E1512 Trial Spotlight

This article is part of an occasional newsletter segment that highlights studies recently activated by the ECOG-ACRIN Cancer Research Group. It was published in the May 2013 issue of “News from ECOG-ACRIN.”

Finding drugs that synergize with epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer is a vexing clinical problem. In its latest trial, the ECOG-ACRIN Thoracic Committee seeks to improve the efficacy of erlotinib and elucidate the role of cabozantinib.

E1512 – A Randomized Phase II Trial of Erlotinib, Cabozantinib, or Erlotinib plus Cabozantinib as 2nd or 3rd Line Therapy in Patients with EGFR Wild-type NSCLC

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Lung cancer is the leading cause of cancer-related mortality in the United States. According to American Cancer Society estimates, about 228,190 people will be diagnosed with lung cancer and about 159,480 people will die of the disease in the US in 2013. At present, more people in the US die of lung cancer than of colon, breast, and prostate cancers combined.

Histologically, lung cancer is mainly classified as either small cell lung cancer or non-small cell lung cancer (NSCLC). Nearly 90% of patients with lung cancer have NSCLC, the three main subtypes of which are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

Most patients with NSCLC present with advanced or metastatic disease and initially respond to platinum-based doublet chemotherapy. Following disease progression, second-line treatment with erlotinib, a small molecule tyrosine kinase inhibitor (TKI) directed against epidermal growth factor receptor (EGFR), further lengthens the survival of patients.

The MET signaling pathway, which plays a role in oncogenesis, has emerged as a promising target for therapeutic intervention in numerous cancers. Recent clinical evidence suggests that inhibition of the MET pathway has the potential to improve response and survival in patients with NSCLC who have high MET expression, as demonstrated by immunohistochemistry. Therefore, the concomitant inhibition of MET and EGFR signaling is an appealing therapeutic approach in NSCLC.

Cabozantinib is a small molecule oral TKI with activity against MET, vascular endothelial growth factor receptor (VEGFR), and RET. In November 2011, Exelixis, the developer of the drug, entered into a Cooperative Research and Development Agreement with the National Cancer Institute’s Cancer Therapy Evaluation Program, making it available for investigation by cooperative groups.

E1512 is a randomized, three-arm phase II trial investigating the clinical efficacy and safety of erlotinib alone, cabozantinib alone, or erlotinib plus cabozantinib as second- or third-line therapy in patients with EGFR wild-type NSCLC.

Joel Neal, MD, PhD, Stanford University/Stanford Cancer Institute, is Study Chair for E1512. Below, he discusses the trial and shares his perspectives on its relevance.

Why is this study important?

It is known that erlotinib is highly active against EGFR-mutant NSCLC, but its therapeutic effect in wild-type NSCLC is more modest as a single agent. E1512 will evaluate the therapeutic potential of the addition of cabozantinib, a combined MET and VEGFR inhibitor, to erlotinib in patients with wild-type EGFR NSCLC. Because MET pathway activation contributes to resistance to EGFR inhibition, we hypothesize that this combination may improve the efficacy of erlotinib in this patient population.

What are the patient characteristics for the study?

To be eligible for participation in E1512, patients must have stage IV NSCLC with predominant nonsquamous histology and previous EGFR mutation testing that does not demonstrate an EGFR TKI-sensitizing mutation. Patients must also have received one to two previous lines of chemotherapy and provide a fresh or archived tissue sample for MET immunohistochemistry analysis.
What is the clinical evidence for the use of cabozantinib in this setting and in combination with erlotinib?
In a small study in patients with NSCLC, cabozantinib alone caused partial tumor regression in about 10% of patients and stabilized disease in about 50% of patients, an efficacy finding that is similar to that of erlotinib alone. The safety and tolerability of the two drugs in combination were established in a phase I/II trial in patients with EGFR-mutant NSCLC.

How are the treatments administered?
All therapies are oral pills taken once per day. Study visits to monitor laboratory and clinical side effects take place every 2 weeks. Upon progression, patients are allowed to cross over from either of the single drug arms to the combination therapy arm. Patients will receive treatment and be followed for response using computed tomography scans. After patients discontinue study therapy, we will continue to follow them for survival.

What are the study objectives?
We are looking for an improvement in progression-free survival in patients treated with the combination arm, compared with that in each of the single drug arms. We are also evaluating overall survival, best objective response, and toxicities in each of the three treatment arms and conducting correlative science studies that will help to select predictive biomarkers of response to therapy, including MET expression and other tissue and plasma biomarkers.

What is your insight on the importance of specimen collection to future research, and why is it important for sites to be diligent about their submissions?
We are now recognizing that NSCLC is not one single disease entity, but rather a spectrum of diseases with a variety of genetic makeups. We require archival tissue for MET testing on all patients to look for an interaction between MET status, response to therapy, and survival. Furthermore, we plan to look for additional exploratory tissue and plasma biomarkers of response to therapy, which may provide insight into the mechanisms of response to erlotinib in EGFR wild-type NSCLC.

What do you think is the most important information to communicate to our member sites as they consider participation in this study?
When discussing this study with potential candidates, please mention the option to cross over at progression to the combination therapy arm, even if initial randomization was to one of the single drug arms. Also, note that erlotinib must be provided outside of the study by the treating physician as the “standard of care,” so I encourage starting the process for erlotinib authorization at the time of initial patient screening and not awaiting randomization. Thank you for considering participation in this study—our team is always available to help answer additional questions by email or phone.

Suresh S. Ramalingam, MD, Emory University and its Winship Cancer Institute, is Chair of the ECOG-ACRIN Thoracic Committee. Below, he describes the committee’s decision to pursue this particular study design and how the trial fits within the committee’s overall research directions.

Increasingly, the treatment of lung cancer is based on the molecular characteristics of an individual patient’s tumor. Patients with a wild-type EGFR represent nearly 80% of all cases of NSCLC. In this group of patients, erlotinib is associated with a modest survival benefit. E1512 is intended to improve the efficacy of erlotinib by the addition of cabozantinib, based on promising preclinical and early phase clinical data. This approach is an example of the Thoracic Committee’s strategy of developing new treatment approaches for each molecular subgroup of lung cancer.

Trial Leadership
This is the first study that Dr. Neal is chairing for ECOG-ACRIN, and he is leading the study under the mentorship of Heather Wakelee, MD, who is also affiliated with Stanford.

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