5 Minute JournalClub

POST-ASH Issue 4, 2015

Results from a Phase II Trial of PRM-151 and a Pilot Study of Imetelstat for Patients with Primary and Secondary 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. As such, 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 unprecedented 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 up-front and salvage therapeutic options and modalities for the evaluation of treatment response in newly diagnosed and relapsed or refractory chronic myeloid leukemia (CML), myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET) 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

- Assess the recent results of the RESPONSE trial evaluating ruxolitinib for PV, and consider this information for the treatment of this disease in patients who are not responsive to or are intolerant of hydroxyurea.
- Appraise the effectiveness and tolerability of the investigational agents PRM-151 and imetelstat as single-agent therapy for patients with MF.
- Examine long-term efficacy and symptomatology results with ruxolitinib in patients with ET who are refractory to or intolerant of hydroxyurea.
- Compare and contrast the benefits and risks of discontinuing second-generation tyrosine kinase inhibitors for patients with CML in chronic phase.
- Analyze efficacy and safety results from Phase III trials evaluating dasatinib or ponatinib in comparison to imatinib for patients with CML in chronic phase.

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Consulting Agreements: Bristol-Myers Squibb Company, Genentech BioOncology, Lilly, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Contracted Research: Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi.

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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 2015
Expiration date: May 2016

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POST-ASH Issue 4, 2015

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

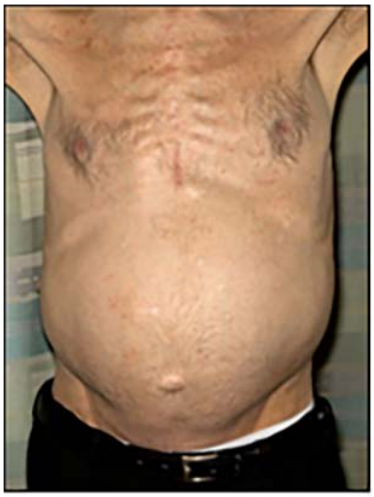
Many physicians (myself included) remember the day they first treated a patient with pulmonary edema from congestive heart failure and the exhilarating feeling of instantly relieving this profound symptomatology with the classic use of an intravenous diuretic and morphine. Medical oncology also provides many opportunities for these types of healing moments, and at the 2011 ASCO meeting the field was introduced to another powerful palliative tool for a disease desperately in need of one. Since the presentation of the aptly named COMFORT-I and II trials in Chicago, we have heard on many of our CME programs a myriad of moving patient case histories of individuals with myelofibrosis (MF) suffering from anorexia, weight loss, fatigue and massive uncomfortable spleens who experienced dramatic, life-altering changes within days or weeks of starting treatment with the JAK1/2 inhibitor ruxolitinib (rux).

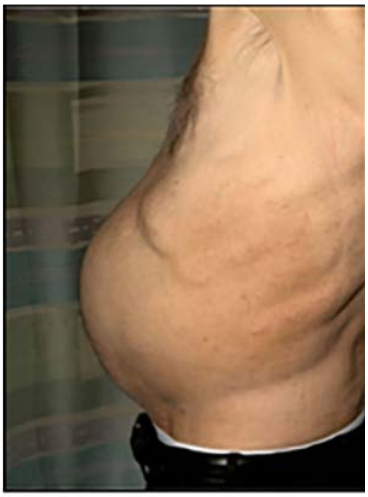
Perhaps not surprisingly, the myeloproliferative neoplasm (MPN) issue of our ASH highlight series focuses in large part on this fascinating therapy, which now is showing its colors in other diseases, including, interestingly enough, pancreatic cancer. We also provide an update on papers related to the other major part of MPNs, chronic myeloid leukemia (CML), and as such I met with one of the research giants in the field, Dr Jorge Cortes, who provides his take on the most important findings.

