The New Biology of Prostate Cancer

Exploring Basic Science to Glimpse the Future of Oncology Practice

CME INFORMATION

TARGET AUDIENCE

This activity has been designed to meet the educational needs of medical and radiation oncologists, urologists and other allied healthcare providers involved in the research and treatment of prostate cancer (PC).

OVERVIEW OF ACTIVITY

Cancer of the genitourinary system affects hundreds of thousands of individuals within the United States each year and accounts for almost 30% of all newly diagnosed tumors in humans. Tumors of the prostate are among the most prevalent and thus a topic of extensive ongoing clinical research. Consequently, the management of PC is continuously in a state of evolution, necessitating rapid and consistent access to learning opportunities for medical oncologists, radiation oncologists, urologists and other healthcare providers who treat the disease. These proceedings from an interactive CME symposium held during the 2013 Genitourinary Cancers Symposium offer medical professionals a multifaceted educational experience focused specifically on the current treatment of PC.

LEARNING OBJECTIVES

- Determine the clinical utility of genomic studies in identifying patients with PC who might benefit from novel targeted agents.
- Develop an understanding of the molecular states of androgen receptor activation and alterations after endocrine intervention to facilitate the rational selection and sequencing of new agents designed to suppress androgen signaling in PC.
- Formulate an understanding of the mechanism(s) of action of antitubulins and their differential antitumor effects, induction of side effects and ability to overcome inherent and acquired resistance to other cytotoxic agents.
- Analyze the effects of stromal-epithelial cross talk on cancer progression and the implications for therapeutic targets.
- Assess investigational tissue- and blood-based biomarkers designed to predict the potential selective benefit of various systemic therapies in castration-resistant disease.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 2.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity consists of a video component. To receive credit, the participant should watch the video, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/GUCancers13/NewBiology/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Kenneth J Pienta, MD
Professor of Medicine and Urology
American Cancer Society Clinical Research Professor
Director of Precision Medicine, Michigan Center for Translational Pathology; Associate Vice President for Research, Health Sciences
University of Michigan
Ann Arbor, Michigan

No real or apparent conflicts of interest to disclose.

Eleni Efstathiou, MD, PhD
Associate Professor
University of Texas MD Anderson Cancer Center
Department of Genitourinary Medical Oncology
Houston, Texas
Assistant Professor
University of Athens Greece Medical School
Department of Clinical Therapeutics
Athens, Greece

Advisory Committee: Bayer HealthCare Pharmaceuticals, Janssen Pharmaceuticals Inc, Millennium: The Takeda Oncology Company, Sanofi; **Contracted Research:** Bristol-Myers Squibb Company, Celgene Corporation, Janssen Pharmaceuticals Inc, Millennium: The Takeda Oncology Company, Sanofi.

William K Oh, MD
Chief, Division of Hematology and Medical Oncology
Professor of Medicine and Urology
Ezra M Greenspan, MD Professor in
Clinical Cancer Therapeutics
Mount Sinai School of Medicine
Associate Director of Clinical Research
The Tisch Cancer Institute
New York, New York

Consulting Agreements: Amgen Inc, Astellas, Bayer HealthCare Pharmaceuticals, Bellicum Pharmaceuticals Inc, Dendreon Corporation, Janssen Pharmaceuticals Inc, Medivation Inc, Pfizer Inc, Sanofi; **Paid Research:** Millennium: The Takeda Oncology Company.

Nima Sharifi, MD
Assistant Professor of Medicine
Division of Hematology/Oncology
University of Texas Southwestern Medical Center
Dallas, Texas

Advisory Committee: Janssen Pharmaceuticals Inc, Medivation Inc.

