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

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Abstract

** Full analysis has been updated with an additional 33 patients which have been profiled since abstract submission*

Background: Evidence is building for the utility of PARP (oral poly (ADP-ribose) polymerase) inhibitors in BRCA-mutated patients, across solid tumors. We examined the presence of somatic BRCA mutations (detected in tumor), in a population of prostate cancer patients. Comparisons between BRCA-mutated and BRCA-wildtype patients were made to determine potential combination strategies.

Methods: 85 advanced prostate cancer patients were included in the study and tested centrally at a CLIA 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: Average age of BRCA-mutated patients was 58, compared to 62 in the non-BRCA-mutated cohort. Metastatic (Stage IV) disease was present in 67% in both cohorts (8/12; 49/73). BRCA2 mutations were more frequent (12%; 10/85) than BRCA1 (2%; 2/85). Of the BRCA-mutated patients, 5 variants are classified as having pathogenic effect; the rest consisted of variants of unknown clinical significance. Concurrent mutations in BRCA1 and BRCA2 were found in 17% (2/12) of patients. One patient harbored multiple BRCA mutations (n=4, c.7977-1G>C, I2068fs, K2077Q, T2337I). Regarding co-occurring alterations, 36% (4/11) and 0% (0/11) exhibited PD1 + TILs and PD-L1+ tumor expression. Amongst theranostic markers tested by IHC, TOPO1 and TUBB3 were differentially expressed in BRCA-mutated vs. BRCA-wildtype groups: 91% (10/11) vs. 59% (41/69); p=0.04 and 64% (7/11) and 23% (16/70); p=0.0099. Co-occurring variants detected by NGS, included high rates of TP53: 42% (5/12) compared to BRCA-wildtype (30% 21/71), not significant. Of 3 patients that included expanded NGS analysis (600 genes), each harbored ≥39 mutations.

Conclusion: The frequency of somatic BRCA mutations observed in prostate cancer, together, with preliminary clinical evidence for the efficacy of targeted therapies for these patients; highlight the potential role of a new class of agents for advanced prostate cancer.

Background

Similar to other tumor types, prostate cancer is becoming molecularly stratified to identify targeted status (overexpressed, ARv7), however new molecular pathways are being determined as having a major role in prostate molecular pathogenesis, with potential treatment impact.

The homologous recombination [HR] pathway is dysregulated in several solid tumors, particularly in patients that are carriers of the breast cancer susceptibility genes, BRCA1 and BRCA2. Mutations in the HR pathway and BRCA1/2 have gained interest for predicting sensitivity to DNA-crosslinking agents, such as mitomycin, platinum analogs and PARP inhibitors (poly (ADP-ribose) polymerase).

We cataloged the frequency of BRCA1/2 alterations (and other DNA-repair defects) and co-occurrence with additional alterations that may present opportunities for novel treatment strategies for prostate cancer.

Methods

In a commercial (Caris Life Sciences, Phoenix, AZ) biomarker data repository, 118 prostate cancers (adenocarcinomas) with BRCA1 and BRCA2 mutation status were identified (2013-2015) and included in this retrospective analysis.

Specific testing was performed and included a multiplatform approach: sequencing (Sanger, NGS [truSeq=47 gene panel/MiSeq=600 gene panel]), protein expression (IHC) and gene amplification (CISH/FISH). Antibodies and cutoffs utilized are available upon request. The following classifications are used to categorize variants detected by NGS (in order of decreasing tumor effect or evidentiary support): pathogenic (P), presumed pathogenic (PP), variant of unknown significance (VUS) and unclassified variant (UV). Pearson's chi-squared test (IBM SPSS Statistics, Version 23.0, Armonk, NY) was utilized to test for significant differences between subgroups. BRCA_MT= BRCA1/2 mutated, BRCA_WT = wildtype.

