5 Minute JournalClub

POST-ASH Issue 4, 2015

Phase III EPIC Trial of Ponatinib versus Imatinib in Newly Diagnosed CML in Chronic Phase

For more visit ResearchToPractice.com/5MJCASH2015

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 up-front and salvage therapeutic options and modalities for the evaluation of treatment response in newly diagnosed and relapsed or refractory chronic myeloid leukemia (CML), myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET) 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

- Assess the recent results of the RESPONSE trial evaluating ruxolitinib for PV, and consider this information for the treatment of this disease in patients who are not responsive to or are intolerant of hydroxyurea.
- Appraise the effectiveness and tolerability of the investigational agents PRM-151 and imetelstat as single-agent therapy for patients with MF.
- Examine long-term efficacy and symptomatology results with ruxolitinib in patients with ET who are refractory to or intolerant of hydroxyurea.
- Compare and contrast the benefits and risks of discontinuing second-generation tyrosine kinase inhibitors for patients with CML in chronic phase.
- Analyze efficacy and safety results from Phase III trials evaluating dasatinib or ponatinib in comparison to imatinib for patients with CML in chronic phase.

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 1.75 *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/5MJCASH2015/4/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
DB 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.

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, Amgen Inc, Astellas Scientific and Medical Affairs Inc, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Medivation Inc, Merck, Myriad Genetic Laboratories Inc, NanoString Technologies, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics,

Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Teva Oncology, Tokai Pharmaceuticals Inc 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 Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Seattle Genetics and Takeda Oncology.

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 2015
Expiration date: May 2016

5 MinuteJournalClub

POST-ASH Issue 4, 2015

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

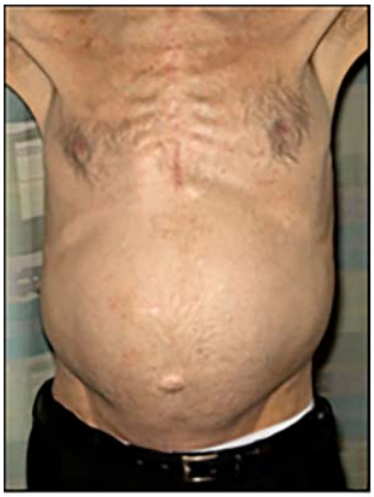
Many physicians (myself included) remember the day they first treated a patient with pulmonary edema from congestive heart failure and the exhilarating feeling of instantly relieving this profound symptomatology with the classic use of an intravenous diuretic and morphine. Medical oncology also provides many opportunities for these types of healing moments, and at the 2011 ASCO meeting the field was introduced to another powerful palliative tool for a disease desperately in need of one. Since the presentation of the aptly named COMFORT-I and II trials in Chicago, we have heard on many of our CME programs a myriad of moving patient case histories of individuals with myelofibrosis (MF) suffering from anorexia, weight loss, fatigue and massive uncomfortable spleens who experienced dramatic, life-altering changes within days or weeks of starting treatment with the JAK1/2 inhibitor ruxolitinib (rux).

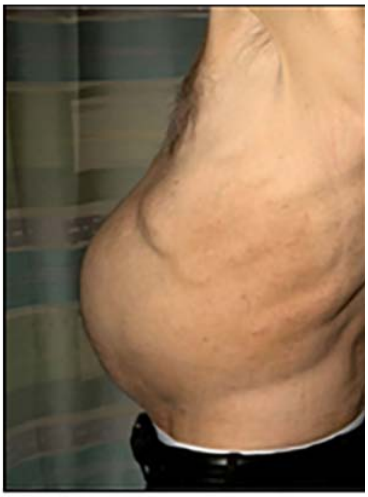
Perhaps not surprisingly, the myeloproliferative neoplasm (MPN) issue of our ASH highlight series focuses in large part on this fascinating therapy, which now is showing its colors in other diseases, including, interestingly enough, pancreatic cancer. We also provide an update on papers related to the other major part of MPNs, chronic myeloid leukemia (CML), and as such I met with one of the research giants in the field, Dr Jorge Cortes, who provides his take on the most important findings.

