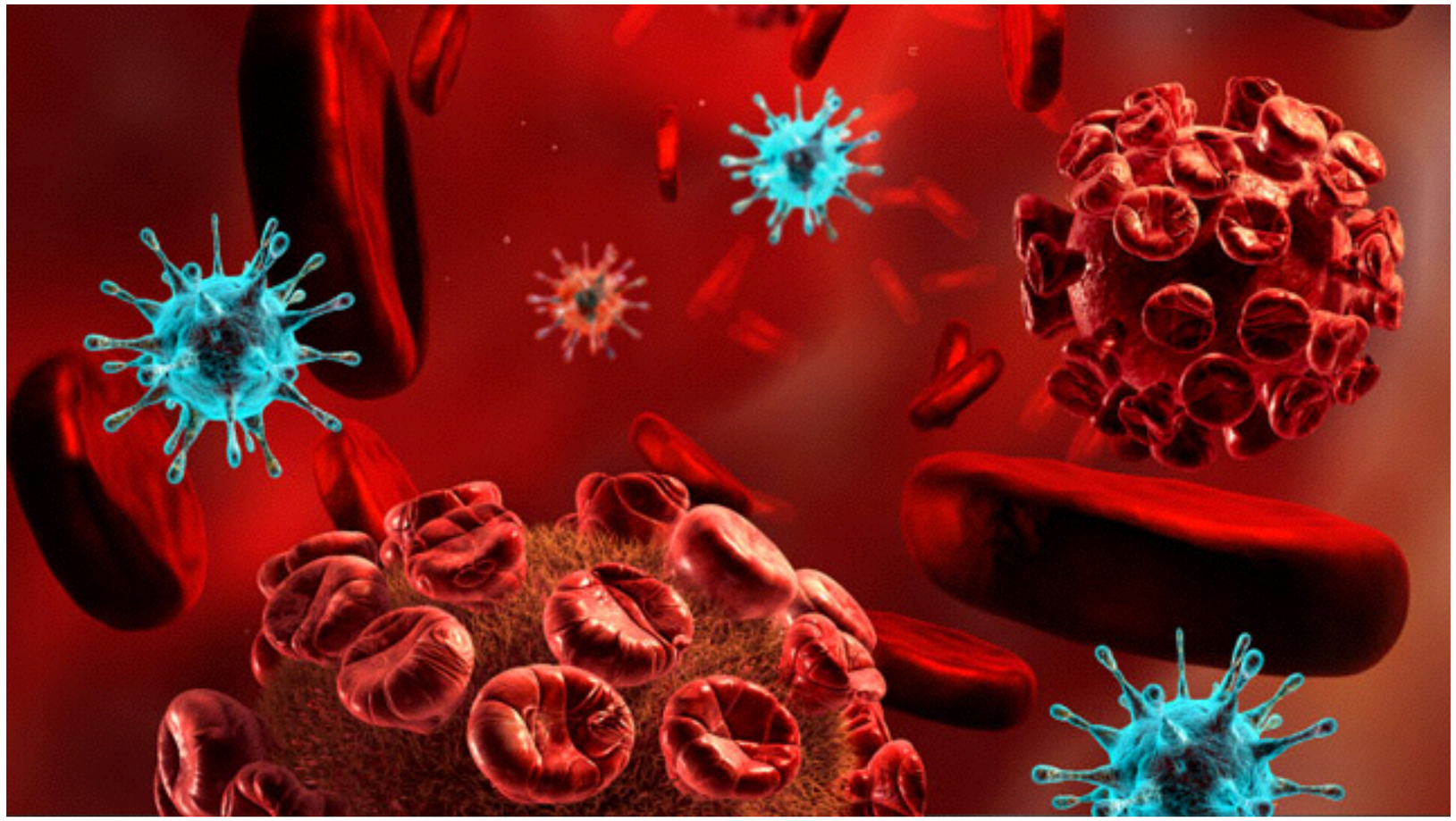


Chronic Myeloid Leukemia

"Just incase you forgot"