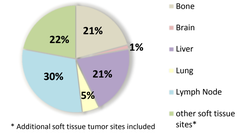
Results

Table 1. Clinicopathologic Characteristics of Patient Cohort Studied

		Disease Site Utilized for Profiling		Age	
Prostate Cancer Group	n (%)	Primary	Metastatic	Median/Average	Range
Prostate (all)	118 (100)	41 (35)	77 (65)	62/62	[38-84]
BRCA_MT Prostate	15 (13)	5 (33)	10 (67)	62/59	[41-73]
BRCA1_MT	2 (2)	1 (50)	1 (50)	59/59	[53-65]
BRCA2_MT	13 (11)	4 (31)	9 (69)	62/60	[41-73]
BRCA_WT Prostate	103 (87)	36 (35)	67 (65)	62/63	[38-84]

Table 1- Distribution of disease site utilized for profiling, BRCA status and age of patients with prostate adenocarcinomas included in this analysis. Presence of somatic variants (P, PP or VUS) in prostate cancer occur at a rate of 13% (11% BRCA2 and 2% BRCA1). More than half of specimens profiled (65%) are from metastatic sites.

Figure 1a. Metastatic Specimen Sites



* Additional soft tissue tumor sites included bladder, adrenal gland, rectum and others.

Figure 1b. Distribution of Gleason Scores

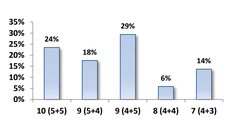


Figure 1a-b– Distribution of metastatic sites for specimens utilized for profiling (n=77) (1a) and Gleason scores available for 51 patients (1b). Gleason scores were not available for 67 patients.

Results, contd.

Table 2. Somatic Variants in BRCA Detected in Prostate Cancer and their Potential Clinical Impact

Patient	BRCA1 or BRCA 2	Variant	% Mutated	Exon	Variant Classification	Pathway targetable in this patient?
1	BRCA1	R496H	49	14	VUS	Yes
	BRCA1	c.301+1G>A	44	19	Pathogenic	
2	BRCA2	K1872fs	59	11	Pathogenic	Yes
3	BRCA2	N900D	51	11	VUS	Unknown
4	BRCA1	D1546N	49	14	Presumed Benign	Unknown
	BRCA2	V145I	42	5	VUS	
5	BRCA1	P930L	16	10	VUS	Unknown
	BRCA1	V1534M	50	14	Presumed Benign	
6	BRCA2	I2068fs	29	11	Pathogenic	Yes
	BRCA2	c.7977-1G>C	63	18	Pathogenic	
	BRCA2	K2077Q	29	11	VUS	
	BRCA2	T2337I	100	14	VUS	
7	BRCA2	N1784fs	48	11	Pathogenic	Yes
8	BRCA2	G1771D	50	11	VUS	Unknown
9	BRCA2	C554W	12	10	VUS	Unknown
10	BRCA2	c.9256_9256+1delinsTA	69	24	Pathogenic	Yes
11	BRCA2	C341R	50	10	VUS	Unknown
12	BRCA2	R2659K	79	17	Presumed Pathogenic	Yes
13	BRCA2	N2781fs	95	19	Pathogenic	Yes
14	BRCA2	R3052W	56	24	Pathogenic	Yes
15	BRCA1	M1652I			VUS	Unknown

Table 2. Description of somatic variants detected in BRCA1/2 in prostate cancers. Mutations are classified by molecular geneticists using pre-defined criteria. Pathogenic and presumed pathogenic variants are those mutations 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.

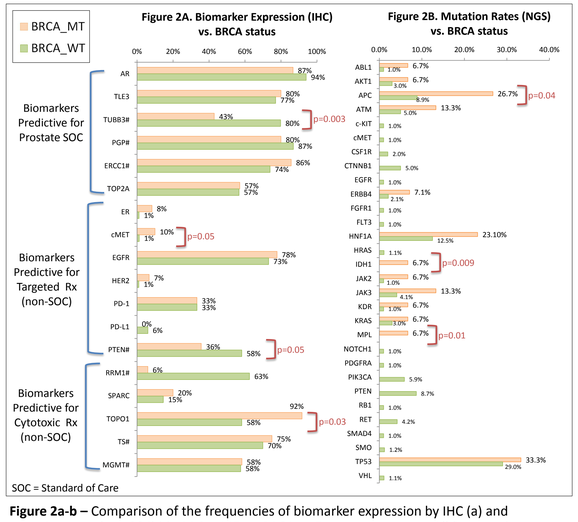
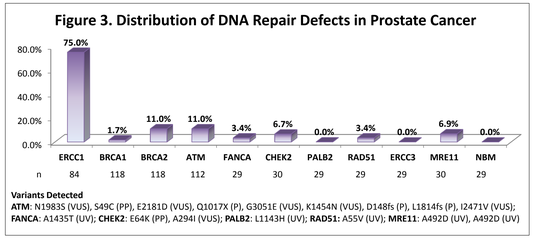


