LMC: nuove tecnologie, nuovi approcci

Roma, 16 novembre 2015

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

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Indicazione AIFA

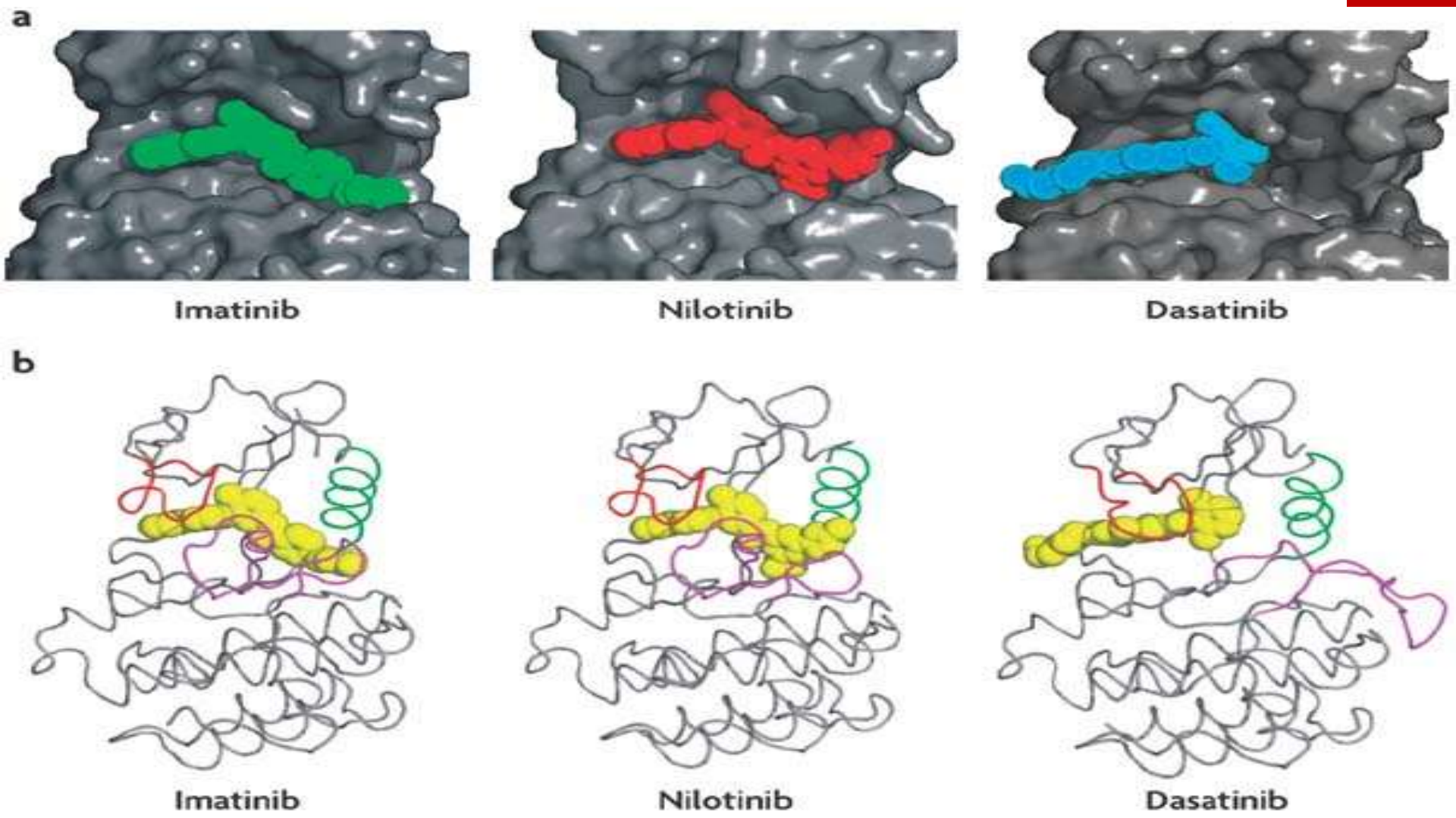
Iclusig è indicato in pazienti adulti affetti da:

- Leucemia mieliode 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 apprpriato, oppure in pazienti nei quali è stata identificata la mutazione T315I;
- Leucemia linfoblastica acuta con cromosoma Philadelphia positivo (ALL 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.

Phase 1 trial (NCT00660920): open-label, dose-escalation trial of ponatinib (starting dose range: 2–60 mg QD) in adults with a relapsed/refractory hematologic malignancy

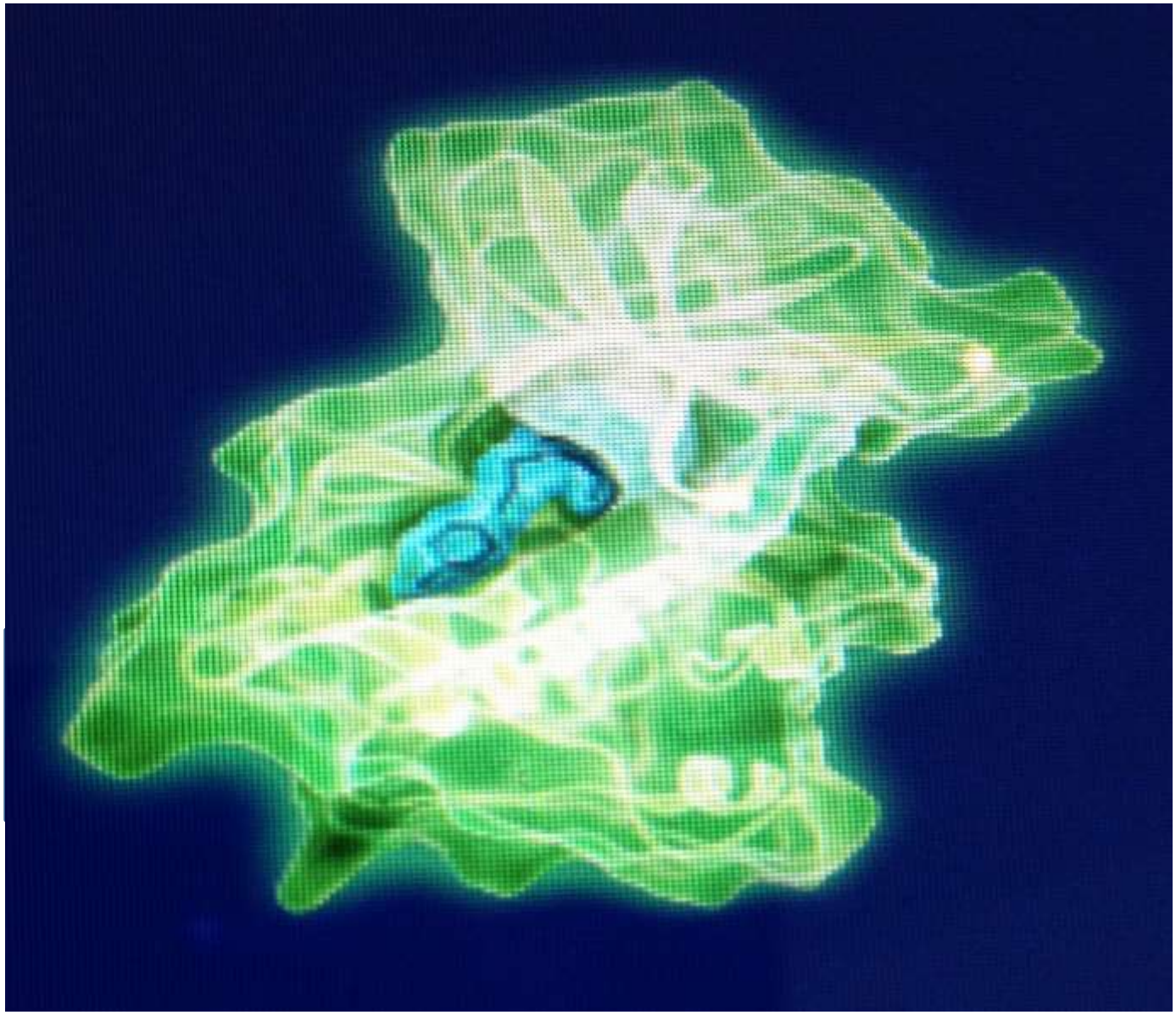
PACE trial (NCT01207440): phase 2, single-arm, open-label trial of ponatinib (starting dose 45 mg QD) in 449 adults with CML or Ph+ ALL who were resistant or intolerant to dasatinib or nilotinib or who had the T315I mutation

