

Pembrolizumab for Urothelial Carcinoma

An HCP Tool From the Immuno-Oncology Essentials Initiative

Pembrolizumab (Keytruda®) is an anti-programmed death receptor-1 (PD-1) monoclonal antibody checkpoint inhibitor. PD-1 is a negative regulator of T-cell activation and proliferation, meaning it “turns the immune response off,” essentially acting as a brake. This type of inhibitory role is necessary to prevent excessive immune reaction and autoimmunity. For this reason, PD-1 and other regulators acting in this manner are known as immune checkpoints. We now understand that some tumors can exploit the PD-1 pathway, enabling them to evade an immune response. Pembrolizumab selectively binds to PD-1, thus blocking the inhibitory pathway and releasing the immune system. This allows the immune response to occur.

Pembrolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and *whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10)*.

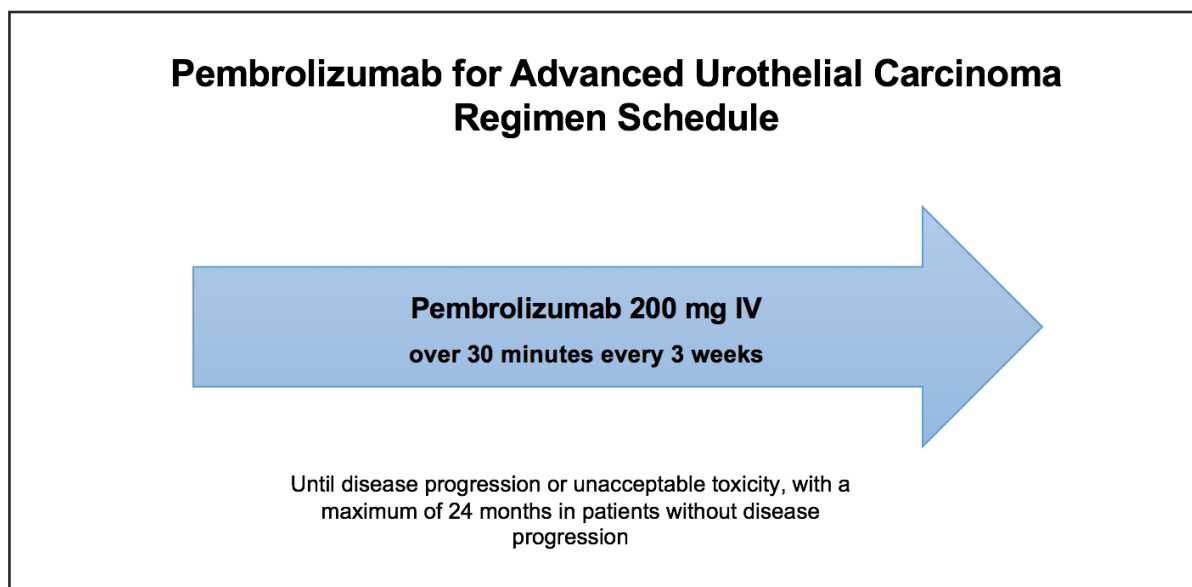
Pembrolizumab is also indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy *regardless of PD-L1 status*.

In addition, pembrolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *regardless of PD-L1 status*.

This document is part of an overall HCP toolkit to assist providers in optimizing management of urothelial carcinoma in patients receiving immunotherapy.

DRUG DOSAGE/ADMINISTRATION

- For locally advanced or metastatic urothelial carcinoma, the recommended dosage of pembrolizumab (Keytruda®) is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression



- Pembrolizumab solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed
- Pembrolizumab is provided as a 50 mg lyophilized powder in a single-dose vial for reconstitution or as a 100 mg/4 mL (25 mg/mL) solution in a single-dose vial. When reconstituting pembrolizumab for injection, slowly swirl the vial. Do NOT shake the vial
- Pembrolizumab is classified as an irritant and may be safely administered via a central or peripheral line. It is important to assure IV access before administration. Pembrolizumab should be administered through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line or add-on filter (pore size of 0.2 – 5 micrometers). Do not coadminister pembrolizumab with other drugs through the same intravenous line

SIDE EFFECTS AND THEIR MANAGEMENT

Because pembrolizumab is an immunotherapy that works by enhancing the patient’s immune system, most adverse reactions associated with pembrolizumab are related to overactivity of the patient’s immune system (ie, immune-related adverse events [irAEs]). Various organ systems (often more than one) or tissues may be affected.

