5 Minute JournalClub

POST-ASH Issue 7, 2013

Early Response to Tyrosine Kinase Inhibitors Predicts Better Outcomes in Untreated Chronic-Phase CML

For more visit ResearchToPractice.com/5MJCASH2013

Research To Practice®

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 and new information 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, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the efficacy and safety of bosutinib as second-line therapy for patients with chronic-phase chronic myeloid leukemia (CML-CP), including those whose disease is resistant or intolerant to imatinib.
- Compare and contrast response patterns and long-term clinical impact of treatment with nilotinib, imatinib or dasatinib as first-line therapy for CML-CP.
- Describe updated clinical research data on the activity and tolerability of ponatinib from the pivotal Phase II study in patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia or those with BCR-ABL T315I mutations, and consider this information when caring for these patients.
- Assess the evolving role of omacetaxine mepesuccinate for patients with treatment-resistant CML, such as those who are in blast crisis.

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 1.5 *AMA PRA Category 1 Credits™*. 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 at ResearchToPractice.com/5MJCASH2013/7/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:

Hagop M Kantarjian, MD
Chairman and Professor, Leukemia Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

Consulting Agreement: Novartis Pharmaceuticals Corporation; Paid Research: ARIAD Pharmaceuticals Inc, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Pfizer Inc.

Moshe Talpaz, MD
Alexander J Trotman Professor of Leukemia Research
Associate Director of Translational Research
UM Comprehensive Cancer Center
Associate Chief, Division of Hematology/Oncology
Director, Hematologic Malignancies
University of Michigan Medical Center
Ann Arbor, Michigan

Advisory Committee: Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Contracted Research: Abbott Laboratories, Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Sanofi; Speakers Bureau: Novartis Pharmaceuticals Corporation.

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: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly USA LLC, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

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 Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: May 2013
Expiration date: May 2014

5 MinuteJournalClub

POST-ASH Issue 7, 2013

CML update: A lot going on, as usual

To go directly to slides and commentary for this issue, **click here**.

With 3 newly approved agents in the past 8 months, chronic myeloid leukemia (CML) is not only the poster child for targeted cancer treatment but also an enormous potential stumbling block for oncologists. So we took a step back after Atlanta, spent some time chatting with investigators and came up with the following CML highlights reel:

1. Selection of an up-front tyrosine kinase inhibitor (TKI)

Unlike ASH in 2010 and 2011, no practice-changing Phase III up-front trials were reported at the 2012 meeting. However, the topic was still center stage in December during a provocative education symposium where Dr David Marin provided a meticulous review that culminated with an interesting conclusion. In Dr Marin's view, for most patients, imatinib is essentially an equivalent clinical option to the second-generation TKIs nilotinib and dasatinib and may become the preferred choice in 2015 because of a cost advantage when its patent expires. He supported his stance by noting that a survival advantage has yet to be demonstrated with the second-generation TKIs and many patients with suboptimal responses to imatinib can be salvaged with other therapies. Of course, this position stands in sharp contrast to the perspectives of most CML investigators, who fully endorse the up-front use of second-generation agents.

2. Ponatinib and bosutinib

At ASH, Dr Jorge Cortes presented yet another impressive data set on ponatinib, the recently approved (12/2012) pan-BCR-ABL TKI and the only one currently known to be effective in cases with T315I gatekeeper mutations. In further follow-up of the **Phase II PACE trial**, major cytogenetic responses were observed in 51% of 203 patients with chronic-phase CML with resistance or intolerance to dasatinib or nilotinib and 70% of 64 patients with chronic-phase CML and T315I mutations. Overall, with a minimum of 12 months of follow-up, 63% of these heavily pretreated patients remain on study. Ponatinib is currently a critical tool in the care of patients who are intolerant to or have suboptimal or no response on other TKIs, and there is considerable excitement about new Phase III trials evaluating this fascinating agent up front.

Another next-generation TKI story is bosutinib, which was approved in September. In Atlanta, we were treated to an **interesting report** looking at 119 patients with chronic-phase CML treated on the Phase I/II trial who had received 2 or 3 prior TKIs. At 2 years most of these individuals had responded and were still on treatment, which was seen as generally tolerable. **Another ASH data set** from the same study demonstrated similarly encouraging efficacy among 285 patients resistant/intolerant to imatinib. Interestingly, this agent previously failed to deliver better outcomes than imatinib up front in a **Phase III trial**, in part because of tolerability issues, resulting in its current positioning as later-line treatment.

