

The logo features a white stopwatch icon with the number '5' inside the circular face, set against a dark blue background.

5 Minute Journal Club

SPECIAL EDITION

Issue 2, 2011

**First-Line Therapy for CML-CP with
Nilotinib or Dasatinib Compared to
Imatinib and the Incidence of Treatment-
Emergent BCR-ABL Mutations in Patients
Who Received Nilotinib or Imatinib for
CML-CP in the ENESTnd Trial**

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and 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 diverse forms of cancer.

LEARNING OBJECTIVES

- Develop an evidence-based approach to the selection of first-line therapy for newly diagnosed chronic-phase chronic myeloid leukemia (CML-CP) considering the efficacy and side effects of the second-generation tyrosine kinase inhibitors compared to those of imatinib.
- Assess the effect of treatment-emergent BCR-ABL mutations in patients in the ENESTnd trial on clinical responses to BCR-ABL targeted therapy.

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

No real or apparent conflicts of interest to disclose.

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This activity is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation and Genentech BioOncology.

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To go directly to the slides and investigator commentary for the featured abstracts, [click here](#).

An oncology specialist would be hard pressed to find a better hour of television than the first half of the oral leukemia/myelodysplasia plenary session from ASCO 2011. This riveting segment of the conference, available for your viewing pleasure as part of the virtual meeting, began with 2 complementary presentations of Phase III trials evaluating the JAK1/2 inhibitor ruxolitinib ([ab 6500](#), [ab LBA6501](#)) in patients with myelofibrosis. These were followed by a fascinating BCR-ABL mutation analysis from the ENESTnd CML study ([ab 6502](#)) comparing nilotinib to imatinib and then a brilliant follow-up discussion by Dr Ross Levine outlining a new paradigm in myeloproliferative disorders focused on the search for mutations and related novel blocking agents. These 3 presentations and 14 other compelling ASCO heme-onc data sets are detailed in our slide sets and profiled below in this, the second half of our super-succinct special edition *5-Minute Journal Club*.

1. Ruxolitinib in myelofibrosis

As mentioned above, this trial duet occupies a unique spot on the ASCO highlights reel, and while our understanding of the exact mechanism of action of this oral TKI may be somewhat hazy and may relate to reduction in elevated cytokine levels, what is crystal clear is that this uncommon but merciless disease has instantly entered a new era. The US-based COMFORT-I study evaluating ruxolitinib versus placebo had a number of interesting and innovative features, including the use of MRI to objectively evaluate spleen size and electronic daily diaries to record patient symptoms. The dramatic waterfall plots visibly illustrate how treatment at least temporarily reversed an otherwise downhill course in most patients.

2. CML

Dr Giuseppe Saglio presented the other previously discussed ASCO standout — the landmark substudy from the ENESTnd trial ([ab 6502](#)) demonstrating that prior to treatment patients had almost no BCR-ABL mutations but after therapy a fascinating panoply of alterations was observed in some individuals. Dr Levine predicted that in the near future, mutation assays will be regularly integrated into the treatment algorithm.

Additionally, 24-month follow-up from 2 key Phase III studies (ENESTnd [\[ab 6511\]](#) and DASISION [\[ab 6510\]](#)) was also unveiled in Chicago, suggesting greater efficacy and perhaps less toxicity with up-front treatment with the second-generation TKIs nilotinib and dasatinib when compared to imatinib.

3. Inotuzumab ozogamicin (our vote for name of the year)

This antibody-drug conjugate in the lineage of brentuximab vedotin in lymphoma and T-DM1 in HER2-positive breast cancer links an anti-CD22 antibody to a cytotoxic agent from the calicheamicins class (runner up). The ASCO findings [\(ab 6507\)](#) in relapsed/refractory ALL demonstrated some type of CR in 61% of patients.

4. Myeloma

For more than a year we have witnessed the evolution of data from 2 major trials (CALGB, French IFM group) demonstrating an impressive delay in disease progression but the suggestion of an increased risk of second primary cancers (SPC) with 2 years of lenalidomide maintenance following stem cell transplant (SCT). At ASCO, 3 additional reports [\(ab 8007, ab 8008, ab 8009\)](#) have for the moment reinforced the concept that if there is an SPC signal it is relatively modest in magnitude and far outweighed by the antimyeloma benefit of maintenance len.

