PRESIDENTE **Ombretta Fumagalli Carulli**
SEGRETARIO NAZIONALE **Claudio Giustozzi**
Via Otranto, 18 - 00192 Roma
Tel. +39 06 3389120 fax +39 06 30603259
e-mail: segreteria@dossetti.it - http://www.dossetti.it

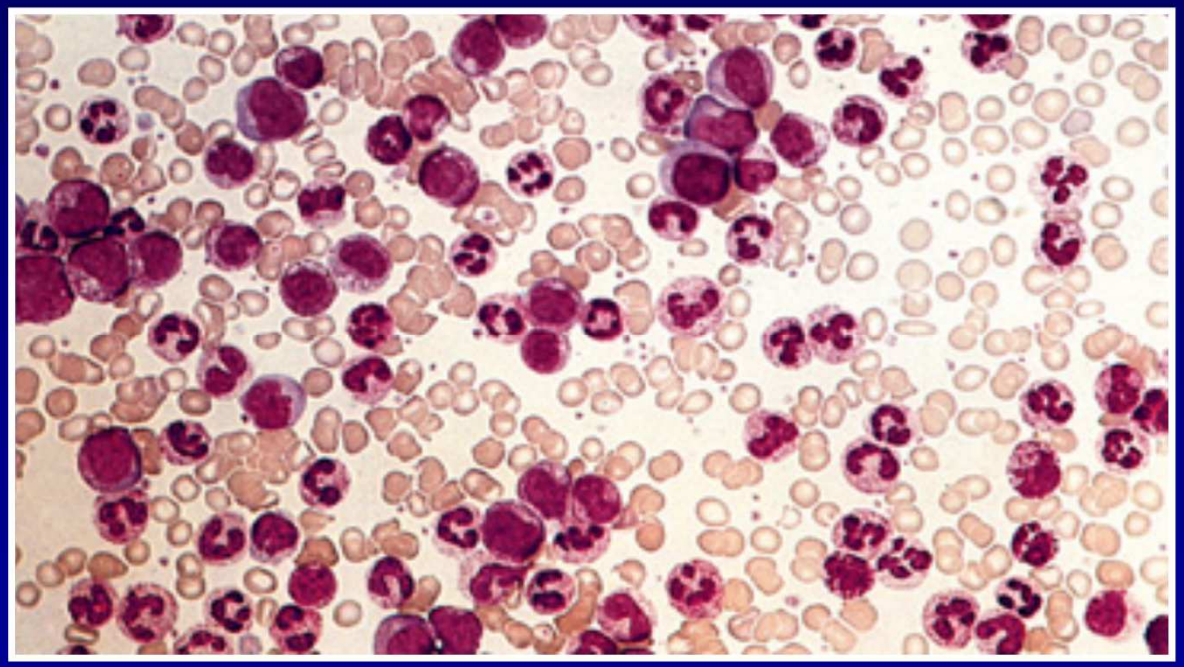
# PATOLOGIE RARE IN ONCOLOGIA

## "TUMORI RARI":

E' POSSIBILE GUARIRE DA UN TUMORE DEL SANGUE CON LA TERAPIA FARMACOLOGICA ORALE:
"IL CASO" DELLA LEUCEMIA MIELOIDE CRONICA

# Chronic Myelogenous Leukemia

- **Rare disease:**
  **1-2 cases per year every 100.000 inhabitants**
- **Typical hematological picture**



- **Association with a specific cytogenetic abnormality:**

**the Philadelphia (Ph)-chromosome**

# CML – Chronic Phase
# Clinical Presentation

Asymptomatic in the majority of cases

Common symptoms at presentation (if present)

