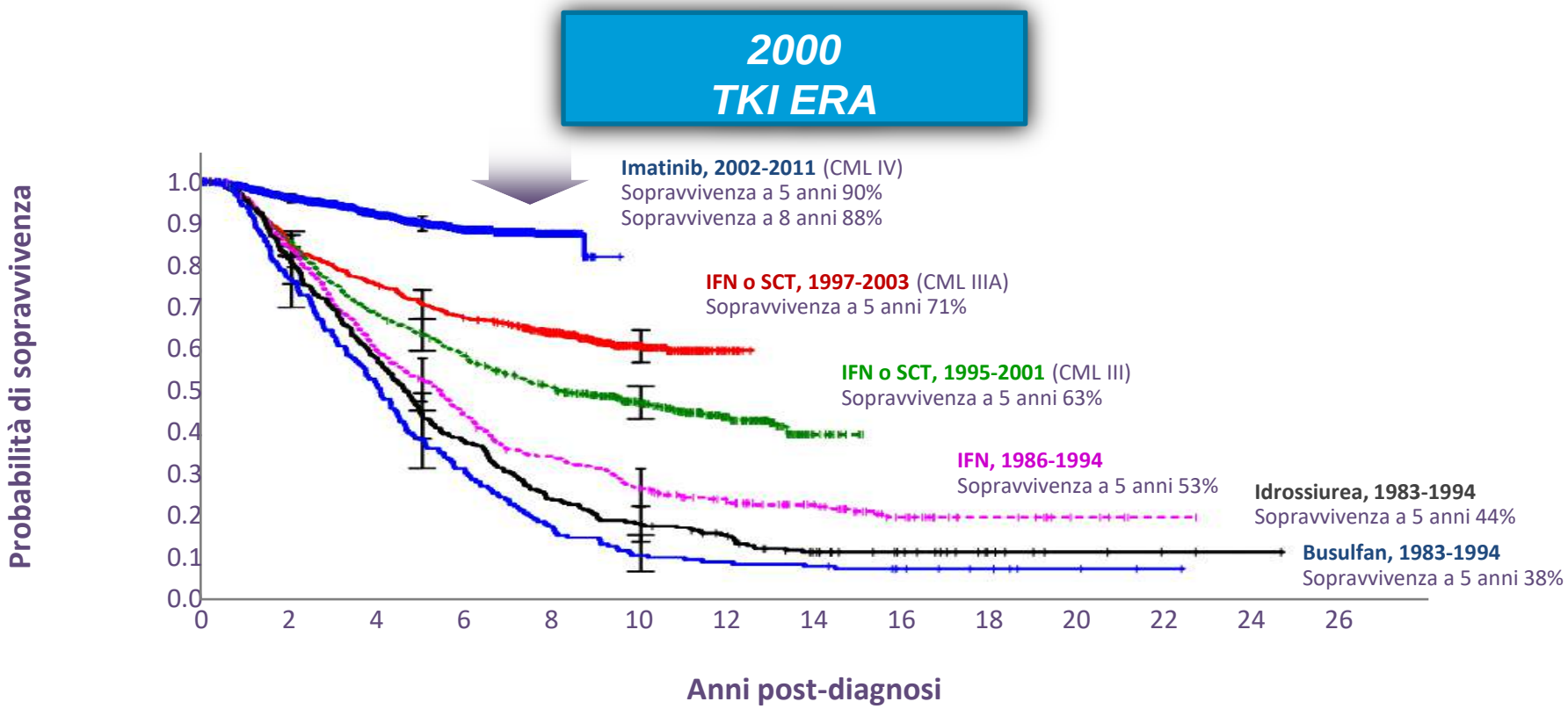
Nuove prospettive di trattamento della leucemia mieloide cronica.

Il progetto sinergia

Dr.ssa Eleonora Arboscello

Miglioramento della sopravvivenza nella LMC in base alla terapia 1983-2011



German CML Study Group

Evoluzione del trattamento nella CML

1844-45	*Description of leukaemia*	*Bennett* *Donnè* *Virchow*	*Edinb Med Surg J C* *ourse de microscopie,* *Froiep's Notizen*
1960	Philadelphia chr	owell&Hungerford	J Natl Cancer Inst
1973	*Ph results from t(9;22)* *translocation*		*Nature*
1980	Discovery of ABL protein kinase		Nature
1985	*BCR-ABL gene consequence* *of t(9;22)*	*Heisterkamp*	*Nature*
1986	BCR_ABL encodes activated ABL kinase	Baltimore	

As_2O_3 1865

Busulfano 1959

Idrossiurea

Interferone

Imatinib 2001

Nilotinib

Dasatinib

Bosutinib

Ponatinib

HR

CHR

MCyR

MMR

CMR

CURE

VOLUME 33 NUMBER 35 DECEMBER 10 2015
JOURNAL OF CLINICAL ONCOLOGY
REVIEW ARTICLE

Tyrosine Kinase Inhibitor–Associated Cardiovascular Toxicity in Chronic Myeloid Leukemia

Javid J. Moslehi and Michael Deininger

Cardiovascular Toxicity of BCR-ABL1 Inhibitors

Kinase/TKI	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib	Sorafenib	Sunitinib
ABL1	100	105	83	98	101	46	92
ABL1(T315I)	93	68	9	15	100	53	97
FGFR1	79	47	0	0	101	78	93
FGFR2	95	73	3	0	100	91	97
FGFR3	83	34	1	0	101	76	97
FGFR4	3	9	8	0	98	19	55
FLT1 (VEGFR1)	97	39	5	0	101	99	98
FLT3	77	17	68	60	99	100	100
FLT4 (VEGFR3)	92	31	3	17	101	97	99
KDR (VEGFR2)	101	22	7	22	94	99	98
KIT	23	100	97	96	101	98	98
PDGFRα	77	100	98	103	103	100	98
PDGFRβ	95	99	91	93	102	98	99
SRC	96	101	5	23	102	12	84
TIE2	22	16	0	41	101	29	21

Fig 1. Activity of approved ABL1 tyrosine kinase inhibitors (TKIs; bosutinib, dasatinib, imatinib, nilotinib, ponatinib), sorafenib, and sunitinib against tyrosine kinases with a known function in vascular biology, ABL1 and $ABL1^{T315I}$. The numbers represent percent inhibition of kinase activity at 1 μmol/L of inhibitor. Reported values less than 0 were set to 0. Red indicates 96% to 100% inhibition; gold indicates 51% to 95% inhibition; and blue indicates 0% to 50% inhibition. Data adapted.[14]

Abstract P228

4-Year Results of the Ponatinib Phase 2 PACE Trial in Heavily Pretreated Leukemia Patients

Jorge E. Cortes,[1] Javier Pinilla-Ibarz,[2] Philipp D. Le Coutre,[3] Ronald Paquette,[4] Charles Chuah,[5] Franck E. Nicolini,[6] Jane Apperley,[7] Hanna Jeen Khoury,[8] Moshe Talpaz,[9] Michele Baccarani,[10] Stephanie Lustgarten,[11] Frank G. Haluska,[12] François Guilhot,[13] Michael W. Deininger,[14] Andreas Hochhaus,[15] Timothy P. Hughes,[16] Neil P. Shah,[17] Hagop M. Kantarjian[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [3]Charité Universitätsmedizin Berlin, Berlin, Germany; [4]Ronald Reagan UCLA Medical Center, University of California, Los Angeles, CA, USA; [5]Singapore General Hospital and Duke-NUS Medical School, Singapore, Singapore; [6]Centre Hospitalier Lyon Sud, Pierre Bénite, France; [7]Centre for Haematology, Imperial College, London, UK; [8]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [9]Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI, USA; [10]S. Orsola-Malpighi University Hospital, Bologna, Italy; [11]ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA; [12]BioCancell Ltd., Jerusalem, Israel (previously employed by ARIAD); [13]Insem CIC 1402, CHU de Poitiers, Poitiers, France; [14]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [15]Jena University Hospital, Jena, Germany; [16]University of Adelaide and South Australian Health and Medical Research Institute, Adelaide, Australia; [17]University of California San Francisco, San Francisco, CA, USA

INTRODUCTION

- Ponatinib is a potent oral tyrosine kinase inhibitor (TKI) with activity against native and resistant BCR-ABL, including T315I[1]
- Ponatinib is approved for adult patients with refractory chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL); it is the only TKI approved for patients with the T315I mutation[2,3]
- The ongoing pivotal phase 2 PACE trial (NCT01207440) evaluated ponatinib (starting dose 45 mg/d) in patients with CML or Ph+ ALL refractory to dasatinib or nilotinib, or with the T315I mutation[4]
- Ponatinib was found to be associated with arterial occlusive events (AOEs) in the PACE trial.[4] While dose reduction recommendations were part of the protocol to manage adverse events (AEs), dose reductions were instructed in Oct 2013 to mitigate AOEs[5]

