# 5 Minute JournalClub

***Key ASH Presentations***
Issue 3, 2011

# Dasatinib in the Initial Management of Chronic-Phase Chronic Myeloid Leukemia (CML-CP)

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## 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 DASISION trial to the evidence-based selection between dasatinib and imatinib as front-line treatment for CML-CP.
- Explain the differential safety profiles of dasatinib and imatinib to patients with CML-CP.

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5 MinuteJournalClub

Key ASH Presentations
Issue 3, 2011

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:

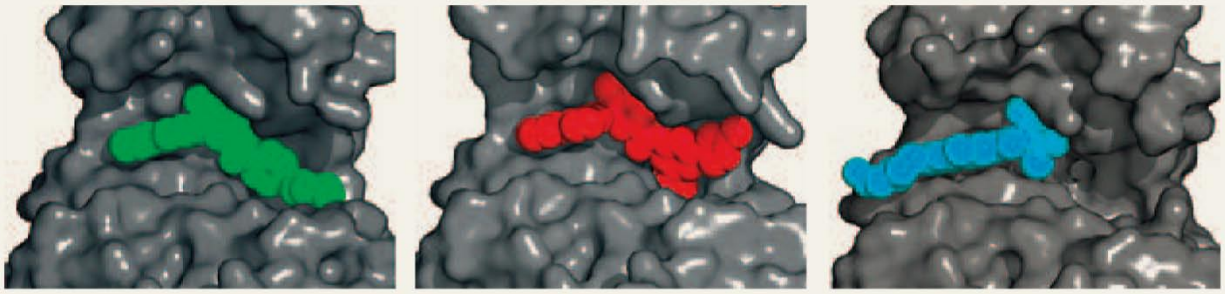
1. **A trial comparing up-front nilotinib to imatinib** and another evaluating a prespecified switch to nilotinib in patients unresponsive to or intolerant of imatinib

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**

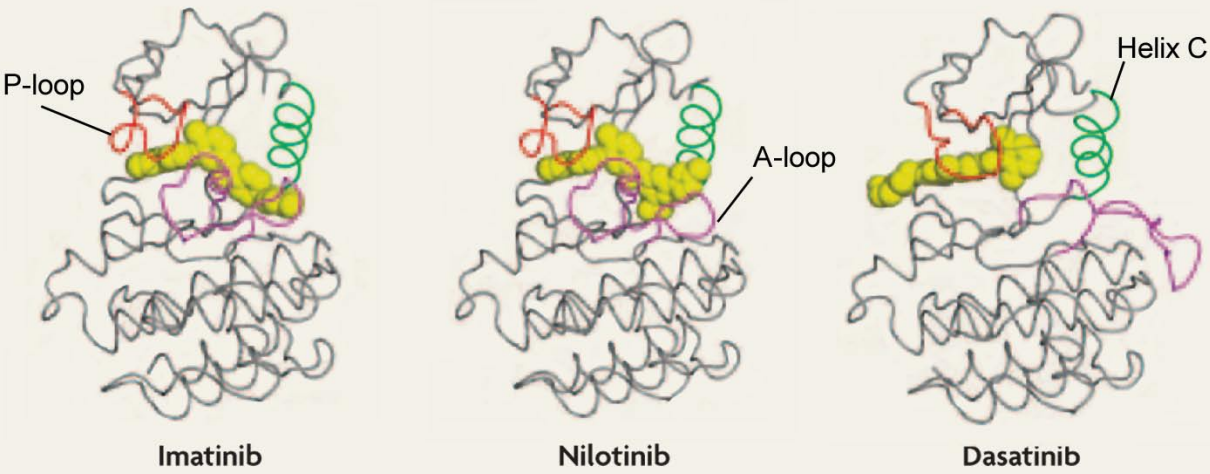
Also at ASH 2009, we heard the first report from the DASISION trial, revealing a higher 12-month confirmed complete cytogenetic response (CCyR) rate with dasatinib than with imatinib. This year, the 18-month update of the study demonstrated continued benefit with this agent, which was first developed 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.