Jorge E Cortes, MD

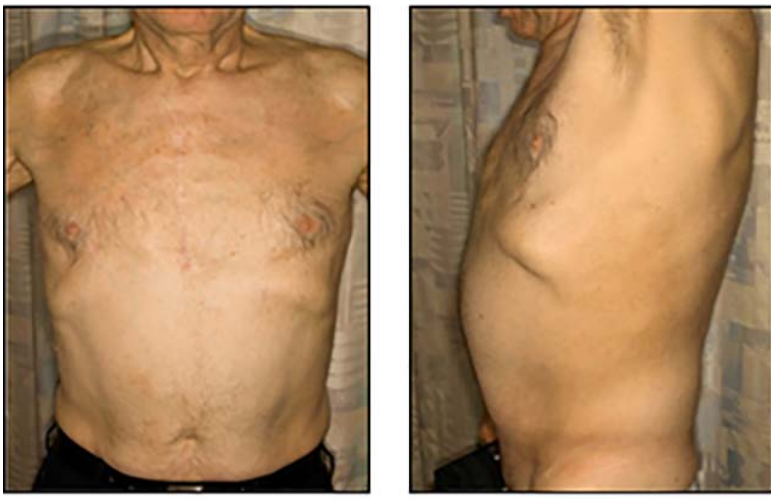
1. Rux in patients with lower-risk MF

The Phase III COMFORT trials focused on patients with intermediate-2 or high-risk MF, but there is no intuitive reason to believe that the palliative effects of this agent would not be similar in other symptomatic patients. At ASH we saw a **"real-world" retrospective analysis** evaluating 108 cases of patients with low- or intermediate-1-risk MF treated by 49 US-based hematologist-oncologists mainly due to symptomatology. Perhaps not surprisingly, marked improvement in spleen size and the severity of





fatigue and other related symptoms was observed with the use of rux. For example, moderate/severe splenomegaly decreased from 64% to 16% in low-risk MF and from 53% to 10% in intermediate-1-risk disease. These findings, along with his own clinical experience, have shaped Dr Cortes' belief that symptomatic patients can benefit from rux regardless of risk status.



Images courtesy of *OncoLog*, The University of Texas MD Anderson Cancer Center

ABOVE: Photos of a patient before therapy with an experimental JAK2 inhibitor show the distended abdomen caused by the enlarged spleen, a common symptom of myelofibrosis. **BELOW:** Photos taken after 2 months of therapy with a JAK2 inhibitor show a marked reduction in the patient's splenomegaly.

2. Rux in polycythemia vera (PV) and essential thrombocythemia (ET)

Perhaps the biggest MPN story at ASH was the presentation of more data from the landmark **Phase III RESPONSE trial** (originally presented last year at ASCO) demonstrating the clinical benefit of rux (10 mg BID) in patients with PV who were either intolerant of or experienced disease progression on hydroxyurea (HU). The initial data set was published in the *New England Journal* in January and revealed significant reductions in hematocrit, splenomegaly and severity of symptoms in patients randomly assigned to rux. Equally relevant, treatment was well tolerated — most patients had stable platelet counts, and secondary drops in hemoglobin were beneficial. Similar clinical improvements were observed in patients who crossed over to rux. Most importantly, as seen with the additional ASH data, patients who received rux experienced a dramatic positive impact on quality of life.

Based on the strength of these results, the FDA made rux the first drug ever approved for PV. In this regard, Dr Cortes has used the agent in patients who meet the criteria for the RESPONSE trial. However, he also believes that the definition of disease progression with PV should be expanded to include individuals with persistent symptomatology who, although not meeting the current criteria for disease progression, often experience dramatic improvements in symptoms with rux.

Several other data sets were unveiled in San Francisco that further support the concept of using rux in PV, including data from the **Phase III RELIEF trial** for patients with PV considered stable on HU but with some persistent symptoms, which demonstrated an improvement in symptoms by switching to rux rather than continuing on HU.

Finally, a Phase II study of rux in 39 patients with ET refractory to or intolerant of HU demonstrated rapid decreases in and normalization of platelet and white blood cell

counts. Hemoglobin levels initially decreased and then stabilized in most patients, and a marked improvement in symptomatology was also observed. As such, Dr Cortes and other investigators believe rux is rational to use in this patient population and are hopeful that this agent will also receive approval in ET for disease palliation.

