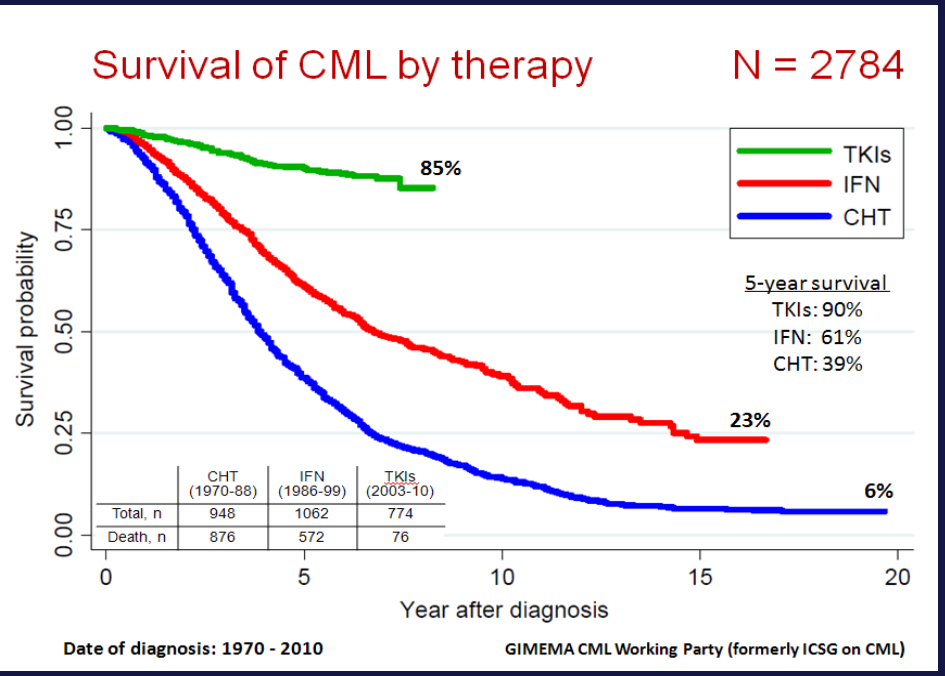


AGGIORNAMENTI IN EMATOLOGIA

Faenza, 7 Giugno 2018

LMC: ALGORITMI TERAPEUTICI ATTUALI E IL PROBLEMA DELLA RESISTENZA

Michele.Baccarani@unibo.it

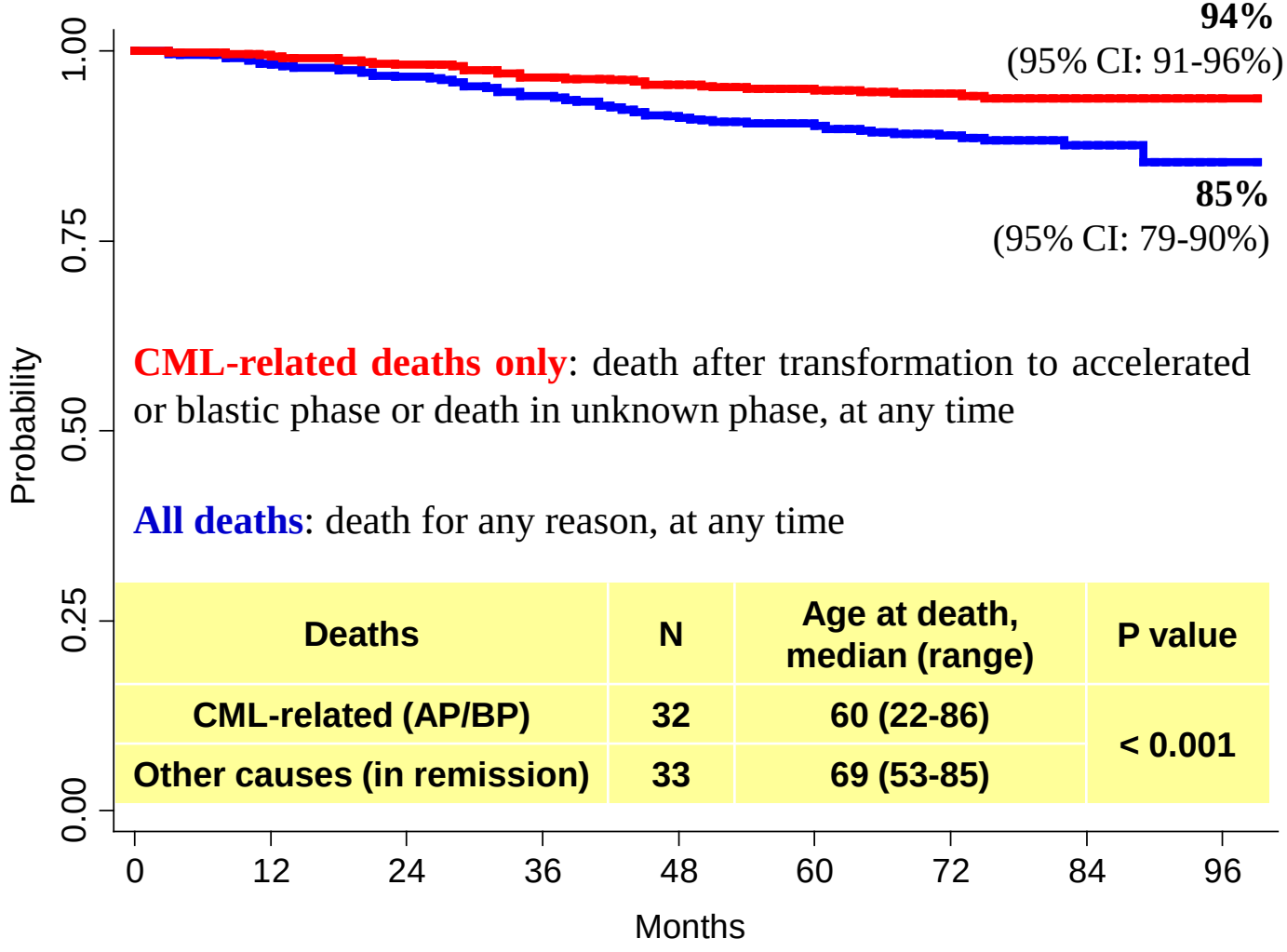
EUROPEAN LEUKEMIANET 2013 (Blood 2013;122:885 892). RESPONSE TO TREATMENT FIRSTLINE (IMATINIB, NILOTINIB, and DASATINIB)

	OPTIMAL	WARNING	FAILURE
BASELINE	NA	- HIGH RISK, - CCA/Ph+ (major route)	NA
3 mo	- BCR-ABL ≤ 10% and/or - Ph+ ≥ 35%	- BCR-ABL ≥ 10% and/or - Ph + 36-95%	- No CHR and/or - Ph + > 95%
6 mo	- BCR-ABL < 1% and/or - Ph+ 0	- BCR-ABL 1-10% and/or - Ph + 1-35%	- BCR-ABL > 10% and/or - Ph + > 35%
12 mo	- BCR-ABL ≤ 0.1%	- BCR-ABL 0.1-1 %	- BCR-ABL > 1% and/or - Ph + ≥ 1%
Then	- BCR-ABL ≤ 0.1%	- BCR-ABL 0.1-1%	- BCR-ABL > 1%

EUROPEAN LEUKEMIANET 2013 TREATMENT RECOMMENDATIONS

1st LINE:	**IMATINIB 400 x 1, DASATINIB 100 x 1, NILOTINIB 300 x 2**
2nd LINE	
- INTOLERANCE	- SWITCH TO ONE OF THE OTHER TKIs approved for firstline treatment, taking into account comorbidities and side effects
- FAILURE	- SWITCH IMATINIB TO OTHER TKIs, taking into account **MUTATIONS**, comorbidities and side effects: - NILO TO DASA, BOSU or PONA (T315I) - DASA TO NILO, BOSU or PONA **(**T315I)
3rd LINE	-SWITCH TO ANOTHER TKI (PONA) - ALLOGENEIC SCT - EXPERIMENTAL TREATMENT

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

CML, CHRONIC PHASE, TREATMENT 2013 - 2018

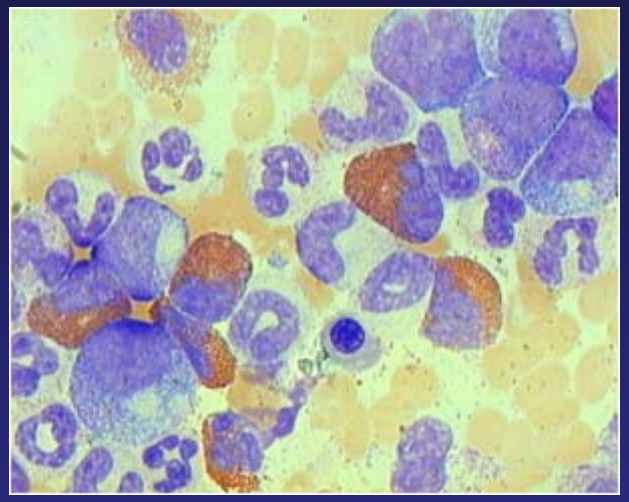
1 st LINE IMATINIB (brand and **GENERIC**)
NILOTINIB
DASATINIB
BOSUTINIB
(Radotinib)

