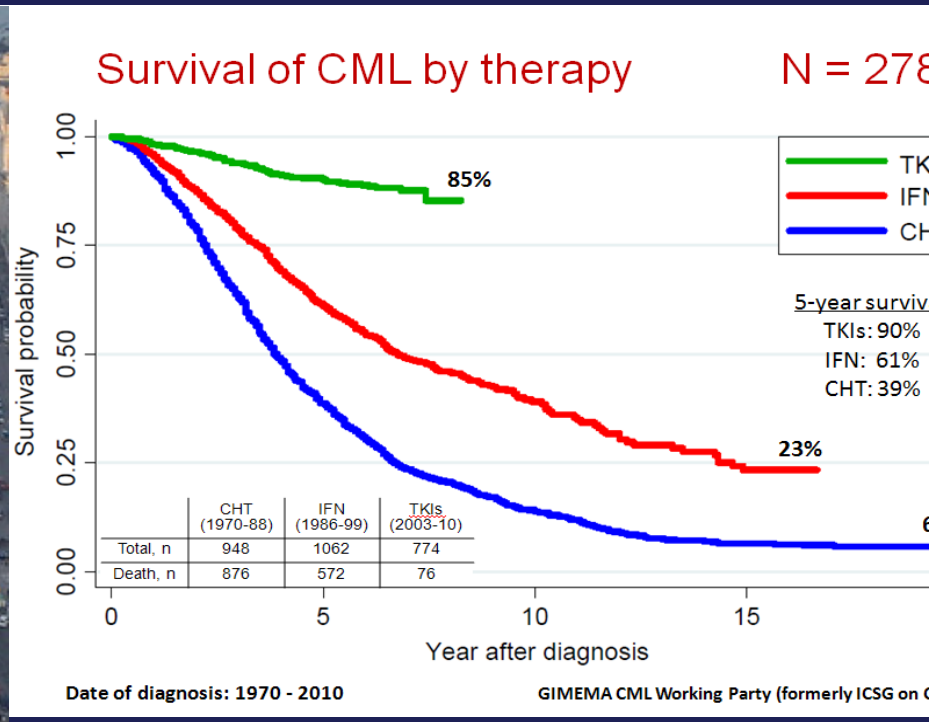
FORUM IN EMATOLOGIA

NOVITA' BIOLOGICHE E TERAPEUTICHE,

BARI, 6-7 Ottobre 2016

LMC: REMINISCENZA E CERTEZZE ATTUALI

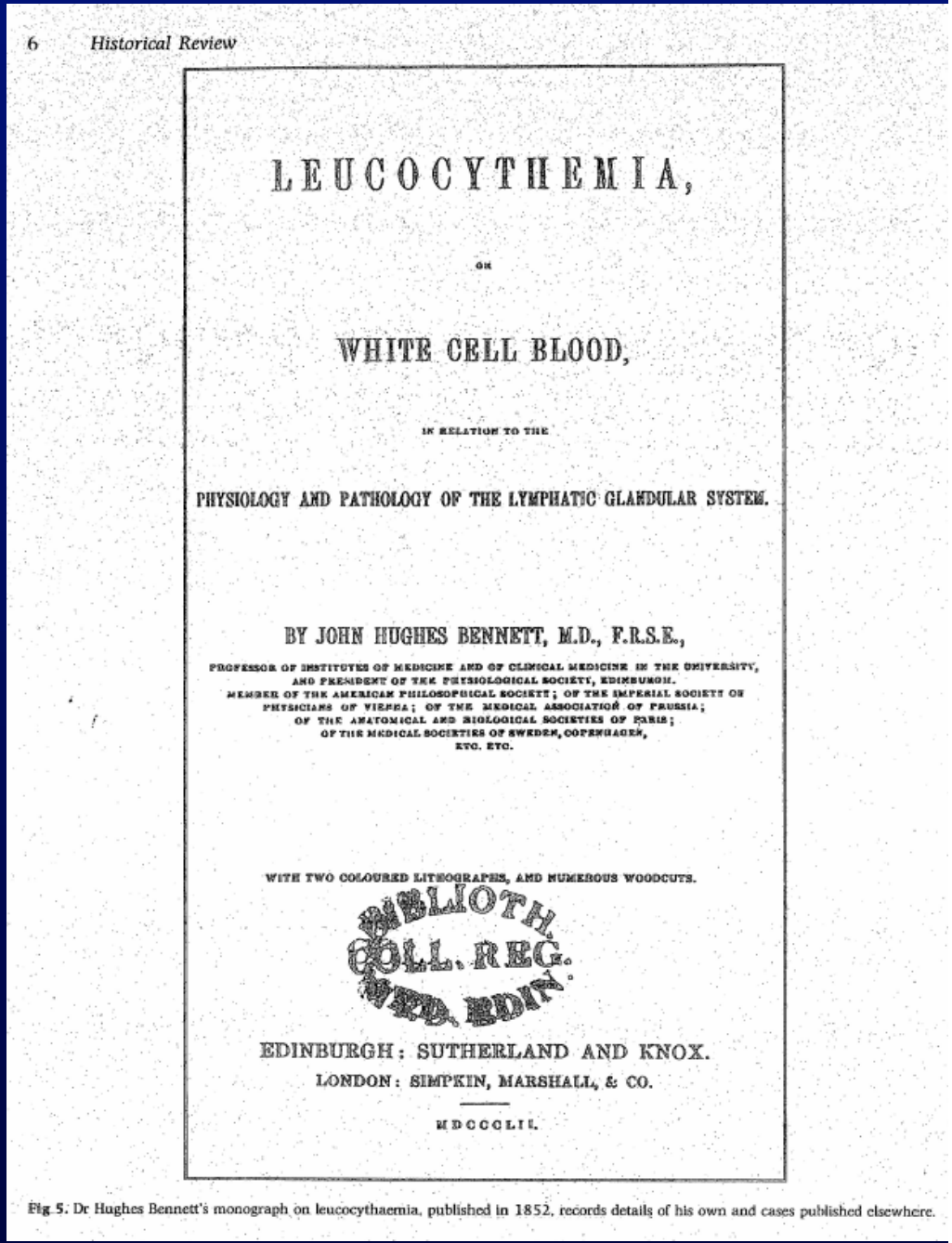
Michele.Baccarani@unibo.it



Craigie D (Bennet JH)
Case of disease of the spleen in which death took place from suppuration of the blood.
Edinburgh Medical and Surgical Journal, 1845;64:400-412

Virchow R
Weiβes Blut (Leukamie)
Archiv fur Path Anat 1847;1:563

Bennet JH
Leucocythaemia or white cell blood in relation to the physiology and the pathology of the lymphatic and glandular system.
1852 Sutherland & Knox, Edinburgh



6 *Historical Review*

LEUCOCYTHEMIA,

OR

WHITE CELL BLOOD,

IN RELATION TO THE

PHYSIOLOGY AND PATHOLOGY OF THE LYMPHATIC GLANDULAR SYSTEM.

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

PROFESSOR OF INSTITUTES OF MEDICINE AND OF CLINICAL MEDICINE IN THE UNIVERSITY, AND PRESIDENT OF THE PHYSIOLOGICAL SOCIETY, EDINBURGH. MEMBER OF THE AMERICAN PHILOSOPHICAL SOCIETY; OF THE IMPERIAL SOCIETY OF PHYSICIANS OF VIENNA; OF THE MEDICAL ASSOCIATION OF PRUSSIA; OF THE ANATOMICAL AND BIOLOGICAL SOCIETIES OF PARIS; OF THE MEDICAL SOCIETIES OF SWEDEN, COPENHAGEN, ETC. ETC.

WITH TWO COLOURED LITHOGRAPHS, AND NUMEROUS WOODCUTS.

BIBLIOTH. COLL. REG. MED. EDIN.

EDINBURGH: SUTHERLAND AND KNOX.
LONDON: SIMPKIN, MARSHALL, & CO.

MDCCCLII.

Fig 5. Dr Hughes Bennett's monograph on leucocythaemia, published in 1852, records details of his own and cases published elsewhere.

A HISTORICAL OVERVIEW OF CHRONIC MYELOID LEUKEMIA

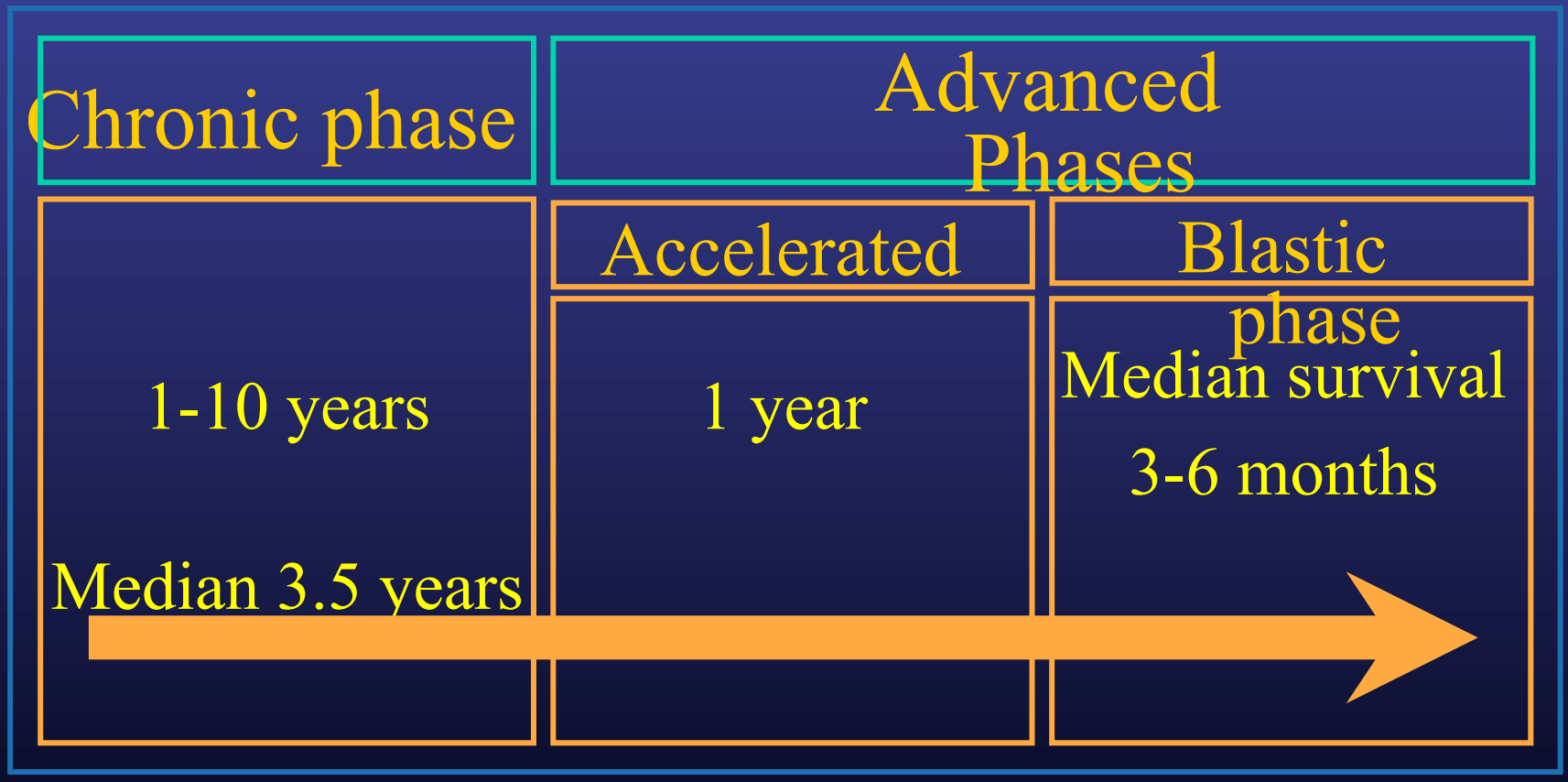
1845 FIRST DESCRIPTION
1879 Ehrlich's BLOOD CELLS STAINING METHODS
1924 EVOLUTION and OUTCOME (Minot)
1960 Ph1 CHROMOSOME (Nowell)
1973 t(9;22) (Rowley)
1984 BCR-ABL (Groffen, Konopka, Stivelman)
1990 BCR-ABL LEUKEMOGENIC IN MICE (Daley)
1996 IMATINIB (Druker)

1865 ARSENIC TRIOXIDE
1895 X-RADIATION

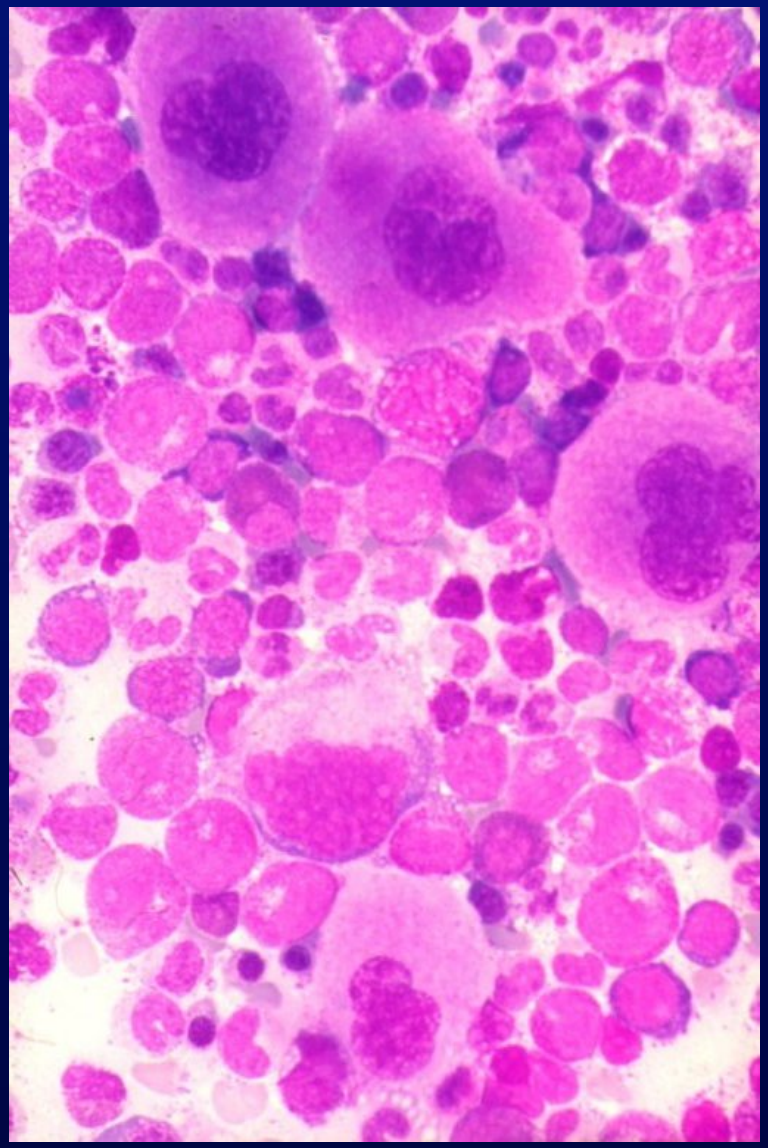
1955 BUSULFAN
1972 HYDROXYUREA
1979 STEM CELL TRANSPLANTATION
1983 INTERFERON alfa

