5 Minute JournalClub

Key ASCO Presentations

Issue 6, 2010

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CME Information

LEARNING OBJECTIVES

- Use emerging clinical trial data comparing nilotinib to imatinib to develop an evidence-based treatment algorithm for newly diagnosed CML-CP.
- Recognize dasatinib as a potential option in the front-line treatment of CML-CP.
- Recall emerging clinical trial data regarding the preliminary safety and efficacy of the dual SRC/ABL tyrosine kinase inhibitor bosutinib for patients with CML-CP who demonstrate intolerance or resistance to imatinib.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
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:

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

Paid Research: Bristol-Myers Squibb Company, Genzyme Corporation, Novartis Pharmaceuticals Corporation.

Comparison of Nilotinib and Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): ENESTnd Beyond One Year

Larson RA et al.

Proc ASCO 2010;Abstract 6501.

Introduction

- Nilotinib is a highly potent and selective inhibitor of BCR-ABL (*Biochim Biophys Acta* 2010;1804:445).
- ENESTnd is a global, multicenter, randomized Phase III study of nilotinib 300 mg BID versus 400 mg BID versus imatinib 400 mg QD.
- Data reported from the primary analysis, with a median follow-up of 13.8 months, showed nilotinib at both doses induced significantly higher and faster rates of major molecular response (MMR) and complete cytogenetic response (CCyR) compared with imatinib (ASH 2009;Abstract LBA1).
- Data reported here have a median follow-up of approximately 18.5 months.

Larson RA et al. *Proc ASCO* 2010;Abstract 6501.

Trial Schema

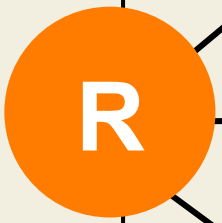
Accrual: 846 (Closed)

Eligibility

Newly diagnosed (within 6 months) CML-CP

Ph+ disease

No prior therapy for CML except:
- Hydroxyurea (HU)/anagrelide
- ≤2 weeks of imatinib



Nilotinib 300 mg BID (n = 282)

Nilotinib 400 mg BID (n = 281)

Imatinib 400 mg QD (n = 283)

Patients stratified by Sokal risk scores
Study conducted at 217 centers in 35 countries
Primary endpoint: MMR at 12 months
Key secondary endpoint: Durable MMR at 24 months

Larson RA et al. *Proc ASCO* 2010;Abstract 6501.

Efficacy Data

	Nilotinib 300 mg BID	Nilotinib 400 mg BID	Imatinib 400 mg qd
MMR rates (patients with PCR assessment)			
18 months (n = 525)	69%	63%	36%
24 months (n = 145)	86%	88%	48%
CCyR rates			
12 months	80%	78%	65%
Overall	85%	82%	74%
Progression to AP/BC on study treatment	0.7%	0.2%	4.2%
Overall survival (OS)			
Estimated 18-month OS	98.5%	99.3%	96.9%
Stratified log-rank test versus imatinib	0.28	0.03	—

Larson RA et al. *Proc ASCO* 2010;Abstract 6501.

Study Drug-Related Fluid Retention (All Grades)

	Nilotinib 300 mg BID (n = 279)	Nilotinib 400 mg BID (n = 277)	Imatinib 400 mg qd (n = 280)
Peripheral edema	5%	6%	14%
Eyelid edema	<1%	2%	14%
Periorbital edema	<1%	<1%	13%
Pericardial effusion	<1%	0	<1%
Pleural effusion	<1%	0	0

Grade 3/4 adverse events were rarely observed in any treatment arm (<1%).
There was no clinically relevant prolongation in QT interval or decrease in left ventricular ejection fraction (LVEF).
Discontinuation due to adverse events or abnormal laboratory values were lowest for nilotinib 300 mg (7%).

Larson RA et al. *Proc ASCO* 2010;Abstract 6501.

Conclusions

- With longer follow-up, rates of MMR and CCyR remain superior for nilotinib compared to imatinib.
- Molecular responses are continuing to deepen over time.
- There continues to be fewer progression events and fewer deaths with nilotinib versus imatinib.
- There were no unexpected safety events.
- Nilotinib at 300 mg BID and 400 mg BID was generally well tolerated.
- Longer follow-up data support nilotinib as a new standard of care in patients with newly diagnosed CML.