2nd–3rd LINE: IMATINIB, NILOTINIB,
DASATINIB, BOSUTINIB,
PONATINIB, (**Radotinib)**

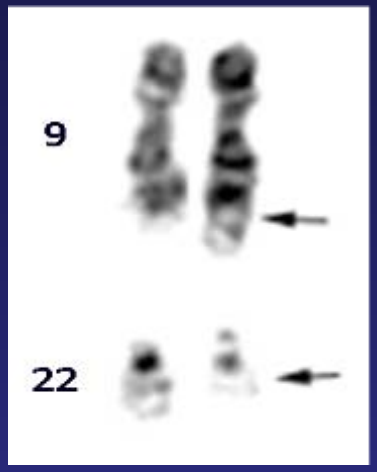
ALLOGENEIC STEM CELL TRANSPLANTATION (in case of resistance to TKIs)

INTERFERONα (when a TKI cannot be used (e.g. pregnancy))

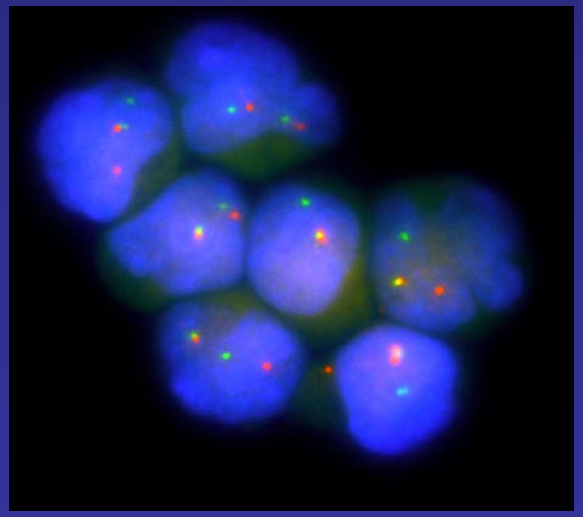
Methods to detect CML Cells



Hematological assessment



Cytogenetics



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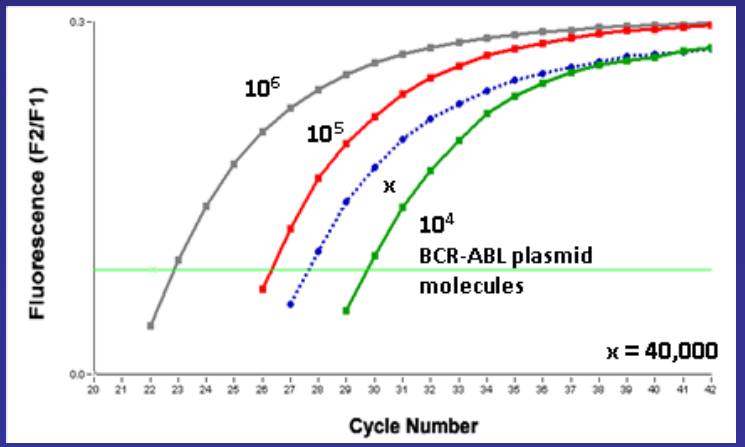


Real time quantitative PCR

EUROPEAN LEUKEMIANET 2013 (Blood 2013;122:885 892). RESPONSE TO TREATMENT FIRSTLINE

TODAY RESPONSE DEFINITION IS BASED ON qPCR

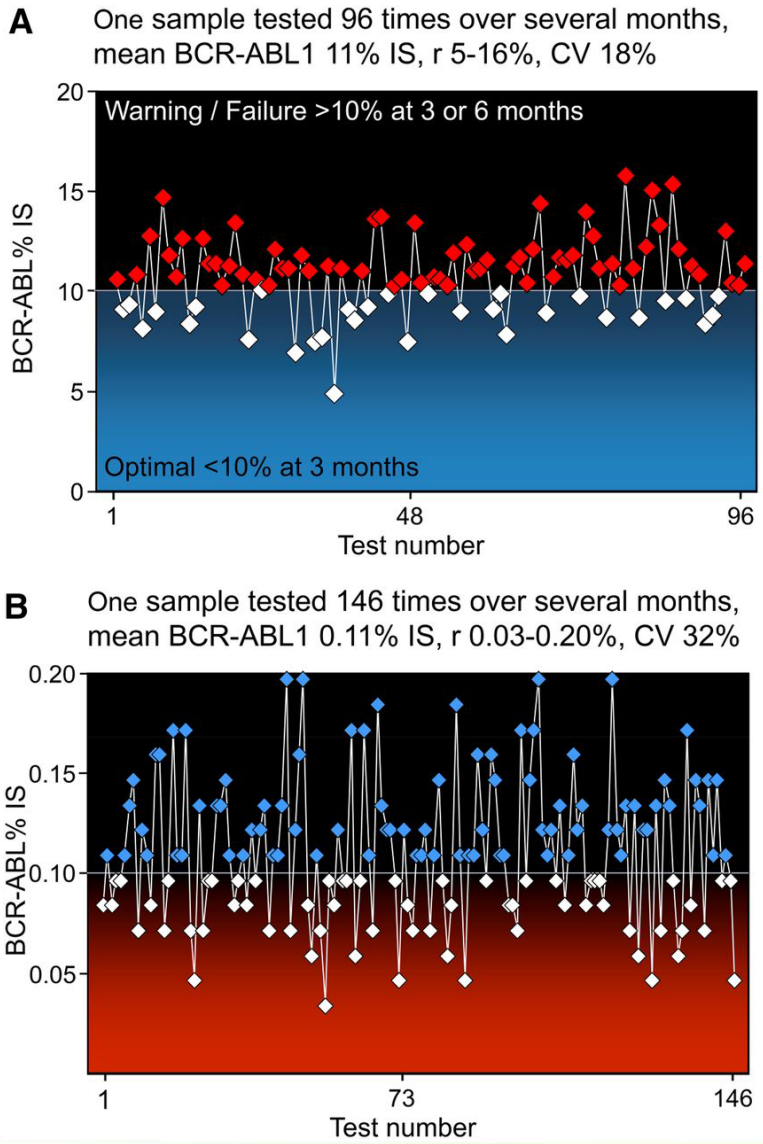
	OPTIMAL	WARNING	FAILURE
BASELINE	NA	- HIGH RISK, - CCA/Ph+ (major route)	NA
3 mo	- BCR-ABL ≤ 10% and/or - Ph+ ≥ 35%	- BCR-ABL ≥ 10% and/or - Ph + 36-95%	- No CHR and/or - Ph + > 95%
6 mo	- BCR-ABL < 1% and/or - Ph+ 0	- BCR-ABL 1-10% and/or - Ph + 1-35%	- BCR-ABL > 10% and/or - Ph + > 35%
12 mo	- BCR-ABL ≤ 0.1%	- BCR-ABL 0.1-1 %	- BCR-ABL > 1% and/or - Ph + ≥ 1%
Then	- BCR-ABL ≤ 0.1%	- BCR-ABL 0.1-1%	- BCR-ABL > 1%

MONITORING THE RESPONSE, 2018 and beyond

CYTOGENETICS: STILL RECOMMENDED ?

qPCR: CONFIRMED ,
BUT,
SHOULD CURRENT (2013) ELN DEFINITIONS BE MODIFIED ?

How reliable is the molecular assay for measuring BCR/ABL transcripts?
Courtesy of Sue Branford



THE DEFINITIONS OF MOLECULAR RESPONSE EMR 10%, MMR 0.1%, MR4.0 0.01%, MR4.5 0.0032% ARE VERY STRINGENT,

THE VALUE THAT HAS BEEN GIVEN TO ONE SINGLE VALUE IS SUCH THAT, EVEN WHEN THE RESULTS OF A qPCR ARE BORDERLINE, MANY DOCTORS TAKE IMMEDIATELY AN ACTION, INSTEAD OF TESTING AGAIN FOR CONFIRMATION

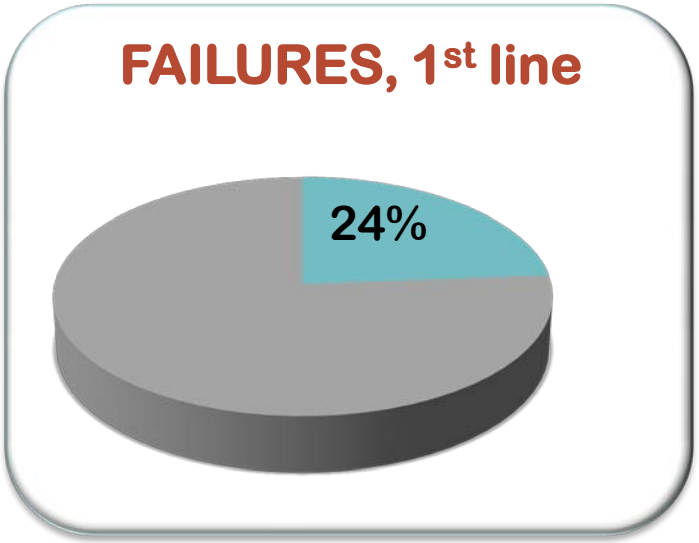
.