Medicine Grandrounds

Dr. Andrew Odhiambo

July 2015

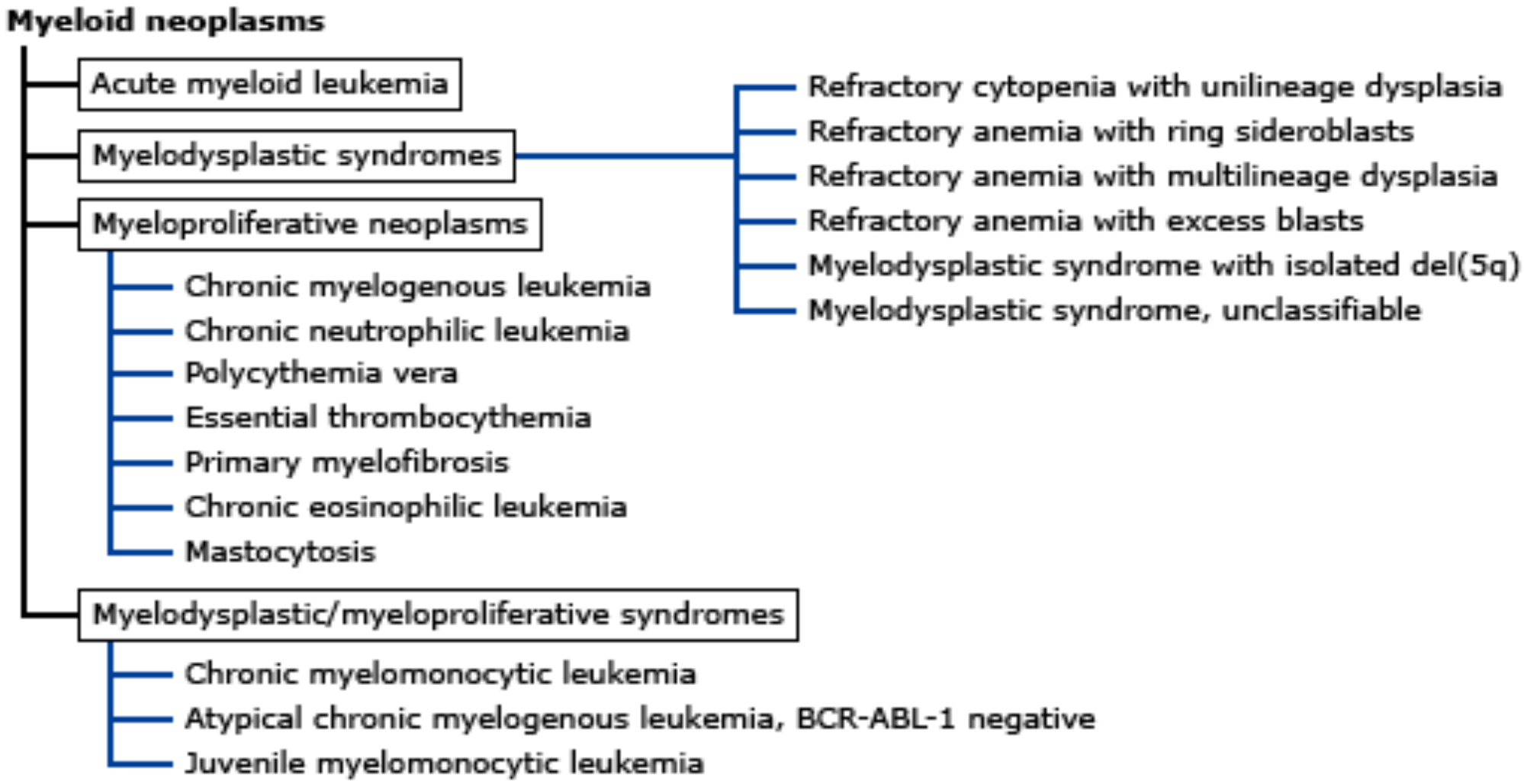
HISTORY

- In 1845, Bennett in Scotland and Virchow in Germany described splenic enlargement, severe anemia, and leukocytosis at autopsy
- Virchow proposed the term ***leukämie***
- In 1878, Neumann proposed – marrow origin for leukemia – ***myelogene*** **(myelogenus)**
- **Nowell and Hungerford in 1960 identified the culprit gene at the Perelman School of Medicine, Philadelphia**
- Dr. Rowley identified the BCR-ABL translocation
- 1998 – Discovery of targeted TKI therapy

The two discoverers of the Philadelphia chromosome in the early 1960s. Peter Nowell is on the left; David Hungerford, right.

What is CML?

Conceptual organization of hematologic malignancies



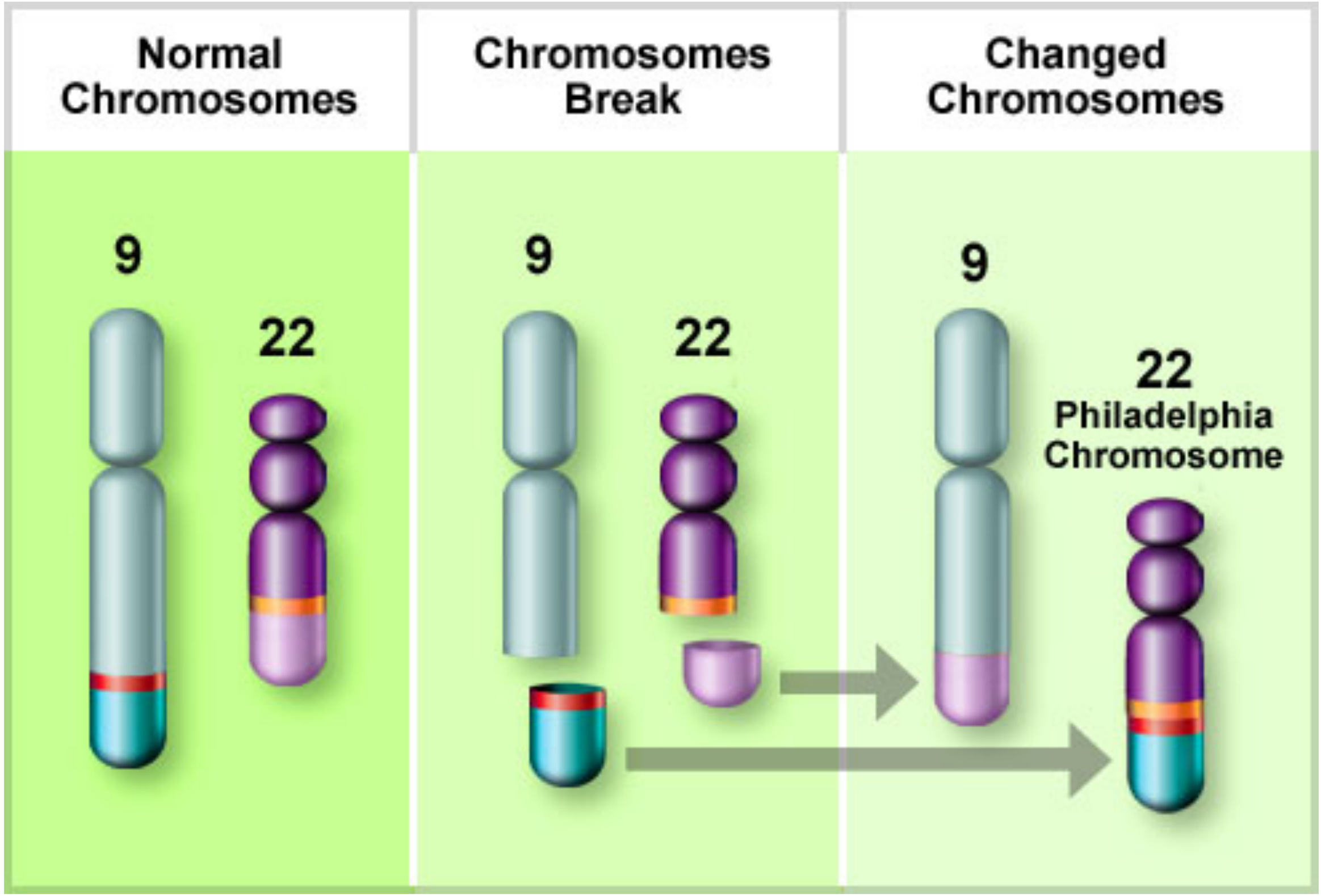
What makes one think CML ?

