Michele BACCARANI, MD

Professor of Hematology at the Universities of Trieste, Udine, and Bologna (retired)

DISCLOSURES

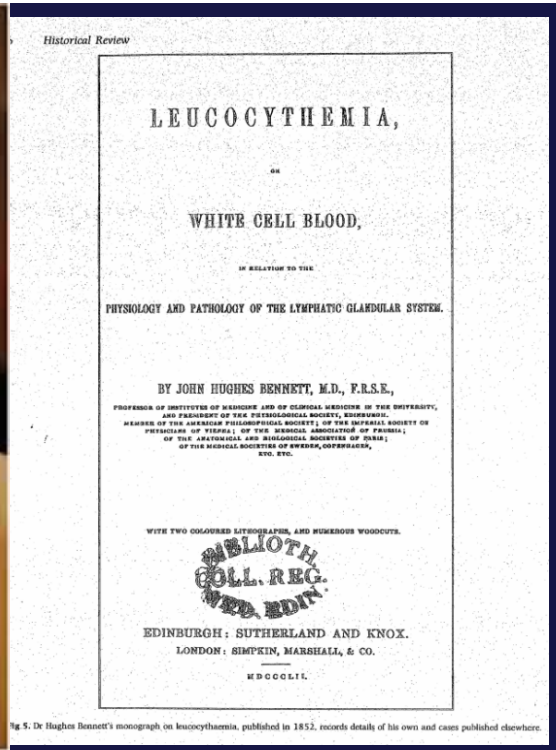
Consultant and speaker, receiving honoraria from

INCYTE

TAKEDA

NOVARTIS

FUSION PHARMA



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.

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

MDCCCLII.

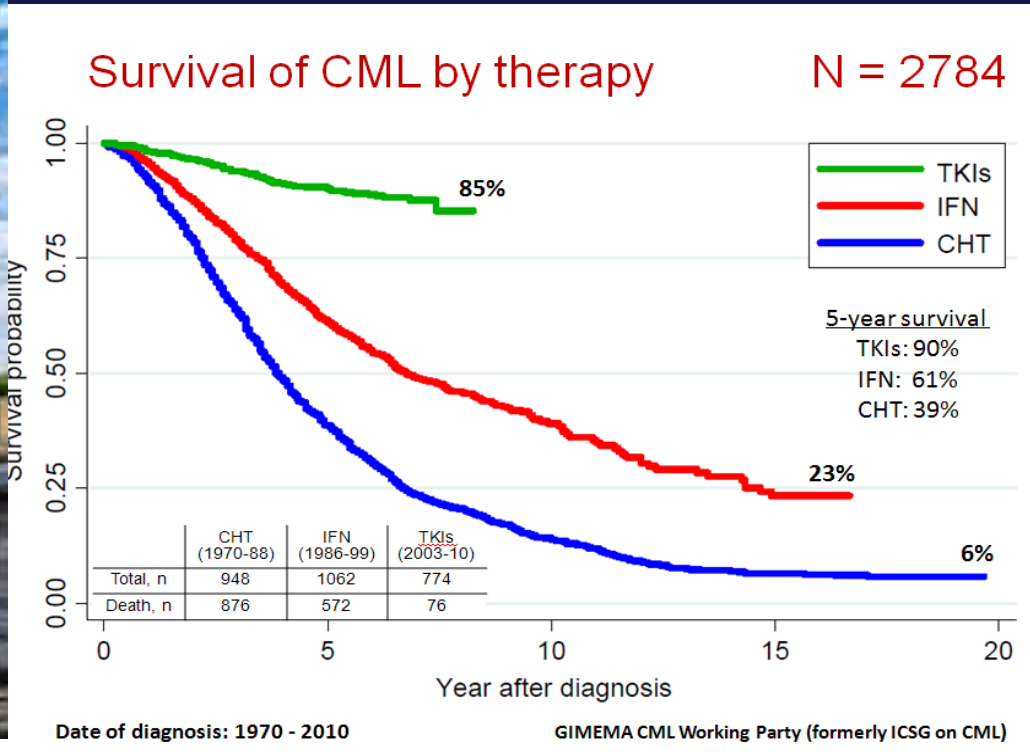
Fig 5. Dr Hughes Bennett's monograph on leucocythaemia, published in 1852, records details of his own and cases published elsewhere.