2001 GLIVEC

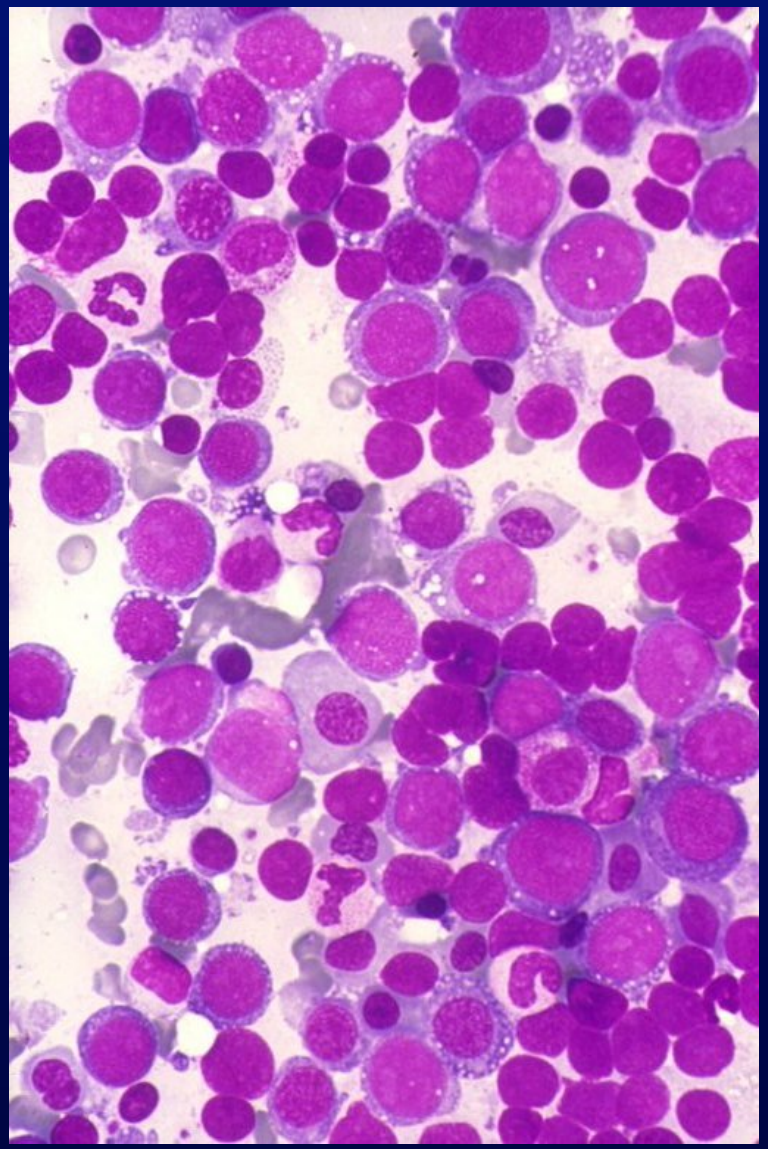
CML biologic and clinical progression



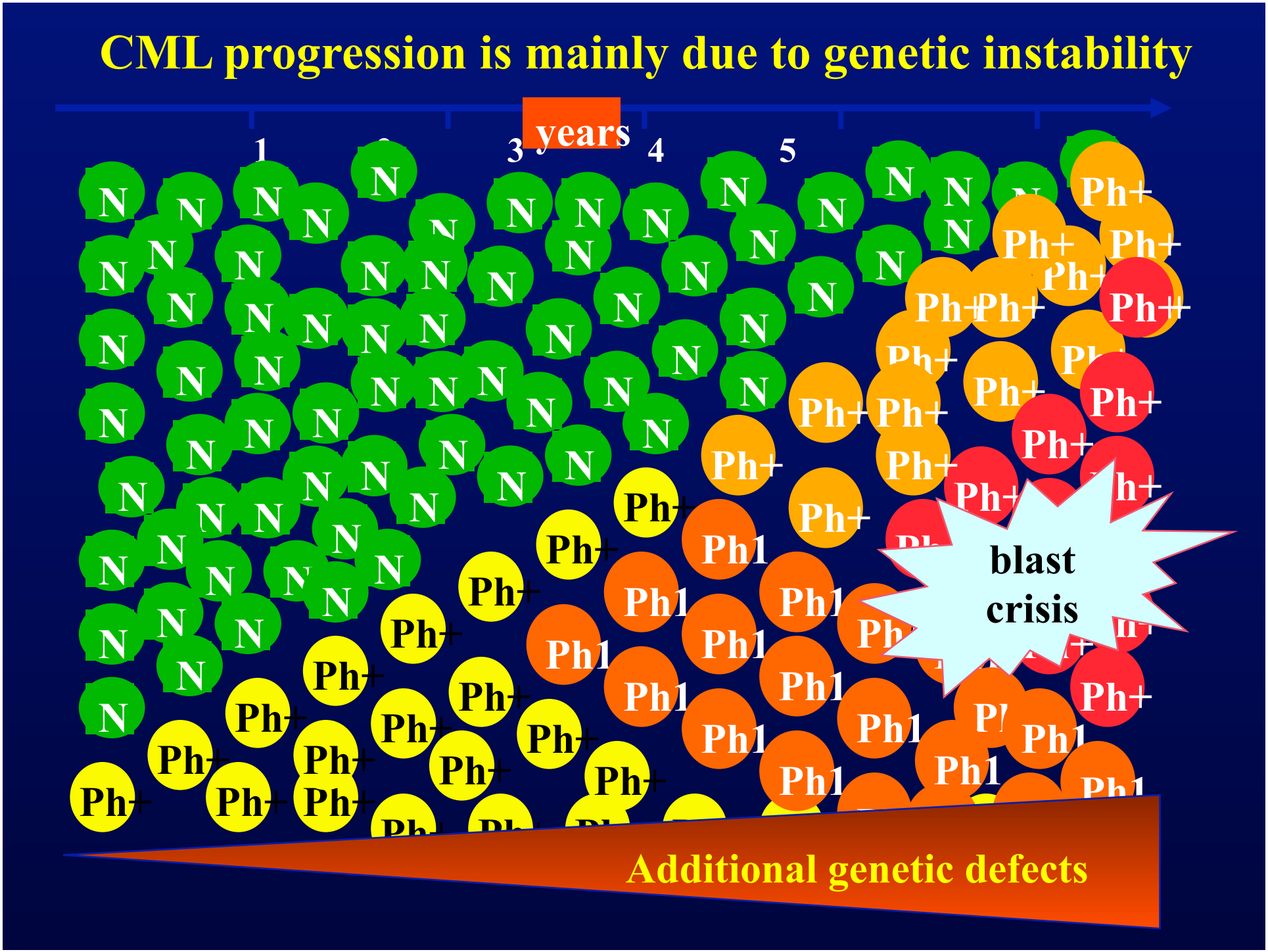
CHRONIC PHASE



BLASTIC PHASE



CML progression is mainly due to genetic instability



CHRONIC MYELOID LEUKEMIA: CONVENTIONAL THERAPY

1865 ARSENIC TRIOXIDE (Fowler liqeur, Lissauer)

1895 X-RADIATION

1912 BENZENE

1924 FIRST REPORT OF TREATMENT OUTCOME (Minot GR et al, JAMA 1924;82:1490-5)

1947 NITROGEN MUSTARD

1955 BUSULFAN (Galton DAG, Lancet 1955;1:425)

1968 BUSULFAN vs. X-RADIATION (MRC, BMJ 1968;1:201-8)

1972 HYDROXYUREA (Kennedy BJ et al, Cancer 1972;29:1052-7)

1981 INTENSIVE CHEMOTHERAPY AND SPLENECTOMY (ICSG on CML, Leuk Res 1981;5:149-157)

1993 **HYDROXYUREA vs BUSULFAN(Hehlmann R et al, Blood 1993;82:398-407)**

1994 HYDROXYUREA vs INTERFERON-alfa (ICSG on CML, NEJM 1994;330:820-7)

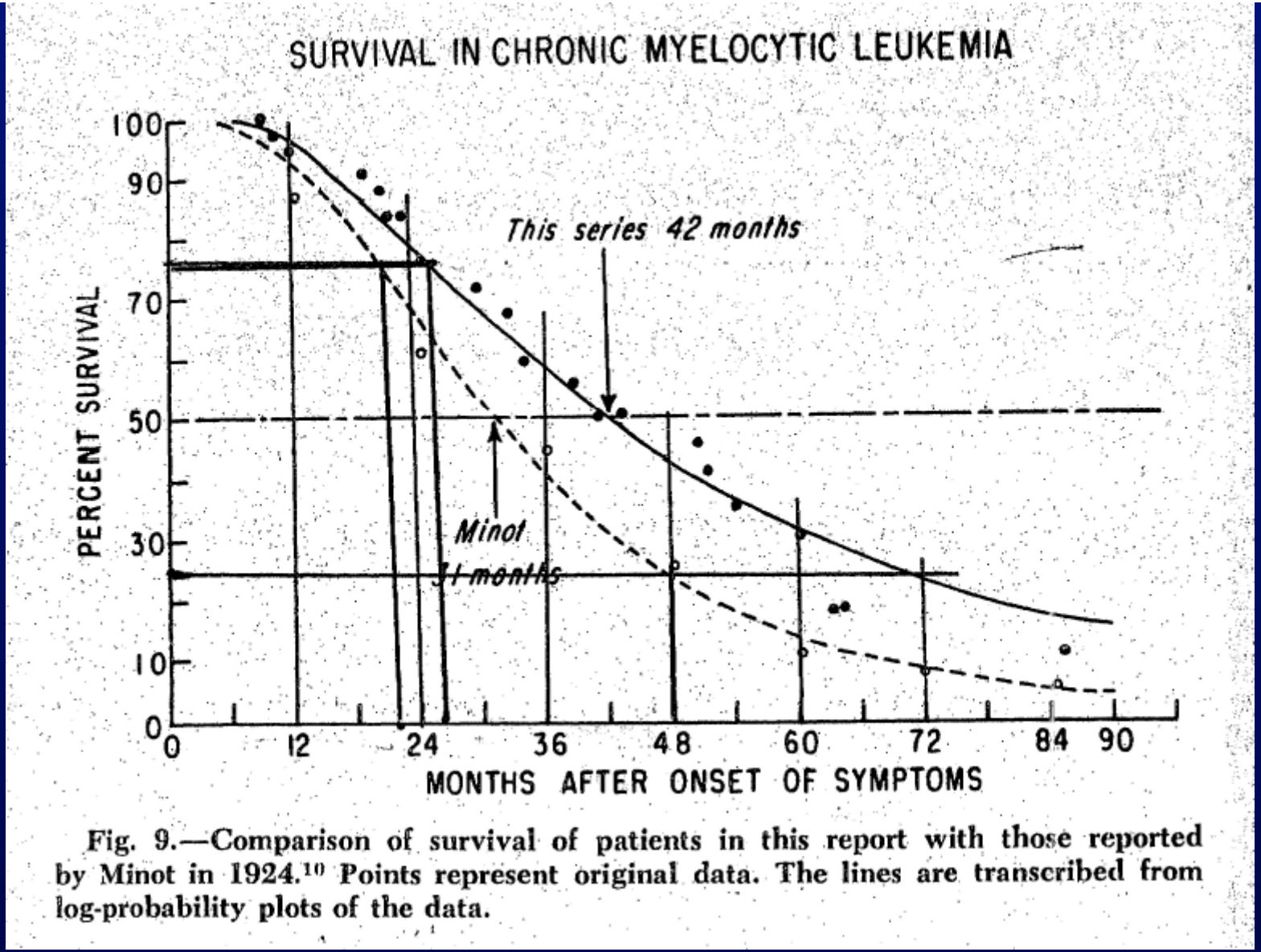


Fig. 9.—Comparison of survival of patients in this report with those reported by Minot in 1924.[10] Points represent original data. The lines are transcribed from log-probability plots of the data.

Haut A et al, Busulfan in the treatment of chronic myelogenous leukemia. The effect of long term intermitten therapy
Blood 1961;17:1-19

MRC Working Party for Therapeutic Trials in Leukemia, Chronic Granulocytic Leukemia: comparison of radiotherapy and busulfan therapy.
Brit Med J 1968;1:201-208

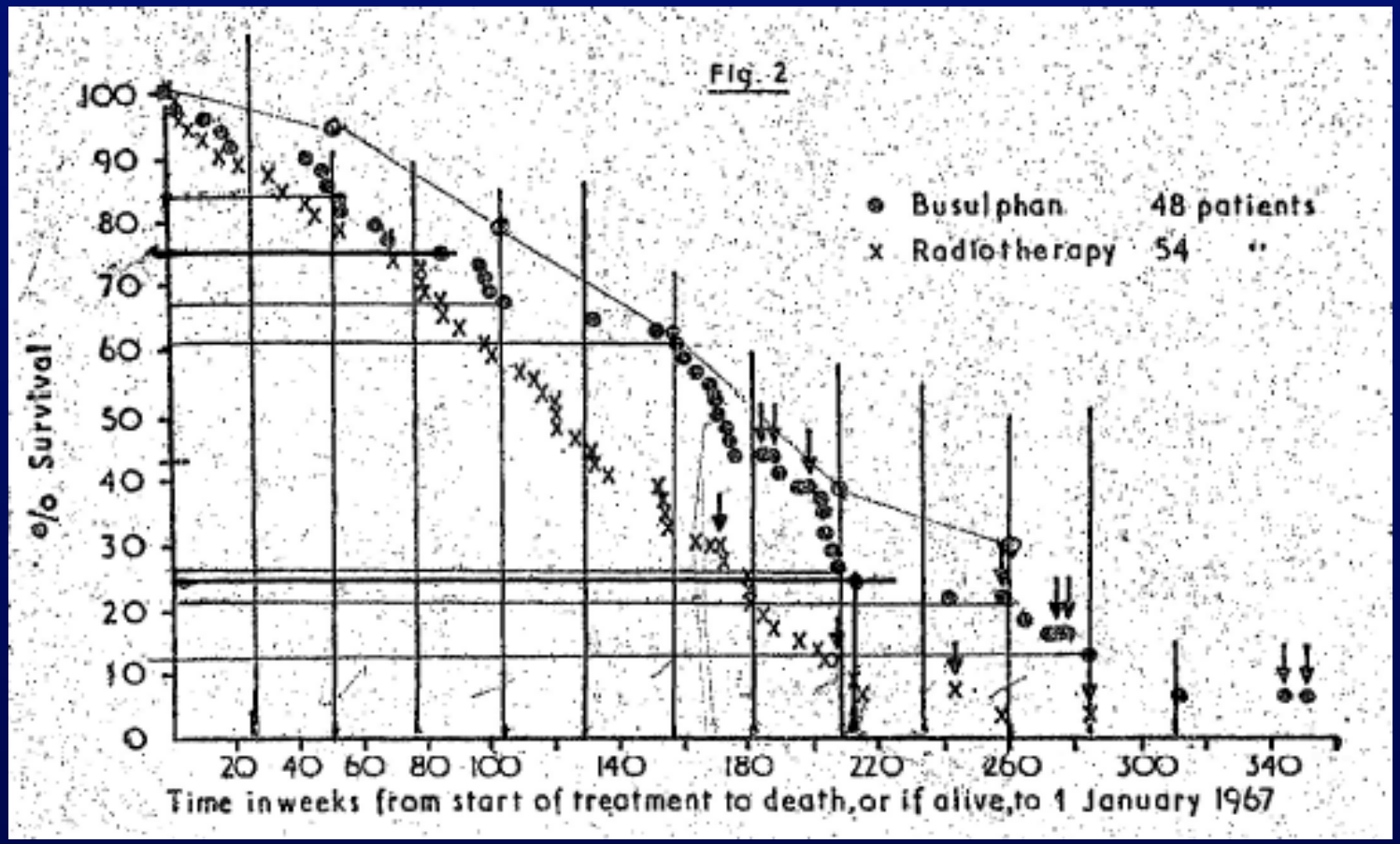


Fig 2. Survival of 102 patients suffering from chronic granulocytic leukaemia from the first day of treatment by busulphan or radiotherapy until 1 January 1967. Each point represent one patient. Arrows indicate living patients.

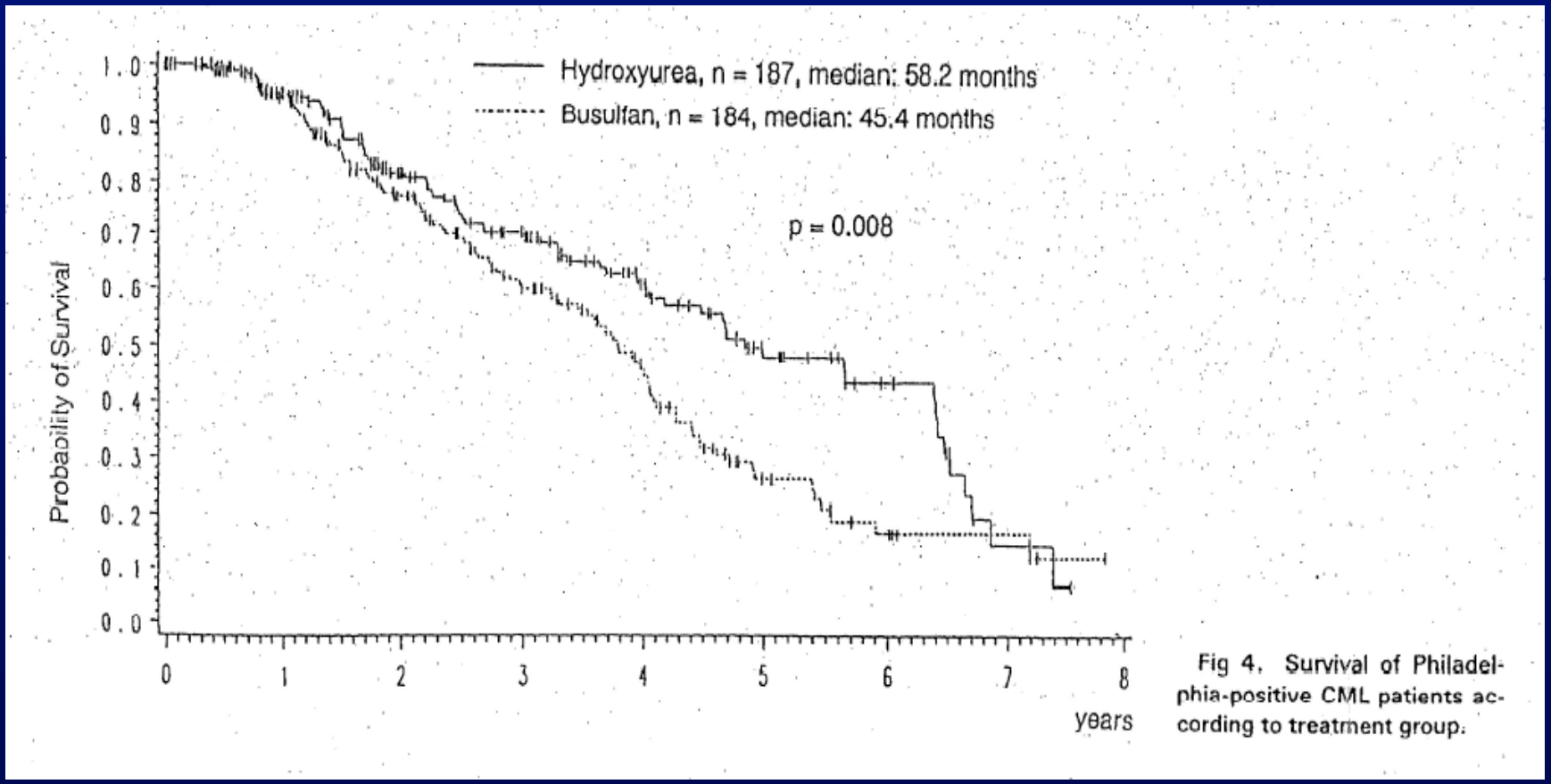
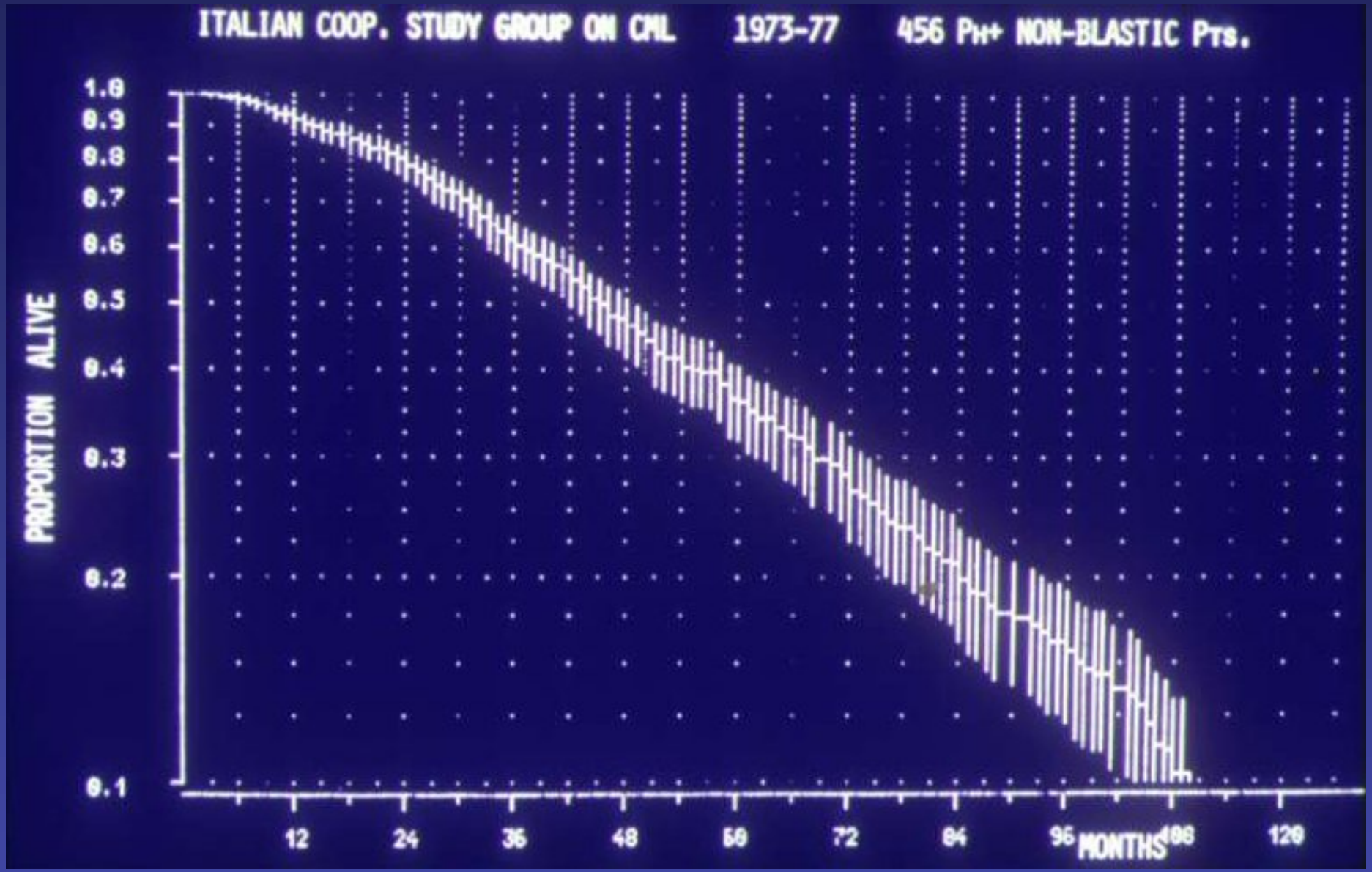


Fig 4. Survival of Philadelphia-positive CML patients according to treatment group.