3. New agents in MF: antifibrotics, telomerase inhibitors

Although much recent MF research has focused on JAK inhibitors, a number of other novel strategies are also being explored in this disease. In this regard, at ASH we saw an **early but encouraging report** of 27 patients receiving PRM-151, a recombinant form of an endogenous protein that is found at sites of inflammation and prevents fibrosis by inducing macrophage differentiation. What was most noteworthy from this study was that not only was the amount of fibrosis decreased in close to half of the patients, but hemoglobin and platelet counts also often improved along with signs and symptoms of the disease. Research on this and other similar agents is proceeding rapidly, and Dr Cortes is particularly interested in trials combining PRM-151 with rux.

Telomerase is known to become more active in MF as the disease progresses, and in a report of 33 patients receiving imetelstat — a novel agent that targets the RNA template of human telomerase reverse transcriptase — 7 patients (21%) experienced a complete or partial remission. Treatment was well tolerated, although myelosuppression was observed. Dr Cortes is intrigued by these data and also the early correlation of response with specific disease mutations.

4. Second-generation tyrosine kinase inhibitors (TKIs) in CML

With the likely availability of generic imatinib in the next year as a potentially less costly alternative, the value of nilotinib and dasatinib will be increasingly discussed and debated, and several new ASH data sets will likely be referred to as part of these conversations. Specifically, in San Francisco we saw the first presentation of data from the large **Phase III SPIRIT 2 trial**, which, like several other prior studies, compared dasatinib to imatinib in patients with newly diagnosed CML. Although the data are not yet fully mature, this study confirms what we have known from other trials, namely that treatment with second-generation TKIs results in improved rates of complete cytogenetic response, faster rates of molecular response and fewer transformations.

It wouldn’t be ASH if we weren’t treated to an update from the landmark DASISION trial, and in addition to continuing to show excellent long-term disease outcomes, this study yielded some interesting data on toxicity over time, specifically the most common complication of dasatinib, pleural effusions, which were observed in 20% of patients, causing discontinuation of treatment in 6%. In discussing this work, Dr Cortes pointed out that multiple studies have suggested that patients experiencing a pleural effusion on dasatinib might have better disease-related outcomes, although the biologic explanation remains to be defined.

None of the second-generation TKI CML papers presented in San Francisco was able to dispel the lack of progression-free or overall survival benefit to this point, and some

investigators prefer imatinib in lower-risk scenarios. Dr Cortes, however, believes that there is an important advantage for the newer agents but that salvage treatment for imatinib failure is delaying the detection of this benefit.

5. Current bottom line with ponatinib in CML

As you may remember, the **Phase III EPIC study** comparing ponatinib to imatinib was stopped in October 2013 because of the increased risk of cardiovascular events. As a result of this toxicity, access to ponatinib is currently restricted to patients with TKI-resistant disease or those with the T315I mutation. However, the updated data from this trial tell us that the agent is associated with faster, deeper and higher rates of response than imatinib and, by way of indirect comparison, perhaps also dasatinib and nilotinib.

In this regard, there is a strong belief among investigators that there is a direct relationship between dose and cardiovascular events, and for that reason ongoing studies are attempting to define a reduced dose that will produce equal efficacy with fewer complications.

6. In what situations, if any, is it safe to stop a TKI in CML?

A number of prospective trials (STIM, TWISTER and EURO SKI, which was presented at ASH) suggest that imatinib may be successfully discontinued for patients with deep and sustained molecular responses, and in San Francisco we saw evidence that the same may apply to second-generation TKIs. Specifically, the **STOP 2G-TKI study** evaluated treatment discontinuation in 52 patients in sustained complete molecular response receiving dasatinib or nilotinib for a median of 39 months, mostly after initial imatinib therapy.

At 24 months, the probability that patients remained in major molecular response off treatment was 57%. The relapses that did occur were mainly in the first 6 months after treatment discontinuation, but those patients responded to reinstitution of second-generation therapy. Importantly, patients receiving treatment because of prior resistance to imatinib were less likely to be able to stay off treatment. Despite this mounting body of data, like most CML investigators, Dr Cortes, although interested in seeing more research on this strategy, believes that for now TKI treatment should only be stopped as part of a clinical trial and with close monitoring.

