5 Minute JournalClub

Key ASH Presentations
Issue 8, 2012

Novel Agents Bosutinib and Ponatinib in CML and ALL: Results from the BELA and PACE Trials

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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

- Apply emerging clinical trial data to the rational selection of treatment with targeted tyrosine kinase inhibitors for patients with refractory or relapsed chronic myeloid leukemia.
- Assess the risks of molecular relapse after the discontinuation of treatment with targeted tyrosine kinase inhibitors in patients with chronic myeloid leukemia.
- Communicate the benefits and risks of therapy with multitargeted tyrosine kinase inhibitors for patients with newly diagnosed, relapsed or refractory chronic myeloid leukemia in chronic, accelerated or blast phase.
- Compare and contrast the benefits and adverse effects of continuous therapy with different targeted tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia.

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

The 2009 ASH meeting marked a high point in the amazing and continuing evolution of the management of chronic phase chronic myelogenous leukemia (CML-CP) with the sudden appearance of several convincing Phase III data sets demonstrating that the second-generation BCR-ABL TKIs nilotinib and dasatinib resulted in improvements in a number of major short-term endpoints and were equally or better tolerated compared to imatinib. These and other recent findings also put into sharp focus the fact that despite the impressive steps forward during the last decade there is room for improvement in CML-related outcomes, including survival. For this issue of our series we briefly review 8 new ASH data sets addressing the following important CML questions:

1. What is the role of second-generation TKIs?

The weight of evidence for the newer agents continues to mount, and at ASH another round of related data sets was reported.

More follow-up on up-front nilotinib versus imatinib

The landmark IRIS trial that established the role of imatinib demonstrated that most disease progression events occurred within 3 years, and as such similar follow-up with the newer TKIs is critical. At ASH, 3-year data from the ENESTnd trial of nilotinib versus imatinib revealed continued separation of the curves for major and deeper molecular response. Importantly, in the imatinib arm a 6% rate of progression to accelerated phase and blast crisis (AP/BC) was observed compared to only 0.7% with 300 mg BID of nilotinib.

Switching TKIs at 1 year

Many/most investigators currently prefer nilotinib or dasatinib as first-line therapy, but any imatinib holdouts will be forced to strongly consider the compelling preliminary results from the ENESTcmr Phase III trial assessing the benefit of switching therapy for individuals who do not achieve complete molecular response (CMR) after treatment with imatinib. In the study, 207 patients in complete cytogenetic response (CCyR) but with detectable BCR-ABL less than 2 years after starting imatinib were randomly assigned

to either continue therapy or switch to nilotinib 400 mg BID. At 12 months of follow-up, the rate of confirmed CMR was 5.8% with imatinib compared to 12.5% for nilotinib.

Nilotinib 400 mg BID

The ENESTnd extension trial reported at ASH evaluated the higher 400-mg BID dose of nilotinib in patients with suboptimal response or treatment failure on imatinib or nilotinib at 300 mg BID. The findings illustrate clear-cut efficacy in patients treated with prior imatinib — even after dose escalation — and also point to a benefit in those escalated to the higher nilotinib dose. Currently, 300 mg BID is still the recommended starting dose up front.

2. Are there even newer TKIs with significant supportive trial data?

Ponatinib

Ponatinib has been previously shown to have notable activity in tumors with otherwise problematic T315I mutations, and the clinical impact of this agent in resistant or intolerant disease was once again displayed in an impressive Phase II trial of 403 patients reported at ASH.

Bosutinib

Another data set presented at ASH came from the Phase III BELA trial comparing bosutinib to imatinib in patients with newly diagnosed CML-CP. The study did not meet its primary endpoint of CCyR at 12 months partly due to early treatment discontinuation in about a quarter of the patients related to bosutinib-associated adverse effects, particularly GI toxicity (diarrhea). However, other endpoints favored the new TKI bosutinib — including a lower rate of progression to AP/BC — and the future role of the agent is still up for debate.

3. How early can suboptimal response be identified?

The answer just might be 3 months, based on findings from an ASH presentation showing that patients on imatinib with >10% BCR-ABL levels or >35% Ph+ cells at the 3-month time point had a 5-year survival rate of only 87%. Ongoing trials are evaluating an early switch to another TKI in these patients.