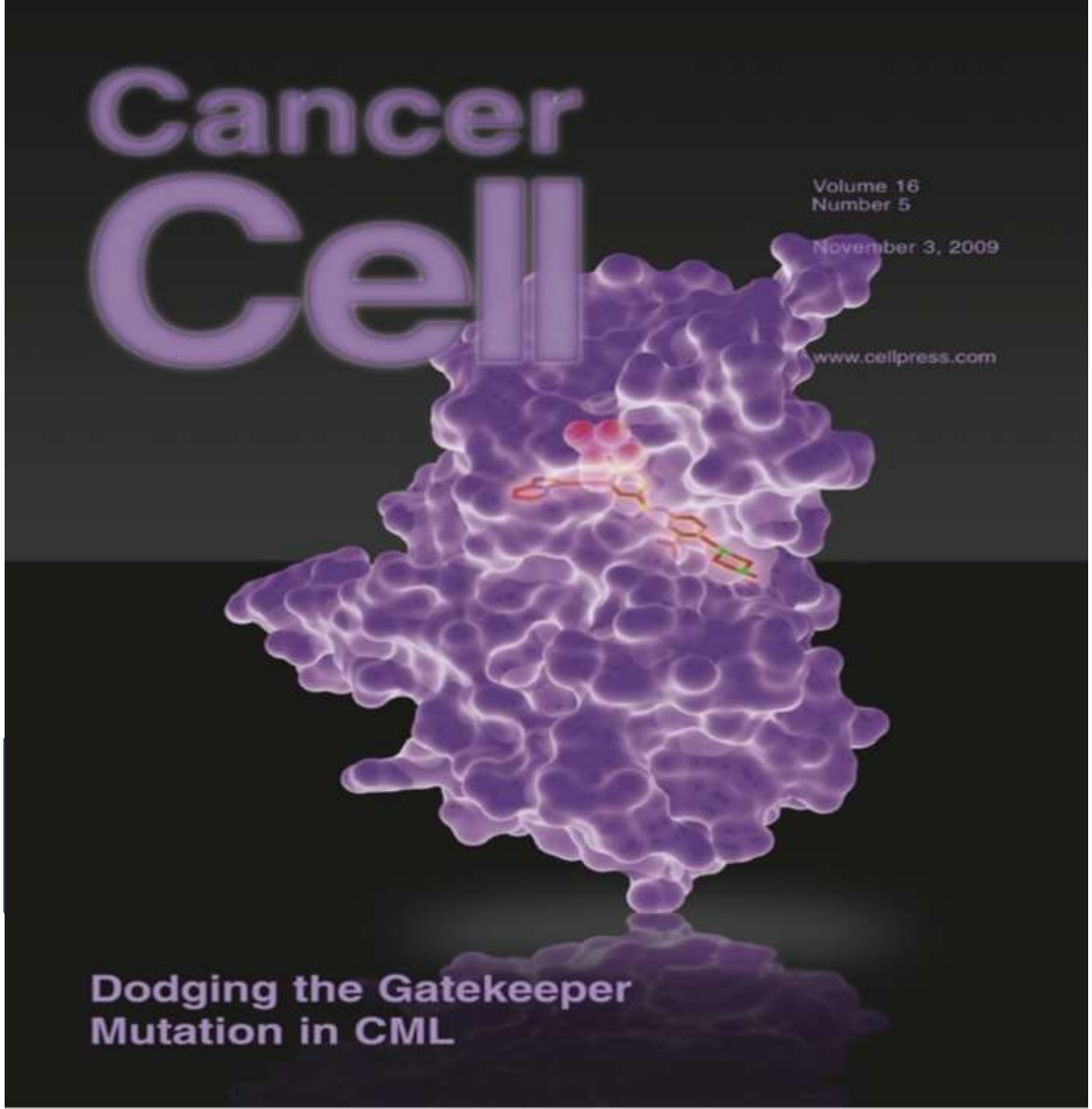
TKI prima e seconda generazione



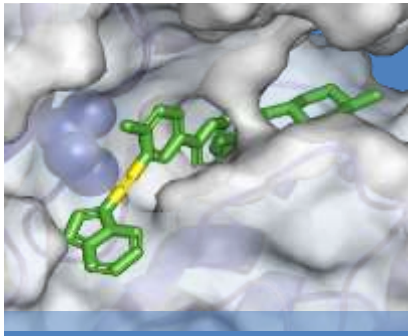
Nature Reviews | Cancer

Bosutinib: dual inhibitor scr and abl kinase




Cancer
Cell
Volume 16
Number 5
November 3, 2009
www.cellpress.com
Dodging the Gatekeeper
Mutation in CML

Ponatinib was designed to overcome mutation-driven resistance



triple bond (*yellow*) is a unique structural feature that evades the T315I gatekeeper mutant (*blue spheres*)

BCR-ABL Inhibitor Activity Against BCR-ABL Single Mutants

BCR-ABL MUTANT	PONATINIB	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB
Native	3	201	15	2	71
M244V	3	287	12	2	147
L248R	8	10000	549	6	874
L248V	4	586	26	5	182
G250E	5	1087	41	4	85
Y253H	5	4908	179	3	40
E255K	6	2487	127	9	181
E255V	16	8322	784	11	214
V299L	4	295	24	16	1228
T315A	4	476	50	59	122
T315I	6	9773	8091	10000	4338
F317C	3	324	16	45	165
F317I	7	266	25	40	232
F317L	4	675	21	10	82
F317V	10	1023	26	104	1280
M351T	4	404	15	2	97
E355A	7	441	18	3	74
F359C	6	728	47	2	70
F359I	11	324	64	3	76
F359V	4	346	41	2	59
H396R	4	395	23	2	60
E459K	5	612	38	4	127

Criteria Used to Classify Drug Potency

Effective C_{ave} at rec. dose	28*	444	131	11	159
IC50 <75% of C_{ave}	<21	<333	<98	<8	<119
IC50 75-150% of C_{ave}	21-32	333-500	98-147	8-12	119-179
IC50 150-300% of C_{ave}	33-95	501-1499	148-442	13-37	180-537
IC50 >300% of C_{ave}	>95	>1499	>442	>37	>537

*Ponatinib 45-mg dose. Data shown as mean IC50 (nM) from 3 separate experiments

SOURCE: Gozgit, et al. *Blood.* 2013;122 (abstr 3992).

	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB	PONATINIB
Standard dose, 1st line	400 mg OD	300 mg TD	100 mg OD	NA	NA
Dose, 2nd line	3-400 mg OD	400 mg TD	70 mg TD, or 140 mg OD	500 mg OD	45 mg OD
Plasma half-life [a]	~ 20h [a]	~ 15 h [a]	~ 5 h [a]	~ 24 h	~ 19 h
Plasma conc., peak	4202 ± 1272 [a]	2329 ± 772 [a]	133 ± 74 [a]	~ 392	145 ± 73
Plasma conc, through	2062 ± 1334 [a]	1923 ± 1233[a]	5.5 ± 1.4[a]	~ 268	64 ± 29
IC50, BCR-ABL 1	260-679	10-25	0.8-1.8	42	0.5
IC50, PDGFRα	72	75	2.9	3.0	1.1
IC50, cKit	99	209	18	10000	12
IC50, Src	>1000	>1000	0.1	3.0	5.4
IC50, VEGFR2	10000	3720	NA	NA	1.5
IC50, BTK	>5000	NA	1.1	2.5	849
Food effect	weak	strong [b]	weak	weak	weak
Gastric ph elevating agents effect	no	weak	strong [c]	strong [c]	NA
Chief side-effects (α)	fatigue, myalgia, fluid retention	skin rash, glucose, bilirubine and lipase elevation	thrombocytopenia, pleural effusion	diarrhea, nausea, liver (AST,ALT)	thrombocytopenia, skin rash, lipase elevation
Chief complications (α)	none	arterial thrombosis	pulmonary hypertension	NA	arterial thrombosis

(α) personal assessment (a) For standard dose, 1st line; (b) 87% increase in AUC after a high-fat meal; (c) 60-80% reduction in AUC by H2 blocker;
OD = Once Daily TD = Twice Daily NA = not available or not known

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

Scopo della terapia

1- remissione ematologica

normalizzazione emocromo, scomparsa segni e sintomi

2- remissione citogenetica (CCyR)

assenza del cromosoma Ph all'esame del cariotipo o % cellule con fusione FISH<3%

3-remissione molecolare

a- maggiore (RMM) – quantita' trascritto <0.1%

b- 4.0 (RM4) – trascritto <0.01%

c- 4.5 (RM 4.5) trascritto <0.0032%

Risposta ottimale

	Cytogenetic Responses			Molecular Responses		
	2006	**2009**	**2013**	**2006**	**2009**	**2013**
	Optimal	**Optimal**	**Optimal**	**Optimal**	**Optimal**	**Optimal**
3 mo	CHR	≥ MinorCyR (Ph+ ≤ 65%)	**PCyR Ph+ ≤ 35%**	NA	NA	**BCR-ABL ≤ 10%**
6 mo	PCgR (Ph+ > 35%)	≥ PCyR (Ph+ ≤ 35%)	**CCyR Ph+ 0%**	NA	NA	**BCR-ABL < 1%**
12 mo	CCgR	CCyR (Ph+ 0%)	**NA**	NA	NA	**BCR-ABL ≤ 0.1%**
18 mo	NA	NA	**NA**	MMolR	MMR (BCR-ABL ≤ 0.1%)	**NA**
At any time	CCA/Ph+ cells, loss of Mmol, mutation	NA	**NA**	CCA/Ph+ cells, loss of Mmol, mutation	≥ MMR	**BCR-ABL ≤ 0.1%**

Baccarani M, et al. *Blood*. 2013;122(6):872-884, Baccarani M, et al. *J Clin Oncol*. 2009;27(35):6041-6051, Baccarani et al. *Blood*, 2006; 108:1809-20

Efficacy data

- In phase 1 and phase 2 (PACE) trials, ponatinib demonstrated significant response in leukemia patients in whom prior TKI therapy had failed[1,2]
  - 56% of chronic-phase (CP)-CML patients in PACE achieved major cytogenetic response (MCyR) by 12 months
- Ponatinib is the only approved oral TKI with clinical activity against the T315I mutant, which is uniformly resistant to other TKIs[3]
- Among patients with the T315I mutation, MCyR by 12 months was achieved with ponatinib in:
  - 92% of CP-CML patients (n=12) in the phase 1 trial[1]
  - 70% of CP-CML patients (n=64) in the PACE trial[2]

1. Cortes JE, et al. *N Engl J Med*. 2012;367:2075-2088. 2. Cortes JE, et al. *N Engl J Med*. 2013;369:1783-1796. 3. O'Hare T, et al. *Cancer Cell*. 2009;16:401-412.

PACE - Study Design

Primary Objective

- **Efficacy of ponatinib in CML or Ph+ ALL patients:**
  - **Resistant or intolerant (R/I) to dasatinib or nilotinib, or**
  - **With T315I mutation (confirmed by a central lab)**

Cohort Assignment	CP-CML	AP-CML	BP-CML/ Ph+ ALL
R/I to dasatinib or nilotinib	203	65	48
T315I mutation	64	18	46
Total*	270	85	94

*Includes 5 additional patients (3 CP-CML, 2 AP-CML) who were non-cohort assigned (post-imatinib, non-T315I), but treated

- Ponatinib 45 mg orally once daily

Baseline Characteristics and Patient Disposition

	Total[a,b] N=449	CP-CML n=270
Median age (range), y	59 (18–94)	60 (18–94)
Median time since diagnosis (range), y	6 (0.3–28)	7 (0.5–27)
Prior TKI therapy,[c] n (%)		
≥2 TKIs	418 (93)	252 (93)
≥3 TKIs	262 (58)	161 (60)
Median duration of treatment (range), mo	16.7 (0.03–48.5)	32.1 (0.1–48.5)
Median follow-up (range), mo	34.2 (0.1–48.6)	38.4 (0.1–48.6)
Ongoing, n (%)	150 (33)	121 (45)
Discontinued treatment, n (%)	299 (67)	149 (55)
Progressive disease	96 (21)	25 (9)
AE	66 (15)	46 (17)
Death[d]	24 (5)	8 (3)
Other[e]	113 (25)	70 (26)

