PROREPAIR-B: A PROSPECTIVE COHORT STUDY OF THE IMPACT OF GERMLINE DNA REPAIR MUTATIONS ON THE OUTCOMES OF METASTATIC CASTRATION RESISTANT PROSTATE CANCER PATIENTS

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Background
Germline mutations in DNA damage repair (DDR) genes are identified in a significant proportion of metastatic prostate cancer patients, but their clinical implications remain unclear. This prospective multicenter cohort study evaluated the prevalence and effect of germline DDR (gDDR) mutations on metastatic castration-resistance prostate cancer (mCRPC) outcomes.

Patients and Methods
Unselected patients were enrolled at diagnosis of mCRPC and screened for gDDR mutations in 107 genes. The primary aim was to assess the impact of *ATM/BRCA1/BRCA2|PALB2* germline mutations on cause-specific survival (CSS) from diagnosis of mCRPC. Secondary aims included the association of gDDR subgroups with response outcomes for mCRPC treatments. Combined progression-free survival from the first systemic therapy until progression on the second systemic therapy (PFS2) was also explored. Median follow-up for these analyses was 40 months.

Results
We identified 68 carriers (16.2%) out of 419 eligible patients, including 14 *BRCA2*, 8 *ATM*, 4 *BRCA1* and 0 *PALB2*. The study did not reach its primary endpoint as the difference in CSS between *ATM/BRCA1/BRCA2/PALB2* carriers and non-carriers was not statistically significant (23.3 vs 33.2 months, p=0.264). CSS was halved in germline *BRCA2* (*gBRCA2*) carriers (17.4 vs 33.2 months, p=0.027) and *gBRCA2* mutations were identified as an independent prognostic factor for CCS (HR 2.11, p=0.033). Significant interactions between *gBRCA2* status and treatment-type (androgen-directed versus taxane therapy) were observed (CSS adjusted-p=0.014, PFS2 adjusted-p=0.005). CSS (24.0 vs 17.0 months) and PFS2 (18.9 vs 8.6 months) were greater in g*BRCA2* carriers treated in first-line with abiraterone or enzalutamide as compared to taxanes. Clinical outcomes did not differ by treatment types in non-carriers.

Conclusions
gBRCA2 mutations have a deleterious impact on mCRPC outcomes that may be affected by the first-line line of treatment used. Determining gBRCA2 status may be of assistance for the selection of the initial treatment in mCRPC. Nonetheless, confirmatory studies are required.

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