- Fatigue
- Abdominal fullness
- Weight loss/anorexia
- Bone pain
- Fever

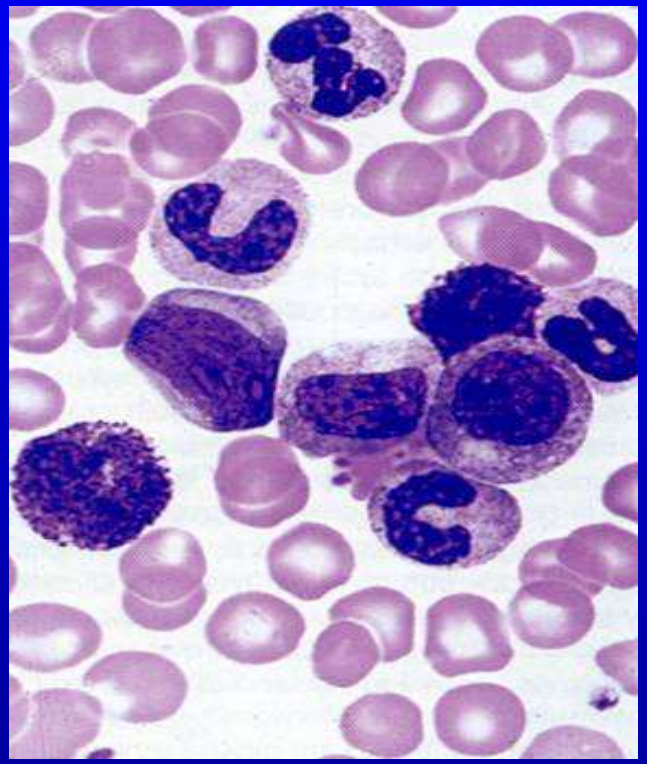
Common signs

- Palpable splenomegaly
- Palpable hepatomegaly

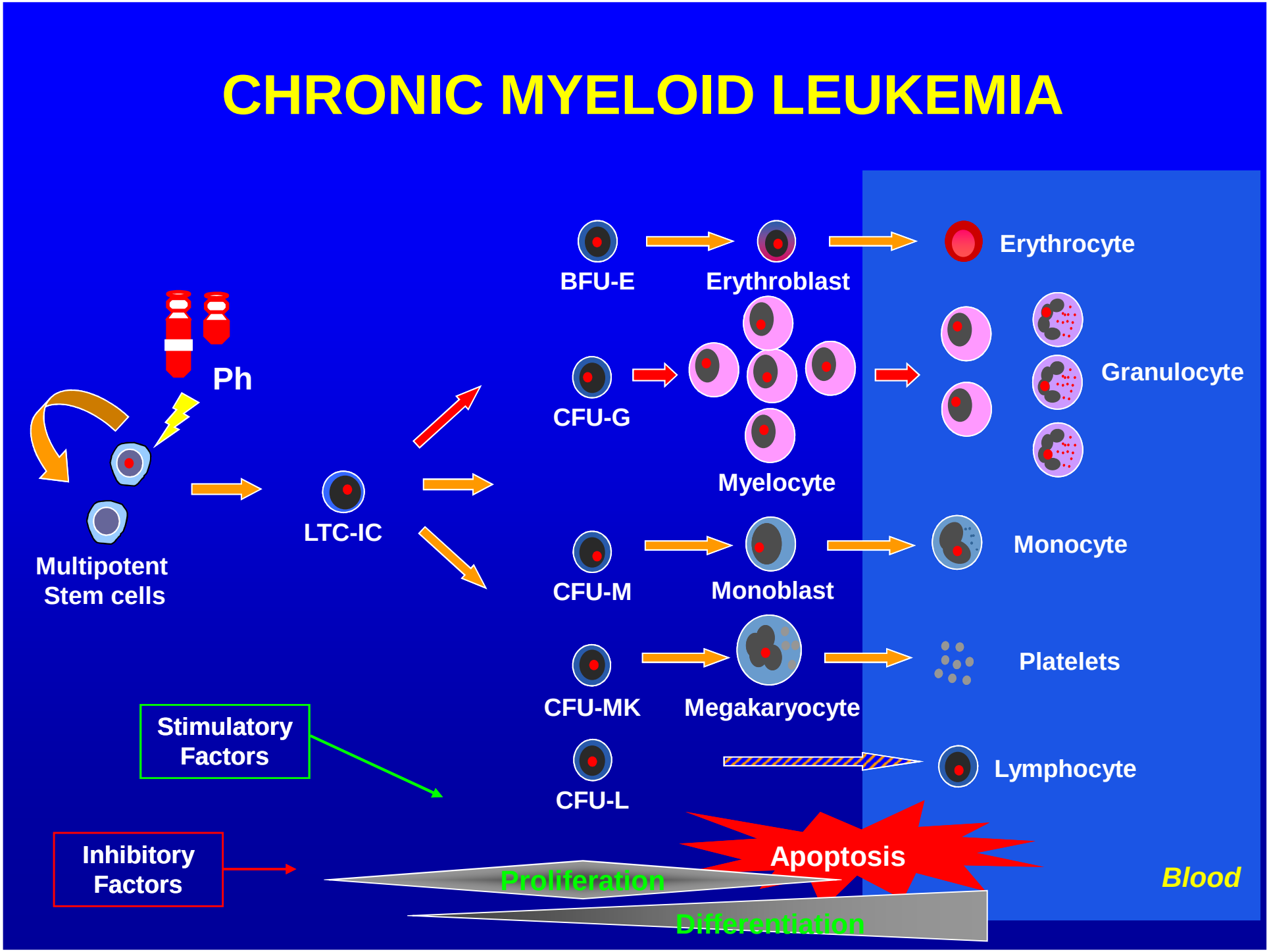
# CML - Chronic Phase

## Common laboratory findings

- Leukocytosis
  - <20.000/mm$^3$ rare
  - 20.000 – 100.000/mm$^3$ 55%
  - >100.000/mm$^3$ 45%
- Abnormal differential (myelocyte peak)
- Platelet count
  - Low 10%
  - Normal 60%
  - High 30%
- Anemia
- Basophilia



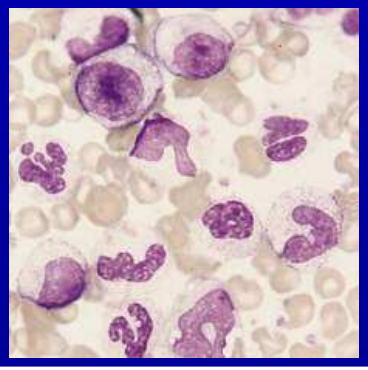
# CHRONIC MYELOID LEUKEMIA

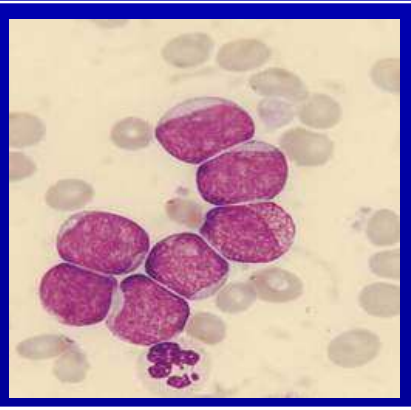


# CML - The natural history of disease

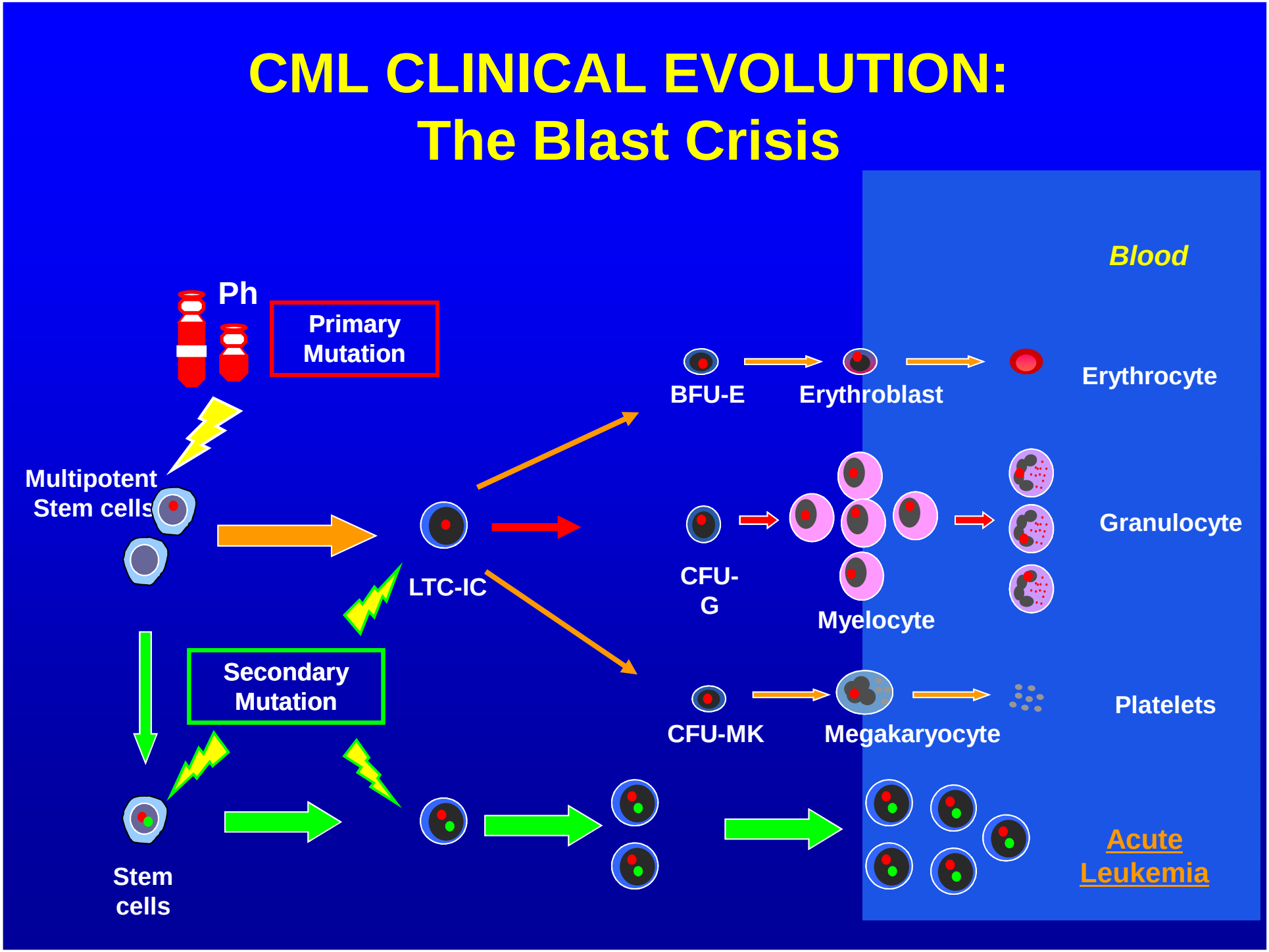
## IFN era (up to 2000)

| Chronic Phase | Advanced Phases | |
|---|---|---|
| | Accelerated Phase | Blast Chrisis |
| Median<br>1-10 years* | Median<br>6–9 months | Median survival<br>3–6 months |



