ITOG Investigators Identify Novel Mutations in Thyroid Cancers That Could Lead to New Therapies

Recent publications from the laboratories of three separate ITOG members have reported the presence of a new type of mutation in certain thyroid cancers that could lead to use of specific use of certain drugs targeting that genetic abnormality. Mutations in the gene ALK have previously been identified in certain lymphomas and types of lung cancer, and patients whose tumors harbor those mutations have often responded well to therapy with ALK inhibitors such as crizotinib. Generally, these mutations are rearrangements of DNA, bringing parts of two genes together to create an active new gene that can cause the malignancy. Now, ALK rearrangements have been found in a subset of tumors from patients with thyroid carcinoma that could lead to new treatment approaches for those patients, as reported by ITOG investigators at scientific meetings in 2013 and published online in the past several months.

A report focusing on the frequency of ALK mutations came from the laboratory of ITOG member Dr. Yuri Nikiforov (abstract available online at http://www.ncbi.nlm.nih.gov/pubmed/24613930). With his colleagues, Nikiforov performed very detailed DNA sequencing and genetic analysis of more than 300 thyroid cancers. A specific new rearrangement, called STRN-ALK was found in nearly 2% of papillary carcinomas, 9% of poorly differentiated carcinomas, and 4% of anaplastic carcinomas; none were identified in a small group of medullary carcinomas. Further laboratory experiments suggested that inhibitors of ALK, such as crizotinib, could block the growth of thyroid cancer cells containing this mutation.

A report describing a beneficial clinical outcome of ALK-directed therapy came from the laboratory of ITOG member Dr. Micheal Demeure (abstract available online at http://www.ncbi.nlm.nih.gov/pubmed/24633422). Demeure and his collaborators studied the tumor DNA from one individual patient who had a highly aggressive form of papillary carcinoma. After identifying another rearrangement, called EML4-ALK, in this patient's tumor, they initiated treatment of the patient's progressive metastatic disease with crizotinib. After six months, the patient's tumor growth remained halted, and thyroglobulin levels had declined.

These two studies build upon the earlier work of ITOG member Dr. Mingzhao Xing (abstract available online at http://www.ncbi.nlm.nih.gov/pubmed/21596819), who first reported rare ALK mutations involving single DNA sequence changes or point mutations in about 11% of anaplastic thyroid carcinomas.

As described in a recent commentary in the influential journal Cancer Discovery, taken together, "these results implicate ALK fusion genes as drivers of thyroid cancer that may be exploited therapeutically." ITOG researchers will be discussing how to translate these early observations into larger clinical studies at the annual meeting of the organization's members to be held later this month in Boston, MA.

Posted:
Apr 12, 2014

Update on ITOG's First Clinical Trial

ITOG's first clinical trial has reached 50% of patient accrual. This multi-institution clinical trial, led by Dr. Manisha H. Shah from Ohio State University,examines whether patients who had progression of their thyroid cancer on a VEGFR inhibitor benefit from treatment with Cabozantinib.

ITOG opened its first clinical trial one year ago for treatment of differentiated thyroid cancer. NCI9312/OSU12154/RU241210I is an investigator-initiated, multicenter, open label, phase II trial of Cabozantinib in patients with radioiodine-refractory, differentiated thyroid cancer (DTC), who progressed on first-line therapy with a VEGFR antagonist. ITOG's first clinical trial is coordinated by the Academic and Community Cancer Research United (ACCRU) and is funded by Cancer Therapy Evaluation Program (CTEP) of National Cancer Institute (NCI). Additional funding for the clinical trial and correlative science is provided by ITOG, which is a 501(c)(3) tax-exempt public charity. ITOG's mission is to catalyze a cure for thyroid cancer.

Led by Ohio State University Comprehensive Cancer Center, this study is open at Massachusetts General Hospital, Mayo Clinic (Jacksonville and Rochester), MD Anderson Cancer Center, Roswell Park Cancer Institute and University of Chicago.