Larson RA et al. *Proc ASCO* 2010;Abstract 6501.

Investigator comment on the results of ENESTnd: Nilotinib versus imatinib for newly diagnosed CML-CP

The two schedules of nilotinib demonstrated superiority to imatinib therapy in terms of the 12-month rate of major molecular response. Additionally, nilotinib was associated with a significantly superior rate of complete cytogenetic response by 12 months, which is another surrogate indicator of long-term prognosis. We also observed a clinically significant reduction in the transformation rate of CML to accelerated and blastic phase, and this is a tangible point in terms of benefit to patients because once the patients develop accelerated or blastic phase, their outcome is bad. The updated data presented at ASCO are from the 18-month follow-up of this study, and nilotinib 400 mg twice per day demonstrated a significant survival advantage.

We also observed that the nilotinib schedules produced less of the bothersome toxicities, such as fluid retention and periorbital edema. Surprisingly, we did not observe significant QT prolongation, so that puts to rest the previous fearful notion of the black box warning. We have to be cautious because this study excluded patients who had QT prolongation over 450 ms and was strict about not allowing drugs that prolonged the QT interval. But as long as we follow these guidelines, then nilotinib and the other tyrosine kinase inhibitors are quite safe in terms of QT prolongation and related cardiotoxicity.

Interview with Hagop M Kantarjian, MD, June 30, 2010

Dasatinib Compared to Imatinib in Patients with Newly Diagnosed Chronic Myelogenous Leukemia in Chronic Phase (CML-CP): Twelve-Month Efficacy and Safety from the Phase III DASISION Study

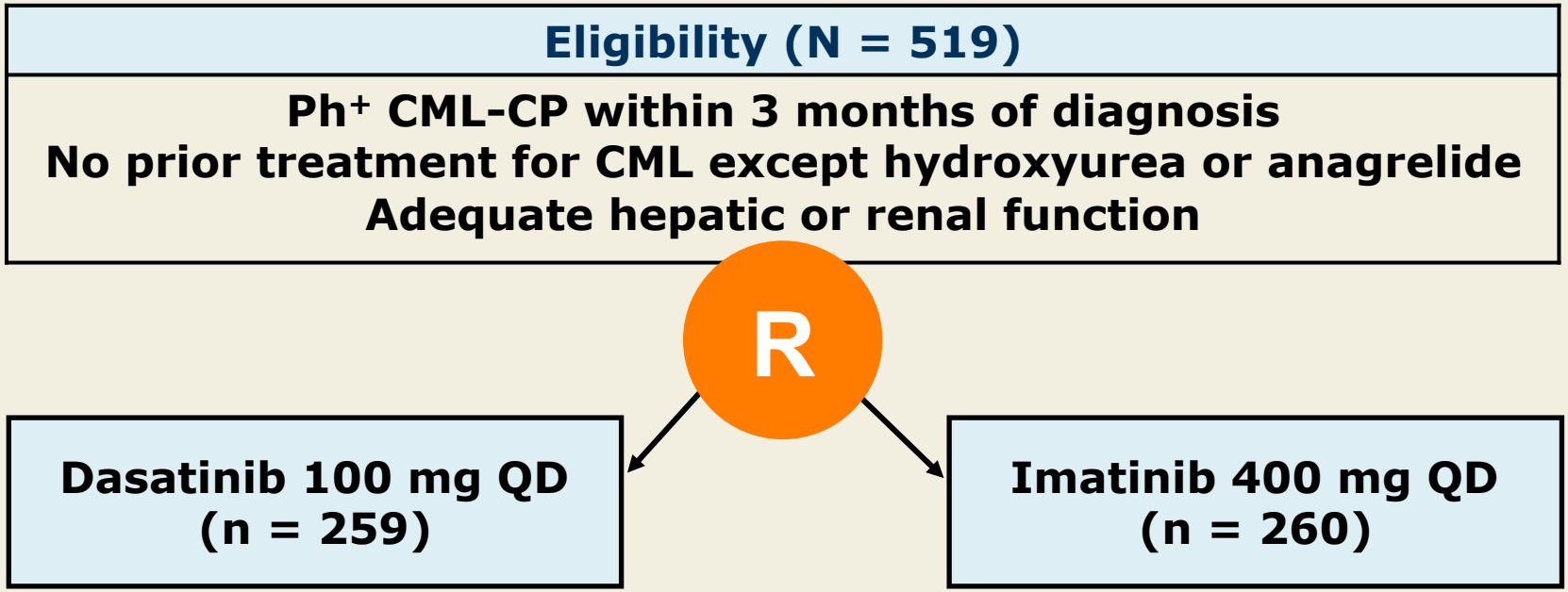
Kantarjian H et al.
Proc ASCO 2010;Abstract LBA6500.
Kantarjian H et al.
N Engl J Med 2010;362(24):2260-70.

