Phase II Results with Pegylated Interferon Alpha-2a Therapy in Polycythemia Vera
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

• Counsel patients with JAK2 mutation-positive and mutation-negative myelofibrosis about the benefits and risks of ruxolitinib treatment.
• Recall ongoing clinical trials with new agents for the treatment of myeloproliferative neoplasms, and consent or refer appropriate patients for participation.

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

It’s easy to criticize regulatory agencies, but it also seems that when stuff clearly works things can move along pretty quickly. This was the case following last June’s spectacular ASCO presentations of 2 Phase III trials (COMFORT-I and II) demonstrating that the JAK1-2 inhibitor ruxolitinib had convincing and impressive activity in patients with myelofibrosis (MF). These landmark data led to FDA approval in November — immediately providing oncologists with both new hope and many additional questions about this unique disease.

I met with the principal investigator of the North American/Australian COMFORT-I trial, MD Anderson’s Dr Srdan Verstovsek, to find out what happened at ASH to follow the ASCO explosion, but before diving into the data we talked about the human side of this profound saga. Dr Verstovsek recounted a number of very memorable real-life stories he has been part of in this new treatment era, including that of a 67-year-old Kansas man with JAK2 mutation-negative disease who had been down the “observation followed by hydroxyurea” route and then started to experience the misery this neoplasm can cause. In desperation 18 months ago he found his way to Houston, enrolled on a Phase I-II trial of ruxolitinib and almost immediately experienced shrinkage of his aching spleen (15 to 3 cm), increased mobility, weight gain and dramatic relief of constitutional symptoms. The patient recently sent Dr V a colorful postcard from a lifelong dream vacation with his wife in Costa Rica.

Dr Verstovsek reflected on what it’s like to see people who thought they were doomed to indefinite misery feel good again, but he also cautioned that ruxolitinib “is a drug and not a magic pill.” In that regard, it is clear that additional research is needed to bring about a profound sea change in this often relentless disease for which up until now we had no good answers. Below find Dr V’s take on which MF happenings at ASH may help further shift the tide in coming years.

1. Ruxolitinib

Although only about half of patients with MF have JAK2V617F mutations, all have dysregulation of the JAK-STAT pathway and benefit from JAK inhibition. At ASH Dr Verstovsek presented an update of COMFORT-I, including a survival benefit (HR = 0.50 with 13 versus 24 deaths), data showing that major symptom palliation was observed across all patient subsets (IPSS risk, age, V617F mutation, spleen size and Hb level) and that these effects were quickly lost when the drug was discontinued (click here for a dramatic graphic).

In addition, the tandem ASH presentation of the COMFORT-II European study follow-up demonstrated nearly identical spleen shrinkage across disease subtypes. Another data set presented by Dr Verstovsek suggested an important survival benefit for patients on MD Anderson Phase I-II trials of ruxolitinib compared to historical controls.
2. **Pure JAK2 inhibitors**

A number of other JAK inhibitors are currently being studied, and new data on several were reported at ASH. The first, pacritinib, is an oral JAK2 but not JAK1 inhibitor, but the waterfall plot for spleen size reduction from the Phase II study presented was similar to what was seen with ruxolitinib. The main downside of this agent was manageable GI toxicity, but of particular note, no myelosuppression was observed. Consequently this molecule and others like it may be particularly useful in patients with thrombocytopenia and anemia. The other JAK2 inhibitor that made an impression at ASH was SAR302503, which demonstrated not only efficacy and safety but also reduction in circulating JAK2V617F allele burden.

3. **Pegylated interferon alpha-2a in polycythemia vera**

Interferon has long been known to have significant activity in this disease, but the side effects have been prohibitive. Long-term follow-up (6.4 years) from this Phase II study of weekly administration of the more tolerable pegylated formulation of this therapy demonstrated that 94% of patients were still in hematologic response and 29% were able to stop treatment without further cytoreductive therapy. Dr Verstovsek notes that the elimination of clones with the JAK2 mutation as seen in this study does not occur with JAK inhibitors.

4. **Panobinostat; pomalidomide**

Dr V becomes visibly animated when he talks about future trials combining JAK inhibition with other novel strategies, and at ASH we saw more data on some potential partners, including the HDAC inhibitor panobinostat, which showed modest activity. However, what really tickles Dr V’s fancy is the idea of combining JAK inhibitors with the IMiD pomalidomide, an agent that at ASH was again demonstrated to frequently alleviate anemia, a benefit usually not seen with JAK inhibitors.

Next we reconsider lung cancer and the most common patient subset in this ubiquitous disease: Patients with EGFR and ALK wild-type metastatic adenocarcinoma.

