SOCIETA' ITALIANA DI FARMACIA OSPEDALIERA
E DEI SERVIZI FARMACEUTICI DELLE AZIENDE SANITARIE

fondata nel 1952

"TRAINING REGIONALE PER FARMACISTI OSPEDALIERI SU LEUCEMIA MIELOIDE CRONICA (LMC): NUOVE TECNOLOGIE NUOVI APPROCCI"

Come si collega nello scenario terapeutico Ponatinib: dati di efficacia e di safety del prodotto

Alessandra Iurlo

Milano, 18 febbraio 2016

Indicazioni terapeutiche

Iclusig è indicato in pazienti adulti affetti da:

leucemia mieloide cronica (LMC) in fase cronica, accelerata o blastica resistenti o intolleranti a dasatinib o nilotinib e per i quali il successivo trattamento con imatinib non è clinicamente appropriato, oppure in pazienti nei quali è stata identificata la mutazione **T315I**

leucemia linfoblastica acuta con cromosoma Philadelphia positivo (LLA Ph+) resistenti o intolleranti a dasatinib e per i quali il successivo trattamento con imatinib non è clinicamente appropriato, oppure in pazienti nei quali è stata identificata la mutazione **T315I**

Iclusig®

- **45 mg**
  Disponibile in flaconi contenenti 30 compresse rivestite con film

- **15 mg**
  Disponibile in flaconi contenenti 60 compresse rivestite con film

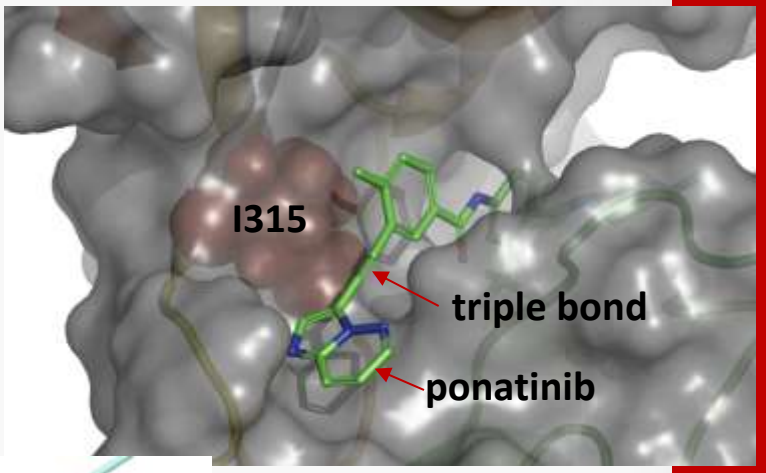
ICLUSIG™
(ponatinib) tablets

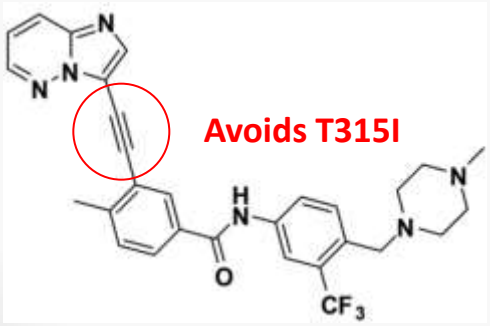
La dose raccomandata inizialmente è 45 mg una volta al giorno
Riduzioni della dose a 30 mg una volta al giorno o a 15 mg una volta al giorno possono essere considerate per gestire le eventuali tossicità del trattamento

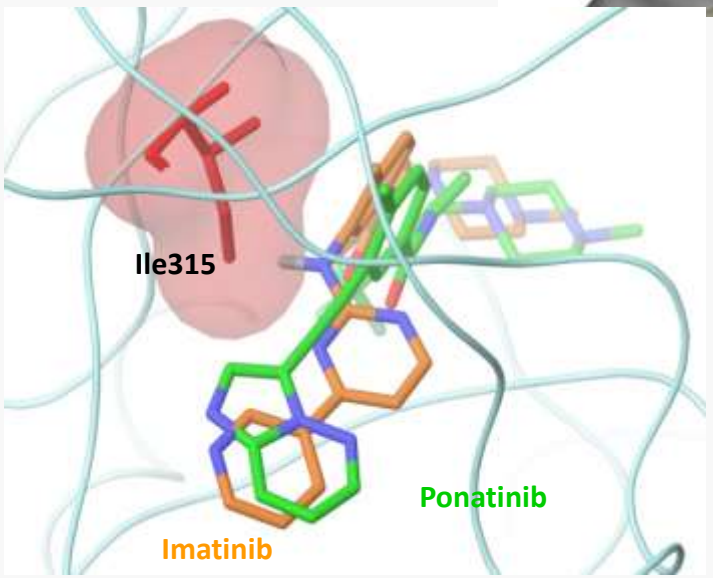
Drug	Dosing and Administration	Food Restrictions
Ponatinib[1]	45 mg orally QD	No
Imatinib[2]	400-600 mg orally QD 400 mg orally BID	Should be taken with a meal and water
Dasatinib[3]	100 mg orally QD (CP-CML) 140 mg orally QD (AP/BP-CML; Ph+ALL)	No
Nilotinib[4]	300 mg orally BID (newly diagnosed CP-CML) 400 mg orally BID (resistant/intolerant CP-CML or AP-CML)	No food should be consumed for at least 2 hours before and at least 1 hour after dose is taken
Bosutinib[5]	500-600 mg orally QD	Should be taken with food
Omacetaxine[6]	1.25 mg/m^2 subcutaneous injection BID	No

PONATINIB

- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Extensive network of optimized molecular contacts and triple bond to accommodate T315I
- Also targets other therapeutically relevant kinases:
  - Inhibits FLT3, FGFR, VEGFR, PDGFR, and c-KIT

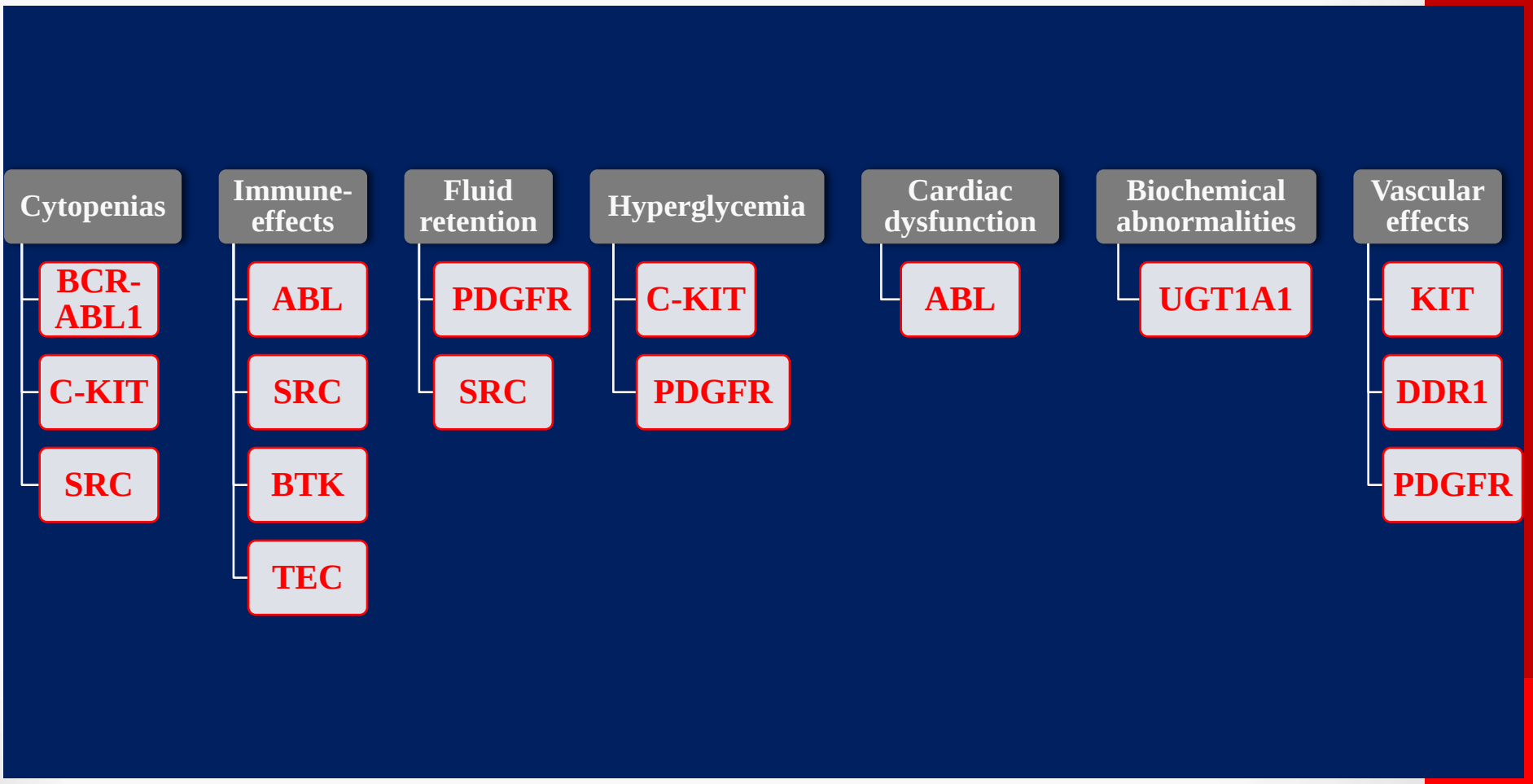






O'Hare T, et al. Cancer Cell 2009

BCR-ABL1 INHIBITORS
PUTATIVE TARGETS AND ASSOCIATED AEs



TARGET DI IMATINIB, NILOTINIB, DASATINIB, BOSUTINIB

Target	IC_{50} (nM)			
	Imatinib[8, 9]	Nilotinib[9, 10]	Dasatinib[11]	Bosutinib[12, 13]
BCR-ABL1	122–466	20–60	< 1.0	1
KIT	96	200	5.0	–
PDGFR	74	71	28	–
Src	–	–	0.50	1.2
YES	–	–	0.50	0.4
LCK	–	–	0.40	1.3

IC_{50} = 50% inhibitory concentration.

Other targets of imatinib and nilotinib include ARG, DDR1, NQO2; other targets of dasatinib include ARG, LYN, HCK, FGR, BLK, FRK, CSK, RTK TEC, BMX, TXK, DDR1, DDR2, ACK, ACTR2B, ACVR2, BRAF, EGFR/ERBBA, EPHA2, EPHA3, EPHA4, EPHA5, EPHA8, EPHB1, EPHB2, EPHB5, ERBB2, ERBB4, FAK, FYN, GAK, GCK, HH 499/TNNI3K, ILK, LIMK1, LIMK2, MAP2K5, MAP3K1, MAP3K2, MAP3K3, MAP3K4, MAP4K5/KHS1, MAPKI 1/p38 beta, MAPKI 4/p38 alpha, MYT1, NLK PTK6/BrK, QIK, QSK, RAF1, RET, RIPK2, SLK, STK36/ULK, SYK, TAO3, TESK2, TYK2, ZAK;[7] other targets of bosutinib include ARG, HCK, FGR, BLK, CSK, BMX, TXK, ACK, EGFR, EPHB2, FYN, LCK, LOK, MINK, MST3, PTK5, TRKA, TRKB.

