P – 043 Global ph 3, randomized, double-blind, placebo-controlled study of PEGylated recombinant human hyaluronidase PH20 (PEGPH20) + nab-paclitaxel & gemcitabine in pts with previously untreated, hyaluronan-high, stage iv pancreatic ductal adenocarcinoma

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Introduction: Poor outcome in pancreatic ductal adenocarcinoma (PDA) is associated partly with stromal hyaluronan (HA) accumulation, which may compromise chemotherapy access to tumors. In animal models, PEGPH20 degrades HA in tumors. Key endpoint data from a Phase 2 study showed that PEGPH20 plus chemotherapy improved efficacy over chemotherapy alone in tumors retrospectively identified to accumulate HA ("HA-High"). The objectives of this Phase 3 study are to compare efficacy and safety of standard-dose nab-paclitaxel (NAB) and gemcitabine (GEM) combined with either PEGPH20 or placebo in patients with HA-High, previously untreated, Stage IV PDA. Primary endpoints are progression-free survival (PFS) and overall survival (OS). Secondary endpoints are objective response rate, duration of response, and safety.

Methods: 420 patients $\geq$18 years with untreated HA-High metastatic PDA, ECOG PS 0-1 will be randomized (stratified by geographic region: North America/Europe/Other) 2:1 to NAB 125 mg/m2 + GEM 1000 mg/m2 + PEGPH20 3.0 μg/kg or to NAB + GEM + placebo, respectively. Patients with HA-High tumors will be prospectively identified by the co-developed VENTANA HA RxDx Assay, which identifies HA in the extracellular matrix. HA-High status (indicating patients who may achieve clinical benefit) was determined by Halozyme to be $\geq$ 50% HA staining based on clinical outcome data from a Phase 2 study. Treatment will be provided in 4-week cycles (Wk 1-3, Wk 4 rest) until disease progression, unacceptable toxicity, death, or consent withdrawal. PEGPH20 or placebo will be given twice weekly (Cycle 1) then weekly (Cycles 2+), NAB + GEM once weekly for all cycles. Dexamethasone will be given before and after PEGPH20 administrations to reduce treatment-related musculoskeletal symptoms and enoxaparin will be given to minimize thromboembolic events. Tumor response will be assessed by an independent central imaging vendor using RECIST v1.1. Adverse events will be graded per NCI CTCAE v4.03. An independent Data Monitoring Committee will evaluate safety and efficacy (PFS and OS) data. Trial initiated Q12016 (EudraCT 2015-004068-13; NCT02715804).

Results:

Conclusion: