



*Key ASH Presentations*

Issue 3, 2011

# **Nilotinib in the Early Management of Chronic-Phase Chronic Myeloid Leukemia (CML-CP)**

## 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 from a plethora of ongoing clinical trials 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 and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

### LEARNING OBJECTIVES

- Apply updated results from the ENESTnd trial to the evidence-based selection between nilotinib and imatinib as front-line treatment for CML-CP.
- Inform patients with CML-CP who exhibit suboptimal responses or intolerance to front-line imatinib about reported rates of benefit from a switch to nilotinib.

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Susan M O'Brien, MD  
Professor of Medicine  
Department of Leukemia  
The University of Texas MD Anderson Cancer Center  
Houston, Texas

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ASH 2010 marked another significant chapter in the decade-long saga that has become a model for molecularly targeted cancer treatment. To that end, [this issue](#) (click for slides) of *5-Minute Journal Club* focuses on some of the most clinically relevant ASH CML highlights, including:

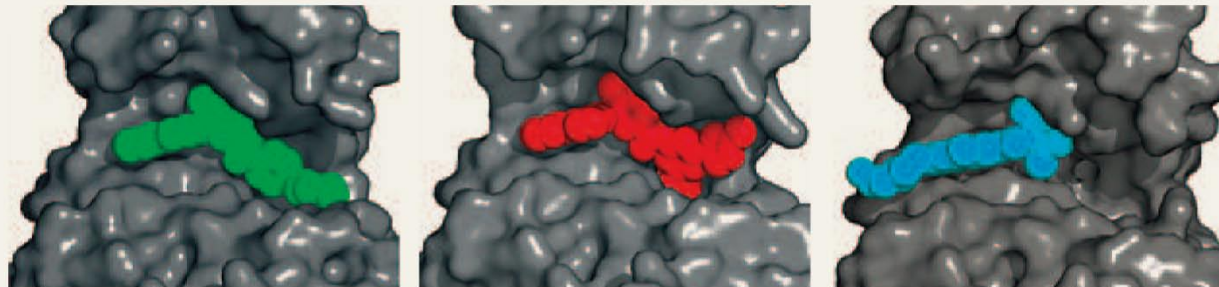
1. [A trial comparing up-front nilotinib to imatinib](#) and another evaluating a prespecified switch to nilotinib in patients unresponsive to or intolerant of imatinib

The ENESTnd up-front trial, which was first reported at ASH 2009, comparing two doses of nilotinib (400 or 300 mg BID) to imatinib was updated in Orlando. Not surprisingly, the 24-month data continue to demonstrate an advantage to nilotinib in the primary endpoint of major molecular response (MMR). Importantly, progression to accelerated or blast phase was more common with imatinib, yet conversely, while the overall level of side effects was similar between the two agents, rash and serum biochemical abnormalities were more common with nilotinib. A second, very innovative pilot study (TIDEL-II) focused on the use of nilotinib in patients with suboptimal response, loss of response or intolerance to imatinib, which was dose escalated in early molecular nonresponders. Of the 21 patients switched to nilotinib either for poor primary response or intolerance, MMR was observed in 10.

2. [Two trials comparing up-front dasatinib to imatinib](#)

Also at ASH 2009, we heard the first report from the DASISION trial, revealing a higher 12-month confirmed complete cytogenetic response (CCyR) rate with dasatinib than with imatinib. This year, the 18-month update of the study demonstrated continued benefit with this agent, which was first developed as an Src kinase inhibitor and interacts with the BCR protein quite differently than imatinib or nilotinib. In this most recent data set we again witnessed higher rates of both CCyR and MMR with dasatinib and, as with ENESTnd, fewer patients with accelerated or blast phase. As was seen previously, the side effects of dasatinib were of similar frequency but were different from those of imatinib and included pleural effusion (which may be PDGF related) in 31 patients (12 percent), usually requiring treatment interruption or dose modification. A second, smaller Phase II study with a similar randomization reported by the SWOG/Intergroup demonstrated a 12-month MMR advantage with dasatinib.

