LE NEOPLASIE MIELOPROLIFERATIVE CRONICHE

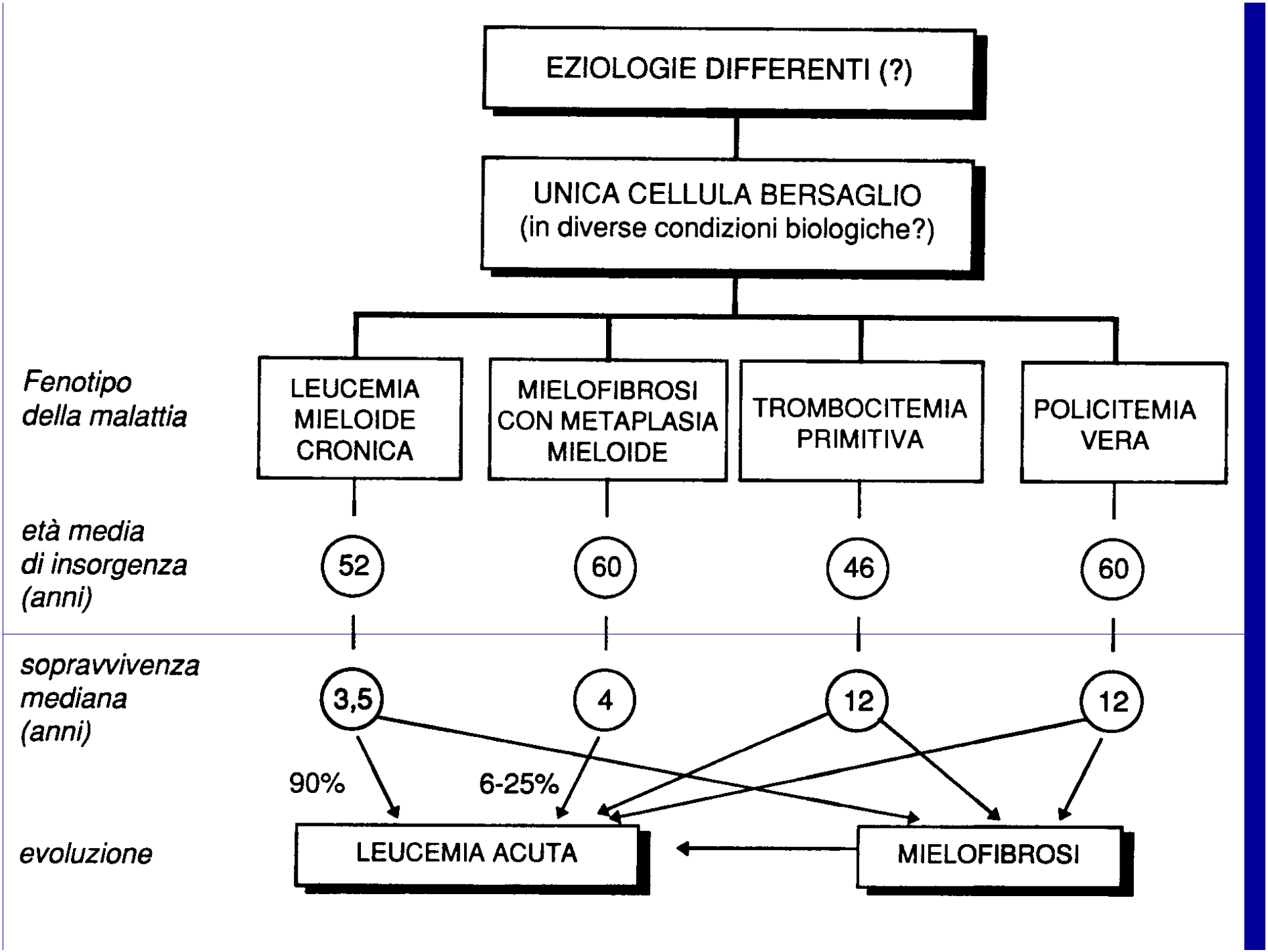
Neoplasie mieloproliferative croniche (NMC) Philadelphia-negative classificazione WHO 2016

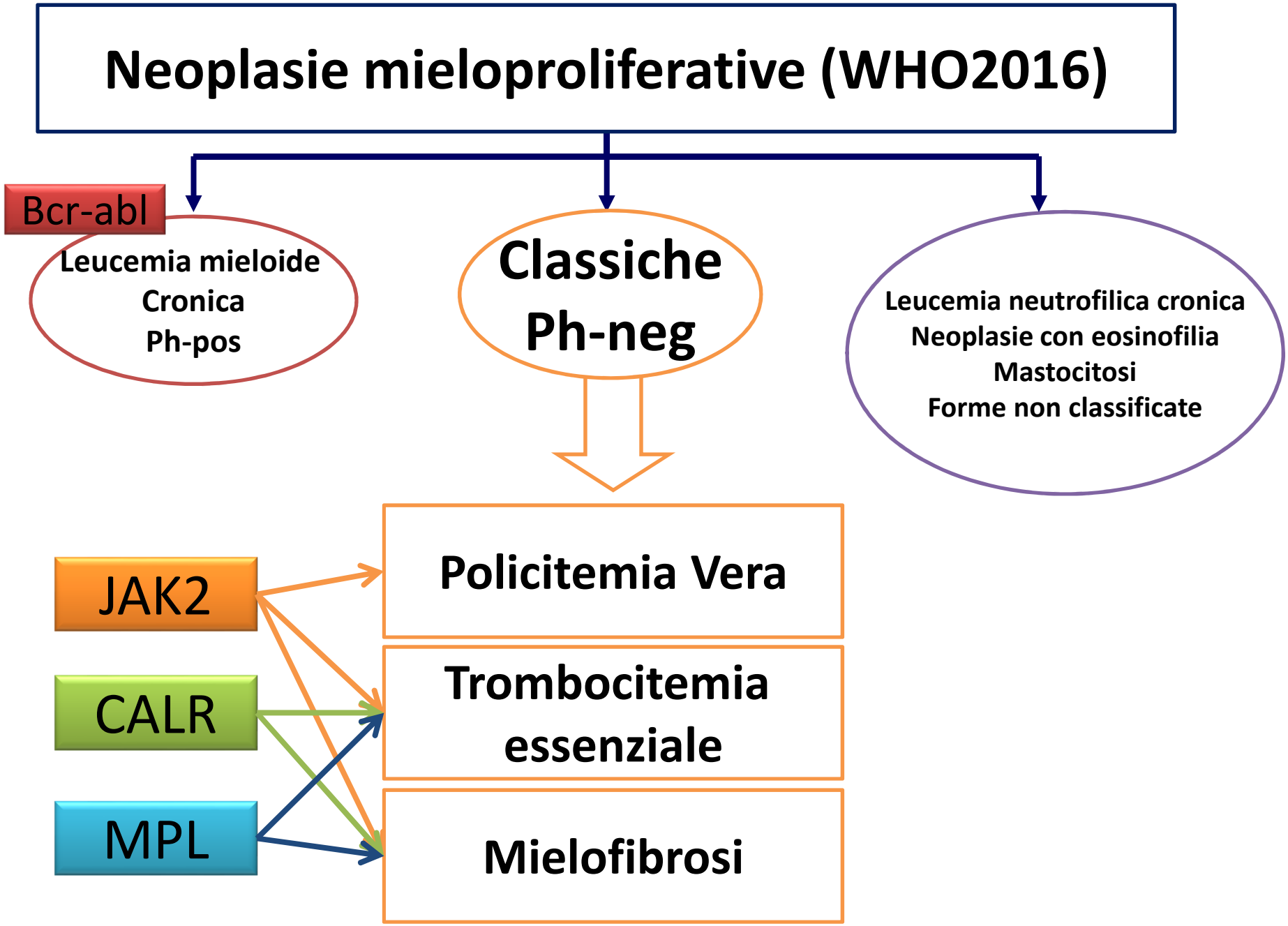
1. **Leucemia Mieloide cronica (LMC)**
2. **Policitemia vera(PV)**
3. **Trombocitemia Essenziale (TE)**
4. **Mielofibrosi Primaria (PMF)**

5. Leucemia neutrofilica cronica (CNL)
6. Leucemia eosinofilica cronica (CEL), non altrimenti specificata
7. Sindrome ipereosinofila (HES)
8. Mastocitosi (MCD)

9. NMC, non classificabile

Arber DA et al. Blood. 2016 May 19;127(20):2391-405.

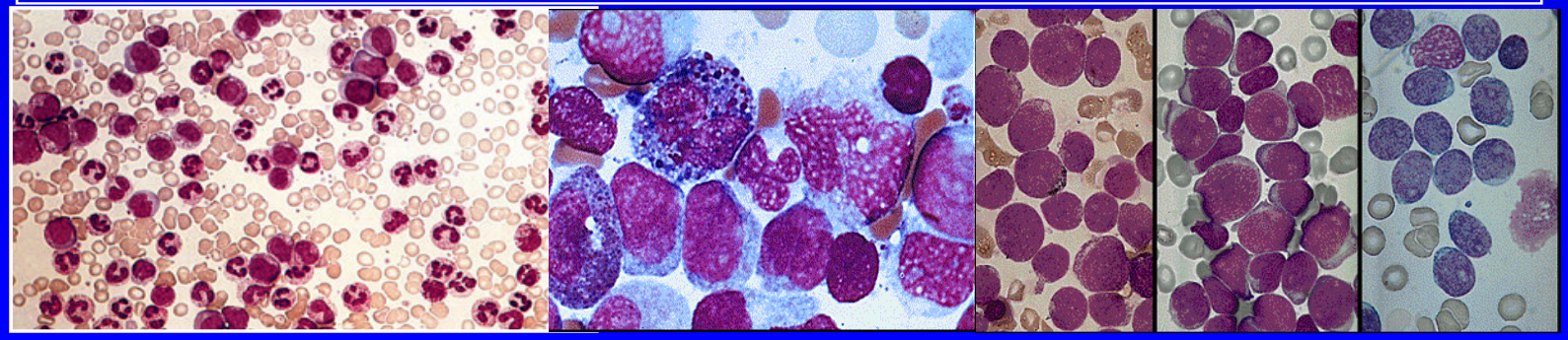

EZIOLOGIE DIFFERENTI (?)
UNICA CELLULA BERSAGLIO
(in diverse condizioni biologiche?)
Fenotipo della malattia
LEUCEMIA MIELOIDE CRONICA
MIELOFIBROSI CON METAPLASIA MIELOIDE
TROMBOCITEMIA PRIMITIVA
POLICITEMIA VERA
età media di insorgenza (anni)
52
60
46
60
sopravvivenza mediana (anni)
3,5
4
12
12
90%
6-25%
evoluzione
LEUCEMIA ACUTA
MIELOFIBROSI



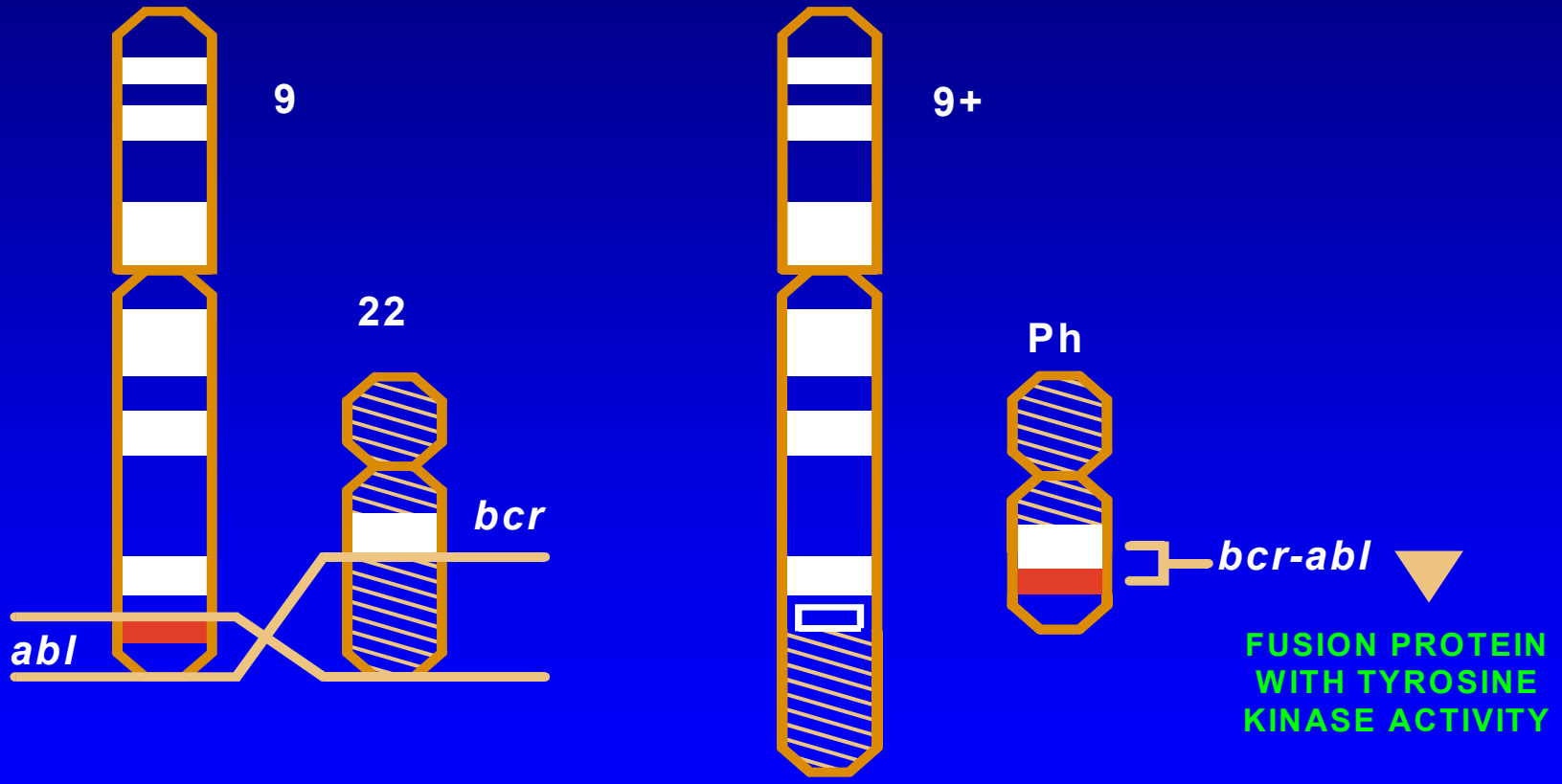
Rielaborato da Vannucchi et al. CA Cancer J Clin. 2009; 59(3):171-91

