abnormality	Incidence (%)	Median survival (months)	Clinical correlation
13q14 most common and have beter survival rate	55-62	133-292	Typical morphology Mutated V_H genes Stable disease
+ 12	16-30	114-122	Atypical morphology Progressive disease
del 11q23	18	79-117	Bulky lymphadenopath Unmutated V_H genes Progressive disease Early relapse post autograft
p53 loss/mutation Worse outcome	7	32-47	Atypical morphology Unmutated V_H genes Advanced disease Drug resistance

Döhner H, et al. *N Engl J Med.* 2000;343:1910-1916.
Oscier DG, et al. *Blood.* 2002;100:1177-1184.

Mutation status of IgHV genes

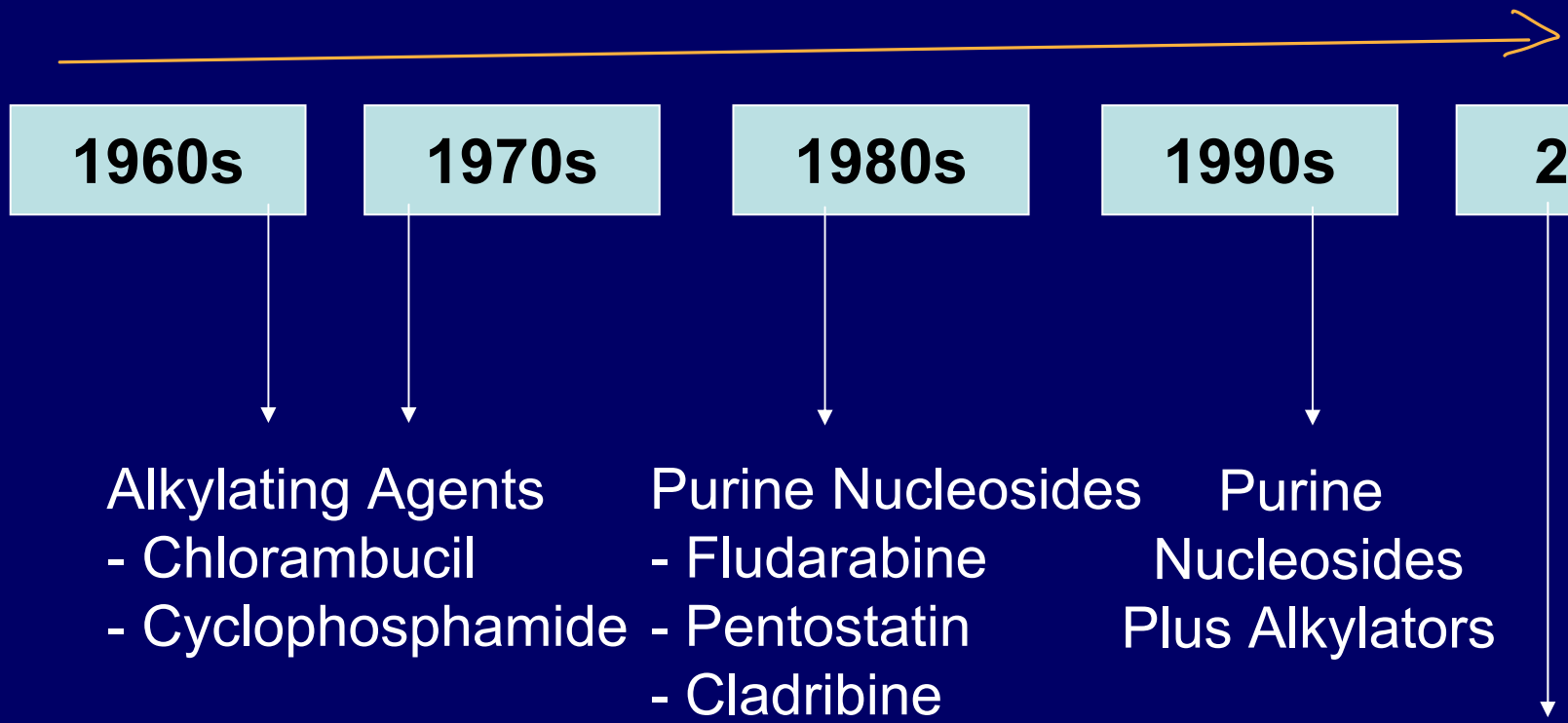
- Unmutated:
  - Pregerminal centre cell
  - Rapid progression
- Mutated:
  - Postgerminal centre cells
  - Slow progression
- Surrogate markers
  - ZAP 70 and CD38

