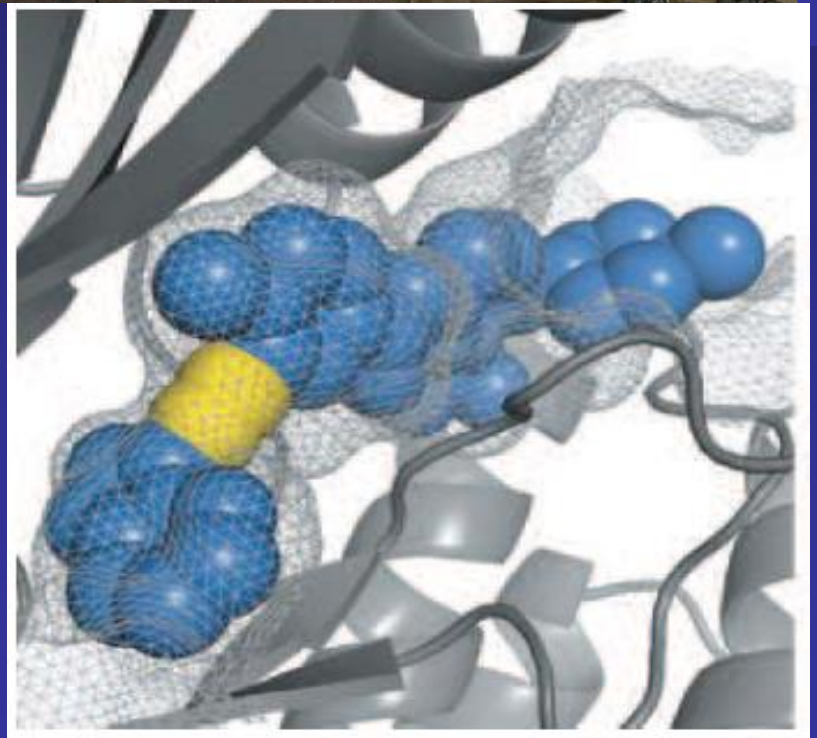
NEW DRUGS IN HEMATOLOGY

Bologna 1-3 October 2018

SESSION VIII: CHRONIC MYELOID LEUKEMIA

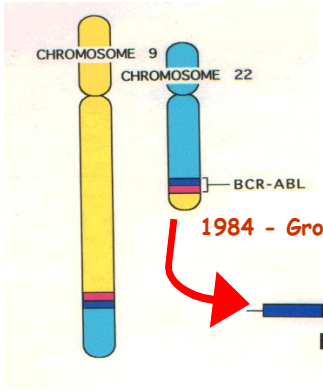
PONATINIB

Michele.Baccarani@unibo.it



MILESTONES IN MOLECULAR BIOLOGY OF CML

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

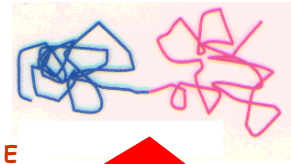


1984 - Groffen J. et al.

1985- Shtivelman E

1984 - Konopka J.B. et al.

Protein BCR-ABL



Consequence: new BCR-ABL fusion proteins with a constitutive TK activity

Michele BACCARANI, MD

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

Chairman, CML Working Parties of European LeukemiaNet and GIMEMA

DISCLOSURES

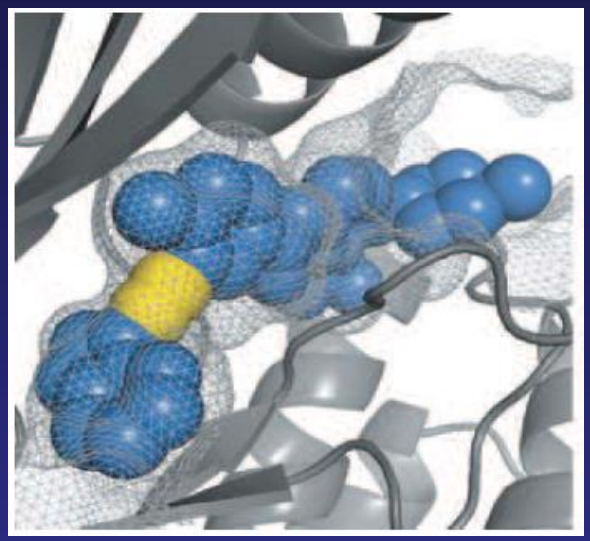
Consultant and speaker, receiving honoraria, from

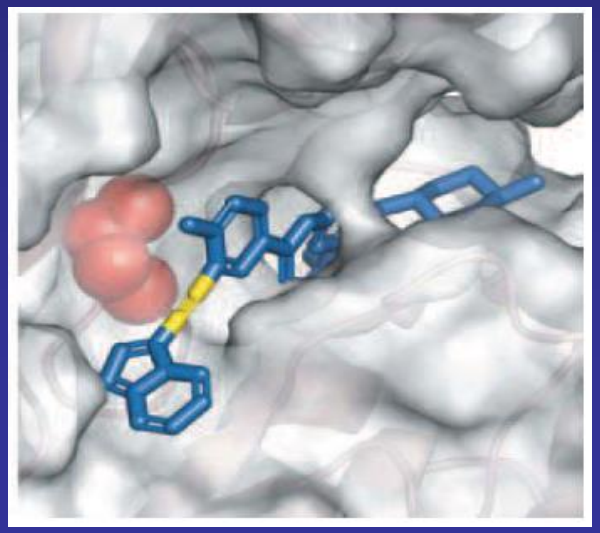
ARIAD/INCYTE

NOVARTIS

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

Phase 1 Study of Ponatinib
Cortes J et al, ASH 2010, Abstract 210 , conclusions

- **Ponatinib has an acceptable safety profile at therapeutic dose levels……..**
- **Clinical evidence of anti-leukemic activity…….**
  - **CML CP: 66% MCyR, 53% CCyR, 42% MMR**
  - **CP with T315I: 100% MCyR, 89% CCyR, 78% MMR**

Phase 2 Study of Ponatinib (PACE)

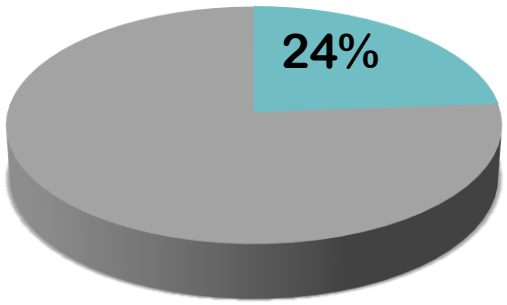
Cortes J et al, ASH 2011, Abstract 109, conclusions

IN THIS FIRST ANALYSIS OF THE PIVOTAL PACE TRIAL, PONATINIB HAS A FAVOURABLE EARLY SAFETY PROFILE….

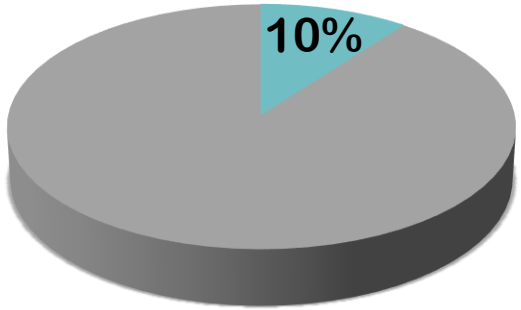
INITIAL RESPONSE DATA AFTER SHORT FOLLOW-UP INDICATE PONATINIB HAS SUBSTANTIAL ANTILEUKEMIC ACTIVITY IN THIS HEAVILY PRETREATED POPULATION, AND IN PATIENTS WITH REFRACTORY T315I

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

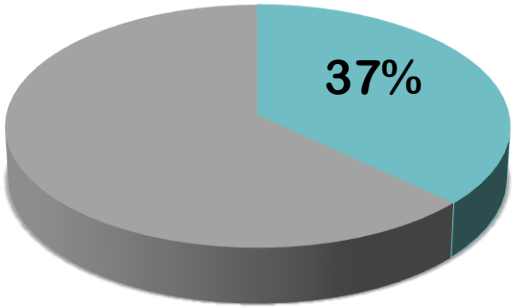
FAILURES, 1st line



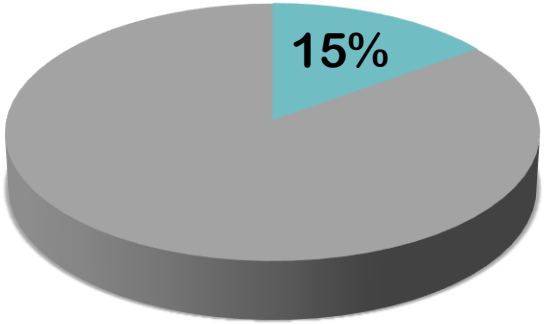
WARNINGS, 1st line



FAILURES, 2nd line



WARNINGS, 2nd line



Pts positive for BCR-ABL mutations:

- by conventional sequencing

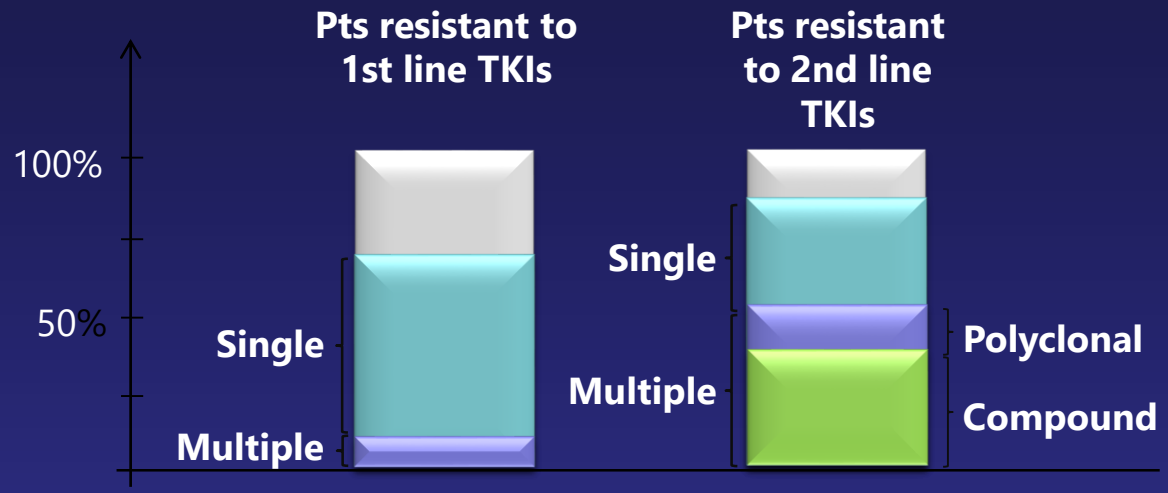
Soverini ASH 2015

IN VITRO SENSITIVITY (IC 50) TO TKIs OF THE 10 MORE FREQUENT ABL KD MUTATIONS, and PLASMA CONCENTRATION OF THE TKIs. ALL VALUES ARE nM

MUTATION	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB	**PONATINIB**
M244V	1600-3100	38-39	1.3	147.4	2.2
G250E	1350-20000	48-219	1.8-8.1	179.2	4.1
Y253K	6000-18000	450-1300	1.3-10	NA	6.2
E255K/V	3000-12000	118-566	5.6-13	394	14
T315I	6000-20000	700-10000	137-1000	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
L384 M	674-2800	39-41	4	19.5	NA
H396R	1750-5400	41-55	1.3-3	33.7	NA
Cmin	2062±1334	1923±1233	5.5±1.4	392	113± 51
Cmax	4402±1272	2329±772	133±74	268	256±128

