5 Minute JournalClub

POST-ASH Issue 7, 2013

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CME Information

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.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

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

CME Information (Continued)

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5 MinuteJournalClub

POST-ASH Issue 7, 2013

CML update: A lot going on, as usual

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

A Pivotal Phase 2 Trial of Ponatinib in Patients with CML and Ph+ ALL Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I BCR-ABL Mutation: 12-Month Follow-Up of the PACE Trial

Cortes JE et al.

Proc ASH 2012;Abstract 163.

Background

- In approximately 25% of patients with CML, the disease does not respond or becomes resistant to imatinib.
  - Resistance is often caused by mutations in the BCR-ABL protein, which prevent imatinib from binding to that protein.
  - Approximately 50% of patients respond to second-generation TKIs dasatinib and nilotinib, but many will become resistant to these drugs as well.
- Ponatinib was molecularly designed to overcome limitations of other TKIs.
- **Current study objective:** To evaluate the efficacy and safety of ponatinib in patients with CML or Philadelphia chromosome-positive (Ph+) ALL.

www.cancer.gov/ncicancerbulletin/121112/page2/AllPages.

Phase II International PACE Trial Design

Eligibility (N = 449)

- CML-CP, CML-AP, CML-BP or Ph+ ALL
- T315I mutation **or**
- Resistant or intolerant (R/I) to dasatinib or nilotinib

→ **Ponatinib**
45 mg orally once daily

Primary endpoints

- Major cytogenetic response (MCyR) at any time within 12 months
- Major hematologic response (MaHR) at any time within 6 months

Cortes JE et al. *Proc ASH* 2012;Abstract 163.

Primary Endpoint: Responses

	CML-CP	CML-AP	CML-BP/ Ph+ ALL
Primary endpoint	**MCyR**	**MaHR**	**MaHR**
R/I to dasatinib or nilotinib (n = 203; 65; 48)	51%	58%	35%
T315I mutation (n = 64; 18, 46)	70%	50%	33%
Total (n = 267, 83, 94)	56%	57%	34%

Patients remaining on study (n, %): CML-CP (171, 63%), CML-AP (45, 53%), CML-BP/Ph+ ALL (6, 6%)

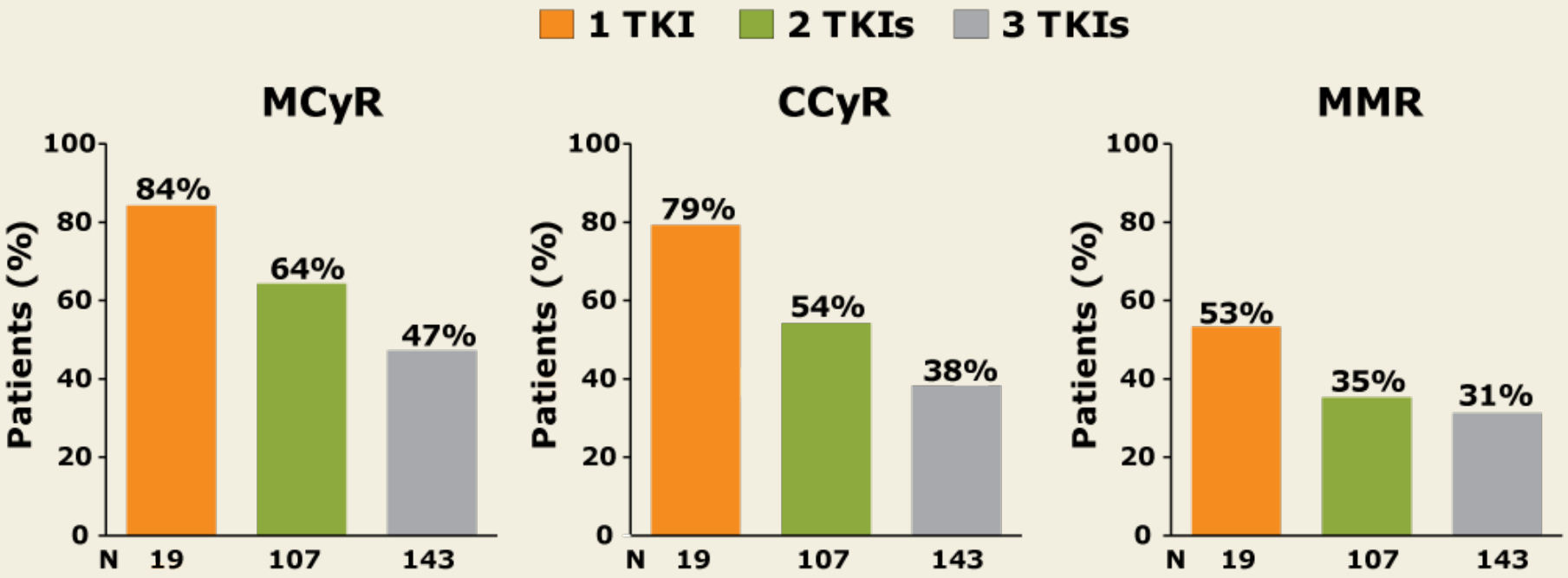
Cortes JE et al. *Proc ASH* 2012;Abstract 163.

