



POST-ASH Issue 4, 2016

Phase I/II Studies of Azacitidine Alone or with Pracinostat for Patients with AML

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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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This activity is supported by educational grants from Celgene Corporation, CTI BioPharma Corp/Baxalta Inc, Jazz Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Seattle Genetics and Takeda Oncology.

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

Expiration date: May 2017



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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.



Richard M Stone, MD

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)

-  (PLENARY) Up-front use of the multikinase inhibitor midostaurin with a "7 plus 3" chemotherapy regimen in FLT3-mutated AML
-  Sorafenib with chemotherapy improves the overall survival of older adults with FLT3-ITD-mutated AML
-  Antileukemic activity and tolerability of the multikinase inhibitor gilteritinib in FLT3-mutated AML
-  Up-front treatment with venetoclax and decitabine or azacitidine for older patients with AML
-  Pracinostat with azacitidine in elderly patients with AML; oral azacitidine monotherapy in AML
-  Allogeneic stem cell transplantation after high- versus reduced-intensity conditioning in MDS and AML
-  Safety and efficacy of AG-221, a potent inhibitor of mutant IDH2 in advanced hematologic cancers
-  Azacitidine with lenalidomide or vorinostat versus azacitidine monotherapy in MDS and CMML
-  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)

-  (PLENARY) Rituximab and chemotherapy in adults with CD20-positive, Philadelphia chromosome-negative, B-cell precursor ALL
-  Dose-intensified pegylated asparaginase pediatric regimen in adults with untreated ALL
-  Blinatumomab in adult patients with relapsed/refractory Philadelphia chromosome-positive ALL
-  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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Phase I/II Studies of Azacitidine Alone or with Pracinostat for Patients with AML

Presentations discussed in this issue

Garcia-Manero G et al. **Final results from a Phase 2 study of pracinostat in combination with azacitidine in elderly patients with acute myeloid leukemia (AML).** *Proc ASH 2015*; **Abstract 453.**

Savona MR et al. **CC-486 (oral azacitidine) monotherapy in patients with acute myeloid leukemia (AML).** *Proc ASH 2015*; **Abstract 452.**

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

Final Results from a Phase 2 Study of Pracinostat in Combination with Azacitidine in Elderly Patients with Acute Myeloid Leukemia (AML)¹

CC-486 (Oral Azacitidine) Monotherapy in Patients with Acute Myeloid Leukemia (AML)²

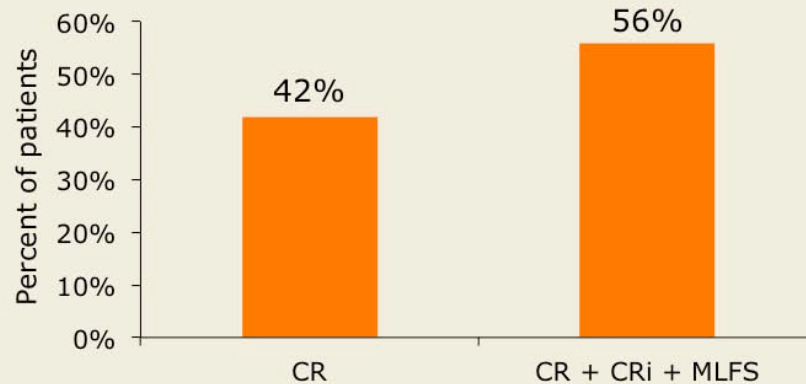
¹ Garcia-Manero G et al.
Proc ASH 2015; Abstract 453.

² Savona MR et al.
Proc ASH 2015; Abstract 452.

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Pracinostat with Azacitidine for Elderly Patients with Acute Myeloid Leukemia (AML)

- Phase II trial of pracinostat, an oral histone deacetylase (HDAC) inhibitor, with azacitidine
- N = 50 patients aged ≥ 65 with untreated AML who are ineligible for intensive induction therapy
- **Primary endpoint:** Complete response (CR) + CR with incomplete blood count recovery (CRi) + morphologic leukemia-free state (MLFS, ie, marrow CR)



Garcia-Manero G et al. *Proc ASH 2015*;Abstract 453.

