Prolonged Low-Dose Pan-Deacetylase Inhibitor Panobinostat and Pomalidomide in Myelofibrosis
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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  - Chairman and Professor, Leukemia Department
  - The University of Texas MD Anderson Cancer Center
  - Houston, Texas

- Srdan Verstovsek, MD, PhD
  - Associate Professor
  - Chief, Section of Myeloproliferative Neoplasms
  - Director, Clinical Research Center for Myeloproliferative Neoplasms
  - Department of Leukemia
  - The University of Texas MD Anderson Cancer Center
  - Houston, Texas
  - No real or apparent conflicts of interest to disclose.

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Last review date: February 2012
Expiration date: February 2013
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.

Neil Love, MD

Research To Practice
Miami, Florida
Prolonged Low-Dose Pan-Deacetylase Inhibitor Panobinostat and Pomalidomide in Myelofibrosis

Presentations discussed in this issue


Begna K et al. Pomalidomide therapy for myelofibrosis: Analysis of results from three consecutive clinical trials. Proc ASH 2011; Abstract 1759.

Slides from presentations at ASH 2011 and transcribed comments from a recent interview with Srdan Verstovsek, MD, PhD (1/25/12)
Prolonged Low Dose Therapy with a Pan-Deacetylase Inhibitor, Panobinostat (LBH589), in Patients with Myelofibrosis


**Background**

- Panobinostat (LBH589) is a novel pan-HDAC (histone deacetylase) inhibitor that specifically enhances the deacetylation of histone and nonhistone cellular proteins.

- Panobinostat has potent antiproliferative activity against a broad range of tumor cell lines, and this activity is associated with increased histone acetylation.

- A preliminary Phase I study in patients with myelofibrosis showed evidence of clinical responses and identified reversible thrombocytopenia as the dose-limiting toxicity (*Proc ASH 2009;Abstract 308*).

- **Current study objective:** Evaluate the effects of long-term administration of panobinostat in patients enrolled in the extension phase of the Phase I trial.

Phase I Study Design

- Phase I, open-label, single-center, standard cohort, dose-escalation study
- Eighteen patients with MF (Lille classification: Intermediate to high risk) enrolled
- Three doses of panobinostat: 20 mg, 25 mg or 30 mg PO TIW QW
- Cycle = 28 days

<table>
<thead>
<tr>
<th>Screening</th>
<th>Evaluable period</th>
<th>Extension phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>28 days</td>
<td>Months 2-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7+ indefinite</td>
</tr>
</tbody>
</table>

Response by IWG criteria


Reduction in Splenomegaly from Baseline

<table>
<thead>
<tr>
<th>% reduction from baseline in palpable splenomegaly by cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>

Characteristics of Patients Evaluable for Response at 6 Months (n = 5)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>4</th>
<th>7</th>
<th>11</th>
<th>15</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF subtype</td>
<td>PMF</td>
<td>PMF</td>
<td>PMF</td>
<td>Post-ET MF</td>
<td>Post-PV MF</td>
</tr>
<tr>
<td>LBH589 dose</td>
<td>20 mg</td>
<td>20 mg</td>
<td>30 mg</td>
<td>25 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Cycles on study</td>
<td>23</td>
<td>33</td>
<td>6</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>JAK2 status</td>
<td>JAK2V16F</td>
<td>WT</td>
<td>JAK2V16F</td>
<td>WT</td>
<td>JAK2V16F</td>
</tr>
<tr>
<td>Best response by IWG-MRT</td>
<td>CI-anemia</td>
<td>CI-spleen</td>
<td>CI-spleen</td>
<td>SD</td>
<td>Near CR</td>
</tr>
</tbody>
</table>

CI = clinical improvement; SD = stable disease; CR = complete response


Select Adverse Events (30 Months Follow-Up)

