5 Minute JournalClub

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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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:

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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.

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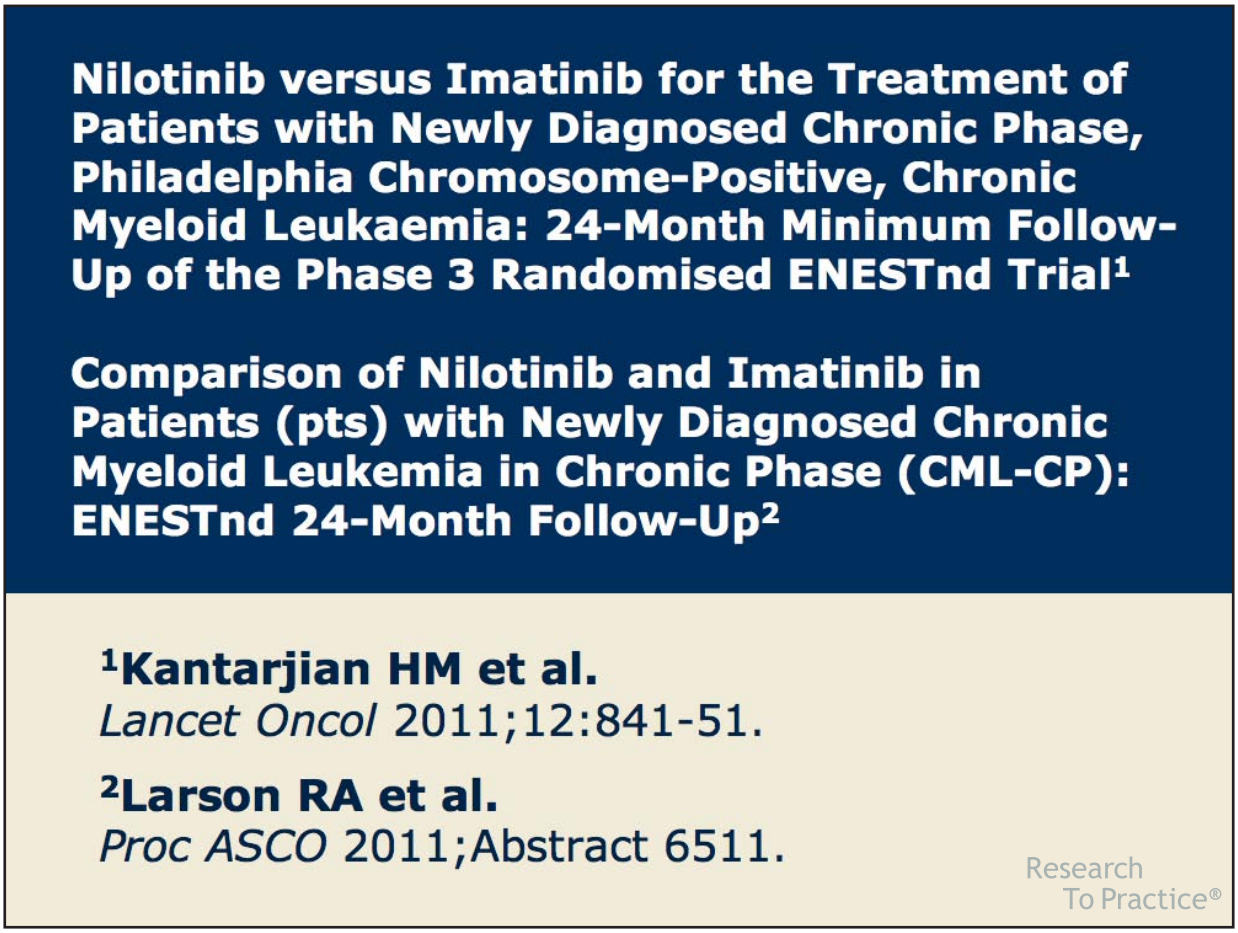
Presentation discussed in this issue

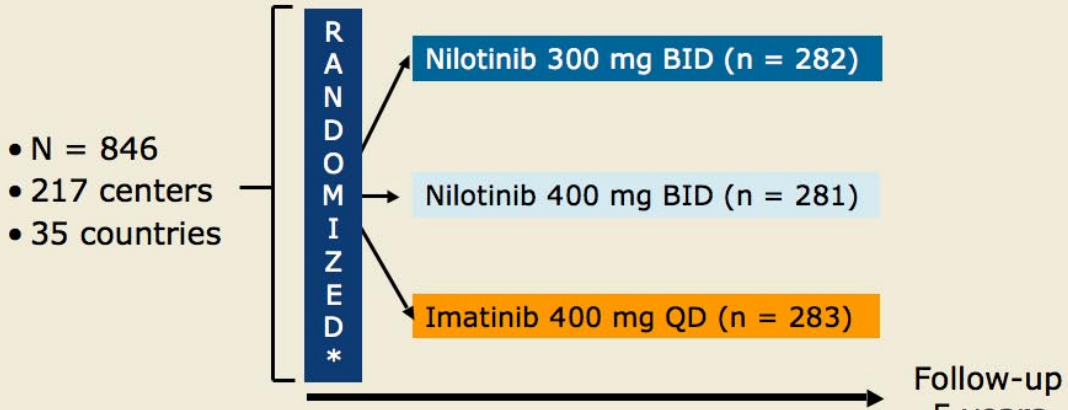
Kantarjian HM et al. **Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the Phase 3 randomised ENESTnd trial.** *Lancet Oncol* 2011;12(9):841-51. **Abstract**