Medical oncologists are hearing a lot nowadays about “value” in cancer care, which is roughly defined as the clinical benefits (and toxicities/complications) of a therapy relative to its financial cost, and there has been a lot of discussion about the importance of incorporating the perspectives of patients themselves in the value equation.

In this regard, it would be interesting to learn more from individuals who have actually experienced the clinical outcomes of therapy for MPNs about their perceptions of the value of treatment — particularly about what it means to face a disease that was

uniformly lethal in the past and to now live a normal lifespan (CML) or to experience progressive and devastating disease-related symptoms and suddenly feel well again (MF, PV, ET).

Next on this series we review ASH papers on acute leukemias and MDS and the surprising plenary presentation on the use of sorafenib in AML.

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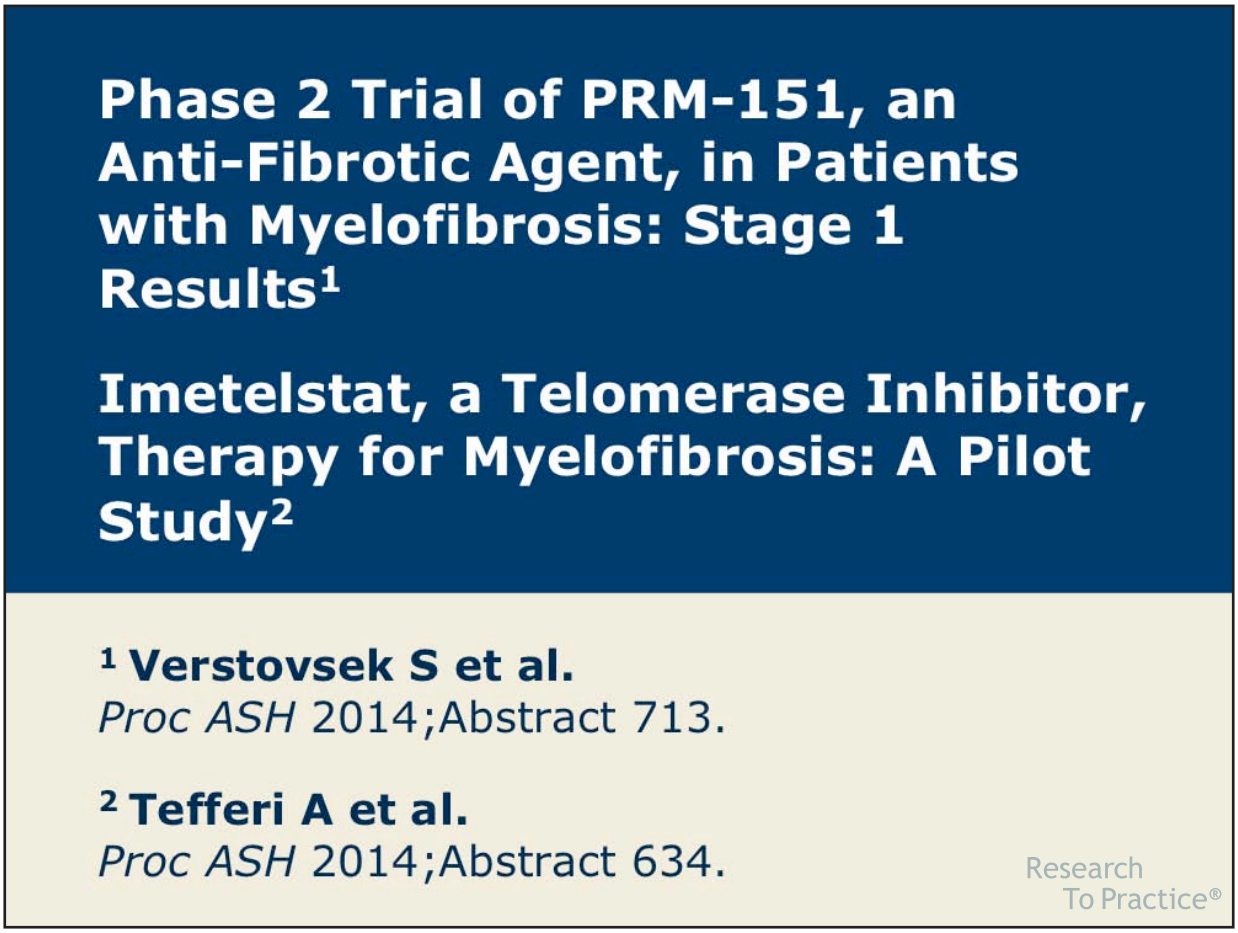
Results from a Phase II Trial of PRM-151 and a Pilot Study of Imetelstat for Patients with Primary and Secondary Myelofibrosis