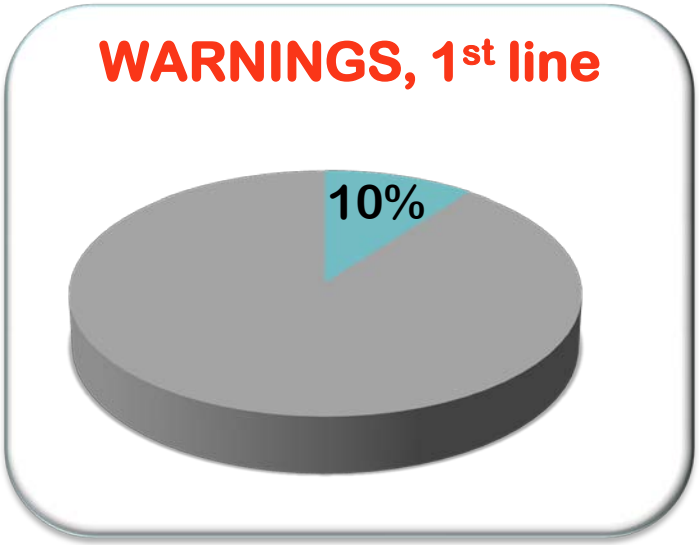
WE SHOULD EITHER CHANGE THE DEFINITION OF MOLECULAR RESPONSE:

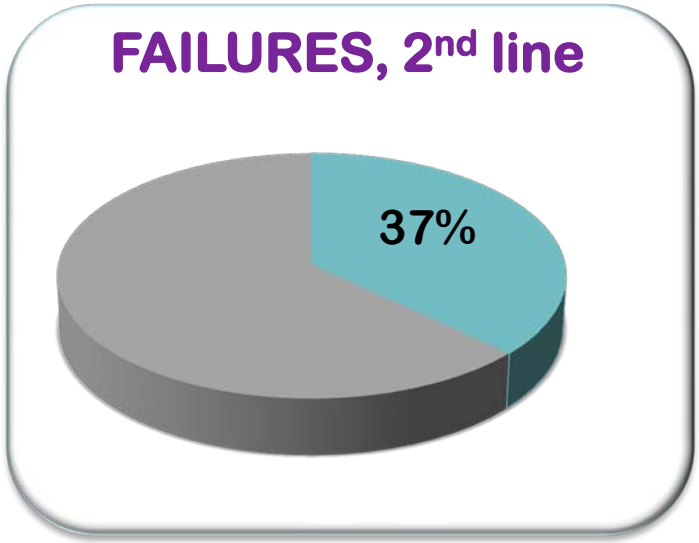
NOT ONE VALUE. BUT A RANGE OF VALUES
FROM 10% TO 8-12%
FROM 0.1% TO 0.08-0.12%

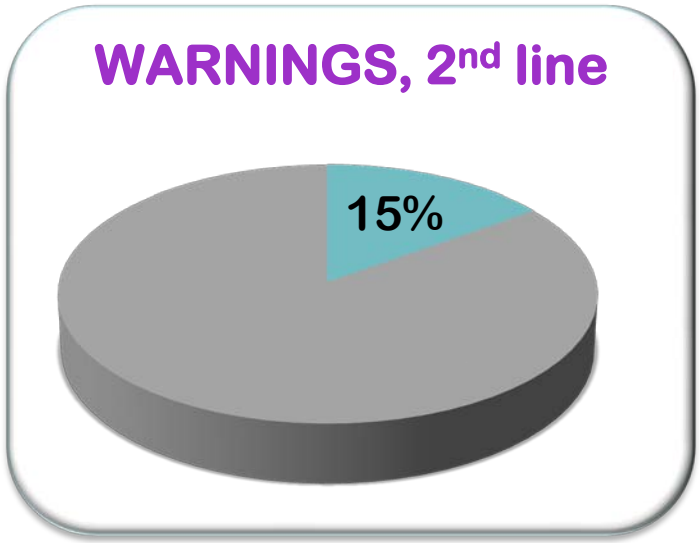
OR DO MORE qPCR
NOT A PCR EVERY THREE MONTHS
BUT MORE FREQUENTLY, EVERY MONTH, UNTIL MMR, remembering that
THE COST OF A PCR IS MUCH LOWER
THAN THE COST OF FEW DAYS OF
INAPPROPRIATE TKI TREATMENT

Summary of mutation frequencies in failures and warnings, 1st and 2nd line









Pts positive for BCR-ABL mutations:

- by conventional sequencing

Soverini ASH 2015

CONVENTIONAL (SANGER) SEQUENCING and NEXT GENERATION SEQUENCING

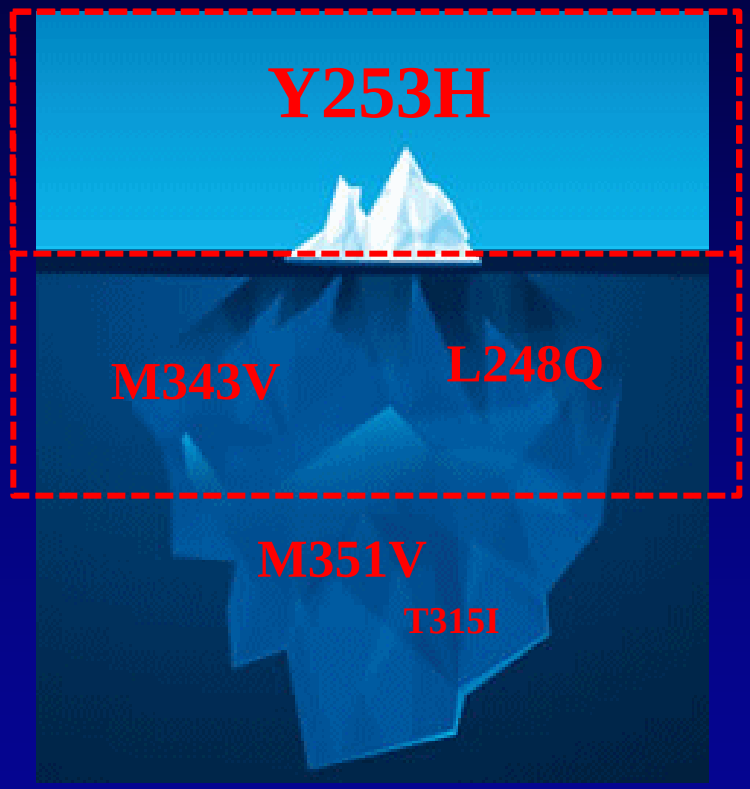
Conventional Sequencing

(20%)