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Phase II Results with Pegylated Interferon Alpha-2a Therapy in Polycythemia Vera

Presentation discussed in this issue


Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Srdan Verstovsek, MD, PhD (1/25/12)
Background

- Recently, 2 Phase II studies showed promising results of efficacy, tolerance and molecular responses of peg-IFNα-2a therapy in polycythemia vera (PV) and essential thrombocythemia (ET) (Blood 2008;112:3065; Cancer 2007;110:2012).
- As a result, there is renewed interest in peg-IFNα-2a therapy in patients with myeloproliferative neoplasms (MPN).
- **Objective:**
  - Analyze the long-term efficacy and safety of peg-IFNα-2a treatment in the PVN1 trial, a Phase II study of peg-IFNα-2a in PV, after a median follow-up of 6.4 years.


Study Methods

- The PVN1 trial (NCT00241241) is a Phase II open-label study of efficacy and safety of peg-IFNα-2a in 40 patients with PV, enrolled from 09/2004 to 09/2005.
- The long-term effects of peg-IFNα-2a were evaluated after a median follow-up time of 6.4 years according to the European LeukemiaNet (ELN) criteria by the analysis of:
  - Hematological response
  - Molecular response
  - Histological response
- Molecular response was assessed by measuring JAK2V617F allele burden in granulocytes of patients with serial samples.
- The median time since diagnosis was 6 months.

### Hematological Responses at Last Evaluation (Abstract Only)

<table>
<thead>
<tr>
<th>Hematological response (HR)</th>
<th>Responding patients (n = 34)*</th>
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<tbody>
<tr>
<td>Overall HR</td>
<td>94%</td>
</tr>
<tr>
<td>Complete response (HCR)</td>
<td>82%</td>
</tr>
<tr>
<td>Partial response (HPR)</td>
<td>12%</td>
</tr>
<tr>
<td>Disease relapse</td>
<td>6%</td>
</tr>
</tbody>
</table>

* Median follow-up time: 77.4 mo; median duration of peg-IFNα-2a therapy: 47.4 mo
* Patients not analyzed: 4 pts were not evaluable and 2 pts were lost to follow-up (FU)

- During FU, 20 patients (59%) stopped treatment after a median time of 42 mo.
- Out of those who stopped, 13 patients (38%) received no other cytoreductive therapy.
  - 10/13 were still in HCR off therapy after mean observation of 28+ mo.


### Molecular and Histological Responses (Abstract Only)

<table>
<thead>
<tr>
<th>Molecular response (%V617F)</th>
<th>Patients (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall molecular response</td>
<td>83%</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>28%</td>
</tr>
<tr>
<td>Patients with TET2 mutation</td>
<td>14%</td>
</tr>
<tr>
<td>Patients with TET2 mutant allele burden decrease with treatment</td>
<td>0</td>
</tr>
</tbody>
</table>

Mean %V617F: 47% at baseline, 10% at 72 mo

**Histological responses:**

- Analysis of bone marrow (BM) biopsies in some patients in HCR after discontinuation of peg-IFNα-2a revealed normalized BM morphology fulfilling the ELN criteria.
- BM biopsies from these patients excluded myelofibrosis evolution as a cause for “apparent” remission.

Adverse Events (AEs) (Abstract Only)

<table>
<thead>
<tr>
<th>AEs leading to discontinuation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Grade 2 neuropathy</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>1</td>
</tr>
<tr>
<td>Auto-antibodies</td>
<td>1</td>
</tr>
<tr>
<td>Liver enzyme elevation</td>
<td>1</td>
</tr>
</tbody>
</table>

> No unexpected AEs in spite of long-term use of peg-IFNα-2a: Median of 45.5 mo
> No patient experienced any vascular event during follow-up


Author Conclusions

- Ninety-four percent of patients with PV treated with peg-IFNα-2a were still in HR (median follow-up 6.4 years).
- Out of the patients still in HR, 82% had CR.
- Patients (29%) who could stop peg-IFNα-2a treatment remained in HR without further cytotherapeutic therapy after a median observation time of 28+ months to 64+ months.
- Histological CR was also achieved in selected patients.
- A major and sustained molecular response in %V617F was confirmed in 83% of patients.
  - Out of these patients, 28% achieved complete molecular response.
  - Patients with TET2 mutated clones appeared resistant to peg-IFNα-2a
- No vascular events were observed and no new safety concerns arose with prolonged use of peg-IFNα-2a.

Investigator Commentary: Complete Hematological, Molecular and Histological Remissions After peg-IFNα-2a Therapy in Polycythemia Vera (PV): Long-Term Results

Traditionally, interferon is occasionally used in early-stage MPN, ET and PV as an agent useful in patients not responding well to front-line therapies such as hydroxyurea. However, interferon has been associated with low-grade chronic toxicities related to myelosuppression, loss of hair, thyroid problems, depression and more. Few patients can tolerate the therapy. Now this study shows that administration of pegylated IFN, a new preparation of IFN, at a dose of 45 to 90 mg/wk is highly effective in normalizing counts in about 80% to 90% of patients with ET and PV. The results obtained in this study in terms of eliminating clones with JAK2 mutation are not attainable with JAK2 inhibitors because they are not specific for the mutation but only control disease signs and symptoms. Therefore, these data show that peg-IFNα-2a can lead to long-term molecular and histological remission.

*Interview with Srdan Verstovsek, MD, PhD, January 25, 2012*