[a]Includes 5 patients (3 CP-CML, 2 AP-CML) who were non–cohort assigned (post-imatinib, non-T315I), but treated; 4 of 5 remain on study; [b]44% of patients had no mutation (51% CP-CML), and 26% had mutations other than T315I (25% CP-CML) at study entry; [c]Includes approved and investigational TKIs; [d]7 deaths were assessed by investigators as possibly or probably related to ponatinib (CP-CML: pneumonia, acute myocardial infarction; AP-CML: fungal pneumonia, gastrointestinal hemorrhage; BP-CML/Ph+ ALL: cardiac arrest, gastric hemorrhage, mesenteric arterial occlusion); [e]Includes withdrawal by subject (including for transplant), lack of efficacy, investigator decision, loss to follow-up, noncompliance, protocol violation, and other reasons

Data as of 06 October 2014

PACE
Best Prior Response to Most Recent Dasatinib or Nilotinib

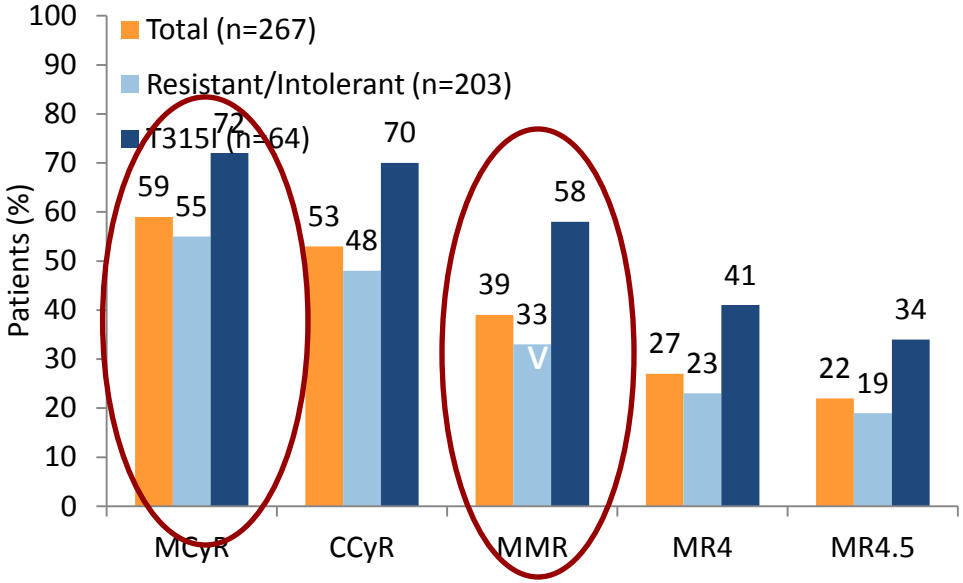
	% Attaining Endpoint		
	CP-CML N=256	AP-CML N=80	BP-CML/ Ph+ALL N=91
MaHR or better	N/A	21%	24%
MCyR or better	26%	15%	16%
MMR or better	3%	3%	7%

Denominator includes only patients who received prior dasatinib or nilotinib
MCyR or better: PCyR + CCyR + MMR + CMR
MaHR or better: MaHR + PCyR + CCyR + MMR + CMR
MMR or better: MMR + CMR

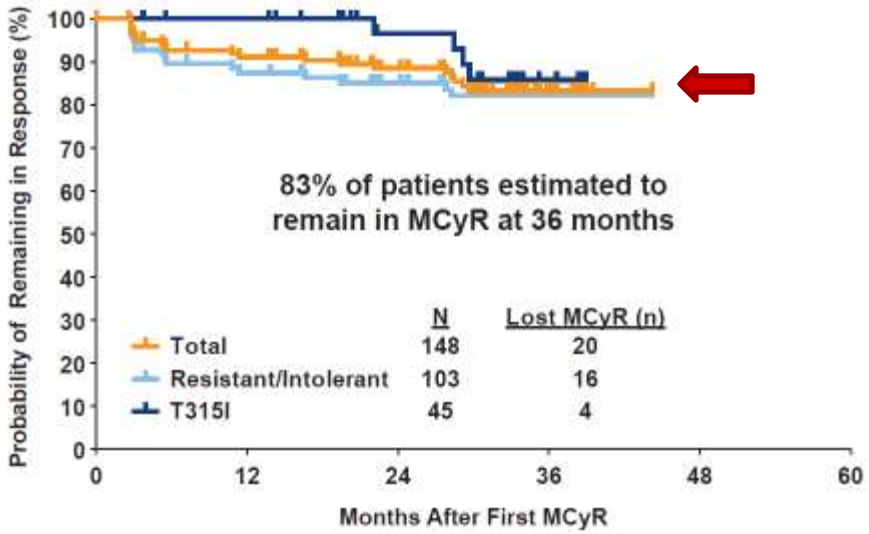
Efficacy of Ponatinib in CP-CML

- 39% of CP-CML patients achieved MMR or better
  - Median times to MCyR, CCyR, and MMR for responders were 2.8 (1.6–24.5) months, 2.8 (1.6–35.7) months, and 5.5 (1.8–32.9) months, respectively
- Responses were durable, with an estimated 83% of patients remaining in MCyR at 36 months

Responses at Any Time



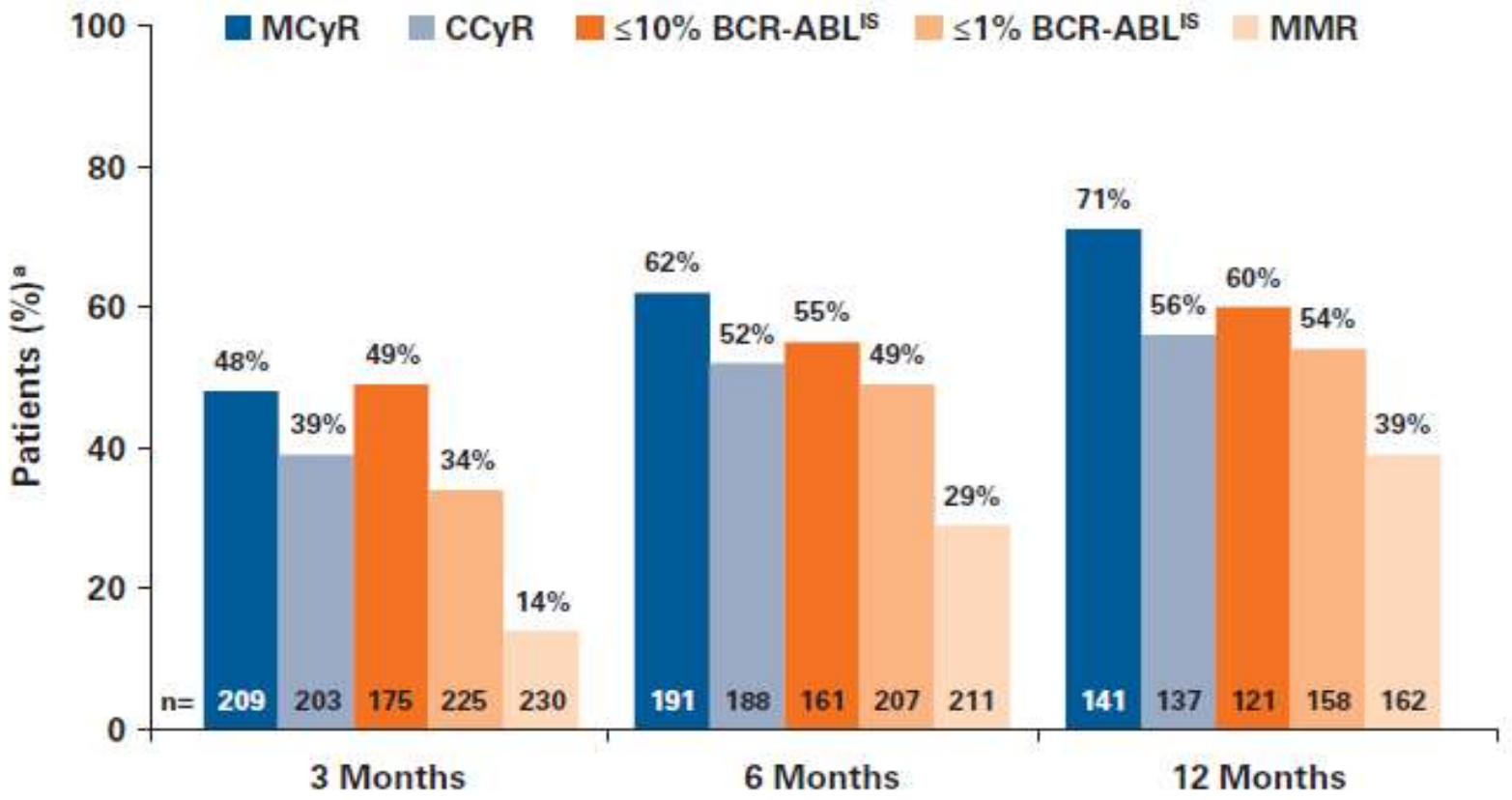
Duration of Response



MR4, 4-log molecular response, ≤0.01% BCR-ABL^{IS}; MR4.5, 4.5-log molecular response, ≤0.0032% BCR-ABL^{IS}