NGS

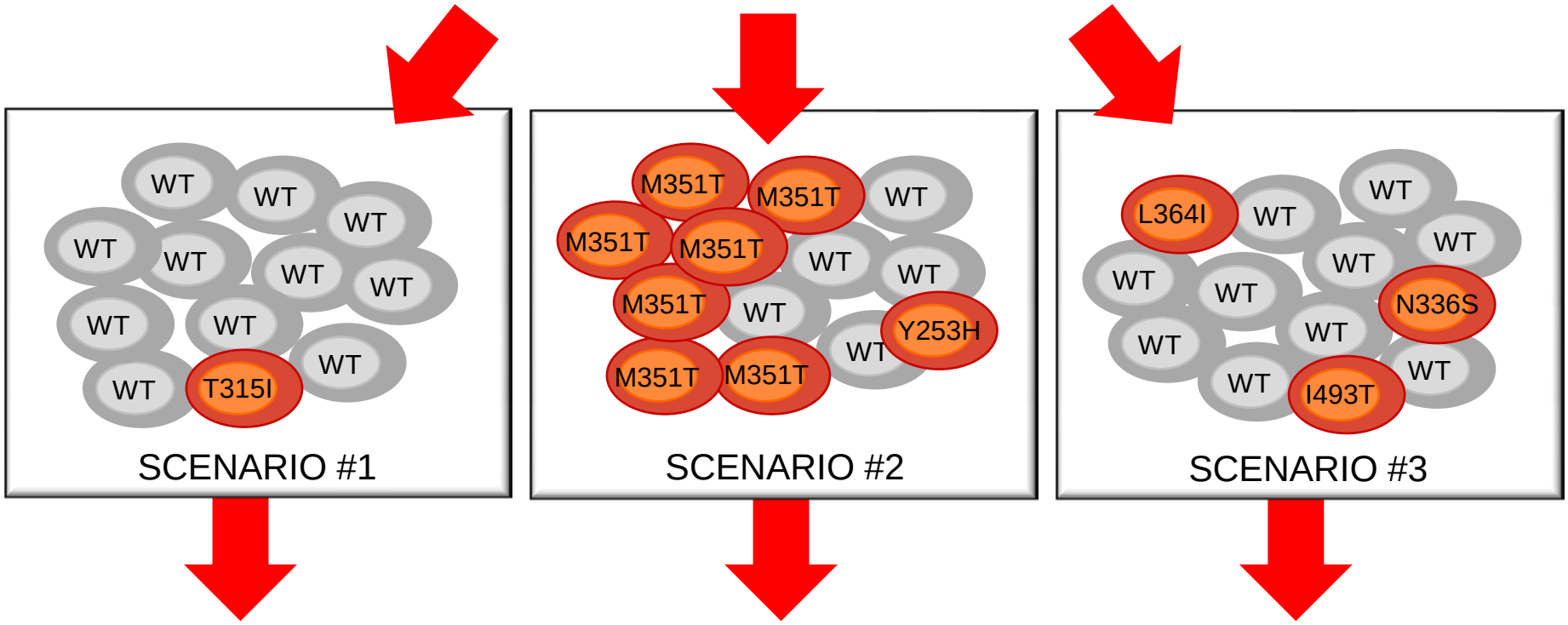
(1%)

ASO-PCR (0.001%; but it is mutation-specific)



From Sanger to NGS

NGS at the time of FAILURE or WARNING



LOW BURDEN CLINICALLY ACTIONABLE MUTATIONS

should be included in therapeutic decision algorithms

LOW BURDEN MUTATIONS OF UNKNOWN SIGNIFICANCE

Should not trigger a therapeutic change (unless failure is observed)

EUROPEAN LEUKEMIANET 2013 TREATMENT RECOMMENDATIONS

1st LINE:	**IMATINIB 400 x 1, DASATINIB 100 x 1, NILOTINIB 300 x 2**
2nd LINE	
- INTOLERANCE	- SWITCH TO ONE OF THE OTHER TKIs approved for firstline treatment, taking into account comorbidities and side effects
- FAILURE	- SWITCH IMATINIB TO OTHER TKIs, taking into account **MUTATIONS**, comorbidities and side effects: - NILO TO DASA, BOSU or PONA (T315I) - DASA TO NILO, BOSU or PONA **(**T315I)
3rd LINE	-SWITCH TO ANOTHER TKI (PONA) - ALLOGENEIC SCT - EXPERIMENTAL TREATMENT

CML, CHRONIC PHASE, 2018, 1st LINE TREATMENT

IMATINIB	NILOTINIB or DASATINIB*
MORE PATIENTS/DATA	LESS PATIENTS/DATA
LONGER OBSERVATION	SHORTER OBSERVATION
LESS COMPLICATIONS	MORE COMPLICATIONS
CHEAPER (generics!)	MORE EXPENSIVE
SLOWER RESPONSE	FASTER RESPONSE
RESPONSES ARE LESS DEEP	RESPONSES ARE DEEPER
LOWER PROBABILITY OF TFR	HIGHER PROBABILITY OF TFR
SURVIVAL 80-90%	**SURVIVAL 80-90%**

***data and follow-up for Bosutinib and Radotinib are not yet sufficient**

THIS SLIDE COULD HAVE BEEN MADE AND PRESENTED IN 2013

CML, CHRONIC PHASE, 2018, 1st LINE TREATMENT

IMATINIB	NILOTINIB or DASATINIB*
MORE PATIENTS/DATA	LESS PATIENTS/DATA
LONGER OBSERVATION	SHORTER OBSERVATION
LESS COMPLICATIONS	MORE COMPLICATIONS
CHEAPER (generics!)	MORE EXPENSIVE
SLOWER RESPONSE	FASTER RESPONSE
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LOWER PROBABILITY OF TFR	HIGHER PROBABILITY OF TFR
SURVIVAL 80-90%	**SURVIVAL 80-90%**

***data and follow-up for Bosutinib and Radotinib are not yet sufficient**

IF ONE PRIVILEGES TOXICITY AND COST: IMATINIB
IF ONE PRIVILEGES RESPONSE : NILOTINIB or DASATINIB

CML, CHRONIC PHASE, 2018, 1st LINE TREATMENT

IMATINIB	NILOTINIB or DASATINIB*
MORE PATIENTS/DATA	LESS PATIENTS/DATA
LONGER OBSERVATION	SHORTER OBSERVATION
LESS COMPLICATIONS	MORE COMPLICATIONS
CHEAPER (generics!)	MORE EXPENSIVE
SLOWER RESPONSE	FASTER RESPONSE
RESPONSES ARE LESS DEEP	RESPONSES ARE DEEPER
LOWER PROBABILITY OF TFR	HIGHER PROBABILITY OF TFR
SURVIVAL 80-90%	**SURVIVAL 80-90%**

***data and follow-up for Bosutinib and Radotinib are not yet sufficient**

BUT WHAT ABOUT TREATMENT-FREE REMISSION?

CHRONIC MYELOID LEUKEMIA, 2-ARM COMPARATIVE STUDIES

TREATMENT	STUDY	RESPONSE	SURVIVAL	TFR
IMA 800 vs IMA 400	GERMANY CML IV	+	=	//
IMA 800 vs IMA 400	GIMEMA	=	=	//
IMA 800 vs IMA 400	TOPS	=	=	//
NIL vs IMA 400	ENESTnd	+	=	//
DAS vs IMA 400	DASISION	+	=	//
BOS vs IMA 400	BFORE	+	(NY)	//
NIL vs IMA→NIL	SUSTRENIM	NY	NY	NY
IFN+IMA vs IMA 400	GERMANY CML IV	=	=	//
IFN+IMA vs IMA 400	FRENCH SPIRIT	+	=	//
IFN+IMA vs IMA 400	NORDIC	+	//	//
NILO+IFN vs NILO	TIGER	NY	NY	NY
DAS+IFN vs DAS	NORDIC/FRANCE	+	//	//
BOS+IFN vs BOS	NORDIC/FRANCE	NY	NY	NY

TREATMENT-FREE REMISSION
WHICH STUDIES, WHICH DATA 2013-2018

MANY RETROSPECTIVE REPORTS

SOME REPORTS OF PROSPECTIVE STUDIES, (mainly the ENEST trials) NONE IN FIRST LINE

ALL REPORTING THE RATE OF TFR IN PATIENTS WHO HAD ACHIEVED A DEEP MOLECULAR RESPONSE

NONE REPORTING THE RATE OF TFR IN NEWLY DIAGNOSED PATIENTS

NONE COMPARING THE RELATIONSHIP BETWEEN FIRST-LINE TREATMENT AND THE RATE OF TFR

PLANNING TREATMENT DISCONTINUATION

CHRONIC PHASE

TRANSCRIPT MEASURABLE BY qPCR: B2A2 (e13a2) or B3A2 (e14a2)

NOT FAILING THE FIRST TKI (NOT RESISTANT TO FIRST TKI)