### Surface representations of crystal structures of ABL kinase in complex with TKIs

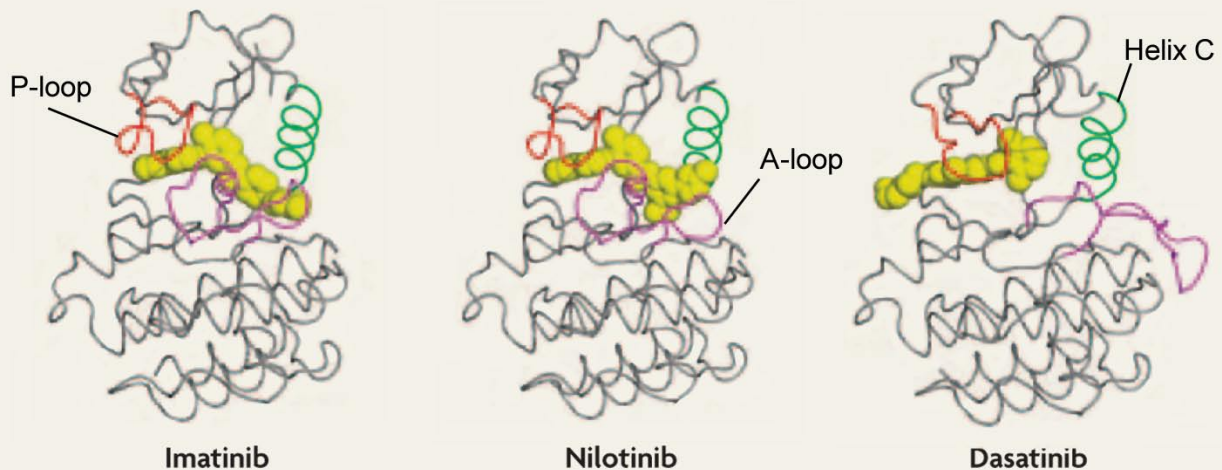


Imatinib

Nilotinib

Dasatinib

### Comparison of the different binding modes of three ABL inhibitors



Imatinib

Nilotinib

Dasatinib

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The aforementioned data sets are helping to fuel extensive debate on the optimal up-front CML chronic phase treatment, and a [mini-metaanalysis](#) also presented at ASH suggested that a similar early advantage exists for both dasatinib and nilotinib. That being said, most investigators I have spoken with agree that imatinib remains a very reasonable tried and true option.

3. [A trial comparing up-front bosutinib to imatinib](#) that did not meet the primary endpoint (12-month CCyR)

Apparently not all TKIs are created equal, and a key issue with bosutinib was that while fewer patients experienced treatment failure, 19 percent discontinued the drug due to toxicity (mainly GI) compared to only five percent with imatinib.

For all the fascinating new ASH data, my personal CML highlight from the meeting was a spectacular review of the field by Jerald Radich from the "Hutch." During his discussion, Dr Radich touched on amazing new translational strategies, including mass spectrometry to instantly differentiate 31 clinically relevant mutations and a dizzying

array of serum assays to detect remnants of the nemesis BCR-ABL. The astonishing pace of this research made me think about the many investigators in solid tumors who complain that CML is an anomaly with few analogies to their genomically complicated diseases, but I disagree. Dr Radich's talk (click [here](#) to order the ASH DVD) makes it abundantly clear that "we have the technology" — the question is whether we have the will, leadership, skills and wisdom to use these powerful tools and concepts to make the dream of a cancer-free world a reality.

Next up on this ASH highlights series: Perhaps the most important ASH paper on lymphoma — the stunning impact of the immunoconjugate brentuximab vedotin in Hodgkin lymphoma.

Neil Love, MD

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# **Nilotinib in the Early Management of Chronic-Phase Chronic Myeloid Leukemia (CML-CP)**

## **Presentations discussed in this issue**

Hughes TP et al. **ENESTnd update: Continued superiority of nilotinib versus imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP).** *Proc ASH 2010*; **Abstract 207.**

Yeung DT et al. **Selective escalation of imatinib therapy and early switching to nilotinib in de novo chronic phase CML patients: Interim results from the TIDEL-II trial.** *Proc ASH 2010*; **Abstract 209.**

**Slides from presentations at ASH 2010 and transcribed comments from a recent interview with Susan M O'Brien, MD (1/4/11)**

## **ENESTnd 24-Month Update: Continued Superiority of Nilotinib versus Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP)**