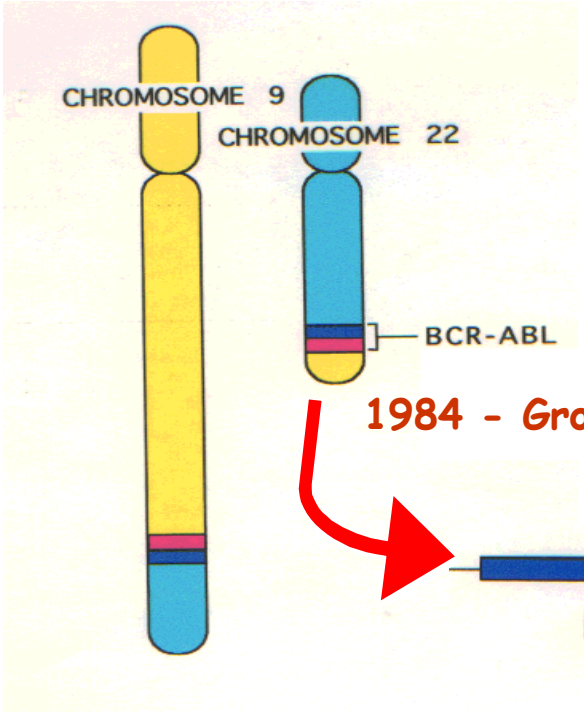


# CML CLINICAL EVOLUTION: The Blast Crisis



# MILESTONES IN MOLECULAR BIOLOGY OF CML

1960 - Nowell P.C. & Hungerford D.A.



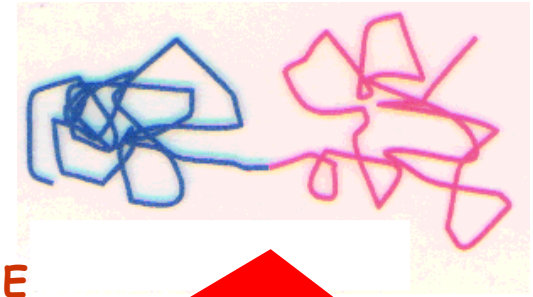

1984 - Groffen J. et al.

1985- Shtivelman E

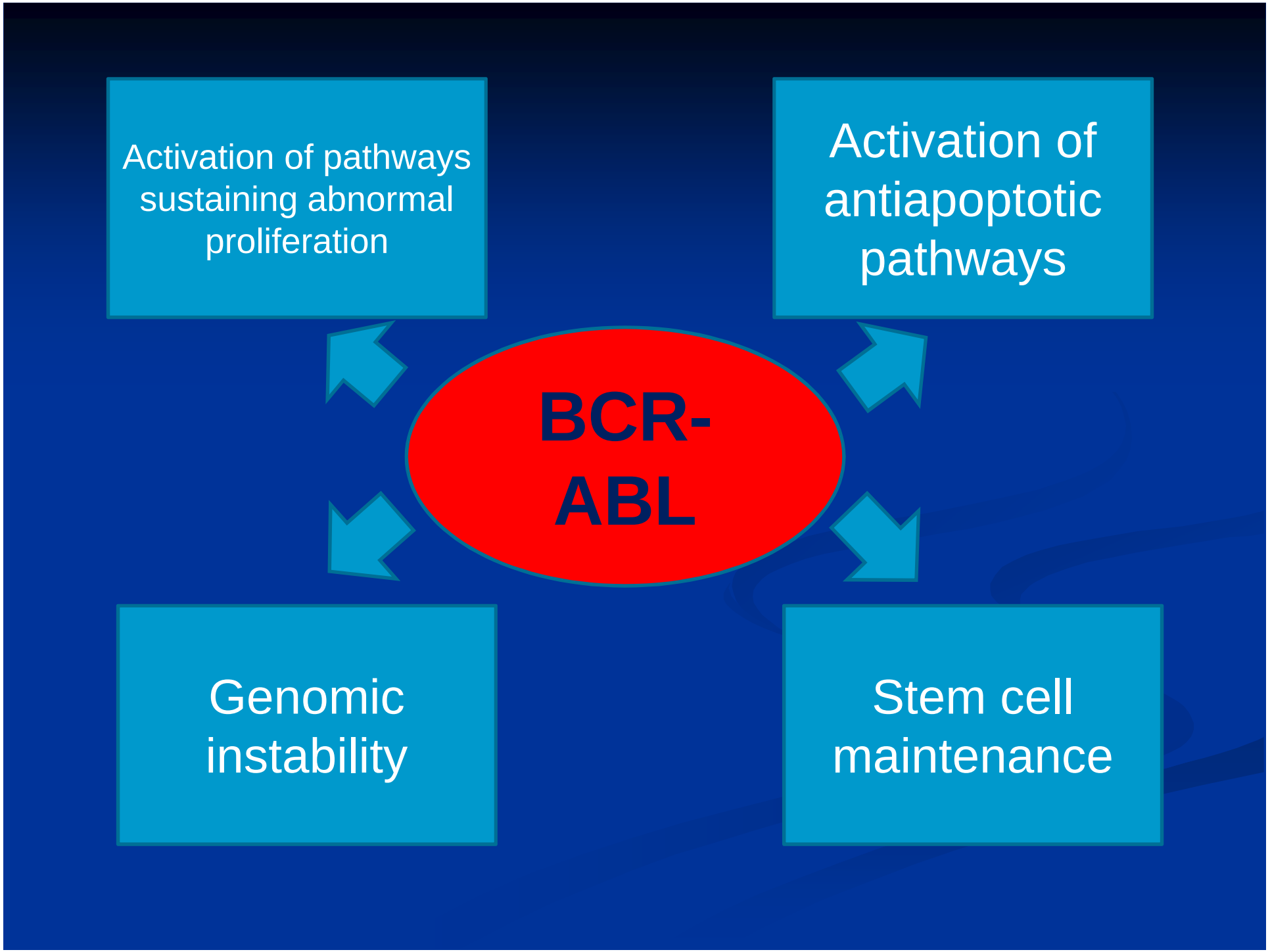



1984 - Konopka J.B. et al.