CLL treatment criteria:

- Patient has symptoms
- Decline in Hb or Plt.
- Lymphadenopathy
- Hepatosplenomegaly
- Recurrent infections
- presence of B symptoms

- the longer the survival the better the treatment is
- for chronic luekemia we rarly do transplant

CLL Treatment Options



CML
- all 3 cells affected
- phases
  - chronic :- discovery ∫ symptoms, ⊕ WBCs
  - accelerated
  - blast

second type

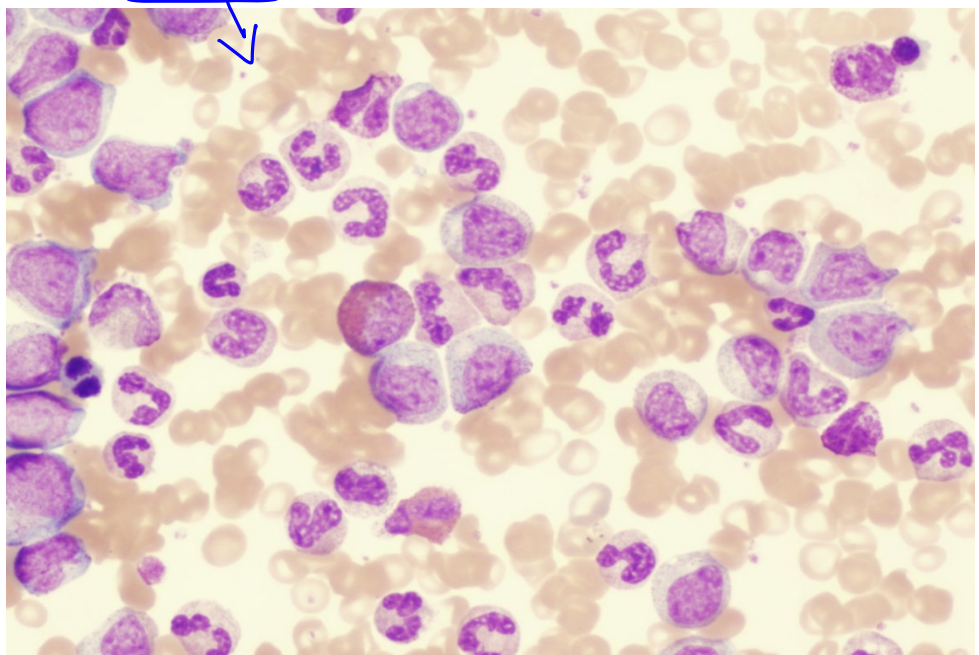
Case 10 B: CML

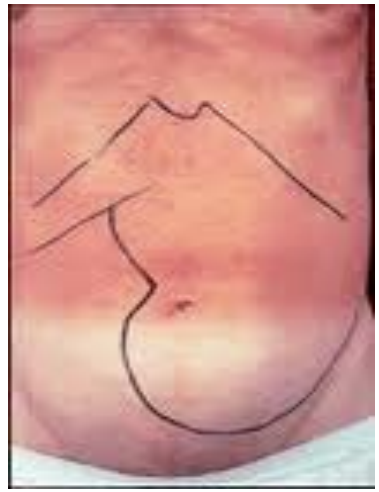
usually dont have lymphoadenopathy

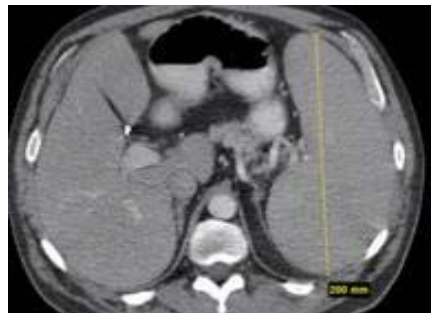