Response Characteristics and Survival: CML-CP

Response rate	**(n = 267)**
Any cytogenetic response	67%
MCyR	56%
CCyR	46%
Major molecular response (MMR)	34%
Median time to response	
MCyR	2.8 months
MMR	5.5 months
Clinical outcomes at 12 months	
MCyR	91%
PFS	80%
OS	94%

Cortes JE et al. *Proc ASH* 2012;Abstract 163.

Response by Number of Prior Approved TKIs: CML-CP



TKIs = imatinib, dasatinib, nilotinib

Cortes JE et al. *Proc ASH* 2012;Abstract 163.

Select Adverse Events (AEs): Total Population (N = 449)

Nonhematologic	Any grade	Grade 3/4
Rash	38%	4%
Abdominal pain	38%	9%
Headache	35%	2%
Dry skin	35%	2%
Constipation	34%	2%
Hypertension	21%	7%
Hematologic	**Any grade**	**Grade 3/4**
Thrombocytopenia	42%	34%
Neutropenia	24%	21%
Anemia	20%	14%

Serious AEs: Pancreatitis: 5%; myocardial infarction: 3%; cardiac failure/atrial fibrillation: 6%

Cortes JE et al. *Proc ASH* 2012;Abstract 163.

Author Conclusions: 12-Month Follow-Up Summary

- Robust clinical activity of ponatinib was observed in patients with heavily pretreated disease, with
  - Responses regardless of mutation status or disease stage
  - Higher response rates in patients with less heavily pretreated disease
- Early and deep responses were observed: 34% MMR and 15% MR.
- Responses were durable: 91% estimated to remain in MCyR at 1 year.
- Ponatinib was generally well tolerated.
- Ponatinib may be an important new treatment for CML and Ph+ ALL resistant or intolerant to prior TKIs.

Cortes JE et al. *Proc ASH* 2012;Abstract 163.

Investigator Commentary: Pivotal Phase II International PACE Trial of Ponatinib in CML and Ph+ ALL

Ponatinib is the fifth TKI approved in CML, and it's perhaps the most powerful of all the TKIs because it "covers" virtually all of the mutations. The PACE study included patients with CML-CP, CML-AP, CML-BP and Ph+ ALL, with or without the T315I mutation. I emphasize the T315I mutation because that is a mutation within the BCR-ABL kinase domain that is resistant to all existing treatments for CML other than ponatinib and the chemotherapeutic agent omacetaxine. So T315I is the ultimate mutation, which renders the disease resistant to imatinib, nilotinib, dasatinib and bosutinib. However, the disease is responsive to ponatinib, which was demonstrated in the PACE study.

Additionally, there were high response rates in patients who were resistant to 1, 2 and even 3 prior TKIs. Surprisingly, major cytogenetic responses were observed in more than 50% of patients, with more than 40% complete cytogenetic responses. Why is this important? This is a group of patients with bad, long-standing disease that is resistant to all other treatments. Nevertheless, the disease responded to ponatinib — not just in terms of hematologic response but also by cytogenetic improvement.

Interview with Moshe Talpaz, MD, February 20, 2013

Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Failure with Imatinib plus Dasatinib and/or Nilotinib: 24-Month Minimum Follow-Up Update

Khoury HJ et al.

Proc ASH 2012;Abstract 3785.

Background

- Bosutinib is an orally active dual inhibitor of the Src and Abl tyrosine kinases, with modest inhibitory activity against platelet-derived growth factor receptor and c-KIT.
- On September 4, 2012, the FDA approved bosutinib for the treatment of chronic-, accelerated- or blast-phase Philadelphia chromosome-positive (Ph+) CML in patients with resistance or intolerance to prior therapy based on a Phase I/II study.
- **Current study objective:** Provide a 24-month update on the safety and efficacy of bosutinib in patients with CML-CP after failure on imatinib and dasatinib and/or nilotinib.

Khoury HJ et al. *Proc ASH* 2012;Abstract 3785.

Phase I/II Open-Label Study (Abstract Only)

- Patients with CML-CP with prior imatinib (IM) failure (N = 119) and:
  - Dasatinib resistance (DAS-R; n = 38)
  - Dasatinib intolerance (DAS-I; n = 50)
  - Nilotinib resistance (NIL-R; n = 27)
  - Nilotinib intolerance (NIL-I; n = 1)
  - Failure of dasatinib and nilotinib (DAS/NIL; n = 3)
- Treated with bosutinib starting at 500 mg/day
- Median follow-up duration: 31.4 months

Khoury HJ et al. *Proc ASH* 2012;Abstract 3785.

Response and Survival (Abstract Only)

Endpoint	IM + DAS-R	IM + DAS-I	IM + NIL-R	IM + DAS/NIL	Total
Evaluable, n	37	49	25	4	115
CHR	62%	80%	76%	75%	73%
Evaluable, n	36	44	26	4	110
MCyR	33%	48%	39%	50%	41%
CCyR	19%	43%	27%	50%	32%
Treated, n	38	50	27	4	119
2-y PFS	70%	81%	79%	38%	75%
2-y OS	77%	85%	92%	75%	84%

CHR = complete hematologic response; MCyR = major cytogenetic response; CCyR = complete cytogenetic response; PFS = progression-free survival; OS = overall survival

On-treatment transformation to CML-AP: 4%

Khoury HJ et al. *Proc ASH* 2012;Abstract 3785.