LEUKEMIA 2021

Roma

JOHN GOLDMAN LECTURE

Michele.Baccarani@unibo.it



THERAPY OF CHRONIC MYELOID LEUKEMIA

1865 ARSENIC TRIOXIDE, X-RADIATION

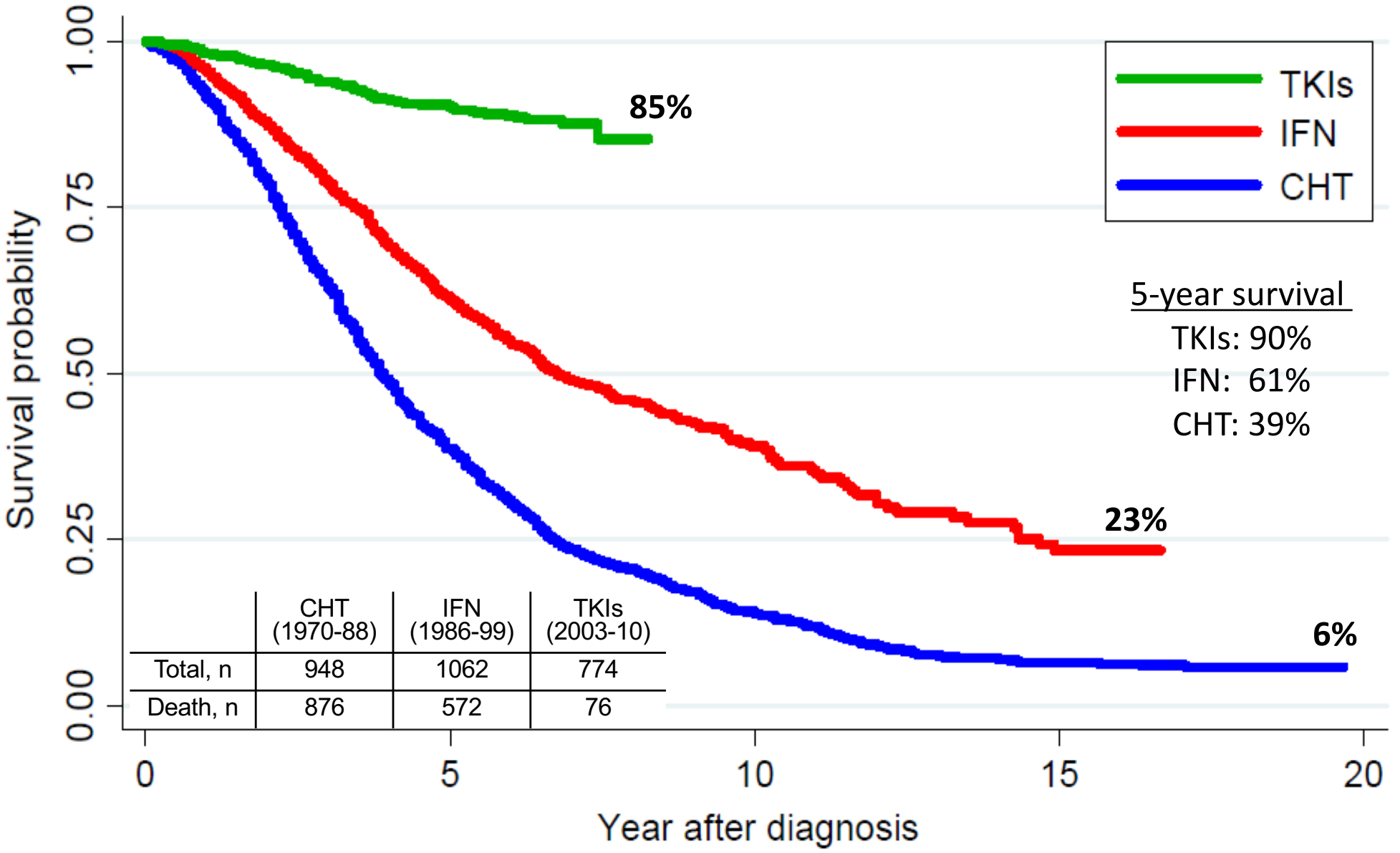
1956 BUSULFAN, HYDROXYUREA

1979 ALLOGENEIC STEM CELL TRANSPLANTATION

1984 INTERFERON-α

2000 TYROSINE KINASE INHIBITORS

Survival of CML by therapy N = 2784



Date of diagnosis: 1970 - 2010

GIMEMA CML Working Party (formerly ICSG on CML)

CML THERAPY, STATE OF THE ART, 2021

TYROSINE KINASE INHIBITORS (TKIs)

- IMATINIB, NILOTINIB, DASATINIB, BOSUTINIB
- PONATINIB second- third line,
- ASCIMINIB second line