54 yr M, complains of L abdominal discomfort, weight loss, sweating and headaches.P/E: signs of weight loss, temp 37.3, BP 135/85. Spleen+++. Hb 13, mcv 88, Retcs. 0.9% .Plt 800k, WBC 120k. S.uric acid 9.5.

Bld film. Abd CT.

Will have granulocytes from all differeint stages
pro ✓
↓
myelo ✓
↓
band ✓
↓
mature ✓



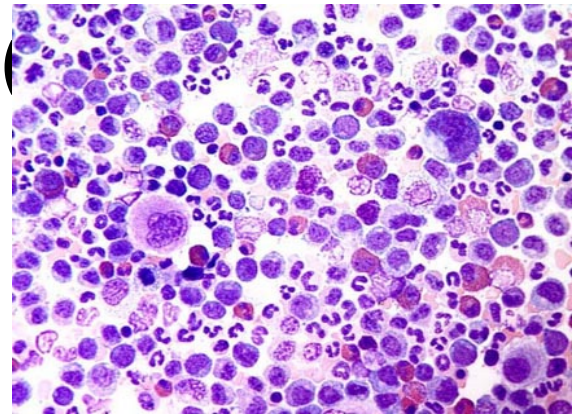




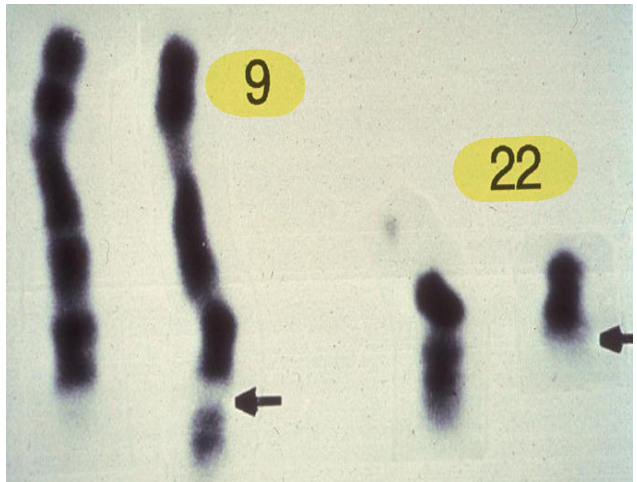
Case 10B

1- BM. 2-Karyotyping. 3- FISH.

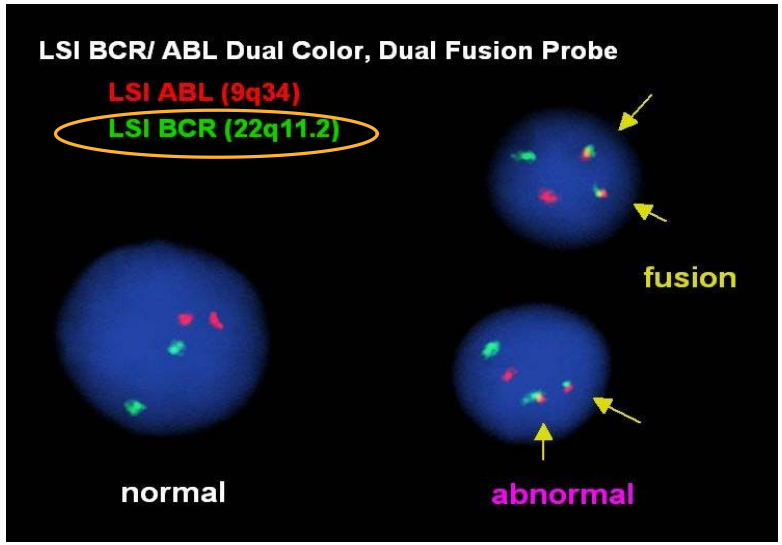
Chromosomal study



Diagnosis: CML in Chronic Phase



Locus specific identifier (LSI)



Epidemiology

- Incidence of CML is 1.5 / 100,000.
- Affects middle-aged individuals.
- CML accounts for 20% of all leukemias affecting adults.

