# 5 Minute JournalClub

## *Key ASH Presentations*

Issue 8, 2012

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# CME Information

## 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.

## CREDIT DESIGNATION STATEMENT

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# CME Information (Continued)

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**FACULTY DISCLOSURES**

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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No real or apparent conflicts of interest to disclose.

**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[1]**

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

**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[3]**


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

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

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

# 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.**

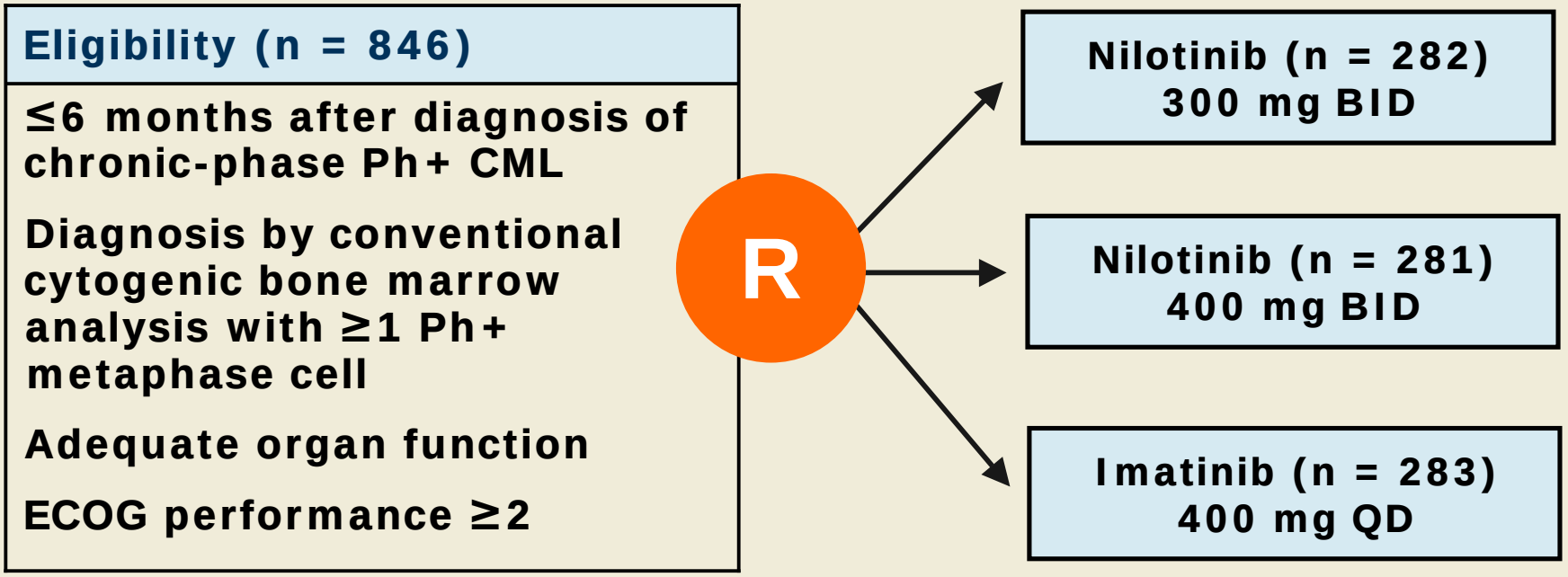
*Proc ASH* 2011;Abstract 452.

# 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.

# ENESTnd Trial Design

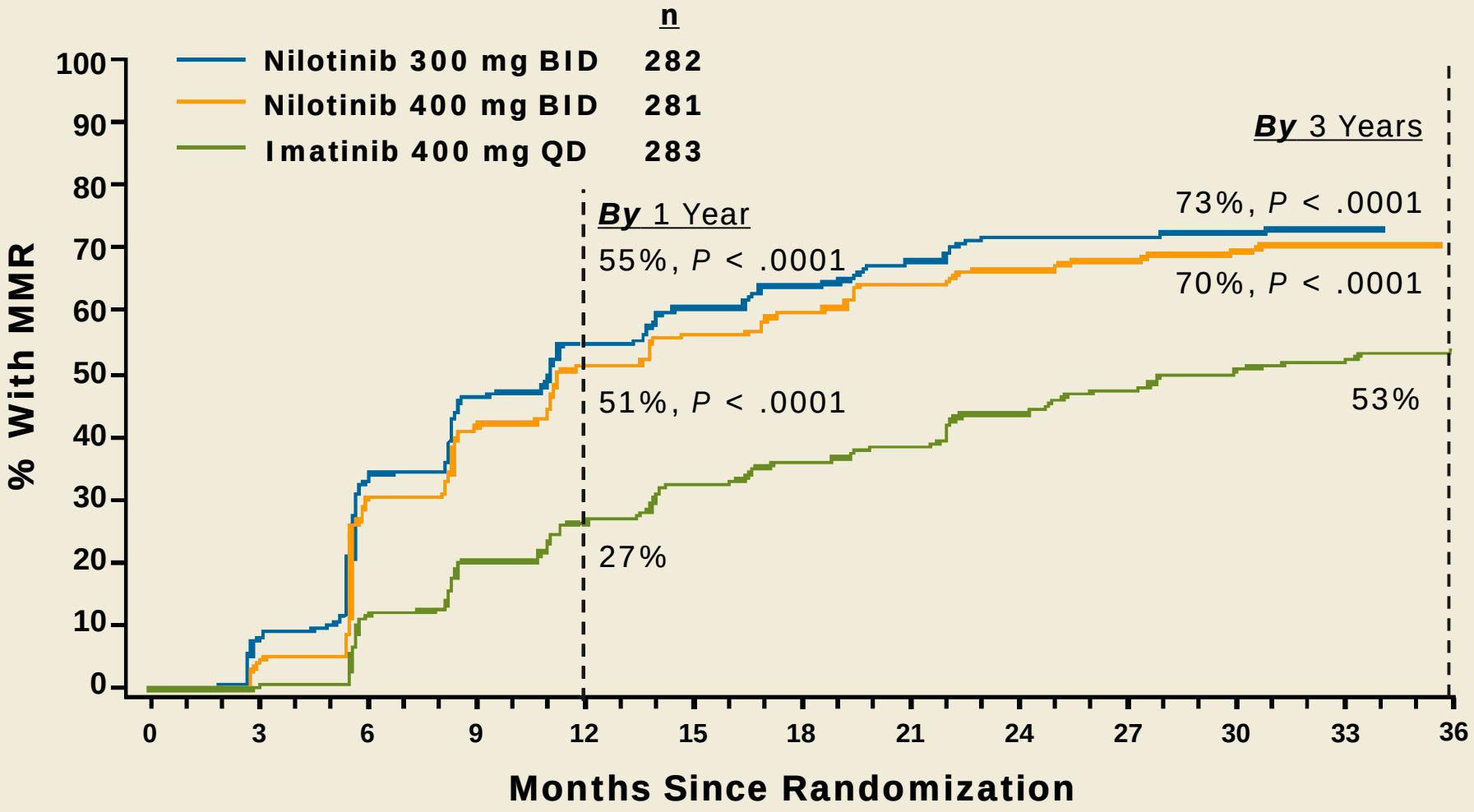



Randomization was stratified by Sokal risk score

- 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.

