

## **Pembrolizumab**

An HCP Tool from AIM with Immunotherapy

Pembrolizumab (Keytruda®) is an anti-programmed death receptor-1 (PD-1) monoclonal antibody that binds to PD-1, a checkpoint inhibitor control. PD-1 is a negative regulator of T-cell activation and proliferation, meaning PD-1 engagement will turn the immune response off, essentially acting as a brake. For this reason, PD-1 and other regulators acting in this manner are known as immune checkpoints.

This type of inhibitory role is necessary for a normal system to prevent an excessive immune reaction and potentially lethal autoimmune response. Unfortunately, some tumors can exploit the PD-1 pathway, enabling them to evade an immune response by engaging the shut-off actions of PD-1. Pembrolizumab selectively binds to PD-1, thus physically blocking the engagement of PD-1 and preventing the immune system from being shut off by tumor cells. This allows the immune response to recognize the tumor cells and take action.

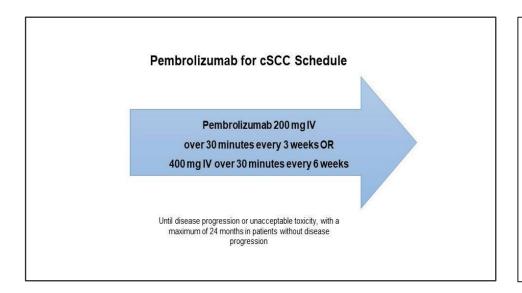
Pembrolizumab has over 41 indications in 20 tumor types. It is approved for the treatment of Stage IIB, IIC, and III melanoma; advanced melanoma; advanced non-small cell lung cancer; advanced malignant pleural mesothelioma; head and neck squamous cell cancer; relapsed or refractory classical Hodgkin lymphoma; refractory primary mediastinal large B-cell lymphoma; advanced Merkel cell carcinoma; metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors; advanced renal cell carcinoma; MSI-H, dMMR or advanced endometrial carcinoma; advanced tumor mutational burden-high solid tumors; advanced cutaneous squamous cell carcinoma; triple negative breast cancer; urothelial cancer; MSI-H or dMMR colorectal cancer; gastric or gastroesophageal junction adenocarcinoma; advanced esophageal cancer; advanced cervical cancer; hepatocellular carcinoma; and advanced biliary tract cancer.

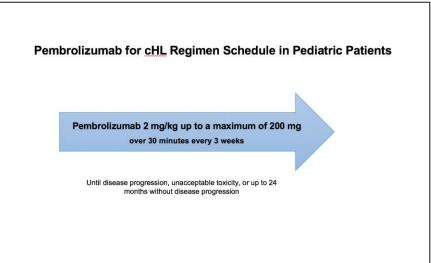
This document is part of an overall provider toolkit intended to assist in optimizing management of pembrolizumab in patients receiving this therapy.



# DRUG DOSAGE/ADMINISTRATION

- In many types of cancer, the recommended dosage of pembrolizumab (Keytruda®) is 200 mg every 3 weeks or 400 mg every 6 weeks, administered as an intravenous infusion over 30 minutes for up to 24 months. The examples pictured below are for cutaneous squamous cell carcinoma (left) and pediatric classical Hodgkin lymphoma (right).
- For more specifics, the tables on the next several pages outline the differences between pembrolizumab's indications.





- 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



Cancer	Indication	Testing Required?	Dosage & Administration
Biliary Tract Cancer	Comb. w/gemcitabine and cisplatin for the treatment of locally advanced unresectable or metastatic biliary tract cancer		200 mg every 3 weeks or 400 mg every 6 weeks
Cervical Cancer	Comb. w/chemoradiotherapy for the treatment of FIGO 2014 Stage III -IVA cervical cancer; Comb. w/chemo, with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1); Single agent for the treatment of recurrent or metastatic cervical cancer with disease progression on or after chemo whose tumors express PD -L1		200 mg every 3 weeks or 400 mg every 6 weeks
Classical Hodgkin Lymphoma	Adult patients with relapsed or refractory cHL; Pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy		200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics
Cutaneous Squamous Cell Carcinoma	Recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation		200 mg every 3 weeks or 400 mg every 6 weeks
Endometrial Carcinoma	Comb. w/carboplatin and paclitaxel, followed by pembro as a single agent for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma; Comb. w/lenvatinib for the treatment of advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation; Single agent for the treatment of advanced endometrial carcinoma that is MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation		200 mg every 3 weeks or 400 mg every 6 weeks in comb. w/chemo regardless of MMR or MSI status, or in combination with lenvatinib 20 mg orally once daily for pMMR or not MSI -H tumors, or as a single agent for MSI-H or dMMR tumors
Esophageal Cancer	Esophageal chemoradiation either: in comb w/ chemo or as a Positive or 4		200 mg every 3 weeks or 400 mg every 6 weeks