Clinical Course: Phases of CML

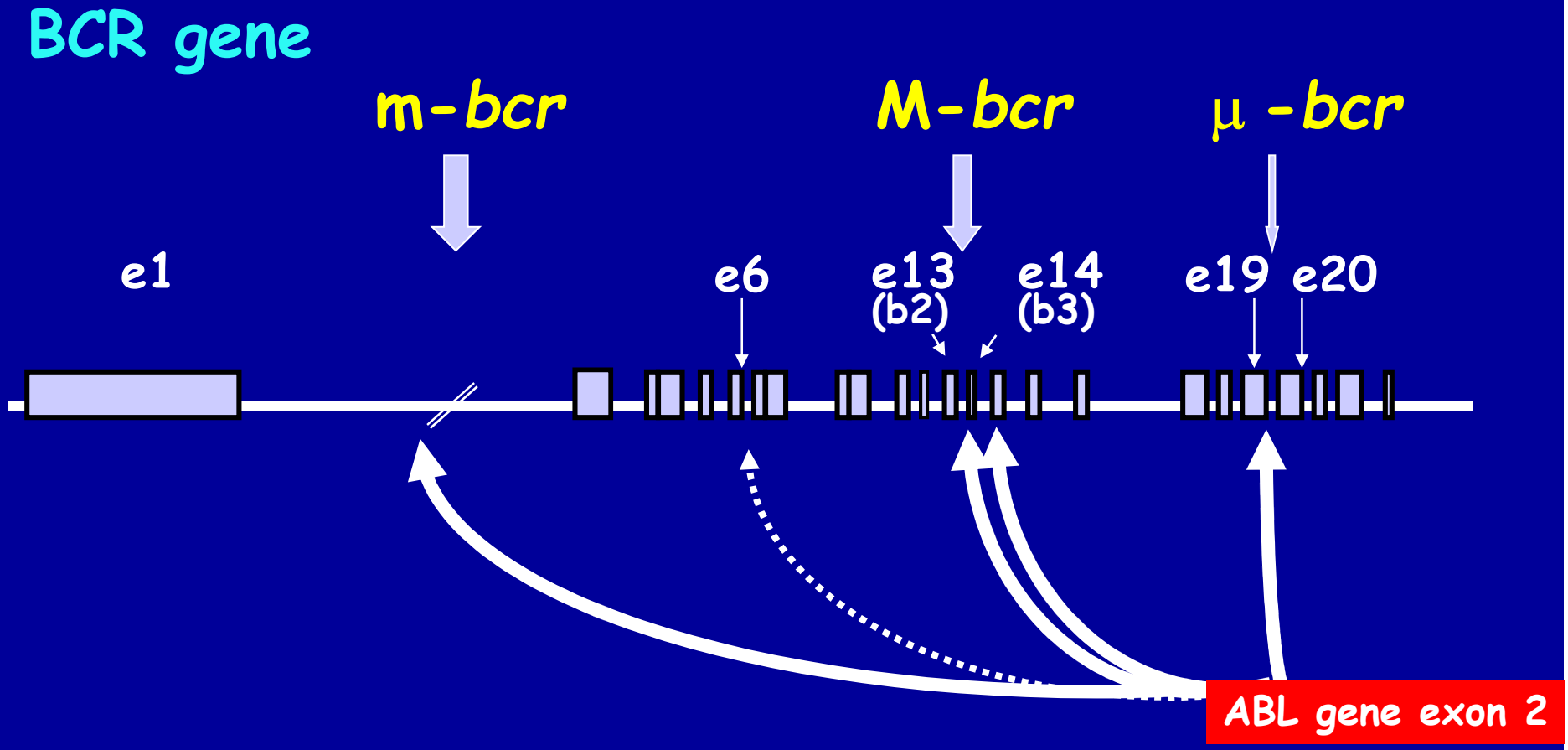
Chronic phase	Advanced phases	
	Accelerated phase	Blastic phase (blast crisis)
Median 4–6 years stabilization	Median duration up to 1 year	Median survival 3–6 months Terminal phase



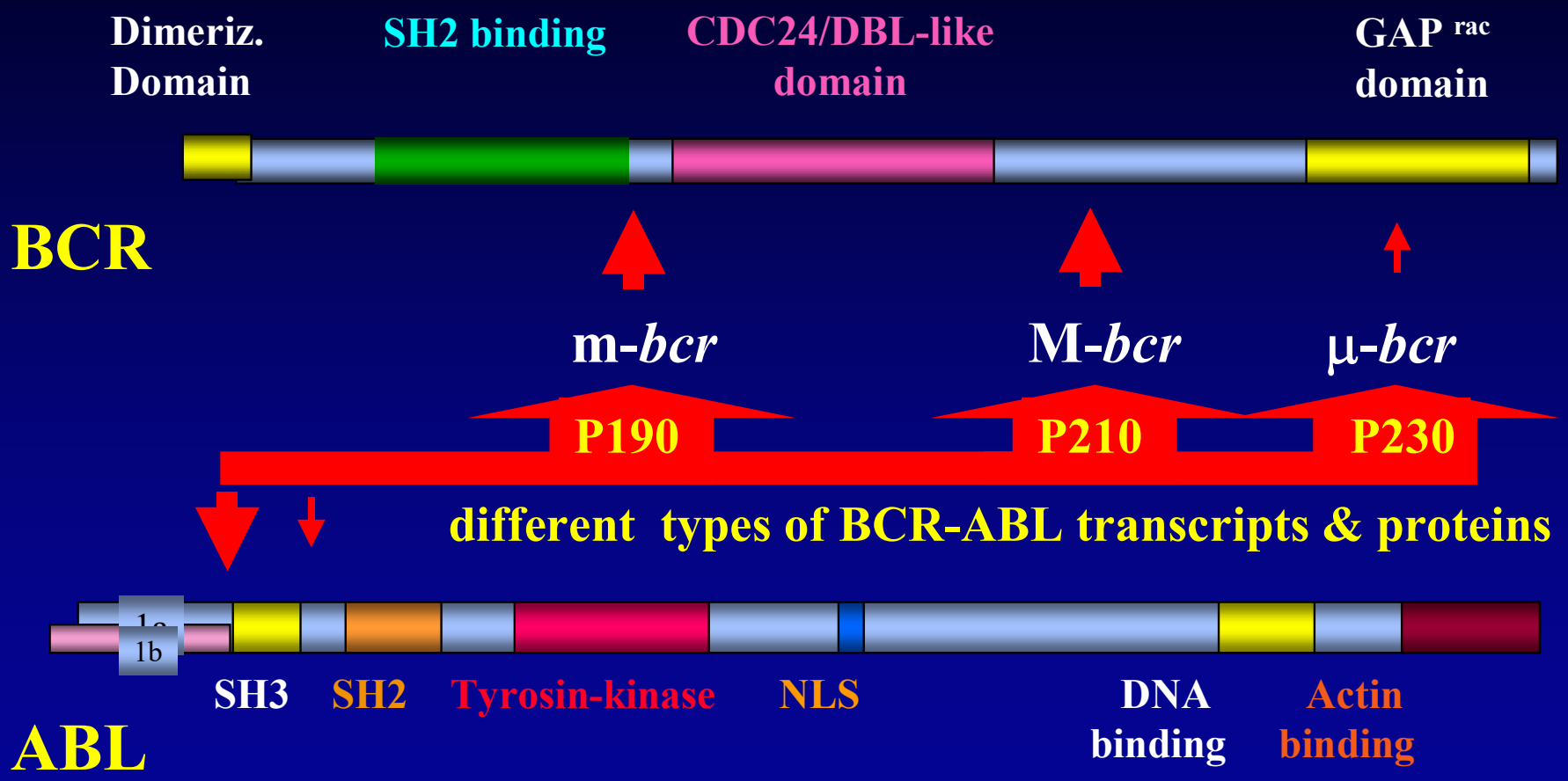
The Philadelphia Chromosome: t(9;22) Translocation