Jorge E Cortes, MD

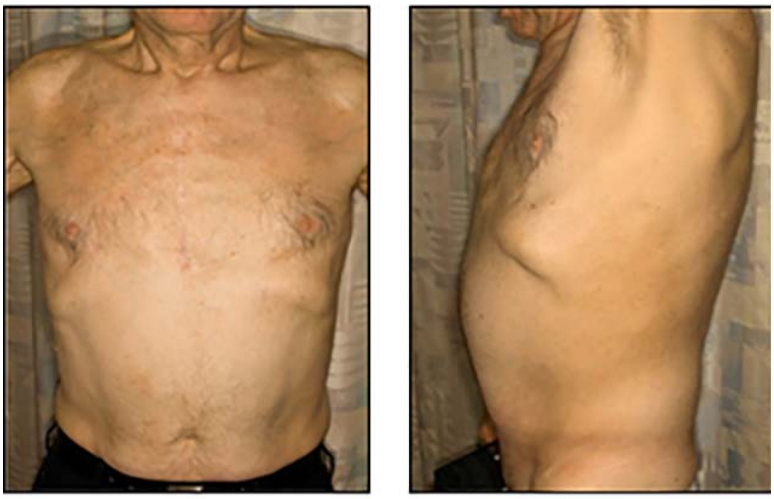
1. Rux in patients with lower-risk MF

The Phase III COMFORT trials focused on patients with intermediate-2 or high-risk MF, but there is no intuitive reason to believe that the palliative effects of this agent would not be similar in other symptomatic patients. At ASH we saw a **"real-world" retrospective analysis** evaluating 108 cases of patients with low- or intermediate-1-risk MF treated by 49 US-based hematologist-oncologists mainly due to symptomatology. Perhaps not surprisingly, marked improvement in spleen size and the severity of





fatigue and other related symptoms was observed with the use of rux. For example, moderate/severe splenomegaly decreased from 64% to 16% in low-risk MF and from 53% to 10% in intermediate-1-risk disease. These findings, along with his own clinical experience, have shaped Dr Cortes' belief that symptomatic patients can benefit from rux regardless of risk status.



Images courtesy of *OncoLog*, The University of Texas MD Anderson Cancer Center

ABOVE: Photos of a patient before therapy with an experimental JAK2 inhibitor show the distended abdomen caused by the enlarged spleen, a common symptom of myelofibrosis. **BELOW:** Photos taken after 2 months of therapy with a JAK2 inhibitor show a marked reduction in the patient's splenomegaly.

2. Rux in polycythemia vera (PV) and essential thrombocythemia (ET)

Perhaps the biggest MPN story at ASH was the presentation of more data from the landmark **Phase III RESPONSE trial** (originally presented last year at ASCO) demonstrating the clinical benefit of rux (10 mg BID) in patients with PV who were either intolerant of or experienced disease progression on hydroxyurea (HU). The initial data set was published in the *New England Journal* in January and revealed significant reductions in hematocrit, splenomegaly and severity of symptoms in patients randomly assigned to rux. Equally relevant, treatment was well tolerated — most patients had stable platelet counts, and secondary drops in hemoglobin were beneficial. Similar clinical improvements were observed in patients who crossed over to rux. Most importantly, as seen with the additional ASH data, patients who received rux experienced a dramatic positive impact on quality of life.

Based on the strength of these results, the FDA made rux the first drug ever approved for PV. In this regard, Dr Cortes has used the agent in patients who meet the criteria for the RESPONSE trial. However, he also believes that the definition of disease progression with PV should be expanded to include individuals with persistent symptomatology who, although not meeting the current criteria for disease progression, often experience dramatic improvements in symptoms with rux.

Several other data sets were unveiled in San Francisco that further support the concept of using rux in PV, including data from the **Phase III RELIEF trial** for patients with PV considered stable on HU but with some persistent symptoms, which demonstrated an improvement in symptoms by switching to rux rather than continuing on HU.

Finally, a Phase II study of rux in 39 patients with ET refractory to or intolerant of HU demonstrated rapid decreases in and normalization of platelet and white blood cell

counts. Hemoglobin levels initially decreased and then stabilized in most patients, and a marked improvement in symptomatology was also observed. As such, Dr Cortes and other investigators believe rux is rational to use in this patient population and are hopeful that this agent will also receive approval in ET for disease palliation.

