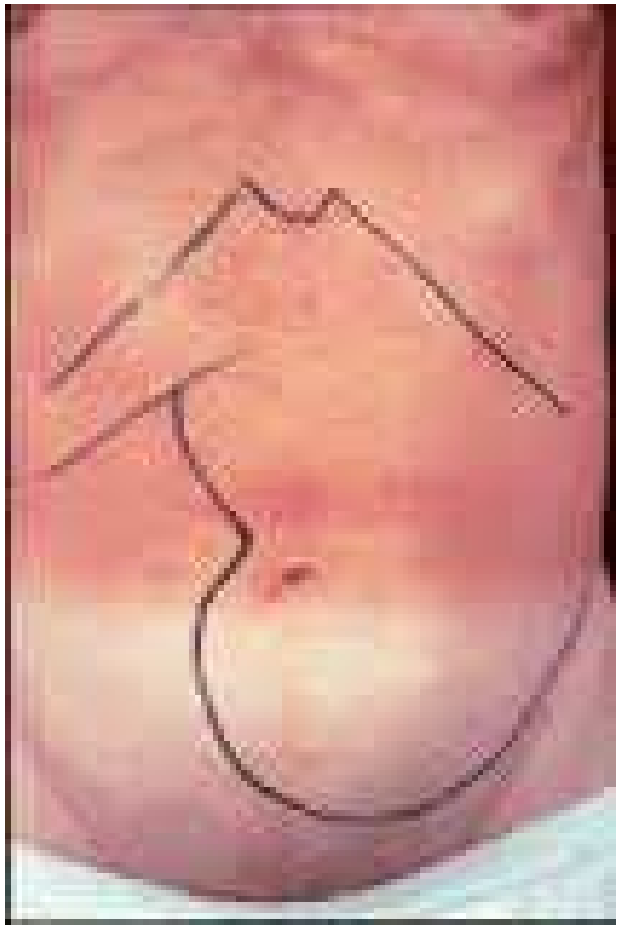
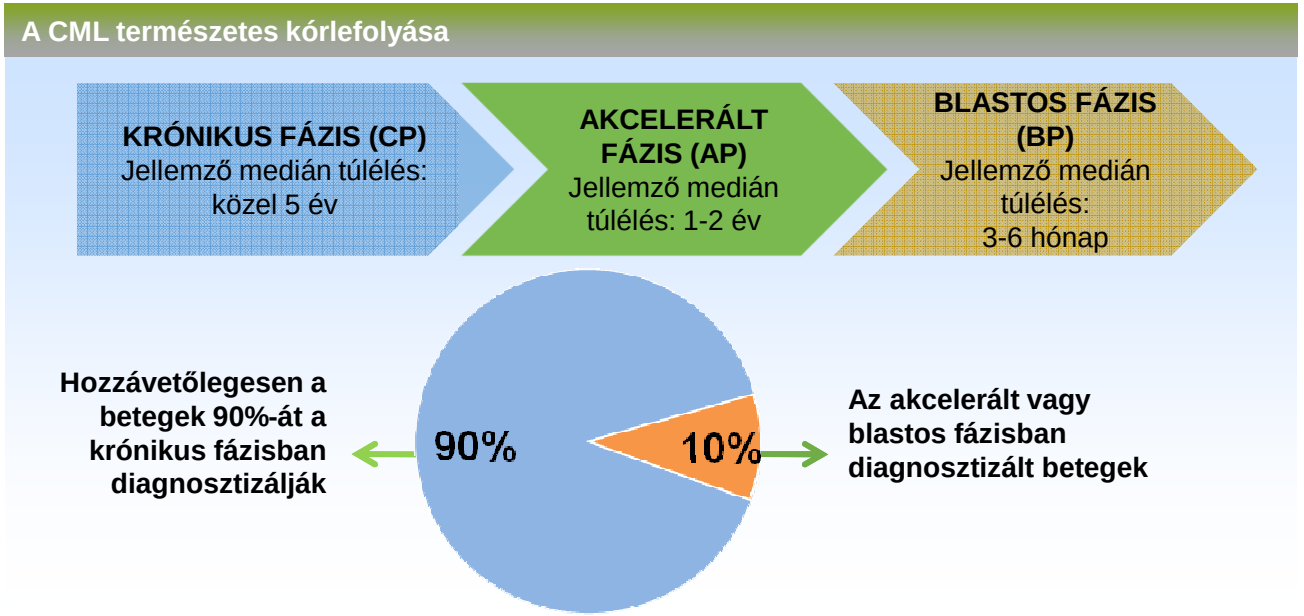
CML