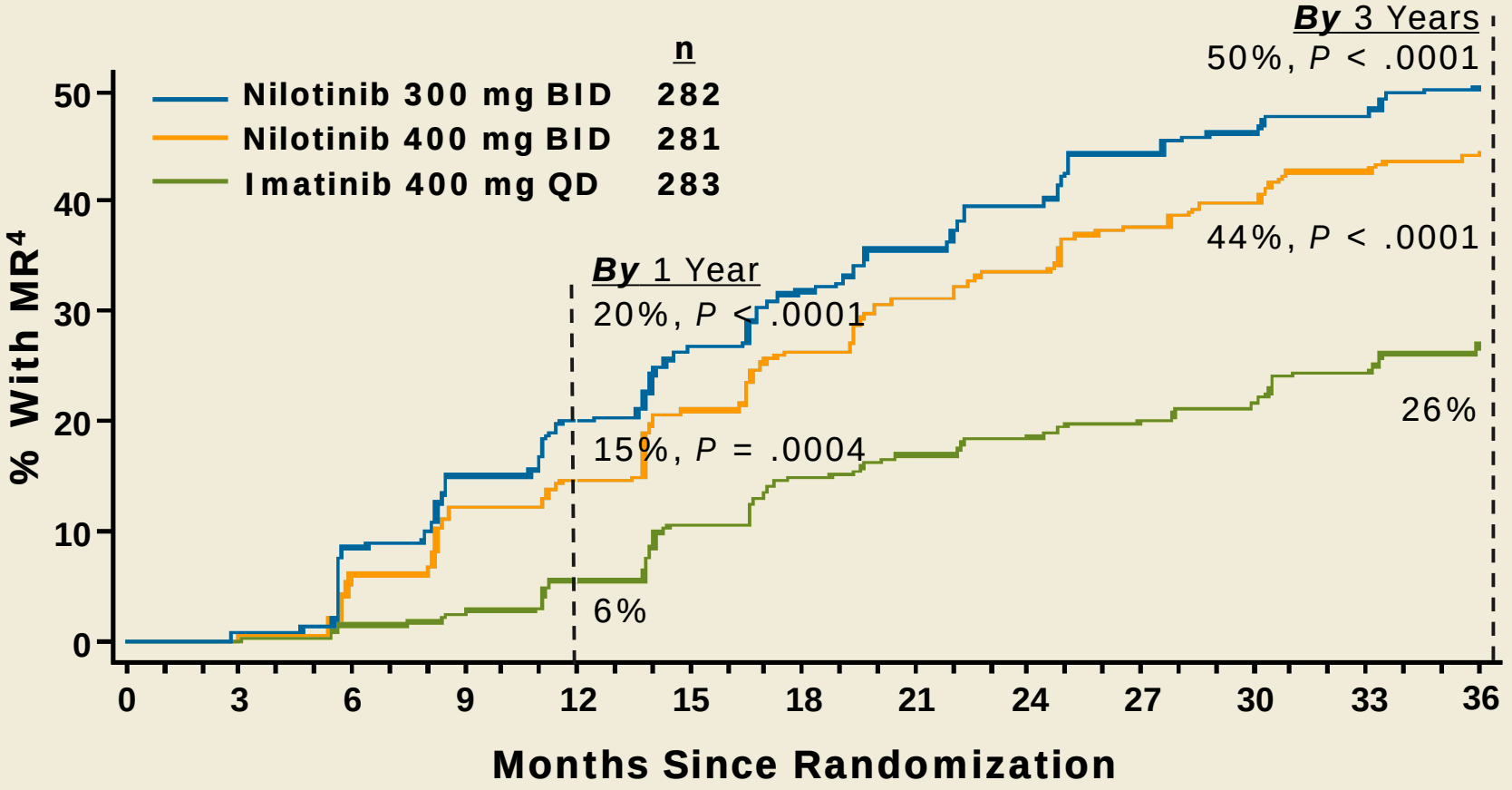
Saglio G et al. *Proc ASH* 2011;Abstract 452.

# Cumulative Incidence of Major Molecular Response (MMR)




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

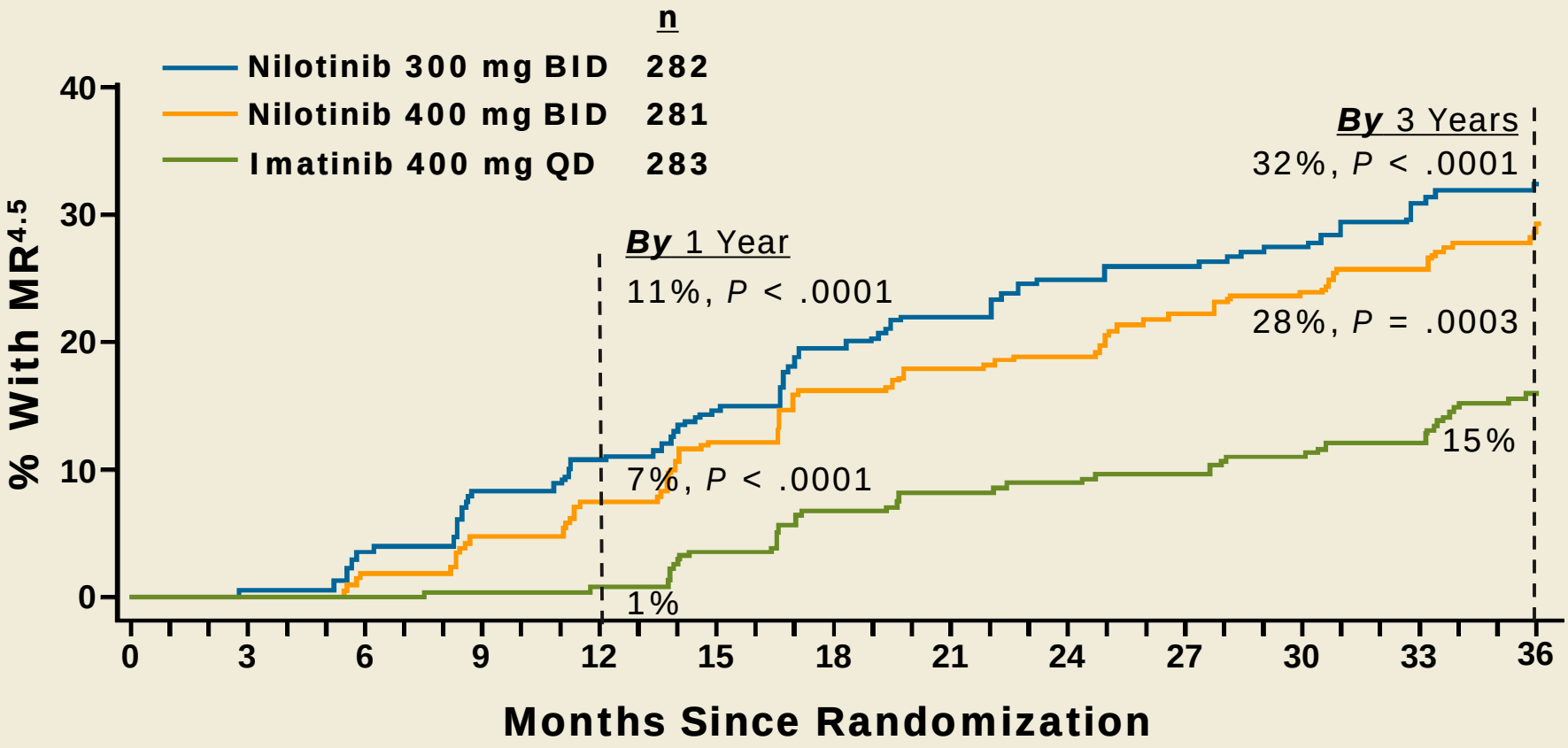
# Cumulative Incidence of Deeper Molecular Response (MR$^{4*}$)




