5 Minute JournalClub

POST-ASH Issue 2, 2014

Phase II PACE Trial: 2-Year Follow-Up of Ponatinib in CML and Ph+ ALL

For more visit ResearchToPractice.com/5MJCASH2014

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on the management of chronic myeloid leukemia (CML) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the impact of early molecular response or dose interruption of tyrosine kinase inhibitors (TKIs) on the prognosis of patients with CML.
- Compare and contrast the benefits and risks of nilotinib versus imatinib therapy in patients with newly diagnosed chronic-phase CML.
- Appraise recent clinical data on the effect of switching to nilotinib in patients with a suboptimal response to imatinib therapy versus continuation of imatinib at a higher dose.
- Analyze the outcomes of the STIM1 and STIM2 studies of discontinuation of imatinib in patients with a deep molecular response, and consider these results in the management of CML.
- Assess the efficacy and safety of ponatinib as initial therapy and in patients with TKI-resistant CML.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2014/2/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Jorge E Cortes, MD
D B Lane Cancer Research
Distinguished Professor for Leukemia Research
Deputy Chairman, Section Chief of AML and CML
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Consulting Agreements: Bristol-Myers Squibb Company, Genentech BioOncology, Lilly, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Contracted Research: Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi.

Hagop M Kantarjian, MD
Chairman and Professor, Leukemia Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

No real or apparent conflicts of interest to disclose.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, Exelixis Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc, Teva Oncology and VisionGate Inc.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Seattle Genetics and Spectrum Pharmaceuticals Inc.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: February 2014
Expiration date: February 2015

5 MinuteJournalClub

POST-ASH Issue 2, 2014

To go directly to slides and commentary for this issue, **click here**.

Jorge E Cortes, MD

Sometimes I have to pinch myself to see if this is a dream or if I really have a job listening to and learning from the great minds in our chosen field. Last week was a perfect reminder of just how cool "work" can be when within the space of a few days my calendar included extensive interviews with Drs Jorge Cortes and then Hagop Kantarjian. As deputy chair and chair of MD Anderson's Department of Leukemia, respectively, these 2 investigators lead a unique clinical and research powerhouse that has contributed perhaps as much to the care of patients with these and other related hematologic disorders as any other institution in the world.

Hagop M Kantarjian, MD

To get a sense of just how prolific they are, peruse the 2013 ASH abstracts and you will find that Drs Cortes and Kantarjian helped author 103 oral presentations and posters, including 30 on chronic myelogenous leukemia (CML) alone. As such, and not surprisingly, each of these conversations focused heavily on that disease — which has become the poster child for targeted oncologic treatment — and below find the bottom line on their thoughts about how the data sets from New Orleans helped address the following important questions in CML.

1. What are the key early markers of response, and when should consideration be given to switching to another tyrosine kinase inhibitor (TKI)?

Another MD Anderson leukemia maven and chair of the NCCN CML guidelines committee, Dr Susan O'Brien frequently reinforces the important concept that although there are many reasons to seek deep molecular responses (DMR), the classic and most important endpoint is complete cytogenetic response (CCyR) — a milestone that is achieved faster and more frequently with the second-generation agents, nilotinib and dasatinib. The question of whether suboptimal molecular response should trigger a switch to another TKI ties directly into the issue of selection of up-front therapy and whether long-term outcomes are compromised when residual disease is present.

Equally relevant and looming in the background is a fascinating question of "quality" and cost associated with oncology care. Specifically, imatinib is due to go off patent in January 2015, and it is expected that this will dramatically lower the annual tab (about $90,000 with imatinib, and with nilotinib and dasatinib closer to $100,000). With a current prevalence of about 100,000 CML cases in the United States alone — a number that will likely double in the next 3 decades before plateauing — researchers, clinicians and policy makers will almost certainly continue the debate about the value of starting with imatinib (the soon-to-be less costly and perhaps slightly less effective agent) and reserving second-generation treatment for patients with higher-risk disease and those with suboptimal initial responses to imatinib. How these potential resource savings stack up against others in oncology related to, for example, futile care and unnecessary imaging will be discussed extensively, and more globally Dr Kantarjian has taken a leadership role in organizing a group of "CML experts" (including Dr Cortes) who have been on a dedicated and major offensive attacking the current CML cost structure.