<table>
<thead>
<tr>
<th>Event (N = 18)</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>94%</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>56%</td>
<td>39%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>39%</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>39%</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Other adverse events of any grade: Fatigue (33%), emesis (11%), anorexia (11%), constipation (11%), paresthesias (11%)
Patients (n) who discontinued treatment due to a related adverse event:
Anemia (4), thrombocytopenia (3), prolonged QTc (1)

Author Conclusions

- In patients with MF, low doses of panobinostat can reduce splenomegaly and are tolerable.
- Prolonged treatment with panobinostat alleviates symptoms, improves anemia and reverses pathologic bone marrow changes (data not shown).
- Signal for activity of panobinostat has led to the initiation of a Phase II study for patients with MF (#NCT01298934).
- The successful use of panobinostat may require prolonged administration and transfusional support as determined by MF severity.


Investigator Commentary: Prolonged Low-Dose Therapy with Panobinostat for Patients with Myelofibrosis

In this study panobinostat was tested as a single agent in patients with myelofibrosis. Benefits in terms of improvement in blood count, reduction in spleen size and amelioration of symptoms were observed in some patients.

Myelofibrosis is a disease that can shorten life expectancy. Average life expectancy is 5 to 7 years and patients usually die from progression of the disease rather than transformation to acute leukemia. The causes of death are related to progression of the enlarged spleen and liver, ultimately resulting in cardiac failure and lung failure.

One way of improving the efficacy of JAK2 inhibitors like ruxolitinib for the treatment of myelofibrosis is to combine them with other drugs like panobinostat. Perhaps because of their synergistic activity, we could expect that when used together the efficacy would be better than with each of them separately. I believe that the next wave of clinical studies for myelofibrosis will look at combination treatment strategies.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012
Phase II Study of Low-Dose Pomalidomide in Patients with Myelofibrosis and Significant Anemia (Hemoglobin <10g/dL)

Shastri A et al.
Proc ASH 2011;Abstract 1757.

Background

- A Phase II trial demonstrated that low-dose pomalidomide (POM) is effective at increasing hemoglobin levels and eliminating the need for transfusions as measured by IWG-MRT criteria in patients with JAK2V16F mutation-positive myelofibrosis (MF) (Leukemia 2011;25:301).

- The ongoing Phase III trial of single-agent POM in MF is currently utilizing a more robust and clinically meaningful set of transfusion dependency criteria known as the “Gale criteria” (Leuk Res 2011;35:8).

- **Objective:**
  - Assess the efficacy of single-agent, low-dose POM in improving hemoglobin levels and reducing transfusion dependency based on the Gale criteria in patients with MF and significant anemia.

Phase II Study Design

Eligibility (N = 28)

- PMF or PPV-MF or PET-MF
- Hemoglobin <10 g/dL
- JAK2V617F-positive or negative

POM 0.5 mg PO continuously daily x 28-day cycles

PMF = primary MF; PPV-MF = postpolycythemia vera MF; PET-MF = postessential thrombocytosis MF

Use of anagrelide on study was allowed to control high platelet counts, if indicated. Other concomitant therapies, such as growth factors, were not allowed.


Results Summary (Abstract Only)

- After median follow-up of more than 1 year, 11 (40%) patients remain on study:
  - Twelve patients were taken off study due to lack of response.
  - Two patients had disease that transformed to acute leukemia.
  - Three patients died from unrelated causes.
- By the Gale criteria, 2 of 8 transfusion-dependent patients achieved transfusion independence:
  - Both patients had JAK2 mutation-negative disease and did not have splenomegaly.
- No patients experienced sustained increase in hemoglobin of 2 g/dL from baseline.
- There were no instances of Grade 3/4 neutropenia, thrombocytopenia or nonhematologic toxicity.

Author Conclusions

- Low-dose, oral POM administered to patients with MF and significant anemia had modest clinical activity as measured by the Gale criteria:
  - Two of 8 transfusion-dependent patients achieved transfusion independence on study.
- Low-dose POM was well tolerated and had a good safety profile in this patient group.