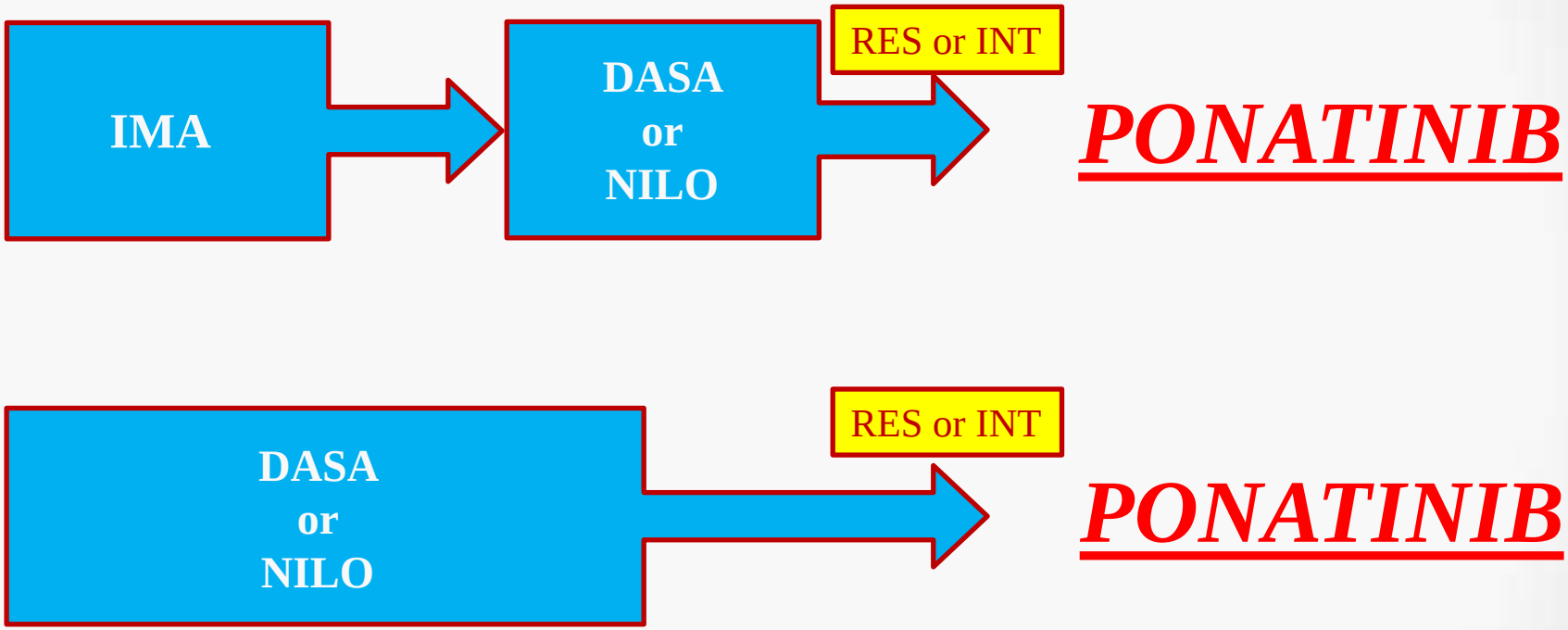
IC_{50} values for imatinib and nilotinib were determined by the capture enzyme-linked immunosorbent assay technique[9, 10] and IC_{50} values for dasatinib by kinase selectivity assay.[11]

PONATINIB

	IC50 (nM)
	0.1-20nM
ABL	0.4
ABL^{T315I}	2
Src-familiy	5.4
c-KIT	12.5
VEGFR-1	1.5
PDGFR-A	1.1
FGFR1	2.2
FLT3	12.6
Ephrin	
RET	0.16
TIE2	

Irvine & Williams, 2013; Price et al, 2013

PONATINIB: POSIZIONAMENTO



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Comparative efficacy of tyrosine kinase inhibitor treatments in the third-line setting, for chronic-phase chronic myelogenous leukemia after failure of second-generation tyrosine kinase inhibitors

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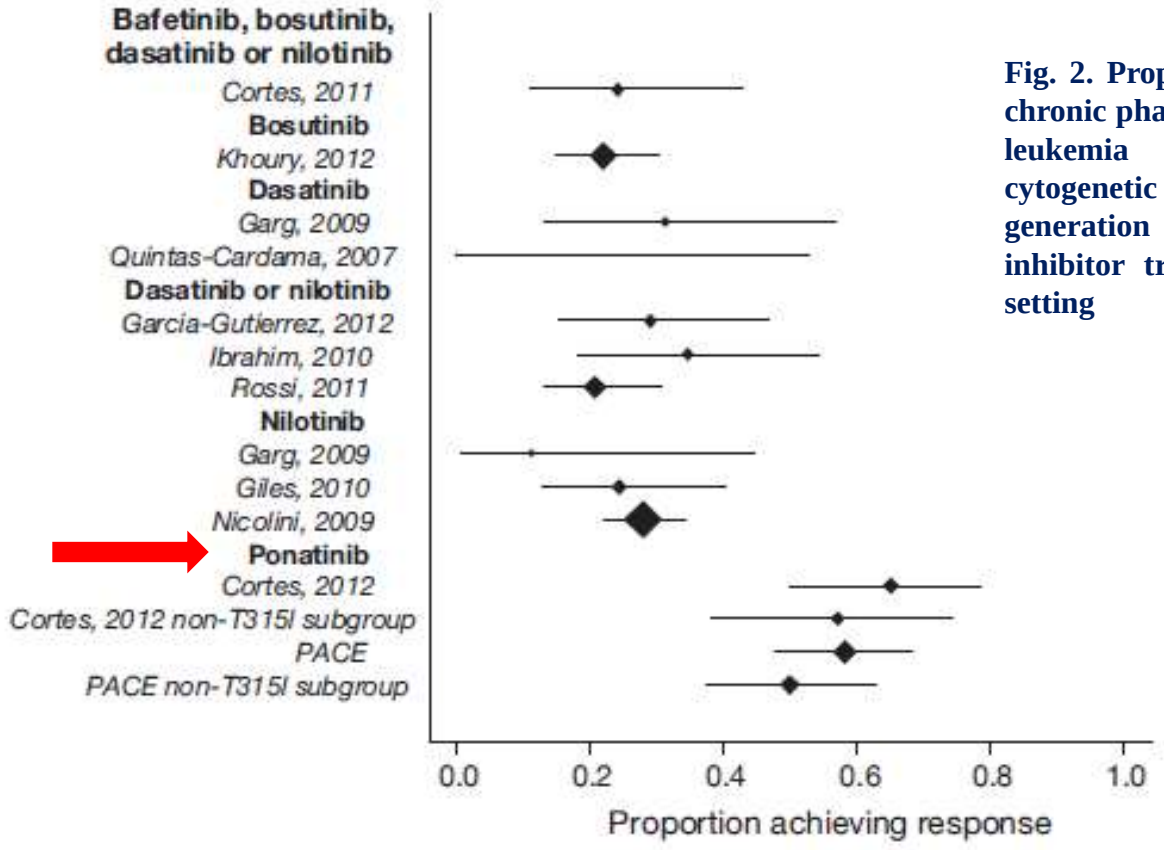


Fig. 2. Proportion of patients with chronic phase chronic myelogenous leukemia achieving complete cytogenetic response, after second-generation tyrosine kinase inhibitor treatment, in third line setting

PACE (Phase 2): Ponatinib Ph+ ALL and CML Evaluation study design

Key Inclusion/Exclusion Criteria

- ≥18 years of age with CML (any phase) or Ph+ ALL
- R/I to dasatinib or nilotinib OR developed the T315I mutation after any TKI
- Mandatory 20 metaphases by conventional cytogenetics with banding technique
- No TKI therapy within 7 days or other anti-cancer therapy within 28 days before enrollment
- Normal organ function, ECOG performance status ≤2

449

Cohorts

Resistant/ intolerant to dasatinib or nilotinib	CP-CML N=203
	AP-CML N=65
	BP-CML/Ph+ ALL N=48
T315I mutation	CP-CML N=64
	AP-CML N=18
	BP-CML/Ph+ ALL N=46

Primary Endpoints

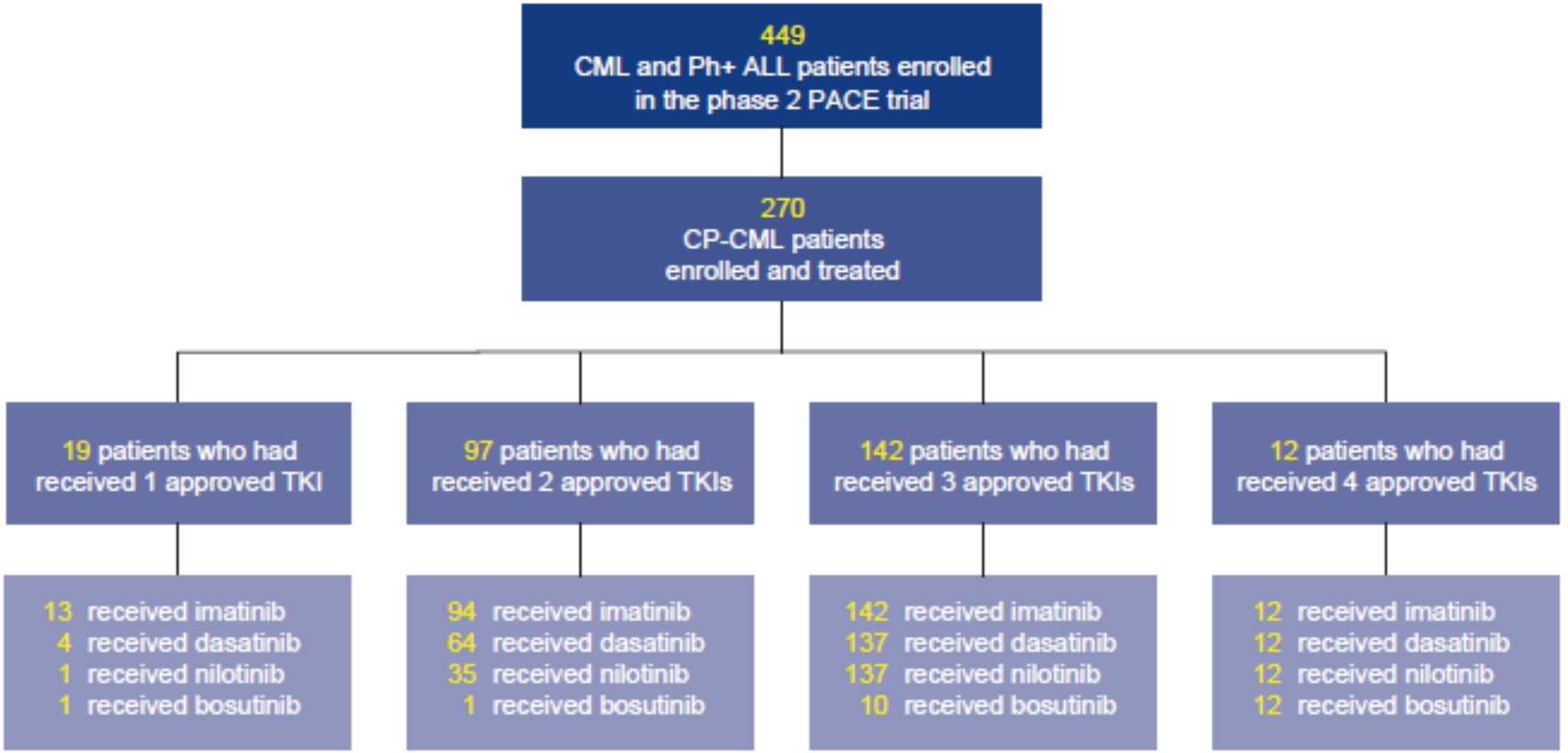
- MCyR by 12 months for CP-CML
- MaHR by 6 months for AP-CML, BP-CML, and Ph+ ALL

Response Assessments

Conducted every

- 3 months for CP-CML patients
- 2 months for AP-CML, BP-CML, and Ph+ ALL patients

Figure 1. Patients Analyzed



Among patients who had received 1, 2, 3, and 4 approved TKIs, 6, 3, 0, and 0, respectively, did not receive imatinib

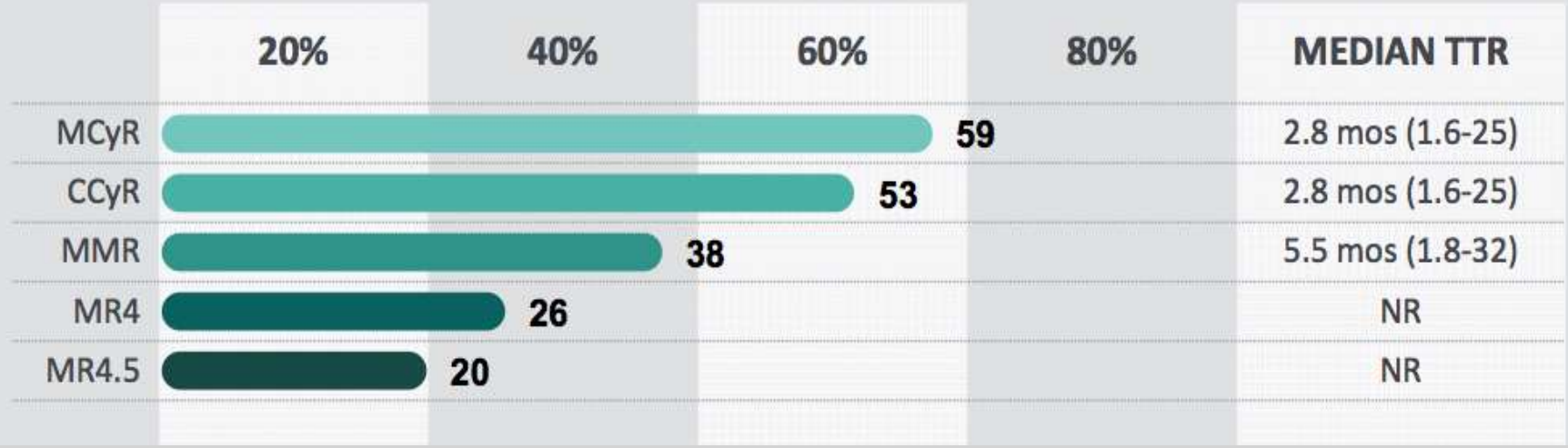
Table 2. Patient Disposition by Number of Prior TKIs

