5 Minute JournalClub

POST-ASH Issue 7, 2013

Pivotal Phase II PACE Trial of Ponatinib in Patients with CML and Philadelphia Chromosome-Positive ALL: 12-Month Follow-Up

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows 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 efficacy and safety of bosutinib as second-line therapy for patients with chronic-phase chronic myeloid leukemia (CML-CP), including those whose disease is resistant or intolerant to imatinib.
- Compare and contrast response patterns and long-term clinical impact of treatment with nilotinib, imatinib or dasatinib as first-line therapy for CML-CP.
- Describe updated clinical research data on the activity and tolerability of ponatinib from the pivotal Phase II study in patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia or those with BCR-ABL T315I mutations, and consider this information when caring for these patients.
- Assess the evolving role of omacetaxine mepesuccinate for patients with treatment-resistant CML, such as those who are in blast crisis.

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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: May 2013
Expiration date: May 2014

5 MinuteJournalClub

POST-ASH Issue 7, 2013

CML update: A lot going on, as usual

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

With 3 newly approved agents in the past 8 months, chronic myeloid leukemia (CML) is not only the poster child for targeted cancer treatment but also an enormous potential stumbling block for oncologists. So we took a step back after Atlanta, spent some time chatting with investigators and came up with the following CML highlights reel:

1. Selection of an up-front tyrosine kinase inhibitor (TKI)

Unlike ASH in 2010 and 2011, no practice-changing Phase III up-front trials were reported at the 2012 meeting. However, the topic was still center stage in December during a provocative education symposium where Dr David Marin provided a meticulous review that culminated with an interesting conclusion. In Dr Marin's view, for most patients, imatinib is essentially an equivalent clinical option to the second-generation TKIs nilotinib and dasatinib and may become the preferred choice in 2015 because of a cost advantage when its patent expires. He supported his stance by noting that a survival advantage has yet to be demonstrated with the second-generation TKIs and many patients with suboptimal responses to imatinib can be salvaged with other therapies. Of course, this position stands in sharp contrast to the perspectives of most CML investigators, who fully endorse the up-front use of second-generation agents.

2. Ponatinib and bosutinib

At ASH, Dr Jorge Cortes presented yet another impressive data set on ponatinib, the recently approved (12/2012) pan-BCR-ABL TKI and the only one currently known to be effective in cases with T315I gatekeeper mutations. In further follow-up of the **Phase II PACE trial**, major cytogenetic responses were observed in 51% of 203 patients with chronic-phase CML with resistance or intolerance to dasatinib or nilotinib and 70% of 64 patients with chronic-phase CML and T315I mutations. Overall, with a minimum of 12 months of follow-up, 63% of these heavily pretreated patients remain on study. Ponatinib is currently a critical tool in the care of patients who are intolerant to or have suboptimal or no response on other TKIs, and there is considerable excitement about new Phase III trials evaluating this fascinating agent up front.

Another next-generation TKI story is bosutinib, which was approved in September. In Atlanta, we were treated to an **interesting report** looking at 119 patients with chronic-phase CML treated on the Phase I/II trial who had received 2 or 3 prior TKIs. At 2 years most of these individuals had responded and were still on treatment, which was seen as generally tolerable. **Another ASH data set** from the same study demonstrated similarly encouraging efficacy among 285 patients resistant/intolerant to imatinib. Interestingly, this agent previously failed to deliver better outcomes than imatinib up front in a **Phase III trial**, in part because of tolerability issues, resulting in its current positioning as later-line treatment.

3. Early assessment of response

In his highly informative **ASH CML wrap-up**, Dr Steve O'Brien ranks as the number 1 meeting theme this year "the 10% thing" — referring to the rapid proliferation of papers demonstrating that failure to achieve a PCR BCR-ABL/ABL level of less than 10% at 3 or 6 months puts patients in a group at higher risk of disease progression or developing early resistance.

One of the key ASH papers in this regard evaluated 483 patients who received treatment at MD Anderson with nilotinib, dasatinib or high- or normal-dose imatinib. In this data set, deep cytogenetic and molecular response at 3 and 6 months was **predictive of outcome with all 4 modalities**, and based on these and similar findings in other studies there is now considerable interest in new trials that randomize between continuing or switching therapy in patients with suboptimal early response.