- Leucocytosis - granulocytic immaturity
- Thrombocytosis
- Absolute basophilia - **ALMOST ALWAYS PRESENT**
- **Splenomegaly**

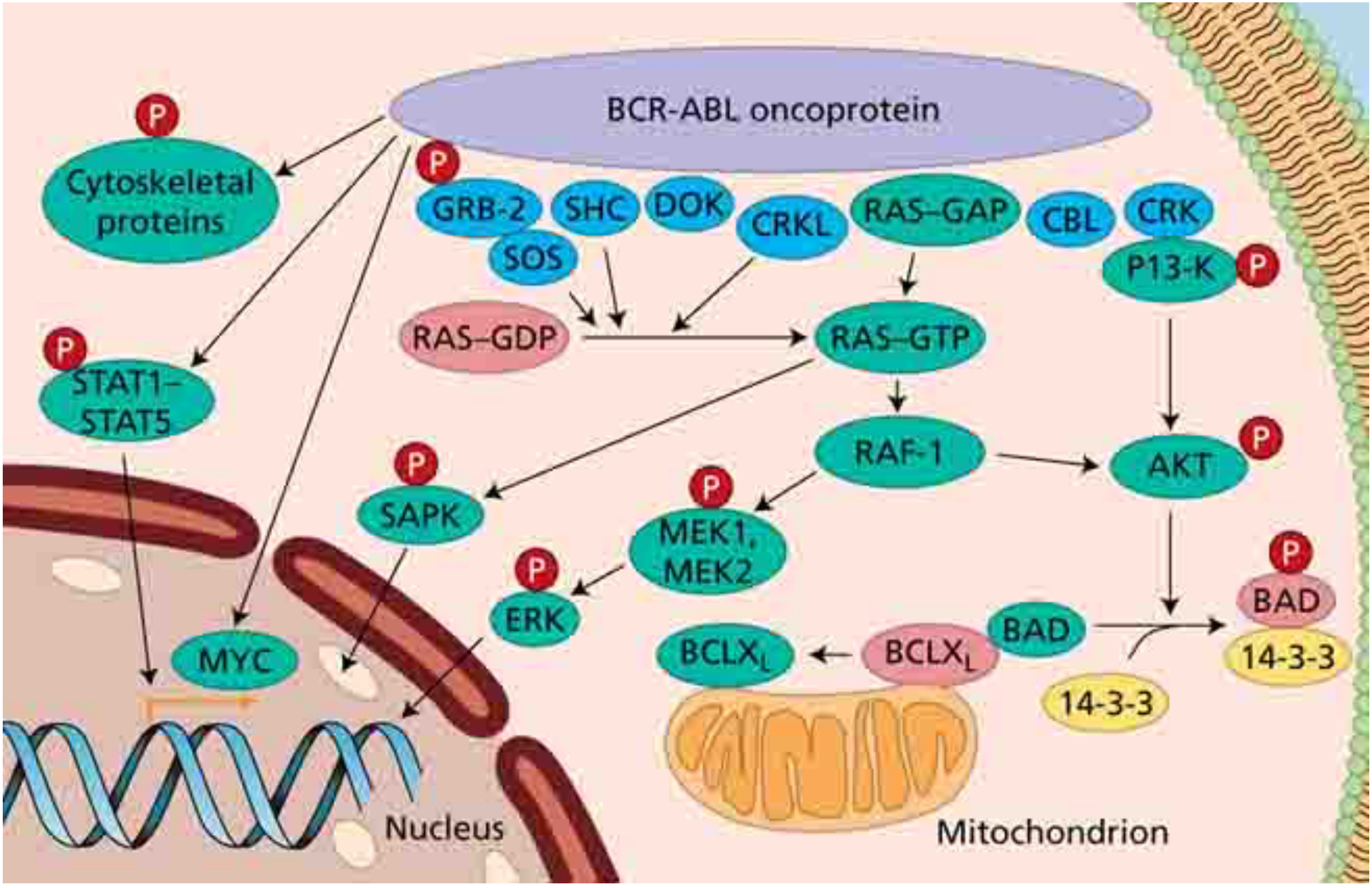
Epidemiology

- 15-20% of all Leukemias
- M:F - 1.4:1
- Median Age 50
- Local **(Abinya et al)**
  - M:F - 1.26:1
  - Median age 44
  - Age range 8-80

Pathogenesis(1)



Pathogenesis(2)



Clinical presentation

- **COMMON**

- At diagnosis – 70% asymptomatic
  (only < 5% Kenya)
  - Easy fatigability
  - Loss of sense of well-being
  - Decreased tolerance to exertion
  - Anorexia
  - Abdominal discomfort
  - Early satiety *
  - Weight loss
  - Excessive sweating

- **UNCOMMON**

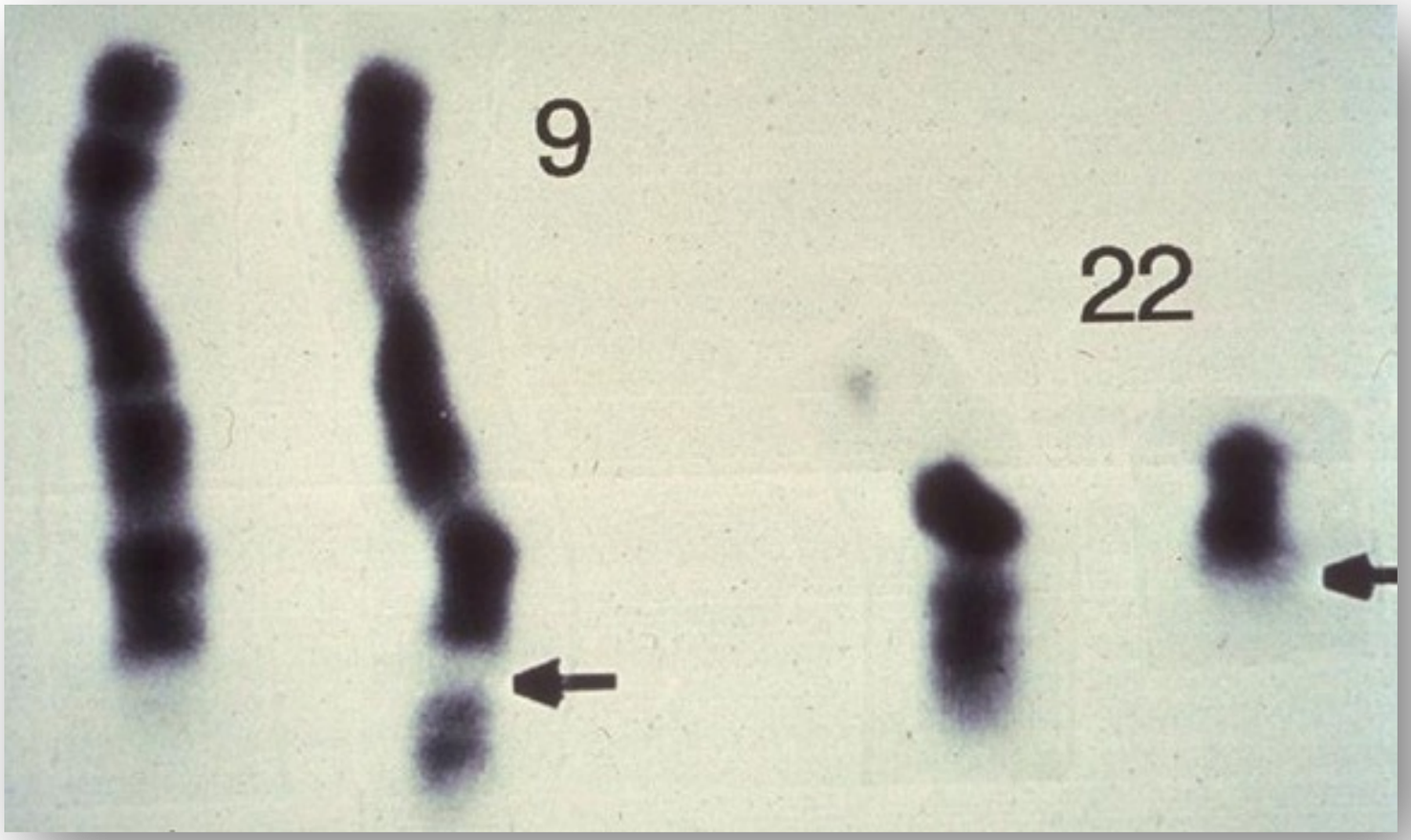
  - Night sweats
  - Heat intolerance
  - **Gouty arthitis**
  - Left upper-quadrant and left shoulder pain*
  - **Urticaria**
  - **Hyperleukocytic Syndrome**
    —dyspnea, tachypnea, hypoxia, lethargy, slurred speech, hearing loss, blindness, priapism