	All CP-CML Patients n=270[a]	CP-CML Patients Who Had Received:			
		1 Prior TKI n=19	2 Prior TKIs n=97	3 Prior TKIs n=142	4 Prior TKIs n=12
Median duration of treatment, mo (range)	32.1 (0.1–58.4)	46.0 (3.3–52.2)	38.4 (0.2–58.1)	28.8 (0.1–58.4)	10.1 (0.1–49.9)
Cumulative exposure, patient-years	668.4	56.0	256.2	340.7	15.5
Median follow-up, mo (range)	48.2 (0.1–58.5)	48.3 (4.5–52.3)	48.2 (0.4–58.2)	48.5 (0.2–58.5)	28.2 (0.1–49.9)
Median dose intensity, mg/d (range)	29.4 (3–45)	31.6 (3–45)	28.6 (5–45)	29.8 (5–45)	31.0 (5–45)
Remain on study, n (%)	110 (41)	10 (53)	44 (45)	55 (39)	1 (8)
Discontinued, n (%)	160 (59)	9 (47)	53 (55)	87 (61)	11 (92)
Primary reason for discontinuation, n (%)					
AE	50 (19)	3 (16)	18 (19)	25 (18)	4 (33)
Withdrawal by patient	30 (11)	1 (5)	11 (11)	15 (11)	3 (25)
Disease progression	28 (10)	3 (16)	5 (5)	20 (14)	0
Lack of efficacy	15 (6)	0	2 (2)	12 (8)	1 (8)
Physician decision	11 (4)	1 (5)	4 (4)	5 (4)	1 (8)
Death[b]	8 (3)	0	2 (2)	4 (3)	2 (17)
Noncompliance	3 (1)	0	1 (1)	2 (1)	0
Protocol violation	1 (<1)	0	0	1 (<1)	0
Other[c]	14 (5)	1 (5)	10 (10)	3 (2)	0

[a] Includes 3 patients who were non–cohort assigned (post-imatinib, non-T315I) but treated; all 3 remain on study
[b] 2 deaths were assessed by investigators as possibly or probably related to ponatinib (pneumonia, acute myocardial infarction)
[c] Including transplant (n=11)

Hochhaus A et al, ASH 2015

PACE



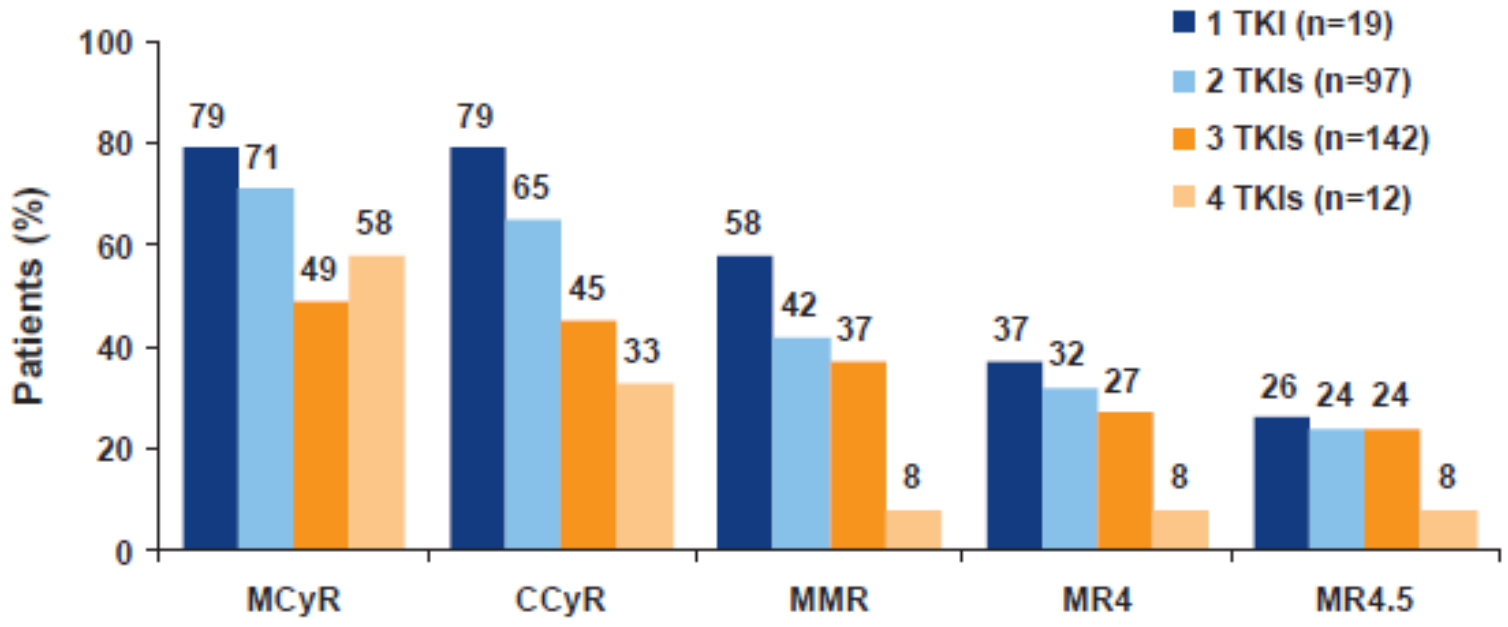
Kantarjian, et al. J Clin Oncol. 2014;32:5s (suppl; abstr 7081)

RESPONSE AT ANY TIME IN PATIENTS WITH T315I MUTATION

n (%)	CP-CML (n=76)	AP-CML (n=19)	BP-CML (n=26)	Ph+ ALL (n=26)
MaHR	NA	11 (58)	7 (27)	10 (38)
MCyR	57 (75)	12 (63)	8 (31)	10 (38)
CCyR	55 (72)	8 (42)	5 (19)	8 (31)
MMR	46 (61)	7 (37)	1 (4)	2 (8)
MR4	34 (45)	0	0	1 (4)
MR4.5	28 (37)	0	0	0

Data as of 6 October 2014 (PACE)

Figure 2A. Response to Ponatinib in CP-CML by Number of Prior TKIs: Response at Any Time (n=270)

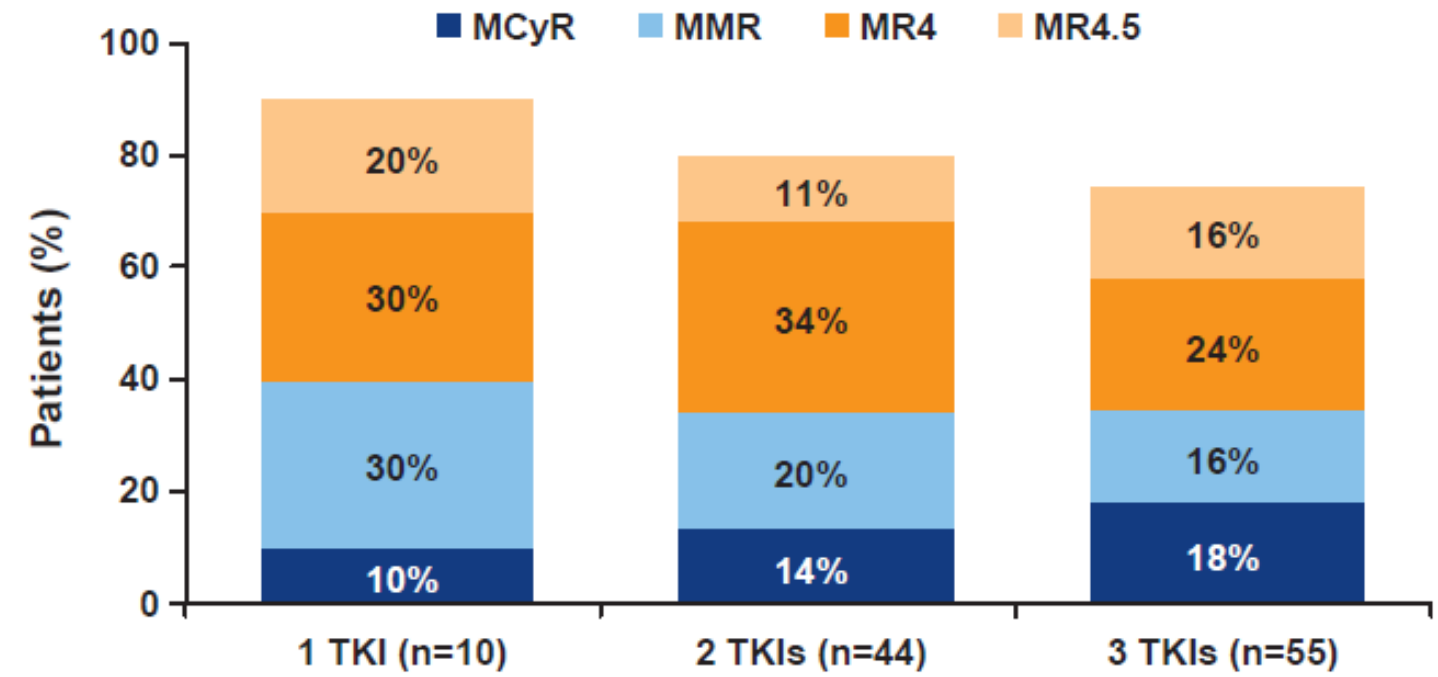


MCyR, 0%–35% Ph+ metaphases; CCyR, 0% Ph+ metaphases; MMR, ≤0.1% BCR-ABL[IS]; MR4, ≤0.01% BCR-ABL[IS] or undetectable disease in cDNA with ≥10,000 ABL transcripts; MR4.5, ≤0.0032% BCR-ABL[IS] or undetectable disease in cDNA with ≥32,000 ABL transcripts

Rates of cytogenetic and molecular response to ponatinib were higher with fewer prior TKIs

Hochhaus A et al, ASH 2015

Figure 2B. Response to Ponatinib in CP-CML by Number of Prior TKIs: Current Response in Ongoing Patients (n=110)



MCyR combines MCyR and MR2 (≤1% BCR-ABL[IS]); patients with lesser responses are not shown
Cytogenetic status was used for determination of current response in patients in <MMR if last cytogenetic assessment was no earlier than 6 months prior to last molecular assessment

Among patients who had received 1, 2, and 3 prior TKIs, the proportion of patients with a current MMR or a better response was higher with fewer TKIs; only 1 patient who had received 4 prior TKIs continues to receive ponatinib (with a current response of MR4.5)

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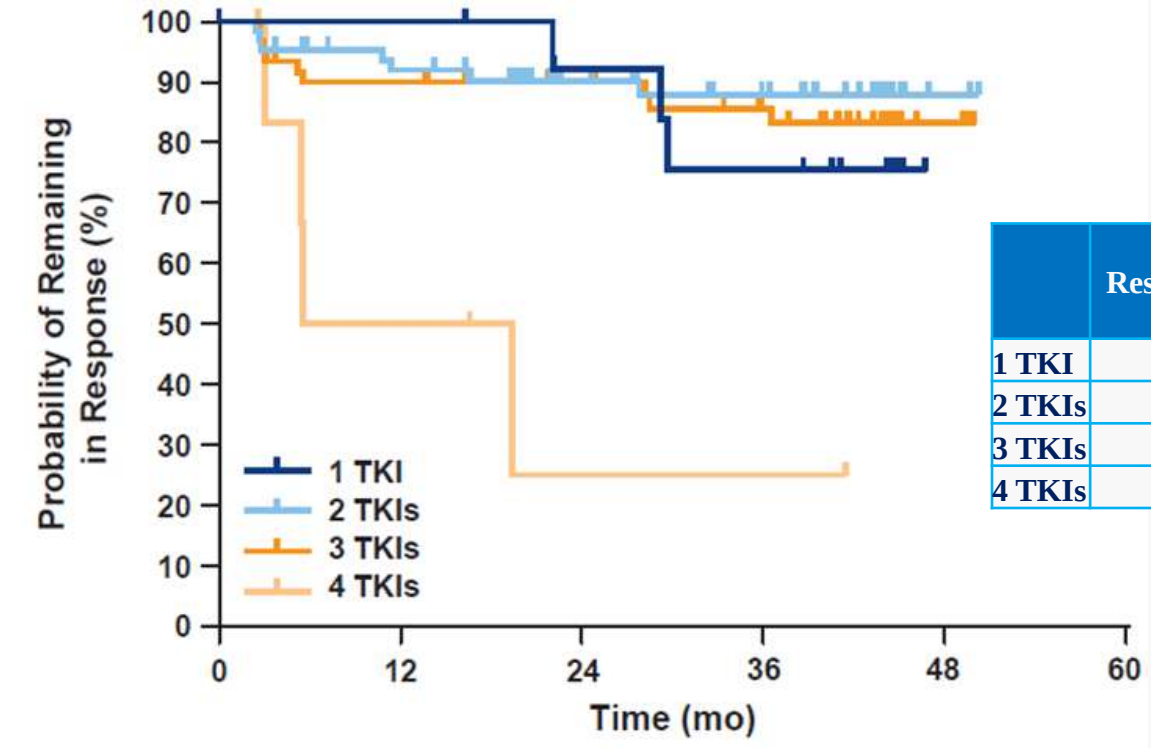
DURATION OF MCyR BY NUMBER OF PRIOR TKIs (N=161)

