e16331 Publication Only

Identification of immune biomarkers in treatment-naive patients with metastatic pancreatic cancer treated with the GSK-3 inhibitor elraglusib (9-ING-41) in combination with gemcitabine/nab-paclitaxel in the 1801 phase 2 study.

Taylor Weiskittel, Austin Koukol, Caroline Kellinger, Leiqing Zhang, Benedito A. Carneiro, Hu Li, Andrey Ugolkov, Wafik S. El-Deiry, Andrew Paul Mazar; Mayo Clinic, Rochester, MN; Actuate Therapeutics, Inc., Fort Worth, TX; Brown University, Legorreta Cancer Center, Providence, RI; Legorreta Cancer Center at Brown University, Providence, RI; Mayo Clinic College of Medicine and Science, Rochester, MN; Brown University, Providence, RI

Background: Elraglusib (9-ING-41), a potent and selective GSK-3 inhibitor, is a targeted anticancer agent with clinical activity in phase 1 trial and undergoing clinical development for the treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC). Elraglusib (9-ING-41) displayed immune-modulatory activity in preclinical models and modulation of serum cytokine profile in clinical specimens. Here, we investigated the correlation between plasma levels of cytokines/chemokines/soluble cell receptors/growth factors (CCSG) and clinical outcomes of patients with mPDAC treated with elraglusib and gemcitabine/nab-paclitaxel (GnP) in an exploratory study. **Methods:** CCSGs were evaluated in the pre-dose plasma samples of patients with newly diagnosed mPDAC enrolled in the 1801 phase 2 study (NCT03678883) treated with GnP (n = 13) or elraglusib/GnP (n = 32). Using a Luminex immunoassay, 40 CCSGs were screened as predictive biomarkers of median overall survival (mOS) in the elraglusib/GnP arm using 5-fold cross-validation and maximally selected rank statistic cutpoint determination. A subset of CCSGs (n = 10) was remeasured using an MSD immunoassay with greater sensitivity. Maximally selected rank statistic cutpoint determinations were conducted using MSD results for elraglusib/GnP samples with mOS and median progression free survival (mPFS). P values < 0.05 were considered statistically significant. **Results:** Luminex screening revealed several CCSGs significantly stratified elraglusib/GnP patients by mOS. IL-6 and IL-8 were identified as top candidates with stable and significant results on cross-validation. Using the MSD assay, both were confirmed to stratify elraglusib/GnP patients by OS and extended to analyze PFS. Low level of IL-8 conferred a better OS prognosis (HR: 0.0919, 95%, CI: 0.0205-0.411, $P < 0.001$) than low IL-6 (HR: 0.205, 95%, CI: 0.063-0.665, P = 0.005) in the elraglusib/GnP treated patients. Correlations with mPFS were similar in the elraglusib/GnP patients for IL-6 (HR: 0.248, 95% CI: 0.072-0.848, P = 0.02) and IL-8 (HR: 0.297, 95%, CI: 0.111-0.743, P = 0.01). **Conclusions:** Preliminary results of our exploratory study identified low plasma levels of IL-6 and IL-8 prior to elraglusib/GnP treatment as potential predictive biomarkers associated with improved outcomes in previously untreated patients with mPDAC. The 1801 Part 3 Arm B clinical trial recruitment has been completed. We plan to analyze additional pre-dose plasma samples obtained from approximately 200 patients by April 2024. These will be analyzed using interim OS data available by April 2024 and included in the final presentation. Clinical trial information: NCT03678883. Research Sponsor: None.