



*Key ASH Presentations*  
Issue 8, 2012

# **Efficacy of Nilotinib in CML-CP: Results from the ENEST Studies**

## 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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This activity is supported by educational grants from Allos Therapeutics, Celgene Corporation, Genentech BioOncology/ Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

Last review date: April 2012  
Expiration date: April 2013

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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This activity is supported by educational grants from Allos Therapeutics, Celgene Corporation, Genentech BioOncology/Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

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# Efficacy of Nilotinib in CML-CP: Results from the ENEST Studies

## Presentations discussed in this issue

Saglio G et al. **Nilotinib versus imatinib in patients (pts) with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd 36-month (mo) follow-up.** *Proc ASH 2011*; [Abstract 452](#).

Hughes TP et al. **Complete molecular response (CMR) rate with nilotinib in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) without CMR after  $\geq 2$  years on imatinib: Preliminary results from the randomized ENESTcmr trial of nilotinib 400 mg twice daily (bid) vs imatinib.** *Proc ASH 2011*; [Abstract 606](#).

Hochhaus A et al. **Results from the ENESTnd extension study: Efficacy and safety of patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP), treated with nilotinib 400 mg twice daily (bid) after suboptimal response (SoR) or treatment failure (TF) to imatinib 400 mg once daily (qd) or nilotinib 300 mg bid.** *Proc ASH 2011*; [Abstract 114](#).

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

**Nilotinib versus Imatinib in Patients (pts) with Newly Diagnosed Philadelphia Chromosome-Positive (Ph+) Chronic Myeloid Leukemia in Chronic Phase (CML-CP): ENESTnd 36-Month (mo) Follow-Up<sup>1</sup>**

**Complete Molecular Response (CMR) Rate with Nilotinib in Patients (pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) without CMR After  $\geq 2$  Years on Imatinib: Preliminary Results from the Randomized ENESTcmr Trial of Nilotinib 400 Mg Twice Daily (BID) vs Imatinib<sup>2</sup>**

**Results From the ENESTnd Extension Study: Efficacy and Safety of Patients (pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP), Treated with Nilotinib 400 Mg Twice Daily (BID) After Suboptimal Response (SoR) or Treatment Failure (TF) to Imatinib 400 Mg Once Daily (QD) or Nilotinib 300 Mg BID<sup>3</sup>**

**<sup>1</sup>Saglio G et al.**

*Proc ASH 2011*;Abstract 452.

**<sup>2</sup>Hughes TP et al.**

*Proc ASH 2011*;Abstract 606.

**<sup>3</sup>Hochhaus A et al.**

*Proc ASH 2011*;Abstract 114.

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# Nilotinib versus Imatinib in Patients (pts) with Newly Diagnosed Philadelphia Chromosome-Positive (Ph+) Chronic Myeloid Leukemia in Chronic Phase (CML-CP): ENESTnd 36-Month (mo) Follow-Up

**Saglio G et al.**

*Proc ASH 2011;Abstract 452.*

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## Background

- At a 2-year minimum follow up, the Phase III ENESTnd trial demonstrated that nilotinib is more effective than imatinib and is well tolerated in patients with newly diagnosed CML (*Lancet Oncol* 2011;12:841).
- However, historical data from the IRIS trial showed that most events of disease progression with imatinib occurred within the first 3 years of treatment (*Leukemia* 2009;23:1054).
- **Objective:**
  - Report on a 3-year minimum follow-up of ENESTnd to verify the benefits of nilotinib in patients with newly diagnosed CML.

Saglio G et al. *Proc ASH 2011;Abstract 452.*

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# ENESTnd Trial Design

## Eligibility (n = 846)

≤6 months after diagnosis of chronic-phase Ph+ CML

Diagnosis by conventional cytogenetic bone marrow analysis with ≥1 Ph+ metaphase cell