4. Can TKI treatment ever be stopped?

Although disease control is everyone's primary concern, lifelong TKI use introduces quality of life and financial constraints, and as such many have wondered if it is safe to stop therapy at some point. At ASH we saw results from the STIM study evaluating treatment discontinuation in 100 patients who received imatinib and experienced a CMR for at least 2 years. Interestingly, 61% of patients experienced molecular relapse upon

stopping therapy (almost all within 7 months). However, most went back into CMR with re-treatment. The ability to stay off the drug seemed to correlate with disease biology (Sokal score) and duration of therapy. Another ASH report of 25 patients who stopped either nilotinib or dasatinib seemed to reflect a similar conclusion, and indefinite treatment is still recommended outside a trial setting.

Next, our final ASH report: More data and perspectives on non-Hodgkin lymphoma and chronic lymphocytic leukemia.

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Novel Agents Bosutinib and Ponatinib in CML and ALL: Results from the BELA and PACE Trials

Presentations discussed in this issue

Cortes JE et al. **Initial findings from the PACE trial: A pivotal Phase 2 study of ponatinib in patients with CML and Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation.** *Proc ASH* 2011;**Abstract 109**.

Cortes JE et al. **Bosutinib versus imatinib in newly diagnosed chronic phase chronic myeloid leukemia — BELA trial: 24-month follow-up.** *Proc ASH* 2011;**Abstract 455**.

Slides from presentations at ASH 2011 and transcribed comments from a recent interview with Srdan Verstovsek, MD, PhD (1/25/12)

Initial Findings from the PACE Trial: A Pivotal Phase 2 Study of Ponatinib in Patients with CML and Ph+ ALL Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I Mutation[1]

Bosutinib versus Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia — BELA Trial: 24-Month Follow-Up[2]

[1] **Cortes JE et al.**
Proc ASH 2011;Abstract 109.

[2] **Cortes JE et al.**
Proc ASH 2011;Abstract 455.

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Initial Findings from the PACE Trial: A Pivotal Phase 2 Study of Ponatinib in Patients with CML and Ph+ ALL Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I Mutation

Cortes JE et al.

Proc ASH 2011;Abstract 109.

Background

- Despite progress with tyrosine kinase inhibitors (TKIs) in the treatment of chronic myeloid leukemia (CML), there are no therapeutic options after dasatinib or nilotinib failure or for T315I mutation-positive disease.
- Ponatinib is a potent, oral, pan-BCR-ABL enzyme inhibitor that is active against the native enzyme and all tested resistant mutants, including the T315I mutation.
- **Objective:**
  - Determine the efficacy and safety of ponatinib in patients with refractory CML.

Cortes JE et al. *Proc ASH* 2011;Abstract 109.

PACE Trial Design

Eligibility (n = 403)*
Patients with refractory CML in chronic, accelerated or blast phase (CP, AP, BP)
Ph+ acute lymphoblastic leukemia (ALL)
Resistant or intolerant (R/I) to dasatinib, nilotinib or with resistant T315I mutation

→ **Ponatinib (n = 397)† PO 45 mg/d**

† Given to 6 patient cohorts:
- CP R/I (n = 188)
- CP T315I (n = 48)
- AP R/I (n = 52)
- AP T315I (n = 15)
- BP/ALL R/I (n = 51)
- BP/ALL T315I (n = 43)

* Patients enrolled at the time of analysis (July 18, 2011). Enrollment is ongoing.

Primary endpoints:

- Major cytogenic response (MCyR) for CP CML
- Major hematologic response (MaHR) for AP CML, BP CML or ALL

Cortes JE et al. *Proc ASH* 2011;Abstract 109.

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Cytogenic Response Rates (Abstract Only)

Patients (n = 159)*	MCyR
CP cohorts (n = 83)†	46%
CP R/I (n = 60)	42%
CP T315I (n = 23)	57%
Patients (n = 159)*	**Complete CyR (CCyR)**
CP cohorts (n = 83)†	31%
CP R/I (n = 60)	25%
CP T315I (n = 23)	48%

* Patients with evaluable disease at time of analysis

† Patients assessed at 3 months (n = 10 at 6 months) or who discontinued treatment

- Median follow-up: 57 days

Cortes JE et al. *Proc ASH* 2011;Abstract 109.

