Multiple randomized phase 2 studies of PEGPH20 in patients with untreated mPDA

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Welcome to Partners in Pancreatic Cancer. My name is Dr. Andrea Bullock. Today I will be providing highlights from three abstracts presented this year at the 2017 ESMO Congress held in Madrid, Spain.

First, I am going to discuss tumor hyaluronan (HA), a novel biomarker: Results of the randomized phase II HALO-202 study of PEGPH20 plus nab-paclitaxel and gemcitabine versus nab-paclitaxel and gemcitabine alone in previously untreated metastatic pancreatic ductal adenocarcinoma. Pancreatic cancer has been refractory to many therapies, and much of this has been attributed to the dense desmoplastic stroma that surrounds pancreatic cancers and serves as a barrier to drug delivery. Previous studies have shown that hyaluronan accumulation in the pancreatic cancer microenvironment is associated with reduced survival. Hyaluronan, or what is often referred to as HA, is one of the main components of the peritumoral stroma. It is a polysaccharide that binds water avidly, compressing tumor vasculature. This, in turn, impedes access of antineoplastic agents as well as antibodies and immune cells to the tumor. PEGPH20 is a pegylated recombinant human hyaluronidase that degrades HA and thereby remolds the peritumoral stroma. The HALO-202 study was a multicenter randomized phase II trial of patients with pancreatic ductal adenocarcinoma metastatic to the liver and/or lung treated in the first line; 279 subjects were randomized to receive either standard of care nab-paclitaxel and gemcitabine (what is referred to as AG) or nab-paclitaxel and gemcitabine plus PEGPH20 (referred to as PAG). The primary endpoints for this study included progression-free survival (PFS) and thromboembolic event rate. Secondary endpoints included PFS by intratumoral HA level, overall response rate, and overall survival. Exploratory endpoints included overall survival by HA level, duration of response, and disease control rate.

The study was conducted in two stages, separated by a temporary clinical hold. During the first stage, 146 subjects were enrolled and randomized to receive AG with or without PEGPH20. Tissue collected from this population was used as a training set to develop a diagnostic HA assay. Efficacy results for this population demonstrated prolongation in PFS and increased overall response rate for subjects with HA-high
tumors treated with AG plus PEGPH20. In stage 2, an additional 133 subjects were enrolled, and tissue collected was used to validate the predetermined HA threshold for clinical benefit. Due to an imbalance in the rate of thromboembolic events identified during stage 1, the protocol was amended in stage 2 to add enoxaparin prophylaxis and to exclude patients at high risk for embolic events. The HA diagnostic assay was developed as an affinity histochemistry assay with a scoring algorithm based on the area of HA staining at any intensity in the extracellular matrix over the entire tumor surface. The HALO-202 study enrolled all-comers regardless of HA level, with the plan to measure HA in tumor tissue retrospectively. The strongest correlation between HA expression and clinical outcome was at 50%. The assay was developed during stage 1 of the trial and validated during stage 2. Abstract 743 provides results from stage 2 of this trial; 133 subjects were enrolled during stage 2, and 125 were treated. Baseline characteristics for subjects enrolled during stage 2 were evenly distributed between the PAG and AG treatment groups, including the all-comer enrolled patients and the subpopulation, later determined to be HA-high. Among those with HA-high tumors, there was an improvement in median PFS and OS for subjects treated with PAG as opposed to AG. Specifically, median progression free-survival was 8.6 months in the PAG arm and 4.5 months in the AG arm, with a hazard ratio of 0.63. This trend, however, did not reach statistical significance owing to the small number of events. Among those with HA-low tumors, PFS was similar across the two arms. Overall survival by HA status was an exploratory endpoint. Among subjects with HA-high tumors treated with PAG, there was an encouraging trend toward improvement with median OS of 11.7 months in the PAG arm and 7.8 months in the AG arm. The hazard ratio was 0.52 favoring PAG, although this difference did not reach statistical significance. Among those with HA-low tumors, median overall survival in the PAG arm was 11.9 months and in the AG arm 10.2 months. Among the AG-treated patients, those with HA-high tumors had shorter progression-free and overall survival outcomes, suggesting that HA may also serve as a prognostic biomarker. Subjects with HA-high tumors derived greater benefit from the addition of PEGPH20 to AG as evidenced by prolongation in progression-free and overall survival in this population, supporting HA as a predictive biomarker for PEGPH20 activity.