- Responses were durable among patients who had received 1, 2, or 3 prior TKIs, and less so among patients who had received 4 prior TKIs



	Responders, n	Lost MCyR, n	Maintained MCyR at 3 Years, %
1 TKI	15	3	76%
2 TKIs	69	7	88%
3 TKIs	70	9	86%
4 TKIs	7	4	25%

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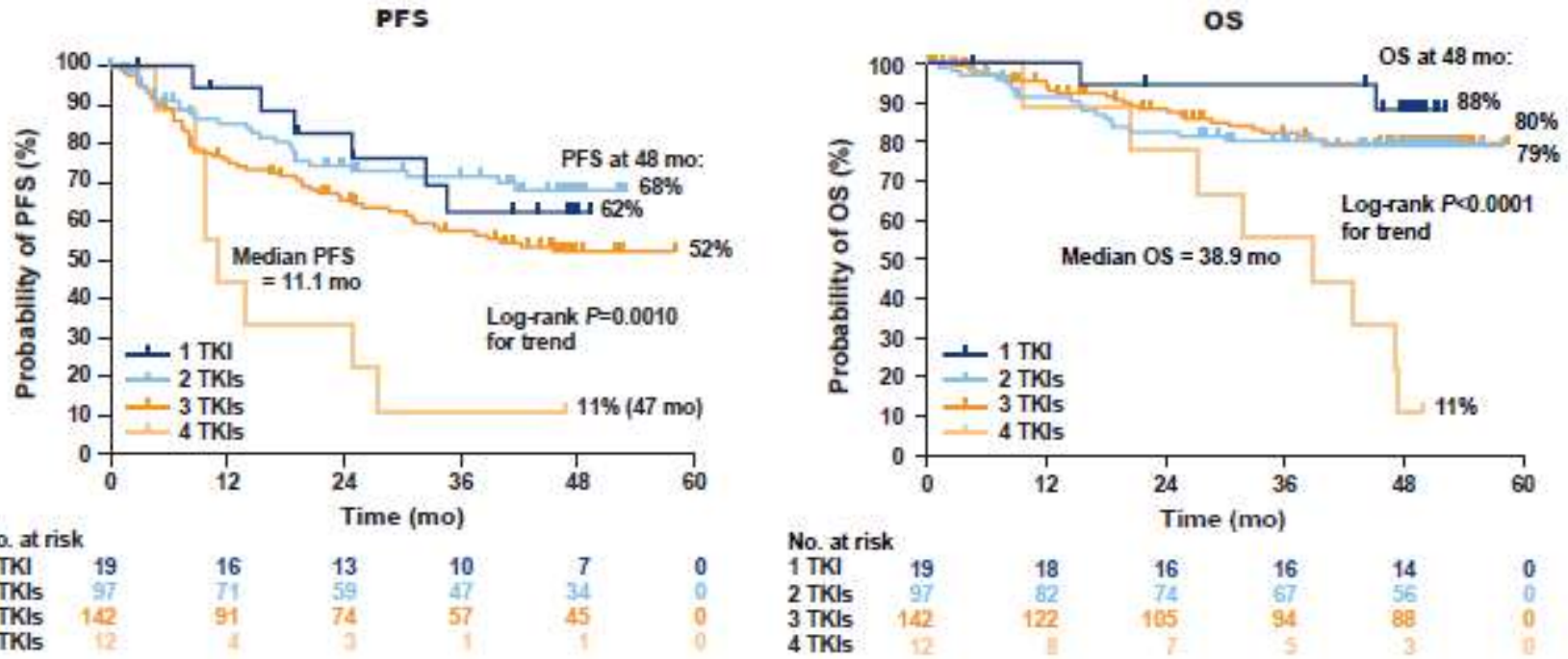
Figure 4. PFS[a] and OS by Number of Prior TKIs (n=270)



[a] Progression from CP was defined as death, development of AP or BP, loss of complete hematologic response (in absence of cytogenetic response), loss of MCyR, or increasing white blood cell count without complete hematologic response

- PFS and OS were higher in patients who had received 1, 2, and 3 prior TKIs (52% to 68%, and 79% to 88% at 4 years, respectively), and lower in patients who had received 4 prior TKIs (11% at 4 years)
- Overall, in the eligible CP-CML population, PFS and OS at 4 years were 56% and 77%, respectively

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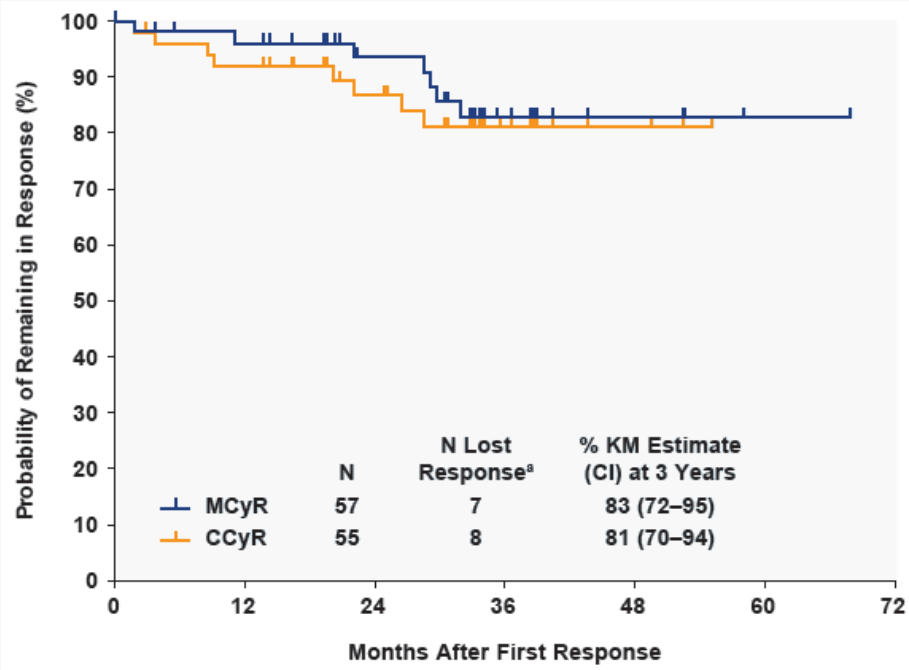
DURATION OF MCyR AND CCyR IN CP-CML PATIENTS WITH T315I MUTATION

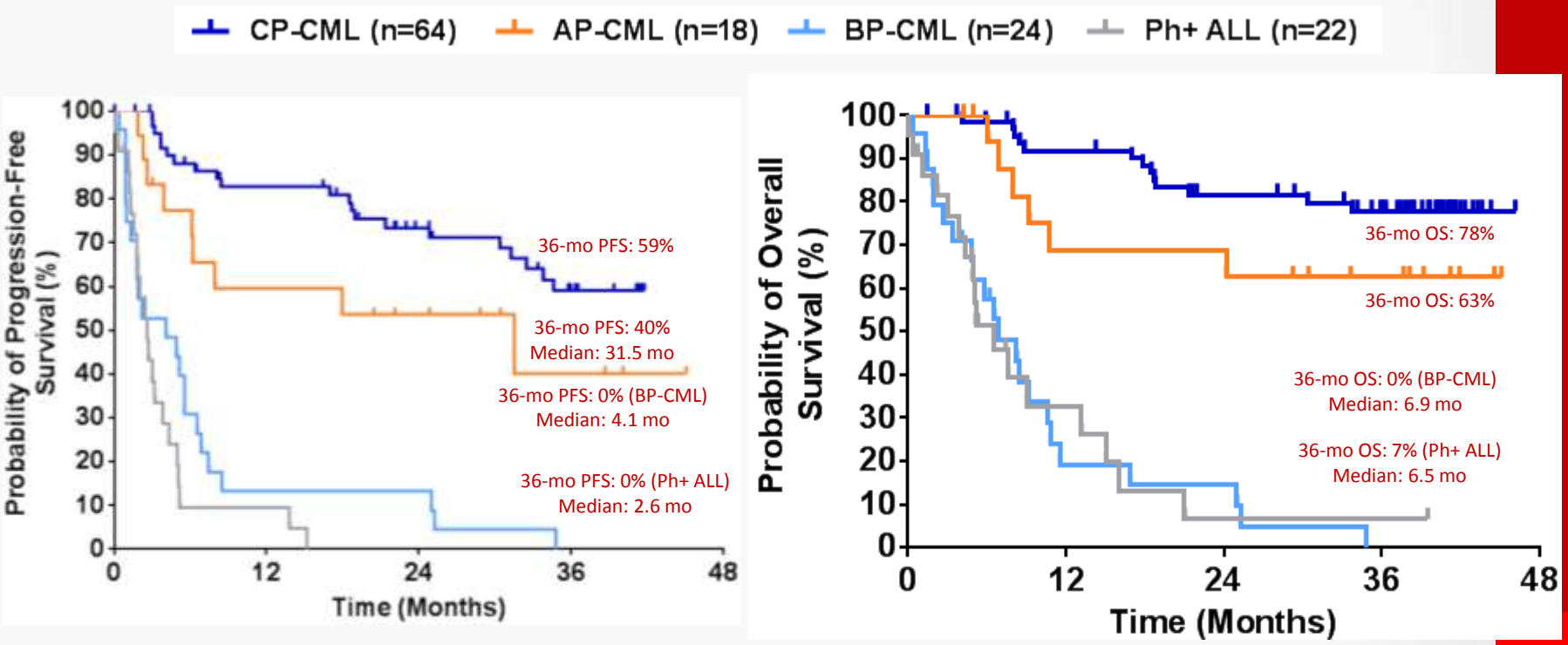
- Majority of CP-CML patients with the T315I mutation at baseline maintained response
  - 83% of patients were estimated to remain in MCyR at 3 years
  - 81% of patients were estimated to remain in CCyR at 3 years
- Median duration of response not reached



Data as of 6 October 2014 (PACE)

PFS AND OS IN PATIENTS WITH T315I MUTATION IN THE PACE TRIAL

- In the phase 1 trial (OS and PFS not collected), 11/12 CP-CML patients are alive and ongoing; 1 patient discontinued because of disease progression



Data as of 6 October 2014 (PACE)

Table 3. Treatment-Emergent AEs in ≥20% of CP-CML Patients by Number of Prior TKIs

	All CP-CML Patients n=270		CP-CML Patients Who Had Received:							
			1 Prior TKI n=19		2 Prior TKIs n=97		3 Prior TKIs n=142		4 Prior TKIs n=12	
	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
At least 1 treatment-emergent AE	270 (100)	236 (87)	19 (100)	15 (79)	97 (100)	83 (86)	142 (100)	126 (89)	12 (100)	12 (100)
Nonhematologic										
Rash[a]	126 (47)	10 (4)	10 (53)	0	42 (43)	4 (4)	70 (49)	5 (4)	4 (33)	1 (8)
Abdominal pain	124 (46)	27 (10)	7 (37)	2 (11)	47 (48)	14 (14)	65 (46)	10 (7)	5 (42)	1 (8)
Headache	115 (43)	9 (3)	8 (42)	0	46 (47)	3 (3)	59 (42)	6 (4)	2 (17)	0
Dry skin	112 (41)	9 (3)	8 (42)	0	37 (38)	1 (1)	61 (43)	7 (5)	6 (50)	1 (8)
Constipation	111 (41)	7 (3)	9 (47)	2 (11)	45 (46)	1 (1)	53 (37)	4 (3)	4 (33)	0
Hypertension[b]	92 (34)	34 (13)	8 (42)	2 (11)	29 (30)	12 (12)	54 (38)	19 (13)	1 (8)	1 (8)
Arthralgia	87 (32)	8 (3)	2 (11)	0	32 (33)	4 (4)	50 (35)	3 (2)	3 (25)	1 (8)
Fatigue	80 (30)	6 (2)	3 (16)	0	31 (32)	3 (3)	44 (31)	3 (2)	2 (17)	0
Nausea	75 (28)	2 (<1)	4 (21)	0	30 (31)	1 (1)	37 (26)	0	4 (33)	1 (8)
Increased lipase	72 (27)	33 (12)	3 (16)	1 (5)	26 (27)	10 (10)	38 (27)	20 (14)	5 (42)	2 (17)
Pyrexia	69 (26)	3 (1)	3 (16)	0	22 (23)	1 (1)	42 (30)	2 (1)	2 (17)	0
Myalgia	65 (24)	3 (1)	4 (21)	0	26 (27)	2 (2)	32 (23)	1 (<1)	3 (25)	0
Pain in extremity	63 (23)	9 (3)	2 (11)	1 (5)	20 (21)	3 (3)	39 (27)	5 (4)	2 (17)	0
Back pain	56 (21)	3 (1)	2 (11)	0	24 (25)	1 (1)	28 (20)	1 (<1)	2 (17)	1 (8)
Hematologic										
Thrombocytopenia	122 (45)	95 (35)	9 (47)	6 (32)	40 (41)	34 (35)	68 (48)	50 (35)	5 (42)	5 (42)