Baccarani M et al, JCO 2009;27:6041-6051, and BLOOD 2013;122(6):872-884

BCR-ABL KD mutations in Ph+ ALL



- High likelihood to acquire TKI-resistant mutations
- High incidence of T315I
- High frequency of highly resistant compound mutants in patients who fail ≥2L of TKI therapy

	Mutations in IM-res Ph+ ALL pts (n=189)	N and % of mutated pts
1°	T315I	49 (37.4%)
2°	E255K	25 (18.3%)
3°	Y253H	25 (18.3%)
4°	F359V	6 (4.6%)
5°	G250E	6 (4.6%)
6°	L387M	5 (3.8%)
7°	M244V	5 (3.8%)
8°	M351T	5 (3.8%)
9°	F317L	5 (3.8%)
10°	Q252H	4 (3.1%)

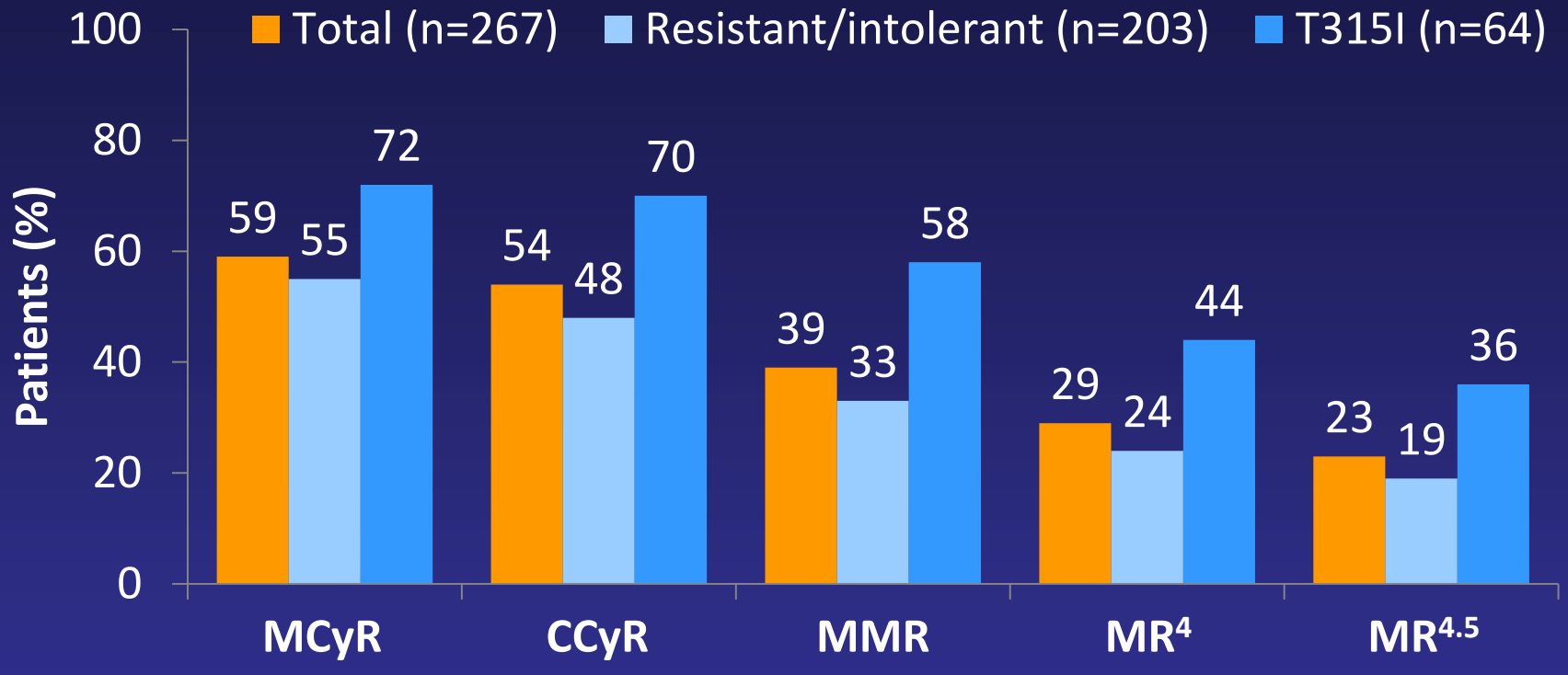
65% in 2nd line TKI-res pts

Importance of BCR-ABL KD sequence surveillance for timely detection of emerging mutations

Soverini et al, Cancer 2014

Five-year results of the ponatinib phase II PACE trial in heavily pretreated CP-CML patients

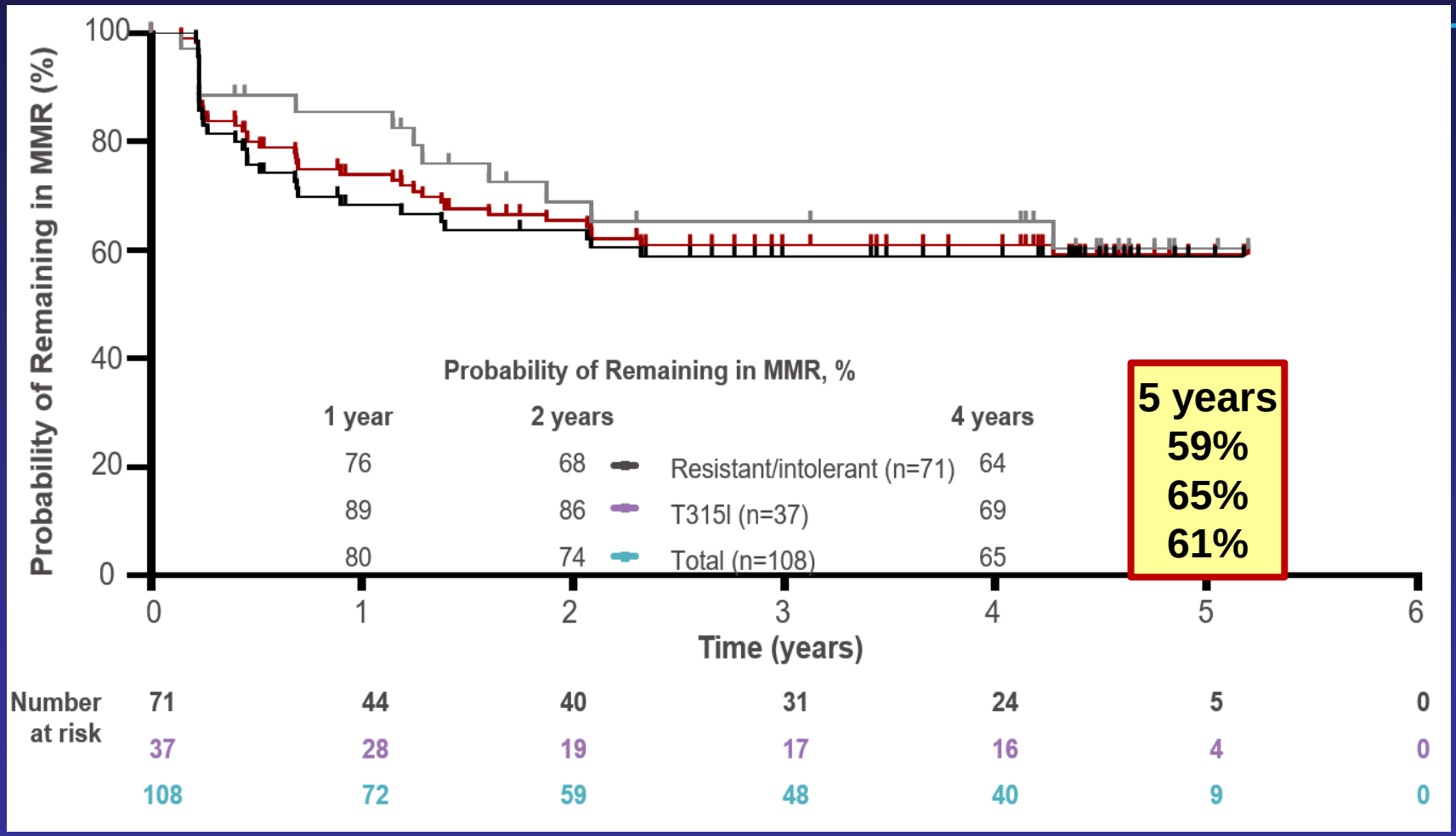
PACE: Response at Any Time in Patients With CP-CML



Response at any time in advanced phase leukemia:

- AP-CML (n=83): MaHR was achieved in 61% of patients, CCyR in 31% and and MMR in 22%
- BP-CML/Ph+ ALL (n=94): MaHR was achieved in 34% of patients, CCyR in 25% and MMR in 12%

