BACKGROUND

Opdivo, a human programmed death receptor-1 blocking antibody, is indicated for the treatment of the following indications:¹

1) Patients with unresectable or metastatic melanoma and disease progression following Yervoy® (ipilimumab intravenous injection) and, if BRAF V600 mutation positive, a BRAF inhibitor (e.g., Tafinlar® [dabrafenib capsules], Zelboraf® [vemurafenib tablets]); AND
2) Metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

For both indications, the recommended dose of Opdivo is 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.¹ The dose of Opdivo should be held or permanently discontinued due to certain adverse events. Opdivo is available as single use, preservative-free vials containing 10 mg/mL of drug (40 mg/4 mL and 100 mg/10 mL vials). Dilute Opdivo with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.

REQUIRED REVIEW AND APPROVALS

This policy involves the use of Opdivo. Prior authorization is recommended for medical benefit coverage of Opdivo. Approval is recommended for those who meet the conditions of coverage in the Criteria, Dosing, Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics for the diagnosis provided. The requirement that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. Waste Management applies for all covered conditions. Conditions Not Recommended for Approval are listed following the recommended authorization criteria and Waste Management section. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Opdivo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Opdivo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

UM129_CCC_ Nivolumab _(Opdivo®)
CRITERIA:

Coverage of Opdivo is recommended in those who meet one of the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Melanoma.

Criteria. The patient must meet the following criteria (A AND B):

A. Opdivo is prescribed by or in consultation with an oncologist; AND
B. The patient has unresectable, advanced, or metastatic melanoma; AND

Opdivo is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following Yervoy therapy and, if BRAF V600 mutation positive, a BRAF inhibitor (e.g., Tafinlar, Zelboraf).¹ This indication was approved as an accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

According to the National Comprehensive Cancer Network (NCCN) guidelines on melanoma (version 3.2015), patients with advanced or metastatic melanoma (distant metastatic disease [Stage IV]) can be managed by systemic therapy, clinical trial, and best supportive care.² Symptomatic patients may receive palliative resection and/or radiation. First-line systemic therapy is based on factors such as BRAF mutation status, the tempo of the disease, and cancer-related symptoms. Clinical studies are underway to assess the optimal sequencing and/or combination of these agents. These guidelines recommend Opdivo as single-agent therapy for metastatic or unresectable disease as first-line therapy or as second-line therapy for disease progression or following maximum clinical benefit from BRAF targeted therapy for patients with performance status 0 to 2. In patients with metastatic or unresectable disease and BRAF V600 wild type, first-line systemic treatment options in patients who are anticipated to be clinically stable for > 12 weeks include Keytruda (category 2A), Opdivo (category 1), Yervoy (category 1), and high-dose Proleukin* (aldesleukin for intravenous infusion) [category 2A]. In patients who are anticipated to be clinically stable for ≤ 12 weeks, the first-line systemic treatment options include Keytruda (category 2A), Opdivo (category 1), cytotoxic agents (e.g., dacarbazine, temozolomide, paclitaxel), Gleevec* (imatinib mesylate tablets, category 2A) [for tumors with activating mutations of C-KIT], or biochemotherapy (category 2B) [for tumors with activating mutations of C-KIT], or biochemotherapy (category 2B). Patients with disease progression on the previously described treatment options and who have performance status 0 to 2 may receive second-line or subsequent therapy with Keytruda, Opdivo, Yervoy (category 1), high-dose Proleukin, cytotoxic agents, Gleevec (for tumors with activating mutations of C-KIT), or biochemotherapy (category 2B). For patients with performance status 3 to 4 it is recommended to consider best supportive care. In patients with metastatic or unresectable disease and BRAF
**Clinical Coverage Criteria**

**V600 Mutant Type (i.e., Mutation Positive)**, first-line systemic treatment options in patients who are anticipated to be clinically stable for > 12 weeks include Keytruda (category 2A), Opdivo (category 1), Yervoy (category 1), Tafinlar plus Mekinist (trametinib tablets) [category 1], or high-dose Proleukin (category 2A). In patients who are anticipated to be clinically stable for ≤ 12 weeks, the first-line systemic treatment options include Tafinlar plus Mekinist [preferred], Zelboraf (category 1), Tafinlar alone (category 1), Keytruda (category 2A), or Opdivo (category 1). Further recommendations are made in the guidelines for patients with disease progression or maximum clinical benefit from BRAF targeted therapy and who have a performance status of 0 to 2.

The efficacy of Opdivo was established in one Phase III, randomized, open-label, multicenter, pivotal study (CheckMate-037) in patients with unresectable or metastatic melanoma who had disease progression with other therapies (i.e., Yervoy and, if BRAF V600 mutation positive, a BRAF inhibitor). Results from a pre-planned interim analysis after 120 patients received treatment with Opdivo for 6 months are available. However, durable antitumor activity and improved overall survival in patients previously treated with other agents and in patients with previously untreated advanced melanoma without BRAF mutation were demonstrated in other published non-pivotal trials.

**Dosing in Advanced, Unresectable or Metastatic Melanoma in Adults.** *Dosing must meet the following:* 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.

The recommended dose is 3 mg/kg given as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Management of adverse events may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician. Of note, there are no recommended dose modifications for hypo- or hyperthyroidism.

**Initial Approval/Extended Approval.**

A) **Initial Approval:** Approve for 6 months.