Hehlmann R et al, Randomized comparison of Busulfan and Hydroxyurea in chronic myelogenous leukemia: prolongation of survival by Hydroxyurea Blood 1993;82:398-407


ITALIAN COOP. STUDY GROUP ON CML 1973-77 456 Ph+ NON-BLASTIC Pts.
PROPORTION ALIVE
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
12
24
36
48
60
72
84
96
MONTHS
108
120

CHRONIC MYELOID LEUKEMIA: STEM CELL TRANSPLANTATION

1978 AUTOLOGOUS SCT FOR BLASTIC PHASE (Goldman JM et al, 1978;40:185-195)

1979 ALLOGENEIC STEM CELL TRANSPLANTATION FROM IDENTICAL TWINS (Feferet al, NEJM 1979;300-33-37)

1981 THE ANTILEUKEMIC EFFECT OF GVHD (Werden PL et al NEJM 1981;304:1529-1533)

1987 UNRELATED MARROW DONOR FOR CML (McGlave P et al, Blood 1987;70:877-881)

1988 T-CELL DEPLETION (Goldman J et al, Ann Intern Med 1988;108:806-814)

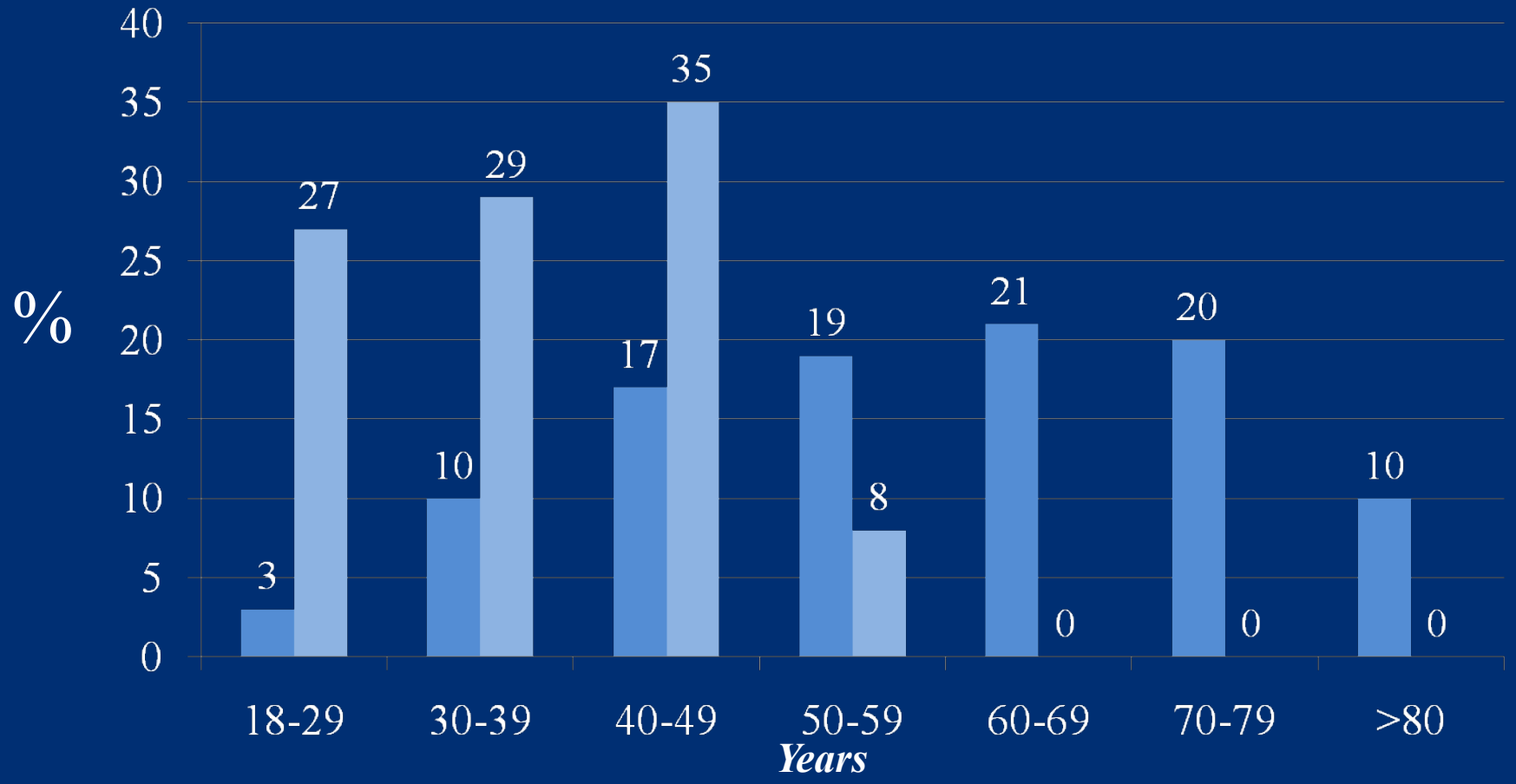
1990 DONOR LYMPHOCYTE INFUSION (Kolb H et al, Blood 1990;76:462-465)

1998 EBMT RISK SCORE (Gratwohl A et al, Lancet 1998;352:1087-1092)

ITALY (EMILIA-ROMAGNA and SICILY)

AGE DISTRIBUTION OF 350 NEWLY DIAGNOSED Ph+ BCR-ABL+ CML PATIENTS, 2008-2011

AGE DISTRIBUTION OF 205 CML PATIENTS WHO HAVE BEEN SUBMITTED TO ALLOGENEIC STEM CELL TRANSPLANTATION IN BOLOGNA , 1983-2012



CHRONIC MYELOID LEUKEMIA and INTERFERONα

1983-1986 FIRST CLINICAL RESULTS (Talpaz M et al, Blood 1983;62:689-692, and NEJM 1986; 314:1065-9)

1994-1998 INTERFERONα vs HYDROXYUREA (ICSG on CML, NEJM, 994;330:820-7, and BLOOD 1998;92:1541-1548)

1997 META-ANALYSIS OF INTERFERONα vs CHEMOTHERAPY (CML Trialists' Collaborative Group, JNCI 1997;89:1616-1620)

1997-2002 INTERFERONα vs INTERFERONα and LOW DOSE ARA-C (Guilhot F et al, NEJM 1997;337:223-230, and Baccarani M et al, Blood, 2002;99:1527-1535)

1999 INTERFERONα and AUTOLOGOUS SCT (ICSG on CML, (Haematologica 1999;84:707-715)

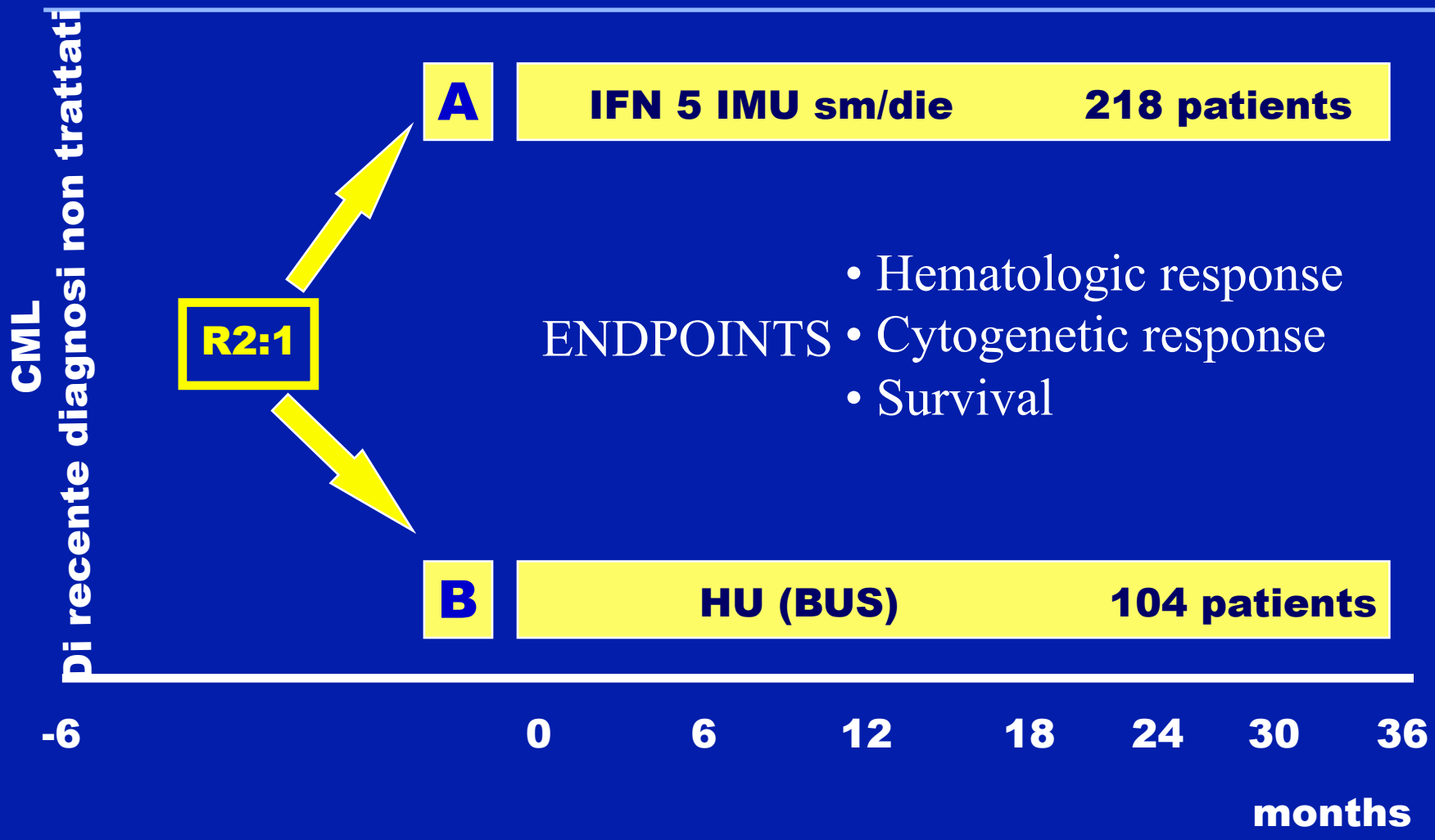
2001 OUTCOME OF COMPLETE CYTOGENETIC RESPONDERS (Bonifazi F et al, Blood 2001;98:3074-3081)

2004 HIGH DOSE vs LOW DOSE (Kluin-Nelemans HC et al, Blood 2004, 103:4408-4415)

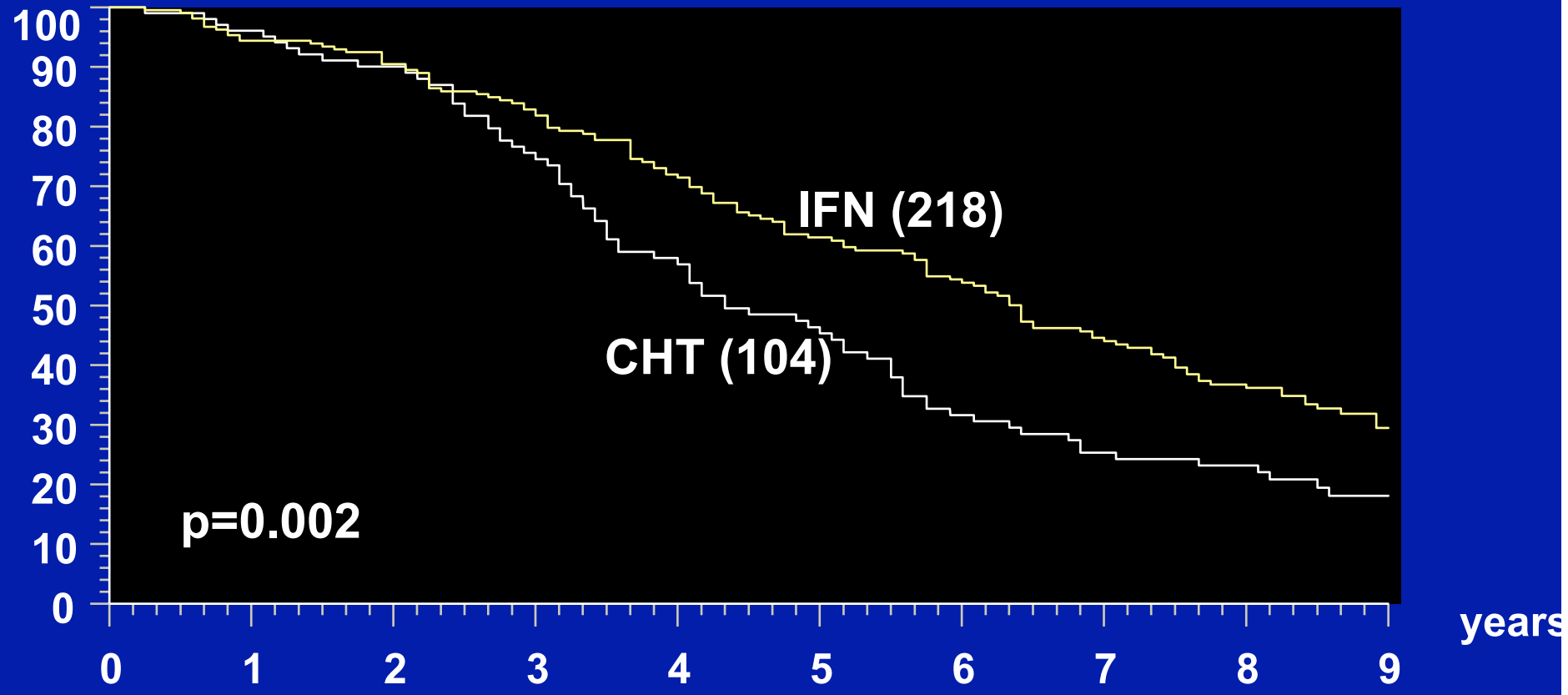
2003 INTERFERONα vs. IMATINIB (O'Brien SG et al, NEJM 2003;348: 994-1004)

2004-2010 INTERFERONα and IMATINIB (Baccarani M et al, Blood 2004;104: 4245-4251, and Preudhomme C et al, NEJM 2010;363:2511-2520)

ICSG on CML, PROTOCOL CML/86



SURVIVAL BY ARM



Median survival

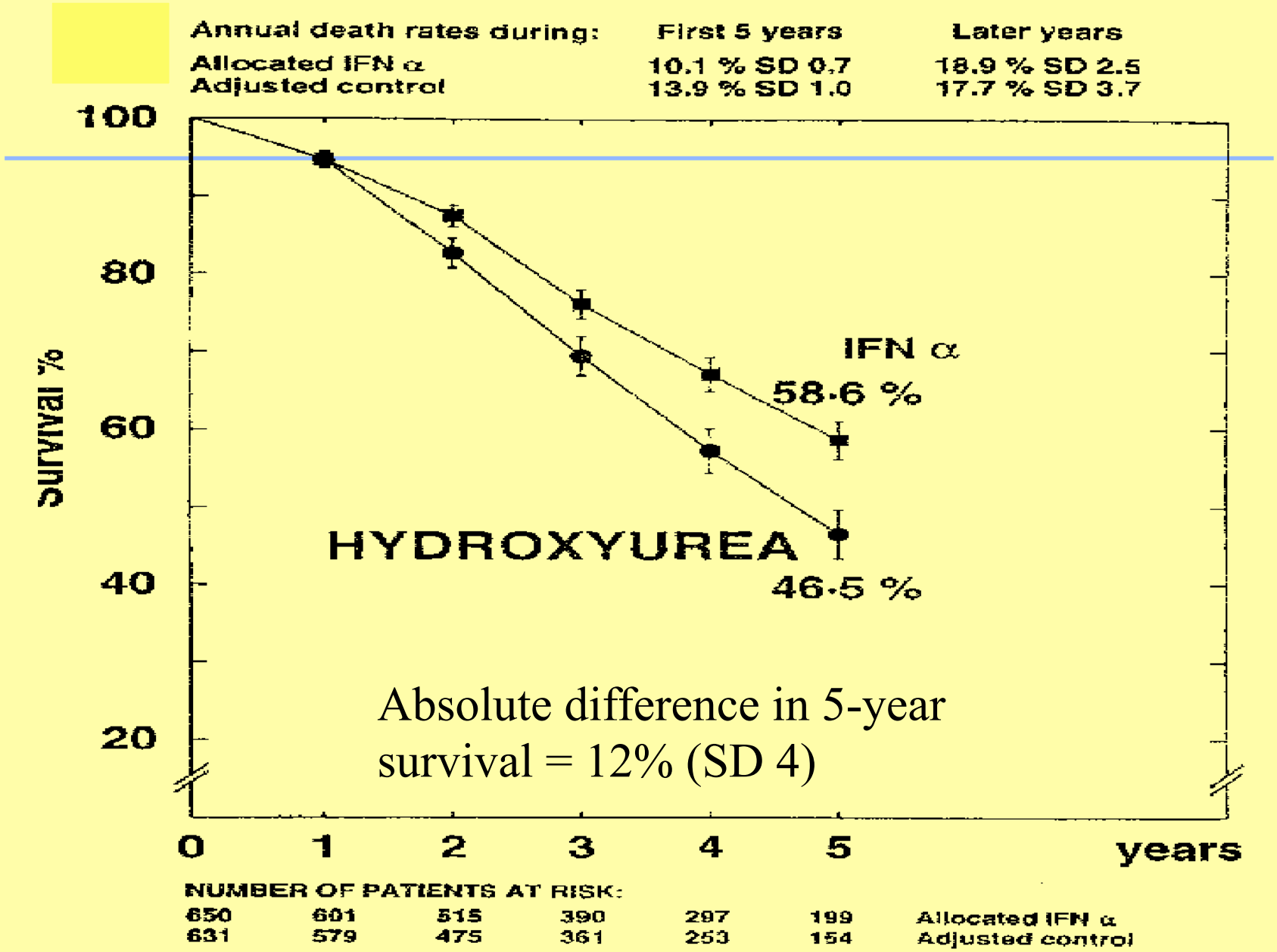
IFN 76 months (69-86)

CHT 52 months (43-66)