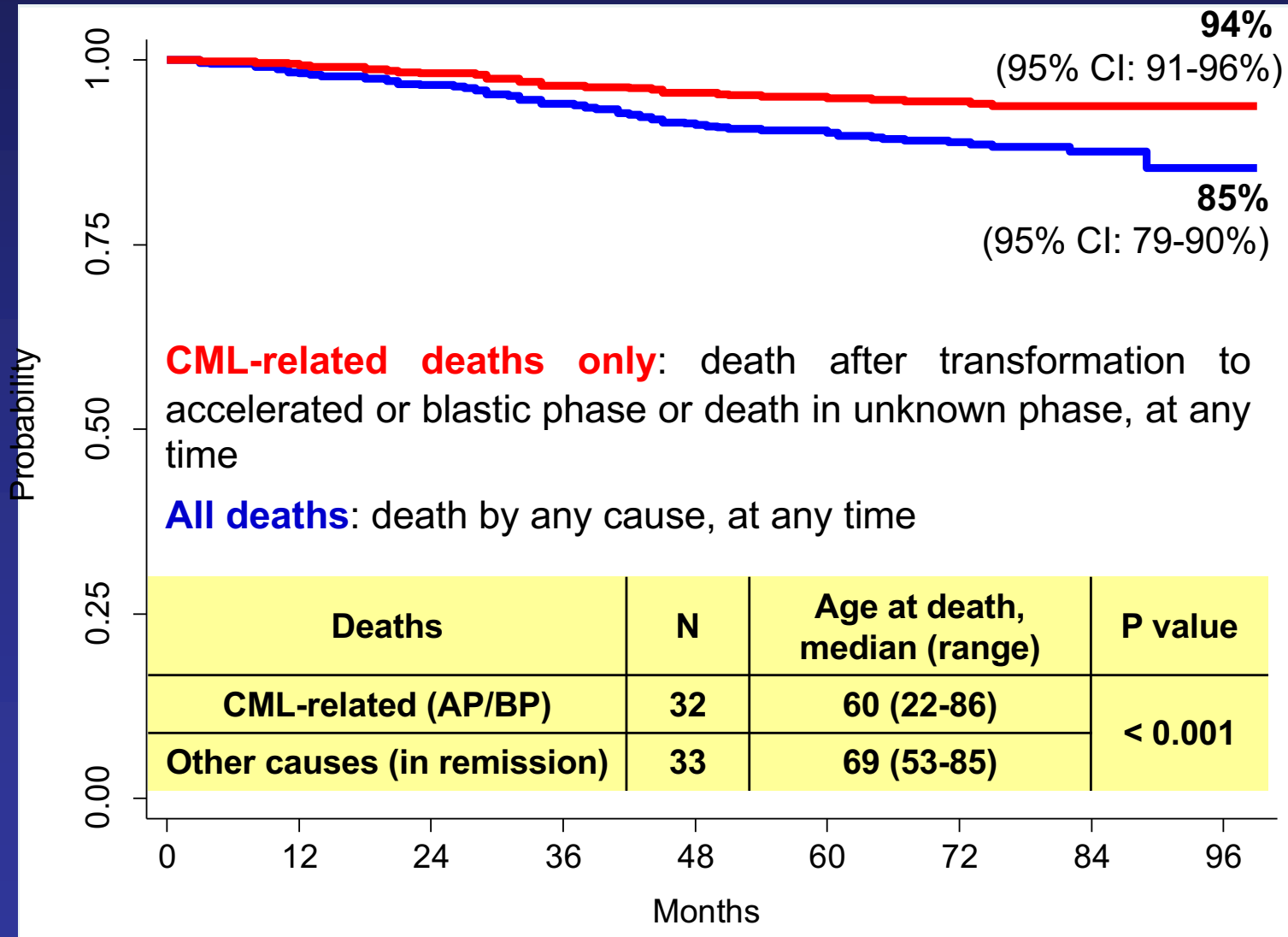
INTERFERONα, pregnancy, investigational

OTHER DRUGS many preclinical, few promising, none approved

ALLOGENEIC STEM CELL TRANSPLANTATION, myeloablative,non-myeloablative, reduced intensity conditioning; from many donors (HLA-ID sibs, HLA-matched and mismatched unrelated donors, haploidentical family donors, cord blood)

EUROPEAN LEUKEMIANET RECOMMENDATIONS,
BLOOD 2006, JOURNAL OF CLINICAL ONCOLOGY 2009, BLOOD 2013,
LEUKEMIA 2020

IT WILL NOT BE EASY TO IMPROVE SURVIVAL FURTER 0N



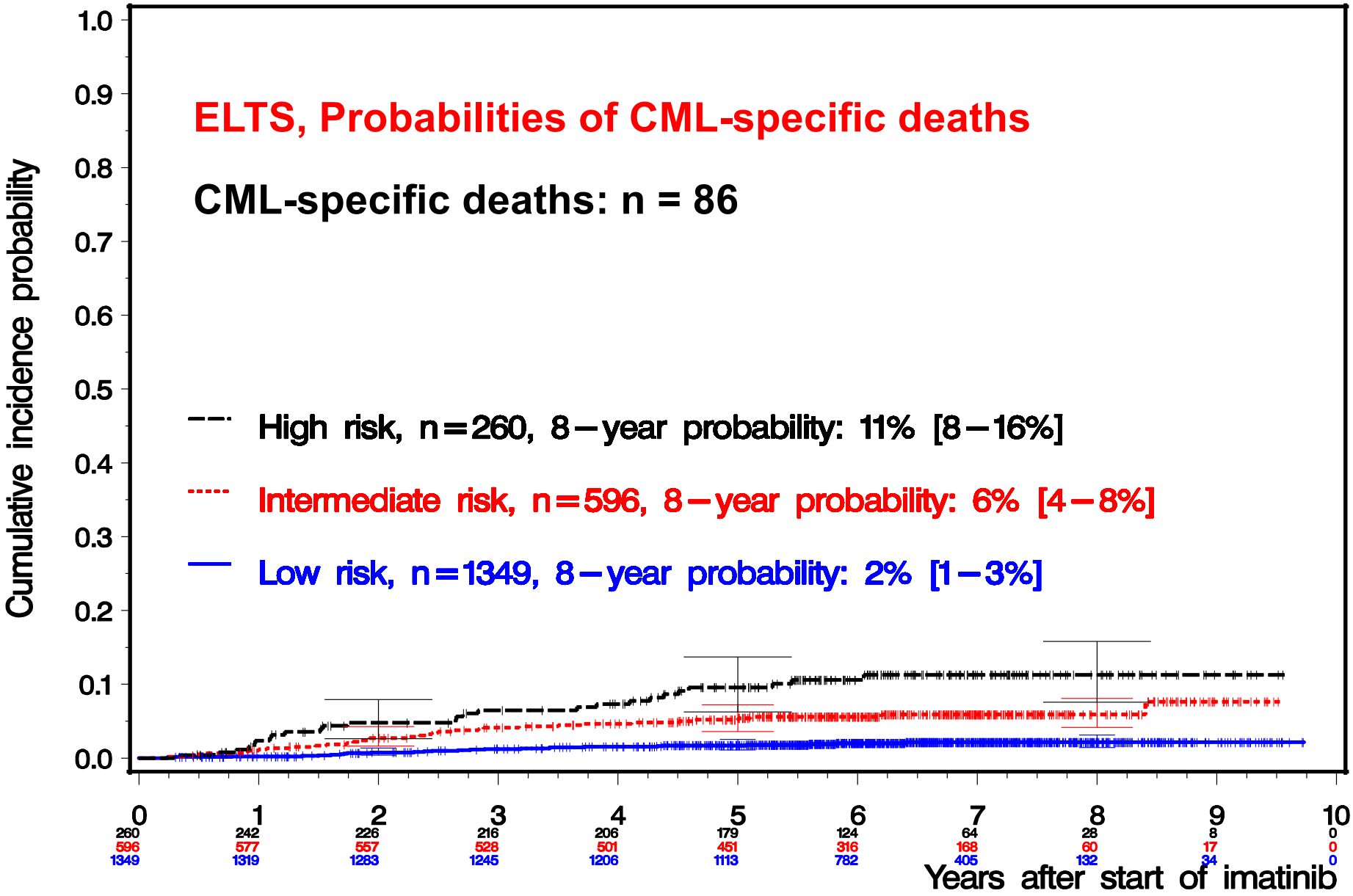
CML-related deaths only: death after transformation to accelerated or blastic phase or death in unknown phase, at any time

All deaths: death by any cause, 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

IT WILL NOT BE EASY TO IMPROVE PROGRESSION-FREE SURVIVAL FURTHER ON



90% OF CML PATIENTS BENEFIT OF TKI THERAPY

FEW PATIENTS ARE OR BECOME RESISTANT TO TKIs AND DIE OF LEUKEMIA:

RESISTANCE

MANY PATIENTS ARE SENSITIVE TO TKIs BUT REQUIRE CHRONIC THERAPY (LIFELONG?)