Data as of 06 October 2014

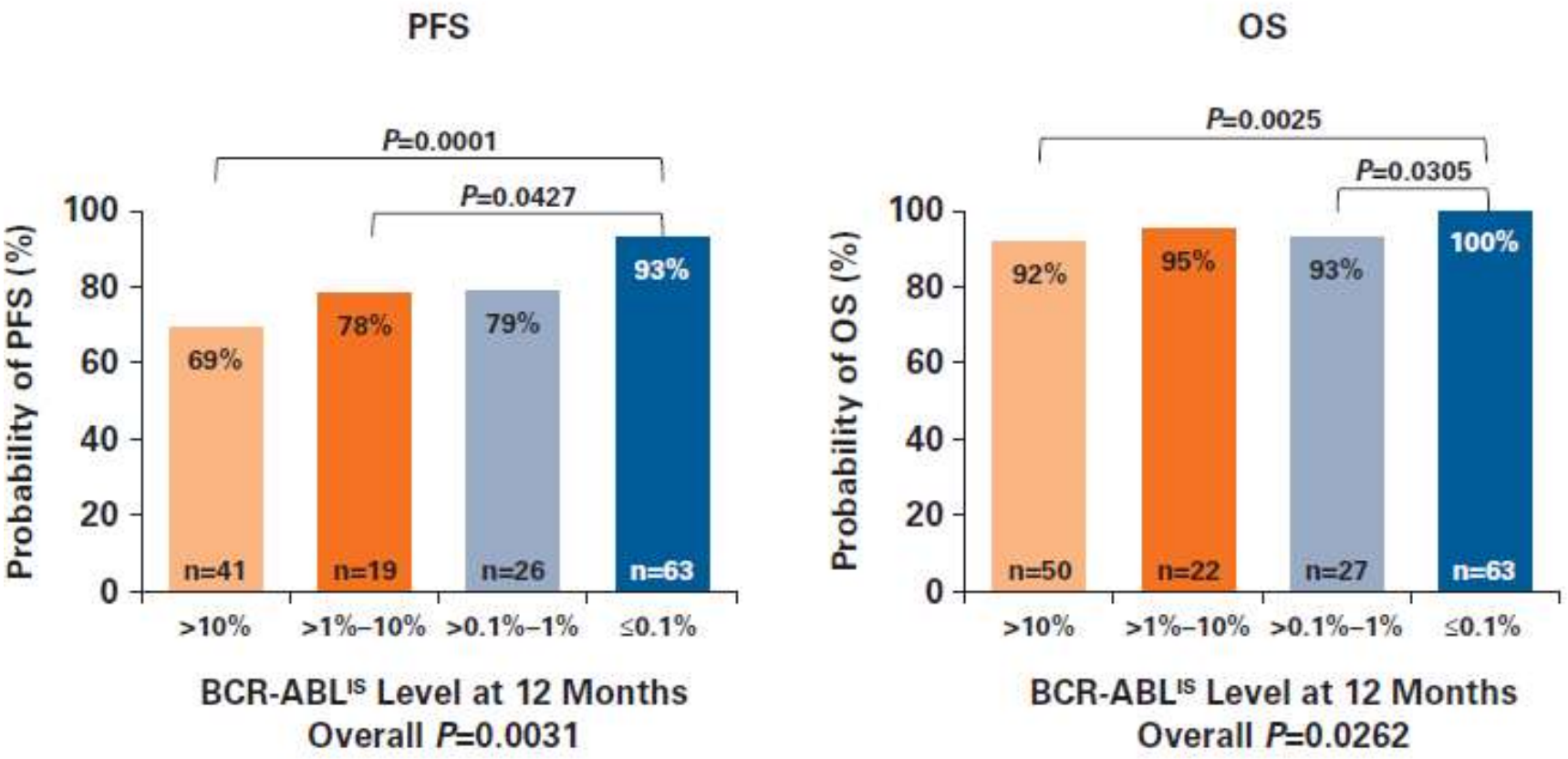
Patients Achieving Landmark Responses



MCyR, 0%–35% Ph+ metaphases; CCyR, 0% Ph+ metaphases; MMR, ≤0.1% BCR-ABLIS or undetectable disease in cDNA with ≥1000 ABL transcripts

a Denominator includes only patients who were evaluable at the landmark time point

PFS and OS at 2 Years Past Landmark by BCR-ABL IS Level at 12 Months



Treatment-Emergent AEs by Disease Group (≥20%, Any Grade)

	Total N=449		CP-CML n=270	
	Any Grade, n (%)	Grade 3/4, n (%)	Any Grade, n (%)	Grade 3/4, n (%)
Nonhematologic				
Abdominal pain	188 (42)	39 (9)	122 (45)	26 (10)
Rash[a]	185 (41)	18 (4)	124 (46)	10 (4)
Constipation	167 (37)	10 (2)	110 (41)	7 (3)
Headache	167 (37)	11 (2)	115 (43)	9 (3)
Dry skin	163 (36)	11 (2)	112 (41)	9 (3)
Fatigue	134 (30)	13 (3)	80 (30)	6 (2)
Pyrexia	132 (29)	11 (2)	69 (26)	3 (1)
Arthralgia	128 (29)	10 (2)	84 (31)	8 (3)
Hypertension[b]	127 (28)	49 (11)	86 (32)	33 (12)
Nausea	126 (28)	3 (<1)	72 (27)	2 (<1)
Vomiting	96 (21)	5 (1)	48 (18)	4 (1)
Increased lipase	95 (21)	53 (12)	70 (26)	32 (12)
Diarrhea	94 (21)	7 (2)	52 (19)	2 (<1)
Myalgia	94 (21)	3 (<1)	64 (24)	3 (1)
Hematologic				
Thrombocytopenia	195 (43)	160 (36)	121 (45)	95 (35)
Neutropenia	113 (25)	100 (22)	53 (20)	45 (17)
Anemia	107 (24)	69 (15)	48 (18)	25 (9)

[a]Combines the terms erythematous, macular, and papular rash; [b]379/449 (84%) patients had elevated blood pressure at baseline (≥140/90, 47%); 306/449 (68%) patients experienced any increase from baseline in blood pressure on study

Data as of 06 October 2014

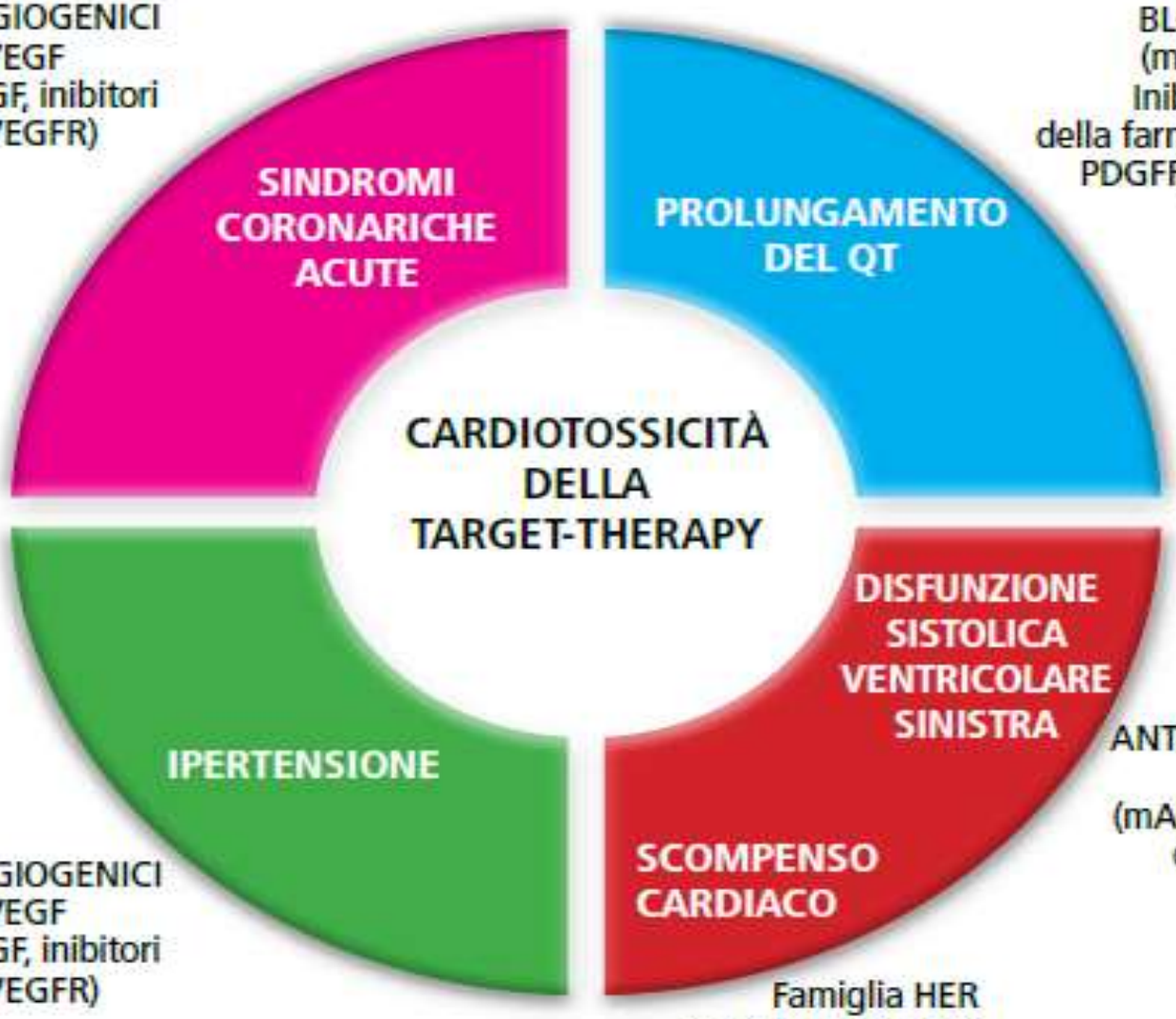
Profilo di tollerabilità studio PACE

- I più frequenti **AEs** registrati sono stati: rash e cute secca, sintomi costituzionali (costipazione, cefalea, fatigue, febbre, nausea, vomito e diarrea), ipertensione, incremento lipasi, mielosoppressione (piastrinopenia, neutropenia e anemia)
- I più frequenti **SAEs** (grado 3/4): piastrinopenia, neutropenia, anemia, incremento lipasi, ipertensione.