Treatment-Emergent Adverse Events (Abstract Only)

Adverse event	All grades	Grade 3/4
Diarrhea	82%	8%
Nausea	49%	1%
Vomiting	40%	1%
Rash	27%	3%
Headache	26%	3%
Fatigue	24%	1%
Abdominal pain	20%	1%
Grade 3/4 laboratory abnormalities		
Thrombocytopenia	25%	
Neutropenia	19%	
Lymphopenia	17%	
Hypermagnesemia	12%	

Khoury HJ et al. *Proc ASH* 2012;Abstract 3785.

Author Conclusions

- Bosutinib continues to demonstrate durable efficacy in CML-CP following resistance or intolerance to multiple TKIs after a minimum of 24 months of follow-up.
  - The majority of patients maintain responses at 2 years.
  - Few patients transformed to accelerated phase (4%) and none entered blast crisis.
- Grade 3/4 nonhematologic toxicity was uncommon.
- Diarrhea, predominantly Grade 1/2, was the most common adverse event and usually occurred early during treatment.
- Dose reductions and interruptions occurred in 50% and 66% of patients.
- 27% of patients discontinued treatment, primarily due to hematologic events.

Khoury HJ et al. *Proc ASH* 2012;Abstract 3785.

Investigator Commentary: Bosutinib for CML-CP After Failure with Imatinib and Dasatinib and/or Nilotinib

This study evaluated bosutinib in patients with CML-CP who had previously received imatinib and were resistant or intolerant to dasatinib and/or nilotinib. Surprisingly, a significant proportion of patients responded to this drug, so it may have a role in the resistant disease setting. It's difficult to say whether it has activity similar to that of ponatinib, which was quite active in this setting.

The major bosutinib-related toxicity was diarrhea, which can be disturbing and may reach a Grade 3/4 level of severity. Otherwise, bosutinib seems to be tolerable over time.

So we have another drug in our treatment arsenal for CML. In particular, I think about using it in elderly patients with heart disease as well as in other settings. Bosutinib may be a nice backup drug, and I do use it occasionally.

Interview with Moshe Talpaz, MD, February 20, 2013

Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Resistance or Intolerance to Imatinib: 36-Month Minimum Follow-Up Update

Cortes JE et al.

Proc ASH 2012;Abstract 3779.

Background

- Bosutinib is an orally active dual inhibitor of the Src and ABL tyrosine kinases with modest inhibitory activity against platelet-derived growth factor receptor or c-KIT.
- On September 4, 2012, the FDA approved bosutinib for the treatment of chronic-, accelerated- or blast-phase Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in patients with resistance or intolerance to prior therapy, based on a Phase I/II study.
- **Current study objective**: To provide updated results on the efficacy, tolerability and safety of the pivotal Phase I/II study of bosutinib as second-line therapy for patients with Ph+ chronic-phase CML (CML-CP) with imatinib resistance (IM-R) or intolerance (IM-I) after ≥36 months minimum follow-up.

Cortes JE et al. *Proc ASH* 2012;Abstract 3779.

Phase I/II, Open-Label Multicenter Study (Abstract Only)

- Part 1 (dose-escalation phase): Determined a recommended starting dose of bosutinib 500 mg/day to be used in part 2
- Part 2: Evaluation of safety, tolerability and efficacy of bosutinib 500 mg/day
  - Patients with confirmed diagnosis of Ph+ CML-CP
  - Imatinib resistance (n = 195) or intolerance (n = 91)

Cortes JE et al. *Proc ASH* 2012;Abstract 3779.

Response, Transformation and Survival (Abstract Only)

	IM-R (n = 194)	IM-I (n = 91)
Complete hematologic response (CHR)	86%	85%
Est probability of maintaining CHR at 3 y	65%	83%
Major cytogenetic response (MCyR, n = 182, 82)	58%	60%
Est probability of maintaining MCyR at 3 y	71%	88%
Complete cytogenetic response (CCyR, n = 182, 82)	48%	51%
On-treatment transformation to accelerated- or blast-phase CML	5%	2%
Est 3-y progression-free survival	72%	89%
Est 2-y overall survival	88%	98%

- Responses to bosutinib observed for different BCR-ABL baseline mutations, including those associated with resistance to other TKIs, but were low (CHR, 22%; MCyR, 22%) among patients with T315I mutation

Cortes JE et al. *Proc ASH* 2012;Abstract 3779.

Nonhematologic Treatment-Emergent Adverse Events (AEs) (Abstract Only)

Nonhematologic AEs	Any grade	Grade 3 or 4
Diarrhea	85%	10%
Nausea	46%	1%
Vomiting	37%	4%
Rash	36%	9%
Pyrexia	26%	1%
Abdominal pain	25%	1%
Fatigue	25%	1%

Cortes JE et al. *Proc ASH* 2012;Abstract 3779.

Grade 3 and 4 On-Treatment Hematologic AEs (Abstract Only)

Hematologic AEs	Grade 3 or 4
Thrombocytopenia	25%
Neutropenia	18%
Lymphocytopenia	16%
Anemia	14%
Hypermagnesemia	11%
Alanine transaminase elevation	11%
Hypophosphatemia	10%

- Proportion of patients with IM-R and IM-I CML and with
  - ≥1 dose reduction: 45% vs 57%
  - Drug discontinuation: 16% vs 41%

Cortes JE et al. *Proc ASH* 2012;Abstract 3779.

