Pembrolizumab and berahyaluronidase alfa-pmph

An HCP Tool from AIM with Immunotherapy

Pembrolizumab 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.

Berahyaluronidase alfa enhances dispersion and permeability to enable subcutaneous administration of pembrolizumab. This is different from pembrolizumab, which is typically administered intravenously.

Pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX) is indicated 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; 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; advanced biliary tract cancer, and advanced ovarian cancer.

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

DRUG DOSAGE/ADMINISTRATION

The recommended dose for adults and pediatric patients 12 years and older who weigh greater than 40 kg is as follows:

- Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa): inject 2.4 mL subcutaneously over 1 minute.
- Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa): inject 4.8 mL subcutaneously over 2 minutes.
- Treatment duration/timing of treatment is dependent on the indication.

For more specifics, the tables on the next several pages outline the different indications.

KEYTRUDA QLEX has different recommended dosage and administration instructions than intravenous pembrolizumab.

- To reduce the risk of medication errors, check the vial labels to ensure that the drug being prepared and administered is KEYTRUDA QLEX for subcutaneous use and not intravenous pembrolizumab.
- Do not substitute KEYTRUDA QLEX with intravenous pembrolizumab because they have different recommended dosages and routes of administration.
- Patients receiving intravenous pembrolizumab can switch to subcutaneous KEYTRUDA QLEX at their next scheduled dose.
- Patients receiving subcutaneous KEYTRUDA QLEX can switch to intravenous pembrolizumab at their next scheduled dose.
- Administer KEYTRUDA QLEX as a subcutaneous injection into the thigh or abdomen, avoiding the 5 cm area around the navel.

Inject into healthy skin and never into areas where the skin is red, bruised, tender, or hard. Ensure the injection site is at least 2.5 cm from the previous injection site.

During treatment with KEYTRUDA QLEX, do not administer other medications for subcutaneous use at the same site as KEYTRUDA QLEX.

Do not administer KEYTRUDA QLEX intravenously.

KEYTRUDA QLEX must be administered by a healthcare provider.

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Dosing & Administration for FDA-Approved Indications

Cancer	Indication	Testing Required?	Dosage & Administration
Biliary Tract Cancer	Comb. with gemcitabine and cisplatin for the treatment of adult patients with locally advanced unresectable or metastatic biliary tract cancer		Every 3-week dosing 395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing 790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer prior to chemotherapy when given on the same day
Cervical Cancer	Comb. with chemoradiotherapy for the treatment of adult patients with FIGO 2014 Stage III-IVA cervical cancer; Comb. with chemotherapy, with or without bevacizumab, for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS≥1); Single agent for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemorapythe whose tumors express PD-L1 (CPS≥1)	PD -L1 [Combined Positive Score (CPS) ≥1]	Every 3-week dosing 395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing 790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer prior to chemoradiotherapy or prior to chemotherapy with or without bevacizumab when given on the same day.
Cutaneous Squamous Cell Carcinoma	Single agent for adult patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation		Every 3-week dosing 395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing 790 mg pembrolizumab/9,600 units berahyaluronidase alfa
Ovarian Cancer	Comb. with paclitaxel, with or without bevacizumab for the treatment of adult patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumors express PD-L1 (CPS ≥1) and who have received one or two prior systemic treatment regimens	PD -L1 [Combined Positive Score (CPS) ≥1]	Every 3-week dosing 395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing 790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer prior to paclitaxel with or without bevacizumab when given on the same day

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Dosing & Administration for FDA-Approved Indications

Cancer	Indication	Testing Required?	Dosage & Administration
Endometrial Carcinoma	Comb. with carboplatin and paclitaxel, followed by pembrolizumab and berahyaluronidase alfa as a single agent for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma; Comb. with lenvatinib for the treatment of adult patients with 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 adult patients with 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	Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)	Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer prior to carboplatin and paclitaxel regardless of MMR or MSI status when given on the same day, 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	For adult patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either in comb. with platinum- and fluoropyrimidine-based chemotherapy for patients with tumors that express PD-L1 (CPS ≥ 1), or as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS≥10)	PD -L1 [Combined Positive Score (CPS ≥1); (CPS ≥10)	Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer prior to chemotherapy when given on the same day