The other much-discussed myeloma paper was a landmark Italian study [\(ab 8020\)](#) that for the first time evaluated the role of autologous SCT in the era of novel antimyeloma agents. A progression-free survival benefit was reported with SCT, but other maturing studies are evaluating this important question.

5. CLL

Maybe the most exciting development in B-cell neoplasm research is the rapid evolution of small molecules that block B-cell receptor signaling, and at ASCO we saw more to be optimistic about with a report on the Bruton's tyrosine kinase inhibitor PCI-32765 in CLL. In this Phase Ib/II single-agent study [\(ab 6508\)](#), response rates in excess of 50% were observed with minimal toxicity.

6. Diffuse large B-cell lymphoma

The lack of progress in this common cancer since the introduction of rituximab was highlighted again this year with 1 trial failing to show an advantage with dose-dense R-CHOP [\(ab 8000\)](#) and another showing no important survival benefit to consolidation autotransplant after R-CHOP induction [\(ab 8001\)](#).

7. AML

AML in the elderly — a true clinical conundrum — was the subject of 3 underwhelming ASCO reports. The first [\(ab 6503\)](#) showed a modest benefit that was counterbalanced by a relatively high early mortality rate when clofarabine was combined with Ara-C. The second [\(ab 6504\)](#) demonstrated a modest benefit for decitabine, but discussant Dr Gail Roboz verbalized hope that better outcomes might be observed in her ongoing trial

evaluating 10 days of decitabine combined with the proteasome inhibitor bortezomib. The third study ([ab 6505](#)) was a Phase I effort evaluating a sequential regimen of azacitidine and lenalidomide that resulted in CRs in 7 of 16 patients.

Finally, we saw another interesting AML study perhaps suggesting a new model for the real-time personalized treatment of the disease. In this Phase I/II trial ([ab 6506](#)), the MEK1/2 inhibitor GSK1120212 was shown to have specific activity in patients with RAS mutations.

Coming soon, an online quintet of virtual presentations delving into new developments in non-small cell lung cancer.

Neil Love, MD

[Research To Practice](#)

Miami, Florida

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Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

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First-Line Therapy for CML-CP with Nilotinib or Dasatinib Compared to Imatinib and the Incidence of Treatment-Emergent BCR-ABL Mutations in Patients Who Received Nilotinib or Imatinib for CML-CP in the ENESTnd Trial

Presentation discussed in this issue

Kantarjian H et al. **Dasatinib or imatinib (IM) in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): Two-year follow-up from DASISION.** *Proc ASCO 2011*; **Abstract 6510**.

Slides from a presentation at ASCO 2011 and comments from Susan M O'Brien, MD

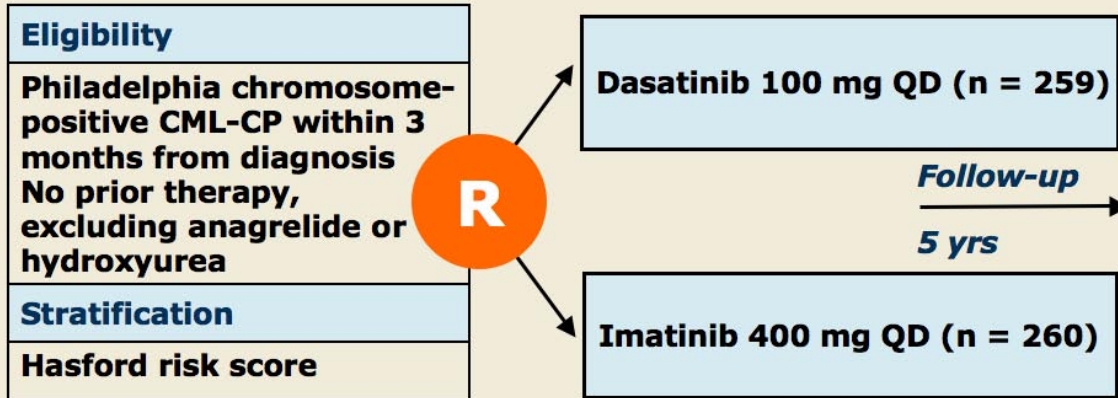
Dasatinib or Imatinib (IM) in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Two-Year Follow-Up from DASISION

Kantarjian H et al.

Proc ASCO 2011; Abstract 6510.