Cabozantinib is an oral multikinase inhibitor targeting several angiogenic proteins such as VEGFR, PDGFR, c-met as well as RET kinase. It was recently approved by the Food and Drug Administration of United States for patients with progressive medullary thyroid cancer. ITOG is testing this drug for its use in a 2nd line setting for patients with DTC who progress on first line VEGFR targeted therapy. Given that c-met is thought to be critical in causing failure of VEGFR targeted therapy, cabozantinib is chosen for testing in 2nd line setting due to its unique activity against c-met. During the trial, the study drug will be administered orally once daily until cancer progression or intolerance. The study will also examine if this drug is effective against bony metastasis.

Eligible patients are required to have locally advanced or metastatic, radioiodine-refractory DTC, measurable disease, progression on exactly one line of prior VEGFR-targeted therapy (including but not limited to sorafenib, sunitinib, vandetanib, pazopanib, or lenvatinib) within 24 weeks prior to study entry. More information related to trial is available at http://clinicaltrials.gov/ct2/show/NCT01811212?term=cabozantinib+in+thyroid&rank=2

For questions related to trial please contact Manisha H. Shah, MD at 614-293-4680 or manisha.shah@osumc.edu

Posted:
Apr 2, 2014

Lenvatinib Extends PFS in Differentiated Thyroid Cancer

The phase III SELECT trial of the investigational agent lenvatinib (E7080) met its primary endpoint of progression-free survival (PFS) in patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC), according to Eisai Inc., the company that is developing the agent.

The trial compared lenvatinib to placebo and demonstrated a statistically significant improvement in PFS, which Eisai plans to submit for marketing authorization in the United States, Japan, and Europe, the company said in a statement. In a phase II study of Lenvatinib, a selective inhibitor of VEGFR 1-3, FGFR 1-4, PDGFR-β, KIT and RET, treatment with the drug resulted in an overall response rate (ORR) of 59% and a PFS of 12.6 months for patients with advanced RR-DTC.

"These results show the potential role of the investigational drug lenvatinib in this rare, hard-to-treat cancer," Kenichi Nomoto, PhD, President, Oncology Product Creation Unit, Eisai Product Creation Systems, said in a press release. "RR-DTC remains an unmet need with a limited number of treatment options."

The randomized, placebo-controlled phase III SELECT study compared the PFS of patients with RR-DTC and radiographic evidence of disease progression within the prior 12 months. The 392 patients enrolled in the trial were treated with once-daily oral lenvatinib (24mg) versus placebo. Secondary endpoints of the study included ORR, overall survival, and safety. The five most common adverse reactions were hypertension, diarrhea, decreased appetite, decreased weight, and nausea, according to preliminary safety analyses. The study took place at over 100 sites in Europe, North and South America, and Asia.

In a phase II study investigating lenvatinib in 58 patients with advanced RR-DTC whose disease had progressed during the prior 12 months, the starting dose of lenvatinib was 24 mg once daily in repeated 28 day cycles until disease progression or development of unmanageable toxicities. Toxicities were managed with dose reduction in 35% of patients and 23% were ultimately withdrawn from the study due to toxicity.

Investigator assessed partial responses were observed in 29 patients (50%). A majority of responses (65%) were identified on the first imaging after initiation of therapy, at approximately 8 weeks. In 17 patients who had received prior treatment with VEGFR inhibitors, the response rate was 41%. For the 41 patients without prior VEGFR-targeted treatment, the response rate was 54%. At an 8-month follow-up presented at the 2012 ASCO Annual meeting, the median PFS was 12.6 months.

In the study, the most frequent reported treatment-related adverse events in this study were: hypertension 74% (Grade 3: 10%), proteinuria 60% (Grade 3: 10%), decreased weight 57% (Grade 3: 7%), diarrhea 55% (Grade 3: 10%) and fatigue 53% (Grade 3: 7%).

Lenvatinib was grated Orphan Drug Designation in the United States in December 2012 for follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer. It is currently under investigation as a potential treatment for thyroid, hepatocellular, endometrial and other solid tumor types.

Thyroid cancer is the most common endocrine malignancy and global figures show that its incidence has increased significantly over the last 50 years. Rates for new thyroid cancer cases in the United States have been rising 6.4 percent each year over the past 10 years, with approximately 60,220 new cases last year. Differentiated thyroid cancer is the most common, accounting for approximately 90% of all thyroid cancers.

Christina Izzo

http://www.onclive.com/web-exclusives/Lenvatinib-Extends-PFS-in-Differen...

Posted:
Feb 3, 2014