CML clinical presentation

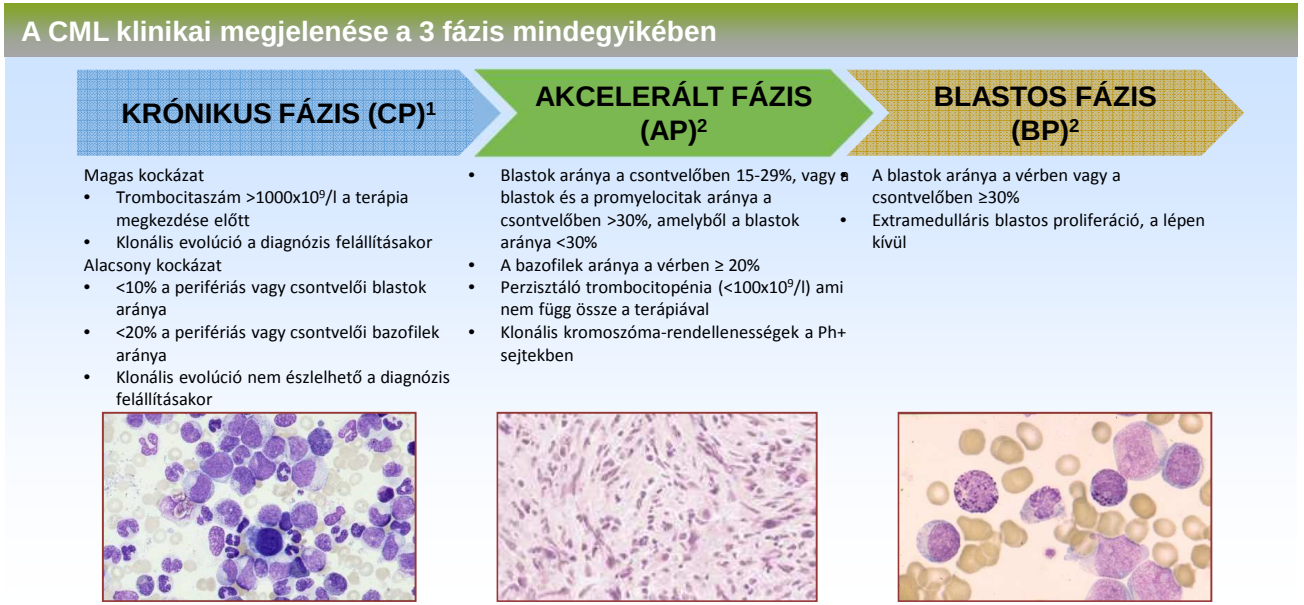


Natural course of CML without TKI therapy



1. Cortes JE, *et al.* Staging of chronic mieloid leukemia in the imatinib era: an evaluation of the World Health Organization proposal. *Cancer*. 2006;106(6):1306-15.

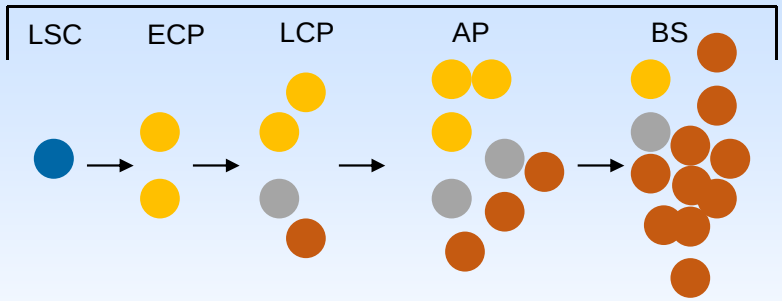
Natural course of CML – lab tests – without TKI therapy



1. Cortes JE, *et al.* Staging of chronic myeloid leukemia in the imatinib era: an evaluation of the World Health Organization proposal. *Cancer*. 2006;106(6):1306-15; 2. Baccarani M, *et al.* European LeukemiaNet recommendations for the management of chronic mieloid leukemia: 2013. *Blood. 2013;*122(6):872-84.

