



POST-ASH Issue 2, 2014

ENESTnd Update: Nilotinib versus Imatinib in Newly Diagnosed CML-CP

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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 the management of chronic myeloid leukemia (CML) 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

- Evaluate the impact of early molecular response or dose interruption of tyrosine kinase inhibitors (TKIs) on the prognosis of patients with CML.
- Compare and contrast the benefits and risks of nilotinib versus imatinib therapy in patients with newly diagnosed chronic-phase CML.
- Appraise recent clinical data on the effect of switching to nilotinib in patients with a suboptimal response to imatinib therapy versus continuation of imatinib at a higher dose.
- Analyze the outcomes of the STIM1 and STIM2 studies of discontinuation of imatinib in patients with a deep molecular response, and consider these results in the management of CML.
- Assess the efficacy and safety of ponatinib as initial therapy and in patients with TKI-resistant CML.

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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:

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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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No real or apparent conflicts of interest to disclose.

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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: February 2014

Expiration date: February 2015

To go directly to slides and commentary for this issue, [click here](#).

Sometimes I have to pinch myself to see if this is a dream or if I really have a job listening to and learning from the great minds in our chosen field. Last week was a perfect reminder of just how cool “work” can be when within the space of a few days my calendar included extensive interviews with Drs Jorge Cortes and then Hagop Kantarjian. As deputy chair and chair of MD Anderson’s Department of Leukemia, respectively, these 2 investigators lead a unique clinical and research powerhouse that has contributed perhaps as much to the care of patients with these and other related hematologic disorders as any other institution in the world.



Jorge E Cortes, MD

To get a sense of just how prolific they are, peruse the 2013 ASH abstracts and you will find that Drs Cortes and Kantarjian helped author 103 oral presentations and posters, including 30 on chronic myelogenous leukemia (CML) alone. As such, and not surprisingly, each of these conversations focused heavily on that disease — which has become the poster child for targeted oncologic treatment — and below find the bottom line on their thoughts about how the data sets from New Orleans helped address the following important questions in CML.



Hagop M Kantarjian, MD

1. What are the key early markers of response, and when should consideration be given to switching to another tyrosine kinase inhibitor (TKI)?

Another MD Anderson leukemia maven and chair of the NCCN CML guidelines committee, Dr Susan O’Brien frequently reinforces the important concept that although there are many reasons to seek deep molecular responses (DMR), the classic and most important endpoint is complete cytogenetic response (CCyR) — a milestone that is achieved faster and more frequently with the second-generation agents, nilotinib and dasatinib. The question of whether suboptimal molecular response should trigger a switch to another TKI ties directly into the issue of selection of up-front therapy and whether long-term outcomes are compromised when residual disease is present.

Equally relevant and looming in the background is a fascinating question of “quality” and cost associated with oncology care. Specifically, imatinib is due to go off patent in January 2015, and it is expected that this will dramatically lower the annual tab (about \$90,000 with imatinib, and with nilotinib and dasatinib closer to \$100,000). With a current prevalence of about 100,000 CML cases in the United States alone — a number that will likely double in the next 3 decades before plateauing — researchers, clinicians and policy makers will almost certainly continue the debate about the value of starting with imatinib (the soon-to-be less costly and perhaps slightly less effective agent) and reserving second-generation treatment for patients with higher-risk disease and those with suboptimal initial responses to imatinib. How these potential resource savings stack up against others in oncology related to, for example, futile care and unnecessary imaging will be discussed extensively, and more globally Dr Kantarjian has taken a leadership role in organizing a group of “CML experts” (including Dr Cortes) who have been on a dedicated and major offensive attacking the current CML cost structure.

At ASH we witnessed a number of related papers that tie in to the issue of imatinib versus the rest, including the **36-month update** of the ENESTcmr study. This landmark Phase III effort demonstrated that among patients in CCyR but with detectable BCR-ABL transcripts, those randomly assigned to switch to nilotinib achieved more DMRs compared to those continuing on imatinib (47% with nilotinib versus 33% with imatinib at 36 months). This benefit came with greater toxicity, which may in part be attributable to the trial design in that patients who transitioned to nilotinib were already tolerating imatinib well.

On a similar note, an ASH data set presented by Dr Cortes from the Phase III **LASOR trial** revealed that switching to nilotinib versus escalating the dose of imatinib in patients who experienced suboptimal response resulted in a better rate of CCyR at 6 months (49% versus 42%, respectively), although the findings were not statistically significant ($p = 0.3844$).