FEW PATIENTS ACHIEVE TREATMENT-FREE REMISSION BUT REMAIN BCR/ABL1+ (FOR EVER?)

PERSISTENCE

ARE THE CAUSES OF RESISTANCE AND PERSISTENCE THE SAME ?

CLINICAL RESISTANCE MAY DEPEND ON SEVERAL FACTORS

BIOLOGIC RESISTANCE IS BCR-ABL1 INDEPENDENT

IT HAS BEEN ALWAYS KNOWN THAT RESISTANCE IS ASSOCIATED WITH OTHER CHROMOSOME ABNORMALITIES (Sokal JE, Blood 1988)

TODAY WE BEGIN TO KNOW THAT RESISTANCE IS ASSOCIATED WITH OTHER GENOMIC EVENTS (Branford S et al, Blood 2018 and Leukemia 2019)

RESISTANCE CANNOT BE OVERCOME BY TKIs

PERSISTENCE IS A CURIOUS PHENOMENON

Ph+ CELLS ARE SENSITIVE TO TKI

BUT THE DEPTH OF RESPONSE IS DIFFERENT, VARYING FROM MAJOR TO «UNDETECTABLE»

AND Ph+ CELLS ARE NOT COMPLETELY ELIMINATED

WHY THE RESPONSE TO THE SAME TKI IS SO VARIABLE?

THE CELLULAR CONCENTRATION REACHED BY TKI IS A VARIABLE THAT AFFECTS RESPONSE

PLASMA LEVEL OF TKI AND THE MECHANISMS REGULATING CELL INFLUX AND EFFLUX OF TKI INFLUENCE RESPONSE,

THEY DO NOT INFLENCE SURVIVAL, BUT MAY INFLUENCE DEPTH OF RESPONSE

TKI TYPE AND CELL CONCENTRATION ARE RELEVANT FOR TREATMENT-FREE REMISSION

WHY THE RESPONSE TO TKI TREATMENT IS SO VARIABLE?

TKI POTENCY AND CELL CONCENTRATION ARE IMPORTANT,

BUT ALSO BCR-ABL1 GENE EXPRESSION (= THE AMOUNT OF THE LEUKEMOGENIC PROTEIN TYROSINE KINASE THAT IS THE TARGET OF TKI) IS IMPORTANT

A HIGH RATIO BETWEEN THE AMOUNT OF THE PROTEIN AND THE TKI FAVORS A DEEPER RESPONSE

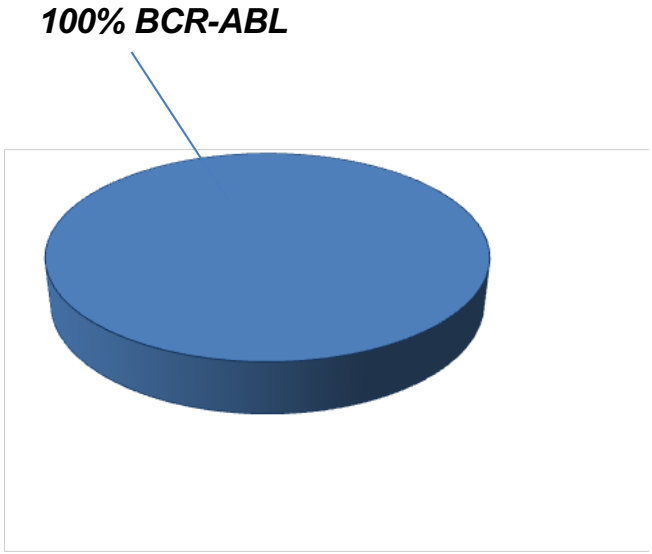
WHY THE RESPONSE TO TKI TREATMENT IS SO VARIABLE?

IS BCR-ABL1 GENE EXPRESSION CONSTANT ?
IS BCR-ABL1 GENE EXPRESSION SAME FOR ALL BCR-ABL1 GENES ?
IS THE SENSITIVITY TO TKI SAME FOR ALL LEKEMOGENIC PROTEINS?

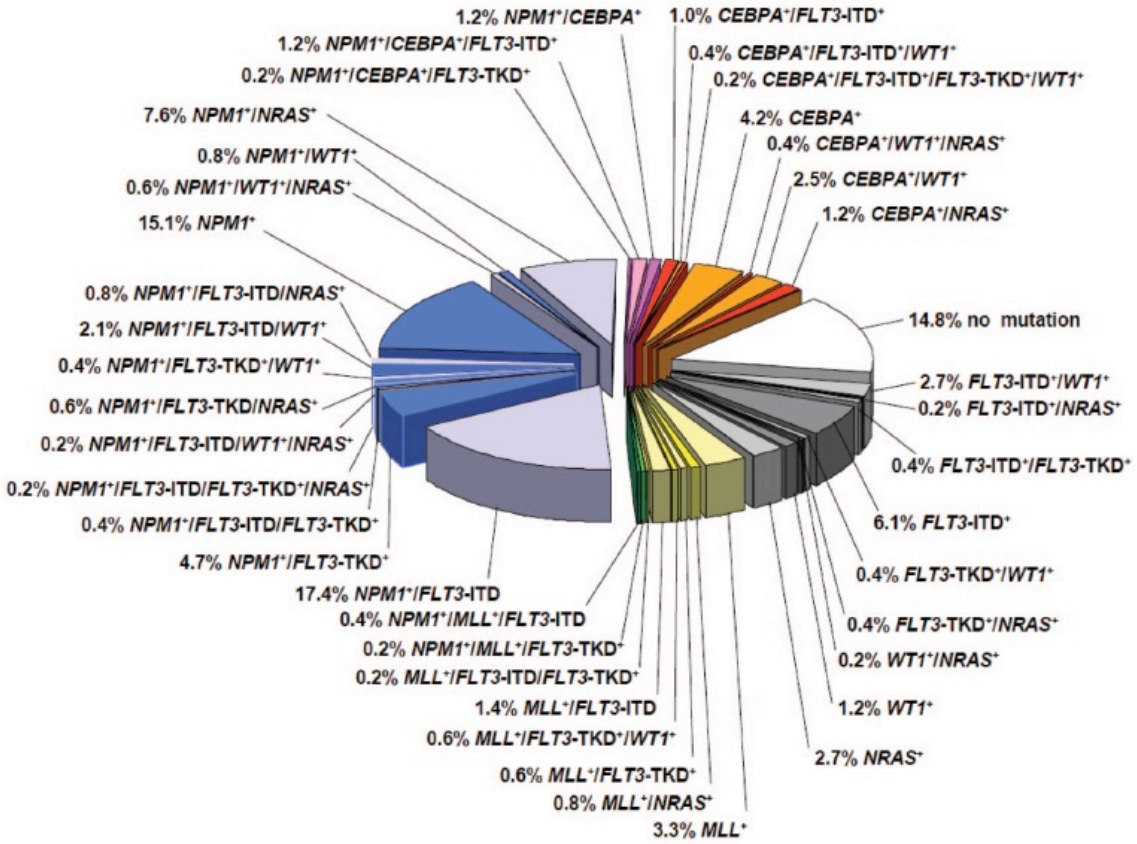
BCR-ABL1 GENE IS NOT UNIQUE AND MAY TRANSLATE IN DIFFERENT PROTEINS (P210 e13a2, P210 e14a2, P190, P230). WE DO NOT KNOW IF CELL PROTEIN AMOUNTS ARE DIFFERENT.