Natural course of CML without TKI therapy[1]

A CML természetes kórlefolyása



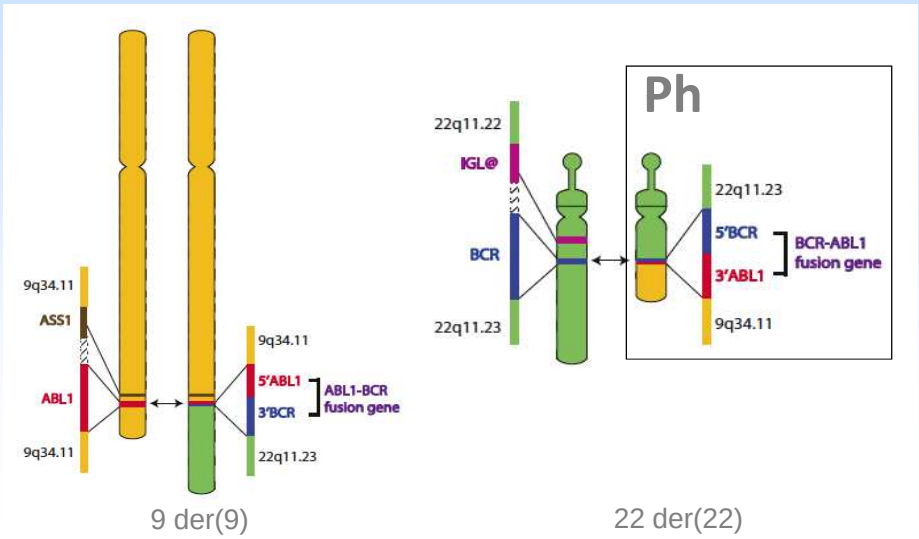
LSC= CML leukaemiás őssejt
ECP= korai, krónikus fázis, amely érzékeny a TK-ra
LCP= késői krónikus fázis potenciális TKI rezisztencia progressziós potenciál
AP= akcelerált fázis
BC= blasztos krízis

- A CML-es leukaemiás őssejt (kék) regenerálódik, de emeli a leukémiás progenitorok mennyiségét. A betegség korai szakaszában valószínűleg a legtöbbjük érzékeny a TKI-re
- Az idő múlásával és az ellenhatás nélküli BCR-ABL aktivitás következtében mutációkkal és/vagy a progresszió genetikai jellemzőivel rendelkező sejtek képződnek
- Az utóbbi végül nagyobb proliferációs előnnyel rendelkezik, és a betegség a blastos krízis fázisba progrediál

1. Radich JP. Chronic mieloid leukemia 2010: Where are we now and where can we go? American Society of Hematology. *Hematology.* 2010:122-8.

Philadelphia chromosome (Ph)[1]

A Philadelphia kromoszóma (Ph)

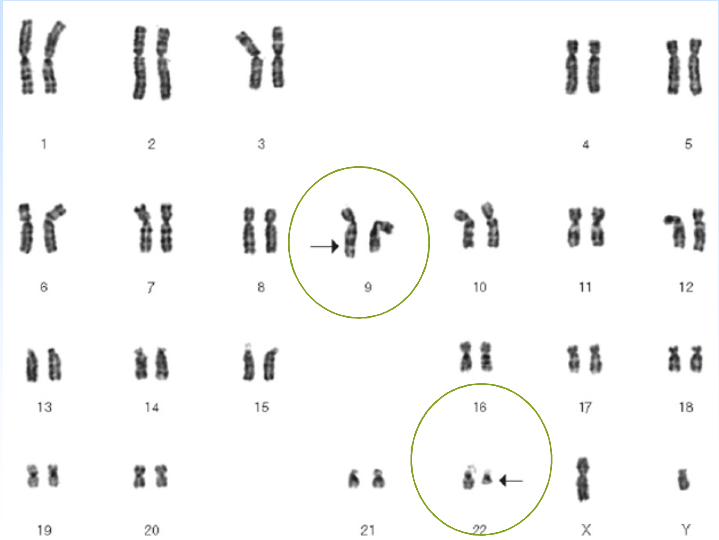


A BCR és ABL1 gének törésének és rekombináció révén a t(9;22)(q34;q11) kialakulásának következményeit sematizáltan szemléltetjük.
A normális 9-es és 22-es kromoszómák a bal, míg a származék kromoszómák minden kromoszómapár esetében a jobb oldalon láthatók.
A duplafejű nyilak jelölik a törések helyét.[1]

1. Morris CM. Chronic mieloid leukemia: cytogenetic methods and applications for diagnosis and treatment. In: Campbell LJ, ed. *Cancer Cytogenetics: Methods and Protocols, Methods in Molecular Biology*, vol. 730. Springer Science+Business, LLC;2011:33-61.

