# Chronic Leukemia (CLL)/MS.4th.2.Nov.15

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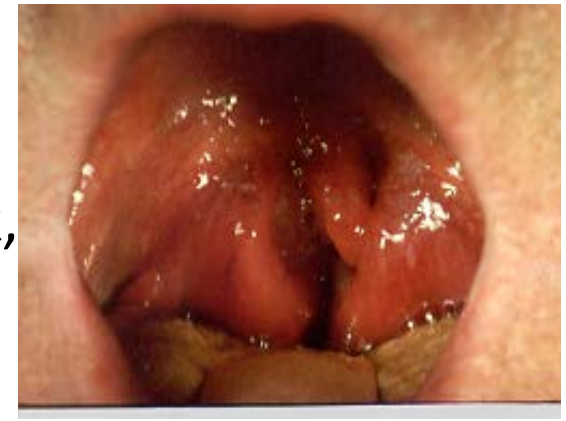
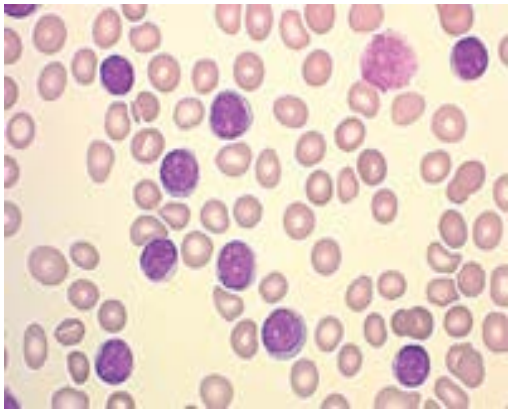
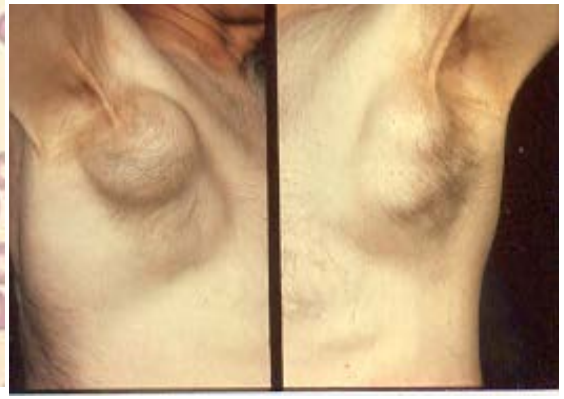
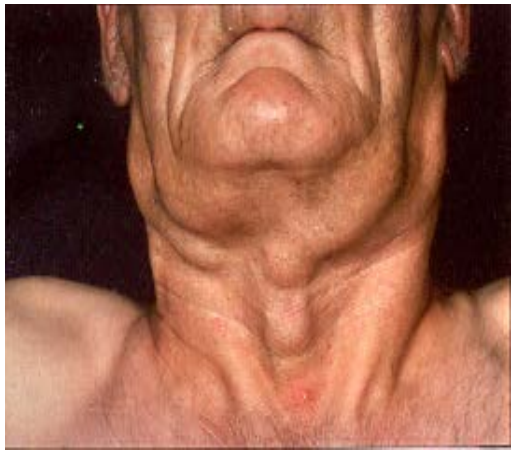
# Case 10

69 yr old man complains of fever and cervical and axillary swelling for several months with recurrent fever and productive purulent 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









# Case Ten：Diagnosis and Management

1- Decide the type of lymphocyte

2- Determine the stage

**Stage IV Rai, C Binet**

3- Cytogenetics

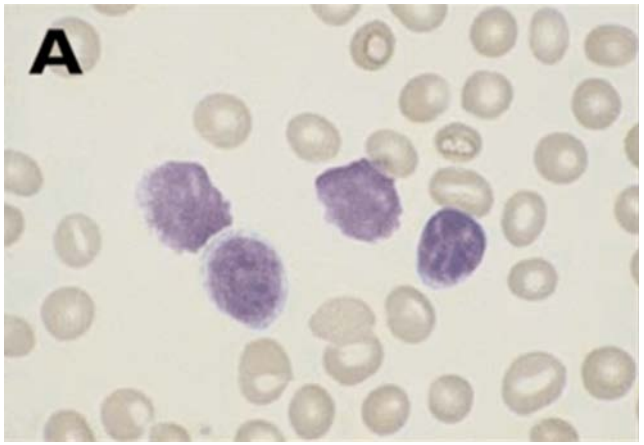
**+ 12**

3- Decide therapy

5- Decide Prognosis

6- Determine follow-up

| | |
|---|---|
| **sIg** | **+** |
| **CD19** | **++** |
| **CD20** | **++** |
| **CD5** | **+** |