* Equivalent to BCR-ABL$^{IS}$ transcript levels of ≤0.01%

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

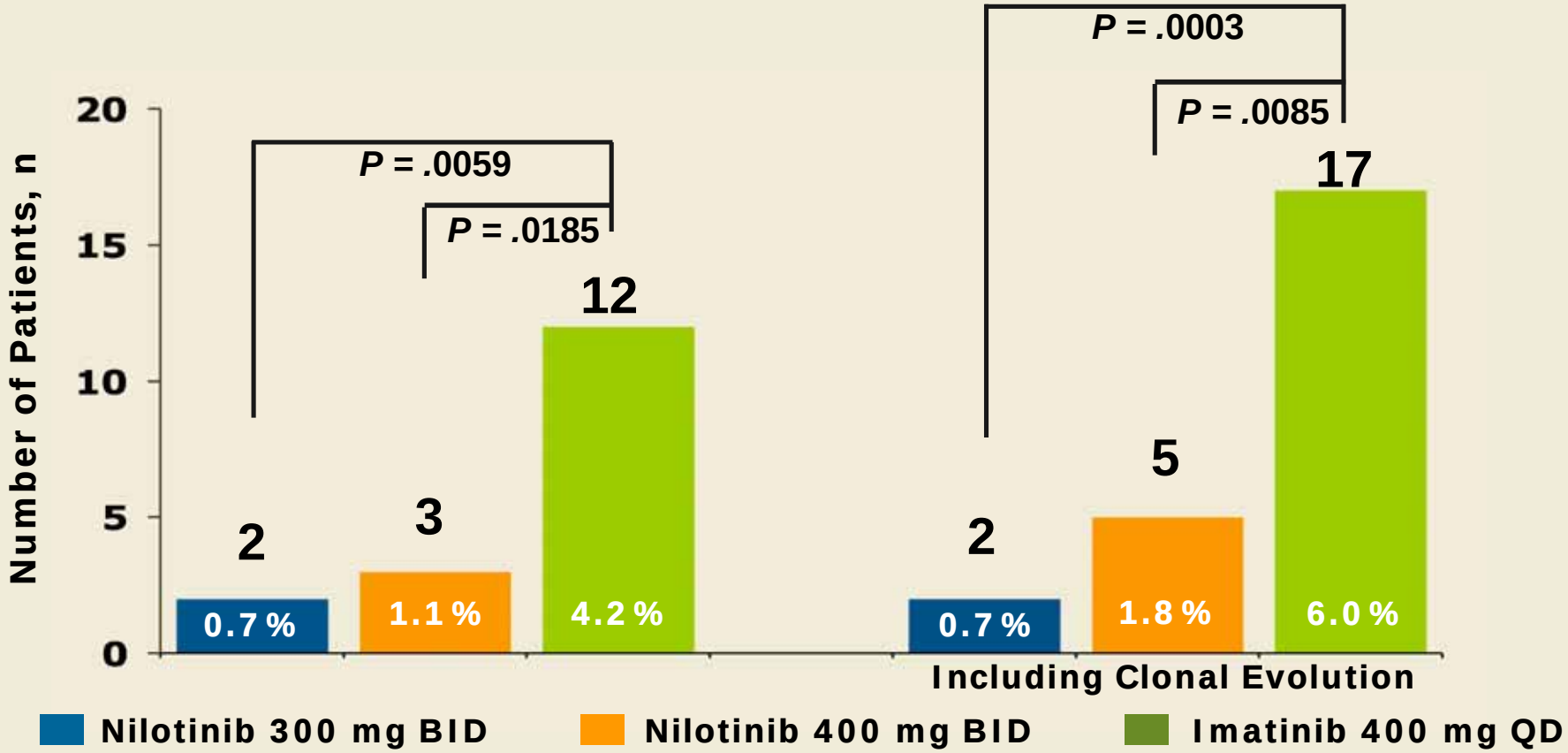
# Cumulative Incidence of Deeper Molecular Response (MR$^{4.5*}$)




* Equivalent to BCR-ABL$^{IS}$ transcript levels of ≤0.0032%

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

# 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.

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

# 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.

# 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, $MR^4$ and $MR^{4.5}$.
  - 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.