- Keys to toxicity management:
 - » Proactive assessment for early signs/symptoms of toxicity
 - » Prompt intervention
 - » irAEs are typically managed with treatment interruption and selective use of corticosteroids
 - » In rare instances, toxicity may be steroid refractory, and additional immunosuppressive agents may be necessary (infliximab, mycophenolate mofetil, cyclophosphamide, etc)
 - » Pembrolizumab will likely be held or discontinued depending on severity and/or persistence
 - » Referral to organ specialist should be considered, given that unique testing and management strategies may be required
- irAEs associated with pembrolizumab treatment can be categorized into those that are most common, less common but serious, and others that are easily overlooked. (Table 1; Appendix 1). Other adverse events associated with pembrolizumab therapy are listed in Appendix 2

Table 1. Care Step Pathways for the management of immune-related AEs associated with pembrolizumab monotherapy.

irAE category	Examples	Location
Most common	Skin toxicities (pruritis, rash, etc) Gastrointestinal toxicity: Diarrhea and colitis Thyroiditis Hepatic toxicities	Appendix 1
Less common but serious	Additional endocrinopathies - Hypophysitis (pituitary) - Adrenal insufficiency (adrenalitis) - Diabetes Pneumonitis	Appendix 1
Easily overlooked	Arthralgia/arthritis Mucositis/xerostomia Neuropathy Nephritis	Appendix 1

CLINICAL PEARLS

- It is important to monitor laboratory values at the start of treatment, periodically during treatment, and as indicated clinically. Laboratory values commonly monitored include: CBC w/ differential, creatinine, alkaline phosphatase, AST/ALT, bilirubin (direct/total), sodium, potassium, calcium, magnesium, thyroid function, and glucose. See individual irAE CSPs for more detail on laboratory monitoring
- Pembrolizumab-related irAEs may occur at any time, including after treatment completion or discontinuation
- Patients sometimes experience signs/symptoms that they think are due to “flu” or a cold, but that actually represent an irAE or an infusion reaction
- Endocrinopathies often present with vague symptoms (fatigue, headache, and/or depression) that can easily be overlooked or initially misdiagnosed. Hypervigilance and follow-up is important on the part of both HCPs and patients
- Endocrinopathies tend to occur somewhat more commonly with pembrolizumab or other PD-1 inhibitor therapies than with ipilimumab monotherapy
- Unlike other irAEs, endocrinopathies usually do not resolve and may require lifelong hormone replacement therapy
- IrAEs have different time courses. New irAEs may become apparent upon tapering of corticosteroids used to treat an earlier onset irAE, since the new irAE can be suppressed or masked by immunosuppressive therapy. Therefore, during the taper period, patients should be advised to be on the lookout for early signs of new irAEs as well as recurrence of the original irAE that was being treated
- HCPs should encourage patients to carry information about their pembrolizumab regimen with them at all times. This might be the Immunotherapy Wallet Card from the Oncology Nursing Society, the pembrolizumab-specific wallet card, or at least emergency phone numbers and the side effects associated with the regimen. You may suggest that they paperclip the wallet and insurance cards together so information about their regimen will be shared whenever they show the insurance card
- Advise patients to take pictures of any skin changes for documentation

QUESTIONS & ANSWERS

Q. How long will patients stay on pembrolizumab?

A. The prescribing information indicates until disease progression or unacceptable toxicity. The interpretation of these criteria varies from institution to institution and from provider to provider.

Q. Is the testing for PD-L1 expression in urothelial cancer the same as it is in lung cancer?

A. When indicated, an FDA-approved test should be used. PD-L1 is measured and reported differently in urothelial cancer versus lung cancer. For the urothelial cancer indication requiring PD-L1 testing, the combined positive score (CPS) is used, which evaluates the number of PD-L1 staining cells (tumor cells & associated immune cells) relative to viable tumor cells. For lung cancer, only the tumor proportion score is used, measuring tumor cells showing partial or complete membrane staining at any intensity. A CPS ≥ 1 is considered a positive PD-L1 test.

Q. Are there standard dosage reductions for irAEs associated with pembrolizumab?

A. There are no dosage reductions for irAEs associated with pembrolizumab. The dose is either held until the irAE resolves sufficiently (typically to Grade 0 or Grade 1) or, if the irAE is severe enough, pembrolizumab is discontinued permanently.

Q. Does the safety profile of pembrolizumab differ when it is used in various tumor types?

A. Generally, the safety profile of pembrolizumab is similar across tumor types. However, the context may be different—patients with other tumor types may have differing comorbidities or underlying organ dysfunction. For example, lung cancer patients may have underlying lung disease that will exacerbate shortness of breath associated with pneumonitis.