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Hematologic Response Rates (Abstract Only)

Patients (n = 159)*	MaHR
AP, BP/ALL cohorts (n = 76)†	46%
AP RI (n = 23)	74%
AP T315I (n = 1)	100%
BP/ALL RI (n = 30)	37%
BP/ALL T315I (n = 22)	27%

* Patients with evaluable disease at time of analysis

† Number of patients assessed at ≥1 month or who discontinued treatment

- Median follow-up: 57 days

Cortes JE et al. *Proc ASH* 2011;Abstract 109.

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Drug-Related Adverse Events (AEs) (Abstract Only)

Most common AE (≥10% any grade)	Patients (n = 397)
Thrombocytopenia Grade 3/4	19% 15%
Rash	18%
Dry skin	13%
Myalgia	12%
Abdominal pain Grade 3/4	11% 3%
Headache	11%
Arthralgia	11%
≥1 serious AE (SAE)	17%

- Patients still on therapy: 85%; discontinued due to progressive disease, AEs or death (15%)
- The most common SAEs included 15 cases of pancreatitis (3.7%)

Cortes JE et al. *Proc ASH* 2011;Abstract 109.

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Author Conclusions

- This initial analysis of the PACE trial showed that ponatinib has a favorable safety profile that was similar to that observed in the previous Phase I study but with a lower incidence of pancreatitis.
- After a short follow-up period, these data demonstrated that ponatinib had a substantial antileukemic activity in a patient population with heavily pretreated refractory T315I CML.
- These initial efficacy signals replicated response results initially reported in the Phase I setting.

Cortes JE et al. *Proc ASH* 2011;Abstract 109.

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Investigator Commentary: Initial Findings from the Pivotal Phase II PACE Trial of Ponatinib in Patients with Refractory CML

Ponatinib is different from other TKIs in that it is also effective against T315I mutations. The T315I mutation is well known as one that is resistant to all the other TKIs available. This trial studied the efficacy of ponatinib in patients with the T315I mutation and TKI-resistant or TKI-intolerant disease. In all patient subgroups, ponatinib was efficacious in inducing hematologic and cytogenic responses. In fact, ponatinib therapy yielded molecular responses, particularly in a difficult-to-treat subselection of patients with pretreated and refractory CP-CML. Overall, ponatinib is an agent that may be approved in the near future.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012

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Bosutinib versus Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia — BELA Trial: 24-Month Follow-Up

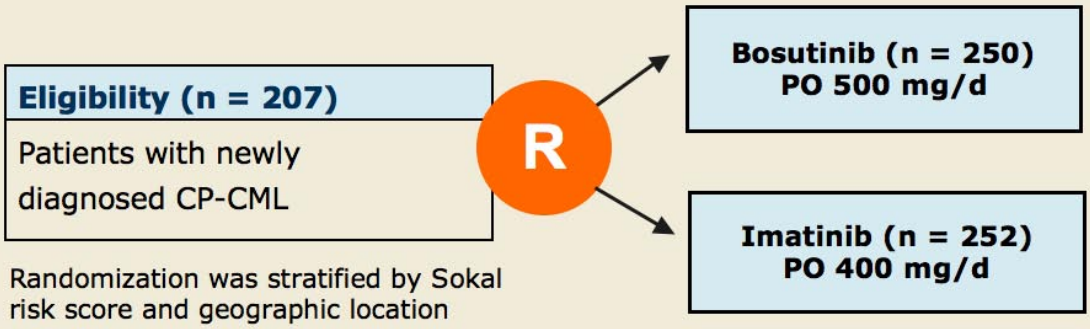
Cortes JE et al.

Proc ASH 2011;Abstract 455.

Background

- Bosutinib (SKI-606) is an orally active, dual competitive inhibitor of the Src and Abl tyrosine kinases.
- The Phase III BELA study compared bosutinib to imatinib in patients with newly diagnosed chronic phase (CP) chronic myeloid leukemia (CML) (*Proc EHA* 2011;Abstract 0485).
- **Objective**:
  - Determine the efficacy and safety of bosutinib versus imatinib after a follow-up period of 24 months in patients with CP-CML.