Cancer	Indication	Testing Required?	Dosage & Administration
Gastric Cancer	Comb. w/trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD -L1; Comb. w/chemo for first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma		200 mg every 3 weeks or 400 mg every 6 weeks
Head and Neck Squamous Cell Cancer	Comb. w/chemo for first-line treatment of metastatic or unresectable, recurrent HNSCC; Single agent for first-line treatment of metastatic or unresectable, recurrent HNSCC whose tumors express PD-L1; Single agent for the treatment of recurrent or metastatic HNSCC with disease progression on or after chemo	PD -L1 [Combined Positive Score (CPS) ≥1]	200 mg every 3 weeks or 400 mg every 6 weeks
Hepatocellular Carcinoma	Hepatocellular carcinoma secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen		200 mg every 3 weeks or 400 mg every 6 weeks
Malignant Pleural Mesothelioma	Comb. w/chemo for first -line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma		200 mg every 3 weeks or 400 mg every 6 weeks
Melanoma	Unresectable or metastatic melanoma; adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection		200 mg every 3 weeks or 400 mg every 6 weeks; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics
Merkel Cell Carcinoma	Adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma		200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics
MSI-H or dMMR solid tumor	Adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, that have progressed following prior treatment and who have no satisfactory alternative treatment options  Microsat instabil high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, that repair deficient deficient (dMMR)		200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics
MSI-H or dMMR colorectal cancer	Unresectable or metastatic MSI -H or dMMR colorectal cancer		200 mg every 3 weeks or 400 mg every 6 weeks



Cancer	Indication	Testing Required?	Dosage & Administration
Non-small Cell Lung Cancer (NSCLC)	Comb. w/chemo, as first-line for metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations; Comb. w/chemo, as first-line treatment of metastatic squamous NSCLC; Single agent for the first-line NSCLC expressing PD -L1, w/no EGFR or ALK genomic tumor aberrations, and is Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic; Single agent for metNSCLC whose tumors express PD -L1, with disease progression after chemo; Patients with EGFR or ALK genomic tumor aberrations w/disease progression; Resectable NSCLC in comb. w/neoadj chemo, and then continued as an adjuv single agent after surgery; Adjuv single agent following resection and chemo for Stage IB, II, or IIIA.	ALK, EGFR, PD -L1 [Tumor Proportion Score (TPS) ≥1%]	200 mg every 3 weeks or 400 mg every 6 weeks
Primary Mediastinal Large B-Cell Lymphoma	Adult and pediatric patients with refractory PMBCL or who have relapsed after 2 or more prior lines of therapy; Limitations of use: not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.		200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics
Renal Cell Carcinoma	Comb. w/axitinib for the first -line treatment of advanced renal cell carcinoma (RCC); Comb. w/lenvatinib for first-line treatment of adult patients with advanced RCC; Adjuv treatment of RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions		200 mg every 3 weeks or 400 mg every 6 weeks as a single agent in the adjuv setting, or in the advanced setting with either: axitinib 5 mg orally twice daily or lenvatinib 20 mg orally once daily



Cancer	Indication	Testing Required?	Dosage & Administration
Triple- negative Breast Cancer	High-risk early-stage triple-negative breast cancer (TNBC) in comb. w/chemo as neoadj treatment, and then continued as a single agent as adjuv treatment after surgery; Comb. w/chemo for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD -L1	PD -L1 [Combined Positive Score (CPS ≥10)]	200 mg every 3 weeks or 400 mg every 6 weeks
Tumor Mutational Burden-High Cancer	Adult and pediatric patients with unresectable or metastatic tumor mutational burden -high (TMB-H) solid tumors, that have progressed following prior treatment and who have no satisfactory alternative treatment options	Tumor mutational burden - high (TMB- H) [≥10 mutations /megabase (mut/Mb)]	200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics
Urothelial Cancer	Comb. w/enfortumab vedotin, for the treatment of adults with locally advanced or metastatic cancer; Single agent for the treatment of locally advanced or metastatic urothelial carcinoma: who are not eligible for any platinum-containing chemo, or who have disease progression during or following chemo or within 12 months of neoadj or adjuv treatment with platinum-containing chemo; Single agent for the treatment of patients with Bacillus Calmette -Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.		200 mg every 3 weeks or 400 mg every 6 weeks



