Biomarker Patterns of Localized and Metastatic Prostate Cancer

Rebecca Feldman, PhD[1] Sandeep Reddy MD[1], Zoran Gatalica MD, DSc[1], Joanne Mahanes, CCRP, NCC, MS [2,3] Charles Myers, M.D.[2,3]
[1]Caris Life Sciences, Phoenix, AZ; [2]American Institute for Diseases of the Prostate, Earlysville, VA, [3]Foundation for Cancer Research and Education, Charlottesville, VA

Background

Prostate cancer remains to be a leading cause of cancer-related death in men. Most prostate cancer–related deaths are due to advanced disease, which results from any combination of lymphatic, blood, or contiguous local spread. Therefore, the presence or absence of metastases is a determining factor for prostate cancer prognosis.

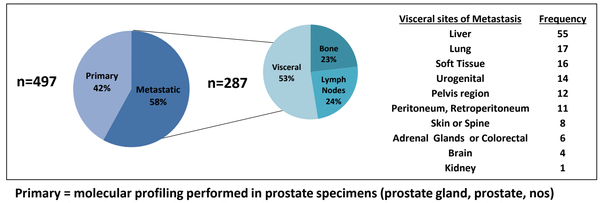
Identifying the molecular mechanisms involved in metastasis of prostate cancer can potentially direct therapy and may result in the introduction of new targets for therapy. Molecular profiling using multiple platforms is a comprehensive approach in identifying molecular aberrations that could be targeted by (1) agents considered standard of care for prostate cancer, (2) FDA-approved agents used in other solid tumors, (3) novel targeted therapies currently in clinical trial or (4) combination treatment. We sought to determine theranostic biomarker differences between primary (P) and metastatic (M) specimens, with subset analysis for differences between metastatic sites, including the most common sites of metastasis: bone (B), lymph nodes (LN) or visceral organs (V).

Methods

Four-hundred ninety seven prostate cancer cases referred to Caris Life Sciences between 2009 and 2014 were evaluated. Specific testing was performed and included a multiplatform approach: sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH/FISH).

Tumor Attributes and Patient Characteristics

Figure 1. Disease Status and Sites of Metastatic Tumor Specimens



Visceral sites of Metastasis	Frequency
Liver	55
Lung	17
Soft Tissue	16
Urogenital	14
Pelvis region	12
Peritoneum, Retroperitoneum	11
Skin or Spine	8
Adrenal Glands or Colorectal	6
Brain	4
Kidney	1

Primary = molecular profiling performed in prostate specimens (prostate gland, prostate, nos)
Metastatic = molecular profiling performed in non-prostate specimens of men with dx prostate cancer

Table 1. Median Age, by subgroup

	Median
Prostate - All (n=497)	66
Prostate - Primary (n=210)	65
Prostate - Metastatic (n= 287)	68

Histology

442/497 (89%) prostate cancers are confirmed adenocarcinomas according to submitted pathology reports.

Results

PRIMARY vs. METASTATIC COMPARISONS

Figure 2. Differences in Protein Expression

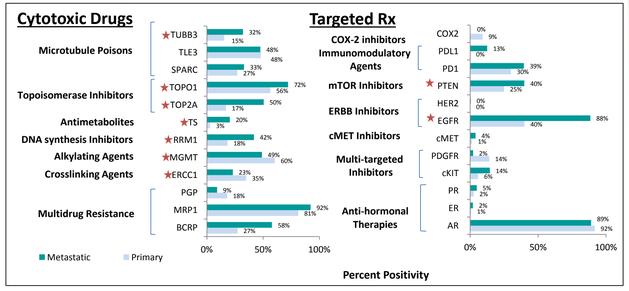


Figure 2. Differences in Protein Expression in Primary vs. Metastatic profiles.

Table 2. Mutational Analysis

Biomarker	Primary % (n)	Metastatic % (n)	p-value
TP53	26 (10/38)	39 (38/97)	ns
PTEN	3 (1/38)	19 (14/80)	0.035
BRCA2	9 (1/11)	13 (2/15)	ns
APC	5 (2/42)	8 (8/98)	ns
CTNNB1	2 (1/42)	8 (8/99)	ns
BRCA1	9 (1/11)	7 (1/15)	ns
PIK3CA	2 (1/58)	5 (7/131)	ns
ATM	2 (1/41)	3 (3/97)	ns
RB1	0 (0/40)	3 (3/98)	ns
RET	3 (1/40)	1 (1/97)	ns
SMAD4	0 (0/41)	3 (3/99)	ns
CDH1	2 (1/42)	0 (0/99)	ns
ALK	0 (0/42)	2 (2/99)	ns
BRAF	1 (1/94)	2 (3/183)	ns
CKIT	2(1/52)	1 (1/119)	ns
CMET	0 (0/42)	2 (2/99)	ns
ERBB4	0 (0/41)	2 (2/98)	ns
HRAS	0 (0/39)	2 (2/85)	ns
IDH1	0 (0/42)	2 (2/99)	ns
MLH1	2 (1/42)	0 (0/99)	ns
ABL1	0 (0/39)	1 (1/96)	ns
AKT1	0 (0/42)	1 (1/99)	ns
CSF1R	0 (0/42)	1 (1/99)	ns
FBXW7	0 (0/42)	1 (1/97)	ns
KRAS	1 (1/102)	1 (1/186)	ns
JAK3	0 (0/42)	1 (1/99)	ns
KDFR	0 (0/42)	1 (1/99)	ns
NRAS	0/45	1 (1/117)	ns
STK11	0/31	1 (1/95)	ns
VHL	0/33	1 (1/90)	ns
Genes Mutated	30 (14/47)	60 (28/47)	0.0067

Frequency: >13% | 5-13% | 3-4% | 1-2%

Figure 3. Differences in GCN

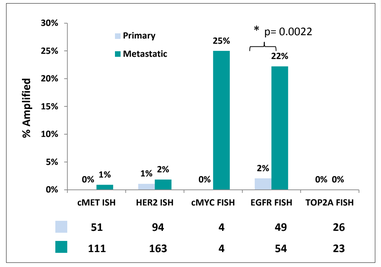


Figure 3. Differences in GCN (gene copy number) demonstrate rare amplification events in HER2, cMET and cMYC, whereas EGFR amplification occurs at higher frequency in metastatic prostate cancer (p=0.0022).