Investigations (1)

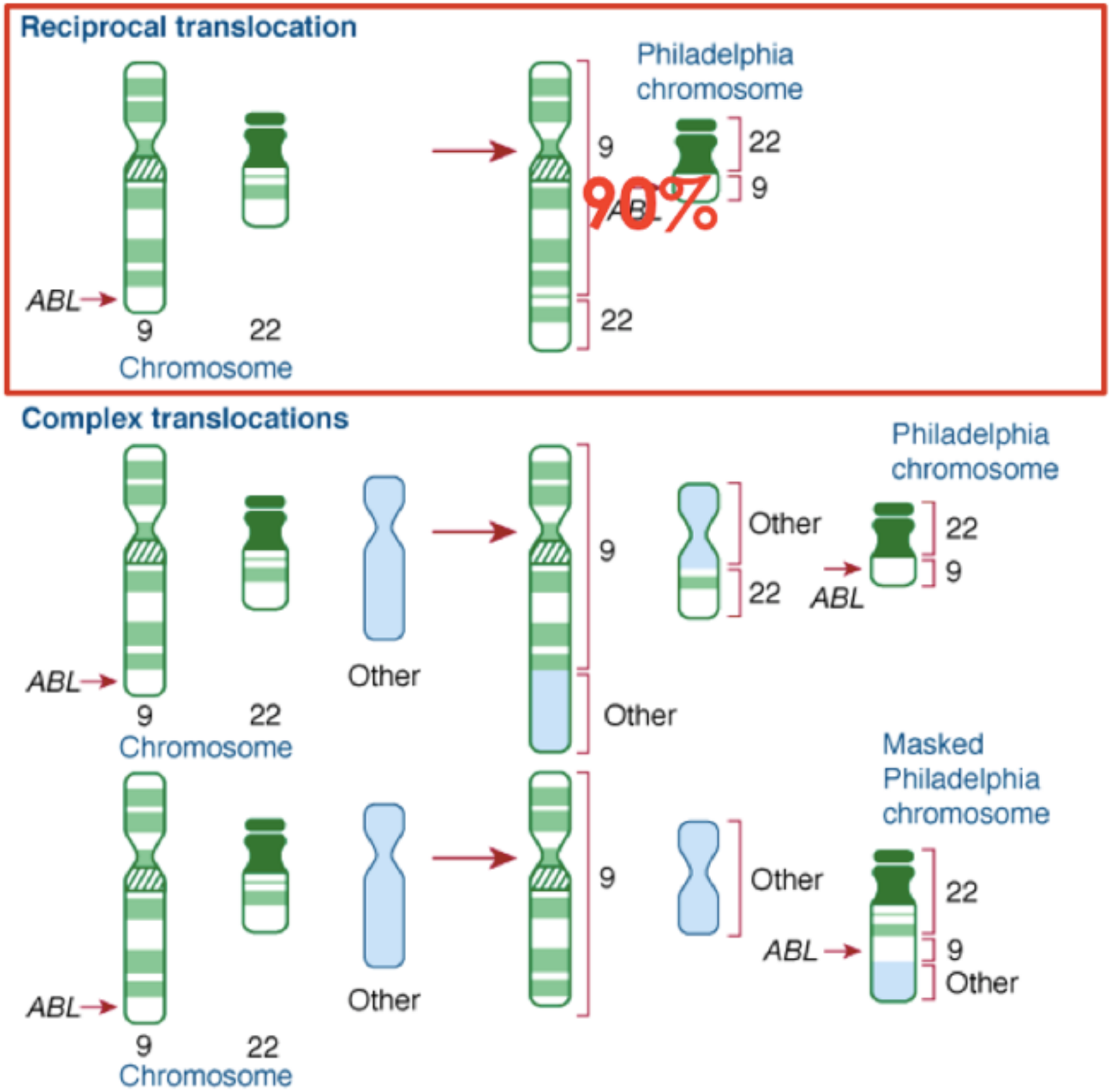
- TBC
- PBF
- BMA - cytology
- Chem-panel
- Other lab features :
  - **Neutrophil Alkaline Phosphatase reduced**
  - **Serum B12 and transcobalamin increased (>10 ULN)**
  - **Serum uric acid increased**
  - **Lactate dehydrogenase increased**
  - **Mean histamine levels increased**

Cytogenetics

- Study of the number and structure of chromosomes
- Samples from bone marrow myeloid cells
- The presence of the Philadelphia chromosome – shortened chromosome 22*
- **Cytogenetics cannot identify complex translocations**



