ASCO: A Focus on Personalized Medicine

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The year 2011 marked a milestone of sorts for new drug approvals by the FDA. Thirty-five new medicines were approved—the second highest number of approvals in the last decade. Seven were oncology drugs, including the first one approved for Hodgkin lymphoma in 30 years.

With the influx of these new drugs, awareness and education for oncologists are paramount, and this year's annual meeting of the American Society of Clinical Oncology (ASCO) will include educational seminars on these latest clinical advances. Leading researchers involved in the development of the oncology drugs will provide practical advice on individual new therapies.

This new feature is part of a set of pre-meeting seminars that start one day before the official meeting kick-off. Notably, six of the seven drugs discussed are targeted treatments. Two of these treatments, axitinib and vismodegib, were approved by the FDA in 2012. Drugs to be discussed include:

- **Vemurafenib** (Zelboraf, Genentech), an oral, small-molecule BRAF inhibitor for patients with metastatic melanoma whose tumors harbor a $BRAF^{V600E}$ mutation.
- **Crizotinib** (Xalkori, Pfizer), an oral, small-molecule, dual inhibitor of the c-MET and ALK receptor tyrosine kinases for advanced non-small cell lung cancer (NSCLC) that expresses the *EML4-ALK* fusion gene.
- **Brentuximab vedotin** (Adcetris, Seattle Genetics), for intravenous infusion, an anti-CD30 antibody for the treatment of CD30-positive relapsed Hodgkin lymphoma and relapsed systemic anaplastic large cell lymphoma.
- **Abiraterone acetate** (Zytiga, Janssen), an oral inhibitor of the cytochrome P450 17A1 protein (CYP17A1) for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in men who have received prior chemotherapy.
- **Axitinib** (Inlyta, Pfizer), an oral small-molecule inhibitor of multiple tyrosine kinases including cKIT, VEGFR 1-3, and PDGFR, for treatment of relapsed advanced renal cell carcinoma (RCC).
- **Vismodegib** (Erivedge, Genentech), an oral inhibitor of the Hedgehog pathway for the treatment of advanced basal cell carcinoma (BCC). Uninhibited signaling of the Hedgehog pathway is the

molecular driver of BCC.

Another pre-meeting session will focus specifically on targeted therapy approaches. Patricia LoRusso, DO, of the Karmanos Cancer Institute, Detroit, Michigan, in the session "Where Did We Come From, Where Do We Go From Here?" will give a bird's-eye view of targeted therapies, discussing past and present development and how to approach the next phase based on what targeted therapies have taught us thus far.

Because many of the new targeted therapies are oral medications that patients take at home, the ways in which patients are educated about their treatments and monitored have fundamentally evolved. The management of side effects of targeted therapies will be discussed in a session by an oncology nurse, Peg Esper, MSN, MSA, RN, ANP-BC, AOCN, from the University of Michigan School of Nursing, Ann Arbor.

"Targeted therapies for such tumors as metastatic melanoma, prostate cancer, and renal cell cancer will most likely be presented at the meeting," said LoRusso. "There is also a lot of activity ongoing with other novel targets, such as agents targeting the PI3 kinase pathway and various isoforms of the *PIK3CA* mutation. Hopefully some of this data will be mature enough and presented as well."

Targeted Therapy Presentations to Watch for at ASCO

Metastatic melanoma: Results of the phase III METRIC clinical trial of trametinib, a MEK inhibitor tested in a global, randomized trial of patients with metastatic melanoma, the results of the phase III BREAK-3 trial of dabrafenib, a BRAF kinase inhibitor; also, an update on a phase I/II trial of dabrafenib combined with trametinib in treatment-naïve patients.

RCC: Results of the global, randomized, phase III TIVO-1 clinical trial testing the efficacy of tivozanib, a receptor tyrosine kinase inhibitor, against sorafenib, the current standard of care, as a first-line treatment for advanced RCC.

Liver cancer, RCC, prostate cancer, and thyroid cancer: Four oral presentations of studies with cabozantinib (XL184) are expected during ASCO. Cabozantinib is a small-molecule inhibitor of the tyrosine kinases c-Met and VEGFR2. The four presentations will be:

- Clinical data of a phase II randomized, discontinuation trial in hepatocellular carcinoma
- Efficacy of cabozantinib in patients with metastatic, refractory RCC
- Phase II nonrandomized, expansion cohort results in chemotherapy-pretreated mCRPC
- Full results of the pivotal phase III EXAM trial in medullary thyroid cancer patients

Non-small cell lung cancer: Results of the pivotal phase III LUX-Lung 3 trial of afatinib in treatment-naïve patients with metastatic NSCLC with *EGFR* mutations. The trial compares the efficacy of afatinib, an irreversible ErbB family inhibitor, to pemetrexed/cisplatin. Mutations in *EGFR*, also known as ErbB1, are found in approximately 12% of Caucasians and as many as 40% of Asian patients with NSCLC.

Acute myeloid leukemia and acute lymphoblastic leukemia: Six-month follow-up data from the pivotal PACE trial of ponatinib, a pan-BCR-ABL inhibitor, in patients with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to the currently approved BCR-ABL inhibitors dasatinib and nilotinib, or who have the T315I mutation. Positive preliminary data were presented at the American Society of Hematology (ASH) meeting in December 2011.