PACE: Estimated Duration of MMR

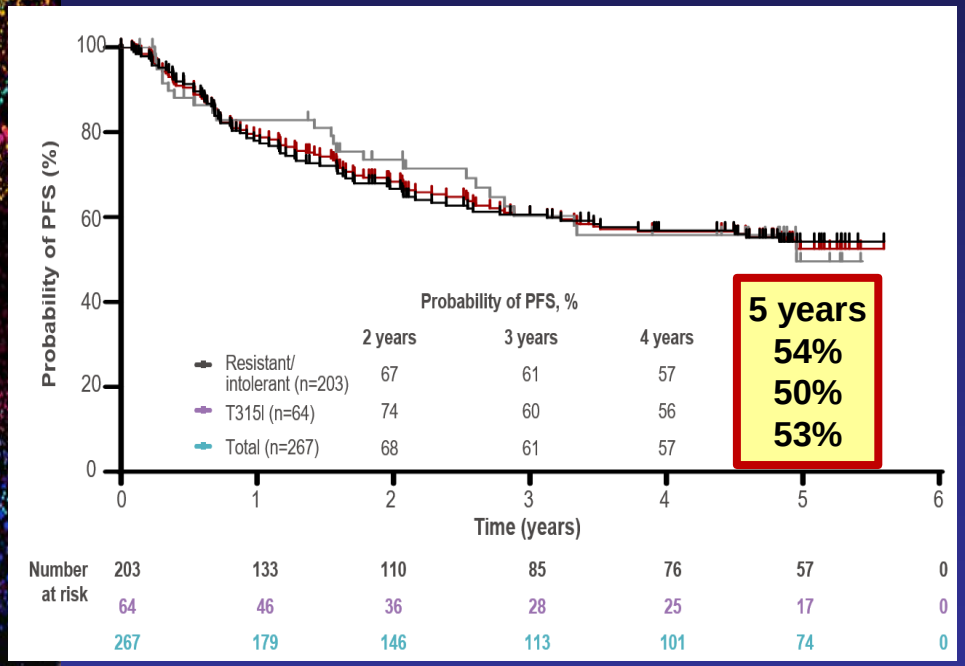


Datacut: February 6, 2017

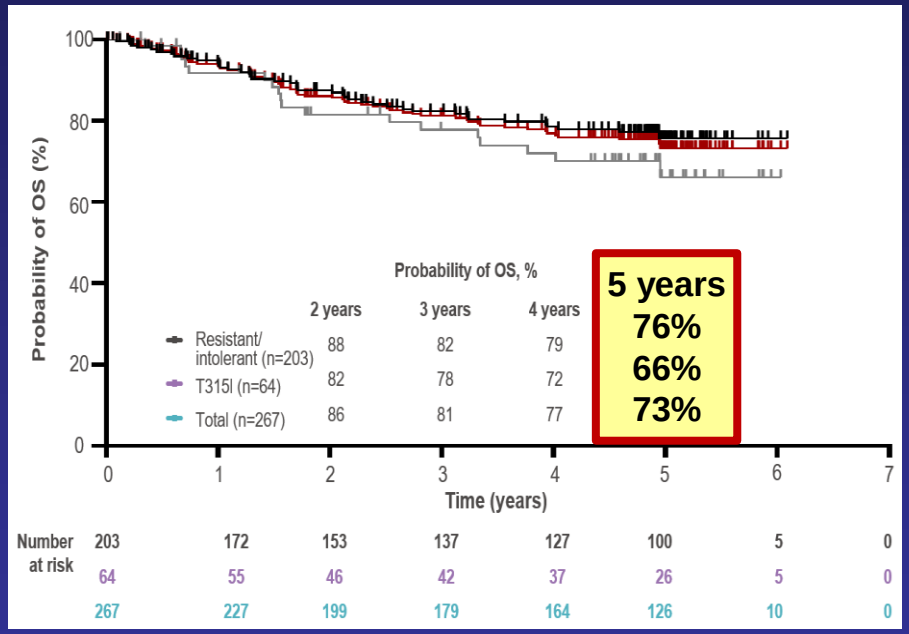
Kantarjian et al. ASCO 2017 Poster 7012

PACE: Estimated PFS and OS

Progression Free Survival



Overall Survival

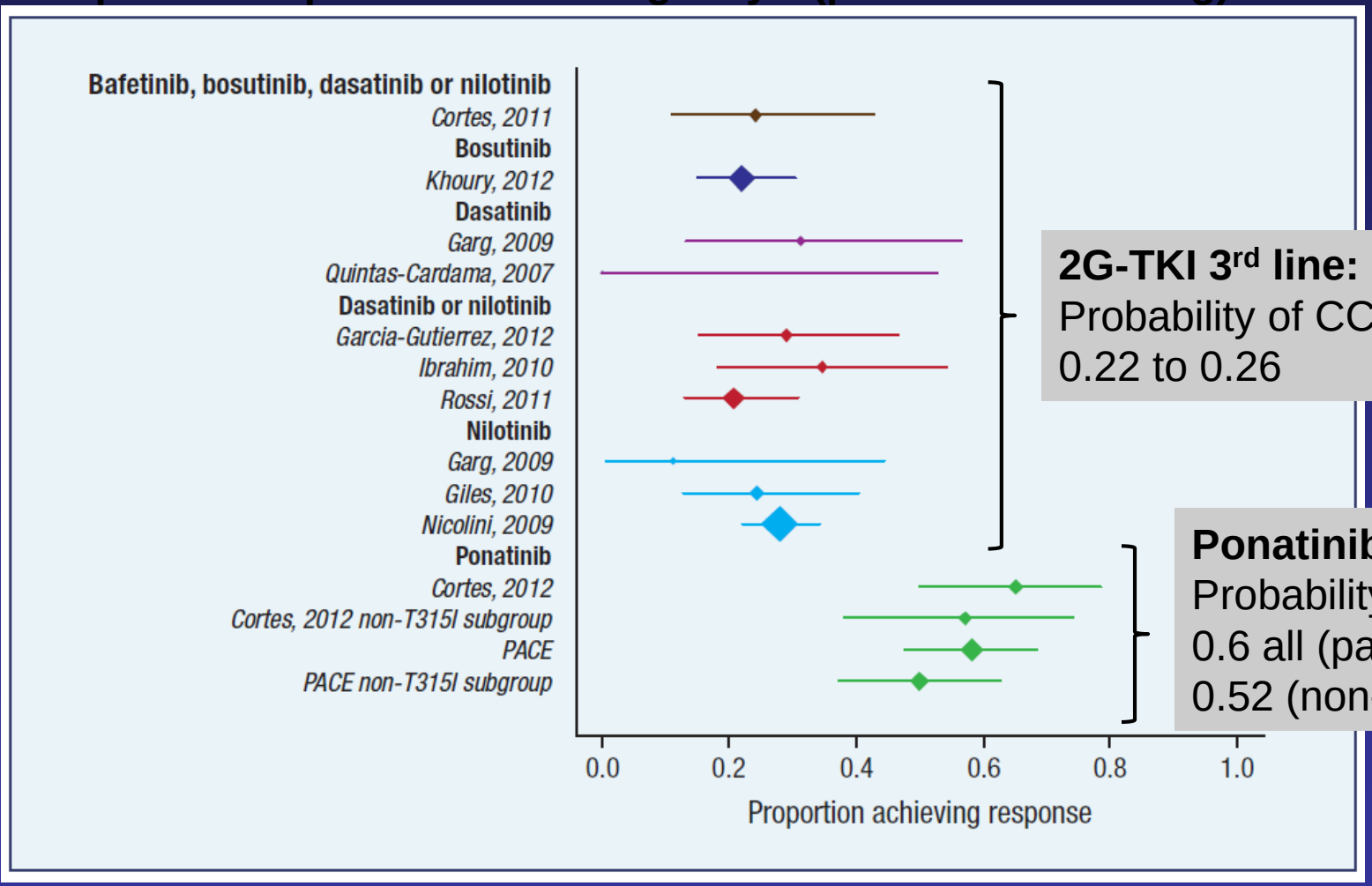


Datacut: February 6, 2017

Kantarjian et al. ASCO 2017 Poster 7012

Responses to 3rd line therapy after resistance or intolerance to 2nd generation TKI

Proportion of patients achieving CCyR (post 2G-TKI setting)



Lipton JH, et al. Blood. 2013;122:[abstract 4010].

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

SINGLE ARM STUDIES (VERY FEW IN THIRD LINE)

NO STUDIES COMPARING NILOTINIB, DASATINIB, BOSUTINIB AND PONATINIB. ONLY ONE STUDY COMPARING HIGH DOSE IMATINIB vs DASATINIB

PONATINIB IN 3rd AND 4th LINE IS AS EFFECTIVE AS NILOTINIB, DASATINIB AND BOSUTINIB IN 2nd LINE@

@

PONATINIB DOSE

IIN THE PHASE 1 STUDY, A DOSE OF 45 mg ONCE DAILY WAS FOUND TO BE VERY EFFECTIVE AND TOLERATED

AT THAT DOSE, THE PLASMA CONCENTRATION **(40 nM)** OF PONATINIB WAS SUFFICIENT TO CONTROL THE DEVELOPMENT OF ANY MUTATION

A DOSE OF 45 mg ONCE DAILY WAS SELECTED FOR THE PHASE 2 «PACE» STUDY

AND ALSO FOR THE PHASE 3 «EPIC» STUDY

BUT, WITH A LONGER FOLLOW-UP OF THE PHASE 2 «EPIC» STUDY……..

PACE study 4-year results: cumulative and exposure-adjusted incidences of AOEs and VTEs*

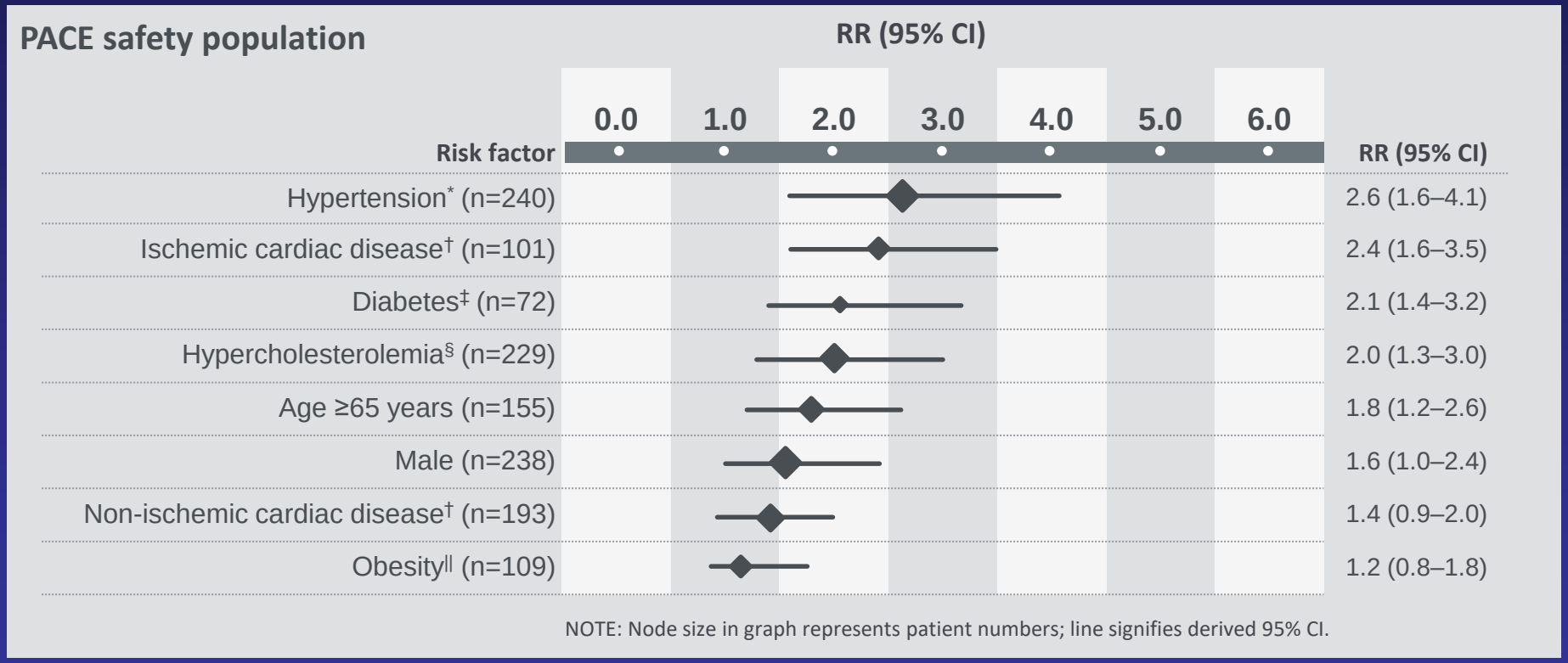
	CP-CML n=270	
	All grades	SAEs
AOEs, n (%):	**77 (29)[a]**	**63 (23)[b]**
Cardiovascular	39 (14)	30 (11)
Cerebrovascular	33 (12)	26 (10)
Peripheral vascular	31 (11)	25 (9)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.2	10.9
VTEs	**13 (5)**	**12 (4)**
Exposure-adjusted VTEs, no. of patients with events per 100 patient-years	2.0	1.8

*Categorization of AOEs and VTEs is based on a broad collection of >400 MedDRA preferred terms related to vascular ischemia or thrombosis;
[a]41 patients had >1 AOE; [b]25 patients had >1 serious AOE; [c]51 patients had >1 AOE; [d]32 patients had >1 serious AOE.
SAEs=serious adverse events

Cortes et al. J Clin Oncol 34, 2016 (suppl; abstr 7013).

PACE study 4-year results: baseline risk factors for the development of serious AOEs

Relative risk of serious AOEs by risk category – univariate analysis



*Includes medical history, prior concomitant medication, and/or baseline blood pressure gr ≥2. †Includes medical history and/or prior concomitant medication. ‡Includes medical history, prior concomitant medication, and/or baseline glucose gr ≥2. §Includes medical history, prior concomitant medication, and/or baseline triglycerides gr ≥1. ‖Includes medical history and/or baseline BMI ≥30 kg/m^2.

Cortes et al. PACE 4-year results. Ariad.