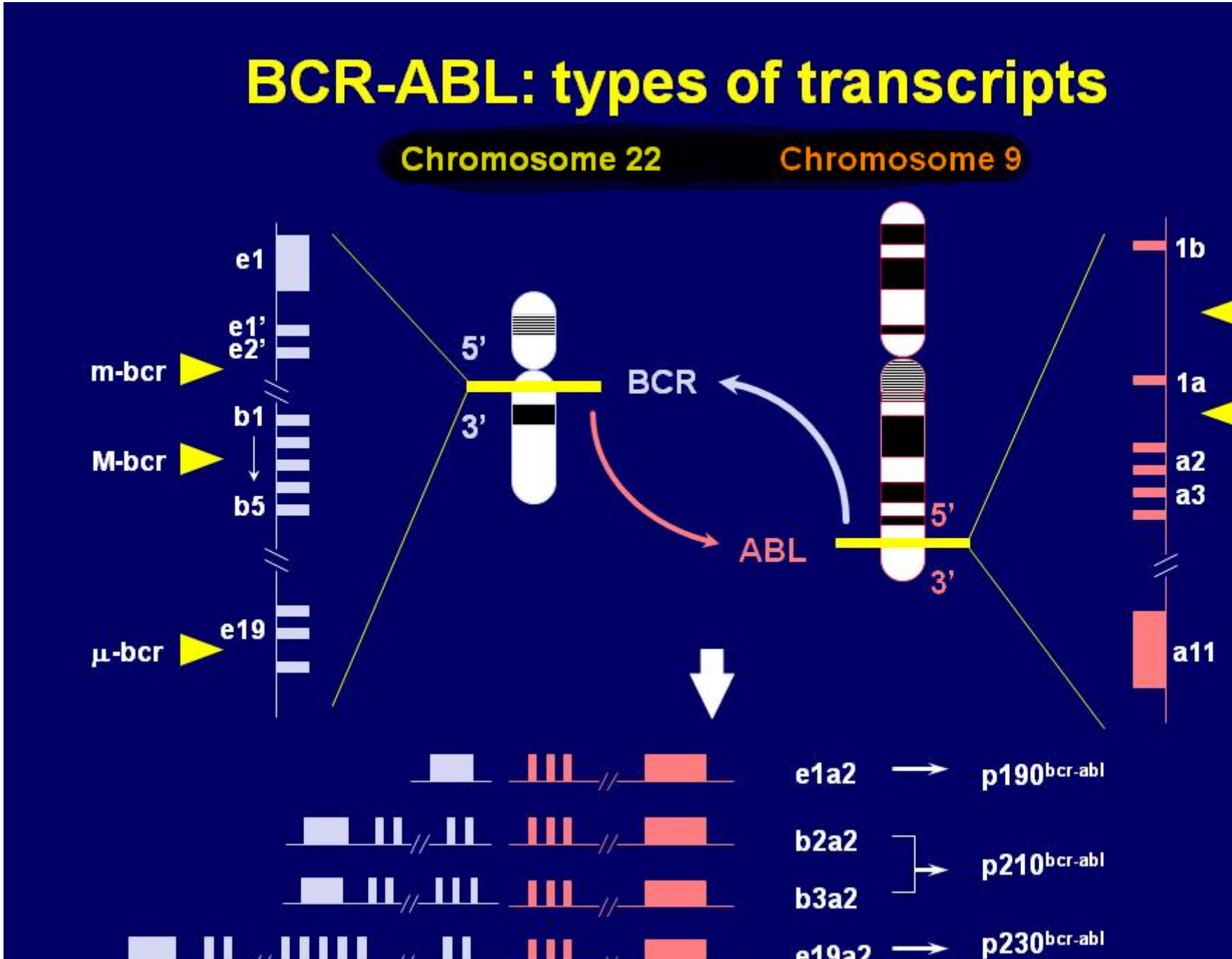
Definition

- Clonal expansion of a hematopoietic stem cel
  possessing a reciprocal translocation betwee
  chromosomes 9 and 22.
- Fusion of *BCR* region on chromosome 22 with
  ABL gene from chromosome 9.
- Disease has three phases:

