5 Minute JournalClub

Key ASCO Presentations
Issue 6, 2010

Update of the ENESTnd Study: Comparison of Nilotinib and Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia (CML-CP)

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Use emerging clinical trial data comparing nilotinib to imatinib to develop an evidence-based treatment algorithm for newly diagnosed CML-CP.

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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:

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

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This program is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology and Millennium Pharmaceuticals Inc.

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To go directly to the slides and commentary, **click here**.

When we launched our *Hematologic Oncology Update* audio series several years ago, one of the first investigators I interviewed was Dr Hagop Kantarjian, and from the moment he began to answer what must have seemed like sophomoric questions, I was transfixed and almost held my breath in anticipation of his every response.

During my most recent chat with this MD Anderson legend, we focused on three groundbreaking ASCO presentations on CML, all of which he coauthored. Two of these studies have been subsequently published in *The New England Journal* (Dr K was first author on one), along with a thought-provoking editorial by Charles Sawyers.

For almost a decade, imatinib has been the pillar of CML treatment, and while the agent produces an approximately 65 percent one-year complete cytogenetic response rate and a major improvement in overall survival, there is room for improvement. This possibility became potentially achievable when significant activity was observed with the more potent second-generation TKIs, nilotinib and dasatinib, in patients with disease progression on imatinib.

In response to these important data, several front-line trials were initiated with these agents. For each of these trials, a key endpoint was major molecular response — defined as a three-log reduction of BCR-ABL from baseline (99.9 percent). The first to report was a study of **nilotinib versus imatinib** unveiled in December at ASH and then updated at ASCO, where **a similar trial comparing dasatinib to imatinib** was also presented. The bottom line is that both of these agents produced superior 12-month complete cytogenetic and major molecular responses along with clinically significant reductions in transformation to accelerated phase or blastic crisis. Dr Kantarjian noted that these impressive findings involve early surrogate endpoints and it will be critical to look at three- to five-year event-free survival. Following closely is yet another TKI, **bosutinib**, which as we heard at ASCO proved to have significant activity in patients with disease progression on TKIs. The Phase III up-front comparison to imatinib is due to report very soon.

Dr Kantarjian agrees with Dr Sawyers' editorial that a key issue moving forward will be the one to two percent a year of patients on TKIs who develop new mutations in the BCR-ABL binding site — particularly T315I lesions, which result in resistance to TKIs.

For these important patients, the key may be to add new agents to the TKIs, and a number are in development.

Next up on 5-Minute Journal Club: Another fascinating example of oncogene addiction and TKIs: EML4-ALK and crizotinib in non-small cell lung cancer... and more.