COMPLEX TRANSLOCATIONS

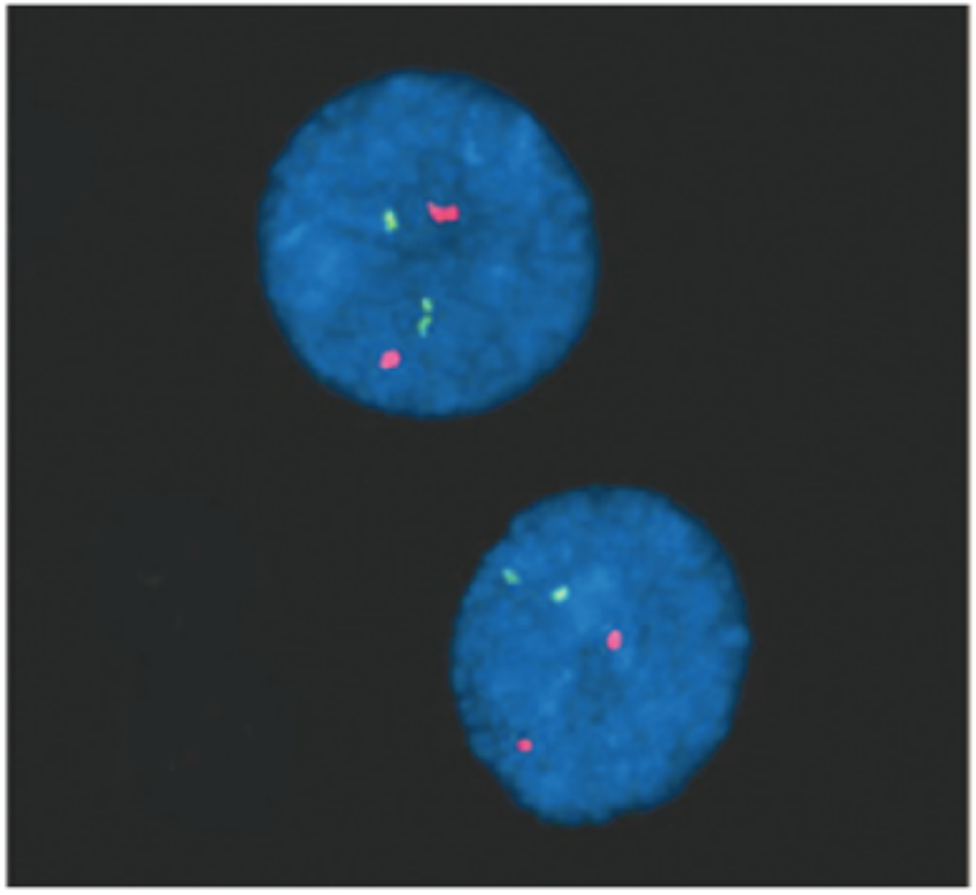


New Molecular Techniques

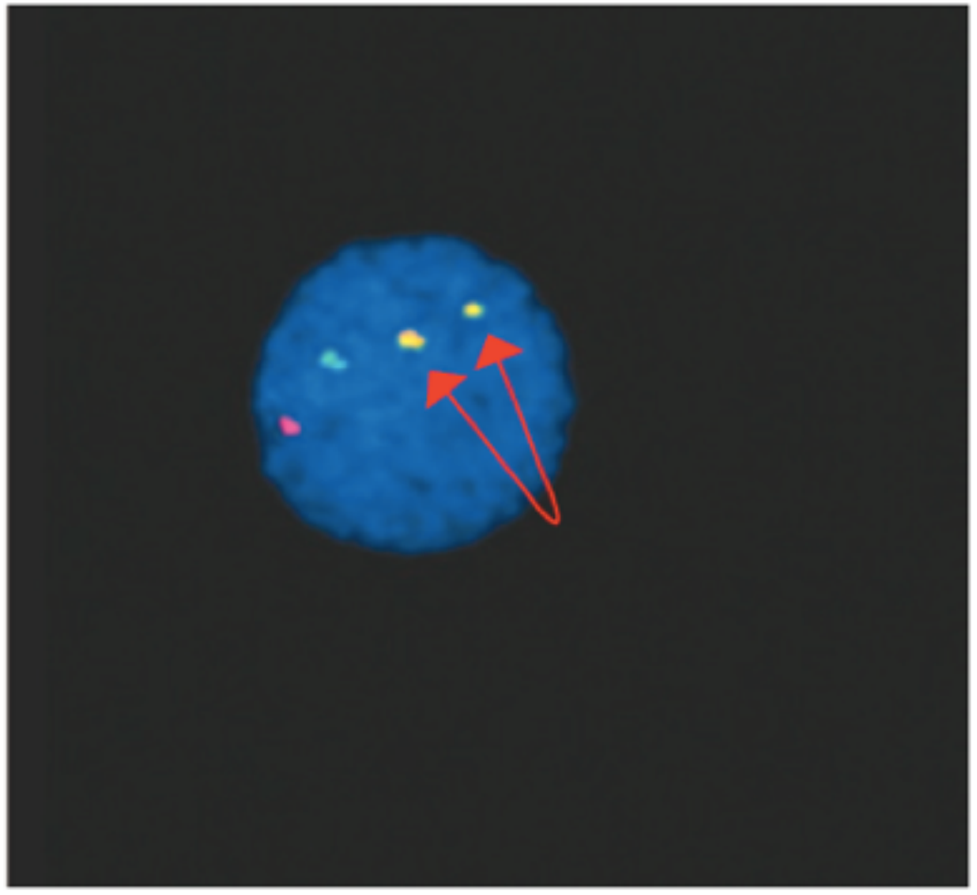
C. Molecular Probes

i. FISH (Fluorescence In Situ Hybridization)