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Dosing & Administration for FDA-Approved Indications

Cancer	Indication	Testing Required?	Dosage & Administration
Gastric Cancer	Comb. with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS≥1); Comb. with fluoropyrimidine- and platinum-containing chemotherapy, for first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS≥1)	PD -L1 [Combined Positive Score (CPS) ≥1]	Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer prior to chemotherapy when given on the same day Administer prior to trastuzumab and chemotherapy when given on the same day.
Head and Neck Squamous Cell Cancer (HNSCC)	Single agent for first-line treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 (CPS≥1) as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin and then as a single agent; Comb. with platinum and fluorouracil (FU) for the first-line treatment of adult patients with metastatic or with unresectable, recurrent HNSCC; Single agent for the first-line treatment of adult patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥ 1)	PD -L1 [Combined Positive Score (CPS) ≥1]	Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer prior to chemotherapy when given on the same day
Hepatocellular Carcinoma	Single agent for adult patients with hepatocellular carcinoma secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen		Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa
Malignant Pleural Mesothelioma	Comb. with pemetrexed and platinum chemotherapy for first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma		Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer prior to chemotherapy when given on the same day

Dosing & Administration for FDA-Approved Indications

Cancer	Indication	Testing Required?	Dosage & Administration
Melanoma	Single agent for adult patients with unresectable or metastatic melanoma; Single agent for the adjuvant treatment of adult and pediatric patients 12 years and older with Stage IIB, IIC, or III melanoma following complete resection		Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa
Merkel Cell Carcinoma	Single agent for adult and pediatric patients 12 years and older with recurrent locally advanced or metastatic Merkel cell carcinoma		Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa
MSI-H or dMMR Solid Tumor	Single agent for adult and pediatric patients 12 years and older 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	Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)	Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa
MSI-H or dMMR Colorectal Cancer	Single agent for adult patients with unresectable or metastatic MSI-H or dMMR colorectal cancer	Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)	Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa

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Dosing & Administration for FDA-Approved Indications

Cancer	Indication	Testing Required?	Dosage & Administration
Non-small Cell Lung Cancer (NSCLC)	Comb. with pemetrexed and platinum chemotherapy, as first-line treatment for adult patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations; Comb. with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of adult patients with metastatic squamous NSCLC; Single agent for the first-line treatment of adult patients with NSCLC expressing PD-L1 (TPS ≥1%), with 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 adult patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%), with disease progression on or after platinum-containing chemotherapy, and patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving therapy; Comb. with platinum-containing chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery for adult patients with resectable NSCLC (tumors ≥4 cm or node positive); Single agent for adjuvant treatment for adult patients following resection and platinum-based chemotherapy for Stage IB, II, or IIIA NSCLC.	ALK, EGFR, PD -L1 [Tumor Proportion Score (TPS) ≥1%]	Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer pembrolizumab and berahyaluronidase prior to chemotherapy when given on the same day
Renal Cell Carcinoma	Comb. with axitinib for the first -line treatment of adult patients with advanced renal cell carcinoma (RCC); Comb. with lenvatinib for the first-line treatment of adult patients with advanced RCC; Adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions		Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer as a single agent in the adjuvant setting, or in the advanced setting in combination with either: axitinib 5 mg orally twice daily or in combination with lenvatinib 20 mg orally once daily

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Dosing & Administration for FDA-Approved Indications

Cancer	Indication	Testing Required?	Dosage & Administration
Triple-Negative Breast Cancer	Comb. with chemotherapy for adult patients with high-risk early-stage triple-negative breast cancer (TNBC) as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery; Comb. with chemotherapy for the treatment of adult patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS≥10)	PD -L1 [Combined Positive Score (CPS ≥10)]	Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer prior to chemotherapy when given on the same day
Tumor Mutational Burden-High Cancer	Single agent for adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] 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)]	Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa
Urothelial Cancer	Comb. w/enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial cancer; Single agent for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy, or who have disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; 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		Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa Administer after enfortumab vedotin when given on the same day.