Finally, a **retrospective analysis** of 3- and 6-month responses in early trials of imatinib demonstrated that some patients who achieve an optimal response by 6 instead of 3 months have long-term outcomes comparable to those who achieved an optimal response at 3 months, suggesting that waiting a few additional months before considering a change in treatment is a rational approach.

Proponents of using imatinib as initial treatment in standard-risk situations often point out that so far, no survival benefit has been demonstrated using the second-generation agents — possibly because these drugs also effectively rescue patients experiencing disease progression on imatinib. Thus, although DMR is an intuitively appealing goal, until further research identifies more accurately who can cease TKI treatment (now there’s a cost saving!), there will be debate and controversy about what to start with and when and if to make a switch. This is particularly true as more follow-up occurs

with the landmark second-generation trials, some of which are documenting more long-term complications, such as the 5-year update of the [ENESTnd trial](#) presented at ASH that now shows not only deeper molecular responses with nilotinib but also an increasing number of cardiovascular events.

2. Are there situations in which it is safe to discontinue TKI treatment?

At ASH we saw more data from [2 French studies](#) (STIM 1 and 2) attempting to define the outcomes of patients with prolonged (more than 2 years) DMRs who discontinued treatment. These studies and others have documented that when taken off therapy more than half the patients experience relapse — usually quickly — and the remainder fare well off treatment. Importantly, although most patients experiencing relapse can be effectively salvaged with the same or a different TKI, at this point there is no way to pick who will do well without treatment and therefore neither professor employs this approach outside a trial setting, although Dr Kantarjian notes that if ongoing research shows how to identify these patients, both long-term toxicity and financial costs can be avoided.

Interestingly, Dr Cortes commented on one situation in which a variation of this stopping strategy is often a consideration — specifically, in women with CML who wish to become pregnant — and so far he has managed about 2 dozen carefully selected patients, most of whom have not required retreatment until after childbirth.

Another fascinating and somewhat [related ASH report](#) documented that in a major Phase III trial of dasatinib versus imatinib patients starting treatment who missed doses due to toxicities like cytopenias had significantly worse 3-month outcomes. Importantly, this effect appears to occur when missing even 1 dose (in the case of imatinib) and increases with the number of doses missed.

3. What is the current role of ponatinib?

In December 2012 this pan-BCR-ABL “super TKI” was approved by the FDA, but last October it was pulled off the market due to toxicity concerns, mainly arteriothrombotic events. By December ponatinib was once again available, accompanied by a new black box warning and a Risk Evaluation and Mitigation Strategy program designed to help clinicians more effectively evaluate the risks and benefits of using the agent.

In discussing ponatinib, Dr Kantarjian noted that the approved daily dose of 45 mg not uncommonly leads to toxicities such as hypertension, vasospastic reactions, pancreatitis and skin rashes that are not acceptable in the up-front setting, where safer effective choices exist. In this regard an MD Anderson single-arm [pilot study](#) of 51 patients presented at ASH was amended to include a starting dose of 30 mg daily. Regardless, accrual was suspended in October, as in another major Phase III up-front study comparing ponatinib to imatinib.

However, in discussing the updated ASH results from the pivotal **[PACE trial](#)** in relapsed disease, Dr Kantarjian reiterated that ponatinib, when used in that indicated setting, can be a life-altering therapy, particularly for those with BCR-ABL T315I mutations. He also pointed out that the vaso-occlusive reactions that have been observed with this drug occur infrequently with the other TKIs.

Next on this series, we provide an update on ASH reports in lymphoma, including encouraging data sets on the nonchemotherapy combination of lenalidomide and rituximab, the antibody-drug conjugate brentuximab vedotin and a fascinating paper on crizotinib in ALK-positive lymphoma.

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ENESTnd Update: Nilotinib versus Imatinib in Newly Diagnosed CML-CP

Presentation discussed in this issue

Saglio G et al. **ENESTnd update: Nilotinib (NIL) vs imatinib (IM) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) and the impact of early molecular response (EMR) and Sokal risk at diagnosis on long-term outcomes.** *Proc ASH 2013*; **Abstract 92.**

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Jorge E Cortes, MD (1/24/14)

ENESTnd Update: Nilotinib (NIL) vs Imatinib (IM) in Patients (pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) and the Impact of Early Molecular Response (EMR) and Sokal Risk at Diagnosis on Long- Term Outcomes

Saglio G et al.

Proc ASH 2013; Abstract 92.