10-year survival

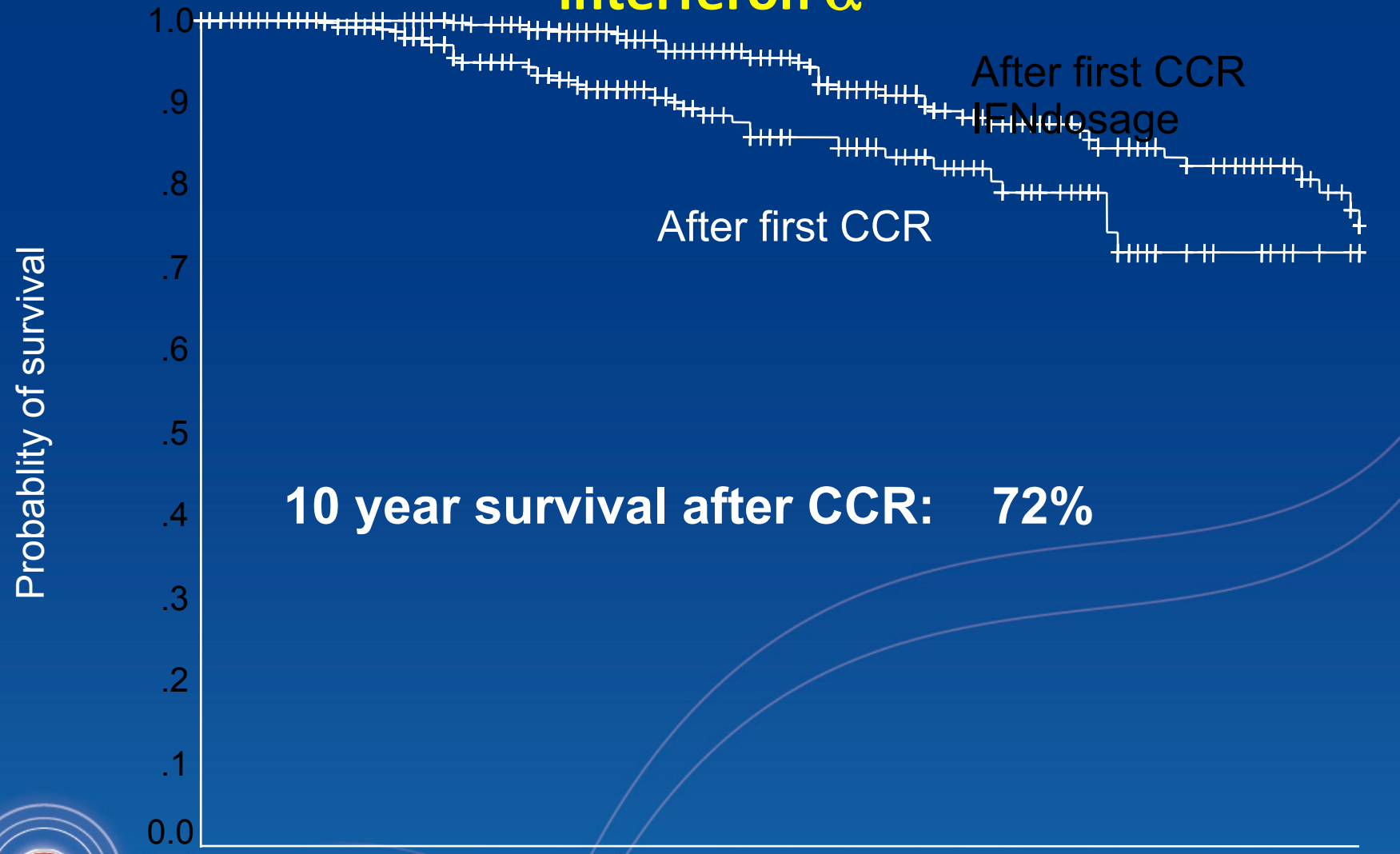
IFN 29% (23-36)

CHT 17% (9-25)



CML Trialists' Collaborative Group, JNCI (1987)

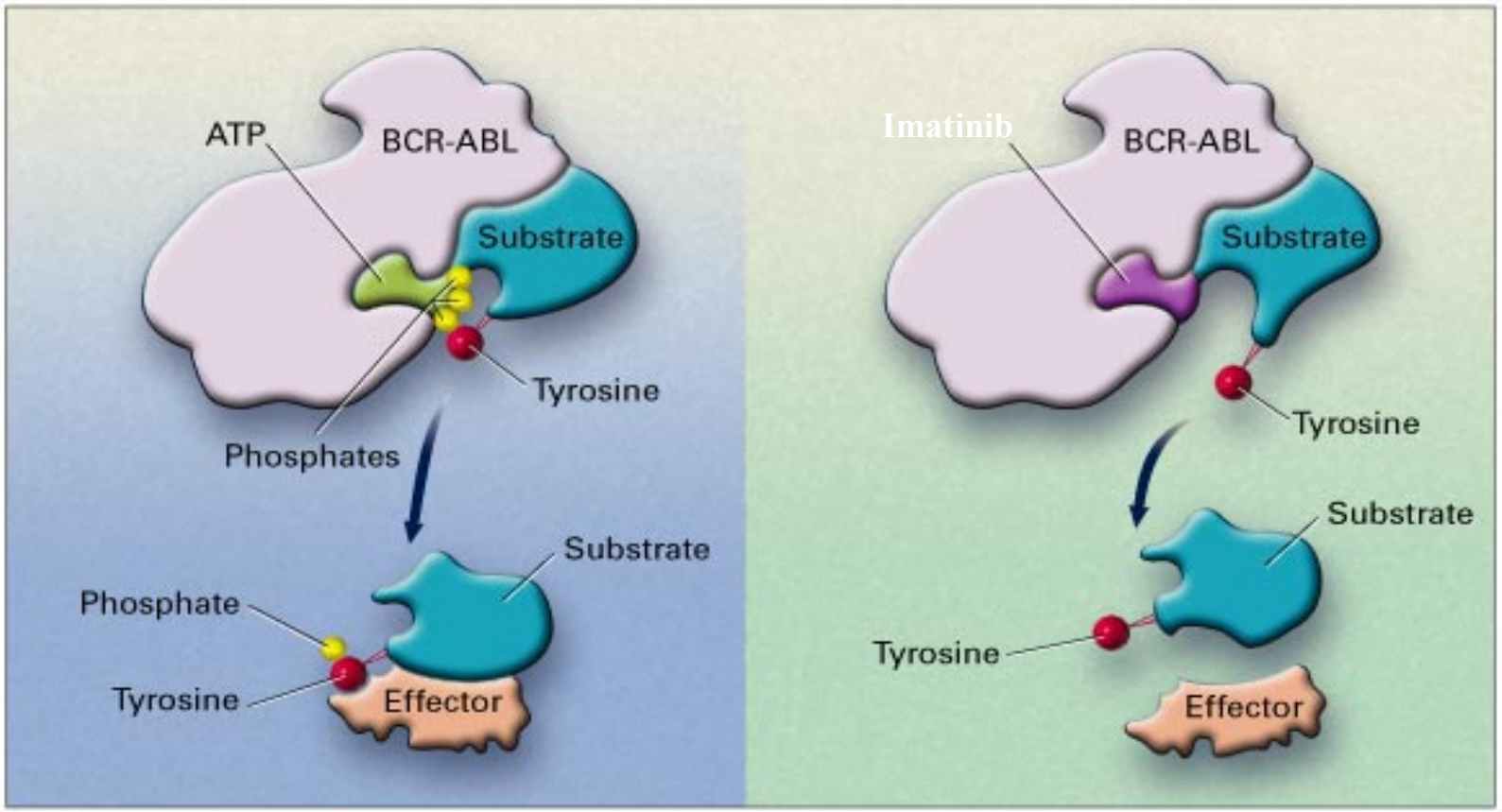
Survival of complete cytogenetic responders to interferon α



Bari
28-29 aprile 2011

Bonifazi et al. Blood 2001; 98:3074-81 (2001)

Inhibition of BCR-ABL Kinase Activity by Imatinib



Reproduced with permission from Goldman JM et al. *N Engl J Med.* 2001;344:1084-1086.

CHRONIC MYELOID LEUKEMIA : TYROSINE KINASE INHIBITORS

1996-2001 **IMATINIB, IN VITRO and IN VIVO (Druker BJ et al, Nat Med 1996;2:561-566, and NEJM 2001;344:1031-7)**

2001 IMATINIB RESISTANCE, MUTATIONS (Weisberg E et al, Blood 2000;95:3498-3505, and Gorre ME et al, Science 2001;293:876-880)

2002 **IMATINIB SECOND LINE** (Kantarjian HM et al, NEJM **2002**;346: 645-657)

2003 **IMATINIB FIRST LINE vs IFNα (IRIS STUDY, O'Brien SG et al, NEJM 2003;**348:994-1004)

2003-2006 MOLECULAR RESPONSE, STANDARDIZATION (Hughes et al, NEJM 2003;349:1423-1432, and Blood 2006;108:28-37)

2006 **DASATINIB SECOND LINE** (Talpaz M et al, NEJM **2006**;354:2531-2541)

2006 **NILOTINIB SECOND LINE** (Kantarjian HM et al, NEJM **2006**;354: 2542-2551)

2007 IMATINIB DISCONTINUATION (Rousselot P et al, Blood 2007; 109:58-60)

2004-2010 IMATINIB AND IFNα (Baccarani M et al, Blood 2004;104:4245-4251, and Preudhomme C et al, NEJM 2010;363:2511-2520)

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Journal of Medicine

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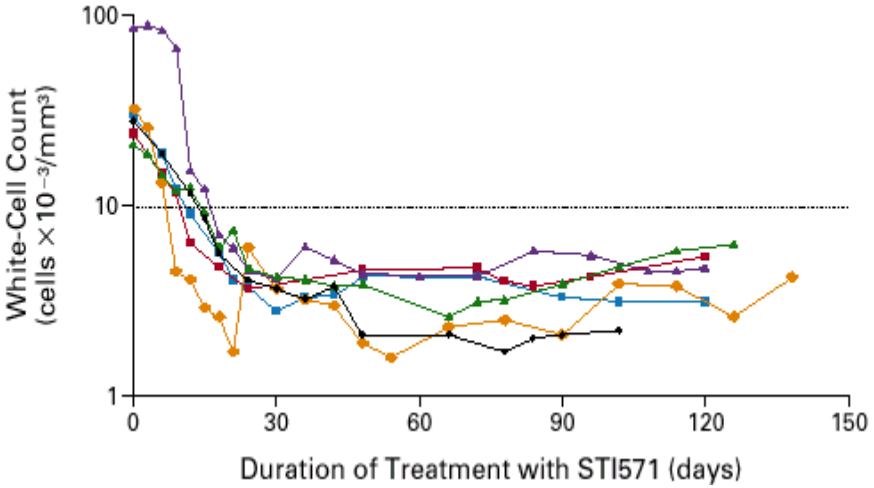
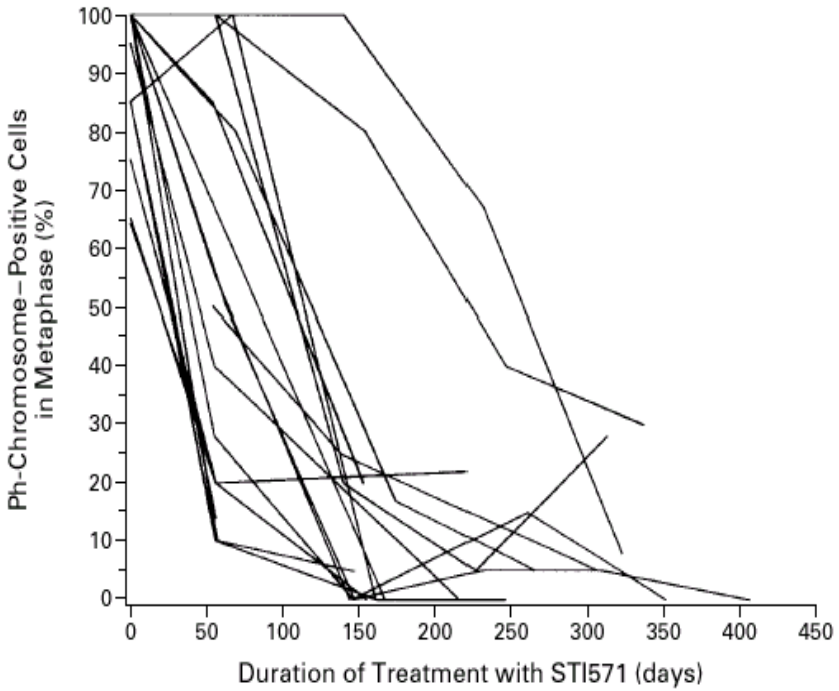
EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

BRIAN J. DRUKER, M.D., MOSHE TALPAZ, M.D., DEBRA J. RESTA, R.N., BIN PENG, PH.D., ELISABETH BUCHDUNGER, PH.D., JOHN M. FORD, M.D., NICHOLAS B. LYDON, PH.D., HAGOP KANTARJIAN, M.D., RENAUD CAPDEVILLE, M.D., SAYURI OHNO-JONES, B.S., AND CHARLES L. SAWYERS, M.D.





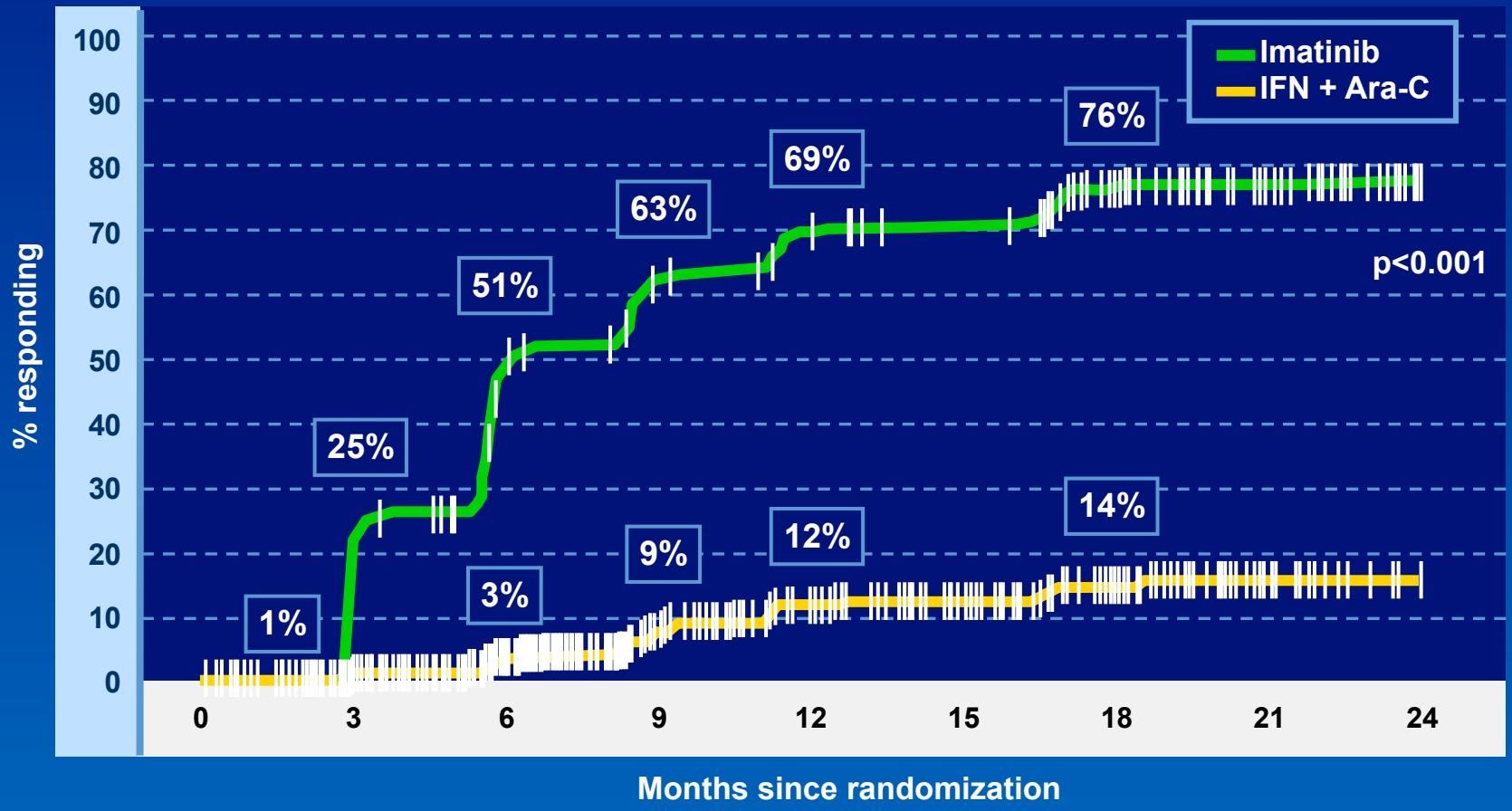
The IRIS Study

International Randomized Study of Interferon + Ara-C vs STI571* in Chronic Myeloid Leukemia

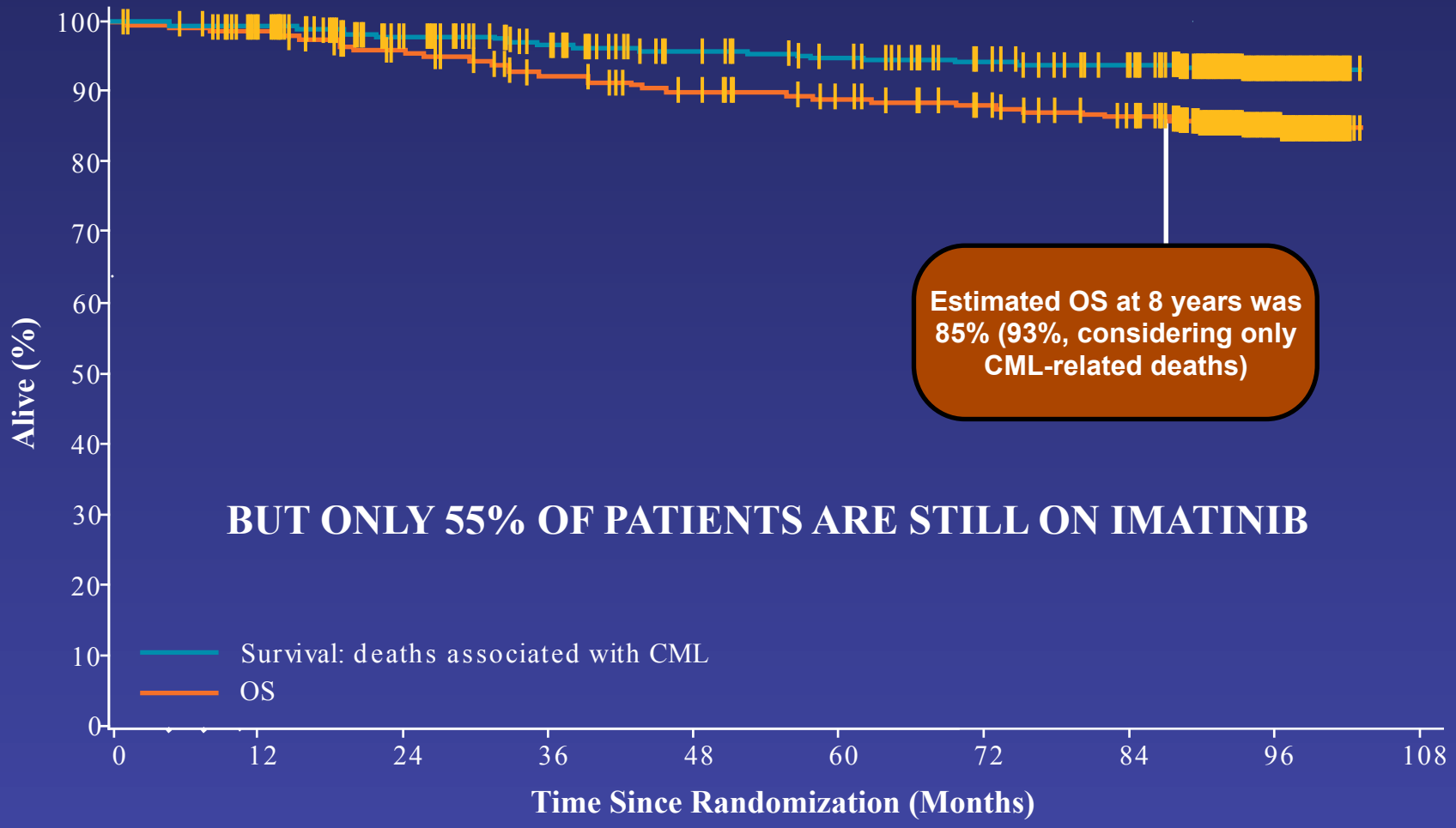
ASH 2002

* Imatinib / Gleevec / Glivec

Complete Cytogenetic Responses



IRIS – OS (ITT) on Imatinib Arm



Deininger, et al. Blood 2009;114. Abstract 1126

CHRONIC MYELOID LEUKEMIA : SECOND GENERATION TYROSINE KINASE INHIBITORS

2010 NILOTINIB FIRST LINE, vs. IMATINIB (ENESTnd STUDY, Saglio G et al, NEJM 2010;362:2251-2259)

2010 DASATINIB FIRSTLINE, vs. IMATINIB (DASISION STUDY, Kantarjian HM et al, NEJM 2010;362:2260-2270)

2011 BOSUTINIB SECONDLINE (Cortes JE et al, Blood 2011;118:4567-4576)

2012 BOSUTINIB FIRSTLINE, vs. IMATINIB (BELA STUDY, Cortes JE et al, JCO 2012;30:3486-3492)

2012 PONATINIB SECONDLINE (Cortes JE et al, NEJM 2012;367:2075-2088)

2016, LA TERAPIA DELLA LMC, LO STATO DELL' ARTE

- **TERAPIA STANDARD, APPROVATA**

- IMATINIB, NILOTINIB e DASATINIB, in prima linea
- BOSUTINIB, in seconda linea
- PONATINIB, in terza linea sempre, in seconda linea in caso di mutazione T315I o di resistenza a nilotinib o dasatinib.