Adequate organ function

ECOG performance ≥2



Nilotinib (n = 282)  
300 mg BID

Nilotinib (n = 281)  
400 mg BID

Imatinib (n = 283)  
400 mg QD

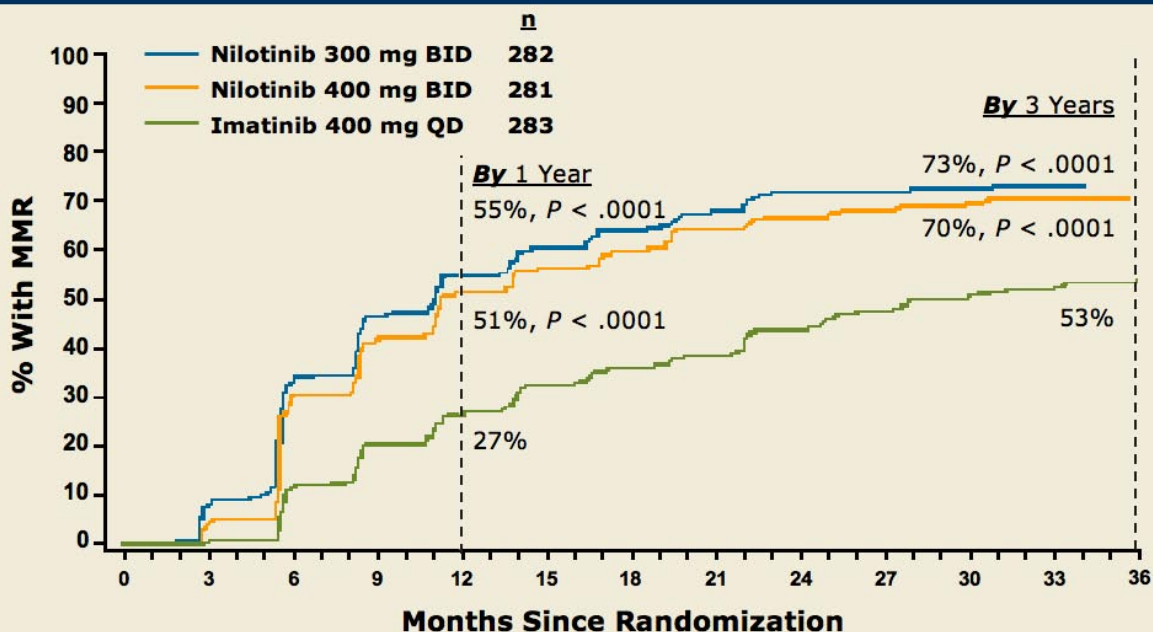
Randomization was stratified by Sokal risk score

- Efficacy analysis based on the intent-to-treat population included all patients.
- Response assessments were performed during study treatment.
- Time to progression to accelerated-phase (AP)/blast crisis (BC) and overall survival (OS) were evaluated during follow-up every 3 months and after treatment discontinuation.

Saglio G et al. *Proc ASH* 2011;Abstract 452.

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# Cumulative Incidence of Major Molecular Response (MMR)

