A PHASE 1/2 STUDY OF RX-3117, AN ORAL ANTIMETABOLITE NUCLEOSIDE, IN COMBINATION WITH NAB-PACLITAXEL (NAB-PAC) AS FIRST LINE TREATMENT OF METASTATIC PANCREATIC CANCER (MET-PC):

Background:
RX-3117 is an oral small molecule antimetabolite, cyclopentyl pyrimidyl nucleoside that is activated by cellular enzymes to inhibit pyrimidine kinase 2. Single agent RX-3117 has shown antitumor activity in non-small cell lung cancer (NCT01894090) and a phase 1 trial of RX-3117 in combination with nab-paclitaxel is being evaluated as first line treatment of metastatic PC.

Methods:
This is a randomized, open label phase 1/2 study (NCT03189914). Eligible subjects aged 18 years have histologically or radiologically proven PC with no prior therapies for metastatic disease. EOGO P1 v1.1, and trial specific criteria. Phase 1 defined the ND3 dose that is further being evaluated in the Phase 2. Phase 1 (ND3) 390 mg administered oral once daily for 5 consecutive days of therapy (1 dose per week) and repeats every 4 weeks for 3 weeks with 1 week off per 4-week cycle. The Safety Committee reviewed data from Phase 1 before moving to Phase 2. The primary endpoint of Phase 2 phase 2 response rate was approximately 10%.

Results:
As of September 21, 2018, 8 Phase 1 subjects and 13 Phase 2 subjects were enrolled and treated 8 males and 12 females, with a median age of 67 years. The most common (≥10%) reported TEAEs during Phase 1 and Phase 2 were nausea (91%), fatigue (71%), vomiting (11%), and pyrexia (14%). In Phase 2, 10 subjects discontinued prior to the first on-study scan, 5 subjects are currently on treatment but have not completed the first on-study imaging assessment. Note: Six subjects discontinued prior to the first on-study scan, 5 subjects are currently on treatment but have not completed the first on-study imaging assessment.

• Complete Response (CR)
• Partial Response (PR)
• Progressive Disease (PD)
• Stable Disease (SD)
• Discontinued
• All grades

• As of 09 January 2019, in the response evaluable population (24 subjects) of the Phase 1 and Phase 2: Overall response rate was 38%.
• 1 CR observed after 6 cycles of therapy and confirmed after 8 cycles.
• 6 PRs were observed: 4 after 2 cycles of therapy and 4 after 4 cycles of therapy.
• Disease control rate (CR+PR+SD) was 92% at 8 weeks (1 Complete Response 8 Partial Response 13 Stable Disease).

• Most Treatment Emergent Adverse Events (TEAEs) considered related to RX-3117, nab-Pac, or the combination were neutropenia (20%), anemia (11%), diarrhea (6%), leukopenia (5%), hypokalemia (5%), and acute kidney injury, dehydration, general weakness, hypomagnesemia, mouth sores, nausea, neutropenic fever, peripheral sensory neuropathy, platelet count decreased, protein-creatinine malformation, vomiting (1%).
• Most subjects (63%) with CA 19-9 results exhibited reductions after 1 cycle of therapy (10% to ~75%). One subject experienced a 46% increase but had a partial response after 4 cycles.

Conclusions:
The combination of RX-3117 and nab-Pac appears safe and well-tolerated when administered at the recommended Phase 2 dose. Early responses were detected with an overall response rate of 38% in 24 subjects. The disease control rate of 92% at 8 weeks was of note. Pharmacodynamic results indicate that RX-3117 and nab-Pac do not appear to interfere with the exposure or clearance of either drug.

The study continues to enroll subjects with metastatic pancreatic cancer in Stage 2.

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