- Nell'ottobre 2013 warning FDA per evidenza di un numero elevato di eventi vascolari suggeriva attento monitoraggio dei pazienti in trattamento (ipertensione, alterazioni metaboliche, riconoscimento precoce problemi vascolari sia arteriosi che venosi) e riduzione del dosaggio a 30 mg e a 15 mg/die
- Lo studio EPIC (I linea) veniva sospeso per precauzione

Cortes et al, ASH 2014 abst 3135

CARDIOTOSSICITÀ ASSOCIATA A TARGET THERAPY



Ederhy et al. Clin Rev Oncol Hematol 2011

Cumulative and Exposure-Adjusted Incidences of Arterial and Venous Thrombotic Events[a]

- Tempo mediano di insorgenza di **ATE**s in CP:

  13.8 mesi

- Tempo mediano di insorgenza **VTE**s in CP:

  21 mesi

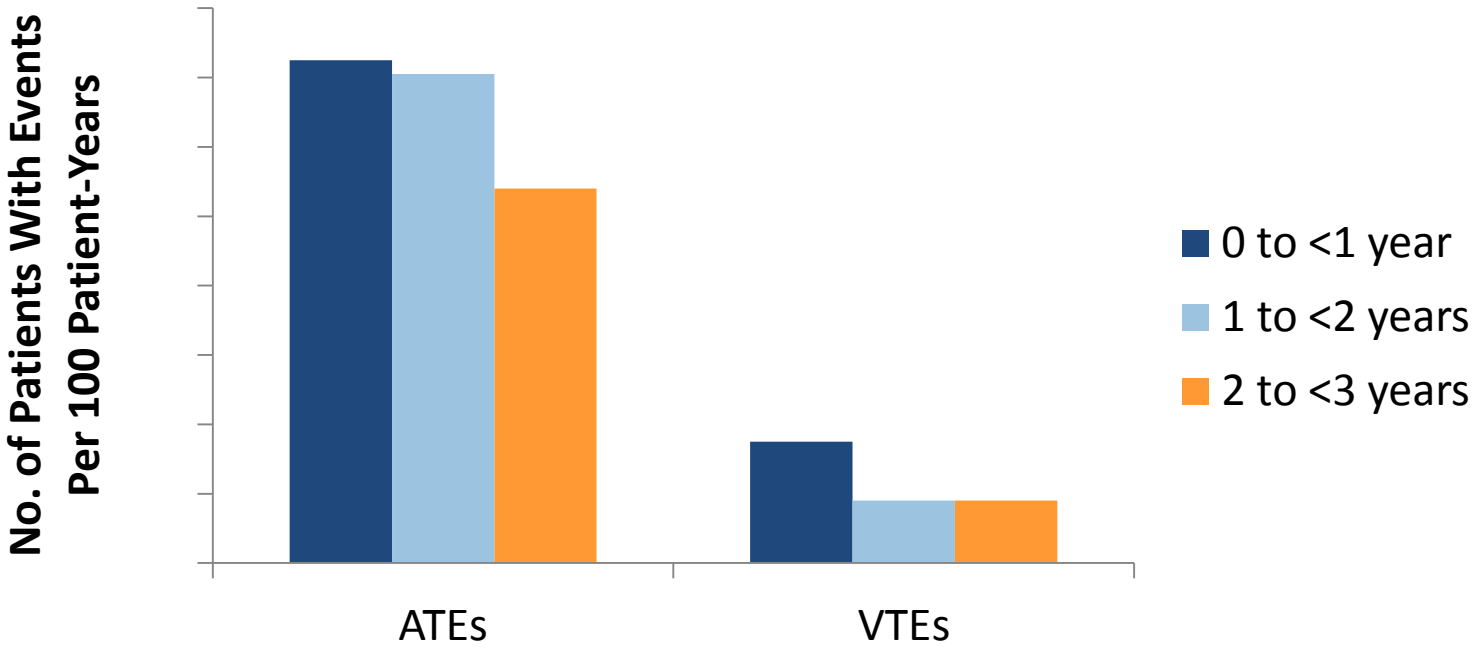
	Total N=449		CP-CML n=270	
	AE	SAE	AE	SAE
Cumulative exposure, patient-years	778.9		577.4	
ATEs, n (%)	99 (22)[b]	78 (17)[c]	74 (27)	60 (22)
Cardiovascular	52 (12)	37 (8)	36 (13)	28 (10)
Cerebrovascular	37 (8)	28 (6)	31 (11)	23 (9)
Peripheral vascular	37 (8)	27 (6)	28 (10)	20 (7)
Exposure-adjusted ATEs, 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

AE, total AEs, including SAEs; SAE, serious AEs only, designated in accordance with standard regulatory criteria

Exposure-Adjusted Yearly Incidence Rates for Newly Occurring Arterial and Venous Thrombotic Events – All Patients

Non c'è stato incremento nell'incidenza di nuovi eventi trombotici arteriosi e venosi con l'aumentare del tempo di esposizione



Relative Risk of Serious Arterial Thrombotic Events by Risk Category (Univariate Analysis)

Risk Category (n)	Rate of Serious ATEs in Patients With Risk Category[f], %	Rate of Serious ATEs in Patients Excluding Those With Risk Category[g], %	Relative Risk (95% CI)
Age ≥65 years (n=155)	24	14	1.7 (1.1–2.6)
Gender, male (n=238)	21	13	1.6 (1.0–2.4)
History of diabetes[a] (n=72)	31	15	2.1 (1.3–3.1)
History of ischemic heart disease[b] (n=101)	32	13	2.4 (1.6–3.6)
History of hypertension[c] (n=240)	25	9	2.7 (1.7–4.4)
History of hypercholesterolemia[d] (n=242)	22	12	1.8 (1.2–2.8)
History of nonischemic heart disease[b] (n=192)	19	16	1.1 (0.8–1.7)
History of obesity[e] (n=109)	19	17	1.1 (0.7–1.8)
Risk factors* + history of ischemic disease			
0 (n=73)	7	19	0.4 (0.1–0.8)
1 (n=96)	11	19	0.6 (0.3–1.1)
2 (n=95)	15	18	0.8 (0.5–1.4)
≥3 (n=185)	26	11	2.3 (1.5–3.5)

Risk category includes intrinsic factors (age, gender), *widely accepted cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, obesity), and history of disease; [a]Includes medical history, prior concomitant medication, and/or baseline glucose grade ≥2; [b]Includes medical history and/or prior concomitant medication; [c]Includes medical history, prior concomitant medication, and/or baseline blood pressure grade ≥2; [d]Includes medical history, prior concomitant medication, and/or baseline triglycerides grade ≥1; [e]Includes medical history and/or baseline BMI ≥30 kg/m2; [f]Patients with risk category who had serious ATE divided by total patients with risk category; [g]Patients without risk category who had serious ATE divided by total patients without risk category

Dose modification was commonly used to manage adverse

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)

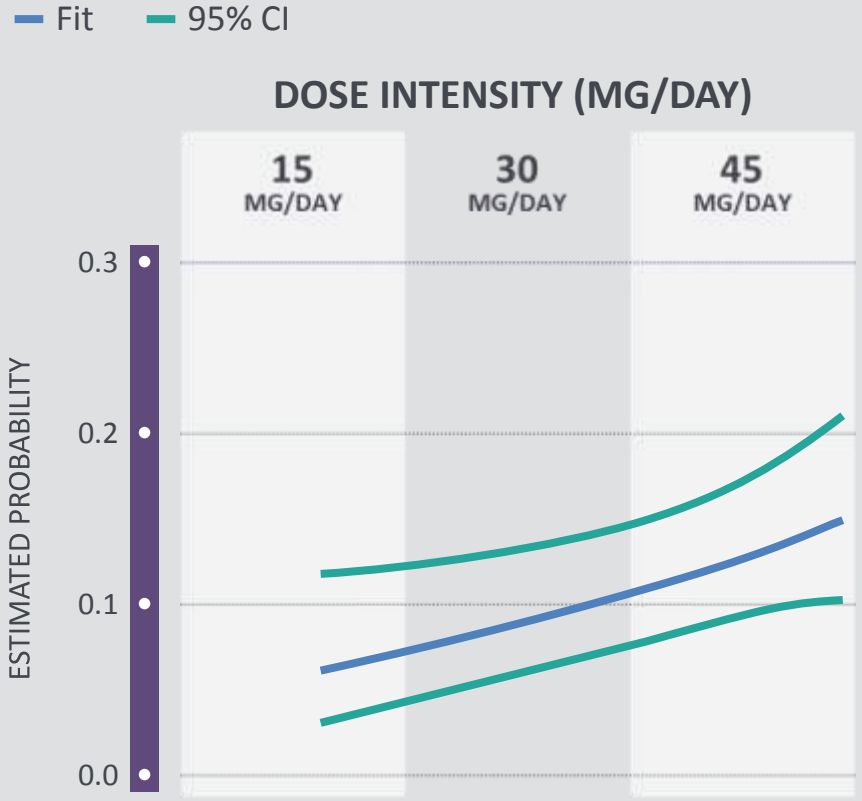
DOSE REDUCTION†	
At least 1 reduction, n (%)	172 (64)
>1 reduction, n (%)	74 (28)
Median time to first reduction, days (range)	64 (2-344)
Median time on reduced dose, days (range)	156 (1-362)

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)

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

Multivariate analysis suggests risk of arterial thrombotic events can be reduced by dose modulation

Probability of Arterial Thrombotic Events vs Dose Intensity in PACE* (N=446)



- Each 15 mg/day reduction in average daily dose intensity is predicted to lead to approximately a 33% reduction in the risk of arterial thrombotic events
- Multivariate analyses suggests that dose modification is a strategy for minimizing risk

*Estimation by reduced multivariate model.

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

SmPC – Febbraio 2015

La dose raccomandata inizialmente è 45 mg di ponatinib una volta al giorno

- Non sono disponibili dati sufficienti a formulare raccomandazioni formali relative alla riduzione della dose (in assenza di eventi avversi) in pazienti con LMC in fase cronica (FC) che abbiano ottenuto una risposta citogenetica maggiore.

- **Se si considera una riduzione della dose, nella valutazione individuale del beneficio/rischio si deve tenere conto dei seguenti fattori: rischio cardiovascolare, effetti indesiderati del trattamento con ponatinib, tempo necessario ad ottenere una risposta citogenetica e livelli di trascrizione di BCR-ABL. In caso di riduzione della dose, si raccomanda un monitoraggio attento della risposta**

Maintenance of Response Following Dose Reductions Implemented in October 2013 in CP-CML Patients Who Achieved **MCyR or MMRa**