Q. How do I counsel my patients about immunizations?

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QUESTIONS & ANSWERS

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- A.** That's a logical question, given that the checkpoint inhibitors alter the immune response. Advise your patients not to receive live vaccines (eg, measles, mumps, and rubella and the varicella vaccine [Zostavax[®]]) because they have not been evaluated in this setting. The use of attenuated vaccines has been and continues to be evaluated. Counsel patients to discuss all immunizations with the oncology team prior to administration so the benefits and risks can be weighed on an individual basis. For example, SHINGRIX[®], approved in 2017, is an attenuated (non-live) varicella vaccine; its use be discussed with the oncology team if a recommendation is being made for the patient to receive the injection series. Annual influenza vaccination with the inactivated influenza vaccine is recommended. The nasal spray flu vaccine is a live attenuated influenza vaccine and should not be administered to patients treated with immune checkpoint inhibitors.

PATIENT RESOURCES

Financial Assistance

The Merck Access Program

1-855-257-3932

www.keytruda.com/keytruda-cost/

Additional Information Resources

Bladder Cancer Advocacy Network

<http://www.bcan.org>

American Cancer Society Resource Section

<http://www.cancer.org/cancer/bladder-cancer/treating/immunotherapy-for-bladder-cancer.html>

ADDITIONAL RESOURCES

- Balar AV, Castellano D, O'Donnell PH, 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;18:1483-1492.
- Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol.* 2017;4:173-182.
- Bellmunt J, de Wit R, Vaughn DJ, et al. KEYNOTE-045 Investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med.* 2017;376:1015-1026.
- Belum VR, Benjuri B, Postow MA, et al. Characterization and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer.* 2016;60:12-25.
- Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol.* 2016;13:473-486.
- Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2018;36:1-60.
- Cappelli LC, Gutierrez AK, Baer AN, et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis.* 2017;76:43-50.
- Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol.* 2016;27:559-574.
- Corsello SM, Barnabei A, Marchetti P, et al. Endocrine side effects induced by immune checkpoint inhibitors. *J Endocrinol Metab.* 2013;98:1361-1375.
- Dadu R, Zobniw C, Diab A. Managing adverse events with immune checkpoint agents. *Cancer J.* 2016;22:121-129.
- Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol.* 2016;2:1346-1353.

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ADDITIONAL RESOURCES

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- Garcia-Neuer M, Marmarelis ME, Jangi SR, et al. Diagnostic comparison of CT scans and colonoscopy for immune-related colitis in ipilimumab-treated advanced melanoma patients. *Cancer Immunol Res.* 2017;5:286-291.
- Gonzalez-Rodriguez E, Rodriguez-Abreu D, et al. Immune checkpoint inhibitors: review and management of endocrine adverse events. *The Oncologist.* 2016;21:804-816.
- Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28(Suppl 4):119-142.
- Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side effects of anti-PD-1 therapy. *Eur J Cancer.* 2016;60:190-209.
- Keytruda® [package insert]. Whitehouse, NJ: Merck & Co., Inc.; 2017.
Available at: http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.
- Keytruda® wallet card. <https://www.keytruda.com/static/pdf/patient-wallet-card.pdf>
- Kottschade L, Brys A, Peikert T, et al. A multidisciplinary approach to toxicity management of modern immune checkpoint inhibitors in cancer therapy. *Melanoma Res.* 2016; 26:469-480.
- Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol.* 2017;8:49. doi: 10.3389/fphar.2017.00049
- McGettigan S, Rubin KM. Managing adverse events with PD-1 inhibitor therapy of advanced melanoma: consensus statements from the faculty of the melanoma nursing initiative. *Clin J Oncol Nurs.* 2017;21(Suppl):42-51.
- Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: A comprehensive review. *Eur J Cancer.* 2016;54:139-148.
- Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint inhibitor antibodies. *Ann Oncol.* 2015;26:2375-2391.

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ADDITIONAL RESOURCES

Continued

- National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities. Version 1.2018. Fort Washington, PA: National Comprehensive Cancer Network; 2018.
- Nishino M, Giobbe-Hurder A, Hatabu H, Ramaiya R, Hodi S. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Oncol.* 2016; 2453:E1-E10.
- Oncology Nursing Society (ONS). Immunotherapy Wallet Cards. <http://www.ons.org/store/accessories/immunotherapy-wallet-cards>
- Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer.* 2017;5:95. doi: 10.1186/s40425-017-0300-z
- Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev.* 2016;44:51-60.
- Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Trans Lung Cancer Res.* 2015;4:560-577.
- Weber JS, Postow M, Lao CD, Schadendorf D. Management of adverse events following treatment with anti-programmed death-1 agents. *Oncologist.* 2016;21:1230-1240.
- Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer.* 2016;60:210-225.

Click here for downloadable action plans to customize for your patients

APPENDIX 1

The 12 Care Step Pathways (CSPs) referenced in this Appendix are housed in the CSP section of the AIMWithImmunotherapy.com IO Essentials website. These CSP are currently universally applicable (i.e., they don't differ across tumor types).

Please click the link below to access the CSPs, which can also be printed from that section of the site.