Background

- Achieving complete cytogenetic response (CCyR) and/or major molecular response (MMR) by 12 months on imatinib is associated with superior long-term progression-free survival (PFS) (*NEJM* 2006;355:2408, *JCO* 2008;26:3358).
- Dasatinib induced high rates of CCyR and PFS in patients with CML after IM failure (*Haematologica* 2010;95:232).
- Phase II single-arm study demonstrated high rates of CCyR and MMR with dasatinib used in the first line for CML-CP (*JCO* 2010;28:398).
- **Current study objective:**
  - Assess the efficacy and safety of dasatinib as first-line treatment for patients with CML-CP.

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

DASISION: Phase III Trial Schema



Primary endpoint was confirmed CCyR (defined as confirmed CCyR on two consecutive assessments at least 28 days apart) by 12 months.

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

Response Rates

	Dasatinib (n = 259)	Imatinib (n = 260)	*p*-value
Confirmed CCyR by 12 months[1]	77%	66%	0.007
CCyR by 12 months[2]	83%	72%	0.001
MMR by 12 months	46%	28%	<0.0001
MMR at any time	52%	34%	<0.0001
Progression to accelerated/ blastic phase	1.9%	3.5%	—

[1] Confirmed CCyR is defined as CCyR detected in two consecutive assessments. The second confirmation could have occurred after 12 months.
[2] CCyR defined as CCyR detected at least once in at least 20 metaphases.

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

Selected Drug-Related Adverse Events

Adverse Event	Dasatinib (n = 258)		Imatinib (n = 258)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Neutropenia	65%	21%	58%	20%
Anemia	90%	10%	84%	7%
Thrombocytopenia	70%	19%	62%	10%
Superficial Edema	9%	0%	36%	<1%
Pleural Effusion	10%	0%	0%	0%
Muscle Inflammation	4%	0%	17%	<1%
Vomiting	5%	0%	10%	0%

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

Conclusions

- Dasatinib has superior efficacy compared to imatinib in first-line CML-CP.
  - Superior confirmed CCyR, CCyR and MMR
  - Lower rate of progression to accelerated/blastic phase
  - Faster rates of confirmed CCyR and MMR
    - Hazard ratio for shorter time to confirmed CCyR: 1.5, $p < 0.0001$
    - Hazard ratio for shorter time to MMR: 2.0, $p < 0.0001$
- Dasatinib was well tolerated.
- Longer follow-up may demonstrate better long-term outcomes with dasatinib in patients with CML-CP based on the association of achieving CCyR by 12 months and improved PFS in response to imatinib.

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

Investigator comment on the results of DASISION: A Phase III study of dasatinib versus imatinib in newly diagnosed CML-CP

This was a two-arm randomized trial of orally administered dasatinib at the dose of 100 mg per day, which was found in the follow-up studies to be as effective and probably less toxic than 70 mg twice a day, the dose at which dasatinib was originally approved. The second arm was the standard approach of imatinib 400 mg per day.

The primary endpoint of the study was the incidence of complete cytogenetic response by 12 months, and the study met its endpoints. There was a significantly superior rate of complete cytogenetic response by 12 months with dasatinib compared to imatinib, a significantly higher incidence of major molecular response and a trend for a reduction in the rate of progression to accelerated phase and blastic phase.

