

Microsatellite instability in prostate cancer and response to immune checkpoint blockade.

Wassim Abida, **Michael L. Cheng**, Joshua Armenia, Sumit Middha, Karen A. Autio, Dana E. Rathkopf, Michael J. Morris, Daniel Costin Danila, Susan F. Slovin, Emily Carbone, Melanie Hullings, Jaclyn Frances Hechtman, Victor E. Reuter, Michael F. Berger, Philip W. Kantoff, Charles L. Sawyers, Nikolaus Schultz, David B. Solit, Anuradha Gopalan, Howard I. Scher; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Immune checkpoint blockade has shown clinical benefit in mismatch repair deficient (dMMR) cancers, leading to accelerated FDA approval of pembrolizumab, a PD1-targeting agent, for the treatment of dMMR or microsatellite instability-high (MSI-H) advanced solid tumors. However, the frequency of MSI-H prostate cancer (PCa), as well as response to PD1/PDL1 agents in this disease subset, remain poorly defined. **Methods:** 839 PCa patients underwent targeted next-generation sequencing (NGS) of tumor and matched normal samples on an institutional protocol for the characterization of somatic mutations, copy number alterations and germline mutations (with specific consent). MSIsensor analysis, a computational method for detecting MSI, was performed. Tumor mutation burden (TMB) was calculated, with additional analysis for mutational signatures and immunohistochemical (IHC) staining of MMR proteins in selected cases. **Results:** 20/839 PCa patients (2.4%) were found to have MSI-H/dMMR tumors, defined as an MSIsensor score of ≥ 3 and TMB of ≥ 10 , confirmed by IHC and mutational signature analysis. Of 13/20 MSI-H patients who consented to germline analysis, 3/13 (23%) had a germline MMR gene mutation. 3/5 MSI-H patients who underwent profiling of ≥ 2 matched tumors demonstrated MSI in the later tumor. In total, 10 patients with MSI-H tumors received a PD1/PDL1 targeting agent. 2/10 had radiographic PR with PSA decline of $> 80\%$. 3/10 are early in their treatment with PSA decline of $> 60\%$. 1/10 had stable disease for 6 months then progressed. 3/10 had no response. 1/10 was inevaluable. **Conclusions:** Tumor profiling for MSI status can be considered for patients with advanced PCa. MSI can develop as a later somatic event, arguing for profiling of a recent tumor when possible. Germline profiling should be recommended for patients with MSI-H PCa. While early in this dataset, responses to PD1/PDL1 therapy may occur in $\sim 50\%$ of patients with MSI-H/dMMR PCa. Longer follow up and additional prospective studies will be necessary to confirm responses in this patient population.

Funding acknowledgements:

This work was supported by Prostate Cancer Foundation Challenge and Young Investigator Awards (W.A., M.C., N.S., H.S.), the National Institutes of Health (NIH/NCI Prostate SPOR P50-CA92629 and NIH/NCI Cancer Center Support Grant P30 CA008748), the Department of Defense Prostate Cancer Research Program (Physician Research Award to W.A., PC071610 and PC121111), the David H. Koch Fund for Prostate Cancer Research, the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, the Robertson Foundation (N.S.)

Disclosures:

Wassim Abida
Honoraria - CARET
Consulting or Advisory Role - Clovis Oncology

Research Funding - AstraZeneca; Clovis Oncology; GlaxoSmithKline (Inst); Zenith Epigenetics
Travel, Accommodations, Expenses - GlaxoSmithKline

Michael L. Cheng

No Relationships to Disclose

Joshua Armenia

No Relationships to Disclose

Sumit Middha

No Relationships to Disclose

Karen A. Autio

Research Funding - ARMO BioSciences (Inst); CytomX Therapeutics (Inst); GlaxoSmithKline (Inst); Merck (Inst); Pfizer (Inst)

Dana E. Rathkopf

Consulting or Advisory Role - Genentech/Roche; Janssen Oncology; TRACON Pharma
Research Funding - AstraZeneca (Inst); Celgene (Inst); Ferring (Inst); Genentech/Roche (Inst);
Janssen Oncology (Inst); Medivation (Inst); Millennium (Inst); Novartis (Inst); Taiho
Pharmaceutical (Inst); Takeda (Inst); TRACON Pharma (Inst)

