5 Minute JournalClub

POST-ASH Issue 4, 2016

Efficacy and Safety of PRM-151 in Myelofibrosis

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. These events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unmatched and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel agents and therapeutic options for the treatment of newly diagnosed and relapsed/refractory acute and chronic leukemias, myelodysplastic syndromes and myeloproliferative neoplasms from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Appraise emerging clinical research findings on the efficacy and safety of novel antibody-based therapies for acute lymphoblastic leukemia.
- Assess the activity of the multitargeted kinase inhibitors midostaurin and sorafenib with chemotherapy for FLT3-mutated acute myeloid leukemia.
- Compare the risks and benefits associated with discontinuing imatinib therapy for patients with chronic myeloid leukemia (CML) who have achieved a deep molecular response.
- Recall recent data on the activity and tolerability of second- and third-generation tyrosine kinase inhibitors for the treatment of CML.
- Evaluate the efficacy and safety of ruxolitinib alone or in combination with other therapies for patients with myelodysplastic syndromes and myeloproliferative neoplasms.

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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 2016
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Listen to interview with Dr Stone

Richard M Stone, MD

The May 17th historic FDA approval (accelerated) of the anti-PD-1 antibody nivolumab for the treatment of classical Hodgkin lymphoma that has relapsed or progressed after autologous stem cell transplantation and post-transplant brentuximab vedotin is a vivid reminder of just how far we have come in moving new options for patients into practice. Nivo's endorsement was predicated on an evaluation of efficacy in just 95 patients, but because the drug as monotherapy produced useful responses in approximately two thirds of individuals with limited treatment options, the FDA's decision is great news to oncologists, and it could be that pembrolizumab, which also has strong but similarly limited supporting data, could soon follow.

However, while it is comforting to see new therapies that are clearly effective become rapidly available, in reality many of the "steps forward" in clinical research continue to come as a result of large randomized trials evaluating standard systemic regimens alone or in combination with novel agents, many of which demonstrate marginal but clearly statistically significant advantages. What makes these kinds of findings and subsequent regulatory approvals so challenging is that they often come in diseases with dismal outcomes and few options for treatment, and usually the drug in question has limited single-agent activity and, most significantly, the benefit provided is far from a home run.

These factors create an environment of constant debate about the relevance of a therapy and how it fits into the risk/benefit/value equation. Recent examples in the hem/onc world include in multiple myeloma the use of panobinostat as an add-on to bortezomib/dexamethasone and the incorporation of elotuzumab with lenalidomide/dexamethasone. The same issue arises in chronic lymphocytic leukemia with the addition of obinutuzumab (as opposed to rituximab) to chlorambucil and in follicular lymphoma to bendamustine.

This is precisely the scenario that is emerging in the world of acute myeloid leukemia (AML) related to the combination of multikinase tyrosine kinase inhibitors (TKIs) with

induction chemotherapy and maintenance for the approximately 35% of patients with AML who have FLT3 genomic alterations — long known to be associated with a particularly adverse prognosis, which has led to the current common practice of following induction treatment with allogeneic stem cell transplantation.

The FLT3 AML debate began during a 2014 ASH plenary presentation of a large German study that demonstrated a progression-free survival advantage with the addition of the multikinase TKI sorafenib to induction chemotherapy and its continuation for a year as maintenance. A key and very provocative finding (and to this point pretty much unexplained) was that the benefit was observed in patients with and without FLT3 abnormalities.

At the ASH 2015 meeting another plenary talk focused on this strategy — specifically the presentation by Dana-Farber's Dr Richard Stone of the international Phase III RATIFY trial led by the CALGB that blindly randomly assigned 717 patients with 1 of the 3 FLT3 alterations, including tyrosine kinase domain mutations and both low and high internal tandem duplication allele burdens, to another multikinase TKI, midostaurin, which, like other similar compounds, has limited single-agent activity but can be safely combined with intensive chemotherapy.