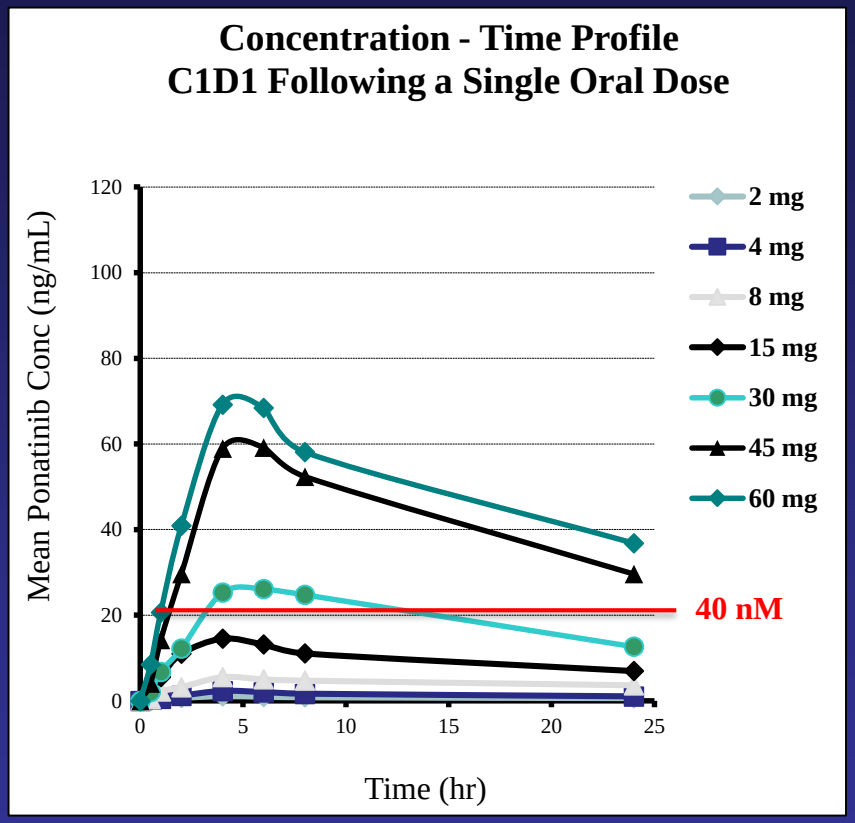
THE AVERAGE CML PATIENT IN EUROPE

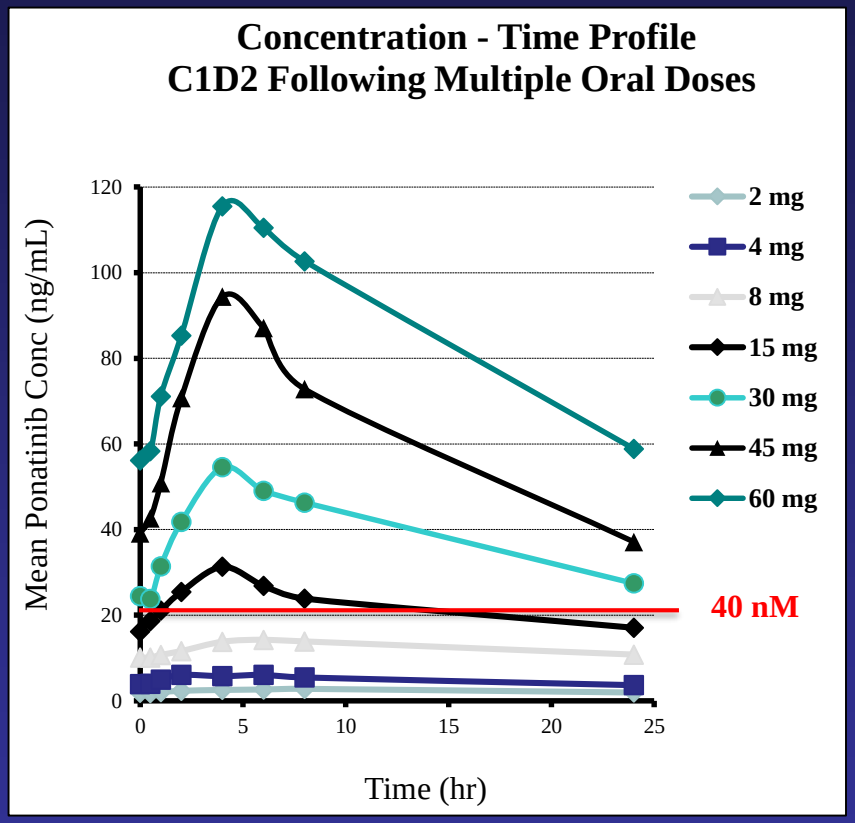
MALE GENDER	54%		
MEDIAN AGE	56 years	≥ 70 years old	22%
HIGH RISK (Sokal)	25%		
WITH COMORBIDITIES	55%		

- Hypertension 26%
- Cardiovascular disorders 17%
- Diabetes mellitus 10%
- Smoking 20%

Hoffmann V, Baccarani M, Hasford J, et al. The EUTOS population-based registry: incidence and clinical characteristics of 2094 CML patients in 20 European countries. Leukemia 2015;29(6):1336-1343.

But a plasma concentration of 40 nM is achieved already at a dose of 30 mg

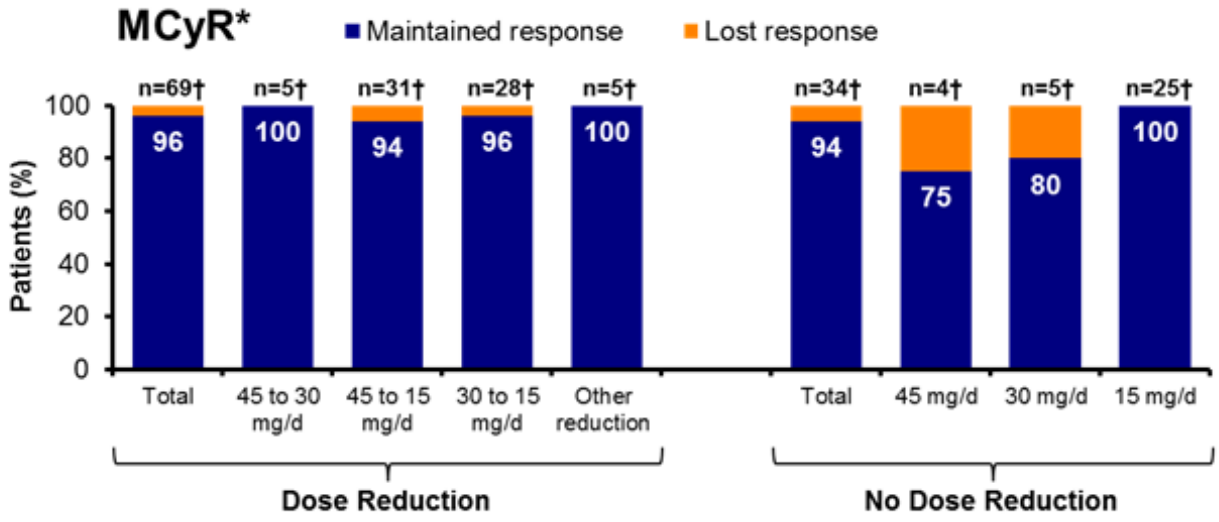


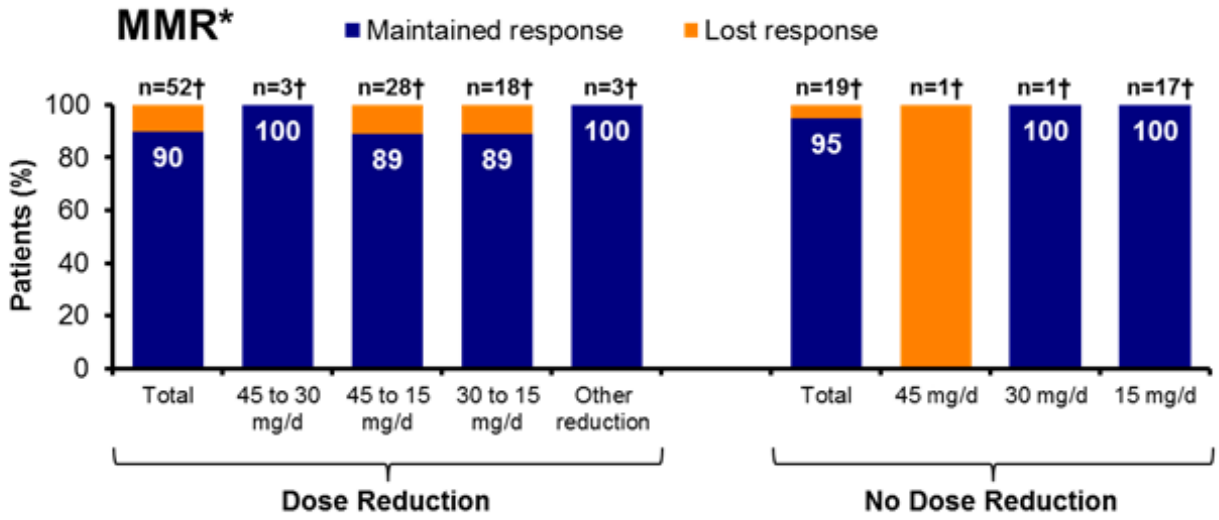


At doses ≥ 30 mg

- Trough plasma concentrations surpass 40 nM level target

IN THE PACE STUDY, REDUCING THE INITIAL DOSE FROM 45 TO 30 or 15 DID NOT RESULT IN A LOSS OF THE RESPONSE THAT WAS ACHIEVED WITH 45 mg