- *Detect the BCR-ABL* fusion gene on chromosome 22
- Qualitative



Normal

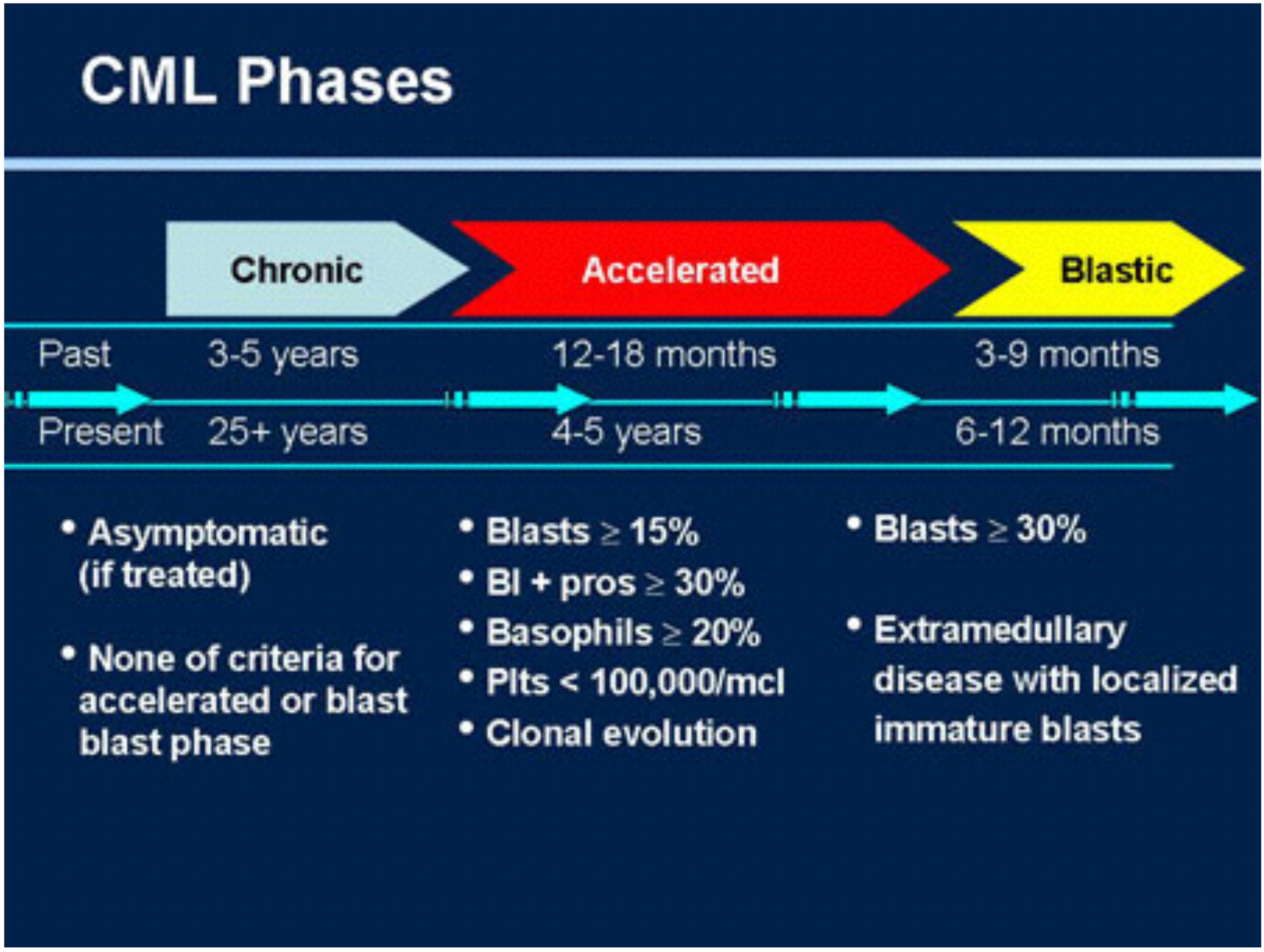


Abnormal

RT-PCR

- Most sensitive test to identify and measure the BCR-ABL gene (Quantitative)
  - Can be performed on blood/marrow cells
  - Amplifies the BCR-ABL derived **abnormal mRNA**
  - One abnormal cell in one million cells can be detected
  - Useful for monitoring

Phases of CML



Treatment overview

- **Initial Cytoreduction Therapy**
  - Hydrea, Anegrilide, allopurinol, Rascburicase, leukapharesis
- **Tyrosine Kinase Inhibitor Therapy**
  - 1st gen - **Imatinib**
  - 2nd gen - Nilotinib, dasatinib, Bosutinib, Ponatinib, Axitinib, Bafetininib
- **Interferon therapy**
  - Older Rx poor CR, Toxic, Pregnancy
- **Chemotherapy**
  - Cytarabine, Busulphan
- **Splenectomy / Splenic irradiation**
- **Other agents - Omacetaxine**
- **Experimental**

  Lonafarnib and tipifarnib , Berbamine, Adaphostin, Third-generation TKIs
- **Allogeneic Stem Cell Transplantation**
- **Treatment of accelerated/blast phases**
  - TKI + Chemo
- **Treatment of CML in pregnancy**
  - Leukostasis - placenta, IFN, TKI - teratogenic, Hydrea - 2/3 Tri
- **Treatment cessation**