Author Conclusions (Abstract Only)

- Bosutinib continues to demonstrate durable clinical efficacy as second-line therapy for patients with CML-CP after 36 months minimum follow-up:
  - High cumulative rates of CHR (~85%) and MCyR (~59%)
  - Responses were durable, with 65% to 83% of IM-R and IM-I patients, respectively, retaining their CHR at 3 years and 71% to 88% of patients retaining their MCyR at 3 years
- Estimated 3-year progression-free survival was 72% (IM-R) and 89% (IM-I).
  - Low rates of transformation to AP (5%) and BP (2%) CML
- Estimated 2-year overall survival was 88% (IM-R) and 98% (IM-I).
- Grade 3 or 4 nonhematologic AEs were infrequent, and Grade 3 or 4 thrombocytopenia (25%) was the most common reason for dose reduction or discontinuation.

Cortes JE et al. *Proc ASH* 2012;Abstract 3779.

Investigator Commentary: 36-Month Follow-Up of Bosutinib for Patients with CML-CP with Resistance or Intolerance to Imatinib

Bosutinib is a second-generation BCR-ABL inhibitor, which means it doesn't inhibit the T315I mutation. In that respect, it's similar to dasatinib and nilotinib. The activity of bosutinib is similar or perhaps even slightly superior to dasatinib and nilotinib in patients with imatinib-resistant disease (IM-R) or those who are intolerant to imatinib (IM-I).

In this particular study, the IM-I group didn't respond better than the IM-R group, which is interesting. More than 50% of the patients experienced major cytogenetic responses, and more than 40% experienced complete cytogenetic responses. In that respect bosutinib is similar to the other second-generation tyrosine kinase inhibitors (TKIs). Surprisingly, the responses were fairly durable and perhaps a little better than those we have seen with nilotinib.

So we have another BCR-ABL inhibitor that is effective. The question is, why should we use one over the others? Perhaps the biggest advantage of bosutinib is that it doesn't cause significant fluid retention like imatinib. It doesn't cause significant pleural effusion or pericardial effusion like dasatinib. It doesn't cause pancreatitis and liver abnormalities like nilotinib. Additionally, the skin toxicity seems to be mild. It has a different toxicity profile than the other TKIs.

Interview with Moshe Talpaz, MD, February 20, 2013

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)[1]

Early Responses Predicts for Better Outcomes in Patients with Newly Diagnosed CML: Results with Four TKI Modalities[2]

[1] **Jain P et al.**
Proc ASH 2012;Abstract 70.

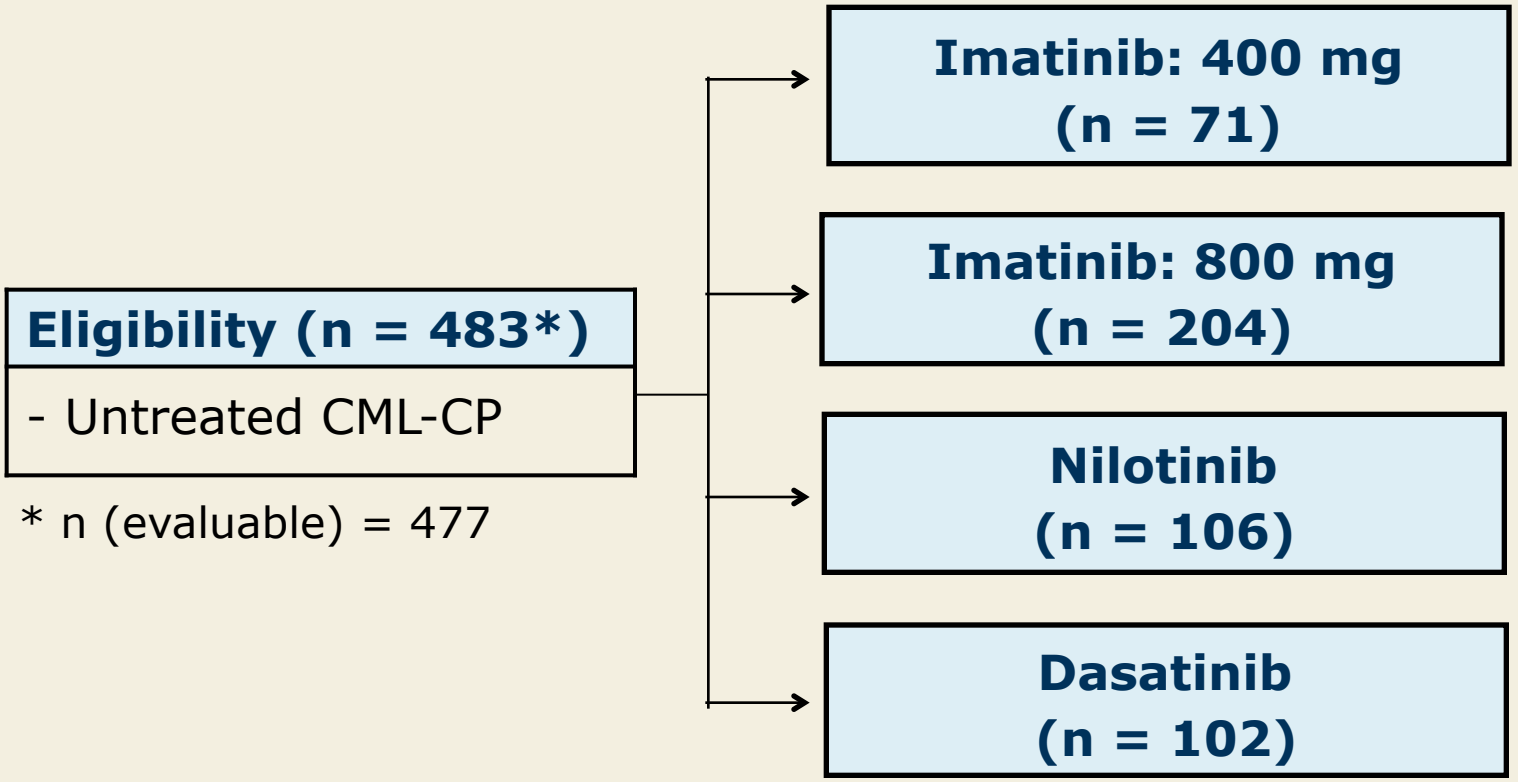
[2] **Jain P et al.**
Blood 2013;[Epub ahead of print].