OBJECTIVE

- To evaluate the efficacy and safety of ponatinib with 4 years median follow-up in the ongoing phase 2 PACE trial (NCT01207440), with a focus on patients with chronic phase (CP)–CML

METHODS

The design of the ongoing PACE trial has been previously described[4]

- Primary endpoints were major cytogenic response (MCyR) by 12 months for CP-CML and major hematologic response (MaHR) by 6 months for accelerated phase (AP)–CML, blast phase (BP)–CML, and Ph+ ALL patients
- Secondary endpoints for all patients included major molecular response (MMR), duration of response, progression-free survival (PFS), overall survival (OS), and safety

Ponatinib dose	• Starting dose: 45 mg once daily • Dose reductions to 30 mg once daily or 15 mg once daily were permitted to manage AEs
Ponatinib dose post Oct 2013	Unless benefit-risk analysis justified treatment with a higher dose, the following dose reductions were instructed in PACE: • 15 mg once daily for CP-CML patients with MCyR • 30 mg once daily for CP-CML patients without MCyR • 30 mg once daily for AP-CML or BP-CML patients
Long-term outcomes assessed at 4 years	• PFS, OS • Maintenance of MCyR, maintenance of MMR • Treatment-emergent AEs, cumulative and exposure-adjusted incidence rates of new AOEs and venous thromboembolic events (VTEs)
Statistics	• Kaplan-Meier method • Exposure-adjusted incidence rates of new AOEs are reported as the no. of events/100 patient-years
Data analysis cut-off	• August 3, 2015
Patients in this analysis	• Total, N=449 • CP-CML, n=270; AP-CML, n=65; BP-CML, n=62 • Ph+ ALL, n=32
Median follow-up	• 48.2 months (range, 0.1–60.5) for patients with CP-CML

RESULTS

Patient Characteristics

	CP-CML, n=270	All n=449
Median age, years (range)	60 (18–94)	59 (18–94)
Sex, male, n (%)	144 (53)	238 (53)
Median time from diagnosis to first dose, years (range)	7 (0.5–27)	6 (0.3–28)
Prior TKI therapy,[a] n (%)		
1 TKI	19 (7)	31 (7)
2 TKIs	90 (33)	158 (35)
≥3 TKIs	162 (60)	253 (56)
Resistant/intolerant to dasatinib or nilotinib, n (%)		
Resistant	215 (80)	375 (84)
Intolerant only	39 (14)	49 (11)
Both resistant and intolerant	52 (19)	91 (18)
Best response of MMR or better to most recent dasatinib or nilotinib, n (%)	8 (3)	18 (4)
No mutation detected, n (%)	134 (51)	198 (44)
T315I mutation, n (%)	64 (24)	128 (28)

[a]Includes approved and investigational TKIs

- Baseline cardiovascular risk factors for all patients[1,2]:
  - Diabetes 16%, hypertension 53%, hypercholesterolemia 51%, obesity 24%
- Baseline history of cardiovascular disease:
  - Ischemic heart disease 22%, ischemic heart disease 43%
- Baseline concomitant medications:
  - Antihypertensives 19%, aspirin[2] 9%, antiplatelet agents[2] 8%, antidiabetes agents 5%, lipid-modifying agents 5%, anticoagulants 3%

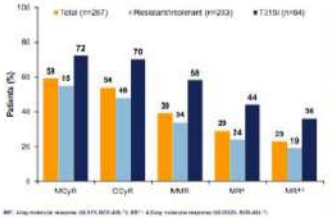
[1]Smoking and hyperlipidemia were not collected as part of the trial. Patients were excluded from the trial with significant or active cardiovascular disease, including myocardial infarction, unstable angina or CHF in prior 6 months, cerebrovascular accident or transient ischemic attack in previous 3 months.
[2]Baseline was defined as the screening/enrollment visit, which was the first visit at which a patient was enrolled in the study. Baseline was used to stratify patients into the ponatinib dose cohorts and to assess baseline characteristics.

Patient Disposition

	CP-CML, n=270	All n=449
Median dose intensity, mg/d (range)	29.4 (3–45)	32.3 (3–52)
Median follow-up, months (range)	48.2 (0.1–60.5)	37.3 (0.1–60.5)
Remained on study at 4 years, n (%)	110 (41)	133 (30)
Discontinued treatment, n (%)	160 (59)	316 (70)
Primary reasons for discontinuation, n (%)		
Disease progression	28 (10)	101 (22)
AEs	30 (11)	72 (16)
Death[a]	8 (3)	25 (6)
Other[b]	74 (27)	118 (26)

[a]Deaths were assessed by investigators as possibly or probably related to ponatinib: CP-CML (pneumonia, acute myocardial infarction; AP-CML (large granulomatosis, gastrointestinal hemorrhage; BP-CML/Ph+ ALL, cardiac arrest, gastric hemorrhage, metastatic prostate cancer).
[b]Includes withdrawal by patient (including non-hemorrhagic CP-CML, n=3; AP-CML, n=1), lost to follow-up (CP-CML, n=5; AP-CML, n=2), investigator decision (CP-CML, n=1; AP-CML, n=1), lack of efficacy (CP-CML, n=3; AP-CML, n=1), noncompliance (CP-CML, n=1; AP-CML, n=1), physician decision (CP-CML, n=1; AP-CML, n=1), or other reasons (CP-CML, n=15; AP-CML, n=4).

Response to Ponatinib in Patients With CP-CML: Response at Any Time



Response at any time in advanced phase leukemia:

- AP-CML (n=65): MaHR was achieved in 61% of patients and MMR in 22%
- BP-CML (n=62): MaHR was achieved in 31%
- Ph+ ALL (n=32): MaHR was achieved in 41%

Maintenance of Response Following Prospective Dose Reductions in CP-CML Patients Who Achieved MCyR or MMR[a]

	MCyR		MMR	
	Patients in MCyR as of Oct 2013 n	Maintained Response as of Aug 2015 n (%)	Patients in MMR as of Oct 2013 n	Maintained Response as of Aug 2015 n (%)
Dose reductions as of Oct 2013				
Total[b]	69	66 (96)	51	46 (90)
45 or 30 to 15 mg/d	59	56 (95)	45	40 (89)
No dose reduction as of Oct 2013				
Total[c]	35	33 (94)	20	19 (95)
15 mg/d	25	25 (100)	17	17 (100)

[a]Censoring patients who lost response prior to Oct 2013.
[b]Other reduction: n=5 (5 mg/d or any other reduction not specified). 19/51 (100%) maintained MCyR and 8/20 (40%) MMR.
[c]Other: n=10 (5 mg/d) 8/10 (80%) maintained MCyR and 3/3 (67%) MMR

- Regardless of dose reduction or no dose reduction in Oct 2013, maintenance of response was high (over 90% of responding patients)
- 81 out of 84 patients who were dose reduced to 15 mg maintained response at 4 years median follow-up

Treatment-Emergent AEs Reported in ≥20% of Patients

	CP-CML, n=270		All, n=449	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Gastrointestinal, n (%)				
Abdominal pain	124 (46)	27 (10)	191 (43)	41 (9)
Rash	126 (47)	18 (4)	187 (42)	18 (4)
Constipation	111 (41)	7 (3)	168 (37)	10 (2)
Headache	119 (43)	9 (3)	167 (37)	11 (2)
Dry skin	112 (42)	5 (2)	162 (36)	11 (2)
Fatigue	83 (30)	6 (2)	136 (30)	13 (3)
Hypertension	92 (34)	34 (13)	136 (30)	55 (12)
Pyrexia	69 (26)	2 (1)	132 (29)	11 (2)
Arthralgia	67 (32)	8 (3)	131 (29)	10 (2)
Nausea	75 (28)	2 (1)	126 (28)	5 (1)
Diarrhea	63 (26)	2 (1)	97 (22)	7 (2)
Increased lipase	72 (27)	32 (12)	97 (22)	34 (12)
Vomiting	48 (18)	4 (2)	96 (21)	5 (1)
Myalgia	65 (24)	3 (1)	95 (21)	5 (1)
Pain in extremity	63 (23)	5 (2)	91 (20)	9 (2)
Back pain	56 (21)	3 (1)	84 (19)	6 (1)
Hematologic, n (%)				
Thrombocytopenia	132 (49)	95 (35)	191 (44)	160 (36)
Neutropenia	53 (20)	43 (17)	113 (25)	100 (22)
Anemia	51 (19)	26 (10)	110 (25)	70 (16)