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DASISION Study Design



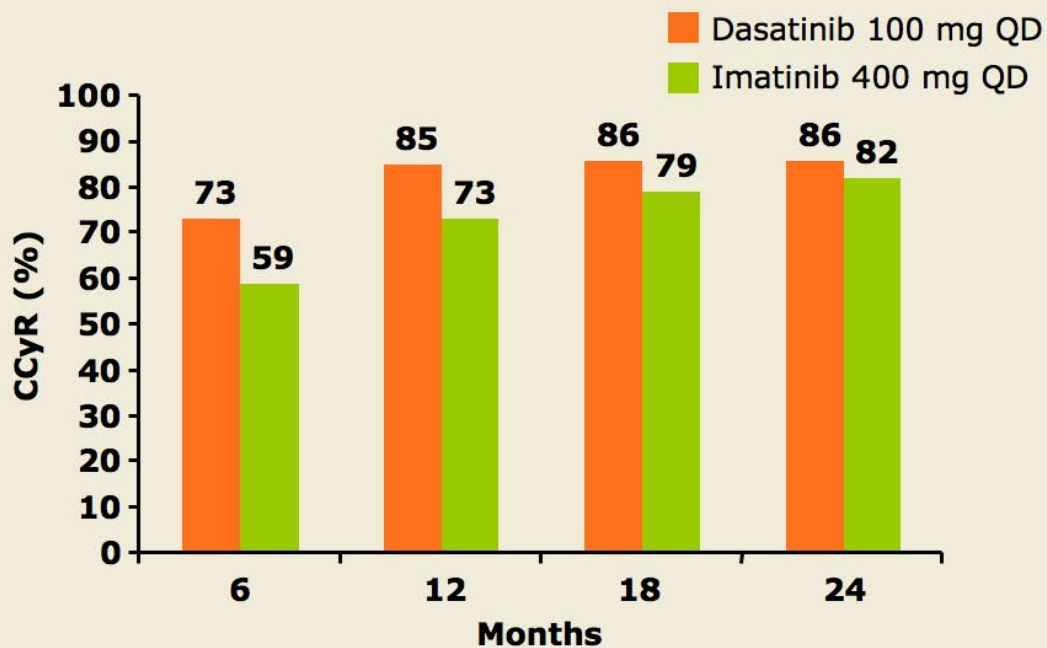
Primary Endpoint: Confirmed CCyR by 12 months

Secondary/Other Endpoints: Rates of CCyR and MMR; times to confirmed CCyR and MMR; time in confirmed CCyR; PFS; OS

Kantarjian H et al. *Proc ASCO* 2011;Abstract 6510.

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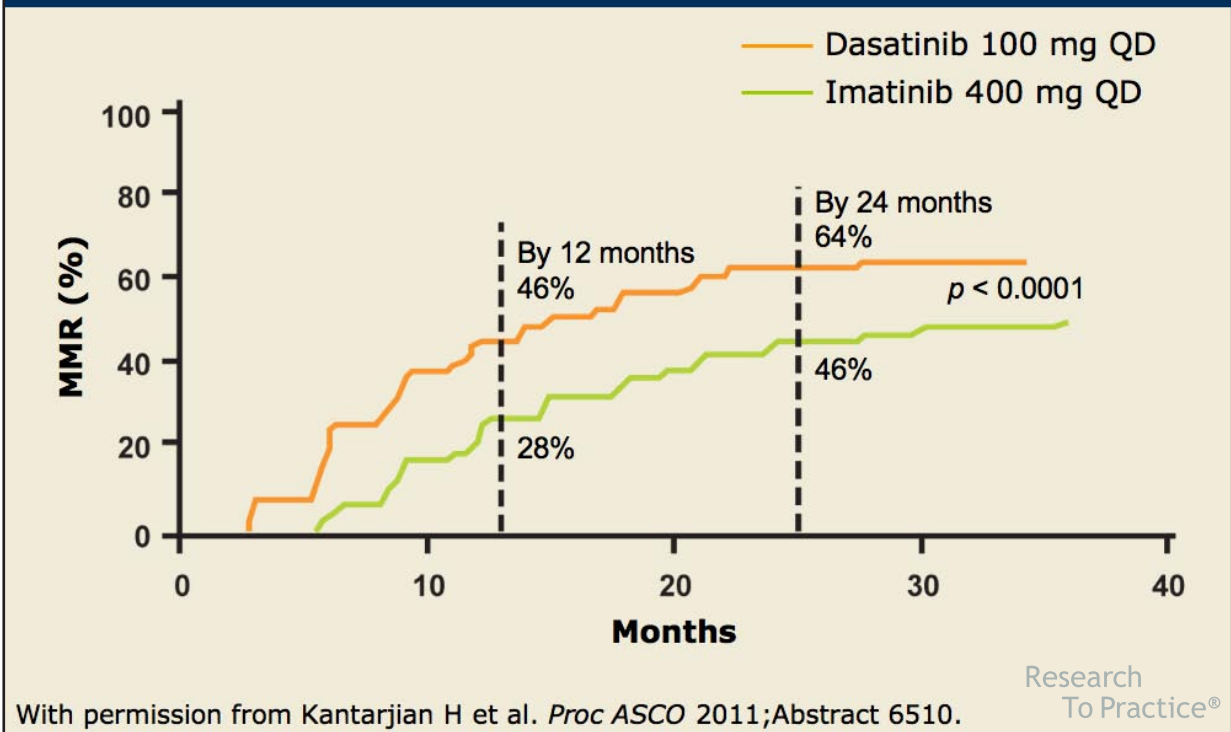
DASISION: Cumulative CCyR Rates by Months of Treatment (ITT Population)