Study Design



Randomization was stratified by Sokal risk score and geographic location

Primary endpoint

- Complete cytogenic response (CCyR) at 12 months in the intent-to-treat population

Secondary endpoints

- Major molecular response (MMR) at 12 months; time to CCyR and MMR; duration of CCyR and MMR; time to and incidence of transformation to accelerated/blast phase (AP/BP) CML; event-free survival (EFS) and overall survival (OS)

Cortes JE et al. *Proc ASH* 2011;Abstract 455.

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Cytogenic Response Rates (Abstract Only)

CCyR	Bosutinib (n = 248)	Imatinib (n = 250)
At 3 months	50%	25%
At 6 months	59%	49%
At 9 months	63%	55%
At 12 months	70%	68%
At 18 months	62%	67%
Cumulative rate by 18 months	79%	79%

- Median time to CCyR was 12.7 weeks (bosutinib) and 24.6 weeks (imatinib).
- Median treatment duration was 19.3 months (bosutinib) and 19.5 months (imatinib).

Cortes JE et al. *Proc ASH* 2011;Abstract 455.

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Molecular Response Rates (Abstract Only)

MMR	Bosutinib (n = 248)	Imatinib (n = 250)
At 3 months	7%	3%
At 6 months	28%	11%
At 9 months	35%	19%
At 12 months	41%	27%
At 18 months	46%	38%
Cumulative rate by 18 months	55%	45%

- Median time to MMR was 36.9 weeks (bosutinib) and 72.3 weeks (imatinib).

Cortes JE et al. *Proc ASH* 2011;Abstract 455.

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Other Trial Outcomes (Abstract Only)

Endpoint	Bosutinib (n = 248)	Imatinib (n = 250)
Transformation to AP/BP CML on treatment	2%	5%
EFS rate (18 months)	95%	91%
OS rate (18 months)	99%	95%
On-study deaths Due to CML progression	2% 2%	5% 4%

- Median on-treatment EFS and OS were not reached for either of the treatment arms.
- Patients still receiving treatment: bosutinib (67%) and imatinib (74%)

Cortes JE et al. *Proc ASH* 2011;Abstract 455.

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Adverse Events (AEs) (Abstract Only)

Event	Bosutinib (n = 248)	Imatinib (n = 250)
Diarrhea	69%	22%
Vomiting	32%	14%
Pyrexia	18%	10%
Abdominal pain	13%	7%
Peripheral edema	4%	11%
Periorbital edema	1%	14%
Muscle cramps	4%	22%
Increased ALT (Grade 3/4)	23%	4%

- The primary reason for bosutinib discontinuation was toxicity (23%).
- The primary reason for imatinib discontinuation was disease progression (13%).

Cortes JE et al. *Proc ASH* 2011;Abstract 455.

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Author Conclusions

- The primary endpoint of this study was not met because there was no difference in CCyR at 12 months between treatments, probably as a result of early discontinuation due to bosutinib-related AEs.
- However, bosutinib therapy resulted in a higher MMR rate at 12 months, faster times to MMR and CCyR, fewer events of transformation to AP/BP CML and fewer overall and CML-related deaths compared to imatinib.
- In addition, 18-month estimates of EFS and OS favor bosutinib over imatinib therapy.
- Both bosutinib and imatinib were associated with acceptable but distinct toxicity profiles.
- These data suggest that bosutinib is superior to imatinib and may offer a new therapeutic option in patients with newly diagnosed CP-CML.

Cortes JE et al. *Proc ASH* 2011;Abstract 455.

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Investigator Commentary: Bosutinib versus Imatinib in Newly Diagnosed CP-CML — BELA Trial: 24-Month Follow-Up

Bosutinib is a TKI that was found to be active in more advanced cases of chronic myeloid leukemia. This study was an attempt to test its efficacy and toxicity in the front-line setting in comparison to imatinib. Unfortunately, the study demonstrated negative primary endpoint results (CCyR at 12 months). This was mainly because about a quarter of the patients discontinued bosutinib therapy as a result of toxicity that was primarily related to gastrointestinal events.

However, the longer-term follow-up studies demonstrated that bosutinib treatment achieved better molecular and cytogenic responses, also reducing the progression to AP/BP CML in comparison to imatinib therapy. Although bosutinib is a good agent with demonstrated activity in CP-CML, I am unsure of how it will be further developed because it has yet to gain approval.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012