Roma, 16 novembre 2015

Leucemia mieloide cronica Ph+: descrizione della patologia, il corretto approccio diagnostico e monitoraggio secondo le ELN e le nuove tecnologie

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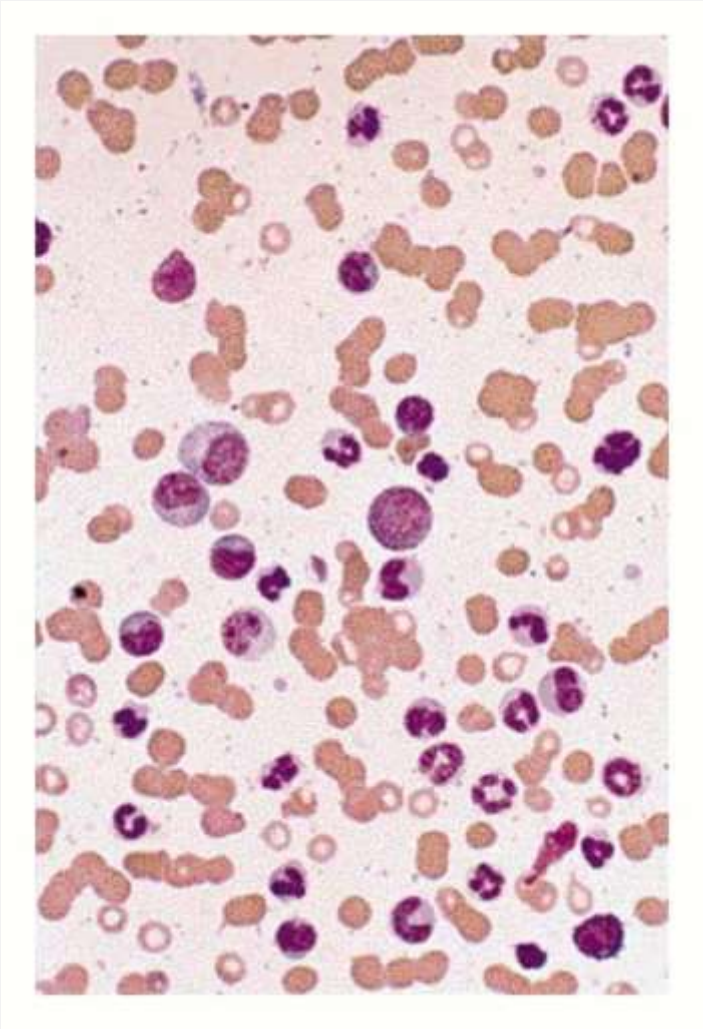
Cenni storici

- 1845 H Bennett ad Edimburgo: "*caso di ipertrofia splenica ed epatica nella quale la morte prende origine dalla suppurazione del sangue"*
- 1845 R Virchow a Berlino "sangue bianco"
- 1847 R Virchow conia il termine "leucemia"
- 1852 H Bennett rilancia il termine "leucocitemia"

Leucemia mieloide cronica

- 1879 P Erlich: introduzione delle colorazioni specifiche per il sangue
- 1891 Classificazione delle leucemie
- 1900 nascita del profilo morfologico della LMC caratterizzata da una predominanza di granulociti segmentati.
- 1920 Basofilia e trombocitosi caratteristiche

Photomicrographs of a Peripheral-Blood Sample and Bone Marrow Samples from a Patient with Chronic Myeloid Leukemia



Sawyers, C. L. N Engl J Med 1999;340:1330-1340

The NEW ENGLAND JOURNAL of MEDICINE

Andamento clinico e prognosi

- 1924 Minot sopravvivenza mediana 3 anni con 12% di pazienti vivi tra 5 e 10 anni dalla diagnosi
- non ancora riconosciute le fasi di malattia
- 1931 riconosciuto ruolo prognostico della percentuale crescente di mieloblasti
- 1947 contenuto anomalo di fosfatasi alcalina leucocitaria
- 1959 “metamorfosi” in corso di LMC (Bernard)
- 1963 riconosciuta fase blastica linfoide (Mathe’)

Il cromosoma Filadelfia

- 1960 Nowell e Hungerford descivono un minuto cromosoma acrocentrico nel sangue periferico di 7 pazienti con LMC
- inizialmente ritenuto cromosoma 21, quindi riconosciuto derivare dal cromosoma 22
- 1973 la porzione deleta è traslocata sul cromosoma 9 (Rowley)
- descrizione del breakpoint cluster regions e caratterizzazione del gene di fusione bcr-abl (Sawyers)

1960: la scoperta del cromosoma Philadelfia

A Minute Chromosome in Human Chronic Granulocytic Leukemia

In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of *acute* granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* **25**, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al., Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

PETER C. NOWELL
School of Medicine, University of Pennsylvania
DAVID A. HUNGERFORD
Institute for Cancer Research

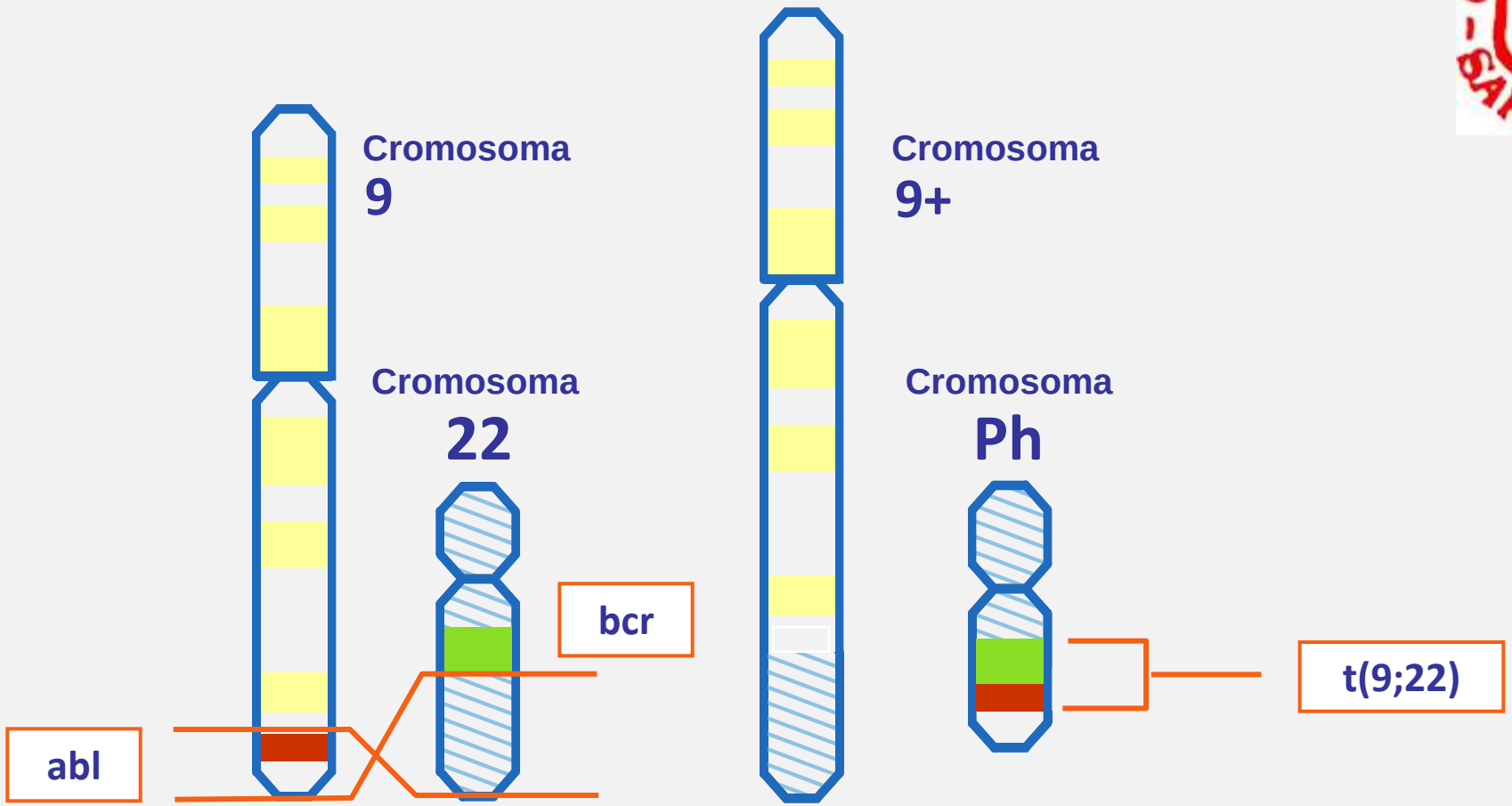
1960

A minute chromosome in human granulocytic leukemia. Science 132, 1960, 1497.

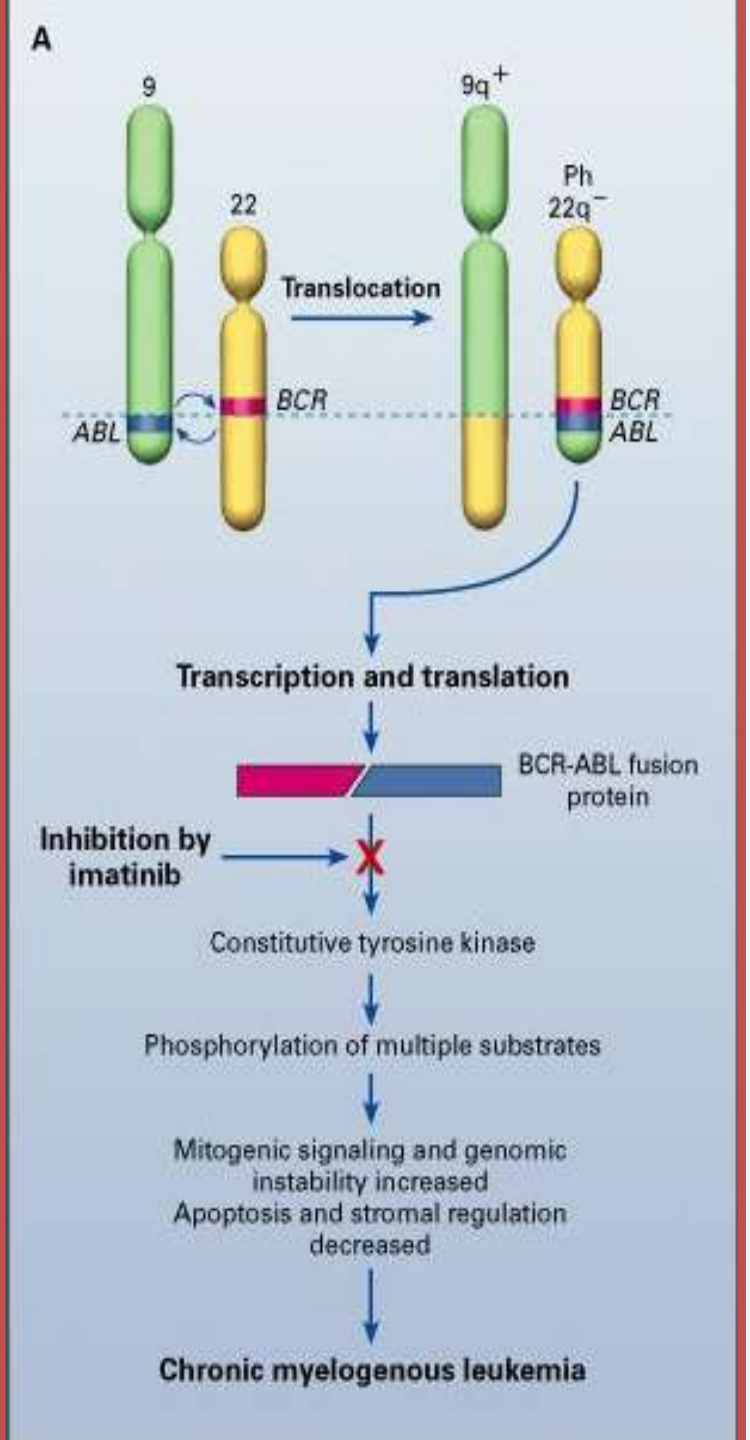
P.C. Nowell, D.A. Hungerford, University of Pennsylvania in Philadelphia

1984: la scoperta della traslocazione t(9;22)

La traslocazione t (9;22)



Janet Rowley 1973, Sawyers 1984



Bone marrow

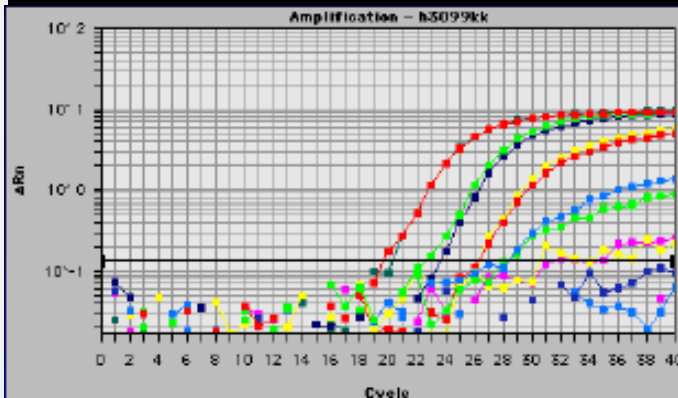
Cytogenetics

FISH

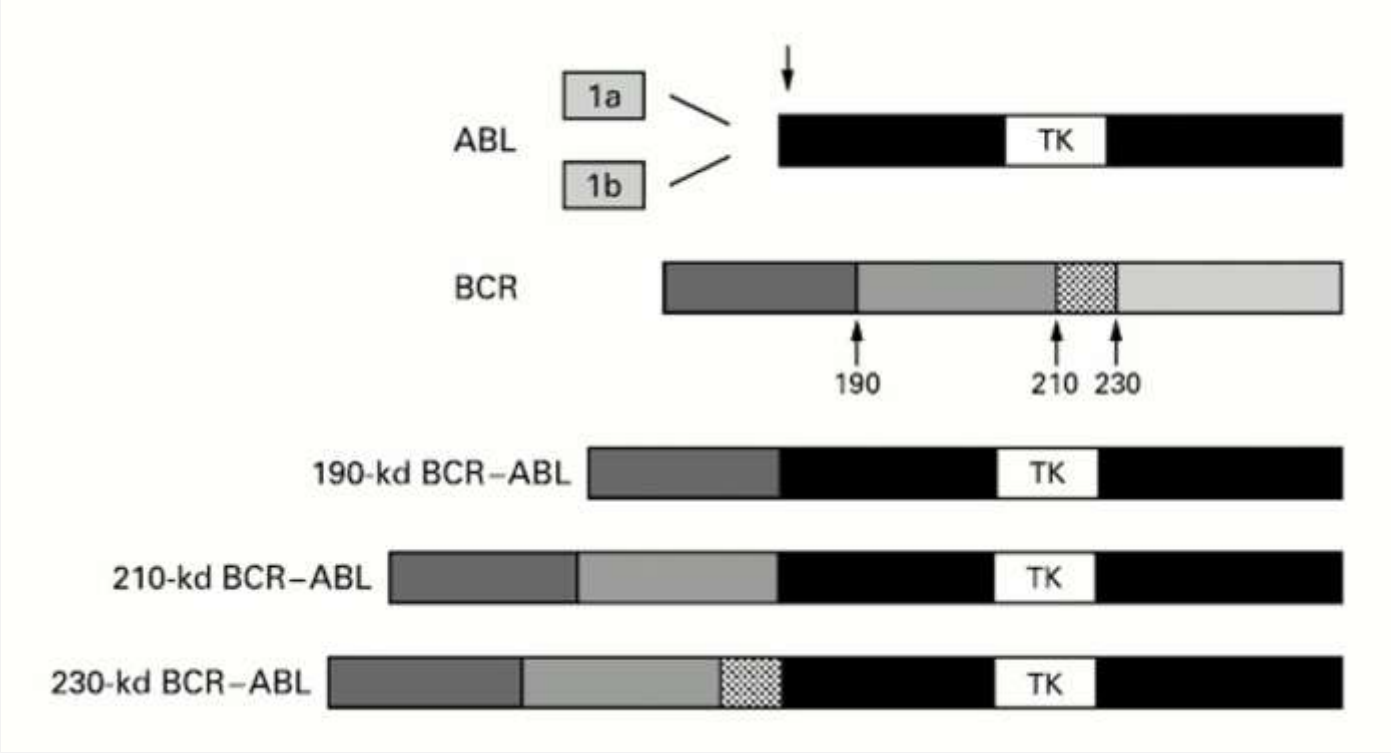
PCR

Philadelphia chromosome

BCR-ABL rearrangement



Structure of BCR-ABL Fusion Proteins



Sawyers, C. L. N Engl J Med 1999;340:1330-1340

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LMC: classificazione WHO

- “a myeloproliferative disease that originates in an abnormal pluripotential bone marrow stem cell and is consistently associated with a Philadelphia (Ph) chromosome and/or the BCR/ABL fusion gene”

Characteristics of Patients with Chronic Myeloid Leukemia at Presentation

TABLE 1. CHARACTERISTICS OF PATIENTS WITH CHRONIC MYELOID LEUKEMIA AT PRESENTATION.

Clinical findings*
Fatigue, anorexia, weight loss
Splenomegaly
Hepatomegaly
Peripheral-blood findings
Elevated white-cell count (usually greater than 25,000/mm^3)
Elevated platelet count in 30 to 50 percent of cases
Basophilia
Reduced leukocyte alkaline phosphatase activity
All stages of granulocyte differentiation visible on peripheral smear
Bone marrow findings
Hypercellularity, reduced fat content
Increased ratio of myeloid cells to erythroid cells
Increased numbers of megakaryocytes
Blasts and promyelocytes constitute less than 10 percent of all cells

*Approximately 40 percent of patients are asymptomatic.

Sawyers, C. L. N Engl J Med 1999;340:1330-1340

The NEW ENGLAND JOURNAL of MEDICINE

Cenni storici del trattamento

- Lissauer 1865: arsenico
- 1903 arsenico
- 1912 benzene → radioterapia

- Senn 1903 rapido effetto di raggi X su milza e leucocitosi
- risposte drammatiche dopo irradiazione splenica

Chemotherapeutic Drugs Used to Treat the Chronic Phase of Chronic Myeloid Leukemia

TABLE 2. CHEMOTHERAPEUTIC DRUGS USED TO TREAT THE CHRONIC PHASE OF CHRONIC MYELOID LEUKEMIA.

DRUG	DOSE*	ADVERSE EFFECTS†
Hydroxyurea	0.5–2.0 g/day orally	Cytopenias, rash, nausea
Busulfan	2.0–6.0 mg/day orally	Cytopenias, rash, bone marrow aplasia
Interferon alfa	5 million U/m²/day subcutaneously	Fever, myalgias, rash, depression, thrombocytopenia
Interferon alfa plus cytarabine	Interferon alfa, 5 million U/m²/day subcutaneously, plus cytarabine, 20 mg/m²/day for 10 days each month	Fever, myalgias, rash, depression, thrombocytopenia, nausea, vomiting, diarrhea, mucositis, weight loss

*Doses are modified on an individual basis according to changes in the patient's peripheral-blood counts.

