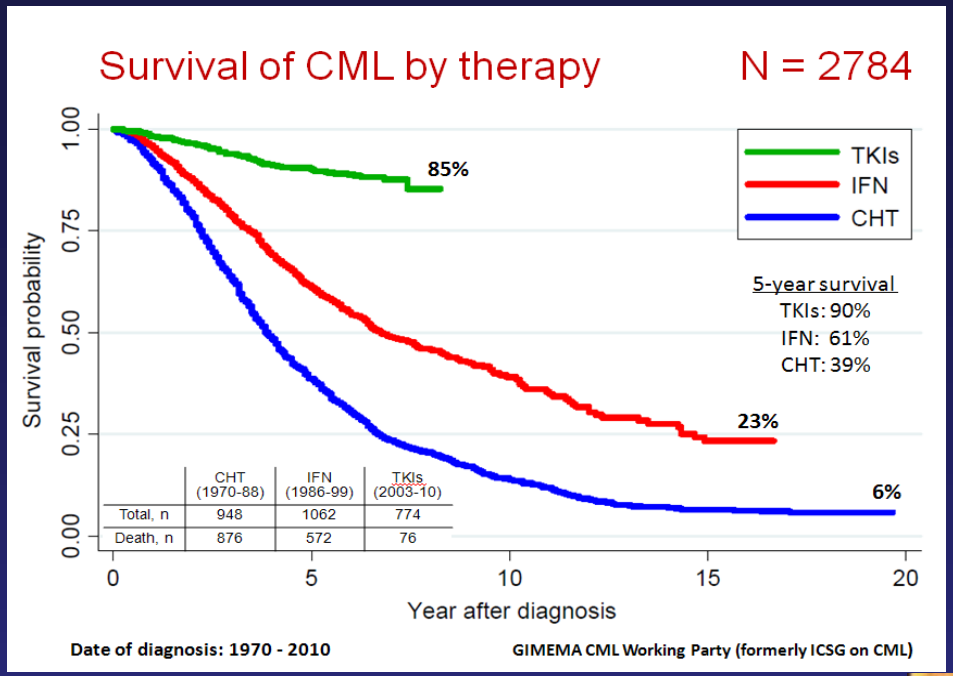

NEW DRUGS IN HEMATOLOGY

Bologna, 9-11 May 2016

CHRONIC MYELOID LEUKEMIA

STATUS OF THE ART OF TREATMENT

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DISCLOSURES

Consultant and speaker, receiving honoraria, from

BRISTOL-MYERS SQUIBB

NOVARTIS

PFIZER

ARIAD

CML THERAPY, STATE OF THE ART, 2016

- TYROSINE KINASE INHIBITORS (TKIs)
  - IMATINIB, NILOTINIB and DASATINIB, first-line
  - BOSUTINIB second-line
  - PONATINIB second-line in case of T315I or resistance to nilotinib or dasatinib, and third line
  - **GENERIC IMATINIB**
  - OTHER TKIs, investigational

- INTERFERONα in combination with TKIs (investigational)

- OTHER DRUGS, investigational

- ALLOGENEIC STEM CELL TRANSPLANTATION

CML IS A SIMPLE CANCER, DRIVEN BY A SINGLE, UNIQUE MOLECULAR ABNORMALITY, BUT

ARE ALL PATIENTS ALIKE ?	Age, gender, comorbidities, etc
ARE ALL CASES ALIKE ?	Phase, risk, etc
ARE ALL TKIs ALIKE ?	PK, potency, specificity, toxicity, cost
IS THE GOAL OF THERAPY ALWAYS THE SAME, FOR EVERYBODY ?	Survival, quality of life, treatment-free remission

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IS THE GOAL OF THERAPY ALWAYS THE SAME, FOR EVERYBODY ?	**Survival, quality of life, treatment-free remission**

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

AGE, LIFESTYLE, EDUCATION, WILLING, EXPECTATION…….

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

……..