# 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
  - Early - >10 years median survival
  - Intermediate - 5-7 years median survival
  - Advanced - 1-3 years median survival
- Heterogeneity of disease

# Staging: Rai and Binet staging systems for CLL

***Clinical staging systems for CLL***

| Stage | | | |
|---|---|---|---|
| **Value** | **Rai** | **Binet** | **Median** |
| Lymphocytosis | 0 | - | 150 months (12.5 years) |
| Lymphocytosis plus involvement | I | A <3 node groups | 101-108 months (8.5-9 years) |
| Lymphocytosis plus | 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 | 55-62 | 133-292 | Typical morphology<br>Mutated $V_H$ genes<br>Stable disease |
| + 12 | 16-30 | 114-122 | Atypical morphology<br>Progressive disease |
| del 11q23 | 18 | 79-117 | Bulky lymphadenopathy<br>Unmutated $V_H$ genes<br>Progressive disease<br>Early relapse post autograft |
| p53 loss/mutation | 7 | 32-47 | Atypical morphology<br>Unmutated $V_H$ genes<br>Advanced disease<br>Drug resistance |

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

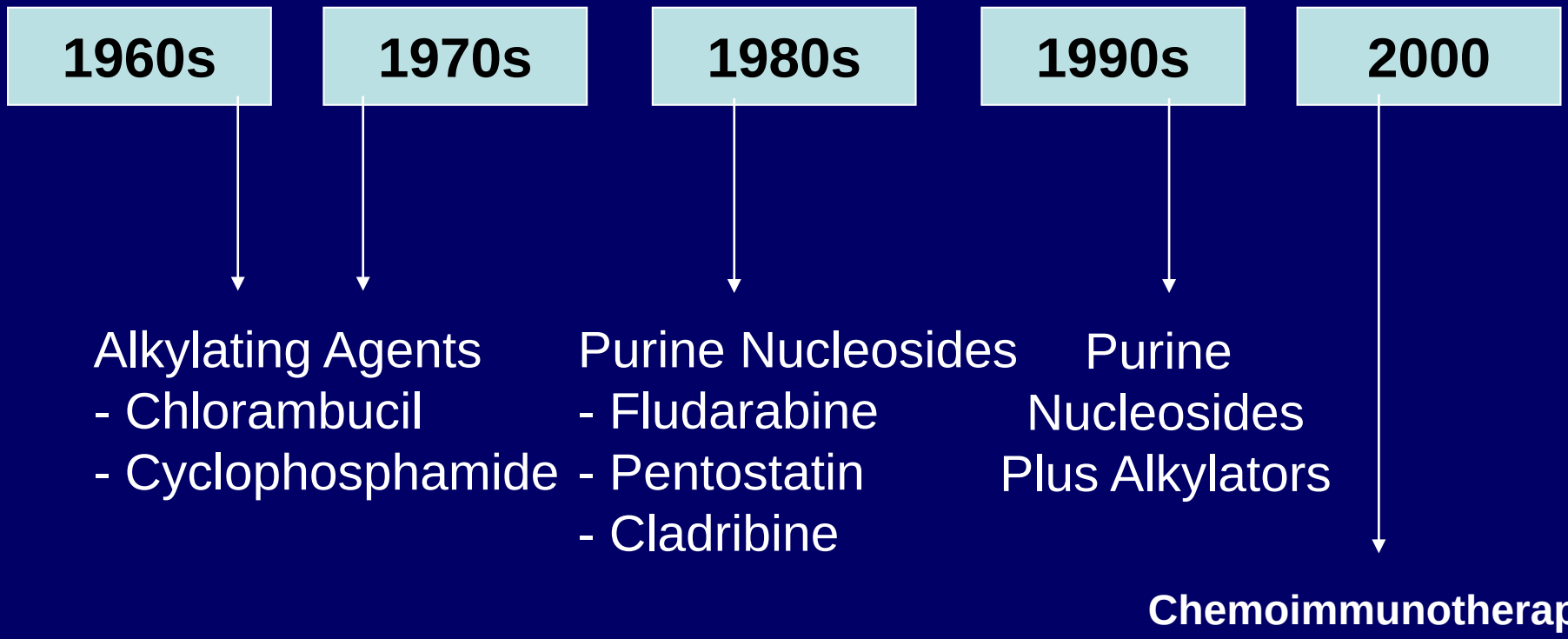
# Mutation status of VH genes

- Unmutated VH genes
  - Pregerminal centre cell
  - Rapid progression
- Mutated VH genes
  - 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

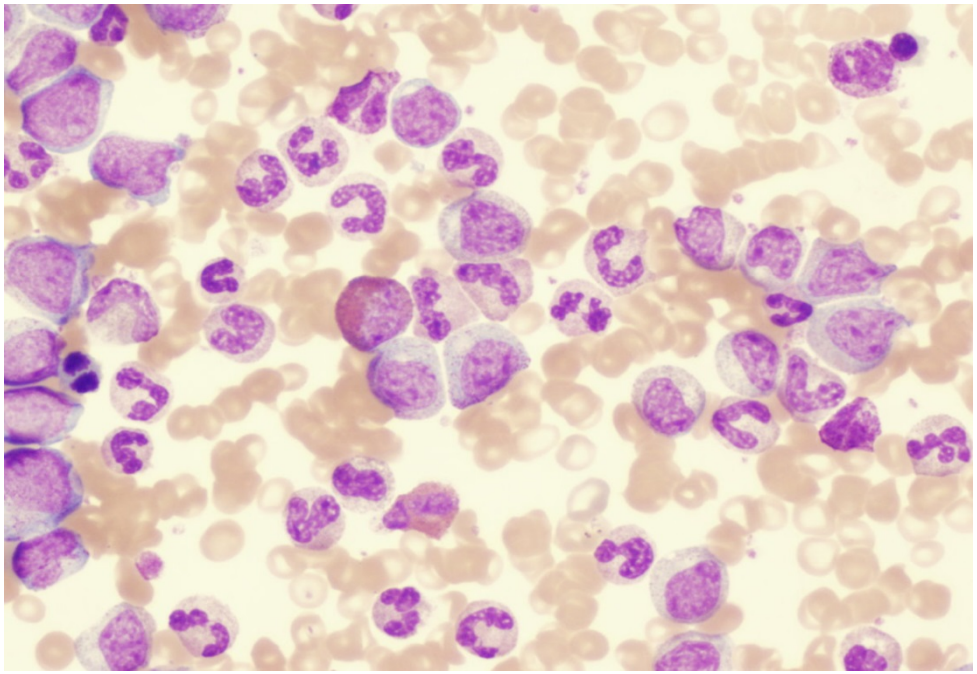
# CLL Treatment Options

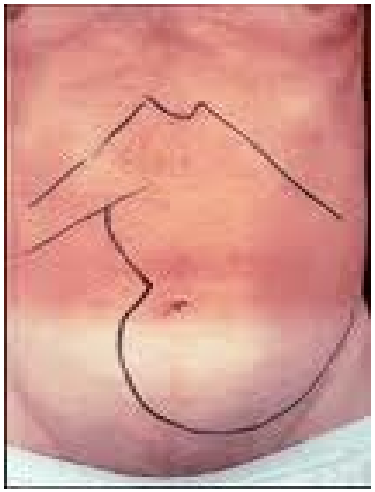


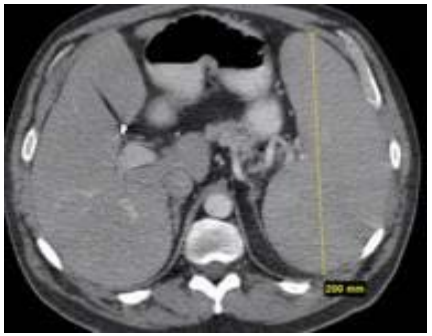
# Case 10 B: CML

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.