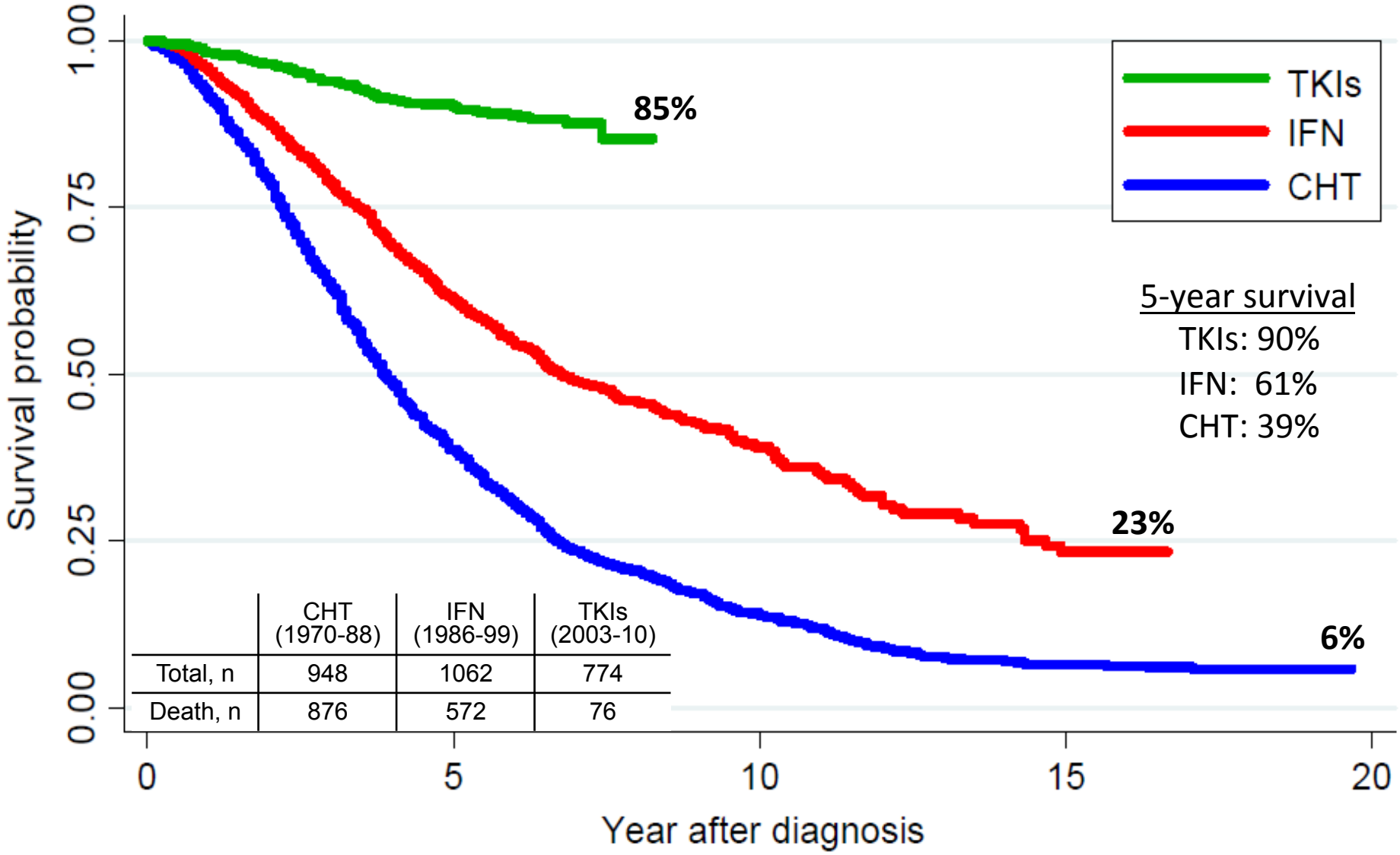
- **TERAPIE "SPERIMENTALI"**

- ALTRI INIBITORI DELLE TIROSINO CHINASI
- INTERFERONα in combinazione con TKIs
- ALTRI FARMACI E ANTICORPI MONOCLONALI

- **TRAPIANTO DI MIDOLLO ALLOGENICO**

Survival of CML by therapy

N = 2784



Date of diagnosis: 1970 - 2010

GIMEMA CML Working Party (formerly ICSG on CML)

CML in 2016: NEWS and CHANGES

GOAL: from survival to cure (treatment-free remission)

MONITORING: from cytogenetics to standardized PCR

MUTATIONS: from Sanger Sequencing to Ultra Deep or Next Generation Sequencing
from imatinib to second generation TKIs to ponatinib

COMPLIANCE and LIFE QUALITY: from one drug to many

THERAPY: from “gold standard” to patient-adapted

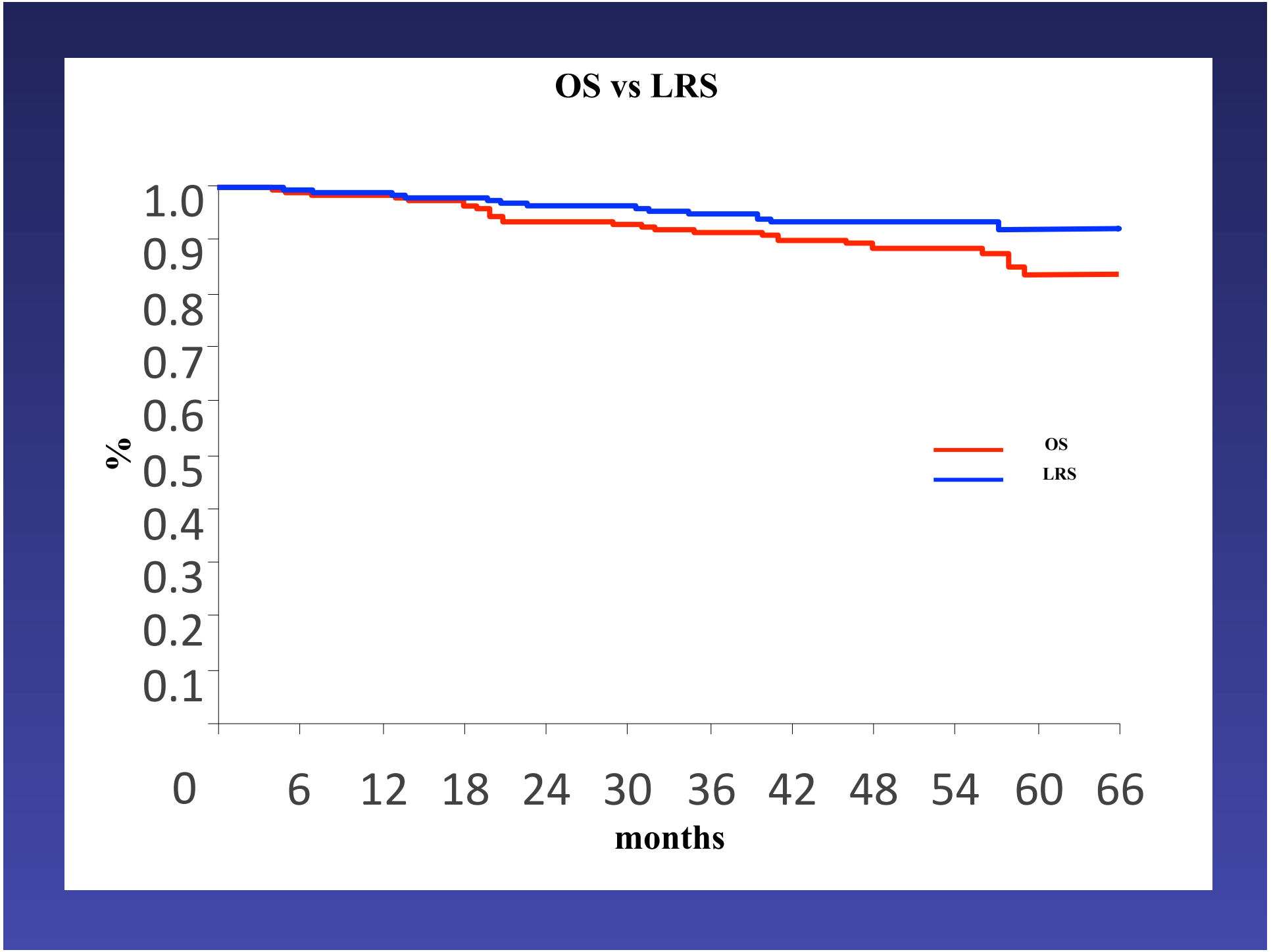
FOR MANY PATIENTS, CML IS NOT THE MAJOR FACTOR LIMITING LIFE AND AFFECTING THE QUALITY OF LIFE

SEVERAL PATIENT-RELATED FACTORS LIMITS THE USE, THE CHOICE AND THE DOSE OF TKIs

PATIENT RELATED FACTORS LIMITING THE CHOICE, THE DOSE AND THE USE OF TKIs

ATHEROSCLEROSIS
ARTERIAL THROMBOTIC DISEASE
CEREBROVASCULAR DISEASE
HYPERTENSION
HEART FAILURE
ISCHEMIC HEART DISEASE
THROMBOPHILIC STATE
DIABETES MELLITUS
DYSLIPIDEMIA
CHRONIC PULMONARY DISEASE (obstructive, enfisema, fibrosis, etc)
AUTOIMMUNE DISEASE
OTHER TUMOR
PSYCHIATRIC DISORDER
ALZHEIMER
PARKINSON
HANDICAP……
AGE, LIFE STYLE, EDUCATION, WILLING……..

BACK-UP


OS vs LRS
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
%
OS
LRS
0
6
12
18
24
30
36
42
48
54
60
66
months

LA LMC E' UNA MALATTIA "SEMPLICE", PROVOCATA DA UNA SOLA ANOMALIA GENICA E MOLECOLARE,

MA……..

I PAZIENTI SONO TUTTI UGUALI ? Sesso, età, altre malattie

I CASI SONO TUTTI UGUALI ? Fase, rischio, ecc

I TKI SONO TUTTI UGUALI ? Specificità, potenza, tossicità, farmacocinetica, costo

GLI SCOPI DELLA TERAPIA SONO SEMPRE GLI STESSI, PER TUTTI ?

Durata di vita, qualità di vita, remissione senza terapia

QUALE TERAPIA DI PRIMA LINEA ?

IMATINIB o TKI DI SECONDA GENERAZIONE ?

DUE STUDI PROSPETTICI CONTROLLATI RANDOMIZZATI CHE HANNO CONFRONTATO IMATINIB 400 MG CON DASATINIB (DASISION) E NILOTINIB (ENESTnd) HANNO DIMOSTRATO UN BENEFICIO MARGINALE PER LA SOPRAVVIVENZA LIBERA DA PROGRESSIONE MA NON PER LA SOPRAVVIVENZA GLOBALE.
MA HANNO MOSTRATO PIU' RISPOSTE MOLECOLARI, PIU' PRECOCI E PIU' PROFONDE.

DA QUI IN AVANTI LA GRANDE SFIDA NON E' PIU' SOLO QUELLA DI MIGLIORARE LA SOPRAVVIVENZA, MA DI OTTENERE UNA REMISSIONE CHE SI MANTENGA ANCHE DOPO LA SOSPENSIONE DELLA TERAPIA.
E UNA MIGLIORE QUALITA' DI VITA.

[1]Kantarjian HM et al, NEJM 2010;362(24);2260-2270; Cortes J et al, JCO 2016
[2]Saglio G et al, NEJM 2010;36:2251-2259; Hochhaus A et al, Leukemia 2016

TERAPIA DI PRIMA LINEA, IN FASE CRONICA

TKI DI SECONDA GENERAZIONE

- TUTTI I PAZIENTI ??? Oppure solo
- "GIOVANI", SENZA COMORBIDITA' IMPORTANTI, e
- ALTI RISCHI (Sokal, EURO, EUTOS, CCA/Ph+)

IMATINIB

- TUTTI I PAZIENTI ??? Oppure solo
- "ANZIANI", CON COMORBIDITA' IMPORTANTI, e
- BASSI RISCHI

- **"SWITCH" SOLO IN CASO DI FALLIMENTO O ANCHE IN CASO DI RISPOSTA NON OTTIMALE ?**

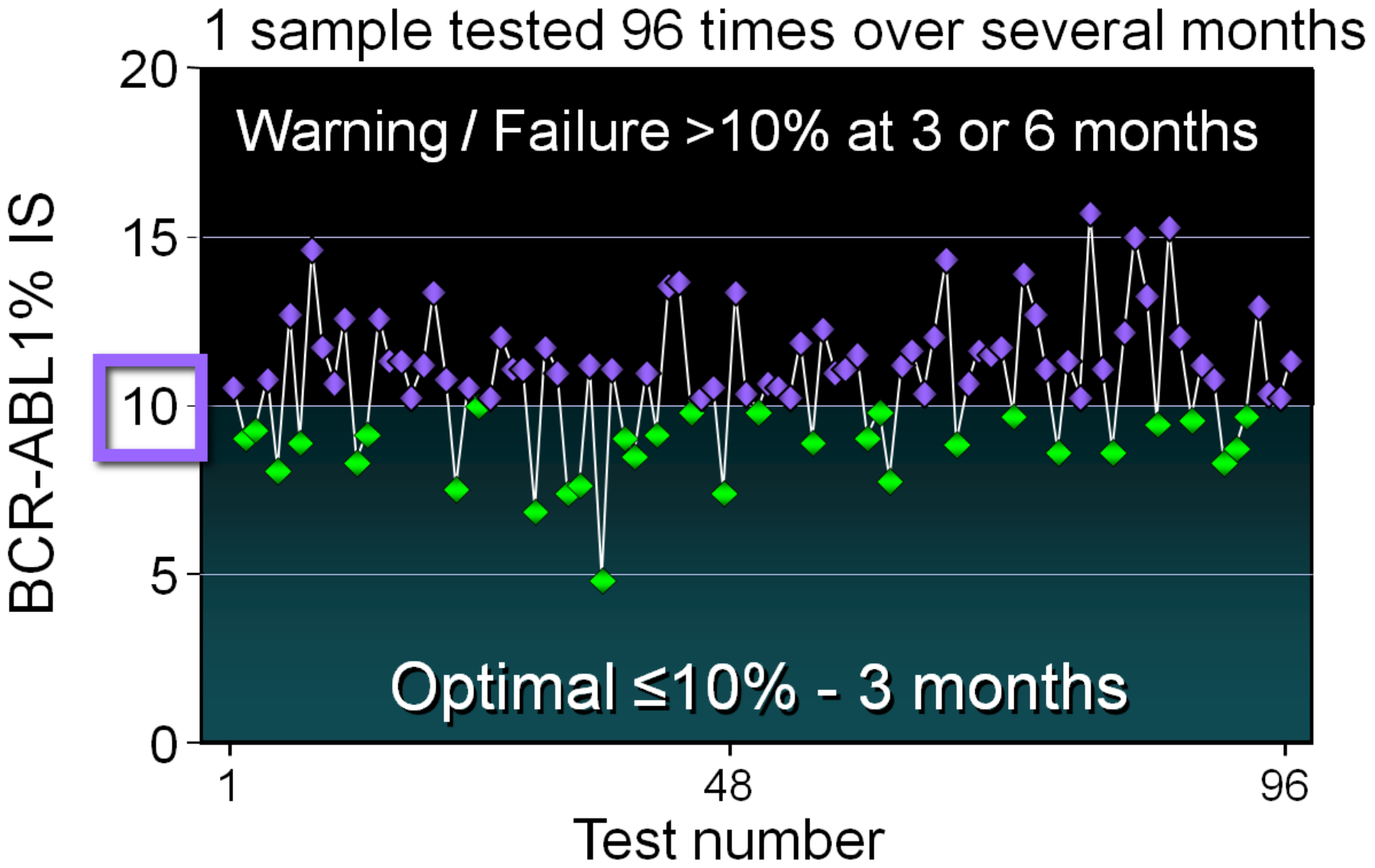
"EARLY SWITCH" DALL' IMATINIB AI TKI DI SECONDA GENERAZIONE: UNA QUESTIONE CALDA E CONTROVERSA : DUE RACCOMANDAZIONI DIVERSE

- **NCCN:** POICHE' UNA RISPOSTA MOLECOLARE PRECOCE SI OTTIENE PIU' CON I TKI DI SECONDA GENERAIONE, UN "EARLY SWITCH" DA IMATINIB A TKI DI SECONDA GENERAZIONE E' RACCOMANDATO

- **ELN:** NON CI SONO DATI NE' STUDI CHE DIMOSTRINO CHE L' "EARLY SWITCH" SIA CONVENIENTE, E QUANTO POSSA ESSERE CONVENIENTE

MA PER DECIDERE LO SWITCH E' SUFFICIENTE UNA SOLA PCR ?

