A RANDOMIZED PHASE 3 STUDY COMPARING FIRST-LINE DOCETAXEL/PREDNISONE (DP) TO DP PLUS CUSTIRSEN IN MEN WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

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Aim: Clusterin is a pro-survival chaperone protein upregulated in response to apoptotic stressors such as chemotherapy. Custirsen (C) is a second-generation antisense oligonucleotide that inhibits production of human clusterin. This randomized, open-label, multicenter, international phase 3 study (SYNERGY; ClinicalTrials.gov #NCT01188187) sought to determine if addition of C to standard first-line chemotherapy with docetaxel (D) and prednisone (P) prolongs overall survival (OS) versus DP alone.

Methods: Patients (pts) with chemotherapy-naive mCRPC were randomized 1:1 to D (75 mg/m2 IV D1 q21d) + P (5 mg PO bid) ± C (640 mg IV weekly after loading dose period) for up to 10 cycles or until disease progression/unsustainable toxicity/withdrawal. Randomization was stratified by opioid use and radiographic evidence of progression. The primary endpoint was OS and the secondary endpoint was proportion of pts alive without disease progression on day 140. Survival data were compared using a stratified log-rank test.

Results: 1022 pts were randomized from Dec 2010 to Nov 2012 (DPC, n = 510; DP, n = 512). Median (range) number of cycles received was 8 (1-32) for DPC and 9 (1-20) for DP. Following a target 509 events, median OS was 23.4 months with DPC and 22.2 months with DP (HR for death 0.93, 95% CI 0.78-1.11; log-rank 1-sided P = 0.21). Incidence of any subsequent therapy was 75 and 76% for DPC and DP (53 vs 54% abiraterone, 19 vs 20% enzalutamide; 17 vs 18% cabazitaxel). More pts in the DPC arm discontinued due to an adverse event (AE) (41 vs 29%). Most common grade ≥3 AEs for DPC vs DP included fatigue (11 vs 8%), febrile neutropenia (11 vs 7%), asthenia (7 vs 3%), diarrhea (6 vs 3%), pulmonary embolism (5 vs 4%), and pneumonia (4 vs 2%). grade ≥3 hematologic laboratory toxicities were neutropenia (43 vs 29%), lymphopenia (37 vs 24%), and anemia (13 vs 5%).

Conclusions: Addition of custirsen to first-line DP did not significantly improve OS in pts with mCRPC and was associated with some increased toxicity. The majority of patients received subsequent life-prolonging therapy. Data on disease progression, response, and serum clusterin will be presented.

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