3. New agents in MF: antifibrotics, telomerase inhibitors

Although much recent MF research has focused on JAK inhibitors, a number of other novel strategies are also being explored in this disease. In this regard, at ASH we saw an **early but encouraging report** of 27 patients receiving PRM-151, a recombinant form of an endogenous protein that is found at sites of inflammation and prevents fibrosis by inducing macrophage differentiation. What was most noteworthy from this study was that not only was the amount of fibrosis decreased in close to half of the patients, but hemoglobin and platelet counts also often improved along with signs and symptoms of the disease. Research on this and other similar agents is proceeding rapidly, and Dr Cortes is particularly interested in trials combining PRM-151 with rux.

Telomerase is known to become more active in MF as the disease progresses, and in a report of 33 patients receiving imetelstat — a novel agent that targets the RNA template of human telomerase reverse transcriptase — 7 patients (21%) experienced a complete or partial remission. Treatment was well tolerated, although myelosuppression was observed. Dr Cortes is intrigued by these data and also the early correlation of response with specific disease mutations.

4. Second-generation tyrosine kinase inhibitors (TKIs) in CML

With the likely availability of generic imatinib in the next year as a potentially less costly alternative, the value of nilotinib and dasatinib will be increasingly discussed and debated, and several new ASH data sets will likely be referred to as part of these conversations. Specifically, in San Francisco we saw the first presentation of data from the large **Phase III SPIRIT 2 trial**, which, like several other prior studies, compared dasatinib to imatinib in patients with newly diagnosed CML. Although the data are not yet fully mature, this study confirms what we have known from other trials, namely that treatment with second-generation TKIs results in improved rates of complete cytogenetic response, faster rates of molecular response and fewer transformations.

It wouldn’t be ASH if we weren’t treated to an update from the landmark DASISION trial, and in addition to continuing to show excellent long-term disease outcomes, this study yielded some interesting data on toxicity over time, specifically the most common complication of dasatinib, pleural effusions, which were observed in 20% of patients, causing discontinuation of treatment in 6%. In discussing this work, Dr Cortes pointed out that multiple studies have suggested that patients experiencing a pleural effusion on dasatinib might have better disease-related outcomes, although the biologic explanation remains to be defined.

None of the second-generation TKI CML papers presented in San Francisco was able to dispel the lack of progression-free or overall survival benefit to this point, and some

investigators prefer imatinib in lower-risk scenarios. Dr Cortes, however, believes that there is an important advantage for the newer agents but that salvage treatment for imatinib failure is delaying the detection of this benefit.

5. Current bottom line with ponatinib in CML

As you may remember, the **Phase III EPIC study** comparing ponatinib to imatinib was stopped in October 2013 because of the increased risk of cardiovascular events. As a result of this toxicity, access to ponatinib is currently restricted to patients with TKI-resistant disease or those with the T315I mutation. However, the updated data from this trial tell us that the agent is associated with faster, deeper and higher rates of response than imatinib and, by way of indirect comparison, perhaps also dasatinib and nilotinib.

In this regard, there is a strong belief among investigators that there is a direct relationship between dose and cardiovascular events, and for that reason ongoing studies are attempting to define a reduced dose that will produce equal efficacy with fewer complications.

6. In what situations, if any, is it safe to stop a TKI in CML?

A number of prospective trials (STIM, TWISTER and EURO SKI, which was presented at ASH) suggest that imatinib may be successfully discontinued for patients with deep and sustained molecular responses, and in San Francisco we saw evidence that the same may apply to second-generation TKIs. Specifically, the **STOP 2G-TKI study** evaluated treatment discontinuation in 52 patients in sustained complete molecular response receiving dasatinib or nilotinib for a median of 39 months, mostly after initial imatinib therapy.

At 24 months, the probability that patients remained in major molecular response off treatment was 57%. The relapses that did occur were mainly in the first 6 months after treatment discontinuation, but those patients responded to reinstitution of second-generation therapy. Importantly, patients receiving treatment because of prior resistance to imatinib were less likely to be able to stay off treatment. Despite this mounting body of data, like most CML investigators, Dr Cortes, although interested in seeing more research on this strategy, believes that for now TKI treatment should only be stopped as part of a clinical trial and with close monitoring.

Medical oncologists are hearing a lot nowadays about “value” in cancer care, which is roughly defined as the clinical benefits (and toxicities/complications) of a therapy relative to its financial cost, and there has been a lot of discussion about the importance of incorporating the perspectives of patients themselves in the value equation.