TREATMENT DURATION 3 YEARS MINIMUM, 5 YEARS BETTER

DEEP MOLECULAR RESPONSE (MR 4.0 MINIMUM, MR 4.5 BETTER) LASTING 1 YEAR MINIMUM, 2 YEARS BETTER

A LABORATORY WITH STANDARDIZED PROCEDURES (LabNet)

qPCR MONTHLY FOR 6 MONTHS MINIMUM, 12 MONTHS BETTER

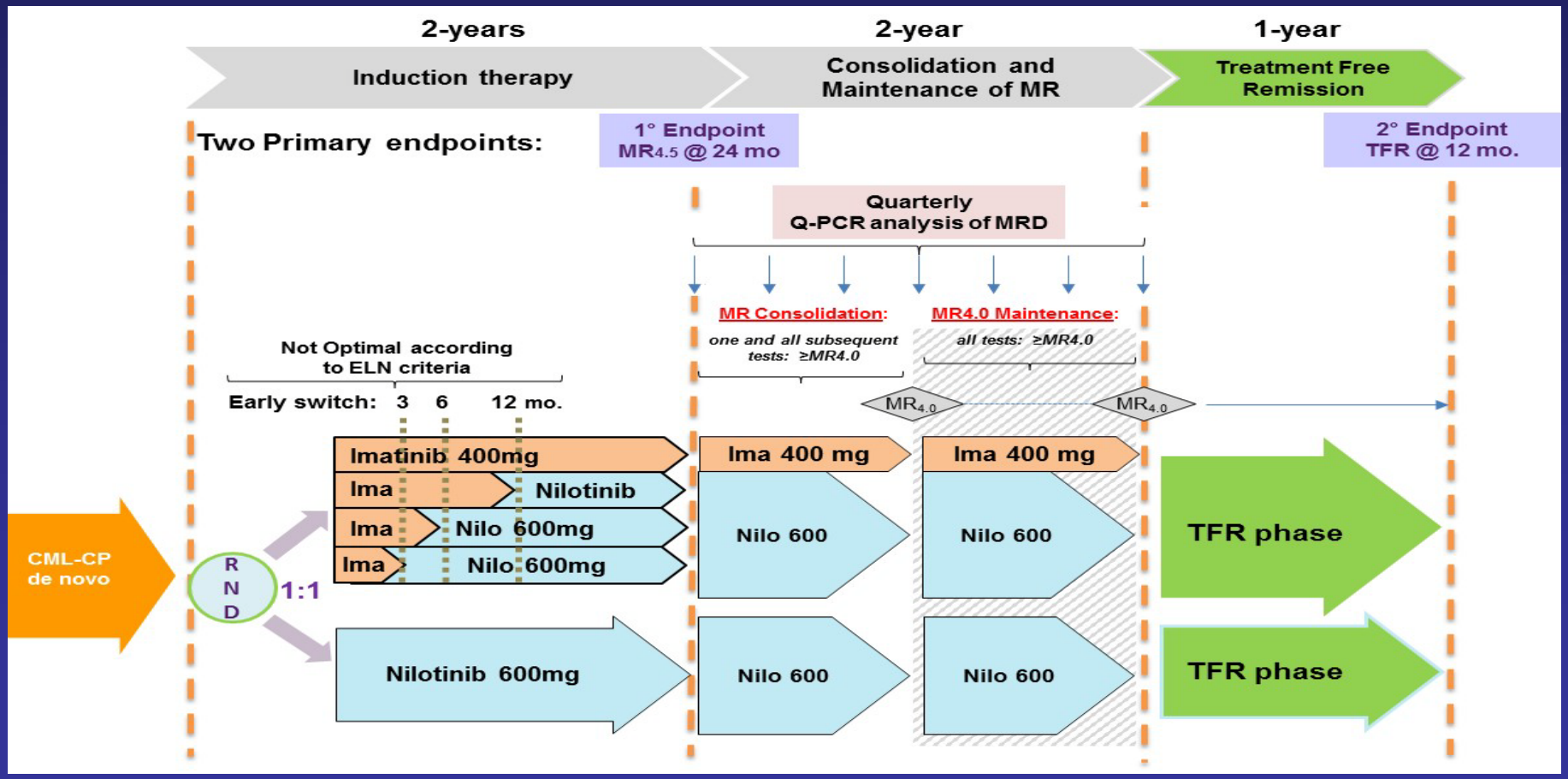
ALL TFR PAPERS REPORT THAT ABOUT 50% OF THE PATIENTS WHO DISCONTINUE TREATMENT IN DEEP AND STABLE MR WILL REMAIN IN TFR

BUT NO STUDIES TELL US WHAT IS THE BEST STRATEGY

IN SEARCH OF THE BEST COST-EFFECTIVE TREATMENT FOR TFR

SUSTRENIM Study (NCT 02602314)

IS A STUDY THAT TESTS PROSPECTIVELY A POLICY OF A SECOND GENERATION TKI (NILOTINIB) FIRSTLINE AGAINST A POLICY OF IMATINIB FIRSTLINE WITH SWITCH TO NILOTINIB IN CASE OF LESS THAN OPTIMAL RESPONSE, **FOR THE ACHIEVEMENT OF TREATMENT-FREE REMISSION**



ELN 2013 RESISTANCE

3 months : no CHR

6 months : BCR/ABL > 10%

1 year : BCR/ABL > 1%

2 years : BCR/ABL > 0.1%

RESPONSE LOSS
MUTATION

A CHANGE OF TREATMENT IS MANDATORY

RESISTANCE

ELN 2013	? 2018 ?
3 months : no CHR	BCR-ABL > 10% ?
6 months : BCR/ABL > 10%	BCR-ABL > 1% ?
1 year : BCR/ABL > 1%	BCR-ABL > 0.1% ?
2 years : BCR/ABL > 0.1%	BCR-ABL > 0.01% ?
RESPONSE LOSS MUTATION	RESPONSE LOSS MUTATION

IS A CHANGE OF TREATMENT ALWAYS MANDATORY ?

PERSPECTIVES IN THE TREATMENT OF CHRONIC MYELOID LEUKEMIA

- TYROSINE KINASE INHIBITORS AND INTERFERONα
- NEW TYROSINE KINASE INHIBITORS

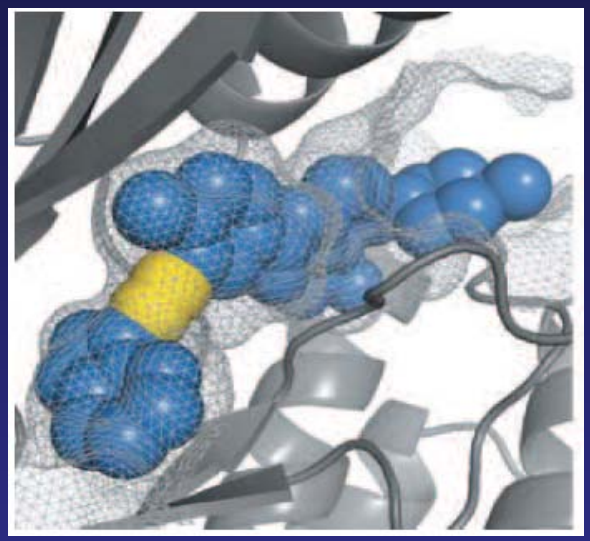
BEYOND TKIs

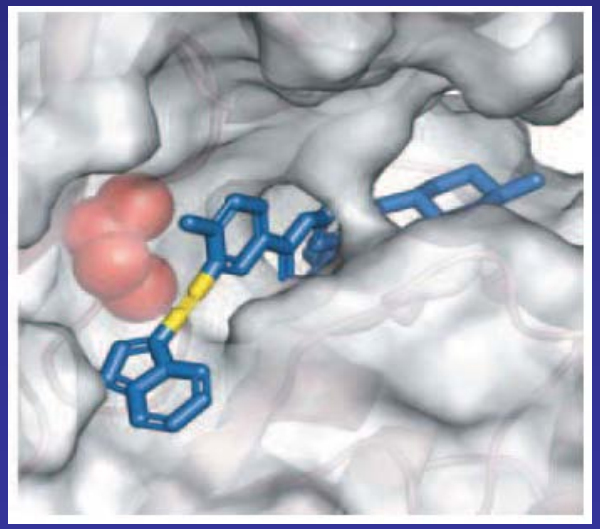
- DRUGS TARGETING OTHER PATHWAYS
- DRUGS TARGETING BCR-ABL1+ STEM CELLS
- DRUGS INHIBITING AUTOPHAGY
- VACCINES
- ANTIBODIES
- CHIMERIC ANTIGEN RECEPTOR MODIFIED T CELLS

