New Investigational Targeted Therapeutic, Entrectinib, Shows Early Promise Against a Range of Cancer Types

NEW ORLEANS — The investigational anticancer therapeutic entrectinib, which targets the proteins TrkA/B/C, ROS1, and ALK, was safe, tolerable, and showed signs of clinical activity in patients who had several different types of cancer with NTRK1/2/3, ROS1, or ALK gene alterations and had not previously been treated with a Trk-, ROS1-, or ALK-directed targeted therapeutic, according to combined results from two phase I clinical trials presented here at the AACR Annual Meeting 2016, April 16-20.

“Alterations called fusions involving the NTRK1/2/3, ROS1, and ALK genes are detected in a variety of types of cancer,” said Alexander Drilon, MD, assistant attending physician of the Developmental Therapeutics Clinic and the Thoracic Oncology Service and principal investigator of STARTRK-1 and STARTRK-2 at Memorial Sloan Kettering Cancer Center in New York. “These fusions cause heightened activity of the TrkA/B/C, ROS1, and ALK proteins coded for by these genes, thus promoting cancer cell proliferation and survival.

“Our data show that entrectinib, a potent oral inhibitor of TrkA/B/C, ROS1, and ALK proteins, can achieve rapid and durable responses in patients with a range of advanced or metastatic solid tumors harboring NTRK1/2/3, ROS1, or ALK gene fusions,” continued Drilon. “A phase II clinical trial, called STARTRK-2, is ongoing to determine whether these early results can be confirmed in a much larger cohort of patients.”

In September 2015, initial results from the two phase I clinical trials, STARTRK-1 and ALKA-372-001, were reported, establishing 600 milligrams of entrectinib administered orally once daily as the recommended phase II dose. Data from these two trials also showed an objective response rate of 72 percent among the 18 patients who met criteria for what was defined as a phase II–eligible population: the presence of NTRK1/2/3, ROS1, or ALK gene fusions in their tumors, no prior treatment with a TrkA/B/C-, ROS1-, or ALK-directed targeted therapeutic, and treatment at or above the recommended phase II dose.

The researchers are now reporting updated data for additional patients in the two trials who met the phase II eligibility criteria, as well as updated safety data in additional patients. After a median follow-up of 11 months, 11 of the 13 patients who responded remain on the study, including one patient who had non–small cell lung cancer (NSCLC) with a ROS1 gene fusion who has had a complete response that has been maintained for more than two years.
The remainder of the 12 patients who responded to entrectinib had partial responses. These responses were seen for patients with a variety of types of cancer: NSCLC, colorectal cancer, and mammary analog secretory carcinoma of the salivary gland with NTRK1/2/3 gene fusions; NSCLC with ROS1 gene fusions; and NSCLC and colorectal cancer with ALK gene fusions.

Drilon explained that the researchers were particularly encouraged by the observation that one patient who had NSCLC with an NTRK1 gene fusion that had metastasized to the brain had an overall partial response but a complete response in the brain. “This was noteworthy because the brain is a relatively common site for NSCLC metastasis and other therapeutics may not be as effective against brain metastases,” he said.

“NTRK1/2/3 gene fusions can be rare within some types of cancer, but are common across many different cancers, and our preliminary data show that tumors with these genetic alterations can be exquisitely sensitive to entrectinib,” added Drilon. “We do need to validate these results in larger numbers of patients, but patients and their physicians should strongly consider comprehensive genetic profiling to determine whether these gene fusions are present in the patient’s tumors. If they are, there is a good chance that treatment with a Trk inhibitor like entrectinib will result in very meaningful benefit.”

This study was funded by Ignyta. Drilon has received travel and lodging reimbursements and honoraria from Ignyta, and has been part of a speakers bureau for Ignyta.

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Abstract: CT007

Presentation Session: Clinical Trials Plenary Session, Sunday, April 17, 4:15-6 p.m. CT, La Nouvelle Orleans Ballroom

Title: Entrectinib, an oral pan-Trk, ROS1, and ALK inhibitor in TKI-naïve patients with advanced solid tumors harboring gene rearrangements - updated phase I results

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Background: Entrectinib is a potent oral inhibitor of the tyrosine kinases TrkA, TrkB, TrkC (encoded by the genes NTRK1, NTRK2, NTRK3, respectively), ROS1, and ALK with IC\(_50\) < 2 nM (biochemical kinase assay). It has been evaluated in two Phase 1 studies (STARTRK-1 and ALKA-372-001) in patients with advanced or metastatic solid tumors harboring NTRK1/2/3, ROS1, or ALK molecular alterations, with or without asymptomatic or controlled CNS disease. Previously, we reported 600 mg daily as the Recommended Phase 2 Dose (RP2D) and an objective response rate of 72% in 18 tyrosine kinase inhibitor (TKI)-naïve patients with NTRK1/2/3 (4), ROS1 (8), or ALK (6) rearrangements treated at or above the RP2D (Siena et al, ESMO 2015).

Methods: A 3+3 dose escalation was used to assess safety, pharmacokinetics, and identify the RP2D of entrectinib. Here we provide an update on anti-tumor activity (RECIST v1.1) and safety with continued follow-up of the cohort of patients with gene rearrangements.

Results: At a median follow-up of 11 months, 11 of the 18 patients remain on study. Objective responses were observed in 3 of 4 (75%) NTRK1/2/3, 6 of 8 (75%; 1 complete response) ROS1 and 4 of 6 (67%) ALK patients, respectively. Responses were observed in NSCLC, colorectal cancer, mammary analog secretory carcinoma, and other solid tumors, as early as cycle 1 and lasting as long as > 2 years. Notably, a 46-year old male patient with SQSTM1-NTRK1-rearranged NSCLC previously treated with 4 lines of chemotherapy and immunotherapy achieved an overall partial response with a complete response in the brain. He remains on study in response at 10 months. The most common (>10%) treatment-related adverse events (AEs) at the RP2D were fatigue/asthenia (47%), dysgeusia (32%), constipation (26%), dizziness (21%), paresthesia (21%), diarrhea (16%), myalgia (16%), and weight gain (16%). Three treatment-related serious AEs were reported (2 occurred above the RP2D); all resolved with dose modifications.
Conclusions: Entrectinib continues to display promising anti-tumor activity in TKI-naive patients across different solid tumor types harboring an NTRK1/2/3, ROS1, or ALK gene rearrangement. Similar patients are now being enrolled in STARTRK-2, a global Phase 2 basket study of entrectinib.