In this regard, it would be interesting to learn more from individuals who have actually experienced the clinical outcomes of therapy for MPNs about their perceptions of the value of treatment — particularly about what it means to face a disease that was

uniformly lethal in the past and to now live a normal lifespan (CML) or to experience progressive and devastating disease-related symptoms and suddenly feel well again (MF, PV, ET).

Next on this series we review ASH papers on acute leukemias and MDS and the surprising plenary presentation on the use of sorafenib in AML.

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 1.75 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

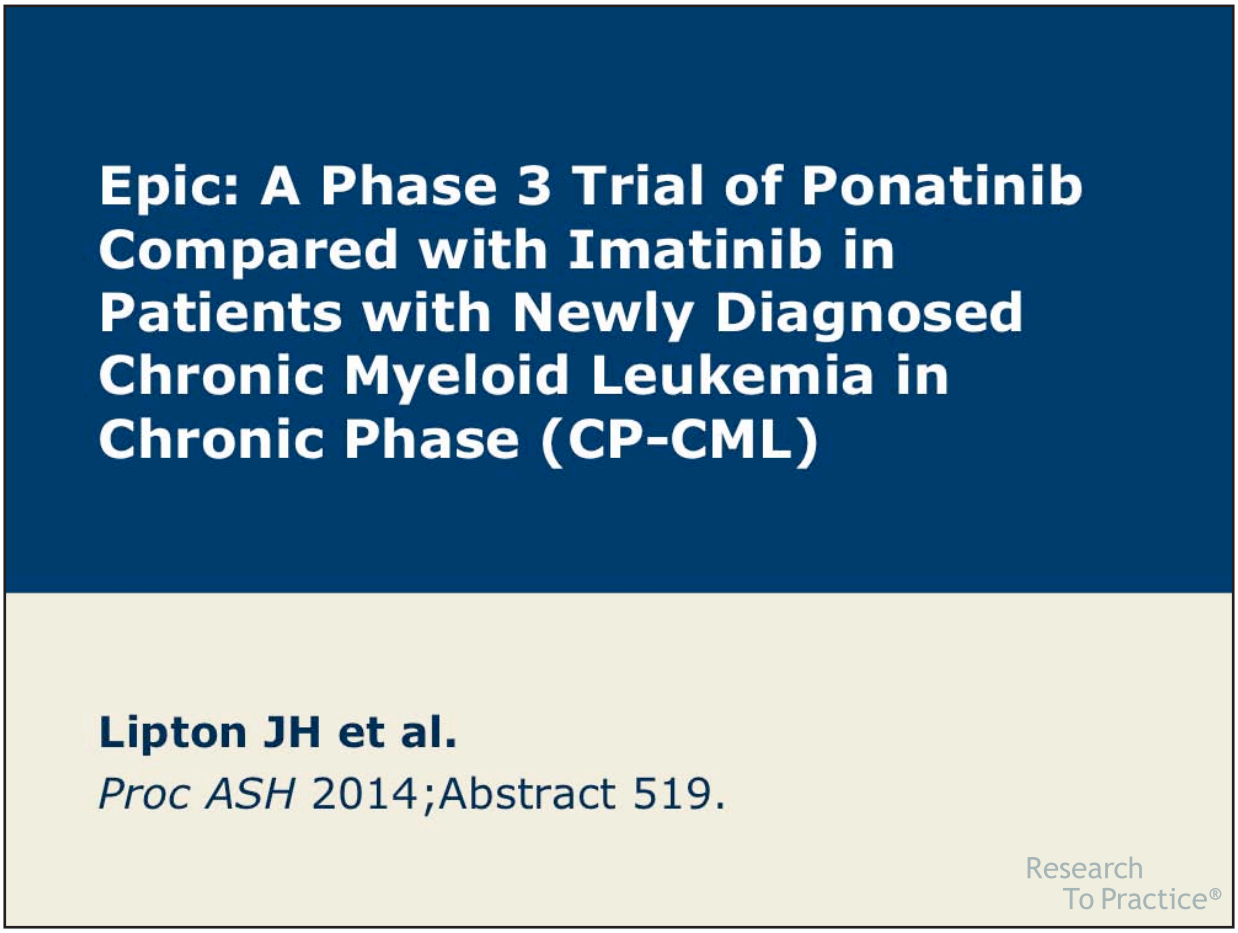
This activity is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Seattle Genetics and Takeda Oncology.