Cytogenetic marker of CML: Philadelphia chromosome (Ph)

A Philadelphia kromoszóma (Ph)



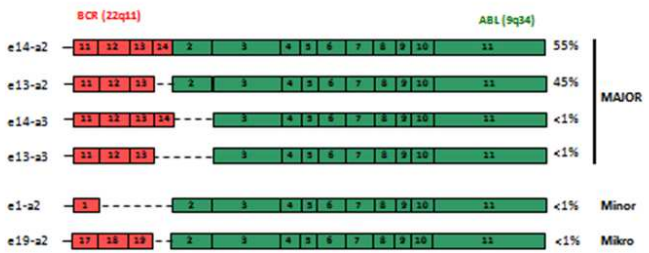
A Ph kromoszóma, ami nem más, mint egy rövidebb 22-es kromoszóma, a 9-es és 22-es kromoszómák hosszú karjai között létrejött reciprok transzlokáció t(9:22)(q34;q11) eredménye [1]

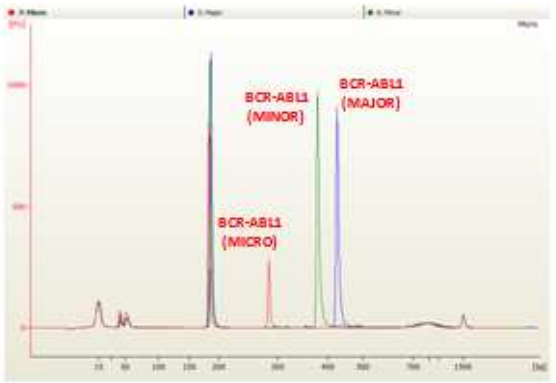
Leukaemiás csontvelői metafázis sejt reprezentatív G-sávozású karyotípusa, ami t(9;22)(q34;q11)-őt mutat.2
A nyilak jelölik a 22-es kromoszóma megrövidült (Ph, 22q- vagy der(22)), illetve a 9-es kromoszóma meghosszabbodott (9q+ vagy der(9)) származékát.[2]

A KÉP CSAK ILLUSZTRÁCIÓKÉNT SZOLGÁL

1. Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. *Blood*. 2008;112(13):4808-17;
2. Morris CM. Chronic mieloid leukemia: cytogenetic methods and applications for diagnosis and treatment. In: Campbell LJ, ed. *Cancer Cytogenetics: Methods and Protocols, Methods in Molecular Biology,* vol. 730. Springer Science+Business, LLC;2011:33-61.

Bcr/abl translocations





CML pathophisiology

- **Translocation on chromosome**
- **DNS**
- **mRNS**
- **Protein**
- **DISEASE**

- Philadelphia chromosome t(9,22)
- BCR-ABL fusion gene on 22 chromosome, ABL-BCR reciprok fusion gene on 9 chomosome
- e13a3 or e14a2 fusion transcript
- Bcr-abl fusion protein (inhibits apoptosis, increase mitotic activity, inhibit cell adhesion, genetic instability, onkogen, constitutionally actice tirozinkinase: ***selection advantage***
- CML: granulopoetic hyperplasia, bi/triphasic disease, progressive, transformation to AML

Treatment I.

- **1850**: arsen
- **1900**: spleen irradiation
- **1950**: mustarnitrogen, busulphan, hydroxiurea
- **1970**: allogenic Tx, interferon-α

Treatment II.

„TKI era”

- 2001: imatinib (Glivec®)
- 2007: dasatinib (Sprycel®)
- 2009: nilotinib (Tasigna®)
- 2012: bosutinib (Bosulif®), ponatinib (Iclusig®)

History I.

- **1846** Rudolph Virchow – Weißes Blut

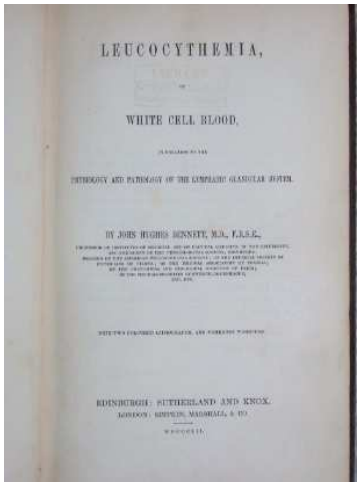
Weißes Blut.

Außer sehr wenig rothen Blutkörperchen bestand der ungleich größere Theil aus denselben farblosen oder weißen Körpern, die auch im normalen Blut vorkommen, nämlich kleinen, nicht ganz regelmäßigen Protoplasmazellen, größeren, körnigen, fetthaltigen, kernlosen Körperchen und granulirten Zellen mit einem rundlichen, hufeisenförmigen oder kleeblattartigen oder mit mehreren maulförmigen, distanten Kernen. Die größeren dieser Zellen hatten ein leicht gelbliches Aussehen. Das Verhältniß zwischen den farbigen und farblosen Blutkörperchen stellte sich hier ungefähr umgekehrt, wie im normalen Blut, indem die farblosen die Regel, die farbigen eine Art von Ausnahme zu bilden schienen. Wenn ich daher von weißem Blute spreche, so meine ich in der That ein Blut, in welchem die Proportion zwischen den rothen und farblosen (in Masse weißen) Blutkörperchen eine umgekehrte ist, ohne daß eine Beimischung fremdartiger chemischer oder morphologischer Elemente zu bemerken wäre.