3. Early assessment of response

In his highly informative **ASH CML wrap-up**, Dr Steve O'Brien ranks as the number 1 meeting theme this year "the 10% thing" — referring to the rapid proliferation of papers demonstrating that failure to achieve a PCR BCR-ABL/ABL level of less than 10% at 3 or 6 months puts patients in a group at higher risk of disease progression or developing early resistance.

One of the key ASH papers in this regard evaluated 483 patients who received treatment at MD Anderson with nilotinib, dasatinib or high- or normal-dose imatinib. In this data set, deep cytogenetic and molecular response at 3 and 6 months was **predictive of outcome with all 4 modalities**, and based on these and similar findings in other studies there is now considerable interest in new trials that randomize between continuing or switching therapy in patients with suboptimal early response.

4. Can CML be "cured"?

While most patients nowadays can expect to achieve and maintain clinical remission, lifelong therapy is required. At ASH we saw **more data on treatment discontinuation** in specific situations — usually CMR (defined as >5 log reduction) for 2 or more years after a total of 3 years of treatment. Using these criteria, perhaps 40% of patients receiving imatinib and 60% receiving nilotinib or dasatinib fare well off therapy. The problem is that currently we have no way to identify patients who will or won't experience relapse, and therefore physicians are universally encouraged to consider discontinuation only within the context of a clinical trial.

Related to this issue, perhaps my favorite ASH CML moment came during **Dr Susan Branford's education session presentation** when she showed serial PCR analyses from several patients who received up to 12 years of imatinib. In one case, a 22-year-old man had an undetectable BCR-ABL for 8 years when a major blip appeared on his PCR curve.

Was this some new mutated, resistant clone? In fact, it was discovered that the patient had recently stopped treatment, essentially replicating the classic discontinuation trials like STIM and CML8 in which patients who experienced disease progression off treatment did so fairly quickly. Dr Branford noted that the first question to ask any

patient with a PCR spike is, "Are you taking your medicine?" Careful assessment of side effects and adherence is particularly important in younger patients who may be less accepting of indefinite treatment.

5. Something non-TKI related

In a previous issue of this series we profiled a fascinating Phase III effort out of China evaluating the subcutaneously administered cephalotaxine, omacetaxine mepesuccinate, in patients with AML. Also known as homoharringtonine, this agent — which inhibits protein synthesis via a mechanism independent of BCR-ABL — was approved in October for CML, and at ASH we saw updated data from **2 Phase II studies**. These findings further illustrate the effectiveness of this agent in later-line disease, including among **patients with T315I mutations**.

That does it for this year's ASH highlights series. Stay tuned for our next hem-onc email program, as we explore the therapeutic revolution in myelofibrosis by providing you with the perspectives and practice patterns of 8 investigators with extensive experience with this complex disease.

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 1.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

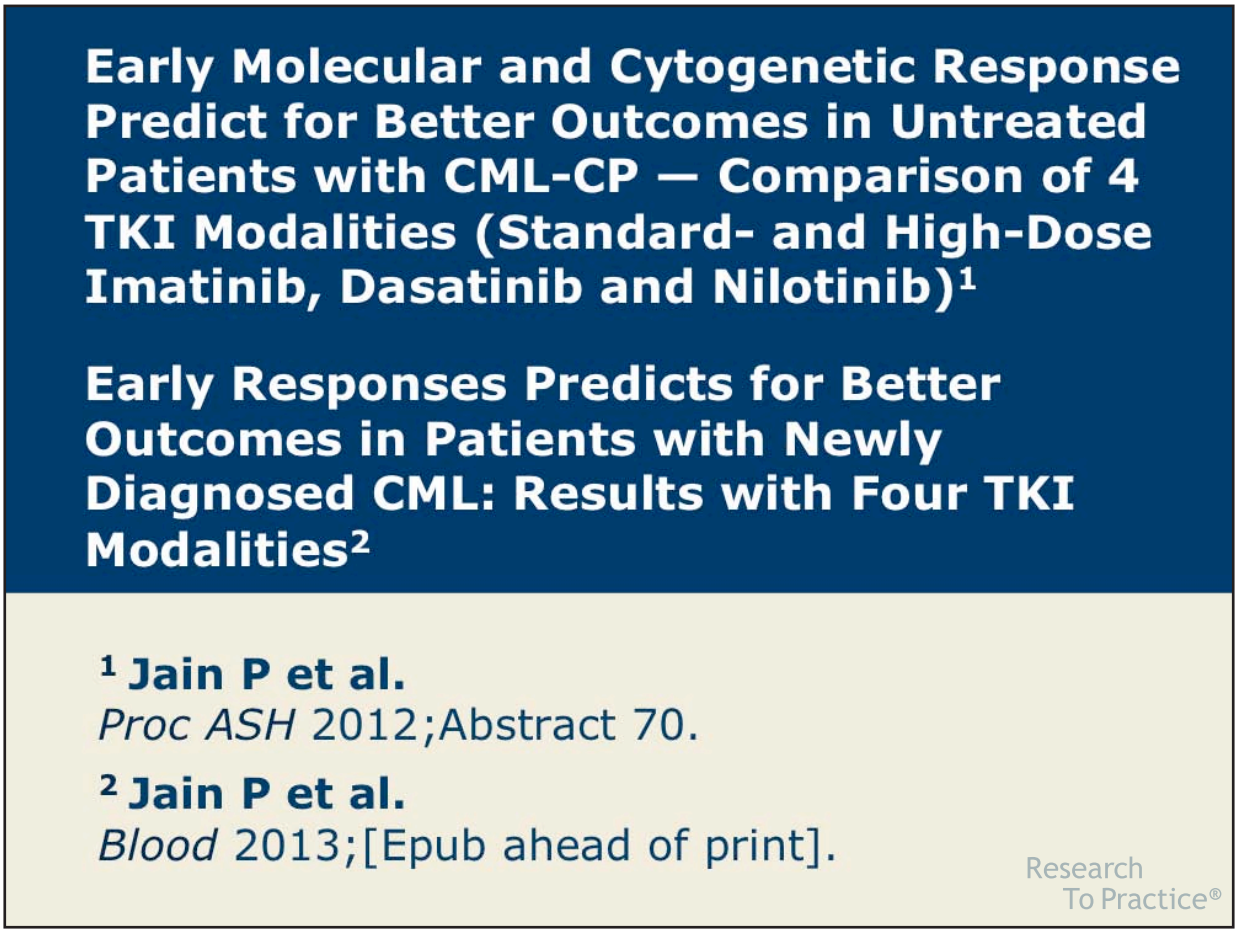
This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/ Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