The study added midostaurin to daunorubicin/cytarabine induction and high-dose ara-C consolidation and then administered it as maintenance therapy in patients age 18 to 60 and met its primary endpoint of improving overall survival, although the 23% relative reduction in risk of death translates to a somewhat modest improvement in 4-year survival from 44.2% to 51%. Of great interest is that the benefit was observed regardless of whether allotransplant occurred or which of the 3 major predetermined FLT3 subtypes were present, which caused some in the audience to wonder if, as with the sorafenib trial, the benefit might accrue to a larger segment of patients.

I met with Dr Stone for his take on these data, what they mean to patient care and whether this is the beginning of the end of an era in AML lasting more than a decade in which the only regulatory action has been in the wrong direction (withdrawal of approval of gemtuzumab ozogamicin).

To make a long story short, the key message from our conversation is that although some caveats exist, Dr Stone believes that these findings are meaningful and the drug should be incorporated into practice. This sentiment appears to be echoed by the FDA, which recently granted midostaurin a breakthrough therapy designation, but we shall see whether it will become another in the recent unprecedented flurry of novel agents entering practice.

Either way, a host of other new small molecules with anti-FLT3 activity such as gilteritinib (formerly ASP2215) are marching on in the research development process with the hope of greater specificity resulting in increased efficacy and more favorable tolerability.

Of course, midostaurin was definitely not the only relevant news coming out of ASH. For that reason and to keep you up to date on what happened, we have created the following 26 slide sets across a number of diseases (AML, myelodysplastic syndromes, acute lymphocytic leukemia, myeloproliferative neoplasms and chronic myeloid leukemia), which review highlights from the data and provide Dr Stone's insights into their relevance and meaning.

Acute myeloid leukemia (AML)/chronic myelomonocytic leukemia (CMML)/myelodysplastic syndromes (MDS)	
PPT	(PLENARY) Up-front use of the multikinase inhibitor midostaurin with a "7 plus 3" chemotherapy regimen in FLT3-mutated AML
PPT	Sorafenib with chemotherapy improves the overall survival of older adults with FLT3-ITD-mutated AML
PPT	Antileukemic activity and tolerability of the multikinase inhibitor gilteritinib in FLT3-mutated AML
PPT	Up-front treatment with venetoclax and decitabine or azacitidine for older patients with AML
PPT	Pracinostat with azacitidine in elderly patients with AML; oral azacitidine monotherapy in AML
PPT	Allogeneic stem cell transplantation after high- versus reduced-intensity conditioning in MDS and AML
PPT	Safety and efficacy of AG-221, a potent inhibitor of mutant IDH2 in advanced hematologic cancers
PPT	Azacitidine with lenalidomide or vorinostat versus azacitidine monotherapy in MDS and CMML
PPT	Eltrombopag for the treatment of thrombocytopenia of low and intermediate-1 IPSS risk MDS; luspatercept in low or intermediate-1 risk MDS
Acute lymphoblastic leukemia (ALL)	
PPT	(PLENARY) Rituximab and chemotherapy in adults with CD20-positive, Philadelphia chromosome-negative, B-cell precursor ALL
PPT	Dose-intensified pegylated asparaginase pediatric regimen in adults with untreated ALL
PPT	Blinatumomab in adult patients with relapsed/refractory Philadelphia chromosome-positive ALL
PPT	Front-line inotuzumab ozogamicin combination with low-intensity chemotherapy for older patients with ALL

Chronic myeloid leukemia (CML)	
PPT	Long-term follow-up of the French 1 Stop Imatinib study in CML
PPT	Personalized daily doses of imatinib by therapeutic drug monitoring in CML
PPT	Clinical significance of early imatinib-induced ABCB1 overexpression in CML
PPT	Dose-optimized nilotinib in newly diagnosed CML
PPT	Impact of age on efficacy and toxicity of nilotinib in patients with CML
PPT	Dasatinib and peginterferon alpha-2b as up-front treatment for CML
PPT	Ponatinib versus allogeneic stem cell transplant in patients with CML/acute lymphoblastic leukemia and the T315I mutation
PPT	Next-generation sequencing versus conventional sequencing to detect BCR-ABL mutations in CML
Myeloproliferative neoplasms (MPN)	
PPT	Long-term efficacy and safety of ruxolitinib (RUX) in myelofibrosis (MF)
PPT	Pacritinib in MF
PPT	The antifibrotic agent PRM-151 in MF
PPT	5-azacytidine with RUX in MDS/MPN; sonidegib with RUX in patients with MF; RUX with pomalidomide in MF; RUX and buparlisib in MF
PPT	Interferon alpha-2 with a JAK1/2 inhibitor in Philadelphia chromosome-negative MPN