4. Can CML be "cured"?

While most patients nowadays can expect to achieve and maintain clinical remission, lifelong therapy is required. At ASH we saw **more data on treatment discontinuation** in specific situations — usually CMR (defined as >5 log reduction) for 2 or more years after a total of 3 years of treatment. Using these criteria, perhaps 40% of patients receiving imatinib and 60% receiving nilotinib or dasatinib fare well off therapy. The problem is that currently we have no way to identify patients who will or won't experience relapse, and therefore physicians are universally encouraged to consider discontinuation only within the context of a clinical trial.

Related to this issue, perhaps my favorite ASH CML moment came during **Dr Susan Branford's education session presentation** when she showed serial PCR analyses from several patients who received up to 12 years of imatinib. In one case, a 22-year-old man had an undetectable BCR-ABL for 8 years when a major blip appeared on his PCR curve.

Was this some new mutated, resistant clone? In fact, it was discovered that the patient had recently stopped treatment, essentially replicating the classic discontinuation trials like STIM and CML8 in which patients who experienced disease progression off treatment did so fairly quickly. Dr Branford noted that the first question to ask any

patient with a PCR spike is, "Are you taking your medicine?" Careful assessment of side effects and adherence is particularly important in younger patients who may be less accepting of indefinite treatment.

5. Something non-TKI related

In a previous issue of this series we profiled a fascinating Phase III effort out of China evaluating the subcutaneously administered cephalotaxine, omacetaxine mepesuccinate, in patients with AML. Also known as homoharringtonine, this agent — which inhibits protein synthesis via a mechanism independent of BCR-ABL — was approved in October for CML, and at ASH we saw updated data from **2 Phase II studies**. These findings further illustrate the effectiveness of this agent in later-line disease, including among **patients with T315I mutations**.

That does it for this year's ASH highlights series. Stay tuned for our next hem-onc email program, as we explore the therapeutic revolution in myelofibrosis by providing you with the perspectives and practice patterns of 8 investigators with extensive experience with this complex disease.

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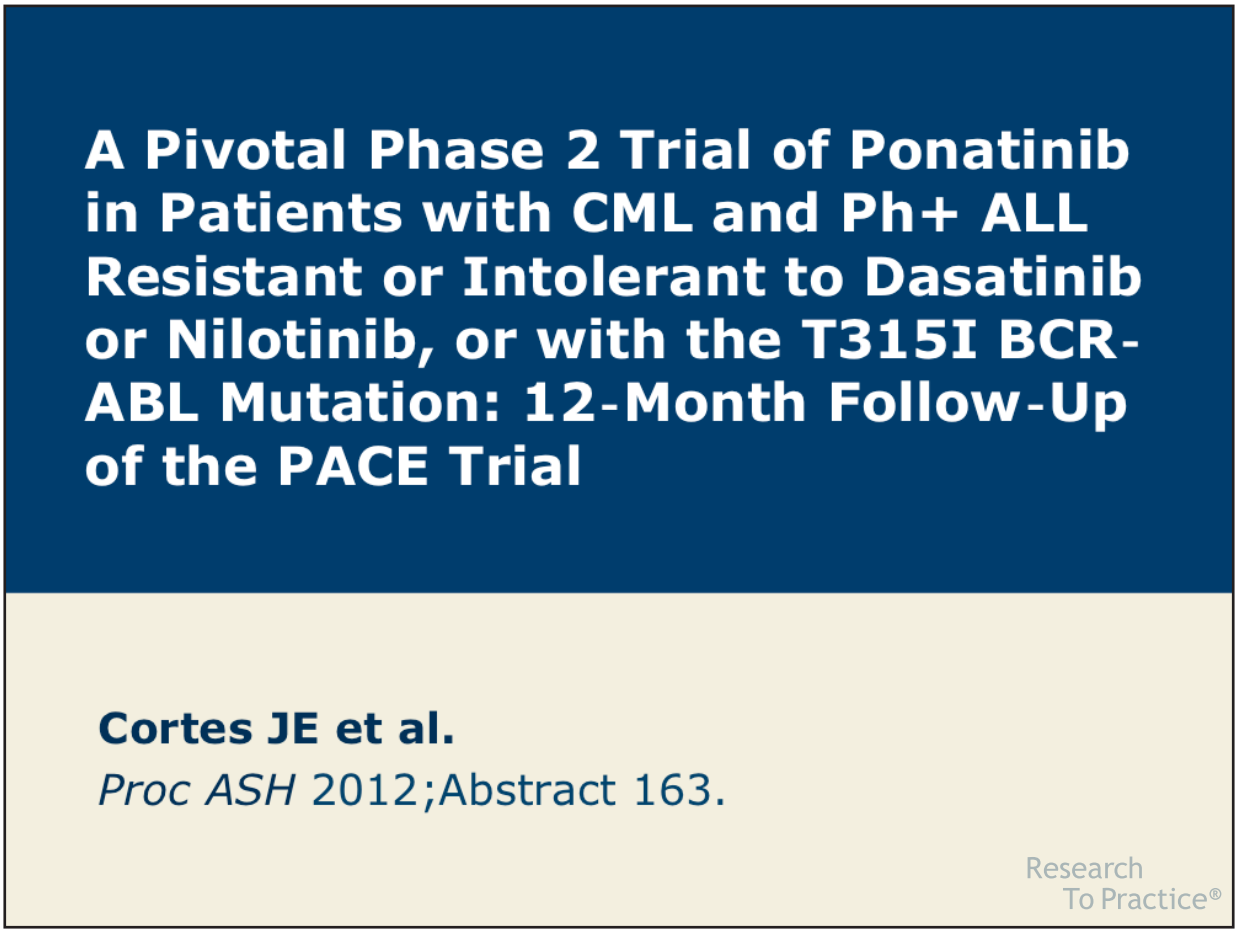
Pivotal Phase II PACE Trial of Ponatinib in Patients with CML and Philadelphia Chromosome-Positive ALL: 12-Month Follow-Up