Michael J. Morris

Consulting or Advisory Role - Advanced Accelerator Applications; Astellas Pharma; Bayer; Blue
Earth Diagnostics; Endocyte; Tokai Pharmaceuticals; Tolmar Pharmaceuticals

Research Funding - Bayer (Inst); Corcept Therapeutics (Inst); Endocyte (Inst); Progenics (Inst);
Roche/Genentech (Inst); Sanofi (Inst)

Travel, Accommodations, Expenses - Bayer; Endocyte

Daniel Costin Danila

Honoraria - Angle; Astellas Scientific and Medical Affairs Inc; Bayer; Xian-Janssen
Pharmaceutical

Consulting or Advisory Role - Angle; Bayer

Research Funding - Genentech; Janssen Research & Development (Inst); Prostate Cancer
Foundation

Patents, Royalties, Other Intellectual Property - GENE EXPRESSION PROFILE ASSOCIATED WITH
PROSTATE CANCER

Travel, Accommodations, Expenses - American Austrian Open Medical Institute; Angle; Bayer;
Cambridge Healthtech Institute; Global Technology Community; Oncology Education; Prostate
Cancer Foundation; Xian-Janssen Pharmaceutical

Susan F. Slovin

Consulting or Advisory Role - Bayer

Emily Carbone
No Relationships to Disclose

Melanie Hullings
No Relationships to Disclose

Jaclyn Frances Hechtman
Consulting or Advisory Role - Navigant Consulting

Victor E. Reuter
No Relationships to Disclose

Michael F. Berger
Research Funding - Illumina

Philip W. Kantoff
Stock and Other Ownership Interests - Bellicum Pharmaceuticals; Context Therapeutics; Druggability Technologies; Placon; Seer; Tarveda Therapeutics
Consulting or Advisory Role - Bavarian Nordic; BIND Biosciences; Context Therapeutics; Druggability Technologies; GE Healthcare; Genentech/Roche; Janssen; Merck; Metamark Genetics; New England Research Institutes; OncoCellMDX; Progenity; Sanofi; Seer; Tarveda Therapeutics; Thermo Fisher Scientific
Patents, Royalties, Other Intellectual Property - Chromosome Copy Number Gain as a Biomarker of Urothelial Carcinoma Lethality; Composition and Methods for Screening and Diagnosis of Prostate Cancer; Drug Combinations to Treat Cancer; Method for Predicting the Risk of Prostate Cancer Morbidity and Mortality; Methods and Kits for Determining Sensitivity to Cancer Treatment; Methods for Predicting Likelihood of Responding to Treatment; Predicting and Treating Prostate Cancer; Somatic ERCC2 Mutations Correlate with Cisplatin sensitivity in muscle-invasive Urothelial Carcinoma (Patent); Up-to-Date Royalties; Wolters Kluwer Royalties
Expert Testimony - Janssen
Travel, Accommodations, Expenses - Sanofi

Charles L. Sawyers
Leadership - Novartis
Stock and Other Ownership Interests - Agios; BeiGene; Blueprint Medicines; Novartis; ORIC Pharmaceuticals
Consulting or Advisory Role - Agios; BeiGene; Blueprint Medicines; Novartis; ORIC Pharmaceuticals
Patents, Royalties, Other Intellectual Property - Xtandi

Nikolaus Schultz
No Relationships to Disclose

David B. Solit

Honoraria - Loxo; Pfizer
Consulting or Advisory Role - Loxo; Pfizer

Anuradha Gopalan
No Relationships to Disclose

Howard I. Scher
Leadership - Asterias Biotherapeutics
Consulting or Advisory Role - Clovis Oncology; Ferring; Janssen Research & Development;
Onclive; Physician Education Resource; Sanofi; WIRB-Copernicus Group
Research Funding - Illumina (Inst); Innocrin Pharma (Inst); Janssen (Inst)
Travel, Accommodations, Expenses - Asterias Biotherapeutics; Onclive; Physician Education
Resource; Sanofi; WIRB-Copernicus Group