## 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
  - o » 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.

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

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



### Management of other AEs associated with pembrolizumab monotherapy

Adverse event	Common symptoms	Common management/anticipatory guidance
Anorexia	Decreased appetite	Monitor weight; query patient about appetite/eating habits; advise dietary modification if necessary (should improve with time)
AHOIGAIA	Decreased appenie	Anticipate standard dose holds/discontinuations*
		Consider referral to nutrition services for counseling on best food choices to avoid excessive weight loss
Constipation/	Infrequent stools/	Consider other causes, such as opioid-induced constipation     Increase fluid, fiber; use laxatives with caution; suggest stool softeners and physical activity
abdominal pain	difficulty stooling, abdominal pain	Consider appropriate testing to evaluate bowel obstruction
	accomma pani	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> <li>Advise of risk to fetus and recommend use of effective contraception during treatment and for 4 months after pembrolizumab is discontinued</li> <li>Advise patients to tell their HCPs immediately if they or their partners suspect they are pregnant while taking therapy</li> </ul>
Encephalitis	Headache, fever, tiredness, confusion, memory problems, sleepiness, hallucinations, seizures, stiff neck	New-onset, moderate-to-severe symptoms: rule out infectious or other causes     Consult neurologist, obtain brain MRI, and lumbar puncture     Anticipate standard dose-holds and discontinuations*
Fatigue	Feeling tired; lack of energy	<ul> <li>Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematological and metabolic abnormalities; standard supportive care</li> <li>Anticipate standard dose holds/discontinuations*</li> <li>Fatigue that interferes with ADLs is concerning and should be evaluated for underlying causes, such as possible endocrinopathy</li> </ul>
Headache	Head pain	<ul> <li>Need to rule out brain metastases, encephalitis, or hypophysitis; otherwise, standard supportive care (should improve with time)</li> <li>Headache occurring in conjunction with fatigue could be indicative of hypophysitis; obtain MRI of brain with pituitary slices/pituitary protocol to confirm/rule out</li> <li>Anticipate standard dose holds/discontinuations*</li> </ul>



### Management of other AEs associated with pembrolizumab monotherapy

Adverse event	Common symptoms	Common management/anticipatory guidance
Infusion reaction	Chills/shaking, back pain, itching, flushing, difficulty breathing, hypotension, fever	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> <li>Counsel patients on good sleep habits; prescription medications can be used if needed (should improve over time)</li> <li>Anticipate standard dose holds/discontinuations*</li> </ul>
Myocarditis	Shortness of breath; arrhythmia; light- headedness; chest pain; fatigue; nausea; edema	<ul> <li>Obtain baseline ECG</li> <li>Assess cardiac biomarkers (BNP; troponin)</li> <li>Control cardiac diseases (and risk factors) optimally</li> <li>Consult cardiologist and consider corticosteroids if myocarditis is suspected</li> <li>Add additional immunosuppressive agents in severe, refractory cases</li> <li>Institute standard dose holds/discontinuations (in consultation with cardiologist)</li> </ul>
Nausea/vomiting	Vomiting, queasiness, RUQ or LUQ pain	<ul> <li>Rule out brain metastases and gastroenteritis</li> <li>Provide standard supportive care, since it is adequate in most cases</li> <li>Check LFTs/lipase/amylase if hepatotoxicity or pancreatitis are suspected</li> <li>Anticipate standard dose holds/discontinuations*</li> </ul>
Upper respiratory tract infection	Cough, runny nose, sore throat, nasal congestion	<ul> <li>Evaluate potential causes—a dry cough and shortness of breath would increase concern for pneumonitis</li> <li>Standard supportive care</li> <li>Anticipate standard treatment holds*</li> </ul>
Vision changes	Eye redness, pain, blurred vision, photophobia	<ul> <li>Test and evaluate for uveitis and episcleritis (by ophthalmologist, preferably)</li> <li>Urgency of ophthalmology referral increases with grade</li> <li>G1: continue immunotherapy, use artificial tears</li> <li>G2: hold immunotherapy; ophthalmic and systemic corticosteroids (under ophthalmologist guidance)</li> <li>G3 or G4: permanently discontinue immunotherapy; treatment by ophthalmologist to include ophthalmic and systemic corticosteroids</li> </ul>

\*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.



## **CLINICAL PEARLS**

- Programmed cell death ligand 1 (PD-L1) status or elevated expression is not a prerequisite for pembrolizumab treatment of cSCC, as it is for some lung-cancer indications
- 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
- 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 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 for up to 24 months. The interpretation of these criteria varies from institution to institution and from provider to provider.