At ASH we witnessed a number of related papers that tie in to the issue of imatinib versus the rest, including the **36-month update** of the ENESTcmr study. This landmark Phase III effort demonstrated that among patients in CCyR but with detectable BCR-ABL transcripts, those randomly assigned to switch to nilotinib achieved more DMRs compared to those continuing on imatinib (47% with nilotinib versus 33% with imatinib at 36 months). This benefit came with greater toxicity, which may in part be attributable to the trial design in that patients who transitioned to nilotinib were already tolerating imatinib well.

On a similar note, an ASH data set presented by Dr Cortes from the Phase III **LASOR trial** revealed that switching to nilotinib versus escalating the dose of imatinib in patients who experienced suboptimal response resulted in a better rate of CCyR at 6 months (49% versus 42%, respectively), although the findings were not statistically significant (p = 0.3844).

Finally, a **retrospective analysis** of 3- and 6-month responses in early trials of imatinib demonstrated that some patients who achieve an optimal response by 6 instead of 3 months have long-term outcomes comparable to those who achieved an optimal response at 3 months, suggesting that waiting a few additional months before considering a change in treatment is a rational approach.

Proponents of using imatinib as initial treatment in standard-risk situations often point out that so far, no survival benefit has been demonstrated using the second-generation agents — possibly because these drugs also effectively rescue patients experiencing disease progression on imatinib. Thus, although DMR is an intuitively appealing goal, until further research identifies more accurately who can cease TKI treatment (now there's a cost saving!), there will be debate and controversy about what to start with and when and if to make a switch. This is particularly true as more follow-up occurs

with the landmark second-generation trials, some of which are documenting more long-term complications, such as the 5-year update of the **ENESTnd trial** presented at ASH that now shows not only deeper molecular responses with nilotinib but also an increasing number of cardiovascular events.

2. Are there situations in which it is safe to discontinue TKI treatment?

At ASH we saw more data from **2 French studies** (STIM 1 and 2) attempting to define the outcomes of patients with prolonged (more than 2 years) DMRs who discontinued treatment. These studies and others have documented that when taken off therapy more than half the patients experience relapse — usually quickly — and the remainder fare well off treatment. Importantly, although most patients experiencing relapse can be effectively salvaged with the same or a different TKI, at this point there is no way to pick who will do well without treatment and therefore neither professor employs this approach outside a trial setting, although Dr Kantarjian notes that if ongoing research shows how to identify these patients, both long-term toxicity and financial costs can be avoided.

Interestingly, Dr Cortes commented on one situation in which a variation of this stopping strategy is often a consideration — specifically, in women with CML who wish to become pregnant — and so far he has managed about 2 dozen carefully selected patients, most of whom have not required retreatment until after childbirth.

Another fascinating and somewhat **related ASH report** documented that in a major Phase III trial of dasatinib versus imatinib patients starting treatment who missed doses due to toxicities like cytopenias had significantly worse 3-month outcomes. Importantly, this effect appears to occur when missing even 1 dose (in the case of imatinib) and increases with the number of doses missed.

3. What is the current role of ponatinib?

In December 2012 this pan-BCR-ABL "super TKI" was approved by the FDA, but last October it was pulled off the market due to toxicity concerns, mainly arteriothrombotic events. By December ponatinib was once again available, accompanied by a new black box warning and a Risk Evaluation and Mitigation Strategy program designed to help clinicians more effectively evaluate the risks and benefits of using the agent.

In discussing ponatinib, Dr Kantarjian noted that the approved daily dose of 45 mg not uncommonly leads to toxicities such as hypertension, vasospastic reactions, pancreatitis and skin rashes that are not acceptable in the up-front setting, where safer effective choices exist. In this regard an MD Anderson single-arm **pilot study** of 51 patients presented at ASH was amended to include a starting dose of 30 mg daily. Regardless, accrual was suspended in October, as in another major Phase III up-front study comparing ponatinib to imatinib.

However, in discussing the updated ASH results from the pivotal **PACE trial** in relapsed disease, Dr Kantarjian reiterated that ponatinib, when used in that indicated setting, can be a life-altering therapy, particularly for those with BCR-ABL T315I mutations. He also pointed out that the vaso-occlusive reactions that have been observed with this drug occur infrequently with the other TKIs.