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Pracinostat + Azacitidine: Conclusions

- Combination of azacitidine and pracinostat is safe for elderly patients with AML:
 - Treatment-related adverse events (AEs) leading to drug discontinuation: Peripheral motor neuropathy (n = 1), parainfluenza (n = 1), atrial fibrillation/prolonged QTc (n = 1), acute kidney injury (n = 1), diverticulitis (n = 1), supraglottic ulcer (n = 1), intermittent fatigue (n = 2) and sepsis (n = 3)
- High response rate in comparison to single-agent azacitidine
- Median event-free survival = 7.7 months; Median overall survival (OS) not reached (1-y OS estimated at 62%)
- Confirmation of these results in a Phase III trial is planned

Garcia-Manero G et al. *Proc ASH 2015*;Abstract 453.

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Oral Azacitidine (CC-486) Monotherapy in AML

- Patients from 2 Phase I/II studies were sequentially assigned to receive oral azacitidine in 4 extended-dosing regimens of 14 days or 21 days per 28-day cycle
- N = 23 patients with AML
- **Endpoints:** Safety and efficacy
 - Reasonably well tolerated
 - Hematologic response rate = 48%, including patients with prior myelodysplastic syndromes and relapsed/refractory AML
 - Patients for whom prior hypomethylating agents (HMA) had failed experienced responses, which may reflect sustained hypomethylation with prolonged oral administration
- Oral azacitidine is an additional option after failure of intravenous or subcutaneous HMA therapy
- Ease of administration facilitates use in combination treatment regimens, which warrants investigation
- Phase III QUAZAR AML Maintenance trial of oral azacitidine and best supportive care after induction therapy is ongoing (NCT01757535)

Savona MR et al. *Proc ASH* 2015;Abstract 452.

Investigator Commentary: Final Results of a Phase II Trial of Pracinostat/Azacitidine for Elderly Patients with AML and Results from a Study of Oral Azacitidine Monotherapy in AML

No consensus has been reached on how best to treat AML in older adults. First, older patients are less able to tolerate the intensive chemotherapy often used for younger adults with AML. Second, older adults tend to have a more intrinsically resistant disease with a higher incidence of adverse cytogenetics and mutations. One standard approach for older adults in the United States who are not deemed to be eligible for chemotherapy due to host or disease factors is the use of a hypomethylating agent, either azacitidine or decitabine.

A trial comparing decitabine (administered for 5 days every month) to supportive care or low-dose Ara-C did not meet its primary endpoint of extending OS but did demonstrate a clear trend in favor of decitabine. Similarly, a large trial, AZA-AML-001, reported by Dombret and colleagues in *Blood* 2015, showed a trend toward a superior yield in OS with azacitidine therapy versus physician-chosen conventional care regimens (either low-dose Ara-C, supportive care or induction chemotherapy) for older adults with newly diagnosed AML.

continued

Investigator Commentary: Final Results of a Phase II Trial of Pracinostat/Azacitidine for Elderly Patients with AML and Results from a Study of Oral Azacitidine Monotherapy in AML

Consequently, efforts are under way to improve hypomethylating agent-based therapy for older adults with AML. One such effort is to develop more convenient formulations of one or both of these drugs. The ASH presentation by Savona and colleagues showed that oral azacitidine could be administered safely and effectively to older adults with AML. Whether oral azacitidine will supplant the use of intravenous or subcutaneous azacitidine remains to be determined.

Another attempt to improve results with hypomethylating agents in older adults with AML is to add another agent. Hypomethylating-agent therapy is believed to allow the transcription of differentiation-associated genes. Preventing deacetylation of histones also potentially opens the genome, allowing transcription of "favorable" genes, and represents a related biological target. Whether the addition of HDAC inhibitors (HDACi) to a hypomethylating agent will improve outcomes in older adults with AML is unclear.

continued

Investigator Commentary: Final Results of a Phase II Trial of Pracinostat/Azacitidine for Elderly Patients with AML and Results from a Study of Oral Azacitidine Monotherapy in AML

A study conducted by the US Intergroup and led by Dr Mikkael Sekeres did not show any benefit to adding the HDACi vorinostat to azacitidine for patients with high-risk myelodysplastic syndromes. The Phase II results of adding the novel HDACi pracinostat to azacitidine for older patients with AML were encouraging but not definitive.

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

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