Presentation discussed in this issue

Cortes JE et al. **A pivotal Phase 2 trial of ponatinib in patients with CML and Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I BCR-ABL mutation: 12-month follow-up of the PACE trial.** *Proc ASH* 2012;**Abstract 163**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Moshe Talpaz, MD (2/20/13)



Background

- In approximately 25% of patients with CML, the disease does not respond or becomes resistant to imatinib.
  - Resistance is often caused by mutations in the BCR-ABL protein, which prevent imatinib from binding to that protein.
  - Approximately 50% of patients respond to second-generation TKIs dasatinib and nilotinib, but many will become resistant to these drugs as well.
- Ponatinib was molecularly designed to overcome limitations of other TKIs.
- **Current study objective:** To evaluate the efficacy and safety of ponatinib in patients with CML or Philadelphia chromosome-positive (Ph+) ALL.

www.cancer.gov/ncicancerbulletin/121112/page2/AllPages.

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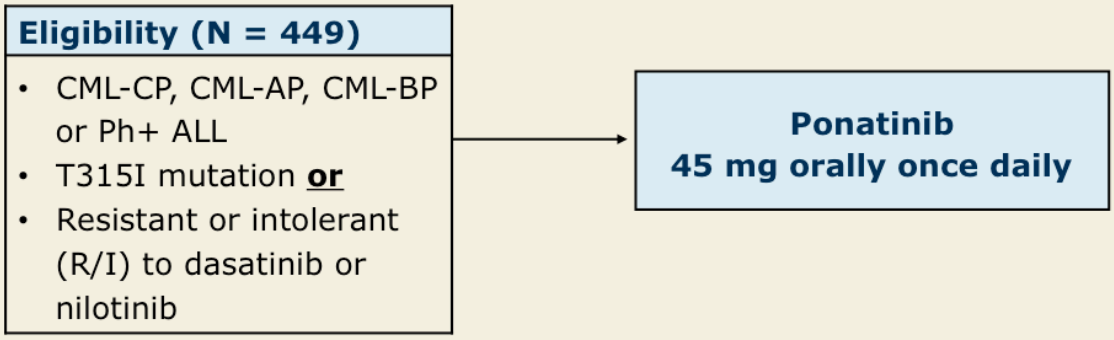
Phase II International PACE Trial Design



Primary endpoints

- Major cytogenetic response (MCyR) at any time within 12 months
- Major hematologic response (MaHR) at any time within 6 months

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

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Primary Endpoint: Responses

	CML-CP	CML-AP	CML-BP/ Ph+ ALL
Primary endpoint	**MCyR**	**MaHR**	**MaHR**
R/I to dasatinib or nilotinib (n = 203; 65; 48)	51%	58%	35%
T315I mutation (n = 64; 18, 46)	70%	50%	33%
Total (n = 267, 83, 94)	56%	57%	34%

Patients remaining on study (n, %): CML-CP (171, 63%), CML-AP (45, 53%), CML-BP/Ph+ ALL (6, 6%)

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

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Response Characteristics and Survival: CML-CP

