[News * Analysis * Commentary * Controversy]

December 25, 2013 * Vol. 35 * No. 24

oncology-times.com

Oncology Times

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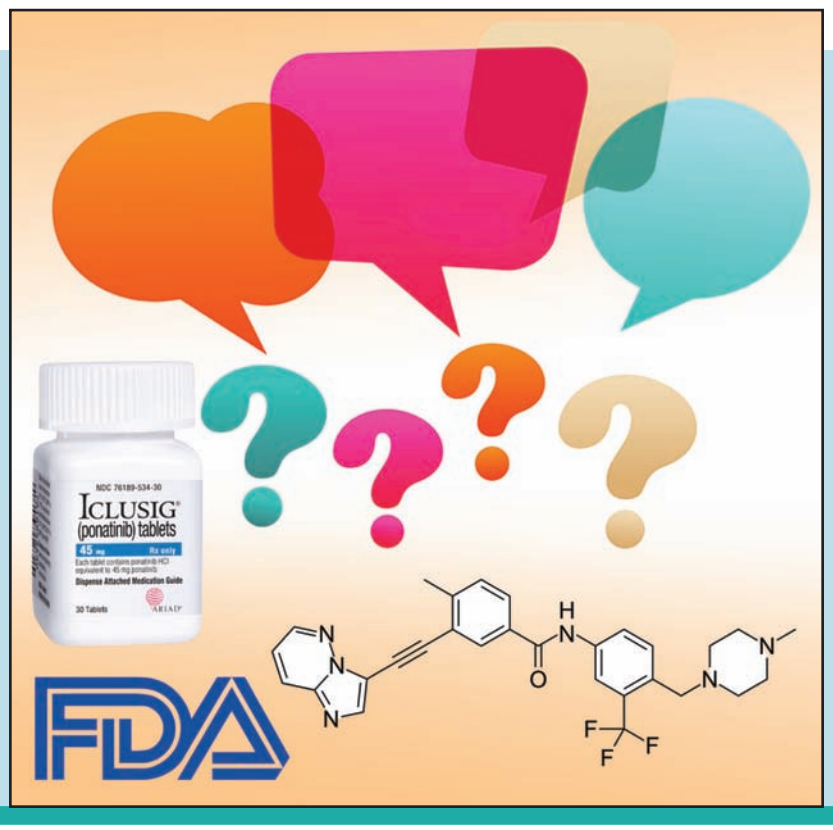

The Ponatinib Problem:

Debating the FDA's Recent Market Suspension

BY SARAH DIGIULIO

Although promising early results led to the accelerated approval of the leukemia drug, recently reported longer follow-up data showed an increased risk of arterial thrombotic events—prompting the FDA to temporarily suspend marketing and sales of the drug. But, several experts told us that for some patients, the potential benefits may still outweigh the risks.

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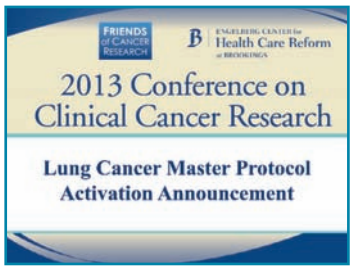

Unique Trial Protocol Announced for Lung Cancer p. 9

Novel Agents Rapidly Emerging for CLL p. 24

Central Line Care Bundle Benefits Ambulatory Pediatric Cancer Patients p. 30

[ALSO]

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PERIODICALS

Study Identifies New Cause of Cancer Wasting—and Potentially, a New Avenue for Treatment

BY SARAH DIGIULIO

A new study shows that cancer cachexia, which causes life-threatening loss of body weight and lean muscle mass, is caused in part by the tumor factors that block muscle repair, according to the research published in the *Journal of Clinical Investigation* (***2013;123:4821-4835***).

"By identifying agents that overcome the block and allow muscle stem cells to differentiate, it might be possible to restore muscle mass and enhance the quality of life of cancer patients with cachexia," principal investigator Denis Guttridge, PhD, Professor of Molecular Virology, Immunology, and Medical Genetics, and a member of Molecular Biology and Cancer Genetics Program, all at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, said in a news release.