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

**Hughes TP et al.**

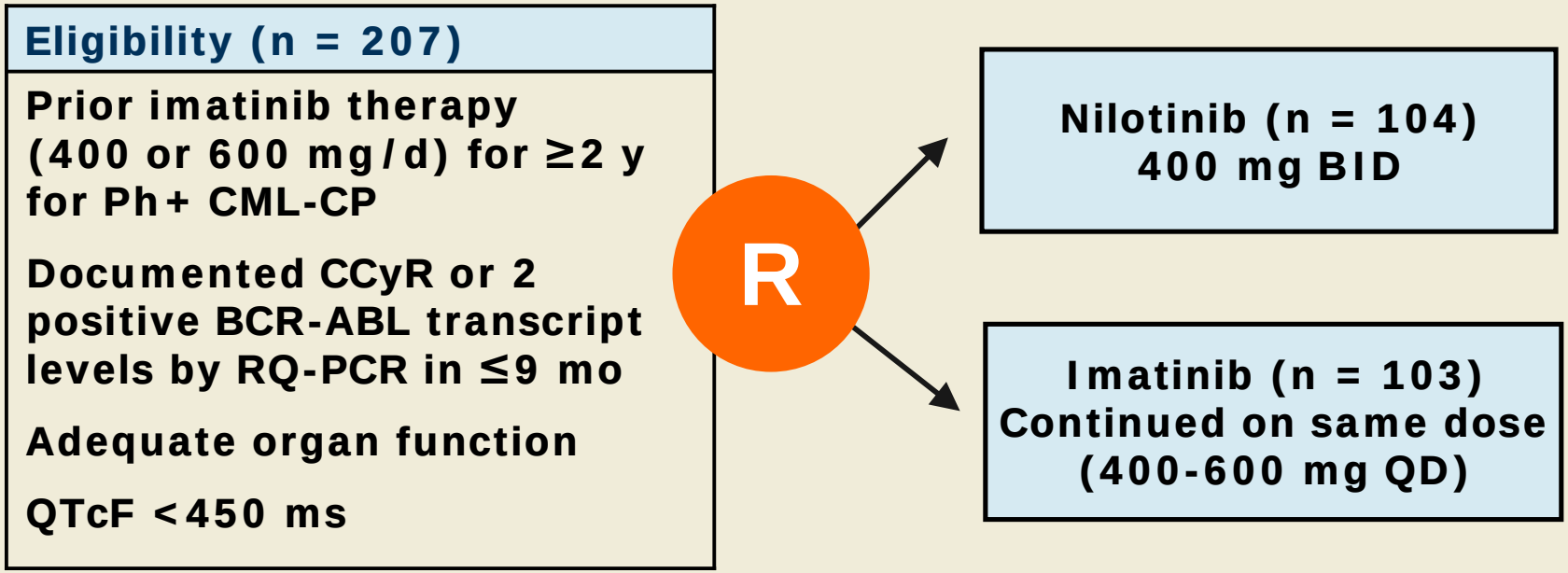
*Proc ASH* 2011;Abstract 606.

# 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, $MR^4$ and $MR^{4.5}$ 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.

# Study Design




CCyR, complete cytogenic response

**Primary endpoint**

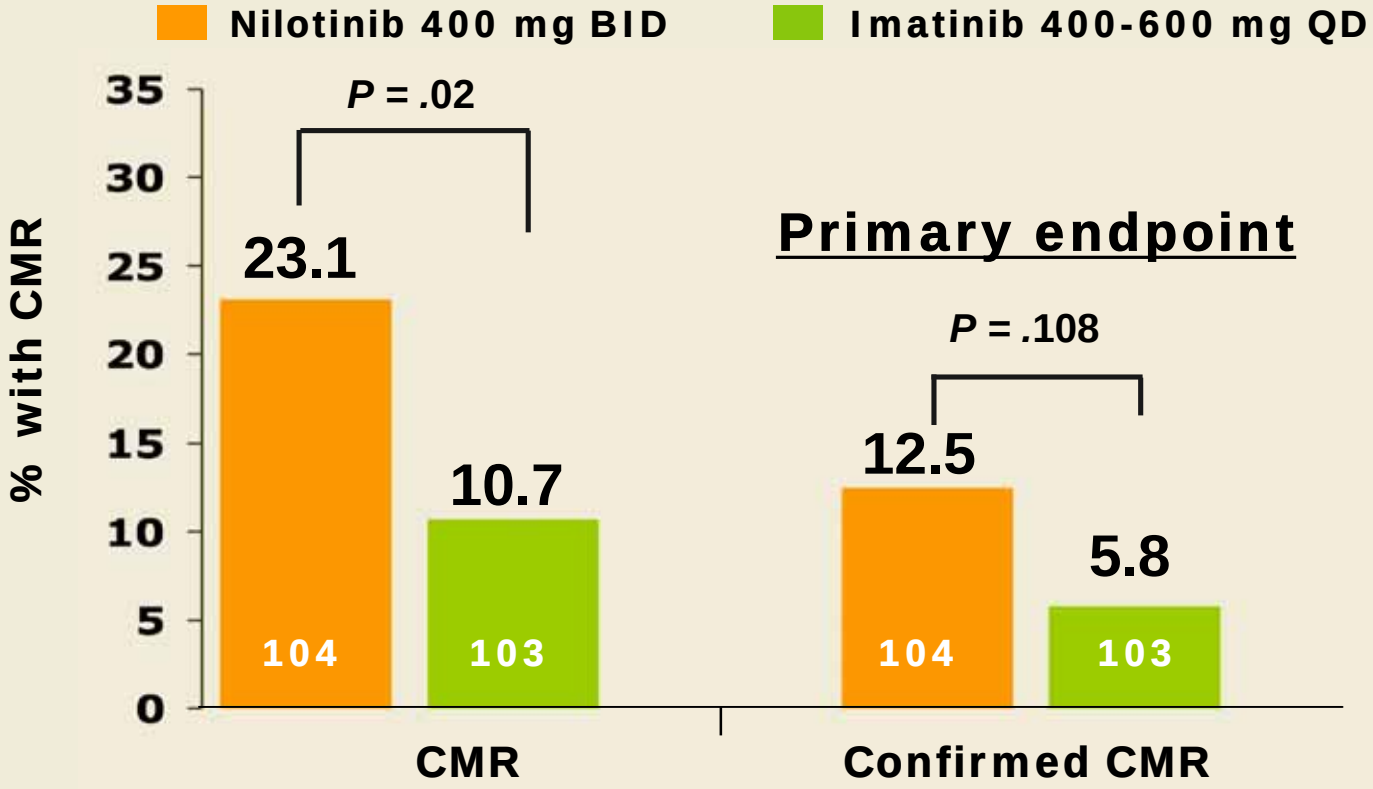
- Confirmed CMR (undetectable BCR-ABL [with ≥4.5-log assay sensitivity]) by 12 months

