



*POST-ASH* Issue 4, 2015

**Phase III DASISION and  
SPIRIT 2 Trials of Dasatinib  
versus Imatinib in Newly  
Diagnosed CML in Chronic Phase**

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## 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.

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**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  
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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.

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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 2015

Expiration date: May 2016

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).

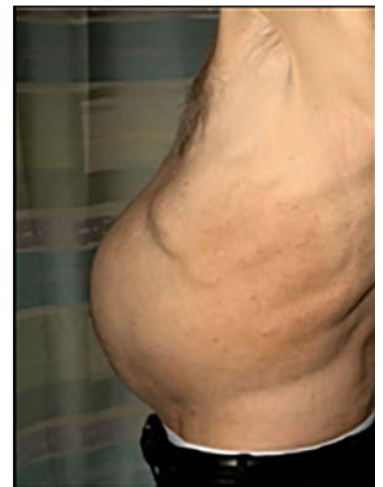
Perhaps not surprisingly, the myeloproliferative neoplasm (MPN) issue of our ASH highlight series focuses in large part on this fascinating therapy, which now is showing its colors in other diseases, including, interestingly enough, pancreatic cancer. We also provide an update on papers related to the 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.

## 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



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.

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

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Miami, Florida

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# Phase III DASISION and SPIRIT 2 Trials of Dasatinib versus Imatinib in Newly Diagnosed CML in Chronic Phase

## Presentations discussed in this issue

Cortes J et al. **Final study results of the phase 3 dasatinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) trial (DASISION, CA180-056).** *Proc ASH 2014*; **Abstract 152.**

O'Brien SG et al. **Spirit 2: An NCI randomised study comparing dasatinib with imatinib in patients with newly diagnosed CML.** *Proc ASH 2014*; **Abstract 517.**

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

**Final Study Results of the Phase III  
Dasatinib versus Imatinib in Newly  
Diagnosed Chronic Myeloid Leukemia  
in Chronic Phase (CML-CP) Trial  
(DASISION, CA180-056)<sup>1</sup>**

**SPIRIT 2: An NCI Randomised Study  
Comparing Dasatinib with Imatinib in  
Patients with Newly Diagnosed CML<sup>2</sup>**

**<sup>1</sup> Cortes J et al.**  
*Proc ASH 2014*; Abstract 152.

**<sup>2</sup> O'Brien S et al.**  
*Proc ASH 2014*; Abstract 517.

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# Final Study Results of the Phase III Dasatinib versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056)

**Cortes J et al.**

*Proc ASH 2014;Abstract 152.*

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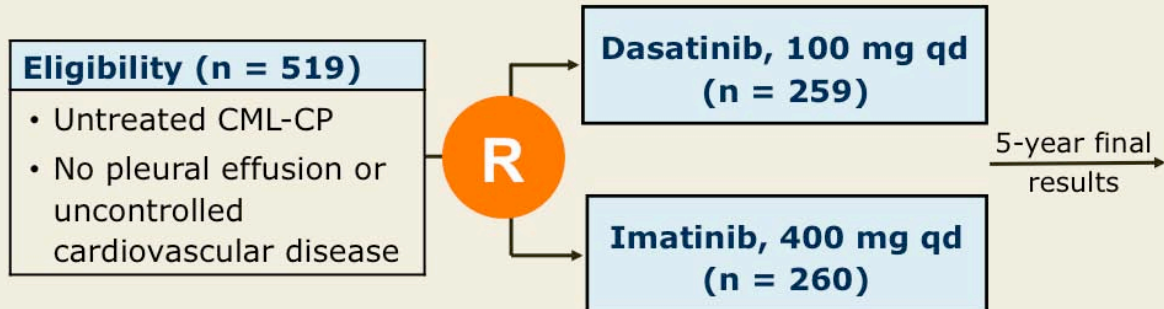
## Background