TKI BINDING EFFICIENCY OF TKI TO DIFFERENT PROTEINS MAY VARY, NOT ENOUGH TO AFFECT SURVIVAL, BUT ENOUGH TO AFFECT THE DEPTH OF THE RESPONSE AND TREATMENTE-FREE REMISSION

CHRONIC MYELOID LEUKEMIA

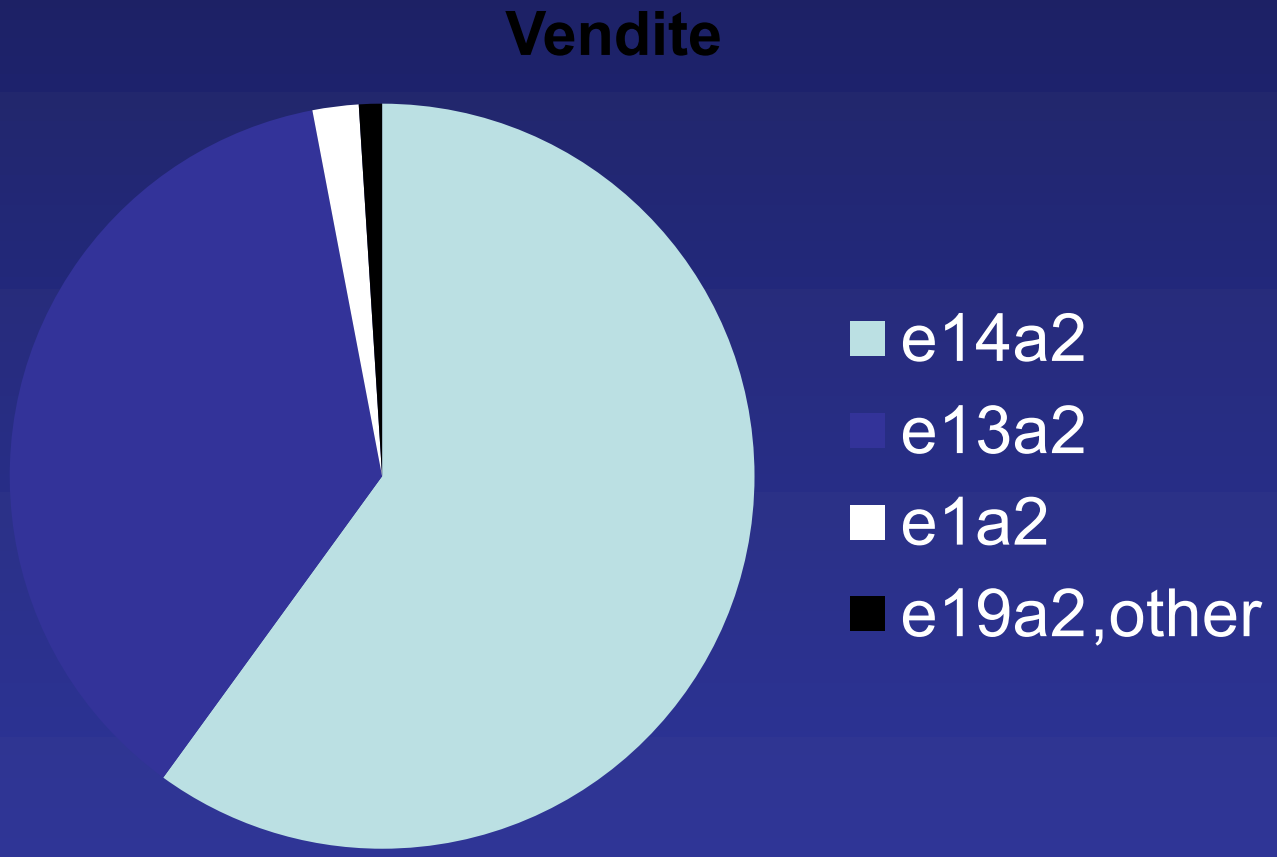


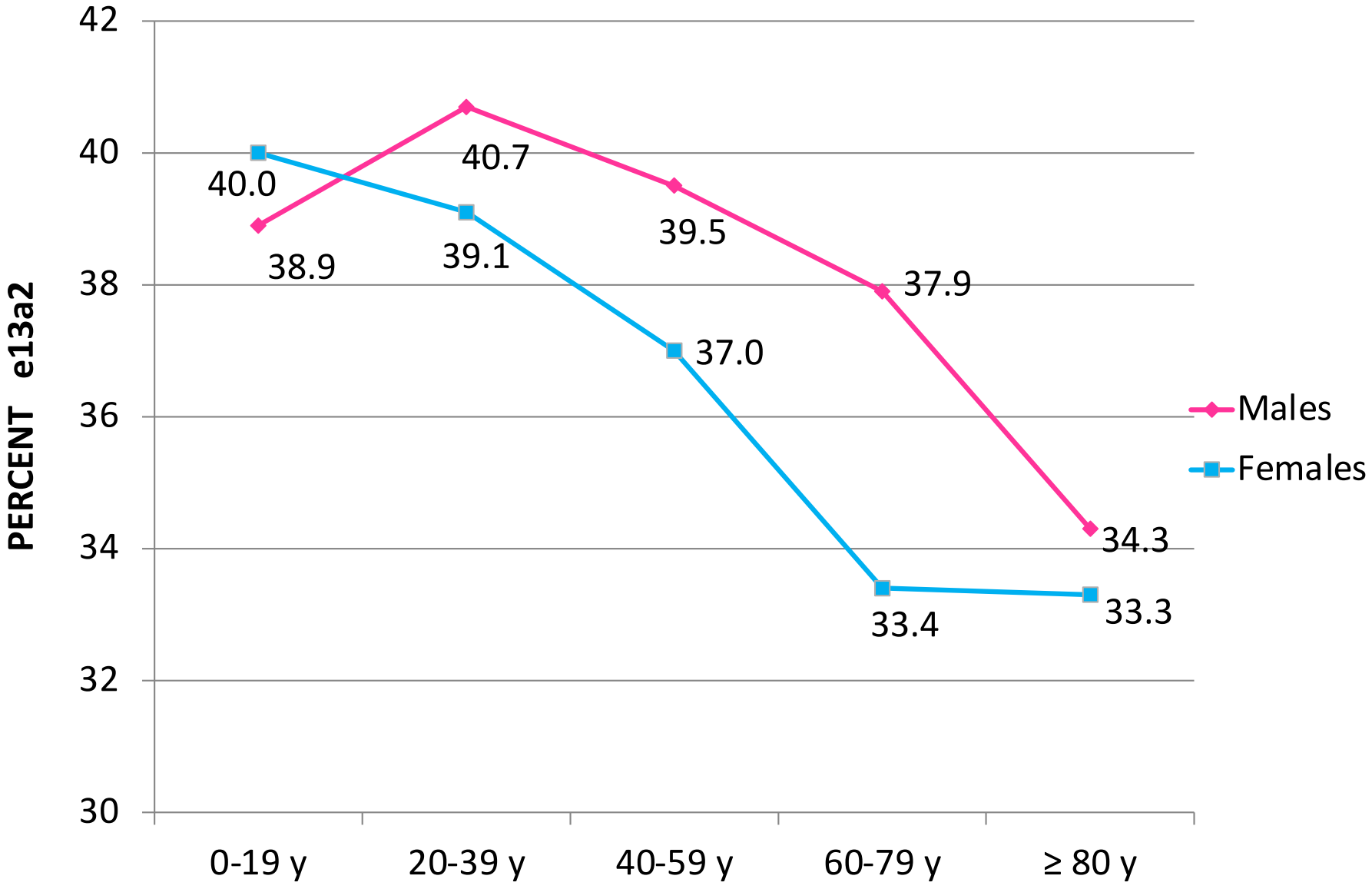
ACUTE MYELOID LEUKEMIA



Roboz GJ. ASH Education Program Book 2011

60% OF PATIENTS ARE e14a2 (B3A2), 37% e13a2 (B2A2), 2% e1a2 (P190) and 1% e19a2 (P230) or other

