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Predictive Genomic Biomarkers in Non-Metastatic Castration Resistant Prostate Cancer (nmCRPC)

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BACKGROUND

- Apalutamide, Enzalutamide, and Darolutamide are androgen receptor axis targeted therapies (ARAT) approved for the treatment of advanced non-metastatic castration-resistant prostate cancer (nmCRPC) with improved metastasis-free survival (MFS) and overall survival (OS) demonstrated in phase III clinical trials.[1-3]
- The magnitude and duration of PSA response to ARATs is highly variable, suggestive of a biologically heterogenous disease state.
- Patients with homologous recombination repair (HRR) and oncogene (OG)/tumour suppressor (TS) mutations seem to have inferior clinical outcomes when treated with ARATs in the metastatic setting. [4,5]
- Genomic profiling of tumour tissue in the nmCRPC setting may allow for the identification of patients most suitable for treatment with these agents.

OBJECTIVES

- Primary: Identify predictive genomic biomarkers corresponding with duration of ARAT treatment effect
- Secondary: Exploratory identification of genomic biomarkers in patients with poor initial PSA response to ARAT

METHODS

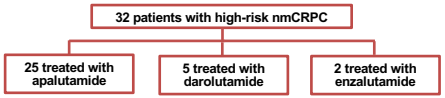
- Charts of patients diagnosed with advanced prostate cancer between 2001-2020 in the province of Alberta, Canada were reviewed.
- We identified patients with nmCRPC per Prostate Cancer Working Group 2 criteria with high risk disease (PSA doubling time <10 months).
- Next generation gene sequencing (NGS) was performed on archival tumour tissue examining for genomic alterations in 500 genes, including HRR, TS, and OG groups.
- Median MFS, time from initial ARAT therapy to disease progression on next line of treatment or death from any cause (PFS2), and OS were entered into a Cox proportional hazard regression model with adjustment for PSA doubling time and presence of pelvic lymphadenopathy.

RESULTS

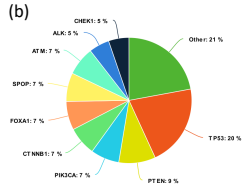
- A total of 32 patients with high risk nmCRPC treated with ARAT were identified (Figure 1a).
- 10 patients (31%) had TS or OG mutations (5 PTEN, 8 TP53, 2 PIK3CA), 3 patients (9%) had HRR gene mutations (2 ATM, 1 BRCA2), and 1 patient (3%) had 2 MLH1 mutations (microsatellite instability) (Figure 1b/c).
- All 5 pts treated with subsequent therapy received abiraterone.
- Figures 2 and 3 demonstrate the MFS and OS outcomes of patients with TS/OG alterations, HRR alterations, and wild type (Wt) status.
- Patients with TS/OG mutations had significantly shorter MFS (16.4 mo; HR 5.2; 95% CI 1.4 - 25.7; p = 0.018) , PFS2 (22.1 mo; HR 15.4; 95% CI 1.9 - 126.3; p = 0.011) and OS (24.1 mo; HR 8.3; 95% CI 1.2 - 58.8; p = 0.035).
- Those with HRR mutations had significantly reduced PFS2 (median not reach [NR]; HR 40.4; 95% CI 1.6 - 1034.2; p = 0.025) and OS (NR; HR 21.7; 95% CI 1.1. - 446.1; p = 0.045).

Figure 1. (a) Proportion of population sample treated by specific ARAT (b) Proportion of pertinent genetic mutations in archival tumour tissue (b) Proportion of genetic mutations categorized as HRR, TS/OG, or wildtype (Wt) (not harboring HRR or TS/OG mutations)

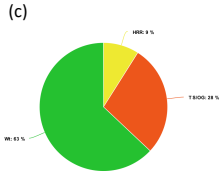
(a)



(b)



(c)



RESULTS

Figure 2. Metastasis-free survival by mutational group in nmCRPC from initiation of ARAT therapy

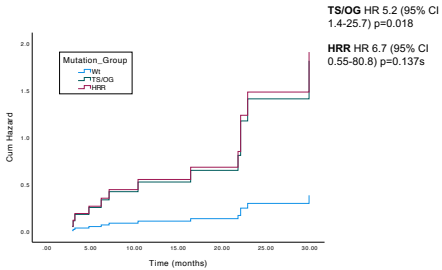
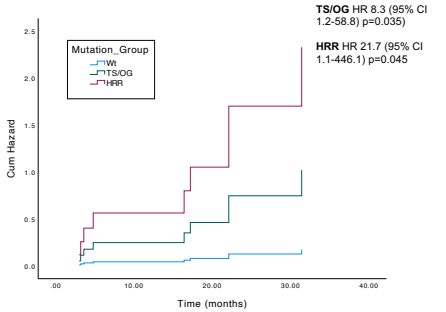


Figure 3. Overall survival by mutational group in nmCRPC from initiation of ARAT therapy



CONCLUSIONS/DISCUSSION

- This retrospective analysis demonstrates that nmCRPC patients treated with ARATs with TS/OG and HRR mutations have significantly worse clinical outcomes.
- TS/OG mutations are primarily found in the PTEN/PI3K/AKT pathway or upstream regulators, reinforcing the importance of this pathway in the development of androgen receptor (AR) pathway independence in castration-resistant prostate cancer.
- Despite small numbers, HRR mutations also seem to be a poor prognostic factor in the nmCRPC setting corresponding with similar findings in the metastatic setting where there is good evidence for PARP inhibition therapy.
- There is biological rational to explore early integration of PARP inhibition and PTEN/PI3K/AKT pathway inhibition in nmCRPC patients with these biomarkers.

FUTURE DIRECTIONS

- We will continue genomic sequencing of our nmCRPC patient cohort and with ongoing updates of their clinical outcomes to identify prognostic/predictive role of less common mutations.
- There is a need for clinical trials exploring early use of targeted agents in nmCRPC patients with high-risk biomarkers.
- Universal access of tumour genetic profiling in this patient population will need to be addressed.

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