- The second-generation tyrosine kinase inhibitor dasatinib is standard first-line therapy for patients with CML-CP
- Patients with newly diagnosed CML-CP treated with dasatinib (compared to imatinib) in the DASISION trial demonstrated
  - Improved rates of confirmed complete cytogenetic response
  - Faster rates of molecular response
  - An acceptable safety profile (*Blood* 2012;119(5):1123; *Blood* 2014;123(4):494-500)
- **Study objective:** To report final, 5-year analysis from DASISION comparing the efficacy and safety of dasatinib to that of imatinib for patients with newly diagnosed CML-CP

Cortes J et al. *Proc ASH 2014;Abstract 152.*

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# Phase III DASISION Trial Design



- **Primary endpoint:** Confirmed complete cytogenetic response (cCCyR) at 12 months

Cortes J et al. *Proc ASH* 2014;Abstract 152; [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

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## Efficacy: Response and Survival at 5 Years

	Dasatinib (n = 259)	Imatinib (n = 260)	Hazard ratio	p-value
Cumulative 5-y MMR	76%	64%	NR	0.0022
Cumulative 5-y MR <sup>4,5</sup>	42%	33%	NR	0.0251
Estimated 5-y PFS	85%	86%	1.06	NR
Estimated 5-y OS	91%	90%	1.01	NR

MMR = major molecular response; NR = not reported; MR = molecular response; PFS = progression-free survival; OS = overall survival

- cCCyR for dasatinib vs imatinib: 77% vs 66%,  $p = 0.007$  at 1 year; 83% vs 78%,  $p = 0.187$  at 5 years
- Number of deaths:  $n = 26$  on each arm
- Transformations to both accelerated and blast phase CML on study or after discontinuation: dasatinib, 4.6%; imatinib, 7.3%

Cortes J et al. *Proc ASH* 2014;Abstract 152.

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## Five-Year Responses and Outcomes by BCR-ABL ( $\leq 10\%$ or $> 10\%$ ) at 3 Months

Outcome	Dasatinib (n = 259)			Imatinib (n = 260)		
	$\leq 10\%$	$> 10\%$	p-value	$\leq 10\%$	$> 10\%$	p-value
BCR-ABL at 3 months (%)	84	16	—	64	36	—
CCyR/MMR/MR <sup>4.5</sup> (%)	94/87/54	41/38/5	—	92/81/48	59/41/12	—
5-y OS (%)	94	81	0.0028	95	81	0.0003
5-y PFS (%)	89	72	0.0014	93	72	<0.0001
5-y TFS (%)	97	83	0.0004	97	80	<0.0001

TFS = transformation-free survival

Cortes J et al. *Proc ASH* 2014;Abstract 152.

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## Author Conclusions

- Final 5-year analysis confirms that compared to imatinib, patients who received dasatinib had
  - Faster times to response
  - Higher cumulative rates of molecular responses
  - Fewer transformations to accelerated or blast phase
- Progression-free and overall survival rates were similar between treatment arms
- Achievement of BCR-ABL  $\leq 10\%$  at 3 months is associated with significantly higher progression-free and overall survival by 5 years
- Safety profile remains consistent, with no new safety signals identified
  - Pleural effusion occurred throughout 5 years (20%) but did not impair the ability of patients to obtain a response. Six percent of patients with pleural effusion discontinued treatment
  - Arterial ischemic events were uncommon (dasatinib 5%, imatinib 2%)

Cortes J et al. *Proc ASH* 2014;Abstract 152.

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### **Investigator Commentary: Final Results of the Phase III DASISION Trial of Dasatinib versus Imatinib in Newly Diagnosed CML-CP**

DASISION established dasatinib as one of the standard treatments for CML. The rate of cCCyR at 12 months, which was the primary endpoint, was shown in a previous publication to be significantly better for patients who received dasatinib, and this led to approval of the drug. The current study reports on the final, 5-year data. It continues to show the superiority of dasatinib over imatinib with most of the endpoints assessed. The rate of cCCyR at 5 years was 83% versus 78% in favor of dasatinib. Importantly, the differences in MMR rates are maintained at 5 years in favor of dasatinib. Also, the rate of transformation to accelerated and blast phase is lower with dasatinib compared to imatinib. This is important because disease that transforms is difficult to treat, and, unfortunately, many of these patients do not survive. BCR-ABL transcripts  $\leq 10\%$  at 3 months correlate with long-term outcome and occurred more frequently on the dasatinib arm.