Neil Love, MD
Research To Practice
Miami, Florida

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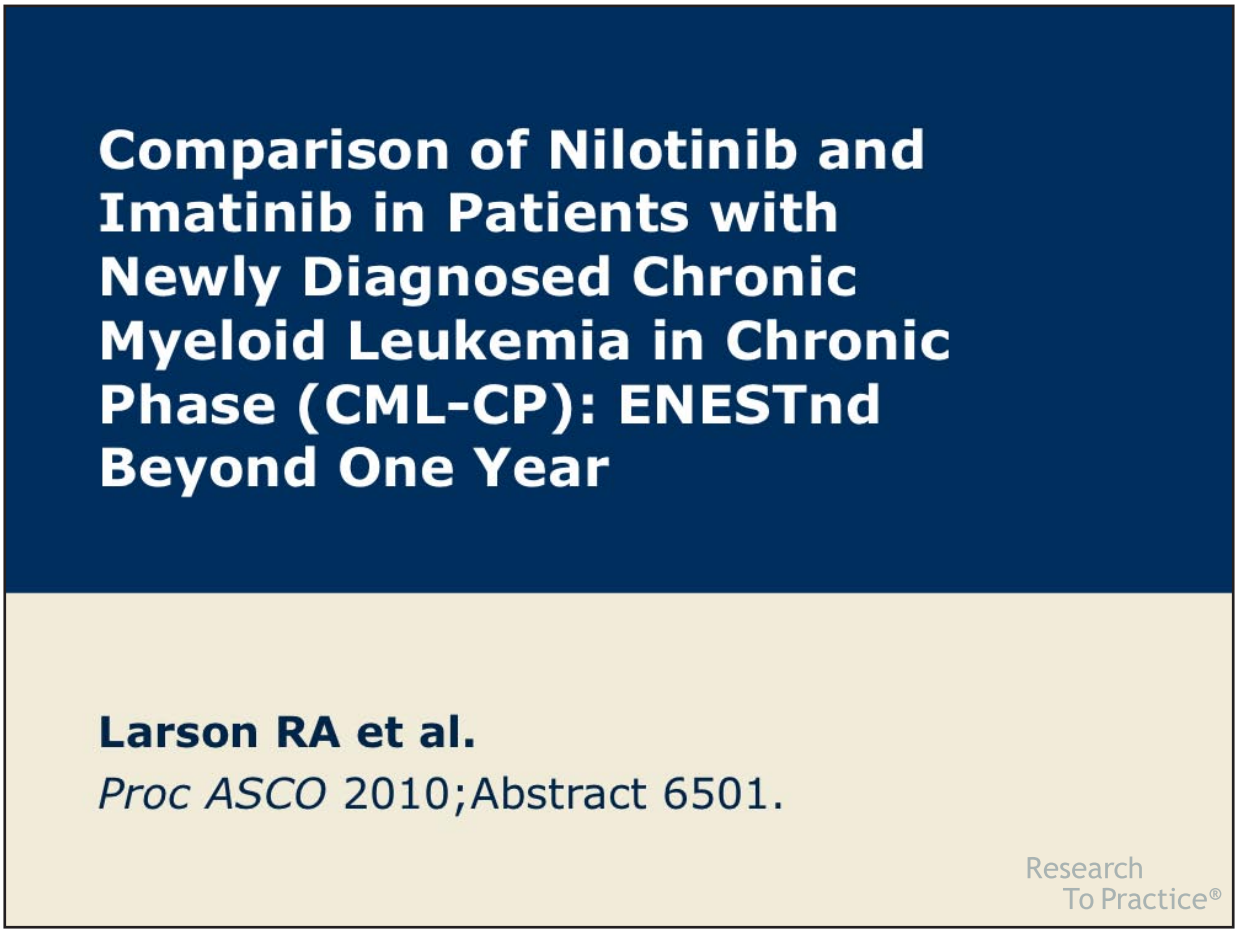
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Update of the ENESTnd Study: Comparison of Nilotinib and Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia (CML-CP)

Presentation discussed in this issue

Larson RA et al. **Comparison of nilotinib and imatinib in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd beyond one year.** *Proc ASCO* 2010;**Abstract 6501**.

Slides from a presentation at ASCO 2010 and transcribed comments from a recent interview with Hagop M Kantarjian, MD (6/30/10)



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.

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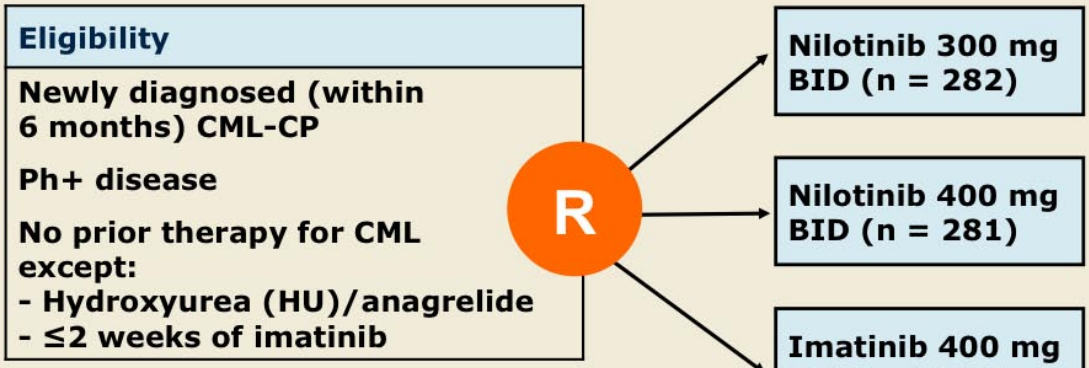
Trial Schema

Accrual: 846 (Closed)



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.

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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.

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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.

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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.

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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

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