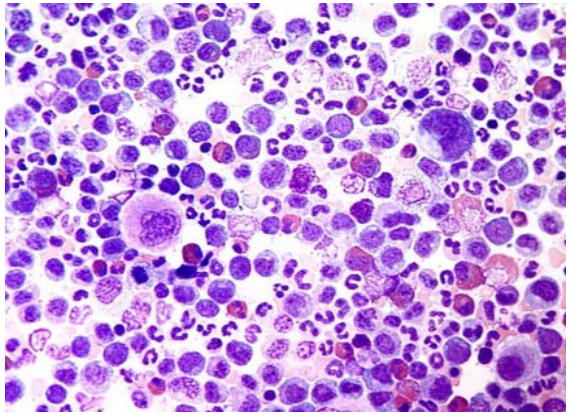


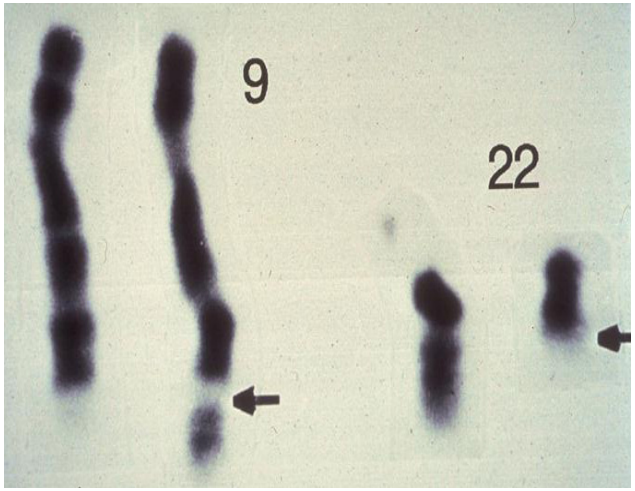


# Case 10B

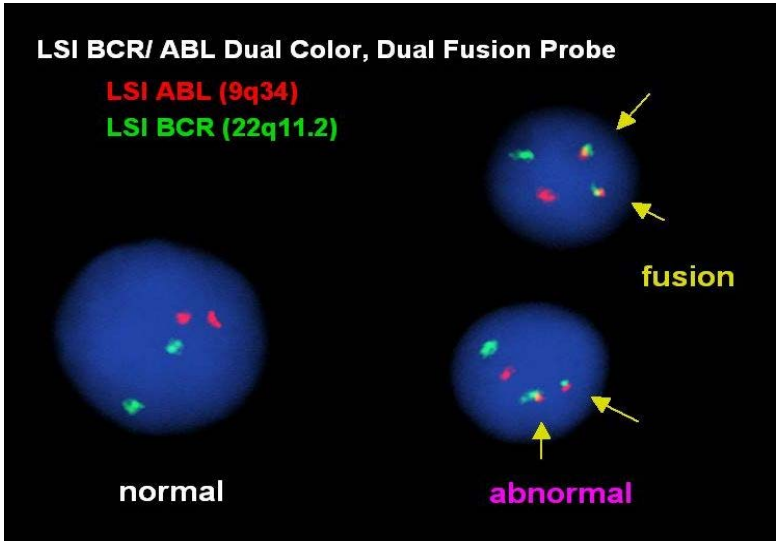
1- BM. 2-Karyotyping. 3- FISH.

