

Cases from the Community

Clinical Investigators Provide Their Perspectives on the Use of Immune Checkpoint Inhibitors in the Management of Actual Patients with Genitourinary Cancers

CME Information

TARGET AUDIENCE

This activity has been designed to meet the educational needs of medical oncologists and other allied healthcare professionals involved in the treatment of prostate cancer, urothelial bladder cancer and renal cell carcinoma (RCC).

OVERVIEW OF ACTIVITY

The past several years have seen an explosion in the emergence of new potential therapies that leverage the natural ability of the human body to attack and treat cancer. Known as immune-mediated therapies, or cancer immunotherapies, these promising treatments are taking center stage at medical conferences and generating excitement all over the world. Not surprisingly, with the many exciting advances rapidly occurring both within the field of genitourinary (GU) tumors and elsewhere, a number of vexing questions and clinical challenges are emerging simultaneously.

These proceedings from a CME symposium during the Genitourinary Cancers Symposium explore the most significant therapeutic advances in the field of immunotherapy by using the perspectives of leading GU cancer experts on challenging cases and questions submitted by clinicians in the community to frame a relevant discussion of how this information has aided in the refinement of current routine clinical practice and ongoing research. This CME activity will help medical oncologists and other allied healthcare professionals find answers to the individualized questions and concerns that they frequently encounter and in turn provide high-quality cancer care.

LEARNING OBJECTIVES

- Compare and contrast the mechanisms of action, efficacy and safety/toxicity of approved and investigational immunotherapies for the treatment of prostate cancer, RCC and bladder cancer to determine the current and/or potential utility of these agents in clinical practice.
- Appraise the rationale for and clinical data with approved anti-PD-1 and anti-PD-L1 antibodies in patients with metastatic RCC and bladder cancer, and use this information to select patients for treatment with an immune checkpoint inhibitor.
- Describe ongoing research to assist in the identification of biomarkers, tumor characteristics or other clinical features

that are indicative of response to immune checkpoint inhibitors in patients with GU cancers.

- Evaluate typical and atypical patterns of response to immune checkpoint inhibitors in an effort to identify patients who may or may not be benefiting from these agents.
- Recognize immune-related adverse events and other common side effects associated with approved and developmental immune checkpoint inhibitors, and use this information to develop supportive management plans for patients with GU cancers undergoing treatment with these agents.
- Consider available and emerging data with investigational anti-PD-1/PD-L1 antibodies alone or in combination with other systemic approaches currently in Phase II/III testing for select GU cancers, and, where applicable, refer eligible patients for trial participation or expanded access programs.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2.5 Medical Knowledge MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Please note, this program has been specifically designed for the following ABIM specialty: **medical oncology**.

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

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Consulting Agreements: Agenus Inc, Dendreon Pharmaceuticals Inc, Genentech BioOncology, ImmuneXcite, Janssen Biotech Inc, Lilly, Merck, NexImmune, Pierre Fabre, Roche Laboratories Inc; **Contracted Research:** Aduro Biotech, Bristol-Myers Squibb Company, Janssen Biotech Inc; **Patents:** AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Janssen Biotech Inc; **Stockholder:** Compugen, NexImmune, Potenza Therapeutics, Tizona Therapeutics Inc; **Other:** Bristol-Myers Squibb Company.

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Hardware/Software Requirements:

A high-speed Internet connection

A monitor set to 1280 x 1024 pixels or more

Internet Explorer 11 or later, Firefox 56 or later, Chrome 61 or later, Safari 11 or later, Opera 48 or later

Adobe Flash Player 27 plug-in or later

Adobe Acrobat Reader

(Optional) Sound card and speakers for audio

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Select Publications

Neil Love, MD

Goodman A et al. **Analysis of over 100,000 patients with cancer for CD274 (PD-L1) amplification: Implications for treatment with immune checkpoint blockade.** *Proc ASCO-SITC 2018;Abstract 47.*

Motzer RJ et al. **IMmotion151: A randomized phase III study of atezolizumab plus bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC).** *Genitourinary Cancers Symposium 2018;Abstract 578.*

Peter H O'Donnell, MD

Balar AV et al; IMvigor210 Study Group. **Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: A single-arm, multicentre, phase 2 trial.** *Lancet 2017;389(10064):64-76.*

Balar AV et al. **First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): A multicentre, single-arm, phase 2 study.** *Lancet Oncol 2017;18(11):1483-92.*

Bambury RM et al. **The safety and efficacy of single-agent pemetrexed in platinum-resistant advanced urothelial carcinoma: A large single-institution experience.** *Oncologist 2015;20(5):508-15.*

Bellmunt J et al. **Pembrolizumab for advanced urothelial carcinoma.** *N Engl J Med 2017;376(23):2304.*

Dogliotti L et al. **Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: Results of a randomized phase 2 trial.** *Eur Urol 2007;52(1):131-41.*

Patel MR et al. **Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): Pooled results from two expansion cohorts of an open-label, phase 1 trial.** *Lancet Oncol 2018;19(1):51-64.*

Pond GR et al. **Cabozantinib for metastatic castration-resistant prostate cancer (mCRPC) following docetaxel: Combined analysis of two phase III trials.** *Genitourinary Cancers Symposium 2018;Abstract 255.*

Powles T et al. **Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): A multicentre, open-label, phase 3 randomised controlled trial.** *Lancet 2017;[Epub ahead of print].*

Powles T et al. **Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: Updated results from a phase 1/2 open-label study.** *JAMA Oncol 2017;3(9):e172411.*

Powles T et al. **A phase 3 study of first-line durvalumab (MEDI4736) ± tremelimumab versus standard of care (SoC) chemotherapy (CT) in patients (pts) with unresectable Stage IV urothelial bladder cancer (UBC): DANUBE.** *Proc ASCO 2016;Abstract TPS4574.*

