Cemiplimab for Cutaneous Squamous Cell Carcinoma

An HCP Tool From the Immuno-Oncology Essentials Initiative

Programmed death receptor-1 (PD-1) is found on T cells and acts as a negative regulator of T-cell activation and proliferation, meaning it "turns the immune system off," essentially acting as a brake. This type of inhibitory role is necessary to prevent excessive immune reactions and autoimmunity. For this reason, PD-1 and other regulators that act in this manner are known as immune checkpoints.

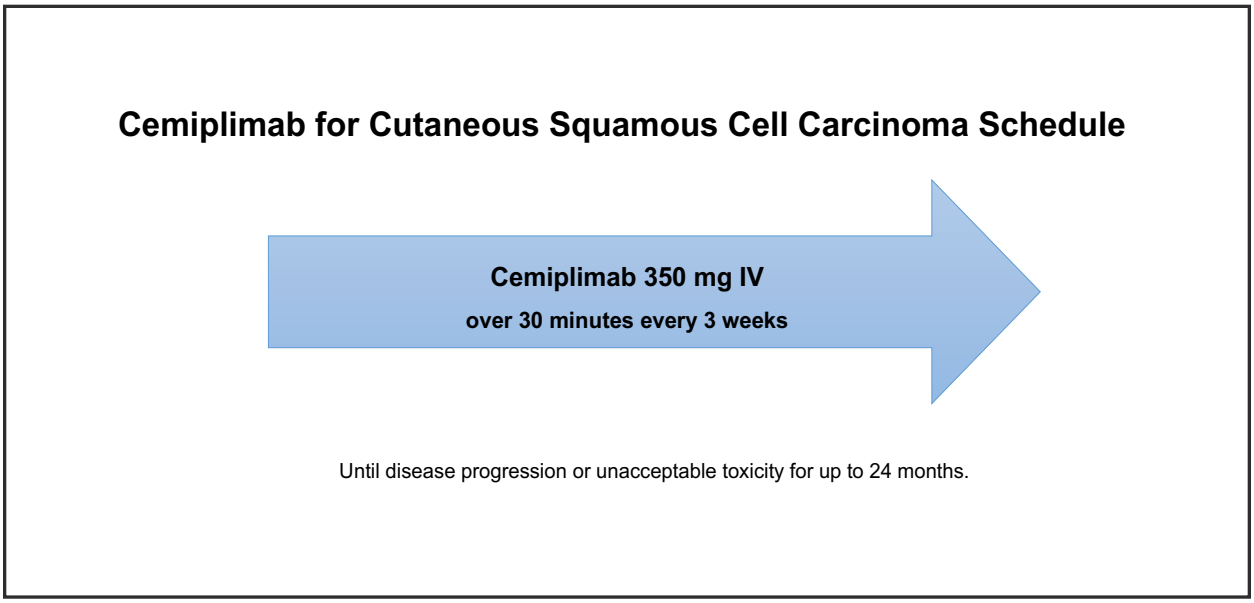
Programmed death ligand-1 (PD-L1) is a protein expressed on the surface of normal cells that helps regulate immune responses by interacting with the PD-1 receptor on T cells. This helps prevent autoimmune reactions. However, we now understand that various tumors can exploit the PD-1/PD-L1 pathway to avoid immune detection. Some tumors will express PD-L1 on their cell surface just like normal cells, allowing them to interact with PD-1 on T cells and "turn off" the immune system, thereby remaining undetected.

Cemiplimab (Libtayo®) is a PD-1 monoclonal antibody checkpoint inhibitor. Cemiplimab selectively binds to PD-1, blocking the PD-1/PD-L1 interaction and thereby "exposing" cancer cells and "turning on" the immune system.

Cemiplimab is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mcSCC) or locally advanced cSCC (lacSCC) who are not candidates for curative surgery or curative radiation. Use of cemiplimab for cSCC does not require testing of PD-L1 expression.

DRUG DOSAGE/ADMINISTRATION

- For cutaneous squamous cell carcinoma, the recommended dose of cemiplimab (Libtayo®) is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity for up to 24 months.



- Cemiplimab is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than trace amounts of translucent to white particles
- Withdraw 7 mL from a vial and dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1 mg/mL to 20 mg/mL. Mix diluted solution by gentle inversion. Do NOT shake. Discard any unused medicinal product or waste material
- Administer by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron to 5-micron filter.