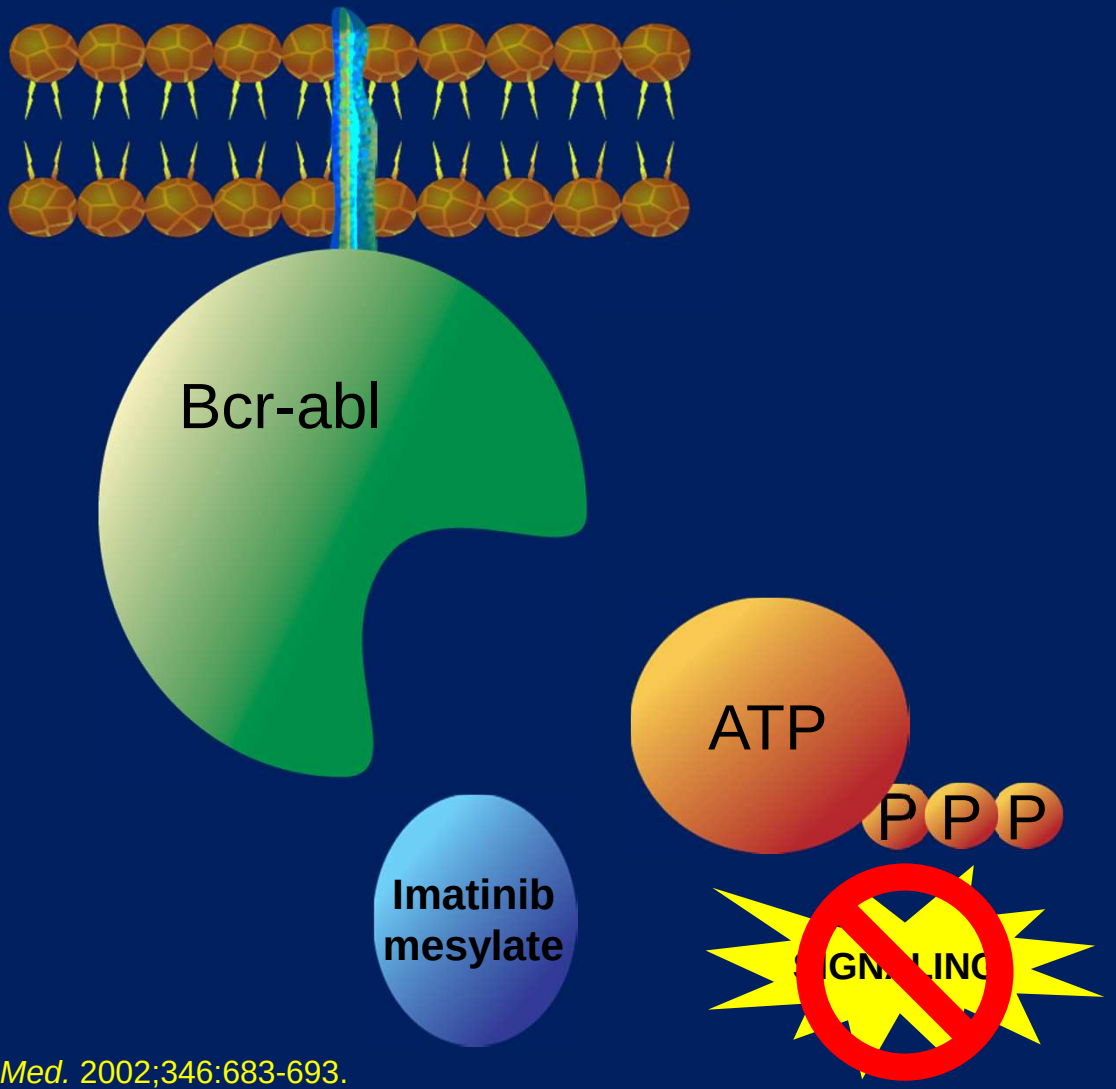
Protein BCR-ABL



Consequence: new BCR-ABL fusion proteins
with a constitutive TK activity


Activation of pathways sustaining abnormal proliferation
Activation of antiapoptotic pathways
BCR-ABL
Genomic instability
Stem cell maintenance

# Imatinib: il meccanismo d'azione su BCR-ABL, causa della malattia

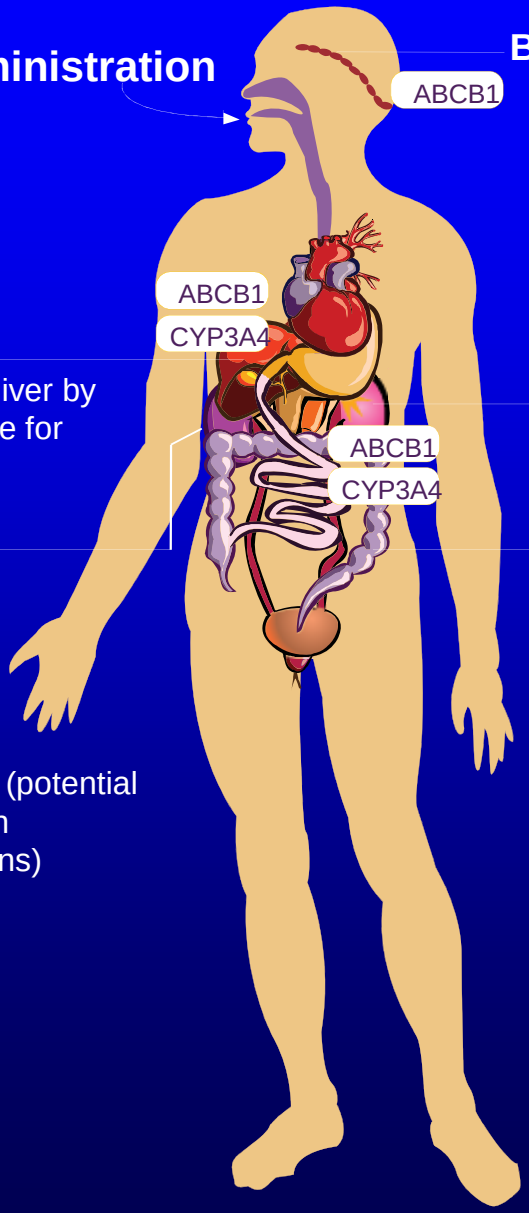



1. Savage DG et al. *N Engl J Med.* 2002;346:683-693.
2. Scheijen B et al. *Oncogene*. 2002;21:3314-3333.

# TKIs Disposition

The life of a drug in the human body is encompassed by ADME

- Absorption (A)
- Distribution (D)
- Metabolism (M)
- Elimination (E)




**Liver**
Metabolism in the liver by CYPs (potential site for drug interactions)

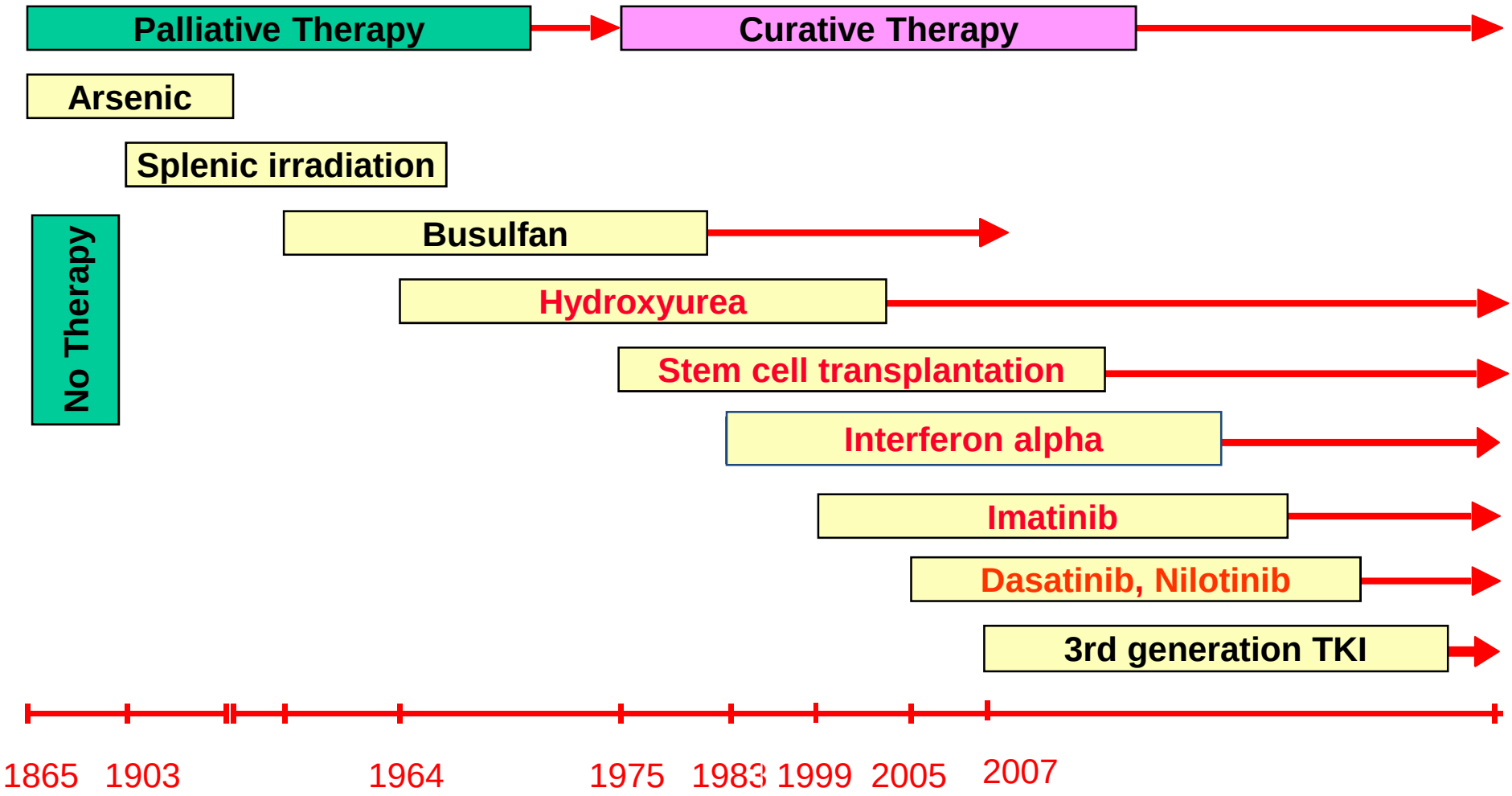
**Stomach**
Absorption in gut depends on the presence or absence of food and on pH