<http://aimwithimmunotherapy.org/care-step-pathways/>

APPENDIX 2

Management of other AEs associated with pembrolizumab monotherapy

Adverse event	Common symptoms	Common management/anticipatory guidance
Anorexia	Decreased appetite	<ul style="list-style-type: none"> • Monitor weight; query patient about appetite/eating habits; advise dietary modification if necessary (should improve with time) • Anticipate standard dose holds/discontinuations* • Consider referral to nutrition services for counseling on best food choices to avoid excessive weight loss
Constipation/ abdominal pain	Infrequent stools/ difficulty stooling, abdominal pain	<ul style="list-style-type: none"> • Consider other causes, such as opioid-induced constipation • Increase fluid, fiber; use laxatives with caution; suggest stool softeners and physical activity • Consider appropriate testing to evaluate bowel obstruction • Anticipate standard dose holds/discontinuations* for Grade 3 and Grade 4 (constipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences)
Embryo-fetal toxicity	—	<ul style="list-style-type: none"> • Advise of risk to fetus and recommend use of effective contraception during treatment and for 4 months after pembrolizumab is discontinued • Advise patients to tell their HCPs immediately if they or their partners suspect they are pregnant while taking therapy
Encephalitis	Headache, fever, tiredness, confusion, memory problems, sleepiness, hallucinations, seizures, stiff neck	<ul style="list-style-type: none"> • New-onset, moderate-to-severe symptoms: rule out infectious or other causes • Counsel neurologist, obtain brain MRI, and lumbar puncture • Anticipate standard dose-holds and discontinuations*
Fatigue	Feeling tired; lack of energy	<ul style="list-style-type: none"> • Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematological and metabolic abnormalities; standard supportive care • Anticipate standard dose holds/discontinuations* • Fatigue that interferes with ADLs is concerning and should be evaluated for underlying causes, such as possible endocrinopathy
Headache	Head pain	<ul style="list-style-type: none"> • Need to rule out brain metastases, encephalitis, or hypophysitis; otherwise, standard supportive care (should improve with time) • Headache occurring in conjunction with fatigue could be indicative of hypophysitis; obtain MRI of brain with pituitary slices/pituitary protocol to confirm/rule out • Anticipate standard dose holds/discontinuations*

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Management of other AEs associated with pembrolizumab monotherapy (Continued)

Adverse event	Common symptoms	Common management/anticipatory guidance
Infusion reaction	Chills/shaking, back pain, itching, flushing, difficulty breathing, hypotension, fever	<ul style="list-style-type: none"> • Monitor patients for signs and symptoms. For grade 3 or 4 reactions: stop infusion and permanently discontinue pembrolizumab
Insomnia	Difficulty falling or staying asleep	<ul style="list-style-type: none"> • Counsel patients on good sleep habits; prescription medications can be used if needed (should improve over time) • Anticipate standard dose holds/discontinuations*
Myocarditis	Shortness of breath; arrhythmia; light-headedness; chest pain; fatigue; nausea; edema	<ul style="list-style-type: none"> • Obtain baseline ECG • Assess cardiac biomarkers (BNP; troponin) • Control cardiac diseases (and risk factors) optimally • Consult cardiologist and consider corticosteroids if myocarditis is suspected • Add additional immunosuppressive agents in severe, refractory cases • Institute standard dose holds/discontinuations (in consultation with cardiologist)
Nausea/vomiting	Vomiting, queasiness, RUQ or LUQ pain	<ul style="list-style-type: none"> • Rule out brain metastases and gastroenteritis • Provide standard supportive care, since it is adequate in most cases • Check LFTs/lipase/amylase if hepatotoxicity or pancreatitis are suspected • Anticipate standard dose holds/discontinuations*
Upper respiratory tract infection	Cough, runny nose, sore throat, nasal congestion	<ul style="list-style-type: none"> • Evaluate potential causes—a dry cough and shortness of breath would increase concern for pneumonitis • Standard supportive care • Anticipate standard treatment holds*
Vision changes	Eye redness, pain, blurred vision, photophobia	<ul style="list-style-type: none"> • Test and evaluate for uveitis and episcleritis (by ophthalmologist, preferably) • Urgency of ophthalmology referral increases with grade • G1: continue immunotherapy, use artificial tears • G2: hold immunotherapy; ophthalmic and systemic corticosteroids (under ophthalmologist guidance) • G3 or G4: permanently discontinue immunotherapy; treatment by ophthalmologist to include ophthalmic and systemic corticosteroids

*Withhold pembrolizumab for any Grade 3 (severe) AE. Permanently discontinue for any Grade 4 (life-threatening) AE, persistent Grade 2–3 AE, any severe (Grade 3) AE that recurs, or when ≥ 10 mg/d prednisone or equivalent is required for 12 weeks. Resume treatment when AE returns to Grade 0 or 1.