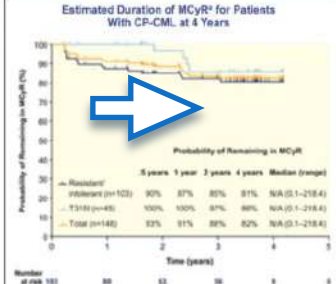
- The most common treatment-emergent AEs included skin-related AEs (including rash, dry skin), constitutional symptoms (including abdominal pain, constipation, headache, fatigue, pyrexia, nausea, diarrhea, vomiting), vascular (hypertension), pancreatic (increased lipase), and myelosuppression (thrombocytopenia, neutropenia, anemia)
- The most common grade 3/4 treatment-emergent AEs (observed in ≥10% of patients) were thrombocytopenia, neutropenia, anemia, increased lipase, and hypertension
- AOEs included a collection of preferred terms where no individual term occurred in >10% of patients; incidence of AOEs is summarized in the table below

Occurrence of New AOEs Following Prospective Dose Reductions in All Ongoing Patients

	Patients With No AOEs Prior to Oct 2013	
	AOE After Oct 2013	No AOE After Oct 2013
Dose reductions as of Oct 2013		
Total	6	69
45 to 15 mg/d	2	39
30 to 15 mg/d	4	21
Other reduction	0	15
No dose reduction as of Oct 2013		
Total	10	52
15 mg/d	7	39
Other	3	23

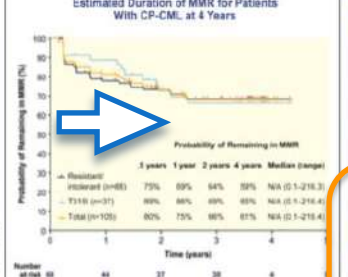
[a]Other reductions: n=8 (5 mg/d or any other reduction not specified). Other = 40 or 30 mg/d.

Estimated Duration of MCyR[a] for Patients With CP-CML at 4 Years

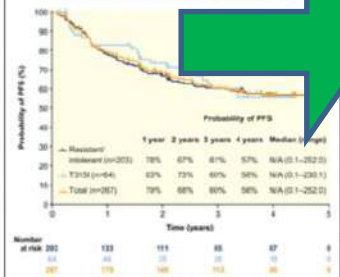


[a]MCyR to 12 months

Estimated Duration of MMR for Patients With CP-CML at 4 Years

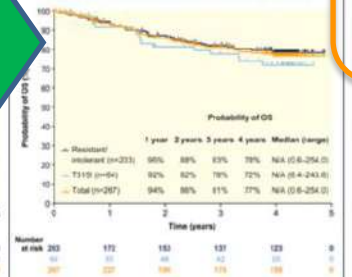


Estimated PFS for Patients With CP-CML at 4 Years



Progression was defined as death, development of MR in CP-CML, loss of (confirmed hematologic response (CHR) in the absence of cytogenetic response, loss of MCyR, or increasing white blood cell count without CHR. Patients who do not demonstrate progression or loss of response are censored at the last response assessment date.

Estimated OS for Patients With CP-CML at 4 Years



In advanced phase leukemia:

- AP-CML (n=65): estimated 4-year PFS was 22%
- BP-CML/Ph+ ALL (n=94): median PFS was 3.0 months (95% CI, 2.0–4.2)

In advanced phase leukemia:

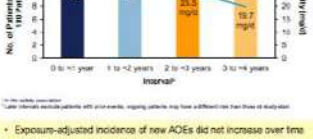
- AP-CML (n=65): estimated 4-year OS was 51%
- BP-CML/Ph+ ALL (n=94): median OS was 6.9 months (95% CI, 5.0–9.2)

Cumulative and Exposure-Adjusted Incidences of AOEs and VTEs[a]

	CP-CML, n=270		All, n=449	
	All Grades	SAEs	All Grades	SAEs
AOEs, n (%)	77 (29)	63 (23)[b]	104 (23)[c]	85 (19)[d]
Cardiovascular	38 (14)	38 (11)	58 (13)	41 (9)
Cerebrovascular	33 (12)	28 (10)	39 (9)	31 (7)
Peripheral vascular	21 (11)	25 (9)	40 (9)	31 (7)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.2	10.8	14.1	10.7
VTEs	13 (5)	12 (4)	25 (6)	22 (5)
Exposure-adjusted VTEs, no. of patients with events per 100 patient-years	2.3	1.8	2.9	2.6

[a]Categorization of AOEs and VTEs is based on a review committee of CHF, MI/ischemic cerebrovascular events/ischemic cardiac or cerebrovascular events, or thrombosis.
[b]41 patients had 1 AOE, 19 patients had 2, and 3 patients had 3 serious AOEs.
[c]1 patient had 1 AOE, 18 patients had 2, and 5 patients had 3 serious AOEs.
[d]15 patients had 1 serious AOE, 14 patients had 2, and 2 patients had 3 serious AOEs.
AOEs, arterial occlusive events

Summary of Exposure-Adjusted Incidence Rates for Newly Occurring AOEs[a] in All Patients



[a]In the safety population
[b]Later intervals exclude patients with prior events, ongoing patients may have a different risk than those at study start

- Exposure-adjusted incidence of new AOEs did not increase over time
- 38% of patients who had an AOE (n=104) remain on study
- Patients with ≥2 risk factors including history of ischemic disease had a relative risk (95% CI) of serious AOEs of 2.6 (1.5–4.3)

SUMMARY

- After 4 years median follow-up in this heavily pretreated CP-CML population, ponatinib responses were:
  - 56% MCyR and 54% CCyR
  - 39% MMR, including 29% MR[4] and 23% MR[4.5]
- Ponatinib treatment continues to result in deep and lasting cytogenetic and molecular responses
  - Kaplan-Meier estimates of 4-year MCyR and MMR were 82% and 61%, respectively
  - The probability of PFS and OS was 56% and 77%, respectively
- Owing to the association of ponatinib with AOEs, prospective dose reductions were introduced in Oct 2013
  - Exposure-adjusted incidence of AOEs has not increased over time
  - Maintenance of response was high, in particular, for patients at 15 mg/d
- OPTIC (Optimizing Ponatinib Treatment in CML) – a prospective trial evaluating a range of ponatinib doses (45, 30, and 15 mg/d) is ongoing (NCT02467270)

ACKNOWLEDGMENTS

The authors would like to thank the patients, their families, and their caregivers, the PACE investigators and their team members at each study site, and colleagues from ARIAD Pharmaceuticals, Inc., MDanderson, and the CML community. Professional medical writing assistance was provided by Elena Ulasek, PhD, OPTIC of Evidence Scientific Solutions, Philadelphia, PA, USA, and funded by ARIAD Pharmaceuticals, Inc.

REFERENCES

1. O'Hare T, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009;16:401-12.
2. Iclusig (ponatinib) [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc; 2014. 3. Study summary [product characteristics]. Leatherhead, UK: ARIAD Pharma Ltd; 2013. 4. Cortes JE, et al. Ponatinib for patients in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013;369:1780-96. 5. Iclusig® (ponatinib) tablets for oral use: highlights of prescribing information [package insert]. ARIAD Pharmaceuticals, Inc; 2014. http://www.ariadpharma.com/iclusig-pi.pdf, downloaded 2016/03/04/08:00 pm. Revised Dec 2015. 6. ARIAD announces changes in the clinical development program of Iclusig (ponatinib). [press release]. Cambridge, MA: ARIAD Pharmaceuticals, Inc; Oct 5, 2013. 7. Cortes JE, et al. Ponatinib efficacy and safety in heavily pretreated leukemia patients: 3-year results of the PACE trial [abstract P234]. Poster presented at: 20th Congress of the European Hematology Association; 11-14 June 2015; Vienna, Austria.