Early Response to Tyrosine Kinase Inhibitors Predicts Better Outcomes in Untreated Chronic-Phase CML

Presentation discussed in this issue

Jain P et al. **Early molecular and cytogenetic response predict for better outcomes in untreated patients with CML-CP — Comparison of 4 TKI modalities (standard- and high-dose imatinib, dasatinib and nilotinib).** *Proc ASH* 2012;**Abstract 70**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Moshe Talpaz, MD (2/20/13)



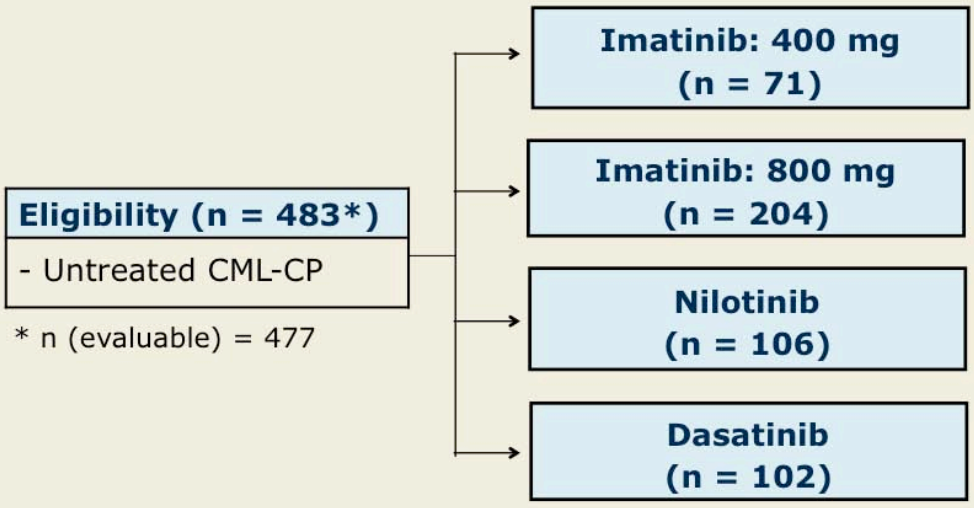
Background

- Early molecular and cytogenetic responses to TKIs are predictive of long-term outcomes of patients with CML (*J Clin Oncol* 2012;30:232).
- Earlier responses have been observed with dasatinib or nilotinib than with imatinib, and these second-generation TKIs show an improvement in long-term outcomes (*J Clin Oncol* 2011;29:4260).
- **Study objective:** Analyze patterns of response and their long-term impact on clinical outcomes among patients with CML-CP treated with 4 TKI modalities as front-line therapy.

Jain P et al. *Blood* 2013;[Epub ahead of print].