[a] Combines the terms erythematous, macular, and papular rash
[b] 241/270 (89%) patients had elevated blood pressure at baseline (148/270 [55%] had ≥140 mm Hg systolic or ≥90 mm Hg diastolic); 187/270 (69%) patients experienced any increase from baseline in blood pressure on study

Table 4. Cumulative and Exposure-Adjusted Incidences of Arterial Occlusive Events[a] in CP-CML Patients by Number of Prior TKIs

	All CP-CML Patients n=270		CP-CML Patients Who Had Received:							
			1 Prior TKI n=19		2 Prior TKIs n=97		3 Prior TKIs n=142		4 Prior TKIs n=12	
	AE	SAE	AE	SAE	AE	SAE	AE	SAE	AE	SAE
AOEs, n (%)	77 (29)[b]	63 (23)[c]	6 (32)	5 (26)	28 (29)	23 (24)	38 (27)	31 (22)	5 (42)	4 (33)
Cardiovascular	39 (14)	30 (11)	4 (21)	3 (16)	15 (15)	12 (12)	18 (13)	14 (10)	2 (17)	1 (8)
Cerebrovascular	33 (12)	26 (10)	2 (11)	2 (11)	13 (13)	10 (10)	16 (11)	13 (9)	2 (17)	1 (8)
Peripheral vascular	31 (11)	25 (9)	3 (16)	2 (11)	11 (11)	10 (10)	14 (10)	10 (7)	3 (25)	3 (25)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.2	10.9	13.6	10.2	12.9	10.1	14.0	10.8	45.1	29.0

AE = total AEs (including SAEs), AOE = arterial occlusive event, SAE = serious AEs only (designated as serious by the investigator, in accordance with standard regulatory criteria)

[a] Categorization of AOEs is based on a broad collection of >300 Medical Dictionary for Regulatory Activities (MedDRA) preferred terms related to vascular ischemia or thrombosis

[b] 41 patients had >1 AOE

[c] 25 patients had >1 serious AOE

Hochhaus A et al, ASH 2015

VENOUS THROMBOTIC EVENTS

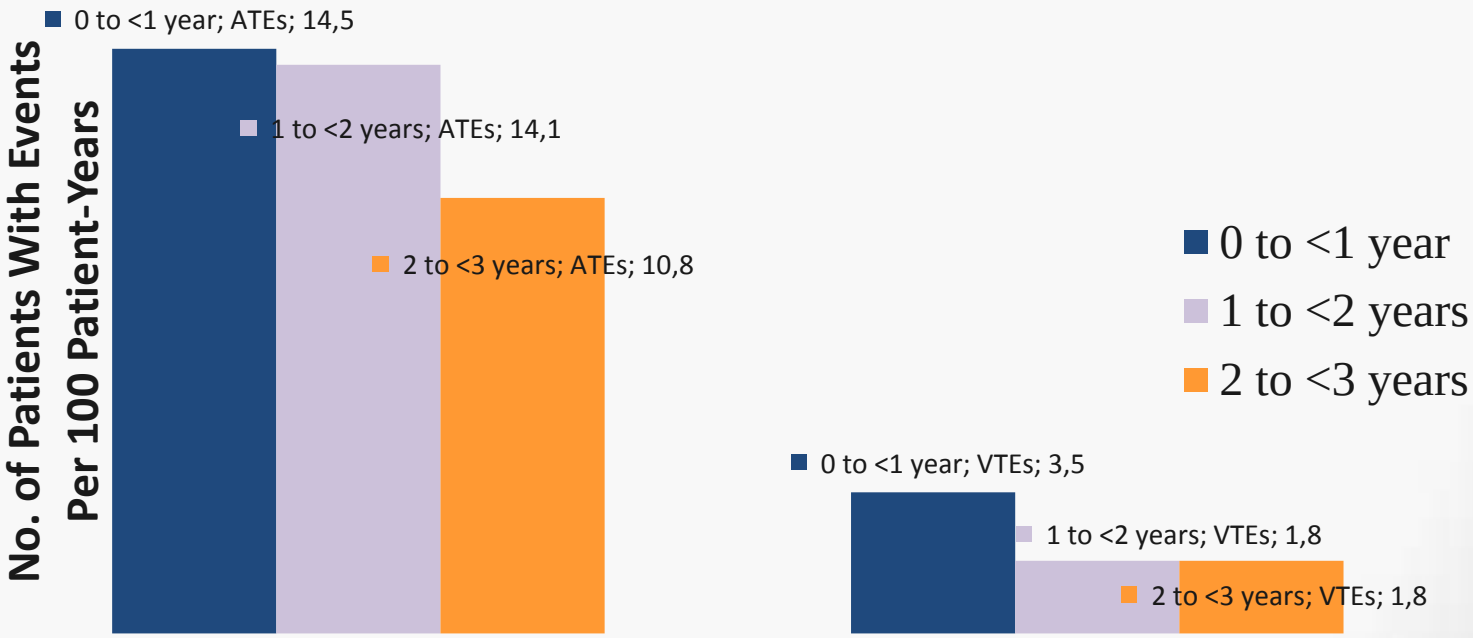
- Median time to onset for ATEs:
  - Total patients
    - 10.8 (0.1–44.0) months
  - CP-CML patients
    - 13.8 (0.3–44.0) months
- Median time to onset for VTEs:
  - Total patients
    - 5.6 (0.1–31.4) months
  - CP-CML patients
    - 21.0 (2.0–31.4) months

	Total N=449		CP-CML n=270	
	AE	SAE	AE	SAE
Cumulative exposure, patient-years	778.9		577.4	
ATEs, n (%)	99 (22)[b]	78 (17)[c]	74 (27)	60 (22)
Cardiovascular	52 (12)	37 (8)	36 (13)	28 (10)
Cerebrovascular	37 (8)	28 (6)	31 (11)	23 (9)
Peripheral vascular	37 (8)	27 (6)	28 (10)	20 (7)
Exposure-adjusted ATEs, number of patients with events per 100 patient-years	12.7	10.0	12.8	10.4
VTEs, n (%)	24 (5)[b]	20 (4)[c]	12 (4)	10 (4)
Exposure-adjusted VTEs, number of patients with events per 100 patient-years	3.1	2.6	2.1	1.7

[a]Combined, arterial and venous thrombotic events are based on a broad collection of >400 Medical Dictionary for Regulatory Activities (MedDRA) preferred terms related to vascular ischemia or thrombosis; [b]43 patients had >1 arterial thrombotic AE; 4 patients had >1 venous thrombotic AE; [c]23 patients had >1 arterial thrombotic SAE; 2 patients had >1 venous thrombotic SAE

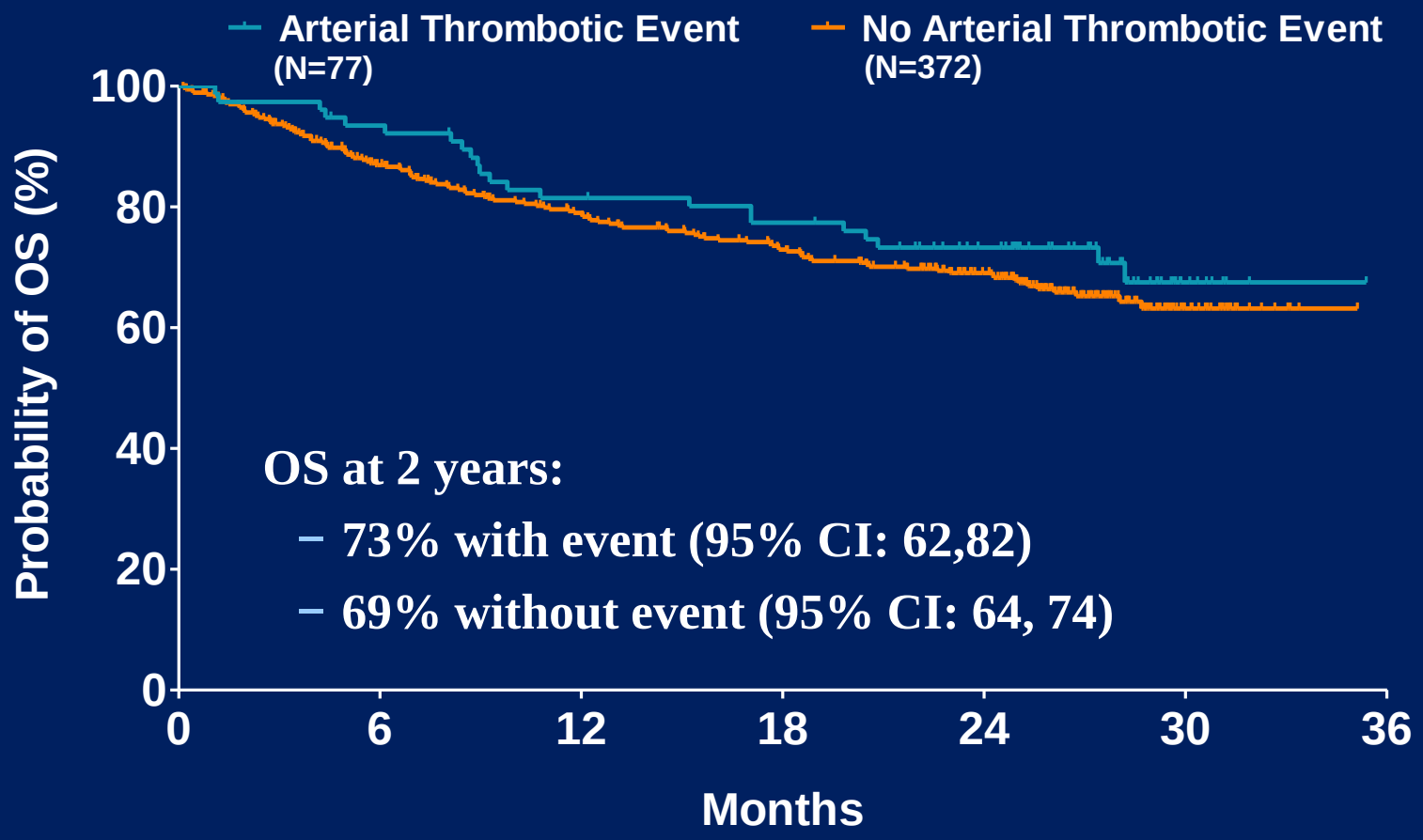
EXPOSURE-ADJUSTED YEARLY INCIDENCE RATES FOR NEWLY OCCURRING ARTERIAL AND VENOUS THROMBOTIC EVENTS – ALL PATIENTS

- There was no increase in the exposure-adjusted incidence of newly occurring ATEs and VTEs with longer duration of ponatinib treatment



Data as of 06 October 2014

Ponatinib Phase 2 Study
OS by Arterial Thrombotic Events



- 5 patients died of a grade 5 vascular event
- 5 additional patients died with vascular events possibly contributing to death

Cortes. Blood 122: abst 650; 2013

PACE Trial

DOSE MODIFICATION WITHIN FIRST 12 MONTHS*

206/267 CP-CML patients=78%

DOSE MODIFICATION AT ANY TIME DURING TREATMENT

229/267 CP-CML patients=86%

MEDIAN TIME TO DOSE MODIFICATION: 29 days (range 2-320)