Andrew J Armstrong, MD, ScM
Associate Professor of Medicine and Surgery
Duke Cancer Institute
Divisions of Medical Oncology and Urology
Duke University
Durham, North Carolina

Advisory Committee: Amgen Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company; **Consulting Agreements:** Active Biotech AB, AstraZeneca Pharmaceuticals LP, Dendreon Corporation, Sanofi; **Contracted Research:** Bristol-Myers Squibb Company, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; **Paid Research:** Active Biotech AB, Astellas, Dendreon Corporation, Janssen Pharmaceuticals Inc, Medivation Inc, Zhejiang Kanglaite Pharmaceutical Co Ltd; **Speakers Bureau:** Amgen Inc, Dendreon Corporation, Pfizer Inc, Sanofi.

MODERATOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly USA LLC, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.

This activity is supported by an educational grant from Sanofi.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: May 2013

Expiration date: May 2014

SELECT PUBLICATIONS

Pienta

Grasso CS et al. **The mutational landscape of lethal castration-resistant prostate cancer.** *Nature* 2012;487(7406):239-43.

Pienta KJ. **Successfully accelerating translational research at an academic medical center: The University of Michigan-Coulter translational research partnership program.** *Clin Transl Sci* 2010;3(6):316-8.

Roychowdhury S et al. **Personalized oncology through integrative high-throughput sequencing: A pilot study.** *Sci Transl Med* 2011;3(111):111ra121.

Efstathiou

Efstathiou E et al. **Integrated Hedgehog signaling is induced following castration in human and murine prostate cancers.** *Prostate* 2013;73(2):153-61.

Efstathiou E et al. **Effects of abiraterone acetate on androgen signaling in castrate-resistant prostate cancer in bone.** *J Clin Oncol* 2012;30(6):637-43.

Efstathiou E et al. **MDV3100 effects on androgen receptor (AR) signaling and bone marrow testosterone concentration modulation: A preliminary report.** Genitourinary Cancers Symposium 2011;**Abstract 4501**.

Oh

Bauer JA et al. **Identification of markers of taxane sensitivity using proteomic and genomic analyses of breast tumors from patients receiving neoadjuvant paclitaxel and radiation.** *Clin Cancer Res* 2010;16(2):681-90.

Berthold DR et al. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: Updated survival in the TAX 327 study.** *J Clin Oncol* 2008;26(2):242-5.

Hasmats J et al. **Identification of candidate SNPs for drug induced toxicity from differentially expressed genes in associated tissues.** *Gene* 2012;506(1):62-8.

Mita AC et al. **Phase I and pharmacokinetic study of XRP6258 (RPR 116258A), a novel taxane, administered as a 1-hour infusion every 3 weeks in patients with advanced solid tumors.** *Clin Cancer Res* 2009;15(2):723-30.

Petrylak DP et al. **Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer.** *N Engl J Med* 2004;351(15):1513-20.

Sartor AO et al. **Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC).** Genitourinary Cancers Symposium 2010;**Abstract 9**.

Tannock IF et al. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351(15):1502-12.

Zhao L et al. **Identification of candidate biomarkers of therapeutic response to docetaxel by proteomic profiling.** *Cancer Research* 2009;69(19):7696-703.

Sharifi

Attard G et al. **Characterization of ERG, AR and PTEN gene status in circulating tumor cells from patients with castration-resistant prostate cancer.** *Cancer Res* 2009;69(7):2912-8.

Chen CD et al. **Molecular determinants of resistance to antiandrogen therapy.** *Nat Med* 2004;10(1):33-9.

Chen T et al. **Interleukin 6 activates androgen receptor-mediated gene expression through a signal transducer and activator of transcription 3-dependent pathway in LNCaP prostate cancer cells.** *Cancer Res* 2000;60(8):2132-5.

De Bono JS et al. **Abiraterone and increased survival in metastatic prostate cancer.** *N Engl J Med* 2011;364(21):1995-2005.

Edwards J et al. **Androgen receptor gene amplification and protein expression in hormone refractory prostate cancer.** *Br J Cancer* 2003;89(3):552-6.