Additionally, we observed less of the bothersome toxicities with dasatinib. There were lower incidences of muscle aches, nausea, vomiting and skin rash. We did observe a little more Grade 3/4 thrombocytopenia, and 10 percent of the patients had pleural effusions, which were all mild to moderate and reversible with modifications of the dose and interruptions.

Interview with Hagop M Kantarjian, MD, June 30, 2010

Safety and Efficacy of Bosutinib (SKI-606) in Patients with Chronic Phase Chronic Myeloid Leukemia Following Resistance or Intolerance to Imatinib (IM)

Cortes JE et al.

Proc ASCO 2010;Abstract 6502.

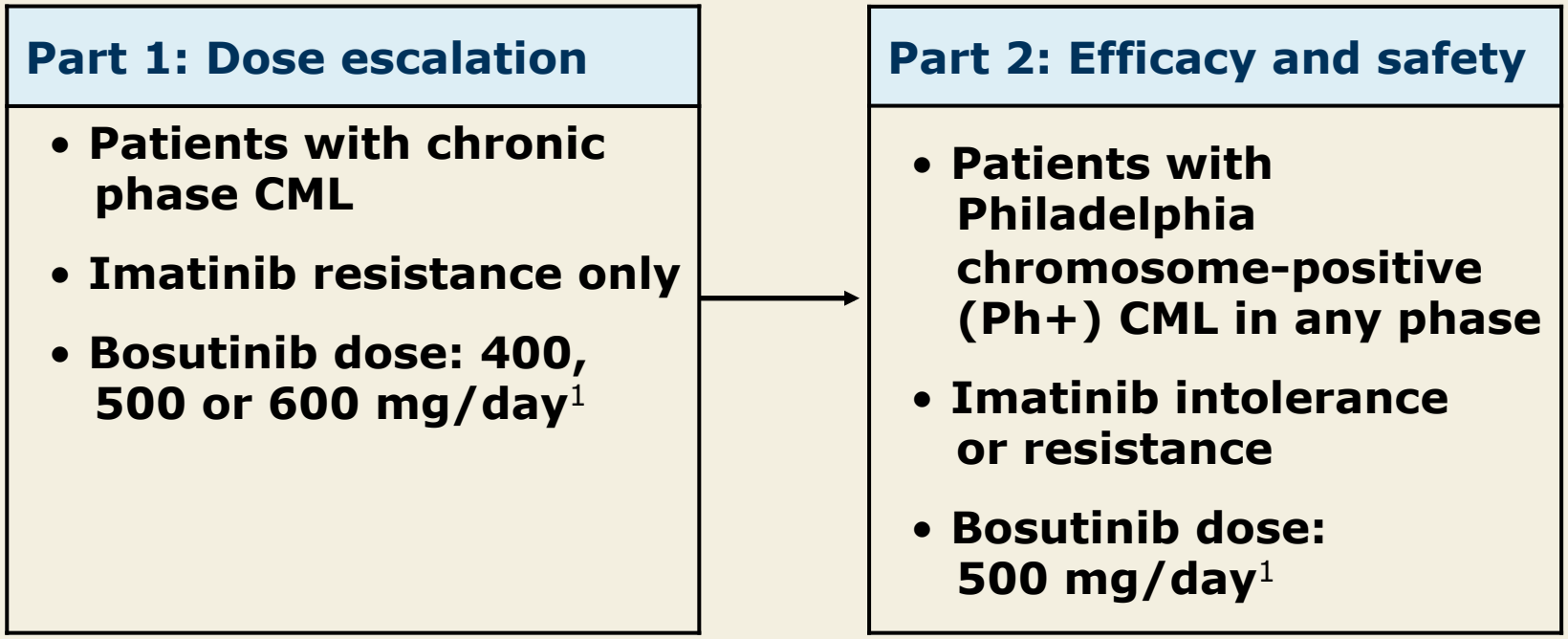
Introduction

- Bosutinib is an orally bioavailable, potent dual SRC/ABL tyrosine kinase inhibitor, with minimal inhibitory activity against PDGFR or c-kit (*Cancer Res* 2006;66:11314).
- Bosutinib inhibits BCR-ABL signaling in chronic myeloid leukemia (CML) cells (*J Cancer Res* 2003;63:375).
- Bosutinib is active against imatinib-resistant mutants of BCR-ABL, except T315I (*Cancer Res* 2006;66:11314).
- **Current study objective:**
  - Investigate the efficacy and safety of bosutinib in patients with imatinib-intolerant or resistant chronic phase (CP) chronic myeloid leukemia (CML).