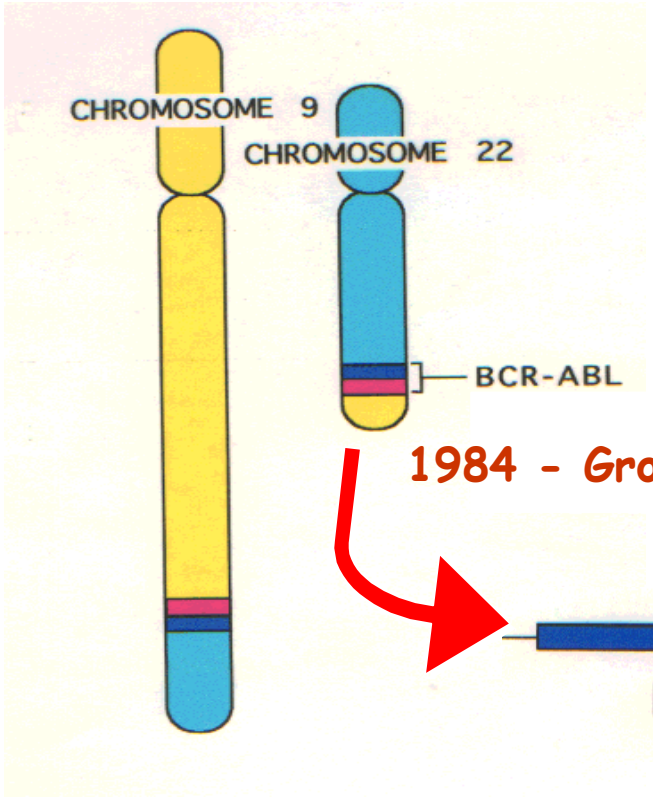




Frequency of e13a2 (B2A2) by age and by gender. Data from 45,000 patients, worldwide (Baccarani M et al, Leukemia 2019;33:1173-83)

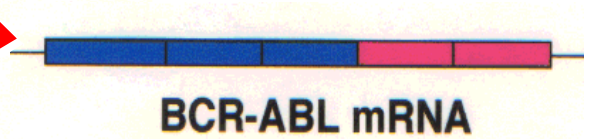
MILESTONES IN MOLECULA BIOLOGY OF CML

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



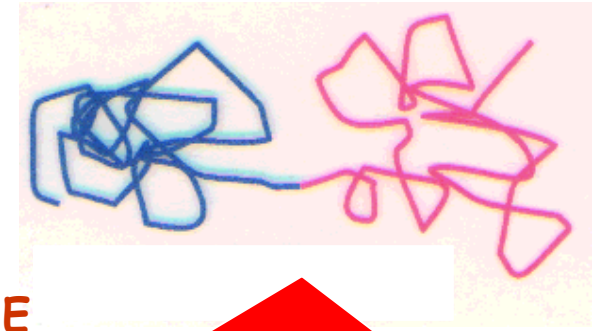
1984 - Groffen J. et al.