Phase III EPIC Trial of Ponatinib versus Imatinib in Newly Diagnosed CML in Chronic Phase

Presentation discussed in this issue

Lipton JH et al. **Epic: A Phase 3 trial of ponatinib compared with imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CP-CML).** *Proc ASH* 2014;**Abstract 519**.

Slides from a presentation at ASH 2014 and transcribed comments from a recent interview with Jorge E Cortes, MD (1/14/15)



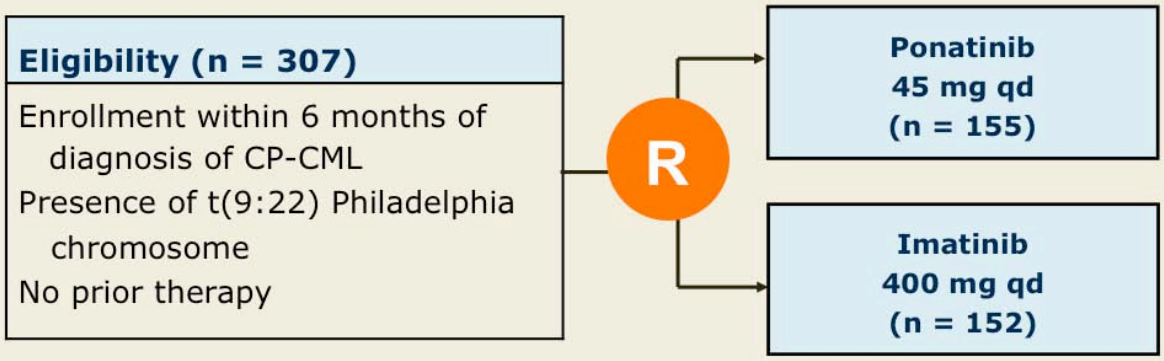
Background

- Ponatinib is an approved potent oral tyrosine kinase inhibitor (TKI) active against native and mutated forms of BCR-ABL, including T315I.
- The Phase II PACE study demonstrated that ponatinib is highly active in patients with heavily pretreated Philadelphia chromosome–positive leukemia (*NEJM* 2013;369:1783).
- The Phase III EPIC trial was established to assess the activity and tolerability of ponatinib versus imatinib in patients with newly diagnosed CP-CML.
  - However, on October 18, 2013, the trial was terminated due to arterial thrombotic events in the ponatinib clinical program and due to patient safety considerations.
- **Study objective:** To report the efficacy and safety of ponatinib in the EPIC trial up to the point of termination.

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Research To Practice®

Phase III EPIC Trial Design



- Patients were stratified by Sokal risk score: low (<0.8) vs intermediate (0.8 to 1.2) vs high (>1.2) before randomization.
- Dose modification was allowed on both arms to manage toxicity. The maximum dose allowed was 45 mg daily (ponatinib) or 800 mg daily (imatinib).
- In the imatinib arm, dose escalation was allowed in case of suboptimal response.
- **Primary endpoint:** Rate of major molecular response (MMR) at 12 months.