Mean value = 11%



LA DINAMICA DELLA RISPOSTA MOLECOLARE PRECOCE E' PIU' IMPORTANTE DI UN UNICO DATO DI qPCR A TRE MESI

LA RIDUZIONE RELATIVA (PIU' O MENO DEL 35%) DEL TRASCRITTO BCR-ABL1 NEI PRIMI TRE MESI

oppure

IL TEMPO DI DIMEZZAMENTO (PIU' O MENO DI 90 GIORNI) DEL TRASCRITTO BCR-ABL1 NEI PRIMI TRE MESI

HANNO UN VALORE PROGNOSTICO PIU' PRECISO DI UN SINGOLO VALORE DI qPCR A TRE MESI

Hanfstein B et al, ASH 2013 and LEUKEMIA 2014
Branford S et al, ASH 2013 and BLOOD 2014

“EARLY SWITCH” e “LATE SWITCH”

POICHE’ UMA RISPOSTA MOLECOLARE PRECOCE (BCR-ABL1 ≤ 10% A TRE MESI) HA VALORE PROGNOSTICO (PIU’ RISPOSTE MOLECOLARI PROFONDE, PIU’ RAPIDAMENTE, MIGLIORE SOPRAVVIVENZA)

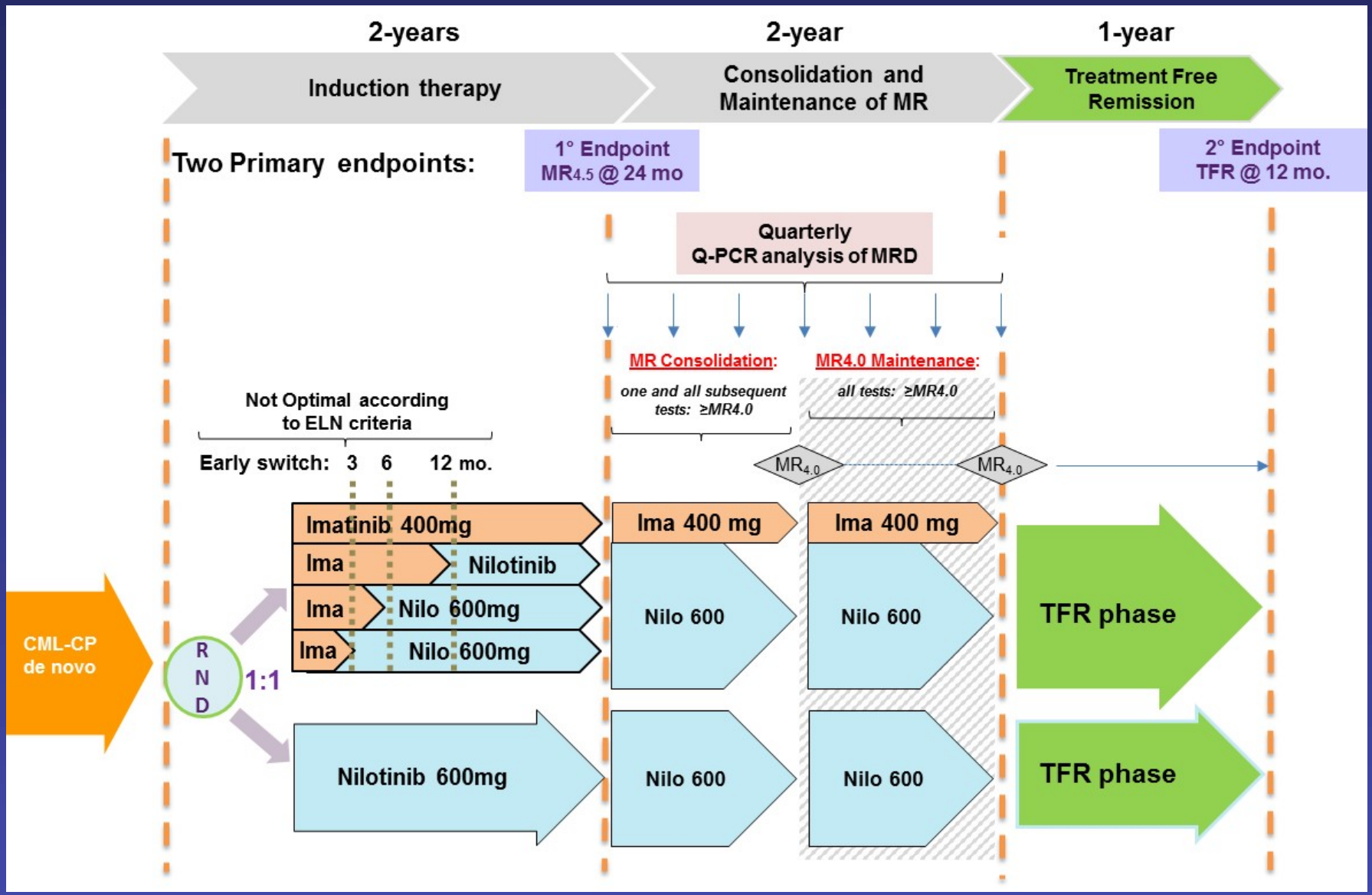
SI DEVE CAMBIARE IL TKI SE A TRE MESI NON E’ STATA ANCORA OTTENUTA LA RISPOSTA MOLECOLRE PRECOCE (SE IL TRASCRITTO BCR-ABL1 E’ ANCORA SUPERIORE A 10%) ?

POICHE’ UNA RISPOSTA MOLECOLARE PROFONDA È NECESSARIA PER OTTENERE UNA REMISSIONE LIBERA DA TERAPIA

SI DEVE CAMBIARE IL TKI SE DOPO UNO O DUE ANNI IL TRASCRITTO BCR-ABL1 E’ ANCORA SUPERIORE A 0.01%

SUSTRENIM Study

Study Design



LA TERAPIA DI SECONDA LINEA (SWITCH)

IN ALCUNI CASI E' OBBLIGATORIA :

IN CASO DI FALLIMENTO (ELN 2013)

IN CASO DI TOSSICITA'

IN ALCUNI CASI E' OPZIONALE:

IN CASO DI EFFETTI TOSSICI LIEVI, CRONICI, RICORRENTI

IN CASO DI RISPOSTA NON OTTIMALE (EARLY e LATE SWITCH)

LEUCEMIA MIELOIDE CRONICA: LA SCELTA DELLA TERAPIA DI SECONDA E DI TERZA LINEA

STUDI "VECCHI" IN PAZIENTI CHE SPESSO ERANO STATI TRATTATI CON IMATINIB IN SECONDA LINEA

NESSUNO STUDIO CHE CONFRONTI NILOTINIB, DASATINIB, BOSUTINIB E PONATINIB

LA SELEZIONE VA FATTA TENENDO CONTO DELLE MUTAZIONI, DELLE COMORBIDITA', DELLA TOSSICITA' DEL PRIMO TKI, E DELL' ESPERIENZA DEL MEDICO.
IN MOLTI PAESI E' DETTATA DAL COSTO

IL MONITORAGGIO DEVE ESSERE MOLTO ATTENTO: UN TKI "sbagliato" COSTA MOLTO DI PIU' DI UNA PCR

LE CAUSE DEL "FALLIMENTO" TERAPEUTICO POSSONO ESSERE MOLTE

LA **MALATTIA** : RISCHIO, CARATTERISTICHE BIOLOGICHE

IL **PAZIENTE**: ETA', EDUCAZIONE, COMORBIDITA', TOLLERANZA, ADERENZA

IL **MEDICO:**

- SCARSA ESPERIENZA (la LMC è una malattia rara)
- MONITORAGGIO INADEGUATO
- PRESCRIZIONE INAPPROPRIATA
- TIMORE DELLA TOSSICITA'

- IN ALCUNI CASI LO SWITCH NON E' IL MODO GIUSTO PER MIGLIORARE IL RISULTATO DELLA TERAPIA

CAMBIARE TKI PER EFFETTI TOSSICI MINORI: UN PROBLEMA DI DIFFICILE SOLUZIONE

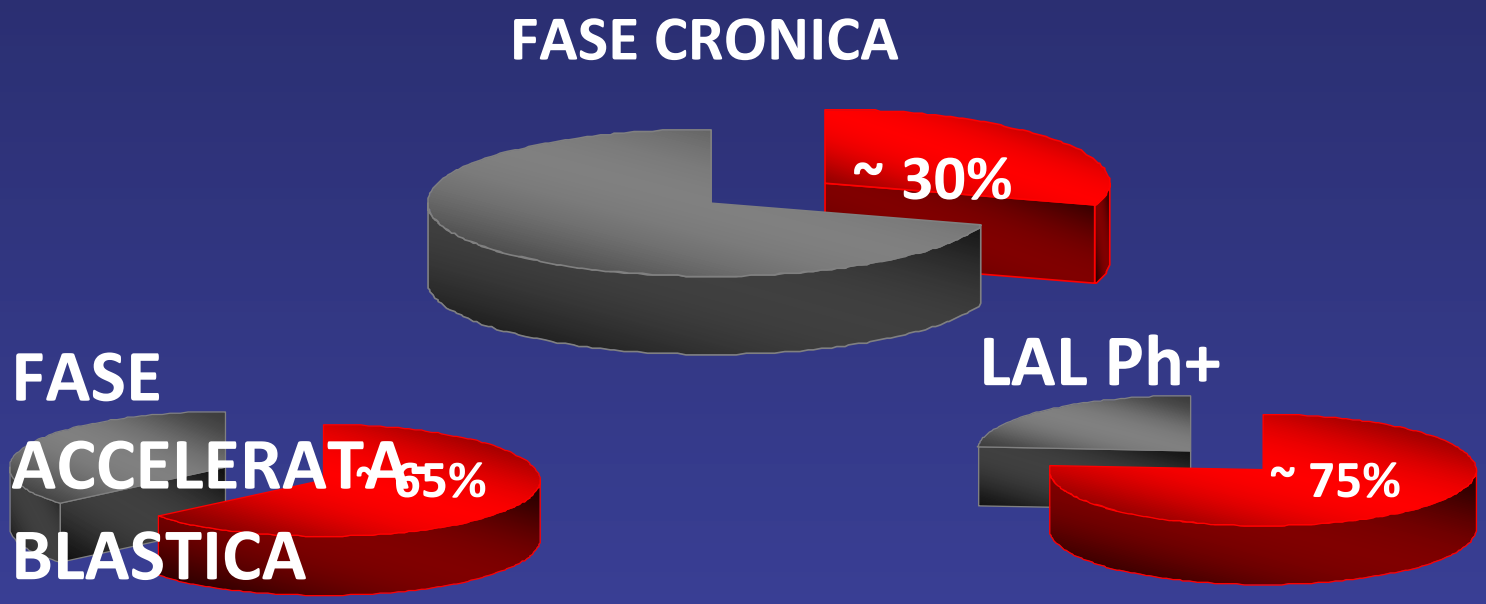
IL NUMERO: QUANTI EFFETTI TOSSICI POSSONO ESSERE TOLLERATI ?

L' INTENSITA' : FINO A CHE PUNTO UN EFFETTO TOSSICO E' TOLLERABILE ?

LA DURATA: PER QUANTO TEMPO SI PUO' TOLLERARE ?

LA RIPETIZIONE: PER QUANTE VOLTE PUO' ESSERE TOLLERATO ?

LA FREQUENZA E IL TIPO DI MUTAZIONI DI BCR-ABL1 VARIANO MOLTO DA FASE A FASE



Soverini et al, Blood 2011

VIVERE (TRANQUILLI) SENZA TERAPIA

(TREATMENT-FREE REMISSION)

SONO I TKI CAPACI DI ELIMINARE TUTTE LE CELLULE (STAMINALI) Ph+ ?

SONO I TKI CAPACI DI RIDURRE IL NUMERO DELLE CELLULE (STAMINALI) Ph+ IN MANIERA TALE CHE LA TERAPIA POSSA ESSERE INTERROTTA SENZA CONSEGUENZE ?