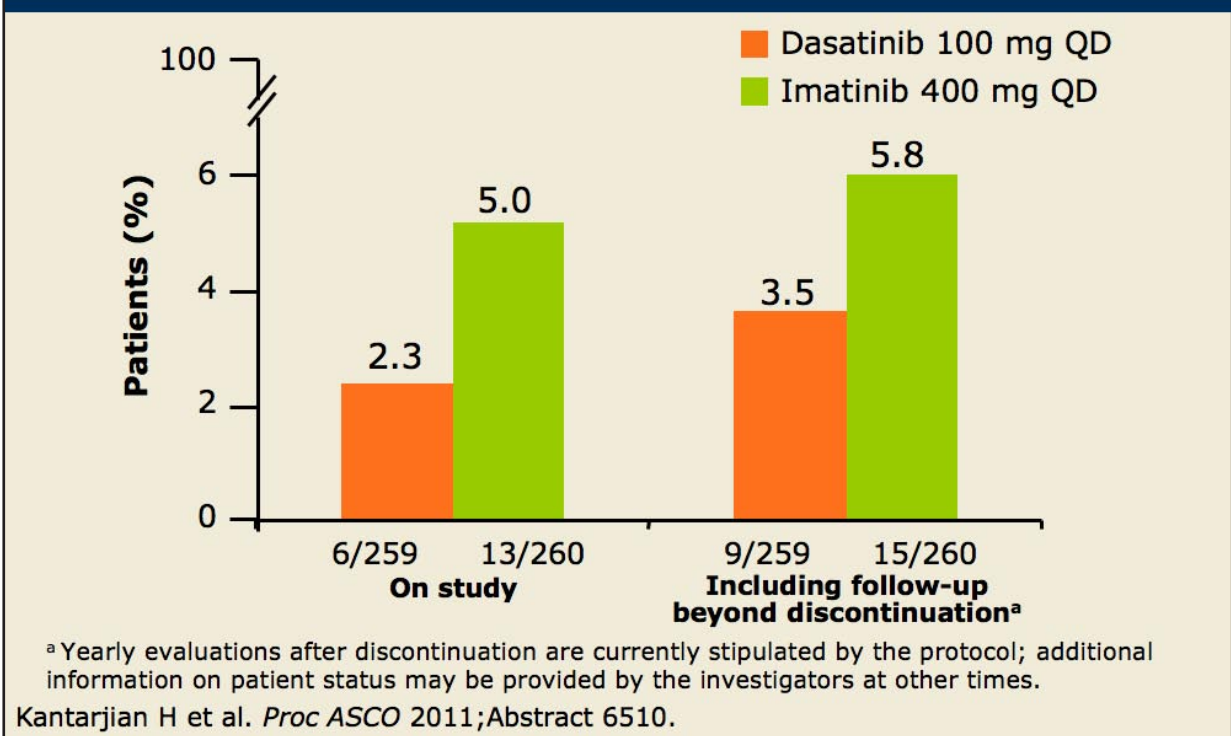
Kantarjian H et al. *Proc ASCO* 2011;Abstract 6510.