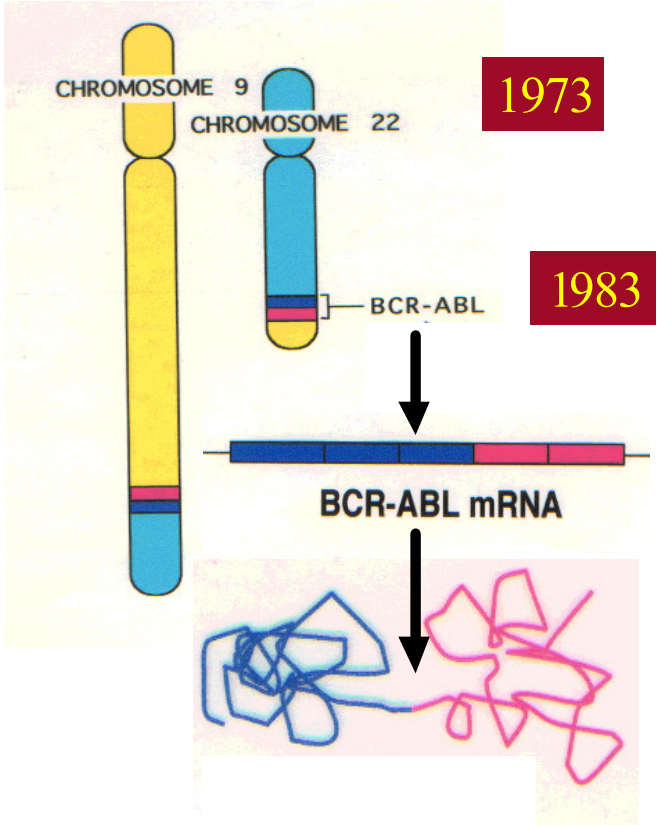


MOLECULAR ANATOMY OF THE BCR-ABL FUSION GENE



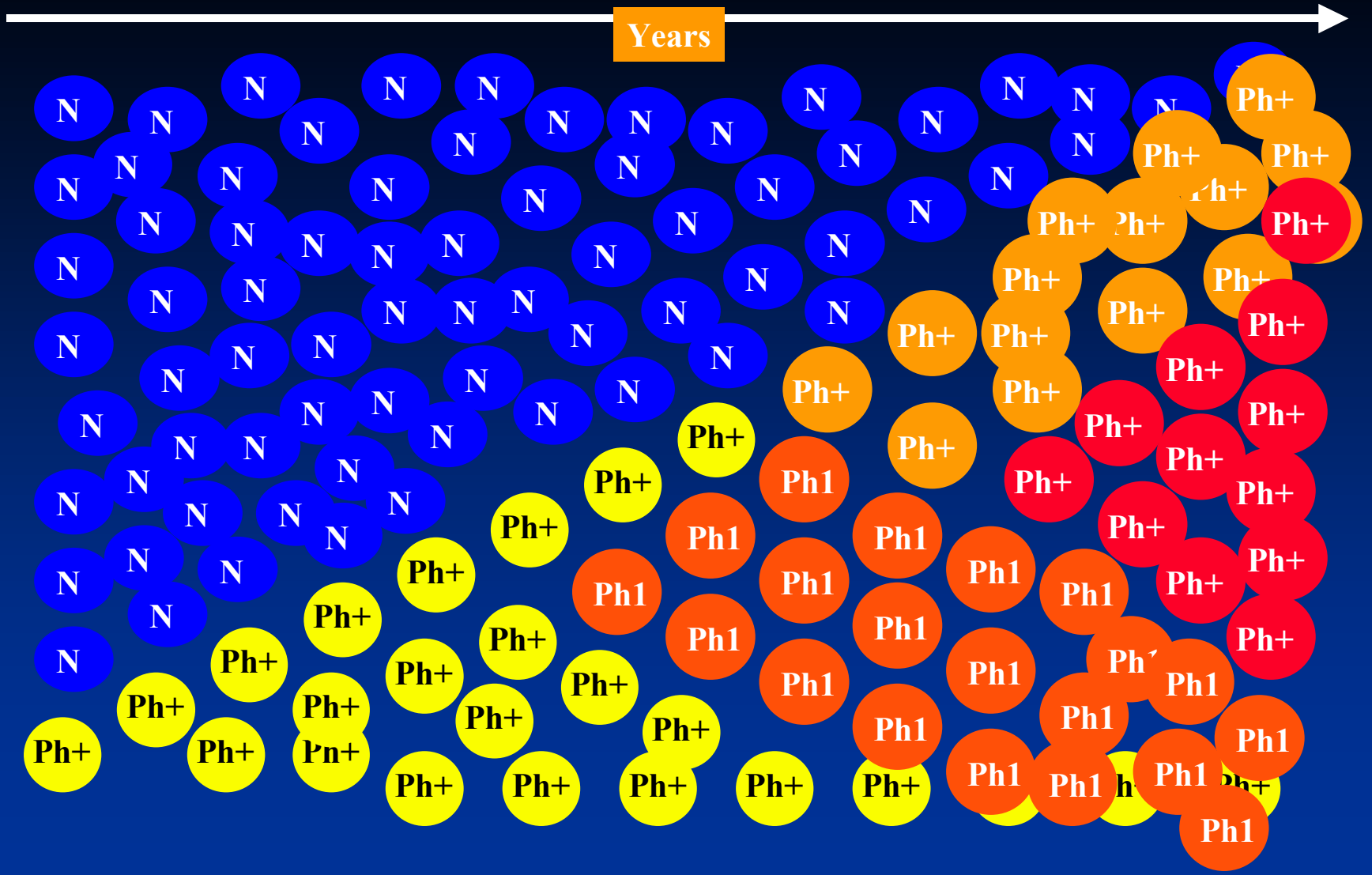
Molecular variability of the BCR/ABL fusion in Ph-positive leukemias



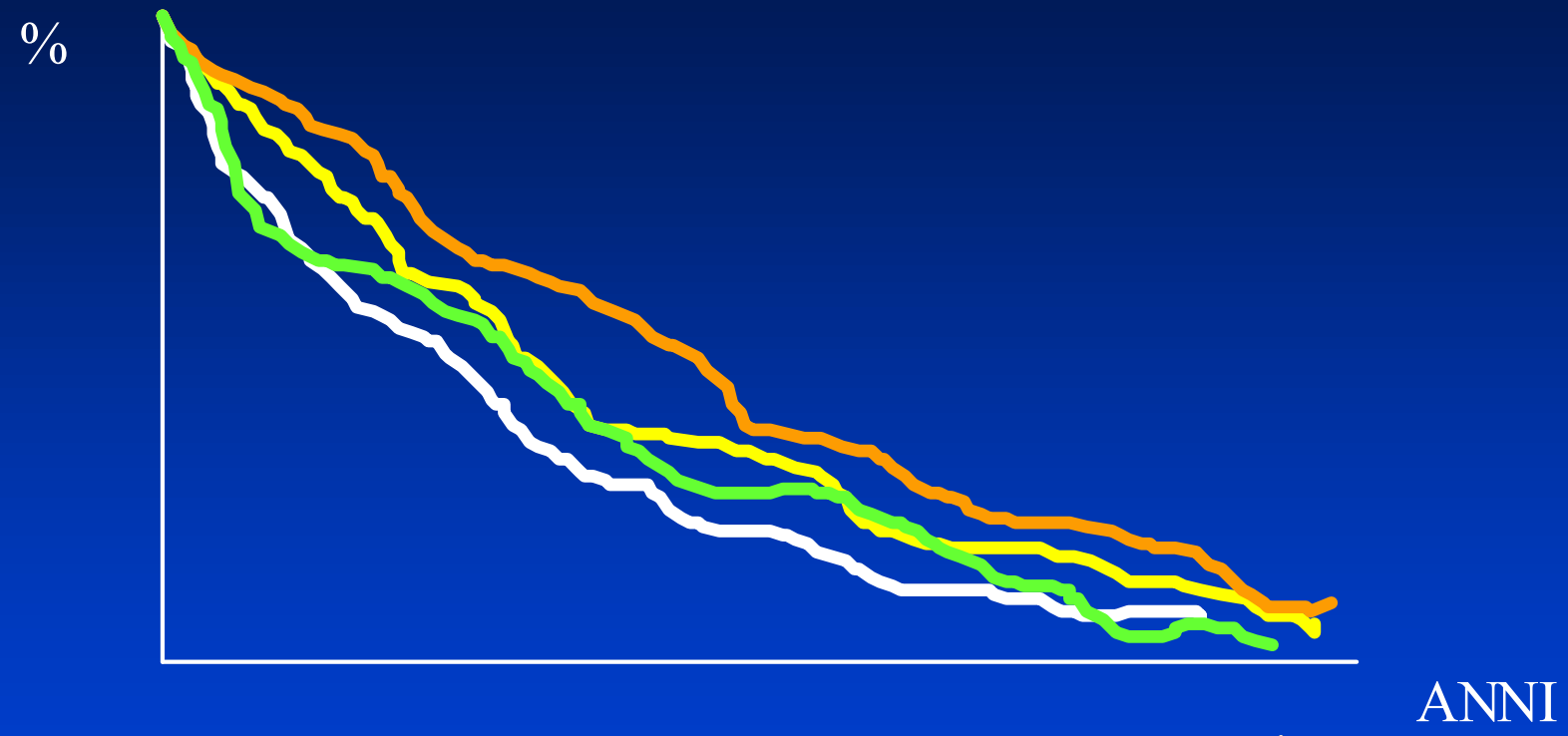


Ibrid Protein BCR-ABL (P210, P190, P230)
Strong tyrosinchinase activity

CML PROGRESSION

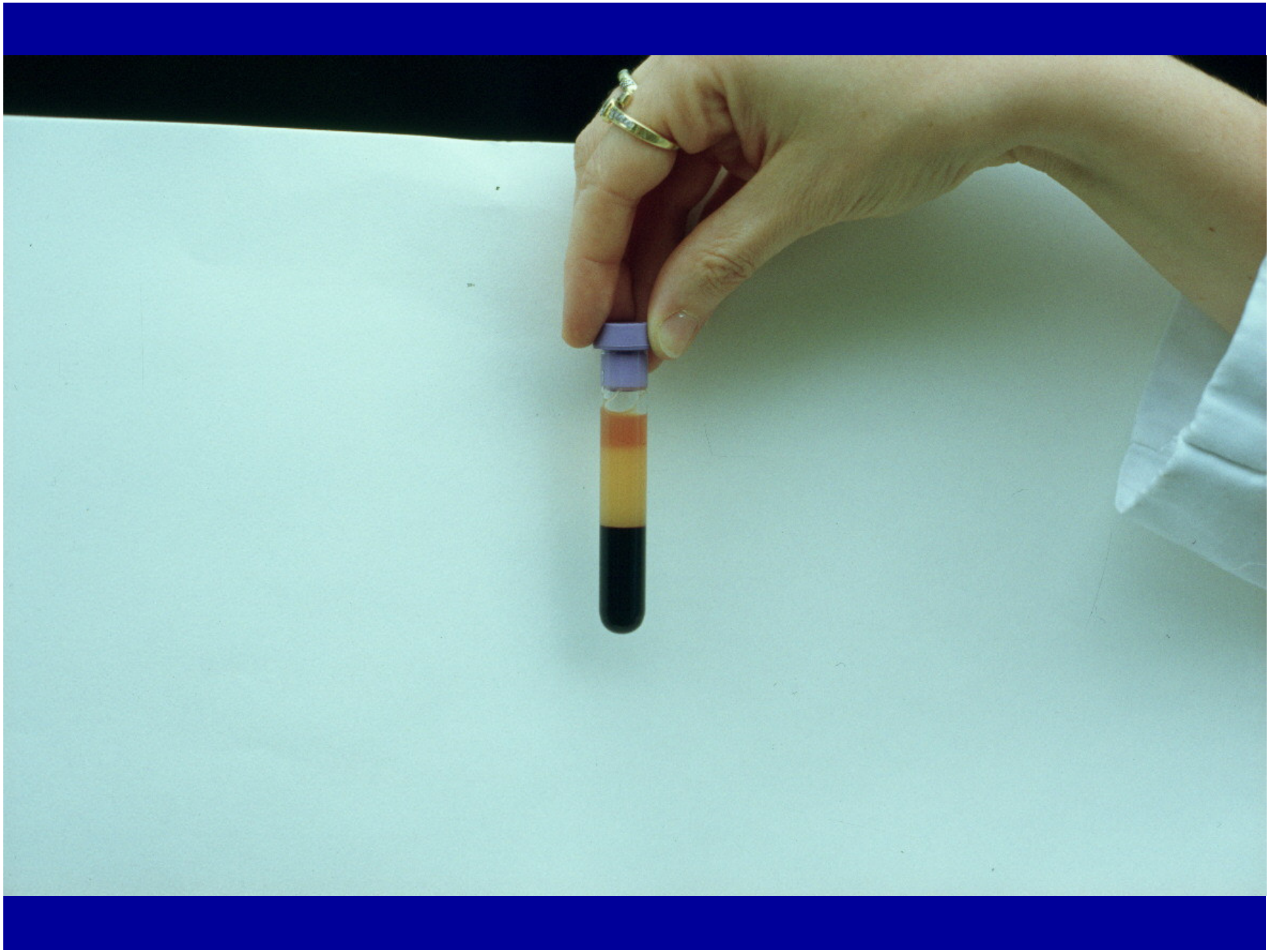


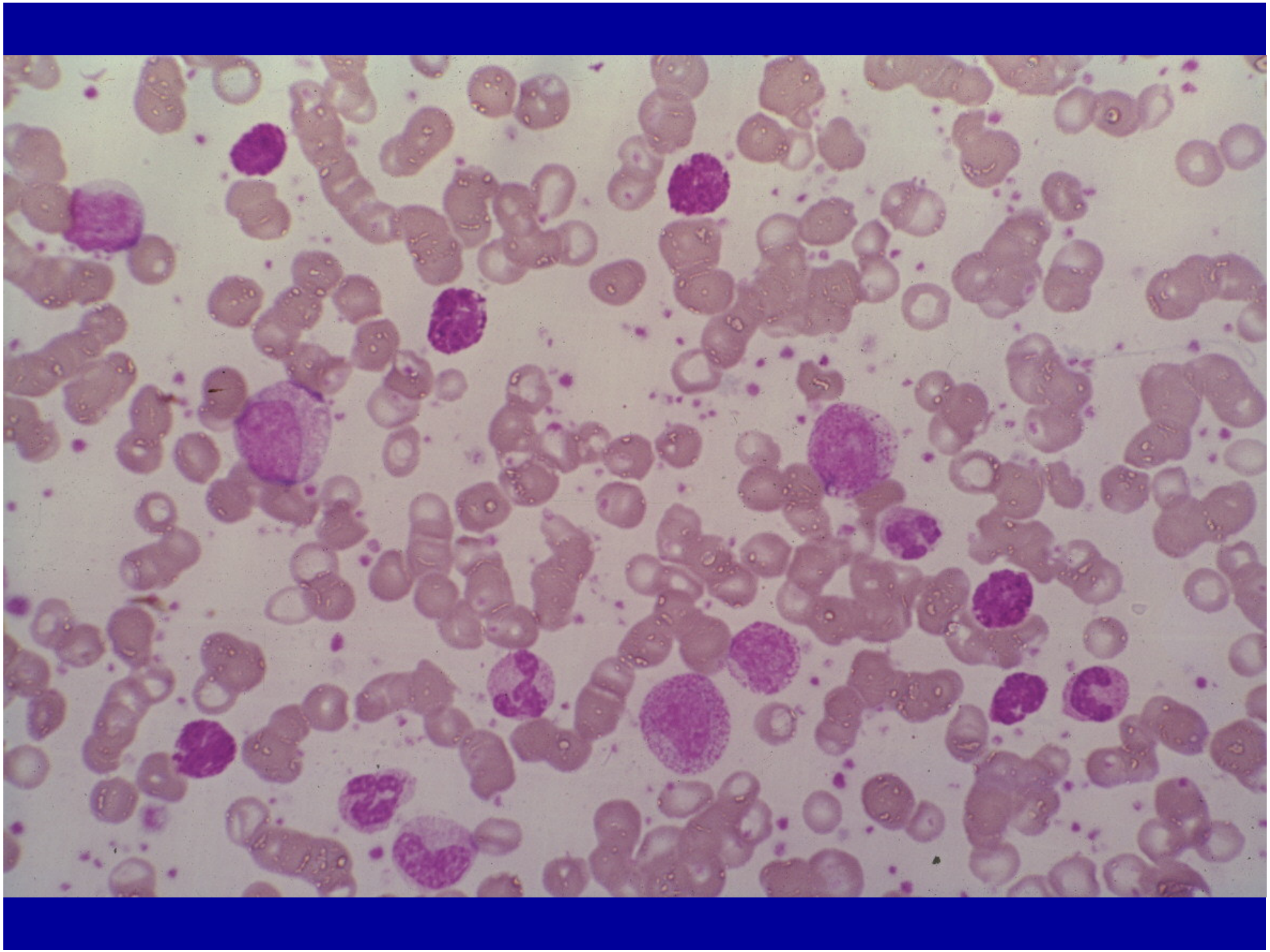
LMC / Risultati della Terapia



LEUCEMIA MIELOIDE CRONICA
DIAGNOSI

- EMOCROMO
- ESAME MORFOLOGICO SANGUE PERIFERICO
- ASPIRATO MIDOLLARE (RARAMENTE BIOPSIA OSSEA)
- CARIOTIPO
- BIOLOGIA MOLECOLARE