ALL CML CASES ARE NOT ALIKE
THE PROGNOSTIC SCORES
FOR CML

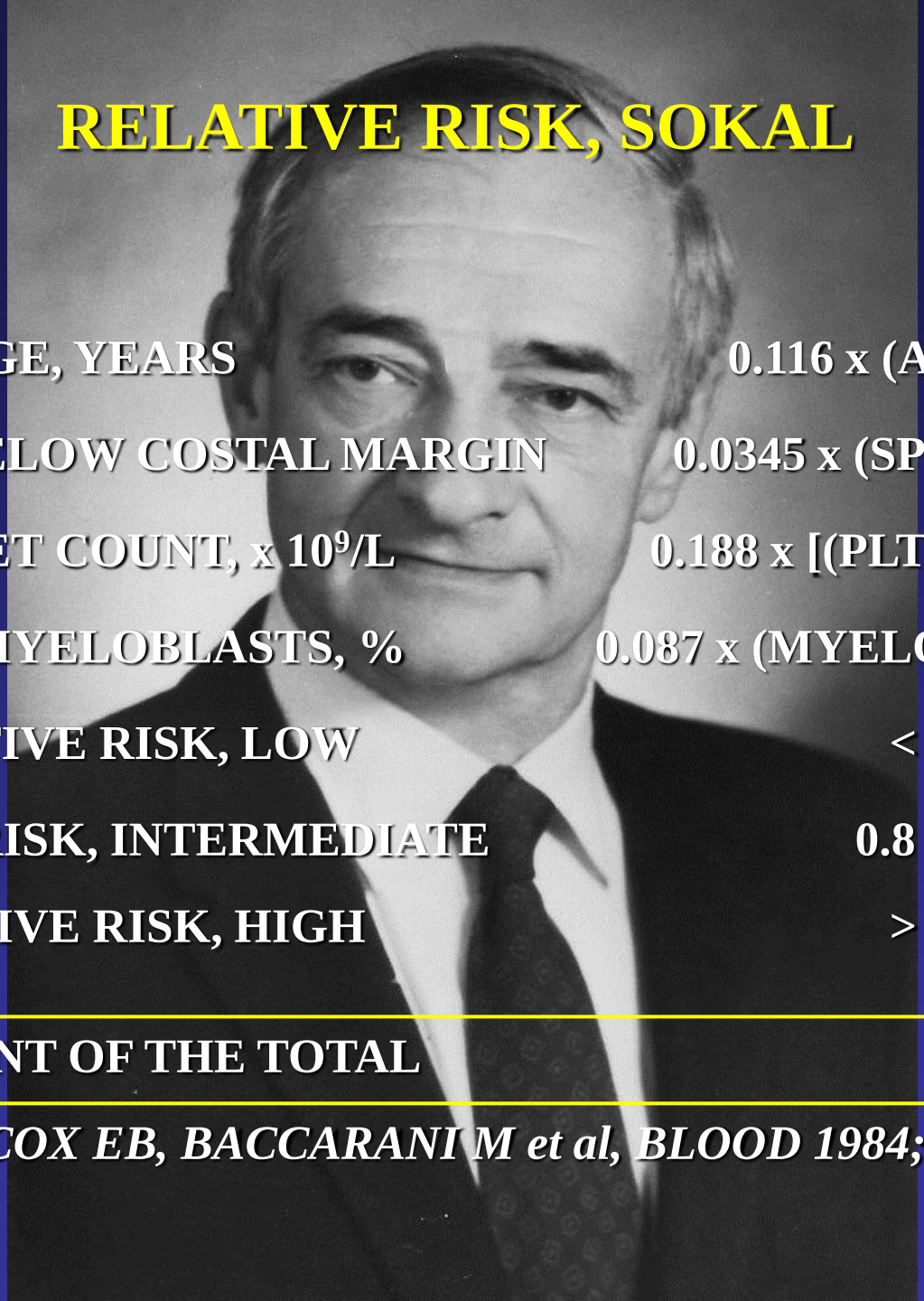
THE INTERNATIONAL SCORE, SOKAL JE et al, BLOOD 1984; 63: 789-799
CONVENTIONAL CHEMOTHERAPY

THE EURO SCORE, HASFORD J et al, J NATL CANCER INST 1998; 90: 850-858
INTERFERONα-BASED REGIMES

THE EUTOS SCORE, HASFORD J et al, BLOOD 2011; 118: 686-692
IMATINIB-BASED REGIMES

THE NEW EUTOS LONG TERM SURVIVAL SCORE, PFIRRMANN M et al, LEUKEMIA 2015
IMATINIB-BASED REGIMES

RELATIVE RISK, SOKAL



AGE, YEARS	0.116 x (AGE – 43.4)
SPLEEN, CM BELOW COSTAL MARGIN	0.0345 x (SPLEEN – 7.51)
PLATELET COUNT, x 10^9/L	0.188 x [(PLT: 700)^2 – 0.563]
BLOOD MYELOBLASTS, %	0.087 x (MYELOBLASTS – 2.10)
*RELATIVE RISK, LOW	< 0.8
*RELATIVE RISK, INTERMEDIATE	0.8 – 1.2
*RELATIVE RISK, HIGH	> 1.2