arsenic

splenic irradiation

busulphan

hydroxyurea

auto - SCT

Palliative therapy

allo – SCT

interferon – α

imatinib

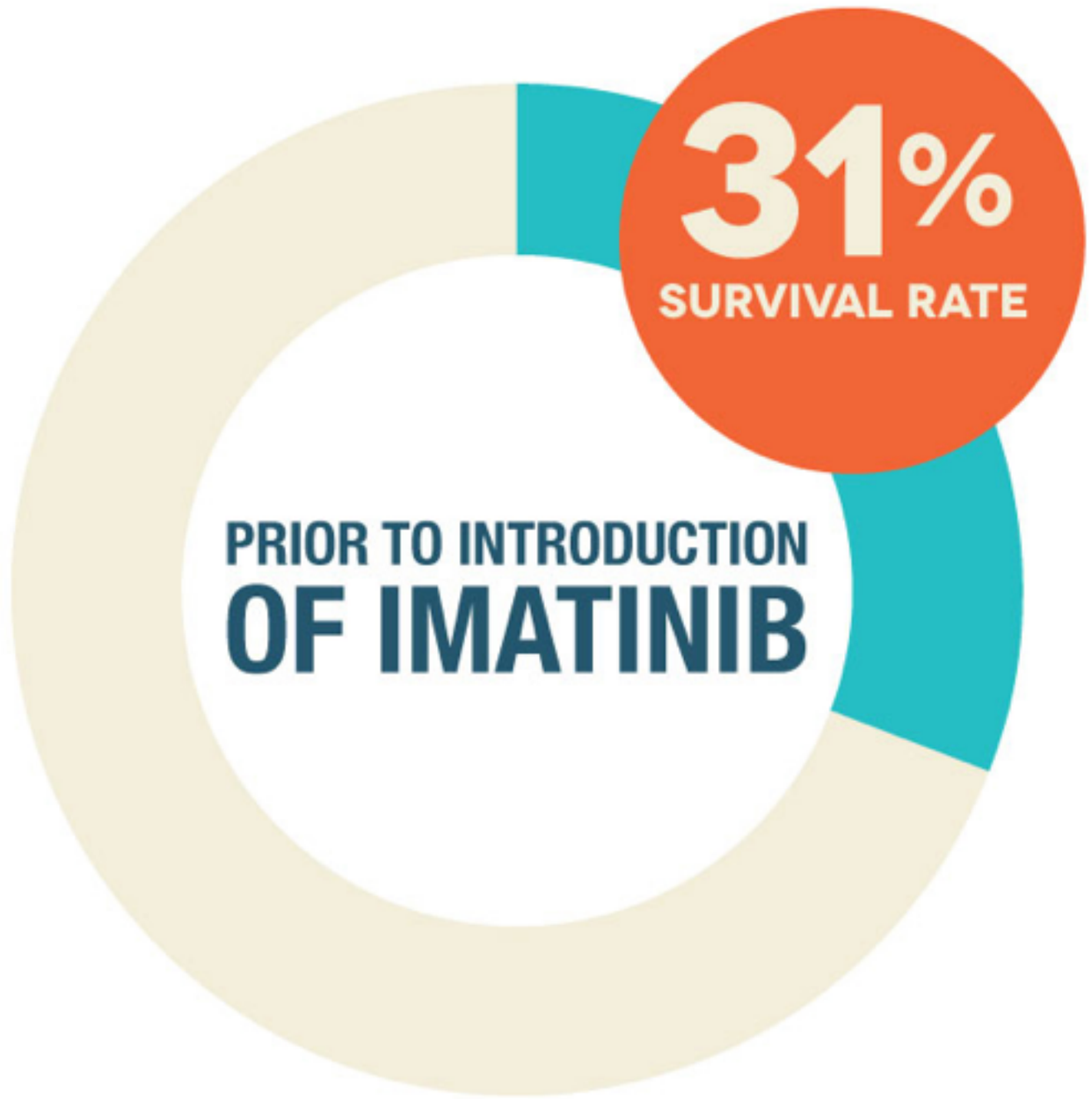
dasatinib

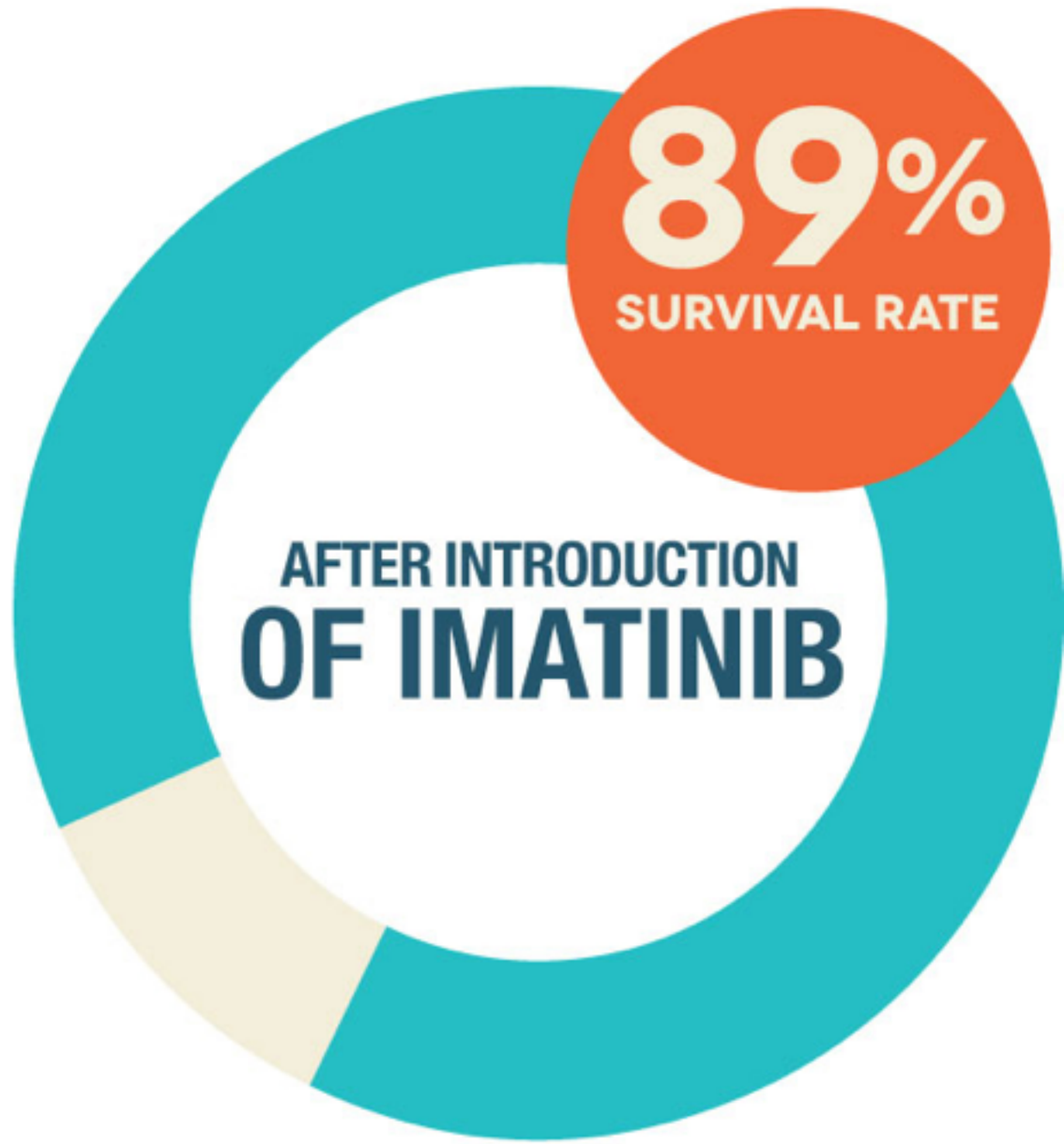
nilotinib

Potentially curative therapy

1850 1900 1950 2000

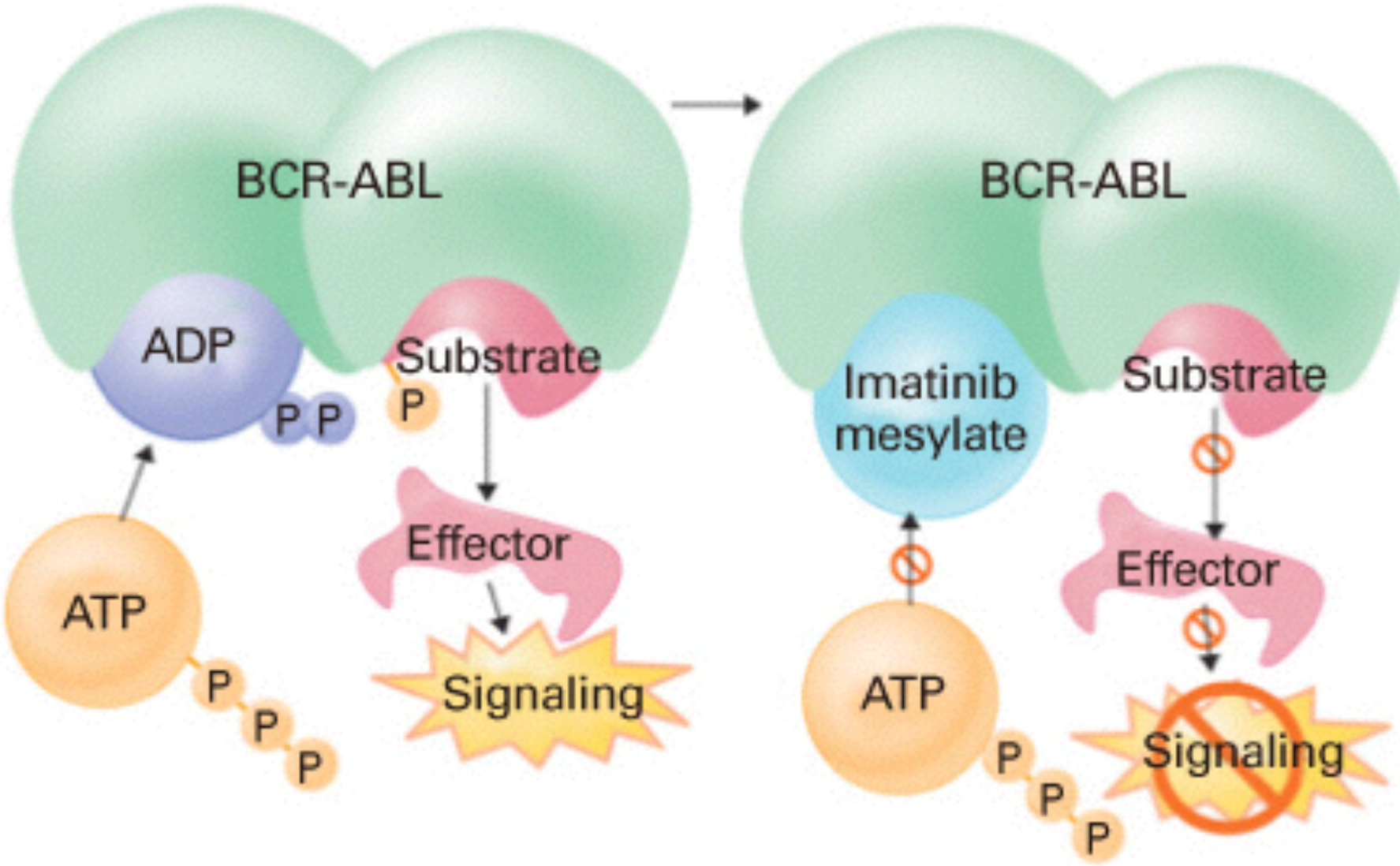
IMATINIB HAS CHANGED LIVES





5-YEAR SURVIVAL RATE FOR CML PATIENTS

How Imatinib works



Imatinib efforts in KENYA

- **GIPAP** - **G**livec **I**nternational **P**atient **A**ssisted **P**rogram
- Began early 2004/5
- The Max foundation/Novartis Pharma
- "Brain child" - **Prof Malkit Riyat, Prof, N. Abinya**
- Ph chromosome - on entry
- Free imatinib (Cost per head per month - **4000 USD)**
- Initially - 10-15 pts/clinic - once a month

GIPAP (1)

- Now close to **700 patient database** from all corners of Kenya & EA (in 2010 only about 100 were registered)
- Runs every fortnight - **The Nairobi Hospital - Anderson Medical Clinic**
- **180 - 200** patients seen per month
- Turnover - **80 Million KES every month**
- Team of doctors has grown
    - Prof. Mwanda, Prof. Kitonyi, Dr. Kiarie, **Myself,** Dr. Sitna, Dr. Matilda, Dr Oyiro & the **“occasional iMed registrar”**
- 79 countries worldwide **(38 Africa)**
- Also caters for patients with GIST - CD117/C-Kit +ve

Chronic myeloid leukaemia in Africa

Yohannie B. Mlombe

Department Of Haematology, College Of Medicine, University Of Malawi

CORRESPONDENCE: Yohannie Mlombe, C/o Division Of Clinical Haematology, Department Of Internal Medicine, Faculty Of Health Sciences, University Of Free State, P.O. box 339(G2), Bloemfontein, South Africa. E-mail: yohanniemlombe@googlemail.com Fax: +27514441036.
Afr J Haematol Oncol 2010;1(1):24-25