chronic phase, accelerated phase, and blast crisis.

Pathophysiology

- *BCR/ABL* gene product plays central role.
- Bcr/Abl fusion proteins $p210^{BCR/ABL}$ and $p230^{BCR/ABL}$ can transform hematopoietic progenitor cells in vitro.
- Irradiated mice injected with BM cells infecte with retrovirus carrying the *BCR/ABL* gene leads to CML-like picture.


BCR-ABL: types of transcripts
Chromosome 22
Chromosome 9
e1
e1'
e2'
m-bcr
b1
M-bcr
b5
e19
μ-bcr
5'
3'
BCR
ABL
5'
3'
1b
1a
a2
a3
a11
e1a2
p190bcr-abl
b2a2
b3a2
p210bcr-abl
e19a2
p230bcr-abl

Symptoms

- Insidious onset: accidental discovery
- Fatigue, malaise, weight loss
- Symptoms due to splenomegaly
  - LUQ pain, early satiety,mass
- Infections, thrombosis, bleeding.
- ?Gout
- Worsening of symptoms heralds progression (fever, weight loss, decreased response to therapy, bone pain).
- Some patients may present in the accelerated or blastic phase.

Physical Findings

- Minimal to moderate splenomegaly
- Mild hepatomegaly
- Lymphadenopathy and myeloid sarcomas rar
  except in terminal stages of the disease.

Hematologic Findings

- Elevated WBC, <5% blasts and <10% blasts and promyelocyt
- Elevated platelets
- Normochromic normocytic anemia
- Basophilia
- The cytogenetic hallmark of CML, found in 95% of patients, i the t(9;22)(q34;q11.2).
- Originally designated as the Philadelphia chromosome.
- All patients should have evidence of the translocation either by cytogenetics, FISH, or molecularly to make a diagnosis of CML.

Hematologic Findings

Accelerated Phase is characterized by:

- Anemia, Blood or BM basophils ≥20%, Platelet count <100,000/µl
- Cytogenetic clonal evolution, Blood or BM blasts between 10 and 20%