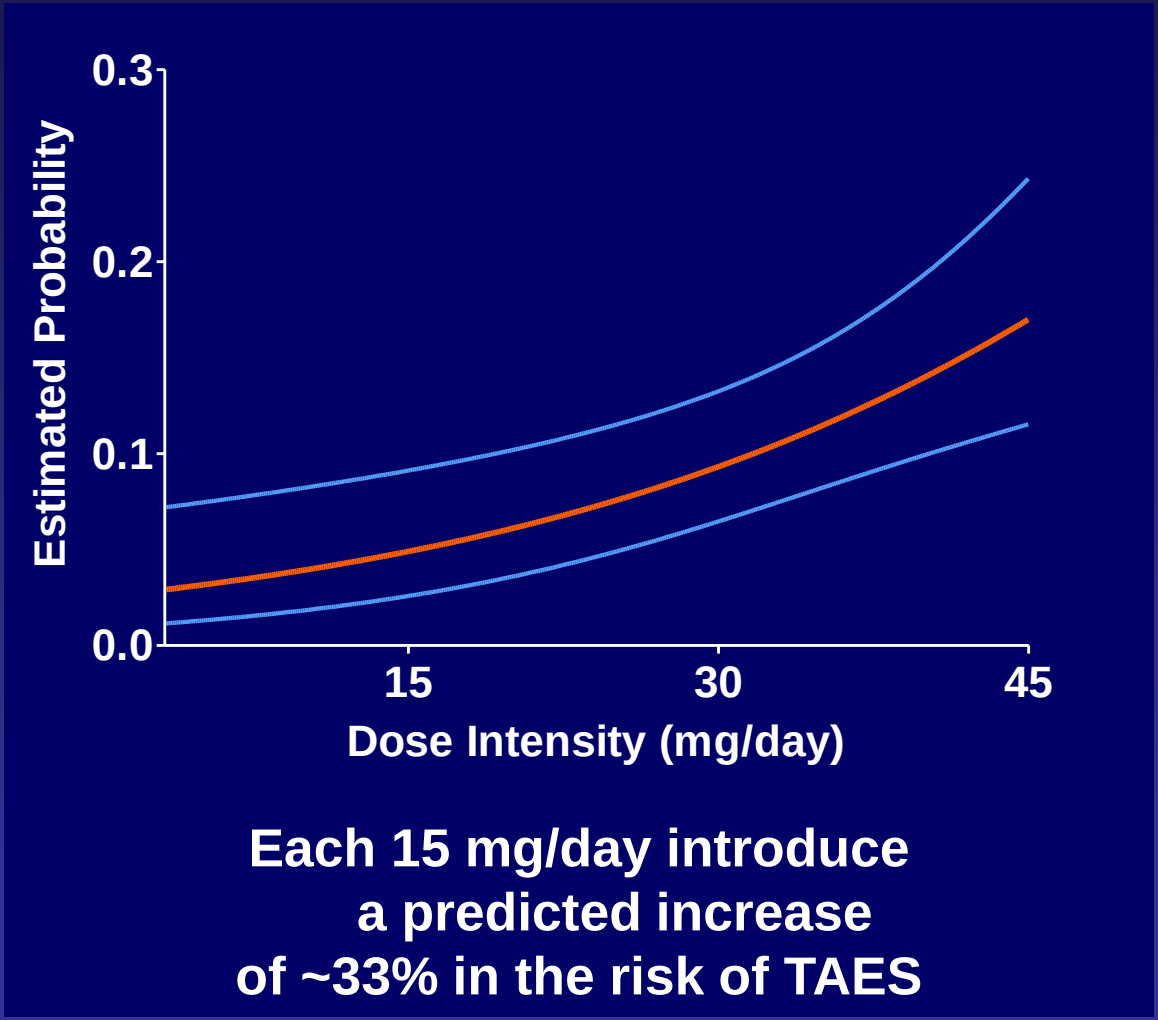


*Response maintained as of last response assessment.

†Number of patients with response as of October 10, 2013.

PACE Study, Cortes J et al, Blood 2018

THERE IS A RELATIONSHIP BETWEEN PONATINIB DOSE AND CARDIOVASCULAR TOICITY



Cortes et al., ASH 2013

PONATINIB DOSE

THE INITIAL DOSE OF 45 mg MUST BE DECREASED TO 30 AND ALSO 15 mg IN CASE OF TOXICITY

THE MEDIAN TIME TO MMR IS ABOUT 6 MONTHS, THE MEDIAN TIME TO THE FIRST CV EVENT IS ABOUT 15 MONTHS

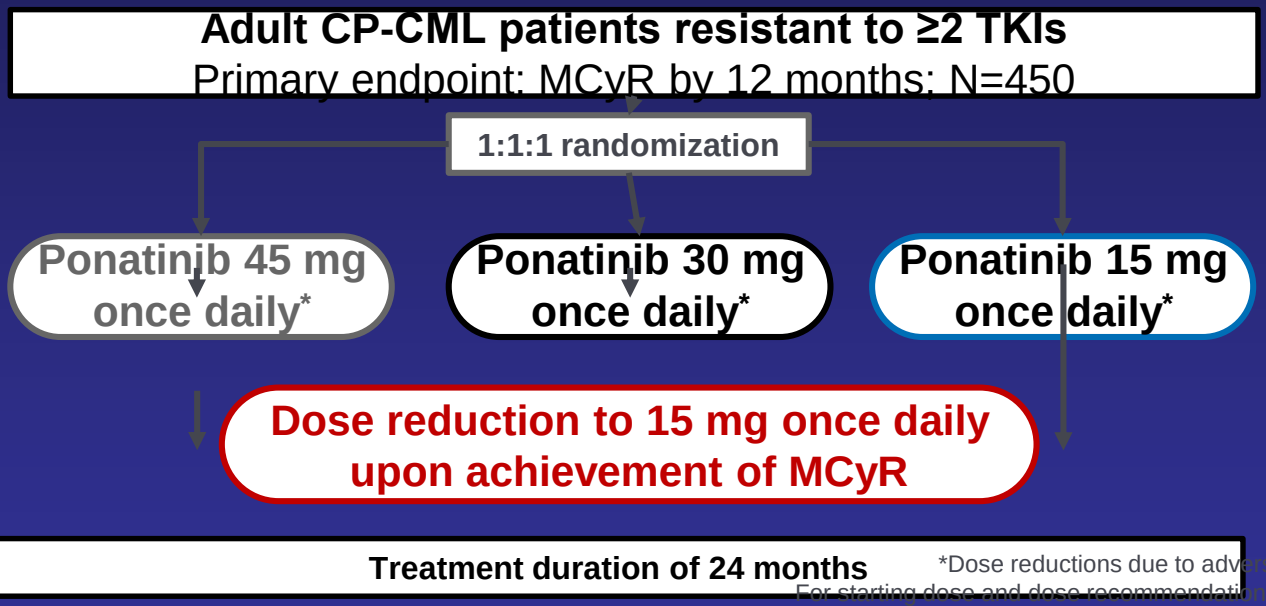
ADJUSTING PONATINIB DOSE WITHIN 6 MONTHS HELPS REDUCING TOXICITY

PONATINIB DOSE CAN BE DECREASED TO 30 AND ALSO TO 15 mg IN CASE OF OPTIMAL RESPONSE (CCyR or MMR)

BUT MORE DATA ON PONATINIB DOSE AND DOSE ADJUSTMENT ARE CRITICAL FOR THE DEVELOPMENT OF THE DRUG.

Optimizing ponatinib treatment in CML (OPTIC): dose-ranging study

An international randomized phase 2 trial to characterize the efficacy and safety of a range of ponatinib doses



CML, chronic myeloid leukemia; CP, chronic phase;
MCyR, major cytogenetic response; TKI, tyrosine kinase inhibitor.

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.

Working Party Leucemia Mieloide Cronica

OPUS Trial

Optimizing **P**onatinib **US**e A GIMEMA phase 2 study of the efficacy and risk profile of ponatinib, 30 mg once daily, in Chronic Myeloid Leukemia (CML) Chronic Phase (CP) patients resistant to imatinib

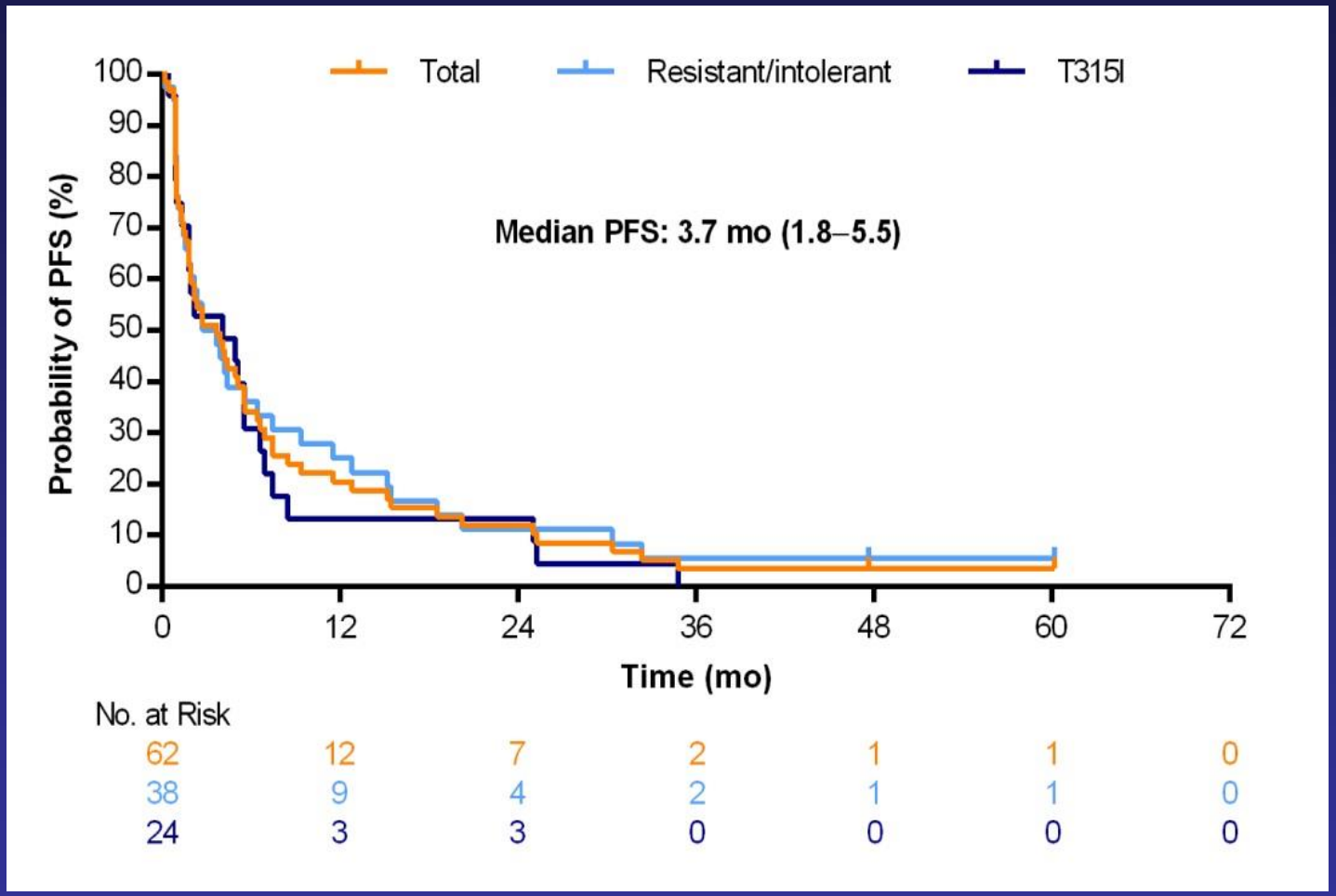
BACK UP

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

(E) BP-CML: Progression-free survival*



*Progression from BP was defined as death, or increasing blasts in peripheral blood or bone marrow over a 4-week period.