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].

Study Design



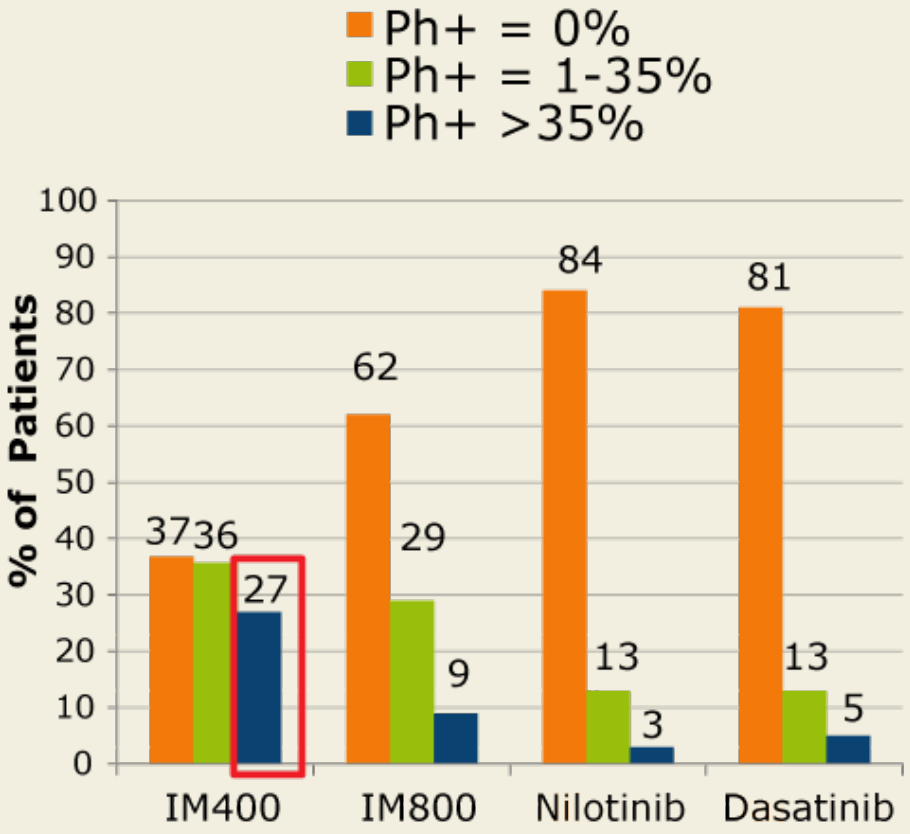
Cytogenetic responses analyzed every 3 months of first year, then every 6 to 12 months

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

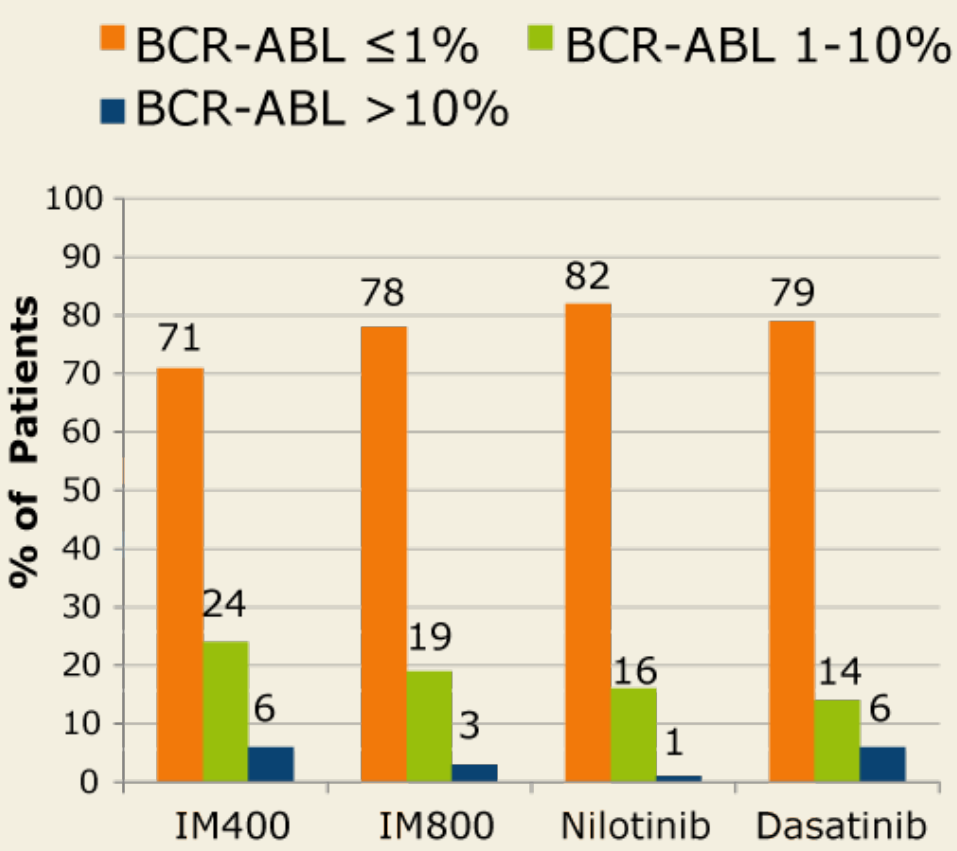
Jain P et al. *Blood* 2013;[Epub ahead of print].

