P034 Phase Ia/Ib dose-escalation study of ABL001 (CTX-009, bispecific antibody targeting DLL4 and VEGF-A) as a single agent in patients with advanced solid tumors.

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VEGF blockade is a validated therapeutic approach and anti-VEGF antibodies are established components of several standard regimens for various malignancies. However, the overall response rate to single agent VEGF blockers is extremely low and many patients develop resistance to regimens that include VEGF blockers. Hence, additional angiogenesis-targeted therapies are necessary to overcome the resistance to VEGF blockade and improve response rates. Delta-like ligand 4 (DLL4), a Notch pathway ligand, plays a key role in the overgrowth of dysfunctional microvasculature, and DLL4 is upregulated by VEGF. ABL001 (CTX-009) is a bispecific antibody targeting both DLL4 and VEGF-A with significant anti-tumor activity in preclinical studies. A phase 1, multicenter, open-label and first-in-human study was conducted to evaluate the safety and tolerability of ABL001 (CTX-009) in patients with advanced solid tumors. The dose escalation phase had 9 dose cohorts from 0.3 to 17.5 mg/kg (IV every 2 weeks), using a traditional 3+3 design. The study was expanded at dose levels of 7.5, 10, 12.5 and 15 mg/kg. Archived tumor tissue samples were collected to assess DLL4 expression levels using an immunohistochemistry (IHC) method. Key selection criteria included: age ≥19 years, metastatic or unresectable advanced solid tumors, ECOG ≤2, and adequate hematologic, hepatic and renal function. A total of 45 patients (31 patients in the dose escalation phase and 14 patients in the dose expansion phase) were enrolled in the study. The patients were heavily pretreated and received a median of 4 lines of prior therapies. 86.7% of the patients were ECOG 1. Gastric cancer (n=19) and colorectal cancer (n=18) were the most common tumors. No dose limiting toxicities (DLTs) were observed. The most common Treatment-Emergent Adverse Events (TEAEs) reported in ≥10% patients were hypertension (37.8%), headache (22.2%), anemia (13.3%), asthenia (13.3%) and fatigue (11.1%). Grade 3 or greater TEAEs reported in ≥5% patients were hypertension (15.6%) and anemia (6.7%). The most common Treatment Related Adverse Events (TRAEs) reported in ≥10% patients were hypertension (37.8%) and headache (15.6%). Of the 39 evaluable patients, there were 4 partial responses (PRs) and 3 of those responses were confirmed by RECIST. Responses began to appear at the 10 mg/kg dose level. The 3 confirmed partial responses included 2 colorectal cancer patients at 10 mg/kg and 1 gastric cancer patient at 12.5 mg/kg. All 3 patients with PRs exhibited high DLL4 expression by IHC on archived tumor tissue samples. The unconfirmed PR was in a patient with gastric cancer dosed at 15 mg/kg who was also DLL4 IHC positive. The recommended Phase 2 doses (RP2Ds) were determined to be 10 mg/kg and 12.5 mg/kg and the Overall Response Rate (ORR) at the RP2D was 18.8% (3/16) and the Disease Control Rate (DCR) was 62.5% (11/16). ABL001 (CTX-009) monotherapy is well tolerated and shows promising antitumor activity. Clinical trial information: NCT03292783