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IDENTIFYING COMBINATION THERAPIES FOR ANDROGEN RECEPTOR POSITIVE AND NEGATIVE PROSTATE CANCER

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OBJECTIVE

Advanced prostate cancer develops varying mechanisms of resistance to androgen receptor (AR)-directed treatments. This includes heterogeneous alterations in the AR pathway and transformation into AR-negative phenotypes. To improve patient outcomes, it is necessary to identify new treatment strategies for diverse forms of advanced prostate cancer. This study aimed to identify effective combination treatments from novel patient-derived models representing the spectrum of prostate cancer.

METHODOLOGY

We obtained samples of castrate-sensitive and castrate-resistant prostate cancer to establish patient-derived xenografts and characterised their features using histopathology, RNA and DNA sequencing. We conducted an *in vivo* screen of candidate therapies (n=1/treatment), and validated them in expansion cohorts (n = 6-8/treatment).

RESULTS

We established the Melbourne Urological Research Alliance (MURAL) cohort of 59 xenografts from 30 patients. The histopathological and genomic features of the xenografts represent diverse subtypes of prostate cancer. This includes tumors with mutations, amplifications and structural rearrangements of the AR gene and AR-negative neuroendocrine pathology. The histopathology of the xenografts recapitulated the original specimens. An *in vivo* screen of eight combination therapies across eight xenografts showed promising activity of talazoparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, combined with carboplatin. In expansion cohorts, this combination treatment significantly decreased tumour growth in 4 out of 5 xenografts with AR-positive and AR-negative prostate cancer.

CONCLUSIONS

Our patient-derived models expand the capacity for preclinical testing of prostate cancer with diverse forms of resistance to AR-directed treatments. In addition, the combination of a PARP inhibitor and carboplatin is effective for both AR-positive and AR-null prostate cancer.