Chinese American Hematologist Oncologist Network (CAHON)

New Cancer Therapeutics and Practice Changing News

By Tina Li

Biweekly News and Information Updates for Members

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Highlights:

- *New Treatment Targets in melanoma and lung cancers*
- *Controversy for ODAC's recommendation to remove bevacizumab in advanced breast cancer*
- *Call for Member and Talent Student Volunteers*
- *Contest for Logo for CAHON*
- *CSCO Annual Meeting in Beijing*

Although chemotherapy is still a cornerstone of cancer therapy, it has reached a plateau or remains ineffective in most, if not all, solid tumors. Recent advances in understanding tumor biology and multiple high-throughput technologies have greatly improved our ability to comprehensively and rapidly interrogate the cancer genome of individual cancer patients from small amount of tumor specimens. Cancer is being defined as a complex genetic syndrome. Increasingly, specific genetic biomarkers have been used to select small subsets of cancer patients sensitive to novel targeted therapeutics. These are among the most important breakthroughs in many solid tumors in recent years. We hope that these agents will improve the cost-effectiveness of cancer treatment and eventually reduce cancer death. We are committed to brief our busy practicing members of promising cancer therapeutics in horizon and potentially practice changing news in our newsletters.

In this issue, we summarize the promising results of targeting EML4-ALK fusion oncogenes in non-small cell lung cancer and targeting BRAF mutation in metastatic melanoma.

New CAHON Executive Team (2010-2012)

President: Weijing Sun, MD
Vice President: Yang-Min (Max) Ning, MD, PhD
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Director, Education and Communications: Janice Lu, MD
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Adviser Board Chairwoman: Ruirong Yuan, MD, PhD

BRAF Inhibitors for Treatment of Advanced Melanoma

By Yang-Min Nin

Exciting clinical trial results about BRAF inhibitors for the treatment of advanced melanoma have floated in the last two years. However, no detailed report was available until a paper was published in New England Journal of Medicine on August 26, 2010.

The reported results were based on a Phase 1 study that had a dose escalation cohort and an extension cohort of 32 patients with advanced melanoma positive for the activating $BRAF^{V600E}$ mutation. A total of 55 patients (49 of whom had melanoma) were enrolled in the dose-escalation phase, and 32 additional patients with metastatic melanoma who had BRAF with the V600E mutation were enrolled in the extension phase. The overall observed response rate in patients with the point mutation was 77%. Of them, 3 patients had complete responses. The response rate was even higher (81%) in the extension cohort patients who received the recommended phase 2 dose, 960 mg twice daily. The estimated progression free time was 7~8 months, close to the historical median survival of patients with advanced melanoma.

The toxicities include grade 2 or 3 rash, fatigue, and arthralgia that appeared manageable. One unique toxicity observed was the frequent incidence of cutaneous squamous-cell carcinoma (SCC), which was reported as localized, well-differentiated tumors, occurring in about 20% of patients treated. No SCC identified in other organs of the body.

Commentary:

Patients with advanced melanoma have a median survival of 8-10 months. The two FDA approved products (IL-2 and DTIC) generally are associated response rates of 10-20%. To date, no effective treatment regimen has prolonged survival in patients with advanced melanoma or has demonstrated such an unprecedented high response rate. Identification of genetic abnormalities in various components of signaling pathways, such as BRAF mutation, involved in the initiation and progression of melanoma has provided potential new therapeutic targets.

Open Call for Logo Design for CAHON

CAHON continues to call for Logo design from all members.

The design should reflect the mission and identity of this organization.

The ideal logo should fulfill the following standards:
1. Simple design.
2. In color or black/white. If it is in color, the content must not be lost if it is copied in black and white.
3. Reflect our primary interests in eliminating cancer.
4. To remind of our mission to serve as a bridge between US and Chinese hematology and oncology community.
5. The designer must agree to release the copyright of the chosen design to CAHON.

Please send us your work before December 31, 2010.

The Winner of Logo Design Will be Honored with A Certificate and Given a Cash Prize of $100.

Call for Member and Talent Student Volunteers

CAHON is our organization. We need your contributions to fulfill our mission and to sustain our growth. We need volunteers in all committees. You have a chance to shape our future.
Have a web master kid in high school or college? We need their talent and energy to help us maintain and upgrade our website (www.cahon.org). It is a great opportunity for bonding and showing your children who we are. Awards and Volunteer Certificate will be available. We would like to hear from you.

Targeting (Anaplastic Lymphoma Kinase) ALK in Lung Cancer

By Tina Li

Lung cancer remains the most common and lethal cancer in the United States and worldwide. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all cases of lung cancer in the United States. Currently, systemic chemotherapy has reached a plateau in both first-line and second-line therapy of NSCLC. The identification of molecular cohorts of NSCLC patients who demonstrate dramatic clinical response to targeted agents has changed the landscape of lung cancer therapy. The *EML4-ALK* fusion oncogene represents a newest molecular target in NSCLC.

First described by a Japanese group in 2007, the *EML4-ALK* fusion gene results from a small inversion within chromosome 2p, which leads to expression of a chimeric tyrosine kinase, in which the N-terminal half of echinoderm microtubule-associated protein-like 4 (EML4) is fused to the intracellular kinase domain of anaplastic lymphoma kinase (ALK). Current evidence support that EML4-ALK is a key driver of lung tumorigenesis in about 5% of non-selected subset of NSCLC patients.