†Data are from randomized clinical trials.[54-56]

Sawyers, C. L. N Engl J Med 1999;340:1330-1340

The NEW ENGLAND JOURNAL of MEDICINE

Fattori di rischio

- Sokal score
- score Euro o Hashford
- Eutos score

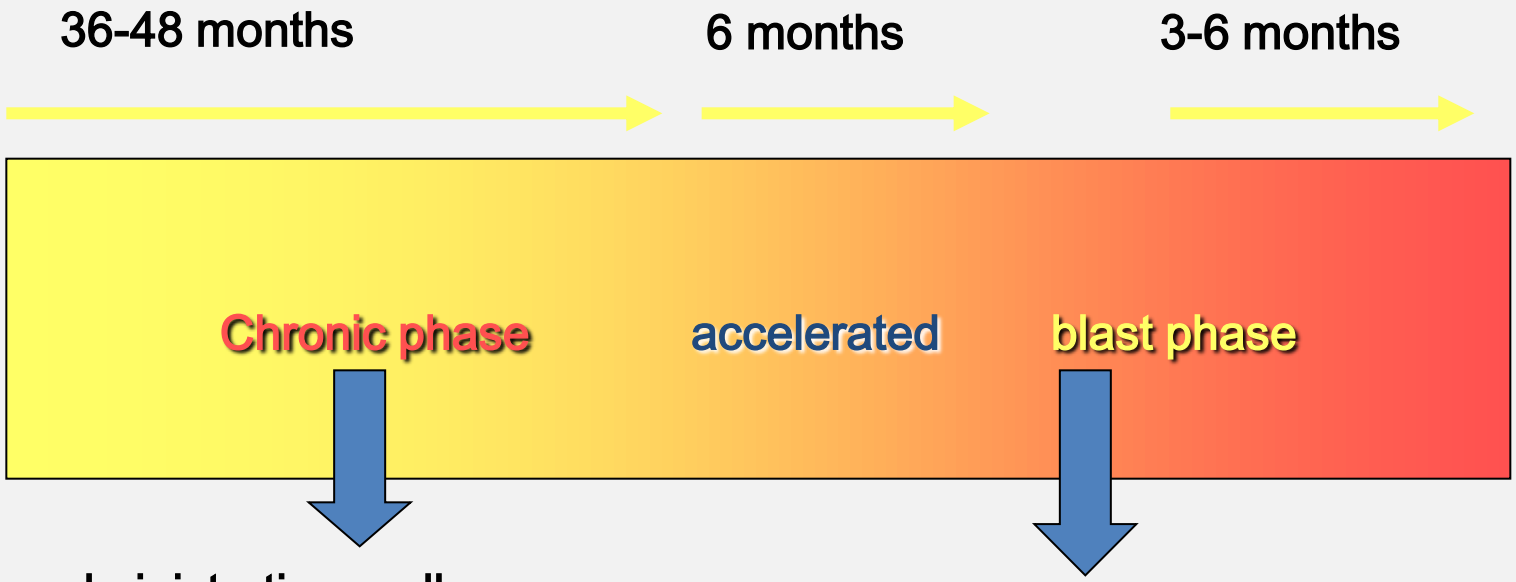
suddividono la popolazione di pazienti con LMC in rischio basso, intermedio ed alto
parametri valutati: età, dimensioni spleniche, conta piastrinica, eosinofili, basofili (Euro) e mieloblasti
Euro maggiormente sensibile nel basso rischio

LMC: HU/BUS - OS per rischio (813 casi) *

	%	4 anni	6 anni	8 anni
Sokal Low	31%	65%	38%	23%
Sokal Int	41%	45%	22%	12%
Sokal High	28%	30%	13%	<10%

* Sokal et al (1984)

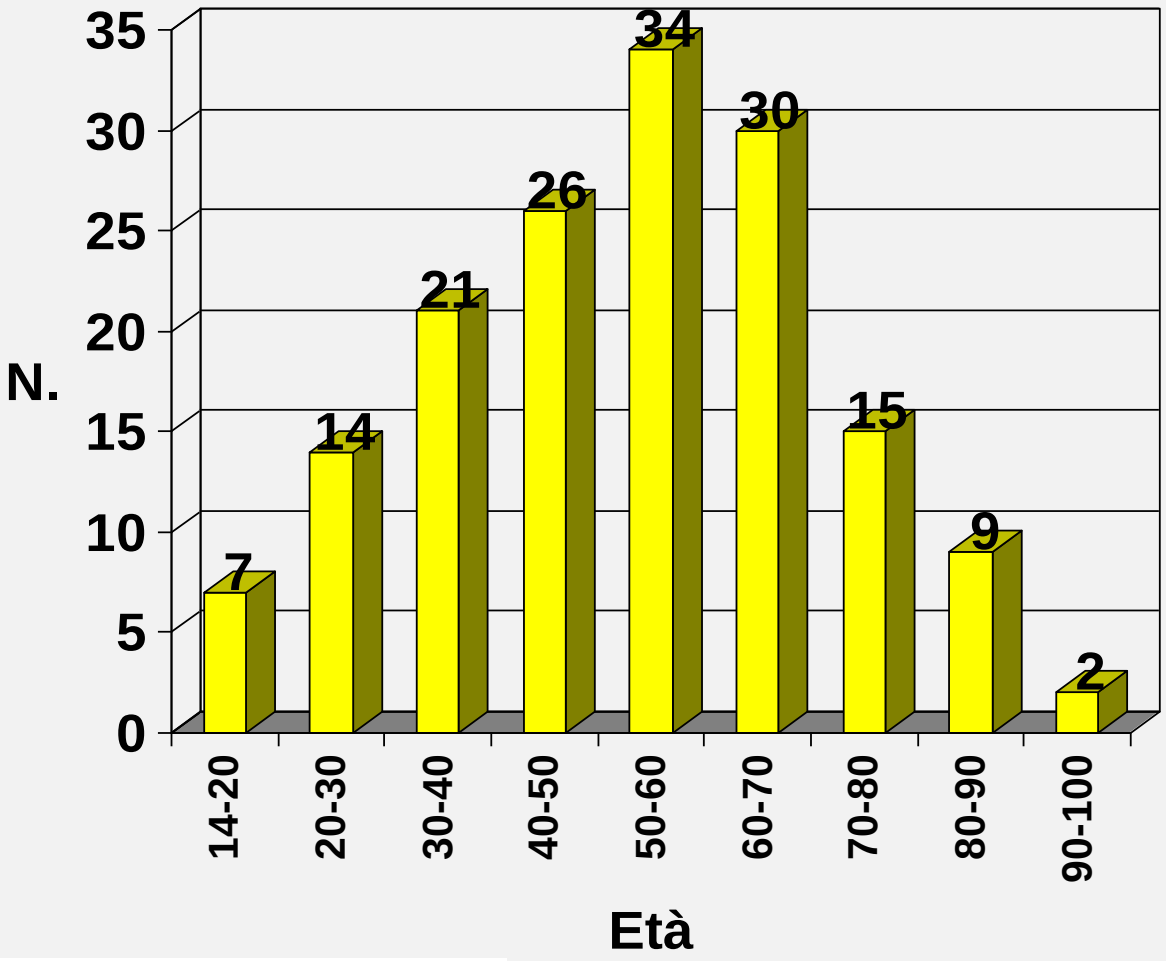
CML
Hydroxyurea period (1975-1985)



- Easy administration orally
- Easy control of blood cells
- Minor side effects
- No cytogenetic responses
- Natural history unchanged

- Resistance of disease
- Difficult or no control of WBC
- Patient in bad condition

CML / AGE DISTRIBUTION

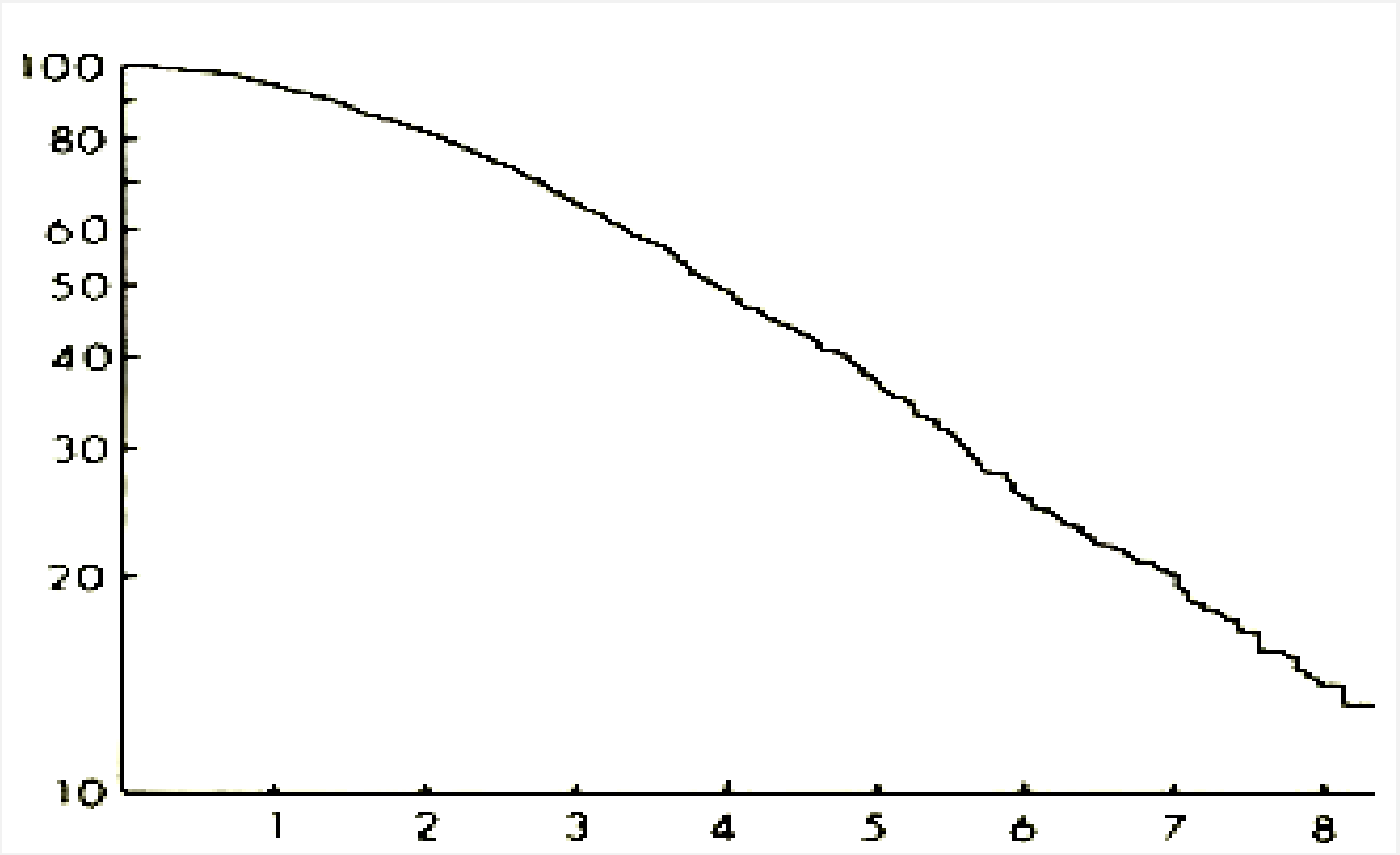


Median age 53
Range 14-96

90/170 above the age of 50 yrs

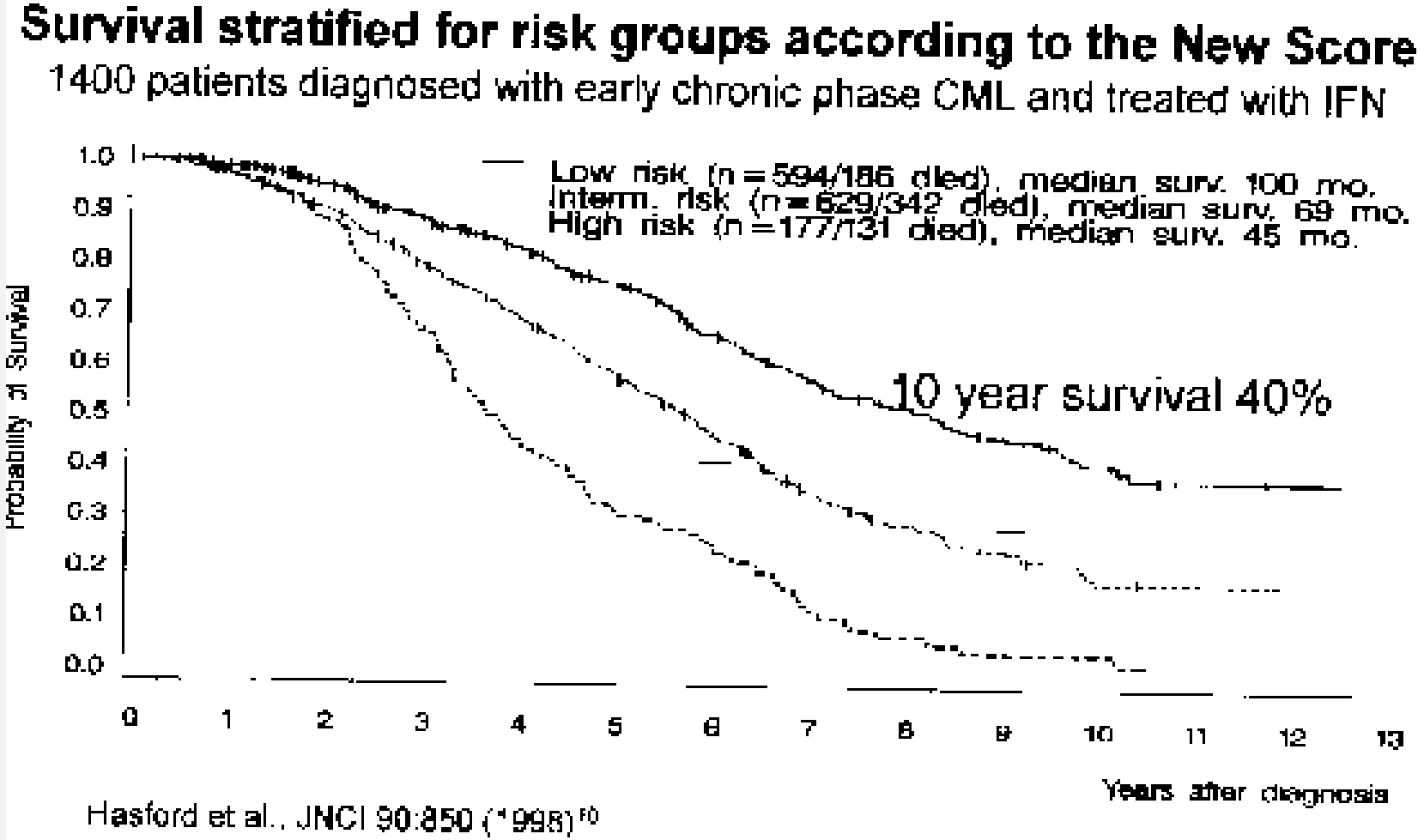
CML

Survival with hydroxyurea treatment



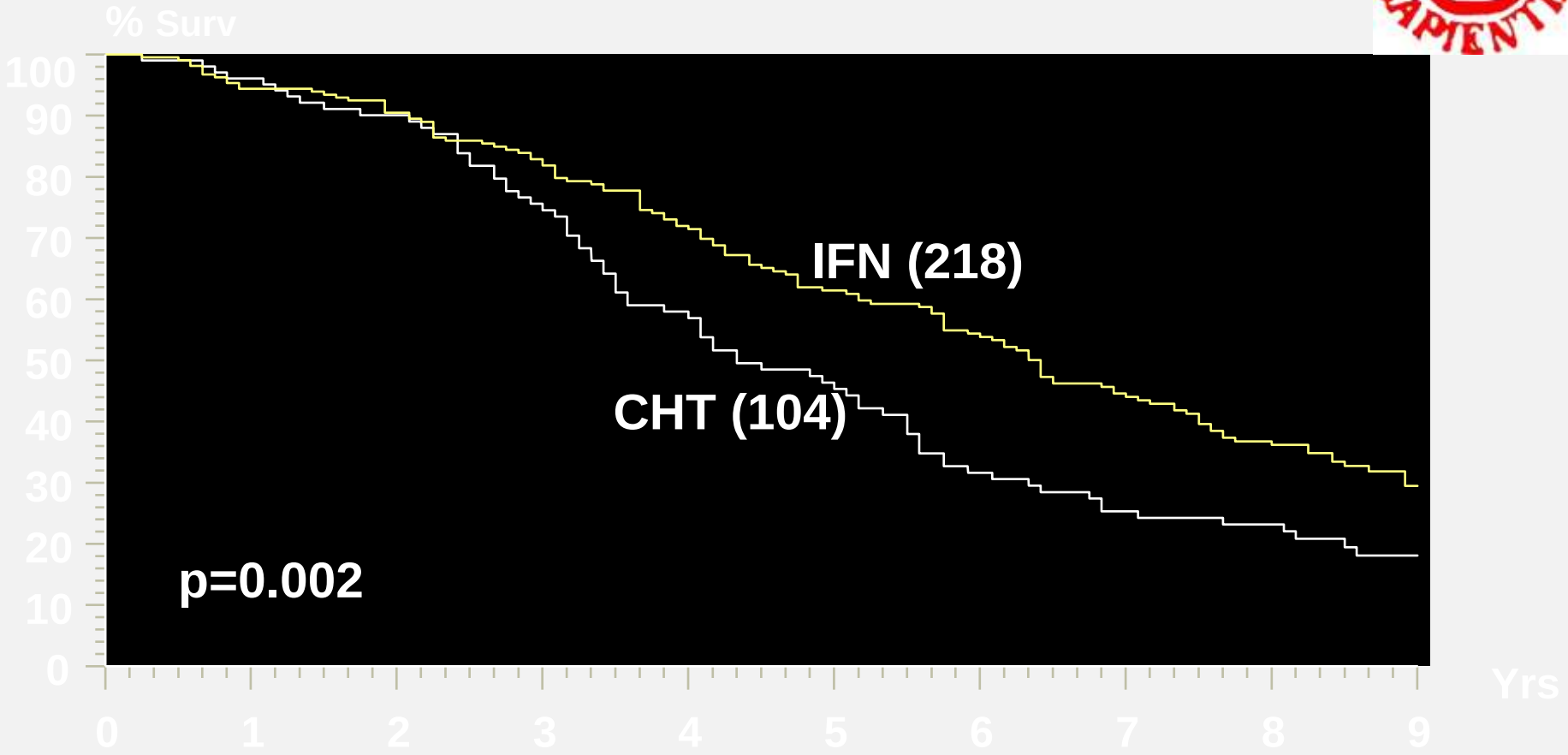
Blood, 1984, 63, 789

SURVIVAL BY EURO RISK
1400 IFN TREATED PATIENTS



ICSG on CML - PROT. ROFERON / CML 86

Survival By Arm



Median Survival (IC)
IFN 76 m. (69-86)
CHT 52 m. (43-66)

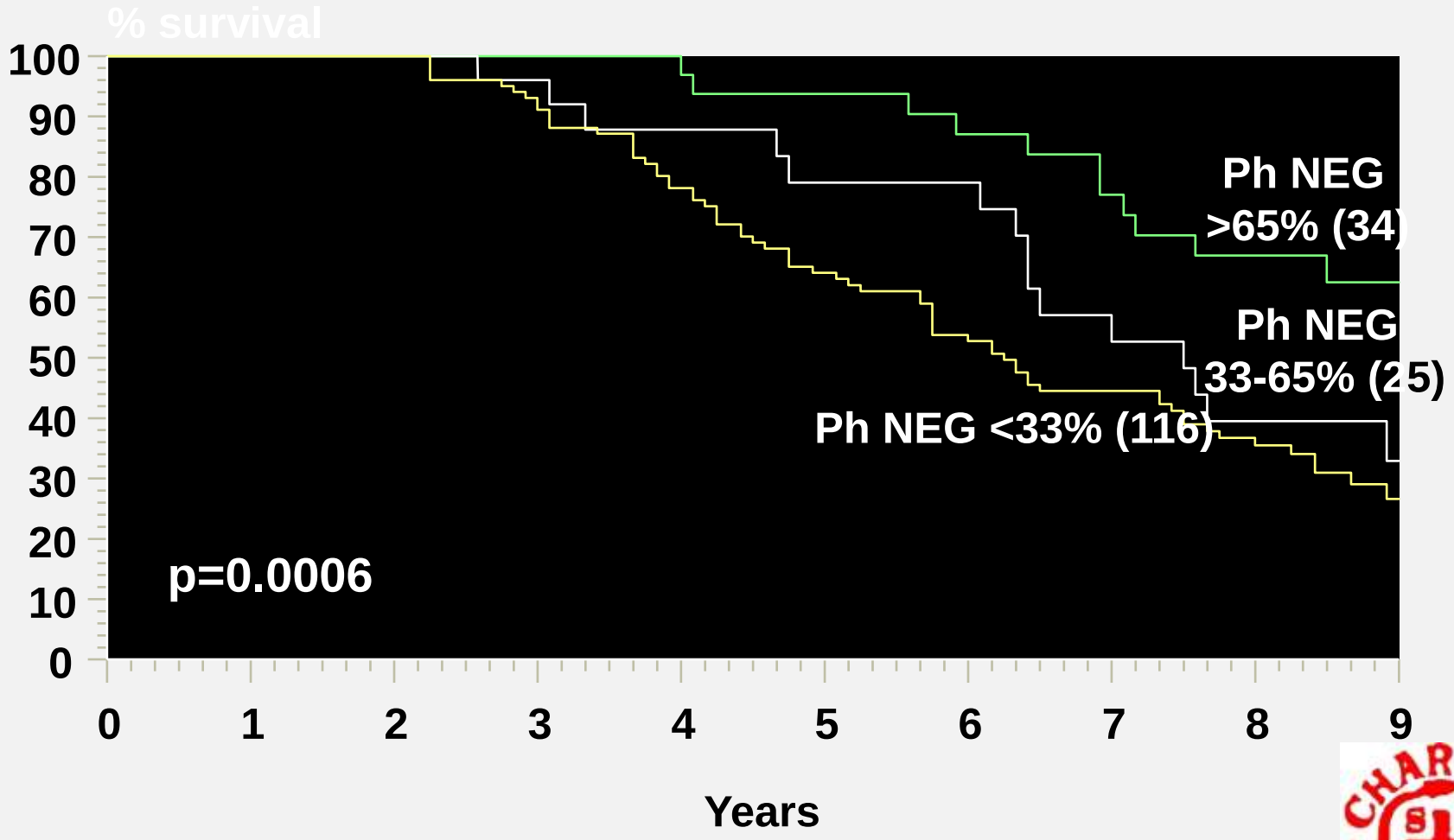
10 Years Survival (IC)
IFN 29% (23-36)
CHT 17% (9-25)

Median Time to AB/P
IFN 74 m.
CHT 46 m.