Immunotherapy for melanoma, RCC, and lung cancer: Several abstracts will be presented on phase I and phase II clinical trials of MDX-1106/ BMS-936558, an anti-PD1 immunotherapy that is seen as the next generation of immunotherapy after ipilimumab. Anti-PD1 is being developed by Bristol-Myers Squibb. Results are expected from the large expansion cohort data of the phase I/II solid tumor trial and potentially from the phase II RCC trial.

According to LoRusso, the face of melanoma has changed completely because of targeted and biologic treatments: "There has been a huge impact." Phase III results of the effectiveness of vemurafenib for melanoma were presented at last year's ASCO plenary session. This compound has had a major impact on the *BRAF*-mutated subset of melanoma. Results of new targeted treatments and their combinations will likely be a highlight of this year's meeting as well.

LoRusso sees combination therapies as the future of targeted therapies. "In metastatic disease, where we are going for one major target because there is one major driver mutation—such as with basal cell cancers,

ALK-mutated lung cancer, or *BRAF*-mutated melanoma, for example—the majority of these patients will eventually go on to progress despite continued therapy," said LoRusso. "Based on this evidence, combination targeted therapies is the way to go forward."

Many monotherapies have not resulted in robust responses, or at least not in long-term responses, according to LoRusso. "We are in the process of being challenged to re-think how we give these targeted therapies, especially if combination data demonstrate better efficacy over monotherapy." LoRusso also pointed out that because of the high potential cost of combining therapies, combinations will have to show robust efficacy in order to be widely utilized.

Science is what is driving the combination therapies. Hypothesis-driven clinical trials based on robust laboratory research results is now much more prevalent, said LoRusso. The challenge will be to not only further develop new therapies, but to find better ways to measure progress and genomic evolution of a tumor through the course of disease and treatment.

ASCO: Targeted Therapy Educational Sessions

Treating patients with targeted therapies requires a new approach to diagnosis (using molecular biomarkers), monitoring of patients, management of new types of adverse events, and cost decisions due to high prices of these medications. We have witnessed a range of successes in the advancement of targeted therapy research and clinical trials, and approvals for different types of cancers. For example, lung cancer, breast cancer, and melanoma are now at the forefront of personalized medicine and targeted therapy options. The following ASCO 2012 educational meeting sessions will highlight the latest research developments in targeted treatments and new ways clinicians need to be thinking about this type of approach to cancer care.

Several sessions specifically highlight personalized medicine for different tumor types:
– "The Cost of Lung Cancer Care: Screening, Personalized Medicine, and Palliative Care" (Friday, June 1)

– "Personalized Medicine in Lung Cancer in 2012" (Saturday, June 2)

– "New Options, New Questions: How to Select and Sequence Therapies for Metastatic Melanoma" (Saturday, June 2)

– "'Personalized' Oncology for Colorectal Cancer: Ready for Prime Time or Stop the Train" (Tuesday, June 5)

– "Mechanisms of Resistance to Targeted Anticancer Agents" (Saturday, June 2)

– "Biologic Principles of Targeted Combination Therapy" (Sunday, June 3)

- Many TKIs are approved for a range of cancers, including imatinib and dasatinib for CML, gefitinib for breast and lung cancers, erlotinib for lung and pancreatic cancers, and sunitinib for RCC. "Laboratory and Clinical Insights into Resistance to Tyrosine Kinase Inhibitors" (Sunday, June 3) will address a key issue in the use of TKIs.
- A novel view on targeted therapies will be discussed on Monday, June 4, in the session "Targeting Critical Molecular Aberrations Early in the Course of Solid Tumors: Is It About Time?" Targeted therapies are now predominantly utilized in the advanced cancer and metastatic setting, but this session will discuss moving these agents into the adjuvant setting, and potentially even to earlier-stage settings.
- A "Meet the Professor" session on Monday, June 4, "Bringing

Serial biopsies are at times necessary and ultimately can benefit a patient by providing accurate information that influences further treatment. However, these biopsies can be invasive and come with many adverse effects. "We realize that the information biopsies provide is important for treatment decisions and assessment of disease. They are important but associated with toxicities," LoRusso said. New technologies such as assaying for circulating tumor cells or circulating DNA are in development as potential ways to access the cancer information less invasively—a topic to be discussed at the ASCO 2012 meeting.

Identifying patients who will benefit most from a medication is also important, both for patient outcomes and to minimize cost of care, two major ongoing issues in oncology. "We need to focus on what is best for the patient," said LoRusso.

Provocative NCI Questions To Be Addressed

A key theme at this year's ASCO meeting will

Personalized Cancer Therapy into Routine Use," will focus on the practical aspect of personalized care for clinicians.

be sessions that aim to address some of the provocative questions that were assembled by the National Cancer Institute (NCI) in 2011. The goal of the questions is to identify and address the most complex cancer care and research problems. The ASCO sessions will be a forum for the oncology community to discuss the problems and think of innovative, "outside-the-box" ways to use laboratory, clinical, and population studies to begin to offer answers. Many educational sessions at ASCO will highlight these questions.

One of the proposed questions, "Why do many cancer cells die when suddenly deprived of a protein encoded by an oncogene?" highlights the ability of targeted therapies to inhibit a specific driver mutation within a tumor. The question also brings to light our relatively meager understanding of why inhibition of oncogenic drivers leads to cancer cell death for some tumor types but not others. Many broad and tumor type-specific sessions will address this question. Some of these sessions include "Biologic Principles of Targeted Combination Therapy," "Developing a Targeted Therapy: Issues in the Age of Personalized Therapy," and "New Options, New Questions: How to Select and Sequence Therapies for Metastatic Melanoma."