5 Minute JournalClub

POST-ASH Issue 4, 2016

Activity and Safety of Ruxolitinib-Based Combination Therapies for Patients with Myelodysplastic Syndromes/ Myeloproliferative Neoplasms

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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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POST-ASH Issue 4, 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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Activity and Safety of Ruxolitinib-Based Combination Therapies for Patients with Myelodysplastic Syndromes/ Myeloproliferative Neoplasms

Presentations discussed in this issue

Daver N et al. **5-azacytidine (AZA) in combination with ruxolitinib (RUX) as therapy for patients (pts) with myelodysplastic/myeloproliferative neoplasms (MDS/MPNs).** *Proc ASH* 2015;**Abstract 823**.

Gupta V et al. **Phase 1b/2 study of the efficacy and safety of sonidegib (LDE225) in combination with ruxolitinib (INC424) in patients with myelofibrosis.** *Proc ASH* 2015;**Abstract 825**.

Stegelmann F et al. **A Phase-Ib/II study of ruxolitinib plus pomalidomide in myelofibrosis.** *Proc ASH* 2015;**Abstract 826**.

Durrant ST et al. **An open-label, multicenter, 2-arm, dose-finding, Phase 1b study of the combination of ruxolitinib and buparlisib (BKM120) in patients with myelofibrosis: Results from HARMONY study.** *Proc ASH* 2015;**Abstract 827**.

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

5-Azacytidine (AZA) in Combination with Ruxolitinib (RUX) as Therapy for Patients (pts) with Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPNs)[1]

Phase 1b/2 Study of the Efficacy and Safety of Sonidegib (LDE225) in Combination with Ruxolitinib (INC424) in Patients with Myelofibrosis[2]

[1] **Daver N et al.**
Proc ASH 2015;Abstract 823.

[2] **Gupta V et al.**
Proc ASH 2015;Abstract 825.

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Azacitidine (AZA) with Ruxolitinib (RUX) for Myelodysplastic Syndromes/ Myeloproliferative Neoplasms (MDS/MPN)

- Single-arm Phase II trial of RUX (a JAK inhibitor) 15 or 20 mg BID with AZA (a hypomethylating agent) IV 25 to 75 mg/m^2 on days 1 to 5 starting approximately at cycle 4
- N = 25 patients with unclassifiable MDS/MPN, chronic myelomonocytic leukemia or atypical chronic myeloid leukemia requiring therapy
- **Primary endpoint:** Clinical improvement (CI)

Characteristic	RUX + AZA (n = 25)
Objective responses, n/N (%)	12/25 (48)
CI spleen, n/N (%) ▪ After AZA addition	7/9 (78) 3/7 (43)
CI transfusion independence, n/N (%)	1/5 (20)
Marrow response, n/N (%) ▪ Partial ▪ Optimal	 5/12 (42) 1/12 (8)

Daver N et al. *Proc ASH* 2015;Abstract 823.

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AZA with RUX for MDS/MPN: Conclusions

- Acceptable safety profile: Expected myelosuppression was the only significant toxicity.
- Response rate was higher for patients with JAK2 mutations than for those without: 5/6 (83%) versus 7/19 (37%), $p = 0.047$.
- Results warrant further evaluation of RUX in combination with AZA in larger, multicenter studies.

Daver N et al. *Proc ASH* 2015;Abstract 823.

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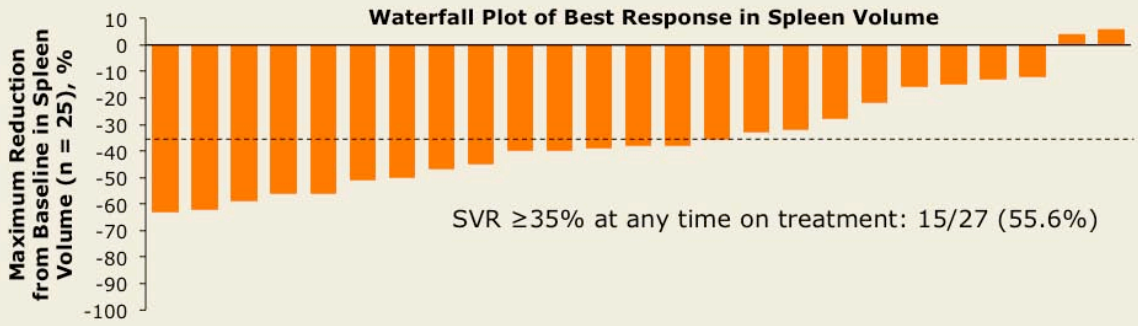
Sonidegib (LDE225) with RUX in Myelofibrosis (MF)

- Phase Ib/II trial of sonidegib (a hedgehog pathway inhibitor) with RUX
- N = 27 patients with primary MF, postessential thrombocythemia MF or post-polycythemia vera MF
- **Primary endpoints:** Splenic volume reduction (SVR) and safety



- Adverse events (AEs) requiring dose adjustment or interruption include elevated creatine kinase and myalgia (n = 5 each)
- **Conclusion:** Sonidegib + RUX is well tolerated and active in MF

Gupta V et al. *Proc ASH* 2015;Abstract 825.