LEUCEMIA MIELOIDE CRONICA
FORMULA LEUCOCITARIA

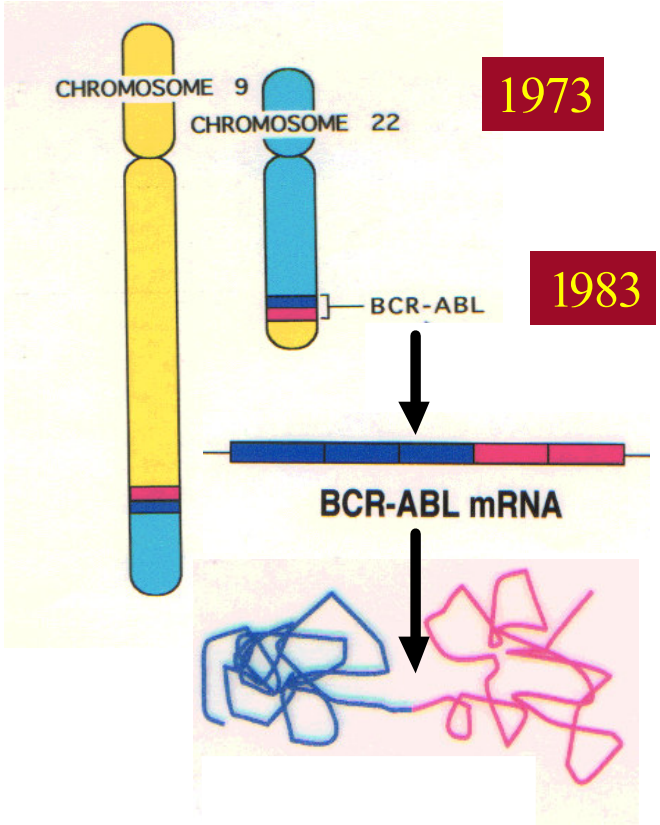
	LMC	*V.I*
• GRANULOCITI NEUTROFILI	50 - 60%	50 - 70%
• METAMIELOCITI	2 - 10%	0%
• MIELOCITI	3 - 20%	0%
• PROMIELOCITI	1 - 6%	0%
• MIELOBLASTI	0 - 5%	0%
• GRANULOCITI EOSINOFILI	1 - 5%	1 - 2%
• GRANULOCITI BASOFILI	1 - 5%	0 -
• LINFOCITI	5 - 10%	25 - 45%
• MONOCITI	2 - 6%	2 - 6%

LEUCEMIA MIELOIDE CRONICA
CLINICA

- ASTENIA
- CALO PONDERALE
- SDR FEBBRILE
- ARTROMIALGIE
- SUDORAZIONI
- ALGIE E TENSIONE ADDOMINALE (SPLENOMEGALIA)
- AMAUROSI O ALTRI DISTURBI DEL VISUS

LEUCEMIA MIELOIDE CRONICA
ESAME OBIETTIVO

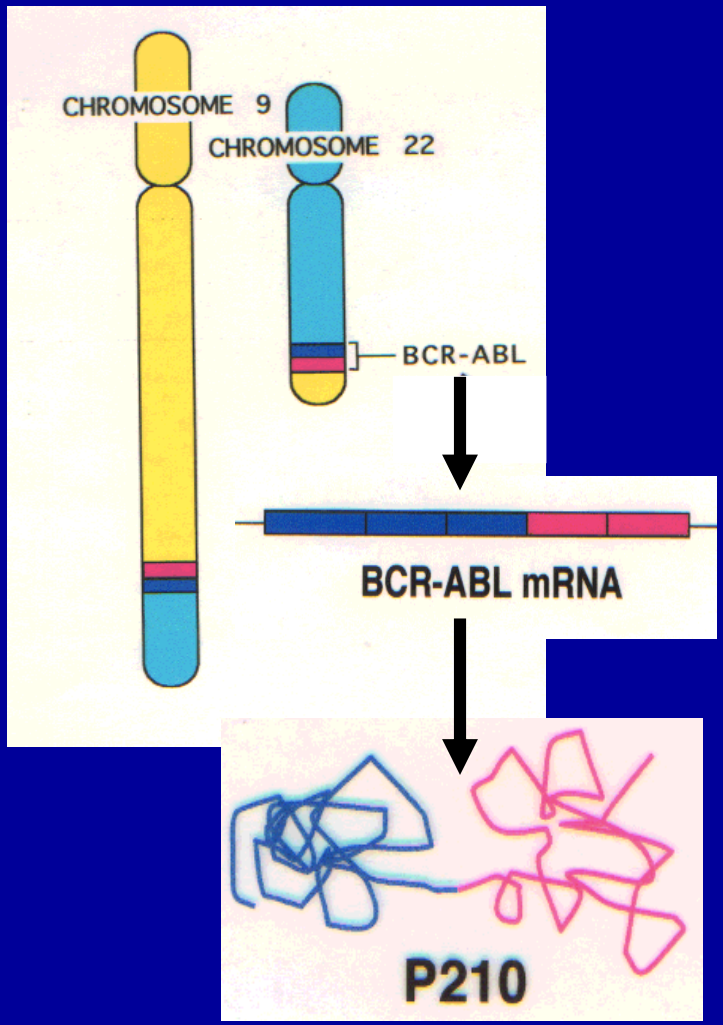
- SPLENOMEGALIA
- EPATOMEGALIA
- LINFOADENOPATIE
- SNC
- ALTRO INTERESSAMENTO EXTRAMIDOLLARE
- AMAUROSI O ALTRI DISTURBI DEL VISUS



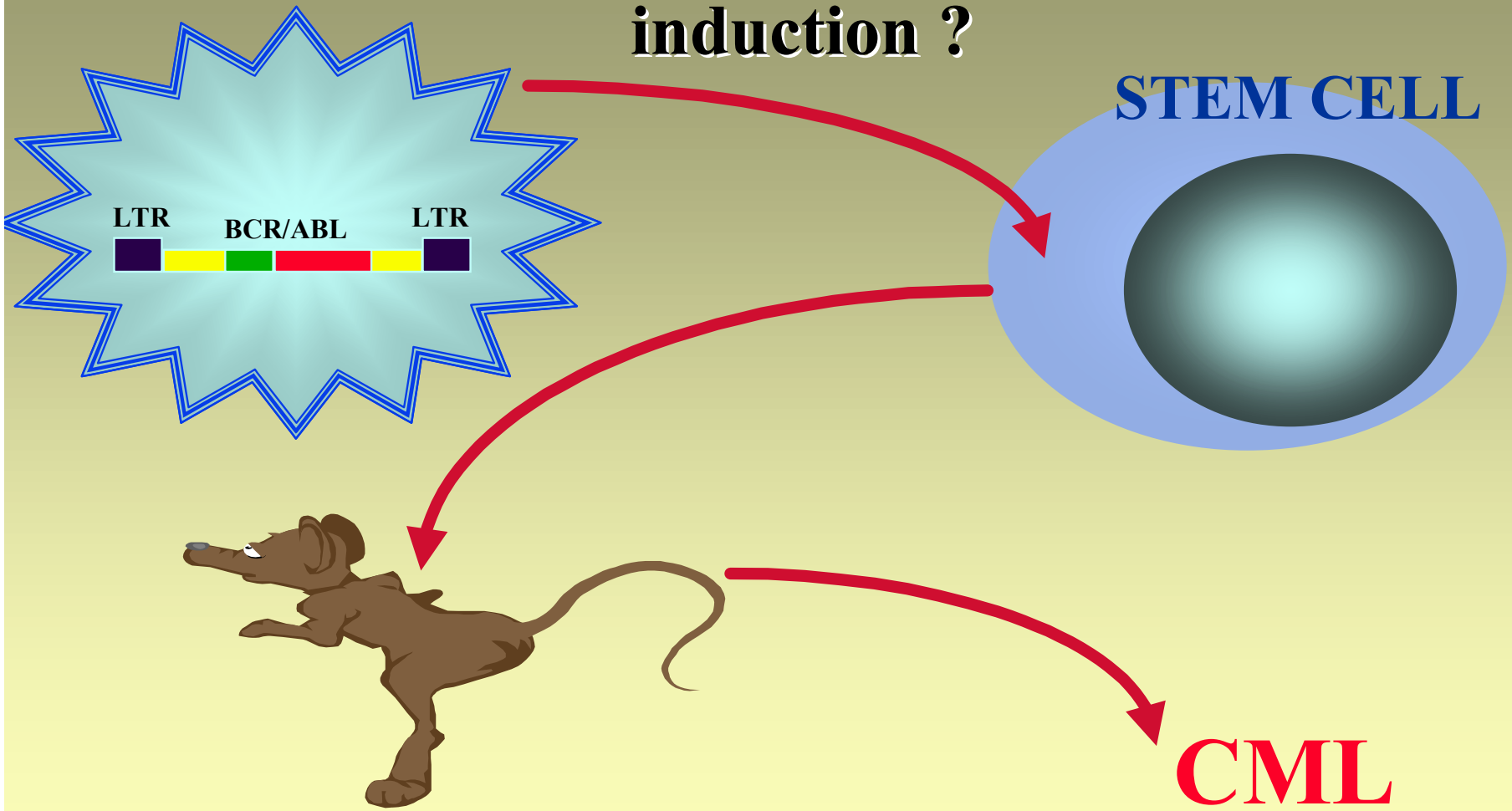
Ibrid Protein BCR-ABL (P210, P190, P230)
Strong tyrosinchinase activity

MIILESTONES IN CML RESEARCH

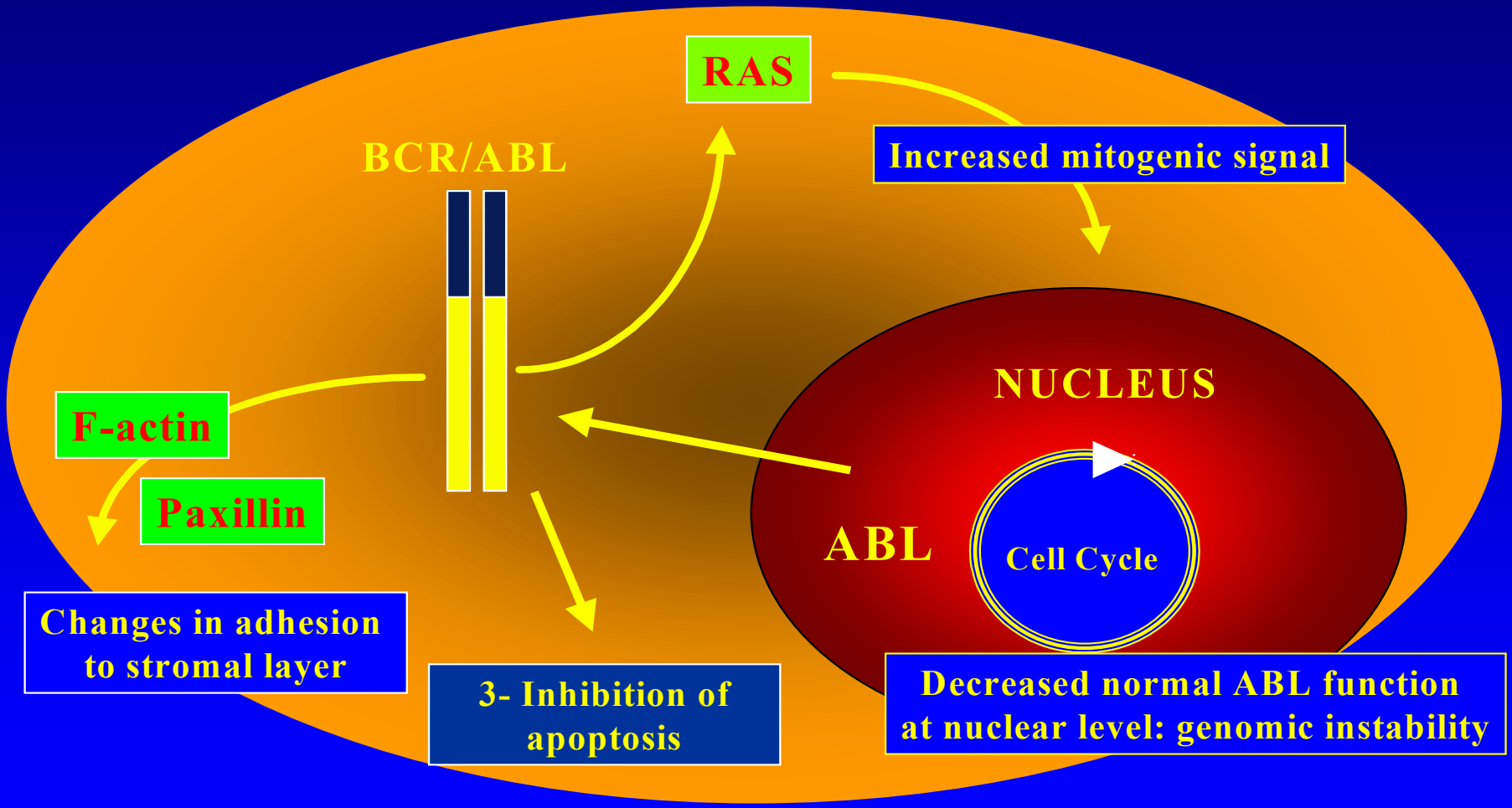
- 1960 - Nowell P.C. & Hungerford D.A.
  IDENTIFICATION OF THE PH+ CHROMOSOME
- 1973 - Rowley J.D.
  ASSOCIATION OF THE PH+ WITH CML
- 1984 - Groffen J. et al.
  BCR/ABL GENE REARRANGEMENT IN CML
- 1984 - Konopka J.B. et al.
  ALTERATION OF THE ABL TK ACTIVITY IN K562
- 1985 - Stievelman e et al.
  CLONING & SEQUENCING OF THE BCR/ABL TRANSCRIPTS
- 1990 - Daley g. q. et al
  INDUCTION OF CML IN VIVO