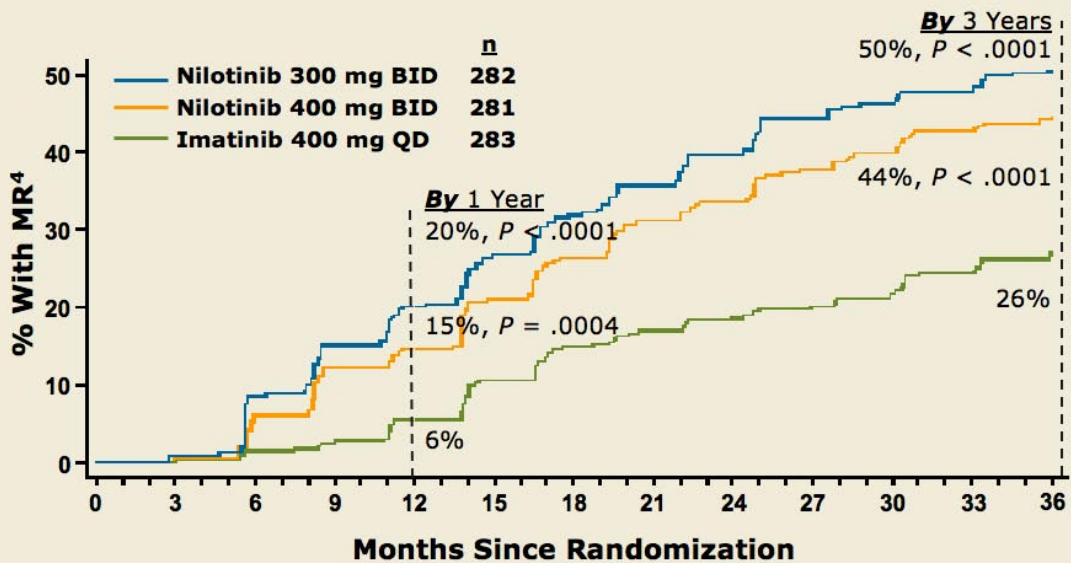


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# Cumulative Incidence of Deeper Molecular Response (MR<sup>4</sup>\*)

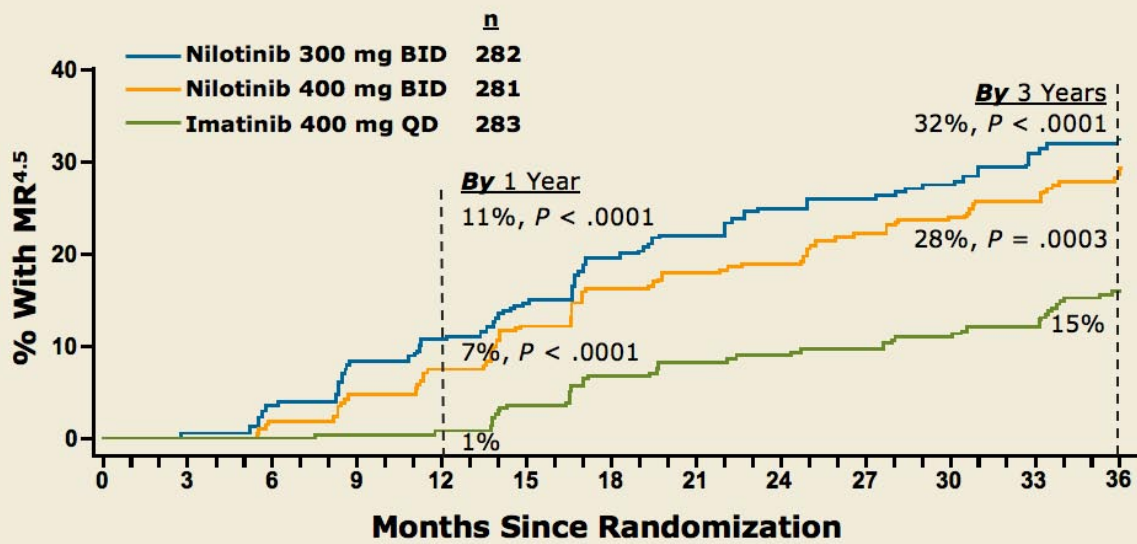


\* Equivalent to BCR-ABL<sup>IS</sup> transcript levels of ≤0.01%

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# Cumulative Incidence of Deeper Molecular Response (MR<sup>4.5</sup>\*)