PACE Study, Cortes J et al, Blood 2018

PONATINIB, A SHORT JOURNEY FROM DESK TO BED

2009 AP24534, a pan-BCR-ABL inhibitor for CML, potently inhibits the T315I mutant and overcomes mutation based resistance
O'Hare et al Cancer Cell 2009;16:401-412

2010 A phase 1 trial of oral Ponatinib (AP24534) in patients with refractory CML and other hematologic malignancies: emerging safety and clinical response findings. Cortes J et al, ASH 2010, abstract 210

2012 Ponatinib in refractory Philadelphia chromosome-positive leukemias
Cortes J et al, NEJM 2012;367:2075-2088

2012 A pivotal phase 2 trial of Ponatinib in patients with CML and Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation: 12-month follow-up of the PACE trial
Cortes J et al, ASH 2012, abstract 163

2013 A phase 2 trial of Ponatinib in Philadelphia chromosome-positive leukemias
Cortes JE et al, NEJM 2013;369:1783-1796

PONATINIB : A LONG CLINICAL JOURNEY

2012 December 14, FDA accelerated approval of Iclusig (Ponatinib) for patients with CML and Ph+ ALL resistant or intolerant o prior tyrosine kinase inhibitor therapy

2013 January, EMA approval of Iclusig for patients with CP CML resistant or intolerant to dasatinib or nilotinib, for whom subsequent treatment with imatinib is clinically inappropriate; or with the T315I mutation

2013 October 10, EPIC study prematurely terminated
2013 October 30, FDA requests to suspend marketing of Iclusig
2013 December 6 and 20, EMA and FDA require new safety measures to address the risk of life-threatening vascular adverse events

2014 January 2, ARIAD resumes marketing Iclusig,

2014 on Dose adaptation studies

THE REGISTERED (APPROVED) DOSE OF TKIs

DRUG	APPROVED/RECOMMENDED DOSE		
	INITIAL	“MAXIMAL”	“MINIMAL”
GLIVEC	400 x 1	400 x 2	300 x 1
SPRYCEL	100 x 1	140 x 1	50 x 1
TASIGNA	300 x 2	400 x 2	400 x 1
BOSULIF	500 x 1	600 x 1	400 x 1
ICLUSIG	45 x 1	45 x 1	15 x 1

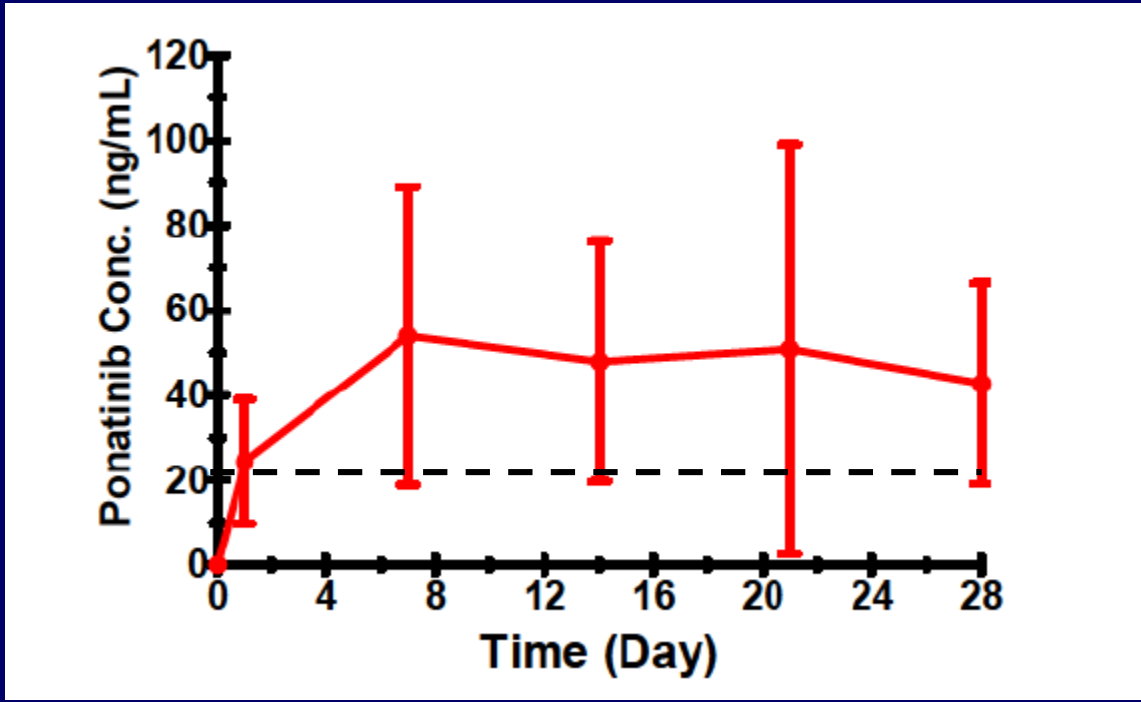
HAS THE RECOMMENDATION OF A DOSE ANY SENSE?
YES, TO ENSURE EFFICAY AND TO PROTECT FROM TOXICITY

USUALLY THE DOSE CAN BE INCREASED FOR BETTER EFFICACY AND CAN BE DECREASED IN CASE OF TOXICITY (TO SOME EXTENT)

BUT WHY THE DOSE COULD OR SHOULD NOT BE DECREASED IN CASE OF OPTIMAL RESPONSE, SO AS TO MAINTAIN EFFICACY AND TO REDUCE TOXICITY?

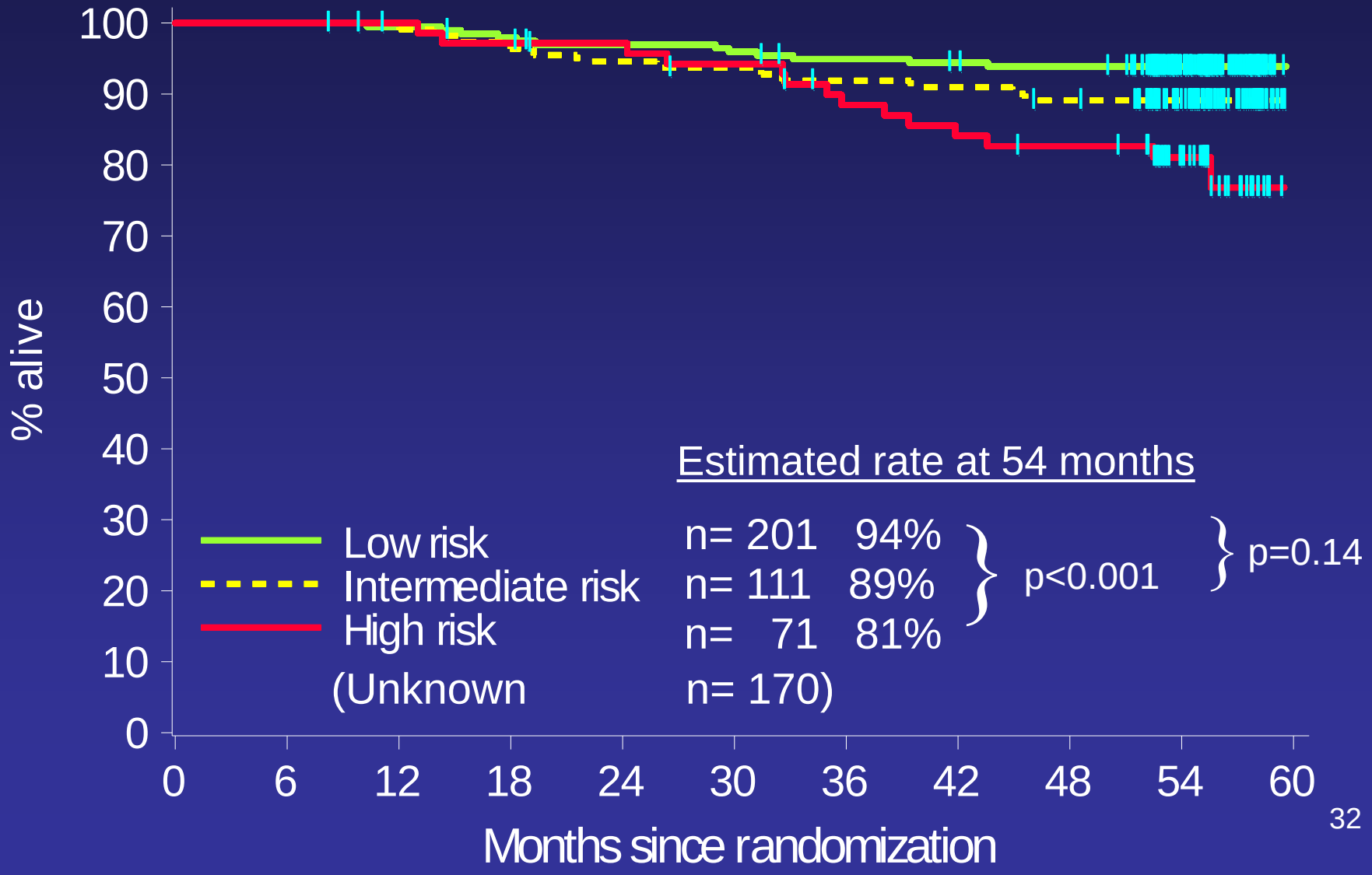
THE DOSE OF PONATINIB CAN (MUST) BE ADAPTED TO EFFICACY (TO BCR-ABL1 LEVEL)

45 mg/die: INTERPATIENT PLASMA PONATINIB CONCENTRATION IS HIGHLY VARIABLE



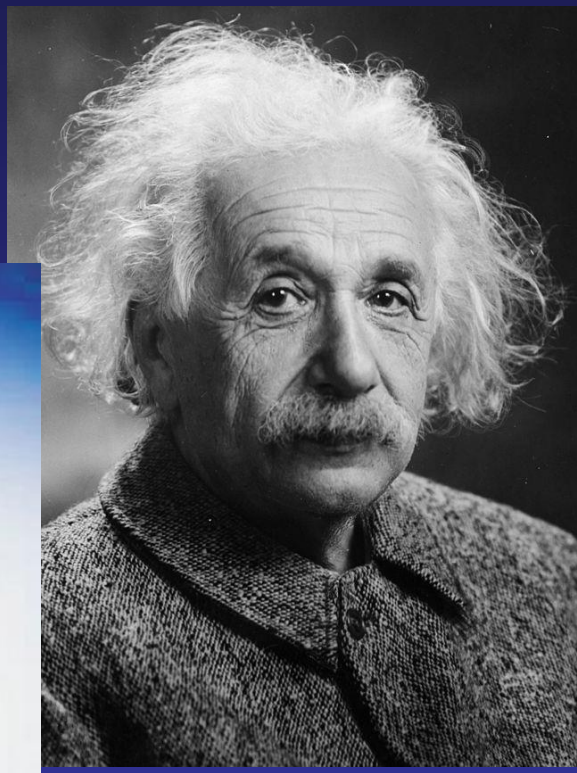
ARIAD-FDA

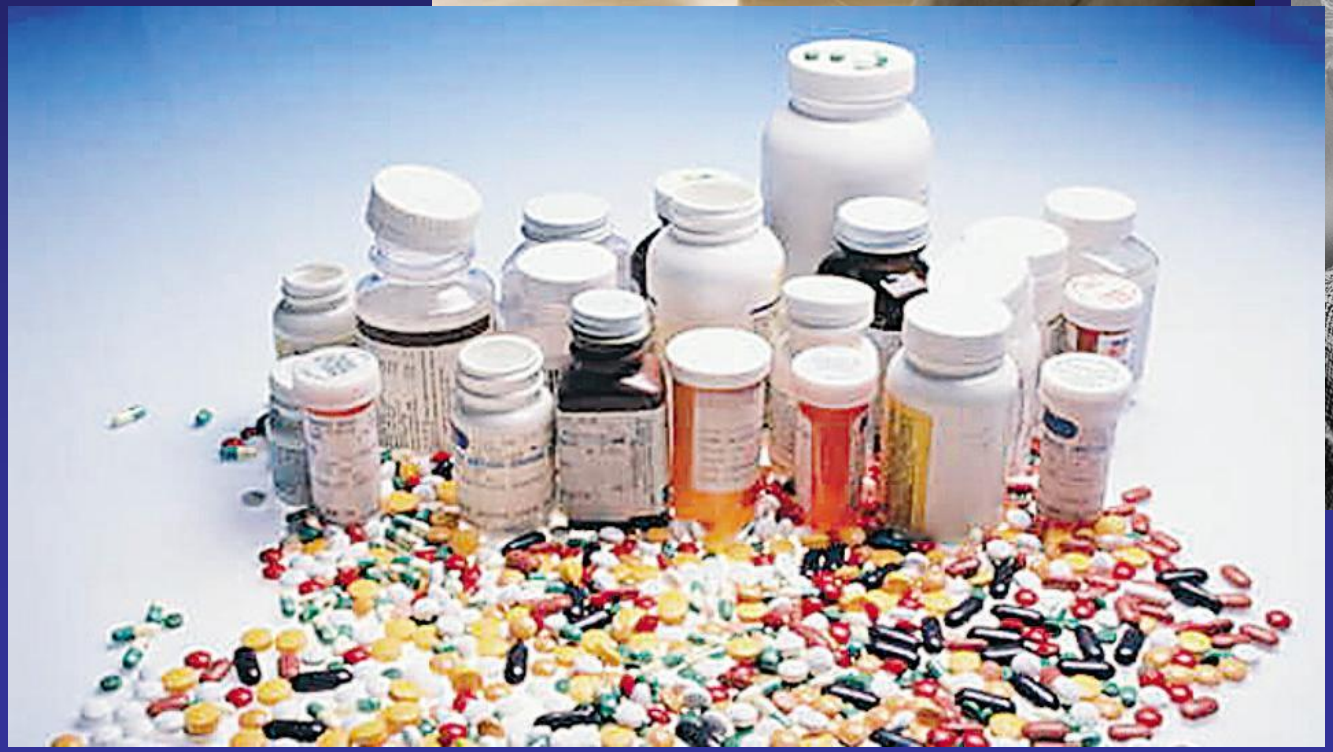
IRIS: Overall Survival by Sokal Group in Patients on First-line Imatinib