* EXPONENT OF THE TOTAL

SOKAL JE, COX EB, BACCARANI M et al, BLOOD 1984; 63: 789-799

THE LIMITS OF THE PROGNOSTIC SCORES

ALL SCORES PREDICT RESPONSE AND SURVIVAL

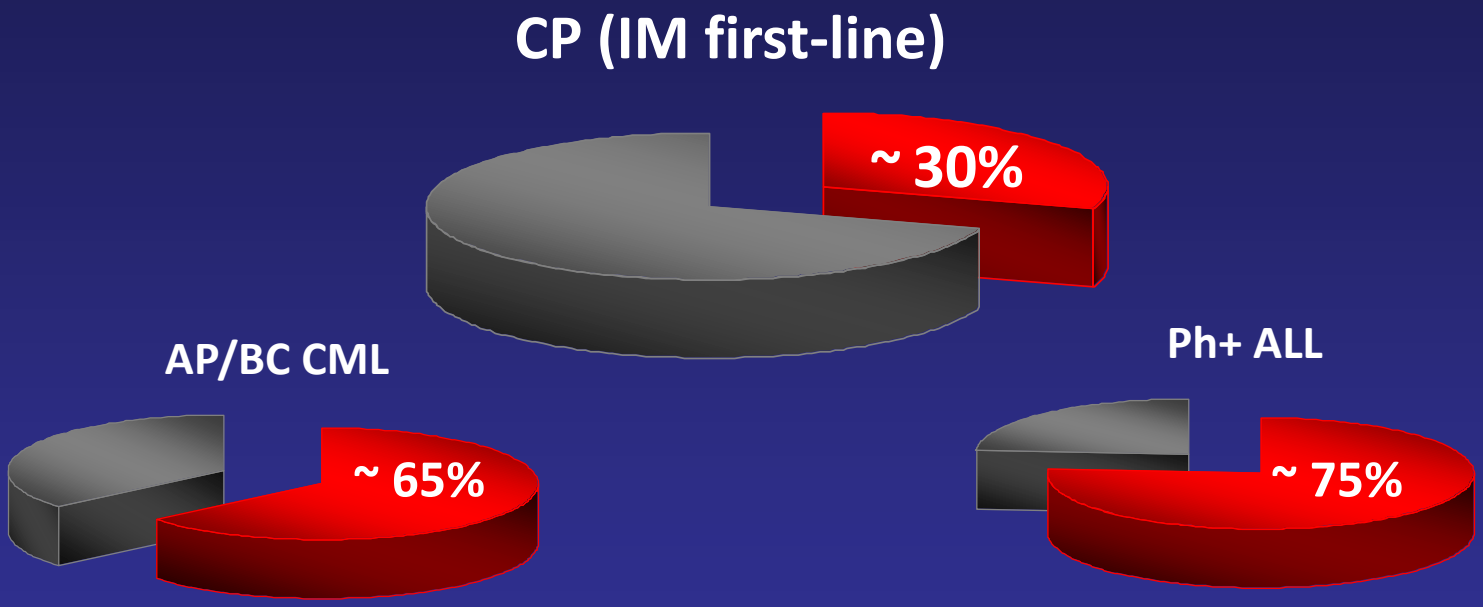
BUT THE RISK OF “HIGH RISK” PATIENTS IS NOT SO HIGH: THE DIFFERENCE BETWEEN LOW AND HIGH RISK PATIENTS IS SMALL

AND NO SCORE HELPS UNDERSTANDING WHY RESPONSE AND SURVIVAL ARE DIFFERENT, AND WHICH TREATMENT COULD IMPROVE RESPONSE AND SURVIVAL

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.

Abl mutations incidence varies greatly by disease phase..