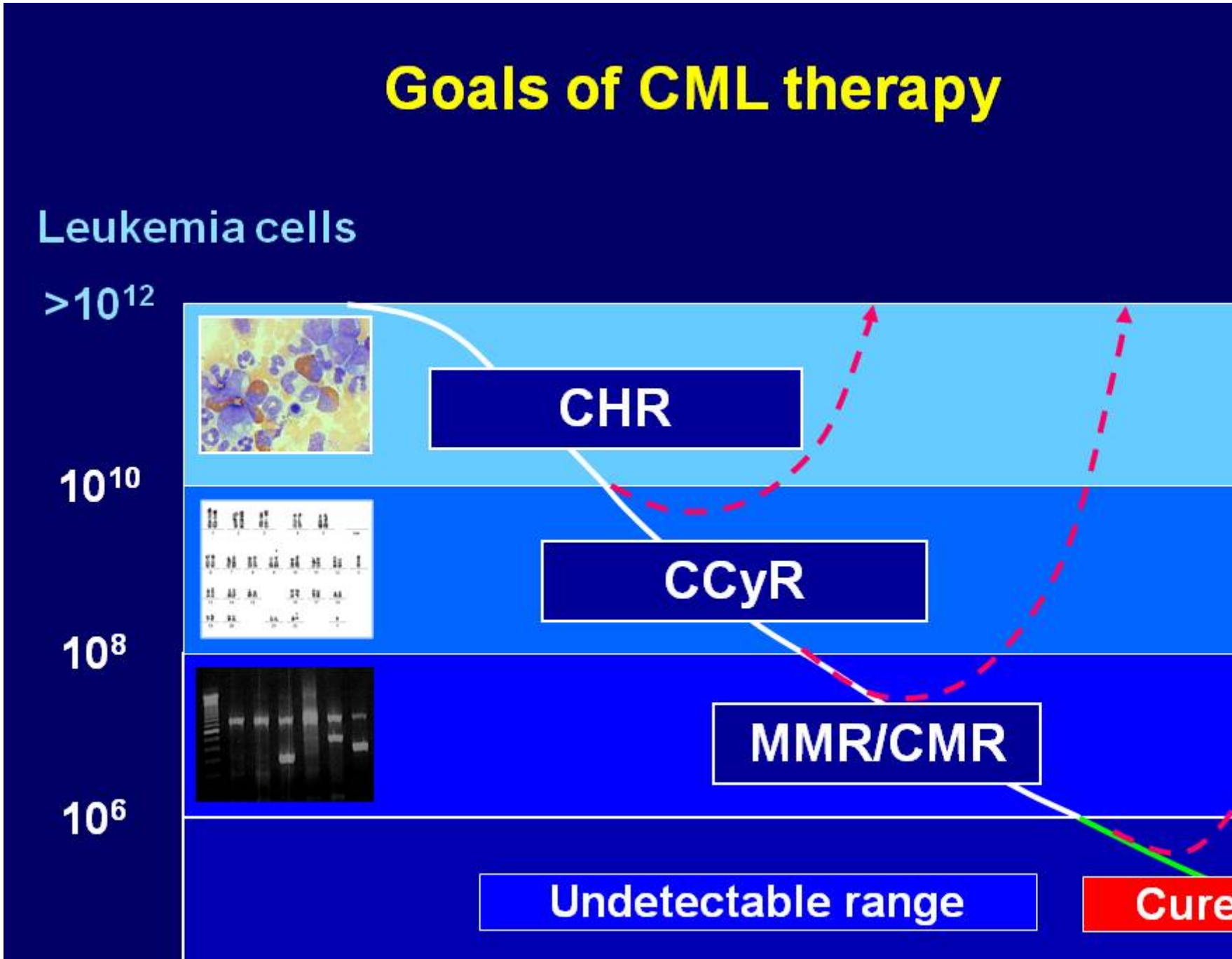
Blastic Phase (Crisis)

- Acute leukemia, with blood or marrow blasts ≥ 20%.
- Hyposegmented neutrophils may appear (Pelger-Huet anomaly).
- Blast cells can be classified as myeloid, lymphoid, erythroid, or undifferentiated.