Ich würde mich glücklich schätzen, der Wissenschaft dadurch zu einer neuen und, wie es mir scheint, nicht unwichtigen Thatsache verholfen zu haben. —

Dr. Virchow.

- **1852** John Hughes Bennett – Leucocythemia, white cell blood



LEUCOCYTHEMIA,

WHITE CELL BLOOD,

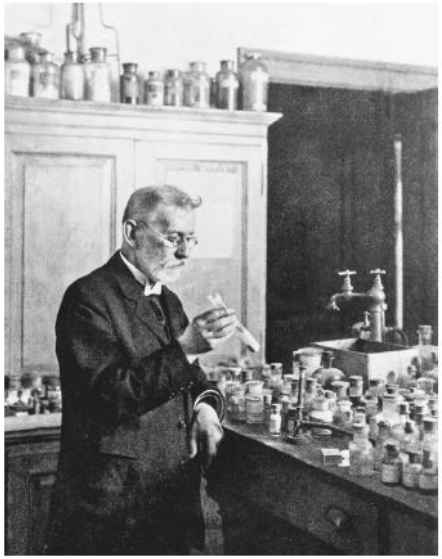
PATHOLOGY AND PATHOLOGY OF THE LYMPHATIC GLANDULAR SYSTEM.

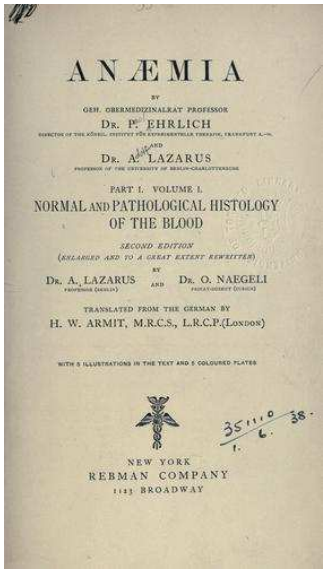
BY JOHN HUGHES BENNETT, M.D., F.R.S.E.,

EDINBURGH: SUTHERLAND AND KNOX.

History II.

- **1880** Paul Ehrlich – chronic myeloid leukaemia





ANÆMIA

BY

GEH. OBERMEDIZINALRAT PROFESSOR

DR. P. EHRLICH

AND

DR. A. LAZARUS

PART I. VOLUME I.

NORMAL AND PATHOLOGICAL HISTOLOGY OF THE BLOOD

SECOND EDITION

(ENLARGED AND TO A GREAT EXTENT REWRITTEN)

BY

DR. A. LAZARUS AND DR. O. NAEGELI

TRANSLATED FROM THE GERMAN BY

H. W. ARMIT, M.R.C.S., L.R.C.P.(LONDON)

WITH 5 ILLUSTRATIONS IN THE TEXT AND 5 COLOURED PLATES

NEW YORK

REBMAN COMPANY

1123 BROADWAY

- **~ 1925** Definition of the disease (3 stages, first granulopoetic hyperplasia, unmatured forms in the peripheral blood, hepato-splenomegaly, accelerated phase then transformation to acute leukaemia, death within 4-5 years)

History III.

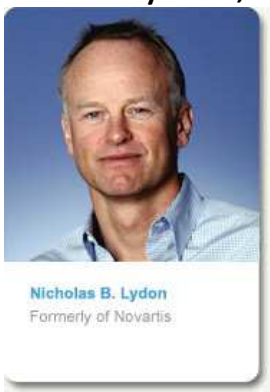
- **1960** Peter Nowell, David Hungerford
  Philadelphia chromosome

- **1973** Janett Rowley
  t(9,22) (q34,q11)

- **1970-1990** Abelson, Goff, Reddy, Shields, Klein and others – bcr/abl gene and protein (active tirozinkinase), Ciba-Geigy

Treatment I.

