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Title

Neoadjuvant niraparib in men with DNA repair gene deficient clinically localized prostate cancer: Clinical and molecular results from a phase 2 investigator-initiated trial.

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Abstract

5104 Background: Many men with clinically localized prostate cancer experience disease progression and recurrence despite curative local therapy. Neoadjuvant treatments may reduce recurrence risk and the need for salvage therapy. Primary prostate cancer is genomically diverse and PARP inhibitors (PARPi) represent a novel class of targeted cancer therapy with known activity in advanced prostate cancers, particularly in the setting of DNA damage repair (DDR) gene alterations. Methods: Men with National Comprehensive Cancer Network unfavorable intermediate to high-risk prostate cancer were screened for somatic or germline DDR gene alterations. Consenting men were enrolled into a single arm phase II pilot study (NCT04030559) of neoadjuvant niraparib 200mg per day for 90 days prior to planned radical prostatectomy (RP). The primary endpoint was complete or partial pathologic response [minimal residual disease (MRD) defined as <0.5 cc of residual tumor]. Secondary endpoints were toxicity and biochemical progression free survival (bPFS). Raw tissue and ctDNA sequencing data was obtained by the clinical NGS vendor

and analyzed. Results: Eleven (of planned 30) men were enrolled with a median age of 68 years and median PSA at diagnosis of 10.7 ng/mL. Germline-mutations were noted in BRCA2 (n=3 patients with loss-of-function, 2 with additional loss-of heterozygosity detected), MSH6 (n=1), CHEK2 (n=1); somatic mutations were noted in ATM (n=3), SPOP (n=4), PPP2R1A (n=1), ZFHX3 (n=1), and ZMYM3 (n=2). No complete or partial pathologic responses were observed. PSA responses were variable on niraparib. There was one grade 3+ adverse event (thrombocytopenia) requiring a dose reduction. After a median follow up of 27 months, bPFS is 56% for the overall cohort. One patient with bi-allelic loss of BRCA2 (germline and somatic) and a coincident ATM mutation had the most dramatic change in PSA (-76%) with notable radiographic regression on MRI. We detected a decline in ctDNA for the somatic mutations seen in the pre-niraparib prostate biopsy NGS (ATM and PIK3R1) within 7 weeks of niraparib treatment. A new reversion mutation in BRCA2 was detected in the serum of this patient by 12 weeks which disappeared after stopping niraparib. This BRCA2 reversion mutation was also detected in the prostatectomy tissue. Conclusions: In this small study, neoadjuvant niraparib did not result in substantial pathologic response after RP in a group of men with prostate cancer and heterogeneous mutations in genes involved in DDR. Variable responses even in the face of bi-allelic BRCA2 loss suggest that additional biomarkers including ctDNA analysis to identify patients who may benefit are needed. Early reversion mutations may contribute to PARPi resistance in hormone sensitive prostate cancer. Clinical trial information: NCT04030559 .

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Clinical trial references - 1