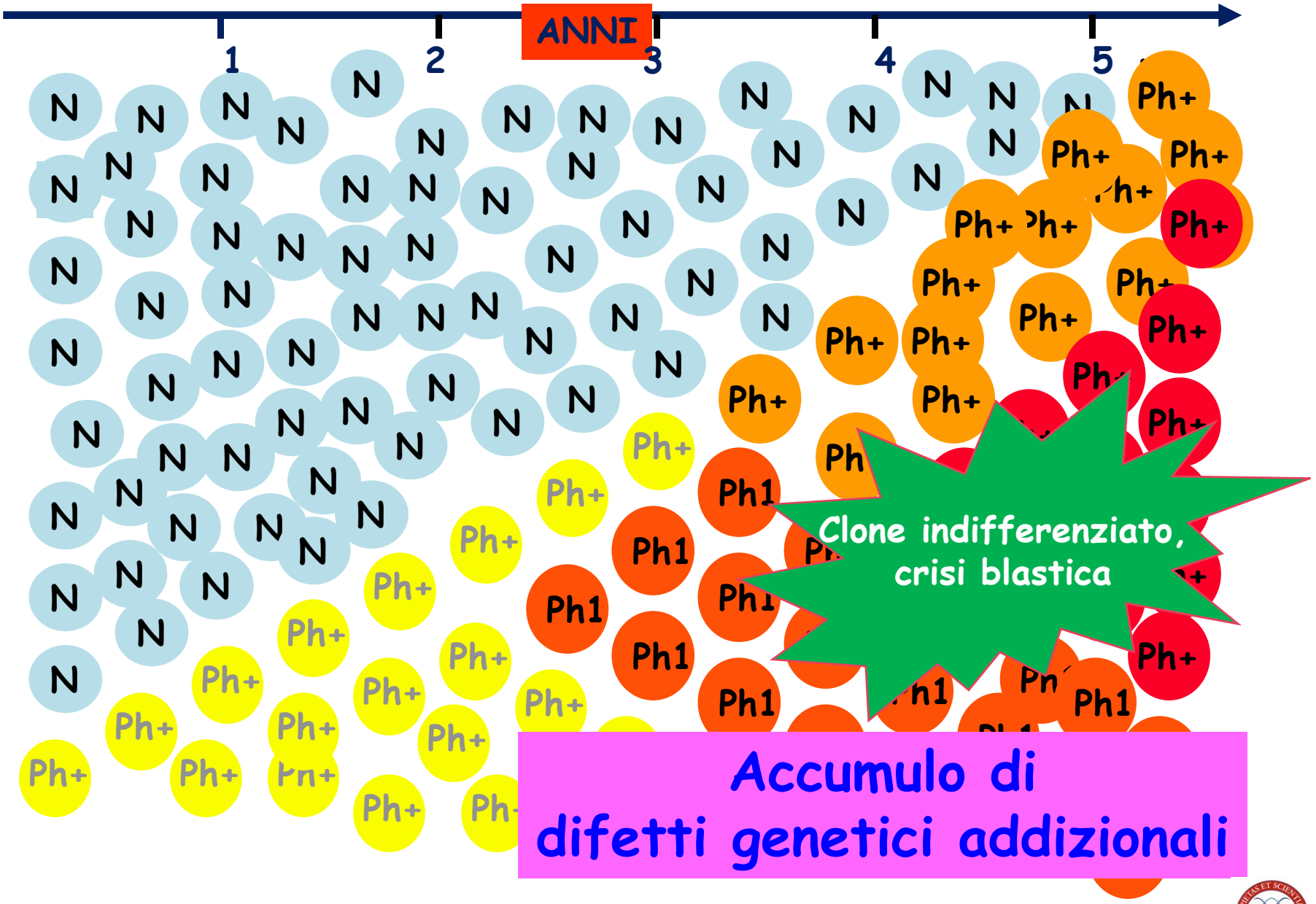
Is BCR-ABL expression sufficient for CML induction ?



Pathways activated by BCR-ABL expression



Progressione della Leucemia Mieloide Cronica



TRASFORMAZIONE DELLA LEUCEMIA MIELOIDE CRONICA

	Fasi		
	cronica	*accelerata*	*blastica*
Febbre	−−−	+−−	++±
Dolori ossei e muscolari	−−−	+−−	++±
Sudorazioni profuse notturne	−−−	+−−	++±
Astenia	−−−	+−−	++±
Splenomegalia	+−−	+±−	++±
Anemia	±−−	+±−	+++
Piastrinopenia o piastrinosi	+−−	++−	+++
Leucocitosi instabile o crescente	−−−	++−	+++
Alterazioni formula leucocitaria	−−−	++−*	+++**
Midollo osseo — fibrosi	+−−	+±−	+++
Midollo osseo — blastosi	±−−	++±	+++
Anomalie aggiuntive del cariotipo	−−−	+±−	++±

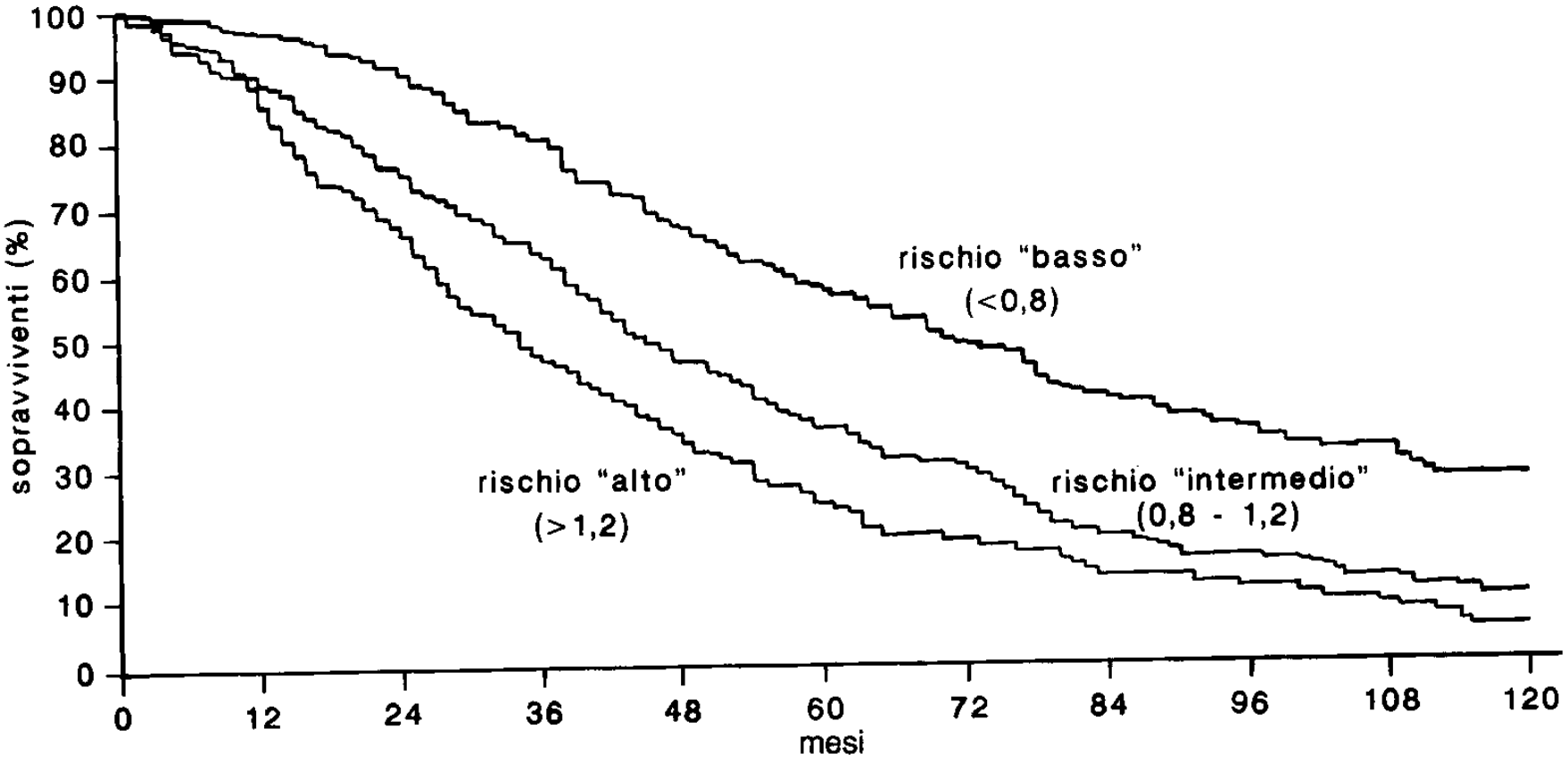
IMATINIB IN Ph POS CML

RISK CALCULATION AND DEFINITION

	SOKAL	EURO
Age (years)	0.116 (age - 43.4)	0.666 when age ≥ 50
Spleen (cm below costal margin, max distance)	0.0345 (spleen - 7.51)	0.042 x spleen
Platelet count ($\times 10^9$/L)	0.188 [(Platelets^2 : 700) - 0.563]	1.0956 when platelets ≥ 1500
PB myeloblasts (%)	0.0887 (myeloblasts – 2.10)	0.0584 × myeloblasts
PB basophils (%)	/	0.20399 when basophils > 3%
PB eosinophils (%)	/	0.0413 × eosinophils