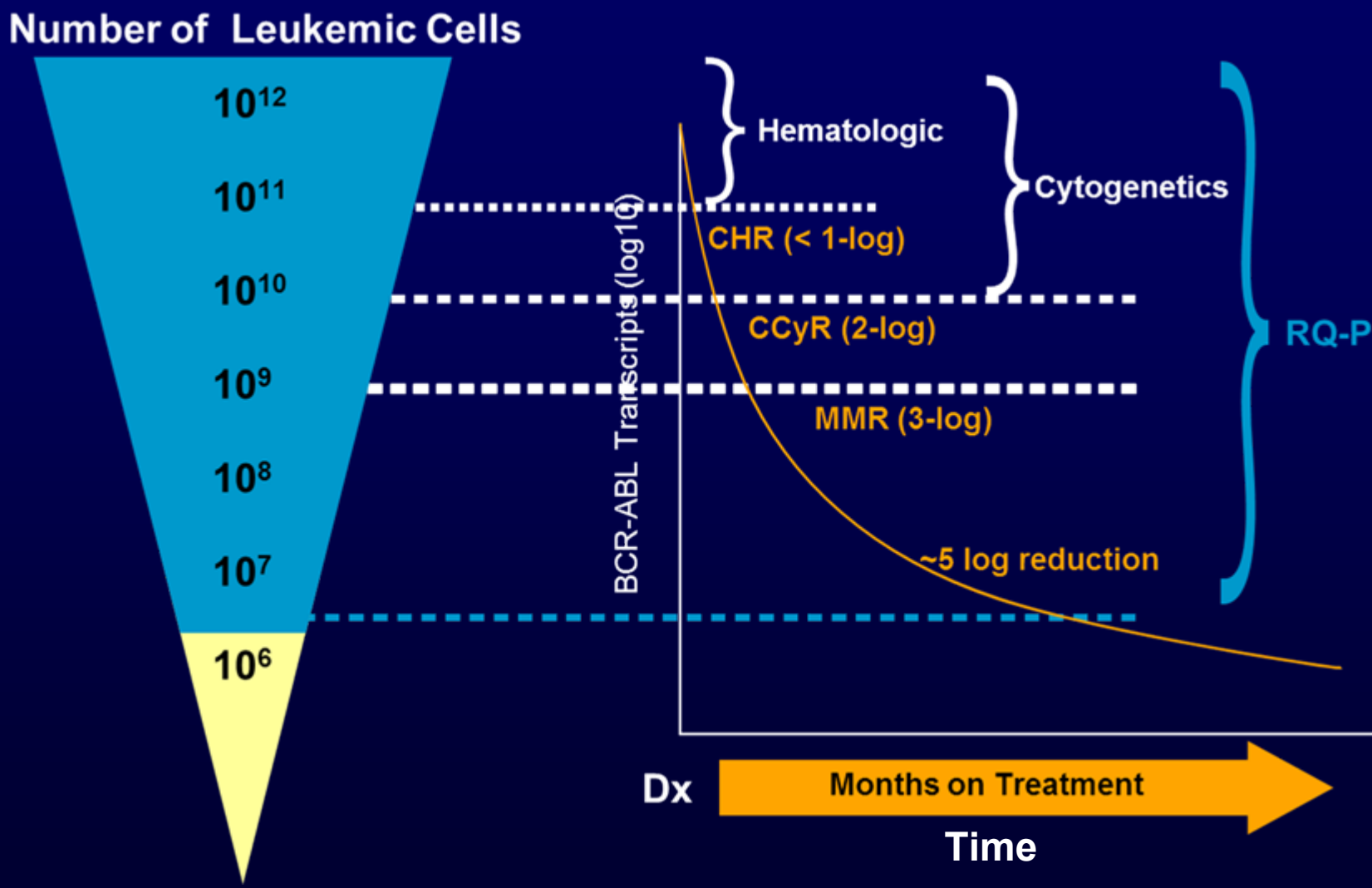
Treatment

- Aim of treatment is to reduce WBC, prevent gout and **target the molecular cause** of the disease
- The treament has been revolutionized by imatinib mesylate, a targeted treatment.
- Stem cell transplant (SCT) is the only definitiv therapy and treatment of choice in some patients.