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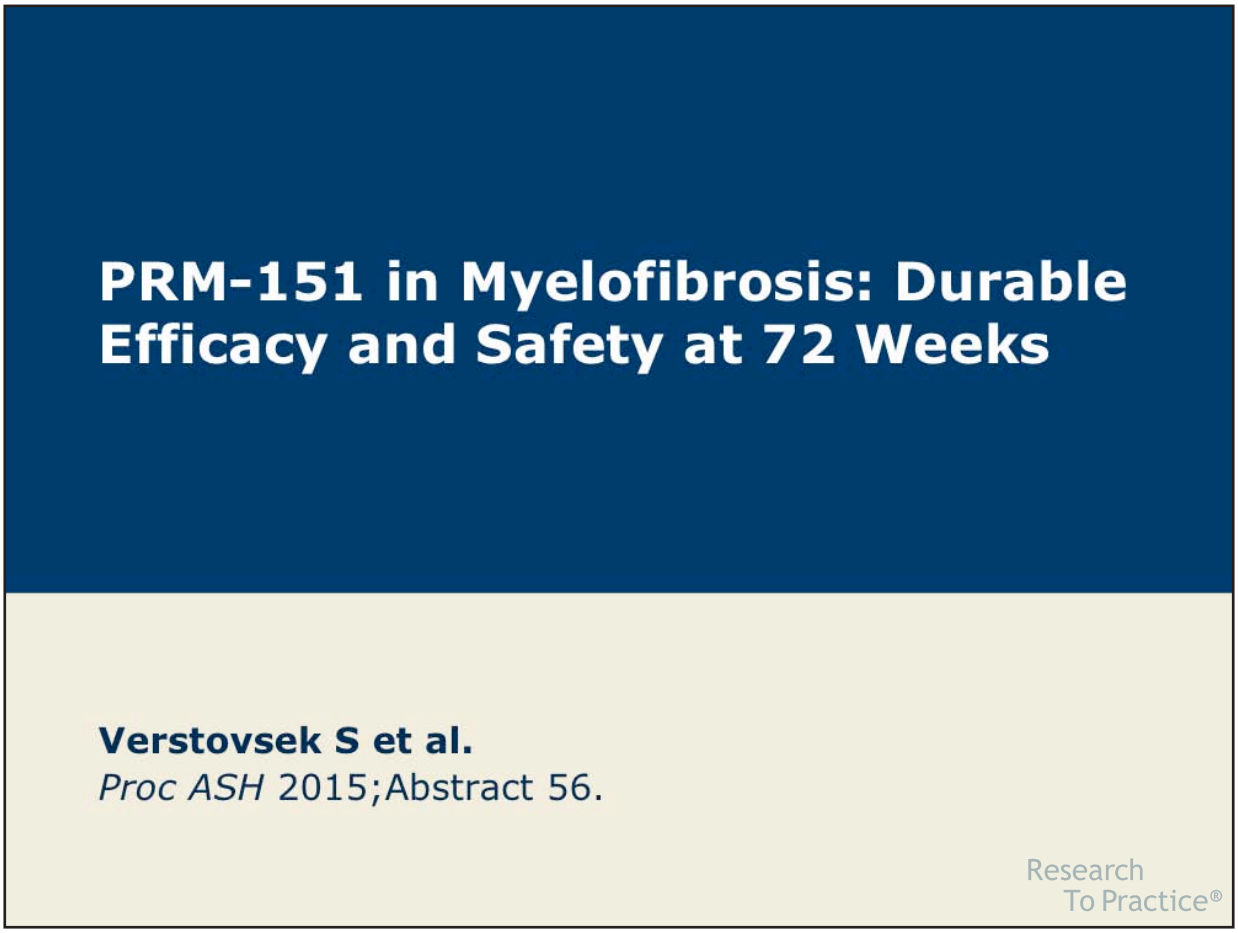
Efficacy and Safety of PRM-151 in Myelofibrosis