THE PLAYERS FOR CML

The patient
The doctor
The good scientist
The Pharma





Outcome upon treatment with 2nd line 2nd generation TKI after failure of imatinib

	Dasatinib 100mg QD	Nilotinib 400mg BID	Bosutinib 500mg QD
Patients (n)	167	321	288
Median age (years)	56	58	53
Imatinib resistance/intolerance	74%/26%	70%/30%	69.5%/30.5%
Minimum follow-up	24 months	24 months	24 months
Best CCyR rate	50%	44%	48%
Best MMR rate	37%	28%	35%
24-months PFS*	80%	64%	81%
24-months OS	91%	87%	91%

*PFS definition variations from a study to another

Shah NP, et al. Haematologica. 2010;95(2):232-240.
Kantarjian HM, et al. Blood. 2011;117(4):1141-1145.
Gambacorti-Passerini C et al. Am J Hematol. 2014;89(7):732-742.
Rosti G, et al. Nat Rev Clin Oncol. 2017;14(3):141-154.

A Phase 1 Trial of Oral Ponatinib (AP24534) in Patients with Refractory Chronic Myelogenous Leukemia (CML) and Other Hematologic Malignancies: Emerging Safety and Clinical Response Findings

Abstract 210: ASH 2010, Orlando, FL

J Cortes, M Talpaz, D Bixby, M Deininger, N Shah, I Flinn, M Mauro, T O'Hare, S Hu, R Kan, V Rivera, T Clackson, FG Haluska, and H Kantarjian

Initial Findings from the PACE Trial: A Pivotal Phase 2 Study of Ponatinib in Patients with CML and Ph+ ALL Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I Mutation

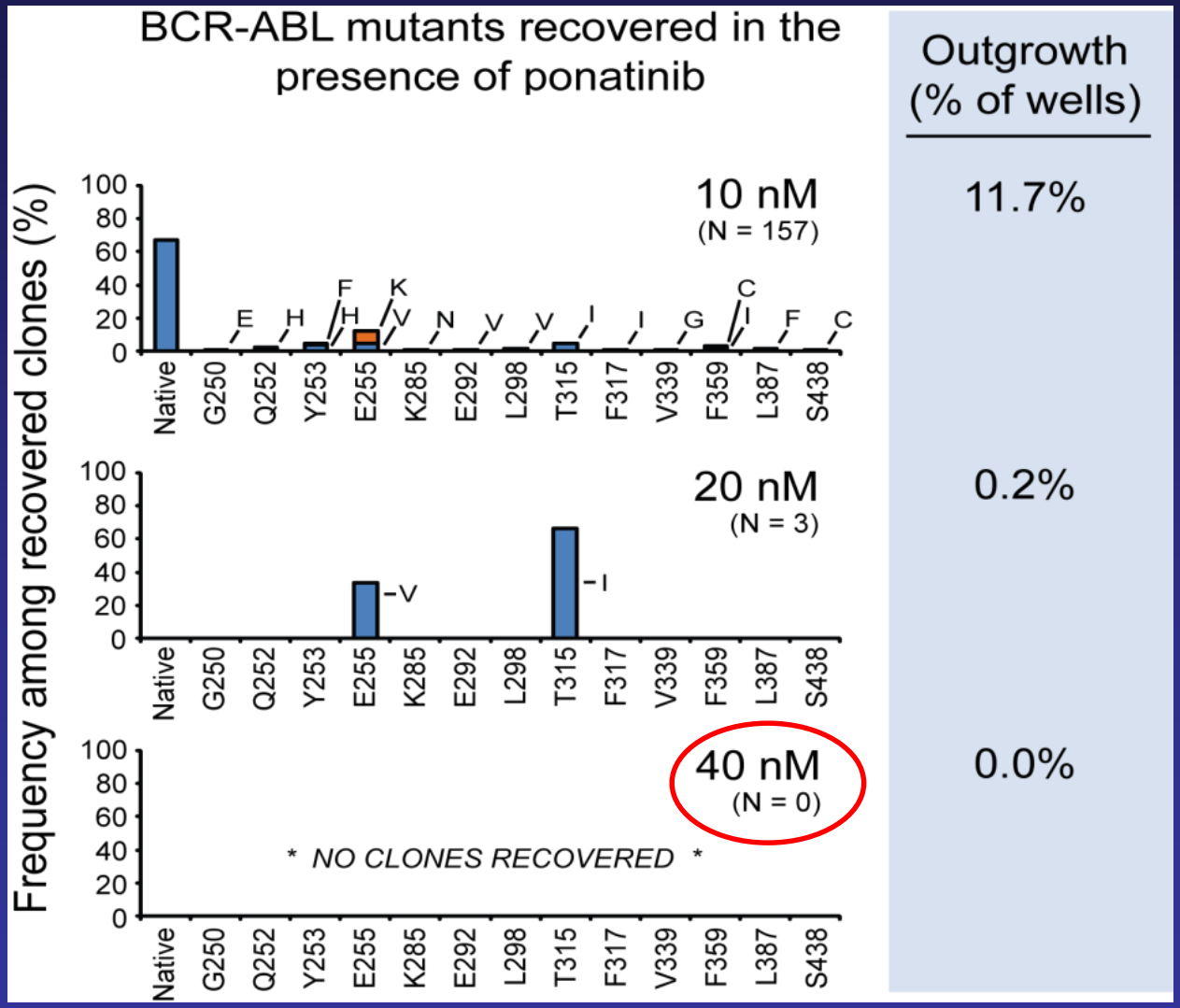
Abstract 109: ASH 2011, San Diego, CA

J Cortes, D-W Kim, J Pinilla, P le Coutre, C Chuah, F Nicolini, R Paquette, J Apperley, J DiPersio, HJ Khoury, D Rea, M Talpaz, DJ DeAngelo, E Abruzzese, M Baccarani, MC Mueller, C Gambacorti-Passerini, S Wong, S Lustgarten, CD Turner, V Rivera, T Clackson, F Haluska, and HM Kantarjian on behalf of the PACE Investigators

PACE
PONATINIB Ph+ ALL AND CML EVALUATION

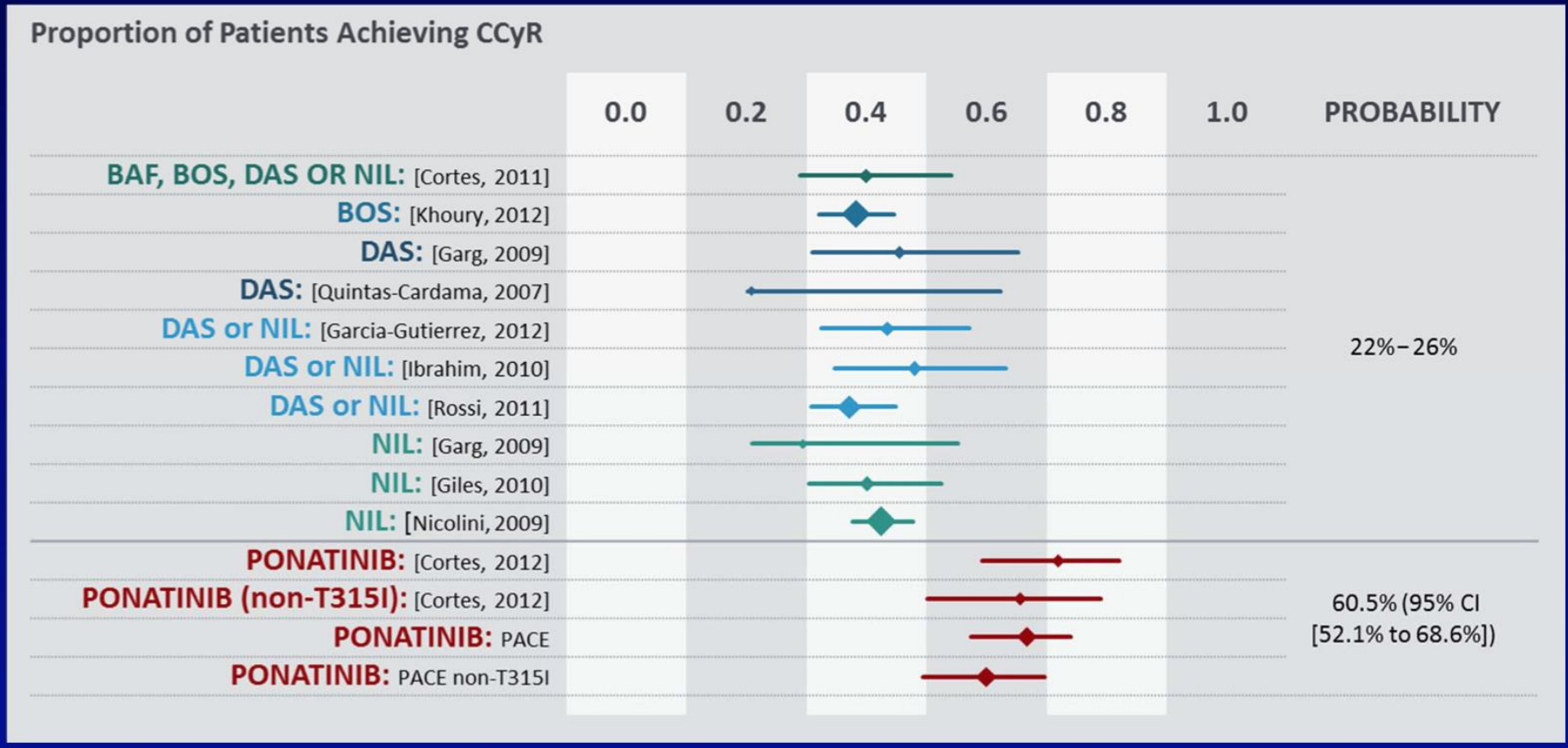
AT 30 mg ONCE DAILY THE PLASMA TARGET CONCENTRATION OF 40nM IS REACHED

Suppression of Mutant Outgrowth



- **Cells exposed to increasing ponatinib concentrations**
- **BCR-ABL resistance mutations completely suppressed at 40 nM**
- **40 nM target trough plasma ponatinib concentration**
- **40 nM attained at doses ≥30 mg**

Systematic Review of CP-CML Patients in Third-line Setting: Response to Ponatinib Was Superior to Other TKIs



These data suggest sequencing of second-generation TKIs may be a suboptimal treatment approach