Goals of CML therapy



Correlation Between Response and Disease Burden: Molecular Response



Imatinib mesylate

MoA

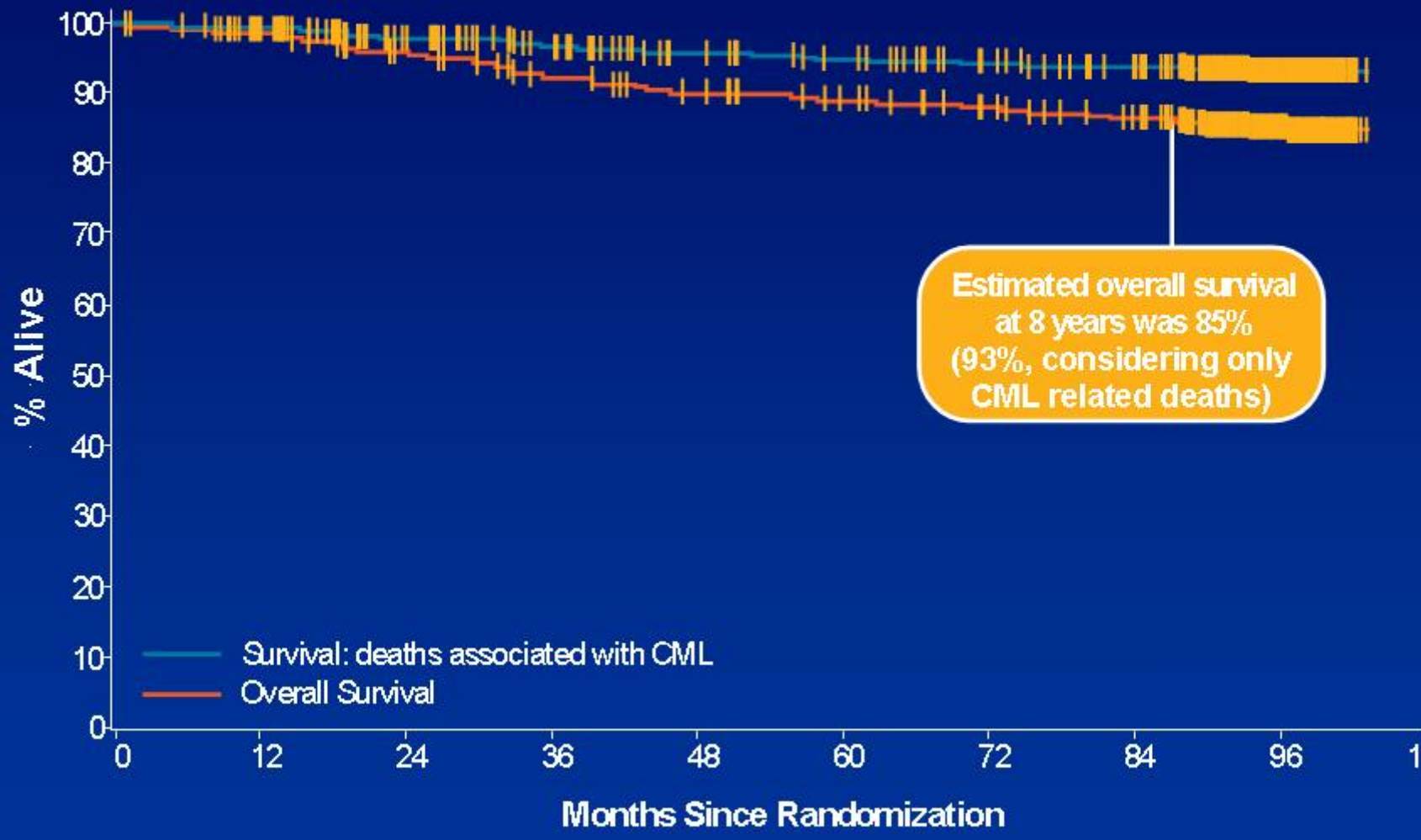
Competitive inhibition at the adenosine triphosphate (ATP) binding site of the Abl kinase

Rapid hematologic response.

95% of patients achieved complete hematologic remission, and 60% achieved major cytogenetic remission within few months.

IRIS 8-Year Update

Results: Overall Survival (Intent-to-Treat) – Imatinib A



Side effects

- The main side effects are fluid retention, nausea, muscle cramps, diarrhea, and skin rashes.

- Myelosuppression is the most common hematologic side effect.

Resistance

Mechanisms include

- Gene amplification
- **Mutations at the kinase site** acquired
- Enhanced expression of multidrug exporter proteins
- Alternative signaling pathways functionally compensating for the imatinib-sensitive mechanisms

Other Treatment Modalities

in blastic phase should treated as acute Leukemia

- Alfa Interferons
- Chemotherapy (hydroxyurea, busulphan)
- Allogeneic BMT (SCT) for selected patients
- 2d generation TKI for failures or relapse or intolerance
- BMT for Crisis