Larson RA et al. **Comparison of nilotinib and imatinib in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd 24-month follow-up.** *Proc ASCO* 2011;**Abstract 6511**.

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



ENESTnd: Phase III Trial Design



* Stratification by Sokal risk score

Primary endpoint: Major molecular response (MMR) at 24 months
Secondary endpoints: Complete cytogenetic response (CCyR), time to MMR and CCyR, event-free survival (EFS), progression-free survival (PFS), time to accelerated phase/blast crisis (AP/BC), overall survival (OS)

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Kantarjian HM et al. *Lancet Oncol* 2011;12:841-51.

ENESTnd: Outcomes — First 24 Months

	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg BID (n = 283)
CCyR	87%	85%	77%
MMR	71%	67%	44%
Transformation	0.7%	1.1%	4.2%
Discontinued therapy	18%	21%	22%
Estimated 24-month rate of PFS *p*-value	98.0% 0.0736	97.7% 0.0437	95.2% —
Estimated 24-month rate of OS *p*-value (OS)	97.4% 0.6485	97.8% 0.2125	96.3% —

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Kantarjian HM et al. *Lancet Oncol* 2011;12:841-51.

Cumulative Incidence of MMR*

Time from randomization	Percent with MMR		
	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg QD (n = 283)
12 months *p*-value	55% <0.0001	51% <0.0001	27% —
24 months *p*-value	71% <0.0001	67% <0.0001	44% —

* ITT population used for all efficacy analyses

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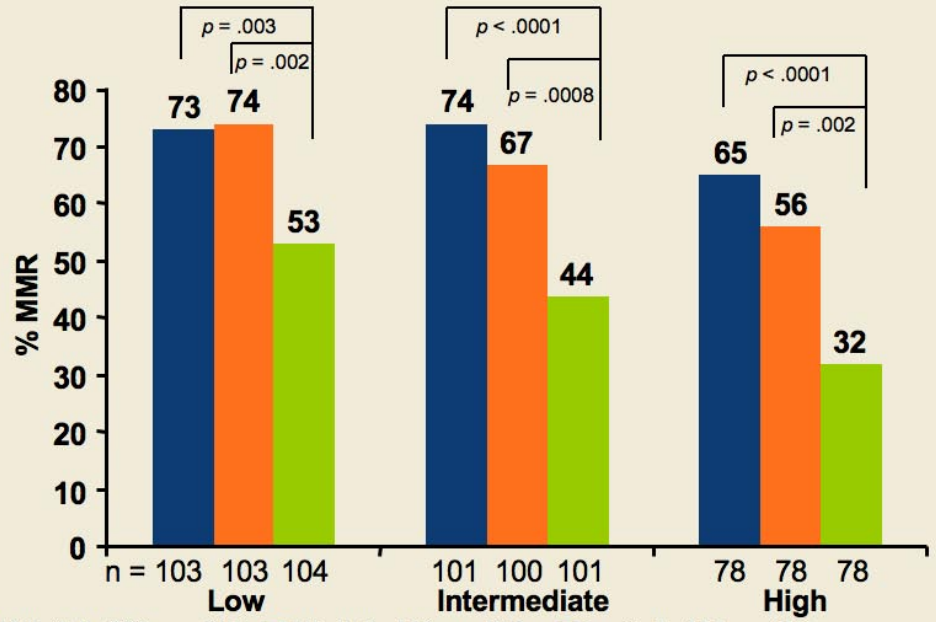
Kantarjian HM et al. *Lancet Oncol* 2011;12:841-51.