RELATIVE RISK	EXPONENTIAL OF THE TOTAL	TOTAL × 1000
• LOW	<0.8	≤ 780
• INTERMEDIATE	0.8-1.2	781-1479
• HIGH	>1.2	≥ 1480

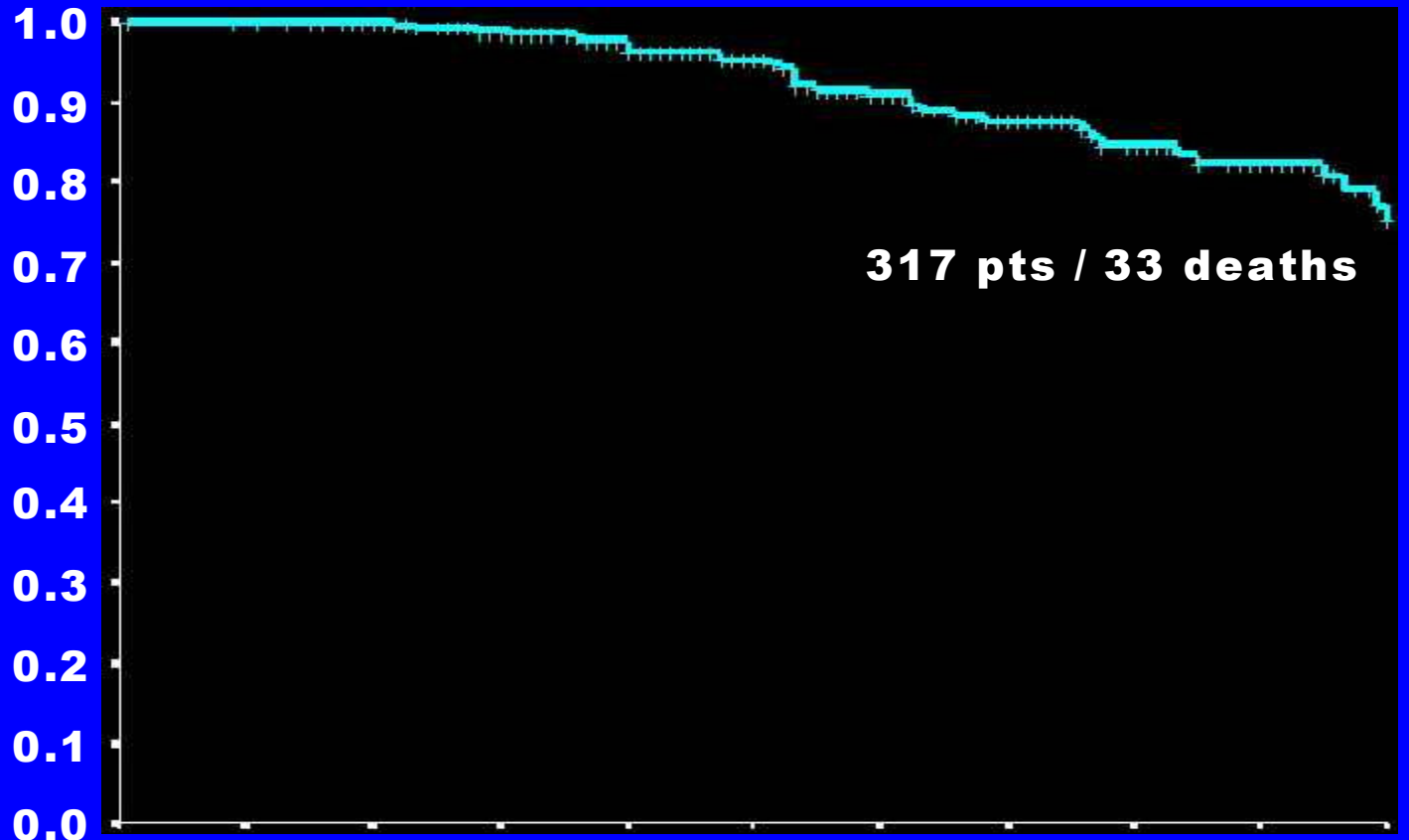
LEUCEMIA MIELOIDE CRONICA
CURVE DI SOPRAVVIVENZA IN BASE AL RISCHIO



THERAPY OF CML

- 1845 recognition of leukemia as a disease entity
- 1865 first treatment with 1% arsenic solution
- 1895 discovery of x-irradiation
- 1946 nitrogen mustard - first effective chemotherapy
- 1953 busulfan
- 1960 hydroxyurea
- 1978 autografts for CML
- 1982 routine use of allografts for CML
- 1983 interferon
- 1990 donor lymphocyte infusions (DLI)
- 1999 Imatinib
- 2004 New Tk inhibitors……..

OVERALL SURVIVAL

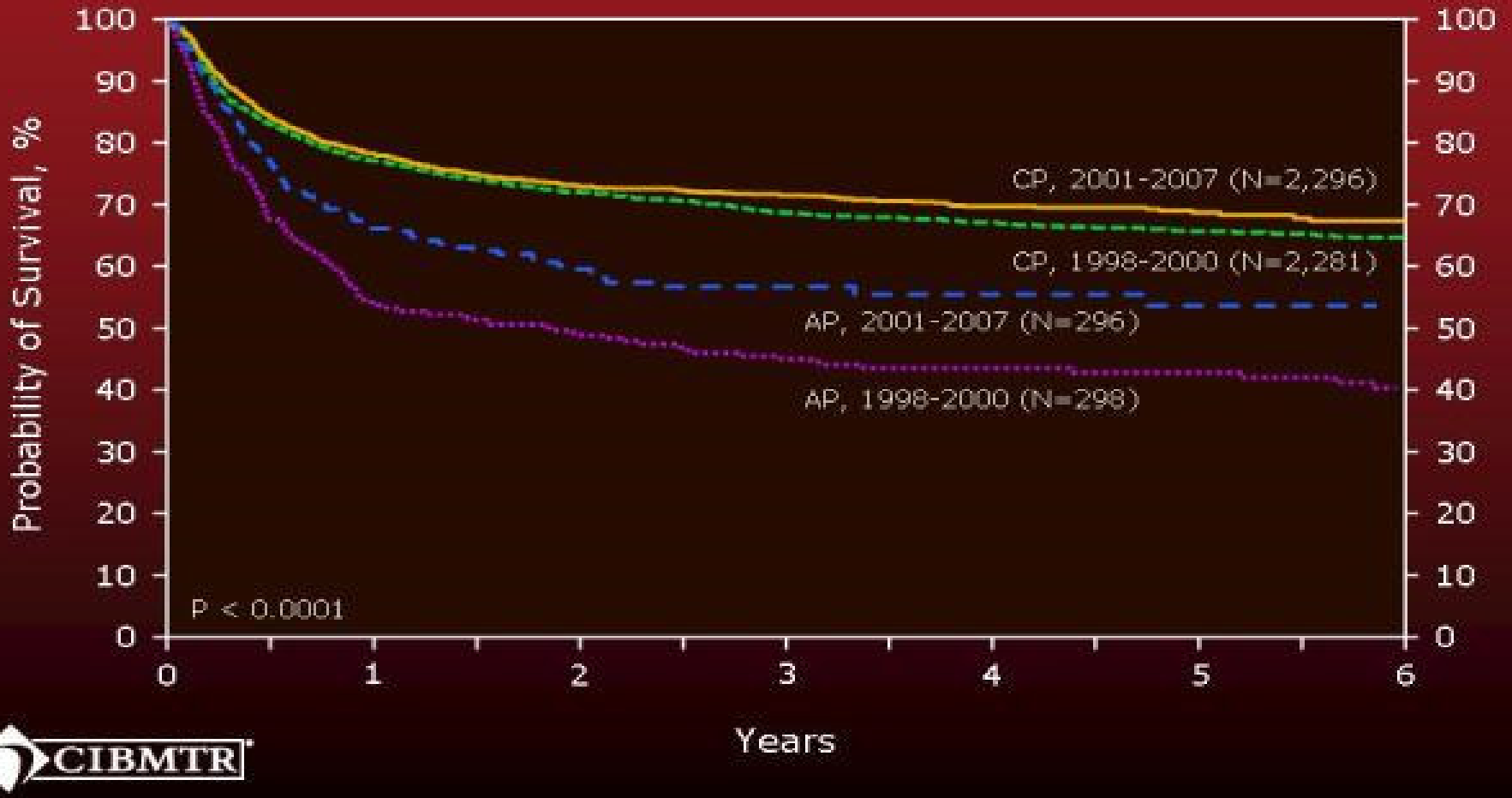


ERCCR / IFN

ICSG on CML

Probability of Survival after HLA-matched Sibling Donor Transplants for CML, 1998-2007

- By Disease Status and Transplant Year -

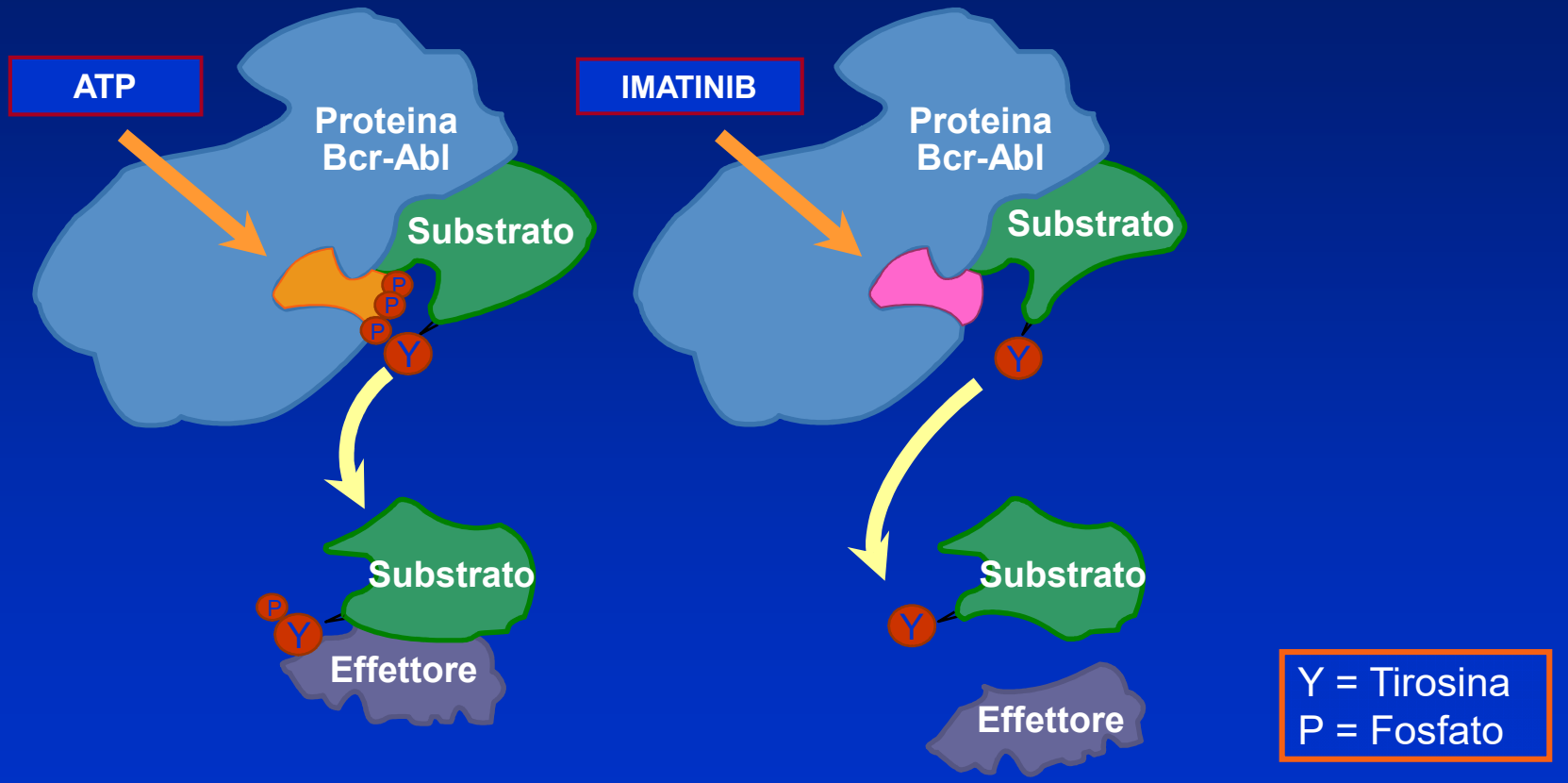


CIBMTR

Imatinib is proof of principle that rationally designed, molecularly targeted therapy works. Imatinib represents a paradigm shift in cancer drug development.