Research To Practice®

Study Design



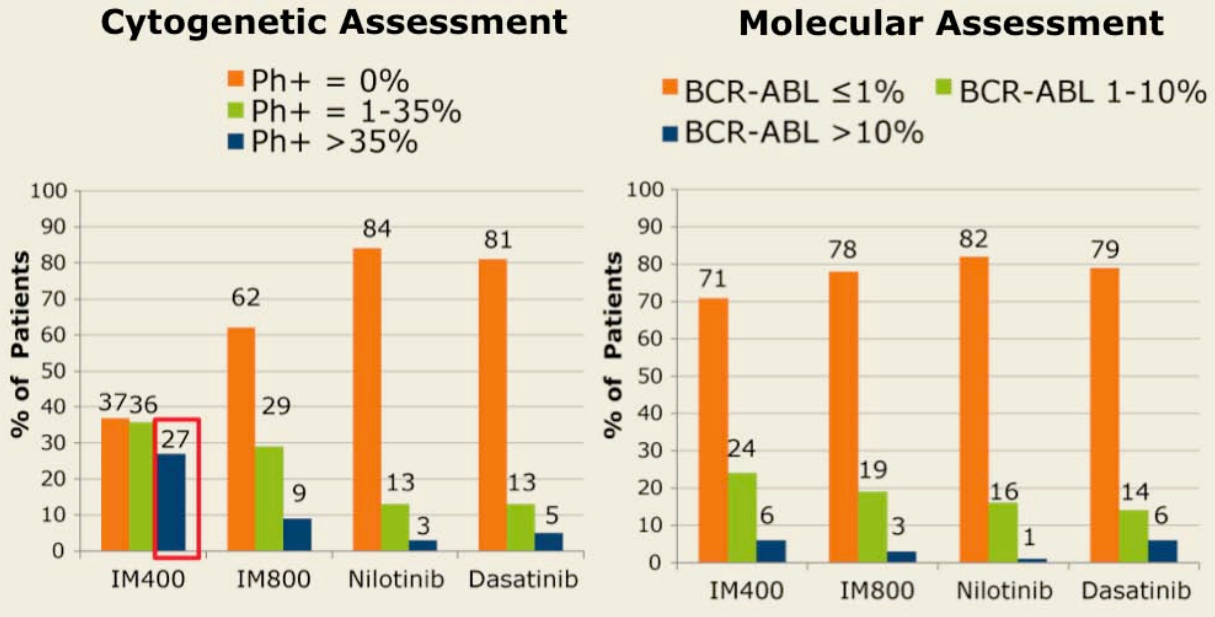
Cytogenetic responses analyzed every 3 months of first year, then every 6 to 12 months

PCR every 3 months for first year, then every 6 months

Jain P et al. *Blood* 2013;[Epub ahead of print].

Research To Practice®

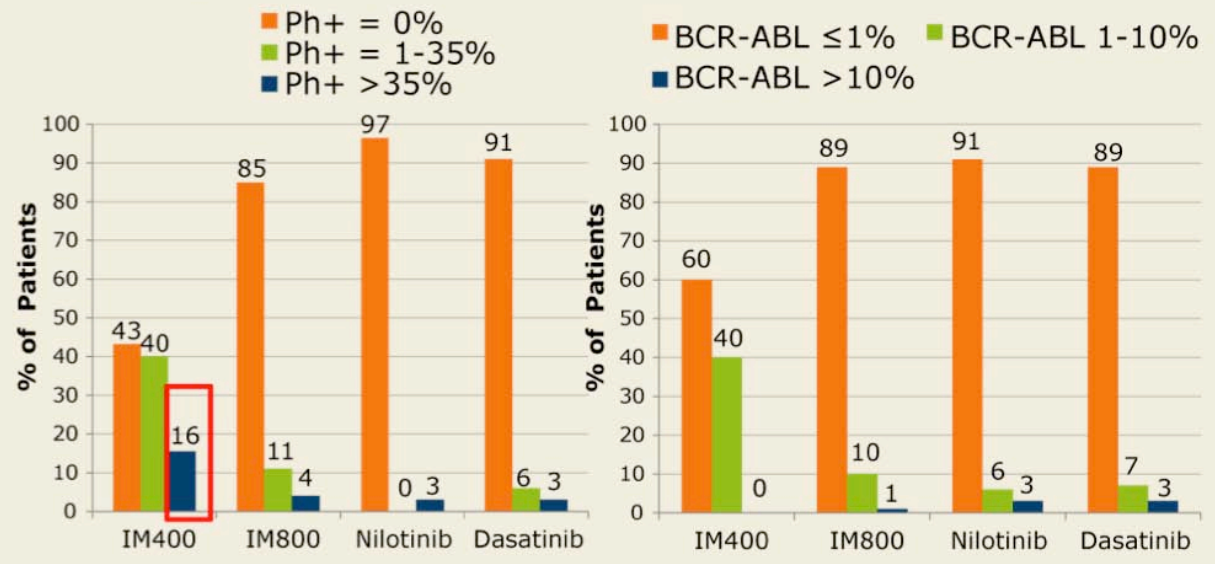
Evaluable Response at 3 Months by TKI



Jain P et al. *Blood* 2013;[Epub ahead of print].