TUR97003.PRS

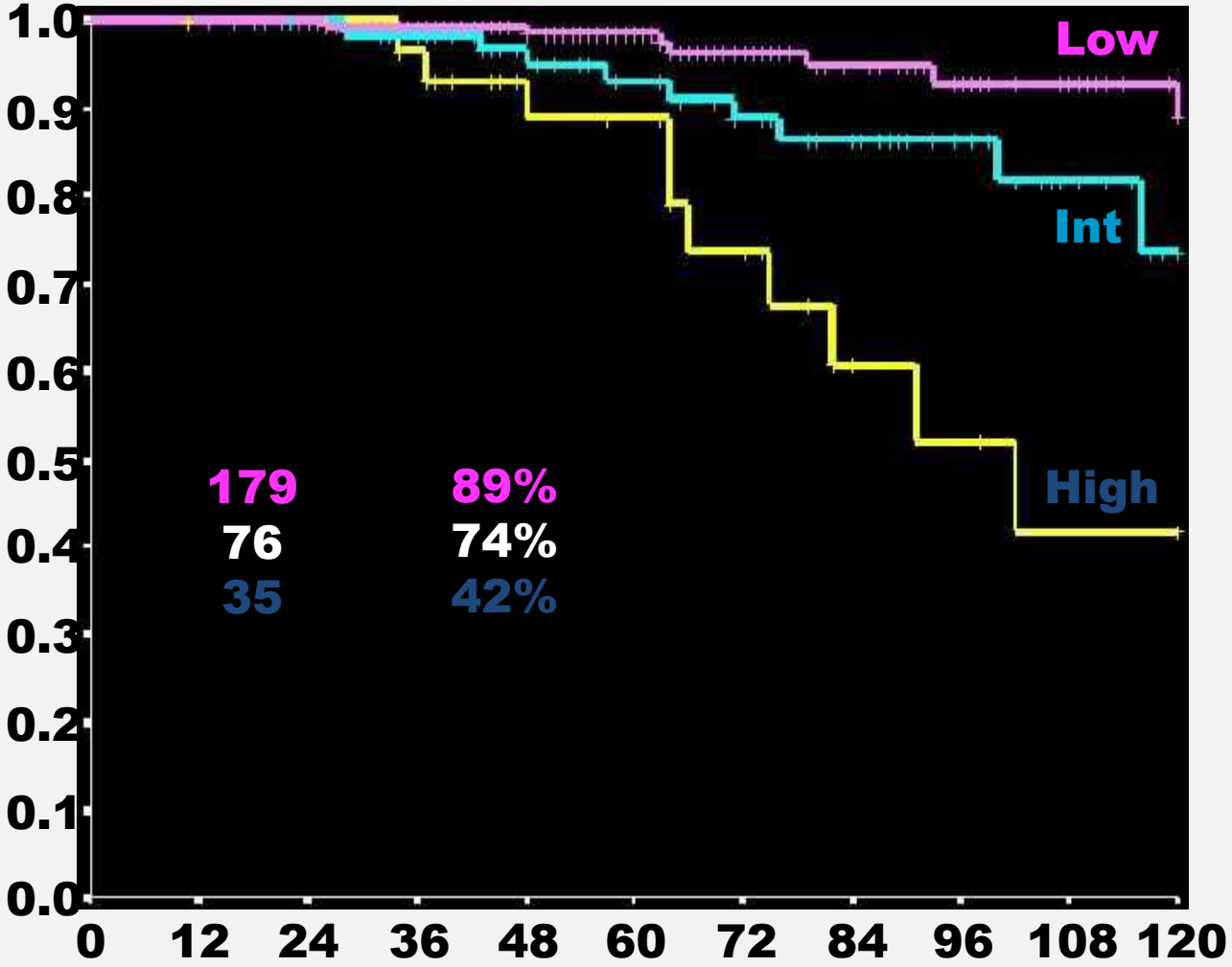
ICSG on CML - PROT. IFN/CML

SURVIVAL BY CYTOGENETIC RESPONSE LANDMARK AT 2 YEARS



TUR97003.PRS

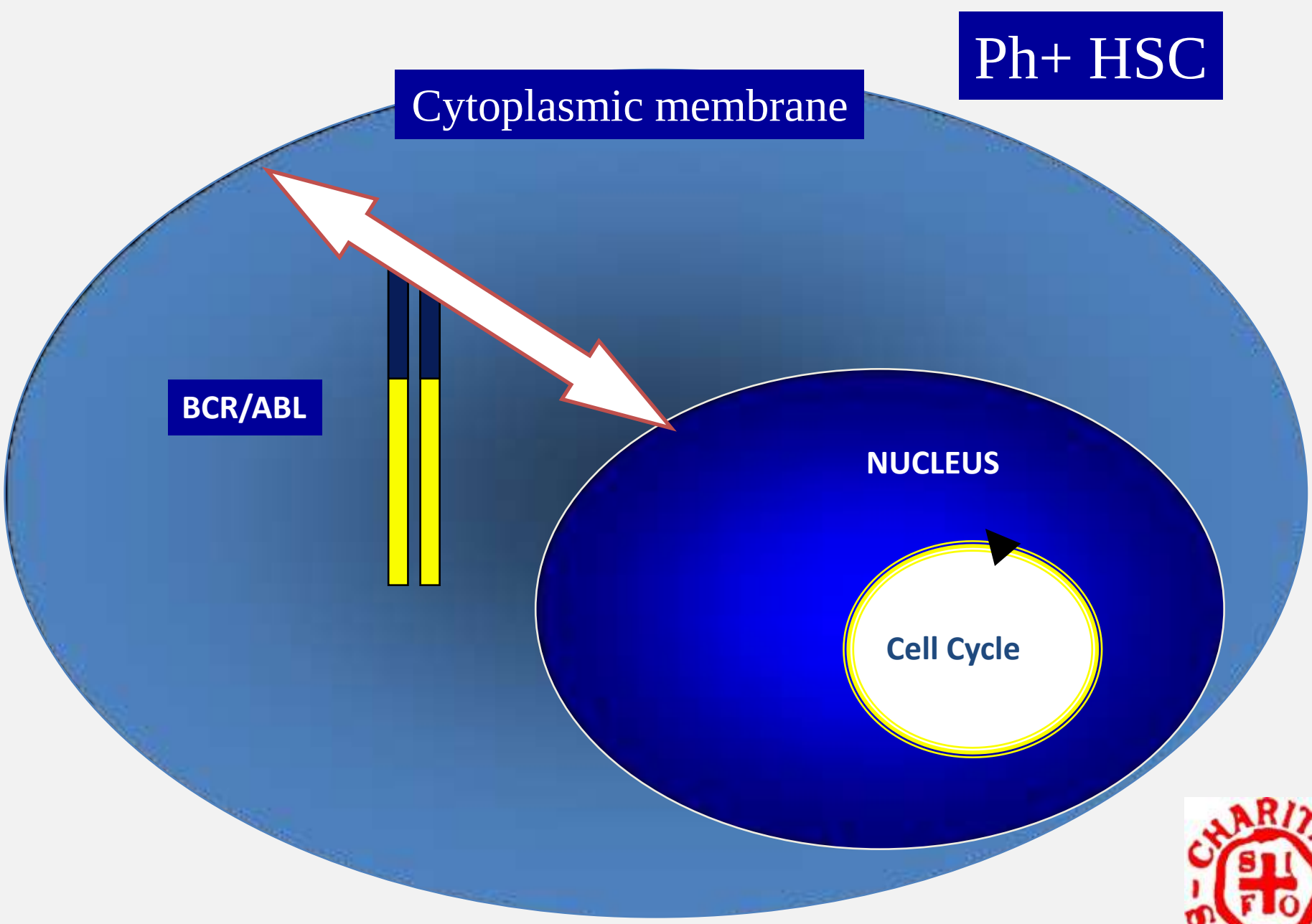
OVERALL SURVIVAL BY SOKAL SCORE

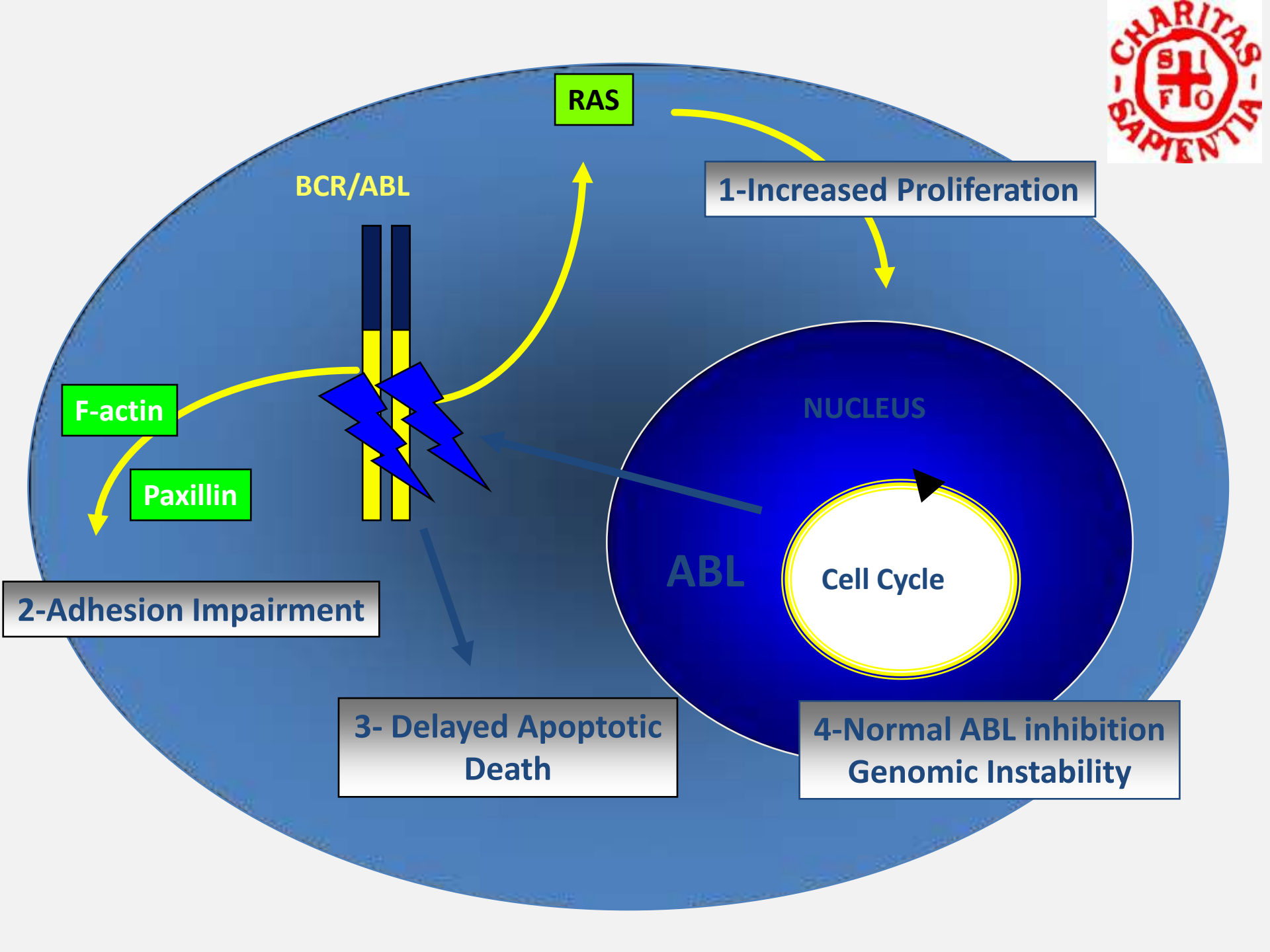


ERCCR / IFN

ICSG on CML

ROS00016.PPT


Ph+ HSC
Cytoplasmic membrane
BCR/ABL
NUCLEUS
Cell Cycle


RAS
BCR/ABL
1-Increased Proliferation
F-actin
Paxillin
NUCLEUS
ABL
Cell Cycle
2-Adhesion Impairment
3- Delayed Apoptotic Death
4-Normal ABL inhibition Genomic Instability

LMC - Obiettivi del Trattamento

PRIMARIO
Prolungare la sopravvivenza e guarire

La mediana di sopravvivenza > 5 anni
Per i bassi rischi > 10 anni
40% del totale, 89% dei CCR

MARKERS SURROGATI

RE **Risposta Ematologica**
RC **Risposta Citogenetica**
R MOL **Risposta Molecolare**

Historical Milestones in CML

1982-1985

John Groffen, Nora Heisterkamp, Gerald Grosveld, E. Cannani, David Baltimore and Owen Witte show that an abnormal gene and protein called *BCR-ABL* is produced as a consequence of the chromosome rearrangement that characterizes CML

Historical Milestones in CML

1987

Nicholas Lydon and Alex Matter commence a drug discovery program to target proteins such as BCR-ABL, in collaboration with Brian Druker, Thomas Roberts and Charles Stiles

Using a new technique called high throughput screening, in which thousands of molecules can be tested for their Biological activity, Lydon identified a compound called CGP57148B,later renamed STI-571

Historical Milestones in CML

1993

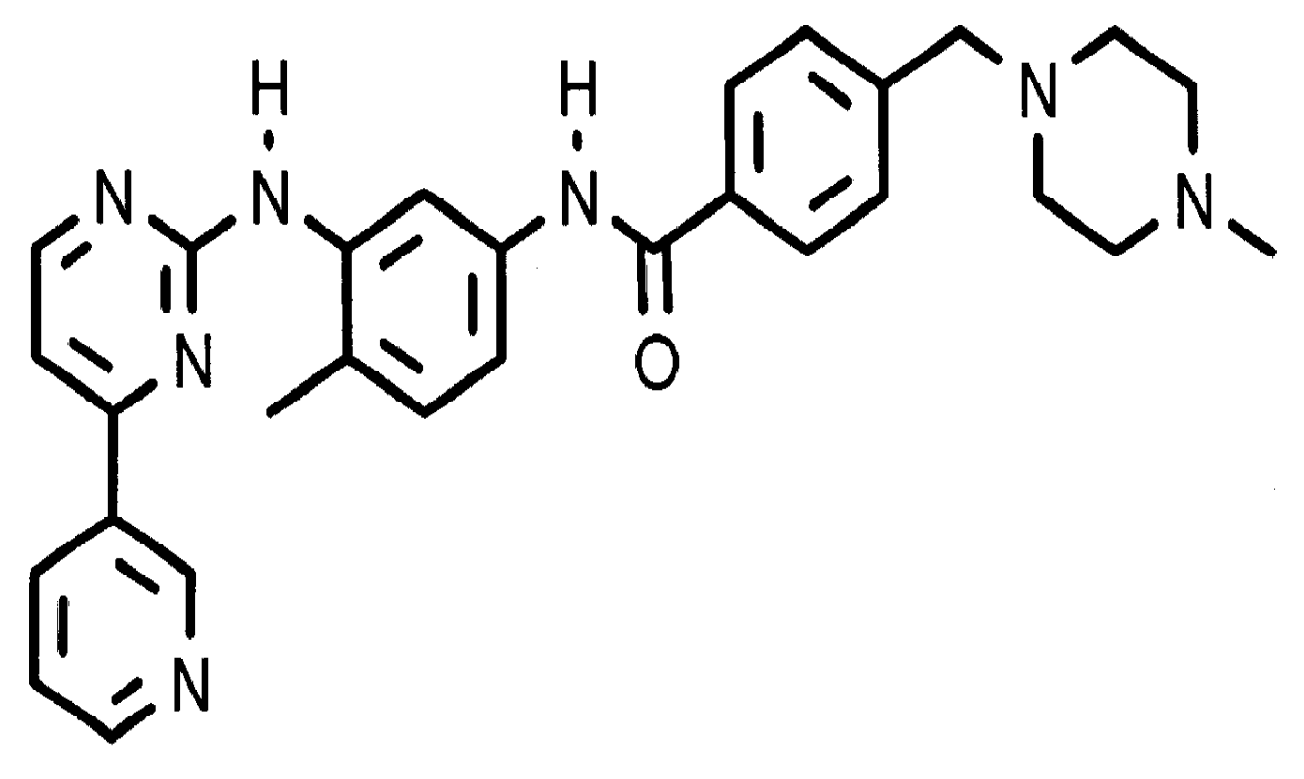
Brain Druker's laboratory shows that STI57I (imatinib) is the best of the compounds developed by Lyndon's group at specifically targeting and killing CML cells

Druker B. et al. *Nat Med* 1996, 2: 561-566

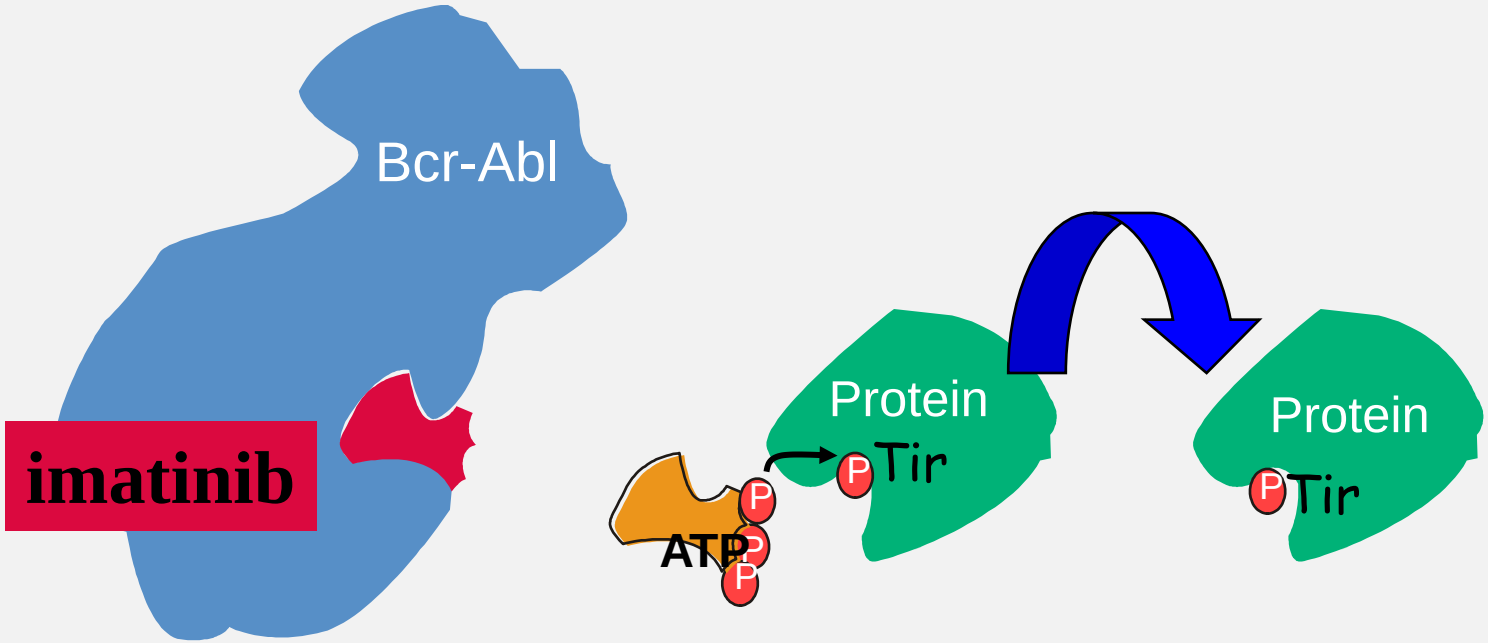
1998

Brian Druker, Charles Sawyers, and Moshe Talpaz begin clinical trials of imatinib

STI571 (CGP 57148B)
Imatinib mesylate Gleevec®
(Glivec®)