- PROGRESS IN ALLOGENEIC SCT

Ponatinib
A Pan-BCR-ABL Inhibitor

- **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**



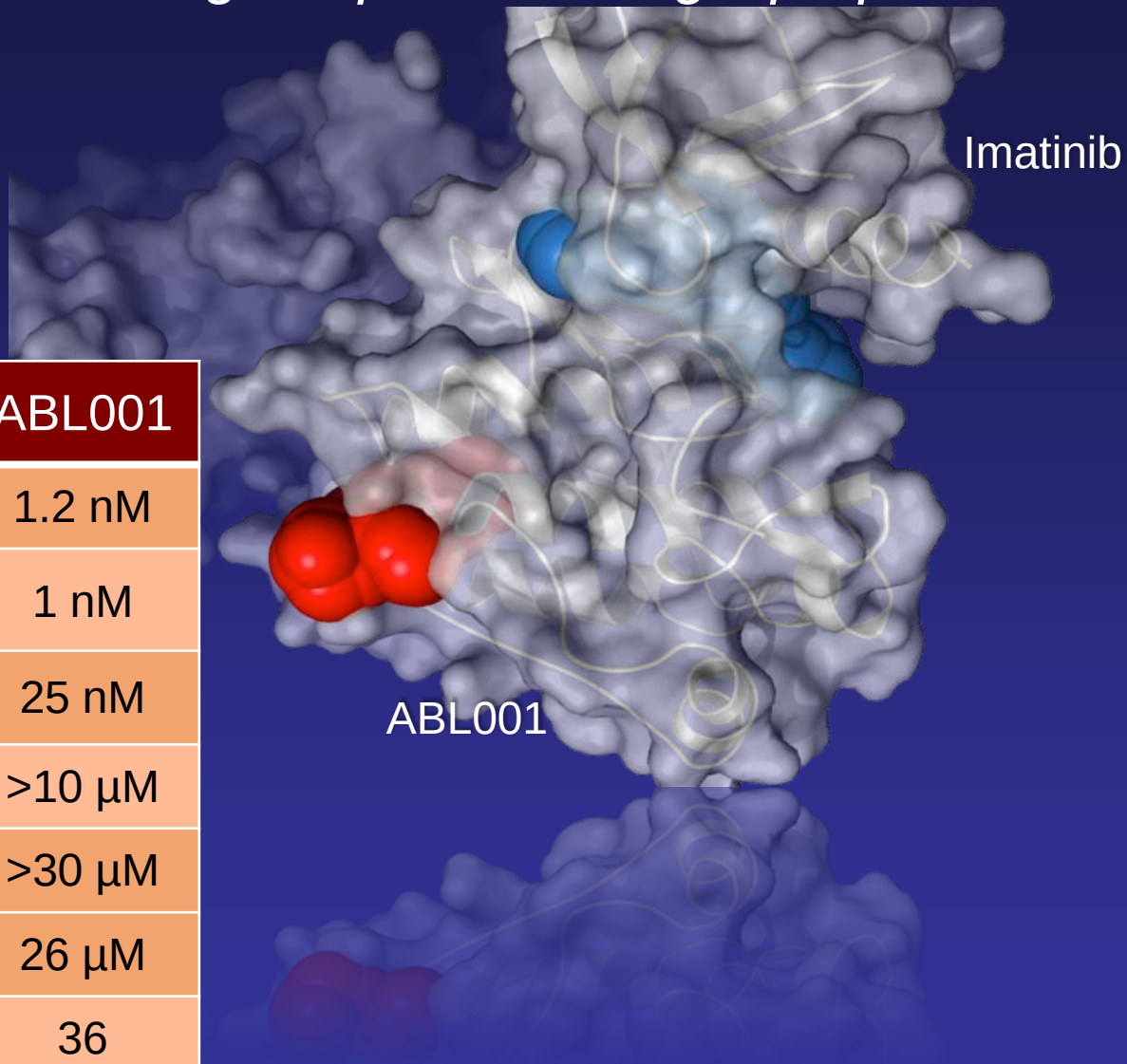


O'Hare T, et al. Cancer Cell. 2009;16:401-412

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



WHAT CAUSES RESISTANCE ?

TO IMPROVE RESULTS THAT ARE ALREADY EXCELLENT WE NEED NOT ONLY NEW DRUGS BUT ALSO MORE KNOWLEDGE

- BCR-ABL1 MUTATIONS
- OTHER MOLECULAR MECHANISMS ?

- THE NUMBER OF BCR-ABL1+ STEM CELLS ?
- THE CELLULAR AMOUNT OF BCR-ABL1 TRANSCRIPT ?
- THE CELLULAR AMOUNT OF THE BCR-ABL1 PROTEIN

WHAT CAUSES RESISTANCE ?

ABOUT 50% OF IMATINIB-RESISTANT PATIENTS WITHOUT A MUTATION RESPOND “OPTIMALLY” TO A 2nd GENERATION TKI; SOME RESPOND ALSO TO A HIGHER DOSE OF IMATINIB

IF RESISTANCE WAS CAUSED BY “ADDITIONAL MOLECULAR ABNORMALITIES”, WHY SHOULD THEY RESPOND TO ANOTHER TKI ?

THEY RESPOND TO 2nd GENERATION TKIs BECAUSE 2nd GENERATION TKIs ARE MORE POTENT, AND THEIR POTENCY RESETS THE BALANCE BETWEEN BCR-ABL1 TYROSINE KINASE ACTIVITY AND THE INHIBITOR

RESISTANCE and PERSISTENCE

-

FEW PATIENTS (LESS THAN 20%) FAIL ON TKI,

MANY PATIENTS (MORE THAN 50%) CONTINUE TO HAVE MEASURABLE RESIDUAL DISEASE

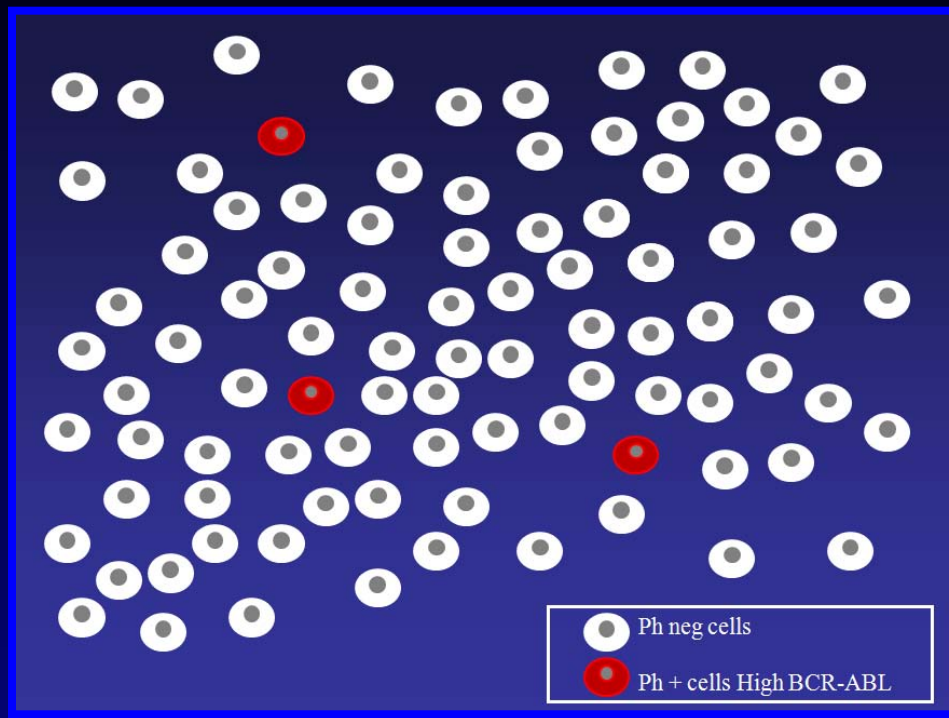
VERY FEW PATIENTS (LESS THAN 10%) CAN GET FREE OF Ph+ CELLS AND CAN BE CURED

ARE THE CAUSES OF RESISTANCE THE SAME AS OF PERSISTENCE OF MINIMAL RESIDUAL DISEASE ?

“HIGH” BCR-ABL /P210 CELLS

MAY BE MORE SENSITIVE TO TKIs, BUT PROLIFERATE, CAN BECOME MORE RESISTANT, AND CAN DEVELOP MUTATIONS.

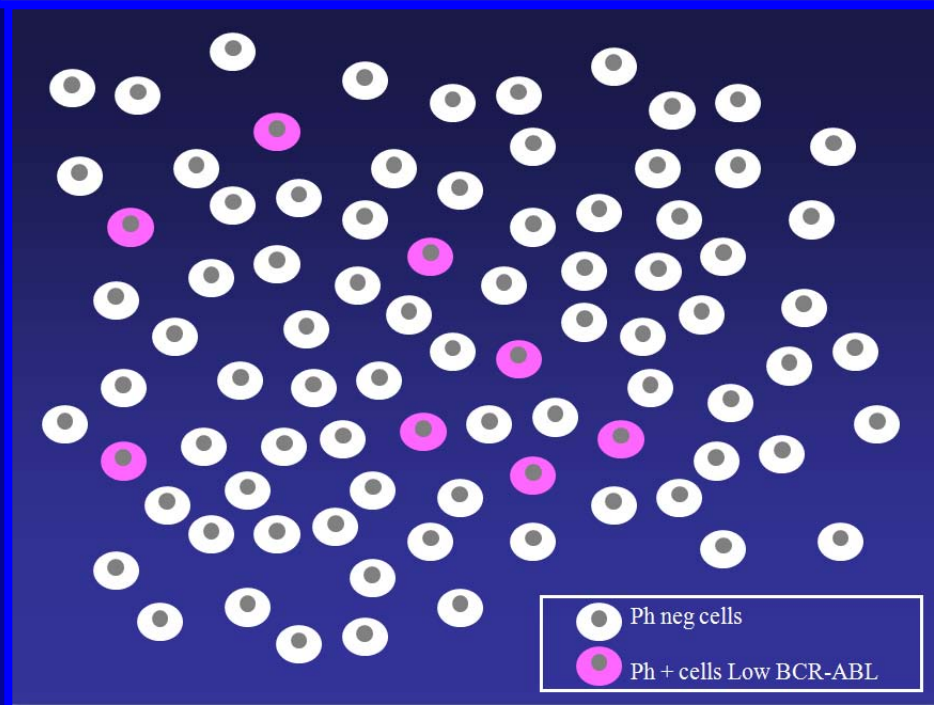
THEY ARE A THREAT TO LIFE



“LOW” BCR-ABL / P210 CELLS

MAY BE LESS SENSITIVE TO TKIs, BUT ARE “QUIESCENT”, AND CAN BE RESPONSIBLE OF THE PERSISTENCE OF MINIMAL RESIDUAL DISEASE.