**Diagnosis: CML in Chronic Phase (CP)**






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

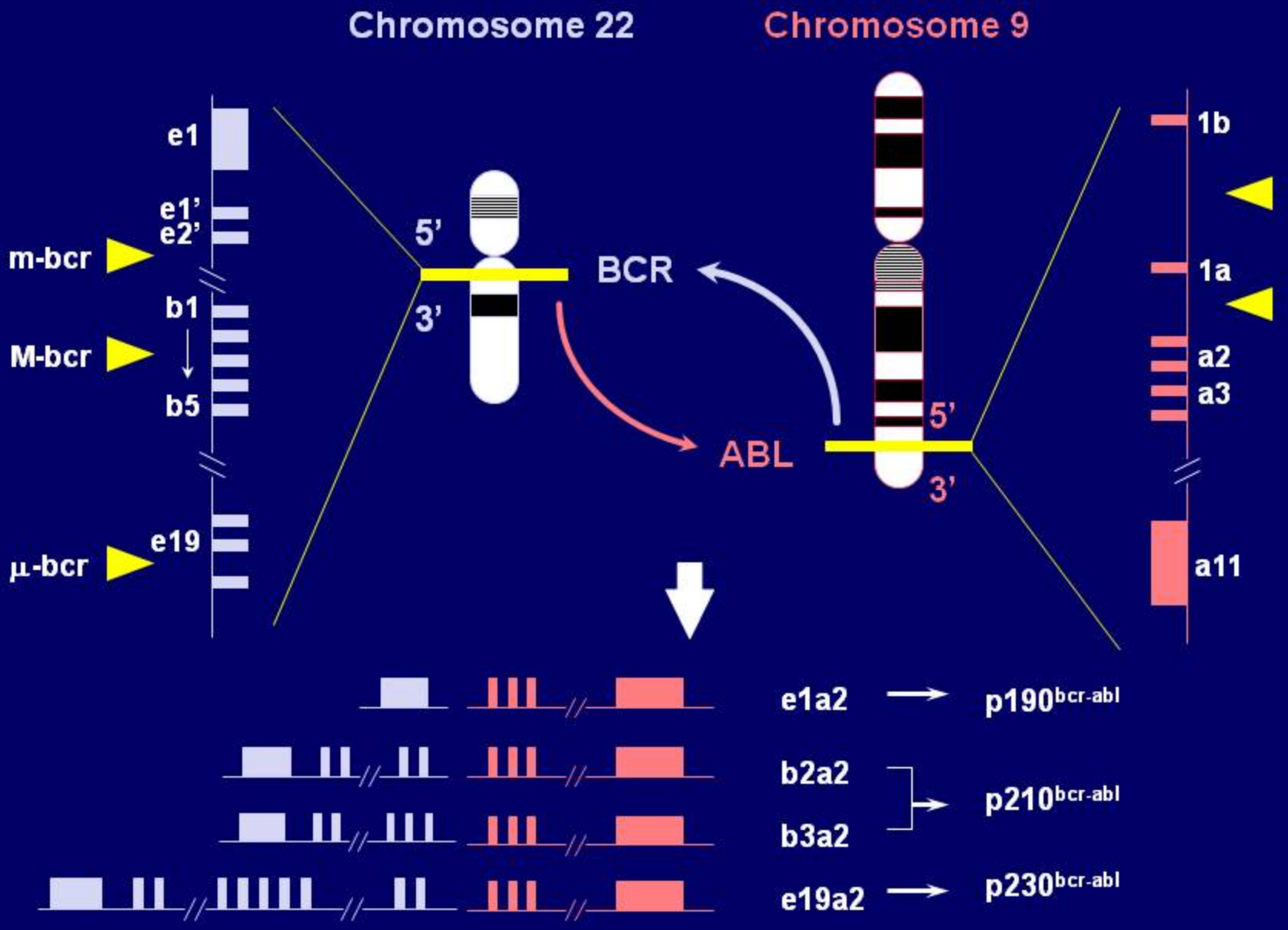
- Clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22.
- Fusion of *BCR* region on chromosome 22 with *ABL* gene from chromosome 9.
- Disease has three phases:

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 infected with retrovirus carrying the *BCR/ABL* gene leads to CML-like picture.