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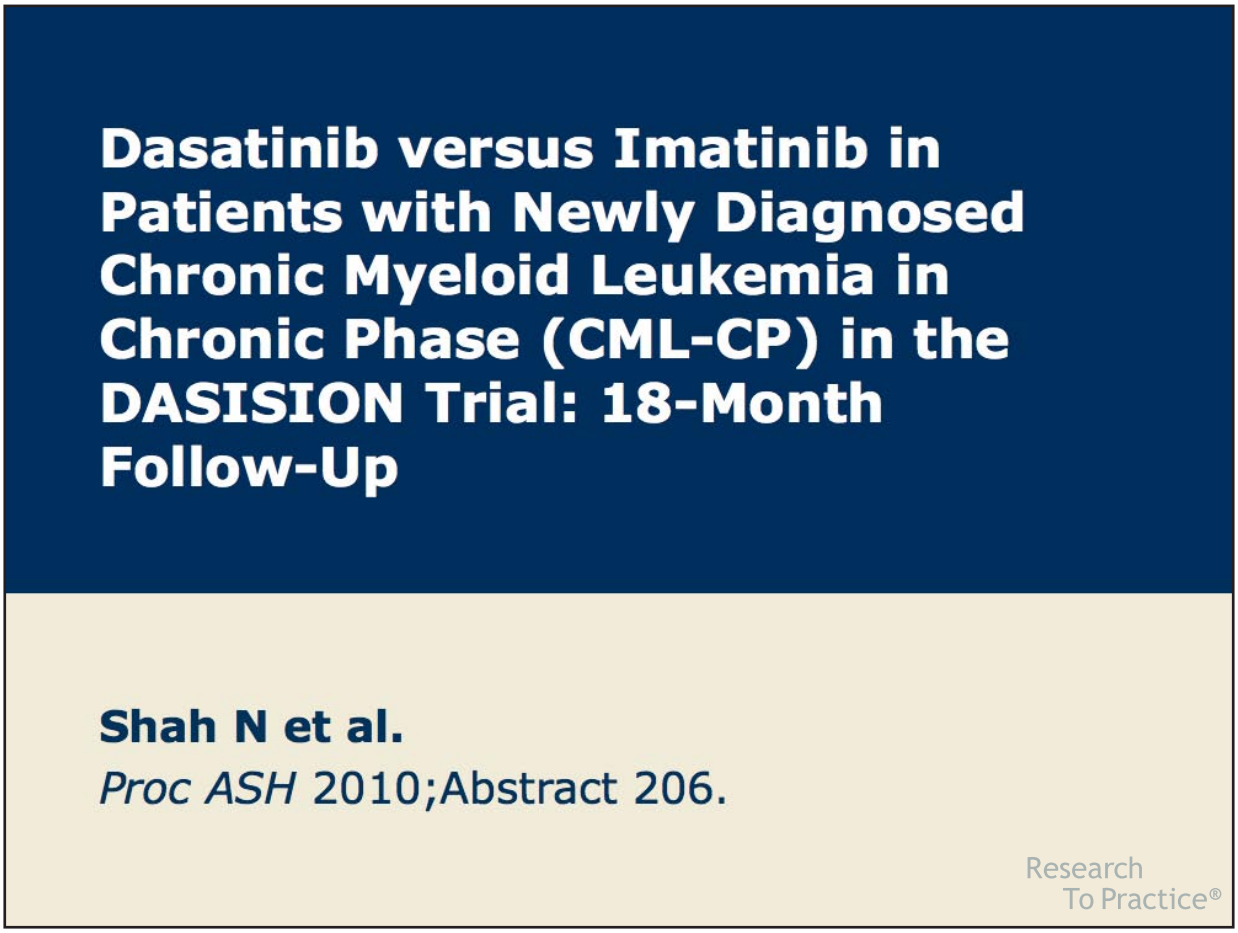
# Dasatinib in the Initial Management of Chronic-Phase Chronic Myeloid Leukemia (CML-CP)

## Presentations discussed in this issue

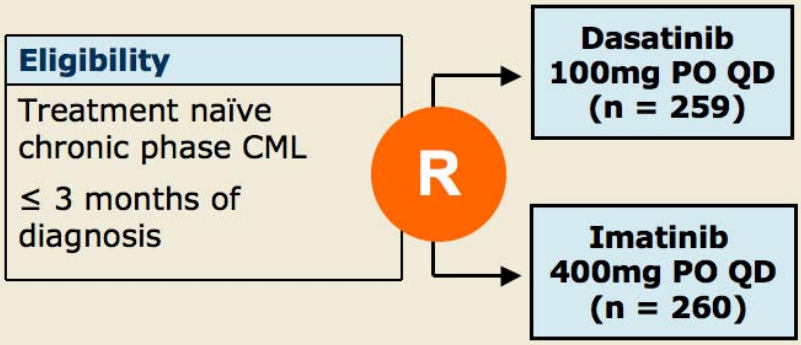
Shah N et al. **Dasatinib versus imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) in the DASISION trial: 18-month follow-up.** *Proc ASH* 2010;**Abstract 206**.