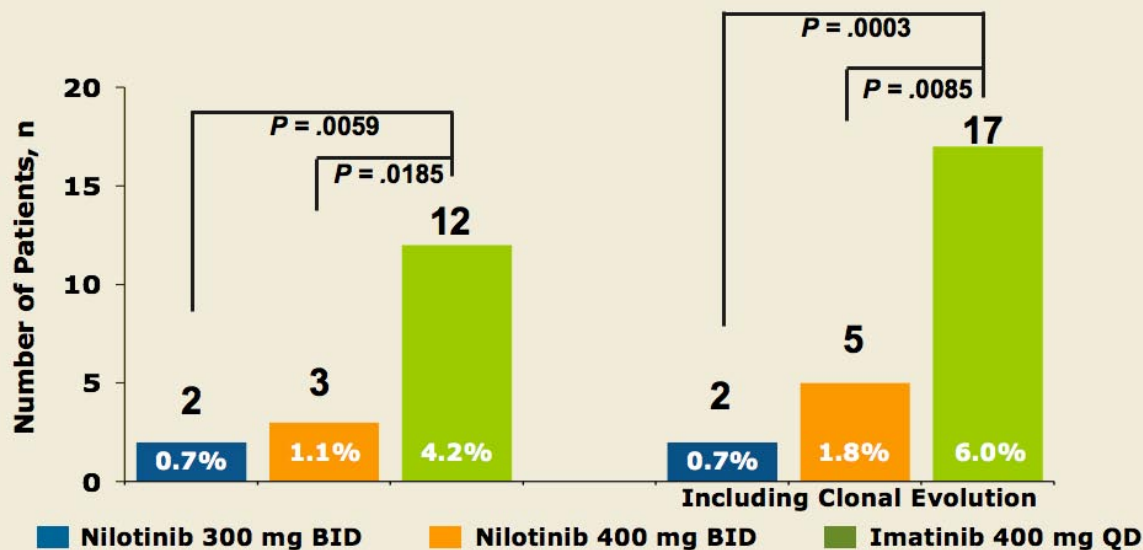


\* Equivalent to BCR-ABL<sup>IS</sup> transcript levels of ≤0.0032%

Saglio G et al. *Proc ASH* 2011;Abstract 452.

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## Progression to AP/BC\* on Core Treatment



\* Progression to AP/BC or death following progression

• No new progressions occurred on core treatment since 2-year analysis.

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## Survival Outcomes

	Nilotinib 300 mg BID	Nilotinib 400 mg BID	Imatinib 400 mg QD
Estimated 3-y OS	95.1%	97.0%	94.0%
Hazard ratio (95% CI)	0.8 (0.4-1.6)	0.5 (0.2-1.1)	—
p-value	0.4413	0.0639	—

• There were 38 deaths in total: nilotinib 300 mg (13), nilotinib 400 mg (8), imatinib 400 mg (17).

• Out of the total deaths, 23 occurred following progression to AP/BC: Nilotinib 300 mg (5), nilotinib 400 mg (4), imatinib 400 mg (14).

Saglio G et al. *Proc ASH* 2011;Abstract 452.

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## Author Conclusions

- Follow-up for 3 years confirmed the superiority of nilotinib over imatinib in the treatment of newly diagnosed CML-CP.
- Nilotinib demonstrated an acceptable tolerability profile in patients with newly diagnosed CML-CP (data not shown).
- Nilotinib continues to demonstrate:
  - Significantly higher and faster rates of MMR, MR<sup>4</sup> and MR<sup>4.5</sup>.
  - Significantly higher responses across all Sokal risk groups (data not shown).
  - Significantly decreased risk of progression to AP/BC and death following progression.

Saglio G et al. *Proc ASH 2011*;Abstract 452.

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## Complete Molecular Response (CMR) Rate with Nilotinib in Patients (pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) without CMR After $\geq 2$ Years on Imatinib: Preliminary Results from the Randomized ENESTcmr Trial of Nilotinib 400 Mg Twice Daily (BID) vs Imatinib

**Hughes TP et al.**

*Proc ASH 2011*;Abstract 606.

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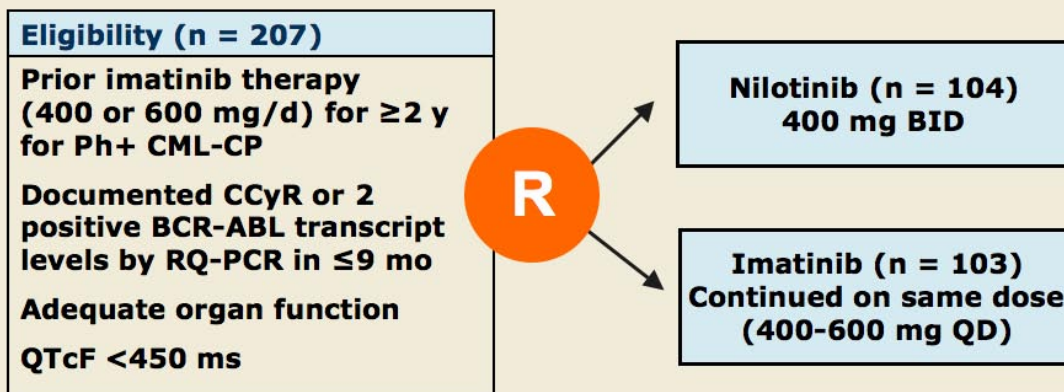
# Background