B) **Extended Approval:** Approve at 6-month intervals if the patient has a response as determined by the prescribing physician.

**Duration of Therapy in Advanced, Unresectable or Metastatic Melanoma in Adults.** Indefinite if the patient is responding to therapy.

In CheckMate-037, patients with unresectable or metastatic melanoma received Opdivo 3 mg/kg every 2 weeks. Median duration of response was not reached for Opdivo; however, of the 38 patients with responses, 87% of patients (n = 33/38) had ongoing responses with durations ranging from 2.6+ to 10+ months. This includes 13 patients with ongoing responses of 6 months or longer. Objective responses occurred in patients with and without BRAF V600 mutations.

**Labs/Diagnostics.** None required.

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2. **Non-Small Cell Lung Cancer (NSCLC).**
Criteria. The patient must meet the following criteria (A, B, AND C):

A. Opdivo is prescribed by or in consultation with an oncologist; AND

B. The patient has metastatic disease; AND

C. The patient has tried a platinum-based chemotherapy (e.g., cisplatin, carboplatin).

Opdivo is indicated in metastatic squamous NSCLC, in patients who progress on or after platinum-based chemotherapy.\(^1\) The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 7.2015) recommend Opdivo as subsequent therapy for patients with metastatic squamous cell carcinoma or nonsquamous cell carcinoma who have progressed on or after a platinum-based therapy.\(^10\) The recommendation for use as subsequent therapy in nonsquamous NSCLC is based on preliminary data from a Phase III study (CheckMate-057) where median overall survival was 12.2 months with Opdivo vs. 9.4 months with docetaxel. Note that NCCN does not recommend testing for PD-1 status because many patients with metastatic NSCLC benefit from Opdivo. Recently, data suggest that mismatch repair deficiency is associated with response to checkpoint antibodies such as Opdivo.

An unpublished, randomized, open-label Phase III study compared Opdivo with docetaxel in patients (n = 272) with squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received Opdivo 3 mg/kg IV every 2 weeks or docetaxel 75 mg/m\(^2\) IV every 3 weeks. At an interim analysis, there was a statistically significant improvement in overall survival in patients receiving Opdivo (9.2 months vs. 6.0 months, respectively, for Opdivo and docetaxel; P = 0.00025). At the interim analysis, there were 86 events in the Opdivo treatment group vs. 113 events in the docetaxel group.

A published Phase II single-arm study evaluated Opdivo in patients (n = 117) with metastatic squamous NSCLC who had progressed after receiving a platinum-based therapy and at least one additional systemic treatment regimen.\(^1,9\) Approximately two-thirds of patients had previously received \(\geq\) three systemic treatments. Median time from initial lung cancer diagnosis to treatment with Opdivo was 1.7 years. All patients received Opdivo 3 mg/kg IV over 60 minutes every 2 weeks. After a minimum follow-up of at least 10 months in all patients, confirmed overall response rate as assessed by the independent radiology review committee was 15% (n = 17/117) [95% confidence interval (CI): 9, 22]), all of which were partial responses. Median duration of response was not reached; median time to response was 3.3 months (range, 1.7, 8.8). Overall, 76% of patients (n = 13/17) with a confirmed response had ongoing responses with duration ranging from 1.9+ to 11.5+ months; 59% patients (n = 10/17) had durable responses of 6 months or longer. In the 26% of patients (n = 30/117) with stable disease, median duration of stable disease was 6.0 months with 20 patients progression-free at time of analysis. In the overall patient population, median PFS was 1.9 months (95% CI: 1.8, 3.2) and median overall survival was 8.2 months (95% CI: 6.1, 10.9).

Dosing in Metastatic NSCLC in Adults. Dosing must meet the following: 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.
CLINICAL COVERAGE CRITERIA

The recommended dose is 3 mg/kg given as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.\(^1\) Management of adverse events may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician. Of note, there are no recommended dose modifications for hypo- or hyperthyroidism.

**Initial Approval/Extended Approval.**
A) *Initial Approval*: Approve for 6 months.
B) *Extended Approval*: Approve at 6-month intervals has responsive or stable disease, as determined by the prescribing physician.

**Duration of Therapy in Metastatic NSCLC in Adults.** Indefinite if the patient is responding to therapy.

In the Phase II CheckMate-063 study, median time to onset of response was 3.3 months (range 1.7, 8.8) after the start of treatment.\(^1\) In all, 76% of patients (n = 13/17) with a confirmed response had an ongoing response with duration ranging from 1.9+ to 11.5+ months. Of the responders, 59% of patients (n = 13/17) had durable responses of 6 months or longer.

2. **Patient has been Started on Opdivo.** Approve if the patient meets the conditions for coverage required for Dosing, Extended Approval, Duration of Therapy, and Labs/Diagnostics for an approved use in this Opdivo Utilization Review policy.

3. **Other Cancer-Related Indications.** Forward to the Medical Director for review on a case-by-case basis.

**Waste Management for All Indications.**
Dosing for Opdivo is based on body weight (mg/kg). The dose should be calculated and the number of vials needed assessed.
**CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Opdivo has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

**SPECIAL CONSIDERATIONS**

None

**LIMITATIONS/ EXCLUSIONS**

Please refer to each product line’s certificate of coverage for benefit limitations and exclusions for these services.

**REFERENCES**

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# CLINICAL COVERAGE CRITERIA

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