**Intestine**

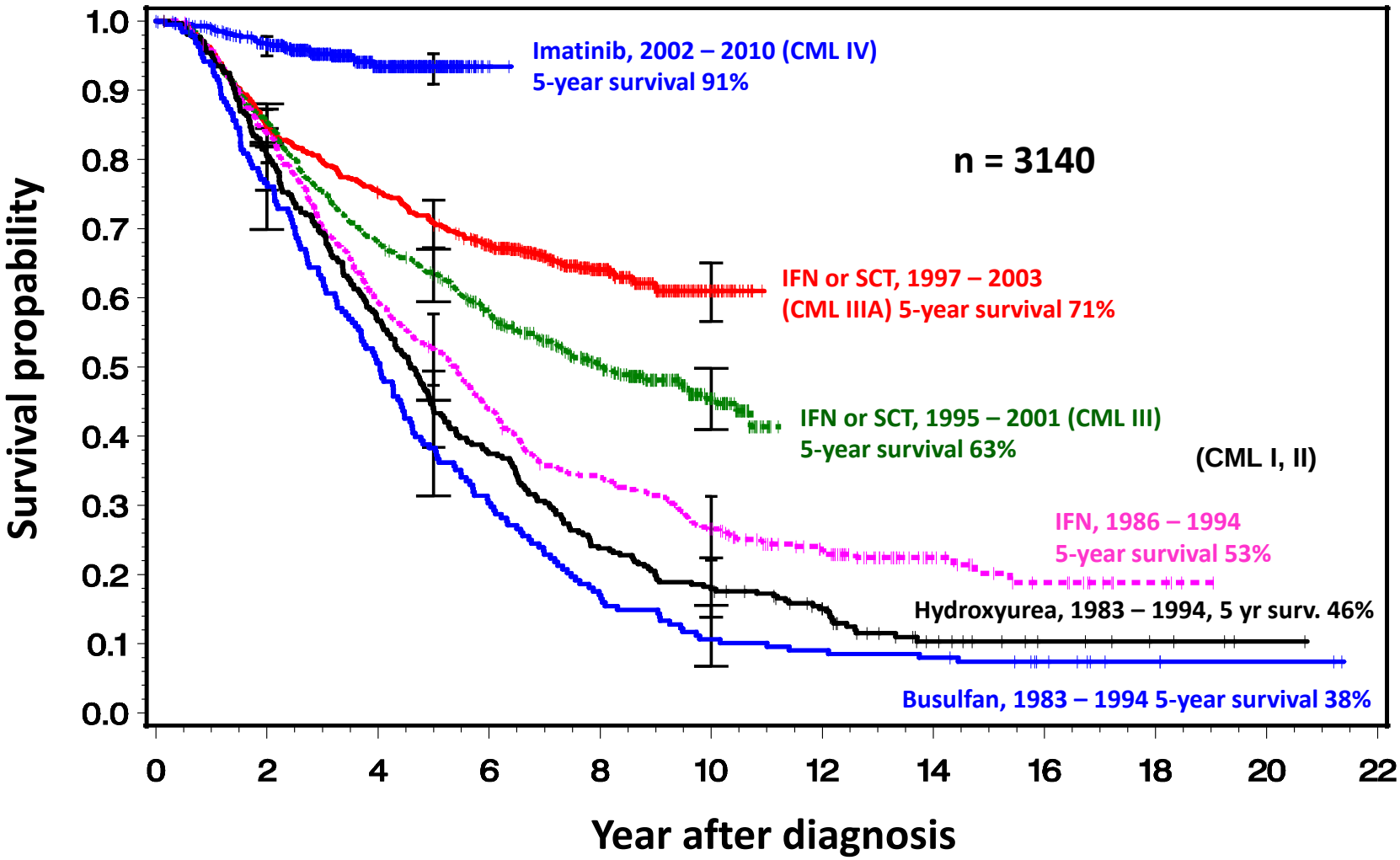
**Kidney**
Excretion in the kidney (potential site for interactions with transporters and proteins)

Scripture CD, et al. *Nat Rev Cancer*. 2006;6:546-558.

# 150 Years of CML Therapy



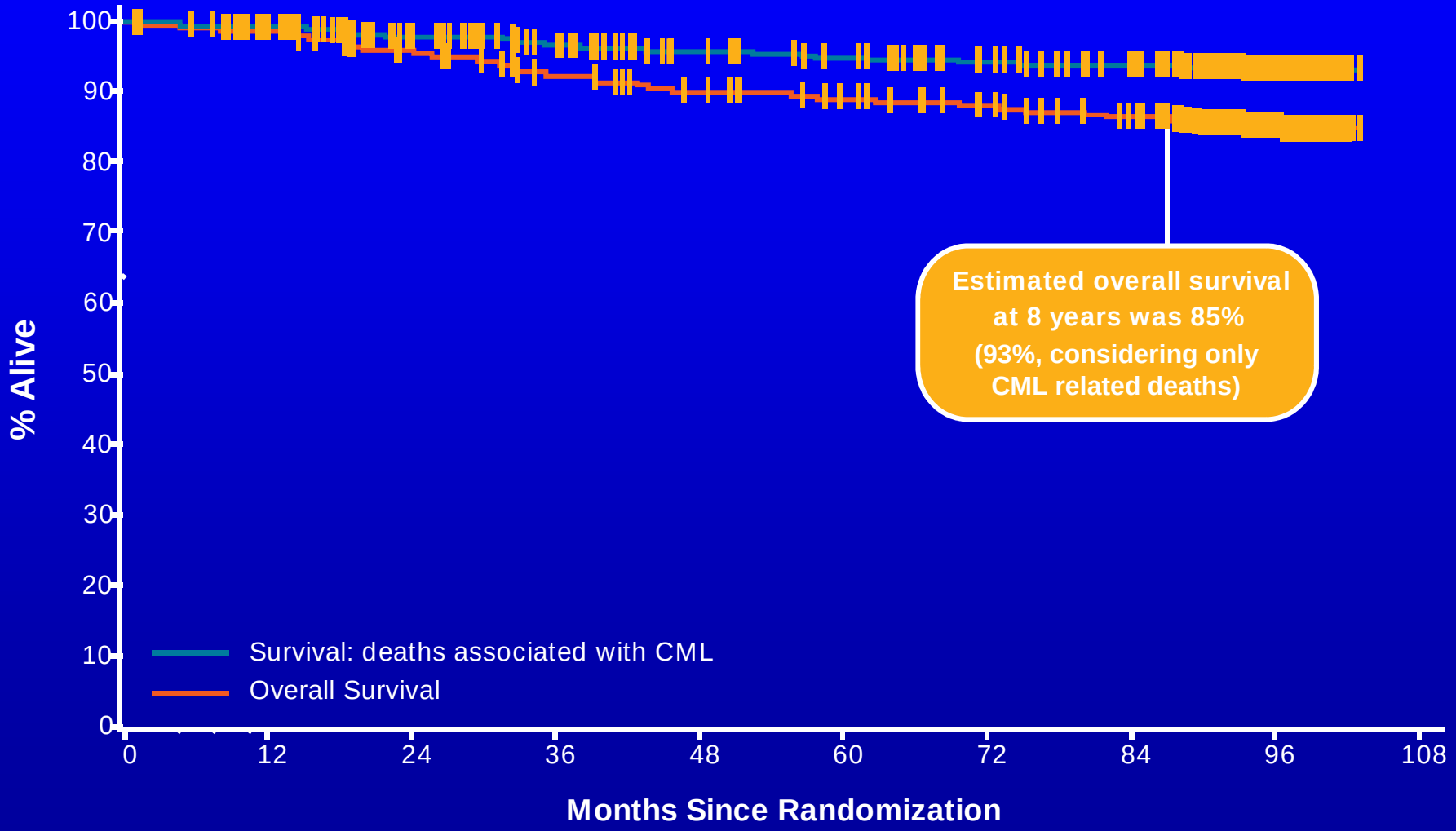
# Improvement of survival of CML 1983 – 2010




