789TiP HALO 109-301: Phase III, randomized, double-blind, placebo-controlled study of pegvorhyaluronidase alfa (PEGPH20) + nab-paclitaxel/gemcitabine (AG) in patients with previously untreated hyaluronan (HA)-high stage IV pancreatic ductal adenocarcinoma (PDA)

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Background: Poor outcome in PDA is associated with high stromal HA content (HA-high). In vitro, PEGPH20 degrades tumor HA and may increase access and efficacy of tumor therapies. In a Phase 2 study, PEGPH20 + standarddose nabpaclitaxel/gemcitabine (PAG) improved PFS over chemotherapy alone (AG) in tumors retrospectively identified as HA-high. In this Phase 3 study, we investigate the efficacy and safety of PAG vs AG in patients with HA-high, previously untreated, Stage IV PDA. There are 2 primary endpoints: PFS and OS. Secondary endpoints are objective response rate, duration of response, and safety.

Trial design: Patients $\geq$18 years with untreated HA-high, Stage IV PDA and ECOG PS 0–1 are eligible. Exclusion criteria include a history of thromboembolic events (TEs) or cerebrovascular accident. Patients ($N \leq 570$) are randomized 2:1 to PAG (PEGPH20=3.0 μg/kg + A = 125 mg/m^2 + G = 1000 mg/m^2) or AG (A = 125 mg/m^2 + G = 1000 mg/m^2) and stratified by region (North America/Europe/Other). HA-high status is prospectively determined by the RxDx Assay and scoring methodology codeveloped by Ventana Medical Systems, Inc., and Halozyme Therapeutics, Inc. The assay identifies HA in the extracellular matrix, with PDA defined as HA-high when the HA score is $\geq$ 50% based on HA staining. Treatment is provided in 4-week cycles (3 weeks on treatment, 1 week off) until disease progression, unacceptable toxicity, death, or consent withdrawal. PEGPH20 or placebo are dosed twice-weekly (Cycle 1) then weekly ($\geq$Cycle 2); AG is dosed weekly (all cycles). Dexamethasone is used before and after PEGPH20 to reduce PEGPH20-related musculoskeletal symptoms, and enoxaparin prophylaxis is administered subcutaneously once daily at 1 mg/kg to minimize TEs. Tumor response is independently assessed per RECIST v1.1. Adverse events are graded per NCI CTCAE v4.03. An independent data monitoring committee is overseeing the safety data. The trial was initiated in 2016, is open at $>$ 200 study sites across $>$20 countries, and is expected to complete by 2020.

Clinical trial identification: EudraCT 2015-004068-13; NCT02715804.

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