**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.

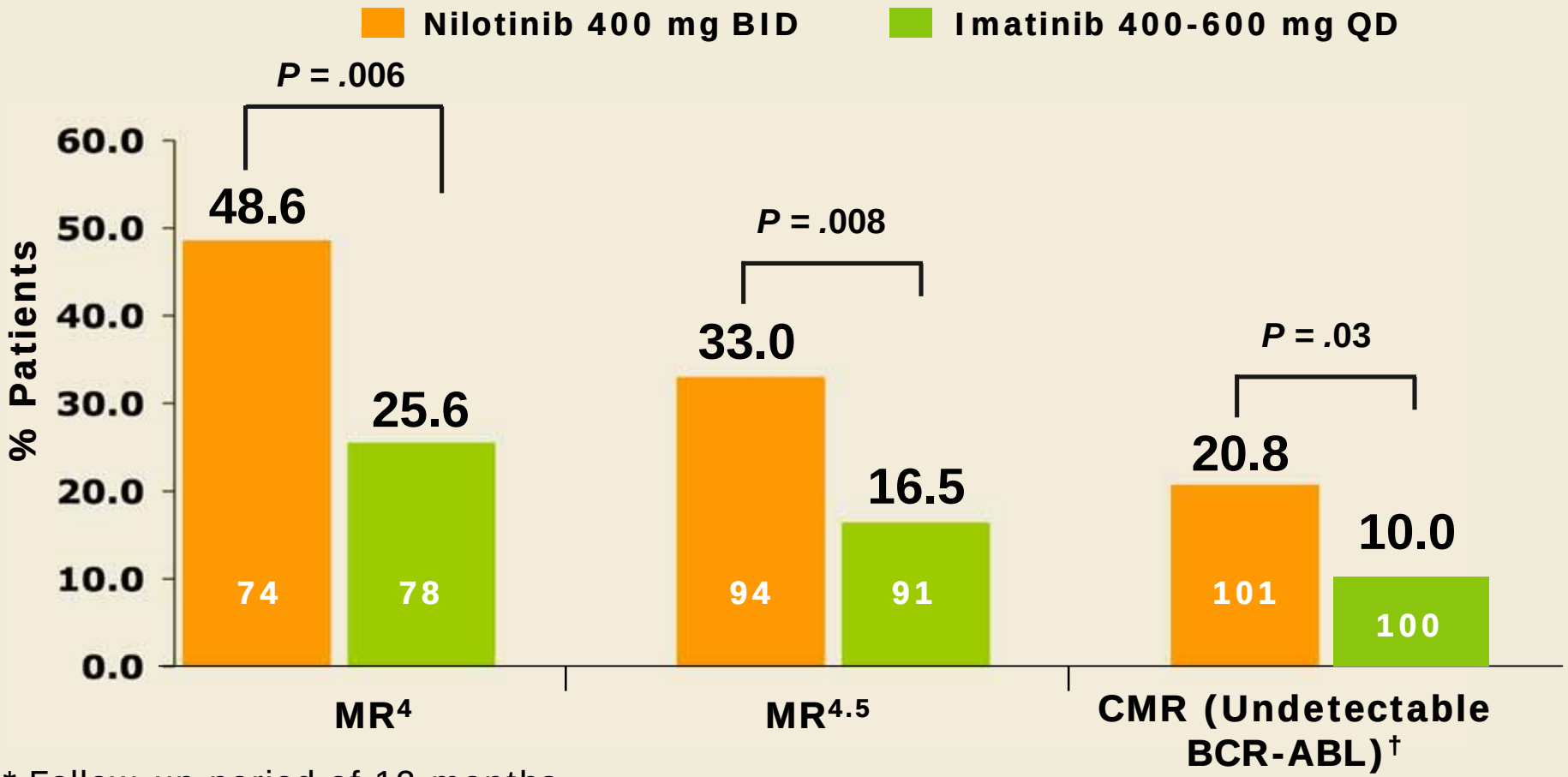
# Primary Endpoint in the Intention-to-Treat Population




- 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.

# Molecular Response* in Patients without Indicated Response at Baseline




* Follow-up period of 12 months

† With ≥4.5-log assay sensitivity

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

# 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.

# 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.

## Investigator Commentary:

## Nilotinib versus Imatinib in Patients with Newly Diagnosed Ph+ CML-CP: 36-Month ENESTnd Follow-Up[1]

## CMR Rate with Nilotinib in Patients with CML-CP without CMR After ≥2 y on Imatinib: Preliminary Results from ENESTcmr Trial[2]

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***

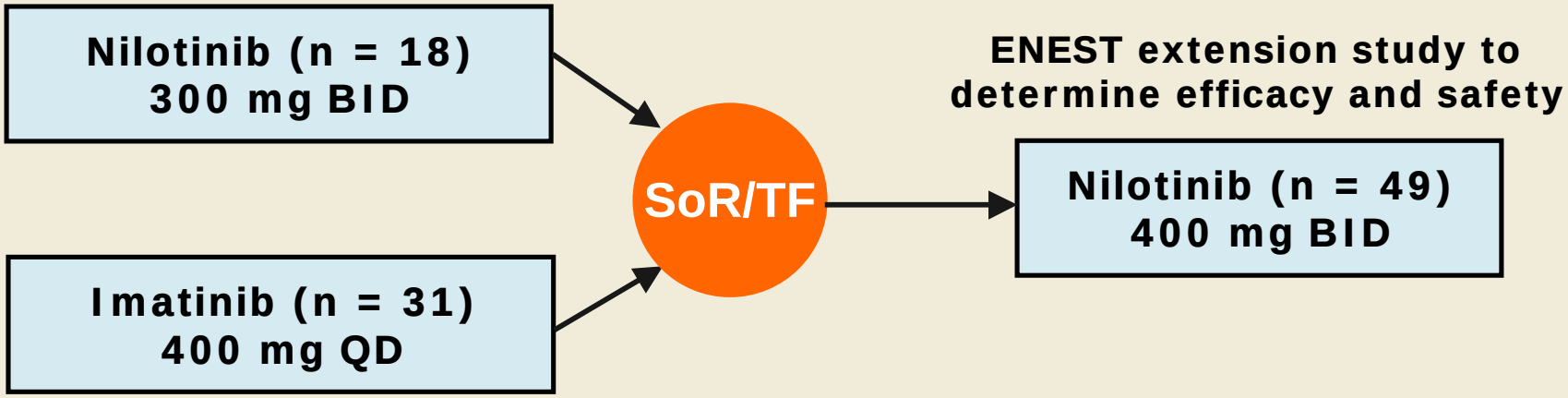
# Results from the ENESTnd Extension Study: Efficacy and Safety of Patients (pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP), Treated with Nilotinib 400 Mg Twice Daily (BID) After Suboptimal Response (SoR) or Treatment Failure (TF) to Imatinib 400 Mg Once Daily (QD) or Nilotinib 300 Mg BID

**Hochhaus A et al.**

*Proc ASH* 2011;Abstract 114.

# 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.

# 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† | 6% | 6% |

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

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

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

# 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.

# 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*<br>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.

# 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.

## 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***

**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.

# 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.

# 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.

# 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.

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

| Most common AE (≥10% any grade) | Patients (n = 397) |
|---|---|
| Thrombocytopenia<br>Grade 3/4 | 19%<br>15% |
| Rash | 18% |
| Dry skin | 13% |
| Myalgia | 12% |
| Abdominal pain<br>Grade 3/4 | 11%<br>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.