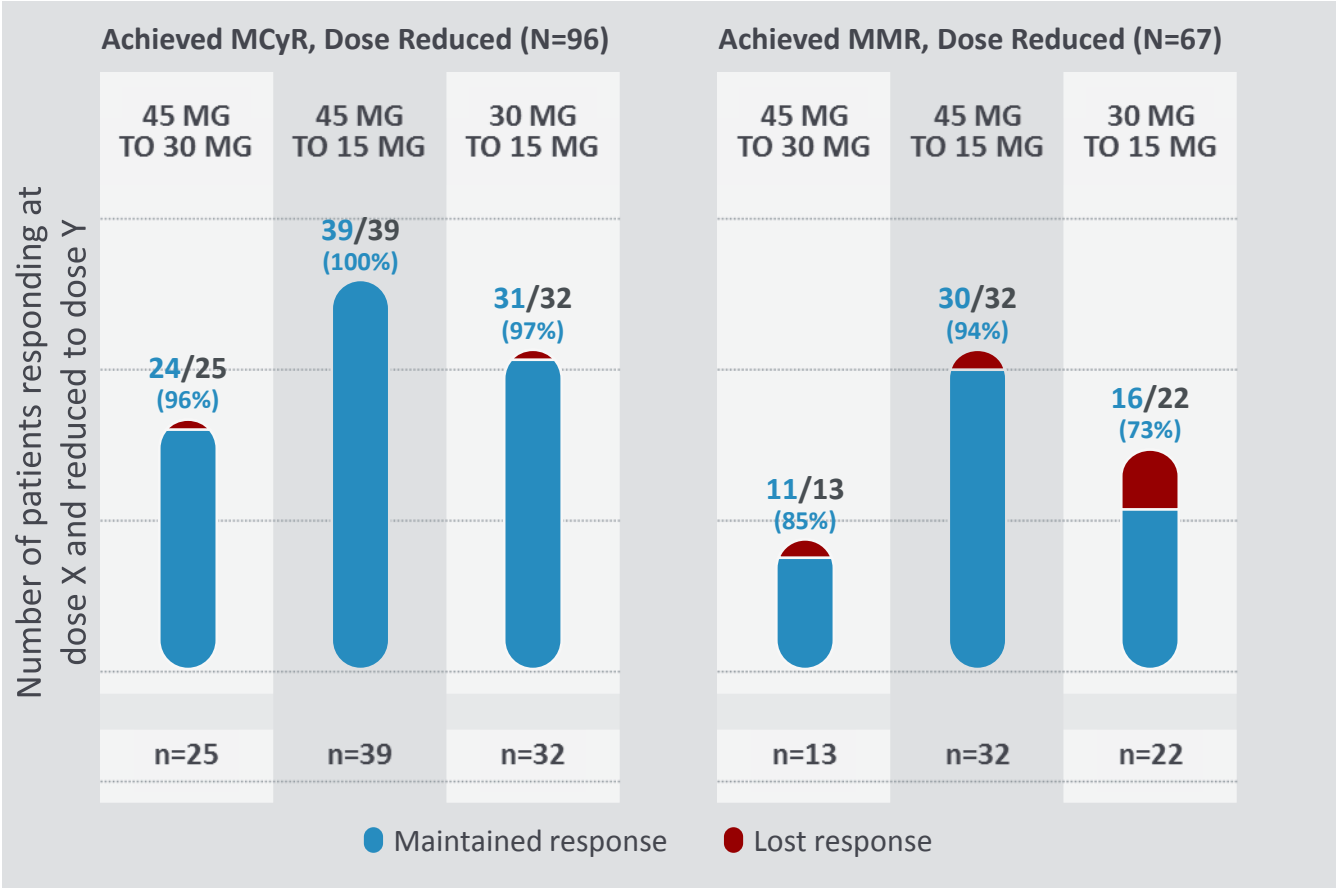
- Maintenance of response was high whether or not patients underwent dose reductions

	MCyR		MMR	
	Patients in MCyR as of Oct 2013 N	Maintained Response as of Oct 2014 n (%)	Patients in MMR as of Oct 2013 N	Maintained Response as of Oct 2014 n (%)
Dose reductions as of Oct 2013	**64**	**61 (95)**	**47**	**44 (94)**
45 to 30 (mg/day)	15	15 (100)	10	10 (100)
45 to 15 (mg/day)	18	17 (94)	17	16 (94)
30 to 15 (mg/day)	25	24 (96)	17	15 (88)
Other reduction	6	5 (83)	3	3 (100)
No dose reduction as of Oct 2013	**42**	**39 (93)**	**24**	**23 (96)**
45 mg/day	6	5 (83)	3	2 (67)
30 mg/day	11	9 (82)	4	4 (100)
15 mg/day	25	25 (100)	17	17 (100)

[a]Excludes patients who lost response prior to Oct 2013

Data as of 06 October 2014

In PACE, response is maintained after dose reduction



SOURCE: Data on file. 07 April 2014.

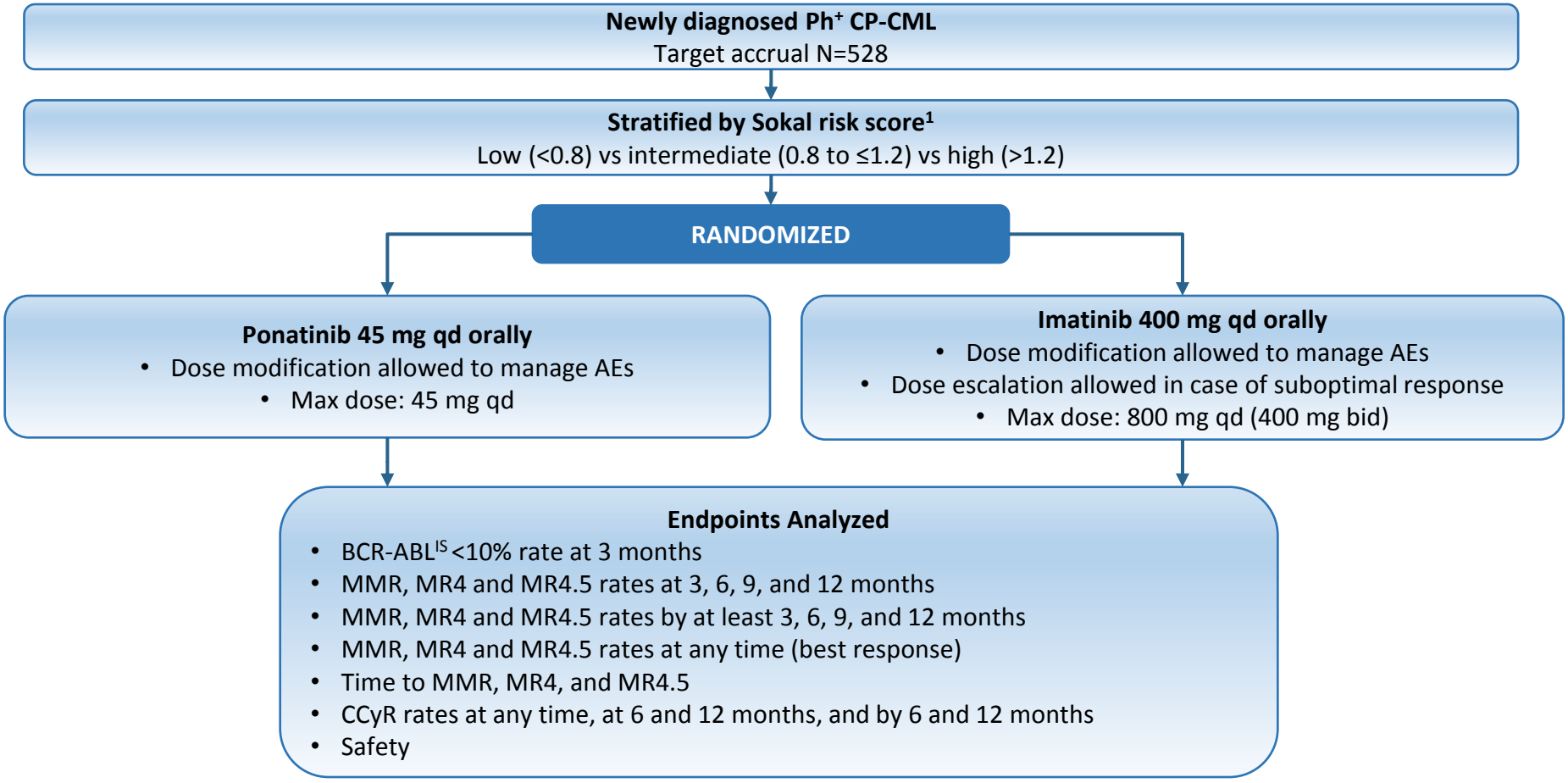
Occurrence of ATEs Following Prospective Dose Reductions in All Ongoing Patients as of October 10, 2013

- 5/70 (7%) patients without prior ATEs had a new ATE after prospective dose reductions

	Patients With No Arterial Thrombotic Events Prior to Oct 2013	
	Arterial Thrombotic Event After Oct 2013	No Arterial Thrombotic Event After Oct 2013
Dose reductions as of Oct 2013	**5**	**65**
45 to 30 (mg/day)	1	26
45 to 15 (mg/day)	1	16
30 to 15 (mg/day)	3	18
Other reduction	0	5
No dose reduction as of Oct 2013	**7**	**60**
45 mg/day	1	8
30 mg/day	0	22
15 mg/day	6	30

Data as of 06 October 2014

EPIC: Study Design



None of the prospectively defined endpoints could be analyzed due to trial termination

1. Sokal JE, et al. *Blood*. 1984;63:789-99.

Demographic and Baseline Characteristics

		Ponatinib N=155	Imatinib N=152	Overall N=307
Median age (range), years		55 (18-89)	52 (18-86)	53 (18-89)
Median time from diagnosis to treatment (range), months		0.95 (0.16-3.91)	1.05 (0.13-5.56)	0.99 (0.13-5.56)
Male, n (%)		97 (63)	92 (61)	189 (62)
ECOG PS, n (%)	0	116 (75)	119 (78)	235 (77)
	1	37 (24)	32 (21)	69 (23)
	2	1 (1)	1 (1)	2 (1)
Sokal score, n (%)	Low risk (<0.8)	64 (41)	62 (41)	126 (41)
	Intermediate risk (0.8-1.2)	64 (41)	67 (44)	131 (43)
	High risk (>1.2)	27 (17)	23 (15)	50 (16)
Total no. CV risk factors* and disease history, n (%)	0	48 (28)	49 (32)	92 (30)
	1	37 (24)	43 (28)	80 (26)
	2	24 (15)	28 (18)	52 (17)
	≥3	50 (32)	32 (21)	82 (27)

*CV risk factors included hypertension, hypercholesterolemia, diabetes, obesity, and smoking.
Only median time from diagnosis to treatment was statistically different between arms ($P<0.05$).

Data as of 1 April 2014

Status and Disposition at Time of Termination

From Aug '12 to Oct '13, 307 patients were randomized (58% of target enrollment)

	Ponatinib N=155*	Imatinib N=152	Overall N=307
Median follow-up, months (range)	5.0 (0.03-17.6)	5.3 (0.5-14.1)	5.1 (0.03-17.6)
Discontinued, N (%)	155 (100)	152 (100)	307 (100)
Study termination	130 (84)	141 (93)	271 (88)
Adverse event	14 (9)	2 (1)	16 (5)
Withdrawal of consent	7 (5)	1 (1)	8 (3)
Lack of efficacy	0	4 (3)	4 (1)
Death	1 (1)	2 (1)	3 (1)
Physician decision	2 (1)	0	2 (1)
Progressive disease	0	1 (1)	1 (<1)
Lost to follow-up	0	1 (1)	1 (<1)
Other	1 (1)	0	1 (<1)

*1 patient was randomized but not treated and not included in safety analyses.