Presentations discussed in this issue

Verstovsek S et al. **Phase 2 trial of PRM-151, an anti-fibrotic agent, in patients with myelofibrosis: Stage 1 results.** *Proc ASH* 2014;**Abstract 713**.

Tefferi A et al. **Imetelstat, a telomerase inhibitor, therapy for myelofibrosis: A pilot study.** *Proc ASH* 2014;**Abstract 634**.

Slides from presentations at ASH 2014 and transcribed comments from a recent interview with Jorge E Cortes, MD (1/14/15)



Phase 2 Trial of PRM-151, an Anti-Fibrotic Agent, in Patients with Myelofibrosis: Stage 1 Results

Verstovsek S et al.

Proc ASH 2014;Abstract 713.

Background

- PRM-151 (PRM) is a recombinant form of pentraxin-2, an endogenous human protein that acts at sites of tissue damage, inducing macrophage differentiation to prevent and reverse fibrosis.
- PRM has broad antifibrotic activity in multiple preclinical models of established fibrotic diseases and no dose-limiting toxicities in Phase I trials (*Proc ATS* 2013;Abstract D94).
- Myelofibrosis (MF) is a myeloid cancer characterized by progressive bone marrow (BM) fibrosis with resultant anemia, abnormal platelet/leukocyte counts, extramedullary hematopoiesis and a well-defined symptom complex.
- **Study objective:** To investigate the potential of PRM to reduce BM fibrosis and to improve key disease features, including abnormal blood counts, symptoms and splenomegaly in patients with MF.

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Ongoing Simon-2-Stage Phase II Trial Design (NCT01981850)

Eligibility

PMF, post-PV MF, post-ET MF
DIPSS
- Intermediate-1 or -2 risk
- High risk

Grade ≥2 BM fibrosis
For cohorts treated with RUX:
- No current therapy/on a stable dose of RUX for ≥12 weeks and no spleen improvement for ≥4 weeks

Stage 1 (n = 27)
PRM (IV) 10 mg/kg q1wk
PRM (IV) 10 mg/kg q4wk
PRM (IV) 10 mg/kg q1wk + RUX
PRM (IV) 10 mg/kg q4wk + RUX

Stage 2 (n = 120)
Any treatment from Stage 1 with ≥1 response

PMF = primary MF; post-PV MF = postpolycythemia vera MF; post-ET MF = postessential thrombocythemia MF; RUX = ruxolitinib

- Schedule: PRM loading on days 1, 3, 5, then weekly or every 4 weeks, with or without RUX, for 24 weeks
- **Primary endpoint:** Overall response rate (ORR)

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

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BM Fibrosis Reduction in 11 Out of 25* Patients

BM fibrosis grade at BL	Best BM fibrosis grade after baseline (BL)			
	Grade 3 (n)	Grade 2 (n)	Grade 1 (n)	Grade 0 (n)
Grade 3 (n = 15)	7	4	3	1
Grade 2 (n = 8)	0	5	3	0
Grade 1 (n = 2)	0	1	1	0

* Two patients had only BL BM. One patient with reduction in BM fibrosis grade had progressive disease (increased splenomegaly) and was not counted as a BM response.