For the study the researchers analyzed animal models and tissue from cachectic pancreatic cancer patients to identify the factor in the muscle microenvironment that contributes to cancer cachexia. Key findings were that:

- Cachexia is associated with tumor-induced damage to skeletal muscle cells and tumor-induced proliferation of muscle stem cells;
- Overexpression of the muscle stem cell factor Pax7 blocks the cells' ability to differentiate and promotes cancer-induced wasting;
- The overexpression of Pax7 promotes cancer wasting by blocking the maturation of muscle cells and their fusion with surrounding fibers, which allows muscle to gain mass;
- The overexpression of Pax7 is controlled by the transcription factor NF-kappa B (NF-kB), which has been shown to play multiple roles in cancer. In cachexia, NF-kB causes the deregulation of Pax7 expression, which in turn impairs differentiation of muscle progenitor cells and promotes muscle atrophy; and

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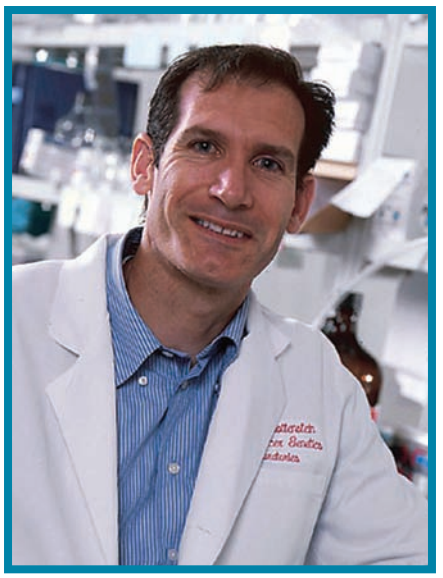

DENIS GUTTRIDGE, PHD: "Our study showed that although muscle stem cells are activated during cachexia, factors released by the tumor block these cells from differentiating into muscle cells, which leaves them unable to repair cachectic muscle fibers."

→MASTER PROTOCOL

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She said it is going to be important to reach out to community oncologists and involve them in the lung cancer master protocol trial, adding, "If there are winners, it will be great for patients."

Immunotherapy

The decision to include an immunotherapy drug in the master trial protocol lung cancer study marks increasing recognition of its importance in the treatment of cancer patients, according to speakers at a session on immunotherapy at the FOCR conference. The FOCR gave conference participants an issue brief, "Facilitating the Development of Immunotherapies: Intermediate Endpoints for Immune Checkpoint Modulators," which explores the intermediate clinical endpoints that will be needed in immunotherapy trials.

"This [immunotherapy] is a whole paradigm shift," said session moderator James Allison, PhD, Immunology Chair at the University of Texas MD Anderson Cancer Center and a coauthor of the issue brief.

Allison pointed out that immunotherapy has a number of advantages in cancer treatment, including the fact that T cells have memory and adaptability; thus the immune system can change as the cancerous tumor changes. "We've gone from a situation where metastatic melanoma was uniformly fatal" to a situation where half the patients respond to immunotherapies, he pointed out. "Our job now is to more effectively evaluate these therapies."

The key difference with immunotherapy is that, in contrast to cytotoxic therapies, "we're not treating the cancer directly," said Axel Hoos, MD, PhD, Vice President of Oncology R & D at GlaxoSmithKline and a coauthor of the immunotherapy issue brief.

He emphasized that there are different patterns of immunotherapy response. With immunotherapies, the actual clinical response may take some time (in months), and the patient may experience delayed treatment effects. "As clinicians, we certainly don't want to miss that [delay] and deny the patient further therapy," he said.

> "To my knowledge there is nothing like this that has been tried before."
> —*David Gandara, MD*

In addition, he noted, there may be tumor volume increase initially (thought to be due to lymphocyte infiltration), which could be mistaken for tumor progression before a response is shown. Also, Hoos said, "You may never detect a response, but you may actually slow down tumor growth."

All of these issues matter for setting up the analysis for a successful immunotherapy clinical trial, he explained.

Also a coauthor of the immunotherapy brief, Steven Rosenberg, MD, PhD, Head of NCI's Tumor Immunology Section, said, "There's no question that you can see progression and then regression with immune modulators. Each kind of immunotherapy might have very different kinetics of response."

So, he noted, as intermediate endpoints for immunotherapies are considered, each has to be specific for the type of immunotherapy under study. "We have to be very careful abut using soft endpoints that haven't been validated," he said. Also, he added, unanswered questions remain about the sequencing of immunotherapy drugs.