Table 2. PTEN is the only gene mutated at statistically significant higher frequency in metastatic prostate cancer. Metastatic profiles are more genetically unstable exhibiting mutations in 60% of genes tested vs. 30% in primary specimens.

no variants detected: EGFR, ERBB2, FGFR1, FGFR2, FLT3, GNA11, GNAQ, GNAS, HNF1A, JAK2, MPL, NOTCH1, NPM1, PDGFRA, PTPN11, SMARCB1, SMO

BONE vs. LYMPH NODES vs. VISCERAL COMPARISONS

Figure 4. Differences in Protein Expression for Cytotoxic Agents

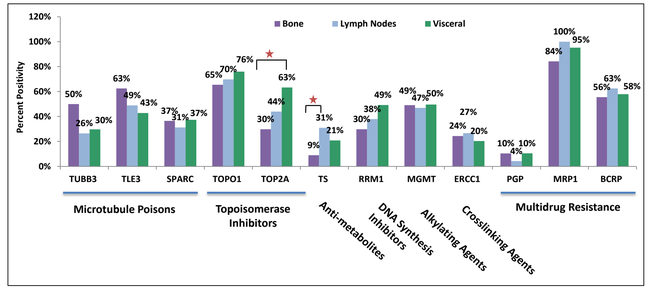


Figure 4. Differences in Protein Expression bone, lymph node and visceral metastases.

Figure 5. Differences in Protein Expression & GCN for Targeted Agents

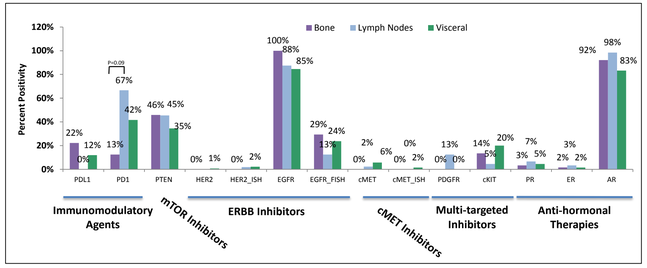


Figure 5. Differences in Protein Expression & GCN for bone, lymph node and visceral metastases.

Figure 6. Selected NGS Variant Frequencies for B, LN and V Metastases

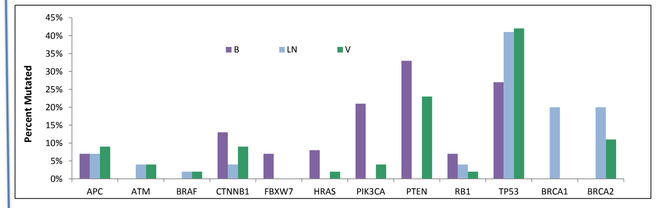


Figure 6. Selected NGS Variant Frequencies for B, LN and V Metastases.

Results

Gene/Protein Change	(n)
BRCA1	
c.301+1G>A	1
BRCA2	
K1872fs	1
APC	
S1465fs	2
T1556fs	3
CTNNB1	
S45del	2
S45P	2
HRAS	
Q61L	2
IDH1	
R132C	2
PIK3CA	
H1047R	3
PTEN	
K267fs	3

Table 3. Selected NGS (Pathogenic) Variants. Each of these mutants display targetable genes, for which drugs are available through clinical trials.

Targetable Alterations Detected

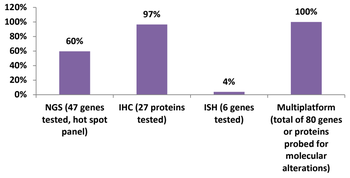


Figure 7. Multiplatform profiling maximizes clinically targetable alterations (100% of cases identified targets) compared to NGS alone (60%) .

Conclusions

- Significant differences for EGFR amplification/overexpression, low MGMT expression, TOPO1/2A overexpression and higher PTEN mutation rate were found in the M subgroup, indicating a role for EGFR/PTEN in progression of prostate cancer, and potential role of MAPK/PAM-targeted therapies, alkylating agents and topoisomerase inhibitors in M disease.
- Mutational profiles of the M subgroup are more genetically unstable exhibiting mutations in 60% of genes tested (notable events include APC & β-Catenin, PTEN, TP53 and BRCA1/2) vs. 30% observed in the P subgroup (p=0.0067).
- EGFR amplification was higher in B (29%) and V (24%) compared to LN (13%); (not significant). Low TS expression was more frequent in B vs. LN (p=0.004), TOPO2A overexpression was higher in V vs. B (p=0.0001) and there was a trend for PD1 positive infiltrating lymphocytes being more abundant in LN vs B (p=0.09).
- cMET overexpression (7/230) and amplification (1/162) were rarely observed across the cohort, providing support for the surprising failure of cabozantinib in castration-resistant prostate cancer.
- Multiplatform profiling maximizes clinically targetable alterations (100% of cases identified targets) compared to NGS alone (60%).

References

Marech, I., F. Dammacco, et al. (2012). "Novel strategies in the treatment of castration-resistant prostate cancer (review). Intl J Oncol 40:1313-1320.

Contact email: rfeldman@carisls.com