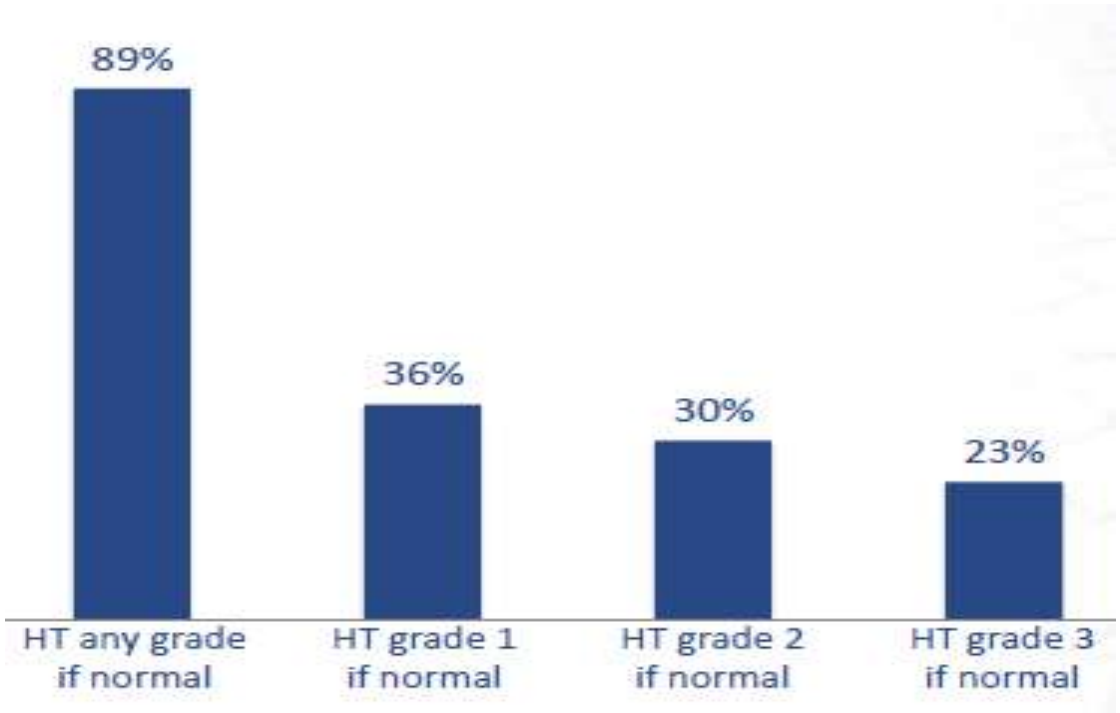
DISCLOSURES

This study was sponsored by ARIAD Pharmaceuticals, Inc. JEC: consulting or advisory role (ARIAD, BMS, Novartis, Pfizer; research funding (ARIAD, BMS, Novartis, Pfizer; Takeda); JNJ: honoraria (ARIAD, BMS, Pfizer); consulting or advisory role (ARIAD); speakers' bureau (BMS, Pfizer); PDLC: honoraria (ARIAD, BMS, Novartis, Pfizer); research funding (Novartis); NP: speakers' bureau (ARIAD, BMS); ESI: honoraria (Novartis, BMS, Novartis); travel, accommodations, expenses (BMS); FGH: honoraria (ARIAD, BMS, Novartis); consulting or advisory role (BMS, Novartis); speakers' bureau (ARIAD, BMS, Novartis); research funding (Novartis); MW: consulting or advisory role (ARIAD, BMS, Novartis, Pfizer); research funding (ARIAD, BMS, Novartis); travel, accommodations, expenses (Novartis); HAH: honoraria (BMS, Novartis, Pfizer); consulting or advisory role (BMS, Novartis, Pfizer); MT: consulting or advisory role (ARIAD, BMS, Novartis, Pfizer); research funding (ARIAD, Pfizer); travel, accommodations, expenses (ARIAD, Pfizer); HBS: honoraria (ARIAD, BMS, Novartis, Pfizer); consulting or advisory role (ARIAD); speakers' bureau (ARIAD, BMS, Novartis, Pfizer); travel, accommodations, expenses (ARIAD, Novartis); BL, FGH: employment (ARIAD); stock and other ownership interests (ARIAD); FGH: honoraria (ARIAD); WMD: consulting or advisory role (ARIAD, BMS, Incyte, Novartis, Pfizer); research funding (BMS, Celgene, Gilead, Novartis); MR: honoraria (ARIAD, BMS, Novartis, Pfizer); research funding (ARIAD, BMS, Novartis, Pfizer); FRH: honoraria (ARIAD, BMS, Novartis); consulting or advisory role (ARIAD, BMS, Novartis); research funding (ARIAD, BMS, Novartis); NPS: research funding (ARIAD, BMS, Deciphera, Novartis, Pfizer); HMW: research funding (Amgen, ARIAD, BMS, Delta-Fly Pharma, Novartis, Pfizer).

For an e-Print, scan this QR code or visit the web at: http://bit.ly/1TUSC0b
Copies of this poster obtained through QR code are for personal use only and may not be reproduced without permission from the authors of this poster.

Presented at the 21st Annual Meeting of the European Hematology Association (EHA), June 9–12, 2016, Copenhagen, Denmark

Ponatinib and increased BP if previouos normal BP



Cortes JE et al. Blood 2013;122 (Abstract 650)

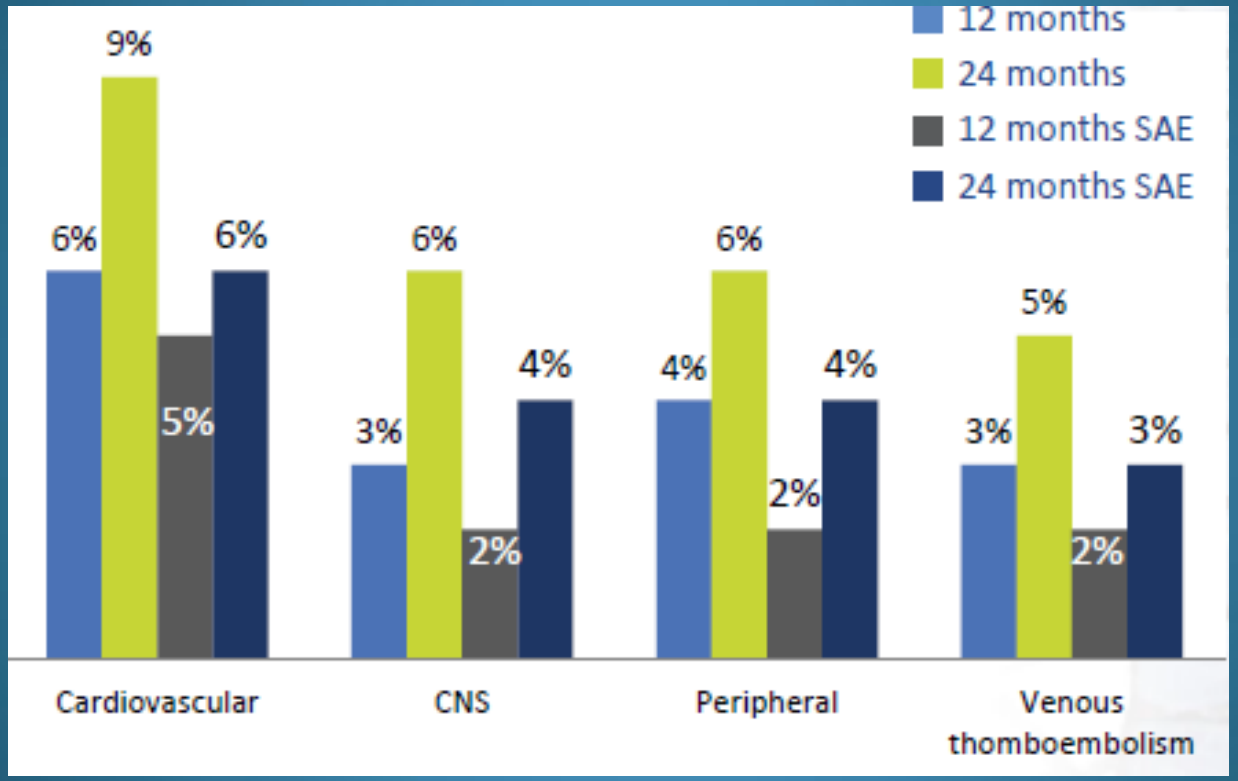
Coutre PD et al. Blood 2013; 122 (Abstract 1496)