Response rate	**(n = 267)**
Any cytogenetic response	67%
MCyR	56%
CCyR	46%
Major molecular response (MMR)	34%
Median time to response	
MCyR	2.8 months
MMR	5.5 months
Clinical outcomes at 12 months	
MCyR	91%
PFS	80%
OS	94%

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

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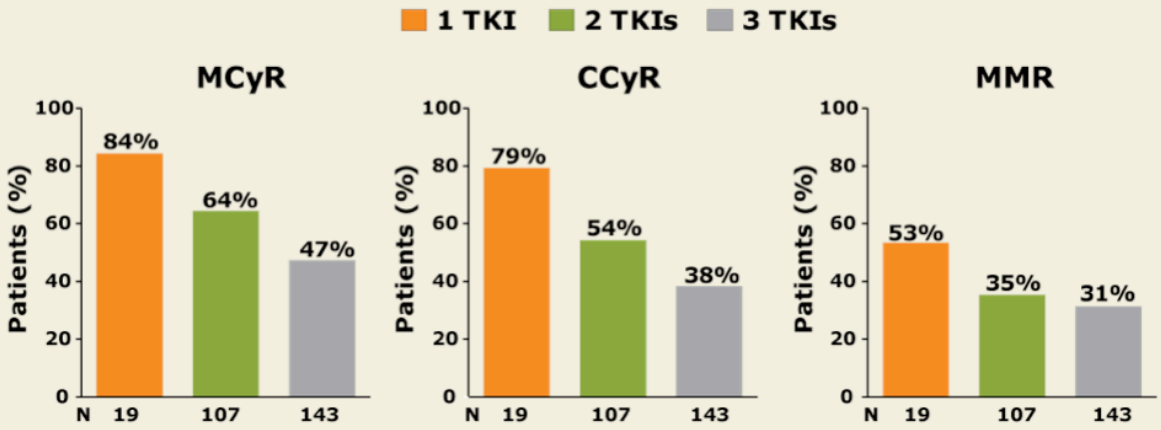
Response by Number of Prior Approved TKIs: CML-CP



TKIs = imatinib, dasatinib, nilotinib

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

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Select Adverse Events (AEs): Total Population (N = 449)

Nonhematologic	Any grade	Grade 3/4
Rash	38%	4%
Abdominal pain	38%	9%
Headache	35%	2%
Dry skin	35%	2%
Constipation	34%	2%
Hypertension	21%	7%
Hematologic	**Any grade**	**Grade 3/4**
Thrombocytopenia	42%	34%
Neutropenia	24%	21%
Anemia	20%	14%

Serious AEs: Pancreatitis: 5%; myocardial infarction: 3%; cardiac failure/atrial fibrillation: 6%

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

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Author Conclusions: 12-Month Follow-Up Summary

- Robust clinical activity of ponatinib was observed in patients with heavily pretreated disease, with
  - Responses regardless of mutation status or disease stage
  - Higher response rates in patients with less heavily pretreated disease
- Early and deep responses were observed: 34% MMR and 15% MR.
- Responses were durable: 91% estimated to remain in MCyR at 1 year.
- Ponatinib was generally well tolerated.
- Ponatinib may be an important new treatment for CML and Ph+ ALL resistant or intolerant to prior TKIs.

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

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Investigator Commentary: Pivotal Phase II International PACE Trial of Ponatinib in CML and Ph+ ALL

Ponatinib is the fifth TKI approved in CML, and it's perhaps the most powerful of all the TKIs because it "covers" virtually all of the mutations. The PACE study included patients with CML-CP, CML-AP, CML-BP and Ph+ ALL, with or without the T315I mutation. I emphasize the T315I mutation because that is a mutation within the BCR-ABL kinase domain that is resistant to all existing treatments for CML other than ponatinib and the chemotherapeutic agent omacetaxine. So T315I is the ultimate mutation, which renders the disease resistant to imatinib, nilotinib, dasatinib and bosutinib. However, the disease is responsive to ponatinib, which was demonstrated in the PACE study.

Additionally, there were high response rates in patients who were resistant to 1, 2 and even 3 prior TKIs. Surprisingly, major cytogenetic responses were observed in more than 50% of patients, with more than 40% complete cytogenetic responses. Why is this important? This is a group of patients with bad, long-standing disease that is resistant to all other treatments. Nevertheless, the disease responded to ponatinib — not just in terms of hematologic response but also by cytogenetic improvement.

Interview with Moshe Talpaz, MD, February 20, 2013