# 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.

## 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***

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

**Cortes JE et al.**

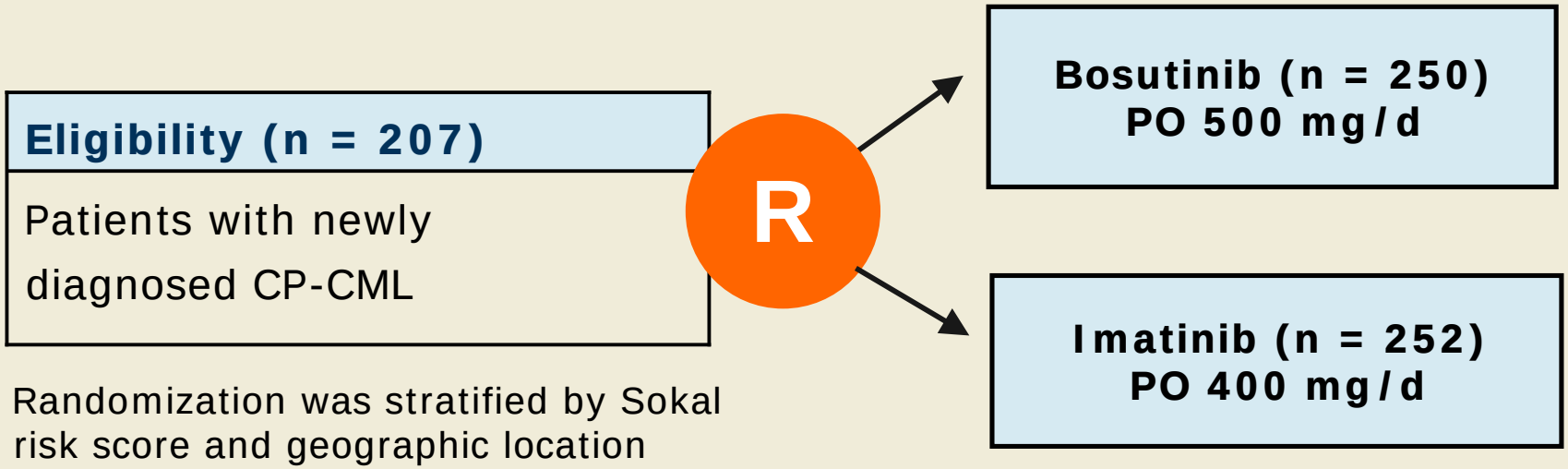
*Proc ASH* 2011;Abstract 455.

# 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.

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

# 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.

# 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.

# 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.

# 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 | 2% | 5% |
| Due to CML progression | 2% | 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.

# 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.

# 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.

## 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***

# Early Molecular and Cytogenic Response Is Predictive for Long-Term Progression-Free and Overall Survival in Chronic Myeloid Leukemia (CML)

**Hanfstein B et al.**
*Leukemia* 2012;[Epub ahead of print].

**Hanfstein B et al.**
*Proc ASH* 2011;Abstract 783.

# Background

- The advent of second-generation tyrosine kinase inhibitors (TKIs) in the front-line treatment setting of chronic myeloid leukemia (CML) has prompted a closer evaluation of the response to imatinib (*N Engl J Med* 2010;362:2251, 2260).
- Early assessment of response markers might identify slow responders harboring a BCR-ABL positive clone with an inferior susceptibility to TKIs.
- Slow responders could benefit from an early dose escalation or a change of treatment to a second-generation TKI, thus avoiding the risk of disease progression.
- **Current study objective**: Evaluate the impact of molecular and cytogenetic response levels after 3 months of an imatinib-based treatment on the course of CML.

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

# CML Study IV Methods

- Patients with CML treated with imatinib (n = 1,303).
- Patients were randomly assigned to receive:
  - Imatinib 400 mg/d
  - Imatinib 400 mg/d + interferon alpha (IFN)
  - Imatinib 400 mg/d + low-dose cytarabine (arm closed 2005)
  - Imatinib 400 mg/d after IFN failure (arm closed 2005)
  - Imatinib 800 mg/d
- Molecular and cytogenetic responses analyzed at 3 months and 6 months.
- BCR-ABL and total ABL transcript levels were measured by quantitative RT-PCR, standardized according to international scale ($BCR\text{-}ABL^{IS}$).
- Cytogenetic response was determined by conventional metaphase analyses with standard G-banding or fluorescence R-banding techniques.
- Endpoints include progression-free survival (PFS) and overall survival (OS).

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

# PFS by Molecular Response

| BCR-ABL$^{IS}$ at 3 months | Five-year PFS | *p*-value | |
|---|---|---|---|
| ≤1% (n = 218) | 96% | NS | — |
| >1%-10% (n = 281) | 92% | | 0.037 |
| >10% (n = 189) | 87% | — | |
| **BCR-ABL$^{IS}$ at 6 months** | **Five-year PFS** | ***p*-value** | |
| ≤1% (n = 498) | 96% | 0.006 | — |
| >1%-10% (n = 194) | 89% | | NS |
| >10% (n = 91) | 86% | — | |

NS = not significant

- PFS was defined as the absence of accelerated phase, blast crisis and death.
- Probability of PFS was calculated from the Kaplan-Meier plot and compared by log-rank statistics.

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

# PFS by Cytogenetic Response

| Ph+ at 3 months | Five-year PFS | *p*-value |
|---|---|---|
| ≤35% (n = 336) | 94% | 0.016 |
| >35% (n = 122) | 87% | |
| **Ph+ at 6 months** | **Five-year PFS** | ***p*-value** |
| 0% (n = 319) | 97% | 0.014 |
| >0% (n = 160) | 91% | |

- Median proportion of Philadelphia chromosome-positive metaphases (Ph+) = 8%

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

# OS by Molecular Response

| BCR-ABL$^{IS}$ at 3 months | Five-year OS | *p*-value | |
|---|---|---|---|
| ≤1% (n = 218) | 97% | NS | — |
| >1%-10% (n = 283) | 94% | | 0.012 |
| >10% (n = 191) | 87% | — | |
| **BCR-ABL$^{IS}$ at 6 months** | **Five-year OS** | ***p*-value** | |
| ≤1% (n = 498) | 97% | 0.002 | — |
| >1%-10% (n = 196) | 90% | | NS |
| >10% (n = 95) | 88% | — | |

- OS was defined as the absence of death from any cause.
- Probability of OS was calculated from the Kaplan-Meier plot and compared by log-rank statistics.

