



POST-ASH Issue 4, 2016

Phase I/II Trial of Gilteritinib (ASP2215) in FLT3-Mutated Relapsed/Refractory AML

For more visit ResearchToPractice.com/5MJCASH2016

Research
To Practice®

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.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.75 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 80% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2016/4/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess conflicts of interest with faculty, planners and managers of CME activities. Conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported relevant conflicts of interest, which have been resolved through a conflict of interest resolution process:

Richard M Stone, MD
Director, Adult Leukemia Program
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Advisory Committee: Agios Pharmaceuticals, Amgen Inc, Arog Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celator Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology, Janssen Biotech Inc, Merck, Novartis Pharmaceuticals Corporation, Pfizer Inc; Clinical Research: Novartis Pharmaceuticals Corporation; Data and Safety Monitoring Board: Celgene Corporation.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Amgen Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Baxalta Inc, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTherapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, CTI BioPharma Corp, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, ImmunoGen Inc, Incyte Corporation, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Medivation Inc, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, NanoString Technologies, Natera Inc, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories

Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Teva Oncology, Tokai Pharmaceuticals Inc and VisionGate Inc.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS —
The scientific staff and reviewers for Research To Practice have no relevant conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

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



[Browse all content
for this issue](#)



[See all PPT slides](#)



[Listen to interview
with Dr Stone](#)

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

Neil Love, MD

Research To Practice

Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 1.75 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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.

Phase I/II Trial of Gilteritinib (ASP2215) in FLT3-Mutated Relapsed/Refractory AML

Presentation discussed in this issue

Altman JK et al. **Antileukemic activity and tolerability of ASP2215 80mg and greater in FLT3 mutation-positive subjects with relapsed or refractory acute myeloid leukemia: Results from a Phase 1/2, open-label, dose-escalation/dose-response study.** *Proc ASH 2015*; **Abstract 321**.

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

Antileukemic Activity and Tolerability of ASP2215 80mg and Greater in FLT3 Mutation-Positive Subjects with Relapsed or Refractory Acute Myeloid Leukemia: Results from a Phase 1/2, Open-Label, Dose-Escalation/Dose-Response Study

Altman JK et al.
Proc ASH 2015; Abstract 321.

Research
To Practice®

Novel FLT3 Inhibitor Gilteritinib (ASP2215) in Relapsed/Refractory (R/R) FLT3-Positive Acute Myeloid Leukemia (AML)

- Phase I/II open label dose-escalation, dose-response study of gilteritinib, a highly selective FLT3 inhibitor
- N = 215 patients with R/R AML treated with gilteritinib ≥ 80 mg; n = 133 evaluable patients with FLT3-mutated disease
- Strong antileukemic activity in patients with heavily pretreated FLT3-positive disease:
 - Overall response rate (ORR) = 73 (55%); composite complete remission (CRc) = 61 (46%)
 - No difference in ORR between patients with TKI-naïve disease and those who received prior tyrosine kinase inhibitor therapy (55% vs 55%)
 - Median overall survival ~ 29 weeks; similar for patients who achieved CRc
- Treatment was well tolerated:
 - Adverse events of all grades reported in $\geq 10\%$ of the safety population were diarrhea (16%), fatigue (13%) and increased AST (11%)
 - $< 2\%$ of patients reported Grade ≥ 3 QTc prolongation

Altman JK et al. *Proc ASH* 2015; Abstract 321.

Research
To Practice®

Investigator Commentary: Results of the Phase I/II Trial of Gilteritinib in FLT3-Positive R/R AML

Approximately 35% of patients with AML have blasts that harbor an FLT3 mutation. Approximately 3/4 of those with the mutation have an FLT3-ITD or length mutation, which is a duplication of between 3 and 100 amino acids in the juxtamembrane region of the transmembrane tyrosine kinase protein. The other 25% of patients with FLT3 mutations have a point mutation in the tyrosine kinase domain. Both types of mutation activate the enzyme, cause spontaneous ligand-independent dimerization and promote cell proliferation. Multiple efforts are under way to inhibit this activated kinase with small molecules both as single agents and in combination with chemotherapy.

Gilteritinib is a relatively specific small molecule inhibitor of FLT3 that, unlike many of the other agents in development (except for midostaurin and crenolanib) inhibits enzymes with both types of mutations. Dr Altman presented the results of a Phase I/II trial using this agent in patients with advanced R/R FLT3-positive AML. The drug was well tolerated at the doses employed. The CRc rate was 49% for the subset of patients with the FLT3-ITD mutation (n = 114). This compares favorably with the other FLT3 inhibitors in clinical development.

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