Evaluable Response at 3 Months by TKI

Cytogenetic Assessment



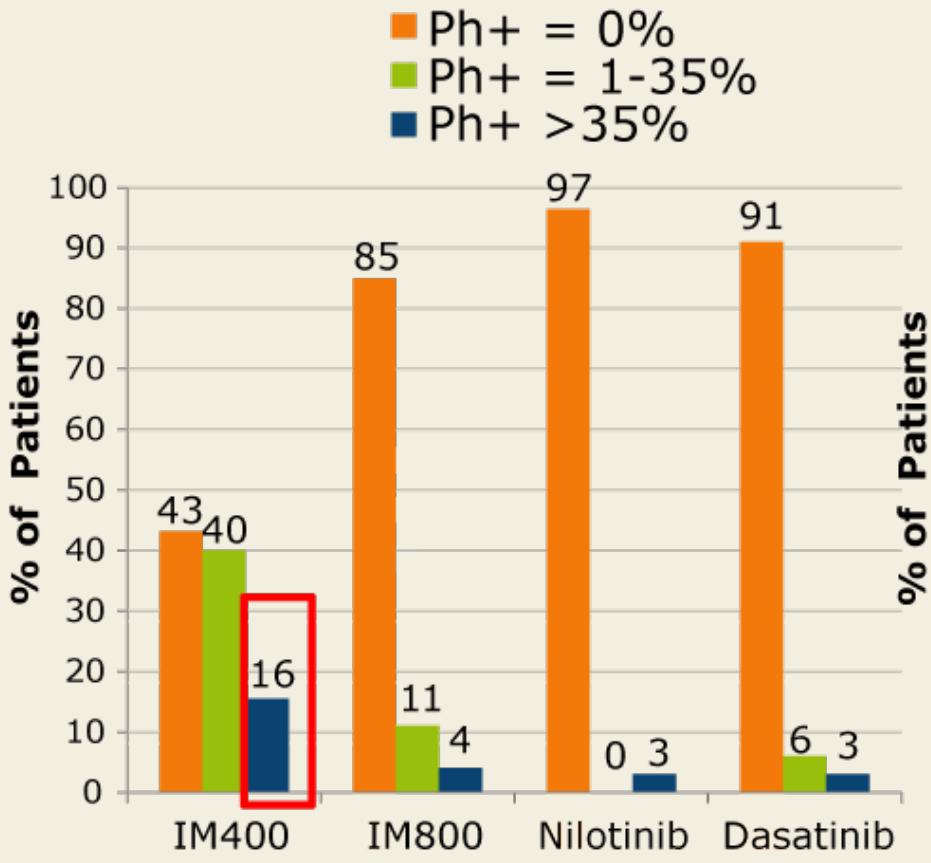
Molecular Assessment



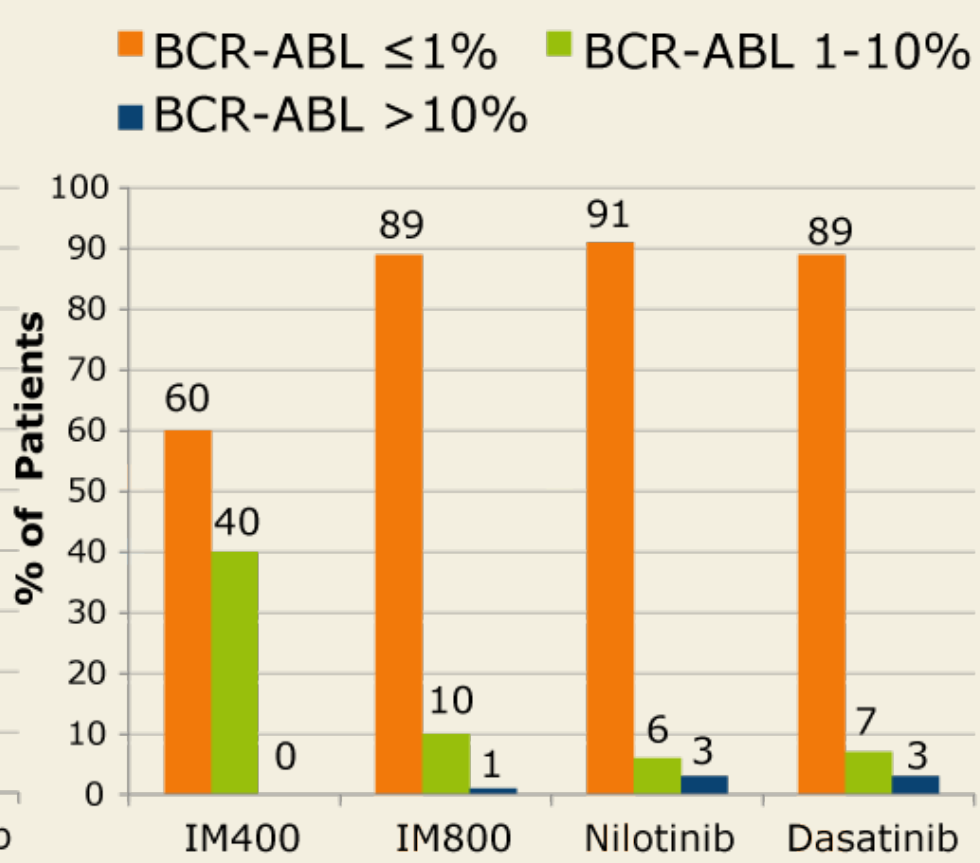
Jain P et al. *Blood* 2013;[Epub ahead of print].

Evaluable Response at 6 Months by TKI

Cytogenetic Assessment



Molecular Assessment



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

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% Ph+ 1%-35% Ph+ >35%	97 89 81	92 88 83	97 89 83	97 92 67	99 91 75
Molecular 3-month	BCR-ABL ≤1% BCR-ABL >1%-10% BCR-ABL >10%	96 98 61	NA NA NA	94 100 80	96 94 100	100 100 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].

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% Ph+ 1%-35% Ph+ >35%	87 70 51	76 67 71	85 67 44	87 92 33	95 81 50
Molecular 3-month	BCR-ABL ≤1% BCR-ABL >1%-10% BCR-ABL >10%	85 73 61	NA NA NA	78 69 60	88 75 100	95 82 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].

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].

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].

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

Long-Term Follow-Up of Ongoing Patients in 2 Studies of Omacetaxine Mepesuccinate for Chronic Myeloid Leukemia

Kantarjian HM et al.

Proc ASH 2012;Abstract 2787.

Background

- Omacetaxine mepesuccinate is a semisynthetic, highly purified homoharringtonine compound that recently received approval for the treatment of chronic myeloid leukemia (CML).
- Omacetaxine reduces levels of multiple oncoproteins, including BCR-ABL, and induces apoptosis in leukemic stem cells.
- In 2 separate Phase II trials, it has demonstrated
  - Clinical activity and tolerability in patients with chronic-phase CML (CML-CP) with T315I BCR-ABL mutation (*Blood* 2012;120:2573).