# BCR-ABL: types of transcripts



# 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 rare except in terminal stages of the disease.

# Hematologic Findings

- Elevated WBC, <5% blasts and <10% blasts and promyelocytes
- Elevated platelets
- Normochromic normocytic anemia
- Basophilia
- The cytogenetic hallmark of CML, found in 95% of patients, is 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%

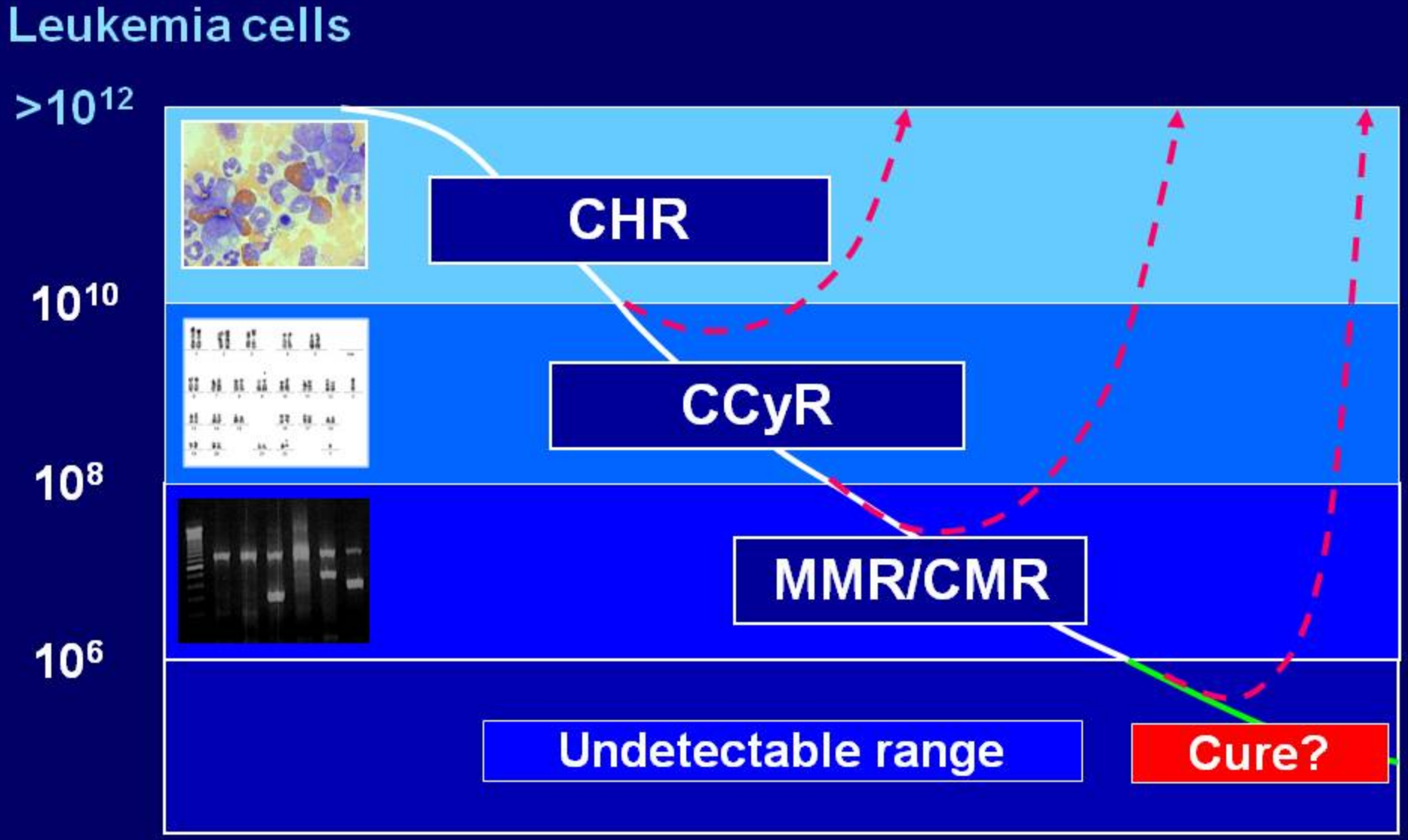
***Blastic Phase (Crisis)***

- 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.