Gelmann EP et al. **Molecular biology of the androgen receptor.** *J Clin Oncol* 2002;20(13):3001-15.

McPhaul MJ. **Mechanisms of prostate cancer progression to androgen independence.** *Best Pract Res Clin Endocrinol Metab* 2008;22(2):373-88.

Mellinghoff IK et al. **HER2/neu kinase-dependent modulation of androgen receptor function through effects on DNA binding and stability.** *Cancer Cell* 2004;6(5):517-27.

Montgomery BR et al. **Maintenance of intratumoral androgens in metastatic prostate cancer: A mechanism for castration-resistant tumor growth.** *Cancer Res* 2008;68(11):4447-54.

Mousses S et al. **Failure of hormone therapy in prostate cancer involves systemic restoration of androgen responsive genes and activation of rapamycin sensitive signaling.** *Oncogene* 2001;20(46):6718-23.

Ryan CJ et al. **Abiraterone in metastatic prostate cancer without previous chemotherapy.** *N Engl J Med* 2013;368(2):138-48.

Titus MA et al. **Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer.** *Clin Cancer Res* 2005;11(13):4653-7.

Armstrong

Antonarakis ES, Eisenberger MA. **Expanding treatment options for metastatic prostate cancer.** *N Engl J Med* 2011;364(21):2055-8.

Armstrong AJ et al. **Serum lactate dehydrogenase predicts for overall survival benefit in patients with metastatic renal cell carcinoma treated with inhibition of mammalian target of rapamycin.** *J Clin Oncol* 2012;30(27):3402-7.

Armstrong AJ et al. **Circulating tumor cells from patients with advanced prostate and breast cancer display both epithelial and mesenchymal markers.** *Mol Cancer Res* 2011;9(8):997-1007.

Armstrong AJ et al. **A pharmacodynamic study of rapamycin in men with intermediate- to high-risk localized prostate cancer.** *Clin Cancer Res* 2010;16(11):3057-66.

Armstrong AJ et al. **A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: A TAX327 study analysis.** *Clin Cancer Res* 2007;13(21):6396-403.

Attard G et al. **Characterization of ERG, AR and PTEN gene status in circulating tumor cells from patients with castration-resistant prostate cancer.** *Cancer Res* 2009;69(7):2912-8.

De Bono JS et al. **Phase I pharmacokinetic and pharmacodynamic study of LAQ824, a hydroxamate histone deacetylase inhibitor with a heat shock protein-90 inhibitory profile, in patients with advanced solid tumors.** *Clin Cancer Res* 2008;14(20):6663-73.

Grasso CS et al. **The mutational landscape of lethal castration-resistant prostate cancer.** *Nature* 2012;487(7406):239-43.

Halabi S et al. **Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer.** *J Clin Oncol* 2003;21(17):1232-7.

Liu W et al. **Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer.** *Nat Med* 2009;15(15):559-65.

Olmos D et al. **Prognostic value of blood mRNA expression signatures in castration-resistant prostate cancer: A prospective, two-stage study.** *Lancet Oncol* 2012;13(11):1114-24.

Ross RW et al. **A whole-blood RNA transcript-based prognostic model in men with castration-resistant prostate cancer: A prospective study.** *Lancet Oncol* 2012;13(11):1105-13.

Scher G et al. **Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): Planned final analysis (FA) of COU-AA-301, a randomized double-blind, placebo-controlled phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel.** *Proc ASCO* 2011;**Abstract LBA4517**.

Shaffer DR et al. **Circulating tumor cell analysis in patients with progressive castration-resistant prostate cancer.** *Clin Cancer Res* 2007;13(7):2023-9.

Sieuwerts AM et al. **Anti-epithelial cell adhesion molecule antibodies and the detection of circulating normal-like breast tumor cells.** *J Natl Cancer Inst* 2009;101(1):61-6.

Smaletz O et al. **Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration.** *J Clin Oncol* 2002;20(19):3972-82.