Research To Practice®

Evaluable Response at 6 Months by TKI



Jain P et al. *Blood* 2013;[Epub ahead of print].

Research To Practice®

Event-Free Survival by Response at 3 Months

		Three-year event-free survival (%)				
Response		**Overall**	**IM 400**	**IM 800**	**Nilotinib**	**Dasatinib**
Cytogenetic 3-month	Ph+ 0%	97	92	97	97	99
	Ph+ 1%-35%	89	88	89	92	91
	Ph+ >35%	81	83	83	67	75
Molecular 3-month	BCR-ABL ≤1%	96	NA	94	96	100
	BCR-ABL >1%-10%	98	NA	100	94	100
	BCR-ABL >10%	61	NA	80	100	27

- Similar results at 6-month landmark
- Events included loss of complete hematologic remission, loss of major cytogenetic response, progression to accelerated or blast phase or death from any cause

Jain P et al. *Blood* 2013;[Epub ahead of print].

Research To Practice®

Failure-Free Survival by Response at 3 Months

		Three-year failure-free survival (%)				
Response		**Overall**	**IM 400**	**IM 800**	**Nilotinib**	**Dasatinib**
Cytogenetic 3-month	Ph+ 0%	87	76	85	87	95
	Ph+ 1%-35%	70	67	67	92	81
	Ph+ >35%	51	71	44	33	50
Molecular 3-month	BCR-ABL ≤1%	85	NA	78	88	95
	BCR-ABL >1%-10%	73	NA	69	75	82
	BCR-ABL >10%	61	NA	60	100	50

- Similar results at 6-month landmark
- Failure included loss of CCyR, intolerance or discontinuation of therapy

Jain P et al. *Blood* 2013;[Epub ahead of print].

Research To Practice®

Overall Survival by Cytogenetic Response at 3 and 6 Months

		Three-year overall survival (%)				
Response		**Overall**	**IM 400**	**IM 800**	**Nilotinib**	**Dasatinib**
Cytogenetic 3-month	Ph+ 0% Ph+ 1%-35% Ph+ >35%	98 96 92	100 91 83	97 96 100	99 100 100	98 100 100
Cytogenetic 6-month	Ph+ 0% Ph+ 1%-35% Ph+ >35%	99 98 75	100 100 64	99 95 86	100 NA 100	99 100 100

Jain P et al. *Blood* 2013;[Epub ahead of print].

Research To Practice®

Author Conclusions

- Early (3- and 6-month) and deep cytogenetic and molecular responses with any TKI were associated with improved EFS and FFS.
- Clinical impact of early response is similar among the 4 TKI modalities.
- Patients treated with high-dose imatinib, dasatinib or nilotinib achieve earlier responses.
- Age, Sokal score and treatment modality were associated with outcome (data not shown).

Jain P et al. *Blood* 2013;[Epub ahead of print].

Research To Practice®

Investigator Commentary: Early Response to TKIs Predicts Better Outcome in Untreated CML-CP

This study found that by 3 months, one can already identify patients with CML-CP who will fare well versus those who will not fare as well after treatment with dasatinib, nilotinib or imatinib (400 mg or 800 mg). The good responders are those who at 3 months have <10% BCR-ABL to ABL ratio or <35% Ph+ cells, which indicates a partial or better cytogenetic response. If patients reach that level of response, the risk of progression is minimal and is not inferior to those who have <1% disease. Patients who have >10% disease appear to be at high risk and are likely to experience disease progression down the road. In that respect, this study was more confirmatory because this is presented in the NCCN guidelines for optimal response at 3 months.

One intriguing finding is that patients treated with high-dose imatinib achieved molecular responses that were at least equal to those achieved with dasatinib and nilotinib. However, I would not advocate high-dose imatinib as a treatment because of the significant toxicity associated with it.

The other interesting finding is the high rate of survival of patients after more than 10 years of follow-up. This is remarkable for a disease that was considered lethal 20 years ago.

Interview with Moshe Talpaz, MD, February 20, 2013