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Research To Practice®

Achievement of <10% BCR-ABL Transcript at 3 Months

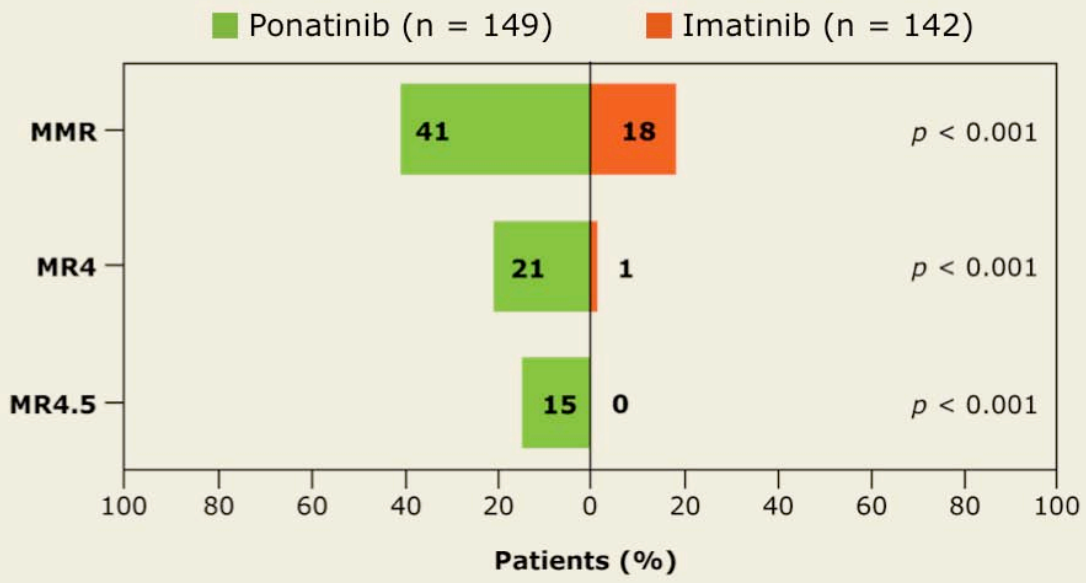
Evaluable patients	Ponatinib (n = 109)	Imatinib (n = 114)	*p*-value
All patients	94%	68%	<0.001
By Sokal risk score	**Ponatinib**	**Imatinib**	***p*-value**
Low risk (n = 45, 50)	98%	76%	0.002
Intermediate risk (n = 44, 45)	96%	69%	0.002
High risk (n = 20, 19)	85%	42%	0.008

- Median follow-up time: 5.1 months

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Research To Practice®

Best Overall Molecular Response at Any Time: Evaluable Patients

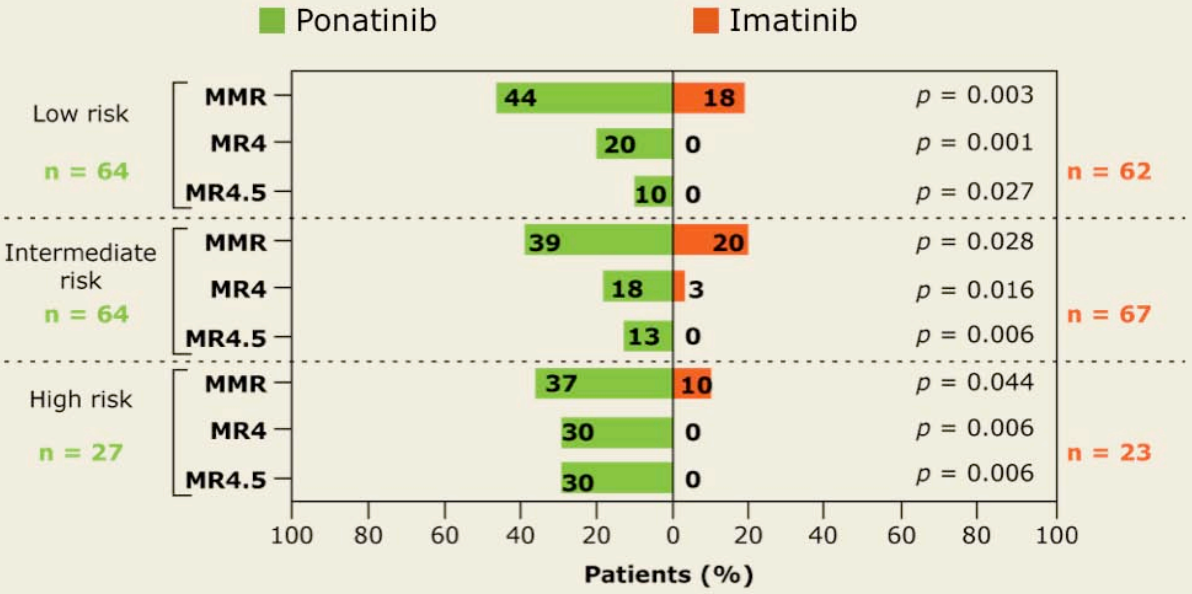


- Median time to MMR: 100 days (ponatinib) versus 169 days (imatinib)

With permission from Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Research To Practice®

