

## Pembrolizumab (KEYTRUDA)

### Criteria for Use

MARCH 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at [www.pbm.va.gov](http://www.pbm.va.gov) or <http://vawww.pbm.va.gov> for further information.

#### Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive pembrolizumab*

- Active or untreated brain metastases.
- History of autoimmune disease or other conditions requiring immunosuppressive therapy. (*see Issues for Consideration*)
- Use of corticosteroids, unless as a stable or decreasing dose of < 10 mg daily prednisone equivalent.
- Symptomatic interstitial lung disease.
- Uveal melanoma.
- Pregnancy [i.e., known pregnancy or positive pregnancy test] or breastfeeding.

Note: Patients with acute or chronic Hepatitis B or C or HIV positive were excluded in some but not all clinical trials. Eligibility in these cases should be determined by the treating provider on an individualized basis.

#### Inclusion Criteria *The answers to one of the following must be fulfilled in order to meet criteria.*

- ECOG Performance Status 0-2.
- Goals of care and role of Palliative Care consult has been discussed and documented.

#### AND ONE OF THE FOLLOWING:

- Unresectable or metastatic melanoma**
- Metastatic Non-small cell lung cancer with disease progression on or after platinum-based chemotherapy.** (*see Issues for Consideration*) Patients with EGFR or ALK tumor mutations are eligible for pembrolizumab if they also have disease progression on FDA-approved therapy for those mutations.
- Pregnancy must be excluded prior to receiving pembrolizumab and patient provided contraceptive counseling on potential risk vs. benefit of taking pembrolizumab if patient were to become pregnant

#### Dosage and Administration

- 2mg/kg as an IV infusion over 30 minutes every 3 weeks until disease progression or significant toxicity.
- Delay treatment for any of the following immune-mediated toxicities (may resume upon recovery to grade 0 or 1 toxicity):
  - **Colitis:** Moderate (grade 2) or severe (grade 3): also administer corticosteroids (prednisone 1 mg to 2 mg/kg daily or equivalent) followed by a taper.
  - **Pneumonitis** (grade 2): also administer corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a taper.
  - **Hepatitis:** moderate (grade 2) AST or ALT >3-5 x ULN or total bilirubin > 1.5-3 x ULN; initiate prednisone 0.5-1.0 mg/kg daily.
  - **Nephritis and Renal dysfunction:** Grade 2: Serum creatinine > 1.5-6 x ULN or >1.5-6 x baseline. Administer corticosteroids (prednisone 1 mg to 2 mg/kg daily or equivalent) followed by a taper.
  - **Endocrinopathies** (hypophysitis, adrenal insufficiency, Type 1 Diabetes Mellitus): Moderate (grade 2) or severe (grade 3). Administer corticosteroids 1-2 mg/kg daily followed by taper and hormone replacement as indicated. Severe (grade 3) type 1 diabetes mellitus: administer insulin until metabolic control is achieved.
  - **Rash:** severe (grade 3); also administer corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a taper.
  - **Other** immune-mediated toxicities: also administer corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a taper.
  - **Other treatment-related** toxicities (severe or grade 3). Based on severity, begin corticosteroids until improvement to Grade 1 or less then initiate taper.
  - **Infusion reactions:** mild to moderate: Interrupt or slow infusion.

#### Monitoring

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Updated versions may be found at <http://www.pbm.va.gov> or <http://vawww.pbm.va.gov>

<ul style="list-style-type: none"> <li>• Baseline labs and every 6 weeks: complete blood count, liver function tests, chemistry profile, TSH</li> <li>• Clinical history and physical exam at baseline and every 6 weeks or more frequently with monitoring for signs and symptoms of immune-related adverse events (e.g. colitis, pneumonitis, etc.)</li> <li>• Tumor assessment: at baseline, after initial 9 weeks of therapy, and then every 6 weeks until progression or discontinuation</li> </ul>
<b>Issues for Consideration</b> <ul style="list-style-type: none"> <li>• <b>Immunosuppressive therapy:</b> Patients requiring systemic therapy with either corticosteroids (&gt;10 mg daily prednisone equivalent) or immunosuppressive agents were not enrolled in clinical trials.</li> <li>• <b>PD-L1 expression:</b> Measurement of PD-L1 expression is still being defined. There is no standardized timing for collection of tissue for an assay and the cut point for determining expression (positive or negative) is not well defined. The FDA approved use in non-small cell lung cancer in patients whose tumors expressed PD-L1 using an FDA approved test; the percent expression of PD-L1 to determine a positive result was not stated. In the non-small cell lung cancer clinical trial, the cut point was PD-L1 expression (staining) in greater than or equal to 50% of tumor cells. However, responses were also seen in tumors expressing 1-49% PD-L1 and even &lt;1% PD-L1 expression although at lower rates than those in the greater than or equal to 50% group.</li> <li>• <b>Immune-mediated hypothyroidism or hyperthyroidism:</b> Administer hormone replacement therapy for hypothyroidism. Initiate medical management of hyperthyroidism. Withhold or discontinue therapy for severe or life-threatening hyperthyroidism. No recommended dose changes for pembrolizumab.</li> <li>• <b>Dosing:</b> Although pembrolizumab was studied in a range of doses, a randomized dose-comparison cohort from the large phase 1 trial compared 2 mg/kg and 10 mg/kg doses. Waterfall plots for changes in the dimensions of target lesions by RECIST criteria, and Kaplan-Meier estimates of progression free survival and overall survival showed similar clinical activity between the 2 doses.<sup>i</sup></li> </ul>
<b>Renewal/Discontinuation Criteria</b> <ul style="list-style-type: none"> <li>• Radiographic or symptomatic disease progression. (Note: Early in immune-therapy a distinct immune related disease flare or pseudo-progression may be seen consisting of inflammatory infiltrates or necrosis followed by delayed tumor regression).</li> <li>• Patient declines further therapy</li> <li>• Permanently discontinue for significant drug-related toxicity: <ul style="list-style-type: none"> <li>• <b>Colitis</b> (grade 4): also administer high dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper</li> <li>• <b>Pneumonitis</b> (grade 3 or 4): also administer high dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper</li> <li>• <b>Hepatitis</b> severe (grade 3) or life-threatening (grade 4) AST or ALT &gt; 5 x ULN or total bilirubin &gt;3 x ULN; high dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper</li> <li>• <b>Nephritis or Renal dysfunction:</b> Serum creatinine &gt; 6x ULN; also administer high dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper</li> <li>• <b>Endocrinopathies:</b> Severe (grade 3) or life-threatening (grade 4) hypophysitis. Also administer corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper. Life-threatening (grade 4) hyperglycemia.</li> <li>• <b>Rash:</b> Life-threatening (grade 4): also administer corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a taper.</li> <li>• <b>Other:</b> Severe (grade 3) that recur or life-threatening (grade 4) adverse reactions. Also administer corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper.</li> <li>• <b>Infusion reactions:</b> Severe or life-threatening.</li> </ul> </li> </ul>

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<sup>i</sup> Robert C, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised, dose-comparison cohort of a phase 1 trial. Lancet 2014; 384:1109-17.