- Previous studies showed that 40% of patients with CML-CP who achieved durable CMR after treatment with imatinib were able to cease therapy without recurrence (*Lancet Oncol* 2010;11:1029).
- A large portion of patients (55%) with CML do not achieve CMR on imatinib, even with long-term therapy (>6 y) (*Clin Cancer Res* 2007;13:7080).
- In the ENESTnd trial, the number of patients who achieved MMR, MR<sup>4</sup> and MR<sup>4.5</sup> was significantly higher with nilotinib therapy than with imatinib (*Lancet Oncol* 2011;12:841).
- **Objective:**
  - Determine whether patients with CML-CP on long-term imatinib would be more likely to achieve undetectable BCR-ABL levels if therapy were switched to nilotinib.

Hughes TP et al. *Proc ASH* 2011;Abstract 606.

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# Study Design



CCyR, complete cytogenetic response

### Primary endpoint

- Confirmed CMR (undetectable BCR-ABL [with  $\geq 4.5$ -log assay sensitivity]) by 12 months

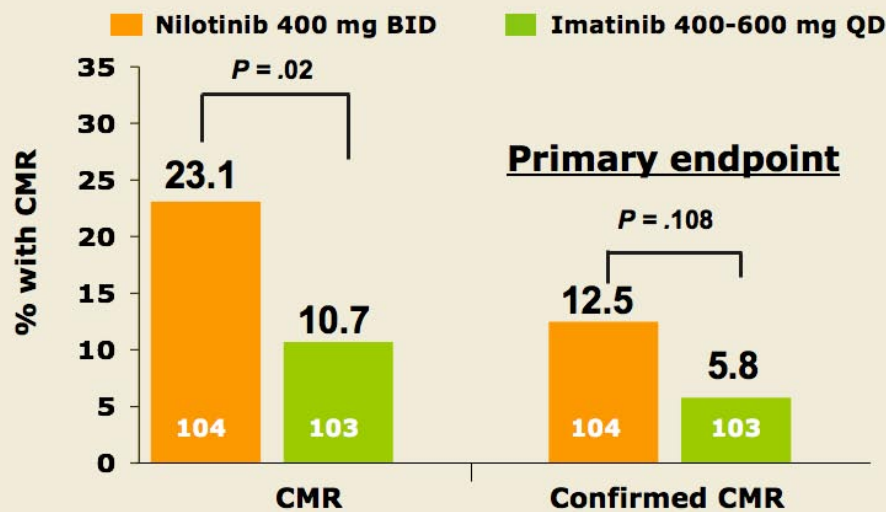
### Secondary endpoints

- Kinetics of molecular response (RQ-PCR for primary and secondary endpoints were performed every 3 months)
- Safety profile

Hughes TP et al. *Proc ASH* 2011;Abstract 606.

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# Primary Endpoint in the Intention-to-Treat Population