SI

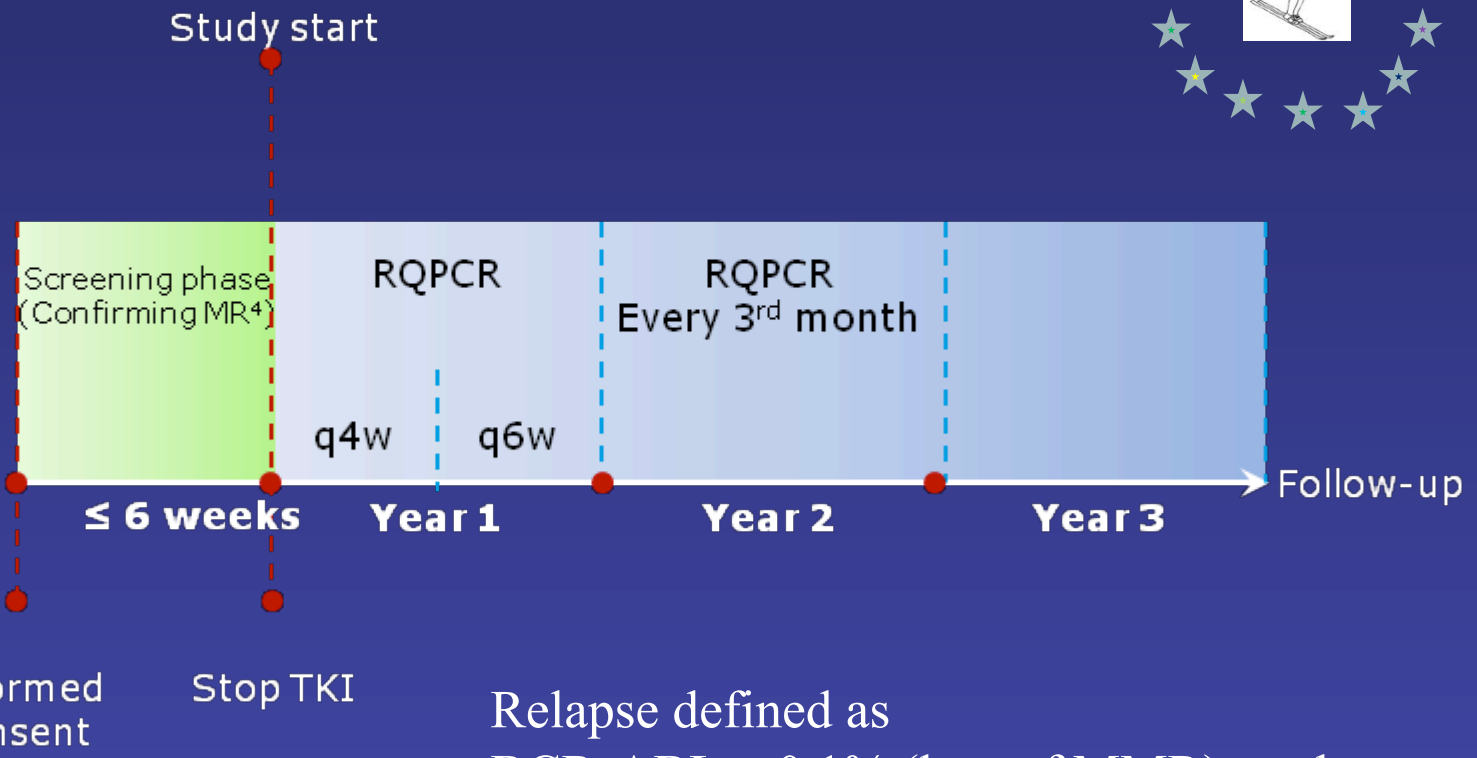
EURO-SKI Study Design

European LeukemiaNet

Inclusion criteria

TKI treatment at least 3 years

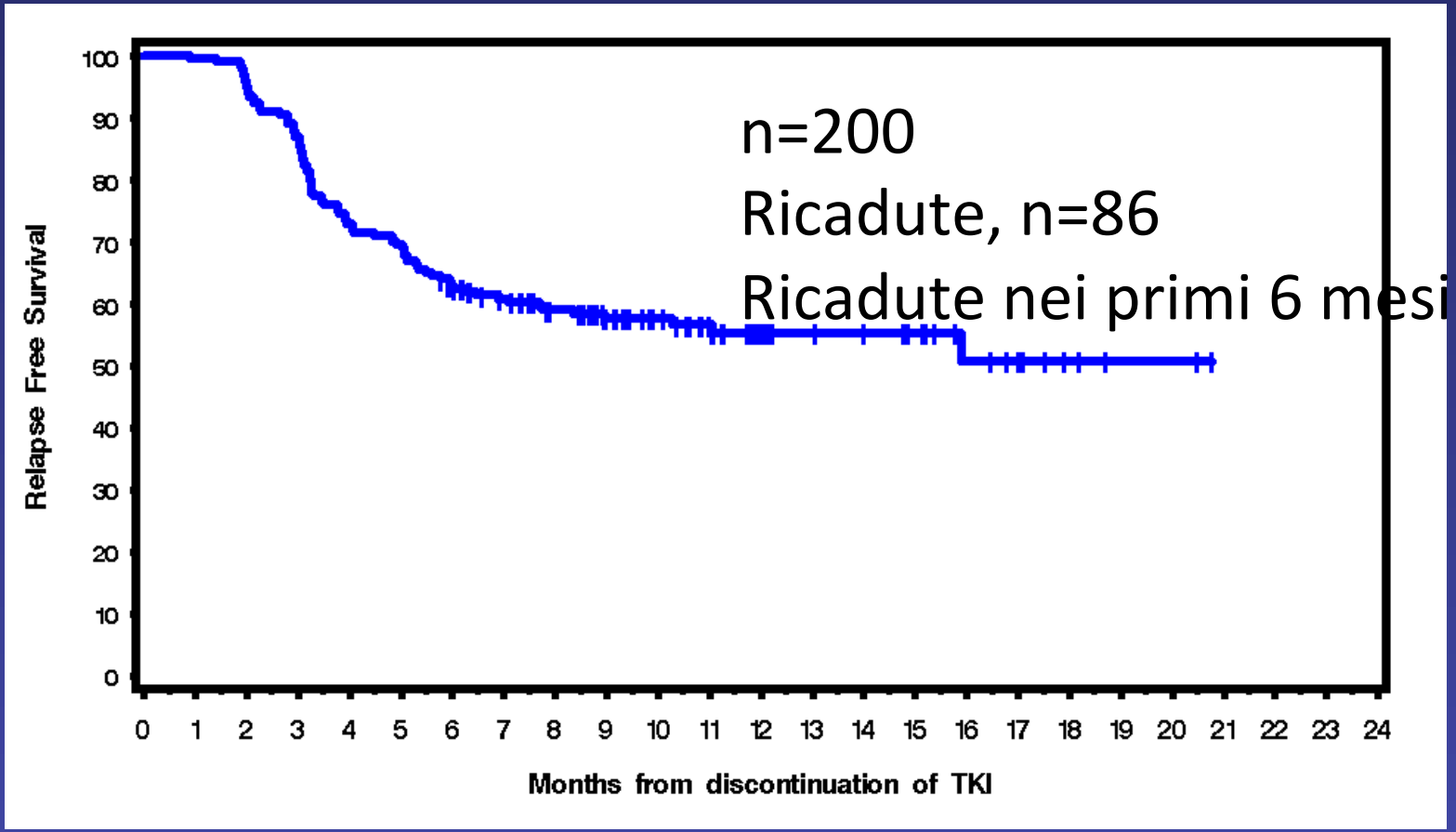
MR^4 at least 1 year



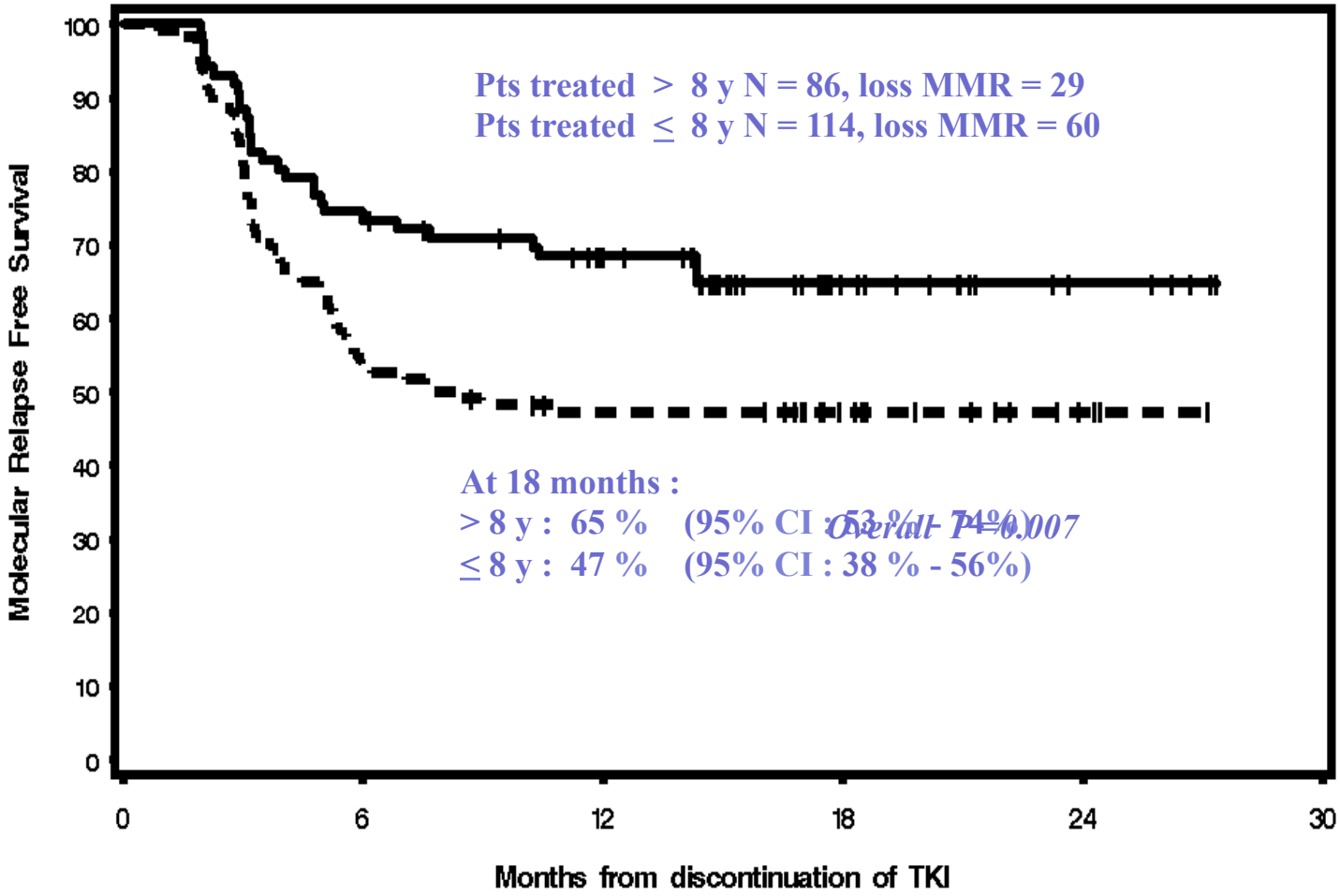
Relapse defined as BCR-ABL > 0.1% (loss of MMR) on the IS at one time point

Courtesy of ELN

EURO-SKI, perdita della risposta molecolare maggiore



EUROSKI: MAGGIORE LA DURATA DELLA TERAPIA CON IMATINIB, MINORE LA PROBABILITA' DI RICADUTA MOLECOLARE



SOSPENSIONE DELLA TERAPIA
REMISSIONE LIBERA DA TERAPIA
"GUARIGIONE"

E' POSSIBLE ? **SI**

QUANDO ? **Dopo "parecchi" anni di terapia**

IN QUALI PAZIENTI ? **Pazienti in risposta molecolare "profonda"**

HA SUCCESSO ? In circa il 50% dei casi

E' SICURA ? SI

QUANTI PAZIENTI SONO ELEGGIBILI PER UN TRIAL DI SOSPENSIONE DELLA TERAPIA ?

CON IMATINIB DA SOLO, E SWITCH A UN TKI DI SECONDA GENERAZIONE IN CASO DI FALLIMENTO	15-30%
CON TKI DI SECONDA GENERAZIONE	30-60%
CON IMATINIB E SWITCH A UN TKI DI SECONDA GENERAZIONE IN CASO DI RISPOSTA NON OTTIMALE	???

CIRCA IL 60% DEI PAZIENTI ELEGGIBILI RIMARRA' LIBERO DA TERAPIA (9%- 36% DEI PAZIENTI INIZIALI)

PROSPETTIVE NELLA TERAPIA DELLA LEUCEMIA MIELOIDE CRONICA

- TKI e INTERFERONα
- NUOVI TKI

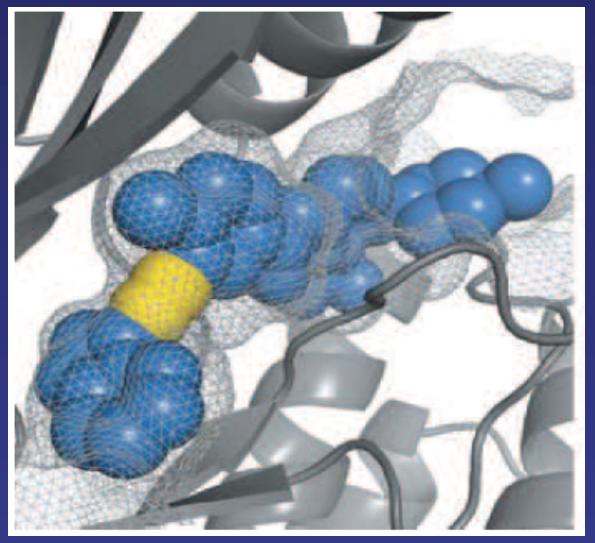
OLTRE I TKI

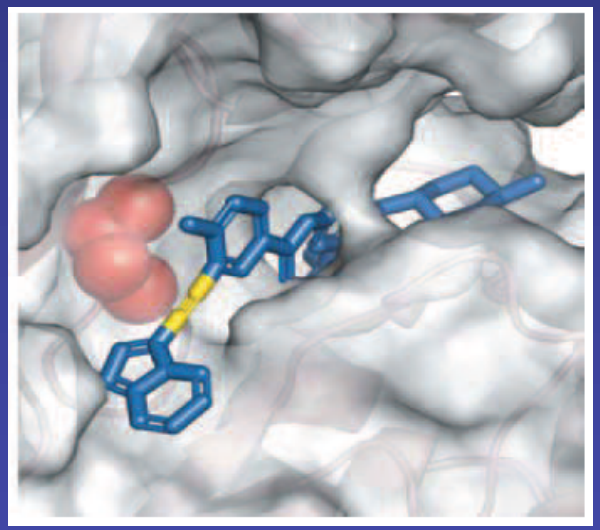
- FARMACI MIRATI SU ALTRI BERSAGLI
- FARMACI CHE AGISCONO SULLE CELLULE STAMINALI
- FARMACI CHE INIBISCONO L' AUTOFAGIA
- VACCINI
- ANTICORPI
- INIBITORI DEL CHECK-POINT
- LINFOCITI T MODIFICATI (CAR-T)

- PROGRESSI NEL TRAPIANTO DI MIDOLLO ALLOGENICO

Ponatinib

- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Potent activity against an array of BCR-ABL variants
- Once-daily oral activity
- Half-life ≈ 22 hours
- Also targets other therapeutically relevant kinases:
  - Inhibits FLT3, FGFR, VEGFR and PDGFR, and c-KIT



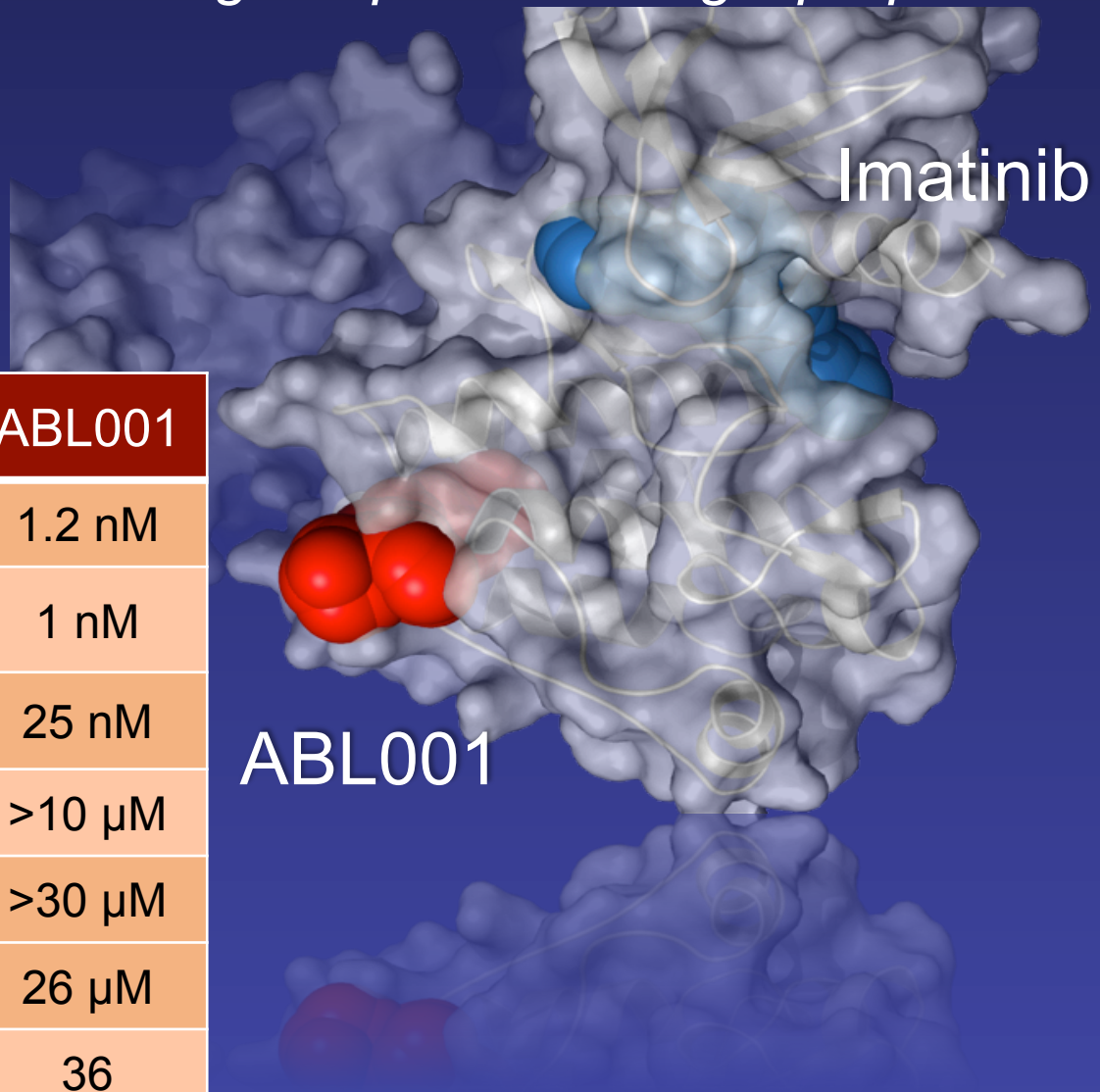


O'Hare T, et al. Cancer Cell. 2009;16:401-412

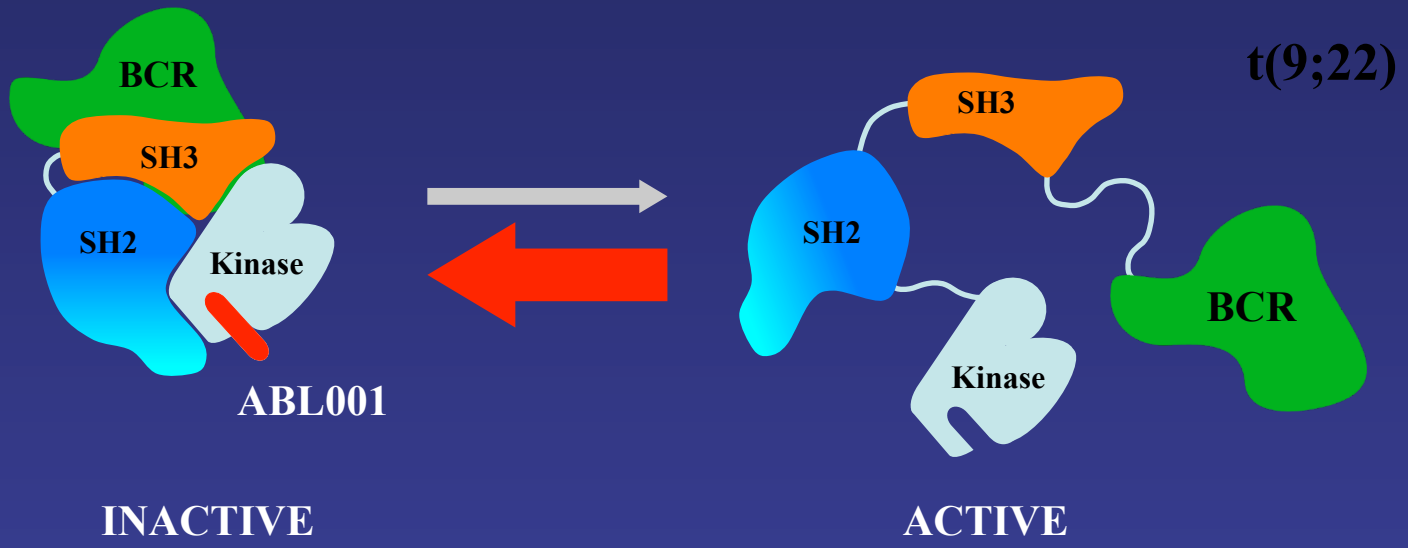
ABL001

Potent allosteric inhibitor with good pharmacologic properties

Assay	ABL001
Biochemical IC_{50}, ABL^{WT}	1.2 nM
Cellular IC_{50} $BCR\text{-}ABL^{WT}$	1 nM
Cellular IC_{50} $BCR\text{-}ABL^{T315I}$	25 nM
Cellular IC_{50} WT BaF/3	>10 μM
hERG	>30 μM
Qpatch Clamp	26 μM
PAMPA class, F %	36
CYP3A4,2D6,2C9	>20 μM



ABL001 Allosterically Inhibits BCR-ABL1 Kinase Activity



- ABL001 functionally mimics the role of myristoylated peptide by occupying its vacant binding site and restoring the negative regulation to the kinase activity

Hantschel et al, Nat Rev Mol Cell Biol 2004
Adrian et al, Nat Chem Biol 2006

Gli inibitori del check-point nella LMC: un sogno ?

- Alcuni inibitori (Nivolumab) sono già stati testati con successo nelle leucemie e nei linfomi

  La combinazione di un inibitore del check-point con un TKI è probabilmente sicura e non tossica
- La combinazione merita di essere testata in caso di fallimento dei TKI
- Gli inibitori del check-point potrebbero aumentare il numero di remissioni senza terapia

MONITORARE IL CORSO DELLA CML

MONITORARE LA RISPOSTA :
MOLECOLARE e CITOGENETICA

MONITORARE LA TOSSICITA'
E LE COMPLICAZIONI :
SISTEMA EMOPOIETICO, FEGATO, PANCREAS, SISTEMA CARDIOVASCOLARE, METABOLISMO SISTEMA RESPIRATORIO, INFEZIONI, etc.

