Phase I Results of the Randomized, Placebo-Controlled, Phase II/I Study of the Novel Oral C-MET Inhibitor, Tivantinib (ARQ 197), Irinotecan (CPT-11), and Cetuximab in Patients With Wild-type KRAS Metastatic Colorectal Cancer Who Have Received Front-line Systemic Therapy

Alberto Bensouda,1 Johanna C. Eendel2, Natasha Y. Gabrilovich3, Michael V. Kopp4, Lothar Muller5, Lowell L. Hart6, Vladimir J. Vladimirov7, Amikumar U. Pande7, Igor Gorbatchevsky8, Cathy Eng9

1Pacific Oncology Hematology Associates, Encinitas, CA, 2Cancer Research Institute, Nashville, TN, 3Gabriel Cancer Center, Canton, OH, 4Salaries Regional Clinical Oncology Dispensary, Sandra, Russia, 5Onkologische Schwerpunktpraxis Leer-Emden, Leer, Germany, 6Florida Cancer Specialists, Fort Myers, FL, 7State Medical Institution Pytjgorsk, Pytjgorsk, Russia, 8Dalich Sankyo, Inc., Edison, NJ, 9University of Texas M. D. Anderson Cancer Center, Houston, TX

Abstract

BACKGROUND

Tivantinib (ARQ 197) is a selective, oral, non–adenosine triphosphate (ATP)-competitive, small-molecule kinase inhibitor of the c-MET receptor tyrosine kinase (RTK), which has been implicated in tumor progression and metastasis.1–3 In a randomized, placebo-controlled, dose-escalation trial (NCT00385213), dose-limiting toxicities (DLTs) were observed at doses ≥ 360 mg BID (twice daily).4,5 This study was designed to evaluate the safety and tolerability of tivantinib in combination with irinotecan (CPT-11) and cetuximab in patients with advanced KRAS wild-type metastatic colorectal cancer who had received prior chemotherapy.5

METHODS

This was a randomized, placebo-controlled, dose-escalation (Phase I) and randomized, double-blind, placebo-controlled, parallel-group, two-arm (Phase II/I) trial. Patients were randomized 2:1 to receive tivantinib 300 mg PO BID (n = 75) or placebo (n = 37) in the Phase I portion of the study.9

RESULTS—Phase I

Objective response rates in the tivantinib and placebo arms were 47% and 0%, respectively. The most common grade ≥ 3 toxicities were neutropenia (3/4: 0/1), fatigue (3/4: 2/0), and 1 case each of grade 3 leukopenia, acneiform rash, vomiting, diarrhea, anemia, and syncope. Preliminary efficacy data in 9 evaluable pts include 1 CR (after 4 cycles), 2 PR (after 2 cycles), 5 SD, and 1 PD (after 2 cycles). At 360 mg BID (n = 3), mean predicted Bayesian estimates were

RESULTS—Phase II (continued)

Figure 5: Hypothetical trial paradigm change from no therapy to target therapy to first line chemotherapy

CONCLUSIONS

The estimated incidence of the novel MET inhibitor tivantinib and combination MET inhibitor and CPT-11 was low. The combination regimen demonstrated no adverse effects in patients with previously untreated colorectal cancer. The study design included a preliminary phase 2 study to engage patients seeking first-line chemotherapy.

Reference


Figure 1: Plasma levels of soluble C-MET and VEGF in patient A (CR) and patient B (PD) during the first 28-day cycle, 360 mg BID would be defined as the RP2D

Figure 2: Antitumor activity of tivantinib in a human colon cancer xenograft model.

Figure 3: Tivantinib effect on stable cell lines and primary tumors.

Figure 4: Stable cell lines and primary tumors.

Figure 5: Hypothetical trial paradigm change from no therapy to target therapy to first line chemotherapy.