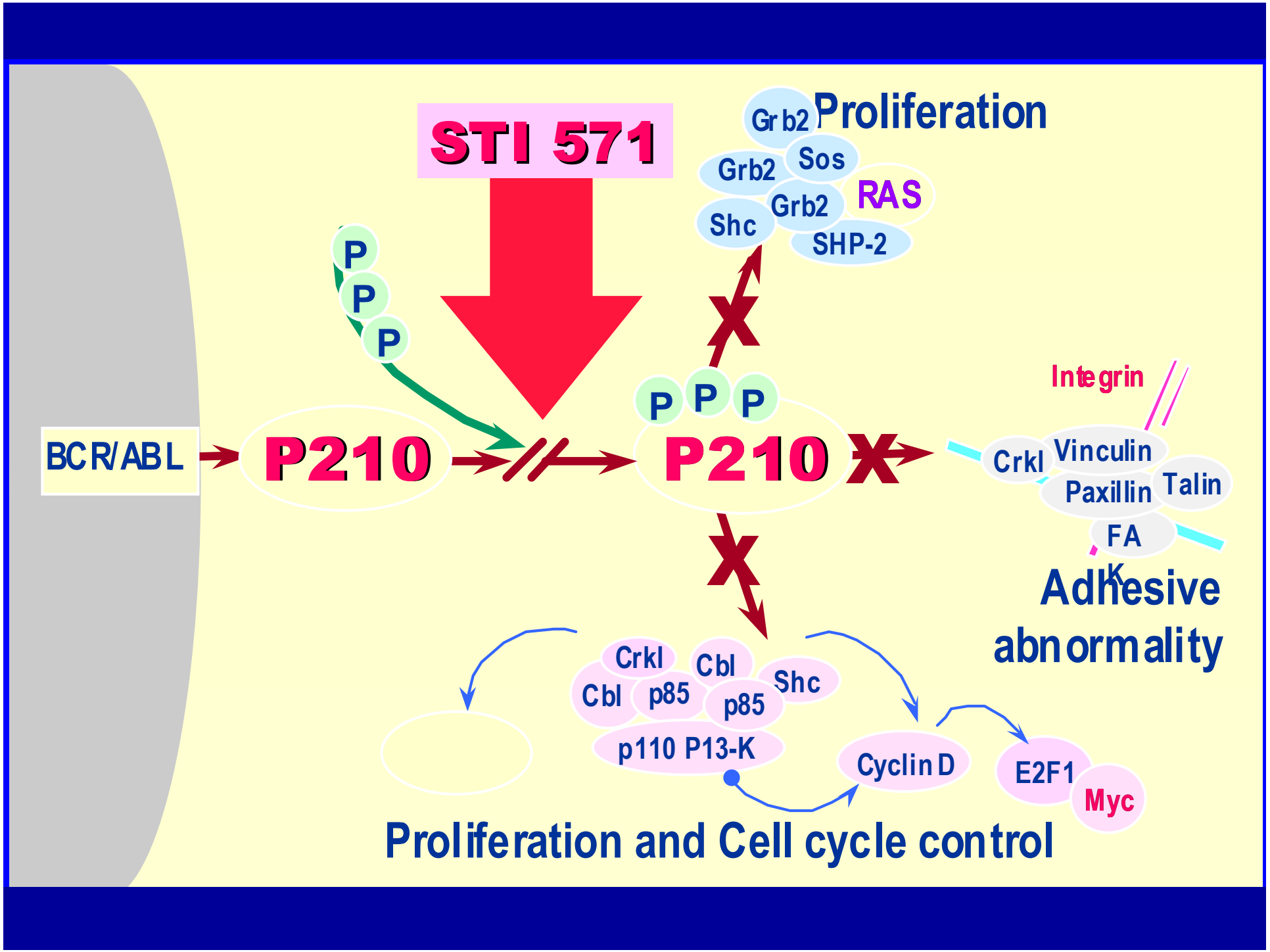
(*Deininiger et al 2005)*

Meccanismo d'azione



Y = Tirosina
P = Fosfato

Goldman JM, Milo JV, NEJM 2001, 344:1084-1086


STI 571
Grb2
Proliferation
Grb2
Sos
RAS
Grb2
Shc
SHP-2
P
P
P
P
P
P
BCR/ABL
P210
P210
Integrin
Crkl
Vinculin
Paxillin
Talin
FA
Adhesive abnormality
Crkl
Cbl
Cbl
p85
Shc
p85
p110 P13-K
Cyclin D
E2F1
Myc
Proliferation and Cell cycle control

LETTER TO THE EDITOR

Outcome of patients with CML after SCT in the era of tyrosine kinase inhibitors

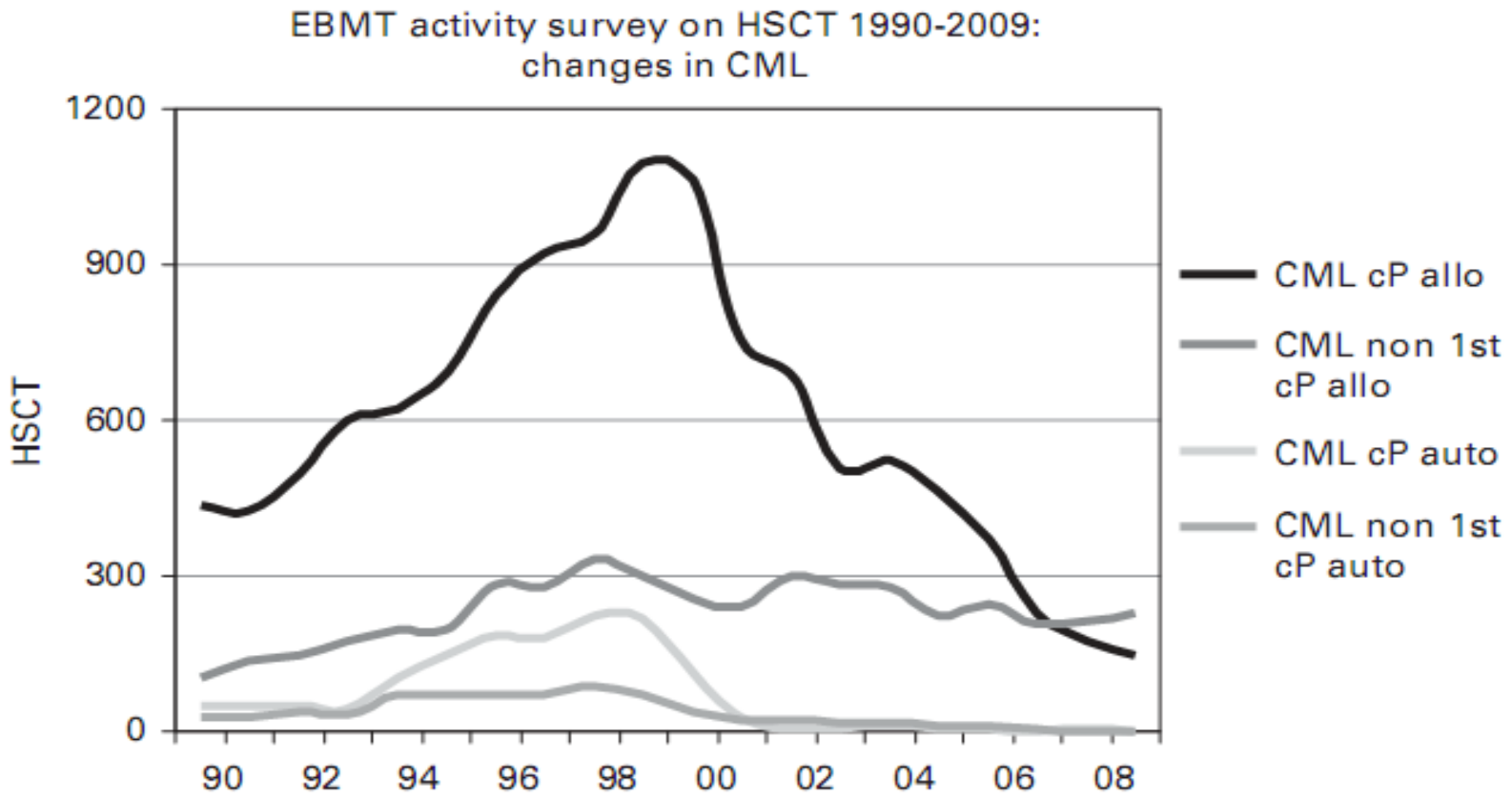
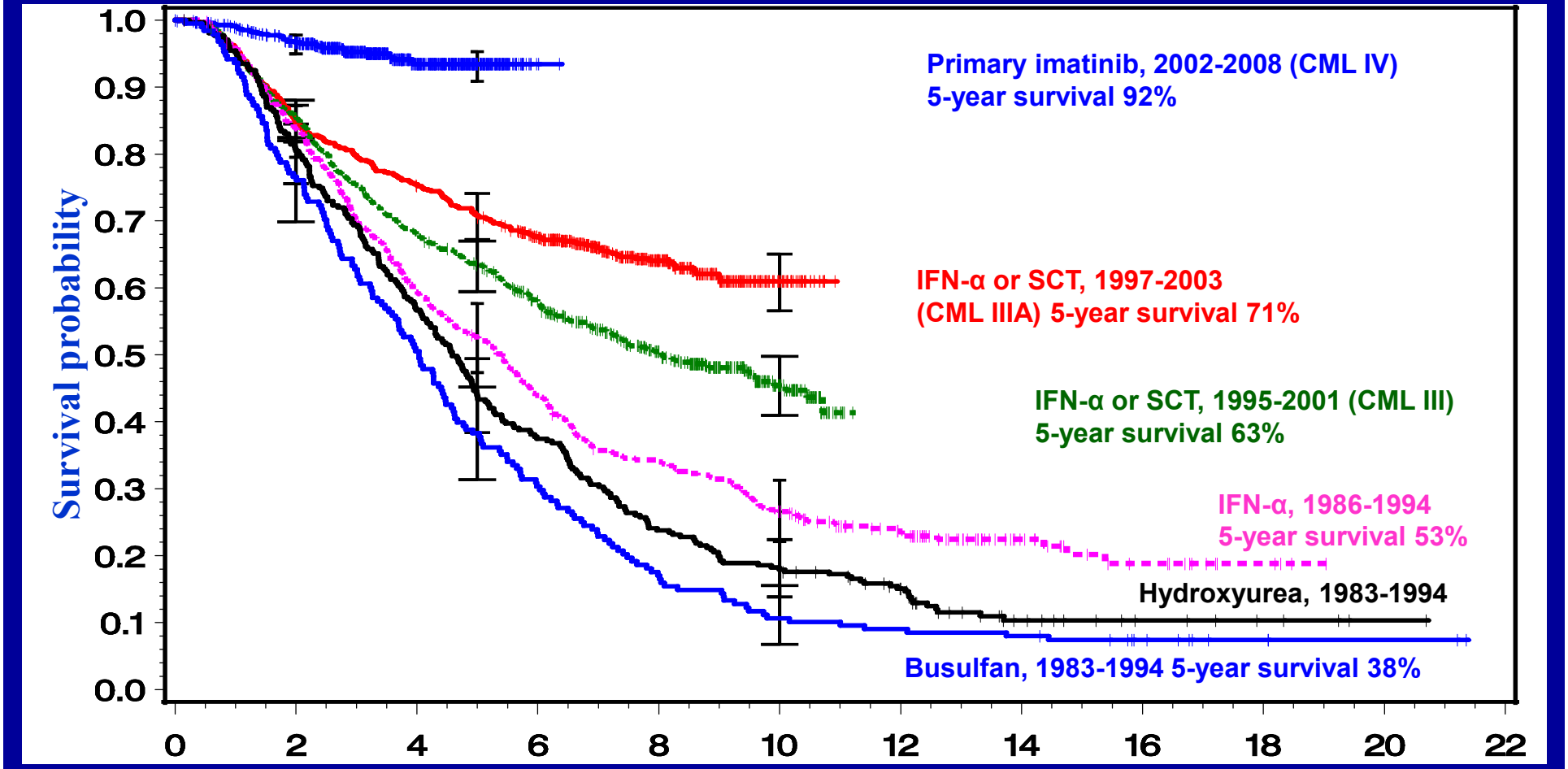


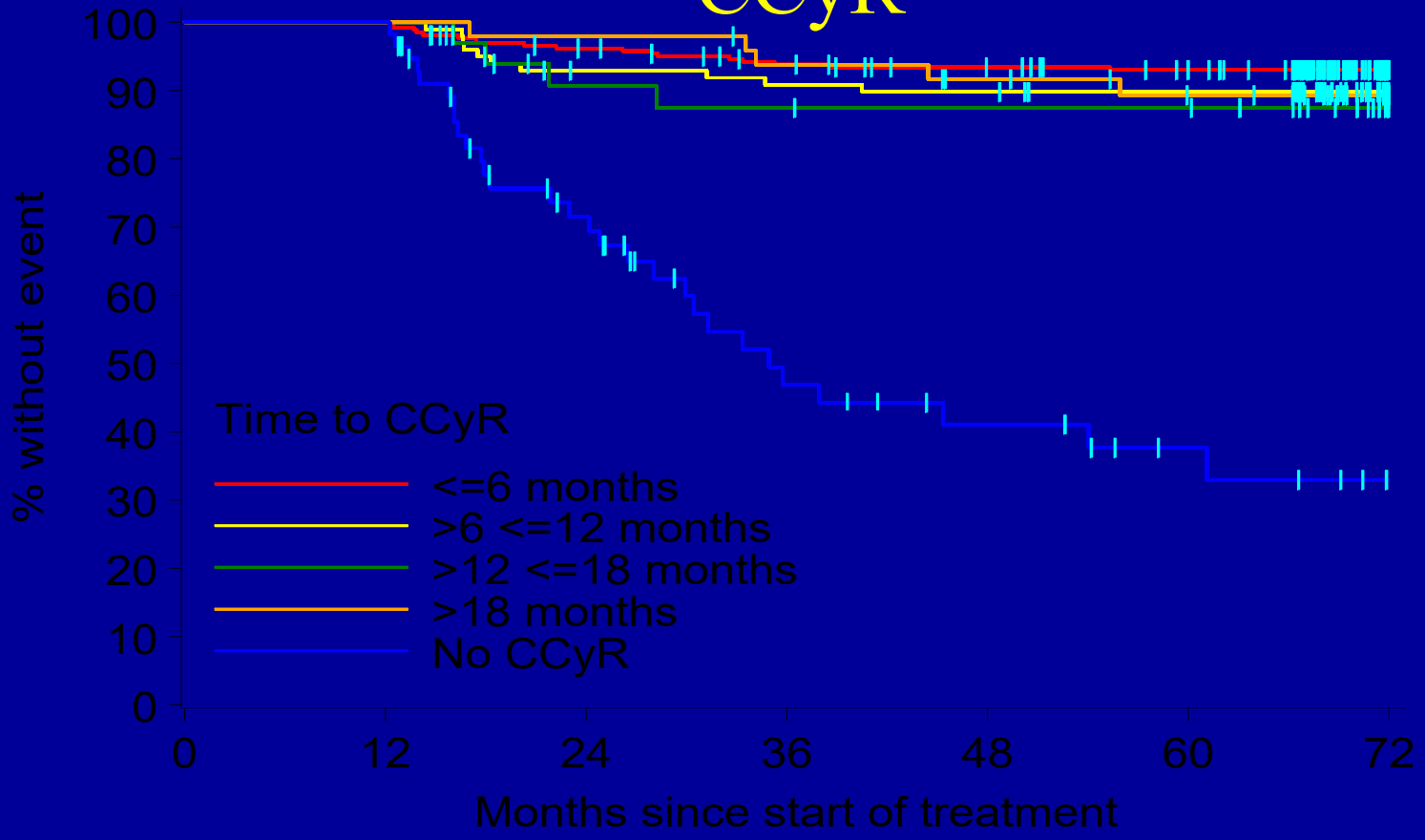
Figure 1 EBMT activity survey on HSCT 1990–2009: changes in CML.