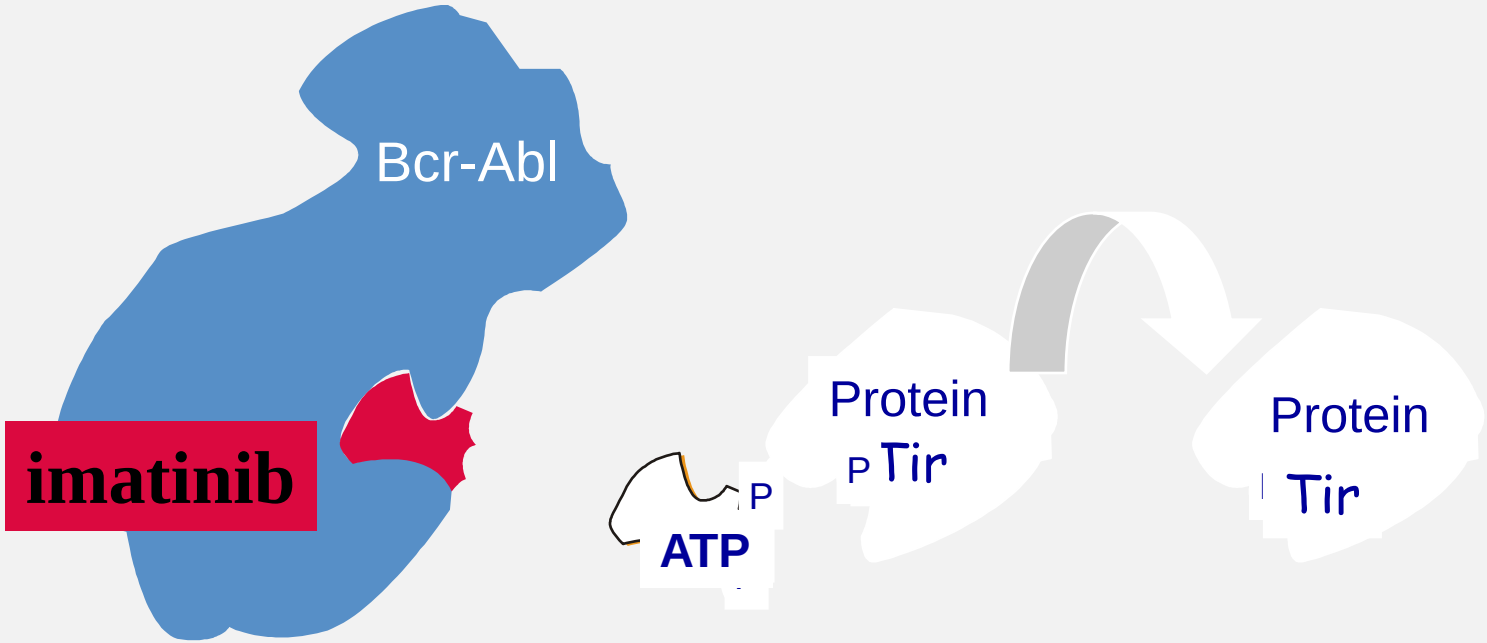


Glivec
Inhibition of BCR-ABL mediated Phosphorilation Of Target Proteins



Signal Transduction

Glivec
Inhibition of BCR-ABL mediated Phosphorilation Of Target Proteins



Signal Transduction inhibition

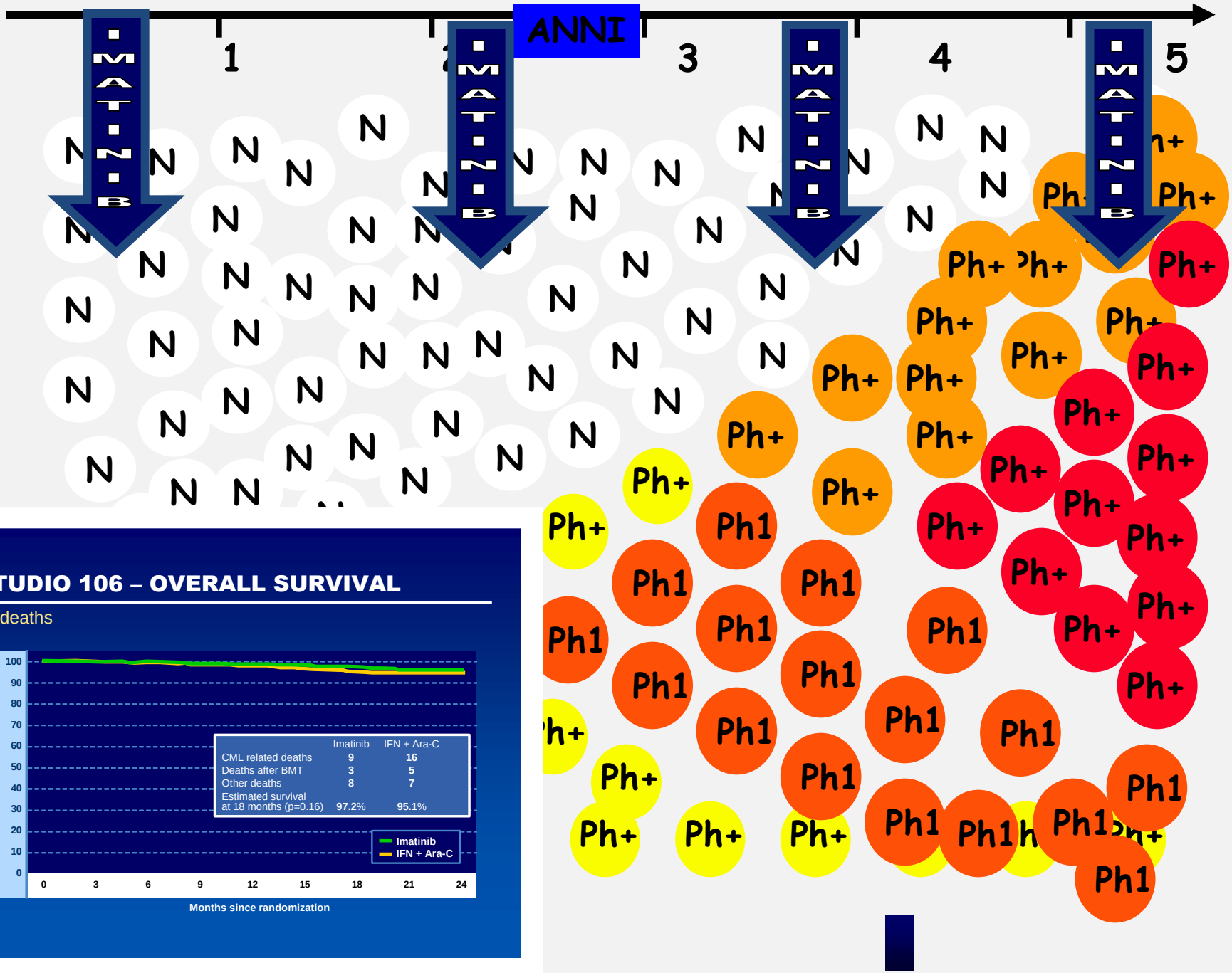
Historical Milestones in CML

2003

The IRIS trial showed that imatinib was superior to the standard combination of interferon-alpha/cytarabine

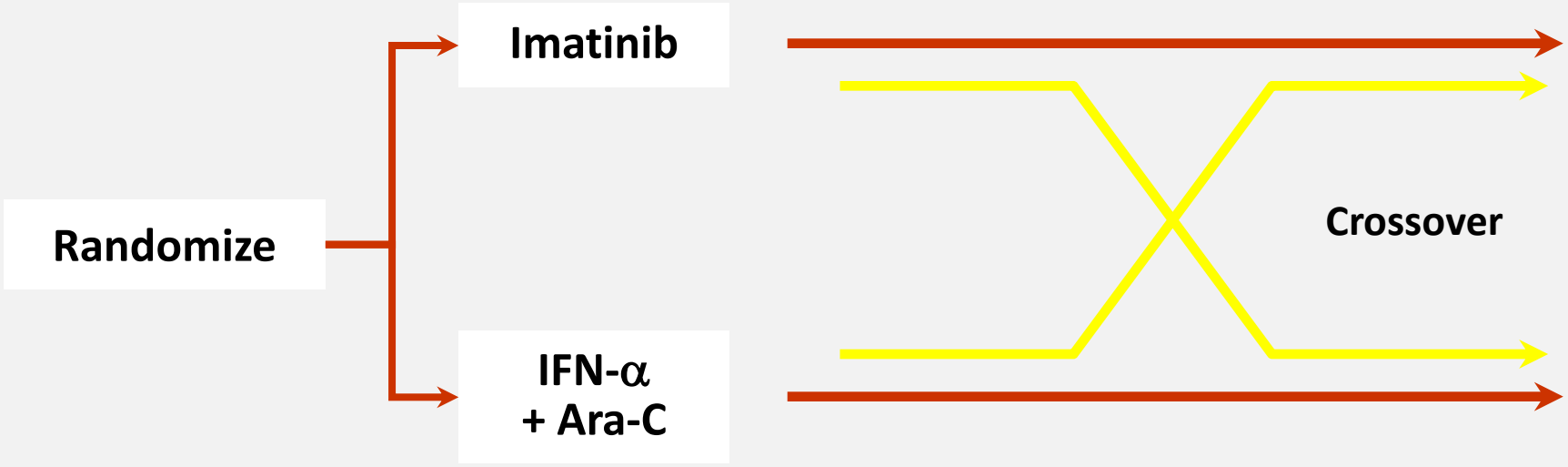
O'Brien S.G. et al . *N Engl J Med* 2003, 348: 994-1004

Charles Sawyers, Brian Druker, Andreas Hochhaus, and Francois-Xavier Mahon report that mutations of BCR-ABL are The major mechanism of imatinib resistance, leading to the development of second generation tyrosine kinase inhibitors such as dasatinib and nilotinib


ANNI
1
3
4
5
IMATINIB
N
Ph+
Ph1
STUDIO 106 – OVERALL SURVIVAL
All deaths
% alive
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
18
21
24
Months since randomization
Imatinib
IFN + Ara-C
Imatinib IFN + Ara-C
CML related deaths 9 16
Deaths after BMT 3 5
Other deaths 8 7
Estimated survival at 18 months (p=0.16) 97.2% 95.1%

106 TRIAL IRIS

Design



- **Crossover for**
  - lack of response
  - loss of response
  - intolerance of treatment

106 TRIAL IRIS

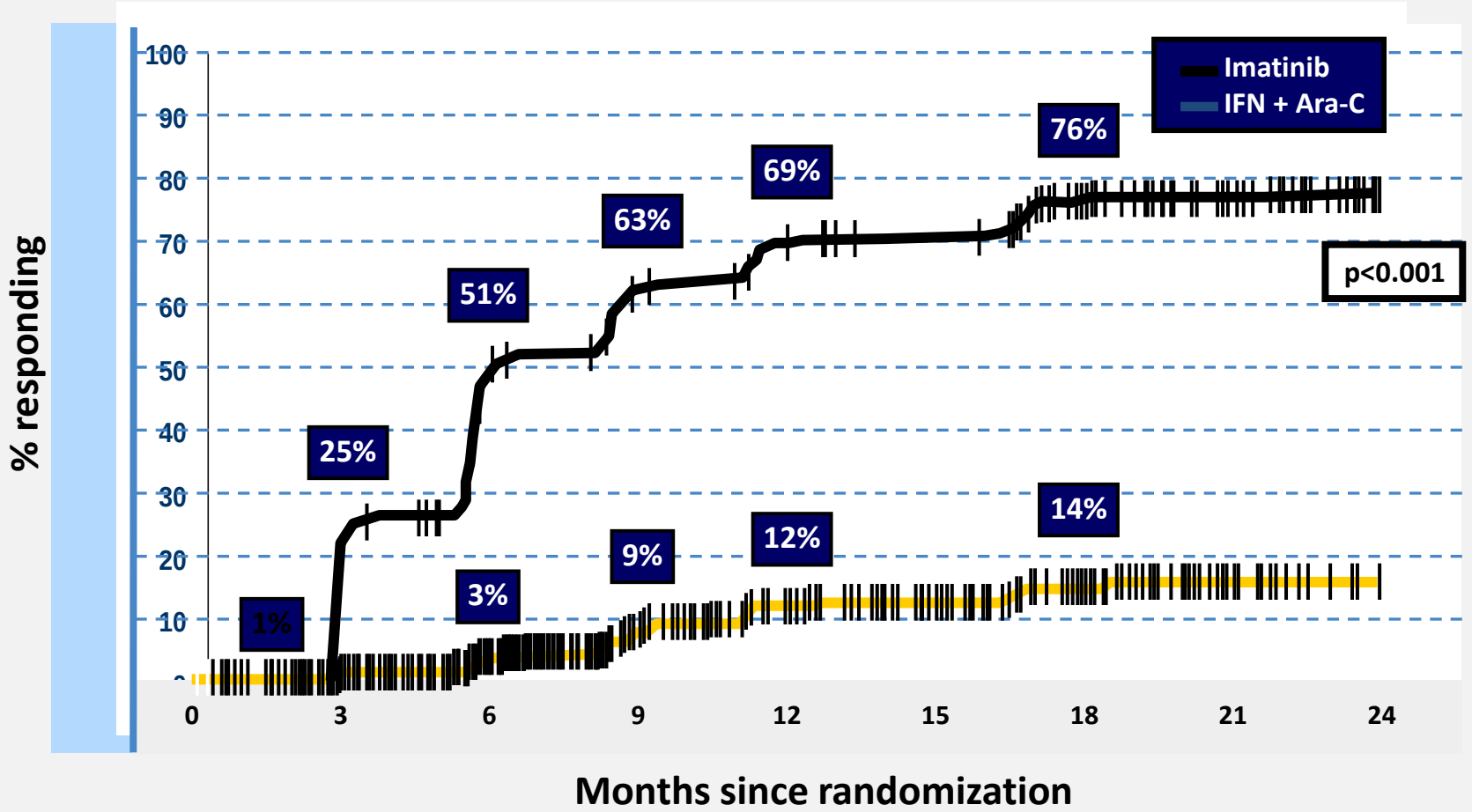
Best Cytogenetic Response on First-line Treatment

Response	Imatinib n=553	IFN + Ara-C n=553
Major (≤35 Ph+)*	**471** (85%)	**122** (22%)
• complete (0% Ph+)*	**408** (74%)	**47** (8%)
• partial (1-35% Ph+)	**63** (11%)	**75** (14%)