  - Efficacy in patients with resistance or intolerance to ≥2 approved tyrosine kinase inhibitors (*Am J Hematol* 2013;88:350).
- **Study objective:** To report updated efficacy and safety results for patients continuing to receive omacetaxine as of March 2012 in these 2 Phase II studies.

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

Study Methods

- Patients with CML-CP, accelerated-phase CML (CML-AP) and blast-phase CML (CML-BP) were enrolled in both Phase II trials (n = 203).
- Patients (n = 11) received omacetaxine 1.25 mg/m^2 BID (SC):
  - Induction: Up to 14 consecutive days/cycle (28-day cycles)
  - Maintenance: Up to 7 days/28-day cycle
- Patients with CML-CP (n = 9) and CML-AP (n = 2) continued to receive omacetaxine as of March 2012.
- Primary efficacy measures differed by disease phase:
  - CML-CP: Complete hematologic response (CHR) for ≥8 weeks and major cytogenetic response (MCyR)
  - CML-AP and CML-BP: Major hematologic response or return to CML-CP, lasting for ≥4 weeks

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

Baseline Characteristics

Characteristic	CML-CP (n = 9)	CML-AP (n = 2)
Median age	61.0 years	57.5 years
Median number of Tx cycles	35	19 and 22
Gender (male)	78%	100%
ECOG PS 0	78%	50%
1	22%	50%
CHR at baseline	66.7%	0%
Mutational status		
BCR-ABL T3151	56%	0%
Other	22%	50%
None	22%	50%

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

Best Responses

Response rate, n (%)	CML-CP (n = 9)	CML-AP (n = 2)
MCyR	7 (77.8%)	0%
CHR at ≥8 weeks	6 (66.7%)	0%
CHR within 3 months of Tx	3 (33.3%)	1 (50%)

- For patients with CML-CP
  - Median time to onset of MCyR was 4.5 months.
  - Median duration of CHR was 24.4 months.
  - Median duration of response was 14.1 months.
- For patients with CML-AP
  - Duration of CHR at <3 months was ongoing at time of analysis (11.4 months).