Next on this series, we provide an update on ASH reports in lymphoma, including encouraging data sets on the nonchemotherapy combination of lenalidomide and rituximab, the antibody-drug conjugate brentuximab vedotin and a fascinating paper on crizotinib in ALK-positive lymphoma.

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

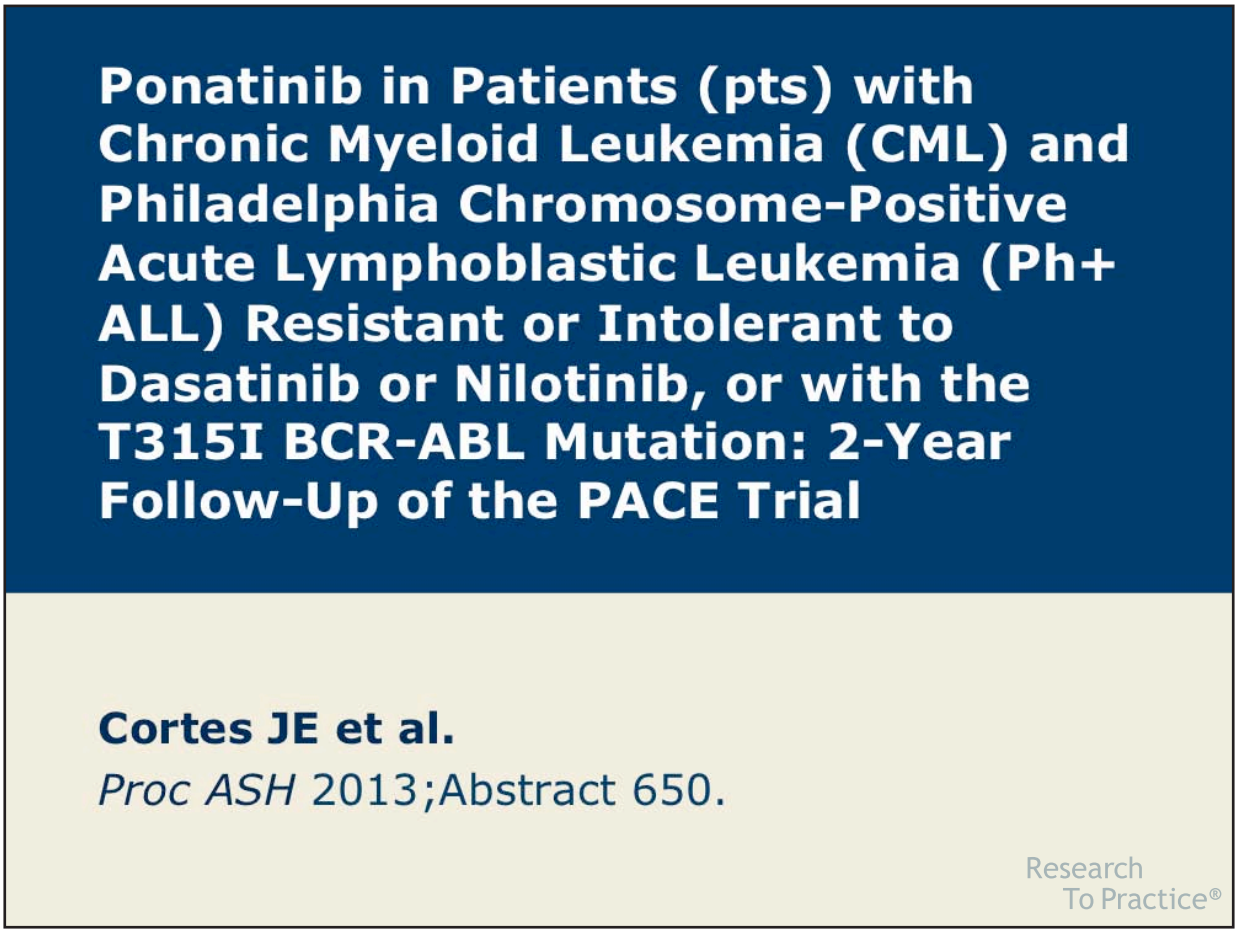
This activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Seattle Genetics and Spectrum Pharmaceuticals Inc.