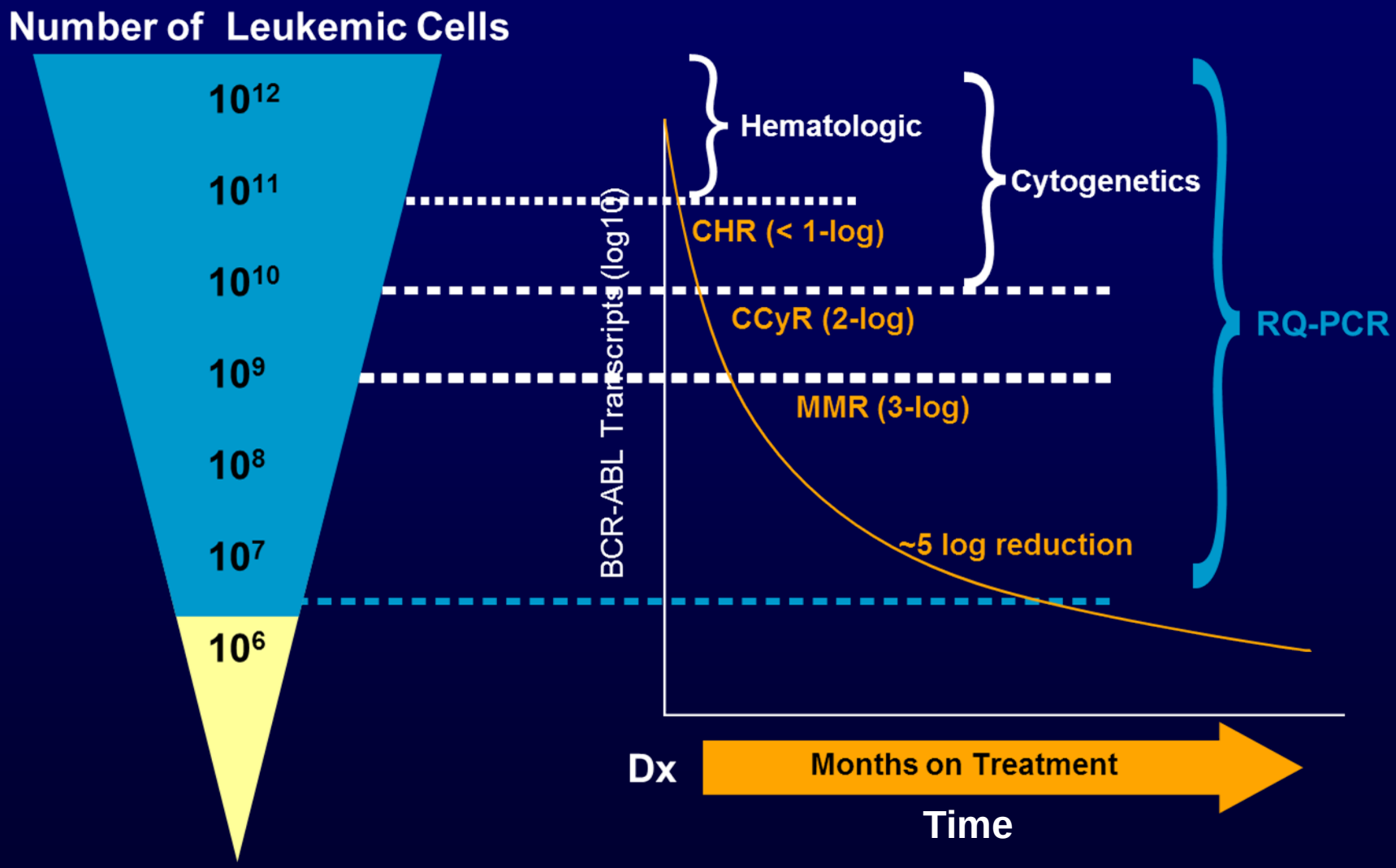
# Treatment

- 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 definitive therapy and treatment of choice in some patients.

# Goals of CML therapy



# Correlation Between Response and Disease Burden: Molecular Response




Baccarani M, et al. *J Clin Oncol*. 2009;27(35):6041-6051.
Radich JP. *Blood*. 2009;114:3376-3381.