AEs Leading to Discontinuation:

Ponatinib: rash (n=4), thrombocytopenia (n=3), abdominal pain (n=2), weight loss (n=1), ALT increase (n=1), AST increase (n=1), pancreatitis (n=1), acute myocardial infarction (n=1), diarrhea (n=1), nausea (n=1), fatigue (n=1), headache (n=1), peripheral arterial occlusive disease (n=1)

Imatinib: eye hemorrhage (n=1), diarrhea (n=1)

Data as of 1 April 2014

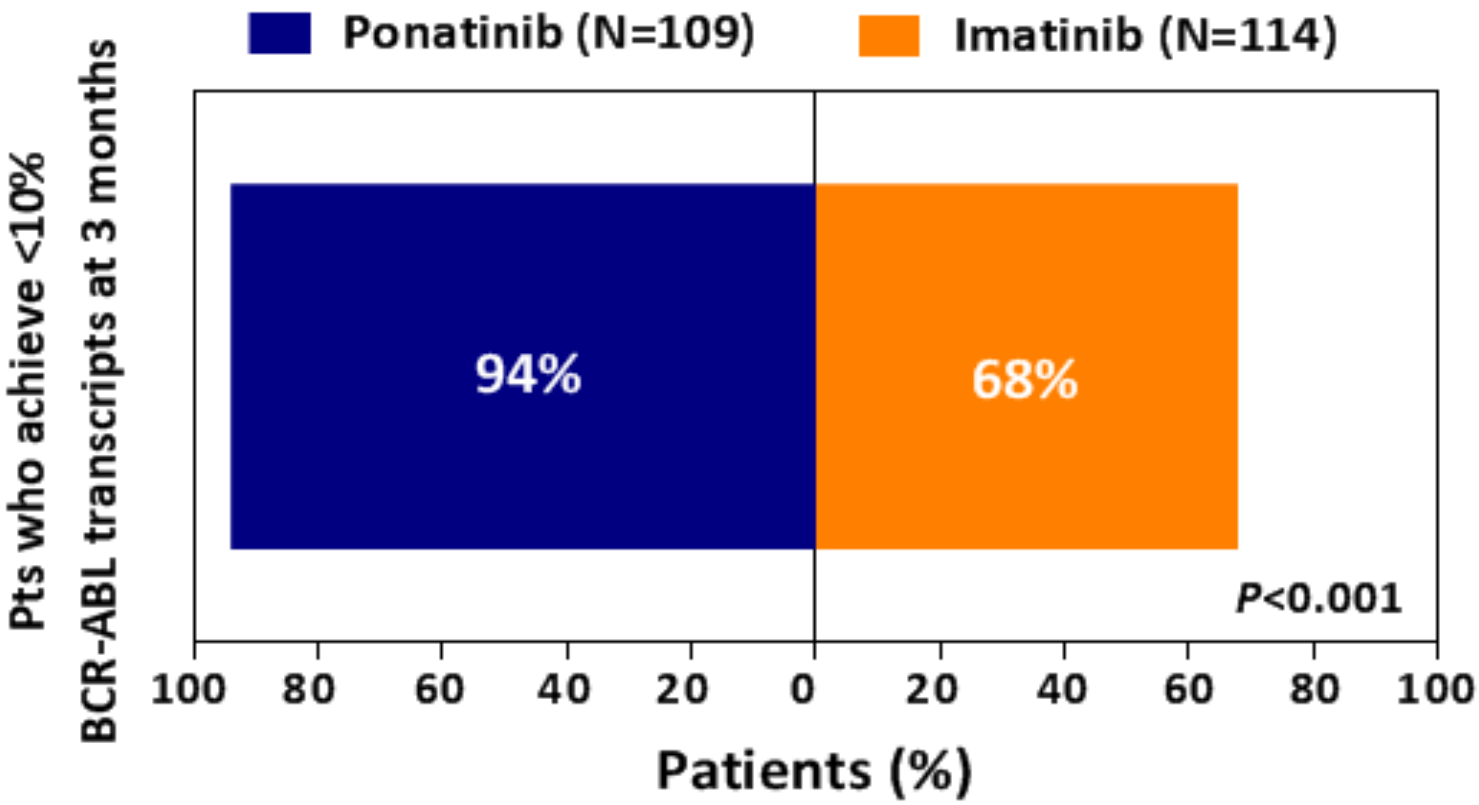
Study Drug Exposure

	Ponatinib N=154	Imatinib N=152
Median (range) duration of exposure, days	114 (2-432)	141 (14-419)
Median (range) dose intensity, mg/day	39 (9-45)	400 (186-574)
Any dose reductions, n (%)	55 (36)*	10 (7)
Dose interruptions of at least 3 days, n (%)	87 (57)	30 (20)

* Additional 60 (39%) patients in the ponatinib arm had a dose reduction following issuance of dose reduction recommendations post clinical hold to new patients enrollment (Oct 2013).

Data as of 1 April 2014

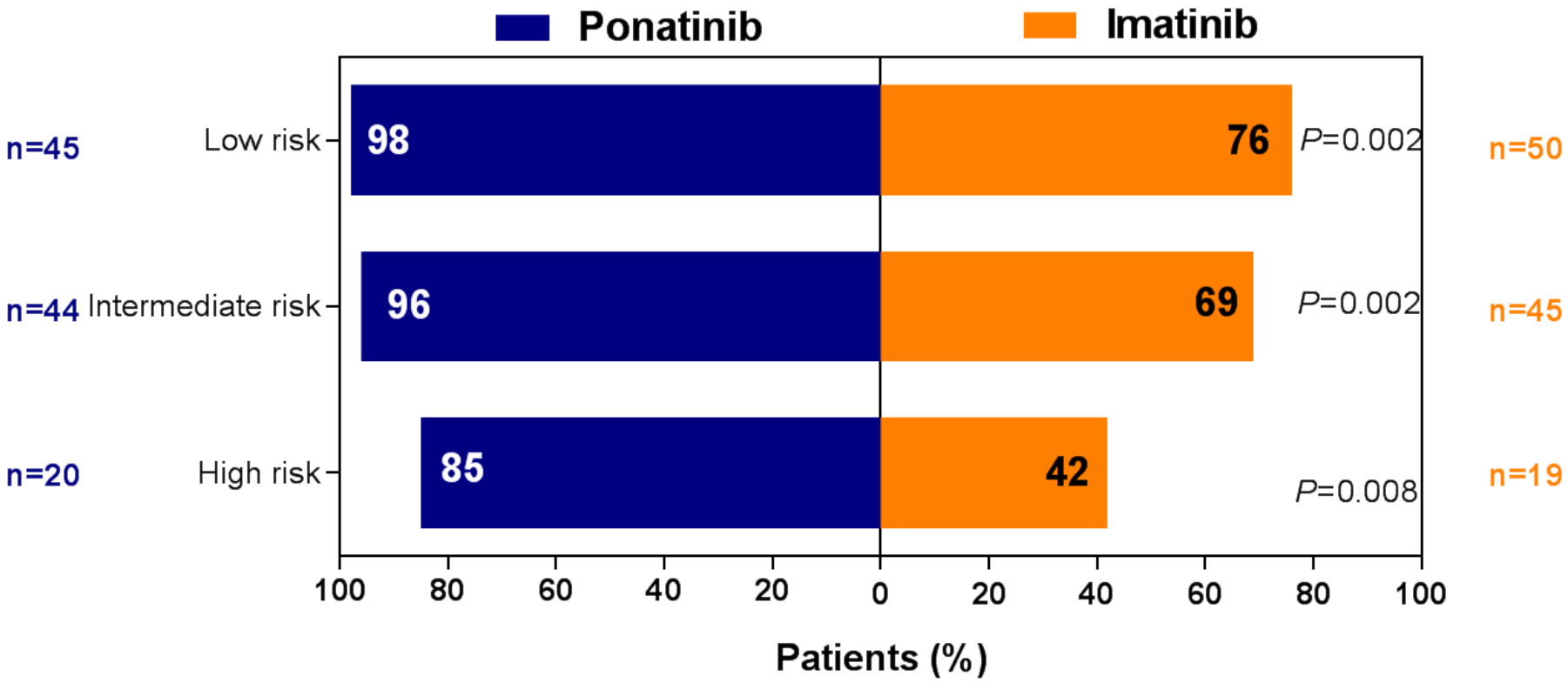
Achievement of <10% BCR-ABL Transcripts at 3 Months: Evaluable Patients



Evaluable: patients with an assessment at 3 months or later.

Data as of 1 April 2014

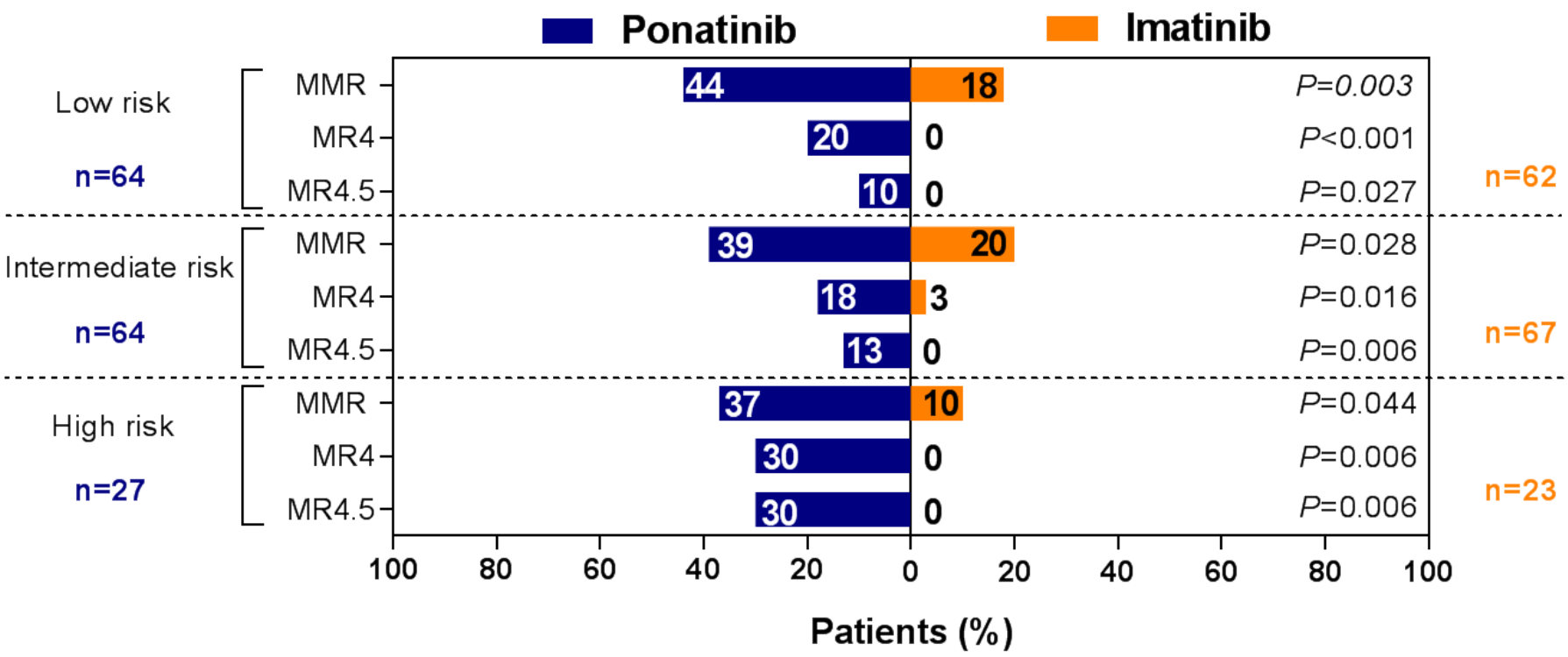
Achievement of <10% BCR-ABL Transcript Levels at 3 Months by Sokal Risk Score: Evaluable Patients