Phase II PACE Trial: 2-Year Follow-Up of Ponatinib in CML and Ph+ ALL

Presentation discussed in this issue

Cortes JE et al. **Ponatinib in patients (pts) with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) resistant or intolerant to dasatinib or nilotinib, or with the T315I BCR-ABL mutation: 2-year follow-up of the PACE trial.** *Proc ASH* 2013;**Abstract 650**.

Slides from a presentation at ASH 2013 and transcribed comments from recent interviews with Jorge E Cortes, MD (1/24/14) and Hagop M Kantarjian, MD (1/29/14)



Background

- Ponatinib — a potent, oral, pan-BCR-ABL inhibitor with activity against native and mutant forms of BCR-ABL, including the tyrosine kinase inhibitor (TKI)-resistant T315I mutant — was approved in December 2012 by the FDA and July 2013 by the EMA.
- Because of an accumulation of vascular events over time, ponatinib was temporarily suspended from commercial distribution in the United States in October 2013 and became available only under a single-patient investigational new drug application or expanded access registry program.
  - In November 2013, the EMA retained the authorized indication with measures to reduce risk.
- **Study objective:** To provide 2-year follow-up data from the PACE trial.

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Research To Practice®

PACE: Phase II Trial Design

Eligibility (n = 449)

- CML-CP, CML-AP, CML-BP or Ph+ ALL
- BCR-ABL T315I mutation **or** resistant or intolerant (R/I) to dasatinib or nilotinib

→ **Ponatinib 45 mg orally once daily**

CML-CP = chronic-phase CML; CML-AP = accelerated-phase CML; CML-BP = blast-phase CML

Primary endpoints

- Major cytogenetic response (MCyR) at any time within 12 months for CML-CP
- Major hematologic response (MaHR) at any time within 6 months for advanced CML or Ph+ ALL

Cortes JE et al. *Proc ASH* 2012;Abstract 163.

Research To Practice®

Responses at Any Time

	CML-CP			CML-AP	CML-BP	Ph+ ALL
	MCyR	CCyR	MMR	MaHR*	MaHR	MaHR
R/I to dasatinib or nilotinib	56%	48%	31%	62%	32%	50%
T315I mutation	72%	70%	58%	61%	29%	36%
Total†	60%	54%	38%	61%	31%	41%

CCyR = complete cytogenetic response; MMR = major molecular response

* 14 patients with CML-AP with baseline MaHR and 1 patient with CML-AP with no baseline MaHR assessment were counted as nonresponders

† Total comprises all eligible patients who received ponatinib. It excludes 5 patients (3 CML-CP, 2 CML-AP) who were not cohort assigned (postimatinib, non-T315I) but received treatment; all 5 achieved MCyR.

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Research To Practice®

Response Characteristics and Survival: CML-CP

Median time to response	
MCyR	2.8 months
CCyR	2.9 months
MMR	5.5 months
Clinical outcomes	
MCyR at 2 years (n = 149)	89%
PFS (n = 267) Median PFS PFS at 2 years	 29 months 67%
OS (n = 267) Median OS OS at 2 years	 Not yet reached 86%

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Research To Practice®

Response Characteristics and Survival: CML-AP, CML-BP and Ph+ ALL

CML-AP	
Median time to response	
MaHR	0.7 months
Clinical outcomes	
MaHR at 2 years	21%
PFS (n = 83) Median PFS PFS at 2 years	 15 months 37%
OS (n = 83) Median OS OS at 2 years	 Not yet reached 72%

OS	
CML-BP (n = 62) Median OS OS at 2 years	 7 months 18%
Ph+ ALL (n = 32) Median OS OS at 2 years	 8 months 21%

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Select Treatment-Emergent Adverse Events (AEs)

	CMP-CP (n = 270)		Total population (n = 449)	
Nonhematologic	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Rash	44%	4%	40%	4%
Abdominal pain	43%	9%	40%	9%
Headache	41%	3%	36%	2%
Dry skin	41%	3%	36%	2%
Constipation	39%	3%	36%	2%
Hypertension	27%	10%	24%	9%
Hematologic	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Thrombocytopenia	44%	35%	43%	35%
Neutropenia	19%	16%	25%	22%
Anemia	16%	9%	22%	15%

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Hypertension

Baseline BP (mm Hg), NCI CTCAE	Increase in BP on study (single measurement)*		
	Grade 1	Grade 2	Grade 3
Normal (<120/<80), N = 70	36%	30%	23%
Grade 1 (120-139)/(80-89), N = 167	—	53%	34%
Grade 2 (140-159)/(90-99), N = 157	—	—	60%
Grade 3 (≥160/≥100), N = 55	—	—	—