Sharma P et al. **Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial.** *Lancet Oncol 2017;18(3):312-22.*

Stadler WM et al. **Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer.** *J Clin Oncol 1997;15(11):3394-8.*

Sternberg CN et al. **Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium.** *J Urol 1985;133(3):403-7.*

Vaughn DJ et al. **Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer.** *J Clin Oncol 2002;20(4):934-40.*

von der Maase H et al. **Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter, phase III study.** *J Clin Oncol 2000;18(17):3068-77.*

Thomas Powles, MBBS, MRCP, MD

Escudier B et al. **CheckMate 214: Efficacy and safety of nivolumab + ipilimumab (N+I) v sunitinib (S) for treatment-naïve advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups.** *Proc ESMO 2017;Abstract LBA5.*

Fehrenbacher L et al; POPLAR Study Group. **Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial.** *Lancet 2016;387(10030):1837-46.*

Herbst RS et al. **Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients.** *Nature 2014;515(7528):536-7.*

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- McDermott DF et al. **A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) versus sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts).** *Proc ASCO 2017;Abstract 431.*
- Powles T et al. **IMmotion150: Novel radiological endpoints and updated data from a randomized phase II trial investigating atezolizumab (atezo) with or without bevacizumab (bev) vs sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC).** *Proc ESMO 2017;Abstract LBA39.*
- Powles T et al. **A randomized phase II study of AZ2014 versus everolimus in patients with VEGF refractory metastatic clear cell renal cancer (mRCC).** *Proc ASCO 2015;Abstract 409.*
- Wallin JJ et al. **Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma.** *Nat Commun 2016;7:12624.*
- David I Quinn, MBBS, PhD**
- Bakhom SF et al. **Chromosomal instability drives metastasis through a cytosolic DNA response.** *Nature 2018;553(7689):467-72.*
- Guedes LB et al. **MSH2 loss in primary prostate cancer.** *Clin Cancer Res 2017;23(22):6863-74.*
- Jain S et al. **Validation of a metastatic assay using biopsies to improve risk stratification in patients with prostate cancer treated with radical radiation therapy.** *Ann Oncol 2018;29(1):215-22.*
- Lemery S et al. **First FDA approval agnostic of cancer site — When a biomarker defines the indication.** *N Engl J Med 2017;377(15):1409-12.*
- Mulligan JM et al. **Identification and validation of an anthracycline/cyclophosphamide-based chemotherapy response assay in breast cancer.** *J Natl Cancer Inst 2014;106(1):djt335.*
- Parkes EE et al. **Activation of STING-dependent innate immune signaling by S-phase-specific DNA damage in breast cancer.** *J Natl Cancer Inst 2016;109(1):djw199.*
- Pritchard CC et al. **Complex MSH2 and MSH6 mutations in hypermutated microsatellite unstable advanced prostate cancer.** *Nature Comm 2014;5:4988.*
- Reilly E et al. **Exploration of the cGAS-STING pathway in prostate cancer.** *Proc ASCO-SITC 2018;Abstract 103.*
- Rosty C et al. **High prevalence of mismatch repair deficiency in prostate cancers diagnosed in mismatch repair gene mutation carriers from the colon cancer family registry.** *Fam Cancer 2014;13(4):573-82.*
- Scher HI et al. **Association of AR-V7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer.** *JAMA Oncol 2016;2(11):1441-9.*
- Walker SM et al. **Molecular subgroup of primary prostate cancer presenting with metastatic biology.** *Eur Urol 2017;72(4):509-18.*
- Charles G Drake, MD, PhD**
- Balar AV et al. **First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): A multicentre, single-arm, phase 2 study.** *Lancet Oncol 2017;18(11):1483-92.*
- Bellmunt J et al; KEYNOTE-045 Investigators. **Pembrolizumab as second-line therapy for advanced urothelial carcinoma.** *N Engl J Med 2017;376(11):1015-26.*
- Carbone DP et al; CheckMate 026 Investigators. **First-line nivolumab in stage IV or recurrent non-small-cell lung cancer.** *N Engl J Med 2017;376(25):2415-26.*
- Gandini S et al. **PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: A systematic review and meta-analysis.** *Crit Rev Oncol Hematol 2016;100:88-98.*
- McLaughlin J et al. **Quantitative assessment of the heterogeneity of PD-L1 expression in non-small-cell lung cancer.** *JAMA Oncol 2016;2(1):46-54.*
- Piha-Paul SA et al. **T-cell inflamed phenotype gene expression signatures to predict clinical benefit from pembrolizumab across multiple tumor types.** *Proc ASCO 2016;Abstract 1536.*
- Powles T et al. **MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer.** *Nature 2014;515(7528):558-62.*
- Rosenberg JE et al. **Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have**

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progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. *Lancet* 2016;387(10031):1909-20.

Socinski M et al. **CheckMate 026: A phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage IV/recurrent programmed death ligand 1 (PD-L1)-positive NSCLC.** *Proc ESMO* 2016;Abstract LBA7_PR.

Elizabeth R Plimack, MD, MS

Danlos FX et al. **Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease.** *Eur J Cancer* 2018;91:21-9.

Haanen JBAG et al; ESMO Guidelines Committee. **Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** *Ann Oncol* 2017;28(Supp 4):iv119-42.

Minchot JM et al. **Immune-related adverse events with immune checkpoint blockade: A comprehensive review.** *Eur J Cancer* 2016;54:139-48.

Richter MD et al. **Cancer immunotherapy in patients with preexisting rheumatologic disease: The Mayo Clinic experience.** *Arthritis Rheumatol* 2018;[Epub ahead of print].

Weber JS et al. **Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma.** *J Clin Onc* 2017;35(7):785-92.