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

continued

### **Investigator Commentary: Final Results of the Phase III DASISION Trial of Dasatinib versus Imatinib in Newly Diagnosed CML-CP (continued)**

We are not yet seeing a difference in overall progression-free survival or overall survival. The question that arises is why no difference is evident in survival outcomes when responses are superior with dasatinib. I believe the reason is that patients who receive imatinib can be salvaged. I think that with longer follow-up we will start to observe a separation of the curves in favor of dasatinib.

In terms of toxicity, there were no unexpected adverse events. The major side effect with dasatinib is pleural effusions, and they can occur late in the treatment phase. Most pleural effusions are Grade 1 or 2 and are manageable. Only 6% of the patients had to discontinue dasatinib because of pleural effusions. There is a trend toward better responses with the development of pleural effusions. My approach is usually not to immediately switch therapy for patients with pleural effusions. Most of these patients can be cared for with treatment interruptions, dose adjustments, corticosteroids and diuretics.

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

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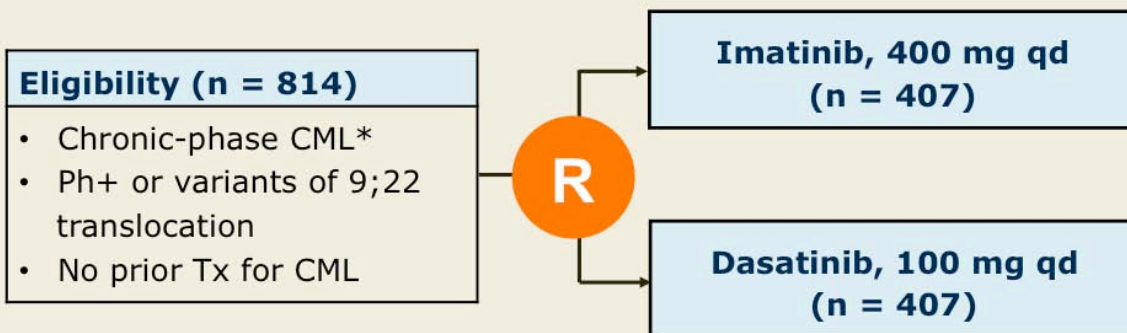
# SPIRIT 2: An NCI Randomised Study Comparing Dasatinib with Imatinib in Patients with Newly Diagnosed CML

**O'Brien S et al.**

*Proc ASH 2014;Abstract 517.*

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## Phase III SPIRIT 2 Trial Design



\* Within 3 months of diagnosis  
CML = chronic myeloid leukemia

- **Primary endpoint:** Event-free survival (5 y)
- **Secondary endpoints** include rates of complete cytogenetic response (CCR), major molecular response (MMR), MR<sup>3</sup>, BCR-ABL1/ABL1 ratio <0.1%, overall survival and toxicity

O'Brien S et al. *Proc ASH 2014;Abstract 517.*

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## Cytogenetics at 12 Months

Best response	Imatinib (n = 406)	Dasatinib (n = 406)	p-value
Major cytogenetic response	209 (51.5%)	228 (56.2%)	0.181*
CCR	169 (41.6%)	217 (53.4%)	<0.001*

\* Analyses missing for 181 of 406 patients on the imatinib arm and 166 of 406 patients on the dasatinib arm

O'Brien S et al. *Proc ASH* 2014;Abstract 517.