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Phase I/II Study Design

Accrual: 299 (Closed)



[1] Open label, continuous daily dosing

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Best Response Data

Response	Number of patients (%)
Hematologic[1] (n = 109)[2]	
Overall	102 (94%)
Complete	99 (91%)
Cytogenetic (n = 214)[2]	
Major	136 (64%)
Complete	106 (50%)
Molecular (n = 151)[2]	
Major	79 (52%)
Complete	49 (32%)

[1] Includes patients with unconfirmed hematologic response.
[2] Patients with complete hematologic response, complete cytogenetic response or complete molecular response at baseline (at time of study entry) and those lacking a baseline or post-baseline assessment are considered non-evaluable for the respective response.

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Efficacy Data

Parameter	Result
Median time to complete cytogenetic response (n = 214)	12.3 months
Median time to major cytogenetic response (n = 214)	6.3 months
Median time to complete hematologic response (n = 109)	0.8 months
Patients progression free at month 24 Imatinib resistant (n = 202) Imatinib intolerant (n = 92)	 77% 86%
Patients alive at month 24 Imatinib resistant (n = 202) Imatinib intolerant (n = 92)	 92% 99%

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Response by BCR-ABL Mutation Status

Mutation type[1]	Complete hematologic response n/n evaluable (%)	Major cytogenetic response n/n evaluable (%)
Any	19/22 (86%)	28/39 (72%)
P-loop	4/4 (100%)	6/9 (67%)
Non-P-loop	15/18 (83%)	22/30 (73%)
No mutation	26/28 (93%)	22/38 (58%)

19 different mutations were identified in 43 of 96 (45%) patients tested.

[1] Patients with complete hematologic, cytogenetic or molecular responses at baseline and patients lacking both a baseline and post-baseline assessment are considered non-evaluable for the respective response.

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Select Grade 3/4 Adverse Events

Adverse event	Rate
Thrombocytopenia	24%
Neutropenia	16%
Anemia	12%
Diarrhea	9%
Rash	9%
Vomiting	3%
Nausea	2%

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Conclusions

- Bosutinib is an active agent for patients with CP CML resistant or intolerant to imatinib (complete cytogenetic response 50%).
- Responses occurred across a wide variety of BCR-ABL mutations.
- Duration of response requires further follow-up.
- Bosutinib demonstrated a favorable toxicity profile
  - Self-limiting gastrointestinal adverse events
  - Low rates of hematologic toxicity
  - Minimal fluid retention
- Results of a Phase III randomized trial of bosutinib versus imatinib for patients with newly diagnosed CML are expected at the end of 2010.

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Investigator comment on the results of a Phase I/II study of bosutinib in CML-CP following resistance or intolerance to imatinib

Bosutinib is a highly potent dual Src/Abl inhibitor like dasatinib. It does not inhibit C-kit or PDGFR, so presumably bosutinib will not cause too much myelosuppression or too many pleural effusions.

We have completed both of the salvage studies for patients who became resistant to imatinib, and we observed positive results, with complete cytogenetic response rates of about 50 percent. In August 2010 we will have the data on bosutinib versus imatinib in the front-line setting. We are hoping that these also will be positive and we will have at least three drugs — nilotinib, dasatinib and bosutinib — that could be superior to imatinib and could replace imatinib in the front-line setting.

Surprisingly, bosutinib is associated with fewer adverse events than several of the other drugs. The one problematic issue is diarrhea, typically Grade 1, which is seen in the first one to two weeks and is usually self-limited. The other complications are liver abnormalities — elevations of either the bilirubin or enzymes — which are mostly Grade 1 or 2 and have not been dose limiting in patients on treatment. We did not observe pleural effusions or significant myelosuppression.

Interview with Hagop M Kantarjian, MD, June 30, 2010