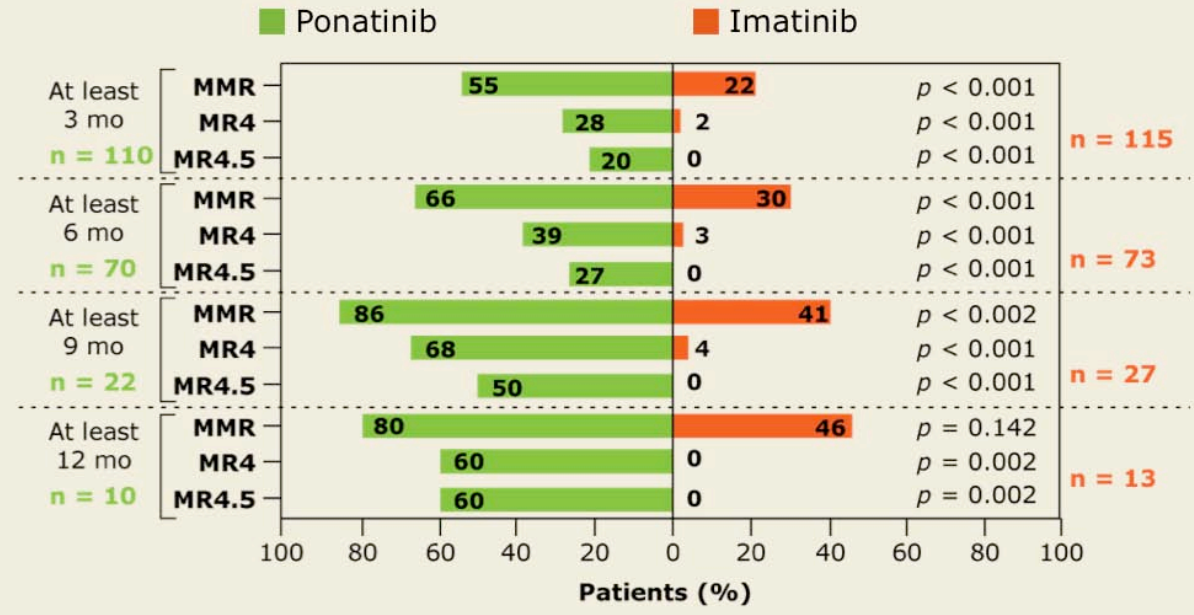
Best Molecular Response at Any Time by Sokal Risk Score: Evaluable Patients



With permission from Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Research To Practice®

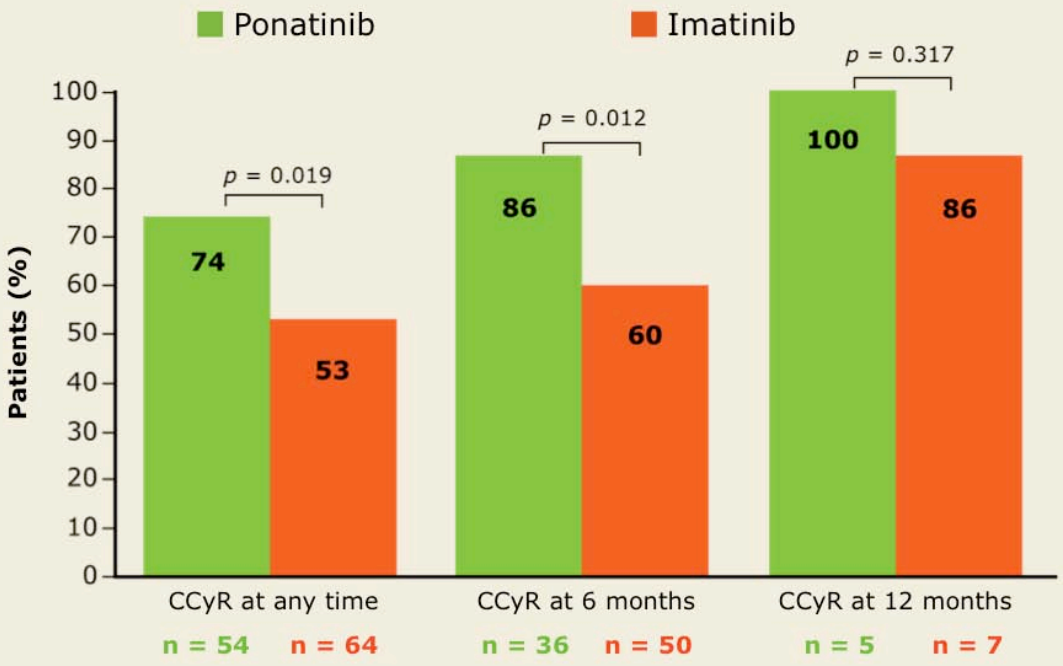
Molecular Response After 3, 6, 9 or 12 Months: Evaluable Patients