1985- Shtivelman E

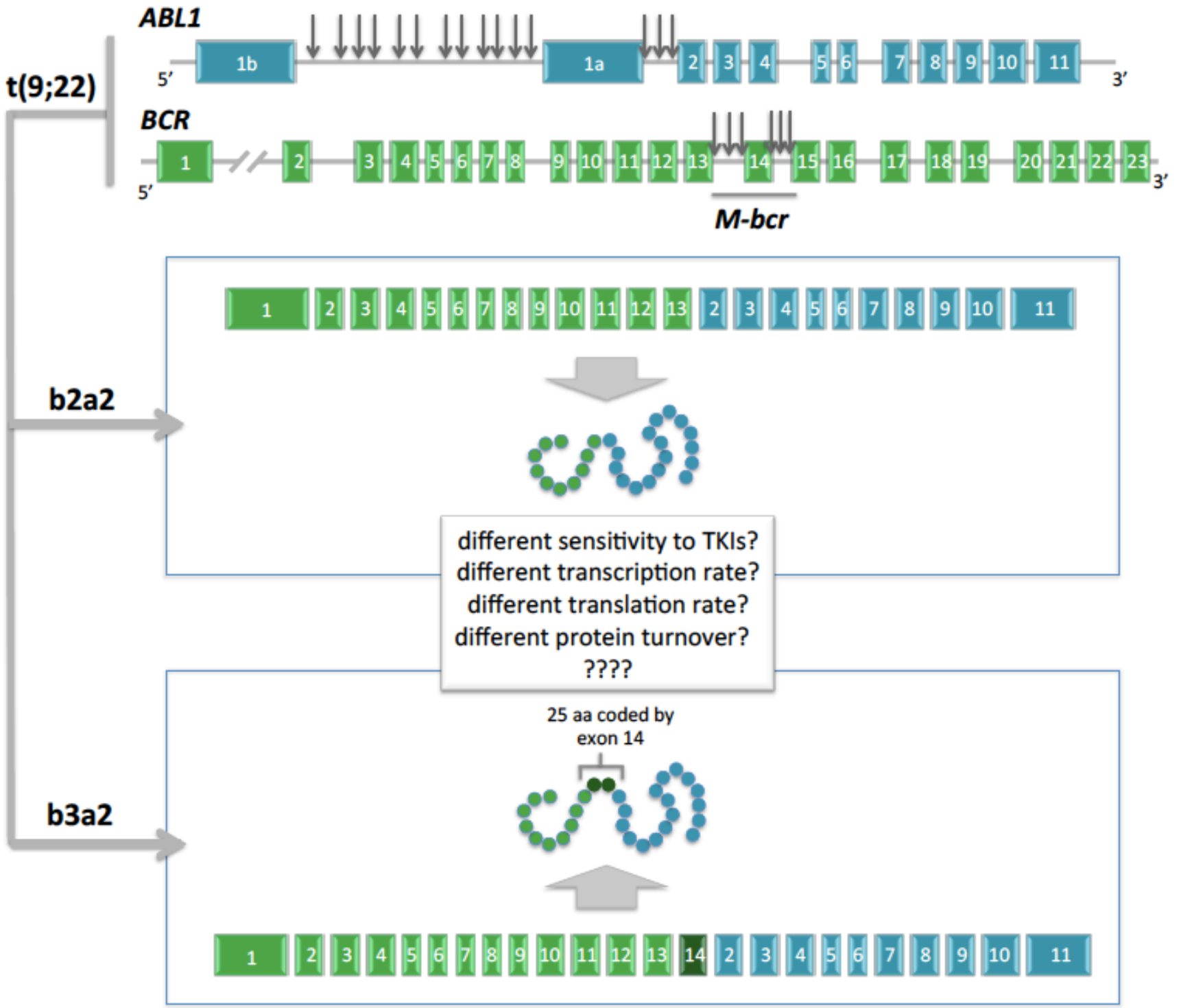


1984 - Konopka J.B. et al.

Protein BCR-ABL



The new fusion protein is a cytoplasmic tyrosine kinase that is constitutively activated


ABL1
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1a
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different sensitivity to TKIs?
different transcription rate?
different translation rate?
different protein turnover?
????
b3a2
25 aa coded by
exon 14
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BCR-ABL1 TRANSCRIPT TYPE (e14a2 vs e13a2), DEPTH OF MOLECULAR RESPONSE AND TFR RATE

ALL STUDIES ANALYSING TRANSCRIPT TYPE DATA REPORT THAT THE RATE OF DEEP MOLECULAR RESPONSE AND OF TFR IS HIGHER AND THAT TFR IS MORE STABLE IN e14a2 (B3A2) PATIENTS THAN IN e13a2 (B2A2) ONES

Lucas Haematologica 2009, Hanfstein Haematologica 2014, Bonifacio Blood 2015, Castagnetti Blood 2016, Jain Blood 2016, Lee Haematologica 2016, Lin Europ J Haematol 2016, Claudiani Haematologica 2017 Castagnetti Am J Hematol 2017, Sasaki Cancer 2018, Borgia Barbosa Pagnano, Clin Lymphoma Myeloma Leukemia 2017, Clark Lancet Haematol 2017, Pfirrmann J Cancer Res Clin Oncol 2017, Da Silva Blood 2018, Erkaliskan Cancer 2018, Shanmuganathan Blood 2018, Pagani Haematologica 2018, Bernardi Cancer Med 2019, Fava Haematologica 2019, D'Adda, Cancer 2019, Genthon Oncotarget 2020

CML: BCR-ABL
P210 e14a2(B3A2), P210 e13a2(B2A2),
P190 (e1a2, e1a3) , P230 (e19a2), etc,etc

FACTS

Different breakpoints

Different fusion genes

Different transcripts

Different proteins

Different responses to TKI

HYPOTHESES

Different gene expression (different efficieny of transcription and translation)

Different protein amount ?