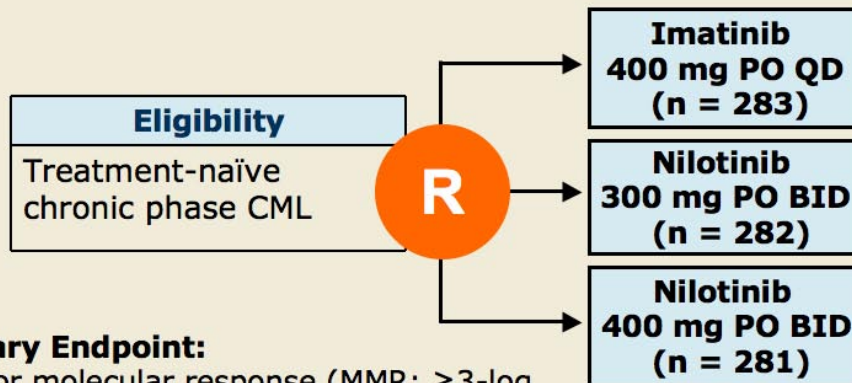
**Hughes TP et al.**

*Proc ASH 2010*; Abstract 207.

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# ENESTnd Study Schema



## Primary Endpoint:

- Major molecular response (MMR:  $\geq 3$ -log reduction in BCR-ABL transcripts) at 12 months

## Other Key Endpoints:

- Durable MMR (at 24 months)
- Complete cytogenetic response (CCyR)
- Progression to accelerated/blast phase (AP/BC)
- Progression-free survival (PFS), overall survival (OS)

Hughes TP et al. *Proc ASH* 2010;Abstract 207.

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# Efficacy Outcome

	Imatinib 400 mg QD	Nilotinib 300 mg BID		Nilotinib 400 mg BID	
<b>With 24-month follow-up</b>			<i>p</i> -value		<i>p</i> -value
Major molecular response	37%	62%	<0.001*	59%	<0.001*
Complete molecular response	6%	21%	<0.0001*	17%	0.0001*
CCyR	77%	87%	0.0018*	85%	0.016*
Progression to AP/BC	4.2%	0.7%	0.0059 <sup>†</sup>	1.1%	0.0196 <sup>†</sup>
CML-related deaths	3.5%	1.8%	—	1.1%	—
Estimated 24-month OS	96.3%	97.4%	0.65 <sup>†</sup>	97.8%	0.21 <sup>†</sup>

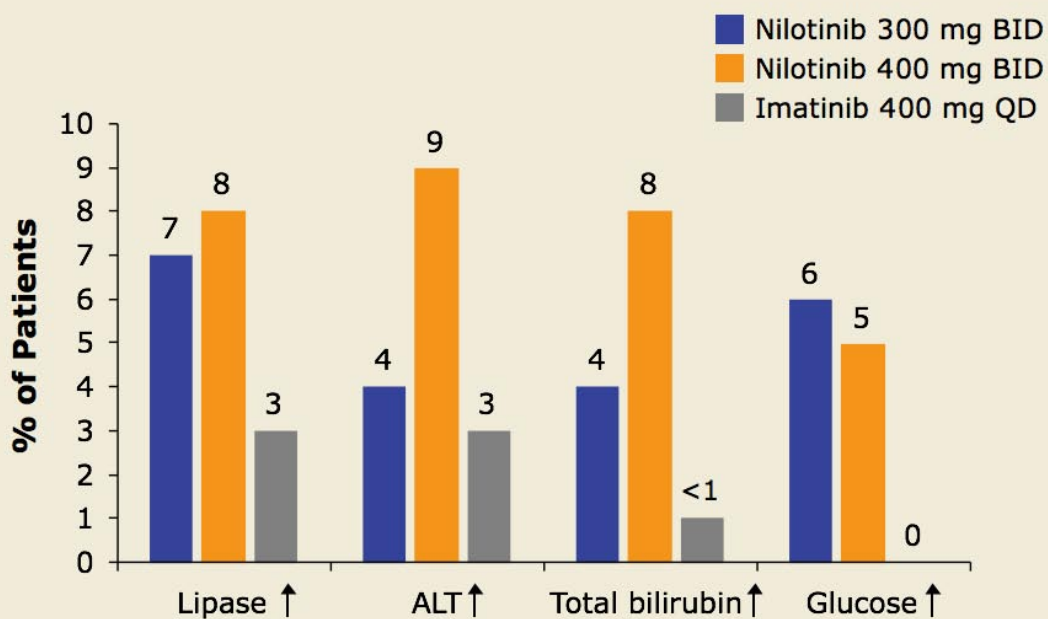
\* CMH test stratified by Sokal vs imatinib

<sup>†</sup> Log-rank test stratified by Sokal vs imatinib for time to AP/BC and OS

Hughes TP et al. *Proc ASH* 2010;Abstract 207.