- **1992:** CGP57148B, phenylaminopyrimidin derivate
  STI-571, Brian Druker, Nicholas Lydon, Charles Sawyers, (Ciba-Geigy)



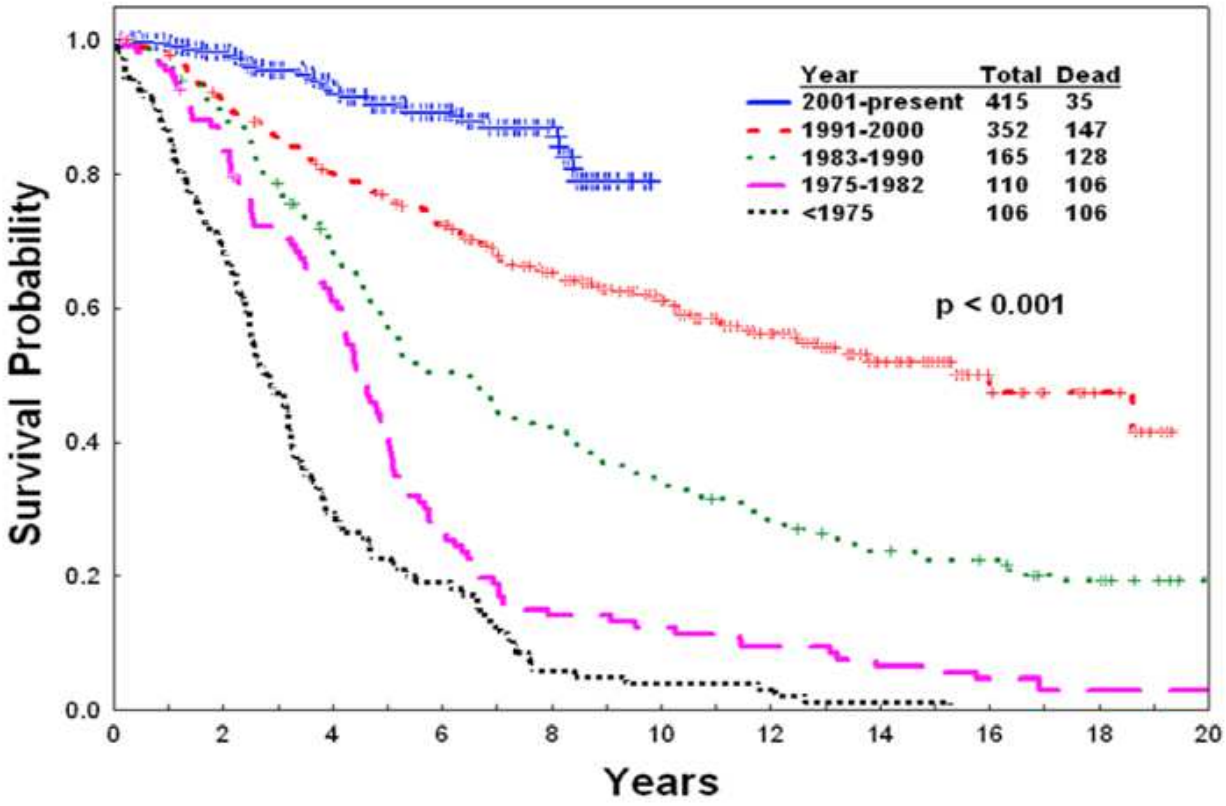
- Inhibits: c-abl, a-kit and PDGFR tirozinkinases
- Water soluble, oral formula, tolerable side effects
- Non mutagenic
- **1998:** first clinical trial with imatinib (vs. IFNα), closed after 1.5 years
- **2001.május:** FDA approval for Gleevec®


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?

A (

- **Kron**
- **DNS**
- **mRN**
- **Fehé**
- **Bete**

CML Survival After Imatinib Introduction
(MD Anderson Experience)