Survival with CML 1983-2008



German CML Study Group, 2008

Time to CCyR Does Not Affect Long-Term Outcomes for Pts on IM Therapy: EFS – by Time to CCyR



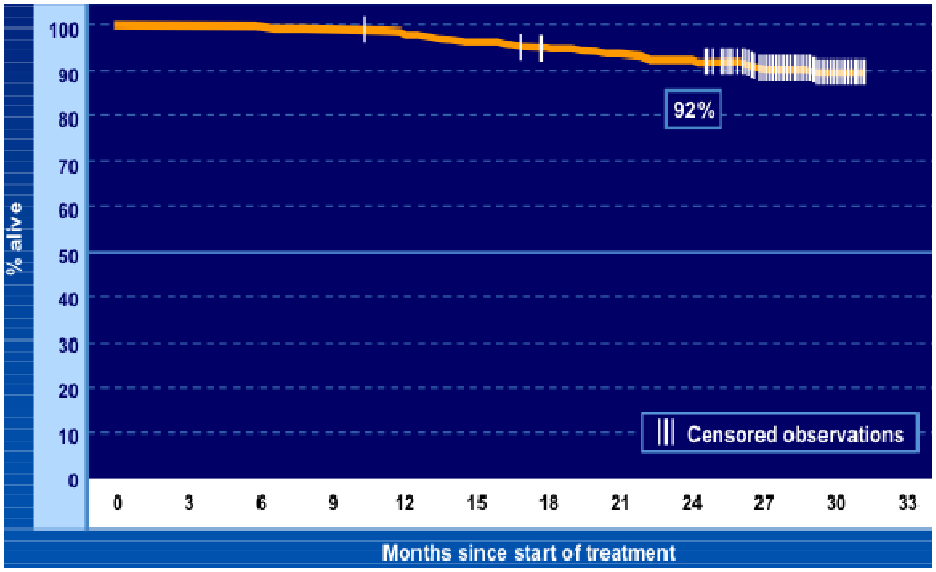
*P = 0.58 for EFS rates among pts who achieved a CCyR

Guilhot F. *et al*, Blood. 2007; 110, 11. Abstract 27. ASH 2007 Oral Presentation

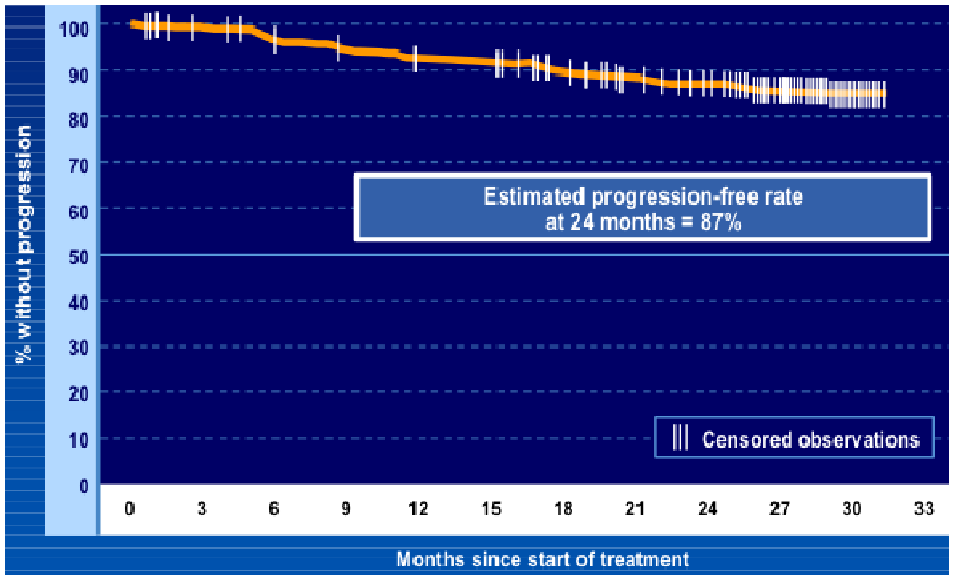
Obiettivo della terapia con TKI

LEUCEMIA MIELOIDE CRONICA
epoca post-inibitori Tyr-chinasi – endpoint clinici

Sopravvivenza



Progression-free survival



Circa il 90% dei pazienti con nuova diagnosi di LMC in fase cronica è vivo dopo cinque anni di follow-up e l'80% non ha presentato progressione di malattia

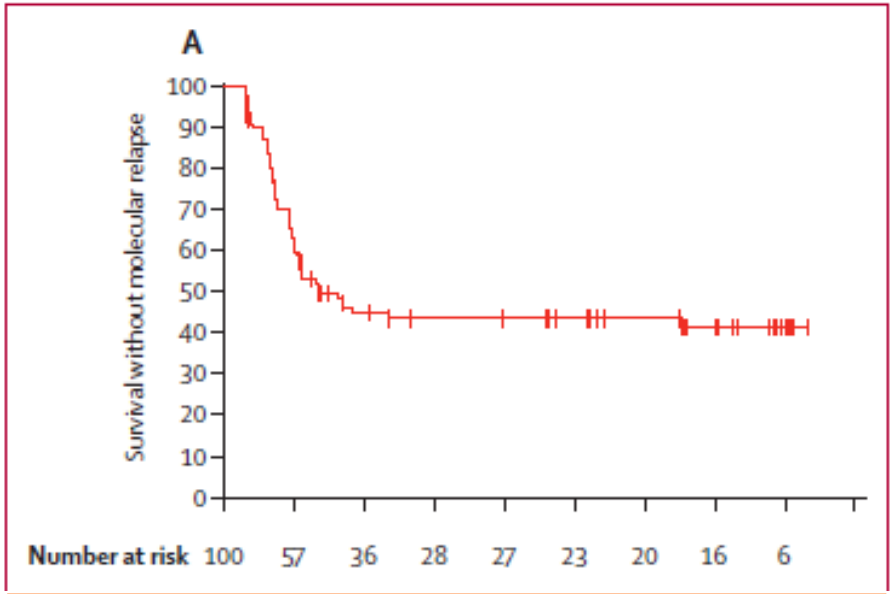
Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial

François-Xavier Mahon, Delphine Réa, Joëlle Guilhot, François Guilhot, Françoise Huguet, Franck Nicolini, Laurence Legros, Aude Charbonnier, Agnès Guerci, Bruno Varet, Gabriel Etienne, Josy Reiffers, Philippe Rousselot, on behalf of the Intergroupe Français des Leucémies Myéloïdes Chroniques (FILMC)

Lancet Oncol
2010

Pivotal Trial on Imatinib Discontinuation

- 100 pts
- 2y IM Therapy
- CMR= <5log undetectable (MR5.0 Und)



60% lost the MR
40% maintained the CMR

Factors POSITIVELY influencing TFR were:

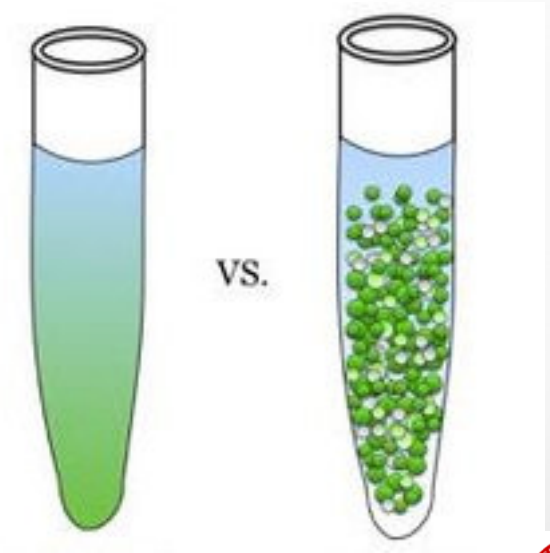
- Sex **(male)**
- Sokal risk **(low-risk)**
- IM duration **(≥ 50 months)**

dPCR advantages in deep responder CML patients monitoring

- **Sensitivity**
- **Accuracy**
- **Reduction of inhibitors sensitivity**
- **Absolute quantification**

QuantStudio 3D (ThermoFisherScientific) measures the absolute number of BCR-ABL copies/mcl of reaction

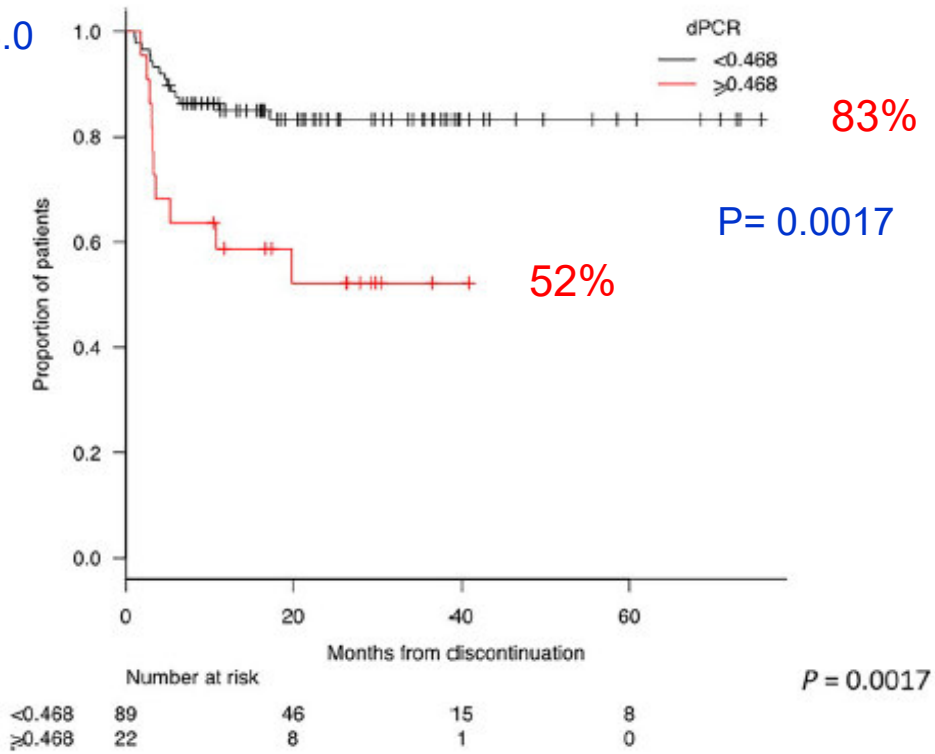
Especially for low levels of target



Digital PCR improves the quantitation of DMR and the selection of CML candidates to TKIs discontinuation

Bernardi et al, Cancer Med 2019

111 pts with ≥ MR 4.0



83%

P= 0.0017

52%

- Patients with dPCR < 0,468 copies/mcl before discontinuation, had a significantly higher probability to maintain TFR (83% vs 52% @ 2 yrs)

- Positive Predictive Value (PPV) of a dPCR < 0,468 copies/mcl was 87%
- vs PPV 47% on RT-qPCR

residual disease by droplet digital PCR and TKI duration are critical predictive factors for molecular recurrence after stopping Imatinib first-line in chronic phase CML Patients: Results of the STIM2 study

ddPCR evaluation, TKI duration as predictors of recurrence after 1st-line Imatinib cessation in CP-CML. The STIM2 study

Franck E. Nicolini[1,2,31], Stéphanie Dulucq[3,31], Lisa Boureau[3], Pascale Cony-Makhoul[4,31], Aude Charbonnier[5,31], Martine Escoffre-Barbe[6,31], Françoise Rigal-Huguet[7,31], Valérie Coiteux[8,31], Bruno Varet[9,31], Viviane Dubruille[10,31], Pascal Lenain[11,31], Philippe Rousselot[12,31], Delphine Rea[13,31], Agnès Guerci-Bresler[14,31], Laurence Legros[15,31], Jixing Liu[16,31], Martine Gardembas[17,31], Jean-Christophe Ianotto[18,31], Pascal Turlure[19,31], Hyacinthe Johnson-Ansah[20,31], Juliana Martiniuc[20], Henry Jardel[22], Bertrand Joly[23], Patricia Zunic[24,31], Tawfiq Henni[25], Bruno Villemagne[26], Marc Berger[27,31], Emilie Cayssials[28,31], François Guilhot[28,31], Fabrice Larosa[29,31], Joëlle Guilhot[28,31], Gabriel Etienne [30,31], François-Xavier Mahon[30,31].