With permission from Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Research To Practice®

Complete Cytogenetic Response: Evaluable Patients



With permission from Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Select Adverse Events (AEs) Occurring in >15% of Patients

Event	Ponatinib (n = 154)		Imatinib (n = 152)	
	All	Grade 3-4	All	Grade 3-4
Rash	38%	7%	16%	1%
Abdominal pain	36%	3%	10%	0%
Headache	33%	1%	13%	0%
Increased lipase	27%	14%	7%	2%
Myalgia	26%	1%	18%	0%
Thrombocytopenia	25%	12%	14%	7%
Nausea	22%	1%	34%	0%
Arthralgia	19%	1%	15%	1%
Hypertension	18%	5%	2%	0%

- 1 patient on each arm had Grade 5 pneumonia

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Patients with Treatment-Emergent Vascular Occlusive Events

Events	Ponatinib (n = 154)		Imatinib (n = 152)	
	All	Grade 3-4	All	Grade 3-4
Arterial thrombotic AEs	7%	7%	2%	0.7%
Cardiovascular AEs	3%	3%	0.7%	0%
Cerebrovascular AEs	2%	2%	0.7%	0.7%
Peripheral vascular AEs	2%	2%	0.7%	0%
Venous thromboembolic AEs	0.6%	0.6%	0%	0%

- Time to onset of vascular occlusive events:
  - 10 to 233 days (ponatinib) versus 2 to 156 days (imatinib)
- Of the 12 patients who received ponatinib and experienced vascular occlusive AEs, 11 had ≥1 risk factor or relevant medical history.

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Research To Practice®

Author Conclusions

- Despite early termination of the EPIC trial, preliminary analyses of data suggest improved efficacy with ponatinib compared to imatinib:
  - <10% BCR-ABL at 3 months: 94% (ponatinib) vs 68% (imatinib). This endpoint correlates with overall survival
  - With ponatinib response rates were higher and responses were deeper and more rapid than with imatinib
- More adverse events were reported in the ponatinib arm:
  - Higher incidence of Grade 3 or 4 and serious adverse events
  - More patients experienced vascular occlusive events
- A dose-ranging trial of ponatinib in refractory CML is planned to evaluate benefit and risk of alternate dosing regimens (NCT02398825).

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Research To Practice®

Investigator Commentary: EPIC — A Phase III Trial of Ponatinib versus Imatinib in Newly Diagnosed CP-CML

The EPIC trial design was based on the principle that ponatinib would be active because it is a potent drug that targets all mutations in CML. Because it can prevent the emergence of resistant clones, it was thought that ponatinib could result in better outcomes and prevent the emergence of mutations. Unfortunately, as the data started to emerge from this study, ponatinib was associated with the risk of arteriothrombotic events. As a result, the study was terminated with only 307 patients.

Very few patients were on the trial for 12 months, which was the primary endpoint. However, at 3 months, 94% of patients had <10% BCR-ABL transcript level with ponatinib, whereas only 68% achieved this with imatinib. This response rate is higher than what is observed with dasatinib or nilotinib. Clearly ponatinib is effective at producing deep responses. The major problem with ponatinib is arteriothrombotic events, with a significant proportion of patients (7%) experiencing this side effect with ponatinib versus 2% on the imatinib arm. Notably, this is after a short exposure, with a median follow-up of 5.1 months. Although ponatinib is a useful drug, we need to be mindful of the cardiovascular arteriothrombotic events.

Interview with Jorge E Cortes, MD, January 14, 2015

continued

Investigator Commentary: EPIC — A Phase III Trial of Ponatinib versus Imatinib in Newly Diagnosed CP-CML (continued)

The cardiovascular adverse events with ponatinib seem to be similar to those observed with other TKIs but more frequent. In my practice, I involve a cardiologist from the beginning of any TKI therapy to help me address all these issues and minimize the risk for the patient. In the case of ponatinib, I start every patient on aspirin to decrease the risk of heart attack in individuals who are older. I am hoping that this approach will improve the safety in patients who need ponatinib.

Interview with Jorge E Cortes, MD, January 14, 2015