SIDE EFFECTS AND THEIR MANAGEMENT

Because pembrolizumab and berahyaluronidase alfa-pmph is an immunotherapy that works by enhancing the patient's immune system, most adverse reactions associated with pembrolizumab and berahyaluronidase alfa-pmph 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.

The most common side effects of pembrolizumab and berahyaluronidase alfa-pmph when given with certain chemotherapy medicines include: nausea, tiredness, and muscle, bone, and joint pain.

The most common side effects seen with pembrolizumab given into the vein (intravenous pembrolizumab), which may happen with pembrolizumab and berahyaluronidase alfa-pmph, are shown below:

- **When used alone include:** feeling tired, pain, including pain in muscles, rash, diarrhea, fever, cough, decreased appetite, itching, shortness of breath, constipation, bones or joints and stomach-area (abdominal) pain, nausea, and low levels of thyroid hormone.

- **When used alone that are more common in children than in adults include:** fever, vomiting, headache, stomach area (abdominal) pain, and low levels of white blood cells.

- **When used with certain chemotherapy or chemotherapy with radiation therapy medicines include:** feeling tired or weak, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, trouble breathing, fever, hair loss, inflammation of the nerves that may cause pain, weakness, and paralysis in the arms and legs, swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina, mouth sores, headache, weight loss, stomach-area (abdominal) pain, joint and muscle pain, trouble sleeping, blisters or rash on the palms of your hands and soles of your feet, urinary tract infection, low levels of thyroid hormone, skin irritation in the radiation area, trouble swallowing and dry mouth.

- **When used with chemotherapy and bevacizumab include:** tingling or numbness of the arms or legs, hair loss, low red blood cell count, feeling tired or weak, nausea, low white blood cell count, diarrhea, high blood pressure, decreased platelet count, constipation, joint aches, vomiting, urinary tract infection, rash, low levels of thyroid hormone, and decreased appetite.

- **When used with axitinib include:** diarrhea, feeling tired or weak, high blood pressure, liver problems, low levels of thyroid hormone, decreased appetite, blisters or rash on the palms of your hands and soles of your feet, nausea, mouth sores or swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina, hoarseness, rash, cough, and constipation.

- **When used with enfortumab vedotin include:** rash, tingling or numbness of the arms or legs, feeling tired, itching, diarrhea, hair loss, weight loss, decreased appetite, dry eye, nausea, constipation, changes in sense of taste, and urinary tract infection.

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 and berahyaluronidase alfa-pmph 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 monotherapy which may happen with pembrolizumab and berahyaluronidase alfa-pmph treatment can be categorized into those that are most common, those that are less common but serious, and those that may be missed because they have a late-onset and/or are long-lasting.

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
Late-onset and/or long-lasting and may be missed	Arthralgia/arthritis Mucositis/xerostomia Neuropathy Nephritis

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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) • 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	• 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	—	• 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	• 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	• 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	• 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

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	• 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	• 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	• 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	• 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	• 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.

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

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QUESTIONS & ANSWERS

Q. How long will patients stay on pembrolizumab and berahyaluronidase alfa-pmph?

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 and berahyaluronidase alfa-pmph?

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 and berahyaluronidase alfa-pmph?

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 and berahyaluronidase alfa-pmph 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 purititc 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 seen 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

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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)
https://aimatskincancer.org/

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

FINANCIAL ASSISTANCE

The Merck Access Program
1-855-257-3932
https://www.merckaccessprogram-keytruda.com/keytrudaqlex/hcp/

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.
www.cancer.org/
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.
www.mercymedical.org/

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