Phase 2 study of 9-ING-41, a small molecule selective glycogen synthase kinase-3 beta (GSK-3β) inhibitor, with gemcitabine/nab-paclitaxel (GnP) in first-line advanced pancreatic ductal adenocarcinoma (PDAC).

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Background: GSK-3β overexpression is associated with worse prognosis and chemotherapy resistance in PDAC. GSK-3β inhibition reverses chemotherapy-resistance by inhibiting chemotherapy-induced, ATR-mediated, DNA damage response. 9-ING-41 has significant anti-tumor activity through apoptosis induction, anti-fibrotic activity and NK/T-cell effector stimulation. We hypothesized that 9-ING-41 in combination with GnP chemotherapy would lead to anti-tumor activity, with improved tumor responses in patients with advanced PDAC in the first line setting. **Methods:** Primary endpoint is disease control rate (DCR). DCR = confirmed complete response (CR), partial response (PR), or stable disease (SD) $\geq$ 16 weeks (wks). Secondary endpoints are safety and ORR (overall response rates). Eligibility: Advanced PDAC, ECOG PS 0-2, no prior therapy in the metastatic setting and no systemic therapy in prior 6 months. Pts received 9-ING-41 15mg/kg IV twice-weekly with G 1,000 mg/m^2 and nP 125 mg/m^2 on days 1,8,15 of a 28-day cycle. Simon 2-Stage Design for DCR of 65% and null hypothesis of 50% (historical control), 80% power and 2 sided-significance level of.05. Up to 23 fully evaluable pts planned for stage 1 and if $\geq$ 12 evaluable patients achieve a DCR 37 additional pts will be enrolled on a second stage or a randomized study commenced. **Results:** As of Sept 27, 2021, 42 pts enrolled. Median age: 67. 24 females, 18 males. 38 pts with metastatic and 4 with locally advanced disease. Prior adjuvant therapy: 4 pts each FOLFIRINOX and gemcitabine-based. No 9-ING-41-attributable SAEs to date. 9-ING-41 attributed AEs: visual disturbance: 24 (75%) G1/2, 1 (3%) G3; infusion reactions 9 (28%) G1/2. Chemotherapy-related AEs: anemia 13 (40%) G1/2, 1 (3%) G3; neutropenia 2 (6%) G1/2, 13 (40%) G3/4; thrombocytopenia 9 (28%) G1/2, 2 (6%) G3/4; diarrhea 8 (25%) G1/2, 4 (13%) G3; fatigue 9 (28%) G1/2, 3 (9%) G3; nausea/vomiting 24 (75%) G1/2, 1 (3%) G3; constipation 9 (28%) G1/2; febrile neutropenia 5 (16%) G3/4. In 21 pts currently evaluable for response, DCR was 62% and ORR 43%. There were 2 confirmed CRs, 6 confirmed and 1 unconfirmed PRs, 4 SD and 8 disease progressions were observed. Amongst responder's median duration of response has not yet been reached. **Conclusions:** 9-ING-41 plus GnP demonstrated encouraging clinical activity but chemotherapy-related AEs were significant. Based on efficacy data to date, including confirmed CRs, we have commenced a randomized phase 2 study, evaluating 9-ING-41 plus GnP vs Gn P alone. Enrollment to the randomized study is now open (NCT03678883). Clinical trial information: NCT03678883. Research Sponsor: Arcuate.