* $p<0.001$

106 TRIAL IRIS

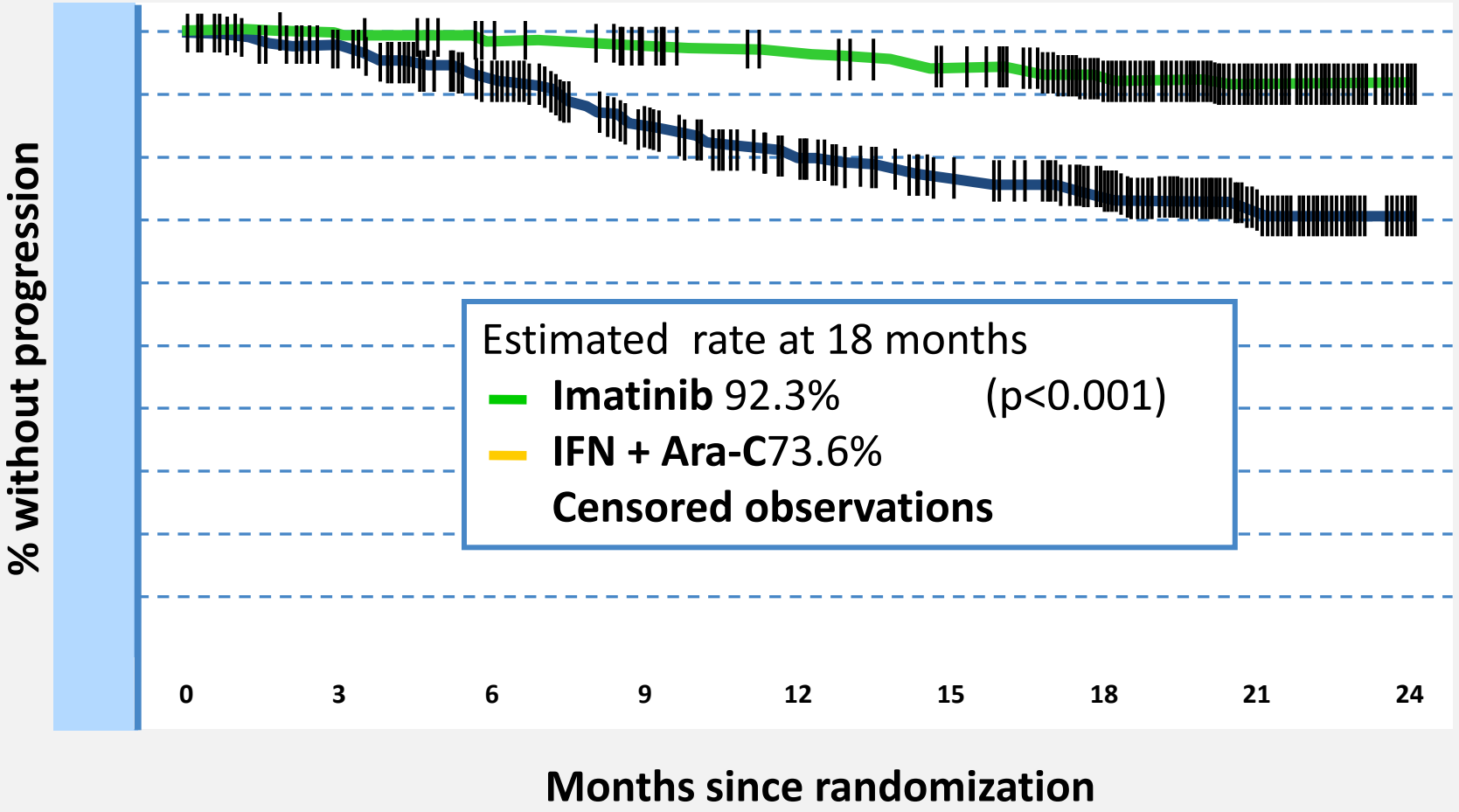
Complete Cytogenetic Responses



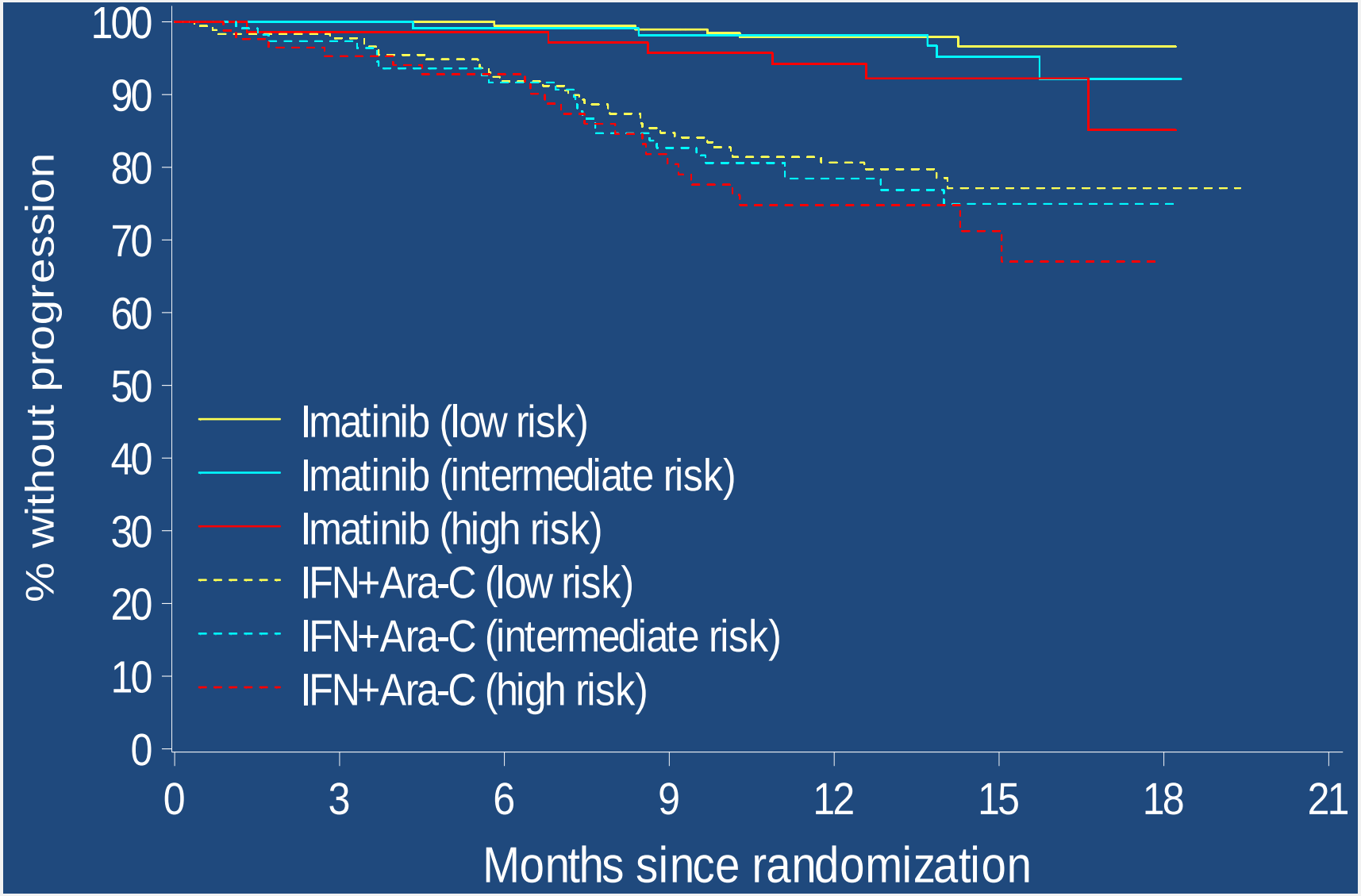
106 TRIAL IRIS

Progression-free Survival

Intention to treat



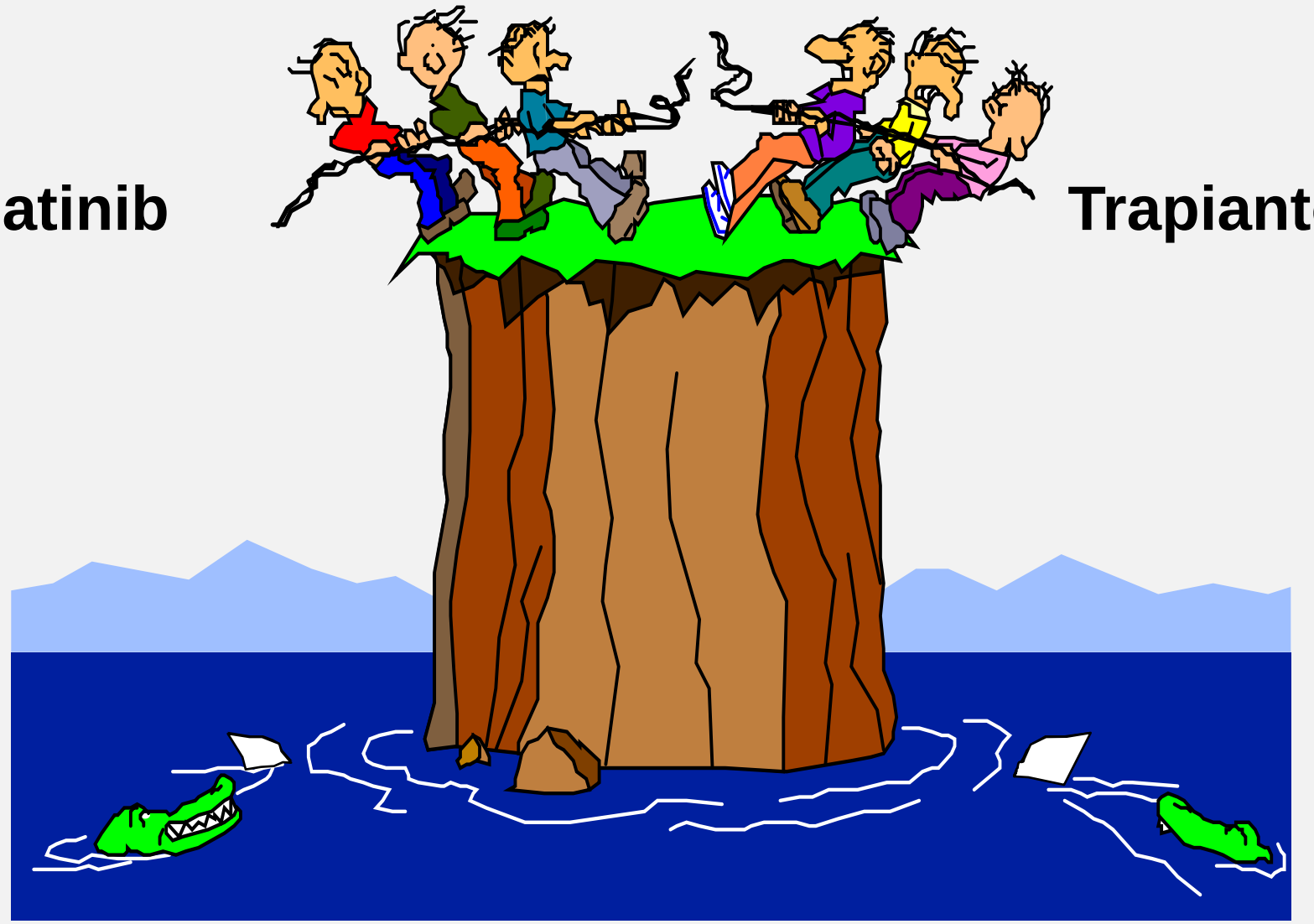
Progression - by Sokal risk group



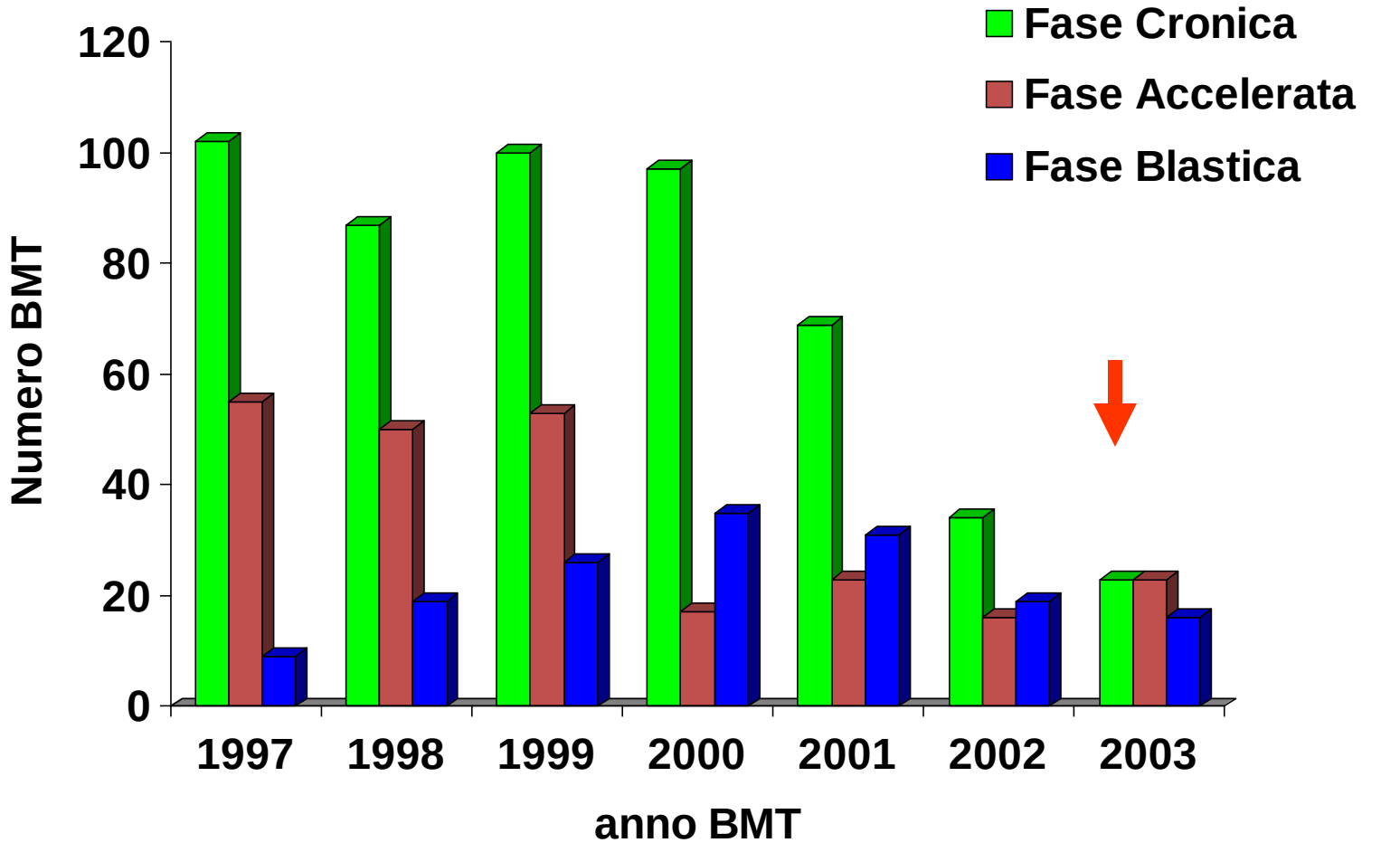
Trattare la LMC nel 2003

Imatinib

Trapianto



Andamento delle LMC negli ultimi 6 anni



Imatinib Resistance

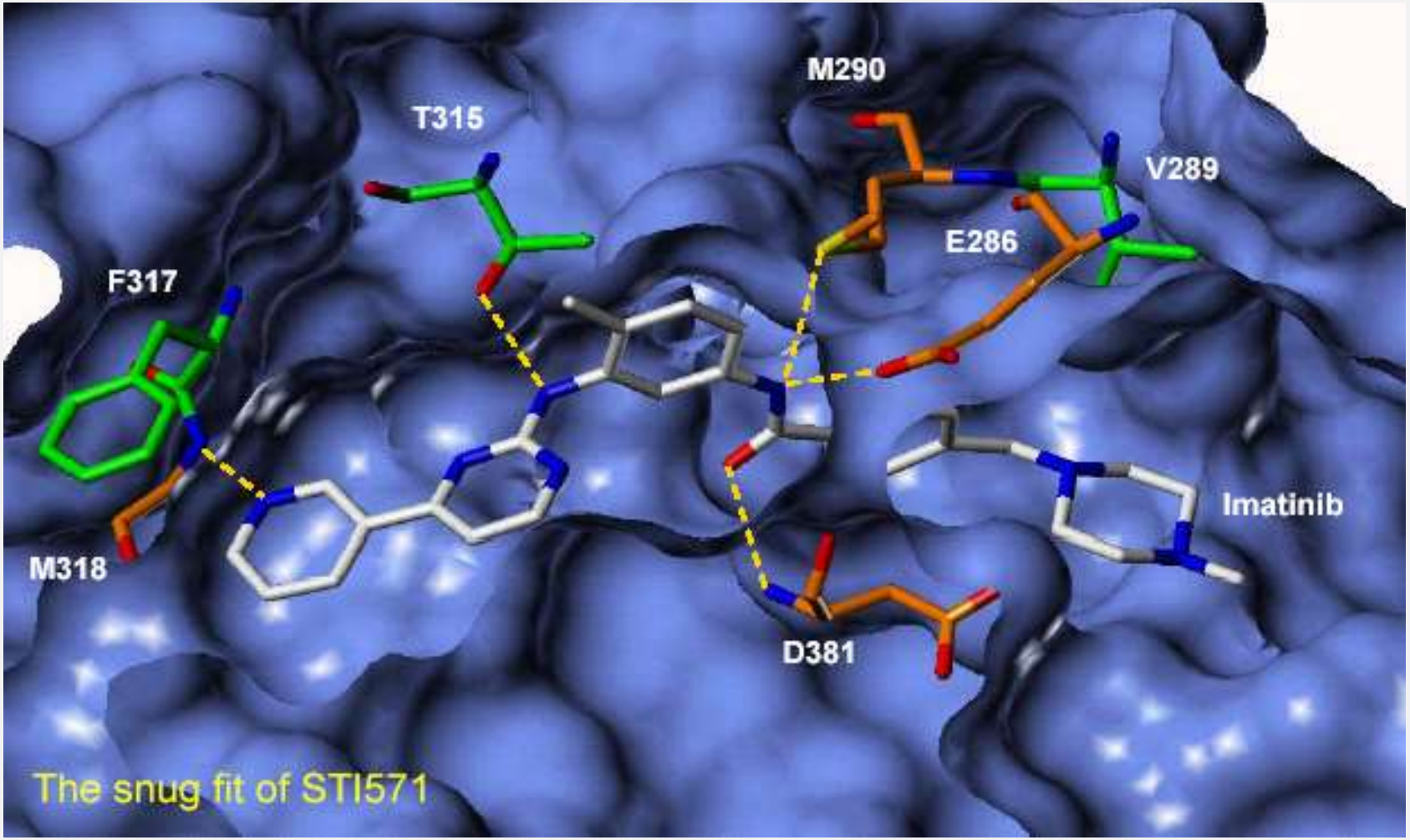
- Resistance at the maximum tolerated dose of imatinib
  - Primary resistance
    - No complete hematologic response at 3 months
    - No cytogenetic response at 6 months
    - No major cytogenetic response at 1 year
  - Secondary resistance
    - Loss of complete hematologic response
    - Loss of major cytogenetic response
    - Progression to accelerated / blast

The entity of imatinib resistance

- Resistance to imatinib is a well-recognized problem
  - 31% of chronic phase (CP) CML patients discontinue imatinib within 4.5 years[1]
  - 16% of CP patients either lose an established response to imatinib or progress to accelerated (AP) or blast phase (BP) after 42 months
  - 15% of CP patients fail to achieve a major cytogenetic response (MCyR) after 12 months and have a significantly increased risk of disease progression
- Patients who progress on imatinib to accelerated (AP) or blast phase (BP) have a poor prognosis[2*]

1Druker *et al.* J Clin Oncol. 2006;24(Suppl):338s
2Kantarjian H et al Cancer 2007**

BCR-ABL: mutazioni puntiformi



Imatinib failure/suboptimal response

- Maximizing imatinib dose
  - Addition of other agent
  - switching to alternate ABL kinase inhibitors
- Abandon kinase inhibitors for SCT
- Prevention

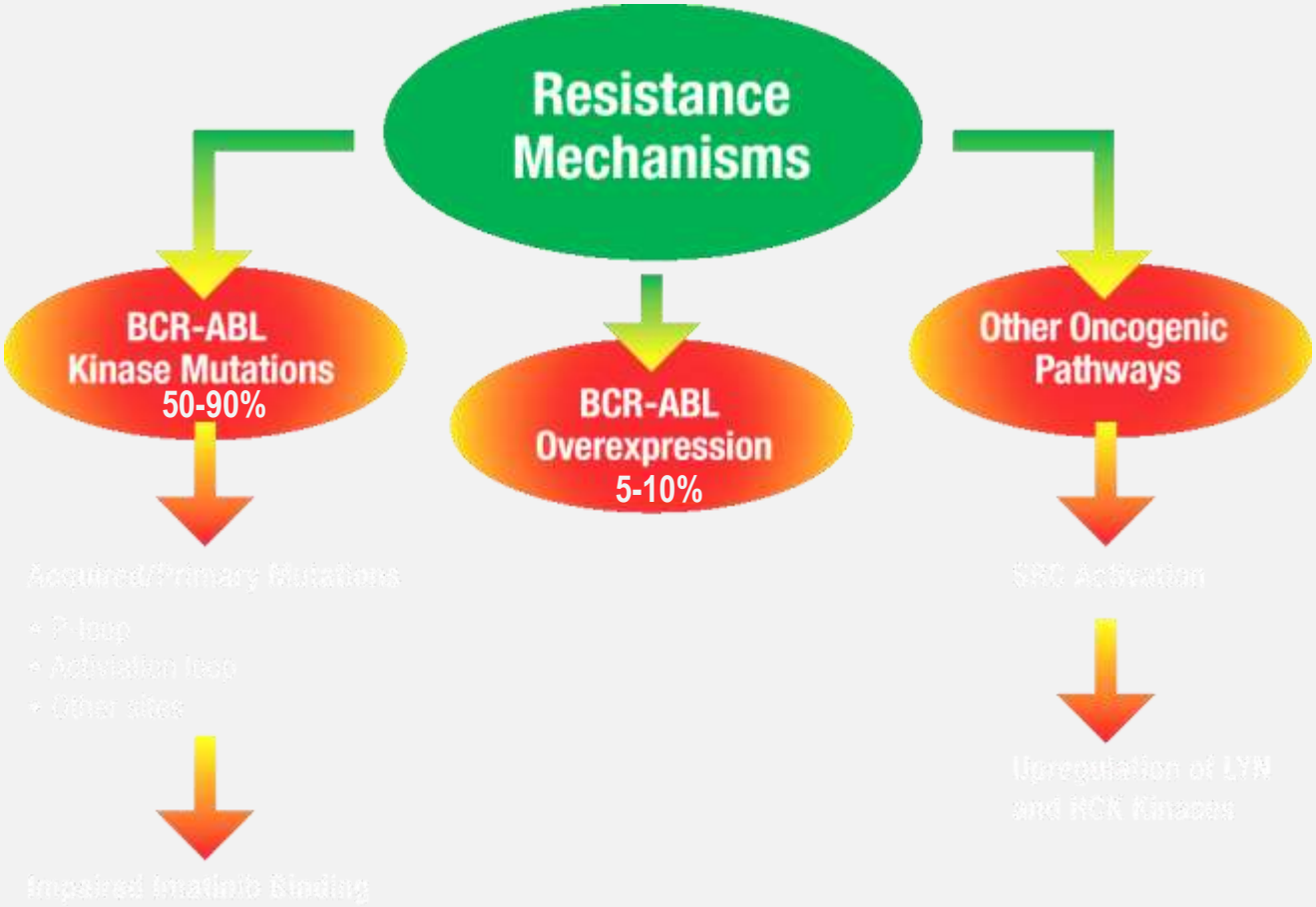
  High dose imatinib

  Imatinib combinations (Ara-C, IFN α)

Imatinib Intolerance

- Imatinib toxicities leading to intolerance
  - Grade 3-4 non-hematologic toxicity
  - Grade 4 hematologic toxicity lasting more than 7 days
- Patients who responded to imatinib
  - Developed intolerance while in response
  - Unable to resume therapy
- Patients who never responded to imatinib
  - Unable to tolerate imatinib at a dose of at least 400 mg

Proposed Mechanisms of Imatinib Resistance



1. Branford S, Rudzki Z, Walsh S, *et al*. *Blood*. 2003;102:276-283.
2. Donato NJ, Wu JY, Stapley, *et al*. *Blood*. 2003;101:690-698.