Soverini et al, Blood 2011

IN VITRO SENSITIVITY (IC 50) TO TKIs OF THE 10 MORE FREQUENT ABL MUTATIONS FOUND IN CML CP, AND PLASMA CONCENTRATION OF THE TKIs AT STANDARD DOSE – VALUES ARE nM (Baccarani et al, JCO 2009;27:6041-6051, and BLOOD 2013;122(6):872-884)

MUTATION	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB	PONATINIB
M244V	1600-3100	38-39	1.3	147	2.2
G250E	1350-9000	48-219	1.8-8.1	179	4.1
Y253K	6000-9000	450-1300	1.3-10	NA	6.2
E255K/V	3000-9000	118-556	5.6-13	394	14
T315I	6000-9000	700-9000	137-900	1900	11
F317L	800-7500	39-91	7.4-18	101	1.1
M351T	900-5000	8-38	1.1-1.6	29	1.5
F359V	1400-1800	91-175	2.2-2.7	38.6	10
L384M	674-2800	39-41	4	19.5	NA
H396R	1750-5400	41-55	1.3-3	33.7	NA
Cmin	**2062**	**1923**	**5.5**	**392**	**113**
Cmax	**4402**	**2329**	**133**	**268**	**256**

Mutations detectable by conventional sequencing: the tip of the iceberg

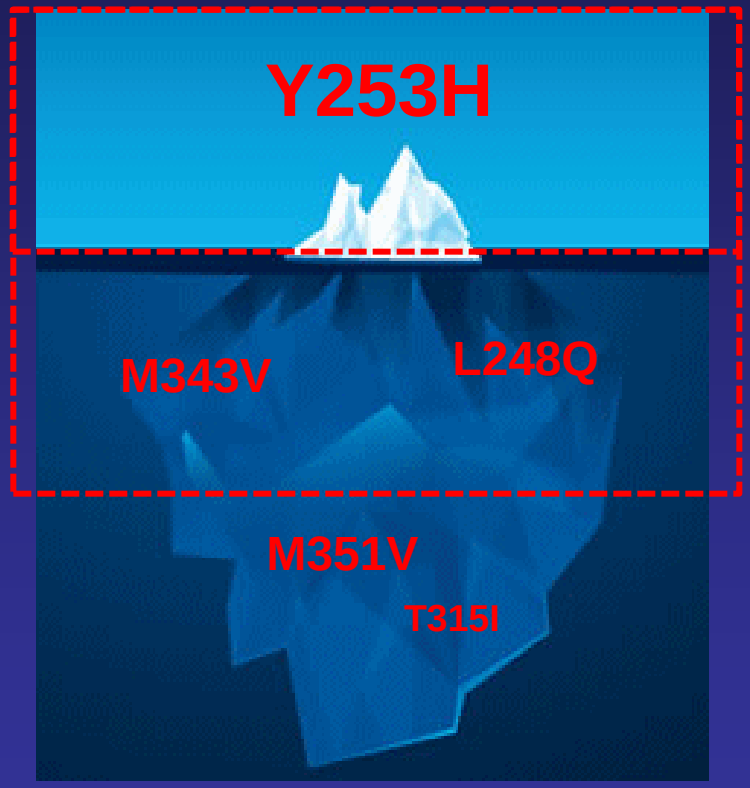
Conventional Sequencing

(20%)

NGS

(1%)

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



IC 50 (BIOCHEMICAL ASSAY, nM) FOR BCR-ABL1 (unmutated) AND FOR SOME "OFF-TARGET" TYROSINE KINASES

	BCR-ABL1	PDGFRα	cKit	Src	VEGFR2	BTK
IMATINIB	**678**	**72**	**99**	1000	10000	10000
NILOTINIB	**25**	**75**	209	1000	3720	10000
DASATINIB	**1.8**	**2.9**	**18**	**0.1**	10000	**1.1**
BOSUTINIB	**42**	**3.0**	10000	**3.0**	10000	**2.5**
PONATINIB	**0.5**	**1.1**	**1.2**	**5.4**	**1.5**	849

Data from Baccarani M et al, Blood 2013;122(6):872-884

TKIs for CML Therapy

	Main Adverse Events	Main Complications
Imatinib	Fatigue Myalgia Fluid retention	None ?
Dasatinib	Hematologic toxicity Pleural effusion	Pulmonary hypertension Infections ?
Nilotinib	Skin rash Glucose and lipid metabolism Bilirubin and lipase elevation	Arterial thrombosis
Bosutinib	Diarrhea Nausea Liver (AS T/ALT)	None ?
Ponatinib	Hematologic toxicity Skin rash Arterial hypertension	Arterial and venous thrombosis Pancreatitis

TWO HOT POINTS

FIRST-LINE : **WHICH TKI?**

IMATINIB or DASATINIB or NILOTINIB ?

SECOND-LINE : **WHEN ?**

ONLY IN CASE OF FAILURE ?

ALSO IN CASE OF WARNING or NON-OPTIMAL RESPONSE ?

EARLY SWITCH OR LATE SWITCH ?

WHICH TKI ?