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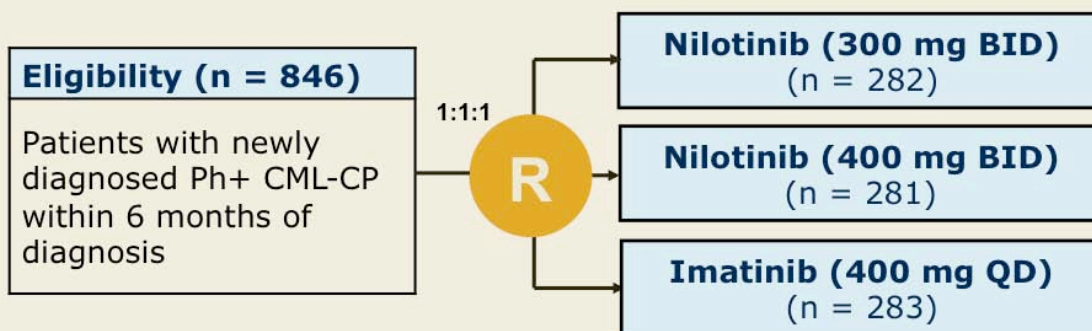
Background

- Previously, the ENESTnd trial for patients with Philadelphia chromosome-positive (Ph+) CML-CP demonstrated that front-line nilotinib (NIL) continues to show benefit over imatinib (IM) (*Lancet Oncol* 2011;12(9):841):
 - Higher rates of major molecular response (MMR): BCR-ABL on the International Scale (BCR-ABL^{IS}) $\leq 0.1\%$
 - Higher rates of deep molecular response (MR^{4.5}): BCR-ABL^{IS} $\leq 0.0032\%$
 - Lower rates of progression to accelerated phase (AP)/blast crisis (BC)
- **Study objective:** To report updated results from the ENESTnd trial for patients with newly diagnosed CML-CP after a long-term follow-up of 4 years based on a 5-year follow-up study.

Saglio G et al. *Proc ASH* 2013;Abstract 92.

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Phase III ENESTnd Trial Design



- **Primary endpoint:** MMR at 12 months, defined as BCR-ABL^{IS} $\leq 0.1\%$ by quantitative real-time PCR in peripheral blood
- Disease progression and overall survival (OS) events were collected prospectively during follow-up, including after discontinuation of study treatment.
- Efficacy in the NIL at 300 mg BID and IM arms was evaluated based on achievement of EMR (BCR-ABL^{IS} $\leq 10\%$ at 3 months).

Saglio G et al. *Proc ASH* 2013;Abstract 92.

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Patient Outcomes at 5 Years

	NIL 300 mg (n = 282)	NIL 400 mg (n = 281)	IM 400 mg (n = 283)
Still on study	86%	88%	83%
Still on core treatment	62%	65%	51%
Response at 5 y (p-value versus IM)			
MMR	77% (<0.0001)	77% (<0.0001)	60%
MR ^{4.5}	54% (<0.0001)	52% (<0.0001)	31%
5-y freedom from progression to AP/BC (p-value versus IM)			
On core treatment	99.3% (0.0059)	98.9% (0.0185)	95.8%
On study	96.5% (0.0588)	97.9% (0.0047)	92.9%
5-y OS (p-value versus IM)			
On study	93.6% (0.58)	96.0% (0.04)	91.6%

Saglio G et al. *Proc ASH* 2013;Abstract 92.

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Landmark Efficacy Analysis by BCR-ABL Levels at 3 Months: NIL (300 mg BID) vs IM (400 mg QD)

Outcome	NIL (300 mg BID) (n = 258)*		IM (400 mg QD) (n = 264)*	
	≤10%	>10%	≤10%	>10%
No. of patients	91%	9%	67%	33%
5-year PFS	95%	78%	97%	80%
p-value	0.001		<0.0001	
5-year OS	97%	82%	97%	80%
p-value	0.0007		<0.0001	

PFS = progression-free survival

* Patients with evaluable BCR-ABL at 3 months

Saglio G et al. *Proc ASH* 2013;Abstract 92.

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Landmark Analysis of Rates of BCR-ABL^{IS} ≤10% at 3 Months by Sokal Risk Score

Outcome	BCR-ABL ≤10% at 3 months	
	NIL 300 mg	IM 400 mg
Sokal risk score		
Low (n = 97, 102)	93%	79%
Intermediate (n = 91, 92)	92%	70%
High (n = 70, 70)	86%	44%

Saglio G et al. *Proc ASH 2013*;Abstract 92.