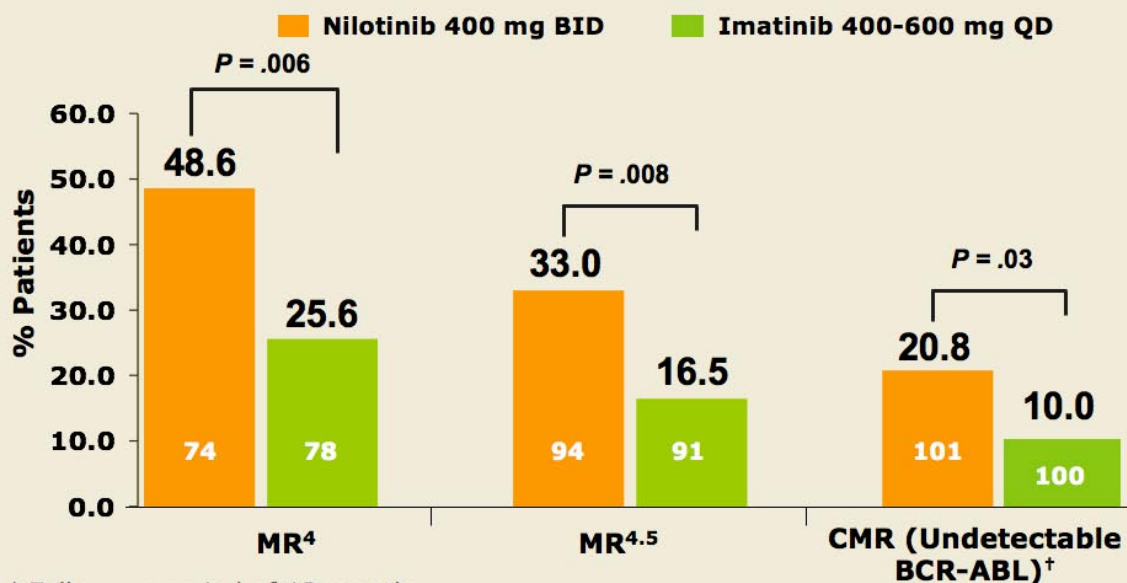


- The intention-to-treat population included all patients randomized to the study.
- At 12 months, 14.9% of patients on nilotinib vs 6.1% on imatinib achieved confirmed CMR ( $p = 0.04$ ).

With permission from Hughes TP et al. *Proc ASH 2011*;Abstract 606.

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# Molecular Response\* in Patients without Indicated Response at Baseline



\* Follow-up period of 12 months

† With  $\geq 4.5$ -log assay sensitivity

With permission from Hughes TP et al. *Proc ASH 2011*;Abstract 606.

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## Drug-Related Adverse Events (AEs)

Event	Nilotinib (n = 104)	Imatinib (n = 103)
Any AE	88%	53%
Grade 3/4 AEs	29%	2%
AEs leading to discontinuation	9%	0%
Serious AEs	4%	0%

- Patients experienced AEs early on nilotinib after switch from long-term imatinib therapy.
- However, these AEs were expected and consistent with the safety profile of nilotinib observed in other studies.

Hughes TP et al. *Proc ASH* 2011;Abstract 606.

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## Author Conclusions

- For patients with ongoing BCR-ABL-positivity on imatinib therapy, switching to nilotinib leads to faster and deeper molecular responses.
- Deeper molecular responses on nilotinib therapy may increase the eligibility of patients for future TKI discontinuation studies.
- The ultimate success of this strategy will be assessed in the prospective ENESTop discontinuation study.

Hughes TP et al. *Proc ASH* 2011;Abstract 606.

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## **Investigator Commentary:**

### **Nilotinib versus Imatinib in Patients with Newly Diagnosed Ph+ CML-CP: 36-Month ENESTnd Follow-Up<sup>1</sup>**

### **CMR Rate with Nilotinib in Patients with CML-CP without CMR After $\geq 2$ y on Imatinib: Preliminary Results from ENESTcmr Trial<sup>2</sup>**

Nilotinib was approved as front-line therapy for patients with chronic myeloid leukemia in chronic phase. These reports confirmed the long-term efficacy and safety of nilotinib versus imatinib. In particular, these studies confirmed that nilotinib therapy results in lower rates of disease progression and treatment discontinuation in comparison to imatinib. These 2 reports demonstrate the utility and choice of nilotinib as first-line therapy for patients with CML-CP.

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

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## **Results from the ENESTnd Extension Study: Efficacy and Safety of Patients (pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP), Treated with Nilotinib 400 Mg Twice Daily (BID) After Suboptimal Response (SoR) or Treatment Failure (TF) to Imatinib 400 Mg Once Daily (QD) or Nilotinib 300 Mg BID**