German CML Study Group

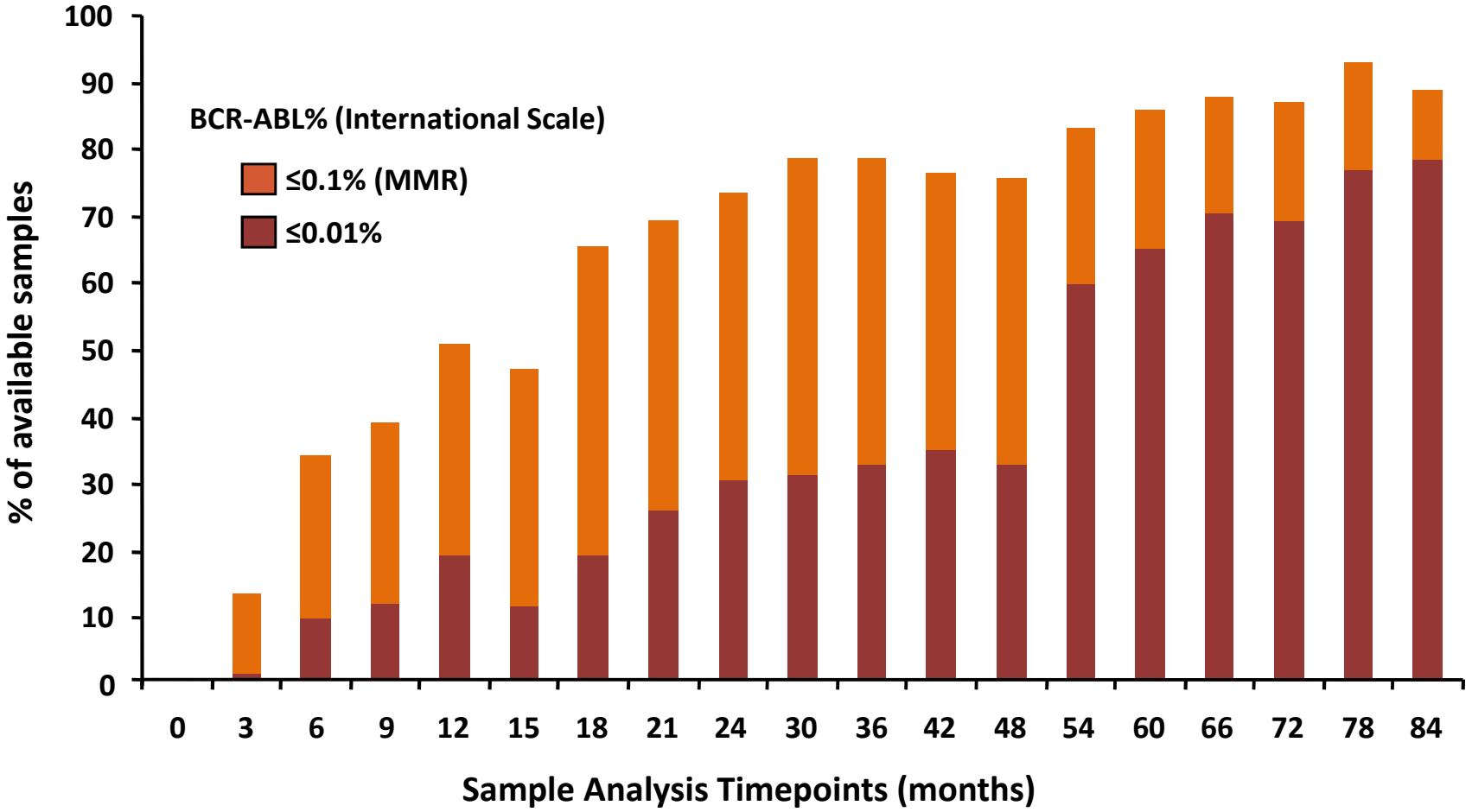
IRIS 8-Year Update

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




Deininger M, et al. *Blood*. 2009;114(22):462. Abstract # 1126.