Historical Milestones in CML

2006-2007

Dasatinib and nilotinib are FDA approved for Patients with imatinib resistance

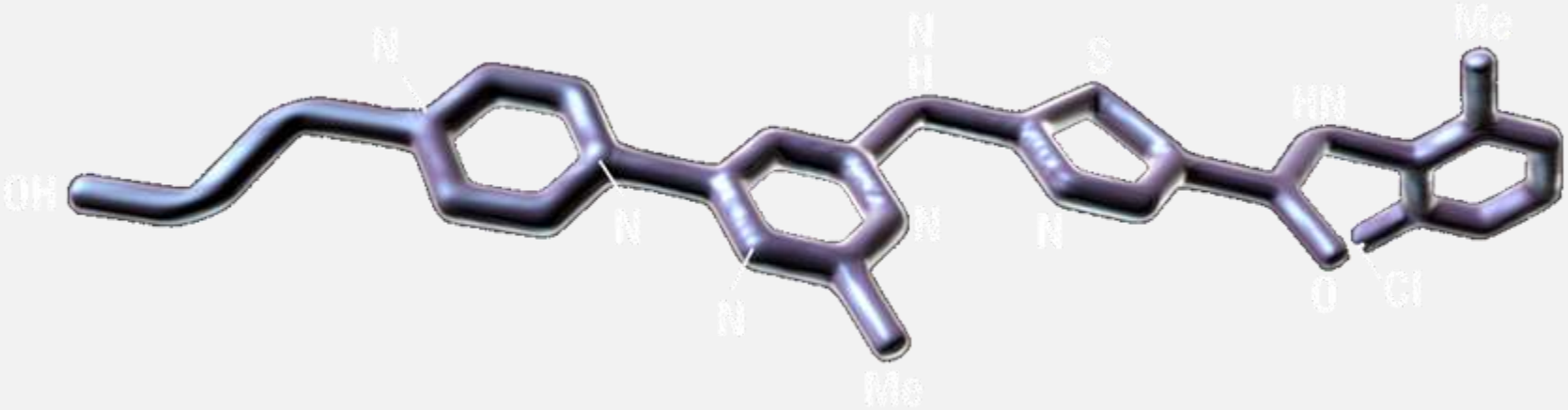
June 2010

FDA approval granted to nilotinib as first-line treatment in Ph+ CML

October 2010

FDA approval granted to dasatinib as first-line treatment in Ph+ CML

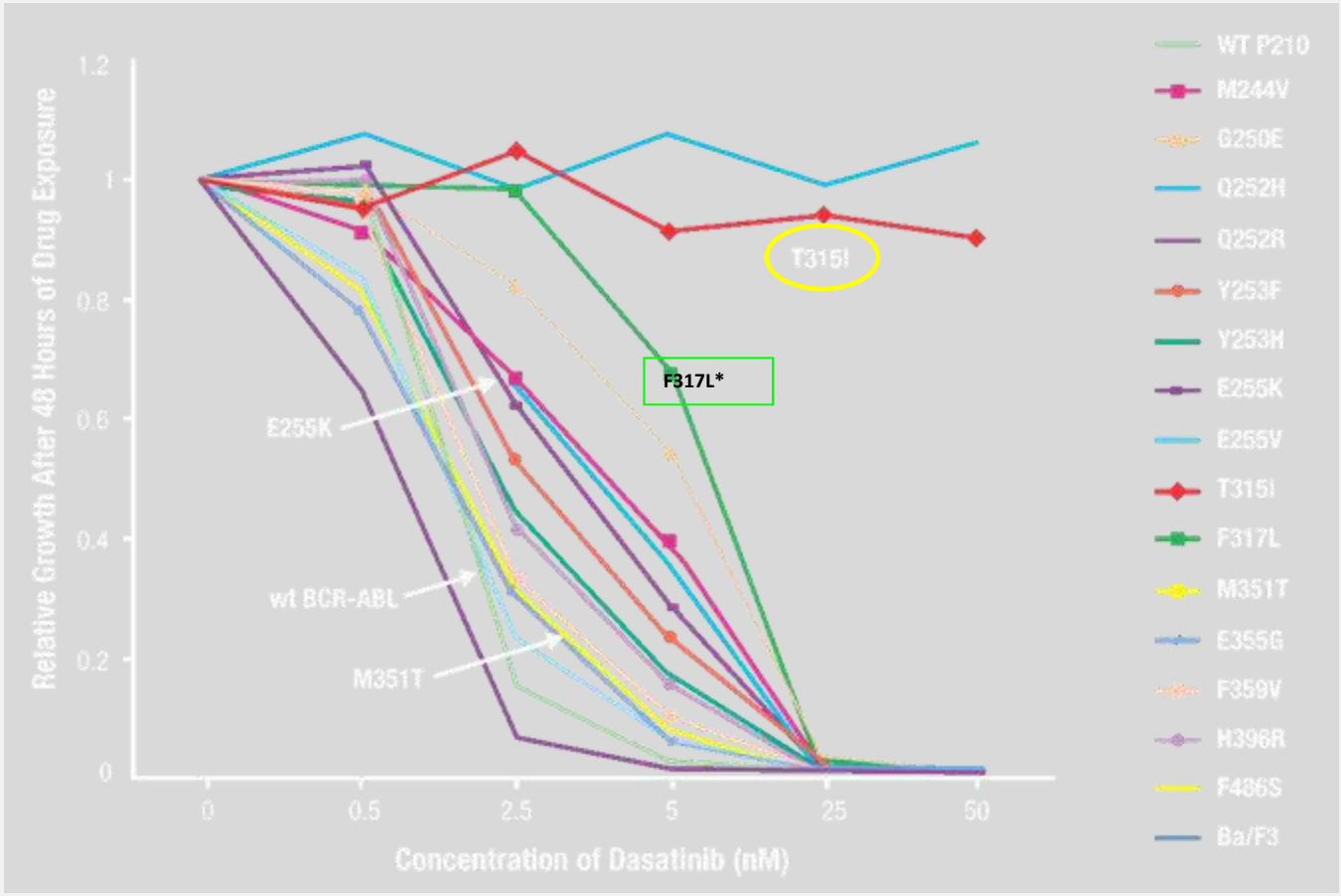
Dasatinib: A Novel Oral Multi-Targeted Kinase Inhibitor



- A novel multi-targeted kinase inhibitor with activity in hematologic and solid tumor cell lines[1]
- Dasatinib binds to Bcr-Abl in both the active and inactive conformations[1,2]

1. Shah NP, Tran C, Lee FY, *et al. Science.* 2004;305:399-401.
2. Sawyers CL, Shah NP, Kantarjian HM, *et al.* ASH 2004. Abstract 1.

Dasatinib Inhibition of Imatinib-Resistant BCR-ABL Mutations



- Dasatinib IC_{50} value <25 nM in 14 of 15 imatinib-resistant mutations tested[1]

1. Shah NP, Tran C, Lee FY, *et al*. *Science*. 2004;305:399-401.

* Soverini et al, Haematologica 2007

Historical Milestones in CML

<u>December 2010</u>

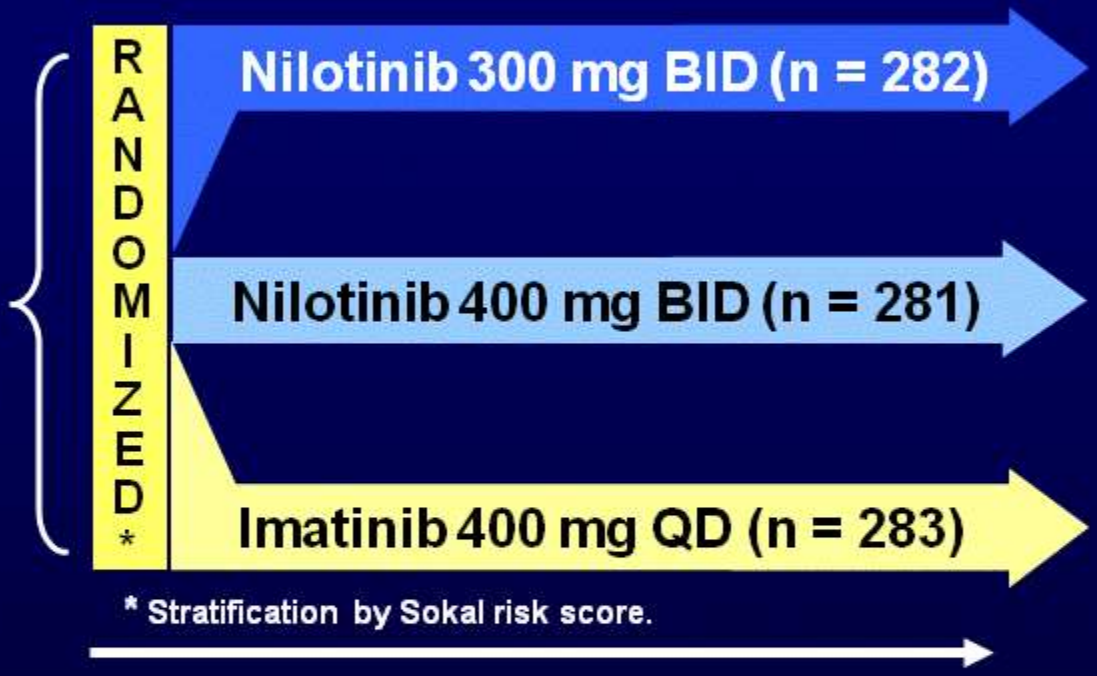
EMA and Swiss Medic approve nilotinib as first line treatment in Ph+ CML

EMA approved dasatinib as first-line treatment in Ph+ CML

(Taken, in part, from “50 Years in Hematology: Research that revolutionized patient care”. Published by the American Society of Hematology. Chapter 2. Targeted Therapy for Chronic Myeloid Leukemia. P 13.)

Study Design

- N = 846
- 217 centers
- 35 countries

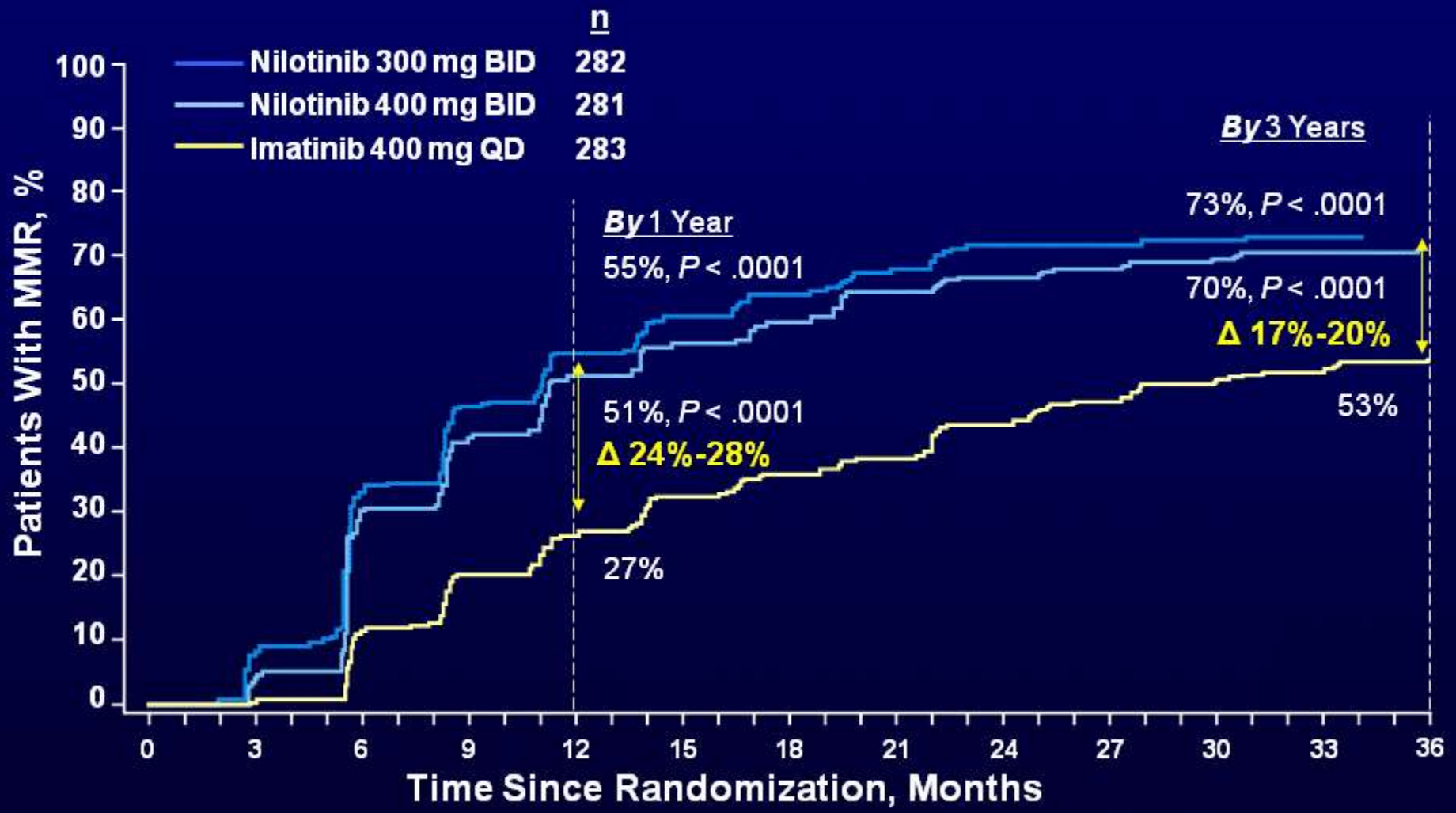


- The ENESTnd trial met its primary endpoint of MMR at 12 months in patients treated with nilotinib 300 or 400 mg BID vs imatinib ($P < .0001$)[1,2]
- 3-year follow-up data from ENESTnd have now been published[3]

1. Saglio G, et al. *N Engl J Med.* 2010;362:2251-2259.
2. Kantarjian HM, et al. *Lancet Oncol.* 2011;12(9):841-851.
3. Larson RA et al. *Leukemia*, May 2012; Epub ahead of print. DOI 10.1038/leu.2012.134.

Clark RE, et al. *Haematologica.* 2012;97(s1):237 [abstract 0583].

Cumulative Incidence of MMR*

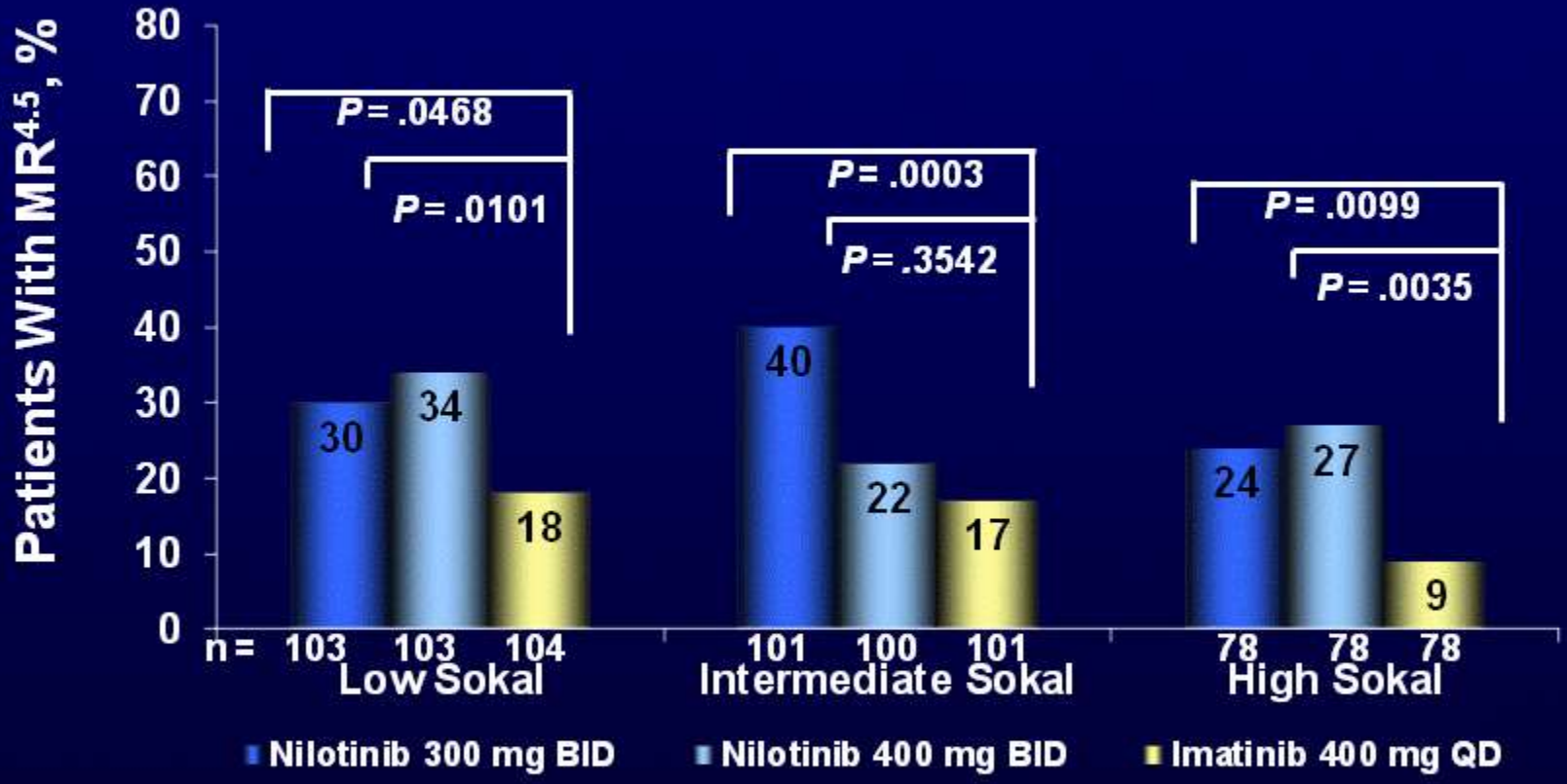


Data cutoff: 27Jul2011.

* Equivalent to BCR-ABL transcript levels of ≤ 0.1% (IS).

Clark RE, et al. *Haematologica*. 2012;97(s1):237 [abstract 0583].

$MR^{4.5}$ by 3 Years According to Sokal Risk

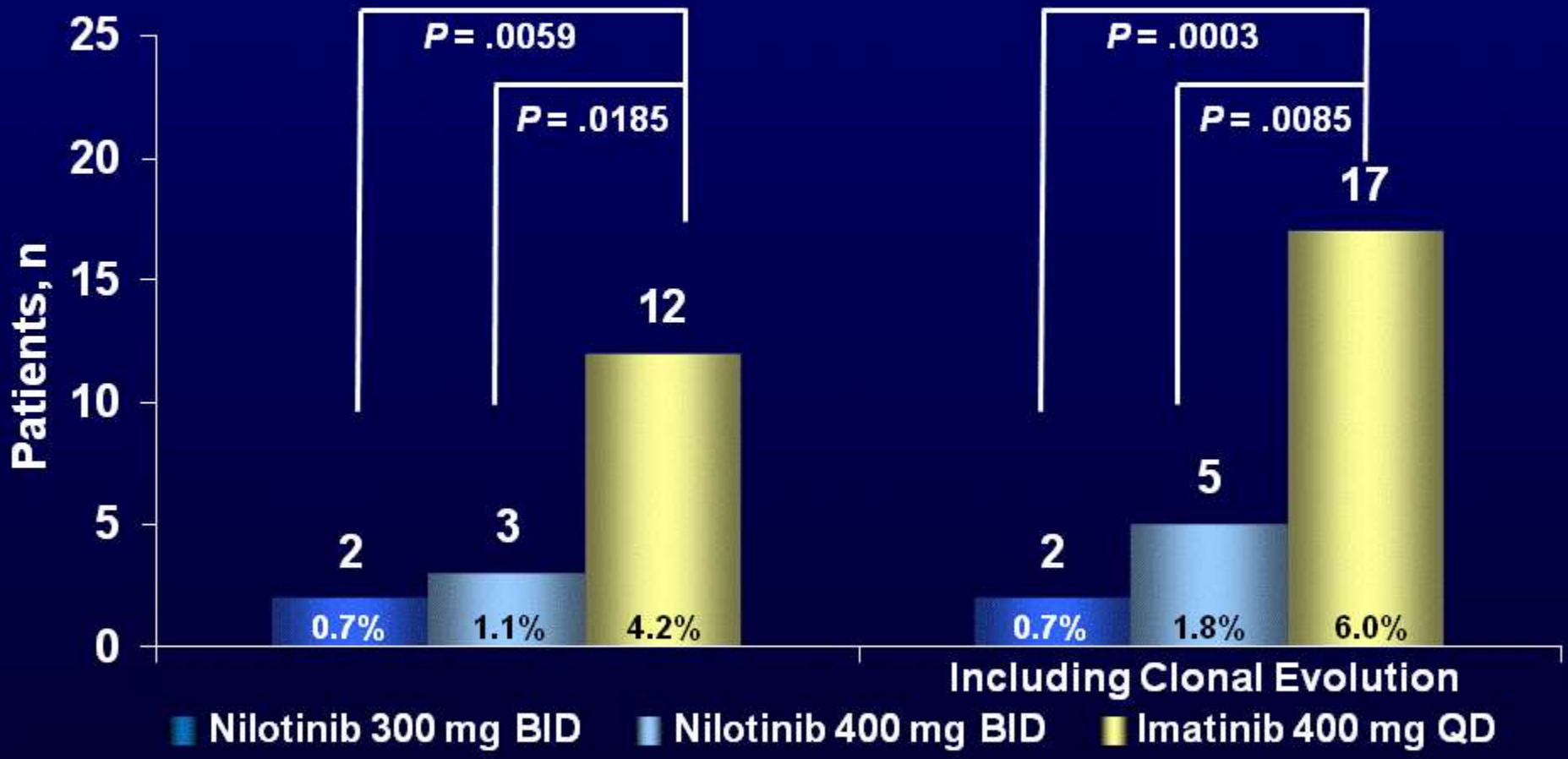


- Rates of $MR^{4.5}$ were consistently higher in patients treated with nilotinib vs imatinib across low, intermediate, and high Sokal risk scores

Data cutoff: 27Jul2011.

Clark RE, et al. *Haematologica*. 2012;97(s1):237 [abstract 0583].