- 379/449 (84%) patients had elevated BP at baseline (≥140/90, 47%)
- 301/449 (67%) patients experienced any increase in BP* on study
- AEs of hypertension were reported in 109/449 (24%) patients (serious AEs in 8/449 [2%])

* Any shift to higher grade (NCI CTCAE v.4.0), based on single BP measurements

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Incidence of Vascular Occlusive Events Over Time

	N = 449 N (%)			
Data as of	**23 July 2012 (USPI)**		**03 Sep 2013**	
Median follow-up (exposure)	**12 months (340 patient years)**		**24 months (578 patient years)**	
Category	**SAE**	**AE**	**SAE**	**AE**
Cardiovascular	21 (5)	29 (6)	28 (6)	41 (9)
Cerebrovascular	8 (2)	13 (3)	18 (4)	25 (6)
Peripheral vascular	7 (2)	17 (4)	16 (4)	28 (6)
Total arterial thrombosis	34 (8)	51 (11)	53 (12)	77 (17)
Venous thromboembolism	10 (2)	15 (3)	13 (3)	23 (5)
Vascular occlusion*				
Method 1†	41 (9)	62 (14)	62 (14)	91 (20)
Method 2‡	47 (10)	81 (18)	67 (15)	109 (24)

* Combined incidence of cardiovascular, cerebrovascular, peripheral vascular, venous thromboembolism events;
† EMA press release Nov 22, 2013; ‡ FDA drug safety communication, Oct 31, 2013

USPI = US package insert; SAE = AE reported as serious by the investigator, per standard criteria

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Multivariate Analysis of Arterial Thrombotic AEs

- Risk factors significantly associated with arterial thrombotic AEs:
  - Older age ($p < 0.0001$)
  - History of diabetes ($p = 0.0003$)
  - Higher dose intensity to time of first event ($p = 0.0009$)
  - History of ischemia ($p = 0.0087$)
  - Longer time since diagnosis ($p = 0.0228$)
  - Higher baseline neutrophil count ($p = 0.0276$)
  - Higher baseline platelet count ($p = 0.0466$)
- Each 15 mg/day reduction in dose intensity results in a predicted reduction of ~40% in the risk of an arterial thrombotic event.

Data are similar for vascular occlusive events.

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Research To Practice®

Author Conclusions: 2-Year Follow-Up Summary

- This study confirmed substantial clinical activity in patients with heavily pretreated Ph+ leukemias.
- Early, deep and durable responses were observed:
  - 89% maintained MCyR for at least 2 years in CML-CP.
- Arterial thrombotic events occurred; higher dose intensity, older age and presence of other risk factors at baseline were associated with a higher likelihood of events.
- Overall survival was not reduced for patients experiencing arterial thrombotic events.
- Ponatinib is an important treatment for patients in whom the need and potential benefit outweigh the risks.

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Research To Practice®

Investigator Commentary: 2-Year Follow-Up of PACE — A Pivotal Phase II Trial of Ponatinib in Refractory CML and Ph+ ALL

With 2 years of follow-up, the PACE trial continues to show outstanding results with regard to major cytogenetic responses in patients with chronic-phase CML for whom more than 2 TKIs have failed. We reported 60% of patients with a major cytogenetic response, and about two thirds of the patients enrolled had experienced disease progression on 3 or more TKIs. We also reported on the risk of cardiovascular events and hypertension, which is common. We need to monitor carefully those patients with cardiovascular risk factors and care for them proactively to minimize complications.

Interview with Jorge E Cortes, MD, January 24, 2014

At our institution we've administered ponatinib to more than 100 patients and have observed the same toxicities that were described at the ASH meeting. Our concerns are mostly with some less common but serious problems such as pancreatitis and vaso-occlusive disorders. We are also concerned about less serious events that in the long run could cause organ damage, such as hypertension, which was a risk in the case of ponatinib at the dose of 45 mg a day. In my opinion using a lower dose of ponatinib, perhaps 30 mg per day, will alleviate most of the associated side effects such as hypertension, pancreatitis and skin rash.

Interview with Hagop M Kantarjian, MD, January 29, 2014