2nd GENERATION TKIs vs. IMATINIB, FRONTLINE ENESTnd + DASISION, 4 years data

	NILO+DAS	vs.	IMATINIB	P
No. of pts	540	vs.	541	
Still on treatment	66%	vs.	61%	0.07
3-mo BCR-ABL ≤ 10%	80%	vs.	62%	<0.001
Cum. prob. of MMR	75%	vs.	58%	<0.001
Cum. prob of MR 4.5	40%	vs.	29%	<0.001
"Progression" (@)	6.8%	vs.	7.6%	
"PFS"	**91%**	vs.	**91%**	
AP/BP (transformation)	3.9%	vs.	7.4%	0.04
Death	6.3%	vs.	7.4%	
Overall survival	**93%**	vs.	**92%**	

Note: Data from different studies, please interpret with care.

@ ENESTnd: AP, BP, death due to any cause at any time
DASISION: rising WBC count, loss of CHR, loss of MCyR, CCA/Ph+, AP, BP

Hochhaus A et al, ASH 2013,
Hughes T. et al, Blood 2014, in press
Cortes J. et al, ASH 2013, Abstract 653,
Jabbour et al, Blood 2013;
Saglio G, ASH 2013.

FRONTLINE TREATMENT

IMATINIB or SECOND GENERATION TKIs ?

TWO PROSPECTIVE RANDOMIZED STUDIES OF DASATINIB (DASISION)[1] AND NILOTINIB (ENESTnd)[2] vs STANDARD DOSE IMATINIB HAVE RESULTED IN MORE, FASTER AND DEEPER MOLECULAR RESPONSES, WITH ONLY A MARGINAL BENEFIT IN PROGRESSION-FREE SURVIVAL, AND NO BENEFIT IN OVERALL SURVIVAL

THE GOALS OF NEXT STUDIES ARE THE PROPORTION OF PATIENTS WHO ACHIEVE TREATMENT-FREE REMISSION, AND THE TIME TO TREATMENT-FREE REMISSION

[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

FRONTLINE TREATMENT

NILOTINIB

or **?**

DASATINIB

There are no studies comparing nilotinib and dasatinib

WARNING (SUBOPTIMAL RESPONSE): BCR-ABL10% AT 3 MONTHS AND THE EARLY SWITCH

SEVERAL STUDIES HAVE SHOWN THAT AN EARLY MOLECULAR RESPONSE IS ACHIEVED MORE WITH SECOND GENERATION TKIs AND THAT AN EARLY MOLECULAR RESPONSE PREDICTS A DEEPER MOLECULAR RESPONSE, AND ALSO A BETTER SURVIVAL

EARLY MOLECULAR RESPONSE

(BCR-ABL1 transcripts level ≤ 10% at 3 months)

Reference	imatinib	nilotinib	dasatinib	bosutinib
Marin et el, Hammersmith, JCO 2012	76%			
Hanfstein et al, German IV, Leukemia 2012	72%			
Marin et al, Spirit UK, Blood 2012			82%	
Brummendorf et al, BELA, ASH 2013	65%			86%
Jabbour et al, DASISION, Blood 2014	64%		84%	
Hughes et al, ENESTnd, Blood 2014	67%	91%		
Wang et al, ENESTchina, Blood 2015	67%	82%		
Hochhaus et al, ENEST1st, EHA 2015		97%		
Castagnetti et al, GIMEMA, EHA 2015		77%		
median	**67%**	**87%**	**83%**	**86%**

EARLY MOLECULAR RESPONSE – RELATIONSHIP BETWEEN THE BCR-ABL1 TRANSCRIPTS LEVEL AT 3 MONTHS AND THE OUTCOME

SIX STUDIES (HAMMERSMITH, GERMAN CML IV, MDANDERSON ENESTnd, DASISION, and BELA) HAVE REPORTED A SUPERIOR OUTCOME IN PATIENTS TREATED FIRSTLINE WITH IMATINIB, NILOTINIB, DASATINIB or BOSUTINIB AND ACHIEVED AN EARLY MOLECULAR RESPONSE (BCR-ABL1 ≤ 10% AT 3 MONTHS)

	PFS	OS
BCR-ABL1 ≤ 10%	**94% (93-98)**	**96% (85-99)**
BCR-ABL1 > 10%	**79% (57-87)**	**86% (57-95)**

Marin et al, JCO 2012;30:232-8; Hanfstein et al, Leukemia 2012;26:2096-2102; Jabbour et al, Blood 2013; Hughes et al, Blood 2013; Brummendorf et al, Blood 2012;120:ASH abst. 69; Jain et al, Blood 2013;121:4867-74