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

# OS by Cytogenetic Response

| Ph+ at 3 months | Five-year OS | *p*-value |
|---|---|---|
| ≤35% (n = 336) | 95% | 0.036 |
| >35% (n = 124) | 87% | |
| **Ph+ at 6 months** | **Five-year OS** | ***p*-value** |
| 0% (n = 320) | 97% | 0.015 |
| >0% (n = 162) | 91% | |

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

# Author Conclusions

- The levels of molecular or cytogenetic response at 3 months of imatinib treatment allow for a risk stratification of patient outcome in terms of PFS and OS.
- Patients (28%) who failed to achieve 10% BCR-ABL$^{IS}$ level at 3 months had a 5-year OS of only 87%.
- Survival rates were significantly better for patients with >1% to 10% and ≤1% BCR-ABL$^{IS}$. However, there was no significant difference between the >1% to 10% and ≤1% BCR-ABL$^{IS}$ groups.
- Therefore, missing the 10% BCR-ABL$^{IS}$ landmark at 3 months predicts inferior survival.
- A similar risk group is defined by failure to achieve the 35% Ph+ landmark at 3 months:
  - 5-year OS with Ph+ >35% at 3 months is 87%.
- Treatment optimization is suggested for patients missing these landmarks.

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

## Investigator Commentary: Molecular and Cytogenetic Response After 3 Months of Imatinib Treatment Predicts Survival in CML

This study reported a significant difference in outcome for patients with CML depending on molecular and cytogenetic responses after 3 months of imatinib treatment. After 3 months of therapy, it is possible to predict the risk of disease progression and death.

Results from this study raised the question as to whether a patient's treatment should be changed early on, depending on the response after 3 months of imatinib therapy. Clinical studies have already been initiated based on these results, in which early use of a different TKI has been attempted to improve outcomes in patients with CML in chronic phase. Second-generation TKIs like dasatinib and nilotinib have received FDA approval in the front-line setting for CML. Although this study suggests the administration of a different second-generation TKI as first-line therapy for patients who will not fare well on imatinib, the question of how such patients will be predefined remains unanswered.

Overall, monitoring of molecular and cytogenetic responses to therapy early on may help community oncologists in treatment decision-making.

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

**Discontinuation of Imatinib in Patients with Chronic Myeloid Leukemia Who Have Maintained Complete Molecular Response: Updated Results of the STIM[1]**

**Discontinuation of Dasatinib or Nilotinib in Chronic Myeloid Leukemia (CML) Patients (pts) with Stable Undetectable Bcr-Abl Transcripts: Results from the French CML Group (FILMC)[2]**


[1] **Mahon FX et al.**
*Proc ASH* 2011;Abstract 603.

[2] **Rea D et al.**
*Proc ASH* 2011;Abstract 604.

# Discontinuation of Imatinib in Patients with Chronic Myeloid Leukemia Who Have Maintained Complete Molecular Response: Updated Results of the STIM

**Mahon FX et al.**

*Proc ASH* 2011;Abstract 603.

# Background

- Imatinib (IM) treatment significantly improves survival in patients with chronic myeloid leukemia (CML) (*J Clin Oncol* 2011;29:2514).
- A 12-month follow-up from the STIM study showed that IM can be safely discontinued in patients with a sustained complete molecular response (CMR) of ≥2 years duration (*Lancet Oncol* 2010;11:1029).
- Little is known about whether treatment can safely be discontinued in the long term.
- **Objective:** Assess the risk of molecular relapse after IM discontinuation after a median follow-up of 34 months.

Mahon FX et al. *Proc ASH* 2011;Abstract 603.

# STIM Study Methods

- Eligibility (N = 100):
  - Patients with CML who had discontinued IM (>2 years duration)
  - Sustained CMR for at least 2 years
  - Patients on prior immunomodulatory Rx (other than IFNa), treatment for other malignancies or allogeneic transplantation excluded
- Rate of relapse assessed by quantitative RT-PCR analysis (positive BCR-ABL transcripts, BCR-ABL/ABL ≥0.001).
- Analysis: Every month first year, every 2 months second year, every 3 months thereafter.

Mahon FX et al. *Proc ASH* 2011;Abstract 603.

# Response Following IM Discontinuation and Rechallenge

- Molecular relapse: 61 patients
  - 58 relapses during first 7 months
  - 3 relapses at 19, 20 and 22 months
- Overall probability of maintenance of CMR at 24 and 36 months: 39%
- Patients in molecular relapse were sensitive to challenge with IM
  - 51 patients returned to CMR
  - 5 patients returned to CMR but with BCR-ABL transcript fluctuation
  - 5 patients did not return to CMR

Mahon FX et al. *Proc ASH* 2011;Abstract 603.