THEY ARE A THREAT TO TFR or TO “CURE”



THE ASSESSMENT OF MINIMAL RESIDUAL DISEASE: ONLY qPCR ?

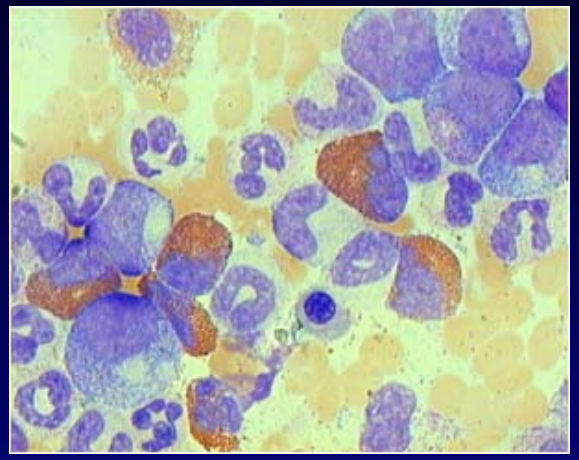
THE EVALUATION AND THE CALCULATION OF BCR-ABL1 TRANSCRIPT AMOUNT BY qPCR, ACCORDING TO THE INTERNATIONAL STANDARD, IS SUFFICIENT FOR PREDICTING THE OUTCOME,

BUT

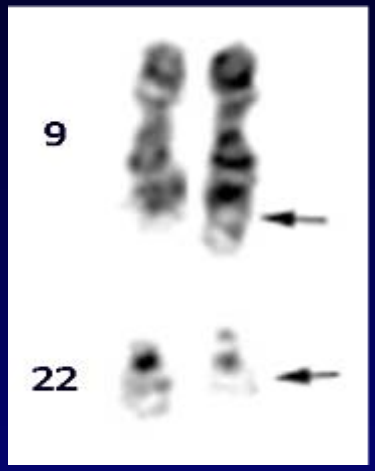
IT MAY NOT BE THE BEST FOR PREDICTING TREATMENT-FREE REMISSION

digital PCR ?
STEM CELL COUNT ?
PROTEOMICS ?

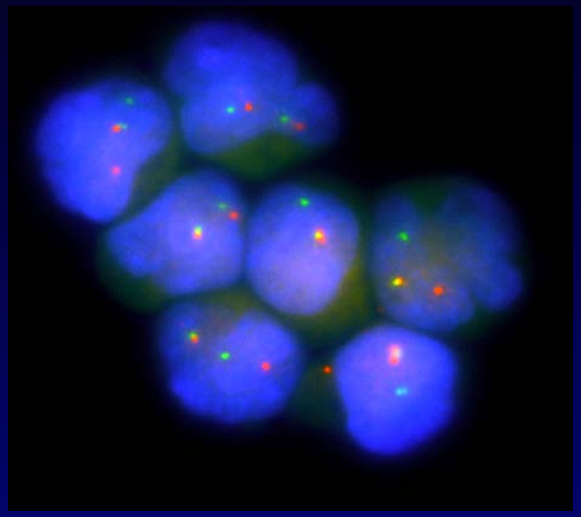
Methods to study and monitor CML



Counts and Microscopy



Cytogenetics



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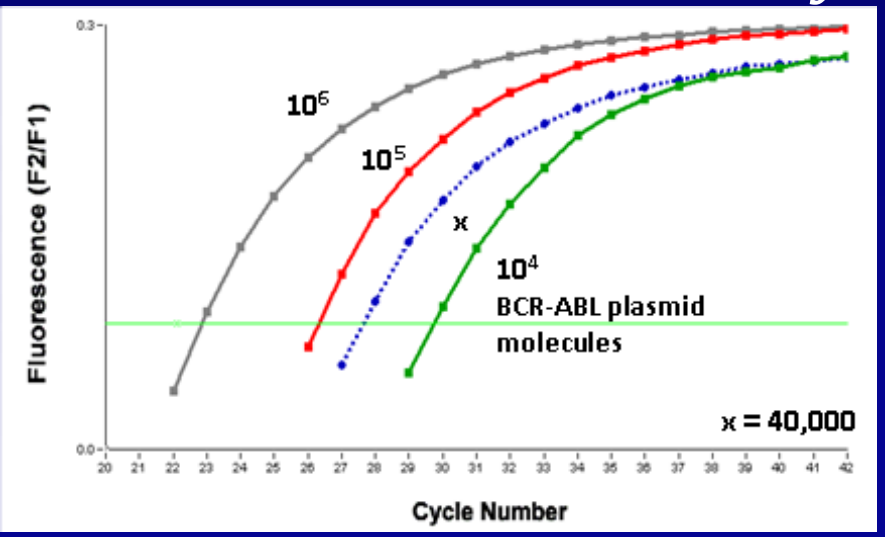


Real time quantitative PCR

DIGITAL PCR

STEM CELLS

PROTEOMICS

WHEN STABLE, OPTIMAL, RESPONDERS DISCONTINUE TREATMENT, SOME RELAPSE AND SOME REMAIN IN TREATMENT-FREE REMISSION, IN SPITE OF THE FACT THAT THEY HAD THE "SAME" BCR-ABL1 TRANSCRIPTS LEVEL

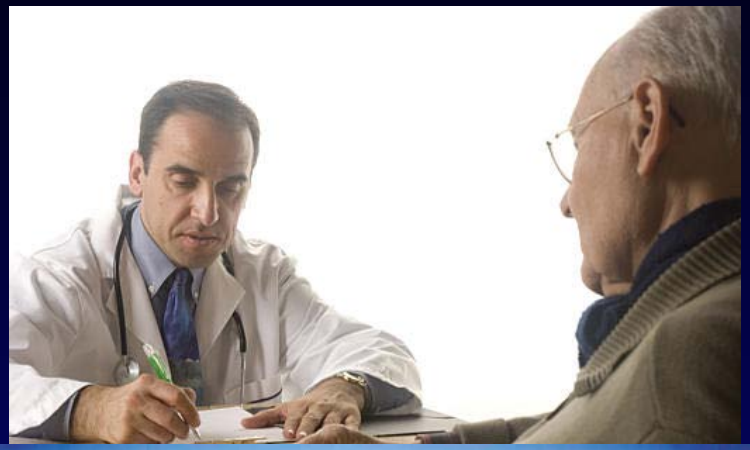
TECHNOLOGY **?** "SAME" IS NOT SO SAME ?

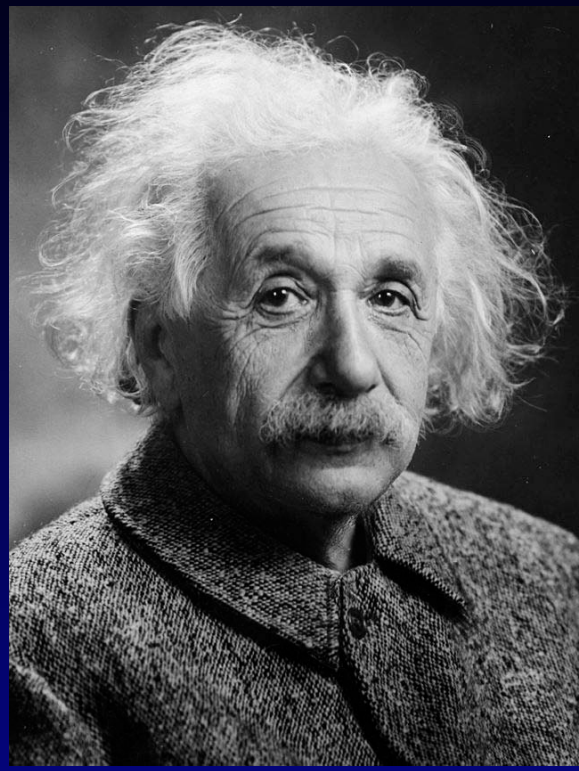
LEUKEMIA? "FEW" Ph+ CELLS WITH "HIGH" TRANSCRIPT/P210 LEVEL or "MANY" Ph+ CELLS WITH "LOW" TRANSCRIPT/P210 LEVEL ?