Ponatinib is a pan-kinase inhibitor

	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	

Prince KE et al. Onco Targets Ther 2013;6:1111-1118

Ponatinib and thrombotic events PACE, by 1 and 2 years

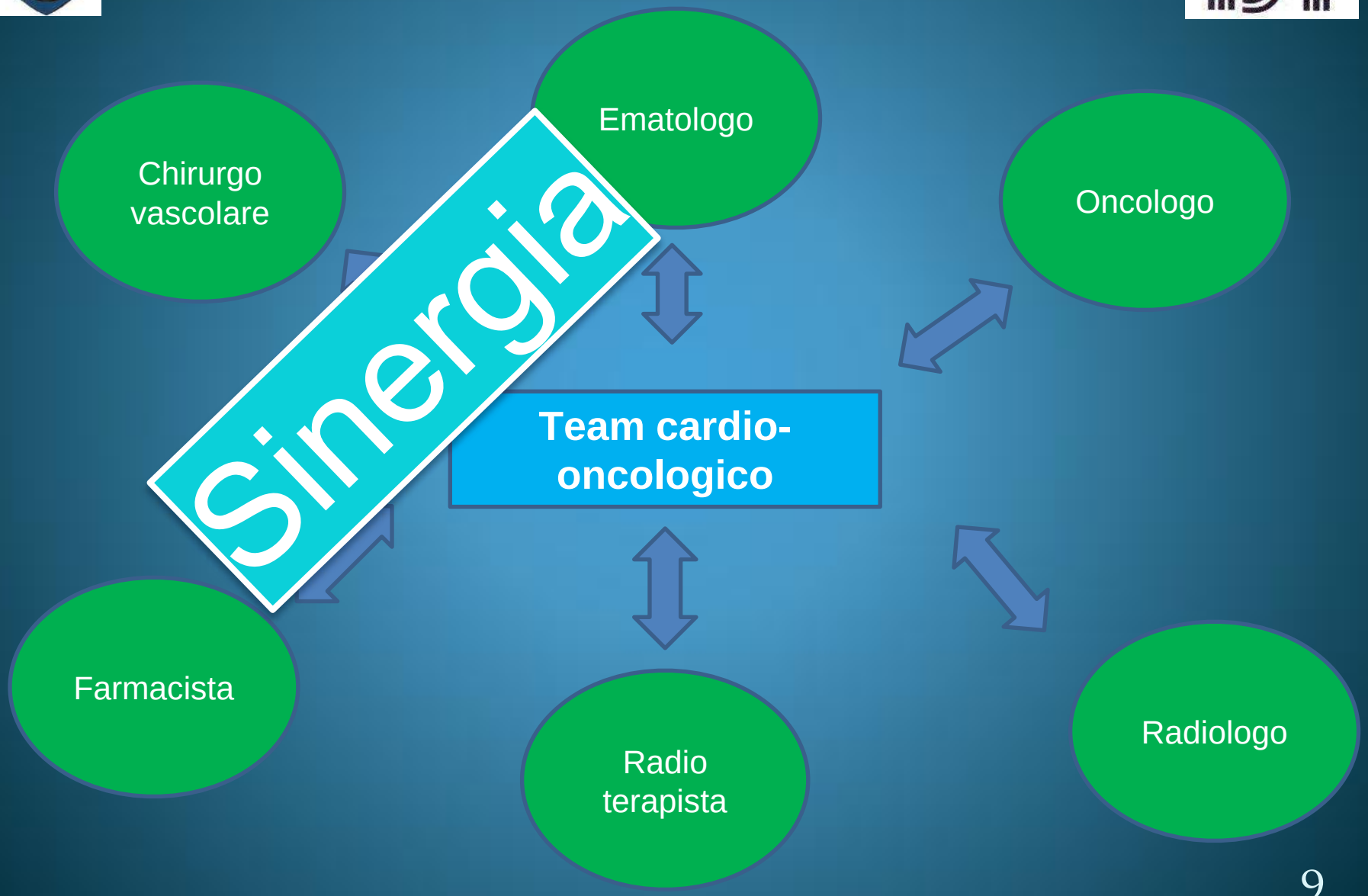


Cortes JE et al. Blood 2013;122(Abstract 650)

Coutre PD et al. Blood 2013; 122 (Abstract 1496)

Adverse effects influence TKI efficacy

LA RETE


Ematologo
Chirurgo vascolare
Oncologo
Sinergia
Team cardio-oncologico
Farmacista
Radio terapista
Radiologo

Ambulatorio di Cardio-Oncologia
IRCSS AOU SAN MARTINO - IST, GENOVA
Paolo Spallarossa, Eleonora Arboscello

Ambulatorio di screening e monitoraggio dei pazienti affetti da LMC in terapia con TKIs

M. Bergamaschi, I .Pierri
UOC Clinica Ematologica
A. Bellodi, I, E. Arboscello
UOC Clinica di Medicina Interna 3
M. Sarocchi, P. Spallarossa
UOC Malattie Cardiovascolari e UTIC
B. Pane, D. Palombo MD
UOC Chirurgia Vascolare

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

Table 3 Factors associated with risk of cardiotoxicity following anti-HER2 compounds and VEGF inhibitors[70–72]

Agent	Risk factors
Anti-HER2 compounds	
- Antibodies - Trastuzumab - Pertuzumab - T-DM1 - Tyrosine kinase inhibitor - Lapatinib	• Previous or concomitant anthracycline treatment *(short time between anthracycline and anti-HER2 treatment)* • Age (>65 years) • High BMI >30 kg/mg^2 • Previous LV dysfunction • Arterial hypertension • Previous radiation therapy
VEGF inhibitors	
- Antibodies - Bevacizumab - Ramucirumab	Pre-existing HF, significant CAD or left side VHD (e.g. mitral regurgitation), chronic ischaemic cardiomyopathy • Previous anthracycline
- Tyrosine kinase inhibitors - Sunitinib - Pazopanib - Axitinib - Neratinib - Afatinib - Sorafenib - Dasatinib	• Arterial hypertension • Pre-existing cardiac disease

BMI = body mass index; CAD = coronary artery disease; HER2 = human epidermal growth factor receptor 2; HF = heart failure; MI = myocardial infarction; VEGF = vascular endothelial growth factor; VHD = valvular heart disease.

European Journal of Heart Failure (2016)

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

Table 4 Baseline risk factors for cardiotoxicity

Current myocardial disease	*Demographic and other CV risk factors*
• Heart failure (with either preserved or reduced ejection fraction) • Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide[a]) • Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia) • Moderate and severe VHD with LVH or LV impairment • Hypertensive heart disease with LV hypertrophy • Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Restrictive cardiomyopathy • Cardiac sarcoidosis with myocardial involvement • Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)	• Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years) • Arterial hypertension • Diabetes mellitus • Hypercholesterolaemia
Previous cardiotoxic cancer treatment	***Lifestyle risk factors***
• Prior anthracycline use • Prior radiotherapy to chest or mediastinum	• Smoking • High alcohol intake • Obesity • Sedentary habit

AF = atrial fibrillation; CABG = coronary artery bypass graft; CAD = coronary artery disease; CV = cardiovascular; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; VHD = valvular heart disease.

[a]B-type natriuretic peptide >100pg/ml or N-terminal pro-B-type natriuretic peptide >400pg/ml with no alternative cause.

European Journal of Heart Failure (2016)

Valutazione preliminare del rischio CV nei pazienti candidati a ponatinib

Tutti i pazienti candidati a ponatinib devono essere sottoposti, ove possibile, ad una valutazione preliminare per definire la condizione e il rischio CV tramite:

1.Valutazione anamnestica

Fattori di rischio modificabili	Fattori di rischio non modificabili
Fumo	Età
Dislipidemia	Sesso
Diabete	Precedente evento CV
Ipertensione	Eventi CV precoci nei familiari I°
Obesità	Insufficienza renale cronica
Unhealthy diet riconosciuta	-Precedenti terapie emato-oncologiche con tossicità CV
Physical inactivity	
Psychosocial factors	-Patologie CV in atto

Ann Hematol. 2017 Apr;96(4):549-558

Valutazione preliminare del rischio CV nei pazienti candidati a ponatinib

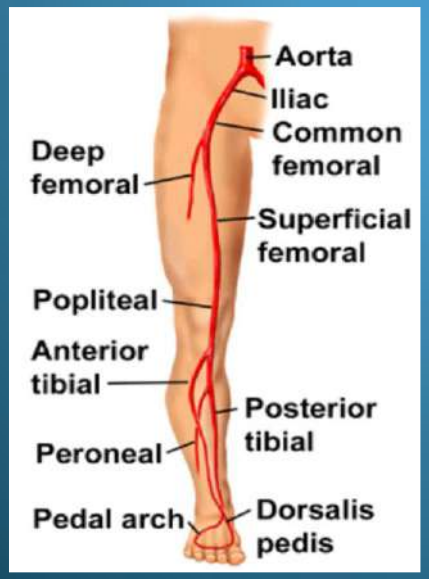
Tutti i pazienti candidati a ponatinib devono essere sottoposti, ove possibile, ad una valutazione preliminare per definire la condizione e il rischio CV tramite:

