

The logo features a white stopwatch icon with the number '5' inside the circular face. To the right of the stopwatch, the word 'Minute' is written in a large, bold, white sans-serif font, and 'Journal Club' is written below it in a smaller, white sans-serif font.

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

For more visit ResearchToPractice.com/5MJCASCOHEME2011

Research
To Practice®

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.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located on our website at ResearchToPractice.com/5MJCASCO2011/CML/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Allos Therapeutics, Amgen Inc, Astellas Pharma Global Development Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly USA LLC, Millennium: The Takeda Oncology

Company, Mundipharma International Limited, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

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

Last review date: September 2011
Expiration date: September 2012

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

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 6 *AMA PRA Category 1 Credits*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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

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

This email was sent to you by Dr Neil Love and Research To Practice. To unsubscribe to future email requests and announcements, [click here](#). To unsubscribe from all email communications, including CME/CNE activities sent by Research To Practice, [click here](#). To update your information on our current distribution lists, [click here](#).

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

Saglio G et al. **The incidence of BCR-ABL mutations in patients (pts) with newly diagnosed chronic myeloid leukemia (CML) in chronic phase (CP) treated with nilotinib or imatinib in ENESTnd: 24-month follow-up.** *Proc ASCO* 2011;**Abstract 6502**.

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

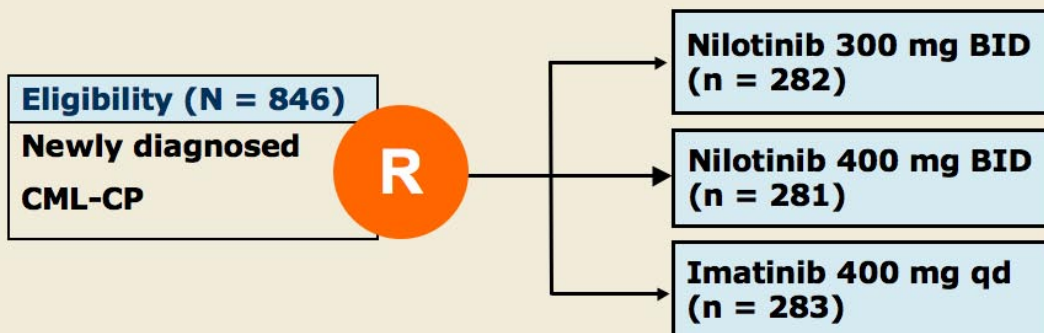
The Incidence of BCR-ABL Mutations in Patients with Newly Diagnosed CML-CP Treated with Nilotinib or Imatinib in ENESTnd: 24-Month Follow-up

Saglio G et al.

Proc ASCO 2011;Abstract 6502.

Research
To Practice®

ENESTnd: Phase III Trial of Nilotinib versus Imatinib in CML-CP



BCR-ABL mutation testing schedule:

- Prior to start of therapy for all patients
- Patients who failed to achieve MMR at 12 mo
- Patients with loss of MMR during study
- Patients with 5-fold increase in BCR-ABL transcript from lowest levels achieved on study
- At end of treatment (including discontinuation)

Saglio G et al. *Proc ASCO* 2011;Abstract 6502.

Research
To Practice®

BCR-ABL Mutations Identified During Treatment*

	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg qd (n = 283)
Patients with any new mutation on treatment, n	10	8	20
Mutation category			
T315I mutation, n	3	2	3
Mutation sensitive to nilotinib, n	2	0	13
Mutation less sensitive to nilotinib, n	5	6	4

*No patient was identified with a BCR-ABL mutation at baseline.

Twice as many mutations were detected in the imatinib arm during treatment, and 2/3 of these were nilotinib-sensitive mutations.

Saglio G et al. *Proc ASCO* 2011;Abstract 6502.

Research
To Practice®

Response Status in Patients with Newly Identified Mutations

Response category	Nilotinib 300 mg BID (n = 10)	Nilotinib 400 mg BID (n = 8)	Imatinib 400 mg qd (n = 20)
Suboptimal response*, n	5	1	4
Treatment failure*, n	4	5	16
Unconfirmed loss of response*, n	1	2	0

*Patients were only counted once under the worst-case response category

The majority of patients with emergent BCR-ABL mutations during treatment had suboptimal response or treatment failure.

Saglio G et al. *Proc ASCO* 2011;Abstract 6502.

Research
To Practice®

BCR-ABL Mutations and Achievement of CMR

- No patient with a CMR at 4.5 log reduction had a BCR-ABL mutation or progressed to accelerated phase/blast crisis (AP/BC) at any time during treatment.
- One patient with a CMR at 4.0 log reduction had a double BCR-ABL mutation (Y253H/T315I) and progressed to AP/BC.

Saglio G et al. *Proc ASCO* 2011;Abstract 6502.

Research
To Practice®

Conclusions

- Twice as many patients with new mutations in BCR-ABL were identified in the imatinib arm as in the nilotinib arms.
- Most patients who developed BCR-ABL mutations had an intermediate or high Sokal risk score at diagnosis (data not shown).
- Incidence of the T315I mutation was similar with nilotinib and imatinib.
- Almost all patients with emergent BCR-ABL mutations during treatment had suboptimal response or treatment failure.
- Data suggest that deeper molecular responses with nilotinib may protect against the development of emerging mutations in BCR-ABL and progression to AP/BC.

Saglio G et al. *Proc ASCO* 2011;Abstract 6502.

Research
To Practice®

Investigator Commentary: The Incidence of Newly Emergent BCR-ABL Mutations Detected in Patients Enrolled in the ENESTnd Trial

Since the early failure rate is higher with imatinib, perhaps not surprisingly one sees that more patients in the imatinib arm of the ENESTnd trial developed mutations in the BCR-ABL gene. One important point is that no patients had a mutation at baseline, which indicates that we should not spend time looking for mutations at that point. The only time you usually find a mutation is when a patient's disease has stopped responding to treatment. It is possible that a patient may not have a mutation in BCR-ABL and experience disease progression, but you don't usually find mutations in patients who are experiencing a successful response.

Interestingly, most of the BCR-ABL mutations that developed on the imatinib arm were sensitive to nilotinib, suggesting that these patients can be salvaged with second-generation tyrosine kinase inhibitors. The incidence of the most concerning mutation, T315I, which is resistant to all of the currently commercially available drugs, was similar in all 3 arms, which is encouraging.

Susan M O'Brien, MD