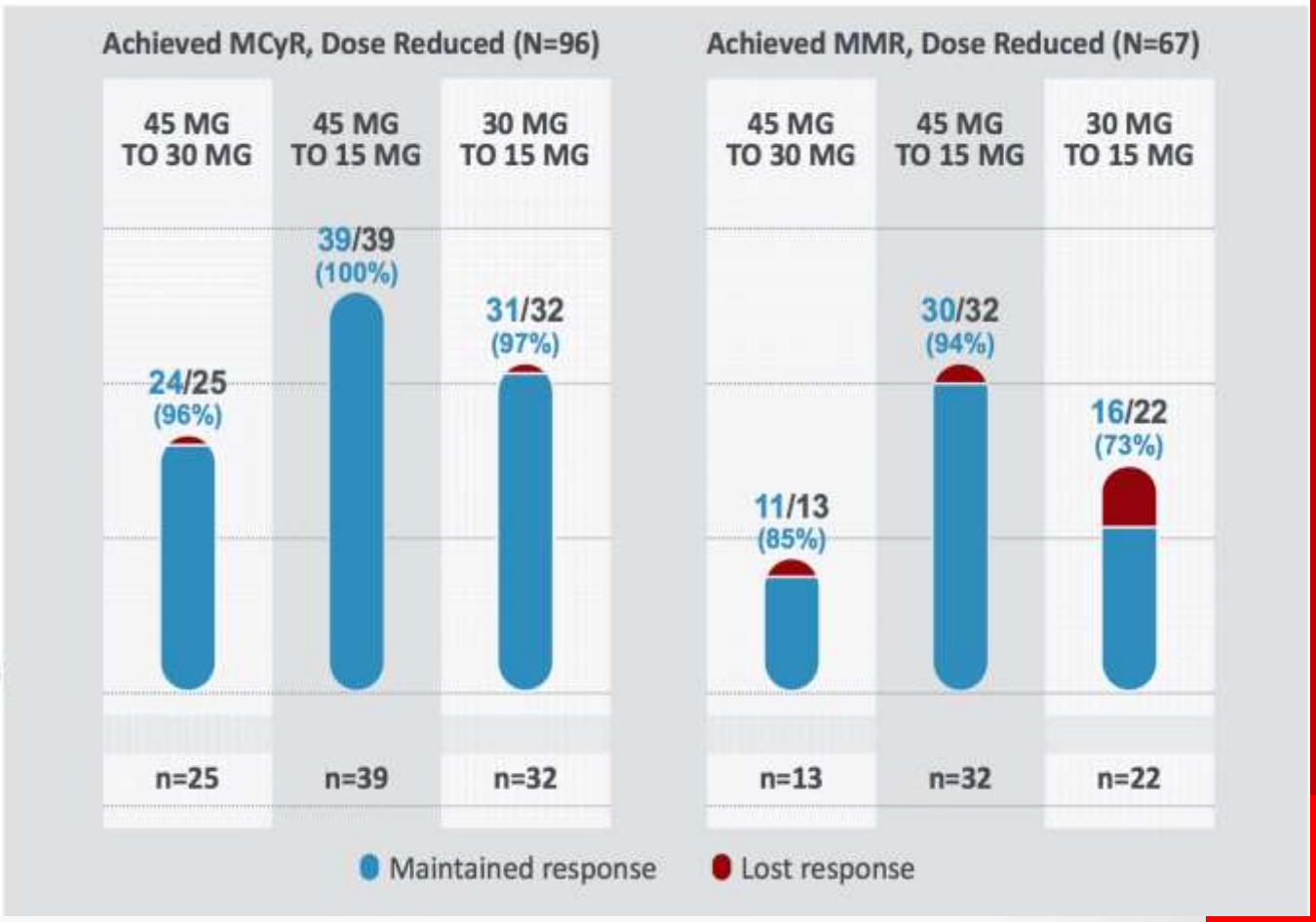
DOSE REDUCTION†	
At least 1 reduction, n (%)	172 (64)
>1 reduction, n (%)	74 (28)
Median time to first reduction, days (range)	64 (2-344)
Median time on reduced dose, days (range)	156 (1-362)

DOSE INTERRUPTION†	
At least 1 interruption, n (%)	199 (75)
>1 interruption, n (%)	126 (47)
Median time to first interruption, days (range)	29 (3-320)
Median duration of interruption, days (range)	35 (3-309)

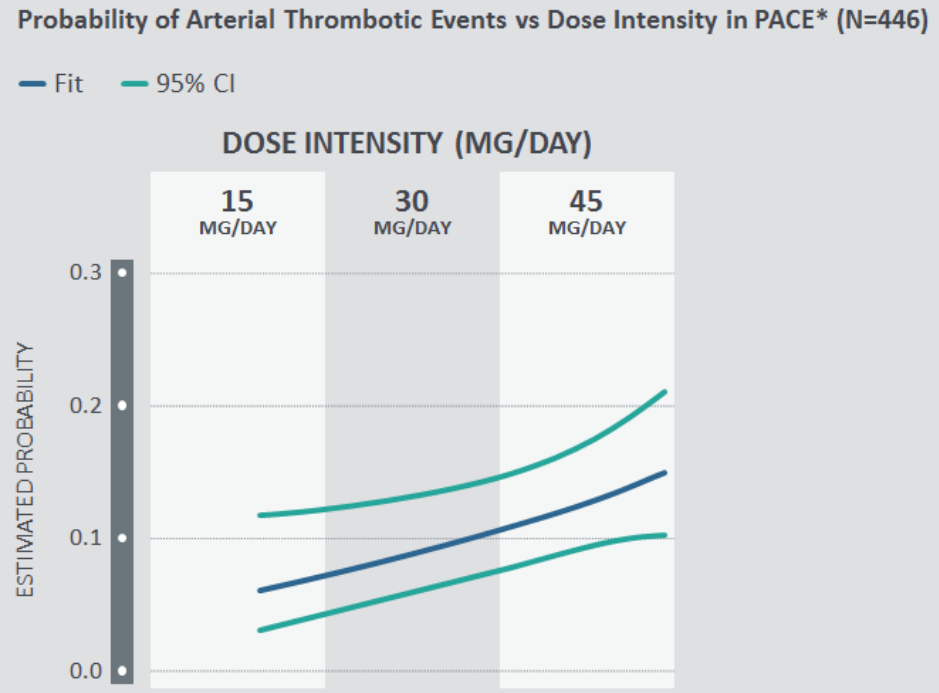
Hochhaus, et al. *J Clin Oncol*. 32:5s,2014 (suppl; abstr 7084)

PACE: Stability of Responses after dose reduction

- The total number of CP-CML patients achieving MCyR was 149 (59%) and MMR was 103 (39%)
- Reductions to 15 mg were frequent and were effective in maintaining responses



DOSE MODIFICATION IS A STRATEGY FOR MINIMIZING RISK



<u>Each 15 mg/day reduction</u>
in average daily dose intensity
leads to approximately
<u>a 33% reduction</u>
in the risk of arterial
thrombotic events

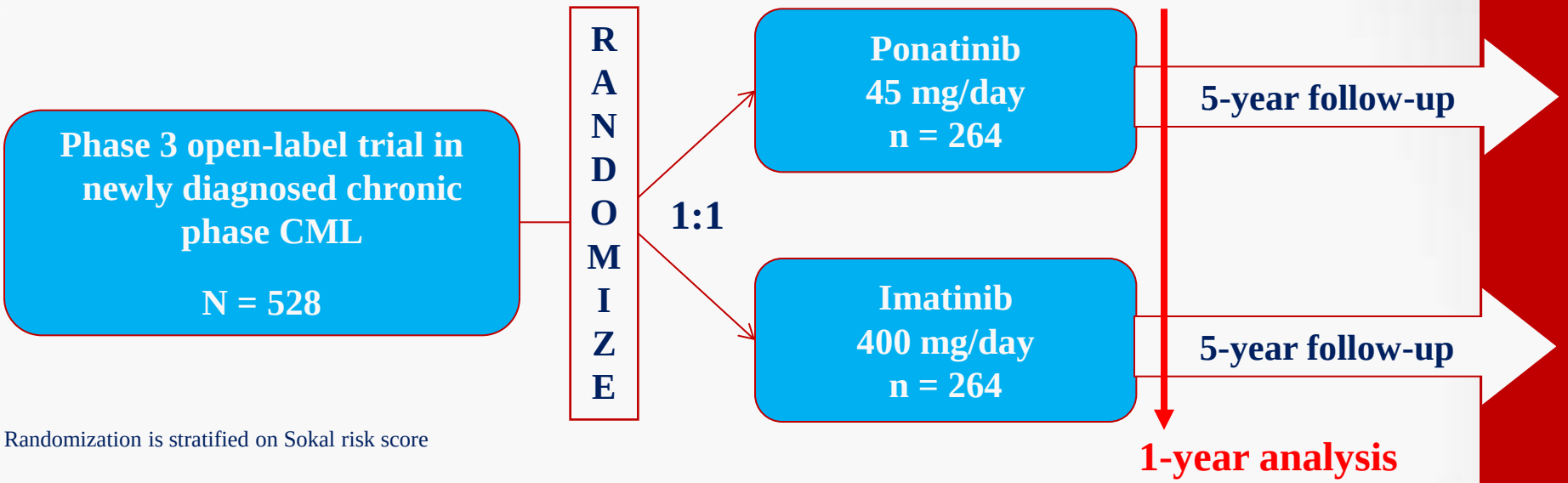
Median time to onset of ATEs in CP-CML: 281 (8-952) days (≈ 9 mesi)

Median time to onset of VTEs in CP-CML: 604 (62-802) days (≈ 20 mesi)

*Estimation by reduced multivariate model.

SOURCE: Hochhaus, et al. *J Clin Oncol*. 2014;32:5s (suppl; abstr 7084).

EPIC TRIAL DESIGN



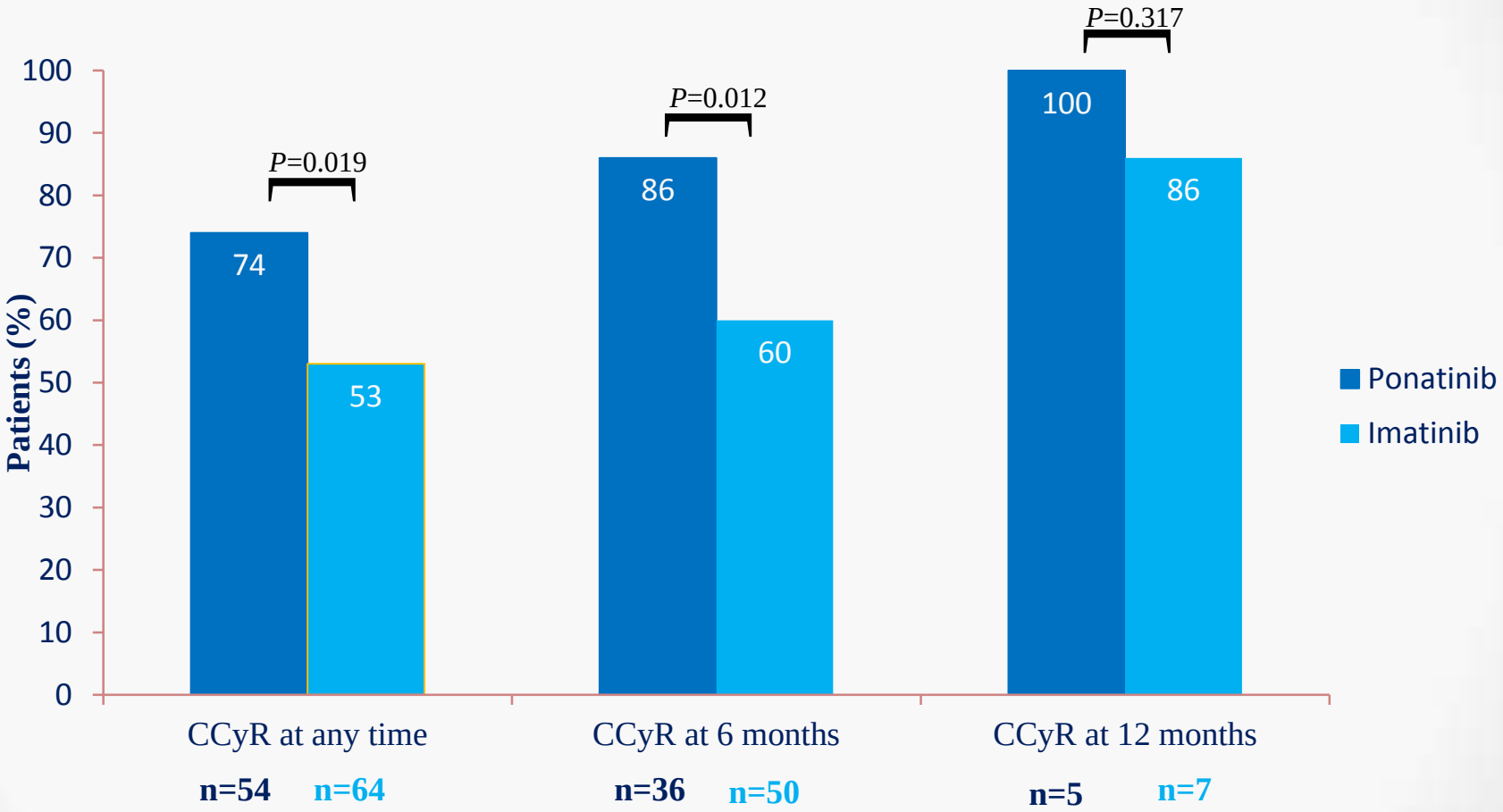
Randomization is stratified on Sokal risk score