### Q. Is PD-L1 testing required for patients to be eligible to receive pembrolizumab?

A. Some, but not all, cancer types require testing. PD-L1 testing is recommended for all patients diagnosed with recurrent or metastatic cancer. PD-L1 expression by an FDA-approved test is required to receive pembrolizumab. The FDA concurrently approved PD-L1 IHC 22C3 pharmDx as a companion diagnostic.

### Q. How do we test for MSI and MMR?

A. Polymerase chain reaction for MSI and immunohistochemistry for MMR can be requested to identify patients appropriate for treatment with pembrolizumab. Your pathologist may be able to perform the testing in your hospital/laboratory or may need to request testing from a reference lab.

### 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. In addition, patients with melanoma may experience a higher proportion of vitiligo than patients with other tumor types. For patients who have cHL patients who have previously undergone allogeneic HCT, it is important to monitor for hyperacute graft versus host disease after treatment with pembrolizumab.



### Q. How do I counsel my patients about immunizations?

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 should 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 and has been found to be safe for patients receiving immune checkpoint inhibitors. The nasal spray flu vaccine is a live attenuated influenza vaccine and should not be administered to patients treated with immune checkpoint inhibitors.

# Q. How is a pembrolizumab-induced rash different from an EGFR-induced rash seen with cetuximab or panitumumab?

A. Generally, and EGFR-induced rash manifests earlier, is more macular-papular, less puritic and responsive to the STEPP skin protocol. A rash induced from pembrolizumab tends to be more puritite with tightness/burning sensation, responds to oral corticosteroids, and can occur at any point during treatment.

# Q. What are the differences between oxaliplatin-induced peripheral neuropathy (PN) and nerve problems see with pembrolizumab?

A. Oxaliplatin PN tends to happen on the hands and feet with tingling and numbness. Pembrolizumab-induced nerve problems manifest as unilateral weakness and difficulty walking, but can also manifest with worsening numbness/tinglings/functional impairment. It is imperative to ascertain baseline neurological deficits prior to initiating pembrolizumab for appropriate evaluation of worsening symptoms.



## **ADDITIONAL RESOURCES**

- Belum VR, Benhuri 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.
- Böger C, Behrens HM, Mathiak M, Krüger S, Kalthoff H, Röcken C. PD-L1 is an independent prognostic predictor in gastric cancer of Western patients. *Oncotarget*. 2016;7:24269- 24283.
- Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology. 2010;138:2073-2087.
- Boland PM, Ma WW. Immunotherapy for colorectal cancer. Cancers (Basel). 2017 May 11;9(5).
   pii: E50. doi: 10.3390/cancers9050050
- 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.
- Chen R, Zinzani PL, Fanale MA, et al; KEYNOTE-087. Phase II study of the efficacy and safety
  of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol*.
  2017;35:2125-2132.
- Chong CR, Park VJ, Cohen B et al. Safety of inactivated influenza vaccine in cancer patients receiving immune checkpoint inhibitors, *Clin Infect Dis.*, 2020;70:193-199.
- 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.
- Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction
- cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol. 2018 Mar 15. doi: 10.1001/jamaoncol.2018.0013
- Geiger JL, Daniels GA, Cohen EEW et al. KEYNOTE-630: Phase 3 study of adjuvant pembrolizumab versus placebo in patients with high-risk, locally advanced cutaneous squamous cell carcinoma. *J Clin Oncol*. 2019 37:15\_suppl, TPS9597-TPS9597
- Haanen JBAG, Carbonnel F, Robert C, et al; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;289(suppl 4):iv119-iv142.
- Haverkos BM, Abbott D, Hamadani M, et al. PD-1 blockade for relapsed lymphoma post—allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. *Blood*. 2017;130: LP-228.
- 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<sup>®</sup> [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



## **ADDITIONAL RESOURCES**

- Koopman M, Kortman GA, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *Br J Cancer*. 2009;100:266-273.
- Kottschade L, Brys A, Peikert T, et al; Midwest Melanoma Partnership. 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
- Langer CJ, Gadgeel SM, Borghaei H, et al, for the KEYNOTE-021 investigators. Carboplatin
  and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell
  lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet
  Oncol. 2016;17:1497–1508.
- Le DT, Uram JN, Wang H, et al. PD-1 blockage in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509-2520.
- 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.
- 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.
- Nishijima TF, Shachar SS, Nyrop KA, Muss HB. Safety and tolerability of PD-1/PD-L1 inhibitors compared with chemotherapy in patients with advanced cancer: a meta-analysis. *Oncologist*. 2017;22:470-479.
- O'Neil BH, Wallmark JM, Lorente D, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma. *PLoS One*. 2017;12(12):e0189848.
- 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
- Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol.* 2016;17:956-965.
- 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.