Kantarjian H. et al Blood. 2012 Mar 1;119(9):1981-7

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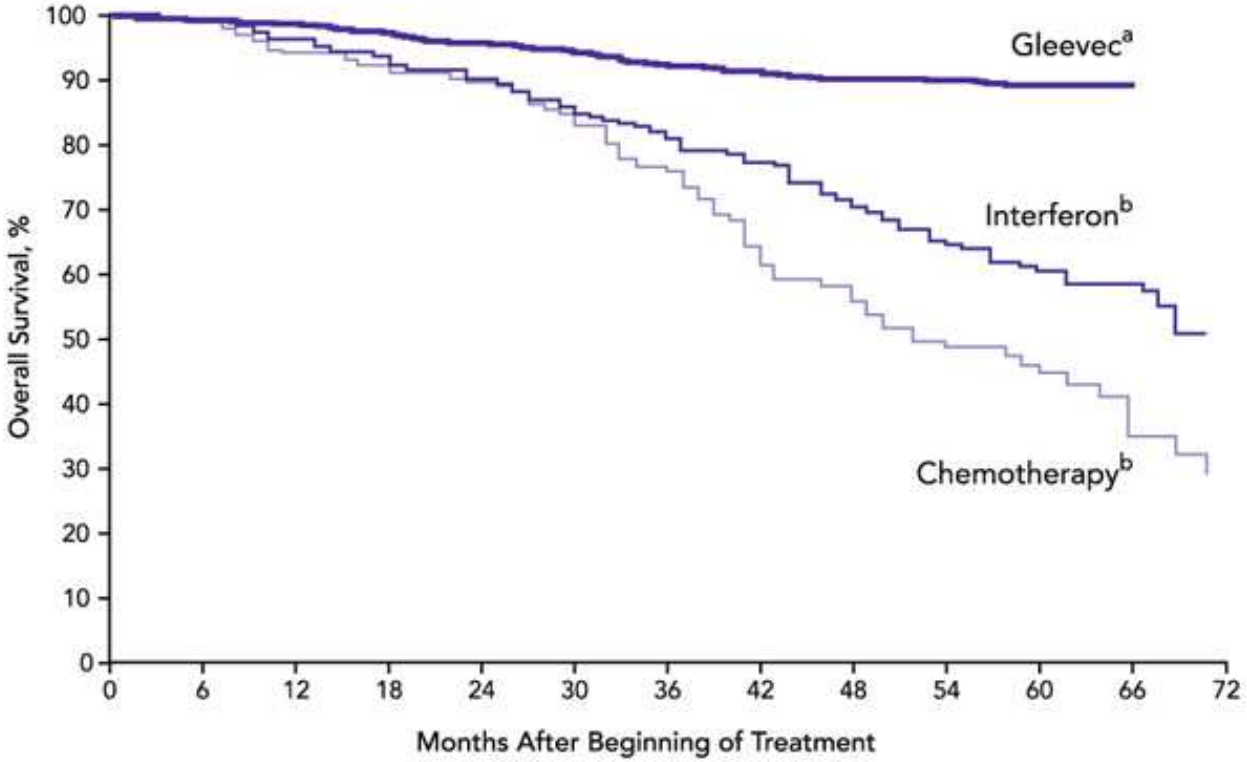
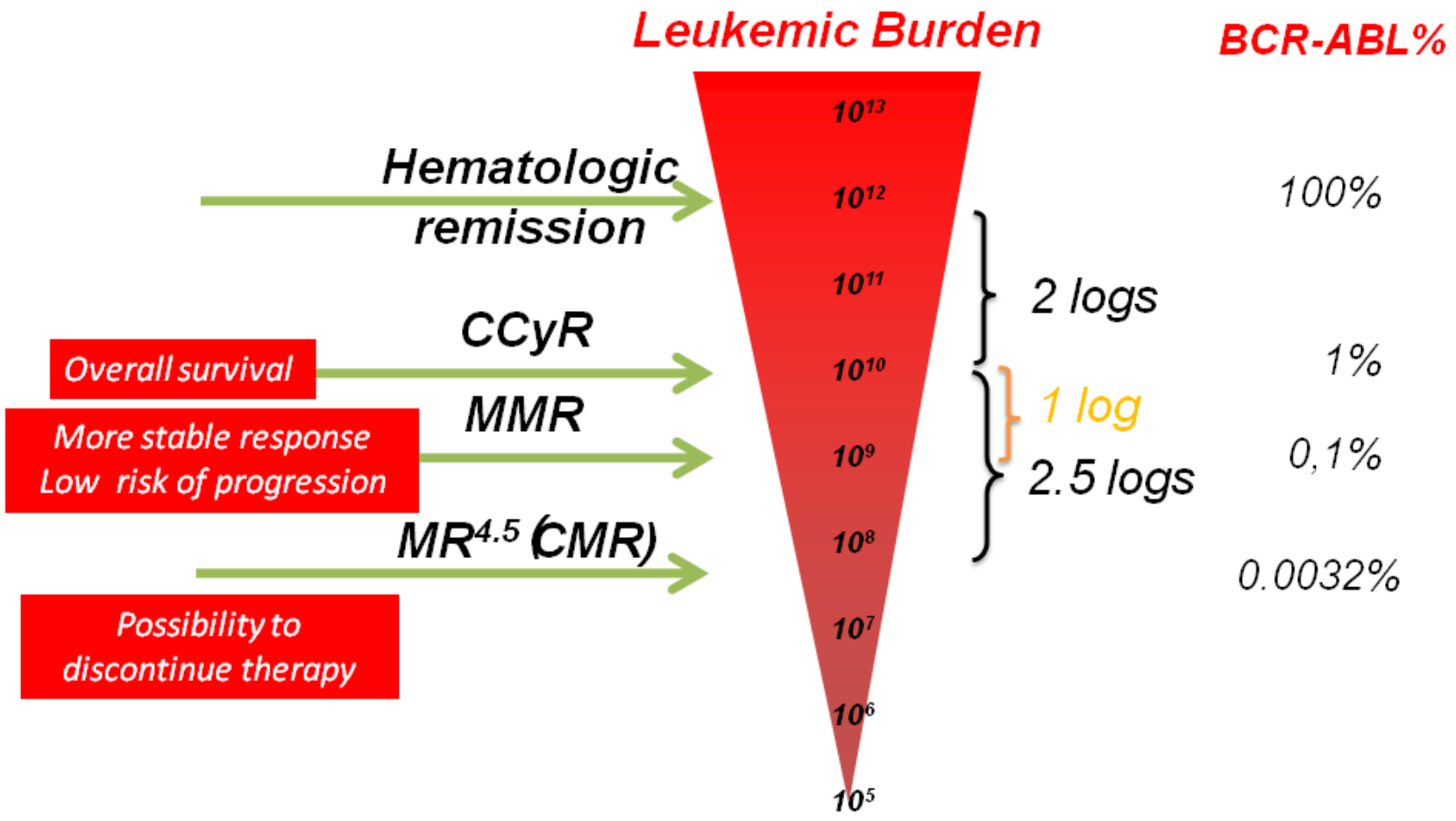
Survival of CML Patients