Next, we are going to discuss musculoskeletal events with PEGPH20 treatment and management in patients with previously untreated metastatic pancreatic ductal adenocarcinoma. PEGPH20 is pegylated recombinant human hyaluronidase, an engineered enzyme that degrades hyaluronan. Musculoskeletal events (termed MSEs) are unique toxicities associated with this agent. These include muscle spasm, arthralgia, and myalgia. Abstract 749 characterizes the incidence, frequency, and severity of MSEs; and the treatments instituted to address them in the phase II study of PEGPH20 plus gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel alone in patients with
previously untreated metastatic pancreatic cancer. During this study, dexamethasone 8 mg was administered orally within two hours before and 8 to 12 hours after PEGPH20 in the PAG arm. It was also administered before and after gemcitabine/nab-paclitaxel in the AG arm to lessen the severity of MSEs; 279 subjects were enrolled in the HALO-202 study, and 260 comprised the safety population. The proportion of patients with treatment-emergent MSEs was greater in the PAG arm as compared to the AG arm; 86% in the PAG arm developed MSEs, compared to 46% of those treated with AG. The incidence of grade 3 events was also higher in the PAG arm, 19% compared to 6% in the AG arm. There were no grade 4 or 5 MSEs. The most common MSEs were muscle spasm, occurring in 58% of those treated with PAG versus 6% of those with AG; followed by arthralgia seen in 28%, and myalgia in 27% of those treated with PAG. The majority of these events were grade 1 and 2 and were more often observed in cycle 1 than in subsequent cycles. The median time to onset of MSE was eight days for those on the PAG arm, with a range of 0 to 287 days. The median duration of grade 3 events was nine days on the PAG arm. Five subjects experienced MSEs that led to PAG discontinuation, four with muscle spasm and one with myalgia. MSEs were managed with muscle relaxants, anti-inflammatory agents (including NSAIDs and corticosteroids), and opioids. Grade 1 muscle spasms resolved without intervention. MSEs were common toxicities in this trial. They were primarily low grade 1 and 2 events, and infrequently led to treatment discontinuation. The majority of grade 3 events were effectively managed with medical interventions.

Now we are going to discuss the randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine in patients with untreated metastatic pancreatic ductal adenocarcinoma. As previously discussed, the HALO-202 study was a multicenter randomized phase II trial of patients with untreated metastatic pancreatic ductal adenocarcinoma randomized to receive either standard of care nab-paclitaxel/gemcitabine (referred to as AG) or nab-paclitaxel/gemcitabine plus PEGPH20 (referred to as PAG). The primary endpoints for this study included progression-free survival and thromboembolic event rate. Secondary endpoints included PFS by intratumoral HA level, overall response rate, and overall survival. Exploratory endpoints included overall survival by HA level, duration of response, and disease control rate. Abstract 763 provides results from the completed phase II trial, including subjects randomized during both stages 1 and 2; 279 subjects were randomized, and 231 were included in the efficacy analysis. Patient demographics and baseline characteristics were evenly distributed between the two arms. Among 246 subjects who had tissue available for retrospective HA testing, 34% were deemed HA-high utilizing the novel immunohistochemistry assay developed during the course of this trial. The primary endpoint was PFS in the all-comer population. There was a statistically significant prolongation in median progression-free survival for those treated with PAG compared
to AG; 6.0 versus 5.3 months, with a hazard ratio of 0.73 and a \( P \) value of 0.048. Thromboembolic event rate was also a primary endpoint. The incidence of VTE was similar across the two arms after initiation of enoxaparin prophylaxis, occurring in 14% of those on the PAG arm and 10% of those treated with AG. PFS by HA status was a secondary endpoint. Among subjects with HA-high tumors, median PFS was 9.2 months for those treated with PAG compared to 5.2 months for those treated with AG, with a hazard ratio of 0.51. Overall response was greater in the HA-high patients treated with PAG, 46% compared to 34% in those treated with AG. Overall survival by HA status was an exploratory endpoint. There was a nonsignificant trend toward improved survival among subjects with HA-high tumors treated with PAG, 11.5 months compared to 8.5 months among those treated with AG. Among those with HA-low tumors, PFS and OS were similar across the two arms. This trial is notable as it represents the first clinical study of a molecularly targeted drug in pancreatic cancer that validates a tumor microenvironment biomarker for patient selection. Efficacy data support the predictive value of HA given positive trends in both PFS and OS seen in the HA-high PAG-treated patients, and support the phase III trial of this combination currently underway in patients with HA-high metastatic pancreatic cancer.

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