TALAPRO-2 Gene by Gene abstract
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Exploratory analyses of homologous recombination repair alterations (HRRm) by gene subgroup and potential associations with efficacy in the HRR-deficient population from TALAPRO-2

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Background: In TALAPRO-2, talazoparib plus enzalutamide significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) vs enzalutamide plus placebo in patients with metastatic castration-resistant prostate cancer harboring HRRm assessed prospectively. We report exploratory biomarker analyses assessing efficacy by HRR gene subgroups in patients enrolled in the HRR-deficient cohort from TALAPRO-2.

Methods: Patients were randomized 1:1 to talazoparib 0.5 mg (N=200) or placebo (N=199) plus enzalutamide 160 mg QD. HRRm testing used a 12-gene HRR panel (HRR12; clinical trial assays based on FoundationOne®CDx/FoundationOne®Liquid CDx). HRRm status categorization by gene incorporated all available tumor and prescreening/screening ctDNA records using an algorithm similar to others (Fallah et al, *JCO* 2024 PMID: 38484203). For non-*BRCA* and *BRCA1* gene analyses, patients with co-occurring *BRCA1/2* and *BRCA2* alterations, respectively, were excluded. The efficacy endpoints assessed were objective response rate (ORR), rPFS, and OS. Data cutoff September 3, 2024.

Results: In HRRm patients, talazoparib plus enzalutamide was superior to enzalutamide plus placebo across all efficacy endpoints: ORR, 69.4% vs 39.1% (odds ratio [OR], 3.55 [95% CI, 1.65–7.68]); rPFS, median 30.7 vs 12.3 months (hazard ratio [HR]=0.47 [0.36–0.62]); OS, median 45.1 vs 30.8 months (HR=0.60 [0.46–0.78]). Talazoparib plus enzalutamide vs enzalutamide plus placebo demonstrated benefit for *BRCA2m* across endpoints: ORR, 86.4% vs 31.0% (OR, 14.07 [95% CI, 2.88–87.70]); rPFS, median not reached (NR) vs 10.9 months (HR=0.25 [0.15–0.42]); OS, median NR vs 28.5 months (HR=0.47 [0.29–0.76]). Similar rPFS and OS benefit was seen for *BRCA1m* and *PALB2m* (allowing for small n); response-evaluable patient numbers were too low (n=8, across arms) to meaningfully assess ORR differences. Benefit for talazoparib plus enzalutamide was also evident for *CDK12m:* ORR, 63.6% vs 22.2% (OR, 6.13 [95% CI, 0.62–81.11]); rPFS, 19.3 vs 13.8 months (HR=0.36 [0.19–0.70]); OS, 36.4 vs 22.8 months (HR=0.41 [0.23–0.74]). *ATMm* also showed benefit for talazoparib plus enzalutamide: ORR, 75.0% vs 33.3% (OR, 6.00 [95% CI, 0.76–52.63]); rPFS, 30.4 vs 18.3 months (HR=0.66 [0.37–1.18]); OS, 45.1 vs 39.5 months (HR=0.70 [0.38–1.29]). *CHEK2m* showed modest overall benefit for talazoparib plus enzalutamide: ORR, 53.3% vs 42.9% (OR, 1.52 [95% CI, 0.18–14.06]); rPFS, 24.8 vs 18.3 months (HR=0.64 [0.34–1.22]); OS, 34.2 vs 39.5 months (HR=0.96 [0.51–1.81]). The remaining six HRR12 genes could not be meaningfully assessed for efficacy benefit by gene with talazoparib plus enzalutamide vs enzalutamide plus placebo due to low mutational prevalence.

Conclusions: An efficacy benefit was evident for talazoparib plus enzalutamide vs placebo plus enzalutamide across multiple mutational subgroups assessed by gene, and was most pronounced for the *BRCA1-PALB2-BRCA2* axis and *CDK12,* with benefit also apparent for *ATM*. Analyses of additional efficacy endpoints will be presented.

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