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Phase 2 study of elraglusib (9-ING-41), a glycogen synthase kinase-3b inhibitor, in combination with gemcitabine plus nab-paclitaxel (GnP) in patients with previously untreated advanced pancreatic ductal adenocarcinoma (PDAC).

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Background: Despite the increasing incidence and low survival rates in PDAC, treatment options remain somewhat limited. Glycogen synthase kinase-3 (GSK-3) has been known to regulate tumor cell survival and proliferation, suppress apoptosis, and counteract chemotherapy resistance through activation of NF-kB-dependent gene transcription. Elraglusib (9-ING-41), a potent small molecule inhibitor of GSK-3β, has demonstrated inhibition of tumor growth and regression of tumors in patient-derived PDAC xenograft models in combination with gemcitabine (G). This provides the rationale for evaluating the efficacy and safety of elraglusib in combination with GnP in advanced PDAC. **Methods:** In an open-label, non-randomized, phase 2 study (NCT03678883), pts with previously untreated advanced PDAC received elraglusib 15 mg/kg IV on Days 1 and 4 of each week and nab-paclitaxel (nP) 125 mg/m^2 plus G 1000 mg/m^2 on Days 1, 8, and 15 in a 28-day cycle. Based on the Simon's 2-stage design, if $>$ 50% of the first 23 efficacy evaluable (EE) pts achieved a disease control rate (DCR) $\geq$16 weeks in Stage 1, an additional 37 pts would be enrolled during Stage 2. The primary endpoint was DCR, defined as stable disease for $\geq$16 weeks, confirmed complete response, or confirmed partial response. Secondary endpoints consisted of objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and treatment-emergent adverse events (TEAEs). **Results:** 42 pts (ITT) with ECOG 0 to 2 were enrolled in the study (38 received elraglusib at 15 mg/kg and 4 at 9.3 mg/kg); 29 pts with complete first post-baseline tumor assessment comprised the EE population. The median duration of treatment (as of February 4, 2023, cutoff) in the EE was 5.5 months. The DCR was 51.7% (95% CI, 32.5 to 70.6), and the ORR was 37.9% (95% CI, 20.7 to 57.7). Given that Stage 1 criterium of Simon's 2-stage design was met, the study proceeded to Stage 2. The median PFS and OS were 4.9 months (95% CI, 4.1 to 7.5) and 15.8 months (95% CI, 7.9 to not estimable), respectively, in the EE and 4.9 months (95% CI, 4.1 to 7.5) and 13.7 months (95% CI, 7.9 to 18.1) in the ITT. Grade $\geq$3 TEAEs occurred in 85.7% of pts in the ITT population. Two pts (4.8%) developed grade $\geq$3 reversible visible disturbances related to elraglusib and 8 pts (19%) developed grade $\geq$3 TEAEs (most common being febrile neutropenia and anemia) related to the combination of elraglusib with GnP. All of these were observed at the highest dose of elraglusib (15 mg/kg). **Conclusions:** Elraglusib in combination with GnP demonstrates early evidence of clinical activity against advanced PDAC and an acceptable safety profile. The study has advanced to randomized phase 2 in pts with metastatic PDAC evaluating the 9.3 mg/kg dose of elraglusib plus GnP compared to GnP alone. Clinical trial information: NCT03678883. Research Sponsor: Actuate Therapeutics.