- Reduction in BM fibrosis was associated with normalization of BM architecture:
  - Normal erythroid clustering (p = 0.07)
  - Normal or decreased myeloid-to-erythroid ratio (p = 0.02)
  - Fewer paratrabecular megakaryocytes (p = 0.07)

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

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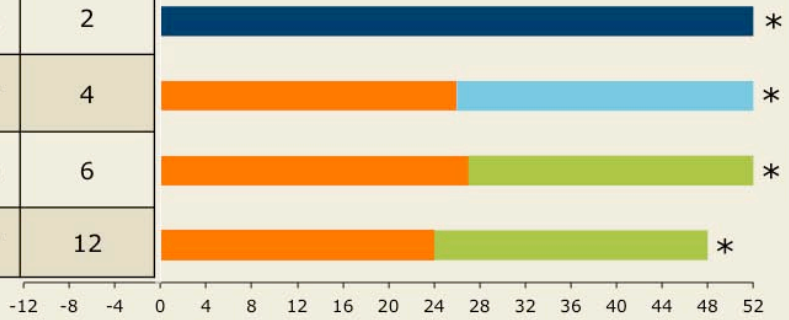
Improvements in Hemoglobin (Hgb) Levels

	Baseline		
Patient #	Hgb (g/L)	Transfusions in 12 weeks pre-C1D1	Best Hgb (g/L) without transfusion
101-004	81	2	103
101-002	97	4	122
101-005	86	6	98
101-006	77	12	105



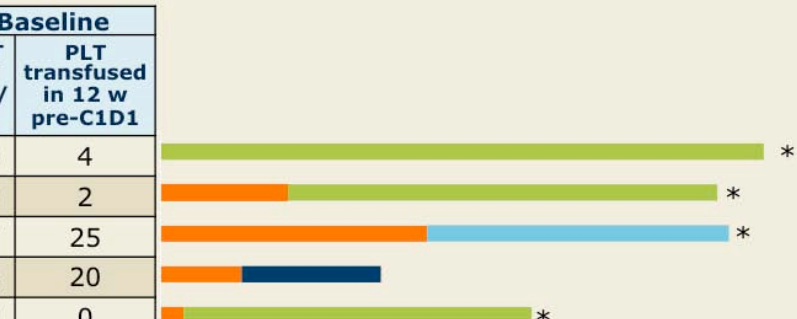
* Patients still on treatment and being followed

- 4 out of 15 patients with baseline Hgb <100 g/L showed improvements

With permission from Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Improvements in Platelet Counts

	Baseline		
Patient #	PLT x 10^9/L	PLT transfused in 12 w pre-C1D1	Best PLT ($x10^9$/L) without transfusions
101-003	23	4	43
101-006	10	2	31
101-011	17	25	29
101-001	22	20	28
101-008	19	0	56
101-004	89	0	163
101-005	18	0	64
103-001	32	0	78



* Patients still on treatment and being followed

- 8 out of 14 patients with baseline platelets <100 x 10^9/L showed improvements

With permission from Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Association between BM Fibrosis Reduction and Hematologic Improvements

Patients with improvements in BM fibrosis, hemoglobin level or platelet counts

Improved | Stable

Group	Weeks since last prior MF therapy	Bone marrow fibrosis	Hemoglobin	Platelets
PRM-151 QW	57	Stable	Stable	Improved
	3	Improved	Improved	Improved
	No prior therapy	Improved	Stable	Stable
	No prior therapy	Improved	Stable	Stable
PRM-151 Q4W	41	Stable	Stable	Improved
	60	Stable	Improved	Improved
	8	Improved	Improved	Improved
	8	Improved	Stable	Improved
	70	Improved	Stable	Stable
PRM-151 QW + RUX	52	Improved	Stable	Improved
	96	Improved	Stable	Stable
PRM-151 Q4W + RUX	156	Improved	Improved	Stable
	96	Stable	Stable	Improved
	83	Improved	Stable	Stable
	77	Improved	Stable	Stable

With permission from Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Summary of the Efficacy of PRM in MF

- ORR at 24 weeks of treatment: 11/26 (43%)
  - 1 patient with BM and symptom response was not included
  - ≥2 responses per treatment arm surpassed criteria to advance to Stage 2 of study
- Patients still on study at >24 weeks in extension (n = 14)
- ORR at 36 weeks of treatment: 13/26 (50%)
  - BM responses (n = 10)
  - International Working Group symptom responses (n = 4)
  - Patients with baseline Hgb <10 g/L and/or platelet count <100 x 10^9/L with improvements in Hgb and/or platelet counts: 10/21 (47.6%)
- Most patients had reductions in symptom scores
- Patients had modest reductions in spleen size by palpation
- Monthly dosing improvements were equivalent to that observed with weekly dosing schedules.