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A Phase-Ib/II Study of Ruxolitinib plus Pomalidomide in Myelofibrosis[3]

An Open-Label, Multicenter, 2-Arm, Dose-Finding, Phase 1b Study of the Combination of Ruxolitinib and Buparlisib (BKM120) in Patients with Myelofibrosis: Results from HARMONY Study[4]

[3] **Stegelmann F et al.**
Proc ASH 2015;Abstract 826.

[4] **Durrant ST et al.**
Proc ASH 2015;Abstract 827.

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POMINC (MPNSG02-12) Trial: RUX with Pomalidomide (POM) in MF

- Phase Ib/II trial of RUX with POM (an immunomodulatory drug)
- N = 28 patients with MF and anemia
- **Primary endpoint:** Response rate after 12 treatment cycles and red blood cell transfusion independence
- CI = 6/28 (21%)
  - Spleen size reduction, 14%; cytopenia improvement, 7%
  - Median time to response: 5 cycles (range, 2-14)
- Stable disease = 10/28 (36%); median number of cycles: 9 (range, 2-17)
- Mean hemoglobin count increased from 8.9 g/dL at baseline (n = 28) to 10.2 g/dL at cycle 12 (n = 5)
- 13 serious AEs; 3 related to treatment: neuropathy, anemia and increased liver enzymes
- Interim analysis planned after 37 patients: Higher POM dose to improve anemia response will be considered

Stegelmann F et al. *Proc ASH* 2015;Abstract 826.

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HARMONY Trial: RUX with Buparlisib (BKM120) in MF

- Open-label, multicenter Phase Ib trial of RUX with buparlisib (a PI3K inhibitor)
- N = 42 patients with DIPSS intermediate- or high-risk MF and palpable splenomegaly ≥5 cm (n = 28 JAK mutation-positive)
- **Endpoints:** Maximum tolerated dose (MTD), safety and efficacy

At week 24	JAK inhibitor naïve (n = 22)	Prior JAK inhibitor (n = 20)
≥50% reduction in palpable spleen length at MTD	12 (54.5%)	4 (20%)

- MTD: RUX 15 mg BID + buparlisib 60 mg qd
- Grade 3 and 4 AEs at MTD included anxiety, multiorgan failure, anemia and thrombocytopenia
- The combination of RUX and buparlisib was generally well tolerated with clinically relevant efficacy

Durrant ST et al. *Proc ASH* 2015;Abstract 827.

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Investigator Commentary: Activity and Safety of RUX-Based Combination Therapies for Patients with MDS/MPN

MF is a particularly difficult disease to treat. Patients develop fibrotic bone marrow that often leads to profound anemia. They have extramedullary hematopoiesis leading to splenomegaly that causes pain, early satiety and partial hypertension. Sclerotic bones elicit bone pain. These patients, particularly those with high-risk disease, often experience profoundly reduced quality and quantity of life.

The standard therapy for patients with MPN (60% have a JAK2 V617F mutation) is RUX, which is approved for patients with intermediate and high-risk MF and is useful for patients with disease harboring a JAK2 V617F mutation in addition to those with other genetic subtypes of this disease. Efforts to improve upon RUX alone have included the addition of a variety of agents.

continued

Investigator Commentary: Activity and Safety of RUX-Based Combination Therapies for Patients with MDS/MPN

At the ASH 2015 Annual Meeting several presentations involved the combination of the following agents with RUX: AZA (48% response rate but 40% rate of new Grade 3 or 4 cytopenia), the hedgehog pathway inhibitor sonidegib (most patients experienced at least a 25% reduction in spleen size, but 63% required a dose reduction or interruption due to increased creatine kinase or myalgia), the immunomodulatory agent POM and the PI3K/AKT inhibitor buparlisib (≥50% spleen-size reduction rates of 54.5% and 20% at MTD in RUX-naïve and RUX pre-exposed patients, respectively). None of these were "home runs," and randomized, controlled trials will be required to determine whether the addition of any of these agents to RUX will be better than RUX alone.

Interview with Richard M Stone, MD, February 16, 2016

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