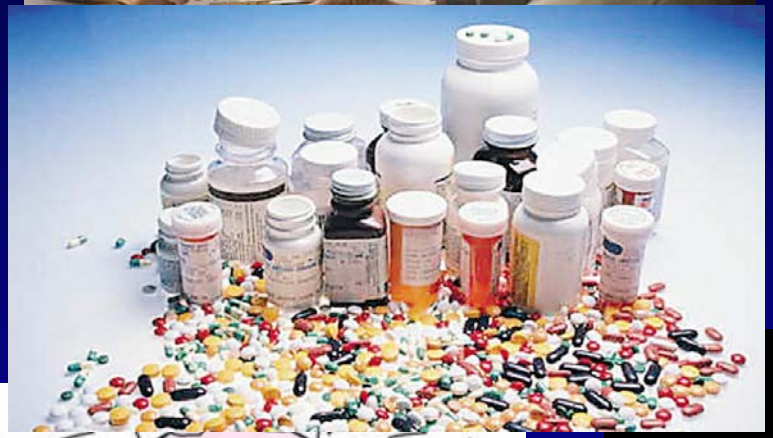
THE ROLE OF THE IMMUNE SYSTEM MAY BE MORE CRITICAL, MORE IMPORTANT THAN TECHNOLOGY AND THE BIOLOGY OF CML

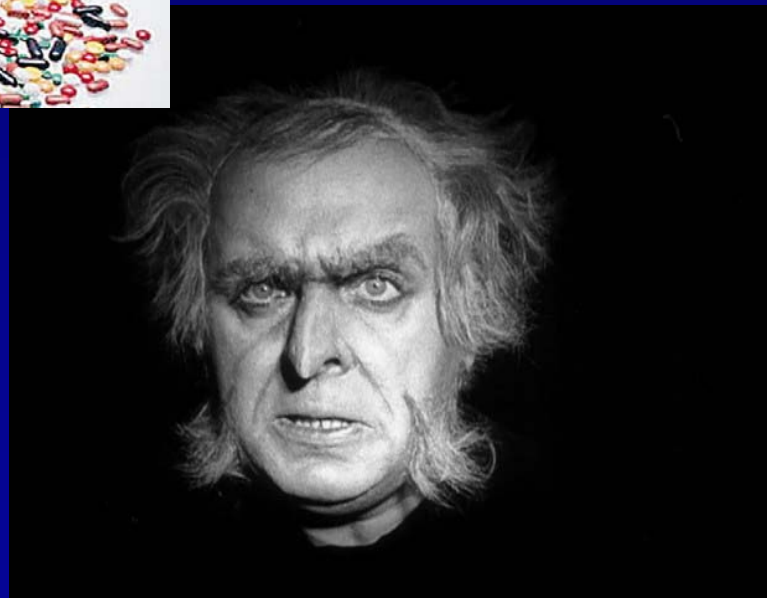
THE PLAYERS

The patient
The doctor
The good scientist
The bad scientist
The crazy scientist
The charlatan
The Pharma









CML 2018 and beyond

THE OBJECTIVES OF TREATMENT OPTIMIZATION

RESPONSE - definition
- methods

SURVIVAL - treatment

TREATMENT-FREE REMISSION - strategy

QUALITY OF LIFE/TOXICITY - treatment

COST-EFFECTIVE USE OF DRUGS - market

PATIENT – ADAPTED STRATEGY

THE TYPE, NUMBER AND GRADE OF COMORBIDITIES INFLUENCE THE CHOICE OF THE TKI.

SEVERAL “COMORBIDITIES” MAY BE EVEN MORE IMPORTANT THAN CHRONIC MYELOID LEUKEMIA ITSELF, BOTH FOR SURVIVAL AND FOR QUALITY OF LIFE

PATIENT RELATED FACTORS LIMITING THE CHOICE, THE DOSE AND THE USE OF TKIs – MANY OF THEM ARE MORE IMPORTANT THAN LEUKEMIA

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……

Michele BACCARANI, MD

Professor of Hematology at the Universities of Trieste, Udine, and Bologna

Chairman, CML Working Parties of European LeukemiaNet and GIMEMA

DISCLOSURES

Consultant and speaker, receiving honoraria, from

ARIAD/INCYTE

BRISTOL-MYERS SQUIBB

NOVARTIS

PFIZER

BACK UP

ABOUT 25% OF THE NEWLY DIAGNOSED PATIENTS REMAIN IN TFR

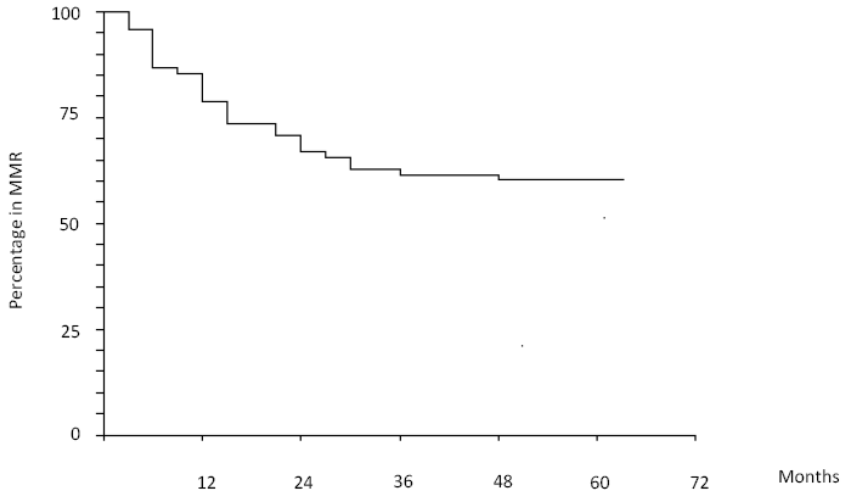
WHAT OF THE PATIENTS WHO WILL NEVER BE ABLE TO DISCONTINUE OR WILL RELAPSE AFTER DISCONTINUATION ??

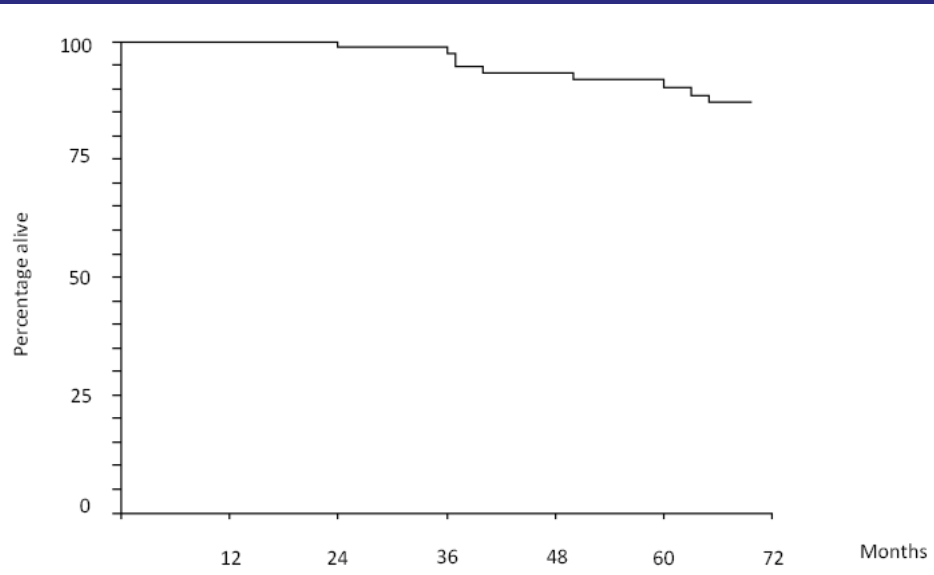
WHICH STRATEGIES FOR A CHRONIC LIFE-LONG THERAPY ?

WHAT ABOUT THE PATIENTS WHO ACHIEVE A MMR BUT NEVER ACHIEVE THE DMR THAT IS REQUIRED FOR TREATMENT DISCONTINUATION? DO THEY NEED FULL STANDARD TKI DOSE FOR EVER ?

THE INTERIM STUDY: Probability of maintaining MMR , and survival

Russo D et al, Blood 2013;121(26):5138-44, and Blood Cancer Journal 2015;5:e347





THE CHOICE OF THE TKI IS INFLUENCED BY EFFICACY, TOXICITY , TOLERABILITY, AND COST

THE AVAILABILITY OF SEVERAL TKIs RESULTS IN A BALANCE OF EFFICACY (RESPONSE), TOXICITY, SURVIVAL, COST, AND TREATMENT-FREE REMISSION.

THE CHOICE OF THE TKI, IN FIRST-LINE AS WELL AS IN SECOND-LINE, IS BECOMING LESS CRITICAL

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"

THE PLAYERS FOR CML

The patient
The doctor
The good scientist
The Pharma