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

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Adverse Events (AEs)*

Grade 1–2	PRM q1wk (n = 8)	PRM q4wk (n = 7)	PRM q1wk + RUX (n = 6)	PRM q4wk + RUX (n = 6)
Diarrhea	25%	0%	0%	17%
Fatigue	13%	0%	17%	0%
Infusion site bruising	0%	0%	33%	0%
Oral herpes	0%	0%	17%	17%
Joint swelling	13%	0%	17%	0%
Headache	0%	0%	33%	0%

* Possibly or probably related to PRM and occurring in >1 patient; no related Grade 3-4 AEs in >1 patient

- 5 possibly related serious AEs: abdominal pain, sialadenitis, pneumonia (all recovered), gastroenteritis/pneumonia (resulting in death in an 85-year-old patient)
- 2 unrelated deaths due to pneumonia, multiorgan failure and cardiac arrest

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Author Conclusions

- Benefits of treatment with PRM:
  - Decreases in BM fibrosis
  - Improvements in hemoglobin levels and platelet counts, including transfusion independence
  - Reduction in symptoms
  - Modest reductions in splenomegaly
- Benefits of PRM increase with longer treatment duration:
  - Increase in the number of patients who benefited from therapy
  - Increase in the magnitude and duration of benefit
- PRM was safe and well tolerated when used alone and in combination with a stable dose of ruxolitinib.
- The Stage 2 portion of the study will be opening soon.

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Investigator Commentary: Efficacy and Safety of PRM in MF

Interestingly, PRM is a recombinant form of pentraxin-2, a protein that acts in areas of inflammation. It induces macrophage differentiation and prevents or reverses fibrosis where there's injury. The primary idea for this study was that with the use of this agent in patients with MF, fibrosis could be reversed. An important question was also to determine whether that reversal resulted in benefits such as improved hematopoiesis. Patients received PRM at 2 different dosing schedules with or without ruxolitinib. About a third of the patients had a significant reduction in BM fibrosis, impressive because such responses are uncommon.

It appears that by improving BM fibrosis it is possible to improve hematopoiesis, with 47.6% of patients showing improvement in their hemoglobin level and/or platelet counts at 36 weeks of treatment. About 60% of patients with baseline platelet counts $<100 \times 10^9$/L had improvement. These are still early results from only 27 patients enrolled on Stage I of the study. However, PRM is an agent that we need to keep our eyes on because it may have a role in the treatment of MF. It will be interesting to know what happens when it is used in combination with ruxolitinib. This may open up lots of possibilities if PRM maintains this level of activity.

Interview with Jorge E Cortes, MD, January 14, 2015

Imetelstat, a Telomerase Inhibitor, Therapy for Myelofibrosis: A Pilot Study

Tefferi A et al.

Proc ASH 2014;Abstract 634.

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Background

- Current drugs for myelofibrosis (MF), including JAK inhibitors, do not induce complete or partial remissions.
- Imetelstat is a 13-mer lipid-conjugated oligonucleotide that targets the RNA template of human telomerase reverse transcriptase.
- Previously, a Phase II study of imetelstat for patients with essential thrombocythemia demonstrated platelet-lowering activity accompanied by reduction in *JAK2*V617F allele burden (*Proc ASH* 2012;Abstract 179).
- **Study objective:** To determine the efficacy and safety of imetelstat in patients with high-risk or intermediate-2-risk MF using the refined Dynamic International Prognostic Scoring System (DIPSS plus).

Tefferi A et al. *Proc ASH* 2014;Abstract 634.