# Imatinib mesylate

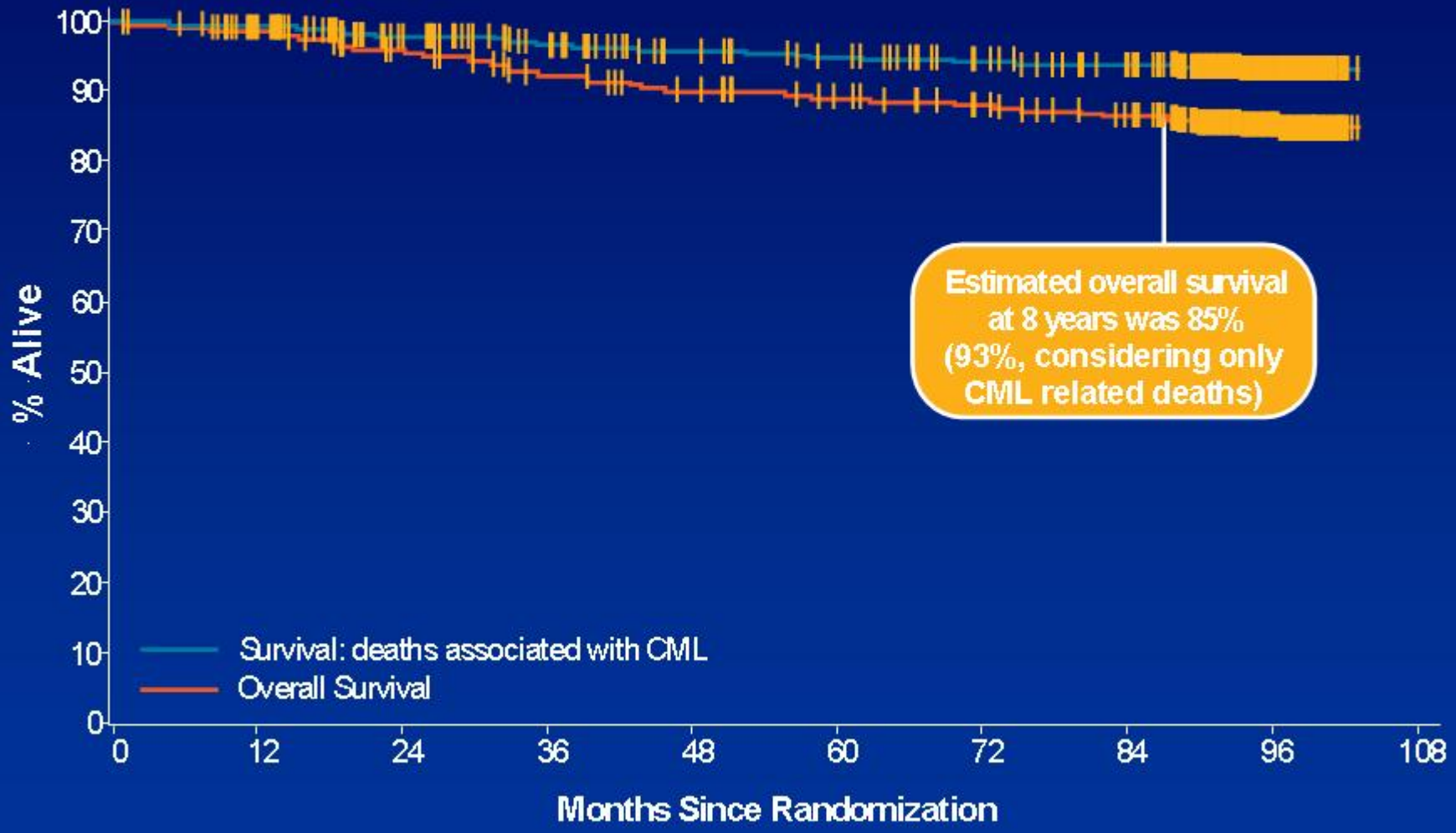
Competitive inhibition at the adenosine triphosphate (ATP) binding site of the Abl kinase

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 Arm




Deininger M. et al. Blood. 2009;114(22):142. Abs # 1126 (Poster).

# 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**
- Enhanced expression of multidrug exporter proteins
- Alternative signaling pathways functionally compensating for the imatinib-sensitive mechanisms

# Other Treatment Modalities

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