Primary endpoint: Major Molecular Remission rate at 12 months

Secondary endpoints:

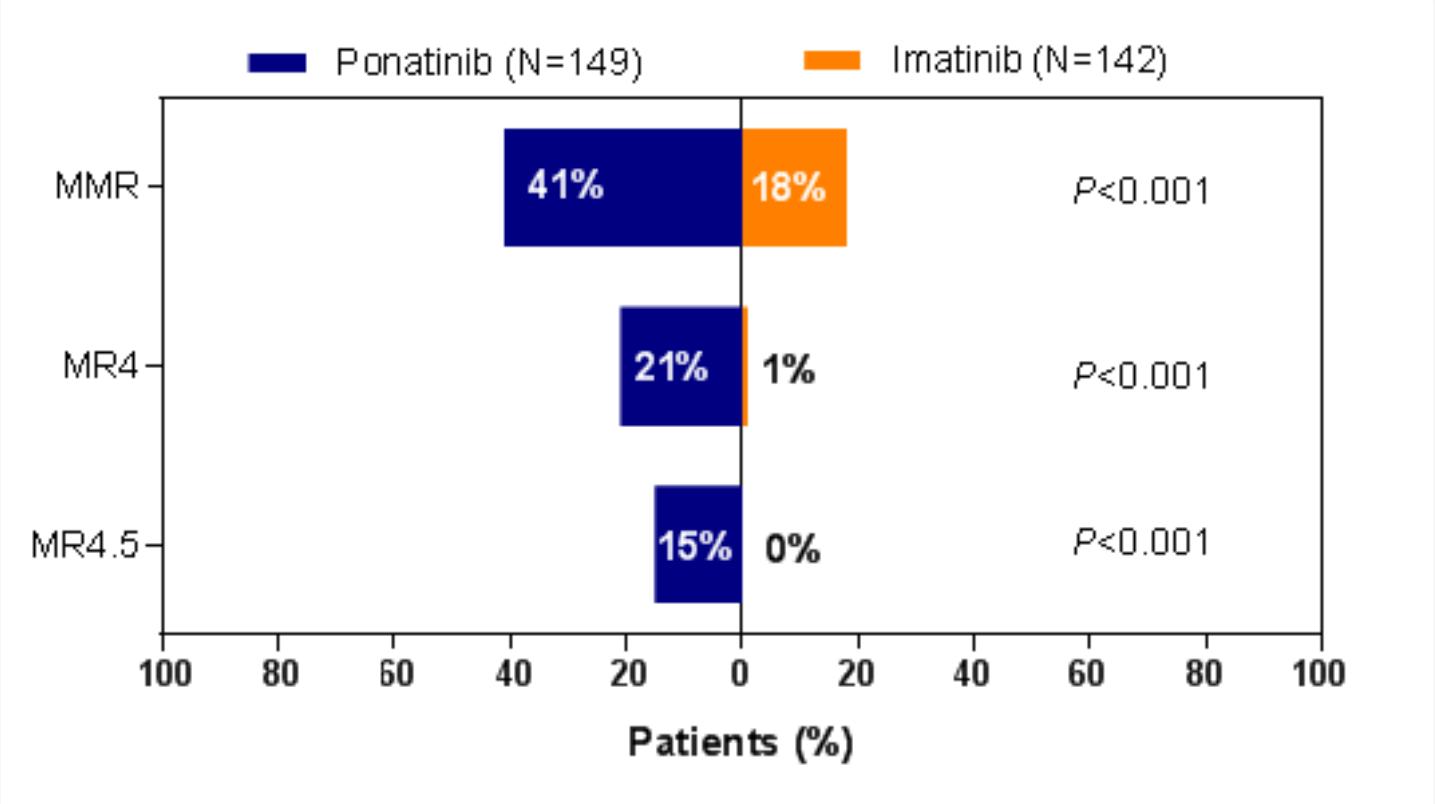
- MMR rate at 5 years
- Proportion of patients with <10% BCR-ABL/ABL at 3 months in both arms
- CCyR rate at 12 months
- PFS
- OS

COMPLETE CYTOGENETIC RESPONSE: EVALUABLE PATIENTS



Data as of 1 April 2014

BEST OVERALL MOLECULAR RESPONSE AT ANY TIME: EVALUABLE PATIENTS



Median time to MMR: ponatinib 100 (56–219) days; imatinib 169 (113–409) days

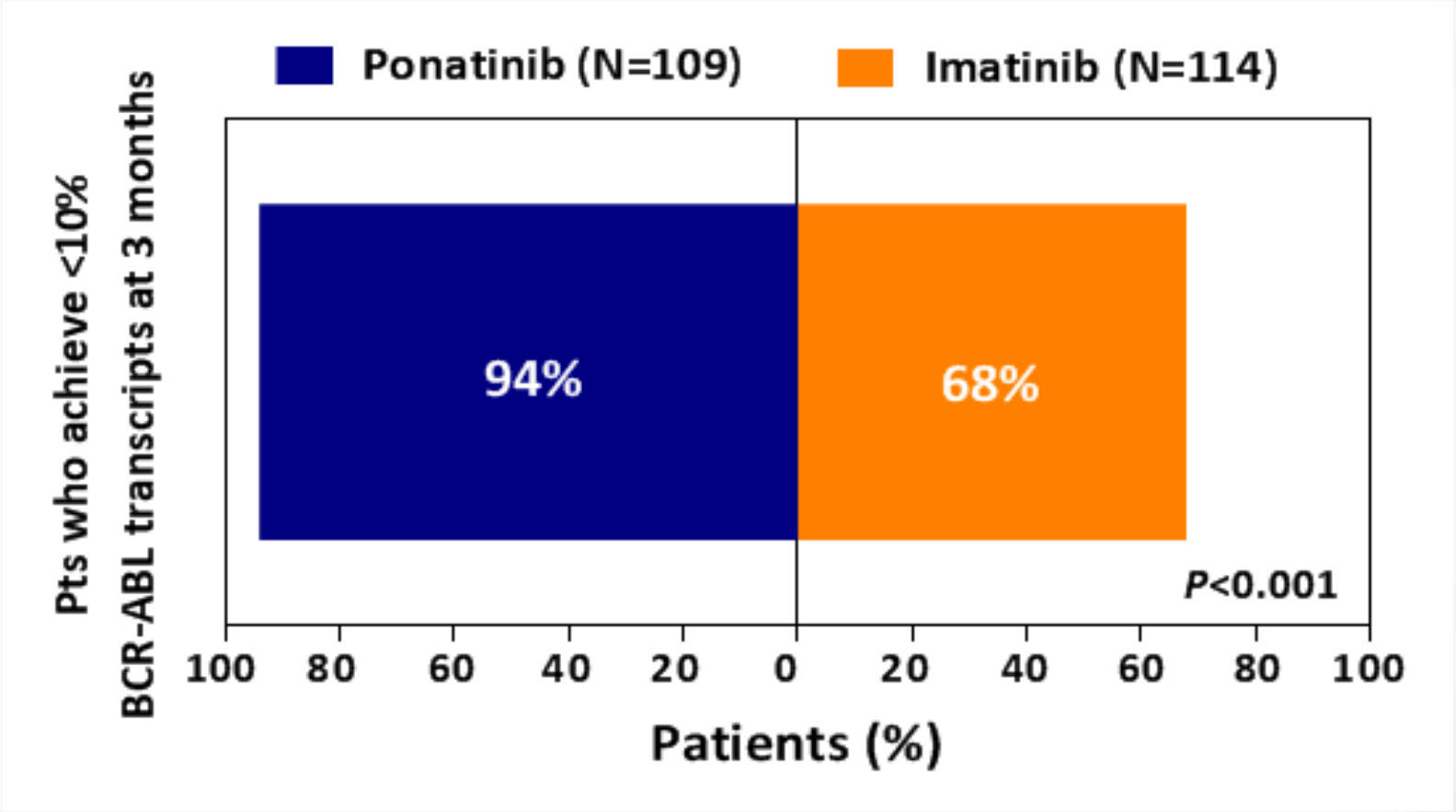
Data as of 1 April 2014

EPIC TRIAL: RESULTS

Table 1.

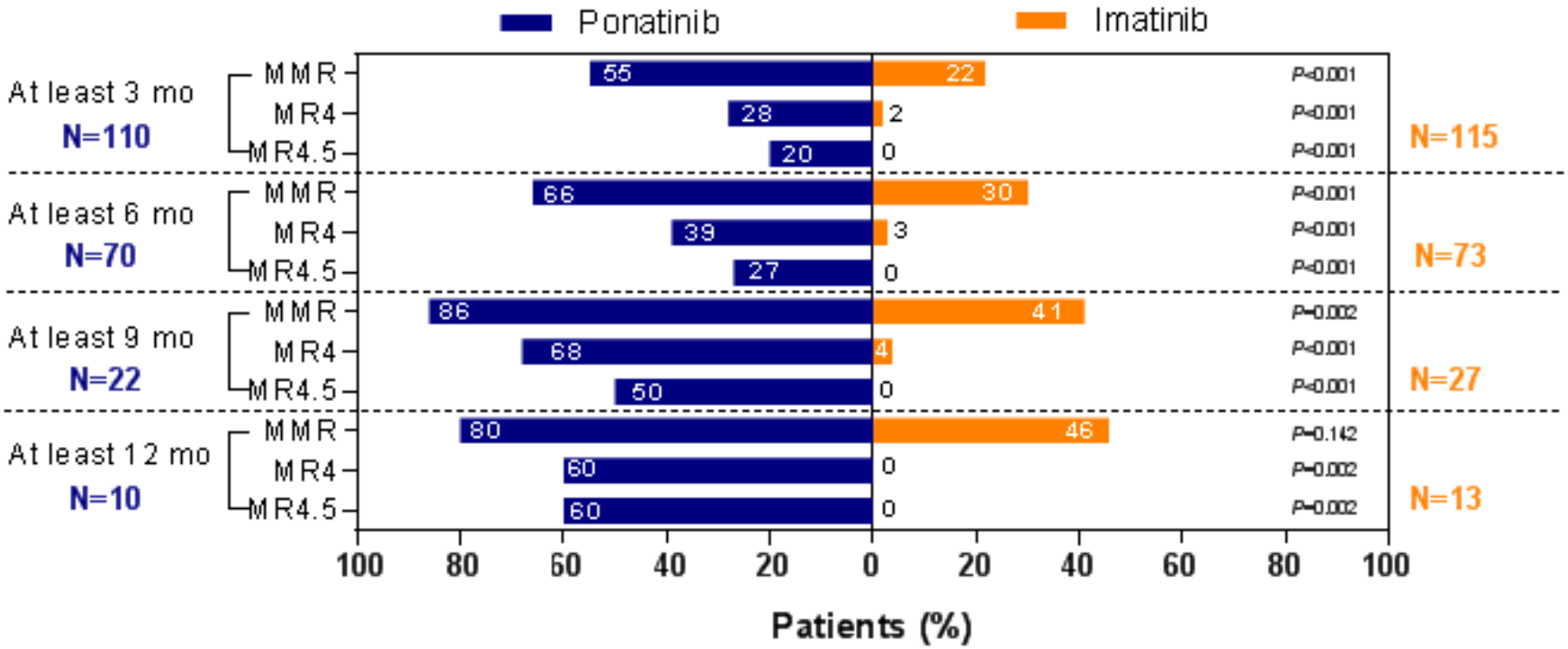
	At 3 months		At 6 months		At 9 months	
	Ponatinib	**Imatinib**	**Ponatinib**	**Imatinib**	**Ponatinib**	**Imatinib**
MMR	29% (28/95)	0% (0/98)	66% (27/41)	21% (9/42)	83% (10/12)	44% (7/16)
MR4.5	4% (4/95)	0% (0/98)	10% (4/41)	0% (0/42)	25% (3/12)	0% (0/16)
≤10% BCR-ABL transcripts	94% (89/95)	68% (67/98)	100% (41/41)	83% (35/42)		