EARLY SWITCH FROM IMATINIB TO SECOND GENERATION TKIs: A HOT AND CONTROVERSIAL POINT

- **NCCN: SINCE EMR IS OBTAINED MORE WITH 2nd GENERATION TKIs FIRSTLINE, AN EARLY SWITCH FROM IMATINIB TO 2nd GENERATION TKIs MAY BE ALSO CONVENIENT**
- **ELN:THERE ARE NO STUDIES, NO DATA, SHOWING THAT SUCH SWITCH IS CONVENIENT, AND IF SO, HOW MUCH**

SOME CONCERNS

- THE SWITCH MAY BE USEFUL IN FEW PATIENTS ("SWITCH MANY TO BENEFIT FEW")
- LATE, "OFF-TARGET", COMPLICATIONS AND COST OF SECOND GENERATION TKIs
- ONE PCR TEST MAY NOT BE SUFFICIENT TO MANDATE A TREATMENT CHANGE

THE DYNAMICS OF EARLY MOLECULAR RESPONSE MAY BE MORE IMPORTANT THAN ONE MOLECULAR TEST AT 3 MONTHS

THE RELATIVE REDUCTION (MORE OR LESS THAN 0.35) OF BCR-ABL1 TRANSCRIPTS LEVEL

and

THE HALVING TIME (MORE OR LESS THAN 90 DAYS) OF BCR-ABL1 TRANSCRIPTS LEVEL

PREDICT THE OUTCOME MORE PRECISELY THAN A SINGLE ASSESSMENT OF BCR-ABL1 TRANSCRIPTS LEVEL AT 3 MONTH

Hanfstein B et al, ASH 2013 and LEUKEMIA 2014

Branford S et al, ASH 2013 and BLOOD 2014

SELECTING THE PATIENTS FOR EARLY SWITCH

THE ASSESSMENT OF THE DYNAMICS OF THE RESPONSE
WOULD REQUIRE AN EXTRA-CHARGE AND AN EXTRA-COST

WOULD SUCH A STRATEGY BE VALUABLE AND COST-EFFECTIVE ?

THERE ARE NO DATA, AS YET, SUPPORTING PROSPECTIVELY
THE CLINICAL PROGNOSTIC VALUE OF THE DYNAMICS
OF MOLECULAR RESPONSE

BASED ON A SINGLE TEST AT 3 MONTHS, **WE SWITCH MANY TO BENEFIT FEW**, BASED ON THE DYNAMICS OF THE RESPONSE **WE SWITCH ONLY THE FEW WHO NEED**

MOREOVER, PUTTING MONEY ON MONITORING WOULD SAVE MONEY FROM THERAPY

THE IMPORTANCE OF SECOND- AND THIRD-LINE TREATMENT

IN ALL STUDIES, **80% TO 90%** OF PATIENTS WERE REPORTED ALIVE AND PROGRESSION-FREE AT 5 YEARS OR MORE

IN ALL STUDIES, ONLY **50% TO 70%** OF PATIENTS WERE REPORTED TO CONTINUE THE FIRST-LINE TKI

SECOND- AND THIRD-LINE TREATMENT ARE VERY IMPORTANT FOR PREVENTING PROGRESSION AND FOR SURVIVAL

CHRONIC MYELOID LEUKEMIA: THE CHOICE OF SECOND-AND THIRD-LINE TREATMENT

ONLY SINGLE ARM STUDIES (VERY FEW IN THIRD LINE)

NO STUDIES COMPARING NILOTINIB, DASATINIB, BOSUTINIB AND PONATINIB

SELECT BY **MUTATIONS,** COMORBIDITIES, TOXICITY OF PRIOR TKI, COST, and EXPERIENCE

SECOND-LINE TREATMENT (SWITCH)

SOMETIMES IS DUE :

IN CASE OF FAILURE (ELN 2013)

IN CASE OF SEVERE ADVERSE EVENTS

SOMETIMES IS OPTIONAL:

IN CASE OF MILD, CHRONIC OR RECURRENT SIDE-EFFECTS

IN CASE OF NON OPTIMAL RESPONSE (EARLY and LATE SWITCH)

SWITCHING FOR “MILD” SIDE-EFFECTS

IN CASE OF MILD SIDE-EFFECTS, BOTH HEMATOLOGIC AND NON-HEMATOLOGIC, THE DECISION OF SWITCHING IS NOT ALWAYS STRAIGHTFORWARD

NUMBER: HOW MANY SIDE EFFECTS CAN BE TOLERATED ?