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## PCR Response

PCR at 12 months	Imatinib (n = 406)	Dasatinib (n = 406)	p-value
Achieved MR <sup>3</sup>	43.1%	58.4%	<0.001
Achieved MR <sup>4.5</sup>	5.9%	13.3%	0.001

### Association of PCR Response with Pleural Effusion

PCR <0.1% (MR <sup>3</sup> )	Imatinib (n = 406)	Dasatinib (n = 406)
No pleural effusion	43.2%	56.3%*
With pleural effusion	33.3%	65.6%*

\* Difference between arms not significant

PCR = polymerase chain reaction analysis of the BCR-ABL transcript levels

O'Brien S et al. *Proc ASH* 2014;Abstract 517.

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## Select Adverse Events (AEs)

All grade AEs	Imatinib (n = 406)	Dasatinib (n = 406)
Pleural effusion	0.7%	22.2%
Vomiting	13.1%	12.1%
Diarrhea	32.0%	25.4%
Headache	13.5%	25.4%
Thrombocytopenia	48.5%	69.2%

- Grade 3 or 4 thrombocytopenia: imatinib, 4.7%; dasatinib, 13.5%
- No significant differences in the rate of cardiovascular AEs
- Total deaths: imatinib, 2.2%; dasatinib, 2.5%

O'Brien S et al. *Proc ASH* 2014;Abstract 517.

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## Author Conclusions

- This is the largest investigator-conducted randomized trial of dasatinib versus imatinib, with a median follow-up of 3 years
- Both drugs were generally well tolerated:
  - 512 of 812 patients (62.9%) continue on study medication
  - Imatinib is associated with GI toxicity; dasatinib with pleural effusions, headaches
  - No difference in cardiovascular events
- MR<sup>3</sup> rate at 1 year: imatinib, 43%; dasatinib, 58%
- 774 of 812 patients (95.3%) remain alive:
  - Imatinib, 95.5%; dasatinib, 95.0%
- No difference in progression-free or overall survival

O'Brien S et al. *Proc ASH* 2014;Abstract 517.

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### **Investigator Commentary: SPIRIT 2 Study Comparing Dasatinib to Imatinib for Newly Diagnosed CML**

This study, like the DASISION trial, compared dasatinib to imatinib for patients with newly diagnosed CML. The primary endpoint was event-free survival at 5 years. The median follow-up for this interim analysis was 3 years, so the analysis does not address the primary endpoint.

A significant difference was evident in the rate of MMR (MR<sup>3</sup>) in favor of dasatinib. An interesting correlation between MR<sup>3</sup> and pleural effusion was observed. Patients who had a pleural effusion had an MR<sup>3</sup> rate of 65%, whereas for those with no pleural effusion it was 56%. The difference was not statistically significant, but a trend is apparent for better responses in patients who have pleural effusions. That observation has also been made in other studies. The rate of CCR also trended in favor of dasatinib, but many data are missing, so it is difficult to draw a conclusion.

The toxicity profile was similar to what we observed in the DASISION study. The rates of thrombocytopenia and pleural effusions were higher with dasatinib, whereas with imatinib more gastrointestinal toxicities were noted. The rates of arterial cardiovascular events and hypertension were higher in the dasatinib arm, although the difference was not significant. All patients receiving tyrosine kinase inhibitors (TKIs) should be monitored for cardiovascular events.

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

continued

### **Investigator Commentary: SPIRIT 2 Study Comparing Dasatinib to Imatinib for Newly Diagnosed CML (continued)**

This is the third randomized study that demonstrates the superiority of dasatinib versus imatinib, the other studies being the DASISION and the SWOG-S0325 trials. It is reassuring that higher rates of response, earlier and deeper responses and a favorable toxicity profile with dasatinib can be confirmed in independent studies.

We also know that although the benefit with second-generation TKIs is greater for patients who are at high risk, those who are at low risk also benefit. A higher rate of MMR and deeper responses are observed with newer TKIs. However, that does not translate into a survival benefit. Future studies will have to address the role of imatinib in the treatment of CML given the cost issues and the fact that a generic version of imatinib should be available soon.

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

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