Radich JP et al. **A randomized Phase II trial of dasatinib 100 mg vs imatinib 400 mg in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): The S0325 Intergroup trial.** *Proc ASH* 2010;**Abstract LBA-6**.

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



# DASISION Study Schema




**Primary Endpoint:**
Confirmed complete cytogenetic response (confirmed CCyR) by 12 months

**Other Key Endpoints:**
Rate of CCyR, time to CCyR, duration of CCyR, rate of major molecular response (MMR), time to MMR, progression-free survival (PFS), overall survival (OS)

Shah N et al. *Proc ASH* 2010;Abstract 206.

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# Confirmed Complete Cytogenetic Response*

| | Imatinib (n = 260) | Dasatinib (n = 259) | *p*-value |
|---|---|---|---|
| Confirmed CCyR (by 12 months) | 67% | 77% | 0.0086 |
| Confirmed CCyR (by 18 months) | 70% | 78% | 0.0366 |

*CCyR = No Philadelphia chromosome-positive metaphases in bone marrow samples (FISH not allowed). Confirmed CCyR at 12 months = CCyR detected in two consecutive assessments at least one month apart.

Shah N et al. *Proc ASH* 2010;Abstract 206.

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# Secondary Endpoints

| | Imatinib | Dasatinib |
|---|---|---|
| CCyR (at any time) | 80% | 85% |
| Time to CCyR | 5.8 months | 3.1 months |
| MMR* (12 months) | 28% | 46% |
| MMR (at any time) | 41% | 57% |
| Time to MMR | 11.8 months | 8.3 months |
| Transformation to advanced phase CML | 3.5% | 2.3% |
| OS (at 18 months) | 97.9% | 96% |
| PFS (at 18 months) | 93.7% | 94.9% |

*MMR = BCR-ABL ≤ 0.1% on International Scale.

Shah N et al. *Proc ASH* 2010;Abstract 206.

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# Select Drug-Related Adverse Events

| | Imatinib (n = 258) | | Dasatinib (n = 258) | |
|---|---|---|---|---|
| **Adverse event** | **All grades** | **Grades 3-4** | **All grades** | **Grades 3-4** |
| Fluid retention<br>Pleural effusion | 43%<br>0% | 1%<br>0% | 23%<br>12% | 1%<br>< 1% |
| Myalgia* | 38% | 1% | 22% | 0% |
| Nausea | 21% | 0% | 9% | 0% |
| Vomiting | 10% | 0% | 5% | 0% |
| Thrombocytopenia | Not reported | 10% | Not reported | 19% |

Grade 3 to 4 bleeding occurred in three imatinib-treated patients and two dasatinib-treated patients.

*Includes myalgia, muscle inflammation and musculoskeletal pain.

Shah N et al. *Proc ASH* 2010;Abstract 206.

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## Conclusions

- With longer follow-up, dasatinib continues to demonstrate superior efficacy compared to imatinib in CML-CP.
  - Higher and faster rates of CCyR and MMR
- Few patients transformed to accelerated or blast phase in either group.
- Dasatinib continues to be generally well tolerated.
  - Pleural effusion (12%) was seen only with dasatinib but it did not impact efficacy.
- Based on the predictive value of early CCyR, further follow-up may demonstrate better long-term outcomes, such as PFS or OS, for first-line dasatinib versus imatinib.

Shah N et al. *Proc ASH* 2010;Abstract 206.

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# A Randomized Phase II Trial of Dasatinib 100 Mg Vs Imatinib 400 Mg in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): The S0325 Intergroup Trial

**Radich JP et al.**

*Proc ASH* 2010;Abstract LBA-6.