Figure 2a-b – Comparison of the frequencies of biomarker expression by IHC (a) and mutation rates by NGS (b) in BRCA_MT vs. BRCA_WT prostate cancers. All frequencies are expressed as % positive expression, unless indicated by # which indicates negative expression frequency, which is predictive for respective therapy response. No amplifications were detected in this cohort, cMET ISH (0/73) and HER2 ISH (0/101).

Results, contd.

Figure 3. Distribution of DNA Repair Defects in Prostate Cancer



Variants Detected
ATM: N1983S (VUS), S49C (PP), E2181D (VUS), Q1017X (P), G3051E (VUS), K1454N (VUS), D148fs (P), L1814fs (P), I2471V (VUS);
FANCA: A1435T (UV); **CHEK2**: E64K (PP), A294I (VUS); **PALB2**: L1143H (UV); **RAD51:** A55V (UV); **MRE11**: A492D (UV), A492D (UV)

Figure 3. Distribution of DNA Repair Defects in Prostate Cancer. Frequencies represent % mutated across prostate cancer cohort studied, with the exception of ERCC1 which represents % of lack of expression of ERCC1 by IHC. Mutations are classified by molecular geneticists using pre-defined criteria for BRCA1/2, ATM and CHEK2, the remaining variants detected are captured as unclassified variants.

Conclusions

- More than half (65%) of specimens submitted for profiling of prostate cancer are from metastatic sites and tend to have higher Gleason Scores (>7). The most common metastatic sites are lymph nodes (30%), liver (21%) and bone (21%). The most frequent Gleason Score is 9 (4+5) at 29%.
- BRCA mutation rate is 13% in prostate cancer (11% BRCA2 and 2% BRCA1), with these mutations occurring in slightly younger men than the overall population (59 vs. 62). Over half (53%) of somatic variants detected in BRCA1/2 are deemed to have a pathogenic or tumor effect, thus potentially targetable with DNA-damaging agents.
- Alterations that have a tendency to co-occur with BRCA mutations vs. BRCA wildtype and reached statistical significance included: overexpression of cMET (10% vs. 1%; p=0.05) and TOPO1 (92% vs. 58%; p=0.03). These co-occurring alterations may suggest the utility of cMET-targeted therapy or topoisomerase inhibitors in combination with DNA-damaging agents.
- Alternatively, co-occurring alterations that were more frequent in BRCA wildtype patients, included a higher frequency of low TUBB3 (80% vs. 43%; p=0.003), suggesting taxanes may not be the best combination strategy with PARP inhibitors for BRCA-mutated patients.
- Alterations in the PIK3CA pathway (PTEN loss, mutations in PIK3CA, PTEN and STK11) occurred at much higher frequency in BRCA wildtype patients, indicating the PIK3CA pathway may stratify a different molecular subtype of prostate cancer.
- With the exception of ERCC1 protein loss, aberrations in DNA repair pathways genes occur in a range of 2-11%, indicating a new subgroup of molecularly-defined prostate cancer patients that may benefit from DNA-damaging agents like PARP inhibitors.

References

1. Mateo, J., J.S. de Bono, et al. "DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer." NEJM 373 (18): 1697-1708.
2. Scott, C.L., S.H. Kaufmann, et al. "Poly (ADP-Ribose) Polymerase Inhibitors: Recent Advances and Future Development." J Clin Oncol 33: 1-10.