MMR Rates by 24 Months According to Sokal Risk*

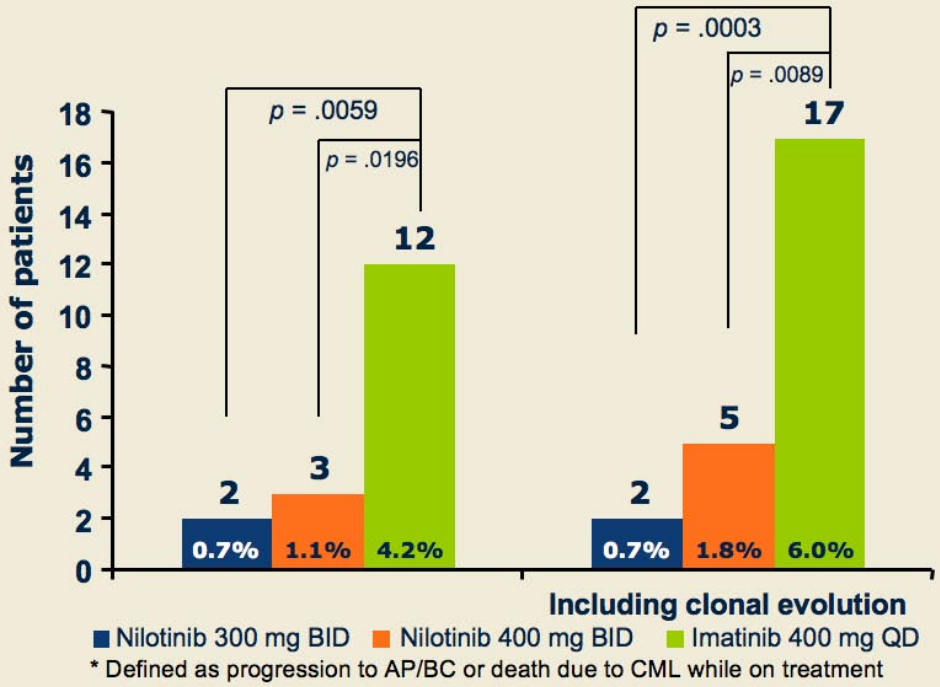


* *p* values are provided for descriptive purposes only and are not adjusted for multiple comparisons

Larson RA et al. *Proc ASCO* 2011;Abstract 6511.

Data cutoff: 20 Aug 2010

Progression to Accelerated Phase/Blast Crisis on Treatment*



* Defined as progression to AP/BC or death due to CML while on treatment

Larson RA et al. *Proc ASCO* 2011;Abstract 6511. Data cutoff: 20 Aug 2010

ENESTnd: Adverse Events (24-Month Follow-Up)

Adverse event, %	Imatinib 400 mg QD (n = 280)	Nilotinib 300 mg BID (n = 279)	Nilotinib 400 mg BID (n = 277)
Headache (Grades 3, 4)	4 (1%)	8 (3%)	2 (<1%)
Neutropenia (Grades 3, 4)	59 (21%)	33 (12%)	30 (11%)
Thrombocytopenia (Grades 3, 4)	24 (9%)	29 (10%)	34 (12%)
Anemia (Grades 3, 4)	14 (5%)	10 (4%)	11 (4%)
Rash (all grades)	61 (22%)	113 (41%)	130 (47%)
Fluid retention (all grades)	155 (55%)	46 (16%)	63 (23%)

No patient had a QT interval corrected for heart rate of more than 500 msec.

Kantarjian HM et al. *Lancet Oncol* 2011;12:841-51.

Author Conclusions

- Compared with imatinib, nilotinib continues to demonstrate:
  - Superior MMR, CMR and CMR
  - Significantly fewer progressions to AP/BC on treatment
- Nilotinib demonstrated significantly higher MMR rates compared with imatinib in all Sokal risk groups.
- Safety and efficacy of nilotinib and imatinib in elderly patients was comparable to younger patients (data not shown).
- Nilotinib at both doses was generally well tolerated, and fewer adverse events led to discontinuation in the nilotinib 300 mg BID arm.
- Longer follow-up confirms the superiority of nilotinib over imatinib for the treatment of patients with newly diagnosed CML-CP.

Kantarjian HM et al. *Lancet Oncol* 2011;12:841-51; Larson RA et al. *Proc ASCO* 2011;Abstract 6511.

Investigator Commentary: The Results from the 24-Month Update of the ENESTnd Trial

This was an update of an important data set previously published in *The New England Journal of Medicine* last year. The primary endpoint for the ENESTnd trial was major molecular response at 12 months, and the primary endpoint was clearly met with both 300 mg and 400 mg of nilotinib twice a day. One issue, however, was that the gold standard is achieving a complete cytogenetic response in terms of long-term survival by 18 months.

Now we have the 18-month follow-up and the complete cytogenetic response that was presented at ASH 2010 and then updated to 24 months at ASCO 2011. The authors reported that the complete cytogenetic response in the nilotinib arms was 87% and 85% versus only 77% with imatinib, and this was statistically significant. We are continuing to see improvement with the second-generation tyrosine kinase inhibitor used up front.

Another aspect first reported in the *NEJM* paper that is clearly a clinically relevant endpoint is that the incidence of progression to accelerated or blast phase was lower. That finding held true with longer follow-up. This is clearly relevant because having patients develop accelerated phase or blast crisis is not good.

Susan M O'Brien, MD