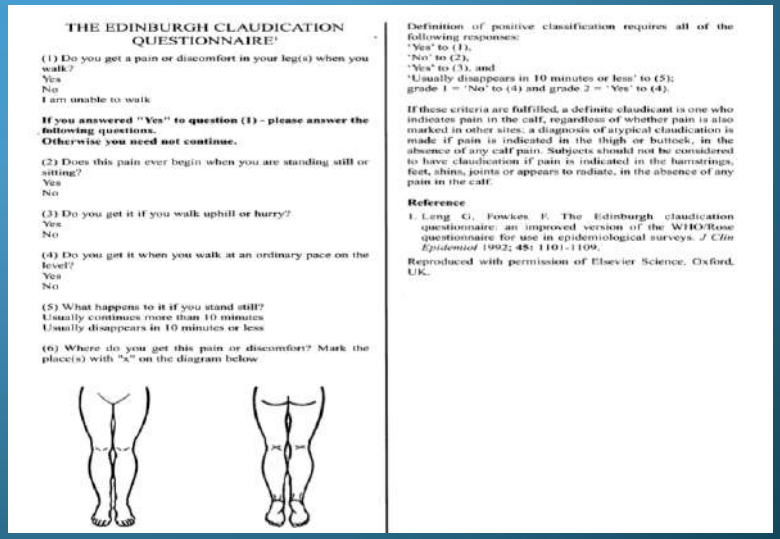
2.Indagine clinica

-Esame obiettivo completo con valutazione polsi arteriosi centrali e periferici

-Pressione arteriosa

-Questionario di Edimburgo per l'arteriopatia periferica





THE EDINBURGH CLAUDICATION QUESTIONNAIRE[1]

(1) Do you get a pain or discomfort in your leg(s) when you walk?
Yes
No
I am unable to walk

If you answered "Yes" to question (1) - please answer the following questions.
Otherwise you need not continue.

(2) Does this pain ever begin when you are standing still or sitting?
Yes
No

(3) Do you get it if you walk uphill or hurry?
Yes
No

(4) Do you get it when you walk at an ordinary pace on the level?
Yes
No

(5) What happens to it if you stand still?
Usually continues more than 10 minutes
Usually disappears in 10 minutes or less

(6) Where do you get this pain or discomfort? Mark the place(s) with "x" on the diagram below

Definition of positive classification requires all of the following responses:
'Yes' to (1),
'No' to (2),
'Yes' to (3), and
'Usually disappears in 10 minutes or less' to (5);
grade 1 = 'No' to (4) and grade 2 = 'Yes' to (4).

If these criteria are fulfilled, a definite claudicant is one who indicates pain in the calf, regardless of whether pain is also marked in other sites; a diagnosis of atypical claudication is made if pain is indicated in the thigh or buttock, in the absence of any calf pain. Subjects should not be considered to have claudication if pain is indicated in the hamstrings, feet, shins, joints or appears to radiate, in the absence of any pain in the calf.

Reference

1. Leng G, Fowkes F. The Edinburgh claudication questionnaire: an improved version of the WHO/Rose questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992; **45**: 1101-1109.

Reproduced with permission of Elsevier Science, Oxford, UK.

Ann Hematol. 2017 Apr;96(4):549-558

Valutazione preliminare del rischio CV nei pazienti candidati a ponatinib

3.Indagini cliniche laboratoristiche e strumentali

VISITA CARDIOLOGICA
ECG A RIPOSO
ECOCARDIOGRAMMA
ABI
VALUTARE DOSAGGIO DELL'OMOCISTEINA

SE PRESENTI:

FATTORI DI RISCHIO CV NOTI
PREGRESSI EVENTI TROMBOTICI ARTERIOSI
ETA' > 65 ANNI
PRECEDENTE USO DI TKI

DOPPLER TSA
DOPPLER ARTERIOSO AAII

SE PRESENTI:

CARDIOPATIA ISCHEMICA NOTA O ALTERAZIONI DELLA CINETICA SEGMENTARIA ALL'ECO

TEST PROVOCATIVO *
HOLTER

SE PREGRESSA:

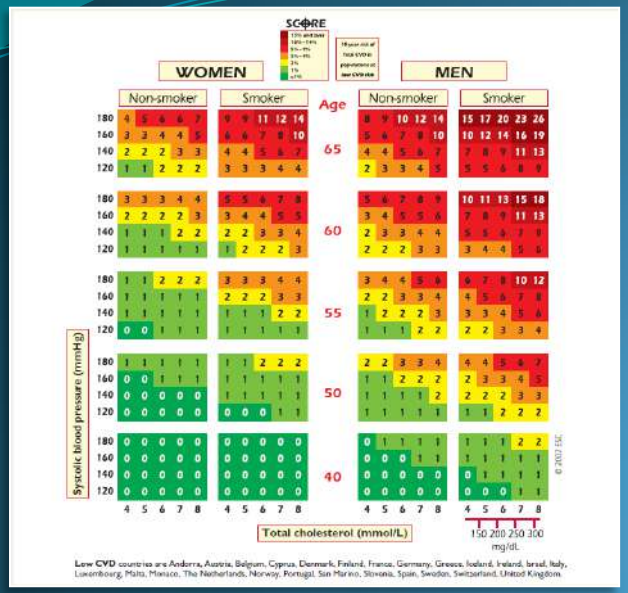
TVP O
EMBOLIA POLMONARE

DOPPLER VENOSO AAII
PROFILO EMOCOAGULATIVO*

*D-Dimero, ATIII
*Proteina C
*Proteina S libera
*Resistenza alla proteina C attivata
*LAC
*Anticorpi anti-cardiolipina
*Anticorpi anti beta-2 glicoproteina
*Mutazione G20201A del gene della protrombina

Ann Hematol. 2017 Apr;96(4):549-558

Valutazione preliminare del rischio CV nei pazienti candidati a ponatinib



Low risk

The low-risk category applies to individuals with a SCORE < 1%

Moderate risk

Subjects are considered to be at moderate risk when their SCORE is ≥1 and < 5% at 10 years. Many middle-aged subjects belong to this category. This risk is further modulated by factors in other categories

High risk

Subjects with any of the following:

•Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension.

•Diabetes mellitus (type 1 or type 2) but without CV risk factors or target organ damage.

•Moderate chronic kidney disease (GFR 30–59 mL/min/1.73 m2).

•A calculated SCORE of ≥5% and < 10%

Very high risk

Subjects with any of the following:
Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography carotid plaque on ultrasound), previous myocardial infarction, ACS, coronary revascularization (PCI, CABG), and other arterial revascularization procedures, ischaemic stroke, peripheral artery disease (PAD).
Diabetes mellitus (type 1 or type 2) with one or more CV risk factors and/or target organ damage (such as microalbuminuria: 30–300 mg/24 h).
Severe chronic kidney disease (CKD) (GFR ,30 mL/min/1.73 m2).
A calculated SCORE ≥10%.

European Guidelines on cardiovascular disease prevention in clinical practice
European Heart Journal (2012) 33, 1635–1701

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

Screening, risk stratification and early detection strategies

The first step to identify patients at increased risk for cardio-toxicity consists of a careful baseline assessment of cardiovascular risk factors.

A limited number of studies have generated risk scores for different oncology patient cohorts.
However, none of these risk scores has been validated prospectively, and clinical judgement is required when evaluating the risk at an individual level.

Risk assessment should include: clinical history and examination and baseline measurement of cardiac function.
Cardiac biomarkers (natriuretic peptides or troponin) may be considered in addition, preferably using the same assay that will be used during follow-up measurements, to increase comparability.

It is critical to detect subclinical cardiac abnormalities, which may influence clinical decisions regarding the choice of chemotherapy, indication for cardio-protection or increased surveillance frequency (e.g. asymptomatic LV dysfunction).

Finally, baseline assessment of cardiovascular risk factors allows appropriate interpretation of subsequent results/changes during regular monitoring.
Baseline risk assessment is often performed by the oncology team, but referral for cardiology evaluation is highly recommended in high-risk patients.
High risk can be determined by both the number of risk factors and their severity. Patients at high risk for developing cardio-toxicity should be examined by a cardiologist with expertise in this field or, if necessary, by a cardio-oncology specialist team.

Strategies for screening and detection of cardio-toxicity include cardiac imaging [echocardiography, nuclear imaging, cardiac magnetic resonance (CMR)] and biomarkers (troponin, natriuretic pep-tides).