GRADE: HOW MUCH IS A SIDE-EFFECT TOLERABLE ?

DURATION: FOR HOW LONG CAN IT BE TOLERATED ?

RECURRENCE: FOR HOW MANY TIMES CAN IT BE TOLERATED ?

EFFICACY: DOES IT COMPROMISE DOSING AND ADHERENCE ?

TO “MANAGE” OR TO SWITCH ?

TREATMENT DISCONTINUATION
TREATMENT FREE-REMISSION
"CURE"

IS IT POSSIBLE ? **Yes**

WHEN ? **After several years of therapy**

IN WHICH PATIENTS ? **Patients in deep molecular response**

IS IT SUCCESSFUL ? **In about 50% of patients**

IS IT SAFE ? **Yes**

HOW MANY PATIENTS ARE ELIGIBLE FOR A TRIAL OF TREATMENT DISCONTINUATION ?

WITH IMATINIB ALONE **15-30%**

WITH 2nd GENERATION TKIs **30-60%**

WITH IMATINIB AND SWITCH TO 2nd GEN TKIs IN CASE OF NON-OPTIMAL RESPONSE **???**

IF THE MOLECULAR RELAPSE RATE IS ABOUT 50%, 7.5% TO 30% OF ALL PATIENTS WILL ACHIEVE TFR

WHAT ABOUT THE OTHER PATIENTS ?

PERSPECTIVES IN THE TREATMENT OF CHRONIC MYELOID LEUKEMIA

- TYROSINE KINASE INHIBITORS AND INTERFERONα
- NEW TYROSINE KINASE INHIBITORS

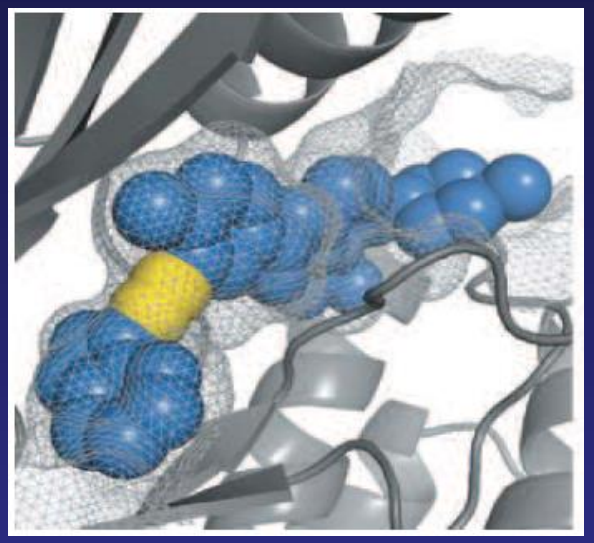
BEYOND TKIs

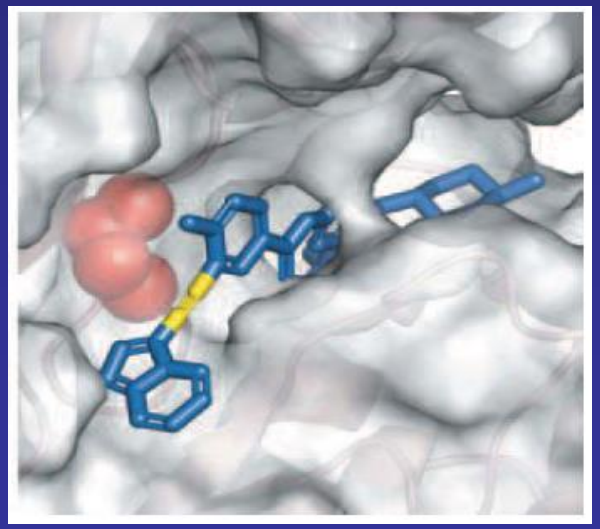
- DRUGS TARGETING OTHER PATHWAYS
- DRUGS TARGETING BCR-ABL1+ STEM CELLS
- DRUGS INHIBITING AUTOPHAGY
- VACCINES
- ANTIBODIES
- CHECK POINT INHIBITORS
- CHIMERIC ANTIGEN RECEPTOR MODIFIED T CELLS