Progression to AP/BC on Treatment

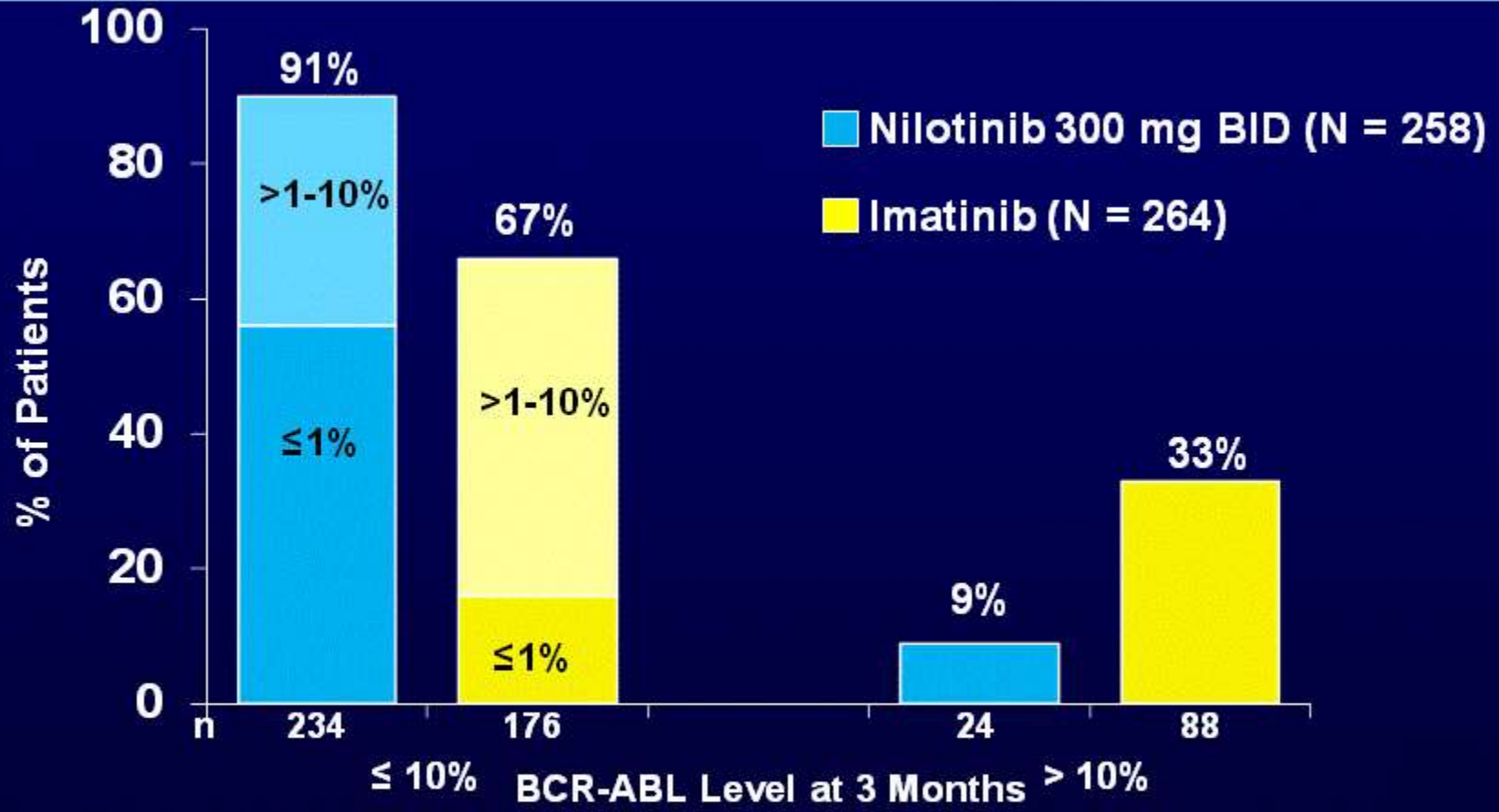


- No new progressions on treatment were observed since the 2-year analysis
- Nilotinib has a significantly lower risk of progression than imatinib

Data cutoff: 27Jul2011.

Clark RE, et al. *Haematologica*. 2012;97(s1):237 [abstract 0583].

BCR-ABL Categories at 3 Months*

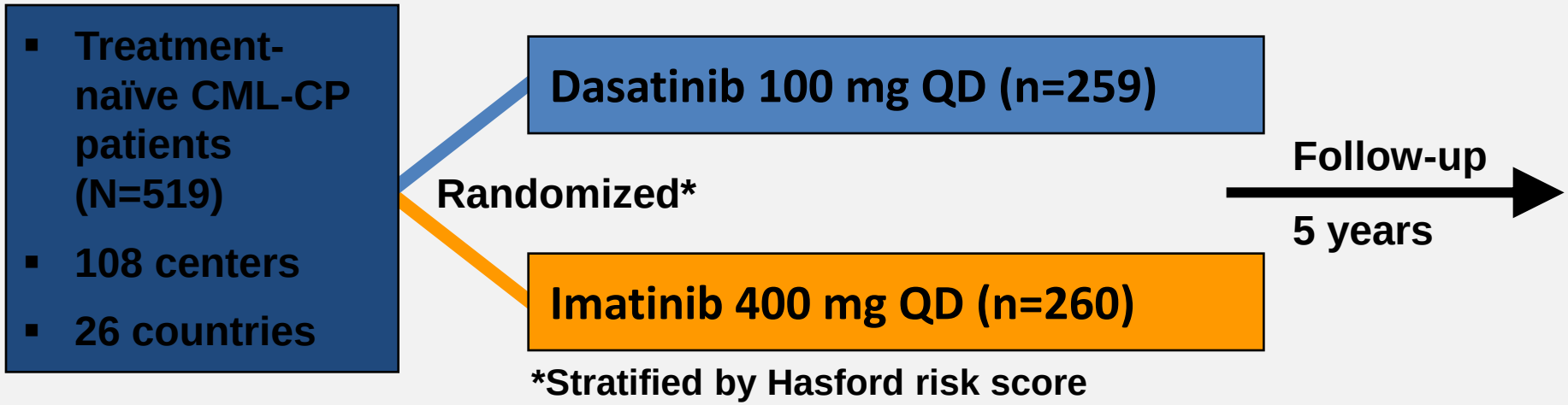


- Reasons for unevaluable samples:
  - Atypical transcripts: 5 patients on nilotinib, 2 patients on imatinib
  - Missing samples: 4 patients on nilotinib, 5 patients on imatinib
  - Discontinued: 15 patients (incl.1 progression) on nilotinib, 12 patients (incl.1 progression) on imatinib
- PFS/OS events prior to 3 months: 1 PFS event in each arm, no deaths

*Calculated from total number of evaluable patients with PCR assessments at 3 months.

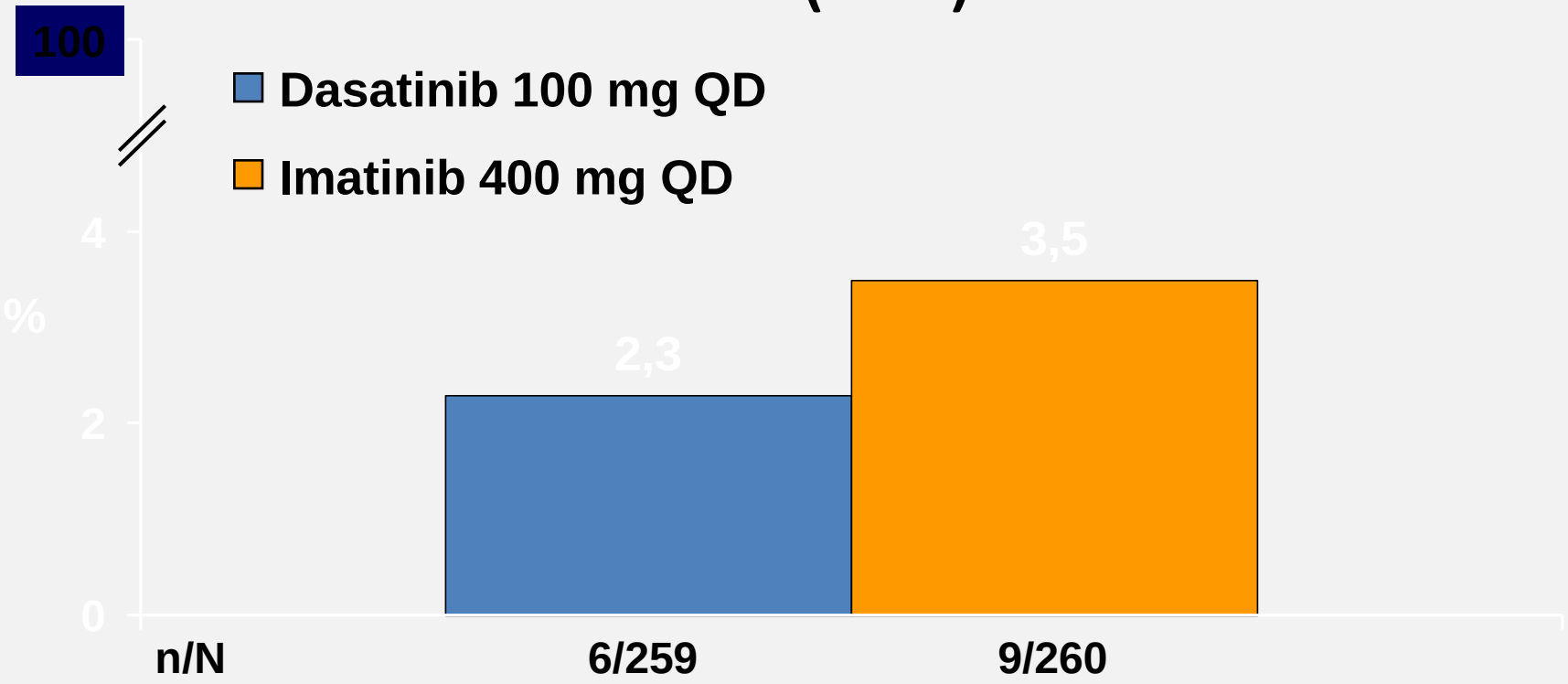
Hochhaus A, et al. *Haematologica*. 2012;97(s1):237 [abstract 0584].

DASISION (CA180-056) Study Design, an Ongoing Global Phase 3 Study



- **Primary endpoint** — **Confirmed CCyR by 12 mos**
- **Other key endpoints** — **Rates of CCyR and MMR, times to CCyR and MMR, time in CCyR (measure of duration), progression-free survival, overall survival**

Transformation to Advanced Phase CML (ITT)



- 5 patients who achieved a CCyR transformed to AP/BP CML (2 dasatinib, 3 imatinib)
- No patient who achieved a MMR transformed to AP/BP CML to date
- Patients were followed for transformation for up to 60 days after the last dose of study drug; clonal evolution without additional criteria for AP CML was NOT counted as transformation

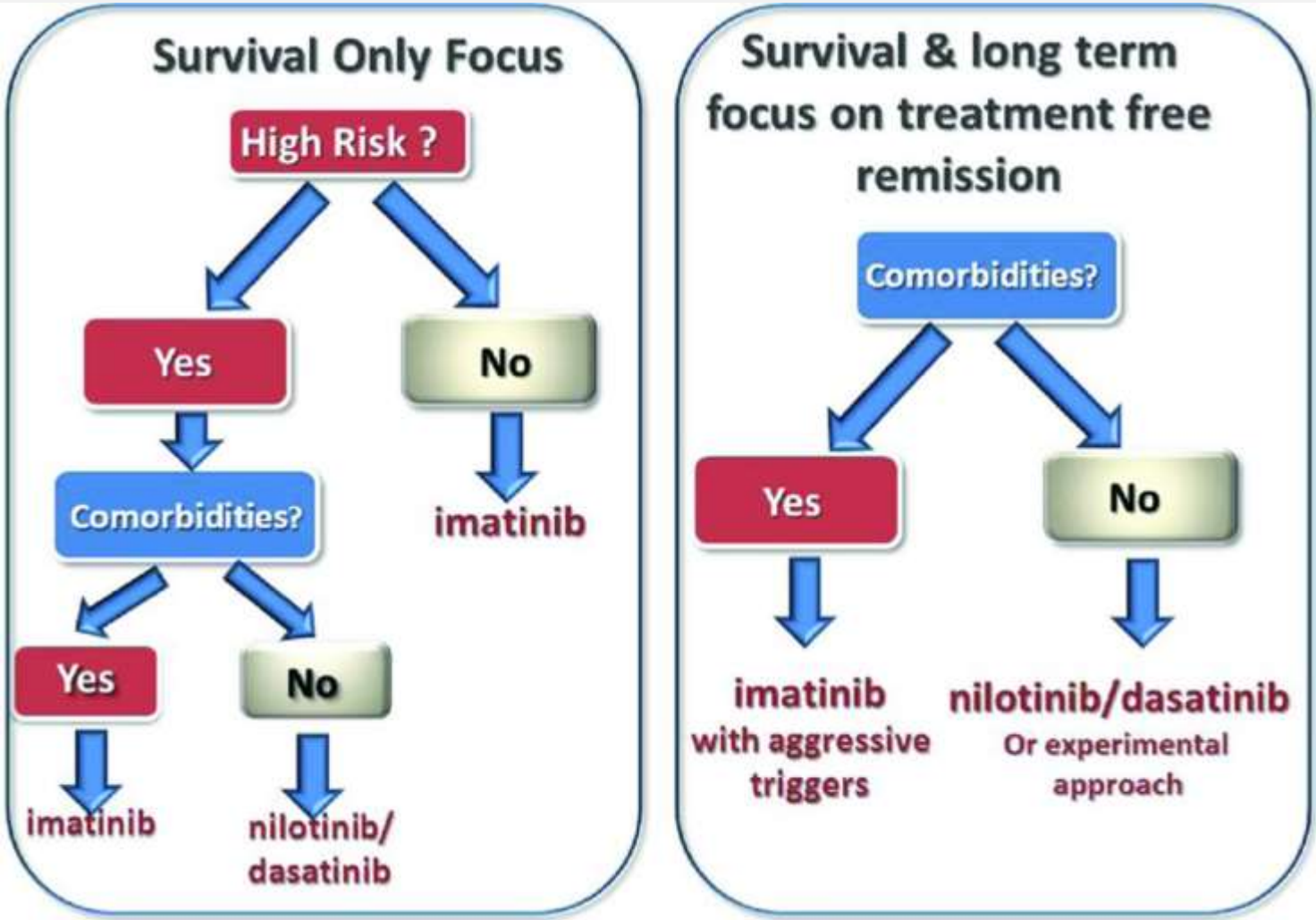
I dati scientifici: l'esperienza Hammersmith

Poor adherence is the main reason for loss of CCyR and imatinib failure for CML on long term therapy
Ibrahim et al, Blood. 2011 Feb 23 prepublished on line.

Correlazione tra risposta e compliance al trattamento

" pazienti con una aderenza <85% hanno una più alta probabilità di perdere la risposta citogenetica completa e hanno una più alta probabilità di interrompere Glivec rispetto a pazienti con aderenza>85% "

Proposed schema for individualizing therapy based on comorbidities, goals of therapy, and disease risk profile.



Timothy Hughes, and Deborah White Hematology 2013;2013:168-175

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Definitions of hematologic, cytogenetic, and molecular response

Response by Type	Definitions
Hematologic	
Complete (CHR)	WBC $< 10 \times 10^9$/L
	Basophils $< 5\%$
	No myelocytes, promyelocytes, myeloblasts in the differential
	Platelet count $< 450 \times 10^9$/L
	Spleen nonpalpable
Cytogenetic*	
Complete (CCgR)	No Ph+ metaphases
Partial (PCgR)	1% to 35% Ph+ metaphases
Minor (mCgR)	36% to 65% Ph+ metaphases
Minimal (minCgR)	66% to 95% Ph+ metaphases
None (noCgR)	> 95% Ph+ metaphases
Molecular†	
Complete (CMolR)	Undetectable *BCR-ABL* mRNA transcripts by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity $> 10^4$)
Major (MMolR)	Ratio of *BCR-ABL* to *ABL* (or other housekeeping genes) $\leq 0.1\%$ on the international scale

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Timing of Cytogenetic and Molecular Monitoring

At diagnosis	CBA, FISH in case of Ph- (for cryptic or variant translocations), qualitative PCR (transcript type)
During treatment	RQ-PCR every 3 months until MMR has been achieved, then every 3 to 6 months and/or CBA at 3, 6, and 12 months until CCyR has been achieved, then every 12 months. Once CCyR is achieved, FISH on blood cells can be used.
Failure, progression	RQ-PCR, mutational analysis, and CBA. Immunophenotyping in blast phase.
Warning	Molecular and cytogenetic tests more frequently. CBA in case of myelodysplasia or CCA/Ph-

CBA: Chromosome banding analysis of marrow cell metaphases at least 20 metaphases analysed

DESIGN AND REALISATION: WWW

CHARITAS - SAPIENTIA - SIFO

Baccarani et al, Blood 20

ELN European LeukemiaNet

UPDATE 2013

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Baccarani et al, Blood 2013;122:872-884

Response definitions for any TKI first line, and 2nd line in case of intolerance, all patients (CP, AP, and BC)

Time	Optimal response	Warning	Failure
Baseline		High risk Major route CCA/Ph+	
3 mos.	BCR-ABL^{IS} ≤10%* Ph+ ≤35% (PCyR)	BCR-ABL^{IS} >10%* Ph+ 36-95%	No CHR* Ph+ >95%
6 mos.	BCR-ABL^{IS} <1%* Ph+ 0% (CCyR)	BCR-ABL^{IS} 1-10%* Ph+ 1-35%	BCR-ABL^{IS} >10%* Ph+ >35%
12 mos.	BCR-ABL^{IS} ≤0.1%* (MMR)	BCR-ABL^{IS} 0.1-1%*	BCR-ABL^{IS} >1%* Ph+ >0%
Then, and at any time	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Treatment recommendations

Line	Event		TKI, standard dosage[1]					Transplantation				
Chronic phase												
								Search for		alloSCT		
			Imatinib 400 mg/qd	Nilotinib 300 mg/bid	Dasatinib 100 mg/qd	Bosutinib 500 mg/qd	Ponatinib 45 mg/qd	HLA type + sibs	unrelated donor	consider	recommended	Chemotherapy
1st	Baseline		X	X	X			X[2]				
2nd	Intolerance to 1st TKI		Any other TKI approved 1st line									
	Failure 1st line of	imatinib		X[8]	X	X	X	X				
		nilotinib			X	X	X	X	X	X		
		dasatinib		X[8]		X	X	X	X	X		
3rd	Intolerance to/failure of two TKI		Any remaining TKI								X	
Any	T315I mutation						X	X	X	X		
Accelerated or blast phase												
In newly diagnosed, TKI naïve patients		start with	X[3]		X[4]			X	X			
		no optimal response, BP									X[7]	X[5]
TKI pre-treated patients			Any other TKI				X[6]				X[7]	X[5]

[1]choice of the TKI consider tolerability and safety, and patient characteristics (age, comorbidities), [2]only in case of baseline warnings (high risk, major route CCA/Ph+), [3]400 mg/bid, [4]70 mg/bid or 140 mg/qd, [5]may be required before SCT to control disease and to make patients eligible to alloSCT, [6]in case of T315I mutation, [7]only patients who are eligible for alloSCT, not in case of uncontrolled, resistant BP, [8]400 mg bid in failure setting

qd: Once daily bid: Twice daily

Baccarani et al, Blood 20

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Timing of Cytogenetic and Molecular Monitoring

At diagnosis	CBA, FISH in case of Ph- (for cryptic or variant translocations), qualitative PCR (transcript type)
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Warning	Molecular and cytogenetic tests more frequently. CBA in case of myelodysplasia or CCA/Ph-

CBA: Chromosome banding analysis of marrow cell metaphases at least 20 metaphases analysed

Response definitions to 2nd line therapy in case of failure of imatinib (can be used provisionally, NOT for the response to 3rd line treatment).

Time	Optimal response	Warnings	Failure
Baseline		No CHR Loss of CHR on imatinib Lack of CyR to 1st line TKI High risk	
3 mos.	BCR-ABL^{IS} ≤10%* Ph+ <65%	BCR-ABL^{IS} >10%* Ph+ 65-95%	No CHR, or Ph+ >95%, or New mutations
6 mos.	BCR-ABL^{IS} ≤10%* Ph+ <35% (PCyR)	BCR-ABL^{IS} ≤10%* Ph+ 35-65%	BCR-ABL^{IS} >10%* Ph+ >65%* New mutations
12 mos.	BCR-ABL^{IS} <1%* Ph+ 0 (CCyR)	BCR-ABL^{IS} 1-10%* Ph+ 1-35%	BCR-ABL^{IS} >10%* Ph+ >35%* New mutations
Then, and at any time	MMR or better	CCA/Ph- (-7 or 7q-) or BCR-ABL^{IS} >0.1%	Loss of CHR, or Loss of CCyR or PCyR New mutations Loss of MMR** CCA/Ph+

*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

Definition of response

Optimal response	Best long-term outcome No indication for a change of treatment.
Failure	Patient should receive a different treatment to limit the risk of progression and death
Warning	Characteristics of disease and response to treatment require more frequent monitoring to permit timely changes in therapy, in case of treatment failure.

