

Nivolumab (OPDIVO)**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 or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria If the answer to ANY item below is met, then the patient should NOT receive nivolumab.

- 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

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

AND ONE OF THE FOLLOWING:

- Diagnosis of Unresectable or Metastatic Melanoma**
 - As a single agent for BRAF V600 wild-type patients.
 - As a single agent for BRAF V600 mutation-positive patient.
 - In combination with ipilimumab. see *Issues for Consideration*
- Metastatic Non-Small Cell Lung Cancer with progression on or after platinum-based chemotherapy in the metastatic setting.** (See *Issues for Consideration*) Patients with EGFR or ALK tumor mutations are eligible for nivolumab if they also have disease progression on FDA-approved therapy for those mutations.
- Advanced Renal Cell Carcinoma who received prior anti-angiogenic therapy.**
- Pregnancy must be excluded prior to receiving nivolumab and patient provided contraceptive counseling on potential risk vs. benefit of taking nivolumab if patient were to become pregnant.

Dosage and Administration

- As a single agent: 3 mg/kg IV over 60 minutes every 2 weeks until disease progression or significant toxicity.
- In combination with ipilimumab: 1 mg/kg IV over 60 minutes followed by ipilimumab on the same day every 3 weeks for 4 doses, then nivolumab alone 3mg/kg IV over 60 minutes every 2 weeks.
- Delay treatment for any of the following immune-mediated toxicities (may resume upon recovery to grade 0 or 1 toxicity):
 - **Colitis**
 - Grade 2 (duration >5 days): also administer corticosteroids (prednisone 0.5 mg to 1 mg/kg daily or equivalent) followed by a taper; may increase to 1 mg to 2 mg/kg daily or equivalent if colitis worsens or does not improve with initial corticosteroid treatment.
 - Grade 3: also administer corticosteroids (prednisone 1 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.

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- **Nephritis and Renal dysfunction:** Grade 2: Serum creatinine > 1.5-6 x ULN or >1.5-6 x baseline. Administer corticosteroids (prednisone 0.5 mg to 1 mg/kg daily or equivalent) followed by a taper; may increase to 1 mg to 2 mg/kg daily or equivalent if nephritis or dysfunction worsens or does not improve with initial corticosteroid treatment.
- **Endocrinopathies** (hypophysitis, adrenal insufficiency, Type 1 Diabetes Mellitus): Moderate (grade 2) or severe (grade 3) hypophysitis. Moderate (grade 2) adrenal insufficiency. Administer corticosteroids 1-2 mg/kg daily followed by taper. 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).
- **Infusion reactions:** mild to moderate: Interrupt or slow infusion.

Monitoring

- Baseline labs and every 6 weeks: complete blood count, liver function tests, chemistry profile, TSH
- 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.)
- Tumor assessment: at baseline, after initial 9 weeks of therapy, and then every 6 weeks until progression or discontinuation

Issues for Consideration

- **Immunosuppressive therapy:** Patients requiring systemic therapy with either corticosteroids (>10 mg daily prednisone equivalent) or immunosuppressive agents were not enrolled in clinical trials.
- **PD-L1 expression:** Measurement of PD-L1 expression is still being defined. There is no standardized timing for collection of tissue for an assay, the cut point for determining expression (positive or negative) is not well defined, and the available assay for PD-L1 expression is a complementary (not mandatory).
 - **Combination therapy in melanoma:** In study 067 comparing nivolumab, nivolumab plus ipilimumab, and ipilimumab in untreated melanoma, the analysis of progression free survival (PFS) by PD-L1 tumor status showed similar results for PFS between nivolumab alone versus nivolumab plus ipilimumab in patients with PD-L1 positive tumors (defined as at least 5% of tumor cells displaying staining). In PD-L1 negative tumors (less than 5% of tumor cells staining) the median PFS was 5.3 months in nivolumab monotherapy patients versus 11.2 months in the nivolumab plus ipilimumab arm. Note: the study was not designed for a formal statistical comparison between the nivolumab and nivolumab plus ipilimumab groups. Overall survival results will be available some time in 2016.
 - **Nonsquamous non-small cell lung cancer:** In the 057 trial in nonsquamous non-small cell lung cancer, nivolumab therapy was correlated with longer overall survival and progression free survival versus docetaxel based on PD-L1 expression levels of 1% or higher, 5% or higher, and 10% or higher.
- **Metastatic Non-Small Cell Lung Cancer with progression on or after platinum-based chemotherapy.** Patients with recurrent disease > 6 months after adjuvant or neoadjuvant platinum based chemotherapy also need to subsequently progress during or after a platinum doublet regimen given to treat the recurrence.
- **Immune-mediated hypothyroidism or hyperthyroidism:** Administer hormone replacement therapy for hypothyroidism. Initiate medical management of hyperthyroidism. No recommended dose changes for nivolumab.

Discontinuation Criteria

- 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).
- Patient declines further therapy
- Permanently discontinue for significant drug-related toxicity:
 - **Colitis** (grade 4): also administer high dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper
 - **Colitis:** Grade 3 or 4 (if in combination with ipilimumab) or recurrent (any grade)
 - **Pneumonitis** (grade 3 or 4): also administer high dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper
 - **Hepatitis** severe (grade 3) or life-threatening (grade 4) AST or ALT > 5 x ULN or total bilirubin >3 x ULN; high dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper
 - **Nephritis or Renal dysfunction:** Serum creatinine > 6x ULN; also administer high dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper
 - **Endocrinopathies:** Life-threatening (grade 4) hypophysitis. Severe (grade 3) or life-threatening (grade 4) adrenal insufficiency. Also administer corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by taper. Life-threatening (grade 4) hyperglycemia.
 - **Rash:** Life-threatening (grade 4): also administer corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a taper.
 - **Other** severe (grade 3) or life-threatening (grade 4) adverse reactions, or severe (grade 3) adverse reactions that recur, or persistent grade 2 or 3 treatment-related toxicity that does not recover to grade 1 or resolve within 12 weeks after the

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last nivolumab dose.

- **Infusion reactions:** Severe or life-threatening.

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