- 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**



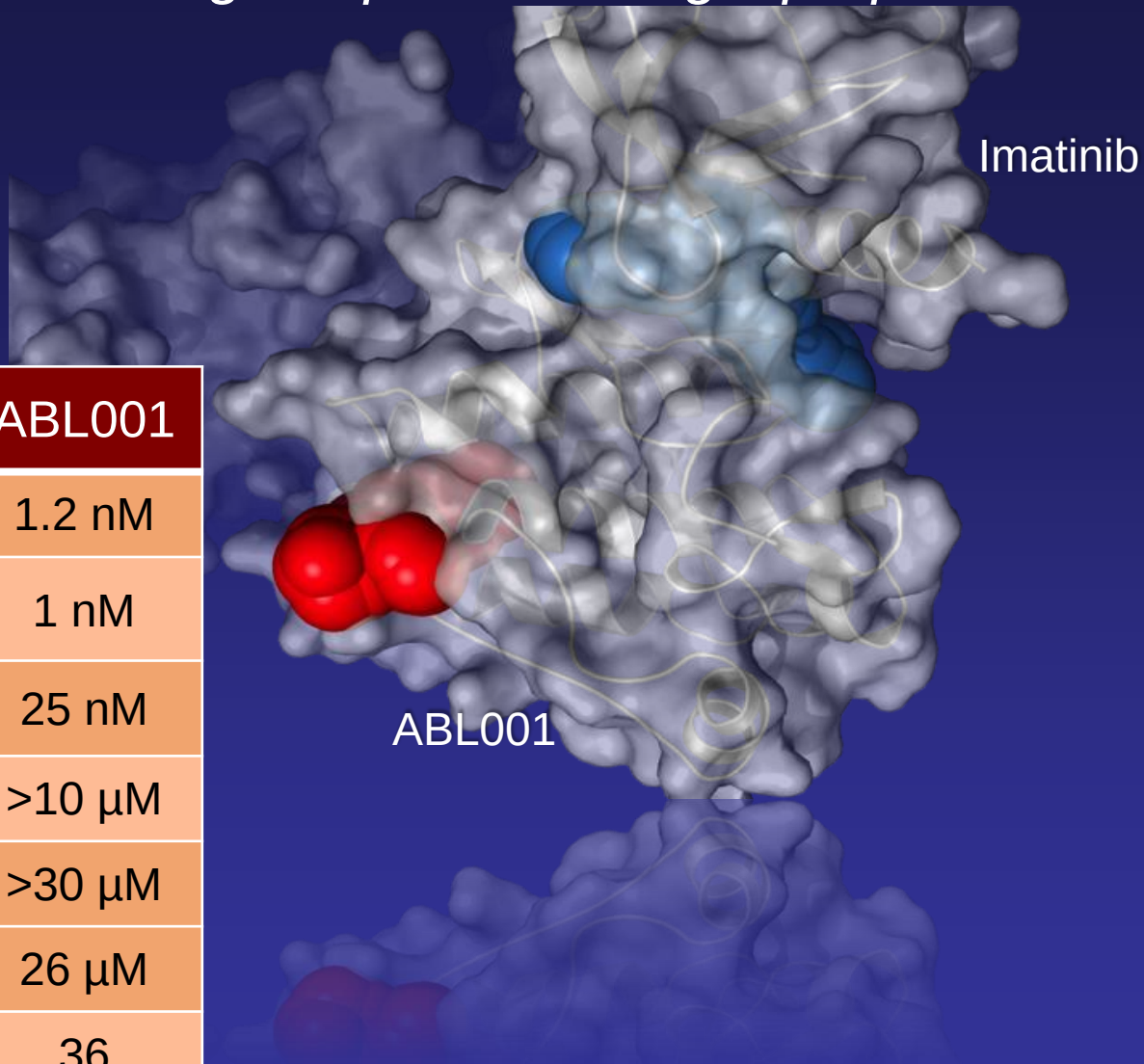


O'Hare T, et al. Cancer Cell. 2009;16:401-412

ABL001

Potent allosteric inhibitor with good pharmacologic properties

Assay	ABL001
Biochemical IC_{50}, ABL^{WT}	1.2 nM
Cellular IC_{50} BCR-ABL^{WT}	1 nM
Cellular IC_{50} BCR-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



Check point inhibitors in CML

- A combination of check point inhibitors and TKI is likely to be safe
- An interesting combination to be tested in case of failure
- Check point inhibitors could also increase TFR rates

CML IN THE 21st CENTURY

MORE KNOWLEDGE, MORE AND BETTER

DRUGS, MORE AND BETTER TECHNOLOGY

…….AND DEDICATED PEOPLE


PORTINERIA