# IRIS – Molecular Response Rates



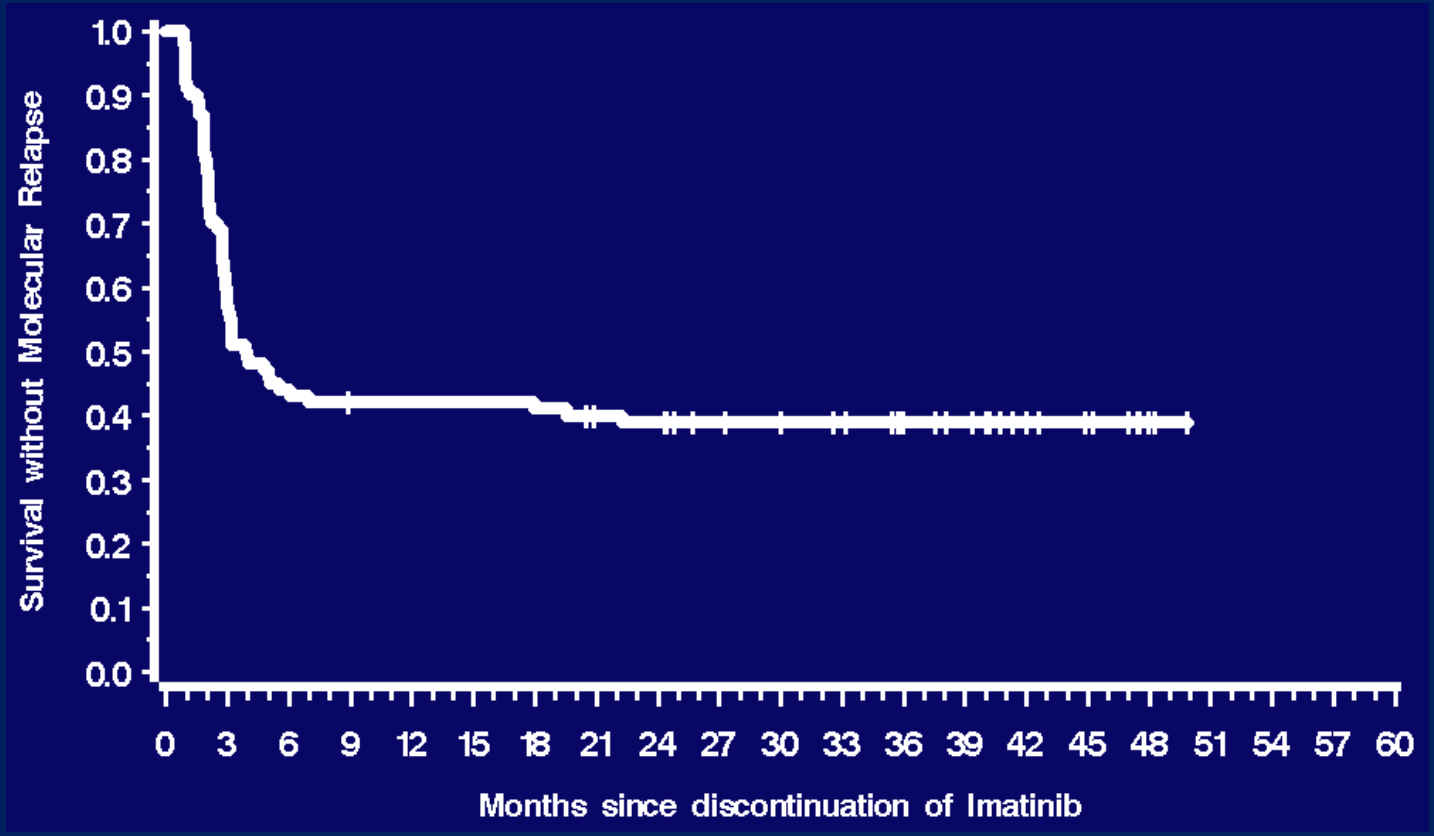

- Major molecular response (MMR) and the depth of molecular response increase over time

Hughes et al. Blood (ASH Annual Meeting Abstracts) 2008; 112: Abstract 334.

# Discontinuation Appears Feasible for Some Patients with CMR on TKI Therapy

## Kaplan-Meier Estimates of CMR after Discontinuation of Imatinib

The overall probability of maintenance of CMR at 24 and 36 months was 39% (95% CI 29-48).




*Molecular relapse occurred in 61 pts with 58 relapses occurring during the first 7 months 3 late relapses at month 19, 20 and 22, respectively*

Mahon FX, et al. ***Blood.*** **2011;118:[abstract 603]**

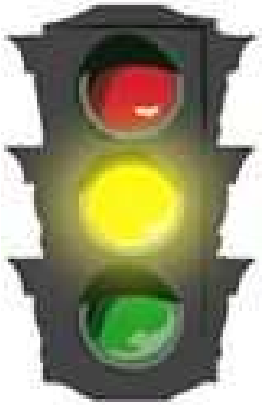
# La terapia con imatinib, i punti deboli:

- **il 18% dei pazienti non raggiunge una risposta soddisfacente (citogenetica completa)**

- **8% dei pazienti che ha raggiunto la risposta citogenetica completa la perde successivamente**

- **20-25% dei pazienti sviluppa resistenza (mutazioni, evoluzione clonale...)**

- **11% dei pazienti interrompe il trattamento per intolleranza**



**per cui imatinib non è sufficiente a garantire le risposte.**

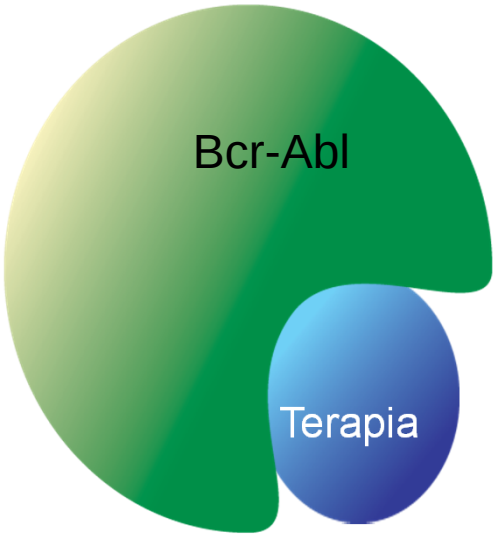
Deininger et al. Blood 2009, 114:126a

# 2013 TKIs approved for CML treatment

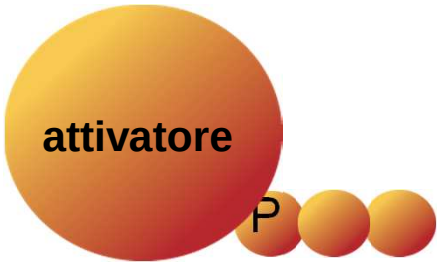
| | Date of FDA approval | |
|---|---|---|
| | 1st | 2nd |
| **Imatinib** | 2002 | 2001 |
| **Dasatinib** | 2010 | 2006 |
| **Nilotinib** | 2010 | 2007 |
| **Bosutinib** | | 2012 |
| **Ponatinib** | | 2013 |