Pomalidomide Therapy for Myelofibrosis: Analysis of Results from Three Consecutive Clinical Trials

Begna K et al. Proc ASH 2011;Abstract 1759.
Background

- Pomalidomide is a second-generation IMiD that is active in the treatment of myelofibrosis (MF)-associated anemia.
- An analysis was conducted on long-term follow-up data for 82 patients with MF who received single-agent pomalidomide during 3 consecutive Phase I and II clinical trials at the Mayo Clinic (5/2007 to 1/2010).
- **Current study objective:** Evaluate the anemia response rate obtained with single-agent pomalidomide.

Begna K et al. *Proc ASH* 2011;Abstract 1759.

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Study Designs and Select Patient Characteristics (n = 82)

**Designs of studies included in analysis**
- Phase I dose-escalation study (2.5-3.5 mg/day), n = 19
- Phase II low-dose pomalidomide (0.5 mg/day), n = 58
- Phase II randomized study (2 mg/day), n = 5

**Select patient characteristics**
- Median age: 67 years
- RBC transfusion dependence at study entry, n = 63 (77%)

Begna K et al. *Proc ASH* 2011;Abstract 1759.
## Treatment Retention and Response* Over Time (Abstract Only)

<table>
<thead>
<tr>
<th></th>
<th>Treatment retention (%)</th>
<th>Anemia response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of treatment (n = 82)</td>
<td>100%</td>
<td>27%</td>
</tr>
<tr>
<td>6 months FU</td>
<td>55%</td>
<td>26%</td>
</tr>
<tr>
<td>12 months FU</td>
<td>29%</td>
<td>23%</td>
</tr>
<tr>
<td>24 months FU</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>36 months FU</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* IWG-MRT criteria
Anemia response occurred in the first 6 months in 21 of 22 responders (96%). Median time for response = 2.3 months; median response duration = 16.5 months.

Begna K et al. *Proc ASH* 2011;Abstract 1759.

## Anemia Response Rates among Patient Subgroups* (Abstract Only)

<table>
<thead>
<tr>
<th></th>
<th>Anemia response (%)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Palpable spleen size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 cm below costal margin</td>
<td>44%</td>
<td>0.002</td>
</tr>
<tr>
<td>≥10 cm above costal margin</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>JAK2 mutated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAK2 nonmutated</td>
<td>30%</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Increase in basophil count, 1st month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50% increase</td>
<td>39%</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt;50% increase</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

*Anemia response rate was not significantly affected by karyotype, transfusion need or leukocyte count.

Begna K et al. *Proc ASH* 2011;Abstract 1759.
Author Conclusions

- Anemia response to pomalidomide therapy in MF
  - Often occurs in the first 6 months of treatment.
  - Is more likely to occur in the presence of JAK2V617F.
  - Is more likely to occur in the absence of marked splenomegaly.

- Long-term treatment with pomalidomide may be associated with sensory peripheral neuropathy in a subset of patients:
  - Among 24 patients who received pomalidomide for at least 12 months, Grade 1 sensory neuropathy was observed in 4 (16%) patients.

Begna K et al. Proc ASH 2011;Abstract 1759.

Investigator Commentary: Pomalidomide Therapy for Myelofibrosis

Three studies of pomalidomide in MF have been published, and it was noted that when administered at a low dose pomalidomide had the potential to improve red blood cell counts by a mechanism that is currently not understood. Pomalidomide has not had an effect on other aspects of the disease, such as spleen size. Its evaluation in ongoing Phase III studies is focused on improvement of red blood cell counts in patients with MF who are anemic.

If pomalidomide is demonstrated to have true value in the current Phase III, placebo-controlled randomized study, then in the future it would be worthwhile to evaluate combining it with the JAK2 inhibitors. This would allow for a 2-pronged approach, with the JAK2 inhibitors affecting spleen size and symptom control and pomalidomide affecting red blood cell counts and anemia.

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