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Proportion of Patients with MR^{4.5} by BCR-ABL Levels at 3 Months

BCR-ABL at 3 mo	Patients with MR ^{4.5}	
	NIL 300 mg BID	IM 400 mg QD
≤1% (n = 144, 43)	56%	16%
>1% to ≤10% (n = 89, 133)	35%	50%
>10% (n = 24, 88)	9%	33%

Saglio G et al. *Proc ASH 2013*;Abstract 92.

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Summary of Efficacy Results

- Patients with EMR failure (BCR-ABL >10% at 3 months) have significantly worse 5-year PFS and OS:
 - Rates of EMR failure are lower with NIL 300 mg BID than with IM.
- Rates of BCR-ABL^{IS} ≤10% at 3 months were improved with NIL regardless of Sokal risk score:
 - IM 400 mg QD = 67%
 - NIL 300 mg BID = 91%
- Patients with BCR-ABL ≤1% at 3 months have significantly higher rates of MR^{4.5} by 5 years in the NIL 300 mg BID arm than in the IM arm (56% vs 16%):
 - Patients with EMR had significantly higher rates of PFS and OS at 5 y than those with BCR-ABL >10% at 3 months.

Saglio G et al. *Proc ASH* 2013;Abstract 92.

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Summary of Efficacy Results (Continued)

- In patients with intermediate or high Sokal risk scores, PFS and OS at 5 years were higher in both NIL arms than in the IM arm (data not shown).

Saglio G et al. *Proc ASH* 2013;Abstract 92.

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Select Adverse Events (AEs) by 5 Years (All Cause, All Grades)

By year 5, n (%)	NIL 300 mg (n = 279)	NIL 400 mg (n = 277)	IM 400 mg (n = 280)
Peripheral arterial disease (PAD)	4 (1.4%)	6 (2.1%)	0 (0%)
Ischemic heart disease (IHD)	11 (3.9%)	21 (7.6%)	5 (1.8%)
Ischemic cerebrovascular event (ICVE)	4 (1.4%)	8 (2.9%)	1 (0.4%)

- Due to the discontinuation rate, more patients were exposed to NIL than IM.
- Approximately 85% of patients with a cardiovascular event had at least 1 risk factor and were suboptimally treated.
- Events reported in year 5 included 9 new cases of IHD (IM n = 2; NIL 400 mg BID, n = 7), 4 new ICVEs (NIL 300 mg BID, n = 1; NIL 400 mg BID, n = 3) and 1 new PAD event (NIL 400 mg BID).

Saglio G et al. *Proc ASH* 2013;Abstract 92.

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Author Conclusions

- NIL demonstrated higher rates of early molecular response and deeper molecular response, including MR^{4.5}, and a reduced risk of progression.
- By 5 years, more than half of patients who received NIL had achieved MR^{4.5}, a key eligibility criterion for many treatment-free remission studies.
- More cardiovascular events were reported in both NIL arms than in the IM arm, but they occurred most frequently in the NIL 400 mg BID arm.
- At 5 years of follow-up, there is a trend toward higher event-free and progression-free survival in patients who received NIL than in those who received IM.
- These long-term data confirm NIL 300 mg BID as a standard treatment for patients with newly diagnosed CML-CP.
- NIL continues to show good tolerability with long-term follow-up.
- Although selected cardiac and vascular events (including PAD) are slightly more frequent with NIL than with IM, no increase in annual incidence of these events over time has been observed.

Saglio G et al. *Proc ASH* 2013;Abstract 92.

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Updated Results of the Phase III ENESTnd Trial for Patients with Newly Diagnosed Ph+ CML-CP

These data show the long-term follow-up results of the ENESTnd trial, and nilotinib continues to show improvement in the overall clinical outcome. An important point is that, to date, we have seen little, if any, difference in event-free survival and overall survival. The investigators now have results from 5 years of follow-up. Perhaps with more time we will start seeing a bit of an improvement in survival. However, that's not significant at this point. The benefit of nilotinib is mostly in terms of the deeper responses observed. From the early days of this trial, we learned that nilotinib elicited a decreased rate of transformation to accelerated and blast phase. Essentially, those results are holding up.

An interesting observation is that more patients appear to develop cardiovascular toxicities, ischemic heart disease, peripheral arterial occlusive disease and cerebrovascular events with nilotinib than with imatinib and to a lesser extent with dasatinib than with imatinib. We are learning that we will see these adverse events with the use of these drugs. We need to be mindful of these adverse events so that we can monitor our patients well.

Interview with Jorge E Cortes, MD, January 24, 2014