Presentation discussed in this issue

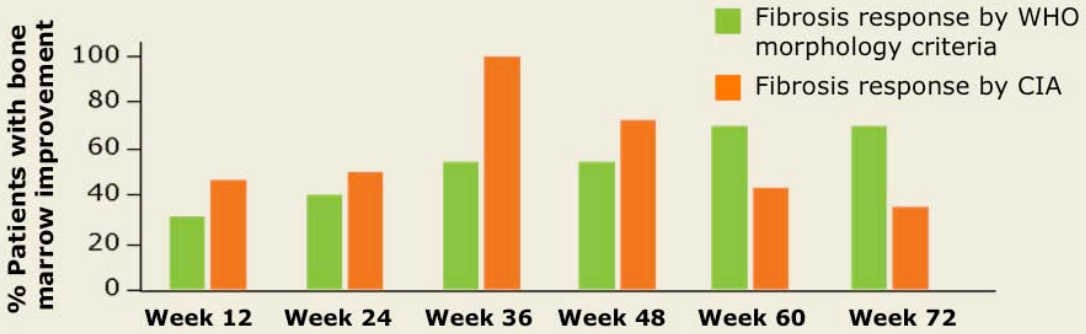
Verstovsek S et al. **PRM-151 in myelofibrosis: Durable efficacy and safety at 72 weeks.** *Proc ASH* 2015;**Abstract 56**.

Slides from a presentation at ASH 2015 and transcribed comments from a recent interview with Richard M Stone, MD (2/18/16)



PRM-151 in Myelofibrosis (MF)

- First stage of a 2-stage adaptive trial evaluating PRM-151 (a recombinant pentraxin-2 protein that reverses fibrosis) 10 mg/kg IV x 24 wk in 4 arms: 2 single agent; 2 with ruxolitinib
- N = 13 patients with MF, originally with Grade 2 or 3 fibrosis, after 72 weeks of treatment (N = 5 received ruxolitinib)
- **Primary endpoint:** Fibrosis response by WHO and CIA criteria:



WHO criteria: Reduction in MF score by 1 grade at any time point
CIA (computer-assisted image analysis) criteria: Decrease in % fibrosis from baseline with negative slope >1

Verstovsek S et al. *Proc ASH* 2015;Abstract 56.

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PRM-151 in MF: Conclusions

- Reductions in fibrosis were observed at week 12 and sustained at week 72.
- PRM-151 was well tolerated with few adverse events.
- Anemia and thrombocytopenia were improved:
  - If baseline hemoglobin <100 g/L,
    - Median hemoglobin increased
    - Need for red blood cell transfusions decreased
  - If baseline platelet count <100 x 10^9/L,
    - Median platelet count increased
    - Need for platelet transfusions decreased
- 62% of patients experienced a symptom score reduction of >50%, and 2 patients experienced a reduction in splenomegaly of >50%.
- Stage 2 of this study is currently enrolling.

Verstovsek S et al. *Proc ASH* 2015;Abstract 56.

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Investigator Commentary: Efficacy and Safety of PRM-151 in MF

MF is a relatively intractable myeloproliferative disorder in which patients often experience anemia, decreased performance status, bone pain and problems due to splenomegaly caused by extramedullary hematopoiesis. The only reasonably effective therapy for MF is the JAK1/2 inhibitor ruxolitinib, which can reduce spleen size and improve quality of life and might be associated with improved overall survival. However, even ruxolitinib has not been shown to reliably decrease the degree of fibrosis found in the blood marrow of patients with this disease. PRM-151 is an antifibrotic agent that has been shown by Dr Verstovsek and colleagues to demonstrate some efficacy and safety in patients with MF who received this agent for 72 weeks. The initial results were encouraging. People experienced reductions in fibrosis in this short-term study.

A prospective randomized trial with large groups of patients is required to determine whether this drug will be used for patients with MF instead of or in addition to ruxolitinib. I'm cautiously optimistic about the ability of this agent to reverse the fibrosis and, therefore, improve outcomes for patients with this disease that is difficult to treat.

Interview with Richard M Stone, MD, February 18, 2016

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