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Open-Label Pilot Trial Design (NCT01731951)

Eligibility (n = 33)

PMF, post-PV MF, post-ET MF
DIPSS plus
- Intermediate-2 risk
- High risk

No chemotherapy, immunomodulatory or suppressive agent, corticosteroid, JAK inhibitor or growth factor therapy ≤14 days before entry

→ **Imetelstat**
9.4 mg/kg (IV)
Every 3 weeks
(Cohort A)

→ **Imetelstat**
9.4 mg/kg (IV)
Every week x 3 → every 3 weeks
(Cohort B)

PMF = primary MF; post-PV MF = postpolycythemia vera MF; post-ET MF = postessential thrombocythemia MF

- **Primary endpoint:** Overall response rate (ORR)

Tefferi A et al. *Proc ASH* 2014;Abstract 634.

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Responses

Response rate	n = 33
ORR*	7 (21.2%)
Complete response (CR)	4 (12.1%)
Partial response (PR)	3 (9.1%)

* Occurring at a median of 5 cycles (range 1-9)

- All 4 patients who achieved CR experienced a reversal of bone marrow fibrosis.
- 6 out of 7 patients remain in remission after a median follow-up of 9.9 months.

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

Other Responses

- Patients who are transfusion dependent (n = 13)
  - Improvement in anemia: 4 (31%)
- Patients who experienced >50% reduction in palpable spleen size out of 23 evaluable patients: 9 (39%)
- Patients with marked leukocytosis (white blood cell count >25 x 10^9/L) (n = 10)
  - ≥50% reduction in leukocyte count: 8 (80%)
- A majority of patients experienced a resolution of leukoerythroblastosis
- Patients with thrombocytosis (n = 12)
  - Normalization of platelet count with treatment: 9 (75%)

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

Laboratory Correlative Studies

Gene	CR/PR rates		
	Mutated	Unmutated	*p*-value
JAK2	27%	0%	0.3
ASXL1	0%	32%	0.07
SF3B1/U2AF1	38%	4%	0.036

- Grade ≥3 neutropenia or thrombocytopenia was more likely to occur in *JAK2*-unmutated ($p = 0.02$) and *ASXL1*-mutated cases ($p = 0.049$).
- Multicytokine panel screening showed significant differences between baseline and post-treatment samples involving several cytokines, including IL-1b, IL-5, IL-7, IL-17, VEGF, IL-8 and TNF-α ($p < 0.001$ for all).
- CR/PR rate did not correlate with baseline cytokine levels.

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

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Treatment-Related Adverse Events (AEs)

Event	n = 33
Intracranial hemorrhage (Grade 5)	3%
Upper gastrointestinal hemorrhage (Grade 5)*	3%
Neutropenia (Grade 4)	18%
Thrombocytopenia (Grade 4)	21%
Anemia (Grade 3)	27%

* Not related to treatment

- Grade ≥3 nonhematologic AEs were seen in only 1 patient.
- Regardless of attribution, treatment-emergent Grade 1 or 2 liver function test abnormalities affected bilirubin (46%), ALP (52%), AST (55%) and ALT (24%).
- There were 3 instances of Grade 3 ALP elevation and 1 of Grade 3 bilirubin elevation.

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

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Author Conclusions

- This study identifies imetelstat as an active drug in patients with MF.
  - However, it also reveals its potential to cause significant myelosuppression.
- The association between CR/PR rates and specific mutations suggests potential targeted activity that might be exploited for patient and disease selection.

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

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Investigator Commentary: Results from a Pilot Study of Imetelstat for Patients with MF

In many cancer types, targeting telomerases is an interesting approach. Telomerases are known to become more active in MF as the disease progresses. Imetelstat specifically inhibits human telomerase reverse transcriptase. This is a small pilot study of imetelstat in 33 patients with primary or secondary MF. Impressively, 7 patients (21%) achieved complete remissions. The main toxicity associated with imetelstat is myelosuppression. Neutropenia and thrombocytopenia were each observed in about 20% of patients, and 27% of the patients experienced Grade 3 anemia.

Some correlation was apparent between response and mutational status. Patients harboring JAK2 mutations responded better than those without. The reverse is true for the ASXL1 mutation: Patients with unmutated disease responded better than those harboring the mutant form. A subset of patients may exist who are particularly prone to respond to this agent. This is another study requiring us to keep our eyes open to see what happens with the drug. So far, the data presented are attractive.

Interview with Jorge E Cortes, MD, January 14, 2015

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