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A phase 2 study of neoadjuvant PARP inhibition followed by radical prostatectomy (RP) in patients with unfavorable intermediate-risk or high-risk prostate cancer with *BRCA1/2* gene alterations (NePtune).

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Background: Patients with localized high-risk prostate cancer have an increased risk of relapse following RP. Approximately 6% of patients with high-risk disease harbor germline alterations in the DNA repair pathway, of which *BRCA1/2* alterations are the most common. Patients with germline *BRCA1/2* mutations have higher rates of aggressive disease, distant metastases, and worse survival compared to non-carriers. Olaparib is a PARP inhibitor which demonstrates improved overall survival in patients with metastatic castration resistant prostate cancer with *BRCA1/2* germline and somatic alterations. Additionally, olaparib has demonstrated improved invasive disease-free survival as adjuvant therapy in patients with germline *BRCA1/2* HER-2 negative breast cancer. Novel, multimodal treatment strategies for patients with high-risk localized prostate cancer with germline or somatic *BRCA1/2* may improve outcomes for these patients. **Methods:** We designed a multicenter phase 2 single arm study evaluating neoadjuvant olaparib in combination with a LHRH agonist for 6 months followed by RP. Eligible patients include those with a Gleason score ≥4+3=7, PSA >20 ng/mL or T3 disease (by DRE or prostate MRI) and lymph node <20 mm. Patients with intraductal carcinoma are eligible independent of Gleason score, PSA, or T stage. Patients must have a germline or somatic *BRCA1/2* pathogenic or likely pathogenic alterations identified on standard of care molecular profiling. Eligible patients receive olaparib 300 mg by mouth twice daily and a LHRH agonist for 6 months followed by RP. The primary endpoint is the rate of a pathologic complete response (pCR) or minimum residual disease (MRD, tumor ≤5 mm) as determined by central pathology review. Secondary endpoints include PSA response, surgical staging at RP, positive margin rate, time to testosterone recovery, and safety. Exploratory endpoints include quality of life assessment, proportion of downstaging on multi-parametric MRI (mpMRI), correlation of mpMRI with pathologic response, and tissue based molecular predictors of response and resistance. The sample size was estimated based a Binomial Exact test to assess the null hypothesis of the pCR/MRD rate ≤10% with one-sided 5% significance level. If the observed rate from this study is ≥32.5%, to have 90% power to conclude that the pCR/MRD rate is above 10%, a total of 30 patients will be enrolled. We can reject the null hypothesis if there are at least 7 responses. This trial is enrolling patients through the Hoosier Cancer Research Network. The study is activated at the University of California San Diego and University of Pennsylvania. Sites pending activation include: Johns Hopkins Hospital, Memorial Sloan Kettering Cancer Center, Columbia University, and University of Buffalo. Clinical trial information: NCT05498272. Research Sponsor: AstraZeneca.