> As intermediate endpoints for immunotherapies are considered, each has to be specific for the type of immunotherapy under study—We have to be very careful about using soft endpoints that haven't been validated."
> —*Steven Rosenberg, MD, PhD*

Overall survival remains the gold standard as a clinical trial endpoint, emphasized Amy McKee, MD, Lead Medical Officer at the FDA's CDER. "There's a lot of work to be done" before the FDA can accept new clinical trial endpoints for immunotherapies, she said, adding, "We have to evaluate each individual trial as we make decisions about these issues."

Richard L. Schilsky, MD, Chief Medical Officer of the American Society of Clinical Oncology, told the FOCR panel, "There's a lot of excitement" about immunotherapy. But, he said, clinicians need specific guidance on how to use immunotherapy in clinical practice.

"What I'm excited about is that it seems to work in a whole variety of tumor types," Schilsky told *OT*. But he noted that for clinicians, specific, unanswered issues remain, including the fact that a patient's response to a given immunotherapy cannot now be predicted in advance.

Also, he said, these questions need answering:

- How long should the physician wait for a response to a given immunotherapy?
- How should the physician sequence immunotherapeutic agents?
- If there is prolonged durable survival, how does that impact subsequent therapy?

In addition to the issue brief on immunotherapy, Friends of Cancer Research also distributed an issue brief on cancer drug dosing, "Optimizing Dosing of Oncology Drugs," and held a panel session on the topic. Schilsky, who moderated that panel, is a coauthor of the issue brief, which describes different potential approaches to the dosing of drugs used in oncology.

FDA Approves Xalkori (Crizotinib) for NSCLC

The U.S. Food and Drug Administration has approved the use of Xalkori (crizotinib) capsules for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive, as detected by an FDA-approved test.

The drug, made by Pfizer, had previously been granted accelerated approval in 2011 based on durable, objective response rates of 50 percent and 61 percent in two single-arm, open-label studies (***OT 9/25/11***). Accelerated approval allows for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint. After a drug receives accelerated approval, manufacturers are still required to conduct studies to confirm the drug's anticipated clinical benefit, known as Phase IV confirmatory trials, in order to receive traditional approval.

The drug's latest approval was based on an open-label, active-controlled, multinational, randomized trial of 347 patients with ALK-positive metastatic NSCLC, which showed superior progression-free survival and overall response rates for Xalkori-treated patients compared with patients receiving chemotherapy.

The patients in the trial had disease progression following platinum-based chemotherapy and had ALK expression in their tumors, which was detected by fluorescence in situ hybridization on central laboratory testing. Patients were randomized to receive either Xalkori or chemotherapy (pemetrexed or docetaxel if they had received prior pemetrexed).

The median progression-free survival for treatment with Xalkori was 7.7 months, compared with three months for patients treated with chemotherapy. The overall response rate was 65 percent for patients receiving Xalkori compared with 20 percent for patients receiving chemotherapy. Approximately 64 percent of the patients on the chemotherapy arm subsequently received Xalkori.

Common adverse reactions in the trials with Xalkori (occurring at rates of 25 percent or higher) included visual disorders, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue. Safety data showed that serious adverse events were reported in 37 percent of the patients treated with Xalkori—the most common included: pneumonia, pulmonary embolism, dyspnea, and interstitial lung disease.

Fatal adverse reactions occurred in nine patients treated with the drug and included: acute respiratory distress syndrome, arrhythmia, dyspnea, pneumonia, pneumonitis, pulmonary embolism, interstitial lung disease, respiratory failure, and sepsis.

The recommended dose and schedule for Xalkori is 250 milligrams orally, twice daily, with or without food.

→STUDY

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- Because of Pax7's tissue specificity, inhibition might be an option for therapeutic approaches.

"Our study showed that although muscle stem cells are activated during cachexia, factors released by the tumor block these cells from differentiating into muscle cells, which leaves them unable to repair cachectic muscle fibers," Guttridge also noted. "It is the first to show proof of concept that events occurring outside the muscle fiber and within the muscle microenvironment also play a part in driving muscle wasting in cancer."

The next step is to use this research to determine the fate of muscle stem cells that are blocked in differentiation and unable to fuse to damaged muscle fibers, Guttridge said via email. "Further cell-based and in vivo studies are need to ascertain whether factors identified in this study that were found to contribute to cachexia can be targeted for therapy."