[a] From Druker BJ, Guilhot F, O'Brien SG *et al. N Engl J Med.* (2006) **355**:2408-2417.
[b] From The Italian Cooperative Study Group On Chronic Myeloid Leukemia. *N Engl J Med.* (1994) **330**:820-825.

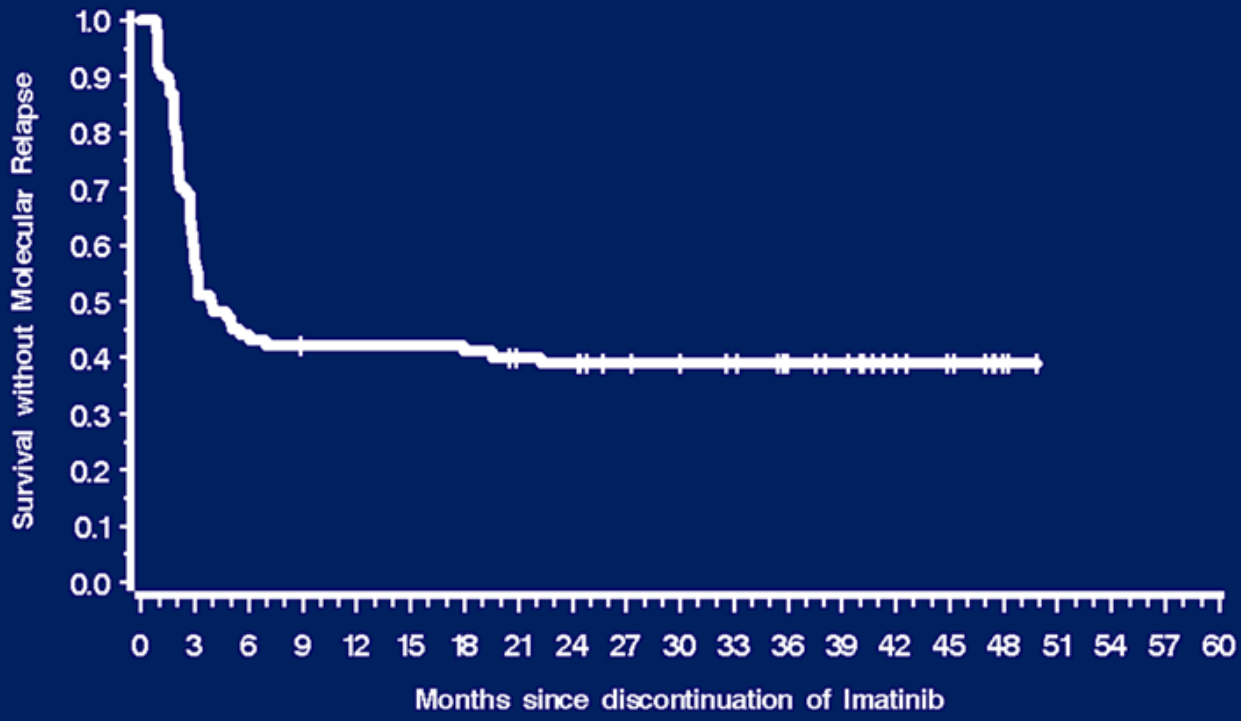
Monitoring Response in CML: Hierarchic Order Of Responses



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, and 3 late relapses at months 19, 20 and 22, respectively

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