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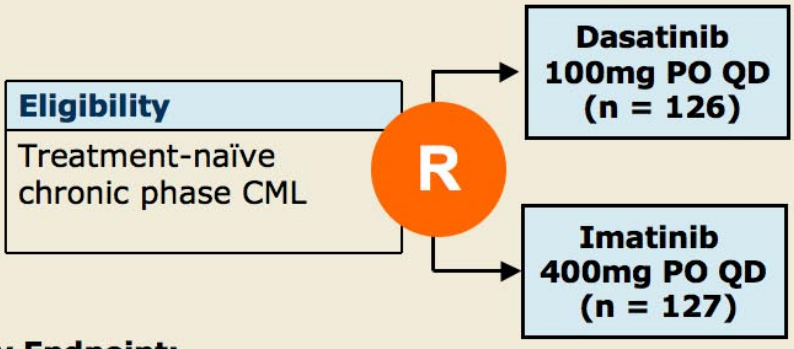
# S0325 Trial Design

**Stratified by Hasford risk category**




**Primary Endpoint:**

- Level of BCR-ABL transcript at 12 months, >4 log reduction (central PCR labs)

**Other Key Endpoints:**

- Best cytogenetic response by 12 months (local cytogenetics)
- Best hematologic response by 12 months
- Adverse events

Radich JP et al. *Proc ASH* 2010;Abstract LBA-6.

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# Treatment Outcomes

| | Imatinib (n = 123) | Dasatinib (n = 123) | *p*-value |
|---|---|---|---|
| Molecular response at 12 months* | | | |
| 3 log reduction | 43% | 59% | 0.042 |
| 4 log reduction | 20% | 27% | 0.31 |
| Cytogenetic CR within 12 months† | 69% | 82% | 0.097 |
| Hematologic CR within 12 months | 90% | 86% | 0.25 |
| PFS at 12 months | 96% | 99% | 0.20 |

*BCR-ABL mRNA levels were available for 90 imatinib- and 99 dasatinib-treated patients at 12 months.

†Cytogenetic data were available for 58 imatinib- and 67 dasatinib-treated patients at 12 months.

Radich JP et al. *Proc ASH* 2010;Abstract LBA-6.

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# Non-Hematologic Toxicities

| | Imatinib 400 mg/d N = 123 | | Dasatinib 100 mg/d N = 122 | |
|---|---|---|---|---|
| | All grades | Grades 3-4 | All grades | Grades 3-4 |
| Fluid retention<br>Edema (any)<br>Pleural | <br>59<br>2 | <br>3<br>1 | <br>24<br>14 | <br>1<br>2 |
| Diarrhea | 49 | 2 | 41 | 6 |
| Nausea | 59 | 0 | 32 | 0 |
| Vomiting | 23 | 0 | 19 | 1 |
| Muscle pain | 44 | 1 | 12 | 0 |
| Rash | 34 | 2 | 40 | 0 |
| Headache | 19 | 2 | 34 | 3 |
| Fatigue | 63 | 1 | 61 | 1 |
| Prolonged QTc | 1 | 0 | 2 | 1 |

Radich JP et al. *Proc ASH* 2010;Abstract LBA-6.

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# Author's Conclusions

- The study provides further evidence that dasatinib appears more efficacious than imatinib for patients with treatment-naïve chronic phase CML.
- Dasatinib and imatinib have different toxicity.
  - Dasatinib — more thrombocytopenia (data not shown) and pleural effusions
  - Imatinib — more fluid retention and nausea

Radich JP et al. *Proc ASH* 2010;Abstract LBA-6.

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## Investigator comment on the trials investigating comparative efficacy of dasatinib versus imatinib as initial treatment of CML

The data from the pivotal IRIS trial of imatinib in first-line CML have shown that if a patient does not have a complete cytogenetic response at 18 months, then they have a worse outcome, and thus 18-month cytogenetic response is a validated endpoint in the initial treatment of CML. The presentation by Shah details the 18-month cytogenetic response data with dasatinib as 78 percent versus 70 percent with imatinib in CML. To me, this update makes it more convincing and compelling than the original paper that the long-term outcome will likely be better for patients with CML receiving up-front dasatinib.

The SWOG study by Radich has the primary endpoint of a four-log reduction of BCR-ABL molecular transcripts at 12 months. Only fifty percent of the patients had cytogenetic data. The study did not meet the primary endpoint, though there was a trend in favor of dasatinib. In my view, this endpoint is not validated and is not known to be correlated with long-term outcomes.

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