MONITORARE LA COMPLIANCE E LA QUALITA' DI VITA

IL PAZIENTE DEVE AVERE UN RUOLO CENTRALE NEL PROCESSO DECISIONALE DELLA TERAPIA DELLA LMC

EORTC QLQ-CML 24

Efficace F, Baccarani M, Breccia M et al, Qual Life Res 2013

http://groups.eortc.be/qol/

MDASI CML

Williams LA, Gonzales AG, Ault P et al, Blood 2013;122:641-647

http://www3.mdanderson.org/depts/symptomresearch

Baccarani M. Efficace F and Rosti G. Moving towards patient-centered decision-making in chronic myeloid leukemia: assessment of quality of life and symptoms burden. Haematologica, 2013

MONITORARE LA TERAPIA DELLA LMC

QUANDO I RISULTATI DEI TEST MOLECOLARI O CITOGENETICI SONO AL LIMITE O CONTRADDITORI, E' SEMPRE RACCOMANDABILE RIPETERE I MEDESIMI TEST

- IL COSTO DEI TEST E' MOLTO INFERIORE AL COSTO DEI FARMACI

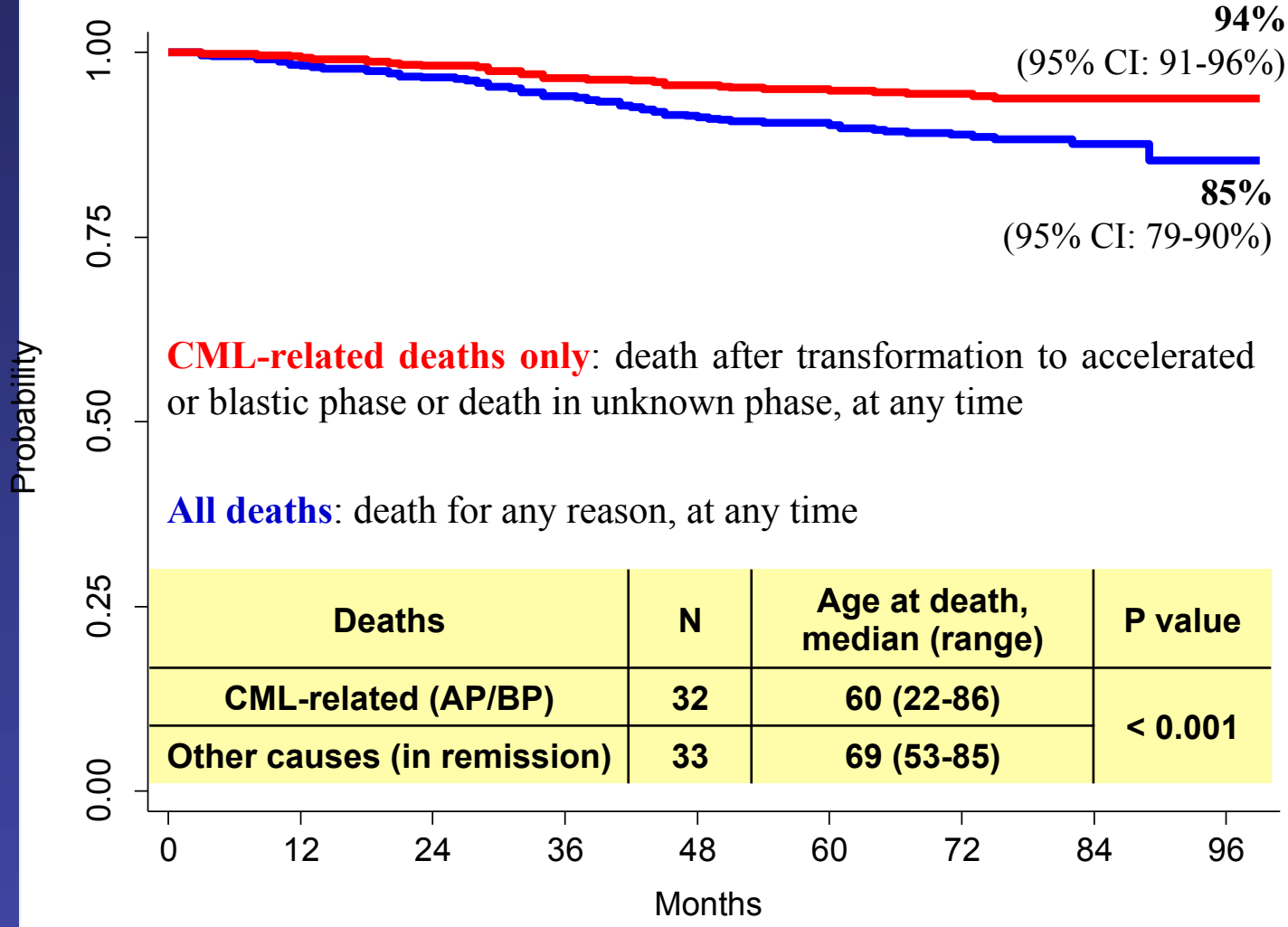
- MONITORARE AIUTA A SELEZIONARE IL FARMACO PIU' ADATTO E A OTTIMIZZARE LA TERAPIA
- UN "ECCESSO" DI MONITORAGGIO PUO' FAR MALE AL PORTAFOGLIO E PUO' ESSERE CAUSA DI CONFUSIONE E ANSIA,

MA

- UN MONITORAGGIO OTTIMALE FA' BENE SIA ALLA VITA CHE AL PORTAFOGLIO, PERCHE' SI TRADUCE IN UN TERAPIA OTTIMALE E IN UN IMPIEGO OTTIMALE DELLE RISORSE

POCHI GIORNI DI UNA TERAPIA INAPPROPRIATA COSTANO MOLTO DI PIU' DI UN TEST, E SONO DANNOSI PER IL PAZIENTE

Survival, overall, and CML-related
550 CP CML Patients, Front-line IMATINIB



CML-related deaths only: death after transformation to accelerated or blastic phase or death in unknown phase, at any time

All deaths: death for any reason, at any time

Deaths	N	Age at death, median (range)	P value
CML-related (AP/BP)	32	60 (22-86)	< 0.001
Other causes (in remission)	33	69 (53-85)	

GIMEMA CML WP

CHRONIC MYELOID LEUKEMIA : THE COST OF PROGRESS

1994 ITALIAN COOPERATIVE STUDY GROUP ON CML
New Engl J Med 1994;330:820-827
INTERFERON ALFA AS COMPARED WITH CONVENTIONAL CHEMOTHERAPY FOR THE TREATMENT OF CHRONIC MYELOID LEUKEMIA

"The cost of interferon treatment was 200 times that of conventional treatment"

2013 EXPERTS IN CML
Blood 2013;121:4439-4442
PRICE OF DRUGS FOR CML

"Reflection on the unsustainable cancer drug prices: perspectives of CML experts"

FIRST-LINE TREATMENT

SECOND GENERATION TKIs

CHRONIC PHASE

- ALL PATIENTS ???
- YOUNG, NO COMORBIDITIES
- HIGH RISK (Sokal, EURO, EUTOS, CCA/Ph+)

ACCELERATED and BLAST PHASE: ALL PATIENTS

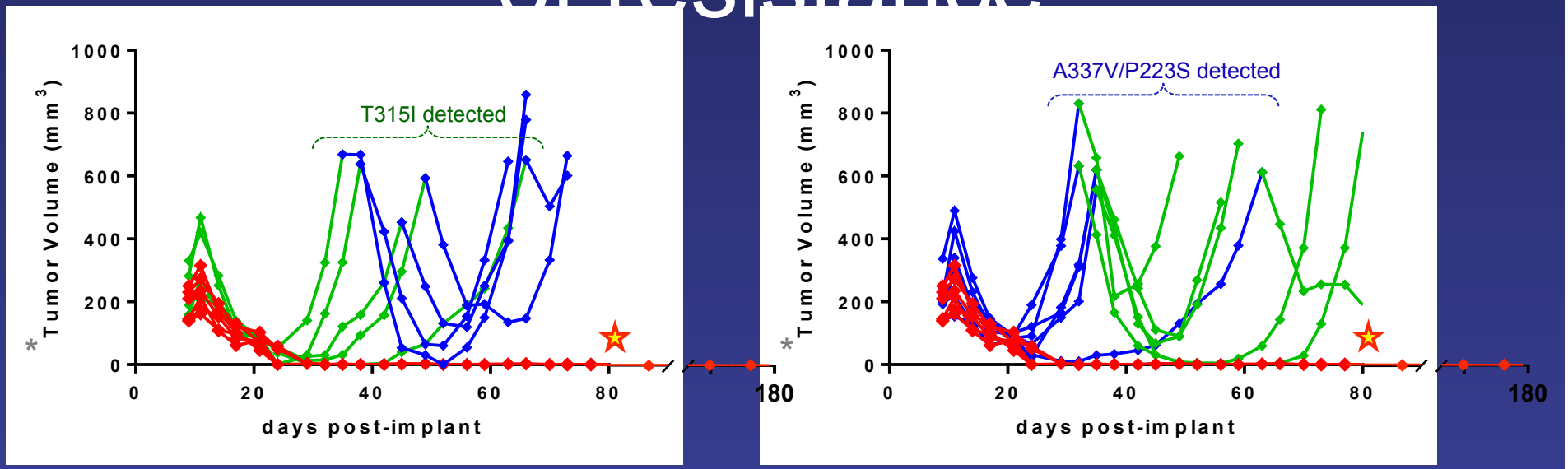
IMATINIB

CHRONIC PHASE

- ALL PATIENTS ???
- ELDERLY, COMORBIDITIES
- LOW RISK
- **SWITCH IN CASE OF FAILURE OR IN CASE OF NON-OPTIMAL RESPONSE?**

Combination of ABL001 and Nilotinib prevents the emergence of resistance

KCL-22 CML Xenograft



Nilotinib (75mg/kg) BID

ABL001 (30mg/kg) BID

Nilotinib (75mg/kg) BID + ABL001 (30mg/kg) BID

Dosing stopped on day 77, all mice remain disease free >176 days

* Each line represents individual animals

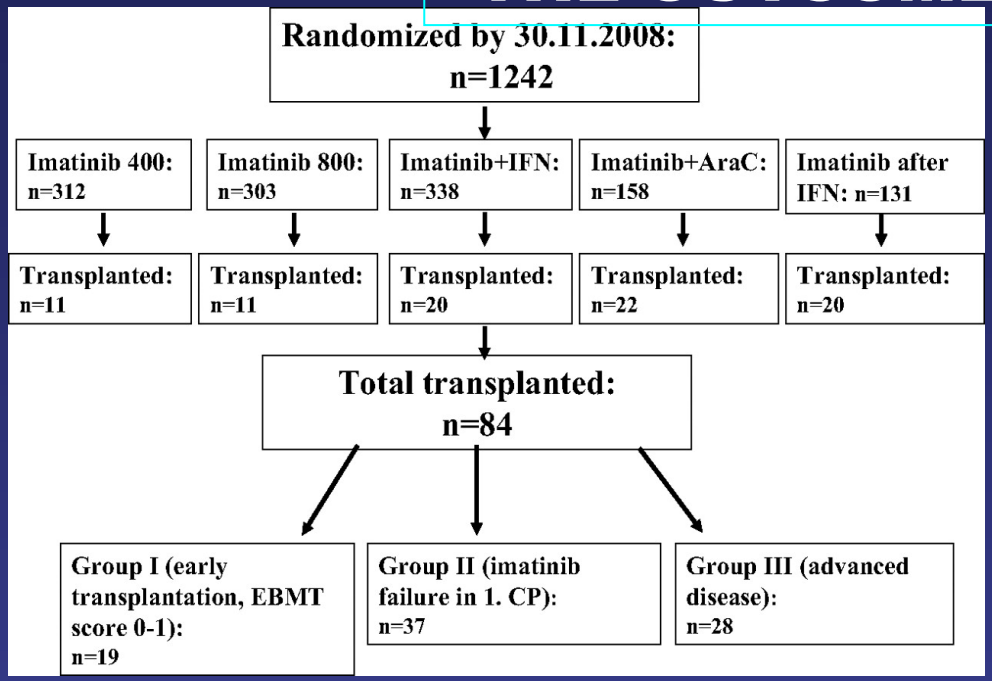
LARSON RA et al, ASH 2014, abstract 738

WE CALCULATED THE COST-EFFECTIVENESS OF IMATINIB vs PHYSICIAN's CHOICE OF IMATINIB vs DASATINIB OR NILOTINIB, FIRST-LINE FOR A PERIOD OF 5 YEARS: "WHEN GENERIC IMATINIB WILL BE AVAILABLE WORLDWIDE, ITS PRICE WILL DECLINE, AND IT WILL BE COST-EFFECTIVE COMPARED TO OTHER TKIs"

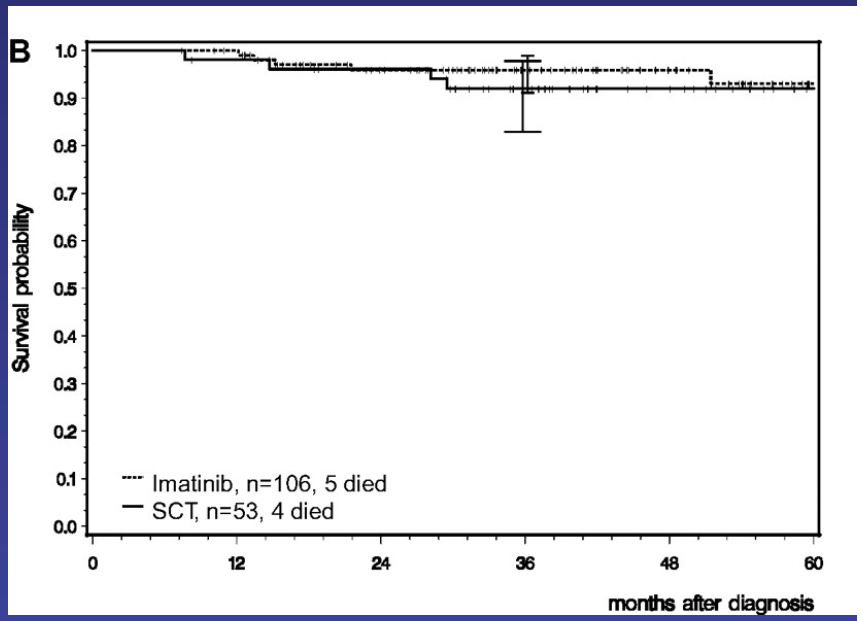
Padula WV, Larson RA, et al. J Natl Cancer Inst 2016;108(7):

•THE OUTCOME

Saussele Blood 2010



OUTCOME OF ALLO TRANSPLANTED PATIENTS



	allo	IMA
N	53	106
age	37	36.5
Euro risk score		
low	41.5%	41.5 %
int	35.8 %	35.8 %
high	22.6 %	22.6 %

MATCHED ANALYSIS WITH PTS IN IMATINIB

CCA/Ph+, major route, unbalanced (trisomy 8, i(17)q10, trisomy 19, +der(22)t(9;22)(q34;q11) (10,12,13)
Chromosome 3 abnormalities (14)
Trisomy 8 plus other CCA/Ph+ (9,11,15)
OCT1 low expression and function (41-48)
MDR1(ABCB1, Pgp, P170) polymorphisms and high expression (49-51)
CIP2A (cancerous inhibitor of PP2A) high level (52,53)
BIM deletion polymorphisms (54-57)
KIR2DS1 genotype (58,59)
Triptase high serum level (60)
PTCH1 low expression (61)
Gene expression profile (62,63)
In-vitro sensitivity and dose-response slope (64)
Immunophenotype (detection of lymphoid markers) (65)

TABLE 5 : A list of some of the factors that have been reported to affect the response to TKIs (mainly imatinib 400 mg OD), baseline. Only the first (CCA/Ph+) has been recognized internationally.

PATIENT RELATED FACTORS LIMITING THE CHOICE, THE DOSE AND THE USE OF TKIs

ATHEROSCLEROSIS
ARTERIAL THROMBOTIC DISEASE
CEREBROVASCULAR DISEASE
HYPERTENSION
HEART FAILURE
ISCHEMIC HEART DISEASE
THROMBOPHILIC STATE
DIABETES MELLITUS
DYSLIPIDEMIA
CHRONIC PULMONARY DISEASE (obstructive, enfisema, fibrosis, etc)
AUTOIMMUNE DISEASE
OTHER TUMOR
PSYCHIATRIC DISORDER
ALZHEIMER
PARKINSON
HANDICAP……
AGE, LIFE STYLE, EDUCATION, WILLING……..

PERSONALIZED TREATMENT ?

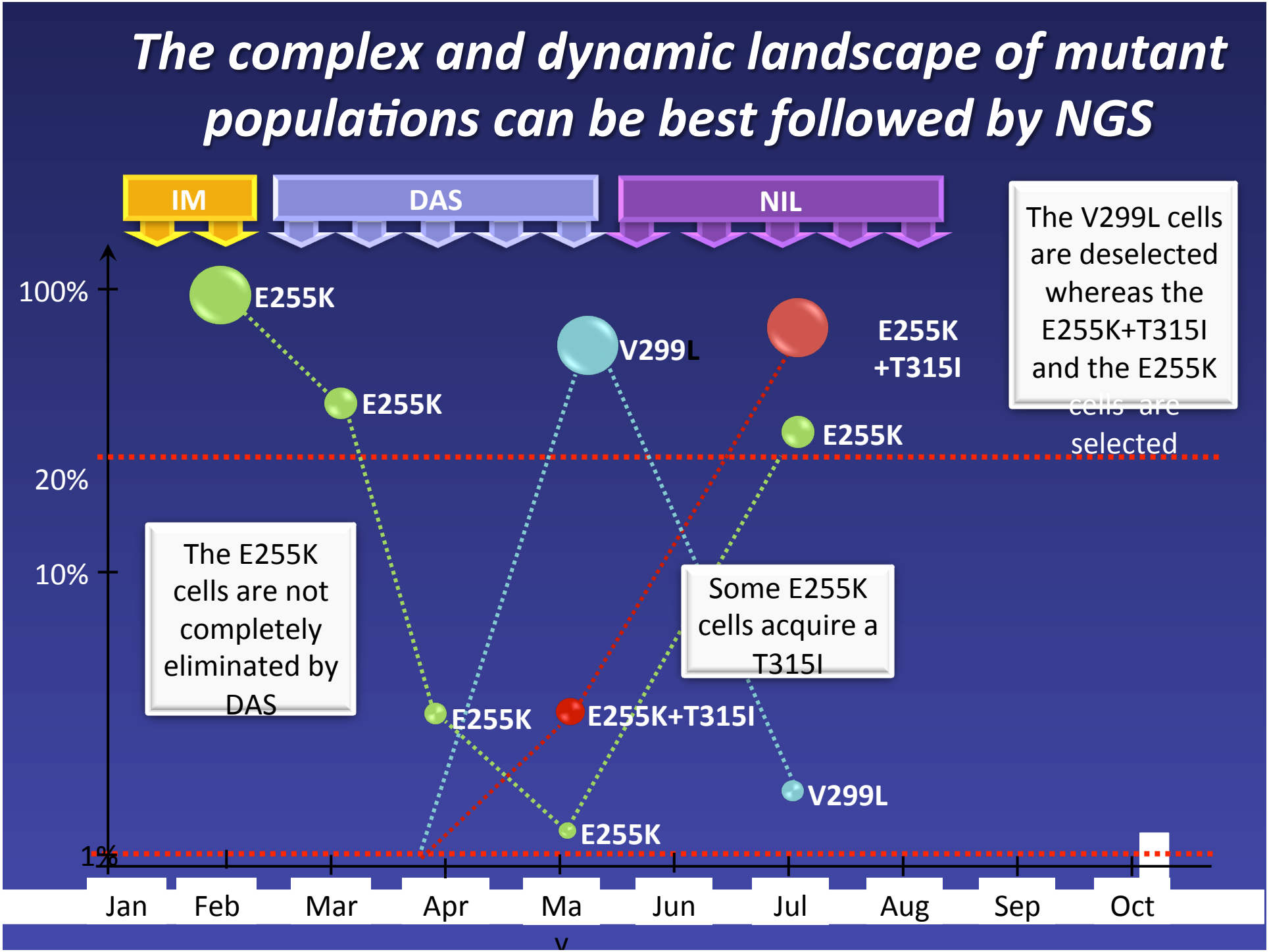
ACCELERATED or BLAST PHASE :
2nd GENERATION TKI

YOUNG, NO COMORBIDITIES, HIGH RISK :
2nd GENERATION TKI FIRST-LINE

ELDERLY, COMORBIDITIES, LOW RISK :
IMATINIB FIRST-LINE

A PERSONALIZED TREATMENT IS NONSENSE WITHOUT A CAREFUL AND PERSONALIZED MONITORING

The complex and dynamic landscape of mutant populations can be best followed by NGS



CML IN THE 21st CENTURY

WHITH FIVE TKIs AVAILABLE, OVERALL SURVIVAL IS 80-90% AND ABOUT 50% OF DEATHS OCCUR IN REMISSION. WE ARE REASONABLY HAPPY, MUCH HAPPIER THAN IN MANY OTHER LEUKEMIAS AND CANCERS.

CAN WE DO BETTER ?

THE MAJOR OBSTACLE TO FULL SATISFACTION IS THE ACCESS TO TYROSINE KINASE INHIBITORS, WORLDWIDE.