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder of granulocytes. According to the latest WHO classification of tumours of the haematopoietic and lymphoid tissues, CML is typically Philadelphia chromosome positive (Ph+) [1]. Ph chromosome negative CML is known as Atypical CML (aCML) and is said to be only 1-2 cases per 100 cases of CML [2]. The role of Ph chromosome in CML poses problems in two areas for CML patients in Africa. The diagnosis of and treatment for CML relies on tests for (cytogenetic analysis, FISH analysis, RT-PCR or Southern blot methods) and drugs targeted at the proteins coded by the Ph chromosome (tyrosine kinase inhibitors). These are costly undertakings. However, all is not lost, thanks to the Glivec International Patient Assistance Programme (GIPAP) which is run by the MAX Foundation and is supported by Novartis, the manufacturers of Glivec (imatinib mesylate/imatinib) or Gleevec (in the USA).

GIPAP (2)

- Before entry - BCR/ABL
    - UNITID, AKUH, NH, & other popular labs in Upperhill area
- BMA - CP, AP, BC
- Personal identification
- Delay to Imatinib Initiation - Resistance **(Dindi Et Al 2010)** & poor survival

GIPAP PHOTO MOMENTS (1)

GIPAP Patients

HENZO KENYA

Home About us Events Get Involved Links Membership Promotional Merchandise Nev

INTERNATIONAL CML DAY 2014

GIPAP PHOTO MOMENTS (2)

Message to Final yr class (Interns to be)

- Quick suspicion
  - **DO NOT OVERTREAT** for typhoid/malaria/brucellosis/sepsis/PUO
  - Dont wait for the **traditional massive splenomegaly** and feel happy about it
- Risk stratify (pre-treated) - **EUTOS SCORE - 7x(Basophil)+4X(Spleen size)**
- Proper disclosure / patient counselling
- BMA + BCR/ABL - need not be done in KNH
  - BMA - is not a consultants' procedure
  - Our Patient Had both BMA + BCR/ABL in one week
- Refer - ready to start Imatinib

“Just incase you forgot”

- CML - needs **early recognition**
- Early treatment - **Better survival**
- You are these patients **first contact**
- Refer **early**
- Imatinib has **changed LIVES**

THE END


MAY 28, 2001
www.time.com AOL Keyword: TIME
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?