Controllo della Pressione Arteriosa

Quando si inizia il trattamento?

PA >140/90 mmHg

Qual è il target?

PA =120-130/70-80 mmHg

-È bene iniziare terapia antipertensiva in monoterapia (in caso di ipertensione arteriosa >160/100 mmHg, partire o arrivare presto a terapia di associazione)

-Raggiungere una stabilità pressoria **prima** dell'inizio di ponatinib

Ann Hematol. 2017 Apr;96(4):549-558

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

- Hypertension should be adequately treated according to the current standing clinical practice guidelines, and blood pressure should be monitored before initiating cancer treatment and periodically during treatment, depending on the patient's characteristics and adequate blood pressure control.
- Hypertension in patients with cancer is manageable with conventional antihypertensive treatment, but early and aggressive treatment is encouraged to prevent the development of cardiovascular complications (i.e. HF).
- ACE inhibitors or ARBs, beta-blockers and dihydropyridine calcium channel blockers are the preferred antihypertensive drugs. Non-dihydropyridine calcium channel blockers should preferably be avoided due to drug interactions.
- Dose reduction and reinforcement of antihypertensive treatment or discontinuation of VEGF inhibitors can be considered if blood pressure is not controlled. Once blood pressure control is achieved, VEGF inhibitors can be restarted to achieve maximum cancer efficacy.

European Journal of Heart Failure (2016)

Controllo della ipercolesterolemia

I pazienti con ipercolesterolemia dovrebbero raggiungere e mantenere i target terapeutici per le LDL prescritti per le specifiche categorie di rischio (ESC)

Rischio CV totale (SCORE) %	Livelli di Col-LDL				
	<70 mg/dL <1.8 mmol/L	70-100 mg/dL 1.8-2.5 mmol/L	100-155 mg/dL 2.5-4.0 mmol/L	155-190 mg/dL 4.0-4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	Nessun intervento	Nessun intervento	Intervento sullo stile di vita	Intervento sullo stile di vita	Intervento sullo stile di vita; se insufficiente considerare farmacoterapia
≥1 a <5	Intervento sullo stile di vita	Intervento sullo stile di vita	Intervento sullo stile di vita; se insufficiente considerare farmacoterapia	Intervento sullo stile di vita; se insufficiente considerare farmacoterapia	Intervento sullo stile di vita; se insufficiente considerare farmacoterapia
>5 a <10, o alto rischio	Intervento sullo stile di vita; considerare farmacoterapia*	Intervento sullo stile di vita; considerare farmacoterapia*	Intervento sullo stile di vita e immediata farmacoterapia	Intervento sullo stile di vita e immediata farmacoterapia	Intervento sullo stile di vita e immediata farmacoterapia
≥10, o rischio molto alto	Intervento sullo stile di vita; considerare farmacoterapia*	Intervento sullo stile di vita e immediata farmacoterapia*	Intervento sullo stile di vita e immediata farmacoterapia	Intervento sullo stile di vita e immediata farmacoterapia	Intervento sullo stile di vita e immediata farmacoterapia

*In pazienti con infarto del miocardio, la terapia con statine dovrebbe essere considerata indipendentemente dai livelli di Col-LDL
CV = Cardiovascolare
Col-LDL= colesterolo a lipoproteine a bassa densità.

Ann Hematol. 2017 Apr;96(4):549-558

La terapia ipocolesterolemizzante di prima scelta è quella con statine.

Tra queste, pravastatina e rosuvastatina possono andare incontro a interazioni farmacocinetiche con ponatinib, con aumento dei livelli plasmatici delle statine e del rischio ad esse correlato.

È consigliabile, dunque, iniziare con ***atorvastatina*** e, se entro 3 mesi il target non è raggiunto, associare *ezetimibe*

Controllo del Diabete

L'aumento della glicemia non è un'alterazione metabolica osservata con ponatinib

E' però importante mantenere il valore della glicemia basale entro i limiti dettati dai criteri WHO e dell'associazione diabetologica americana (ADA)

considerando

il diabete (valori di glicemia superiori a 126 mg/dl)
e
l'alterata glicemia a digiuno
(glicemia basale compresa tra 100 e 126 mg/dl)

come fattori di rischio cardiovascolare modificabili

	Dasatinb	Ponatinib	Busutinib
Insulina	***Nessuna interazione***	***Nessuna interazione***	***Nessuna interazione***
Metformina	***Nessuna interazione***	***Nessuna interazione***	***Nessuna interazione***
Acarbosio	***Nessuna interazione***	***Nessuna interazione***	***Nessuna interazione***
Rosiglitazone	***Nessuna interazione***	***Nessuna interazio ne***	***Nessuna interazione***
Pioglitazone	***Dasatinib aumenta i livelli di pioglitazone (CYP 3A4)***	***Nessuna interazione***	***Nessuna interazione***
Repaglinide	***Dasatinib aumenta i livelli di repaglinide (CYP 3A4)***	***Nessuna interazione***	***Nessuna interazione***

il farmaco di prima scelta è la metformina

Gli obiettivi della terapia ipoglicemizzante sono quindi mantenere:

un livello di emoglobina glicosilata inferiore al 7%

un livello di glicemia basale pre-prandiale compreso tra 70 e 130 mg/dl

un picco glicemico post-prandiale inferiore a 180 mg/dl

Ann Hematol. 2017 Apr;96(4):549-558

Prevenzione Primaria delle Sindromi Arteriose Acute -I-

L'elevata incidenza di eventi trombotici arteriosi osservata negli studi clinici con ponatinib può suggerire una profilassi antitrombotica primaria in tutti i pazienti candidati al farmaco, senza rischio emorragico elevato

Tale prassi non ha riscontro in formali linee guida e deve basarsi esclusivamente sulla percezione del curante del rischio trombotico introdotto da ponatinib, e sul grado del rischio CV

Una profilassi primaria ex novo con aspirina 75-100 mg/die e, in caso di controindicazioni/intolleranza all'aspirina, clopidogrel 75 mg/die, sarà valutata caso per caso e concordata tra ematologo e cardiologo

In questi pazienti è necessario monitorare la conta delle piastrine ed eventualmente sospendere la profilassi, a giudizio dell'ematologo, quando ponatinib ne determinasse una riduzione a $<50x10^9$/L, valore soglia suggerito dalla Scheda Tecnica.

Ann Hematol. 2017 Apr;96(4):549-558

Prevenzione Secondaria

-I-

Ann Hematol. 2017 Apr;96(4):549-558

Pazienti con pregresso evento ischemico coronarico (STEMI, SCA, NSTEMI, CABG superiore a un anno), o evento ischemico cerebrale

Terapia antiaggregante piastrinica con aspirina 75-100 mg/die, da proseguire per tutto il periodo di terapia con Ponatinib e, in caso di intolleranza, con clopidogrel 75 mg/die.

Pazienti con evento ischemico coronarico trattati con stent convenzionale (“bare-metal stent”)

Doppia anti-aggregazione piastrinica (aspirina 75-100 mg/die + clopidogrel 75 mg), per almeno un mese dal posizionamento dello stent

Pazienti con stent medicato

Doppia anti-aggregazione piastrinica (aspirina 75-100 mg/die + clopidogrel, 75 mg) per almeno un anno dal posizionamento dello stent

Antiaggreganti piastrinici	Imatinib	Dasatinib	Bosutinib	Ponatinib	Nilotinib
Clopidogrel	***Nessuna interazione***	***Dasatinib aumenta livelli di clopidogrel (CYP 3A4)***	***Nessuna interazione***	***Nessuna interazione***	***Nilotinib riduce i livelli/l’efficacia di clopidogrel (CYP 3A4)***
Ticagrelor	***Interazione con aumento livello entrambi. Imatinib aumenta i livelli di ticagrelor (CYP 3A4 e 2D6)***	***Nessuna interazione***	***Nessuna interazione***	***Nessuna interazione***	***Nessuna interazione***
Prasugrel					***Nessuna interazione***

Prevenzione Secondaria
- II -

Pazienti con evento ischemico coronarico ed ecocardiografia positiva per trombi o rischio di formazione di trombi ventricolari (FEVS <35%, acinesia apicale)

- Associazione di aspirina (75-100 mg/die) con trattamento anticoagulante orale (TAO) dicumarolico, mantenendo un obiettivo terapeutico di INR 2-3

Pazienti in TAO dicumarolico per FA o pregresso tromboembolismo venoso

E' raccomandato il mantenimento della terapia anticoagulante per tutto il periodo di terapia con ponatinib, mantenendo un obiettivo terapeutico di INR fra 2.0 e 3.0

Pazienti in terapia con i nuovi anticoagulanti orali (NAO) apixaban o dabigatran o rivaroxaban o edoxaban (per i quali non è previsto il monitoraggio dello stato coagulativo)

E' raccomandata l'assoluta aderenza alla posologia consigliata per ogni specifico principio attivo ed il periodico controllo della funzionalità renale.