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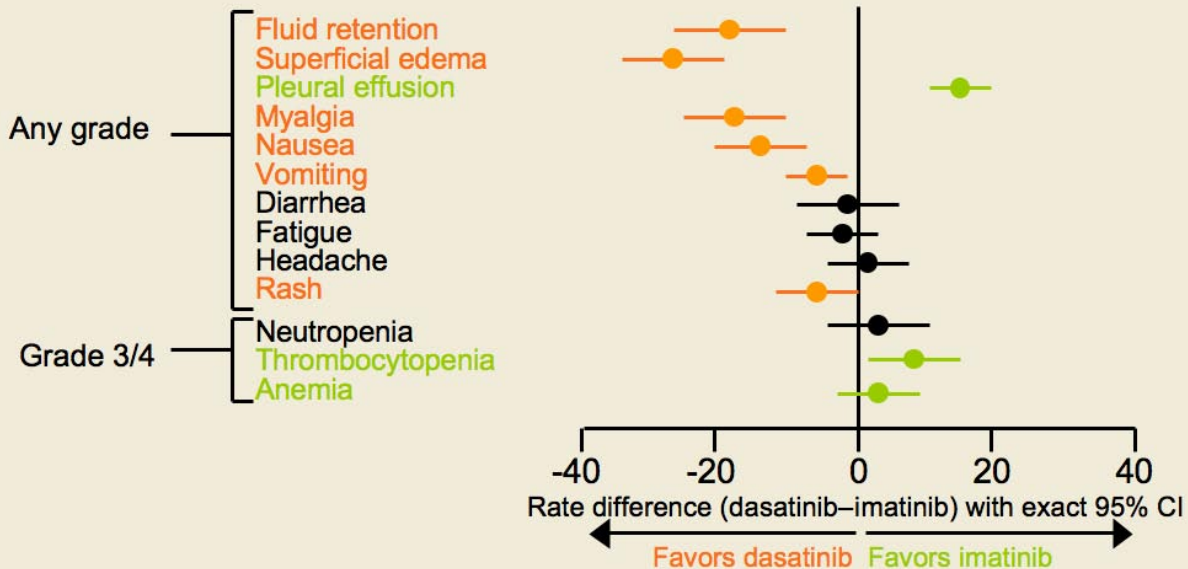
DASISION: Cumulative Incidence of MMR



DASISION: Transformation to AP/BP CML (ITT Population)



DASISION: Difference in Adverse Event Rates for Dasatinib and Imatinib



Patients w/QTc intervals 450 msec - 500 msec: Dasatinib 2%, Imatinib 4%
 Median QTc interval change from baseline: Dasatinib 3.0 msec, Imatinib 8.2 msec

With permission from Kantarjian H et al. *Proc ASCO* 2011;Abstract 6510.

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Conclusions

- 24-month follow-up of patients with newly diagnosed CML-CP in the DASISION trial continues to demonstrate
 - High rate of CCyR with dasatinib
 - Higher and faster rate of MMR with dasatinib over imatinib
- Few patients transformed to AP/BP CML
 - 6 on dasatinib, 13 on imatinib
- Dasatinib was associated with fewer discontinuations due to toxicity (data not shown)
 - Frequency of many of the most common nonhematologic AEs were comparable or lower than imatinib
 - Most cytopenias occurred within the first year
- Longer follow-up continues to support the use of dasatinib 100 mg once daily as first-line treatment of newly diagnosed CML-CP

Kantarjian H et al. *Proc ASCO* 2011;Abstract 6510.

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Investigator Commentary: DASISION Study of Dasatinib versus Imatinib in Newly Diagnosed CML-CP

The primary endpoint of DASISION was confirmed complete cytogenetic response (CCyR) at 12 months. Now with 18-month follow-up, the response rates were clearly higher for dasatinib compared to imatinib. So the relevance of this follow-up is that this is an endpoint at 18 months that would clearly define failure of imatinib if CCyR is not reached. With this clinically relevant endpoint, the second-generation TKI dasatinib is clearly better than imatinib as up-front therapy for CML-CP.

Generally, I will use a second-generation TKI up front, with my selection based on comorbidities. If I have patient who has congestive heart failure who I know is prone to pleural effusions, I might not choose dasatinib. If I have a diabetic patient, who can't eat around the time that he or she receives nilotinib, I might not choose nilotinib for that patient.

I don't believe one can say at this point that if you want to use a second-generation TKI you can choose on the basis of efficacy. We have nothing to suggest, at this point, that one is better than the other. The toxicity profiles are slightly different, and nilotinib is administered BID, whereas dasatinib has the advantage of being once a day.

Susan M O'Brien, MD