Frequency of BRCA mutations and co-occurring alterations in prostate cancer

Background
Similar to other tumor types, prostate cancer is becoming molecularly stratified to identify targeted strategies (imnoonmune, ARKi), however new molecular pathways are being determined as having a major role in prostate molecular pathways, with potential treatment impact.

The homologous recombination (HR) pathway is dysregulated in several solid tumors, particularly in patients that are carriers of the most common susceptibility genes, BRCA1 and BRCA2. Mutations in the HR pathway and BRCA2 have gained interest for predicting sensitivity to DNA-crosslinking agents, such as irinotecan, platinum and PARP inhibitors (poly (ADP-ribose) polymerase).

We cataloged the frequency of BRCA2 alterations (and other DNA repair defects) and co-occurrence with additional alterations that may present opportunities for novel treatment strategies for prostate cancer.

Methods
A total of 85 advanced prostate cancer patients were included in the study and tested centrally at a UGIA laboratory (Caris Life Sciences, Phoenix, AZ). Tests included one or more of the following: gene sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]) and gene amplification (C/FISH).

Results
Distribution of disease site utilized for profiling, BRCA status and age of patients with prostate cancer. The distribution of metastatic sites for specimens utilized for profiling (n=77) (1a) and distribution of disease site utilized for profiling, BRCA status and age of patients with prostate cancer. BRCA and co-occurring alterations in prostate cancer. Mutations are classified by molecular genetics using pre-defined criteria. Pathogenic and presumed pathogenic variants are called when the variants demonstrated to have a disease-driving effect in tumor cells, and/or have been shown in the clinical literature to be targetable with DNA-damaging agents. Over half (53%) of prostate cancer patients demonstrating BRCA mutations have variants that are targetable with DNA-damaging therapies, e.g. PARP inhibitors.

Conclusions
More than half (53%) of specimens submitted for profiling of prostate cancer are from metastatic sites and tend to have higher Glesion Score (>7). The most common metastatic sites are lymph nodes (30%), liver (21%) and bone (21%). The most frequent Gleason Score in patients with BRCA mutations is 9 (43%), vs. 10 (57%).

BRCA-mutated patients are 1.9x more likely to have a Gleason Score of 8-10 vs. BRCA wildtype (p=0.04). Significant co-occurring alterations were more frequent in BRCA-mutated patients: TUBB3 expression (10% vs. 1%; p=0.05) and TUBB3 was more often reduced (80% vs. 43%; p=0.003), suggesting taxanes may not be the best combination strategy with PARP inhibitors.

 Alterations that have a tendency to co-occur with BRCA mutations vs. BRCA wildtype and metastatic prostate cancer. With the exception of ERCC1 protein expression, alterations in DNA repair pathways genes occur in a range of 3-21%, indicating a new subgroup of molecularly defined prostate cancer patients that may benefit from DNA-damaging agents like PARP inhibitors.

Table 1: Distribution of somatic variants detected in BRCA1/2 in prostate cancer. Mutations are classified by molecular genetics using pre-defined criteria. Pathogenic and presumed pathogenic variants are called when the variants demonstrated to have a disease-driving effect in tumor cells, and/or have been shown in the clinical literature to be targetable with DNA-damaging agents.

Table 2: Distribution of disease site utilized for profiling, BRCA status and age of patients with prostate cancer. BRCA and co-occurring alterations in prostate cancer. Mutations are classified by molecular genetics using pre-defined criteria. Pathogenic and presumed pathogenic variants are called when the variants demonstrated to have a disease-driving effect in tumor cells, and/or have been shown in the clinical literature to be targetable with DNA-damaging agents.

Table 3: Distribution of somatic variants detected in BRCA1/2 in prostate cancer. Mutations are classified by molecular genetics using pre-defined criteria. Pathogenic and presumed pathogenic variants are called when the variants demonstrated to have a disease-driving effect in tumor cells, and/or have been shown in the clinical literature to be targetable with DNA-damaging agents.

References