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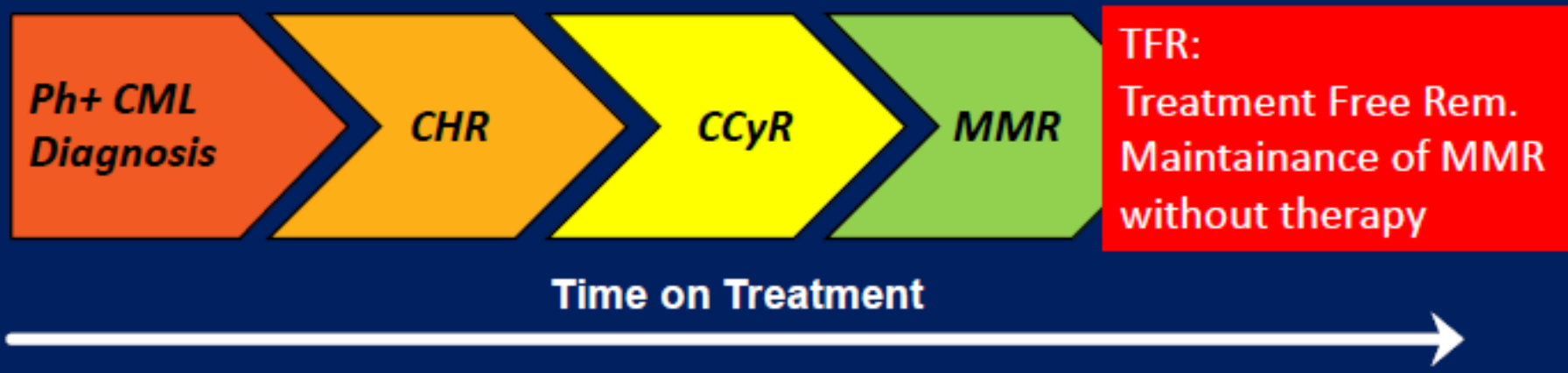
Baccarani et al, Blood 2013;122:872-884

Expectations for Best Achievable Response to Therapy in CML Continue to Increase

- As treatments for chronic myeloid leukaemia (Ph+ CML) have improved, expectations for responses have increased: HR → CCyR → MMR[1] UMRD



CCyR, complete cytogenetic response; CHR, complete haematologic response; UMRD, undetectable molecular residual disease; HR, haematologic response; MMR, major molecular response.

Baccarani et al., J Clin Oncol. 2009;27(35):6041-6051.

La necessità di raggiungere una risposta molecolare profonda e sostenuta

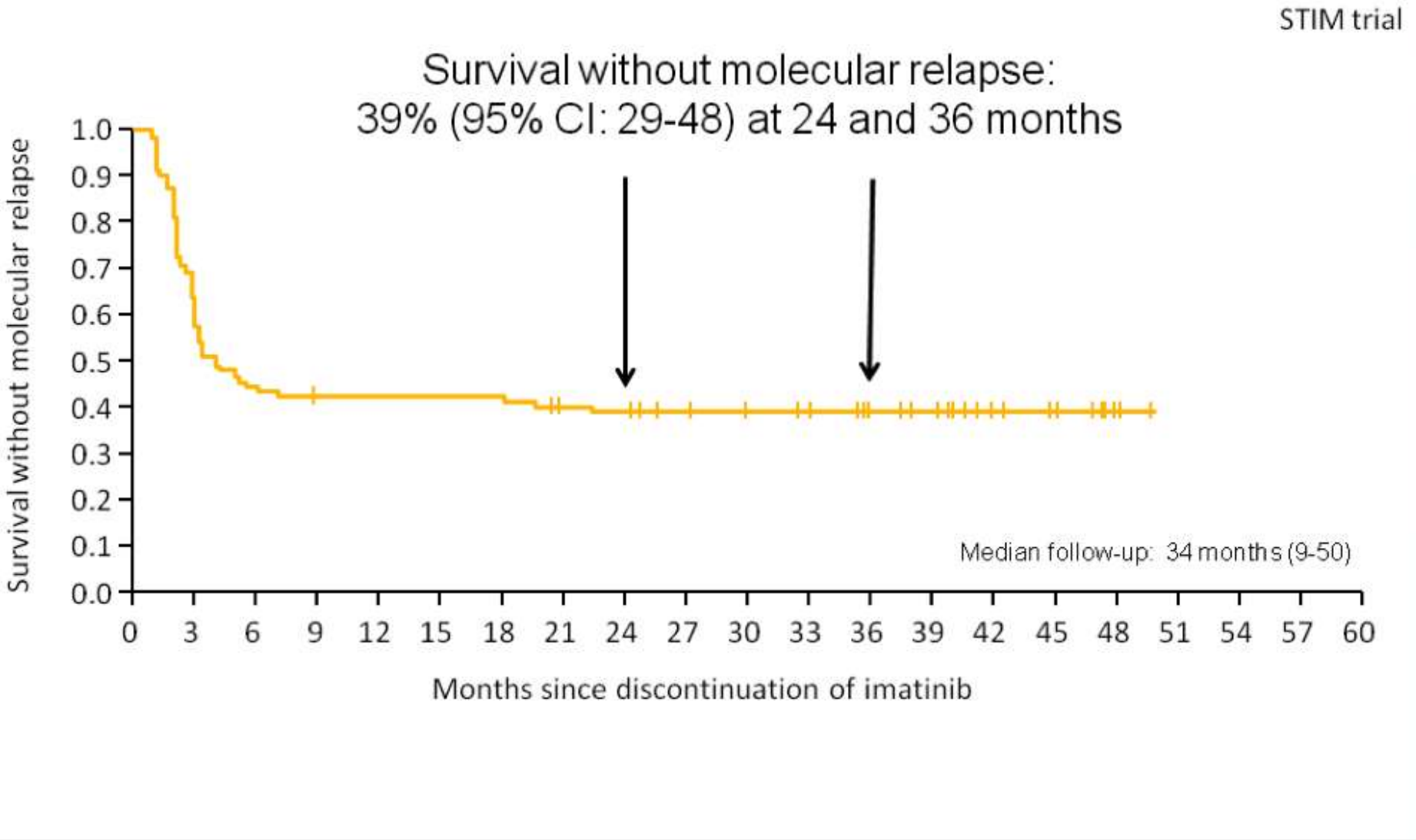
- More intensive TKI
- Combination therapy
- Immunotherapy
- Stem cell targeting

- More intensive TKI
- Combination therapy
- Immunotherapy
- Stem cell targeting

- Possible need for intermittent therapy with 2nd generation TKI or immune 'boosters' (e.g. IFN)

Mahon et al, EHA 2013

STIM trial: 36-mos follow-up



Mahon et al, ASH 2012

Altre esperienze di discontinuazione

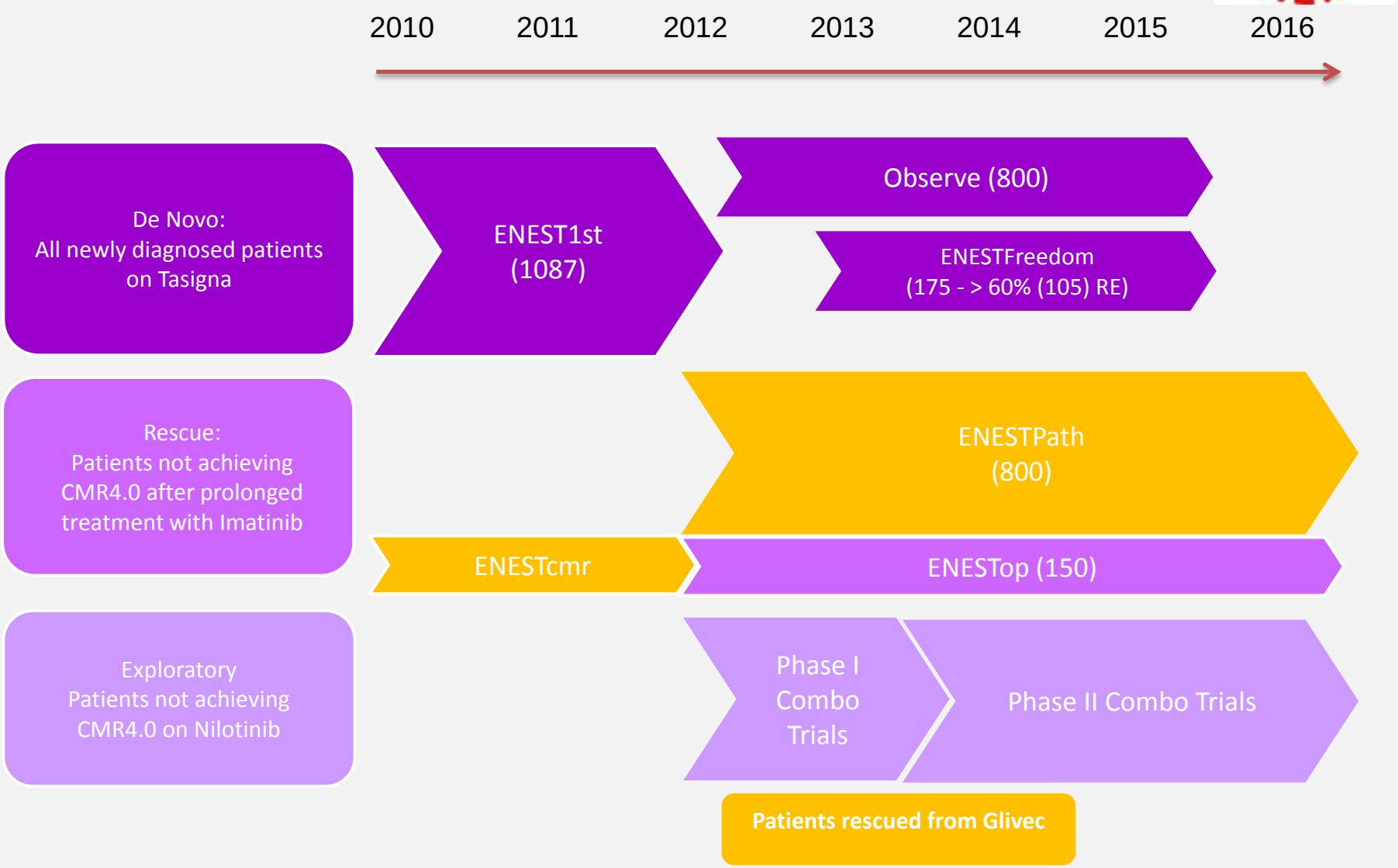
Studio	Criteri di eleggibilità	No	Definizione di recidiva molecolare	Follow-up e Relapse rate
Japanese Survey	Imatinib > 36 mos Undetectable BCR-ABL >24 mos	43	BCR-ABL in 2 RQ-PCR consecutive	FU mediano 22.4 mos Relapse rate 44%
Korean Retrospective study	Undetectable BCR-ABL >12 mos	14	BCR-ABL in 2 RQ-PCR consecutive	FU mediano 23 mos Relapse rate 71.4%
A-STIM (according to)	Undetectable BCR-ABL >24 mos Or CMR (MR4.5) > 24 mos	58	Perdita di MMR Incremento 1 log in 2 RQ-PCR consecutive	FU mediano 23 mos Relapse rate 34%
KEIO STIM	Undetectable BCR-ABL >24 mos	41	BCR-ABL in 2 RQ-PCR consecutive	FU mediano 15 mos Relapse rate 55.4%

Takahashi et al, Haematologica 2012; Yhim et al, Leuk Res 2012; Rousselot et al, Haematologica EHA 2012; Matsuki et al, Blood ASH 2012

STUDI DI INTERRUZIONE

	Tx before stop/ MR	Def relapse	RFS	Median fu	Pts responding new Tx
STIM	IM36m **MR5** 24m	Loss MR5	39%	30m	56/61
A-STIM	IM36m **MR4.5** 24m	Loss MR3	64%	23m	24/24
KOREAN	IM36m **MR4** 24m	Loss MR3	81%	16m	8/9
JAPANESE	IM stop >6m **MR4**	Loss MR4	44%	23m	NA
TWISTER	IM36m **MR4.5** 24m	Loss MR4.5	45%	42m	22/22
STOP 2G-TKI	DAS/NIL 36m **MR4.5** 24m	Loss MR3	58%	12m	10/13

A comprehensive trial program on the Path to Cure: ENEST



I dati scientifici: lo studio ADAGIO

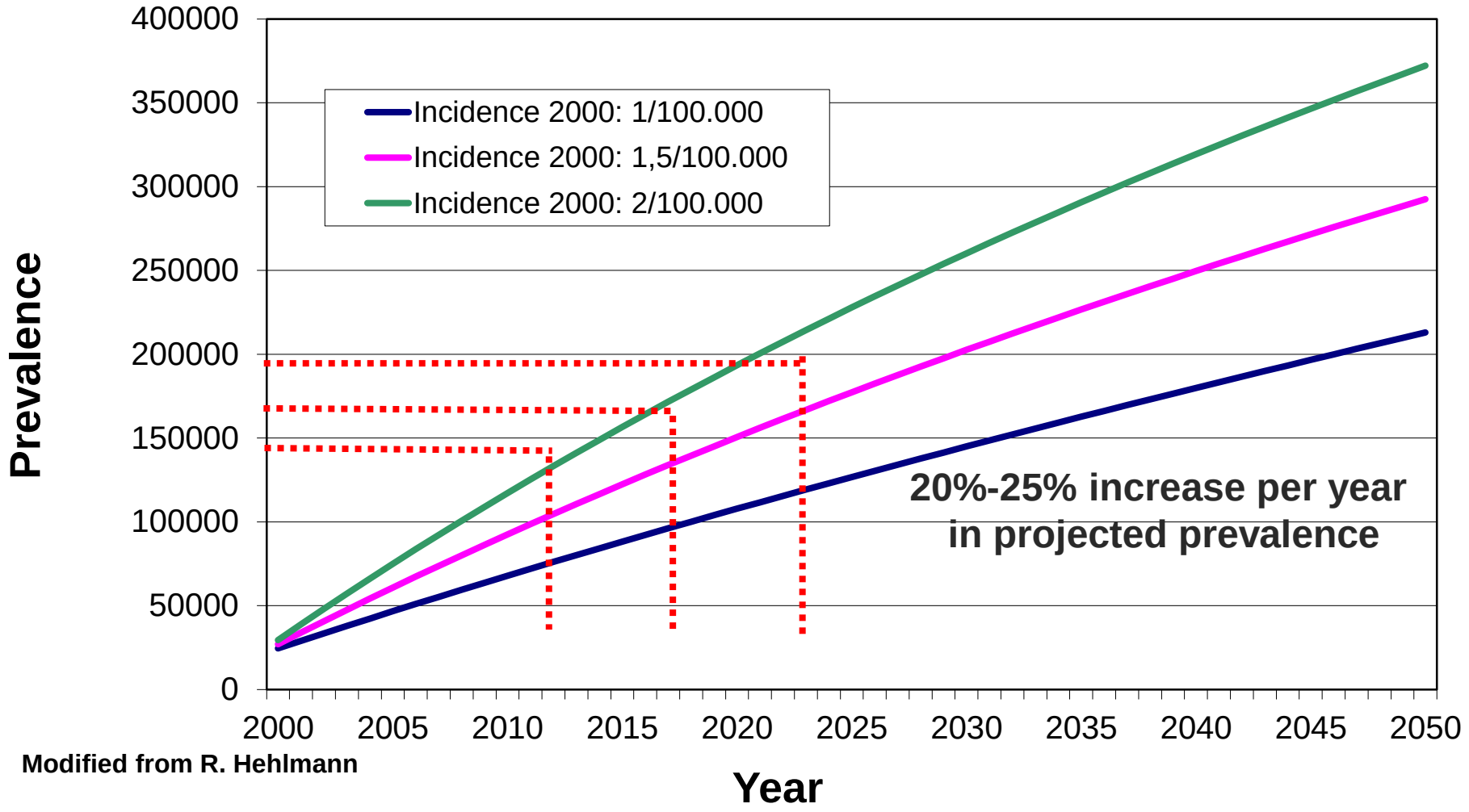
Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study.
Noens L, Blood. 2009 May 28;113(22):5401-11.

Correlazione tra risposta e compliance al trattamento

“ pazienti con risposta sub-ottimale hanno un tasso superiore di mancata assunzione di imatinib *(23.2%) rispetto a pazienti con risposta ottimale (7.3%)”*

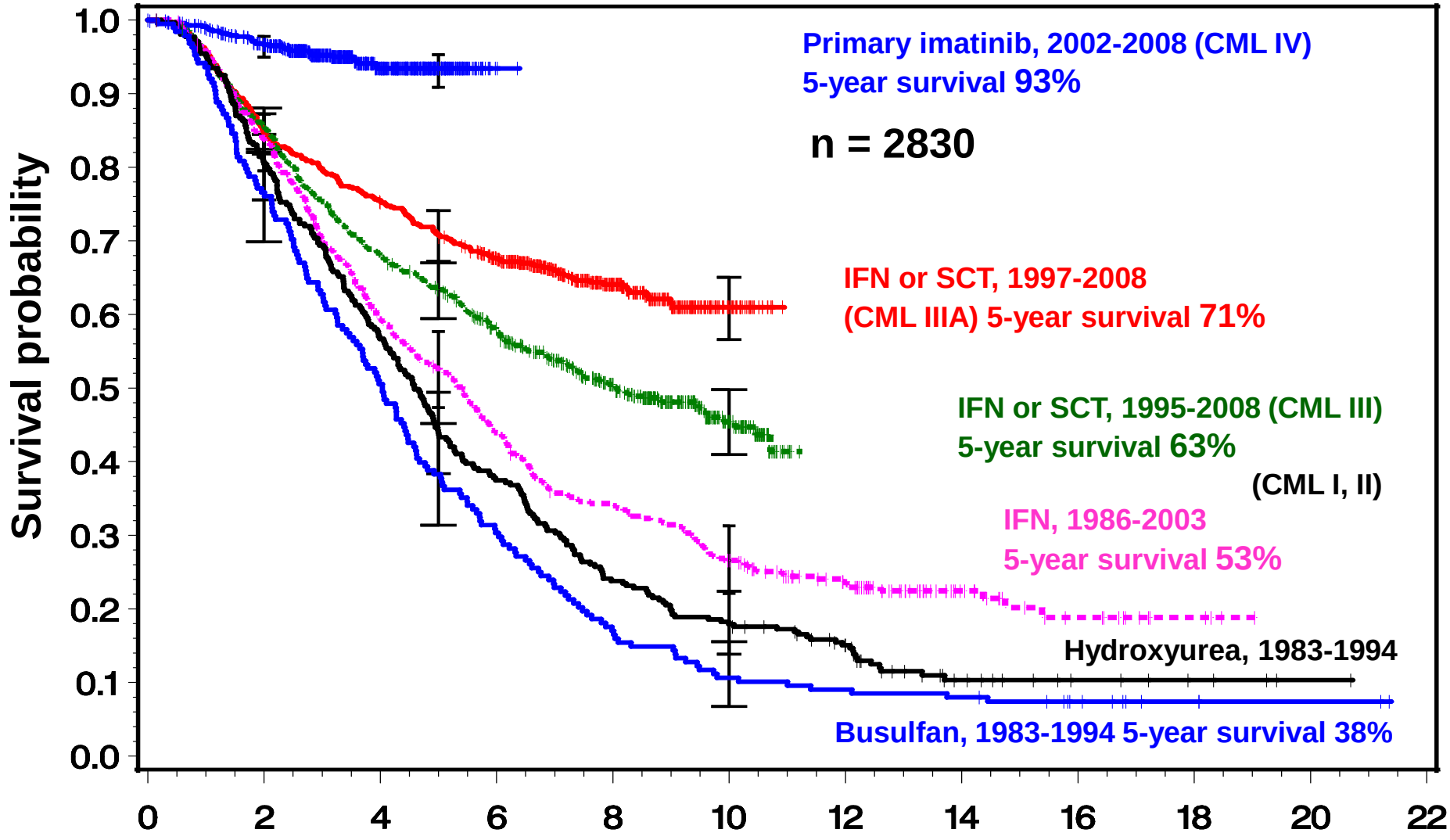
Projection of CML Prevalence up to 2050

Assumptions: **Population: 500 Mill., mortality: 2% per year, Incidence increasing by about 0.01/100.000 per year**



Modified from R. Hehlmann

Survival 1983-2008



Courtesy of the German CML Study Group

Dedicato a Cosima

Settembre 2000