# Imatinib: il problema della resistenza al trattamento (II)

In caso di resistenza la struttura della proteina Bcr-Abl subisce una modifica

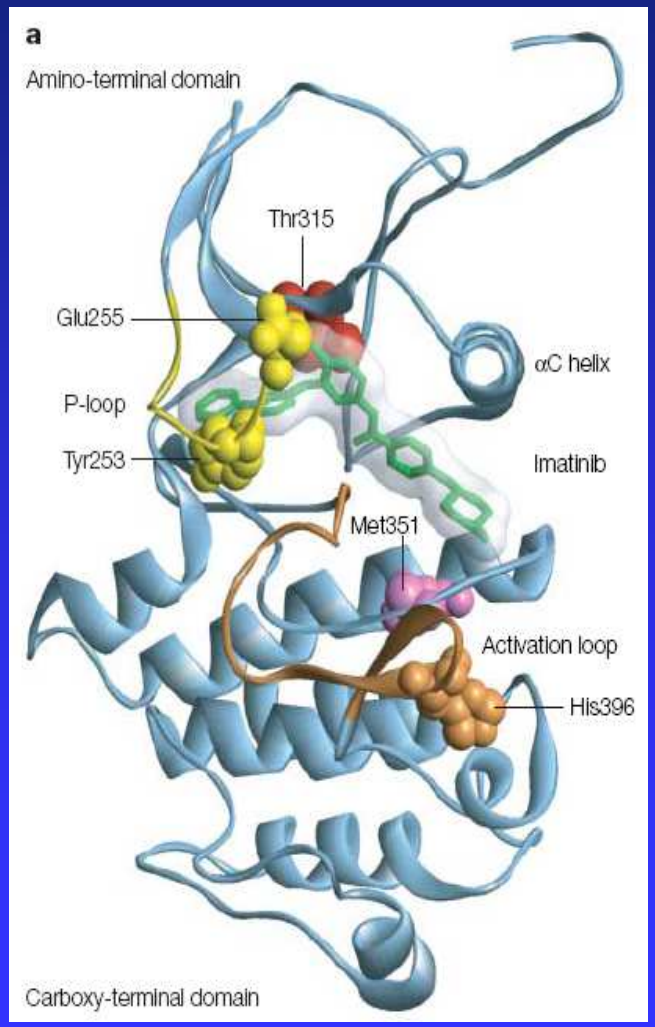


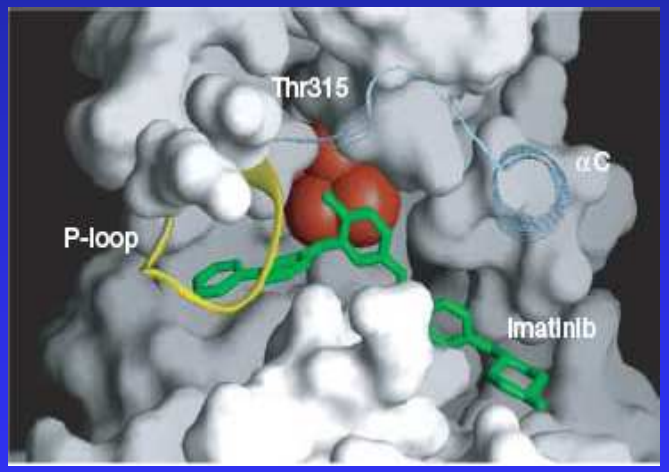

Il farmaco non riesce più a legarsi




**L'attivatore si lega e attiva la cellula malata**

# Imatinib interaction to the gate-closed BCR/ABL conformation



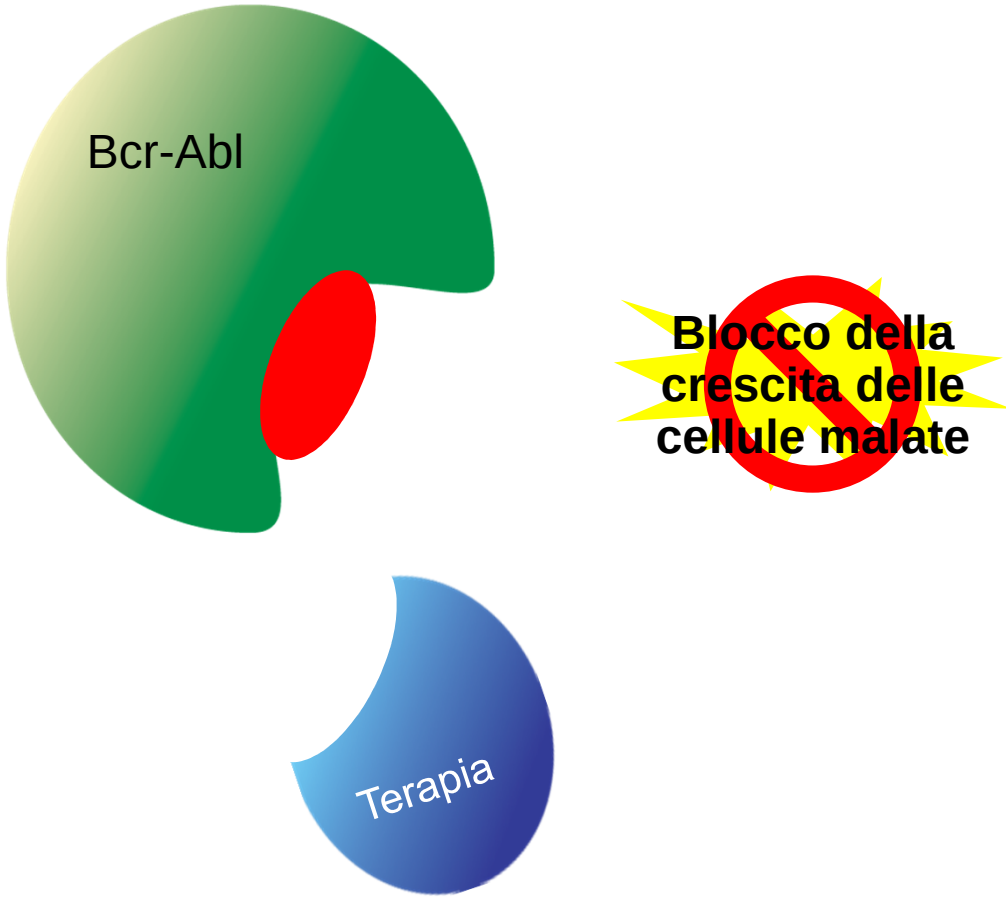



# TKI II e III generazione: il meccanismo d'azione

Nonostante la proteina Bcr-Abl sia modificata

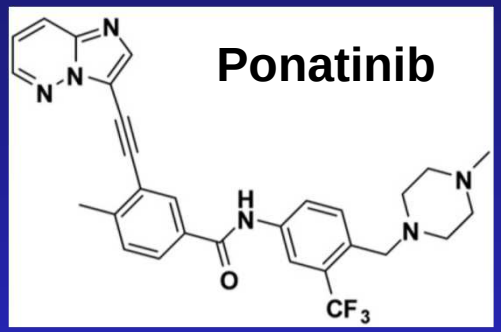
↓

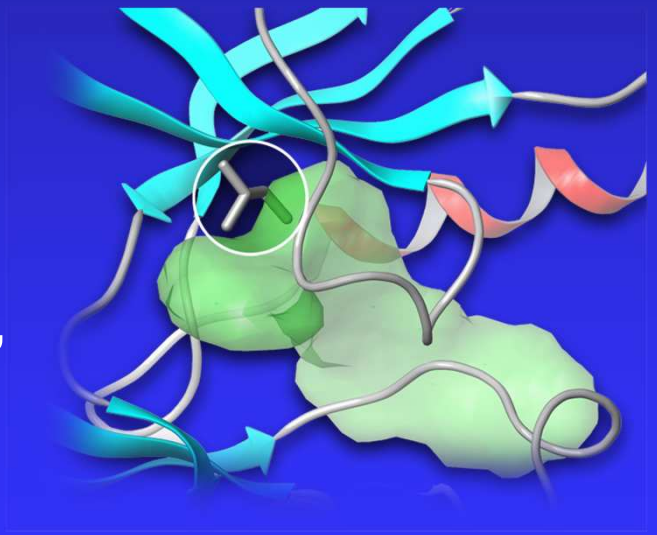
Il TKI di II e III generazione riesce a legarsi



# Ponatinib: A Pan-BCR-ABL Inhibitor

- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
  - Binds inactive (closed) ABL conformation
- Broad spectrum of activity against an array of BCR-ABL variants
- Multi-targeted kinase inhibitor
  - Tyrosine kinases, including VEGF, FGF, and PDGF receptors, c-KIT and SRC kinase, FLT3
- Once-daily oral activity in murine models



Ponatinib cocrystal structure with $ABL^{T315I}$

*O'Hare T, et al. Cancer Cell. 2009;16:401-412.*

# Treatment of CML: Perspectives

| | Historical (…. – 1999) | Modern (2000 –2010) | Future (2010-…..) |
|---|---|---|---|
| Course | Fatal | Indolent | Cure |
| Prognosis | Poor | Good | Excellent |
| Median survival (yrs) | 3-6 | 25+ (est.) | Norm. Life span |
| Front line therapy | AlloSCT, IFNα | Imatinib | Better TKIs |
| Second line therapy | Chemotherapy AlloSCT | new TKIs, AlloSCT | |

# Cure

- Absence of any signs and symptoms of the disease,
- no therapy required

## Operational Cure

- Absence of symptoms, no therapy required,
- residual signs of the disease