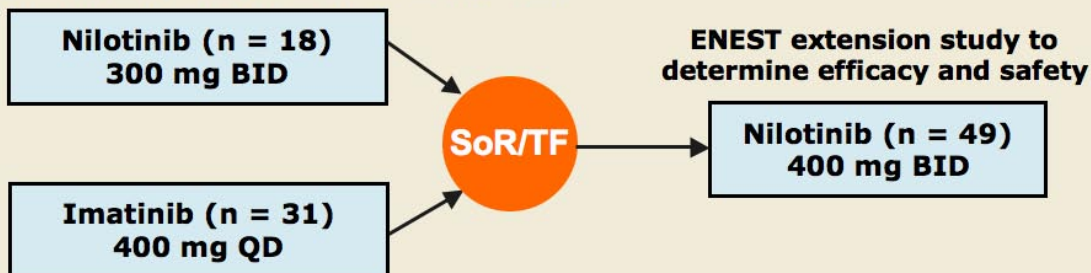
**Hochhaus A et al.**

*Proc ASH 2011;Abstract 114.*

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# Study Design

Patients initially assigned on ENESTnd trial



SOR/TF, suboptimal response/treatment failure

TF: no CyR at 6 months; <partial CyR (PCyR) at 12 months; <CCyR at 18 months; loss of confirmed complete hematologic response, PCyR, CCyR, progression to AP/BC or clonal evolution at any time

SoR: <PCyR at 6 months; <CCyR at 12 months; <MMR at 18 months

- Entrance into the extension study was not allowed for intolerance.

Hochhaus A et al. *Proc ASH* 2011;Abstract 114.

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## Reason for Patient Entry Into ENEST Extension Study (Abstract Only)

Reason	Initially assigned to ENESTnd nilotinib (n = 18)	Initially assigned to ENESTnd imatinib* (n = 31)
TF	17%	68%
SoR	78%	26%
Other <sup>†</sup>	6%	6%

\* Patients (n = 20) escalated to 400 mg/d of imatinib before extension study entry.

<sup>†</sup> Entry into extension study per investigator assessment without satisfying SOR/TF criteria

Hochhaus A et al. *Proc ASH* 2011;Abstract 114.

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## Extension Treatment Outcomes (Abstract Only)

Outcomes	Nilotinib (n, %)
Response during extension	
Response prior to entry: <CCyR (n = 6)	1 (17%)
Response prior to entry: <MMR (n = 17)	5 (29%)
Progression to AP/BC	1 (6%)
≤1 month after discontinuation	1 (6%)
Outcome achieved during ENEST extension	Imatinib (n, %)
Response during extension	
Response prior to entry: <CCyR (n = 26)	12 (46%)
Response prior entry: <MMR (n = 30)	7 (23%)
Progression to AP/BC	13%
During extension study	7%
≤1 month after discontinuation	3%
>12 months after discontinuation	3%

Hochhaus A et al. *Proc ASH* 2011;Abstract 114.

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## Adverse Events (AEs) (Abstract Only)

Event	Nilotinib (n = 18)	Imatinib (n = 31)
Grade 3/4 AEs	28%	52%
Drug-related AEs leading to discontinuation	0%	10%
Deaths*		
During extension treatment or ≤28 d of discontinuation	0%	0%

\* Deaths (n = 4) occurred >28 days after treatment discontinuation: 3 were CML related (1 and 2 for nilotinib and imatinib, respectively) and occurred 8-10 months after discontinuation

Hochhaus A et al. *Proc ASH* 2011;Abstract 114.

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## Author Conclusions

- These data confirm the efficacy of nilotinib at 400 mg BID for patients with CML-CP who had SOR or TF, even after dose escalation of imatinib.
- Although dose escalation of imatinib may overcome OCT-1 transporter activity in patients with correspondingly low imatinib plasma levels, nilotinib is not a substrate for OCT-1.
- Although further evaluation is required, the modest (~16%) increase in systemic exposure to nilotinib from 300 to 400 mg BID may benefit some patients with SoR/TF.
- Dose escalation of nilotinib from 300 to 400 mg BID appears safe with no additional safety signals.
- The extension study is ongoing and additional follow-up results will provide further information.

Hochhaus A et al. *Proc ASH* 2011;Abstract 114.

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### **Investigator Commentary: Results from the ENESTnd Extension Study – Efficacy and Safety of 400 mg BID of Nilotinib in Patients with CML-CP after SOR/TF**

Nilotinib is becoming a strong player for front-line therapy instead of imatinib in patients with CML-CP. It is one of the major agents that improves outcomes as second-line treatment when there is no optimal response to imatinib. Based on these data, nilotinib therapy quickly produced better responses than imatinib, particularly molecular responses, and also has an excellent toxicity profile.

Therefore, nilotinib is a viable first choice as front-line therapy because there is good evidence from several studies that a rapid and deep response is crucial for long-term outcomes in patients with CML-CP.

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

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