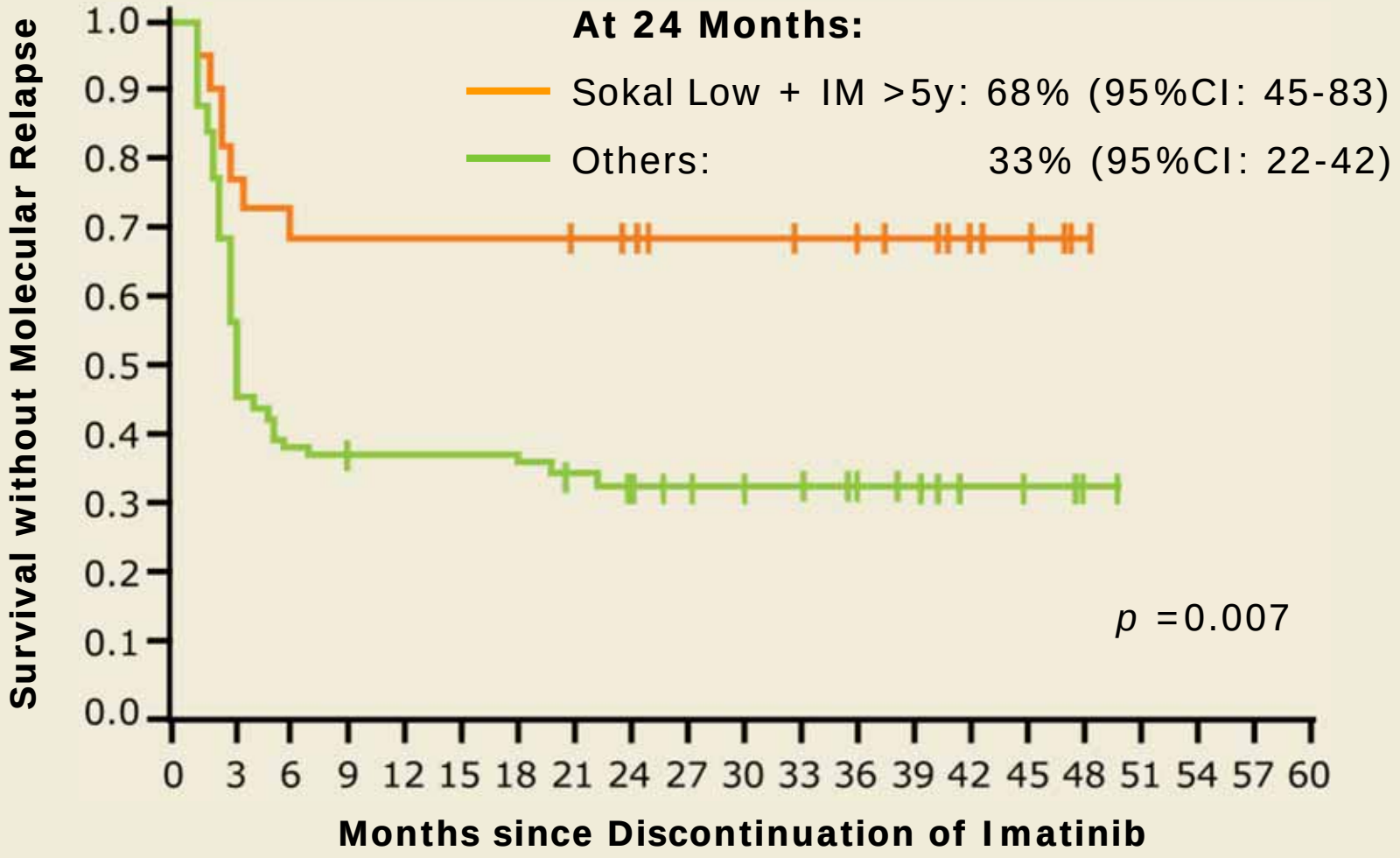
# Multivariate Analysis of Relapse

| Multivariate analysis Cox model over all patients and all relapses | | |
|---|---|---|
| **Factor** | **Hazard ratio** | ***p*-value** |
| Sokal score | 2.555 | 0.008 |
| Duration of IM therapy (>60 mo vs ≤60 mo) | 0.582 | 0.047 |

In multivariate analysis of relapse at 8 months, using the Final model, a higher Sokal score ($p = 0.005$) and shorter IM duration ($p = 0.028$) were independent prognostic factors of relapse.

Mahon FX et al. *Proc ASH* 2011;Abstract 603.

# Kaplan-Meier Estimates of CMR After IM Discontinuation According to Combined Factors




With permission from Mahon FX et al. *Proc ASH* 2011;Abstract 603.

# Author Conclusions

- Discontinuation of IM is recommended only in a clinical trial with close molecular monitoring.
- The most important factors that can predict recurrence after discontinuation are:
  1. The inherent nature of the disease (illustrated by the Sokal score)
  2. The duration of therapy

Mahon FX et al. *Proc ASH* 2011;Abstract 603.

# Discontinuation of Dasatinib or Nilotinib in Chronic Myeloid Leukemia (CML) Patients (pts) with Stable Undetectable Bcr-Abl Transcripts: Results from the French CML Group (FILMC)

**Rea D et al.**

*Proc ASH* 2011;Abstract 604.

# Background

- Dasatinib and nilotinib, 2 highly potent second-generation TKIs (2G-TKI), have been approved in the front-line setting in chronic phase (CP)-CML. However, their curative potential remains uncertain.
- Most patients with CML relapse following treatment discontinuation and require lifelong TKI treatment.
- Results from the STIM trial suggest imatinib (IM) treatment may be discontinued in patients with stable undetectable molecular residual disease (UMRD) (*Lancet Oncol* 2010;11:1029).
- **Objective:** Evaluate the risk of losing major molecular responses (MMR) following discontinuation of 2G-TKI in patients with stable UMRD.

Rea D et al. *Proc ASH* 2011;Abstract 604.

# Study Design

- Eligibility (N = 25):
  - Patients with CP-CML and UMRD proposed discontinuation of 2G-TKI if:
    1. No prior progression to accelerated phase or blast crisis
    2. UMRD was sustained on therapy
- Sixteen patients evaluated with a median follow-up of 15 months.
- BCR-ABL transcripts measured by quantitative RT-PCR every month during first 6 months and every 2-3 months thereafter.
- Dasatinib or nilotinib reintroduced upon loss of MMR.

CP = chronic phase; UMRD was defined by undetectable BCR-ABL using quantitative RT-PCR; MMR = BCR-ABL/ABL internationally standardized (IS) ratio ≤0.1% by 6 months

Rea D et al. *Proc ASH* 2011;Abstract 604.

# Response at the Start of 2G-TKI Therapy (Abstract Only)

| Response (n = 16) | n |
|---|---|
| Chronic phase | 1 |
| Complete hematologic response | 1 |
| Partial cytogenetic response | 2 |
| Complete cytogenetic response, no MMR | 3 |
| MMR, detectable BCR-ABL transcripts | 4 |
| UMRD | 5 |

- Dasatinib (n = 9) or nilotinib (n = 7) administered due to IM intolerance (n = 13) or resistance to IM (n = 1) or as a front-line drug (n = 1)
- Median time on 2G-TKI = 32 months
- Median duration of sustained UMRD = 27 months

Rea D et al. *Proc ASH* 2011;Abstract 604.

# Response Following Discontinuation (Abstract Only)

| Response (n = 16) | n / mo |
|---|---|
| MMR lost (n)* | 5 |
| Median time off treatment (mo) | 4 |
| Stable UMRD or low levels of BCR-ABL (n) | 11 |
| Median time off treatment (mo) | 13 |

* Treatment with 2G-TKI restarted in 4/5 and in another patient without MMR loss but with MRD. MMR and UMRD regained following reintroduction of treatment.

- Gender, age, Sokal risk group, type of 2G-TKI and duration of treatment and of UMRD prior to discontinuation did not differ markedly between patients who lost MMR and those with treatment-free persistent MMR.

Rea D et al. *Proc ASH* 2011;Abstract 604.

# Author Conclusions

- 2G-TKI may be safely discontinued in patients with CML and long-lasting UMRD under strict molecular monitoring conditions.
- The emergence of a low level of detectable residual disease below the MMR threshold after withdrawal of 2G-TKI may not automatically herald CML relapse and may not preclude the possibility to remain treatment-free.
- A longer follow-up is required to ascertain whether CML will recur. This study provides a basis for subsequent large-scale prospective trials.

Rea D et al. *Proc ASH* 2011;Abstract 604.

## Investigator Commentary: Discontinuation of TKI in Patients with CML

The 61 patients who experienced relapse in the STIM trial responded to rechallenge with IM. Of the patients, 39% maintained their CMR for several years, and this is rather impressive. Multivariate analysis showed that a high risk score and a short duration of IM therapy were 2 independent prognostic factors for prediction of molecular relapse after IM cessation. This suggests that these patients can potentially be taken off therapy and may not experience relapse. The disease may still be present at low levels that cannot be detected.

The patients in the Rea study received dasatinib or nilotinib before discontinuation and fared slightly worse than those on the STIM study. Following treatment discontinuation, some of these patients maintained CMR after a long follow-up. So in these patients you can achieve a functional cure. Whether we have the appropriate tools to assess who will or will not experience relapse after stopping therapy is the question. I don't believe that therapy should be routinely discontinued in practice, but this topic warrants further study.

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