## **PATIENT RESOURCES**

#### ADDITIONAL INFORMATION RESOURCES

**AIM at Melanoma Foundation** (Ask an Expert program, patient symposia, drug resources, etc) https://www.aimatmelanoma.org/

**AIM at Skin Cancer Foundation** (Ask a Skin Cancer Nurse, patient symposia, drug resources, webinars, etc) <a href="https://aimatskincancer.org/">https://aimatskincancer.org/</a>

American Cancer Society https://www.cancer.org/

#### **FINANCIAL ASSISTANCE**

#### The Merck Access Program

1-855-257-3932

www.keytruda.com/keytruda-cost/

#### **Cancer Financial Aid Coalition**

Facilitates communication, educates and advocates for patients.

www.cancerfac.org

#### **Centers for Medicare and Medicaid Services (CMS)**

Apply to determine if you are eligible for government assistance.

www.cms.gov or www.medicare.gov

800-633-4227

#### **Lazarex Foundation**

Provides assistance with travel costs for clinical trial participation. Ask your social work counselor for a referral if you have been consented to a clinical trial for melanoma.

www.lazarex.org

#### Needymeds

Database to search for free or low-cost medications, help with medical transportation and other resources. www.needymeds.org

#### **Patient Advocate Foundation**

Provides assistance with mediation, financial stability, and other assistance. Funds subject to availability. Patient must meet their eligibility for financial assistance.

www.patientadvocate.org

800-532-5274

#### The Sam Fund for Young Adult Survivors of Cancer

Assists cancer survivors ages 21-39 with their transition into post-treatment life. This program distributes grants and scholarships in an effort to enable survivors to pursue goals.

www.thesamfund.org

info@thesamfund.org



#### PRESCRIPTION ASSISTANCE

#### **CancerCare Co-Payment Assistance Foundation**

Helps with the cost of medication. Availability of funds for patients subject to availability.

www.cancercarecopay.org

1-866-552-6729

#### **Medicine Assistance Tool**

Database to search for patient assistance resources offered by pharmaceutical companies. www.medicineassistancetool.org/

#### **Patient Advocate Foundation Co-Pay Relief**

Provides direct financial support to patients who medically qualify. Availability of funds for patients subject to availability.

www.copays.org

1-866-512-3861

#### **Good Days**

Formerly known as the Chronic Disease Fund. Provides assistance with insurance co-pays, and prescription medications. Availability of funds for patients subject to availability. www.mygooddays.org

#### **HealthWell Foundation**

For patients who cannot afford insurance premiums, co-payments, co-insurance, or other out-of-pocket health care costs. Availability of funds for patients subject to availability. Patient must also meet eligibility for financial assistance.

www.healthwellfoundation.org or grants@healthwellfoundation.org

1-800-675-8416

#### The Assistance Fund, Inc

Provides prescription copay and financial assistance, including health insurance premiums. Availability of funds for patients subject to availability.

www.theassistancefund.org

1-855-845-3663

#### **PAN Foundation**

Provides financial assistance to cover out-of-pocket treatment costs. Availability of funds for patients subject to availability.

www.panfoundation.org

1-866-316-PANF (7263)

#### **Patient Assistance Program**

Comprehensive database of patient assistance programs offering free medications.

www.rxassist.org

info@rxassist.org



#### HOUSING

#### **American Cancer Society – Hope Lodge**

Provides free housing during treatment appointments. Requires a referral from your social worker. <a href="https://www.cancer.org/">www.cancer.org/</a>

1-800-227-6333

#### TRANSPORTATION (AIR AND GROUND)

#### Medicaid

Ground transportation only. Sets up rides and provides mileage reimbursement for Medicaid patients only.

1-877-633-8747

#### **Mercy Medical Angels**

Provides free medical transportation (flights, gas cards, bus and train tickets) for patients with financial needs who need to travel more than 50 miles. Patients must meet their eligibility for financial assistance. <a href="https://www.mercymedical.org/">www.mercymedical.org/</a>

#### **Pilots for Patients**

Provides free flights to people in need of medical treatment. Patient must be medically stable to fly and be ambulatory. Ask your social worker about a referral.

www.pilotsforpatients.org

318-322-5112