Anche in questi pazienti, è necessario monitorare la conta delle piastrine ed eventualmente sospendere la profilassi a giudizio dell'ematologo, quando ponatinib ne determinasse una riduzione a <50x10^9/L.

Nei pazienti che assumono anche altri farmaci noti per interagire con warfarin o NAO, valgono le stesse raccomandazioni che si applicano alla popolazione generale

Ann Hematol. 2017 Apr;96(4):549-558

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The initial approach to the management of atrial fibrillation and atrial flutter requires the usual decisions regarding rhythm management, thromboembolic prophylaxis and effective stroke prevention with oral anticoagulation

The balance between thromboembolic and bleeding risks of atrial fibrillation, assessed by the CHA2DS2-VASc and HAS-BLED, is particularly challenging in patients with cancer. While cancer may cause a pro-thrombotic state, it may also predispose to bleeding. On the other hand, the CHA2DS2-VASc and HAS-BLED risk scores have not been validated in patients with cancer

In patients with a CHA2DS2-VASc score ≥2, anticoagulation can generally be considered if the platelet count is .50 000/mm3, usually with a vitamin K antagonist and with good anticoagulation control (with time in the therapeutic range .70%). Close liaison with haematologists/oncologists is advised.

Full assessment of the patient, including echocardiography, is advised, and decisions on anticoagulation should consider other co-morbidities, bleeding risks and patient values and preferences

Anticoagulation options include therapeutic low molecular weight heparin (LMWH) (as a short- to intermediate-term measure), a vitamin K antagonist (VKA; e.g. warfarin) if the international normalized ratio control is stable and effective or a non-VKA oral anticoagulant (NOAC). Warfarin is often avoided in cancer patients with metastatic disease and high bleeding risk, with LMWH the traditionally preferred option, given the risk for variations in the international normalized ratio.

The role and safety of NOACs in this patient group remains to be clarified. Although trials generally excluded patients with a platelet count of 100 000/mm3
or limited survival, a meta-analysis of the patients with cancer in NOAC trials suggested these new drugs are safe

European Journal of Heart Failure (2016)

Lancet Oncology 2016; 17: e452–66

International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer

Dominique Farge et at

Panel 2: Treatment of established venous thromboembolism

Early maintenance (10 days to 3 months) and long-term (beyond 3 months)

International Advisory Panel ranking: 8·48 out of 9·00

1 LMWHs are preferred over vitamin K antagonists (VKAs) for the treatment of VTE in patients with cancer (grade 1A). Values and preferences: daily subcutaneous injection might be a burden for patients.

2 LMWH should be used for a minimum of 3 months to treat established VTE in patients with cancer (grade 1A).

Although the two largest studies[25,28] in this setting treated patients for 6 months, the strength of the evidence for treatment up to 6 months is low (inconsistency). Values and preferences: daily subcutaneous injection might be a burden for patients.

3 Direct oral anticoagulants can be considered for VTE treatment of patients with stable cancer not receiving systemic anticancer therapy, and in cases where VKA is an acceptable, but not an available, treatment choice (guidance).

4 After 3–6 months, termination or continuation of anticoagulation (LMWH, VKA, or direct oral anticoagulants) should be based on individual assessment of the benefit-to-risk ratio, tolerability, drug availability, patient preference, and cancer activity (guidance, in the absence of data).

Panel 5: VTE treatment in unique situations

6 In patients with severe renal failure (creatinine clearance <30 mL/min), an external compression device can be applied, and pharmacological prophylaxis should be considered on a case-by-case basis; in patients with severe renal failure (creatinine clearance <30 mL/min), UFH can be used on a case-by-case basis (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the level of VTE risk).

7 In patients with cancer and thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is >50 g/L and bleeding is not evident; for patients with a platelet count <50 g/L, decisions on treatment and dose should be made on a case-by-case basis with the utmost caution (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs VTE risk).

8 In patients with cancer with mild thrombocytopenia, a platelet count >80 g/L, pharmacological prophylaxis might be used; if the platelet count is <80 g/L, pharmacological prophylaxis should only be considered on a case-by-case basis and careful monitoring is recommended (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs VTE risk).

Monitoraggio in corso di terapia

MONITORAGGIO DEL RISCHIO CARDIOVASCOLARE DURANTE TRATTAMENTO

A TUTTI

VISITA CARDIOLOGICA
ECG A RIPOSO
ABI

DA RIPETERE DOPO 1, 3, 6, 12 MESI

A TUTTI

DOPPLER TSA
DOPPLER ARTERIOSO AAII

DA RIPETERE DOPO 6-12 MESI

SE PRESENTI:

DISPNEA DI NUOVA INSORGENZA
EDEMI PERIMALLEOLARI
EO CARDIOPOLMONARE ALTERATO

ECOCARDIOGRAMMA

SE PRESENTI:

PRECORDIALGIE DI NUOVA INSORGENZA
ALTERAZIONI ECG DI POSSIBILE NATURA ISCHEMICA

TEST PROVOCATIVO

SE PRESENTI:

CLAUDICATIO DI NUOVA INSORGENZA

DOPPLER ARTERIOSO AAII

Ann Hematol. 2017 Apr;96(4):549-558

Ambulatorio di Cardio-Oncologia
Paolo Spallarossa, Eleonora Arboscello

Follow-up	Trimestrale
Anamnesi -Valutazione dei fattori di rischio cardiovascolari -Comorbidità -Terapia domiciliare	**Esame obiettivo** -Pressione arteriosa -Frequenza cardiaca -Peso e altezza -Polsi periferici -Acc e Ar
Esami ematochimici -Emocromo -Creatinina, acido urico, sodio, potassio, calcio, magnesio, ALT, AST, ALP, gamma GT, colesterolo LDL e HDL, trigliceridi, glicemia, HbA1c -Coagulazione completa	**Esami strumentali** **(in relazione al TKI e se clinicamente indicati)** -ECG con valutazione QT e QTcf -Ecocardiogramma con misurazione pressioni polmonari* -Questionario di Edimburgo -Valutazione chirurgo vascolare con ABI** -Eco-color-doppler TSA** -Eco-color-doppler arterioso arti inferiori** -Eco-color-doppler venoso arti inferiori**
stratificazione dinamica del rischio CV -Chart score -Classi ri rischio	**Interazioni farmacologiche**

* annuale o se clinicamente indicato, ** semestrale o se clinicamente indicato

Riduzione della dose

La riduzione della dose a 30 o 15 mg/die può essere considerata nei pazienti con evidenza clinica o sub-clinica di eventi cardiovascolari, nei pazienti con importante risposta alla terapia con ponatinib, in particolare con risposta molecolare profonda

I dati suggeriscono che ogni riduzione della dose di 15 mg di ponatinib sembra determinare una riduzione del 33% circa del rischio di eventi trombotici

Conclusioni

Ponatinib rappresenta una terapia estremamente efficace nel trattamento della leucemia mieloide cronica e unica, salvavita nella leucemia linfoblastica acuta PH+

Le basi fisiopatologiche della cardiotossicità di ponatinib sono ancora sconosciute

Il rischio di sviluppare eventi cardiovascolari non deve scoraggiare lo specialista ematologo nel somministrare ponatinib soprattutto nei pazienti ad alto rischio di decesso per leucemia

La collaborazione multidisciplinare, in primis tra cardiologo ed ematologo, è fondamentale ai fini della più corretta gestione del paziente che deve e può accedere alle terapie più efficaci

Conclusioni

La valutazione e la gestione del rischio cardiovascolare del paziente candidato a ponatinib

L’approccio farmacologico relativo alla gestione dei fattori di rischio e delle complicanze ca

Queste raccomandazioni hanno lo scopo di ridurre il rischio cardiovascolare ottimizzando l

Un Particolare Ringraziamento

Prof. Riccardo Ghio

Prof. Claudio Brunelli

Dr. Paolo Spallarossa

Prof. Francesco Puppo

Dr. Bellodi Andrea

Dr. Matteo Sarocchi

Dr.ssa Vera Sicbaldi

Grazie dell'attenzione

Dott.ssa Eleonora Arboscello