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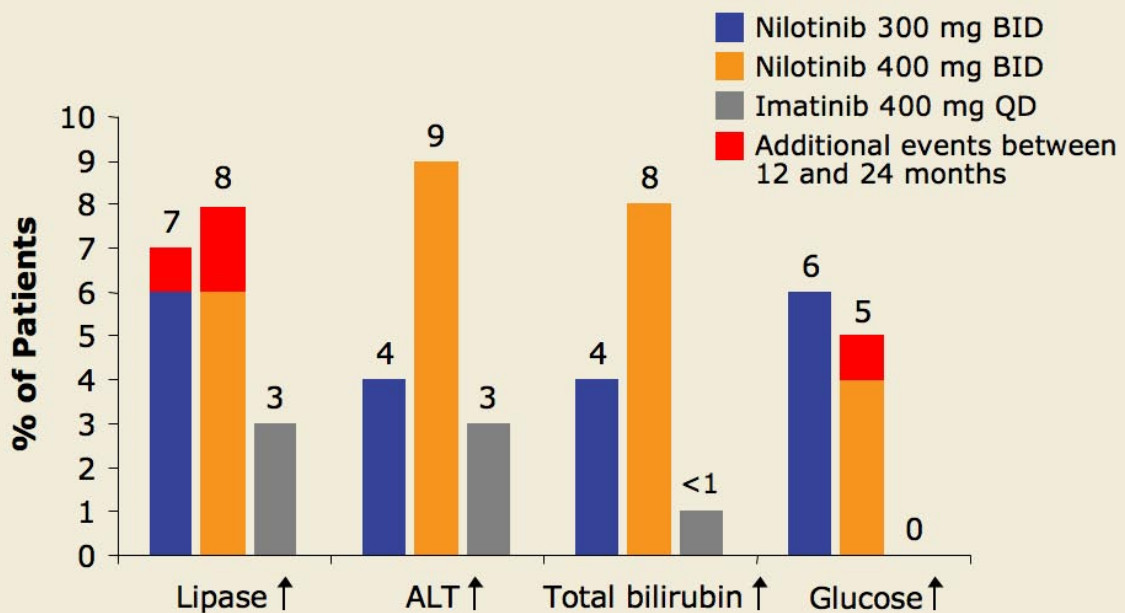
## Selected Grade 3 and 4 Biochemical Abnormalities



Hughes TP et al. *Proc ASH 2010*;Abstract 207.

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## Selected Grade 3 and 4 Biochemical Abnormalities



Hughes TP et al. *Proc ASH 2010*;Abstract 207.

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## Author Conclusions

- With longer follow-up, nilotinib continues to demonstrate superior efficacy compared to imatinib.
  - Higher rates of MMR and CCyR
  - Lower rates of transformation to accelerated/blast phase
- Nilotinib resulted in fewer CML-related deaths compared to imatinib.
- Longer follow-up does not show any change in the adverse-event profile of nilotinib.
- Taken together, these data support nilotinib as a new standard of care for patients with newly diagnosed chronic phase CML.

Hughes TP et al. *Proc ASH 2010*;Abstract 207.