ACHIEVEMENT OF <10% BCR-ABL AT 3 MONTHS: EVALUABLE PATIENTS



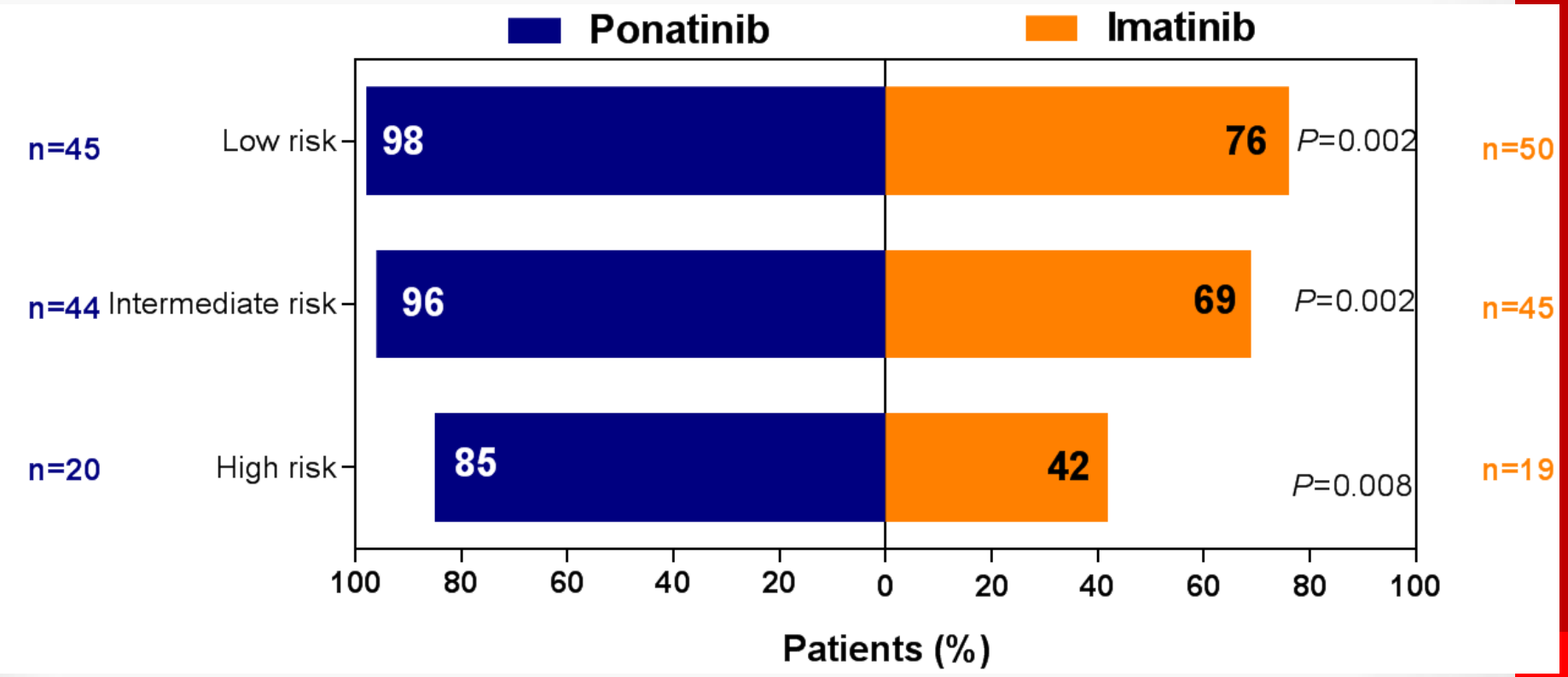
Data as of 1 April 2014

Best Molecular Response after at least 3, 6, 9, and 12 months: evaluable patients



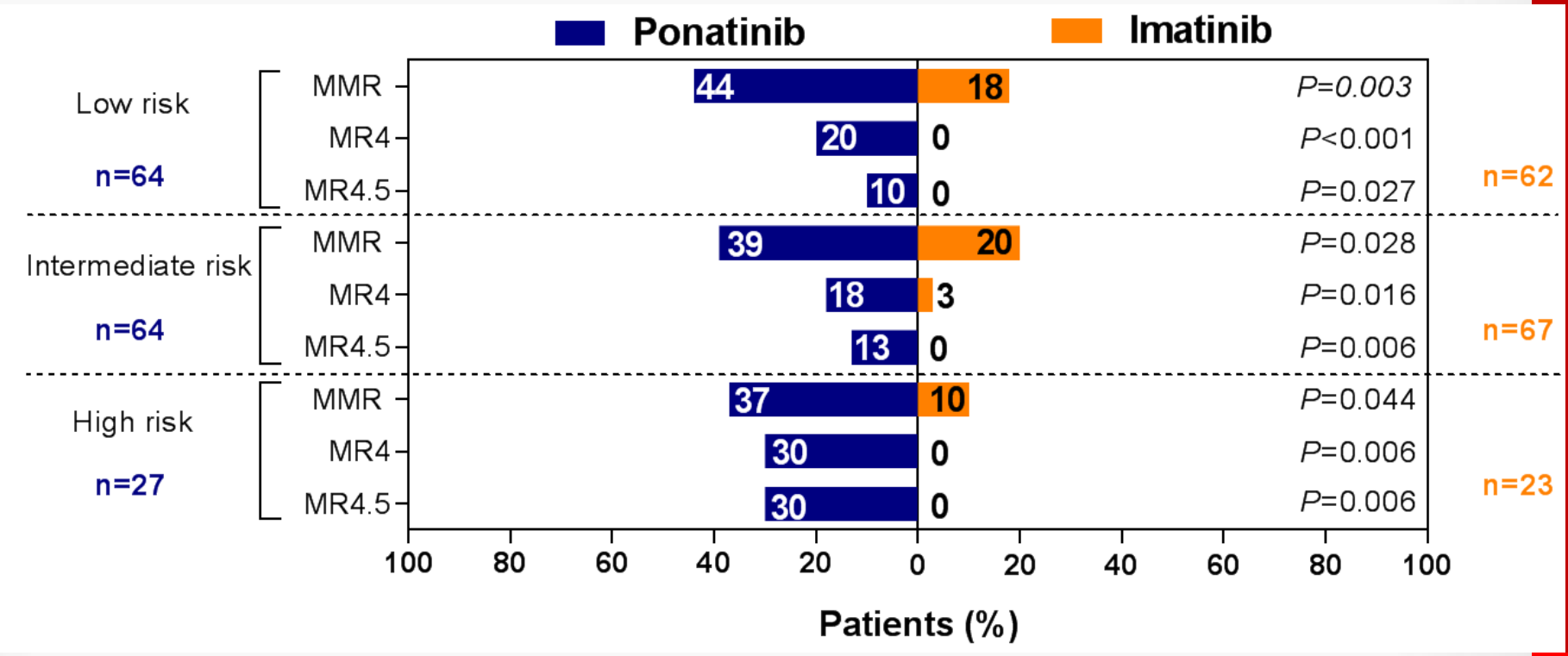
Data as of 1 April 2014

ACHIEVEMENT OF <10% BCR-ABL AT 3 MONTHS BY SOKAL RISK SCORE



Data as of 1 April 2014

BEST MOLECULAR RESPONSE AT ANY TIME BY SOKAL RISK SCORE



Data as of 1 April 2014

Patients With Treatment-Emergent AEs

Preferred Term	Ponatinib n=154		Imatinib n=152	
	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
Non-hematologic				
Rash	58 (38)	10 (7)	25 (16)	2 (1)
Abdominal pain	55 (36)	4 (3)	15 (10)	0
Headache	50 (33)	1 (1)	20 (13)	0
Constipation	41 (27)	0	3 (2)	0
Increased lipase	41 (27)	22 (14)	11 (7)	3 (2)
Myalgia	40 (26)	1 (1)	27 (18)	0
Nausea	34 (22)	2 (1)	52 (34)	0
Fatigue	32 (21)	1 (1)	30 (20)	0
Arthralgia	29 (19)	2 (1)	23 (15)	1 (1)
Pyrexia	28 (18)	0	7 (5)	1 (1)
Dry skin	27 (18)	1 (1)	5 (3)	0
Hypertension	27 (18)	7 (5)	3 (2)	0
Diarrhea	20 (13)	1 (1)	41 (27)	1 (1)
Vomiting	18 (12)	1 (1)	28 (18)	0
Peripheral edema	14 (9)	0	22 (15)	0
Muscle spasm	11 (7)	0	52 (34)	2 (1)
Periorbital edema	1 (1)	0	33 (22)	0
Hematologic				
Thrombocytopenia	38 (25)	19 (12)	21 (14)	10 (7)

Data as of 1 April 2014

Patients With Treatment-Emergent SAEs

Preferred Term	Ponatinib n=154		Imatinib n=152	
	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
Non-hematologic				
Pancreatitis	5 (3)	5 (3)	0	0
Atrial fibrillation	3 (2)	2 (1)	0	0
Acute myocardial infarction	2 (1)	2 (1)	0	0
Angina pectoris	2 (1)	0	0	0
Cardiac failure	2 (1)	1 (0.6)	0	0
Abdominal pain	2 (1)	1 (0.6)	0	0
Pyrexia	2 (1)	0	1 (0.7)	1 (0.7)
Pneumonia	2 (1)	1 (0.6)	1 (0.7)	0
Peripheral arterial occlusive disease	2 (1)	2 (1)	0	0
Plural effusion	0	0	2 (1)	1 (0.7)
Hematologic				
Thrombocytopenia	3 (2)	3 (2)	0	0

Data as of 1 April 2014

PATIENTS WITH TREATMENT-EMERGENT VASCULAR OCCLUSIVE EVENTS

	Ponatinib n=154 n (%)		Imatinib n=152 n (%)	
	AE	SAE	AE	SAE
Arterial thrombotic events	11 (7)	10 (7)	3 (2)	1 (0.7)
Cardiovascular	5 (3)	4 (3)	1 (0.7)	0
Cerebrovascular	3 (2)	3 (2)	1 (0.7)	1 (0.7)
Peripheral vascular	3 (2)	3 (2)	1 (0.7)	0
Venous thromboembolic events	1 (0.6)	1 (0.6)	0	0
Total vascular occlusive events	12 (8)	11 (7)	3 (2)	1 (0.7)

- Time to onset of vascular occlusive events:
  - Ponatinib 10–233 days; imatinib 2–156 days
- Of the 12 patients treated with ponatinib with vascular occlusive events, 11 had at least 1 risk factor or relevant medical history

Data as of 1 April 2014

VASCULAR OCCLUSIVE EVENTS

List of Vascular Occlusive AEs	
Ponatinib n=12[a]	Imatinib n=3[a]
• Cardiac discomfort (n=1) • Coronary artery stenosis (n=1) • Intermittent claudication (n=1) • Acute myocardial infarction (n=2) • Angina pectoris (n=2) • Coronary artery disease (n=2) • Cerebrovascular accident (n=1) • Dysarthria (n=1) • Peripheral artery thrombosis (n=1) • Retinal vein thrombosis (n=1) • Transient ischemic attack (n=1) • Peripheral arterial occlusive disease (n=2)	• Electrocardiogram ST-segment depression (n=1) • Peripheral vascular disorder (n=1) • Hypoxic-ischemic encephalopathy (n=1)

Data as of 1 April 2014

EPIC TRIAL: ADVERSE EVENTS

Ponatinib

- AE ≥25%, all-grade, treatment related
  - rash (36%)
  - abdominal pain (32%),
  - headache (31%)
  - lipase increased (26%)
  - myalgia (26%)
- 11% G3/4 thrombocytopenia
- 3% G3/4 neutropenia
- 9 (7%) ponatinib pts experienced vascular occlusive events (SAEs: 6)

Imatinib

- AE ≥25%, all-grade, treatment related
  - nausea (32%)
  - muscle spasms (31%)
- 2% G3/4 thrombocytopenia
- 8% G3/4 neutropenia
- 5 (4%) imatinib pts experienced vascular occlusive events (SAE: 1)

SAEs occurring in ≥3 ponatinib patients were pancreatitis (5), atrial fibrillation (3), and thrombocytopenia (3); no individual SAEs occurred in ≥3 imatinib patients

SUMMARY

- With 4 years of follow-up, ponatinib continues to provide benefit to ongoing CP-CML patients in PACE

- Analysis by treatment history indicates that patients who had received fewer TKIs prior to study entry appeared to exhibit better efficacy and safety profiles, though even heavily pretreated patients benefitted

- For CP-CML patients who achieved MCyR, reduction to 15 mg/day was recommended. Lowering the overall dose intensity may reduce the risk of ATEs

- Treatment decisions should be primarily guided by individual patient and disease factors, including mutation status, and physicians should weigh both the benefits and risks of prescribing ponatinib

GRAZIE PER L'ATTENZIONE!

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