Evaluable: patients with an assessment at 3 months or later.

Data as of 1 April 2014

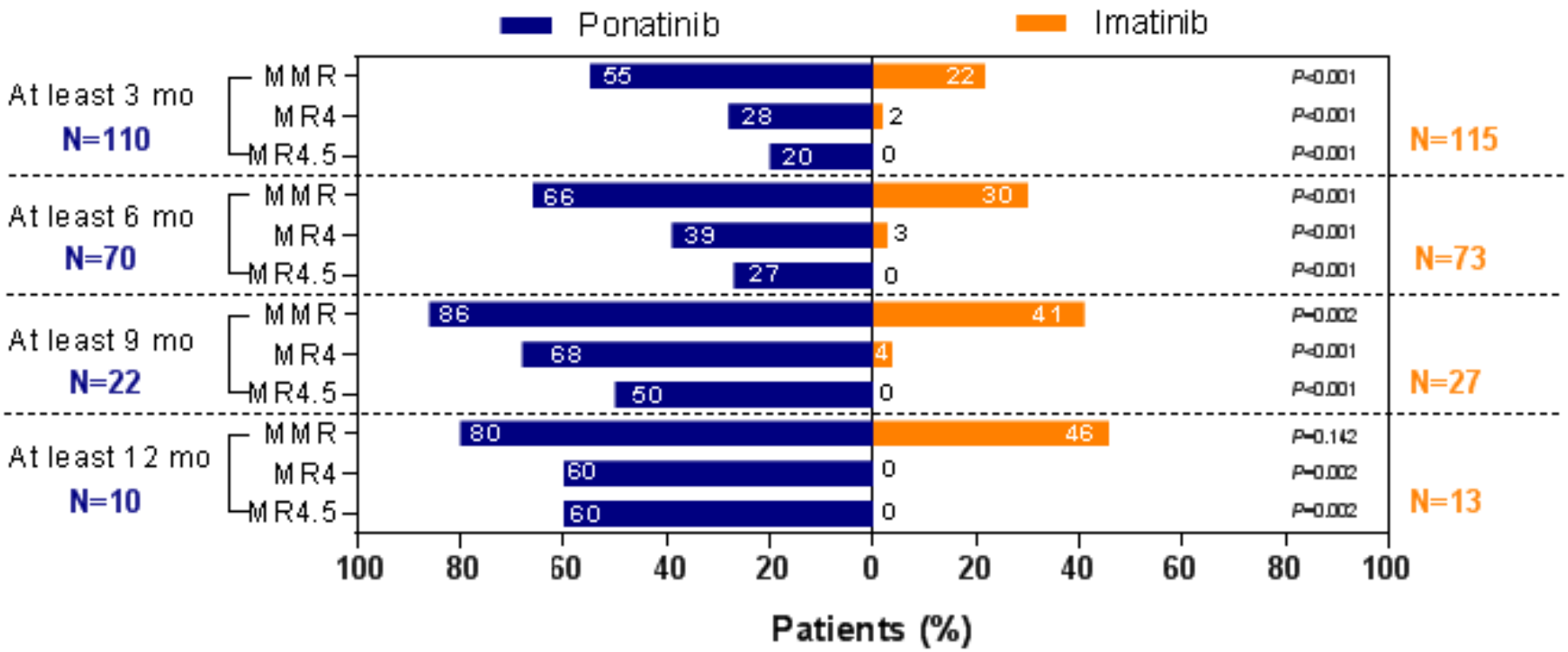
Best Molecular Response at Any Time by Sokal Risk Score: Evaluable Patients



Evaluable: patients with an assessment at each time point or later.

Data as of 1 April 2014

Best Molecular Response After at Least 3, 6, 9, and 12 Months: Evaluable Patients



Evaluable: patients with an assessment at each time point or later.

Data as of 1 April 2014

Risposte globali in I linea a 12 mesi

	Nilotinib Enest	Dasatinib Dasision	Ponatinib EPIC	Ima-N	Ima-D	Ima-P
<10%3m	91%	84%	94%	64%	67%	68%
MMR	55-51%	46%	80%	17%	23%	46%
MR4	15-20%	12%	60%	6%	5%	0%
MR4.5	7-11%	3%	60%	1%	2%	0%

Patients With Treatment-Emergent AEs (>15%)

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 (≥2 Pts)

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

1 patient each in the ponatinib arm & the imatinib arm had grade 5 pneumonia

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)

*15 events reported in 12 patients; 3 patients had multiple events.

- 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 (serious AEs indicated by *)	
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)*

[a]Patients can have more than 1 event.

Data as of 1 April 2014

Raccomandazioni

- **Iclusig non dovrebbe essere utilizzato in pazienti con storia pregressa di infarto miocardico**, precedente rivascolarizzazione o stroke, bilanciando rischi-benefici del trattamento. In questi pazienti dovrebbero essere considerate strategie terapeutiche opzionali.

- **Un monitoraggio continuo per occlusioni vascolari e possibile tromboembolismo dovrebbe essere eseguito** e il farmaco interrotto immediatamente in caso di occlusione. Considerare poi i rischi/benefici per riprendere successivamente la terapia.

- L'**ipertensione** può contribuire al rischio di eventi arteriosi trombotici. Durante il trattamento con Iclusig è importante **monitorizzare la pressione arteriosa** e correggerla ad ogni visita di controllo. Iclusig dovrebbe essere temporaneamente interrotto se la pressione arteriosa non è controllata.

Conclusioni

- Ponatinib è un farmaco molto potente ed efficace nelle CML e nelle LLA Ph+ (dove quasi tutte le resistenze sono dovute alla comparsa di un clone T315I)
- A 3 anni di follow up dello studio di fase II (PACE) Ponatinib contnua a mostrare risposte durature e profonde, specie nei pazienti CML-CP, sebbene pesantemente pretrattati, con OS 83% e MR4.5 22%
- A fronte dell'indubbia efficacia del farmaco sono state rilevate tossicita' cardiovascolari superiori rispetto agli altri inibitori
- L'inicdenza cumulativa di questi eventi aumenta col tempo, ma risulta essere direttamente correlata al dosaggio utilizzato.
- Nell'ottobre 2013 la suggerita riduzione di dosaggio in rapporto alla risposta ottenuta ha comportato ad un anno
  - Il mantenimento della risposta nel 94% dei pazienti
  - Non incremento nell'incidenza di nuovi eventi trombotici arteriosi e venosi con l'aumentare del tempo di esposizione
  - 5 pazienti su 70 (7%) senza precedenti eventi vascolari ha presentato un evento dopo riduzione dosaggio
- Malgrado la terminazione precoce del trial di I linea (EPIC), le analisi preliminari evidenziano efficacia superiore di ponatinib rispstto ad imatinib (follow up mediano 5.1 mesi) con piu' alto tasso di risposte, rapide e profonde (MMR a 12 mesi 80%)
- Nel braccio Ponatinib si sono manifestati piu' AE grado 3-4 e SAE (ipertensione; pancreatite, eventi vascolari)
- Per efficacia e durata nel tempo delle risposte ponatinib e' un farmaco importante nel trattamento LMC e soprattutto ALL Ph+; il rapporto rischio/beneficio e la conoscenza dei possibili effetti secondari del farmaco (e le contromisure atte a limitarli) devono guidare il suo utilizzo.

LMC: la comunicazione della diagnosi

1994

La fase cronica dura solo 4-5 anni
Avra' stanchezza, febbre, dolori osteoarticolari
Solo un trapianto potra' guarirla

2004

Abbiamo una medicina mirata
Dobbiamo raggiungere una CCyR
La possiamo curare bene ma non guarire
La terapia sara' «per sempre»

2014

Possiamo scegliere tra diversi farmaci molto efficaci
Potra' raggiungere una risposta molecolare profonda
La sua aspettativa di vita sara' quella di una persona della sua stessa eta'
Potra' avere dei figli
In alcuni casi e' possibile sospendere la terapia

Courtesy of Monica Bocchia

CML 2015: presente e futuro

Le LMC Ph+ sono ora un gruppo di patologie trattabili per le quali possiamo scegliere tra diversi TKIs.

I TKIs sono farmaci specifici che possono «spegnere» la molecola alterata che inizia e fa sviluppare la malattia (BCR-ABL).

E' molto importante caratterizzare la biologia della malattia (rischio biologico, mutazioni) e studiare bene il paziente (patologie concomitanti, fattori di rischio non ematologici) per scegliere il farmaco migliore (terapia personalizzata) sia in prima linea che nelle linee successive.

Abbiamo degli obiettivi da raggiungere entro determinati periodi (3-6 -12 mesi) secondo le direttive ELN

Con il tempo i pazienti possono conseguire una risposta molecolare profonda (MR4-MR4.5-MR5) che e' alla base di qualsiasi possibilita' di sospensione del trattamento.

Grazie per l'attenzione