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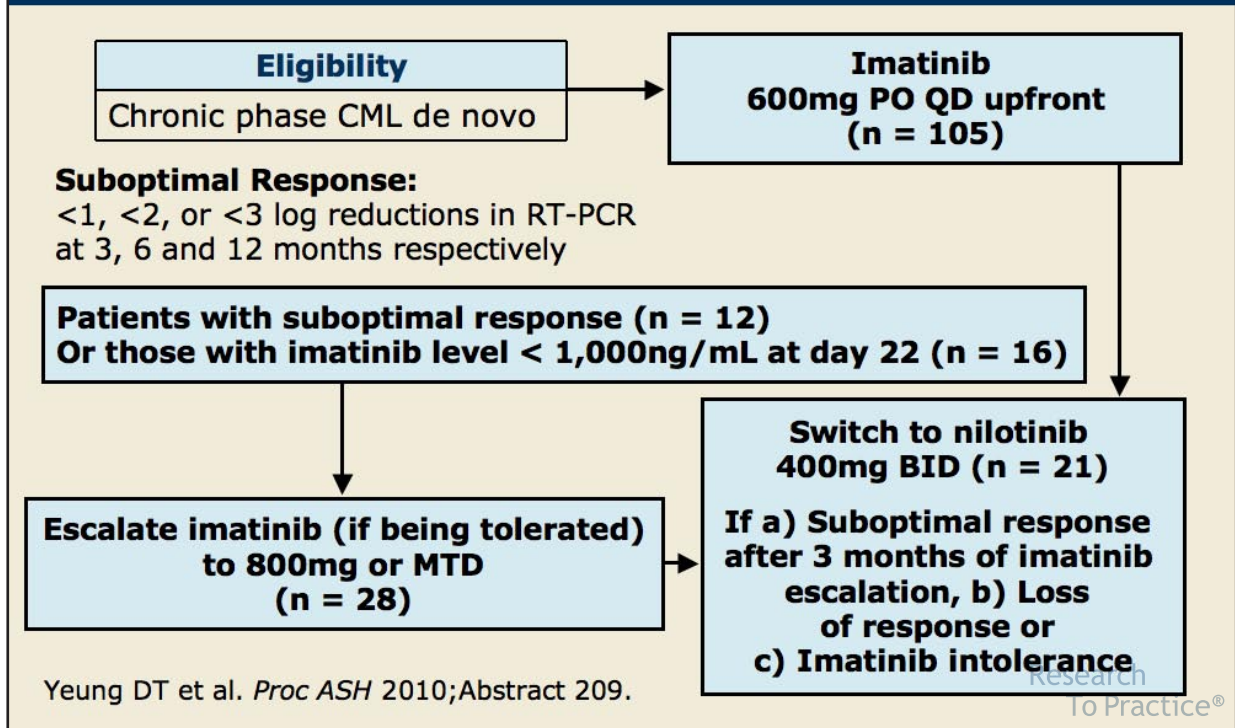
## Selective Escalation of Imatinib Therapy and Early Switching to Nilotinib in De Novo Chronic Phase CML Patients: Interim Results from the TIDEL-II Trial (Abstract Only)

**Yeung DT et al.**

*Proc ASH 2010*;Abstract 209.

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# TIDEL-II Trial Design



## Treatment Outcome (from Abstract)

**N = 105, median follow-up 18.9 months**

<b>Response at 12 months in patients with a minimum of 12 months of follow-up (n = 80/105*)</b>	
Complete cytogenetic response (CCyR)	92%
Major molecular response (MMR: $\geq 3$ -log reductions at 12 months)	66%
Complete molecular response	11%
<b>Efficacy endpoints in patients who switched to nilotinib (n = 21)</b>	
Achieved or maintained CCyR (20/21)	95%
MMR <sup>†</sup> (10/19 not in MMR prior to switch)	53%
Imatinib intolerant (9/12)	75%
Suboptimal imatinib responders (1/7)	14%

\* Includes all patients regardless of imatinib dose or switch to nilotinib

† MMR evaluated at median follow-up 295 days after switch

Yeung DT et al. *Proc ASH 2010*;Abstract 209.

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## Author Conclusions

- A strategy of selective intensification of BCR-ABL inhibitor therapy (either imatinib dose escalation or switch to second-generation TKI) based on molecular response and PK values resulted in a 66% MMR rate and 92% CCyR rate by 12 months.
- Only a minority (20%) of patients required a switch to nilotinib.
  - Patients experiencing imatinib intolerance (n = 14) demonstrated excellent response rates after switching to nilotinib.

Yeung DT et al. *Proc ASH 2010*;Abstract 209.

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### Investigator comment on the ENESTnd trial in CML

Just like the dasatinib front-line trial, the update of the nilotinib ENESTnd trial by Hughes shows the second-generation TKIs to be more effective front-line treatments than imatinib. The 24-month follow-up presentation from the ENESTnd trial, comparing nilotinib to imatinib as first-line therapy for CML, talks about the best MMR and CCyR. The 24-month CCyR, and not MMR, is a validated endpoint in predicting longer-term outcomes.

I believe what is probably more compelling is the difference in transformation. Even though the numbers are low, the rate of progression to accelerated or blast phase was significantly lower in patients treated with nilotinib, and that is a clinically relevant endpoint. If a patient experiences disease transformation, then they would generally have a poorer survival. The overall trend is definitely in favor of nilotinib.

***Interview with Susan M O'Brien, MD, January 4, 2011***

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