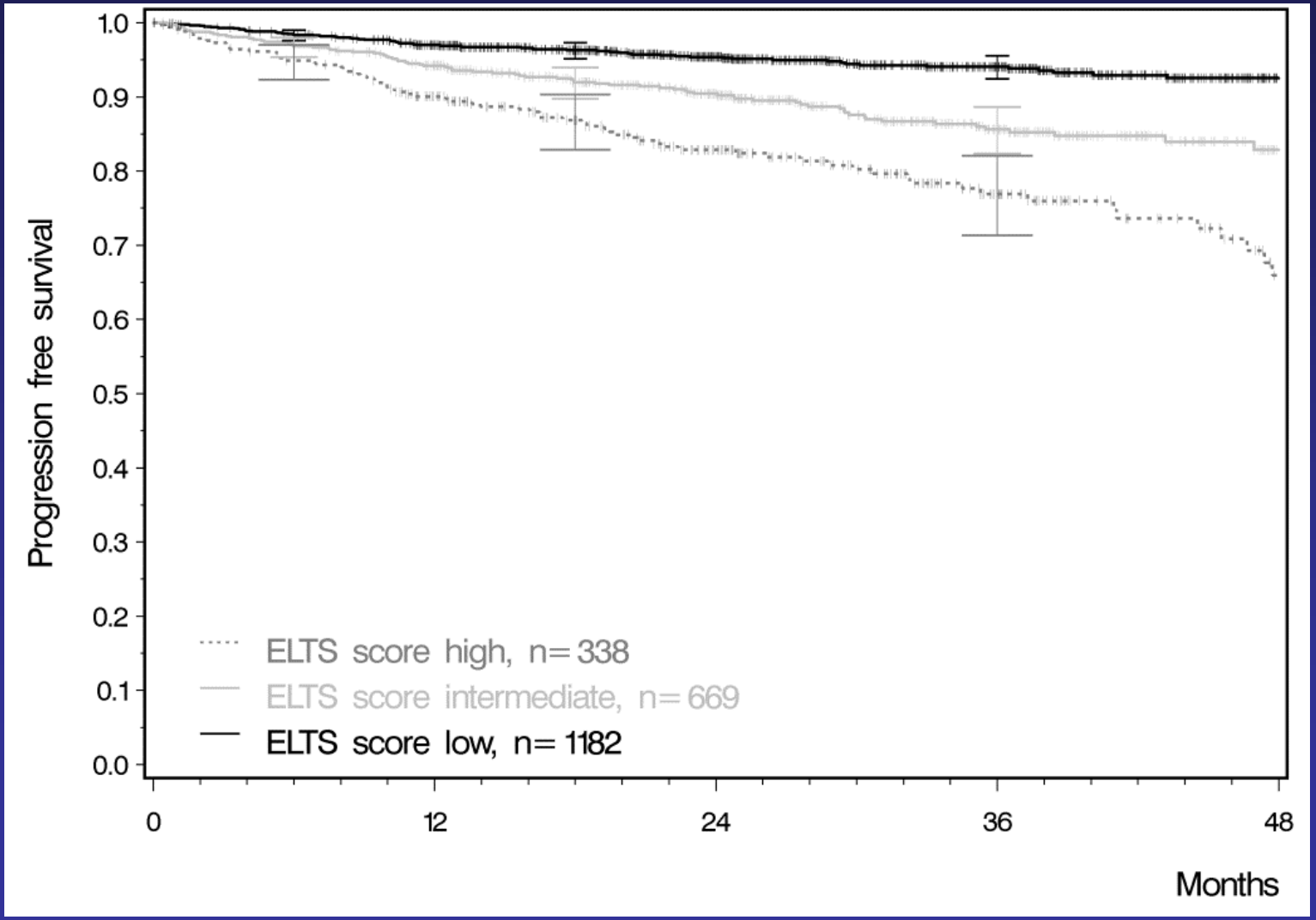
NOTE: Node size in graph represents patient numbers; line signifies derived 95% confidence interval.
AF=bafetinib; BOS=bosutinib; DAS=dasatinib; NIL=nilotinib.
Lipton et al, *Blood*. 2013;122(21) (abstr 4010).

Lipton et al. Leuk Res 39 (2015) 58–6

OUT OF 100 NEWLY DIAGNOSED PATIENTS, 10-20% ARE HIGH RISK OR ALREADY IN ACCELERATED OR BLASTIC PHASE

WE NEED TO DESIGN AND TO TEST THE STRATEGIES OF TREATMENT OF HIGH RISK PATIENTS AND OF THE PATIENTS NEWLY DIAGNOSED IN ACCELERATED OR BLASTIC PHASE

The EUTOS Long Term Survival score
Pfirrmann M et al, Leukemia 2016;30:48-56



HIGH RISK PATIENTS

MAJOR MOLECULAR RESPONSE (MMR) and COMPLETE CYTOGENETIC RESPONSE (CCyR) AT 12 MONTHS
IMATINIB, NILOTINIB, DASATINIB

DRUG	STUDY	Reference	No.pts	**MMR%**	CCyR%
IMA 400	DASISION	Kantarjian NEJM 2010	50•	**16**	64
IMA 400	ENESTnd	Saglio NEJM 2010	78	**17**	48
IMA 400	TOPS	Cortes ICO 2008	42	**26**	62
IMA 400	ELN	Baccarani Blood 2009	108	**33**	58
IMA 400	IRIS	Hughes NEJM 2003	71	**38**	49
IMA 800	TOPS	Cortes JCO 2008	75	**40**	63
IMA 800	ELN	Baccarani Blood 2009	108	**40**	64
DAS 400	DASISION	Kantarjian NEJM 2010	49	**31**	64
NIL 600	ENESTnd	Saglio NEJM 2010	78•	**41**	74

ITALIAN GUIDELINES (PROVISIONAL)

BASELINE EVALUATION, ALL PATIENTS

- CV/CeV EVENTS, personal (current and previously) and in 1st grade rel
- AGE and WEIGHT
- LIFE STYLE
- PRIOR THERAPY WITH CARDIOTOXIC DRUGS
- EDINBURGH CLAUDICATION QUESTIONNAIRE
- PHYSICAL EXAMINATION (central and peripheral arterial pulses)
- BLOOD PRESSURE
- SCREENING FOR DIABETES MELLITUS (glicemia, HbA1C)
- SCREENING FOR DYSLIPIDEMIA (cholesterol, LDL, HDL, tryglicerides)
- ECG
- **SYSTEMATIC CORONARY RISK EVALUATION (SCORE)**
- (ECHOCARDIOGRAPHY ?)
- (ANKLE BRACHIAL INDEX ?)
- (NATRIURETIC HORMONE “B-type” ?)
- (FIBRINOGEN, CRP, OMOCYSTEIN, …….. ?)

ITALIAN GUIDELINES PROVISIONAL

CHOLESTEROL LEVEL CONTROL

LDL < 100 mg/dl (< 2.50 mmol/l) always
< 70 mg/dl (< 1.75 mmol/l) in “high risk” patients
at least < 50% of baseline in familiar dyslipidemia

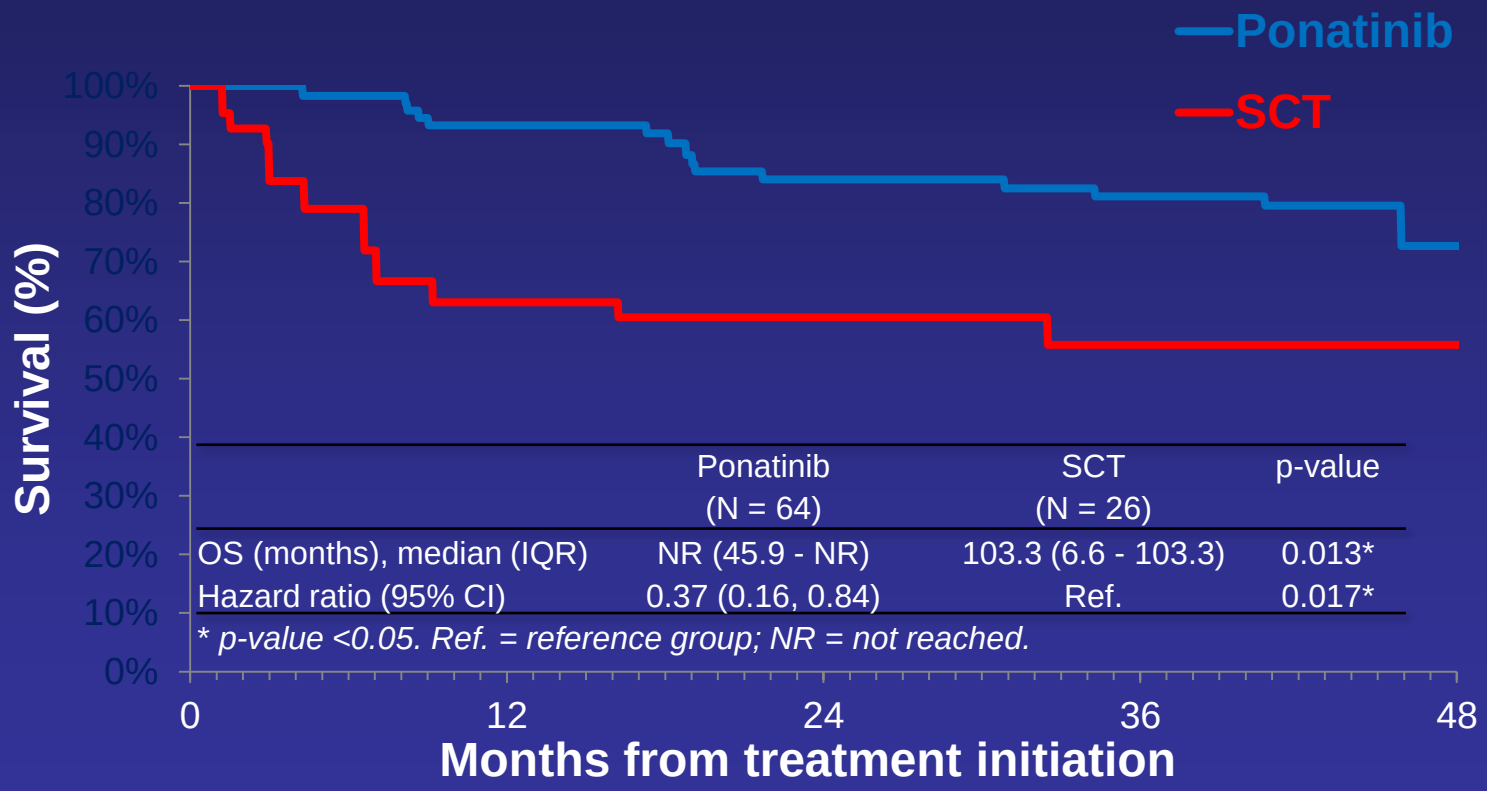
Recommended drug: atorvastatine

BLOOD PRESSURE AND DIABETES CONTROL

as required, according to guidelines

Overall survival with ponatinib *versus* Allo-SCT in patients with CP-CML and T315I mutation

Post hoc, retrospective, indirect comparison of OS among patients who received ponatinib (PACE trial) with those who underwent allo-SCT (EBMT registry).



	Ponatinib (N = 64)	SCT (N = 26)	p-value
OS (months), median (IQR)	NR (45.9 - NR)	103.3 (6.6 - 103.3)	0.013*
Hazard ratio (95% CI)	0.37 (0.16, 0.84)	Ref.	0.017*

** p-value <0.05. Ref. = reference group; NR = not reached.*

Nicolini FE, t al. Cancer. 2017 Apr 7. doi: 10.1002/cncr.30558. [Epub ahead of print]