Crizotinib (PF-02341066), an oral multi-targeted TKI mainly against c-MET and ALK kinases. The first-in-human phase I trial of crizotinib included a part 1 dose escalation phase that determined 250 mg twice daily as the recommended phase II dose. The part 2 expansion cohort included patients with *ALK*-positive NSCLC. Recently, Bang et al reported update results of this expansion cohort at the 2010 ASCO Annual Meeting.

By April 7 of 2010, 82 patients were enrolled and the study is ongoing. Median age was 51 years and 43 (52%) were male. The majorities of patients had adenocarcinoma (96%), an ECOG performance status of 0 or 1 (83%), and were never smokers (76%). Twenty-seven (33%) patients had 1 prior regimen, 15 (18%) had 2 prior regimens and 34 (41%) had ≥ 2 prior regimens. The updated overall response rate (ORR) was 63% including 1 patient with a complete response. The duration of response ranged from 1 to 15 months and the disease control rate at 8 weeks was 87%. With a median follow-up time of 6.4 months, the median progression-free survival (PFS) was not reached and 70% of patients were still in follow-up. The 6-month PFS probability was 72%. The most common grade 1/2 adverse events were nausea (54%), diarrhea (48%), vomiting (44%) and visual disturbance (42%). Ten patients (12%) experienced grade 3 adverse events including 4 (5%) with alanine aminotransferase (ALT) elevation, 5 (6%) with aspartate aminotransferase elevation, and 2 (2%) with lymphopenia. One patient (1%) had grade 4 ALT elevation. These results suggest in a rare population of patients with *EML4-ALK* fusion oncogenes-positive advanced NSCLC, crizotinib may offer a new standard of care.

Meanwhile, a phase III trial comparing crizotinib to pemetrexed or docetaxel as second-line treatment of *EML4-ALK*-positive advanced NSCLC is ongoing. A separate phase III trial comparing crizotinib to standard first-line chemotherapy in previously untreated patients with *ALK*-positive advanced NSCLC will open later in 2010.

The 13th Annual meeting of Chinese Society of Clinical Oncology (CSCO) is being held in Beijing from September 16-19. The theme of this year is “Paying much Attention to Molecular Marks and Optimizing Therapeutic Strategies”. The conference is organized by CSCO, Beijing University School of Oncology (Beijing Cancer Hospital) and Beijing CSCO Clinical Research Foundation.

Several CAHON members are attending the meeting, including Drs. Weijing Sun, Yang-Min Ning. We will hear the updates from them in the next issue of CAHON eNewsletter.

Biweekly News and Information Updates

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Our Logo?

(Please Submit Your Design)

CAHON's MISSION

CAHON, Chinese American Hematologists and Oncologist Network, was founded in 2005. CAHON is dedicated to fostering communications amongst Chinese-American medical professionals for delivering high-quality health care to patients with neoplastic and hematological diseases, and to promoting medical information exchange between the United States and China in the field of hematology and oncology. CAHON strives to serve as a vital bridge between American and Chinese Hematology-Oncology communities at all levels of academia, industry, government regulation, and private practice.

The Fate of Bevacizumab for Metastatic Breast Cancer

By Janice Lu

The Oncology Drugs Advisory Committee (ODAC) recommended to the US FDA to withdraw the indication for bevacizumab given with paclitaxel in the first-line treatment of metastatic breast cancer. The FDA will decide whether or not to accept this recommendation later this year.

The recommendation from ODAC on July 20, 2010 was based on the efficacy and safety data from three trials: E2100, AVADO, and RIBBON-1. E2100 was the pivotal trial which demonstrated a 5.5-month improvement in progression-free survival (PFS), but no overall survival (OS) difference. The FDA granted accelerated approval on February 22, 2008, based on the data from this single trial, but advised Genentech that confirmatory trials needed to be conducted. AVADO and RIBBON-1 were placebo-controlled, randomized trials that were subsequently conducted in part for that purpose. While both AVADO and RIBBON-1 showed a reduction in hazard ratio (HR) for PFS similar to E2100, the differences in median PFS were less impressive. None of the studies demonstrated a benefit for OS even when the results were pooled. As expected, toxicities were increased with the addition of bevacizumab. ODAC was charged reviewing the results of these three trials and determining if the benefits demonstrated by the trials were sufficient relative to the toxicities to support conversion to full approval for first-line therapy of metastatic breast cancer. The committee members voted 12-1 to remove the advanced breast cancer indication for bevacizumab.

It could be a tough decision for the treating physicians, patients and even perhaps FDA to decide on the fate of bevacizumab for use in advanced breast cancer patients. Although ODAC argued that the drug's performance didn't offer a "clinically meaningful" benefit for patients, more than 6,000 people have signed a petition urging the Agency to keep the drug approved for breast cancer patients who have responded well. If the FDA does revoke bevacizumab's approval, doctors would still have the option to prescribe it "off-label," for breast cancer patients. But many insurers do not reimburse drugs that don't have the FDA's stamp of approval. Without insurance coverage, bevacizumab's enormous cost would put the treatment out of reach for most patients. Roche sells the drug at a wholesale price of $7,700 a month. Perhaps FDA made the smartest and best choice to extend its review of the drug by 90 days, or until Dec. 17. Is it going to be a Christmas gift? We are interested to hear your opinion!