Final overall survival (OS) with talazoparib plus enzalutamide as first-line treatment in patients with homologous recombination repair (HRR)-deficient metastatic castration-resistant prostate cancer (mCRPC) in the Phase 3 TALAPRO-2 trial

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Background: Approximately one-quarter of advanced prostate cancers have alterations in DNA damage response genes directly or indirectly involved with HRR, sensitizing them to treatment with poly(ADP-ribose) polymerase inhibitors. The Phase 3 TALAPRO-2 trial met its primary endpoint, showing improved radiographic progression-free survival (rPFS) for talazoparib plus enzalutamide vs

placebo plus enzalutamide as first-line treatment in patients with mCRPC in the HRR-deficient cohort (cohort 2). At the first interim analysis, immature OS data favored talazoparib plus enzalutamide vs placebo plus enzalutamide. Here we report final OS, a descriptive update of rPFS, and extended safety follow-up in cohort 2.

Methods: Patients with HRR-deficient tumors were randomized 1:1 to enzalutamide 160 mg plus either talazoparib 0.5 mg (0.35 mg if moderate renal impairment) or placebo once daily and stratified by prior abiraterone or docetaxel (yes/no) for castration-sensitive PC. Key eligibility criteria included asymptomatic or mildly symptomatic mCRPC, ECOG PS ≤1, ongoing androgen deprivation therapy, and no prior life-prolonging therapy for CRPC. The primary endpoint was rPFS by blinded independent central review. OS was an alpha-protected key secondary endpoint. To achieve statistical significance at the final OS analysis, the stratified log-rank 2-sided *P* value needed to be ≤0.024 using a group sequential design with O'Brien-Fleming spending function.

Results: Overall, 399 patients were randomized (N=200, talazoparib plus enzalutamide; N=199, placebo plus enzalutamide). At data cutoff (Sept 3, 2024), 93 patients (46%) in the talazoparib plus enzalutamide arm and 126 patients (63%) in the placebo plus enzalutamide arm had died; median follow-up was 44.2 and 44.4 months, respectively. Hazard ratio (HR) for OS with talazoparib plus enzalutamide vs placebo plus enzalutamide was 0.622 (95% CI, 0.475–0.814; 2-sided *P*=0.0005); median OS (95% CI), 45.1 months (35.4–not reached) vs 31.1 months (27.3–35.4 months), respectively. In exploratory analyses, OS favored talazoparib plus enzalutamide vs placebo plus enzalutamide in patients with *BRCA1/2* alterations (n=155; HR, 0.497; 95% CI, 0.318–0.776; *P*=0.0017) and patients without *BRCA1/2* alterations (n=244; HR, 0.727; 95% CI, 0.516–1.024; *P*=0.0665). Updated rPFS data were consistent with the primary analysis, favoring the talazoparib plus enzalutamide vs placebo plus enzalutamide arm (HR, 0.468; 95% CI, 0.359–0.612; *P*<0.0001); median rPFS, 30.7 vs 12.3 months, respectively. Consistent with primary results, the most common grade 3–4 TEAEs with talazoparib plus enzalutamide were anemia (43%) and neutropenia (20%). TEAEs were generally manageable; 26 patients (13%) discontinued talazoparib due to TEAEs.

Conclusions: Talazoparib plus enzalutamide demonstrated a statistically significant and clinically meaningful improvement in OS vs enzalutamide. These data establish talazoparib plus enzalutamide as a standard of care for first-line treatment in patients with HRR-deficient mCRPC. rPFS continued to favor talazoparib plus enzalutamide. Safety was consistent with previous reports; no new safety signals were identified.

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