Different protein sensitivity to TKIs ?

Different leukemogenic properties of proteins ?

Different immunogenicity of proteins ?

WHY Ph+ CELLS PERSISTS OFF-TREATMENT ?

TKI THERAPY SELECTS Ph+ CELLS WITH DECREASING GENE EXPRESSION

WHEN THE AMOUNT OF LEUKEMOGENIC PROTEIN IS VERY LOW (SOMETIMES UNDETECTABLE WITH CURRENT TECHNOLOGY) Ph+ CELLS LOOSE PROLIFERATION OR SURVIVAL ADVANTAGE. THEY ARE NO LONGER SENSITIVE TO TKIs BECAUSE THEY BEHAVE AS NORMAL HEMATOPOIETIC CELLS. MAY BECOME QUIESCENT.

THE RELATIONSHIP OF TKI WITH Ph+ CELLS IS BIDIRECTIONAL:

TKI LIMIT AND CONTROL Ph+ CELLS, PROTECT THE PATIENTS.

GENE EXPRESSION PROTECTS Ph+ CLONE FROM EXTINCTION

TKIs CANNOT CURE CML

THE AVAILABILITY OF SEVERAL TKI AND A PROPER USE OF TKI MAY IMPROVE SURVIVAL AND TFR RATE

SEVERAL STUDIES ARE INVESTIGATING OTHER GENOMIC ABNORMALITIES, OUTSIDE BCR-ABL1

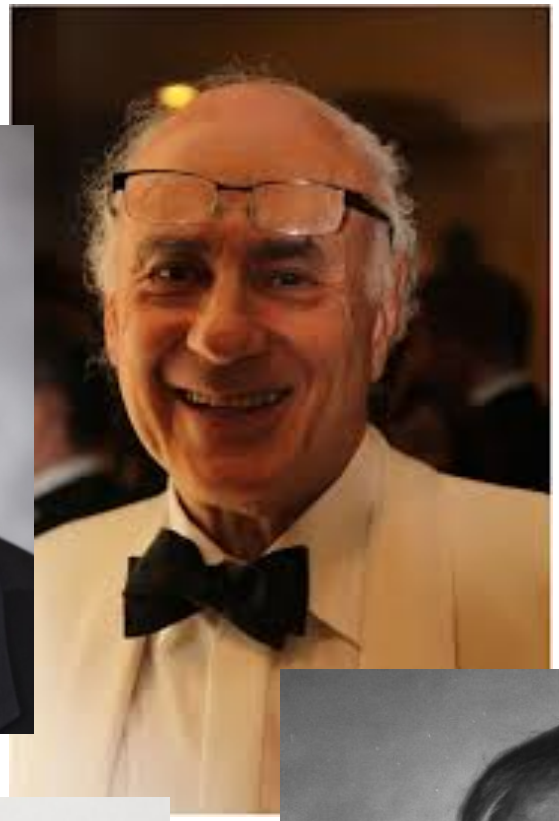
IF THEY ARE TARGETABLE WITH A POSITIVE RISK/BENEFIT RATIO, THESE STUDIES MAY HELP PATIENTS WHO ARE BIOLOGICALLY RESISTANT TO TKI

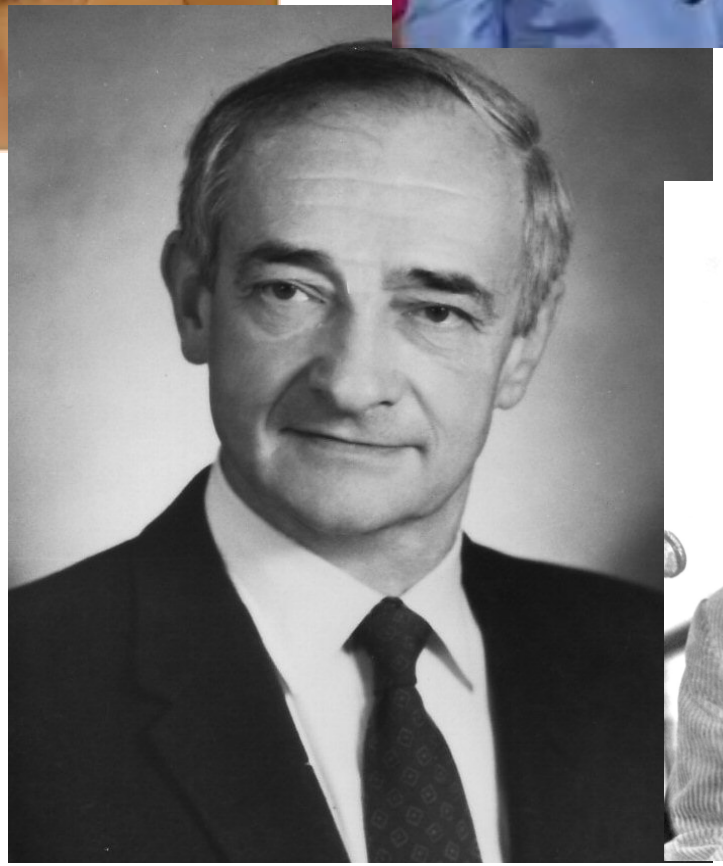
BUT CANNOT ELIMINATE PERSISTENCE OF Ph+ CELLS, BECAUSE Ph+ CELLS WITH A VERY LOW EXPRESSION OF BCR-ABL1 BEHAVE AS NORMAL HEMATOPOIETIC CELLS.

LEUKEMIC CELLS, AS NORMAL CELLS, MAY BE ELIMINATED WITH ALLOGENEIC STEM CELL TRANSPLANTATION.

WILL CAR-T CELLS AND CRISP EDITING OPEN NEW WAYS TO BIOLOGIC CURE OF CML?

STRETTA LA FOGLIA LARGA LA VIA DITE LA VOSTRA CHE HO DETTO LA MIA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