SIDE EFFECTS AND THEIR MANAGEMENT

Because cemiplimab is an immunotherapy that works by enhancing the patient's immune system, most adverse reactions associated with cemiplimab 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 not be responsive to steroid treatment, and additional immunosuppressive agents may be necessary (infliximab, mycophenolate mofetil, cyclophosphamide, etc)
  - » Cemiplimab 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 cemiplimab 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 cemiplimab therapy are listed in Appendix 2

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

IrAEs category	Examples	Location
Most common	Musculoskeletal pain 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 Myocarditis	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
- Cemiplimab-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 cemiplimab 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 cemiplimab regimen with them at all times. This might be the cemiplimab-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 their insurance card. Here is the link to the wallet card: https://www.libtayo.com/resources/pdf/patient-wallet-card.pdf
- Advise patients to take pictures of any skin changes for documentation

QUESTIONS & ANSWERS

Q. **How long will patients stay on cemiplimab?**

A. The prescribing information indicates until disease progression or unacceptable toxicity for up to 24 months.

Q. **Is PD-L1 testing required for patients to be eligible to receive cemiplimab?**

A. No PD-L1 testing is required for patients receiving cemiplimab for cSCC.

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

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

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

A. Generally, the safety profile of cemiplimab 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. The side-effect profile may vary if given as monotherapy or in combination with pneumonitis.

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. Patients should be encouraged to get the inactivated influenza vaccine annually. 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

Regeneron/Sanofi-Genzyme
Libtayo Surround Program
Libtayo injection (cemiplimab-rwlc)
1-877-542-8296
https://www.libtayohcp.com/libtayo-surround

Additional Information Resources

Skin Cancer Education & Research Foundation
https://skincancerinfo.org

ADDITIONAL RESOURCES

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Click here for downloadable action plans to customize for your patients

APPENDIX 1

The 13 Care Step Pathways (CSPs) referenced in this Appendix are housed in the CSP section of the AIMWithImmunotherapy.com IO Essentials website. These CSPs 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 PD-1 inhibitor monotherapy

Adverse event	Common symptoms	Common management/anticipatory guidance
Anemia	Weakness, pale skin, irregular heartbeat, shortness of breath, dizziness, cold hands and feet	• Complete laboratory evaluation; rule out other potential causes for symptoms • Anticipate standard dose holds/discontinuations* • Provide close clinical follow-up • Evaluate growth factor support or red blood cell transfusions as needed
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 cemiplimab 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 • Counsel neurologist, obtain brain MRI, and lumbar puncture • Anticipate standard dose-holds and discontinuations*

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Management of other AEs associated with PD-1 inhibitor monotherapy

Adverse event	Common symptoms	Common management/anticipatory guidance
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*
Hypoparathyroidism	Tingling or twitching sensations, muscle aches, weakness, dry skin, depression, confusion, heart arrhythmia, fainting	• Complete laboratory evaluation (calcium, parathyroid hormone, albumin, etc.); rule out other potential causes for symptoms • Obtain urgent endocrinology referral • Standard dose holds/discontinuations* • IV calcium may be required, followed by oral therapy • Provide close clinical follow-up
Infusion reaction	Chills/shaking, back pain, itching, flushing, difficulty breathing, hypotension, fever	• Monitor patients for signs and symptoms. For grade 1 or 2 reactions, slow or interrupt infusion. For grade 3 or 4 reactions, stop infusion and permanently discontinue cemiplimab.
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*
Lower respiratory tract infection (pneumonia)	Shortness of breath, productive or dry cough, fever, sweating, or chills	• Chest Xray, oxygen levels, infectious diseases workup • Differential from irAE pneumonitis • Antimicrobials (if appropriate), antipyretics, supportive care • Anticipate standard treatment holds

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Management of other AEs associated with PD-1 inhibitor monotherapy

Adverse event	Common symptoms	Common management/anticipatory guidance
Meningitis (aseptic)	Headache, photophobia, skin neck, nausea and vomiting, fever, cognition typically unaffected	• Rule out infectious, endocrine/metabolic, or other causes • Counsel neurologist, obtain brain MRI and lumbar puncture • Anticipate standard dose-holds and discontinuations* • Anticipate requirement for corticosteroids, empiric antimicrobials, supportive care, and hospitalization, depending on severity • Permanently discontinue cemiplimab for Grades 2,3, or 4
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*
Vasculitis	Pain, swelling, vein visibility/ rash, cyanosis, unexplained fever, pleuritic pain, cough, wheezing, or hemoptysis	• Work-up for vasculitis (urinalysis, angiography, other imaging, blood work), rule out other causes • Consult rheumatology • Anticipate standard dose holds/discontinuations* and requirement for high-dose corticosteroids
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

*Permanently discontinue cemiplimab for Grade 3 or Grade 4 AEs. Hold cemiplimab for Grade 2 AEs. Resume treatment when AE returns to Grade 0 or 1.