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

Select Adverse Events (AEs)

Nonhematologic AEs (all grades)	CML-CP (n = 9)	CML-AP (n = 2)
Upper respiratory infection	55.6%	100%
Nausea	77.8%	Not reported (NR)
Diarrhea	55.6%	NR
Fatigue	55.6%	NR
Headache	44.4%	NR
Peripheral edema	44.4%	NR

- No Grade 3 or 4 nonhematologic AEs reported in ≥2 patients
- Treatment-related blast crisis was reported in 1 patient with CML-AP; treatment was discontinued for this patient
- Grade 3 and 4 laboratory hematologic and nonhematologic AEs were common in early cycles but less frequent as treatment progressed for patients with CML-CP

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

Author Conclusions

- A subset of heavily pretreated patients with CML-CP or CML-AP who participated in 2 Phase II studies of omacetaxine were able to continue treatment for up to 53 cycles.
- Seven out of 9 patients with CML-CP experienced a durable MCyR, and all 9 patients maintained a CHR.
- One of 2 patients with CML-AP experienced a durable CHR.
- Grade 3 and 4 adverse events were primarily hematologic, and these results were consistent with the known safety profile of omacetaxine.

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

Investigator Commentary: Long-Term Follow-Up of Patients Continuing to Receive Omacetaxine in 2 Phase II Trials

With omacetaxine we observe quite a bit of clinical activity in patients who have CML refractory to several lines of therapy — major cytogenetic responses in about 20% of patients. Aside from the potential for combining this agent with TKIs, which is currently being explored in a pilot study, I believe omacetaxine may also have a role for elderly patients with acute myeloid leukemia (AML) and as consolidation therapy in younger patients with AML as part of a combination regimen.

I have administered this agent to patients for up to 4 years and have achieved long-term disease control. However, if we stop therapy the disease will relapse. There are no long-term side effects that we know of, and the main toxicity observed is myelosuppression, which can be managed by adjusting the number of days of administration anywhere from 1 to 7 days, depending on the degree of myelosuppression with each course.

Interview with Hagop M Kantarjian, MD, February 20, 2013

Blast Phase Chronic Myeloid Leukemia: A Pooled Analysis of Subcutaneous Omacetaxine Mepesuccinate in Treatment-Resistant Patients

Khoury HJ et al.

Proc ASH 2012;Abstract 3753.

Background

- Subcutaneous omacetaxine mepesuccinate has demonstrated clinical activity and adequate tolerability in 2 Phase II international multicenter studies for patients with
  - A history of T315I mutations who experienced failure of prior imatinib therapy (*Blood* 2012;120:2573)
  - Resistance or intolerance to ≥2 tyrosine kinase inhibitors (TKIs) (*Am J Hematol* 2013;88:350)
- **Current study objective:** To evaluate the safety and efficacy of omacetaxine for patients with CML in the blast phase (CML-BP) from the 2 Phase II trials through a pooled analysis.

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

Methods (Abstract Only)

- Pooled analysis of patients (N = 44) with CML-BP from 2 Phase II studies
- Patients received omacetaxine 1.25 mg/m^2 subcutaneously twice daily for up to 14 consecutive days every 28 days for induction.
- Patients received the same dosage for up to 7 days every 28 days as maintenance therapy.
- The number of consecutive days of dosing could be adjusted as clinically indicated.
- Primary outcomes:
  - Major hematologic response (MaHR)
  - Major cytogenetic response (MCγR)

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

Prior TKI Therapy and Primary Response Endpoints (Abstract Only)

Number of prior TKIs

1	11%
2	45%
3	43%

Efficacy endpoints	
MaHR	9%
Median duration of MaHR	1.7 months
MCγR	0%
Median OS	3.5 months
Median OS with MaHR	Not yet reached as of >1 year follow-up
Median OS without MaHR	3.5 months
Median PFS	2.2 months

OS = overall survival; PFS = progression-free survival

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

Grade 3 and 4 Adverse Events (Abstract Only)

Grade 3 or 4 adverse events	
Thrombocytopenia	98%
Anemia	82%
Neutropenia	82%
Leukopenia	66%

Two patients discontinued treatment because of AEs.
One treatment-related death (sepsis) was recorded.

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

Author Conclusions

- Among heavily pretreated patients with CML-BP who had experienced failure of prior TKI therapy, omacetaxine demonstrated limited activity:
  - 13% of patients experienced hematologic improvement.
  - 2 patients experienced responses with a duration exceeding 1 year.
- Most Grade 3 and 4 adverse events were hematologic.
- Grade 3 or 4 nonhematologic events were uncommon.

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

Investigator Commentary: Omacetaxine in Patients with Treatment-Resistant CML in Blast Crisis

I was involved in the early studies of omacetaxine in the 1990s, and I have not used it frequently. Omacetaxine can be effective for patients with longstanding disease that is resistant to all our other treatments. I don't view it as being useful in "pushing" for cytogenetic responses. Rather, it can be used to maintain hematologic remission in some patients whose disease is still in the chronic or accelerated phase and is resistant to our other treatments. I don't believe it has much of a role in blast crisis.

Interview with Moshe Talpaz, MD, February 20, 2013

We conducted the pivotal trials in CML that led to the recent FDA approval of omacetaxine. I believe that the role of this agent could be broader than its current indication. I can envision omacetaxine potentially being used with TKIs in the stage of minimal molecular disease to produce durable complete molecular responses — the final step to possibly curing CML and stopping therapy.

Interview with Hagop M Kantarjian, MD, February 20, 2013